University of Glasgow

TOTAL SYNTHESIS OF THE PROPOSED STRUCTURE OF SCLEROPHYTIN F AND STRUCTURE RE-EVALUATION

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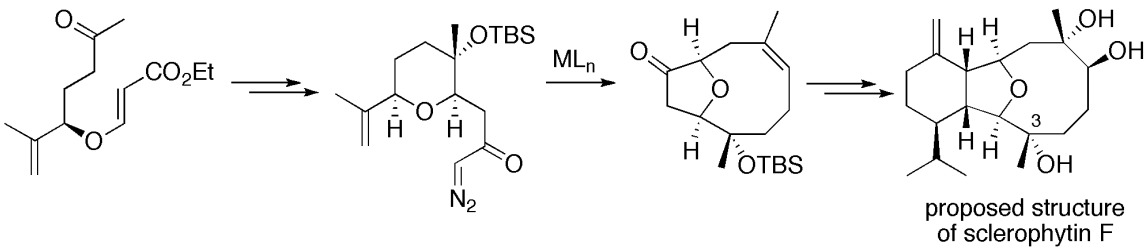
ABSTRACT

Sclerophytin F is a marine natural product that was isolated in 1989 from the soft coral *Sclerophytum capitalis* and belongs to the cladiellin family. Following intensive study towards the synthesis of cladiellins, the original structure of the natural product was revised in 2002. Importantly, the new structure possesses *S*-configuration at C-3, whereas the majority of other related compounds have the *R*-configuration at this position. The first section of this thesis provides details background to sclerophytin F as well as different strategies which have been developed towards the total syntheses of members of the cladiellin family. This is followed by a review of oxonium ylide formation and [2,3]-sigmatropic rearrangement, and radical cyclisation; two key reactions to this project.

The thesis presents the first enantioselective synthesis of the proposed structure of sclerophytin F and consequently, the first total synthesis of a cladiellin family member having the *S*-configuration at the C-3 stereocentre. Three novel enantioselective routes are described to access a pivotal intermediate; then, the synthesis follows three key steps: *i*) radical-mediated cyclisation, *ii*) oxonium ylide formation and [2,3]-sigmatropic rearrangement, *iii*) Diels-Alder cycloaddition to deliver the core of the natural product. The novelty of the route relies on the introduction of the C-3 methyl group at an early stage of the synthesis. As anticipated, the presence of this extra methyl had significant influence on many transformations. Finally, the elaboration of the core to meet the proposed structure was completed. Unfortunately, none of the recorded data matched those originally reported for the natural compound. A further three stereoisomers were synthesised but their data also did not match the original.



proposed structure of sclerophytin F

Overall, a successful synthesis of the proposed structure of sclerophytin F and three of its isomers was developed. Analysis of the spectroscopic data led to the conclusion that this structure is not sclerophytin F. Further comparison of the original isolation data for this natural product with data of securely considered cladiellins suggests that the sclerophytins F and E would be the same compound, the C-3 acetylated sclerophytin A.

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AUTHOR'S DECLARATION

I declare that, except where explicit reference is made to the contribution of others, that 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.

Portion of the work described herein have been published elsewhere as listed below.

Total Synthesis of the Purported Structure of Sclerophytin F, J. Stephen Clark, Laetitia Delion and Louis J. Farrugia, *Org. Lett*. **2014**, *16*, 4300.

Laëtitia Delion

Prof. J. Stephen. Clark

ABBREVIATIONS

Ac	Acetyl
acac	Acetylacetone
AIBN	2,2'-Azo *bis*isobutyronitrile
aq.	Aqueous
BHT	Butylhydroxytoluene
Bn	Benzyl
Bp	Boiling point
brsm	Based on recovered starting material
BTX	Brevetoxin
Bu	Butyl
Bz	Benzoyl
c.a	Circa
CBS	Corey-Bakshi-Shibata
CI	Chemical ionisation
COD	1,5-cyclooctadiene
COSY	Correlation spectroscopy
CSA	Camphorsulfonic acid
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
DEPT	Distortionless enhancement by polarisation transfer
DET	Diethyl tartrate
DIBAL-H	Diisobutylaluminium hydride
DIPEA	Diisopropylethylamine
DMAP	*N*,*N*-4-Dimethylaminopyridine
DMDO	Dimethyl dioxirane

DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
DMSO	Dimethyl sulfoxide
dppm	1,1-*Bis*(diphenylphosphino)methane
dppp	1,3-*Bis*(diphenylphosphino)propane
dr	Diastereomeric ratio
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
EI	Electron ionisation
ESI	Electrospray ionisation
Et	Ethyl
h	Hour
HBpin	Pinacolborane
hfacac	Hexafluoroacetylacetonate
HMDS	1,1,1,3,3,3-Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HPLC	High pressure liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence spectroscopy
hv	Irradiation with light
i	*iso*
i.e	Id est
IBX	*o*-Iodoxybenzoic acid
IC_{50}	Half maximal inhibitory concentration
IR	Infrared spectroscopy
IUPAC	International union of pure and applied chemistry
LDA	Lithium diisopropylamide
LRMS	Low resolution mass spectrometry
LUMO	Lowest unoccupied molecular orbital

m	*meta*
m-CPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
Men	(2-Methoxyethoxy)methyl
min	Minute
MLn	Transition metal with ligands
Mp	Melting point
Ms	Methanesulfonyl
MS	Mass spectrometry
MVK	Methyl vinyl ketone
NMM	*N*-methylmorpholine
NMO	*N*-methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
o	*ortho*
p	*para*
PCC	Pyridinium chlorochromate
pfb	Perfluorbutyrate
pfm	Heptafluorobutanamide
Ph	Phenyl
PMB	*p*-Methoxybenzyl
PPTS	Pyridinium *p*-toluenesulfonate
Pr	Propyl
quant.	Quantitative
R_f	Retention factor in chromatography
rt	Room temperature
s	*sec*

t	*tert*
TBAF	tetra-*n*-Butylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBHP	*tert*-Butyl hydroperoxide
TBS	*tert*-Butyldimethylsilyl
Temp.	Temperature
TEMPO	2,2,6,6-Tetramethyl-1-piperinyloxy
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl (triflyl)
tfa	Trifluoroacetate
TFA	Trifluoroacetic acid
tfacac	Trifluoroacetylacetonate
tfacam	Trifluoroacetamide
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMCDA	*trans*-N,N'-Dimethylcyclohexane-1,2-diamine
TMS	Trimethylsilyl
tpa	Triphenylacetate
TPAP	Tetra-*n*-propylammonium perruthenate
Tr	Triphenylmethyl (trityl)
Ts	*p*-Toluenesulfonyl
VAZO®	1,1'-Azobis(cyclohexanecarbonitrile)

INTRODUCTION

1 The 2,11-Cyclised Cembranoids

Over the last four decades, many 2,11-cyclised cembranoids have been isolated from marine invertebrates of *Octocorallia* species.[1] These natural products have a unique skeleton that has not been found in natural products extracted from terrestrial sources. Their large structural diversity, as well as their varied biological and pharmacological activities,[2] have made them very attractive as synthetic targets.

1.1 Classification and Biosynthesis

The 2,11-cyclised cembranoids are ether-bridged tricyclic diterpenes which fall into four subclasses depending on the substitution patterns of the tricyclic core: the cladiellins (also known as eunicellins), the briarellins, the asbestinins and the sarcodictyins (Figure 1). All of them are characterised by an oxatricyclic ring system. An ether bridge between C-2 and C-9 is common to the cladiellins, the briarellins and the asbestinins. However, the latter possess an additional oxepane ring between C-3 and C-16. In the sarcodictyins the ether bridge is found between C-4 and C-7.

[1] Bernardelli, P.; Paquette, L. A. *Heterocycles* **1998**, *49*, 531.
[2] Welford, A. J.; Collins, I. *J. Nat. Prod.* **2011**, *74*, 2318.

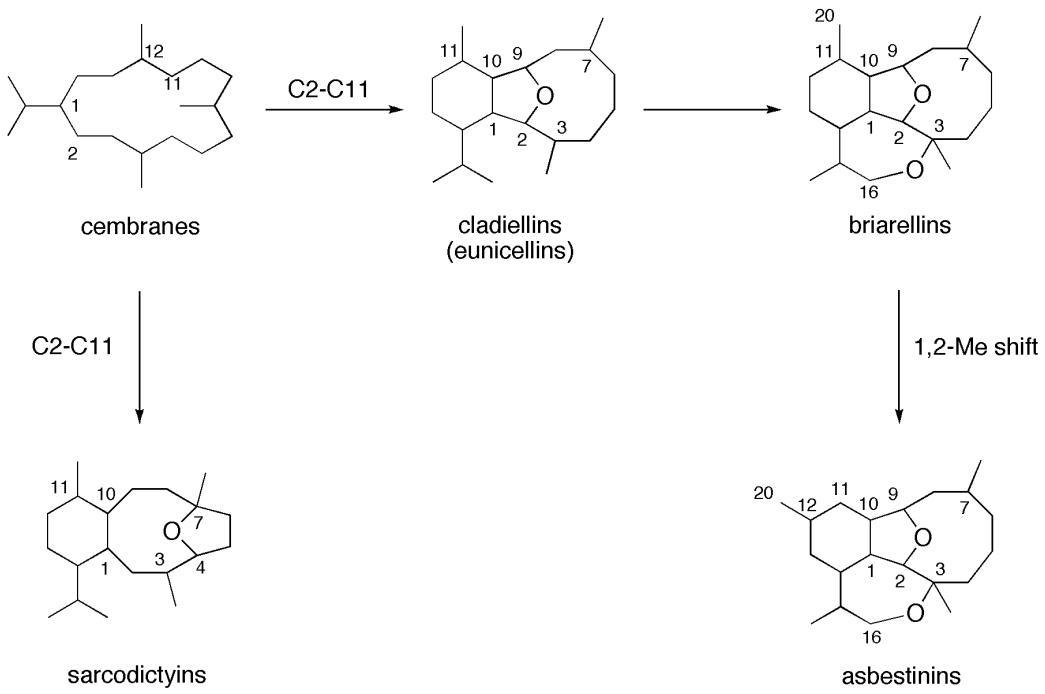

Figure 1. Faulkner's proposed biosynthesis of the four classes of oxygenated 2,11-cembranoids.[3]

Upon the isolation of the first sarcodictyin,[3] Faulkner *et al*. suggested that 2,11-cyclisation of the cembranoid diterpene backbone accounted for the biosynthetic origin of the four subclasses of marine diterpenes (Figure 1). Cyclisation of the cembrane skeleton between C-2 and C-11 and ether ring formation between C-4 and C-7 affords the sarcodictyins. Alternatively, when ether bridge formation occurs between C-2 and C-9, cladiellins are obtained. Briarellins and asbestinins feature an additional oxepane ring, which results from an oxygen bridge from C-3 to C-16 and the asbestinins arise from a suprafacial 1,2-methyl shift from C-11 to C-12 of the briarellins. Although Faulkner's biosynthetic hypothesis is viable, it is important to note that there is no evidence to support it other than the fact that all members are isolated from a common class of organism.

[3] Stierle, D. B.; Carté, B.; Faulkner, D. J.; Tagle, B.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *102*, 5088.

1.2 The Cladiellin Class of Natural Products

The cladiellins represent the most abundant class of 2,11-cyclised cembranoids. Currently, more than 100 members of the cladiellin family have been isolated from marine invertebrates.[1,2] Overall, the cladiellins can be characterised by a common oxatricyclo[6.6.1.$0^{2,7}$]pentadecane ring system bearing carbon substituents at C-3, C-7 and C-11[4] and an isopropyl group (or oxidised equivalent) at C-14.[1,2] In some cases, an additional ether bridge exists and varying levels of oxygenation and unsaturation can be found (Figure 2).

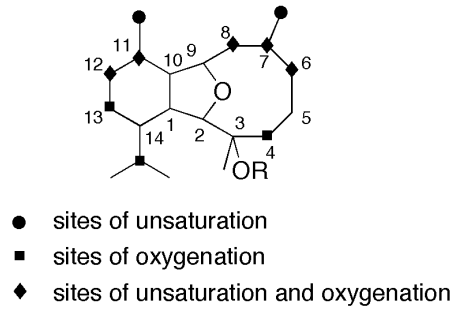

Figure 2. Representative skeleton of the cladiellin compounds.

1.2.1 Isolation and Characterisation

The first member of the cladiellin family to be isolated was eunicellin (**1**) in 1968 by Kennard *et al* (Figure 3).[5] This diterpene was extracted from soft coral *Eunicella stricta* discovered off the coast of Banyuls-sur-Mer in France. The chemical structure was determined by NMR spectroscopy and X-ray analysis of a crystalline dibromide derivative **2**.

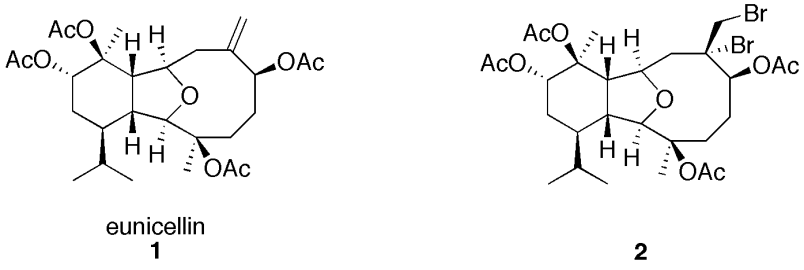

Figure 3. Eunicellin (**1**) and its dibromide derivative **2**.

[4] Cladiellin numbering
[5] Kennard, O.; Watson, D. G.; di Sanseverino, L. R.; Tursch, B.; Bosmans, R.; Djerassi, C. *Tetrahedron Lett*. **1968**, *9*, 2879.

Since then, numerous cladiellin natural products have been isolated from marine invertebrates. Among them, sclerophytins A (**3**) and B (**4**) were isolated from the coral *Sclerophytum capitalis* in 1988 (Figure 4).[6] The original structures were proved to be incorrect and synthetic studies demonstrated that sclerophytin A is the triol **3** and sclerophytin B is the corresponding acetate **4**.[7,8,9,10,11,12] From this soft coral were also isolated four natural products, sclerophytins C–F (**7**–**10**).[13] NMR experiments and X-ray analysis of sclerophytin C (**7**) confirmed its structure. Furthermore, comparison of the spectroscopic data concluded that sclerophytin D was the acetate (**8**).[14] Sclerophytins C (**7**) and E (**9**) were also present in the marine invertebrate *Cladiella australis*.[14] In addition to these cladiellins, this *alcyoniidae* contained 3-butanoyloxy sclerophytin E or litophynin E (**11**) and 6-isovaleroyl sclerophytin E (**14**). 6-Ethoxy sclerophytin E (**13**) was isolated as well, but was considered to be an artefact by the authors. Finally, the sclerophytin-type diterpene litophynin E (**11**)[15,16] was extracted from *Lytophyton sp* and its acetylated form **12** was obtained by synthetic manipulations.

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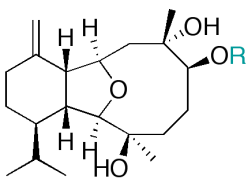
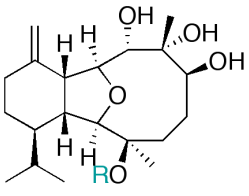
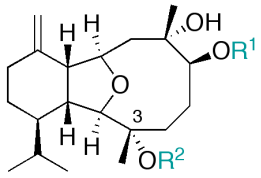
[6] Sharma, P.; Alam, M. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2537.
[7] Paquette, L. A.; Moradei, O. M.; Bernardelli, P.; Lange, T. *Org. Lett.* **2000**, *2*, 1875.
[8] Overman, L. E.; Pennington L. D.; *Org. Lett.* **2000**, *2*, 2683.
[9] Friedrich, D.; Doskotch, R. W.; Paquette, L. A. *Org. Lett.* **2000**, *2*, 1879.
[10] Gallou, F.; MacMillan, D. W. C.; Overman, L. E.; Paquette, L. A.; Pennington, L. D.; Yang, J. *Org. Lett.* **2001**, *3*, 135.
[11] Bernardelli, P.; Moradei, O. M.; Friedrich, D.; Yang, J.; Gallou, F.; Dyck, B. P.; Doskotch, R. W.; Lange, T.; Paquette, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 9021.
[12] MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D.; *J. Am. Chem. Soc.* **2001**, *123*, 9033.
[13] Alam, M.; Sharma, P.; Zektzer, A. S.; Martin, G. E.; Ji, X.; van der Helm, D. *J. Org. Chem.* **1989**, *54*, 1896.
[14] Rao, C. B; Rao, D. S; Satyanarayana, C.; Rao, D. V.;Kassühlke, K. E.; Faulkner, D. J. *J. Nat. Prod.* **1994**, *57*, 574.
[15] Ochi, M.; Yamada, K.; Futatsugi, K.; Kotsuki, H.; Shibata, K. *Chem. Lett.* **1990**, 2183.
[16] Miyamoto, T.; Yamada, K.; Ikeda, N.; Komori, T.; Higuchi, R. *J. Nat. Prod.* **1994**, *57*, 1212.



R = H, sclerophytin A **3**
R = Ac, sclerophytin B **4**
R = Et, patagonicol **5**
R = Me, sclerophytin F methyl ether **6**



R = Ac, sclerophytin C **7**
R = H, sclerophytin D **8**



R^1 = H, R^2 = Ac, sclerophytin E **9**
R^1 = H, R^2 = H, sclerophytin F **10**
R^1 = H, R^2 = CO*n*-Pr, litophynin E **11**
R^1 = Ac, R^2 = CO*n*-Pr, 6-acetoxy litophynin E **12**
R^1 = Et, R^2 = Ac, 6-ethoxy sclerophytin E **13**
R^1 = CO*i*-Bu, R^2 = Ac, 6-isovaleroyl sclerophytin E **14**

Figure 4. Sclerophytin type-diterpenes.

1.2.2 Bioactivity

Many of the cladiellins have shown interesting biological properties.[1,2] The role of these metabolites seems to be the defence of octorals from predators as suggested by their repellent and molluscicidal activity against the muricid gastropods, their lethal activity towards the brine shrimp and their capacity to inhibit the cell division of starfish eggs at low concentrations.

In vitro, cladiellins present cytotoxic activity against various human cancer cell lines, anti-inflammatory and anti-microbial properties, increasing the interest in these natural products. As an example, sclerophytin A (**3**) shows cytotoxicity to L1210 cells (mouse lymphocytic leukemia cells) at a concentration of 1 nM *in vitro*.[6] It also possesses anti-invasive and anti-metastatic activities toward the PC-3 human prostate cancer cells.[17]

[17] Hassan, H. M.; Khanfar, M. A.; Elnagar, A. Y.; Mohammed, R.; Shaala, L. A.; Youssef, D. T. A.; Hifnawy, M. S.; El Sayed, K. A. *J. Nat. Prod.* **2010**, *73*, 848.

1.3 Structural Determination and Reassignment

The structural determination of the members of the cladiellin family was achieved using NMR spectroscopy; however, where possible, X-ray crystallography was used in order to elucidate the relative configuration of the stereocentres. The absolute configuration of a cladiellin natural product was first established by the Ochi group in 1988 for litophynin C.[18] Since then, the configuration of other natural products have been made by analogy to this original assignment and the development of the modified Mosher method,[19] has allowed further determination of the absolute configuration of several members of the cladiellin family.

Total synthesis of natural products has provided confirmation of the structures without ambiguity, but, owing to the size of the natural product family, many of the cladiellins have not yet been synthesised. Importantly, the structures of sclerophytins E (**9**) and F (**10**) (Figure 4), 3-butanoyloxy sclerophytin E or litophynin E (**11**), 6-acetoxy litophynin E (**12**), 6-ethoxy sclerophytin E (**13**) and 6-isovaleroyl sclerophytin E (**14**) remain unproven. These examples are especially relevant because of discrepancies that were observed following significant studies within the Paquette research group. [20]

Differences for sclerophytins A and B between the synthetic compounds and the natural products led the Paquette group to re-evaluate the original assignments.[9] In 2002, following the determination of the structure of these natural products **3** and **4**,[7,9,10] Paquette *et al*. revised the structural assignment of several sclerophytins for which the structures were deduced from the incorrect structures of sclerophytins A (**3**) and B (**4**).[20] Spectroscopic comparisons with structurally secured compounds, sclerophytins A (**3**), B (**4**), C (**7**), D (**8**) (Figure 4), patagonicol (**5**)[21] and sclerophytin F methyl ether (**6**),[22] suggested the presence of the *R*-configuration at the C-3 stereogenic centre in all of the

[18] Ochi, M.; Futatsugi, K.; Kume, Y.; Kotsuki, H.; Asao, K.; Shibata, K. *Chem. Lett.* **1988**, 1661.
[19] Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092.
[20] Friedrich, D.; Paquette, L. A. *J. Nat. Prod.* **2002**, *65*, 126.
[21] Su, J.; Zheng, Y.; Zeng, L.; Pordesimo, E. O.; Schmitz, F. J.; Hossain, M. B.; van der Helm, D. *J. Nat. Prod.* **1993**, *56*, 1601.
[22] Sarma, N. S.; Chavakula, R.; Rao, I. N.; Kadirvelraj, R.; Row, T. N. G.; Saito, I. *J. Nat. Prod.* **1993**, *56*, 1977.

cladiellins. In fact, the *S* configuration was proposed in a number of cases, the configuration at the C-3 stereocentre is modified for: sclerophytins E (**9**), F (**10**), 3-butanoyloxy sclerophytin E (**11**) which is the same natural product than litophynin E, 6-acetoxy litophynin E (**12**), 6-ethoxy sclerophytin E (**13**) and 6-isovaleroyl sclerophytin E (**14**).

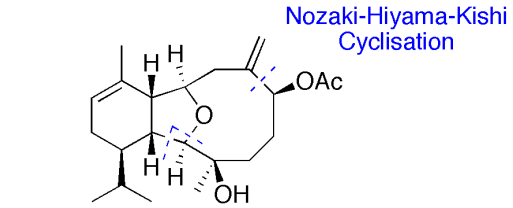
2 Synthetic Approaches to Cladiellin Natural Products

The complex architecture of the cladiellins has inspired many total syntheses using a vast array of strategies to access the tricyclic core which is common to this family of natural products. This section details the approaches used by different research groups, with a particular focus on the key strategies used to construct the natural framework and then functionalization.

2.1 Overman: Prins-pinacol and Nozaki-Hiyama-Kishi Reaction

The first total synthesis of a member of the cladiellin family was the synthesis of (−)-7-deacetoxyalcyonin acetate (**15**)[23] reported in 1995 by Overman *et al* (Figure 5).[24] The group pioneered the use of the Prins-pinacol cyclisation in natural product synthesis [25] and this reaction was used to build the hydroisobenzofuran ring system within the target compound. A chromium-promoted Nozaki-Hiyama-Kishi coupling reaction closed the medium ring.

[23] Uchio, Y.; Kodama, M.; Usui, S.; Fukazawa, Y. *Tetrahedron Lett.* **1992**, *33*, 1317.
[24] MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391.
[25] Hopkins, M. H.; Overman, L. E.; Rishton, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 5354.



(–)-7-deacetoxyalcyonin acetate
15

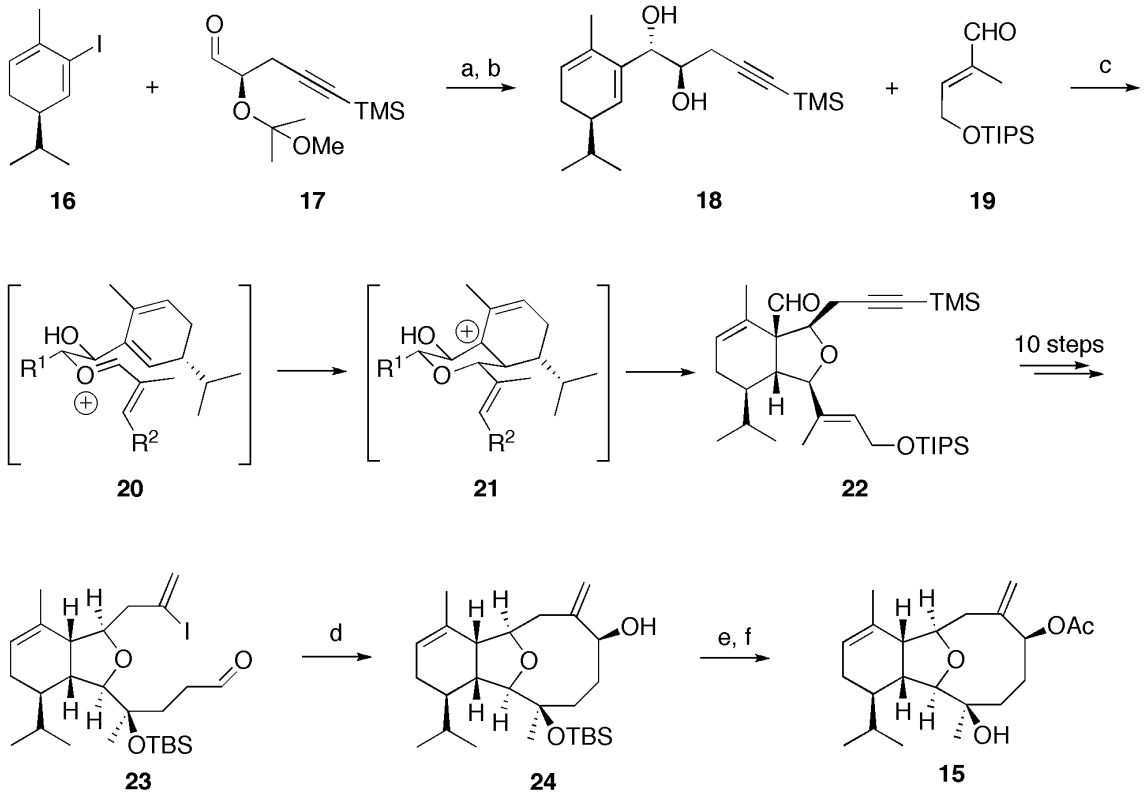
Figure 5. Overman's approach.

The precursor for the pivotal reaction was readily constructed from iodide **16** and aldehyde **17** (Scheme 1). The key Prins-pinacol rearrangement reaction between dienyl diol **18** and enal **19** was promoted by BF_3•Et_2O and delivered the hexahydroisobenzofuran **22** as a single stereoisomer in 79% yield.

The 1,2-diol **18** reacts with enal **19** to form the more stable (*E*)-oxacarbenium ion **20**. The transition state orients all substituents in a pseudo-equatorial position, leading to the bicyclic carbocation **21** which subsequently undergoes the pinacol rearrangement forming the desired aldehyde **22**.

Further functionalization resulted in the installation of vinyl iodide and aldehyde moieties within the present side chains. The preparation of oxacyclononane **24** was achieved employing a $NiCl_2$-$CrCl_2$ promoted Nozaki-Hiyama-Kishi reaction in DMSO.[26] In this way the tricycle **24** was formed in 65% yield with excellent diastereoselectivity (>20:1). With the correct oxygen functionality in place, acetylation of the secondary alcohol **24** and silyl ether deprotection provided (−)-7-deacetoxyalcyonin acetate (**15**). Overall, the synthesis was achieved in 4% yield over 20 steps.

[26] a) Jin, H.; Uenishi, J.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644; b) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281.



16 17 18 19 20 21 22 23 24 15

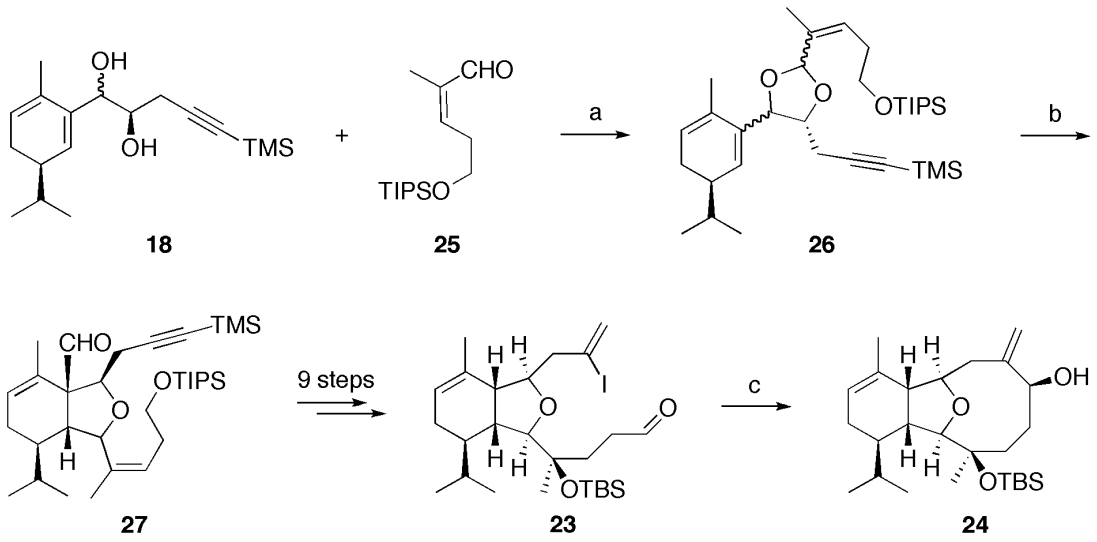
a) *t*-BuLi, THF, −78 °C; b) PPTS, MeOH, rt, 64% (2 steps); c) BF_3•Et_2O, $MgSO_4$, CH_2Cl_2, −55 to −20 °C, 79%; d) $NiCl_2$-$CrCl_2$, DMSO, rt, 65%; e) Ac_2O, DMAP, pyridine, rt; f) TBAF, THF, rt, 88% (2 steps).

Scheme 1. Total synthesis of (−)-7-deacetoxyalcyonin acetate (**15**) by the Overman group.[24]

The group also investigated the synthesis of two other members of this family: sclerophytin A and cladiell-11-ene-3,6,7-triol, using the same strategy.[8,12] However, in order to access the targets, the Prins-pinacol rearrangement was modified to use (*Z*)-α,β-unsaturated aldehydes (e.g **25**, Scheme 2), that contain one more carbon atom than the substrate **19**, which had been employed in the previous synthesis of (−)-7-deacetoxyalcyonin acetate (**15**) (Scheme 1).

First, condensation of the enal **25** and the dienyl diol **18** was carried out in the presence of *p*-toluenesulfonic acid and magnesium sulfate to give the acetal **26** as a mixture of four diastereomers in 76% yield (Scheme 2). Compound **26** was transformed into the hexahydroisobenzofuran on exposure to 10 mol% of tin tetrachloride, affording the Prins-pinacol rearranged product **27** in 88% yield. With compound **27** in hand, a nine-steps synthetic pathway led to iodoaldehyde

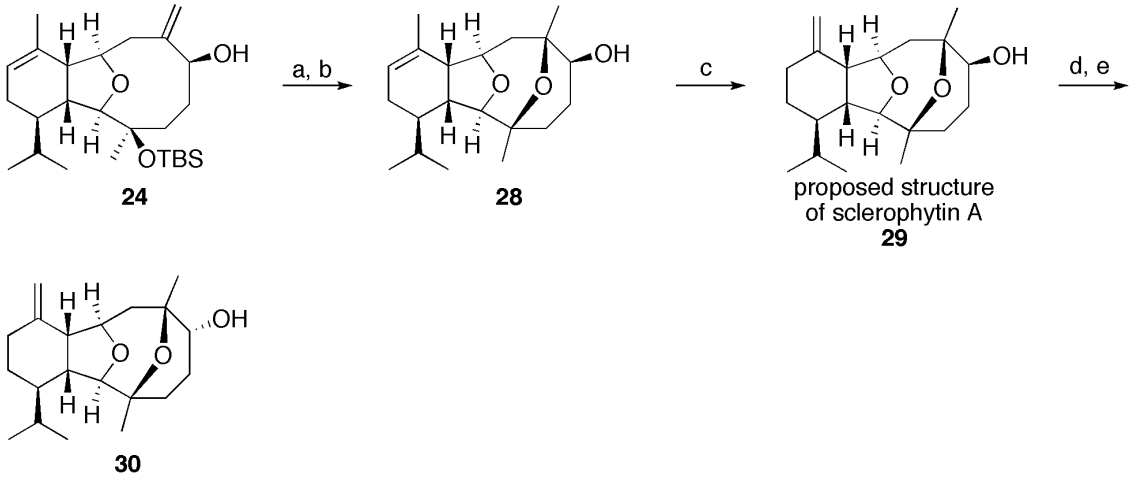
23 which underwent the Nozaki-Hiyama-Kishi cyclisation using $NiCl_2$-$CrCl_2$, to deliver the oxonene ring **24** in moderate yield (61%).



a) *p*-TsOH, $MgSO_4$, CH_2Cl_2, −20 °C, 76%; b) $SnCl_4$, CH_2Cl_2, $MeNO_2$, −50 °C, 88%; c) $NiCl_2$-$CrCl_2$, DMSO, 61%.

Scheme 2. Modified synthesis of the allylic alcohol **24,** a late stage intermediate in the total synthesis of the proposed structure of (−)-sclerophytin A.[8]

Tricyclic alcohol **24** could be transformed into the originally proposed sclerophytin A in a five-step sequence (Scheme 3). Desilylation of **24** and treatment of the diol with mercury(II) acetate and sodium borohydride furnished the tetracyclic diether **28** in 47% yield. The light-induced isomerisation of **28** generated the exocyclic alkene **29** in high yield. Although the alcohol **29** was the proposed structure of the natural product sclerophytin A, the spectroscopic data for this compound did not match those reported for the natural product.[6] This observation led the Overman group to synthesise the epimeric alcohol **30** in an oxidation-reduction sequence, but the ^{1}H and ^{13}C NMR spectra were still different to those reported for the natural product.



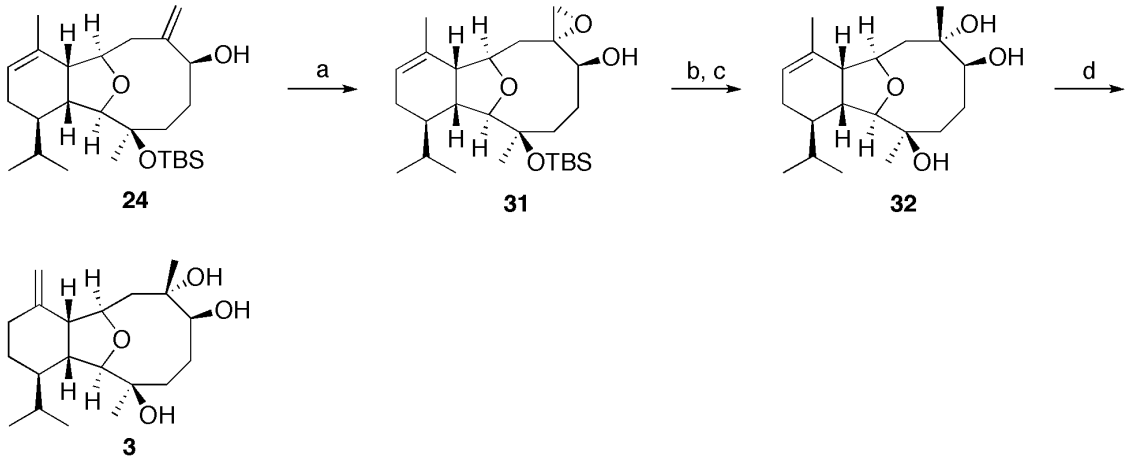
a) TBAF, THF, 70 °C, 86%; b) $Hg(OAc)_2$, THF, rt, then $NaBH_4$, NaOH, rt, 47%; c) hv, *p*-xylene, AcOH, 2-propanol, rt, 80% (4 :1); d) DMP, CH_2Cl_2, rt, 78%; e) $NaBH_4$, MeOH, rt, 96%.

Scheme 3. Completion of the synthesis of the proposed structure of (−)-sclerophytin A by the Overman group.[8,12]

At the same time, spectroscopic studies of sclerophytin B demonstrated that this compound did not contain two ether bridges as had been proposed originally.[9] Following these studies, Overman *et al.* undertook the synthesis of revised structure of sclerophytin A on the base of their retrosynthetic methodology.[24,10,12]

Tricycle alcohol **24** was subjected to an hydroxyl-directed epoxidation reaction to give **31** in 95% yield (Scheme 4). Subsequent regioselective reductive epoxide opening and removal of the silyl ether afforded cladiell-11-ene-3,6,7-triol (**32**).[27] Conversion of the triol **32** by photochemical isomerisation concluded the synthesis of the sclerophytin A (**3**), albeit in a poor 28% yield. Importantly, the spectroscopic data and the optical rotation correlated to those of the natural product.[6]

[27] Uchio, Y.; Nakatani, M.; Hase, T.; Kodama, M.; Usui, S.; Fukazawa, Y. *Tetrahedron Lett.* **1989**, *30*, 3331.



a) $VO(acac)_2$, TBHP, C_6H_6, rt, 95%; b) DIBAL-H, C_6H_6, rt, 78%; c) TBAF, THF, 70 °C, 100%; d) hv, *p*-xylene, AcOH, 2-propanol, rt, 28%.

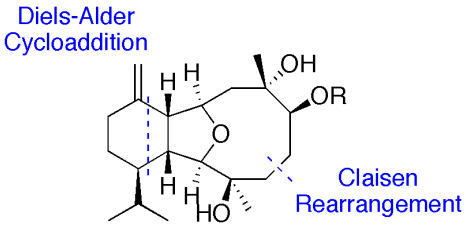
Scheme 4. Synthesis of (−)-sclerophytin A (**3**) by the Overman group.[10,12]

Since then Overman *et al*. have worked on total syntheses of several other 2,11-cyclised cembranoids and the total syntheses of briarellin E and F were successfully completed using analogous strategies.[28,29]

2.2 Paquette: Diels-Alder and Claisen Rearrangement

Concurrently with the Overman group,[8] Paquette *et al*. successfully reported the total synthesis of the originally proposed structure of sclerophytin A in 2000.[7] Shortly after the correct configuration had been determined, Paquette *et al*. published the total synthesis of the correct structures of sclerophytins A and B in 2001.[10,11,30] The strategy relied upon a Diels-Alder reaction to construct the hydroisobenzofuran core of the natural products and ring expanding Claisen rearrangement sequence to prepare the nine-membered cyclic ether embedded in the tricyclic core (Figure 6).

[28] Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc*. **2003**, *125*, 6650.
[29] Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *J. Org. Chem*. **2009**, *74*, 5458.
[30] Paquette, L. A. *Chem. Rec*. **2001**, *1*, 311.

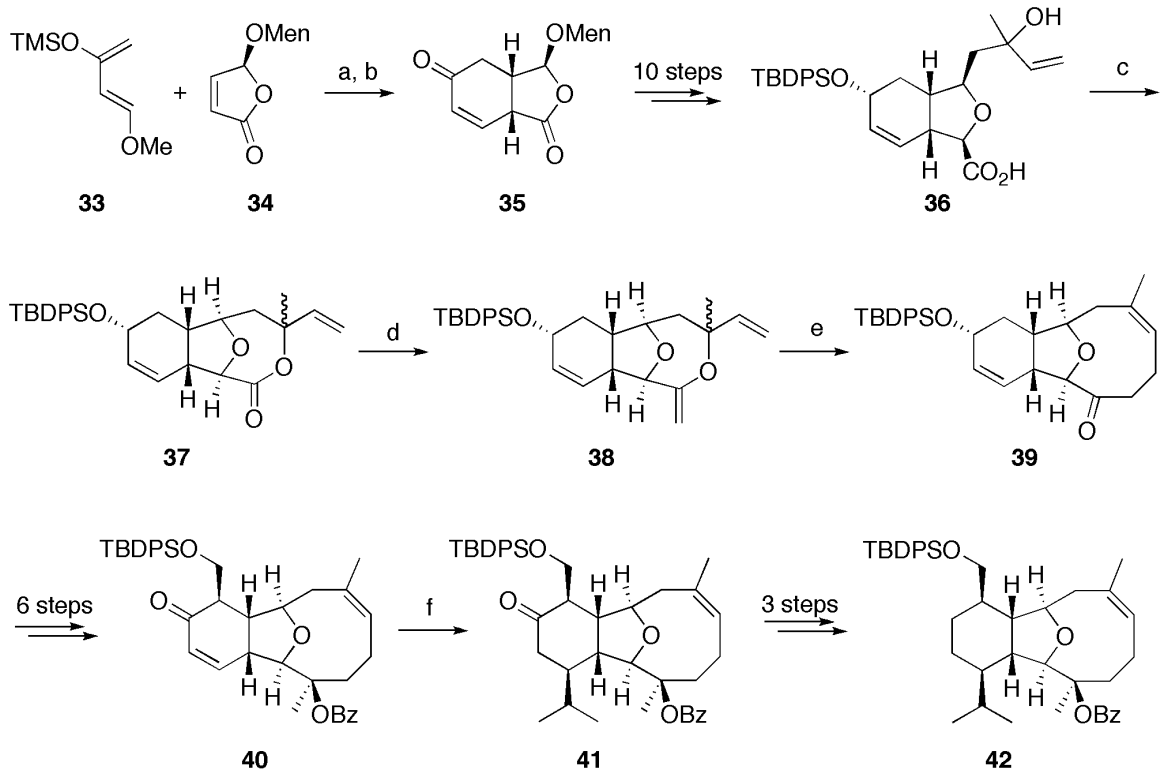


R = H, (–)-sclerophytin A **3**
R = Ac, (–)-sclerophytin B **4**

Figure 6. Paquette's approach.

The synthesis commenced with an intramolecular Diels-Alder cycloaddition reaction between the Danishefsky diene **33** and the dienophile **34** to complete the hydroisobenzofuran ring system (Scheme 5). A further 10 steps were required to access the carboxylic acid **36**. Yamaguchi macrolactonisation[31] afforded the lactone **37** as a separable mixture of diastereomers. Subsequent Tebbe methylenation of the diastereomeric lactones (independently treated) led to the diene **38**. Following this, Claisen rearrangement formed compound **39**, establishing the core structure of the cladiellin. The next stage of the synthesis involved the preparation of the enone **40** in 6 steps form ketone **39**. The copper-catalysed addition of isopropyl magnesium chloride proceeded in good yield with complete stereocontrol and installed the isopropyl side-chain of the natural product delivering **41**. An additional 3 steps furnished the advance intermediate **42**.

[31] a) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *Tetrahedron* **1990**, *46*, 4613; b) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367.



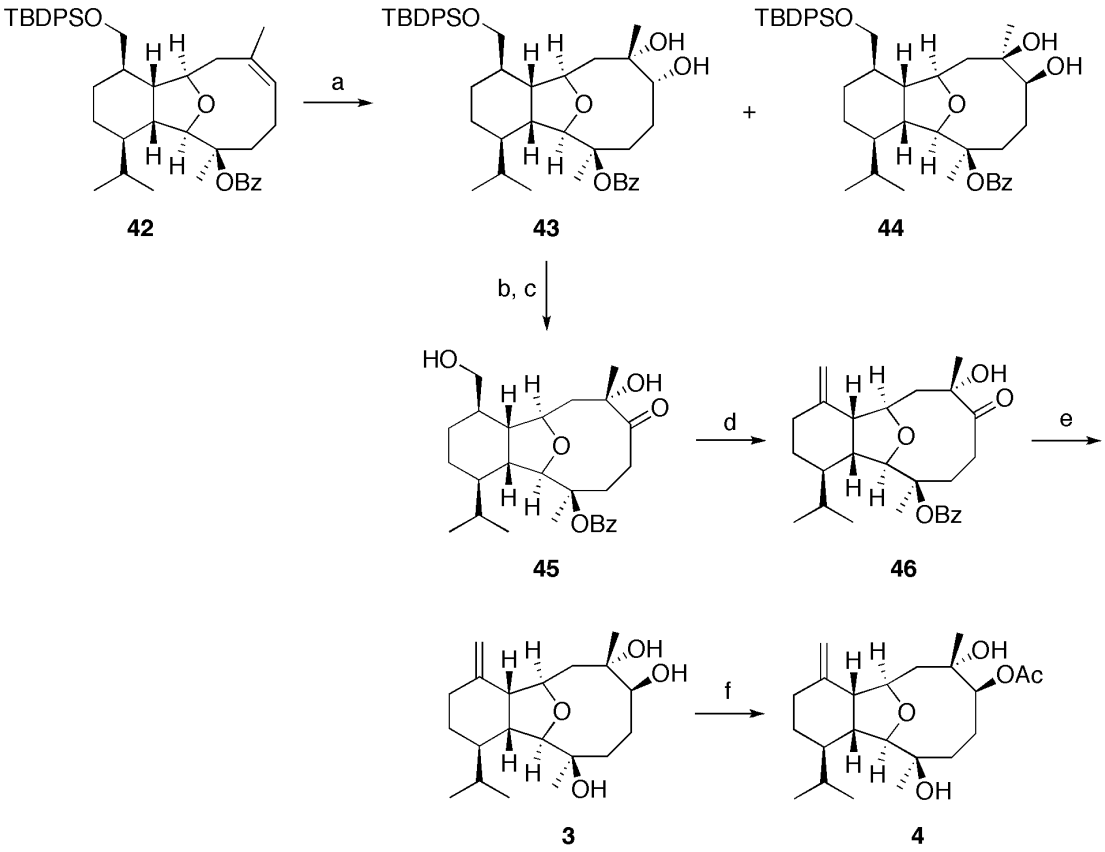
33 **34** **35** **36** **37** **38** **39** **40** **41** **42**

a) $PhCH_3$, reflux; b) TMSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; c) $Cl_3C_6H_2COCl$, Et_3N, DMAP, $PhCH_3$; d) $(C_5H_5)_2TiCH_2ClAl(CH_3)_2$, THF, pyridine, −50 to −20 °C, 67%; e) $NaBF_4$, $PhCH_3$, reflux, 80%; f) *i*-PrMgCl, CuBr.SMe_2, Et_3N, HMPA, THF, rt, 90%.

Scheme 5. Total syntheses of (−)-sclerophytin A (**3**) and B (**4**) by the Paquette group.[11]

Dihydroxylation of the alkene **42** in the presence of a molar equivalent of osmium tetroxide proceeded with a poor facial selectivity leading to the formation of the two diols **43** and **44** as a separable mixture (1:1.5). Oxidation and silyl ether cleavage afforded the alcohol **45**. Subsequent dehydration using the Grieco process[32] introduced the exocyclic double bond in good yield. Finally, conversion of **46** into the desired natural product (−)-sclerophytin A (**3**) was afforded by dissolving sodium pieces in ethanol. Acetylation generated (−)-sclerophytin B (**4**). The total synthesis of (−)-sclerophytin A (**3**) was achieved in 28 steps with an overall yield of 0.46%.

[32] Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.



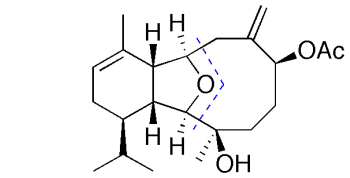
a) OsO_4, THF:pyridine (4:1), rt, 80%, **43**:**44** 1:1.5; b) IBX, DMSO, 60 °C, 70%; c) TBAF, THF, rt, 100%; d) *o*-$NO_2C_6H_4SeCN$, PBu_3, H_2O_2, rt, 98%; e) Na, EtOH, rt, 50%; f) Ac_2O, pyridine, DMAP, rt, 85%.

Scheme 6. Completion of the total syntheses of (−)-sclerophytin A (**3**) and B (**4**) by the Paquette group.[11]

2.3 Molander: [4+3]-Annulation

In 2003, the Molander group completed the total synthesis of (−)-7-deacetoxyalcyonin acetate (**15**),[33] a compound that had been synthesised previously by Overman *et al.*[24] Molander and co-workers developed a [4+3]-annulation for the total syntheses of several natural products[34, 35, 36] and extended this methodology to the cladiellin family (Figure 7).

[33] Molander, G. A.; St. Jean, Jr, D. J., Haas, J. *J. Am. Chem. Soc.* **2004**, *126*, 1642.
[34] Molander, G. A.; Eastwood, P. R. *J. Org. Chem.* **1995**, *60*, 4559.
[35] Molander, G. A.; Carey, J. S. *J. Org. Chem.* **1995**, *60*, 4845.
[36] Molander, G. A.; Haas, J. *Tetrahedron* **1999**, *55*, 617.



[4+3] annulation

(–)-7-deacetoxyalcyonin acetate
15

Figure 7. Molander's approach.

The first step of the synthesis was a thermally induced [2+2] cycloaddition reaction between α-phellandrene **47** and methoxy ketene (Scheme 7). Photochemical rearrangement of the cyclobutanone **48** occurred to give acetal **49** with complete retention of the configuration. The stage was set for the key reaction and treatment of the bis-acetal **49** with alkoxydiene in the presence of titanium tetrachloride allowed the [4+3] annulation to take place to deliver the tricyclic ester **51**.

The reaction proceeded by Lewis acid promoted formation of the oxocarbenium ion **50** which underwent nucleophilic attack and a second ionisation followed by cyclisation to form the hydroisobenzofuran core **51** found in the diterpenes in a single step. The reaction occurred with complete regio- and stereoselectivity, which was assumed to be controlled by the approach of the nucleophile from the convex face of the oxocarbenium ion **50**.

A further 7 steps were required to form the enol triflate **52** which was subjected to the Nozaki-Hiyama-Kishi cyclisation reaction[37] providing a 2:1 diastereomeric mixture of cyclopentanols **53**. The undesired alcohol was recycled *via* a Mitsunobu inversion in 71% yield. Acetylation of the required cyclopentanol delivered **54**. Chemoselective epoxidation of the trisubstituted alkene and treatment of the allylic acetate with ozone furnished the epoxy dione **55**, and subsequent tungsten-mediated deoxygenation of the epoxide delivered the diketone **56**. Chemoselective silyl enol ether formation, Wittig olefination and diastereoselective methylation provided the desired (−)-7-deactoxyalcyonin acetate (**15**). The total synthesis was achieved in only 17 steps from commercially available (*R*)-(−)-α-phellandrene with an overall yield of 4%.

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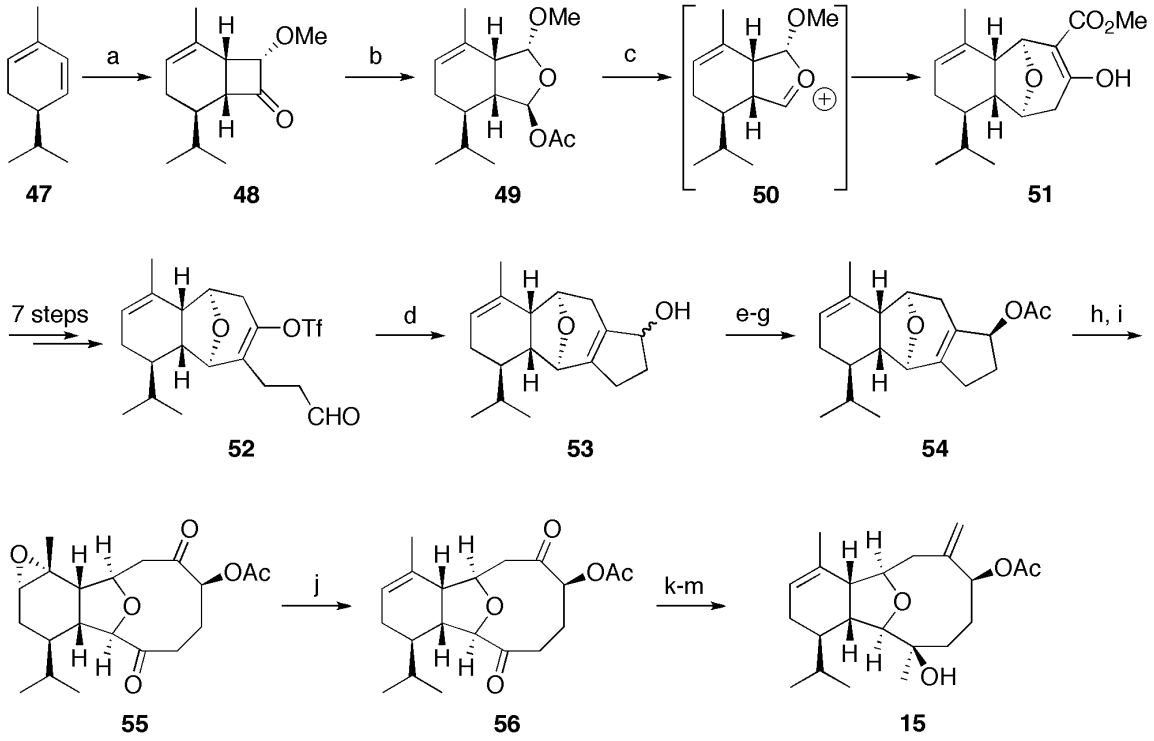
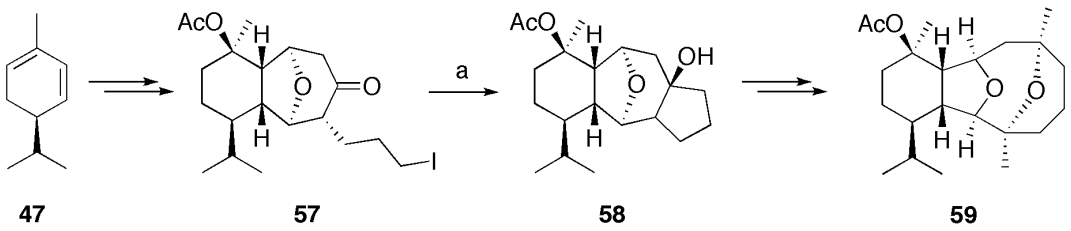
[37] a) Kishi, Y. *Pure Appl. Chem.* **1992**, *64*, 343; b) Chen, C.; Tagami, K.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 5386.



a) methoxyacetyl chloride, Et_3N, $PhCH_3$, rt, 25%; b) AcOH, hv, CH_2Cl_2, rt, 86%; c) $CH_2C(OSiEt_3)CHC(OMe)(OSiEt_3)$, $TiCl_4$, CH_2Cl_2, −80 °C, 43-80%; d) $CrCl_2$, $NiCl_2$, DMF/THF, rt, 88%; e) DEAD, BzOH, PPh_3, THF, rt; f) MeONa, MeOH, rt, 71% (2 steps); g) Ac_2O, DMAP pyridine, rt, 100%; h) *m*-CPBA, CH_2Cl_2, 0 °C ; i) O_3, CH_2Cl_2, −78 °C, then DMS, rt, 43% (3 steps); j) WCl_6, *n*-BuLi, THF, 93% ; k) TBSOTf, KHMDS, THF, −78 °C; l) Ph_3PCH_3Br, *t*-BuOK, THF, 0 °C, then 1M HCl, 61% (2 steps); m) MeLi, $YbOTf_3$, THF, −78 °C, 66% (BRSM).

Scheme 7. Total synthesis of (−)-7-deacetoxyalcyonin acetate (**15**) by the Molander group.[33]

Molander *et al*. also considered the possibility of using a SmI_2-mediated cyclisation reaction in order to construct the oxacyclononane sub-unit instead of the Nozaki-Hiyama-Kishi reaction.[38] However, this new methodology proved to be unsuccessful and the only product formed was the 3,7-diastereomer of polyanthellin A **59** (Scheme 8).



a) SmI_2, HMPA, THF, 0 °C to rt, 88%.

Scheme 8. Formation of the oxacyclononane unit by SmI_2-mediated cyclisation.[38]

[38] Molander, G. A.; Czakó, B.; St. Jean, Jr, D. J. *J. Org. Chem.* **2006**, *71*, 1172.

2.4 Crimmins: Ring-Closing Metathesis and Intramolecular Diels-Alder Cycloaddition

Crimmins *et al*. entered the field of the 2,11-cyclised cembranoid synthesis with the total synthesis of ophirin B in 2004[39] and astrogorgin in 2006.[40] Both syntheses relied upon the formation of the core ring-system by a route incorporating an intramolecular ring closing metathesis reaction and a Diels-Alder cycloaddition reaction (Figure 8).

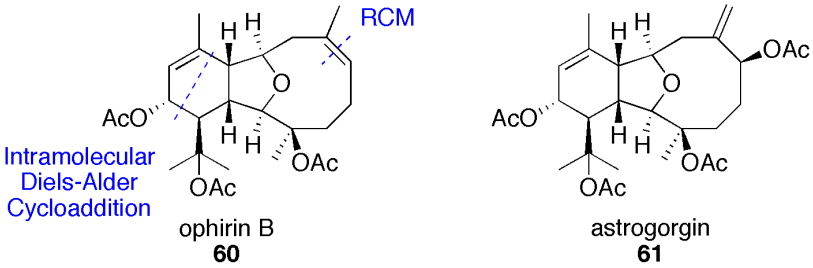
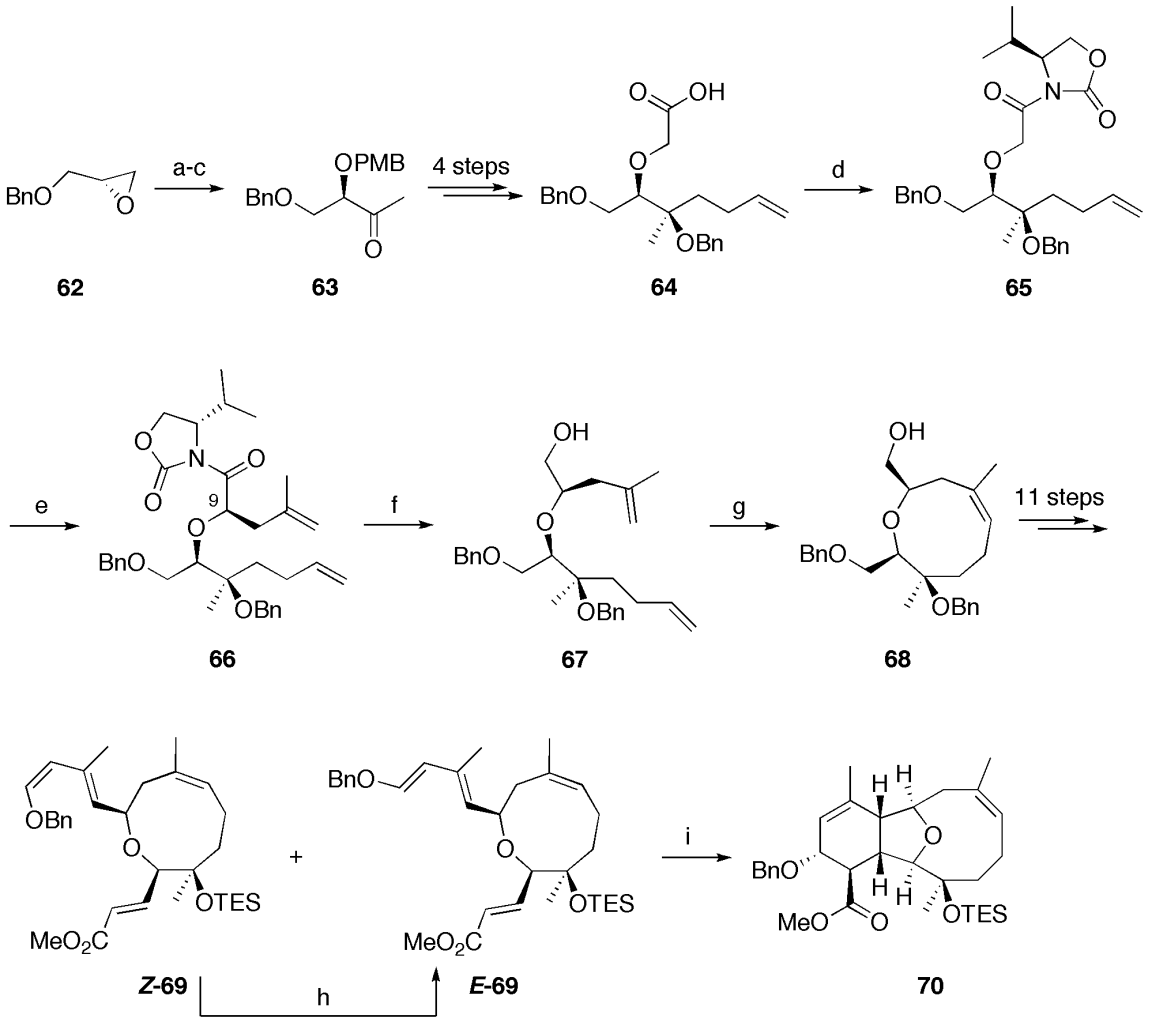


Figure 8. Crimmins approach.

The synthesis of the oxonene unit of the ophirin B commenced with (*S*)-benzylglycidyl ether **62** (Scheme 9). Treatment with dimethyl sulfonium methylide followed by protection of the allylic alcohol and oxidation under modified Wacker oxidation provided the methyl ketone **63**. Further manipulations led to the carboxylic acid **64** in a 73% overall yield. Acylation and reaction with the oxazolidinone delivered the *N*-acyloxalidinone **65**. An alkylation reaction was then employed to introduce the C-9 stereogenic centre selectively (>92:2 dr) and gave the ring-closing metathesis precursor **66**. Unfortunately, only dimerization was observed when substrate **66** was subjected to the ring-closing metathesis reaction. To circumvent this problem, the chiral auxiliary was removed to the alcohol **67** and then cyclisation was performed in benzene at 80 °C in the presence of the Grubbs II catalyst leading to the oxonene **68** in 89% yield (isolated from a 15:1 mixture of oxonene and dimer). The oxonene **68** was then converted into the Diels-Alder substrate using an eleven-step sequence. A 3:1 mixture of tetraenes ***Z*-69** and ***E*-69** was obtained and the *E*-isomer underwent spontaneous intramolecular Diels-Alder

[39] Crimmins, M. T.; Brown, B. H. *J. Am. Chem. Soc.* **2004**, *126*, 10264.
[40] Crimmins, M. T.; Brown, B. H.; Plake, H. R. *J. Am. Chem. Soc.* **2006**, *128*, 1371.

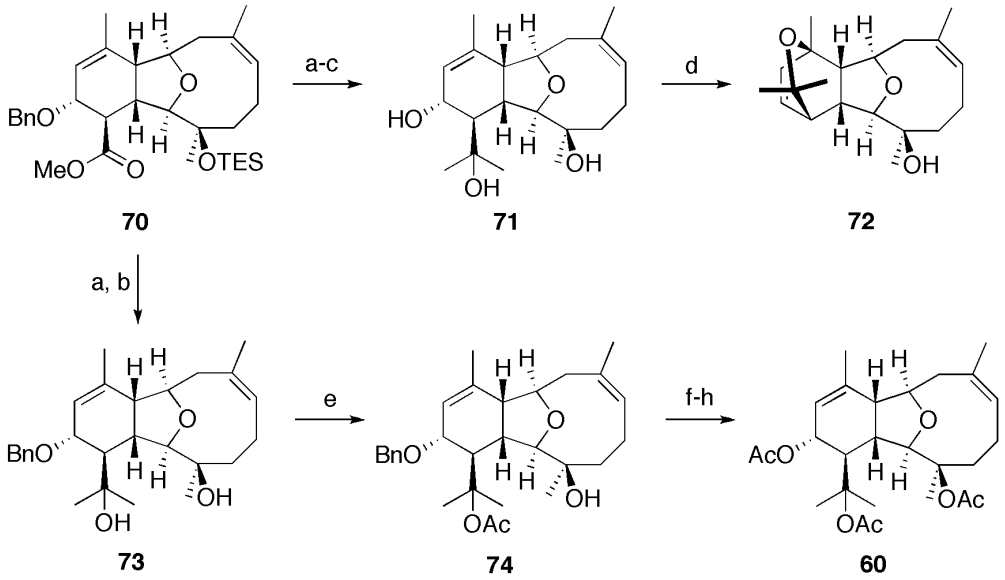
cycloaddition at 25°C delivering the oxatricyclic core **70**. The unreacted *Z*-isomer **69** was irradiated in the presence of a sub-stoichiometric amount of diphenyl disulfide and slowly converted into the *E*-isomer. The process was repeated until consumption of the starting material was complete.



a) Me_3SI, *n*-BuLi, THF, −10 °C to rt, 99%; b) NaH, PMBCl, THF, rt, 90%; c) $Hg(OAc)_2$, H_2O, then $PdCl_2$, LiCl, $CuCl_2$, H_2O, O_2, rt, 89%; d) Me_3CCOCl, Et_3N, THF, −78 to 0 °C; (*S*)-lithio-4-isopropyl-oxazolidin-2-one, 89%; e) NaHMDS, $CH_2C(CH_3)CH_2I$, THF, −78 to −45 °C, 93%; f) $LiBH_4$, MeOH, Et_2O, 0 °C 92%; g) Grubbs II, C_6H_6, 80 °C, 89%, 15:1 oxonene: dimer; h) hv, PhSSPh; i) C_6H_6, 78%.

Scheme 9. Synthesis of intermediate **70** in the total synthesis of ophirin B (**60**) performed by the Crimmins group.[39]

The initial end-game strategy involved addition of methyl magnesium chloride followed by the cleavage of the benzyl and triethylsilyl groups to generate triol **71** (Scheme 10). In a final step, ophirin B would have been obtained in an acetylation reaction. However, all attempts to perform direct acetylation failed and delivered the bridged ether **72** instead.

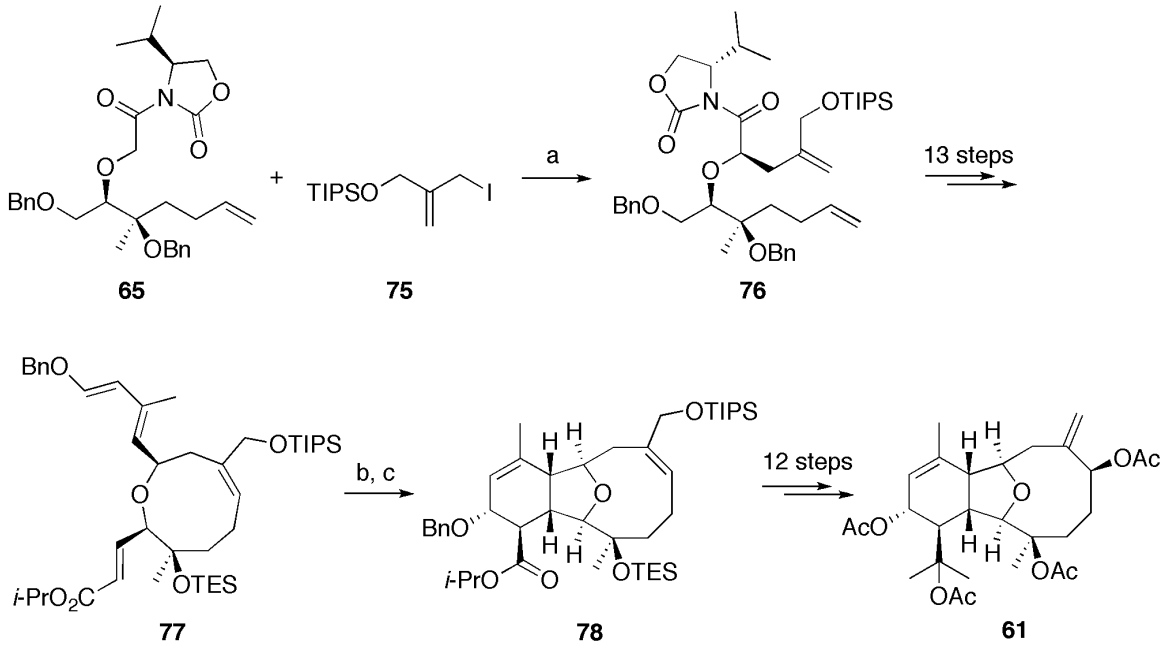


a) MeMgCl, THF, rt, 85%; b) TBAF, THF, rt, 94%; c) Na, naphtalene, THF, −78 °C, 90%; d) Ac_2O or AcCl, with a variety of bases and Lewis acid conditions; e) KHMDS, Ac_2O, THF, 90% (brsm); f) $Bi(OTf)_3$, Ac_2O, rt, 75%; g) H_2, Pd/C, EtOAc, rt, 70%; h) Ac_2O, DMAP, pyridine, CH_2Cl_2, 95%.

Scheme 10. Completion of the total synthesis of ophirin B (**60**).[39]

Crimmins *et al.* devised an alternative pathway in which the triethylsilyl ether **70** was firstly cleaved and the intermediate **73** was converted into the monoacetate **74** (Scheme 10). Reaction with bismuth trifluoromethanesulfonate, and acetic anhydride, followed by hydrogenolysis and acetylation afforded ophirin B (**60**) in 8% yield over 27 steps from commercially available starting material.

The same strategy was applied to the synthesis of the more complex natural product, astrogorgin (**61**) (Scheme 11). The intermediate **65** was subjected to an asymmetric alkylation reaction with allylic iodide **75** leading to the diene **76**. The oxonene ring was formed by ring-closing metathesis and a further eleven-step sequence provided the Diels-Alder precursor **77**. Intramolecular cycloaddition provided the desired oxatricycle **78** as a single diastereomer in the same manner as for the synthesis of ophirin B (**60**). Finally another twelve-step sequence afforded the target natural product.



a) NaHMDS, THF, −78 to −45 °C, 90%; b) C_6H_6, 25 °C; c) hv, PhSSPh, C_6H_6.

Scheme 11. Completion of the total synthesis of astrogorgin (**61**) by the Crimmins group.[40]

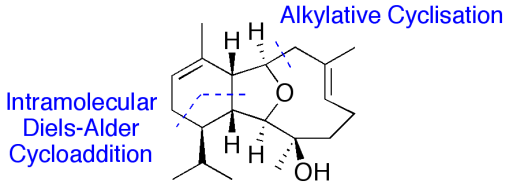
Following the publication of these results, the Crimmins group reported the total synthesis of 11-acetoxy-4-deoxyasbestinin D,[41] asbestinin-12,[42] the proposed structure of briarellin J,[43] (+)-vigulariol and (−)-sclerophytin A[44] using the same key-steps.

2.5 Kim: Alkylative Cyclisation and Diels-Alder Cycloaddition

In 2006, the Kim research group reported the first total synthesis of an (*E*)-cladiellin diterpene with the total synthesis of (−)-cladiella-6,11-dien-3-ol (**79**) (Figure 9).[45] In order to achieve this synthesis, new methodology was developed to form the (*E*)-geometric isomer of the oxacyclononane core, while other synthesis efforts were focused on the synthesis of the (*Z*)-geometric isomer. The key strategy involved intramolecular amide acetate enolate

[41] Crimmins, M. T.; Ellis, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 17200.
[42] Crimmins, M. T.; Ellis, J. M. *J. Org. Chem.* **2008**, *73*, 1649.
[43] Crimmins, M. T.; Mans, M. C.; Rodriguez, A. D. *Org. Lett.* **2010**, *12*, 5028.
[44] Crimmins, M. T.; Stauffer, C. S.; Mans, M. C. *Org. Lett.* **2011**, *13*, 4890.
[45] Kim, H.; Lee, H.; Kim, J.; Kim, S; Kim, D.; *J. Am. Chem. Soc.* **2006**, *128*, 15851.

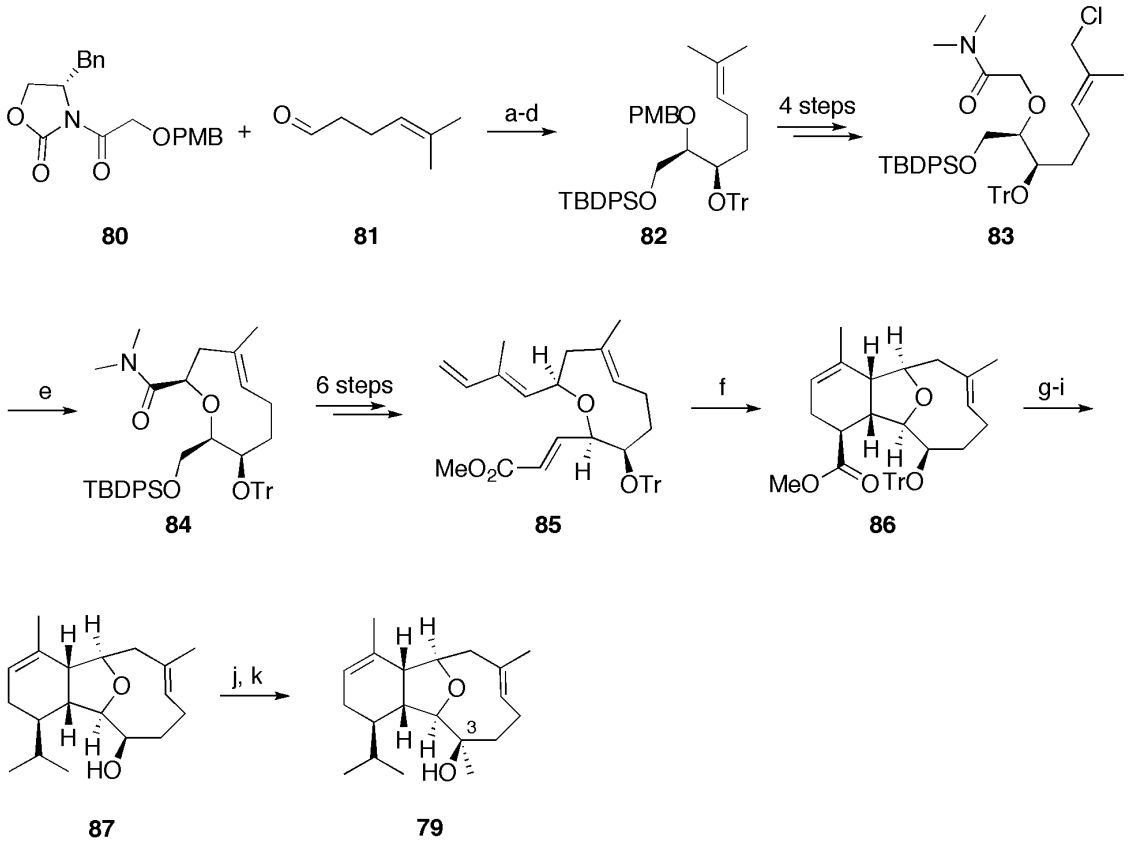
alkylation to construct the (*E*)-cycloxanonene and intramolecular Diels-Alder cycloaddition to afford the hydroisobenzofuran ring system.



(–)-cladiella-6,11-dien-3-ol
79

Figure 9. Kim's approach.

The synthesis of the (*E*)-cycloxanonane unit started with an aldol reaction between glycolate oxazolidinone **80** and 5-methylhex-4-enal **81** (Scheme 12). The *syn*-aldol product was obtained in a highly diastereoselective fashion (dr 98:2) and moderate yield. Reductive cleavage of the chiral oxazolidinone and protection of hydroxyl groups led to the protected triol **82** in a 76% overall yield. The (*E*)-allylic chloride **83** was obtained in 4 steps. Upon treatment with lithium *bis*(trimethylsilyl)amide, the *cis*-(*E*)-oxonene **84** was obtained as a single diastereomer in excellent yield. A further 6 steps yielded the Diels-Alder precursor **85**. The intramolecular Diels-Alder cyclisation was carried out in refluxing xylene. The addition of butylated hydroxytoluene to the reaction mixture was essential to avoid decomposition. The tricyclic core of the cladiellin **86** was subjected to a double methylation of the ester followed by deoxygenation to deliver the isopropyl group **87**. Oxidation and addition of a methyl group introduced the C-3 tertiary alcohol and completed the synthesis of (−)-cladiella-6,11-dien-3-ol (**79**). Overall, the total synthesis was realised in 6% yield over 21 steps.



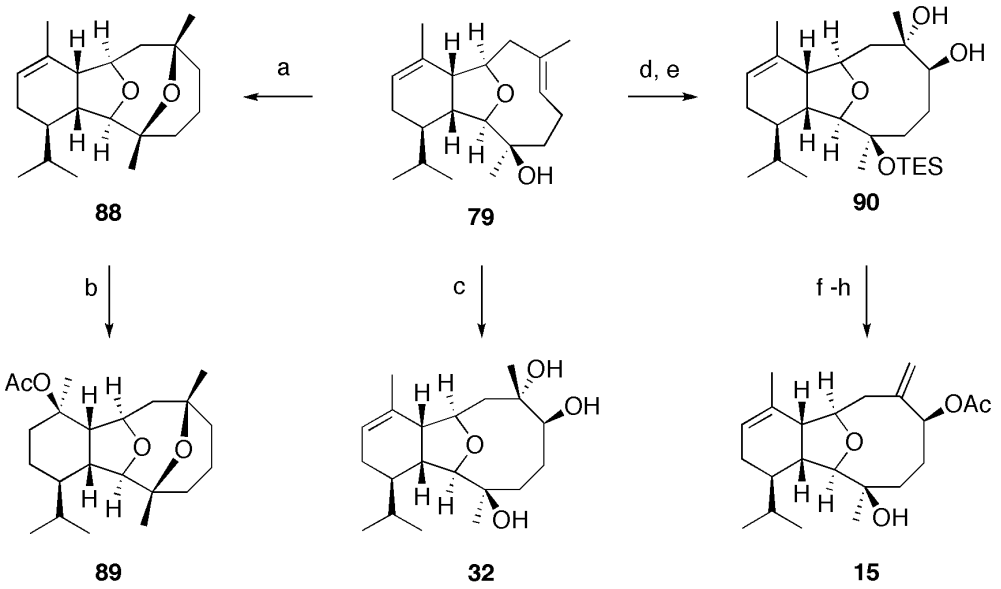
80 **81** **82** **83** **84** **85** **86** **87** **79**

a) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, −78 to −40 °C, then **81**, −78 to 0 °C, 75%, dr 98:2; b) $NaBH_4$, THF/H_2O, rt, 89%; c) TBDPSCl, imidazole, 0 °C, 92%; d) trityl bromide, DMAP, pyridine, 100 °C, 93%; e) LiHMDS, THF, 45 °C, 92%; f) BHT, xylene, reflux, 85%; g) MeLi, $CeCl_3$, THF, −78 °C, 89%; h) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt; i) K, 18-crown-6, *t*-$BuNH_2$, THF, rt, 62% (2 steps); j) DMP, pyridine, CH_2Cl_2, rt; k) MeLi, $NaBF_4$, THF, −78 °C, 82% (2 steps).

Scheme 12. Total synthesis of (−)-cladiella-6,11-dien-3-ol (**79**) by the Kim group.[45]

(−)-Cladiella-6,11-dien-3-ol (**79**) can be used as a common precursor for the synthesis of other diterpenes as shown in Scheme 13. Treatment with osmium tetroxide delivered (−)-cladiell-11-ene-3,6,7-triol (**32**) in a highly stereo- and chemo-selective manner. (+)-Polyanthellin A (**89**) was obtained using an oxymercuration, demercuration protocol followed by an acetylation reaction. Finally, (−)-7-deacetoxyalcyonin acetate (**15**) was obtained in 5 steps from (−)-cladiella-6,11-dien-3-ol (**79**). Protection of the tertiary hydroxyl group and dihydroxylation provided the corresponding diol **90**. The secondary alcohol was acetylated and exposure of the resulting acetate to Burgess salt[46] followed by desilylation delivered the natural product **15**.

[46] Burgess, E. M.; Penton, Jr, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.



a) BF_3•Et_2O, Et_2O, rt, 84%; b) *i*. $Hg(OAc)_2$, THF/H_2O, rt, then Et_3B, $NaBH_4$, 62%, *ii*. Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt, 78%; c) OsO_4, NMO, THF/H_2O, 0 °C, 94%; d) TESOTf, CH_2Cl_2, rt, 97%; e) OsO_4, NMO, THF/H_2O, 0 °C, 99%; f) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 0 °C, 97%; g) Burgess salt, $PhCH_3$, 70 °C; h) TBAF, THF, 50 °C, 92% (2 steps).

Scheme 13. Completion of the syntheses of three cladiellin natural products from (−)-cladiellia-6,11-dien-3-ol (**79**).[45]

2.6 Hoppe: Homo-aldol, Krämer Tetrahydrofuran Synthesis and Ring-Closing Metathesis

(+)-Vigulariol (**91**) was synthesised first by the Paquette group as a by-product during work on the sclerophytins before its discovery as a natural product.[11] A few years later, Hoppe *et al*. reported a short total synthesis of (+)-vigulariol.[47] The strategy relied on an asymmetric homo-aldol reaction followed by Krämer's tetrahydrofuran synthesis and a ring-closing metathesis reaction (Figure 10).

[47] Becker, J.; Bergander, K; Fröhlich, R; Hoppe, D. *Angew. Chem. Int. Ed.* **2008**, *47*, 1654.

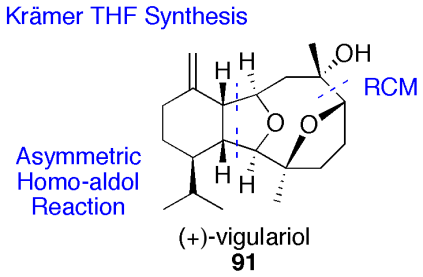
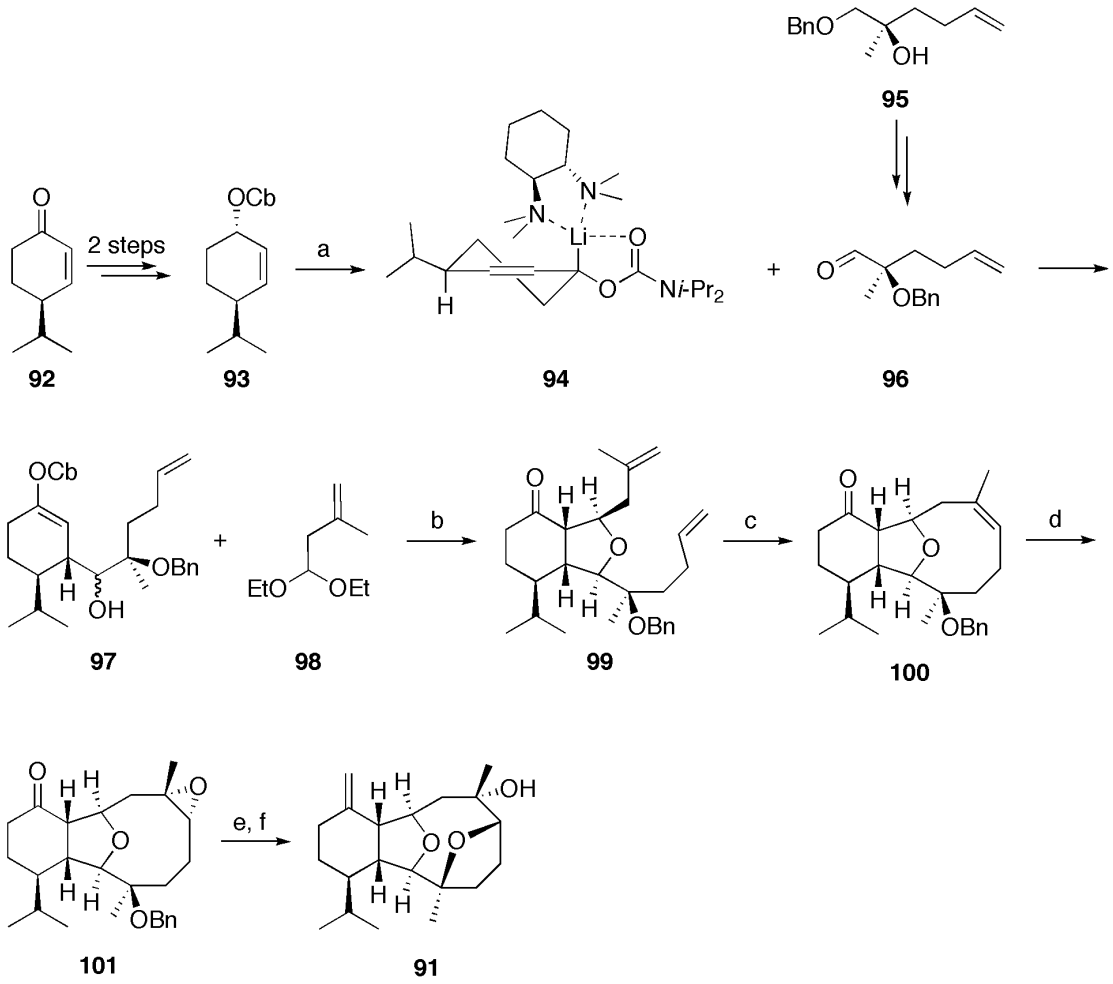


Figure 10. Hoppe's approach.

The starting materials **93** and **96** were prepared in a few steps from commercially available cyclohexanone **92** and diol **95** respectively. Coupling by stereospecific deprotonation of the carbamate **93,** using *sec*-butyllithium and *N*,*N*,*N*',*N*'-tetramethyl-1,2-diaminocyclohexane delivered the lithiated intermediate **94** which underwent a lithium-titanium exchange in presence of chlorotriisopropoxytitanium (Scheme 14). Subsequent addition of aldehyde **96** led to a diastereomeric mixture of alcohols **97** (dr 83:17). Lewis acid mediated reaction with the acetal **98** and intramolecular aldol reaction delivered the hexahydroisobenzofuran products as separable diastereoisomers. The desired diastereoisomer **99** was the major product and was obtained in 71% yield. Ring closure was achieved using Grubbs II catalyst to give the ten-membered ring in a 45% yield. Epoxidation on the α-face of alkene **100** with dimethyldioxirane produced epoxide **101**. *O*-Debenzylation and Wittig olefination delivered (+)-vigulariol (**91**). The natural product was afforded in 8 steps from the cyclohexanone **92** and in an overall yield of 63%.



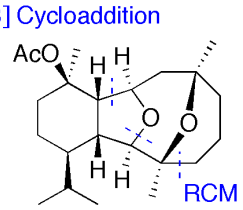
a) *i*. *s*-BuLi/TMCDA, Et_2O, −78 °C, *ii*. $ClTi(O\textit{i}\text{-}Pr)_3$, −78 °C, *iii*. **96**, −78 °C to rt, 40%, dr 83:17; b) **98**, $BF_3{\bullet}OEt_2$, Et_2O, 0 °C, 71%; c) Grubbs II (10 mol%), C_6H_6, reflux, 45%; d) DMDO, acetone, −20 °C, 81%; e) Pd/C, H_2, EtOAc, 91%; f) Ph_3PCH_3Br, NaHMDS, $PhCH_3$, 80 °C, 93%.

Scheme 14. Synthesis of (+)-vigulariol (**91**) by the Hoppe group.[47]

2.7 Johnson: [2+3] Cycloaddition and Ring-Closing Metathesis

Three years following the publication of the total synthesis of (+)-polyanthellin A (**89**) by the Kim group,[45] Johnson *et al*. reported this synthesis in 15 steps from methallyl alcohol (Figure 11).[48] The hydroisobenzofuran core was formed by a [2+3] cycloaddition reaction and a ring-closing metathesis reaction afforded the oxonane ring.

[48] Campbell, M. J.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 10370.

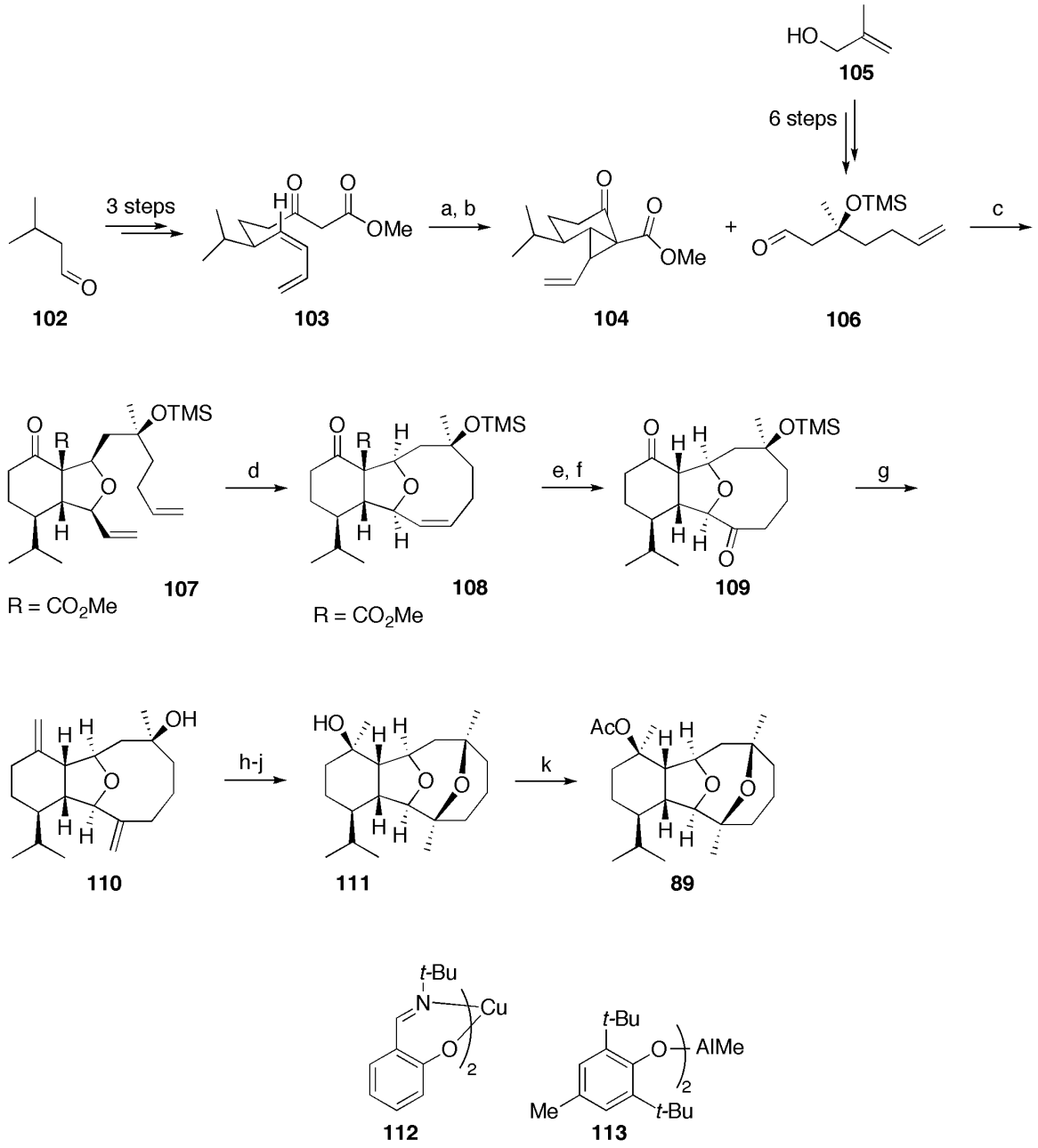


(+)-polyanthellin A
89

Figure 11. Johnson's approach.

The ß-ketoester **103** was prepared from 3-methylbutanal **102** (Scheme 15). Intramolecular cyclopropanation of **103** in presence of iodine, triethylamine and magnesium perchlorate as Lewis acid failed.[49] The problem was circumvented by the use of a two-step sequence involving an intermediate diazo compound. Intramolecular copper-catalysed cyclopropanation of **103** delivered compound **104** in 78% yield. The cycloaddition reaction between the aldehyde **106,** which was obtained in 6 steps from methallyl alcohol **105,** and the cyclopropane **104** failed to proceed in presence of a conventional Lewis acid. It was found that the sterically hindered $MADNTf_2$ catalyst **113** was able to drive the reaction and the desired product **107** was afforded in 76% yield. Ring-closing metathesis using the Grubbs II catalyst delivered the nine-membered ring **108**. Removal of the ester function under Krapcho conditions[50] led only to the *cis*-5,6-ring junction. Hydroboration and TPAP oxidation formed the ketone **109** selectively. Double Wittig olefination and cleavage of the silyl ether delivered the dienol **110**, and this compound was then subjected to a sequential iodoetherification, oxymercuration and radical reduction to deliver a mixture of diastereomers (6:1) **111**. Finally, acetylation and separation of diastereomers provided (+)-polyanthellin A (**89**). The total synthesis was realised in an overall yield of 3.1% in 15 linear steps from methallyl alcohol **105**.

[49] Yang, D.; Gao, Q.; Lee, C. -S.; Cheung, K. -K. *Org. Lett.* **2002**, *4*, 3271.
[50] Krapcho, A. P.; Glynn, G. A.; Grenon, B. J. *Tetrahedron Lett.* **1967**, *8*, 215.

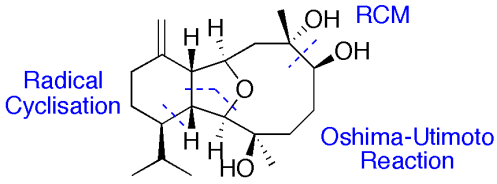


a) *p*-$AcHNC_6H_4SO_2N_3$, Et_3N, MeCN; b) **112** (4 mol%), C_6H_6, reflux, 71% (2 steps); c) **113** (15 mol%), $HNTf_2$ (10 mol%), CH_2Cl_2, −30 °C, 76%; d) Grubbs II (10 mol%), CH_2Cl_2 80 °C, 70%; e) NaBr, DMF, 120 °C, 76%; f) *i*. BH_3•THF, Et_2O, rt, *ii*. NMO, 4 Å MS, CH_2Cl_2, *iii*. TPAP, 49%; g) *i*. $MePPh_3Br$, NaHMDS, C_7H_8, 80 °C, *ii*. THF, HCl 1M, 90%; h) I_2, $NaHCO_3$, 4 Å MS, MeCN; i) $Hg(OAc)_2$, acetone/H_2O (1:1); j) Bu_3SnH, AIBN, C_6H_6, 60 °C, 55% (3 steps); k) Ac_2O, DMAP, Et_3N, CH_2Cl_2, rt, 73%.

Scheme 15. Total synthesis of (+)-polyanthellin A (**89**) by the Johnson group.[48]

2.8 Morken: Oshima-Utimoto Reaction, Radical Cyclisation and Ring-Closing Metathesis

The total synthesis of (−)-sclerophytin A had been previously described by various research teams, but in 2010 Morken *et al*. reported the shortest total synthesis of this compound in 13 steps and 2.7% overall yield.[51] The key components to the strategy involved palladium-catalysed coupling to form the furan ring and radical cyclisation to construct the hydroisobenzofuran core (Figure 12). Finally, a ring-closing metathesis reaction delivered the oxonane ring system.



(−)-sclerophytin A
3

Figure 12. Morken's approach.

The synthesis started with Brown methallylation of geranial **114** leading to the (*E*)-allylic alcohol **115** with 98% *ee* (Scheme 16). Oshima-Utimoto reaction[52] delivered the cyclic acetal **116** as a mixture of epimers in 62% yield. Jones oxidation and α-iodination allowed the formation of **117** which upon stereoselective radical cyclisation (>10:1 in presence of indium chloride and sodium borohydride) and reduction of the corresponding lactone afforded lactol **118**. Ketone **119** was then formed through a three-steps sequence. Acylation of the alcohol, displacement with cyanide in presence of scandium triflate and addition of butenylmagnesium chloride led to the formation of ketone **119**. Ring-closing metathesis, catalysed by the Grubbs II catalyst, provided the oxonane **120**. Epoxidation with *m*-chloroperbenzoic acid gave a 1.8:1 mixture of the α- and ß-stereoisomers **121**. The mixture was treated successively under basic and acidic conditions and in this way only stereoisomer **122** was isolated in 88% yield. A final reaction with methylmagnesium chloride was required to deliver (−)-sclerophytin A (**3**).

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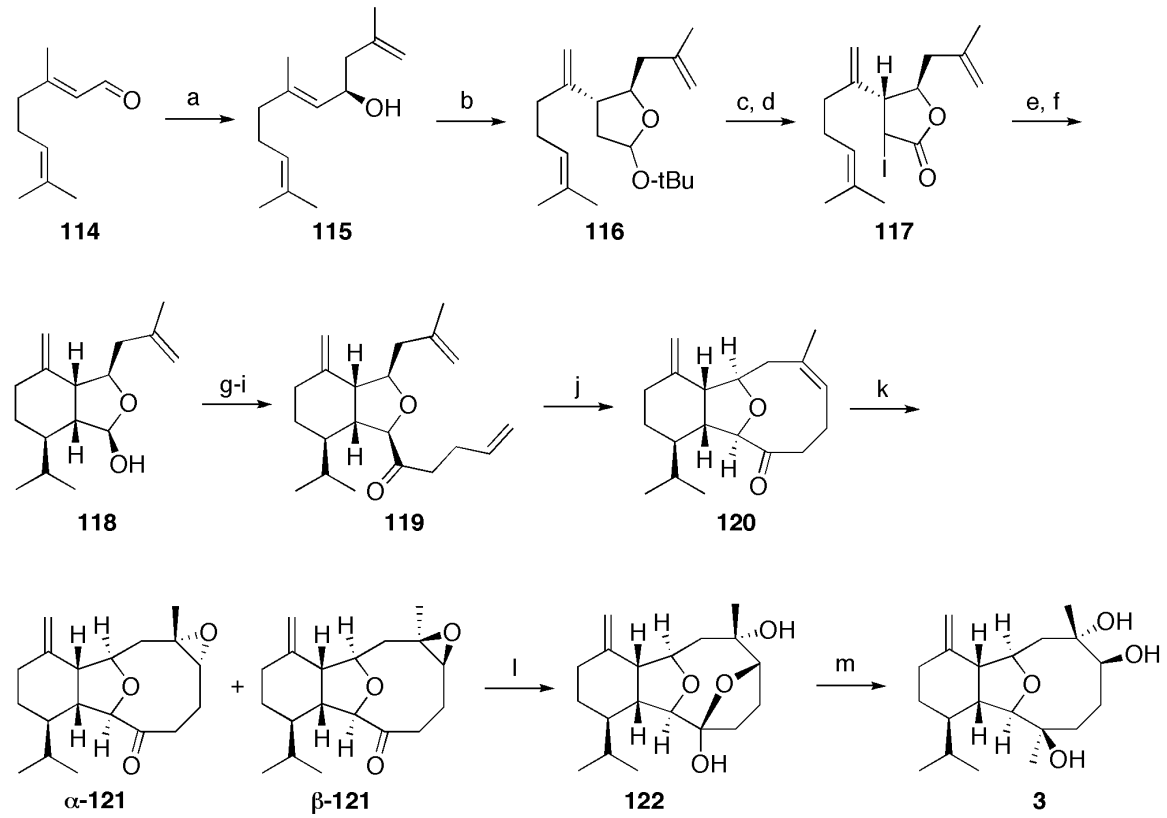
[51] Wang, B.; Ramirez, A. P.; Slade, J. J.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 16380.
[52] Evans, M. A.; Morken, J. P. *Org. Lett.* **2005**, *7*, 3367.



a) Brown methallylation, 92%, 98% *ee*; b) $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$, CH_2=CHO*t*-Bu, MeCN, reflux, 62%; c) H_2CrO_4, acetone, 0 °C, 64%; d) LDA, I_2, THF, −78 °C, 87%; e) $InCl_3$, $NaBH_4$, MeCN, −78 °C to rt, 56%; f) DIBAL-H, CH_2Cl_2, −78 °C, 85%; g) Ac_2O, DMAP, Et_3N, CH_2Cl_2, −45 °C; h) $Sc(OTf)_3$, TMSCN, MeCN, −22 °C, 67% (2 steps); i) CH_2=$CHCH_2CH_2MgBr$, C_6H_6, 40 °C, 78%; j) Grubbs II (10 mol%), C_6H_6, reflux, 55%; k) *m*-CPBA, $CHCl_3$, −12 °C, 68%; l) LiOH, H_2O, dioxane, then $KHSO_4$, $Sc(OTf)_3$, MeCN, rt, 88%; m) MeMgCl, THF, 52 °C, >99%.

Scheme 16. Total synthesis of (−)-sclerophytin A (**3**) completed by the Morken group.[51]

2.9 Yang: Gold-Catalysed Cascade Reaction and Ring-Closing Metathesis

In 2014, the Yang research group reported a new synthetic strategy to form cladiellin natural products based on a gold-catalysed cascade reaction and ring-closing metathesis (Figure 13).[53] They were able to use this strategy to synthesise 9 natural products.

[53] Yue, G.; Zhang, Y.; Fang, L.; Li, C.; Luo, T.; Yang, Z. *Angew. Chem. Int. Ed.* **2014**, *53*, 1837.

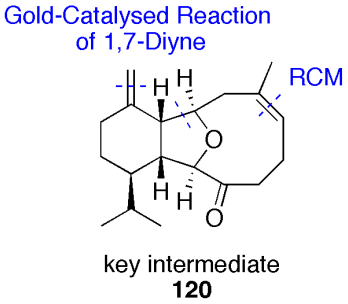
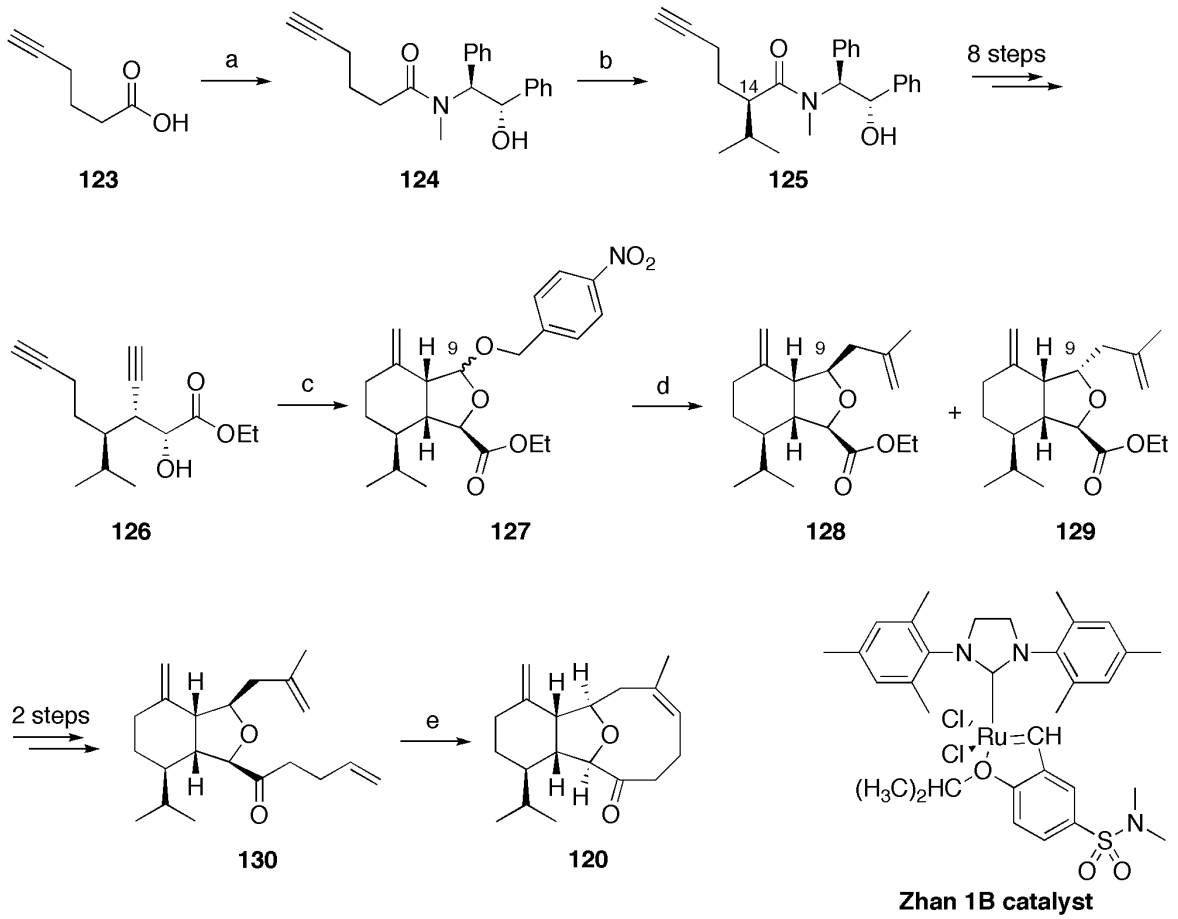


Figure 13. Yang's approach.

Commercially available hex-5-ynoic acid **123** was first coupled with a chiral auxiliary to form amide **124**. Subsequent diastereoselective α-alkylation installed the isopropyl group found at the C-14 of the cladiellin compounds **125**. A further 8 steps were required to obtain the precursor for the gold-catalysed reaction **126**. The 1,7-diyne, in the presence of an excess of *p*-nitrobenzyl alcohol and a gold catalyst, underwent a cascade reaction delivering the 6,5-bicyclic core **127** of the cladiellins. The resulting diastereomeric mixture was treated with (methylallyl)trimethylsilane and trimethylsilyl trifluoromethane-sulfonate, and the two epimers **128** and **129** were separated. Ester **128** was transformed into the ring-closing metathesis precursor **130** by Weinreb amide formation and Grignard reaction. Finally, formation of the oxonane was performed by exposure to the Zhan metathesis catalyst[54] and key intermediate **120** was isolated in 70% yield.

[54] a) Zhan, Z. -Y. US Patent, 20070043180A1, **2007**; b) Zhan, Z. -Y., WO Patent, 003135A1, **2007**.

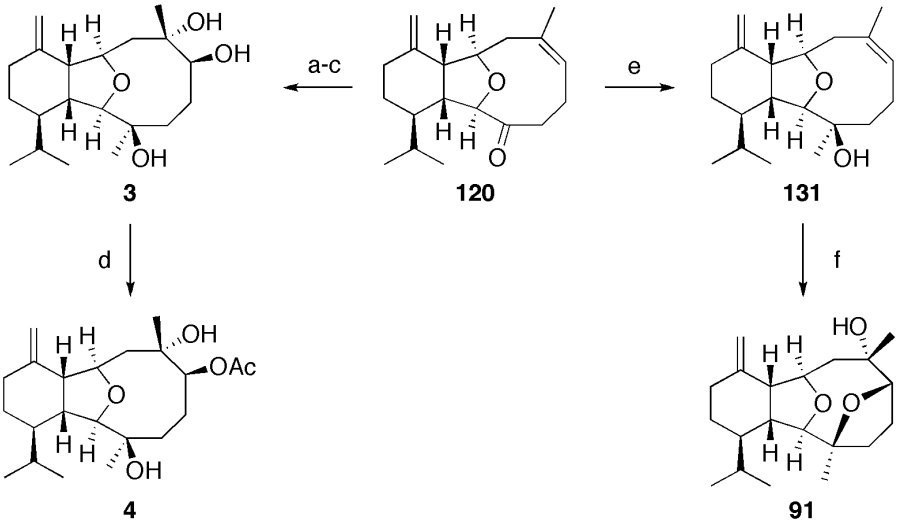


a) EDCI, *t*-BuOH, (−)-(1*S*,2*S*)-pseudoephenamine, DIPEA, DMF, rt, 90%; b) LiCl, LDA, isopropyl iodide, THF, −78 °C to rt, 86%; c) [(IPr)AuCl] (5 mol%), $AgSbF_6$ (5 mol%), *p*-$NO_2C_6H_6CH_2OH$, CH_2Cl_2, rt, 65%; d) TMSOTf, methylallyl trimethylsilane, MeCN, −40 °C to rt, 60% of **128** and 20% of **129**; e) Zhan 1B catalyst (10 mol%), $PhCH_3$, reflux, 70%.

Scheme 17. Synthesis of intermediate **120**.[53]

Applying known reaction conditions to this intermediate **120**,[11,44,48,55] Yang *et al*. prepared four natural products: (−)-sclerophytin A (**3**) and B (**4**), (+)-cladiella-6*Z*,11(17)-dien-3-ol (**131**) and (+)-vigulariol (**91**) (Scheme 18).

[55] Clark, J. S.; Berger, R.; Hayes, S. T.; Senn, H. M.; Farrugia, L. J.; Thomas, L. H.; Morrison, A. J.; Gobbi, L. *J. Org. Chem.* **2013**, *78*, 673.

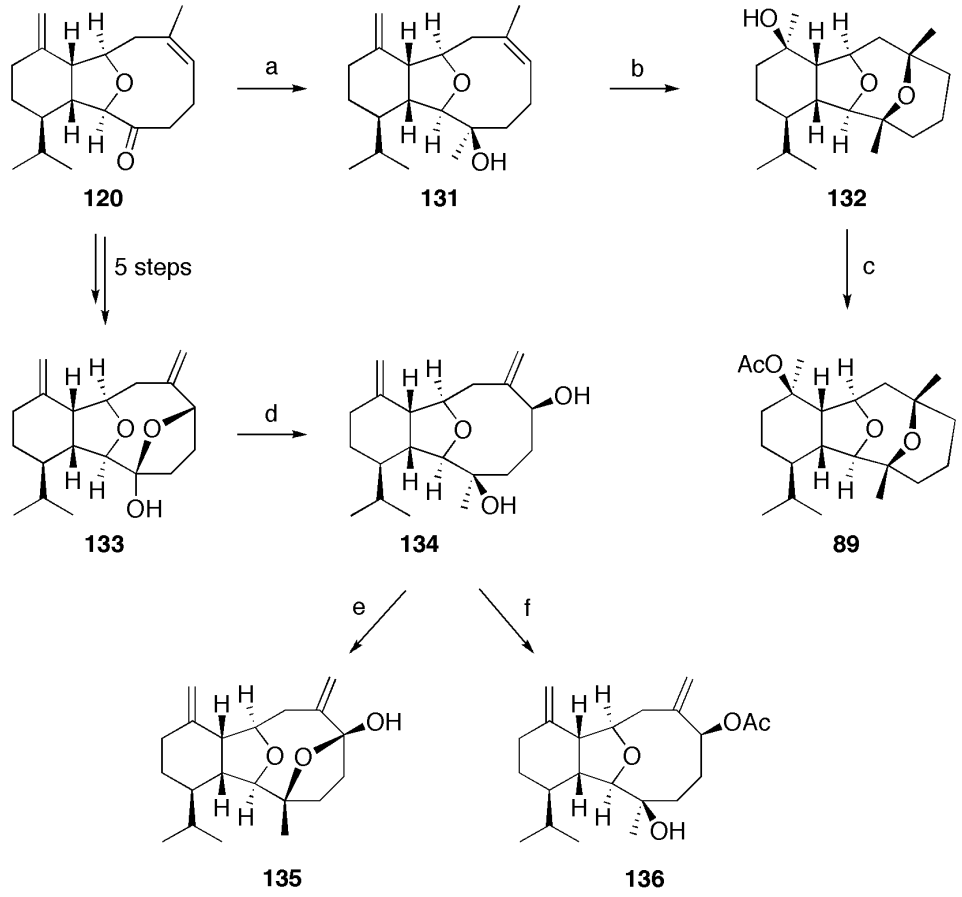


a) *m*-CPBA, CH_2Cl_2, −12 °C; b) LiOH, dioxane, H_2O, then $KHSO_4$, $Sc(OTf)_3$, MeCN, H_2O, rt; c) MeMgCl, THF, 52 °C, 37% (3 steps); d) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C, 78%; e) MeMgCl, THF, 0 °C, 80%; f) *m*-CPBA, CH_2Cl_2, 0 °C (51%).

Scheme 18. Completion of the total syntheses of four cladiellins by the Yang group.[53]

Five other cladiellin natural products were also synthesised from the key intermediate **120** (Scheme 19). Methyl addition using methylmagnesium chloride delivered (+)-cladiella-6*Z*,11(17)-dien-3-ol (**131**) which was transformed into (+)-deacetylpolyanthellin A (**132**) by a double oxymercuration reaction followed by reduction. Acetylation of the alcohol **132** afforded (+)-polyanthellin A (**89**).

The final 3 natural products were obtained from intermediate **133** that was prepared from **120** in 5 steps. Treatment of the hemiketal **133** with methylmagnesium chloride delivered (−)-cladiellisin (**134**) as a single diastereomer. Acetylation led to the formation of (−)-pachycladin C (**136**), while oxidation with manganese oxide revealed (−)-pachycladin D (**135**).



a) MeMgCl, THF, 0 °C, 80%; b) *i*. $Hg(OAc)_2$, THF, rt, *ii*. H_2O, $Hg(OAc)_2$, *iii*. BEt_3, $NaBH_4$, −20 °C to rt, 52%; c) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 62%; d) MeMgCl, $PhCH_3$, 100 °C, 93%; e) MnO_2, CH_2Cl_2, rt, 83%; f) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C, 88%.

Scheme 19. Completion of the total syntheses of five cladiellins by the Yang group.[53]

2.10 Clark: Oxonium Ylide and Rearrangement

After various studies towards the synthesis of the cladiellin family compounds[56], Clark *et al*. completed the racemic total synthesis of vigulariol in 2007 (Figure 14).[57] The synthetic strategy involved reductive cyclisation to form the furan ring system. A [2,3]-sigmatropic rearrangement reaction was used to build the five- and nine-membered rings of the tricyclic core and an intermolecular Diels-Alder cycloaddition reaction installed the cyclohexane ring.

[56] a) Clark, J. S.; Wong, Y. S. *Chem. Commun*. **2000**. 1079; b) Clark, J. S.; Winfield, L. J.; Wilson, C.; Blake A. J. *Synlett*, **2006**, *14*, 2191.
[57] Clark, J. S.; Hayes, S. T.; Wilson, C.; Gobbi, L. *Angew. Chem. Int. Ed*. **2007**, *46*, 437.

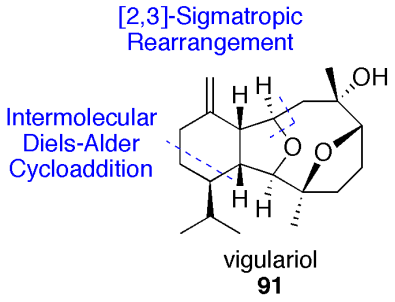


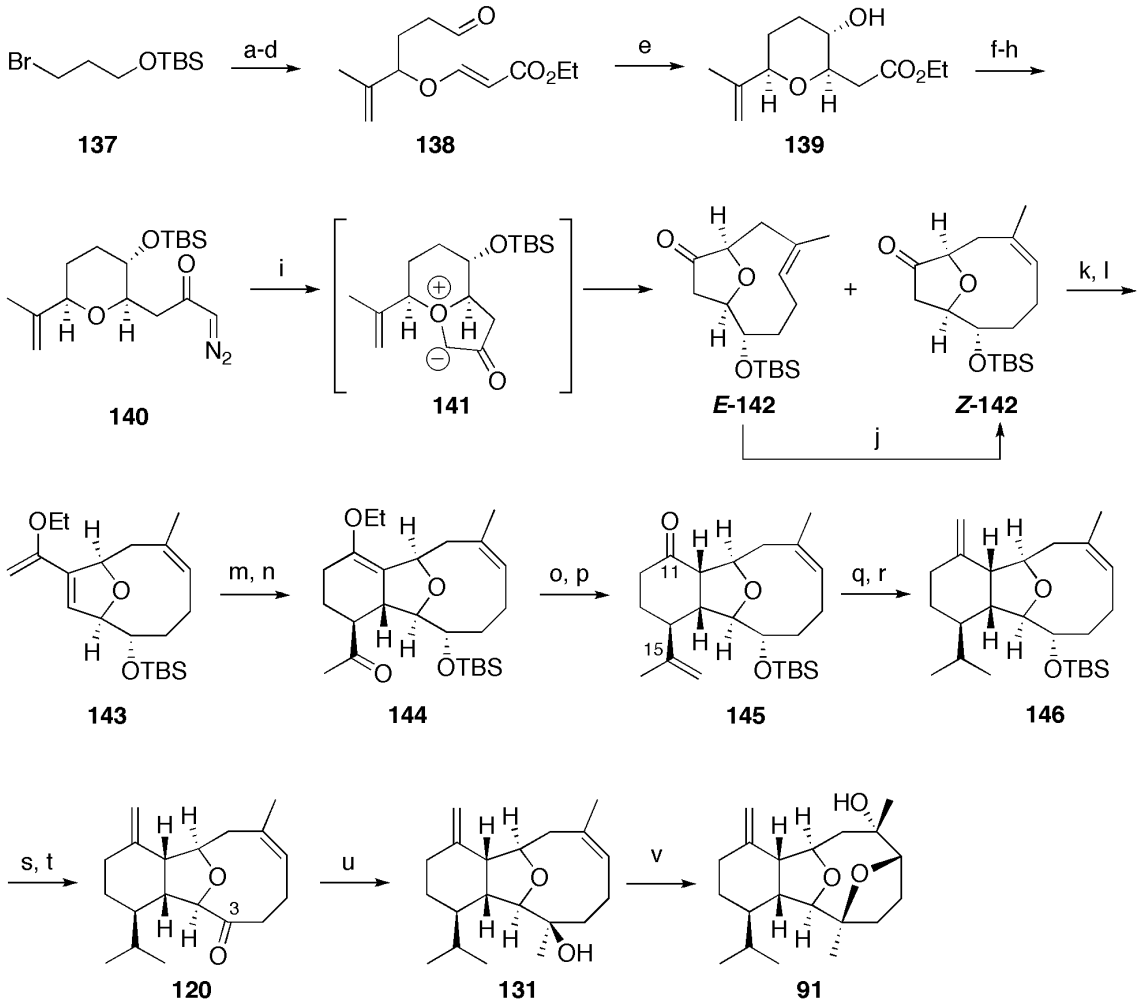
Figure 14. Clark's approach.

The synthesis started with reaction of acrolein with the Grignard reagent generated from the *tert*-butyldimethylsilyl protected bromopropanol **137** (Scheme 20). The allylic alcohol was *O*-alkenylated with ethyl propiolate. After cleavage of the silyl ether, the resulting alcohol was subjected to a Swern oxidation to afford aldehyde **138**. The stage was set for the first pivotal ring formation reaction. Samarium diiodide-mediated reductive cyclisation reactions have successfully been applied to the synthesis of a wide range of natural products with excellent yield and selectivity (see introduction, section 4). In this instance, the samarium-mediated reaction gave the tetrahydropyranol **139** with excellent diastereoselectivity. Protection of the hydroxyl group as a silyl ether and saponification of the ethyl ester delivered the carboxylic acid, which was transformed into a mixed anhydride prior to being converted into the diazoketone **140** by treatment with an excess of diazomethane. The reaction with $Cu(hfacac)_2$ in refluxing dichloromethane delivered the oxonium ylide **141** (or a metal-bound ylide equivalent) that underwent a [2,3]-sigmatropic rearrangement delivering a 5:1 mixture of *E*- and *Z*-isomers ***E*-142** and ***Z*-142** in high yield. The influence of the solvent on the reaction outcome was investigated but the *E*:*Z* ratio remained in favour of the formation of the *Z*-bicyclic ketone ***Z*-142**.[58] In the same way, the temperature of the reaction did not influence the isomer ratio significantly. The *E*-alkene ***E*-142** was converted into the desired *Z*-isomer ***Z*-142** in presence of azobisisobutyronitrile and ethanethiol in only 56% yield. Enol triflate formation and Stille cross-coupling delivered the unstable diene **143**, which was immediately subjected to a Diels-Alder cycloaddition reaction. This reaction produced a 2:1 mixture of *exo* and *endo* diastereoisomers. Luckily, treatment of the mixture with potassium

[58] Hayes, S. T., *PhD Thesis* University of Nottingham **2007**.

carbonate led to the epimerisation at the C-14 stereogenic centre adjacent to the carbonyl group and only the required ketone **144** was isolated. Wittig olefination formed the exocyclic alkene and hydrolysis of the enol ether afforded intermediate **145**. The isopropyl substituent was installed by regioselective hydrogenation of the exocyclic alkene. A second Wittig olefination reaction furnished the exocyclic alkene at C-11 found in many of the cladiellin natural products and delivered **146**. It is worth noting that while mild conditions (2 equivalents of phosphonium ylide at room temperature) were required for the transformation of the ketone into the alkene at C-15; the olefination at the C-11 position involved the use of 10 equivalents of ylide and high temperature (80 °C).

The next challenge was introduction of the methyl group at C-3. For this transformation, TBS removal and a Dess-Martin oxidation took place resulting in the formation of the ketone **120**. Addition of methyl magnesium chloride produced the tertiary alcohol **131** as a single diastereomer, also known as natural product (+)-cladiella-6*Z*,11(17)-dien-3-ol. Finally, the natural product was produced by a regio- and stereoselective alkene epoxidation and subsequent nucleophilic ring-opening of the epoxide with the tertiary hydroxyl group. The total synthesis of vigulariol (**91**) was completed in 20 steps and in 4.1% overall yield.



a) Mg, THF, reflux then methacrolein, rt, 90%; b) $HCCCO_2Et$, NMM, CH_2Cl_2, rt, 91%; c) TBAF, THF, rt, 91%; d) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C; then Et_3N, rt, 83%; e) SmI_2, MeOH, THF, rt, 76% dr>20:1; f) TBSCl, imidazole, DMF, rt, 91%; g) LiOH aq., MeOH, rt, 82%; h) *i*. i-BuO_2CCl, Et_3N, Et_2O, rt, *ii*. CH_2N_2, Et_2O, 0 °C to rt, 81%; i) $Cu(hfacac)_2$ (5 mol%), CH_2Cl_2, reflux, 96% 5:1 *Z*/*E*; j) AIBN, EtSH, C_6H_6, reflux, 56%; k) $PhN(O_2SCF_3)_2$, NaHMDS, THF, −78 °C; l) $CH_2C(OEt)SnBu_3$, LiCl, $Pd(PPh_3)_4$, THF, reflux; m) MVK, $PhCH_3$, reflux, 67% (3 steps); n) K_2CO_3, MeOH, rt, 87%; o) Ph_3PCH_2Br, *t*-BuOK, THF, rt, 85%; p) HCl (5% aq.), THF, rt, 86%; q) H_2, PtO_2, rt, 81%; r) Ph_3PCH_2, $PhCH_3$, reflux, 98%; s) TBAF, THF, rt, 84%; t) DMP, pyridine, CH_2Cl_2, rt; u) MeMgCl, THF, 0 °C, 89% (2 steps); v) *m*-CPBA, CH_2Cl_2, 0 °C, 69%.

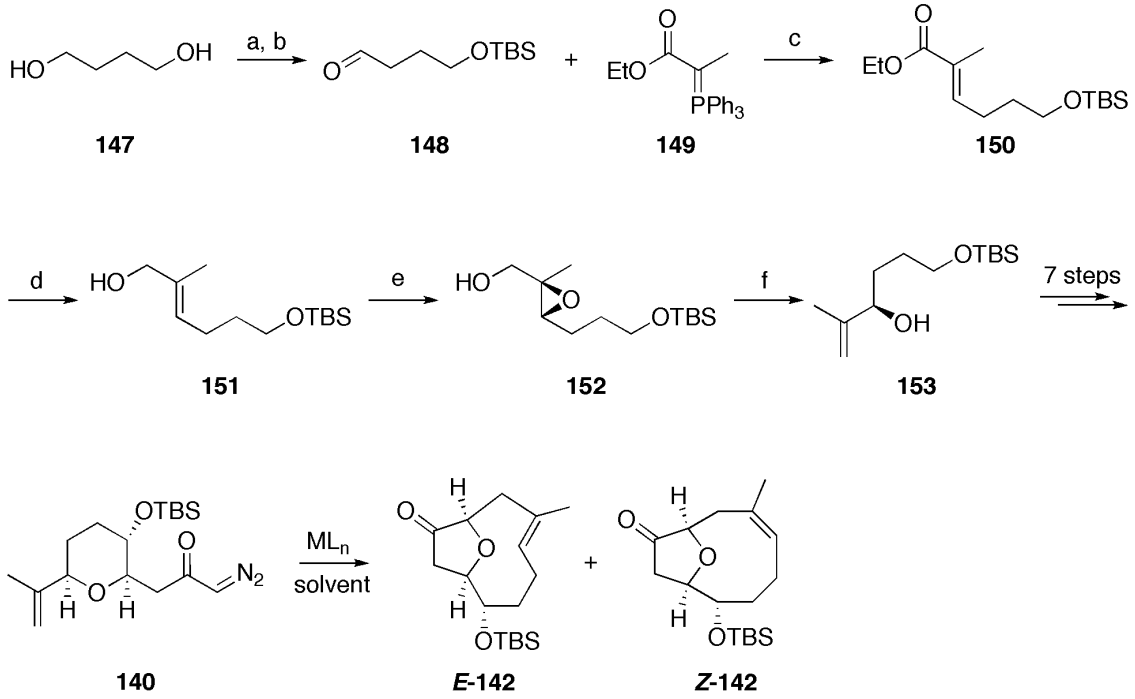
Scheme 20. Total synthesis of (±)-vigulariol (**91**) by Clark *et al*. [57]

Since then, Clark *et al*. developed an enantioselective synthesis of the cladiellin core ring system based on this route. This approach was used to synthesise 10 cladiellin natural products.[55,59]

The commercially available 1,4-butanediol **147** was selectively mono-protected as a silyl ether and the remaining free hydroxyl was oxidised into aldehyde **148**. Wittig olefination with the stabilized ylide **149** delivered the α,ß-unsaturated

[59] Clark, J. S.; Berger, R.; Hayes, S. T.; Thomas, L. H.; Morrison, A. J.; Gobbi, L. *Angew. Chem. Int. Ed.* **2010**, *49*, 9867.

ester **150** which was subsequently reduced into the allylic alcohol **151**. Sharpless asymmetric epoxidation installed the stereocentre with 94% *ee*. Mesylation of the hydroxyl group **152** and treatment with sodium iodide and zinc powder furnished the allylic alcohol **153**. The diazoketone **140** was obtained in 7 steps from the enantio-enriched allylic alcohol **153** by following the route used in the synthesis of (±)-vigulariol (**91**).



a) TBSCl, Et_3N, CH_2Cl_2, rt, 90%; b) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, rt; c) **153**, THF, rt, 95% (2 steps); d) DIBAL-H, CH_2Cl_2, −78 °C, 94%; e) (−)-DET, Ti(O*i*-Pr)$_4$, *t*-BuO_2H, CH_2Cl_2, −25 °C, 95%; f) *i*. MsCl, Et_3N, CH_2Cl_2, −10 °C, *ii*. NaI, butanone, reflux, then, Zn powder, 97% (2 steps).

Scheme 21. Enantioselective synthesis of the *E*- and *Z*-bridged bicyclic ether **142** by Clark *et al*.[55]

Additional studies on the catalytic oxonium ylide formation and [2,3]-sigmatropic rearrangement reaction demonstrated that the choice of the catalyst, the solvent and the temperature of the reaction influence the yields and the diastereoselectivity significantly (Table 1). While the use of a copper complex gave a mixture of *E* and *Z* isomers in favour of the less strained bicyclic ketone ***Z*-142** (entries 1-5), it appeared that the diastereoselectivity was reversed in presence of a rhodium catalyst affording the *E*-isomer as the major product (entries 8-12). Therefore, it was possible to tune the reaction towards

the synthesis of the *E* or the *Z* alkene selectively.[55,59,60] Indeed, the use of the copper catalyst $Cu(hfacac)_2$ in refluxing dichloromethane (entry 3) or tetrahydrofuran (entry 4) furnished the *Z*-bicyclic ketone ***Z*-142** selectively with *Z*:*E* ratios of a 5.0:1 and 6.9:1 respectively, while the rhodium catalyst $Rh_2(tpa)_4$ in refluxing DCE (entry 12) delivered a 1:6.3 mixture of ***Z*-142** and ***E*-142** in 53% yield. The use of different solvents also influenced the yield and the isomer ratio (entries 2, 4, 5, 10-12).

Entry	Catalyst [a]	Solvent	Temp.	Time	Yield [b] (%)	Ratio *Z*:*E* [c]
1	$Cu(acac)_2$	CH_2Cl_2	reflux	3 h	30	3.5:1
2	$Cu(hfacac)_2$	CH_2Cl_2	reflux	15 min	95	5.0:1
3	$Cu(hfacac)_2$	CH_2Cl_2	rt	3 h	94	5.9:1
4	$Cu(hfacac)_2$	THF	reflux	45 min	74	6.9:1
5	$Cu(hfacac)_2$	MeCN	reflux	2 h	78	1.3:1
6	$Rh_2(OAc)_4$	CH_2Cl_2	reflux	1 h	52	1.2:1
7	$Rh_2(tfa)_4$	CH_2Cl_2	reflux	25 min	90	1.7:1
8	$Rh_2(tfacam)_4$	CH_2Cl_2	reflux	15 min	63	1:1.2
9	$Rh_2(pfm)_4$	CH_2Cl_2	reflux	15 min	71	1:2.7
10	$Rh_2(tpa)_4$	CH_2Cl_2	reflux	15 min	63	1:4.3
11	$Rh_2(tpa)_4$	THF	rt	18 h	32	1.4:1
12	$Rh_2(tpa)_4$	DCE	reflux	15 min	56	1:6.3

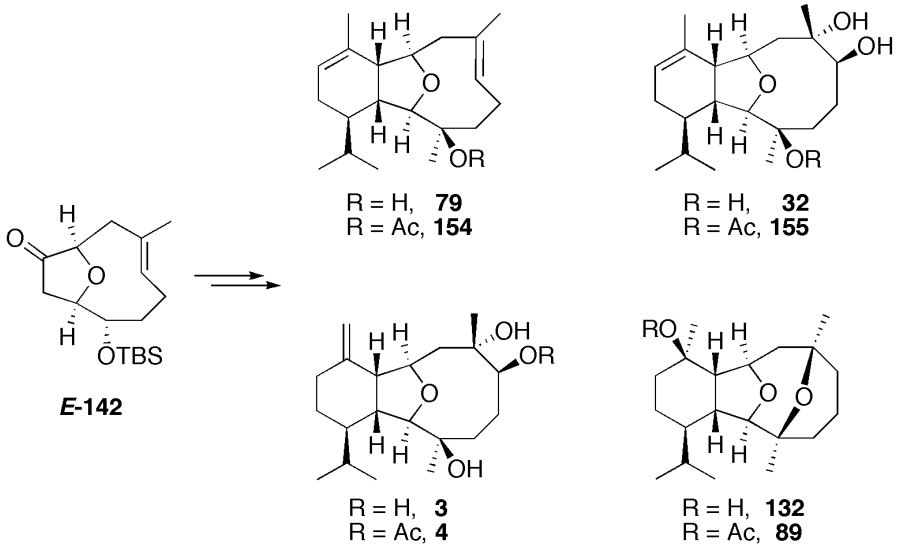
[a] Catalyst loading 5 mol%; [b] Isolated yield of *Z* and *E* isomers; [c] Isomeric ratio determined by ^1H NMR analysis on the crude mixture of isomers.

Table 1. Previous studies on metal-catalyzed reactions of diazoketone **140** to give bridged-bicyclic ethers ***E*-142** and ***Z*-142**.

The intermediate *Z*-bridged bicyclic ether ***Z*-142** led to the formation of (+)-cladiella-6*Z*,11(17)-dien-3-ol (**131**) and (+)-vigulariol (**91**) following the synthetic pathway described in the racemic synthesis of the natural product (Scheme 20). Further synthetic manipulations transformed the *E*-isomer ***E*-142** into another 8 cladiellin natural products (Scheme 22): (−)-cladiella-6,11-dien-3-ol (**79**), (−)-3-acetoxycladiella-6,11-diene (**154**), (−)-cladiell-11-ene-3,6,7-triol (**32**), (−)-3-acetoxycladiell-11-ene-6,7-diol (**155**), (−)-sclerophytin A (**3**), (−)-

[60] Berger, R. *PhD Thesis* University of Glasgow, **2010**.

sclerophytin B (**4**), (+)-deacetylpolyanthellin A (**132**) and (+)-polyanthellin A (**89**).



Scheme 22. Cladiellin natural products synthesised by Clark *et al.*[55]

The *E*-bicyclic ketone was converted into the tricyclic core **156** by sequential enol triflate formation, Stille coupling, Diels-Alder cycloaddition and epimerisation. Wittig olefination and hydrolysis of the enol ether delivered the exocyclic alkene **157**. Attempted selective hydrogenation as well as hydroboration failed to install the isopropyl group and to deliver ketone **158**. Consequently, a reaction sequence used in Kim's approach to the total synthesis of cladiellin natural product was employed.[45] Methyl addition to ketone **156** produced the tertiary alcohol **159** which, after acetylation, was cleaved under reduction conditions to form the isopropyl group on **160** in good overall yield.[61] Hydrolysis of the enol ether and protection of the tertiary alcohol revealed the ketone **161**. Kinetic enol triflate formation and a Kumada-type coupling reaction[62] with methylmagnesium chloride produced the diene **162**. Removal of the TBS group, oxidation of the resulting alcohol and addition of methyllithium furnished (−)-cladiella-6,11-dien-3-ol (**79**).

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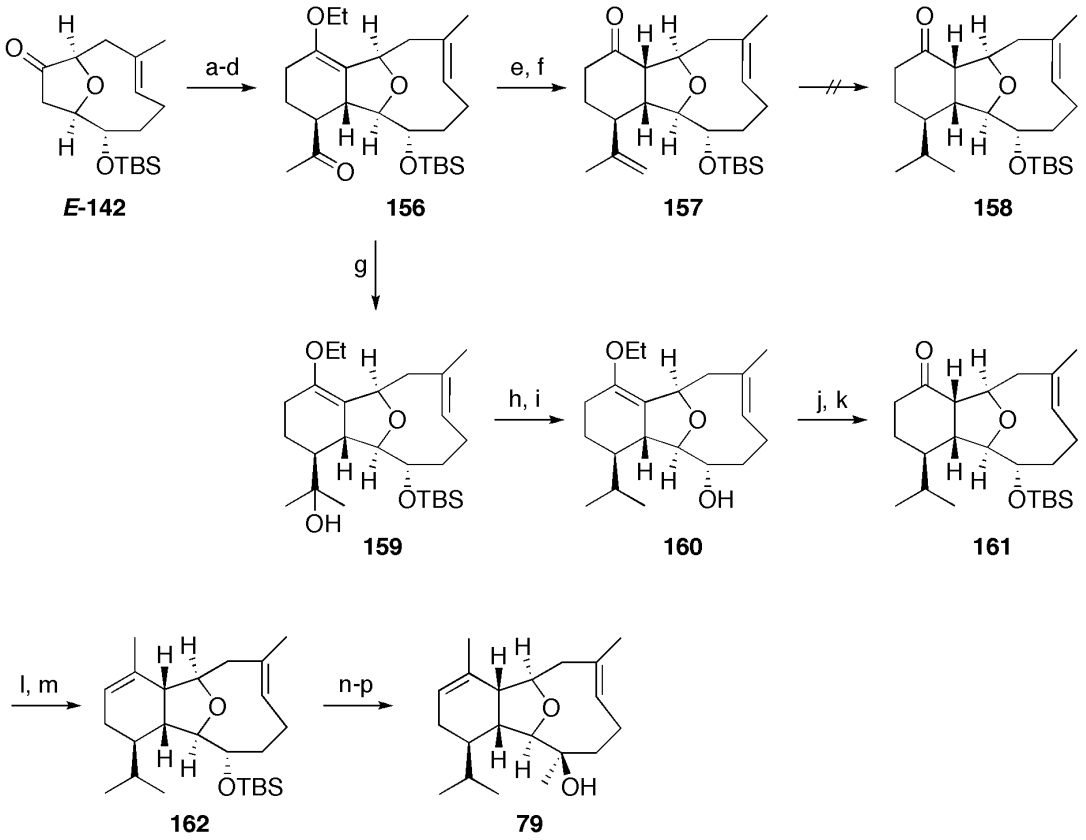
[61] Barett, A. G. M.; Godfrey, C. R. A.; Hollinshead, D. M.; Prokopiou, P. A.; Barton, D. H. R.; Boar, R. B.; Joukhadar, L.; McGhie, J. F.; Misra, S. C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1501.
[62] a) Ruprah, P. K.; Cros, J. -P.; Pease, J. E.; Wittingham, W. G.; Williams, J. M. J. *Eur. J. Org. Chem.* **2002**, 3145; b) Giuffredi, G.; Bobbio, C.; Gouverneur, V. *J. Org. Chem.* **2006**, *71*, 5361.

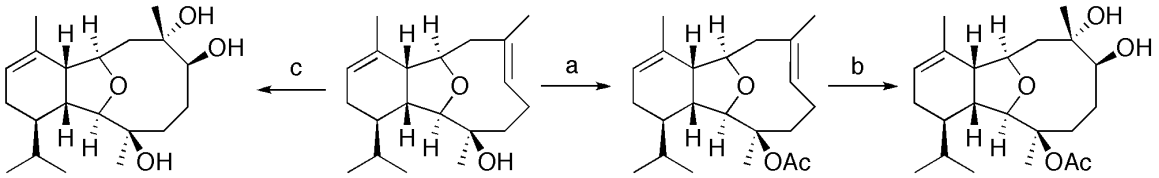


***E*-142** **156** **157** **158** **159** **160** **161** **162** **79**

a) NaHMDS, $PhN(Tf)_2$, THF, −78 °C; b) $CH_2C(OEt)SnBu_3$, $Pd(PPh_3)_4$, LiCl, THF, reflux; c) MVK, $PhCH_3$, 130 °C, 68% (3 steps); d) K_2CO_3, MeOH, rt, 85%; e) Ph_3PCH_3Br, NaHMDS, THF, rt, 80%; f) 1M HCl aq., THF, rt, 87%; g) MeMgBr, THF, 0 °C to rt, 78%; h) Ac_2O, Et_3N, DMAP, 40 °C; i) K, *t*-$BuNH_2$, 18-crown-6, THF, rt, 65% (2 steps); j) HCl aq. THF, rt, 89%; k) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 78%; l) NaHMDS, $PhN(Tf)_2$, THF, −78 °C; m) MeMgCl, $Pd(PPh_3)_4$, LiCl, THF, rt; n) TBAF, THF, rt, 68% (3 steps); o) DMP, pyridine, CH_2Cl_2, rt; p) MeLi, $NaBF_4$, THF, −78 °C, 69% (2 steps).

Scheme 23. Total synthesis of (−)-cladiella-6,11-dien-3-ol (**79**) by Clark *et al.*[55]

This alcohol **79** was used to prepare 3 other natural products (Scheme 24). Acetylation at the C-3 hydroxyl group furnished (−)-3-acetoxycladiella-6,11-diene (**154**). Subsequent dihdroxylation afforded (−)-3-acetoxycladiell-11-ene-6,7-diol (**155**). Finally, a last natural product was obtained from diene **79** by its dihydroxylation that delivered (−)-cladiell-11-ene-3,6,7-triol (**32**) as a single diastereomer in 66% yield.

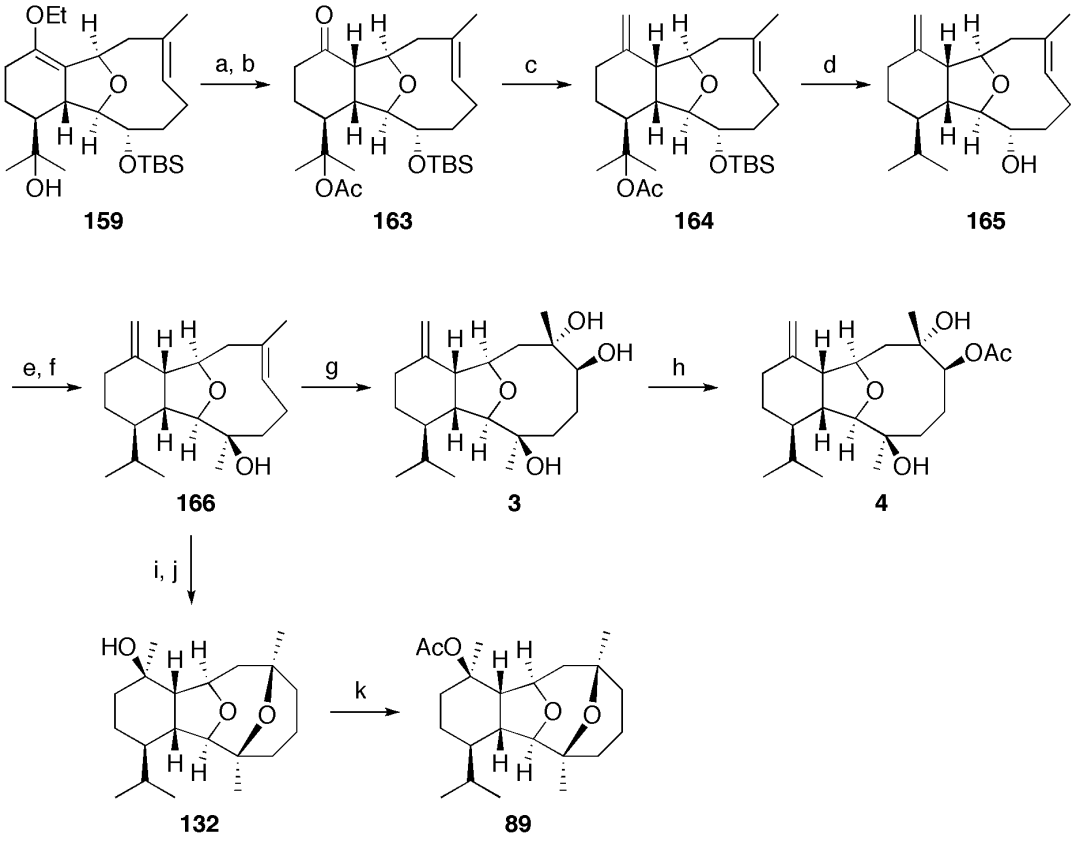


a) Ac_2O, Et_3N, DMAP, 40 °C, 25%; b) OsO_4, NMO, THF, H_2O, 0 °C to rt, 36%; c) OsO_4, NMO, THF, H_2O, 0 °C to rt, 66%.

Scheme 24. Total syntheses of (−)-3-acetoxycladiella-6,11-diene (**154**), (−)-3-acetoxycladiell-11-ene-6,7-diol (**155**) and (−)-cladiell-11-ene-3,6,7-triol (**32**) by Clark *et al*.[55]

Following the successful completion of the total syntheses of members of the cladiellin family having an endocyclic alkene at C-11–C-12, the Clark group reported the total syntheses of members possessing an exocyclic alkene at C-11–C-20.

The isopropyl group was installed by acetylation and deoxygenation of the tertiary alcohol, following a Wittig olefination on ketone **163**. The common intermediate **166** allowed the synthesis of (−)-sclerophytin A (**3**) by dihydroxylation. Acetylation of the latter led to (−)-sclerophytin B (**4**). A two steps-sequence from tertiary alcohol **166** afforded (+)-deacetylpolyanthellin A (**132**) and (+)-polyanthellin A (**89**) after acetylation of the tertiary alcohol.



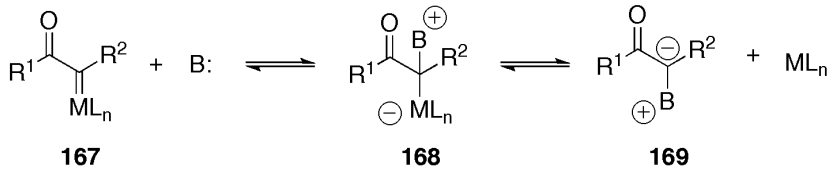
a) Ac_2O, DMAP, Et_3N, 40 °C; b) 1M HCl aq., THF, rt; c) Ph_3PCH_3Br, NaHMDS, THF, reflux, 60% (3 steps); d) K, *t*-$BuNH_2$, 18-crown-6, THF, rt, 78%; e) DMP, pyridine, CH_2Cl_2, rt; f) MeLi, $NaBF_4$, THF, −78 °C, 78% (2 steps); g) OsO_4, NMO, THF aq. 0 °C to rt, 59%; h) Ac_2O, DMAP, Et_3N, CH_2Cl_2, 0 °C, 79%; i) $CH_3C(CH_2)OAc$, TsOH, rt, 90 %; j) $Hg(OAc)_2$, THF, H_2O, rt, then Et_3B, $NaBH_4$, THF, H_2O, −20 °C, 77%; k) Ac_2O, DMAP, Et_3N, rt, 55%.

Scheme 25. Total syntheses of (−)-sclerophytin A (**3**) and B (**4**), (+)-deacetylpolyanthellin A (**132**) and (+)-polyanthellin A (**89**) by Clark *et al.*[55]

The route developed within the Clark group proved its efficiency with regard to the synthesis of cladiellin natural products in high yield. That is why this synthetic approach would be used as the basis for the total synthesis of the proposed structure of sclerophytin F.

3 Oxonium Ylide Formation and [2,3]-Sigmatropic Rearrangement

The interaction of an electron-deficient metal carbenoid intermediate **167** with a lone pair of electrons from a Lewis basic atom (Scheme 26), such as nitrogen, oxygen or sulfur, results in the formation of an ylide. The latter can be defined as a metal complex-associated ylide **168** or as a –"free"- ylide **169**.



167 **168** **169**

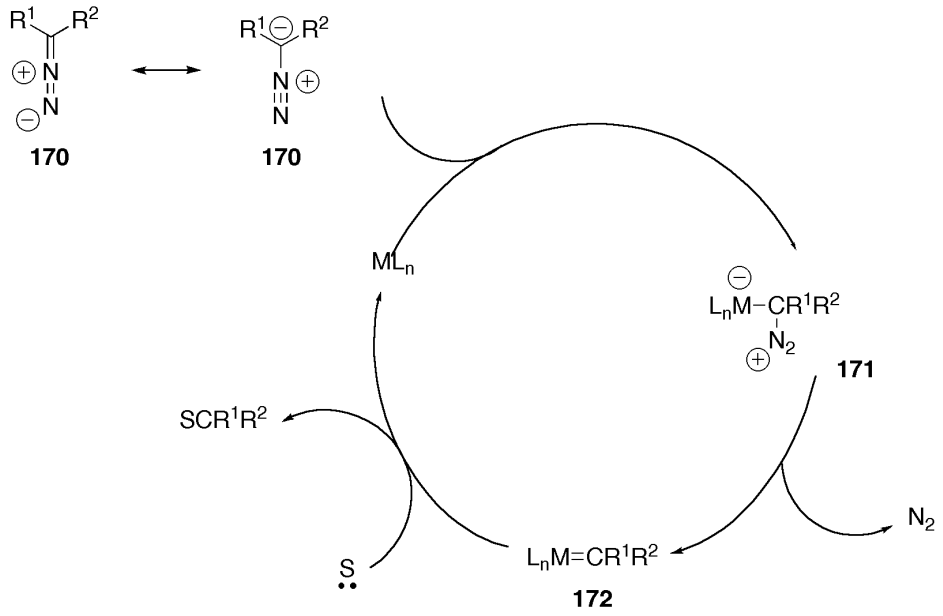
Scheme 26. Mechanism of ylide formation.

3.1 Metal Carbenes or Carbenoids

Generated from the decomposition of diazo compounds with transition metals, metal carbenoids are usually more stable and longer lived than "free" carbenes. Although they are stabilised by the formation of a complex with a transition metal, metal carbenoids remain highly reactive. Consequently, high yields and good to excellent selectivities are affordable *via* metal carbenoid

mediated transformations and multiple synthetic transformations result from the use of these intermediates.[63]

Mechanistically, the generally accepted scheme for the catalytic decomposition of diazo compounds starts with the nucleophilic addition of the diazo compound **170** to the metal complex ML_n to form the diazonium ion **171** (Scheme 27). Subsequent loss of nitrogen gas generates the metal-stabilised carbene or metal carbenoid intermediate **172**. Finally, transfer of the electrophilic carbene to an electron-rich substrate "S:" regenerates the metal complex and completes the catalytic cycle.



Scheme 27. Catalytic decomposition of diazo compounds.[63a]

Studies concerning metal-catalysed decomposition of the diazo compounds demonstrated that the diazonium ion intermediate **171** is formed thanks to spectroscopic analysis of reactions involving a iodorhodium(III) tetra-*p*-

[63] Reviews on metal carbenoid reactions: a) Doyle, M. P. *Chem. Rev.* **1986**, *86*, 919; b) Adams, J.; Spero, D. M. *Tetrahedron* **1991**, *47*, 1765; c) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385; d) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091; e) Padwa, A.; Austin, D. J. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1797; f) Doyle, M. P.; McKervey, M.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley: New York, **1998**; g) Clark, J. S. *Nitrogen, Oxygen and Sulfur Ylide Chemistry*; Oxford University Press: New York, **2002**; h) Merlic, C. A.; Zechman, A. L. *Synthesis* **2003**, 1137; i) Zhang, Z.; Wang, J. *Tetrahedron* **2008**, *64*, 6577.

tolylporphyrin complex; [64] and spectroscopic and X-ray analysis of an intermediate (porphyrinatorhodium)-diaminocarbene complex confirmed the formation of a metal-stabilised carbene **172**.[65]

Effective transition metals for the conversion of diazo compounds into metal carbenoids are Lewis acidic in character. Coordinative unsaturation at the metal centre allows them to react as electrophiles with diazo compounds. The stability and the reactivity of the resulting metal carbenoids depend on the degree of π back-donation from the metal to the carbene. The ligand-metal combination influences significantly the regio-, the chemo- and the stereo-selectivity of the reaction.

Since the first reported metal-catalysed reaction of a diazo compound with copper dust in 1906,[66] copper had remained the metal of choice despite the development of diverse ligands until 1973, when rhodium(II) acetate dimer was found to be a highly efficient catalyst for the decomposition of diazocarbonyl compounds.[67] So far, great advances have been made in the field and a wide variety of transition metals such as cobalt, palladium, platinium, rhodium, ruthenium, nickel, zinc, chromium, molybdenum, iron and osmium have been used for catalytic decomposition of diazo compounds. In addition, catalysts bearing various ligands (both chiral and achiral) are available for these reactions.

One of the most studied metal-catalysed reactions of the α-diazo compounds is cyclopropanation (Scheme 28). Due to the importance of the cyclopropanes in natural products, numerous approaches to the synthesis of these motifs have been investigated. Intermolecular and intramolecular reactions as well as asymmetric variants exist. Insertion reactions of metal carbenoids are also of great interest in organic synthesis. Although X-H insertion reactions proved effective with different heteroatoms (X = C, O, N, S and Si),

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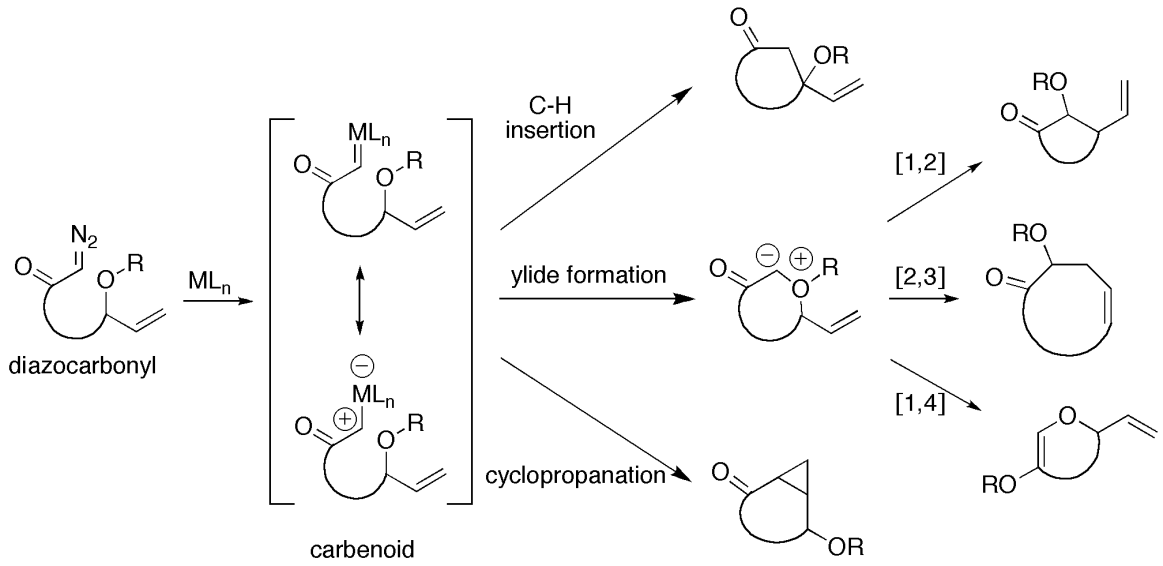
[64] Maxwell, J. L.; Brown, K. C.; Bartley, D.; Kodadek, T. *Science* **1992**, *256*, 1544.
[65] Boschi, T.; Licoccia, S.; Paolesse, R.; Togliatesta, P.; Pelizzi, G.; Vitali, F. *Organomettalics* **1989**, *8*, 330.
[66] Silberrad, O.; Roy, C. S. *J. Chem. Soc. Trans.* **1906**, *89*, 179.
[67] Paulissen, R.; Reimlinger, H.; Hayez, E.; Hubert, A. J.; Teyssié, P. *Tetrahedron Lett.* **1973**, *14*, 2233.

the most synthetically valuable transformation is C-H insertion because it creates a new carbon-carbon bond. Selective and asymmetric procedures for the X-H insertion have been developed.

A further important transformation involving α-diazo compounds is ylide formation. Highly reactive oxygen, nitrogen and sulfur ylide intermediates undergo rearrangement reactions to form stable products. Common reactions of ylide intermediates are the [1,2]-shift reaction, the [2,3]-sigmatropic rearrangement, the [1,4]-shift and, less frequently, ß-hydride elimination and the dipolar cycloaddition can be observed.



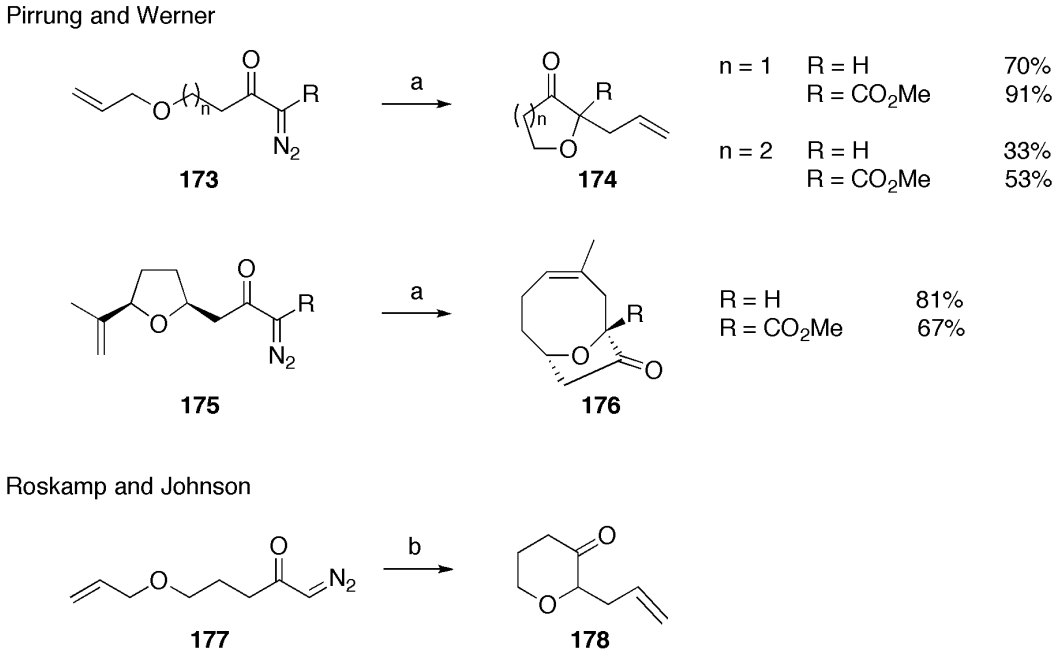
Scheme 28. Overview of metal carbenoid transformations.[68]

Although metal carbenoids can undergo a wide range of reactions depending on substrate structure, only the formation of oxonium ylides and their subsequent [2,3]-sigmatropic rearrangement have relevance to this work.

[68] Guérot, C. *PhD Thesis* University of Glasgow, **2009**.

3.2 Intramolecular Oxonium Ylide Formation and [2,3]-Sigmatropic Rearrangement

A significant development of the chemistry involving intramolecular oxonium ylide formation and [2,3]-sigmatropic rearrangement was the synthesis of cyclic ethers independently reported by Pirrung and Werner,[69] and by Roskamp and Johnson in 1986.[70] Intramolecular rhodium-catalysed reaction between the allylic ethers and the α-diazoketone in substrate **173**, **175** and **177** produced oxonium ylides that underwent subsequent [2,3]-sigmatropic rearrangement to afford the five-, six- and eight-membered heterocycles **174**, **176** and **178** in moderate to good yields (Scheme 29). The authors noticed that for some substrates, a competing C-H insertion reaction resulted in lower yields. The efficient synthesis of medium-sized cyclic ethers demonstrated the value of this reaction to organic chemistry. Indeed, cyclic ethers are building blocks found in numerous natural products and the one-pot sequence of intramolecular [2,3]-sigmatropic rearrangement of oxonium ylides represented an acceptable method for the formation of *O*-heterocycles.



a) $Rh_2(OAc)_4$, CH_2Cl_2, rt; b) $Rh_2(OAc)_4$, C_6H_6, rt, 61%.

Scheme 29. The first reported examples of intramolecular [2,3]-rearrangement of oxonium ylides.[69,70]

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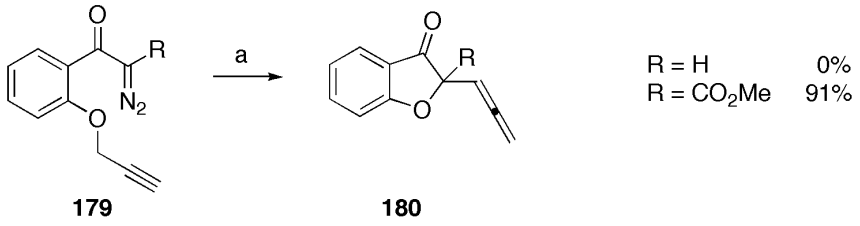
[69] Pirrung, M. C.; Werner, J. A. *J .Am. Chem. Soc.* **1986**, *108*, 6060.
[70] Roskamp, E. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1986**, *108*, 6062.

Pirrung *et al*. also demonstrated that the [2,3]-sigmatropic rearrangement of an oxonium ylide was possible in the case of propargylic ethers **179** (Scheme 30).[69] Treatment of the α-diazo ß-keto ester **179** (R = CO_2Me) with $Rh_2(OAc)_4$ furnished the allene **180** in 91% yield. However, as previously reported, the reaction was found to be substrate dependent and the reaction of the corresponding α-diazoeketone **179** (R = H) failed.



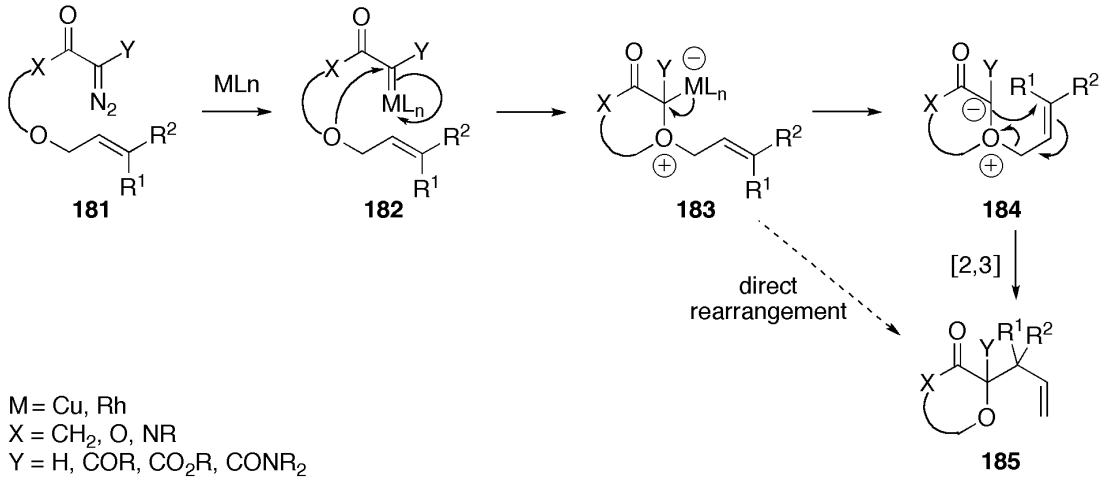
179 **180**

a) $Rh_2(OAc)_4$, CH_2Cl_2, rt.

Scheme 30. Formation and [2,3]-rearrangement of propargylic oxonium ylides generated from the propargylic ethers **179**.[69]

The proposed and widely assumed mechanism for the [2,3]-sigmatropic rearrangement is shown in Scheme 31. The diazo substrate **181** is converted into the electrophilic metal carbenoid **182**. Nucleophilic attack by one of the lone pair of electrons gives the metal-bound intermediate **183** and dissociation of the metal complex forms the oxonium ylide **184** which then undergoes a symmetry-allowed [2,3]-sigmatropic rearrangement. The existence of a metal-bound ylide or a free ylide is still the subject of debate.[71,72,73] Results from some studies suggest that direct rearrangement from a metal bound ylide can occur, whereas results from other reactions are consistent with a rearrangement of a free oxonium ylide.

[71] Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911.
[72] Hodgson, D. M.; Pierard, F. Y. T. M.; Stupple, P. A. *Chem. Soc. Rev.* **2001**, *30*, 50.
[73] Clark, J. S.; Hansen, K. E. *Chem. Eur. J.* **2014**, *20*, 5454.



Scheme 31. Proposed mechanism for the intramolecular reaction of an allylic ether with a metal cabenoid.[73]

Clark *et al*. have contributed significantly to the development of intramolecular formation and [2,3]-sigmatropic rearrangement of oxonium ylides as a method for the synthesis of cyclic ethers and carbocycles.[72,74,75,76,77,78,79,80,81,82]

In the field of diastereoselective synthesis of tetrahydrofurans, the group demonstrated that the treatment of α-diazoketone **186** with $Cu(acac)_2$ or $Rh_2(OAc)_4$ furnished a diastereomeric mixture of the 2,5-dialkyltetrahydrofuran-3-ones **188** and **189** (Scheme 32).[74] Although the *cis*:*trans* ratio of the products fluctuated as a function of the catalyst, the *trans* product **188** predominated in all cases.

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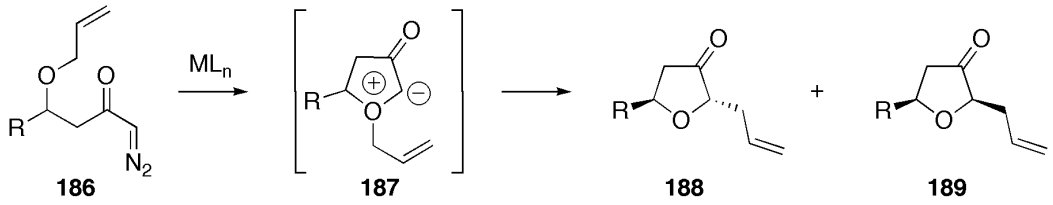
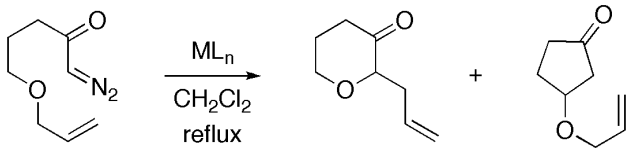
[74] Clark, J. S. *Tetrahedron Lett*. **1992**, *33*, 6193.
[75] Clark, J. S.; Krowiak, S. A.; Street, L. J. *Tetrahedron Lett*. **1993**, *34*, 4385.
[76] Clark, J. S.; Dossetter, A. G.; Whittingham, W. G. *Tetrahedron Lett*. **1996**, *37*, 5605.
[77] Clark, J. S.; Fretwell, M.; Whitlock, G. A.; Burns, C. J.; Fox, D. N. A. *Tetrahedron Lett*. **1998**, *39*, 97.
[78] Clark, J. S.; Bate, A. L.; Grinter, T. *Chem. Commun*. **2001**, *5*, 459.
[79] Clark, J. S.; Whitlock, G.; Jiang, S.; Onyia, N. *Chem. Commun*. **2003**, *20*, 2578.
[80] Clark, J. S.; Walls, S. B.; Wilson, C.; East, S. P.; Drysdale, M. J. *Eur. J. Org. Chem*. **2006**, *2*, 323.
[81] Clark, J. S; Guérot, C.; Wilson, C.; Blake, A. J. *Chem. Commun*. **2007**, *40*, 4134.
[82] Clark, J. S.; *Nitrogen, Oxygen, Sulfur Ylide Chemistry*, Oxford University Press, New York **2002**.



R = $CHMe_2$	$Cu(acac)_2$, THF, reflux	83 - 85%	(>97:3)
R = $CHMe_2$	$Rh_2(OAc)_4$	51 - 68%	(<81:19)
R = $(CH_2)_2Me$	$Cu(acac)_2$, THF, reflux	83%	(>97:3)

Scheme 32. Synthesis of *trans*- versus *cis*-tetrahydrofuran-3-ones.[74]

When the reaction was applied to the synthesis of tetrahydropyran-3-ones **191**, Clark *et al.* found that the use of a copper catalysts such as $Cu(acac)_2$, $Cu(hfacac)_2$ and $Cu(tfacac)_2$ was preferred compared to $Rh_2(OAc)_4$ (Scheme 33).[75] Indeed, although a mixture of tetrahydropyran-3-one **191** and the C-H insertion product **192** was obtained when the reaction was catalysed by $Cu(acac)_2$, the use of fluorinated analogues, $Cu(tfacac)_2$ and $Cu(hfacac)_2$, led to the formation of the [2,3]-sigmatropic rearrangement product **191** exclusively. Replacing the catalyst with $Rh_2(OAc)_4$ led to a dramatic increase in the amount of the undesired C-H insertion product **192**.

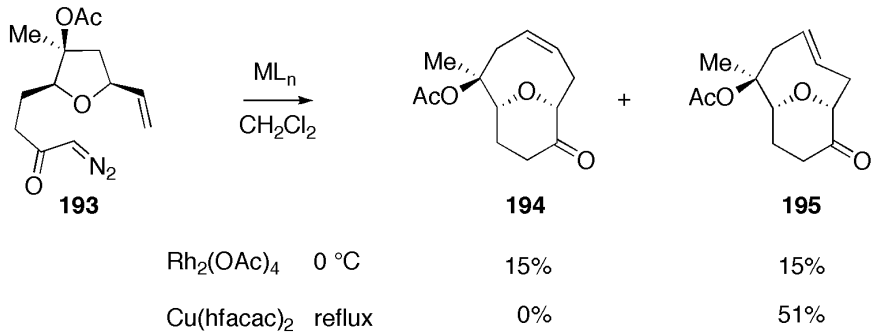


$Rh_2(OAc)_4$	37%	22%
$Cu(acac)_2$	61%	12%
$Cu(tfacac)_2$	78%	0%
$Cu(hfacac)_2$	83%	0%

Scheme 33. C-H Insertion *versus* oxonium ylide and rearrangement during cyclisation of the diazoketone **190**.[75]

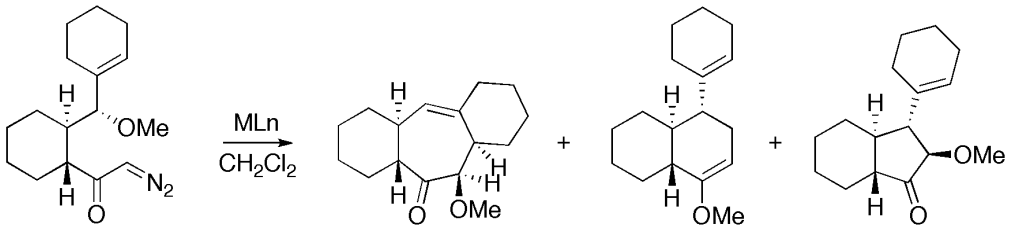
Based on these results, the methodology was successfully used for the synthesis of cyclic ethers containing six-, seven- and eight-membered rings.[75]

In addition to the possibility of forming heterocycles, [2,3]-rearrangement of an allylic oxonium ylide can provide access to bridged-bicyclic ethers. As an example, the α-diazoketone **193**, in presence of a metal catalyst, reacted to give an oxonium ylide which underwent a [2,3]-sigmatropic rearrangement affording the bicyclic ethers **194** and **195** (Scheme 34).[76] Again, the choice of the catalyst appeared to be important in controling the stereochemical outcome of the reaction. $Rh_2(OAc)_4$ led to the formation of a mixture of the *E*- and *Z*-alkenes, whereas $Cu(hfacac)_2$ furnished the *E*-alkene **195** exclusively.



Scheme 34. Synthesis of bridged-bicyclic ethers.[76]

Finally, polycyclic ethers can also be synthesised using oxonium ylide and rearrangement chemistry.[81] Treatment of the α-diazoketone **196** with $Cu(hfacac)_2$ produced a mixture of three rearrangement products: the [2,3]-rearrangement product **197** was obtained in 10% yield, the [1,4]-shift migration product **198** in 28% yield and the ring-contracted [1,2]-shift product **199**, as the major product in 34% yield. The [2,3]-rearrangement product **197** was isolated as the sole product of the reaction when the latter was performed using $Rh_2(OAc)_4$.



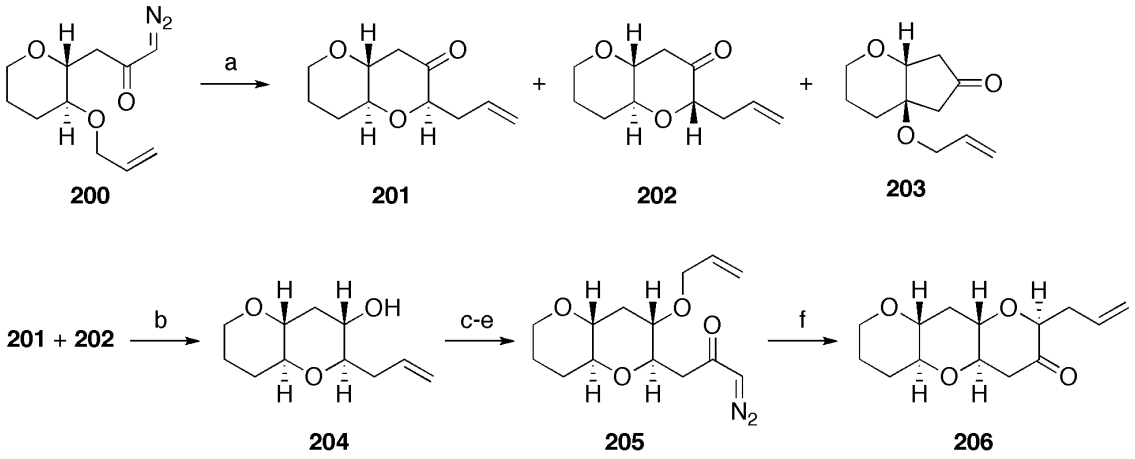
196 **197** **198** **199**

$Cu(hfacac)_2$, reflux	10%	28%	34%
$Rh_2(OAc)_4$, rt	90%		

Scheme 35. Synthesis of fused carbocycles.[81]

West *et al*. used the oxonium ylide formation and subsequent [2,3]-rearrangement reaction to synthesise *trans*-fused polycyclic ethers (Scheme 36).[83] In the presence of $Cu(tfacac)_2$ in refluxing dichloromethane, diazoketone **200** reacted to give the [2,3]-rearrangement product **202** as major diastereomer along with the isomeric compound **201**. The competing C-H insertion reaction led to the formation of the ketone **203**. Epimerisation and reduction of the diastereomeric mixture of **201** and **202** gave the alcohol **204** which was subsequently converted into the α-diazoketone **205**. A further copper-catalysed oxonium ylide formation and [2,3]-rearrangement reaction produced the *trans*-fused tricyclic ether **206** as a single diastereomer.

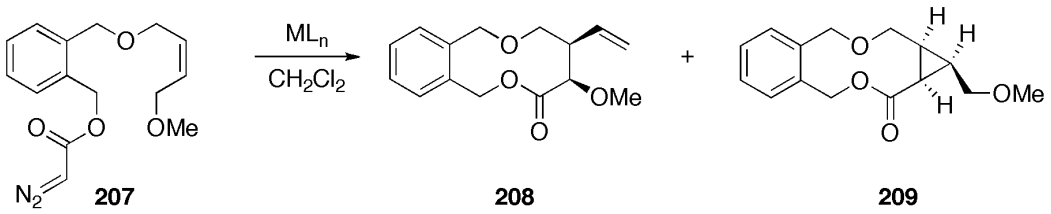
[83] a) Marmsäter, F. P.; West, F. G. *J. Am. Chem. Soc.* **2001**, *123*, 5144; b) Marmsäter, F. P.; West, F. G. *Chem. Eur. J.* **2002**, *8*, 4346; c) Marmsäter, F. P.; Vanecko, J. A.; West, F. G. *Tetrahedron* **2002**, *58*, 2027.



a) $Cu(tfacac)_2$, CH_2Cl_2, reflux, 80 %, **201**:**202**:**203** 1:30:2; b) *i*) DBU, THF, rt, *ii*) $LiAlH_4$, THF, 0 °C, 86%; c) O_3, CH_2Cl_2, MeOH, −78 °C, then H_2O_2, HCO_2H, 70°C; d) KH, CH_2CHCH_2Br, DME, 0 °C, 67% (2 steps); e) *i*-BuO_2CCl, Et_3N, Et_20, rt, then CH_2N_2, 0 °C to rt, 44%; f) $Cu(tfacac)_2$, CH_2Cl_2, reflux, 80%.

Scheme 36. Synthesis of fused polycyclic ethers *via* an iterative approach.[83a]

The synthesis of macrocyles has also been a subject of attention. Doyle *et al*. successfully synthesised the lactone **208** chemoselectively (Scheme 37).[84] In presence of a metal carbenoid, the α-diazo ester **207** was transformed into a 13-membered cyclic oxonium ylide. Subsequent [2,3]-sigmatropic rearrangement with three atoms contraction delivered the lactone **208** as well as **209** due to the competitive cyclopropanation.



$Rh_2(pfb)_4$	79%	(77:23)
$Rh_2(OAc)_4$	77%	(81:19)
$Cu(MeCN)_4PF_6$	70%	(85:15)

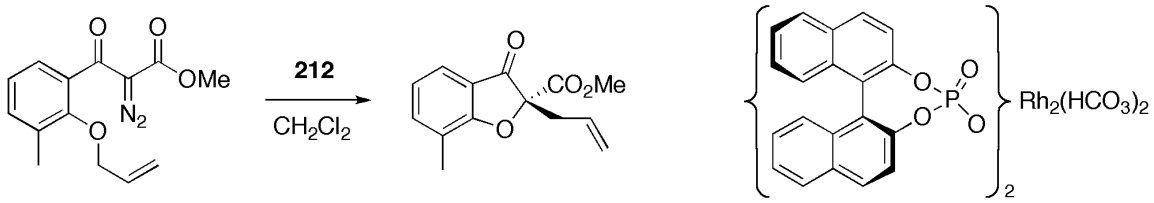
Scheme 37. Synthesis of macrocycles.[84]

The same year, an analogous transformation was reported for similar substrates and chiral complexes were employed as catalysts.[85] However, in spite of

[84] Doyle, M. P.; Peterson, C. S. *Tetrahedron Lett*. **1997**, *38*, 5265.
[85] Doyle, M. P.; Peterson, C. S. Parker, Jr, D. L. *Angew. Chem. Int. Ed. Engl*. **1996**, *35*, 1334.

promising levels of asymmetric induction, macrocyclic cyclopropanes were the major products.

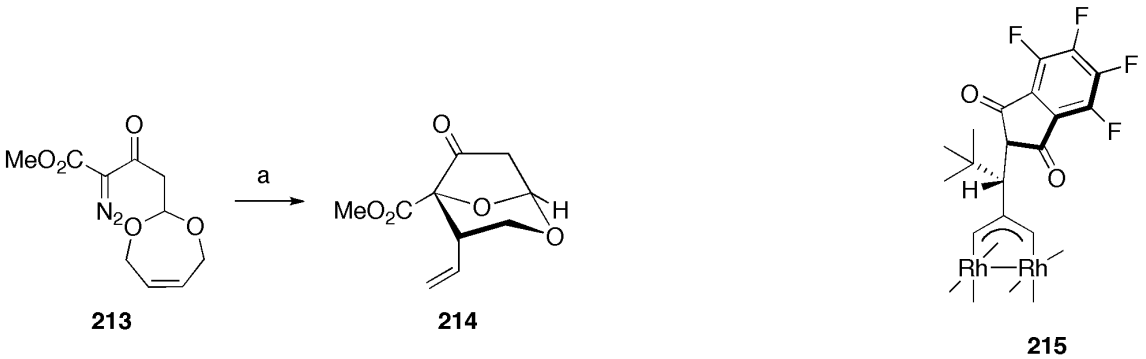
The asymmetric diazo decomposition to synthesise a chiral non-racemic [2,3]-sigmatropic rearrangement product was first reported by McKervey *et al*. in 1992.[86] Treatment of the diazoketone **210** with a chiral dirhodium complex **212** afforded the furanone **211** in 92% yield and 30% enantiomeric excess (Scheme 38). Further studies on similar substrates with catalyst bearing different chiral ligands afforded products with higher enantiomeric excesses (up to 60% *ee*).[87]



210 **211** **212**

Scheme 38. First example of asymmetric oxonium ylide and rearrangement.[86]

Recently, Hashimoto *et al*. succeeded in synthesising the 2,8-dioxabicyclo [3.2.1]octane ring system found in the zaragozic acid C in high enantiomeric excess.[88] Oxonium ylide formation and [2,3]-sigmatropic rearrangement of the α-diazoketone **213** delivered the bicyclic compound **214** in 72% yield and 93% *ee* when the reaction was catalysed by the rhodium complex **215**.



213 **214** **215**

a) Rh_2L_4, **219**, $PhCH_3$, 0 °C, 72%, 93% *ee*.

Scheme 39. Enantioselective synthesis of the ring system of zaragozic acid C.[88]

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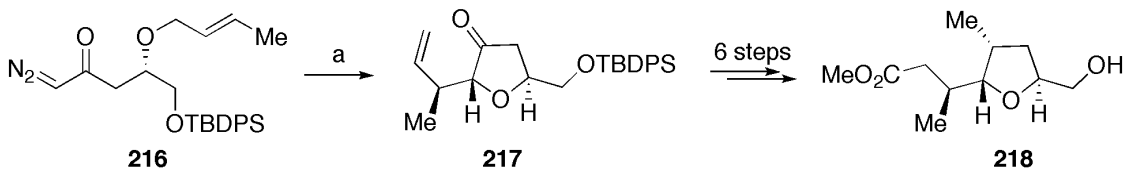
[86] McCarthy, N.; McKervey, M. A.; Ye, T.; McCann, M.; Murphy, E.; Doyle, M. P.; *Tetrahedron Lett*. **1992**, *33*, 5983.
[87] Pierson, N.; Fernández-Garcia, C.; McKervey, M. A. *Tetrahedron Lett*. **1997**, *38*, 4705.
[88] Shimada, N.; Nakamura, S.; Anada, M.; Shiro, M.; Hashimoto, S. *Chem. Lett*. **2009**, *38*, 488.

3.3 Application of Oxonium Ylide Formation and [2,3]-Sigmatropic Rearrangement to Total Synthesis within the Clark Group

Functionalised cyclic ethers are important motifs that are found in a wide range of natural compounds. Therefore, oxonium ylide formation and [2,3]-sigmatropic rearrangement offers rapid access to the important cores of many natural products.[89,90,91,92,93,94,95,96,97,98] Examples of total syntheses using this methodology are described in this section.

In 2004, Clark *et al*. reported the successful synthesis of the A-ring fragment **218** of the gamberic acids (Scheme 40).[92] Starting from (*S*)-dimethyl malate, the diazoketone **216** was obtained by a six-step synthesis. Copper-catalysed oxonium ylide formation and [2,3]-sigmatropic rearrangement delivered the *trans*-tetrahydrofuranone **217** in good yield and high diastereomeric excess. Further functionalisation completed the synthesis of the A-ring fragment of the gamberic acids.



216 **217** **218**

a) $Cu(acac)_2$, THF, reflux, 75%, dr >95:5.

Scheme 40. Synthesis of the A-ring fragment of the gamberic acids.[92]

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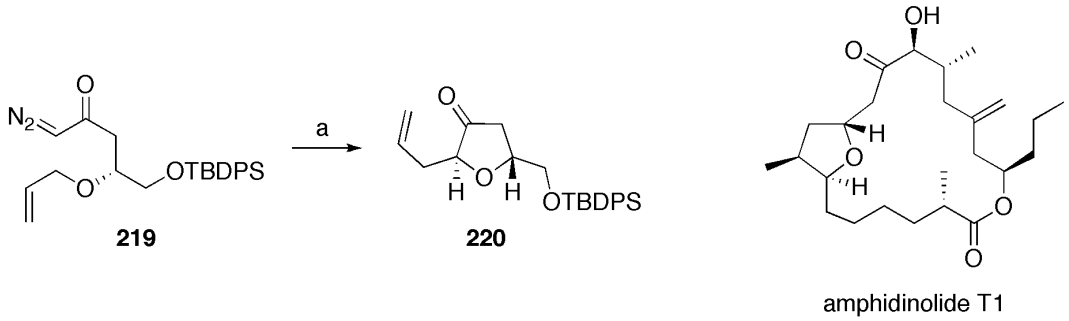
[89] Pirrung, M. C.; Brown, W. L.; Rege, S.; Laughton, P. *J. Am. Chem. Soc.* **1991**, *113*, 8561.
[90] Hodgson, D. M.; Angrish, D.; Erickson, S. P.; Kloesges, J.; Lee, C. H. *Org. Lett.* **2008**, *10*, 5553.
[91] Clark, J. S.; Dossetter, A. G.; Blake, A. J.; Li, W. -S.; Whittingham, W. G.; *Chem. Commun.* **1999**, 749.
[92] Clark, J. S.; Fessard, T. C.; Wilson, C. *Org. Lett.* **2004**, *6*, 1773.
[93] Clark, J. S.; Baxter, C. A.; Castro, J. L. *Synthesis* **2005**, *19*, 3398.
[94] Clark, J. S.; Fessard, T. C.; Whitlock, G. A. *Tetrahedron*, **2006**, *62*, 73.
[95] Clark, J. S.; Vignard, D.; Parkin, A. *Org. Lett.* **2011**, *13*, 3980.
[96] Clark, J. S.; Romiti, F. *Angew. Chem. Int. Ed.* **2013**, *52*, 10072.
[97] Clark, J. S.; Yang, G.; Osnowski, A. P. *Org. Lett.* **2013**, *15*, 1460.
[98] Clark, J. S.; Yang, G.; Osnowski, A. P. *Org. Lett.* **2013**, *15*, 1464.

More recently, the synthetic strategy to form tetrahydrofuranones was employed in the total syntheses of amphilodinolides T1, T3 and T4 (Scheme 41).[96] Oxonium ylide formation and [2,3]-sigmatropic rearrangement of the α-diazoketone **219** led to the formation of the heterocycle **220** as a single diastereomer. This reaction was also a key step in the syntheses of the C-1–C-17 and C-18–C34 fragments of the amphidinolides C, C2 and C3.[97,98]

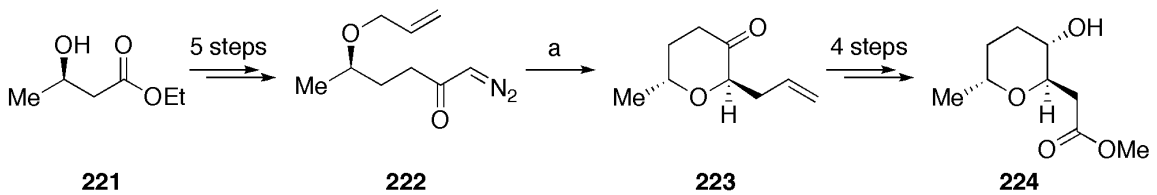


219 **220**

a) $Cu(acac)_2$, THF, reflux, 91%.

Scheme 41. Synthesis of the tetrahydrofuran motif of amphidinolides T1, T3 and T4.[96]

An example of the application of the reaction to the construction of tetrahydropyranones is the total synthesis of (+)-decarestrictine L.[94] The route began with the conversion of ethyl (*R*)-3-hydroxybutyrate **221** into the α-diazoketone **222** through a five-step sequence (Scheme 42). Oxonium ylide formation promoted by $Cu(tfacac)_2$ and subsequent [2,3]-rearrangement delivered the tetrahydropyranone **223** in 60% yield and with good diastereoselectivity. An additional four steps were required to complete the synthesis of decarestrictine L (**224**).

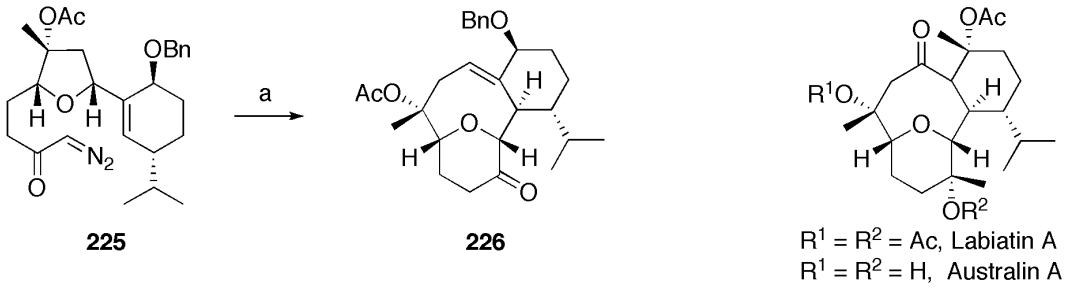


221 **222** **223** **224**

a) $Cu(tfacac)_2$, CH_2Cl_2, reflux, 60%, dr 91:9.

Scheme 42. Synthesis of the (+)-decarestrictine L (**224**).[94]

The methodology developed for the oxonium ylide formation and [2,3]-sigmatropic rearrangement can be applied to the construction of oxygen-containing heterocycles in more complex bridged-bicyclic ether systems. Clark *et al*. reported the synthesis of the tricyclic core of the natural products labiatin A and australin A from the diazoketone **225** (Scheme 43).[95,93] Copper-catalysed tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement delivered the tricyclic ketone **226** in 76% yield. This compound corresponds to the core of the natural products.



225 **226**

a) $Cu(hfacac)_2$, CH_2Cl_2, reflux, 76%.

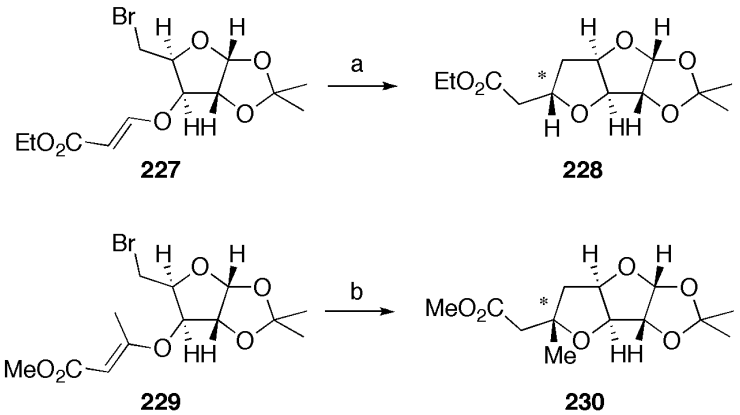
Scheme 43. Synthesis of the tricyclic core of labiatin A and australin A.

Oxonium ylide chemistry offers many synthetic possibilities. Tandem oxonium ylide formation and [2,3]-sigmatropic rearrangement allows the synthesis of highly substituted cyclic ethers, which are of great importance due to their presence in numerous natural products. Clark *et al*. reported this reaction for the synthesis of tetrahydropyrans, tetrahydrofurans but also more complex bridged-bicyclic ethers. This transformation will be a key step in the synthesis of the proposed structure of sclerophytin F.

4 Radical Cyclisation Reactions for the Synthesis of Oxacycles

Many natural products possess cyclic ether skeletons and a wide range of methodology to build these systems has been developed. One efficient method to synthesise oxacycles is the radical cyclisation using ß-alkoxyacrylates as acceptors.

The first examples of such a reaction were reported by Araki *et al*. in 1989. [99] Addition of tributyltin hydride to a solution of terminal halogenofuranoses **227** bearing an *O*-acrylate group in presence of azobisisobutyronitrile afforded the bicyclic compound **228** in high yield and as a single diastereomer (Scheme 44). Five- and six-membered cyclic ethers were obtained efficiently in this fashion, but the use of highly substituted acrylates **229** led to a reduction in the level of diastereocontrol.



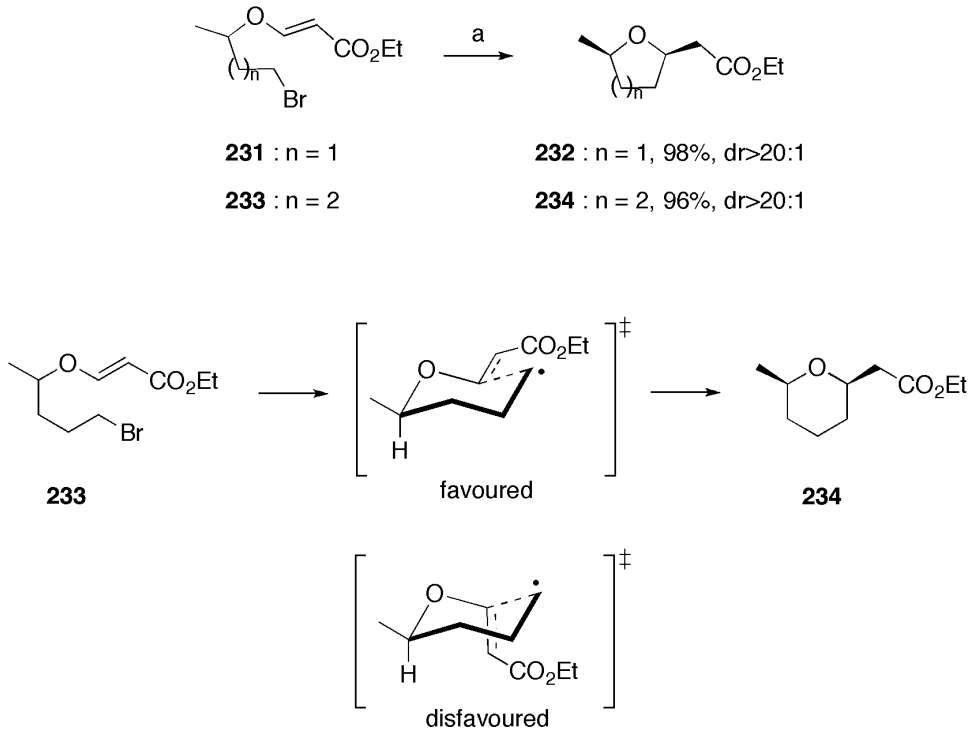
227 **228** **229** **230**

a) Bu_3SnH, AIBN, C_6H_6, reflux, 69%, dr>20:1; b) Bu_3SnH, AIBN, C_6H_6, reflux, 89%, dr 4:1.

Scheme 44. Radical-mediated cyclisations of sugar-derived alkoxyacrylates.[99]

[99] Araki, Y.; Endo, T.; Arai, Y.; Tanji, M.; Ishido, Y. *Tetrahedron Lett*. **1989**, *30*, 2829.

Lee *et al*. extended this methodology to the general synthesis of tetrahydrofurans and tetrahydropyrans. [100] It was demonstrated that halogenoalkanes bearing a ß-alkoxyacrylate moiety **231**/**233** cyclised into the corresponding five- or six-membered oxacycles (Scheme 45). The yields were excellent and the radical cyclisation proceeded with complete diastereoselectivity affording *cis*-2,5-disubstituted tetrahydrofurans **232** and *cis*-2,6-disubstituted tetrahydropyrans **234**. To explain the selectivity, Lee *et al*. suggested that the reaction proceeds through a chair-like transition state that favours formation of the *cis*-disubstituted cyclic ether **234**.



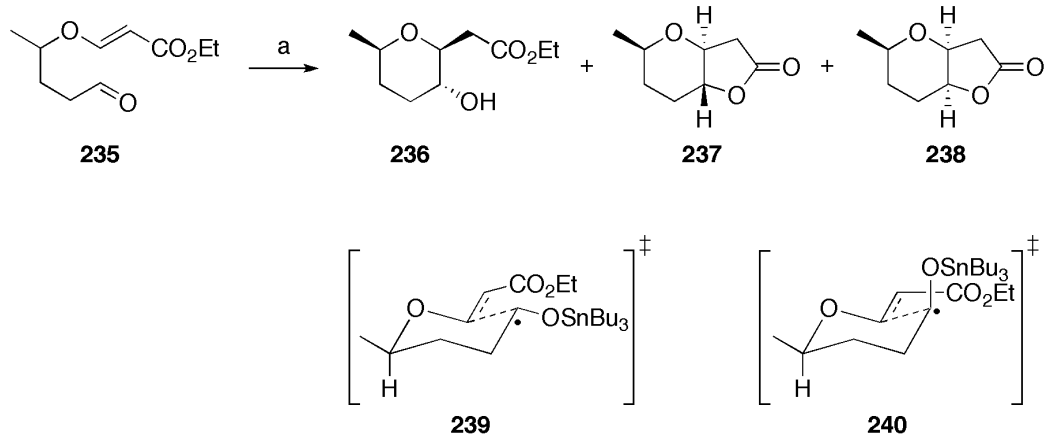
a) Bu_3SnH, AIBN, C_6H_6, reflux.

Scheme 45. Synthesis of tetrahydrofurans and tetrahydropyrans by radical mediated-cyclisations of β-alkoxyacrylates.[100]

The reaction was extended to the formation of 3-hydroxy oxacyclic rings.[101] In this case, a ketyl radical was generated from the corresponding aldehyde **235** and intramolecular radical cyclisation delivered the hydroxy tetrahydropyran **236** (Scheme 46). It is important to note that under the reaction conditions, some of the products were converted to the corresponding

[100] Lee, E.; Tae, J. S.; Lee, C.; Park, C. M.; *Tetrahedron Lett*. **1993**, *34*, 4831.
[101] Lee, E.; Tae, J. S.; Chong, Y. H.; Park, Y. C. *Tetrahedron Lett*. **1994**, *35*, 129.

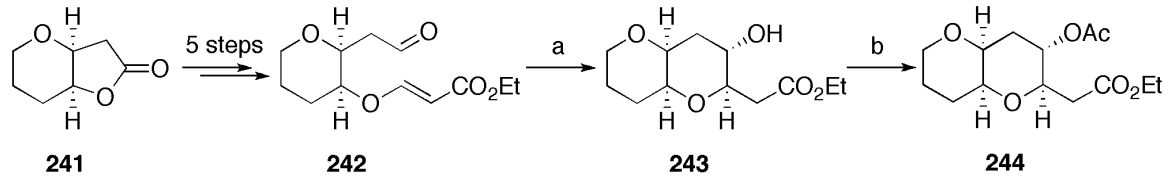
lactones **237**/**238**. Although high yields were obtained, the diastereoselectivity was only 54:46, which was explained by similar energies for transition states **239** and **240**.



a) Bu_3SnH, AIBN, C_6H_6, reflux, 97%, **236**:**237**:**238** 43:11:46.

Scheme 46. Synthesis of tetrahydropyrans, the radical mediated-cyclisation of aldehydes onto ß-alkoxyacrylates.[101]

The possibility of using the methodology for the iterative synthesis of polycyclic ethers was also formulated and the fused *bis*-tetrahydropyran **243** was synthesised in 6 steps from lactone **241** (Scheme 47).



a) Bu_3SnH, AIBN, C_6H_6, reflux, dr>20:1; b) Ac_2O, pyridine, DMAP, 91%.

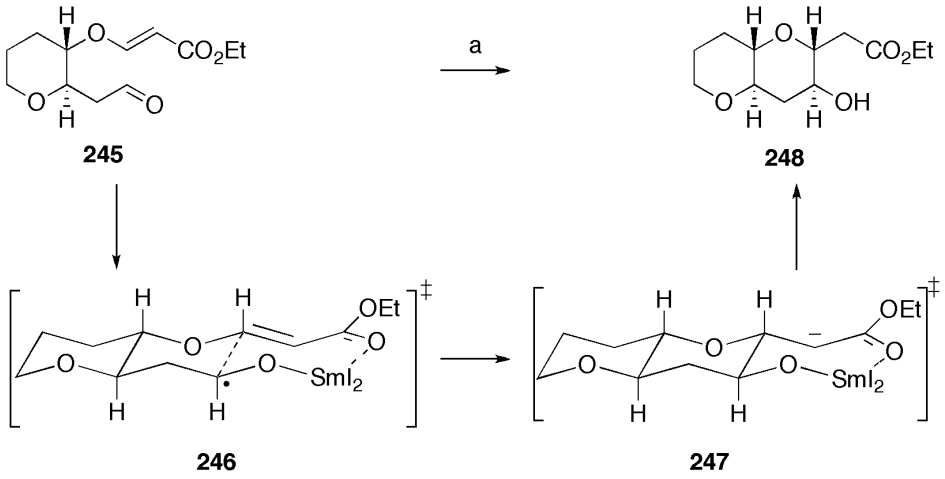
Scheme 47. Iterative synthesis of polycyclic ethers.[101]

More recently, major advances have been made in the field of radical cyclisation following the discovery of SmI_2 as a powerful reducing agent.[102,103,104] In 1977, Molander and Kenny reported the first SmI_2-mediated radical cyclisation

[102] Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371.
[103] Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 7140.
[104] Girard, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.

between a carbonyl and an alkene.[105,106] During the following decade many publications attested the use of SmI_2 as initiator for radical cyclisation to form 2,3-*trans*-tetrahydropyrans by intramolecular cyclisation between carbonyls and α,β-unsaturated esters.[107]

In 1999, Nakata *et al*. reported the use of SmI_2 for intramolecular cyclisation using β-alkoxyacrylates as electron acceptors.[108] This single electron transfer reagent allowed the formation of a 2,6-*syn*-2,3-*trans*-tetrahydropyran **248** as a single diastereoisomer (Scheme 48). In this process, aldehyde **245** is first reduced into a ketyl radical with coordination to the samarium and chelation to the ester **246**. The reaction then proceeds through a transition state in which the samarium is chelated to the ester functional group, which accounts for the observed selectivity. Finally, a new carbon-carbon bond is formed and a second electron transfer delivers the intermediate **247** which ultimately picks up a proton from methanol to give the product **248**.

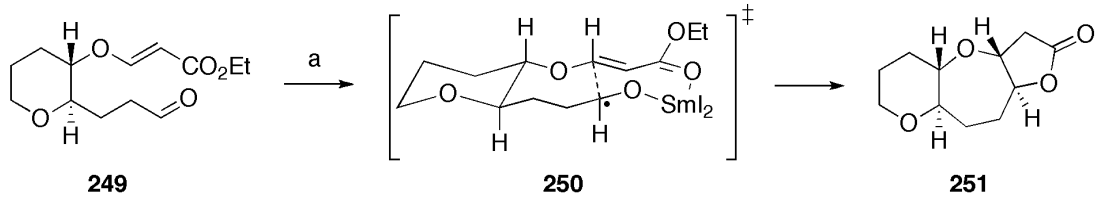


a) SmI_2, MeOH, THF, 0 °C, 92%, dr>20:1.

Scheme 48. Proposed mechanism of the SmI_2-mediated cyclisation of **245**.[108]

[105] Molander, G. A.; Kenny, C. *Tetrahedron Lett*. **1987**, *28*, 4367.
[106] Molander, G. A.; Kenny, C. *J. Am. Chem. Soc.* **1989**, *111*, 8236.
[107] a) Enholm E. J.; Trivellas, A. *Tetrahedron Lett*. **1989**, *30*, 1063; b) Enholm, E. J.; Trivellas, A. *J. Am. Chem. Soc.* **1989**, *111*, 6463; c) Kito, M.; Sakai, T.; Yamada, K.; Matsuda, F.; Shirahama, H. *Synlett*, **1993**, 158; d) Kito, M.; Sakai, T.; Haruta, N.; Shirahama, H.; Matsuda, F. *Synlett*, **1996**, 1057.
[108] Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron Lett*. **1999**, *40*, 2811.

By increasing the distance between the aldehyde and the ß-alkoxyacrylate, the SmI_2-mediated radical cyclisation reaction could be used to construct the 2,7-*syn*-2,3-*trans*-oxepane **251** (Scheme 49).[109]

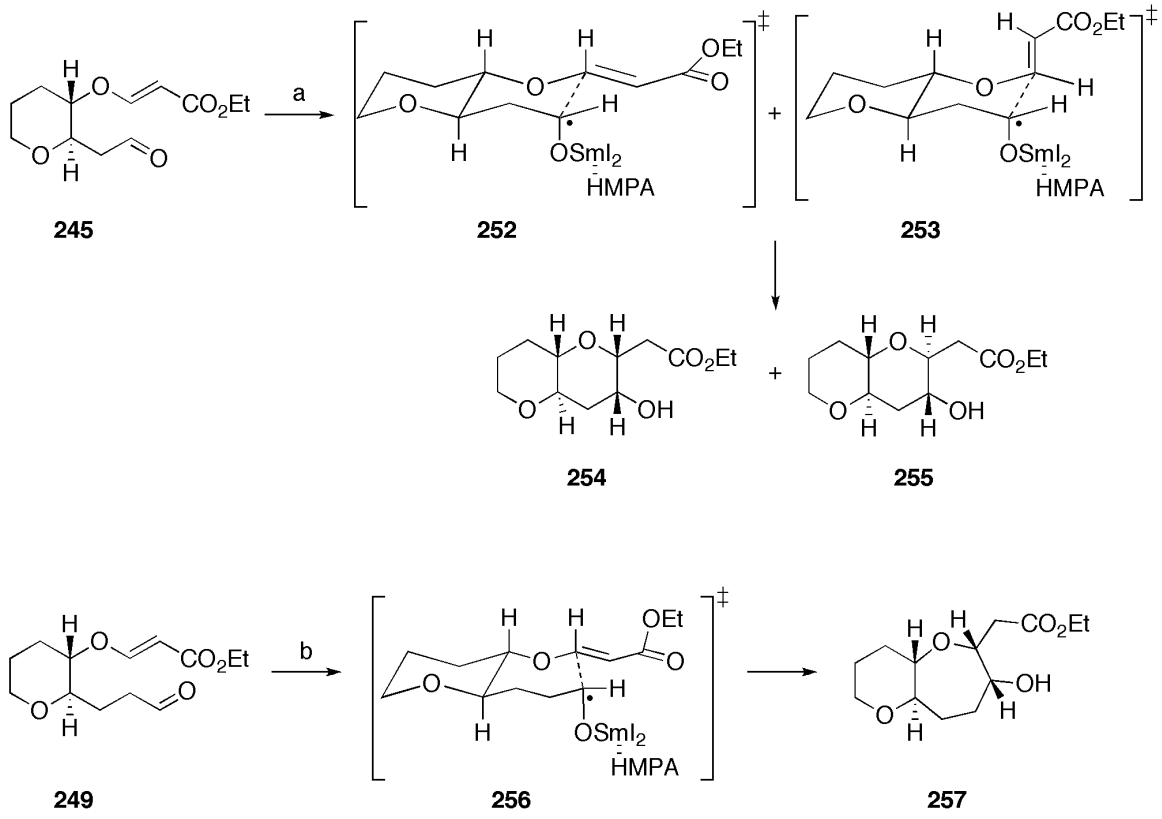


a) SmI_2, MeOH, THF, rt, 84%, dr>20:1.

Scheme 49. Synthesis of an oxepane ring by SmI_2-mediated cyclisation.[109]

Further studies, in the presence of an additive, confirmed the importance of chelation between the samarium and the ester functional group.[110] In the presence of HMPA, the same starting materials **245**/**249** and reagents resulted in the formation of a complimentary set of products **254**/**255** and **257**. In these cases, the selectivity was altered due to the coordination between the HMPA and the samarium. Indeed, steric hindrance is created in the transition state which results in different favoured conformations (Scheme 50).

[109] Hori, N.; Matsukura, H.; Nakata, T. *Org. Lett*. **1999**, *1*, 1099.
[110] Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. *Tetrahedron*, **2002**, *58*, 1853.



245 **252** **253** **254** **255** **249** **256** **257**

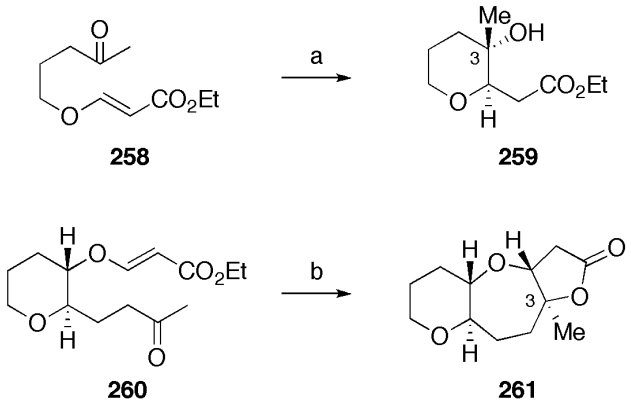
a) SmI_2, MeOH, THF/HMPA (3:1), −78 °C, 56% of **254** and 17% of **255**; b) SmI_2, MeOH, THF/HMPA (2:1), rt, 84%.

Scheme 50. SmI_2-mediated cyclisation in presence of HMPA.[110]

Impressively, this powerful SmI_2-mediated cyclisation reaction could be applied to the iterative synthesis of complex polycyclic natural products.[108, 109]

Not only aldehydes but also ketones can be subjected to the SmI_2-mediated radical cyclisation. Nakata *et al*. demonstrated that the intramolecular reaction between a methyl ketone and ß-alkoxyacrylate in the substrates **258** and **260** leads to the formation of 3-hydroxy tetrahydropyrans **259** and **261** bearing a quaternary stereocentre at the C-3 position **(**Scheme 51).[111, 112]

[111] Matsuo, G.; Hori, N.; Nakata, T. *Tetrahedron Lett*. **1999**, *40*, 8859.
[112] Suzuki, K.; Matsukura, H.; Matsuo, G.; Koshino, H.; Nakata, T. *Tetrahedron Lett*. **2002**, *43*, 8653.



a) SmI_2, MeOH, THF, rt, 100%, dr>20:1; b) SmI_2, MeOH, THF, rt, 94%, dr>20:1.

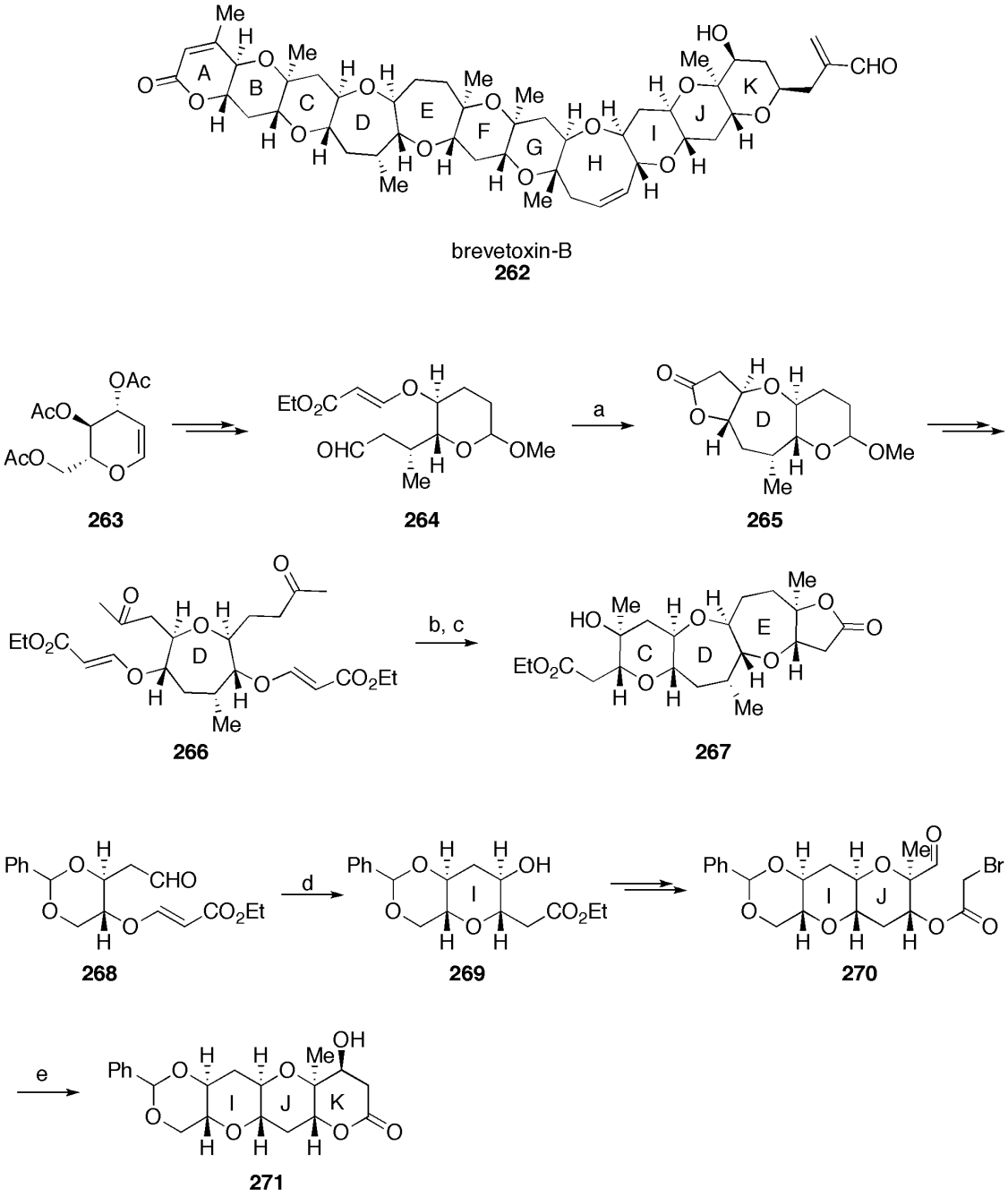
Scheme 51. SmI_2-mediated cyclisation of methyl ketone and ß-alkoxyacrylates.[111,112]

As pioneers of the SmI_2-mediated radical cyclisation cyclisation, Nakata *et al*. have applied this methodology to the total synthesis of several natural products containing *trans*-fused polycyclic ether ring systems.[113]

An excellent example is the total synthesis of brevetoxin-B (BTX-B). [114] The skeleton of this marine polycyclic ether comprises six-, seven- and eight-membered fused cyclic ethers and possesses 23 chiral centres (Scheme 52). Overall, Nakata *et al*. achieved the total synthesis of this natural product in 59 steps.

Starting from the *O*-acetyl-D-glucal **263** a few synthetic steps led to the ß-alkoxyacrylate **264**, which underwent the radical cyclisation reaction. According to the methodology mentioned previously, lactone **265** was obtained in 86% yield and further transformations gave diketone **266**. A bi-directional SmI_2-promoted intramolecular cyclisation reaction was then used to close the C- and the E-rings simultaneously to afford the tetracyclic core **267** in good yield. The I-ring **269** was also prepared from aldehyde **268.** Subjecting **270** to a SmI_2-induced intramolecular Reformatsky-type reaction, the ß-hydroxy lactone **271** was obtained to complete the IJK ring system.

[113] Nakata, T. *Chem. Rec.* **2010**, *10*, 159.
[114] Matsuo, G.; Kawamura, K.; Hori, N.; Matsukura, H.; Nakata, T. *J. Am. Chem. Soc.* **2004**, *126*, 14374.



a) SmI_2, MeOH, THF, rt, 83%; b) SmI_2, MeOH, THF, rt; c) *p*-TsOH, 79% (2 steps); d) SmI_2, MeOH, THF, 0 °C, 95%; e) SmI_2, THF.

Scheme 52. Total synthesis of the CDE and IJK ring systems within BTX-B.[114]

One of the most challenging targets in the field of total synthesis is maitotoxin (Figure 15). This polyether marine natural product is one of the most complex natural products ever isolated with 32 fused-ether rings and 98 chiral centres. Impressively, Nakata has also applied the samarium-mediated

cyclisation reaction to the synthesis of several key fragments, namely the C'D'E'F'-, WXYZA'- and BCDE-ring systems.[115,116,117]

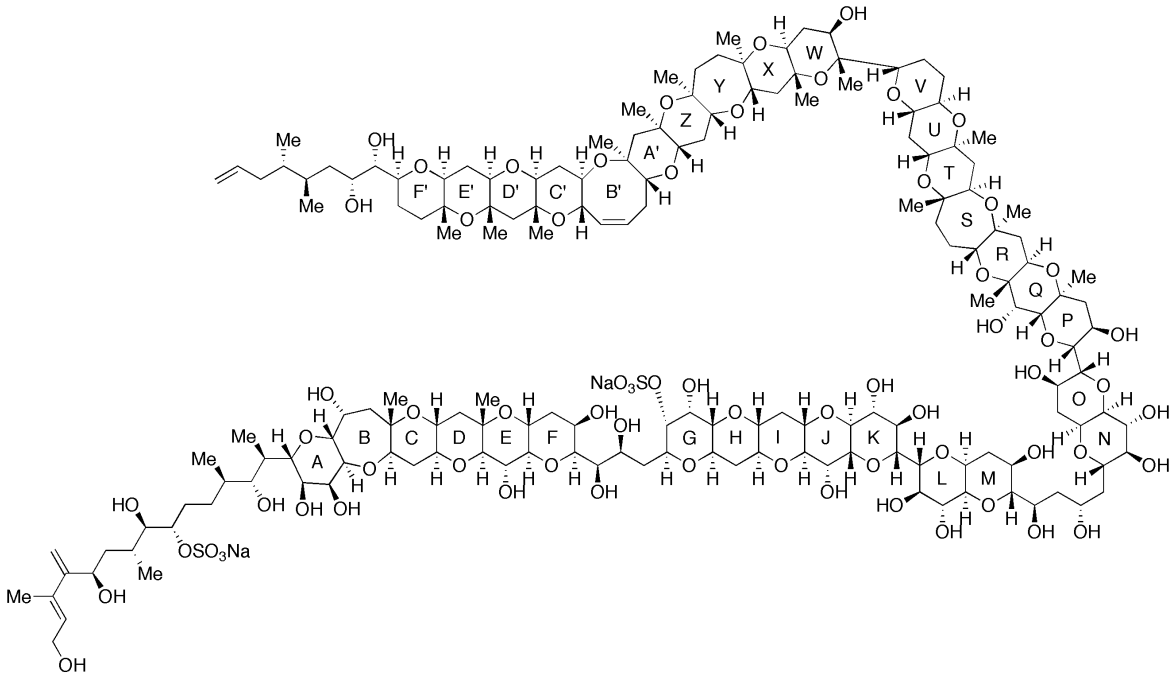


Figure 15. Maitotoxin.

In summary, the SmI_2-mediated radical cyclisation is a powerful method for the formation of oxacyclic motifs and has been used very successfully for the synthesis of complex natural products.

[115] Sakamoto, Y.; Matsuo, G.; Matsukura, H.; Nakata, T. *Org. Lett.* **2001**, *3*, 2749.
[116] Morita, M.; Haketa, T.; Koshino, H.; Nakata, T. *Org. Lett.* **2008**, *10*, 1679.
[117] Satoh, M.; Koshino, H.; Nakata, T. *Org. Lett.* **2008**, *10*, 1683.

5 Synthesis Strategy

Cladiellins represent the largest sub-class of 2,11-cyclised cembranoids and the biological activity that this family display contributes to the interest in them by the scientific community. This is not only in synthetic research but also in biology because cladiellins possess great potential in pharmacology due to their cytotoxic activity against various cancer cell lines.[1,2]

The relative configurations of these natural products has been deduced by comparison of spectroscopic data and X-ray analysis where possible. Later, the modified Mosher method allowed the determination of the absolute configuration.[19]

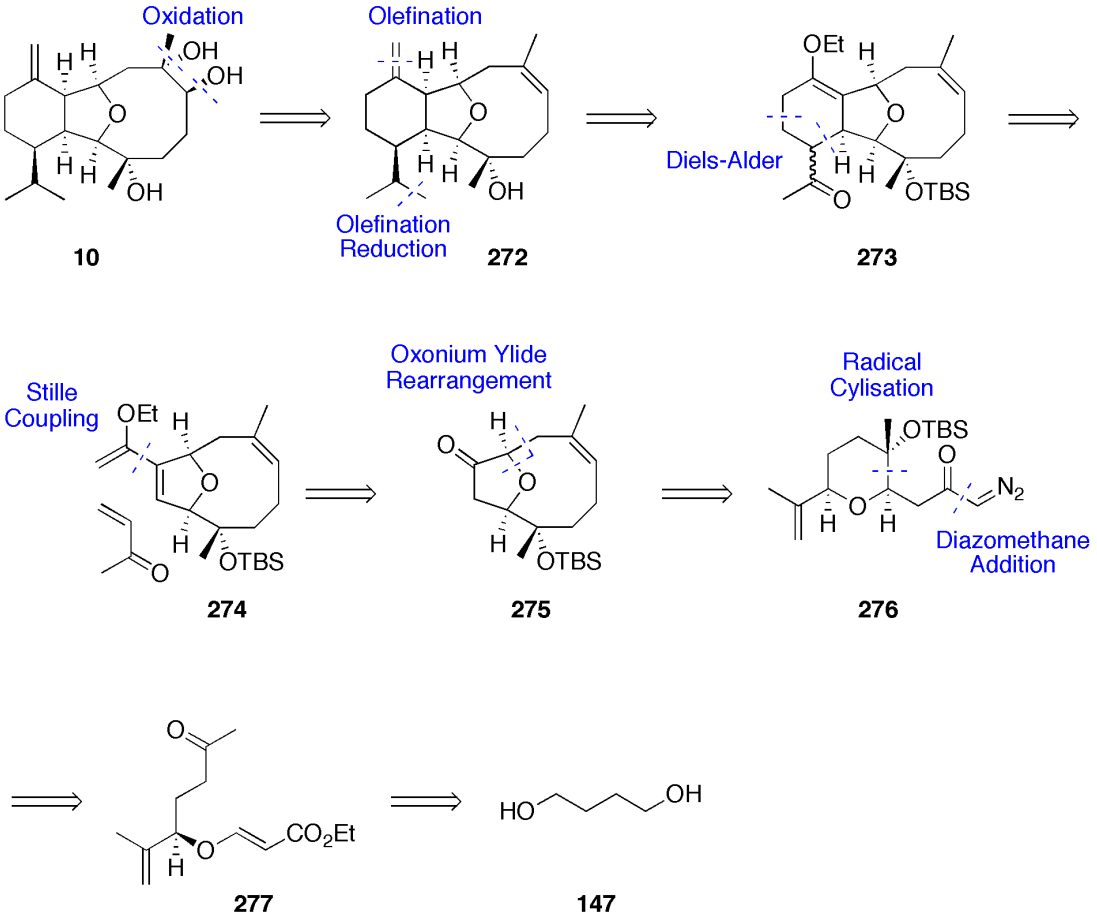
However, for some of the natural products, only total synthesis can confirm their structures. Indeed, the original structure of sclerophytin A, proposed by Sharma and Alam following its isolation was revealed to be incorrect after synthetic studies.[6,7,9,11,12,13] Consequently, the structure of several sclerophytins, for which the structure has been deduced by comparison of spectroscopic data with those of sclerophytin A, had to be re-evaluated.[20]

Structural reassignments of several sclerophytin-type natural products by Paquette and Friedrich challenged the assumption that all cladiellin natural products possess the *R*-configuration at the C-3 stereocentre. The obvious and most reliable way to confirm the existence of the *S*-configuration at this stereocentre in some of the cladiellin family members is by total synthesis.

Sclerophytin F is an important compound because it should be possible to prepare all of the other sclerophytins that have been proposed to have *S*-configuration at the C-3 position by functionalization of the hydroxyl groups.

The general approach to the synthesis of the cladiellin family of compounds developed in the Clark group proved to be efficient, as several natural products have been synthesised.[55,57,59] By expanding this methodology, the retrosynthetic analysis for sclerophytin F is shown in Scheme 53. Disconnections of triol **10** reveal alkene **272**. Conversion of the isopropyl group into a methyl ketone and the exocyclic alkene into an enol ether give the tricyclic system **273**. The latter could be obtained by Diels-Alder cycloaddition between diene **274** and methyl vinyl ketone. Disconnection of **274** revealed the bicyclic ketone **275**. Although no precedent has been reported for the synthesis of the oxonane unit **275** having the *S*-configuration at the C-3 stereocentre, we believe that the diazoketone **276** could be converted into an oxonium ylide and undergo a [2,3]-sigmatropic rearangment to form the bicyclic ketone **275**. Disconnections of the tetrahydropyran **276** give the methyl ketone **277**. Finally, further functional group manipulations reveal the commercially available 1,4-butanediol **147**.

Functional group manipulations at late stages in the synthesis of sclerophytin F (**10**) should allow the preparation of five other natural products: sclerophytin E (**9**), litophynin E (**11**), 6-acetoxy litophynin E (**12**), 6-ethoxy sclerophytin E (**13**) and 6-isovaleroyl sclerophytin E (**14**) (see Figure 4, introduction, section 1.2.1).

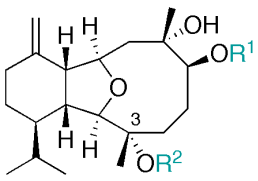


Scheme 53. Retrosynthetic analysis.

RESULTS AND DISCUSSION

1 Project Aim

The cladiellin family is the largest subclass of cembranoids with more than 100 members isolated to date. The intriguing architecture and biological and pharmacological activities of the cladiellins make them very attractive targets.[1,2] In 2002, Paquette and Friedrich performed a structural re-evaluation of several cladiellins and came to the conclusion that these natural products possess the *S*-configuration at the C-3 stereocentre (Figure 16) while the majority of the cladiellin natural products present a *R*-configuration at this position.[7,9,20] Following the successful syntheses of ten cladiellin natural products in the Clark group,[55] the total synthesis of the natural products with a different configuration at C-3 was an interesting challenge. Initial efforts were focused towards the total synthesis of the proposed structure of sclerophytin F.

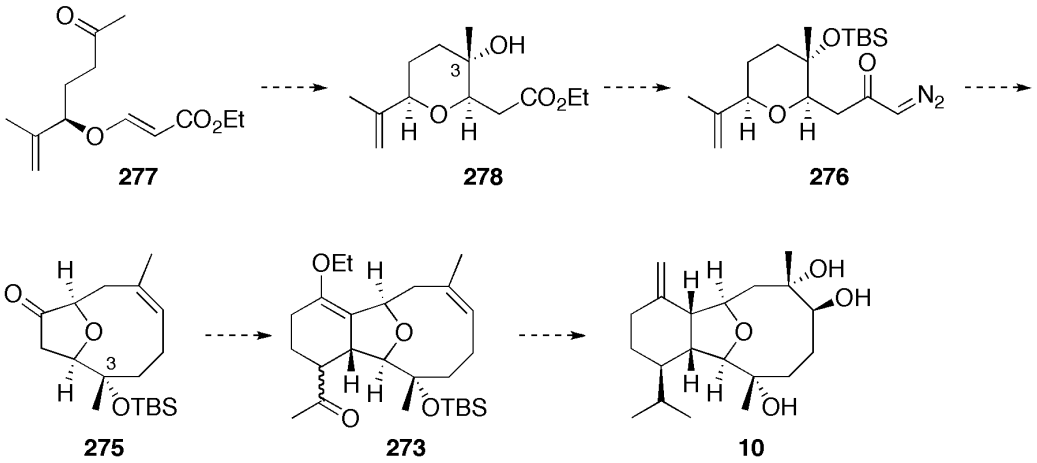


R^1 = H, R^2 = Ac, sclerophytin E **9**
R^1 = H, R^2 = H, sclerophytin F **10**
R^1 = H, R^2 = CO*n*-Pr, litophynin E **11**
R^1 = Ac, R^2 = CO*n*-Pr, 6-acetoxy litophynin E **12**
R^1 = Et, R^2 = Ac, 6-ethoxy sclerophytin E **13**
R^1 = CO*i*-Bu, R^2 = Ac, 6-isovaleroyl sclerophytin E **14**

Figure 16. Proposed structure of the cladiellin natural products having a *S*-configuration at C-3.

By expanding the methodology developed for the synthesis of the cladiellins,[55] the synthetic strategy was dependent upon a SmI_2-mediated radical cyclisation, a [2,3]-sigmatropic rearrangement to form the oxabicyclo[6.2.1]-5-undecen-9-one **275** and an intermolecular Diels-Alder cycloaddition to build the tricyclic core **273** (Scheme 54). The novelty of the route stems from installation

of the methyl substituent at the C-3 position at an early stage of the synthesis and prior to the key ring-forming steps. In the case of the total syntheses of the cladiellins having a *R*-configuration at C-3, the methyl group was introduced stereoselectively at a very late stage, after the formation of the tricyclic core.



Scheme 54. General approach towards the proposed structure of sclerophytin F.

2 Synthesis of the Methyl Ketone 277

Previous work performed in the Clark group on the total synthesis of cladiellins showed that the tetrahydropyranol **278** having a *S*-configuration at the C-3 position (Scheme 54) could be obtained by reductive cyclisation of the methyl ketone **277**.[58, 118] With this information in mind, three routes were designed to prepare methyl ketone **277** from diverse starting materials: 1,4-butanediol, 6-methyl-5-hepten-2-one and D-glutamic acid.

The synthesis of the proposed structure of sclerophytin F and the optimisation of some reactions were carried out using racemic material. The symbol (±) before the molecule number emphasizes the racemic form of the compound. Then, the enantioselective synthesis was reproduced under the optimised conditions.

2.1 Synthesis Starting from 1,4-Butanediol

Methyl ketone **277** can be prepared in racemic or enantiopure form from commercially available 1,4-butanediol **147**.

Racemic allylic alcohol **(±)-153** was obtained using a three-step sequence. Selective mono-protection of diol **147**, oxidation of remaining alcohol functionality followed by Grignard addition produced the racemic allylic alcohol **(±)-153** in good yield (Scheme 55).

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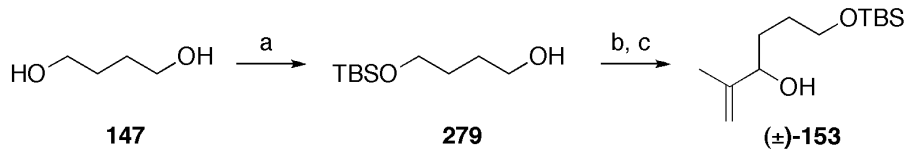
[118] Clark, J. S.; Hayes, S. T.; Blake, A. J.; Gobbi, L. *Tetrahedron Lett.* **2007**, *48*, 2501.

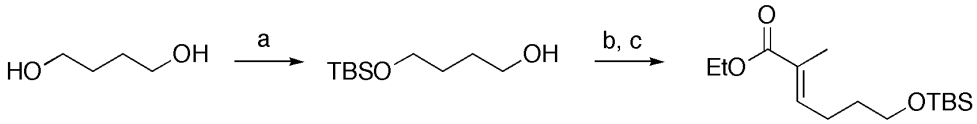


147 **279** **(±)-153**

a) TBSCl, Et_3N, CH_2Cl_2, 0 °C to rt, 93%; b) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, rt; c) 2-bromopropene, Mg, I_2, THF, reflux to 0 °C, 67% (2 steps).

Scheme 55. Synthesis of the racemic allylic alcohol **(±)-153**.

The enantioenriched allylic alcohol **153** was prepared from 1,4-butanediol **147** as well following the route developed in the Clark group.[55] Mono-protection, oxidation into the corresponding aldehyde and Wittig olefination with (carboxyethylidene)triphenylphosphorane furnished the α,ß-unsaturated ester **150** (Scheme 56).



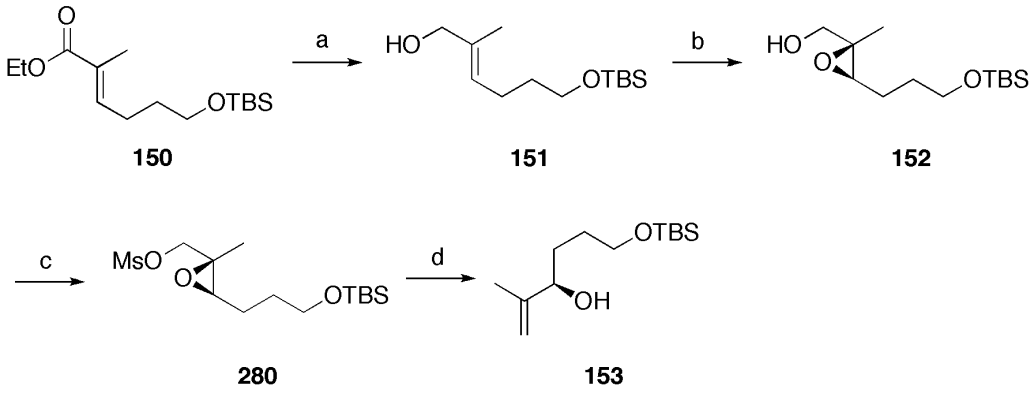
147 **279** **150**

a) TBSCl, Et_3N, CH_2Cl_2, 0 °C to rt, 93%; b) TEMPO, NaOCl, aq. $NaHCO_3$, H_2O, CH_2Cl_2, 0 °C; c) $Ph_3PC(CH_3)CO_2Et$, THF, rt, 86% (2 steps).

Scheme 56. Synthesis of the α,ß-unsaturated ester **150**.

Ester **150** was then reduced to give a primary alcohol **151** by treatment with DIBAL-H (Scheme 57). Sharpless asymmetric epoxidation[119] installed the first stereocentre and delivered epoxy alcohol **152** in high yield and with high enantiomeric excess.[120] Mesylation of the primary alcohol and epoxide opening by treatment with NaI and Zn powder provided allylic alcohol **153** as a single isomer in 94% yield over two steps.[121]

[119] Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
[120] Enantiomeric excess was determined by HPLC analysis of intermediate **281**. Column AD-H, temperature 25 °C, hexane:(hexane:propan-2-ol [98:2]) 90:10, flowrate 0.5 $mL.min^{-1}$, RT 46.3 min.
[121] Williams, D. R.; Meyer, K. G.; Shamim, K.; Patnaik, S. *Can. J. Chem.* **2004**, *82*, 120.

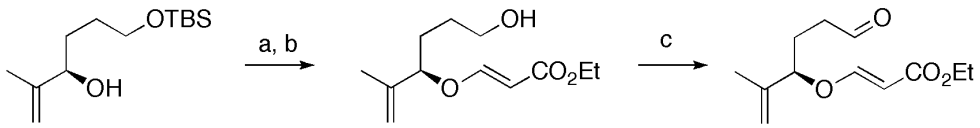


150 **151** **152** **280** **153**

a) DIBAL-H, CH_2Cl_2, −78 °C, 98%; b) (−)-DET, Ti(O*i*-Pr)$_4$, *t*-BuO_2H, CH_2Cl_2, −25 °C, 93%; c) MsCl, Et_3N, CH_2Cl_2, −10 °C; d) NaI, Zn, butan-2-one, 80 °C, 94% (2 steps).

Scheme 57. Synthesis of the enantiopure allylic alcohol **153**.

With a large quantity of allylic alcohol **153** in hand, efforts were turned towards the formation of the methyl ketone **277**. Alkylation of **153** with ethyl propiolate in presence of *N*-methyl morpholine afforded the *E*-vinylogous carbonate selectively (Scheme 58).[122] Subsequent treatment under acidic conditions cleaved the silyl ether to reveal the primary alcohol **281** (91-94% *ee* by chiral HPLC analysis). Finally, Swern or PCC oxidation of the alcohol afforded aldehyde **138**.



153 **281** **138**

a) $HCCCO_2Et$, NMM, CH_2Cl_2, rt; b) CSA, MeOH, 78% (2 steps); c) PCC, CH_2Cl_2, rt, 85% or $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, rt, 81%.

Scheme 58. Synthesis of the aldehyde **138**.

Previous work carried out in our group had shown that treatment of aldehyde **(±)-138** with an excess of trimethylaluminium installed the methyl group at the C-3 position, and subsequent Swern oxidation furnished the desired methyl ketone **(±)-277** in 45% yield over two steps (Scheme 59).[118]

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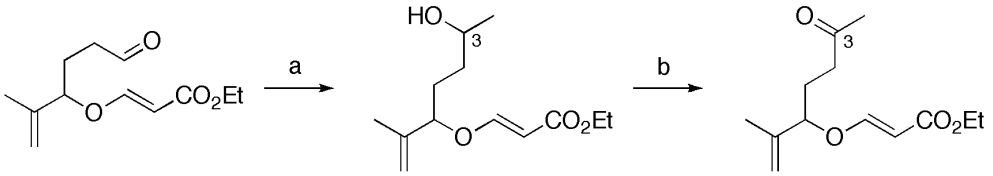
[122]a) Winterfeldt, E. *Chem. Ber.* **1964**, *97*, 1952; b) Winterfeldt, E.; Preuss, H. *Chem. Ber.* **1966**, *99*, 450.

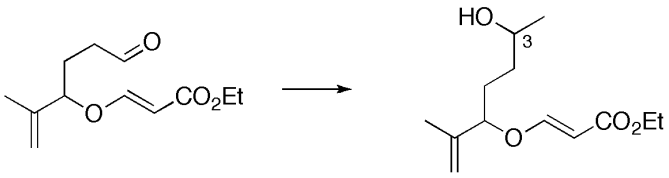


(±)-138 **(±)-282** **(±)-277**

a) $AlMe_3$, CH_2Cl_2, −78 °C to 0 °C; b) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, rt; 45% (2 steps).

Scheme 59. Clark synthesis of the methyl ketone **(±)-277**.

The relatively low yield of the reaction sequence led us to investigate other methylation conditions (Table 2). In a first approach, methylmagnesium bromide appeared to be the reagent of choice as the alcohol **(±)-282** was obtained in 71% yield (entry 2) while the use of trimethylaluminium and methyl lithium delivered **(±)-282** in yields of 58% and 37% respectively (entries 1 and 3). An excess of trimethylaluminium increased the yield dramatically (entries 4 and 5) and on large scale (≈31 mmol), these optimised conditions produced very satisfying results with the product isolated in 87% yield (entry 6). It is noteworthy that a moderate yield of 60% was obtained when the reaction was carried in presence of methylmagnesium bromide at this scale (entry 7).



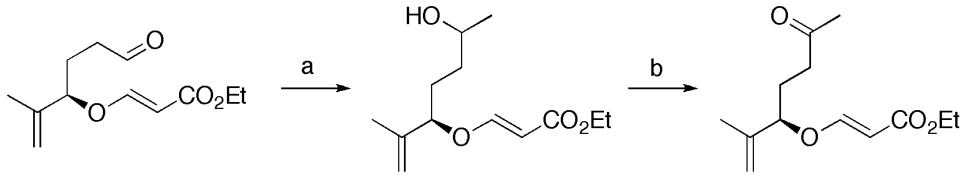
(±)-138 **(±)-282**

Entry	Conditions			Yield (%)
1	$AlMe_3$	1.0 eq	CH_2Cl_2	58 [a]
2	MeMgBr	1.2 eq	THF	71 [a]
3	MeLi	1.2 eq	Et_2O	37 [a]
4	$AlMe_3$	1.5 eq	CH_2Cl_2	72 [a]
5	$AlMe_3$	2.0 eq	CH_2Cl_2	83 [a]
6	$AlMe_3$	2.0 eq	CH_2Cl_2	87 [b]
7	MeMgBr	1.2 eq	THF	60 [b]

Reagents were added at −78 °C, then reactions were warmed to 0 °C until completion.
[a] Reactions carried on 1 mmol scale; [b] reactions carried on 31 mmol scale.

Table 2. Methylation of the aldehyde **(±)-138**.

The optimised procedure was then applied to non-racemic aldehyde **138** having high *ee* (Scheme 60). The synthesis of the desired methyl ketone **277** was completed by Swern oxidation of alcohol **282**.



138 **282** **277**

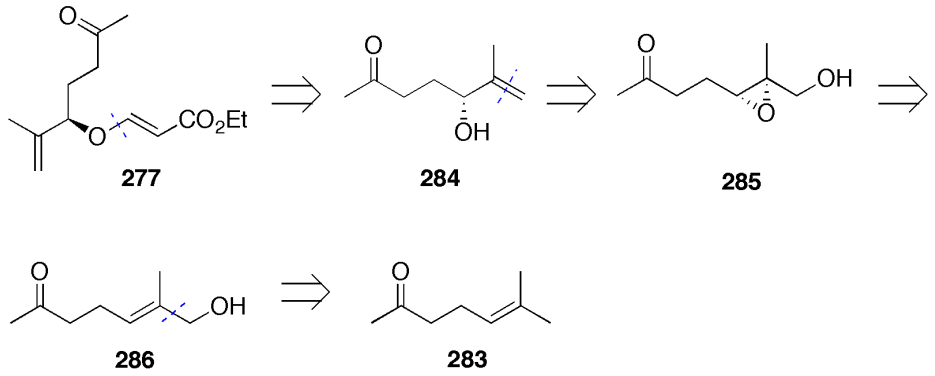
a) $AlMe_3$, CH_2Cl_2, −78 °C to 0 °C, 87%; b) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, rt, 89%.

Scheme 60. Completion of the synthesis of the methyl ketone **277**.

Methyl ketone **277** was obtained in 13 steps from commercially available 1,4-butanediol **147** and in 33% overall yield. More than 50 g of this intermediate was prepared with 91-94% *ee*. In parallel, other routes were investigated with the aim of shortening the synthesis of the methyl ketone **277**.

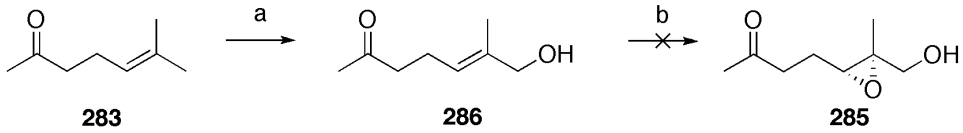
2.2 Synthesis Starting from 6-Methyl-5-hepten-2-one

A second approach towards the formation of the cyclisation precursor **277** was envisaged starting from 6-methyl-5-hepten-2-one **283** (Scheme 61). With the methyl ketone in place, only a few steps would be required to achieve the synthesis of the desired intermediate **277**. In this case, disconnection of the vinylogous carbonate **277** leads to the allylic alcohol **284** that can derive from epoxy-alcohol **285**. Further disconnections revealed the commercially available starting material **283**.



Scheme 61. Retrosynthetic analysis of methyl ketone **277** staring from the 6-methyl-5-hepten-2-one.

The synthesis started with an allylic oxidation of the alkene **283** in presence of a catalytic quantity of SeO_2 and *tert*-butyl hydroperoxide (Scheme 62).[123] The next step was the enantioselective allylic epoxidation of the alkene **286** but this reaction failed (Table 3, entries 1-4).

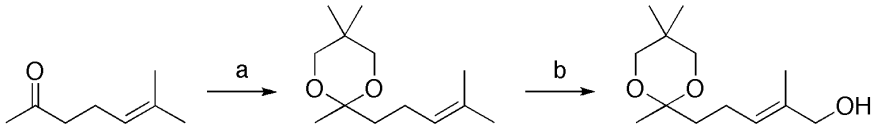


a) SeO_2, *t*-BuO_2H, CH_2Cl_2, rt, 54%; b) (−)-DET, Ti(O*i*-Pr)$_4$, *t*-BuO_2H, CH_2Cl_2.

Scheme 62. Attempted Sharpless asymmetric epoxidation.

In the total synthesis of (+)- and (−)-frontaline, Lee reported the formation of an analogous epoxide with the ketone functionality protected as an acetal in excellent yield and with good enantiomeric excess.[124] It is worth noting that the ketone moiety on **283** has to be protected as a bulky acetal using for example that derived from 2,2-dimethylpropane-1,3-diol; the use of ethylene glycol was proved to be unsuccessful. So, substrate **288** was synthesised in order to identify the appropriate reaction conditions for the formation of the epoxy-alcohol **285** (Scheme 63).

[123] Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526.
[124] Lee, A. W. M. *J. Chem. Soc., Chem. Commun.* **1984**, 578.



283 **287** **288**

a) 2,2-dimethylpropane-1,3-diol, *p*-TsOH, $HC(OEt)_3$, 55 °C, 91%; b) $C_6H_4(OH)CO_2H$, SeO_2, *t*-BuO_2H, CH_2Cl_2, rt, then $NaBH_4$, EtOH, 0 °C to rt, 38% (2 steps).

Scheme 63. Synthesis of acetal **288**.

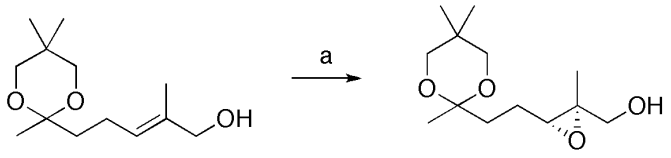
With the two substrates **286** and **288** in hand, Sharpless asymmetric epoxidation[119] was carried out at different temperatures and with various catalyst loadings (Table 3).

Entry	Substrate	Catalyst loading (%)		Temp. (°C)	Time (h)	Outcome
		$Ti(Oi\text{-}Pr)_4$	(−)-DET			
1	**286**	20	30	−20	168	complex mixture
2	**286**	20	30	rt	168	complex mixture
3	**286**	50	50	rt	120	complex mixture
4	**286**	100	100	rt	28	complex mixture
5	**288**	20	30	−20	18	47%
6	**288**	20	30	rt	18	51%
7	**288**	100	100	rt	48	decomposition

Reactions were carried on 0.10 mmol scale.

Table 3. Attempted epoxidation of allylic alcohols **286** and **288** using Sharpless asymmetric epoxidation conditions.

The results were consistent with Lee's observations. In the absence of an acetal protecting group (entries 1-4), the reaction led to a complex mixture of products. The products were observed by ^1H NMR analysis when the ketone was masked as an acetal with a bulky group only (entries 5 and 6). Under these conditions, epoxy-alcohol **289** was isolated in 47% yield (Scheme 64). The low yields and difficulties in obtaining reproducible yields meant that this route was abandoned.



288 **289**

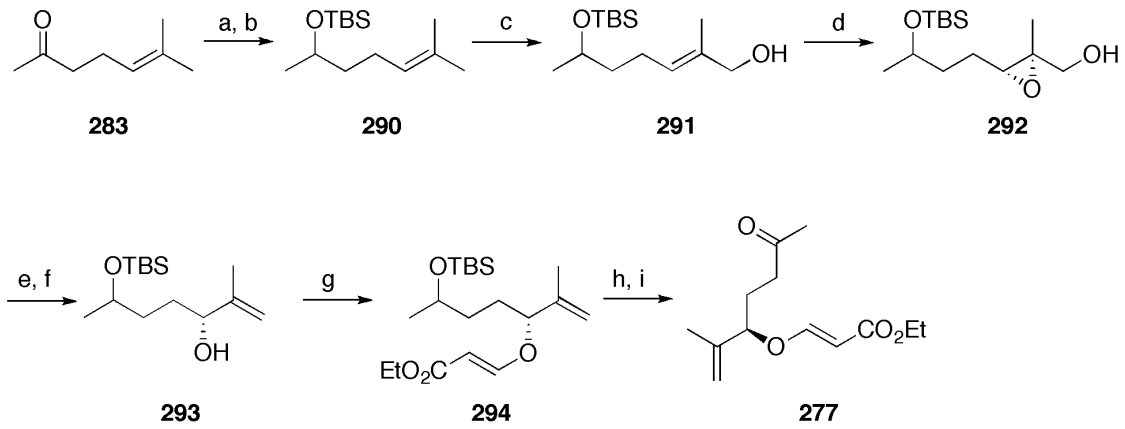
a) (−)-DET, Ti(O*i*-Pr)$_4$, *t*-BuO$_2$H, CH_2Cl_2, −25 °C, 47%.

Scheme 64. Sharpless asymmetric epoxidation on substrate **288**.

In parallel to these attempts, a completely different approach was envisaged. In this case, the ketone was masked as the corresponding TBS protected alcohol.

Reduction of the ketone **283** to give the corresponding alcohol[125] followed by protection as a silyl ether furnished **290** (Scheme 65).[126] Catalytic selenium allylic oxidation in presence of *tert*-butyl hydroperoxide provided the allylic alcohol **291**.[123] The enantioenriched epoxy-alcohol **292** (a mixture of diastereomers) was afforded by asymmetric Sharpless epoxidation[119] in high yield and enantiomeric excess.[127] As previously observed (see results and discussion, section 2.1.), mesylation of the epoxy-alcohol **292** and treatment with NaI and Zn powder in refluxing butane-2-one led to the formation of the allylic alcohol **293** in 79% yield over two steps. The reaction-sequence ended by an *O*-alkylation with ethyl propiolate, TBS removal and oxidation of the corresponding secondary alcohol. Following this pathway, methyl ketone **277** was obtained in 26% yield over 10 steps and with 82-95% *ee*.

[125] Liang, S.; Paquette, L. A. *Tetrahedron Asymmetry*, **1990**, *1*, 445.
[126] Hanessian, S.; Cantin, L. D.; Andreotti, D. *J. Org. Chem.* **1999**, *64*, 4893.
[127] Enantiomeric excess was determined on methyl ketone **277**. Column AD-H, temperature 25 °C, hexane:propan-2-ol 50:1, flowrate 1.0 mL.min^{-1}, RT 23.9 min.

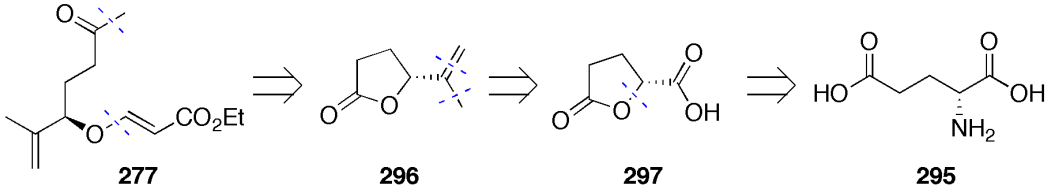


a) $LiAlH_4$, Et_2O, 0 °C, 88%; b) TBSCl, imidazole, DMF, rt, 93%; c) *i*. $C_6H_4(OH)CO_2H$, SeO_2, *t*-BuO_2H, CH_2Cl_2, rt, *ii*. $NaBH_4$, EtOH, 0 °C to rt, 55%; d) (−)-DET, Ti(O*i*-Pr)$_4$, *t*-BuO_2H, CH_2Cl_2, −25 °C, 93%; e) MsCl, Et_3N, CH_2Cl_2, −15 °C; f) NaI, Zn, butan-2-one, 80 °C, 79% (2 steps); g) $HCCCO_2Et$, NMM, CH_2Cl_2, rt; h) CSA, MeOH, 83% (2 steps); i) PDC, CH_2Cl_2, rt, 93%.

Scheme 65. Synthesis of methyl ketone **277** starting from 6-methyl-5-hepten-2-one.

2.3 Synthesis Starting from D-Glutamic acid

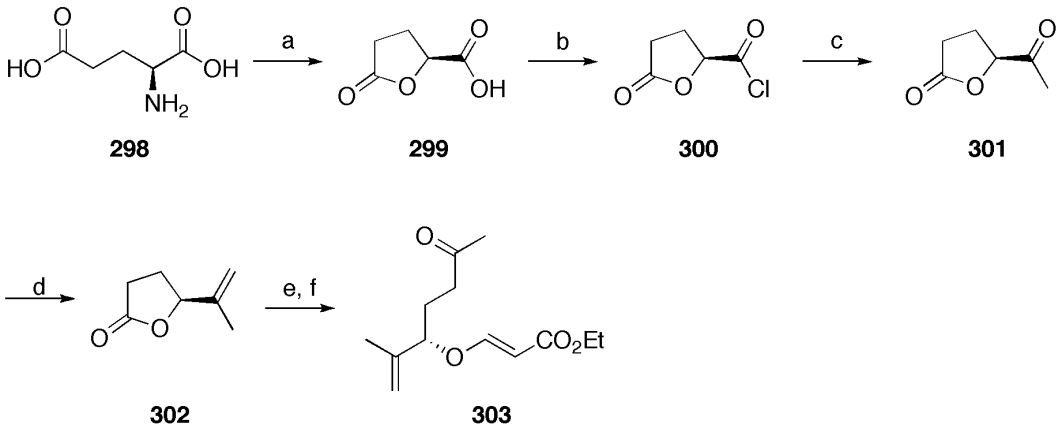
In order to decrease the number of steps for the synthesis of the methyl ketone **277**, another route using enantiopure D-glutamic acid **295** as a starting material was investigated (Scheme 66). Disconnection through the methyl ketone and the α,β-unsaturated ester bonds of compound **277** revealed lactone **296**. The propene moiety could be derived from the corresponding carboxylic acid **297** that could be formed by cyclisation of the D-glutamic acid **295**. However, due to the fact that the unnatural D-glutamic acid is 25 times more expensive than the natural amino acid, the route was developed using the natural enantiomer, L-glutamic acid **298**.[128]



Scheme 66. Retrosynthetic analysis of methyl ketone **277** using D-glutamic acid as starting material.

[128] Sigma-Aldrich prices, December 2014.

Two intramolecular cyclisations of **298** under acidic conditions furnished lactone **299** in quantitative yield (Scheme 67).[129] Treatment with oxalyl chloride in toluene at 60 °C produced the acyl chloride **300** which, after distillation, was reacted with methylmagnesium bromide to form **301.**[130] A Wittig olefination reaction was used to install the propene motif.[131] Finally, methyl addition followed by alkylation with ethyl propiolate in presence of *N*-methylmorpholine provided the methyl ketone **303** in 65% yield over two steps but in only 62% *ee* (chiral HPLC analysis).[132]



a) HCl, H_2O, $NaNO_2$, 0 °C to rt, 100%; b) $(COCl)_2$, $PhCH_3$, 60 °C, 67%; c) MeMgBr, THF, −78 °C, 56%; d) Ph_3PCH_3Br, *t*-BuOK, THF, 0 °C to rt, 42%; e) MeLi, Et_2O, −78 °C; f) $HCCCO_2Et$, NMM, CH_2Cl_2, rt, 65% (2 steps).

Scheme 67. Synthesis of the methyl ketone **303** starting from L-glutamic acid.

It is necessary to understand which step is responsible of the erosion of the enantiomeric excess in order to improve the efficiency of the route. Berti *et al*. reported that an optical purity of only 80% was obtained when the lactone **299** was distilled whereas crystallisation from chloroform furnished the product in 96% *ee*. [133] It was also suggested that a racemisation could be observed during the concentration of the strongly acidic solution. Finally, the use of ethyl acetate or ethanol should be avoided because the solvent could react with the lactone.

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[129] Larchevêque, M.; Lalande, J. *Bull. Chem. Soc. Fr.* **1987**, 116.
[130] Cavé, A.; Chaboche, C.; Figadère, B.; Harmange, J. C.; Laurens, A.; Peyrat, J. F.; Pichon, M.; Szlosek, M.; Cotte-Lafitte, J.; Quéro, A. M. *Eur. J. Med. Chem.* **1997**, *32*, 617.
[131] Hô, P.-T.; Kolt, R. J. *Can. J. Chem.* **1982**, *60*, 663.
[132] Nagano, H.; Mikami, A. ; Yajima, T. *Tetrahedron Lett.* **2003**, *44*, 6867.
[133] Berti, G.; Caroti, P.; Catelani, G.; Monti, L. *Carbohydrate Research,* **1983**, *124*, 35.

It is unlikely that epimerisation occurred during the conversion of the acid into the acyl chloride **300** or the Grignard addition since the $[\alpha]_D$ recorded for methyl ketone **301** corresponded to the one reported by Berti.[133] No information about the enantiopurity of intermediate **302** had been reported previously, thus the main factor responsible for the erosion of the enantiopurity are the reaction conditions used in the Wittig olefination step.

Despite the modest yields and enantiomeric excess, we were pleased to observe the feasibility of this much shorter route. With further optimisations, this route would deliver the methyl ketone **277** in just 6 steps.

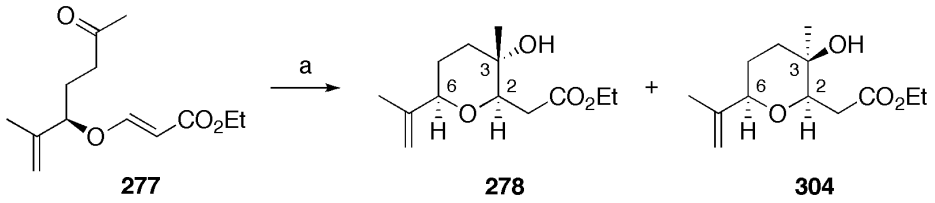
2.4 Summary

Three different routes have been developed to achieve the synthesis of methyl ketone **277**. Building on previous experience, Sharpless asymmetric epoxidation allowed the installation of the key stereocentre in high enantiomeric excess. Overall, the desired intermediate **277** was prepared in 13 steps from 1,4-butanediol **147**. The route was then improved and starting from 6-methyl-5-hepten-2-one **283**, the methyl ketone **277** was obtained in only 10 steps.

A third promising route beginning from L-glutamic acid **298** was also investigated. Although the methyl ketone **303** was accessed in only 6 steps, erosion of the enantiomeric excess of the starting amino acid was observed. Thus this route requires further optimisation before being applied to the total synthesis of methyl ketone **277**.

3 Synthesis of the Diazoketone 276

With access to a large quantity of methyl ketone **277**, the synthesis of the diazoketone **276** was investigated. Treatment of methylketone **277** with a freshly prepared solution of SmI_2 in tetrahydrofuran provided a mixture (12:1) of inseparable diastereomers in which the desired 2,3-*trans*-tetrahydropyranol **278** predominated (Scheme 68).[118,134]



277 **278** **304**

a) SmI_2, MeOH, THF, rt, dr 12:1, 89%.

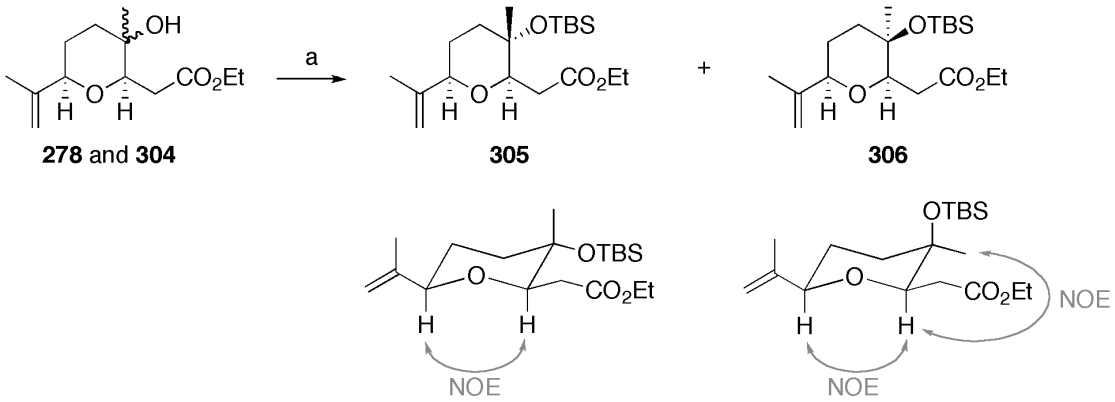
Scheme 68. SmI_2-mediated radical cyclisation of methyl ketone **277**.

Separate signals for the diastereomeric alcohols **278** and **304** are clearly distinguishable in the ^1H NMR spectrum. The methyl group at the C-3 position appears as a singlet at 1.21 ppm for **278** while it is shifted to 1.15 ppm for the 2,3-*cis* tetrahydropyranol **304**. The chemical shifts for H-2 are also representative of the presence of the two diastereomers. They are found at 3.73 ppm and 3.98 ppm depending on the configuration. In the same way, the signal of the proton H-6 is at 3.79 ppm for **278** and at 4.12 ppm for **304**. Finally, the representative signals of the alkene moiety are also slightly shifted. One of the protons of the CH_2 of the 2,3-*trans* product **278** can be seen at 4.81 ppm,

[134] Matsuo, G.; Kadohama, H.; Nakata, T. *Chem. Lett.* **2002**, 148.

the second one appearing at 4.93 ppm. In contrast, the minor diastereomer **304** shows the alkene signals at 4.93 ppm and 4.96 ppm.

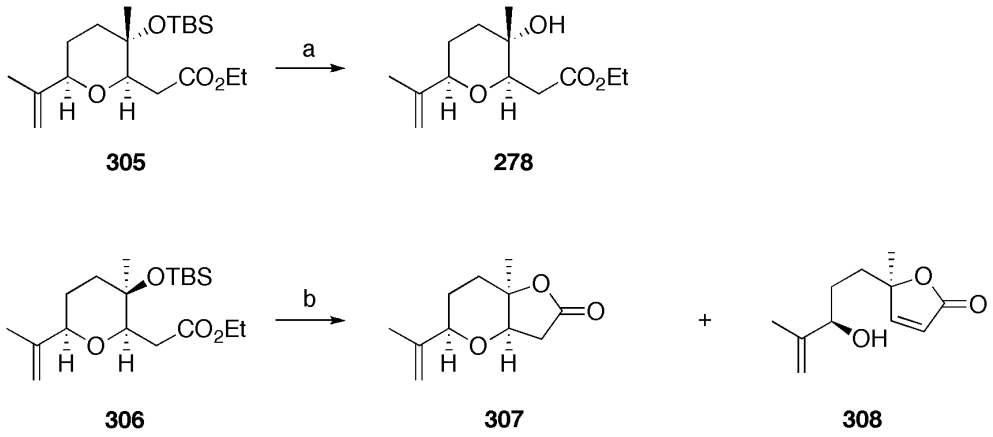
Silylation of the two alcohols **278** and **304** in the mixture meant a change of the polarity and allowed the separation of the two diastereoisomers **305** and **306** by flash column chromatography (Scheme 69). NOE experiments on the two pure silyl ethers **305** and **306** confirmed that the 2,3-*trans* tetrahydropyranol was the major product derived from the SmI_2-mediated cyclisation reaction.[118]



a) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C to rt, 87% **305** and 5% **306**.

Scheme 69. Silyl ether protection of the tetrahydropyranols **278** and **304**.

In order to characterise without ambiguity the diastereomers **278** and **304**, small quantities of the corresponding silyl ethers **305** and **306** were treated with TBAF (Scheme 70).

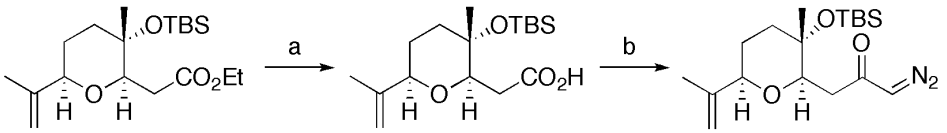


a) TBAF, THF, rt, 45%; b) TBAF, AcOH, THF, rt, 47% **307**, traces of **308**.

Scheme 70. Silyl ether cleavage of the tetrahydropyrans **305** and **306**.

While TBS removal on substrate **305** led to the isolation of tetrahydropyranol **278**, the corresponding tertiary alcohol **304**, deriving from **306**, was not observed. Instead, lactonisation occurred providing the lactone **307** (Scheme 70), a natural product that was isolated in 1993 from the sun-cured leaves of Greek tobacco.[118,135] In the absence of acetic acid, after 24 hours, the lactone **307** was isolated in 41% yield as well as the unreacted starting material **306** (18% yield). It is noteworthy that, under the previously described conditions, the reaction was completed after 10 days at room temperature and traces of the corresponding opened diol **308** were observed.

The synthesis continued with the saponification of the ester **305** to give the corresponding carboxylic acid **309**. Finally, the carboxylic acid **309** was converted into a mixed anhydride prior to be treated with a freshly distilled ethereal solution of diazomethane.[136] After 4 days at room temperature, diazoketone **276** was isolated in 89% yield.



305 **309** **276**

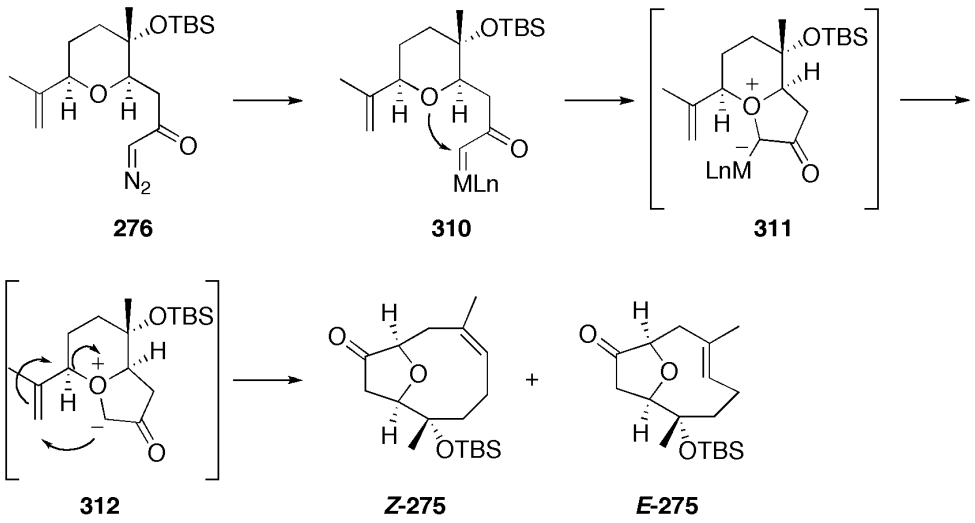
a) LiOH, EtOH:H_2O (3:1), rt, 96%; b) *i*-BuO_2CCl, Et_3N, Et_2O, rt, then CH_2N_2, Et_2O, 0 °C to rt, 89%.

Scheme 71. Completion of the synthesis of the diazoketone **276**.

[135] Petterson, T.; Eklund, A. –M.; Wahlberg, I. *J. Agric. Food. Chem.* **1993**, *41*, 2097.
[136] Hudlický, M. *J. Org. Chem.* **1980**, *45*, 5377.

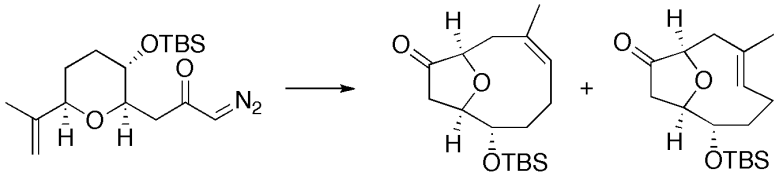
4 Synthesis of the Bicyclic Ketone: Oxonium Ylide Formation and [2,3]-Sigmatropic Rearrangement

Based on the previous work on the total synthesis of the cladiellin natural products within the Clark group,[55,57,59] it was anticipated that the oxonene unit of the cladiellin natural products could be formed by treatment of the diazoketone **276** with a transition metal complex to produce a metal carbenoid **310** (Scheme 72). The latter would evolve into the oxonium ylide **312**, or its metal-bound equivalent, that undergoes a [2,3]-sigmatropic rearrangement leading to an isomeric mixture of *Z*- and *E*- bicyclic ketones ***Z*-275** and ***E*-275**.



Scheme 72. Mechanism of the oxonium ylide formation followed by the [2,3]-sigmatropic rearrangement.

This transformation had been carried out previously in our group on the closely related diazoketone **(±)-140**. It had been demonstrated that the choice of the catalyst, the solvent and the temperature of the reaction influence the yields and the diastereoselectivity significantly (Table 1 and see introduction, section 2.10).[55] While the use of a copper complex gave a mixture of *Z* and *E* isomers in favour of the less strained bicyclic ketone ***Z*-142**, it appeared that the diastereoselectivity was reversed in presence of a rhodium catalyst affording the *E*-isomer as the major product. The use of different solvents also influenced the yield and the isomer ratio.



(±)-140	(±)-*Z*-142	(±)-*E*-142
$Cu(hfacac)_2$, CH_2Cl_2, relfux, 95%	5	1
$Rh_2(tpa)_4$, DCE, reflux, 56%	1	6.3

Scheme 73. Previous studies on metal-catalyzed reactions of diazoketone **(±)-140** to give bridged-bicyclic ethers **(±)-*Z*-142** and **(±)-*E*-142**.

In light of these results, investigations on the metal-mediated reactions of diazoketone **(±)-276** were undertaken (Table 4). A good yield and *Z*:*E* ratio had been observed previously when copper(II) hexafluoroacetylacetonate was employed in refluxing dichloromethane (Scheme 73) and so, the diazoketone **(±)-276** was initially subjected to these conditions. Interestingly, the ratio of the two isomers was only 1.8:1 in favour of the bicyclic ketone **(±)-*Z*-275** with an excellent overall yield of 98%. The major product was isolated by flash column chromatography on silica gel impregnated with silver nitrate;[137] subsequent ^{1}H NMR, NOE experiments and X-ray analysis (Figure 17) allowed confirmation of the relative stereochemistry.

[137] a) Williams, C. M.; Mander, L. N. *Tetrahedron* **2001**, *57*, 425; b) Cert, A.; Moreda, W. *J. Chromatography A* **1998**, *823*, 291.

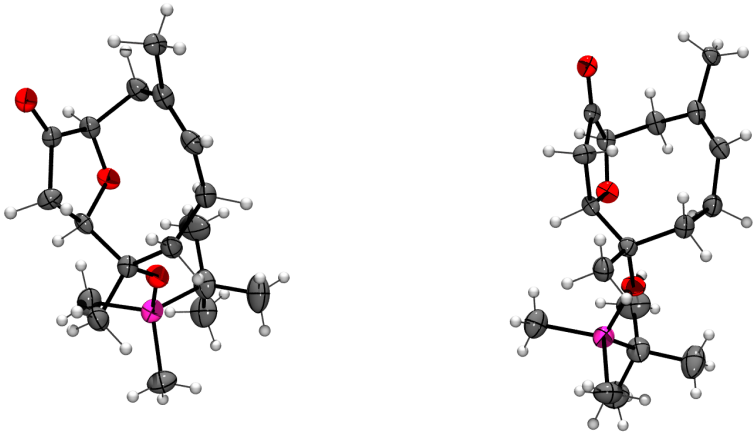
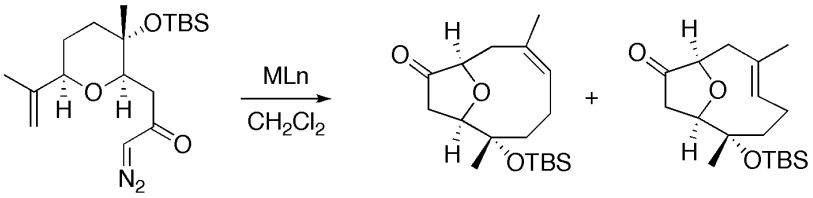


Figure 17. X-ray crystal structure of bridged-bicyclic ether **(±)-*Z*-275** (ORTEP plot with 50% thermal elipsoids).

The significant differences between the *Z*:*E* ratios resulting from the metal-mediated reactions of diazoketone **(±)-140** and those from the corresponding reactions of the C-3 methyl-substituted diazoketone **(±)-276** was noteworthy. In order to probe the behaviour of the reaction when a methyl group is present at the C-3 position of the diazoketone, and hopefully increase the isomeric ratio, various catalysts were screened in refluxing dichloromethane. In the presence of copper(II) acetylacetonate, only the starting material was evident after 8 hours (entry 2). A slight increase in the *Z*:*E* ratio was observed by the use of copper(II) trifluoroacetylacetonate (entry 3) but this was accompanied of a lower yield (70%). Replacing the copper complex with a rhodium catalyst increased the diastereoselectivity towards the formation of the *Z*-bicyclic ketone, leading to a ratio of 7.5:1 with rhodium acetate (entry 4), and 5.0:1 when rhodium(II) heptafluorobutanamide was employed as catalyst (entry 5). However, these improved isomer ratios were accompanied by decreases in yield (61% and 42% respectively). Other rhodium catalysts such as rhodium(II) triluoroacetate, rhodium(II) trifluoroacetamide or rhodium(II) tetrakis (perfluorobutyrate) led to similar observations with moderate yields and diastereomeric ratios (entries 6, 7, 8). It is worth noting that *Z*-isomer **(±)-*Z*-275** was isolated as the sole isomer but in poor yield (14%) when rhodium(II) triphenylacetate was used as the catalyst (entry 9).



Entry	Catalyst [a]	Time	Yield [b] (%)	Ratio *Z*:*E* [c]
1	$Cu(hfacac)_2$	1 h	98	1.8:1
2	$Cu(acac)_2$	8 h	-	-
3	$Cu(tfacac)_2$	30 min	70	2.3:1
4	$Rh_2(OAc)_4$	30 min	42	7.5:1
5	$Rh_2(pfm)_4$	15 min	61	5.0:1
6	$Rh_2(tfacam)_4$	1.5 h	72	2.0:1
7	$Rh_2(tfa)_4$	15 min	69	3.1:1
8	$Rh_2(pfb)_4$	30 min	69	2.1:1
9	$Rh_2(tpa)_4$	30 min	14	1.0:0

Reactions were performed on 55-156 μmol scale. [a] Catalyst loading 5 mol%; [b] Isolated yield of the *E* and *Z* isomers; [c] Isomer ratio determined by ^{1}H NMR analysis of the crude mixture of isomers. For the Rh catalyst, filtration on alumina was done prior to the ^{1}H NMR.

Table 4. Studies on metal-catalyzed reactions of diazoketone **(±)-276** to give bridged-bicyclic ethers **(±)-*Z*-275** and **(±)-*E*-275** in refluxing dichloromethane.

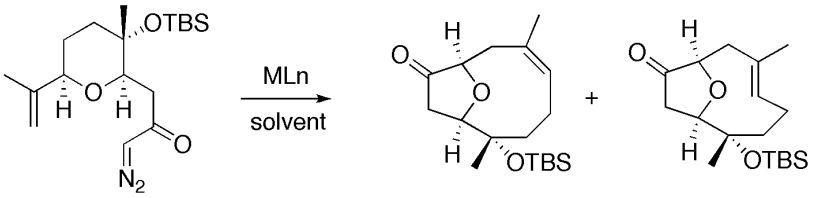
Based on these results, two catalytic systems required further attention: copper(II) hexafluoroacetylacetonate, which furnished a 1.8:1 mixture of *Z*- and *E*-bridged-bicyclic ethers in an excellent yield of 98%, and rhodium(II) heptafluorobutanamide, which delivered the bicyclic ketones **(±)-275** with an improved ratio of 5:1 favouring the less strained *Z*-alkene but with a moderate yield of 61%.

Consequently, the metal-mediated reaction of diazoketone **(±)-276** was studied in the presence of these two complexes in different solvents (Table 5). The reaction was completed in only one hour in refluxing dichloromethane in the presence of copper(II) hexafluoroacetylacetonate (entry 1), while a longer reaction time was necessary at room temperature (entry 2), affording the two bicyclic ketones **(±)-*Z*-275** and **(±)-*E*-275** in similar yields and ratios. An increase of the ratio in favour of the *Z*-isomer was observed when the reaction was

performed in refluxing DCE and toluene, but moderate to poor yields were obtained (entries 3 and 4). Interestingly, only the less strained *Z*-alkene was detected on ^{1}H NMR analysis of the crude mixture when the reaction was performed in refluxing tetrahydrofuran. In this case, the desired product was isolated in low yield along with an unidentified by-product[138] (entry 6). Using acetonitrile (entry 7) the formation of side-products was also observed correlating with a low isolated yield of 22% of the desired *Z*-isomer.

Similar observations were made when a rhodium complex catalysed the reaction. Reactions performed in chlorinated solvents (dichloromethane and DCE) gave a moderate yields and *Z*:*E* ratios favouring the desired bridged-bicyclic ether **(±)-275** (entries 8 and 9). A higher temperature and switching the solvent to toluene resulted in a slight increase in the *Z*:*E* ratio (entry 10) but was accompanied of a dramatic reduction in yield and the formation of by-products was observed. Reactions performed in tetrahydrofuran or acetonitrile led to the formation of the *Z*-bicyclic ketone exclusively, along with an unknown by-product (entries 11 and 12). It should be noted that different side-products were obtained under each set of reaction conditions. Despite their isolation and their NMR characterisation, we were not able to fully elucidate their structure.

[138] NMR analysis did not allow the determination of its structure.



(±)-276 **(±)-*Z*-275** **(±)-*E*-275**

Entry	Catalyst [a]	Solvent	Temp.	Time	Yield [b] (%)	Ratio *Z*:*E* [c]
1	$Cu(hfacac)_2$	CH_2Cl_2	reflux	1 h	98	1.8:1
2	$Cu(hfacac)_2$	CH_2Cl_2	rt	7 h	92	1.2:1
3	$Cu(hfacac)_2$	DCE	reflux	30 min	77	2.9:1
4	$Cu(hfacac)_2$	$PhCH_3$	reflux	30 min	49	3.0:1
5	$Cu(hfacac)_2$	Et_2O	reflux	4 h	17 [d]	1.0:1
6	$Cu(hfacac)_2$	THF	reflux	30 min	39	>20:1
7	$Cu(hfacac)_2$	MeCN	reflux	2.5 h	22	1.3:1
8	$Rh_2(pfm)_4$	CH_2Cl_2	reflux	15 min	61	5.0:1
9	$Rh_2(pfm)_4$	DCE	reflux	30 min	68	6.3:1
10	$Rh_2(pfm)_4$	$PhCH_3$	reflux	30 min	29	13:1
11	$Rh_2(pfm)_4$	THF	reflux	30 min	31	>20:1
12	$Rh_2(pfm)_4$	MeCN	reflux	20 min	32	>20:1

Reactions were performed on 55-156 μmol scale; [a] Catalyst loading 5 mol%; [b] Isolated yield of the *E* and *Z* isomers; [c] Isomer ratio determined by ^{1}H NMR analysis of the crude mixture. For reactions involving the Rh catalyst, filtration on alumina was done prior to the ^{1}H NMR analysis; [d] Only the *Z* isomer was isolated.

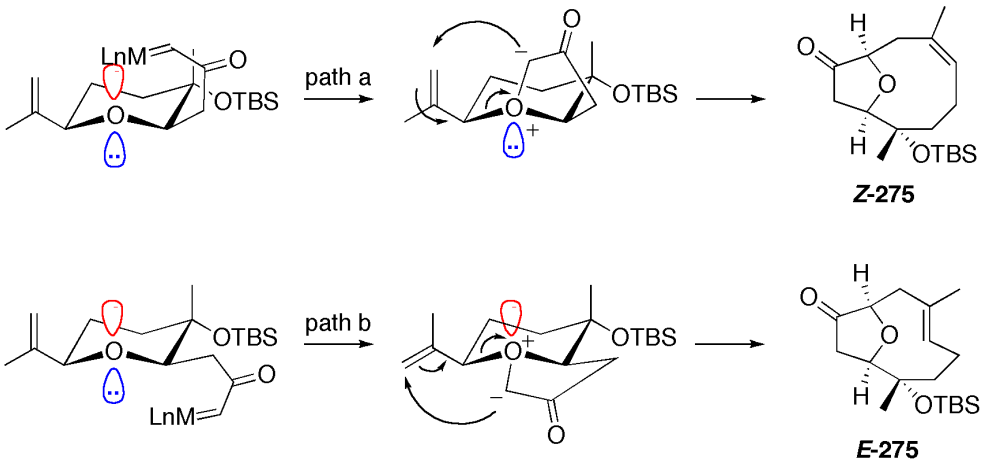
Table 5. Studies on $Cu(hfacac)_2$- and $Rh_2(pfm)_4$-catalyzed reactions of the diazoketone **(±)-276** to give bridged-bicyclic ethers **(±)-*Z*-275** and **(±)-*E*-275** in various solvents.

The temperature did not significantly affect the yield and the diastereoselectivity. In contrast, the choice of the solvent appeared to be much more important, influencing the *Z*:*E* ratio and the formation of by-products. The best compromise between *Z*:*E* ratio and yield was observed when the reactions were carried in chlorinated solvents. Although a reversal of diastereoselectivity was reported by Clark *et al*. for reactions on substrate **(±)-140**, during the total synthesis of members of the cladiellin family of natural products, the presence of a methyl group at the C-3 position modified the outcomes of these reactions significantly. In no case was the bicyclic ketone **(±)-*E*-275** formed as the major

product of the reaction. The best ratios in favour of the *Z*-alkene were accompanied of poor yields due to the formation of unidentified by-products.

In order to prove that isomerisation of the bicyclic ketone **(±)-*E*-275** into the corresponding *Z*-alkene **(±)-*Z*-275** had not occurred under the reaction conditions, several control reactions were performed: the *E*-isomer **(±)-*E*-275** was re-subjected to the reaction conditions reported in Table 5 (entries 4, 6, 7, 10, 11 and 12). After 6 hours, the bridged-bicyclic ether **(±)-*E*-275** was recovered and neither the alkene **(±)-*Z*-275** nor by-products were detected.

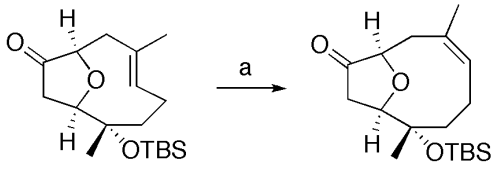
In terms of the mechanism for the key process, analysis of the metal carbenoid and ylide conformers (Scheme 74) suggests that the transition state leading to the formation of the less strained bicyclic ketone ***Z*-275** is more favourable than leading to the corresponding *E*-alkene ***E*-275**. Indeed, the formation of the oxonium ylide should occur preferentially *via* path a, since this reaction with the "axial" lone pair of the oxygen produces a less strained five-membered ring compared to path b. In path b, the lone pair of the ether oxygen is in an "equatorial" position giving a more strained bicyclic intermediate.



Scheme 74. Metal carbenoid conformers leading to the formation of the bicyclic ketones ***Z*-275** and ***E*-275**.

Previous experiments and computational studies on the [2,3]-sigmatropic rearrangement reaction within the Clark group[55] have led to the conclusion that the reaction proceeds through a metal-bound ylide and that the *E*:*Z*-ratio reflects the kinetics of the reaction. The low-yielding experiments can be attributed to formation of a number of by-products. It is important to note that other rearrangements (see introduction, section 3.1) could occur including: C-H insertion, [1,2]- and [1,4]- rearrangement, cyclopropanation reaction, dimerization and participation of the solvent. In conclusion, the presence of a methyl group had a significant influence on the outcome of the rearrangement reaction. Further studies need to be undertaken to completely understand the mechanism, the kinetics and the diastereoselectivity of the reaction.

Since none of the conditions tested for the tandem oxonium ylide formation and the [2,3]-sigmatropic rearrangement sequence proved to be particularly efficient for the selective formation of the desired *Z*-isomer ***Z*-275** in high yield, isomerisation was considered (Scheme 75).[57] Total conversion of the *E*- into the *Z*-alkene was achieved in one hour when the reaction was performed in toluene in presence of sub-stoichiometric amounts of 1,1'-azobis(cyclohexane-carbonitrile) and ethanethiol. The bicyclic ketone ***Z*-275** was isolated in 85% yield. When the isomerisation was performed on the crude product of the previous reaction, the desired *Z*-alkene was obtained in an excellent 89% overall yield. This good result was unexpected. Indeed, in the absence of the methyl group at the C-3 position, the isomerisation proceeded with a low yield of 56%.[57]



***E*-275** ***Z*-275**

a) VAZO 88®, EtSH, $PhCH_3$, 90 °C, 85%.

Scheme 75. Isomerisation of the *E*- into the *Z*-bridged bicyclic ether.

Gratifyingly, the outstanding 98% yield obtained from the reaction catalysed by copper(II) hexafluoroacetylacetonate combined with the ability to isomerise the undesired *E*-alkene into the corresponding *Z*-alkene constituted a very efficient way to obtain the desired bicyclic ketone ***Z*-275** selectively.

5 Synthesis of the Oxatricyclic Ring System

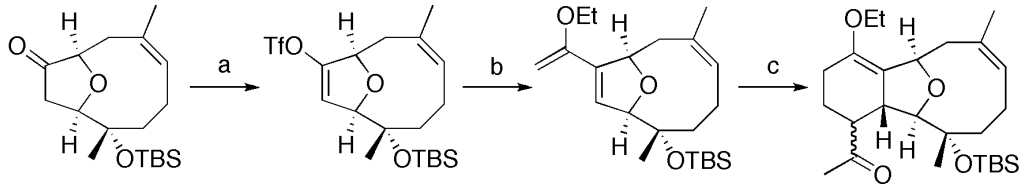
5.1 General Approach

5.1.1 Construction of the Tricyclic Core

As outlined in the retrosynthetic analysis, it was anticipated that the tricyclic skeleton of sclerophytin F could be constructed using a three-step sequence as previously reported in the total syntheses of cladiellin natural products.[55,57,59]

The bicyclic ketone ***Z*-275** was first converted into the corresponding enol triflate **313** by treatment with *N*-phenyl-*bis*(trifluoromethanesulfonimide) and sodium *bis*(trimethylsilyl)amide (Scheme 76). Stille coupling of the triflate **313** with tributyl(1-ethoxyvinyl)tin furnished the unstable diene **274**,[139] and this diene was reacted with freshly distilled methyl vinyl ketone in a thermal Diels-Alder cycloaddition reaction. The intermolecular Diels-Alder reaction delivered a 1:1 mixture of *exo* and *endo* cycloadducts **273** in 65% yield over three steps.

[139] Kwon, H. B.; McKee, B. H.; Stille, J. K. *J. Org. Chem.* **1990**, *55*, 3114.



a) NaHMDS, $PhN(Tf)_2$, THF, −78 °C; b) $CH_2C(OEt)SnBu_3$, $Pd(PPh_3)_4$, LiCl, THF, 80 °C; c) $CH_2CHCOCH_3$, $PhCH_3$, 120 °C, 65% (3 steps), *exo*:*endo* 1:1.

Scheme 76. Synthesis of the tricyclic core **273** by Stille coupling and Diels-Alder cycloaddition.

The thermal Diels Alder cycloaddition reaction proceeded regioselectively and with diastereofacial selectivity. There was poor *endo*:*exo* selectivity but this was of no consequence. The matched electronics of the electron-rich diene and the electron-deficient dienophile in the two transition states **314** and **315** (Figure 18) results in high regioselectivity. It is assumed that the facial selectivity arises from the concave shape of the *Z*-bicyclic ketone ***Z*-275** leading to an attack on the convex face.

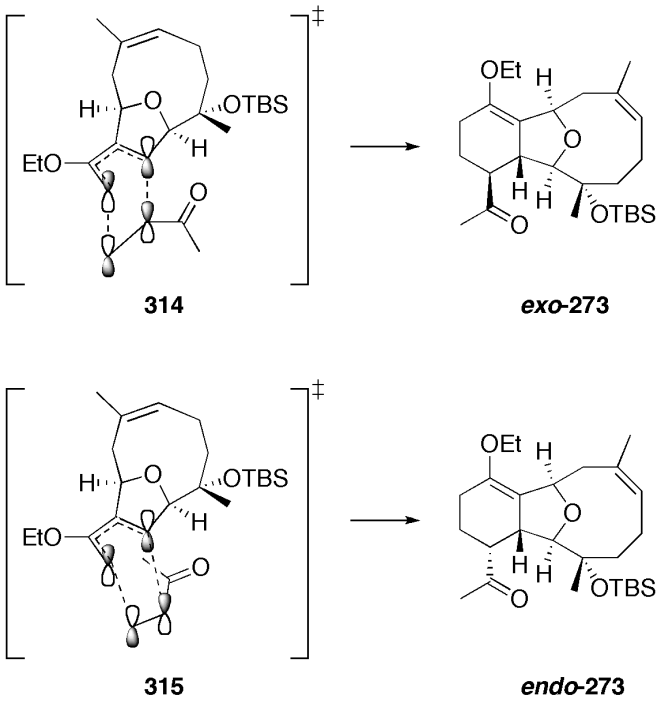
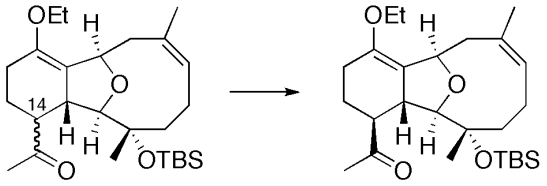


Figure 18. Transition states involved in the Diels-Alder cycloaddition reaction.

Given that the tricyclic core was isolated as a 1:1 mixture of *endo* and *exo* cycloadducts, epimerisation at the C-14 position was undertaken (Table 6). Unexpectedly, treatment of the mixture with potassium carbonate did not lead to the formation of **(±)-*exo*-273** (entry 1). ^{1}H NMR analysis of the crude material revealed that the *endo*:*exo* ratio had remained unchanged. It was postulated that an equilibrium between the two epimeric compounds could account for this observation, and so the based-induced epimerisation was performed in deuterated methanol to test the hypothesis. However, ^{1}H NMR analysis showed that the characteristic proton at the C-14 position had not undergone proton-deuterium exchange, and so deprotonation at this position had not occurred. Consequently, different epimerisation conditions were screened (Table 6).



(±)-273 **(±)-*exo*-273**

Entry	Conditions	Outcome	
		Initial ratio *endo* : *exo*	Final ratio *endo* : *exo*
1	K_2CO_3, MeOH, rt, 18 h	1 : 1	1 : 1
2	NaOH, EtOH, rt, 18 h	1 : 1.3	1 : 1.7
3	NaOH, EtOH, 85 °C, 18 h	1 : 1.7	1 : 2.5
4	NaOH, EtOH, 85 °C, 48 h	1 : 2.5	1 : 2.7
5	NaOMe, MeOH, rt, 18 h	1 : 2.7	1 : 2.7
6	*t*-BuOK, EtOH, rt, 18 h	1 : 2.7	1 : 2.7
7	*t*-BuOK, EtOH, rt, 72 h	1 : 2.7	1 : 3.4
8	DBU, CH_2Cl_2, rt, 18 h	1 : 2.5	1 : 2.5
9	DBU, $PhCH_3$, 110 °C, 18 h	1 : 2.5	1 : 2.5

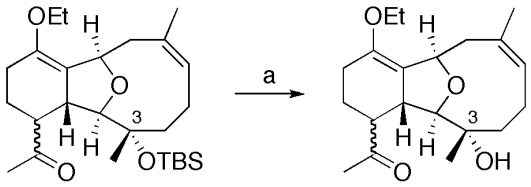
Table 6. Studies on the based-induced epimerisation of ketone **(±)-273**.

While the epimerisation proceeded under smooth conditions, potassium carbonate in methanol at room temperature, in the absence of the methyl group,[55,57,59] in this case the reaction revealed to be problematic. The *endo*:*exo* ratio remained unchanged under these reaction conditions (entry 1). The use of

other bases such as sodium hydroxide (entries 2-4), sodium methoxide (entry 5) or potassium *tert*-butoxide (entries 6 and 7) at room temperature or in refluxing solvent did not induce the epimerisation of the C-14 stereocentre. Likewise, the non-nucleophilic base DBU proved to be inefficient (entries 8 and 9). Considering that the steric hindrance of the silyl group may prevent the access to the stereocentre C-14, it was decided to cleave the protecting group prior to perform the epimerisation reaction.

5.1.2 Cleavage of the Silyl Ether

Removal of the TBS group from the hydroxyl group at the C-3 position of related cladiellin systems has been reported by several groups.[8,10,12,41,42,43,57,59] The use of TBAF under various conditions turned out to be efficient. Consequently, the 1:1 mixture of *exo* and *endo* cycloadducts **(±)-273** was treated with TBAF. Unfortunately, after 6 hours at room temperature, the cycloadducts **(±)-273** were recovered unreacted in 88% yield (Scheme 77). When harsher conditions were employed –neat reaction performed in sealed tube at 70 °C with a large excess of TBAF– there were marginal improvements and the product **(±)-316** was isolated in only 37% yield with recovery of substantial amounts (42%) of starting material.



(±)-273 **(±)-316**

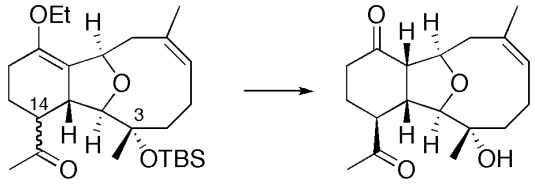
a) TBAF, 70 °C, **(±)-316** 37% and **(±)-273** 42%.

Scheme 77. Attempted cleavage of the TBS-ether using TBAF.

Following the failure of the deprotection reaction under standard reaction conditions, acid-catalysed TBS-ether cleavage was explored using a variety of acids (Table 7).[140] Pleasingly, hydrolysis of the enol ether, epimerisation at the C-14 position and removal of the TBS group from the tertiary alcohol took place

[140] Wutz, P.G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, 3rd edition.

in a tandem fashion leading to the formation of the diketone **(±)-317** with the desired C-3 configuration. On a small scale, the use of a 5% solution of HF in acetonitrile[141] seemed to be optimal and the diketone **(±)-317** was isolated in an excellent 93% yield (entry 2). However, scale-up of the reaction revealed that treatment of the cycloadducts **(±)-273** with hydrochloric acid[142] gave similar results (entries 4 and 5). Furthermore, the manipulation of aqueous hydrochloric acid at large scale proved to be easier than the use of hydrofluoric acid on a large scale.



(±)-273 **(±)-317**

Entry	Conditions	Yield (%)
1	HF.pyridine, THF (0.046 M), rt, 6h	36[a,b]
2	HF.MeCN (5%), rt, 2 h	93 [a]
3	HCl conc., MeOH (0.015 M), rt, 18 h	72 [a]
4	HF.MeCN (5%), rt, 3h	74 [c]
5	HCl conc., MeOH (0.034 M), rt, 18 h	79 [c]

[a] Reactions were performed on 46-84 μmol scale; [b] 42% brsm; [c] Reactions were performed on larger scale (entry 4: 343 μmol; entry 5: 673 μmol).

Table 7. Studies on the TBS-ether cleavage under acidic conditions.

The configuration of the diketone **(±)-317** was confirmed by X-ray crystallography (Figure 19).

At this stage in the enantiopure synthesis, six stereocentres were in place. The first one was introduced thanks to a Sharpless asymmetric epoxidation reaction while a further two stereocentres had been installed during the radical cyclisation. After the synthesis of the oxabicyclo[6.2.1]-5-undecen-9-one **275**, the diastereofacial Diels-Alder cycloaddition allowed the formation of a fourth stereocentre. Finally, two stereocentres were created by hydrolysis of the enol ether and the epimerisation under acidic conditions.

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[141] Pratt, D. V.; Hopkins, P. B. *J. Org. Chem.* **1988**, *53*, 5885.
[142] Abad, A.; Agulló,C.; Arnò, C. A. M.; Cuñat, A. C.; Meseguer, B.; Zaragozá, R. J. *J. Org. Chem.* **1998**, *63*, 5100.

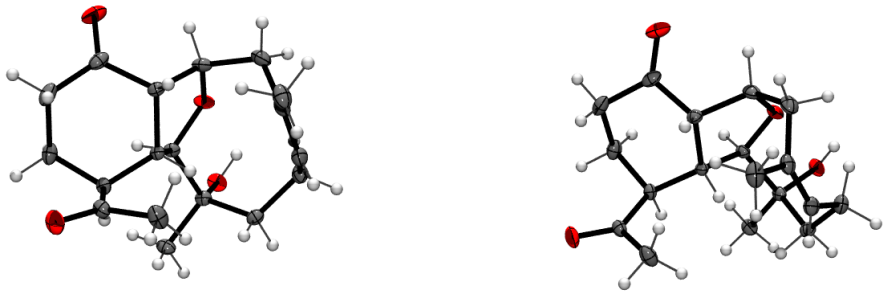

Figure 19. X-ray crystal structure fo the diketone **(±)-317** corresponding to the tricyclic core of sclerophytin F (ORTEP plot with 50% thermal elipsoids).

5.2 Optimisation of the Palladium-Mediated Cross-Coupling

Since the first report of the Stille cross-coupling reaction in the late 1970s, this reaction has demonstrated its utility to form C-C bonds during the total synthesis of many natural products.[143] However, the toxicity of stannane reagents, their cost and other drawbacks linked to the product of tin waste prompted an investigation of other methods for the synthesis of diene **274**.

Over the last forty years, palladium-catalysed cross-coupling reactions have become very powerful and widely used in synthesis.[144, 145] Of these palladium-catalysed reactions, the Negishi[146] and the Heck[147] cross-couplings captured our attention as potential alternatives to the Stille reaction.

It was hypothesised that coupling between enol triflate **313** and ethyl vinyl ether **318** could be accomplished in presence of a palladium catalyst leading to the formation of diene **274** (Scheme 78). In this case, the procedure would present the advantages that it would be catalytic, cheaper and avoid the formation of tin by-products.

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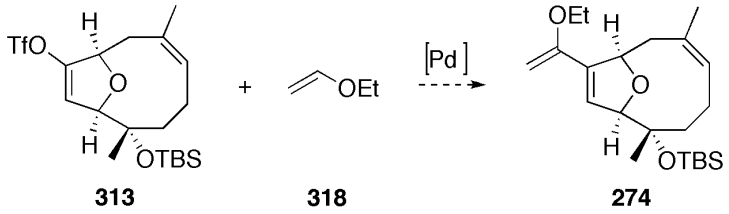
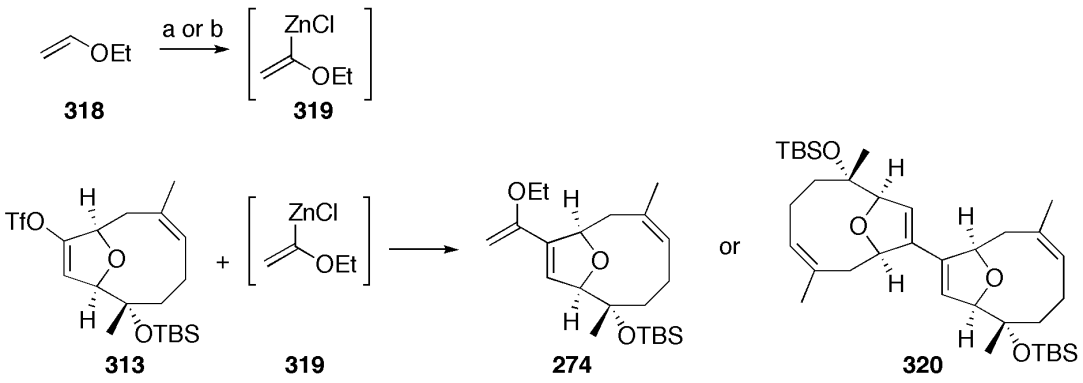
[143] Heravi, M. M.; Hashemi, E.; Azimian, F. *Tetrahedron*, **2014**, *70*, 7 and see references herein.
[144] Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417.
[145] Yin, L.; Liebscher, J. *Chem. Rev.* **2007**, *107*, 133.
[146] King, A. O.; Okuhado, N.; Negishi, E. *J. Org. Chem.* **1977**, *42*, 1821.
[147] Heck, R. F.; Nolley, Jr. J. P. *J. Org. Chem.* **1972**, *37*, 2320.



Scheme 78. General approach towards the palladium catalysed-coupling of enol triflate **313** and ethyl vinyl ether **318**.

5.2.1 The Negishi Cross-Coupling

Negishi cross-coupling is characterised by the use of organozinc reagents. For this purpose ethyl vinyl ether **318** was first transformed into the corresponding alkenylzinc **319** by treatment with *tert*-butyllithium and zinc dichloride in tetrahydrofuran (Scheme 79, Table 8).[148] Attempted coupling between the organozinc **319** and enol triflate **313** was performed in presence of two different sources of palladium(0): palladium tetrakis(triphenylphosphine)[149] (entries 1 and 3) or palladium bis(dibenzylideneacetone) and triphenylphosphine (entries 2 and 4).[150]



a) *t*-BuLi, THF, −78 to 0 °C, then $ZnCl_2$, −78 °C to rt; b) *t*-BuLi, −78 °C, then $ZnCl_2$, −78 °C to rt.

Scheme 79. Negishi cross-coupling of enol triflate **313** and ethyl vinyl ether **318**.

Under mild conditions (50 °C in THF) and in presence of 10 mol% of catalyst, only the starting material **313** was observed by ^{1}H NMR analysis of the crude product after 20 hours when palladium tetrakis(triphenylphosphine) was

[148] Negishi, E.; Luo, F. -T. *J. Org. Chem.* **1983**, *48*, 1560.
[149] Inoue, M.; Yokota, W.; Katoh, T. *Synthesis*, **2007**, *4*, 622.
[150] Legros, J. -Y.; Primault, G.; Fiaud, J. -C. *Tetrahedron*, **2001**, *57*, 2507.

used as the catalyst (entry 1). When a mixture of palladium bis(dibenzylideneacetone) and triphenylphosphine were employed, 11% conversion of triflate **313** to diene **274** was observed (entry 2). The lack of the reactivity prompted an increase in temperature of the reaction to 70 °C (entries 3 and 4). Using both catalyst systems, the starting material was consumed in less than one hour. The characteristic signals for the desired diene **274**, a singlet at 5.92 ppm and a multiplet at 3.79-3.74 ppm, were absent in the ^{1}H NMR spectrum. After purification of the crude mixture by flash column chromatography, the dimer **320** was isolated along with other unidentified side products.

Entry	Conditions	Outcomes
1	$Pd(PPh_3)_4$ (10 mol%) THF, 50 °C, 20 h [a]	**313**
2	$Pd(dba)_2$ (10 mol%), PPh_3 (15 mol%) THF, 50 °C, 20 h [a]	**313**:**274** (8:1)
3	$Pd(PPh_3)_4$ (10 mol%), THF, 70 °C, 1 h [b]	**320** and by-products
4	$Pd(dba)_2$ (10 mol%), PPh_3 (15 mol%) THF, 70 °C, 1 h [b]	**320** and by-products

Reactions were performed on 0.15 mmol scale in THF. [a] Conditions a) were used for the preparation of **319**; [b] Conditions b) were used for the preparation of **319**.

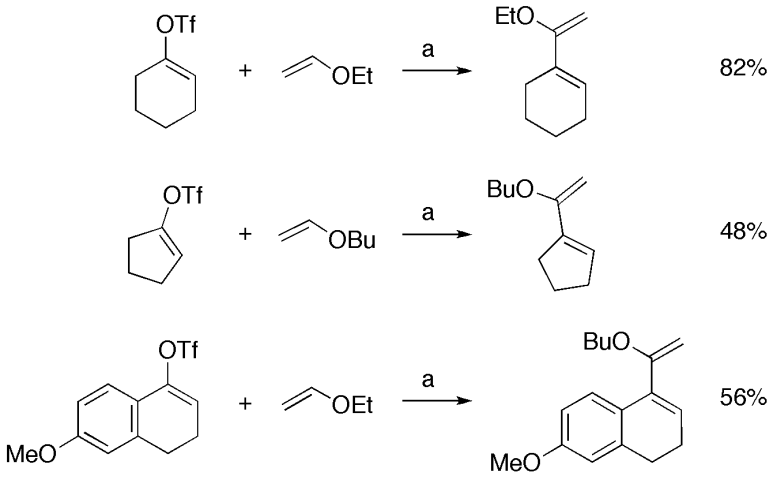
Table 8. Studies on the Negishi cross-coupling of enol triflate **313** and ethyl vinyl ether **318**.

As a consequence of the failure of this and other reactions, the Heck reaction was examined as an alternative.

5.2.2 The Heck Cross-Coupling

The Heck reaction was discovered in the 1970's and has the advantage that it catalyses direct coupling to an sp^2 hybridized carbon centre. Thus, compared to the Neigishi cross-coupling, vinyl ethyl ether **318** could be used without modification.

In 1989, Halberg *et al.* published a procedure for the preparation of 2-alkoxy 1,3-dienes that involves palladium-catalysed reaction between a vinyl ether and an enol triflate (Scheme 80).[151] Products were isolated in moderate to good yields and a good selectivity in favour of the α-substituted products.



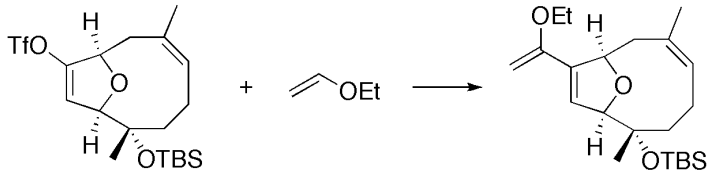
a) $Pd(OAc)_2$ (3 mol%), Et_3N (1.5 eq), vinyl ether (5 eq), DMSO, 60 °C, 3h.

Scheme 80. Selected examples of palladium-catalysed vinylation of alkyl vinyl ether with enol triflates.[151]

This precedent encouraged us to explore the palladium-catalysed coupling between enol triflate **313** and ethyl vinyl ether **318** (Table 9). Previous studies demonstrated that: *i*) palladium acetate is an efficient pre-catalyst, giving good yields for vinylation reaction and *ii*) ligand selection influences the regioselectivity of the reaction. Thus, the choice of palladium acetate as catalyst was obvious. Furthermore, it was observed that ligands such as triphenylphosphine delivered poor selectivities while bidentate ligands improved these favouring α-vinylation of the alkyl vinyl ether significantly.[152] The first palladium-catalysed trial reactions between enol triflate **313** and ethyl vinyl ether **318** (entries 1 and 3) were performed with 3 mol% of catalyst and either triphenylphosphine or dppp as ligands. Under these conditions, a mixture of starting material **313** and diene **274** was observed on ^1H NMR analysis of crude material. It is noteworthy that the presence of other products was observed when triphenylphosphine was employed as a ligand (entries 1 and 2). However in

[151] Andersson, C. -M.; Halberg, A. *J. Org. Chem.* **1989**, *54*, 1502.
[152] Cabri, W.; Candiani, I.; Bedeschi, A.; Penco, S.; Santi; R. *J. Org. Chem.* **1992**, *57*, 1481.

the presence of the bidendate ligand dppp, the reaction furnished the diene **274** without formation of by-products (entries 4 and 5). Increasing the catalyst loadings to 10-15 mol% depending on the conditions, allowed the reaction to reach completion (entries 2, 4 and 5).



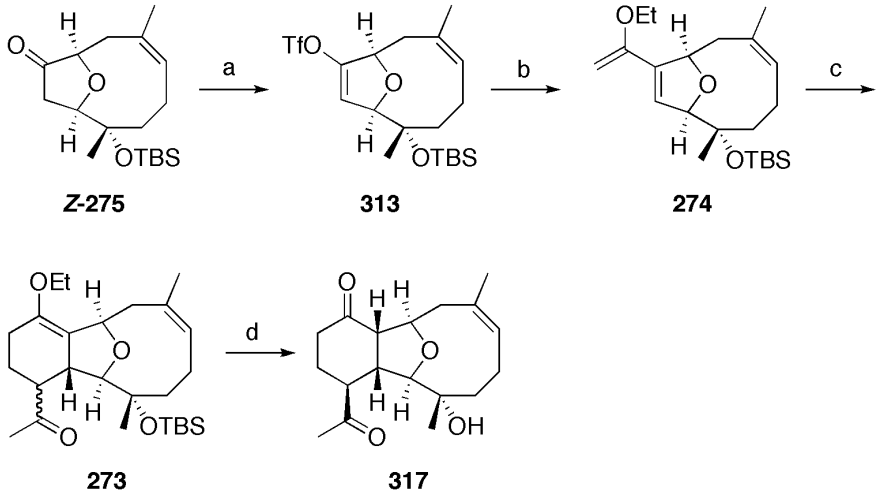
313 **318** **274**

Entry	Catalyst		Ligand		Outcomes
1	$Pd(OAc)_2$	3 mol%	PPh_3	6 mol%	**313**:**274** (2.6:1); other products
2	$Pd(OAc)_2$	10 mol%	PPh_3	20 mol%	**274** and other products
3	$Pd(OAc)_2$	3 mol%	dppp	3.5 mol%	**313**:**274** (1.7:1)
4	$Pd(OAc)_2$	10 mol%	dppp	12 mol%	**274**
5	$Pd(OAc)_2$	15 mol%	dppp	18 mol%	**274**

Reactions were carried out with an excess of ethyl vinyl ether (10 eq.) and triethylamine (1.5 eq.) in DMF in sealed tube at 80 °C overnight.

Table 9. Heck cross-coupling of enol triflate **313** with ethyl vinyl ether **318**.

Following identification of conditions for clean conversion, cheap reagents and simple reaction conditions, the three-step sequence, including the enol triflate formation, the Heck cross-coupling and the Diels-Alder cycloaddition, was undertaken (Scheme 81). Delightfully, a good overall yield of 69% was obtained. Subsequent treatment of the enol ether **273** under acidic conditions delivered the tricyclic skeleton **317**.



***Z*-275** **313** **274**

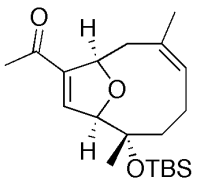
273 **317**

a) NaHMDS, $PhN(Tf)_2$, THF, −78 °C; b) $CH_2C(OEt)H$, $Pd(OAc)_2$, Et_3N, dppp, DMF, 80 °C; c) $CH_2CHCOCH_3$, $PhCH_3$, 120 °C, 65% (3 steps), 1:1 *exo*:*endo*; d) HCl conc., MeOH, rt, 79%.

Scheme 81. Synthesis of the tricyclic core **273** by sequential Heck coupling and Diels-Alder cycloaddition.

5.3 Recycling of the By-Product 321

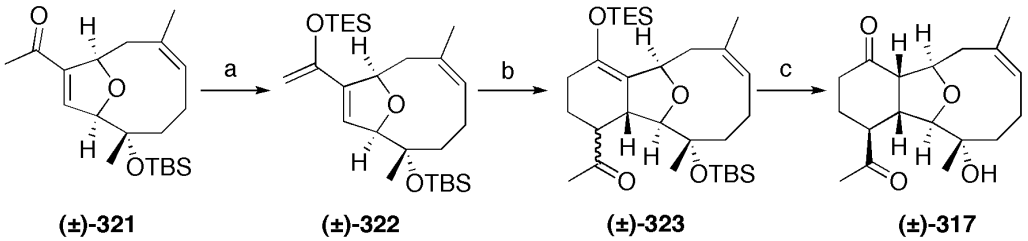
The three-step sequence delivering the tricyclic core of the natural product proceeded in good yield. However, the formation of the by-product **321** was sometimes observed (Figure 20). Its presence in the reaction mixture was detected by TLC or by ^1H NMR analysis of the crude material obtained from the coupling reaction between the enol triflate **313** and the corresponding coupling partner [tributyl(1-ethoxyvinyl)tin or ethyl vinyl ether]. There were concerns about the loss of advanced intermediate ***Z*-275**, and so, recycling of the methyl ketone **321** was explored.



321

Figure 20. α,β-Unsaturated methyl ketone **321**.

Silyl ether formation followed by Diels-Alder cycloaddition produced a mixture of *exo* and *endo* products **(±)-323** (Scheme 82). The mixture of cycloadducts was subjected to a solution of hydrochloric acid in methanol and desired tricyclic core **(±)-317** was isolated in a 35% overall yield.



(±)-321 **(±)-322** **(±)-323** **(±)-317**

a) NaHMDS, THF, −78 °C then TESCl −78 °C to rt; b) $CH_2CHCOCH_3$, $PhCH_3$, 120 °C; c) HCl, MeOH, 0 °C to rt, 35% (3 steps).

Scheme 82. Conversion of the α,ß-unsaturated methyl ketone **(±)-321** into the diketone **(±)-317**.

With the assurance that the by-product **321** could be transformed into the tricyclic core **317**, the synthesis was progressed to the next step: functionalization of the tricyclic core.

6 Functionalization of the Tricyclic Core

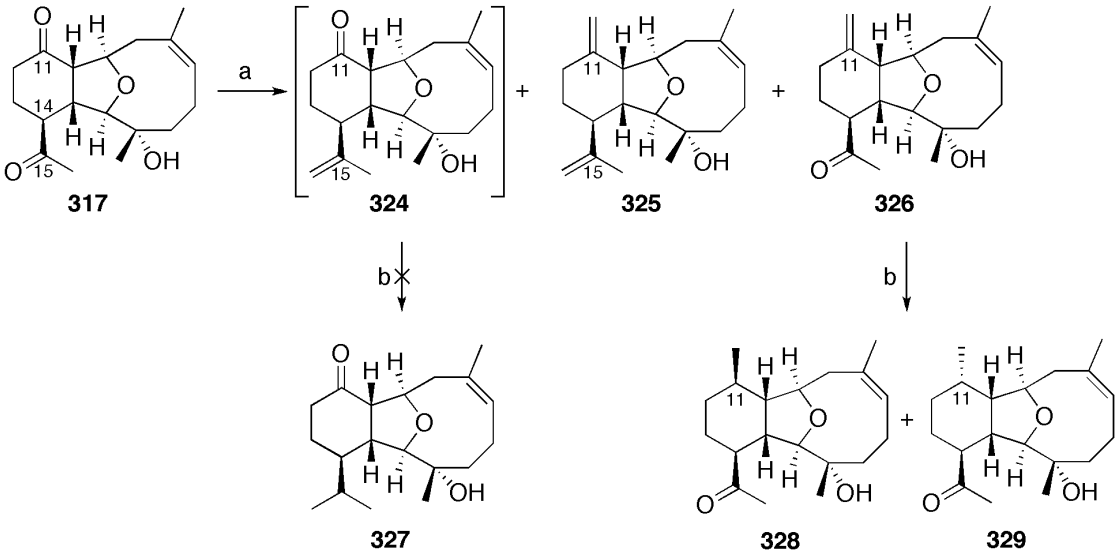
6.1 Installation of the Isopropyl Group

Following construction of the tricyclic skeleton, the next challenge was the installation of the isopropyl group at the C-14 position. In the previous syntheses of cladiellin family natural products within our group, the desired motif was prepared by Wittig methylenation followed by hydrogenation (see introduction, section 2.10).[55,57] However, when these conditions were applied to a similar intermediate having 6*E*-conformation, installation of the isopropyl moiety appeared to be problematic.[57,59] The difficulty was circumvented by the transformation of the methyl ketone into the tertiary alcohol, acetylation and subsequent deoxygenation reported by Kim *et al.* [45](see introduction, section 2.5).

By analogy with the route employed in total synthesis of the (±)-vigulariol,[57] it was anticipated that methylenation of the diketone **317** followed by selective hydrogenation of **324** would introduce the desired isopropyl group at the C-14 position leading to the formation of **327** (Scheme 83).

The diketone **317** was treated with two equivalents of methylene triphenylphosphonium ylide at room temperature (Scheme 83). Two products were obtained and they were separated by flash column chromatography. NMR analysis revealed that one of them corresponded to the triene **325** while the second product possessed a ketone (210.2 ppm in the ^{13}C NMR spectrum). It was presumed that this compound was the desired ketone **324** and so hydrogenation

was carried out in presence of 10 mol% of platinium oxide. The reaction was completed within 30 minutes and two products were isolated. Surprisingly, neither of them had the characteristic signals of the isopropyl group present in their ^{1}H NMR spectra. However, the presence of a ketone was clearly visible at 210.2 ppm and 211.3 ppm in the ^{13}C NMR spectra. X-ray crystallography of the crystalline products revealed that they were diastereomeric compounds **328** and **329** (Figure 21). In fact, under optimised conditions, the methylenation occurred preferentially at C-11 *versus* C-15 furnishing a 1:5 mixture of separable triene **325** and ketone **326**. Subsequent hydrogenation of the latter compound reduced the C-11 alkene to give two diastereomers **328** and **329** in a 2.4:1 ratio.



a) *t*-BuOK, Ph_3PCH_3Br, THF, rt, **325** 14%, **326** 69%; b) H_2, PtO_2, EtOAc, rt, **328** 64% and **329** 26%.

Scheme 83. First approach to the construction of the isopropyl group.

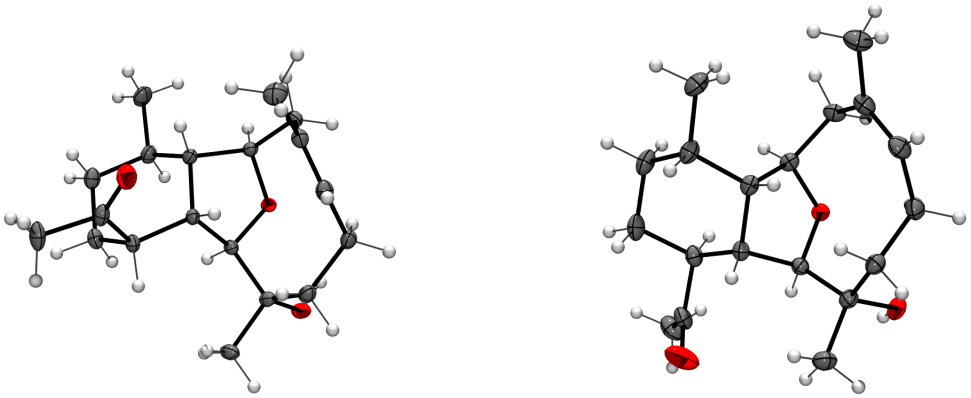
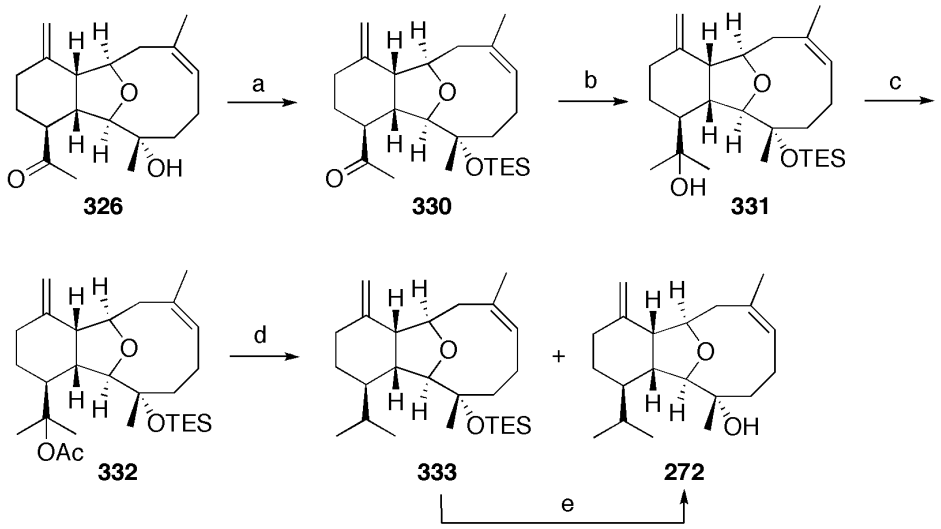


Figure 21. X-ray crystal structures of ketones **(±)-328** and **(±)-329** (ORTEP plot with 50% thermal elipsoids).

Originally, the methylenation reaction was performed using 5 equivalents of methyltriphenylphosphonium bromide and 4 equivalents of potassium *tert*-butoxide, leading to the isolation of ketone **326** in 33% yield while the triene **325** was afforded in 64% yield. Careful monitoring of the reaction allowed the quantity of ylide to be reduced. Two equivalents of ylide was found to be sufficient for complete of the reaction within one hour and the ketone **326** was isolated in 60-80% yield.

The isopropyl group could not be installed by a selective methylenation followed by the hydrogenation, and so an alternative approach analogous to that used in the synthesis of cladiellin natural products having the 6*E*-configuration was explored.[45,61] As previously described, methylenation of diketone **317** delivered a 1:5 mixture of triene **325** and methyl ketone **326** in good yield (Scheme 83). After separation of the products by flash column chromatography, the alcohol **326** was protected to form the corresponding triethylsilyl ether **330** (Scheme 84). Addition of methylmagnesium chloride then provided tertiary alcohol **331** in 84% yield. Despite the high yield, it should be appreciated that the reaction was not complete. A large excess of Grignard reagent as well as a prolongation of the reaction time did not lead to full conversion. Under the best conditions identified, 86% conversion to the desired tertiary alcohol **331** was observed upon ^{1}H NMR analysis of the crude reaction mixture. Unreacted starting material **330** could be recovered and re-subjected to the methyl addition reaction. The tertiary alcohol **331** was then acetylated by treatment with acetic anhydride as solvent, triethylamine and DMAP at 40 °C. The required isopropyl group was finally formed by deoxygenation of the crude acetate **332** under dissolving metal reduction conditions. For this purpose and by analogy to the Kim and Clark syntheses of other cladiellins,[45,55] potassium metal pieces were solvated in *tert*-butylamine in presence of 18-crown-6. The solution of crude acetate **332** in tetrahydrofuran was then added to the deep blue mixture. After reappearance of the blue colour, the reaction was quenched by addition of isopropanol and aqueous ammonium chloride furnishing **333** in 49% yield and the deprotected alcohol **272** in 7% yield. With the isopropyl substituent in place, cleavage of the silyl ether under acidic conditions revealed the crystalline

alcohol **272**, the advanced precursor to sclerophytin F. The structure of compound **272** was fully confirmed by X-ray crystallography (Figure 22).



a) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 93%; b) MeMgCl, THF, rt, **331** 84% and recovered **330** 15%; c) Ac_2O, DMAP, Et_3N, 40 °C; d) K, 18-crown-6, *t*-$BuNH_2$, THF, rt, **333** 49% and **272** 7% (2 steps); e) HCl, MeOH, 0 °C, 95%.

Scheme 84. Completion of the synthesis of the advanced precursor to the proposed structure of sclerophytin F.

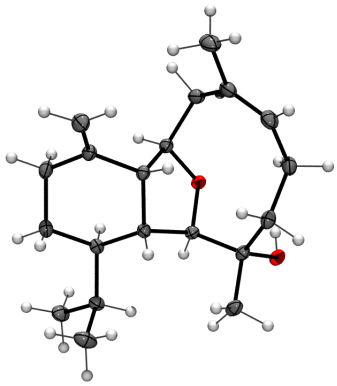
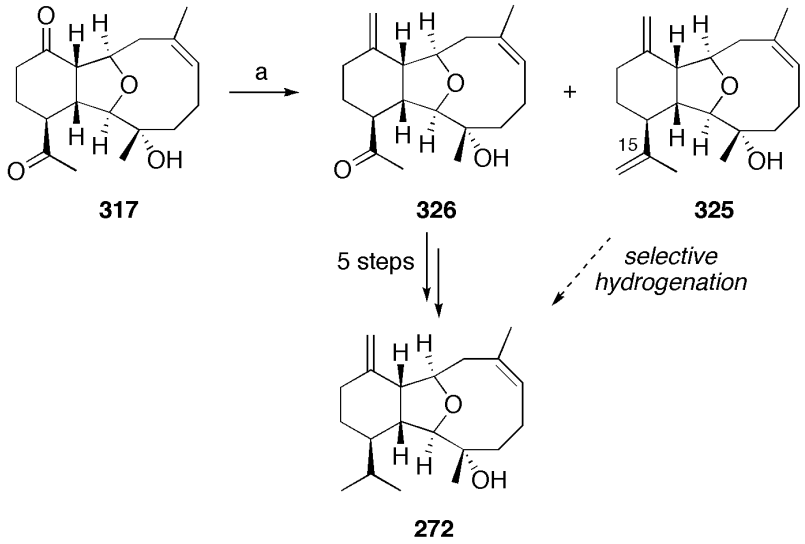


Figure 22. X-ray crystal structure of the tricyclic skeleton **272** of the proposed structure of the sclerophytin F (ORTEP plot with 50% thermal elipsoids).

6.2 Studies on Selective Alkene Hydrogenation at C-15

6.2.1 Selective Hydrogenation

Methylenation of diketone **317** delivered a mixture of two products: the ketone **326** and the triene **325**. As described previously, methyl ketone **326** was successfully transformed into intermediate **272** through a five-step sequence, while the triene **325** was left aside. It was decided to investigate the possibility of converting the triene **325** into alcohol **272** in one step by selective hydrogenation of the side chain alkene. If this strategy proved to be effective, the transformation would not only increase the quantity of intermediate **272** available for the completion of the synthesis, but would also reduce the number of steps required to prepare this key intermediate (Scheme 85). However, this approach was extremely challenging due to the presence of three alkenes in the starting material **325**.



317 **326** **325** **272**

a) *t*-BuOK, Ph_3PCH_3Br, THF, rt, **325** 14%, **326** 69%.

Scheme 85. Proposed selective hydrogenation of the double bond at C-15.

The highly reactive Adam's catalyst was tested first (Table 10, entry 1). The reaction was performed in presence of 5 mol% of PtO_2. Because of the similar polarity of the triene **(±)-325** and the corresponding product **(±)-272**, TLC analysis was difficult and so the reaction was monitored by ^1H NMR. After 1.5 hours at room temperature, NMR analysis revealed a complex mixture of

products. A shorter reaction time, *i.e* 30 min (entry 2), gave analogous results, but the characteristic doublet of the isopropyl group was observed in the ^{1}H NMR spectrum of the crude material at 0.74 ppm. Taking into account that hydrogenation might proceed too quickly to be selective, the catalyst was poisoned by addition of quinoline to the reaction mixture (entry 3). The reaction was slower under these new conditions: after one hour only the starting material was observed and the hydrogenation was still not complete after 24 hours. Characteristic signals corresponding to intermediate **(±)-272** were observed in the crude ^{1}H NMR spectrum. Unfortunately, several by-products were also formed under the reaction conditions. The second choice of catalyst was palladium on charcoal (entry 4). The hydrogenation reaction was performed with a catalyst loading of 10 mol%. Unexpected isomerisation of the double bond at C-11 occurred and the product **(±)-334** was isolated in 22% yield along with the starting material **(±)-325**. Triene **(±)-325** was then subjected to the hydrogenation in presence of the Wilkinson catalyst (entry 5). Upon treatment of **(±)-325** with hydrogen in presence of 5 mol% of $RhCl(PPh_3)_3$ as catalyst for 24 hours at room temperature, only unreacted starting material was observed. A more powerful homogeneous catalyst –Crabtree's catalyst– was tested (entries 6-8). Increasing the catalyst loading from 10 mol% to 100 mol% did not affect the rate of the reaction and the starting material **(±)-325** was recovered after 24 hours in each case. Traces of product **(±)-272** were seen in the ^{1}H NMR spectrum of the crude reaction mixture when the hydrogenation was carried out using a stoichiometric quantity of catalyst (entry 8); characteristic signals at 5.69 ppm, 4.28 ppm and a singlet at 3.87 ppm were present among those of side-products and triene **(±)-325**. The reaction was repeated with a slow addition of the catalyst, but unfortunately no significant improvement in the level of conversion was observed.

When Crabtree's catalyst was employed, traces of the desired product **(±)-272** could be detected, so other iridium complexes were screened. Recently, Kerr *et al*. reported the synthesis of modified Crabtree-type catalysts in which the pyridine has been substituted with a NHC ligand to increase the efficiency

(Figure 23).[153] When hydrogenation of various substrates was performed with these catalysts and the results were compared to those obtained using the standard Crabtree catalyst, it was clear that reaction times were shorter, and that yields and selectivities were improved even using a reduced loading of the new catalyst.

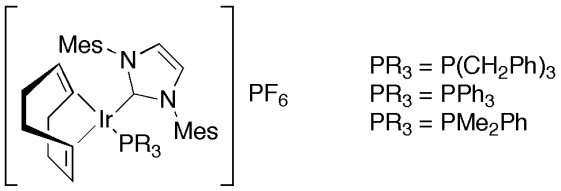
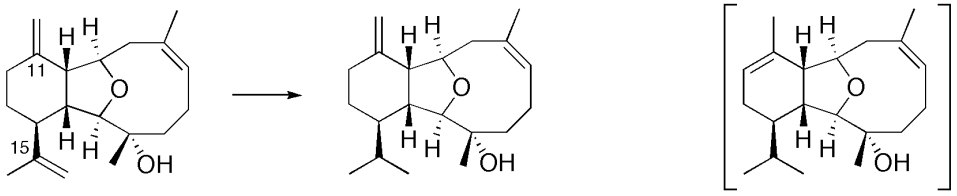


Figure 23. Kerr's catalysts.

The first reaction was carried out in presence of $[Ir(COD)PPh_3(C_{21}H_{26}N_2)]PF_6$ for 2.5 hours (entry 9). Although the reaction was not complete, traces of **(±)-272** were clearly visible in the ^1H NMR spectrum. Purification by flash column chromatography and analysis of the fractions revealed that the hydrogenation had occurred at the C-15 position. The reaction was repeated with a catalyst loading of 1 mol% and allowed to proceed to completion (entry 10). The starting material was consumed within 3.5 hours and the reaction mixture was purified. However, the desired intermediate **(±)-272** could not be separated from several by-products by flash column chromatography. Nevertheless, the mixture was subjected to the regioselective epoxidation at C-6 (see results and discussion, section 7) and the desired product was formed. Unfortunately, it was not possible to isolate the epoxide from the reaction mixture at this stage of the synthesis either.

[153] Bennie, L. S.; Fraser, C. J.; Irvine, S.; Kerr, W. J.; Andersson, S.; Nilsson, G. N. *Chem. Commun*, **2011**, *47*, 11653.



(±)-325 **(±)-272** **(±)-334**

Entry	Conditions	Outcomes [a]
1	PtO_2 (5 mol%), H_2	complex mixture
	EtOAc 0.02 M, 1.5 h, rt	
2	PtO_2 (5 mol%), H_2	complex mixture
	EtOAc 0.02 M, 30 min, rt	
3	PtO_2 (5mol%), H_2	complex mixture
	EtOAc 0.02 M, quinoline (1.2eq), 1 h, rt	traces of **(±)-272**
4	Pd/C (10mol%), H_2	22% **(±)-334** and 44% **(±)-325**[b]
	EtOAc 0.02 M, 16 h, rt	
5	$RhCl(PPh_3)_3$ (5mol%), H_2	**(±)-325**
	EtOH 0.02 M, 24 h, rt	
6	[Ir(COD)PCy_3pyridine]PF_6 (10 mol%), H_2	**(±)-325**
	CH_2Cl_2 0.03 M, 24 h, rt	
7	[Ir(COD)PCy_3pyridine]PF_6 (50 mol%), H_2	**(±)-325**
	CH_2Cl_2 0.03 M, 24 h, rt	
8	[Ir(COD)PCy_3pyridine]PF_6 (100 mol%), H_2	**(±)-325**
	CH_2Cl_2 0.03 M, 24 h, rt	traces of **(±)-272**
9	[Ir(COD)$PPh_3(C_{21}H_{26}N_2)$]PF_6, H_2	**(±)-325**
	CH_2Cl_2 0.03 M, 2 h, rt	traces of **(±)-272**; by-products
10	[Ir(COD)$PPh_3(C_{21}H_{26}N_2)$]PF_6 (1 mol%), H_2	**(±)-325**
	CH_2Cl_2 0.05 M, 3.5 h, rt	by-products

[a] Detected by ^1H NMR analysis of the crude material; [b] Isolated yield.

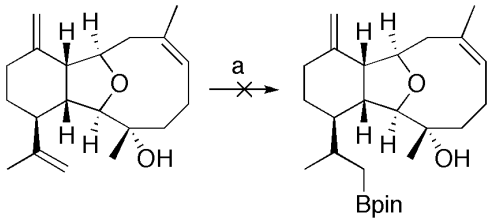
Table 10. Attempted conditions for the selective hydrogenation at C-15.

Selective hydrogenation of the isopropenyl group proved to be more challenging than expected even though promising results were obtained with the Kerr's catalysts. Difficulties in developing an efficient hydrogenation method and time constraints meant the reaction was not further investigated.

6.2.2 Selective Hydroboration

To circumvent the unsuccessful hydrogenation of the isopropenyl group, an alternative approach based on a selective hydroboration was considered.

In 2004, Miyaura *et al*. reported the use of iridium-phosphine complexes as catalysts for the selective hydroboration of terminal and internal alkenes.[154] Following this procedure, triene **325** was treated with pinacolborane in presence of 15 mol% of iridium catalyst $[Ir(COD)Cl]_2$ and 1,1-bis(diphenylphosphino) methane in dichloromethane at room temperature (Scheme 86). After 24 hours no trace of the desired product **335** was observed. Additional amounts of catalyst, ligand, dppm, and pinacolborane were added and the solution was stirred for a further 60 hours. NMR analysis of the crude mixture revealed the formation of unknown products but unreacted starting material **325** was still the major component. The reaction was repeated using a stoichiometric amount of catalyst and ligand, but these conditions did not lead to any improvement. The starting material **325** was recovered after stirring for 22 hours at room temperature.



(±)-325 **(±)-335**

a) HBpin, $[Ir(COD)Cl]_2$ (1.5 mol%), dppm (3 mol%), CH_2Cl_2, rt.

Scheme 86. Attempted selective hydrobration of the isopropenyl group.

Following the failure of both the hydrogenation and the hydroboration reactions, our efforts were re-focused on the completion of the synthesis of the proposed structure of sclerophytin F.

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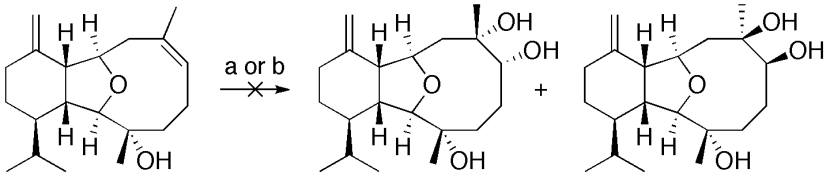
[154] Yamamoto, Y.; Fujikawa, R.; Umemoto, T.; Miyaura, N. *Tetrahedron* **2004**, *60*, 10695.

7 Completion of the Synthesis of the Proposed Structure of Sclerophytin F

From the tricyclic skeleton **272**, the next objective was the functionalization of the oxonene unit in order to complete the total synthesis of the natural product.

The total synthesis of (−)-sclerophytin A by Paquette *et al*. was achieved by dihydroxylation of the *endo*-cyclic alkene and an inversion of the configuration at the C-6 position (see introduction, section 2.2).[10,11,30] A few years later, the dihydroxylation proved to be efficient as well on the *endo*-cyclic *E*-alkene and was reported by Kim *et al*.[45] and Clark *et al*.[55] (see introduction, sections 2.5 and 2.10).

Therefore dihydroxylation using osmium tetroxide was attempted on substrate **272** (Scheme 87). In the presence of one molar equivalent of osmium tetroxide, decomposition of the diene **272** was observed after one hour at room temperature. Under aqueous conditions, the reaction proceeded slowly and portionwise addition of one equivalent of osmium tetroxide over a period of 6 hours was required to consume the starting material completely. The reaction gave a complex mixture of products, but unfortunately the desired products **336** and **337** were not detected.

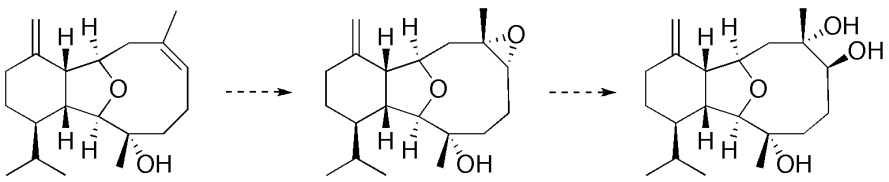


272 **336** **337**

a) OsO_4 (2.5% wt in *t*-BuOH), THF:pyridine (4:1), 0 °C to rt; b) OsO_4 (4% wt in H_2O), NMO, THF:H_2O (1:1), rt, (portionwise addition of OsO_4 over 6 hours).

Scheme 87. Attempted selective dihydroxylation of the diene **272**.

In a different approach, starting from the intermediate **272**, regioselective epoxidation of the more electron-rich trisubstituted double bond followed by nucleophilic opening of the resulting epoxide would be expected to deliver sclerophytin F (**10**) (Scheme 88).



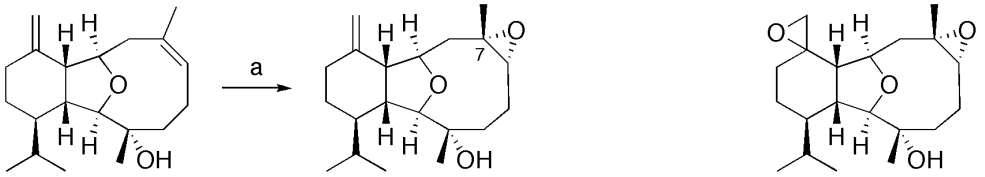
272 **338** **10**

Scheme 88. General approach to the synthesis of sclerophytin F by regioselective epoxidation and nucleophilic opening.

Clark *et al.*[55,57] as well as Hoppe *et al.*[47] had succeeded in accomplishing the regioselective and stereoselective epoxidation of the trisubstituted double bond during their total syntheses of vigulariol, using *m*-CPBA and DMDO respectively (see introduction, sections 2.1.6 and 2.1.10). By way of contrast, Morken and co-workers had observed the formation of two epoxides in their total synthesis of (−)-sclerophytin A (see introduction, section 2.8).[51] Although the DMDO epoxidation was performed on a similar substrate to that used by Hoppe in his synthesis of vigulariol, the presence of an additional C-3 carbonyl group caused a dramatic decrease in stereoselectivity (a 1.8:1 mixture of epoxides was obtained).

Epoxidation of the cycloalkene **272** was carried out under conditions described by Clark *et al.* (Scheme 89).[57] Pleasingly, oxidation of the alkene occurred on the α-face selectively, installing the C-7 stereocentre. Epoxide **338**

was isolated in an excellent 91% yield and NOE-experiments confirmed its configuration. To avoid the overepoxidation of the second alkene present in the molecule, resulting in the formation of the compound **339**, the reaction had to be performed at low temperature and *m*-CPBA had to be added as a solution in dichloromethane with careful monitoring of the reaction.

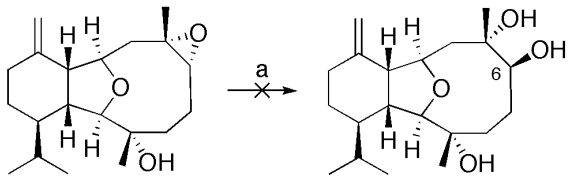


272 **338** **339**

a) *m*-CPBA, CH_2Cl_2, 0 °C, 91%.

Scheme 89. Stereoselective epoxidation of the C-6–C-7-alkene.

With epoxide **338** in hand, the next challenge was to open the epoxide regioselectively. Nucleophilic attack under basic conditions would introduce the hydroxyl group at the C-6 position (Scheme 90). Studies towards the synthesis of other cladiellin family members[58] demonstrated that the opening of epoxide similar to **338** was not possible under basic conditions. However, it appeared that small differences between the substrates modified significantly the reaction outcomes. Opening of epoxide **338** was attempted in presence of an excess of sodium hydroxide. The reaction was stirred for several hours at room temperature, but progression of the reaction was not observed. Addition of a Lewis acid, such as scandium triflate, did not have any beneficial effect either and starting material **338** was recovered intact.

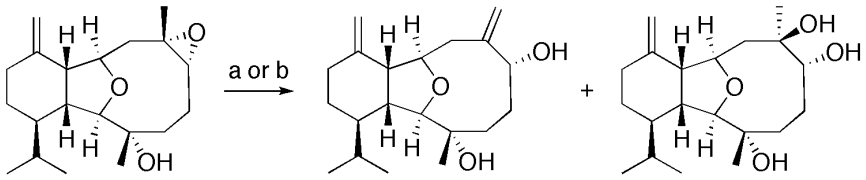


338 **10**

a) NaOH, THF:H_2O (10:1), rt, then addition of $Sc(OTf)_3$.

Scheme 90. Attempted opening of the epoxide under basic conditions.

Due to the failure of the epoxide opening reaction under basic conditions, the analogous transformation under acidic conditions was explored. Thus, epoxide **338** was subjected to treatment with a large excess of potassium bisulfate in presence of scandium triflate as Lewis acid in a mixture of tetrahydrofuran and water (Scheme 91). Interestingly, ring opening furnished the allylic alcohol **340** as the major product in 63% yield. The use of a strong Brønsted acid, such as sulfuric acid, delivered the allylic alcohol **340** as well, in a slightly higher yield of 77%, and the triol **341** was isolated in 15% yield.

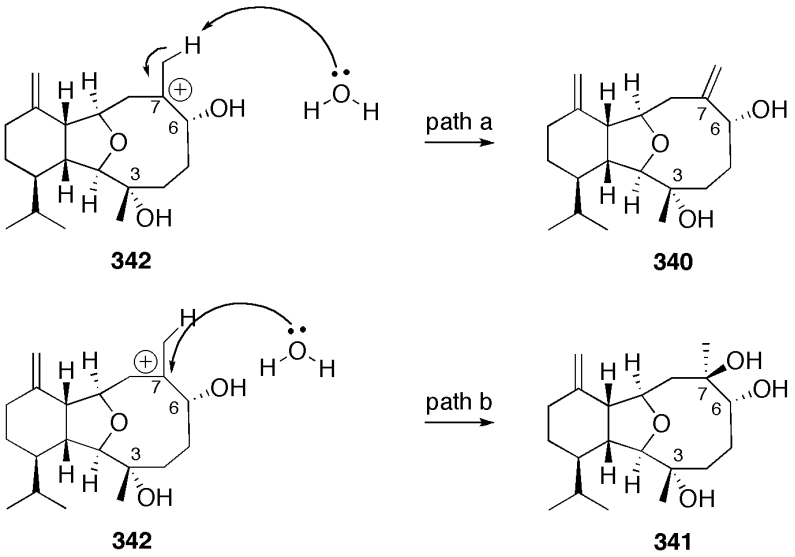


338 **340** **341**

a) $KHSO_4$, $Sc(OTf)_3$, THF:H_2O (1:1), rt, **340** 63%; b) H_2SO_4, THF:H_2O (1:1), rt, **340** 77% and **341** 15%.

Scheme 91. Opening of the epoxide **338** under acidic conditions.

The formation of this unexpected product could be explained by protonation of the epoxide functionality under acidic conditions resulting in the formation of the stabilised tertiary carbocation intermediate at the C-7 position **342** (Scheme 92). In this case, the elimination reaction which leads to the formation of the allylic alcohol **340** (path a) is favoured over the nucleophilic attack (path b). Steric hindrance at C-7 due to the configuration of the α-epoxide and the two methyl groups at C-3 and C-7 pointing to the ß-face could explain why the reaction proceeds preferentially through the elimination pathway delivering the crystalline alcohol **340** as major product.



Scheme 92. Mechanism of the formation of the allylic alcohol **340**.

The X-ray crystal structure of **340** was obtained. This data not only confirmed the structure of the allylic alcohol **340**, but also fully confirmed the regiochemical and the stereochemical outcome of the epoxidation reaction of cycloalkene **272**.

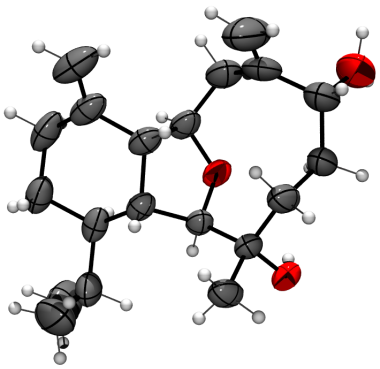
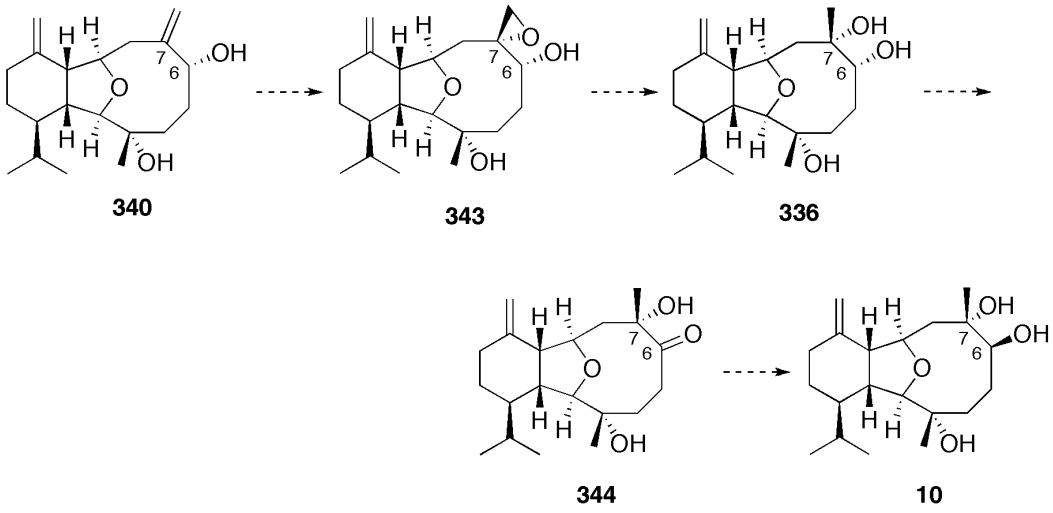


Figure 24. X-ray crystal structure of the allylic alcohol **340** (ORTEP plot with 50% thermal elipsoids).

The fact that opening of the epoxide generated the allylic alcohol **340** meant that efforts were focused on the transformation of this compound into the final target. Stereospecific directed epoxidation of the allylic alcohol **340** had the potential to deliver the requisite *S* stereocentre at C-7 (Scheme 93). Reductive opening of the epoxide **343** followed by inversion of the configuration

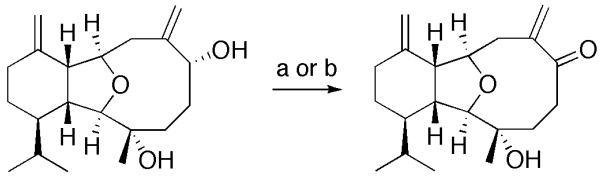
at the C-6 position using an oxidation–reduction sequence would complete the synthesis of the proposed structure of sclerophytin F (**10**).



Scheme 93. General approach to the completion of the synthesis of the proposed structure of sclerophytin F.

Allylic alcohol **340** was subjected to Sharpless asymmetric epoxidation conditions. The reaction was performed in presence of 10 mol% of titanium isopropxide and 15 mol% of (+)-diethyl tartrate at −30 °C. After 2 days, only the starting material was observed. The amounts of reagents: titanium isopropoxide and (+)-diethyl tartrate; were increased to 20 and 30 mol% respectively and the reaction was warmed to −20 °C. Further progression of the reaction was not observed after 24 hours, so the reaction was carried out using stoichiometric quantities of titanium isopropoxide and diethyl tartrate and the temperature was raised to 0 °C. After 5 days, a new major product was clearly visible by TLC analysis. Despite some remaining starting material, it was decided to isolate and characterise this new compound. Neither characteristic signal of the C-6 proton nor the formation of an epoxide was evident from the ^{1}H NMR spectrum. Furthermore, the ^{13}C NMR revealed the presence of a ketone, showing a characteristic peak at 207.7 ppm. Further analyses led to the conclusion that oxidation of the allylic alcohol **340** had occurred instead of epoxidation, providing allylic ketone **345** rather than the expected epoxide **343** (Scheme 94).

The structure of the product was confirmed by treatment of allylic alcohol **340** with Dess-Martin periodinane,[155] which afforded quantitatively ketone **345**.

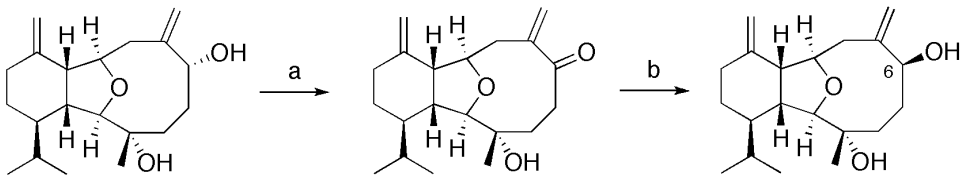


340 **345**

a) (+)-DET, Ti(O*i*-Pr)$_4$, *t*-BuO$_2$H, CH_2Cl_2, −25 °C to rt; b) DMP, CH_2Cl_2, rt, 100%.

Scheme 94. Attempted Sharpless asymmetric epoxidation of allylic alcohol **340**.

It seemed possible that the *R*-configuration at the C-6 position might be responsible for the failure of the Sharpless asymmetric epoxidation because of a mismatch between substrate and catalyst. Consequently, inversion of the configuration at this carbon was undertaken prior to the epoxidation of the alkene (Scheme 95). The used of Dess-Martin periodinane[155] delivered the enone **345** in quantitative yield. Luche reduction[156] produced a 2:3 mixture of allylic alcohol **340** and **346** in 95% overall yield with the 6*S*-epimer **346** predominating. After separation of the isomers, the 6*R*-configured alcohol **340** was re-subjected to the oxidation–reduction sequence. Repetition of the reaction sequence allowed the almost complete transformation of allylic alcohol **340** into the 6*S*-diastereomer **346**.



340 **345** **346**

a) DMP, CH_2Cl_2, rt, 100%; b) $NaBH_4$, $CeCl_3$. $7H_2O$, MeOH, 0 °C, **346** 57% and **340** 38%.

Scheme 95. Conversion of the 6*R*-allylic alcohol **340** into the 6*S*-allylic alcohol **346**.

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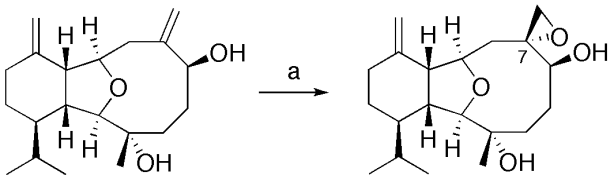
[155] a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1981**, *113*, 7277; b) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
[156] Luche, J. –L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

Upon isolation of a sufficient quantity of the 6*S*-allylic alcohol **346**, catalytic Sharpless asymmetric epoxidation was carried out. Pleasingly, the reaction proceeded to completion in 22 hours at −20 °C, setting the last stereocentre at the C-7 position. The desired epoxy-alcohol **347** was isolated in an excellent yield.



346 **347**

a) (+)-DET, Ti(O*i*-Pr)$_4$, CH_2Cl_2, −20 °C, 89%.

Scheme 96. Sharpless asymmetric epoxidation of allylic alcohol **346**.

Epoxide **347** is a crystalline solid and was submitted to X-ray analysis (Figure 25). The crystal structure confirmed that the eight stereocentres installed possess the configuration of those present in the proposed structure of the natural product.

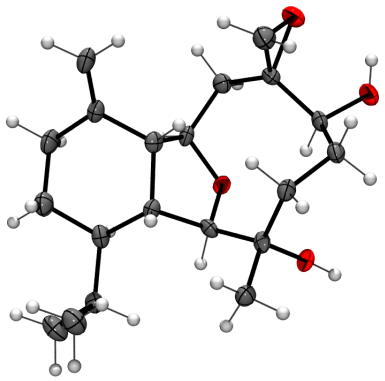
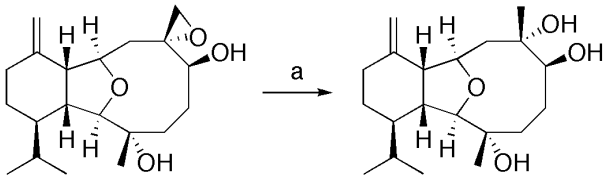


Figure 25. X-ray crystal structure of the epoxide **347** (ORTEP plot with 50% thermal elipsoids).

The last step of the synthesis −the opening of the epoxide **347** under reductive conditions− was accomplished with a large excess of diisobutylaluminium hydride (Scheme 97).[12] Following addition of the reducing agent at 0 °C, the reaction mixture was stirred at room temperature for several days. To our delight, the final product was obtained in 45% yield.



347 **10**

a) DIBAL-H, CH_2Cl_2, 0 °C to rt, 45%.

Scheme 97. Completion of the synthesis of the proposed structure of sclerophytin F.

The synthesis of the proposed structure of sclerophytin F (**10**) was completed in 33 steps from the commercially available 1,4-butanediol **147**. Mass, IR spectrum and the R_f value were close with the reported data.[13] However the ^1H and ^{13}C NMR spectra recorded on a 500 MHz spectrometer at room temperature did not match with the NMR data reported for the natural product. Characteristic signals of some hydrogen atoms were not visible. Moreover, five signals of carbon atoms were of very low intensity and appeared to be absent in the ^{13}C NMR spectrum. In order to increase the quality of the spectroscopic data, NMR analyses were performed at higher (40 and 55 °C) and at lower temperatures (−30 °C). Unfortunately, the resolution was not improved and so no conclusions could be derived from these experiments. High quality data were recorded on a Bruker 600 MHz spectrometer equipped with a cryoprobe. Major differences in the chemical shifts and multiplicity of the signals were observed between the ^1H NMR spectra of the natural and the synthetic sample. Comparison of the ^{13}C NMR spectra confirmed that the synthetic structure does not match with the natural product. This topic will be discussed in more details in the next section.

The crystal structure of the compound **347** gave a high degree of confidence that the compound corresponding to the proposed structure of sclerophytin F had been prepared. It was decided to synthesise the other three diastereomers at the C-6 and C-7 positions in order to investigate a mis-assignment of the natural product (Figure 26).

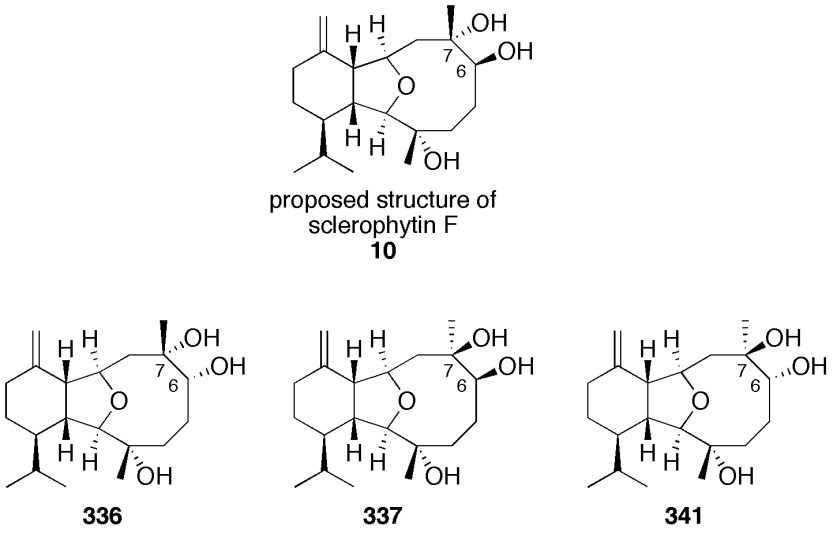


Figure 26. Proposed structure of sclerophytin F and its diastereomers.

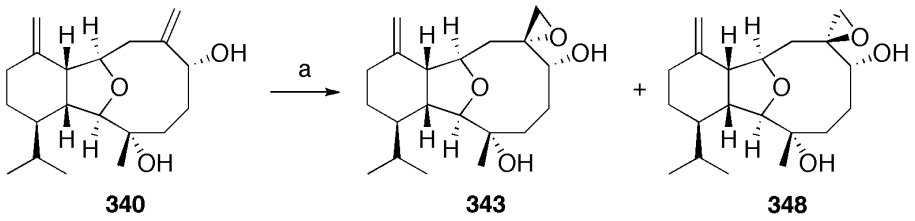
8 Synthesis of the C-6 and C-7 Diastereoisomers of the Proposed Structure of Sclerophytin F

The synthesis of the proposed structure of sclerophytin F (**10**) revealed that it was in fact not the natural product. To investigate the possibility of a misassignment of the stereochemistry at the C-6 and C-7 positions, the synthesis of the three other diastereomers at these positions was undertaken.

The first barrier to the synthesis was the formation of the triol **336**. As previously mentioned, when Sharpless asymmetric epoxidation was performed on the allylic alcohol **340** having the *R*-configuration at C-6, the desired product was not obtained (Scheme 94), and an alternative method was explored.

Hydroxyl-directed epoxidation of allylic alcohol **340** was attempted following the Overman conditions (see introduction, section 2.1).[12,157] Treatment with vanadyl acetoacetonate and *tert*-butylhydroperoxide delivered a separable diastereomeric mixture (1:1.6) of epoxy-alcohols **343** and **348** in 73% overall yield (Scheme 98). The two crystalline solids were submitted to X-ray crystallography allowing the identification of the *cis*- and the *trans*-epoxy-alcohol (Figure 27). Surprisingly, the *trans*-epoxy-alcohol **348** was the major diastereomer formed in the reaction.

[157] Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.



a) $VO(acac)_2$, *t*-BuO_2H, $PhCH_3$, rt, dr 1:1.6, 73%.

Scheme 98. Epoxidation of allylic alcohol **340** using $VO(acac)_2$.

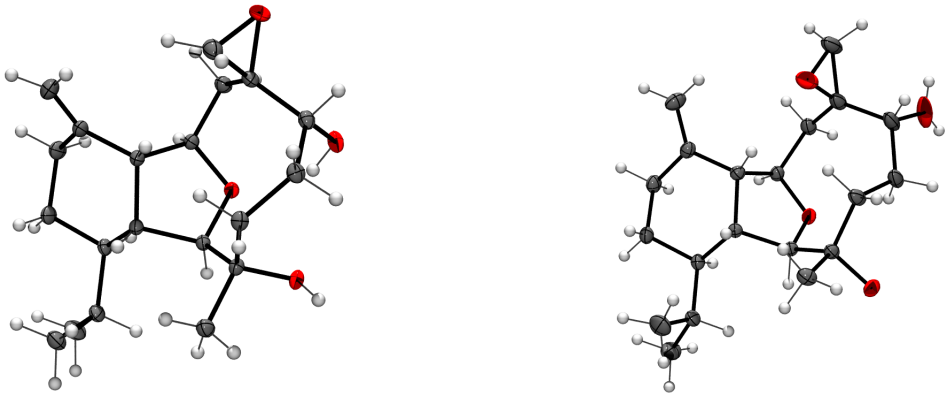
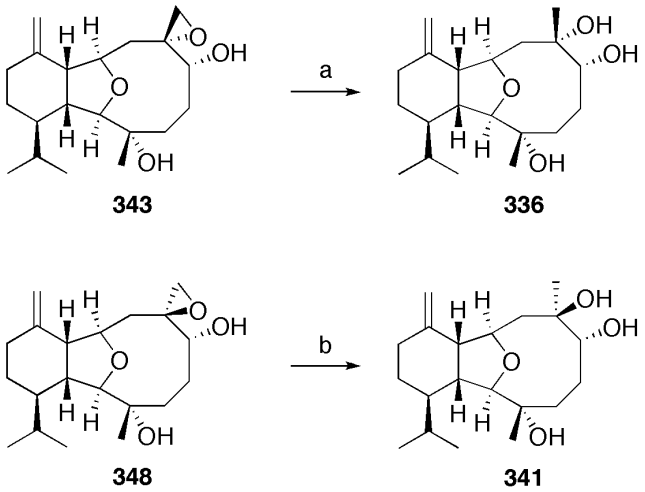


Figure 27. X-ray crystal structures of epoxy-alcohols **343** and **348** (ORTEP plot with 50% thermal elipsoids).

The α-epoxy-alcohol **343** was expected to be the major product of the directed epoxidation reaction because *i*) the X-ray structure of the allylic alcohol **340** (Figure 24) shows that there is a steric hindrance on the ß-face and *ii*) there is the potential for the hydroxyl group to form an oxygen-coordinated intermediate during the reaction. However, the reaction furnished the two epoxides in almost a 1:1 ratio.

With the two epoxy-alcohols in hand, regioselective ring opening using diisobutylaluminium hydride was carried out to obtain triols **336** and **341** in 43% and 22% yield respectively (Scheme 99).



343 **336**

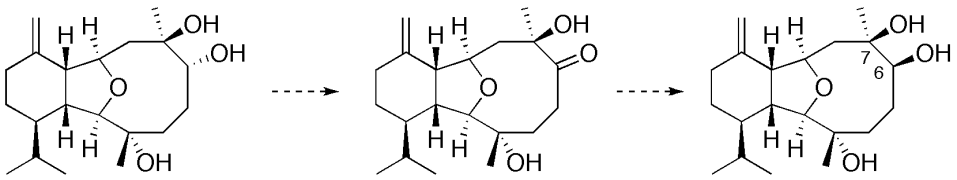
348 **341**

a) DIBAL-H, CH_2Cl_2, rt, 43%; b) DIBAL-H, CH_2Cl_2, rt, 22%.

Scheme 99. Completion of the synthesis of the diastereomers **336** and **341**.

Important differences in the ^{1}H NMR and ^{13}C NMR spectra (see results and discussion, section 9) between the natural product and the two synthetic samples **336** and **341** confirmed that neither of these diastereomers corresponds to the structure of the natural sclerophytin F.

At this stage, only the diastereomer **337** having *R*- and *S*-configuration at C-7 and C-6 respectively remained to be synthesised. It was suggested that starting from triol **341**, oxidation of the secondary alcohol followed by the reduction of the resulting ketone **349** would produce the desired triol **337** as the major isomer under appropriate conditions.

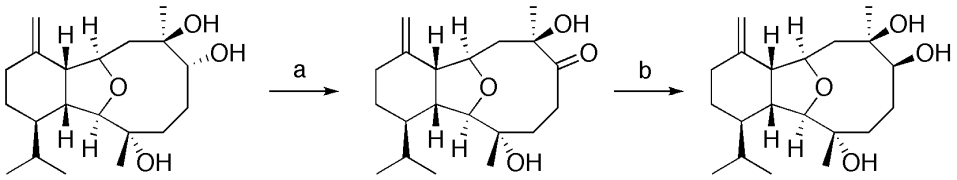


341 **349** **337**

Scheme 100. General approach towards the synthesis of the diastereomer **337**.

Oxidation of the secondary alcohol in triol **341** using Dess-Martin periodinane[155] furnished ketodiol **349** and the subsequent reduction was performed without purification of this compound (Scheme 101). The use of

lithium aluminium hydride led to the formation of a 1:4 mixture of triols in favour of the triol **341** (Table 11, entry 1). Treatment of ketodiol **349** with sodium borohydride reversed the selectivity of the reaction that delivered a 2.5:1 mixture of triols **337** and **341** (entry 2). Since a promising result had been obtained using a boron reducing agent, enantioselective ketone reduction with the CBS reagent was investigated (entry 3). Disappointingly only unreacted ketodiol **349** was recovered. When L-selectride was tested, no traces of the reduction products were detected (entry 4).



341 **349** **337**

a) DMP, CH_2Cl_2, rt; b) see Table 11.

Scheme 101. Completion of the synthesis of the diastereomer **337**.

Entry	Conditions	Ratio *cis*:*trans*
1	$LiAlH_4$, Et_2O, 0 °C to rt	1:4
2	$NaBH_4$, MeOH, rt	2.5:1
3	BH_3.THF, (*R*)-CBS, $PhCH_3$, 0 °C to rt	[a]
4	L-selectride, THF, 0 °C to rt	[a]
5	DIBAL-H, CH_2Cl_2, 0 °C to rt	2.3:1

[a] The starting material **349** was recovered.

Table 11. Attempted conditions for the formation of triol **337**.

Reduction of the α-hydroxy ketone **349** with diisobutylaluminium hydride at room temperature afforded a poor 2.3:1 mixture in favour of the triol **337** (Table 11, entry 5). Careful purification by flash column chromatography delivered a fraction with a 6.2:1 ratio of the triols **337** and **341** and data were recorded on this sample. Comparison of the ^1H NMR and ^{13}C NMR spectra with those reported for the natural sample showed that the structure of compound **337** is not sclerophytin F.

It was clear that the NMR data for none of the synthetic triols correspond to those reported for the natural product, and so a mistake had been made during the structural re-assignment. The four possible diastereomers at the C-6 and C-7 positions with the opposite *R*-configuration (at the C-3 position) have been previously synthesised and characterised by Paquette *et al*.[9,10,11] which means the NMR data of all eight possible diastereoisomers with different configurations at C-3, C-6 and C-7 have now been recorded. Unfortunately none of them was in accordance with the spectroscopic data reported for the natural sclerophytin F. Consequently, a further re-evaluation of the structure of sclerophytin F is required.

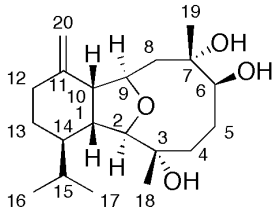
9 Re-evaluation of the Proposed Structure of Sclerophytin F

In the 2000's, the total syntheses of (−)-sclerophytin A[7,8,9,10,11,12] confirmed the structure of the natural product. Following this discovery, Paquette *et al*. revised the structure of the other sclerophytins[20] for which the structures had been previously deduced on the basis of the incorrect structures originally assigned to sclerophytins A and B. Analysis of the spectroscopic data for these compounds highlighted important differences in the chemical shifts in the ^{13}C NMR spectra at C-3 and it was concluded that some of the natural products possess a *S*-configuration at this streocentre while the majority of the cladiellin natural products have a *R*-configuration. Among the revised natural products was sclerophytin F. However, the synthesis of the proposed structure of the natural product as well as of all its possible diastereoisomers at the C-6 and C-7 stereocentres concluded without any doubt that the proposed structure of sclerophytin F is incorrect. Furthermore it showed that compounds with both *R*- and *S*-configuration at C-3 have similar chemical shifts.

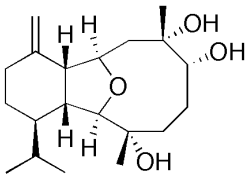
NMR differences were noticeable, in particular on the signal corresponding to the carbon C-3. Indeed, there is a difference of at least 10 ppm between the C-3 signal of natural sclerophytin F and the C-3 signal of (−)-sclerophytin A and other related compounds having an *R* configuration at this stereocentre as confirmed by X-ray crystallography or synthesis. It was discrepancies of the ^{13}C signal of adjacent carbon atoms at the C-2 and C-18 positions between structurally known natural products and the revised compounds which agreed with a structural modification at the C-3 stereocentre.

On the basis of the new information obtained from the synthetic sample of the proposed structure of sclerophytin F and its diastereomers, an attempt to re-evaluate the structure of sclerophytin F is presented.

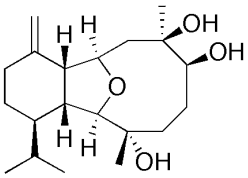
The data recorded for ^{13}C NMR analysis of the proposed structure of sclerophytin F and its diastereomers are summarized in Table 12. The chemical shift of the C-3 for natural sclerophytin F is reported at 86.6 ppm.[13] However, the characteristic signal for the synthetic sample of the proposed structure and its diastereomers is shifted upfield and the signal is found in the range of 76-74 ppm. With a significant difference of *ca.* 10 ppm, the C-3 signal is the major inconsistency. The adjacent carbon atoms to C-3 showed some discrepancies as well; the C-2 signal is shifted upfield by 4 ppm and the methyl at C-18 is shifted downfield by 4-5 ppm compared to the values recorded for the natural product.



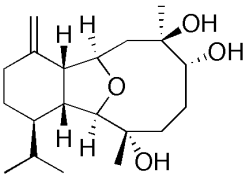
proposed structure of sclerophytin F
10



336



337



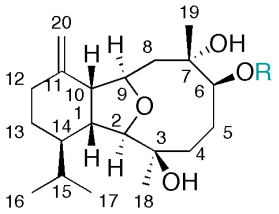
341

Carbon	Sclerophytin F	Sclerophytin F synthetic sample[a]	**336** [b]	**337** [b],[c]	**341** [b]
1	45.4	42.3	43.3	44.1	44.4
2	91.9	87.0	90.4	90.8	91.8
3	86.6	75.1 / 73.9	74.7 / 73.6	75.5 / 74.8	76.3 / 74.4
4	35.9	33.2	33.2	35.1	34.2
5	30.5	29.8	28.2	29.2	30.8
6	80.1	75.4	76.8	76.3	79.8
7	77.0	75.1 / 73.9	74.7 / 73.6	75.5 / 74.8	76.3 / 74.4
8	45.8	45.2	46.3	45.6	44.2
9	78.2	75.8	76.1	77.5	77.4
10	52.9	47.8	48.4	50.8	48.5
11	147.6	146.1	146.0	146.7	146.2
12	31.4	30.3	30.4	30.9	28.7
13	24.7	24.8	24.8	24.9	25.0
14	43.9	40.5	41.2	42.1	41.8
15	29.1	29.4	29.5	29.4	29.0
16	21.9	22.2	22.1	22.0	22.0
17	15.7	20.7	19.8	18.5	18.4
18	23.2	28.5	29.8	27.5	27.9
19	22.3	22.7	28.3	26.1	26.5
20	109.3	107.9	108.8	108.9	109.7

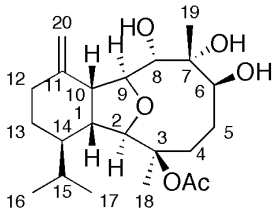
^{13}C NMR spectra recorded in $CDCl_3$. [a] Data recorded on Bruker 151 MHZ; [b] Data recorded on Bruker 126 MHz; [c] Data from DEPTQ spectra.

Table 12. Comparison of the ^{13}C NMR chemical shifts for the natural sclerophytin F with those of the synthetic sample corresponding to the proposed structure and the C-6 and C-7 diastereomers.

In Table 13, the ^{13}C chemical shifts of the known cladiellin type-natural products are presented. Looking at the reported data for sclerophytins A (**3**) and B (**4**), the signal of the C-3 stereocentre is seen at 74.8 ppm.[6] The same displacement is noted for the three corresponding diastereomers at the C-6 and C-7 positions of sclerophytin A (**3**), since the C-3 signal is found between 74.0 ppm and 75.1 ppm.[10,11,30] The case of sclerophytin B (**4**) is interesting because while the ^{13}C NMR signal for C-3 appears at 74.8 ppm, the carbon atom bearing an acetylated hydroxyl at the C-6 position gives a signal at 85.0 ppm. The corresponding carbon for sclerophytin A (**3**), *i.e* in the absence of an acetate moiety, is shifted upfield by *ca*. 5 ppm and is found at 79.9 ppm. This observation suggests that the hydroxy group at the C-3 is acetylated in natural sclerophytin F and this would be consistent with the reported value of 86.6 ppm for this carbon atom. In order to confirm this idea, other acetylated natural products were analysed.



R = H, sclerophytin A **3**
R = Ac, sclerophytin B **4**
R = Et, patagonicol **5**
R = Me, sclerophytin F methyl ether **6**



sclerophytin C **7**

Carbon	A [a]	B [a]	F [a]	C [a,c]	F methyl ether [a,c]	Patagonicol [b,c]
1	45.2	45.5	45.4	45.0	44.6	45.3
2	90.5	90.5	91.9	91.4	90.5	91.1
3	74.8	74.8	86.6	86.2	76.1	74.4
4	39.9	39.8	35.9	34.5	41.0	40.9
5	29.4	28.1	30.5	29.5	30.0	27.2
6	79.9	85.0	80.1	77.0	90.5	88.4
7	77.0	75.9	77.0	79.6	74.9	76.1
8	45.4	45.5	45.8	79.5	45.1	45.1
9	78.2	78.0	78.2	81.1	78.1	78.6
10	52.6	53.2	52.9	52.5	53.0	53.8
11	147.9	147.9	147.6	148.6	147.9	148.4
12	31.6	31.9	31.4	31.6	31.6	31.9
13	24.9	24.8	24.7	24.8	29.4	25.2
14	43.7	43.6	43.9	43.7	43.7	44.0
15	29.1	29.0	29.1	29.0	29.0	29.3
16	16.0	16.1	15.7	16.2	15.9	15.7
17	22.0	21.9	21.9	21.9	22.0	22.1
18	30.3	30.2	23.2	23.0	23.9	29.9
19	23.1	23.7	22.3	17.7	25.9	24.8
20	109.1	109.2	109.3	109.9	109.1	109.2
		171.8		169.5	57.0	64.8
		21.5		22.7		15.3

[a] ^{13}C NMR in $CDCl_3$; [b] ^{13}C NMR in C_6D_6; [c] X-ray analysis confirmed the structure.

Table 13. Comparison of the ^{13}C chemical shifts for some sclerophytin-type diterpenes.

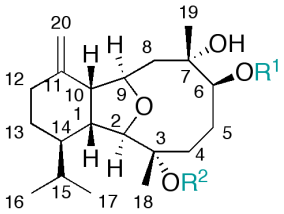
Sclerophytin C (**7**), patagonicol (**5**) and sclerophytin F methyl ether (**6**) are natural products for which X-ray analyses have confirmed their structures.[13,21,22] An acetate substituent is found at the C-3 carbon atom of sclerophytin C and there is an extra hydroxyl at the C-8 position. In the ^{13}C NMR spectra, the chemical shift of the C-3 carbon atom is 86.2 ppm, while the secured structures of the other natural products bearing free alcohol at the C-3 show a chemical shift between 74.4 and 76.1 ppm. In the same way, alkyl substitution of the alcohol at the C-6 stereocentre causes a shift in the signal which is found in the range of 85.0 to 91.0 ppm instead of 77.0 to 80.0 ppm. The ^{13}C NMR spectrum of sclerophytin F has signals at 86.6 ppm and 80.1 ppm attributed to the C-3 and C-6 carbon atoms respectively. The close correspondence between the ^{13}C NMR spectra of sclerophytin F and the other sclerophytin-type diterpenes depicted in Table 13 strongly suggests that sclerophytin F possesses the same configuration as these natural products and has a substituted alcohol at the C-3 position. Other C-3 acetylated products having the *R*-configuration at this stereocentre, such as 3-acetylcladiellisin,[14] simplexin I, [158] palmonines A-D, [159] and epoxycladins A-D [160] exhibit the characteristic signal of C-3 in the range of 84 to 87 ppm in the ^{13}C NMR spectra.

The original goal of this project was the total syntheses of all the natural products belonging to the cladiellin family having a *S*-stereocentre at the C-3 position. According to Paquette's reassignments (Table 14),[20] these compounds bear, at this stereocentre, a free hydroxyl group (sclerophytin F (**10**)), or a substituted alcohol with an acetate group (sclerophytin E (**9**), 6-ethoxysclerophytin E (**13**)14 and 6-isovaleroylsclerophytin E (**14**)[14]) or a butyrate group (litophynin E (**11**)[14] and 6-acetoxylitophynin E (**12**)). In these cases, the C-3 carbon atom appears in the range of 86 to 87 ppm in the ^{13}C NMR spectra. In the same way, the cladiellin sub-classes such as the simplexins A-H[158] and hirsutalin E,[161] which have a tertiary alcohol substituted with a butyrate motif, give rise to a signal between 84.6 and 86.0 ppm on the ^{13}C NMR spectra

[158] Wu, S, -L.; Su, J. –H.; Wen, Z, -H; Hsu, C, -H.; Chen, B.-W.;Dai, C.-F; Kuo, Y.-H.; Sheu, J.-H. *J. Nat. Prod.* **2009**, *72*, 994.
[159] Ortega, M. J.; Zubía, E.; He, H.-Y.; Salvá, J. *Tetrahedron* **1993**, *49*, 7823.
[160] Chill, L.; Berrer, N.; Benayahu, Y.; Kashman, Y. *J. Nat. Prod.* **2005**, *68*, 19.
[161] Chen, B. –W.; Chang, S. – M; Huang, C. –Y.; Chao, C. –H.; Su, J.-H.; Wen, Z. –H.; Hsu, C. –H.; Dai, C. –F.; Wu, Y. –C.; Sheu, J. –H. *J. Nat. Prod.* **2010**, *73*, 1785.

corresponding to the C-3 carbon atom as well. However, these natural products possess the *R*-configuration at the C-3 position as it is the case for all the cladiellin diterpenes for which structures have been successfully confirmed by total synthesis and/or X-ray crystallography.

The natural products that had been the subject of structural re-evaluation have their ^{13}C NMR data presented in Table 14. A chemical shift at 86 ppm, assigned to the C-3 carbon atom is evident for all of these compounds. As previously noted, despite the absence of an ester substituent at C-3, sclerophytin F (**10**) also has this characteristic signal in its ^{13}C NMR spectrum. Moreover, a close correspondence between the chemical shifts of the carbons of sclerophytin F (**10**) and E (**9**) −0.4 ppm or less for all the carbon atoms with ten identical signals− is remarkable. A second point to be considered is the origin of sclerophytins E (**9**) and F (**10**), which have been isolated from the same species of soft coral. It is important to appreciate that typographical errors in the paper concerning the isolation of sclerophytins C-F have been identified by Faulkner *et al*.[14]



R^1 = H,	R^2 = Ac	sclerophytin E **9**
R^1 = H,	R^2 = H	sclerophytin F **10**
R^1 = H,	R^2 = CO*n*-Pr	litophynin E **11**
R^1 = Ac,	R^2 = CO*n*-Pr	6-acetoxy litophynin E **12**
R^1 = Et,	R^2 = Ac	6-ethoxy sclerophytin E **13**
R^1 = CO*i*-Bu,	R^2 = Ac	6-isovaleroyl sclerophytin E **14**

Carbon	F [a]	E [a]	6-ethoxy E [a]	6-isovaleroyl E [a]	litophynin E [a]
1	45.4	45.2	45.3	45.8	45.4
2	91.9	92.0	92.1	92.1	92.0
3	86.6	86.3	86.4	86.7	86.4
4	35.9	36.1	36.6	35.7	36.1
5	30.5	30.4	27.5	29.3	30.4
6	80.1	80.1	88.3	84.5	80.1
7	77.0	77.0	75.9	75.5	76.8
8	45.8	45.7	44.9	45.8	45.8
9	78.2	78.2	78.5	78.1	78.2
10	52.9	52.9	53.9	53.8	53.6
11	147.6	147.6	147.8	147.6	147.6
12	31.4	31.4	31.5	31.5	31.4
13	24.7	24.8	24.6	24.6	24.6
14	43.9	43.9	44.0	43.8	43.8
15	29.1	29.0	29.0	29.0	29.0
16	15.7	16.1	15.5	15.4	15.6
17	21.9	21.9	21.9	21.9	21.9
18	23.2	23.2	23.1	22.9	23.2
19	22.3	22.6	23.8	23.8	22.6
20	109.3	109.3	109.5	109.5	109.3
		170.1	64.6	173.9	172.5
		22.7	15.5	43.8	37.3
			169.9	25.8	18.3
			22.3	22.4	13.7
				169.6	
				22.9	

[a] ^{13}C NMR in $CDCl_3$

Table 14. Comparison of the ^{13}C chemical shifts for the sclerophytins structurally re-evaluated by Friedrich and Paquette in 2002.[20]

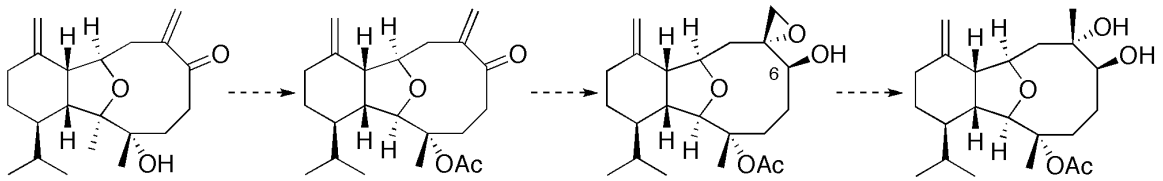
These observations led us to conclude that sclerophytins F and E are in fact the same compound that is consistent with the original mass spectrometry data. If they were structurally different (*i.e* with a C-3 acetate group on one of the compounds) the ^{13}C NMR chemical shifts should be significantly different. In addition, comparison of the NMR data of several sclerophytins for which the structures had been confirmed without ambiguity, and the data reported for the re-evaluated natural products, highlighted similarities. On the other hand, significant discrepancies were seen between the NMR data for the natural product and that for the synthetic sample of the proposed structure of sclerophytin F or its diastereomers. It is worth of noting that the *S*-configuration at the C-3 stereocentre does not result in a shift of the signal for this carbon in the ^{13}C NMR spectra to 86 ppm as has been reported for these structurally re-evaluated natural products.

The most likely explanation to account for the data is that sclerophytins E and F are the same and that the natural product corresponds to sclerophytin A with an acetylated hydroxyl group at the C-3 position. The fact that sclerophytins E and F are the same structure is also supported by the reported optical rotation. Indeed they are quite similar considering the quantity of the natural products available for data ($[\alpha]_D$ +55, $CHCl_3$, *c* = 0.20 for sclerophytin F and $[\alpha]_D$ +80, $CHCl_3$, *c* = 0.42 for sclerophytin E). Moreover, the absence of the acetate signals on the carbon spectrum could be easily explained by the sensitivity of the apparatus (NMR spectra were recorded at 74.5 MHz). Typographical errors also have to be taken in account as discussed previously. In an analogous manner to the structure reassignments of sclerophytins E and F, the four other natural products would also possess the *R*-configuration at the C-3 stereocentre, the chemical shift of this carbon atom being due to esterification of the hydroxyl group. Consequently, the biological common origin of the skeleton of the cladiellins would be consistent with the general stereochemistry found in these natural products; they all possess a *R*-configuration at the C-3 position. Only the total syntheses of sclerophytins for which the structures remain unconfirmed (with either *S*- or *R*-configuration at the C-3 stereocentre) will finally confirm these reassignments.

10 Towards the Synthesis of the Proposed Structure of Sclerophytin E

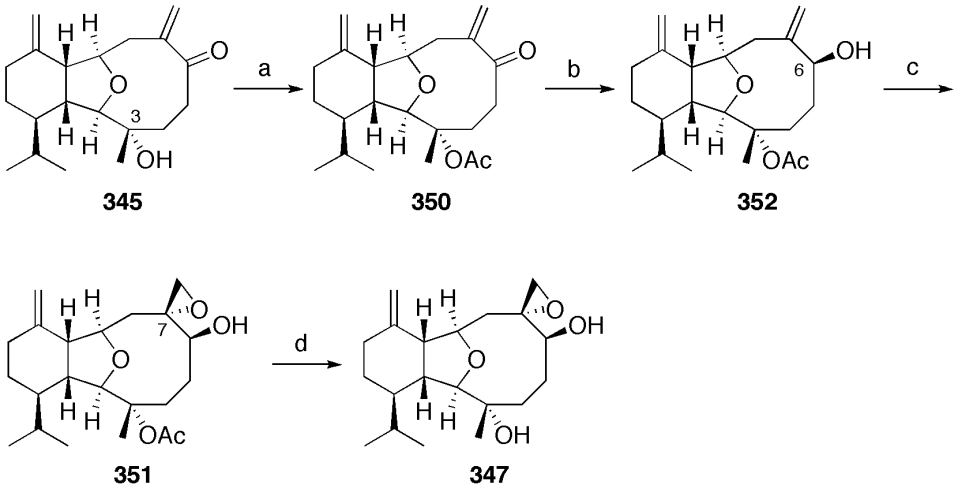
The proposed structure of sclerophytin F (**10**) had been shown to be incorrect and the existence of the *S*-configuration at the C-3 stereocentre for some of the cladiellin natural products remained to be demonstrated.
The original aim of this project was the total synthesis of the six natural products that had been proposed to possess the *S*-configuration at the C-3 position. The absence of correlation between the four diastereomers of the proposed structure of sclerophytin F and the natural product revives the debate about the structure of this cladiellin natural product and closely related compounds. In order to confirm or refute the presence of the *S*-configuration at the C-3 streocentre for other revised natural products, the total synthesis of sclerophytin E (**9**) was undertaken.

An acetate group at the C-3 position has been suggested to be the difference between the proposed structures of sclerophytins F (**10**) and E (**9**). The first approach towards the synthesis of the proposed structure of sclerophytin E (**9**) involved the acetylation of the hydroxyl group on the allylic ketone **345** followed by the reduction of the ketone to install the C-6 stereocentre (Scheme 102). Finally, Sharpless asymmetric epoxidation and reductive epoxide opening, as described in the total synthesis of the proposed structure of sclerophytin F (**10**), would be expected to deliver the proposed structure of sclerophytin E (**9**).



Scheme 102. General approach towards the total synthesis of the proposed structure of sclerophytin E.

Acetylation of the C-3 hydroxyl group followed by the reduction of the allylic ketone under Luche conditions[156] furnished the allylic alcohol **352** in moderate yield. The presence of the acetate group was clearly visible in the ^{1}H NMR spectra (peak at 2.07 ppm). By analogy with the recorded data of the corresponding allylic alcohol **346**, it was assumed that the configuration at the C-6 stereocentre was the desired *S*-configuration. Indeed, for both compounds the proton H-6 appears as a doublet of doublets in the ^{1}H NMR spectra with similar coupling constants (4.48 ppm, J = 10.6, 4.8 Hz for **346**; 4.55 ppm, J = 9.9, 4.4 ppm for **352**), while the characteristic signal is a multiplet when this stereocentre has an *R*-configuration. Subsequent catalytic asymmetric Sharpless epoxidation was performed in the presence of titanium tetraisopropoxide and (+)-diethyl tartrate installing the C-7 stereocentre with *S*-configuration. The reaction was complete within 24 hours and the epoxy-alcohol **351** was isolated in 34% yield. The success of the reaction and the signature of an epoxide in the ^{1}H NMR spectrum (a doublet of doublets at 3.16 ppm and a doublet at 2.99 ppm) suggested that the product possessed the desired configuration at the eight stereocentres. As previously observed (see results and discussion, section 8), epoxidation to form the *cis* α-epoxy-alcohol did not occur under the Sharpless asymmetric reaction conditions and oxidation of the alcohol was observed when the C-6 stereocentre had the *R*-configuration. Opening of the epoxide **351** was attempted by treatment with diisobutylaluminium hydride. Unfortunately, under these conditions the acetate was cleaved producing the epoxy-alcohol **347** in 87% yield.

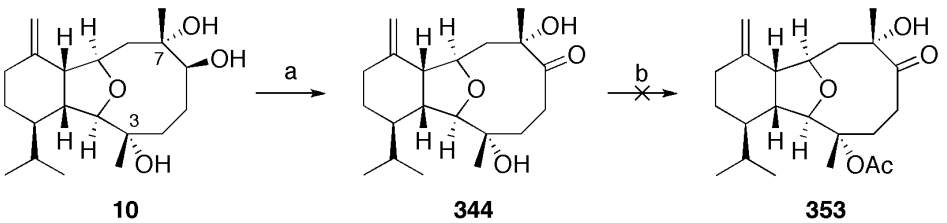


a) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt to reflux; b) $NaBH_4$, $CeCl_3.7H_2O$, MeOH, 0 °C, 43% (2 steps); c) (+)-DET, $Ti(O\textit{i}\text{-}Pr)_4$, *t*-$BuO_2H$, CH_2Cl_2, −20 °C, 34%; d) DIBAL-H, CH_2Cl_2, 87%.

Scheme 103. Attempted synthesis of the proposed structure of sclerophytin E from the allylic alcohol **345**.

Since the acetate group appeared to be more reactive than the epoxide under reduction conditions, the C-7 stereocentre has to be introduced prior to the functionalization of the C-3 hydroxyl.

In this synthetic strategy, the proposed structure of sclerophytin F was oxidised to give ketone **344** and this was subjected to acetylation conditions (Scheme 104). The reaction mixture was stirred at room temperature for 18 hours affording a complex mixture of products.

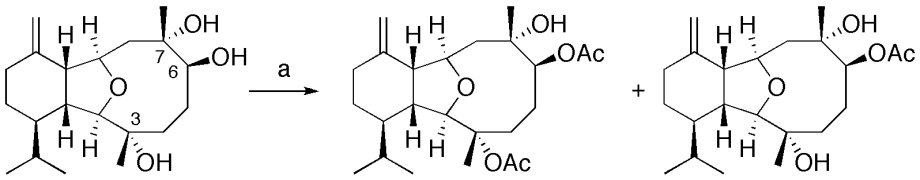


a) DMP, CH_2Cl_2; b) Ac_2O, DMAP, Et_3N, rt.

Scheme 104. Oxidation and acetylation of the proposed structure of sclerophytin F.

A final approach based upon the acetylation of the hydroxyl groups at the C-3 and C-6 positions followed by a selective de-acetylation of the secondary

alcohol was explored. It was expected that treatment of the proposed structure of sclerophytin F (**10**) with acetic anhydride in presence of pyridine would deliver the *bis*-acetate **354** resulting from acetylation at both the C-3 and C-6 positions. However, acetylation occurred at the C-6 position only (Scheme 105) and acetate **355** was isolated in 20% yield along with 24% of recovered starting material. It is worth noting that acetate **355** is the C-3 epimer of (−)-sclerophytin B (**4**).



10 **354** **355**

a) Ac_2O, pyridine, rt, **355** 20%.

Scheme 105. Acetylation at C-6 of the proposed structure of sclerophytin F.

Attempted acetylation of the triol was then repeated under harsher conditions. The use of acetic anhydride, 4-dimethylaminopyridine, and triethylamine at high temperature led to the formation of two major products. The acetate groups were visible in the ^{1}H NMR at 2.08 ppm and 2.07 ppm for the first product and at 2.06 and 2.01 ppm for the second one. However, due to the inability to get thoroughly clean material for analysis, cleavage of the acetates by treatment with potassium carbonate was undertaken on both products. After complete consumption of the starting materials, crude ^{1}H NMR analysis revealed the proposed structure of sclerophytin F (**10**) as the major product in both cases. Due to the lack of material and time constraints the synthesis of the proposed structure of sclerophytin E (**9**) could not be studied further.

11 Conclusions and Future Work

11.1 Conclusions

The first enantioselective total synthesis of the proposed structure of sclerophytin F (**10**) was achieved in a total of 33 steps starting from the commercially available 1,4-butanediol **147**. The route featured SmI_2-mediated reductive cyclisation, oxonium ylide formation followed by a [2,3]-sigmatropic rearrangement to form the oxabicyclo[6.2.1]-5-undecen-9-one core and a thermal Diels-Alder cycloaddition reaction to give the tricyclic skeleton of the natural product.

In the reported total syntheses of cladiellin natural products having *R*-configuration at the C-3 position, the methyl group at this position was introduced at a very late stage in the synthesis. However, the stereocentre bearing the *S*-configuration was installed in the very beginning of this synthesis, requiring a modification of the route and careful optimisation of the reaction conditions. A relevant example is the [2,3]-sigmatropic rearrangement reaction: in the absence of the methyl group at the C-3 position, the reaction can be tuned to deliver selectively the *Z*- or the *E*-bicyclic ketone, but control of the outcome was impossible in our case. The rearrangement reaction led to the formation of a mixture of *Z* and *E* isomers although in excellent yield.

Unfortunately, spectroscopic data obtained for the synthetic sample of the proposed structure of sclerophytin F (**10**) did not match with those reported for the natural product revealing a mistake in the structural reassignment.[20] The

syntheses of the three other diastereomers at the C-6 and C-7 positions of the proposed structure of sclerophytin F were also accomplished, but none of these compounds corresponded to the natural product either. These results combined with careful re-analysis of the NMR data reported for the sclerophytin natural products led to the conclusion that all the members of this family of natural products possess *R* configuration at the C-3 position, and that sclerophytins E and F are in fact the same product. However, this hypothesis has yet to be confirmed by total synthesis of the natural product.

11.2 Outlook

The lack of agreement between the recorded data for the synthetic sample of the proposed structure of sclerophytin F and those of the natural product calls into question the presence of the 3*S*-configuration in the cladiellin family natural products. Following structural re-evaluation of these products, the syntheses of these new sclerophytin diastereomers would be necessary in order to determine their configuration at the C-3 position.

As described in the introduction, many cladiellin natural products possess interesting biological properties, particularly sclerophytin A. In the course of this study a wide range of complex products have been synthesised and intermediates as well as the final products will be sent for biological evaluation. Furthermore, the proposed structure of sclerophytin F corresponds to the C-3 epimer of sclerophytin A, so testing of this final product will provide preliminary information about any correlation between the C-3 configuration and the biological activity of the cladiellins.

EXPERIMENTAL SECTION

General Experimental Conditions

General Comments

Air and/or moisture sensitive reactions were performed under an atmosphere of argon in flame dried apparatus. Organic solvents were purified using a Pure Solv™ 500 Solvent Purification System. Starting materials were obtained from commercial sources and used as received unless otherwise specified. Petroleum ether used for column chromatography was the fraction with boiling point 40-60 °C.

Chromatography

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 and stained using either potassium permanganate solution or acidic ethanolic anisaldehyde solution or phosphomolybdic acid solution. Flash column chromatography was accomplished with silica gel (Fluorochem LC60A, 35-70 micron, or Geduran® Si 60, 40-63 micron) as solid support.

Analysis Apparatus

Melting points were recorded with Electrothermal IA 9100 apparatus.
Specific rotations of the chiral non-racemic compounds were recorded with an error ≤±0.1 using an automatic polarimeter Autopol® V. The wavelength of the light was 589 nanometers.

IR spectra were recorded with a type IIa diamond single reflection element on a Shimadzu FTIR-8400 instrument. The compound (solid or liquid) was analysed directly as a thin layer at ambient temperature.

NMR spectra were recorded on a Bruker 400 MHz Spectrospin spectrometer (^{1}H NMR at 400 MHz and ^{13}C NMR at 101 MHz) or on a Bruker 500 MHz Spectrospin spectrometer (^{1}H NMR at 500 MHz and ^{13}C NMR at 126 MHz) or on a Bruker 600 MHz Spectrospin spectrometer (^{1}H NMR at 600 MHz and ^{13}C NMR at 151 MHz) at ambient temperature. Chemical shifts are reported in ppm. ^{1}H NMR spectra were recorded with $CDCl_3$ as solvent using (d = 7.26) as internal standard, and for ^{13}C NMR spectra, the chemical shifts are reported relative to the central resonance of $CDCl_3$ (d = 77.16). Signals in NMR spectra are described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), septet (sept), multiplet (m), broad (br), apparent (app) or combination of these, which refers to the spin-spin coupling pattern observed. DEPT 135, and two dimensional (COSY, HSQC) NMR spectroscopy were used where appropriate to assist the assignment of signals in the ^{1}H and ^{13}C NMR spectra.

HRMS were recorded using positive chemical ionization (CI+), positive ion impact (EI+), positive or negative ion electrospray (ESI+/ESI−) techniques on a Jeol M-STATION JMS-700 instrument. Low resolution mass spectra (LRMS) were recorded using the same instrument. The intensity of each peak is quoted as a percentage of the largest, in cases where this information was available.

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

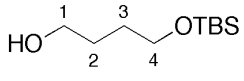
X-ray crystallography was performed at the University of Glasgow by Dr. L. J. Farrugia.

Nomenclature

Compounds were named according to the IUPAC rules, whereas numbering of the carbons has been done independently to these rules to help at their identification.

Procedures and Products Characterisations

4-(*tert*-Butyldimethylsilyloxy)butan-1-ol (279)[55,60]

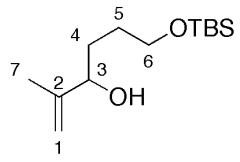


$C_{10}H_{24}O_2Si$

To a stirred solution of 1,4-butanediol (75 mL, 0.42 mol) and triethylamine (60 mL, 0.43 mol) in anhydrous CH_2Cl_2 (790 mL) at 0 °C was added *tert*-butyldimethylsilyl chloride (42.0 g, 278 mmol). The mixture was stirred overnight at room temperature and the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (400 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 100 mL). The organic extracts were combined, washed with brine (300 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 8:1 to 5:1) afforded alcohol **279** (53.3 g, 93%) as a colourless oil.

R_f = 0.55; (petroleum ether-ethyl acetate, 2:1); ν_{max} (neat) 3324, 2929, 2884, 2856, 1472, 1254, 1098, 1059, 991, 975, 832, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.69–3.60 (4H, m, CH_2-C1, CH_2-C4), 2.56 (1H, br s, OH), 1.69–1.59 (4H, m, CH_2-C2, CH_2-C3), 0.89 (9H, s, CH_3-*t*Bu), 0.06 (6H, s, Si-CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 63.5 (CH_2-C1), 62.9 (CH_2-C4), 30.4 (CH_2-C2), 30.0 (CH_2-C3), 26.0 (CH_3-*t*Bu), 18.4 (C-*t*Bu), −5.3 (Si-CH_3); HRMS (CI+, Me_3CH) for $C_{10}H_{25}O_2Si$ $[M+H]^+$ calcd. 205.1624, found 205.1625, Δ +0.4 ppm; LRMS (CI+, Me_3CH) *m/z* (intensity); 205.2 (100%).

6-(*tert*-Butyldimethylsilanyloxy)-2-methyl-hex-1-en-3-ol (153)



$C_{13}H_{28}O_2Si$

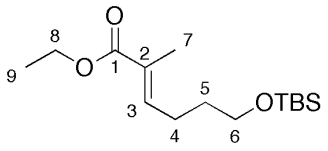
To a solution of oxalyl chloride (1.10 mL, 12.8 mmol) in anhydrous CH_2Cl_2 (10 mL) at −78 °C was added a solution of anhydrous DMSO (0.90 mL, 12.7 mmol) in anhydrous CH_2Cl_2 (10 mL) dropwise. The solution was stirred for 15 min and alcohol **279** (2.06 g, 10.1 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h and triethylamine (7.00 mL, 94.7 mmol) was added. The solution was allowed to warm to room temperature and was stirred for an additional hour. The reaction was diluted with CH_2Cl_2 (20 mL) and quenched by the addition of a saturated aqueous solution of NH_4Cl (50 mL). The organic phase was separated and washed with brine (40 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the corresponding aldehyde.

To a stirred slurry of magnesium turnings (489 mg, 20.1 mmol) and iodine (trace) in anhydrous THF (10 mL) at reflux was added a solution of 2-bromopropene (1.50 mL, 17.2 mmol) in anhydrous THF (20 mL) dropwise while maintaining the reflux. After complete addition, the solution was stirred for 1.25 h and cooled to 0 °C. A solution of crude aldehyde in anhydrous THF (20 mL) was added dropwise and the mixture was stirred at 0 °C for a further 30 min. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (30 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (2 × 20 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography (petroleum ether-ethyl acetate from pure to 1:1) afforded the desired allylic alcohol **153** (1.68 g, 67%) as a colourless oil.

R_f = 0.43 (petroleum ether–ethyl acetate, 4:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 (1H, br s, CH_2-C1), 4.81 (1H, br s, CH_2-C1), 4.08−4.04 (1H, m, CH-C3), 3.64 (2H, t, *J* = 5.6 Hz, CH_2-C6), 2.62 (1H, d, *J* = 3.6 Hz, OH), 1.71 (3H, s, CH_3-C7), 1.70−1.54 (4H, m, CH_2-C5, CH_2-C4), 0.89 (9H, s, CH_3-*t*Bu), 0.05 (6H, s, Si-CH_3); ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7 (C-C2), 110.9 (CH_2-C1), 75.4 (CH-C3), 63.3 (CH_2-C6), 32.3 (CH_2-C4), 28.9 (CH_2-C5), 25.9 (CH_3-*t*Bu), 18.3 (C-*t*Bu), 17.9 (CH_3-

C7), −5.3 (Si-CH_3); ν_{max} (neat) 3348, 2931, 2858, 1651, 1466, 1389, 1250, 1096, 1003, 895, 833, 771, 717, 663 cm^{-1}; HRMS (CI+, Me_3CH) calcd. for $C_{13}H_{29}O_2Si$ $[M+H]^+$ calcd. 245.1937, found 245.1940, Δ −1.1 ppm; LRMS (CI+, Me_3CH) *m/z* (intensity) 245.4 (87%), 227.3 (89%), 95.2 (100%).

Ethyl (2*E*)-(6)-(*tert*-butyldimethylsilyloxy)-2-methylhex-2-enoate (150)[55,60]



$C_{15}H_{30}O_3Si$

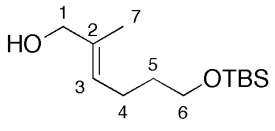
To a stirred solution of alcohol **279** (5.00 g, 24.5 mmol) in anhydrous CH_2Cl_2 (25 mL) was added TEMPO (0.15 g, 0.96 mmol). The solution was cooled to 0 °C and a solution of NaOCl (23 mL of a 1.4 M solution in water, 32.2 mmol), saturated aqueous solution of $NaHCO_3$ (60 mL), NaBr (397 mg, 3.86 mmol) and water (3.8 mL) was added dropwise over 20 min. The mixture was stirred for 10 min and the reaction was quenched by the addition of MeOH (50 mL). The phases were separated and the aqueous phase was extracted with EtOAc (2 × 100 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude aldehyde which was used directly in the next step.

To a solution of the crude aldehyde in anhydrous THF (240 mL) was added ethyl 2-(triphenylphosphoranylidene)propanoate (13.8 g, 38.1 mmol) in one portion. The mixture was stirred at room temperature for 48 h and the reaction was quenched by the addition of water (100 mL). The aqueous phase was separated and extracted with EtOAc (2 × 50 mL). The organic extracts were combined, washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 50:1) delivered ester **150** (6.03 g, 86% over two steps) as a colourless oil.

R_f = 0.45; (petroleum ether-ethyl acetate, 10:1); ν_{max} (neat) 2955, 2929, 2857, 1710, 1256, 1094, 833, 774 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.76 (1H, tq, *J* = 7.3, 1.2 Hz, CH-C3), 4.18 (1H, q, *J* = 7.1 Hz, CH_2-C8), 4.18 (1H, q, *J* = 7.1 Hz,

CH_2-C8), 3.62 (2H, t, *J* = 6.3 Hz, CH_2-C6), 2.24 (2H, q, *J* = 7.3 Hz, CH_2-C4), 1.83 (3H, s, CH_3-C7), 1.64 (2H, tt, *J* = 7.3, 6.3 Hz, CH_2-C5), 1.28 (3H, td, *J* = 7.1, 0.6 Hz, CH_3-C9), 0.89 (9H, s, CH_3-*t*Bu), 0.04 (6H, s, Si-CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.4 (C-C1), 142.0 (CH-C3), 128.2 (C-C2), 62.5 (CH_2-C6), 60.5 (CH_2-C8), 31.8 (CH_2-C5), 26.1 (CH_3-*t*Bu), 25.3 (CH_2-C4), 18.4 (C-*t*Bu), 14.4 (CH_3-C9), 12.4 (CH_3-C7), −5.2 (Si-CH_3); HRMS (CI+, Me_3CH) for $C_{15}H_{31}O_3Si$ $[M+H]^+$ calcd. 287.2042, found 287.2047, Δ +1.5 ppm; LRMS (CI+, Me_3CH) *m/z* (intensity); 287.2 (100%), 241.2 (23%), 229.2 (13%).

(2*E*)-(6)-(*tert*-Butyldimethylsilyloxy)-2-methylhex-2-en-1-ol (151)[55,60]



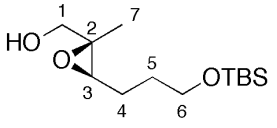
$C_{13}H_{28}O_2Si$

To a stirred solution of ester **150** (20.2 g, 70.6 mmol) in anhydrous CH_2Cl_2 (720 mL) at −78 °C was added DIBAL-H (180 mL of a 1.0 M solution in CH_2Cl_2, 180 mmol) dropwise over 1 h. The resulting solution was stirred for 1.5 h and the reaction was quenched with a saturated aqueous solution of sodium potassium tartrate (250 mL). The solution was allowed to warm to room temperature, diluted with EtOAc (750 mL) and stirred vigorously until the appearance of two clear phases. The phases were separated and the aqueous phase was extracted with EtOAc (3 × 100 mL). The organic extracts were combined, washed with brine (300 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 20:1 to 5:1) delivered desired the allylic alcohol **151** (17.1 g, 98%) as a colourless oil.

R_f = 0.55; (petroleum ether-ethyl acetate, 2:1); ν_{max} (neat) 3337, 2955, 2929, 2856, 1472, 1387, 1253, 1095, 1004, 833, 772, 659 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.42 (1H, tq, *J* = 7.2, 1.3 Hz, CH-C4), 4.00 (2H, d, *J* = 6.0 Hz, CH_2-C1), 3.61 (2H, t, *J* = 6.4 Hz, CH_2-C6), 2.09 (2H, q, *J* = 7.2 Hz, CH_2-C4), 1.67 (3H, s, CH_3-C7), 1.59 (2H, tt, *J* = 7.2, 6.4 Hz, CH_2-C5), 1.24 (1H, t, *J* = 6.0 Hz, OH), 0.89 (9H, s, CH_3-*t*Bu), 0.05 (6H, s, Si-CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.2 (C-C2), 126.1 (CH-C3), 69.2 (CH_2-C1), 62.8 (CH_2-C6), 32.8 (CH_2-C5), 26.1 (CH_3-*t*Bu), 24.1

(CH_2-C4), 18.5 (C-*t*Bu), 13.8 (CH_3-C7), −5.1 (Si-CH_3); HRMS (ESI) for $C_{13}H_{28}NaO_2Si$ $[M+Na]^+$ calcd. 267.1751, found 267.1745, Δ −2.2 ppm.

{(2*R*,3*R*)-3-[3-(*tert*-Butyldimethylsilyloxy)propyl]-2-methyloxiran-2-yl}methanol (152)[55,60]



$C_{13}H_{28}O_3Si$

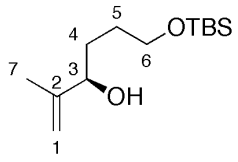
To a suspension of 4 Å powdered molecular sieves (2.70 g) in anhydrous CH_2Cl_2 (540 mL) at −25 °C were added freshly distilled titanium tetraisopropoxide (0.80 mL, 2.7 mmol), freshly distilled (−)-diethyl tartrate (0.70 mL, 4.1 mmol) and *tert*-butylhydroperoxide (18 mL of a 4.7 M solution in decane, 84.6 mmol) dropwise over 15 min. The solution was stirred for 1 h and a solution of the allylic alcohol **151** (13.2 g, 54.1 mmol) in anhydrous CH_2Cl_2 (50 mL) was added slowly over a period of 1 h, while the temperature maintained at −25 °C. The mixture was stirred for a further 1 h and the reaction was quenched by the addition of water (100 mL). The solution was warmed to 0 °C and a solution of 30% wt NaOH in brine (100 mL) was added. The mixture was allowed to warm to room temperature and then stirred for an additional 30 min. The molecular sieves were removed by filtration. The aqueous phase was separated and extracted with CH_2Cl_2 (3 × 100 mL). The organic extracts were combined, washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 20:1 to 2:1) afforded the desired epoxy alcohol **152** (13.0 g, 93%) as a colourless oil.

The enantiomeric excess (92%) was determined by normal phase chiral HPLC analysis of the corresponding vinylogous carbonate **281**.

R_f = 0.37; (petroleum ether-ethyl acetate, 2:1); $[\alpha]_D^{23}$ +12.5 (*c* = 1.04, $CHCl_3$), {Lit.[55] $[\alpha]_D^{23}$ +14.9 (*c* = 1.00, $CHCl_3$)}; ν_{max} (neat) 3440, 2953 2929, 2856, 1472, 1386, 1252, 1094, 1038, 833, 773, 660 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.71−3.55 (4H, m, CH_2-C1, CH_2-C6), 3.06 (1H, t, *J* = 5.6 Hz, CH-C3), 1.73−1.61 (5H, m, CH_2-C4, CH_2-C5, OH), 1.29 (3H, s, CH_3-C7), 0.89 (9H, s, CH_3-*t*Bu), 0.05

(6H, s, Si-CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 65.5 (CH_2-C1), 62.7 (CH_2-C6), 61.0 (C-C2), 60.1 (CH-C3), 29.8 (CH_2-C5), 26.1 (CH_3-*t*Bu), 25.0 (CH_2-C4), 18.5 (C-*t*Bu), 14.3 (CH_3-C7), −5.2 (Si-CH_3); HRMS (CI+, Me_3CH) for $C_{13}H_{29}O_3Si$ $[M+H]^+$ calcd. 261.1886, found 261.1884, Δ −0.7 ppm; LRMS (CI+, Me_3CH) *m/z* (intensity); 261.2 (69%), 243.2 (63%), 203.2 (100%), 129.1 (61%).

(3*R*)-6-(*tert*-Butyldimethylsilyloxy)-2-methylhex-1-en-3-ol (153)[55,60]



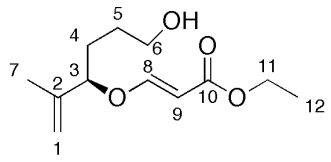
$C_{13}H_{28}O_2Si$

To a stirred solution of epoxy alcohol **152** (4.70 g, 18.1 mmol) and triethylamine (3.80 mL, 27.4 mmol) in anhydrous CH_2Cl_2 (90 mL) at −10 °C was added methanesulfonyl chloride (1.80 mL, 23.3 mmol) while the temperature was maintained at −10 °C. The solution was stirred for 25 min and the reaction was quenched by the addition of water (30 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL). The organic phase was washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude mesylate was immediately used in the next step without further purification.

To a stirred solution of the crude mesylate in butan-2-one (90 mL) was added sodium iodide (13.9 g, 92.8 mmol) and the mixture was stirred at 80 °C for 30 min during which time the reaction mixture turned brown. Zinc powder (1.92 g, 23.4 mmol) was then added and the reaction mixture was stirred for a further 1 h at reflux. The reaction mixture was cooled to room temperature. The grey solution was diluted with EtOAc (160 mL) and the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (80 mL). The aqueous phase was separated and extracted with EtOAc (3 × 40 mL). The organic extracts were combined, washed with brine (200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 30:1 to 20:1) yielded the enantio-enriched allylic alcohol **153** (4.16 g, 94%) as a colourless oil.

R_f = 0.44; (petroleum ether-ethyl acetate, 4:1); $[\alpha]_D^{27}$ +9.9 (*c* = 1.05, $CHCl_3$), {Lit.[55] $[\alpha]_D^{21}$ +8.7 (*c* = 1.01, $CHCl_3$)}; ν_{max} (neat) 3372, 2952, 2929, 2856, 1472, 1388, 1254, 1095, 1004, 896, 832, 772, 660 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.96 (1H, quint, *J* = 1.2 Hz, CH_2-C1), 4.83 (1H, quint, *J* = 1.2 Hz, CH_2-C1), 4.07 (1H, br t, *J* = 5.7 Hz, CH-C3), 3.66 (2H, t, *J* = 5.6 Hz, CH_2-C6), 2.51 (1H, br s, OH), 1.72 (3H, s, CH_3-C7), 1.71−1.56 (4H, m, CH_2-C4, CH_2-C5), 0.90 (9H, s, CH_3-*t*Bu), 0.06 (6H, s, Si-CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.7 (C-C2), 110.9 (CH_2-C1), 75.6 (CH-C3), 63.5 (CH_2-C6), 32.5 (CH_2-C4), 29.0 (CH_2-C5), 26.1 (CH_3-*t*Bu), 18.5 (C-*t*Bu), 18.0 (CH_3-C7), −5.2 (Si-CH_3); HRMS (CI+, Me_3CH) for $C_{13}H_{29}O_2Si$ $[M+H]^+$ calcd. 245.1937, found 245.1937, Δ 0.0 ppm; LRMS (CI+, Me_3CH) *m/z* (intensity); 245.3 (68%), 227.3 (100%), 94.1 (87%).

Ethyl (*E*)-3-{[(3*R*)-6-hydroxy-2-methylhex-1-en-3-yl]oxy}-prop-2-enoate (281)[55,60]



$C_{12}H_{20}O_4$

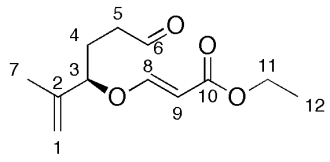
To a stirred solution of alcohol **153** (12.5 g, 51.1 mmol) in anhydrous CH_2Cl_2 (200 mL) were added ethyl propiolate (11.0 mL, 108 mmol) and *N*-methylmorpholine (12.0 mL, 109 mmol). The resulting brown solution was stirred at room temperature overnight and concentrated *in vacuo*. The residue was filtered through a pad of silica gel (petroleum ether–ethyl acetate, gradient elution from 50:1 to 30:1) to afford the crude ester which was used in the next step without further purification.

To a stirred solution of the above silyl ether in MeOH (520 mL) was added camphorsulfonic acid (1.22 g, 5.25 mmol). The mixture was stirred at room temperature overnight and the reaction was quenched by the addition of $NaHCO_3$ (4.30 g). The remaining solid was removed by filtration and the solution was concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution

from 5:1 to 5:2) delivered the alcohol **281** (9.03 g, 78% over two steps) as a colourless oil.

R_f = 0.41; (petroleum ether-ethyl acetate, 1:1); $[\alpha]_D^{18}$ −9.0 (*c* = 1.08, $CHCl_3$), {Lit.[55] $[\alpha]_D^{18}$ −8.3 (*c* = 1.01, $CHCl_3$)}; ν_{max} (neat) 3450, 2978, 2946, 2872, 1706, 1636, 1620, 1200, 1126, 1045, 958, 935, 908, 831 cm^{-1}; ^1H NMR (500 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, quint, *J* = 1.4 Hz, CH_2-C1), 4.97 (1H, br s, CH_2-C1), 4.27 (1H, dd, *J* = 7.7, 5.5 Hz, CH-C3), 4.19−4.09 (2H, m, CH_2-C11), 3.72−3.63 (2H, m, CH_2-C6), 1.86−1.52 (4H, m, CH_2-C4, CH_2-C5), 1.67 (3H, s, CH_3-C7), 1.37 (1H, t, *J* = 5.2 Hz, OH), 1.26 (3H, t, *J* = 7.1 Hz, CH_3-C12); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2 (C-C10), 161.5 (CH-C8), 142.8 (C-C2), 114.8 (CH_2-C1), 98.2 (CH-C9), 86.5 (CH-C3), 62.5 (CH_2-C6), 59.9 (CH_2-C11), 29.7 (CH_2-C4), 28.7 (CH_2-C5), 17.1 (CH_3-C7), 14.5 (CH_3-C12); HRMS (ESI, Me_3OH:H_2O) for $C_{12}H_{20}O_4Na$ $[M+Na]^+$ calcd. 251.1254, found 251.1250, Δ −1.4 ppm.

Ethyl (*E*)-3-{[(3*R*)-2-methyl-6-oxohex-1-en-3-yl]oxy}-prop-2-enoate (138)[55,60]



$C_{12}H_{18}O_4$

Method A: PCC oxidation

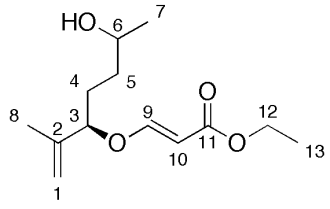
To a suspension of 4 Å powdered molecular sieves (4.56 g) in a stirred solution of alcohol **281** (9.35 g, 40.9 mmol) in anhydrous CH_2Cl_2 (210 mL) was added pyridinium chlorochromate (11.1 g, 51.3 mmol) portionwise. The mixture was stirred at room temperature overnight. The resulting solid was filtered through a pad of silica gel (petroleum ether-ethyl acetate 5:1) to afford the aldehyde **138** (7.89 g, 85%) as a colourless oil.

Method B: Swern oxidation

To a stirred solution of oxalyl chloride (1.40 mL, 16.6 mmol) in anhydrous CH_2Cl_2 (39 mL) at −78 °C was added anhydrous DMSO (2.20 mL, 31.0 mmol) in anhydrous CH_2Cl_2 (11 mL) slowly. The resulting solution was stirred for 30 min at −78 °C and the alcohol **281** (1.90 g, 8.32 mmol) in anhydrous CH_2Cl_2 (25 mL) was added slowly. The mixture was stirred at −78 °C for 2 h and the reaction was quenched by the addition of distilled triethylamine (6.00 mL, 43.3 mmol). The solution was allowed to warm to room temperature, stirred for an additional hour and diluted with CH_2Cl_2 (20 mL) and water (40 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (3 × 10 mL). The organic extracts were combined, washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 5:1) yielded the aldehyde **138** (1.53 g, 81%) as a colourless oil.

R_f = 0.32; (petroleum ether-ethyl acetate, 5:1); $[\alpha]_D^{21}$ −1.4 (*c* = 1.06, $CHCl_3$), {Lit.[55] $[\alpha]_D^{23}$ −1.9 (*c* = 1.00, $CHCl_3$)}; ν_{max} (neat) 2979, 2938, 1703, 1638, 1621, 1199, 1125, 1045, 953, 909, 832 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.78 (1H, t, *J* = 1.1 Hz, CH-C6), 7.44 (1H, d, *J* = 12.5 Hz, CH-C8), 5.26 (1H, d, *J* = 12.5 Hz, CH-C9), 5.02 (1H, quint, *J* = 1.4 Hz, CH_2-C1), 4.99 (1H, br s, CH_2-C1), 4.29 (1H, dd, *J* = 7.8, 5.4 Hz, CH-C3), 4.19–4.10 (2H, m, CH_2-C11), 2.57–2.51 (2H, m, CH_2-C5), 2.09–1.93 (2H, m, CH_2-C4), 1.67 (3H, s, CH_3-C7), 1.27 (3H, t, *J* = 7.1 Hz, CH_3-C12); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.1 (CH-C6), 167.9 (C-C10), 161.0 (CH-C8), 142.3 (C-C2), 115.2 (CH_2-C1), 98.7 (CH-C9), 85.1 (CH-C3), 59.9 (CH_2-C11), 39.8 (CH_2-C5), 25.8 (CH_2-C4), 17.2 (CH_3-C7), 14.5 (CH_3-C12); HRMS (CI+, Me_3CH) for $C_{12}H_{19}O_4$ $[M+H]^+$ calcd. 227.1283, found 227.1277, Δ −2.6 ppm; LRMS (CI+, Me_3CH) *m*/*z* (intensity); 257.1 (29%), 227.1 (100%), 111.1 (79%).

Ethyl (*E*)-3-{[(3*R*)-6-hydroxy-2-methylhept-1-en-3-yl]oxy}-prop-2-enoate (282)[58]



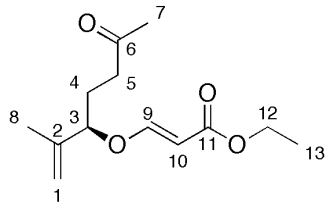
$C_{13}H_{22}O_4$

To a stirred solution of aldehyde **138** (7.89 g, 34.5 mmol) in anhydrous CH_2Cl_2 (350 mL) at −78 °C was added trimethylaluminium (36 mL of a 2.0 M solution in hexane, 72 mmol) slowly. The mixture was warmed to 0 °C, stirred for 2 h at this temperature and the reaction was quenched by the addition of a saturated aqueous solution of potassium sodium tartrate (60 mL). The mixture was allowed to warm to room temperature and diluted with water (150 mL). The solution was stirred vigorously at room temperature until the appearance of two clear phases. The aqueous phase was separated and extracted with EtOAc (3 × 100 mL). The organic extracts were combined, washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 5:1 to 5:2) delivered a 1:1 mixture of diastereomers of alcohol **282** (7.55 g, 87%) as a colourless oil.

R_f = 0.59; (petroleum ether - ethyl acetate, 5:1); ν_{max} (neat) 3428, 2965, 2929, 1706, 1691, 1637, 1620, 1199, 1123, 1095, 953, 906, 832 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47 (2H, d, *J* = 12.4 Hz, CH-C9a, CH-C9b), 5.26 (2H, d, *J* = 12.4 Hz, CH-C10a, CH-C10b), 4.99 (2H, q, *J* = 1.4 Hz, CH_2-C1a, CH_2-C1b), 4.97 (2H, d, *J* = 1.4 Hz, CH_2-C1a, CH_2-C1b), 4.26 (2H, dd, *J* = 12.3, 5.8 Hz, CH-C3a, CH-C3b), 4.19−4.09 (4H, m, CH_2-C12a, CH_2-C12b), 3.86−3.77 (2H, m, CH-C6a, CH-C6b), 1.93−1.63 (4H, m, CH_2-C4a, CH_2-C4b), 1.68 (6H, s, CH_3-C8a, CH_3-C8b), 1.60−1.32 (6H, m, CH_2-C5a, CH_2-C5b, OHa, OHb), 1.26 (6H, t, *J* = 7.1 Hz, CH_3-C13a, CH_3-C13b), 1.21 (6H, d, *J* = 6.1 Hz, CH_3-C7a, CH_3-C7b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2 (C-C11a, C-C11b), 161.5 (CH-C9a, CH-C9b), 142.9 (C-C2a or C-C2b), 142.8 (C-C2a or C-C2b), 114.8 (CH_2-C1a, CH_2-C1b), 98.3 (CH-C10a or CH-C10b), 98.2 (CH-C10a or CH-C10b), 86.9 (CH-C3a or CH-C3b), 86.6 (CH-C3a or CH-C3b), 67.9 (CH-C6a or CH-C6b), 67.7 (CH-C6a or CH-C6b), 59.9 (CH_2-C12a, CH_2-C12b), 35.1 (CH_2-C5a or CH_2-C5b), 34.9 (CH_2-C5a or CH_2-C5b), 29.7 (CH_2-C4a or CH_2-C4b),

29.4 (CH_2-C4a or CH_2-C4b), 23.9 (CH_3-C7a or CH_3-C7b), 23.8 (CH_3-C7a or CH_3-C7b), 17.1 (CH_3-C8a, CH_3-C8b), 14.5 (CH_3-C13a, CH_3-C13b); HRMS (CI+, Me_3CH) for $C_{13}H_{23}O_4$ $[M+H]^+$ calcd. 243.1596, found 243.1594, Δ −1.0 ppm; LRMS (CI+, Me_3CH) *m/z* (intensity); 243.2 (100%), 117.1 (68%).

Ethyl (*E*)-3-{[(3*R*)-2-methyl-6-oxohept-1-en-3-yl]oxy}-prop-2-enoate (277)[58]



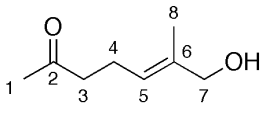
$C_{13}H_{20}O_4$

To a stirred solution of oxalyl chloride (4.60 mL, 54.4 mmol) in anhydrous CH_2Cl_2 (120 mL) at −78 °C was added anhydrous DMSO (7.00 mL, 98.5 mmol) in anhydrous CH_2Cl_2 (34 mL) over 10 min. The resulting mixture was stirred for 30 min at −78 °C and a solution of the alcohol **282** (6.50 g, 26.8 mmol) in anhydrous CH_2Cl_2 (75 mL) was added over 25 min. The solution was stirred at −78 °C for 2 h and distilled triethylamine (20.0 mL, 143 mmol) was added. The mixture was allowed to warm to room temperature, stirred for an additional 1.5 h and diluted with CH_2Cl_2 (100 mL) and water (100 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 75 mL). The organic extracts were combined, washed with brine (200 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 8:1 to 5:1) delivered the ketone **277** (5.78 g, 89%) as a colourless oil.

R_f = 0.61; (petroleum ether-ethyl acetate, 2:1); $[\alpha]_D^{24}$ −1.5 (*c* = 1.03, $CHCl_3$); ν_{max} (neat) 2982, 1704, 1639, 1621, 1368, 1281, 1197, 1122, 1046, 950, 909, 831 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (1H, d, *J* = 12.4 Hz, CH-C9), 5.25 (1H, d, *J* = 12.4 Hz, CH-C10), 4.99 (1H, quint, *J* = 1.4 Hz, CH_2-C1), 4.96 (1H, br s, CH_2-C1), 4.28 (1H, dd, *J* = 7.8, 5.4 Hz, CH-C3), 4.19−4.09 (2H, m, CH_2-C12), 2.56−2.44 (2H, m, CH_2-C5), 2.15 (3H, s, CH_3-C7), 2.03−1.87 (2H, m, CH_2-C4), 1.67 (3H, s, CH_3-C8), 1.26 (3H, t, *J* = 7.1 Hz, CH_3-C13); ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.7 (C-C6), 168.0 (C-C11), 161.3 (CH-C9), 142.5 (C-C2), 114.9 (CH_2-C1), 98.4 (CH-C10),

85.3 (CH-C3), 59.9 (CH_2-C12), 39.1 (CH_2-C5), 30.3 (CH_3-C7), 27.0 (CH_2-C4), 17.2 (CH_3-C8), 14.5 (CH_3-C13); HRMS (CI+, Me_3CH) for $C_{13}H_{21}O_4$ $[M+H]^+$ calcd. 241.1440, found 241.1438, Δ −0.8 ppm; LRMS (CI+, Me_3CH) *m/z* (intensity); 241.1 (87%), 125.1 (100%), 73.0 (85%).

(5*E*)-7-Hydroxy-6-methylhept-5-en-2-one (286)[162]



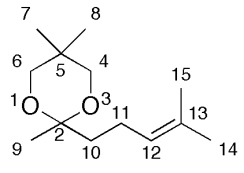
$C_8H_{14}O_2$

To a stirred solution of 6-methylhept-5-en-2-one (4.00 g, 31.5 mmol) in anhydrous CH_2Cl_2 (100 mL) was added selenium dioxide (0.70 g, 6.3 mmol) and *tert*-buytlhydroperoxide (8.50 mL of a 5.6 M solution in CH_2Cl_2, 47.3 mmol). The mixture was stirred at room temperature for 3 h. The solution was concentrated under *vacuum* and the residue was dissolved in EtOAc (50 mL). The solution was treated with a 1 M aqueous solution of NaOH (50 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 50 mL). The organic extracts were combined and washed with brine (65 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 4:1 to 1:1) delivered the desired allylic alcohol **286** (2.42 g, 54%) as a pale yellow oil.

R_f = 0.39; (petroleum ether-ethyl acetate, 1:1); ν_{max} (neat) 3429, 2915, 2859, 1708, 1358, 1160, 1068, 1009, 953, 863, 817, 788, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.39−5.34 (1H, m, CH-C5), 3.99 (2H, d, *J* = 4.6 Hz, CH_2-C7), 2.49 (2H, t, *J* = 7.3 Hz, CH_2-C3), 2.32 (2H, q, *J* = 7.3 Hz, CH_2-C4), 2.14 (3H, s, CH_3-C1), 1.68 (3H, s, CH_3-C8), 1.30 (1H, t, *J* = 4.6 Hz, OH); ^{13}C NMR (126 MHz, $CDCl_3$) δ 208.4 (C-C2), 136.1 (C-C6), 124.2 (CH-C5), 68.8 (CH_2-C7), 43.4 (CH_2-C3), 30.1 (CH_3-C1), 22.1 (CH_2-C4), 13.8 (CH_3-C8); HRMS (CI+, Me_3CH) for $C_8H_{13}O$ $[M-OH]^+$ calcd. 125.0966, found 125.0964, Δ −1.8 ppm; LRMS (CI+, Me_3CH) *m/z* (intensity); 125.2 (100%), 124.1 (81%), 84.0 (86%).

[162] Johnston, B. D.; Oehlschlager, A. C. *Can. J. Chem.* **1984**, *62*, 2148.

2,5,5-Trimethyl-2-(4-methylpent-3-en-1-yl)-1,3-dioxane (287)[124]



$C_{13}H_{24}O_2$

Method A: *p*-TsOH, neopentyl glycol, triethyl orthoformate

To a stirred solution of 6-methylhept-5-en-2-one (1.97 g, 15.6 mmol) were added *p*-toluenesulfonic acid monohydrate (0.61 g, 3.2 mmol), 2,2-dimethyl-1,3-propanediol (11.6 g, 111 mmol) and triethyl orthoformate (8.0 mL, 48 mmol). The mixture was stirred at 55 °C for 3 h and the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (8 mL). The mixture was diluted with Et_2O (25 mL). The phases were separated and the aqueous phase was 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*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 50:1) afforded the desired acetal **287** (3.01 g, 91%) as a colourless oil.

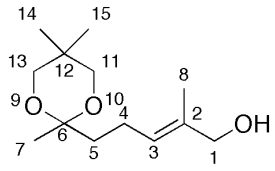
Method B: *p*-TsOH, neopentyl glycol

To a stirred solution of 6-methylhept-5-en-2-one (5.05 g, 40.0 mmol) in toluene (100 mL) were added *p*-toluenesulfonic acid monohydrate (370 mg, 1.95 mmol) and 2,2-dimethyl-1,3-propanediol (4.56 g, 43.8 mmol). The mixture was heated at reflux until the theoretical amount of water was collected in the Dean-Stark apparatus (2.5 h). The solution was cooled to room temperature and washed with 1 M aqueous solution of NaOH (50 mL) and water (4 × 50 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-diethyl ether, gradient elution from pure to 5:1) delivered the desired acetal **287** (1.46 g, 17%) as a colourless oil.

R_f = 0.51; (petroleum ether-ethyl acetate, 8:1); ν_{max} (neat) 2954, 2858, 1371, 1249, 1210, 1186, 1125, 1084, 1043, 1023, 949, 906, 857, 791 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.15–5.10 (1H, m, CH-C12), 3.52 (2H, d, *J* = 11.3Hz, CH_2-C4, CH_2-C6), 3.46 (2H, d, *J* = 11.3 Hz, CH_2-C4, CH_2-C6), 2.12–2.05 (2H, m, CH_2-C11),

1.73−1.69 (2H, m, CH_2-C10), 1.68 (3H, s, CH_3-C14 or CH_3-C15), 1.62 (3H, s, CH_3-C14 or CH_3-C15), 1.37 (3H, s, CH_3-C9), 0.98 (3H, s, CH_3-C7 or CH_3-C8), 0.92 (3H, s, CH_3-C7 or CH_3-C8); ^{13}C NMR (126 MHz, $CDCl_3$) δ 131.8 (C-C13), 124.5 (CH-C12), 99.1 (C-C2), 70.6 (CH_2-C4, CH_2-C6), 37.5 (CH_2-C10), 30.2 (C-C5), 25.9 (CH_3-C14 or CH_3-C15), 23.0 (CH_3-C7 or CH_3-C8), 22.9 (CH_3-C7 or CH_3-C8), 22.4 (CH_2-C11), 21.2 (CH_3-C9), 17.9 (CH_3-C14 or CH_3-C15); HRMS (CI+, Me_3CH) for $C_{10}H_{25}O_2$ $[M+H]^+$ calcd. 213.1855, found 213.1850, Δ −2.4 ppm; LRMS (CI+, Me_3CH) *m/z* (intensity); 213.2 (100%), 212.2 (17%), 129.1 (19%); Anal. calcd. for $C_{13}H_{24}O_2$: C, 73.54%; H, 11.39%; found: C, 73.39%; H, 11.56%.

(2*E*)-2-Methyl-5-(2,5,5-trimethyl-1,3-dioxan-2-yl)pent-2-en-1-ol (288)[124]



$C_{13}H_{24}O_3$

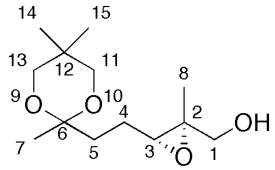
To a stirred solution of acetal **287** (1.20 g, 5.65 mmol) in anhydrous CH_2Cl_2 (2.0 mL) were added salicylic acid (84 mg, 0.61 mmol), selenium dioxide (14 mg, 0.13 mmol) and *tert*-butyl hydroperoxide (3.3 mL of a 5.92 M solution in decane, 19 mmol). The mixture was stirred at room temperature for 24 h and the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (25 mL). The solution was diluted with CH_2Cl_2 (25 mL) and the aqueous phase was extracted with Et_2O (3 × 25 mL). The organic extracts were combined and washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a mixture of the alcohol, aldehyde and starting material (12:1:11). The crude mixture was used in the next step without further purification.

To a stirred solution of the above crude mixture in EtOH (15 mL) at 0 °C was added sodium borohydride (0.21 g, 5.7 mmol). The mixture was stirred at room temperature overnight. The reaction was quenched by the addition of water and diluted with EtOAc (30 mL). The mixture was acidified to pH 6 with 1 M aqueous solution of HCl and the aqueous phase was separated and extracted with EtOAc (3 × 25 mL). The organic extracts were combined and washed with brine (30

mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 10:1 to 3:1) afforded the desired alcohol **288** (0.48 g, 38% over two steps) as a colourless oil.

R_f = 0.40; (petroleum ether-ethyl acetate, 7:4); ν_{max} (neat) 3427, 2952, 2865, 1373, 1249, 1210, 1125, 1084, 1017, 950, 907, 860, 737 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.45–5.40 (1H, m, CH-C3), 4.00 (2H, br s, CH_2-C1), 3.55 (2H, d, *J* = 11.4, CH_2-C11, CH_2-C13), 3.45 (2H, d, *J* = 11.4 Hz, CH_2-C11, CH_2-C13), 2.20–2.14 (2H, m, CH_2-C4), 1.76–1.72 (2H, m, CH_2-C5), 1.69 (3H, s, CH_3-C8), 1.38 (3H, s, CH_3-C7), 1.30 (1H, br s, OH), 1.01 (3H, s, CH_3-C14 or CH_3-C15), 0.91 (3H, s, CH_3-C14 or CH_3-C15); ^{13}C NMR (126 MHz, $CDCl_3$) δ 135.1 (C-C2), 126.2 (CH-C3), 98.9 (C-C6), 70.5 (CH_2-C11, CH_2-C13), 69.1 (CH_2-C1), 37.5 (CH_2-C5), 30.1 (C-C12), 22.9 (CH_3-C14 or CH_3-C15), 22.7 (CH_3-C14 or CH_3-C15), 21.9 (CH_2-C4), 20.8 (CH_3-C7), 13.8 (CH_3-C8); HRMS (ESI) for $C_{13}H_{24}NaO_3$ $[M+Na]^+$ calcd. 251.1618, found 251.1614, Δ −1.3 ppm; Anal. calcd. for $C_{13}H_{24}O_2$: C, 68.38%; H, 10.59%; found: C, 67.51%; H, 10.80%.

(2*R*,3*R*)-2-Methyl-3-[2-(2,5,5-trimethyl-1,3-dioxan-2-yl)ethyl]oxiran-2-yl]methanol (289)[124]



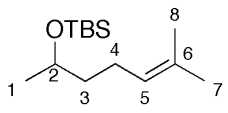
$C_{13}H_{24}O_4$

To a stirred suspension of 4 Å powdered molecular sieves (0.10 g) in anhydrous CH_2Cl_2 (1.5 mL) at −25 °C were successively added freshly distilled titanium tetraisopropoxide (15 µL, 51 µmol), freshly distilled (−)-diethyl tartrate (10 µL, 58 µmol) and *tert*-butyl hydroperoxide (200 µL of a 1.86 M solution in CH_2Cl_2, 0.37 mmol). The mixture was stirred at −25 °C for 30 min and a solution of allylic alcohol **288** (52 mg, 0.23 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added dropwise. The mixture was stirred at −20 °C for 18 h and the reaction was quenched by the addition of water (2 mL). The solution was allowed to warm to room temperature and was stirred for an additional 15 min. A saturated aqueous

solution of NaOH (30% wt) in brine (3 mL) was then added and the mixture was stirred at room temperature for a further 20 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 4 mL). The organic extracts were combined and washed with brine (6 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 3:1 to 1:1) delivered the desired epoxy alcohol **289** (26.0 mg, 47%) as a colourless oil.

R_f = 0.33; (petroleum ether-ethyl acetate, 1:1); $[\alpha]_D^{30}$ +9.5 (*c* = 0.43, EtOH), {Lit.[124] $[\alpha]_D^{25}$ +9.0 (*c* = 2.00, EtOH)}; ν_{max} (neat) 3444, 2953, 2868, 1473, 1374, 1273, 1250, 1212, 1086, 1039, 950, 907, 863 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.66 (1H, dd, *J* = 12.1, 5.2 Hz, CH_2-C1), 3.60−3.53 (3H, m, CH_2-C1, CH_2-C11, CH_2-C13), 3.42 (2H, d, *J* = 11.1 Hz, CH_2-C11, CH_2-C13), 3.08−3.04 (1H, m, CH-C3), 1.94−1.85 (1H, m, CH_2-C5), 1.82 (1H, dd, *J* = 10.5, 5.2 Hz, OH), 1.79−1.67 (3H, m, CH_2-C4, CH_2-C5), 1.37 (3H, s, CH_3-C7), 1.30 (3H, s, CH_3-C8), 1.02 (3H, s, CH_3-C14 or CH_3-C15), 0.87 (3H, s CH_3-C14 or CH_3-C15); ^{13}C NMR (126 MHz, $CDCl_3$) δ 98.6 (C-C6), 70.5 (CH_2-C11, CH_2-C13), 65.7 (CH_2-C1), 61.1 (C-C2), 60.3 (CH-C3), 35.2 (CH_2-C5), 30.1 (C-C12), 23.0 (CH_3-C14 or CH_3-C15), 22.6 (CH_2-C4, CH_3-C14 or CH_3-C15), 20.3 (CH_3-C7), 14.3 (CH_3-C8); HRMS (CI+, Me_3CH) for $C_{13}H_{25}O_4$ $[M+H]^+$ calcd. 245.1753, found 245.1758, Δ +2.0 ppm; LRMS (CI+, Me_3CH) *m/z* (intensity); 245.0 (70%), 141.0 (100%).

tert-Butyldimethyl[(6-methylhept-5-en-2-yl)oxy]silane (290)[163]



$C_{14}H_{30}OSi$

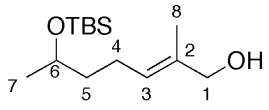
To a stirred solution of 6-methyl-5-hepten-2-ol (4.00 g, 31.2 mmol) in DMF (10 mL) were added imidazole (2.75 g, 40.4 mmol) followed by *tert*-butyldimethylsilyl chloride (11.7 g, 77.6 mmol). The mixture was stirred at room temperature for 36 h and the reaction was quenched by the addition of water

[163] Sugai, T.; Katoh, O.; Ohta, H. *Tetrahedron* **1995**, *51*, 11987.

(50 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 50 mL). The organic extracts were combined, washed with water (4 × 25 mL) and brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-diethyl ether, 40:1) delivered the silyl ether **290** (7.07 g, 93%) as a colourless oil.

R_f = 0.26; (petroleum ether); ν_{max} (neat) 2957, 2928, 2856, 1463, 1376, 1254, 1135, 1078, 1036, 1004, 939, 901, 888, 832, 800, 771, 710, 663 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.14–5.09 (1H, m, CH-C5), 3.78 (1H, app sext, *J* = 6.0 Hz, CH-C_2), 2.10–2.01 (1H, m, CH_2-C4), 1.98–1.89 (1H, m, CH_2-C4), 1.68 (3H, s, CH_3-C7 or CH_3-C8), 1.60 (3H, s, CH_3-C7 or CH_3-C8), 1.50–1.35 (2H, m, CH_2-C3), 1.12 (3H, d, *J* = 6.0 Hz, CH_3-C1), 0.89 (9H, s, CH_3-*t*Bu), 0.05 (6H, s, Si-CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 131.5 (C-C6), 124.7 (CH-C5), 68.5 (CH-C2), 40.0 (CH_2-C3), 26.1 (CH_3-*t*Bu), 25.8 (CH_3-C7 or CH_3-C8), 24.6 (CH_2-C4), 23.9 (CH_3-C1), 18.3 (C-*t*Bu), 17.8 (CH_3-C7 or CH_3-C8), −4.2 (Si-CH_3), −4.6 (Si-CH_3); HRMS (CI+, Me_3CH) for $C_{14}H_{31}OSi$ $[M+H]^+$ calcd. 243.2144, found 243.2148, Δ +1.6 ppm; LRMS (CI+, Me_3CH) *m/z* (intensity); 243.2 (100%), 185.2 (30%), 111.2 (27%).

(2*E*)-6-[(tert-butyldimethylsilyl)oxy]-2-methylhept-2-en-1-ol (291)



$C_{14}H_{30}O_2Si$

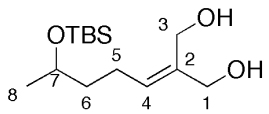
To a stirred solution of salicylic acid (278 mg, 2.01 mmol) in anhydrous CH_2Cl_2 (8.0 mL) were added selenium dioxide (45 mg, 0.41 mmol) and *tert*-butyl hydroperoxide (13.5 mL of a 5.38 M solution in decane, 72.6 mmol). A solution of the silyl ether **290** (4.85 g, 20.0 mmol) in anhydrous CH_2Cl_2 (8.0 mL) was added. The mixture was stirred at room temperature for 24 h. Selenium dioxide (49 mg, 0.44 mmol) and *tert*-butyl hydroperoxide (13.0 mL of a 5.38 M solution in decane, 69.9 mmol) were added and the mixture was stirred for an additional 24 h. The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (30 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic extracts were combined, dried

($MgSO_4$), filtered and concentrated *in vacuo* to afford a mixture of the alcohol and the corresponding aldehyde (4.9:1). The crude mixture was used in the next step without further purification.

To a stirred solution of the above mixture in EtOH (20 mL) at 0 °C was added sodium borohydride (0.78 g, 21 mmol). The mixture was stirred at 0 °C for 1 h. Sodium borohydride (0.76 g, 20 mmol) was added and the mixture was stirred at room temperature for an additional 24 h. The reaction was quenched by the addition of a 1 M aqueous solution of HCl (to pH 5) and diluted with Et_2O (50 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 30 mL). The organic extracts were combined, washed with water (30 mL) and brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 40:1 to pure ethyl acetate) delivered the alcohol **291** (2.84 g, 55% over two steps) and the diol **S1** (0.44 g, 8% over two steps) as colourless oils.

R_f = 0.51; (petroleum ether-ethyl acetate, 3:1); ν_{max} (neat) 3346, 2956, 2929, 2856, 1472, 1373, 1254, 1135, 1074, 1004, 938, 902, 889, 833, 771, 711, 662 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.44–5.39 (1H, m, CH-C3), 4.00 (2H, s, CH_2-C1), 3.80 (1H, app sext, *J* = 6.2 Hz, CH-C6), 2.17–2.08 (1H, m, CH_2-C4), 2.04–1.96 (1H, m, CH_2-C4), 1.67 (3H, s, CH_3-C8), 1.53–1.38 (2H, m, CH_2-C5), 1.28 (1H, br s, OH), 1.13 (3H, d, *J* = 6.2 Hz, CH_3-C7), 0.89 (9H, s, CH_3-*t*Bu), 0.05 (6H, s, Si-CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 134.8 (C-C2), 126.5 (CH-C3), 69.2 (CH_2-C1), 68.4 (CH-C6), 39.6 (CH_2-C5), 26.0 (CH_3-*t*Bu), 24.1 (CH_2-C4), 23.9 (CH_3-C7), 18.3 (C-*t*Bu), 13.8 (CH_3-C8), −4.2 (Si-CH_3), −4.6 (Si-CH_3); HRMS (ESI, MeOH:H_2O) for $C_{14}H_{30}NaO_2Si$ $[M+Na]^+$ calcd. 281.1907, found 281.1898, Δ −3.5 ppm.

2-[4-[{*tert*-Butyldimethylsilyl)oxy]pentylidene}propane -1,3-diol (S1)

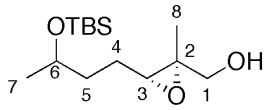


$C_{14}H_{30}O_3Si$

R_f = 0.47; (petroleum ether-ethyl acetate, 1:2); ν_{max} (neat) 3341, 2955, 2928, 2855, 1472, 1374, 1253, 1133, 1088, 1069 1003, 938, 901, 832, 772, 711, 656

cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.56 (1H, t, *J* = 7.4 Hz, CH-C4), 4.32 (2H, s, CH_2-C1 or CH_2-C3), 4.21 (2H, s, CH_2-C1 or CH_2-C3), 3.81 (1H, app sext, *J* = 6.2 Hz, CH-C7), 2.23–2.13 (1H, m, CH_2-C5), 2.13–2.04 (1H, m, CH_2-C5), 1.54–1.41 (3H, m, CH_2-C6, OH), 1.13 (3H, d, *J* = 6.2 Hz, CH_3-C8), 0.88 (9H, s, CH_3-*t*Bu), 0.05 (3H, s, Si-CH_3), 0.04 (3H, s, Si-CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.1 (C-C2), 131.3 (CH-C4), 68.3 (CH-C7), 67.8 (CH_2-C1 or CH_2-C3), 60.2 (CH_3-C1 or CH_3-C3), 39.6 (CH_2-C6), 26.0 (CH_3-*t*Bu), 23.9 (CH_3-C8), 23.8 (CH_2-C5), 18.3 (C-*t*Bu), −4.2 (Si-CH_3), −4.6 (Si-CH_3); HRMS (CI+, Me_3CH) for $C_{14}H_{31}O_3Si$ $[M+H]^+$ calcd. 275.2042, found 275.2045, Δ +1.0 ppm; LRMS (CI+, Me_3CH) *m/z* (intensity); 275.3 (47%), 257.3 (73%), 125.2 (76%), 107.1 (100%).

(2*R*,3*R*)-3-{3-[(*tert*-Butyldimethylsilyl)oxy]butyl}-2-methyloxiran-2-yl]methanol (292)



$C_{14}H_{30}O_3Si$

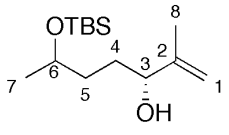
To a stirred suspension of 4 Å powdered molecular sieves (0.56 g) in anhydrous CH_2Cl_2 (40 mL) at −25 °C were added freshly distilled titanium tetraisopropoxide (60 μL, 0.2 mmol), freshly distilled (−)-diethyl tartrate (50 μL, 0.3 mmol) and *tert*-butyl hydroperoxide (1.0 mL of a 5.92 M solution in decane, 5.9 mmol). The mixture was stirred at −25 °C for 30 min and a solution of the allylic alcohol **291** (1.00 g, 3.87 mmol) in anhydrous CH_2Cl_2 (8.0 mL) was added dropwise over 10 min. The mixture was stirred for an additional hour at −20 °C and the reaction was quenched by the addition of water (10 mL). The mixture was allowed to warm to room temperature and was stirred for a further 15 min. A saturated aqueous solution of NaOH (30% wt) in brine (20 ml) was added and the solution was stirred for 45 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined, washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 10:1 to 5:1) afforded

the desired epoxy alcohol **292** as a mixture of diastereomers (1:1, 0.94 g, 89%) as a colourless oil.

The enantiomeric excess (93%) was determined by normal phase chiral HPLC analysis of the corresponding methyl ketone **277**.

R_f = 0.40; (petroleum ether-ethyl acetate, 2:1); $[\alpha]_D^{23}$ +10.9 (*c* = 0.97, $CHCl_3$); ν_{max} (neat) 3435, 2956, 2929, 2857, 1472, 1374, 1253, 1147, 1124, 1038, 939, 902, 869, 832, 804, 772, 709, 678, 663 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.91−3.80 (2H, m, CH-C6a, CH-C6b), 3.67 (2H, ddd, *J* = 12.1, 4.5, 0.8 Hz, CH_2-C1a, CH_2-C1b), 3.57 (2H, dd, *J* = 12.1, 8.6 Hz, CH_2-C1a, CH_2-C1b), 3.05−3.01 (2H, m, CH-C3a, CH-C3b), 1.69 (2H, dd, *J* = 8.6, 4.5 Hz, OHa, OHb), 1.67−1.47 (8H, m, CH_2-C4a, CH_2-C4b, CH_2-C5a, CH_2-C5b), 1.28 (6H, s, CH_3-C8a, CH_3-C8b), 1.15 (6H, dd, *J* = 6.1, 2.2 Hz, CH_3-C7a, CH_3-C7b), 0.89 (18H, s, CH_3-*t*Bua, CH_3-*t*Bub), 0.05 (6H, s, Si-CH_3a, Si-CH_3b), 0.04 (6H, s, Si-CH_3a, Si-CH_3b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 68.4 (CH-C6a or CH-C6b), 68.1 (CH-C6a or CH-C6b), 65.6 (CH_2-C1a, CH_2-C1b), 61.0 (C-C2a, C-C2b), 60.3 (CH-C3a or CH-C3b), 60.2 (CH-C3a or CH-C3b), 36.4 (CH_2-C4a or CH_2-C4b or CH_2-C5a or CH_2-C5b), 36.2 (CH_2-C4a or CH_2-C4b or CH_2-C5a or CH_2-C5b), 26.0 (CH_3-*t*Bua, CH_3-*t*Bub), 24.9 (CH_2-C4a or CH_2-C4b or CH_2-C5a or CH_2-C5b), 24.4 (CH_2-C4a or CH_2-C4b or CH_2-C5a or CH_2-C5b), 24.1 (CH_3-C7a or CH_3-C7b), 23.7 (CH_3-C7a or CH_3-C7b), 18.3 (C-*t*Bua or C-*t*Bub), 18.2 (C-*t*Bua or C-*t*Bub), 14.3 (CH_3-C8a, CH_3-C8b), −4.2 (Si-CH_3a, Si-CH_3b), −4.6 (Si-CH_3a, Si-CH_3b); HRMS (ESI) for $C_{14}H_{30}NaO_3Si$ $[M+Na]^+$ calcd. 297.1856, found 297.1850, Δ −2.3 ppm.

(3*R*)-6-[(*tert*-Butyldimethylsilyl)oxy]-2-methylhept-1-en-3-ol (293)



$C_{14}H_{30}O_2Si$

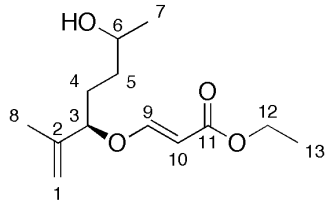
To a stirred solution of epoxy alcohol **292** (0.70 g, 2.6 mmol) in anhydrous CH_2Cl_2 (12 mL) at −15 °C were added triethylamine (0.55 mL, 4.0 mmol) and methanesulfonyl chloride (0.25 mL, 3.2 mmol) dropwise. The mixture was stirred at −15 °C for 30 min and the reaction was quenched by the addition of water (10 mL). The aqueous phase was separated and extracted with CH_2Cl_2 (3 ×

10 mL). The organic extracts were combined, washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude mesylate was used immediately in the next step without further purification.

To a stirred solution of the above crude mesylate in butan-2-one (15 mL) was added sodium iodide (1.96 g, 13.1 mmol). The solution was stirred at 80 °C for 30 min during which time the solution turned brown. Zinc powder (0.29 g, 4.5 mmol) was added and the mixture was stirred for an additional 20 min. The grey solution was cooled to room temperature and the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (20 mL). The mixture was diluted with EtOAc (20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The organic extracts were combined, washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 20:1) afforded the allylic alcohol **293** as a mixture of diastereomers (1:1, 0.52 g, 79%) as a colourless oil.

R_f = 0.41; (petroleum ether-ethyl acetate, 4:1); $[\alpha]_D^{23}$ +7.2 (*c* = 0.98, $CHCl_3$); ν_{max} (neat) 3387, 2955, 2929, 2856, 1463, 1373, 1254, 1137, 1050, 1004, 896, 831, 806, 771, 713, 663 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.94 (2H, br s, CH_2-C1a, CH_2-C1b), 4.85−4.82 (2H, m, CH_2-C1a, CH_2-C1b), 4.08−4.00 (2H, m, CH-C3a, CH-C3b), 3.89−3.81 (2H, m, CH-C6a, CH-C6b), 2.06 (1H, d, *J* = 3.5 Hz, OHa or OHb), 1.81 (1H, d, *J* = 4.1 Hz, OHa or OHb), 1.73−1.71 (6H, m, CH_3-C8a, CH_3-C8b), 1.70−1.56 (4H, m, CH_2-C4a, CH_2-C4b), 1.56−1.39 (4H, m, CH_2-C5a, CH_2-C5b), 1.14 (6H, dd, *J* = 6.1, 4.1 Hz, CH_3-C7a, CH_3-C7b), 0.89 (9H, s, CH_3-*t*Bua), 0.89 (9H, s, CH_3-*t*Bub), 0.06 (6H, s, Si-CH_3a or Si-CH_3b), 0.05 (6H, br d, *J* = 1.2 Hz, Si-CH_3a or Si-CH_3b); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.8 (C-C2a or C-C2b), 147.7 (C-C2a or C-C2b), 111.1 (CH_2-C1a or CH_2-C1b), 111.0 (CH_2-C1a or CH_2-C1b), 76.2 (CH-C3a or CH-C3b), 75.9 (CH-C3a or CH-C3b), 68.7 (CH-C6a or CH-C6b), 68.6 (CH-C6a or CH-C6b), 35.9 (CH_2-C5a or CH_2-C5b), 35.2 (CH_2-C5a or CH_2-C5b), 31.3 (CH_2-C4a or CH_2-C4b), 30.8 (CH_2-C4a or CH_2-C4b), 26.1 (CH_3-*t*Bua, CH_3-*t*Bub), 23.8 (CH_3-C7a or CH_3-C7b), 23.7 (CH_3-C7a or CH_3-C7b), 18.3 (C-*t*Bua, C-*t*Bub), 17.8 (CH_3-C8a, CH_3-C8b), −4.2 (Si-CH_3a, Si-CH_3b), −4.5 (Si-CH_3a or Si-CH_3b), −4.6 (Si-CH_3a or Si-CH_3b); HRMS (ESI) for $C_{14}H_{30}NaO_2Si$ $[M+Na]^+$ calcd. 281.1907, found 281.1905, Δ −0.6 ppm.

Ethyl (*E*)-3-{[(3*R*)-6-hydroxy-2-methylhept-1-en-3-yl]oxy}prop-2-enoate (282)



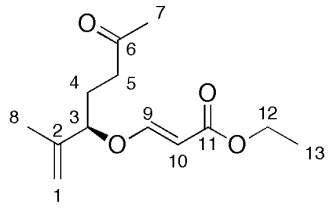
$C_{13}H_{22}O_4$

To a stirred solution of allylic alcohol **293** (0.52 g, 2.0 mmol) in anhydrous CH_2Cl_2 (10 mL) were added ethyl propiolate (0.40 mL, 4.0 mmol) and *N*-methylmorpholine (0.45 mL, 4.1 mmol). The mixture was stirred at room temperature overnight and concentrated *in vacuo*. The residue was filtered through a pad of silica gel (petroleum ether–ethyl acetate, 50:1). The solvent was removed *in vacuo* and the crude product was used in the next step without further purification.

To a stirred solution of the crude vinylogous carbonate in MeOH (12 mL) was added camphorsulfonic acid (64.1 mg, 0.28 mmol). The mixture was stirred at room temperature overnight and the reaction was quenched by the addition of $NaHCO_3$ (0.24 g). The solid was filtered off and the filtrate was concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from petroleum ether to petroleum ether–ethyl acetate 5:3) afforded the alcohol **282** (0.40 g, 83% over two steps) as a colourless oil.

The recorded data were in accordance with those previously reported.

Ethyl (*E*)-3-{[(3*R*)-2-methyl-6-oxohept-1-en-3-yl]oxy}-prop-2-enoate (277)



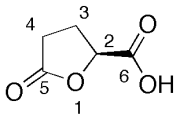
$C_{13}H_{20}O_4$

To a suspension of activated 4 Å powdered molecular sieves (1.02 g) in anhydrous CH_2Cl_2 (10 mL) and alcohol **282** (0.20 g, 0.83 mmol) was added pyridinium dichromate (0.77 g, 2.1 mmol). The mixture was stirred at room

temperature overnight. The solution was filtered through silica gel (petroleum ether-ethyl acetate 5:1) to afford the desired methyl ketone **277** as a colourless oil (0.18 g, 93%).

The data were in accordance with those reported previously.

(2*S*)-5-Oxooxolane-2-carboxylic acid (299)[129,133]

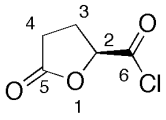


$C_5H_6O_4$

To a stirred solution of L-glutamic acid (10 g, 68 mmol) in water (135 mL) was added concentrated HCl (10 mL, 0.10 mol). The solution was cooled to 0 ºC and a solution of sodium nitrite (6.20 g, 89.6 mmol) in water (35 mL) was added dropwise over 10 min. The mixture was stirred for 30 min at 0 ºC and then allowed to warm to room temperature. The solution was stirred overnight and volatiles were removed *in vacuo*. The residue was dissolved in warm EtOAc, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The product was purified by crystallisation in petroleum ether-ethyl acetate to afford the desired lactone **299** (8.80 g, 100%) as a colourless solid.

R_f = 0.35; (ethyl acetate-methanol, 1:1); $[\alpha]_D^{28}$ +15.4 (*c* = 1.13, MeOH), {Lit.[133] $[\alpha]_D^{20}$ +14.6 (*c* = 5.8, MeOH)}; ν_{max} (film) 3533, 1756, 1417, 1178, 1150, 1066, 899 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.01–4.97 (1H, m, CH-C2), 2.68–2.51 (3H, m, CH_2-C3, CH_2-C4), 2.44–2.37 (1H, m, CH_2-C3); ^{13}C NMR (126 MHz, DMSO-d_6) δ 176.4 (C-C5 or C-C6), 171.2 (C-C5 or C-C6), 75.2 (CH-C2), 26.5 (CH_2-C4), 25.1 (CH_2-C3); HRMS (EI) for $C_5H_6O_4$ $[M]^+$ calcd. 130.0266, found 130.0266, Δ −0.2 ppm; LRMS (EI) *m/z* (intensity); 130.0 (11%), 85.0 (100%), 57.0 (50%);

(2*S*)-5-Oxooxolane-2-carbonyl chloride (300)[129,133]

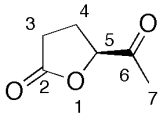


$C_5H_5ClO_3$

To a stirred solution of carboxylic acid **299** (2.00 g, 15.4 mmol) in anhydrous toluene (4.0 mL) was added oxalyl chloride (2.50 mL, 30.8 mmol) dropwise at 60 ºC. The mixture was stirred at 60 ºC for 4 h and volatiles were removed under *vacuum*. The crude product was purified by distillation (bp = 96–102 °C at 3 mbar) to afford the unstable acyl chloride **300** (1.53 g, 67%) as a colourless oil.

ν_{max} (neat) 1780, 1138, 1057, 1043, 967, 907, 822, 771, 672 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.13 (1H, dd, *J* = 8.6, 4.4 Hz, CH-C2), 2.74–2.66 (1H, m, CH_2-C4), 2.65–2.54 (2H, m, CH_2-C3, CH_2-C4), 2.52–2.46 (1H, m, CH_2-C3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3 (C-C5 or C-C6), 171.9 (C-C5 or C-C6), 81.3 (CH-C2), 26.2 (CH_2-C3), 25.5 (CH_2-C4).

(5*S*)-5-Acetyloxolan-2-one (301)[133]



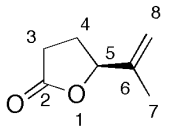
$C_6H_8O_3$

To a stirred solution of acyl chloride **300** (1.44 g, 9.73 mmol) in anhydrous THF (33 mL) at −78 ºC was added methylmagnesium bromide (8.50 mL of a 1.4 M in THF/toluene 1:3, 11.9 mmol) dropwise. The mixture was stirred at −78 ºC for 3.5 h and the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (15 mL). The solution was allowed to warm to room temperature and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 15 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 3:2) delivered methyl ketone **301** (0.69 g, 56 %) as a colourless oil.

R_f = 0.48; (petroleum ether-ethyl acetate, 1:4); $[\alpha]_D^{26}$ +18.8 (*c* = 1.14, MeOH), {Lit.[133] $[\alpha]_D^{20}$ +12.9 (*c* = 0.35, MeOH)}; ν_{max} (neat) 1774, 1722, 1419, 1360, 1139,

1063, 1011, 963, 874, 815, 688, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.79 (1H, dd, *J* = 8.1, 6.7 Hz, CH-C5), 2.56–2.46 (3H, m, CH_2-C3, CH_2-C4), 2.29 (3H, s, CH_3-C7), 2.28–2.23 (1H, m, CH_2-C4); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.4 (C-C6), 175.7 (C-C2), 82.2 (CH-C5), 27.5 (CH_2-C3), 26.3 (CH_3-C7), 24.6 (CH_2-C4); HRMS (EI) for $C_6H_8O_3$ $[M]^+$ calcd. 128.0473, found 128.0471, Δ −1.6 ppm; LRMS (EI) *m/z* (intensity); 128.0 (29%), 85.0 (100%), 83.9 (83%), 56.9 (33%), 42.9 (96%).

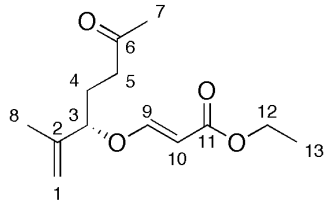
(5*S*)-5-(Prop-1-en-2-yl)oxolan-2-one (302)[131]



$C_7H_{10}O_2$

To a stirred solution of methyltriphenylphosphonium bromide (2.42 g, 6.77 mmol) in anhydrous THF (7 mL) at 0 ºC was added potassium *tert*-butoxide (0.75 g, 6.7 mmol). The yellow suspension was stirred at 0 ºC for 1.2 h and methyl ketone **301** (0.68 g, 5.3 mmol) in anhydrous THF (4 mL) was added dropwise. The mixture was allowed to warm to room temperature and was stirred for 1 h. The reaction was quenched by the addition of water (10 mL) and was subsequently diluted with Et_2O (10 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 10mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (solid load, petroleum ether-ethyl acetate, gradient elution from petroleum ether to petroleum ether-ethyl acetate 5:1) yielded the lactone **302** (0.28 g, 42 %) as a colourless oil.
$[\alpha]_D^{26}$ +4.5 (*c* = 1.09, $CHCl_3$), {Lit.[131] $[\alpha]_D^{20}$ +6.3 (*c* = 1.30, $CHCl_3$)}; ν_{max} (neat) 1766, 1453, 1326, 1177, 1141, 1047, 1005, 979, 901, 843, 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.06 (1H, d, *J* = 0.9 Hz, CH_2-C8), 4.95 (1H, d, *J* = 0.9 Hz, CH_2-C8), 4.88 (1H, br t, *J* = 7.4 Hz, CH-C5), 2.57–2.52 (2H, m, CH_2-C3), 2.41–2.33 (1H, m, CH_2-C4), 2.09–2.00 (1H, m, CH_2-C4), 1.77 (3H, s, CH_3-C7); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.8 (C-C2), 142.4 (C-C6), 112.5 (CH_2-C8), 82.6 (CH-C5), 28.6 (CH_2-C3), 27.2 (CH_2-C4), 17.7 (CH_3-C7).

Ethyl (*E*)-3-{[(3*S*)-2-methyl-6-oxohept-1-en-3-yl]oxy}prop-2-enoate (303)



$C_{13}H_{20}O_4$

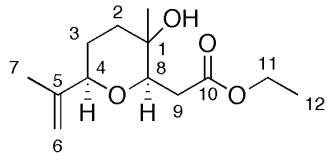
To a stirred solution of lactone **302** (197 mg, 1.56 mmol) in anhydrous Et_2O (8 mL) at −78 °C was added methyl lithium (1.2 mL of a 1.6 M solution in Et_2O, 1.7 mmol) dropwise. The mixture was stirred at −78 °C for 2.5 h and the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (5 mL). The aqueous phase was separated and extracted with Et_2O (3 × 10 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude alcohol which was used in the next step without further purification.

To a stirred solution of the above crude alcohol in anhydrous CH_2Cl_2 (13 mL) were added ethyl propiolate (0.35 mL, 3.4 mmol) and *N*-methylmorpholine (0.35 mL, 3.2 mmol). The mixture was stirred at room temperature for 15 h and the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from petroleum ether to petroleum ether–ethyl acetate 5:1) delivered the methyl ketone **303** (244 mg, 65%, 52% *ee*) as a colourless oil.

R_f = 0.51; (petroleum ether-ethyl acetate, 2:1); $[\alpha]_D^{25}$ +1.45 (*c* = 1.19, $CHCl_3$); ν_{max} (neat) 1704, 1638, 1621, 1368, 1323, 1281, 1199, 1123, 1045, 949, 909, 832 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44 (1H, d, *J* = 12.4 Hz, CH-C9), 5.26 (1H, d, *J* = 12.4 Hz, CH-C10), 4.99 (1H, quint, *J* = 1.4 Hz, CH_2-C1), 4.96 (1H, br s, CH_2-C1), 4.28 (1H, dd, *J* = 7.8, 5.5 Hz, CH-C3), 4.18–4.12 (2H, m, CH_2-C12), 2.52–2.47 (2H, m, CH_2-C5), 2.14 (3H, s, CH_3-C7), 2.03–1.89 (2H, m, CH_2-C4), 1.68 (3H, s, CH_3-C8), 1.26 (3H, t, *J* = 7.1 Hz, CH_3-C13); ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.3 (C-C6), 168.0 (C-C11), 161.2 (CH-C9), 142.7 (C-C2), 114.7 (CH_2-C1), 98.7 (CH-C10), 85.4 (CH-C3), 59.9 (CH_2-C12), 39.1 (CH_2-C5), 30.1 (CH_3-C7), 27.3 (CH_2-C4), 17.2

(CH_3-C8), 14.5 (CH_3-C13); HRMS (CI+, Me_3CH) for $C_{13}H_{21}O_4$ $[M+H]^+$ calcd. 241.1440, found 241.1438, Δ −0.9 ppm; LRMS (CI+, Me_3CH) *m/z* (intensity); 241.2 (97%), 125.2 (100%).

Ethyl 2-[(2*R*,6*R*)-3-hydroxy-3-methyl-6-(prop-1-en-2-yl)oxan-2-yl] acetate (278 and 304)[58,118]



$C_{13}H_{22}O_4$

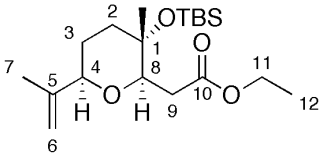
To a stirred solution of methyl ketone **277** (6.08 g, 25.3 mmol) and MeOH (4.20 mL, 104 mmol) in anhydrous THF (250 mL) was added a freshly prepared samarium diiodide solution (50 mL of a 0.2 M solution in THF, 0.10 mol) until the reaction mixture remained dark blue in colour. The mixture was stirred at room temperature for 2 h and the reaction was quenched by the addition of a saturated aqueous solution of $Na_2S_2O_3$ (400 mL). The solution was diluted with EtOAc (200 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 100 mL) and the organic extracts were combined, washed with brine (300 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the product as a 1:12.4 mixture of diastereomers. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 6:1 to 3:2) delivered an inseparable mixture of the diastereomeric tetrahydropyranols **278** and **304** (5.47 g, 89%) as a colourless solids.

A sample of the alcohol **278** was obtained for characterisation purposes following separation of diastereomers in the next steps of the synthesis.

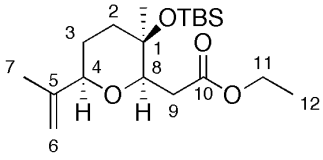
R_f = 0.58; (petroleum ether-ethyl acetate, 3:2); ν_{max} (neat) 3288, 2945, 2875, 1735, 1429, 1373, 1288, 1184, 1128, 1072, 1033, 933, 902, 865, 843 cm^{-1}; Major diastereomer: ^1H NMR (500 MHz, $CDCl_3$) δ 4.93 (1H, br s, CH_2-C6), 4.81 (1H, s, CH_2-C6), 4.15 (2H, q, *J* = 7.2 Hz, CH_2-C11), 3.79 (1H, br d, *J* = 11.5 Hz, CH-C4), 3.73 (1H, dd, *J* = 8.7, 4.2 Hz, CH-C8), 2.70 (1H, dd, *J* = 15.3, 4.2 Hz, CH_2-C9), 2.42 (1H, dd, *J* = 15.3, 8.7 Hz, CH_2-C9), 1.92 (1H, ddd, *J* = 12.3, 3.8, 2.6 Hz,

CH_2-C2), 1.77−1.53 (4H, m, CH_2-C2, CH_2-C3, OH), 1.72 (3H, s, CH_3-C7), 1.25 (3H, t, *J* = 7.2 Hz, CH_3-C12), 1.21 (3H, s, CH_3-Me); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6 (C-C10), 145.2 (C-C5), 110.7 (CH_2-C6), 81.1 (CH-C8), 81.0 (CH-C4), 69.5 (C-C1), 60.7 (CH_2-C11), 40.4 (CH_2-C2), 35.7 (CH_2-C9), 29.1 (CH_2-C3), 20.1 (CH_3-Me), 19.2 (CH_3-C7), 14.4 (CH_3-C12); Minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.96 (1H, s, CH_2-C6) 4.93 (1H, s, CH_2-C6), 4.15 (2H, q, *J* = 7.2 Hz, CH_2-C11), 4.12 (1H, m, CH-C4), 3.98 (1H, dd, *J* = 9.8, 4.7 Hz, CH-C8), 2.64 (1H, dd, *J* = 14.5, 9.8 Hz, CH_2-C9), 2.58 (1H, dd, *J* = 14.5, 4.7 Hz, CH_2-C9), 1.88−1.84 (1H, m, CH_2-C2), 1.77−1.53 (4H, m, CH_2-C2, CH_2-C3, OH), 1.72 (3H, s, CH_3-C7), 1.26 (3H, t, *J* = 7.2 Hz, CH_3-C12), 1.15 (3H, s, CH_3-Me); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6 (C-C10), 145.2 (C-C5), 112.0 (CH_2-C6), 77.7 (CH-C8), 72.9 (CH-C4), 69.4 (C-C1), 60.9 (CH_2-C11), 35.2 (CH_2-C9), 33.5 (CH_2-C2 or CH_2-C3), 25.0 (CH_2-C2 or CH_2-C3), 22.9 (CH_3-Me), 19.6 (CH_3-C7), 14.4 (CH_3-C12); HRMS (ESI) for $C_{13}H_{22}NaO_4$ $[M+Na]^+$ calcd. 265.1410, found 265.1408, Δ −1.0 ppm.

Ethyl-2-[(2*R*,3*S*,6*R*)-3-(*tert*-butyldimethylsilyloxy)-3-methyl-6-(prop-1-en-2-yl)oxan-2-yl]acetate (305) and **Ethyl-2-[(2*R*,3*R*,6*R*)-3-(*tert*-butyldimethylsilyloxy)-3-methyl-6-(prop-1-en-2-yl)oxan-2-yl]acetate (306)**



$C_{19}H_{36}O_4Si$



$C_{19}H_{36}O_4Si$

To a stirred solution of tetrahydropyranols **278** and **304** (5.47 g, 22.6 mmol) in anhydrous CH_2Cl_2 (225 mL) and freshly distilled 2,6-lutidine (5.5 mL, 47 mmol) at −78 °C was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (16.0 mL, 69.7 mmol) dropwise. After 10 min, the mixture was allowed to warm to room temperature and was stirred overnight. The reaction was quenched by the addition of 1 M aqueous HCl (100 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 40 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica

gel (petroleum ether-ethyl acetate, gradient elution from 60:1 to 10:1) delivered esters **305** (6.97 g, 87%) and **306** (0.43 g, 5%) as colourless oils.

Ethyl-2-[(2*R*,3*S*,6*R*)-3-(*tert*-butyldimethylsilyloxy)-3-methyl-6-(prop-1-en-2-yl)oxan-2-yl]acetate (305)

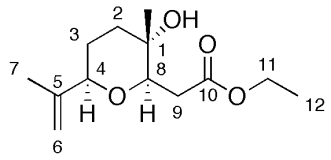
R_f = 0.51; (petroleum ether-ethyl acetate, 5:1); $[\alpha]_D^{24}$ +48.8 (*c* = 0.99, $CHCl_3$); ν_{max} (neat) 2952, 2929, 2858, 1740, 1654, 1472, 1375, 1297, 1251, 1189, 1151, 1130, 1075, 1047, 957, 899, 834, 773, 677 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.90 (1H, s, CH_2-C6), 4.78 (1H, s, CH_2-C6), 4.14 (2H, q, *J* = 7.1 Hz, CH_2-C11), 3.78 (1H, br d, *J* = 11.3 Hz, CH-C4), 3.72 (1H, dd, *J* = 10.4, 2.1 Hz, CH-C8), 2.69 (1H, dd, *J* = 15.3, 2.1 Hz, CH_2-C9), 2.31 (1H, dd, *J* = 15.3, 10.4 Hz, CH_2-C9), 1.91 (1H, ddd, *J* = 12.3, 4.9, 3.0 Hz, CH_2-C2), 1.79–1.69 (2H, m, CH_2-C2, CH_2-C3), 1.71 (3H, s, CH_3-C7), 1.57–1.48 (1H, m, CH_2-C3), 1.24 (3H, t, *J* = 7.1 Hz, CH_3-C12), 1.19 (3H, CH_3-Me), 0.85 (9H, s, CH_3-*t*Bu), 0.10 (3H, s, Si-CH_3), 0.09 (3H, s, Si-CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6 (C-C10), 145.4 (C-C5), 110.4 (CH_2-C6), 81.6 (CH-C8), 80.7 (CH-C4), 71.8 (C-C1), 60.4 (CH_2-C11), 40.2 (CH_2-C2), 35.2 (CH_2-C9), 29.0 (CH_2-C9), 25.9 (CH_3-*t*Bu), 20.9 (CH_3-Me), 19.3 (CH_3-C7), 18.1 (C-*t*Bu), 14.4 (CH_3-C12), −1.7 (Si-CH_3), −1.8 (Si-CH_3); HRMS (CI+, Me_3CH) for $C_{19}H_{37}O_4Si$ $[M+H]^+$ calcd. 357.2461, found 357.2460, Δ −0.2 ppm; LRMS (CI+, Me_3CH) *m*/*z* (intensity); 357.2 (100%), 299.1 (24%), 225.1 (74%); Anal. calcd. for $C_{19}H_{36}O_4Si$: C, 64.00%; H, 10.18%; found: C, 63.98%; H, 10.22%.

Ethyl-2-[(2*R*,3*R*,6*R*)-3-(*tert*-butyldimethylsilyloxy)-3-methyl-6-(prop-1-en-2-yl)oxan-2-yl]acetate (306)

R_f = 0.41; (petroleum ether-ethyl acetate, 5:1); $[\alpha]_D^{23}$ −32.7 (*c* = 1.00, $CHCl_3$); ν_{max} (neat) 2954, 2929, 2856, 1738, 1472, 1375, 1302, 1251, 1188, 1142, 1125, 1084, 1056, 1031, 1004, 966, 897, 834, 772, 670 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.04 (1H, q, *J* = 1.4 Hz, CH_2-C6), 4.98 (1H, br s, CH_2-C6), 4.19–4.09 (3H, m, CH-C4, CH_2-C11), 3.77 (1H, dd, *J* = 10.4, 2.3 Hz, CH-C8), 2.67 (1H, dd, *J* = 14.6, 2.3 Hz, CH_2-C9), 2.33 (1H, dd, *J* = 14.6, 10.4 Hz, CH_2-C9), 2.02–1.96 (1H, m, CH_2-C2), 1.87–1.76 (2H, m, CH_2-C2, CH_2-C3), 1.74 (3H, s, CH_3-C7), 1.68–1.64 (1H, m, CH_2-C3), 1.26 (3H, t, *J* = 7.1 Hz, CH_3-C12), 1.20 (3H, s, CH_3-Me), 0.84 (9H, s,

CH_3-*t*Bu), 0.08 (6H, s, Si-CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7 (C-C10), 143.7 (C-C5), 112.7 (CH_2-C6), 75.4 (C-C1), 74.6 (CH-C8), 72.4 (CH-C4), 60.6 (CH_2-C11), 35.8 (CH_2-C3), 35.5 (CH_2-C9), 25.9 (CH_3-*t*Bu), 24.5 (CH_2-C2), 21.7 (CH_3-Me), 20.2 (CH_3-C7), 18.2 (C-*t*Bu), 14.4 (CH_3-C12), −1.8 (Si-CH_3), −1.9 (Si-CH_3); HRMS (CI+, Me_3CH) for $C_{19}H_{37}O_4Si$ $[M+H]^+$ calcd. 357.2461, found 357.2462, Δ +0.3 ppm; LRMS (CI+, Me_3CH) *m/z* (intensity); 357.2 (16%), 299.2 (8%), 225.2 (100%), 95.1 (30%).

Ethyl 2-[(2*R*,3*S*,6*R*)-3-hydroxy-3-methyl-6-(prop-1-en-2-yl)oxan-2-yl]acetate (278)



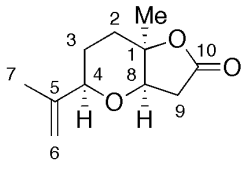
$C_{13}H_{22}O_4$

To a suspension of 4 Å powdered molecular sieves in anhydrous THF (8 mL) and silyl ether **305** (272 mg, 763 μmol) was added TBAF (4.0 mL of a 1.0 M solution in THF, 4.0 mmol). The mixture was stirred at room temperature overnight and the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The organic extracts were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 10:1 to 10:3) afforded desired alcohol **278** (83.6 mg, 45%) as colourless solid.

R_f = 0.43; (petroleum ether-ethyl acetate, 5:3); m.p. 84.6-86.5°C; $[\alpha]_D^{25}$ +42.5 (*c* = 0.53, $CHCl_3$); ν_{max} (film) 3326, 2978, 2946, 2876, 1735, 1654, 1442, 1366, 1287, 1183, 1127, 1070, 1032, 1000, 967, 933, 903, 865, 843 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.93 (1H, s, CH_2-C6), 4.81 (1H, s, CH_2-C6), 4.15 (2H, q, *J* = 7.1 Hz, CH_2-C11), 3.79 (1H, br d, *J* = 11.5 Hz, CH-C4), 3.73 (1H, dd, *J* = 8.7, 4.2 Hz, CH-C8), 2.69 (1H, dd, *J* = 15.3, 4.2 Hz, CH_2-C9), 2.42 (1H, dd, *J* = 15.3, 8.7 Hz, CH_2-C9), 1.92 (1H, ddd, *J* = 12.2, 3.8, 2.6 Hz, CH_2-C2), 1.78−1.53 (4H, m, CH_2-C2, CH_2-C3, OH), 1.73 (3H, s, CH_3-C7), 1.26 (3H, t, *J* = 7.1 Hz, CH_3-C12), 1.21 (3H, s, CH_3-Me); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6 (C-C10), 145.2 (C-C5), 110.7 (CH_2-

C6), 81.1 (CH-C8), 81.0 (CH-C4), 69.5 (C-C1), 60.7 (CH_2-C11), 40.4 (CH_2-C2), 35.7 (CH_2-C9), 29.1 (CH_2-C3), 20.1 (CH_3-Me), 19.2 (CH_3-C7), 14.4 (CH_3-C12); HRMS (CI+, Me_3CH) for $C_{13}H_{23}O_4$ $[M+H]^+$ calcd. 243.1596, found 243.1602, Δ +2.5 ppm; LRMS (CI+, Me_3CH) *m/z* (intensity); 243.2 (100%), 225.2 (95%), 197.2 (22%); Anal. calcd. for $C_{13}H_{22}O_4$: C, 64.44%; H, 9.15%; found: C, 64.02%; H, 9.20%.

(3*aR*,5*R*,7a*R*)-7a-Methyl-5-(prop-1-en-2-yl)-hexahydro-2H-furo[3,2-b]pyran-2-one (307)[118]



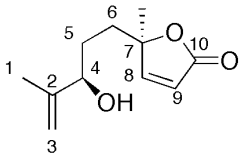
$C_{11}H_{16}O_3$

To a suspension of 4 Å powdered molecular sieves in anhydrous THF (4.5 mL) and silyl ether **306** (155 mg, 435 μmol) were added acetic acid (0.15 mL, 2.17 mmol) and TBAF (2.2 mL of a 1.0 M solution in THF, 2.2 mmol). The mixture was stirred at room temperature for 10 days and the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The organic extracts were combined, washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate from 10:1 to 1:1) afforded the lactone **307** (40.5 mg, 47%) as a colourless oil.

R_f = 0.56; (petroleum ether-ethyl acetate, 10:7); $[\alpha]_D^{23}$ +53.3 (*c* = 0.44, $CHCl_3$); ν_{max} (film) 2974, 2939, 2926, 1774, 1452, 1288, 1224, 1180, 1157, 1114, 1074, 1031, 935, 918, 856, 831, 817, 796, 694 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.97–4.96 (1H, m, CH_2-C6), 4.85 (1H, quint, *J* = 1.4 Hz, CH_2-C6), 4.08 (1H, d, *J* = 4.2 Hz, CH-C8), 3.73 (1H, br d, *J* = 9.3 Hz, CH-C4), 2.88 (1H, dd, *J* = 17.5, 4.2 Hz, CH_2-C9), 2.54 (1H, d, *J* = 17.5 Hz, CH_2-C9), 2.34–2.26 (1H, m, CH_2-C3), 1.72 (3H, s, CH_3-C7), 1.76–1.61 (2H, m, CH_2-C2, CH_2-C3), 1.61–1.55 (1H, m, CH_2-C2), 1.31 (3H, s, CH_3-Me); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9 (C-C10), 145.0 (C-C5), 111.6 (CH_2-C6), 81.8 (C-C1), 78.8 (CH-C4), 77.7 (CH-C8), 38.4 (CH_2-C9), 32.5 (CH_2-C3), 25.4 (CH_3-Me), 25.2 (CH_2-C2), 18.6 (CH_3-C7); HRMS (CI+, Me_3CH) for

$C_{11}H_{17}O_3$ $[M+H]^+$ calcd. 197.1178, found 197.1178, Δ −0.1 ppm; LRMS (CI+, Me_3CH) *m/z* (intensity); 197.1 (100%).

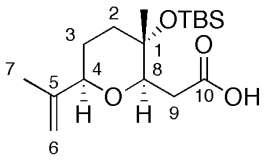
(5*R*)-5-[(3*R*)-3-Hydroxy-4-methylpent-4-en-1-yl]-5-methyl-2,5-dihydrofuran-2-one (308)



$C_{11}H_{16}O_3$

Colourless oil; R_f = 0.25; (petroleum ether-ethyl acetate, 6:10); ν_{max} (film) 3444, 2935, 2870, 1735, 1448, 1311, 1261, 1112, 1072, 1028, 952, 898, 821, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33 (1H, d, *J* = 5.6 Hz, CH-C9), 6.02 (1H, d, *J* = 5.6 Hz, CH-C8), 4.95−4.90 (1H, m, CH_2-C3), 4.83 (1H, br t, *J* = 1.0 Hz, CH_2-C3), 4.03 (1H, dd, *J* = 7.4, 5.2 Hz, CH-C4), 1.91−1.79 (2H, m, CH_2-C6), 1.69 (3H, s, CH_3-C1), 1.58 (1H, br s, OH), 1.58−1.50 (1H, m, CH_2-C5), 1.48 (3H, s, CH_3-Me), 1.45−1.34 (1H, m, CH_2-C5); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6 (C-C10), 160.3 (CH-C9), 147.2 (C-C2), 120.9 (CH-C8), 111.5 (CH_2-C3), 88.8 (C-C7), 75.5 (CH-C4), 34.3 (CH_2-C6), 28.9 (CH_2-C5), 24.5 (CH_3-Me), 17.8 (CH_3-C1); HRMS (CI, Me_3CH) for $C_{11}H_{17}O_3$ $[M+H]^+$ calcd. 197.1178, found 197.1179, Δ +0.8 ppm; LRMS *m/z* (intensity); 197.1 (29%), 179.1 (100%).

2-[(2*R*,3*S*,6*R*)-3-(*tert*-Butyldimethylsilyloxy)-3-methyl-6-(prop-1-en-2-yl)oxan-2-yl]acetic acid (309)



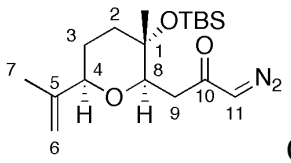
$C_{17}H_{32}O_4Si$

To a stirred solution of ester **305** (6.97 g, 19.5 mmol) in EtOH (150 mL) and water (50 mL) was added lithium hydroxide (8.26 g, 197 mmol) portionwise. The mixture was stirred at room temperature overnight and acidified to pH 2−3 with 1 M aqueous HCl. The solution was diluted with EtOAc (300 mL) and water

(150 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 100 mL). The organic extracts were combined, washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 20:1 to 5:1) afforded the carboxylic acid **309** (6.13 g, 96%) as a colourless oil.

R_f = 0.61; (petroleum ether-ethyl acetate-acetic acid, 10:3:0.1); $[\alpha]_D^{22}$ +67.1 (*c* = 1.02, $CHCl_3$); ν_{max} (film) 2955, 2930, 2859, 1715, 1437, 1311, 1253, 1153, 1132, 1080, 1051, 901, 835, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.20 (1H, br s, CO_2H), 4.95 (1H, s, CH_2-C6), 4.84 (1H, s, CH_2-C6), 3.87 (1H, br d, *J* = 10.7, CH-C4), 3.68 (1H, dd, *J* = 10.5, 2.3 Hz, CH-C8), 2.77 (1H, dd, *J* = 15.8, 2.3 Hz, CH_2-C9), 2.40 (1H, dd, *J* = 15.8, 10.5 Hz, CH_2-C9), 1.97−1.90 (1H, m, CH_2-C2), 1.79−1.68 (2H, m, CH_2-C2, CH_2-C3), 1.73 (3H, s, CH_3-C7), 1.62−1.52 (1H, m, CH_2-C3), 1.21 (3H, s, CH_3-Me), 0.85 (9H, s, CH_3-*t*Bu), 0.10 (3H, s, Si-CH_3), 0.09 (3H, s, Si-CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0 (C-C10), 144.7 (C-C5), 111.3 (CH_2-C6), 81.4 (CH-C4), 81.1 (CH-C8), 71.6 (C-C1), 39.9 (CH_2-C2), 34.5 (CH_2-C9), 29.0 (CH_2-C3), 25.9 (CH_3-*t*Bu), 20.6 (CH_3-Me), 19.1 (CH_3-C7), 18.1 (C-*t*Bu), −1.7 (Si-CH_3), −1.9 (Si-CH_3); HRMS (CI+, Me_3CH) for $C_{17}H_{33}O_4Si$ $[M+H]^+$ calcd. 329.2148, found 329.2156, Δ +2.3 ppm; LRMS (CI+, Me_3CH) *m/z* (intensity); 329.2 (74%), 197.1 (100%), 85.1 (26%); Anal. calcd. for $C_{17}H_{32}O_4Si$: C, 62.15%; H, 9.82%; found: C, 62.18%; H, 9.72%.

1-[(2*R*,3*S*,6*R*)-3-(*tert*-Butyldimethylsilyloxy)-3-methyl-6-(prop-1-en-2-yl)oxan-2-yl]-3-diazopropan-2-one (276)



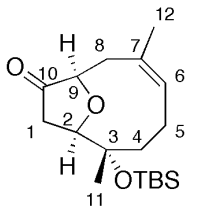
$C_{18}H_{32}N_2O_3Si$

To a stirred solution of carboxylic acid **309** (3.07 g, 9.34 mmol) and distilled triethylamine (2.0 mL, 14 mmol) in anhydrous Et_2O (120 mL) was added isobutyl chloroformate (1.8 mL, 14 mmol) dropwise. The mixture was stirred at room temperature for 3 h. The solution was filtered and the solid residue was washed

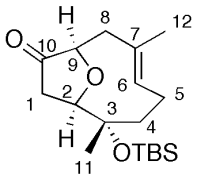
with Et_2O (3 × 10 mL). The filtrate was immediately poured into a freshly prepared ethereal solution of diazomethane (92.5 mmol) at 0 °C. The mixture was stirred at room temperature for 4 days and the reaction was quenched by careful addition of glacial acetic acid (5 mL). The solution was added to a saturated aqueous solution of $NaHCO_3$ (200 mL) and the mixture was vigorously stirred for 15 min. The phases were separated and the aqueous phase was extracted with EtOAc (3 × 80 mL). The organic extracts were combined, washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 20:1 to 10:1) afforded the diazoketone **276** (2.92 g, 89%) as a yellow oil.

R_f = 0.68; (petroleum ether-ethyl acetate, 5:2); $[\alpha]_D^{25}$ +92.9 (*c* = 1.03, $CHCl_3$); ν_{max} (neat) 2952, 2929, 2857, 2099, 1643, 1472, 1341, 1250, 1131, 1048, 990, 955, 899, 833, 797, 773, 664 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.37 (1H, br s, CH-C11), 4.93 (1H, s, CH_2-C6), 4.80 (1H, s, CH_2-C6), 3.78 (1H, d, *J* = 11.2 Hz, CH-C4), 3.63 (1H, d, *J* = 10.2 Hz, CH-C8), 2.66 (1H, dd, *J* = 14.5, 1.7 Hz, CH_2-C9), 2.32 (1H, br s, CH_2-C9), 1.91 (1H, ddd, *J* = 12.3, 4.8, 2.9 Hz, CH_2-C2), 1.78−1.69 (2H, m, CH_2-C2, CH_2-C3), 1.72 (3H, s, CH_3-C7), 1.58−1.48 (1H, m, CH_2-C3), 1.18 (3H, s, CH_3-Me), 0.85 (9H, s, CH_3-*t*Bu), 0.10 (3H, s, Si-CH_3), 0.09 (3H, s, Si-CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.3 (C-C10), 145.4 (C-C5), 110.5 (CH_2-C6), 81.8 (CH-C8), 80.9 (CH-C4), 71.8 (C-C1), 54.9 (CH-C11), 41.4 (CH_2-C9), 40.2 (CH_2-C2), 29.2 (CH_2-C3), 25.9 (CH_3-*t*Bu), 20.8 (CH_3-Me), 19.2 (CH_3-C7), 18.2 (C-*t*Bu), −1.7 (Si-CH_3), −1.8 (Si-CH_3); HRMS (ESI) for $C_{18}H_{32}N_2NaO_3Si$ $[M+Na]^+$ calcd. 375.2074, found 375.2079, Δ +1.4 ppm; Anal. calcd. for $C_{18}H_{32}N_2O_3Si$: C, 61.32%; H, 9.15%; N, 7.95%; found: C, 61.16%; H, 9.25%; N, 7.95%.

(1*R*,2*S*,5*Z*,8*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-2,6-dimethyl-11-oxabicyclo[6.2.1]undec-5-en-9-one (*Z*-275) and **(1*R*,2*S*,5*E*,8*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-2,6-dimethyl-11-oxabicyclo[6.2.1]undec-5-en-9-one (*E*-275)**



$C_{18}H_{32}O_3Si$



$C_{18}H_{32}O_3Si$

To a stirred solution of $Cu(hfacac)_2$ (108 mg, 0.218 mmol) in anhydrous CH_2Cl_2 (45 mL) at 55 °C was added the α-diazoketone **276** (1.5 g, 4.4 mmol) in anhydrous CH_2Cl_2 (300 mL) dropwise over a period of 2.5 h. The resulting solution was stirred for 1 h at 55 °C, allowed to cool to room temperature and concentrated *in vacuo* to give a mixture of the *E*- and *Z*-alkene (1:1.6). Purification of the residue by flash column chromatography on silica gel impregnated with silver nitrate (10%) (petroleum ether-ethyl acetate, gradient elution from 50:1 to 1:1) delivered the *Z*-alkene ***Z*-275** (0.77 g, 54%) as a colourless liquid and the *E*-alkene ***E*-275** (0.44 g, 31%) as a colourless solid.

Preparation of silica gel impregnated with silver nitrate

To a stirred solution of silica gel in water was added silver nitrate (10% weight). The mixture was heated at 130-140 °C in order to remove the water. The silica gel was finally dried for in the oven (120 °C) for 24 to 48 h.

(1*R*,2*S*,5*Z*,8*R*)-2-[(*tert*-Butyldimethylsilyl)oxy]-2,6-dimethyl-11-oxabicyclo[6.2.1]undec-5-en-9-one (*Z*-275)

R_f = 0.37; (petroleum ether-ethyl acetate, 5:1); $[\alpha]_D^{25}$ +109.3 (*c* = 1.17, $CHCl_3$); ν_{max} (neat) 2953, 2928, 2885, 2855, 1755, 1444, 1377, 1249, 1166, 1118, 1093, 1049, 995, 964, 878, 827, 802, 771, 700, 682 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.41 (1H, dd, *J* = 11.7, 6.0 Hz, CH-C6), 4.29 (1H, ddd, *J* = 8.4, 8.2, 2.2 Hz, CH-C2), 4.20 (1H, dd, *J* = 4.3, 2.2 Hz, CH-C9), 3.19 (1H, dddd, *J* = 13.2, 11.7, 7.8, 1.1 Hz, CH_2-C5), 2.78 (1H, br d, *J* = 14.5 Hz, CH_2-C8), 2.43 (1H, dd, *J* = 18.6, 8.2 Hz, CH_2-C1), 2.20 (1H, dd, *J* = 18.6, 8.4 Hz, CH_2-C1), 2.10 (1H, dd, *J* = 14.5, 4.3

Hz, CH_2-C8), 1.94–1.87 (1H, m, CH_2-C4), 1.83–1.75 (1H, m, CH_2-C5), 1.63 (3H, s, CH_3-C12), 1.51 (1H, dd, *J* = 15.2, 7.8 Hz, CH_2-C4), 1.03 (3H, s, CH_3-C11), 0.92 (9H, s, CH_3-*t*Bu), 0.14 (3H, s, Si-CH_3), 0.12 (3H, s, Si-CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 216.5 (C-C10), 130.9 (CH-C6), 129.7 (C-C7), 82.8 (CH-C2), 79.3 (CH-C9), 76.4 (C-C3), 40.4 (CH_2-C1), 37.9 (CH_2-C4), 35.4 (CH_2-C8), 28.6 (CH_3-C11 or CH_3-C12), 28.5 (CH_3-C11 or CH_3-C12), 26.0 (CH_3-*t*Bu), 22.7 (CH_2-C5), 18.6 (C-*t*Bu), −2.00 (Si-CH_3); HRMS (EI+) for $C_{18}H_{32}O_3Si$ $[M]^+$ calcd. 324.2121, found 324.2117, Δ −1.2 ppm; LRMS (EI+) *m/z* (intensity); 324.2 (29%), 267.1 (100%), 171.1 (42%), 147.1 (52%), 75.0 (41%); Anal. calcd. for $C_{18}H_{32}O_3Si$: C, 66.62%; H, 9.94%; found: C, 66.57%; H, 10.13%.

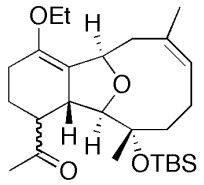
(1*R*,2*S*,5*E*,8*R*)-2-[(tert-butyldimethylsilyl)oxy]-2,6-dimethyl-11-oxabicyclo[6.2.1]undec-5-en-9-one (*E*-275)

R_f = 0.35; (petroleum ether-ethyl acetate, 5:1); m.p. 68.8–71.4 °C; $[\alpha]_D^{24}$ +64.1 (*c* = 0.87, $CHCl_3$); ν_{max} (film) 2954, 2926, 2883, 2851, 1751, 1462, 1386, 1245, 1166, 1119, 1065, 1045, 996, 964, 886, 863, 835, 813, 772, 739, 685 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (1H, dddd, *J* = 9.2, 7.9, 1.2, 0.7 Hz, CH-C6), 4.47 (1H, dd, *J* = 9.7, 7.4 Hz, CH-C2), 4.12 (1H, d, *J* = 6.4 Hz, CH-C9), 2.54 (1H, ddd, *J* = 19.9, 9.7, 1.1 Hz, CH_2-C1), 2.47 (1H, ddd, *J* = 13.3, 6.4, 0.7 Hz, CH_2-C8), 2.34 (1H, dd, *J* = 13.3, 1.2 Hz, CH_2-C8), 2.23–2.17 (2H, m, CH_2-C5), 2.03 (1H, dd, *J* = 19.9, 7.4 Hz, CH_2-C1), 1.63–1.54 (2H, m, CH_2-C4), 1.51 (3H, d, *J* = 1.2 Hz, CH_3-C12), 1.10 (3H, s, CH_3-C11), 0.96 (9H, s, CH_3-*t*Bu), 0.19 (3H, s, Si-CH_3), 0.15 (3H, s, Si-CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 218.6 (C-C10), 132.9 (CH-C6), 124.0 (C-C7), 83.5 (CH-C2), 79.2 (CH-C9), 78.6 (C-C3), 42.0 (CH_2-C8), 38.8 (CH_2-C1), 36.0 (CH_2-C4), 31.7 (CH_3-C11), 26.2 (CH_3-*t*Bu), 23.0 (CH_2-C5), 18.7 (C-*t*Bu), 17.7 (CH_3-C12), −1.7 (Si-CH_3), −1.9 (Si-CH_3); HRMS (EI+) for $C_{18}H_{32}O_3Si$ $[M]^+$ calcd. 324.2121, found 324.2123, Δ +0.6 ppm; LRMS (EI+) *m/z* (intensity); 324.2 (15%), 267.1 (100%), 239.2 (84%), 75.0 (73%); Anal. calcd. for $C_{18}H_{32}O_3Si$: C, 66.62%; H, 9.94%; found: C, 66.69%; H, 10.15%.

Conversion of the *E*-alkene into the *Z*-alkene

To a stirred solution of *E*-alkene ***E*-275** (0.69 g, 2.1 mmol) in anhydrous toluene (40 mL) was added 1,1'-azobis(cyclohexane-carbonitrile) (0.10 g, 0.42 mmol) and ethanethiol (6.0 mL, 80 μmol). The mixture was stirred at 90 °C for 1 h and the volatiles were removed under *vacuum*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 50:1) afforded the *Z*-alkene **Z-275** (0.58 g, 85%) as a colourless oil.

1-[(*Z*)-(1*R*,2*R*,8*R*,14*S*)-14-(*tert*-butyl-dimethyl-silanyloxy)-6-ethoxy-10,14-dimethyl-15-oxa-tricyclo[6.6.1.$0^{2,7}$]pentadeca-6,10-dien-3-yl]-ethanone (273)



$C_{26}H_{44}O_4Si$

Method A: Heck coupling

To a stirred solution of *Z*-bicyclic ketone ***Z*-275** (1.00 g, 3.08 mmol) in anhydrous THF (60 mL) was added *N*-phenyl-*bis*(trifluoromethanesulfonimide) (2.23 g, 6.24 mmol). The solution was cooled to −78 °C and sodium bis(trimethylsilyl)amide (8.0 mL of a 1.0 M solution in THF, 8.0 mmol) was added. The mixture was stirred at −78 °C for 2 h and the reaction was quenched by the addition of water (20 mL). The solution was warmed to room temperature and diluted with Et_2O (25 mL). The aqueous phase was separated and extracted with Et_2O (3 × 25 mL). The organic extracts were combined, washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude enol triflate **313**, which was used in the next step without purification.

In a sealed tube were successively added palladium acetate (0.10 g, 0.46 mmol), 1,3-bis(diphenylphosphino)propane (0.24 g, 0.58 mmol), distilled triethylamine (0.65 mL, 4.7 mmol), a solution of the crude triflate in DMF (6.0 mL) and freshly distilled ethyl vinyl ether (3.0 mL, 31 mmol). The mixture was stirred at 80 °C overnight, cooled to room temperature and diluted with water (25 mL) and Et_2O

(20 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 15 mL). The organic extracts were combined, washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 20:1 in presence of 1% triethylamine) removed baseline impurities. The unstable diene **274** was immediately used in the next.

To a solution of diene in anhydrous toluene (120 mL) in a sealed tube was added freshly distilled methyl vinyl ketone (3.0 mL, 37 mmol). The mixture was stirred at 120 °C overnight and the volatiles were removed under *vacuum*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 30:1 in presence of 1% triethylamine) delivered the tricyclic compound **273** (0.93 g, 69% over 3 steps) as a 1:1 mixture of *exo* and *endo* cycloadducts.

Method B: Stille coupling

To a stirred solution of *Z*-bicyclic ketone ***Z*-275** (0.18 g, 0.55 mmol) in anhydrous THF (11 mL) was added *N*-phenyl-*bis*(trifluoromethanesulfonimide) (0.40 g, 1.1 mmol). The solution was cooled to −78 °C and sodium bis(trimethylsilyl)amide (1.4 mL of a 1.0 M solution in THF, 1.4 mmol) was added. The mixture was stirred at −78 °C for 3 h and the reaction was quenched by the addition of water (10 mL). The solution was warmed to room temperature and diluted with Et_2O. The aqueous phase was separated and extracted with Et_2O (3 × 15 mL). The organic extracts were combined, washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the crude enol triflate **313**, which was used in the next step without purification.

To a solution of the crude trifalte in anhydrous THF (33 mL) were added tributyl(1-ethoxyvinyl)stannane (0.60 mL, 1.8 mmol), lithium chloride (0.49 g, 3.7 mmol) and tetrakis(triphenylphosphine)palladium (96 mg, 83 μmol). The mixture was stirred at 80 °C overnight. At room temperature, the solution was diluted with water (10 mL) and Et_2O (15 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Flash column chromatography on silica gel (petroleum ether-ethyl acetate, 20:1 in presence of

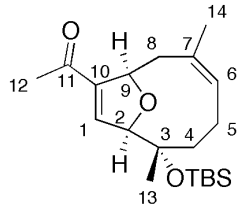
1% triethylamine) removed baseline impurities. The unstable diene **274** was immediately used in the next step.

To a solution of diene in anhydrous toluene (20 mL) in a flame dried pressure tube was added freshly distilled methyl vinyl ketone (0.50 mL, 6.2 mmol). The mixture was stirred at 120 °C overnight and volatiles were removed under *vacuum*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 20:1 in presence of 1% triethylamine) afforded the tricyclic compound **273** (0.16 g, 65% over 3 steps) as a 1:1 mixture of *exo* and *endo* cycloadducts.

Since they exist as an inseparable mixture, the diastereomeric cycloadducts were not characterised at this stage.

Note: By-product **321** was sometimes obtained as a colourless solid.

1-[(1*R*,2*S*,5*Z*,8*R*)-2-[(*Tert*-butyldimethylsilyl)oxy]-2,6-dimethyl-11-oxabicyclo[6.2.1]undeca-5,9-dien-9-yl]ethan-1-one (321)

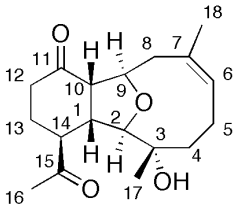


$C_{20}H_{34}O_3Si$

R_f = 0.57; (petroleum ether-ethyl acetate, 5:1); m.p. 78.3–80.6 °C; $[\alpha]_D^{24}$ +9.9 (*c* = 1.07, $CHCl_3$); ν_{max} (neat) 2928, 2855, 1674, 1462, 1370, 1246, 1186, 1141, 1102, 1084, 1043, 988, 940, 834, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.49 (1H, br t, *J* = 1.9 Hz, CH-C1), 5.45 (1H, dd, *J* = 11.5, 6.7 Hz, CH-C6), 5.32–5.28 (1H, m, CH-C9), 4.77 (1H, dt, *J* = 4.2, 1.9 Hz, CH-C2), 3.11–3.03 (1H, m, CH_2-C5), 2.86 (1H, br d, *J* = 15.0 Hz, CH_2-C8), 2.37 (1H, dd, *J* = 15.0, 4.9, CH_2-C8), 2.32 (3H, s, CH_3-C12), 1.90–1.82 (1H, m, CH_2-C4), 1.74–1.64 (1H, m, CH_2-C5), 1.49 (3H, s, CH_3-C14), 1.19 (1H, dd, *J* = 4.9, 2.7 Hz, CH_2-C4), 1.17 (3H, s, CH_3-C13), 0.91 (9H, s, CH_3-*t*Bu), 0.14 (3H, s, Si-CH_3), 0.11 (3H, s, Si-CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.7 (C-C11), 144.7 (C-C10), 139.4 (CH-C1), 130.5 (CH-C6), 129.6 (C-C7), 93.9 (CH-C2), 83.2 (CH-C9), 77.0 (C-C3), 39.5 (CH_2-C4), 36.7 (CH_2-C8), 28.7 (CH_3-C13), 27.6 (CH_3-C14), 27.5 (CH_3-C12), 26.0 (CH_3-*t*Bu), 22.0 (CH_2-C5),

18.6 (C-*t*Bu), −2.0 (Si-CH_3), −2.1 (Si-CH_3); HRMS (CI+, Me_3CH) for $C_{20}H_{35}O_3Si$ $[M+H]^+$ calcd. 351.2355, found 351.2357, Δ +0.3 ppm; LRMS (CI+, Me_3CH) *m/z* (intensity); 351.2 (67%), 219.2 (100%), 109.1 (37%).

(1*R*,2*R*,6*S*,7*S*,8*R*,9*S*,12*Z*)-6-Acetyl-9-hydroxy-9,13-dimethyl-15-oxatricyclo[6.6.1.$0^{2,7}$]pentadec-12-en-3-one (317)



$C_{18}H_{26}O_4$

Method A: conversion of the *endo* and *exo* cycloadducts

The diastereomeric mixture (1:1) of cycloadducts **273** (923 mg, 2.06 mmol) was dissolved in MeOH (70 mL). Concentrated HCl (10 mL) was added and the mixture was stirred at room temperature overnight. The solution was neutralised by the addition of a saturated aqueous solution of $NaHCO_3$ until pH 8 was reached. The mixture was diluted with water (50 mL) and EtOAc (50 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 80 mL). The organic extracts were combined, washed with brine (80 ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate 1:1) delivered the diketone **317** (0.43 g, 69%) as a colourless thick oil.

Method B: synthesis of the diketone **317** from *Z*-bicyclic methyl ketone **321**

To a stirred solution of *Z*-bicyclic methyl ketone **321** (137 mg, 391 μmol) in anhydrous THF (7.5 mL) at −78 °C was added sodium bis(trimethylsilyl)amide (0.5 mL of a 1.0 M solution in THF, 0.5 mmol). The mixture was stirred for 15 min and triethylsilyl chloride (0.10 mL, 0.59 mmol) was added dropwise. After 15 min the mixture was allowed to warm to room temperature and was stirred for a further 1 h. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (5 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The organic extracts were

combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude diene **322** was immediately used in the next step.

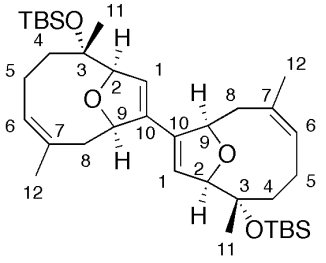
To a solution of diene **322** in anhydrous toluene (14 mL) in a sealed tube was added freshly distilled methyl vinyl ketone (0.30 mL, 3.67 mmol). The reaction was stirred at 120 °C overnight and volatiles were removed under *vacuum*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 50:1 to 20:1 in presence of 1% triethylamine) afforded the tricyclic compound **323** as a 1:1 mixture of *endo* and *exo* cycloadducts.

The diastereomeric mixture of cycloadducts (104 mg, 232 μmol) was dissolved in MeOH (6 mL) and concentrated HCl (1 mL) was added at 0 °C. The reaction was warmed to room temperature and stirred overnight. The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ until pH 6 was reached and the solution was subsequently diluted with EtOAc (15 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The organic extracts were combined, washed with brine (25 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 10:1 to 1:1) gave the desired diketone **317** (20.6 mg, 35% over four steps) as a colourless oil.

R_f = 0.27; (petroleum ether-ethyl acetate, 1:2); $[\alpha]_D^{27}$ +22.3 (*c* = 1.07, $CHCl_3$); ν_{max} (neat) 3496, 2964, 2929, 2854, 1707, 1452, 1356, 1251, 1161, 1087, 1057, 970, 899, 827 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.59–5.54 (1H, m, CH-C6), 4.86 (1H, ddd, *J* = 4.6, 2.6, 2.4 Hz, CH-C9), 3.57 (1H, d, *J* = 9.1 Hz, CH-C2), 3.37 (1H, td, *J* = 9.1, 4.3 Hz, CH-C1), 3.22 (1H, s, OH), 2.98 (1H, dd, *J* = 9.1, 2.6 Hz, CH-C10), 2.85 (1H, d, *J* = 14.9 Hz, CH_2-C8), 2.78–2.74 (1H, m, CH-C14), 2.71– 2.64 (1H, m, CH_2-C5), 2.42–2.31 (2H, m, CH_2-C12), 2.27 (3H, s, CH_3-C16), 2.18–2.06 (2H, m, CH_2-C13), 1.90–1.82 (3H, m, CH_2-C4, CH_2-C5, CH_2-C8), 1.85 (3H, s, CH_3-C18), 1.54–1.49 (1H, m, CH_2-C4), 1.02 (3H, d, *J* = 0.5 Hz, CH_3-C17); ^{13}C NMR (126 MHz, $CDCl_3$) δ 209.0 (C-C11 or C-C15), 208.2 (C-C11 or C-C15), 130.5 (CH-C6), 130.4 (C-C7), 89.4 (CH-C2), 75.1 (CH-C9), 73.4 (C-C3), 54.0 (CH-C10), 48.9 (CH-C14), 42.5 (CH-C1), 37.9 (CH_2-C4), 37.6 (CH_2-C12), 37.2 (CH_2-C8), 28.8 (CH_3-C16), 28.4 (CH_3-C18), 27.2 (CH_3-C17), 24.6 (CH_2-C13), 22.2 (CH_2-C5); HRMS (EI+)

for $C_{18}H_{26}O_4$ $[M]^+$ calcd. 306.1831, found 306.1834, Δ +0.9 ppm; LRMS (EI+) *m/z* (intensity); 306.0 (29%), 194.0 (100%), 181.0 (92%), 113.0 (66%); Anal. calcd. for $C_{18}H_{26}O_4$: C, 70.56%; H, 8.55%; found: C, 70.08%; H, 8.62%;
In the racemic form, the compound crystallised at room temperature, m.p. 119–120 °C.

tert-Butyl({[(1*R*,2*S*,5*Z*,8*R*)-9-[(1*R*,2*S*,5*Z*,8*R*)-2-(_tert_-butyldimethylsilyloxy)-2,6-dimethyl-11-oxabicyclo[6.2.1]undec-5-en-9-yl]-2,6-dimethyl-11-oxabicyclo[6.2.1]undeca-5,9-dien-2-yl]oxy})dimethylsilane (320)

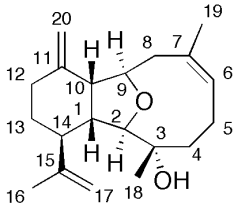


$C_{36}H_{62}O_4Si_2$

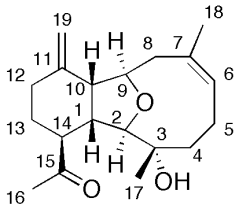
In a round bottom flask, freshly distilled vinyl ethyl ether (30 µL, 0.31 µmol) in anhydrous THF (0.5 mL) was cooled to −78 °C. *tert*-Butyllithium (250 µL of a 1.9 M solution in pentane, 475 µmol) was added slowly. The yellow solution was stirred for 1 h and zinc chloride (500 µL of a 1.0 M solution in THF, 500 µmol) was added. The mixture turned colourless and was warmed to room temperature. A solution of crude triflate **313** (154 µmol), tris(dibenzylideneacetone)dipalladium (14.6 mg, 15.9 µmol) and triphenylphosphine (6.09 mg, 23.2 µmol) in anhydrous THF (1 mL) was added dropwise. The mixture was stirred at 70 °C for an additional 1 h and the reaction was quenched by the addition of water (2 mL). The solution was diluted with Et_2O and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 5 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The proton NMR highlighted the presence of several by-products among them, a pure sample of the dimer **320** was obtained as a colourless solid.
R_f = 0.41; (petroleum ether-ethyl acetate, 10:1); m.p. 119.4–121.5 °C; ν_{max} (film) 2954, 2928, 2854, 1472, 1373, 1253, 1141, 1101, 1084, 1043, 990, 834,

809, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.63 (2H, s, CH-C1), 5.43 (2H, dd, *J* = 11.8, 6.6 Hz, CH-C6), 5.10 (2H, br s, CH-C9), 4.68 (2H, br s, CH-C2), 3.17−3.10 (2H, m, CH_2-C5), 3.01 (2H, d, *J* = 15.4 Hz, CH_2-C8), 2.17 (2H, dd, *J* = 15.4, 4.6 Hz, CH_2-C8), 1.85−1.76 (2H, m, CH_2-C4), 1.74−1.65 (2H, m, CH_2-C5), 1.69 (6H, s, CH_3-C12), 1.23 (2H, ddd, *J* = 13.4, 5.0, 2.5 Hz, CH_2-C4), 1.12 (6H, s, CH_3-C11), 0.90 (18H, CH_3-*t*Bu), 0.13 (6H, s, Si-CH_3), 0.10 (6H, s, Si-CH_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 136.4 (C-C10), 130.7 (CH-C6), 129.0 (C-C7), 125.9 (CH-C1), 94.4 (CH-C2), 84.2 (CH-C9), 77.1 (C-C3), 38.8 (CH_2-C4), 37.9 (CH_2-C8), 29.4 (CH_3-C12), 28.8 (CH_3-C11), 26.1 (CH_3-*t*Bu), 22.1 (CH_2-C5), 18.6 (C-*t*Bu), −2.0 (Si-CH_3), −2.0 (Si-CH_3); HRMS (ESI) for $C_{36}H_{62}NaO_4Si$ $[M+Na]^+$ calcd. 637.4079, found 637.4049, Δ −4.7 ppm.

(1*R*,2*S*,6*S*,7*S*,8*R*,9*S*,12*Z*)-9,13-Dimethyl-3-methylidene-6-(prop-1-en-2-yl)-15-oxatricyclo[6.6.1.0^{2,7}]pentadec-12-en-9-ol (325) and **1-[(1*R*,2*R*,3*S*,7*S*,8*R*,10*Z*,14*S*)-14-Hydroxy-10,14-dimethyl-6-methylidene-15-oxatricyclo[6.6.1.0^{2,7}]pentadec-10-en-3-yl]ethan-1-one (326)**



$C_{20}H_{30}O_2$



$C_{19}H_{28}O_3$

In a round bottom flask methyltriphenylphosphonium bromide (133 mg, 372 µmol) was suspended in anhydrous THF (7 mL). Potassium *tert*-butoxide (42.0 mg, 374 µmol) was added. The yellow suspension was stirred at room temperature for 1 h and diketone **317** (57.0 mg, 186 µmol) in anhydrous THF (5.5 mL) was added dropwise. The mixture was stirred for 30 min and the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (7 mL) and diluted with Et_2O (10 mL). The phases were separated and the aqueous phase was extracted Et_2O (3 × 10 mL). The organic extracts were combined, washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to deliver a mixture (1:5) of triene **325** and ketone **326**. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl

acetate, gradient elution from 10:1 to 5:2 and from 3:1 to 1:1) afforded the triene **325** (8.00 mg, 14%) and ketone **326** (39.2 mg, 69%) as colourless solids.

(1*R*,2*S*,6*S*,7*S*,8*R*,9*S*,12*Z*)-9,13-Dimethyl-3-methylidene-6-(prop-1-en-2-yl)-15-oxatricyclo[6.6.1.$0^{2,7}$]pentadec-12-en-9-ol (325)

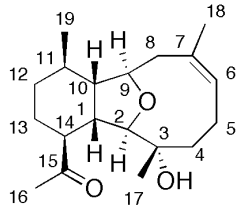
R_f = 0.34; (petroleum ether-ethyl acetate, 5:1); m.p. 121.4–123.7 °C; $[\alpha]_D^{29}$ −94.8 (*c* = 0.87, $CHCl_3$); ν_{max} (film) 3397, 3074, 2969, 2925, 2902, 2880, 2855, 1645, 1455, 1375, 1187, 1115, 1087, 1054, 974, 899, 826, 769, 652 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.76–5.71 (1H, m, CH-C6), 4.84–4.80 (2H, m, CH_2-C17, CH_2-C20), 4.81 (1H, s, CH_2-C17), 4.73 (1H, s, CH_2-C20), 4.31 (1H, ddd, *J* = 10.3, 5.2, 1.2 Hz, CH-C9), 3.85 (1H, s, CH-C2), 3.17 (1H, dd, *J* = 10.3, 7.2 Hz, CH-C10), 2.88 (1H, d, *J* = 16.1 Hz, CH_2-C8), 2.77–2.70 (1H, m, CH_2-C5), 2.59 (1H, s, OH), 2.26 (1H, dt, *J* = 13.4, 3.8 Hz, CH_2-C12), 2.22–2.14 (2H, m, CH_2-C12, CH-C14), 1.98 (1H, dd, *J* = 16.1, 5.2 Hz, CH_2-C8), 1.97–1.93 (1H, m, CH-C1), 1.92–1.85 (2H, m, CH_2-C4, CH_2-C5), 1.78–1.73 (1H, m, CH_2-C13), 1.76 (3H, s, CH_3-C19), 1.61 (3H, s, CH_3-C16), 1.39 (1H, qd, *J* = 12.7, 3.8 Hz, CH_2-C13), 1.33–1.28 (1H, m, CH_2-C4), 0.93 (3H, s, CH_3-C18); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.6 (C-C11 or C-C15), 145.8 (C-C11 or C-C15), 131.7 (C-C7), 129.4 (CH-C6), 113.6 (CH_2-C17), 112.2 (CH_2-C20), 92.6 (CH-C2), 78.8 (CH-C9), 72.4 (C-C3), 48.3 (CH-C14), 47.2 (CH-C10), 46.2 (CH-C1), 36.7 (CH_2-C4), 35.9 (CH_2-C8), 32.5 (CH_2-C13), 31.9 (CH_2-C12), 28.5 (CH_3-C19), 26.8 (CH_3-C18), 22.5 (CH_2-C5), 18.7 (CH_3-C16); HRMS (EI+) for $C_{20}H_{30}O_2$ $[M]^+$ calcd. 302.2246, found 302.2245, Δ −0.4 ppm; LRMS (EI+) *m/z* (intensity); 302.1 (31%), 177.1 (100%), 176.0(38%).

1-[(1*R*,2*R*,3*S*,7*S*,8*R*,10*Z*,14*S*)-14-Hydroxy-10,14-dimethyl-6-methylidene-15-oxatricyclo[6.6.1.$0^{2,7}$]pentadec-10-en-3-yl]ethan-1-one (326)

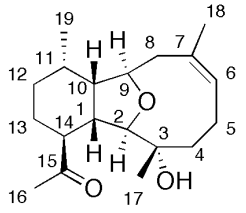
R_f = 0.49; (petroleum ether-ethyl acetate, 1:1); m.p. 123.4–125.8 °C; $[\alpha]_D^{28}$ −53.8 (*c* = 0.72, $CHCl_3$); ν_{max} (neat) 3455, 2961, 2930, 2866, 1711, 1646, 1456, 1373, 1194, 1165, 1083, 1057, 972, 959, 898, 830 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.74–5.68 (1H, m, CH-C6), 4.87 (1H, s, CH_2-C19), 4.78 (1H, s, CH_2-C19), 4.32 (1H, ddd, *J* = 8.8, 5.2, 1.5 Hz, CH-C9), 3.58 (1H, s, CH-C2), 3.14 (1H, dd, *J* = 8.8, 7.6 Hz, CH-C10), 2.88 (1H, d, *J* = 15.9 Hz, CH_2-C8), 2.76–2.66 (2H, m, CH_2-C5,

CH-C14), 2.65 (1H, s, OH), 2.60 (1H, ddd, *J* = 9.6, 7.6, 2.4 Hz, CH-C1), 2.30−2.22 (2H, m, CH_2-C12), 2.20 (3H, s, CH_3-C16), 2.03−1.97 (1H, m, CH_2-C13), 1.97 (1H, dd, *J* = 15.9, 5.2 Hz, CH_2-C8), 1.93−1.86 (2H, m, CH_2-C4, CH_2-C5), 1.77 (3H, s, CH_3-C18), 1.41−1.32 (2H, m, CH_2-C4, CH_2-C13), 1.02 (3H, s, CH_3-C17); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.2 (C-C15), 144.3 (C-C11), 131.4 (C-C7), 129.6 (CH-C6), 112.6 (CH_2-C19), 93.7 (CH-C2), 78.6 (CH-C9), 72.7 (C-C3), 52.7 (CH-C14), 46.5 (CH-C10), 44.0 (CH-C1), 36.9 (CH_2-C4), 36.1 (CH_2-C8), 31.4 (CH_2-C12), 30.0 (CH_3-C16), 29.7 (CH_2-C13), 28.4 (CH_3-C18), 27.1 (CH_3-C17), 22.4 (CH_2-C5); HRMS (EI+) for $C_{19}H_{28}O_3$ $[M]^+$ calcd. 304.2038, found 304.2036, Δ −0.9 ppm; LRMS (EI+) *m/z* (intensity); 304.0 (19%), 286.1 (12%), 179.0 (100%), 95.0 (44%), 82.9 (73%).

1-[(1*R*,2*S*,3*S*,6*R*,7*S*,8R,10*Z*,14*S*)-14-Hydroxo-6,10,14-trimethyl-15-oxatricyclo [6.6.1.0^{2,7}]pentadec-10-en-3-yl]ethan-1-one (328) and **1-[(1*R*,2*S*,3*S*,6*S*,7*S*,8*R*,10*Z*,14*S*)-14-Hydroxo-6,10,14-trimethyl-15-oxatricyclo [6.6.1.0^{2,7}]pentadec-10-en-3-yl]ethan-1-one (329)**



$C_{19}H_{30}O_3$



$C_{19}H_{30}O_3$

Exocyclic ketone **326** (16.7 mg, 53.1 µmol) was dissolved in EtOAc (1.5 mL). Platinium oxide (1.4 mg, 6.2 µmol) was added and the suspension was purged 3 times with H_2. The mixture was stirred at room temperature under an atmosphere of H_2 for 0.3 h. The residue was filtered off and washed with EtOAc. The solvent was concentrated under *vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 3:1 to 1:1) delivered two epimers **328** (10.7 mg, 64%) and **329** (4.4 mg, 26%) as colourless solids.

1-[(1*R*,2*S*,3*S*,6*R*,7*S*,8*R*,10*Z*,14*S*)-14-Hydroxo-6,10,14-trimethyl-15-oxatricyclo [6.6.1.0^{2,7}]pentadec-10-en-3-yl]ethan-1-one (328)

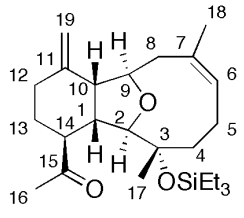
R_f = 0.26; (petroleum ether-ethyl acetate, 5:2); m.p. 82.9–84.8 °C; ν_{max} (film) 3583, 2923, 1708, 1445, 1377, 1354, 1315, 1237, 1166, 1088, 1050, 964, 873, 817 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.47 (1H, br d, *J* = 8.9 Hz, CH-C6), 4.05 (1H, t, *J* = 1.9 Hz, CH-C9), 3.86 (1H, d, *J* = 10.6 Hz, CH-C2), 3.38 (1H, s, OH), 2.96 (1H, dd, *J*= 10.6, 7.7 Hz, CH-C1), 2.79 (1H, br d, *J* = 14.7 Hz, CH_2-C8), 2.76–2.66 (1H, m, CH_2-C5), 2.63 (1H, t, *J* = 3.2 Hz, CH-C14), 2.16 (3H, s, CH_3-C16), 1.97–1.90 (1H, m, CH_2-C13), 1.90–1.87 (1H, m, CH-C10), 1.89 (3H, s, CH_3-C18), 1.87–1.78 (3H, m, CH_2-C4, CH_2-C5, CH_2-C8), 1.78–1.68 (1H, m, CH_2-C13), 1.56–1.47 (2H, m, CH_2-C4, CH_2-C12), 1.39–1.22 (1H, m, CH-C11), 1.08 (3H, s, CH_3-C17), 0.88 (1H, qd, *J* = 13.4, 3.2 Hz, CH_2-C12), 0.87 (3H, d, *J* = 6.4 Hz, CH_3-C19); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.2 (C-C15), 131.2 (C-C7), 129.8 (CH-C6), 87.2 (CH-C2), 80.9 (CH-C9), 73.9 (C-C3), 48.3 (CH-C10), 48.0 (CH-C14), 39.1 (CH-C1), 38.7 (CH_2-C8), 38.1 (CH_2-C4), 32.8 (CH-C11), 29.4 (CH_2-C12), 28.3 (CH_3-C16), 28.3 (CH_3-C18), 27.8 (CH_3-C17), 22.9 (CH_2-C13), 22.1 (CH_2-C5), 21.2 (CH_3-C19); HRMS (EI) for $C_{19}H_{30}O_3$ $[M]^+$ calcd. 306.2195, found 306.2197, Δ +0.8 ppm; LRMS *m/z* (intensity); 306.2 (27%), 181.1 (76%), 149.0 (43%), 82.9 (100%).

1-[(1*R*,2*S*,3*S*,6*S*,7*S*,8*R*,10*Z*,14*S*)-14-Hydroxo-6,10,14-trimethyl-15-oxatricyclo [6.6.1.0^{2,7}]pentadec-10-en-3-yl]ethan-1-one (329)

R_f = 0.33; (petroleum ether-ethyl acetate, 1:1); m.p. 117.4–119.4 °C; ν_{max} (film) 3448, 2921, 2861, 1711, 1453, 1356, 1167, 1080, 963, 937, 830, 768 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.70–5.64 (1H, m, CH-C6), 4.16 (1H, ddd, *J* = 8.7, 5.8, 3.3 Hz, CH-C9), 3.50 (1H, d, *J* = 1.6 Hz, CH-C2), 2.89 (1H, br d, *J* = 15.6 Hz, CH_2-C8), 2.72–2.64 (1H, m, CH_2-C5), 2.60 (1H, br s, OH), 2.59–2.51 (2H, m, CH-C1, CH_2-C4), 2.44–2.38 (1H, m, CH-C10), 2.18 (3H, s, CH_3-C16), 2.00 (1H, dd, *J* = 15.6, 5.8 Hz, CH_2-C8), 1.97–1.90 (1H, m, CH_2-C13), 1.90–1.84 (2H, m, CH_2-C4, CH_2-C5), 1.80 (3H, s, CH_3-C17 or CH_3-C18), 1.81–1.75 (1H, m, CH-C11), 1.57–1.52 (1H, m, CH_2-C12), 1.44–1.37 (1H, m, CH_2-C4), 1.37–1.22 (2H, m, CH_2-C12, CH_2-C13), 1.05 (3H, s, CH_3-C17 or CH_3-C18), 0.98 (3H, d, *J* = 7.2 Hz, CH_3-C19); ^{13}C NMR (126 MHz, $CDCl_3$) δ 211.3 (C-C15), 131.3 (C-C7), 129.9 (CH-C6), 93.6 (CH-C2), 77.7 (CH-C9), 73.2 (C-C3), 52.9 (CH-C14), 43.0 (CH-C1 or CH-C10), 42.6

(CH-C1 or CH-C10), 38.5 (CH_2-C8), 37.1 (CH_2-C4), 30.5 (CH-C11), 29.9 (CH_3-C16), 29.2 (CH_2-C12), 27.9 (CH_3-C17 or CH_3-C18), 27.3 (CH_3-C17 or CH_3-C18), 27.2 (CH_2-C13), 23.1 (CH_2-C5), 20.5 (CH_3-C19); HRMS (ESI) for $C_{19}H_{30}NaO_3$ $[M+Na]^+$ calcd. 329.2087, found 329.2092, Δ +1.4 ppm.

1-[(1*R*,2*R*,3*S*,7*S*,8*R*,10*Z*,14*S*)-10,14-Dimethyl-6-methylidene-14-(triethylsilyloxy)-15-oxatricyclo[6.6.1.0^{2,7}]pentadec-10-en-3-yl]ethan-1-one (330)



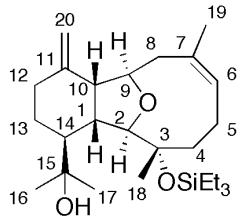
$C_{25}H_{42}O_3Si$

To a stirred solution of ketone **326** (95.0 mg, 312 μmol) in anhydrous CH_2Cl_2 (3.0 mL) and distilled 2,6-lutidine (0.20 mL, 1.72 mmol) at −78 °C was added triethylsilyl trifluoromethanesulfonate (0.15 mL, 0.66 mmol). The mixture was stirred for 1 h at −78 °C and the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (3 mL). The solution was allowed to warm to room temperature and was diluted with Et_2O (10 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 5 mL). The organic extracts were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 20:1 to 10:1) delivered the desired silyl ether **330** (0.12 g, 93%) as a colourless oil.

R_f = 0.26; (petroleum ether-ethyl acetate, 10:1); $[\alpha]_D^{27}$ −41.7 (*c* = 1.02, $CHCl_3$); ν_{max} (film) 3082, 2951, 2948, 2933, 2875, 1715, 1457, 1363, 1236, 1193, 1123, 1086, 1013, 992, 949, 847, 742, 668 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71 (1H, dd, *J* = 9.5, 9.0 Hz, CH-C6), 4.83 (1H, t, *J* = 1.9 Hz, CH_2-C19), 4.75 (1H, s, CH_2-C19), 4.26 (1H, ddd, *J* = 10.4, 5.2, 1.2 Hz, CH-C9), 3.58 (1H, s, CH-C2), 3.16−3.07 (2H, m, CH-C10, CH_2-C5), 2.91 (1H, d, *J* = 16.0 Hz, CH_2-C8), 2.77 (1H, ddd, *J* = 12.7, 11.0, 3.4 Hz, CH-C14), 2.42 (1H, dd, *J* = 11.0, 7.1 Hz, CH-C1),

2.28 (1H, dt, *J* = 13.7, 3.5 Hz, CH_2-C12), 2.25–2.20 (1H, m, CH_2-C12), 2.19 (3H, s, CH_3-C16), 2.00 (1H, dq, *J* = 12.7, 3.5 Hz, CH_2-C13), 1.93 (1H, dd, *J* = 16.0, 5.2 Hz, CH_2-C8), 1.90–1.83 (1H, m, CH_2-C4), 1.78–1.70 (1H, m, CH_2-C5), 1.73 (3H, s, CH_3-C18), 1.30–1.20 (2H, m, CH_2-C4, CH_2-C13), 1.04 (3H, s, CH_3-C17), 0.94 (9H, t, *J* = 7.9 Hz, CH_3-SiEt), 0.64–0.52 (6H, m, CH_2-SiEt); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.8 (C-C15), 144.5 (C-C11), 130.8 (C-C7), 130.3 (CH-C6), 112.9 (CH_2-C19), 95.1 (CH-C2), 78.8 (CH-C9), 75.3 (C-C3), 53.4 (CH-C14), 46.5 (CH-C10), 45.1 (CH-C1), 38.0 (CH_2-C4), 35.8 (CH_2-C8), 31.4 (CH_2-C12), 30.4 (CH_3-C16), 30.4 (CH_2-C13), 28.5 (CH_3-C17 or CH_3-C18), 28.4 (CH_3-C17 or CH_3-C18), 22.8 (CH_2-C5), 7.4 (CH_3-SiEt), 7.0 (CH_2-SiEt); HRMS (EI+) for $C_{25}H_{42}O_3Si$ $[M]^+$ calcd. 418.2903, found 418.2897, Δ −1.6 ppm; LRMS (EI+) *m/z* (intensity); 418.1 (86%), 389.1 (59%), 271.1 (62%), 225.1 (100%), 185.1 (80%); Anal. calcd. for $C_{25}H_{42}O_3Si$: C, 71.72%; H, 10.11%; found: C, 71.62%; H, 10.08%.

2-[(1*R*,2*R*,3*S*,7*S*,8*R*,10*Z*,14*S*)-10,14-Dimethyl-6-methylidene-14-(triethylsilyloxy)-15-oxatricyclo[6.6.1.0^{2,7}]pentadec-10-en-3-yl]propan-2-ol (331)



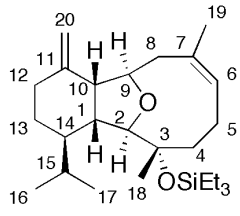
$C_{26}H_{46}O_3Si$

To a stirred solution of ketone **330** (235 mg, 561 μmol) in anhydrous THF (12 mL) was added methylmagnesium chloride (4.0 mL of a 3.0 M solution in THF, 12.0 mmol) dropwise. The mixture was stirred at room temperature for 3.5 h and the reaction was quenched by the addition a saturated aqueous solution of NH_4Cl (5 mL). The phases were separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The organic extracts were combined, washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 50:1 to 10:1) afforded the desired alcohol **331**

(218 mg, 84%) as a colourless oil and recovered the starting material **XX** (37.2 mg, 15%).

R_f = 0.77; (petroleum ether-ethyl acetate, 5:1); $[\alpha]_D^{26}$ −28.3 (*c* = 1.01, $CHCl_3$); ν_{max} (film) 3468, 2950, 2933, 2917, 2874, 1648, 1457, 1372, 1236, 1192, 1125, 1088, 1007, 968, 946, 895, 782, 741, 725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.61 (1H, dd, *J* = 10.6, 6.9 Hz, CH-C6), 4.76 (1H, s, CH_2-C20), 4.69 (1H, d, *J* = 1.8 Hz, CH_2-C20), 4.60 (1H, br s, CH-C2), 4.18 (1H, ddd, *J* = 8.3, 4.0, 2.6 Hz, CH-C9), 3.15−3.06 (1H, m, CH-C5), 2.92 (1H, t, *J* = 8.3 Hz, CH-C10), 2.82 (1H, d, *J* = 15.2 Hz, CH_2-C8), 2.29 (1H, td, *J* = 8.3, 2.0 Hz, CH-C1), 2.19 (2H, dd, *J* = 7.8, 4.4 Hz, CH_2-C12), 1.95−1.79 (4H, m, CH_2-C4, CH_2-C5, CH_2-C8, CH_2-C13), 1.77 (3H, s, CH_3-C19), 1.72 (1H, ddd, *J* = 11.1, 9.1, 4.3 Hz, CH-C14), 1.52−1.46 (1H, m, CH_2-C4), 1.26 (3H, s, CH_3-C16 or CH_3-C17), 1.25 (3H, s, CH_3-C16 or CH_3-C17), 1.18−1.15 (1H, m, CH_2-C13), 1.14 (3H, s, CH_3-C18), 0.95 (9H, t, *J* = 7.9 Hz, CH_3-SiEt), 0.61 (6H, m, CH_2-SiEt); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.5 (C-C11), 131.3 (C-C7), 130.2 (CH-C6), 110.0 (CH_2-C20), 93.3 (CH-C2), 79.9 (CH-C9), 77.4 (C-C15), 74.5 (C-C3), 48.1 (CH-C10), 46.9 (CH-C14), 44.7 (CH-C1), 39.5 (CH_2-C4), 35.8 (CH_2-C8), 31.3 (CH_3-C16 or CH_3-C17), 31.0 (CH_2-C12), 29.5 (CH_2-C13), 28.6 (CH_3-C16 or CH_3-C17 or CH_3-C19), 28.5 (CH_3-C16 or CH_3-C17 or CH_3-C19), 25.3 (CH_3-C18), 24.2 (CH_2-C5), 7.3 (CH_3-SiEt), 7.0 (CH_2-SiEt); HRMS (EI+) for $C_{26}H_{46}O_3Si$ [M^+] calcd. 434.3216, found 434.3208, Δ −1.8 ppm; LRMS (EI+) *m/z* (intensity); 434.2 (71%), 225.1 (92%), 185.1 (100%).

{[(1*R*,2*R*,6*R*,7*R*,8*R*,9*S*,12*Z*)-9,13--Dimethyl-3-methylidene-6-(propan-2-yl)-15-oxatricylo[6.6.1.$0^{2,7}$]pentadec-12-en-9-yl]oxy}triethylsilane (333)



$C_{26}H_{46}O_2Si$

To a stirred solution of alcohol **331** (85.0 mg, 195 μmol) in distilled triethylamine (0.60 mL, 4.33 mmol) were added recrystallised DMAP (119 mg, 974 μmol) and freshly distilled acetic anhydride (0.28 mL, 2.96 mmol). The

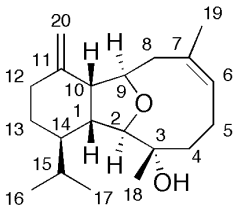
mixture was stirred at 40 °C for 2.5 h and the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (3 mL). The solution was diluted with Et_2O (5 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 5 mL). The organic extracts were combined, washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 20:1) removed baseline impurities. The crude acetate **332** was used in the next step without further purification.

Small, freshly cut pieces of oil-free potassium metal were added to a solution of recrystallised 18-crown-6 (0.26 g, 0.99 mmol) in freshly distilled *tert*-butylamine (10 mL). The mixture was stirred at room temperature for 30 min during which time the solution turned dark blue in colour. Anhydrous THF (10 mL) was added and the mixture was stirred for further 30 min. A solution of the crude acetate **332** in anhydrous THF (0.4 mL) was added slowly. After complete the addition of the substrate, the mixture was stirred for 1.5 h and the reaction was quenched by the addition of 2-propanol (5 mL) and a saturated aqueous solution of NH_4Cl (10 mL). The solution was diluted with Et_2O (10 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 5 mL). The organic extracts were combined, washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 50:1 to 10:1) delivered the silyl ether **333** (40.0 mg, 49%) as a colourless oil and the alcohol **272** (3.8 mg, 7%) as a colourless solid.

R_f = 0.61; (petroleum ether-ethyl acetate, 40:1); $[\alpha]_D^{23}$ −19.0 (*c* = 0.84, $CHCl_3$); ν_{max} (film) 2956, 2932, 2874, 1646, 1456, 1373, 1190, 1123, 1088, 1013, 992, 896, 727 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.69 (1H, dd, *J* = 9.3, 9.0 Hz, CH-C6), 4.77 (1H, t, *J* = 2.0 Hz, CH_2-C20), 4.66 (1H, s, CH_2-C20), 4.24 (1H, ddd, *J* = 10.3, 4.9, 1.3 Hz, CH-C9), 3.89 (1H, s, CH-C2), 3.21−3.13 (1H, m, CH_2-C5), 3.06 (1H, dd, *J* = 10.3, 7.5 Hz, CH-C10), 2.88 (1H, d, *J* = 15.9 Hz, CH_2-C8), 2.22 (1H, dt, *J* = 13.3, 3.2 Hz, CH_2-C12), 2.13−2.06 (1H, m, CH_2-C12), 1.92 (1H, dd, *J* = 15.9, 4.9 Hz, CH_2-C8), 1.89−1.75 (5H, m, CH-C1, CH_2-C4, CH_2-C5, CH_2-C13, CH-C15), 1.74 (3H, s, CH_3-C19), 1.40−1.33 (1H, m, CH-C14), 1.28−1.23 (1H, m, CH_2-C4), 1.05 (3H, s, CH_3-C18), 0.98 (3H, d, *J* = 6.9 Hz, CH_3-C16 or CH_3-C17), 0.96 (9H, d, *J* = 6.9 Hz, CH_3-SiEt), 0.89−0.81 (1H, m, CH_2-C13), 0.70 (3H, d, *J* = 6.9 Hz, CH_3-C16

or CH_3-C17), 0.67–0.55 (6H, m, CH_2-SiEt); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.3 (C-C11), 131.3 (C-C7), 130.0 (CH-C6), 111.0 (CH_2-C20), 93.7 (CH-C9), 78.8 (CH-C2), 75.7 (C-C3), 47.6 (CH-C10), 47.2 (CH-C1), 43.9 (CH-C14), 38.2 (CH_2-C4), 35.9 (CH_2-C8), 31.9 (CH_2-C12), 28.6 (CH_3-C18, CH_3-C19), 28.0 (CH-C15), 26.0 (CH_2-C13), 23.1 (CH_2-C5), 22.1 (CH_3-C16 or CH_3-C17), 15.4 (CH_3-C16 or CH_3-C17), 7.4 (CH_3-SiEt), 7.1 (CH_2-SiEt); HRMS (ESI) for $C_{26}H_{46}NaO_2Si$ $[M+Na]^+$ calcd. 441.3159, found 441.3144, Δ −3.4 ppm.

(1*R*,2*R*,6*R*,7*R*,8*R*,9*S*,12*Z*)-9,13--Dimethyl-3-methylidene-6-(propan-2-yl)-15-oxatricylo[6.61.0^{2,7}]pentadec-12-en-9-ol (272)



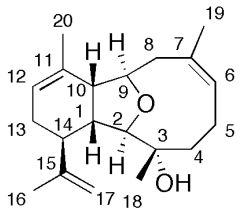
$C_{20}H_{32}O_2$

To a stirred solution of silyl ether **333** (40.0 mg, 95.5 μmol) in MeOH (0.95 mL) at 0 °C was added concentrated HCl (0.2 mL). The mixture was stirred at 0 °C for 3 h and the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (3 mL). The solution was diluted with Et_2O (5 mL) and the aqueous phase was extracted with Et_2O (3 × 5 mL). The organic extracts were combined, washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 25:1 to 10:1) delivered the desired alcohol **272** (27.4 mg, 95%) as a colourless solid.

R_f = 0.32; (petroleum ether-ethyl acetate, 5:1); m.p. 106.2–108.2 °C; $[\alpha]_D^{25}$ −69.2 (*c* = 0.87, $CHCl_3$); ν_{max} (film) 3414, 2959, 2938, 2869, 1646, 1456, 1373, 1198, 1118, 1085, 1058, 1022, 974, 898, 837, 821, 763, 653 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.74–5.67 (1H, m, CH-C6), 4.80 (1H, t, *J* = 1.6 Hz, CH_2-C20), 4.69 (1H, s, CH_2-C20), 4.30 (1H, ddd, *J* = 9.6, 4.9, 0.9 Hz, CH-C9), 3.87 (1H, s, CH-C2), 3.09 (1H, dd, *J* = 9.6, 7.3 Hz, CH-C10), 2.86 (1H, d, *J* = 16.0 Hz, CH_2-C8), 2.78–2.70 (1H, m, CH_2-C5), 2.23 (1H, dt, *J* = 13.4, 3.9 Hz, CH_2-C12), 2.14–2.06 (1H, m, CH_2-C12), 1.97–1.81 (5H, m, CH-C1, CH_2-C4, CH_2-C5, CH_2-C8, CH-C15),

1.75 (3H, s, CH_3-C19), 1.77–1.71 (1H, m, CH_2-C13), 1.60 (1H, br s, OH), 1.38–1.31 (2H, m, CH_2-C4, CH-C14), 1.13–1.03 (1H, m, CH_2-C13), 1.02 (3H, s, CH_3-C18), 0.97 (3H, d, *J* = 6.9 Hz, CH_3-C16 or CH_3-C17), 0.73 (3H, d, *J* = 6.9 Hz, CH_3-C16 or CH_3-C17); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.7 (C-C11), 131.7 (C-C7), 129.3 (CH-C6), 111.2 (CH_2-C20), 92.8 (CH-C2), 78.8 (CH-C9), 72.9 (C-C3), 47.4 (CH-C10), 46.5 (CH-C1), 43.7 (CH-C14), 36.9 (CH_2-C4), 36.0 (CH_2-C8), 31.7 (CH_2-C12), 28.5 (CH_3-C19), 28.1 (CH-C15), 27.1 (CH_3-C18), 25.8 (CH_2-C13), 22.6 (CH_2-C5), 22.1 (CH_3-C16 or CH_3-C17), 15.8 (CH_3-C16 or CH_3-C17); HRMS (ESI) for $C_{20}H_{32}NaO_2$ $[M+Na]^+$ calcd. 327.2295, found 327.2284, Δ −3.3 ppm.

(1*R*,2*R*,6*S*,7*R*,8*R*,9S,12*Z*)-3,9,13-Trimethyl-6-(prop-1-en-2-yl)-15-oxatricyclo [6.6.1.0^{2,7}]pentadeca-3,12-dien-9-ol (334)



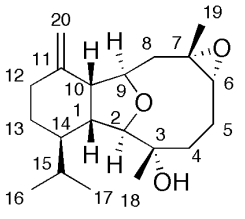
$C_{20}H_{30}O_2$

Triene **325** (26.0 mg, 85.9 μmol) was dissolved in EtOAc (4.4 mL). Pd/C (~10 mol%) was added and the solution was purged 3 times with H_2. The mixture was stirred at room temperature under an atmosphere of H_2 for 16 h. The catalyst was filtered off through a pad of celite and the solvent was removed *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, 10:1) afforded **334** (5.80 mg, 22%) as a colourless solid and recovered the starting material **325** (11.5 mg, 44%).

R_f = 0.24; (petroleum ether-ethyl acetate, 5:1); m.p. 102.3–104.9 °C; ν_{max} (film) 3416, 2964, 2919, 1452, 1376, 1321, 1274, 1203, 1119, 1090, 1057, 973, 902, 839, cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.59 (1H, dd, *J* = 10.2, 3.9 Hz, CH-C6), 5.47 (1H, br s, CH-C12), 4.79 (1H, quint, *J* = 1.4 Hz, CH_2-C17), 4.75 (1H, s, CH_2-C17), 4.17–4.13 (1H, m, CH-C9), 3.86 (1H, d, *J* = 6.6 Hz, CH-C2), 3.13 (1H, s, OH), 2.88 (1H, d, *J* = 15.0 Hz, CH_2-C8), 2.78–2.70 (1H, m, CH_2-C5), 2.54–2.47 (2H, m, CH-C1, CH-C10), 2.23–2.15 (2H, m, CH_2-C13, CH-C14), 2.12–2.04 (1H, m, CH_2-C13), 1.94 (1H, dd, *J* = 15.0, 4.5 Hz, CH_2-C8), 1.92–1.77 (2H, m, CH_2-C4,

CH_2-C5), 1.82 (3H, s, CH_3-C19), 1.70 (3H, s, CH_3-C16), 1.66 (3H, s, CH_3-C20), 1.59−1.51 (1H, m, CH_2-C4), 1.09 (3H, s, CH_3-C18); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.2 (C-C11 or C-C15), 132.4 (C-C11 or C-C15), 130.7 (C-C7), 130.4 (CH-C6), 121.3 (CH-C12), 111.3 (CH_2-C17), 89.1 (CH-C2), 79.9 (CH-C9), 73.7 (C-C3), 45.2 (CH-C1 or CH-C10), 42.6 (CH-C1 or CH-C10), 40.1 (CH-C14), 38.8 (CH_2-C8), 37.8 (CH_2-C4), 28.7 (CH_3-C19), 27.4 (CH_3-C18), 26.0 (CH_2-C13), 22.6 (CH_3-C20), 22.6 (CH_2-C5), 21.5 (CH_3-C16); HRMS (ESI) for $C_{20}H_{30}NaO_2$ [M+Na$^+$] calcd. 325.2138, found 325.2126, Δ −3.7 ppm.

(1*R*,3*S*,5*R*,8*S*,9*R*,10*R*,11*R*,15*R*)-3,8-Dimethyl-14-methylidene-11-(propan-2-yl)-4,16-dioxatetracyclo[7.6.1.0^{3,5}.0^{10,15}]hexadecan-8-ol (338)



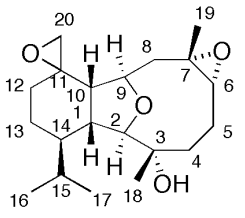
$C_{20}H_{32}O_3$

To a stirred solution of diene **272** (78.0 mg, 256 μmol) in anhydrous CH_2Cl_2 (2.3 mL) at 0 °C was added a solution of *m*-CPBA (2.6 mL of a 0.15 M solution in CH_2Cl_2, 384 μmol). The mixture was stirred at 0 °C for 2.5 h and the reaction was quenched by the addition of a saturated aqueous solution of $Na_2S_2O_3$ (6 mL). The solution was diluted with Et_2O (10 mL) and the phases were separated. The aqueous phase was extracted with Et_2O (3 × 6 mL). The organic extracts were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 5:1 to 3:1) delivered the epoxide **338** as a colourless solid (74.2 mg, 91%).

R_f = 0.33; (petroleum ether-ethyl acetate, 2:1); $[\alpha]_D^{30}$ +62.9 (*c* = 0.62, $CHCl_3$); ν_{max} (film) 3430, 2959, 2929, 2892, 2873, 1645, 1454, 1377, 1186, 1090, 1071, 1056, 1027, 983, 901, 879, 845, 775, 736, 681 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.93 (1H, s, CH_2-C20), 4.85 (1H, s, CH_2-C20), 4.42 (1H, ddd, *J* = 6.7, 5.6, 1.8 Hz, CH-C9), 3.81 (1H, d, *J* = 3.8 Hz, CH-C2), 3.06 (1H, dd, *J* = 7.9, 6.7 Hz, CH-C10), 2.84 (1H, dd, *J* = 11.1, 4.0 Hz, CH-C6), 2.69 (1H, br s, OH), 2.24−2.06 (6H, m,

CH-C1, CH_2-C5, CH_2-C8, CH_2-C12), 2.04–1.97 (1H, m, CH_2-C5), 1.95–1.87 (1H, m, CH_2-C4), 1.86–1.81 (1H, m, CH-C15), 1.77–1.71 (1H, m, CH_2-C13), 1.63–1.56 (1H, m, CH_2-C4), 1.43 (3H, s, CH_3-C19), 1.42–1.28 (2H, m, CH_2-C13, CH-C14), 1.11 (3H, s, CH_3-C18), 0.99 (3H, d, *J* = 6.8 Hz, CH_3-C16 or CH_3-C17), 0.80 (3H, d, *J* = 6.8 Hz, CH_3-C16 or CH_3-C17); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.4 (C-C11), 111.2 (CH_2-C20), 90.9 (CH-C2), 77.5 (CH-C9), 73.8 (C-C3), 65.7 (CH-C6), 59.7 (C-C7), 48.1 (CH-C10), 46.6 (CH-C1), 42.9 (CH-C14), 39.3 (CH_2-C8), 33.2 (CH_2-C4), 31.6 (CH_2-C12), 28.5 (CH-C15), 27.6 (CH_3-C19), 27.1 (CH_3-C18), 26.3 (CH_2-C13), 24.3 (CH_2-C5), 22.2 (CH_3-C16 or CH_3-C17), 16.8 (CH_3-C16 or CH_3-C17); HRMS (ESI) for $C_{20}H_{32}NaO_3$ [M+Na$^+$] calcd. 343.2244, found 343.2236, Δ −2.4 ppm.

(1'*R*,3'*S*,5'*R*,8'*S*,9'*R*,10'*S*,11'*R*,15'*S*)-3',8'-Dimethyl-11'-(propan-2-yl)-4',16'-dioxaspiro[oxirane-2,14'-tetracyclo[7.6.1.0.^{3,5}0^{10,15}]hexadecane-8'-ol (339)

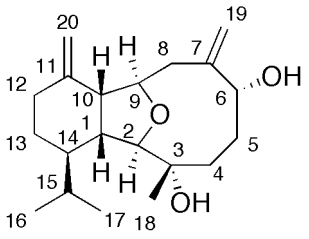


$C_{20}H_{32}O_4$

Colourless oil; R_f = 0.63; (ethyl acetate); ν_{max} (neat) 3494, 2961, 2932, 2872, 1453, 1379, 1107, 1040, 958, 860, 750, 635 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.85 (1H, d, *J* = 11.0 Hz, CH-C9), 3.69 (1H, t, *J* = 3.3 Hz, CH-C2), 3.20 (1H, s, OH), 2.83 (1H, dd, *J* = 4.2, 1.8 Hz, CH_2-C20), 2.74 (1H, dd, *J* = 10.9, 2.9 Hz, CH-C6), 2.69 (1H, d, *J* = 5.9 Hz, CH-C1), 2.59 (1H, dd, *J* = 11.0, 5.9 Hz, CH-C10), 2.54 (1H, dd, *J* = 4.2, 0.9 Hz, CH_2-C20), 2.07–1.95 (5H, m, CH_2-C4, CH_2-C5, CH_2-C12, CH_2-C8), 1.93–1.84 (2H, m, CH_2-C5, CH_2-C13), 1.82–1.78 (1H, m, CH-C15), 1.70 (1H, dt, *J* = 14.1, 3.8 Hz, CH_2-C12), 1.65 (1H, dd, *J* = 14.7, 7.5 Hz, CH_2-C4), 1.40–1.37 (1H, m, CH-C14), 1.38 (3H, s, CH_3-C18), 1.19–1.15 (1H, m, CH_2-C13), 1.17 (3H, s, CH_3-C19), 1.08 (3H, d, *J* = 6.4 Hz, CH_3-C16 or CH_3-C17), 0.98 (3H, d, *J* = 6.4 Hz, CH_3-C16 or CH_3-C17); ^{13}C NMR (125 MHz, $CDCl_3$) δ 86.4 (CH-C9), 73.8 (C-C3), 73.3 (CH-C2), 66.3 (CH-C6), 59.4 (C-C7 or C-C11), 57.6 (C-C7 or C-C11), 52.2 (CH_2-C20), 44.2 (CH-C1), 42.7 (CH-C10), 41.1 (CH_2-C8), 39.6 (CH-C14), 34.0 (CH_2-C4), 29.4 (CH_2-C13), 29.3 (CH-C15), 27.8 (CH_3-C18), 26.6 (CH_3-C19), 23.2

(CH_2-C12), 22.7 (CH_2-C5), 22.7 (CH_3-C16 or CH_3-C17), 20.7 (CH_3-C16 or CH_3-C17); HRMS (ESI) for $C_{20}H_{32}NaO_4$ $[M+Na]^+$ calcd. 359.2193, found 359.2179, Δ −3.7 ppm.

(1*R*,2*R*,6*R*,7*R*,8*R*,9*S*,12*R*)-9-Methyl-3,13-dimethylidene-6-(propan-2-yl)-15-oxatricyclo[6.6.1.$0^{2,7}$]pentadecane-9,12-diol (340)



$C_{20}H_{32}O_3$

Method A: Scandium triflate and $KHSO_4$

To a stirred solution of epoxide **338** (12.5 mg, 39 µmol) in a mixture (1:1) of THF and water (0.8 mL) were added potassium bisulfate (208 mg, 1.53 mmol) and scandium triflate (38 mg, 77 µmol). The mixture was stirred at room temperature for 24 h and the reaction was quenched by the addition of a saturated aqueous solution of Na_2CO_3 (3 mL). The solution was diluted with water (1.5 mL) and EtOAc (5 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 5:1 to 1:1) afforded the allylic alcohol **340** (7.90 mg, 63%) as a colourless solid.

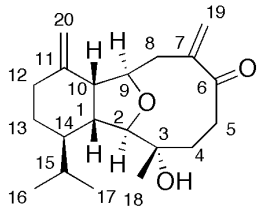
Method B: H_2SO_4

To a stirred solution of epoxide **338** (43.0 mg, 0.13 mmol) in a mixture (1:1) of THF and water (2.60 mL) was added sulphuric acid (0.15 mL, 2.81 mmol). The mixture was stirred at room temperature for 30 h and the reaction was quenched by the addition of a saturated aqueous solution of Na_2CO_3 (5 mL). The solution was diluted with water (6 mL) and EtOAc (6 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 8 mL). The organic extracts were combined, washed with brine (15 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column

chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 5:1 to pure ethyl acetate) delivered the allylic alcohol **340** (33.2 mg, 77%) as a colourless solid and the triol **341** (7.2 mg, 15%).

R_f = 0.29; (petroleum ether-ethyl acetate, 1:1); m.p. 168–170 °C; $[\alpha]_D^{27}$ +9.0 (*c* = 0.16, $CHCl_3$); ν_{max} (film) 3403, 2957, 2932, 2871, 1646, 1458, 1370 1183, 1066, 1040, 969, 939, 897, 833, 732, 668 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.68 (1H, d, *J* = 10.4 Hz, OH-C6), 5.07 (1H, s, CH_2-C19), 5.06 (1H, s, CH_2-C19), 4.84 (1H, t, *J* = 2.0 Hz, CH_2-C20), 4.73 (1H, s, CH_2-C20), 4.53–4.51 (1H, m, CH-C6), 4.13 (1H, ddd, *J* = 10.5, 4.8, 1.1 Hz, CH-C9), 3.94 (1H, s, CH-C2), 3.22 (1H, dd, *J* = 10.4, 7.7 Hz, CH-C10), 3.13 (1H, br s, OH-C3), 2.98 (1H, dd, *J* = 14.5, 4.8 Hz, CH_2-C8), 2.32–2.22 (3H, m, CH_2-C5, CH_2-C8, CH_2-C12), 2.11–2.05 (1H, m, CH_2-C12), 1.95–1.82 (4H, m, CH-C1, CH_2-C4, CH_2-C5, CH-C15), 1.76 (1H, qd, *J* = 13.1, 3.3 Hz, CH_2-C13), 1.56–1.49 (1H, m, CH_2-C4), 1.35–1.27 (1H, m, CH-C14), 1.10 (3H, s, CH_3-C18), 1.01 (1H, qd, *J* = 13.1, 3.1 Hz, CH_2-C13), 0.98 (3H, d, *J* = 6.9 Hz, CH_3-C16 or CH_3-C17), 0.72 (3H, d, *J* = 6.9 Hz, CH_3-C16 or CH_3-C17); ^{13}C NMR (126 MHz, $CDCl_3$) δ 147.4 (C-C7 or C-C11), 145.7 (C-C7 or C-C11), 116.3 (CH_2-C19), 111.9 (CH_2-C20), 94.6 (CH-C2), 78.8 (CH-C9), 74.0 (C-C3), 72.4 (CH-C6), 47.2 (CH-C10), 45.9 (CH-C1), 44.3 (CH-C14), 35.5 (CH_2-C8), 35.0 (CH_2-C5), 31.7 (CH_2-C4), 31.7 (CH_2-C12), 29.1 (CH_3-C18), 28.0 (CH-C15), 25.3 (CH_2-C13), 22.1 (CH_3-C16 or CH_3-C17), 15.2 (CH_3-C16 or CH_3-C17); HRMS (CI+, Me_3CH) for $C_{20}H_{33}O_3$ $[M+H]^+$ calcd. 321.2430, found 321.2426, Δ −1.2 ppm; LRMS *m/z* (intensity); 321.0 (96%), 303.0 (100%).

(1*R*,2*R*,3*R*,7*R*,8*R*,14*S*)-14-Hydroxy-14-methyl-6,10-dimethylidene-3-(proparyl)-15-oxatricyclo[6.6.1.$0^{2,7}$]pentadecan-11-one (345)



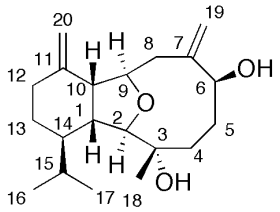
$C_{20}H_{30}O_3$

To a stirred solution of allylic alcohol **340** (8.7 mg, 27 μmol) in anhydrous CH_2Cl_2 (1.40 mL) was added Dess-Martin periodinane (15.7 mg, 37.0 μmol). The mixture was stirred at room temperature for 2 h and the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (1 mL) and $Na_2S_2O_3$ (1 mL). The solution was stirred vigorously at room temperature for an additional 15 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The organic extracts were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the enone **345** (8.80 mg, 100%) as a colourless solid.

R_f = 0.62; (petroleum ether-ethyl acetate, 1:1); m.p. 160.6–161.9 °C; $[\alpha]_D^{27}$ −66.3 (*c* = 0.33, $CHCl_3$); ν_{max} (film) 3568, 2962, 2939, 2882, 2855, 1676, 1431, 1382, 1304, 1078, 1029, 983, 924 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.44 (1H, s, CH_2-C19), 5.31 (1H, s, CH_2-C19), 4.85 (1H, t, *J* = 2.0 Hz, CH_2-C20), 4.69 (1H, s, CH_2-C20), 4.08 (1H, dd, *J* = 10.7, 5.2 Hz, CH-C9), 3.80 (1H, s, CH-C2), 3.26 (1H, ddd, *J* = 13.6, 5.2, 1.0 Hz, CH_2-C8), 3.04 (1H, dd, *J* = 10.7, 7.9 Hz, CH-C10), 2.85–2.75 (2H, m, CH_2-C5), 2.45 (1H, s, OH), 2.28 (1H, dt, *J* = 13.8, 3.1 Hz, CH_2-C12), 2.25 (1H, d, *J* = 13.6 Hz, CH_2-C8), 2.08 (1H, ddd, *J* = 15.4, 11.4, 4.8 Hz, CH_2-C4), 2.06–1.98 (1H, m, CH_2-C12), 1.88–1.78 (2H, m, CH-C1, CH-C15), 1.76–1.68 (2H, m, CH_2-C4, CH_2-C13), 1.33–1.20 (1H, m, CH-C14), 1.10 (3H, s, CH_3-C18), 1.00 (1H, qd, *J* = 13.0, 3.1 Hz, CH_2-C13), 0.96 (3H, d, *J* = 6.9 Hz, CH_3-C16 or CH_3-C17), 0.71 (3H, d, *J* = 6.9 Hz, CH_3-C16 or CH_3-C17); ^{13}C NMR (126 MHz, $CDCl_3$) δ 207.7 (C-C6), 146.4 (C-C7 or C-C11), 145.6 (C-C7 or C-C11), 117.9 (CH_2-C19), 111.8 (CH_2-C20), 93.6 (CH-C2), 78.2 (CH-C9), 74.0 (C-C3), 47.2 (CH-C10), 45.2 (CH-C1), 44.7 (CH-C14), 39.4 (CH_2-C5), 36.7 (CH_2-C8), 33.1 (CH_2-C4), 31.9 (CH_2-C12), 27.7 (CH-C15), 27.4 (CH_3-C18), 25.2 (CH_2-C13), 22.1 (CH_3-C16 or CH_3-C17), 15.1 (CH_3-C16 or CH_3-C17); HRMS (EI+) for $C_{20}H_{30}O_3$ $[M]^+$ calcd.

318.2195, found 318.2192, Δ −0.8 ppm; LRMS (EI+) *m/z* (intensity); 318.3 (15%), 300.3 (17%), 162.2 (22%).

(1*R*,2*R*,6*R*,7*R*,8*R*,9*S*,12*S*)-9-Methyl-3,13-dimethylidene-6-(propan-2-yl)-15-oxatricyclo[6.6.1.$0^{2,7}$]pentadecane-9,12-diol (346)



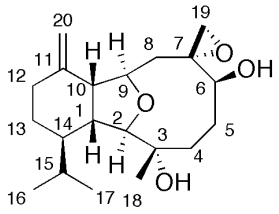
$C_{20}H_{32}O_3$

To a stirred solution of enone **345** (8.8 mg, 27 μmol) in MeOH (1.35 mL) at 0 °C were added cerium chloride heptahydrate (11.5 mg, 30.5 μmol) and sodium borohydride (2.3 mg, 74. μmol). The mixture was stirred at 0 °C for 30 min and the reaction was quenched by the addition of a 1 M aqueous solution of HCl (0.5 mL) and brine (0.5 mL). The solution was diluted with cold EtOH (1 mL) and a saturated aqueous solution of NH_4Cl (1 mL). The phases were separated and the aqueous phase extracted with EtOAc (3 × 5mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vaccuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 5:1 to pure ethyl acetate) afforded alcohols **340** (3.30 mg, 38%) and **346** (5.00 mg, 57%) as colourless solids.

R_f = 0.41; (ethyl acetate); m.p. 149.3–152.5 °C; $[\alpha]_D^{25}$ −23.8 (*c* = 0.83, $CHCl_3$); ν_{max} (film) 3409, 3070, 2957, 2930, 2909, 2862, 1645, 1448, 1371, 1192, 1082, 1063, 1030, 1006, 923, 894, 794 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.46 (1H, br s, CH_2-C19), 5.13 (1H, s, CH_2-C19), 4.82 (1H, t, *J* = 2.0 Hz, CH_2-C20), 4.69 (1H, t, *J* = 2.0 Hz, CH_2-C20), 4.48 (1H, dd, *J* = 10.8, 4.9 Hz, CH-C6), 4.15 (1H, ddd, *J* = 10.5, 4.9, 1.2 Hz, CH-C9), 3.76 (1H, s, CH-C2), 3.06 (1H, dd, *J* = 10.5, 7.8 Hz, CH-C10), 2.78 (1H, ddd, *J* = 13.7, 4.9, 1.2 Hz, CH_2-C8), 2.32–2.24 (3H, m, CH_2-C5, CH_2-C8, CH_2-C12), 2.08– 2.00 (1H, m, CH_2-C12), 1.87–1.79 (2H, m, CH-C1, CH-C15), 1.74 (1H, dq, *J* = 13.0, 3.3 Hz, CH_2-C13), 1.68–1.50 (5H, m, OH-C3, CH_2-C4, CH_2-C5, OH-C6), 1.33–1.23 (1H, m, CH-C14), 1.08 (3H, s, CH_3-C18), 1.00 (1H, qd, *J* = 13.0, 3.3 Hz, CH_2-C13), 0.97 (3H, d, *J* = 6.9 Hz, CH_3-C16 or CH_3-

C17), 0.71 (3H, d, *J* = 6.9 Hz, CH_3-C16 or CH_3-C17); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.4 (C-C7 or C-C11), 146.1 (C-C7 or C-C11), 116.8 (CH_2-C19), 111.6 (CH_2-C20), 92.8 (CH-C2), 79.9 (CH-C9), 74.5 (C-C3), 72.5 (CH-C6), 47.2 (CH-C10), 45.3 (CH-C1), 44.6 (CH-C14), 39.0 (CH_2-C8), 34.4 (CH_2-C5), 32.6 (CH_2-C4), 31.9 (CH_2-C12), 28.6 (CH_3-C18), 27.9 (CH-C15), 25.3 (CH_2-C13), 22.1 (CH_3-C16 or CH_3-C17), 15.2 (CH_3-C16 or CH_3-C17); HRMS (ESI) for $C_{20}H_{32}NaO_3$ $[M+Na]^+$ calcd. 343.2244, found 343.2232, Δ −3.5 ppm.

(1'*R*,2*R*,2'*R*,3'*R*,7'*R*,8'*R*,11'*S*,14'*S*)-14'-Methyl-6'-methylidene-3'-(propan-2-yl)-15'-oxaspiro[oxirane-2,10'-tricyclo [6.6.1.0^{2,7}]pentadecane]-11',14'-diol (347)

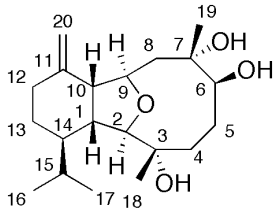


$C_{20}H_{32}O_4$

In a round bottom flask charged with 4 Å powdered molecular sieves in CH_2Cl_2 (1.0 mL) at −20 °C were added successively freshly distilled (+)-diethyl tartrate (80 µL of a 116 µmol/mL solution in CH_2Cl_2, 9.3 µmol), freshly distilled titanium tetraisopropoxide (90 µL of a 67.5 µmol/mL solution in CH_2Cl_2, 6.1 µmol) and *tert*-butylhydroperoxide (60 µL of a 1.9 M solution in CH_2Cl_2, 0.11 mmol). The solution was stirred at −20 °C for 30 min and allylic alcohol **346** (19.0 mg, 59.3 µmol) in CH_2Cl_2 (1.0 mL) was added dropwise. The mixture was stirred for 22 h at −20 °C and the reaction was quenched by the addition of water (1 mL) and 30% wt solution of NaOH in brine (5 mL). The solution was allowed to warm to room temperature and was stirred for an additional 1 h. The mixture was diluted with CH_2Cl_2 (10 mL) and the aqueous phase was extracted with CH_2Cl_2 (3 × 6 mL). The organic extracts were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (dichloromethane-methanol, gradient elution from dichloromethane to 2% methanol) delivered the desired epoxyalcohol **347** (17.8 mg, 89%) as colourless crystals.

R_f = 0.35; (dichloromethane-methanol, 40:1); m.p. 168.1–170.3 °C; $[\alpha]_D^{24}$ +19.7 (*c* = 1.22, $CHCl_3$); ν_{max} (film) 3462, 2956, 2933, 2868, 1646, 1452, 1373, 1189, 1084, 1049, 1031, 927, 893, 846, 788, 736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.82 (1H, t, *J* = 1.6 Hz, CH_2-C20), 4.63 (1H, s, CH_2-C20), 4.41 (1H, ddd, *J* = 10.2, 5.2, 4.8 Hz, CH-C6), 4.24 (1H, ddd, *J* = 10.7, 4.9, 1.5 Hz, CH-C9), 3.84 (1H, s, CH-C2), 3.12 (1H, dd, *J* = 4.6, 1.8 Hz, CH_2-C19) 3.09 (1H, dd, *J* = 10.7, 7.7 Hz, CH-C10), 2.98 (1H, d, *J* = 4.6 Hz, CH_2-C19), 2.71 (1H, ddd, *J* = 14.5, 4.9, 1.8 Hz, CH_2-C8), 2.53 (1H, d, *J* = 4.8 Hz, OH-C6), 2.37–2.28 (1H, m, CH_2-C5), 2.27–2.22 (1H, m, CH_2-C12), 2.23 (1H, br s, OH-C3), 2.09–2.01 (1H, m, CH_2-C12), 1.92 (1H, dd, *J* = 11.0, 7.7 Hz, CH-C1), 1.89–1.82 (1H, m, CH-C15), 1.77–1.67 (2H, m, CH_2-C4, CH_2-C13), 1.60 (1H, dt, *J* = 15.5, 4.8 Hz, CH_2-C4), 1.37 (1H, dd, *J* = 14.5, 1.5 Hz, CH_2-C8), 1.37–1.30 (1H, m, CH-C14), 1.26–1.18 (1H, m, CH_2-C5), 1.11 (3H, s, CH_3-C18), 1.02 (1H, qd, *J* = 13.6, 3.3 Hz, CH_2-C13), 0.97 (3H, d, *J* = 6.8 Hz, CH_3-C16 or CH_3-C17), 0.73 (3H, d, *J* = 6.8 Hz, CH_3-C16 or CH_3-C17); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.9 (C-C11), 111.7 (CH_2-C20), 93.0 (CH-C2), 79.1 (CH-C9), 74.4 (C-C3), 69.5 (CH-C6), 59.0 (C-C7), 53.0 (CH_2-C19), 48.6 (CH-C10), 45.7 (CH-C1), 44.2 (CH-C14), 37.6 (CH_2-C8), 32.1 (CH_2-C5), 31.9 (CH_2-C4), 31.5 (CH_2-C12), 28.4 (CH_3-C18), 28.0 (CH-C15), 25.4 (CH_2-C13), 22.0 (CH_3-C16 or CH_3-C17), 15.2 (CH_3-C16 or CH_3-C17); HRMS (ESI) for $C_{20}H_{32}NaO_4$ $[M+Na]^+$ calcd. 359.2193, found 359.2185, Δ −2.2 ppm.

(1*R*,2*R*,6*R*,7*R*,8*R*,9*S*,12*S*-13*S*)-9,13-Dimethyl-3-methylidene-6-(propan-2-yl)-15-oxatricyclo[6.6.1.0^{2,7}]pentadecane-9,12,13-triol – proposed structure of sclerophytin F (10)[13]



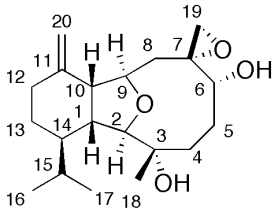
$C_{20}H_{34}O_4$

To a stirred solution of epoxyalcohol **347** (12.0 mg, 35.6 μmol) in anhydrous CH_2Cl_2 (2.0 mL) was added DIBAL-H (400 μL of a 1.0 M solution in CH_2Cl_2, 400 μmol) at 0 ºC. The mixture was stirred at room temperature for 72 h and the

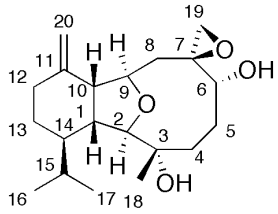
reaction was quenched by the addition of a saturated aqueous solution of sodium potassium tartrate (2 mL). The solution was diluted with CH_2Cl_2 (1 mL) and was vigorously stirred at room temperature until the clear phases formed. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The organic extracts were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (dichloromethane-methanol, gradient elution from pure to 2%) afforded the triol **10** (5.1 mg, 45%) as a colourless oil.
R_f = 0.26; (ethyl acetate); $[\alpha]_D^{25}$ +51.0 (*c* = 0.20, $CHCl_3$); ν_{max} (film) 3422, 2960, 2932, 2928, 1462, 1374, 1260, 1088, 1067, 1026, 1009, 920, 888, 803, 743 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$)[164] δ 4.91 (1H, s, CH_2-C20), 4.85 (1H, s, CH_2-C20), 4.75 (1H, d, *J* = 10.1 Hz, CH-C9), 4.64 (1H, br s, CH-C6), 3.72 (1H, d, *J* = 8.7 Hz, CH-C2), 2.50 (1H, d, *J* = 6.1 Hz, CH-C10), 2.40–2.33 (1H, m, CH-C1), 2.17–2.04 (4H, m), 1.93–1.85 (1H, ddd, *J* = 15.5, 12.9, 3.3 Hz), 1.84–1.69 (4H, m), 1.69 (1H, dd, *J* = 15.2, 3.6 Hz), 1.66–1.48 (4H, m), 1.42–1.36 (1H, m, CH-C14), 1.19 (3H, s, CH_3-C18), 1.09 (3H, s), 1.01 (3H, d, *J* = 6.6 Hz, CH_3-C16), 0.93 (3H, d, *J* = 6.6 Hz, CH_3-C17); ^{13}C NMR (151 MHz, $CDCl_3$) δ 146.1 (C-C11), 107.9 (CH_2-C20), 87.0 (CH-C2), 75.8 (CH-C9), 75.4 (CH-C6), 75.1 (C-C3 or C-C7), 73.9 (C-C3 or C-C7), 47.8 (CH-C10), 45.2 (CH_2-C8), 42.3 (CH-C1), 40.5 (CH-C14), 33.2 (CH_2-C4), 30.3 (CH_2-C12), 29.8 (CH_2-C5), 29.4 (CH-C15), 28.5 (CH_3-C18), 24.8 (CH_2-C13), 22.7 (CH_3-C19), 22.2 (CH_3-C16), 20.7 (CH_3-C17); HRMS (ESI) for $C_{20}H_{34}NaO_4$ $[M+Na]^+$ calcd. 361.2338, found 361.2349, Δ +3.1 ppm.

[164] The low quality of the COSY and HSQC analyses, partial assignment has been done.

(1'*R*,2*R*,2'*R*,3'*R*,7'*R*,8'*R*,11'*R*,14'*S*)-14'-Methyl-6'-methylidene-3'-(propan-2-yl)-15'-oxaspiro[oxirane-2,10'-tricyclo[6.6.1.0^{2,7}]pentadecane]-11',14'-diol (343) and **(1'*R*,2*S*,2'*R*,3'*R*,7'*R*,8'*R*,11'*R*,14'*S*)-14'-Methyl-6'-methylidene-3'-(propan-2-yl)-15'-oxaspiro[oxirane-2,10'-tricyclo[6.6.1.0^{2,7}]pentadecane]-11',14'-diol (348)**



$C_{20}H_{32}O_4$



$C_{20}H_{32}O_4$

In a round bottom flask charged with allylic alcohol **340** (25.0 mg, 78.0 μmol) was added $VO(acac)_2$ (1.95 mL of a 0.001 M solution in toluene, 1.95 μmol. *tert*-Butyl hydroperoxide (24.0 μL of a 5.9 M solution in decane, 118 μmol) was added dropwise. The mixture was stirred at room temperature for 24 h. $VO(acac)_2$ (1.95 μL of a 0.001 M solution in toluene, 1.95 μmol) was added and the mixture was stirred for an additional 24 h at room temperature. The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (5 mL) and was diluted with EtOAc (10 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 8 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (petroleum ether-ethyl acetate, gradient elution from 2:1 to 1:1) yielded the epoxyalcohol **343** (7 mg, 27%) and its epimer **348** (12 mg, 46%) as colourless crystalline solids.

(1'*R*,2*R*,2'*R*,3'*R*,7'*R*,8'*R*,11'*R*,14'*S*)-14'-Methyl-6'-methylidene-3'-(propan-2-yl)-15'-oxaspiro[oxirane-2,10'-tricyclo[6.6.1.0^{2,7}]pentadecane]-11',14'-diol (343)

R_f = 0.40; (ethyl acetate); m.p. 166.6–177.1 °C; $[\alpha]_D^{19}$ +20.8 (*c* = 0.22, $CHCl_3$); ν_{max} (film) 3427, 2954, 2929, 2892, 1461, 1376, 1066, 1032, 925, 895 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19 (1H, br s, OH-C6), 4.85 (1H, s, CH_2-C20), 4.69 (1H, s, CH_2-C20), 4.22 (1H, ddd, *J* = 11.1, 4.5, 1.3 Hz, CH-C9), 3.99 (1H, s, CH-C2), 3.65 (1H, br s, CH-C6), 3.22 (1H, dd, *J* = 11.1, 8.1 Hz, CH-C10), 3.01 (1H, ddd, *J*

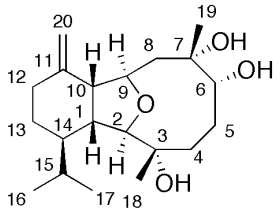
= 15.3, 4.5, 1.9 Hz, CH_2-C8), 2.99 (1H, d, *J* = 4.3 Hz, CH_2-C19), 2.93 (1H, dd, *J* = 4.3, 1.9 Hz, CH_2-C19), 2.78 (1H, br s, OH-C3), 2.30–2.17 (2H, m, CH_2-C5, CH_2-C12), 2.11–2.03 (1H, m, CH_2-C12), 1.97 (1H, dd, *J* = 11.4, 8.1 Hz, CH-C1), 1.89–1.74 (4H, m, CH_2-C4, CH_2-C5, CH_2-C13, CH-C15), 1.67 (1H, dt, *J* = 14.9, 5.7 Hz, CH_2-C4), 1.39–1.31 (1H, m, CH-C14), 1.25–1.20 (1H, m, CH_2-C8), 1.14 (3H, s, CH_3-C18), 1.03 (1H, qd, *J* = 13.1, 3.2 Hz, CH_2-C13), 0.98 (3H, d, *J* = 6.8 Hz, CH_3-C16 or CH_3-C17), 0.74 (3H, d, *J* = 6.8 Hz, CH_3-C16 or CH_3-C17); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.7 (C-C11), 112.1 (CH_2-C20), 94.5 (CH-C2), 78.6 (CH-C9), 75.1 (CH-C6), 74.0 (C-C3), 59.1 (C-C7), 53.8 (CH_2-C19), 48.4 (CH-C10), 46.3 (CH-C1), 44.0 (CH-C14), 34.5 (CH_2-C8), 33.0 (CH_2-C4), 31.4 (CH_2-C5 or CH_2-C12), 31.2 (CH_2-C5 or CH_2-C12), 28.6 (CH_3-C18), 28.1 (CH-C15), 25.5 (CH_2-C13), 22.0 (CH_3-C16 or CH_3-C17), 15.2 (CH_3-C16 or CH_3-C17); HRMS (ESI) for $C_{20}H_{32}NaO_4$ $[M+Na]^+$ calcd. 359.2193, found 359.2177, Δ −4.4 ppm.

(1'*R*,2*S*,2'*R*,3'*R*,7'*R*,8'*R*,11'*R*,14'*S*)-14'-Methyl-6'-methylidene-3'-(propan-2-yl)-15'-oxaspiro[oxirane-2,10'-tricyclo[6.6.1.0^{2,7}]pentadecane]-11',14'-diol (348)

R_f = 0.38; (ethyl acetate); m.p. decomposition; $[\alpha]_D^{22}$ +7.3 (*c* = 0.31, $CHCl_3$); ν_{max} (film) 3412, 2961, 2919, 1458, 1368, 1075, 1027, 909 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.53 (1H, br s, OH-C6), 4.84 (1H, t, *J* = 1.9 Hz, CH_2-C20), 4.79 (1H, t, *J* = 1.9 Hz, CH_2-C20), 4.16 (1H, ddd, *J* = 10.7, 4.8, 1.9 Hz, CH-C9), 4.03 (1H, s, CH-C2), 3.79 (1H, br s, CH-C6), 3.69 (1H, dd, *J* = 10.7, 7.6 Hz, CH-C10), 2.74 (1H, dd, *J* = 15.7, 4.8 Hz, CH_2-C8), 2.60 (1H, d, *J* = 5.3 Hz, CH_2-C19), 2.56 (1H, d, *J* = 5.3 Hz, CH_2-C19), 2.25 (1H, dt, *J* = 13.0, 3.4 Hz, CH_2-C12), 2.17–2.08 (1H, m, CH_2-C4), 2.08–2.00 (2H, m, CH_2-C5, CH_2-C12), 1.96 (1H, dd, *J* = 11.2, 7.6 Hz, CH-C1), 1.91–1.82 (2H, m, CH_2-C5, CH-C15), 1.73 (1H, dq, *J* = 13.0, 3.4 Hz, CH_2-C13), 1.70–1.64 (1H, m, CH_2-C4), 1.41–1.34 (1H, m, CH_2-C8), 1.31–1.21 (1H, m, CH-C14), 1.15 (3H, s, CH_3-C18), 1.05 (1H, qd, *J* = 13.0, 3.0 Hz, CH_2-C13), 0.99 (3H, d, *J* = 6.8 Hz, CH_3-C16 or CH_3-C17), 0.75 (3H, d, *J* = 6.8 Hz, CH_3-C16 or CH_3-C17); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.1 (C-C11), 112.4 (CH_2-C20), 94.6 (CH-C2), 78.9 (CH-C9), 74.2 (C-C3), 72.2 (CH-C6), 58.7 (C-C7), 54.3 (CH_2-C19), 47.6 (CH-C10), 45.6 (CH-C1), 43.5 (CH-C14), 33.9 (CH_2-C8), 33.0 (CH_2-C4), 31.2 (CH_2-C12), 30.7 (CH_2-C5), 28.9 (CH_3-C18), 28.1 (CH-C15), 25.1 (CH_2-C13), 22.1 (CH_3-C16 or

CH_3-C17), 15.4 (CH_3-C16 or CH_3-C17); HRMS (ESI) for $C_{20}H_{32}NaO_4$ $[M+Na]^+$ calcd. 359.2193, found 359.2179, Δ −3.8 ppm.

(1*R*,2*R*,6*R*,7*R*,8*R*,9*S*,12*R*-13*S*)-9,13-Dimethyl-3-methylidene-6-(propan-2-yl)-15-oxatricyclo[6.6.1.0^{2,7}]pentadecane-9,12,13-triol (336)



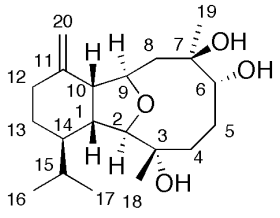
$C_{20}H_{34}O_4$

To a stirred solution of epoxyalcohol **343** (4.2 mg, 12.5 μmol) in anhydrous CH_2Cl_2 (0.6 mL) was added DIBAL-H (60 μL of a 1.0 M solution in CH_2Cl_2, 60 μmol). The mixture was stirred at room temperature for 1 h and DIBAL-H (60 μL of a 1.0 M solution in CH_2Cl_2, 60 μmol) was added. The mixture was stirred for an additional 1 h and the reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The solution was diluted with CH_2Cl_2 (1 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The organic extracts were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (dichloromethane-methanol, gradient elution from dichloromethane to methanol 2%) afforded the triol **336** (1.8 mg, 43%) as a colourless oil.

R_f = 0.27; (ethyl acetate); $[\alpha]_D^{23}$ +36.1 (*c* = 0.36, $CHCl_3$); ν_{max} (film) 3399, 2964, 2925, 2854, 1445, 1371, 1260, 1059, 1028, 976, 953, 933, 889, 794 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.85 (2H, s, CH_2-C20), 4.61 (1H, ddd, *J* = 11.2, 3.9, 1.9 Hz, CH-C9), 3.88 (1H, d, *J* = 8.0 Hz, CH-C2), 3.55 (1H, br s, CH-C6), 2.62 (1H, d, *J* = 6.9 Hz, CH-C10), 2.39 (1H, ddd, *J* = 7.5, 6.0, 3.4 Hz, CH-C1), 2.34−2.25 (1H, m, CH_2-C5), 2.16−2.11 (2H, m, CH_2-C12), 2.06−1.98 (1H, m, CH_2-C4), 1.93−1.87 (1H, m, CH_2-C5), 1.86−1.74 (3H, m, CH_2-C8, CH-C15), 1.72−1.61 (3H, m, CH_2-C4, CH_2-C13), 1.40−1.35 (1H, m, CH-C14), 1.28 (3H, s, CH_3-C18) 1.13 (3H, s, CH_3-C19), 1.01 (3H, d, *J* = 6.7 Hz, CH_3-C16), 0.91 (3H, d, *J* = 6.7 Hz, CH_3-C17); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.0 (C-C11), 108.8 (CH_2-C20), 90.4 (CH-C2), 76.8 (CH-C6),

76.1 (CH-C9), 74.7 (C-C3 or C-C7), 73.6 (C-C3 or C-C7), 48.4 (CH-C10), 46.3 (CH_2-C8), 43.3 (CH-C1), 41.2 (CH-C14), 33.2 (CH_2-C4), 30.4 (CH_2-C12), 29.8 (CH_3-C18), 29.5 (CH-C15), 28.3 (CH_3-C19), 28.2 (CH_2-C5), 24.8 (CH_2-C13), 22.1 (CH_3-C16), 19.8 (CH_3-C17); HRMS (ESI) for $C_{20}H_{34}NaO_4$ $[M+Na]^+$ calcd. 361.2349, found 361.2334, Δ −4.3 ppm.

(1*R*,2*R*,6*R*,7*R*,8*R*,9*S*,12*R*-13*R*)-9,13-Dimethyl-3-methylidene-6-(propan-2-yl)-15-oxatricyclo[6.6.1.$0^{2,7}$]pentadecane-9,12,13-triol (341)



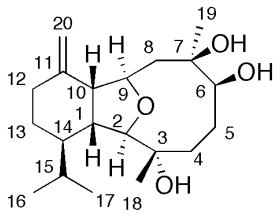
$C_{20}H_{34}O_4$

To a stirred solution of epoxyalcohol **348** (6.0 mg, 17.8 μmol) in anhydrous CH_2Cl_2 (0.9 mL) was added DIBAL-H (90 μL of a 1.0 M solution in CH_2Cl_2, 90 μmol). The mixture was stirred at room temperature for 1.5 h and DIBAL-H (90 μL of a 1.0 M solution in CH_2Cl_2, 90 μmol) was added. The mixture was stirred for an additional 1 h and DIBAL-H (350 μL of a 1.0 M solution in CH_2Cl_2, 350 μmol) was added and the mixture was stirred for a further 1h. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (2 mL) and diluted with CH_2Cl_2 (2 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 4 mL). The organic extracts were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (dichloromethane-methanol, gradient elution from dichloromethane to methanol 2.5%) afforded the triol **341** (1.3 mg, 22%) as a colourless oil.

R_f = 0.33; (ethyl acetate); $[\alpha]_D^{22}$ +50.5 (*c* = 0.26, $CHCl_3$); ν_{max} (film) 3381, 2961, 2923, 2874, 1653, 1464, 1457, 1373, 1261, 1091, 1071, 1025, 976, 930, 888, 846, 801, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.85 (1H, s, CH_2-C20), 4.83 (1H, s, CH_2-C20), 4.39−4.34 (1H, m, CH-C9), 3.90 (1H, d, *J* = 5.9 Hz, CH-C2), 3.59 (1H, dd, *J* = 6.3, 1.0 Hz, CH-C6), 3.03 (1H, br s, CH-C10), 2.22−2.08 (4H, m, CH-C1, CH_2-C5, CH_2-C12), 1.98−1.88 (4H, m, CH_2-C4, CH_2-C8, CH_2-C12), 1.84−1.75 (2H,

m, CH_2-C4, CH-C15), 1.70−1.63 (1H, m, CH_2-C13), 1.48−1.41 (1H, m, CH_2-C13), 1.40 (3H, s, CH_3-C19), 1.38−1.33 (1H, m, CH-C14), 1.10 (3H, s, CH_3-C18), 0.99 (3H, d, *J* = 6.7 Hz, CH_3-C16), 0.85 (3H, d, *J* = 6.7 Hz, CH_3-C17); ^{13}C NMR (126 MHz, $CDCl_3$) δ 146.2 (C-C11), 109.7 (CH_2-C20), 91.8 (CH-C2), 79.8 (CH-C6), 77.4 (CH-C9), 76.3 (C-C3 or C-C7), 74.4 (C-C3 or C-C7), 48.5 (CH-C10), 44.4 (CH-C1), 44.2 (CH_2-C8), 41.8 (CH-C14), 34.2 (CH_2-C4), 30.8 (CH_2-C5), 29.0 (CH-C15), 28.7 (CH_2-C12), 27.9 (CH_3-C18), 26.5 (CH_3-C19), 25.0 (CH_2-C13), 22.0 (CH_3-C16), 18.4 (CH_3-C17); HRMS (CI, Me_3CH) for $C_{20}H_{35}O_4$ $[M+H]^+$ calcd. 339.2535, found 339.2539, Δ +1.0 ppm; LRMS *m/z* (intensity); 339.4 (38%), 319.3 (100%), 303.3 (52%).

(1*R*,2*R*,6*R*,7*R*,8*R*,9*S*,12*S*-13*R*)-9,13-Dimethyl-3-methylidene-6-(propan-2-yl)-15-oxatricyclo[6.6.1.0^{2,7}]pentadecane-9,12,13-triol (337)



$C_{20}H_{34}O_4$

To a stirred solution of triol **341** (2.4 mg, 7.1 μmol) in anhydrous CH_2Cl_2 (0.7 mL) was added Dess-Martin periodinane (8.9 mg, 21. μmol). The mixture was stirred at room temperature for 2 h and an additional portion of Dess Martin periodinane (6.1 mg, 14 μmol) was added. The mixture was stirred for further 2 h and the reaction was quenched by the addition of saturated aqueous solutions of $NaHCO_3$ (1 mL) and $Na_2S_2O_3$ (5 mL). The solution was diluted with CH_2Cl_2 (5 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The organic extracts were combined, washed with a saturated aqueous solution of $NaHCO_3$ (2 × 5 mL) and brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford ketone **349**.

HRMS (ESI) for $C_{20}H_{32}NaO_4$ $[M+Na]^+$ calcd. 359.2193, found 359.2180, Δ −3.6 ppm.

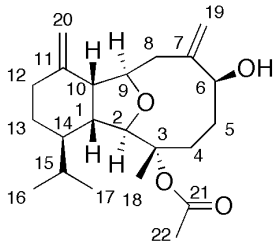
To a stirred solution of ketone **349** in anhydrous CH_2Cl_2 (0.7 mL) at 0 °C was added DIBAL-H (70 μL of a 1.0 M solution in CH_2Cl_2, 70 μmol). The mixture was stirred at room temperature for 1 h and the reaction was quenched by the

addition of a saturated aqueous solution of sodium potassium tartrate (1 mL). The solution was diluted with CH_2Cl_2 (2 mL) and was stirred vigorously until two clear phases formed. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The organic extracts were combined, washed with brine (10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford a mixture of *syn* and *anti* diol (1:2.3). Purification of the residue by flash column chromatography on silica gel (dichloromethane-methanol, gradient elution from dichloromethane to methanol 2.5%) delivered *syn*- and *anti*-diol **337** and **341** (0.6 mg, 25% over two steps) enriched in the *syn*-diol **337** (6.2:1) as a colourless oil.

R_f = 0.52; (ethyl acetate); $[\alpha]_D^{23}$ +108.3 (*c* = 0.12, $CHCl_3$); ν_{max} (film) 3392, 2959, 2923, 2853, 1472, 1374, 1261, 1101, 1016, 971, 888, 799 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.81 (1H, s, CH_2-C20), 4.78 (1H s, CH_2-C20), 4.28 (1H, ddd, *J* = 8.5, 8.2, 2.9 Hz, CH-C9), 4.15 (1H, br d, *J* = 10.3 Hz, CH-C6), 3.76 (1H, d, *J* = 6.1 Hz, CH-C2), 2.67 (1H, dd, *J* = 6.9, 4.7 Hz CH-C10), 2.28 (1H, app q, *J* = 6.6 Hz, CH-C1), 2.21–2.10 (2H, m, CH_2-C12), 2.10–2.01 (1H, m, CH_2-C8), 2.01–1.84 (3H, m, CH_2-C4, CH_2-C5), 1.84–1.76 (1H, m, CH-C15), 1.74–1.63 (3H, m, CH_2-C4, CH_2-C8, CH_2-C13), 1.48–1.42 (1H, m, CH_2-C13), 1.41 (3H, s, CH_3-C19), 1.34–1.29 (1H, m, CH-C14), 1.15 (3H, s, CH_3-C18), 0.99 (3H, d, *J* = 6.7 Hz, CH_3-C16), 0.85 (3H, d, *J* = 6.7 Hz, CH_3-C17); ^{13}C NMR (126 MHz, $CDCl_3$)[165] δ 146.7 (C-C11), 108.9 (CH_2-C20), 90.8 (CH-C2), 77.5 (CH-C9), 76.3 (CH-C6), 75.5 (C-C3 or C-C7), 74.8 (C-C3 or C-C7), 50.8 (CH-C10), 45.6 (CH_2-C8), 44.1 (CH-C1), 42.1 (CH-C14), 35.1 (CH_2-C4), 30.9 (CH_2-C12), 29.4 (CH-C15), 29.2 (CH_2-C5), 27.5 (CH_3-C18), 26.1 (CH_3-C19), 24.9 (CH_2-C13), 22.0 (CH_3-C16), 18.5 (CH_3-C17); HRMS (ESI) for $C_{20}H_{34}NaO_4$ $[M+Na]^+$ calcd. 361.2349, found 361.2336, Δ −3.7 ppm.

[165] Due to the low quantity of product, the assignment has been done from DEPTQ analysis.

(1*R*,2*R*,6*R*,7*R*,8*R*,9*S*,12*S*)-12-Hydroxy-9-Methyl-3,13-dimethylidene-6-(propan-2-yl)-15-oxatricyclo[6.6.1.$0^{2,7}$]pentadecane-9-yl acetate (352)



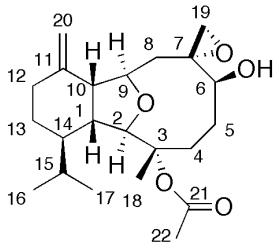
$C_{22}H_{34}O_4$

To a stirred solution of enone **345** (19.0 mg, 59.0 μmol) in anhydrous CH_2Cl_2 (0.6 mL) were added distilled triethylamine (0.16 mL, 1.18 mmol), recrystallised DMAP (37.1 mg, 303 μmol) and freshly distilled acetic anhydride (80 μL, 85 μmol). The mixture was stirred at room temperature for 32 h and the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (0.8 mL). The solution was diluted with CH_2Cl_2 (2 mL and stirred for an additional 15 min. The two phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 3 mL). The organic extracts were concentrated and the residue was diluted in Et_2O (10 mL) and washed successively with a 1 M aqueous solution of HCl (2 × 5mL), a saturated aqueous solution of $CuSO_4$ (2 × 5 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The crude acetate was used in the next step without further purification.

Crude acetate **350** was dissolved in MeOH (3 mL) and the solution was cooled to 0 °C. Cerium chloride heptahydrate (26.7 mg, 71.7 μmol) and sodium borohydride (3.6 mg, 95 μmol) were added. The mixture was stirred at 0 °C for 1 h. Additional portion of cerium chloride heptahydrate (24.8 mg, 66.6 μmol) and sodium borohydride (2.8 mg, 74 μmol) were added and the mixture was stirred for a further 4 h. The reaction was quenched by the addition of a 1 M aqueous solution of HCl (3 mL) and brine (3 mL). The solution was diluted with EtOAc (6 mL) and a saturated aqueous solution of NH_4Cl (3 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 5mL). The organic extracts were combined, dried ($MgSO_4$), filtered and concentrated *in vaccuo*. Purification of the residue by flash column chromatography on silica gel (dichloromethane-methanol, gradient elution from dichloromethane to methanol 2%) afforded the acetate **352** (8.7 mg, 43% over two steps).

R_f = 0.67; (ethyl acetate); ^{1}H NMR (500 MHz, $CDCl_3$)[166] δ 5.47 (1H, s), 5.11 (1H, s), 4.82 (1H, t, *J* = 2.0 Hz), 4.70 (1H, s), 4.55 (1H, dd, *J* = 9.9, 4.4 Hz), 4.20–4.12 (2H, m), 3.04 (1H, dd, *J* = 10.3, 7.8 Hz), 2.78 (1H, dd, *J* = 13.3, 4.2 Hz), 2.32–2.23 (3H, m), 2.15–2.11 (1H, m), 2.07 (3H, s), 2.06–2.00 (1H m), 1.92–1.83 (2H, m), 1.79–1.56 (4H, m), 1.43 (3H, s), 1.38–1.28 (2H, m), 0.97 (3H, d, *J* = 6.8 Hz), 0.71 (3H, d, *J* = 6.8 Hz); HRMS (ESI) for $C_{22}H_{34}NaO_4$ $[M+Na]^+$ calcd. 385.2349, found 385.2339, Δ −2.8 ppm.

(1'*R*,2*R*,2'*R*,3'*R*,7'*R*,8'*R*,11'*S*,14'*S*)-11'-Hydroxy-14'-methyl-6'-methylidene-3'-(propan-2-yl)-15'-oxaspiro[oxirane-2,10'-tricyclo[6.6.1.0^{2,7}]pentadecane]-14'-yl acetate (351)



$C_{22}H_{34}O_5$

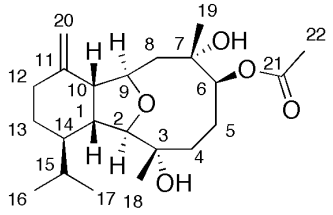
To a suspension of 4 Å powdered molecular sieves in anhydrous CH_2Cl_2 (0.5 mL) at −20 °C were added freshly distilled (+)-diethyl tartrate (30 μL of a 116 μmol/mL solution in CH_2Cl_2, 3.5 μmol), freshly distilled titanium tetraisopropoxide (40 μL of a 67 μmol/mL solution in CH_2Cl_2, 2.7 μmol), and *tert*-butyl hydroperoxide (36 μL of a 1.9 M solution in CH_2Cl_2, 68 μmol). The solution was stirred for 30 min and allylic alcohol **352** (8.70 mg, 24.0 μmol) in CH_2Cl_2 (1.0 mL) was added slowly. The mixture was stirred at −20 °C for 24 h and the reaction was quenched by the addition of water (1.5 mL) and 30% wt solution of NaOH in brine (3.5 mL). The solution was allowed to warm to room temperature and was stirred for an additional 30 min. The mixture was diluted with CH_2Cl_2 and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 6 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 (dichloromethane-diethyl ether, gradient elution

[166] The low quantity and due to time constraints, only ^{1}H NMR analysis has been done and the next stage of the synthesis was performed.

from pure dichloromethane to 1:1) afforded the desired epoxyalcohol **351** (3.10 mg, 34%) as a colourless solid.

R_f = 0.72; (ethyl acetate); $[\alpha]_D^{25}$ +34.6 (*c* = 0.26, $CHCl_3$); ν_{max} (film) 3475, 2957, 2934, 2869, 1728, 1691, 1444, 1370, 1252, 1187, 1078, 1049, 1031, 924, 896 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.84 (1H, s, CH_2-C20), 4.66 (1H, s, CH_2-C20), 4.44 (1H, dd, *J* = 9.4, 4.0 Hz, CH-C6), 4.26 (1H, s, CH-C2), 4.26 (1H, ddd, *J* = 10.7, 4.8, 1.6 Hz, CH-C9), 3.16 (1H, dd, *J* = 4.7, 1.6 Hz, CH_2-C19), 3.07 (1H, dd, *J* = 10.7, 7.6 Hz CH-C10), 2.99 (1H, d, *J* = 4.7 Hz, CH_2-C19), 2.71 (1H, ddd, *J* = 14.5, 4.8, 1.6 Hz, CH_2-C8), 2.35 (1H, br s, OH), 2.25 (1H, dt, *J* = 13.8, 3.1 Hz, CH_2-C12), 2.22−2.13 (2H, m, CH_2-C4, CH_2-C5), 2.08 (3H s, CH_3-C22), 2.07−2.05 (1H, m, CH_2-C12), 1.99 (1H, dd, *J* = 11.8, 7.6 Hz, C-C1), 1.94−1.87 (1H, m, CH-C15), 1.77 (1H, dq, *J* = 13.0, 3.1 Hz, CH_2-C13), 1.72−1.65 (1H, m, CH_2-C4), 1.46 (3H, s, CH_3-C18), 1.41−1.24 (3H, m, CH_2-C5, CH_2-C8, CH-C14), 1.04 (1H, qd, *J* = 13.0, 3.1 Hz, CH_2-C13), 0.99 (3H, d, *J* = 6.8 Hz, CH_3-C16 or CH_3-C17), 0.74 (3H, d, *J* = 6.8 Hz, CH_3-C16 or CH_3-C17); ^{13}C NMR (126 MHz, $CDCl_3$)[165] δ 170.9 (C-C21), 145.8 (C-C11), 111.9 (CH_2-C20), 89.7 (CH-C2 or CH-C9), 86.2 (C-C3), 79.1 (CH-C2 or CH-C9), 69.7 (CH-C6), 59.1 (C-C7), 52.9 (CH_2-C19), 48.6 (CH-C10), 45.8 (CH-C1), 44.1 (CH-C14), 37.3 (CH_2-C8), 32.2 (CH_2-C5), 31.5 (CH_2-C12), 30.9 (CH_2-C4), 27.9 (CH-C15), 25.5 (CH_2-C13), 24.2 (CH_3-C18), 22.5 (CH_3-C22), 22.1 (CH_3-C16 or CH_3-C17), 15.3 (CH_3-C16 or CH_3-C17); HRMS (ESI) for $C_{22}H_{34}NaO_5$ $[M+Na]^+$ calcd. 401.2298, found 401.2287, Δ −2.8 ppm.

(1*R*,2*R*,3*R*,7*R*,8*R*,10*S*,11*S*,14*S*)-10,14-Dihydroxy-10,14-dimethyl-6-methylidene-3-(propan-2-yl)-15-oxatricyclo[6.6.1.0^{2,7}]pentadecane-11-yl acetate (355)



$C_{22}H_{34}O_5$

To a stirred solution of triol **10** (5.0 mg, 15 μmol) in anhydrous pyridine (0.25 mL) was added freshly distilled acetic anhydride (12 μL, 0.13 mmol). The

mixture was stirred at room temperature for 9 h and the reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (5 mL). The solution was diluted with CH_2Cl_2 (5 mL) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 4 mL). The organic extracts were combined and successively washed with water (5 mL), a saturated aqueous solution of $CuSO_4$ (2 × 5 mL) and brine (10 mL). The organic phase was dried ($MgSO_4$), filtered and concentrated *in vacuo*. Purification of the residue by flash column chromatography on silica gel (dichloromethane-methanol, gradient elution from dichloromethane to methanol 3%) afforded mono-acetate **355** (1.1 mg, 20%) and recovered the starting material **10** (1.2 mg, 24%).

R_f = 0.29; (petroleum ether-ethyl acetate, 1:1); $[\alpha]_D^{24}$ +49.1 (*c* = 0.22, $CHCl_3$); ν_{max} (film) 3452, 2957, 2925 2848, 1716, 1465, 1370, 1251, 1067, 1023, 894, 803 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$)[167] δ 5.80 (1H, br s), 4.84 (1H, s), 4.82 (1H, s), 4.64 (1H, br s), 3.83 (1H, d, *J* = 6.4 Hz), 2.58 (1H, br s), 2.32–2.25 (1H, m), 2.15–2.10 (2H, m), 2.09 (3H, s), 2.07–1.99 (1H, m), 1.93–1.85 (1H, m), 1.83–1.74 (3H, m), 1.70–1.48 (6H, m), 1.40–1.34 (1H, m), 1.25 (3H, s), 1.11 (3H, s), 1.00 (3H, d, *J* = 6.7 Hz), 0.89 (3H, d, *J* = 6.7 Hz); ^{13}C NMR (126 MHz, $CDCl_3$)[165] δ 167.5, 146.3, 108.7, 79.3, 77.4, 76.4, 75.0, 72.0, 49.7, 43.7, 41.5, 30.6, 30.5, 29.5, 29.4, 27.8, 24.9, 22.8, 22.1, 21.1, 19.7, 14.3; HRMS (ESI) for $C_{22}H_{36}NaO_5$ $[M+Na]^+$ calcd. 403.2455, found 403.2435, Δ −4.9 ppm.

[167] The quality of the spectra did not allow the assignments.

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(164) The low quality of the COSY and HSQC analyses, partial assignment has been done.

(165) Due to the low quantity of product, the assignment has been done from DEPTQ analysis.

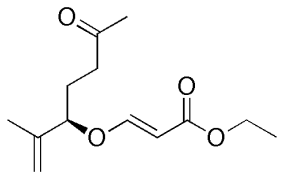
(166) The low quantity and due to time constraints, only ^{1}H NMR analysis has been done and the next stage of the synthesis was performed.

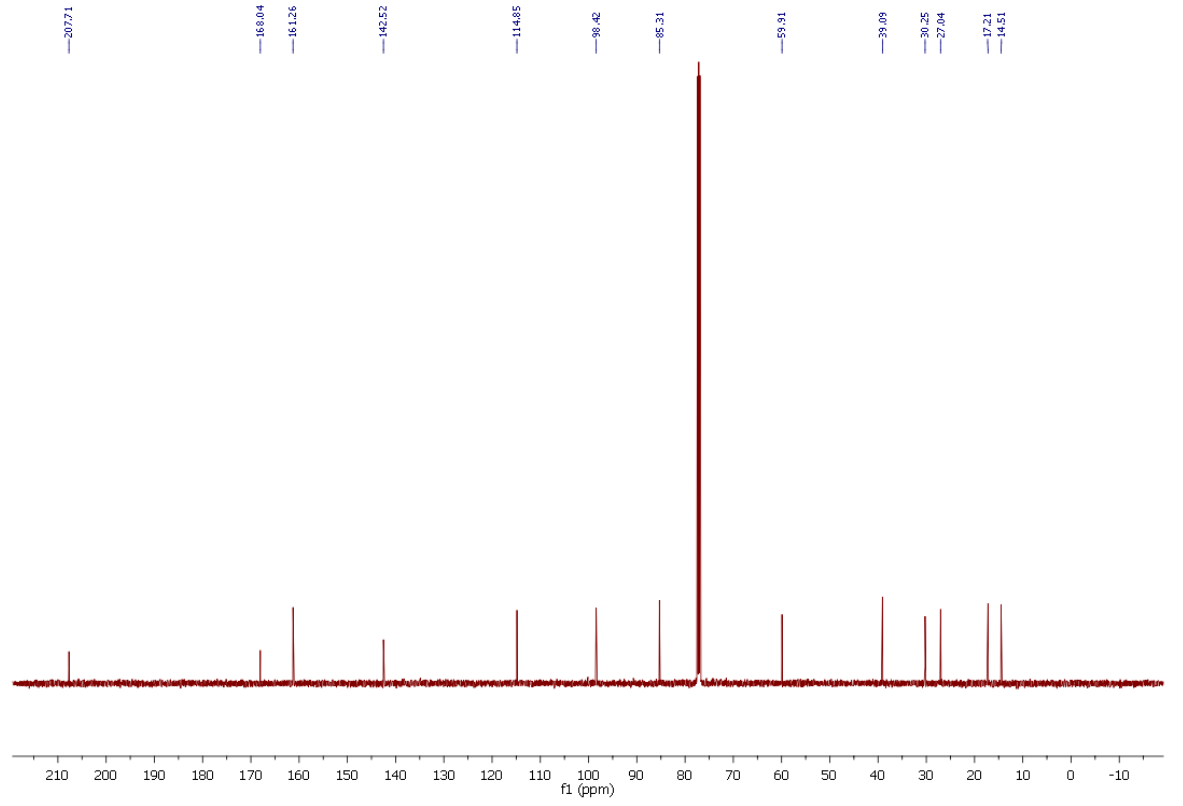
(167) The quality of the spectra did not allow the assignments.

APPENDICES

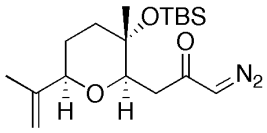
Appendix 1: H^1 and C^{13} NMR spectra of compound **277**.
Appendix 2: H^1 and C^{13} NMR spectra of compound **276**.
Appendix 3: H^1 and C^{13} NMR spectra of compound ***Z*-275**.
Appendix 4: H^1 and C^{13} NMR spectra of compound ***E*-275**.
Appendix 5: H^1 and C^{13} NMR spectra of compound **317**.
Appendix 6: H^1 and C^{13} NMR spectra of compound **272**.
Appendix 7: H^1 and C^{13} NMR spectra of compound **347**.
Appendix 8: H^1 and C^{13} NMR spectra of compound **10**.
Appendix 9: H^1 and C^{13} NMR spectra of compound **343**.
Appendix 10: H^1 and C^{13} NMR spectra of compound **348**.
Appendix 11: H^1 and C^{13} NMR spectra of compound **336**.
Appendix 12: H^1 and C^{13} NMR spectra of compound **341**.
Appendix 13: H^1 and C^{13} NMR spectra of compound **337**.
Appendix 14: H^1 and C^{13} NMR spectra of compound **351**.
Appendix 15: Crystal and structure refinement **SVC_18** (**Z-275**).
Appendix 16: Crystal and structure refinement **SVC_21** (**317**).
Appendix 17: Crystal and structure refinement **SVC_23** (**329**).
Appendix 18: Crystal and structure refinement **SVC_24** (**328**).
Appendix 19: Crystal and structure refinement **SVC_38** (**272**).
Appendix 20: Crystal and structure refinement **SVC_40** (**340**).
Appendix 21: Crystal and structure refinement **SVC_60** (**347**).
Appendix 22: Crystal and structure refinement **SVC_49** (**343**).
Appendix 23: Crystal and structure refinement **SVC_48** (**348**).

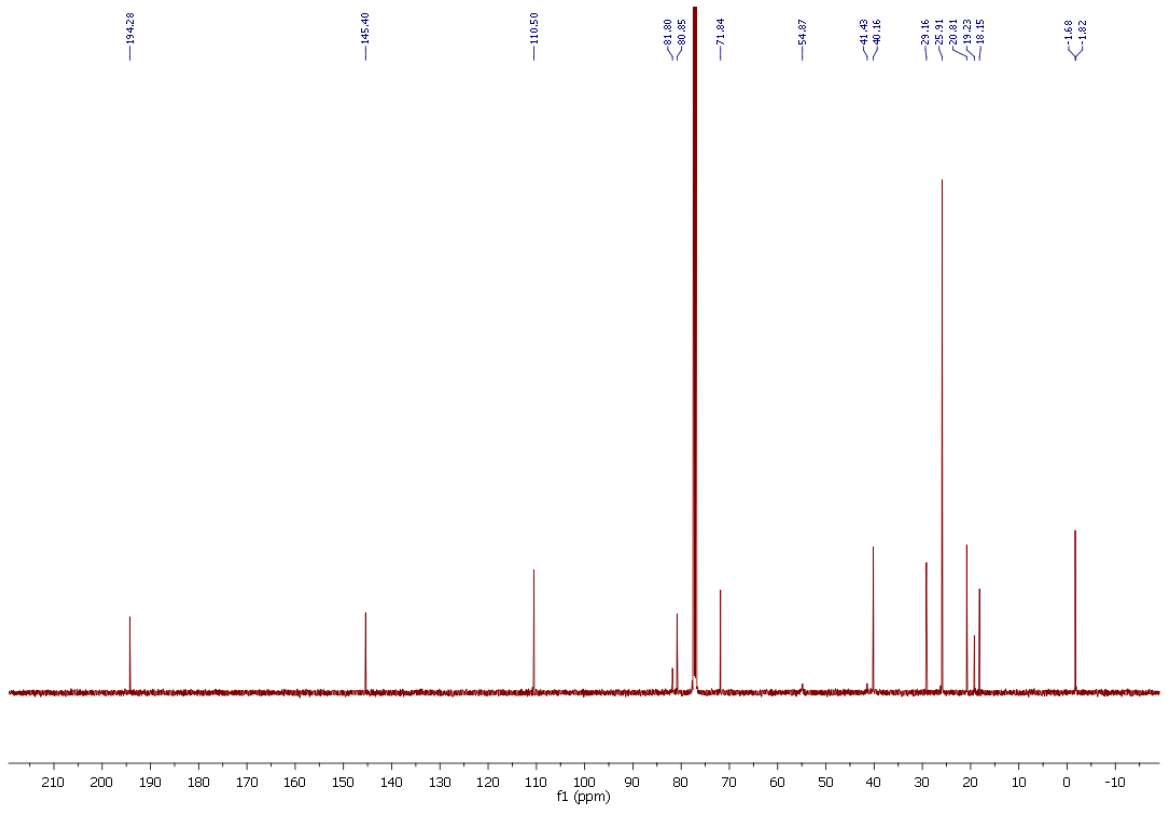
Appendix 1: H^1 and C^{13} NMR spectra of compound **277**.



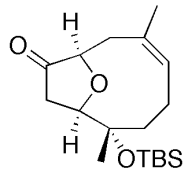


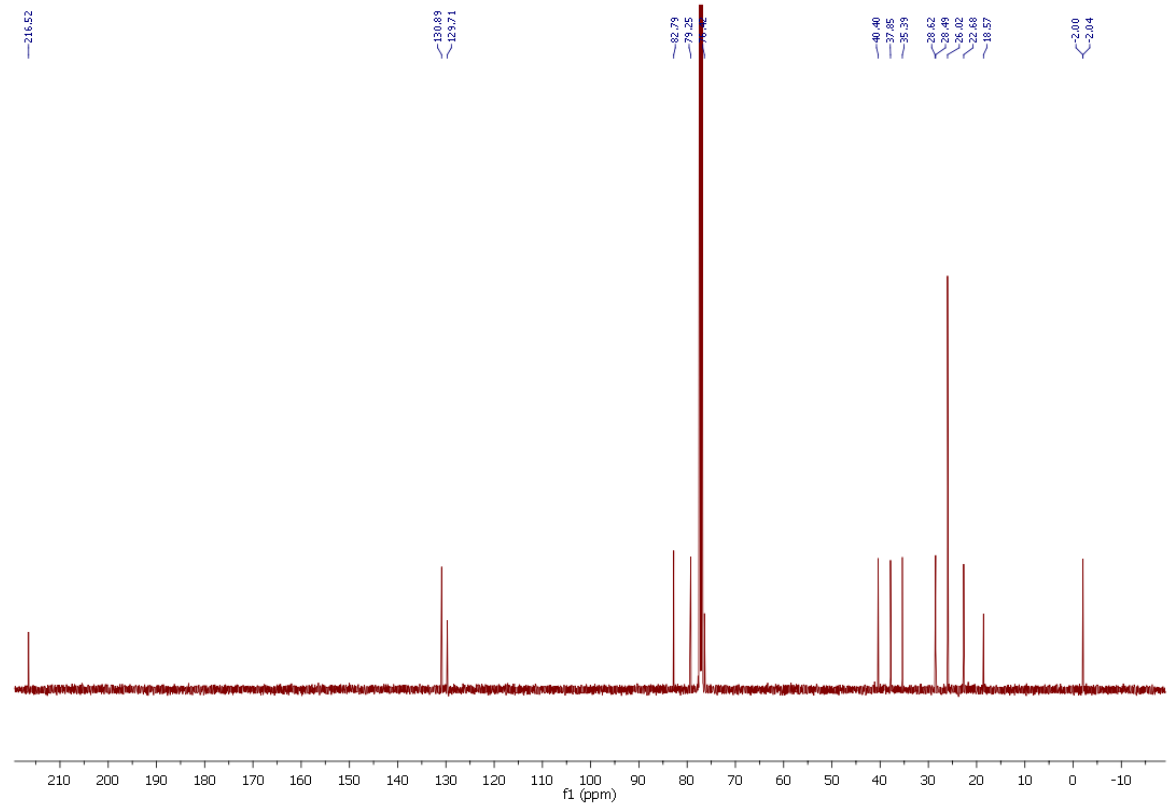
Appendix 2: H^1 and C^{13} NMR spectra of compound **276**.



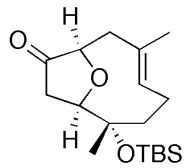


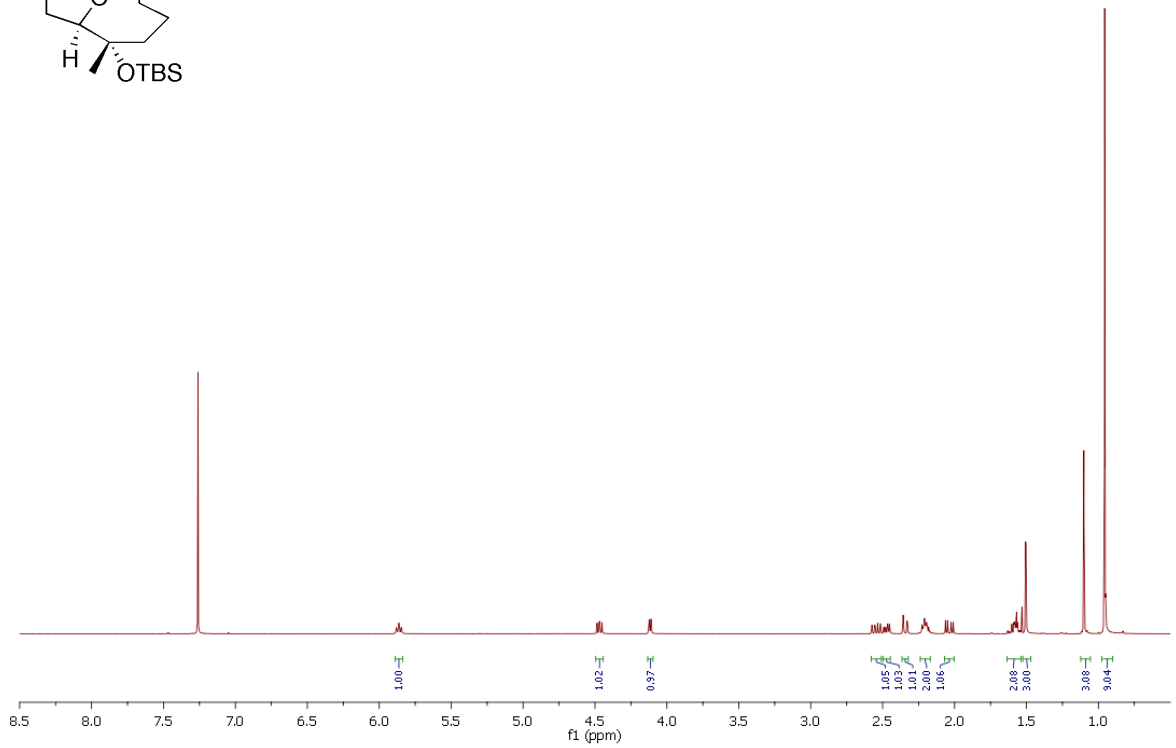
Appendix 3: H^1 and C^{13} NMR spectra of compound ***Z*-275**.

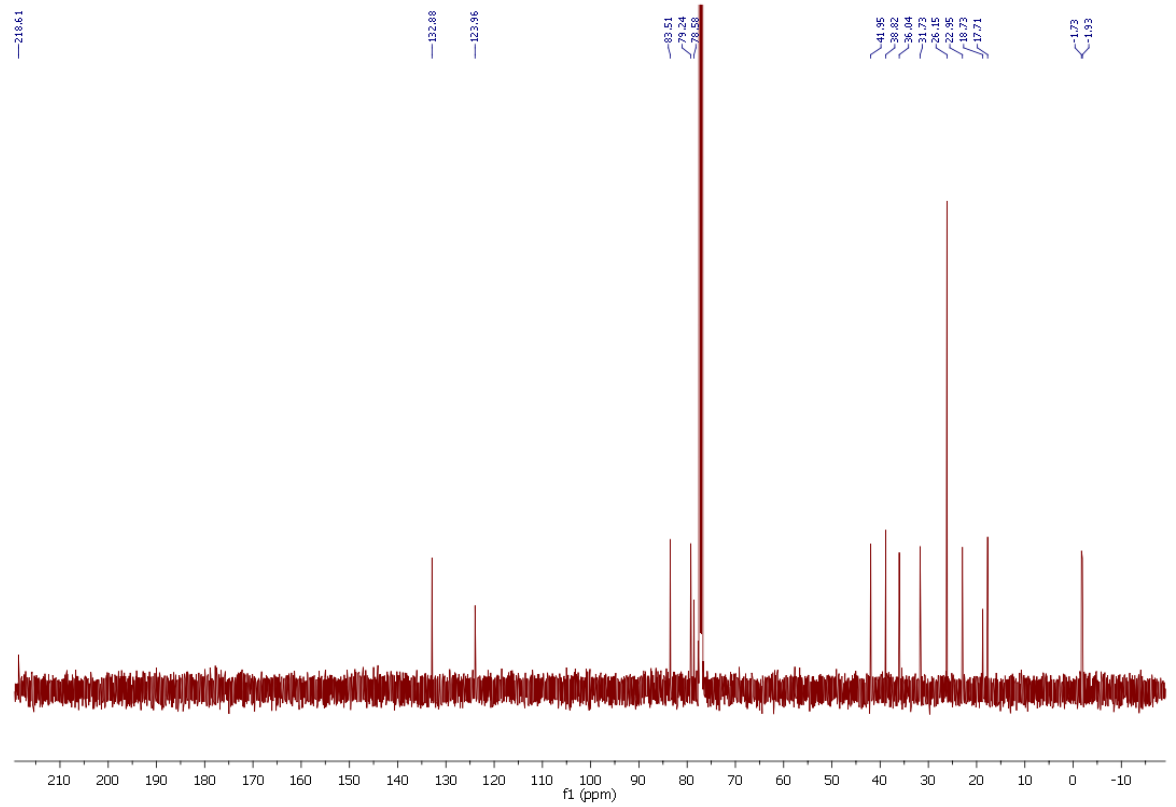




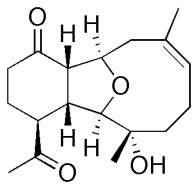
Appendix 4: H^1 and C^{13} NMR spectra of compound ***E*-275**.

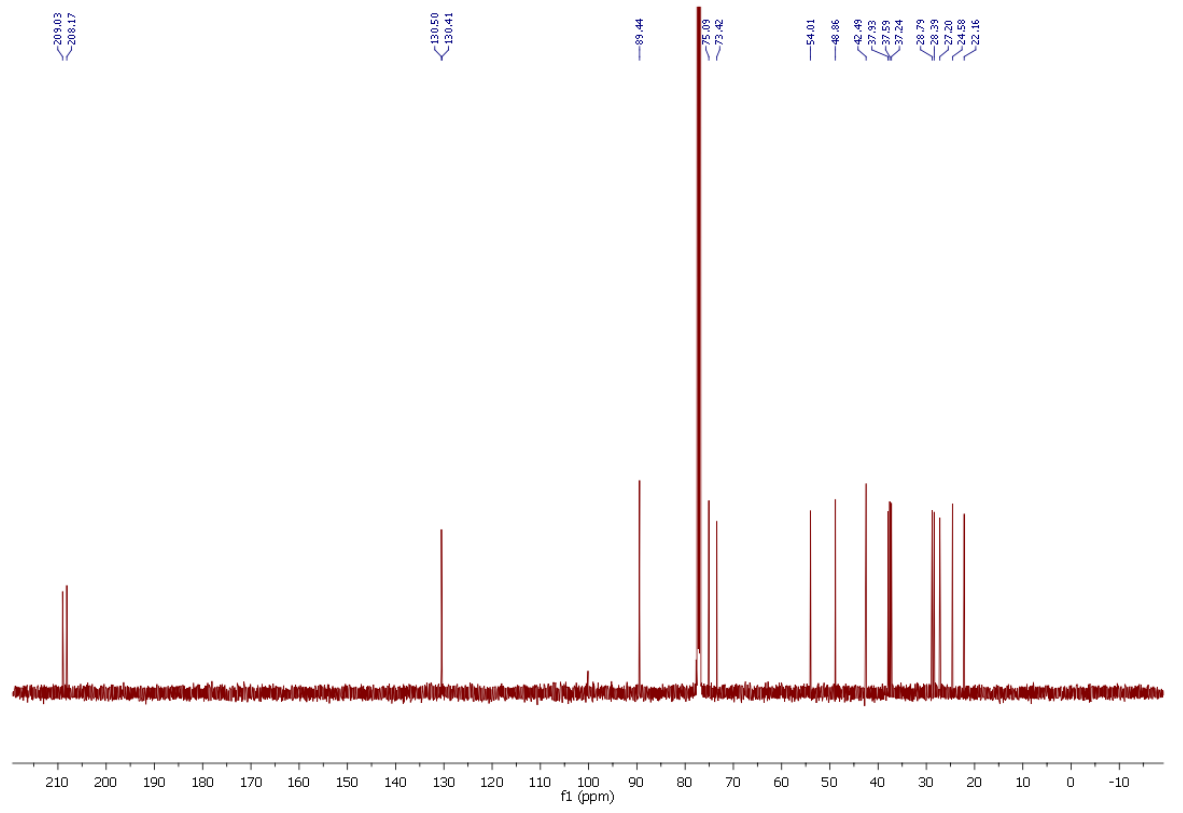




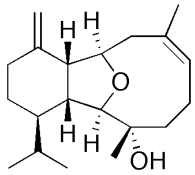


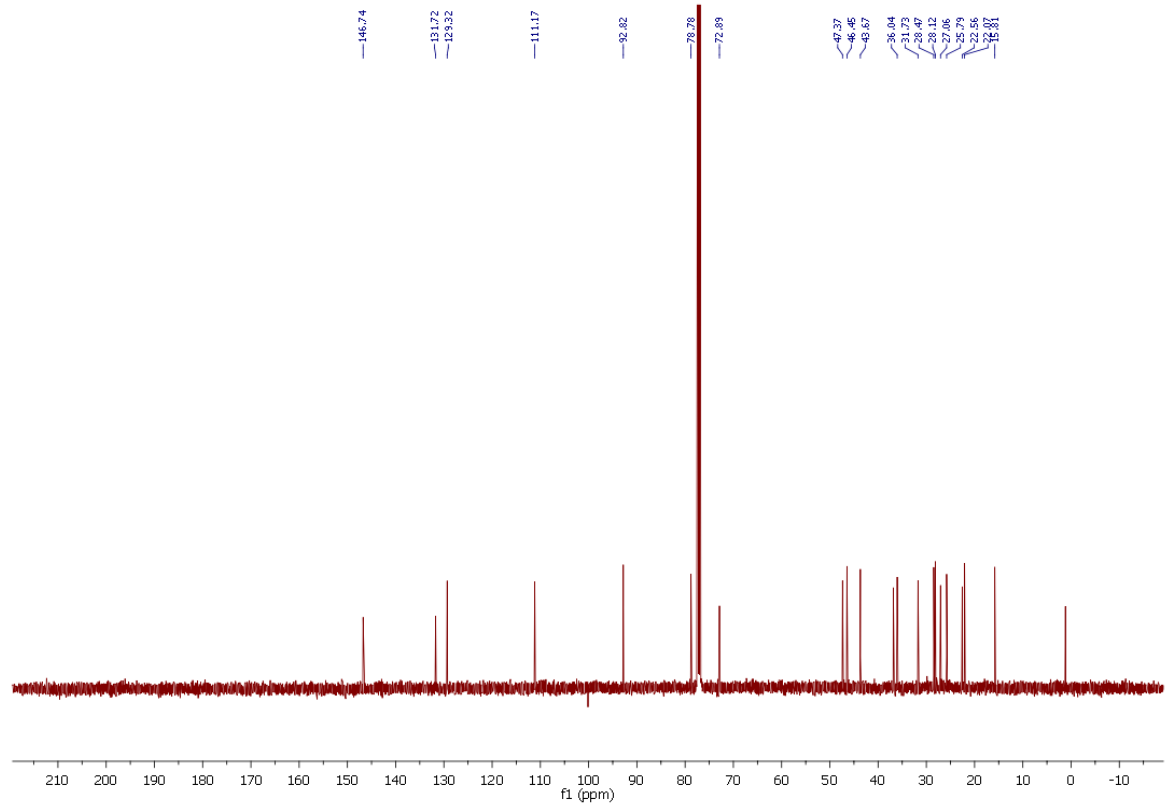
Appendix 5: H^1 and C^{13} NMR spectra of compound **317**.



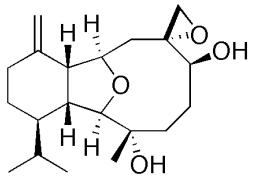


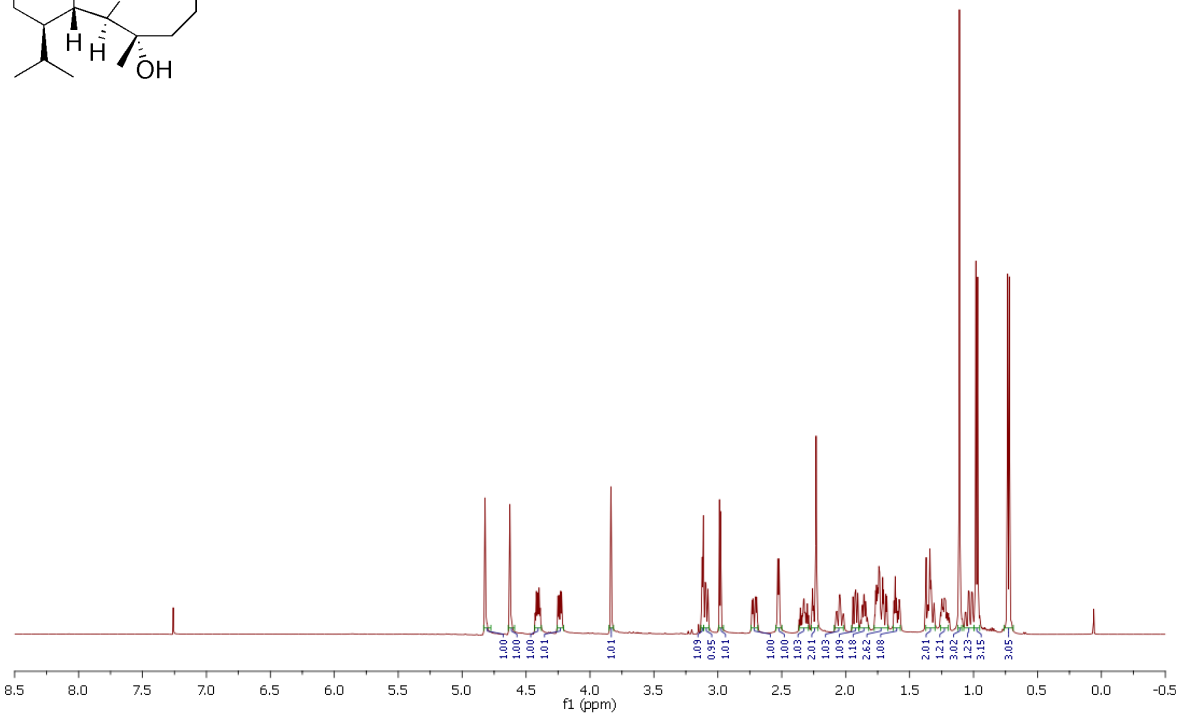
Appendix 6: H^1 and C^{13} NMR spectra of compound **272**.

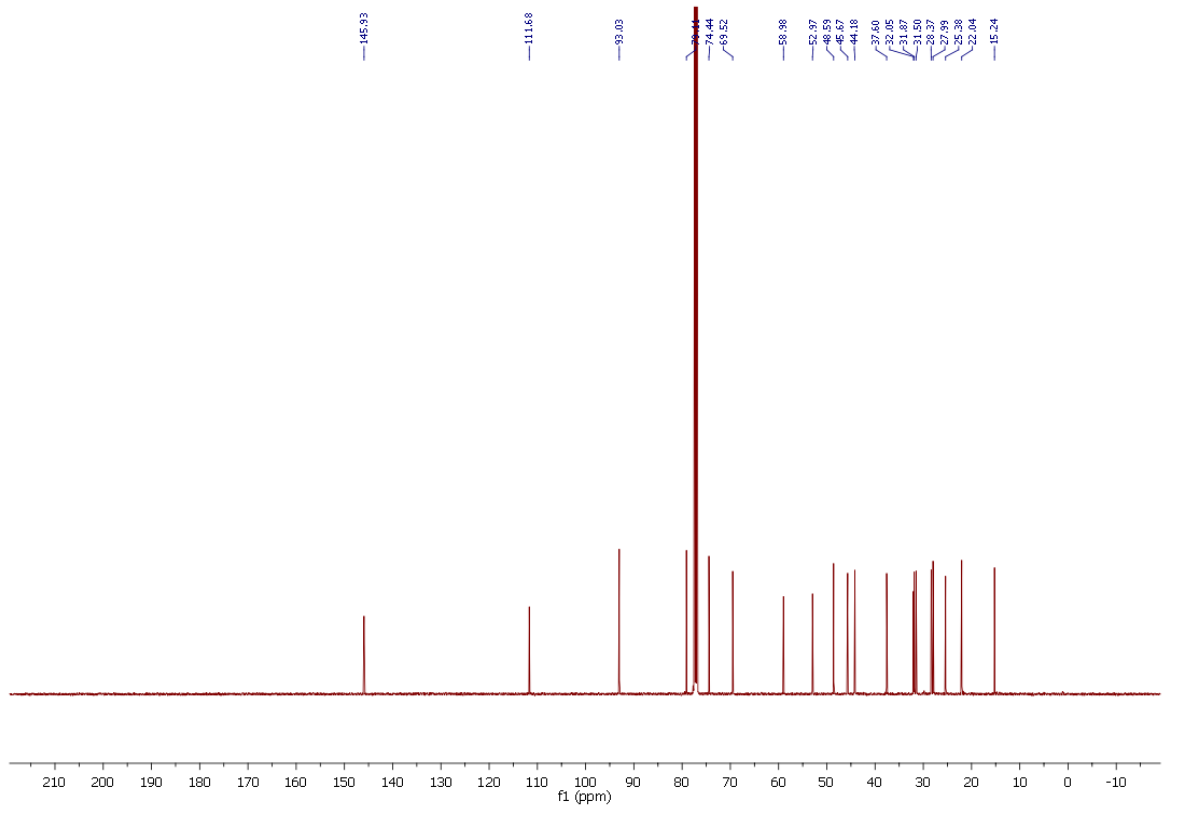




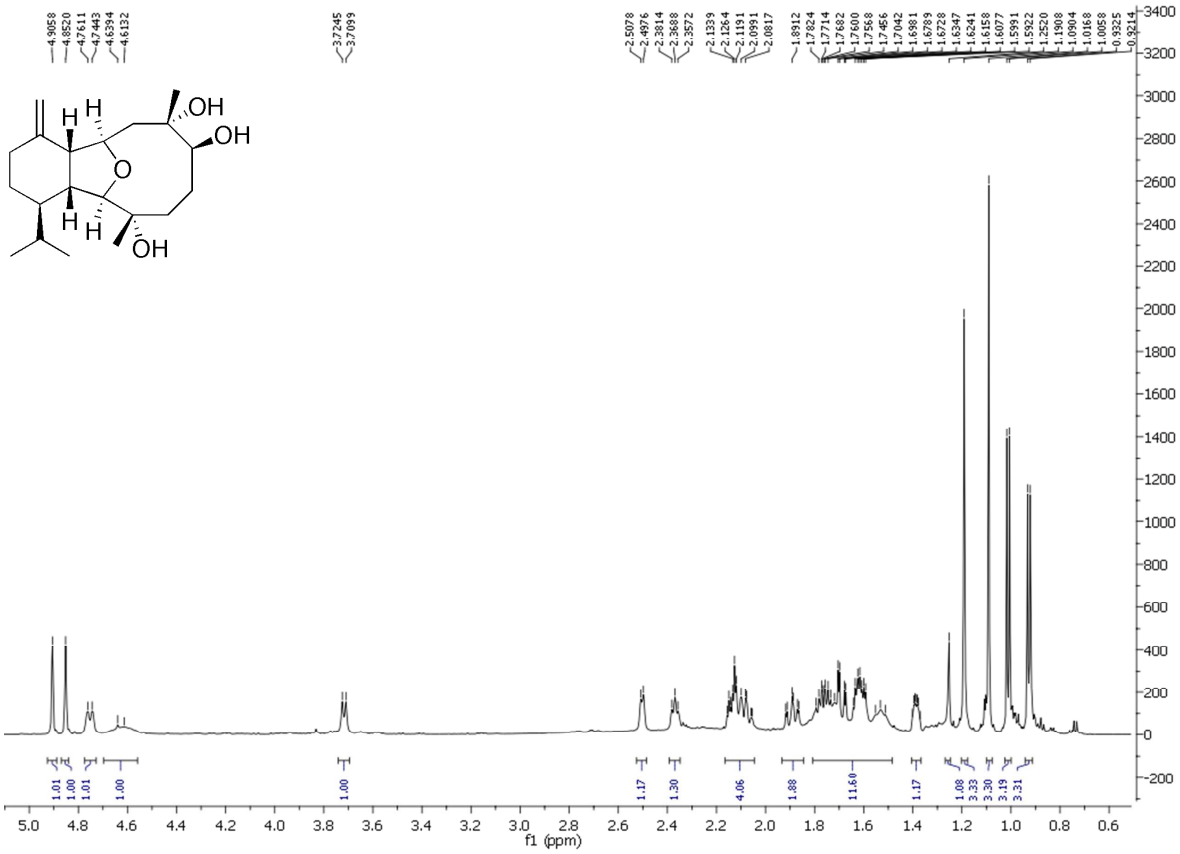
Appendix 7: H^1 and C^{13} NMR spectra of compound **347**.

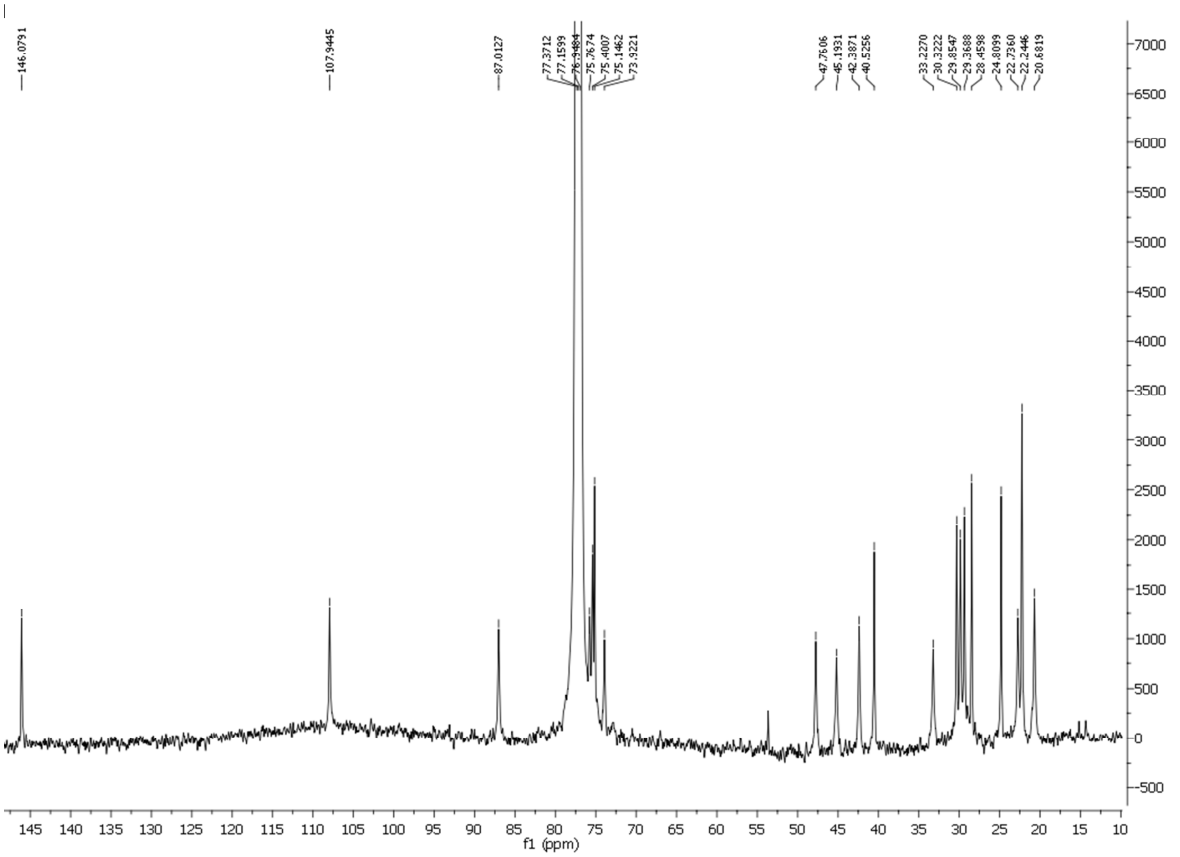




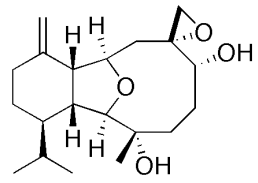


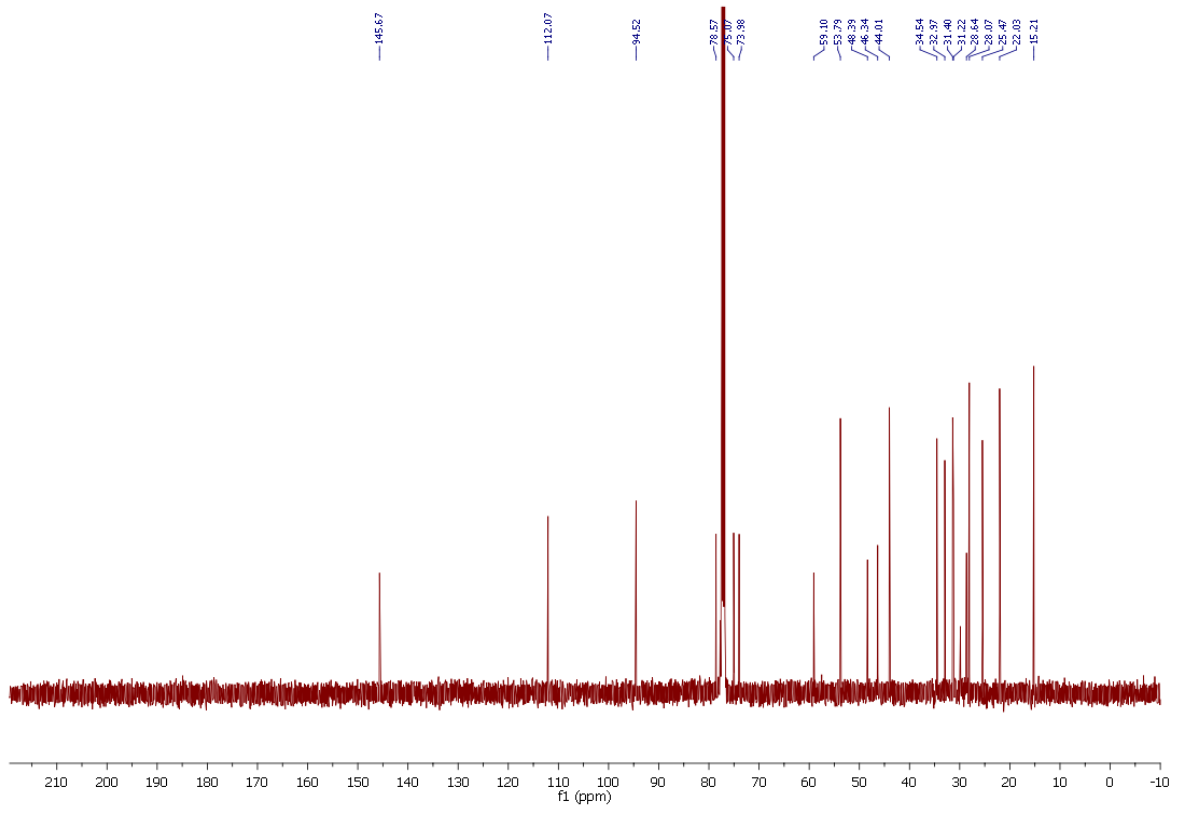
Appendix 8: H^1 and C^{13} NMR spectra of compound **10**.



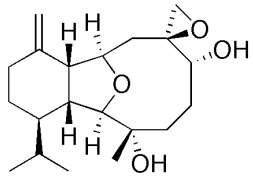


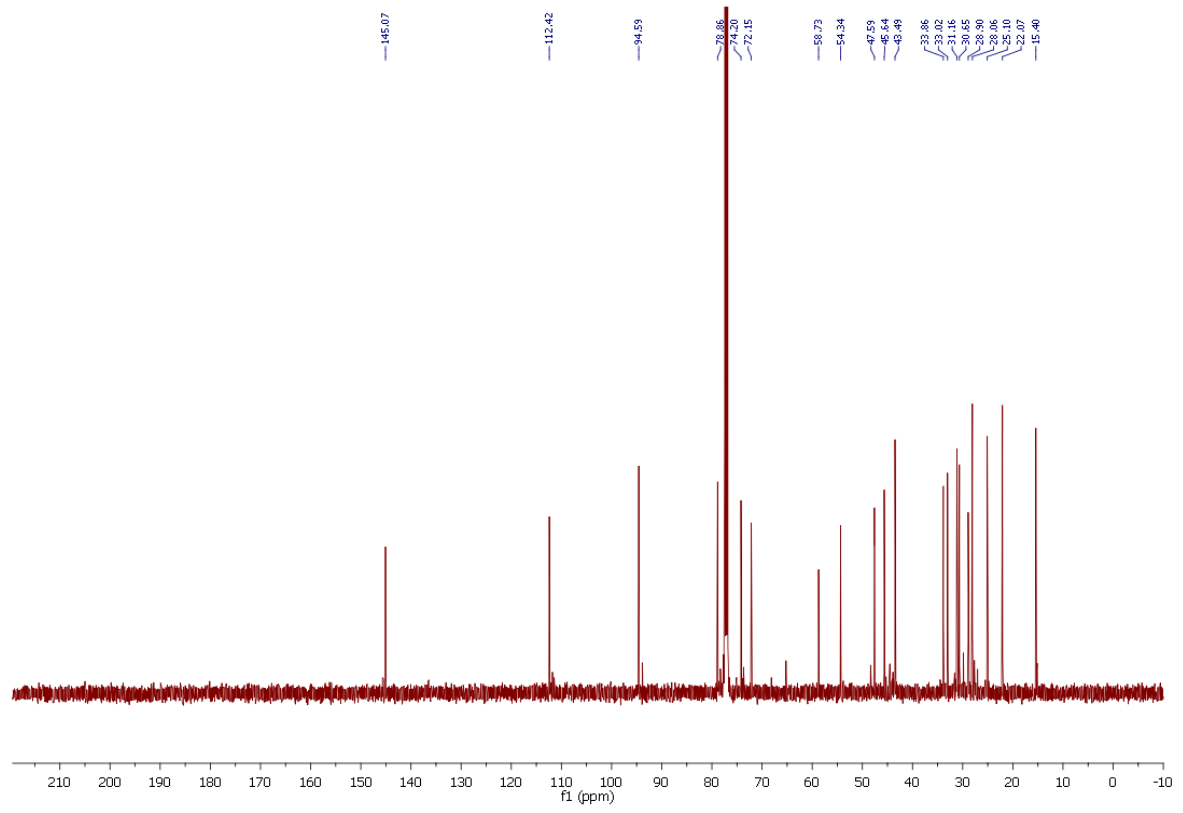
Appendix 9: H^1 and C^{13} NMR spectra of compound **343**.



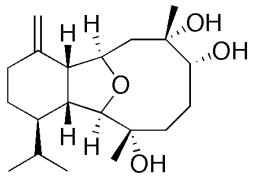


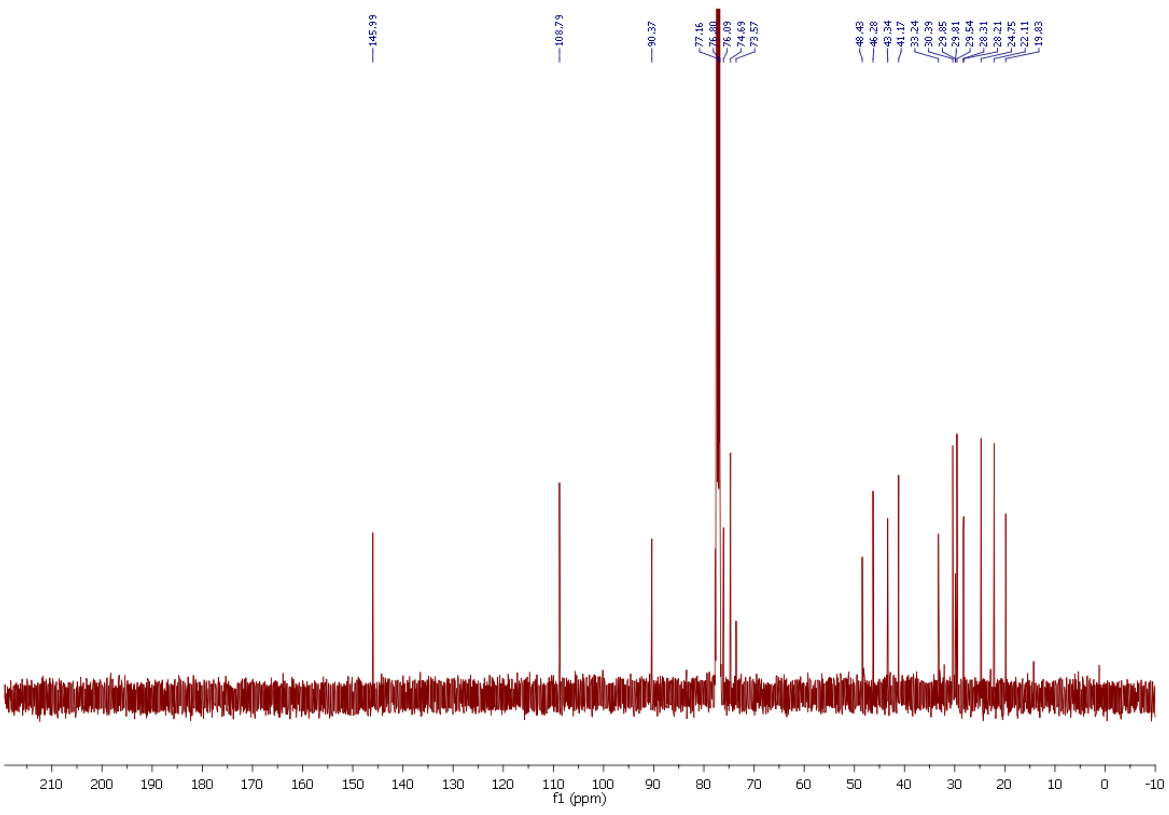
Appendix 10: H^1 and C^{13} NMR spectra of compound **348**.



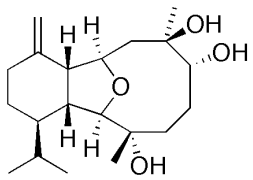


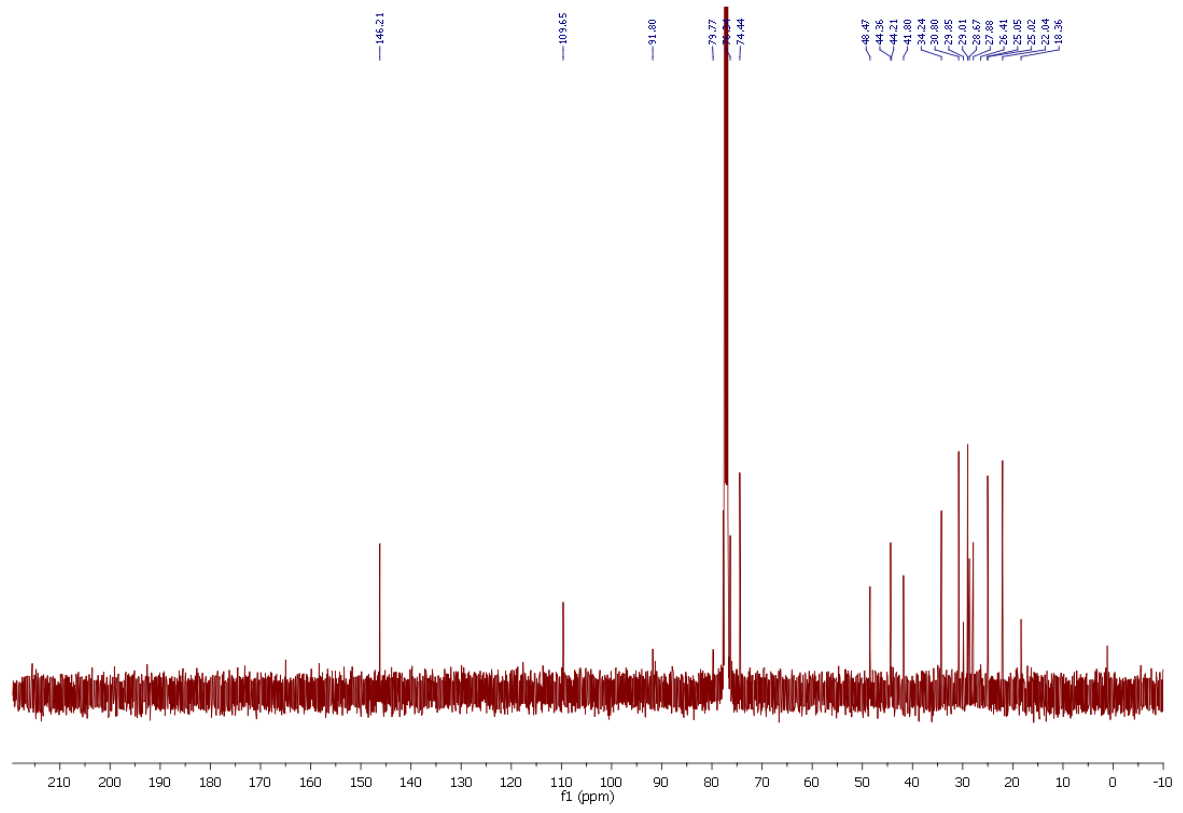
Appendix 11: H^1 and C^{13} NMR spectra of compound **336**.



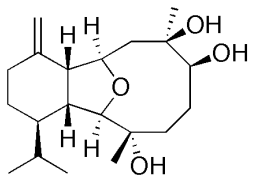


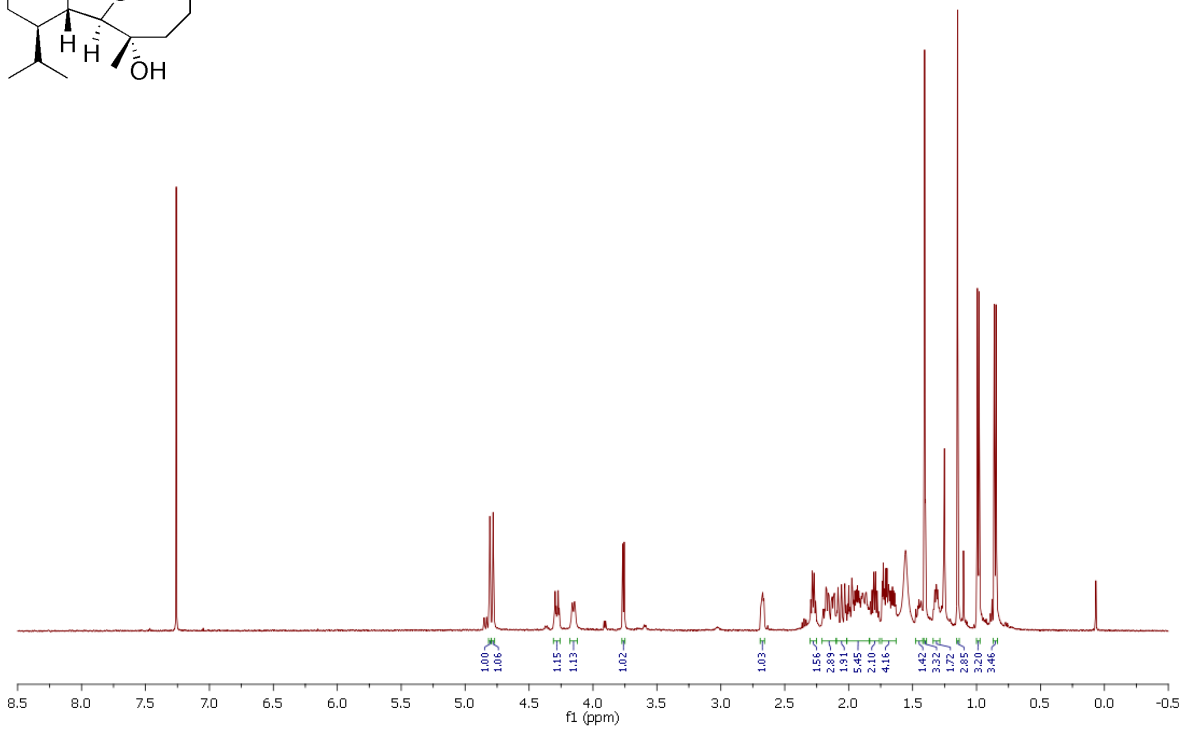
Appendix 12: H^1 and C^{13} NMR spectra of compound **341**.

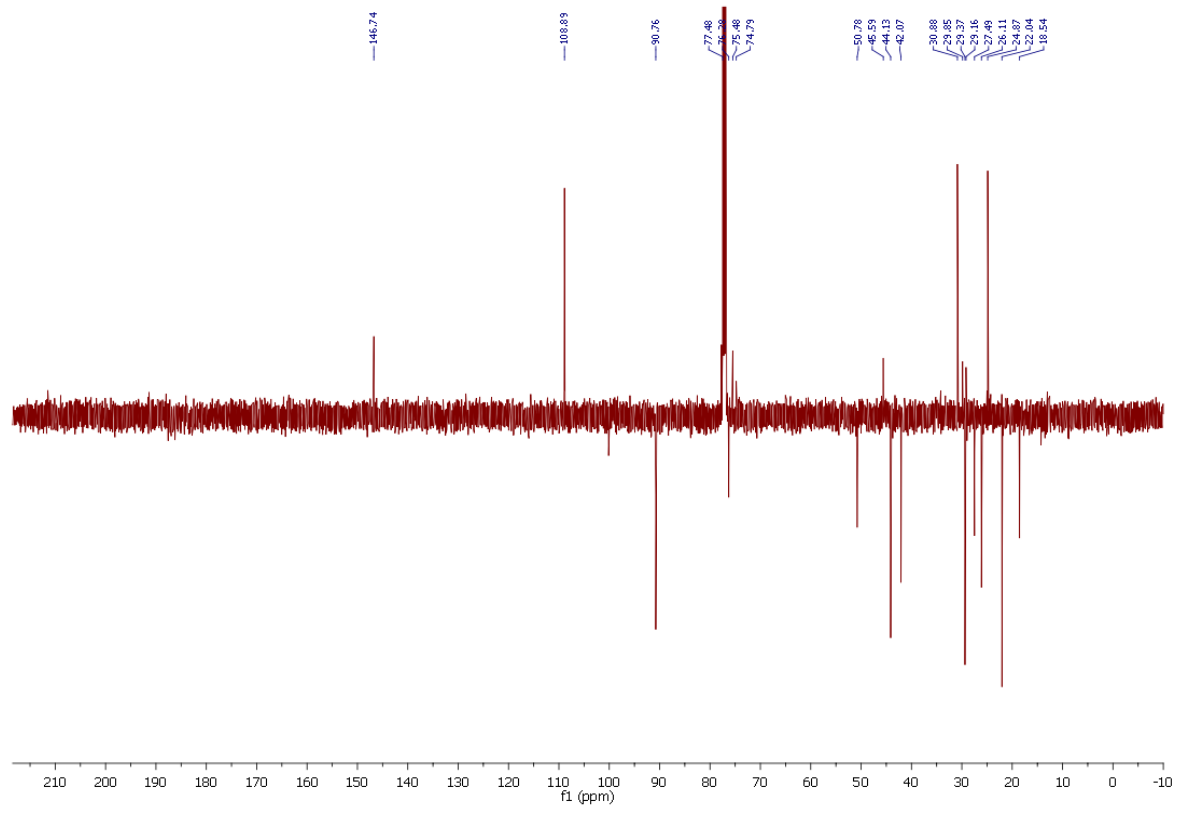




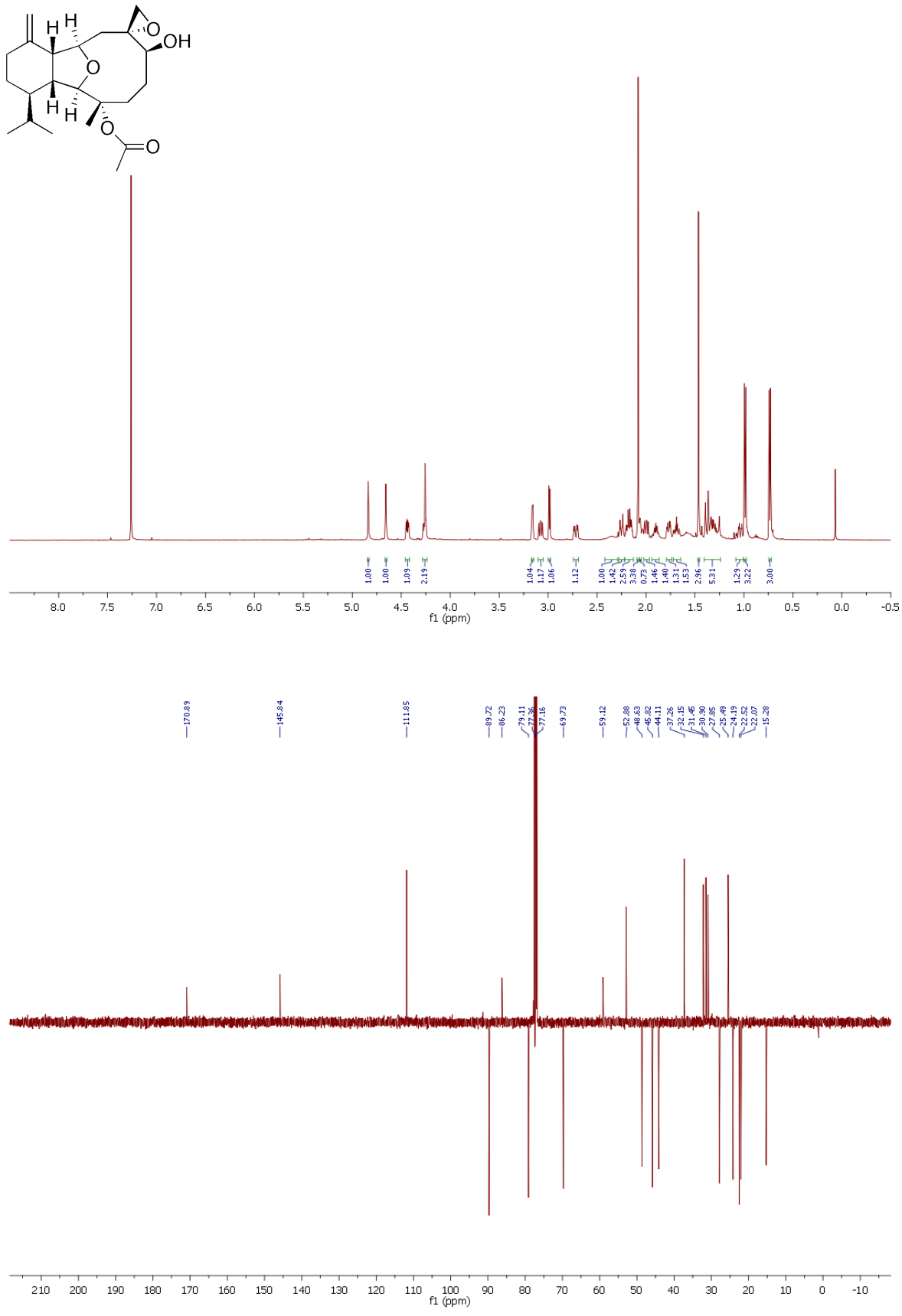
Appendix 13: H^1 and C^{13} NMR spectra of compound **337**.



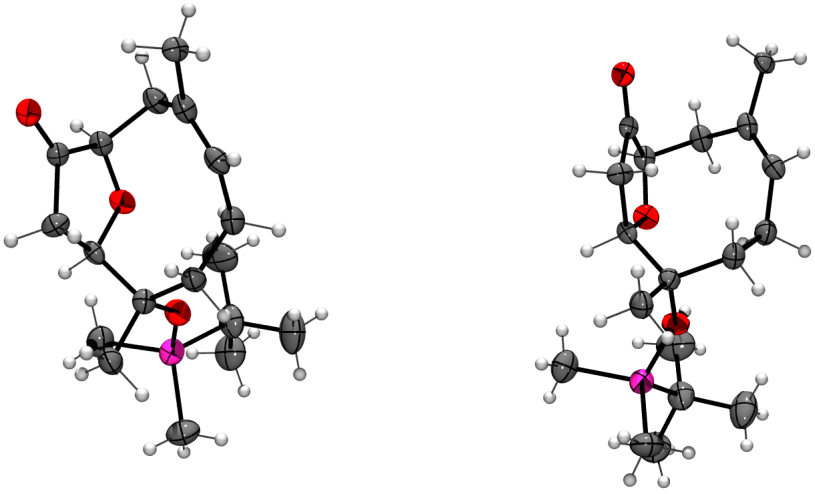




Appendix 14: H^1 and C^{13} NMR spectra of compound **351**.

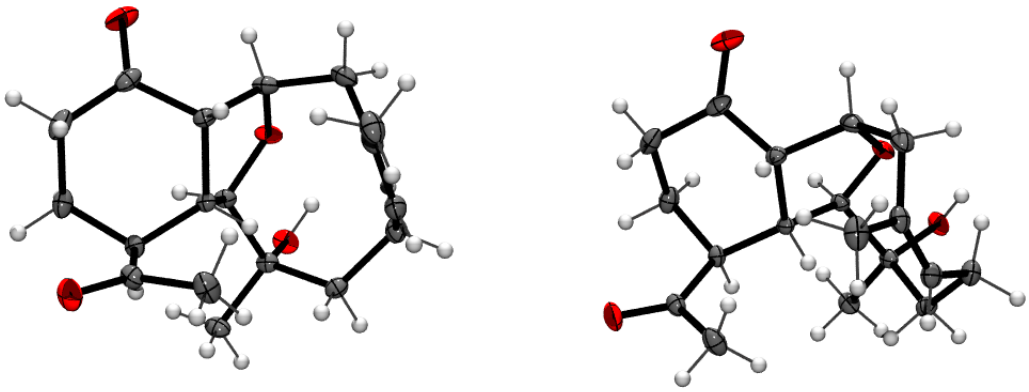


Appendix 15: Crystal data and structure refinement for **SVC_18** (***Z*-275**).



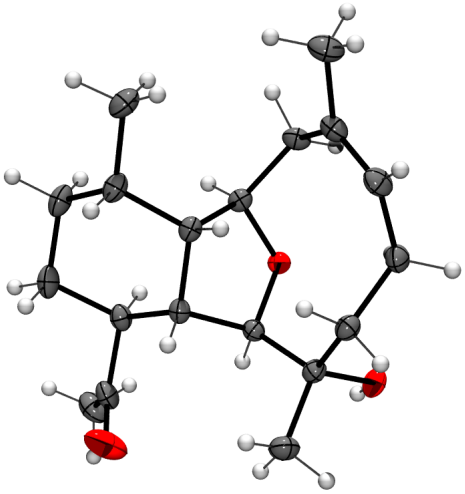
Identification code	SVC_18
Empirical formula	C18 H32 O3 Si
Formula weight	324.52
Temperature	100 (2) K
Wavelength	0.71073
Crystal system	Triclinic
Space group	P-1
Unit cell dimension	a = 6.6456(9) Å α = 84.612(8) ° b = 8.4081(11) Å β = 87.679(8) ° c = 18.488(2) Å γ = 73.945(6) °
Volume	988.2(2) $Å^3$
Z	2
Density (calculated)	1.091 mg/m^3
Radiation type	MoK\a
Absorption coefficient	0.128 µ/mm
F(000)	356
Crystal size	0.4 × 0.25 × 0.2
Theta range for data collection	2.213 – 27.709 °
Index ranges	−8<=h<=+8; −10<= k<=+10; −24<=l<=+24
Number of reflections measured	25266
Number of independent reflections	4551
Rint	0.155
Completeness to theta = 25.242	1
Absorption correction type	Multi-scan
Max. and min. transmission	0.746 and 0.535
Refinement method	Full-matrix least-squares on F^2
Data / restraints/ parameters	4551 / 0 / 207
Goodness-of-fit on F^2	1.554
Final R indices [I>2sigma(I)]	R1 = 0.1626, wR2 = 0.4041
R indices (all data)	R1 = 0.237, wR2 = 0.4469
Largest diff. peak and hole	1.150 and −0.621 $e.Å^{-3}$

Appendix 16: Crystal data and structure refinement for **SVC_21** (**317**).



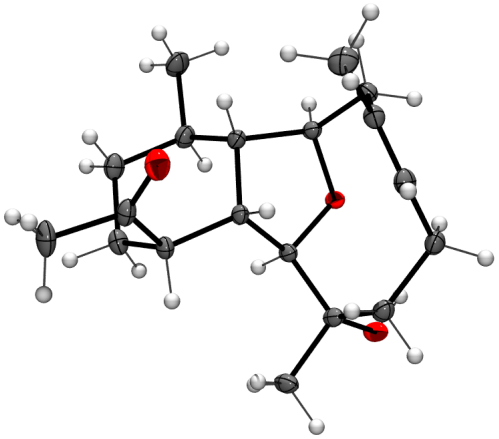
Identification code	SVC_21
Empirical formula	C18 H26 O4
Formula weight	306.39
Temperature	100 (2) K
Wavelength	0.71073
Crystal system	Triclinic
Space group	P-1
Unit cell dimension	a = 8.1038(2) Å α = 71.5650(10) ° b = 13.1776(3) Å β = 85.8090(10) ° c = 16.2542(4) Å γ = 75.3090(10) °
Volume	1592.81(7) $Å^3$
Z	4
Density (calculated)	1.278 mg/m^3
Radiation type	MoK\a
Absorption coefficient	0.089 µ/mm
F(000)	654
Crystal size	0.65 × 0.467 × 0.256
Theta range for data collection	2.436 – 34.947 °
Index ranges	−13<=h<=+13; −21<=k<=+21; −26<=l<=+26
Number of reflections measured	130578
Number of independent reflections	13962
R*int*	0.029
Completeness to theta = 25.242	0.991
Absorption correction type	Gaussian
Max. and min. transmission	0.978 and 0.936
Refinement method	Full-matrix least-squares on F^2
Data / restraints/ parameters	13962 / 0 / 461
Goodness-of-fit on F^2	1.026
Final R indices [I>2sigma(I)]	R1 = 0.0358, wR2 = 0.102
R indices (all data)	R1 = 0.0426, wR2 = 0.1055
Largest diff. peak and hole	0.460 and −0.398 $e.Å^{-3}$

Appendix 17: Crystal data and structure refinement for **SVC_23** (**329**).



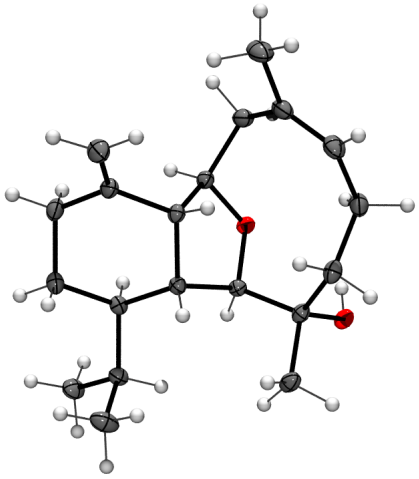
Identification code	SVC_23
Empirical formula	C19 H30 O3
Formula weight	306.43
Temperature	100 (2) K
Wavelength	0.71073
Crystal system	Monoclinic
Space group	P 21/n
Unit cell dimension	a = 12.0614(2) Å α = 90(10) ° b = 13.1921(2) Å ß = 118.3700(10) ° c = 12.2087(2) Å γ = 90(10) °
Volume	1709.28(5) $Å^3$
Z	4
Density (calculated)	1.191 mg/m^3
Radiation type	MoK\a
Absorption coefficient	0.078 µ/mm
F(000)	672
Crystal size	0.516 × 0.209 × 0.201
Theta range for data collection	2.445 – 27.422 °
Index ranges	−15<=h<=+15; −17<=k<=+71; −15<=l<=+15
Number of reflections measured	57772
Number of independent reflections	3895
R*int*	0.039
Completeness to theta = 25.242	1
Absorption correction type	Gaussian
Max. and min. transmission	0.989 and 0.964
Refinement method	Full-matrix least-squares on F^2
Data / restraints/ parameters	3895 / 0 / 234
Goodness-of-fit on F^2	1.078
Final R indices [I>2sigma(I)]	R1 = 0.0379, wR2 = 0.1022
R indices (all data)	R1 = 0.0477, wR2 = 0.1061
Largest diff. peak and hole	0.320 and −0.167 $e.Å^{-3}$

Appendix 18: Crystal data and structure refinement for **SVC_24** (**328**).



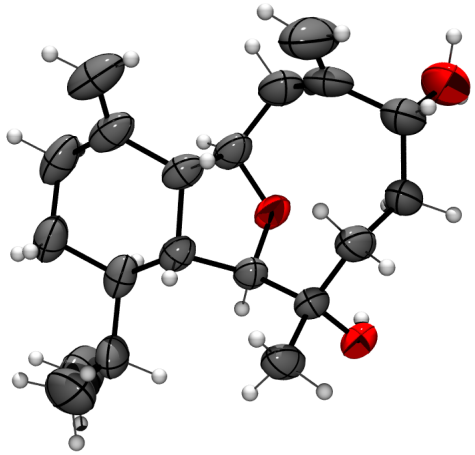
Identification code	SVC_24	
Empirical formula	C19 H30 O3	
Formula weight	306.43	
Temperature	100(2) K	
Wavelength	0.71073	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimension	a = 8.4212(2) Å	α = 94.845(10) °
	b = 9.4762(2) Å	β = 104.155(10) °
	c = 11.7943(2) Å	γ = 108.298(10) °
Volume	853.08(3) $Å^3$	
Z	2	
Density (calculated)	1.193 mg/m^3	
Radiation type	MoK\a	
Absorption coefficient	0.078 µ/mm	
F(000)	336	
Crystal size	0.6 × 0.5 × 0.4	
Theta range for data collection	2.299 – 30.022 °	
Index ranges	−11<=h<=+11; −13<=k<=+13; −16<=l<=+16	
Number of reflections measured	55875	
Number of independent reflections	4987	
R*int*	0.027	
Completeness to theta = 25.242	1	
Absorption correction type	Multi-scan	
Max. and min. transmission	0.928 and 0.782	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints/ parameters	4987 / 0 / 236	
Goodness-of-fit on F^2	1.045	
Final R indices [I>2sigma(I)]	R1 = 0.0349, wR2 = 0.0977	
R indices (all data)	R1 = 0.038, wR2 = 0.0996	
Largest diff. peak and hole	0.411 and −0.163 $e.Å^{-3}$	

Appendix 19: Crystal data and structure refinement for **SVC_38** (**272**).



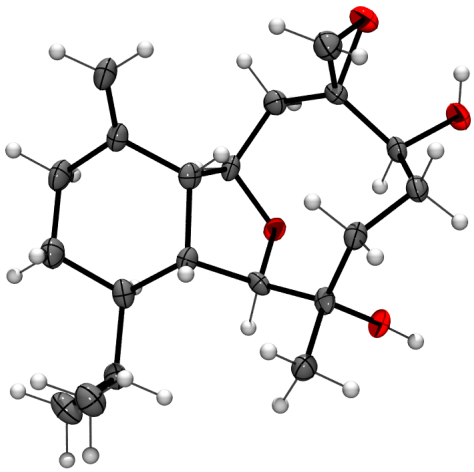
Identification code	SVC_38
Empirical formula	C20 H32 O2
Formula weight	304.45
Temperature	100(2) K
Wavelength	0.71073
Crystal system	Orthorhombic
Space group	C 2 2 21
Unit cell dimension	a = 10.2463(2) Å α = 90 °
	b = 19.1470(3) Å ß = 90 °
	c = 36.5947(6) Å γ = 90 °
Volume	7179.4(2) $Å^3$
Z	16
Density (calculated)	1.127 mg/m^3
Radiation type	MoK\a
Absorption coefficient	0.07 µ/mm
F(000)	2688
Crystal size	0.6 × 0.35 × 0.15
Theta range for data collection	2.199 – 32.98 °
Index ranges	−16<=h<=+16; −30<=k<=+30; −56<=l<=+56
Number of reflections measured	86896
Number of independent reflections	13517
R*int*	0.045
Completeness to theta = 25.242	0.998
Absorption correction type	Gaussian
Max. and min. transmission	0.992 and 0.96
Refinement method	Full-matrix least-squares on F^2
Data / restraints/ parameters	13517 / 0 / 475
Goodness-of-fit on F^2	0.984
Final R indices [I>2sigma(I)]	R1 = 0.0375, wR2 = 0.0884
R indices (all data)	R1 = 0.048, wR2 = 0.092
Largest diff. peak and hole	0.302 and −0.169 $e.Å^{-3}$

Appendix 20: Crystal data and structure refinement for **SVC_40** (**340**).



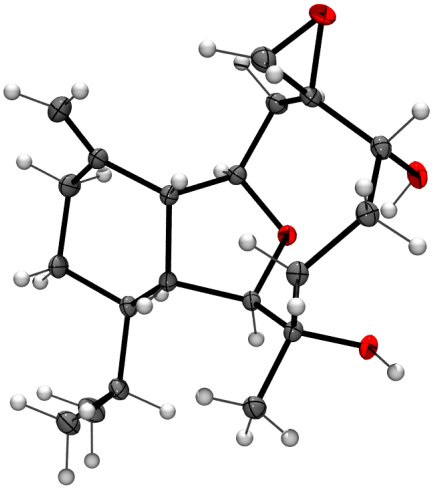
Identification code	SVC_40
Empirical formula	C20 H32 O3
Formula weight	320.45
Temperature	298(2) K
Wavelength	0.71073
Crystal system	Trigonal
Space group	P 32 2 1
Unit cell dimension	a = 17.4587(6) Å α = 90 ° b = 17.4587(6) Å β = 90 ° c = 10.7319(6) Å γ = 120 °
Volume	2832.9(2) $Å^3$
Z	6
Density (calculated)	1.127 mg/m^3
Radiation type	MoK\a
Absorption coefficient	0.074 µ/mm
F(000)	1056
Crystal size	0.6 × 0.2 × 0.1
Theta range for data collection	1.347 – 25.958 °
Index ranges	−22<=h<=+22; −22<=k<=+22; −13<=l<=+13
Number of reflections measured	74902
Number of independent reflections	3714
R*int*	0.091
Completeness to theta = 25.242	1
Absorption correction type	Multi-scan
Max. and min. transmission	0.746 and 0.638
Refinement method	Full-matrix least-squares on F^2
Data / restraints/ parameters	3714 / 0 / 212
Goodness-of-fit on F^2	1.055
Final R indices [I>2sigma(I)]	R1 = 0.0509, wR2 = 0.1122
R indices (all data)	R1 = 0.0764, wR2 = 0.1192
Largest diff. peak and hole	0.244 and −0.223 $e.Å^{-3}$

Appendix 21: Crystal data and structure refinement for **SVC_60** (**347**).



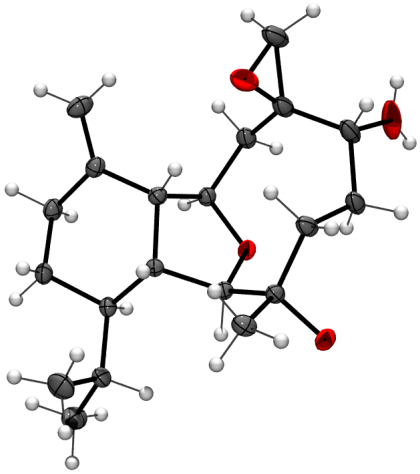
Identification code	SVC_60	
Empirical formula	C20 H32 O4	
Formula weight	336.45	
Temperature	100(2) K	
Wavelength	0.71073	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimension	a = 5.624(3) Å	α = 90 °
	b = 16.550(10) Å	ß = 90 °
	c = 19.160(12) Å	γ = 90 °
Volume	1783.3 19) $Å^3$	
Z	4	
Density (calculated)	1.253 mg/m^3	
Radiation type	MoK\a	
Absorption coefficient	0.085 µ/mm	
F(000)	736	
Crystal size	0.5 × 0.2 × 0.2	
Theta range for data collection	1.626 – 22.443 °	
Index ranges	−6<=h<=+6; −17<=k<=+17; −20<=l<=+20	
Number of reflections measured	13824	
Number of independent reflections	2295	
R*int*	0.097	
Completeness to theta = 25.242	0.727	
Absorption correction type	Multi-scan	
Max. and min. transmission	0.655 and 0.527	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints/ parameters	2295 / 0 / 223	
Goodness-of-fit on F^2	1.014	
Final R indices [I>2sigma(I)]	R1 = 0.044, wR2 = 0.0941	
R indices (all data)	R1 = 0.0701, wR2 = 0.1027	

Appendix 22: Crystal data and structure refinement for **SVC_49** (**343**).



Identification code	SVC_49
Empirical formula	C20 H32 O4
Formula weight	336.45
Temperature	100(2) K
Wavelength	0.71073
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimension	a = 5.9153(10) Å α = 90 ° b = 16.5335(2) Å β = 90 ° c = 18.3733(3) Å γ = 90 °
Volume	1796.92(5) $Å^3$
Z	4
Density (calculated)	1.244 mg/m^3
Radiation type	MoK\a
Absorption coefficient	0.085 µ/mm
F(000)	736
Crystal size	0.5 × 0.5 × 0.5
Theta range for data collection	2.217 – 30.029 °
Index ranges	−8<=h<=+8; −23<=k<=+23; −25<=l<=+25
Number of reflections measured	55772
Number of independent reflections	5246
R*int*	0.039
Completeness to theta = 25.242	0.999
Absorption correction type	Multi-scan
Max. and min. transmission	0.862 and 0.698
Refinement method	Full-matrix least-squares on F^2
Data / restraints/ parameters	5246 / 0 / 258
Goodness-of-fit on F^2	1.022
Final R indices [I>2sigma(I)]	R1 = 0.0295, wR2 = 0.0317
R indices (all data)	R1 = 0.0792, wR2 = 0.0805
Largest diff. peak and hole	0.315 and −0.159 $e.Å^{-3}$

Appendix 23: Crystal data and structure refinement for **SVC_48** (**348**).



Identification code	SVC_48
Empirical formula	C20 H32 O4
Formula weight	336.45
Temperature	100(2) K
Wavelength	0.71073
Crystal system	Trigonal
Space group	P 32 2 1
Unit cell dimension	a = 17.4404(4) Å α = 90 ° b = 17.4404(4) Å β = 90 ° c = 10.4848(2) Å γ = 120 °
Volume	2761.87(14) $Å^3$
Z	6
Density (calculated)	1.214 mg/m^3
Radiation type	MoK\a
Absorption coefficient	0.083 µ/mm
F(000)	1104
Crystal size	0.6 × 0.5 × 0.5
Theta range for data collection	2.336 – 34.998 °
Index ranges	−28<=h<=+28; −28<=k<=+28; −16<=l<=+16
Number of reflections measured	285176
Number of independent reflections	8105
R*int*	0.044
Completeness to theta = 25.242	0.999
Absorption correction type	Multi-scan
Max. and min. transmission	0.747 and 0.485
Refinement method	Full-matrix least-squares on F^2
Data / restraints/ parameters	8105 / 0 / 252
Goodness-of-fit on F^2	1.047
Final R indices [I>2sigma(I)]	R1 = 0.0364, wR2 = 0.0955
R indices (all data)	R1 = 0.0398, wR2 = 0.0975
Largest diff. peak and hole	0.653 and −0.541 $e.Å^{-3}$