The Enantioselective Total Syntheses of Eight Cladiellin Natural Products

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Abstract

The cladiellins (also known as eunicellins) are oxygen-bridged 2,11–cyclised cembranoids, isolated from gorgonian octocorals and soft corals. They present an unusual oxatricyclic ring system composed of a hydroisobenzofuran and an oxonene unit. The natural role of these cembranoids is proposed to involve predatation deterrence, and biologically they have been shown to exhibit in vitro cytotoxicity against various cancer cell lines, anti inflammatory properties antimicrobial activities.

The Clark group has been interested in the synthesis of cladiellins for some time, and in 2007 Clark and co-workers reported the total synthesis of vigulariol. This thesis describes the investigation of the synthesis of both *E*- and *Z*-cladiellins using our general strategy.

The key transformations in the synthetic route are ring formation reactions. Firstly, a SmI_2-mediated reductive cyclisation forms the tetrahydropyran ring, then a tandem oxonium ylide formation [2,3]-sigmatropic rearrangement constructs the oxabicyclo[6.2.1]undecenone bicyclic core. Finally, a Diels-Alder cycloaddition reaction forms the third ring of the tricyclic core of the cladiellins. Particular interest was given to the tandem oxonium ylide formation [2,3]-sigmatropic rearrangement reaction. This transformation was studied in order to develop conditions allowing the selective formation of the *E*-oxonene ring needed for the synthesis of the *E*-cladiellin tricyclic core.

Herein, is presented work towards the synthesis of ophirin B, a cladiellin bearing a *Z*-oxonene alkene, as well as the enantioselective total synthesis of eight cladiellins obtained from an *E*-cladiellin tricyclic core: (−)-cladiella-6,11-dien-3-ol, (−)-cladiell-11-ene-3,6,7-triol, (−)-3-acetoxycladiella-6,11-diene, 3-acetoxy-cladiellin-11-ene-6,7-diol, (−)-sclerophytin A, (−)-sclerophytin B, (+)-deacetylpolyanthellin A and (+)-polyanthellin A in 20 to 24 steps from our allylic alcohol precursor.

Declaration

I declare that, except where explicit reference is made to the contribution of others, the substance of this thesis is the result of my own work and has not been submitted for any other degree at the University of Glasgow or any other institution.

A portion of the work described herein has been published elsewhere as listed below.

Enantioselective Total Syntheses of Three Cladiellins (Eunicellins): A General Approach to the Entire Family of Natural Products J. Stephen Clark, Raphaëlle Berger, Stewart T. Hayes, Lynne H. Thomas, Angus J. Morrison and Luca Gobbi *Angew. Chem. Int. Ed.* **2010**, *49*, 9867–9870.

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Raphaëlle Berger

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Prof. J. Stephen Clark

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Finally I would like to thank my family for their understanding and support from a distance.

Abbreviations

9-BBN	9-borabicyclo[3,3,1]-nonane
Ac	acetyl
acac	acetylacetonate
acam	acetamide
AIBN	2,2'-azo*bis*isobutyronitrile
aq	aqueous
Ar	aryl
atm	1 atmosphere
BHT	2,6-bis(1,1-dimethylethyl)-4-methylphenol
Bn	benzyl
bp	boiling point
brsm	based on recovered starting material
Bu	butyl
Bz	benzoyl
cap	caprolactamate
Cb	*N*,*N*,diisopropyl carbonyl
CBS	Corey-Bakshi-Shibata
CI	chemical ionization
CIDNP	chemically induced dynamic nuclear polarization
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarization transfer
DET	diethyl tartrate
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DIPT	diisopropyl tartrate
DMAP	*N*,*N*-4-dimethylaminopyridine
DMDO	dimethyl dioxirane
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
DPPP	1,3-*bis*(diphenylphosphino)propane
dr	diastereomeric ratio
ee	enantiomeric excess

EI	electron ionization
ES	electrospray ionization
Et	ethyl
FAB	fast atom bombardment
h	hour
hfacac	hexafluoroacetylacetonate
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HMPA	hexamethylphosphoramide
HPLC	high-pressure liquid chromatography
HRMS	high resolution mass spectrometry
hv	irradiation with light
i	iso
IBX	*o*-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration
Ipc	isopinocampheyl
IR	infrared spectroscopy
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	*meta*
MAD	methyl aluminum *bis*(2,6-di-*tert*-butyl-4-methylphenoxide)
m-CPBA	*meta*-chloroperbenzoic acid
Me	methyl
Mem	(2-methoxyethoxy)methyl
MLn	transition metal with ligands
mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry
MS	molecular sieves
MVK	methyl vinyl ketone
NIS	*N*-iodosuccinimide
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
o	*ortho*
p	*para*
pfm	heptafluorobutanamide

Ph	phenyl
Piv	pivaloyl
PMB	*p*-methoxybenzyl
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
p-TSA	*p*-toluenesulfonic acid
quant	quantitative
R_f	retention factor in chromatography
rt	room temperature
SFC	supercritical fluid chromatography
t	*tert*
TBAF	tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxyde
TBS	*tert*-butyldimethylsilyl
TCBn	tetrachlorobenzyl
TES	triethylsilyl
Tf	trifluromethanesulfonyl (triflyl)
tfa	trifluoroacetate
tfacam	trifluoroacetamide
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMCDA	trans-*N*,*N*′-dimethylcyclohexane-1,2-diamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
tpa	triphenylacetate
TPAP	tetra-*n*-propylammonium perruthenate
tr	triphenylmethyl (trityl)
Ts	*p*-toluenesulfonyl
TS	transition state
Δ	heat

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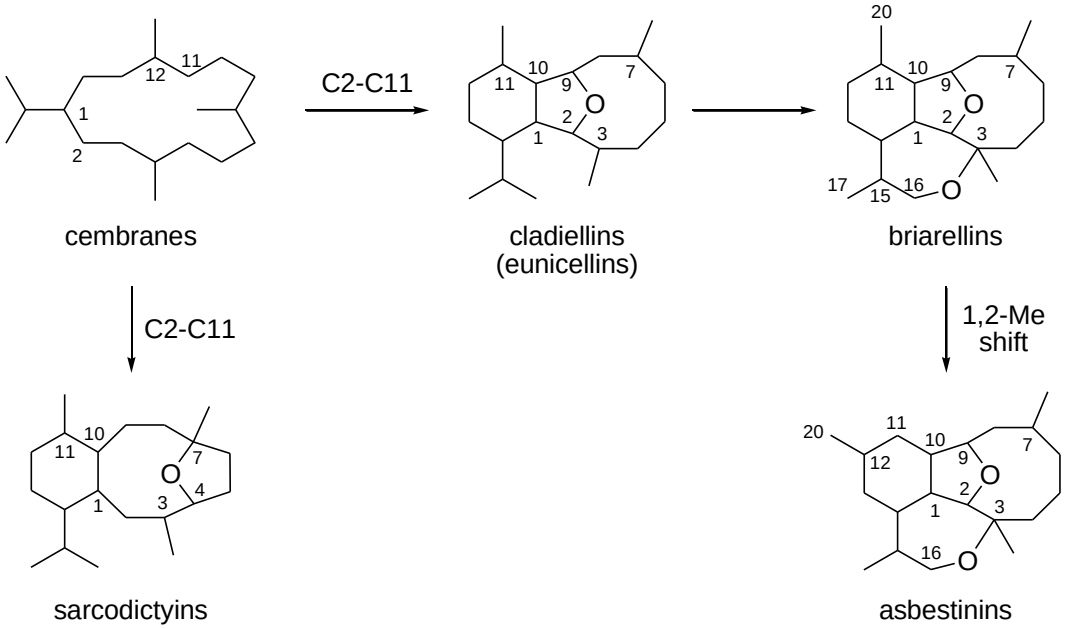
1 Introduction

1.1 The 2,11-Cyclised Cembranoid Family of Natural Product

Over the last forty three-years a large number of biologically active oxygen-bridged 2,11-cyclised cembranoids have been isolated from marine invertebrates such as gorgonians and soft corals. These marine metabolites possess unique structures that are not found in natural products isolated from terrestrial sources. This family of natural products displays a large degree of structural diversity as well as varied biological and pharmacological activities such as cytotoxicity, anti-inflammatory effects, and anti-malarial properties. Oxygen-bridged diterpenes have been classified in four categories;[1] the cladiellins (also known as eunicellins), the briarellins, the asbestinins, and the sarcodictyins (**Scheme 1**). The cladiellins, briarellins, and asbestinins are characterised by a tricyclic diterpenoid structure associated with an unusual ether bridge between C-2 and C-9 (cladiellin numbering). The briarellins and the asbestinins posses an additional seven-membered ether ring between C-3 and C-16. The sarcodictyins, unlike the others, feature an ether bridge between C-4 and C-7.



Scheme 1

1.1.1 Proposed Biosynthesis

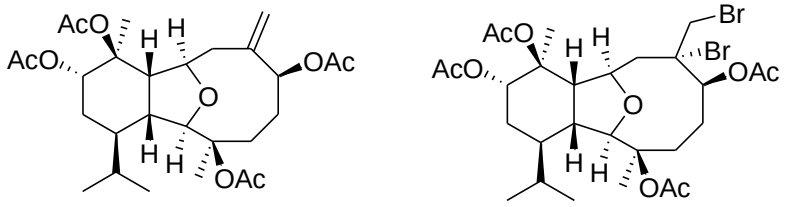
A possible biosynthetic pathway to the ether-bridged diterpenes was first postulated by Faulkner and co-workers upon isolation of the first sarcodictyin.[2] In this report, Faulkner proposed that a 2,11-cyclisation reaction (cembrane nomenclature) of the cembrane ring skeleton initiates the biosynthetic pathway that leads to all four sub-classes of compound (**Scheme 1**). Cyclisation of the cembrane skeleton between C-2 and C-11 (cembrane nomenclature) and ether ring formation between C-2 and C-9 (cladiellin nomenclature) affords the cladiellin. Additional seven-membered cyclic ether formation between C-3 and C-16 (cladiellin nomenclature) gives the briarellins. The asbestinin skeleton is obtained from the briarellins *via* a 1,2 methyl shift from C-11 to C-12. The sarcodictyins are obtained by the same initial 2,11-cyclisation reaction of the cembrane skeleton, but with ether ring formation occurring between C-4 and C-7 (cladiellin nomenclature). Although no systematic study of the biosynthesis has been reported, the isolation of members of the different sub-classes from a common organism provided circumstantial evidence for Faulkner's proposed biosynthetic pathway.

1.1.2 The Cladiellin Family

The cladiellin (eunicellin) family is the most abundant class of oxygenated 2,11-cyclised cembranoids. Currently, more than 60 members of the cladiellin family have been isolated from marine source.

1.1.2.1 Isolation and Characterisation

The first oxygenated 2,11-cyclised cembranoid isolated was eunicellin (**Figure 1**). The isolation of this compound was reported in 1968 by Kennard and co-workers, from the soft coral *Eunicella stricta* found off the coast of Banyuls-sur-Mer in France.[3] The structure of eunicellin was determined based on NMR studies and on the X-ray diffraction analysis of its dibromide **1** derivative.



Eunicellin **1**

Figure 1

The structures of the majority of the cladiellins have been determined by NMR analyses alone. However, some of the cladiellins have been subjected to X-ray crystallography in order to determine their relative configuration. The first determination of the absolute configuration of a cladiellin was performed by Ochi and co-workers in 1988 for litophynin C.[4] Since then, the absolute configurations of other natural products in the family have been deduced base on this assignment. Subsequent development of the modified Mosher method[5] enabled the absolute configuration of many members of the family to be solved with reasonable certainty.

The cladiellins possess a large degree of functional diversity, but in all cases C-3, C-6, C-7 and C-11 are either oxygenated or sp^2 hybridised (**Figure 2**). The C-3 stereogenic centre was long thought to have the *R* configuration in all the cladiellins, but Paquette and co-workers have recently re-evaluated previous assignments and have concluded that, in some cases, the other configuration is found at C-3.[6] Functionalisation at positions C-4, C-8, C-12, C-13, C-15, C19 and C-20 (marked with a *, **Figure 2**) varies significantly across the cladiellin family.

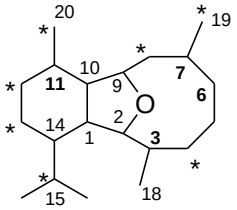
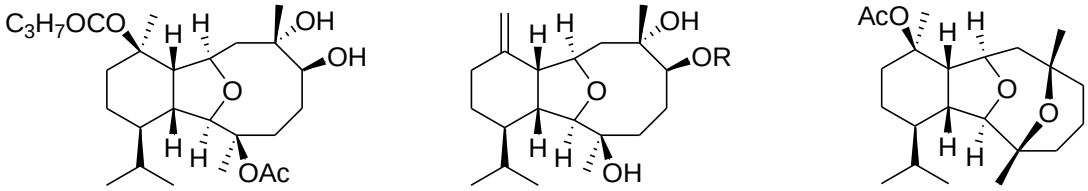


Figure 2

1.1.2.2 Bioactivity

The natural role of these marine metabolites was proposed to involve predation deterrence based on the results of mollusc and fish lethality assays. Their

mollusicidal and repellent activity against muricid gastropods, ichthyotoxicity, brine shrimp lethality and inhibition of the cell division in fertilised starfish eggs provides strong evidence that they are used by octocorals as defence against predators. Many of the cladiellins have also been shown to possess interesting pharmaceutical activities, with several compound reported to be anti-inflammatory and anti-tumour agents. Sclerophytin A seems to be one of the most potent cladiellins and it was reported that this compound exhibits growth inhibitory activity against the murine L1210 leukemia cell line with an IC_{50} = 1.0 ng/mL.[7] Recently studies have shown that pachycladin A, sclerophytin F methyl ether, polyanthelin A and sclerophytin A possess interesting prostate cancer invasion and migration inhibition (**Figure 3**).[8]



Pachycladin A

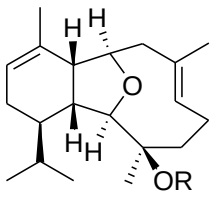
R = H, sclerophytin A
R = Me, sclerophytin F methyl ether

Polyanthelin A

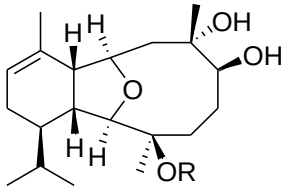
Figure 3

1.1.2.3 Isolation and Characteristics of the Compounds of Interest

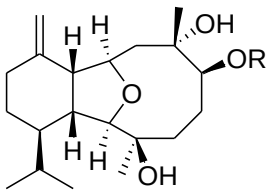
The isolation and biological activity of the cladiellins of interest are presented in **Table 1** (**Figure 4**).



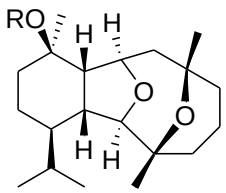
R = H, cladiella-6,11-dien-3-ol
R = Ac, 3-acetoxycladiella-6,11-diene



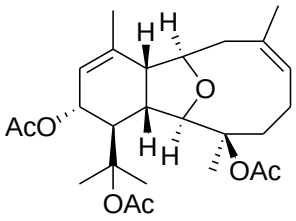
R = H, cladiell-11-ene-3,6,7-triol
R = Ac, 3-acetoxycladiellin-11-ene-6,7-diol



R = H, sclerophytin A
R = Ac, sclerophytin B



R = H, deacetylpolyanthellin A
R = Ac, polyanthellin A



Ophirin B

Figure 4

Table 1

Name	Isolation	Source	Biological activity
Cladiella-6,11-dien-3-ol	1980[9]	*Cladiella sp.*	LD_{50} (brine shrimp) = 1.8 ppm
3-Acetoxycladiella-6,11-diene	1997[10]	*Muricella sp.*	LD_{50} (brine shrimp) = 0.3 ppm; in vitro cytotoxicity against A-549 non-small cell lung cancer 12.7 µg/mL; SKOV-3 ovarian cancer 21.3 µg/mL; SK-MEL-2 melanoma 21.3 µg/mL ; HCT-15 colon cancer 11.6 µg/mL.
Cladiell-11-ene-3,6,7-triol	1989[11]	*Cladiella sp*	No biological assay
3-Acetoxycladiellin-11-ene-6,7-diol	1992[12]	*Cladiella sp*	No biological assay
Sclerophytin A	1988[7]	*Sclerophytum capitalis*	Cytotoxic against L1210 leukemia cell line IC_{50} = 1.0 ng/mL
Sclerophytin B	1988[7]	*Sclerophytum capitalis*	No biological assay
Deacetylpolyanthellin A	1989[13]	*Briareum*	Inhibition of *Plasmodium falciparum* (malaria parasite) 16 µg/mL
Polyanthellin A	1989[13]	*Briareum*	Inhibition of *Plasmodium falciparum* (malaria parasite) 16 µg/mL
Ophirin B	1997[10]	*Muricella sp.*	No biological assay

1.1.3 Previous Syntheses of Members of the Cladiellin Family

1.1.3.1 The Overman Group Approach

The Overman group was the first to report a total synthesis of a member of the cladiellin family with the synthesis of 7-deacetoxyalcyonin acetate in 1995.[14] Since then, this group has reported the synthesis of two other members of this family: sclerophytin A and cladiell-11-ene-3,6,7-triol (**Figure 5**).[15]

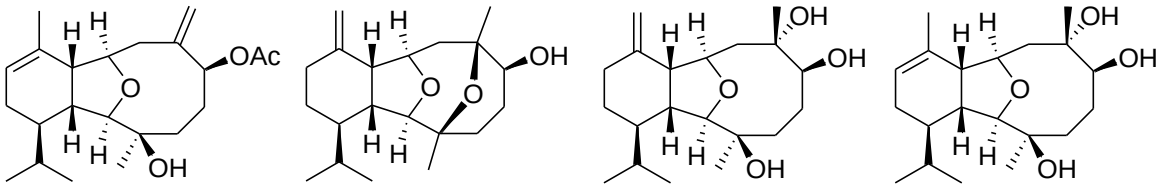


Figure 5

The disconnection used by Overman and co-workers in their planning of the synthesis of their target is show in **Figure 6**. The hydroisobenzofuran was to be formed *via* a Prins-pinacol condensation-rearrangement, and closure of the medium size ring was to be accomplished using a Nozaki-Hiyama-Kishi coupling.

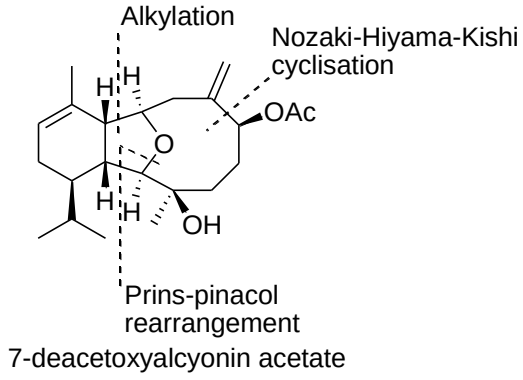
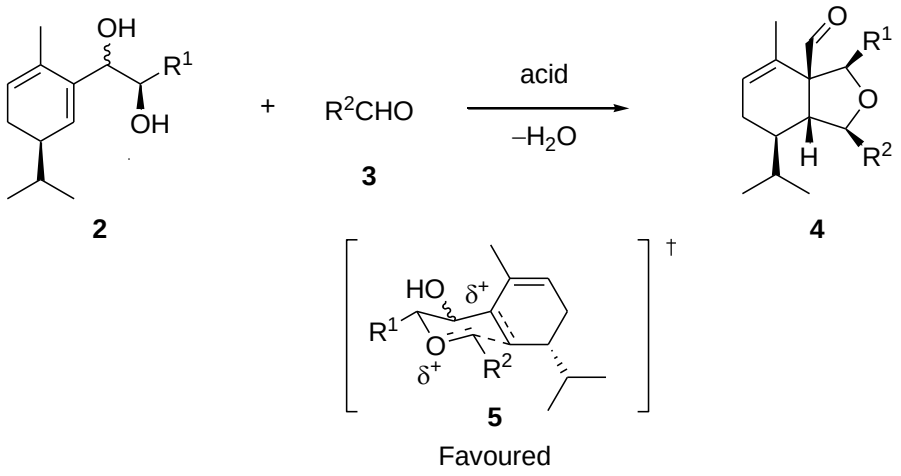


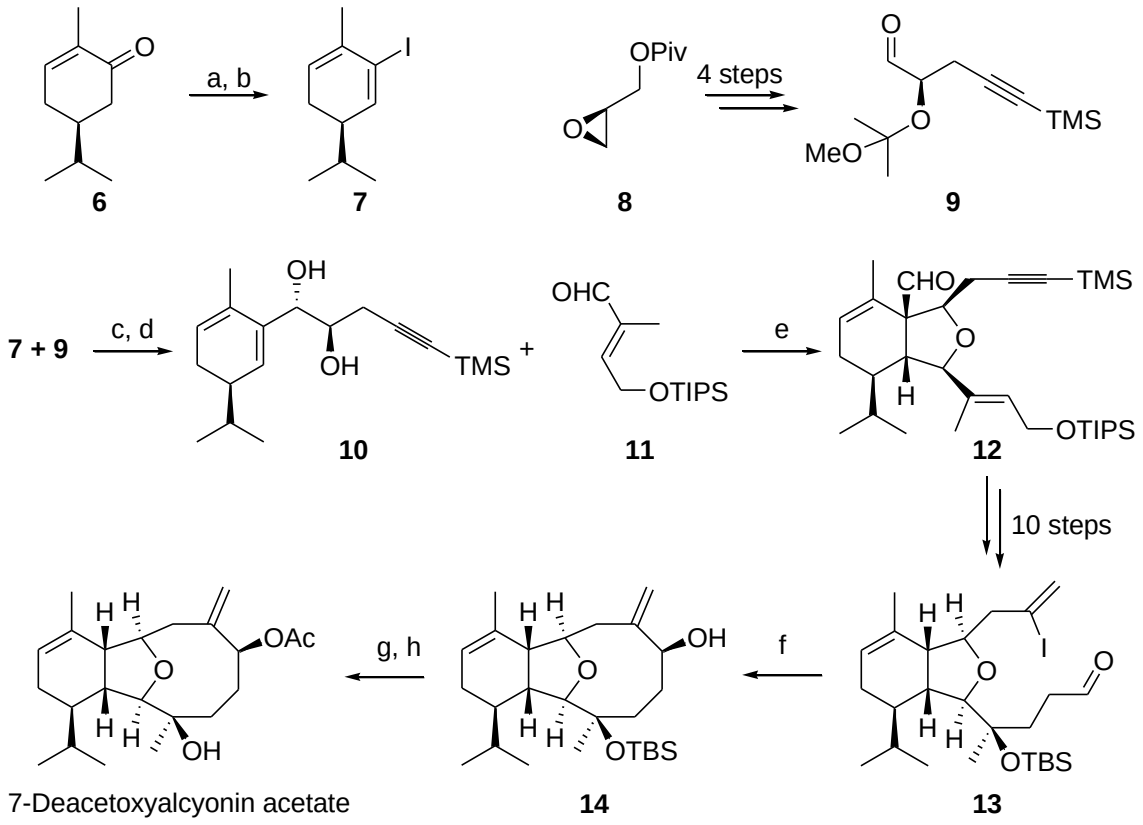
Figure 6

The defining reaction in this synthesis is the diastereoselective Prins-pinacol condensation-rearrangement[16] of dienyl diol **2** with aldehyde **3**, which proceeds through the chair-like transition state **5**, to assemble the hydroisobenzofuran core of 7-deacetoxyalcyonin acetate **4** (**Scheme 2**).



Scheme 2

Overman achieved the total synthesis in 20 steps from (*S*)-glycidyl pivalate **8** with an overall yield of 4%. The Prins-pinacol condensation-rearrangement precursor **10** was obtained by a convergent protocol, starting from (*S*)-carvone **6** and (*S*)-glycidyl pivalate **8** (**Scheme 3**). The key Prins–pinacol rearrangement reaction was achieved by exposure of diol **10** and an excess of enal **11** to $BF_3{\cdot}Et_2O$, giving the hexahydroisobenzofuran **12** as a single stereoisomer in 79% yield. After further functionalisations, the oxanane ring was fashioned by treating **13** with $NiCl_2$-$CrCl_2$ in DMSO following the Nozaki-Hiyama-Kishi procedure,[17] to provide the tricyclic alcohol **14** in 65% yield. Finally, acetylation of **14** followed by cleavage of the silyl ether gave the natural product in 88% yield.



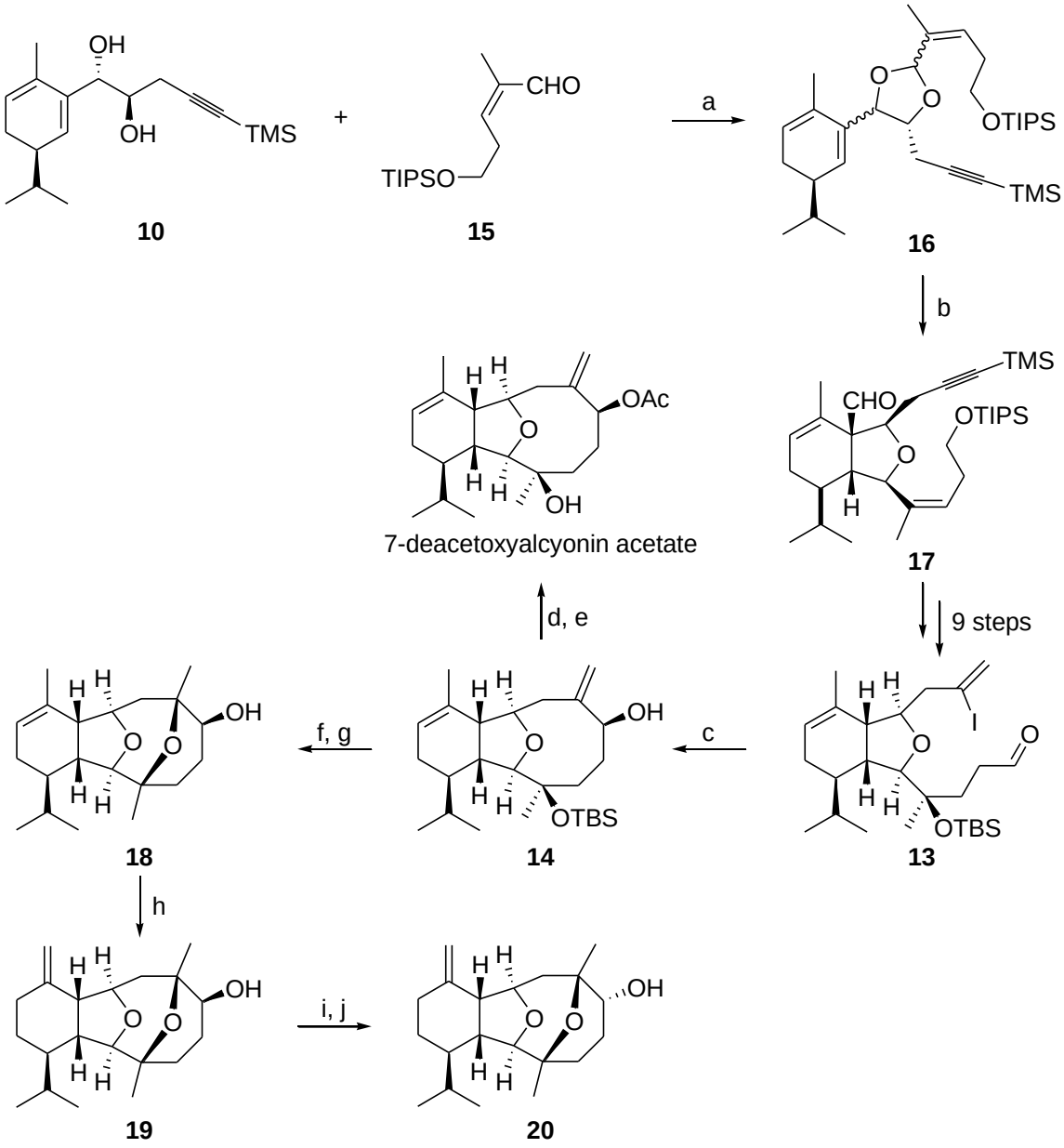
6 **7** **8** **9** **10** **11** **12** **13** **14**

a) LDA, $PhN(Tf)_2$; b) $(Me_3Sn)_2$, $Pd(PPh_3)_4$, NIS, 78% (2 steps); c) *t*-BuLi; d) PPTS, MeOH, 64% (2 steps); e) $BF_3 \bullet Et_2O$, 79%; f) $NiCl_2$–$CrCl_2$, 65%; g) Ac_2O, pyridine; h) TBAF, 88% (2 steps).

Scheme 3

Overman used the synthesis sclerophytin A as an opportunity to demonstrate that the strategy developed for the synthesis of 7-deacetoxyalcyonin acetate could be used to address the synthesis of other natural products of the same family containing either exocyclic or endocyclic unsaturation in the cyclohexane ring.[18] They improved the synthesis by using (*Z*)-*α*,β-unsaturated aldehyde **15** (**Scheme 4**) containing one more carbon than that used during the original synthesis of the 7-deacetoxyalcyonin acetate. A two-step procedure, in which the enal **15** and dienyl diol **10** were combined to produce hydroisobenzofuran **17**, was developed. Condensation of **10** with **15** using *p*-toluenesulfonic acid afforded acetal **16** as a mixture of diastereomers in 76% yield. Prins-pinacol rearrangement of **16** proceeded efficiently in the presence of a catalytic amount of $SnCl_4$ to give the aldehyde **17** in 88% yield. At this point, all the carbon atoms of the target molecule were installed. After further modifications, the oxonene ring was formed by treating **13** with $NiCl_2$-$CrCl_2$, following the Nozaki-Hiyama-Kishi procedure, to provide tricyclic ether **14** in 61% yield. Compound **14** served as a common intermediate in the synthesis of 7-deacetoxyalcyonin acetate and

sclerophytin A. 7-Deacetoxyalcyonin acetate was obtained following the route previously reported. Completing the synthesis of the presumed structure of sclerophytin A required formation of a bridging tetrahydropyran ring between carbon C-3 and C-7. Desilylation of **14** and subsequent sequential treatment with $Hg(OAc)_2$ and $NaBH_4$ furnished the single tetracyclic diether **18** in 47% yield. Light–induced isomerisation of **18** was realised in high yield to give exocyclic alkene **19**. However, when Overman and co-workers compared spectroscopic data of **19** with that reported for the natural product there were significant discrepancies. To investigate the possibility that sclerophytin A was epimeric at the hydroxyl-bearing stereogenic centre, the synthesis of the compound **20** from alcohol **19** was performed. However, the ^{1}H and ^{13}C NMR spectra for compound **20** were distinctly different to those reported for the natural product.



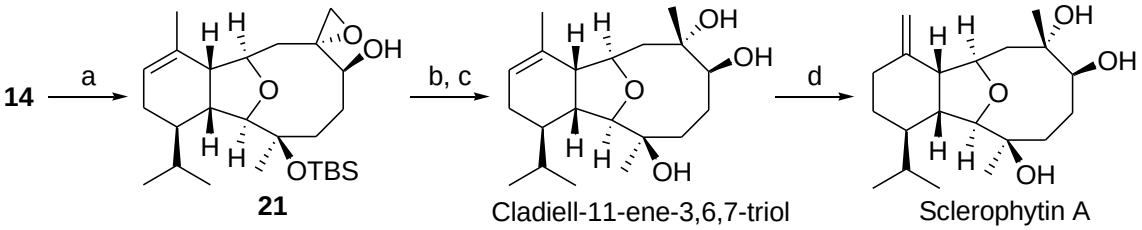
a) *p*-TsOH, $MgSO_4$, 76%; b) $SnCl_4$, 88%; c) $NiCl_2$-$CrCl_2$, 61%; d) Ac_2O, pyridine; e) TBAF, 88% (2 steps); f) TBAF; g) $Hg(OAc)_2$, $NaBH_4$, NaOH, 41% (2 steps); h) hν, 80%; i) DMP; j) $NaBH_4$; 75% (2 steps).

Scheme 4

Further detailed spectroscopic studies of sclerophytin B, the monoacetate of sclerophytin A, published by Paquette and co-workers indicated that these substances were probably lacking the second ether bridge.[19] This structural revision allowed the total synthesis of the natural product to be performed.

The Overman group obtained sclerophytin A using their previously reported synthetic methodology. Compound **14** was obtained form (*S*)-carvone in 17 steps and 6% overall yield (**Scheme 5**). Epoxidation of the exocyclic alkene of **14** afforded epoxy-alcohol **21** in very good yield. Subsequent epoxide opening and deprotection afforded cladiell-11-ene-3,6,7-triol, which underwent

photochemical isomerisation to give the revised structure of sclerophytin A. The NMR data of the compound, as well as the $[\alpha]_{D,}$ matched those of the natural product.[15, 20]



a) $VO(acac)_2$, TBHP, 95%; b) DIBAL-H; c) TBAF, 75% (2 steps); d) hν, 28%.

Scheme 5

The Overman group has continued its work on the synthesis of oxygen-bridged 2,11-cyclised cembranoids. This work has culminated in the recent total synthesis of two briarellins.[21]

1.1.3.2 The Paquette Group Approach

The Paquette group embarked on the total synthesis of the 2,11-cyclised cembranoids a few years after Overman. Paquette also completed a review of these natural products and their bioactivity.[1] Concurrently to the Overman group, Paquette and co-workers undertook the challenge of synthesising sclerophytin A. Their strategy involved the formation of the hydroisobenzofuran ring using a Diels-Alder cycloaddition reaction and construction of the medium ring *via* a Claisen rearrangement reaction (**Figure 7**). [22]

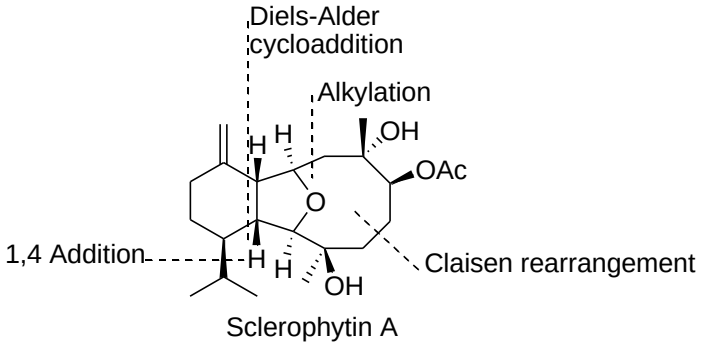
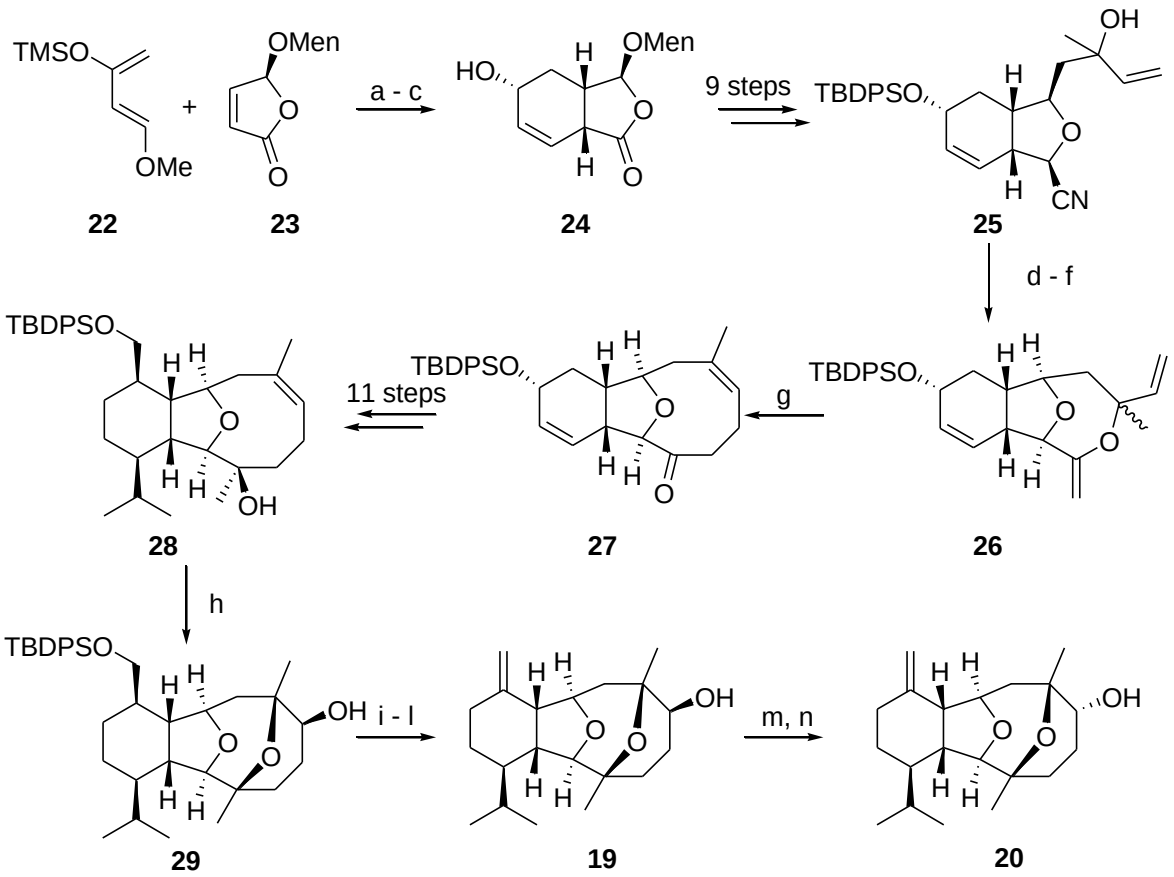


Figure 7

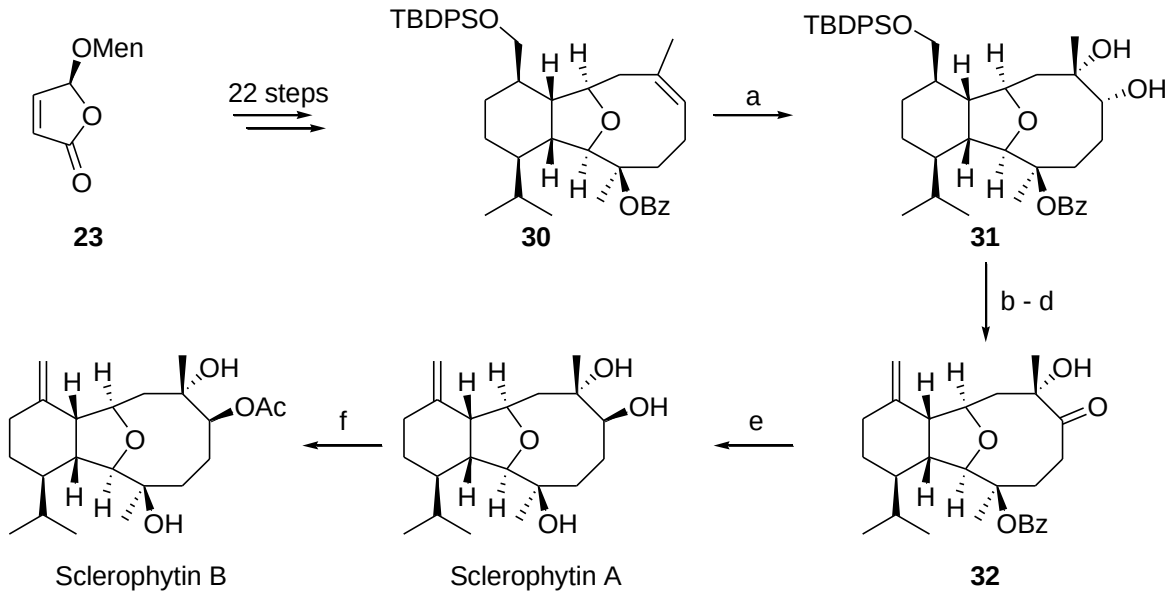
The synthesis started with an intermolecular Diels-Alder cycloaddition reaction between the Danishesky diene **22** and lactone **23** to form the hydroisobenzofuran ring (**Scheme 6**). Further functionalisation of lactone **24** gave nitrile **25**. Mild hydrolysis of the nitrile afforded a carboxylic acid which upon submission to Yamaguchi macrolactonisation conditions gave a separable mixture of lactone diastereomers. Both diastereomeric lactones were independently subjected to Tebbe methylenation to give the enol ether **26**. Claisen rearrangement promoted by $NaBF_4$ transformed cleanly both isomers of **26** into **27**. The next stage of the synthesis involved the functionalisation of the cyclohexyl ring. This was achieved in eleven steps *via* an aldol reaction with formaldehyde and conjugate addition of an isopropyl group, both reactions occuring from the least hindered face. Finally, reductive removal of the carbonyl group gave **28**. Formation of the fourth ring was achieved by oxymercuration and subsequent oxidative demercuration, giving a mixture of epimeric alcohols **29**. The purported structure of sclerophytin A was obtained in three more steps. However, as observed by Overman and co-workers the spectroscopic data of **19** differed from that reported for the natural product. Oxidation and reduction of the secondary alcohol afforded the diastereomeric alcohol **20** the data for which did not match that for the natural product data either.



a) toluene; b) TMSOTf, pyridine; c) $NaBH_4$, $CeCl_3$, MeOH, 71% (3 steps); d) i) NaOMe, H_3O^+; ii) LiOH; e) $Cl_3C_6H_2COCl$, Et_3N, DMAP; f) $(C_5H_5)_2TiCH_2ClAl(CH_3)_2$, 52% (3 steps); g) $NaBF_4$, 75%; h) $Hg(OCOCF_3)_2$, O_2, $NaBH_4$, 54% (3:7 dr); i) Ac_2O, pyridine; j) TBAF; k) *o*-$NO_2C_6H_4SeCN$, PBu_3, pyridine, H_2O_2; l) DIBAL-H, 73% (4 steps); m) $(n\text{-}Pr)_4NRuO_4$, NMO; n) DIBAL-H, 90% (2 steps).

Scheme 6

After extensive NMR studies on sclerophytin B, Paquette and co-workers proposed the reassignment of the structures of sclerophytins A and B to those lacking the second ether bridge.[19] The synthesis of the new structure was achieved in 27 steps and 0.5% overall yield using the previous synthetic route (**Scheme 7**). Compound **30** was obtained in 22 steps from lactone **23**. Upjohn dihydroxylation afforded the *syn*-diol **31**. Oxidation of the secondary alcohol followed by deprotection and Grieco elimination of the primary alcohol gave hydroxyl-ketone **32**. Concomitant removal of the tertiary benzoate and reduction of the ketone revealed the new structure of sclerophytin A.[20, 23] Spectroscopic data for this compound matched those reported for the natural product. Finally, selective acetylation of the secondary alcohol delivered sclerophytin B.



a) OsO_4, 80%; b) IBX, 70%; c) TBAF, 100%; d) *o*-$NO_2C_6H_4SeCN$, PBu_3, pyridine, H_2O_2, 98%; e) Na, EtOH, 50%; f) Ac_2O, pyridine, DMAP, 85%.

Scheme 7

Following the synthesis of sclerophytin A and B, the Paquette group conducted further NMR studies on sclerophytin type diterpenes and proposed the structural or stereochemical reassignment of eight other natural products.[6]

1.1.3.3 The Molander Group Approach

Several years after the Overman synthesis of 7-deacetoxyalcyonin acetate, the Molander group divulged a strategically unique approach to the synthesis of this natural product. A [2+2] cycloaddition reaction followed by photochemical rearrangement formed the hydroisobenzofuran core common to all the cladiellins, which was further functionalised using a Lewis acid-mediated [4+3] annulation reaction (**Figure 8**).[24]

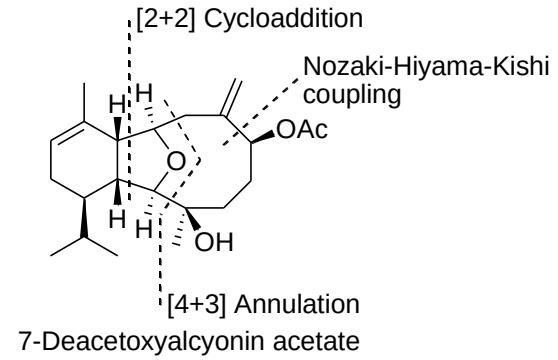
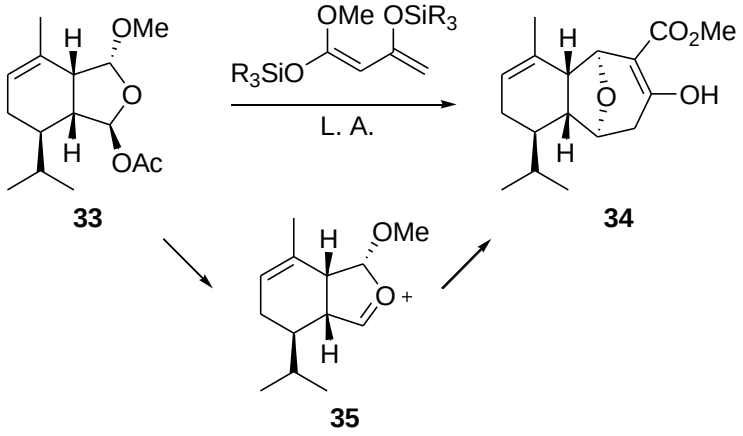


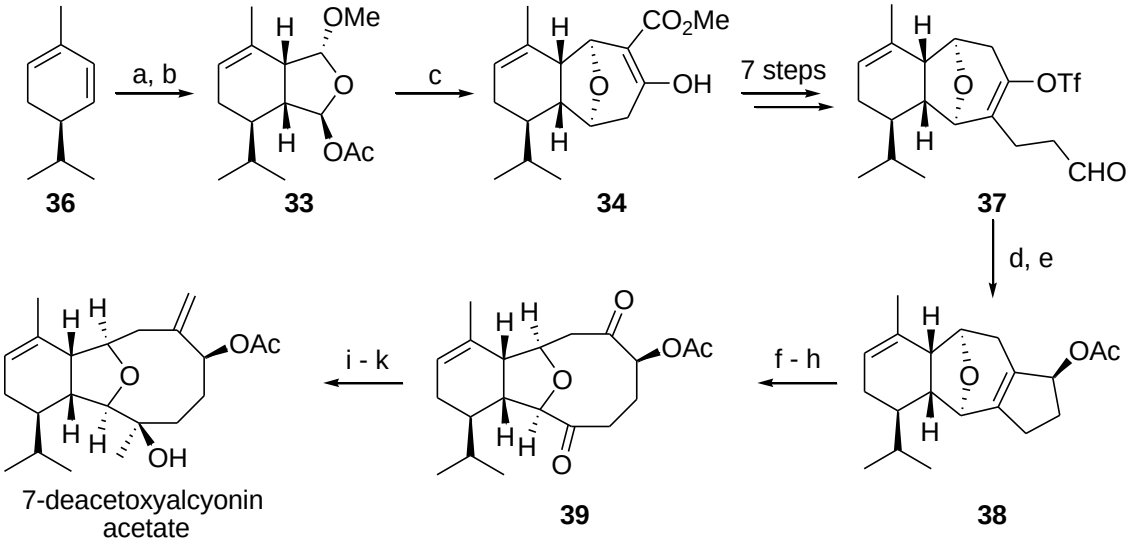
Figure 8

This annulative approach required a chemically differentiable 1,2-dialdehyde such as a bis-acetal to serve as a double-electrophile (**Scheme 8**). Upon exposure to a Lewis acid the bis-acetal **33** ionised selectively to give a single oxocarbenium ion **35** which underwent nucleophilic attack. A second ionisation, followed by cyclisation, resulted in the formation of the hydroisobenzofuran core **34** present in the cladiellin diterpenes in a single operation. The stereochemical outcome of the process is controlled by the attack of the nucleophile from the convex face of the bicyclic ionic intermediate.



Scheme 8

Molander and co-workers completed the total synthesis of 7-deacetoxyalcyonin acetate in 17 steps with an overall yield of 4% (**Scheme 9**). Starting from *a*-phelladrene **36**, a [2+2] cycloaddition reaction followed by a photochemical rearrangement yielded the desired mixed acetal **33**. This *bis*-acetal underwent $TiCl_4$-mediated [4+3] annulation with complete regio- and stereo-selectivity to form **34**. Further functional group interconvertion delivered the aldehyde **37** precursor for the Nozaki-Hiyama-Kishi cyclisation reaction. Tetracyle **38** was obtained by protection of the secondary alcohol resulting from the Nozaki-Hiyama-Kishi coupling. Chemoselective epoxidation of the trisubstitued alkene, followed by oxidative cleavage of the allylic acetate with ozone and epoxide deoxygenation provided olefin **39**. Finally, chemoselective silyl ether formation, Wittig olefination and cleavage of the silyl ether revealed a ketone which was diastereoselectively methylated to give 7-deacetoxyalcyonin acetate.



a) $MeOCH_2C(O)Cl$, Et_3N; b) AcOH, hν, 22% (2 steps); c) 1-methoxy-1,3-bis(triethylsilanyloxy) buta-1,3-diene, $TiCl_4$, 43–80%; d) $CrCl_2$–$NiCl_2$; e) Ac_2O, DMAP, pyridine, 63% (2 steps); f) *m*-CPBA; g) O_3, SMe_2, 43% (2 steps); h) WCl_6, *n*-BuLi, 93%; i) KHMDS, TBSOTf; j) Ph_3PCH_3Br, *t*-BuOK, 61% (2 steps); k) MeLi, $Yb(OTf)_3$, 66% brsm.

Scheme 9

The Molander group investigated another approach to the synthesis of the cladiellins using a SmI_2-mediated cyclisation instead of the Nozaki-Hiyama-Kishi coupling. However, this methodology failed to deliver any of the natural products giving only the 3,7-diastereomer of polyanthellin A.[25]

1.1.3.4 The Crimmins Group Approach

In 2004, Crimmins and co-workers reported the synthesis of the ophirin B and in 2006 they completed the synthesis of astrogorgin using the same synthetic strategy (**Figure 8**).[26, 27] Crimmins was the first to use a strategy where the hydroisobenzofuran unit was not incorporated prior to oxonene formation. The synthesis featured an intramolecular ring closing metathesis reaction for the formation of the oxonene followed by an intramolecular Diels-Alder cycloaddition reaction which afforded the cyclohexene. Ophirin B was obtained in 27 steps with an overall yield of 6%.

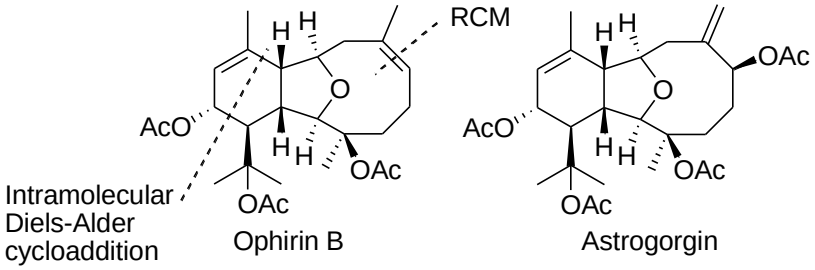
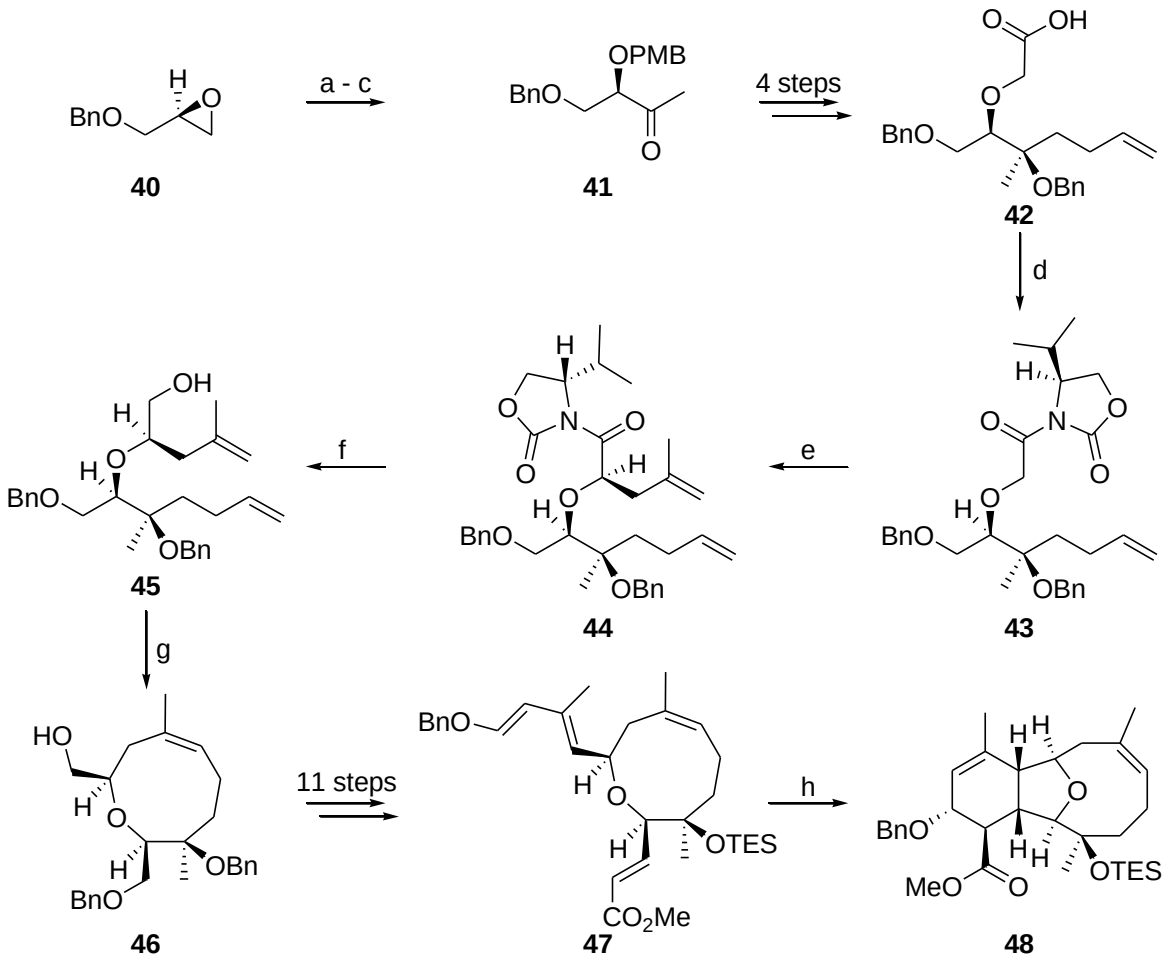


Figure 9

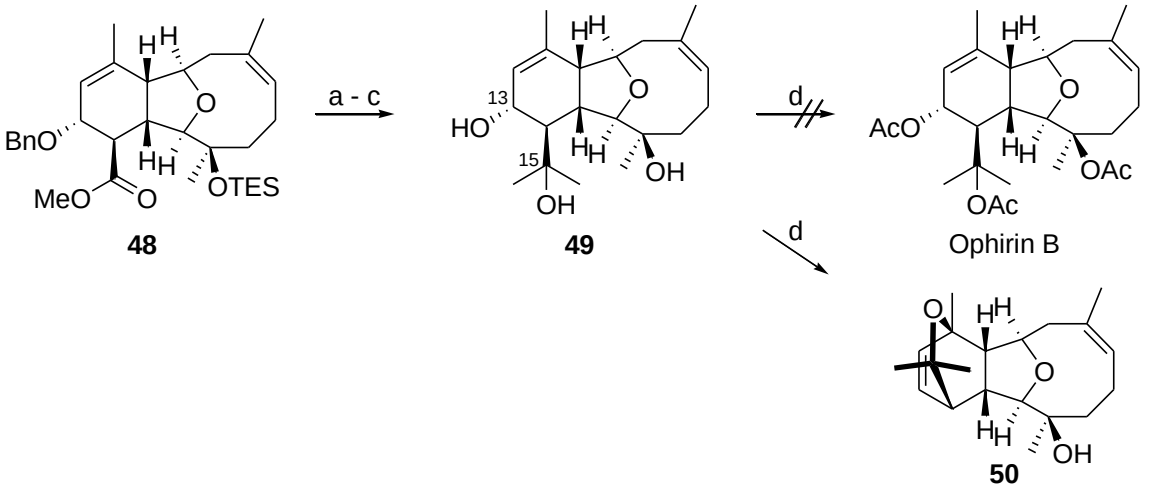
The synthesis started with the reaction of (*S*)-benzylglycidyl ether **40** with dimethylsulfonium methylide delivering a secondary alcohol, which was protected prior to Wacker oxidation to form the methyl ketone **41** (**Scheme 10**). Further alkylation and protecting group modification delivered **42** in four steps. Reaction of the activated carboxylic acid with the oxazolidinone formed the compound **43**, the key intermediate for the installation of the C-9 stereogenic centre *via* a diasteroselective alkylation. This centre was created with high diastereomeric excess >98:2. Removal of the chiral auxiliary gave the diene **45** which was submitted to ring-closing metathesis conditions. This cyclisation reaction proceeded in high yield using Grubbs 2nd generation catalyst in benzene at reflux. With the cyclic ether in place, Crimmins and co-workers focused on the synthesis of the Diels-Alder precursor **47**. This was prepared from **46** in 11 steps involving protecting group modifications, oxidation reactions and Wittig olefinations. The Diels-Alder reaction proceeded simply by allowing compound **47** to stand at room temperature. The tetraene **47** was rapidly converted into the desired tricyclic system **48** in high yield as a single diastereomer in about 2 hours.



a) Me_3SI, *n*-BuLi, 99%; b) NaH, PMBCl, 90%; c) $Hg(OAc)_2$, H_2O, $PdCl_2$, LiCl, $CuCl_2$, H_2O, O_2, 89%; d) Me_3CCOCl, Et_3N, (*S*)-lithio-4-isopropyloxazolidin-2-one, 89%; e) NaHMDS, $CH_2C(CH_3)CH_2I$, 93%; f) $LiBH_4$, MeOH, 92%; g) Grubbs 2nd Gen., 15:1 oxonene:dimer, 89%; h) THF, 78%.

Scheme 10

The original end game of the synthesis involved the formation of the triol **49** which would then undergo acetylation to afford the natural product. However, all attempts to form the triacetate ophirin B directly from the triol **49** were thwarted by the formation of the bridged ether **50** (**Scheme 11**). A wide range of standard or Lewis acid catalysed acetylation reactions were tested, but these produced either the tetracyclic alcohol **50** or resulted in decomposition of the triol **49**. Crimmins and co-workers postulated that the sterically less hindered C-13 secondary alcohol underwent acetylation first. The axial orientation of the C-15 hydroxypropyl group suitably positioned the hydroxyl group for allylic displacement of the C-13 allylic acetate.

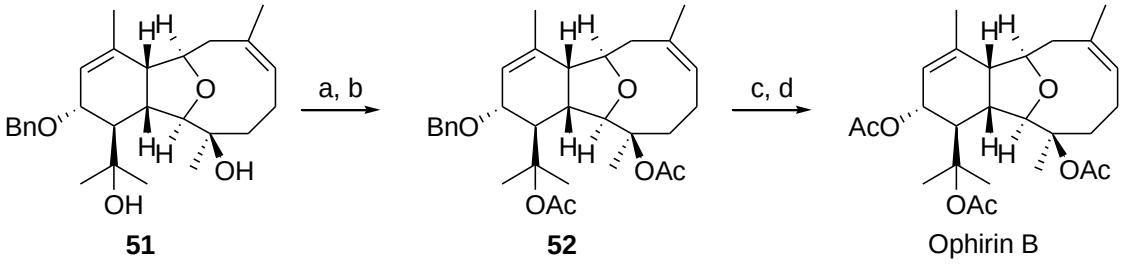


48 **49**

a) MeMgCl, 85%; b) TBAF, 94%; c) Na naphthalene, 90%; d) Ac_2O, DMAP, pyridine.

Scheme 11

To achieve the synthesis of the ophirin B, Crimmins and co-workers firstly acetylated the C-15 hydroxypropyl group of **51** in order to suppress the formation of the bridged ether (**Scheme 12**). Lewis acid catalysed acetylation then afforded the bis-acetate **52**. Careful hydrogenolysis of the C-13 benzyl ether and subsequent acetylation afforded the natural product ophirin B.

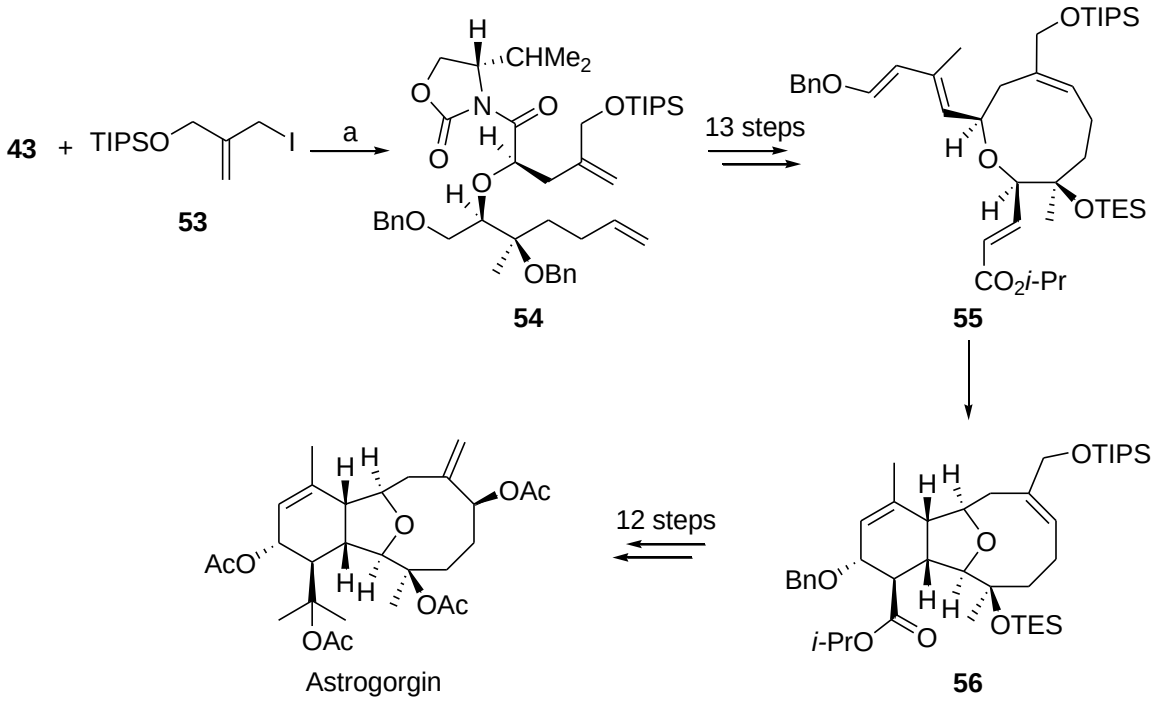


51 **52**

a) KH, Ac_2O, 90%; b) $Bi(OTf)_3$, Ac_2O, 75%; c) H_2, Pd/C, 70%; d) Ac_2O, DMAP, pyridine, 95%.

Scheme 12

The synthesis of the cladiellin astrogorgin was completed using the same general strategy. The two routes diverge from the compound **43** (**Scheme 13**). Asymmetric alkylation with the allylic iodide **53** provided the diene **54** in excellent yield. Ring-closing metathesis followed by further functional transformations gave the Diels-Alder precursor **55**. As was the case for the ophirin B intermediate, when the tetraene **55** was allowed to stand at room temperature it was converted to the desired oxatricyclic compound **56** in high yield, which was converted into the natural product in several steps.



a) NaHMDS, 90%.

Scheme 13

As well as completing the synthesis of the cladiellins ophirin B and astrogorgin, the Crimmins group have synthesised other oxygen-bridged 2,11-cyclised cembranoids. They have reported, the synthesis of the asbestinins 11-acetoxy-4-deoxyasbestinin D and asbestinins-12,[28, 29] as well as the proposed structure of briarellins J using the same methodology.[30]

1.1.3.5 The Kim Group Approach

Recently, Kim and co-workers reported the first total synthesis of an *E*-cladiellin diterpene, cladiella-6,11-dien-3-ol.[31] The significance of this compound is that it can be easily transformed into other members of the cladiellin diterpene family, such as polyanthellin A, cladiell-11-ene-3,6,7-triol, and deacetoxyalcyonin acetate (**Figure 10**). The strategy used by Kim and co-workers featured an intramolecular amide enolate alkylation reaction and an intramolecular Diels-Alder cycloaddition.

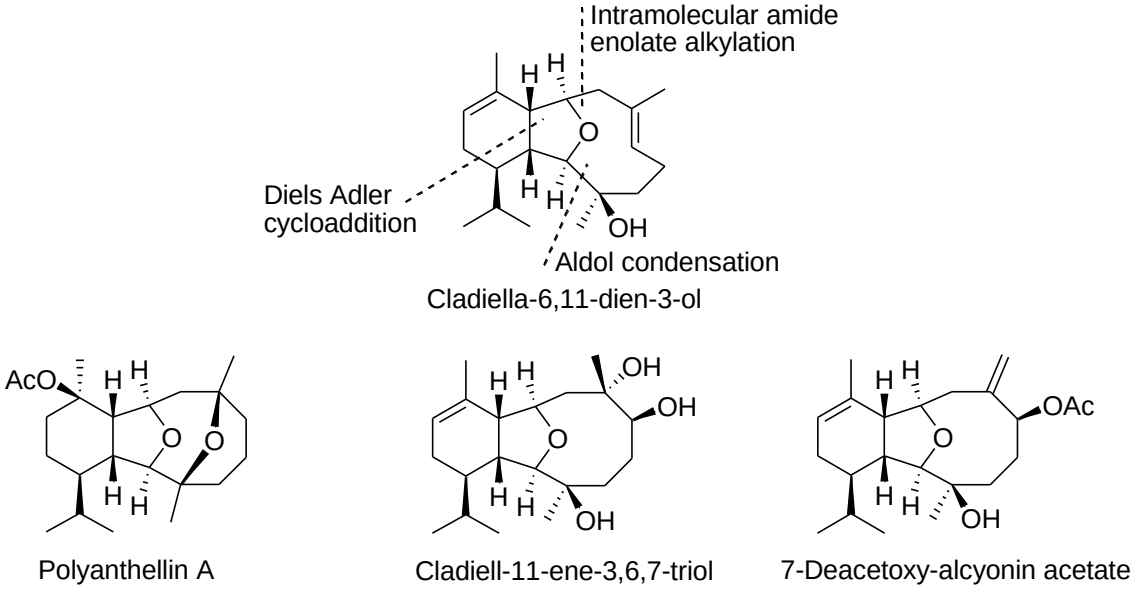
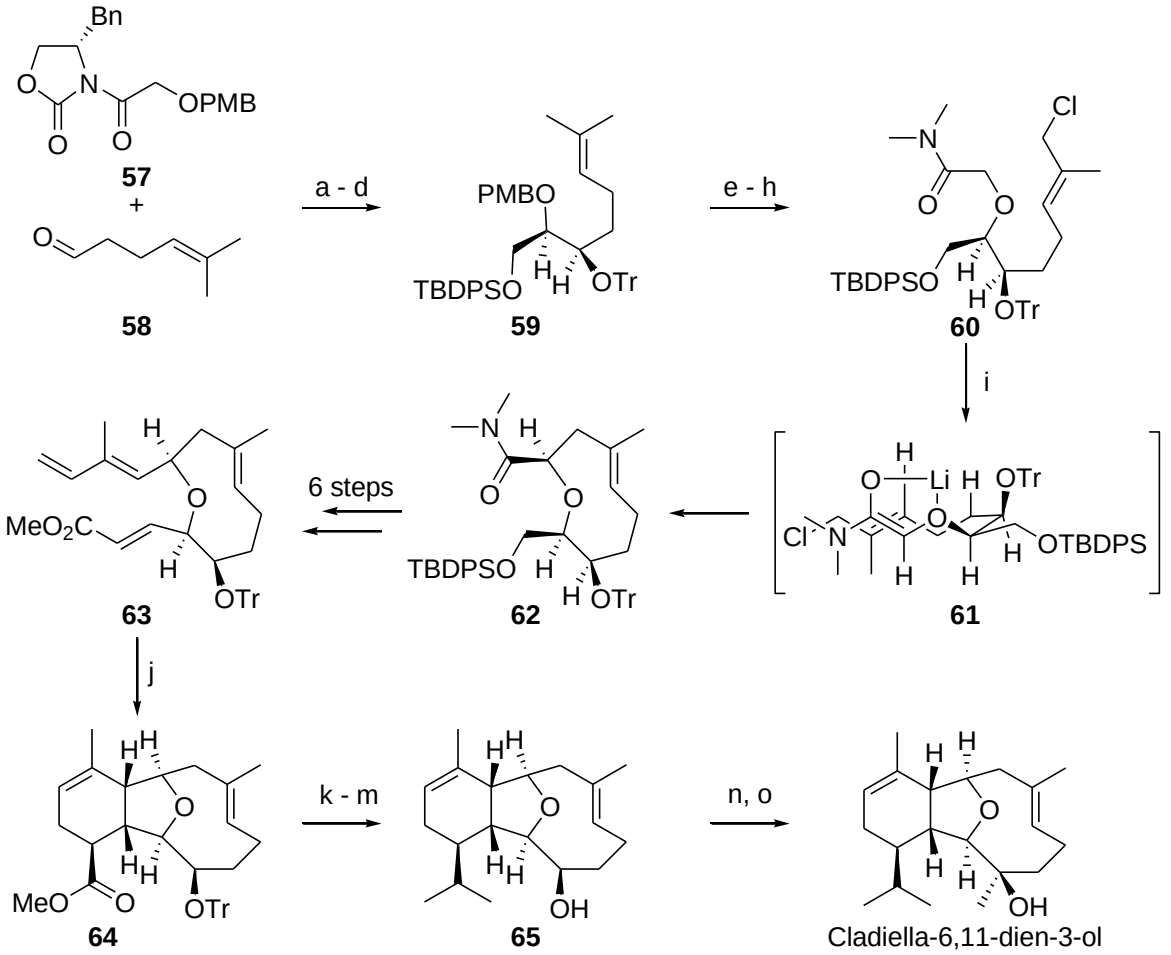


Figure 10

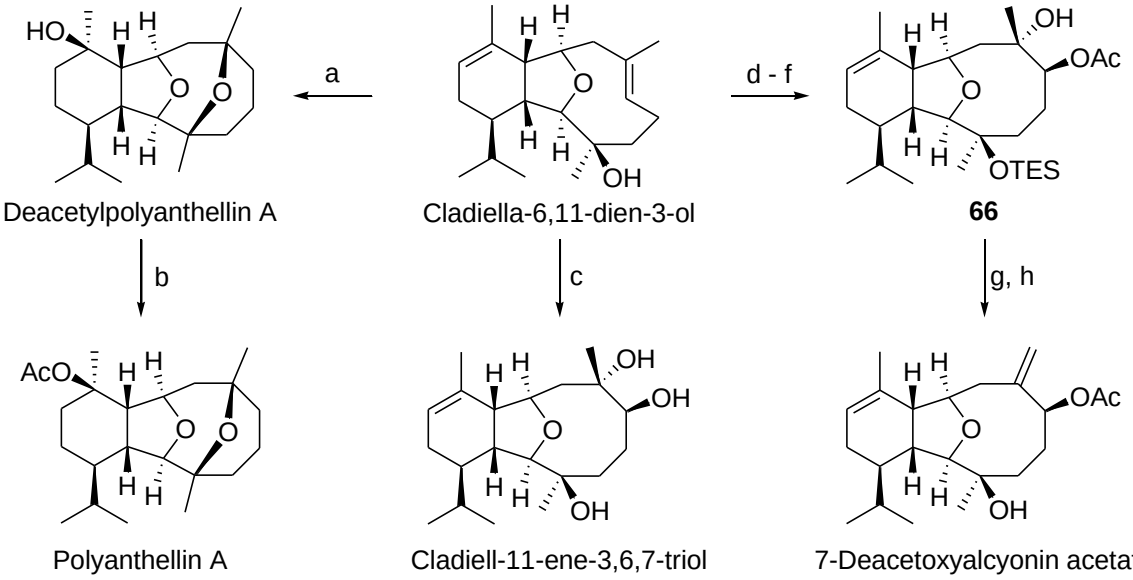
Cladiella-6,11-dien-3-ol was obtained in 21 steps with an overall yield of 6%, starting from a glycolate oxazolidinone **57** and 5-methylhex-4-enal **58** (**Scheme 14**). Aldol addition followed by protective group modification gave **59**. An additional deprotection and *O*-alkylation provided the desired amide. Stereoselective allylic oxidation with selenium dioxide furnished the corresponding allylic alcohol which was chlorinated under standard condition to deliver the *E*-allylic chloride **60**. Intramolecular amide enolate alkylation of **60** led to the formation of the desired cis-*E*-oxonene **62** as a single diastereomer in excellent yield, presumably through the lithiated intermediate **61**. Compound **62** was converted into the required Diels-Alder precursor **63** over several steps. Intramolecular Diels-Alder cycloaddition afforded product **64** in good yield when **63** was heated at reflux in xylene with butylated hydroxytoluene (BHT). Double methylation of the ester followed by dissolving metal reduction delivered the isopropyl moiety **65**. Finally, introduction of the C-3 methyl produced cladiella-6,11-dien-3-ol.



a) *n*-Bu_2BOTf, Et_3N, 75%, 98:2 dr; b) $NaBH_4$, 89%; c) TBDPSCl, imidazole, 92%; d) trityl bromide, DMAP, pyridine, 93%; e) DDQ, 88%; f) $ClCH_2CONMe_2$, NaH, 88%; g) SeO_2, pyridine, $NaBH_4$, EtOH, 76%; h) PPh_3, CCl_4, pyridine, 93%; i) LiHMDS, 92%; j) BHT, xylene reflux, 85%; k) MeLi, $CeCl_3$, 89%; l) Ac_2O, DMAP, Et_3N; m) K,18-crown-6, *t*-$BuNH_2$, 62% (2 steps); n) DMP, o) MeLi, $NaBF_4$, 82% (2 steps).

Scheme 14

Cladiella-6,11-dien-3-ol can be used as an advanced intermediate for the synthesis of several other members of the cladiellin family as shown in **Scheme 15**. Only two steps were necessary to obtain polyanthellin A from cladiella-6,11-dien-3-ol. First, a one-pot protocol of sequential oxymercuration and demercuration furnished the tertiary alcohol deacetylpolyanthellin A. Simple acetylation gave then polyanthellin A. Cladiell-11-ene-3,6,7-triol was readily obtained by treatment of cladiella-6,11-dien-3-ol with osmium tetroxide and 7-deacetoxyalcyonin acetate was obtained in 5 steps from cladiella-6,11-dien-3-ol by sequential dihydroxylation, hydroxyl protection and elimination.

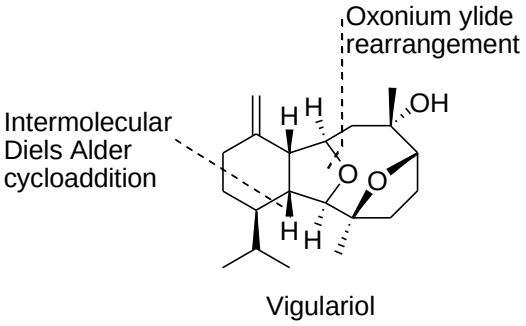


a) $Hg(OAc)_2$, Et_3B, $NaBH_4$, 69%; b) Ac_2O, DMAP, Et_3N, 78%; c) OsO_4, NMO, 94%; d) TESOTf, 97%; e) OsO_4, NMO, 99%; f) Ac_2O, DMAP, Et_3N, 97%; g) Burgess salt; h) TBAF, 92% (2 steps).

Scheme 15

1.1.3.6 The Clark Group Approach

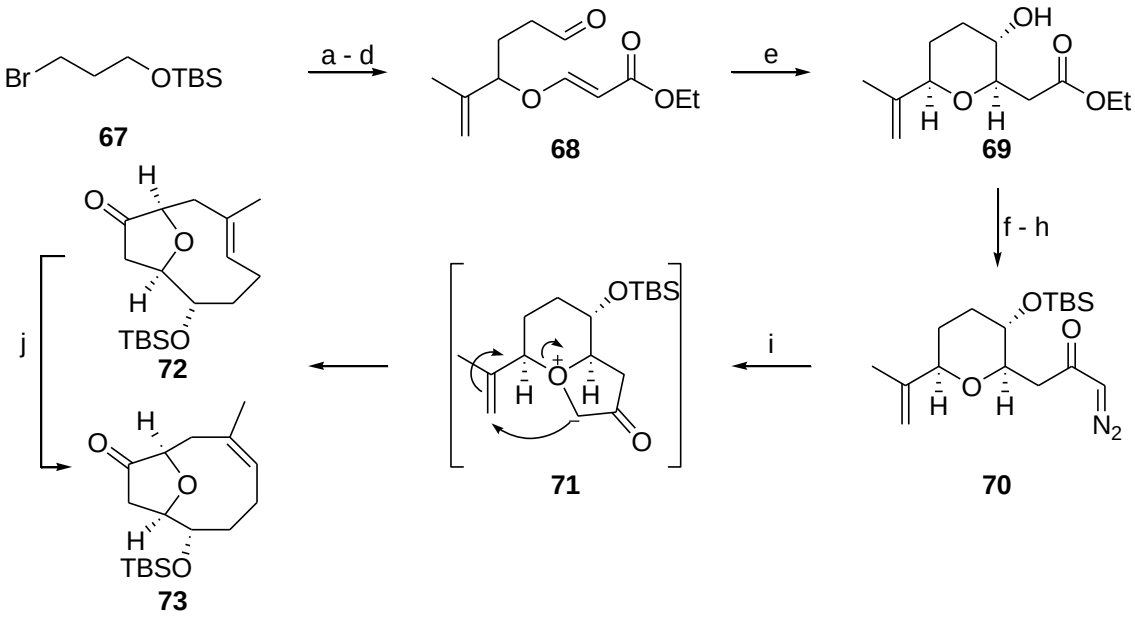
The Clark group has been interested in the synthesis of the cladiellin natural products for some time,[32] and in 2007 reported the total synthesis of vigulariol in the racemic form (**Figure 11**).[33] This natural product was isolated from the octocoral *Vigularia juncea* by Sheu and co-workers and was found to possess *in vitro* cytotoxicity against A 549 (human lung adenocarcinoma) cell culture system with an IC_{50} of 18 μg/mL.[34] Vigulariol possesses an additional ring in comparison to most of the other cladiellins. The synthesis was completed in 20 steps with an overall yield of 4% and featured three key ring formation reactions. The first being a SmI_2 mediated cyclisation to prepare the key tetrahydropyranyl alcohol (**Scheme 16**). The second used a copper carbenoid to deliver a bicyclic oxonium ylide which then rearranged to give the oxabicyclico[6.2.1]undecene system. Finally a highly regioselective intermolecular Diels-Alder cycloaddition reaction constructed the cyclohexane ring.



Vigulariol

Figure 11

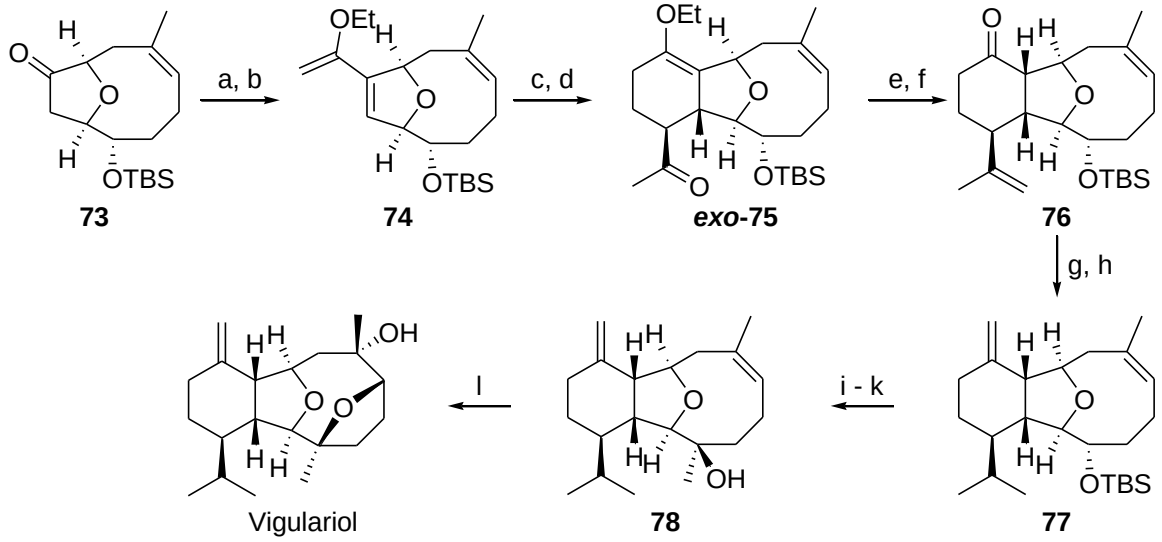
Grignard reaction of the TBS protected bromo-propanol **67** with methacrolein delivered an allylic alcohol (**Scheme 16**). *O*-alkylation of the allylic alcohol followed by removal of the silyl ether protecting group and oxidation of the resulting alcohol gave the aldehyde precursor **68** required for the samarium mediated ring formation. The tetrahydropyranol **69** was obtained as a single diastereoisomer by reductive cyclisation using freshly prepared SmI_2 in the presence of methanol. Protection of the hydroxyl group as a TBS ether and cleavage of the ethyl ester furnished the carboxylic acid, which was activated as a mixed anhydride and then treated with an excess of diazomethane to afford diazoketone **70**. Treatment of **70** with copper(II) hexafluoroacetylacetonate produced an electrophilic copper carbenoid and then an oxonium ylide **71** or its metal-bound equivalent that underwent a [2,3]-sigmatropic rearrangement with three-carbon ring expansion. The reaction delivered a 5:1 mixture of bicyclic ketones **73** and **72**. The *E*-isomer **72** could be converted into the *Z*-alkene **73** by treatment with AIBN and ethanethiol.



a) Mg, methacrolein, 90%; b) $HCCCO_2Et$, *N*-methylmorpholine, 91%; c) TBAF, 91%; d) $(COCl)_2$, DMSO, Et_3N, 83%; e) SmI_2, MeOH, 76%; f) TBSCl, imidazole, 91%; g) LiOH, 82%; h) i) *i*-BuO_2CCl, Et_3N, ii) CH_2N_2, 81%; i) $Cu(CF_3COCHCOCF_3)_2$ (5 mol%), 96% 5:1 *Z*:*E*); j) AIBN, EtSH, 56%.

Scheme 16

With bicyclic ketone **73** in hand, the next goal was the formation of the third ring (**Scheme 17**). The unstable diene **74** was formed by Stille cross-coupling and was immediately subjected to Diels-Alder cycloaddition with methyl vinyl ketone. The reaction was both highly regio-selective and exhibited high facial diastereoselectivity on the diene to deliver a 2:1 mixture of *exo* and *endo* diastereoisomers. Isomerisation of the *endo*:*exo* mixture with potassium carbonate delivered uniquely the required ketone ***exo*-75** (*exo* adduct). Wittig olefination formed the exocyclic alkene and cleavage of the enol ether under acidic condition revealed the ketone **76**. Chemoselective hydrogenation of the exocyclic alkene and subsequent ketone methylenation furnished the diene **77**. Removal of the silyl ether protecting group and Dess-Martin oxidation gave the corresponding ketone, which was treated with methylmagnesium chloride to install the C-3 methyl group affording the desired tertiary alcohol **78** as single diastereomer. Regioselective and stereoselective alkene epoxidation and subsequent nucleophilic epoxide opening with the tertiary hydroxyl group was achieved in a single step using *m*-CPBA, which to completed the synthesis of vigulariol.



a) $PhN(Tf)_2$, NaHMDS; b) $CH_2C(OEt)SnBu_3$, LiCl, $Pd(PPh_3)_4$; c) methyl vinyl ketone, 67% (3 steps); d) K_2CO_3, 87%; e) Ph_3PCH_3Br, *t*-BuOK, 85%; f) HCl, 86%; g) H_2, PtO_2, 81%; h) Ph_3PCH_3Br, *t*-BuOK, 98%; i) TBAF, 84%; j) DMP; k) MeMgCl, 89% (2 steps); l) *m*-CPBA, 69%.

Scheme 17

1.1.3.7 The Hoppe Group Approach

Recently, Hoppe and co-workers reported an asymmetric total synthesis of vigulariol.[35] The synthesis was completed in ten steps with an overall yield of 5% from enantiomerically pure starting material. The principal features of the synthesis were an asymmetric homoaldol reaction and a ring-closing methathesis to form the medium sized ring (**Figure 12**).

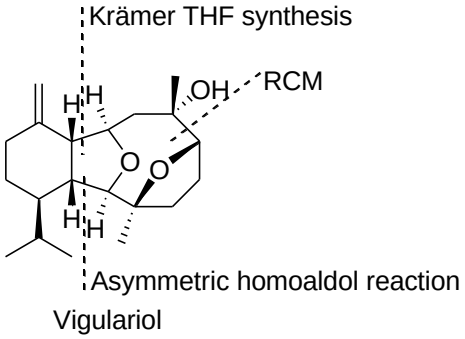
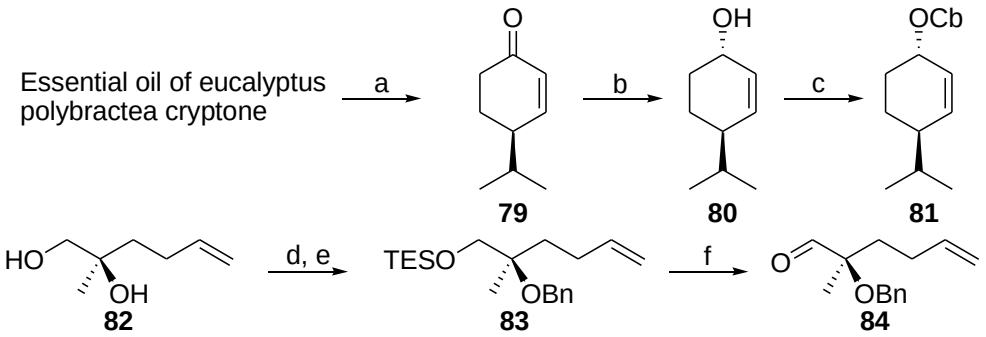


Figure 12

Hoppe and co-workers were able to obtain their starting material, (*R*)-cryptone **79**, in 97% ee by flash chromatography of eucalyptus oil (**Scheme 18**). This compound was then reduced with $LiAlH_4$ to yield cycloalkenol **80**, which gave **81**

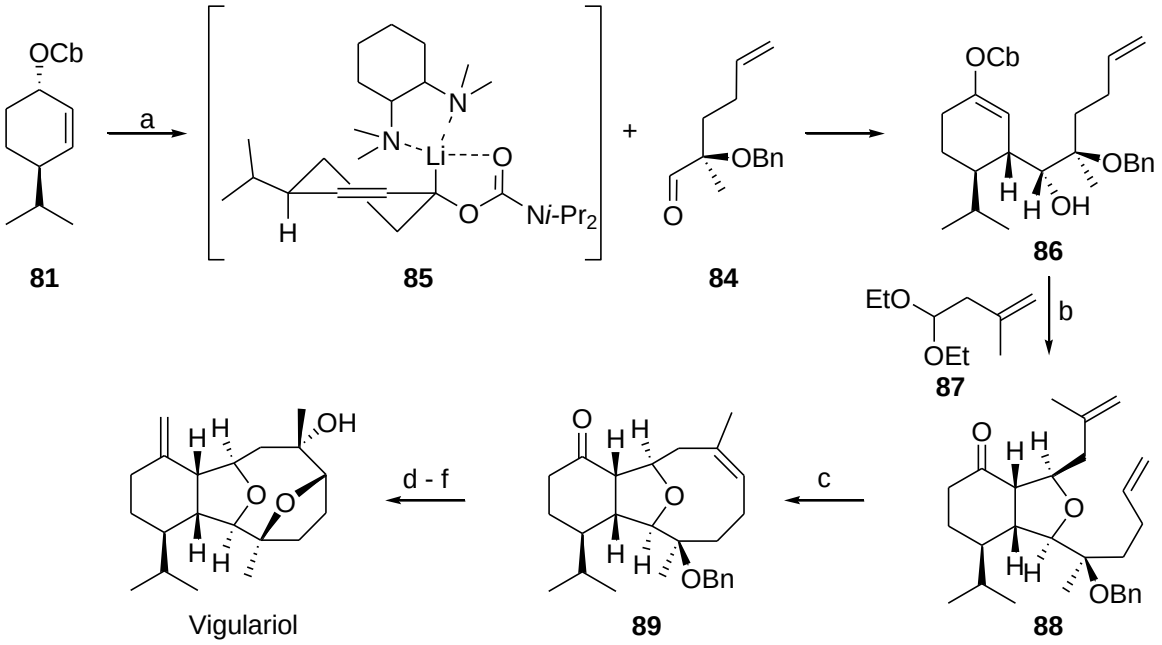
after carbamoylation. Enantiomerically pure diol **82** was selectively protected and oxidised to afford the aldehyde coupling partner **84**.



a) Flash column chromatography, (97% ee); b) $LiAlH_4$, (84:16 dr); c) NaH, *i*-$Pr_2NC(O)Cl$, 78% (97% ee); d) TESCl, imidazole, 99%; e) $BnOC(NH)CCl_3$, F_3CSO_3H, 86%; f) DMSO, $(COCl)_2$, DIPEA, 81%.

Scheme 18

The two fragments, **81** and **84**, were then coupled to give the alcohol **86** (**Scheme 19**). This was achieved by stereospecific deprotonation using *s*-BuLi and *N,N,N',N'*-tetramethyl-1,2-diaminocyclohexane, subsequent lithium-titanium exchange using $ClTi(O\textit{i}\text{-}Pr)_3$ and trapping with fragment **84** to give the required diastereomer **86** in just 33% yield. Condensation with acetal **87** provided diene **88**. The tricyclic core of vigulariol was formed by ring closing metathesis using Grubbs 2nd generation catalyst. The resulting alkene **89** was subjected to epoxidation before the removal of the benzyl protecting group revealed the tertiary alcohol, which underwent rapid and stereospecific attack onto the epoxide moiety. Finally, the natural product was obtained by Wittig methylenation of the ketone.

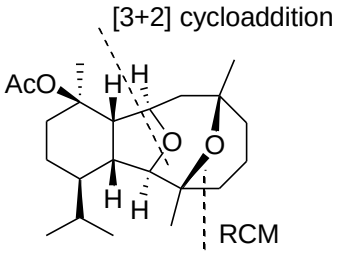


a) i) *s*-BuLi / TMCDA ii) ClTi(O*i*-Pr)$_3$ 33%; b) BF_3•OEt_2, 71%; c) Grubbs 2nd Gen., 45%; d) DMDO, 81%; e) Pd/C, H_2, 91%; f) Ph_3PCH_3Br, NaHMDS, 93%.

Scheme 19

1.1.3.8 The Johnson Group Approach

The Johnson group recently reported the synthesis of polyanthellin A in 15 linear steps and 2% overall yield.[36] Their strategy featured the formation of the hydroisobenzofuran *via* a [3+2] cyclopropane - aldehyde cycloaddition reaction and the construction of the oxonane ring by ring-closing metathesis (**Figure 13**).

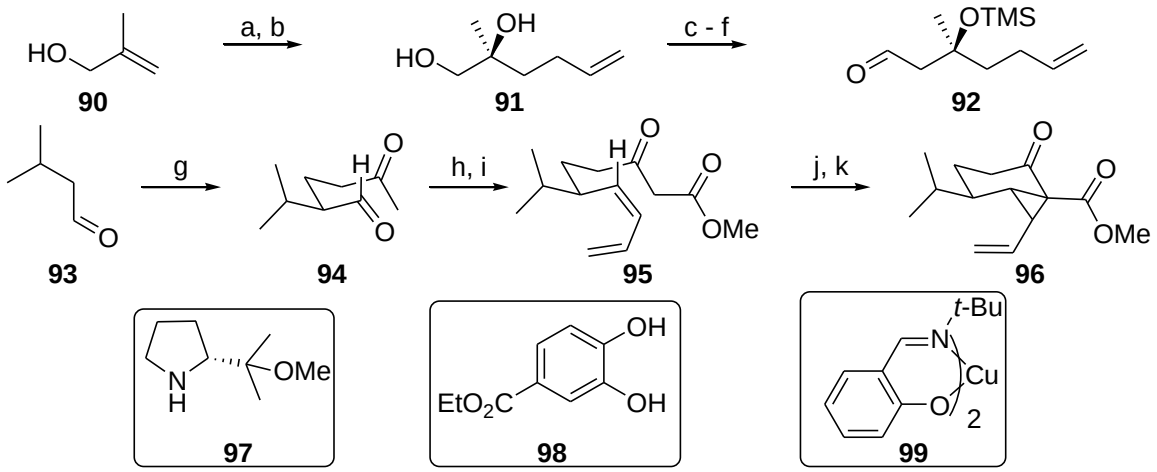


Polyanthellin A

Figure 13

The cyclopropane **96** and aldehyde **92** adducts required for the key cycloaddition reaction were synthesised in five and six steps respectively (**Scheme 20**). Sharpless epoxidation of the methallyl alcohol **90** was followed by opening of the epoxide using allyl cuprate. One-carbon homologation and

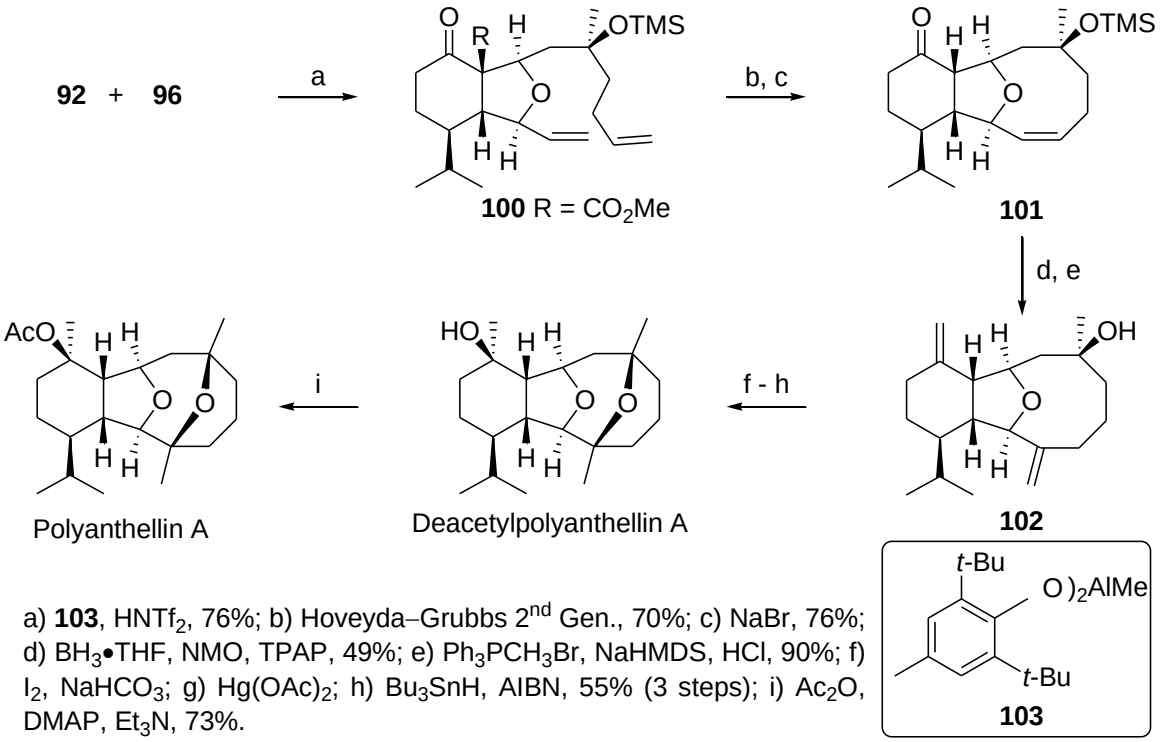
protection of the tertiary alcohol afforded aldehyde **92**. Enantioselective organocatalytic conjugate addition of isovaleraldehyde **93** to methyl vinyl ketone gave **94**. Olefination of the aldehyde gave the diene and carboalkoxylation revealed the ketoester **95**. The formation of the cyclopropane **96** was obtained *via* a two-step protocol through a diazo carbonyl compound.



a) Ti(O*i*-Pr)$_4$, (–)-DET, TBHP, 69%; b) Li_2CuCl_4, AllylMgCl, 77%; c) *p*-TsCl, Et_3N, DMAP; d) KCN; e) TMSCl, imidazole, 76% (3 steps); f) DIBAL-H, 68%; g) MVK, **97**, **98**, 90%; h) $Ph_2PCH_2CHCH_2$, *t*-BuLi, Ti(O*i*-Pr)$_4$, MeI, 71%; i) LiTMP, HMPA, MeOC(O)CN, 72%; j) *p*-$AcHNC_6H_4SO_2N_3$, Et_3N; k) **99**, 71% (2 steps).

Scheme 20

The cycloaddition of aldehyde **92** and cyclopropane **96** proved problematic but after Lewis acid screening Johnson and co-workers found that the use $MADNTf_2$ as a catalyst formed *in situ* from **103** and $HNTf_2$ afforded the hydroisobenzofuran **100** in 76% yield and good diastereoselectivity (**Scheme 21**). Further ring-closing metathesis and Krapcho decarboxylation gave the cladiellin skeleton **101**. Direct hydroboration and TPAP oxidation of alkene **101** afforded the corresponding ketone, which underwent double Wittig olefination to yield diene **102**. Finally a three-step protocol involving iodoetherification, oxymercuration and reduction delivered deacetylpolyanthellin A as a 6:1 mixture of diastereomers. Both diastereomers were acetylated under standard condition to deliver polyanthellin A.



a) **103**, $HNTf_2$, 76%; b) Hoveyda–Grubbs 2nd Gen., 70%; c) NaBr, 76%; d) BH_3•THF, NMO, TPAP, 49%; e) Ph_3PCH_3Br, NaHMDS, HCl, 90%; f) I_2, $NaHCO_3$; g) $Hg(OAc)_2$; h) Bu_3SnH, AIBN, 55% (3 steps); i) Ac_2O, DMAP, Et_3N, 73%.

Scheme 21

1.1.3.9 The Morken Group Approach

Recently the Morken group published a concise synthesis of sclerophytin A in 13 steps and 2.7% yield from geranial using a new route.[37] Their strategy is unique because it involves the synthesis of the furan ring first using the Oshima–Utimoto reaction,[38] then the formation of the hydroisobenzofuran *via* a radical cyclisation reaction and finally oxonene formation by ring-closing metathesis (**Figure 14**).

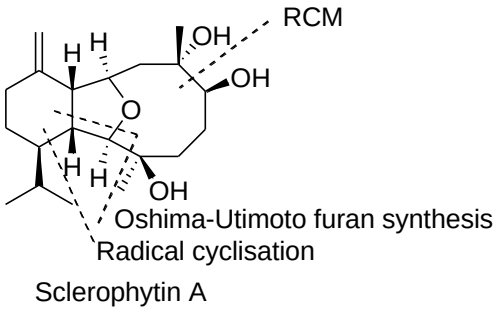
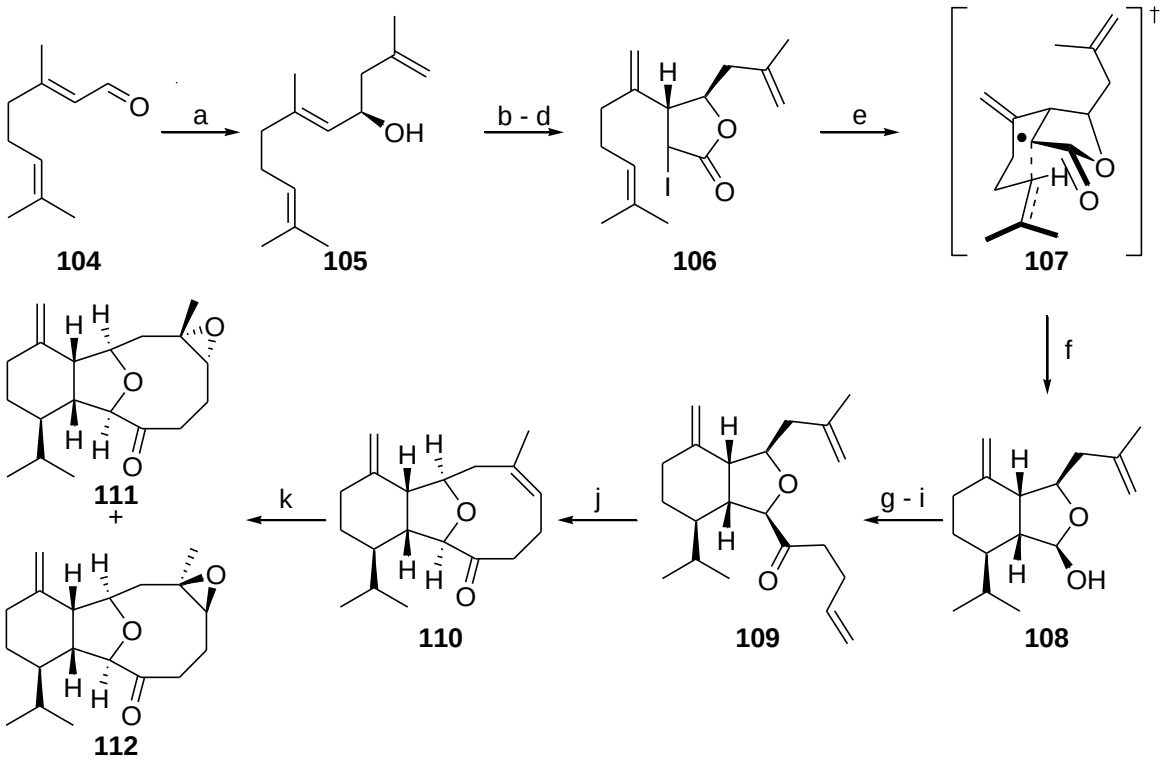
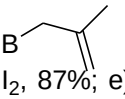


Figure 14

The synthesis started with a Brown methallylation of geranial **104** giving alcohol **105** with 98% ee (**Scheme 22**). Oshima–Utimoto reaction formed the furan ring,

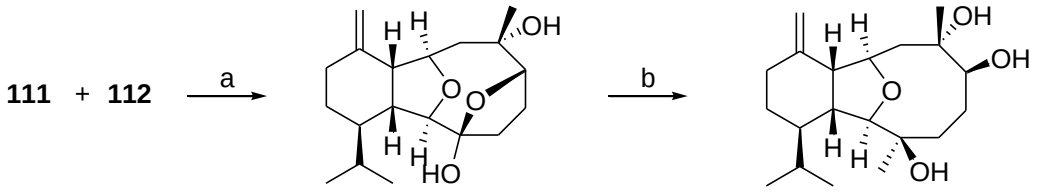
subsequent Jones oxidation delivered the lactone and *a*-iodination yielded the cyclisation precursor **106**. $InCl_3$ and $NaBH_4$ mediated reductive radical cyclisation delivered the hydroisobenzofuran moiety which was reduced to the lactol **108**. Three straight forward steps delivered the triene **109**. The tricyclic core **110** was obtained by ring-closing metathesis using Grubbs 2nd generation catalyst subsequent chemoselective epoxidation of the trisubstituted alkene gave a 1.8:1 mixture of **111**:**112**.



a) $(Ipc)_2B$  , 92%; b) $Pd(OAc)_2$, $Cu(OAc)_2$, $CH_2CHOC(CH_3)_3$, 62%; c) H_2CrO_4, 68%; d) LDA, I_2, 87%; e) $InCl_3$, $NaBH_4$, 56%; f) DIBAL-H, 85%; g) Ac_2O; h) $Sc(OTf)_3$, TMSCN, 67% (2 steps); i) $CH_2CHCH_2CH_2MgBr$, 78%; j) Grubbs 2nd Gen., 55%; k) *m*-CPBA, 68%, 1.8:1, **111**:**112**.

Scheme 22

Treatment of the mixture of **111** and **112** with LiOH and then $Sc(OTf)_3$ resulted in the formation of the hemiketal **113** which upon reaction with methyl magnesium chloride afforded sclerophytin A (**Scheme 23**).



113 Sclerophytin A

a) i) LiOH; ii) $KHSO_4$, $Sc(OTf)_3$, 88%; b) MeMgCl, 99%.

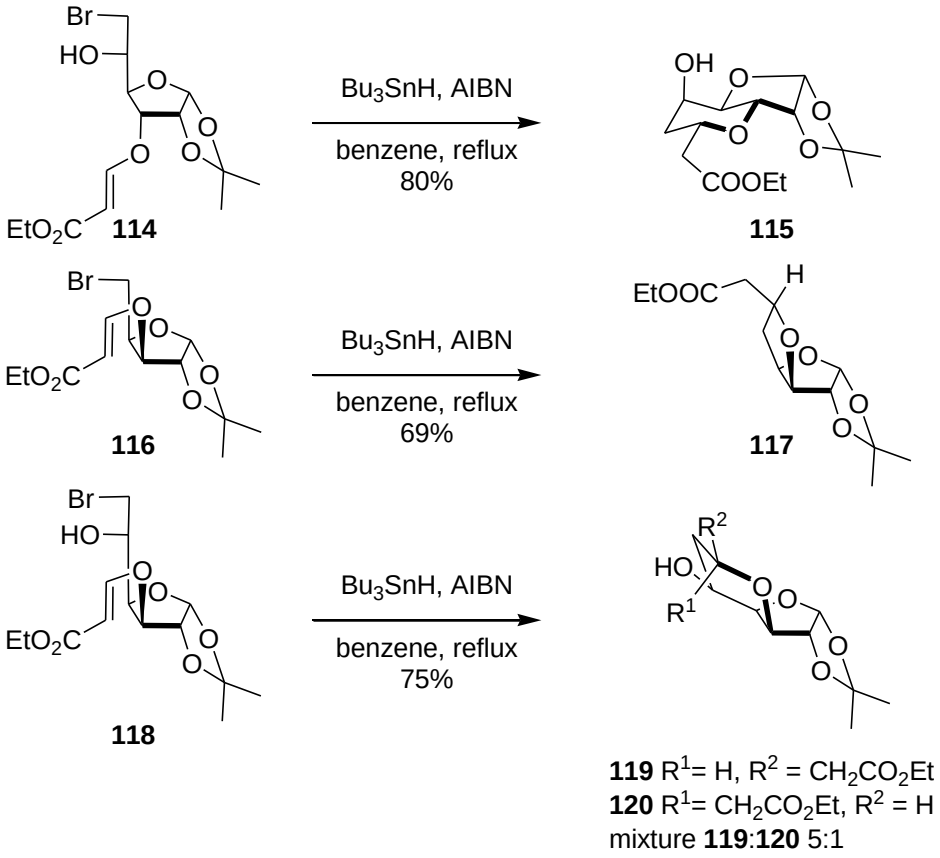
Scheme 23

The cladiellin family of natural products have interested many synthetic research groups over the past fifteen years.[39] The synthesis of these natural products has enabled many research groups to test and prove the utility of their methodology. However, only Kim and co-workers have reported the synthesis of an *E*-cladiellin and have developed a general route that is applicable to the synthesis of many members of the family.

1.2 Radical Cyclisation Reactions

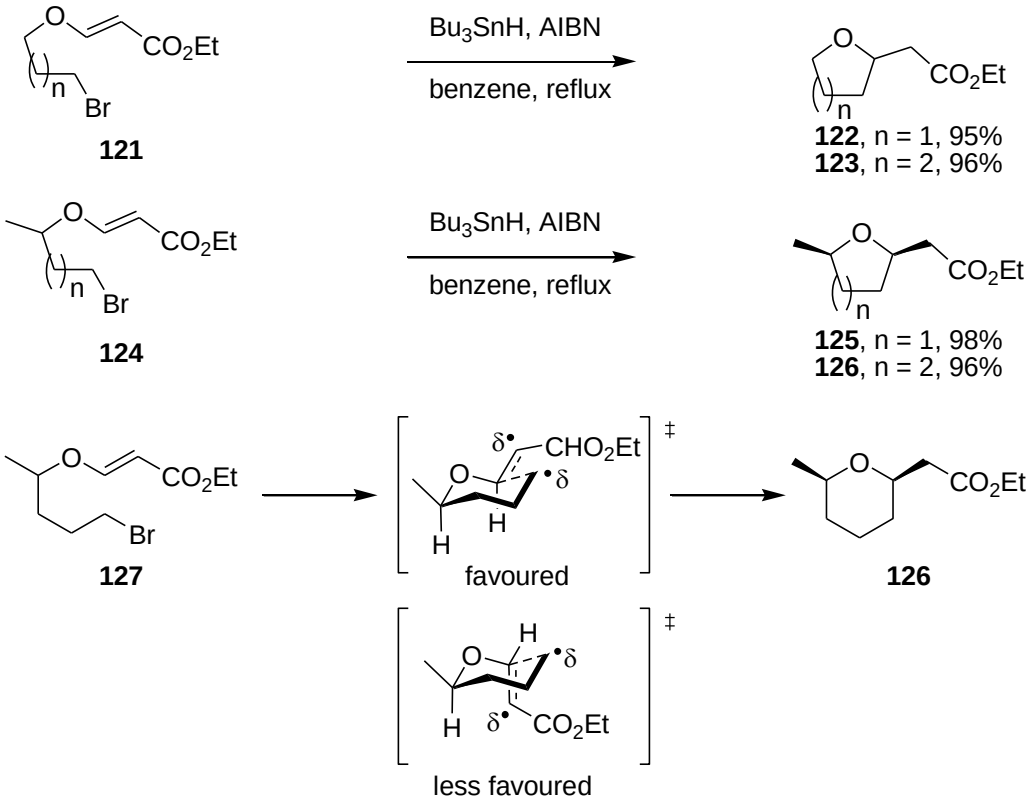
Radical reactions, and in particular radical cyclisations, are very important tools for organic chemists. The scope of these reactions is very wide, and the focus herein will be on the formation of oxacycles using *β*-alkoxyacrylates as acceptors in intramolecular radical cyclisation reactions.

Araki and co-workers first reported such reaction in 1989 for the synthesis of higher-carbon sugars.[40] The cyclisation of terminal halogenofuranoses bearing an *O*-alkoxycarbonyethenyl group proceeded in good yield when they were treated with tributyl tin hydride and AIBN as radical initiator (**Scheme 24**). Five and six-membered rings were formed diasteroselectively (**115** and **117**) when the substituents were orientated favourably. However, mixtures of diastereomers **119** and **120** were obtained when the substituents were orientated less favourably, as in bromide **118**. Four- and seven-membered oxacycles were also obtained using these conditions, as mixtures of diastereomers.



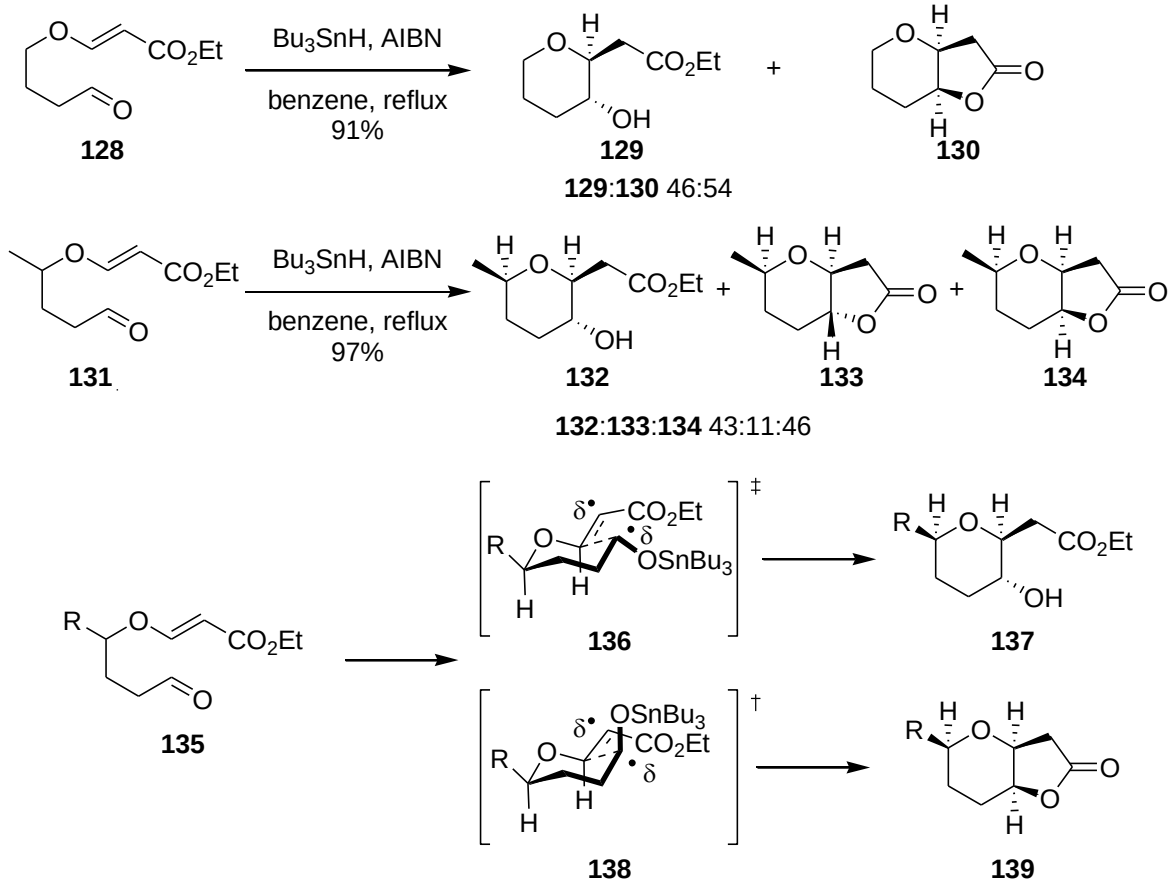
Scheme 24

Some years later Lee and co-workers studied the synthesis of tetrahydrofurans and tetrahydropyrans and reported that *β*-alkoxyacrylates were exceptionally efficient radical acceptors in radical mediated intramolecular cyclisation reaction.[41] These workers demonstrated that both five- and six-membered cyclic ethers can be obtained in high yield and with complete *exo*-selectivity, starting from halogenoalkane bearing a *β*-alkoxyacrylate (**Scheme 25**). They postulated that the *exo*-selectivity is due to the large orbital coefficient at the *β*-carbon in the LUMO of the *β*-alkoxyacrylate. The reaction was also found to exhibit *cis*-selectivity, forming *cis*-2,5-disubstituted tetrahydrofuran **125** and *cis*-2,6-disubstituted tetrahydropyran **126**, which can be explained by formation of a chair-like transition state.



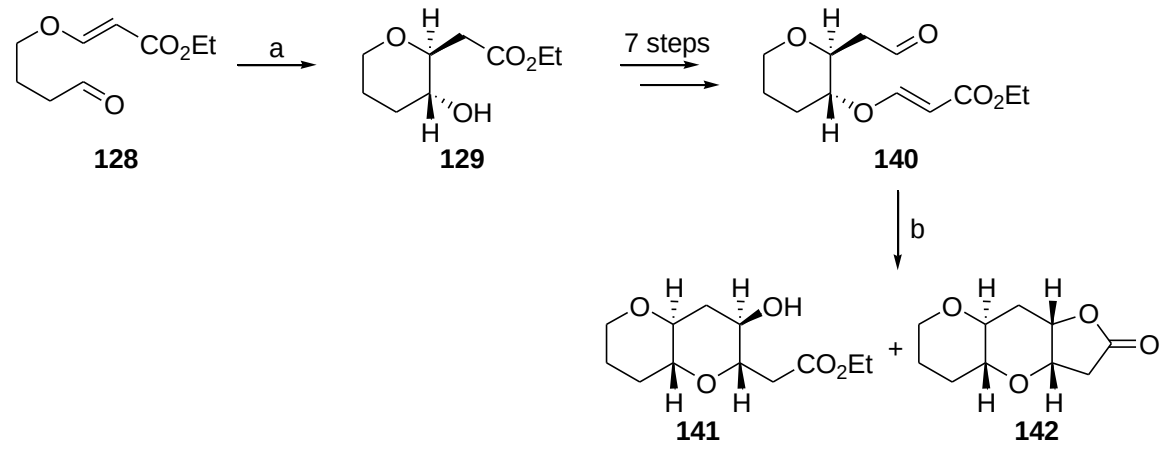
Scheme 25

Lee and co-workers then studied the radical cyclisation of *β*-alkoxyacrylates with stannyloxyalkyl radicals, forming oxacyclic rings bearing a secondary hydroxyl group (**Scheme 26**).[42] Hydroxyl-substituted tetrahydrofurans and tetrahydropyrans were formed in high yield but in each case two diastereomers were observed, meaning that the two transition states **136** and **138** possess similar energies. However, only *cis*-2,6-disubstitued tetrahydropyranyls were isolated, confirming the chair-like transition state postulated previously.



Scheme 26

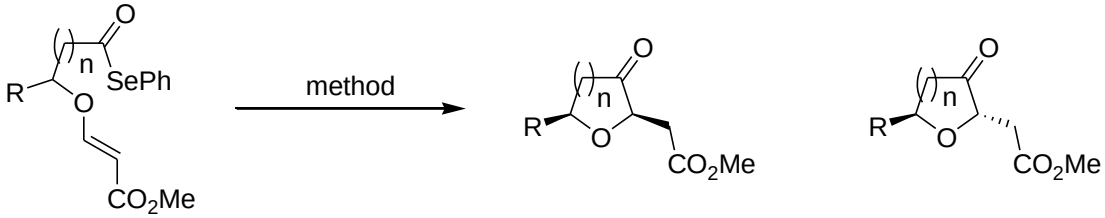
Even though the reaction conditions needed to be developed to give a more diastereoselective cyclisation, Lee and co-workers showed that this methodology could be used in an iterative manner by building fused bicyclic ethers **141** and **142** in 9 steps (**Scheme 27**).[42]



a) Bu_3SnH, AIBN, 42% of **129**; b) Bu_3SnH, AIBN, 23% of **141**, 72% of **142**.

Scheme 27

Concurrently the Evans group worked on the synthesis of 5-, 6-, 7-membered cyclic ethers *via* radical cyclisation using acyl selenide and *β*-alkoxyacrylate.[43] Tetrahydrofuran-3-ones, tetrahydropyran-3-ones and oxepan-3-ones were obtained in high yields and good *cis*-selectivities (**Table 2**). However, the lower diastereoselectivity of this reaction compare to alkyl radical cyclisation made it less attractive.



143 **144** **145**

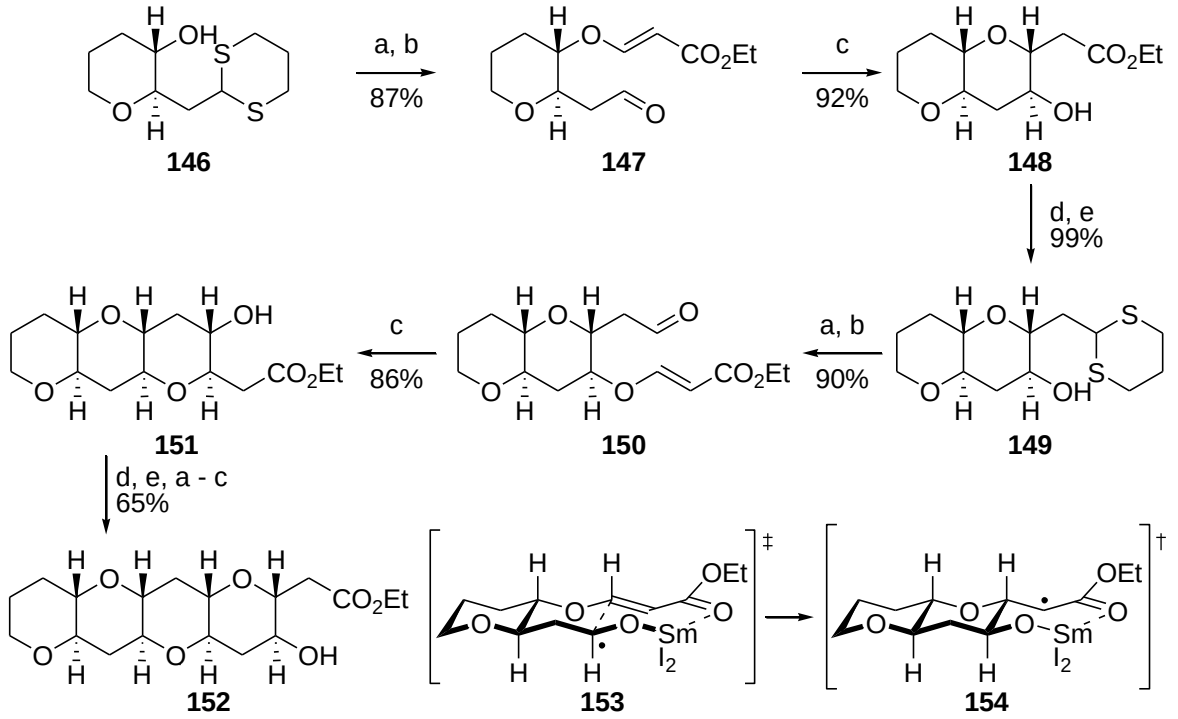
Entry	n	R	Method	Yield	Ratio
1	1	Me	A	97%	10:1
2	1	Ph	A	90%	>19:1
3	2	Me	B	94%	5.7:1
4	3	Me	B	89%	19:1

Method A: Ph_3SnH, Et_3B, benzene, reflux; B: $(TMS)_3SiH$, Et_3B, benzene, rt.

Table 2

Nakata and co-workers developed new conditions for Lee's radical cyclisation of aldehydes with *β*-alkoxyacrylates, forming hydroxy-tetrahydropyrans.[44] The use of SmI_2 for the reductive intramolecular cyclisation of aldehydes or ketones compound with α,β-unsaturated esters had already been developed for the formation of carbocycles.[45] Nakata and co-workers used SmI_2 for the reductive formation of hydroxy-tetrahydropyrans with great success (**Scheme 28**). The reaction proceeded in excellent yield and complete stereoselectivity, allowing the construction of the *trans*-fused polyether **152** in an iterative fashion. Only four different reactions were needed for the synthesis of tetracycle **152** from **146**. The cyclisation reaction giving **148** is thought to proceed *via* the transition state **153**, which is generated by initial single-electron reduction of the aldehyde with SmI_2 and chelation of the samarium(III) to the ester. The resulting ketyl radical attacks the *β*-position of *β*-alkoxyacrylate giving **154**, which is then reduced to an anion by a second equivalent of SmI_2 and finally protonated by MeOH to give the corresponding 2,3-trans-tetrahydropyran **148**. The chelation of

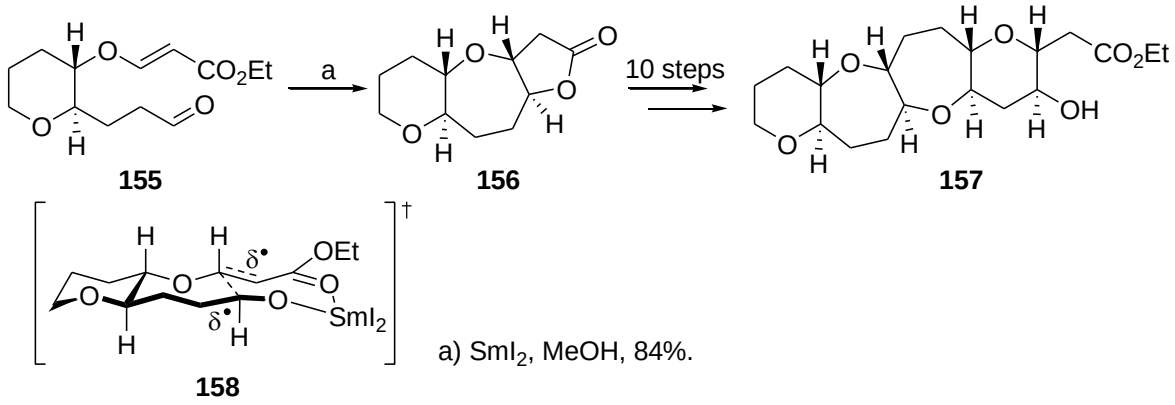
the samarium(III) to the ester contributes to the high diastereoselectivity of the reaction. This explains the lower diastereoselectivity obtained in cases where this chelation is absent, such as when Bu_3SnH is used to generate a radical.



a) ethyl propiolate, *N*-methylmorpholine; b) MeI, aqueous MeCN; c) SmI_2, MeOH; d) DIBAL-H; e) 1,3-propanedithiol, $BF_3 \bullet OEt_2$.

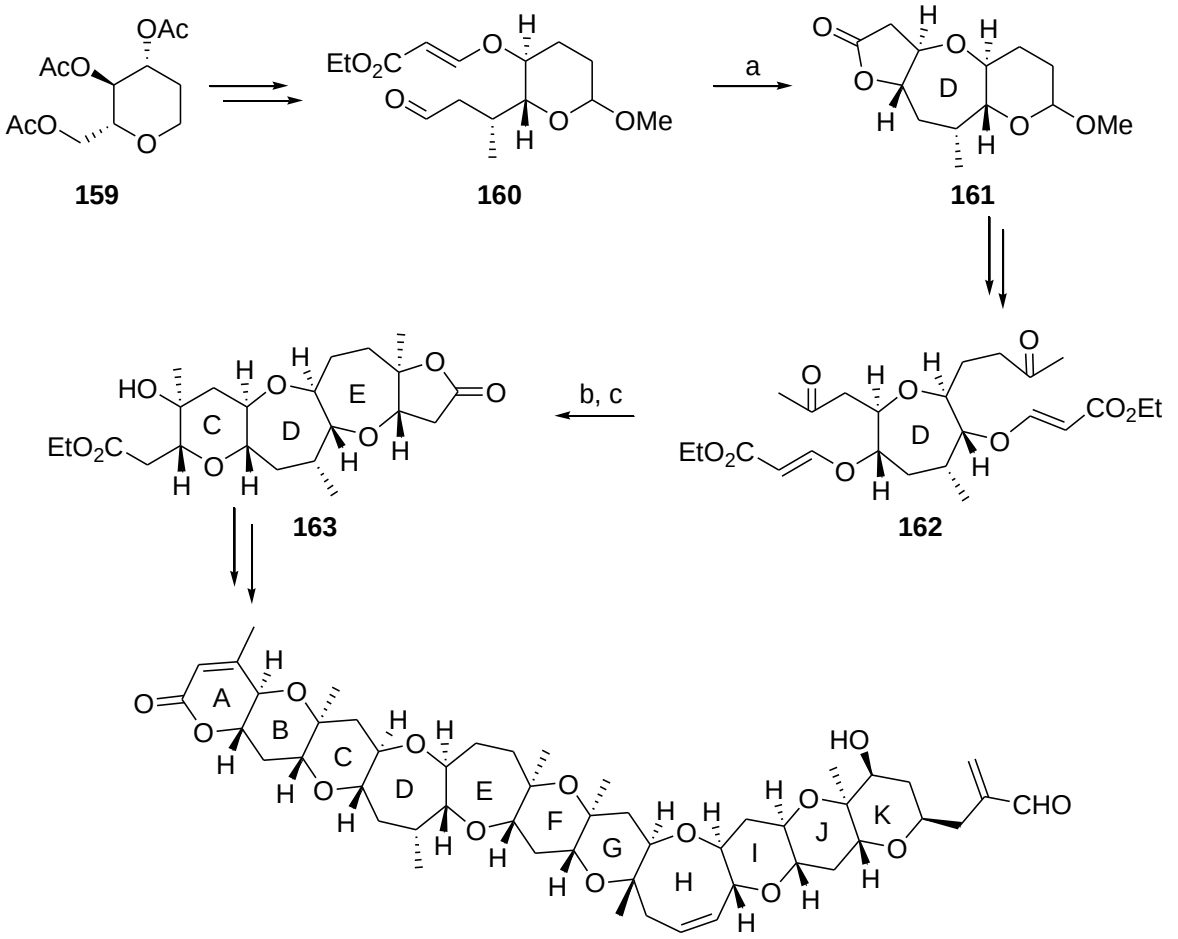
Scheme 28

Oxepane rings were also obtained diastereoselectively using this samarium-mediated reaction (**Scheme 29**).[46] However, the cyclisation reaction was always accompanied by lactonisation in this case. The reaction proceeded *via* the transition state **158** in which the chelation of samarium to the ester would explain the 2,3-*trans* selectivity. Tetracycle **157** was obtained using an iterative strategy based on the SmI_2 inducted cyclisation.



Scheme 29

This iterative protocol was an important innovation for the synthesis of polycyclic ethers. In 2004 the Nakata group was able to complete the synthesis of brevetoxin B using this methodology.[47] The synthetic route featured SmI_2-mediated oxepane ring formation to construct the D ring **161** (**Scheme 30**). Subsequently, a bi-directional synthetic strategy, using a ketone instead of an aldehyde afforded the C and E rings bearing a methyl group **163**. Brevetoxin B was obtained with a longest linear sequence of 59 steps and the route showcased the utility of this cyclisation.



a) SmI_2, MeOH, 83%; b) SmI_2, MeOH; c) *p*-TsOH, 79% (2 steps).

Scheme 30

Over the last twenty years the development of the SmI_2-mediated cyclisation reaction has resulted in a facile, efficient and diastereoselective route for the formation of cyclic ethers.

1.3 Chemistry of *a*-Diazo Carbonyl Compounds

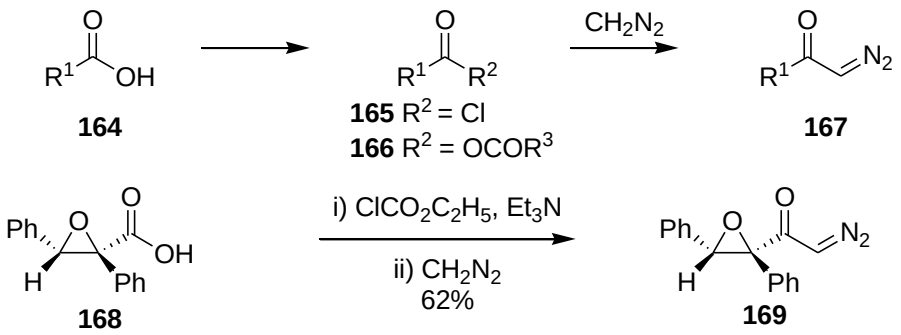
Since the first synthesis of an *a*-diazo ester, ethyl diazoacetate, by Curtius in 1883,[48] *a*-diazo carbonyl compounds have been the centre of attention of many chemists.[49] The growing interest in this type of compound can be explained by the vast number of transformations they can undergo, as well as the development of more efficient methods for their synthesis. Moreover since the 70's and the introduction of dirhodium catalysts to generate carbenoids from diazo compounds, the opportunities for highly chemoselective transformations

have increased.[50] In addition the introduction of chiral catalysts to promote asymmetric transformations of *a*-diazo carbonyl compounds has provided new possibilities.

1.3.1 Formation of a-Diazo Carbonyl Compounds

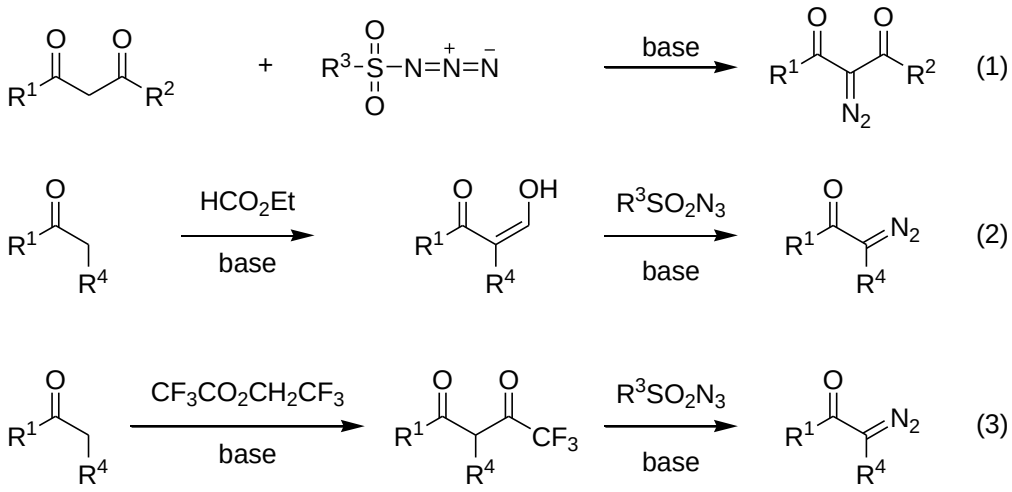
Curtius reported the first preparation of an *a*-diazo carbonyl compound by diazotisation of natural *a*-amino acids.[48] Since then, various other methodologies for the preparation of *a*-diazo carbonyl have been developed. Acylation of diazomethane with an acyl chloride or an anhydride is the most common method for the synthesis of acyclic terminal *a*-diazo carbonyl compounds. The diazo group transfer technique, which enables the formation of both terminal and non-terminal systems, also occupies an important place in the *a*-diazo carbonyl preparation.

A common synthesis of diazoketones involves reaction of an acyl chloride **165** with at least two equivalents of diazomethane (**Scheme 31**).[51] This excess of diazomethane is crucial as it reacts with the hydrogen chloride formed during the reaction and thereby prevents its addition to the diazoketone. Anhydrides **166** are also suitable acylating agents for diazomethane.[52] A convenient method involves the *in situ* generation of a mixed anhydride **166** by the reaction of a carboxylic acid **164** with a chloroformate, followed by treatment with ethereal diazomethane. This is the method of choice in cases where the formation of an acid chloride would not be possible due to the presence of other reactive functional groups. For example, diazoketone **169** containing a sensitive epoxide was synthesised by this route.[52]



Scheme 31

The diazo transfer method was first developed to address the problem of the synthesis of cyclic *a*-diazo carbonyl compounds which are not accessible by acylation reactions. It is a general method that is widely used not only for the synthesis of cyclic compounds. Diazo transfer refers to the transfer of a complete diazo group from a diazo donor, generally a sulfonyl azide, to an acceptor, which for *a*-diazo carbonyl products are carboxylic acid or ketone derivatives. The acceptors can be divided into two different categories, those in which the *a*-methylene position is sufficiently reactive towards diazo transfer, and those that require prior activation to facilitate the transfer reaction. Malonic esters, *B*-ketoester, *B*-ketoamides and *B*-diketones are sufficiently reactive to react directly with tosyl azide using a weak base such as triethylamine (**Scheme 32**, eq 1).[53] One technique that is used when prior activation is required is Regitz deformylating diazo transfer.[54] This procedure involves Claisen condensation of the ketone with ethyl formate to introduce the strongly activating formyl group, which is later released as sulphonamide during the diazo transfer reaction (eq 2). Danheiser and co-workers modified the Regitz procedure in order to synthesise base sensitive *a*-diazo carbonyls by using the trifluoroacetyl group as an activator (eq 3).[55] This allows milder coupling conditions to be employed than in the case of the Claisen condensation reaction.

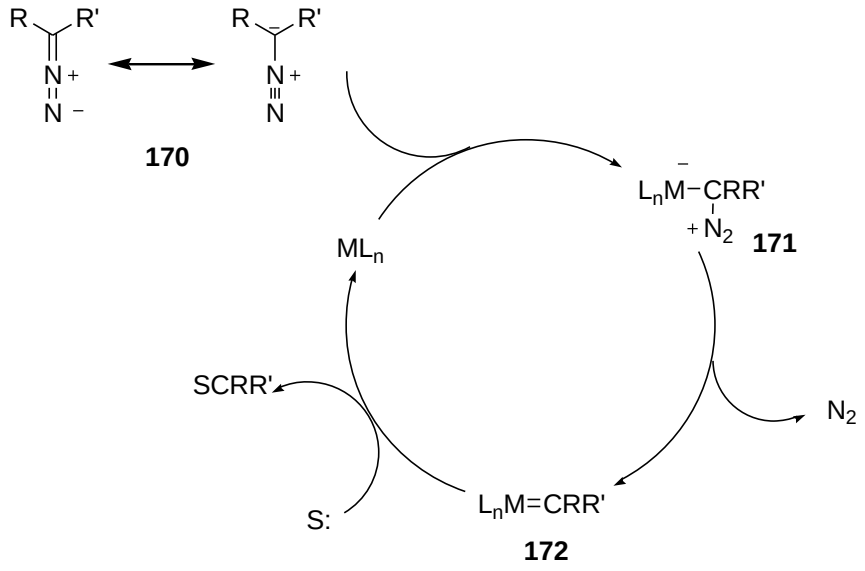


R^1, R^2 = aryl, alkyl, *O*-alkyl, *O*-aryl, NR_2; R^3 = Me, *p*-tolyl, *p*-CO_2H-phenyl; R^4 = aryl, alkyl.

Scheme 32

1.3.2 Metal Carbenoid Formation

Free carbenes are very reactive species, but their utility for organic chemists is diminished by the methods required for their generation (usually thermal or photochemical) and their high reactivity that causes low selectivity and instability. Transition metals have been found to stabilise these carbenes and attenuate their reactivity thus increasing their synthetic utility. Metal carbenes are usually generated by the reaction of diazo compounds with transition metals, resulting in the production of complexes commonly referred to as metal carbenoids. Metal carbenoid mediated transformations usually display higher yield and selectivity that the corresponding free carbene transformations. The generally accepted mechanism for catalytic decomposition of diazo compounds starts with the nucleophilic addition of the diazo compound **170** to the metal complex, followed by the loss of nitrogen gas to form the metal-stabilised carbene or metal carbenoid **172** (**Scheme 33**).[49] Transfer of the electrophilic carbene species to an electron-rich substrate (S:) regenerates the catalyst and completes the catalytic cycle. Spectroscopic evidence for the formation of the diazonium adduct **171** has been obtained thanks to studies on the decomposition of diazo compounds with iodorhodium(III) tetra-*p*-tolylporphyrin, generating a spectroscopically stable (porphyrinatorhodium)-diaminocarbene complex.[56]

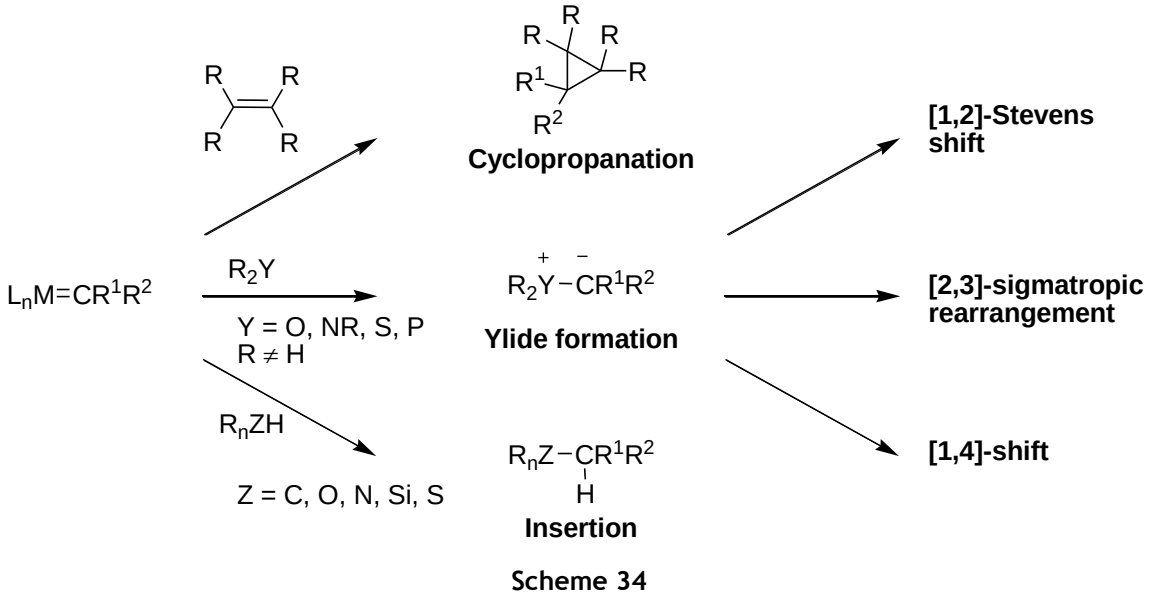


Scheme 33

Transition metals that are effective catalysts for diazo decomposition are Lewis acidic in character.[49] Their catalytic activities are due to coordinative unsaturation at the metal centre, which allow them to react as electrophiles with diazo compounds. The metal used as well as the ligands have a profound effect on the regio-, chemo- and stereo-selectivity of the reaction. The first example of a metal-carbenoid reaction was described in 1906 when copper dust was used for the decomposition of ethyl diazoacetate.[57] Copper remained the metal of choice for the decomposition of diazo compounds until the late 1970's and the discovery of rhodium(II) acetate dimer.[50] This air stable catalyst became the single most widely used catalyst for metal carbenoid transformations. The most common complexes used for carbene generation are those of copper and rhodium but cobalt, palladium, ruthenium, osmium, iron, platinum and nickel compounds have also been used successfully.[49]

1.3.3 Metal Carbenoid Reactions

As previously discussed, metal carbenoids are synthetically useful because they are a less reactive versions of free carbenes. A large range of reactions can be performed with these compounds. The most widely studied metal-catalysed reaction of *α*-diazo carbonyl compounds is certainly cyclopropanation (**Scheme 34**). This is the reaction of a metal carbenoid with an alkene to generate a cyclopropyl group. It has been developed as both an inter- and intramolecular reaction and asymmetric variants are known. Other transformations, such as ylide formation and insertion reactions can also be observed. Insertion reactions can be obtained with C–H, O–H, S–H, N–H, and Si–H bonds but the most synthetically valuable transformation is the C–H bond insertion, because a new C–C bond is created. Ylides are formed by the attack on the metal carbenoid by nucleophiles lacking acidic protons, such as ethers, tertiary amines and thioethers leading to oxonium, ammonium and sulfonium ylides respectively. These ylides can then undergo further reactions such as [1,2]-Stevens shift, [2,3]-sigmatropic rearrangement, and to a lesser extent [1,4]-shift and *β*-elimination.

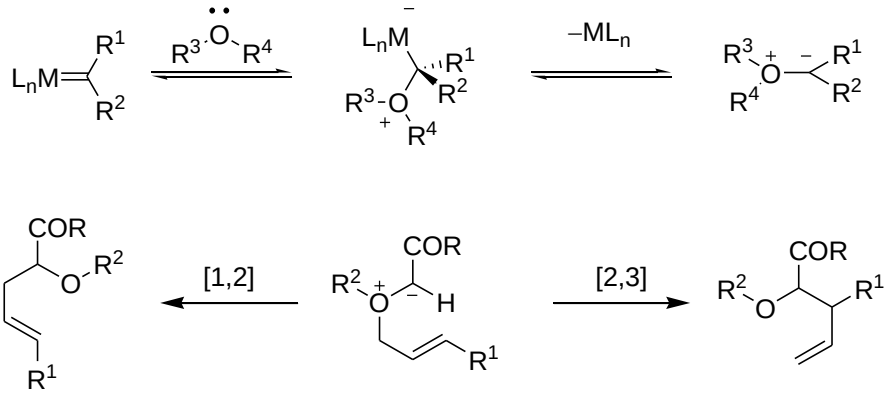


Scheme 34

Although metal carbenoids can undergo a wide range of reactions, the focus of this thesis will be on the formation of oxonium ylides and their subsequent rearrangement.

1.4 Oxonium Ylide Generation and Rearrangement

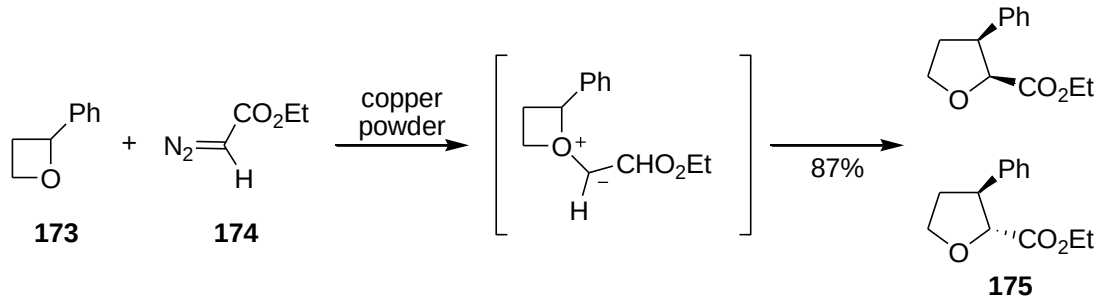
Unlike ammonium and sulfonium ylide systems which are stable and have been well studied, free oxonium ylides are not isolable intermediates. For many years, metal catalysed reactions between *a*-diazo carbonyl compounds and ethers were thought to proceed by direct C–O insertion.[58] However, conclusive evidence suggested that these reactions proceeded through formation and rearrangement of an oxonium ylide. This was deduced from the isolation of [2,3]-sigmatropic rearrangement products from reactions of allylic substrates that were analogous to those obtained from allylic sulfonium, ammonium and phosphonium ylides (**Scheme 35**). Over the past decade, the development of mild catalytic methods for the preparation of those oxonium ylides has resulted in a dramatic increase in their study and synthetic use. However, some questions remain about the exact identity of the ylide intermediate. Some evidence suggests that in certain cases rearrangement proceeds through a metal-bound intermediate rather than a free oxonium ylide. Nevertheless, in most cases the intermediate can be regarded as if it were a free oxonium ylide.



Scheme 35

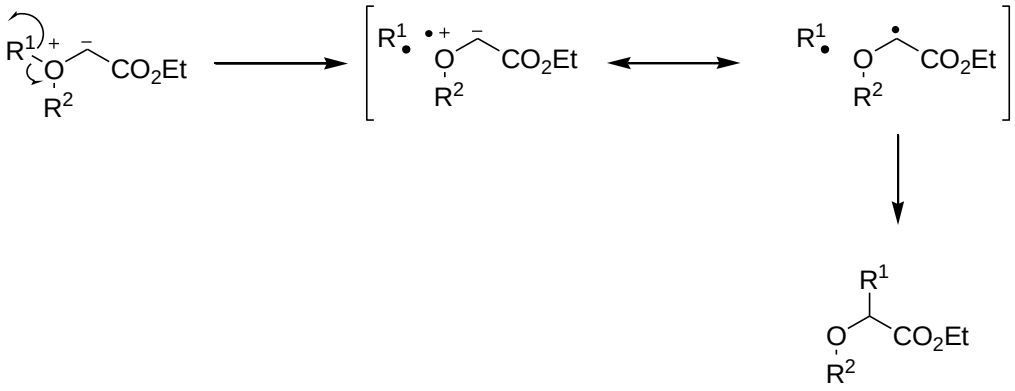
1.4.1 The [1,2]-Stevens Shift

One of the first examples of oxonium ylide formation and subsequent [1,2]-Stevens shift was reported by Nozaki and co-workers (**Scheme 36**).[59] The copper-catalysed reaction of 2-phenyloxetane **173** with methyl diazoacetate **174** afforded a mixture of the *cis* and *trans*-tetrahydrofuran **175**.



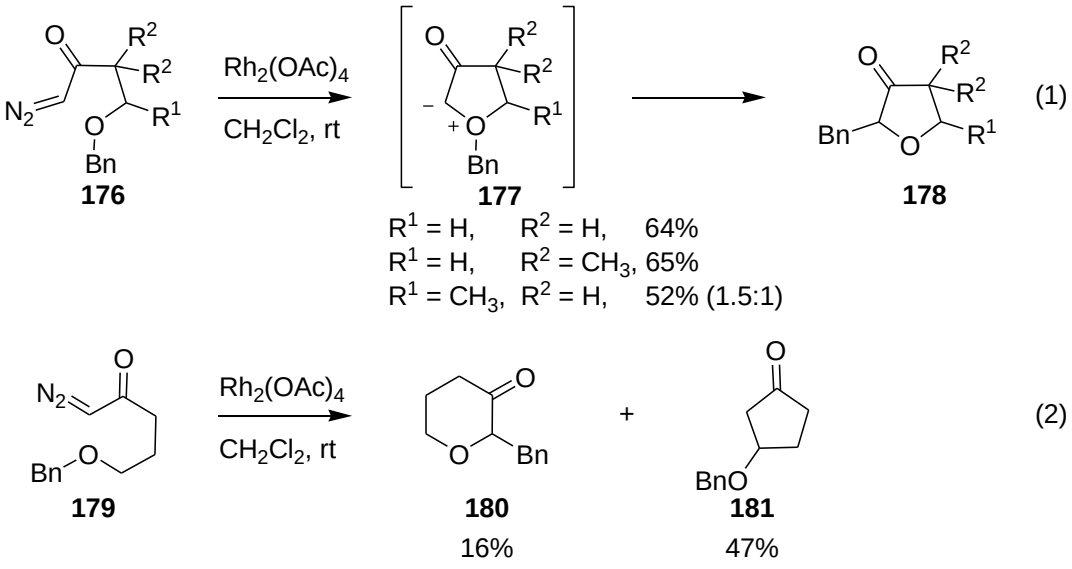
Scheme 36

This [1,2]-shift cannot operate through a concerted process because this would contravene the Woodward-Hoffmann rules.[60] A free oxonium ylide rearranges *via* a homolysis-recombination mechanism (**Scheme 37**), established on the basis of CIDNP NMR data, consistent with an oxonium ylide intermediate undergoing homolytic cleavage to produce a singlet radical pair, followed by cage recombination.[61]



Scheme 37

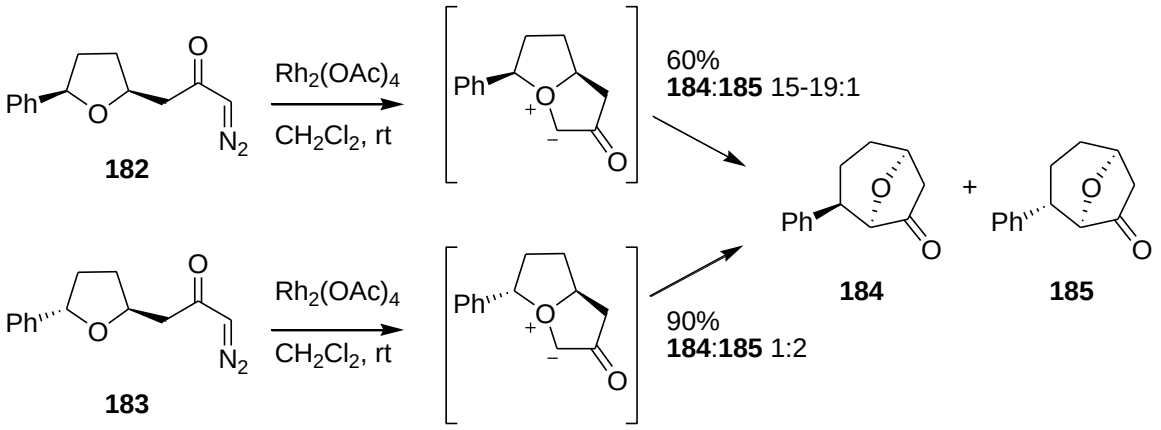
West and co-workers investigated the formation of tetrahydrofuranones and tetradropyranones using the tandem oxonium ylide formation [1,2]-shift protocol (**Scheme 38**).[62] The tetrahydrofuranones **178** were obtained in relatively good yields (eq 1). However, it was noticed that the C–H insertion reaction was competitive to the oxonium ylide formation, when there was a choice between formation of a five-membered ring *via* insertion and formation of a six-membered cyclic oxonium ylide (eq 2). This resulted in formation of cyclopentanone **181** in higher yield than the tetrahydropyranone **180**.



Scheme 38

West and co-workers then studied the synthesis of bridged bicyclic ethers (**Scheme 39**).[63] All their substrates displayed complete group selectivity, meaning that the carbon atom bearing the best radical stabilising substituent migrated preferentially. Both compound **182** and **183** promoted efficient

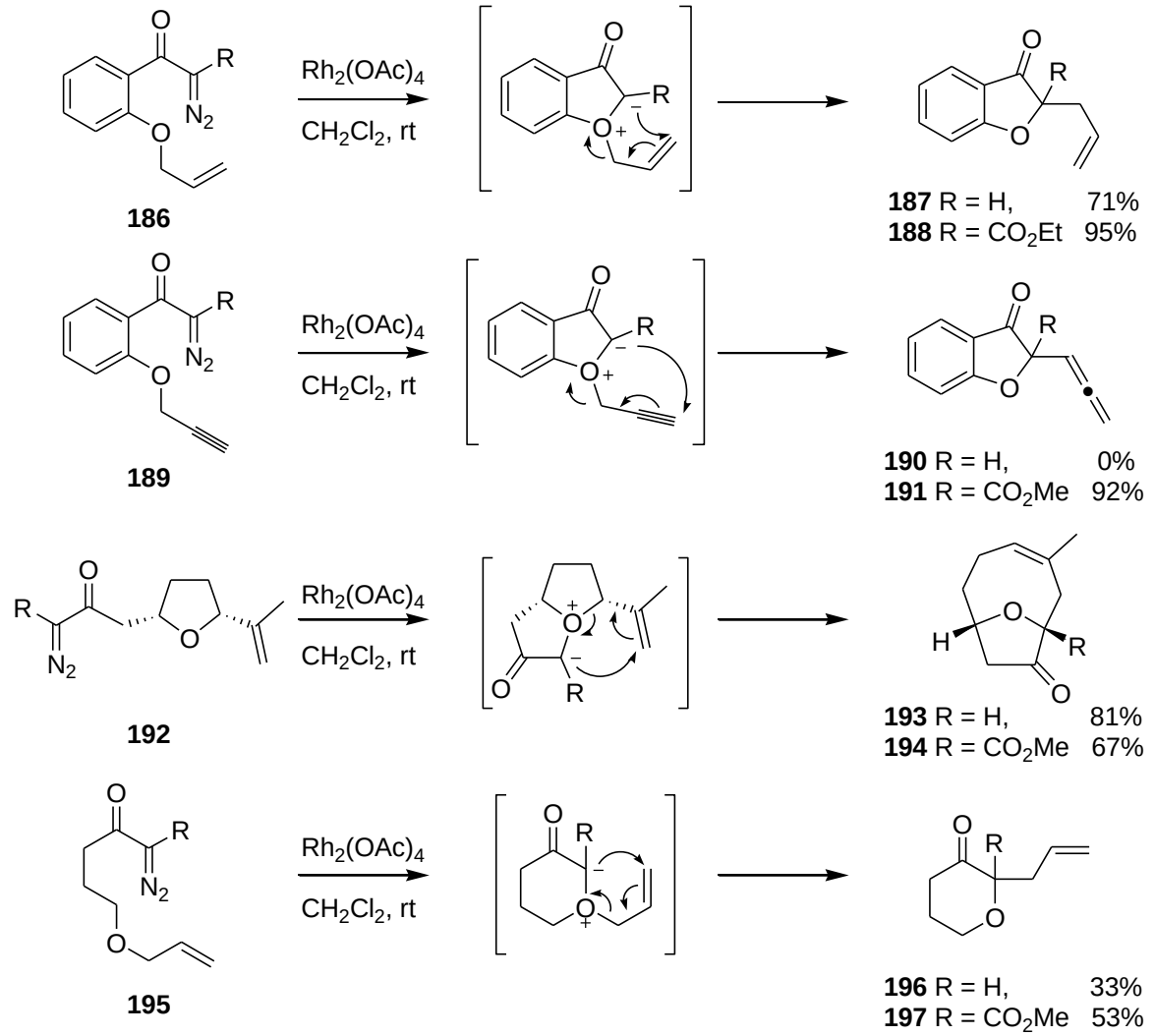
[1,2]-Stevens shift affording the bicyclic ethers **184** and **185** as a diastereoisomeric mixture. In each case, the major diastereomer was the one in which there was retention of configuration. The *cis*-compound **182** showed higher retention of configuration, whereas the substrate **183** afforded the bicyclic products in higher yield.



Scheme 39

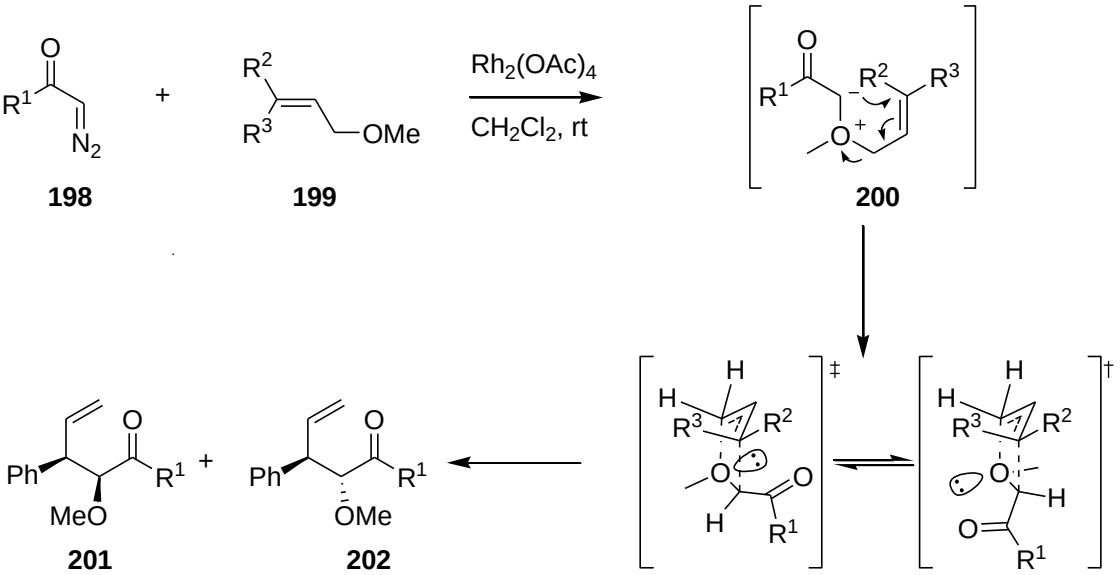
1.4.2 The [2,3]-Sigmatropic Rearrangement

Intramolecular oxonium ylide formation and subsequent [2,3]-sigmatropic rearrangement was developed and reported independently by Pirrung and Werner[64] as well as Roskamp and Johnson[65] in 1986. The intramolecular reaction of an allylic ether with an *a*-diazoketone catalysed by rhodium(II) acetate formed a cyclic allylic oxonium ylide that readily underwent [2,3]-sigmatropic rearrangement to deliver five-, six- and eight-membered cyclic ethers (**Scheme 40**). Furanones were obtained in good yields, apart from the alkene-containing compound **190** which proved to be unstable. Six-membered rings **196** and **197** were formed in lower yields due to C-H insertion, which competed affectively with oxonium ylide formation. The formation of eight-membered bicyclic ethers **193** and **194** *via* a three-carbon ring expansion is particularly noteworthy as eight-membered ethers are a common feature of several natural products.



Scheme 40

Intermolecular formation of oxonium ylides from allylic ethers can result in poor yields due to the competing cyclopropanation reaction. The ratio between cyclopropanation and ylide formation is dependent of the steric environment of both, the ether oxygen and the alkene, as well as the nature of the catalyst used. In some cases, good selectivities for the oxonium ylide formation and subsequent [2,3]-sigmatropic rearrangement can be obtained. Following the successful development of the intramolecular protocol, Doyle and co-workers developed an intermolecular version of this tandem procedure.[66] Oxonium ylide **200** was obtained almost exclusively when diazoketone **198** and allylic methyl ether **199** were treated with rhodium(II) acetate dimer (**Scheme 41**). Rearrangement of the putative oxonium ylide was thought to proceed *via* an envelope transition state where the *O*-methyl and the ketone group were in a *trans* position in order to minimise steric interactions. The geometry of the alkene starting material dictated the relative stereochemistry of the product.



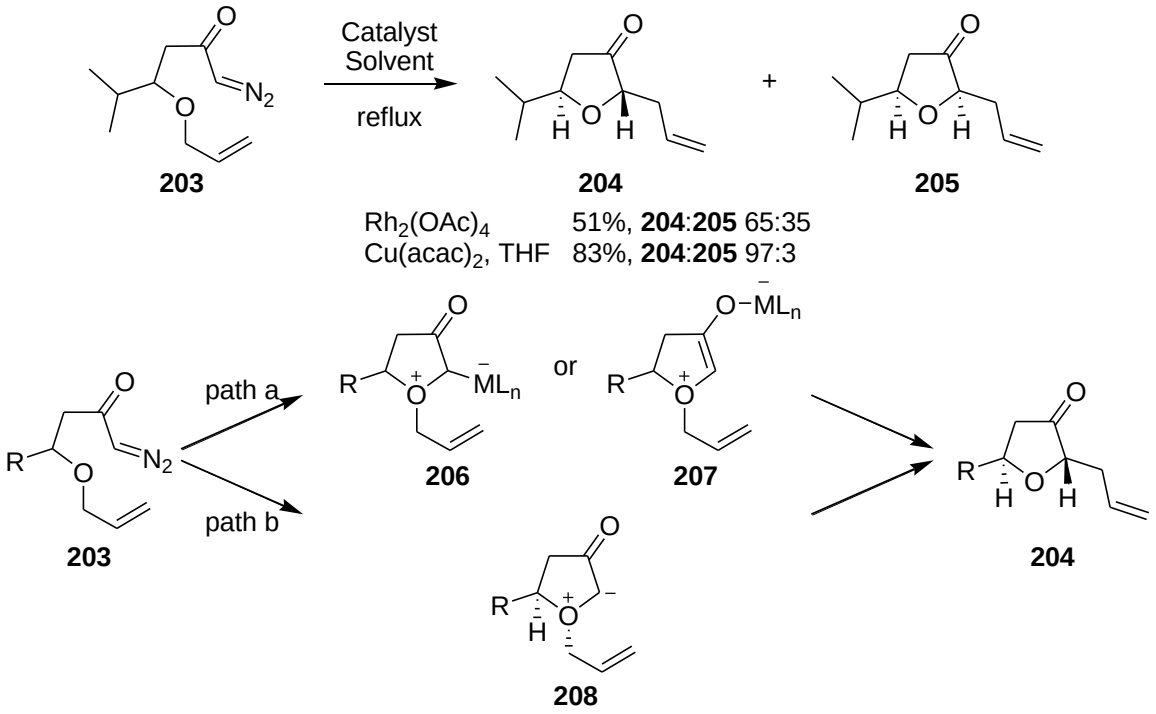
198 **199** **200**

201 **202**

R^1 = Ph, R^2 = Ph, R^3 = H , 80%, **201**:**202**, 91:1
R^1 = Ph, R^2 = H, R^3 = Ph, 64%, **201**:**202**, 19:81

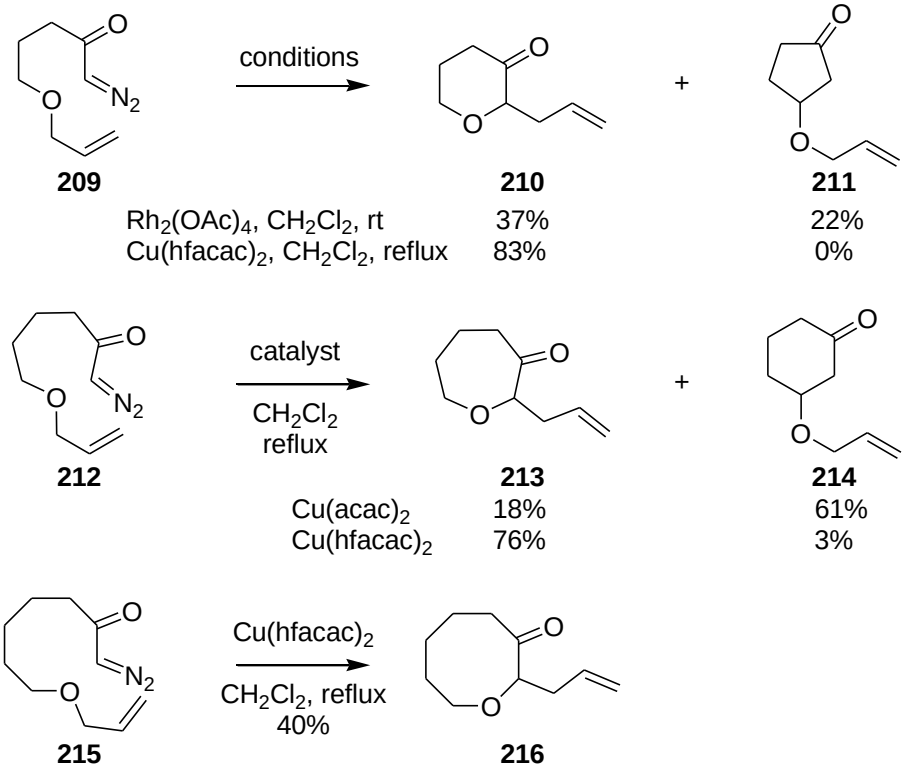
Scheme 41

Clark studied the diastereochemical outcome of the intramolecular reaction to give dihydrofuranones (**Scheme 42**).[67] Treatment of the diazoketone **203** with a copper or rhodium catalyst delivered the tetrahydrofurans **204** and **205**. The ratios in which the *cis* or *trans* products were obtained varied, depending on the catalyst used. This suggested that the rearrangement was occurring *via* a metal-bound ylide (path a), or that ylide formation was selective for one of the diastereotopic lone pair of electrons of the oxygen leading to **208** (path b). In order to obtain stereocontrol with path b, the rearrangement rate needs to be greater than the rate of inversion at the oxonium centre which seems unlikely.



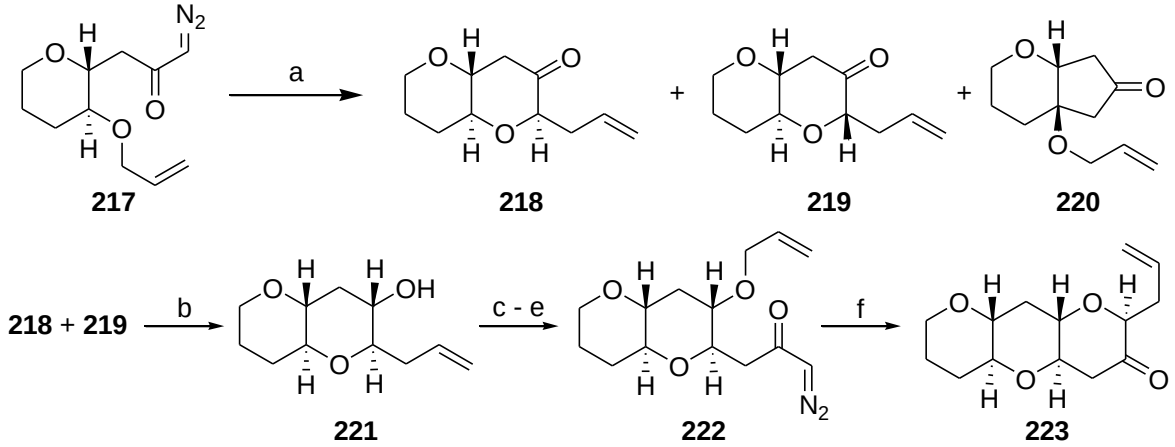
Scheme 42

Clark and co-workers also explored the challenging synthesis of six-, seven- and eight-membered rings known to be difficult to obtain due to the competing C-H insertion reactions (**Scheme 43**).[68] Once again the catalyst as well as the solvent system proved to have a dramatic influence on the formation of the desired product. Copper appeared to be the metal of choice, favouring oxonium ylide formation over C-H insertion. The six- and seven-membered cyclic ethers **210** and **213** were obtained in good yield, and the oxocan-3-one **216** was formed in moderate yield. The role of the catalyst for these reactions was unclear but it appeared that increasing the electron demand of the catalyst ligands promoted the reaction. It was thought that the high yield obtained when $Cu(hfacac)_2$ was used as catalyst resulted from the stabilisation of the metal-bound ylide intermediate. This would either suppress reformation of the original carbenoid species or would reduce the energy difference between the metal-bound ylide-species and the transition state of the rearrangement reaction.



Scheme 43

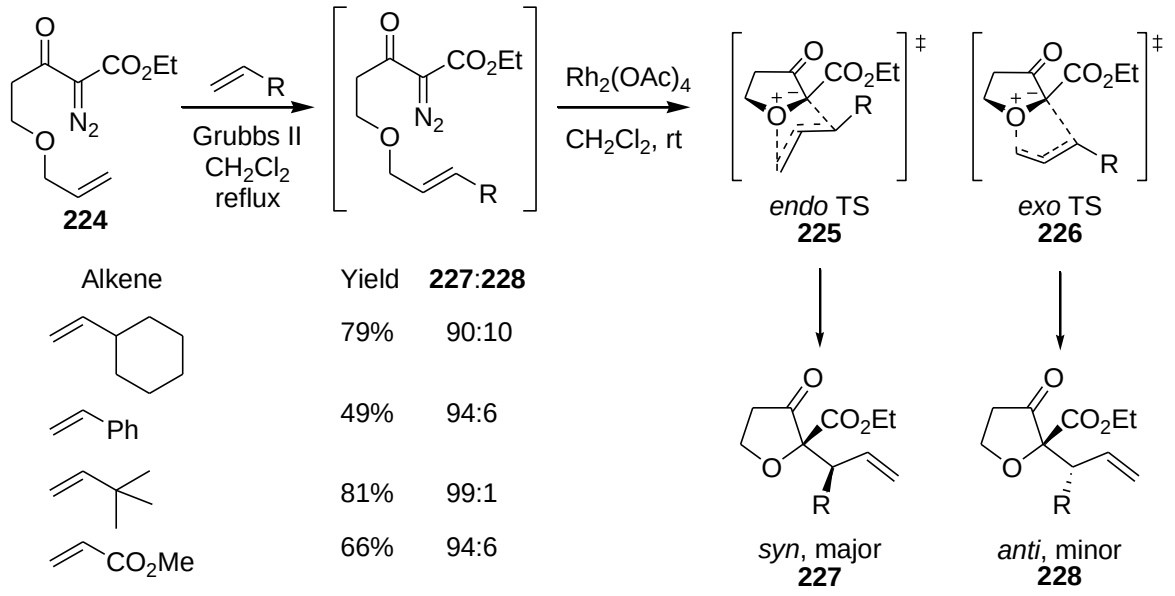
Some years later West and co-workers developed an iterative method for the synthesis of polycyclic ether natural products (**Scheme 44**).[69] Under optimised conditions, diazoketone **217** underwent oxonium ylide formation and subsequent [2,3]-sigmatropic rearrangement in good yield giving a mixture of the rearrangement products **218**, **219** and the C-H insertion product **220**. A two step procedure gave the desired *cis* product **221** from the mixture of diastereomers **218** and **219**. Alcohol **221** was readily transformed into the diazoketone **222** in three steps. Copper-catalysed oxonium ylide formation and [2,3]-sigmatropic rearrangement then delivered the tricyclic ether **223** in good yield as the only diastereomer.



a) $Cu(tfacac)_2$, CH_2Cl_2, reflux, 80%, **218**:**219**:**220,** 1:30:2; b) i) DBU; ii) $LiAlH_4$, 86% (TPAP/NMO recycling 88%); c) O_3, H_2O_2, HCO_2H; d) KH, DME, CH_2CHCH_2Br, 67% (2 steps); e) *i*-BuOCOCl, CH_2N_2, 44%; f) $Cu(tfacac)_2$, CH_2Cl_2, reflux, 80%.

Scheme 44

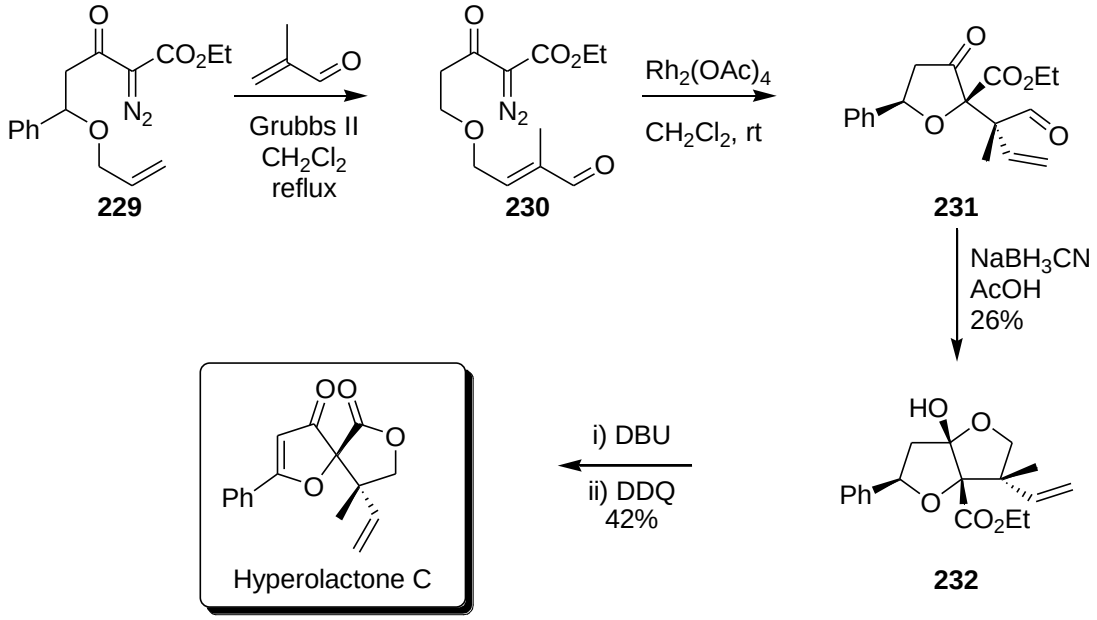
Recently Hodgson and co-workers reported one-pot alkene cross-metathesis, oxonium ylide formation and highly diastereoselective [2,3]-sigmatropic rearrangement for the synthesis of hyperolactone C, an anti-HIV agent (**Scheme 45**).[70] The one-pot procedure was first explored using model systems, resulting in good yield and diastereoselectivity in favour of the *syn* product **227** obtained from the endo transition state **225**.



Scheme 45

Hyperolactone C was obtained in five steps from the diazoketone **229** (**Scheme 46**). Cross-metathesis with methacrolein formed the enone **230**, which underwent oxonium ylide formation and subsequent [2,3]-sigmatropic

rearrangement. Reduction of **231** gave hemiketal **232** in 26% yield over 3 steps. Spirolactonisation of the hemiketal **232** using DBU was followed by dehydrogenation to afford hyperolactone C.

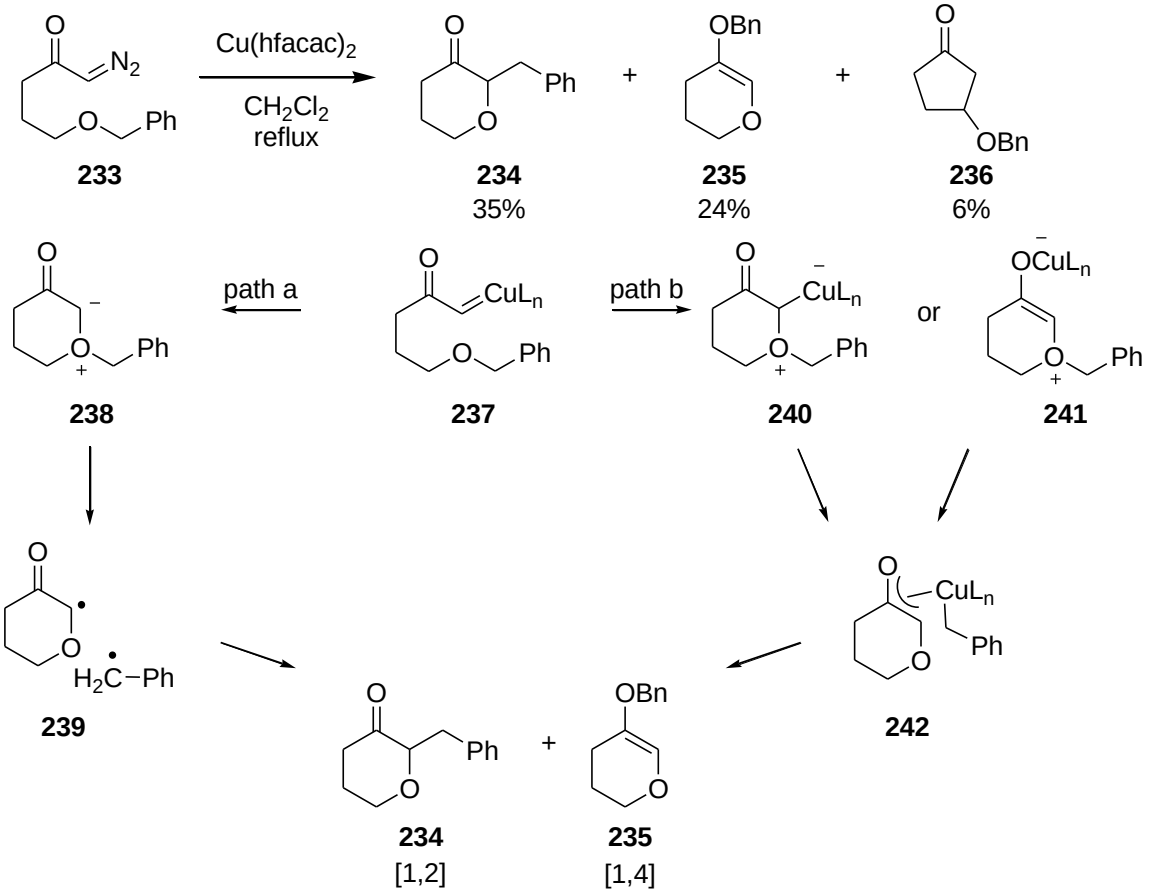


Scheme 46

1.4.3 The [1,4]-Shift

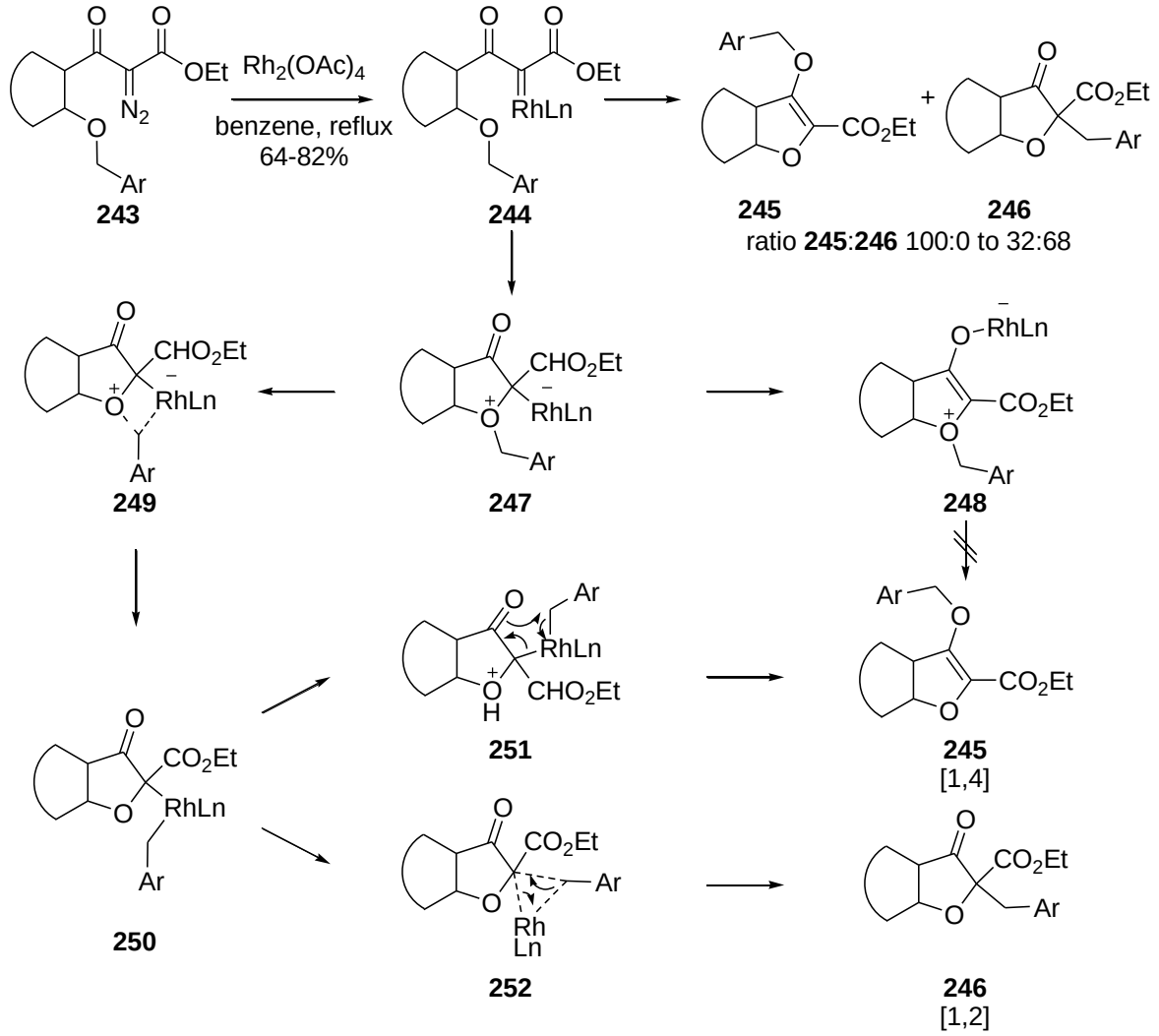
In general, oxonium ylides can undergo two major transformations, the [1,2]-Stevens shift or the [2,3]-sigmatropic rearrangement. A less common oxonium ylide transformation is the [1,4]-shift reaction. Products from this reaction were first detected by Pirrung and co-workers in rhodium(II)-mediated reactions.[71] Products resulting from [1,4]-shift reactions have also been isolated in low yield by West[72] and Clark[73] from copper(II)-catalysed reactions. Treatment of diazoketone **233** with copper(II) gave a mixture of three products (**Scheme 47**). The major product **234** was the [1,2]-Stevens shift product, whereas the C-H insertion product **236** was obtained in a very small amount. Compound **235** resulting from the [1,4]-shift was obtained in a surprisingly high 24% yield.[72] West proposed a mechanism for the formation of the [1,2]- and [1,4]-products. It was assumed that the [1,4]-product was formed from the radical pair intermediate **239** (path a) that led to recombination at the oxygen rather than at the carbon for the [1,2]-shift. However the radical homodimer

was never isolated and so an alternative metal-assisted mechanism was proposed (path b).



Scheme 47

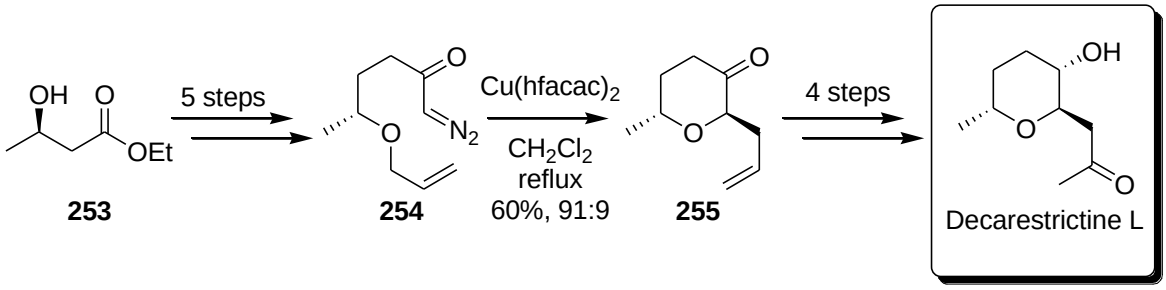
Dhavale and co-workers observed that rhodium catalysed decomposition of *α*-diazo *β*-keto esters afforded high yields of [1,4]-shift product **245** (**Scheme 48**).[74] Competitive studies on the [1,4]-shift versus the [1,2]-shift showed that in general the increase in electron density on the benzylic carbon of the migratory group resulted in the preferential [1,4]-migration pathway, while a decrease in the electron density led to a predominance of the [1,2] product. Dhavale proposed an independent mechanistic pathway for the rhodium-catalysed formation of [1,4]-migrated product. This mechanism involved the formation of metal-bound oxonium ylides **247** and **248**. However, **248** would be unproductive for the [1,4]-shift due to the large distance between the migration origin and its terminus. Instead, the reaction would proceed *via* the migration of the benzylic group from oxygen to rhodium. **250** would be the common intermediate in both the [1,2]- and [1,4]-shift pathways.



Scheme 48

1.4.4 Clark Group Approach Towards Natural Product Synthesis via Diazo Carbonyl Chemistry

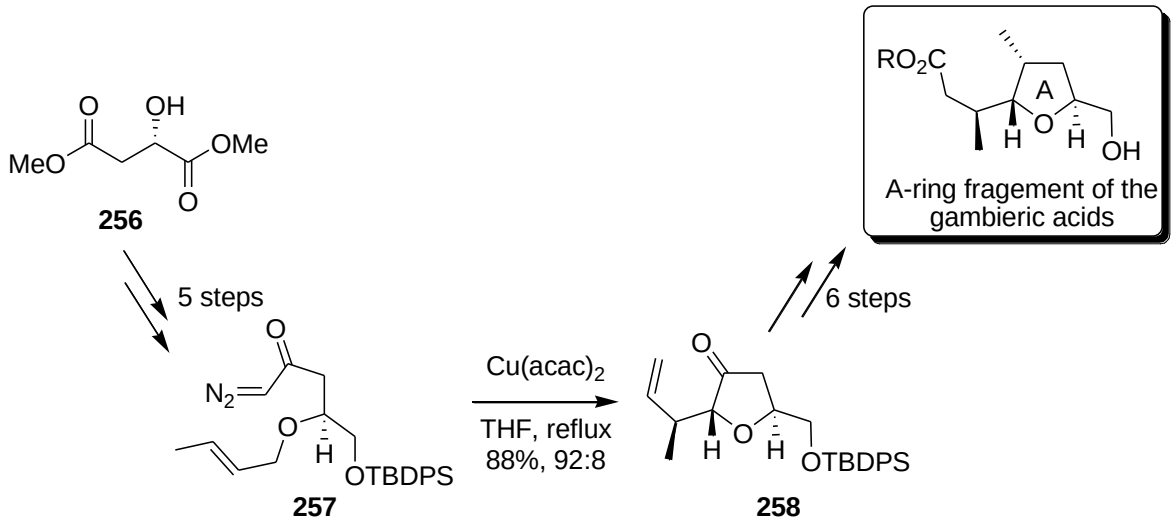
Following the successful synthesis of five-, six- and seven-membered cyclic ethers presented earlier (**Scheme 43, 44**), Clark and co-workers embarked on the synthesis of a small natural product using the [2,3]-sigmatropic rearrangement of oxonium ylide as a key step, decarestrictine L was synthesised in both racemic[75] and enantiopure[76] form (**Scheme 49**). Diazoketone **254** was obtained in 5 steps from the chiral starting material **253**. Tetrahydropyran **255** was formed in good yield and with high diastereomeric excess in favour of the *trans*-product, using $Cu(hfacac)_2$ as catalyst.



253 254 255

Scheme 49

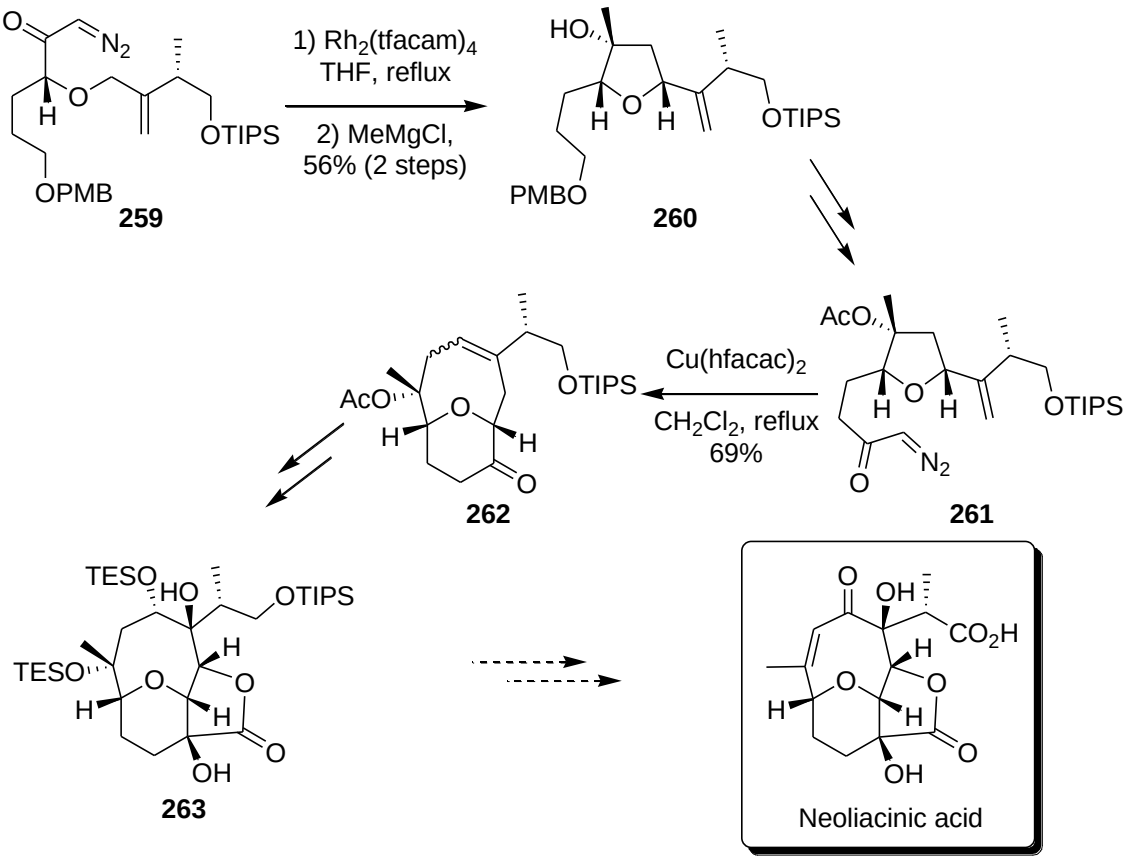
Clark and co-workers have also demonstrated that the catalyst has a great influence on the diastereomeric outcome in the synthesis of tetrahydrofurans *via* [2,3]-sigmatropic rearrangement (**Scheme 42**). This methodology was used for the synthesis of the A-ring fragment of the gambieric acids (**Scheme 50**).[77] Diazoketone **257** underwent smooth tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement to afford tetrahydrofuran **258** in good yield. The use of $Cu(acac)_2$ enables products possessing the *trans* configuration to be obtained with high diastereomeric excess. Further functionalisation of the *trans*-dihydrofuranone **258** afforded the A-ring fragment of the gambieric acids.



Scheme 50

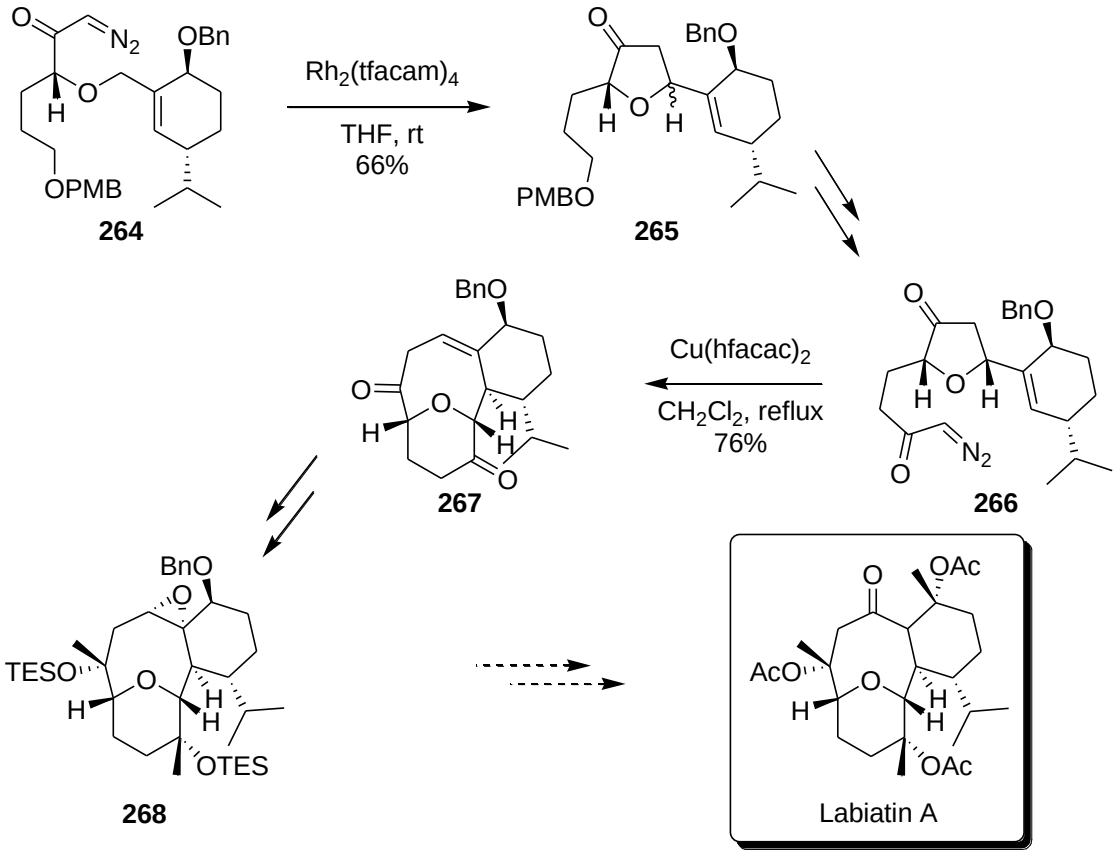
Metal carbenoid reactions have also been used for the synthesis of the core ring systems of complex terpenoids such as neoliacinic acid (**Scheme 51**).[78] The synthetic route involved two metal carbenoid transformations. First diazoketone **259** was treated with $Rh_2(tfacam)_4$ to promote C-H insertion, producing *cis*-tetrahydrofuran **260**. A few steps were required for the preparation of the second metal carbenoid precursor diazoketone **261**. This time copper(II) was

used to catalyse oxonium ylide formation and subsequent [2,3]-sigmatropic rearrangement, delivering the bridged bicyclic ether **262** in 69% yield as a 3:2 mixture of *Z*- and *E*-isomers. Further transformations afforded the late stage intermediate lactone **263**. Studies towards the total synthesis of neoliacinic acid are ongoing in the Clark group.



Scheme 51

The tricyclic core of the cladiellin labiatin A,[79] was synthesised using a similar approach (**Scheme 52**). Rhodium(II) catalysed C-H insertion of diazoketone **264** afforded tetrahydrofuran **265** in 66% yield as 7:1 *cis:trans* ratio. Diazoketone **266** was prepared in a few steps from **265**, before treatment with a copper(II)-catalyst induced oxonium ylide generation. The [2,3]-sigmatropic rearrangement with the cyclic alkene afforded, diastereoselectively, the tricyclic core **267** of labiatin A in 76% yield. Further transformations afforded the late stage epoxide **268**. Work is ongoing in the Clark group towards the completion of the synthesis of labiatin A.

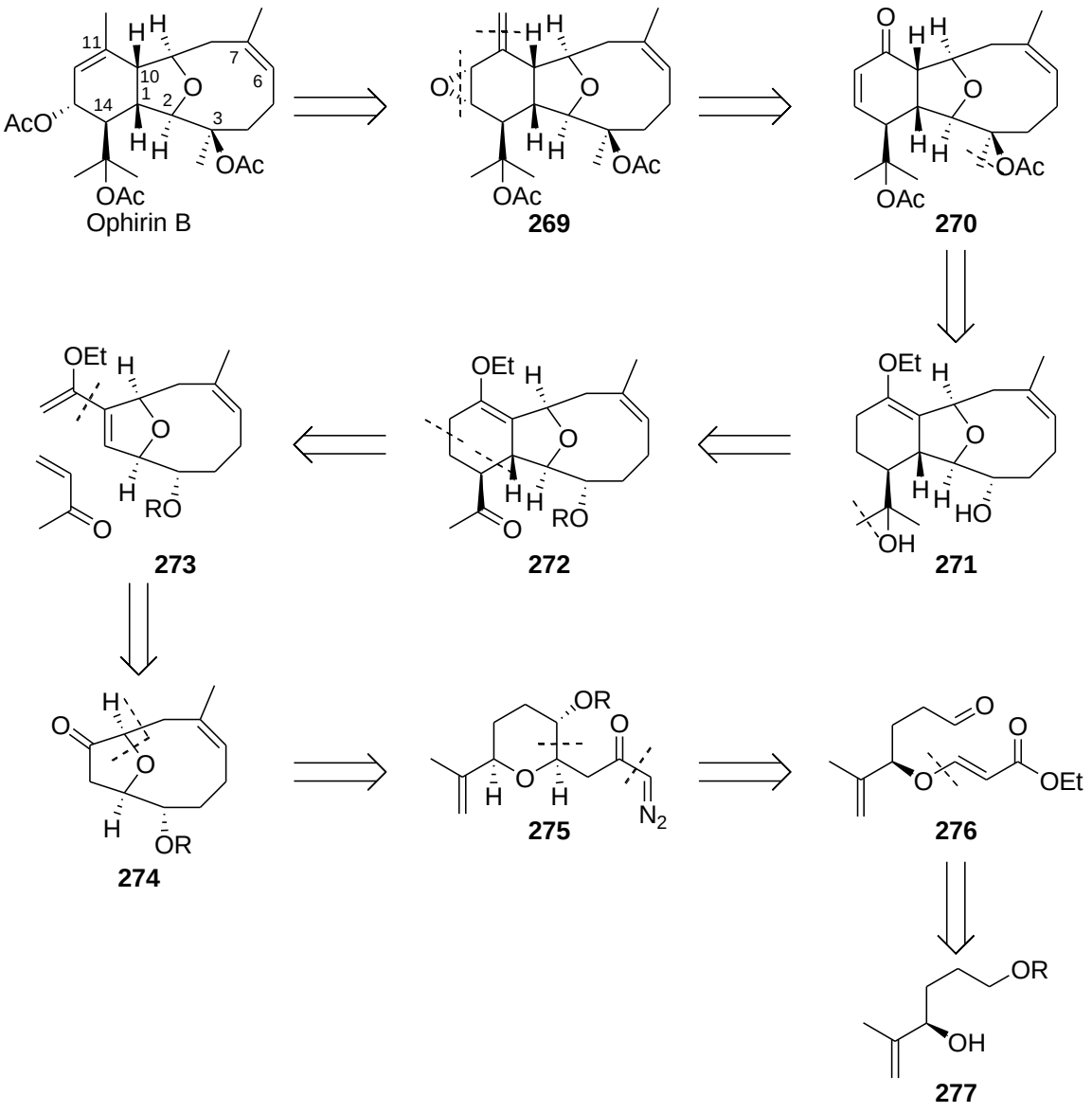


Scheme 52

1.5 Retrosynthetic Analysis

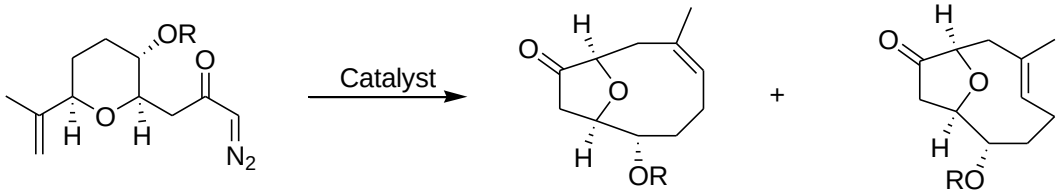
Following the success of the total synthesis of vigulariol, other members of the cladiellin family were identified as targets. First, the synthesis of a cladiellin bearing a *Z*-alkene within the medium-sized ring was designed. Our retrosynthetic analysis of ophirin B is shown in **Scheme 53**. Epoxide formation gives the compound **269**. Replacement of the methylene group with a carbonyl group, and removal of the epoxide affords the enone **270**. Reduction of the alkene, conversion of the carbonyl group into an enol ether gives diol **271**. Removal of the C-3 (cladiellin numbering) methyl group and Grignard disconnection of the hydroxypropyl group to give a methyl ketone afford the key intermediate **272.** The synthesis of an intermediate corresponding to synthon **272** had already been reported during the synthesis of the vigulariol. A Diels-Alder disconnection gives the bridged bicyclic diene **273** and methyl vinyl ketone. Conversion of the diene into a carbonyl group leads to the bicyclic ketone **274** which can be obtained from the diazo ketone **275**. Removal of the diazo group gives the tetrahydropyranyl ester which leads to the aldehyde **276**

by ring-opening. Further disconnection gives the allylic alcohol **277** as the starting material.



Scheme 53

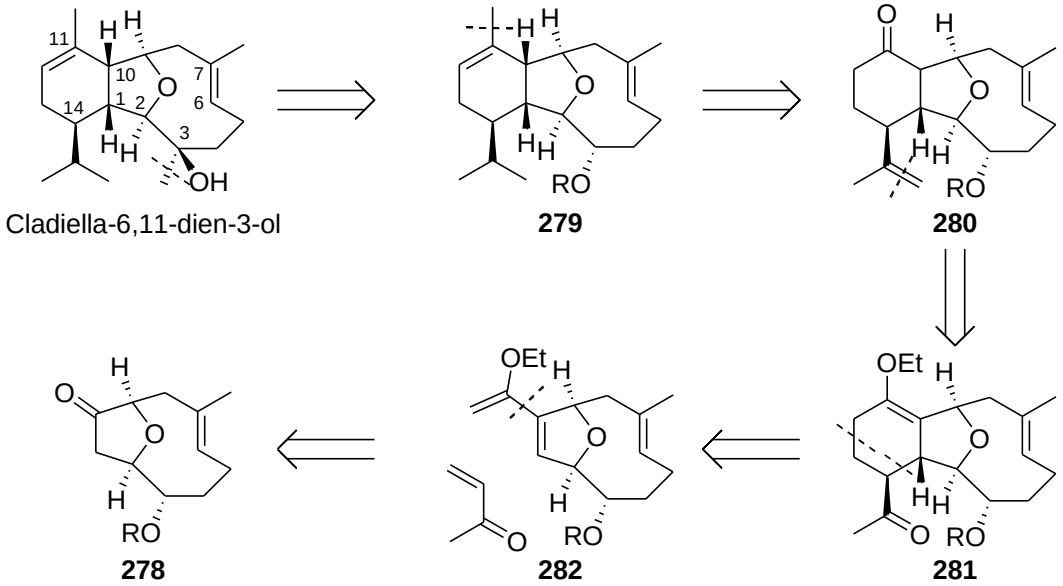
The tandem oxonium ylide formation [2,3]-sigmatropic rearrangement of diazoketone **275** (**Scheme 54**) is the key step of our synthetic route. Studies toward the selective formation of *E*-bicyclic ketone **278** will be undertaken in order to construct cladiellins possessing an *E*-alkene embedded in the medium-sized ring.



275 **274** **278**

Scheme 54

Cladiella-6,11-dien-3-ol was selected as our initial *E*-cladiellin target because Kim and co-workers had already shown that it can easily be transformed into more complex natural products.[31] Once again, we aimed to use the strategy developed for the synthesis of the vigulariol to obtain this product (**Scheme 55**). Removal of the C-3 (cladiellin numbering) methyl group gives **279**. Ketone formation and oxidation of the isopropyl group affords the alkene **280**. Conversion of the carbonyl group into an enol ether, and of the methylene into a methyl ketone gives **281**. Diels-Alder disconnection affords the bicyclic diene **282** and methyl vinyl ketone. Transformation of the diene unit into a carbonyl group gives the bicyclic ketone **278**. This ketone can be obtained from diazo ketone **275** an intermediate common to the synthesis of vigulariol and ophirin B.



Cladiella-6,11-dien-3-ol **279** **280**

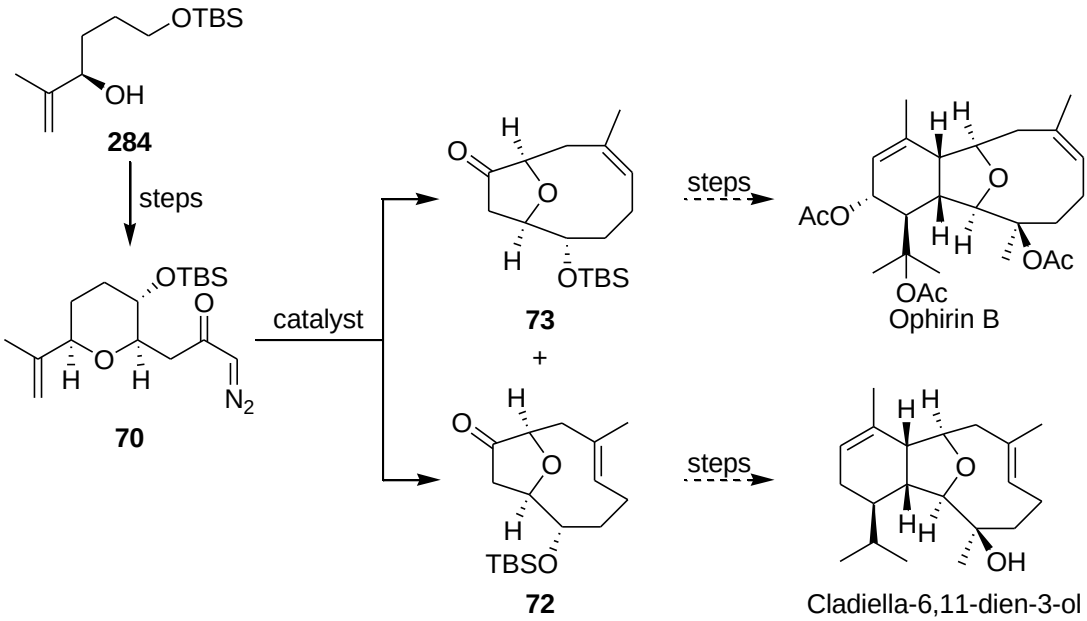
278 **282** **281**

Scheme 55

2 Results and Discussion

2.1 Introduction

Following the successful total synthesis of vigulariol, the synthesis of other members of the cladiellin family was proposed (**Scheme 56**). The first challenge was the development of an efficient enantioselective synthesis of the allylic alcohol **284**, a common intermediate in the synthesis of all our targets. Indeed, our proposed synthetic route was highly diastereoselective and the single stereocentre in **284** would control all the other stereocentres introduced during the synthesis. Our next challenge was to develop conditions for the oxonium ylide formation and subsequent [2,3]-sigmatropic rearrangement giving *E*-bicyclic ketone **72** in good yield and selectivity. The tricyclic core of the *Z*-cladiellins was already accessible using the route developed for the synthesis of vigulariol. The completion of the total synthesis of ophirin B would require functionalisation of the tricyclic core. The formation of the *E*-cladiellin core and its functionalisation was the aim of the second part of the project.

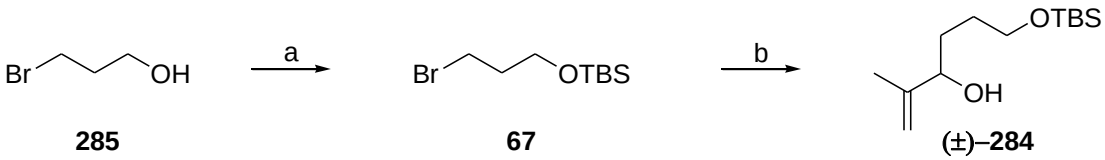


Scheme 56

2.2 Synthesis of the Bicyclic Ketones Intermediates 72 and 73

2.2.1 Synthesis of the Allylic Alcohol Precursor 284

Racemic allylic alcohol **(±)-284** was easily obtained in two steps (**Scheme 57**). First, protection of commercially available 3-bromopropan-1-ol **285** gave the TBS silyl ether **67**. Subsequent treatment with magnesium afforded the corresponding Grignard reagent, which was reacted with methacrolein to produce allylic alcohol **(±)-284**. The yield of this reaction was dependent on the number of equivalents of the Grignard reagent used. Optimised conditions required 2 equivalents of bromide **67** relative to methacrolein, and gave **(±)-284** in excellent 93% yield.

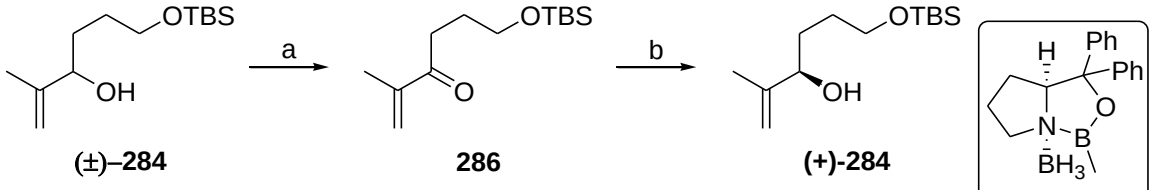


285 **67** **(±)–284**

a) TBSCl, DMAP, Et_3N, CH_2Cl_2, rt, 86%; b) i) Mg, I_2, THF, ii) methacrolein, THF, rt, 93%.

Scheme 57

Previous work in the Clark group has shown that the enantiopure allylic alcohol **(+)-284** could be obtained with 96% ee using the Corey-Bakshi-Shibata (CBS) reduction of the corresponding enone (**Scheme 58**).[80, 81] Manganese(IV) oxide oxidation of allylic alcohol **(±)-284** formed enone **286** in 78% yield, which was reduced using CBS-oxazaborolidine **287** to afford the allylic alcohol **(+)-284** in 86% yield. Good enantiomeric excesses were only obtained when 1.2 equivalents of high purity oxazaborolidine were used. Although this method delivered the allylic alcohol **(+)-284** with high selectivity, the fact that substantial quantities of a chiral reagent were required made this route too expensive to be used for the formation of very large quantities of the synthesis precursor.

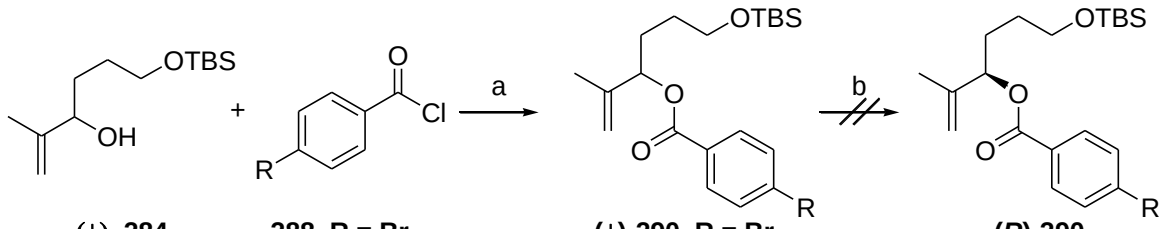


(±)–**284** **286** **(+)-284** **287**

a) MnO_2, CH_2Cl_2, rt, 78%; b) (*S*)-Me CBS•BH_3 **287**, THF, –78 °C, 86%, 96% ee.

Scheme 58

The search for an efficient, scalable and affordable route to the enantiopure allylic alcohol **(+)-284** started with the synthesis of the esters **290** and **291** (**Scheme 59**). It was thought that taking advantage of our industrial sponsor's supercritical fluid chromatography (SFC), the two enantiomers of esters **290** and **291** could be separated. It was hoped that the enantiopure esters would be crystalline, and that co-crystallisation with the racemic product would afford large quantities of enantiopure product. However, despite many attempts by the Merck's SFC specialist, esters **290** and **291** enantiomers could not be separated.



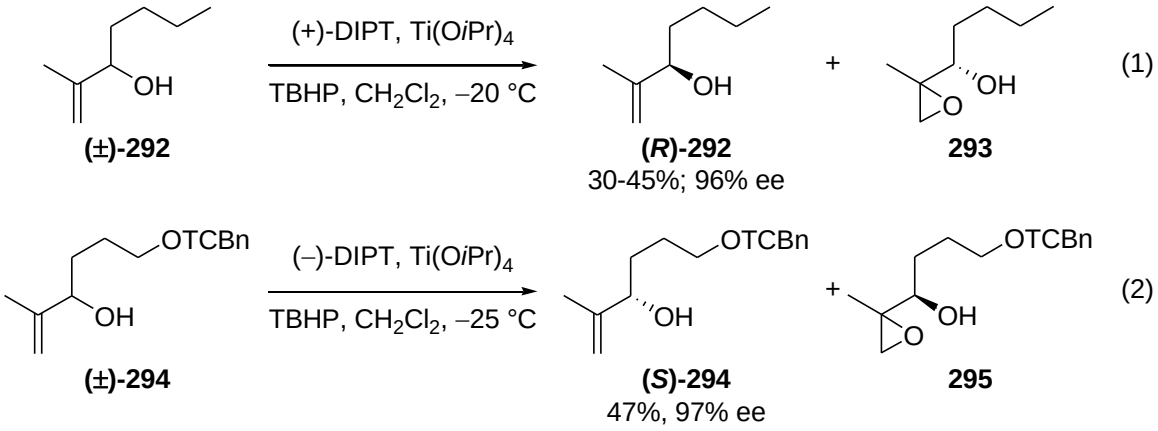
(±)–**284** **288, R = Br** **289, R = NO_2** **(±)-290, R = Br** **(±)-291, R = NO_2** **(*R*)-290** **(*R*)-291**

a) Et_3N, DMAP, CH_2Cl_2, rt, (**288**, 63%); (**289**, 17%); b) SFC separation.

Scheme 59

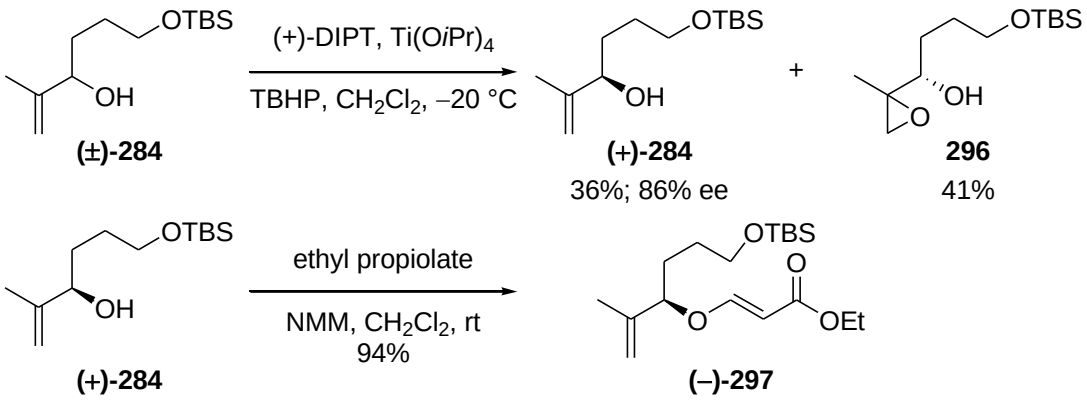
We then considered the kinetic resolution of racemic allylic alcohol **(±)-284**. First, the well established Sharpless kinetic resolution method was investigated.[82] This method, relies on the difference in reactivity towards epoxidation of the two enantiomers of a racemic allylic alcohol in the presence of a chiral tartrate. Sharpless and co-workers reported the kinetic resolution of **292**, a substrate similar to ours (**Scheme 60,** eq. 1). The *R*-enantiomer of allylic alcohol **(*R*)-292** was obtained in 96% ee when **(±)-292** was treated with (+)-diisopropyltartrate, titanium isopropoxide and *tert*-butyl hydroperoxide. More recently, Fujiwara and co-workers have used the Sharpless kinetic resolution on an almost identical substrate to ours **(±)-294** during their formal

synthesis of hemibrevetoxin B (eq. 2).[83] This time the (−)-diisopropyltartrate was used, delivering the *S*-allylic alcohol **(*S*)-294** in 97% ee.



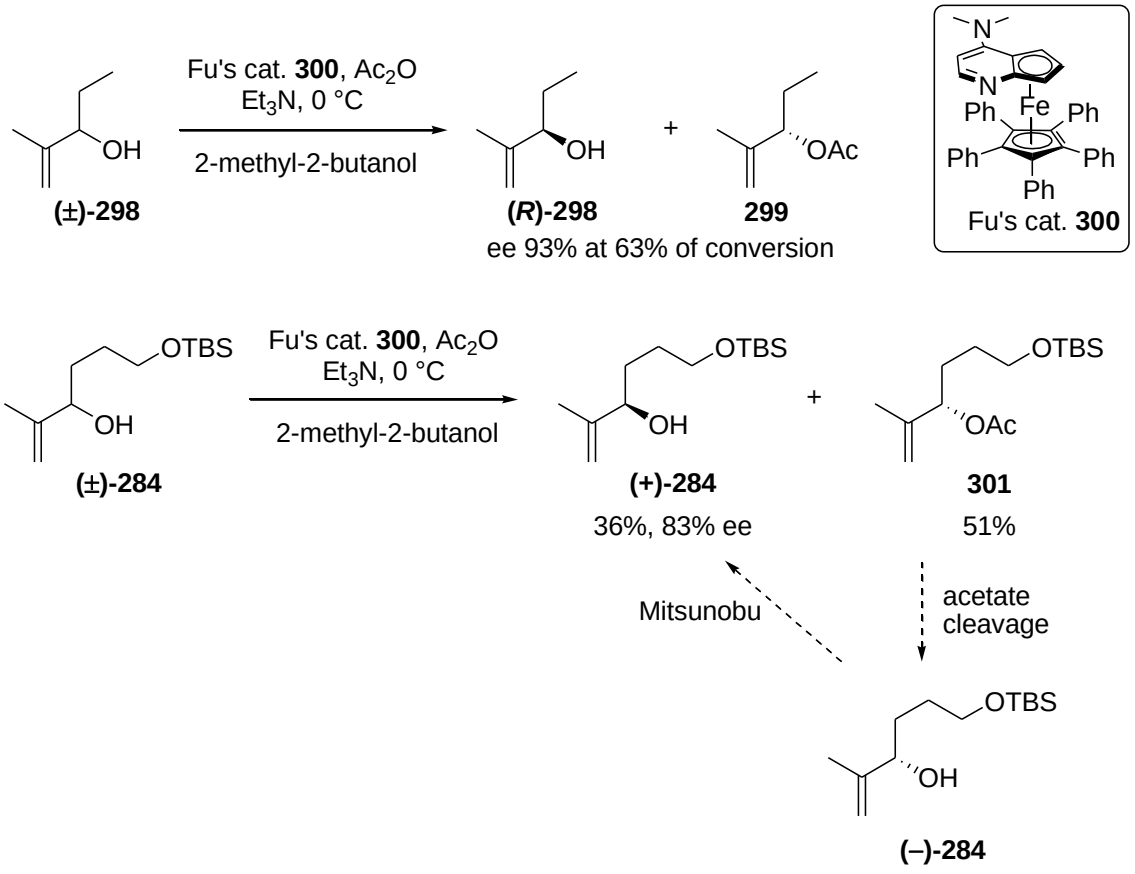
Scheme 60

The same conditions were applied to our substrate **(±)-284** (**Scheme 61**). (+)-Diisopropyl tartrate was used in order to obtain *R*-allylic alcohol **(+)-284**. The reaction was followed by NMR and quenched when it reached 60% conversion. On small scale (250 mg) the reaction afforded 41% yield of epoxy alcohol **296**, and the unreacted *R*-allylic alcohol **(+)-284** was recovered in 36% yield. The enantiomeric purity was assayed by normal phase chiral HPLC analysis[84] of the corresponding vinylogous carbonate **(−)-297**, obtained by treatment of **(+)-284** with ethyl propiolate and *N*-methylmorpholine. In this case material with an 86% enantiomeric excess was obtained. However, on larger scale (5 g) the reaction failed to deliver any epoxy alcohol **296**. This was explained by the fact that as reported by Sharpless, the reaction was carried out without stirring in the freezer at −20 °C.[82b] On large scale, the lack of stirring seemed to have a great impact on the reactivity.



Scheme 61

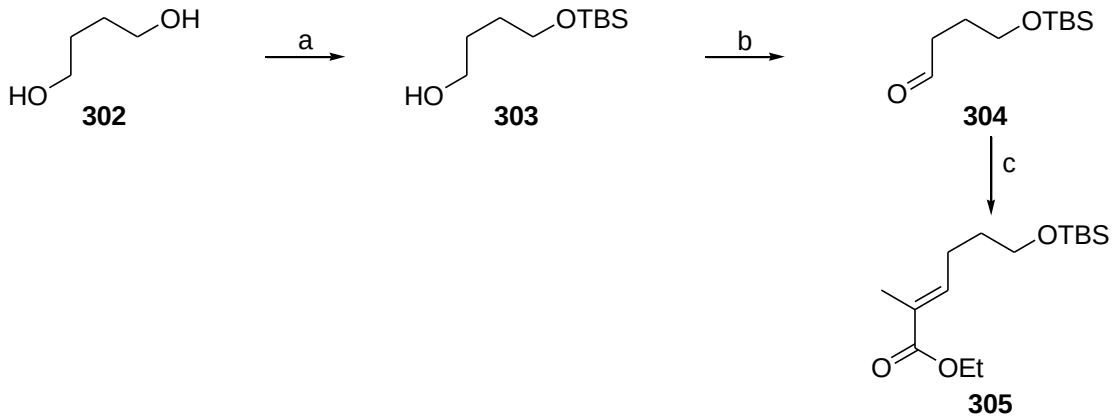
The second kinetic resolution protocol considered was developed by Fu and co-workers.[85] In this protocol a planar-chiral DMAP derivative **300** was used as an efficient catalyst for the kinetic resolution of racemic allylic alcohols *via* acetylation (**Scheme 62**). Fu and co-workers reported the kinetic resolution of allylic alcohol **(±)-298**, a similar substrate to ours, affording **(*R*)-298** with 93% ee. One of the advantages of this method is that the unwanted enantiomer is acetylated. In our case after separation of acetate **301** from unreacted allylic alcohol **(+)-284**, the ester should easily be cleaved revealing the unwanted enantiomer **(−)-284** of the allylic alcohol. Mitsunobu protocol would then be used to invert the configuration delivering more allylic alcohol **(+)-284**. However, applying Fu's conditions to our substrate afforded allylic alcohol **(+)-284** in 36% yield and with only 83% ee. Moreover, the drawback of this technique was the very slow reaction rate. On a small scale (120 mg) the reaction needed 12 days to reach the 60% of conversion needed. The slow reaction rate made this technique unsuitable for large scale synthesis of our enantiopure precursor **(+)-284**.



Scheme 62

Due to the poor results obtained with various kinetic resolution procedures another approach was considered. Williams and co-workers have reported the four-step synthesis of allylic alcohol **(+)-284** from 4-(tert-butyldimethylsilyloxy)butanal **304** in 61% overall yield and 97% ee.[86] This synthesis featured the introduction of the stereogenic centre in a highly enantioselective manner by Sharpless asymmetric epoxidation of an allylic alcohol. Repetition of the published synthesis had been attempted by a previous member of the Clark group. However, as no experimental procedures were available in the original paper,[86] the six-step synthesis of the allylic alcohol **(+)-284** from butandiol was performed in only 35% overall yield and gave the product with 85% ee.[80] Nevertheless, we thought that optimisation of the reaction conditions could afford the allylic alcohol **(+)-284** in both higher yield and enantiomeric excess.

Butandiol **302** was mono-protected, delivering the TBS ether **303** in 90% yield (**Scheme 63**). The remaining primary alcohol of **303** was oxidised using Swern conditions and the newly formed aldehyde **304** was immediately used in a Wittig olefination reaction with commercially available (carbethoxyethylidene) triphenylphosphorane delivering the *a*,ß-unsaturated ester **305** in 95% yield over two steps. For large scale synthesis the phosphorane was readily prepared from ethyl-2-bromopropionate and triphenylphosphine.[87]

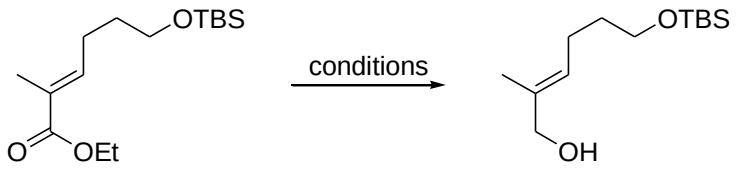


a) TBSCl, Et_3N, CH_2Cl_2, rt, 90%; b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –78 °C; c) $Ph_3PC(CH_3)COOEt$, THF, rt, 95% (2 steps).

Scheme 63

Following formation of the *a*,ß-unsaturated ester **305** in very good yield, synthesis of the Sharpless epoxidation precursor, allylic alcohol **306**, and its

subsequent epoxidation was investigated. The highest yield for the reduction of the ester **305** was obtained when the reaction was kept at −78 °C and only 2.5 equivalents of DIBAL-H were used (**Table 3**, entry 2).

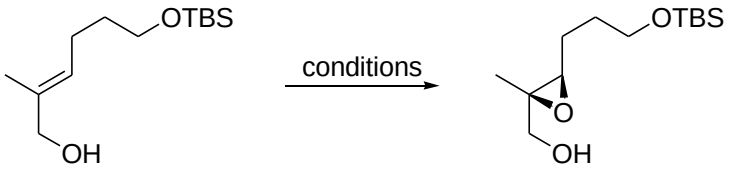


305 **306**

Entry	Conditions	Yield
1	3.0 eq DIBAL-H (1M in hexane), −78 °C to 0 °C	31%
2	2.5 eq DIBAL-H (1M in hexane), −78 °C	94%

Table 3

Various conditions were explored for the Sharpless enantioselective epoxidation (**Table 4**). Epoxide **(+)-307** was obtained in higher yield and ee when each reagent was used in low loading (entry 2). In order to determine the enantiomeric excess obtained with the different Sharpless conditions, the synthesis was continued up to the formation of the corresponding vinylogous carbonates **(−)-297** (**Scheme 61**). The carbonates **(−)-297** were then assayed as previously by normal phase chiral HPLC analysis.[84]



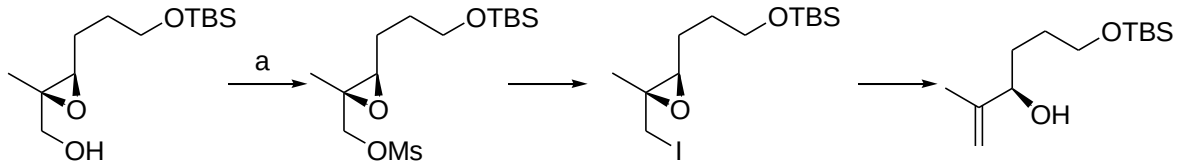
306 **(+)-307**

Entry	Conditions	Yield	ee
1[88]	20 mol% (−)-DET, 15 mol% Ti(O*i*Pr)$_4$, 2 eq TBHP (5.6 M in CH_2Cl_2), 4 Å MS, −20 °C	64%	93%
2[82b,89]	7.5 mol% (−)-DET, 5 mol% Ti(O*i*Pr)$_4$, 1.5 eq TBHP (5.6 M in CH_2Cl_2), 4 Å MS, −20 °C	95%	94%

Table 4

Epoxy alcohol **(+)-307** was then converted into the enantio-enriched allylic alcohol **(+)-284** (**Scheme 64**). Mesylation of the primary alcohol **(+)-307**

afforded the corresponding epoxy mesylate **308** which was immediately treated with sodium iodide to form the epoxy iodide **309** *in situ*. Addition of zinc powder formed an organometallic intermediate and opening of the epoxide delivered the corresponding allylic alcohol **(+)-284** in 97% yield.



(+)-307 **308** **309** **(+)-284**

a) i) MsCl, Et_3N, CH_2Cl_2, 0 °C; ii) NaI, Zn, butan-2-one, 80 °C, 97%.

Scheme 64

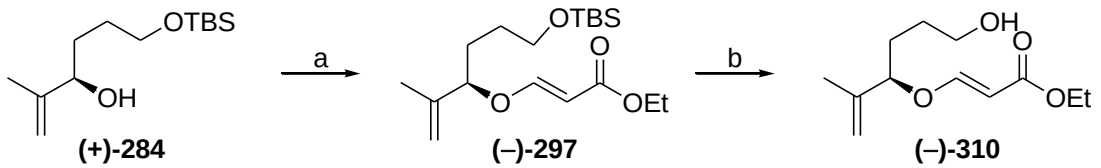
These optimised conditions gave access to enantioenriched allylic alcohol **(+)-284** with 94% ee and in sufficient quantities to continue the enantioselective synthesis of our target. All the chemicals used for the synthesis of **(+)-284** were affordable in large quantities. The scale-up of the synthesis was performed without problem in batches of 30 g delivering 90 g of allylic alcohol **(+)-284** with 94% ee and in 74% yield over the six steps.

In order to define a viable route for the synthesis of our natural product targets, primary work was carried out using racemic material. Most of the reactions were optimised using only racemic material. This will be emphasised in the following parts of this thesis by the (±) symbol before the molecule number. The enantioselective synthesis was then accomplished using the optimised synthetic route, all compounds prepared as single enantiomers will have their number preceded by the sign of their optical rotation.

2.2.2 Synthesis of the diazoketone 70

With allylic alcohol precursor **(+)-284** now available on large scale in both racemic and enantiopure form, the synthesis of diazoketone **(+)-70** was undertaken using the route developed for the synthesis of vigulariol. Allylic alcohol **(+)-284** was first alkylated with ethyl propiolate to produce the corresponding *E*-vinylogous carbonate **(−)-297** in 94% yield (**Scheme 65**).[90] Then

acidic cleavage of the silyl ether protecting group revealed primary alcohol **(−)-310**.

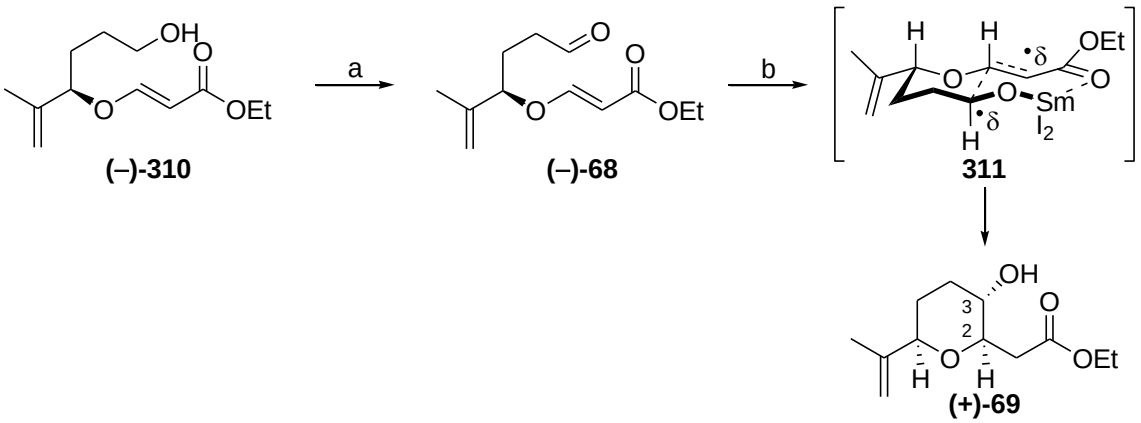


(+)-284 **(–)-297** **(–)-310**

a) ethyl propiolate, NMM, CH_2Cl_2, rt, 94%; b) CSA, MeOH, rt, 86%.

Scheme 65

Primary alcohol **(−)-310** was oxidised using Swern conditions to afford aldehyde **(−)-68** in 97% yield (**Scheme 66**). Then reductive cyclisation was realised using the conditions developed by Nakata and co-workers.[44, 91] Treatment of aldehyde **(−)-68** with freshly prepared SmI_2 and methanol afforded the tetrahydropyranol **(+)-69** in 86% yield. As previously reported, the tetrahydropyranol exhibited a 2,3 *trans* geometry confirmed by the large 9.2 Hz coupling constant between H-2 and H-3.



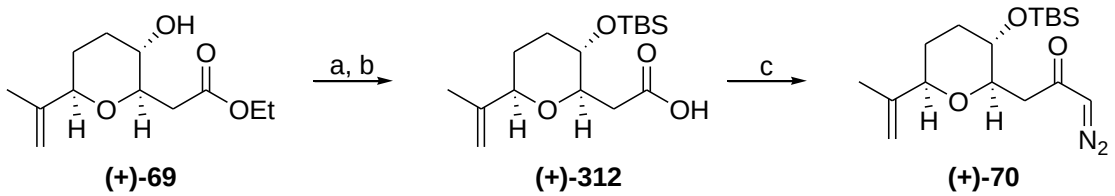
(–)-310 **(–)-68** **311** **(+)-69**

a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C, 97%; b) SmI_2, MeOH, THF, rt, 86%.

Scheme 66

Tetrahydropyranol **(+)-69** was protected as a TBS ether in 96% yield before lithium hydroxide mediated saponification formed carboxylic acid **(+)-312** in 89% yield (**Scheme 67**). Diazoketone formation was achieved *via* activation of the carboxylic acid as a mixed anhydride. Treatment of carboxylic acid **(+)-312** with *iso*butylchloroformate formed the mixed anhydride, which was added directly to a freshly prepared ethereal solution of diazomethane. A large excess (10 eq) of diazomethane was needed in order to obtain high yields. Batches of 100 mmol of

diazomethane were prepared from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald®) using macro Diazald apparatus.[92]



(+)-69 **(+)-312** **(+)-70**

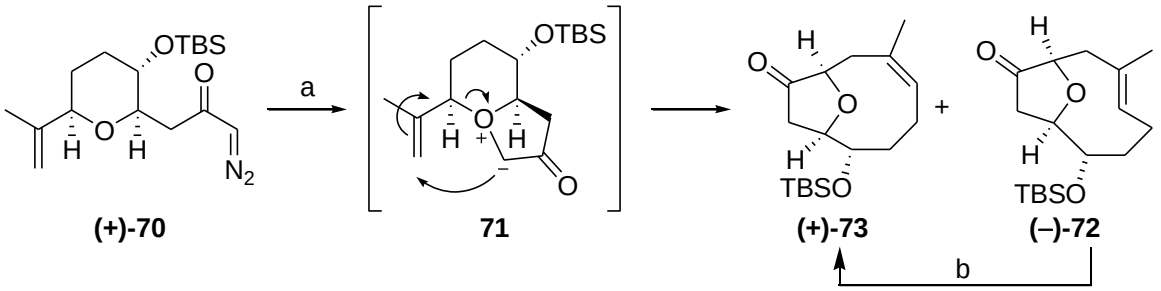
a) TBSCl, imidazole, DMF, rt, 96%; b) LiOH, EtOH:H_2O 3:1, rt, 89%; c) i) *i*-BuO_2CCl, Et_3N, Et_2O, rt; ii) CH_2N_2, Et_2O, 0 °C → rt, 88%.

Scheme 67

2.2.3 Studies on the Tandem Oxonium Ylide Formation and [2,3]-Sigmatropic Rearrangement

Diazoketone **(+)-70** is an important intermediate in our synthesis. It is the precursor of our key transformation: the oxonium ylide formation and subsequent [2,3]-sigmatropic rearrangement, and the point of divergence of the synthetic routes to the *E*- and *Z*-cladiellin natural product series.

Previous work has shown that treatment of diazoketone **(+)-70** with copper(II) hexafluoroacetylacetonate in CH_2Cl_2 at reflux delivered in 95% yield a mixture of bicyclic ketones **(+)-73** and **(−)-72** in a 5:1 ratio (**Scheme 68**). These two bicyclic ketones were separable using silica gel impregnated with 10% silver nitrate.[93] Moreover, the strained *E*-isomer **(−)-72** could be isomerised to the less strained *Z*-compound **(+)-73** using ethanethiol and AIBN. This technique allowed an efficient synthesis of *Z*-bicyclic ketone **(+)-73** used in the synthesis of *Z*-cladiellins such as vigulariol and ophirin B.



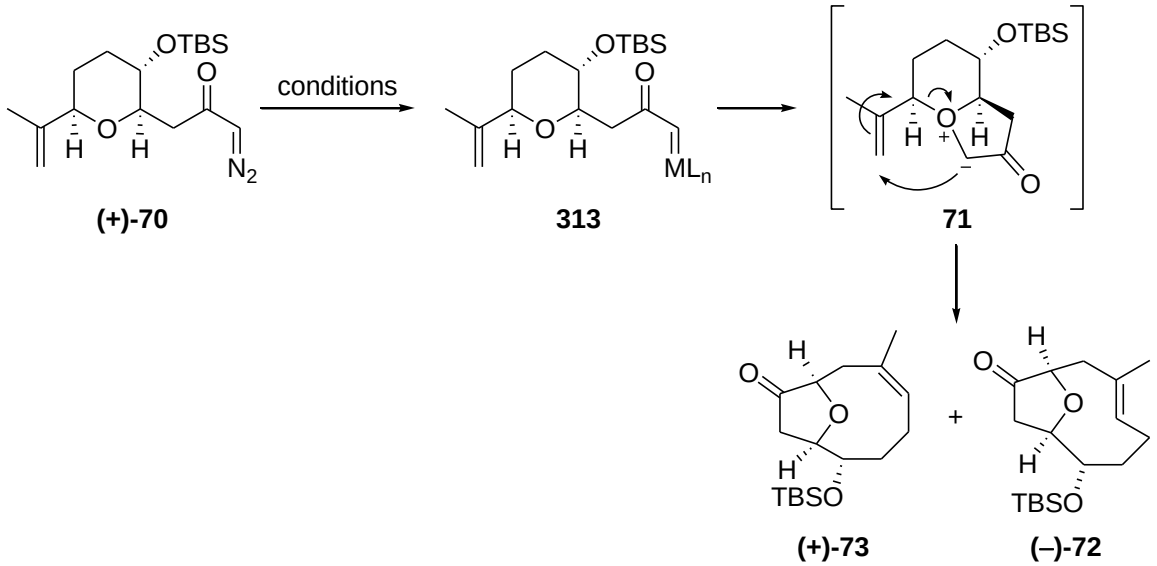
(+)-70 **71** **(+)-73** **(–)-72**

a) $Cu(hfacac)_2$, CH_2Cl_2, reflux, 95%, *Z*:*E* 5:1; b) AIBN, EtSH, PhH, reflux, 56%.

Scheme 68

However, in order to target the synthesis of the *E*-cladiellin natural products, conditions that delivered *E*-bicyclic ketone **(−)-72** selectively and in higher yields were needed. The oxonium ylide formation and subsequent rearrangement protocol is greatly influenced by the nature of the catalyst used, its ligands as well as the reaction temperature and solvent in which it is performed. Copper catalysts usually favour oxonium ylide formation over C-H insertion. In our case, conditions facilitating the formation of the strained *E*-bicyclic ketone **(−)-72** via oxonium ylide formation and subsequent [2,3]-sigmatropic rearrangement from diazoketone **(+)-70** were required.

Previous work in the Clark group has shown that $Cu(hfacac)_2$ was the metal of choice for the oxonium ylide formation and subsequent [2,3]-sigmatropic rearrangement from diazoketone **(+)-70**. It was also known that the solvent in which the reaction was performed had an influence on both the yield and the ratio of compounds **(−)-72** and **(+)-73** obtained (**Table 5**).[80] However no correlation could be made between the solvent polarity and the yield or product distribution of the reaction. Performing the reaction in refluxing THF (**Table 5**, entry 3) gave a higher proportion of the *Z*-bicyclic ketone **(+)-73** in a lower yield (74%) compared to that obtained when the reaction was performed in refluxing dichloromethane. All the solvents previously tested for the $Cu(hfacac)_2$ catalysed reaction gave preferentially the *Z*-isomer **(+)-73** in ratios ranging from 3.1:1 up to 6.9:1 and in good yield (entries 1 to 7). Temperature had little effect on the yield or the product distribution when dichloromethane was used as solvent, but increasing the temperature allowed a shorter reaction time (**Table 5**, entries 1, 6, 7). Finally, it was observed that switching from a copper to a rhodium catalyst resulted in a drop in yield to 52% (entry 8) and gave a nearly equimolar amount of bicyclic products **(−)-72** and **(+)-73**.



(+)-70 **313** **71** **(+)-73** **(–)-72**

Entry	Catalyst	Solvent	Temperature	Duration	Ratio *Z*:*E*	Yield
1	$Cu(hfacac)_2$	CH_2Cl_2	reflux	15 min	5.0:1	95%
2	$Cu(hfacac)_2$	DCE	reflux	15 min	3.9:1	85%
3	$Cu(hfacac)_2$	THF	reflux	45 min	6.9:1	74%
4	$Cu(hfacac)_2$	Et_2O	reflux	15 min	3.1:1	93%
5	$Cu(hfacac)_2$	benzene	reflux	30 min	4.8:1	94%
6	$Cu(hfacac)_2$	CH_2Cl_2	rt	3 h	5.9:1	94%
7	$Cu(hfacac)_2$	CH_2Cl_2	0°C	7 h	5.5:1	96%
8	$Rh_2(OAc)_4$	CH_2Cl_2	reflux	1 h	1.2:1	52%

Table 5[80]

In the light of these preliminary results, it was decided to screen more polar solvent systems for $Cu(hfacac)_2$ catalysed reactions (**Table 6**). These tests were performed on racemic material in order to save valuable enantiopure material. When using acetonitrile at reflux a nearly equimolar mixture of **72** and **73** was obtained in a poor yield (entry 1). Adding water to the solvent mixture lowered the yield even further (entry 2). The use of a 19:1 mixture of acetonitrile:water gave, for the first time, a ratio slightly favouring the *E*-bicyclic ketone **72** (*Z*:*E* 1:1.2) in a poor yield (entry 3). The reaction performed in DMF gave a 4.2:1 mixture favouring the *Z*-bicyclic ketone **73** in poor yield (entry 4). It was then thought that complexing the copper catalyst with pyridine would change its catalytic sphere and this could increase the ratio of the *E*-isomer **72**. However, the addition of pyridine to the reaction mixture did not have the desired effect;

bicyclic ketone **72** and **73** were obtained in good yield but the *Z*-product **72** was obtained preferentially (entries 5 and 6).

Entry	Catalyst[a]	Solvent	Temperature	Duration	Ratio *Z*:*E*[b]	Yield[c]
1	$Cu(hfacac)_2$	MeCN	reflux	1 h	1.2:1	27%
2	$Cu(hfacac)_2$	MeCN:H_2O 9:1	reflux	1 h	2.6:1	9%
3	$Cu(hfacac)_2$	MeCN:H_2O 19:1	reflux	1 h	1:1.2	23%
4	$Cu(hfacac)_2$	DMF	40 °C	1 h	4.2:1	18%
5	$Cu(hfacac)_2$ + pyridine (3 mol%)	DCM	reflux	20 min	4.3:1	78%
6	$Cu(hfacac)_2$ + pyridine (10 mol%)	DCM	reflux	40 min	3.0:1	94%

[a] catalyst loading 5 mol%; [b] determined by NMR; [c] yield of the mixture

Table 6

Our failure to identify suitable conditions for the copper catalysed synthesis of the *E*-bicyclic ketone **72**, led us to expand the scope of our study to include rhodium catalysts. Indeed, preliminary results had shown that refluxing diazoketone **70** and catalytic quantities of rhodium acetate in dichloromethane delivered a nearly equimolar mixture of products **72** and **73** in 52% yield (**Table 5**, entry 8).[80] Moreover, rhodium(II) complexes would provide additional opportunities to tune the reaction to deliver the *E*-isomer **72**, by varying the steric and electronic characteristics of the ligands. Five different rhodium catalysts were screened using dichloromethane at reflux as the standard conditions (**Figure 15, Table 7**). Rhodium(II) trifluoroacetate [$Rh_2(tfa)_4$] gave bicyclic ketones **72** and **73** in a good 90% yield and a ratio (*Z*:*E* 1.7:1) slightly in favour of the *Z*-isomer (entry 1), while rhodium(II) trifluoroacetamide[94] [$Rh_2(tfacam)_4$] gave a ratio which was very slightly in favour of the *E*-bicyclic ketone **72** (*Z*:*E* 1:1.2) in 63% yield (entry 2). When the reaction was carried out with rhodium(II) caprolactamate [$Rh_2(cap)_4$] neither bicyclic ketone **72** nor **73** were obtained (entry 3). More promising results were obtained with rhodium(II)

perfluorobutyrate[95] [$Rh_2(pfm)_4$] and rhodium(II) triphenylacetate[96] [$Rh_2(tpa)_4$] (entries 4, 5). These catalysts delivered moderate yields of mixtures of products **72** and **73** with 1:2.7 and 1:4.3 *Z*:*E* ratios in favour of the *E*-isomer.

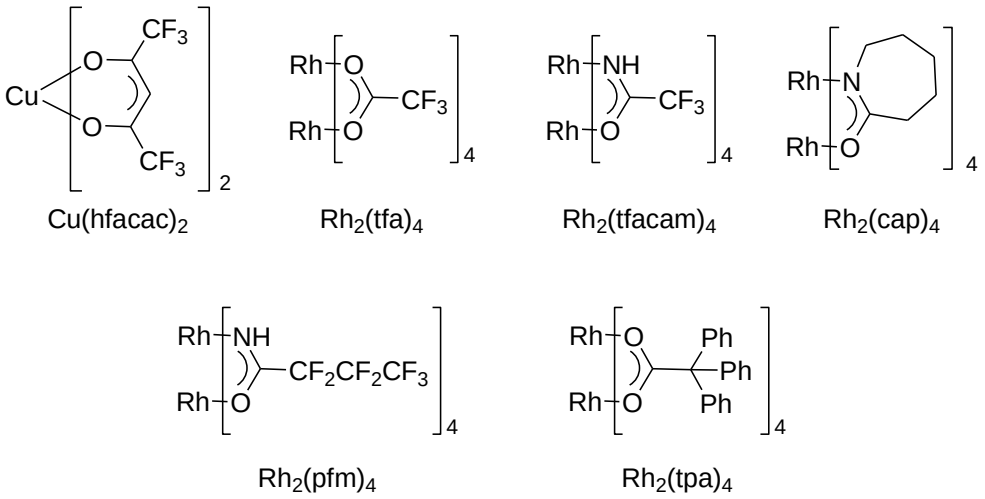


Figure 15

Entry	Catalyst[a]	Solvent	Temperature	Duration	Ratio *Z*:*E*[b]	Yield[c]
1	$Rh_2(tfa)_4$	CH_2Cl_2	reflux	25 min	1.7:1	90%
2	$Rh_2(tfacam)_4$	CH_2Cl_2	reflux	15 min	1:1.2	63%
3	$Rh_2(cap)_4$	CH_2Cl_2	reflux	15 min	-	-
4	$Rh_2(pfm)_4$	CH_2Cl_2	reflux	15 min	1:2.7	71%
5	$Rh_2(tpa)_4$	CH_2Cl_2	reflux	15 min	1:4.3	63%

[a] catalyst loading 5 mol%; [b] determined by NMR; [c] yield of the mixture

Table 7

Early results obtained with rhodium(II) perfluorobutyrate and rhodium(II) triphenylacetate were very promising and these two catalysts were selected for further investigation (**Table 8**). First, the reactions were carried out in dichloromethane at room temperature. This time the temperature at which the reaction was performed had an influence on both the yield and the product distribution. For the two catalysts nearly equal amounts of each isomer were obtained in modest yield (entries 1, 2). Switching the solvent to THF did not improve the *Z*:*E* ratio. Using rhodium(II) perfluorobutyrate in THF at reflux gave a relatively good yield (74%) of the mixture with a 1:1.7 *Z*:*E* ratio (entry 3), but performing the reaction at room temperature considerably decreased the yield

(entry 4). The rhodium(II) triphenylacetate catalysed reaction delivered the same 1:2.7 *Z*:*E* ratio when performed in THF at reflux as when carried out in dichloromethane at reflux, but in a lower yield (45%) (entry 5). The reaction was sluggish and low yielding when performed at room temperature in THF (entry 6). It was noticeable that the best *E*-selectivities were obtained when the reactions were performed at reflux. We decided to test 1,2-dichloroethane (DCE) as solvent as it displays similar solvent properties to dichloromethane but has a higher boiling point. We wanted to determine if increasing the temperature would increase the ratio to favour the *E* isomer. The use of 1,2-dichloroethane as a higher boiling point version of dichromethane did not produce the desired effect on the rhodium(II) perfluorobutyrate catalysed reaction (entry 7). It lowered both the yield and the selectivity of the reaction for the formation of the *E*-isomer. However, the highest *E*-selectivity was obtained when rhodium(II) triphenylacetate was used in 1,2-dichloroethane at reflux (entry 8). This gave a 1:6.3 selectivity in favour of the desired *E*-bicyclic ketone **72** in 56% yield.

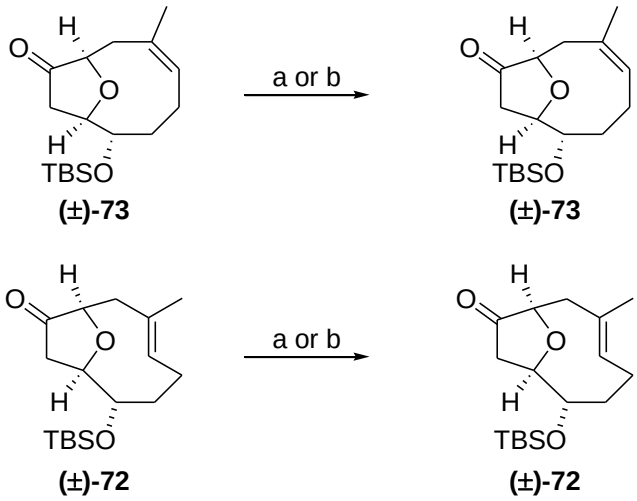
Entry	Catalyst[a]	Solvent	Temperature	Duration	Ratio *Z*:*E*[b]	Yield[c]
1	$Rh_2(pfm)_4$	CH_2Cl_2	rt	30 min	1.5:1	36%
2	$Rh_2(tpa)_4$	CH_2Cl_2	rt	1 h	1:1.8	49%
3	$Rh_2(pfm)_4$	THF	reflux	15 min	1:1.7	74%
4	$Rh_2(pfm)_4$	THF	rt	30 min	1:1.1	19%
5	$Rh_2(tpa)_4$	THF	reflux	15 min	1:2.7	45%
6	$Rh_2(tpa)_4$	THF	rt	18 h	1.4:1	32%
7	$Rh_2(pfm)_4$	DCE	reflux	15 min	1:1.4	66%
8	$Rh_2(tpa)_4$	DCE	reflux	15 min	1:6.3	56%

[a] catalyst loading 5 mol%; [b] determined by NMR; [c] yield of the mixture

Table 8

The screening of different catalysts, solvents and temperatures has enabled us to identify reaction conditions that favour formation of the *E*-bicyclic ketone **72** which is needed for the synthesis of the *E*-cladiellins. However, we were not able to correlate the solvent polarity and reaction temperature to the product distribution or the yield of the reaction. The fact that the change in catalyst produced such drastic changes in the reactivity seems to suggest that the

reaction proceeds through a metal bounded ylide intermediate rather than a free ylide. In order to prove that the [2,3]-sigmatropic process was irreversible and that the *E*-selectivity was not due to product isomerisation, control reactions were carried out (**Scheme 69**). Each of the bicyclic ketones was heated at reflux in dichloromethane in presence of the catalysts $Cu(hfacac)_2$ or $Rh_2(tpa)_4$ for two hours. In all the four cases, the starting material was recovered unchanged, no isomerisation of the double bound was observed. This proved that the [2,3]-sigmatropic rearrangement of the oxonium ylide is an irreversible process and that the rhodium- and copper-catalysts are not able to change the configuration of the double bond after rearrangement has taken place. Given that the [2,3]-sigmatropic rearrangement reaction is irreversible the different isomers observed must arise from different oxonium ylide configurations or from differing transition states.

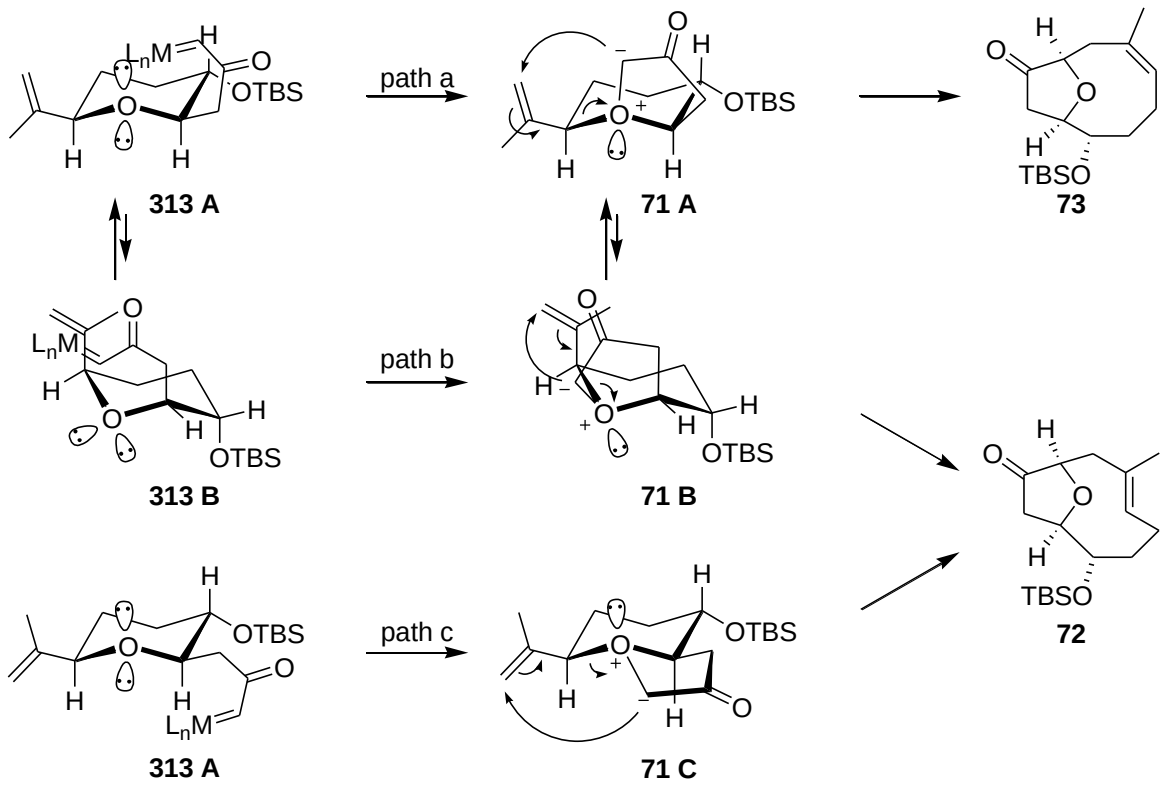


a) $Cu(hfacac)_2$, CH_2Cl_2, reflux, quant; a) $Rh_2(tpa)_4$, CH_2Cl_2, reflux, quant.

Scheme 69

In order to explain how the different isomers are formed, we need to look at the various metal carbenoid conformers (**Scheme 70**). The more stable conformer **313 A** has all its substituents in equatorial positions, whereas less stable conformer **313 B** has all its substituents in axial positions. From metal carbenoid conformer **313 A** the formation of the oxonium ylide should process preferentially *via* path a, since the reaction with the "axial" lone pair of the oxygen should be easier and form a less strained five-membered ring compared to path c, where the reaction with the equatorial lone pair gives a more strained

five-membered ring. [2,3]-Sigmatropic rearrangement of oxonium ylide **71 A** should give the *Z*-bicyclic ketone **73** whereas [2,3]-sigmatropic rearrangement of oxonium ylide **71 C** would form the *E*-bicyclic ketone **72**. The less stable metal carbenoid conformer **313 B** should form the oxonium ylide conformer **71 B** *via* path b. Conformer **71 B** would then undergo the [2,3]-sigmatropic rearrangement to give the *E*-bicyclic ketone **72**. Ongoing computational calculation of the energy of the different oxonium ylide conformers **71 A**, **B**, **C** have shown that the difference in energy between them is rather small, only around 22 kJmol^{-1}.[97] This means that all conformers should exist in equilibrium and transition states of the [2,3]-sigmatropic rearrangement need to be considered in order to understand the reaction outcome. The results obtained have shown that catalyst, solvent and temperature have a significant influence on the formation of the bicyclic ketones which cannot be explained by this "free" oxonium ylide representation. This finding tends to support the metal-bound ylide intermediate hypothesis.

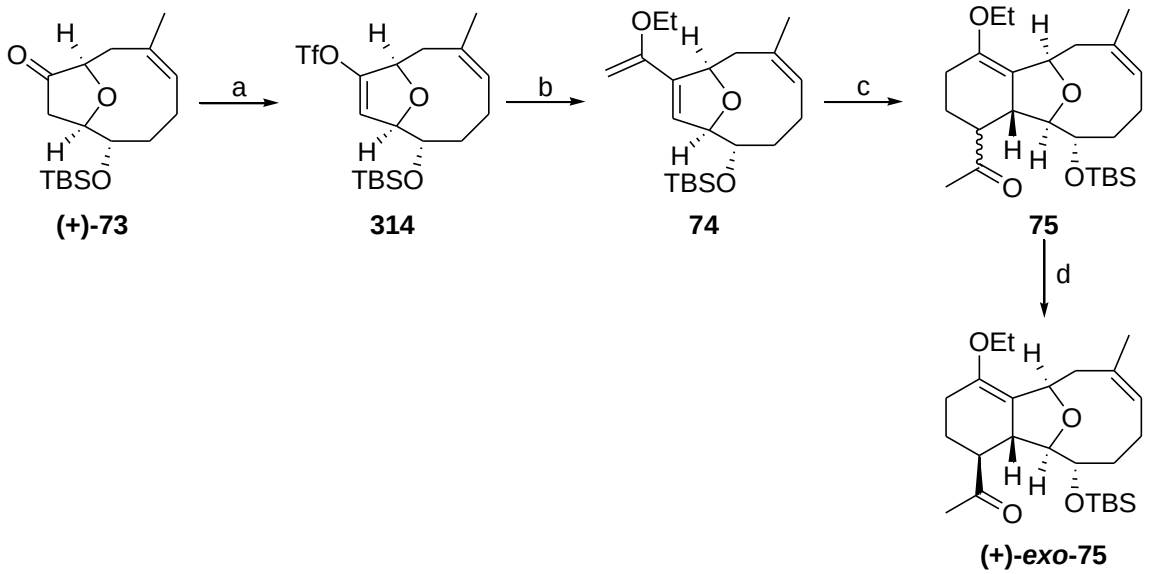


Scheme 70

2.3 Studies Towards the Synthesis of Ophirin B

2.3.1 Results

With the *Z*-bicyclic ketone **(+)-73** formed, the synthesis of the tricylic core of the *Z*-cladiellins was undertaken. As developed in the synthesis of vigulariol, the cladiellin skeleton was built in three steps (**Scheme 71**). First the enol triflate **314** was formed from ketone **(+)-73**. It was then used in a Stille cross-coupling with tributyl(1-ethoxyvinyl)tin to deliver the unstable diene **74**.[98] The diene **74** was immediately used in a thermal Diels-Alder cycloaddition with methyl vinyl ketone to yield the tricyclic core of the *Z*-cladiellin **75** as a 2:1 *exo*:*endo* mixture. Optimised conditions enabled the formation of tricycle ketone **75** in 69% yield over three steps. Base-induced epimerisation of the mixture of *endo* and *exo* isomers with potassium carbonate provided the more stable *exo*-product **(+)-*exo*-75**, having the methyl ketone group in the equatorial position.



(+)-73 **314** **74** **75** **(+)-*exo*-75**

a) NaHMDS, $PhN(Tf)_2$, THF, −78 °C; b) $CH_2C(OEt)SnBu_3$, $Pd(PPh_3)_4$, LiCl, THF, reflux; c) $CH_2CHCOCH_3$, toluene, reflux, 69% (3 steps) 2:1 *exo*:*endo*; d) K_2CO_3, MeOH, rt, 91%.

Scheme 71

The Diels-Alder cycloaddition reaction is thought to proceed *via* transition states **315** and **316** (**Figure 16**). The cycloaddition reaction proceeded with complete regioselectivity and facial selectivity on the diene component. High regioselectivity resulted from the matched electronics of the electron-rich

alkoxy diene and the electron-deficient dienophile. The diene facial selectivity resulted from the bowl shaped conformation adopted by the molecule blocking the top face of the diene. Cycloaddition was carried out using a large excess of methyl vinyl ketone. As thermal activation was needed and methyl vinyl ketone is volatile, reactions were performed in sealed tubes. Optimisation of the reaction conditions revealed that tricyclic product **75** was obtained in higher yield when the reaction was executed at relatively low concentration (0.025 $molL^{-1}$). In cases were higher concentrations were used, uncharacterised sides products were obtained leading to a decrease in the yield of the reaction.

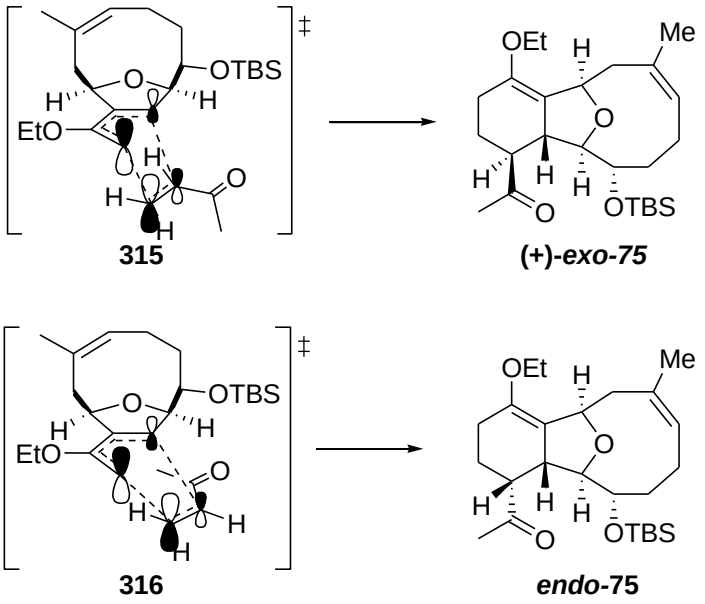
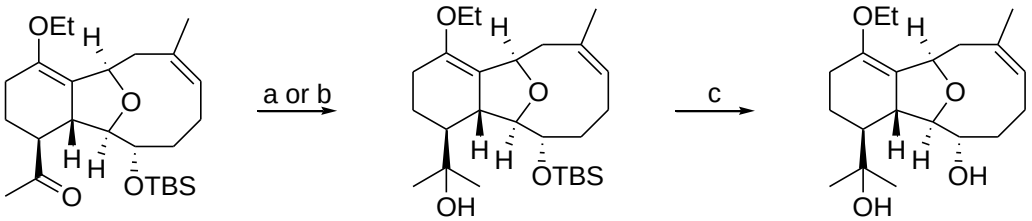


Figure 16

Tricyclic ketone **(+)-exo-75** corresponds to the point of divergence between the synthesis of vigulariol and the route towards ophirin B. With the tricylic skeleton of the cladiellin formed all that remained was functional group manipulations around the molecule. Our first goal was to form the two tertiary alcohols present on ophirin B as tertiary acetates. Initially, the ketone was methylated to deliver the first tertiary alcohol **(+)-317** (**Scheme 72**). Various alkylation reagents were tested and the best yield was obtained by Grignard addition of methyl magnesium chloride. Cleavage of the TBS ether proceeded smoothly revealing the diol **(+)-271** in 91% yield.

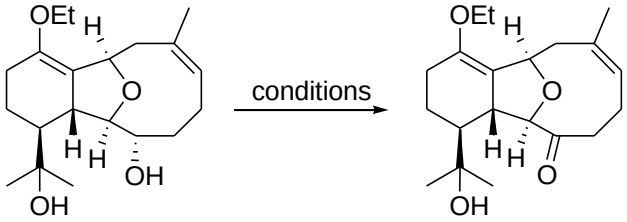


(+)-*exo*-75 **(+)-317** **(+)-271**

a) MeLi, THF, −78 °C, 47%; b) MeMgCl, THF, 0 °C → rt, 84%; c) TBAF, 4Å MS, THF, rt, 91%.

Scheme 72

Secondary alcohol **(±)-271** was then oxidised to form the cyclic ketone **(±)-319**. Different oxidation procedures were tested, but unfortunately all of them afforded the ketone **(±)-319** in poor yield due to its instability (**Table 9**).

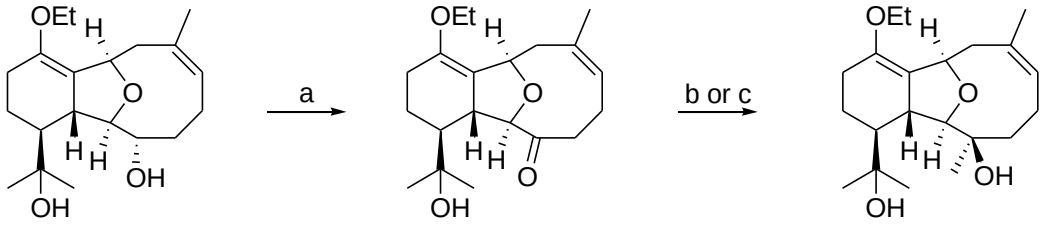


(±)-271 **(±)-319**

Method	Conditions	Outcome / Yield
Swern[99]	$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C	Decomposition
Parikh-Doering[100]	SO_3 pyridine complex, DMSO, DIPEA, CH_2Cl_2, 0 °C	56%; 92% brsm
Dess-Martin[101]	DMP, pyridine, CH_2Cl_2, rt	47%

Table 9

In order to avoid decomposition of ketone **319** the decision was taken to use the crude material directly in the next step (**Scheme 73**). Dess-Martin oxidation immediately followed by Grignard addition with methyl magnesium chloride afforded the diol **(+)-320** in 54% over two steps. The successful use of methyl lithium in presence of sodium tetrafluoroborate for the introduction of the C-3 methyl group had been reported by Paquette[23] and Kim[31] on similar cladiellin systems. However, in our case this protocol gave inferior yields.

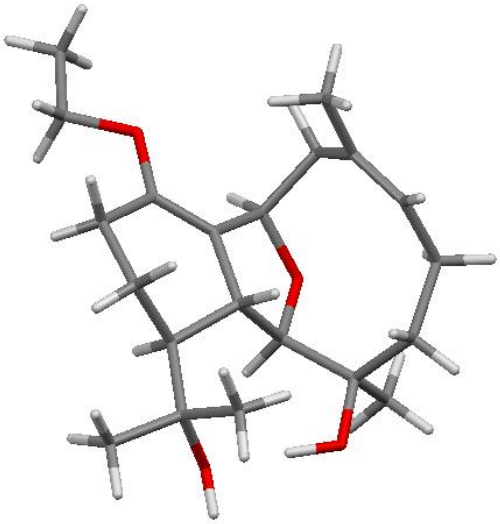


(+)-271 **319** **(+)-320**

a) DMP, pyridine, CH_2Cl_2, rt; b) MeLi, $NaBF_4$, THF, −78°C, 24% (2 steps); c) MeMgCl, THF, 0 °C → rt, 54% (2 steps).

Scheme 73

The addition of the methyl group was diasteroselective with attack of the ketone from the under face of the molecule as drawn. This was due once again to the bowl shape of the cladiellin skeleton forcing nucleophilic to attack from the convex face of the molecule. Diol **(±)-320** was a crystalline solid and X-ray crystallography confirmed the relative configuration of the stereogenic centres in the molecule (**Figure 17**).

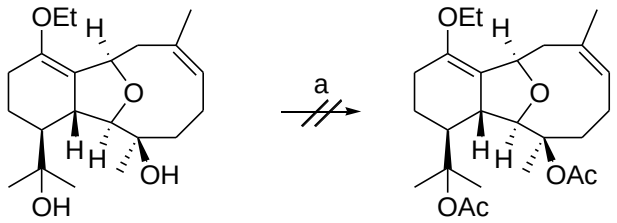


(±)-320

Figure 17

The synthesis of the diol **(+)-320** meant that our next goal was the protection of the two tertiary alcohols as acetates. In his synthesis of ophirin B, Crimmins[26] reported that the bis-acetylation of these two alcohols was problematic. It required a three-step procedure of acetylation, acetate migration and second acetylation (**Scheme 12**). In order to avoid such a problem at the end of our synthesis, we decided to acetylate the alcohols early in the synthesis. To

achieve this difficult bis-acetylation DMAP catalysed, base and solvent-free conditions were tested (**Scheme 74**).[102] However, when the reaction was performed at room temperature, only the starting material **(+)-320** was recovered. Attempts to increase the reactivity by raising the temperature to 60 °C only caused decomposition of the starting material.



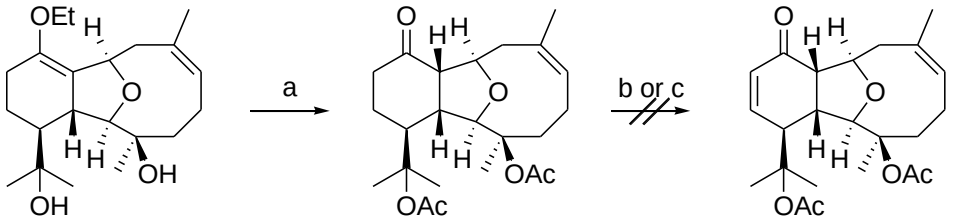
(+)-320 **321**

a) Ac_2O, DMAP, rt or 60 °C.

Scheme 74

Crimmins and co-workers recently reported the synthesis of the proposed structure of briarellin J.[103] This synthesis features the use of isopropenyl acetate as acetylation agent for the formation of the acetate of a hindered tertiary alcohol. This reaction was promoted by *p*-toluenesulfonic acid (*p*-TSA) and has been used generally for the acetylation of tertiary alcohols.[104] Using this protocol with our system would allow us to cleave the enol ether and protect the two hydroxyl groups in one step. Bis-acetate **(+)-322** was formed in 59% yield by stirring diol **(+)-320** with *p*-TSA in isopropenyl acetate as solvent (**Scheme 75**).

With the bis-acetate in place, our next goal was the formation of enone **270**. Nicolaou and co-workers have developed an efficient IBX-mediated reaction for the oxidation of a ketone to give an enone.[105] It was reported that this protocol could be used to oxidise cyclohexanones. However, treatment of ketone **(+)-322** with IBX alone or complexed with 4-picoline *N*-oxide, as reported by Nicolaou, did not yield the required enone **270.** Only the ketone starting material **(+)-322** was recovered in both cases.



(+)-320 **(+)-322** **270**

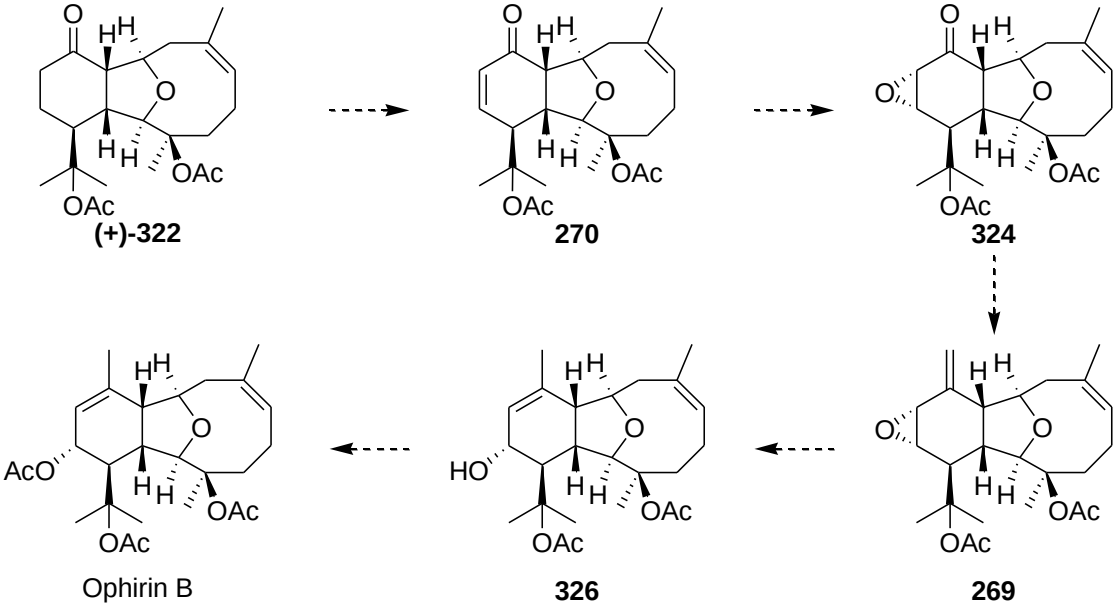
a) isopropenyl acetate, *p*-TSA, rt, 59%; b) IBX, toluene:DMSO 2:1, 65 °C; c) IBX, 4-picoline *N*-oxide, DMSO, 70 °C.

Scheme 75

In the light of the good results that had been obtained during the development of the tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement reaction, and the difficulty encountered for the formation of enone **270**, it was decided to focus our effort on the synthesis of members of the *E*-cladiellin series. Indeed, the development of an efficient synthesis of the *E*-bicyclic ketone **(−)-72** allowed us to target those cladiellins featuring a *E*-alkene or *trans*-1,2-diol on the medium-sized ring. This opened to us a wide range of new possible targets. Moreover only Kim and co-workers have reported a general strategy that can be applied to the synthesis of both *E*- and *Z*-cladiellins and we were keen to demonstrate that our strategy offered the same flexibility.

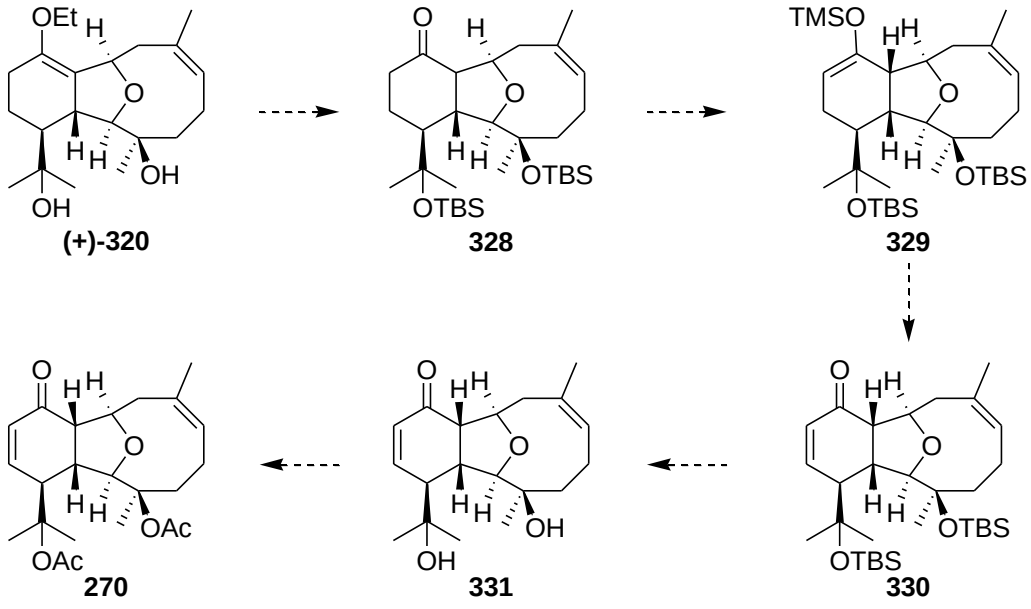
2.3.2 Future Work for the Completion of the Synthesis of Ophirin B

Only five steps remain for the completion of the synthesis of ophirin B (**Scheme 76**). First, conditions would need to be identified to allow the formation of enone **270** from ketone **(+)-322**. Increasing the temperature of the reaction or using microwave activation could provide a solution to the problem of the poor reactivity of IBX. Epoxidation of the enone should deliver epoxy ketone **324**. This epoxidation should be diasteroselective due to the bowl shape of the molecule. Subsequent Wittig methylenation and partial reduction of the resulting alkene **269** using PtO_2/H_2 should give allylic alcohol **326**. Simple acetylation would then deliver ophirin B.



Scheme 76

If conditions for the oxidation for ketone **(+)-322** to enone **270** cannot be found, an alternative route to enone **270** will have to be considered (**Scheme 77**). Starting from diol **(+)-320** bis-TBS protection and subsequent acidic cleavage of the enol ether would form ketone **328**. Then a Saegusa-Ito oxidation should deliver enone **330**.[106] Removal of the TBS-protecting groups and bis-acetylation of the tertiary alcohols should form enone **270**. This synthesis of enone **270** should be relatively straightforward, but would require several more steps than the route presented in **Scheme 76**.



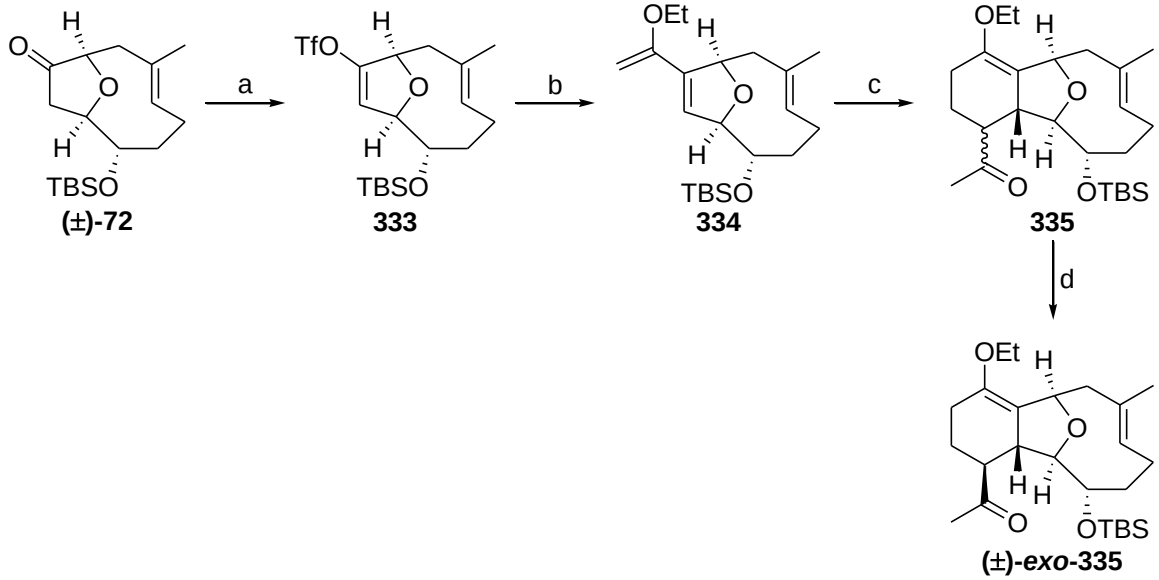
Scheme 77

2.4 Synthesis of the *E*-Cladiellin Natural Products

2.4.1 Formation of the Tricyclic Core found in the E-Cladiellins

Having successfully developed conditions that deliver the *E*-bicyclic ketone **72** with a good selectivity from diazoketone **70**, the synthesis of the cladiellins possessing an *E*-alkene or *trans*-1,2-diol within the medium-sized ring was attempted. The first challenge was construction of the tricyclic core of the *E*-cladiellins.

The three-step sequence developed for the synthesis of the tricyclic core of the *Z*-cladiellins was first employed (**Scheme 78**). Enol triflate formation, Stille cross-coupling and Diels-Alder cycloaddition reaction protocol delivered the tricyclic ketone **335** in modest yield (34%) over the three steps, as a 1.6:1 *exo*:*endo* mixture. Isomerisation of the *endo*:*exo* mixture with potassium carbonate afforded the desired *exo* product **(±)-*exo*-335** in 85% yield. The yield obtained for the formation of the tricyclic compound needed to be improved before attempting the rest of the synthesis. The low yield obtained in the synthesis of the tricyclic core appeared to be due to the instability of diene **334**. Enol triflate **333** was indeed obtained without problem from ketone **(±)-72**, but considerable decomposition of intermediates was observed during both the Stille cross-coupling and the Diels-Alder reaction. In order to improve the overall yield during the synthesis of the *E*-tricyclic core, these two steps were optimised.

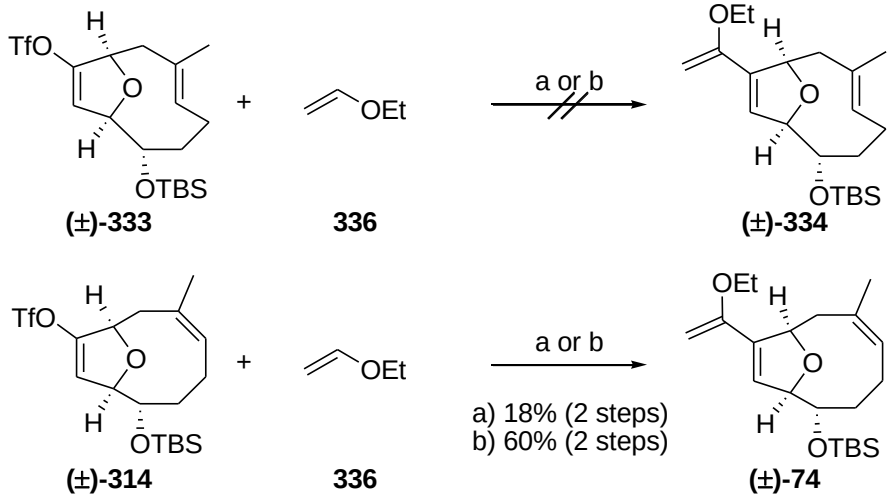


a) NaHMDS, $PhN(Tf)_2$, THF, −78 °C; b) $CH_2C(OEt)SnBu_3$, $Pd(PPh_3)_4$, LiCl, THF, reflux; c) $CH_2CHCOCH_3$, toluene, reflux, 34% (3 steps), 1.6:1 *exo*:*endo*; d) K_2CO_3, MeOH, rt, 85%.

Scheme 78

2.4.1.1 Studies Concerning Diene Formation

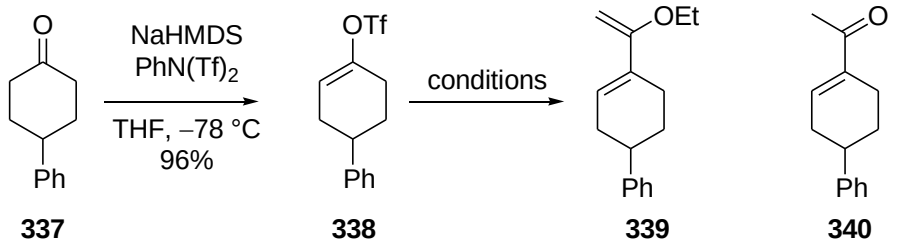
In order to avoid using a toxic and expensive organostannane and to be able to use a cheaper palladium source, the Heck coupling reaction was considered as an alternative to the Stille cross-coupling reaction (**Scheme 79**). Hallberg and co-workers have reported the coupling of vinyl ethers with enol triflates to synthesise 2-alkoxy-1,3-butadienes.[107] Applying these conditions in the cross-coupling of enol triflates **(±)-333** and **(±)-314** using palladium acetate as catalyst gave mixed results. Although diene **(±)-74** was formed in 18% yield over two steps (enol triflate formation and Heck coupling), significant decomposition was observed using the same conditions on triflate **(±)-333**. This illustrates the difference in reactivity and stability of the two enol triflates, induced by the oxonene alkene geometry. Addition of 1,3-bis(diphenylphosphino)propane (DPPP) to the reaction mixture increased the yield to 60% over two steps for the synthesis of diene **(±)-74** but once again only decomposition products were obtained from the reaction of enol triflate **(±)-333**.



a) $Pd(OAc)_2$, Et_3N, DMSO, 60 °C; b) $Pd(OAc)_2$, DPPP, Et_3N, DMSO, 60 °C.

Scheme 79

In order to spare valuable material, further optimisation reactions were performed using a model system. Formation of enol triflate **338** was achieved in 96% yield, and this compound was used to test different palladium coupling conditions. Heck coupling delivered diene **339** in 74% yield (**Table 10**, entry 1) but Stille cross-coupling with tributyl(1-ethoxyvinyl)tin using lithium chloride or copper iodide and cesium fluoride as additives afforded only decomposition products (entries 2, 3).[108] Methyl ketone **340** was the main product isolated from the reaction mixture.



337 **338** **339** **340**

Entry	Conditions	Outcome / Yield
1	CH_2CHOEt, $Pd(OAc)_2$, DPPP, Et_3N, DMSO, 60 °C	74%
2	$CH_2C(OEt)SnBu_3$, $Pd(PPh_3)_4$, LiCl, THF, reflux	Decomposition
3	$CH_2C(OEt)SnBu_3$, $Pd(PPh_3)_4$, CuI, CsF, THF, reflux	Decomposition

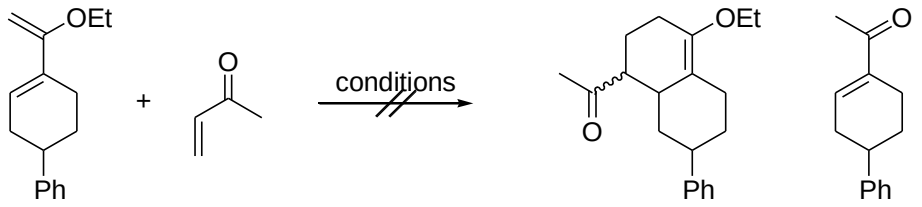
Table 10

The inability to identify conditions for the more efficient synthesis of diene **334** meant that the focus shifted to optimisation of the Diels-Alder reaction.

2.4.1.2 Studies on the Diels-Alder Cycloaddition Reaction

Diels-Alder reactions can be promoted by altering various reaction parameters. One of the more common tricks is to carry the reaction without solvent. However, it was demonstrated earlier that for our system the reaction yield was higher at low concentration. Another frequent technique relies on the use of Lewis acid for the activation of dienophiles bearing electron withdrawing groups.[109] Indeed, binding of a Lewis acid to the electron-withdrawing group of the dienophile lowers its LUMO resulting in an increase of reactivity.

The effect of different Lewis acids on the Diels-Alder cycloaddition of methyl vinyl ketone with our dienes was studied. First different Lewis acids were tested for the cycloaddition reaction between methyl vinyl ketone and the model diene **339** formed by Heck coupling (**Table 11**). The use of two equivalents of $BF_3 \bullet OEt_2$ at −40 °C caused decomposition of diene **339** (entry 1). Lowering further the temperature to −78 °C did not prevent the decomposition (entry 2) and use of catalytic amounts of $AlCl_3$ at −78 °C did not afford any bicyclic product **342** either (entry 3). Methyl ketone **340** was again the main product isolated from the reaction mixture.



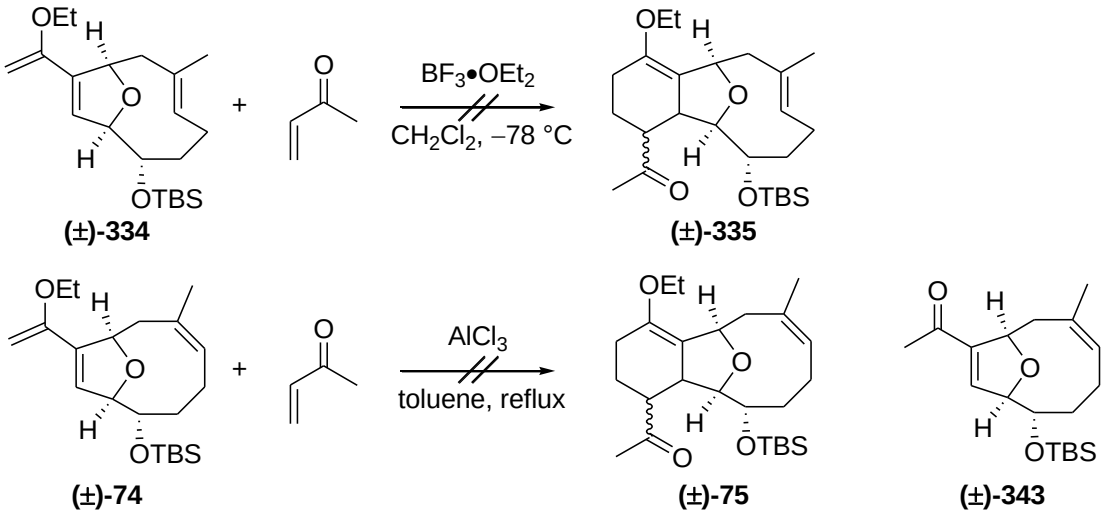
339 **342** **340**

Entry	Conditions	Outcome
1	$BF_3 \bullet OEt_2$ (2 eq), CH_2Cl_2, −40 °C	Decomposition
2	$BF_3 \bullet OEt_2$ (2 eq), CH_2Cl_2, −78 °C	Decomposition
3	$AlCl_3$ (10 mol%), CH_2Cl_2, −78 °C	Decomposition

Table 11

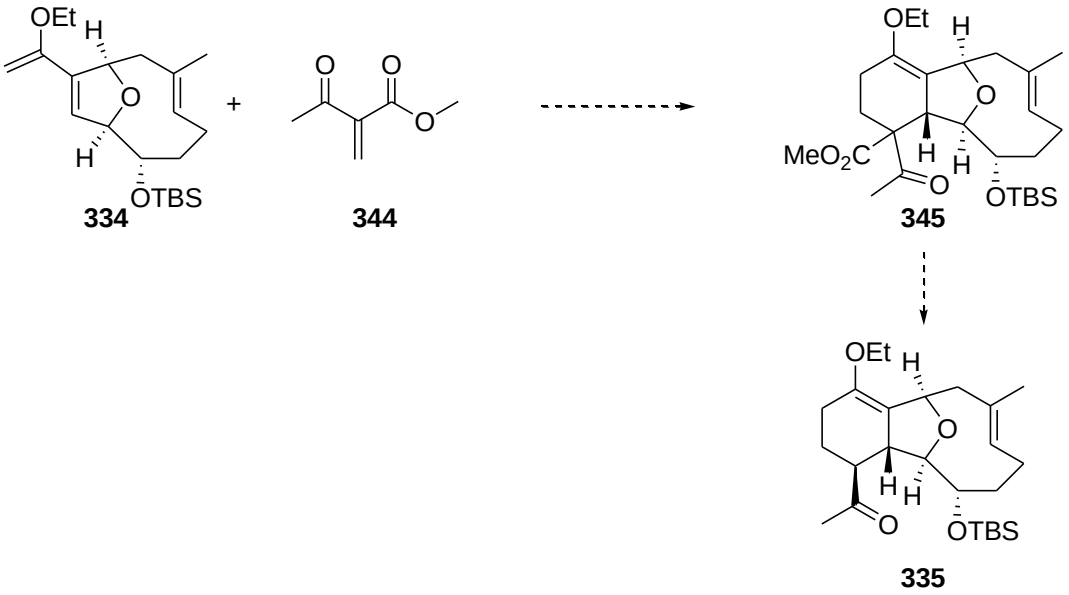
In order to make sure that the decomposition was not due to the instability of the model diene **339**, the fully functionalised substrates **(±)-334** and **(±)-74** were subjected to the Lewis acid catalysed Diels-Alder reaction with methyl vinyl ketone (**Scheme 80**). The $BF_3 \bullet OEt_2$ catalysed cycloaddition reaction of

diene **(±)-334** with methyl vinyl ketone at −78 °C gave only decomposition products. Adding $AlCl_3$ and performing the reaction under thermal conditions used for the cycloaddition of diene **(±)-74** previously also caused decomposition of the starting material; methyl ketone **(±)-343** was the major product isolated from the reaction mixture.



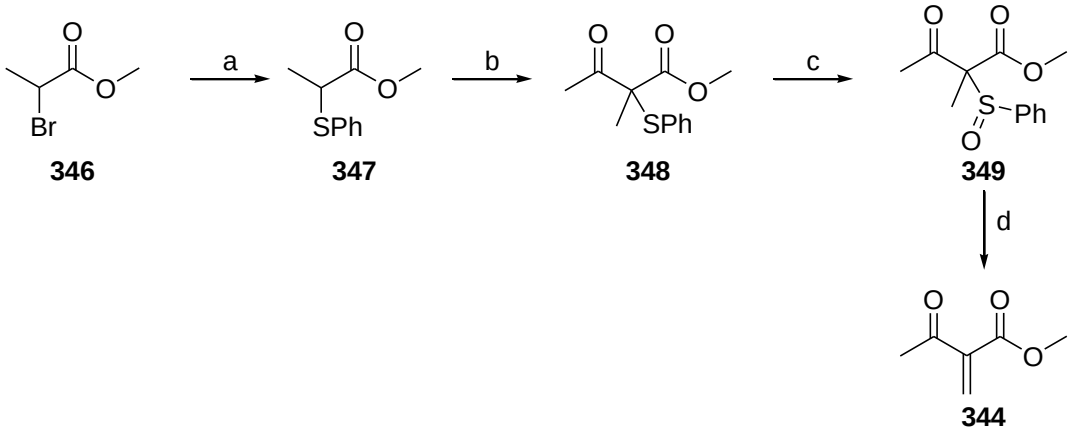
Scheme 80

In the light of these results, it was clear that the dienes used, bearing the ethyl ether, were extremely unstable, especially in presence of Lewis acids. Another approach was then considered. Hoye and co-workers have reported the use of 1,1-dicarbonylalkene **344** as activated dienophile in Diels-Alder cycloaddition reactions.[110] Cycloaddition of diene **334** with highly reactive dienophile **344** should afford tricycle **345** as a *endo*:*exo* mixture and subsequent decarboxylation should reveal the tricylic core **335** found in the *E*-cladiellins (**Scheme 81**).



Scheme 81

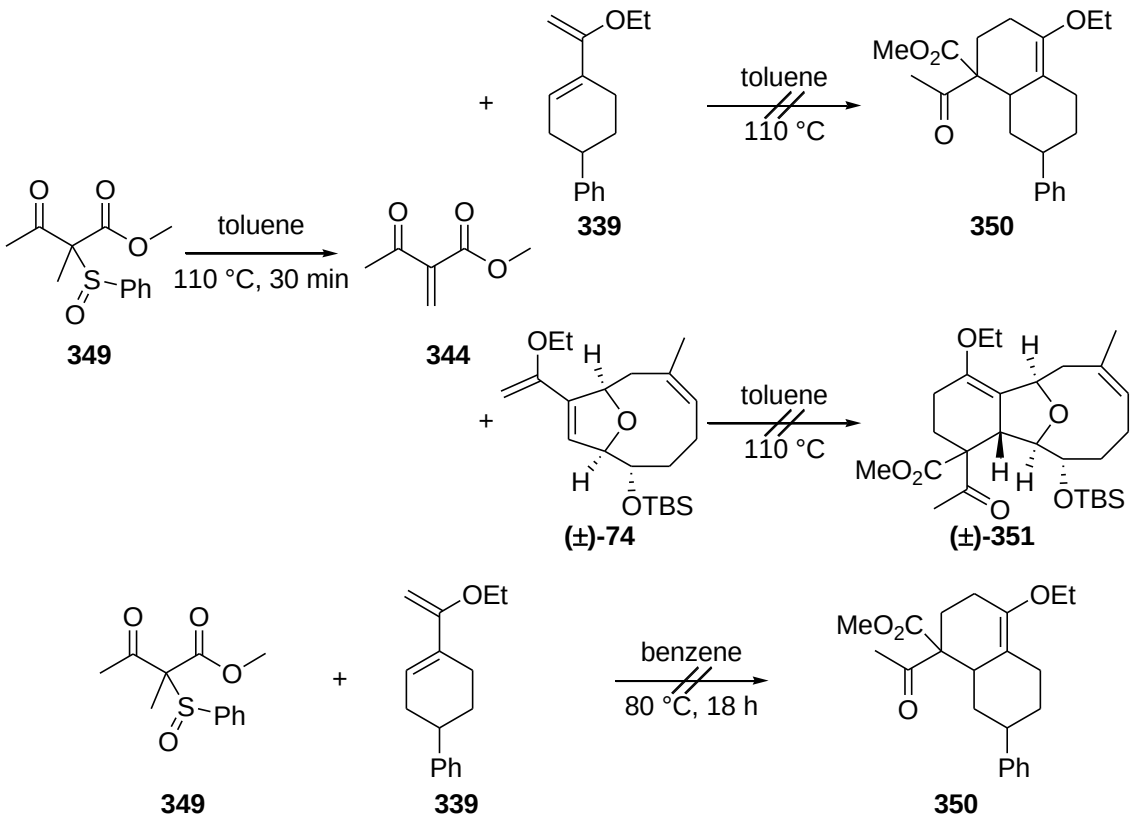
1,1-Dicarbonylalkene **344** was synthesised in four steps from methyl 2-bromopropionate **346** (**Scheme 82**). Nucleophilic substitution of **346** with thiophenol gave thioether **347** in 98% yield. Acylation of the *a*-phenylthio ester enolate with acetyl chloride yielded *β*-keto ester **348** in 80% yield. The thioether **348** was then oxidised with *m*-CPBA to give the non-isolated sulfoxide **349**. Finally, thermolysis of sulfoxide **349** afforded 1,1-dicarbonylalkene **344**, which was reported to be highly unstable and therefore kept in solution before the Diels-Alder reaction.



a) PhSH, NaH, THF, 0 °C, 98%; b) LiHMDS, CH_3COCl, THF, −78 °C, 80%, 91% brsm; c) *m*-CPBA, CH_2Cl_2, 0 °C; d) CH_2Cl_2, Δ.

Scheme 82

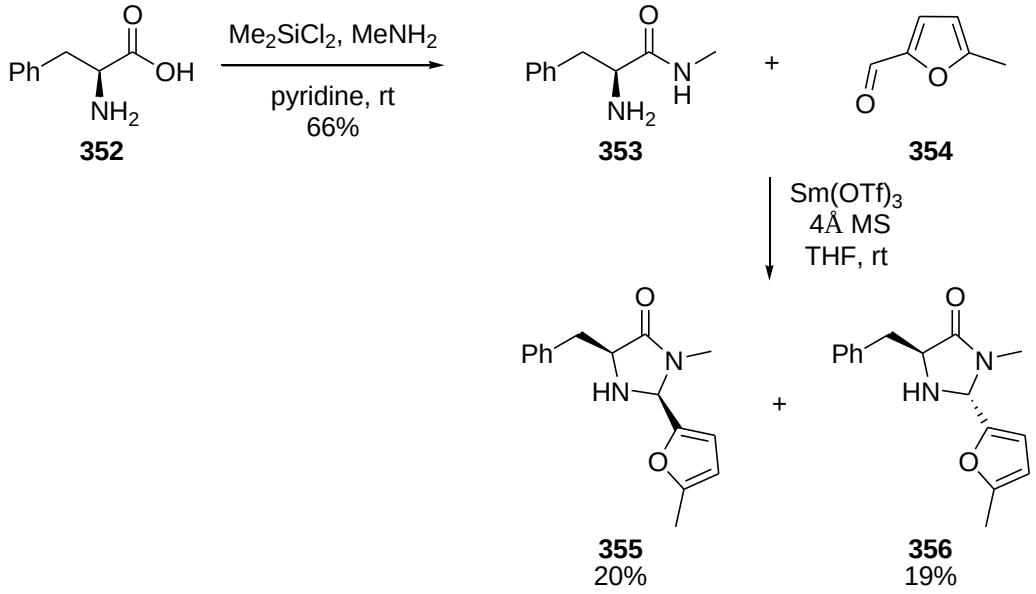
The reactivity of dienophile **344** was tested with both the model diene **339** and the bicyclic diene **(±)-74** (**Scheme 83**). Sulfoxide **349** was heated in toluene at reflux for 30 min to form 1,1-dicarbonylalkene **344** before addition of either diene following Hoye's conditions. However in both cases only decomposition was observed. It was thought that the failure of the reactions could be due to the decomposition of alkene **344** prior to diene addition. In order to prevent such decomposition, sulfoxide **349** and diene **339** were directly stirred together in benzene at 80 °C such that dienophile **344** could react with diene **339** as soon as it was formed. However, these conditions did not yield the desired Diels-Alder product **350** either.



Scheme 83

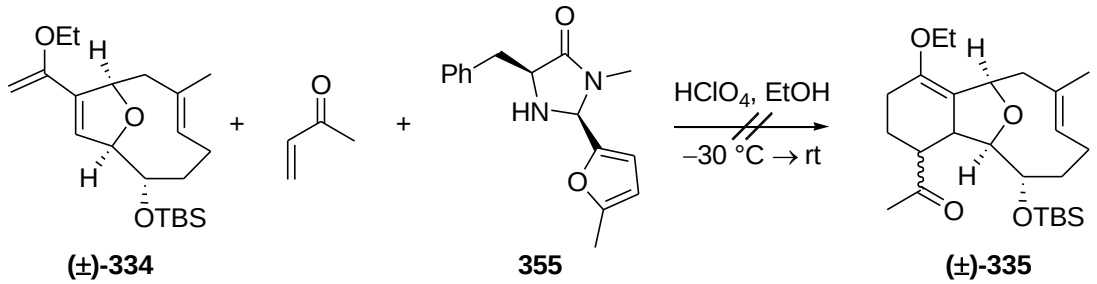
Having failed to identify an efficient method for the construction of the tricyclic core of the *E*-cladiellins, an organocatalysed mode of activation was studied. MacMillan and co-workers have reported the use of imidazolidinone **355** as an efficient catalyst for the Diels-Alder cycloaddition of *a*,ß-unsaturated ketones.[111] The increase in reactivity results from formation of an iminium cation from the reaction of the *a*,ß-unsaturated ketone and the imidazolidinone, which lowers the LUMO of the dienophile. Imidazolidinones **355** and **356** were formed in two

steps (**Scheme 84**). First methylamide **353** was obtained from L-phenylalanine **352** in 66% yield.[112] The imidazolidinone ring was then formed by reaction of **353** with 5-methylfurfural **354**. Both (2*S*, 5*S*) **355** and (2*R*, 5*S*) **356** imidazolidinone were obtained and separated by column chromatography.



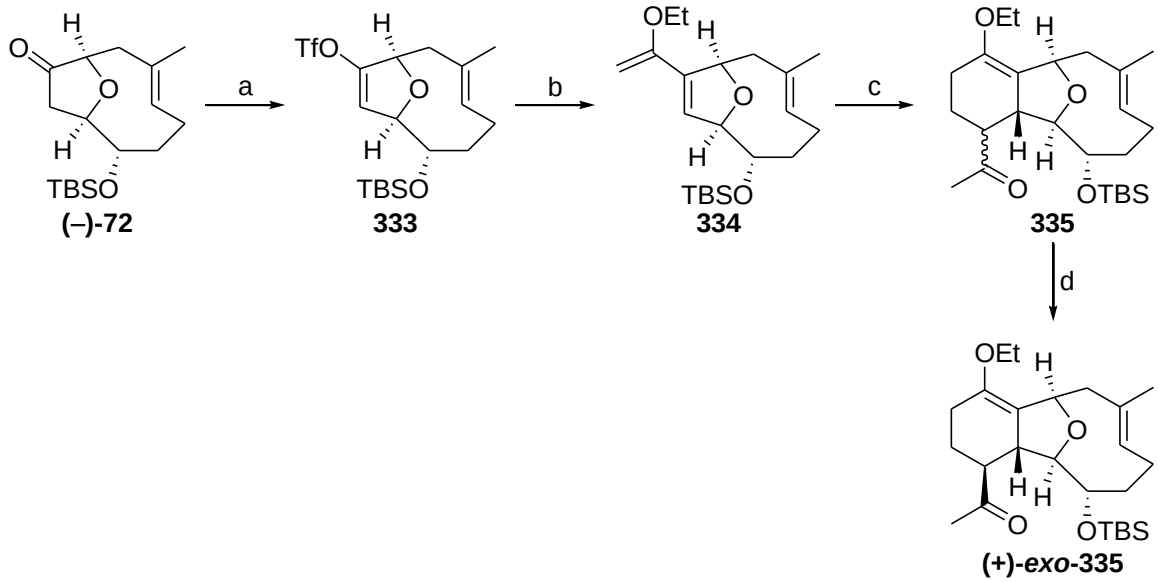
Scheme 84

With imidazolidinone **355** in hand the organocatalysed Diels-Alder cycloaddition reaction was carried out (**Scheme 85**). The diene **(±)-334** was stirred at −30 °C with methyl vinyl ketone and imidazolidinone **355** (20 mol%) for ten hours, as no reaction was observed the mixture was slowly warmed up to −10 °C. After stirring at this temperature for eighteen hours it was warmed up to −5 °C for 10 hours and finally stirred at room temperature. Unfortunately, none of the tricyclic product **335** was obtained out of the complex mixture of side products that was produced.



Scheme 85

Having failed to optimise the formation of diene **334** and its Diels-Alder cycloaddition with methyl vinyl ketone, it was decided to revert back to the original protocol. The standard three-step procedure was employed, delivering this time a much improved 68% yield over three steps. The increase in the yield was explained through a combination of small experimental changes. Firstly as the high instability of the diene **334** had been demonstrated, especially its decomposition to the corresponding methyl ketone under acidic conditions, extra care was taken. An alternative, basic work-up was used for the Stille reaction,[113] and no purification of the diene apart from a quick filtration through a small plug of silica treated with triethylamine to remove baseline impurities was done. Moreover, the tributyl(1-ethoxyvinyl)tin used was freshly prepared from ethyl vinyl ether and distilled prior to use, and not purchased from Aldrich.[114] These optimised conditions afforded a good and reproducible yield.



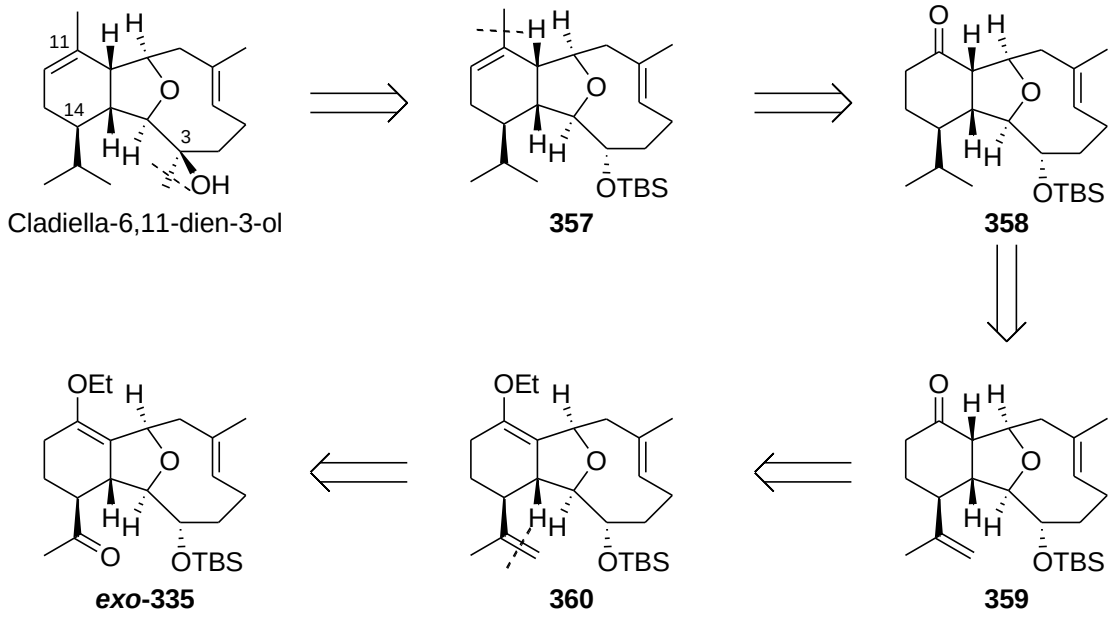
a) NaHMDS, $PhN(Tf)_2$, THF, −78 °C; b) $CH_2C(OEt)SnBu_3$, $Pd(PPh_3)_4$, LiCl, THF, reflux; c) $CH_2CHCOCH_3$, toluene, reflux, 68% (3 steps), 1.6:1 *exo*:*endo*; d) K_2CO_3, MeOH, rt, 85%.

Scheme 86

Having finally found efficient conditions for the formation of tricyclic core of the *E*-cladiellins **(+)-*exo*-335** our attention turned to the functionalisation of this core structure.

2.4.2 Formation of the Isopropyl Group

Our next challenge was the formation of the isopropyl group present on the six-membered ring of cladiella-6,11-dien-3-ol and many other cladiellins. As presented in the retrosynthetic analysis the addition of the C-3 methyl group and the formation of the C-11 trisubstituted alkene would be addressed last (**Scheme 87**). The proposed route towards the formation of the isopropyl group involved the formation of alkene **360** by Wittig olefination of methyl ketone ***exo*-335** followed by selective hydrogenation of the terminal alkene in presence of the trisubstituted one to form compound **358**.

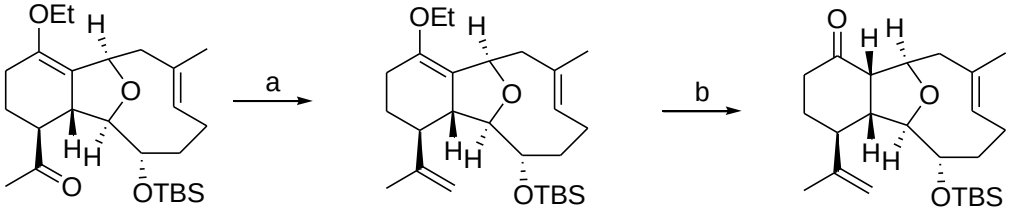


Cladiella-6,11-dien-3-ol **357** **358**

***exo*-335** **360** **359**

Scheme 87

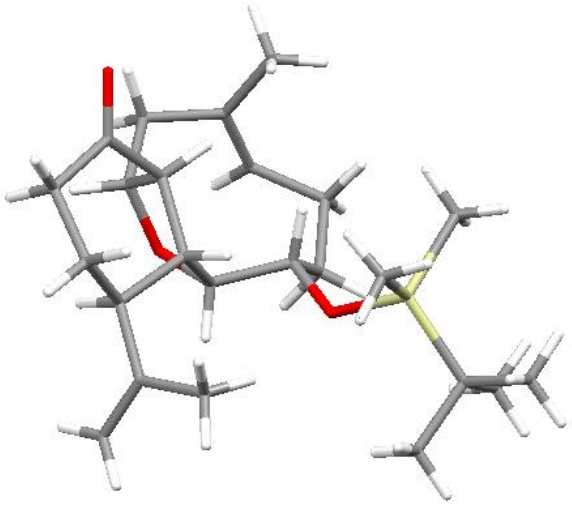
Wittig olefination of ketone **(±)-*exo*-335** delivered triene **(±)-360** in 80% yield (**Scheme 88**). Subsequent acidic cleavage of the enol ether in **(±)-360** produced ketone **(±)-359** as a crystalline solid in 87% yield. X-ray crystallography of **(±)-359** confirmed the relative configuration of the stereogenic centres in the molecule (**Figure 18**).



(±)-*exo*-335 **(±)-360** **(±)-359**

a) Ph_3PCH_3Br, NaHMDS, THF, rt, 80%; b) 1M HCl, THF, rt, 87%.

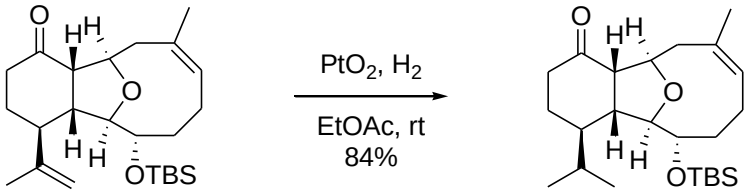
Scheme 88



(±)-359

Figure 18

The selective hydrogenation of **76** a similar compound, had been achieved in 84% yield during the synthesis of vigulariol using platinum oxide and hydrogen at atmospheric pressure (**Scheme 89**).[80]

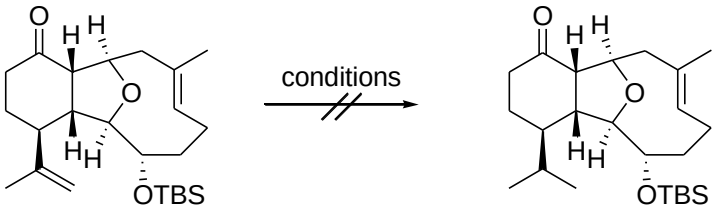


76 **361**

Scheme 89

The only difference between the two compounds **76** and **(±)-359** was the geometry of the oxonene alkene. Using these original conditions with diene **(±)-359** resulted in decomposition of the starting material (**Table 12**, entry 1). Various catalysts including Wilkinson's catalyst (entry 2), titanocene dichloride

(entry 3)[115] and Raney nickel (entry 4) were tested using an atmospheric pressure of hydrogen or the H-cube, but in all cases decomposition was obtained. A complicated mixture of *Z*-isomerised starting material and fully hydrogenated compound was observed in the reaction mixture.



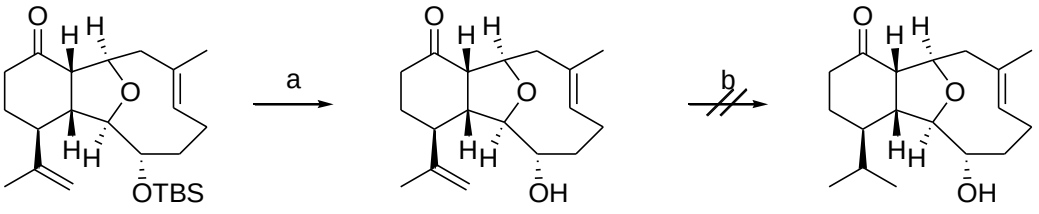
(±)-359 **(±)-358**

Entry	Conditions	Method	Outcome
1	PtO_2, EtOAc, rt	H_2 atm	Decomposition
2	Wilkinson's catalyst, EtOH, rt	H_2 atm	Decomposition
3	Cp_2TiCl_2, Mg, THF, rt	H_2 atm	Decomposition
4	Raney Ni, EtOH, rt	H-cube[a]	Decomposition
5	PtO_2, EtOH, rt	H-cube[a]	Decomposition

[a] H-cube conditions: full flow H_2 (6 bar), flow rate: 1 mLmin^{-1}, rt.

Table 12

It was thought that the bulky TBS-protecting group was probably blocking access of the catalyst to the terminal alkene. To test this hypothesis the silyl protecting group was removed using TBAF to deliver the primary alcohol **(±)-363** in 72% yield (**Scheme 90**). However, once again, treatment of **(±)-363** with platinum oxide under an atmosphere of hydrogen caused isomerisation and decomposition of the starting material.

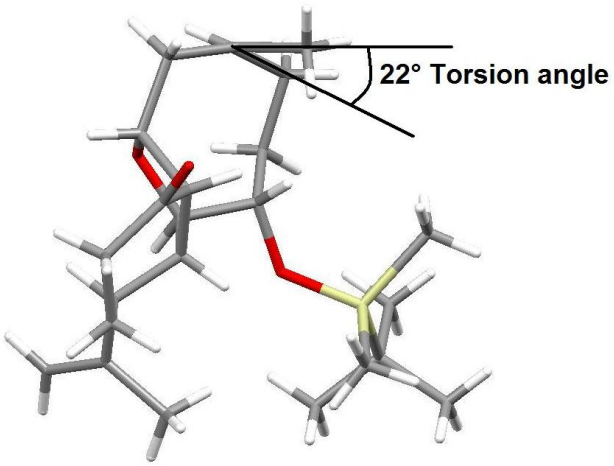


(±)-359 **(±)-363** **(±)-364**

a) TBAF, THF, rt, 72%; b) PtO_2, H_2 atm, EtOAc, rt.

Scheme 90

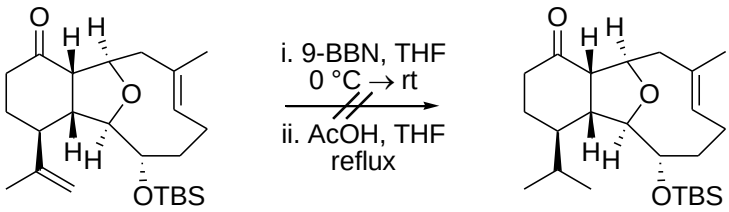
Further observation of the 3D structure of diene **(±)-359** obtained by X-ray crystallography revealed that the *E*-trisubstituted oxonene alkene had a 22° torsion angle explaining its reactivity with respect to hydrogenation. This torsion angle can be seen in **Figure 19**, where the view is made in line with the oxonene double bound.



(±)-359

Figure 19

Having been unable to form the isopropyl group by selective alkene hydrogenation, alternative approaches were considered. First, selective hydroboration of the terminal alkene of diene **(±)-359** with 9-BBN followed by acidic treatment was explored (**Scheme 91**).[116] However, this reaction resulted in decomposition.

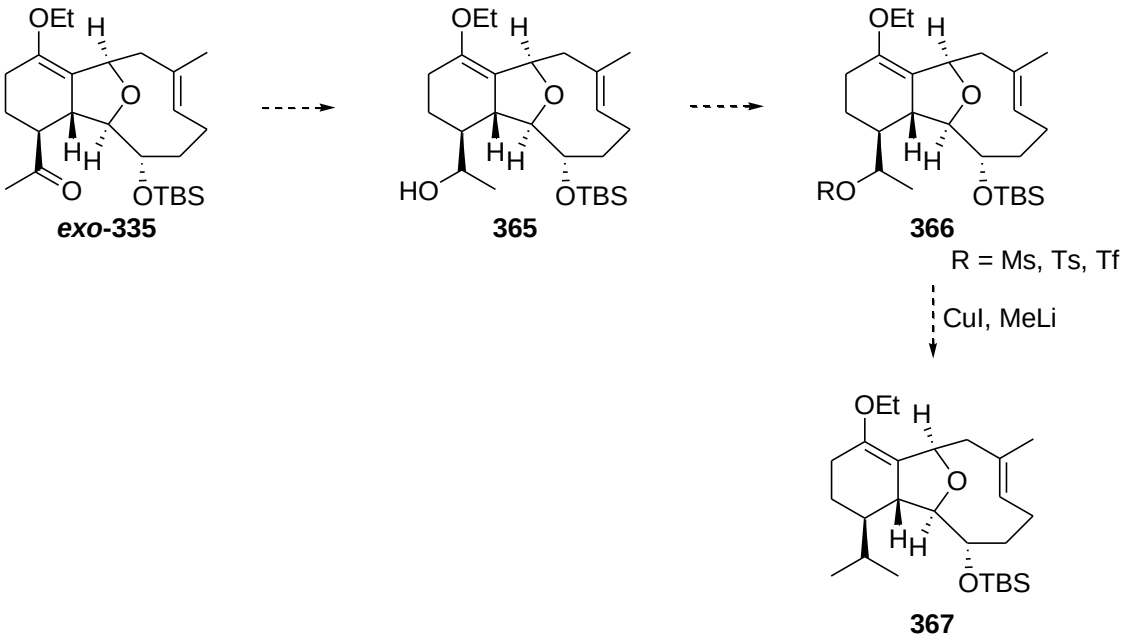


(±)-359 **(±)-358**

Scheme 91

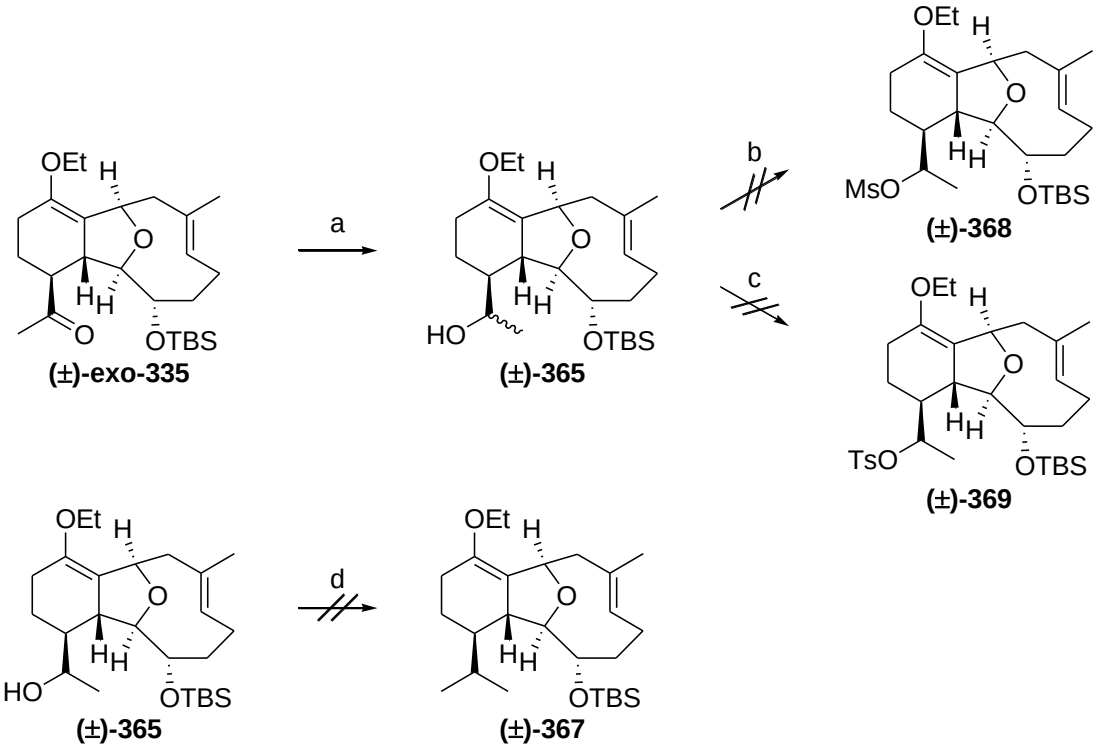
A new route for the introduction of the isopropyl group was designed starting from the Diels-Alder product ***exo*-335** (**Scheme 92**). Reduction of the methyl ketone would give the secondary alcohol **365**, and the hydroxyl group would

then be transformed into a good leaving group. Cuprate displacement of the leaving group would then form **367**, bearing the isopropyl moiety.[117]



Scheme 92

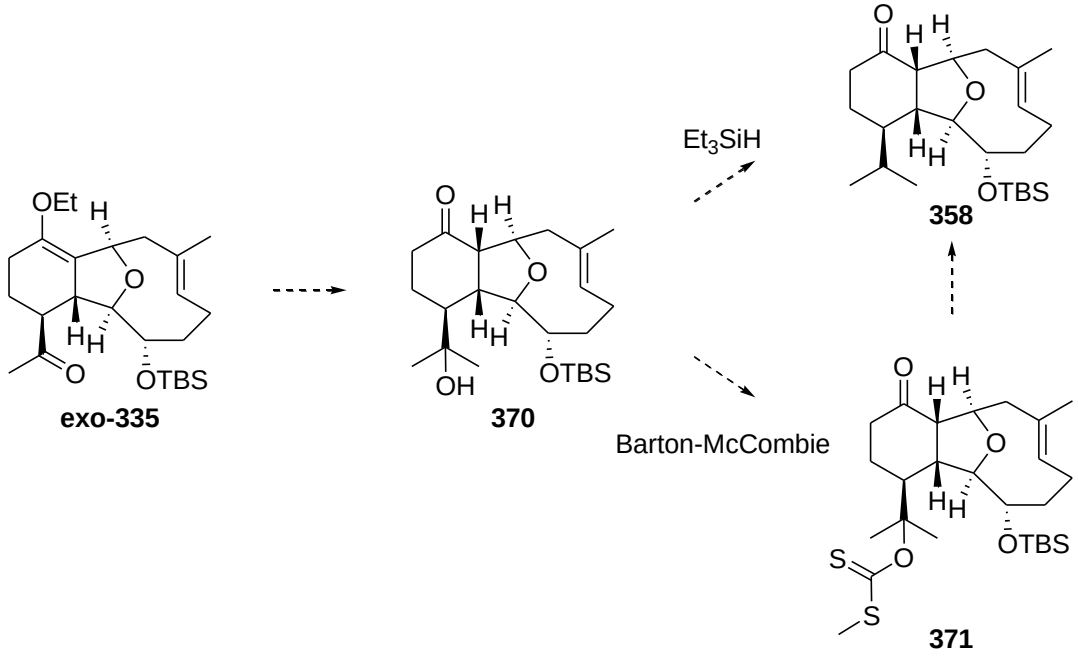
Reduction of ketone **(±)-*exo*-335** with sodium borohydride delivered alcohol **(±)-365** in 78% yield as a 1 : 1.9 mixture of diastereomers (**Scheme 93**). The two diastereomers were separated by column chromatography. Treatment of the secondary alcohol **(±)-365** with mesyl or tosyl chloride failed to deliver any product **(±)-368** or **(±)-369**; in both cases only decomposition was observed. To prevent decomposition, the triflate intermediate was formed and used directly in the cuprate displacement reaction. Treatment of alcohol **(±)-365** with triflic anhydride at −78 °C delivered the triflate which was not isolated but kept at −78 °C before being treated with a solution of Me_2CuLi obtained by stirring together methyl lithium and copper iodide. Unfortunately, once again, only decomposition was observed.



a) $NaBH_4$, MeOH:CH_2Cl_2 1:1, rt, 78%, dr (1:1.9); b) MsCl, Et_3N, CH_2Cl_2, 0 °C; c) TsCl, DMAP, pyridine, 0 °C → rt; d) i) 2,6-lutidine, Tf_2O, Et_2O, −78 °C; ii) MeLi, CuI, −78 °C → 0°C.

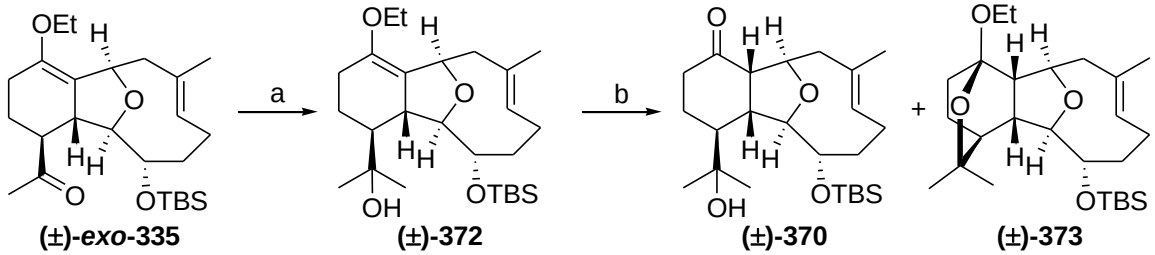
Scheme 93

Due to the failure of the cuprate displacement, an alternative route to compound **358** was proposed (**Scheme 94**). Starting from the Diels-Alder product ***exo*-335**, Grignard addition to the ketone and subsequent acidic hydrolysis of the enol ether would form tertiary alcohol **370**. Compound **358** bearing the isopropyl moiety could then be obtained by reductive deoxygenation of the tertiary alcohol **370** using triethylsilane or by Barton-McCombie deoxygenation.



Scheme 94

Grignard addition of methyl magnesium bromide to the methyl ketone **(±)-*exo*-335** afforded the tertiary alcohol **(±)-372** in 78% yield (**Scheme 95**). Acidic treatment of enol ether **(±)-372** gave a mixture of the desired ketone **(±)-370** and the cyclised product **(±)-373**. Formation of the tetracyclic product was explained by the attack of the suitably positioned hydroxypropyl group into the intermediate oxonium ion. A similar cyclisation process had been reported by Crimmins and co-workers during their synthesis of ophirin B (**Scheme 11**).[26]

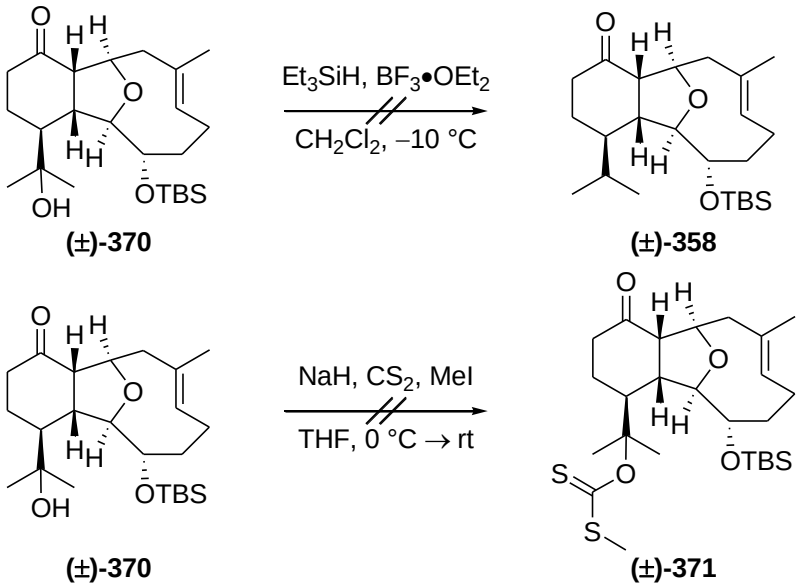


a) MeMgBr, THF, 0 °C → rt, 78%; b) HCl, THF, rt, 43% **370**, 17% **373**.

Scheme 95

With tertiary alcohol **(±)-370** formed, the two deoxygenation techniques were investigated (**Scheme 96**). Direct reductive deoxygenation of **(±)-370** using triethylsilane and $BF_3 \bullet OEt_2$ did not afford the desired product **(±)-358**, but gave a complex mixture composed of *Z*-isomerised and desilylated starting material.[118] The second technique considered was the Barton-McCombie

deoxygenation, but the xanthate intermediate **(±)-371** could not be formed from the hindered tertiary alcohol **(±)-370** using standard conditions.[119]

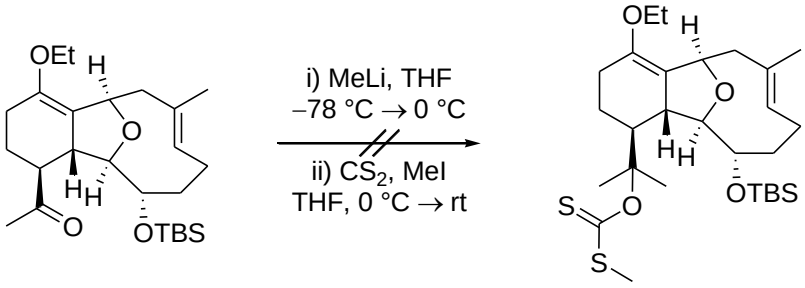


(±)-370 **(±)-358**

(±)-370 **(±)-371**

Scheme 96

In order to test whether the failure of the xanthate formation was due to the difficulty to deprotonate the tertiary alcohol, a one-pot procedure to form the xanthate **(±)-374** from methyl ketone **(±)-*exo*-335** was explored (**Scheme 97**). First, nucleophilic attack at the carbonyl centre was performed with methyl lithium to form the lithiated intermediate. Upon complete consumption of the ketone starting material, carbon disulfide and methyl iodide were added to the reaction mixture to react with the lithiated intermediate. Unfortunately, this one-pot procedure did not afforded any of the xanthate product **(±)-374** either.

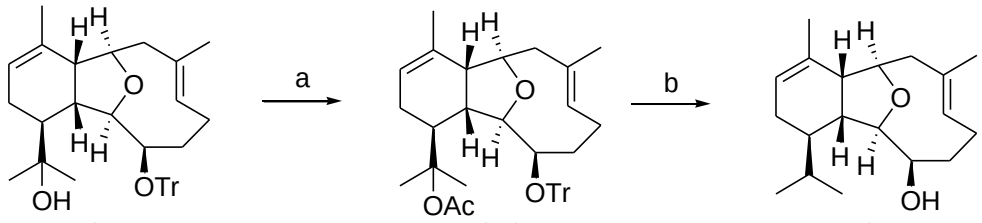


(±)-*exo*-335 **(±)-374**

Scheme 97

Looking back at the previous total syntheses of cladiellin natural products, it was observed that Kim and co-workers had reported that the formation of the

isopropyl group in presence of the reactive 6*E*-oxonene alkene was a challenge during the synthesis of cladiella-6,11-dien-3-ol.[31] Kim and co-workers succeeded in forming the isopropyl group in **65** by converting tertiary alcohol **375** into the corresponding acetate **376** and subjecting this tertiary acetate to dissolving metal reduction conditions (**Scheme 98**). [120]

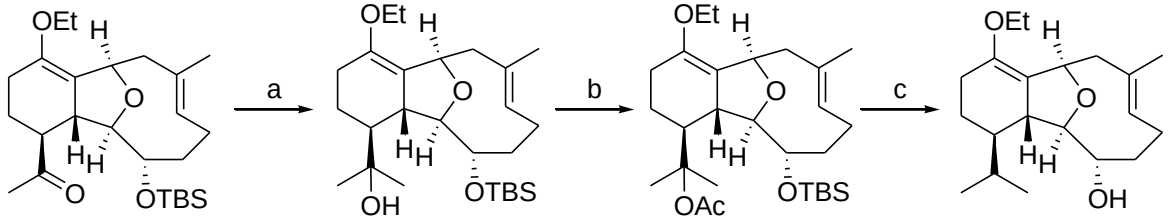


375 **376** **65**

a) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt; b) K, 18-crown-6, *t*-$BuNH_2$, THF, rt, 62% (2 steps).

Scheme 98

Applying the same protocol to our substrate seemed possible. The enol ether **(+)-372** was selected as the starting material in order to avoid formation the tetracyclic side-product **373** (**Scheme 95**). Synthesis of the tertiary acetate **377** was achieved by treatment of alcohol **(+)-372** with acetic anhydride as solvent, DMAP and triethylamine at 40 °C (**Scheme 99**). A solution of acetate **377** in THF was then added to the deep blue solution resulting from the solvation of the potassium metal by 18-crown-6 in *tert*-butylamine and THF. After reappearance of the royal-blue colour, the remaining potassium metal was carefully quenched by the addition of absolute ethanol. The reaction delivered compound **(+)-378** having lost the TBS-protecting group in 65% yield over two steps. The cleavage of the TBS ether was due to the very basic conditions generated upon quenching of the remaining potassium metal. Various conditions were explored to prevent deprotection during the destruction of the excess of the potassium metal, but all failed. The dissolving metal reduction reaction was highly moisture sensitive and in order to obtain the royal-blue solution the crown ether used had to be carefully recrystallised from acetonitrile and thoughtfully vacuum dried, and the potassium metal had to be cut and transfered into the reaction mixture coated in oil.



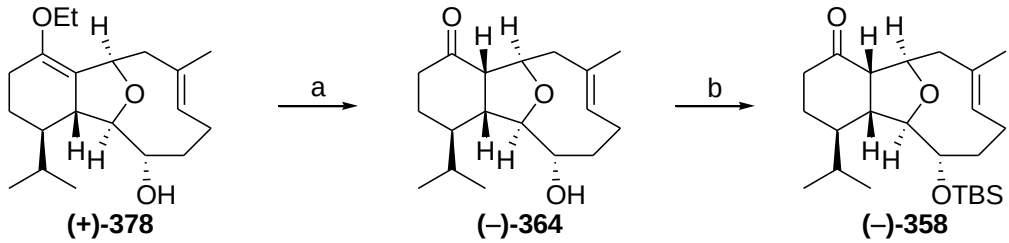
a) MeMgBr,THF, 0 °C → rt, 78%; b) Ac_2O, Et_3N, DMAP, 40 °C; c) K, 18-crown-6, *t*-$BuNH_2$, THF, rt, 65% (2 steps).

Scheme 99

Having successfully synthesised alcohol **(+)-378** bearing the desired isopropyl moiety on the six-membered ring, the final functional group modifications were performed.

2.4.3 Completion of the Synthesis of Cladiella-6,11-dien-3-ol

Following the successful synthesis of the alcohol **(+)-378** the next goal was formation of the trisubtituted alkene present in the six-membered ring of cladiella-6,11-dien-3-ol. It was proposed to build this alkene *via* a Kumada coupling.[121] Hydrolysis of the enol ether **(+)-378** under acidic conditions afforded ketone **(−)-364** in 89% yield (**Scheme 100**). The yield of this reaction was improved by performing it after the deoxygenation reaction in order to prevent formation of the tetracyclic side-product **373**. Protection of the secondary alcohol as TBS ether was achieved in 78% yield.

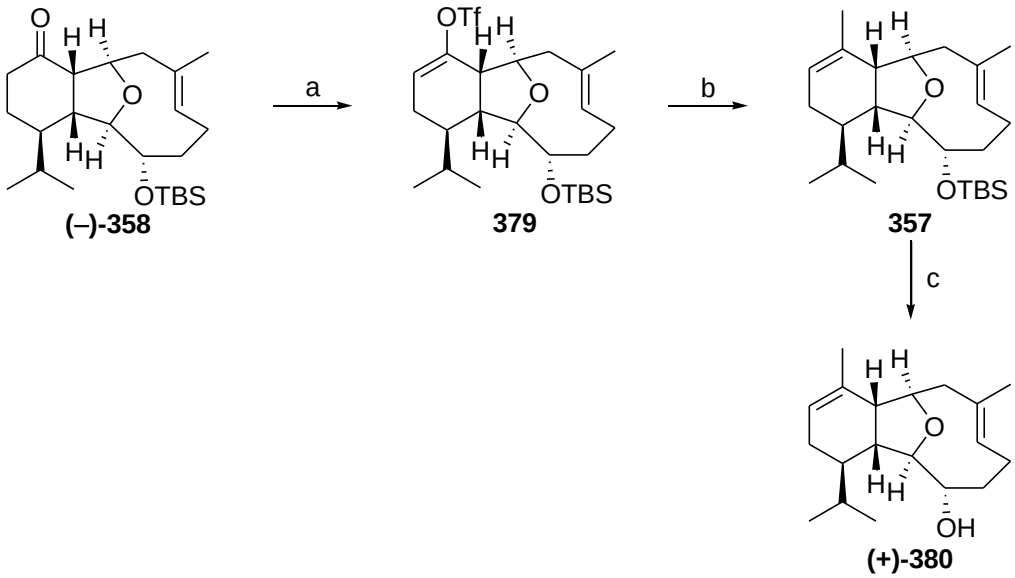


a) HCl, THF, rt, 89%; b) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 78%.

Scheme 100

Formation of the kinetic enol triflate **379** was achieved by treatment of ketone **(−)-358** with a solution of NaHMDS in presence of $PhNTf_2$ at −78 °C (**Scheme 101**). The vinyl triflate was used in a palladium(0) mediated Kumada

cross-coupling reaction with methyl magnesium chloride to afford diene **357** bearing the desired trisubstituted alkene in the six-membered ring.[122] Diene **357** was highly non-polar and could not be separated from the triphenylphosphine impurities resulting from the palladium catalyst. Treatment of the crude diene **357** with TBAF afforded the secondary alcohol **(+)-380**. This product being more polar than **357** could be easily purified to give 68% yield over three steps for the formation of the trisubstituted alkene.

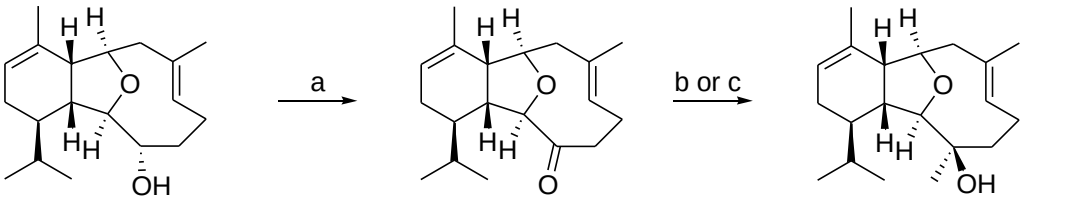


a) NaHMDS, $PhN(Tf)_2$, THF, −78 °C; b) MeMgCl, $Pd(PPh_3)_4$, LiCl, THF, rt; c) TBAF, 4Å MS, THF, rt, 68% (3 steps).

Scheme 101

Compound **65** (**Scheme 14, 98**), the C-3 epimer of alcohol **(+)-380** had been reported by Kim and co-workers as a late stage intermediate in their synthesis of (−)-cladiella-6,11-dien-3-ol.[31] Completion of the synthesis of (−)-cladiella-6,11-dien-3-ol was accomplished in two additional steps involving oxidation of the secondary alcohol to the corresponding ketone followed by a methyl group addition (**Scheme 102**). As a similar cyclic ketone had been found to be unstable during our work towards the synthesis of ophirin B, it was decided to use the crude ketone **381** obtained from Dess-Martin oxidation of **(+)-380** directly in the methylation reaction. Standard Grignard addition of methyl magnesium chloride to the crude ketone **381** afforded (−)-cladiella-6,11-dien-3-ol in 58% over the two steps. This yield was improved to 69% over two steps by the use of the Paquette protocol[22] involving the reaction of the crude ketone **381** with methyl lithium in presence of sodium tetrafluoroborate at −78 °C. In both cases the

addition was highly diastereoselective, with the nucleophile attacking form convex (back) side of the molecule. The spectroscopic and other characterisation data of synthetic (−)-cladiella-6,11-dien-3-ol were identical to those reported for the natural product.

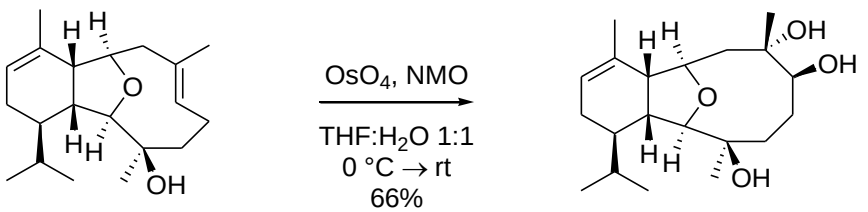


(+)-380 **381** (−)-Cladiella-6,11-dien-3-ol

a) DMP, pyridine, CH_2Cl_2, rt; b) MeMgCl, THF, 0 °C → rt, 58% (2 steps); c) MeLi, $NaBF_4$, THF, −78 °C, 69% (2 steps).

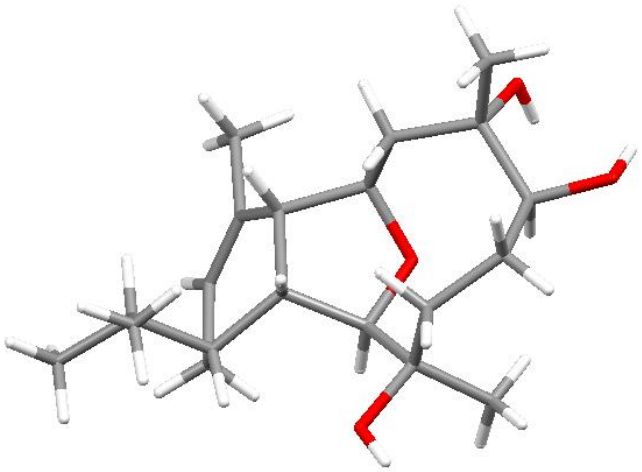
Scheme 102

As previously reported by Kim and co-workers (−)-cladiell-11-ene-3,6,7-triol was formed by selective Upjohn dihydroxylation of the 6*E*-oxonene alkene of (−)-cladiella-6,11-dien-3-ol (**Scheme 103**). Kim demonstrated that this dihydroxylation is selective for the more reactive 6*E*-oxonene alkene; this high reactivity results from the torsion angle of the alkene caused by the ring strain. This process is also diasteroselective with attack from the convex (back) side of the molecule due to the bowl shape and the rigidity of the 6*E*-oxonene ring. The triol was obtained as a single diastereomer in 66% yield by treatment of the diene with 2 mol% of osmium tetroxide and *N*-methylmorpholine-*N*-oxide (NMO) as stoichiometric oxidant. The reaction was followed carefully by TLC in order to prevent over-oxidation of the compound to give the corresponding quintaol. The spectroscopic and other characterisation data of synthetic (−)-cladiell-11-ene-3,6,7-triol were identical to those reported for the natural product.[123] Moreover the triol was isolated as a colourless crystalline solid allowing a X-ray crystal structure to be obtained (**Figure 20**).



(−)-Cladiella-6,11-dien-3-ol (−)-Cladiell-11-ene-3,6,7-triol

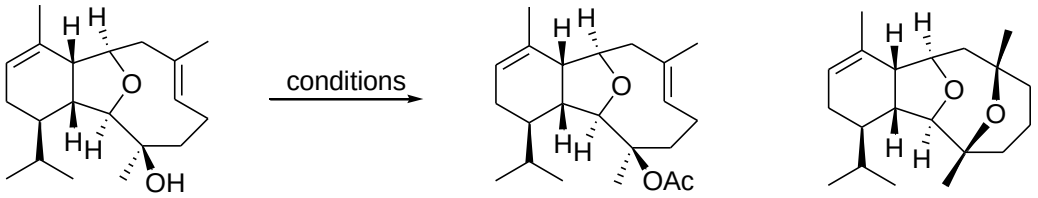
Scheme 103



(−)-Cladiell-11-ene-3,6,7-triol

Figure 20

Our next target was (−)-acetoxycladiella-6,11-diene as this natural product had never been synthesised before. Acetylation of the hindered tertiary alcohol proved to be difficult. Treatment of (−)-cladiella-6,11-dien-3-ol with triethylamine and DMAP, using acetic anhydride as solvent at 40 °C afforded the acetate in a modest 25% yield (**Table 13**, entry 1). Substituting acetic anhydride for acetyl chloride in dichloromethane gave a complicated decomposition mixture (entry 2). Using more powerful, Lewis acid catalysed acylation conditions did not afford any of the desired acetate.[124] Instead treatment of (−)-cladiella-6,11-dien-3-ol with acetic anhydride and TMSOTf as catalyst produced oxatetracycle **(+)-382** in 84% yield (entry 3). Such ether ring formation had already been reported with the use of Lewis acids by Hochlowski and Faulkner[9] and Kim and co-workers had reported the formation of **(+)-382** during the synthesis of polyanthellin A.[31] The shape of the molecule implies that the tertiary alcohol is very close to the alkene, which upon activation formed the ether ring. Despite the low yield of the acetylation reaction due to the position of the tertiary alcohol hindered inside the bowl created by the molecule skeleton, (−)-3-acetoxycladiella-6,11-diene was synthesised for the first time. Spectroscopic and other characterisation data were identical to those reported for the natural product.

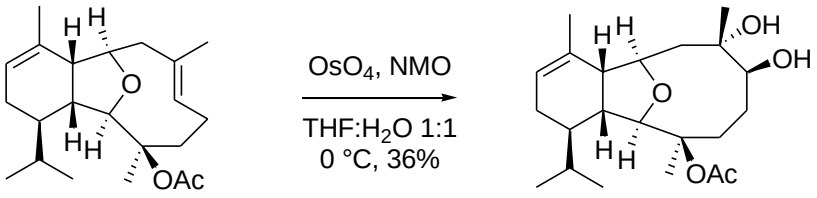


(–)-Cladiella-6,11-dien-3-ol (–)-3-Acetoxycladiella-6,11-diene **(+)-382**

Entry	Conditions	Outcome / Yield
1	Et_3N, DMAP, Ac_2O as solvent, 40 °C	25%
2	AcCl, Et_3N, DMAP, CH_2Cl_2, rt	decomposition
3	Ac_2O, TMSOTf, CH_2Cl_2, 0 °C	81% of **(+)-382**

Table 13

With the small quantity of (–)-3-acetoxycladiella-6,11-diene available, the synthesis of 3-acetoxycladiellin-11-ene-6,7-diol was attempted. Selective Upjohn dihydroxylation of the 6*E*-oxonene alkene was carried out as in the case of the synthesis of (–)-cladiell-11-ene-3,6,7-triol (**Scheme 104**). Treatment of (–)-3-acetoxycladiella-6,11-diene with catalytic quantities of OsO_4 in presence of NMO as a stoichiometric oxidant at 0 °C afforded 3-acetoxycladiellin-11-ene-6,7-diol in 36% yield and this is the first reported synthesis of this particular natural product. Due to the lack of starting material this reaction was not optimised but nevertheless, enough 3-acetoxycladiellin-11-ene-6,7-diol was obtained to prove that the spectroscopic and other characterisation data were identical to those reported for the natural product.[125] Due to the low concentration in which the optical rotation was carried out and our instrument sensitivity we were unable to determine the sign of the optical rotation, our measurements oscillating around 0, $[\alpha]^{28}_D$ 0 (*c* = 0.30, $CHCl_3$) {Lit.[12] $[\alpha]_D$ –1.87 (*c* = 2.17, $CHCl_3$)}.



(–)-3-Acetoxycladiella-6,11-diene 3-Acetoxycladiellin-11-ene-6,7-diol

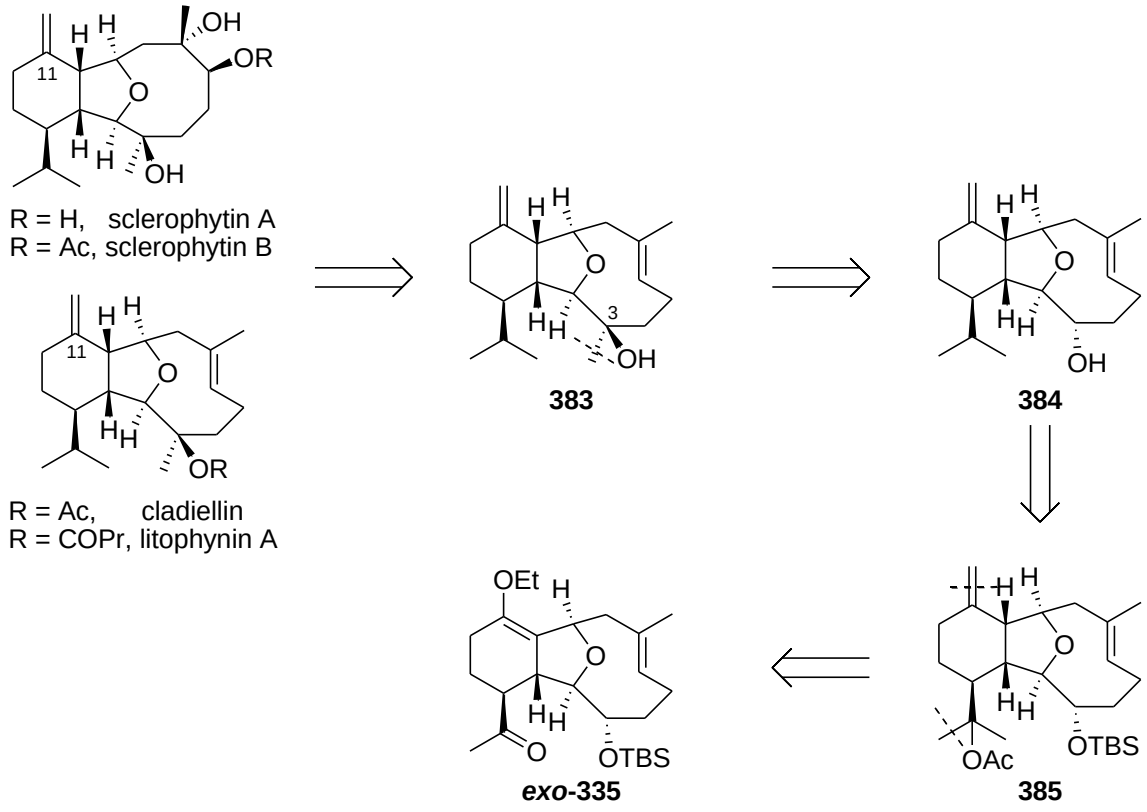
Scheme 104

Having completed the enantioselective total syntheses of four members of the cladiellin family of natural products featuring an endo-cyclic alkene in the

six-membered ring, our focus then turned to the synthesis of other members of this family of natural products.

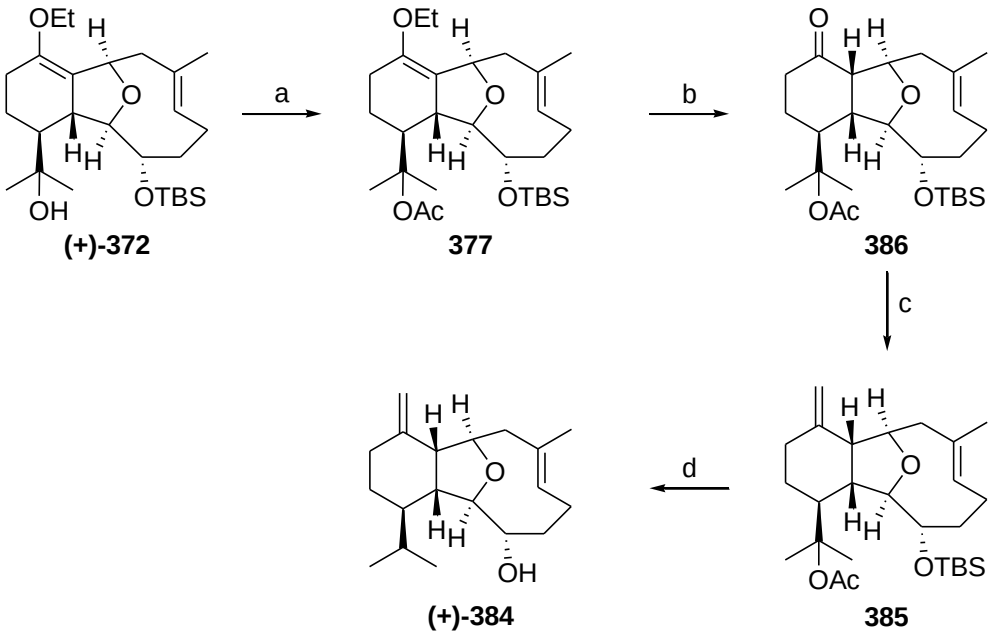
2.4.4 Synthesis of Cladiellins Containing an exo-Cyclic Alkene

Following the synthesis of four cladiellins bearing a cyclic trisustituted alkene on the six-membered ring, the versatility of our synthetic route was tested through the selection of four other related natural product bearing an exo-cyclic alkene on the six-membered ring (**Scheme 105**). Sclerophytin A and B have had their structures corrected by the simultaneous syntheses of Paquette[23] and Overman[15] and have been chosen has targets by many groups, unlike cladiellin or litophytin A for which no syntheses have yet been reported. It was postulated that these four compounds could be formed from the same intermediate, alcohol **383**. Removal of the C-3 methyl group of **383** would reveal secondary alcohol **384**, which could be obtained by deoxygenation of acetate **385**. Acetate **385** could be formed from methyl ketone **exo-335**, the synthesis of which has already been presented in this thesis.



Scheme 105

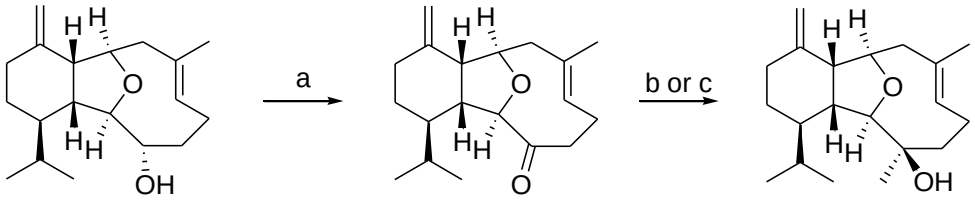
The synthesis of the targets started as previously by a Grignard addition to the methyl ketone **(+)-*exo*-335** delivering the tertiary alcohol **(+)-372**. Subsequent acetylation of the tertiary alcohol was performed as previously reported and followed by acidic enol ether hydrolysis to afford ketone **386** (**Scheme 106**). Formation of the exocyclic alkene was obtained by Wittig olefination of ketone **386**. Subjecting the tertiary acetate **385** to the dissolving metal conditions presented previously afforded diene **(+)-384** in 47% yield over 4 steps.



a) Ac_2O, Et_3N, DMAP, 40 °C; b) HCl, THF, rt; c) Ph_3PCH_3Br, NaHMDS, THF, reflux, d) K, 18-crown-6, *t*-$BuNH_2$, THF, rt, 47% (4 steps).

Scheme 106

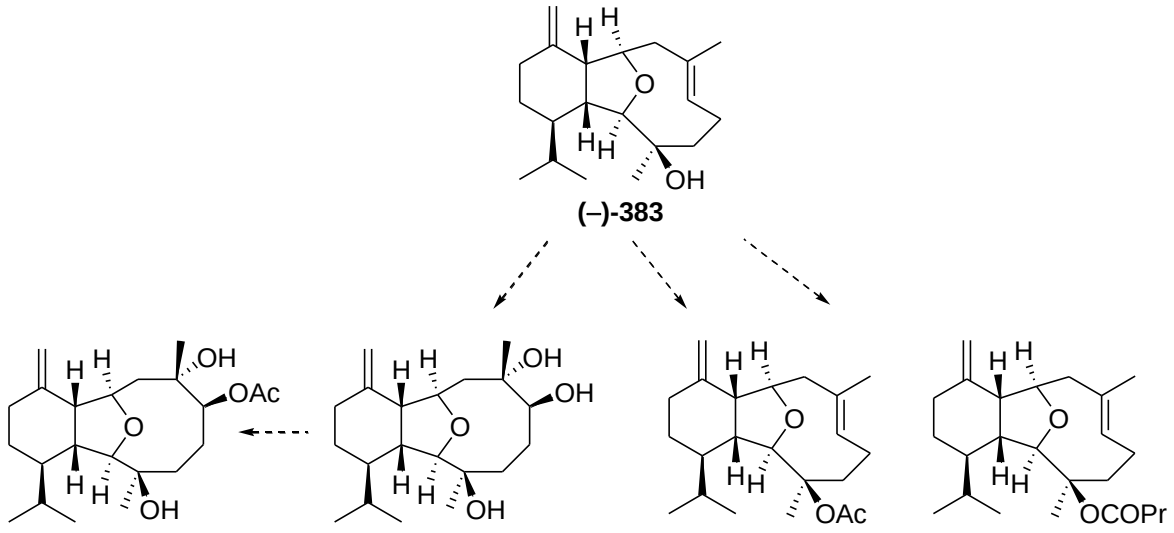
With diene **(+)-384** formed, only the introduction of the methyl group at C-3 remained to obtain the tertiary alcohol **(−)-383**, the common intermediate to the four natural product targets. This was achieved in two steps by oxidation of secondary alcohol with Dess-Martin periodinane followed by methyl addition (**Scheme 107**). The two standard methyl addition conditions were tested and once again the Paquette protocol[22] using methyl lithium and sodium tetrafluoroborate at −78 °C afforded tertiary alcohol **(−)-383** with the best yield (78% over the two steps).



a) DMP, pyridine, CH_2Cl_2, rt; b) MeMgCl, THF, 0 °C → rt, 42% (2 steps); c) MeLi, $NaBF_4$, THF, – 78 °C, 78% (2 steps).

Scheme 107

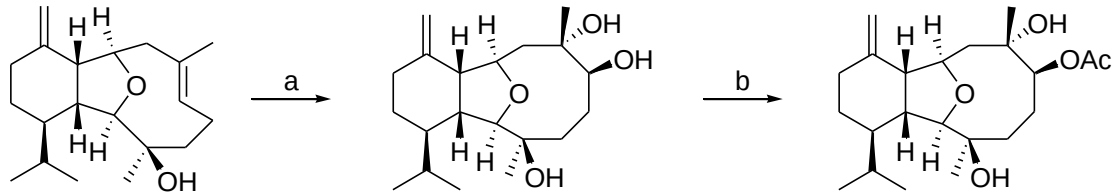
Alcohol **(–)-383** was not itself a natural product but, as in the case of (–)-cladiella-6,11-dien-3-ol, it could be transformed into several cladiellin natural products (**Scheme 108**). Dihydroxylation of **(–)-383** should afford sclerophytin A which itself would give sclerophytin B. Esterification of the tertiary alcohol in **(–)-383** with acetic anhydride or butanoyl chloride should form cladiellin and litophytin A respectively.



Scheme 108

Selective Upjohn dihydroxylation of the trisubstituted alkene in presence of the terminal alkene of **(–)-383** was performed using the same conditions as for the synthesis of (–)-cladiell-11-ene-3,6,7-triol and afforded (–)-sclerophytin A in 59% yield (**Scheme 109**). Once again this process was chemoselective for the trisubstituted oxonene and diastereoselective with dihydroxylation occurring from the convex face of the molecule. The spectroscopic and other characterisation data for synthetic (–)-sclerophytin A were identical to those reported for the natural product. As previously reported by Paquette,[23] selective

acetylation of the secondary alcohol in presence of the two tertiary alcohols afforded (−)-sclerophytin B in 79% yield. Synthetic (−)-sclerophytin B had spectroscopic and other characterisation data that were identical to those previously reported.

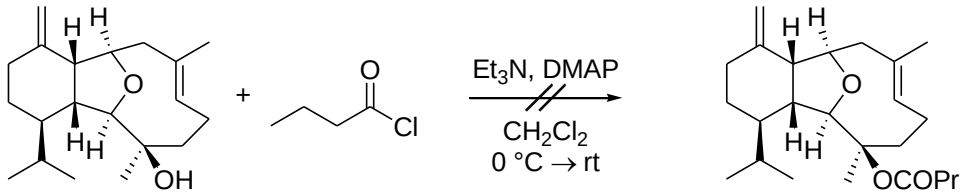


(–)-383 (–)-Sclerophytin A (–)-Sclerophytin B

a) OsO_4, NMO, THF:H_2O 1:1, 0 °C → rt, 59%; b) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C, 79%.

Scheme 109

Esterification of the tertiary alcohol **(−)-383** was then attempted. Initially it was decided to target the synthesis of litophytin A but the esterification of the hindered tertiary alcohol proved to be problematic. Treatment of alcohol **(−)-383** with butanoyl chloride, triethylamine and DMAP afforded a complex mixture from which the required product could not be isolated. Given the size of the butanoyl moiety it was decided to target cladiellin instead of litophynin A because acetylation of this tertiary alcohol should be easier.



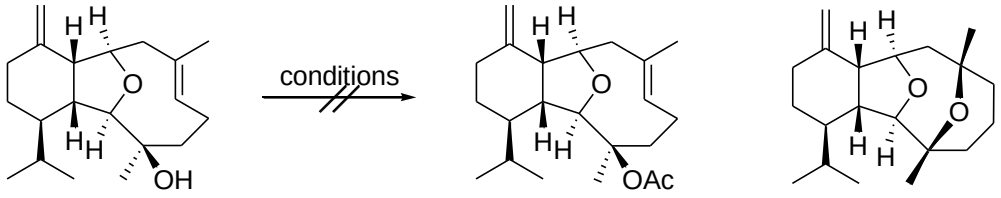
(–)-383 Litophynin A

Scheme 110

Having successfully accomplished the acetylation of (−)-cladiella-6,11-dien-3-ol, a compound very similar to the alcohol **(−)-383**, it was thought that using the same conditions on **(−)-383** would afford cladiellin (**Table 14**). It was known that this alcohol was highly hindered and acetylation was expected to proceed in low yield. Initially similar conditions to those used in the synthesis of (−)-3-acetoxycladiella-6,11-diene were attempted. Alcohol **(−)-383** was stirred in acetic anhydride with triethylamine and DMAP at room temperature and at 40 °C but in both cases only a complex mixture of side-products was obtained

(**Table 14**, entries 1 and 2). Performing the reaction in dichloromethane at room temperature did not afford the required product either (entry 3). Attempts to deprotonate the tertiary alcohol with potassium hydride prior to the addition of acetic anhydride or acetic anhydride and DMAP did not afford any of the desired acetate (entries 4 and 5). Changing the acetylating agent from acetic anhydride to acetyl chloride did not improve the reaction (entry 6). Finally, the use isopropenyl acetate in the presence of *p*-TSA as the acetylating agent[103, 104] was attempted, but only oxatetracycle **(−)-388** was obtained in this case. This compound had been reported by Paquette[23] and co-workers during their synthesis of the original structure of sclerophytin A and the spectroscopic data of oxatetracycle **(−)-388** matched that reported previously, confirming the configuration of the ring. Formation of the ether ring can be explained as in the case of the Lewis acid induced cyclisation of **(+)-382** from cladiella-6-11-dien-3-ol (**Table 13**). Due to the bowl shape of the molecule and the ring strain, the hydroxyl group is held close to the trisubstituted alkene and upon treatment with a Brønsted acid the oxygen attacks the activated alkene to form the ether ring.

Despite having investigated a wide range of acetylation conditions, the synthesis of cladiellin was not achieved. The fact that the conditions employed in the synthesis of (−)-3-acetoxycladiella-6,11-diene failed to deliver the required ester (entry 2) suggested that the *exo*-cyclic alkene on the six-membered ring has changed the conformation of the molecule to the extent that the tertiary hydroxyl group is buried more deeply inside the bowl created by the bridge ether system.



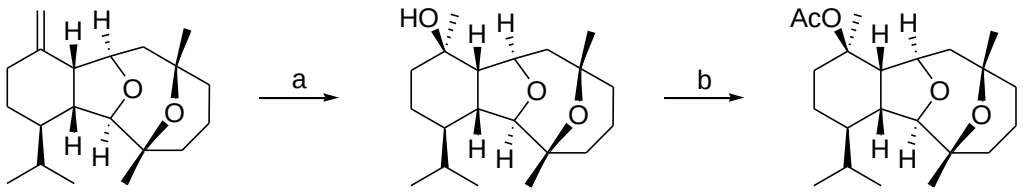
(–)-383 Cladiellin **(–)-388**

Entry	Conditions	Outcome / Yield
1	Ac_2O, Et_3N, DMAP, rt	Decomposition
2	Ac_2O, Et_3N, DMAP, 40 °C	Decomposition
3	Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt	Decomposition
4	KH, Ac_2O, THF, 0 °C to rt	Decomposition
5	KH, Ac_2O, DMAP, THF, 0 °C to rt	Decomposition
6	AcCl, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt	Decomposition
7	isopropenyl acetate, *p*-TSA, CH_2Cl_2, rt	90% of **(–)-388**

Table 14

Despite the failure to esterify the tertiary alcohol **(–)-383** to deliver cladiellin and litophytin A, the screening of acetylation conditions had revealed an efficient synthesis of oxatetracycle **(–)-388**. This extra ether-ring is present in some natural products of the cladiellin family, such as deacetylpolyanthellin A and polyanthellin A. These two natural products were synthesised from oxatetracycle **(+)-382** [a regioisomer of **(–)-388**] by Kim and co-workers[31] and so their oxymercuration-demercuration conditions were tested on the oxatetracycle **(–)-388** (**Scheme 111**). Treatment of **(–)-388** with $Hg(OAc)_2$ in a 1:1 mixture THF:water was followed by low temperature demercuration with sodium borohydride and triethylborane[126] affording (+)-deacetylpolyanthellin A in 77% yield, as a 10:1 mixture of diastereomers. The diastereoselectivity of the oxymercuration was lower with substrate **(–)-388** possessing an exocyclic alkene compared to that reported by Kim with the oxatetracycle **(+)-382** possessing an endocyclic trisubstituted alkene, probably due to the difference in the shape of the molecule. Acetylation of the tertiary alcohol was achieved using acetic anhydride as solvent, triethylamine and DMAP delivering (+)-polyanthellin A in 55% yield. Both enantiomers of deacetylpolyanthellin A and polyanthellin A exist in the nature and the present synthesis provided the dextrorotary compound as reported by Kim, Johnson and Bowden.[13, 31, 36, 127] Spectroscopic and other

characterisation data for both synthetic (+)-deacetylpolyanthellin A and (+)-polyanthellin A were identical to those reported for the natural products.



(–)-388 (+)-Deacetylpolyanthellin A (+)-Polyanthellin A

a) i) $Hg(OAc)_2$, THF:H_2O 1:1, rt; ii) $NaBH_4$, Et_3B, THF:H_2O 4:1, –20 °C, 77%, dr 10:1;
b) Ac_2O, Et_3N, DMAP, rt, 55%.

Scheme 111

Despite the failure to synthesise of cladiellin and litophytin A, the tertiary alcohol **(−)-383** was successfully used in the synthesis of four natural products: sclerophytin A and B, deacetylpolyanthellin A and polyanthellin A.

3 Summary and Future Work

3.1 Summary

The enantioselective total synthesis of eight natural products from the cladiellin family; (−)-cladiella-6,11-dien-3-ol, (−)-cladiell-11-ene-3,6,7-triol, (−)-3-acetoxycladiella-6,11-diene, 3-acetoxycladiellin-11-ene-6,7-diol, (−)-sclerophytin A, (−)-sclerophytin B, (+)-deacetylpolyanthellin A and (+)-polyanthellin A have been accomplished in 20 to 24 steps and 3% overall yield from allylic alocohol precursor **(+)-284**. These syntheses featured three important ring-forming reactions to construct the tricyclic core of the cladiellins. Firstly, a SmI_2-mediated reductive cyclisation formed the tetrahydropyran, then a tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement reaction constructed the oxabicyclo[6.2.1]undecenone bicyclic core. Finally a Diels-Alder cycloaddition reaction formed the third ring of the tricyclic core of the cladiellins.

The development of a scalable and efficient synthesis of the enantiopure allylic alcohol precursor **(+)-284** has permitted the formation of sufficient quantities of material for completion of the asymmetric total syntheses of the targets.

Studies on the tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement reaction have allowed the development of conditions for the selective formation of either the *E*- or *Z*-bicyclic ketone **72 73**. It is now possible to tune the reaction to obtain selectively the *E*-bicyclic ketone **72**, using rhodium(II) triphenylacetate, or the *Z*-bicyclic ketone **73**, with copper(II) hexafluoroacetylacetonate as catalyst.

Seventeen steps have been accomplished towards the synthesis of the *Z*-cladiellin ophirin B from allylic alcohol precursor **(+)-284**. An efficient bis-acetylation of the tertiary alcohols has been achieved, and only five steps remain to complete the asymmetric total synthesis of this natural product.

The tricyclic core of the *E*-cladiellin has been obtained in good yield allowing its synthesis in multi-gram quantities. Further functionalisation of the tricycle core, and in particular the formation of the isopropyl group present on six-membered ring has allowed the completion of the synthesis of the targets.

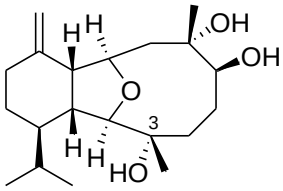
3.2 Future work

Future work should concentrate on the completion of the synthesis of ophirin B as proposed in Chapter 2.3.2. This synthesis would demonstrate even further the versatility of our synthetic route by the synthesis of a cladiellin bearing a 6*Z*-oxonene alkene.

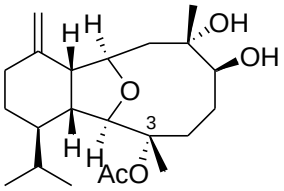
Ongoing computational calculations on the stability of the various intermediates and possible transition states for the oxonium ylide formation and [2,3]-sigmatropic rearrangement reaction will deliver a more detailed understanding of this transformation and account for the selectivity obtained with the different catalysts.

Some of the natural products that have been synthesised will be sent for biological evaluation in order to discover if they have any interesting pharmaceutical properties, especially anti-cancer activity.

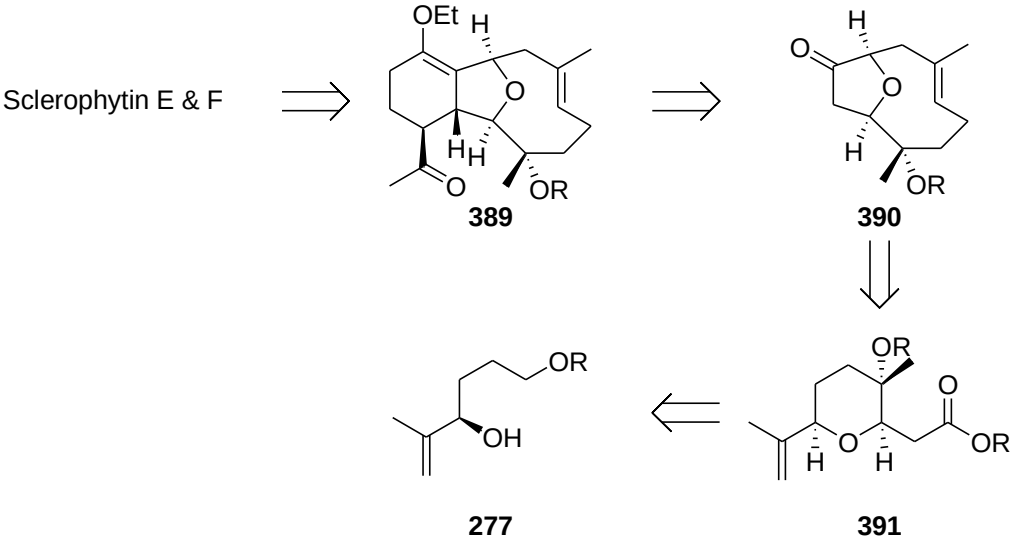
Finally, using the strategy developed during the project, the synthesis of other 2,11-cyclised cembranoid natural products such as the briarellins and cladiellins will be undertaken. Of particular interest will be cladiellins having a *S*-configuration at the C-3 carbon. These compounds, such as sclerophytin E and F, have had their structures reassigned by Paquette and co-workers and only total synthesis would confirm this reassignment (**Scheme 112**).[6] Sclerophytin E and F could be obtained using a similar synthetic route where the C-3 methyl group would be installed just after the SmI_2-cyclisation. This modified route would also allow the effect that the C-3 centre has on the outcome of the oxonium ylide formation and [2,3]-sigmatropic rearrangement reaction to be assessed.



Sclerophytin F



Sclerophytin E



Scheme 112

4 Experimental

General comment

Air and/or moisture sensitive reactions were performed under an atmosphere of Argon in flame dried apparatus. Organic solvents were dried using a Pure Solv™ solvent purification systems. All reagents were purchased from commercial suppliers and used without further purification, unless otherwise stated. All reactions were monitored by thin layer chromatography using Merck silica gel 60 covered alumina plates F_{254}. Thin layer chromatography plates were viewed under UV light or were visualised using either potassium permanganate solution or acidic ethanolic anisaldehyde solution. Column chromatography was performed under pressure using silica gel (Fluorochem LC60A, 35-70 micron, 60A) as solid support and HPLC-graded solvents as eluent. Petroleum ether used for column chromatography was 40-60 °C fraction.

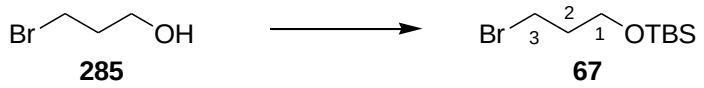
IR spectra were recorded using a type IIa diamond single reflection element on a Shimadzu FTIR-8400 instrument. The IR spectrum of the compound (solid or liquid) was directly detected as a thin layer at ambient temperature.
^{1}H NMR spectra were recorded on a Bruker 400 MHz or 500 MHz Spectrospin spectrometer at ambient temperature. The carbon numbering drawn on the molecule corresponds to the cladiellin numbering used for the NMR signal assignment. IUPAC numbering is used for the molecule names. Data are reported as follows: chemical shift in ppm relative to $CDCl_3$ (7.27) on the δ scale, 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 recorded on a Bruker 400 MHz or 500 MHz Spectrospin spectrometer at 100 MHz or 125 MHz at ambient temperature and multiplicities were obtained using a DEPT sequence. Data are reported as follows: chemical shift in ppm relative to $CHCl_3$ (77.16) on the δ scale and assignment.
High resolution mass spectra (HRMS) were obtained under EI, FAB, CI and ES conditions by the analytical services of the University of Glasgow on a Jeol MStation JMS-700 instrument. Low resolution mass spectra (LRMS) were carried

out on the same instrument; the intensity of each peak is quoted as a percentage of the largest, where this information was available.

Elemental analyses were carried out on an Exeter Analytical Elemental Analyser EA 440.

Melting points were recorded with an Electrothermal IA 9100 apparatus.

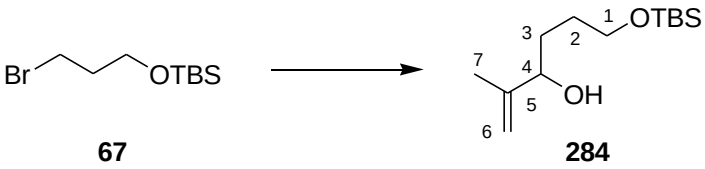
(3-Bromopropoxy)(tert-butyl)dimethylsilane 67



To a stirred solution of 3-bromopropanol **285** (30.0 g, 216 mmol), TBSCl (38.8 g, 259 mmol) and DMAP (90 mg) in anhydrous CH_2Cl_2 (450 mL) at rt was added triethylamine (39.3 g, 389 mmol). The resulting solution was stirred at rt 18 h before being diluted with CH_2Cl_2 (100 mL). The organic layer was separated and washed with water (2 x 200 mL), 1 M HCl (200 mL), water (200 mL) and brine (200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a colourless oil. Vacuum distillation (b.p. 94-96 °C at 14 mmHg) {Lit.[128] 182 °C at 760 mmHg} furnished the bromide **67** (44.3 g, 86%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (2H, t, *J* = 5.7 Hz, CH_2-C1), 3.51 (2H, t, *J* = 6.4 Hz, CH_2-C3), 2.03 (2H, tt, *J* = 6.4, 5.7 Hz, CH_2-C2), 0.89 (9H, s, CH_3-*t*Bu), 0.07 (6H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 60.6 (CH_2-C1), 35.7 (CH_2-C2), 30.9 (CH_2-C3), 26.1 (CH_3-*t*Bu), 18.5 (C-*t*Bu), −5.2 ($SiCH_3$); HRMS (CI, Me_3CH) $[M+H]^+$ for $C_9H_{22}O^{79}BrSi$ calcd 253.0624, found 253.0626, Δ +1.1 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 255.3 (10%), 253.3 (10%), 89.2 (100%); IR ν_{max} 2955, 2929, 2857, 951, 832, 774 cm^{-1}.

6-*tert*-Butyldimethylsilyloxy-2-methyl-1-hexen-3-ol 284

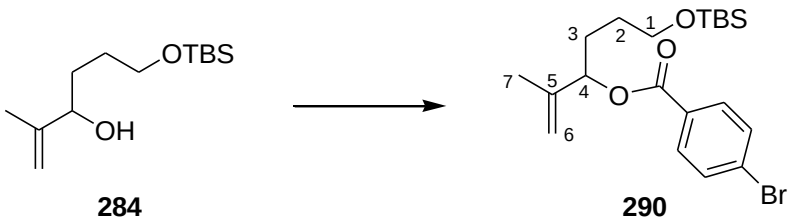


To a stirred slurry of magnesium turnings (2.8 g, 86 mmol) and iodine (trace) in anhydrous THF (12 mL) was added bromide **67** (20 g, 78 mmol) in anhydrous THF (130 mL) dropwise. After complete addition, the resulting brown solution was stirred for a further 1 h before freshly distilled methacrolein (2.7 g, 39 mmol) in anhydrous THF (8 mL) was added dropwise over 30 min. The resulting solution was stirred for further 1 h and then quenched by the addition of a saturated aqueous solution of NH_4Cl (160 mL) and Et_2O (120 mL). The aqueous phase was separated and extracted with Et_2O (3 × 80 mL). The organic extracts were

combined, washed with brine (160 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a colourless oil. Flash column chromatography on silica gel (petroleum ether - ethyl acetate, 5:1) afforded the alcohol **284** as a colourless oil (8.8 g, 93%).

R_f = 0.42 (petroleum ether - ethyl acetate, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (1H, br s, CH_2-C6), 4.83 (1H, br s, CH_2-C6), 4.08–4.04 (1H, m, CH-C4), 3.66 (2H, t, *J* = 5.7 Hz, CH_2-C1), 2.53 (1H, d, *J* = 3.8 Hz, OH), 1.72 (3H, s, CH_3-C7), 1.71–1.56 (4H, m, CH_2-C2, CH_2-C3), 0.90 (9H, s, *t*Bu), 0.06 (6H, s, $SiCH_3$); ^{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 (CH_3-*t*Bu), 18.5 (C-*t*Bu), 18.0 (CH_3-C7), −5.2 ($SiCH_3$); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{13}H_{29}O_2Si$ 245.1937, found 245.1932, Δ −2.1 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 245.5 (80%), 227.4 (100%), 137.3 (60%), 113.3 (80%); Anal. Calcd for $C_{13}H_{28}O_2Si$: C, 63.88%; H, 11.55%; Found: C, 63.73%; H, 11.65%; IR ν_{max} 3378, 2954, 2929, 2885, 2857, 898, 835, 774 cm^{-1}.

6-[(*tert*-Butyldimethylsilyl)oxy]-2-methylhex-1-en-3-yl 4-bromobenzoate 290



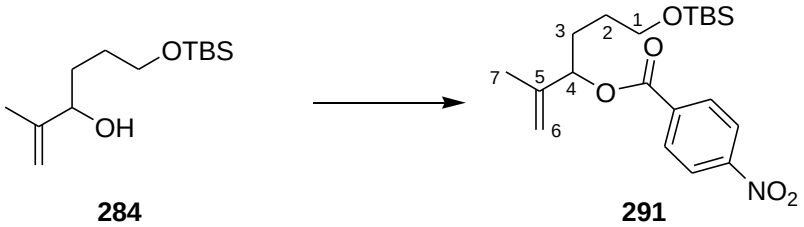
284 **290**

To a solution of alcohol **284** (400 mg, 1.63 mmol), triethylamine (828 mg, 8.18 mmol) and DMAP (200 mg, 1.63 mmol) in anhydrous CH_2Cl_2 (15 mL) at rt was added 4-bromobenzoyl chloride (718 mg, 3.27 mmol). The reaction was stirred for 2 h before being quenched by the addition of a saturated aqueous solution of NH_4Cl (5 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 10 mL). The organic extracts were combined and washed with brine (10 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a colourless oil. Flash column chromatography on silica gel (petroleum ether - ethyl acetate, 10:1) afforded the ester **290** (442 mg, 63%) as a colourless oil.

R_f = 0.59 (petroleum ether - ethyl acetate, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) 7.92–7.92 (2H, m, CH-Ar), 7.58–7.56 (2H, m, CH-Ar), 5.42 (1H, t, *J* = 6.6 Hz, CH-C4), 5.02 (1H, s, CH_2-C6), 4.93 (1H, t, *J* = 1.5 Hz, CH_2-C6), 3.65 (1H, t,

J = 6.3 Hz, CH_2-C1), 3.64 (1H, t, *J* = 6.3 Hz, CH_2-C1), 1.88–1.81 (2H, m, CH_2-C3), 1.78 (3H, s, CH_3-C7), 1.62–1.50 (2H, m, CH_2-C2), 0.89 (9H, s, CH_3-tBu), 0.04 (6H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2 (C-CO), 143.1 (C-C5), 131.8 (CH-Ar), 131.3 (CH-Ar), 129.6 (C-Ar), 128.1 (C-Ar), 113.1 (CH_2-C6), 78.2 (CH-C4), 62.7 (CH_2-C1), 29.2 (CH_2-C3), 28.7 (CH_2-C2), 26.1 (CH_3-*t*Bu), 18.5 (C-*t*Bu), 18.3 (CH_3-C7), −5.2 ($SiCH_3$); HRMS (CI, Me_3CH) $[M+H]^+$ for $C_{20}H_{32}O_3Si^{79}Br$ calcd 427.1305, found 427.1311, Δ +1.6 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 429.3 (7%), 427.3 (7%), 298.4 (84%), 297.4 (100%), 227.4 (90%); IR ν_{max} 2953, 2928, 2856, 1720, 1590, 1012, 834, 755 cm^{-1}.

6-[(*tert*-Butyldimethylsilyl)oxy]-2-methylhex-1-en-3-yl 4-(hydroxynitroso) benzoate 291



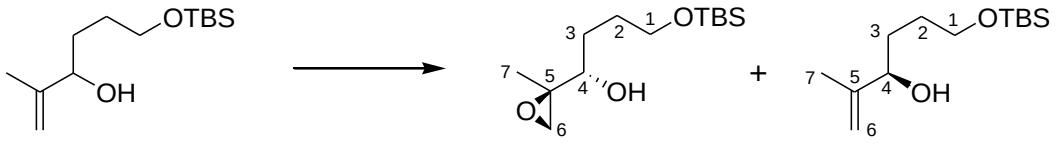
284 **291**

To a solution of alcohol **284** (0.40 g, 1.6 mmol), triethylamine (0.83 g, 8.2 mmol) and DMAP (0.20 g, 1.6 mmol) in anhydrous CH_2Cl_2 (15 mL) at rt was added 4-nitrobenzoyl chloride (0.60 g, 3.3 mmol). The reaction was stirred for 48 h before being quenched by the addition of a saturated aqueous solution of NH_4Cl (5 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 10 mL). The organic extracts 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, 10:1) afforded the ester **291** (111 mg, 17%) as a colourless oil.

R_f = 0.52 (petroleum ether - ethyl acetate, 5:1); ^1H NMR (400 MHz, $CDCl_3$) δ 8.38–8.18 (4H, m, CH-Ar), 5.47 (1H, t, *J* = 6.7 Hz, CH-C4), 5.05 (1H, s, CH_2-C6), 4.97 (1H, br s, CH_2-C6), 3.65 (1H, t, *J* = 6.2 Hz, CH_2-C1), 3.64 (1H, t, *J* = 6.2 Hz, CH_2-C1), 1.91–1.83 (2H, m, CH_2-C3), 1.80 (3H, s, CH_3-C7), 1.66–1.53 (2H, m, CH_2-C2), 0.89 (9H, s, CH_3-*t*Bu), 0.05 (6H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0 (C-CO), 150.7 (C-Ar), 142.6 (C-C5), 136.1 (C-Ar), 130.8 (CH-Ar), 123.7 (CH-Ar), 113.7 (CH_2-C6), 79.1 (CH-C4), 62.6 (CH_2-C1), 29.2 (CH_2-C3), 28.7 (CH_2-C2), 26.1 (CH_3-*t*Bu), 18.5 (C-*t*Bu), 18.3 (CH_3-C7), −5.2 ($SiCH_3$); HRMS (CI, Me_3CH)

$[M+H]^+$ for $C_{20}H_{32}O_5NSi$ calcd 394.2051, found 394.2053, Δ +0.7 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 394.4 (19%), 382.4 (18%), 227.4 (100%); IR ν_{max} 2954, 2928, 2856, 1726, 1530, 835, 776, 719 cm^{-1}.

(1*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-1-[(2*R*)-2-methyloxiran-2-yl]butan-1-ol 296 and (*R*)-6-*tert*-butyldimethylsilyloxy-2-methyl-1-hexen-3-ol 284

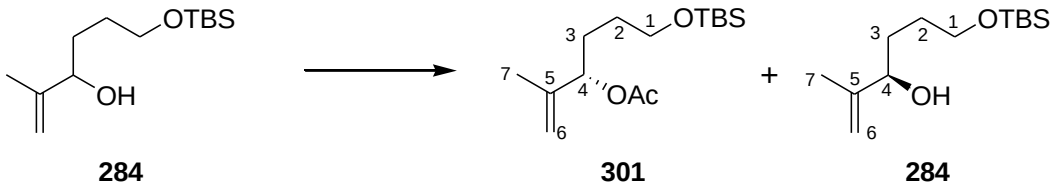


To a solution of the racemic alcohol **284** (0.24 g, 0.97 mmol) and freshly distilled (+)-diisopropyl tartrate (34 mg, 0.14 mmol), in anhydrous CH_2Cl_2 (4 mL) at −20 °C was added powdered molecular sieves (≈70 mg) and freshly distilled titanium tetraisopropoxide (27 mg, 97 μmol). The reaction mixture was stirred for 30 min and then *tert*-butylhydroperoxide (0.13 mL of a 5.2 M solution in CH_2Cl_2, 0.68 mmol) was added, the reaction mixture was stirred at −20 °C for 48 h before being quenched by the addition of an aqueous solution of $FeSO_4$ and citiric acid (5 mL) at −20 °C and stirred vigorously until two clear phases appeared. The aqueous phase was separated and extracted with CH_2Cl_2 (2 × 5 mL) the organic extracts were combined and stirred 30 min with a solution of 30% wt of NaOH in brine (5 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2 × 5 mL). The organic extracts were combined and washed with brine (5 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether - ethyl acetate, 10:1) afforded the allylic alcohol **284** (86 mg, 36%) and the epoxy alcohol **296** (102 mg, 41%). A 86% enantiomeric purity of **284** was obtained by normal phase chiral HPLC analysis[84] of the corresponding vinylogous carbonate **297**.

(1*S*)-4-[(*tert*-butyldimethylsilyl)oxy]-1-[(2*R*)-2-methyloxiran-2-yl]butan-1-ol **296**; R_f = 0.36 (petroleum ether - ethyl acetate, 2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 3.70−3.63 (2H, m, CH_2-C1), 3.55 (1H, ddd, *J* = 9.0, 2.0, 2.0 Hz, CH-C4), 2.87 (1H, d, *J* = 4.8 Hz, CH_2-C6), 2.76 (1H, br s, OH), 2.61 (1H, d, *J* = 4.8 Hz, CH_2-C6), 1.86−1.76 (1H, m, CH_2-C3), 1.74−1.65 (2H, m, CH_2-C2), 1.52−1.40 (1H, m, CH_2-C3), 1.33 (3H, s, CH_3-C7), 0.90 (9H, s, CH_3-*t*Bu), 0.06 (6H, s, $SiCH_3$); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 72.5 (CH-C4), 63.3 (CH_2-C1), 59.1 (C-C5), 51.4 (CH_2-C6), 30.0 (CH_2-C3), 29.1 (CH_2-C2), 26.1 (CH_3-*t*Bu), 18.4 (C-*t*Bu), 17.7 (CH_3-C7), −5.2 ($SiCH_3$); HRMS (CI, Me_3CH) $[M+H]^+$ for $C_{13}H_{29}O_3Si$ calcd 261.1887, found 261.1884, −0.9 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 261.3 (25%), 243.3 (18%), 203.3 (31%), 129.2 (79%); IR ν_{max} 3441, 2954, 2929, 2857, 834, 774 cm^{-1}.

(3*S*)-6-[(*tert*-Butyldimethylsilyl)oxy]-2-methylhex-1-en-3-yl acetate 301 and (*R*)-6-*tert*-butyldimethylsilyloxy-2-methyl-1-hexen-3-ol 284

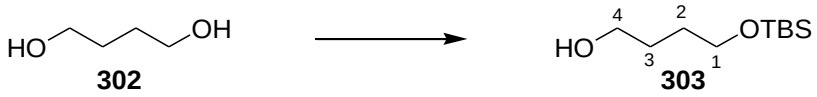


To a solution of the racemic alcohol **284** (0.12 g, 0.49 mmol), freshly distilled triethylamine (38 mg, 0.37 mmol) and (R)-(+)-4-dimethylaminopyrindinyl(penta phenylcyclopentadienyl)iron (6.6 mg, 9.9 μmol) in freshly distilled 2-methyl-2-butanol (1 mL) at 0 °C was added freshly distilled acetic anhydride (32 mg, 0.37 mmol). The reaction was kept in the fridge at 2 °C for 12 days and then the volatiles were removed. Residual material was purified by flash column chromatography on silica gel (petroleum ether - ethyl acetate, 5:1) to afford the allylic alcohol **284** (43 mg, 36%) and the acetate **301** (73 mg, 51%). A 83% enantiomeric purity of **284** was obtained by normal phase chiral HPLC analysis[84] of the corresponding vinylogous carbonate **297**.

(3*S*)-6-[(*tert*-butyldimethylsilyl)oxy]-2-methylhex-1-en-3-yl acetate **301**:

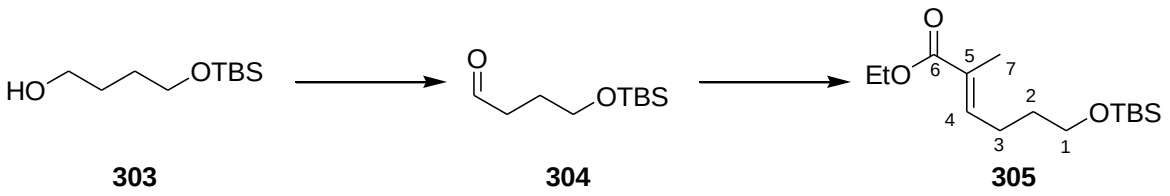
R_f = 0.65 (petroleum ether - ethyl acetate, 2:1); ^1H NMR (400 MHz, $CDCl_3$) δ 5.18 (1H, t, *J* = 6.7 Hz, CH-C4), 4.94 (1H, s, CH_2-C6), 4.88 (1H, br t, *J* = 1.5 Hz, CH_2-C6), 3.61 (1H, t, *J* = 6.3 Hz, CH_2-C1), 3.60 (1H, t, *J* = 6.3 Hz, CH_2-C1), 2.06 (3H, s, CH_3-Ac), 1.71 (3H, s, CH_3-C7), 1.71−1.65 (2H, m, CH_2-C3), 1.55−1.42 (2H, m, CH_2-C2), 0.88 (9H, s, CH_3-*t*Bu), 0.04 (6H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (C-Ac), 143.3 (C-C5), 112.8 (CH_2-C6), 77.2 (CH-C4), 63.8 (CH_2-C1), 29.1 (CH_2-C3), 28.7 (CH_2-C2), 26.1 (CH_3-*t*Bu), 21.4 (CH_3-Ac), 18.5 (C-*t*Bu), 18.3 (CH_3-C7), −5.2 ($SiCH_3$); Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89%; H, 10.55%; Found: C, 62.92%; H, 10.66%; IR ν_{max} 2955, 2929, 2857, 1740, 835, 775 cm^{-1}.

4-(*tert*-Butyldimethylsilyl)oxy-1-butanol 303



To a stirred solution of butandiol **302** (33.8 g, 375 mmol) and triethylamine (37.9 g, 375 mmol) in anhydrous CH_2Cl_2 (750 mL) was added TBSCl (37.7 g, 250 mmol). The resulting solution was stirred 18 h at rt and the reaction was then quenched by the addition of a saturated aqueous solution of NH_4Cl (250 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 100 mL). The organic extracts were combined and washed with brine (100 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a colourless oil. Flash column chromatography on silica gel (petroleum ether - ethyl acetate, gradient elution 8:1 → 5:1) afforded the alcohol **303** (45.9 g, 90%) as a colourless oil.
R_f = 0.53 (petroleum ether - ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69−3.62 (4H, m, CH_2-C1, CH_2-C4), 2.46 (1H, br s, OH), 1.68−1.61 (4H, m, CH_2-C2, CH_2-C3), 0.90 (9H, s, *t*Bu), 0.07 (6H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$); δ 63.5 (CH_2-C4), 62.9 (CH_2-C1), 30.4 (CH_2-C3), 30.0 (CH_2-C2), 26.0 (CH_3-*t*Bu), 18.4 (C-*t*Bu), −5.3 (CH_3-$SiCH_3$); HRMS (CI, Me_3CH) $[M+H]^+$ for $C_{10}H_{25}O_2Si$ calcd 205.1625, found 205.1621, Δ −1.5 ppm; LRMS (CI, Me_3CH) *m/z* (intensity); 205.4 (100%), 137.2 (40%), 121.2 (18%); IR ν_{max} 3348, 2953, 2929, 2858, 835, 775 cm^{-1}.

(*E*)-6-(*tert*-Butyldimethylsilanyloxy)-2-methyl-hex-2-enoic acid ethyl ester 305 [80, 86]



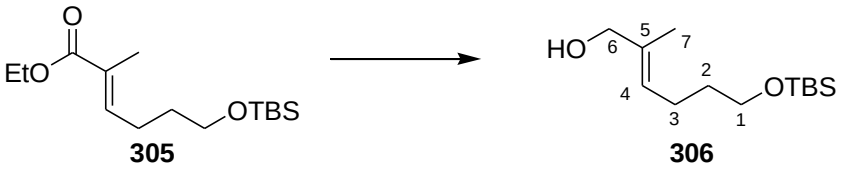
To a stirred solution of oxalyl chloride (33.0 g, 373 mmol) in anhydrous CH_2Cl_2 (640 mL) cooled at −78°C was added slowly a solution of anhydrous DMSO (40.0 mL, 562 mmol) in anhydrous CH_2Cl_2 (200 mL) and the resulting solution was stirred for 30 min. The alcohol **303** (31.0 g, 152 mmol) in anhydrous CH_2Cl_2

(460 mL) was then added dropwise. The resulting solution was stirred at the same temperature for a further 2 h and then quenched with triethylamine (76.8 g, 760 mmol) at −78 °C. The reaction mixture was allowed to warm to rt and stirred for 30 min then diluted with CH_2Cl_2 (500 mL) and water (300 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 150 mL). The organic extracts were combined and washed with brine (300 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude aldehyde **304** which was used for the next step without purification.

To a stirred solution of the crude aldehyde **304** in anhydrous THF (1.5 L) was added ethyl 2-(triphenylphosphoranylidene)propanoate (82.5 g, 227 mmol) in one portion. The resulting solution was stirred at rt for 48 h and the reaction was then quenched by the addition of ethyl acetate (500 mL) and water (500 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 300 mL). The organic extracts were combined, washed with brine (300 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a white solid. Flash column chromatography on silica gel (petroleum ether – ethyl acetate, 20:1) afforded the alkene **305** (40.8 g, 95% over two steps) as a colourless oil.

R_f = 0.77 (petroleum ether - ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77 (1H, tq, *J* = 7.5, 1.4 Hz, CH-C4), 4.18 (2H, q, *J* = 7.1 Hz, CH_2-Et), 3.62 (2H, t, *J* = 6.2 Hz, CH_2-C1), 2.26−2.21 (2H, m, CH_2-C3), 1.82 (3H, br d, *J* = 1.4 Hz, CH_3C7), 1.65 (2H, tt, *J* = 7.6, 6.2 Hz, CH_2-C2), 1.30 (3H, t, *J* = 7.1 Hz, CH_3-Et), 0.89 (9H, s, *t*Bu), 0.04 (6H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$); δ 168.4 (C-C6), 142.0 (CH-C4), 128.2 (C-C5), 62.5 (CH_2-C1), 60.5 (CH_2-Et), 31.8 (CH_2-C3), 26.1 (CH_3-*t*Bu), 25.2 (CH_2-C2), 18.4 (C-*t*Bu), 14.5 (CH_3-Et), 12.5 (CH_3-C7), −5.2(CH_3-$SiCH_3$); HRMS (CI, Me_3CH) $[M+H]^+$ for $C_{15}H_{31}O_3Si$ calcd 287.2044, found 287.2041, Δ −0.4 ppm; LRMS (CI, Me_3CH) *m/z* (intensity); 287.3 (100%), 241.3 (18%), 229.3 (11%); Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89%; H, 10.55%; Found: C, 62.89%; H, 10.48%; IR ν_{max} 2955, 2929, 2887, 2858, 1710, 833, 775 cm^{-1}.

(*E*)-6-(*tert*-Butyldimethylsilanyloxy)-2-methyl-hex-2-en-1-ol 306[80, 86]

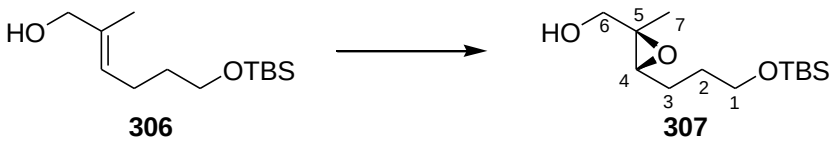


305 **306**

To a stirred solution of the ester **305** (39.8 g, 139 mmol) in anhydrous CH_2Cl_2 (1.40 L) at −78 °C was added DIBAL-H (350 mL of a 1.0 M solution in hexane, 350 mmol) dropwise over 1.5 h. The resulting solution was stirred for 30 min then quenched with a saturated aqueous solution of sodium potassium tartrate (500 mL) and allowed to warm to rt. The reaction mixture was then diluted with ethyl acetate (800 mL) and stirred vigorously until the appearance of two phases. The aqueous phase was separated and extracted with ethyl acetate (3 × 500 mL). The organic extracts were combined, washed with brine (500 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a colourless oil. Flash column chromatography on silica gel (petroleum ether – ethyl acetate, 7:1) afforded the allylic alcohol **306** (31.8 g, 94%) as a colourless oil.

R_f = 0.48 (petroleum ether - ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 (1H, tq, *J* = 7.2, 1.2 Hz, CH-C4), 3.99 (2H, br d, *J* = 6.0 Hz, CH_2-C6), 3.61 (2H, t, *J* = 6.4 Hz, CH_2-C1), 2.09 (2H, q, *J* = 7.5 Hz, CH_2-C3), 1.66 (3H, br s, CH_3-C7), 1.58 (2H, tt, *J* = 7.5, 6.4 Hz, CH_2-C2), 1.27 (1H, m, OH), 0.89 (9H, s, *t*Bu), 0.04 (6H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$); δ 135.2 (C-C5), 126.1 (CH-C4), 69.2 (CH_2-C6), 62.7 (CH_2-C1), 32.7 (CH_2-C2), 26.1 (CH_3-*t*Bu), 24.1 (CH_2-C3), 18.5 (C-*t*Bu), 13.8 (CH_3-C7), −5.2 (CH_3-$SiCH_3$); HRMS (CI, Me_3CH) $[M-OH]^+$ for $C_{13}H_{27}OSi$ calcd 227.1833, found 227.1832, Δ +0.5 ppm; LRMS (CI, Me_3CH) *m/z* (intensity); 245.5 (15%), 227.5 (100%), 95.2 (80%); Anal. Calcd for $C_{13}H_{28}O_2Si$: C, 63.87%; H, 11.55%; Found: C, 63.75%; H, 11.64%; IR ν_{max} 3339, 2955, 2929, 2887, 2858, 813, 775 cm^{-1}.

[(2*R*,3*R*)-3-[3-(*tert*-Butyldimethylsilanyloxy)-propyl]-2-methyl-oxiranyl]-methanol 307[80, 86]

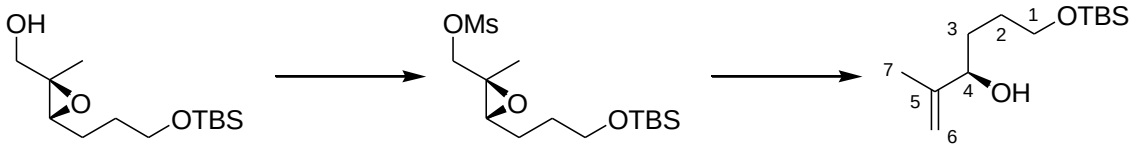


306 **307**

To a suspension of 4 Å powdered molecular sieves (6 g) in anhydrous CH_2Cl_2 (1.0 L) at −20 °C was added freshly distilled titanium tetraisopropoxide (1.74 g, 6.13 mmol), freshly distilled (−)-diethyl tartrate (1.89 g, 9.20 mmol) and *tert*-butylhydroperoxide (32.6 mL of a 5.62 M solution in CH_2Cl_2, 184 mmol). The reaction mixture was stirred for 20 min at −20 °C and then a solution of the allylic alcohol **306** (30.0 g, 123 mmol) in anhydrous CH_2Cl_2 (200 mL) was added slowly, maintaining the temperature at −20 °C. The reaction was stirred for a further hour and quenched by the addition of water (100 mL) and a solution of 30% wt of NaOH in brine (100 mL). The reaction mixture was stirred for a further 30 min and then allowed to warm to rt. The molecular sieves were removed by filtration and the aqueous phase was separated and extracted with CH_2Cl_2 (3 × 300 mL). The organic extracts were combined, washed with brine (300 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a colourless oil. Flash column chromatography on silica gel (petroleum ether - ethyl acetate, gradient elution 5:1 → 2:1) afforded the epoxy alcohol **307** (30.3 g, 95%) as a colourless oil.

R_f = 0.40 (petroleum ether - ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70−3.55 (4H, m, CH_2-C1, CH_2-C6), 3.07 (1H, dd, *J* = 6.0, 5.9 Hz, CH-C4), 1.74−1.60 (5H, m, CH_2-C2, CH_2-C3, OH), 1.28 (3H, s, CH_3-C7), 0.89 (9H, s, *t*Bu), 0.05 (6H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.5 (CH_2-C6), 62.7 (CH_2-C1), 61.0 (C-C5), 60.1 (CH-C4), 29.8 (CH_2-C2), 26.1 (CH_3-*t*Bu), 24.9 (CH_2-C3), 18.4 (C-*t*Bu), 14.3 (CH_3-C7), −5.2 (CH_3-$SiCH_3$); HRMS (CI, Me_3CH) $[M+H]^+$ for $C_{13}H_{29}O_3Si$ calcd 261.1887, found 261.1888, Δ +0.7 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 261.5 (30%), 243.5 (42%), 203.4 (100%), 129.3 (90%); Anal. Calcd for $C_{13}H_{28}O_3Si$: C, 59.95%; H, 10.84%; Found: C, 59.98%; H, 10.88%; IR ν_{max} 3433, 2955, 2929, 2885, 2857, 834, 773 cm^{-1}; $[\alpha]^{23}_D$ +14.9 (*c* = 1.00, $CHCl_3$); {Lit.[80] $[\alpha]^{28}_D$ +11.1 (c = 1.04, $CHCl_3$)}.

(*R*)-6-*tert*-Butyldimethylsilyloxy-2-methyl-1-hexen-3-ol 284[80, 86]

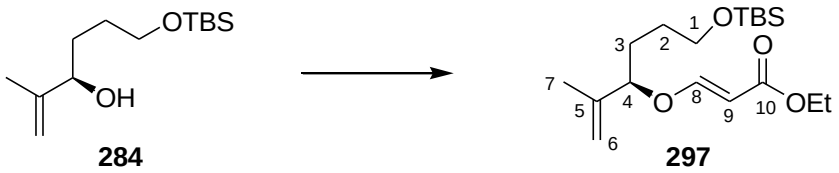


307 **308** **284**

To a stirred solution of the epoxy alcohol **307** (30.3 g, 117 mmol) and triethylamine (17.7 g, 175 mmol) in anhydrous CH_2Cl_2 (580 mL) at −10 °C was slowly added methanesulfonyl chloride (16.0 g, 140 mmol). The solution was stirred for 10 min then quenched by the addition of water (100 mL) and diluted with CH_2Cl_2 (250 mL). The organic phase was washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a colourless oil. The crude epoxy mesylate **308** was carried on to the next step without further purification.
To a stirred solution of the crude epoxy mesylate **308** in butan-2-one (580 mL) was added sodium iodide (87.4 g, 583 mmol) and the reaction mixture was heated at reflux for 1 h giving a brown slurry. Zinc powder (11.4 g, 175 mmol) was then added and the reaction was stirred at reflux for a further 1 h giving a grey solution. The reaction mixture was then allowed to cool to rt, diluted with ethyl acetate (500 mL) and a saturated aqueous solution of NH_4Cl (300 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 300 mL). The organic extracts were combined, washed with brine (300 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a brown oil. Flash column chromatography on silica gel (petroleum ether – diethyl ether, gradient elution 30:1 → 20:1 → 15:1) afforded the alcohol **284** as a colourless oil (27.6 g, 97% over two steps). A 94% enantiomeric purity of **284** was obtained by normal phase chiral HPLC analysis[84] of the corresponding vinylogous carbonate **297**.
R_f = 0.42 (petroleum ether - ethyl acetate, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.96 (1H, br s, CH_2-C6), 4.83 (1H, br s, CH_2-C6), 4.08−4.04 (1H, m, CH-C4), 3.66 (2H, t, *J* = 5.7 Hz, CH_2-C1), 2.53 (1H, d, *J* = 3.8 Hz, OH), 1.72 (3H, s, CH_3-C7), 1.71−1.56 (4H, m, CH_2-C2, CH_2-C3), 0.90 (9H, s, *t*Bu), 0.06 (6H, s, $SiCH_3$); ^{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 (CH_3-*t*Bu), 18.5 (C-*t*Bu), 18.0 (CH_3-C7), −5.2 ($SiCH_3$); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{13}H_{29}O_2Si$ 245.1937, found 245.1932, Δ −2.1 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 245.5 (80%),

227.4 (100%), 137.3 (60%), 113.3 (80%); Anal. Calcd for $C_{13}H_{28}O_2Si$: C, 63.88%; H, 11.55%; Found: C, 63.73%; H, 11.65%; IR ν_{max} 3378, 2954, 2929, 2885, 2857, 898, 835, 774 cm^{-1}; $[\alpha]^{23}_D$ +8.7 (*c* = 1.01, $CHCl_3$) {Lit.[80] $[\alpha]^{21}_D$ +9.11 (c = 1.25, $CHCl_3$)}.

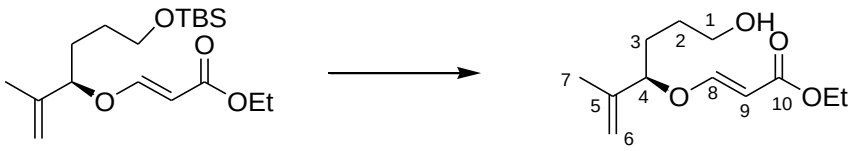
Ethyl (*E*)-3-[6-(*tert*-butyldimethylsilyloxy)-2-methyl-1-hexen-3-yl] oxy propenoate 297[80]



To a stirred solution of alcohol **284** (668 mg, 2.73 mmol) in anhydrous CH_2Cl_2 (7 mL) at rt was added ethyl propiolate (537 mg, 5.47 mmol) and *N*-methylmorpholine (553 mg, 5.47 mmol). The resulting brown solution was stirred for 18 h then concentrated *in vacuo* to yield a dark brown oil. Flash column chromatography on silica gel (petroleum ether - ethyl acetate, 30:1) afforded the ester **297** as a colourless oil (881 mg, 94%).

R_f = 0.71 (petroleum ether - ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (1H, d, *J* = 12.4 Hz, CH-C8), 5.25 (1H, d, *J* = 12.4 Hz, CH-C9), 4.97 (1H, dd, *J* = 1.4, 1.4 Hz, CH_2-C6), 4.95 (1H, br s, CH_2-C6), 4.26 (1H, br t, *J* = 6.7 Hz, CH-C4), 4.13 (1H, q, *J* = 7.1 Hz, CH_2-Et), 4.12 (1H, q, *J* = 7.1 Hz, CH_2-Et), 3.66−3.57 (2H, m, CH_2-C1), 1.81−1.67 (2H, m, CH_2-C2), 1.66 (3H, s, CH_3-C7), 1.61−1.47 (2H, m, CH_2-C3), 1.25 (3H, t, *J* = 7.1 Hz, CH_3-Et), 0.88 (9H, s, *t*Bu), 0.04 (6H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2 (C-C10), 161.6 (CH-C8), 142.9 (C-C5), 114.7 (CH_2-C6), 98.0 (CH-C9), 86.6 (CH-C4), 62.6 (CH_2-C1), 59.8 (CH_2-Et), 29.6 (CH_2-C3), 28.6 (CH_2-C2), 26.1 (CH_3-*t*Bu), 18.4 (C-*t*Bu), 17.0 (CH_3-C7), 14.5 (CH_3-Et), −5.2 ($SiCH_3$); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{18}H_{35}O_4Si$ 343.2305, found 343.2302, Δ −0.8 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 343.5 (7%), 227.4 (18%), 137.2 (100%); Anal. Calcd for $C_{18}H_{34}O_4Si$: C, 63.11%; H, 10.00%; Found: C, 63.14%; H, 10.04%; IR ν_{max} 2955, 2929, 2897, 2859, 1713, 1643, 1624, 909, 835, 775 cm^{-1}; $[\alpha]^{23}_D$ −8.4 (*c* = 1.00, $CHCl_3$) {Lit.[80] $[\alpha]^{18}_D$ −7.94 (c = 1.41, $CHCl_3$)}.

(*R*)-Ethyl (*E*)-3-(6-hydroxy-2-methyl-1-hexen-3-yl)oxypropenoate 310[80]

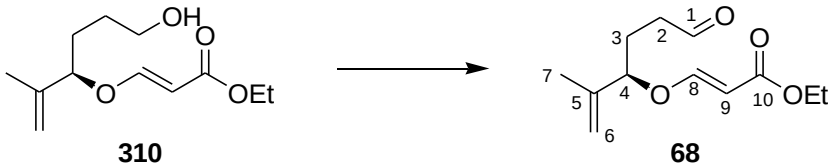


297 **310**

To a stirred solution of the silyl ether **297** (1.0 g, 2.9 mmol) in MeOH (30 mL) at rt was added camphorsulfonic acid (CSA) (67 mg, 0.29 mmol). The resulting solution was stirred for 30 min at rt and $NaHCO_3$ was added to neutralise the CSA. The remaining solid was filtered and the solution was concentrated *in vacuo* to yield a yellow oil. The crude product was purified by flash column chromatography on silica gel (petroleum ether - ethyl acetate, gradient elution 5:1 → 2:1) to give the alcohol **310** as a colourless oil (578 mg, 86%).

R_f = 0.19 (petroleum ether - ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (1H, d, *J* = 12.4 Hz, CH-C8), 5.26 (1H, d, *J* = 12.4 Hz, CH-C9), 4.99 (1H, dd, *J* = 1.4, 1.4 Hz, CH_2-C6), 4.97 (1H, br s, CH_2-C6), 4.27 (1H, dd, *J* = 7.7, 5.5 Hz, CH-C4), 4.15 (1H, q, *J* = 7.1 Hz, CH_2-Et), 4.14 (1H, q, *J* = 7.1 Hz, CH_2-Et), 3.70−3.63 (2H, m, CH_2-C1), 1.87−1.51 (4H, m, CH_2-C2, CH_2-C3), 1.67 (3H, s, CH_3-C7), 1.35 (1H, br s, OH), 1.26 (3H, t, *J* = 7.1 Hz, CH_3-Et); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.2 (C-C10), 161.5 (CH-C8), 142.8 (C-C5), 114.9 (CH_2-C6), 98.2 (CH-C9), 86.5 (CH-C4), 62.5 (CH_2-C1), 59.9 (CH_2-Et), 29.6 (CH_2-C3), 28.7 (CH_2-C2), 17.1 (CH_3-C7), 14.5 (CH_3-Et); 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) 229.4 (100%), 221.4 (10%), 183.3 (8%), 137.3 (10%), 117.2 (80%); 113.2 (50%); Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14%; H, 8.83%; Found: C, 62.86%; H, 8.91%; IR ν_{max} 3436, 2979, 2949, 1707, 1640, 1622, 960, 911, 833 cm^{-1}; $[\alpha]^{24}_D$ −8.3 (*c* = 1.01, $CHCl_3$) {Lit.[80] $[\alpha]^{18}_D$ −8.44 (c = 1.35, $CHCl_3$)}.

(*R*)-Ethyl (*E*)-3-(5-methyl-5-hexenal-4-yl)oxypropenoate 68[80]

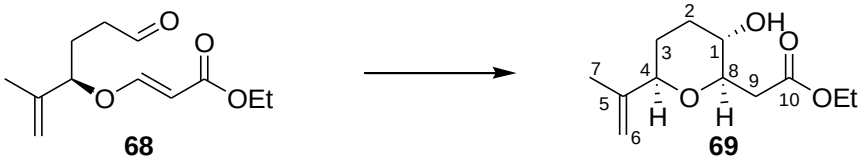


310 **68**

To a stirred solution of oxalyl chloride (12.7 g, 158 mmol) in dry CH_2Cl_2 (370 mL) at −78 °C was added anhydrous DMSO (25.3 g, 324 mmol) in anhydrous CH_2Cl_2 (115 mL) dropwise by cannula. The resulting solution was stirred for 30 min at −78 °C then the alcohol **310** (20.0 g, 87.6 mmol) in anhydrous CH_2Cl_2 (260 mL) was added dropwise by cannula. The resulting solution was stirred for a further 3 h at −78 °C and then quenched with Et_3N (44.3 g, 438 mmol). The reaction mixture was allowed to warm to rt and stirred for 30 min then diluted with CH_2Cl_2 (200 mL) and water (100 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 200 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether - ethyl acetate, 5:1) afforded the aldehyde **68** as a colourless oil (19.3 g, 97%).

R_f = 0.41 (petroleum ether - ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (1H, s, CH-C1), 7.44 (1H, d, *J* = 12.4 Hz, CH-C8), 5.25 (1H, d, *J* = 12.4 Hz, CH-C9), 5.01 (1H, br s, CH_2-C6), 4.98 (1H, s, CH_2-C6), 4.29 (1H, dd, *J* = 7.9, 5.4 Hz, CH-C4), 4.15 (1H, q, *J* = 7.1 Hz, CH_2-Et), 4.14 (1H, q, *J* = 7.1 Hz, CH_2-Et), 2.56−2.52 (2H, m, 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-Et); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.2 (C-C1), 168.0 (C-C10), 161.0 (CH-C8), 142.2 (C-C5), 115.2 (CH-C6), 98.6 (CH-C9), 85.1 (CH-C4), 59.9 (CH_2-Et), 39.8 (CH_2-C2), 25.7 (CH_2-C3), 17.2 (CH_3-C7), 14.5 (CH_3-Et); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{12}H_{19}O_4$ 227.1283, found 227.1279, Δ −2.0 ppm; LRMS (CI, Me_3CH) *m/z* (intensity); 227.4 (100%), 209.4 (5%), 111.2 (59%); Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70%; H, 8.02%; Found: C, 63.27%; H, 8.04%; IR ν_{max} 2980, 2940, 1706, 1641, 1623, 957, 912, 834 cm^{-1}; $[\alpha]^{23}_D$ −1.9 (*c* = 1.00, $CHCl_3$) {Lit.[80] $[\alpha]^{22}_D$ −2.20 (c = 1.00, $CHCl_3$)}.

Ethyl [(*2R*,*3S*,*6R*)-3-hydroxy-6-isopropenyltetrahydropyran-2-yl]acetate 69[80]

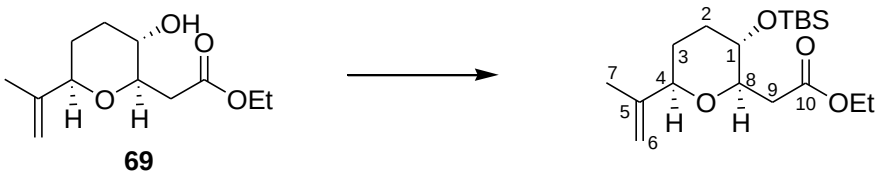


68 **69**

To a stirred solution of the aldehyde **68** (244 mg, 1.08 mmol) and anhydrous MeOH (138 mg, 4.31 mmol) in anhydrous THF (11 mL) at rt was added a freshly prepared solution of samarium diiodide (0.1 M in THF) until the solution remained deep blue in colour (approx. 4 equivalents added). The resulting solution was stirred for 30 min then quenched with ethyl acetate (5 mL) and a saturated aqueous solution of $Na_2S_2O_3$ (12 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 10 mL). The organic extracts were combined, washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to yield a yellow oil. Flash column chromatography on silica gel (petroleum ether - ethyl acetate, gradient elution 4:1 → 1:1) afforded the tetrahydropyranol **69** (212 mg, 86%) as a yellow oil.

R_f = 0.22 (petroleum ether - ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93 (1H, s, CH-C6), 4.81 (1H, s, CH-C6), 4.15 (2H, q, *J* = 7.1 Hz, CH_2-Et), 3.74 (1H, br d, *J* = 9.7 Hz, CH-C4), 3.60 (1H, ddd, *J* = 9.2, 7.0, 5.0 Hz, CH-C8), 3.44−3.34 (1H, m, CH-C1), 2.81 (1H, dd, *J* = 15.1, 5.0 Hz, CH_2-C9), 2.57 (1H, dd, *J* = 15.1, 7.0 Hz, CH_2-C9), 2.19−2.12 (1H, m, CH_2-C2), 2.02−1.96 (1H, m, OH), 1.88−1.81 (1H, m, CH_2-C3), 1.72 (3H, s, CH_3-C7), 1.56−1.48 (2H, m, CH_2-C2, CH_2-C3), 1.25 (3H, t, *J* = 7.1 Hz, CH_3-Et); ^{13}C NMR (100 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-Et), 38.9 (CH_2-C9), 33.2 (CH_2-C2), 29.7 (CH_2-C3), 19.3 (CH_3-C7), 14.4 (CH_3-Et); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{12}H_{21}O_4$ 229.1439, found 229.1438, Δ −0.8 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 229.4 (100%), 211.4 (5%), 183.3 (10%); Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14%; H, 8.83%; Found: C, 62.73%; H, 8.95%; IR ν_{max} 3456, 2979, 2942, 2861, 1738, 1721, 901 cm^{-1}; $[\alpha]^{25}_D$ +42.6 (*c* = 1.02, $CHCl_3$) {Lit.[80] $[\alpha]^{22}_D$ +36.7 (c = 1.00, $CHCl_3$)}.

Ethyl[(*2R*,*3S*,*6R*)-3-(*tert*-butyldimethylsilyloxy)-6-isopropenyl tetrahydropyran-2-yl] acetate[80]

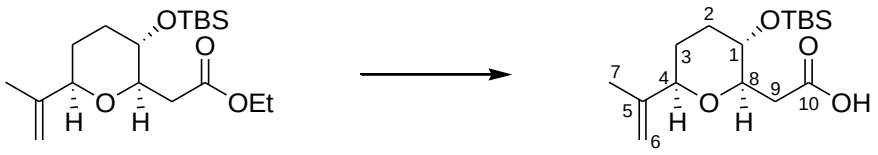


69

To a stirred solution of the alcohol **69** (7.44 g, 32.6 mmol) and imidazole (4.43 g, 65.2 mmol) in anhydrous DMF (75 mL) was added *t*-butyldimethylsilyl chloride (8.84 g, 58.7 mmol) portionwise over 5 min. The resulting solution was stirred overnight at rt then quenched by addition of Et_2O (300 mL) and water (600 mL). The aqueous phase was separated and the organic phase was washed with water (5 × 300 mL). The aqueous extracts were combined and extracted with Et_2O (300 mL). The organic extracts were combined and washed with brine (200 mL) dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil. Flash column chromatography on silica gel (petroleum ether - ethyl acetate, 20:1) afforded the silyl ether (10.7 g, 96%) as a colourless oil.

R_f = 0.73 (petroleum ether - ethyl acetate, 2:1); ^{1}H 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-Et), 3.69 (1H, br d, *J* = 9.9 Hz, CH-C4), 3.65 (1H, ddd, *J* = 9.2, 9.1, 3.3 Hz, CH-C8), 3.40−3.32 (1H, m, CH-C1), 2.80 (1H, dd, *J* = 14.8, 3.3 Hz, CH_2-C9), 2.37 (1H, dd, *J* = 14.8, 9.2 Hz, CH_2-C9), 2.07−2.00 (1H, m, CH_2-C2), 1.84−1.77 (1H, m, CH_2-C3), 1.70 (3H, s, CH_3-C7), 1.56−1.48 (2H, m, CH_2-C2, CH_2-C3), 1.25 (3H, t, *J* = 7.1 Hz, CH_3-Et), 0.87 (9H, s, CH_3-*t*Bu), 0.06 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$); ^{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-Et), 38.4 (CH_2-C9), 33.5 (CH_2-C2), 29.7 (CH_2-C3), 25.9 (CH_3-*t*Bu), 19.4 (CH_3-C7), 18.1 (C-*t*Bu), 14.4 (CH_3-Et), −3.9 ($SiCH_3$), −4.6 ($SiCH_3$); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{18}H_{35}O_4Si$ 343.2304, found 343.2307, Δ +0.6 ppm; LRMS (CI, Me_3CH) *m*/*z* (intensity); 343.5 (100%), 329.5 (11%), 285.4 (15%), 113 (44%); Anal. Calcd for $C_{18}H_{34}O_4Si$: C, 63.11%; H, 10.00%; Found: C, 62.95%; H, 10.07%; IR ν_{max} 2951, 2930, 2858, 1740, 898, 858, 835, 774 cm^{-1}; $[\alpha]^{24}_D$ +59.0 (*c* = 1.03, $CHCl_3$) {Lit.[80] $[\alpha]^{28}_D$ +53.0 (c = 0.50, $CHCl_3$)}.

(*2R*,*3S*,*6R*)-3-(*tert*-Butyldimethylsilyloxy)-6-isopropenyltetrahydropyran-2-yl acetic acid 312[80]

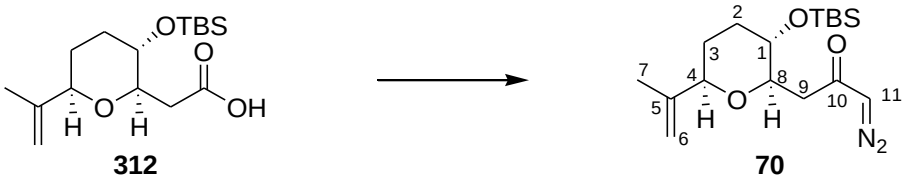


312

To a stirred solution of ester (10.2 g, 29.7 mmol) in ethanol (150 mL) and water (50 mL) was added lithium hydroxide (3.74 g, 89.2 mmol) portionwise over 5 min. The resulting solution was stirred at rt overnight and then acidified to pH 2-3 with 1 M HCl. The reaction mixture was diluted with ethyl acetate (300 mL) and water (200 mL) and aqueous phase was then separated and extracted with ethyl acetate (3 × 150 mL). The organic extract were combined washed with brine (100 mL) dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether - ethyl acetate, gradient elution 20:1 → 4:1) afforded the carboxylic acid **312** as a colourless gummy oil (8.28 g, 89%).

R_f = 0.57 (petroleum ether - ethyl acetate, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.88 (1H, br s, COOH), 4.94 (1H, s, CH_2-C6), 4.82 (1H, s, CH_2-C6), 3.80 (1H, br d, *J* = 9.6 Hz, CH-C4), 3.62 (1H, ddd, *J* = 8.9, 8.9, 3.2 Hz, CH-C8), 3.40−3.32 (1H, m, CH-C1), 2.86 (1H, dd, *J* = 15.6, 3.2 Hz, CH_2-C9), 2.46 (1H, dd, *J* = 15.6, 8.9 Hz, CH_2-C9), 2.08−2.02 (1H, m, CH_2-C2), 1.85−1.79 (1H, m, CH_2-C3), 1.72 (3H, s, CH_3-C7), 1.59−1.50 (2H, m, CH_2-C2, CH_2-C3), 0.87 (9H, s, CH_3-*t*Bu), 0.07 (6H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5 (C-C10), 144.7 (C-C5), 111.1 (CH_2-C6), 80.6 (CH-C4), 79.1 (CH-C8), 70.8 (CH-C1), 37.9 (CH_2-C9), 33.4 (CH_2-C2), 29.7 (CH_2-C3), 25.9 (CH_3-*t*Bu), 19.2 (CH_3-C7), 18.0 (C-*t*Bu), −3.9 ($SiCH_3$), −4.6 ($SiCH_3$); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{16}H_{31}O_4Si$ 315.1992, found 315.1995, Δ +1.1 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 315.4 (100%), 297.4 (12%), 257.4 (20%), 183.8 (55%); IR ν_{max} 2951, 2930, 2887, 2859, 1715, 899, 837, 775 cm^{-1}; $[\alpha]^{25}_D$ +67.5 (*c* = 1.00, $CHCl_3$) {Lit.[80] $[\alpha]^{25}_D$ +36.7 (c = 0.21, $CHCl_3$)}.

1-Diazo-3-[(2*R*,3*S*,6*R*)-3-(*tert*-butyldimethylsilyloxy)-6-isopropenyl tetrahydropyran-2-yl]-propan-2-one 70[80]

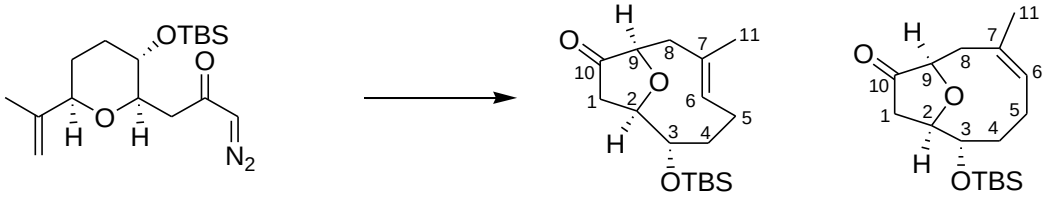


To a stirred solution of the carboxylic acid **312** (3.00 g, 9.55 mmol) and triethylamine (1.32 g, 13.0 mmol) in anhydrous diethyl ether (120 mL) was added *iso*butyl chloroformate (1.64 g, 12.0 mmol) dropwise and the resulting solution was stirred for 2.5 h (a white precipitate formed). The solution of the anhydride was filtered under suction, washing the residue with diethyl ether, and then immediately added to a freshly prepared ethereal solution of diazomethane (~100 mmol) dropwise. The solution was stirred for 2 days and quenched by addition of glacial acetic acid (5 mL) then poured into a saturated aqueous solution of $NaHCO_3$ (200 mL) and vigorously stirred for 15 min. The aqueous phase was separated and extracted with ethyl acetate (3 × 75 mL). The combined organic extracts were washed with brine (75 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil. Flash column chromatography on silica gel (petroleum ether - ethyl acetate 10:1) afforded the diazo ketone **70** as a yellow oil (2.83 g, 88%).

R_f = 0.51 (petroleum ether - ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 (1H, br s, CH-C11), 4.92 (1H, s, CH_2-C6), 4.80 (1H, s, CH_2-C6), 3.72 (1H, d, *J* = 10.1 Hz, CH-C4), 3.58 (1H, ddd, *J* = 9.1, 9.1, 2.4 Hz, CH-C8), 3.37–3.29 (1H, m, CH-C1), 2.77 (1H, dd, *J* = 14.3, 2.4 Hz, CH_2-C9), 2.45–2.30 (1H, m, CH_2-C9), 2.07–2.01 (1H, m, CH_2-C2), 1.83–1.77 (1H, m, CH_2-C3), 1.71 (3H, s, CH_3-C7), 1.60–1.43 (2H, m, CH_2-C2, CH_2-C3), 0.87 (9H, s, CH_3-*t*Bu), 0.06 (6H, s, $SiCH_3$); ^{13}C NMR (125 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), 33.6 (CH_2-C2), 29.8 (CH_2-C3), 25.9 (CH_3-*t*Bu), 19.4 (C-*t*Bu), 18.1 (CH_3-C7), −3.9 ($SiCH_3$), −4.6 ($SiCH_3$); HRMS (FAB) $[M+H]^+$ calcd for $C_{17}H_{31}O_3N_2Si$ 339.2104, found 339.2105, Δ +0.2 ppm; LRMS (FAB) *m*/*z* (intensity) 339.1 (100%), 297.2 (18%), 281.1 (99%), 255.2 (25%), 207.0 (37%), 171.0 (62%); IR ν_{max} 2949, 2929, 2883,

2857, 2099, 1640, 897, 835, 774 cm^{-1}; $[\alpha]^{23}_D$ +95.7 (*c* = 1.01, $CHCl_3$) {Lit.[80] $[\alpha]^{25}_D$ +74.3 (c = 1.10, $CHCl_3$)}.

(1*R*,2*S*,5*E*,8*R*)-2-(*tert*-Butyldimethylsilyloxy)-6-methyl-11-oxabicyclo[6.2.1]-5-undecen-9-one 72 and (1*R*,2*S*,5*Z*,8*R*)-2-(*tert*-butyldimethylsilyloxy)-6-methyl-11-oxabicyclo[6.2.1]-5-undecen-9-one 73[80]



70 **72** **73**

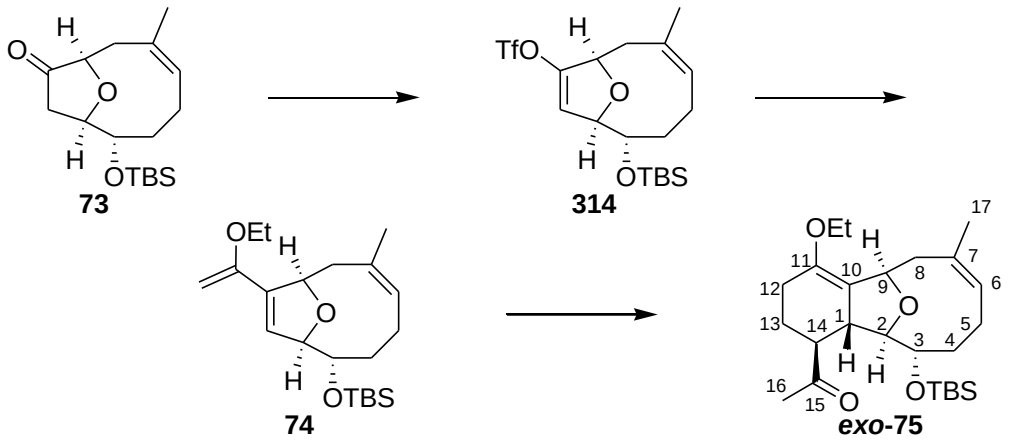
To a stirred solution of $Rh_2(pfm)_2$ (360 mg, 0.34 mmol) in anhydrous CH_2Cl_2 (175 mL) at reflux was added the diazo ketone **70** (5.95 g, 17.5 mmol) in anhydrous CH_2Cl_2 (880 mL) over 45 min, maintaining a good reflux. The resulting solution was stirred for a further 15 min, allowed to cool and concentrated *in vacuo* to give a brown solid. Rapid column chromatography on deactivated alumina (petroleum ether - ethyl acetate, 15:1) allowed the removal of the catalyst. Flash column chromatography on $AgNO_3$ (10%) impregnated silica gel (petroleum ether - ethyl acetate, gradient elution 30:1 → 1:1) afforded the *Z*-alkene ***73*** (1.20 g, 22%) as a colourless crystalline solid and the *E*-alkene ***72*** (2.26 g 41%) as colourless crystalline solide.

***72*:** R_f = 0.56 (petroleum ether - Et_2O, 5:1); m.p. 55–57 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 5.35 (1H, dd, *J* = 11.9, 4.3 Hz, CH-C6), 4.17–4.12 (2H, m, CH-C2, CH-C9), 3.02 (1H, dd, *J* = 8.9, 7.8 Hz, CH-C3), 2.78 (1H, ddd, *J* = 18.0, 9.1, 1.4 Hz, CH_2-C1), 2.55–2.50 (2H, m, CH_2-C8), 2.28 (1H, br d, *J* = 18.0 Hz, CH_2-C1), 2.28–2.11 (2H, m, CH_2-C5), 1.96 (1H, dddd, *J* = 14.1, 11.8, 7.8, 3.9 Hz, CH_2-C4), 1.71 (1H, ddd, *J* = 14.1, 3.6, 3.6 Hz, CH_2-C4), 1.55 (3H, s, CH_3-C11), 0.86 (9H, s, CH_3-*t*Bu), 0.08 (3H, s, $SiCH_3$), 0.03 (3H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.4 (C-C10), 133.4 (CH-C6), 124.8 (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 (CH_3-*t*Bu), 18.9 (CH_3-C11), 18.0 (C-*t*Bu), −3.7 ($SiCH_3$), −4.6 ($SiCH_3$); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{17}H_{31}O_3Si$ 311.2042, found 311.2038, Δ −1.5 ppm; LRMS (CI, Me_3CH) *m/z* (intensity); 311.6 (100%), 253.4 (18%), 179.4 (10%); Anal. Calcd for $C_{17}H_{30}O_3Si$: C, 65.76%; H, 9.74%. Found: C, 65.78% H, 9.81%; IR ν_{max}

2950, 2931, 2860, 1755, 837, 774 cm^{-1}; $[\alpha]^{28}_D$ −38.7 (*c* = 0.99, $CHCl_3$) {Lit.[80] $[\alpha]^{23}_D$ −14.2 (c = 1.55, $CHCl_3$)}.

***73*:** R_f = 0.56 (petroleum ether - Et_2O, 5:1); m.p. 88−90 °C {Lit.[80] m.p. 87−89 °C}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.41 (1H, dd, *J* = 11.6, 5.8 Hz, CH-C6), 4.23 (1H, t, *J* = 4.4 Hz, CH-C9), 4.17 (1H, t, *J* = 8.7 Hz, CH-C2), 3.42 (1H, ddd, *J* = 10.8, 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 Hz, CH_2-C8), 2.02−1.93 (1H, m, CH_2-C5), 1.86 (1H, dddd, *J* = 13.6, 10.8, 6.1, 2.7 Hz, CH_2-C4), 1.75 (3H, s, CH_3-C11), 1.69−1.58 (1H, m, CH_2-C4), 0.86 (9H, s, CH_3-*t*Bu), 0.05 (3H, s, $SiCH_3$), 0.01 (3H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.0 (C-C10), 132.5 (CH-C7), 127.7 (CH-C6), 80.4 (CH-C2), 78.9 (CH-C9), 75.5 (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_3-*t*Bu, CH_2-C5), 18.0 (C-*t*Bu), −3.7 ($SiCH_3$), −4.4 ($SiCH_3$); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{17}H_{31}O_3Si$ 311.2042, found 311.2039, Δ −1.3 ppm; LRMS (CI, Me_3CH) *m*/*z* (intensity); 311.6 (100%), 253.4 (18%), 179.4 (18%); Anal. Calcd for $C_{17}H_{30}O_3Si$: C, 65.76%; H, 9.74%. Found: C, 65.78% H, 9.83%; IR ν_{max} 2954, 2927, 2856, 1754, 835, 775 cm^{-1}; $[\alpha]^{28}_D$ +31.8 (*c* = 1.03, $CHCl_3$) {Lit.[80] $[\alpha]^{22}_D$ +30.0 (c = 1.00, $CHCl_3$)}.

1-[(1*R*,2*R*,3*S*,8*R*,10*Z*,14*S*)-14-[(*tert*-Butyldimethylsilyl)oxy]-6-ethoxy-10-methyl-15- oxatricyclo[6.6.1.$0^{2,7}$]pentadeca-6,10-dien-3- yl]ethan-1-one exo-75[80]



To a solution of the bicyclic ketone **73** (1.06 g, 3.31 mmol) and $PhN(Tf)_2$ (2.44 g, 6.82 mmol) in anhydrous THF (70 mL) at −78 °C was added NaHMDS (8.53 mL of a 1.0 M solution in THF, 8.53 mmol) dropwise over 10 min. The resulting solution was stirred at −78 °C for 2 h, then quenched with water (20 mL) at −78 °C and

allowed to warm to rt. The aqueous phase was separated and extracted with Et_2O (3 × 80 mL). The organic extracts were combined washed with brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude enol triflate **314** as a yellow oil which as used without any further purification in the next step.

To a solution of the above crude enol triflate **314** and $CH_2C(OEt)SnBu_3$ (3.69 g, 10.2 mmol) in anhydrous THF (70 mL) was added LiCl (434 mg, 10.2 mmol) and $Pd(PPh_3)_4$ (591 mg, 510 μmol), the solution was heated at reflux overnight. The reaction mixture was cooled and diluted with ethyl acetate (30 mL). The organic phase was washed with brine (20 mL), 5% aqueous solution of NH_4OH (20 mL), brine (20 mL). The organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil. Quick flash column chromatography on silica gel (petroleum ether - ethyl acetate, 15:1 with 1% Et_3N) afforded the highly unstable diene **74** as a colourless oil which was used immediately.

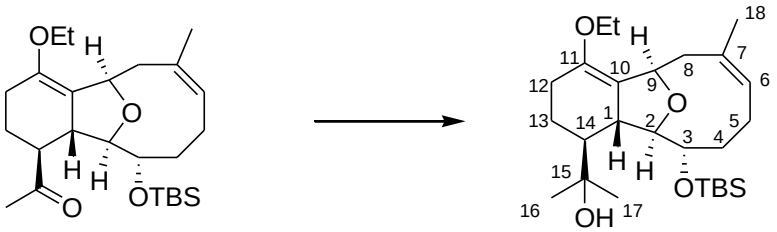
The above diene **74** and freshly distilled methyl vinyl ketone (2.39 g, 34.1 mmol) were dissolved in anhydrous toluene (140 mL) and heated to reflux in a sealed tube overnight. The volatiles were removed *in vacuo* to give a yellow oil. Flash column chromatography on silica gel (petroleum ether - ethyl acetate, 15:1 with 1% Et_3N) delivered a *endo*-*exo* mixture of Diels-Alder cycloadducts **75** (1.02 g, 69% over 3 steps) as colourless oil.

To a stirred solution of the *endo*-*exo* mixture of cycloadducts **75** (1.02 g, 2.35 mmol) in methanol (25 mL) was added potassium carbonate (389 mg, 2.80 mmol) and the solution stirred at rt overnight. The reaction mixture was diluted with a saturated aqueous solution of NH_4Cl (25 mL) and ethyl acetate (40 mL). The aqueous phase was separated and extracted with ethyl acetate (2 × 40 mL). The organic extracts were combined and washed with brine (20 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil. Flash column chromatography on silica gel (petroleum ether - ethyl acetate, 20:1 with 1% Et_3N) afforded the ketone ***exo*-75** as a colourless oil (929 mg, 91%).

R_f = 0.40 (petroleum ether - ethyl acetate, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (1H, dd, *J* = 11.5, 5.6 Hz, CH-C6), 4.87–4.85 (1H, m, CH-C9), 3.78 (2H, q, *J* = 7.0 Hz, CH_3-Et), 3.70 (1H, dd, *J* = 9.3, 2.6 Hz, CH-C2), 3.59–3.57 (1H, m, CH-C3), 3.15–3.05 (1H, m, CH_2-C5), 2.91 (1H, br dd, *J* = 9.3 Hz, CH-C1), 2.82 (1H, d, *J* = 14.0 Hz, CH_2-C8), 2.35–2.16 (3H, m, CH_2-C12, CH-C14), 2.15 (3H, s, CH_3-C16), 2.06–1.98 (1H, m, CH_2-C13), 1.92 (1H, dd, *J* = 14.0, 4.0 Hz, CH_2-C8),

1.88–1.72 (3H, m, CH_2-C4, CH_2-C5), 1.66 (3H, s, CH_3-C17), 1.65–1.54 (1H, m, CH_2-C13), 1.26 (3H, t, *J* = 7.0 Hz, CH_3-Et), 0.88 (9H, s, CH_3-*t*Bu), 0.04 (3H, s, $SiCH_3$), 0.03 (3H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3 (C-C15), 143.8 (C-C11), 130.5 (C-C7), 130.2 (CH-C6), 119.2 (C-C10), 88.2 (CH-C2), 75.2 (CH-C9), 72.0 (CH-C3), 63.2 (CH_2-Et), 52.3 (CH-C14), 43.5 (CH-C1), 37.5 (CH_2-C8), 32.9 (CH_2-C4), 29.8 (CH_3-C16), 28.4 (CH_3-C17), 27.2 (CH_2-C13), 26.3 (CH_3-*t*Bu), 24.6 (CH_2-C12), 22.1 (CH_2-C5), 18.7 (C-*t*Bu), 15.8 (CH_3-Et), −4.3 ($SiCH_3$), −4.4 ($SiCH_3$); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{25}H_{43}O_4Si$ 435.2933, found 435.2935, Δ +1.1 ppm; LRMS (CI, Me_3CH) *m/z* (intensity); 435.5 (100%), 377.4 (7%); IR ν_{max} 2928, 2855, 1713, 833, 771 cm^{-1}; $[\alpha]^{24}_D$ +142.6 (*c* = 0.99, $CHCl_3$) {Lit.[80] $[\alpha]^{26}_D$ +225 (c = 1.28, $CHCl_3$)}.

2-[(1*R*,2*R*,3*S*,8*R*,10*Z*,14*S*)-14-[(*tert*-Butyldimethylsilyl)oxy]-6-ethoxy-10-methyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadeca-6,10-dien-3-yl]propan-2-ol 317



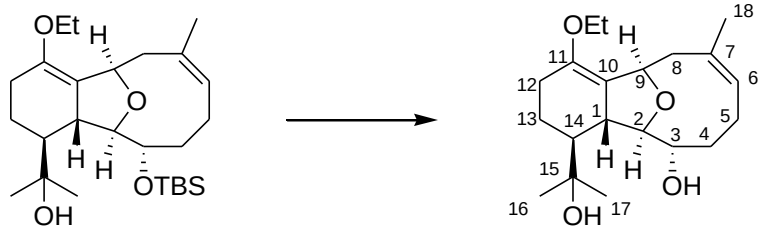
***exo*-75** **317**

To a solution of the ketone **exo-75** (300 mg, 690 μmol) in anhydrous THF (35 mL) at 0 °C was slowly added MeMgCl (1.38 mL of a 3 M solution in THF, 4.14 mmol). The reaction mixture was allowed to warm to rt and was stirred for 4 h before being quenched with a saturated aqueous solution of NH_4Cl (20 mL) and Et_2O (20 mL). The aqueous phase was separated and extracted with Et_2O (3 × 20 mL). The organic extracts were combined and washed with brine (20 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude alcohol as a yellow oil. Flash column chromatography on silica gel (petroleum ether - Et_2O, gradient elution 20:1 → 10:1 → 5:1 with 1% Et_3N) afforded the alcohol **317** as a colourless oil (263 mg, 84%).

R_f = 0.35 (petroleum ether - ethyl acetate, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (1H, dd, *J* = 11.3, 5.8 Hz, CH-C6), 4.83–4.81 (1H, m, CH-C9), 4.48–4.45 (1H, m, CH-C3), 4.07 (1H, dd, *J* = 8.2, 3.3 Hz, CH-C2), 3.78 (1H, q, *J* = 7.0 Hz, CH_2-Et), 3.77 (1H, q, *J* = 7.0 Hz, CH_2-Et), 3.08–3.04 (1H, m, CH_2-C5), 2.73 (1H, d, *J* = 13.7

Hz, CH_2-C8), 2.55–2.42 (1H, m, CH-C1), 2.23–2.18 (2H, m, CH_2-C12), 1.97 (1H, dd, *J* = 13.7, 4.6 Hz, CH_2-C8), 1.95–1.68 (4H, m, CH_2-C4, CH_2-C5, CH_2-C13), 1.67 (3H, s, CH_3-C18), 1.56–1.50 (1H, m, OH), 1.37–1.28 (2H, m, CH_2-C13, CH-C14), 1.27 (3H, s, CH_3-C16), 1.22 (3H, t, *J* = 7.0 Hz, CH_3-Et), 1.07 (3H, s, CH_3-C17), 0.90 (9H, s, CH_3-*t*Bu), 0.07 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2 (C-C11), 131.4 (CH-C6), 129.2 (C-C7), 121.7 (C-C10), 88.2 (CH-C2), 75.0 (CH-C9), 73.4 (CH-C15), 73.4 (CH-C3), 62.8 (CH_2-Et), 51.3 (CH-C14), 45.6 (CH-C1), 37.4 (CH_2-C8), 33.4 (CH_2-C4), 31.7 (CH_3-C16), 27.9 (CH_3-C18), 27.4 (CH_2-C13), 26.4 (CH_3-*t*Bu), 25.2 (CH_2-C12), 24.0 (CH_3-C17), 22.4 (CH_2-C5), 18.6 (C-*t*Bu), 15.8 (CH_3-Et), −3.5 ($SiCH_3$), −4.1 ($SiCH_3$); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{26}H_{47}O_4Si$ 451.3246, found 451.3238, Δ −1.2 ppm; LRMS (CI, Me_3CH) *m*/*z* (intensity) 451.6 (100%), 433.5 (16%); IR ν_{max} 3444, 2957, 2927, 2853, 1713, 936, 832, 772 cm^{-1}; $[\alpha]^{24}_D$ +83.9 (*c* = 0.99, $CHCl_3$).

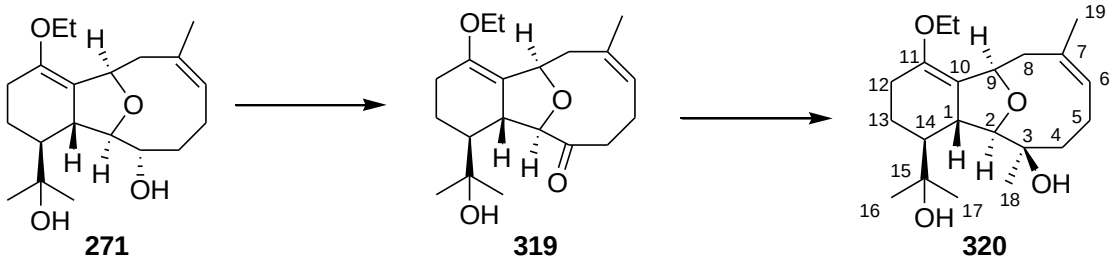
(1*R*,6*S*,7*R*,8*R*,9*S*,12*Z*)-3-Ethoxy-6-(2-hydroxypropan-2-yl)-13-methyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadeca-2,12-dien-9-ol 271



To a solution of the silyl ether **317** (234 mg, 520 μmol) and 4 Å molecular sieves in anhydrous THF (10 mL) was added TBAF (1.04 mL of a 1 M solution in THF, 1.04 mmol). The reaction mixture was stirred at rt for 1.5 h before being quenched by the addition of a saturated aqueous solution of NH_4Cl (5 mL). The molecular sieves were filtered off and rinsed with ethyl acetate. The aqueous phase was separated and extracted with ethyl acetate (3 × 10 mL). The organic extracts were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether - ethyl acetate, gradient elution 2:1 → 1:1 → 1:2 with 1% Et_3N) to deliver the diol **271** (160 mg, 91%) as a colourless solid.

R_f = 0.35 (petroleum ether - ethyl acetate, 4:1); m.p. 86–89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (1H, dd, *J* = 11.1, 6.0 Hz, CH-C6), 4.82 (1H, br s, CH-C9), 4.18 (1H, br s, CH-C3), 4.07 (1H, dd, *J* = 7.7, 4.0 Hz, CH-C2), 3.79 (1H, d, *J* = 7.0 Hz, CH_2-Et), 3.78 (1H, d, *J* = 7.0 Hz, CH_2-Et), 2.75–2.63 (2H, m, CH_2-C5, CH_2-C8), 2.57–2.50 (1H, m, CH-C1), 2.28–2.15 (2H, m, CH_2-C12), 2.05–1.99 (1H, m, CH_2-C4), 1.96 (1H, dd, *J* = 13.7, 4.2 Hz, CH_2-C8), 1.91–1.82 (2H, m, CH_2-C5, CH_2-C13), 1.75 (1H, dddd, *J* = 13.6, 10.1, 3.5, 3.5 Hz, CH_2-C4), 1.69 (3H, s, CH_3-C18), 1.40–1.29 (4H, m, CH_2-C13, CH-C14, OH, OH), 1.28 (3H, s, CH_3-C16), 1.23 (3H, t, *J* = 7.0 Hz, CH_3-Et), 1.10 (3H, s, CH_3-C17); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3 (C-C11), 131.8 (C-C7), 128.4 (CH-C6), 121.2 (C-C10), 88.2 (CH-C2), 74.9 (CH-C9), 74.9 (CH-C3), 73.6 (CH-C15), 62.8 (CH_2-Et), 51.0 (CH-C14), 46.6 (CH-C1), 37.4 (CH_2-C8), 33.0 (CH_2-C4), 31.4 (CH_3-C16), 27.4 (CH_2-C13), 27.3 (CH_3-C18), 25.1 (CH_2-C12), 23.8 (CH_3-C17), 23.0 (CH_2-C5), 15.8 (CH_3-Et); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{20}H_{33}O_4$ 337.2381, found 337.2380, Δ +0.4 ppm; LRMS (CI, Me_3CH) *m/z* (intensity); 337.4 (100%), 319.4 (72%), 291.7 (13%); IR ν_{max} 3336, 2973, 2923, 2877, 1713, 908, 731cm^{-1}; $[\alpha]^{24}_D$ +126.0 (*c* = 1.02, $CHCl_3$).

(1*R*,6*S*,7*R*,8*R*,9*R*,12*Z*)-3-Ethoxy-6-(2-hydroxypropan-2-yl)-9,13-dimethyl-15-oxatricyclo[6.6.1.0^{2,7}]pentadeca-2,12-dien-9-ol 320



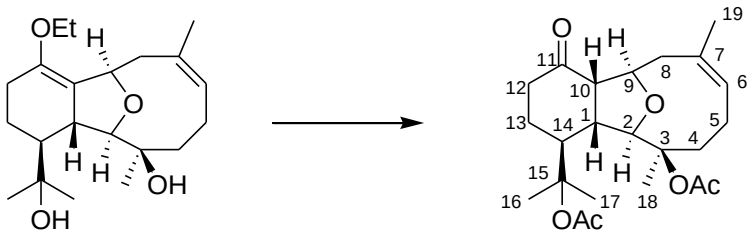
To a solution of the diol **271** (159 mg, 470 μmol) in anhydrous CH_2Cl_2 (20 mL) was added pyridine (150 mg, 1.88 mmol) and Dess-Martin periodinane (0.30 g, 0.70 mmol) at rt. The reaction mixture was stirred at this temperature for 40 min before being quenched with a saturated aqueous solution of $Na_2S_2O_3$ and $NaHCO_3$ (5:1, 5 mL). The mixture was diluted with Et_2O (20 mL) and stirred vigorously for 1 h. The aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The organic extracts were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was filtered

through a pad of silica gel (petroleum ether - ethyl acetate, 2:1 with 1% Et_3N) to afford crude ketone **319** which was used without further purification in the next step.

To a solution of the above crude ketone in anhydrous THF (20 mL) at 0 °C was slowly added MeMgCl (1.57 mL of a 3 M solution in THF, 4.16 mmol). The reaction mixture was allowed to warm to rt and stirred for 2 h before being quenched with a saturated aqueous solution of NH_4Cl (5 mL) and Et_2O (20 mL). The aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The organic extracts were combined washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether - ethyl acetate, gradient elution 3:1 → 2:1 with 1% Et_3N) afforded the diol **320** as a colourless solid (90 mg, 54% over 2 steps).

R_f = 0.46 (petroleum ether - ethyl acetate, 1:4); m.p. 56–58 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.37 (1H, dd, *J* = 11.1, 5.4 Hz, CH-C6), 4.88 (1H, br s, CH-C9), 3.79 (1H, q, *J* = 7.0 Hz, CH_2-Et), 3.78 (1H, q, *J* = 7.0 Hz, CH_2-Et), 3.69 (1H, d, *J* = 8.8 Hz, CH-C2), 3.55 (2H, br s, OH, OH), 2.95–2.89 (1H, m, CH-C1), 2.69 (1H, br d, *J* = 13.5 Hz, CH_2-C8), 2.67–2.59 (1H, m, CH_2-C5), 2.17–2.04 (2H, m, CH_2-C12), 2.00 (1H, dd, *J* = 13.5, 4.0 Hz, CH_2-C8), 1.95–1.86 (2H, m, CH_2-C4, CH_2-C5), 1.85–1.72 (2H, m, CH_2-C4, CH-C14), 1.67 (3H, s, CH_3-C19), 1.66–1.55 (2H, m, CH_2-C13), 1.44 (3H, s, CH_3-C18), 1.29 (3H, s, CH_3-C16), 1.23 (3H, t, *J* = 7.0 Hz, CH_3-Et), 1.14 (3H, s, CH_3-C17); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.7 (C-C11), 131.6 (C-C7), 129.2 (CH-C6), 120.7 (C-C10), 90.3 (CH-C2), 76.7 (CH-C9), 74.7 (C-C15), 74.5 (C-C3), 62.8 (CH_2-Et), 47.3 (CH-C14), 41.2 (CH-C1), 39.5 (CH_2-C4), 37.3 (CH_2-C8), 31.3 (CH_3-C16), 29.0 (CH_3-C18), 28.0 (CH_3-C19), 25.7 (CH_2-C13), 25.4 (CH_3-C17), 23.4 (CH_2-C5), 23.2 (CH_2-C12), 15.9 (CH_3-Et); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{21}H_{35}O_4$ 351.2537, found 351.2534, Δ −0.2 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 351.4 (66%), 333.4 (100%), 315.4 (66%); IR ν_{max} 3199, 2969, 2922, 1713, 974 cm^{-1}; $[\alpha]^{26}_D$ +121.7 (*c* = 0.86, $CHCl_3$).

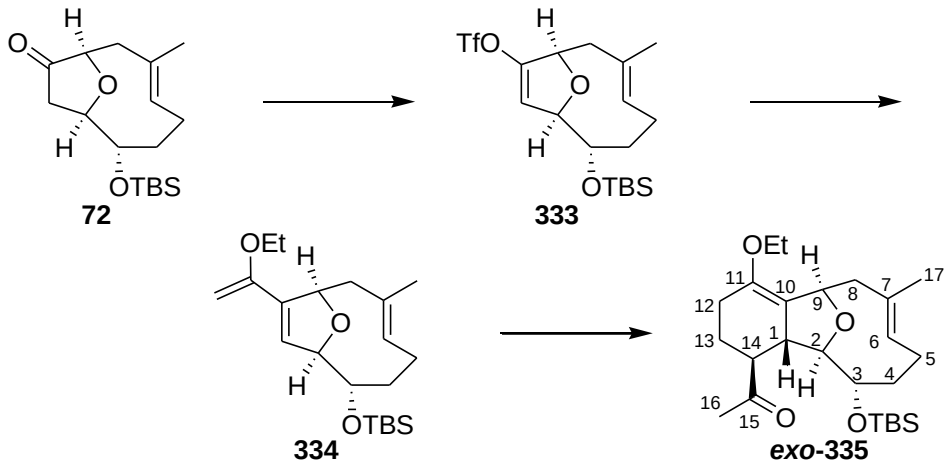
2-[(1*R*,2*R*,3*S*,7*S*,8*R*,10*Z*,14*R*)-14-(Acetyloxy)-10,14-dimethyl-6-oxo-15-oxatricyclo[6.6.1.0^{2,7}]pentadec-10-en-3-yl]propan-2-yl acetate 322



To a solution of diol **320** (10 mg, 28 μmol) in freshly distilled isopropenyl acetate (2 mL) was added *p*-toluenesulfonic acid monohydrate (22 mg, 0.11 mmol). The reaction mixture was stirred at rt 24 h before being quenched with a saturated aqueous solution of $NaHCO_3$ (2 mL) and diluted with ethyl acetate (2 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 3 mL). The organic extracts were combined, washed with brine (3 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether - ethyl acetate, gradient elution 10:1 → 7:1) to deliver the ketone **322** (7 mg, 59%) as a colourless solid.

R_f = 0.54 (petroleum ether - ethyl acetate, 1:1); m.p. 132–135°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.53 (1H, dd, *J* = 10.9, 6.2 Hz, CH-C6), 4.75–4.72 (1H, m, CH-C9), 4.06 (1H, d, *J* = 9.0 Hz, CH-C2), 3.26 (1H, dd, *J* = 9.0, 9.0 Hz, CH-C1), 2.83 (1H, dd, *J* = 9.0, 2.5 Hz, CH-C10), 2.78 (1H, dd, *J* = 14.8 Hz, CH_2-C8), 2.63–2.48 (3H, m, CH_2-C4, CH_2-C5, CH_2-C12), 2.35 (1H, ddd, *J* = 16.0, 5.0, 5.0 Hz, CH_2-C12), 2.14–1.97 (4H, m, CH_2-C5, CH_2-C13, CH-C14), 1.95 (3H, s, CH_3-Ac), 1.94 (3H, s, CH_3-Ac), 1.88 (1H, dd, *J* = 14.8, 4.5 Hz, CH_2-C8), 1.78 (3H, s, CH_3-C19), 1.76–1.70 (1H, m, CH_2-C4), 1.74 (3H, s, CH_3-C18), 1.65 (3H, s, CH_3-C16), 1.64 (3H, s, CH_3-C17); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.7 (C-C11), 169.9 (C-Ac), 169.8 (C-Ac), 131.0 (C-C7), 130.0 (CH-C6), 86.4 (C-C3), 86.1 (CH-C2), 85.2 (C-C15), 77.9 (CH-C9), 54.4 (CH-C10), 43.3 (CH-C1), 42.6 (CH-C14), 37.6 (CH_2-C8), 36.7 (CH_2-C12), 34.4 (CH_2-C4), 28.3 (CH_3-C19), 25.9 (CH_3-C17), 24.9 (CH_3-C16), 23.9 (CH_3-C18), 22.9 (CH_3-Ac), 22.8 (CH_3-Ac), 22.7 (CH_2-C5), 21.9 (CH_2-C13); IR ν_{max} 2966, 2344, 2332, 1734, 1706, 1559 cm^{-1}; $[\alpha]^{25}_D$ +7.0 (*c* = 1.00, $CHCl_3$).

1-[(1*R*,2*R*,8*R*,10*E*)-14-(*tert*-Butyldimethylsilyloxy)-6-ethoxy-10-methyl-15-oxa-tricyclo-[6.6.1.0^{2,7}]pentadeca-6,10-dien-3-yl]-ethanone *exo*-335



To a solution of the *E*-ketone ***72*** (1.53 g, 4.93 mmol) and $PhN(Tf)_2$ (3.52 g, 9.87 mmol) in anhydrous THF (100 mL) at −78 °C was added NaHMDS (12.4 mL of a 1.0 M solution in THF, 12.4 mmol) dropwise over 10 min. The resulting solution was stirred at −78 °C for 2 h then quenched with water (30 mL) at −78 °C and allowed to warm to rt. The aqueous phase was separated and extracted with Et_2O (3 × 80 mL). The organic extracts were combined and washed with brine (60 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude enol triflate **333** as a yellow oil.

To a solution of the above crude enol triflate **333** and $CH_2C(OEt)SnBu_3$ (5.35 g, 14.8 mmol) in anhydrous THF (100 mL) was added LiCl (628 mg, 14.8 mmol) and $Pd(PPh_3)_4$ (856 mg, 740 µmol) and the solution was heated at reflux overnight. The reaction mixture was cooled and diluted with ethyl acetate (50 mL). The organic phase was washed with brine (30 mL), 5% aqueous solution of NH_4OH (30 mL) and brine (30 mL). The organic extract were dried (Na_2SO_4), filtered and concentrated *in vacuo* to give a yellow oil. Quick flash column chromatography on silica gel (petroleum ether - ethyl acetate, 15:1 with 1% Et_3N) afforded the highly unstable diene **334** as a colourless oil which was used immediately.

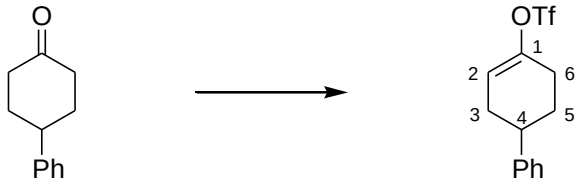
The above diene **334** and freshly distilled methyl vinyl ketone (3.45 g, 49.3 mmol) were dissolved in anhydrous toluene (200 mL) and heated at 130 °C in a sealed tube overnight. The volatiles were removed *in vacuo* to give a yellow oil. Flash column chromatography on silica gel (petroleum ether - ethyl acetate,

15:1 with 1% Et_3N) delivered an *endo*-*exo* mixture of Diels-Alder cycloadducts **335** (1.47 g, 68% over 3 steps) as colourless oil.

To a stirred solution of the *endo*-*exo* mixture of cycloadducts (1.44 g, 3.31 mmol) in methanol (35 mL) was added potassium carbonate (550 mg, 3.97 mmol) and the solution stirred at rt overnight. The reaction mixture was diluted with a saturated aqueous solution of NH_4Cl (35 mL) and ethyl acetate (60 mL). The aqueous phase was separated and extracted with ethyl acetate (2 × 50 mL). The organic extracts were combined, washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a yellow oil. Flash column chromatography on silica gel (petroleum ether - ethyl acetate, 20:1 with 1% Et_3N) afforded the ketone ***exo*-335** as a colourless oil (1.22 g, 85%).

R_f = 0.30 (petroleum ether - ethyl acetate, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (1H, t, *J* = 8.4 Hz, CH-C6), 4.84 (1H, d, *J* = 6.0 Hz, CH-C9), 3.91 (1H, dd, *J* = 8.3, 4.9 Hz, CH-C2), 3.80 (1H, q, *J* = 7.0 Hz, CH_2-Et), 3.79 (1H, q, *J* = 7.0 Hz, CH_2-Et), 3.66 (1H, dd, *J* = 6.3, 4.9 Hz, CH-C3), 2.68−2.62 (1H, m, CH-C1), 2.49 (1H, dd, *J* = 13.5, 6.0 Hz, CH_2-C8), 2.35−1.96 (8H, m, CH_2-C4, CH_2-C5, CH_2-C8, CH_2-C12, CH_2-C13, CH-C14), 2.15 (3H, s, CH_3-C16), 1.70−1.59 (2H, m, CH_2-C4, CH_2-C13), 1.65 (3H, s, CH_3-C17), 1.23 (3H, t, *J* = 7.0 Hz, CH_3-Et), 0.92 (9H, s, CH_3-*t*Bu), 0.05 (3H, s, $SiCH_3$), 0.04 (3H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.7 (C-C15), 143.3 (C-C11), 130.6 (CH-C6), 125.5 (C-C7), 121.3 (C-C10), 88.0 (CH-C2), 74.7 (CH-C9), 74.0 (CH-C3), 63.3 (CH_2-Et), 52.9 (CH-C14), 43.5 (CH_2-C8), 42.8 (CH-C1), 30.3 (CH_3-C16), 28.9 (CH_2-C13), 27.1 (CH_2-C4), 26.1 (CH_3-*t*Bu), 24.4 (CH_2-C12), 21.6 (CH_2-C5), 18.5 (C-*t*Bu), 18.3 (CH_3-C17), 15.7 (CH_3-Et), −4.5 ($SiCH_3$), −4.6 ($SiCH_3$); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{25}H_{43}O_4Si$ 435.2930, found 435.2922, Δ −2.0 ppm; LRMS (CI, Me_3CH) *m*/*z* (intensity) 435.7 (100%), 303.6 (10%), 113.3 (20%); Anal. Calcd for $C_{25}H_{42}O_4Si$ C, 69.08%; H, 9.74%; found C, 68.93%; H, 9.73%; IR ν_{max} 2951, 2927, 2856, 1713, 935, 896, 869, 836, 774 cm^{-1}; $[\alpha]^{25}_D$ +118.9 (*c* = 1.04, $CHCl_3$).

4-Phenylcyclohex-1-en-1-yl trifluoromethanesulfonate 338

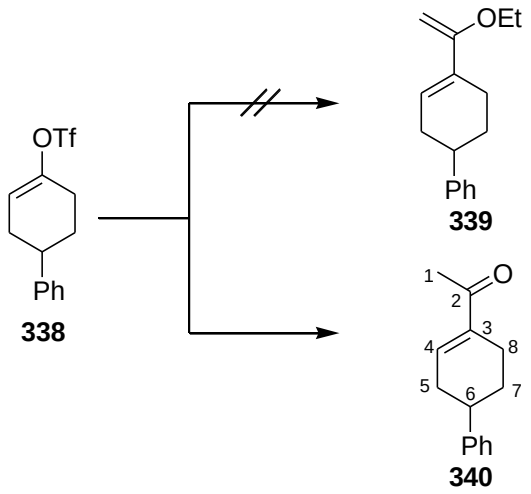


337 **338**

To a stirred solution of the 4-phenylcyclohexanone **337** (1.00 g, 5.73 mmol) and $PhN(Tf)_2$ (4.09 g, 11.5 mmol) in anhydrous THF (110 mL) at −78 °C was added NaHMDS (14.4 mL of a 1.0 M solution in THF, 14.4 mmol) dropwise over 10 min. The resulting solution was stirred for 2 h before being quenched with water (35 mL) at −78 °C and allowed to warm to rt. The aqueous layer was separated and extracted with Et_2O (3 × 75 mL). The organic extracts were combined, washed with brine (75 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude enol triflate as a yellow oil. Flash column chromatography on silica gel (petroleum ether - ethyl acetate, 98:2 with 1% Et_3N) afforded the enol triflate **338** (1.69 g, 96%) a colourless solid.

R_f = 0.80 (petroleum ether - ethyl acetate, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.19 (5H, m, CH-Ar), 5.87−5.83 (1H, m, CH-C2), 2.91−2.80 (1H, m, CH-C4), 2.61−2.25 (4H, m, CH_2-C3, CH_2-C6), 2.11−2.01 (1H, m, CH_2-C5), 2.01−1.89 (1H, m, CH_2-C5); ^{19}F NMR (400 MHz, $CDCl_3$) δ −73.71 (CF_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1 (C-C1), 144.7 (C-Ar), 128.8 (CH-Ar), 126.9 (CH-Ar), 126.8 (CH-Ar), 118.7 (q, J = 320 Hz, CF_3), 118.3 (CH-C2), 38.9 (CH-C4), 31.7 (CH_2-C6), 29.8 (CH_2-C5), 28.0 (CH_2-C3); HRMS (EI) $[M]^+$ for $C_{13}H_{13}F_3O_3S$ calcd 306.0540, found 306.0540, Δ +0.9 ppm; LRMS (EI) *m/z* (intensity) 306.0 (20%), 115.0 (18%), 104.0 (100%); IR ν_{max} 3030, 2926, 1691, 1602, 891, 856, 759 cm^{-1}.

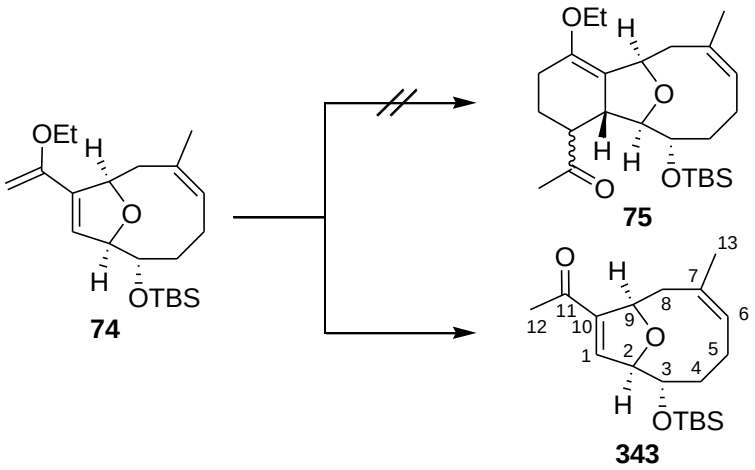
1-(4-Phenylcyclohex-1-en-1-yl)ethan-1-one 340



A mixture of palladium acetate (8.0 mg, 39 μmol), 1,3-bis(diphenylphosphino) propane (16 mg, 39 μmol) and molecular sieves in anhydrous DMSO (1 mL) was stirred at rt for 30 min. Freshly distilled triethylamine (99 mg, 0.97 mmol) was then added, followed by ethyl vinyl ether (94 mg, 1.3 mmol) and a solution of the vinyltriflate **338** (0.20 g, 0.65 mmol) in anhydrous DMSO (1 mL). The reaction mixture was stirred overnight at 60 °C and then poured into a 1 M solution of NaOH (3 mL). The aqueous layer was separated and extracted with Et_2O (3 × 10 mL). The organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The undesired enone **340** was obtained as a colourless solid instead of the expected diene **339**.

R_f = 0.29 (petroleum ether - ethyl acetate, 5:1); m.p. 55–56 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32–7.21 (5H, m, CH-Ar), 6.98 (1H, brs, CH-C4), 2.78 (1H, m, CH-C6), 2.60–2.55 (2H, m, CH_2-C5, CH_2-C8), 2.41–2.39 (1H, m, CH_2-C5), 2.33 (3H, s, CH_3-C1), 2.29–2.20 (1H, m, CH_2-C8), 2.06–2.03 (1H, m, CH_2-C7), 1.76–1.66 (1H, m, CH_2-C7); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5 (C-C2), 146.4 (C-C3), 140.5 (CH-C4), 139.9 (C-Ar), 128.9 (CH-Ar), 127.1 (CH-Ar), 126.7 (CH-Ar), 39.6 (CH-C6), 34.5 (CH_2-C5), 29.6 (CH_2-C7), 25.7 (CH_3-C1), 24.1 (CH_2-C8); HRMS (EI) $[M]^+$ for $C_{14}H_{16}O$ for calcd 200.1202, found 200.1205, Δ +1.7 ppm; LRMS (EI) *m/z* (intensity) 200.1 (57%), 104.0 (100%); IR ν_{max} 2931, 2920, 2891, 1656, 1637, 958, 767, 704 cm^{-1}.

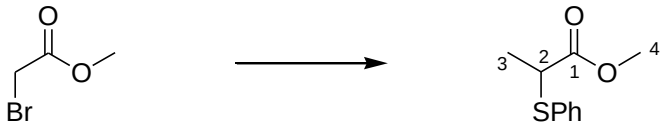
1-[(1*R,2*S**,5*Z*,8*R**)-2-[(*tert*-Butyldimethylsilyl)oxy]-6-methyl-11-oxabicyclo [6.2.1]undeca-5,9-dien-9-yl]ethan-1-one 343**



To a solution of freshly distilled methyl vinyl ketone (202 mg, 2.89 mmol) in anhydrous toluene (5 mL) was added $AlCl_3$ (3.8 mg, 28 µmol) and a solution of the diene **74** (106 mg, 289 µmol) in anhydrous toluene (5 mL). The reaction mixture was stirred at 60 °C for 18 h then the volatile were removed *in vacuo*. Flash column chromatography on silica gel (petroleum ether - ethyl acetate, 20:1 with 1% Et_3N) afforded the undesired methyl ketone **343**.

R_f = 0.55 (petroleum ether - ethyl acetate, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (1H, br t, *J* = 1.6 Hz, CH-C1), 5.38 (1H, dd, *J* = 12.0, 5.5 Hz, CH-C6), 5.20–5.17 (1H, m, CH-C9), 4.68 (1H, ddd, *J* = 7.5, 1.9, 1.6 Hz, CH-C2), 3.60 (1H, ddd, *J* = 11.0, 7.5, 3.5 Hz, CH-C3), 2.84 (1H, dd, *J* = 14.3, 4.2 Hz, CH_2-C8), 2.81–2.71 (1H, m, CH_2-C5), 2.53 (3H, s, CH_3-C12), 2.30 (1H, dd, *J* = 14.3, 2.9 Hz, CH_2-C8), 1.98–1.85 (2H, m, CH_2-C4, CH_2-C5), 1.71–1.61 (1H, m, CH_2-C4), 1.52 (3H, s, CH_3-C13), 0.89 (9H, s, CH_3-*t*Bu), 0.07 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.7 (C-C11), 142.9 (CH-C1), 141.6 (C-C10), 131.7 (C-C7), 127.2 (CH-C6), 90.9 (CH-C2), 84.0 (CH-C9), 75.5 (CH-C3), 35.4 (CH_2-C8), 33.0 (CH_2-C4), 27.3 (CH_3-C12), 27.0 (CH_3-C13), 25.9 (CH_3-*t*Bu), 24.9 (CH_2-C5), 18.1 (C-*t*Bu), −3.9 ($SiCH_3$), −4.4 ($SiCH_3$); HRMS (CI, Me_3CH) $[M+H]^+$ for $C_{19}H_{33}O_3Si$ calcd 337.2200, found 337.2196, Δ −1.0 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 337.4 (78%), 319.4 (33%), 227.3 (55%); IR ν_{max} 2955, 2929, 2856, 1675, 954, 868, 838, 774 cm^{-1}.

Methyl 2-(phenylsulfanyl)propanoate 347

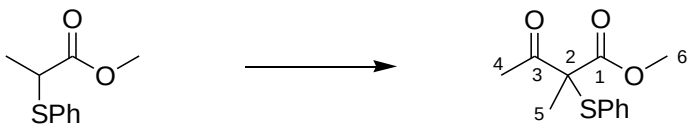


346 **347**

To a solution of sodium hydride (60% in mineral oil, 0.36 g, 9.0 mmol) in anhydrous THF (90 mL) cooled at 0 °C was added dropwise thiophenol (0.72 g, 6.6 mmol). After the addition was complete, the solution was warmed to rt and stirred for a further 30 min before methyl-2-bromopropionate **346** (1.0 g, 6.0 mmol) was added. After 1 h at rt the reaction mixture was cooled to 0 °C and quenched with water (20 mL). The aqueous layer was separated and extracted with ethyl acetate (3 × 40 mL). The organic extracts were combined, washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude thioether as a yellow oil. Flash column chromatography on silica gel (petroleum ether - ethyl acetate, 15:1) afforded the thioether **347** (1.19 g, 98%) a colourless oil.

R_f = 0.52 (petroleum ether - ethyl acetate, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46–7.44 (2H, m, CH-Ar), 7.31–7.30 (3H, m, CH-Ar), 3.79 (1H, q, *J* = 7.1 Hz, CH-C2), 3.67 (3H, s, CH_3-C4), 1.48 (3H, d, *J* = 7.1 Hz, CH_3-C3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3 (C-C1), 133.2 (CH-Ar), 133.1 (C-Ar), 129.1 (CH-Ar), 128.2 (CH-Ar), 52.4 (CH_3-C4), 45.4 (CH-C2), 17.6 (CH_3-C3); HRMS (CI, Me_3CH) $[M+H]^+$ for $C_{10}H_{13}O_2S$ calcd 197.0637, found 197.0638, Δ +1.0 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 197.2 (100%), 195.2 (45%), 137.2 (20%); IR ν_{max} 1734, 854, 749 cm^{-1}.

Methyl 2-methyl-3-oxo-2-(phenylsulfanyl)butanoate 348



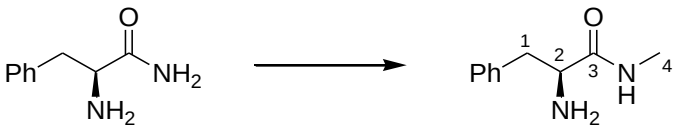
347 **348**

To a solution of lithium bis(trimethylsilyl)amide (5.98 mL of a 1.0 M solution in THF, 5.98 mmol) in anhydrous THF (6 mL) cooled at −78 °C was added a solution

of **347** (1.18 g, 5.98 mmol) in anhydrous THF (6 mL). The solution was stirred for 30 min at 0 °C before being cooled to −78 °C. A solution of acetyl chloride (0.45 g, 6.0 mmol) in anhydrous THF (6 mL) was then added. The resulting mixture was stirred for 40 min at 0 °C before being quenched with a saturated aqueous solution of NH_4Cl (5 mL). The aqueous layer was separated and extracted with Et_2O (3 × 20 mL). The organic extracts were combined, washed with water (10 mL), a saturated aqueous solution of $NaHCO_3$ (10 mL) and brine (10 mL) then dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude butanoate. Flash column chromatography on silica gel (petroleum ether - ethyl acetate, 15:1) afforded the butanoate **348** (1.14 g, 80%, 91% brsm) as a colourless oil.

R_f = 0.29 (petroleum ether - ethyl acetate, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.30 (5H, m, CH-Ar), 3.79 (3H, s, CH_3-C6), 2.36 (3H, s, CH_3-C4), 1.50 (3H, s, CH_3-C5); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.5 (C-C3), 170.6 (C-C1), 137.1 (CH-Ar), 130.1 (CH-Ar), 129.3 (C-Ar), 129.1 (CH-Ar), 65.8 (C-C2), 53.4 (CH_3-C6), 26.2 (CH_3-C4), 20.9 (CH_3-C5); HRMS (CI, Me_3CH) $[M+H]^+$ for $C_{12}H_{15}O_3S$ calcd 239.0743, found 239.0740, Δ −0.8 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 239.2 (100%), 221.2 (18%), 131.2 (33%); IR ν_{max} 1740, 1711, 974, 869, 753, 693 cm^{-1}.

L-Phenylalanine methylamide 353[112, 129]



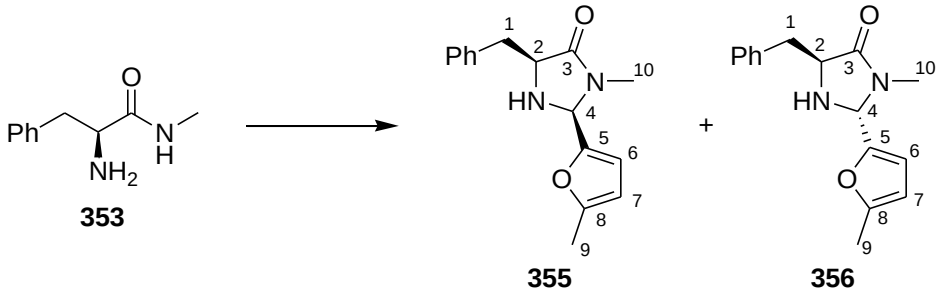
352 **353**

To a suspension of L-phenylalanine **352** (4.0 g, 24 mmol) in freshly distilled pyridine (120 mL) at rt, was added dichlorodimethylsilane (3.4 g, 27 mmol) in one portion. During 2 min the mixture turned clear and methylamine gas (≈ 4 g, 130 mmol) was then bubbled through the reaction. The reaction mixture was stirred for 18 h at rt and then concentrated *in vacuo*. Flash column chromatography on silica gel (CH_2Cl_2 - MeOH, gradient elution 100% CH_2Cl_2 → 3:2) afforded L-phenylalanine-methylamide **353** (2.8 g, 66%) as a colourless solid.

R_f = 0.73 (CH_2Cl_2 – MeOH, 3:1); m.p. 66−68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.21 (5H, m, CH-Ar), 3.60 (1H, dd, *J* = 9.5, 4.0 Hz, CH-C2), 3.29 (1H, dd,

J = 13.8, 4.0 Hz, CH_2-C1), 2.82 (3H, d, *J* = 4.9 Hz, CH_3-C4), 2.67 (1H, dd, *J* = 13.8, 9.5 Hz, CH_2-C1), 1.33 (3H, br s, NH_2, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9 (C-C3), 138.3 (C-Ar), 129.4 (CH-Ar), 128.8 (CH-Ar), 126.9 (CH-Ar), 56.6 (CH-C2), 41.2 (CH_2-C1), 25.9 (CH_3-C4); HRMS (CI, Me_3CH) $[M+H]^+$ for $C_{10}H_{15}N_2O$ calcd 179.1185, found 179.1183, Δ −0.9 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 179.2 (100%); IR ν_{max} 3371, 3344, 3298, 3030, 2916, 2359, 1651, 853, 732, 700 cm^{-1}; $[\alpha]^{25}_D$ −94.8 (*c* = 1.00, $CHCl_3$) {Lit.[129] $[\alpha]^{20}_D$ −6.8 (c = 1.1, $CHCl_3$)}.

(2*S*,5*S*)-5-Benzyl-3-methyl-2-(5-methylfuran-2-yl)imidazolidin-4-one 355[111] **and (2*R*,5*S*)-5-Benzyl-3-methyl-2-(5-methylfuran-2-yl)imidazolidin-4-one 356**



To a flame dried flask under argon containing some samarium(III) trifluoromethanesulfonate (0.33 g, 0.56 mmol), powdered 4Å molecular sieve (1.1 g) and (*S*)-phenylalanine methyl amide **353** (2.5 g, 14 mmol) was added a solution of freshly distilled 5-methylfurfural (1.2 g, 11 mmol) in anhydrous THF (25 mL). After stirring for 29 h at rt the reaction, the mixture was filtered through a plug of silica with dichloromethane and then concentrated. Flash column chromatography on silica gel (petroleum ether - ethyl acetate, gradient elution 2:1 → 1:2) gave the (2*S*,5*S*) isomer **355** as a yellow oil (0.76 g, 20%) and the faster eluting (2*R*,5*S*) isomer **356** as a pale yellow oil (0.73 g, 19%).

(2*S*, 5*S*)-5-Benzyl-3-methyl-2-(5-methyl-furan-2-yl)-imidazolidin-4-one **355**;

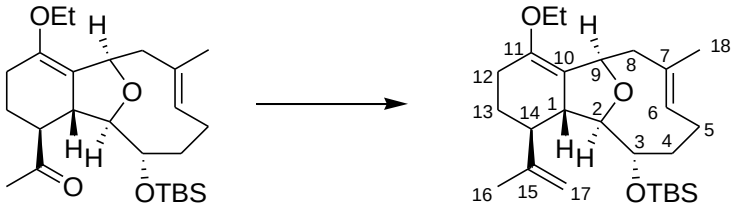
R_f = 0.25 (petroleum ether - ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.24 (5H, m, Ar), 6.11 (1H, d, *J* = 3.0 Hz, CH-C6), 5.89 (1H, d, *J* = 3.0 Hz, CH-C7), 5.19 (1H, s, CH-C4), 3.80 (1H, m, CH-C2), 3.27 (1H, dd, *J* = 14.2, 4.0 Hz, CH_2-C1), 3.10 (1H, dd, *J* = 14.2, 7.7 Hz, CH_2-C1), 2.65 (3H, s, CH_3-C10), 2.22 (3H, s, CH_3-C9), 2.13 (1H, brs, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1 (C-C3), 153.5 (C-C8), 148.6 (C-C5), 137.4 (C-Ar), 129.6 (CH-Ar), 128.8 (CH-Ar), 126.9 (CH-Ar), 111.1 (CH-C6), 106.6 (CH-C7), 71.1 (CH-C4), 60.3 (CH-C2), 37.6 (CH_2-C1), 27.1

(CH_3-C10), 13.7 (CH_3-C9); HRMS (EI) $[M]^+$ for $C_{16}H_{18}N_2O_2$ calcd 270.1369, found 270.1371, Δ 1.0 ppm; LRMS (EI) *m/z* (intensity) 270.2 (16%), 179.1 (100%), 124.1 (74%), 91.0 (34%); IR ν_{max} 2922, 1691, 1563, 966, 789, 701 cm^{-1}; $[\alpha]^{25}_D$ −164.1 (*c* = 1.00, $CHCl_3$) {Lit.[111] $[\alpha]^{25}_D$ −156.5 (c = 1.0, $CHCl_3$)}.

(2*R*,5*S*)-5-Benzyl-3-methyl-2-(5-methylfuran-2-yl)-imidazolidin-4-one **356**;

R_f = 0.34 (petroleum ether - ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28−7.21 (5H, m, Ar), 6.18 (1H, d, *J* = 3.1 Hz, CH-C6), 5.89 (1H, dd, *J* = 3.1, 1.0 Hz, CH-C7), 4.94 (1H, s, CH-C4), 4.04 (1H, dd, *J* = 7.0, 4.0 Hz, CH-C2), 3.14 (1H, dd, *J* = 13.8, 4.0 Hz, CH_2-C1), 2.94 (1H, dd, *J* = 13.8, 7.0 Hz, CH_2-C1), 2.65 (3H, s, CH_3-C10), 2.23 (3H, s, CH_3-C9), 1.56 (1H, brs, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9 (C-C3), 153.5 (C-C8), 149.2 (C-C5), 137.8 (C-Ar), 129.7 (CH-Ar), 128.6 (CH-Ar), 126.8 (CH-Ar), 110.5 (CH-C6), 106.4 (CH-C7), 71.0 (CH-C4), 59.8 (CH-C2), 38.3 (CH_2-C1), 27.1 (CH_3-C10), 13.7 (CH_3-C9); HRMS (EI) $[M]^+$ for $C_{16}H_{18}N_2O_2$ calcd 270.1369, found 270.1367, Δ −0.6 ppm; LRMS (EI) *m/z* (intensity) 270.2 (26%), 179.0 (100%), 124.1 (87%), 91.0 (46%); IR ν_{max} 2922, 1691, 941, 787, 739, 701 cm^{-1}; $[\alpha]^{25}_D$ +15.9 (*c* = 1.00, $CHCl_3$).

tert-Butyl({[(1*R,6*S**,7*R**,8*R**,9*S**,12*E*)-3-ethoxy-13-methyl-6-(prop-1-en-2-yl)-15-oxatricyclo[6.6.1.0^{2,7}]pentadeca-2,12-dien-9-yl]oxy})dimethylsilane 360**



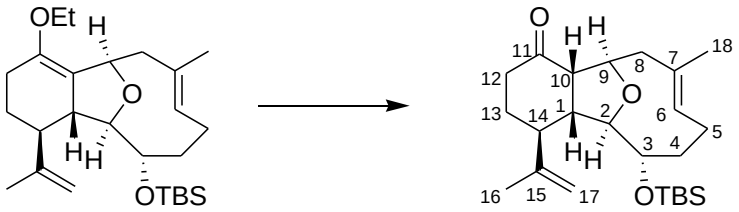
***exo*-335** **360**

To a solution of Ph_3PCH_3Br (1.50 g, 4.19 mmol) in anhydrous THF (20 mL) at 0 °C was added dropwise NaHMDS (3.35 mL of a 1M solution in THF, 3.35 mmol). The resulting yellow reaction mixture was stirred for 1 h at 0 °C. The ketone ***exo*-335** (363 mg, 840 μmol) in anhydrous THF (10 mL) was then added dropwise to the solution of the ylide. The solution was stirred at rt for 1.5 h before being quenched with a saturated aqueous solution of NH_4Cl (50 mL) and diluted with Et_2O (100 mL). The aqueous phase was separated and extracted with Et_2O (2 × 100 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column

chromatography on silica gel (petroleum ether – ethyl acetate, 25:1) to afford the alkene **360** (289 mg, 80%) as a colourless solid.

R_f = 0.56 (petroleum ether - ethyl acetate, 4:1); m.p. 80–82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.67 (1H, m, CH-C6), 4.85 (1H, d, *J* = 6.2 Hz, CH-C9), 4.75 (1H, br s, CH_2-C17), 4.71 (1H, br s, CH_2-C17), 3.86 (1H, dd, *J* = 8.1, 4.6 Hz, CH-C2), 3.84–3.74 (3H, m, CH-C3, CH_2-Et), 2.49 (1H, dd, *J* = 13.7, 6.2 Hz, CH_2-C8), 2.28–2.11 (5H, m, CH-C1, CH_2-C5, CH_2-C4), 2.06 (1H, d, *J* = 13.7 Hz, CH_2-C8), 1.90–1.70 (4H, m, CH_2-C12, CH_2-C13), 1.64 (3H, s, CH_3-C18), 1.63–1.60 (1H, m, CH-C14), 1.59 (3H, s, CH_3-C16), 1.23 (3H, t, *J* = 7.0 Hz, CH_3-Et), 0.92 (9H, s, CH_3-*t*Bu), 0.04 (3H, s, $SiCH_3$), 0.02 (3H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7 (C-C11), 144.0 (C-C15), 130.4 (CH-C6), 126.0 (C-C7), 122.3 (C-C10), 112.2 (CH_2-C17), 88.2 (CH-C2), 75.1 (CH-C9), 74.1 (CH-C3), 63.3 (CH_2-Et), 48.8 (CH-C14), 43.9 (CH_2-C8), 43.8 (CH-C1), 29.3 (CH_2-C12), 29.1 (CH_2-C13), 26.4 (CH_3-*t*Bu), 24.9 (CH_2-C5), 21.9 (CH_2-C4), 18.8 (C-*t*Bu), 18.6 (CH_3-C18), 18.5 (CH_3-C16), 15.9 (CH_3-Et), −4.2 ($SiCH_3$), −4.6 ($SiCH_3$); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{26}H_{45}O_3Si$ 433.3140, found 433.3137, Δ −0.3 ppm; LRMS (CI, Me_3CH) *m*/*z* (intensity) 433.3 (100%); Anal. Calcd for $C_{26}H_{45}O_3Si$: C, 72.17%; H, 10.25%; Found: C, 72.14%; H, 10.32%; IR ν_{max} 2949, 2926, 2854, 1705, 895, 862, 835, 773 cm^{-1}.

(1*R,2*S**,6*S**,7*R**,8*R**,9*S**,12*E*)-9-[(*tert*-Butyldimethylsilyl)oxy]-13-methyl-6-(prop-1-en-2-yl)-15-oxatricyclo[6.6.1.0^{2,7}]pentadec-12-en-3-one 359**



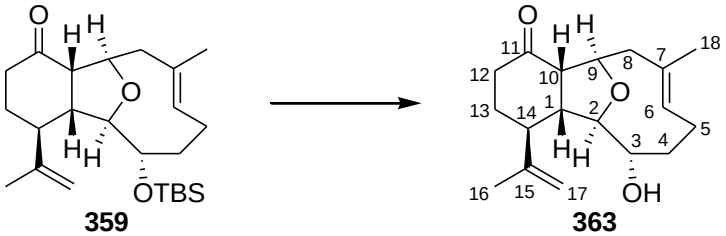
360 **359**

To a stirred solution of the enol ether **360** (26 mg, 60 μmol) in THF (6 mL) was added 1M HCl (60 μL, 60 μmol). The solution was stirred at rt overnight and then diluted with CH_2Cl_2 (15 mL) and water (12 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (2 × 15 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give a white

solid. Flash column chromatography on silica gel (petroleum ether – ethyl acetate, 15:1) delivered the ketone **359** (21 mg, 87%) as colourless solid.

R_f = 0.46 (petroleum ether – ethyl acetate, 4:1); m.p. 96–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30 (1H, br d, *J* = 12.3 Hz, CH-C6), 4.87 (1H, s, CH_2-C17), 4.85 (1H, t, *J* = 1.7 Hz, CH_2-C17), 4.29 (1H, dd, *J* = 10.0, 5.9 Hz, CH-C9), 3.70 (1H, d, *J* = 9.2 Hz, CH-C2), 2.96 (1H, dd, *J* = 9.2, 7.6 Hz, CH-C3), 2.74 (1H, dd, *J* = 10.0, 4.9 Hz, CH-C10), 2.59–2.50 (2H, m, CH_2-C8, CH_2-C12), 2.45–2.42 (1H, m, CH_2-C12), 2.41–2.33 (2H, m, CH-C1, CH-C14), 2.25 (1H, dddd, *J* = 12.3, 12.3, 12.3, 3.9 Hz, CH_2-C5), 2.18–2.12 (1H, m, CH-C5), 2.09 (1H, d, *J* = 13.8 Hz, CH_2-C8), 1.99–1.92 (1H, m, CH_2-C13), 1.88 (3H, s, CH_3-C18), 1.86–1.70 (3H, m, CH_2-C4, CH_2-C13), 1.67 (3H, s, CH_3-C16), 0.87 (9H, s, CH_3-*t*Bu), 0.09 (3H, s, $SiCH_3$), 0.02 (3H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.4 (C-C11), 146.5 (C-C15), 134.6 (CH-C6), 124.4 (C-C7), 113.8 (CH_2-C17), 88.4 (CH-C2), 80.6 (CH-C9), 73.9 (CH-C3), 54.2 (CH-C10), 49.0 (CH-C14), 44.6 (CH-C1), 40.5 (CH_2-C8), 38.6 (CH_2-C12), 37.6 (CH_2-C4), 30.8 (CH_2-C13), 27.5 (CH_2-C5), 26.2 (CH_3-*t*Bu), 21.1 (CH_3-C18), 19.4 (CH_3-C16), 18.2 (C-*t*Bu), −3.8 ($SiCH_3$), −4.0 ($SiCH_3$); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{24}H_{41}O_3Si$ 405.2827, found 405.2829, Δ +1.0 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 405.5 (100%), 347.4 (20%), 273.4 (56%); Anal. Calcd for $C_{24}H_{40}O_3Si$: C, 71.23%; H, 9.96%; Found: C, 71.22%; H, 10.11%; IR ν_{max} 2949, 2929, 2858, 1707, 837, 773 cm^{-1}.

(1*R,2*S**,6*S**,7*R**,8*R**,9*S**,12*E*)-9-Hydroxy-13-methyl-6-(prop-1-en-2-yl)-15-oxatricyclo[6.6.1.0^{2,7}]pentadec-12-en-3-one 363**

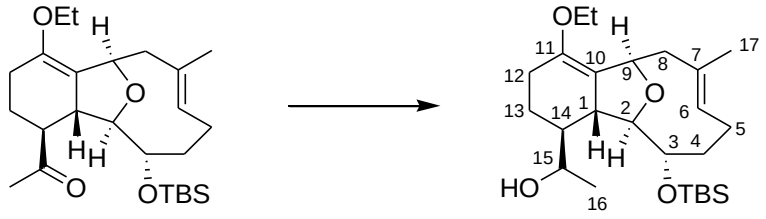


To a solution of the silyl ether **359** (30 mg, 74 μmol) and 4 Å molecular sieves in anhydrous THF (2 mL) was added TBAF (148 μL of a 1M solution in THF, 148 μmol). The reaction mixture was stirred at rt for 4 h and then quenched with a saturated aqueous solution of NH_4Cl (1 mL). The molecular sieve was filtered off and rinsed with ethyl acetate. The aqueous phase was separated and

extracted with ethyl acetate (3 × 5 mL). The organic extracts were combined, washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether - ethyl acetate, gradient elution 10:1 → 7:1 → 5:1) to deliver the alcohol **363** (16 mg, 72%) as a colourless solid.

R_f = 0.30 (petroleum ether – ethyl acetate, 2:1); m.p. 113–115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.30 (1H, br d, *J* = 12.4 Hz, CH-C6), 4.89 (1H, br s, CH_2-C17), 4.86 (1H, br t, *J* = 1.6 Hz, CH_2-C17), 4.29 (1H, dd, *J* = 9.6, 5.8 Hz, CH-C9), 3.60 (1H, d, *J* = 9.4 Hz, CH-C2), 2.93–2.90 (1H, m, CH-C3), 2.78 (1H, dd, *J* = 9.6, 6.7 Hz, CH-C10), 2.58–2.48 (3H, m, CH-C1, CH_2-C8, CH_2-C12), 2.45–2.35 (2H, m, CH_2-C12, CH-C14), 2.30 (1H, dddd, *J* = 12.4, 12.3, 12.3, 4.3 Hz, CH_2-C5), 2.21–2.13 (1H, m, CH_2-C5), 2.10 (1H, d, *J* = 13.7 Hz, CH_2-C8), 1.99–1.86 (2H, m, CH_2-C4, CH_2-C13), 1.85 (3H, s, CH_3-C18), 1.81–1.71 (2H, m, CH_2-C4, CH_2-C13), 1.69 (3H, s, CH_3-C16), 1.19 (1H, br s, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.9 (C-C11), 146.5 (C-C15), 133.8 (CH-C6), 124.4 (C-C7), 113.5 (CH_2-C17), 88.5 (CH-C2), 80.5 (CH-C9), 74.1 (CH-C3), 53.6 (CH-C10), 49.5 (CH-C1), 44.8 (CH-C14), 40.6 (CH_2-C8), 38.5 (CH_2-C12), 37.5 (CH_2-C4), 30.5 (CH_2-C13), 27.5 (CH_2-C5), 20.8 (CH_3-C18), 18.8 (CH_3-C16); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{18}H_{27}O_3Si$ 291.1961, found 291.1959, Δ –0.3 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 291.3 (17%), 273.3 (7%), 113.2 (13%); IR ν_{max} 3440, 2925, 2864, 1736, 897 cm^{-1}.

1-[(1*R,2*R**,3*S**,8*R**,10*E*,14*S**)-14-[(*tert*-Butyldimethylsilyl)oxy]-6-ethoxy-10-methyl-15- oxatricyclo[6.6.1.0^{2,7}]pentadeca-6,10-dien-3-yl]ethan-1-ol 365**



***exo*-335** **365**

To a solution of ketone ***exo*-335** (100 mg, 230 μmol) in CH_2Cl_2 (4 mL) and methanol (4 mL) was added sodium borohydride (9.0 mg, 0.23 mmol). The mixture was stirred at rt for 4 h and the reaction was then quenched by the addition of a saturated aqueous solution of NH_4Cl (1 mL). The aqueous phase was

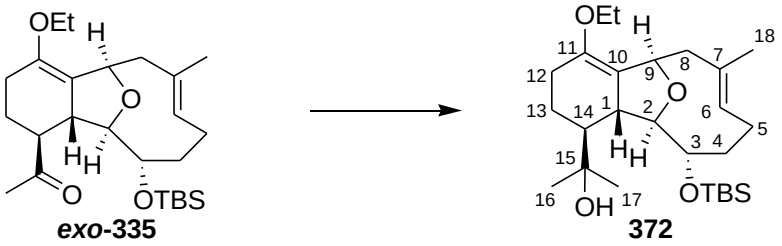
separated and extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether - ethyl acetate, 40:1 with 1% Et_3N) to deliver the alcohol **365** as a separable mixture of diastereomers: Faster eluting (52 mg, 52%) and slower eluting (27 mg, 27%). Both diastereomers are colourless solids.

R_f = 0.38 (*n*-hexane – ethyl acetate, 3:1); m.p. 136–138 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.69 (1H, br t, *J* = 8.4 Hz, CH-C6), 4.85 (1H, br d, *J* = 6.0 Hz, CH-C9), 4.06–3.98 (2H, m, CH-C2, CH-C3), 3.82–3.76 (3H, m, CH-C15, CH_2-Et), 2.47 (1H, dd, *J* = 12.9, 6.0 Hz, CH_2-C8), 2.46–2.41 (1H, m, CH-C1), 2.34–2.21 (2H, m, CH_2-C5, CH_2-C12), 2.20–2.10 (2H, m, CH_2-C5, CH_2-C12), 2.07 (1H, d, *J* = 12.9 Hz, CH_2-C8), 2.05–1.98 (1H, m, CH_2-C4), 1.88 (1H, dd, *J* = 13.0, 7.0 Hz, CH_2-C13), 1.68–1.64 (1H, m, CH_2-C4), 1.64 (3H, s, CH_3-C17), 1.48–1.38 (2H, m, CH_2-C13, OH), 1.22 (3H, t, *J* = 7.0 Hz, CH_3-Et), 1.21 (3H, d, *J* = 6.4 Hz, CH_3-C16), 1.18–1.13 (1H, m, CH-C14), 0.94 (9H, s, CH_3-*t*Bu), 0.09 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6 (C-C11), 130.1 (CH-C6), 126.1 (C-C7), 122.9 (C-C10), 87.9 (CH-C2), 75.2 (CH-C9), 74.8 (CH-C3), 68.0 (CH-C15), 63.1 (CH_2-Et), 45.5 (CH-C14), 43.6 (CH_2-C8), 42.6 (CH-C1), 29.2 (CH_2-C4), 26.1 (CH_3-*t*Bu), 24.6 (CH_2-C5), 21.8 (CH_2-C12), 21.7 (CH_2-C13), 21.5 (CH_3-C16), 18.5 (C-*t*Bu), 18.3 (CH_3-C17), 15.7 (CH_3-Et), −4.3 ($SiCH_3$), −4.6 ($SiCH_3$); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{25}H_{45}O_4Si$ 437.3089, found 437.3082, Δ −1.1 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 437.5 (100%), 305.4 (10%); IR ν_{max} 3361, 2953, 2926, 2855, 866, 837, 774 cm^{-1}.

R_f = 0.26 (*n*-hexane – ethyl acetate 3:1); m.p. 124–126 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 (1H, br t, *J* = 8.4 Hz, CH-C6), 4.85 (1H, br d, *J* = 6.2 Hz, CH-C9), 4.08 (1H, dd, *J* = 7.8, 5.2 Hz, CH-C2), 3.92 (1H, br t, *J* = 5.2 Hz, CH-C3), 3.85–3.76 (3H, m, CH-C15, CH_2-Et), 2.47 (1H, dd, *J* = 13.8, 6.2 Hz, CH_2-C8), 2.35–2.05 (6H, m, CH-C1, CH_2-C8, CH_2-C5, CH_2-C12), 2.04–1.97 (1H, m, CH_2-C13), 1.87–1.78 (1H, m, CH_2-C4), 1.71–1.64 (1H, m, CH_2-C4), 1.62 (3H, s, CH_3-C17), 1.49 (1H, m, OH), 1.45–1.37 (1H, m, CH-C14), 1.34–1.26 (1H, m, CH_2-C13), 1.22 (3H, t, *J* = 7.0 Hz, CH_3-Et), 1.07 (3H, d, *J* = 6.4 Hz, CH_3-C16), 0.93 (9H, s, CH_3-*t*Bu), 0.07 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3 (C-C11), 130.2 (CH-C6), 126.0 (C-C7), 122.3 (C-C10), 87.6 (CH-C2), 75.2 (CH-C9), 74.5 (CH-C3), 68.9 (CH-C15), 63.0 (CH_2-Et), 46.7

(CH-C14), 44.2 (CH-C1), 43.6 (CH_2-C8), 29.6 (CH_2-C4), 26.1 (CH_3-*t*Bu), 24.5 (CH_2-C5), 22.8 (CH_2-C13), 21.9 (CH_2-C12), 18.4 (C-*t*Bu), 18.3 (CH_3-C17), 18.1 (CH_3-C16), 15.7 (CH_3-Et), −4.3 ($SiCH_3$), −4.6 ($SiCH_3$); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{25}H_{45}O_4Si$ 437.3089, found 437.3084, Δ −0.7 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 437.5 (100%), 305.4 (12%); IR ν_{max} 3425, 2948, 2926, 2855, 1700, 863, 837, 774 cm^{-1}.

2-[(1*R*,2*R*,3*R*,8*R*,10*E*)-14-(*tert*-Butyldimethylsilyloxy)-6-ethoxy-10-methyl-15-oxatricyclo-[6.6.1.$0^{2,7}$]pentadeca-6,10-dien-3-yl]-propan-2-ol 372



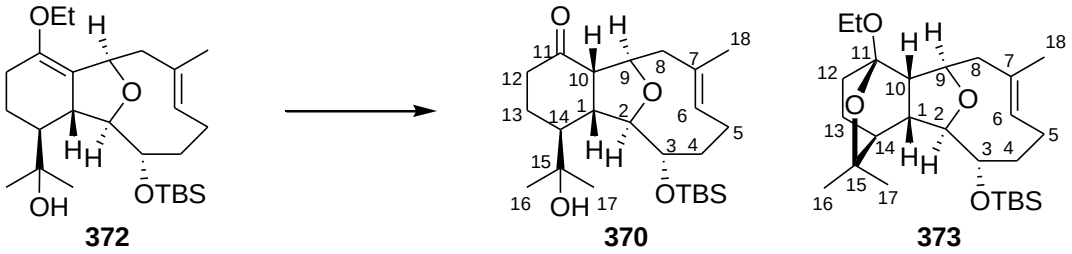
***exo*-335** **372**

To a solution of the ketone ***exo*-335** (462 mg, 1.06 mmol) in anhydrous THF (50 mL) at 0 °C was added slowly MeMgBr (2.12 mL of a 3M solution in Et_2O, 6.37 mmol). The reaction mixture was allowed to warm to rt and stirred for 3 h then quenched with a saturated aqueous solution of NH_4Cl (45 mL) and Et_2O (15 mL). The aqueous phase was separated and extracted with Et_2O (3 × 30 mL). The organic extracts were combined, washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the crude alcohol as a yellow oil. Flash column chromatography on silica gel (petroleum ether - Et_2O, gradient elution 20:1 → 5:1 with 1% Et_3N) afforded the alcohol **372** as a colourless oil (373 mg, 78%).

R_f = 0.39 (petroleum ether - ethyl acetate, 4:1); ^1H NMR (400 MHz, $CDCl_3$) δ 5.71 (1H, br t, *J* = 8.9 Hz, CH-C6), 4.82 (1H, d, *J* = 5.9 Hz, CH-C9), 4.64 (1H, dd, *J* = 7.2, 4.6 Hz, CH-C3), 4.34 (1H, dd, *J* = 7.8, 4.6 Hz, CH-C2), 3.79 (1H, q, *J* = 7.0 Hz, CH_2-Et), 3.78 (1H, q, *J* = 7.0 Hz, CH_2-Et), 2.45 (1H, dd, *J* = 13.2, 5.9, CH_2-C8), 2.31−2.09 (6H, m, CH-C1, CH_2-C5, CH_2-C8, CH_2-C12), 1.94−1.82 (2H, m, CH_2-C4, CH_2-C13), 1.68−1.63 (1H, m, CH_2-C4), 1.63 (3H, s, CH_3-C18), 1.37−1.31 (2H, m, CH_2-C13, CH-C14), 1.28 (3H, s, CH_3-C16), 1.23 (3H, t, *J* = 7.0 Hz, CH_3-Et), 1.03 (3H, s, CH_3-C17), 0.97 (1H, s, OH), 0.93 (9H, s, CH_3-*t*Bu), 0.06 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.6 (C-C11), 130.3

(CH-C6), 125.9 (C-C7), 123.9 (C-C10), 88.0 (CH-C2), 74.6 (CH-C9), 73.7 (C-C15), 71.6 (CH-C3), 62.9 (CH_2-Et), 51.6 (CH-C14), 43.6 (CH_2-C8), 43.6 (CH-C1), 32.1 (CH_3-C16), 28.7 (CH_2-C4), 27.5 (CH_2-C13), 26.2 (CH_3-*t*Bu), 25.1 (CH_2-C12), 23.7 (CH_3-C17), 21.9 (CH_2-C5), 18.4 (C-*t*Bu), 18.2 (CH_3-C18), 15.7 (CH_3-Et), −4.2 ($SiCH_3$), −4.7 ($SiCH_3$); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{26}H_{47}O_4Si$ 451.3243, found 451.3243, Δ −0.2 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 451.4 (100%), 433.3 (13%), 319.3 (8%); IR ν_{max} 3458, 2953, 2926, 2855, 1708, 935, 899, 863, 774 cm^{-1}; $[\alpha]^{23}_D$ +79.3 (*c* = 0.91, $CHCl_3$).

(1*R,2*S**,6*S**,7*R**,8*R**,9*S**,12*E*)-9-[(*tert*-Butyldimethylsilyl)oxy]-6-(2-hydroxy propan-2-yl)-13-methyl-15-oxatricyclo[6.6.1.$0^{2,7}$]pentadec-12-en-3-one 370 and *tert*-Butyl([(1*S**,2*R**,3*R**,4*S**,7*E*,10*R**,11*S**,12*R**)-12-ethoxy-8,14,14-trimethyl-13,17-dioxatetracyclo[10.2.2.1^{3,10}.$0^{2,11}$]heptadec-7-en-4-yl]oxy) dimethylsilane 373**



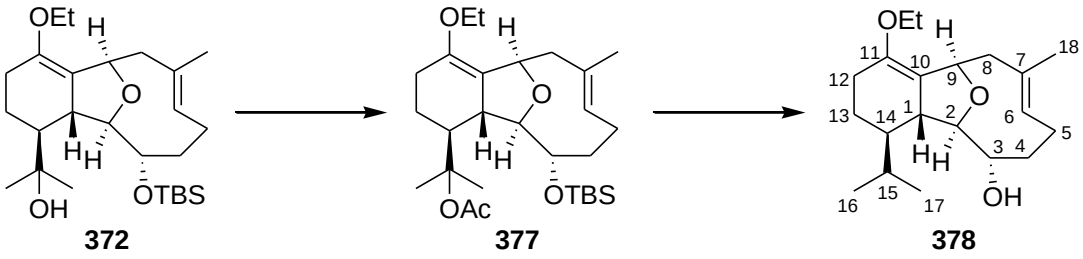
To a solution of the enol ether **372** (96 mg, 0.21 mmol) in THF (10 mL) was added 1M HCl (210 µL, 210 µmol). The solution was stirred at rt for 1 h and then diluted with Et_2O (30 mL) and water (20 mL). The aqueous phase was separated and extracted with Et_2O (3 × 20 mL). The organic extracts were combined, washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether - ethyl acetate, 10:1) to deliver the ketone **370** (39 mg, 43%) as a colourless oil and the tetracycle **373** (15 mg, 17%) as a colourless oil.

370; R_f = 0.50 (petroleum ether – ethyl acetate, 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.32 (1H, br d, *J* = 12.3 Hz, CH-C6), 4.45 (1H, d, *J* = 9.4 Hz, CH-C2), 4.27 (1H, dd, *J* = 9.8, 6.1 Hz, CH-C9), 3.04 (1H, dd, *J* = 9.4, 7.8 Hz, CH-C3), 2.78–2.73 (1H, m, CH-C10), 2.62–2.40 (3H, m, CH-C1, CH_2-C8, CH_2-C12), 2.34–2.27 (1H, m, CH_2-C12), 2.23 (1H, ddd, *J* = 12.3, 12.3, 4.0 Hz, CH_2-C5), 2.18–2.11 (1H, m, CH_2-C5), 2.08 (1H, d, *J* = 13.8 Hz, CH_2-C8), 2.02 (1H, dddd, *J* = 13.5, 4.2, 4.2,

4.2 Hz, CH_2-C13), 1.96–1.87 (1H, m, CH-C14), 1.86 (3H, s, CH_3-C18), 1.86–1.81 (1H, m, CH_2-C4), 1.71 (1H, ddd, *J* =14.2, 4.0, 2.8 Hz, CH_2-C4), 1.60 (1H, s, OH), 1.55–1.42 (1H, m, CH_2-C13), 1.28 (3H, s, CH_3-C16), 1.17 (3H, s, CH_3-C17), 0.90 (9H, s, CH_3-*t*Bu), 0.15 (3H, s, $SiCH_3$), 0.08 (3H, s, $SiCH_3$); NMR (100 MHz, $CDCl_3$) δ 210.9 (C-C11), 134.3 (CH-C6), 124.1 (C-C7), 90.5 (CH-C2), 81.2 (CH-C9), 76.0 (CH-C3), 74.1 (C-C15), 54.6 (CH-C10), 48.3 (CH-C1), 45.6 (CH-C14), 40.6 (CH_2-C8), 37.6 (CH_2-C12), 37.0 (CH_2-C4), 29.5 (CH_3-C16), 28.6 (CH_2-C13), 27.1 (CH_2-C5), 26.2 (CH_3-*t*Bu), 25.8 (CH_3-C17), 20.9 (CH_3-C18), 18.0 (C-*t*Bu), −3.6 ($SiCH_3$), −4.1 ($SiCH_3$); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{24}H_{43}O_4Si$ 423.2933, found 423.2936, Δ +1.2 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 423.3 (100%), 405.3 (40%), 365.5 (13%), 291.3 (60%); Anal. Calcd for $C_{24}H_{42}O_4Si$: C, 68.20%; H, 10.02%; Found: C, 68.06%; H, 10.06%; IR ν_{max} 3455, 2954, 2929, 2858, 1709, 837, 779 cm^{-1}.

373; R_f = 0.76 (petroleum ether – ethyl acetate, 1:1); ^1H NMR (400 MHz, $CDCl_3$) δ 5.24 (1H, br d, *J* = 8.6 Hz, CH-C6), 4.32–4.29 (1H, m, CH-C9), 3.63–3.52 (3H, m, CH-C2, CH_2-Et), 3.26 (1H, dd, *J* = 8.1, 8.1 Hz, CH-C3), 2.66–2.58 (2H, m, CH-C1, CH_2-C8), 2.44 (1H, dd, *J* = 11.0, 3.6 Hz, CH-C10), 2.30–2.18 (1H, m, CH_2-C5), 2.17–2.09 (1H, m, CH_2-C5), 2.04 (1H, d, *J* = 13.3 Hz, CH_2-C8), 1.92–1.75 (5H, m, CH_2-C4, CH_2-C12, CH_2-C13), 1.78 (3H, s, CH_3-C18), 1.69–1.66 (1H, m, CH_2-C4), 1.42–1.36 (1H, m, CH-C14), 1.29 (3H, s, CH_3-C16), 1.26 (3H, s, CH_3-C17), 1.16 (3H, t, *J* = 7.0 Hz, CH_3-Et), 0.87 (9H, s, CH_3-*t*Bu), 0.11 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.5 (CH-C6), 125.8 (C-C7), 101.3 (C-C11), 89.8 (CH-C2), 81.8 (CH-C9), 78.7 (CH-C3), 76.6 (C-C15), 56.8 (CH_2-Et), 50.8 (CH-C10), 46.6 (CH-C1), 44.7 (CH_2-C8), 37.6 (CH-C14), 37.1 (CH_2-C4), 29.0 (CH_3-C16), 28.7 (CH_3-C17), 27.5 (CH_2-C5), 26.0 (CH_3-*t*Bu), 23.9 (CH_2-C13), 19.8 (CH_3-C18), 17.9 (CH_2-C12), 17.0 (C-*t*Bu), 15.7 (CH_3-Et), −3.5 ($SiCH_3$), −4.6 ($SiCH_3$); IR ν_{max} 2956, 2928, 2856, 1730, 836, 772 cm^{-1}.

(1*R*,7*R*,6*S*,8*R*,9*S*,12*E*)-3-Ethoxy-6-isopropyl-13-methyl-15-oxatricyclo [6.6.1.$0^{2,7}$]pentadeca-2,12-dien-9-ol 378

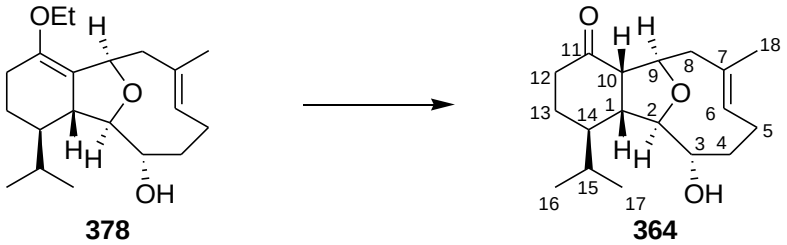


To a flask containing the alcohol **372** (95 mg, 0.21 mmol), DMAP (135 mg, 1.11 mmol) and distilled triethylamine (561 mg, 5.54 mmol) was added freshly distilled acetic anhydride (1.13 g, 11.1 mmol). The resulting solution was heated at 40 °C for 30 min, then cooled at 0 °C and quenched with a saturated aqueous solution of NH_4Cl (3 mL) and Et_2O (5 mL). The aqueous phase was separated and extracted with Et_2O (3 × 5 mL). The organic extracts were combined, washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was filtered through a pad of silica gel (petroleum ether - ethyl acetate, 10:1 with 1% Et_3N) to afford the crude acetate as a colourless oil. Without further purification, the crude acetate **377** was engaged to the next step.

A small freshly cut piece of potassium (≈100 mg) was added to a solution of recrystallised 18-crown-6 (530 mg, 2.00 mmol) in freshly distilled *t*-butylamine (20 mL) at rt. The mixture was sonicated and then stirred at the same temperature until a dark blue colour developed after which anhydrous THF (20 mL) was then added. The crude acetate **377** in anhydrous THF (4 mL) was added on reappearance of the blue colour at such a rate that the colour did not disappear for a long time. After addition of the substrate and reappearance of the blue colour, the excess potassium was destroyed by addition of absolute ethanol, neutralised by addition of a saturated aqueous solution of NH_4Cl and diluted with Et_2O (20 mL). The aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The organic extracts were combined, washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether - ethyl acetate, gradient elution 100:1 → 30:1 with 1% Et_3N) to afford the alcohol **378** as a colourless oil (44 mg, 65% over 2 steps).

R_f = 0.30 (petroleum ether - ethyl acetate, 3:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45 (1H, tt, *J* = 8.8, 1.2 Hz, CH-C6), 4.86 (1H, d, *J* = 5.9 Hz, CH-C9), 4.05 (1H, dd, *J* = 8.2, 5.2 Hz, CH-C2), 3.95–3.88 (1H, m, CH-C3), 3.82 (1H, q, *J* = 7.0 Hz, CH_2-Et), 3.81 (1H, q, *J* = 7.0 Hz, CH_2-Et), 2.52 (1H, d, *J* = 9.5 Hz, OH), 2.41 (1H, dd, *J* = 13.2, 5.9 Hz, CH_2-C8), 2.38–2.09 (6H, m, CH-C1, CH_2-C5, CH_2-C8, CH_2-C12), 1.91–1.85 (2H, m, CH_2-C4), 1.79 (1H, dd, *J* = 12.8, 6.5 Hz, CH_2-C13), 1.67 (3H, s, CH_3-C18), 1.66–1.60 (1H, m, CH-C15), 1.23 (3H, t, *J* = 7.0 Hz, CH_3-Et), 1.22–1.12 (2H, m, CH_2-C13, CH-C14), 0.92 (3H, d, *J* = 6.9 Hz, CH_3-C16), 0.72 (3H, d, *J* = 6.9 Hz, CH_3-C17); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.7 (C-C11), 128.8 (CH-C6), 127.8 (C-C7), 122.1 (C-C10), 87.1 (CH-C2), 75.2 (CH-C9), 74.0 (CH-C3), 62.9 (CH_2-Et), 45.4 (CH-C14), 44.0 (CH_2-C8), 43.3 (CH-C1), 28.7 (CH_2-C4), 28.5 (CH-C15), 24.9 (CH_2-C12), 22.2 (CH_2-C13), 21.8 (CH_3-C16), 21.3 (CH_2-C5), 18.3 (CH_3-C18), 15.7 (CH_3-C17) 15.7 (CH_3-Et); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{20}H_{33}O_3$ 321.2429, found 321.2433, Δ +1.1 ppm; LRMS (CI, Me_3CH) *m/z* (intensity); 321.5 (100%); IR ν_{max} 3442, 2956, 2914, 2871, 1709, 966, 942, 895, 837, 803 cm^{-1}; $[\alpha]^{25}_D$ +106.0 (*c* = 1.00, $CHCl_3$).

(1*R*,2*S*,7*R*,8*R*,9*S*,12*E*)-9-Hydroxy-6-isopropyl-13-methyl-15-oxatricyclo [6.6.1.0^{2,7}]-pentadec-12-en-3-one 364

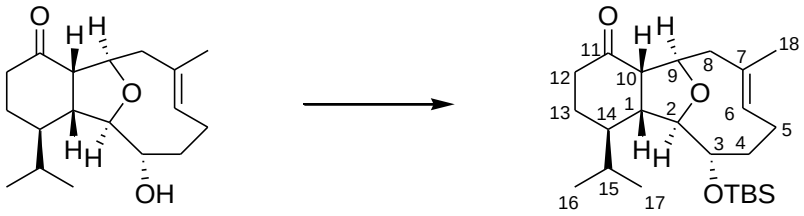


378 **364**

To a stirred solution of enol ether **378** (33 mg, 0.10 mmol) in THF (5 mL) was added 1M HCl (100 µL, 100 µmol) and the solution was stirred at rt 1 h then diluted with Et_2O (10 mL) and water (10 mL). The aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The organic extracts were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether - ethyl acetate, gradient elution 10:1 → 7:1 → 5:1) delivered the ketone **364** (27 mg, 89%) as a colourless solid.

R_f = 0.23 (petroleum ether - ethyl acetate, 3:1); m.p. 175–177 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34–5.27 (1H, m, CH-C6), 4.26 (1H, dd, *J* = 9.8, 5.7 Hz, CH-C9), 3.76 (1H, d, *J* = 9.0 Hz, CH-C2), 2.96 (1H, dt, *J* = 9.0, 6.6 Hz, CH-C3), 2.75 (1H, dd, *J* = 9.8, 7.5 Hz, CH-C10), 2.52 (1H, dd, *J* = 13.6, 5.7 Hz, CH_2-C8), 2.49–2.37 (3H, m, CH-C1, CH_2-C12), 2.31 (1H, dddd, 12.3, 12.3, 12.3, 4.3 Hz, CH_2-C5), 2.23–2.14 (1H, m, CH_2-C5), 2.09 (1H, d, *J* = 13.6 Hz, CH_2-C8), 2.02–1.87 (3H, m, CH_2-C4, CH_2-C13, CH-C15), 1.85 (3H, s, CH_3-C18), 1.75 (1H, ddd, *J* = 13.6, 3.6, 3.6 Hz, CH_2-C4), 1.64–1.58 (1H, m, CH-C14), 1.48–1.34 (1H, m, CH_2-C13), 1.21 (1H, d, *J* = 6.6 Hz, OH), 1.00 (3H, d, *J* = 6.9 Hz, CH_3-C16), 0.79 (3H, d, *J* = 6.9 Hz, CH_3-C17); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.3 (C-C11), 133.7 (CH-C6), 124.5 (C-C7), 88.4 (CH-C2), 80.5 (CH-C9), 74.4 (CH-C3), 53.9 (CH-C10), 50.5 (CH-C1), 40.7 (CH-C14), 40.6 (CH_2-C8), 38.4 (CH_2-C12), 37.5 (CH_2-C4), 28.1 (CH-C15), 27.4 (CH_2-C5), 24.1 (CH_2-C13), 22.0 (CH_3-C16), 20.8 (CH_3-C18), 15.3 (CH_3-C17); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{18}H_{29}O_3$ 293.2116, found 293.2120, Δ +1.1 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 293.5 (100%), 275.5 (9%), 222.4 (11%); Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93%; H, 9.65%. Found: C, 73.94% H, 9.63%; IR ν_{max} 3531, 2954, 2926, 2855, 1694, 969, 937, 896, 856, 794 cm^{-1}; $[\alpha]^{24}_D$ −19.5 (*c* = 1.00, $CHCl_3$).

(1*R*,2*S*,7*R*,8*R*,9*S*,12*E*)-9-(*tert*-Butyldimethylsilyloxy)-6-isopropyl-13-methyl-15-oxatricyclo-[6.6.1.0^{2,7}]pentadec-12-en-3-one 358



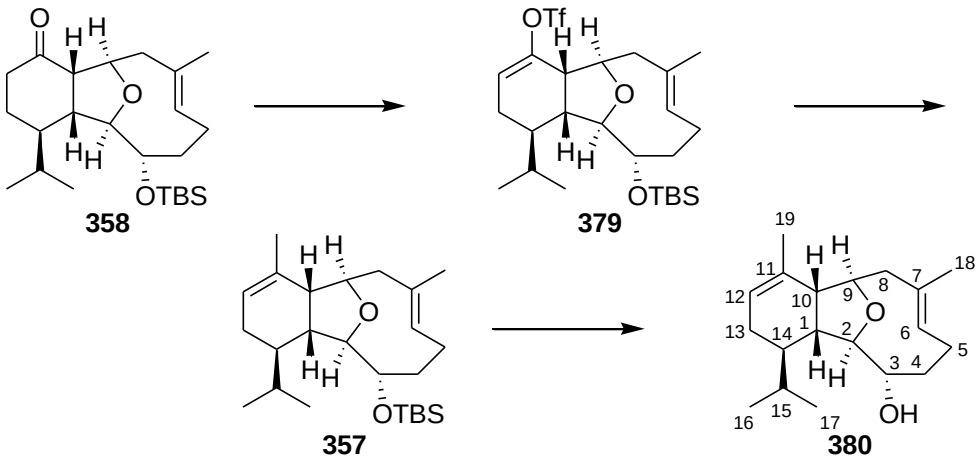
364 **358**

To a solution of alcohol **364** (33 mg, 0.11 mmol) and 2,6-lutidine (35 mg, 0.33 mmol) in anhydrous CH_2Cl_2 (1 mL) at −78 °C was added TBSOTf (45 mg, 0.17 mmol). The reaction mixture was stirred at the same temperature for 1 h then quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (2 mL) and diluted with ethyl acetate (3 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 3 mL). The organic extracts were combined, washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*.

The residue was purified by flash column chromatography on silica gel (petroleum ether - ethyl acetate, 50:1) delivered the silyl ether **358** (36 mg, 78%) as a colourless solid.

R_f = 0.58 (petroleum ether - ethyl acetate, 4:1); m.p. 108−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34−5.27 (1H, m, CH-C6), 4.26 (1H, dd, *J* = 10.0, 6.0 Hz, CH-C9), 3.78 (1H, d, *J* = 9.0 Hz, CH-C2), 2.96 (1H, dd, *J* = 9.0, 7.8 Hz, CH-C3), 2.69 (1H, dd, *J* = 10.0, 6.9 Hz, CH-C10), 2.51 (1H, dd, *J* = 13.7, 6.0 Hz, CH_2-C8), 2.50−2.43 (1H, m, CH_2-C12), 2.36 (1H, br d, *J* = 15.4 Hz, CH_2-C12), 2.31−2.19 (2H, m, CH-C1, CH_2-C5), 2.18−2.11 (1H, m, CH_2-C5), 2.07 (1H, d, *J* = 13.7 Hz, CH_2-C8), 2.01−1.81 (3H, m, CH_2-C4, CH_2-C13, CH-C15), 1.87 (3H, s, CH_3-C18), 1.70 (1H, ddd, *J* = 10.7, 3.3, 3.3 Hz, CH_2-C4), 1.59−1.53 (1H, m, CH_2-C14), 1.36 (1H, dddd, *J* = 13.2, 13.2, 13.2, 3.6 Hz, CH_2-C13), 0.99 (3H, d, *J* = 6.9 Hz, CH_3-C16), 0.87 (9H, s, CH_3-*t*Bu), 0.75 (3H, d, *J* = 6.9 Hz, CH_3-C17), 0.10 (3H, s, $SiCH_3$), 0.01 (3H, s, $SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.5 (C-C11), 134.4 (CH-C6), 124.2 (C-C7), 88.8 (CH-C2), 80.7 (CH-C9), 74.0 (CH-C3), 54.4 (CH-C10), 50.0 (CH-C1), 40.8 (CH-C14), 40.5 (CH_2-C8), 38.2 (CH_2-C12), 37.5 (CH_2-C4), 27.8 (CH-C15), 27.3 (CH_2-C5), 26.0 (CH_3-*t*Bu), 24.5 (CH_2-C13), 22.2 (CH_3-C16), 20.8 (CH_3-C18), 17.9 (C-*t*Bu), 16.3 (CH_3-C17), −4.1 ($SiCH_3$), −4.2 ($SiCH_3$); HRMS (CI, Me_3CH) $[M+H]^+$ calc for $C_{24}H_{43}O_3Si$ 407.2981 found 407.2986, Δ +1.1 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 407.6 (18%), 113.3 (18%); IR ν_{max} 2956, 2930, 2859, 1707, 837, 824, 776 cm^{-1}; $[\alpha]^{27}_D$ −44.5 (*c* = 0.99, $CHCl_3$).

(1*R*,2*R*,6*S*,7*R*,8*R*,9*S*,12*E*)-6-Isopropyl-3,13-dimethyl-15-oxatricyclo [6.6.1.$0^{2,7}$]penta-deca-3,12-dien-9-ol 380



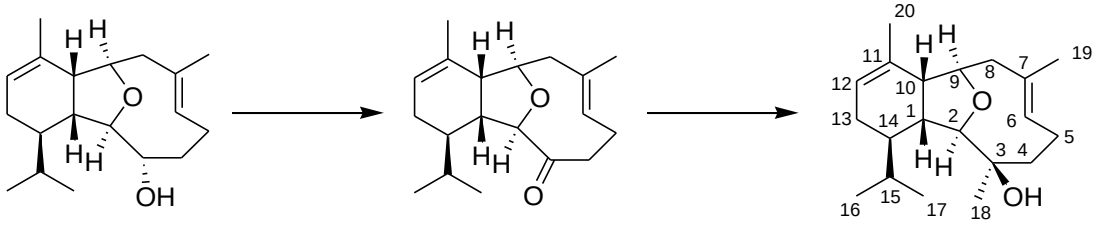
To a stirred solution of the ketone **358** (44 mg, 0.11 mmol) and $PhN(Tf)_2$ (78 mg, 0.22 mmol) in anhydrous THF (1.5 mL) at −78 °C was added NaHMDS (270 µL of a 1.0 M solution in THF, 0.27 mmol) dropwise. The resulting solution was stirred at −78 °C for 2 h then quenched with water (3 mL) at −78 °C, allowed to warm to rt and diluted with Et_2O (3 mL). The aqueous phase was separated and extracted with Et_2O (3 × 5 mL). The organic extracts were combined washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was filtered through a pad of silica gel (petroleum ether – ethyl acetate, 10:1) to afford crude enol triflate **379** that was used for the next step without further purification.

To a solution of the crude enol triflate **379**, LiCl (23 mg, 0.54 mmol) and $Pd(PPh_3)_4$ (12 mg, 11 µmol) in anhydrous THF (10 mL) was added dropwise MeMgCl (180 µL of a 3M solution in THF, 0.54 mmol). The reaction mixture was stirred at rt for 4 h and then quenched at 0 °C by the addition of a saturated aqueous solution of NH_4Cl (5 mL). The reaction mixture was allowed to warm to rt and diluted with Et_2O (5 mL). The aqueous phase was separated and extracted with Et_2O (3 × 5 mL). The organic extracts were combined, washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether - ethyl acetate, 100:1) to deliver the crude alkene **357** contaminated with traces of PPh_3. Without further purification the crude alkene was used for the next step.

To a solution of the crude alkene **357** and 4 Å molecular sieves in anhydrous THF (2 mL) was added TBAF (220 μL of a 1M solution in THF, 0.22 mmol). The reaction mixture was stirred at rt for 5 h and then quenched by the addition of a saturated aqueous solution of NH_4Cl (1 mL). The molecular sieves were removed by filtration and rinsed with ethyl acetate. The aqueous phase was separated and extracted with ethyl acetate (3 × 5 mL). The organic extracts were combined, washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether - ethyl acetate, gradient elution 100:1 → 20:1 → 10:1) to deliver the alcohol **380** (21 mg, 68% over four steps) as a colourless oil.

R_f = 0.26 (petroleum ether - ethyl acetate, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 (1H, br d, *J* = 4.6 Hz, CH-C12), 5.37−5.30 (1H, m, CH-C6), 3.95 (1H, dd, *J* = 9.2, 5.8 Hz, CH-C9), 3.78 (1H, d, *J* = 9.1 Hz, CH-C2), 3.13−3.06 (1H, m, CH-C3), 2.60 (1H, dd, *J* = 13.6, 5.8 Hz, CH_2-C8), 2.42 (1H, br dd, *J* = 9.2, 7.0 Hz, CH-C10), 2.32 (1H, dddd, *J* = 12.2, 12.2, 12.2, 4.3 Hz, CH_2-C5), 2.23 (1H, d, *J* = 13.6 Hz, CH_2-C8), 2.22−2.16 (1H, m, CH_2-C5), 2.10−1.89 (4H, m, CH-C1, CH_2-C4, CH-C15, CH_2-C13), 1.85 (3H, s, CH_3-C18), 1.82−1.68 (2H, m, CH_2-C4, CH_2-C13), 1.75 (3H, s, CH_3-C19), 1.53−1.44 (1H, m, CH-C14), 1.29 (1H, br d, *J* = 6.1 Hz, OH), 0.93 (3H, d, *J* = 6.9 Hz, CH_3-C16), 0.78 (3H, d, *J* = 6.9 Hz, CH_3-C17); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.5 (CH-C6), 131.9 (C-C11), 124.8 (C-C7), 122.9 (CH-C12), 86.0 (CH-C2), 83.8 (CH-C9), 74.9 (CH-C3), 45.8 (CH-C1), 44.8 (CH-C10), 42.8 (CH_2-C8), 37.7 (CH_2-C4), 36.8 (CH-C14), 27.5 (CH_2-C5), 27.4 (CH-C15), 23.6 (CH_3-C19), 23.5 (CH_2-C13), 21.6 (CH_3-C16), 20.8 (CH_3-C18), 14.9 (CH_3-C17); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{19}H_{31}O_2$ 291.2324, found 291.2328, Δ +1.3 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 291.5 (100%), 273.4 (20%); IR ν_{max} 3416, 2955, 2928, 2894, 2867, 943, 798 cm^{-1}; $[\alpha]^{28}_D$ +16.5 (*c* = 1.00, $CHCl_3$).

(−)-Cladiella-6,11-dien-3-ol [9, 10, 31]



380 **381** (−)-Cladiella-6,11-dien-3-ol

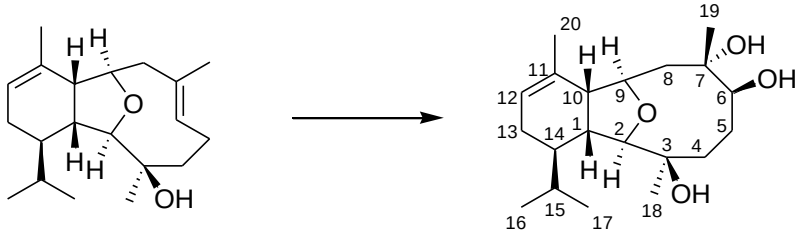
To a solution of the alcohol **380** (26 mg, 90 μmol) in anhydrous CH_2Cl_2 (4 mL) was added pyridine (29 mg, 0.36 mmol) and Dess-Martin periodinane (57 mg, 0.13 mmol). The reaction mixture was stirred at rt for 30 min and then quenched with a saturated aqueous solution of $Na_2S_2O_3$: $NaHCO_3$ (5:1, 2 mL). The mixture was diluted with Et_2O (10 mL) and stirred vigorously for 1 h. The aqueous phase was separated and extracted with Et_2O (3 × 5 mL). The organic extracts were combined, washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was filtered through a pad of silica gel (petroleum ether - ethyl acetate, 10:1) to afford crude ketone **381** which was used without further purification in the next step.

To a solution of the above crude ketone **381** in anhydrous THF (3 mL) was added $NaBF_4$ (100 mg, 900 μmol) at rt. The mixture was stirred at rt for 10 min and then cooled at −78 °C. MeLi (170 μL of a 1.6 M solution in THF, 0.27 mmol) was added and the reaction mixture was stirred at −78 °C for 30 min. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$, diluted with Et_2O (5 mL) and allowed to warm to rt. The aqueous phase was separated and extracted with Et_2O (3 × 5 mL). The organic extracts were combined, washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane - ethyl acetate, 15:1) to deliver (−)-cladiella-6,11-dien-3-ol (19 mg, 69% over two steps) as a colourless solid.

R_f = 0.25 (petroleum ether - ethyl acetate, 4:1); m.p. 51–53 °C {Lit.[9] 48–52°C; Lit.[10] 56–57 °C ; Lit.[31] 51–52 °C}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56–5.48 (1H, m, CH-C6), 5.42–5.37 (1H, m, CH-C12), 4.10 (1H, dd, *J* = 5.7, 2.8 Hz, CH-C9), 3.82 (1H, d, *J* = 7.4 Hz, CH-C2), 2.50 (1H, dd, *J* = 13.8, 5.7 Hz, CH_2-C8), 2.47–2.34 (3H, m, CH-C1, CH_2-C5, CH-C10), 2.17–1.89 (5H, m, CH_2-C4, CH_2-C5, CH_2-C8, CH_2-C13), 1.82 (3H, s, CH_3-C19), 1.68 (3H, s, CH_3-C20), 1.62–1.50 (3H, m,

CH_2-C4, CH-C14, CH-C15), 1.41 (3H, s, CH_3-C18), 1.06 (1H, br s, OH), 0.96 (3H, d, *J* = 6.6 Hz, CH_3-C16), 0.84 (3H, d, *J* = 6.6 Hz, CH_3-C17); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.9 (C-C11), 129.4 (CH-C6), 126.8 (C-C7), 121.5 (CH-C12), 89.8 (CH-C2), 81.0 (CH-C9), 77.3 (C-C3), 47.0 (CH-C10), 44.4 (CH_2-C8), 40.3 (CH-C1), 38.4 (CH-C14), 36.8 (CH_2-C4), 29.1 (CH-C15), 27.5 (CH_3-C18), 23.1 (CH_2-C13), 22.9 (CH_2-C5), 22.2 (CH_3-C20), 21.7 (CH_3-C16), 20.8 (CH_3-C17), 19.0 (CH_3-C19); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{20}H_{33}O_2$ 305.2480, found 305.2477, Δ −1.1 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 305.5 (100%), 287.5 (85%); IR ν_{max} 3423, 2956, 2921, 2868, 1697, 1459, 1367, 1259, 1071 cm^{-1}; $[\alpha]^{26}_D$ −25.7 (*c* = 0.30, $CHCl_3$) {Lit.[9] $[\alpha]^{25}_D$ −22.7 (*c* = 0.3, $CHCl_3$); Lit.[10] $[\alpha]^{25}_D$ −18.1 (*c* = 0.07, $CHCl_3$); Lit.[31] $[\alpha]^{24}_D$ −24.4 (*c* = 0.25, $CHCl_3$)}.

(−)-Cladiell-11-ene-3,6,7-triol [11, 15, 31]



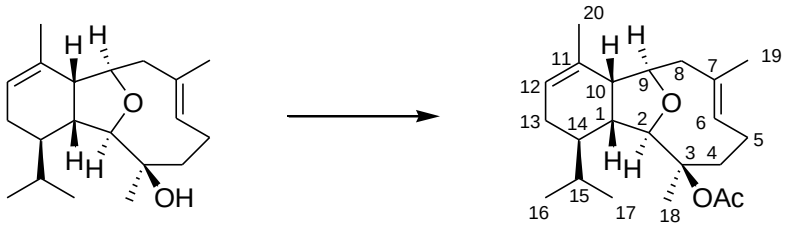
(−)-Cladiella-6,11-dien-3-ol (−)-Cladiell-11-ene-3,6,7-triol

To a solution of cladiella-6,11-dien-3-ol (5.0 mg, 16 μmol) in a THF:H_2O (1:1) mixture (1 mL) at 0 °C was added NMO (19 μL of a 1.0 g/mL solution in H_2O, 0.16 mmol) and OsO_4 (2 μL of a 4.0 wt% solution in H_2O, 0.3 μmol). The reaction mixture was stirred at 0 °C for 1 h and then allowed to warm to rt and stirred at this temperature for 1 h. The reaction was then quenched with a saturated aqueous solution of $Na_2S_2O_3$ (2 mL) and stirred vigorously for 30 min before being diluted with CH_2Cl_2 (2 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 3 mL). The organic extracts were combined, washed with brine (3 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane - ethyl acetate, gradient elution 2:1 → ethyl acetate 100%) to deliver (−)-cladiell-11-ene-3,6,7,triol (3.7 mg, 66%) as colourless crystals.

R_f = 0.16 (petroleum ether - ethyl acetate, 1:2); m.p. 195–198 °C {Lit.[11] 205.5–206.0 °C; Lit.[15] 205–206 °C, Lit.[31] 196.8–198.4 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.44 (1H, br s, CH-C12), 4.56 (1H, br s, CH-C6), 4.34–4.28 (1H, m, CH-

C9), 3.73 (1H, d, *J* = 6.8 Hz, CH-C2), 2.61 (1H, ddd, *J* = 6.8, 6.5, 4.6 Hz, CH-C1), 2.28 (1H, br d, *J* = 6.5 Hz, CH-C10), 2.21−2.13 (1H, m, CH_2-C13), 2.11−1.94 (3H, m, CH_2-C4, CH_2-C8, CH_2-C13), 1.88−1.78 (2H, m, CH_2-C5, OH), 1.73−1.53 (6H, m, CH_2-C4, CH_2-C5, CH_2-C8, CH-C15, OH, OH), 1.66 (3H, s, CH_3-C20), 1.50−1.45 (1H, m, CH-C14), 1.36 (3H, s, CH_3-C18), 1.18 (3H, s, CH_3-C19), 0.97 (3H, d, *J* = 6.6 Hz, CH_3-C16), 0.87 (3H, d, *J* = 6.6 Hz, CH_3-C17); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.5 (C-C11), 122.2 (CH-C12), 87.0, (CH-C2), 76.6 (CH-C9), 76.1 (C-C7), 75.4 (CH-C6), 75.1 (C-C3), 48.1 (CH-C10), 46.6 (CH_2-C8), 40.0 (CH-C1), 39.6 (CH-C14), 36.2 (CH_2-C4), 30.6 (CH_2-C5), 29.5 (CH-C15), 28.9 (CH_3-C18), 23.2 (CH_2-C13), 22.9 (CH_3-C19), 22.0 (CH_3-C20), 21.5 (CH_3-C16), 20.7 (CH_3-C17); HRMS (CI, Me_3CH) $[M-OH]^+$ calcd for $C_{20}H_{33}O_3$ 321.2429, found 321.2434, Δ +1.5 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 321.4 (100%), 305.4 (25%), 303.4 (21%), 287.4 (10%); IR ν_{max} 3423, 2960, 2926, 1726, 1078, 1047, 1024, 929, 883, 798, cm^{-1}; $[\alpha]^{28}_D$ −12.1 (*c* = 0.70, $CHCl_3$) {Lit.[11] $[\alpha]_D$ −16.1 (*c* = 0.75, $CHCl_3$), Lit.[15] $[\alpha]^{25}_D$ −12.3 (*c* = 1.00, $CHCl_3$), Lit.[31] $[\alpha]^{25}_D$ −11.9 (*c* = 0.43, $CHCl_3$)}.

(−)-3-Acetoxycladiella-6,11-diene [10]

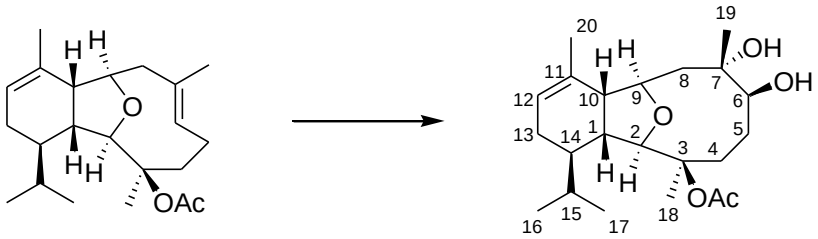


(−)-Cladiella-6,11-dien-3-ol (−)-3-Acetoxycladiella-6,11-diene

To a flask containing cladiella-6,11-dien-3-ol (7.2 mg, 23 μmol), DMAP (14 mg, 0.12 mmol) and distilled triethylamine (60 mg, 0.59 mmol) was added freshly distilled acetic anhydride (128 mg, 1.18 mmol). The resulting solution was heated at 40 °C for 30 min, then cooled at 0 °C and the reaction was quenched with a saturated aqueous solution of NH_4Cl (1 mL) and Et_2O (2 mL). The aqueous phase was separated and extracted with Et_2O (3 × 2 mL). The organic extracts were combined, washed with brine (2 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether - ethyl acetate, 40:1) to afford (−)-3-acetoxycladiella-6,11-diene (2.0 mg, 25%) as a colourless oil.

R_f = 0.50 (petroleum ether - Et_2O, 1:4); ^1H NMR (500 MHz, $CDCl_3$) δ 5.47 (1H, dd, *J* = 11.3, 6.3 Hz, CH-C6), 5.41 (1H, br s, CH-C12), 4.07 (1H, dd, *J* = 5.5, 3.5 Hz, CH-C9), 4.05 (1H, d, *J* = 6.4 Hz, CH-C2), 2.52 (1H, dd, *J* = 13.7, 5.5 Hz, CH_2-C8), 2.44−2.33 (3H, m, CH-C1, CH_2-C5, CH-C10), 2.32−2.24 (1H, m, CH_2-C5), 2.18−2.08 (2H, m, CH_2-C5 CH_2-C13), 2.05 (1H, d, *J* = 13.7 Hz, CH_2-C8), 2.00 (1H, ddd, *J* = 13.4, 11.0, 6.2 Hz, CH_2-C4), 1.93 (3H, s, CH_3-Ac), 1.93−1.90 (1H, m, CH_2-C13), 1.81 (3H, d, *J* = 1.5 Hz, CH_3-C19), 1.74 (3H, s, CH_3-C18), 1.70 (3H, s, CH_3-C20), 1.65 (1H, heptet, *J* = 6.7 Hz, CH-C15), 1.43−1.41 (1H, m, CH-C14), 0.96 (3H, d, *J* = 6.7 Hz, CH_3-C16), 0.84 (3H, d, *J* = 6.7 Hz, CH_3-C17); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0 (C-Ac), 132.7 (C-C11), 129.7 (CH-C6), 126.6 (C-C7), 121.6 (CH-C12), 89.5 (C-C3), 87.9 (CH-C2), 81.1 (CH-C9), 46.7 (CH-C10), 43.9 (CH_2-C8), 40.7 (CH-C1), 38.4 (CH-C14), 32.6 (CH_2-C4), 28.7 (CH-C15), 23.1 (CH_2-C13), 23.1 (CH_2-C5), 23.0 (CH_3-Ac), 22.4 (CH_3-C20), 22.1 (CH_3-C18), 21.9 (CH_3-C16), 20.3 (CH_3-C17), 19.4 (CH_3-C19); HRMS (EI+) $[M]^+$ calc for $C_{22}H_{34}O_3$ 346.2508, found 346.2506, Δ −0.6 ppm; LRMS (EI+) *m/z* (intensity) 346.3 (18%), 286.2 (62%), 243.2 (32%), 218.2 (54%), 217.2 (45%), 177.1 (20%), 147.1 (56%), 105.1 (76%), 93.1 (100%); IR ν_{max} 2959, 2929, 2870, 1732, 1450, 1370, 1246, 1069, 1022, 802 cm^{-1}; $[\alpha]^{26}_D$ −28.5 (*c* = 0.60, $CHCl_3$) {Lit.[10] $[\alpha]^{25}_D$ −34.7 (*c* = 0.5, $CHCl_3$)}.

3-Acetoxycladiellin-11-ene-6,7-diol [12]



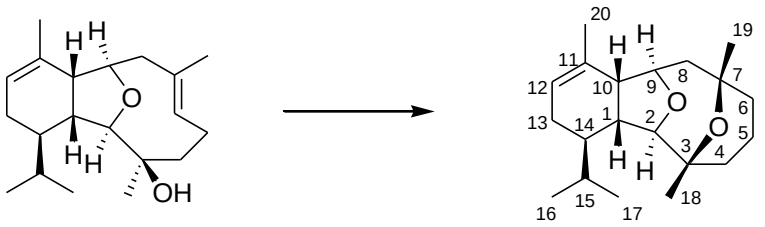
(−)-3-Acetoxycladiella-6,11-diene — 3-Acetoxycladiellin-11-ene-6,7-diol

To a solution of (−)-3-acetoxycladiella-6,11-diene (3.1 mg, 8.9 μmol) in a THF:H_2O (1:1) mixture (0.6 mL) at 0 °C was added NMO (10 μL of a 1.0 g/mL solution in H_2O, 89 μmol) and OsO_4 (1.1 μL of a 4.0 wt% solution in H_2O, 0.17 μmol). The reaction mixture was stirred at 0 °C for 1 h before being allowed to warm to rt and stirred at this temperature for 1.5 h. The reaction was then quenched with a saturated aqueous solution of $Na_2S_2O_3$ (2 mL) before being stirred vigorously for 30 min and diluted with CH_2Cl_2 (2 mL). The aqueous

phase was separated and extracted with CH_2Cl_2 (3 × 3 mL). The organic extracts were combined, washed with brine (3 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether - ethyl acetate, gradient elution 2:1 → 1:1 → ethyl acetate 100%) to deliver 3-acetoxycladiellin-11-ene-6,7-diol (1.1 mg, 36%) as colourless crystals.

R_f = 0.23 (petroleum ether - ethyl acetate, 1:2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45 (1H, br s, CH-C12), 4.55 (1H, br s, CH-C6), 4.30 (1H, dt, *J* = 11.8, 3.0 Hz, CH-C9), 3.89 (1H, d, *J* = 6.3 Hz, CH-C2), 2.60 (1H, ddd, *J* = 6.3, 6.3, 6.3 Hz, CH-C1), 2.32 (1H, br d, *J* = 6.3 Hz, CH-C10), 2.25−2.09 (3H, m, CH_2-C4, CH_2-C5, CH_2-C13), 1.99 (3H, s, CH_3-Ac), 1.94−1.83 (3H, m, CH_2-C5, CH_2-C8, CH_2-C13), 1.73 (1H, br dd, *J* = 15.0, 3.0 Hz, CH_2-C8), 1.67 (3H, s, CH_3-C20), 1.64 (3H, s, CH_3-C18) 1.63−1.56 (4H, m, CH_2-C4, CH-C15, OH, OH), 1.39−1.35 (1H, m, CH-C14), 1.17 (3H, s, CH_3-C19), 0.96 (3H, d, *J* = 6.7 Hz, CH_3-C16), 0.86 (3H, d, *J* = 6.7 Hz, CH_3-C17); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8 (C-Ac), 132.2 (C-C11), 121.9 (CH-C12), 86.6 (CH-C2), 86.4 (C-C3), 77.6 (CH-C9), 77.3 (C-C7), 75.9 (CH-C6), 48.5 (CH-C10), 46.8 (CH_2-C8), 40.3 (CH-C1), 39.4 (CH-C14), 31.4 (CH_2-C4), 30.5 (CH_2-C5), 29.1 (CH-C15), 23.4 (CH_3-C18), 22.9 (CH_2-C13), 22.9 (CH_3-C19), 22.5 (CH_3-Ac), 22.0 (CH_3-C20), 21.6 (CH_3-C16), 20.2 (CH_3-C17); HRMS (EI) $[M]^+$ calcd for $C_{22}H_{36}O_5$ 380.2565, found 380.2567, Δ +1.0 ppm; LRMS (EI) *m/z* (intensity) 380.3 (7%), 362.3 (5%), 320.3 (50%), 302.3 (55%), 93.1 (100%); IR ν_{max} 3446, 2963, 2959, 2934, 1734, 910, 731 cm^{-1}; $[\alpha]^{28}_D$ 0 (*c* = 0.30, $CHCl_3$) {Lit.[12] $[\alpha]_D$ −1.87 (*c* = 2.17, $CHCl_3$)}.

(1*R*,2*R*,6*S*,8*R*,9*R*,13*R*,14*R*)-2,6,10-Trimethyl-13-(propan-2-yl)-15,16-dioxatetracyclo[6.6.1.1^{2,6}.0^{9,14}]hexadec-10-ene 382 [31]

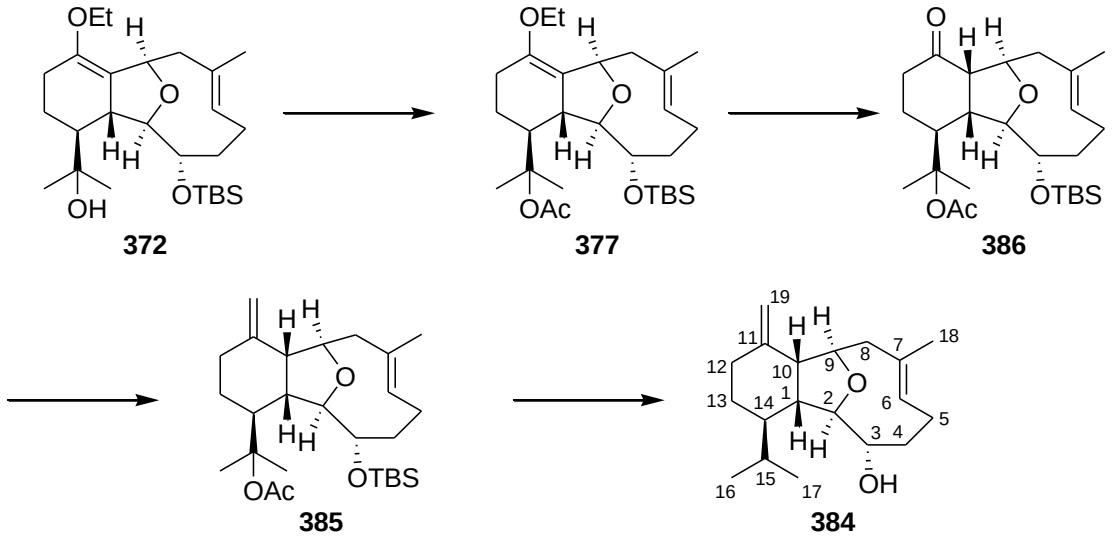


(–)-Cladiella-6,11-dien-3-ol **382**

To a solution of cladiella-6,11-dien-3-ol (3.0 mg, 9.8 μmol) in anhydrous CH_2Cl_2 (300 μL) at 0 °C was added freshly distilled acetic anhydride (11 mg, 98 μmol) and a solution of trimethylsilyl trifluoromethanesulfonate (10 μL of a 1 mg/mL solution in anhydrous CH_2Cl_2, 0.49 μmol). The reaction mixture was stirred for 30 min at 0 °C then quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (1 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 3 mL). The organic extracts were combined, washed with brine (5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether - ethyl acetate, 10:1) to deliver the tetracycle **382** (2.2 mg, 81%) as a colourless oil.

R_f = 0.65 (petroleum ether - ethyl acetate, 6:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.45 (1H, br d, *J* = 5.4 Hz, CH-C12), 4.02–4.01 (1H, m, CH-C9), 3.85 (1H, s, CH-C2), 2.95–2.91 (1H, m, CH-C10), 2.42–2.28 (2H, m, CH-C1, CH_2-C5), 2.21 (1H, dd, *J* = 14.4, 5.2 Hz, CH_2-C8), 1.92–1.82 (4H, m, CH_2-C4, CH_2-C8, CH_2-C13, CH-C15), 1.73–1.67 (1H, m, CH_2-C13), 1.66 (3H, s, CH_3-C20), 1.54–1.33 (5H, m, CH_2-C4, CH_2-C5, CH_2-C6, CH-C14), 1.31 (3H, s, CH_3-C19), 1.09 (3H, s, CH_3-C18), 0.93 (3H, d, *J* = 6.8 Hz, CH_3-C16), 0.77 (3H, d, *J* = 6.8 Hz, CH_3-C17); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.7 (C-C11), 121.2 (CH-C12), 91.7 (CH-C2), 81.4 (CH-C9), 75.9 (C-C3), 74.3 (C-C7), 48.3 (CH-C10), 48.2 (CH_2-C8), 42.1 (CH-C1), 39.7 (CH_2-C6), 38.9 (CH-C14), 36.3 (CH_2-C4), 35.8 (CH_3-C19), 28.4 (CH-C15), 28.2 (CH_3-C18), 22.6 (CH_3-C20), 22.3 (CH_2-C13), 22.0 (CH_3-C16), 18.4 (CH_2-C5), 15.6 (CH_3-C17); IR ν_{max} 2959, 2923, 1761, 1734 cm^{-1}; $[\alpha]^{25}_D$ +17.1 (*c* = 0.73, $CHCl_3$) {Lit.[31] $[\alpha]^{23}_D$ +19.0 (*c* = 0.37, $CHCl_3$)}.

(1*R*,2*R*,6*R*,7*R*,8*R*,9*S*,12*E*)-13-Methyl-3-methylidene-6-(propan-2-yl)-15-oxatricyclo[6.6.1.$0^{2,7}$]pentadec-12-en-9-ol 384



To a flask containing the alcohol **372** (265 mg, 590 μmol), DMAP (359 mg, 2.94 mmol) and distilled triethylamine (1.48 g, 14.7 mmol) was added freshly distilled acetic anhydride (3.00 g, 29.4 mmol). The resulting solution was heated at 40 °C for 30 min before being cooled at 0 °C and quenched with a saturated aqueous solution of NH_4Cl (10 mL) and Et_2O (20 mL).The aqueous phase was separated and extracted with Et_2O (3 × 20 mL). The organic extracts were combined, washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was filtered through a pad of silica gel (petroleum ether - ethyl acetate, 10:1 with 1% Et_3N) to afford crude acetate **377** as a colourless oil which was used without further purification in the next step.

To a solution of the above crude acetate **377** in THF (30 mL) was added 1M HCl (630 μL, 630 μmol) and the solution was stirred at rt 1 h then diluted with Et_2O (30 mL) and water (30 mL). The aqueous phase was separated and extracted with Et_2O (3 × 20 mL). The organic extracts were combined, washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was filtered through a pad of silica gel (petroleum ether - ethyl acetate, 10:1) and the solvent removed *in vacuo* to deliver the crude ketone **386** which was used without further purification in to the next step.

To a solution of Ph_3PCH_3Br (1.13 g, 3.16 mmol) in anhydrous THF (10 mL) at 0 °C was added dropwise NaHMDS (0.34 mL of a 1M solution in THF, 0.34 mmol). The resulting yellow reaction mixture was stirred for 1 h at rt. The above crude

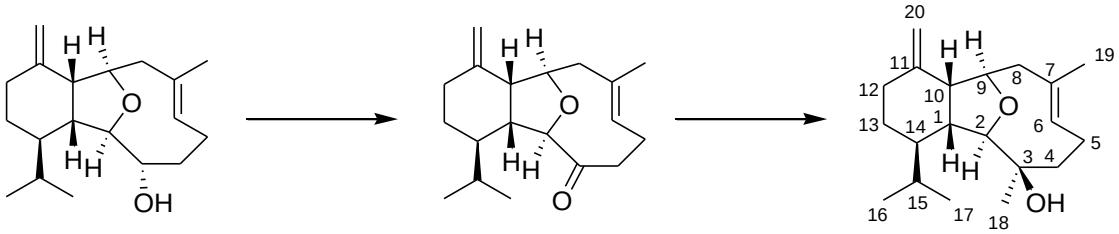
ketone **386** in anhydrous THF (10 mL) was added dropwise to the solution of ylide. The solution was stirred at reflux for 1 h and then cooled to rt before being quenched with a saturated aqueous solution of NH_4Cl (10 mL) and diluted with Et_2O (20 mL). The aqueous phase was separated and extracted with Et_2O (2 × 20 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was filtered through a pad of silica gel (petroleum ether – ethyl acetate 10:1) and the solvent removed *in vacuo* to give the crude diene **385** which was used without further purification in the next step.

A small freshly cut piece of potassium (≈200 mg) was added to a solution of recrystallised 18-crown-6 (780 mg, 2.95 mmol) in freshly distilled *t*-butylamine (30 mL) at rt. The mixture was sonicated and stirred at rt until a dark blue colour developed after which anhydrous THF (30 mL) was added. The crude diene **385** in anhydrous THF (10 mL) was added on reappearance of the blue colour at such a rate that the colour did not disappear for a long time. After addition of the substrate and reappearance of the blue colour, the excess potassium was destroyed by addition of absolute ethanol, neutralised by addition of a saturated aqueous solution of NH_4Cl and diluted with Et_2O (30 mL). The aqueous phase was separated and extracted with Et_2O (3 × 20 mL). The organic extracts were combined washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether - ethyl acetate, gradient elution 100:1 → 10:1 with 1% Et_3N) to afford the alcohol **384** as a colourless solid (81 mg, 47% for four steps).

R_f = 0.58 (petroleum ether - ethyl acetate, 2:1); m.p. 149−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.33 (1H, m, CH-C6), 4.78 (1H, t, *J* = 1.9 Hz, CH_2-C19), 4.72 (1H, t, *J* = 1.9 Hz, CH_2-C19), 4.03 (1H, dd, *J* = 9.9, 5.9 Hz, CH-C9), 3.63 (1H, d, *J* = 9.2 Hz, CH-C2), 3.04 (1H, ddd, 9.2, 8.2, 6.5 Hz, CH-C3), 2.70 (1H, dd, *J* = 9.9, 6.5 Hz, CH-C10), 2.45 (1H, dd, *J* =13.8, 5.9 Hz, CH_2-C8), 2.29 (1H, dddd, *J* = 12.3, 12.3, 12.3, 4.2 Hz, CH_2-C5), 2.26 (1H, ddd, *J* = 13.5, 3.2, 3.2 Hz, CH_2-C12), 2.24−2.16 (1H, m, CH_2-C5), 2.16−2.10 (1H, m, CH_2-C12), 2.05 (1H, d, *J* = 13.8 Hz, CH_2-C8), 2.01 (1H, dd, *J* = 11.8, 6.5 Hz, CH-C1), 1.95−1.85 (2H, m, CH_2-C4, CH-C15), 1.85 (3H, s, CH_3-C18), 1.79−1.71 (2H, m, CH_2-C4, CH_2-C13), 1.41−1.32 (1H, m, CH-C14), 1.13 (1H, d, *J* = 6.5 Hz, OH), 1.02−0.98 (1H, m, CH_2-C13), 0.95 (3H, d, *J* = 6.9 Hz, CH_3-C16), 0.74 (3H, d, *J* = 6.9 Hz, CH_3-C17); NMR (100 MHz,

$CDCl_3$) δ 146.7 (C-C11), 133.5 (CH-C6), 124.8 (C-C7), 110.5 (CH_2-C19), 88.2 (CH-C2), 80.6 (CH-C9), 74.7 (CH-C3), 48.7 (CH-C1), 47.5 (CH-C10), 41.1 (CH-C14), 39.4 (CH_2-C8), 37.5 (CH_2-C4), 31.2 (CH_2-C12), 28.3 (CH-C15), 27.7 (CH_2-C5), 25.3 (CH_2-C13), 22.0 (CH_3-C16), 21.1 (CH_3-C18), 15.6 (CH_3-C17); HRMS (EI) $[M]^+$ calcd for $C_{19}H_{30}O_2$ 290.2247, found 290.2245, Δ −0.1 ppm; LRMS (EI) *m*/*z* (intensity) 290.2 (62%), 272.3 (15%), 229.2 (12%), 193.2 (21%), 93.1 (71%), 59.1 (100%); IR ν_{max} 3425, 2932, 2870, 2360, 895 cm^{-1}; $[\alpha]^{26}_D$ +5.95 (*c* = 1.00, $CHCl_3$).

(1*R*,2*R*,6*R*,7*R*,8*R*,9*R*,12*E*)-9,13-Dimethyl-3- methylidene-6-(propan-2-yl)-15-oxatricyclo[6.6.1.$0^{2,7}$]pentadec-12-en-9-ol



384 **387** **383**

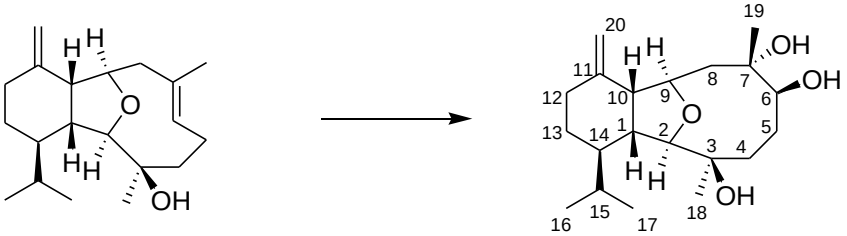
To a solution of the alcohol **384** (80 mg, 0.27 mmol) in anhydrous CH_2Cl_2 (12 mL) was added pyridine (87 mg, 1.1 mmol) and Dess-Martin periodinane (175 mg, 410 μmol) at rt. The reaction mixture was stirred at this temperature for 30 min before being quenched with a saturated aqueous solution of $Na_2S_2O_3$ and $NaHCO_3$ (5:1, 6 mL). The mixture was diluted with Et_2O (20 mL) and stirred vigorously for 1 h. The aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The organic extracts were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was filtered through a pad of silica gel (petroleum ether - ethyl acetate, 15:1) to afford crude ketone **387** which was used without further purification in the next step.

To a solution of the above crude ketone **387** in THF (10 mL) was added $NaBF_4$ (301 mg, 2.75 mmol) at rt. The mixture was stirred at rt for 10 min and then cooled at −78 °C. MeLi (0.52 mL of a 1.6 M solution in THF, 0.83 mmol) was added and the reaction mixture was stirred at −78 °C for 30 min. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL), diluted with Et_2O (10 mL) and allowed to warm to rt. The aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The organic extracts were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The

residue was purified by flash column chromatography on silica gel (*n*-hexane - ethyl acetate, 20:1) to deliver the alcohol **383** (65 mg, 78% over two steps) as a colourless solid.

R_f = 0.64 (petroleum ether - Et_2O, 1:1); m.p. 139–140 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 5.58 (1H, br s, CH-C6), 4.77 (1H, t, *J* = 2.0 Hz, CH_2-C20), 4.70 (1H, s, CH_2-C20), 4.01 (1H, br s, CH-C9), 3.74 (1H, s, CH-C2), 2.69 (1H, br s, CH-C10), 2.45 (1H, dd, *J* = 13.8, 5.4 Hz, CH_2-C8), 2.44–2.36 (1H, m, CH_2-C5), 2.25 (1H, *J* = 12.9, 3.4 Hz, CH_2-C12), 2.20–2.05 (3H, m, CH-C1, CH_2-C5, CH_2-C12), 2.02 (1H, d, *J* = 13.8 Hz, CH_2-C8), 1.87 (3H, s, CH_3-C19), 1.86–1.80 (1H, m, CH-C15), 1.72 (1H, dddd, 12.9, 3.5, 3.5, 3.4 Hz, CH_2-C13), 1.70–1.63 (2H, m, CH_2-C4), 1.35–1.25 (2H, m, CH-C14, OH), 1.17 (3H, br s, CH_3-C18), 1.03 (1H, dddd, *J* = 12.9, 12.9, 12.9, 3.5 Hz, CH_2-C13), 0.95 (3H, d, *J* = 6.9 Hz, CH_3-C16), 0.75 (3H, d, *J* = 6.9 Hz, CH_3-C17); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.8 (C-C11), 132.8 (CH-C6), 124.8 (C-C7), 110.4 (CH_2-C20), 92.3 (CH-C2), 80.4 (CH-C9), 75.3 (C-C3), 48.1 (CH-C10), 46.3 (CH-C1), 42.7 (CH-C14), 39.0 (CH_2-C4), 38.7 (CH_2-C8), 31.5 (CH_2-C12), 29.8 (CH_3-C18), 28.2 (CH-C15), 25.4 (CH_2-C13), 24.5 (CH_2-C5), 22.1 (CH_3-C16), 20.6 (CH_3-C19), 15.5 (CH_3-C17); HRMS (EI) $[M]^+$ calcd for $C_{20}H_{32}O_3$ 304.2404, found 304.2401, Δ −0.3 ppm; LRMS (EI) *m/z* (intensity) 304.3 (25%), 286.3 (10%), 243.2 (9%), 219.2 (19%), 179.1 (91%), 59.1 (100%); IR ν_{max} 3427, 2957, 2929, 2914, 2874, 1643, 1448, 890 cm^{-1}; $[\alpha]^{26}_D$ −37.6 (*c* = 1.00, $CHCl_3$).

(−)-Sclerophytin A [7, 20, 37]



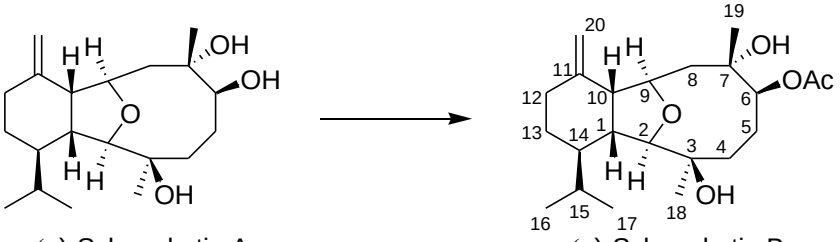
383 (−)-Sclerophytin A

To a solution of the alcohol **383** (4.0 mg, 13 μmol) in a THF:H_2O (1:1) mixture (0.8 mL) at 0 °C was added NMO (15 μL of a 1.0 g/mL solution in H_2O, 0.13 mmol) and OsO_4 (1.7 μL of a 4.0 wt% solution in H_2O, 0.26 μmol). The reaction mixture was stirred at 0 °C for 1 h and at rt for 1 h. The reaction was then quenched with a saturated aqueous solution of $Na_2S_2O_3$ (2 mL), and the

mixture was stirred vigorously for 30 min before being diluted with CH_2Cl_2 (2 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 3 mL). The organic extracts were combined, washed with brine (3 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane - ethyl acetate, 4:1) to deliver (−)-sclerophytin A (2.6 mg, 59%) as colourless crystals.

R_f = 0.23 (petroleum ether - ethyl acetate, 1:2); m.p. 186−188°C {Lit.[7] m.p. 187 °C, Lit.[37] m.p. 185−186 ºC}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.66 (1H, br s, CH_2-C20), 4.64 (1H, br s, CH_2-C20), 4.56 (1H, br d, *J* = 5.8 Hz, CH-C6), 4.11 (1H, ddd, *J* = 10.8, 6.6, 3.8 Hz, CH-C9), 3.62 (1H, s, CH-C2), 2.97 (1H, dd, *J* = 7.7, 6.6 Hz, CH-C10), 2.30−2.21 (2H, m, CH_2-C8, CH_2-C12), 2.16 (1H, dd, *J* =10.1, 7.7 Hz, CH-C1), 2.06−1.96 (2H, m, CH_2-C5, CH_2-C12), 1.90−1.75 (2H, m, CH_2-C4), 1.75−1.56 (6H, m, CH_2-C8, CH_2-C13, CH-C15, OH, OH, OH), 1.30−1.24 (2H, m, CH_2-C5, CH-C14), 1.20 (3H, s, CH_3-C19), 1.15 (3H, s, CH_3-C18), 1.05 (1H, dddd, *J* =12.5, 12.5, 12.5, 3.0 Hz, CH_2-C13), 0.96 (3H, d, *J* = 6.9 Hz, CH_3-C16), 0.79 (3H, d, *J* = 6.9 Hz, CH_3-C17); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0 (C-C11), 109.3 (CH_2-C20), 90.6 (CH-C2), 80.2 (CH-C6), 78.2 (CH-C9), 75.0 (C-C3), 53.1 (CH-C10), 45.4 (CH_2-C8), 45.3 (CH-C1), 43.8 (CH-C14), 40.1 (CH_2-C4), 31.7 (CH_2-C12), 30.4 (CH_3-C18), 29.4 (CH_2-C5), 29.2 (CH-C15), 24.9 (CH_2-C13), 23.1 (CH_3-C19), 22.1 (CH_3-C16), 16.1 (CH_3-C17); HRMS (CI, Me_3CH) $[M\text{–}OH]^+$ calcd for $C_{20}H_{33}O_3$ 321.2429, found 321.2433, Δ +1.2 ppm ; LRMS (CI, Me_3CH) *m/z* (intensity) 321.4 (18%), 303.4 (15%), 287.4 (10%); IR ν_{max} 3415, 2961, 2927, 2363, 2331, 797 cm^{-1}; $[\alpha]^{25}_D$ −6.2 (*c* = 1.00, $CHCl_3$) {Lit.[20] $[\alpha]^{20}_D$ −2.7 (c = 0.11, $CHCl_3$), Lit.[37] $[\alpha]^{20}_D$ −3.0 (*c* = 1.00, $CHCl_3$)}.

(−)-Sclerophytin B [7]

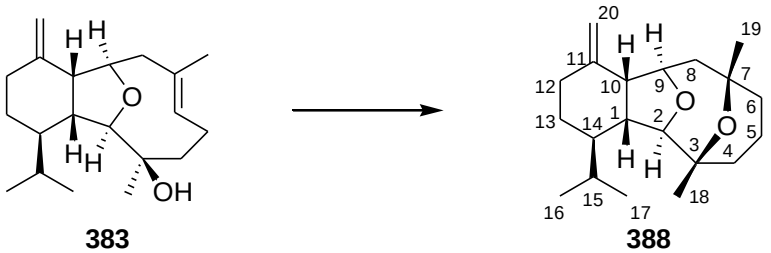


(−)-Sclerophytin A (−)-Sclerophytin B

To a solution of (−)-sclerophytin A (3.5 mg, 10 μmol) in anhydrous CH_2Cl_2 (0.5 mL) at 0°C was added DMAP (1.3 mg, 10 μmol), distilled triethylamine

(3.1 mg, 31 μmol) and distilled acetic anhydride (1.7 mg, 15 μmol). The resulting solution was stirred for 30 min, before being concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (*n*-hexane - ethyl acetate, 5:1) to afford (−)-sclerophytin B (3.0 mg, 79%) as a colourless solid.
R_f = 0.60 (petroleum ether - ethyl acetate, 1:2); m.p. 186−188 °C {Lit.[7] 190−192 °C}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63 (1H, br d, *J* = 4.8 Hz, CH-C6), 4.65 (1H, t, *J* = 2 Hz, CH_2-C20), 4.61 (1H, br s, CH_2-C20), 4.13 (1H, ddd, *J* = 11.2, 7.3, 3.8 Hz, CH-C9), 3.68 (1H, s, CH-C2), 3.02 (1H, dd, *J* = 7.3, 7.3 Hz, CH-C10), 2.26 (1H, dd, *J* = 14.6, 11.2 Hz, CH_2-C8), 2.26−2.21 (2H, m, CH_2-C12, OH), 2.15−2.00 (4H, m, CH-C1, CH_2-C4, CH_2-C5, CH_2-C12), 2.08 (3H, s, CH_3-Ac), 1.78−1.67 (4H, m, CH_2-C4, CH_2-C8, CH_2-C13, CH-C15), 1.57 (1H, br s, OH), 1.43−1.37 (1H, m, CH_2-C5), 1.34−1.24 (1H, m, CH-C14), 1.23 (3H, s, CH_3-C19), 1.14 (3H, s, CH_3-C18), 1.01−0.98 (1H, m, CH_2-C13), 0.96 (3H, d, *J* = 6.9 Hz, CH_3-C16), 0.78 (3H, d, *J* = 6.9 Hz, CH_3-C17); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0 (C-Ac), 148.0 (C-C11),109.5 (CH_2-C20), 90.7 (CH-C2), 85.2 (CH-C6), 78.1 (CH-C9), 76.1 (C-C7), 75.0 (C-C3), 53.4 (CH-C10), 45.6 (CH-C1), 45.5 (CH_2-C8), 43.7 (CH-C14), 40.0 (CH_2-C4), 31.7 (CH_2-C12), 30.4 (CH_3-C18), 29.2 (CH-C15), 28.2 (CH_2-C5), 24.9 (CH_2-C13), 23.9 (CH_3-C19), 22.1 (CH_3-C16), 21.7 (CH_3-Ac), 15.7 (CH_3-C17); HRMS (CI, Me_3CH) $[M–OH]^+$ calcd for $C_{22}H_{35}O_4$ 363.2537, found 363.2536, Δ +0.1 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 363.4 (40%), 321.4 (100%), 303.4 (60%); IR ν_{max} 3434, 2934, 2959, 1707, 990 cm^{-1}; $[\alpha]^{25}_D$ −19.4 (*c* = 1.00, $CHCl_3$).

(1*R*,2*R*,6*S*,8*R*,9*R*,13*R*,14*R*)-2,6-Dimethyl-10-methylidene-13-(propan-2-yl)-15,16- dioxatetracyclo[6.6.1.1^{2,6}.0^{9,14}]hexadecane 388 [23a]



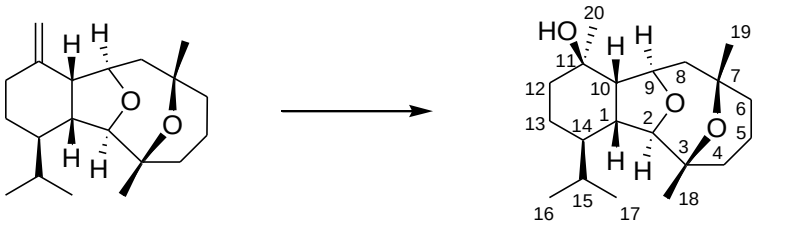
383 **388**

To a flask containing the alcohol **383** (5.0 mg, 16 μmol), and *p*-toluenesulfonic acid monohydrate (12 mg, 65 μmol) was added freshly distilled isopropenyl acetate (1 mL). The reaction mixture was stirred at rt 3 h then quenched with a saturated aqueous solution of $NaHCO_3$ (1 mL) and diluted with ethyl acetate

(2 mL). The aqueous phase was separated and extracted with ethyl acetate (3 × 3 mL). The organic extracts were combined, washed with brine (3 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether - Et_2O, 20:1) to deliver the tetracycle **388** (4.5 mg, 90%) as colourless solid.

R_f = 0.58 (petroleum ether - Et_2O, 6:1); m.p. 101−102 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.64 (2H, m, CH_2-C20), 3.91 (1H, m, CH-C9), 3.64 (1H, s, CH-C2), 3.42 (1H, dd, *J* = 6.8, 6.8 Hz, CH-C10), 2.36 (1H, dtt, *J* =13.1, 13.1, 4.0 Hz, CH_2-C5), 2.26−2.21 (2H, m, CH-C1, CH_2-C12), 2.13 (1H, dd, *J* = 14.3, 5.1 Hz, CH_2-C8), 1.97 (1H, br t, *J* = 13.3 Hz, CH_2-C12), 1.90 (1H, d, *J* = 14.3 Hz, CH_2-C8), 1.80 (1H, dddd, *J* = 13.5, 4.1, 2.8, 1.3 Hz, CH_2-C4), 1.79−1.65 (2H, m, CH_2-C13, CH-C15), 1.56−1.51 (1H, m, CH_2-C5), 1.47−1.33 (3H, m, CH_2-C4, CH_2-C6), 1.32 (3H, s, CH_3-C19), 1.28−1.23 (1H, m, CH-C14), 1.06 (3H, s, CH_3-C18), 0.96 (1H, dddd, *J* = 13.0, 13.0, 13.0, 2.8 Hz, CH_2-C13), 0.94 (3H, d, *J* = 6.9 Hz, CH_3-C16), 0.76 (3H, d, *J* = 6.9 Hz, CH_3-C17); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.8 (C-C11), 108.6 (CH_2-C20), 93.8 (CH-C2), 81.9 (CH-C9), 75.7 (C-C3), 74.5 (C-C7), 50.3 (CH-C10), 46.3 (CH_2-C8), 45.2 (CH-C1), 43.9 (CH-C14), 39.8 (CH_2-C6), 36.4 (CH_2-C4), 35.9 (CH_3-C19), 31.5 (CH_2-C12), 29.6 (CH-C15), 27.9 (CH_3-C18), 24.8 (CH_2-C13), 22.1 (CH_3-C16), 18.4 (CH_2-C5), 15.9 (CH_3-C17); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{20}H_{33}O_2$ 305.2482, found 305.2487, Δ +2.1 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 305.5 (11%), 140.3 (10%); IR ν_{max} 2961, 2929, 2871, 1458, 1370, 1108, 1062 cm^{-1}; $[\alpha]^{25}_D$ −8.5 (*c* = 1.00, $CHCl_3$) {Lit.[23a] $[\alpha]^{20}_D$ −8.5 (*c* = 0.07, $CHCl_3$)}.

(+)-Deacetylpolyanthellin A [13, 31, 127]



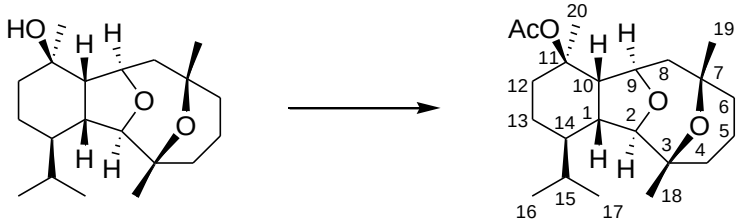
388 (+)-Deacetylpolyanthellin A

To a solution of the tetracyclic alkene **388** (3.2 mg, 10 μmol) in H_2O:THF (1:1) mixture (1 mL) was added $Hg(OAc)_2$, (6.7 mg, 21 μmol) at rt. The mixture was stirred for 30 min then additional $Hg(OAc)_2$ (6.7 mg, 21 μmol) was added. The resulting mixture was stirred for 1 h, diluted with THF (2 mL), and cooled to −20

°C before successive addition of Et_3B (1.0 M in THF, 136 µL, 136 µmol) and $NaBH_4$ (6.7 mg, 0.18 mmol). The resulting mixture was stirred overnight, and then diluted with Et_2O (3 mL). The aqueous phase was separated and extracted with Et_2O (3 × 3 mL). The organic extracts were combined, washed with brine (3 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether - ethyl acetate, 2:1) to deliver (+)-deacetylpolyanthellin A (2.6 mg, 77%) as colourless oil (mixture of diastereomers 10:1).

R_f = 0.44 (petroleum ether - ethyl acetate, 2:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.87 (1H, br dd, *J* = 5.3, 5.1 Hz, CH-C9), 3.58 (1H, s, CH-C2), 2.89–2.83 (1H, m, CH-C10), 2.40–2.29 (2H, m, CH-C1, CH_2-C5), 2.18 (1H, dd, *J* = 14.2, 5.1 Hz, CH_2-C8), 1.85 (1H, d, *J* = 14.2 Hz, CH_2-C8), 1.81–1.74 (1H, m, CH_2-C4), 1.68 (1H, septuplet d, *J* = 7.0, 2.2 Hz, CH-C15), 1.55–1.33 (9H, m, CH_2-C4, CH_2-C5, CH_2-C6, CH_2-C12, CH_2-C13, OH), 1.29 (3H, s, CH_3-C19), 1.19 (3H, s, CH_3-C20), 1.15–1.12 (1H, m, CH-C14), 1.06 (3H, s, CH_3-C18), 0.93 (3H, d, *J* = 7.0 Hz, CH_3-C16), 0.82 (3H, d, *J* = 7.0 Hz, CH_3-C17); ^{13}C NMR (125 MHz, $CDCl_3$) δ 93.3 (CH-C2), 78.6 (CH-C9), 75.6 (C-C3), 74.4 (C-C7), 70.4 (C-C11), 53.9 (CH-C10), 47.7 (CH_2-C8), 42.4 (CH-C14), 41.8 (CH-C1), 39.8 (CH_2-C6), 36.6 (CH_2-C4), 36.0 (CH_3-C19), 33.8 (CH_2-C12), 29.8 (CH-C15), 29.7 (CH_3-C20), 27.6 (CH_3-C18), 22.0 (CH_3-C16), 18.4 (CH_2-C5), 17.5 (CH_2-C13), 16.0 (CH_3-C17); HRMS (CI, Me_3CH) $[M+H]^+$ calcd for $C_{20}H_{35}O_3$ 326.2688, found 323.2583, Δ −1.1 ppm; LRMS (CI, Me_3CH) *m/z* (intensity) 323.3 (9%), 305.5 (18%), 113.3 (15%); IR ν_{max} 3437, 2960, 2929, 2872, 955, 813 cm^{-1}; $[\alpha]^{25}_D$ +14.6 (*c* = 0.86, $CHCl_3$) {Lit.[31] $[\alpha]^{25}_D$ +18.1 (*c* = 0.29, $CHCl_3$), Lit.[13] $[\alpha]^{25}_D$ +19.4 (*c* = 0.57, $CHCl_3$), Lit.[127] $[\alpha]^{25}_D$ −11.0 (*c* = 0.6, $CHCl_3$)}.

(+)-Polyanthellin A [8, 13, 31, 36, 127]



(+)-Deacetylpolyanthellin A (+)-Polyanthellin A

To a flask containing (+)-deacetylpolyanthellin A (2.6 mg, 8.0 μmol), DMAP (5.0 mg, 40 μmol) and distilled triethylamine (41 mg, 0.40 mmol) was added freshly distilled acetic anhydride (44 mg, 0.40 mmol). The resulting solution was stirred at rt for 1 h, then cooled at 0 °C and the reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (1 mL) and Et_2O (2 mL). The aqueous phase was separated and extracted with Et_2O (3 × 2 mL). The organic extracts were combined washed with brine (2 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel (petroleum ether - ethyl acetate, 30:1) to afford (+)-polyanthellin A (1.6 mg, 55%) as a colourless oil.

R_f = 0.60 (petroleum ether - ethyl acetate, 4:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.91−3.89 (1H, m, CH-C9), 3.54 (1H, s, CH-C2), 3.23−3.19 (1H, m, CH-C10), 2.45−2.40 (1H, m, CH_2-C12), 2.40−2.31 (1H, m, CH_2-C5), 2.30 (1H, dd, *J* = 10.4, 7.6 Hz, CH-C1), 2.19 (1H, dd, *J* = 14.3, 5.0 Hz, CH_2-C8), 2.00 (3H, s, CH_3-Ac), 1.86 (1H, d, *J* = 14.3 Hz, CH_2-C8), 1.79−1.76 (1H, m, CH_2-C4), 1.65 (1H, septuplet, *J* = 6.9 Hz, CH-C15), 1.55−1.47 (1H, m, CH_2-C5), 1.48 (3H, s, CH_3-C20), 1.47−1.34 (4H, m, CH_2-C4, CH_2-C6, CH_2-C13), 1.33 (3H, s, CH_3-C19), 1.25−1.20 (1H, m, CH_2-C12), 1.19−1.15 (2H, m, CH_2-C13, CH-C14), 1.08 (3H, s, CH_3-C18), 0.92 (3H, d, *J* = 6.9 Hz, CH_3-C16), 0.80 (3H, d, *J* = 6.9 Hz, CH_3-C17); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5 (C-Ac), 93.9 (CH-C2), 83.3 (C-C11), 77.6 (CH-C9), 75.7 (C-C3), 74.5 (C-C7), 51.2 (CH-C10), 47.7 (CH_2-C8), 42.5 (CH-C14), 41.8 (CH-C1), 39.8 (CH_2-C6), 36.4 (CH_2-C4), 35.8 (CH_3-C19), 29.9 (CH_2-C12), 29.8 (CH-C15), 27.7 (CH_3-C18), 24.2 (CH_3-C20), 22.7 (CH_3-Ac), 21.8 (CH_3-C16), 18.3 (CH_2-C5), 17.7 (CH_2-C13), 15.7 (CH_3-C17); HRMS (EI) $[M\text{-AcOH}]^+$ calcd for $C_{20}H_{32}O_2$ 304.2404, found 304.2398, Δ −1.5 ppm; LRMS (EI) *m/z* (intensity) 304.3 (100%), 261.2 (13%), 243.2 (18%), 219.2 (19%), 179.1 (22%); IR ν_{max} 2952, 2927, 2875, 2363, 1731 cm^{-1}; $[\alpha]^{24}_D$ +9.0 (*c* = 0.40, $CHCl_3$) {Lit.[31] $[\alpha]^{20}_D$ +10.5 (*c* = 0.31, $CHCl_3$), Lit.[13] $[\alpha]^{25}_D$ +8.9 (*c* = 0.22, $CHCl_3$), Lit.[127] $[\alpha]^{25}_D$ −9.9 (*c* = 1.0, $CHCl_3$), Lit.[36] $[\alpha]^{25}_D$ +9.9 (*c* = 0.085, $CHCl_3$), Lit.[8] $[\alpha]^{25}_D$ +8.0 (*c* = 0.75, $CHCl_3$)}.

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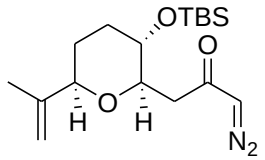
Appendices

Appendix 1: H^1 and C^{13} NMR spectra of compound **70**



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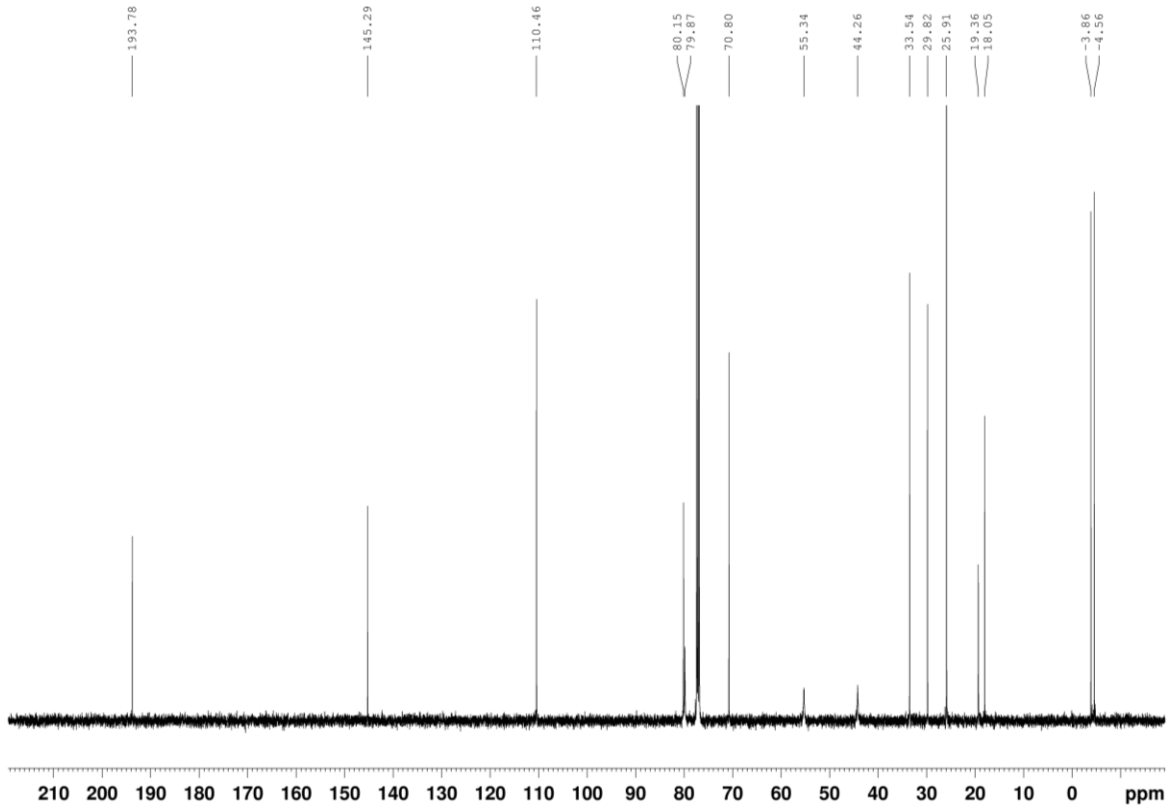
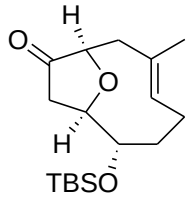


Appendix 2: H^1 and C^{13} NMR spectra of compound **72**



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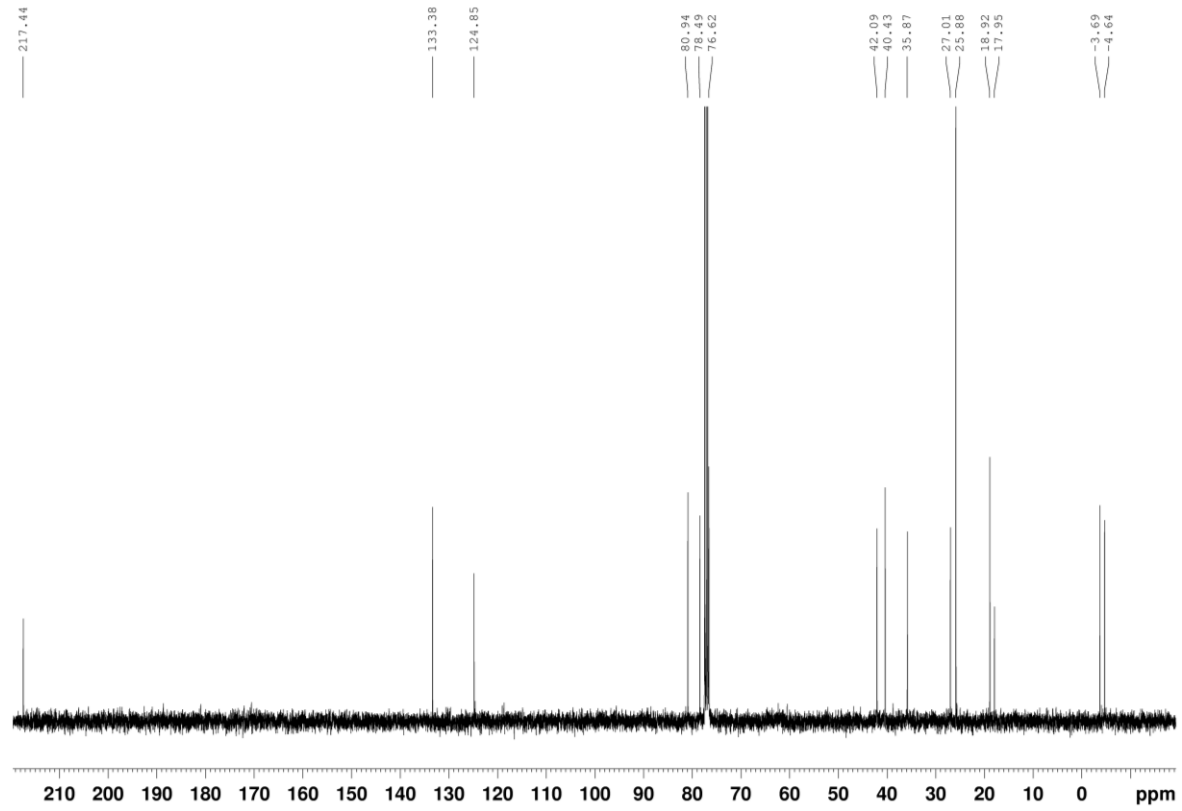
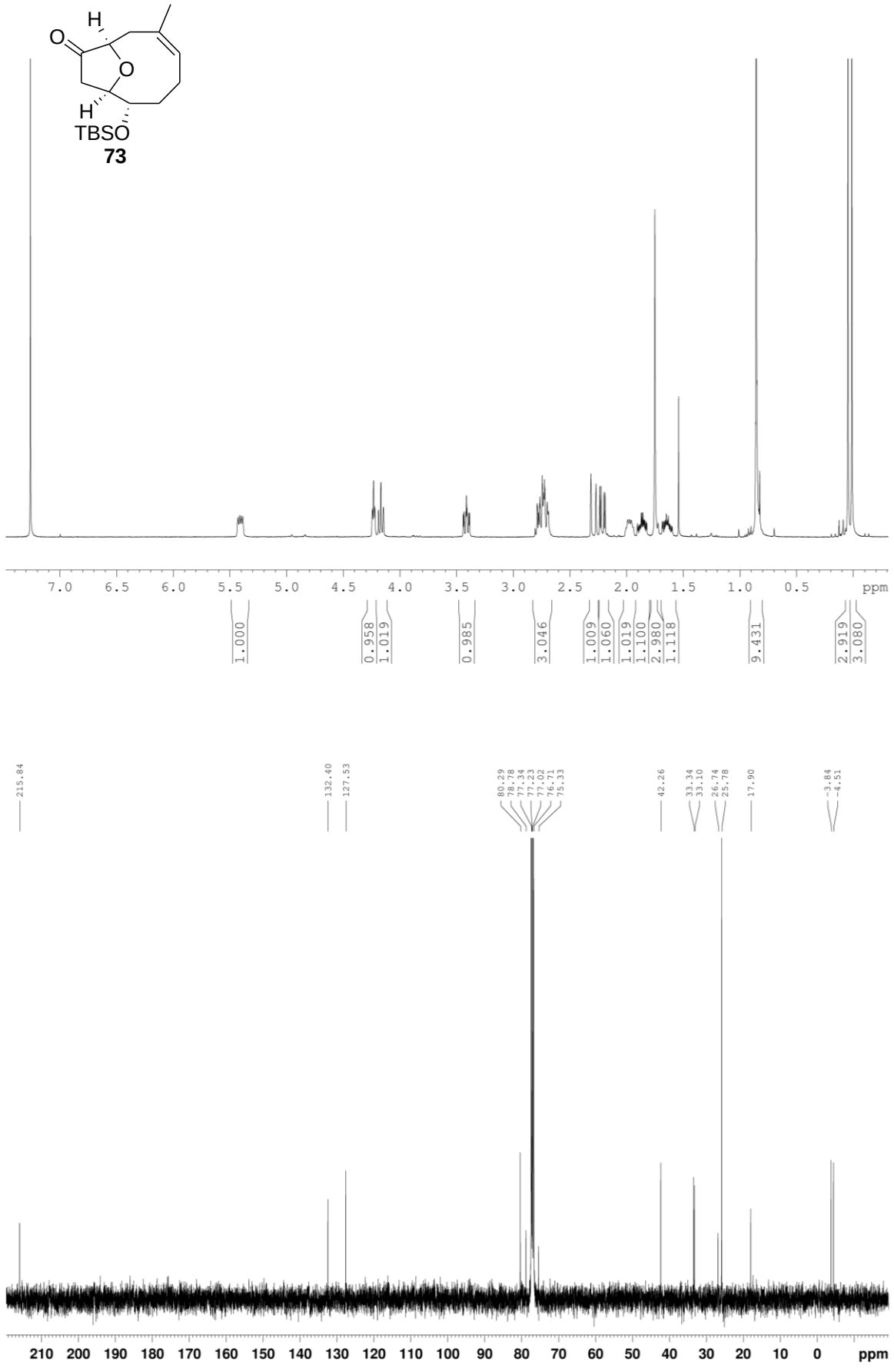
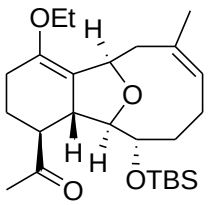


Appendix 3: H^1 and C^{13} NMR spectra of compound **73**



Appendix 4: H^1 and C^{13} NMR spectra of compound ***exo*-75**



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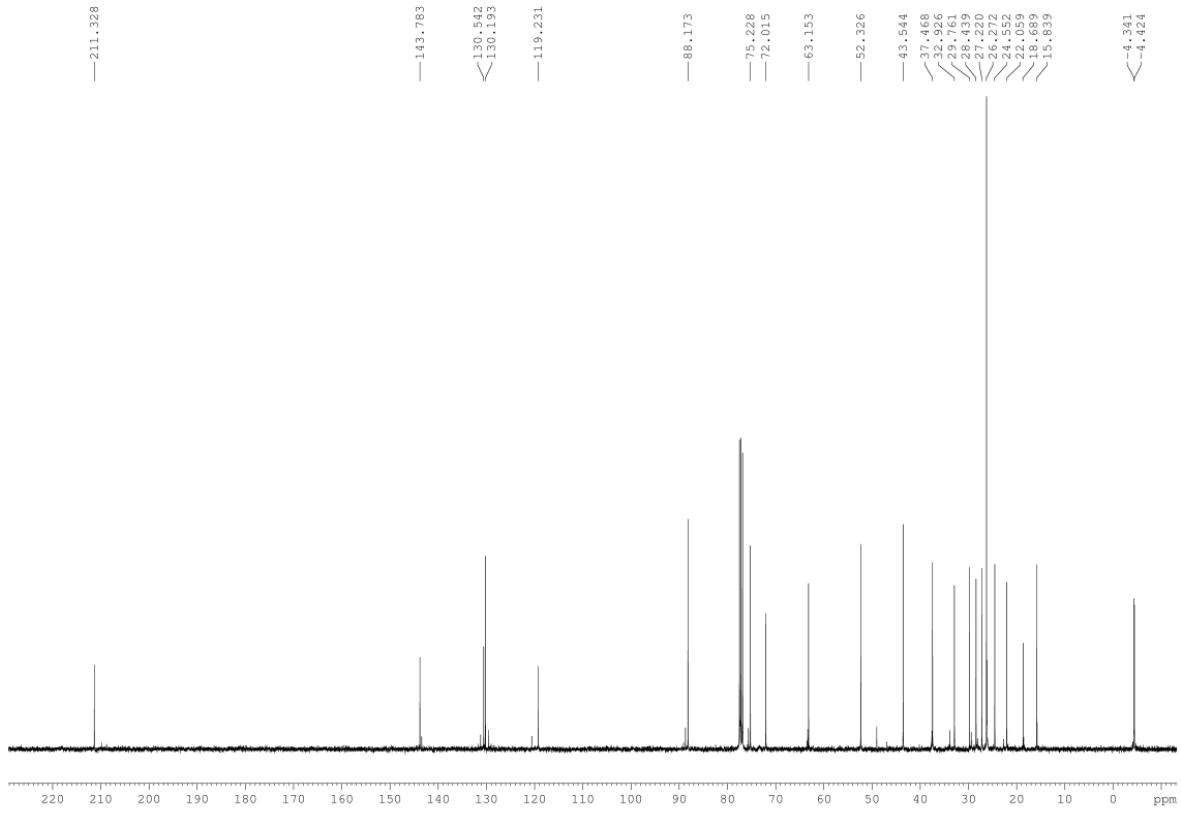
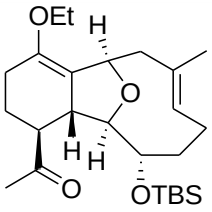


Appendix 5: H^1 and C^{13} NMR spectra of compound ***exo*-335**



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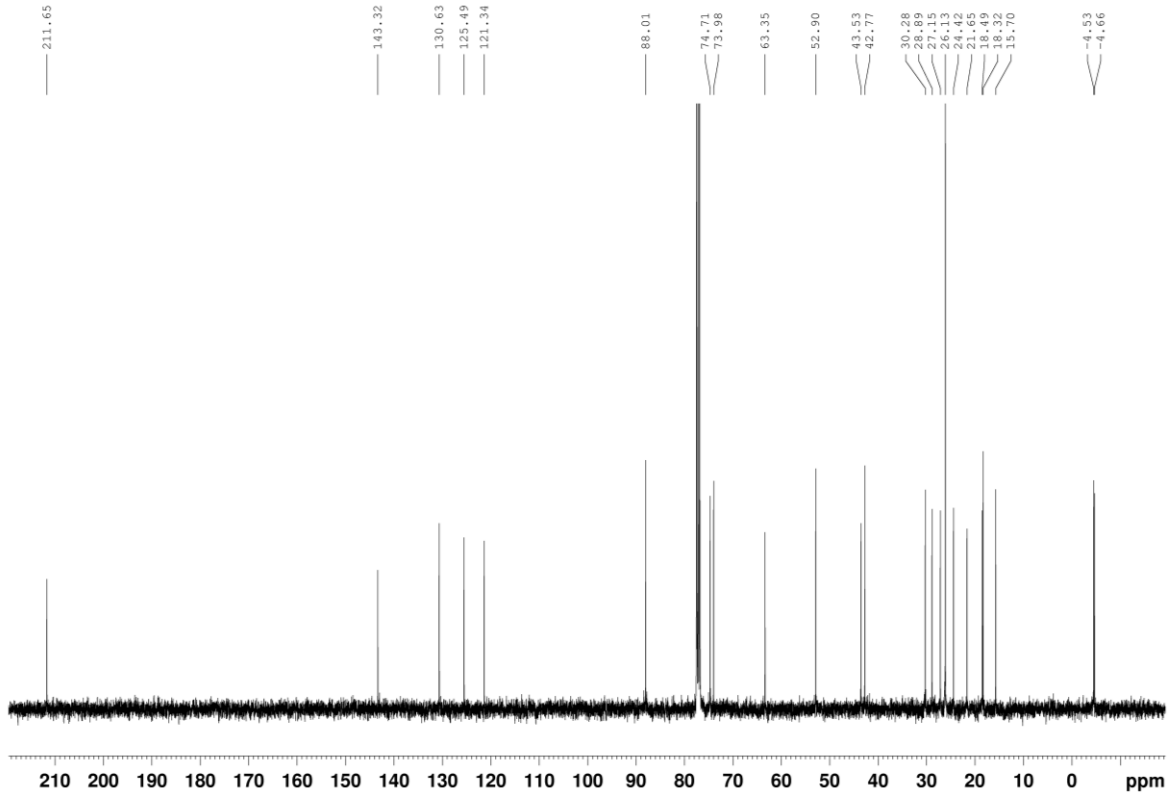
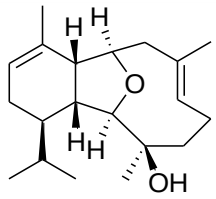
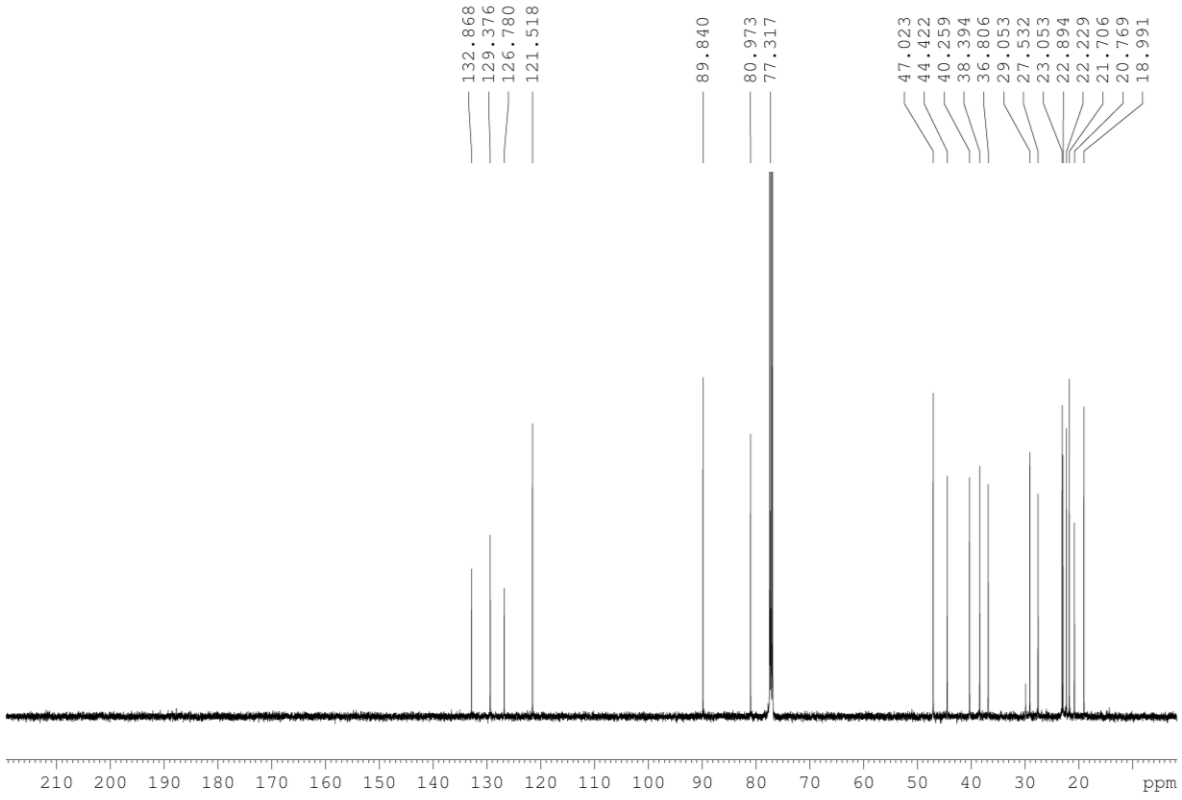


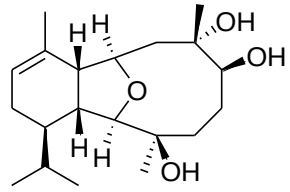
Appendix 6: H^1 and C^{13} NMR spectra of cladiella-6,11-dien-3-ol



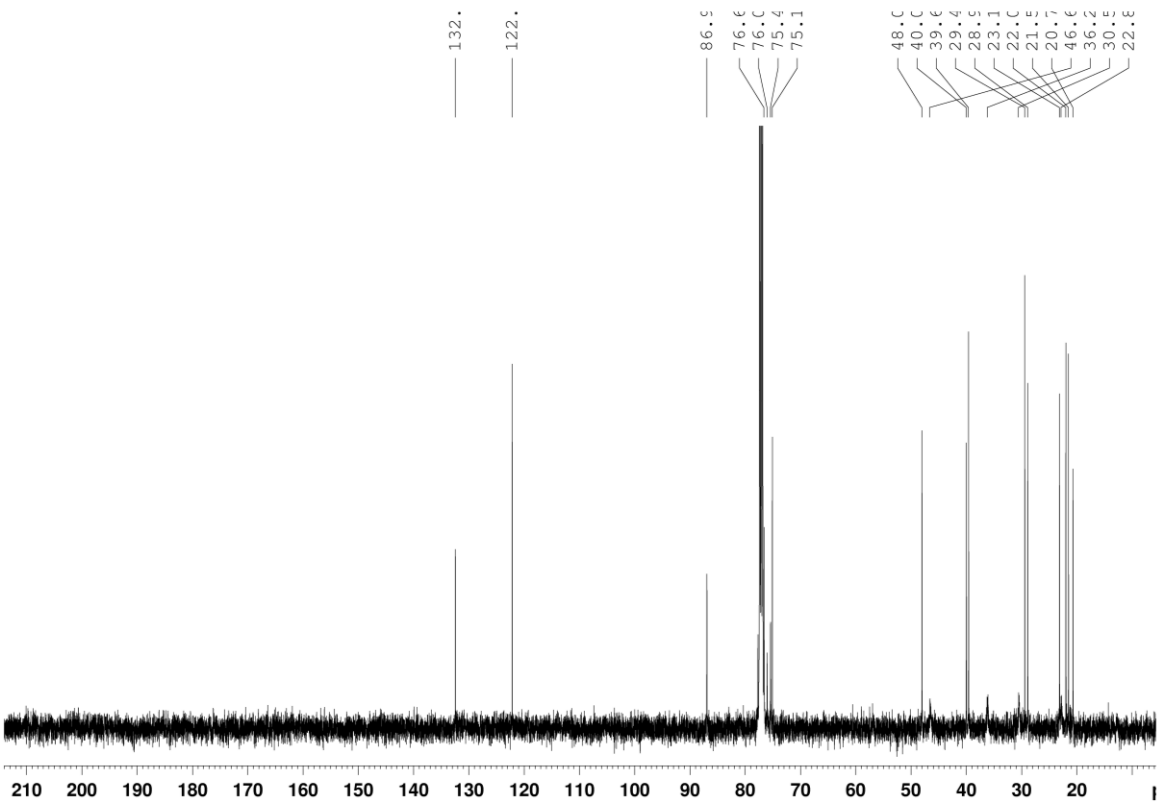
(–) Cladiella-6,11-dien-3-ol



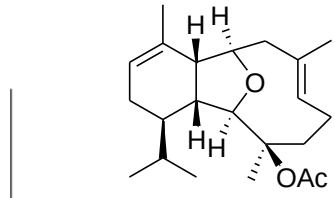
Appendix 7: H^1 and C^{13} NMR spectra of cladiell-11-ene-3,6,7-triol



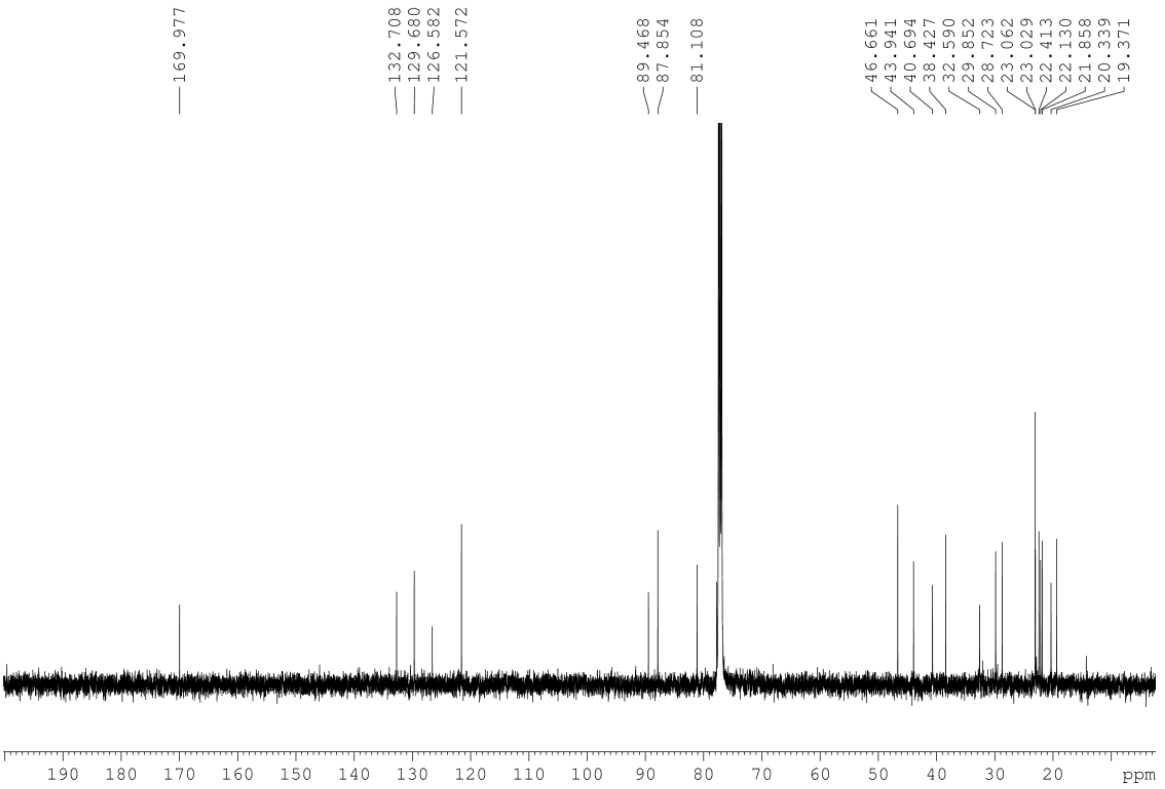
(–) Cladiell-11-ene-3,6,7-triol



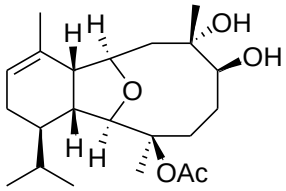
Appendix 8: H^1 and C^{13} NMR spectra of 3-acetoxycladiella-6,11-diene



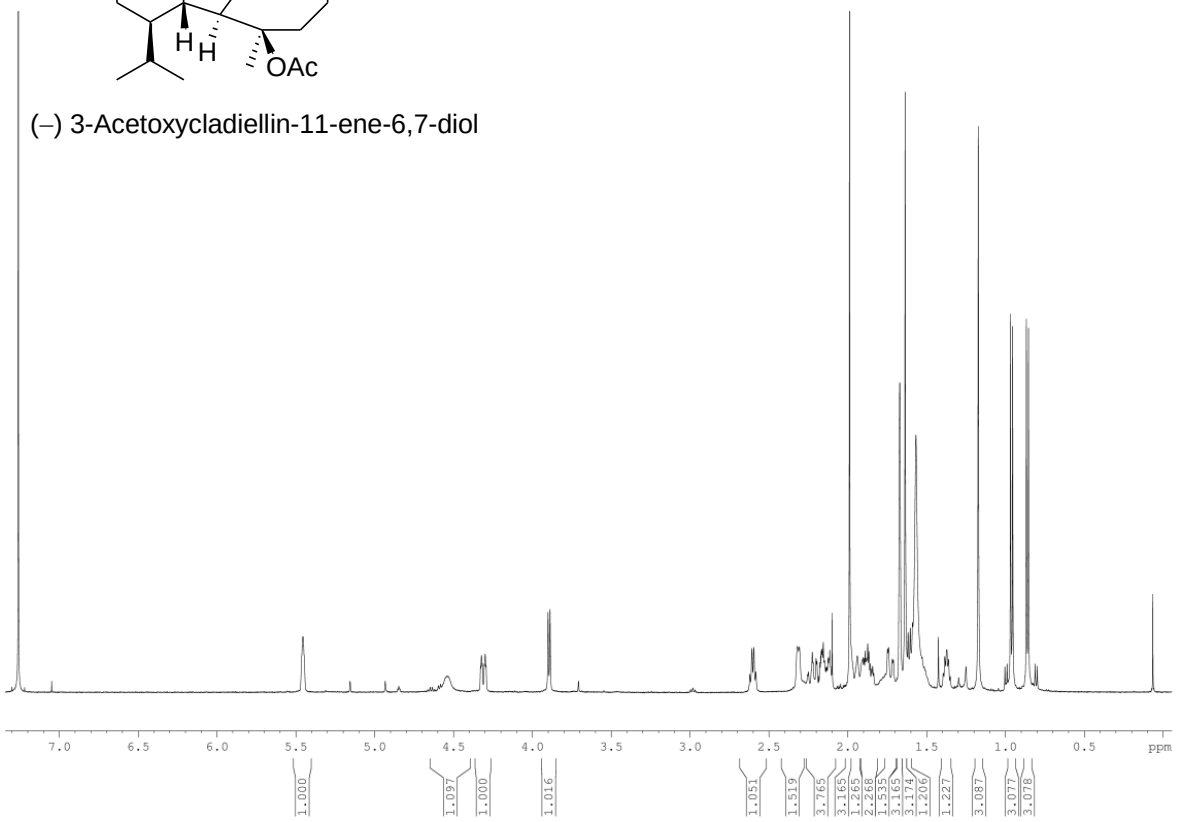
(–) 3-Acetoxycladiella-6,11-diene

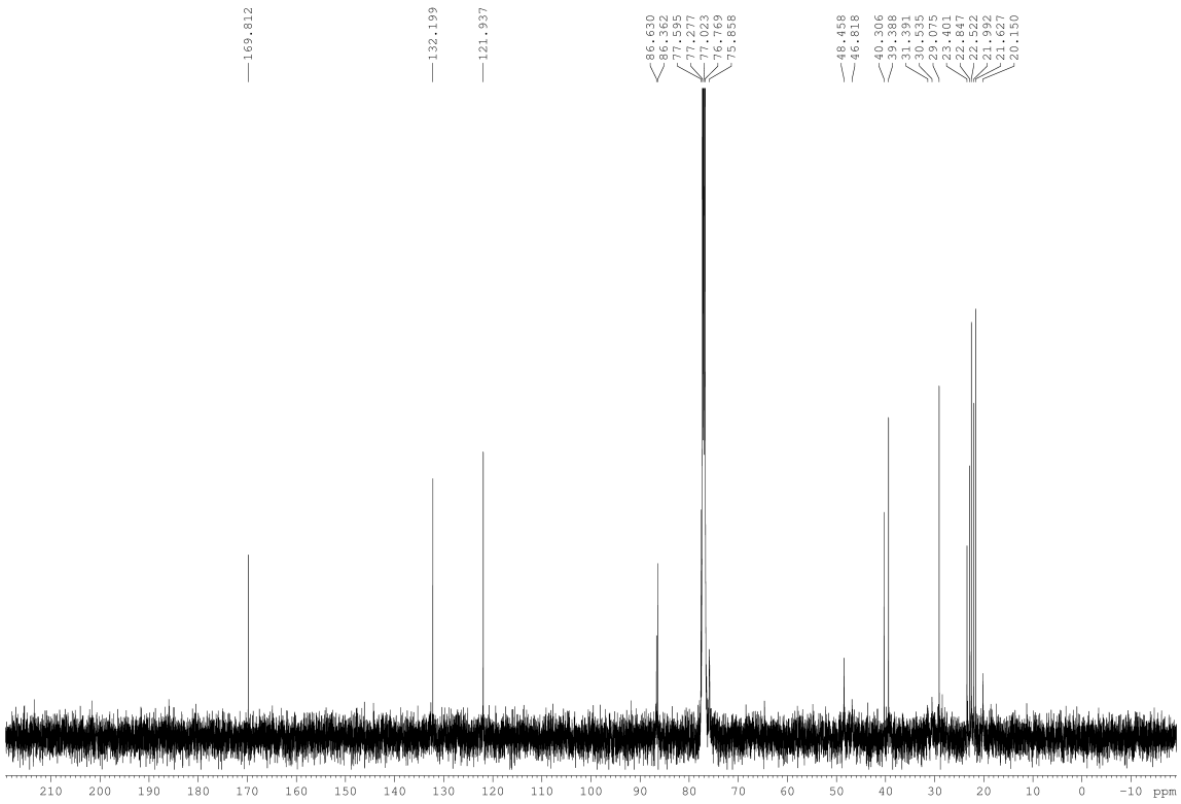


Appendix 9: H^1 and C^{13} NMR spectra of 3-acetoxycladiellin-11-ene-6,7-diol

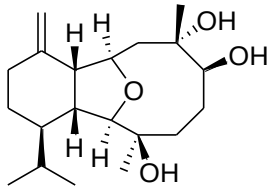


(–) 3-Acetoxycladiellin-11-ene-6,7-diol

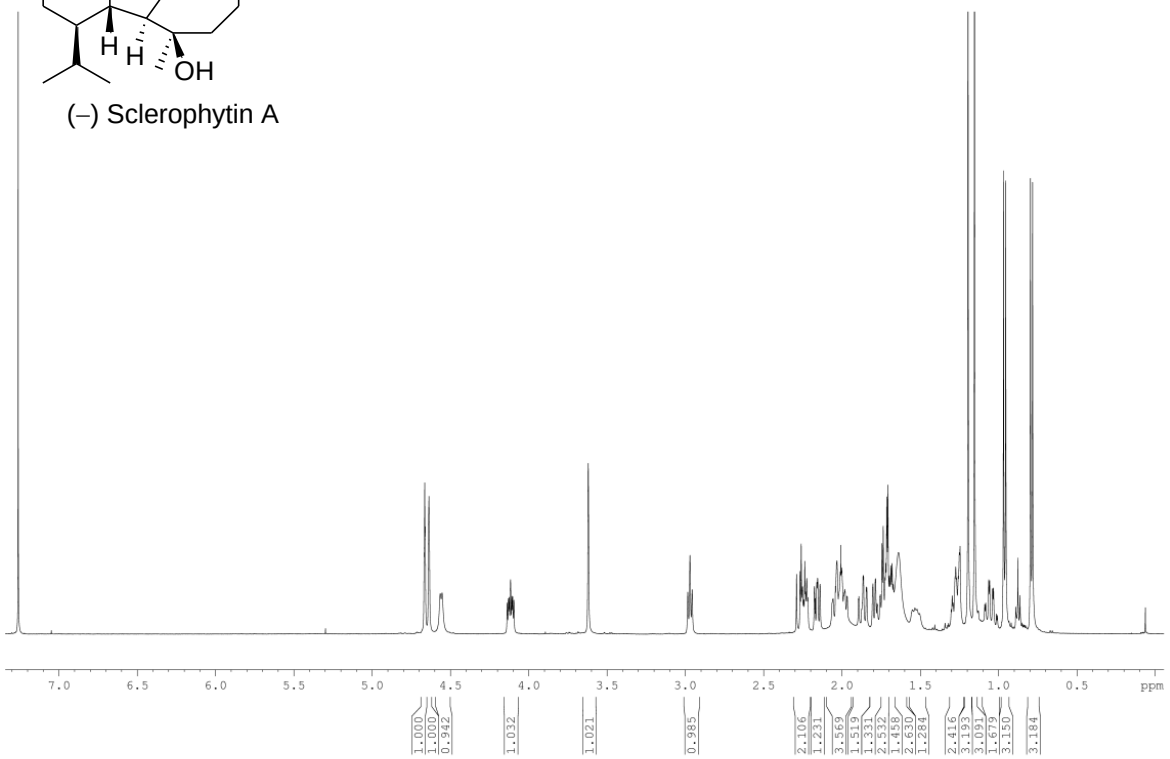


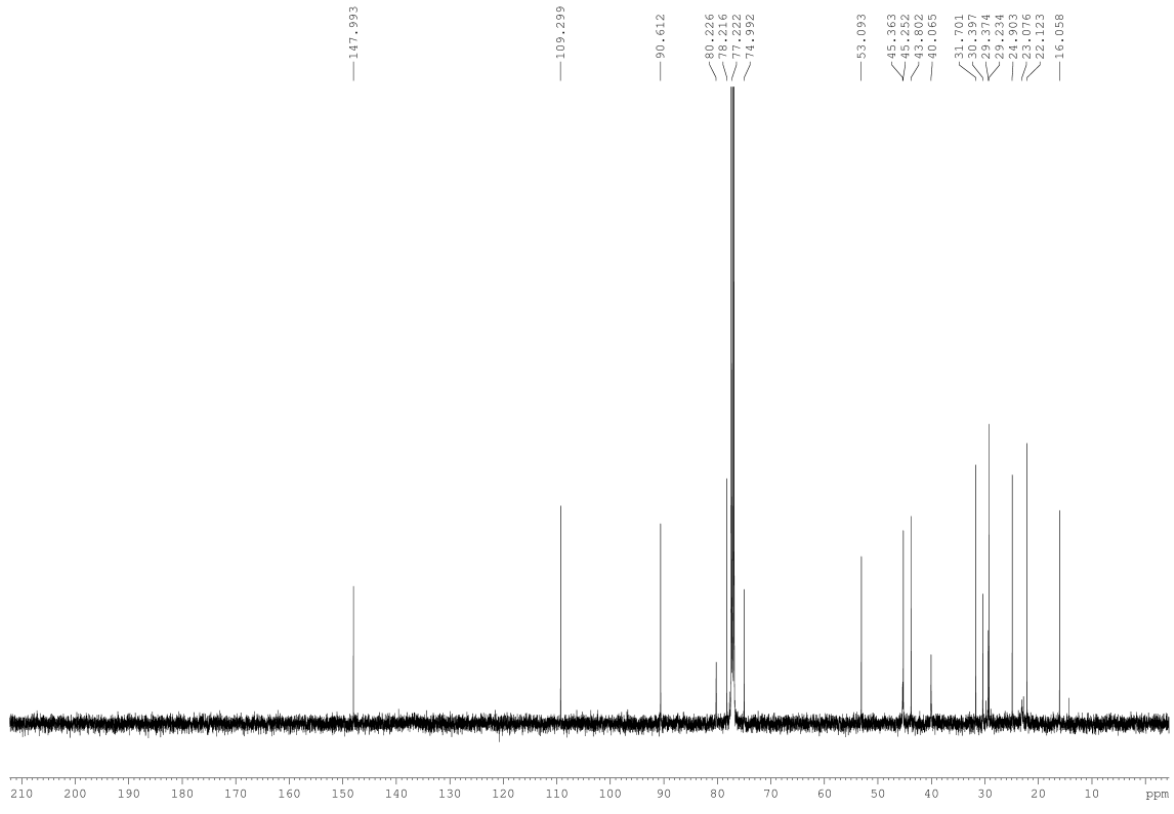


Appendix 10: H^1 and C^{13} NMR spectra of sclerophytin A

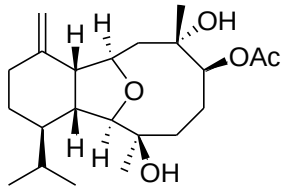


(–) Sclerophytin A

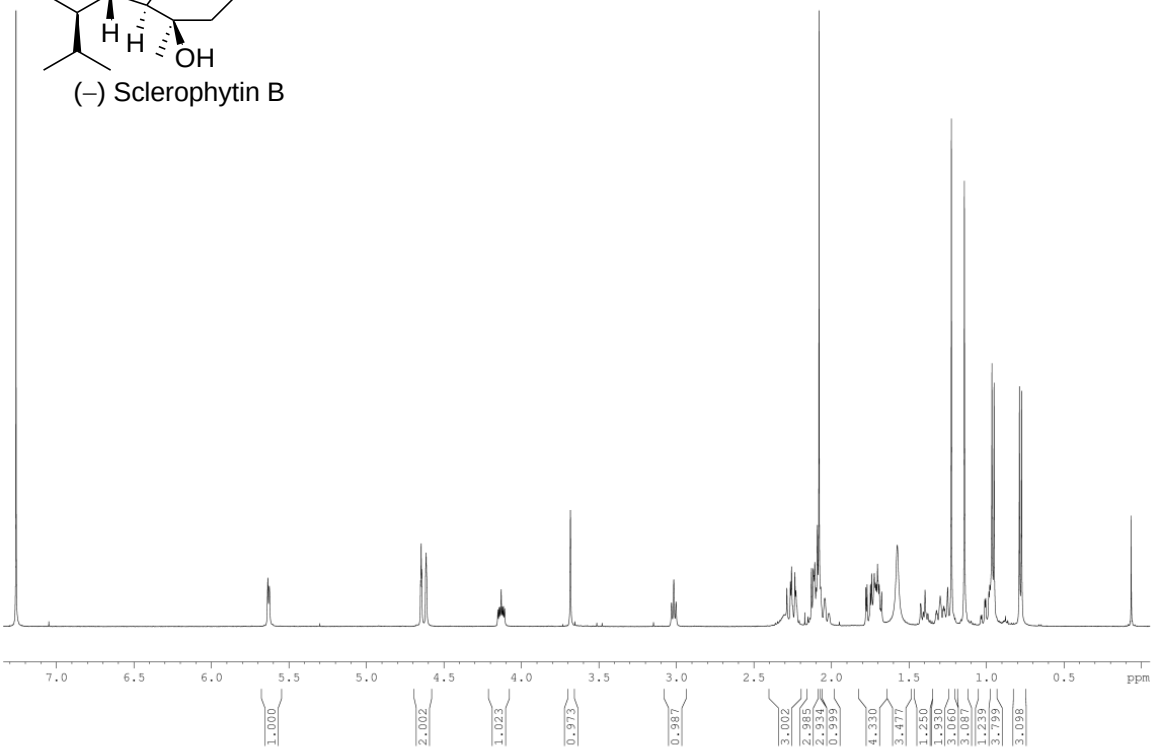


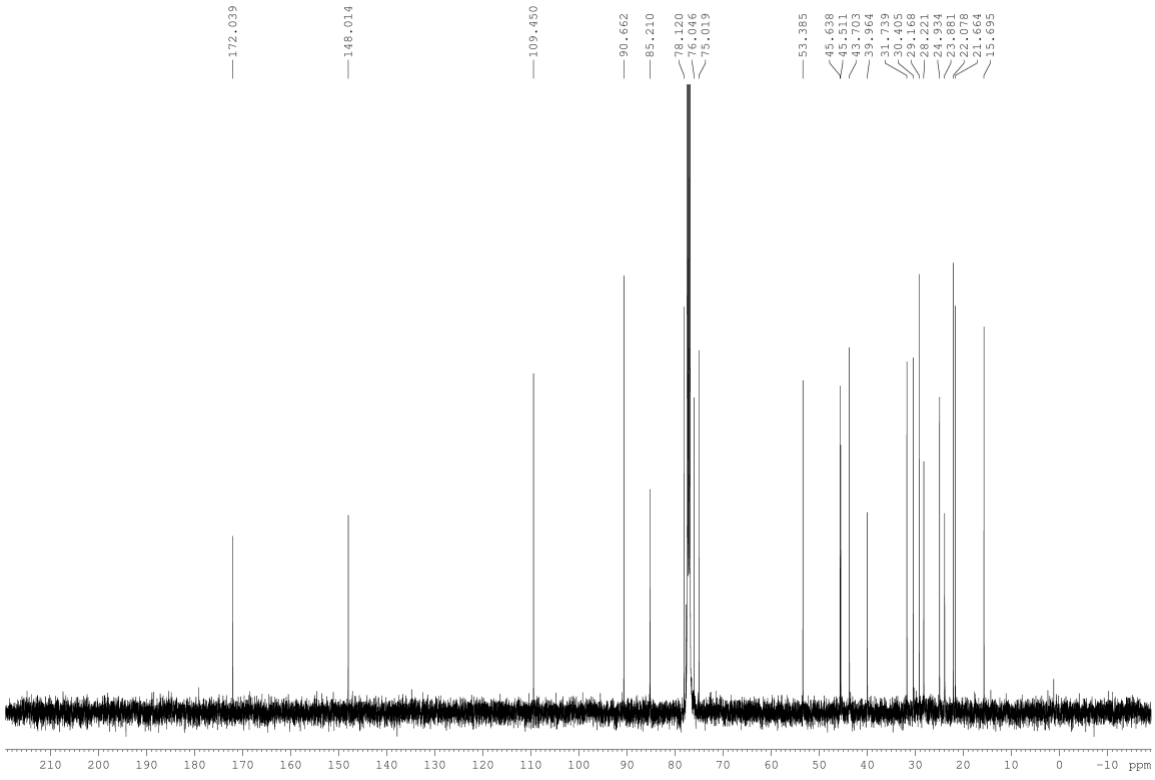


Appendix 11: H^1 and C^{13} NMR spectra of sclerophytin B

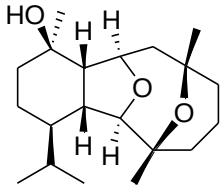


(–) Sclerophytin B

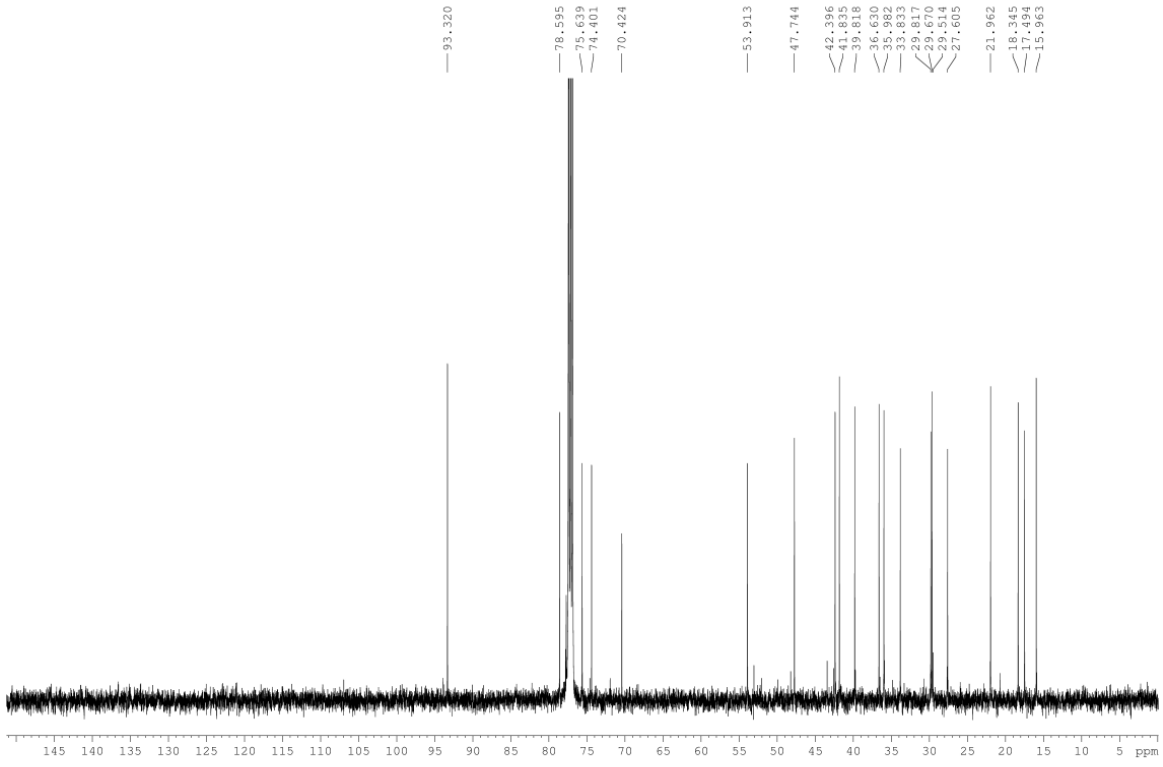




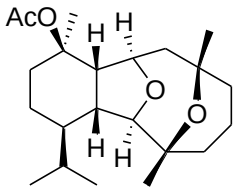
Appendix 12: H^1 and C^{13} NMR spectra of deacetylpolyanthellin A



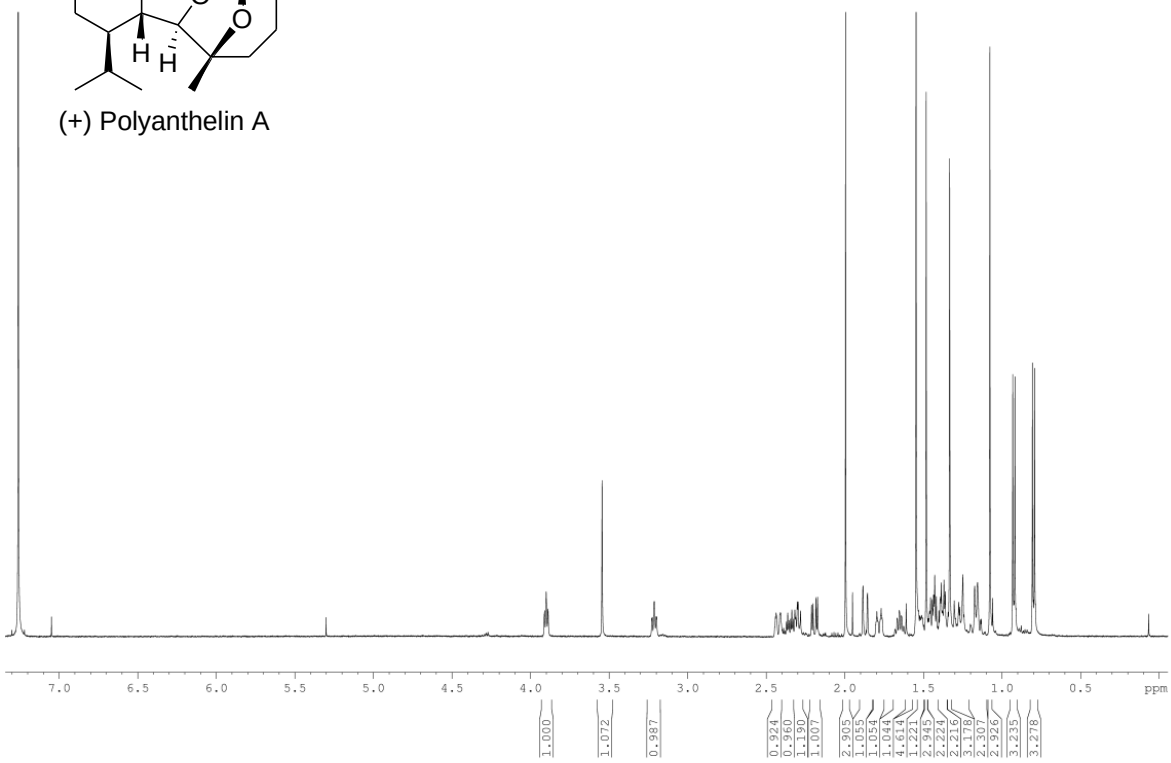
(+) Deacetylpolyanthellin A

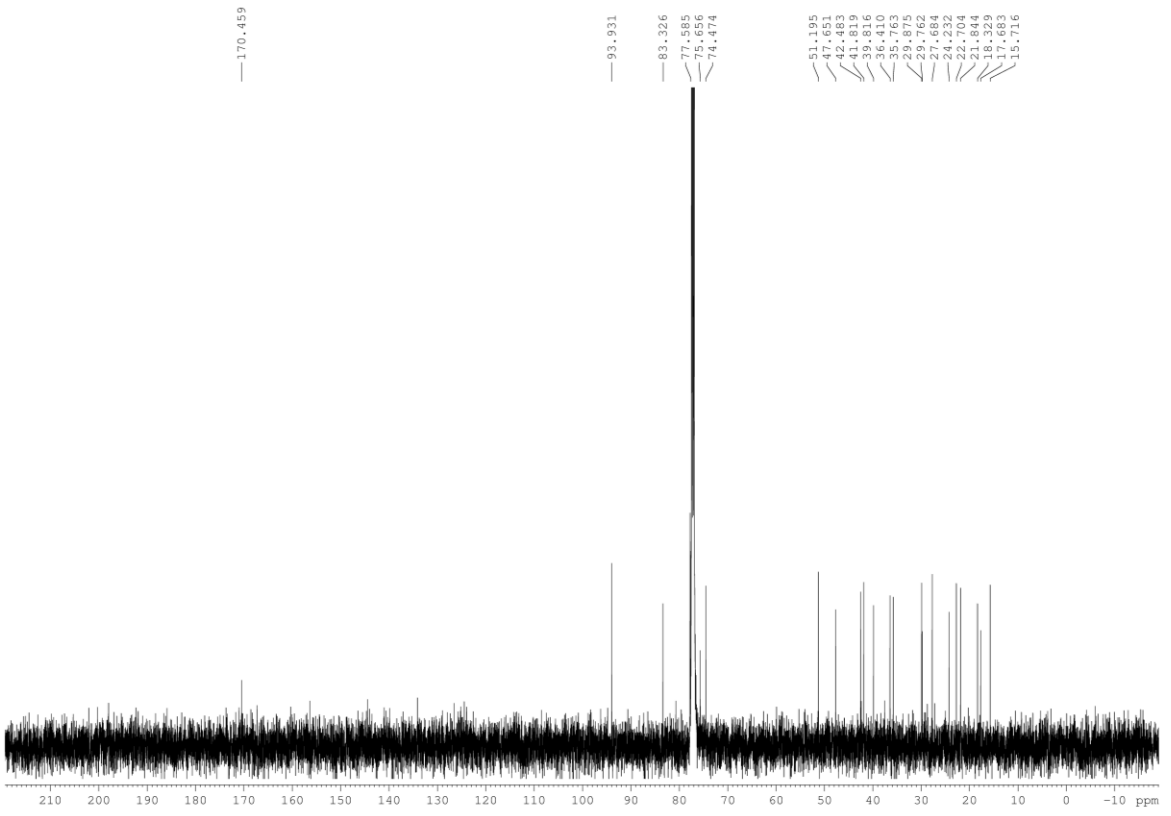


Appendix 13: H^1 and C^{13} NMR spectra of polyanthelin A



(+) Polyanthelin A





Appendix 14: X-ray crystallography of compound **320**

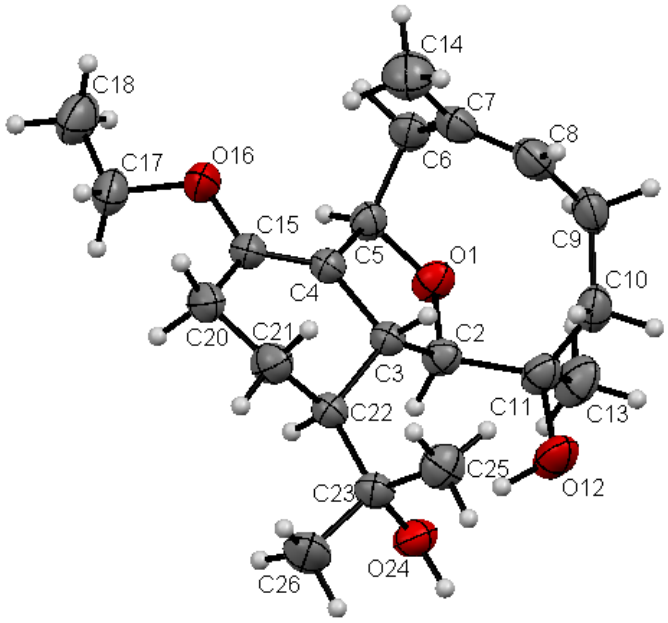


Table 1. Crystal data and structure refinement for sx175_publish.

Identification code	sx175_publish	
Empirical formula	C21 H34 O4	
Formula weight	350.50	
Temperature	293 K	
Wavelength	1.54180 Å	
Crystal system	Monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 15.8663(7) Å	α= 90°.
	b = 10.8611(5) Å	ß= 83.649(3)°.
	c = 11.4116(6) Å	γ = 90°.
Volume	1954.44(16) $Å^3$	
Z	4	
Density (calculated)	1.191 Mg/m^3	
Absorption coefficient	0.640 mm^{-1}	
F(000)	768	
Crystal size	0.40 x 0.20 x 0.15 mm^3	
Theta range for data collection	6.939 to 65.221°.	
Index ranges	-16<=h<=18, -10<=k<=12, -12<=l<=7	
Reflections collected	7419	
Independent reflections	3184 [R(int) = 0.025]	
Completeness to theta = 65.000°	95.1 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.91 and 0.76	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3184 / 0 / 227	
Goodness-of-fit on F^2	0.9084	
Final R indices [I>2sigma(I)]	R1 = 0.0393, wR2 = 0.1034	
R indices (all data)	R1 = 0.0475, wR2 = 0.1087	
Extinction coefficient	93(9)	
Largest diff. peak and hole	0.21 and -0.21 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for sx175_publish. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	2088(1)	6367(1)	3835(1)	43
C(2)	2929(1)	5865(1)	3841(1)	37
C(3)	2996(1)	4755(1)	2970(1)	33
C(4)	2276(1)	5047(1)	2231(1)	34
C(5)	1643(1)	5866(2)	2915(1)	38
C(6)	819(1)	5247(2)	3441(2)	45
C(7)	929(1)	3968(2)	3923(2)	46
C(8)	1238(1)	3741(2)	4938(2)	50
C(9)	1535(1)	4637(2)	5797(2)	51
C(10)	2511(1)	4637(2)	5793(2)	49
C(11)	3032(1)	5681(2)	5163(1)	43
O(12)	3899(1)	5384(1)	5281(1)	59
C(13)	2845(1)	6900(2)	5811(2)	59
C(14)	674(1)	2933(2)	3164(2)	67
C(15)	2260(1)	4759(2)	1108(1)	38
O(16)	1557(1)	5117(1)	567(1)	51
C(17)	1686(1)	5448(2)	-654(2)	54
C(18)	885(1)	5988(2)	-989(2)	68
C(20)	2946(1)	4047(2)	411(1)	47
C(21)	3577(1)	3569(2)	1218(2)	48
C(22)	3814(1)	4533(1)	2110(1)	35
C(23)	4640(1)	4161(2)	2625(1)	39
O(24)	4884(1)	5212(1)	3293(1)	47
C(25)	4533(1)	3033(2)	3420(2)	51
C(26)	5364(1)	3954(2)	1643(2)	61

Table 3. Bond lengths [Å] and angles [°] for sx175_publish.

O(1)-C(2)	1.4423(17)
O(1)-C(5)	1.4356(19)
C(2)-C(3)	1.559(2)
C(2)-C(11)	1.548(2)
C(2)-H(21)	0.995
C(3)-C(4)	1.527(2)
C(3)-C(22)	1.5566(18)
C(3)-H(31)	0.983
C(4)-C(5)	1.495(2)
C(4)-C(15)	1.322(2)
C(5)-C(6)	1.533(2)
C(5)-H(51)	0.985
C(6)-C(7)	1.511(2)
C(6)-H(61)	0.989
C(6)-H(62)	0.990
C(7)-C(8)	1.330(2)
C(7)-C(14)	1.501(3)
C(8)-C(9)	1.494(3)
C(8)-H(81)	0.959
C(9)-C(10)	1.549(2)
C(9)-H(91)	0.989
C(9)-H(92)	1.002
C(10)-C(11)	1.535(2)
C(10)-H(101)	0.975
C(10)-H(102)	0.990
C(11)-O(12)	1.4340(18)
C(11)-C(13)	1.530(2)
O(12)-H(2)	0.977
C(13)-H(131)	0.962
C(13)-H(132)	0.981
C(13)-H(133)	0.980
C(14)-H(141)	0.967
C(14)-H(142)	0.979
C(14)-H(143)	0.961
C(15)-O(16)	1.3884(18)
C(15)-C(20)	1.491(2)
O(16)-C(17)	1.431(2)
C(17)-C(18)	1.487(3)
C(17)-H(171)	0.981
C(17)-H(172)	0.989
C(18)-H(181)	0.964
C(18)-H(182)	0.978
C(18)-H(183)	0.957
C(20)-C(21)	1.525(2)
C(20)-H(201)	0.977
C(20)-H(202)	0.991
C(21)-C(22)	1.536(2)
C(21)-H(211)	0.975
C(21)-H(212)	0.968
C(22)-C(23)	1.548(2)

C(22)-H(221)	0.982
C(23)-O(24)	1.4484(19)
C(23)-C(25)	1.523(2)
C(23)-C(26)	1.531(2)
O(24)-H(1)	0.972
C(25)-H(251)	0.969
C(25)-H(252)	0.968
C(25)-H(253)	0.972
C(26)-H(261)	0.984
C(26)-H(262)	0.973
C(26)-H(263)	0.966

C(2)-O(1)-C(5)	112.97(11)
O(1)-C(2)-C(3)	106.71(11)
O(1)-C(2)-C(11)	104.55(12)
C(3)-C(2)-C(11)	120.95(13)
O(1)-C(2)-H(21)	107.4
C(3)-C(2)-H(21)	108.7
C(11)-C(2)-H(21)	107.8
C(2)-C(3)-C(4)	100.91(11)
C(2)-C(3)-C(22)	121.05(12)
C(4)-C(3)-C(22)	107.85(11)
C(2)-C(3)-H(31)	108.0
C(4)-C(3)-H(31)	110.0
C(22)-C(3)-H(31)	108.5
C(3)-C(4)-C(5)	109.61(12)
C(3)-C(4)-C(15)	125.63(13)
C(5)-C(4)-C(15)	124.24(14)
C(4)-C(5)-O(1)	104.56(11)
C(4)-C(5)-C(6)	115.98(14)
O(1)-C(5)-C(6)	110.32(12)
C(4)-C(5)-H(51)	109.7
O(1)-C(5)-H(51)	108.2
C(6)-C(5)-H(51)	107.8
C(5)-C(6)-C(7)	114.68(13)
C(5)-C(6)-H(61)	108.0
C(7)-C(6)-H(61)	109.5
C(5)-C(6)-H(62)	107.3
C(7)-C(6)-H(62)	108.6
H(61)-C(6)-H(62)	108.7
C(6)-C(7)-C(8)	123.78(17)
C(6)-C(7)-C(14)	115.41(16)
C(8)-C(7)-C(14)	120.81(18)
C(7)-C(8)-C(9)	128.64(18)
C(7)-C(8)-H(81)	115.9
C(9)-C(8)-H(81)	115.4
C(8)-C(9)-C(10)	112.72(14)
C(8)-C(9)-H(91)	108.4
C(10)-C(9)-H(91)	107.0
C(8)-C(9)-H(92)	111.2
C(10)-C(9)-H(92)	109.7
H(91)-C(9)-H(92)	107.6

C(9)-C(10)-C(11)	119.24(14)
C(9)-C(10)-H(101)	108.0
C(11)-C(10)-H(101)	105.3
C(9)-C(10)-H(102)	107.8
C(11)-C(10)-H(102)	108.1
H(101)-C(10)-H(102)	108.1
C(10)-C(11)-C(2)	116.26(14)
C(10)-C(11)-O(12)	105.24(14)
C(2)-C(11)-O(12)	109.06(13)
C(10)-C(11)-C(13)	110.34(14)
C(2)-C(11)-C(13)	108.88(14)
O(12)-C(11)-C(13)	106.59(13)
C(11)-O(12)-H(2)	112.5
C(11)-C(13)-H(131)	109.8
C(11)-C(13)-H(132)	109.6
H(131)-C(13)-H(132)	106.8
C(11)-C(13)-H(133)	112.2
H(131)-C(13)-H(133)	108.4
H(132)-C(13)-H(133)	109.9
C(7)-C(14)-H(141)	110.0
C(7)-C(14)-H(142)	110.4
H(141)-C(14)-H(142)	109.2
C(7)-C(14)-H(143)	109.1
H(141)-C(14)-H(143)	110.0
H(142)-C(14)-H(143)	108.1
C(4)-C(15)-O(16)	117.90(14)
C(4)-C(15)-C(20)	123.25(14)
O(16)-C(15)-C(20)	118.83(13)
C(15)-O(16)-C(17)	117.91(13)
O(16)-C(17)-C(18)	108.42(15)
O(16)-C(17)-H(171)	110.2
C(18)-C(17)-H(171)	110.7
O(16)-C(17)-H(172)	109.5
C(18)-C(17)-H(172)	111.4
H(171)-C(17)-H(172)	106.5
C(17)-C(18)-H(181)	110.2
C(17)-C(18)-H(182)	108.2
H(181)-C(18)-H(182)	110.2
C(17)-C(18)-H(183)	111.7
H(181)-C(18)-H(183)	108.4
H(182)-C(18)-H(183)	108.1
C(15)-C(20)-C(21)	110.09(13)
C(15)-C(20)-H(201)	109.9
C(21)-C(20)-H(201)	109.7
C(15)-C(20)-H(202)	110.2
C(21)-C(20)-H(202)	110.2
H(201)-C(20)-H(202)	106.8
C(20)-C(21)-C(22)	113.16(14)
C(20)-C(21)-H(211)	108.3
C(22)-C(21)-H(211)	109.9
C(20)-C(21)-H(212)	108.8
C(22)-C(21)-H(212)	108.5

H(211)-C(21)-H(212)	108.1
C(21)-C(22)-C(3)	105.98(12)
C(21)-C(22)-C(23)	110.70(13)
C(3)-C(22)-C(23)	118.85(12)
C(21)-C(22)-H(221)	107.0
C(3)-C(22)-H(221)	106.0
C(23)-C(22)-H(221)	107.7
C(22)-C(23)-O(24)	106.30(12)
C(22)-C(23)-C(25)	113.18(13)
O(24)-C(23)-C(25)	109.81(13)
C(22)-C(23)-C(26)	111.04(13)
O(24)-C(23)-C(26)	106.16(13)
C(25)-C(23)-C(26)	110.06(14)
C(23)-O(24)-H(1)	108.0
C(23)-C(25)-H(251)	110.3
C(23)-C(25)-H(252)	110.0
H(251)-C(25)-H(252)	109.9
C(23)-C(25)-H(253)	108.0
H(251)-C(25)-H(253)	110.6
H(252)-C(25)-H(253)	108.0
C(23)-C(26)-H(261)	106.6
C(23)-C(26)-H(262)	108.7
H(261)-C(26)-H(262)	110.7
C(23)-C(26)-H(263)	110.6
H(261)-C(26)-H(263)	111.1
H(262)-C(26)-H(263)	109.2

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for sx175_publish. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	39(1)	47(1)	44(1)	-8(1)	-9(1)	12(1)
C(2)	32(1)	38(1)	40(1)	-2(1)	-5(1)	4(1)
C(3)	30(1)	37(1)	31(1)	0(1)	-2(1)	0(1)
C(4)	29(1)	40(1)	32(1)	3(1)	-2(1)	-1(1)
C(5)	35(1)	44(1)	35(1)	2(1)	-5(1)	7(1)
C(6)	33(1)	61(1)	40(1)	-1(1)	-1(1)	9(1)
C(7)	33(1)	58(1)	44(1)	2(1)	5(1)	1(1)
C(8)	42(1)	57(1)	48(1)	9(1)	5(1)	2(1)
C(9)	50(1)	69(1)	33(1)	6(1)	4(1)	5(1)
C(10)	52(1)	63(1)	32(1)	2(1)	-6(1)	11(1)
C(11)	37(1)	54(1)	39(1)	-9(1)	-10(1)	11(1)
O(12)	39(1)	89(1)	50(1)	-13(1)	-14(1)	17(1)
C(13)	64(1)	66(1)	50(1)	-22(1)	-15(1)	12(1)
C(14)	66(1)	65(1)	70(1)	-1(1)	-10(1)	-9(1)
C(15)	32(1)	49(1)	33(1)	3(1)	-4(1)	-4(1)
O(16)	41(1)	80(1)	34(1)	7(1)	-7(1)	2(1)
C(17)	61(1)	67(1)	35(1)	6(1)	-13(1)	-9(1)
C(18)	72(1)	80(2)	56(1)	17(1)	-26(1)	-6(1)
C(20)	41(1)	64(1)	35(1)	-9(1)	0(1)	-4(1)
C(21)	40(1)	57(1)	45(1)	-13(1)	-1(1)	4(1)
C(22)	31(1)	41(1)	32(1)	1(1)	-1(1)	0(1)
C(23)	31(1)	46(1)	40(1)	0(1)	-1(1)	3(1)
O(24)	39(1)	51(1)	52(1)	2(1)	-14(1)	-4(1)
C(25)	51(1)	47(1)	56(1)	6(1)	-9(1)	8(1)
C(26)	36(1)	90(2)	56(1)	-3(1)	2(1)	10(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for sx175_publish.

	x	y	z	U(eq)
H(21)	3338	6512	3529	40
H(31)	2867	4000	3430	37
H(51)	1491	6549	2412	43
H(61)	549	5784	4075	53
H(62)	441	5196	2808	53
H(81)	1299	2889	5132	55
H(91)	1290	4397	6599	54
H(92)	1334	5491	5648	54
H(101)	2638	4669	6609	59
H(102)	2728	3846	5450	59
H(131)	2977	6830	6611	71
H(132)	3213	7548	5437	71
H(133)	2250	7145	5826	71
H(141)	815	2151	3498	76
H(142)	64	2961	3103	76
H(143)	966	3020	2385	76
H(171)	2154	6039	-792	69
H(172)	1855	4712	-1131	69
H(181)	960	6248	-1802	81
H(182)	734	6692	-474	81
H(183)	428	5409	-891	81
H(201)	3239	4571	-200	53
H(202)	2700	3352	1	53
H(211)	4084	3294	729	58
H(212)	3331	2864	1650	58
H(221)	3925	5307	1676	38
H(251)	5065	2832	3719	60
H(252)	4100	3185	4071	60
H(253)	4345	2353	2960	60
H(261)	5892	3947	2021	77
H(262)	5367	4628	1081	77
H(263)	5288	3186	1241	77
H(1)	5394	4994	3644	50
H(2)	4253	5374	4524	50

Table 6. Hydrogen bonds for sx175_publish [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(24)-H(1)...O(12)#1	0.97	1.80	2.737(2)	161
O(12)-H(2)...C(23)	0.98	2.55	3.398(2)	145
O(12)-H(2)...O(24)	0.98	1.64	2.615(2)	174

Symmetry transformations used to generate equivalent atoms:
#1 -x+1,-y+1,-z+1

Appendix 15: X-ray crystallography of compound **359**

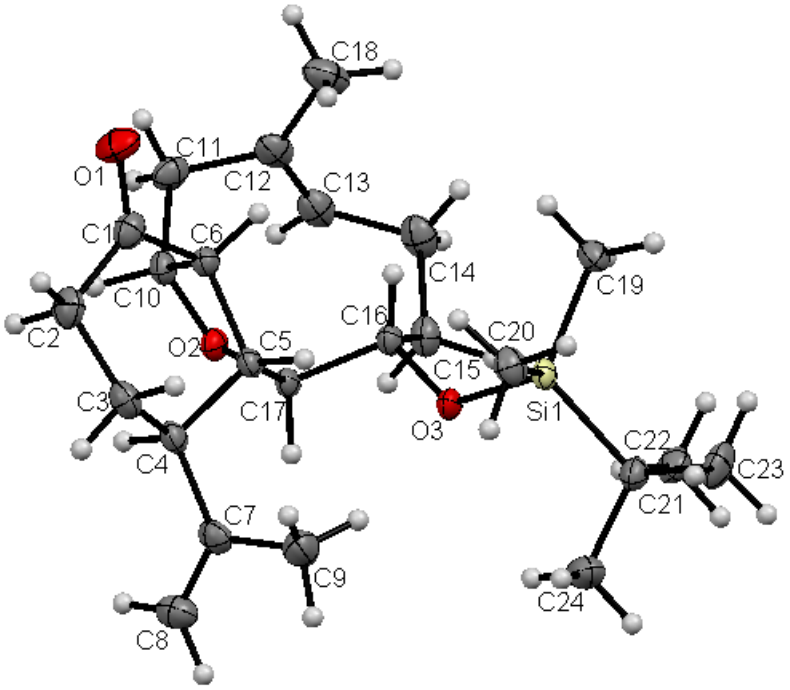


Table 1. Crystal data and structure refinement for berger3_publ.

Identification code	berger3	
Empirical formula	C24 H40 O3 Si	
Formula weight	404.65	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.8106(11) Å	α= 73.623(8)°.
	b = 9.7886(14) Å	β= 87.036(7)°.
	c = 16.251(2) Å	γ= 63.785(7)°.
Volume	1202.0(3) $Å^3$	
Z	2	
Density (calculated)	1.118 Mg/m^3	
Absorption coefficient	0.118 mm^{-1}	
F(000)	444	
Crystal size	0.30 x 0.20 x 0.10 mm^3	
Theta range for data collection	1.31 to 27.50°.	
Index ranges	-11<=h<=11, -12<=k<=12, -20<=l<=21	
Reflections collected	18131	
Independent reflections	5478 [R(int) = 0.0432]	
Completeness to theta = 27.50°	99.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9883 and 0.9655	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5478 / 0 / 260	
Goodness-of-fit on F^2	1.030	
Final R indices [I>2sigma(I)]	R1 = 0.0501, wR2 = 0.1263	
R indices (all data)	R1 = 0.0766, wR2 = 0.1407	
Largest diff. peak and hole	0.585 and -0.380 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for berger3_publ. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Si(1)	7359(1)	9390(1)	3033(1)	18(1)
O(1)	3380(2)	9394(2)	-448(1)	34(1)
O(2)	1490(2)	10018(2)	2122(1)	20(1)
O(3)	5514(2)	9306(2)	3117(1)	18(1)
C(1)	3460(2)	8624(3)	298(1)	25(1)
C(2)	3662(3)	6939(3)	538(1)	29(1)
C(3)	4782(3)	5876(2)	1378(1)	26(1)
C(4)	4085(2)	6629(2)	2110(1)	21(1)
C(5)	4218(2)	8216(2)	1906(1)	18(1)
C(6)	3310(2)	9367(2)	1018(1)	18(1)
C(7)	4921(3)	5513(2)	2986(1)	24(1)
C(8)	4060(3)	4931(3)	3556(2)	32(1)
C(9)	6761(3)	5075(3)	3186(2)	34(1)
C(10)	1430(2)	10200(2)	1216(1)	22(1)
C(11)	442(2)	11981(2)	694(1)	26(1)
C(12)	1133(2)	12975(2)	960(1)	28(1)
C(13)	792(3)	13178(2)	1743(2)	28(1)
C(14)	1860(3)	13365(3)	2339(2)	31(1)
C(15)	2838(2)	11703(2)	2985(1)	25(1)
C(16)	3961(2)	10381(2)	2577(1)	19(1)
C(17)	3224(2)	9241(2)	2493(1)	17(1)
C(18)	2332(3)	13457(3)	400(2)	37(1)
C(19)	7045(2)	11428(2)	2413(1)	23(1)
C(20)	8822(2)	7946(3)	2470(1)	26(1)
C(21)	8227(2)	8855(2)	4177(1)	22(1)
C(22)	7167(3)	10234(3)	4554(1)	28(1)
C(23)	10092(3)	8575(3)	4202(2)	36(1)
C(24)	8126(3)	7332(3)	4725(1)	34(1)

Table 3. Bond lengths [Å] and angles [°] for berger3_publ.

Si(1)-O(3)	1.6604(12)
Si(1)-C(19)	1.865(2)
Si(1)-C(20)	1.869(2)
Si(1)-C(21)	1.886(2)
O(1)-C(1)	1.220(2)
O(2)-C(10)	1.432(2)
O(2)-C(17)	1.444(2)
O(3)-C(16)	1.442(2)
C(1)-C(2)	1.512(3)
C(1)-C(6)	1.516(3)
C(2)-C(3)	1.533(3)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.533(3)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-C(7)	1.511(3)
C(4)-C(5)	1.551(2)
C(4)-H(4A)	1.0000
C(5)-C(17)	1.536(3)
C(5)-C(6)	1.548(2)
C(5)-H(5A)	1.0000
C(6)-C(10)	1.553(3)
C(6)-H(6A)	1.0000
C(7)-C(8)	1.331(3)
C(7)-C(9)	1.510(3)
C(8)-H(8A)	0.9500
C(8)-H(8B)	0.9500
C(9)-H(9A)	0.9800
C(9)-H(9B)	0.9800
C(9)-H(9C)	0.9800
C(10)-C(11)	1.555(3)
C(10)-H(10A)	1.0000
C(11)-C(12)	1.514(3)
C(11)-H(11A)	0.9900
C(11)-H(11B)	0.9900
C(12)-C(13)	1.341(3)
C(12)-C(18)	1.505(3)
C(13)-C(14)	1.485(3)
C(13)-H(13A)	0.9500
C(14)-C(15)	1.543(3)
C(14)-H(14A)	0.9900
C(14)-H(14B)	0.9900
C(15)-C(16)	1.542(3)
C(15)-H(15A)	0.9900
C(15)-H(15B)	0.9900
C(16)-C(17)	1.557(2)
C(16)-H(16A)	1.0000
C(17)-H(17A)	1.0000
C(18)-H(18A)	0.9800

C(18)-H(18B)	0.9800
C(18)-H(18C)	0.9800
C(19)-H(19A)	0.9800
C(19)-H(19B)	0.9800
C(19)-H(19C)	0.9800
C(20)-H(20A)	0.9800
C(20)-H(20B)	0.9800
C(20)-H(20C)	0.9800
C(21)-C(22)	1.537(3)
C(21)-C(23)	1.543(3)
C(21)-C(24)	1.544(3)
C(22)-H(22A)	0.9800
C(22)-H(22B)	0.9800
C(22)-H(22C)	0.9800
C(23)-H(23A)	0.9800
C(23)-H(23B)	0.9800
C(23)-H(23C)	0.9800
C(24)-H(24A)	0.9800
C(24)-H(24B)	0.9800
C(24)-H(24C)	0.9800

O(3)-Si(1)-C(19)	110.65(8)
O(3)-Si(1)-C(20)	110.38(8)
C(19)-Si(1)-C(20)	108.57(10)
O(3)-Si(1)-C(21)	105.08(8)
C(19)-Si(1)-C(21)	111.08(9)
C(20)-Si(1)-C(21)	111.08(9)
C(10)-O(2)-C(17)	110.93(13)
C(16)-O(3)-Si(1)	126.85(11)
O(1)-C(1)-C(2)	122.25(19)
O(1)-C(1)-C(6)	119.96(19)
C(2)-C(1)-C(6)	117.77(17)
C(1)-C(2)-C(3)	113.04(16)
C(1)-C(2)-H(2A)	109.0
C(3)-C(2)-H(2A)	109.0
C(1)-C(2)-H(2B)	109.0
C(3)-C(2)-H(2B)	109.0
H(2A)-C(2)-H(2B)	107.8
C(2)-C(3)-C(4)	110.03(17)
C(2)-C(3)-H(3A)	109.7
C(4)-C(3)-H(3A)	109.7
C(2)-C(3)-H(3B)	109.7
C(4)-C(3)-H(3B)	109.7
H(3A)-C(3)-H(3B)	108.2
C(7)-C(4)-C(3)	112.90(17)
C(7)-C(4)-C(5)	112.87(15)
C(3)-C(4)-C(5)	108.82(15)
C(7)-C(4)-H(4A)	107.3
C(3)-C(4)-H(4A)	107.3
C(5)-C(4)-H(4A)	107.3
C(17)-C(5)-C(6)	100.07(15)
C(17)-C(5)-C(4)	113.15(15)

C(6)-C(5)-C(4)	112.28(14)
C(17)-C(5)-H(5A)	110.3
C(6)-C(5)-H(5A)	110.3
C(4)-C(5)-H(5A)	110.3
C(1)-C(6)-C(5)	116.57(16)
C(1)-C(6)-C(10)	110.97(14)
C(5)-C(6)-C(10)	103.16(15)
C(1)-C(6)-H(6A)	108.6
C(5)-C(6)-H(6A)	108.6
C(10)-C(6)-H(6A)	108.6
C(8)-C(7)-C(9)	121.4(2)
C(8)-C(7)-C(4)	120.80(19)
C(9)-C(7)-C(4)	117.78(17)
C(7)-C(8)-H(8A)	120.0
C(7)-C(8)-H(8B)	120.0
H(8A)-C(8)-H(8B)	120.0
C(7)-C(9)-H(9A)	109.5
C(7)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(7)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
O(2)-C(10)-C(6)	105.29(14)
O(2)-C(10)-C(11)	111.07(16)
C(6)-C(10)-C(11)	115.05(15)
O(2)-C(10)-H(10A)	108.4
C(6)-C(10)-H(10A)	108.4
C(11)-C(10)-H(10A)	108.4
C(12)-C(11)-C(10)	110.54(15)
C(12)-C(11)-H(11A)	109.5
C(10)-C(11)-H(11A)	109.5
C(12)-C(11)-H(11B)	109.5
C(10)-C(11)-H(11B)	109.5
H(11A)-C(11)-H(11B)	108.1
C(13)-C(12)-C(18)	124.7(2)
C(13)-C(12)-C(11)	116.01(18)
C(18)-C(12)-C(11)	118.7(2)
C(12)-C(13)-C(14)	127.43(19)
C(12)-C(13)-H(13A)	116.3
C(14)-C(13)-H(13A)	116.3
C(13)-C(14)-C(15)	105.86(17)
C(13)-C(14)-H(14A)	110.6
C(15)-C(14)-H(14A)	110.6
C(13)-C(14)-H(14B)	110.6
C(15)-C(14)-H(14B)	110.6
H(14A)-C(14)-H(14B)	108.7
C(16)-C(15)-C(14)	114.94(17)
C(16)-C(15)-H(15A)	108.5
C(14)-C(15)-H(15A)	108.5
C(16)-C(15)-H(15B)	108.5
C(14)-C(15)-H(15B)	108.5
H(15A)-C(15)-H(15B)	107.5

O(3)-C(16)-C(15)	110.20(15)
O(3)-C(16)-C(17)	102.33(14)
C(15)-C(16)-C(17)	115.88(15)
O(3)-C(16)-H(16A)	109.4
C(15)-C(16)-H(16A)	109.4
C(17)-C(16)-H(16A)	109.4
O(2)-C(17)-C(5)	104.08(14)
O(2)-C(17)-C(16)	115.06(15)
C(5)-C(17)-C(16)	112.10(14)
O(2)-C(17)-H(17A)	108.5
C(5)-C(17)-H(17A)	108.5
C(16)-C(17)-H(17A)	108.5
C(12)-C(18)-H(18A)	109.5
C(12)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
C(12)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5
Si(1)-C(19)-H(19A)	109.5
Si(1)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
Si(1)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
Si(1)-C(20)-H(20A)	109.5
Si(1)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5
Si(1)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5
C(22)-C(21)-C(23)	108.95(16)
C(22)-C(21)-C(24)	109.36(17)
C(23)-C(21)-C(24)	109.17(17)
C(22)-C(21)-Si(1)	108.92(13)
C(23)-C(21)-Si(1)	110.38(14)
C(24)-C(21)-Si(1)	110.04(13)
C(21)-C(22)-H(22A)	109.5
C(21)-C(22)-H(22B)	109.5
H(22A)-C(22)-H(22B)	109.5
C(21)-C(22)-H(22C)	109.5
H(22A)-C(22)-H(22C)	109.5
H(22B)-C(22)-H(22C)	109.5
C(21)-C(23)-H(23A)	109.5
C(21)-C(23)-H(23B)	109.5
H(23A)-C(23)-H(23B)	109.5
C(21)-C(23)-H(23C)	109.5
H(23A)-C(23)-H(23C)	109.5
H(23B)-C(23)-H(23C)	109.5
C(21)-C(24)-H(24A)	109.5
C(21)-C(24)-H(24B)	109.5
H(24A)-C(24)-H(24B)	109.5
C(21)-C(24)-H(24C)	109.5

H(24A)-C(24)-H(24C) 109.5
H(24B)-C(24)-H(24C) 109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for berger3_publ. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Si(1)	15(1)	21(1)	20(1)	-6(1)	1(1)	-10(1)
O(1)	42(1)	36(1)	20(1)	-7(1)	1(1)	-14(1)
O(2)	15(1)	25(1)	22(1)	-6(1)	0(1)	-11(1)
O(3)	15(1)	21(1)	21(1)	-5(1)	-1(1)	-9(1)
C(1)	20(1)	29(1)	26(1)	-9(1)	0(1)	-10(1)
C(2)	31(1)	32(1)	29(1)	-15(1)	2(1)	-16(1)
C(3)	27(1)	22(1)	32(1)	-10(1)	4(1)	-14(1)
C(4)	19(1)	20(1)	26(1)	-6(1)	1(1)	-12(1)
C(5)	17(1)	19(1)	22(1)	-5(1)	1(1)	-11(1)
C(6)	18(1)	18(1)	19(1)	-4(1)	0(1)	-9(1)
C(7)	31(1)	17(1)	28(1)	-7(1)	3(1)	-12(1)
C(8)	38(1)	26(1)	31(1)	-4(1)	4(1)	-16(1)
C(9)	33(1)	30(1)	37(1)	0(1)	-7(1)	-16(1)
C(10)	19(1)	27(1)	24(1)	-7(1)	0(1)	-13(1)
C(11)	19(1)	28(1)	25(1)	-3(1)	-3(1)	-7(1)
C(12)	18(1)	18(1)	38(1)	0(1)	-4(1)	-4(1)
C(13)	18(1)	19(1)	42(1)	-5(1)	-1(1)	-5(1)
C(14)	25(1)	22(1)	47(1)	-13(1)	1(1)	-8(1)
C(15)	20(1)	27(1)	31(1)	-13(1)	1(1)	-11(1)
C(16)	16(1)	20(1)	22(1)	-4(1)	-1(1)	-9(1)
C(17)	13(1)	18(1)	20(1)	-3(1)	-1(1)	-8(1)
C(18)	30(1)	27(1)	44(2)	3(1)	3(1)	-12(1)
C(19)	25(1)	26(1)	23(1)	-6(1)	4(1)	-16(1)
C(20)	21(1)	29(1)	33(1)	-12(1)	5(1)	-12(1)
C(21)	21(1)	28(1)	22(1)	-7(1)	0(1)	-13(1)
C(22)	32(1)	35(1)	21(1)	-10(1)	1(1)	-17(1)
C(23)	23(1)	53(2)	35(1)	-16(1)	-4(1)	-17(1)
C(24)	45(1)	29(1)	26(1)	0(1)	-7(1)	-18(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for berger3_publ.

	x	y	z	U(eq)
H(2A)	4166	6469	67	34
H(2B)	2526	6966	599	34
H(3A)	5958	5739	1302	31
H(3B)	4806	4814	1526	31
H(4A)	2851	6894	2110	25
H(5A)	5435	8007	1937	22
H(6A)	3750	10181	835	22
H(8A)	4602	4224	4103	39
H(8B)	2903	5223	3417	39
H(9A)	7208	4195	3718	51
H(9B)	6852	5997	3259	51
H(9C)	7416	4750	2711	51
H(10A)	826	9610	1097	26
H(11A)	547	12091	72	32
H(11B)	-777	12369	794	32
H(13A)	-254	13205	1938	34
H(14A)	1143	14145	2643	38
H(14B)	2660	13736	2019	38
H(15A)	3565	11776	3399	30
H(15B)	2007	11391	3314	30
H(16A)	4238	10872	1998	23
H(17A)	3290	8518	3079	20
H(18A)	2668	14094	651	56
H(18B)	1767	14087	-177	56
H(18C)	3344	12503	363	56
H(19A)	6651	11655	1814	35
H(19B)	8123	11490	2429	35
H(19C)	6196	12209	2669	35
H(20A)	8283	8173	1903	40
H(20B)	9068	6861	2812	40
H(20C)	9882	8048	2400	40
H(22A)	7601	9961	5150	42
H(22B)	5978	10422	4538	42
H(22C)	7244	11198	4212	42
H(23A)	10499	8379	4794	53
H(23B)	10171	9517	3829	53
H(23C)	10791	7650	4000	53
H(24A)	8554	7077	5320	51
H(24B)	8817	6447	4491	51
H(24C)	6943	7504	4710	51

Appendix 16: X-ray crystallography of cladiell-11-ene-3,6,7-triol

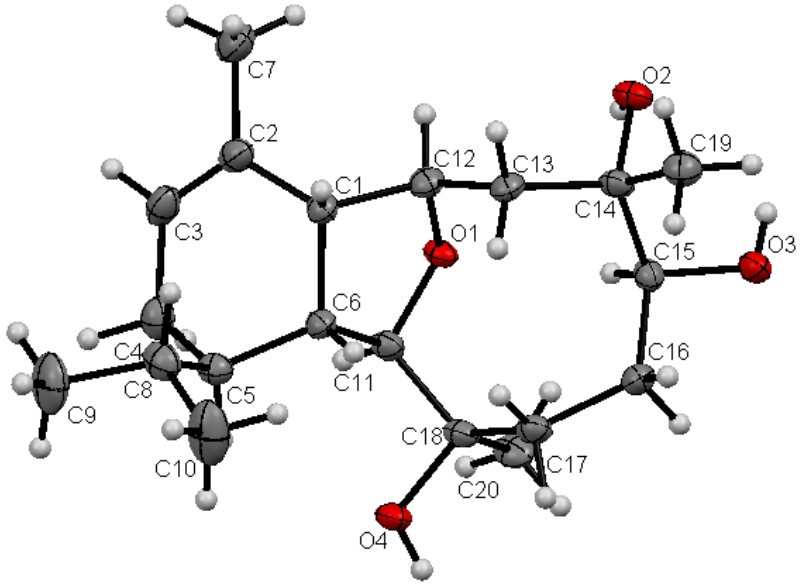


Table 1. Crystal data and structure refinement for rbvii563_final.

Identification code	rbvii563	
Empirical formula	C20 H34 O4	
Formula weight	338.47	
Temperature	100(2) K	
Wavelength	0.71075 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 6.9388(6) Å	α= 90°.
	b = 8.1850(10) Å	ß= 90°.
	c = 33.548(3) Å	γ = 90°.
Volume	1905.3(3) $Å^3$	
Z	4	
Density (calculated)	1.18 Mg/m^3	
Absorption coefficient	0.08 mm^{-1}	
F(000)	744	
Crystal size	0.3 x 0.1 x 0.05 mm^3	
Theta range for data collection	3.08 to 27.49°.	
Index ranges	-7<=h<=9, -10<=k<=10, -43<=l<=43	
Reflections collected	13485	
Independent reflections	4356 [R(int) = 0.1051]	
Completeness to theta = 27.49°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.000 and 0.5809	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4356 / 0 / 225	
Goodness-of-fit on F^2	1.045	
Final R indices [I>2sigma(I)]	R1 = 0.0743	
R indices (all data)	R1 = 0.12, wR2 = 0.0957	
Absolute structure parameter	0.3(15)	
Largest diff. peak and hole	0.251 and -0.246 e.$Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for rbvii563_final. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(3)	1749(3)	7036(2)	10030(1)	24(1)
O(1)	6194(3)	6064(2)	9197(1)	19(1)
O(2)	3664(3)	9372(2)	9549(1)	23(1)
O(4)	4842(3)	1841(2)	9008(1)	26(1)
C(20)	5379(4)	3056(3)	9658(1)	27(1)
C(17)	2544(4)	3865(3)	9216(1)	22(1)
C(13)	3392(4)	7682(3)	8953(1)	21(1)
C(18)	4674(4)	3354(3)	9232(1)	21(1)
C(11)	6093(4)	4463(3)	9010(1)	20(1)
C(15)	2668(4)	6592(3)	9656(1)	21(1)
C(1)	6059(4)	6620(3)	8505(1)	20(1)
C(14)	2566(4)	8050(3)	9366(1)	21(1)
C(4)	9001(4)	4089(4)	8316(1)	27(1)
C(16)	1664(4)	5000(3)	9538(1)	23(1)
C(6)	5699(4)	4763(3)	8564(1)	20(1)
C(19)	530(4)	8711(3)	9318(1)	27(1)
C(2)	8075(4)	7038(4)	8367(1)	25(1)
C(5)	6850(4)	3672(3)	8278(1)	22(1)
C(12)	5541(4)	7305(3)	8921(1)	22(1)
C(7)	8450(5)	8845(4)	8299(1)	35(1)
C(8)	6062(5)	3816(4)	7847(1)	28(1)
C(3)	9366(4)	5898(4)	8281(1)	29(1)
C(9)	7390(5)	3061(5)	7537(1)	47(1)
C(10)	4098(5)	3011(5)	7815(1)	50(1)

Table 3. Bond lengths [Å] and angles [°] for rbvii563_final.

O(3)-C(15)	1.455(3)
O(3)-H(3)	0.82
O(1)-C(12)	1.447(3)
O(1)-C(11)	1.455(3)
O(2)-C(14)	1.458(3)
O(2)-H(2)	0.82
O(4)-C(18)	1.453(3)
O(4)-H(4)	0.82
C(20)-C(18)	1.530(3)
C(20)-H(20A)	0.96
C(20)-H(20B)	0.96
C(20)-H(20C)	0.96
C(17)-C(18)	1.537(4)
C(17)-C(16)	1.551(4)
C(17)-H(17A)	0.97
C(17)-H(17B)	0.97
C(13)-C(12)	1.527(4)
C(13)-C(14)	1.530(4)
C(13)-H(13A)	0.97
C(13)-H(13B)	0.97
C(18)-C(11)	1.533(4)
C(11)-C(6)	1.539(3)
C(11)-H(11)	0.98
C(15)-C(16)	1.529(4)
C(15)-C(14)	1.541(4)
C(15)-H(15)	0.98
C(1)-C(2)	1.514(4)
C(1)-C(12)	1.546(4)
C(1)-C(6)	1.553(4)
C(1)-H(1)	0.98
C(14)-C(19)	1.522(4)
C(4)-C(3)	1.507(4)
C(4)-C(5)	1.536(4)
C(4)-H(4A)	0.97
C(4)-H(4B)	0.97
C(16)-H(16A)	0.97
C(16)-H(16B)	0.97
C(6)-C(5)	1.535(4)
C(6)-H(6)	0.98
C(19)-H(19A)	0.96
C(19)-H(19B)	0.96
C(19)-H(19C)	0.96
C(2)-C(3)	1.325(4)
C(2)-C(7)	1.518(4)
C(5)-C(8)	1.550(4)
C(5)-H(5)	0.98
C(12)-H(12)	0.98
C(7)-H(7A)	0.96
C(7)-H(7B)	0.96
C(7)-H(7C)	0.96

C(8)-C(10)	1.518(4)
C(8)-C(9)	1.521(4)
C(8)-H(8)	0.98
C(3)-H(3A)	0.93
C(9)-H(9A)	0.96
C(9)-H(9B)	0.96
C(9)-H(9C)	0.96
C(10)-H(10A)	0.96
C(10)-H(10B)	0.96
C(10)-H(10C)	0.96

C(15)-O(3)-H(3)	109.5
C(12)-O(1)-C(11)	109.93(19)
C(14)-O(2)-H(2)	109.5
C(18)-O(4)-H(4)	109.5
C(18)-C(20)-H(20A)	109.5
C(18)-C(20)-H(20B)	109.5
H(20A)-C(20)-H(20B)	109.5
C(18)-C(20)-H(20C)	109.5
H(20A)-C(20)-H(20C)	109.5
H(20B)-C(20)-H(20C)	109.5
C(18)-C(17)-C(16)	121.2(2)
C(18)-C(17)-H(17A)	107
C(16)-C(17)-H(17A)	107
C(18)-C(17)-H(17B)	107
C(16)-C(17)-H(17B)	107
H(17A)-C(17)-H(17B)	106.8
C(12)-C(13)-C(14)	118.0(2)
C(12)-C(13)-H(13A)	107.8
C(14)-C(13)-H(13A)	107.8
C(12)-C(13)-H(13B)	107.8
C(14)-C(13)-H(13B)	107.8
H(13A)-C(13)-H(13B)	107.1
O(4)-C(18)-C(20)	108.7(2)
O(4)-C(18)-C(11)	101.6(2)
C(20)-C(18)-C(11)	110.1(2)
O(4)-C(18)-C(17)	106.9(2)
C(20)-C(18)-C(17)	112.5(2)
C(11)-C(18)-C(17)	116.1(2)
O(1)-C(11)-C(18)	110.7(2)
O(1)-C(11)-C(6)	106.5(2)
C(18)-C(11)-C(6)	116.9(2)
O(1)-C(11)-H(11)	107.4
C(18)-C(11)-H(11)	107.4
C(6)-C(11)-H(11)	107.4
O(3)-C(15)-C(16)	103.7(2)
O(3)-C(15)-C(14)	109.3(2)
C(16)-C(15)-C(14)	118.5(2)
O(3)-C(15)-H(15)	108.3
C(16)-C(15)-H(15)	108.3
C(14)-C(15)-H(15)	108.3
C(2)-C(1)-C(12)	114.2(2)

C(2)-C(1)-C(6)	114.2(2)
C(12)-C(1)-C(6)	101.6(2)
C(2)-C(1)-H(1)	108.9
C(12)-C(1)-H(1)	108.9
C(6)-C(1)-H(1)	108.9
O(2)-C(14)-C(19)	105.4(2)
O(2)-C(14)-C(13)	109.3(2)
C(19)-C(14)-C(13)	108.7(2)
O(2)-C(14)-C(15)	106.6(2)
C(19)-C(14)-C(15)	112.7(2)
C(13)-C(14)-C(15)	113.7(2)
C(3)-C(4)-C(5)	112.0(2)
C(3)-C(4)-H(4A)	109.2
C(5)-C(4)-H(4A)	109.2
C(3)-C(4)-H(4B)	109.2
C(5)-C(4)-H(4B)	109.2
H(4A)-C(4)-H(4B)	107.9
C(15)-C(16)-C(17)	120.7(2)
C(15)-C(16)-H(16A)	107.1
C(17)-C(16)-H(16A)	107.1
C(15)-C(16)-H(16B)	107.1
C(17)-C(16)-H(16B)	107.1
H(16A)-C(16)-H(16B)	106.8
C(5)-C(6)-C(11)	114.9(2)
C(5)-C(6)-C(1)	113.9(2)
C(11)-C(6)-C(1)	104.6(2)
C(5)-C(6)-H(6)	107.7
C(11)-C(6)-H(6)	107.7
C(1)-C(6)-H(6)	107.7
C(14)-C(19)-H(19A)	109.5
C(14)-C(19)-H(19B)	109.5
H(19A)-C(19)-H(19B)	109.5
C(14)-C(19)-H(19C)	109.5
H(19A)-C(19)-H(19C)	109.5
H(19B)-C(19)-H(19C)	109.5
C(3)-C(2)-C(1)	122.1(3)
C(3)-C(2)-C(7)	122.5(3)
C(1)-C(2)-C(7)	115.1(3)
C(6)-C(5)-C(4)	109.0(2)
C(6)-C(5)-C(8)	110.8(2)
C(4)-C(5)-C(8)	113.8(2)
C(6)-C(5)-H(5)	107.7
C(4)-C(5)-H(5)	107.7
C(8)-C(5)-H(5)	107.7
O(1)-C(12)-C(13)	113.7(2)
O(1)-C(12)-C(1)	104.5(2)
C(13)-C(12)-C(1)	111.3(2)
O(1)-C(12)-H(12)	109
C(13)-C(12)-H(12)	109
C(1)-C(12)-H(12)	109
C(2)-C(7)-H(7A)	109.5
C(2)-C(7)-H(7B)	109.5

H(7A)-C(7)-H(7B)	109.5
C(2)-C(7)-H(7C)	109.5
H(7A)-C(7)-H(7C)	109.5
H(7B)-C(7)-H(7C)	109.5
C(10)-C(8)-C(9)	108.6(3)
C(10)-C(8)-C(5)	110.6(2)
C(9)-C(8)-C(5)	113.2(3)
C(10)-C(8)-H(8)	108.1
C(9)-C(8)-H(8)	108.1
C(5)-C(8)-H(8)	108.1
C(2)-C(3)-C(4)	124.2(3)
C(2)-C(3)-H(3A)	117.9
C(4)-C(3)-H(3A)	117.9
C(8)-C(9)-H(9A)	109.5
C(8)-C(9)-H(9B)	109.5
H(9A)-C(9)-H(9B)	109.5
C(8)-C(9)-H(9C)	109.5
H(9A)-C(9)-H(9C)	109.5
H(9B)-C(9)-H(9C)	109.5
C(8)-C(10)-H(10A)	109.5
C(8)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
C(8)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for rbvii563_final. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(3)	32(1)	18(1)	21(1)	-3(1)	3(1)	-2(1)
O(1)	27(1)	13(1)	17(1)	1(1)	-2(1)	2(1)
O(2)	29(1)	14(1)	25(1)	-1(1)	-4(1)	-1(1)
O(4)	38(1)	13(1)	27(1)	-1(1)	4(1)	-2(1)
C(20)	40(2)	21(2)	19(2)	5(1)	-4(2)	3(2)
C(17)	28(2)	17(2)	22(2)	-2(1)	-1(1)	-5(1)
C(13)	25(2)	18(2)	21(2)	5(1)	2(1)	-1(1)
C(18)	30(2)	13(2)	20(2)	-1(1)	-3(1)	-1(1)
C(11)	26(2)	17(2)	18(2)	-3(1)	-1(1)	-2(1)
C(15)	25(2)	19(2)	17(2)	-1(1)	2(1)	3(1)
C(1)	24(2)	19(2)	17(1)	2(1)	1(1)	0(1)
C(14)	27(2)	15(2)	21(2)	-3(1)	-2(1)	-3(1)
C(4)	24(2)	34(2)	24(2)	-5(1)	1(1)	0(2)
C(16)	26(2)	19(2)	24(2)	1(1)	5(2)	-4(1)
C(6)	25(2)	17(2)	17(1)	2(1)	2(1)	-1(1)
C(19)	29(2)	25(2)	27(2)	2(1)	-2(1)	0(1)
C(2)	32(2)	26(2)	19(2)	-2(1)	2(2)	-9(2)
C(5)	25(2)	19(2)	22(2)	1(1)	-2(1)	0(1)
C(12)	27(2)	19(2)	21(2)	5(1)	1(1)	0(1)
C(7)	44(2)	34(2)	28(2)	2(2)	8(2)	-9(2)
C(8)	38(2)	27(2)	19(2)	-3(1)	-3(2)	2(2)
C(3)	26(2)	37(2)	25(2)	-4(2)	5(2)	-11(2)
C(9)	49(2)	71(3)	21(2)	-12(2)	3(2)	1(2)
C(10)	36(2)	83(3)	31(2)	-21(2)	-4(2)	-6(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for rbvii563_final.

	x	y	z	U(eq)
H(3)	2242	7875	10117	35
H(2)	4584	8990	9671	34
H(4)	4455	1078	9145	39
H(20A)	4478	2365	9795	40
H(20B)	5482	4080	9795	40
H(20C)	6618	2534	9651	40
H(17A)	1786	2869	9215	27
H(17B)	2338	4390	8960	27
H(13A)	2691	6758	8844	26
H(13B)	3122	8613	8783	26
H(11)	7373	3965	9031	24
H(15)	4028	6351	9709	25
H(1)	5131	7040	8310	24
H(4A)	9472	3707	8572	33
H(4B)	9712	3522	8109	33
H(16A)	375	5283	9451	28
H(16B)	1523	4355	9779	28
H(6)	4326	4557	8517	24
H(19A)	10	8976	9575	40
H(19B)	-264	7899	9193	40
H(19C)	560	9676	9155	40
H(5)	6679	2537	8364	26
H(12)	6274	8311	8967	27
H(7A)	9746	8994	8205	53
H(7B)	8278	9427	8544	53
H(7C)	7563	9255	8103	53
H(8)	5914	4978	7785	34
H(3A)	10575	6236	8194	35
H(9A)	7657	1947	7608	70
H(9B)	8575	3666	7527	70
H(9C)	6777	3093	7281	70
H(10A)	3661	3063	7543	75
H(10B)	3199	3572	7984	75
H(10C)	4192	1890	7896	75