Towards the Total Synthesis of Hypoestoxide and Dihypoestoxide

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Abstract

The involvement of hetero Diels-Alder dimerisations in the biosynthesis of natural products has been a source of debate for many years. Hypoestoxide and dihypoestoxide are two verticillane-type diterpenoids with closely related structures. Both were isolated from the same extracts of *Hypoestes rosea* in Nigeria. These two natural products constitute another example of a potential hetero Diels-Alder dimerisation in biosynthesis. Therefore, this thesis reports the work towards the diterpene hypoestoxide in order to study the hetero Diels-Alder dimerisation.

The introduction emphasises the different biological properties of hypoestoxide and the isolation of dihypoestoxide. The biosynthesis of terpenes, the only previous synthesis of an isomer of hypoestoxide reported to date and the hetero Diels-Alder dimerisation in biosynthesis are described. Former Hayes group work about the stereochemical assignment of dihypoestoxide is also detailed in this part.

The results and discussion suggests a synthetic route to hypoestoxide starting from geraniol, which constitutes a sustainable source of starting material for this synthesis. Different approaches towards the formation of the exocyclic enone moiety of hypoestoxide at a later stage in the synthesis would be discussed. Challenges to remove the additional carbon at C12 position would be detailed in this part. A brief conclusion and future work in this regard are given.

Experimental procedures and full characterisation data of the different intermediates synthesised by this route are detailed.

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Abbreviations

Ac: acetate

Aq: aqueous

bFGF: basic fibroblast growth factor

BQ: benzoquinone

DBU: 1,8-diazabicycloundec-7-ene

DIBAL-H: diisobutylaluminium hydride

DIPEA: diisopropylethylamine

DMAP: 4-dimethylaminopyridine

DMAPP: *N*,*N*-dimethylallyl pyrophosphate

DMDO: dimethyldioxirane

DMF: *N*,*N*-dimethylformamide

DMP: Dess-Martin periodinane

DMSO: dimethyl sulfoxide

eq: equivalents

Et: ethyl

FPP: farnesyldiphosphate

GPP: geranyldiphosphate

GGPP: geranylgeranyldiphosphate

h: hours

HOMO: highest occupied molecular orbital

^{i}Bu: isobutyl

IKK: IκB kinase

IPP: isopentyl pyrophosphate

LDA: lithium diisopropylamide

LHMDS: lithium hexamethyldisilazide

LUMO: lowest unoccupied molecular orbital

m-CPBA: *m*-chloroperbenzoic acid

Me: methyl

min: minutes

MOM: methoxymethyl

Ms: mesyl

NMO: *N*-methylmorphline-*N*-oxide

NMR: nuclear magnetic resonance

PCC: pyridinium chlorochromate

Ph: phenyl

Pi: inorganic phosphate

PPi: inorganic pyrophosphate

ppm: parts per million

Pr: propyl

psi: pounds per square inches

p-TSA: *para*-toluenesulfonic acid

RRCM: relay ring-closing metathesis

r.t: room temperature

SCF: self-consistent field

TBS: *tert*-butyldimethylsilyl

^{t}Bu: *tert*-butyl

TFA: trifluoroacetic acid

THF: tetrahydrofuran

TLC: thin layer chromatography

TMP: 2,2,6,6-tetramethylpiperidine

TMS: trimethylsilyl

TPAP: tetrapropylammonium perruthenate

Ts: tosyl

VEGF: vascular endothelial growth factor

Wt: weight

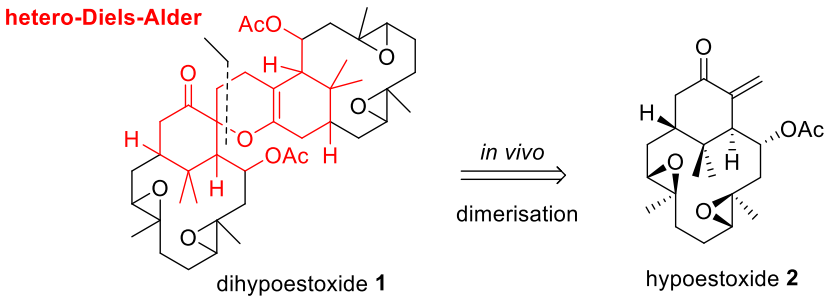
Chapter 1: Introduction

1.1. Hypoestoxide and Dihypoestoxide Isolation

Dihypoestoxide **1** was isolated in 1984 from *Hypoestes rosea* (Acanthaceae), an evergreen tropical shrub, which can be found in the rainforests of Nigeria.[1] Its structure was determined using a combination of NMR spectroscopy and mass spectrometry, but the stereochemical assignment was not determined at the time of isolation. Contrary to the other natural products containing a spirochroman ring system, the biological properties of **1** have not been investigated.

Interestingly, one year prior the isolation of **1**, another closely related diterpene, hypoestoxide **2** was isolated from extracts of the same plant.[2] Therefore, it was suggested that hypoestoxide **2** could be the biosynthetic precursor of the dimer **1** by undergoing an *in vivo* hetero Diels-Alder dimerisation (Scheme 1).

It was also shown that dihypoestoxide **1** was not an artifact of the isolation process when an attempt to dimerise hypoestoxide **2** under the same conditions (hexane, 24 hours, reflux) as those used in the isolation failed to provide any dihypoestoxide **1**.



Scheme 1: Dihypoestoxide **1** and hypoestoxide **2**

Extracts of *Hypoestes rosea* have been used in folk medicine for a long time to treat a wide range of conditions such as skin rashes and fungal infections.[3] Therefore, the

biological properties for hypestoxide **2** have been tested and it displays anti-inflammatory properties by inhibiting nuclear factor-κB activation through direct inhibition of IκB kinase (IKK) activity.[4] Hypoestoxide **2** could therefore be useful in treating various inflammatory diseases and may represent a prototype of a novel class of IKK inhibitors.

It was also shown that hypoestoxide **2** possesses anticancer properties. It displays significant *in vivo* antitumor activities that were comparable or better than most of the standard chemotherapeutic antiangiogenic agents tested such as cortisone acetate.[5]-[6] It was found that it inhibited vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF). Moreover, it exhibits antimalarial properties comparable to other antimalarial drugs.[7]

1.2 Verticillane-type Diterpenoids

Structurally, hypoestoxide **2** is a bicyclo[9.3.1]pentadecane diterpenoid containing a rigid "inside-outside" *trans* fused ring system decorated with an exocyclic enone, two epoxide moieties and an acetate group. Other natural products belonging to the verticillane family possess the same ring system[8] such as verticillol **3**,[9] verticillene **4** and epiverticillol **5** (Figure 1).

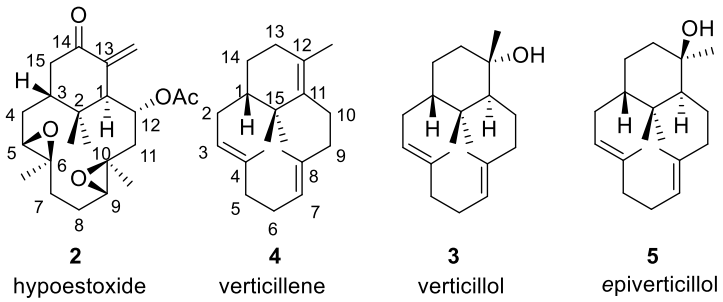
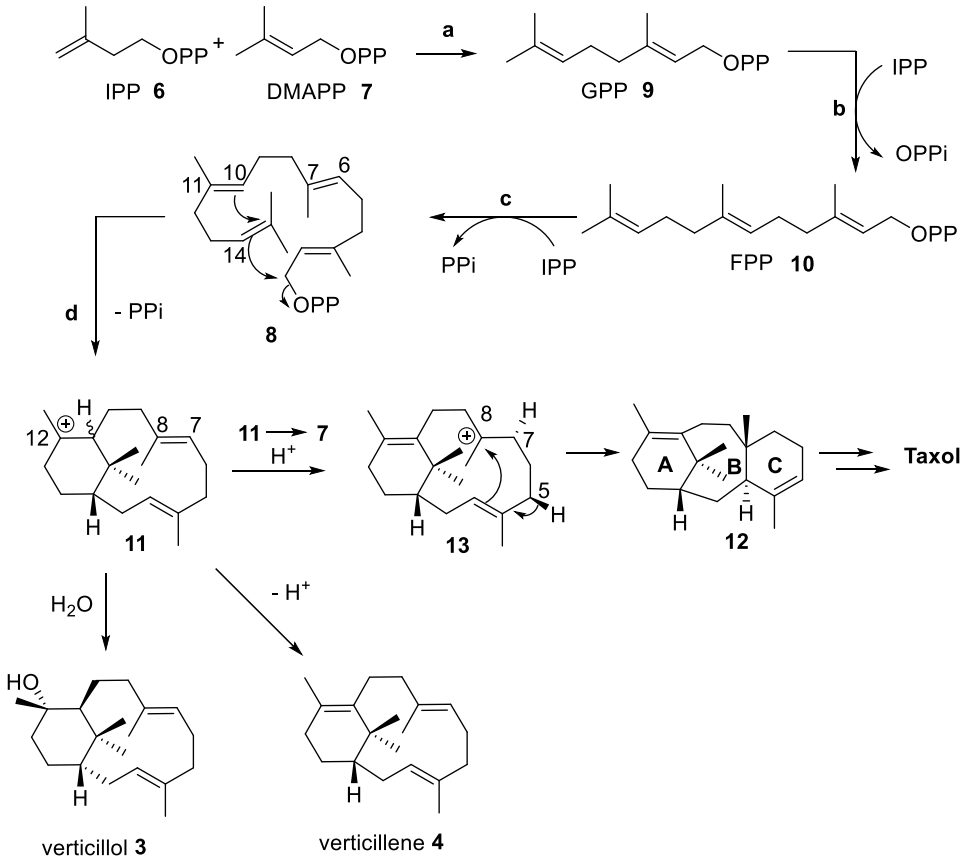


Figure 1: Some verticillane-type diterpernoids

1.2.1. Verticillane Biosynthesis

All terpenoids are assembled biosynthetically from only two precursors: isopentenyl pyrophosphate (IPP) **6** and dimethylallyl pyrophosphate (DMAPP) **7**.

From these precursors, all plants possess a central route to the universal building blocks needed for mono-, sesqui-, di-, tri and tetra-terpene biosynthesis. Geranylgeranyldiphosphate (GGPP) **8** is the common precursor for the biosynthesis of all diterpenes. IPP **6** and DMAPP **7** react together *via* a transferase enzyme to form geranyldiphosphate (GPP) **9**, which is subsequently converted into farnesyldiphosphate (FPP) **10** by reaction with another molecule of IPP **6** catalysed by a synthase enzyme. Then the formation of GGPP **8** is proceeded through a reaction between FPP **10** and IPP **6.** The cyclisation *via* a diterpene cyclase leads to verticillen-12-yl carbocation **11**, which can then be trapped by water to provide verticillol **3** or lose a proton to afford verticillene **4**, thus forming verticillane-type diterpenoids (Scheme 2).



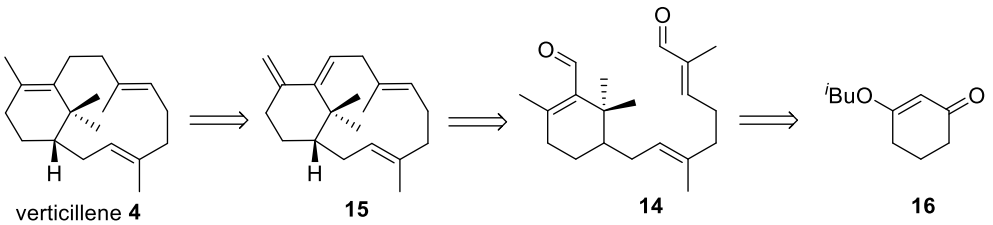
a: Dimethylallyl*trans*-transferase; **b:** (2*E*,6*E*)-Farnesyldiphosphate synthase;
c: Geranylgeranyldiphosphate synthase; **d:** Diterpene synthase.

Scheme 2: Verticillane and taxane biosynthesis

Further interest in verticillanes is linked to the role they play in the biosynthesis of the taxane family, where they are a precursor to the tricyclic taxane skeleton.[10]-[11] Indeed, it has been shown that the cyclisation mechanism from (*E,E,E*)-geranylgeranyl diphosphate **8** to taxa-4,11-diene **12** proceeds through a verticillen-12-yl carbocation intermediate **11**.[12] Subsequently, **11** is converted by a transannular proton transfer (C11 to C7) to the isomeric verticillen-8-yl cation **13** and a final cyclisation forms the C ring of **12** (Scheme 2).

1.2.2. Pattenden's Verticillene Total Synthesis

In 1985, Pattenden described the only total synthesis of verticillene **4** to date as part of studies towards biomimetic synthesis of the taxane family.[13] The synthesis route featured an intramolecular McMurry reaction of the *bis*-aldehyde **14** with concomitant 1,5 hydrogen sigmatropic rearrangement to elaborate the twelve-membered ring **15**. The 1,4-reduction of the 1,3-diene **15** using sodium in liquid ammonia generated verticillene **4** (Scheme 3).

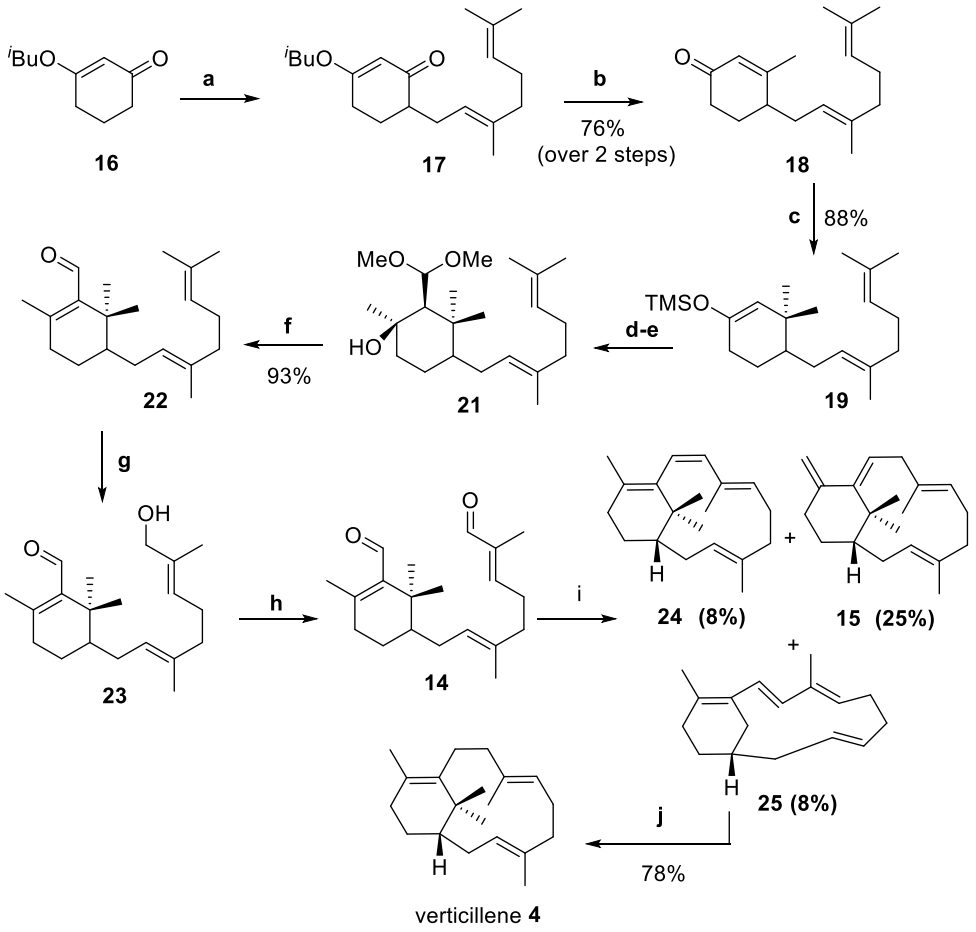


Scheme 3: Verticillene **4** retrosynthesis

Synthesis of the key intermediate *bis*-aldehyde **14** started with an alkylation of the enolate derived from 3-isobutoxycyclo-2-enone **16** with geranyl bromide to give the 4-substituted-1,3-dione enol ether **17**. Addition of methyl lithium to **17**, followed by acid hydrolysis provided the disubstituted cyclohexenone **18**, which was then added to a solution of lithium dimethylcuprate. The resulting enolate was quenched at -78 °C using chlorotrimethylsilane to afford the intermediate **19** (Scheme 4).

The silyl enol ether **19** and trimethyl orthoformate were added concurrently to a solution of $TiCl_4$ in dichloromethane to afford the *cis*-ketoacetal **20**. Tertiary alcohol **21**, provided by the addition of methylmagnesium iodide to **20**, underwent a dehydration in the presence of $POCl_3$ in pyridine to give the unsaturated aldehyde **22**. Oxidation of the trienal **22** using catalytic SeO_2 afforded the *E*-allylic alcohol **23**,

which on oxidation using MnO_2 generated the desired key intermediate **14** (Scheme 4).



a: LDA,THF, -78 °C, 1 h, then geranyl bromide, -78 °C,10 min; **b:** MeLi, THF, -40 °C, 1 h then 0 °C, 3 h; **c:** Me_2CuLi, TMSCl, Et_2O, -5 °C, 30 min, then <0 °C, 2 h; **d:** trimethyl orthoformate, $TiCl_4$, CH_2Cl_2, -78 °C, 3 h (58%); **e:** MeMgI, Et_2O, r.t, 14 h (98%); **f:** $POCl_3$, pyridine, 0 °C, 30 min then 65 °C, 3 h; **g:** ^tBuOOH, SeO_2, CH_2Cl_2, r.t, 3 h (21%); **h:** MnO_2, CH_2Cl_2, r.t, 45 min (98%) ; **i:** $TiCl_3$, Zn-Cu, 1,2-dimethoxyethane, r.t, 22 h, then reflux, 3 h ; **j:** NH_3 liquid, Na metal, reflux, 30 min.

Scheme 4: Synthesis of verticillene **4**

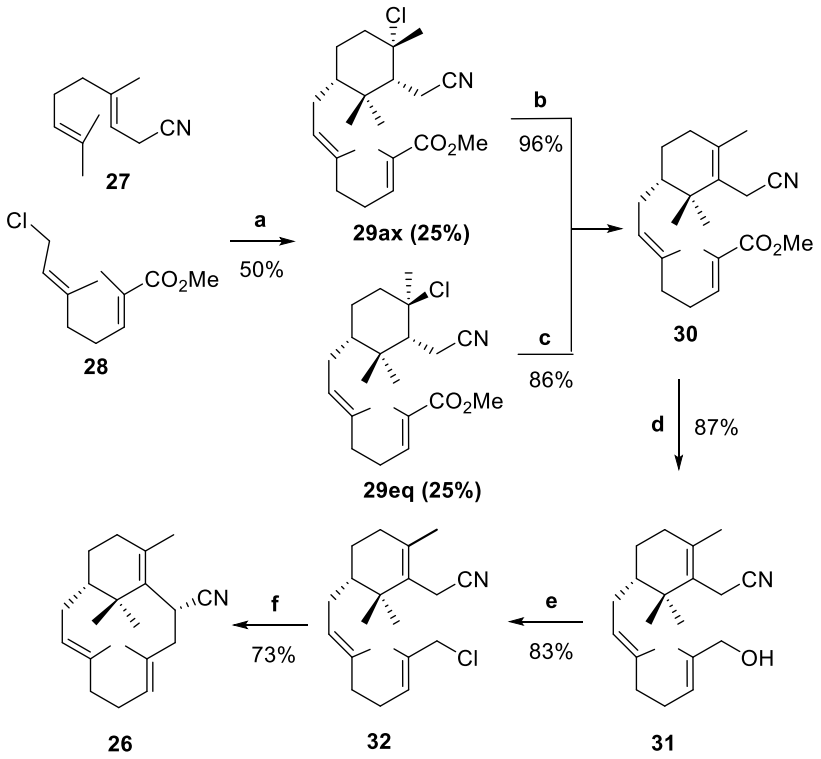
Addition of a solution of the *bis*-aldehyde **14** in dimethoxyethane over 20 hours to a slurry of $TiCl_3$ and Zn-Cu couple in the same solvent led to a mixture of the three hydrocarbons **13**, **24**, **25**, which were separable after chromatography on silica gel impregnated with silver nitrate. The bicyclic tetraene **15** was assumed to be formed *via*

1,5-hydrogen sigmatropic rearrangement of the initial coupled product **24** (Scheme 4). The synthesis of verticillene **4** was then completed by treating the 1,3-diene **15** with sodium in liquid ammonia, followed by quenching with ammonium chloride.

1.2.3. Kato's Epiverticillol Total Synthesis

In 1996, Kato reported the synthesis of 10-cyanoverticillene **26** as a key intermediate in his attempt to form verticillol **3** (Scheme 5).[14] In 2002, using the same approach, he successfully synthesised an isomer of verticillol namely epiverticillol **5**.[15]

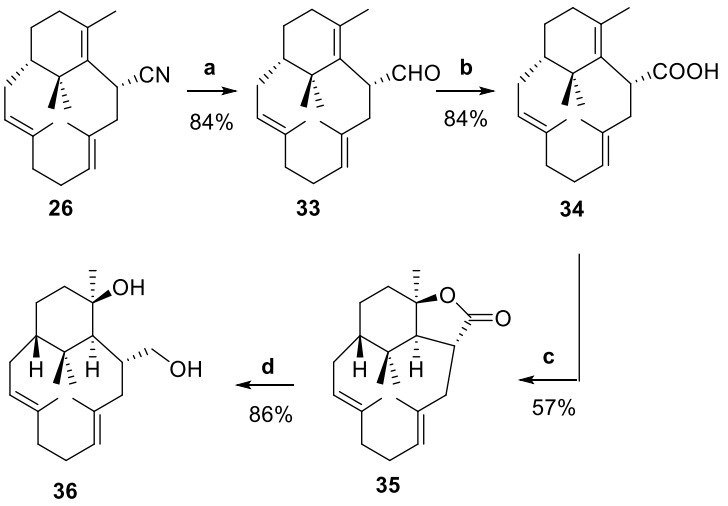
10-Cyanoverticillene **26** is obtained after a five-step synthesis from two different aliphatic precursors **27** and **28** (Scheme 5), which were coupled together with tin tetrachloride to form an axial chloride **29ax** and an equatorial chloride **29eq**. The mechanism of this reaction will be discussed later in this report (see part 2.3.1 chapter 2). Dehydrochlorination of **29ax** using LiCl in dimethylformamide at 100 °C afforded cyanoester **30**. However, the same conditions employed on the equatorial chloride **29eq** failed to provide the desired product **30**. Therefore, Kato employed $ZnCl_2$ at room temperature for two days before addition of 2-methyl-2-butene to afford the intermediate **30**. The methyl ester **30** was reduced using AlH_3 to allyl alcohol **31**, which then underwent chlorination using Appel conditions to afford chloride **32**. Deprotonation in α position to the nitrile group in **32** using LHMDS formed a carbanion which allowed the formation of the twelve-membered ring of **26** by intramolecular displacement of the chloride group.



a: $SnCl_4$ (1.2 eq), **27** (1.1 eq), CH_2Cl_2, -78 °C to -30 °C, 3 h; **b:** LiCl (9 eq), DMF, 100 °C, 3 h; **c:** $ZnCl_2$ (1.1 eq), CH_2Cl_2, r.t, 2 days, then 2-methyl-2-butene (13.7 eq); **d:** AlH_3 (2.5 eq), Et_2O, -78 °C, 3 h; **e:** PPh_3 (1.5 eq), CCl_4, reflux, 1 h; **f:** LHMDS (5 eq), THF, 60 °C, 2 h.

Scheme 5: Kato's synthetic route of 10-cyanoverticillene **26**

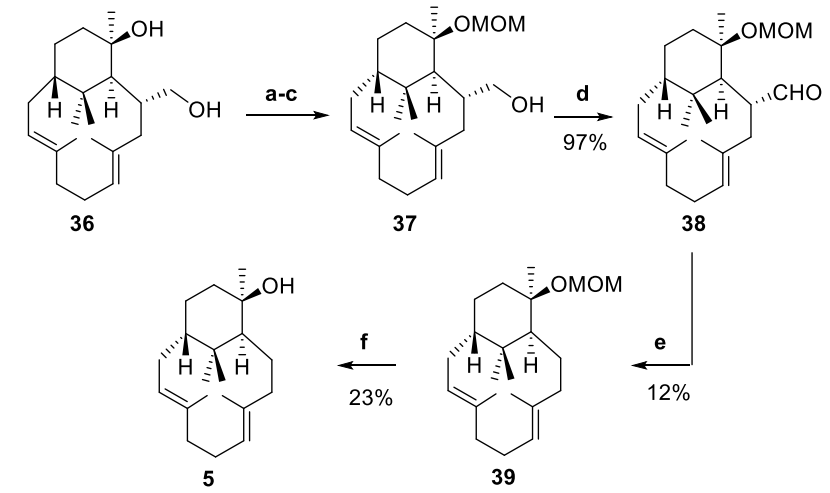
Reduction of intermediate **26** using DIBAL-H gave the aldehyde **33**, which was oxidised to the carboxylic acid **34** using Pinnick's conditions. Formation of lactone **35** was afforded from carboxylic acid **34** and TFA under reflux conditions. Cleavage of lactone **35** using $LiAlH_4$ provided diol **36**, and therefore the introduction of the tertiary hydroxyl function present in epiverticillol **5** (Scheme 6).



a: DIBAL-H (2 eq), CH_2Cl_2, -78 °C, 2 h; **b**: NaH_2PO_4 (1 eq), $NaClO_2$ (1.2 eq), 2-methyl-2-butene (10 eq), ^tBuOH,H_2O r.t, 7 h; **c**: TFA, reflux, 30 min; **d**: $LiAlH_4$ (4.8 eq), THF, reflux, 1 h.

Scheme 6: Synthesis of diol **36**

Protection of the two hydroxyl groups in **36** by an acetate and a MOM-protected group, followed by the selective deprotection of the acetate group provided intermediate **37**. Primary alcohol **37** was then oxidised with TPAP and *N*-methylmorpholine *N*-oxide to afford aldehyde **38.** Decarbonylation of **38** was achieved by the action of Wilkinson's catalyst in a 12% yield to provide the MOM-protected epiverticillol **39**. The completion of the epiverticillol **5** total synthesis then proceeded through the deprotection of the MOM group from **39** with $BF_3.Et_2O$ in ether (Scheme 7).



a: Ac_2O (5.0 eq), pyridine, r.t, 3 h, 77%; **b:** DIPEA, MOMCl, 60 °C, 14 h, 79%; **c:** 2 M KOH-MeOH, r.t, 6 h, 100%; **d:** TPAP (0.05 eq),NMO (1.5 eq), CH_2Cl_2, r.t, 14 h; **e:** $RhCl(PPh_3)_3$ (1.3 eq), toluene, 110 °C, 10 min; **f:** $BF_3.Et_2O$ (3.3 eq), Et_2O, 0 °C, 3 h.

Scheme 7: Synthesis of epiverticillol **5**

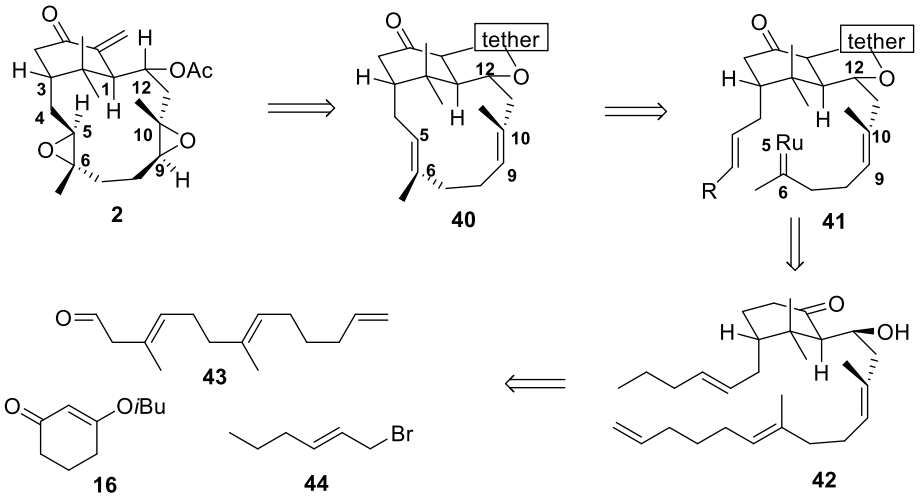
1.3. Previous Work Towards the Synthesis of Hypoestoxide

1.3.1 Njardarson's Approach : Synthesis of an Isomer of Hypoestoxide

In 2008, Njardarson *et al.* synthesised an isomer of hypoestoxide during their initial attempt to make hypoestoxide **2**, thus constituting the only synthesis work reported to date towards hypoestoxide.[16]

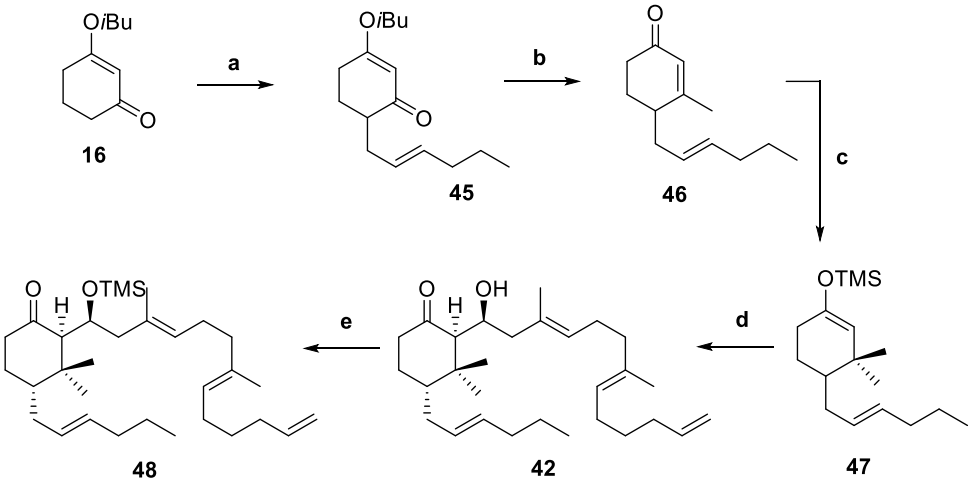
Njardarson's attempted synthesis of **2** was based on a macrocyclisation using a conformationally controlled relay ring-closing metathesis as a key step. The retrosynthesis proceeds through diene **40**, from which access to other verticillane-type diterpenoids shoud be possible. Intermediate **40** would be provided *via* a controlled relay ring-closing metathesis (RRCM) of ruthenium carbene **41**. In order to bring together the two olefin termini, rigidification of the six-membered ring was required and this was achieved by tethering the six-membered ring to form ruthenium carbene intermediate **41**. Ketone **42** was the precursor of the tethering and was the result of the

combination of three simple building blocks: aldehyde **43**, enone **16** and (*E*)-1-bromo-2-hexene **44** (Scheme 8).



Scheme 8: Njardarson's retrosynthesis of hypoestoxide **2**

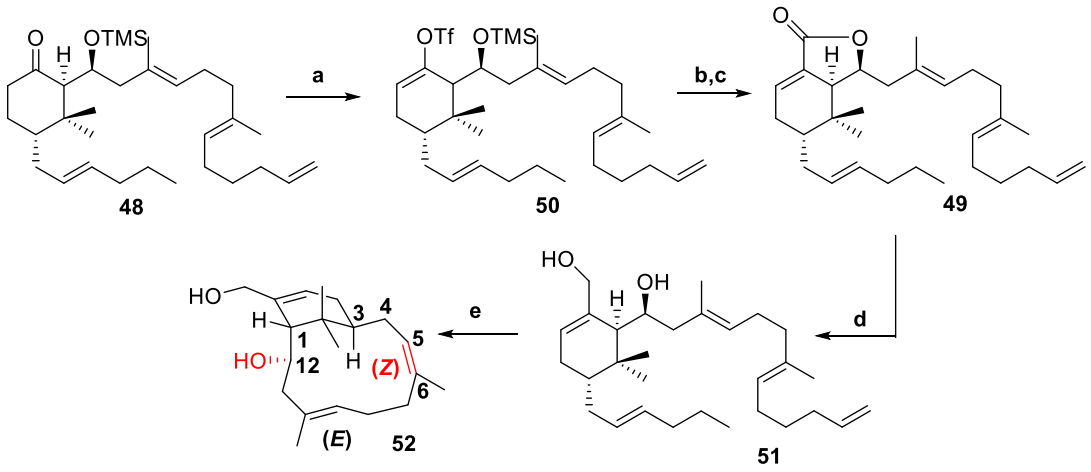
The key intermediate **42** was produced in four steps as described in Scheme 9. Enone **16** was deprotonated using LDA to form an enolate which reacted with (*E*)-1-bromo-2-hexene **44** to give the intermediate **45**. Methylation on **45** using methyl lithium, followed by an enone transposition in acidic conditions afforded enone **46** (Scheme 9). Conjugate addition of methyl cuprate to enone **46**, followed by trapping of the resultant enolate *in situ* afforded the trimethylsilyl enol ether **47**. This was then coupled with aldehyde **43**, facilitated by the addition of zinc chloride which promoted the desired aldol reaction in order to form tetraene **42** with the desired *anti*-configuration. The hydroxy group of **42** was protected in the next step with a TMS group to give the key intermediate **48** (Scheme 8).



a: LDA (1.05 eq), (*E*)-1-bromo-2-hexene **44** (1.2 eq), THF, -78 °C to 0 °C, 2 h; **b:** MeLi (2.7 eq), THF then HCl, -78 °C to 23 °C, 12 h, 72% (over 2 steps); **c**: MeLi (2.5 eq), CuI (1.25 eq), Et_2O then TMSCl (5 eq), Et_3N (5 eq), -5 °C, 2.5 h, 88%; **d:** MeLi (1.06 eq), Et_2O, then $ZnCl_2$ (1.1 eq), then **43** (0.5 eq), -45 °C, 2 h; **e:** TMSCl (1.9 eq), Et_3N, CH_2Cl_2, 0 °C to 23 °C, 18 h, 65% (over 2 steps).

Scheme 9: Synthesis of a common macrocyclisation precursor **48**

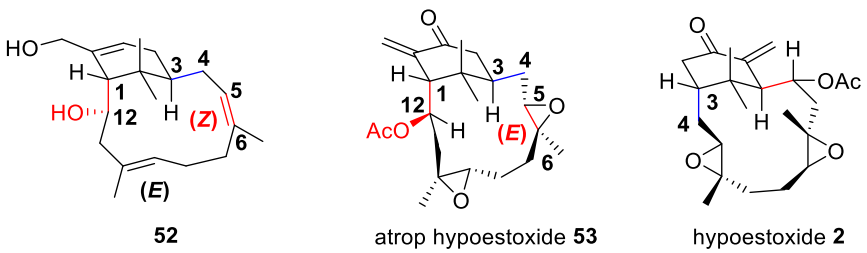
From this stage of the synthesis, Njardarson investigated the ring closing metathesis methodology on five- and seven-membered ring tethers. All the ring closing metathesis attempts on five-membered ring tethers **50** failed, thus Njardarson focused all his efforts on the formation of the seven-membered ring tether. Synthesis of lactone **49** proceeded in three steps from ketone **48**. Reduction of **49** to the diol **51,** followed by the addition of an excess of titanium isopropoxide prior to the addition of the Grubbs catalyst allowed formation of triene **52** in one-pot directly from diol **51** by tethering *in situ* prior to performing the metathesis reaction (Scheme 10).



a: LHMDS (2.9 eq), Comins' reagent (1.9 eq), THF, -78 °C, 5 h, 95%; **b:** Amberlyst-15 (cat), MeOH, THF, 23 °C, 3 h, 95%; **c:** $[Pd(PPh_3)_4]$ (0.25 eq), CO (60 psi) , Et_3N (12 eq), DMF, 50 °C, 15 h, 92%; **d:** DIBAL-H (8 eq), toluene, -78 to 23 °C, 1h, 93%; **e:**$Ti(O\textit{i}Pr)_4$ (10 eq), then Grubbs II catalyst (20 mol %), toluene, reflux, 8 min, 95%.

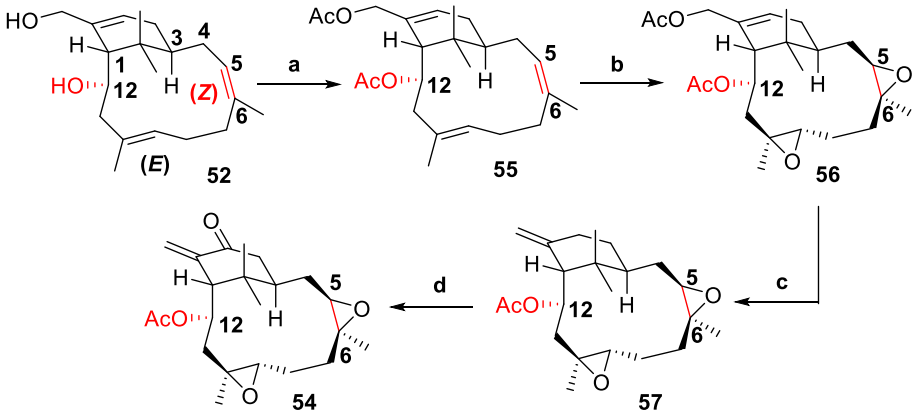
Scheme 10: Synthesis of intermediate **52**

However, NMR spectroscopy analysis of **52** showed that the molecule possessed the wrong conformation to that required for hypoestoxide **2**. In fact, the single bond C3-C4 was equatorial and C1-C12 possessed an axial conformation whereas the same single bonds on the natural product **2** were respectively axial and equatorial, thus **52** had a closer structure to atrop-hypoestoxide **53** than to the natural product **2** (Scheme 11). Moreover the ring closing metathesis gave the *Z* olefin at the C5=C6 double bond instead of the *E* desired conformation. The C12 stereocentre also had the wrong configuration, established from intermediate **42** (Scheme 11).



Scheme 11: Conformation of intermediate **52** compared with atrop hypostoxide **53**

Nonetheless, the synthesis was continued to provide an isomer of the atrop-hypoestoxide **54** by first *bis*-acetylating the metathesis product **52**, followed by performing a substrate controlled *bis*-epoxidation on the two macrocyclic olefins using DMDO to afford intermediate **56**. By using Tsuji's reductive allylic transposition the exocyclic double bond in **57** was formed, and a subsequent allylic oxidation with selenium dioxide provided an allylic alcohol. Oxidation using Dess-Martin periodinane (DMP) afforded enone **54**, which constitutes the wrong atropisomer of the natural product **2** and an isomer of **53** (Scheme 12).



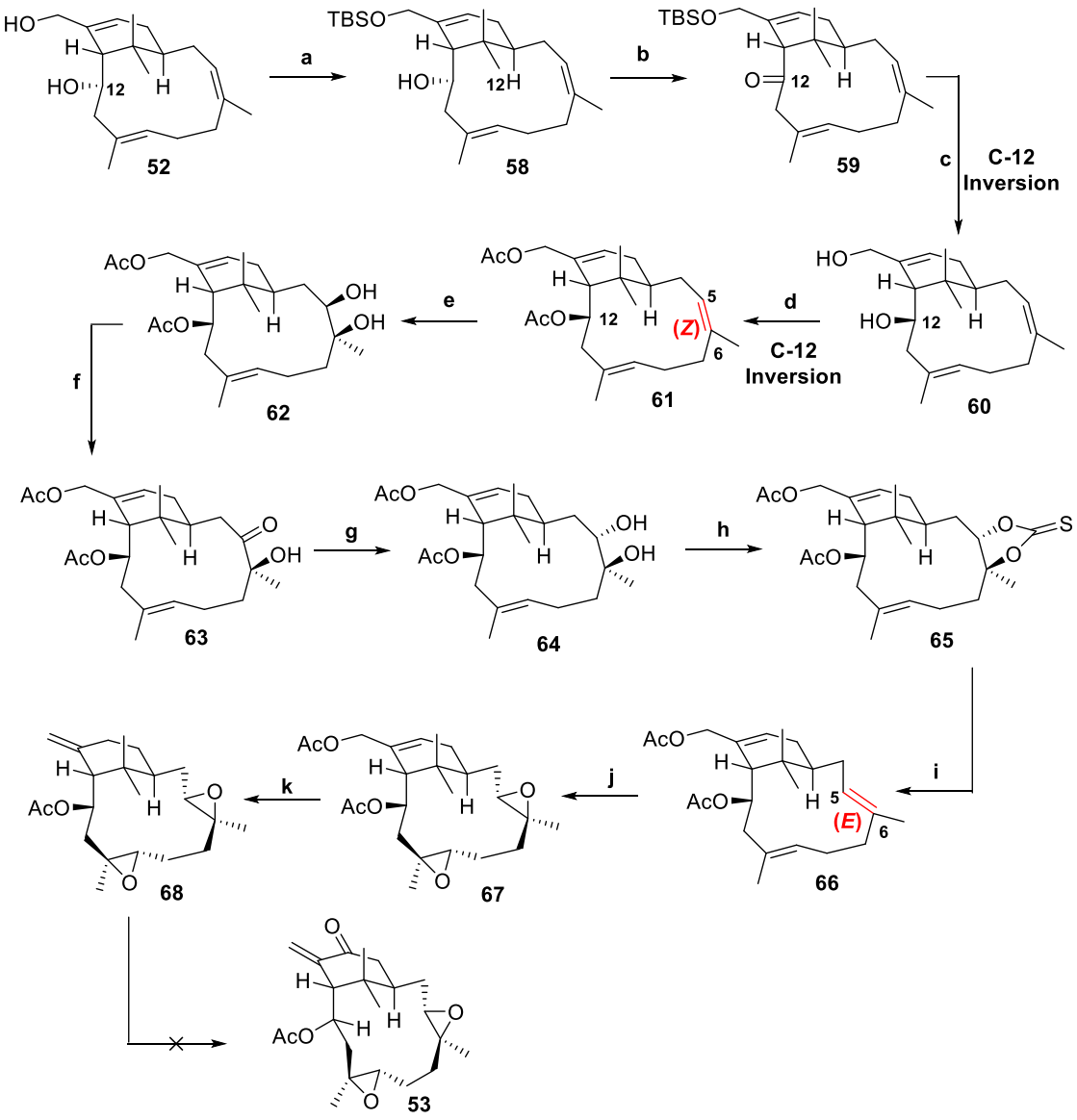
a: Ac_2O (10 eq), DMAP (2 eq), Et_3N (20 eq), CH_2Cl_2, 23 °C, 1 h, 92%; **b**: DMDO (2 eq), acetone, 23 °C, 10 min, 93%: **c**: $Pd(PPh_3)_4$ (0.04 eq), Et_3N, HCO_2H, THF, 75 °C, 15 h, 87%; **d**: SeO_2 (2 eq), CH_2Cl_2:MeOH (1:1), 65 °C, 15 h then DMP (2 eq), CH_2Cl_2, 1 h, 77%.

Scheme 12: Synthesis of hypoestoxide isomer **54**

To synthesise atrop-hypoestoxide **53** from bicyclic substrate **52**, inversion of the C12 stereocentre and the C5=C6 bond geometry are required (Scheme 13). The first challenge considered was inverting the C12 stereocentre.

This was done in a four-step sequence starting by the protection of the primary alcohol of **52** by a TBS group. Oxidation of the secondary alcohol using the Ley conditions afforded ketone **59** which was reduced stereoselectively to the alcohol in order to

inverse the C12 stereocenter. The secondary alcohol was then protected with an acetate group to afford *bis*-acetylated product **61** as a single product. In order to invert the geometry of the C5=C6 double bond, a three-step sequence was developed. The C5=C6 double bond of **61** was dihydroxylated in order to form *syn* diol **62**. Secondary hydroxyl group of **62** was converted to the ketone **63** by Swern oxidation. Stereoselective reduction of **63** using sodium borohydride afforded the *anti* diol **64**. The hydroxyl groups of diol **64** were then converted into a cyclic thiocarbonate **65**, which, when subjected to the Corey-Winter deoxygenation conditions afforded the *E*,*E*,*E*-triene **66**. A *bis*-epoxidation of the macrocyclic diene moiety, and a palladium-mediated allylic transposition were again employed to form the exocyclic double bond moiety **68**. Unfortunately, the last step of the synthesis which involved oxidising the allylic position to atrop-hypoestoxide **53** failed using a range of oxidising reagents including selenium dioxide (Scheme 13).



a: TBSCl (3 eq), imidazole (9 eq), CH_2Cl_2, 23 °C, 30 min, 62%; **b:** TPAP (0.05 eq), NMO (1.5 eq), CH_2Cl_2, 23 °C, 45 min; **c:** $LiAlH_4$ (25 eq), THF, then HCl, 0 to 23 °C, 1 h, 96% (over 2 steps), **d:** Ac_2O (10 eq), Et_3N (20 eq), DMAP (2 eq), CH_2Cl_2, 23 °C, 1.5 h, 98%; **e:** OsO_4 (1.1 eq), THF, 0 to 23 °C, 3 h, 74%; **f:** $(COCl)_2$ (9 eq), Et_3N (36 eq), DMSO (18 eq), CH_2Cl_2, -78 to 0 °C, 1 h, 80%; **g:** $NaBH_4$ (10 eq), MeOH, 23 °C, 30 min, 80%; **h:** $Cl_2C{=}S$ (10.5 eq), DMAP(40 eq), CH_2Cl_2, 45 °C, 20 h, 91%; **i:** $P(OEt)_3$ (500 eq), 160 °C, 15 h, 86%; **j:** DMDO (2 eq), acetone, 23 °C, 4 h, 99%; **k:** $[Pd(PPh_3]_4$ (1 eq), Et_3N (10 eq), HCOOH (10 eq), THF, 75 °C, 15 h, 55%.

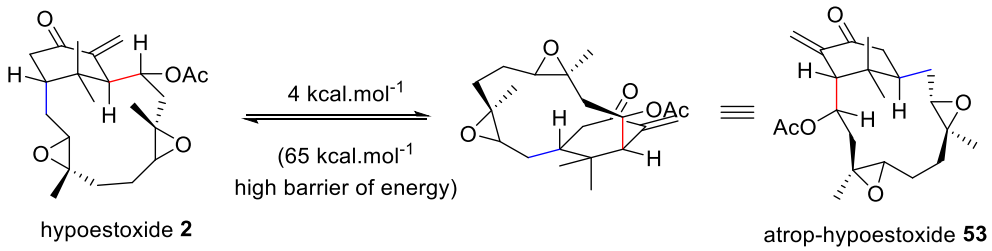
Scheme 13: Synthesis of 18-deoxy-atrop-hypoestoxide **68**

In summary, Njardarson reported the first synthesis efforts towards the natural product hypoestoxide **2**. An isomer of atrop-hypoestoxide, compound **54**, was formed using ring-closing metathesis as a key step, and the synthesis of 18-deoxy-atrop-hypoestoxide **68** was accomplished, which was one step away from atrop-hypoestoxide **53**.

This synthetic route potentially allowed access to a wide range of verticillanes. However the ring-closing metathesis methodology gave the undesired conformation on the twelve-membered ring required for hypoestoxide **2**.

1.3.2. Atropisomerism of Hypoestoxide

Verticillane skeleton containing an "inside-outside" ring system like hypoestoxide **2** can exist under two different atropisomers by flipping the half-chair conformation of the six-membered ring. Calculations (B3LYP/6-311 + G(d,p)) performed by Njardarson indicated that hypoestoxide **2** is 4.1 kcal/mol more stable than its atropisomer **53**. Moreover, the energy change attributed to the process of interconverting hypoestoxide **2** and its atropisomer **53** was estimated to be 65 kcal/mol.[16] This high barrier prevents the interconversion process between both atropisomers. Consequently, the stereochemistry of any cyclisation to form the twelve-membered ring has to be controlled in order to obtain hypoestoxide **2** instead of the undesired atrop-hypoestoxide **53** (Scheme 14).



Scheme 14: Hypoestoxide **2** and atrop-hypoestoxide **53**

1.4 Natural Products Containing Spirochroman Ring System

As already mentioned in this introduction, dihypoestoxide **1** contains a spirochroman ring system and is assumed to be formed by hetero Diels-Alder dimerisation of hypoestoxide **2**. Other examples where terpenes constitute a source of plausible hetero Diels-Alder adducts for dimerisation can be found in nature. Family of compounds such as the one containing a spirochroman ring system might result of this [4+2] cycloaddition. Some examples of natural products belonging to this family are shown in Figure 2.

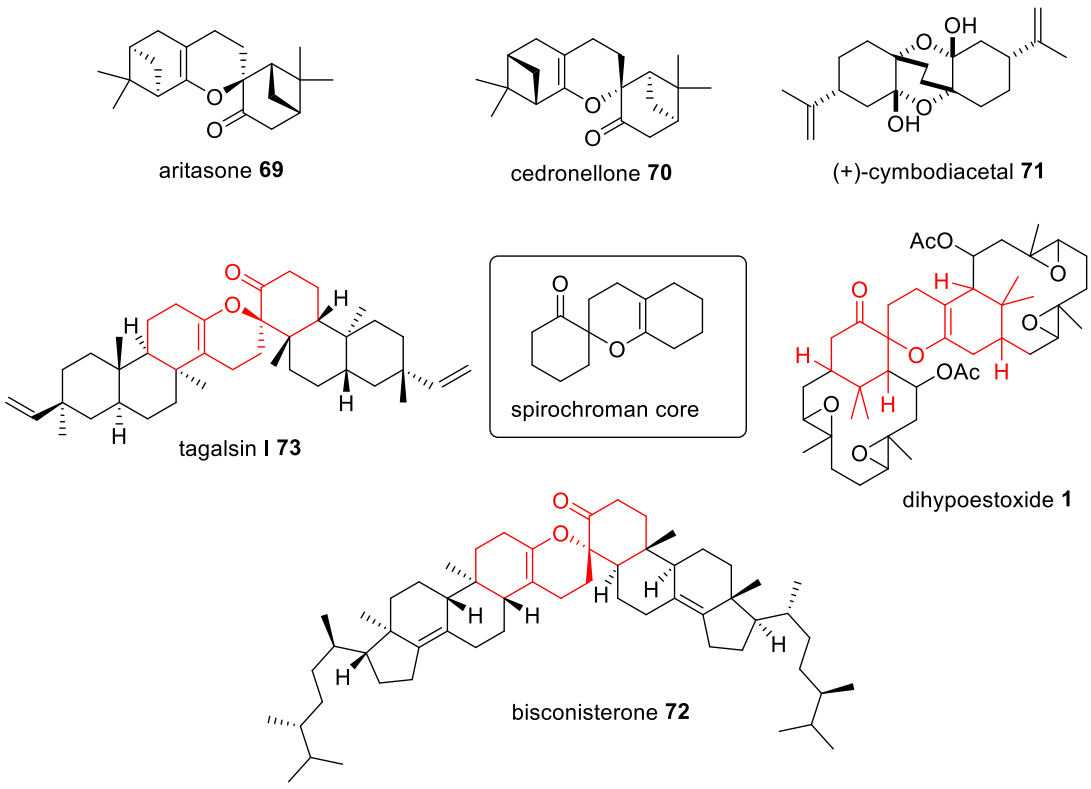


Figure 2: Natural products containing spirochroman core

Aritasone **69** and cedronellone **70** are enantiomers of each other but interestingly are extracted from two different plants. Aritasone **69** was isolated from the essential oil of

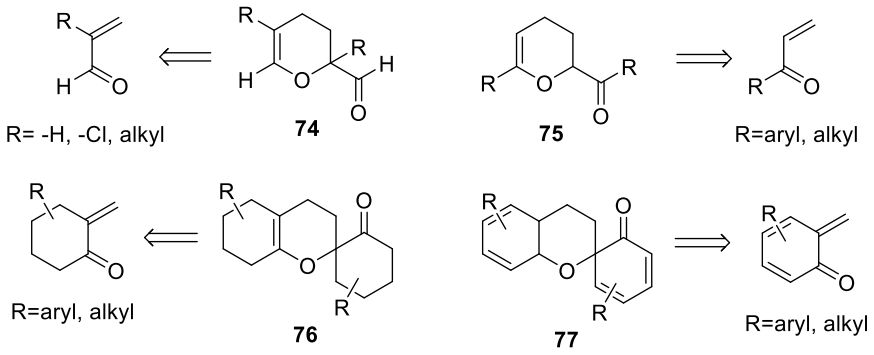
Chenopodium ambrosioides in 1955 [17] whereas cedronellone **70** was isolated from the aerial parts of *Cedronella canariensis* in 1987.[18] The spirochroman ring system at a high level of oxidation can be found in nature such as cymbodiacetal **71**, isolated from the essential oil of aerial parts of flowering *Cymbopogon martini* (cf p.26).

The wide variety of compounds expands to even more structurally complex natural products such as bisconiscasterone [19] **72** and tagalsin I [20] **73** isolated from marine sponge *Theonella Swinhoei* and mangrove plant *Ceriops Tagal* respectively.

1.5. Hetero Diels-Alder Dimerisation

The first thermal dimerisation of an α,β−unsaturated carbonyl was conducted on acrolein by Sherlin [21] to provide a dihydropyran derivative. In 1938, several compounds have been found to dimerise if heated with solvent or neat unusually under extreme conditions.[22]

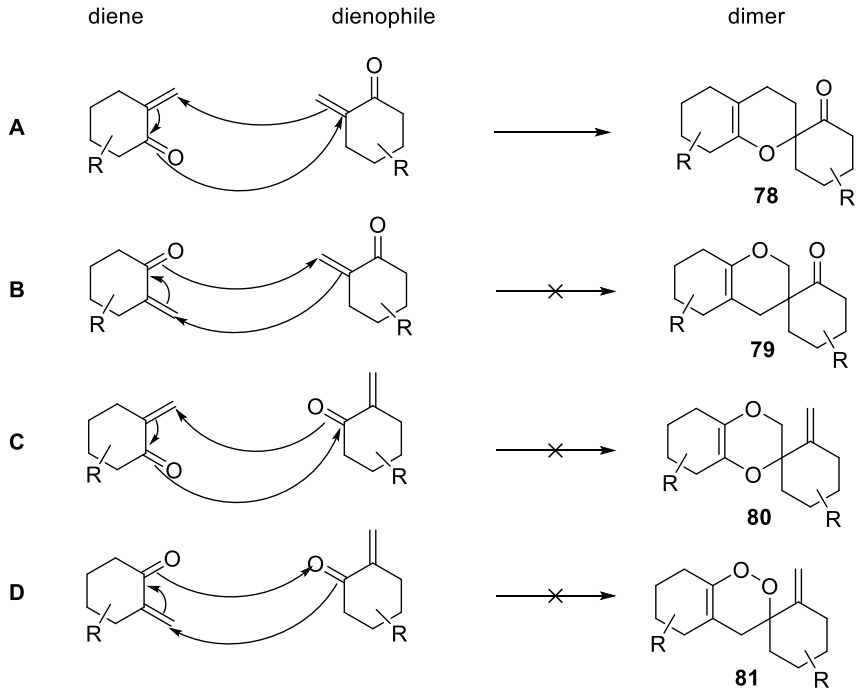
α,β−unsaturated carbonyls such as acrolein, α-alkylacroleins and α-chloroacrolein gave 2-formyl-3,4-dihydropyran derivatives **74**. Alkyl and aryl vinyl ketones gave 2-acyl-3,4-dihydropyrans **75** but α-alkylidene- and arylidenecyclanones gave spirochroman derivatives **776**. Similar behaviour was demonstrated for *o*-quinonemethides leading to **77** (Scheme 15).



Scheme 15: Dimerisation products of α,β−unsaturated carbonyls

1.5.1. Formation of Spirochroman Derivatives: Regioselectivity and Stereoselectivity

The exocyclic enone monomers such as hypoestoxide **2**, responsible for the formation of spirochroman derivatives (dihypoestoxide **1**) can in principle orientate themselves in four different ways to potentially give four different products (Scheme 16).

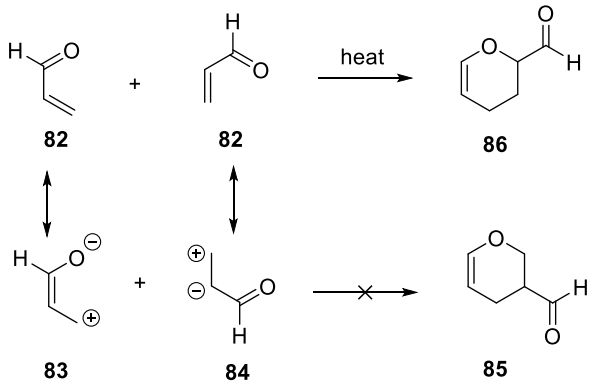


Scheme 16: Potential spirochroman derivatives

In the case of A and B, the two possible orientations of the diene are reacting with the C=C double bond of the dienophile to afford dimers **78** and **79**, whereas in the case of C and D, the same two orientations of the diene are reacting this time with the C=O double bond of the dienophile to provide dimers **80** and **81**.

However, only dimer **78** was formed, as the C=C bond of the dienophile has a higher reactivity towards the corresponding diene than the C=O bond of the same dienophile.[23]

This observation has been reinforced by studying in detail the dimerisation of acrolein **82**. The "polarity" model predicts that the dimerisation should occur through resonance forms **83** and **84** to form predominantly **85**. However the experience showed that only product **86** was formed regioselectively (Scheme 17).



Scheme 17: Dimerisation of acrolein **82**

The coefficients of the molecular orbitals for the HOMO and LUMO of acrolein **82** are described in Figure 3. Since this reaction is a dimerisation, the HOMO/LUMO gap is the same for both possible LUMO/HOMO pairings.

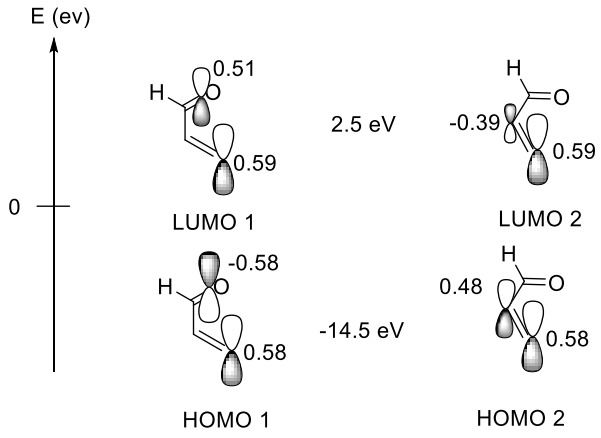


Figure 3: HOMO and LUMO of acrolein **82**

Products **86** and **85** are formed through two separate and independent chemical reactions, each of which has a different activation energy. If we use the coefficient provided in Figure 3 in the perturbation equation to calculate the overall energy savings for the formation of product **86** and **85**, this energy is lower for the formation of product **86** than the one to form product **85**. Although the energy differences are very close, 0.0393 for **86** and 0.0387 for **85**, it means the activation energy to form **86** is lower than **85**, thus explaining the observed regioselectivity.

The Diels-Alder reaction is not only characterised by its regioselectivity but also by its stereoselectivity and stereospecificity. The reaction of the C=C bond of the dienophile with the diene can give two regioisomers **78** and **79** *via* an *endo* or *exo* transition state (Scheme 16). The *endo* pathway is the most favoured due to the formation of secondary orbital interactions as described below (Figure 4).[23]

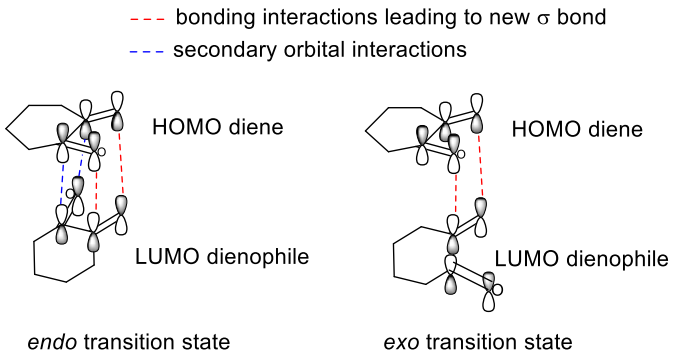


Figure 4: *endo* and *exo* transition states

Therefore, the hetero Diels-Alder dimerisation of exocyclic enones lead mainly to the formation of spirochroman derivatives similar to **78** via an *endo* transition state.

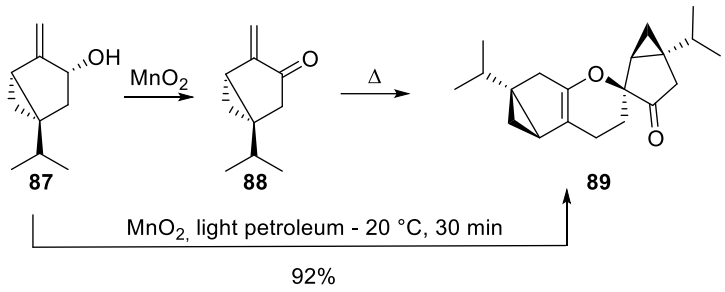
1.5.2. Hetero Diels-Alder Cycloaddition in Biosynthesis

Several examples of natural product dimers formed from terpene monomers via hetero Diels Alder dimerisation can be found in the literature. Surprisingly, the conditions used for this reaction can change substantially depending on the enone monomer. Some dimers are reported to be provided spontaneously by keeping the monomer neat or in solution at room temperature for several days, whereas others required moderately high temperature or high pressure over a long period of time to be formed.

1.5.2.1. Spontaneous Hetero Diels-Alder Dimerisation Reactions

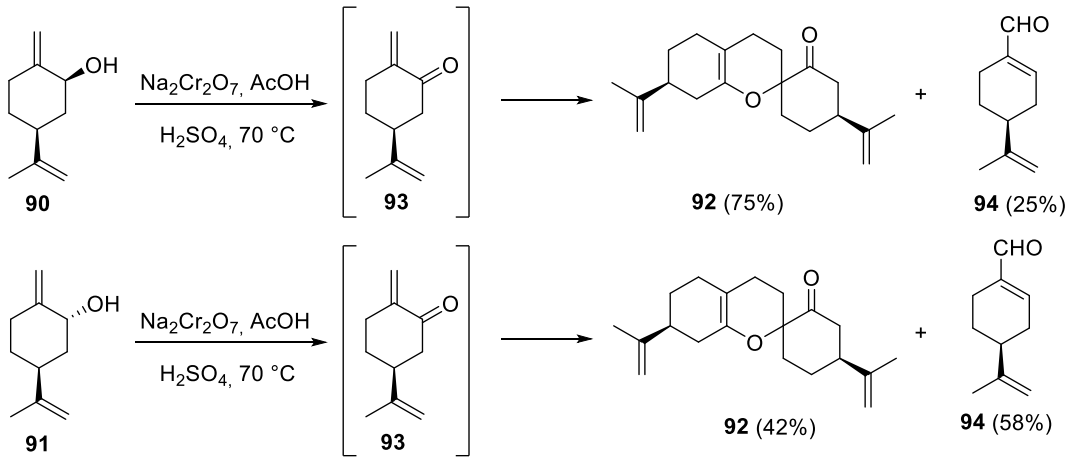
(+)-Sabinol **87** is a monoterpene isolated from the essential oil of *Juniperus Sabina*,[24] and oxidation of **87** with manganese dioxide gave sabinone **88**, which upon heating was rapidly converted into the spirochroman dimer **89**.[25] In 2003, it was reported that oxidation of sabinol **87** in light petroleum with manganese dioxide at -20 °C for 30

minutes afforded dimer **89** in 92% yield. The dimerisation was spontaneous and no traces of sabinone **88** were detected (Scheme 18).[26]



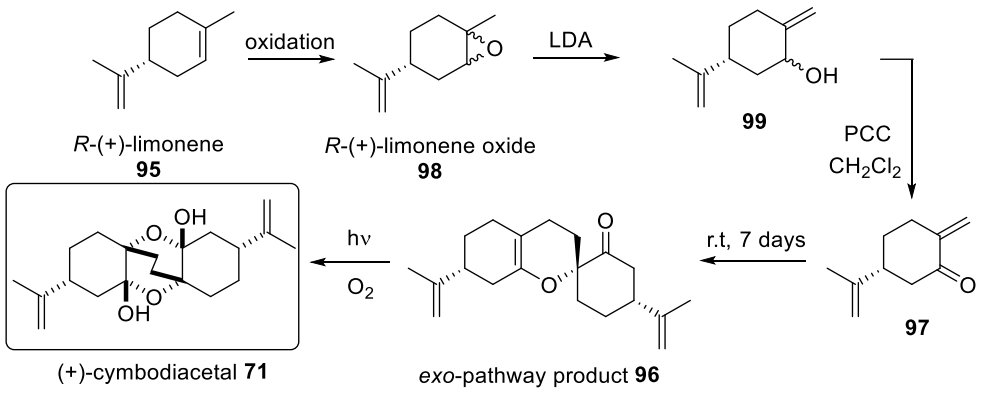
Scheme 18: Sabinol hetero Diels-Alder dimerisation

A similar oxidation of both *cis* and *trans* isocarveol (respectively **90** and **91**) using sodium dichromate in acetic acid and sulfuric acid at 70 °C, afforded directly the corresponding spirochroman dimer **92** via the intermediate enone **93**, which was not isolable during this reaction.[27]-[28] The conjugated aldehyde **94** was also formed along with the dimer **92**. Although both **90** and **91** produce the same intermediate **93**, *cis*-isocarveol **90** gave the dimer **91** as the major product (75%) and **94** as the minor product (25%), whereas *trans*-isocarveol **91** gave the conjugated aldehyde **94** as the major product (58%) and the desired dimer **92** in 42% yield (Scheme 19).[29]



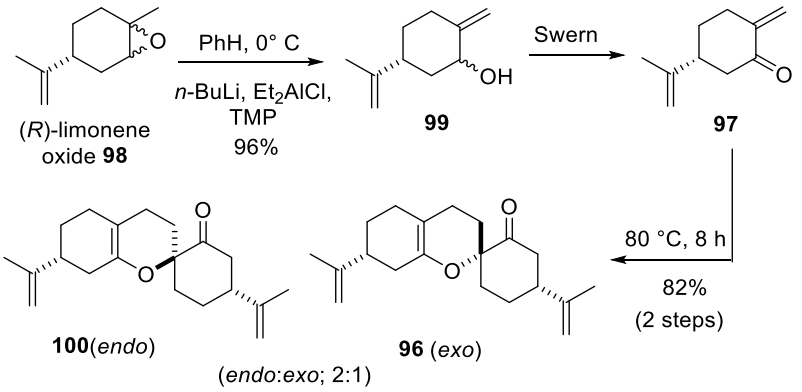
Scheme 19: Example of *cis*-isocarveol **90** and *trans*-isocarveol **91**

Previously in the introduction, (+)-cymbodiacetal **71** was presented as a spirochroman at a high level of oxidation. In 2004, Kamat and co-workers reported a biomimetic route to **71**.[30] This natural product was isolated along with *R*-(+) limonene **95** from the essential oil of aerial parts of flowering *Cymbopogon martini*. Therefore, Kamat proposed that the biogenesis of **71** involves the key intermediate dimer **96**, which can be formed from enone **97** starting from (+)-limonene oxide **98**. Surprisingly, it was reported that enone **97** was unstable and provided only the *exo* spirochroman **96** (97% pure) after one week at room temperature. Kamat stated that cymbodiacetal **71** was afforded in an unexpected manner after leaving impure dimer **96** oxidised in air in the presence of "diffused daylight" after column chromatography (Scheme 20).



Scheme 20: Kamat's biomimetic of (+)-cymbodiacetal **71**

In 2011, Hayes *et al.* tried to access cymbodiacetal **71** as the representation derived from X-Ray analysis and the structure drawn of **71** are presented as enantiomers. Moreover, the original X-Ray data were not available from the Cambridge Crystallographic database. In this study Hayes *et al.* tried to repeat Kamat's cymbodiacetal synthesis, however discrepancies with what Kamat's work were uncovered. A re-evaluation of the biomimetic route of cymbodiacetal **71** was published and Hayes *et al.* managed to obtain an X-Ray structure of **71**.[31] Enone **97** was obtained in two steps by converting (*R*)-(+)-limonene oxide **98** into the corresponding allylic alcohol **99** followed by a Swern oxidation. In contrast to Kamat's previous work, it was found that enone **97** was stable and after column chromatography **97** was afforded in 62% yield. The by-products were isolated and showed the presence of spirochroman **96** (*exo*-pathway product) and its diastereoisomer **100** (*endo*-pathway product) in a ratio 1:2 (20% yield). As the compounds **96** and **100** appeared to be produced *via* the hetero Diels-Alder dimerisation of enone **97** during purification, the separated pure sample of **97** was heated at 80 °C for 8 hours to yield **100** and **96**. This reaction proved to be very efficient as the desired spirochromans **100** and **96** were obtained in quantitative yield (2:1 ratio respectively). Thus constitutes a major difference to Kamat's biosynthesis as only the formation of the *exo*-pathway product **96** was reported. Moreover, using Kamat's dimerisation conditions (seven days at room temperature), Hayes *et al.* managed to afford compound **100** as the major product and the *exo* Diels-Alder product **96** which was stable and could be purified by column chromatography (Scheme 21).

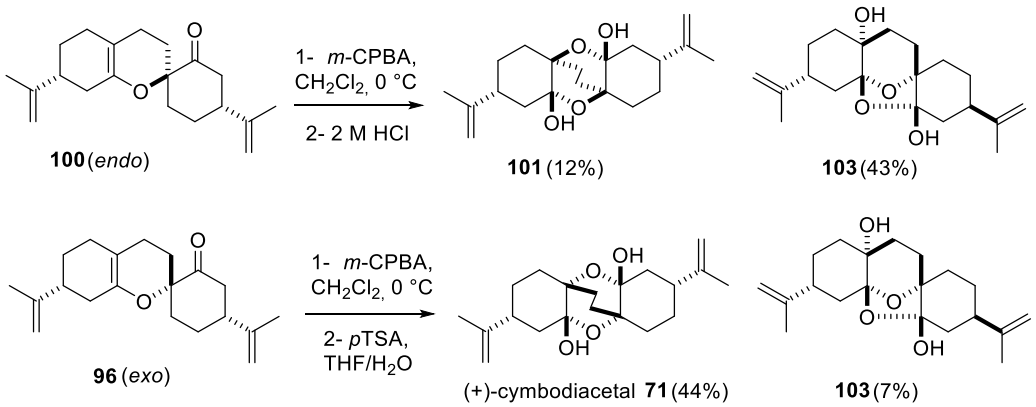


Scheme 21: Hayes re-evaluation of the biomimetic route of cymbodiacetal **71**

Kamat *et al.* stated that **96** was difficult to obtain in pure form and it was oxidised in air, in a presence of diffused daylight to afford cymbodiacetal **71** after column chromatography. Hayes *et al.* checked this hypothesis by exposing a sample of pure **96** to air and sunlight for over 15 days and **96** was recovered unchanged after this time. Hayes *et al.* suggested that the main difference of reactivity of **96** observed by both groups could stem from the method used to prepare the enone **97**. In fact, Kamat *et al.* used a PCC oxidation whereas Hayes *et al.* used a Swern oxidation. It is possible that chromium-based impurities from PCC were contaminating Kamat's samples of **97** and **96**, thus were responsible for the observed instability of **96** and for the oxidation of **96** to **71** upon standing in air/sunlight.[32]

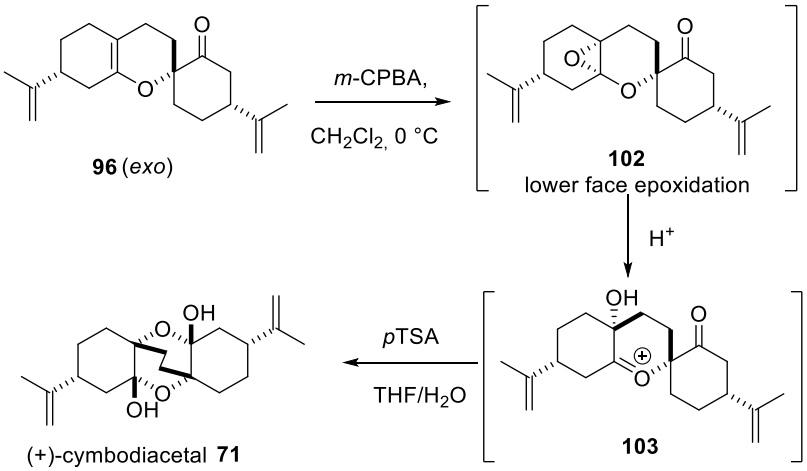
Hayes *et al.* finished the synthesis of **71** by treating **96** with *m*-CPBA which resulted in rapid oxidation to provide a mixture of unstable products that were immediately treated with 2 M aqueous HCl. Work up and subsequent purification led to the isolation of two new oxidation products **101** and **102** neither of which had spectroscopic data that match with natural product **71**.

The *exo*-Diels-Alder product **96** was treated with *m*-CPBA, then a THF solution of the crude material was reacted with water in the presence of *p*-TSA and cymbodiacetal **71** was produced in 44% yield along with acetal **102** (7%) (Scheme 22).



Scheme 22: Oxidation of *endo* and *exo* hetero Diels-Alder products

The mechanism for the formation of cymbodiacetal **71** from *exo*-spirochroman **96** involved the epoxidation of enol ether **96** on the lower face to form epoxide **102**, which underwent a ring opening under acidic conditions to form intermediate **103**. Intermediate **103** reacts with water under strong acidic conditions to form the hemiacetal moieties of cymbodiacetal **71** (Scheme 23).

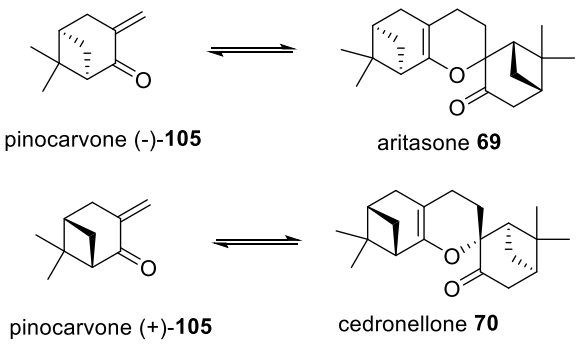


Scheme 23: Formation of cymbodiacetal **71**

1.5.2.2. High Barrier Hetero Diels-Alder Dimerisation Reactions

As mentioned previously some hetero Diels-Alder dimerisations are not spontaneous and occur under more forcing conditions, such as high pressure, as a result of higher activation barriers.

Aritasone **69** was isolated with a large amount of (–)-pinocarvone (–)-**105** from the essential oil of *Chenopodium ambrosioides*.[17] Whereas cedronellone **70** was isolated with a large amount of (+)-pinocarvone (+)-**105** from the aerial parts of *Cedronella canariensis* in 1987.[18] Although the two natural products **69** and **70** have different origins and biological properties, their common feature is that both are hetero Diels-Alder adducts of pinocarvone **105**: **69** is a dimer of (–)-**105** whereas **70** is a dimer of (+)-**105** (Scheme 24). It was found out separately by the isolation chemists that upon vacuum distillation, both of the natural products quantitatively yield the corresponding monomer. The stereochemistry was not determined for aritasone **69** by the isolation chemists contrary to cedronellone **70**.

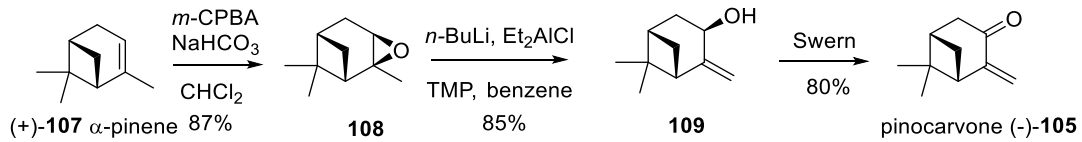


Scheme 24: Formation of aritasone **69** and cedronellone **70** from pinocarvone **105**

The only report for the formation of aritasone **69** came from Kohlemainer *et al.* where aritasone **69** was one of the oxidation products formed during SeO_2 oxidation of β-

pinene **106** in 10% yield. However no experimental procedures were published.[33] Therefore, Hayes *et al.* investigated the dimerization of pinocarvone (-)-**105** in order to synthesise aritasone **69** and establish if aritasone **69** and cedronellone **70** were enantiomers of each other.

The two enantiomers of pinocarvone (–)- and (+)-**105** are the proposed monomer precursors to the two natural products, aritasone **69** and cedronellone **70** respectively. Thus (–) and (+)-**105** were synthesised starting from α-pinene (+)- and (–)-**107** respectively using the sequence of reactions shown in Scheme 25.[34]

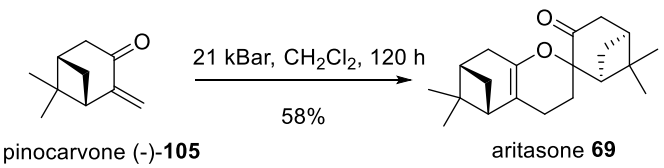


(+)-**107** α-pinene 87% **108** 85% **109** pinocarvone (-)-**105**

Scheme 25: Synthesis of (-) and (+)-pinocarvone **107**

Surprisingly, the enone **105** was not only stable at room temperature but also when heated at temperatures ranging from 80-220 ^{o}C for extended periods of time, where no dimerisation products were observed. Microwave conditions under pressure were also attempted without success. Acid catalysis such as $ZnCl_2$, $BF_3.OEt_2$, *p*-TSA, and the organocatalysed reactions using proline were attempted to dimerise **105** without success.

After all these unsuccessful attempts to dimerise (–)-**105**, suitable conditions were found under extremely high pressure (21 kBar) in dichloromethane and gave aritasone **69** in 58% yield (Scheme 26).[34]



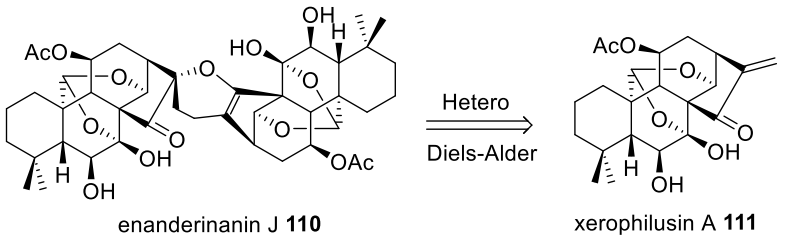
Scheme 26: Hetero Diels-Alder dimerisation of (-)-**105** into **69**

Although, there is literature precedent for carrying out Diels-Alder cycloaddition reactions under high pressure, the simulation of such conditions within plant cells is very unlikely.[8] A possible explanation could be the presence of a specific Diels-Alderase in the plants, which catalyses the dimerisation of pinocarvone (–)-**105** to aritasone **69**.

1.5.2.3. Hetero Diels-Alderases in Nature

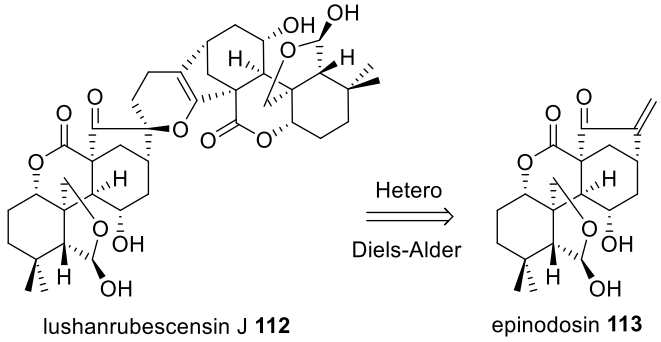
Natural products that are presumably biosynthesised via a [4+2] cycloaddition frequently occur in the literature.[9],[35]-[37] Several observations suggest that a Diels-Alder reaction is involved in the biosynthesis of natural products such as the isolation of an adduct with the corresponding precursor as shown previously. Some recent examples of plausible natural Diels-Alder adducts are described in this section.

In 2002, Sun *et al.* isolated enanderianin J **110** among traces of xerophilusin A **111** from *Isodon enanderianus*.[38]-[39] It was assumed that **110** is the dimer of **111** and was probably formed by a [4+2] cycloaddition of the 5-membered ring exocyclic enone moiety of **111** (Scheme 27).



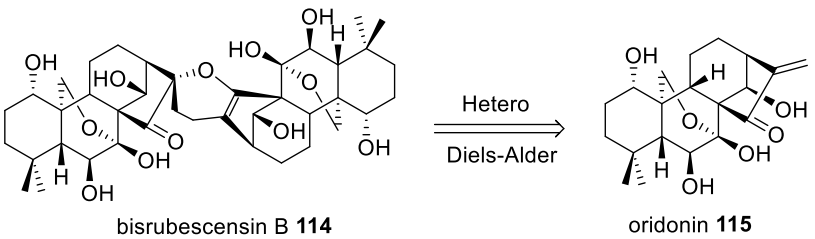
Scheme 27: Proposed biosynthesis of enanderianin J **110**

In 2005, lushanrubescensin J **112**, another *ent*-kauranoid dimer was isolated from *Isodon rubescens* var. *lushanensis* [40] among with one of the major constituents of this plant epinodosin **113** (Scheme 28).[41]



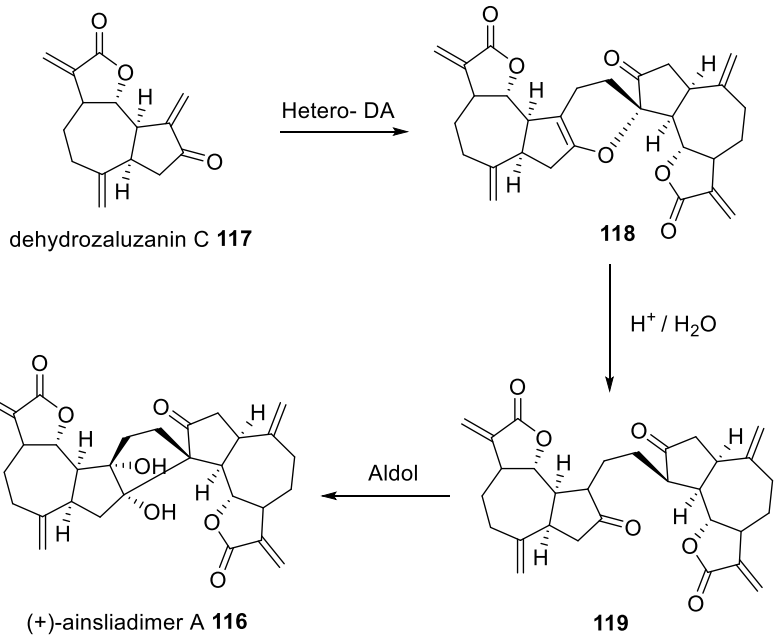
Scheme 28: Proposed biosynthesis of lushanrubescensin J **112**

Bisrubenscensin B **114** from *Isodon rubescens* is another example of hetero Diels-Alder adduct.[42] It was proposed that **114** was biosynthesised by an hetero Diels Alder from the monomer oridonin **115**,[43] present in the same extract of plant (Scheme 27).



Scheme 27: Proposed biosynthesis of bisrubenscensin B **114**

In 2010, Zhang and co-workers discovered a new sesquiterpene lactone dimer, (+)-Ainsliadimer A **116** from *Ainsliaea macrocephala*.[44] In this paper, they described a plausible biosynthesis of **116** starting from the monomer and natural product dehydrozaluzanin C **117**. Dehydrozaluzanin C **117** would undergo an hetero Diels-Alder dimerisation to provide dimer **118** which can be hydrolysed to form **119**. Aldolisation of **119** would provide the natural product **116** (Scheme 28).



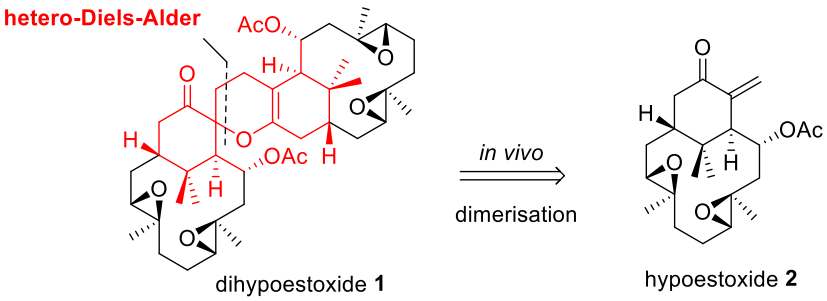
Scheme 28: Proposed biosynthesis of (+)-Ainsliadimer A **116**

Until recently, the existence of a Diels-Alderase has been uncertain. The role of protein organisation in natural systems and the possible mechanism of catalysis has long been a source of debate. It was reconsidered by the recent characterisation of three naturally occurring potential Diels-Alderases: solanapyrone synthase,[43] lovastatin nonaketide synthase,[46] and macrophomated synthase.[47] Therefore a number of investigations have been carried out to identify and prove the existence of potential Diels-Alderases involved in the biosynthesis of natural products.

1.5.3. Hayes Proposed Stereochemistry of Dihypoestoxide Spirochroman Core

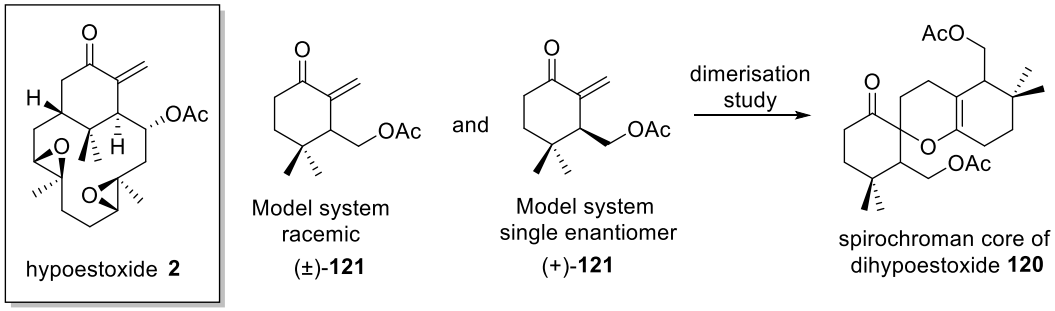
As previously mentioned in this introduction, the stereochemistry of dihypoestoxide **1** was not assigned at the time of its isolation. However, it was proposed that dihypoestoxide **1** was formed *in vivo via* the hetero Diels-Alder dimerisation of hypoestoxide **2**. Before working on the synthesis of dihypoestoxide **1**, Hayes *et al.* reported studies towards the stereochemical assignment of dihypoestoxide **1**.[48]

Hayes *et al.* suggested that **1** shared the same stereochemistry as **2** at the common stereocentres (Scheme 29) and hypothetised that only the configuration at the quaternary stereocentre located on the spirochroman ring system, which was formed during the dimerisation, has to be determined.



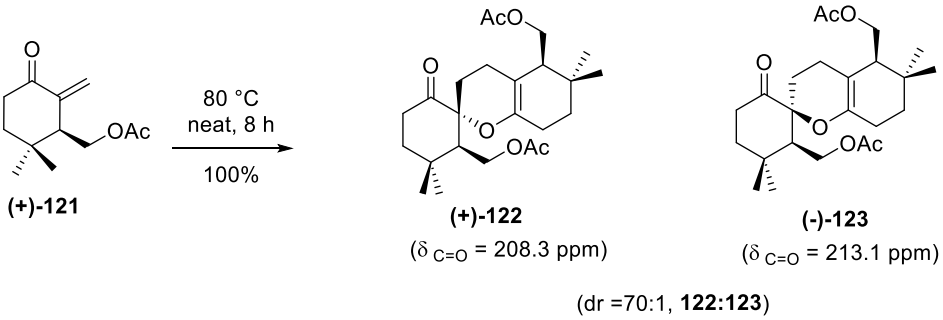
Scheme 29: Proposed biosynthesis of dihypoestoxide **1**

The Hayes group studies started with the synthesis of all four possible diastereoisomers of a simplified tricyclic spirochroman core structure **120** in order to assign the stereochemistry at the spirochroman centre (Scheme 30). By comparing the ^{13}C NMR, they obtained the same chemical shift of the carbonyl as the natural product **1**; Hayes *et al.*then proposed a complete stereochemical assignment of dihypoestoxide **1**.



Scheme 30: Hayes group work

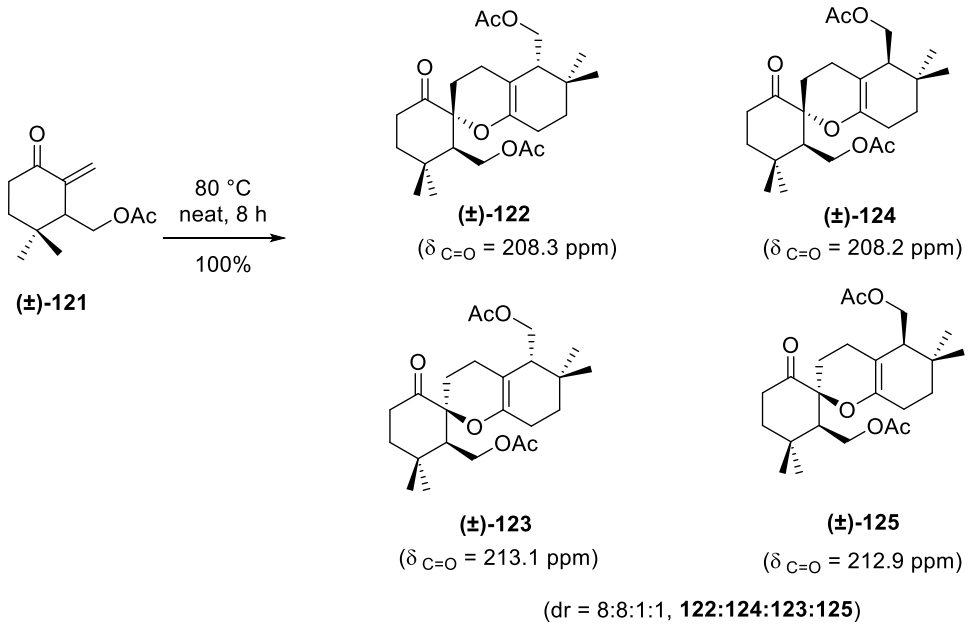
With the racemic and enantiomerically enriched enone **121**, Hayes *et al.* subsequently investigated the hetero Diels-Alder dimerisation process starting with the enantiomerically enriched enone **(+)-121**. The dimerisation yielded the spirochroman **(+)-122** as the major product with **(-)-123** as the minor product (dr = 70:1) (Scheme 31).



Scheme 31: Hetero Diels-Alder dimerisation of enantiomerically enriched enone **(+)-121**

Most of Diels-Alder cycloadditions proceed mainly through an *endo*-pathway, which means that compound (+)-**122** could be the *endo*-pathway product at the spirochroman centre and (-)-**123** is the minor compound, namely the *exo*-pathway product and should therefore have the opposite stereochemistry to (+)-**122** at the spirochroman centre.

The same reaction was performed starting with the racemic enone **(±)-121** (Scheme 32) to provide all four possible diastereoisomers of the corresponding spirochroman the products **122**, **124**, **123**, and **125** in a 8:8:1:1 ratio.



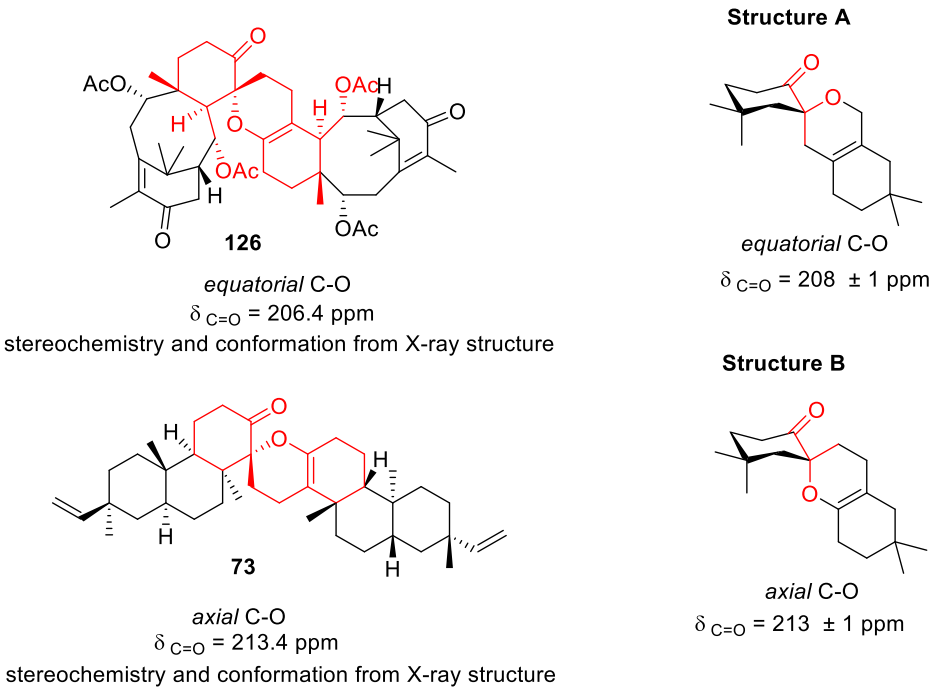
Scheme 32: Hetero Diels-Alder dimerisation of racemic enone **(±)-121**

Having gained access to the enantiomerically enriched material before, (+)-**122** and (-)-**123** were easily assigned and formed in a 8:1 ratio respectively. Therefore the remaining two compounds were **124** and **125**, but at this stage it was impossible to predict which one was which.

Stereochemical assignments of **122** and **124** were reinforced by analysis of the ^{13}C NMR data for the carbonyl present in the spirochroman ring system, with compound (+)-**122** having a $\delta_{C=O}$ = 208.3 ppm and (-)-**123** having $\delta_{C=O}$ = 213.1 ppm. This difference in ^{13}C NMR suggests that (+)-**122** and (-)-**123** possess the opposite configuration on the quaternary centre of the spirochroman ring. However it was

difficult to attribute with certainty the right configuration for each compound. A literature search was realised to find if a correlation existed between the configuration of the quaternary centre and ^{13}C NMR data for the carbonyl present in similar spirochromans.

Two dimers possessing a spirochroman ring were found in the literature, one is the dimer of 5-oxotaxinine **126** [49] and the other one is tagalsin I **73**,[20] and both of these structures had been solved by X-ray crystallography (Scheme 33).

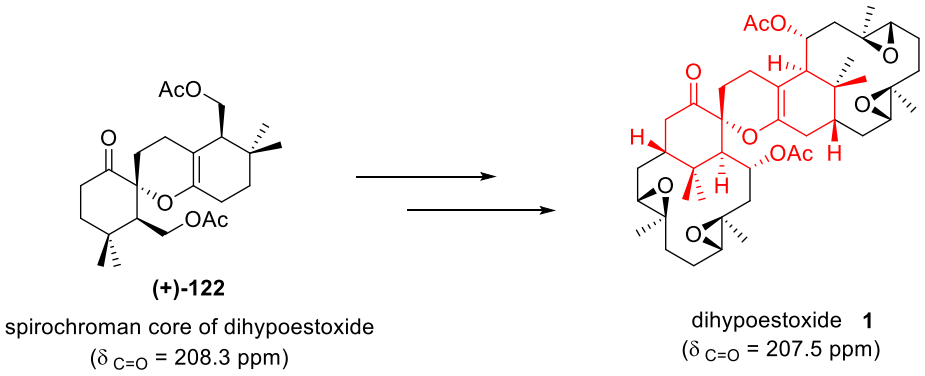


Scheme 33: Correlation of spirochroman configuration with ^{13}C data

From the X-ray structures it was shown that the value of the chemical shift for the carbonyl present in the spirochroman ring system changes depending upon the position of the ethereal C-O bond of the dihydropyran fragment. The dimer of 5-oxotaxinine **126** contains an equatorial C-O bond on the cyclohexanone fragment (structure A, scheme 33) and the $\delta_{C=O}$ = 208 ± 1 ppm. The equivalent bond of tagalsin

I **73** is in an axial position on the cyclohexanone fragment corresponding to structure B in Scheme 33 and has a shift in the ^{13}C NMR of $\delta_{C=O}$ = 213 ± 1 ppm. Hayes *et al.* used this observation to confirm the structure of the dihypoestoxide spirochroman core (Scheme 23).

Spirochromans **122** and **124** possess the stereochemistry represented by structure A as they all have $\delta_{C=O}$ = 208 ± 1 ppm, and spirochromans **123** and **125** possess the stereochemistry represented by structure B as they all have $\delta_{C=O}$ = 213 ± 1 ppm (Scheme 33). The ability to assign configuration at the spirochroman spirocentre (relative to the protected hydroxymethyl substituent on the cyclohexanone ring) using ^{13}C NMR allowed Hayes to propose the stereochemistry shown in Scheme 34 as dihypoestoxide **1** has $\delta_{C=O}$ = 207.5 ppm,[1] which matches with the data of the core **122**.

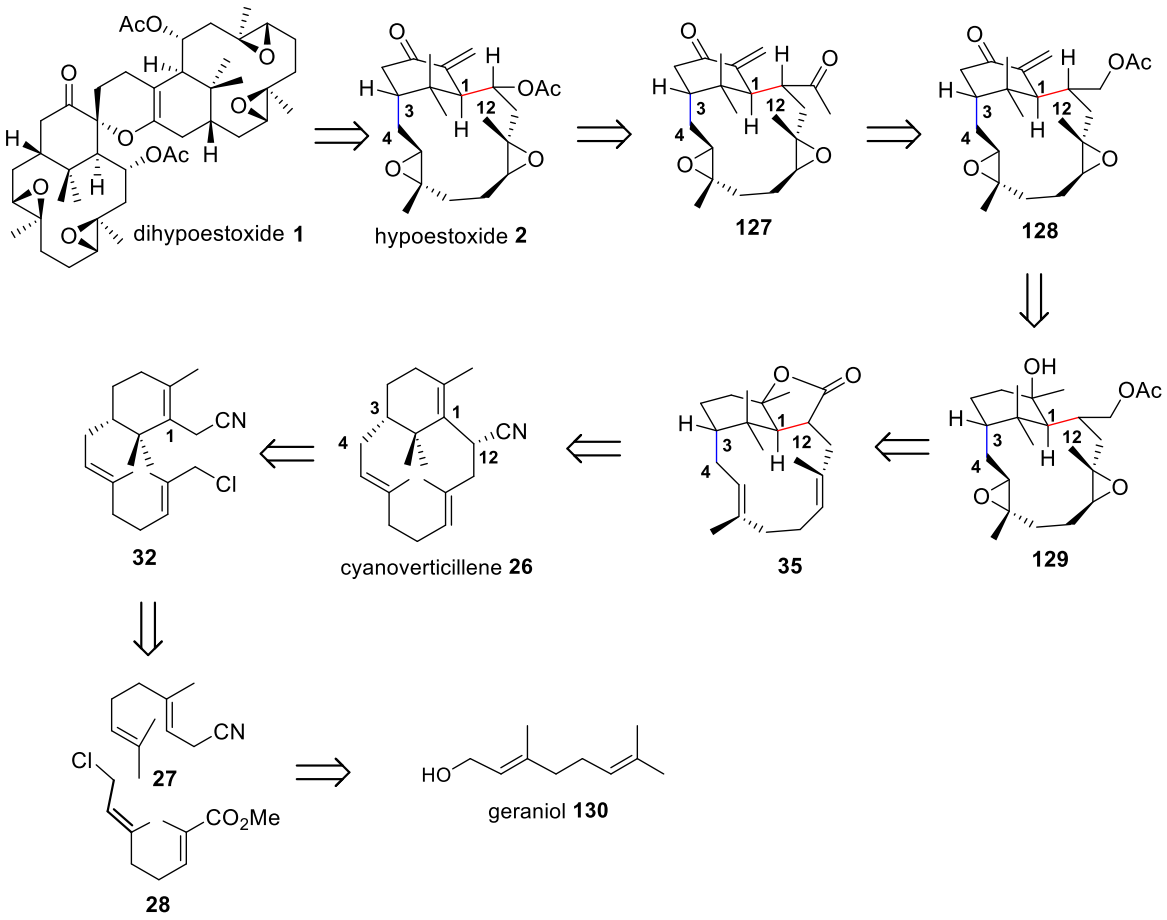


Scheme 34: Proposed stereochemistry of dihypoestoxide **1**

In summary, the Hayes group proposed a complete stereochemical assignment of dihypoestoxide based upon analysis of its ^{13}C NMR data. It was also shown that hetero Diels-Alder dimerisation could account for the formation of dihypoestoxide **1**, even if the conditions required to accomplish this transformation *in vivo* are yet to be established.

1.6 Aims of Work and Retrosynthetic Analysis

After solving the stereochemical assignment of dihypoestoxide **1**, we focused our efforts on the total synthesis of hypoestoxide **2** in order to investigate the hetero Diels-Alder dimerisation to lead to dimer **1**. Our approach takes into account the atropisomerism of hypoestoxide **2** associated with the Njardarson synthesis. We planned to access hypoestoxide **2** from methyl ketone **127** *via* a Baeyer-Villiger oxidation. The exocylic enone moiety of **128** can be installed from the tertiary alcohol **129**, which can be synthesised from the lactone intermediate **35** described in Kato's epiverticillol synthesis. Cyanoverticillene **26** constitutes the precursor to **35** and allows us to control the atropisomerism problem. In fact, the sp^2 hybridised C1 of **26** forces the C1-C12 bridgehead bond of **35** to be equatorial and therefore the C3-C4 bond to be axial. The formation of key intermediate **26** can be afforded by intramolecular cyclisation of chloride **32**, which can be accessed from aliphatic precursors **27** and **28** in three steps featuring a key intermolecular metal-mediated cyclisation. Both of these intermediates **27** and **28** derived from geraniol **130** (Scheme 35).



Scheme 35: Our retrosynthetic approach of hypoestoxide **2**

This analysis has the attribute of carbon efficiency, as we start from an unexpensive monoterpene **130**, providing all the 21 carbons of hypoestoxide **2**. To date, the Hayes group has managed to synthesise the key intermediate **129**.[34] However, the next step to install the exocyclic enone moiety and the removal of the additional carbon at the C12 position still needs to be investigated.

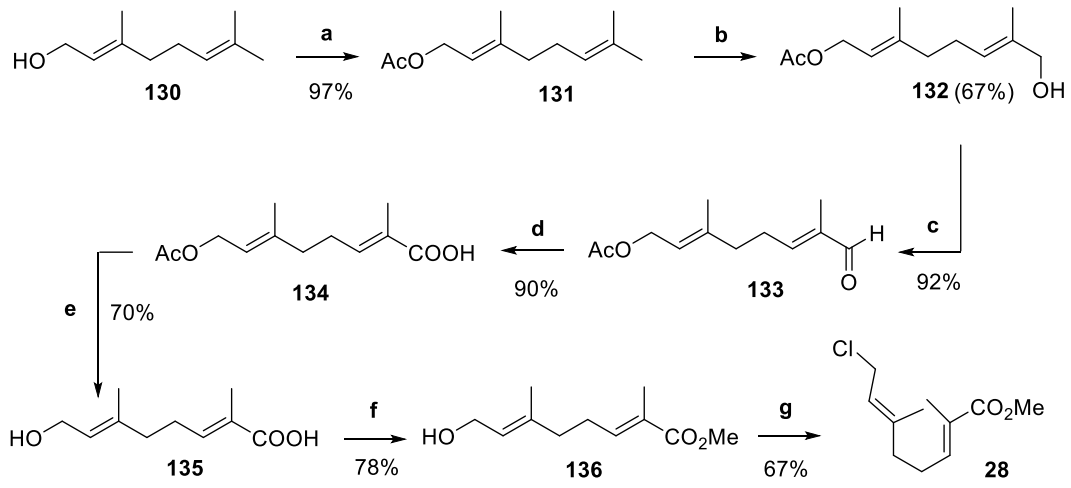
Chapter 2: Results and Discussion

2.0 Results and Discussion

As discussed previously in our retrosynthetic analysis, we began our studies by synthesising geranyl cyanide **27** and chloroester **28** from geraniol **130**.

2.1 Synthesis of Chloroester 28

The chloroester **28** was synthesised from geraniol **130** *via* a seven step synthesis (Scheme 36).



a: Ac_2O (3.3 eq), pyridine (7.7 eq), 0 °C to r.t, 12 h; **b:** SeO_2 (0.1 eq), ^tBuOOH (2.5 eq), CH_2Cl_2, r.t, 24 h; **c:** MnO_2 (20 eq), CH_2Cl_2, r.t, 18 h; **d:** NaH_2PO_4 (4 eq), $NaClO_2$ (4 eq), 2-methyl-2-butene (10 eq), ^tBuOH, H_2O, r.t, 14 h; **e:** K_2CO_3 (2 eq), MeOH, H_2O, r.t, 18 h; **f:** K_2CO_3 (1.75 eq), MeI (3.4 eq), DMF, r.t, 14 h; **g:** MsCl (1.5 eq), DIPEA (1.5 eq), 0 °C to r.t, 18 h.

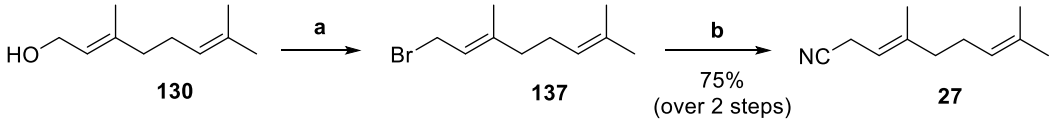
Scheme 36: Synthesis of chloroester precursor **28**

Protection of geraniol **130** with an acetate group gave intermediate **131**, which underwent an allylic oxidation using selenium dioxide to provide a mixture of allylic alcohol **131** and aldehyde **132** in 50% and 17% yield respectively. Allylic alcohol **131** was then converted into aldehyde **133** by oxidation using activated manganese dioxide. Pinnick oxidation of aldehyde **133** provided carboxylic acid **134** in 90%

yield[50] and subsequent deprotection of the acetate group generated the free alcohol **135**. Esterification of **135** using methyl iodide lead to methyl ester **136** in reasonable yield. **136** reacted with methylsulfonylchloride in presence of 1.5 equivalent of DIPEA to afford chloroester **28** in 67% yield.

2.2 Synthesis of Geranyl Cyanide 27

The synthesis of geranyl cyanide **27** was achieved in only two steps. Geraniol **130** underwent deoxybromination using phosphorous tribromide providing bromide **137**, which was unstable and used directly in the next step. Nucleophilic substitution of **137** using sodium cyanide then gave the desired nitrile **27** in 75% yield over two steps (Scheme 37).



130 **137** **27**

a: PBr_3 (0.5 eq), Et_2O, 0 °C to r.t, 3 h; **b:** NaCN (1.1 eq), DMF, 0 °C to r.t, 72 h.

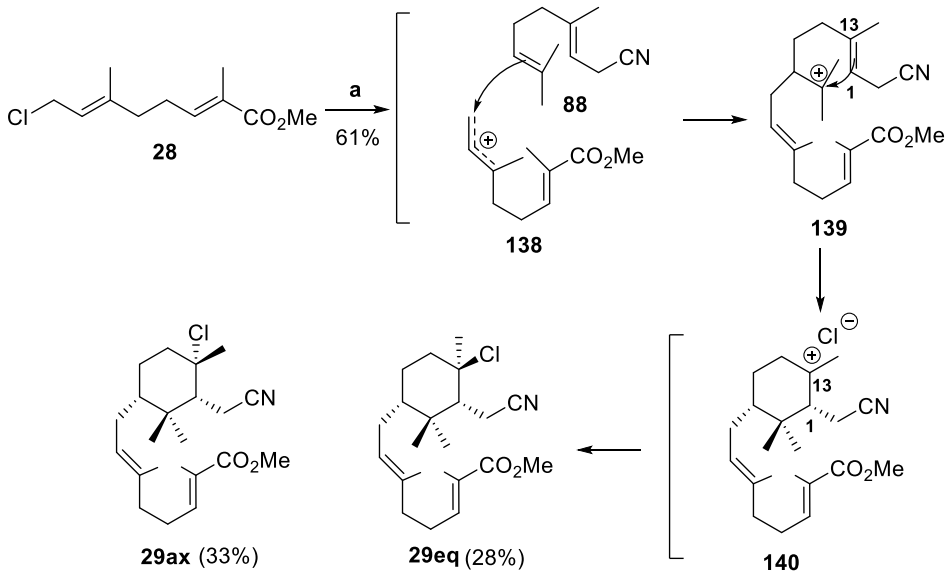
Scheme 37: Synthesis of geranyl cyanide precursor **27**

2.3 Synthesis of Cyanoverticillene 26

2.3.1 Coupling Reaction Between Allylic Chloride 28 and Geranyl Cyanide 27

Allylic chloride **28** was activated using tin tetrachloride to form carbocation **138**, which reacted with a double bond of geranyl cyanide **27** in order to form another carbocation **139**. The double bond C1=C13 present in the intermediate **139** then

attacks the tertiary carbocation forming another tertiary carbocation **140**, which is trapped by a chloride to provide carbocyclic framework needed for verticillanes **29** (Scheme 38).



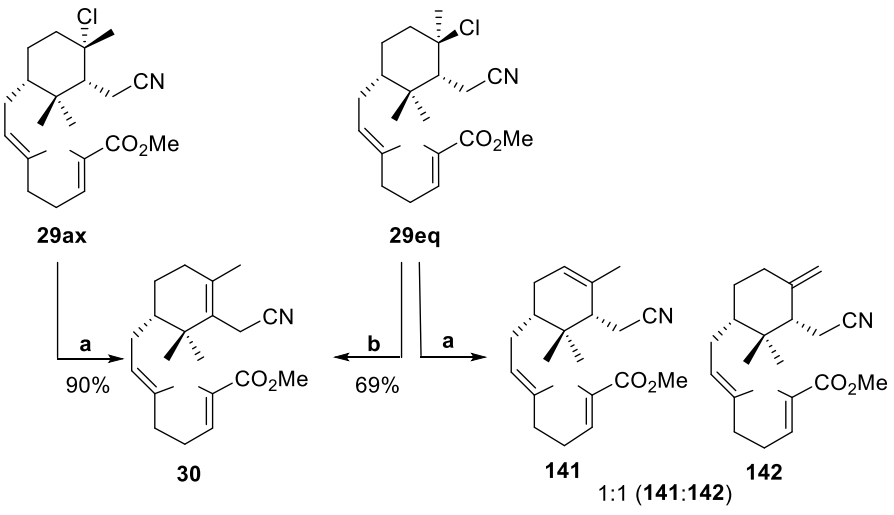
a: $SnCl_4$ (1.2 eq), **27** (1.1 eq), CH_2Cl_2, -78 °C to -30 °C, 3 h.

Scheme 38: Suggested mechanism of the coupling reaction between **27** and **28**

Trapping of the carbocation **140** can occur from the upper face or the lower face, which explains the formation of two diastereoisomers, the axial chloride **29ax** and the equatorial chloride **29eq**. The reaction proceeds in a reasonable overall yield (61%), and it is possible to separate the two diastereoisomers by column chromatography. This reaction allows to us to combine all the 21 carbons required for the structure of hypoestoxide **2**.

2.3.2 Synthesis of Macrocyclisation Precursor 32

The next step was elimination of hydrochloric acid from the two diastereoisomers **29ax** and **29eq** to form tetrasubstituted alkene **30**. The method used was different depending on which diastereoisomer was undergoing the elimination, it was therefore crucial to separate them by column chromatography after the tin (IV) coupling reaction. Axial chloride **29ax** was dehydrochlorinated using lithium chloride in DMF at 100 °C for 3 hours to provide alkene **30** in excellent yield (90%). Equatorial chloride **29eq** required treatment with $ZnCl_2$ in dichloromethane at room temperature to give the desired triene **30** in a moderate yield (69%). If the conditions used to dehydrochlorinate the axial product **29ax** was employed to dehydrochlorinate the equatorial product **29eq**, a mixture of two undesired isomers **141** and **142** were obtained (Scheme 39).[14]



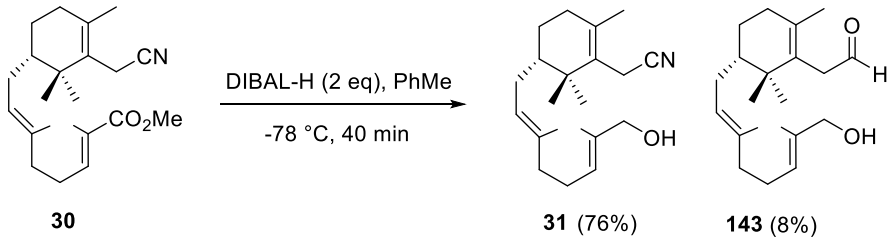
a: LiCl (9 eq), DMF, 100 °C, 3 h; **b:** $ZnCl_2$ (1.1 eq), CH_2Cl_2, r.t, 48 h, then 2-methyl-2-butene (13.7 eq), 24 h.

Scheme 39: Elimination of the axial and equatorial chloride **29**

The synthesis of the 10-cyanoverticillene precursor **32** was achieved in two steps starting from methyl ester **30**. We needed first to selectively reduce the α,β-

unsaturated ester **30** in presence of a nitrile. Previous work used a solution of AlH_3 at -78 °C to selectively reduce the methyl ester function on triene **30** into allylic alcohol **31** in 76% yield.[14] When these conditions were repeated, allylic alcohol **31** was afforded in 40% yield. The AlH_3 solution was freshly prepared using 2.5 equivalents of $LiAlH_4$ and 4.5 equivalents of $ZnCl_2$ dissolved in ether and then was slowly transferred to the reaction mixture. The main drawback of this method was to prepare fresh reagent and to transfer the slurry AlH_3 solution *via* a cannula.

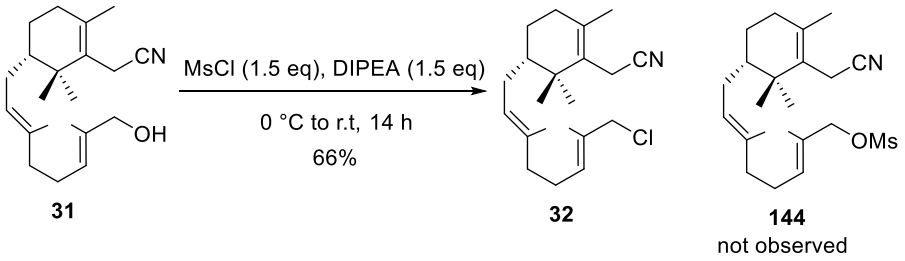
Several previous investigations [51] had demonstrated that the result was obtained by using 2 equivalent of DIBAL-H in toluene for 40 minutes at -78 °C. This resulted in a 48% yield (76% based on the recovery of starting material. After 40 minutes, a slow reduction of the nitrile group of **30** into the aldehyde **143** was observed in 8% yield (Scheme 40).



Scheme 40: Selective reduction of allylic ester **30** into **31**

We then needed to introduce a good leaving group, such as a chloride, from the hydroxyl group of **31** in order to attempt the macrocyclisation which would lead us to the cyanoverticllene **26**. The previous optimisations of the conversion of allylic alcohol **31** into chloride **32** showed that using methylsulfonylchloride and 1.5 equivalent of DIPEA was better than Appel conditions with a yield of 66% and 59% respectively (Scheme 41).[51] Moreover, we think that the modest yield of the Appel reaction is possibly due to the fact that our product was bound to the

triphenylphosphine oxide formed during the reaction. These mesylation conditions have never produced the mesylate alcohol **144**, which would have been an interesting precursor for the macrocyclisation. The use of a hindered base such as DIPEA was preferred to triethylamine in order to avoid the possible secondary reaction between the excess of amine and chloride **32**.

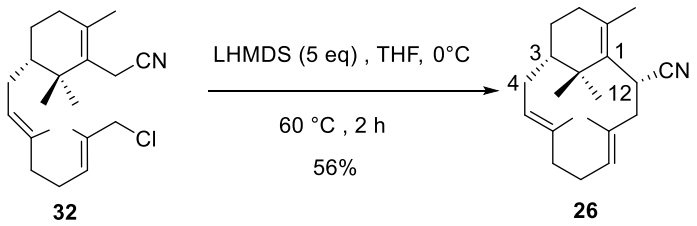


31 **32** **144** not observed

Scheme 41: Chlorination of allylic alcohol **32**

2.3.3 Macrocyclisation

After chlorination of allylic alcohol **31**, precursor **32** underwent a macrocyclisation at 60 °C in anhydrous THF, using LHMDS freshly prepared *in situ,* to afford 10-cyanoverticillene **26** (Scheme 42).[14] The addition rate of the starting material **32** as a very dilute solution in THF is a key factor in determining the success of this reaction as it is possible to form a polymer as a result of an intermolecular reaction. The optimal addition rate was previously determined as being 250 μL/min,[51] which provided the desired product in 50 - 60%. The stability of the starting material **32** may also have an impact on the consistency of the yield. Indeed, the consistency of this reaction has been observed when starting material **32** was synthesised from the allylic alcohol **31** the day before the cyclisation.



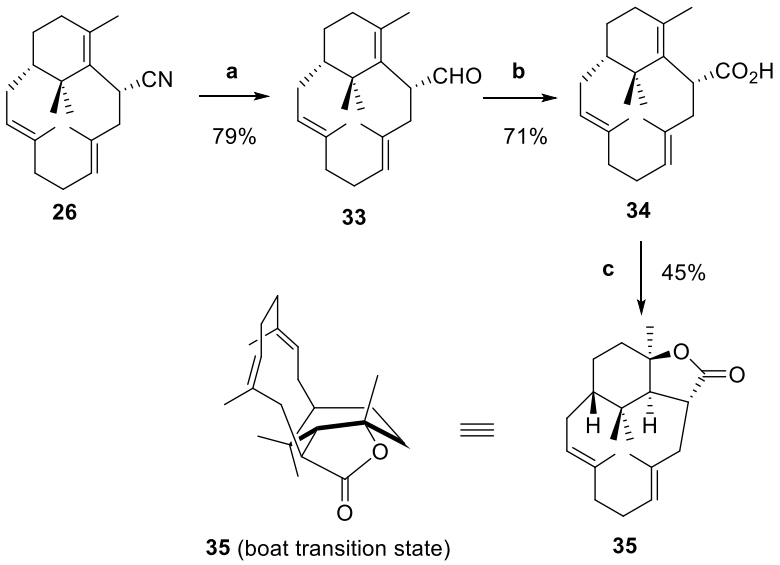
32 26

Scheme 42: Synthesis of 10-cyanoverticillene **26**

At the point in the synthesis, we managed to access the verticillane skeleton of hypoestoxide **2**. We also established the correct atropisomer in which sp^2 hybridised C1 of **26** forced the C1-C12 bridgehead bond to be equatorial and therefore the C3-C4 bond to be axial.

2.4 Synthesis of Lactone 35

In order to avoid this process of reduction / oxidation, hydrolysis of the nitrile group of **26** into a carboxylic acid **34** in one step was attempted.[51] However, all these attempts under basic conditions failed to provide any desired product and resulted in quantitative recovery of starting material **26**. Therefore, the conversion of the nitrile group of cyanoverticillene **26** into a carboxylic acid was performed in two steps by first reducing the nitrile group using DIBAL-H to give aldehyde **33** in 79% yield. Pinnick's oxidation of **33** afforded carboxylic acid **34** in 71% yield (Scheme 43). The key intermediate lactone **35** was obtained by refluxing carboxylic acid **34** in TFA for 30 minutes in 45% yield (Scheme 43).[15]



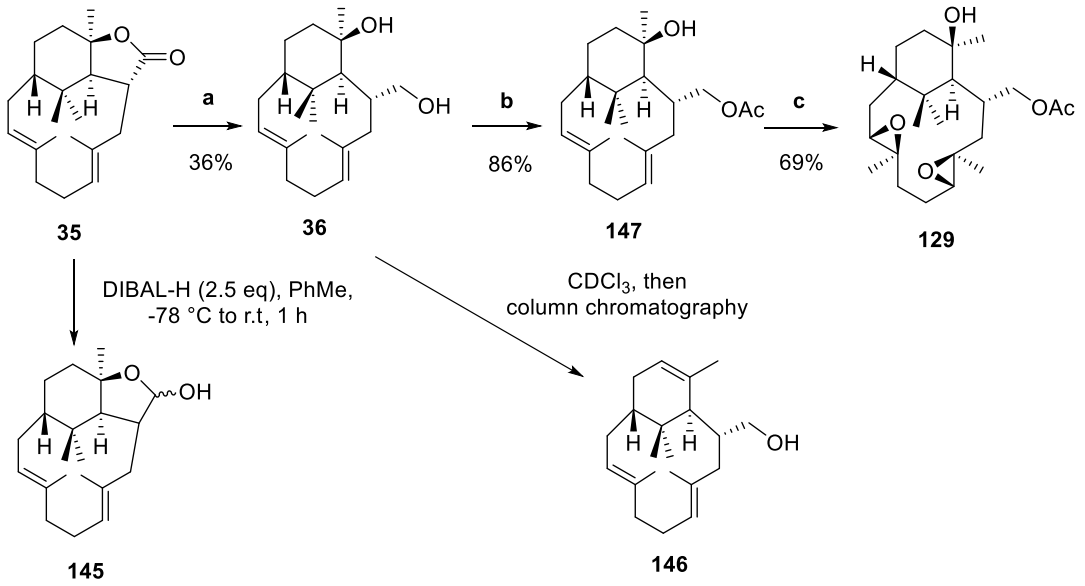
a: DIBAL-H (2 eq), toluene, -78 °C, 2 h; **b:** NaH_2PO_4 (1.0 eq), $NaClO_2$ (1.2 eq), 2-methyl-2-butene (10 eq), $^tBuOH,H_2O$ r.t, 8 h; **c:** TFA, reflux, 30 min.

Scheme 43: Synthesis of key intermediate lactone **35**

2.5 Synthesis of Acetate Protected Bisepoxide 129

Lactone **35** was then reduced using $LiAlH_4$ in refluxing THF to provide diol **36** in 36% yield (Scheme 44). Attempted cleavage using 2.5 equivalent of DIBAL-H fails to provide the desired diol **36**, but potentially forms lactol **145**. NMR spectroscopy of diol **36** was performed in d_6-benzene as decomposition was observed in $CDCl_3$ possibly due to some traces of acid in the deuterated chloroform. Alcohol **147** has been isolated after the purification of the decomposed $CDCl_3$ NMR sample.

The primary alcohol **36** was then protected to afford acetate **147** in excellent yield (86%). Bisepoxidation of intermediate **147** using either DMDO or *m*-CPBA in CH_2Cl_2 proceeds in 69 and 61% yield respectively to give the desired product **129** as a single diastereoiomer (Scheme 44).



a: $LiAlH_4$ (5.0 eq), THF, reflux, 1 h; **b:** Ac_2O (5.1 eq), pyridine (7.0 eq), CH_2Cl_2, r.t, 14 h; **c:** *m*-CPBA (4.0 eq), CH_2Cl_2, 0 °C, 2 h.

Scheme 44: Synthesis of bisepoxide **129**

A crystal structure of bisepoxide **129** was performed in order to confirm stereochemistry of the epoxide moieties and the conformation of the bridgehead single bonds (Figure 5). It showed that C1-C2 single bond was equatorial and C10-C11 axial as required for the synthesis of hypoestoxide **2**.

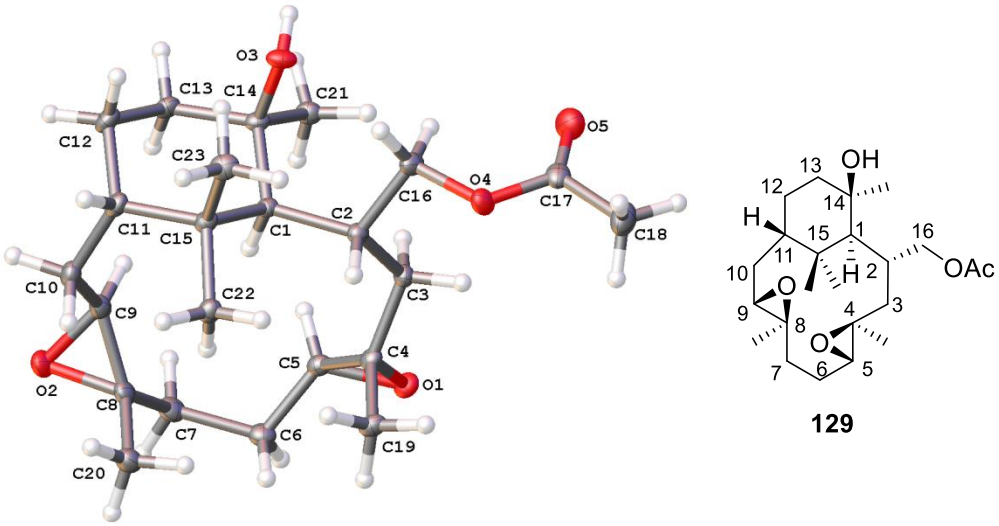
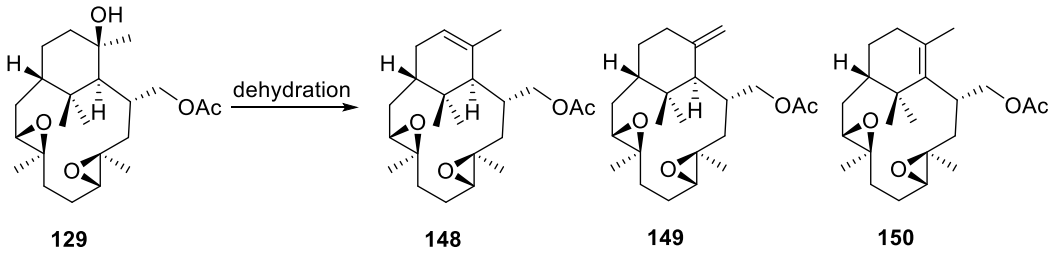


Figure 5: Crystal structure of bisepoxide **129**

Moreover, the tertiary alcohol of **129** at C14 is axial, therefore three possible regioisomers could be formed during the dehydration step as shown in scheme 45. For the later stage of the synthesis of hypoestoxide **2**, the exocyclic moiety **149** or the formation of the trisubstituted alkene **148** is preferential to the formation of the tetrasubstituted alkene **150**.

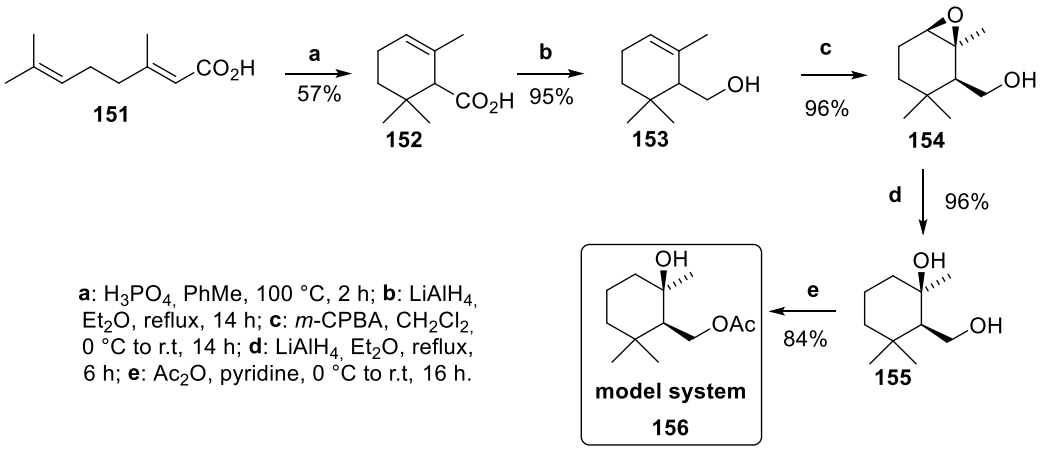


Scheme 45: Potential dehydrated products

2.6. Optimisation of the Dehydration Reaction

2.6.1 Synthesis of Model System 156

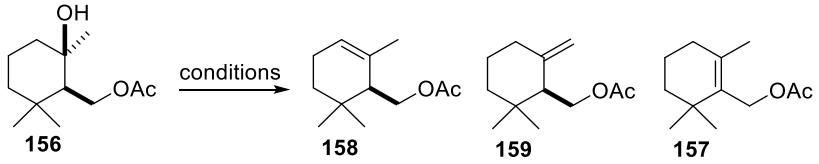
In order to study some dehydration conditions to provide mainly the exocyclic double bond, a model system was built starting from geranoic acid **151**. Cyclisation of **151** using phosphoric acid in toluene afforded cyclogeranoic acid **152**, which was reduced to alcohol **153**.[52] The double bond of **153** was epoxidised to form **154** as a single diastereoisomer.[53] The epoxide **154** was ring-opened with a large excess $LiAlH_4$ in ether at reflux to provide the tertiary alcohol **155**. The primary hydroxyl group of **155** was protected with an acetate to afford the model system **156** (Scheme 46).



Scheme 46: Synthesis of model system **156**

2.6.2 Optimisation of Dehydration on Model System 156

We investigated some dehydration procedures on the model system **156** in order to find some conditions to form predominantly the exocyclic double bond (Table 1).



Entry	Conditions	Ratio[a]		
		158	**159**	**157**
1	$SOCl_2$, NEt_3, CH_2Cl_2, -78 °C, 30 min	32	3	65
2	$POCl_3$, pyridine, 0 °C to r.t., 15 h	0	0	0
3	Martin's sulfurane, CH_2Cl_2, r.t., 2 h	82[b]	12	6
4	Burgess reagent, benzene, r.t., 16 h	63	23	14
5	**Burgess reagent, benzene, 60 °C, 1 h**	**63**	**21**	**16**

[a] ratio was determined by ^{1}H NMR of the crude mixture; [b] by-products were inseparable.

Table 1 (part1): Dehydration conditions optimisation

Entry	Conditions	Ratio[a]		
		158	**159**	**157**
6	MsCl, NEt_3, CH_2Cl_2, r.t., 16 h[c]	41	5	54
7	MsCl, NEt_3, CH_2Cl_2, reflux, 16 h[c]	41	7	52
8	MsCl, DBU, CH_2Cl_2, reflux, 16 h	0	0	0
9	TsCl, NaH, DMF, 0 °C to r.t., 16 h	60	26	14

[a] ratio was determined by ^{1}H NMR of the crude mixture; [c] 72% conversion.

Table 1(part 2): Dehydration conditions optimisation

In the presence of thionyl chloride and triethylamine in dichloromethane, all the three possible regioisomers were formed and are inseparable from each each other. However crude ^{1}H NMR of the crude reaction mixture allows us to determine the ratio of regioisomers. The tetrasubstituted alkene **157** was formed predominantly compared to the two other alkenes (**158** and **159**), as it is the more stable regioisomer (Table 1, entry 1). Similar conditions using phosphoryl chloride as activating agent in pyridine provided the recovery of the starting material **156** (Table 1, entry 2). Other reagents such as Martin's sulfurane and Burgess reagent are well known to be used to dehydrate tertiary alcohols *via* a *anti*-elimination and *syn*-elimination respectively.[54][55] We observed that the dehydration using one or the other reagent favoured the formation of the trisubstituted alkene **158** and increased the ratio of the exocyclic double bond **159** in preference to the tetrasubstituted alkene **157** (Table 1, entry 3-5). The best conditions found used Burgess reagent in benzene at 60 °C for one hour (Table 1, entry 5).

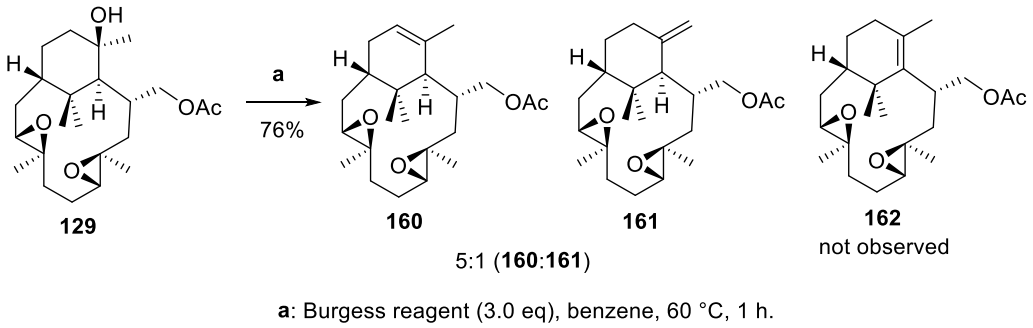
Martin's sulfurane reagent showed a better selectivity to the trisubstituted alkene **158** however, the reaction was less clean than the dehydration using Burgess reagent.

Indeed, the diphenylsulfone formed during the reaction was inseparable from the alkene mixture. Conditions using the introduction of a good leaving group such a mesylate under basic conditions had been attempted and showed mainly the formation of the tetrasubstituted alkene **157** and the recovery of starting material **156** (Table 1, entry 6-7). By using a more hindered base such as DBU instead of the triethylamine in order to control the selectivity of the alkene formed, we recovered only the starting material **156** (Table 1, entry 8).

As a mesylate group is a good leaving group, the isolation of the mesylated product is very difficult, as the elimination of the mesylate group occurs immediately to form the most stable product **157**. In order to tackle this problem, we tried to set up a tosylate group, still a good leaving group for the elimination. Therefore, it should be easier to isolate the tosylated product in order to screen different bases for the elimination. However we never managed to isolate the tosylate, it eliminates instantenously to form predominantly the trisubstituted alkene **158** (Table 1, Entry 9).

2.6.3 Dehydration of Bisepoxide 129

At this stage, we decided to try our best conditions, namely three equivalents of Burgess reagent at 60 °C for one hour in benzene (Table 1, entry 5) on tertiary alcohol **129** (Scheme 47).



Scheme 47: Dehydration of bisepoxide **129**

Pleasingly using Burgess reagent, the dehydration proceeded in 76% yield and provided a mixture of trisubstituted alkene **160** and the exocyclic alkene **161** in a ratio 5:1 respectively. The formation of the tetrasubstituted alkene **162** was not observed. Trisubstituted alkene **160** could be separated from **161** by HPLC, however **161** could not be completely separated from **160** and was isolated as a 2:1 mixture of **160:161** after the HPLC purification.

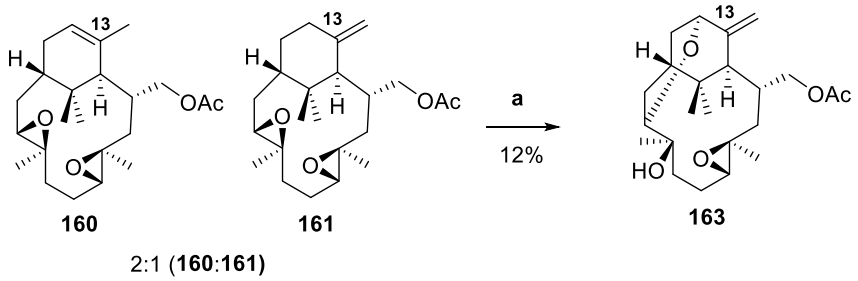
2.7 Studies Towards the Formation of the Exocyclic Enone Moiety

After the dehydration of bisepoxide **129** we predominantly obtained the trisubstituted alkene **160**, therefore we needed to find some alternatives to convert this alkene into the exocyclic enone moiety required for hypoestoxide **2** in order to examine the hetero Diels-Alder dimerisation.

2.7.1 Allylic Oxidation of Exocyclic Alkene 161

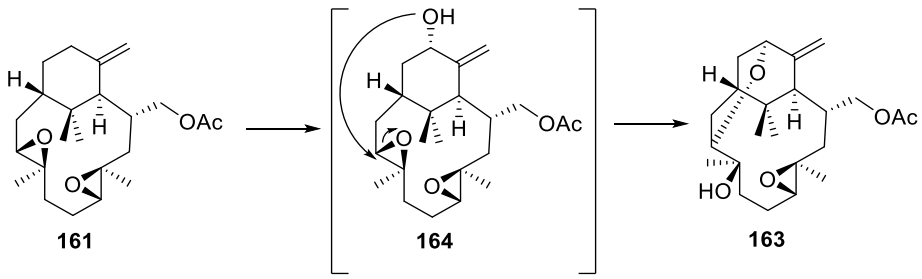
After HPLC purification we managed to isolate a mixture 2:1 of **160**:**161**. Using this fraction, we attempted an allylic oxidation with selenium dioxide and *tert*-butylhydrogen peroxide in dichloromethane at 50 °C.[56] After 3 hours we observed the

conversion of the exocyclic alkene **161** into this unusual ether **163** in the modest yield of 12% along with recovery of the trisubstituted alkene **160**, which can be explained by the small scale of the reaction (13μmol) (Scheme 48).



Scheme 48: Allylic oxidation of **161**

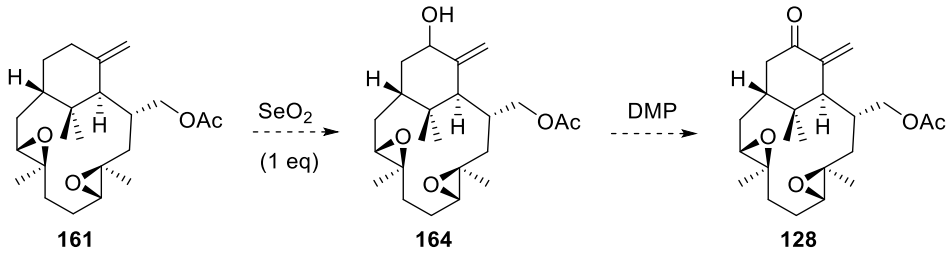
The exocyclic alkene **161** reacted faster than **160** as **160** is potentially sterically more hindered than **161**. Mechanistically, the structure of **163** let us think that the desired allylic alcohol **164** was produced during the reaction. The lone pair of the oxygen of **164** attacks the less hindered end of the epoxide to ring open it and form ether **163** (Scheme 49).



Scheme 49: Suggested mechanism for the formation of **163**

The conditions for this reaction using excess of selenium dioxide and excess of peroxide were attempted in order to force the reaction to go to completion. However, it seems that these conditions were too extreme and forced the desired allylic alcohol

164 to overeact with one of the epoxides. Unfortunately at this time, we did not have enough material to have another attempt using selenium dioxide in stoichiometric amount at room temperature and isolate the desired allylic alcohol **164**. Oxidation of the secondary hydroxyl group of **164** using Dess-Martin periodinane (DMP) could presumably afford the exocyclic enone **128** (Scheme 50).

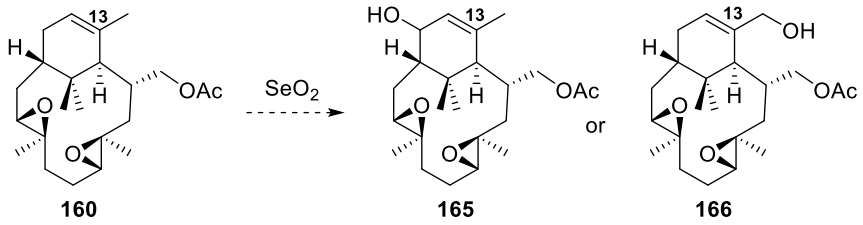


Scheme 50: Suggested synthesis of the exocyclic enone **128**

As the dehydration step allowed us to access mainly trisubstituted alkene **160**, we needed to find conditions to convert **160** into the exocyclic enone moiety. Three methods were examined (selenium dioxide, palladium catalysed acetoxylation and the dihydroxylation) and these will be discussed below.

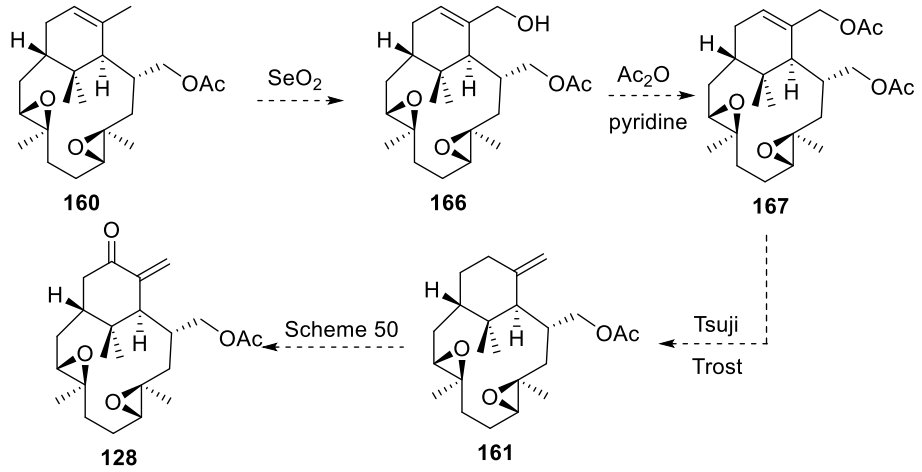
2.7.2 Selenium Dioxide Allylic Oxidation of 160

Selenium dioxide is well-known to oxidise the allylic position of alkenes.[57]-[58] The main idea was to explore the regiochemical outcome of this reaction on trisubstituted alkene **160**, as it could oxidise on the six-membred ring to afford **165** or on the methyl group at the C13 position to provide **166** as shown in Scheme 51.



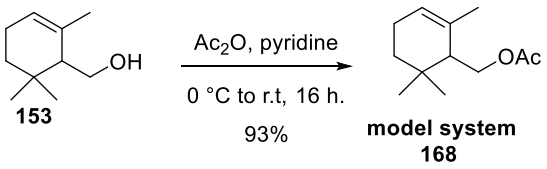
Scheme 51: Problem of the regioselectivity of the allylic oxidation

Ideally, the oxidation on the methyl group at C13 would be preferential in order to protect the free alcohol with an acetate to provide **167** and then by a Tsuji Trost allylic palladium catalysed transposition, we could obtain the exocyclic alkene **161** (Scheme 52).



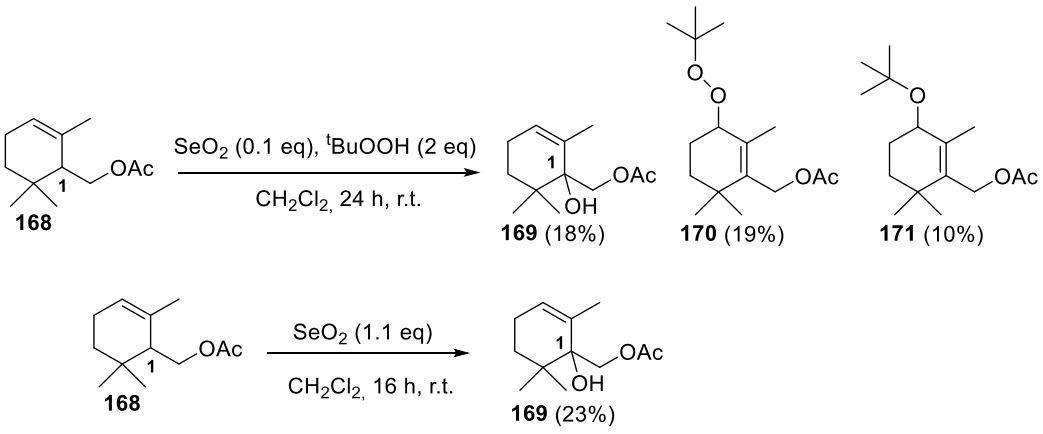
Scheme 52: Selenium dioxide / Tsuji Trost allylic transposition approach

The regioselectivity of the allylic oxidation was investigated on model system **168**, which was easily synthesised from alcohol **153** described in Scheme 46 (paragraph 2.6.1) by protection it with an acetate group (Scheme 53).



Scheme 53: Synthesis of model system **168**

The allylic oxidation was then performed on the model system **168** using selenium dioxide (0.1 eq) and two equivalents of *tert*-butylhydrogen peroxide. This lead to the formation of the tertiary alcohol **169** and the peroxide **170** (19%) and ^{t}butyl ether **171** in 10% yield (Scheme 54). The same reaction was performed using a stoichiometric amount of selenium dioxide without *tert*-butylhydroperoxide this time. In this case, we only observed the formation of **169** (Scheme 54).

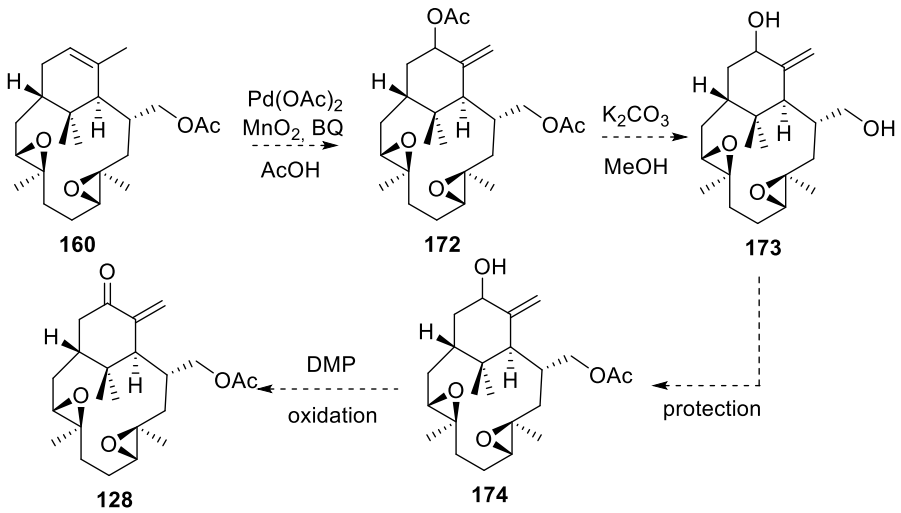


Scheme 54: Allylic oxidation of model system **168**

In both cases we did not observe any allylic oxidation on the methyl group, it occurred each time on the ring. The C1 position of **168** is regioselectively oxidised and similar allylic oxidation has been reported in the synthetic approach of ring B of forskolin.[59]

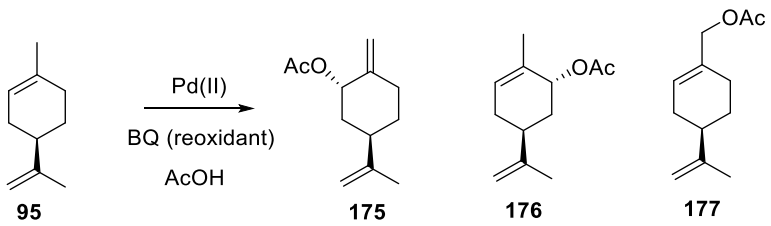
2.7.3 Palladium Catalysed Acetoxylation

An alternative method to form the exocyclic enone moiety required in the structure of **2** is to go through the palladium catalysed acetoxylation route to provide the allylic acetate **172**. Deprotection of the acetate **172** followed by oxidation using Dess-Martin periodinane for example could afford the exocyclic enone moiety **128** (Scheme 55).



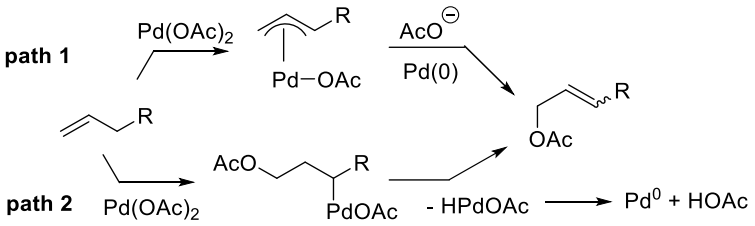
Scheme 55: Palladium Catalysed Acetoxylation Route

The quinone-based palladium catalysed allylic acetoxylation of alkene stands out as a pratical and highly useful process for the synthesis of allylic alcohol derivatives.[60]-[64] Allylic acetoxylation on (+)-limonene **95** is well-described in the literature[65]-[68] and we chose this substrate to find some conditions to form preferentially allylic acetate **175** over **176** and **177** (Scheme 56).



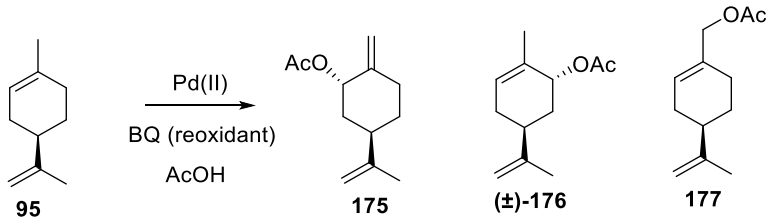
Scheme 56: Allylic acetoxylation of limonene **95**

Two different mechanisms for this palladium catalysed process have been suggested however its mechanism is not yet perfectly clear.[69]-[72] One involves the formation of a (π-allyl)palladium complex followed by a nucleophilic attack on the less substituted carbon (path 1, Scheme 57) whereas the other one proceeds via palladation of alkene followed by β-H elimination (path 2, Scheme 57). The second way seems more probable in the case of linear terminal olefins whereas with internal or cyclic alkenes, the first path is favoured. Benzoquinone re-oxidises Pd(0) during the catalytic cycle into Pd(II).



Scheme 57: Proposed mechanisms for the palladium catalysed allylic acetoxylation

Most of the time a co-oxidant such as MnO_2 is used as well as benzoquinone to reoxidise the hydroquinone formed during the process of reoxidation of Pd(0) to Pd(II). In the following table we tested different oxidant / reoxidant combinations in order to find selective conditions to form predominantly **175** (Table 2).



Entry	Pd (II)	Oxidant Reoxidant	Additives	T (°C) / t (h)	Ratio[a]		
					175	**176**	**177**
1	$Pd(OAc)_2$	MnO_2/ BQ	-	50°C / 24 h	50	50	0
2	$Pd(OAc)_2$	Anisole / BQ	-	50°C / 24 h	25	62	13
3	$Pd(OAc)_2$	LiOAc / BQ	-	25°C / 8 h	33	67	0
4	$PdCl_2$	$CuCl_2$/ NaOAc	-	25°C / 72 h	0	55[b]	0
5	$Pd(OAc)_2$	MnO_2/ BQ	*p*-TSA	50°C / 24 h	67	33	0
6	$Pd(OAc)_2$	$Cu(OAc)_2$/ BQ /air	*p*-TSA	80°C / 3.5 h	87	0	13
7	$Pd(OAc)_2$	$Cu(OAc)_2$/ BQ / O_2	*p*-TSA	80°C / 3.5 h	92	0	8
8	$Pd(OAc)_2$	$Cu(OAc)_2$/ BQ /Ar	*p*-TSA	80°C / 3.5 h	83	0	17

[a] ratio was determined by ^1H NMR after column chromatography; [b] isolated yield, formation of carvone (4%) and allylic alcohol (11%);

Table 2: Palladium catalysed allylic acetoxylation

Classical conditions used 2 equivalents of MnO_2 and 0.2 equivalent of benzoquinone (Table 2, Entry 1) which lead us to a mixture 1:1 of **175**:**176**.[70] We did not observe the formation of **177**. In his attempt to oxidise C5 position of taxadiene Baran used anisole instead of MnO_2.[73] Therefore we tried to reproduce the same conditions on limonene **95** to afford mainly **176** along with **175** and **177** (Table 2, Entry 2). The role of anisole in this case is still not known. However in our case, this did not seem to be the most successful conditions.

In 1981, Backvall reported the palladium catalysed 1,4-diacetoxylation of cyclic 1,3-diene where the use of 3.3 equivalents of lithium acetate is a key factor.[74] Following the same conditions we obtained with a 2:1 mixture of **176**:**175** (Table 2, Entry 3). However it is noticeable that this reaction is performed at room temperature and for only 8 hours (Entry 3) contrary to one day for the previous examples (Entry 1 and 2). The increase of the rate of the reaction could be explained by the excess of lithium acetate which can provide, as well as the acetic acid, the acetoxy needed to attack the (π-allyl)palladium complex.

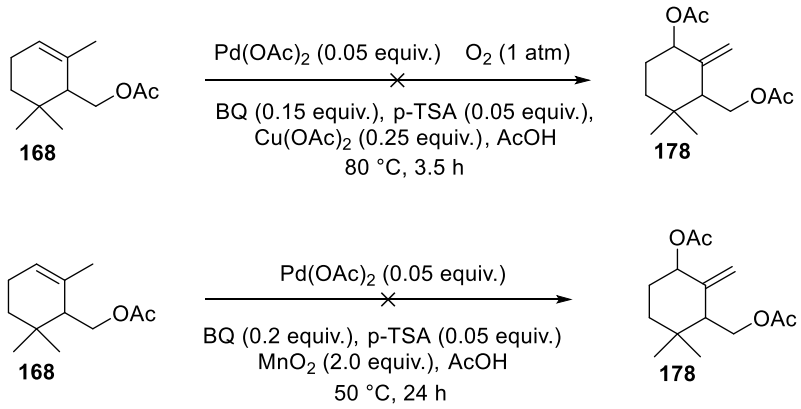
When we changed the palladium II source from $Pd(OAc)_2$ to $PdCl_2$ which constitutes the classical Wacker catalyst ($PdCl_2$-$CuCl_2$-NaOAc) (Table 2, Entry 4),[67] we only observed the formation of **176** in 55% yield as well as (+)-carvone (4%) and the free alcohol corresponding to the deprotection of the acetate **176** in 14% yield.

It is known that the addition of small amounts of stong acids such as *p*-TSA benefits oxidation with $Pd(OAc)_2$ and benzoquinone, favouring a benzoquinone mediated re-oxidations of Pd(0) and sometimes increasing the reaction rate.[75] Consequently we repeated the same conditions used for Entry 1, Table 2 ($Pd(OAc)_2$, BQ, MnO_2) with 0.05 equivalent of *p*-TSA (Table 2, Entry 5). Pleasingly we managed to reverse the selectivity: allylic acetate **175** is formed predominantly over **176**. Conditions using 0.15 equivalent of benzoquinone, 0.25 equivalent of $Cu(OAc)_2$ and 0.05 equivalent of *p*-TSA under air (Entry 6, Table 2), under O_2 (Entry 7, Table 2)[68] or under argon (Entry 8, Table 2) afforded mainly allylic acetate **175** over **177**. The best conditions were found in the presence of oxygen (Entry 7, Table 2) as it helps to reoxidise hydroquinone to benzoquinone more quickly. Using this system of catalyst allows us

to reduce the time of the reaction, and avoid the potential formation of addition product or oligomers resulting of the isomerisation of the double bond.

The addition of *p*-TSA, probably acting as another bulky coordinating molecule on the palladium, makes the formation of the sterically less demanding exocyclic (π-allyl)palladium complexes more favourable.[68] This could explain the regioselectivity observed for allylic acetate **175** and **177** over **176**.

Having found good conditions to convert limonene **95** to the exocyclic alkene **176**, we next examined their use on our model system **168**, which mimics the top part of trisubstituted alkene **148** (Scheme 58). Unfortunately, the reaction failed to provide any of the allylic acetate **178**, only the starting material was recovered in almost quantitative yield. The same observation was made when using benzoquinone, MnO_2 and *p*-TSA (Entry 5, Table 2).

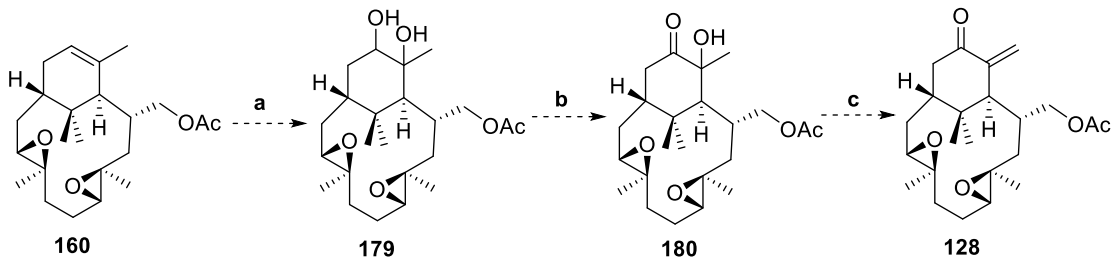


Scheme 58: Allylic acetoxylation on model system **168**

The reasons are not clear, but it could be possible that the palladium catalyst coordinates to the acetate group of **168** and does not react with the trisubstituted alkene moiety. At this point, we needed to find an alternative to this method.

2.7.4 Dihydroxylation

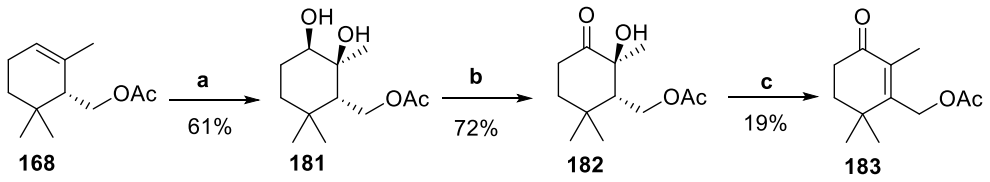
We next decided to see if we could dihydroxylate the trisubstituted alkene **160** to form diol **179**, then oxidise **179** to form hydroxyketone **180**. We have shown previously that Burgess reagent dehydrated **129** to form only the trisubstituted alkene **160** and the exocyclic alkene **161**. There in that case Burgess reagent should dehydrate **180** to form exocyclic enone moiety **128** as we never observed the formation of the tetrasubstituted alkene (Scheme 59).



a: dihydroxylation; **b:** Swern oxidation; **c:** Burgess reagent dehydration.

Scheme 59: Proposed dihydroxylation route to form exocyclic enone moiety **128**

Due to limited supplies of **160**, we decided to work on model system **168** to optimise this route. Trisubstituted alkene **168** was successfully oxidised to diol **181** using the Upjohn method in reasonable yield (61%).[76] Swern oxidation on the secondary alcohol of **181** afforded hydroxyketone **182** in 72% yield, which underwent a dehydration to form endocyclic enone **183** in only 19% yield (Scheme 60).

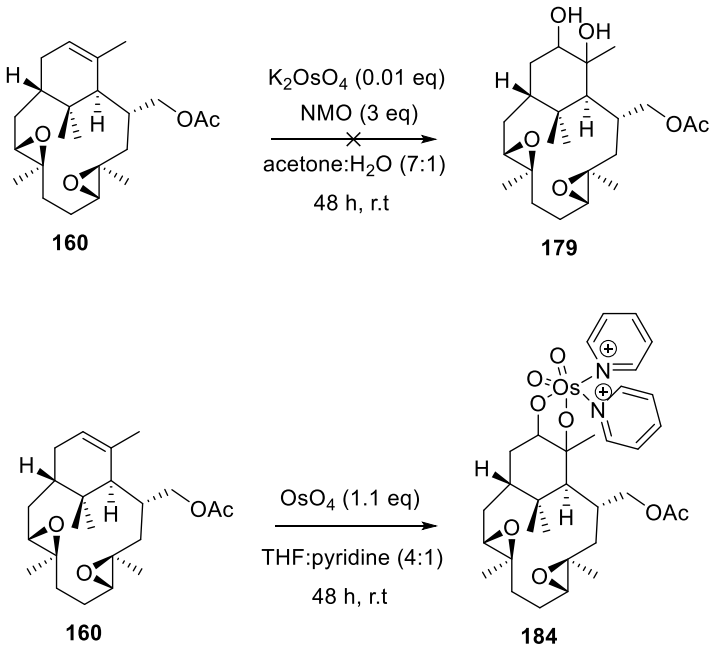


a: NMO (3 eq), K_2OsO_4 (0.01 eq), acetone, H_2O, r.t, 48 h; **b:** $(COCl)_2$ (2 eq), DMSO (4 eq), NEt_3 (8 eq), CH_2Cl_2, -78 °C to r.t, 3 h; **c:** Burgess reagent (3 eq), benzene, 1 h, 60°C.

Scheme 60: Dihydroxylation route on model system **168**

Despite the fact we did not obtain the desired exocyclic enone after dehydration of **183**, we are confident that if we have to perform the same route starting from trisubstituted alkene **160**, this will lead us to the exocyclic enone after dehydration as previously in the same conditions we did not observe any of the tetrasubstituted alkene **162**. Moreover the proton located at the C1 position of **160** is sterically hindered thus favouring the exocyclic enone moiety formation.

When we used potassium osmate with three equivalents of NMO for 2 days at room temperaturature on trisubstituted alkene **160**, we recovered only the starting material **160**, and no traces of the desire diol **179** were observed (Scheme 61). So we decided to use a stoichiometric amount of osmium tetroxide in a mixture 4:1 THF:pyridine as it is known that pyridine accelerates the rate of the reaction.[77] After two days at room temperature, ^{1}H NMR of the crude reaction showed the formation of the osmate ester **184** with two ligands of pyridine on it. We showed as well the disappearance of the alkene peak of the starting material at 5.64 ppm. This observation was reinforced by mass spectrometry and by column chromatography where a mixture of 9:1 ethyl acetate: methanol is required to elute the osmate ester.

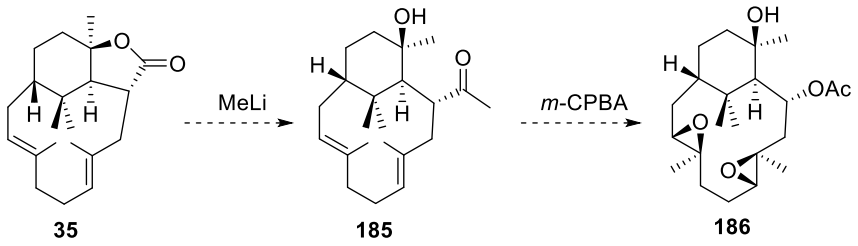


Scheme 61: Dihydroxylation attempts on trisubstituted alkene **160**

It seemed that the osmate ester **184** was not easily cleaved using a saturated aqueous solution of sodium bisulfite for four hours. This can explain why the catalytic dihydroxylation did not afford any of the diol **179** as the osmium tetroxide was not regenerated within the catalytic cycle during the reaction. Full characterisation of the osmate ester **184** could not be provided, only mass spectrometry and proton NMR were obtained at this time. The small amount of **184** recovered after two column chromatographies did not allow us to optimise some conditons in order to cleave the osmate ester **184**. However, in the literature similar examples were found where the cleavage of the osmate ester was difficult. In this case, they left it for 1 day at reflux in a solution of saturated aqueous solution of sodium bisulfate.[56]

2.8 Removal of the Additional Carbon using a Baeyer-Villiger Oxidation

Whilst bringing moe material through for the synthesis of hypostoxide **2**, we tried to improve our route. Our efforts were focused on the removal of the additional carbon next to the acetate group on **160**. We knew that lactone **35** allows us to obtain the desire stereochemistry for natural product **2**. Therefore we decided to investigate if you could methylate and ring open **35** to afford methyl ketone **185**. This intermediate **185** would constitute a precursor of choice for the Baeyer-Villiger oxidation as using an excess of *m*-CPBA we should be able to bisepoxidise at the same time to provide **186** (Scheme 62).



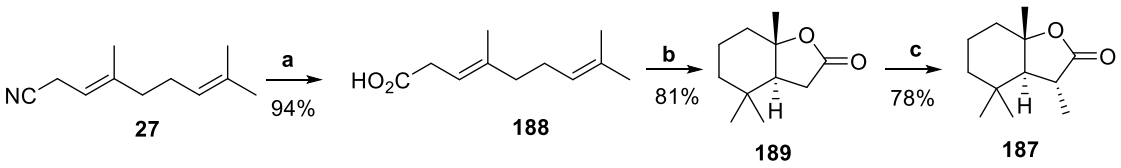
35 **185** **186**

Scheme 62: Proposed Baeyer-Villiger oxidation route

2.8.1 Synthesis of a Model System 187

To study the Baeyer-Villiger oxidation we decided to mimic the top part of lactone **35** by designing a model system **187** (Scheme 63). The lactone **187** was synthesised in three steps from geranyl cyanide **27** itself obtained from geraniol **130** in two steps (see Scheme 37 part 2.2). Geranyl cyanide **27** was converted by basic hydrolysis of the nitrile group to homogeranic acid **188**, which underwent cationic cyclisation using

TFA to form *trans* lactone **189** in 81% yield. Deprotonation of **189** followed by methylation afforded the model system **187** in 78% yield (Scheme 63).

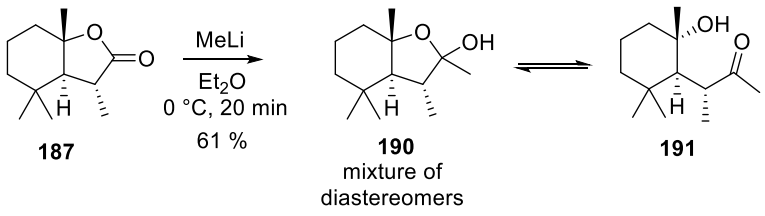


a: NaOH 25% aq, MeOH, reflux, 48 h; **b:** TFA, 30 min, reflux; **c:** HMDS (1.1 eq), n-BuLi (1.2 eq), THF, 0 °C, 1 h then MeI (1.5 eq), -78 °C to r.t, 2 h.

Scheme 63: Synthesis of model system **187**

2.8.2 Optimisation on Model System 187

We subjected our model system **187** to nucleophilic addition by adding 1.1 equivalent of MeLi in diethyl ether at 0 °C for 20 minutes to afford hemiketal **190** as a mixture of two diastereomers (Scheme 64).

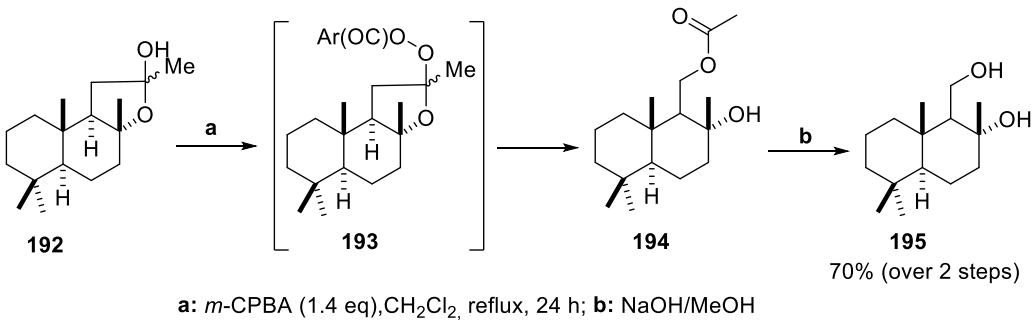


Scheme 64: Single methylation of model system **187**

We did not observe the formation of any tertiary alcohol, which could have been the result of the potential reaction between methyl ketone **191** and MeLi. In our case, hemiketal **190** is the most stable form despite the fact that this intermediate could be in equilibrium with the desired methyl ketone **191**. No signs of the methyl ketone **191**

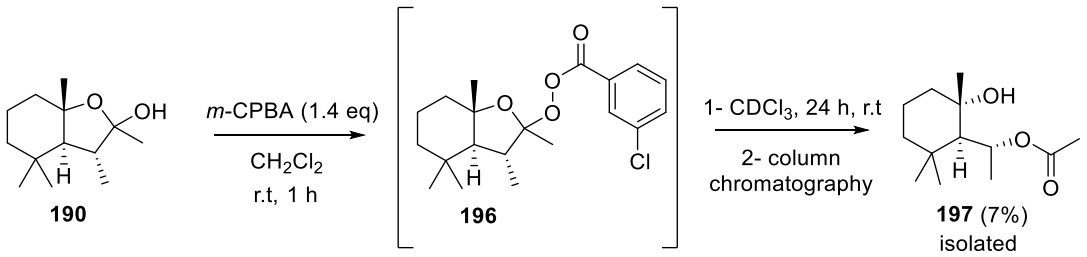
have been shown by ^{1}H NMR (no singlet at 2.10 ppm corresponding to the methyl ketone moiety).

We wanted to see if hemiketal **190** could undergo a Baeyer-Villiger oxidation. In 2000, Grieco *et al.* reported a Baeyer-Villiger oxidation on hemiketal **192** using 1.4 equivalents of *m*-CPBA in dichloromethane to afford acetate **194** as shown in scheme 65.[78] Deprotection of the acetate **194** provided diol **195** in 70% yield over two steps.



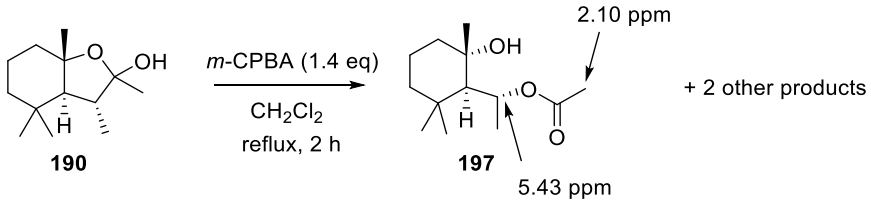
Scheme 65: Baeyer-Villiger oxidation on hemiketal **192**

Therefore we decided to apply the same conditions used by Grieco on our hemiketal **190**. After 1 hour at room temperature, the reaction went to completion and we presumably formed peroxide **196**, which decomposes in $CDCl_3$ after 24 hours. In fact, the NMR sample in $CDCl_3$ was recolumn over silica to isolate and characterise the desire product **197** in 7% yield (Scheme 66).



Scheme 66: Baeyer-Villiger oxidation on hemiketal **190**

We heated the reaction at reflux in dichloromethane for 2 hours and this time we noticed the formation of two different products along with the desire product **197** (Scheme 67).

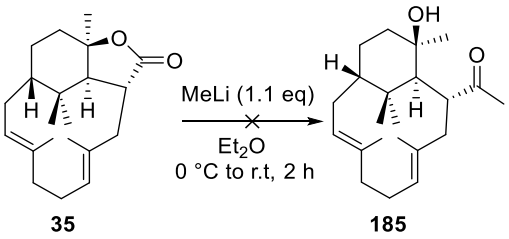


Scheme 67: Baeyer-Villiger oxidation on hemiketal **190**

Unfortunately, we could not obtain an accurate yield for this reaction as we could not determine the structure of these two new products, inseparable from each others using column chromatography. Pleasingly, we did not form the methyl ester **198** as no evidence of it was detected in ^{1}H NMR. It means that the single bond linked to the six-membered has a more favoured migratory aptitude than the methyl group. Consequently, we decided to follow this route on our lactone **35**.

2.8.3 Methylation of Lactone 35 and Baeyer-Villiger Oxidation

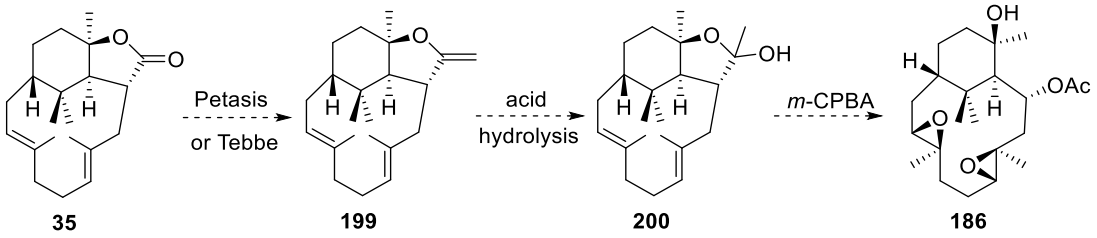
Nucleophilic addition on lactone **35** using 1.1 equivalent of MeLi in Et_2O at 0 °C provided the recovery of the starting material (monitored by TLC), therefore we warmed up the reaction at room temperature for 2 hours and we observed no evolution of the reaction mixture, just the recovery of lactone **35** (Scheme 68).



Scheme 68: Attempted methylation of lactone **35**

As the reaction was performed on small scale (20 mg of starting material), traces of water could quench MeLi during the reaction. The reaction was therefore performed using 4 equivalents of MeLi in Et_2O at room temperature for 24 hours, and once again we only recovered starting material. It seems that our starting material **35** was much less reactive than expected.

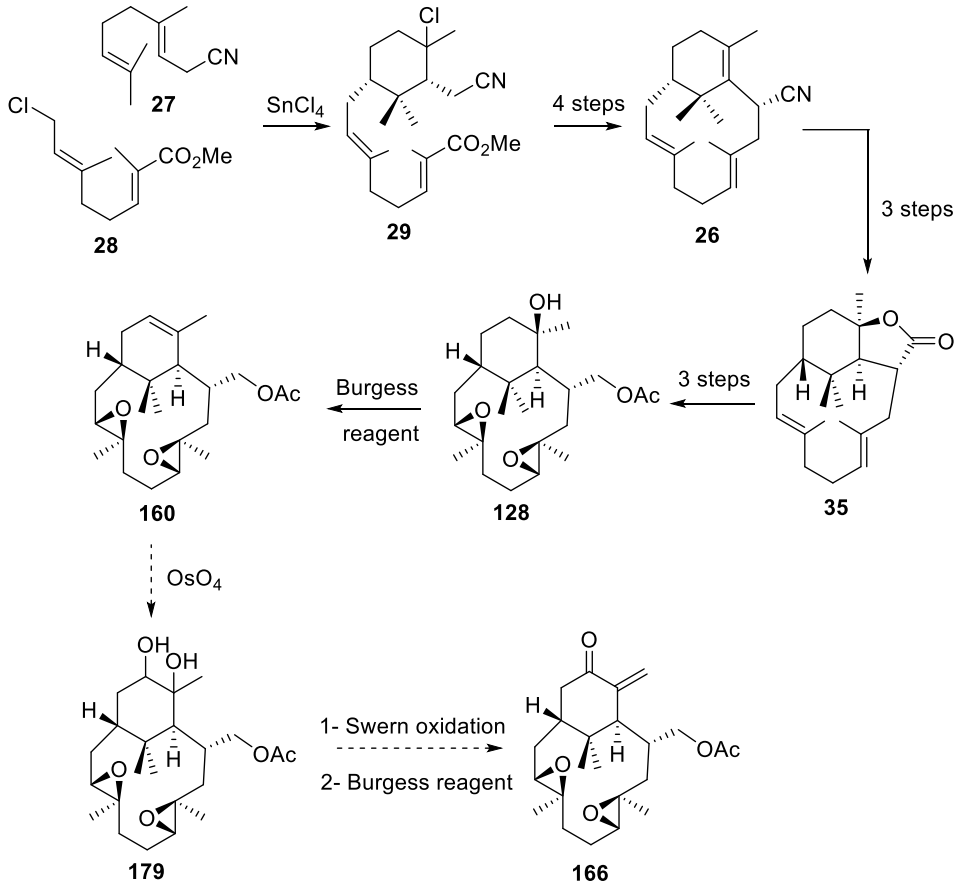
Another alternative method would be to use Petasis reagent on lactone **35** to obtain vinyl ether **199**,[79] which could undergo a reaction with acid to form hemiketal **200** to attempt the Baeyer-Villiger oxidation and form the desire acetate **186** (Scheme 69).



Scheme 69: Alternative approach for the Baeyer-Villiger oxidation

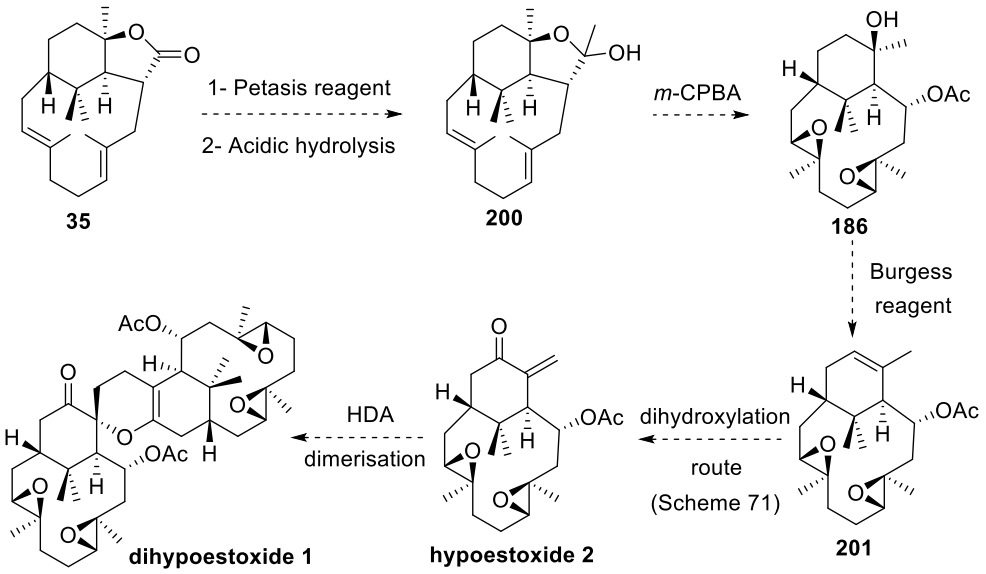
2.9 Conclusions and Future Work

In summary, the ongoing synthesis of hypoestoxide **2** starts from the coupling of chloroester **28** and geranyl cyanide **27** in twelve linear steps**.** We showed that cyanoverticillene **26** allows us to control the atropisomerism of **2**. Lactone **35** is another key compound in this synthesis as it sets up the correct stereochemistry of the natural product. Conditions for the dehydration of bisepoxide **129** were found and applied to this substrate to give a mixture of trisubstituted alkene **160** and the exocyclic double bond **161** (5:1 ratio). The dihydroxylation route seems to be the better method to form the exocyclic enone moiety **128** from trisubstituted alkene **160** (Scheme 70).



Scheme 70: Synthesis of exocyclic enone **128**

The final challenge will be removing the additional carbon on the C12 stereocentre in order to finally complete the total synthesis of hypoestoxide **2** (Scheme 71). This could be achieved by treating lactone **35** with Petasis reagent to form vinyl ether **199**, which could be hydrolysed using acid to afford hemiketal **200**. Then, a Baeyer-Villiger oxidation/epoxidation could be attempted in order to provide acetate **186**. Dehydration using Burgess reagent on **186** could form trisubstituted alkene **201**. Promising dihydroxylation route to convert trisubstituted alkene **201** into the exocyclic enone moiety could be followed in order to achieved the first total synthesis of hypoestoxide **2**. Several conditions such as screening different lewis acids, or the use of high pressure could be tested in order to form by hetero Diels-Alder dimerisation dihypoestoxide **1** (Scheme 71).



Scheme 71: Proposed removal of the additional carbon

Chapter 3: Experimental

3.0 Experimental Procedures

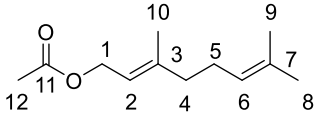
Starting materials were obtained from suppliers and used without further purification unless stated otherwise. Dichloromethane was distilled from calcium hydride, pyridine was distilled from potassium hydroxide, DIPEA was distilled from potassium hydroxide, dimethylformamide was distilled from calcium sulfate under reduced pressure, ether and tetrahydrofuran were taken from alumina towers under nitrogen, hexamethyldisilazide and trimethylamine were distilled from calcium hydride. ^{n}Butyl lithium was titrated two times before use with *N*-pivoyl-*o*-toluidine.[80] DMDO was titrated three times before use using an iodometric titration with sodium thiosulfate as the titrant.[81] All water used was previously deionised and petrol refers to petroleum ether (b.p. 40-60°C). Thin layer chromatography was carried out using Merck silica gel precoated sheets SIL G/UV_{254}, which were visualised under UV light before developing with basic potassium permanganate solution. Column chromatography was performed using Merck silica gel 60, 35-70 μm particles as the packing agent.

NMR spectra were obtained at 298 K as dilute solution in deuterated solvent. The spectra were recorded on the δ scale in ppm referenced to the residual solvent peak ($CDCl_3$ δ_H 7.26, δ_C 77.1, C_6D_6 δ_H 7.16, δ_C 128.1).[82] Spectra were recorded using Bruker DPX 400 MHz, AV 400 MHz, AV(III) 400 MHz, AV(III) 500 MHz spectrometers. Assignments were made based on the chemical shift with the aid of DEPT sequences and correlations techniques such as COSY, HMQC, HMBC. The multiplicity of each signal is designated by the following abbreviations: s, singlet ; d, doublet ; t, triplet ; q, quartet ; quin, quintet ; sext, sextet ; app, apparent ; br, broad. J values are reported in Hertz (Hz) to the nearest decimal place and are rationalised. Relative stereochemistry was assigned using NOESY or nOe techniques.

Infrared spectra were recorded on a Perkin-Elmer 1600 FT spectrometer as dilute solutions in chloroform or as thin films on NaCl discs. Mass spectra were recorded on a Micro TOF 61 spectrometer using electrospray or electron impact ionisation techniques with positive ion detection. Melting points (mp) were measured using a Stuart SMP3 melting point apparatus and are uncorrected.

3.1 General Procedures

(2*E*)-3,7-dimethylocta-2,6-dien-1-yl acetate 131 [83]

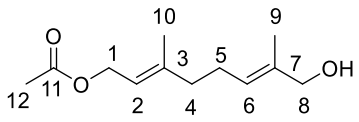


131

To a suspension of geraniol **130** (35.0 g, 227 mmol) in pyridine (70 mL) was added acetic anhydride (70.8 mL, 749 mmol) at 0 °C under an argon atmosphere. The suspension was stirred at room temperature for 14 hours. The reaction mixture was diluted with ethyl acetate (400 mL), and the organic layer was washed successively with a saturated aqueous solution of copper sulfate (3 x 200 mL), water (3 x 200 mL) and brine (100 mL). The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography eluting with 9:1 petrol:ethyl acetate afforded the pure product **131** as a colorless oil (43.0 g, 97%). R_f 0.32 (9:1 petrol:ethyl acetate); ν_{max}/cm^{-1} ($CHCl_3$): 3011, 2970, 2930, 2857, 2733, 1728, 1670; δ_H (400 MHz, $CDCl_3$): 5.33 (1H, tq, *J* 7.1, 1.1, C^2H), 5.07 (1H, tq, *J* 6.8, 1.4, C^6H), 4.58 (2H, d, *J* 7.1, C^1H_2), 2.13-2.01 (4H, m, C^4H_2, C^5H_2), 2.04 (3H, s, $C^{12}H_3$), 1.69 (3H, br s, $C^{10}H_3$), 1.67 (3H, br s, C^9H_3), 1.59 (3H, s, C^8H_3); δ_C (100 MHz, $CDCl_3$): 171.2 (C), 142.3 (C), 131.9 (C), 123.9 (CH), 118.4 (CH), 61.5 (CH_2), 39.6

(CH_2), 26.4 (CH_2), 25.8 (CH_3), 21.1 (CH_3), 17.8 (CH_3), 16.5 (CH_3); *m/z* (ES^+) found 219.1342 ($[M+Na]^+$, $C_{12}H_{20}O_2Na^+$ requires 219.1356). All data agreed with that previously published.[83]

(2*E*,6*E*)-8-hydroxy-3,7-dimethylocta-2,6-dien-1-yl acetate 132 [84]



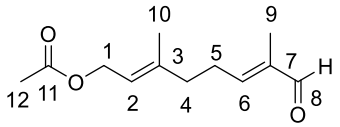
132

Selenium dioxide (2.43 g, 21.9 mmol) was dissolved in dichloromethane (80 mL), then *tert*-butylhydroperoxide (43.0 mL, 438 mmol) and a solution of geranyl acetate **131** (43.0 g, 219 mmol) in dichloromethane (90 mL) were sequentially added to the reaction mixture. The resulting mixture was stirred for 24 hours at room temperature. The mixture was concentrated *in vacuo* to remove volatiles, then diluted with diethyl ether (300 mL). The organic layer was washed successively with a 10% aqueous solution of potassium hydroxide (3 x 100 mL), water (3 x 100 mL) and brine (100 mL). The combined organic layers were dried over magnesium sulfate, and concentrated *in vacuo*. Purification by column chromatography eluting from 15:1 to 2:1 petrol:ethyl acetate afforded the pure product **132** as a colorless oil (21.8 g, 47%). R_f 0.21 (2:1 petrol:diethyl ether); ν_{max}/cm^{-1} ($CHCl_3$): 3611, 3011, 2931, 2861, 1728; δ_H (400 MHz, $CDCl_3$): 5.34 (1H, tq, *J* 6.9, 1.4, C^6H), 5.31 (1H, tq, *J* 7.1, 1.4, C^2H), 4.56 (2H, d, *J* 7.1, C^1H_2), 3.96 (2H, br s, C^8H_2), 2.15 (2H, app q, *J* 8.0, C^5H_2), 2.07 (2H, t, *J* 8.0, C^4H_2), 2.03 (3H, s, $C^{12}H_3$), 1.68 (3H, br s, $C^{10}H_3$), 1.64 (3H, br s, C^9H_3); δ_C (100 MHz, $CDCl_3$): 171.3 (C), 141.8 (C), 135.4 (C), 125.3 (CH), 118.7 (CH), 68.9 (CH_2), 61.5 (CH_2), 39.1 (CH_2), 25.7 (CH_2), 21.1 (CH_3), 16.5 (CH_3), 13.8 (CH_3); *m/z* (ES^+)

found 235.1305 ([M+Na]$^+$, $C_{12}H_{20}O_3Na^+$ requires 235.1305). All data agreed with that previously published.[84]

Aldehyde **133** (8.09 g, 17%) as a clear oil and starting material **131** (9.61 g, 22%) were also recovered after the purification. Data for the starting material matched perfectly with that obtained previously. Data for the aldehyde will be given in the next procedure.

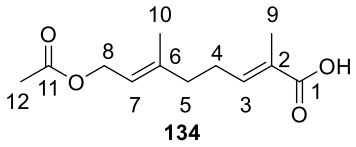
(2*E*,6*E*)-3,7-dimethyl-8-oxoocta-2,6-dien-1-ylacetate 133 [85]



133

To a solution of allylic alcohol **132** (49.9 g, 235 mmol) in dichloromethane (500 mL) was added activated manganese (IV) dioxide (195 g, 2.24 mol). The reaction mixture was stirred for 14 h at room temperature before being filtered through a pad of celite, and washed with dichloromethane (250 mL). The filtrate was concentrated *in vacuo* to afford aldehyde **133** (45.8 g, 92%) as a colorless oil, used in the next step without further purification. R_f 0.35 (2:1 petrol:diethyl ether); ν_{max}/cm^{-1} ($CHCl_3$): 3011, 2856, 2831, 2767, 1736, 1683, 1644; δ_H (400 MHz, $CDCl_3$): 9.33 (1H, s, C^8H), 6.42 (1H, tq, *J* 7.2, 1.3, C^6H), 5.35 (1H, tq, *J* 7.0, 1.2, C^2H), 4.56 (2H, d, *J* 7.0, C^1H_2), 2.47 (2H, app q, *J* 7.5, C^5H_2), 2.20 (2H, t, *J* 7.5, C^4H_2), 2.02 (3H, s, $C^{12}H_3$), 1.71 (6H, br s, C^9H_3, $C^{10}H_3$); δ_C (100 MHz, $CDCl_3$): 195.2 (CH), 171.1 (C), 153.5 (CH), 140.4 (C), 139.7 (C), 119.7 (CH), 61.2 (CH_2), 37.8 (CH_2), 27.0 (CH_2), 21.0 (CH_3), 16.4 (CH_3), 9.30 (CH_3); *m/z* (ES^+) found 233.1146 ([M+Na]$^+$, $C_{12}H_{18}O_3Na^+$ requires 233.1148). All data agreed with that previously published.[85]

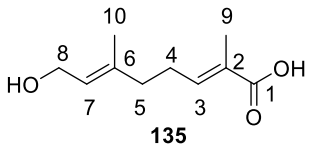
(2*E*,6*E*)-8-(acetyloxy)-2,6-dimethylocta-2,6-dienoic acid 134 [85]



134

To a stirring solution of aldehyde **133** (19.0 g, 90.3 mmol) in *tert*-butyl alcohol (290 mL) was added 2-methyl-2-butene (95 mL, 897 mmol) and a solution of sodium dihydrogenophosphate (56.5 g, 361 mmol) in water (290 mL). Sodium chlorite (32.6 g, 361 mmol) was then added portionwise. The mixture was vigourously stirred at room temperature for 14 hours. It was then diluted with ethyl acetate (400 mL) and the organic layer was separated. The aqueous layer was acidified to pH 3 by addition of a 6 M aqueous solution of hydrogen chloride and re-extracted with ethyl acetate (3 x 400 mL). The combined organic layers were washed with brine (400 mL), dried over magnesium sulfate, and concentrated *in vacuo* to afford the carboxylic acid **134** as a colorless oil (18.3 g, 90%) used in the next step without further purification. R_f 0.81 (3:1 ethyl acetate:petrol); ν_{max}/cm^{-1} ($CHCl_3$): 3011, 2990, 2937, 1725, 1687, 1643; δ_H (400 MHz, $CDCl_3$): 6.86 (1H, tq, *J* 7.3, 1.4, C^3H), 5.36 (1H, tq, *J* 7.0, 1.3, C^7H), 4.58 (2H, d, *J* 7.0, C^8H_2), 2.33 (2H, app q, *J* 7.5, C^4H_2), 2.17 (2H, t, *J* 7.5, C^5H_2), 2.05 (3H, s, $C^{12}H_3$), 1.83 (3H, br s, C^9H_3), 1.72 (3H, br s, $C^{10}H_3$); δ_C (100 MHz, $CDCl_3$): 173.5 (C), 171.3 (C), 144.1 (CH), 140.9 (C), 127.6 (C), 119.4 (CH), 61.3 (CH_2), 38.0 (CH_2), 27.1 (CH_2), 21.1 (CH_3), 16.5 (CH_3), 12.1 (CH_3); *m/z* (ES^-) found 225.1109 ([M-H], $C_{12}H_{17}O_4$ requires 225.1108). All data agreed with that previously published.[85]

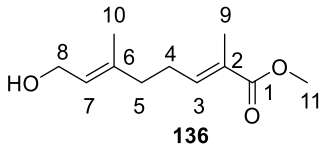
(2*E*,6*E*)-8-hydroxy-2,6-dimethylocta-2,6-dienoic acid 135 [85]



135

To a solution of acid **134** (18.3 g, 81.0 mmol) in methanol (365 mL) was added a solution of potassium carbonate (22.4 g, 138 mmol) in water (92 mL). The mixture was vigorously stirred at room temperature for 14 hours. Before being extracted with dichloromethane (300 mL) the organic layer was separated and the aqueous layer was acidified to pH 3 by addition of a 6 M aqueous solution of hydrogen chloride and re-extracted with dichloromethane (3 x 300 mL). The combined organic layers were washed with brine (300 mL), dried over magnesium sulfate, and concentrated *in vacuo* to give hydroxyacid **135** as a colorless oil (10.5 g, 70%) used in the next step without further purification. R_f 0.66 (3:1 ethyl acetate:petrol); ν_{max}/cm^{-1} ($CHCl_3$): 3612, 3011, 2935, 2889, 1687, 1643; δ_H (400 MHz, $CDCl_3$): 6.85 (1H, tq, *J* 7.3, 1.3, C^3H), 5.42 (1H, tq, *J* 6.9, 1.2, C^7H), 4.16 (2H, d, *J* 6.9, C^8H_2), 2.32 (2H, q app, *J* 7.5, C^4H_2), 2.15 (2H, t, *J* 7.5, C^5H_2), 1.82 (3H, br s, C^9H_3), 1.68 (3H,br s, $C^{10}H_3$); δ_C (100 MHz, $CDCl_3$): 173.2 (C), 144.1 (CH), 138.4 (C), 127.6 (C), 124.2 (CH), 59.3 (CH_2), 38.0 (CH_2), 27.2 (CH_2), 16.3 (CH_3), 12.2 (CH_3); *m/z* (ES^-) found 183.1015 ([M-H], $C_{10}H_{15}O_3$ requires 183.1013). All data agreed with that previously published.[85]

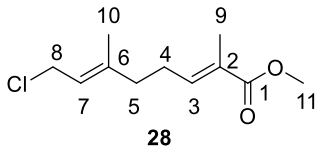
methyl (2*E*,6*E*)-8-hydroxy-2,6-dimethylocta-2,6-dienoate 136 [85]



136

To a solution of hydroxy acid **135** (10.5 g, 57.0 mmol) in dimethylformamide (210 mL) was added a solution of potassium carbonate (8.65 g, 63.0 mmol) in water (42 mL). The resulting mixture was stirred for 15 minutes before the addition of methyl iodide (3.90 mL, 63.0 mmol). The reaction mixture was vigorously stirred for 14 hours at room temperature. Then it was diluted with ethyl acetate (200 mL) and water (200 mL). The organic layer was separated and the aqueous layer was acidified to pH 3 by addition of a 6 M aqueous solution of hydrogen chloride and re-extracted with ethyl acetate (3 x 150 mL). The combined organic layers were washed successively with water (3 x 400 mL), a saturated solution of sodium bicarbonate (200 mL), and brine (200 mL). The organic phase was dried over magnesium sulfate, and concentrated *in vacuo*. Purification by column chromatography eluting with 25:1 dichloromethane:methanol afforded the hydroxy ester **136** as a pale yellow oil (8.85 g, 78%). R_f 0.51 (25:1 dichloromethane:methanol); ν_{max}/cm^{-1} ($CHCl_3$): 3612, 3011, 2952, 1707, 1649; δ_H (400 MHz, $CDCl_3$): 6.70 (1H, tq, *J* 7.3, 1.4, C^3H), 5.40 (1H, tq, *J* 6.8, 1.2, C^7H), 4.12 (2H, d, *J* 6.8, C^8H_2), 3.70 (3H, s, $C^{11}H_3$), 2.27 (2H, app q, *J* 7.6, C^4H_2), 2.11 (2H, t, *J* 7.6, C^5H_2), 1.80 (3H, br s, C^9H_3), 1.65 (3H, br s, $C^{10}H_3$); δ_C (100 MHz, $CDCl_3$): 168.7 (C), 141.8 (CH), 138.2 (C), 127.9 (C), 124.4 (CH), 59.3 (CH_2), 51.8 (CH_3), 38.1 (CH_2), 27.0 (CH_2), 16.3 (CH_3), 12.5 (CH_3); *m/z* (ES^+) found 221.1152 ($[M+Na]^+$, $C_{11}H_{18}O_3Na^+$ requires 221.1148). All data agreed with that previously published.[85]

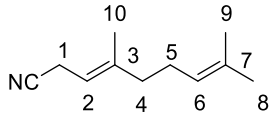
methyl (2*E*,6*E*)-8-chloro-2,6-dimethylocta-2,6-dienoate 28 [14]



28

To a stirring solution of hydroxyl ester **136** (8.85 g, 44.8 mmol) in anhydrous dichloromethane (170 mL) was added diisopropylethylamine (11.7 mL, 67.2 mmol). The resulting mixture was cooled to 0 °C and methanesulfonyl chloride (5.20 mL, 67.2 mmol) was added dropwise. The reaction mixture was stirred overnight at room temperature. The resulting mixture was washed with water (150 mL) and extracted with dichloromethane (200 mL). The aqueous layer was re-extracted with dichloromethane (3 x 300 mL). The combined organic layers were washed with brine (300 mL), dried over magnesium sulfate, concentrated *in vacuo*. Purification by column chromatography eluting with 40:1 to 30:1 petrol:diethyl ether afforded the pure chloroester **28** as a pale yellow oil (6.50 g, 67%). R_f 0.17 (20:1 petrol:diethyl ether); ν_{max}/cm^{-1} ($CHCl_3$): 3010, 2952, 1707, 1650; δ_H (400 MHz, $CDCl_3$): 6.71 (1H, tq, *J* 7.3, 1.4, C^3H), 5.47 (1H, tq, *J* 7.9, 1.3, C^7H), 4.09 (2H, d, *J* 7.9, C^8H_2), 3.73 (3H, s, $C^{11}H_3$), 2.31 (2H, app q, *J* 7.3, C^4H_2), 2.17 (2H, t, *J* 7.3, C^5H_2), 1.84 (3H, br s, C^9H_3), 1.74 (3H, br s, $C^{10}H_3$); δ_C (100 MHz, $CDCl_3$): 168.5 (C), 141.5 (C), 141.2 (CH), 128.1 (C), 121.2 (CH), 51.7 (CH_3), 40.8 (CH_2), 38.0 (CH_2), 26.8 (CH_2), 16.1 (CH_3), 12.5 (CH_3); *m/z* (ES^+) found 239.0797 ($[M+Na]^+$, $C_{11}H_{17}O_2{}^{35}ClNa^+$ requires 239.0809). All data agreed with that previously published.[14]

(2*E*,6*E*)-3,7-dimethylnona-2,6-dienenitrile 27 [86]



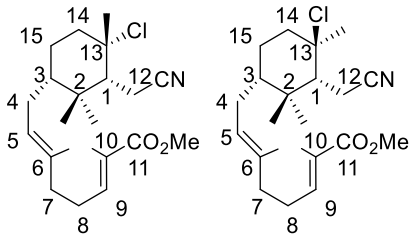
27

To a solution of geraniol **130** (15.0 g, 97.2 mmol) in anhydrous diethyl ether (300 mL) at 0 °C was added phosphorous tribromide (4.60 mL, 48.6 mmol) over the course of 10 min. The resulting reaction mixture was stirred for 3 hours at room temperature, before being cooled to 0 °C and quenched dropwise with an aqueous solution of sodium bicarbonate (70 mL). The organic layer was separated and the aqueous phase was re-extracted with diethyl ether (3 x 50 mL). The combined organic layers were washed with water (70 mL), dried over magnesium sulfate, and concentrated *in vacuo* to afford the crude geranyl bromide **137** as a yellow oil (21.3 g, 100%), which was used directly in the next step without further purification.

To a suspension of sodium cyanide (5.54 g, 113 mmol), in anhydrous dimethylformamide (75 mL), was added freshly synthesised geranyl bromide **137** (21.3 g, 103 mmol) at 0 °C. The resulting reaction mixture was stirred for 72 hours at room temperature. Upon completion (TLC), the reaction mixture was poured into water (300 mL), and then extracted with diethyl ether (500 mL). The organic layer was separated and the aqueous layer was re-extracted with diethyl ether (3 x 200 mL). The combined organic layers were washed with water (2 x 500 mL), dried over magnesium sulfate, and concentrated *in vacuo*. Purification by column chromatography eluting with 15:1 petrol:diethyl ether afforded the pure compound **27** as a colorless oil (12.0 g, 75% over two steps). R_f (15:1 petrol:diethyl ether); ν_{max}/cm^{-1} ($CHCl_3$): 2971, 2918, 2857, 2251, 1669; δ_H (400 MHz, $CDCl_3$): 5.14 (1H, tq, *J* 7.0, 1.3, C^2H), 5.04 (1H, tq, *J* 8.2, 1.4, C^6H), 3.02 (2H, d, *J* 7.0, C^1H_2), 2.12 – 1.99 (4H, m, C^5H_2, C^4H_2), 1.66 (3H,br

s, $C^{9}H_3$), 1.65 (3H, br s, $C^{10}H_3$), 1.58 (3H, s, $C^{8}H_3$); δ_C (100 MHz, $CDCl_3$): 142.2 (C), 132.2 (C), 123.4 (CH), 118.7 (C), 111.7 (CH), 39.2 (CH_2), 26.2 (CH_2), 25.7 (CH_3), 17.7 (CH_3), 16.3 (CH_3), 16.2 (CH_2); *m/z* (ES^+) found 186.1266 ([M+H], $C_{11}H_{18}N$ requires 186.1253). All data agreed with that previously published.[86]

Coupling reaction of geranyl cyanide 27 and allyl chloride 28 [14]



To a solution of geranyl cyanide **27** (1.66 g, 10.1 mmol) and chloroester **28** (2.00 g, 9.20 mmol) in dry CH_2Cl_2 (30 mL) at -78 °C was added dropwise a pre-cooled solution of tin (IV) chloride (1.30 mL, 11.1 mmol) in anhydrous dichloromethane (7 mL) at -78 °C. The temperature of the reaction mixture was gradually raised up to -30 °C and the stirring was continued for an additional 3 hours at -30 °C. A mixture (1:1) of pyridine:dichloromethane (10 mL) was added at -30 °C to quench the reaction. The reaction mixture was then extracted with diethyl ether (150 mL), and a light yellow coloured precipitate formed, was removed by filtration through a pad of silica. The precipitate was washed with diethyl ether (75 mL), and the filtrate concentrated *in vacuo*. Purification by column chromatography eluting with 30:1 to 15:1 petrol:ethyl acetate afforded the axial chloride **29ax** as a colorless oil (1.15 g, 33%) and the equatorial chloride **29eq** as a colorless oil (1.00 g, 28%).

(5*E*,9*E*)-methyl-11-((1*S*,3*S*,13*S*)-13-chloro-1-(cyanomethyl)-2,2,13-trimethylcyclohexyl)-6,10-dimethylocta-5,9-dienoate 29ax [14]

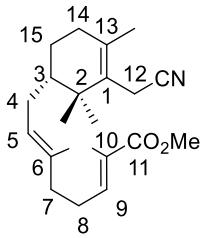
R_f 0.22 (15:1 petrol:ethyl acetate); ν_{max}/cm^{-1} ($CHCl_3$): 3011, 2951, 2873. 2247, 1707, 1649; δ_H (400 MHz, $CDCl_3$): 6.72 (1H, app t, *J* 5.1, C^9H), 5.11 (1H, app t, *J* 4.9, C^5H), 3.71 (3H, s, $C^{11}O_2CH_3$), 2.63 (1H, dd, *J* 18.2, 6.5, $C^{12}H_{2A}$), 2.46 (1H, dd, *J* 18.2, 2.9, $C^{12}H_{2B}$), 2.30-2.07 (6H, m, C^8H_2, C^7H_2, C^4H_{2A}, $C^{14}H_{2A}$), 1.81 (3H, s, $C^{10}CH_3$), 1.77-1.63 (6H, m, $C^{14}H_{2B}$, C^1H, C^4H_{2B}, $C^{13}ClCH_3$), 1.63-1.45 (5H, m, C^6CH_3, $C^{15}H_{2A}$, $C^{15}H_{2B}$), 1.10-1.04 (4H, m, C^3H, C^2CH_3), 0.85 (3H, s, C^2CH_3); δ_C (100 MHz, $CDCl_3$): 168.6 (C), 142.0 (CH), 135.2 (C), 127.6 (C), 124.7 (CH), 121.3 (C), 74.3 (C), 55.5 (CH), 51.8 (CH_3), 48.5 (CH), 43.0 (CH_2), 38.7 (CH_2), 38.4 (C), 34.3 (CH_3), 28.9 (CH_2), 28.6 (CH_3), 27.2 (CH_2), 23.3 (CH_2), 16.1 (CH_3), 16.0 (CH_3), 15.2 (CH_2), 12.5 (CH_3); *m/z* (ES^+) found 402.2184 ($[M+Na]^+$, $C_{22}H_{34}{}^{35}ClNO_2Na^+$ requires 402.2170). All data agreed with that previously published.[14]

(5*E*,9*E*)-methyl-11-((1*S*,3*S*,13*R*)-13-chloro-1-(cyanomethyl)-2,2,13-trimethylcyclohexyl)-6,10-dimethylocta-5,9-dienoate 29eq [14]

R_f 0.19 (15:1 petrol:ethyl acetate); ν_{max}/cm^{-1} ($CHCl_3$): 2950, 2871, 2249, 1707, 1649; δ_H (400 MHz, $CDCl_3$): 6.71 (1H, app t, *J* 6.5, C^9H), 5.10 (1H, app t, *J* 5.9, C^5H), 3.73 (3H, s, $C^{11}O_2CH_3$), 2.81 (1H, dd, *J* 17.5, 2.9, $C^{12}H_{2,A}$), 2.45 (1H, dd, *J* 17.5, 7.1, $C^{12}H_{2,B}$), 2.31-1.99 (8H, m, C^8H_2, C^1H, $C^{14}H_{2A}$, C^7H_2, C^4H_{2A}, $C^{14}H_{2B}$), 1.83 (3H, s, $C^{10}CH_3$), 1.73-1.58 (5H, m, $C^{15}H_{2A}$, C^4H_{2B}, C^6CH_3), 1.50 (3H, s, $C^{13}ClCH_3$), 1.23-1.09 (5H, m, $C^{15}H_{2B}$, C^3H, C^2CH_3), 0.79 (3H, s, C^2CH_3); δ_C (100 MHz, $CDCl_3$): 168.7 (C), 142.2 (CH), 135.4 (C), 127.7 (C), 124.5 (CH), 121.1 (C), 75.7 (C), 57.2 (CH), 51.8

(CH_3), 48.3 (CH), 44.9 (CH_2), 40.5 (C), 38.3 (CH_2), 29.0 (CH_3), 28.5 (CH_2), 27.1 (CH_2), 25.6 (CH_2), 25.4 (CH_3), 16.3 (CH_3), 16.2 (CH_3), 15.1 (CH_2), 12.6 (CH_3); *m/z* (ES^+) found 402.2187 ($[M+Na]^+$, $C_{22}H_{34}{}^{35}ClNO_2Na^+$ requires 402.2170). All data agreed with that previously published.[14]

(5*E*,9*E*)-methyl-11-((3*S*)-1-(cyanomethyl)-2,2,13-trimethylcyclohex-1-en-1-yl)-6,10-dimethylocta-5,9-dienoate 30



30

Method A: Dehydrochlorination of equatorial chloride 29eq[14]

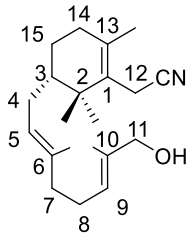
To a solution of equatorial chloride **29eq** (1.00 g, 2.63 mmol) in anhydrous dichloromethane (40 mL) was added anhydrous zinc chloride (400 mg, 2.90 mmol) and the resulting reaction mixture was stirred at room temperature for 48 hours, then 2-methyl-2-butene (3.80 mL, 36.0 mmol) was added and the reaction mixture was stirred one additional day at room temperature. The reaction mixture was diluted in dichloromethane (150 mL) and washed with a aqueous saturated solution of sodium bicarbonate (50 mL). Then the aqueous layer was re-extracted with dichloromethane (3 x 100 mL). The combined organic layers were washed with brine (150 mL), dried over magnesium sulfate, concentrated *in vacuo*. Purification by column chromatography eluting with 15:1 petrol:ethyl acetate afforded the pure ester **30** as a colorless oil (574 mg, 69%). R_f 0.43 (5:1 petrol:ethyl acetate); ν_{max}/cm^{-1} ($CHCl_3$): 3011, 2953, 2247, 1707, 1649; δ_H (400 MHz, $CDCl_3$): 6.72 (1H, app t, *J* 7.0, C^9H),

5.13 (1H, app t, *J* 7.3, $C^{5}H$), 3.71 (3H, s, $C^{11}O_2CH_3$), 3.01 (1H, d, *J* 17.4, $C^{12}H_{2,A}$), 2.95 (1H, d, *J* 17.4, $C^{12}H_{2,B}$), 2.30-2.07 (5H, $C^{7}H_2$, $C^{8}H_2$, $C^{4}H_{2,A}$), 2.02-1.92 (2H, m, $C^{14}H_2$), 1.82 (3H, s, $C^{10}CH_3$), 1.78-1.68 (4H, m, $C^{4}H_{2B}$, $C^{13}CH_3$), 1.64-1.57 (4H, m, $C^{15}H_{2A}$, $C^{6}CH_3$), 1.27-1.18 (2H, m, $C^{3}H$, $C^{15}H_{2B}$), 1.10 (3H, s, $C^{2}CH_3$), 0.87 (3H, s, $C^{2}CH_3$); δ_C (100 MHz, $CDCl_3$): 168.7 (C), 142.3 (CH), 134.8 (C), 133.7 (C), 127.8 (C), 127.6 (C), 125.1 (CH), 119.3 (C), 51.7 (CH_3), 45.4 (CH), 38.5 (CH_2), 38.4 (C), 32.2 (CH_2), 28.7 (CH_2), 27.2 (CH_2), 26.1 (CH_3), 23.1 (CH_2), 21.3 (CH_3), 20.2 (CH_3), 16.6 (CH_2), 16.1 (CH_3), 12.5 (CH_3); *m/z* (ES^+) found 366.2391 ($[M+Na]^+$, $C_{22}H_{33}NO_2Na^+$ requires 366.2404). All data agreed with that previously published.[14]

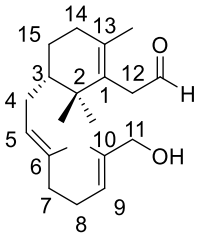
Method B: Dehydrochlorination of axial chloride 29ax[14]

To a solution of axial chloride **29ax** (1.01 g, 2.67 mmol) dissolved in dimethylformamide (30 mL) was added lithium chloride (1.02 g, 24.0 mmol) at room temperature. The resulting mixture was heated at 100 °C for 3 hours. After being cooled to room temperature, the reaction mixture was diluted in diethyl ether (250 mL) and washed with a aqueous saturated solution of sodium bicarbonate (75 mL). The aqueous layer was re-extracted with diethyl ether (3 x 150 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, concentrated *in vacuo*. Purification by column chromatography eluting with 15:1 petrol:ethyl acetate afforded the pure ester **30** as a colorless oil (824 mg, 90%).

((3*S*,5*E*,9*E*)-11-hydroxy-6,10-dimethylocta-5,9-dien-3-yl)-2,2,13-trimethylcyclohex-1-en-1-yl)acetonitrile 31 and 1-((*S*)-3-((5*E*,9*E*)-11-hydroxy-6,10-dimethylocta-5,9-dien-1-yl)-2,2,13-trimethylcyclohex-1-en-1-yl)acetaldehyde 143



31



143

To a stirring solution of ester **30** (973 mg, 2.84 mmol) in anhydrous toluene (40 mL), was added diisobutylaluminium hydride (1.5 M in toluene, 3.78 mL, 5.67 mmol) dropwise at -78 °C. The resulting mixture was stirred for 40 min at -78 °C before being quenched slowly with methanol (1 mL) at -78 °C, then a 2 M aqueous solution of potassium sodium tartrate (10 mL) was added to the mixture before it was warmed gradually to room temperature and stirred for 30 minutes. The reaction was diluted in ethyl acetate (75 mL) and the two layers were separated. The aqueous layer was re-extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (75 mL), dried over magnesium sulfate, and concentrated *in vacuo*. Purification by column chromatography eluting with 5:1 petrol: ethyl acetate afforded the pure allylic alcohol **31** as a colorless oil (337 mg, 76% based on the recovery of starting material) aldehyde **143** (69 mg, 8%) and starting material **30** (275 mg, 36%).

((3S,5*E*,9*E*)-11-hydroxy-6,10-dimethylocta-5,9-dien-3-yl)-2,2,13-trimethylcyclohex-1-en-1-yl)acetonitrile 31:

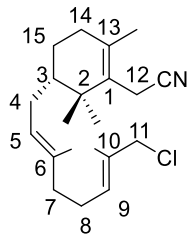
R_f 0.54 (2:1 petrol: ethyl acetate); ν_{max}/cm^{-1} ($CHCl_3$): 3610, 3011, 2970, 2938, 2247, 1719, 1681; δ_H (400 MHz, $CDCl_3$): 5.39 (1H, app t, *J* 6.6, C^9H), 5.13 (1H, app t, *J* 7.3, C^5H), 3.99 (2H, s, $C^{11}H_2$), 3.03 (1H, d, *J* 17.5, $C^{12}H_{2A}$), 2.96 (1H, d, *J* 17.5, $C^{12}H_{2B}$), 2.17-1.93 (7H, m, C^8H_2, C^4H_{2A}, C^7H_2, $C^{14}H_2$), 1.77-1.70 (4H, m, C^4H_{2B}, $C^{13}CH_3$), 1.67-1.62 (4H, m, $C^{15}H_{2A}$, $C^{10}CH_3$), 1.60 (3H, s, C^6CH_3), 1.31-1.22 (2H, m, C^3H, $C^{15}H_{2B}$), 1.12 (3H, s, C^2CH_3), 0.89 (3H, s, C^2CH_3); δ_C (100 MHz, $CDCl_3$): 135.7 (C), 134.9 (C), 133.8 (C), 127.9 (C), 126.2 (CH), 124.5 (CH), 119.4 (C), 69.2 (CH_2), 45.5 (CH), 39.6 (CH_2), 38.4 (C), 32.3 (CH_2), 28.7 (CH_2), 26.3 (CH_2), 26.2 (CH_3), 23.2 (CH_2), 21.4 (CH_3), 20.3 (CH_3), 16.6 (CH_2), 16.3 (CH_3), 13.8 (CH_3); *m/z* (ES^+) found 338.2438 ($[M+Na]^+$, $C_{21}H_{33}NONa^+$ requires 338.2454). All data agreed with that previously published.[14]

1-((*S*)-3-((5*E*,9*E*)-11-hydroxy-6,10-dimethylocta-5,9-dien-1-yl)-2,2,13-trimethylcyclohex-1-en-1-yl)acetaldehyde 143

R_f 0.56 (2:1 petrol: ethyl acetate); ν_{max}/cm^{-1} ($CHCl_3$): 3677, 3610, 3009, 2967, 2935, 2871, 2725, 1716, 1454; δ_H (400 MHz, $CDCl_3$): 9.51 (1H, t, *J* 2.3, CHO), 5.38 (1H, tq, *J* 7.0, 1.3, C^9H), 5.13 (1H, tq, *J* 7.2, 1.2, C^5H), 3.98 (2H, s, $C^{11}H_2$), 3.10 (2H, s, $C^{12}H_2$), 2.18-2.10 (3H, m, C^8H_2, C^4H_{2A}), 2.07-1.89 (4H, m, C^7H_2, $C^{14}H_2$), 1.77-1.65 (2H, m, C^4H_{2B}, $C^{15}H_{2A}$,), 1.66 (3H, s, $C^{10}CH_3$), 1.60 (3H, s, C^6CH_3), 1.56 (3H, s, $C^{13}CH_3$), 1.32-1.23 (2H, m, C^3H, $C^{15}H_{2B}$), 1.00 (3H, s, C^2CH_3), 0.84 (3H, s, C^2CH_3); δ_C (100 MHz, $CDCl_3$): 201.6 (CH), 135.6 (C), 134.9 (C), 132.6 (C), 129.1 (C), 126.2 (CH), 124.7 (CH), 69.1 (CH_2), 45.7 (CH), 44.2 (CH2), 39.6 (CH_2), 38.1 (C), 32.4

(CH_2), 28.9 (CH_2), 26.5 (CH_3), 26.3 (CH_2), 23.4 (CH_2), 21.6 (CH_3), 20.4 (CH_3), 16.2 (CH_3), 13.8 (CH_3); *m/z* (ES^+) found 341.2449 ($[M+Na]^+$, $C_{21}H_{34}O_2Na^+$ requires 341.2451).

((3*S*,5*E*,9*E*)-11-chloro-6,10-dimethylocta-5,9-dien-3-yl)-2,2,13-trimethylcyclohex-1-en-1-yl)acetonitrile 32

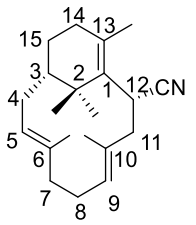


32

To a stirring solution of alcohol **31** (370 mg, 1.17 mmol) in anhydrous dichloromethane (10 mL) was added diisopropylethylamine (307 µL, 1.76 mmol). The resulting mixture was cooled down to 0 °C and methanesulfonyl chloride (136 µL, 1.76 mmol) was added dropwise. The reaction mixture was stirred overnight at room temperature. The resulting mixture was washed with water (30 mL) and extracted with dichloromethane (60 mL). The aqueous layer was extracted with dichloromethane (3 x 60 mL). The combined organic layers were washed with brine (50 mL), dried over magnesium sulfate, concentrated *in vacuo*. Purification by column chromatography eluting with 10:1 to 5:1 petrol:ethyl acetate afforded the pure chloride **32** as a colorless oil (258 mg, 66%). R_f 0.36 (15:1 petrol:ethyl acetate); ν_{max}/cm^{-1} ($CHCl_3$): 2968, 2938, 2253; δ_H (400 MHz, $CDCl_3$): 5.49 (1H, app t, *J* 6.5, C^9H), 5.11 (1H, app t, *J* 7.0, C^5H), 3.99 (2H, s, $C^{11}H_2$), 3.02 (1H, d, *J* 17.4, $C^{12}H_{2A}$), 2.95 (1H, d, *J* 17.4, $C^{12}H_{2B}$), 2.17-1.92 (7H, m, C^8H_2, C^4H_{2A}, C^7H_2, $C^{14}H_2$), 1.77-1.67 (7H, m, C^4H_{2B}, $C^{10}CH_3$, $C^{13}CH_3$), 1.66-1.59 (4H, m, $C^{15}H_{2A}$, C^6CH_3), 1.30-1.22 (2H, m, C^3H, $C^{15}H_{2B}$), 1.11 (3H, s, C^2CH_3), 0.88 (3H, s, C^2CH_3); δ_C (100 MHz, $CDCl_3$): 135.2 (C), 133.7 (C),

131.7 (C), 130.7 (CH), 127.7 (C), 124.7 (CH), 119.3 (C), 52.6 (CH_2), 45.4 (CH), 39.1 (CH_2), 38.3 (C), 32.2 (CH_2), 28.7 (CH_2), 26.6 (CH_2), 26.1 (CH_3), 23.1 (CH_2), 21.3 (CH_3), 20.2 (CH_3), 16.5 (CH_2), 16.2 (CH_3), 14.2 (CH_3); *m/z* (ES^+) found 356.2104 ($[M+Na]^+$, $C_{21}H_{32}{}^{35}ClNNa^+$ requires 356.2115). All data agreed with that previously published.[14]

(3*S*,5*E*,9*E*)-2,2,6,10,13-pentamethylbicyclo[9.3.1]pentadeca-1(13),5,9-triene-12-carbonitrile 26 [14]

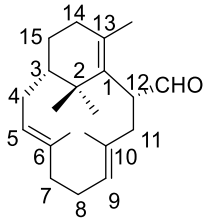


26

Freshly distilled hexamethyldisilazide (875 µL, 4.12 mmol) was diluted in anhydrous tetrahydrofuran (13.0 mL), and the resulting mixture was cooled to 0 °C before the dropwise addition of *n*-Butyllithium (1.9 M in hexanes, 2.0 mL, 3.85 mmol) at 0 °C. After 1 hour of stirring at 0 °C, the reaction was transferred into an oil bath and heated at 60 °C. Then a solution of chloride **32** (258 mg, 0.77 mmol) in anhydrous tetrahydrofuran (39 mL) was added to the mixture at the rate of 250 µL/min *via* syringe pump. After the complete addition of **32**, the reaction mixture was heated at 60 °C for further 2 hours. The reaction was cooled to room temperature and quenched with methanol (4 mL). The volatile materials were removed by concentrating *in vacuo*. The residue was dissolved in diethyl ether (50 mL). The resulting white precipitate was removed by filtration through a pad of celite. The filtrate was concentrated *in vacuo* and purified by column chromatography eluting with 30:1 petrol:ethyl acetate to yield cyanoverticillene **26** (128 mg, 56%) as a white solid. R_f 0.62 (20:1 petrol: ethyl

acetate); mp 147-149 °C; (lit[14] mp 149-150 °C) ν_{max}/cm^{-1} ($CHCl_3$): 3011, 2919, 2231, 1441; δ_H (400 MHz, $CDCl_3$): 5.08 (1H, app d, *J* 11.4, C^5H), 4.81 (1H, app d, *J* 11.6, C^9H), 3.42 (1H, dd, *J* 12.8, 3.8, $C^{12}H$), 2.89 (1H, app t, *J* 12.8, $C^{11}H_{2A}$), 2.62 (1H, m, C^4H_{2A}), 2.39-2.26 (2H, m, C^8H_{2A}, $C^{11}H_{2B}$), 2.22-2.03 (3H, m, C^7H_{2A}, $C^{14}H_{2A}$, $C^{15}H_{2A}$), 2.01-1.82 (7H, m, C^7H_{2B}, C^4H_{2B}, C^8H_{2B}, $C^{15}H_{2B}$, $C^{13}CH_3$), 1.66-1.54 (2H, m, C^3H, $C^{14}H_{2B}$), 1.53 (3H, s, $C^{10}CH_3$), 1.48 (3H, s, C^6CH_3) 1.10 (3H, s, C^2CH_3), 0.84 (3H, s, C^2CH_3) ; δ_C (100 MHz, $CDCl_3$): 133.0 (C), 132.2 (CH), 132.1 (C), 131.4 (C), 128.8 (C), 126.3 (CH), 123.0 (C), 42.7 (CH), 42.2 (CH_2), 40.0 (CH_2), 37.8 (C), 33.9 (CH_2), 32.7 (CH_3), 32.3 (CH_2), 27.4 (CH), 26.8 (CH_2), 26.1 (CH_2), 24.3 (CH_3), 22.1 (CH_3), 16.6 (CH_3), 15.4 (CH_3); *m/z* (ES^+) found 320.2344 ($[M+Na]^+$, $C_{21}H_{31}NNa^+$ requires 320.2349). All data agreed with that previously published.[14]

(12*R*,5*E*,9*E*,3S)-2,2,6,10,13-pentamethylbicyclo[9.3.1]pentadeca-1(13),5,9-triene-12-carbaldehyde 33 [14]

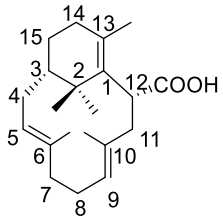


33

To a stirring solution of cyanoverticillene **26** (128 mg, 0.61 mmol) in anhydrous toluene (5.0 mL), was added diisobutylaluminium hydride (1.5 M in toluene, 610 µL, 0.91 mmol) dropwise at -78 °C. The resulting mixture was stirred for 2 hours at -78 °C before being quenched slowly with an aqueous saturated solution of ammonium chloride (5 mL) at -78 °C, followed by the addition of a 1 M aqueous solution of hydrogen chloride and then warmed gradually to room temperature. The reaction was poured onto water (20 mL) and stirred for 20 min. The reaction was extracted with

diethyl ether (30 mL) and the layers were separated. The aqueous layer was re-extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed successively with water (3 x 20 mL) and brine (15 mL), dried over magnesium sulfate, and concentrated *in vacuo*. Purification by column chromatography eluting with 40:1 petrol:ethyl acetate afforded the pure aldehyde **33** as a white solid (102 mg, 79%). R_f 0.35 (40:1 petrol: ethyl acetate); mp 104-106 °C; (lit[14] mp 108-110 °C); ν_{max}/cm^{-1} ($CHCl_3$): 3156, 2924, 1710, 1463, 1384; δ_H (400 MHz, $CDCl_3$): 9.60 (1H, s, CHO), 5.12 (1H, app d, *J* 11.6, C^5H), 4.76 (1H, app d, *J* 11.4, C^9H), 3.18 (1H, dd, *J* 11.9, 4.3, $C^{12}H$), 2.72-2.62 (1H, m, C^4H_{2A}), 2.54 (1H, app t, *J* 11.9, $C^{11}H_{2A}$), 2.47-2.04 (5H, m, C^8H_{2A}, $C^{11}H_{2B}$, C^7H_{2A}, $C^{14}H_{2A}$,$C^{15}H_{2A}$), 1.99-1.83 (4H, m, C^7H_{2B}, C^4H_{2B}, C^8H_{2B}, $C^{15}H_{2B}$), 1.72-1.49 (11H, m, C^3H, $C^{14}H_{2B}$ $C^{10}CH_3$ C^6CH_3, $C^{13}CH_3$), 1.08 (3H, s, C^2CH_3), 0.90 (3H, s, C^2CH_3) ; δ_C (100 MHz, $CDCl_3$): 203.4 (C), 132.6 (C), 132.2 (C), 131.9 (C), 131.0 (C), 130.0 (CH), 126.4 (CH), 52.2 (CH), 42.9 (CH), 40.2 (CH_2), 38.6 (CH_2), 37.5 (C), 34.0 (CH_2), 32.4 (CH_3), 32.3 (CH_2), 27.2 (CH_2), 26.0 (CH_2), 24.5 (CH_3), 21.6 (CH_3), 17.0 (CH_3), 15.5 (CH_3); *m/z* (ES^+) found 323.2341 ($[M+Na]^+$, $C_{21}H_{32}ONa^+$ requires 323.2345). All data agreed with that previously published.[14]

(12*R*,5*E*,9*E*,2*S*)-2,2,6,10,13-pentamethylbicyclo[9.3.1]pentadeca-1(13),5,9-triene-12-carboxylic acid 34 [15]

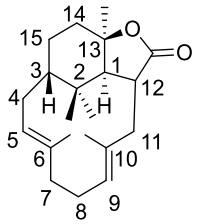


34

Aldehyde **33** (20 mg, 0.07 mmol) was dissolved first in 2-methyl-2-butene (500 µL), then *tert*-butyl alcohol (300 µL). A solution of sodium dihydrogenophosphate (10 mg,

0.07 mmol) and sodium chlorite (7.0 mg, 0.08 mmol) in water (200 µL) was then slowly added at 0 °C to the mixture. The reaction mixture was stirred at room temperature for 8 hours. Volatiles material were removed under vacuum, and then the residue was diluted with diethyl ether (10 mL) and the organic layer was separated. The aqueous layer was acidified to pH 3 by addition of a 1 M aqueous solution of hydrogen chloride and re-extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over magnesium sulfate, and concentrated *in vacuo.* Purification by column chromatography eluting with 15:1 petrol:ethyl acetate yielded the pure carboxylic acid **34** as a white solid (15 mg, 71%) used in the next step without further purification. R_f 0.36 (5:1 petrol: ethyl acetate); mp 138-140 °C; ν_{max}/cm^{-1} ($CHCl_3$): 2978, 2963, 2921, 2880, 2360, 2341, 1734, 1698; δ_H (400 MHz, $CDCl_3$): 5.14 (1H, app d, *J* 11.3, C^5H), 4.79 (1H, app d, *J* 11.2, C^9H), 3.36 (1H, dd, *J* 12.6, 3.9, $C^{12}H$), 2.75 (1H, app t, *J* 12.6, $C^{11}H_{2A}$), 2.64 (1H, m, C^4H_{2A}), 2.47 (1H, bd, *J* 12.6, $C^{11}H_{2B}$), 2.36-2.03 (4H, m, C^8H_{2A}, C^7H_{2A}, $C^{14}H_{2A}$, $C^{15}H_{2A}$), 1.97-1.82 (4H, m, C^7H_{2B}, C^4H_{2B}, C^8H_{2B}, $C^{15}H_{2B}$), 1.71-1.61 (5H, m, C^3H, $C^{14}H_{2B}$, $C^{13}CH_3$), 1.54 (3H, s, $C^{10}CH_3$), 1.50 (3H, s, C^6CH_3), 1.10 (3H, s, C^2CH_3), 0.87 (3H, s, C^2CH_3) ; δ_C (100 MHz, $CDCl_3$): 181.2 (C), 133.5 (C), 131.9 (C), 131.4 (C), 130.9 (C), 130.6 (CH), 126.7 (CH), 43.2 (2 x CH), 41.3 (CH_2), 40.1 (CH_2), 37.8 (C), 34.1 (CH_2), 33.3 (CH_3), 32.3 (CH_2), 27.2 (CH_2), 26.2 (CH_2), 24.9 (CH_3), 22.3 (CH_3), 17.0(CH_3), 16.0 (CH_3); *m/z* (ES^+) found 339.2305 ($[M+Na]^+$, $C_{21}H_{32}O_2Na^+$ requires 339.2295). All data agreed with that previously published.[15]

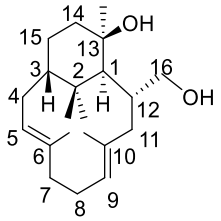
Synthesis of lactone 35



35

Carboxylic acid **34** (29 mg, 0.09 mmol) was dissolved in trifluoroacetic acid (1.3 mL). The mixture was allowed to reflux for 30 minutes. The reaction mixture was then cooled to room temperature, and extracted with diethyl ether (30 mL). The organic layer was successively washed with an aqueous saturated solution of sodium bicarbonate (10 mL), then water (2 x 10 mL), then brine (10 mL). The organic extract was dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography eluting with 10:1 petrol:ethyl acetate afforded the pure lactone **35** as a white solid (13 mg, 45%). R_f 0.43 (4:1 petrol:ethyl acetate); mp 166-168 °C; (lit[15] mp 169-170 °C); ν_{max}/cm^{-1} ($CHCl_3$): 3010, 2958, 2936, 2875, 1748, 1702, 1458; δ_H (400 MHz, $CDCl_3$): 5.32 (1H, d, *J* 12.2, C^5H), 4.96 (1H, d, *J* 10.5, C^9H), 2.60 (1H, dd, *J* 12.6, 5.2, C^4H_{2A}), 2.55 (s, 1H, C^1H), 2.51-1.95 (9H, m, $C^{12}H$, $C^{11}H_{2B}$, C^8H_{2A}, C^8H_{2B}, C^4H_{2B}, C^7H_{2A}, C^7H_{2B}, $C^{14}H_{2A}$,$C^{15}H_{2A}$), 1.82-1.68 (3H, m, $C^{14}H_{2B}$,$C^{15}H_{2B}$, C^3H), 1.58 (3H, s), 1.52 (6H, br s, 2 x CH_3), 1.45-1.40 (1H, m, $C^{15}H_{2B}$), 0.93 (3H, s, C^2CH_3), 0.62 (3H, s, C^2CH_3) ; δ_C (100 MHz, $CDCl_3$): 180.4 (C), 134.4 (C), 132.5 (CH), 131.9 (C), 123.5 (CH), 86.1 (C), 46.9 (CH), 41.9 (CH_2), 41.5 (CH_2), 40.3 (CH), 40.2 (CH), 34.5 (C), 32.8 (CH_2), 31.6 (CH_2), 29.4 (CH_3), 28.4 (CH_3), 26.6 (CH_2), 25.8 (CH_3), 23.4 (CH_2), 16.4 (CH_3), 16.1 (CH_3); *m/z* (ES^+) found 339.2303 ($[M+Na]^+$, $C_{21}H_{32}O_2Na^+$ requires 339.2295). All data agreed with that previously published.[15]

(1*S*,3*S*,5*E*,9*E*,12*R*,13*R*)-12-(hydroxymethyl)2,2,6,10,13-pentamethylbicyclo[9.3.1]pentadeca-5,9-dien-12-ol 36

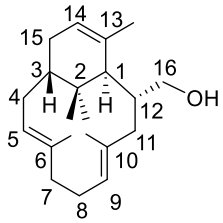


36

Lactone **35** (22 mg, 0.07 mmol) was dissolved in anhydrous tetrahydrofuran (0.5 mL), then lithium aluminium hydride (15 mg, 0.35 mmol) was added at room temperature. The resulting mixture was heated at reflux for 1 hour. The mixture was then cooled to room temperature before being quenched slowly with ethyl acetate (15 mL). The organic layer was washed with a 2 M aqueous solution of sodium hydroxide (5 mL), then water (3 x 10 mL) then brine (10 mL). The organic extract was then dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography eluting from 15:1 to 1:1 pentane:diethyl ether provided the pure diol **36** as a white solid (8 mg, 36%). R_f 0.34 (1:1 pentane:diethyl ether); mp 142-144 °C; (lit[15] mp 141-143 °C); ν_{max}/cm^{-1} ($CHCl_3$): 3601, 3445, 3002, 2956, 2918, 1453 ; δ_H (400 MHz, C_6D_6): 5.44 (1H, d, *J* 12.2, C^5H), 4.84 (1H, d, *J* 11.3, C^9H), 4.01 (1H, dd, *J* 11.3, 8.0, $C^{16}H_{2A}$), 3.79 (1H, dd, *J* 11.4, 5.2, $C^{16}H_{2B}$), 2.67 (1H, m, C^4H_{2A}), 2.42 -1.78 (11H, m, $C^{12}H$, $C^{11}H_{2A}$, $C^{11}H_{2B}$,C^4H_{2B}, C^7H_{2A}, C^7H_{2B}, C^8H_{2A}, C^8H_{2B}, C^1H, $C^{14}H_{2A}$, $C^{15}H_{2A}$), 1.49-1.41 (1H, m, C^3H), 1.45 (3H, s, CH_3), 1.44 (6H, s, 2 x CH_3), 1.35-1.25 (2H, m, $C^{14}H_{2B}$, $C^{15}H_{2B}$), 1.29 (3H, s, CH_3), 0.74 (3H, s, CH_3) ; δ_C (100 MHz, C_6D_6): 133.4 (C), 132.9 (C), 130.1 (CH), 129.1 (CH), 74.3 (C), 66.4 (CH_2), 46.0 (CH), 44.7 (CH and CH_2), 42.1 (CH_2), 41.5 (CH_2), 37.5 (CH), 37.2 (C), 34.5 (CH_2), 33.3 (CH_3), 28.9

(CH_3), 28.7 (CH_3), 27.2 (CH_2), 26.7 (CH_2), 16.5 (CH_3), 15.2 (CH_3); *m/z* (ES^+) found 343.2615 ($[M+Na]^+$, $C_{21}H_{36}O_2Na^+$ requires 343.2608). All data agreed with that previously published.[15]

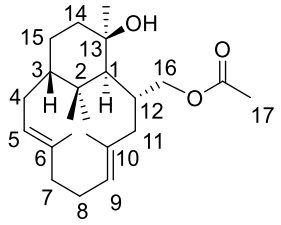
((1*R*,3*R*,5*E*,9*E*,12*R*)-2,2,6,10,13-pentamethylbicyclo[9.3.1]pentadeca-5,9,13-trien-12-yl)methanol 146



146

An NMR sample of diol **36** (15 mg) was analysed in $CDCl_3$ for 2 days. The sample showed that diol **36** in $CDCl_3$ started to decompose. Purification by column chromatography eluting with 1:1 pentane:EtOAc afforded the pure alcohol **146** as a white solid (1 mg) and diol **36** as a white solid (9 mg, 60 %). R_f 0.43 (1:1 pentane:EtOAc); δ_H (500 MHz, C_6D_6): 5.49 (1H, br s, $C^{14}H$), 5.41 (1H, br d, *J* 8.0, C^5H), 4.96 (1H, br d, *J* 8.0 C^9H), 3.71 (1H, dd, *J* 8.0, $C^{16}H_{2A}$), 3.35 (1H, app t, *J* 8.0, $C^{16}H_{2B}$), 3.23 (1H, br s, C^1H), 2.64 (1H, m, C^4H_{2A}), 2.51-2.40 (2H, m), 2.41-2.34 (1H, m, $C^{11}H_{2A}$), 2.16 (1H, t, *J* 8.0), 2.10 - 1.75 (6H, m), 1.70 (3H, s, CH_3), 1.50 (3H, s, CH_3), 1.37-1.30 (1H, m, C^3H) 1.04 (3H, s, CH_3), 0.88 (3H, s, C^2CH_3), 0.40 (3H, s, C^2CH_3) ; δ_C (125 MHz, C_6D_6): 134.5 (C), 133.6 (C), 132.6 (C), 130.8 (CH), 124.7 (CH), 124.1 (CH), 66.5 (CH_2), 45.4 (CH_2), 43.8 (CH), 41.2 (CH), 41.0 (CH_2), 37.9 (CH), 36.3 (C), 34.1 (CH_2), 30.8 (CH_2), 27.7 (CH_3), 26.3 (CH_2), 25.3 (CH_3), 25.0 (CH_3), 15.7(CH_3), 14.9 (CH_3); *m/z* (ES^+) found 303.2662 (M+H, $C_{21}H_{35}O$ requires 302.2684).

((1*S*,3*S*,5*E*,9*E*,12*R*,13*S*)-13-hydroxy-2,2,6,10,13-pentamethylbicyclo[9.3.1]pentadeca-5,9-dien-12-yl)methyl acetate 147

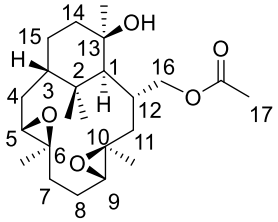


147

To a solution of diol **36** (43mg, 0.13 mmol) in anhydrous dichloromethane (1.1 mL) was added pyridine (75 µL, 0.91 mmol) and acetic anhydride (62 µL, 0.67 mmol). The resulting mixture was stirred at room temperature for 14 hours. An excess methanol (1 mL) was added to remove an excess of acetic anhydride. The mixture was then diluted with water (5 mL) and extracted with diethyl ether (25 mL). The combined ether solutions were washed with an aqueous saturated solution of copper sulfate (7 mL), then water (3 x 10 mL) and brine (10 mL).The organic extract was then dried over magnesium sulfate and concentrated *in vacuo* to afford the protected alcohol **147** as a white solid (42 mg, 86%). R_f 0.19 (10:1 pentane:ethyl acetate); mp 154-156 °C; (lit[15] mp 155-157 °C); ν_{max}/cm^{-1} ($CHCl_3$): 3603, 2958, 2917, 2871, 1725; δ_H (400 MHz, $CDCl_3$): 5.45 (1H, d, *J* 12.4, C^5H), 4.87 (1H, d, *J* 11.3, C^9H), 4.77 (1H, dd, *J* 11.4, 2.9, $C^{16}H_{2A}$), 4.20 (1H, app t, *J* 11.4, $C^{16}H_{2A}$), 2.71 (1H, dddd, *J* 14.5, 12.8, 6.4, 1.3 C^4H_{2A}), 2.45-2.16 (5H, m), 2.12-1.93 (6H, m), 2.07 (3H, s), 1.83 (1H, br d, *J* 14.5, C^4H_{2B}), 1.54 (3H, s), 1.51 (3H, s), 1.49-1.35 (3H, m), 1.34 (3H, s), 1.18 (3H, s), 0.78 (3H, s) ; δ_C (100 MHz, $CDCl_3$): 171.5 (C), 133.4 (C), 133.2 (C), 130.4 (CH), 127.6 (CH), 74.3 (C), 68.3 (CH_2), 45.2 (CH), 43.9 (CH), 43.1 (CH_2), 42.2 (CH_2), 41.4 (CH_2), 37.6 (C), 34.4 (CH), 34.2 (CH_2), 33.7 (CH_3), 28.9 (CH_3), 27.7 (CH_3), 26.7 (CH_2), 26.5 (CH_2),

21.4 (CH_3), 16.2 (CH_3), 15.3 (CH_3); *m/z* (ES^+) found 385.2715 ($[M+Na]^+$, $C_{23}H_{38}O_3Na^+$ requires 385.2713). All data agreed with that previously published.[15]

Synthesis of bisepoxide 129



129

Method A: using *m*-CPBA

To a stirred solution of diene **147** (18 mg, 0.05 mmol) in dichloromethane (1.8 mL) at 0 °C was added *m*-chloroperoxybenzoic acid 70% (49 mg, 0.2 mmol) in one portion. The resulting mixture was stirred for 2 hours at 0 °C in an ice bath.

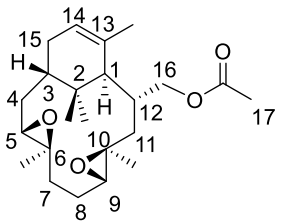
The reaction was quenched with a saturated aqueous solution of sodium thiosulfate (2 mL) and extracted with dichloromethane (20 mL). The organic layer was then washed with a 1 M aqueous solution of sodium hydroxide (5 mL). The aqueous layer was re-extracted with dichloromethane (2 x 10 mL). The combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography eluting from pentane to 1:1 pentane:ethyl acetate afforded the pure bisepoxide **129** as a white solid (12 mg, 61%). R_f 0.63 (1:1 pentane: ethyl acetate); mp 160-162 °C; ν_{max}/cm^{-1} ($CHCl_3$): 3602, 3009, 2961, 2929, 1727, 1458, 1388, 1370 ; δ_H (400 MHz, $CDCl_3$): 4.77 (1H, dd, *J* 11.6, 3.1 $C^{16}H_{2A}$), 4.11 (1H, app t, *J* 11.6, $C^{16}H_{2B}$), 3.16 (1H, d, *J* 9.8, C^9H), 2.68 (1H, d, *J* 8.5, C^5H), 2.40-2.19 (4H, m), 2.08 (3H, s, $C^{17}H_3$), 2.03-1.79 (4H, m), 1.69-1.36 (6H, m), 1.32 (3H, s, CH_3), 1.31 (3H, s, CH_3), 1.28 (3H, s, CH_3), 1.27 (3H, s, CH_3), 1.27-1.22 (1H, m, CH_{2B}), 1.02 (3H, s, CH_3) ; δ_C

(100 MHz, $CDCl_3$): 171.4 (C), 73.4 (C), 67.7 (C), 66.3 (CH), 64.0 (CH), 63.1 (C), 61.2 (CH_2), 48.2 (CH), 44.3 (CH), 42.6 (CH_2), 42.2 (CH_2), 38.2 (CH_2), 37.9 (C), 35.0 (CH), 34.5 (CH_2), 34.2 (CH_3), 31.1 (CH_3), 27.1 (CH_3), 26.1 (CH_2), 24.0 (CH_2), 21.3 (CH_3), 17.2 (CH_3), 15.8 (CH_3); *m/z* (ES^+) found 417.2620 ($[M+Na]^+$, $C_{23}H_{38}O_5Na^+$ requires 417.2611).

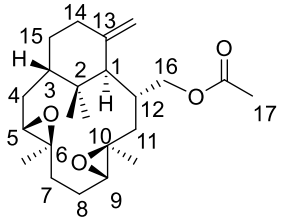
Method B: using DMDO

To a cooled solution of diene **147** (4 mg, 0.011 mmol) in anhydrous CH_2Cl_2 (0.5 mL) was added DMDO previously titrated at 0.035 M (800 µL, 0.028 mmol) at 0 °C. The reaction was stirred for 1 hour at the same temperature. The resulting mixture was concentrated *in vacuo*. Purification by column chromatography eluting from pentane to 1:1 pentane:EtOAc afforded the pure bisepoxide **129** as a white solid (3 mg, 69%).

Dehydration



160



161

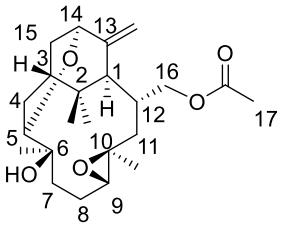
To a stirred solution of alcohol **129** (58 mg, 0.15 mmol) in anhydrous benzene (2.9 mL) was added Burgess reagent (105 mg, 0.44 mmol) at room temperature under inert atmosphere. Then the reaction mixture was stirred for 1 hour at 60 °C. A saturated aqueous solution of sodium bicarbonate (10 mL) was added to the reaction mixture and it was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine (20 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography eluting from 9:1 petrol: ethyl acetate to

5:1 petrol:ethyl acetate afforded an mixture of trisubstituted alkene **160** and exocyclic double bond compound **161** in a 5:1 ratio (**160**:**161**) as a white solid (42 mg, 76%).

Data for compound **160** (major compound) : R_f 0.32 (5:1 petrol: ethyl acetate); ν_{max}/cm^{-1} ($CHCl_3$): 3011, 2968, 2926, 2883, 1731; δ_H (400 MHz, $CDCl_3$): 5.64 (1H, br s, $C^{14}H$), 4.18 (1H, dd, *J* 11.2, 3.0, $C^{16}H_{2A}$), 3.96 (1H, dd, *J* 11.2, 7.6, $C^{16}H_{2B}$), 3.01 (1H, d, *J* 9.4, $C^{9}H$), 2.72 (1H, d, *J* 9.6, $C^{5}H$), 2.55 (1H, m, CH_{2A}), 2.39 (1H, dd, *J* 13.9, 4.9, CH_{2A}), 2.33-2.19 (3H, m, $C^{1}H$, $C^{12}H$, CH_{2A}), 2.08 (3H, s, $C^{17}H_3$), 2.13-2.04 (1H, m, CH_{2A}), 2.02-1.83 (2H, m, $CH_{2B,}$ CH_{2B}), 1.76 (3H, s, CH_3), 1.75-1.68 (1H, m, CH_{2B}), 1.63-1.56 (1H, m, $C^{3}H$), 1.55-1.40 (2H, m, $CH_{2B,}$ CH_{2B}), 1.37 (3H, s, CH_3), 1.29 (3H, s, CH_3), 1.26-1.19 (1H, m, CH_{2B}), 1.10 (3H, s, $C^{2}CH_3$), 1.00 (3H, s, $C^{2}CH_3$) ; δ_C (100 MHz, $CDCl_3$): 171.3 (C), 132.4 (C), 127.6 (CH), 68.2 (CH_2), 66.6 (CH), 62.3 (CH), 62.2 (C), 61.2 (C), 44.4 (CH_2), 43.4 (CH), 43.0 (CH), 36.9 (C), 36.7 (CH_2), 34.6 (CH), 33.6 (CH_2), 29.9 (CH_2), 28.9 (CH_3), 25.4 (CH_3), 25.2 (CH_3), 24.1 (CH_2), 21.2 (CH_3), 16.7 (2 x CH_3); *m/z* (ES^+) found 399.2500 ($[M+Na]^+$, $C_{23}H_{36}O_4Na^+$ requires 399.2506).

Data for compound **161** (minor compound), when it can be clearly identify: R_f 0.32 (5:1 petrol: ethyl acetate); δ_H (400 MHz, $CDCl_3$): 4.98 (1H, br s, $C^{13}CH_{2A}$), 4.51 (1H, dd, *J* 11.2, 3.0, $C^{16}H_{2A}$), 4.48 (1H, br s, $C^{13}CH_{2B}$), 4.09 (2H, m, $C^{16}H_{2A}$), 3.25 (1H, d, *J* 9.4, $C^{9}H$), 2.09 (3H, s, $C^{17}H_3$), 1.35 (3H, s, CH_3), 1.31 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$): 171.3 (C), 145.3 (C), 111.0 (CH_2), 66.7 (CH_2), 65.1 (CH), 64.0 (CH), 62.8 (C), 61.4 (C), 48.9 (CH), 46.1 (CH), 41.1 (CH_2), 38.7 (CH_2), 37.5 (CH_2), 36.9 (C), 35.6 (CH), 32.7 (CH_3), 27.8 (CH_3), 27.6 (CH_2), 26.6 (CH_3), 24.3 (CH_2), 17.1 (CH_3), 16.2 (CH_3); *m/z* (ES^+) found 399.2500 ($[M+Na]^+$, $C_{23}H_{36}O_4Na^+$ requires 399.2506).

Allylic oxidation of 161



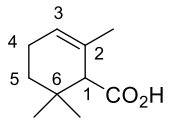
163

To a 2:1 mixture of trisubstituted alkene **160**: exocyclic alkene **161** (5 mg, 13 µmol) dissolved in dichloromethane (2 mL) was added selenium dioxide (59 mg, 531 µmol), salicylic acid (26 mg, 186 µmol) then *tert*-butylhydroperoxide (70% in water) (72 µL, 559 µmol). The reaction mixture was stirred at 50 °C for 3 hours in a sealed tube. Then it was quenched with a 10% aqueous solution of thiosulfate (5 mL) at room temperature. After stirring for 5 minutes, the mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were washed with a saturated aqueous solution of sodium bicarbonate (2 x 10 mL) and brine (15 mL), dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography eluting from 5:1 petrol: ethyl acetate to 1:2 petrol:ethyl acetate afforded compound **163** as a solid (0.5 mg, 12%) and trisubstituted alkene **160** (1 mg, 25%). R_f 0.15 (2:1 pentane: ethyl acetate); δ_H (500 MHz, $CDCl_3$): 5.64 (1H, br s, $C^{14}H$), 4.18 (1H, dd, *J* 11.2, 3.0, $C^{16}H_{2A}$), 3.96 (1H, dd, *J* 11.2, 7.6, $C^{16}H_{2B}$), 3.01 (1H, d, *J* 9.4, $C^{9}H$), 2.72 (1H, d, *J* 9.6, $C^{5}H$), 2.55 (1H, m, CH_{2A}), 2.39 (1H, dd, *J* 13.9, 4.9, CH_{2A}), 2.33-2.19 (3H, m, $C^{1}H$, $C^{12}H$, CH_{2A}), 2.08 (3H, s, $C^{17}H_3$), 2.13-2.04 (1H, m, CH_{2A}), 2.02-1.83 (2H, m, $CH_{2B,}$ CH_{2B}), 1.76 (3H, s, CH_3), 1.75-1.68 (1H, m, CH_{2B}), 1.63-1.56 (1H, m, $C^{3}H$), 1.55-1.40 (2H, m, $CH_{2B,}$ CH_{2B}), 1.37 (3H, s, CH_3), 1.29 (3H, s, CH_3), 1.26-1.19 (1H, m, CH_{2B}), 1.10 (3H, s, $C^{2}CH_3$), 1.00 (3H, s, $C^{2}CH_3$) ; δ_C (125 MHz, $CDCl_3$): 171.2 (C), 149.0 (C), 113.1 (CH_2), 72.6 (CH), 66.5 (CH_2), 64.1 (CH), 63.3 (CH), 62.6 (C), 61.4 (C), 44.7 (CH), 44.3 (CH), 41.0 (CH_2), 38.0 (C), 37.3 (CH_2), 35.2 (CH), 33.9 (CH_2), 32.2

(CH_2), 28.0 (CH_3), 27.1 (CH_3), 24.0 (CH_2), 21.1 (CH_3), 17.3 (CH_3), 16.4 (CH_3); *m/z* (ES^+) found 415.2448 ($[M+Na]^+$, $C_{23}H_{36}O_5Na^+$ requires 415.2455).

General procedures for dehydration model system

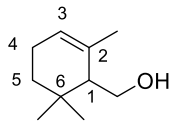
2,6,6-trimethylcyclohex-2-ene-1-carboxylic acid 152 [52]



152

To a solution of geranoic acid **151** (16 g, 0.10 mmol) in toluene (30 mL) was added a 85% solution of phosphoric acid (667 µL, 0.01 mmol). The reaction mixture was heated at 100 °C for 2 hours. Then the reaction was extracted with diethyl ether and washed with water. The aqueous layer was re-extracted with diethyl ether and the combined organic layers were washed with brine, then dried over magnesium sulfate and concentrated *in vacuo*. The crude mixture was recrystallised in hot hexane to afford **152** as a white solid (9.18 g, 57%). R_f 0.56 (4:1 petrol: diethyl ether); mp 71-73 °C; (lit[52] mp 70-72 °C); ν_{max}/cm^{-1} ($CHCl_3$): 3043, 2963, 2929, 2874, 2715, 1735, 1701; δ_H (400 MHz, $CDCl_3$): 5.61 (1H, br s, C^3H), 2.59 (1H, s, C^1H), 2.15-1.97 (2H, m, C^4H_2), 1.81 (1H, ddd, *J* 13.1, 9.9, 6.7, C^5H_{2A}), 1.70 (3H, s, C^2CH_3), 1.23-1.14 (1H, m, C^5H_{2B}) 1.01 (3H, s, C^6CH_3), 0.98 (3H, s, C^6CH_3); δ_C (100 MHz, $CDCl_3$): 180.8 (C), 129.3 (C), 124.3 (CH), 56.8 (CH), 31.8 (C), 30.9 (CH_2), 27.7 (CH_3), 27.3 (CH_3), 23.0 (CH_3), 22.8 (CH_2); *m/z* (ES^-) found 167.1072 ([M-H], $C_{10}H_{15}O_2$ requires 167.1078). All data agreed with that previously published.[52]

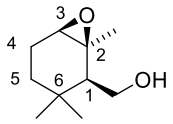
(2,6,6-trimethylcyclohex-2-en-1-yl)methanol 153 [52]



153

Cyclogeranoic acid **152** (4.0 g, 23.8 mmol) was added portionwise to a suspension of lithium aluminium hydride (2.71 g, 71.4 mmol) in anhydrous diethyl ether (250 mL) at 0 °C. The reaction mixture was heated at reflux for 14 hours and then cooled at room temperature. The reaction mixture was quenched at 0 °C by slow addition of water (2.70 mL), then an aqueous solution of 20% in wt of sodium hydroxide (2.70 mL), and water (6.8 mL). The mixture was stirred for 1 hour at room temperature. The grey precipitate formed was filtered under vacuum and washed with diethyl ether (200 mL). The filtrate was concentrated *in vacuo* to provide the desire product **153** as a colorless oil (3.49 g, 95%) without further purification. R_f 0.56 (4:1 petrol: diethyl ether); ν_{max}/cm^{-1} ($CHCl_3$): 3626, 3565, 3009, 2958, 2733; δ_H (400 MHz, $CDCl_3$): 5.59 (1H, br s, C^3H), 3.73 (1H, d, *J* 3.2, C^1CH_2), 2.03-1.95 (2H, m, C^4H_2), 1.74 (3H, s, C^2CH_3), 1.62 (2H, m, C^5H_{2A} ,C^1H), 1.22-1.14 (2H, m, OH, C^5H_{2B}) 1.02 (3H, s, C^6CH_3), 0.88 (3H, s, C^6CH_3); δ_C (100 MHz, $CDCl_3$): 132.0 (C), 124.7 (CH), 61.6 (CH_2), 52.2 (CH), 32.6 (CH_2), 31.9 (C), 27.9 (CH_3), 27.8 (CH_3), 23.1 (CH_2), 22.9 (CH_3); *m/z* (ES^+) found 177.1253 ($[M+Na]^+$, $C_{10}H_{18}O_2Na^+$ requires 177.1250). All data agreed with that previously published.[52]

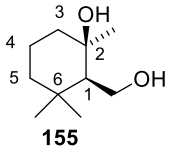
((1*R*, 2*S*, 3*R*)-2,6,6-trimethyl-7-oxabicyclo[4.1.0]heptan-1-yl)methanol 154 [53]



154

To a solution of alcohol **153** (4.30 g, 27.9 mmol) in anhydrous dichloromethane (110 mL) at 0 °C was added *m*-chloroperoxybenzoic acid 70% (8.93 g, 36.3 mmol) in two portions. The resulting mixture was stirred for 18 hours at room temperature. The reaction was quenched with saturated aqueous solution of sodium thiosulfate (50 mL) and extracted with dichloromethane (100 mL). The organic layer was then washed with a saturated aqueous solution of sodium bicarbonate (70 mL). The aqueous layer was re-extracted with dichloromethane (2 x 100 mL). The combined organic extracts were dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography eluting from 5:1 to 1:1 petrol: diethyl ether afforded the pure epoxide **154** as a colorless oil (4.54 g, 96%). R_f 0.63 (1:1 pentane:ethyl acetate); ν_{max}/cm^{-1} ($CHCl_3$): 3672, 3616, 3508, 3054, 3006, 2962, 2873; δ_H (400 MHz, $CDCl_3$): 3.93 (1H, dd, *J* 11.5, 3.8, C^1CH_{2A}), 3.77 (1H, dd, *J* 11.5, 6.1, C^1CH_{2B}), 2.98 (1H, br s, C^3H), 2.72 (1H, br s, OH), 1.94 (1H, ddt, *J* 15.5, 5.9, 1.6, C^4H_{2A}), 1.88-1.78 (1H, m, C^4H_{2B}), 1.58-1.49 (1H, m, C^5H_{2A}), 1.46-1.41 (1H, m, C^1H), 1.37 (3H, s, C^2CH_3), 0.92 (3H, s, C^6CH_3), 0.92-0.90 (1H, m, C^5H_{2B}), 0.86 ((3H, s, C^6CH_3); δ_C (100 MHz, $CDCl_3$): 62.5 (CH_2), 60.7 (C), 59.8 (CH), 47.6 (CH), 30.7 (C), 28.8 (CH_2), 28.4 (CH_3), 27.1 (CH_3), 25.6 (CH_3), 21.9 (CH_2); *m/z* (ES^+) found 193.1189 ($[M+Na]^+$, $C_{10}H_{18}O_2Na^+$ requires 193.1199). All data agreed with that previously published.[53]

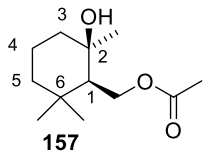
(1*R*, 2*R*)-1-(hydroxymethyl)-2,6,6-trimethylcyclohexan-2-ol 155 [87]



155

To a stirred solution of epoxide **154** (2.00 g, 11.8 mmol) in anhydrous diethyl ether (250 mL) was added portionwise lithium aluminium hydride (3.53 g, 92.9 mmol). The reaction mixture was heated at reflux for 6 hours and then cooled at room temperature. The reaction mixture was quenched at 0 °C by slow addition of water (3.50 mL), then an aqueous solution of 20% in wt of sodium hydroxide (3.50 mL), and water (10.5 mL). The mixture was stirred for 1 hour at room temperature. The grey precipitate formed was filtered under vacuum and washed with diethyl ether (200 mL). The filtrate was concentrated *in vacuo* to provide the desire product **155** as a colorless oil (1.93 g, 96%) without further purification. R_f 0.56 (4:1 petrol: diethyl ether); ν_{max}/cm^{-1} ($CHCl_3$): 3629, 3486, 2970, 2931, 2930, 2857; δ_H (400 MHz, $CDCl_3$): 4.13 (1H, dd, *J* 11.5, 4.0, C^1CH_{2A}), 4.05 (1H, dd, *J* 11.5, 1.7, C^1CH_{2B}), 3.42 (2H, br s, 2 OH), 1.92-1.79 (1H, m, C^3H_{2A}), 1.62 (1H, m, C^4H_{2A}), 1.41-1.28 (3H, m, C^3H_{2B}, C^4H_{2B}, C^5H_{2A}), 1.33 (3H, s, C^2CH_3), 1.22-1.16 (1H, m, C^5H_{2B}), 1.19 (3H, s, C^6CH_3), 0.98 (1H, dd, *J* 4.0, 1.7, C^1H), 0.94 (3H, s, C^6CH_3); δ_C (100 MHz, $CDCl_3$): 74.0 (C), 60.3 (CH_2), 52.8 (CH), 42.6 (CH_2), 41.6 (CH_2), 33.9 (C), 32.6 (CH_3), 30.7 (CH_3), 23.5 (CH_3), 18.3 (CH_2); *m/z* (ES^+) found 195.1346 ($[M+Na]^+$, $C_{10}H_{20}O_2Na^+$ requires 195.1356). All data agreed with that previously published.[87]

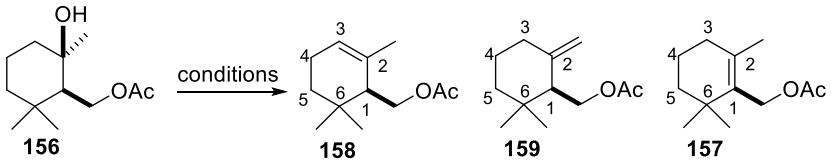
((1*R*,2*R*)-2-hydroxy-2,6,6trimethylcyclohexyl)methyl acetate 156 [88]



157

To a suspension of diol **155** (1.84 g, 10.8 mmol) in anhydrous pyridine (5 mL) was added acetic anhydride (4.15 mL, 35.7 mmol) at 0 °C under inert atmosphere. The suspension was stirred at room temperature for 16 hours. the reaction mixture was extracted with diethyl ether (50 mL) and the organic layer was washed successively with a saturated aqueous solution of copper sulfate (3 x 20 mL), water (3 x 20 mL) then brine (20 mL). The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography eluting from 5:1 to 2:1 petrol: diethyl ether afforded the desired product **156** as a white solid (1.92 g, 84%). R_f 0.39 (1:1 pentane: diethyl ether); mp 71-73 °C; (lit[88] mp 70-72 °C); ν_{max}/cm^{-1} ($CHCl_3$): 3609, 3009, 2933, 1731 1457; δ_H (400 MHz, $CDCl_3$): 4.42 (1H, dd, *J* 12.0, 5.1, C^1CH_{2A}), 4.30 (1H, dd, *J* 12.0, 3.1, C^1CH_{2B}), 2.05 (3H, s, OAc), 1.86-1.73 (1H, m, C^3H_{2A}), 1.68-1.62 (1H, m, C^4H_{2A}), , 1.46-1.34 (3H, m, $C^3H_{2B,}$ C^4H_{2B}, C^5H_{2A}), 1.30 (1H, dd, *J* 5.1, 3.1, C^1H), 1.24 (3H, s, C^2CH_3), 1.26-1.17 (1H, m, C^5H_{2B}), 1.00 (3H, s, C^6CH_3), 0.98 (3H, s, C^6CH_3); δ_C (100 MHz, $CDCl_3$): 171.0 (C), 72.2 (C), 63.0 (CH_2), 52.5 (CH), 42.3 (CH_2), 41.6 (CH_2), 33.7 (C), 32.5 (CH_3), 31.2 (CH_3), 22.3 (CH_3), 21.4 (CH_3), 18.3 (CH_2); *m/z* (ES^+) found 237.1456 ($[M+Na]^+$, $C_{12}H_{22}O_3Na^+$ requires 237.1461).[88]

General Procedures for dehydration conditions optimisation (chapter 2 part 2.6.2 Table 1)



Procedure Table 1 Entry 1:

Freshly distilled thionyl chloride (68 µL, 0.93 mmol) in anhydrous dichloromethane (620 µL) was addes slowly at -78 °C under inert atmosphere to a solution of alcohol **156** (100 mg, 0.47 mmol) in anhydrous dichloromethane and trimethylamine (390 µL, 2.82 mmol). The reaction mixture was stirred for 30 minutes at -78 °C, then was quenched with methanol (1 mL) and concentrated *in vacuo*. The residue was dissolved in anhydrous dimethylformamide (10 mL) and potassium carbonate (650 mg, 4.7 mmol) was added to the reaction mixture. It was then heated at 50 °C for 1 hour, then cooled to room temperature. The reaction was extracted with diethyl ether (30 mL) and the organic layer was washed successively with water (3 x 10 mL), a saturated aqueous solution of sodium bicarbonate (3 x 10 mL) and brine (15 mL). It was then dried over magnesium sulfate and concentrated *in vacuo* to afford a mixture of all three regioisomers **157** (65%), **158** (32%) and **159** (3%) (63 mg, 71% crude yield). All the ratios were determined using ^{1}H crude NMR by integrating for 1 proton the singulet at 5.42 ppm corresponding to $C^{3}H$ of **158**, 1 proton the singulet at 4.79 ppm corresponding to one of the $C^{2}H_{2A}$ of **159** and 3 protons the singulet at 4.56 ppm corresponding to the $C^{1}CH_{2}$ of **157** $C^{2}H_{2B}$ of **159**.

Procedure Table 1 Entry 2:

Phosphoryl chloride (216 µL, 2.31 mmol) was added dropwise to an ice cooled solution of alcohol **156** (50 mg, 0.23 mmol) in anhydrous pyridine (4.3 mL). The reaction was stirred for 1 hour at 0 °C then warmed to room temperature and stirred for 15 h. The reaction mixture was quenched with ice water (1.5 mL) and extracted with petroleum ether (15 mL). The aqueous layer was then acidified with a n aqueous solution of 2 M hydrochloric acid (5 mL) and reextracted with petroleum ether (3 x 15 mL). The combined organic layers were washed with water and then dried over magnesium sulfate, concentrated *in vacuo* to recover starting material **156** (40 mg, 80% crude).

Procedure Table 1 Entry 3:

To a flame-dried flask containing Martin's sulfurane (632 mg, 0.94 mmol) was added a solution of alcohol **156** (100 mg, 0.47 mmol) in anhydrous dichloromethane (16 mL) at room temperature under inert atmosphere. The resulting mixture was stirred for 2 hours at this temperature before being concentrated *in vacuo*. Purification by column chromatography eluting from petrol to 9:1 petrol: diethyl ether afforded a mixture of **158** (82%), **157** (6%) and **159** (12%) and diphenylsulfone (408 mg, up to 100%).

Procedure Table 1 Entry 4:

To a stirred solution of alcohol **156** (100 mg, 0.47 mmol) in anhydrous benzene (4.5 mL) at room temperature was added Burgess reagent (386 mg, 1.41 mmol), then additional anhydrous benzene (1.1 mL). The reaction mixture was stirred at room

temperature for 16 hours. A saturated aqueous solution of sodium bicarbonate (3 mL) was added to the reaction mixture and the aqueous layer was extracted with diethyl ether (2 x 10 mL). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated *in vacuo* to afford a mixture of three regioisomers of **158** (63%), **157** (23%) and **159** (14%) (86 mg, 93% crude).

Procedure Table 1 Entry 5:

To a stirred solution of alcohol **156** (54 mg, 0.23 mmol) in anhydrous benzene (2.2 mL) at 60 °C was added Burgess reagent (167 mg, 0.70 mmol), then additional anhydrous benzene (550 µL). The reaction mixture was stirred at 60 °C for 1 hour. A saturated aqueous solution of sodium bicarbonate (3 mL) was added to the reaction mixture and the aqueous layer was extracted with diethyl ether (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over magnesium sulfate and concentrated *in vacuo* to afford a mixture of three regioisomers of **158** (63%), **157** (21%) and **159** (16%) respectively (42 mg, 85% crude).

Procedure Table 1 Entry 6, 7 and 8:

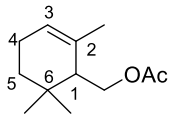
To a solution of alcohol **156** (100 mg, 0.47 mmol) at 0 °C in anhydrous dichloromethane (1 mL) under inert atmosphere were added triethylamine (238 mg, 2.35 mmol, Entry 6 and 7), or DBU (351 µL, 2.35 mmol, Entry 8). The reaction was then stirred for 16 hours at room temperature (Entry 6) or reflux (Entry 7 and 8). The reaction mixture was diluted with cold water and extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried over

magnesium sulfate, concentrated *in vacuo* to afford a mixture of **158** (41%), **159** (5%), and **157** (54%) respectively (Entry 6), and a mixture **158** (41%), **159** (7%), and **157** (52%) respectively (Entry 7).

Procedure Table 1 Entry 9:

To a flame-dried flask containing a solution of alcohol **156** (100 mg, 0.47 mmol) in anhydrous dimethylformamide (2 mL) under inert atmosphere was added sodium hydride (25 mg, 0.607 mmol) at 0 °C, then the reaction was warmed at room temperature for 1 hour, then tosyl chloride (177 mg, 0.93 mmol) was added at 0 °C, then the reaction was left at room temperature for 16 hours. It was quenched with a saturated solution of ammonium chloride (2 mL) and extracted with diethyl ether (20 mL), then the organic layer was washed with water (3 x 5 mL) and brine (10 mL), dried ver magnesium sulfate, concentrated *in vacuo* to afford a mixture of of **158** (60%), **159** (26%), and **157** (14%) respectively (32 mg, 35 % crude yield)

(2,6,6-trimethylcyclohex-2-en-1-yl)methyl acetate 168

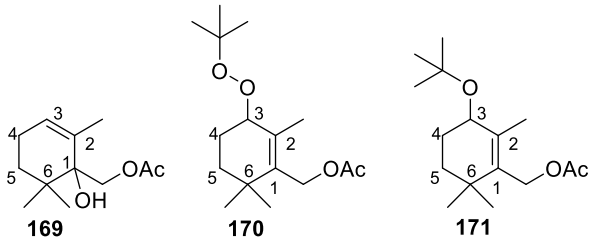


168

To a suspension of alcohol **153** (3.5 g, 22.7 mmol) in anhydrous pyridine (10.5 mL) was added acetic anhydride (8.7 mL, 75.0 mmol) at 0 °C under inert atmosphere. The suspension was stirred at room temperature for 16 hours. The reaction mixture was diluted with diethyl ether (200 mL) and washed successively with a saturated aqueous solution of copper acetate (3 x 100 mL), water (2 x 100 mL) and brine (100 mL). The organic layer was dried over magnesium sulfate and concentrated *in vacuo*.

Purification by column chromatography eluting from 95:5 to 90:10 petrol:diethyl ether provided the desire product **168** as a colorless oil (4.15 g, 93%). R_f 0.47 (19:1 petrol: diethyl ether); ν_{max}/cm^{-1} ($CHCl_3$): 2967, 2918, 2872, 1730, 1471; δ_H (400 MHz, $CDCl_3$): 5.38 (1H, br s, C^3H), 4.11 (1H, dd, *J* 5.8, 12.3 C^1CH_{2A}), 3.99 (1H, dd, *J* 2.8, 12.3 C^1CH_{2B}), 1.96 (3H, s, $COCH_3$), 1.91 (2H, app br s, C^4H_2), 1.72 (1H, br s, C^1H), 1.66 (3H, s, C^2CH_3), 1.41 (1H, dt, *J* 8.1, 13.8, C^5H_{2A}), 1.14 (1H, dt, *J* 4.8, 8.1, C^5H_{2B}), 0.88 (3H, s, C^6CH_3), 0.85 (3H, s, C^6CH_3); δ_C (100 MHz, $CDCl_3$): 170.9 (C), 132.2 (C), 123.1 (CH), 64.2 (CH_2), 48.8 (CH), 32.0 (CH_2), 31.7 (C), 27.3 (CH_3), 27.0 (CH_3), 22.9 (CH_3), 22.9 (CH_2), 21.1 (CH_3); *m/z* (ES^+) could not be found.

(1-hydroxy-2,6,6-trimethylcyclohex-2-en-1-yl)methyl acetate 169, (3-(tert-butylperoxy)-2,6,6-trimethylcyclohex-1-en-1-yl)methyl acetate 170 and (3-(tert-butoxy)-2,6,6-trimethylcyclohex-1-en-1-yl)methyl acetate 171



To a suspension of selenium dioxide (6 mg, 0.05 mmol) dissolved in dichloromethane (400 µL) was added tertbutylhydrogen peroxide (96 µL, 1.02 mmol), then acetate **168** (100 mg, 0.51 mmol) previously dissolved in dichloromethane (200 µL). The reaction mixture was stirred for 14 hours at room temperature. The mixture was then concentrated *in vacuo* to remove volatiles. The residual mixture was diluted in diethyl ether (30 mL) and washed successively with a 10% aqueous solution of potassium hydroxide (2 x 10 mL), water (2 x 10 mL) and brine (10 mL). The organic layer was

dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography eluting from 100% petrol to 2:1 petrol:diethyl ether provided **169** as a colorless oil (20 mg, 18%), **170** as a colorless oil (27 mg, 19%) and **171** as a colorless oil (14 mg, 10%).

1-hydroxy-2,6,6-trimethylcyclohex-2-en-1-yl)methyl acetate 169

R_f 0.17 (5:1 petrol: diethyl ether); ν_{max}/cm^{-1} ($CHCl_3$): 3605, 3008, 2970, 2927, 2876, 2843, 2732, 1733; δ_H (400 MHz, $CDCl_3$): 5.51 (1H, br s, C^3H), 4.25 (1H, d, *J* 11.6 C^1CH_{2A}), 4.12 (1H, d, *J* 11.6 C^1CH_{2B}), 2.08 (3H, s, $COCH_3$), 2.04-1.96 (2H, m, C^4H_2), 1.76 (3H, s, C^2CH_3), 1.65-1.59 (1H, m, C^5H_{2A}), 1.47-1.42 (1H, m, *J* 4.8, 8.1, C^5H_{2B}), 0.98 (3H, s, C^6CH_3), 0.97 (3H, s, C^6CH_3); δ_C (100 MHz, $CDCl_3$): 171.2 (C), 134.8 (C), 126.0 (CH), 75.7 (C), 67.4 (CH_2), 36.8 (C), 34.0 (CH_2), 24.2 (CH_3), 23.0 (CH_3), 22.7 (CH_2), 21.2 (CH_3), 19.0 (CH_3); *m/z* (ES^+) found 235.1291 ($[M+Na]^+$, $C_{12}H_{20}O_3Na^+$ requires 235.1305).

(3-(tert-butylperoxy)-2,6,6-trimethylcyclohex-1-en-1-yl)methyl acetate 170

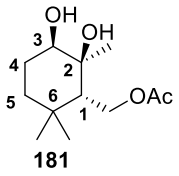
R_f 0.55 (5:1 petrol: diethyl ether); ν_{max}/cm^{-1} ($CHCl_3$): 2969, 2930, 2871, 1730, 1471; δ_H (400 MHz, $CDCl_3$): 4.60 (1H, d, *J* 12.0, C^1CH_{2A}), 4.55 (1H, d, *J* 12.0, C^1CH_{2B}), 4.23 (1H, t, *J* 3.2 C^3H), 2.04 (3H, s, $COCH_3$), 2.10-2.02 (1H, m, C^4H_{2A}), 1.80 (3H, s, C^2CH_3), 1.70-1.64 (2H, m, C^4H_{2B}, C^5H_{2A}), 1.34-1.30 (1H, m, C^5H_{2B}), 1.26 (9H, s, $OOC(CH_3)_3$), 1.01 (3H, s, C^6CH_3), 0.96 (3H, s, C^6CH_3); δ_C (100 MHz, $CDCl_3$): 171.4 (C), 139.5 (C), 132.6 (C), 81.1 (CH), 80.0 (C), 60.8 (CH_2), 34.8 (C), 34.2 (CH_2), 28.1

(CH_3), 26.8 (3 x CH_3), 26.5 (CH_3), 23.5 (CH_2), 21.1 (CH_3), 17.7 (CH_3); *m/z* (ES^+) found 307.1902 ($[M+Na]^+$, $C_{16}H_{28}O_4Na^+$ requires 307.1904).

(3-(tert-butoxy)-2,6,6-trimethylcyclohex-1-en-1-yl)methyl acetate 171

R_f 0.41 (5:1 petrol: diethyl ether); ν_{max}/cm^{-1} ($CHCl_3$): 2977, 2935, 2871, 1728, 1454, 1388, 1365; δ_H (400 MHz, $CDCl_3$): 4.59 (1H, d, *J* 12.0, C^1CH_{2A}), 4.54 (1H, d, *J* 12.0, C^1CH_{2B}), 3.86 (1H, t, *J* 5.6 C^3H), 2.04 (3H, s, $COCH_3$), 1.88-1.79 (1H, m, C^4H_{2A}), 1.72 (3H, s, C^2CH_3), 1.74-1.66 (1H, m, C^4H_{2B}), 1.64-1.57 (1H, m, C^5H_{2A}), 1.42-1.35 (1H, m, C^5H_{2B}), 1.25 (9H, s, $OC(CH_3)_3$), 1.02 (3H, s, C^6CH_3), 0.96 (3H, s, C^6CH_3); δ_C (100 MHz, $CDCl_3$): 171.6 (C), 137.6 (C), 136.0 (C), 74.0 (C), 70.3 (CH), 61.4 (CH_2), 35.6 (CH_2), 34.5 (C), 29.2 (3 x CH_3), 28.9 (CH_2), 27.7 (CH_3), 27.7 (CH_3), 21.2 (CH_3), 16.8 (CH_3); *m/z* (ES^+) found 291.1952 ($[M+Na]^+$, $C_{16}H_{28}O_3Na^+$ requires 291.1955).

((1*S*,2*S*,3*R*)-2,3-dihydroxy-2,6,6-trimethylcyclohexyl)methyl acetate 181

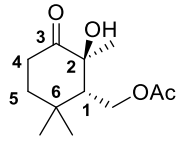


181

To a solution of acetate **168** (100 mg, 0.51 mmol) dissolved in water (310 µL) and acetone (3.1 mL) was added potassium osmate dihydrated (2 mg, 5.0 µmol) and NMO (206 mg, 1.53 mmol). The reaction mixture was stirred for 2 days at room temperature and then quenched with sodium thiosulfate (15 mg) and stirred for 3 hours at room temperature. The reaction was then extracted with dichloromethane (20 mL). The layers were separated and the aqueous phase was reextracted with dichloromethane (3

x 20 mL). The combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography eluting from 4:1 to 1:1 pentane:diethyl ether provided **181** as a colorless oil (72 mg, 61%). R_f 0.22 (2:1 petrol: diethyl ether); ν_{max}/cm^{-1} ($CHCl_3$): 3570, 3482, 2987, 2958, 1720; δ_H (400 MHz, $CDCl_3$): 4.36 (1H, dd, *J* 11.7, 5.4, C^1CH_{2A}), 4.23 (1H, dd, *J* 11.7, 5.4 C^1CH_{2B}), 3.55 (1H, app t, *J* 2.4 C^3H), 3.43 (1H, br s, OH), 3.00 (1H, br s, OH), 2.04 (3H, s, $COCH_3$), 1.88 (1H, t, *J* 5.4, C^1H), 1.78-1.67 (2H, m, C^4H_2), 1.66 (1H, dt, *J* 15.2, 2.5 C^5H_{2A}), 1.16 (3H, s, C^2CH_3), 1.08 (1H, dt, *J* 5.8, 2.5, C^5H_{2B}), 0.99 (3H, s, C^6CH_3), 0.86 (3H, s, C^6CH_3); δ_C (100 MHz, $CDCl_3$): 171.4 (C), 74.0 (C), 73.7 (CH), 63.4 (CH_2), 49.2 (CH), 34.1 (CH_2), 33.7 (C), 33.5 (CH_3), 25.2 (CH_2), 22.9 (CH_3), 21.6 (CH_3), 21.3 (CH_3); *m/z* (ES^+) found 253.1409 ($[M+Na]^+$, $C_{12}H_{22}O_4Na^+$ requires 253.1410).

((1*S*,2*S*)-2-hydroxy-2,6,6-trimethyl-3-oxocyclohexyl)methyl acetate 182

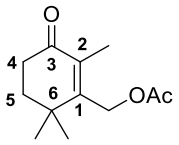


182

To a solution of oxalyl chloride (53 µL, 0.62 mmol) in anhydrous dichloromethane (3.6 mL) was added anhydrous DMSO (89 µL, 1.25 mmol) at -78 °C under inert atmosphere. The reaction mixture was stirred for one hour at -78 °C then diol **184** (72 mg, 0.31 mmol) dissolved in anhydrous dichlomethane (1 mL) was added dropwise at -78 °C. The reaction was stirred for 2 hours at this temperature then distilled trimethylamine (346 µL, 2.48 mmol) was added dropwise before allowing the reaction mixture to warm to room temperature and stirred for one additional hour. The reaction was diluted in dichloromethane (20 mL) and washed with an aqueous saturated solution of sodium bicarbonate (10 mL). The layers were separated and the aqueous

phase was reextracted with dichloromethane (3 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography eluting from 3:1 to 1:1 pentane:diethyl ether provided **182** as white solid (51 mg, 72%). R_f 0.34 (2:1 petrol: diethyl ether); mp 94-96 °C; ν_{max}/cm^{-1} ($CHCl_3$): 3470, 3010, 2952, 2871, 1725, 1715; δ_H (400 MHz, $CDCl_3$): 4.42 (1H, dd, *J* 11.7, 6.3, C^1CH_{2A}), 4.36 (1H, dd, *J* 11.7, 4.2 C^1CH_{2B}), 4.00 (1H, br s, OH), 2.73 (1H, td, *J* 14.2, 5.7 C^4H_{2A}), 2.41 (1H, dt, *J* 14.2, 3.8 C^4H_{2B}), 2.04 (3H, s, $COCH_3$), 1.89 (1H, dd, *J* 6.3,4.2 C^1H), 1.77 (1H, ddd, *J* 14.0, 5.7, 3.7 C^5H_{2A}), 1.65 (1H, td, *J* 14.0, 3.7, C^5H_{2B}), 1.32 (3H, s, C^2CH_3), 1.16 (3H, s, C^6CH_3), 1.06 (3H, s, C^6CH_3); δ_C (100 MHz, $CDCl_3$): 213.6 (C), 171.1 (C), 76.8 (C), 62.2 (CH_2), 56.1 (CH), 41.4 (CH_2), 34.1 (CH_2), 33.9 (C), 31.7 (CH_3), 23.2 (CH_3), 21.3 (CH_3), 21.3 (CH_3); *m/z* (ES^+) found 229.1434 ($[M+H]^+$, $C_{12}H_{21}O_4$ requires 229.1434).

(2,6,6-trimethyl-3-oxocyclohex-1-en-1-yl)methyl acetate 183

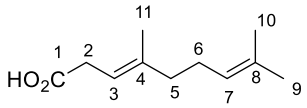


183

To a solution of hydroxyketone **182** (51 mg, 0.22 mmol) in anhydrous benzene (3.6 mL) was added Burgess reagent (160 mg, 0.67 mmol), then anhydrous benzene (550 µL) under inert atmosphere at room temperature. The reaction mixture was stirred for one hour at 60 °C. The reaction was cooled to room temperature, then diluted with diethyl ether (20 mL) and washed with an a saturated aqueous solution of sodium bicarbonate (10 mL). The aqueous layer was reextracted with diethyl ether (2 x 10 mL). The combined organic layers were washed with brine (15 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by column chromatography

eluting with 2:1 pentane:diethyl ether provided **183** as white solid (9 mg, 19%). R_f 0.34 (2:1 petrol: diethyl ether); mp 113-115 °C; ν_{max}/cm^{-1} ($CHCl_3$): 3007, 2968, 2931, 2873, 1737, 1672, 1603; δ_H (400 MHz, $CDCl_3$): 4.74 (2H, s, C^1CH_2), 2.51 (2H, dd, *J* 7.4, 6.4 C^4H_2), 2.08 (3H, s, $COCH_3$), 1.85 (2H, dd, *J* 7.4, 6.4 C^5H_2), 1.81 (3H, s, C^2CH_3), 1.17 (6H, s, 2x C^6CH_3); δ_C (100 MHz, $CDCl_3$): 199.2 (C), 170.9 (C), 155.2 (C), 135.3 (C), 61.1 (CH_2), 37.4 (CH_2), 35.6 (C), 34.4 (CH_2), 26.6 (2 x CH_3), 21.0 (CH_3), 11.7 (CH_3); *m/z* (ES^+) found 233.1140 ($[M+Na]^+$, $C_{12}H_{18}O_3Na^+$ requires 233.1148).

(*E*)-4,8-dimethylnona-3,7-dienoic acid 188

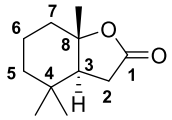


188

To a solution of geranyl cyanide **27** (700 mg, 4.29 mmol) dissolved in methanol (77 mL) was added a 25% in weight aqueous solution of sodium hydroxide (17.5 mL). The resulting mixture was refluxed for 24 hours, then cooled ro room temperature and diluted with dichloromethane (250 mL). The reaction mixture was washed with a 6 M aqueous solution of hydrogen chloride (100 mL). The organic layer was separated and the aqueous phase was extracted with dichloromethane (3 x 200 mL). The combined organic layers were washed with brine (200 mL), dried over magnesium sulfate, concentrated *in vacuo*. Purification by column chromatography eluting with 25:1 dichloromethane : methanol provided **188** as a colorless oil (739 mg, 94%). R_f 0.20 (25:1 dichloromethane : methanol); ν_{max}/cm^{-1} ($CHCl_3$): 3626, 3565, 3009, 2958, 2733; δ_H (400 MHz, $CDCl_3$): 11.10 (1H, br s, COOH), 5.32 (1H, tq, *J* 7.2, 1.1, C^3H), 5.08 (1H, m, C^7H), 3.08 (2H, d, *J* 7.2, C^2H_2), 2.14-2.02 (4H, m, C^6H_2, C^5H_2), 1.67 (3H, s,

$C^{11}H_3$), 1.64 (3H, s, $C^{10}H_3$), 1.60 (3H, s, C^9H_3); δ_C (100 MHz, $CDCl_3$): 179.2 (C), 139.8 (C), 131.8 (C), 124.0 (CH), 115.1 (CH), 39.6 (CH_2), 33.7 (CH_2), 26.6 (CH_2), 25.8 (CH_3), 17.8 (CH_3), 16.5 (CH_3); *m/z* (ES^-) found 181.1238 ($[M-H]^-$, $C_{11}H_{17}O_2$ requires 181.1234).

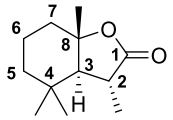
(3*S*,8*S*)-4,4,8-trimethylhexahydrobenzofuran-2(3*H*)-one 189



189

Homogeranoic acid **188** (739 mg, 4.06 mmol) was dissolved in TFA (11 mL) and the resulting mixture was heated at reflux for 30 minutes, then cooled to room temperature. The reaction mixture was diluted in toluene (20 mL) and concentrated *in vacuo*. The residual mixture was dissolved in diethyl ether (100 mL) and washed successively with water (3 x 50 mL) and brine (40 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography eluting from 7:1 to 5:1 petrol: ethyl acetate provided **189** as a colorless oil (600 mg, 81%). R_f 0.21 (7:1 petrol: ethyl acetate); ν_{max}/cm^{-1} ($CHCl_3$): 3011, 2983, 2963, 2944, 2873, 1755; δ_H (400 MHz, $CDCl_3$): 2.49 (1H, dd, *J* 17.2, 12.7, C^2H_{2A}), 2.40 (1H, dd, *J* 17.2, 8.3, C^2H_{2B}), 2.04 (1H, dd, *J* 12.7, 8.3, C^3H), 1.86-1.81 (1H, m, C^7H_{2A}), 1.62-1.56 (1H, m, C^6H_{2A}), 1.54-1.47 (1H, m, C^7H_{2B}), 1.51 (3H, s, C^8CH_3), 1.45-1.38 (1H, m, C^6H_{2B}), 1.35-1.26 (2H, m, C^5H_{2A}, C^5H_{2B}), 1.51 (3H, s, C^4CH_3), 1.51 (3H, s, C^4CH_3); δ_C (100 MHz, $CDCl_3$): 175.8 (C), 86.1(C), 50.2 (CH), 34.8 (CH_2), 33.7 (CH_2), 33.3 (CH_2), 32.3 (C), 30.2 (CH_3), 28.5 (CH_3), 27.0 (CH_3), 19.2 (CH_2); *m/z* (ES^+) found 183.1400 ($[M+H]^+$, $C_{11}H_{19}O_2$ requires 183.1380).

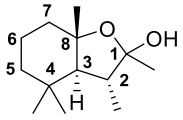
(2*R*,3*S*,8*S*)-2,4,4,8-tetramethylhexahydrobenzofuran-2(3*H*)-one 187



187

To a solution of distilled hexamethyldisilazane (316 µL, 1.51 mmol) in anhydrous THF (2 mL) was added ^{n}BuLi (713 µL, 1.64 mmol) dropwise at 0 °C. The reaction mixture was cooled to -78 °C before the addition of lactone **189** (250 mg, 1.37 mmol) previously dissolved in anhydrous THF (2 mL). The reaction mixture was then stirred at 0 °C for 1 hour, then methyl iodide (127 µL, 2.05 mmol) was added dropwise at -78 °C. The reaction mixture was warmed to room temperature and stirred for 2 hours and then quenched with a saturated aqueous solution of ammonium chloride (10 mL) and extracted with diethyl ether (40 mL). The organic layer was washed with water (3 x 25 mL), then brine (20 mL), dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography eluting from 30:1 to 10:1 petrol : ethyl acetate provided **187** as a colorless oil (186 mg, 78% based on recovery of starting material) and **189** (17 mg, 7%). R_f 0.86 (5:1 petrol: ethyl acetate); ν_{max}/cm^{-1} ($CHCl_3$): 3004, 2942, 2874, 1752, 1455; δ_H (400 MHz, $CDCl_3$): 2.55 (1H, dq, *J* 11.7, 6.9, C^2CH), 1.92-1.87 (1H, m, C^7H_{2A}), 1.67 (3H, d, *J* 11.7, C^3H), 1.60-1.56 (1H, m, C^6H_{2A}), 1.54 (3H, s, C^8CH_3), 1.51-1.43 (1H, m, C^6H_{2B}), 1.42-1.39 (1H, m, C^7H_{2B}), 1.35 (3H, d, *J* 6.9, C^2CH_3), 1.39-1.34 (2H, m, C^5H_{2A}, C^5H_{2B}), 1.06 (3H, s, C^4CH_3), 1.01 (3H, s, C^4CH_3); δ_C (100 MHz, $CDCl_3$): 179.2 (C), 84.0 (C), 59.4 (CH), 38.7 (CH), 36.1 (CH_2), 34.7 (CH_2), 32.9 (C), 31.6 (CH_3), 29.2 (CH_3), 27.5 (CH_3), 18.9 (CH_2), 18.5 (CH_3); *m/z* (ES^+) found 219.1376 ($[M+Na]^+$, $C_{12}H_{20}O_2Na^+$ requires 219.1356).

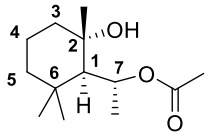
(2*R*,3*S*,8*S*)-1,2,4,4,8-pentamethyloctahydrobenzofuran-1-ol 190



190

To a solution of methyl lactone **187** (1.04 g, 5.30 mmol) in anhydrous diethyl ether (40 mL) was added at 0 °C a 1.6 M solution of methyl lithium in diethyl ether (3.6 mL, 5.80 mmol) dropwise over 10 minutes *via* a syringe pump under inert atmosphere. The mixture was then stirred for 30 minutes at 0 °C, then quenched at the same temperature with a 10 % aqueous solution of sulphuric acid (10 mL). The organic layer was washed successively with a 1% aqueous solution of sodium hydroxide (3 x 15 mL), water (3 x 15 mL) and brine (20 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography eluting from 15:1 to 5:1 petrol : ethyl acetate provided **190** as a white solid (479 mg, 61% based on recovery of starting material) and **187** (320 mg, 31%). R_f 0.39 (5:1 petrol: ethyl acetate); ν_{max}/cm^{-1} ($CHCl_3$): 3691, 3602, 3005, 2938, 2872; δ_H (400 MHz, $CDCl_3$): 2.06 (1H, br s, OH), 1.99 (1H, dq, *J* 12.3, 6.5, C^2H), 1.65 (1H, d, *J* 12.3, C^3H), 1.59 (1H, dd, *J* 8.6, 3.5 C^7H_{2A}), 1.50-1.42 (1H, m, C^6H_{2A}), 1.42-1.33 (2H, m, C^6H_{2A},C^7H_{2A}), 1.39 (3H, s, C^8CH_3), 1.38 (3H, s, C^1CH_3), 1.30-1.20 (2H, m, C^5H_{2A},C^5H_{2B}), 1.09 (3H, d, *J* 6.5, C^2CH_3), 1.00 (3H, s, C^4CH_3), 0.97 (3H, s, C^4CH_3); δ_C (100 MHz, $CDCl_3$): 104.1 (C), 82.5 (C), 58.7 (CH), 45.4 (CH), 36.0 (CH_2), 35.5 (CH_2), 32.8 (C), 31.2 (CH_3), 30.9 (CH_3), 30.7 (CH_3), 27.1 (CH_3), 18.9 (CH_2), 16.1 (CH_3); *m/z* (ES^+) found 235.1669 ($[M+Na]^+$, $C_{13}H_{24}O_2Na^+$ requires 235.1669).

(*R*)-1-((1*R*,2*S*)-2-hydroxy-2,6,6-trimethylcyclohexyl)ethyl acetate 197



197

To a solution of hemiketal **190** (57 mg, 0.27 mmol) in dichloromethane (2.5 mL) was added *m*-CPBA (70%) (93 mg, 0.38 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 hour. The reaction was diluted with ethyl acetate (25 mL) and quenched with a 10% aqueous solution of sodium sulfite (5 mL). The two layers were separated and the organic layer was washed with a saturated aqueous solution of sodium bicarbonate (2 x 10 mL), then dried over sodium sulfate and concentrated *in vacuo*. Purification by column chromatography eluting from 20:1 to 5:1 petrol: ethyl acetate provided fraction 1, which was left in $CDCl_3$ for 24 hours at room temperature. Another purification of fraction 1 by column chromatography eluting from 20:1 to 10:1 petrol: ethyl acetate provided the desired compound **197** as white solid (4.0 mg, 7%). R_f 0.20 (15:1 petrol: ethyl acetate); ν_{max}/cm^{-1} ($CHCl_3$): 3631, 3591, 3007, 2944, 2874, 2840, 1740; δ_H (500 MHz, $CDCl_3$): 5.41 (1H, q, *J* 7.4, C^7H), 3.01 (1H, app d, *J* 2.6, OH), 2.10 (3H, s, $COCH_3$), 1.87 (1H, qt, *J* 13.3, 3.3, C^4H_{2A}), 1.66 (1H, ddd, *J* 13.3, 5.3, 2.8, C^3CH_{2A}), 1.45-1.40 (1H, m, C^5H_{2A}), 1.43 (3H, s, C^2H_3), 1.42 (3H, d, *J* 7.4, C^7CH_3), 1.37-1.33 (1H, m, C^4H_{2B}), 1.29 (1H, dd, *J* 3.8, 2.8, C^3H_{2B}), 1.20-1.16 (2H, m, C^1H, C^5H_{2B}), 1.00 (3H, s, C^6CH_3), 0.92 (3H, s, C^6CH_3); δ_C (125 MHz, $CDCl_3$): 169.4 (C), 73.3 (C), 72.4 (CH), 56.9 (CH), 42.4 (CH_2), 42.1 (CH_2), 36.2 (C), 32.5 (CH_3), 32.5 (CH_3), 24.0 (CH_3), 21.8 (CH_3), 18.4 (CH_2), 15.8 (CH_3), ; *m/z* (ES^+) found 251.1623 ($[M+Na]^+$, $C_{13}H_{24}O_3Na^+$ requires 251.1618).

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Appendix

X-ray crystallographic data for bisepoxide 129

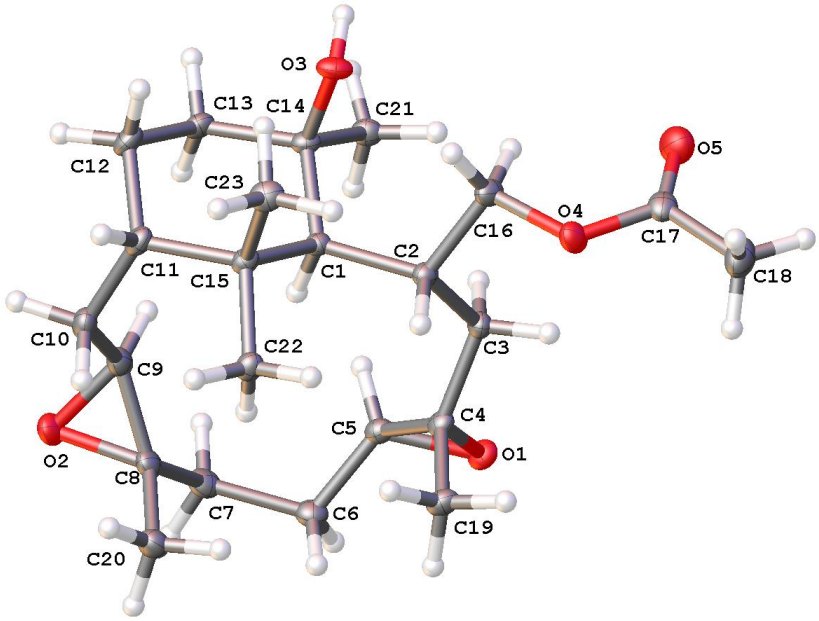


Table 1 Crystal data and structure refinement for 129

Empirical formula	$C_{23}H_{38}O_5$
Formula weight	394.53
Temperature/K	120(2)
Crystal system	Monoclinic
Space group	$P2_1/n$
a/Å	13.5044(8)
b/Å	10.6800(6)
c/Å	15.1335(11)
α/°	90
β/°	97.978(7)
γ/°	90
Volume/Å^3	2161.5(2)
Z	4
ρ_{calc}mg/mm^3	1.212
m/mm^{-1}	0.669
F(000)	864.0
Crystal size/mm^3	0.6535 × 0.599 × 0.4911
2Θ range for data collection	8.228 to 148.91°
Index ranges	$-16 \leq h \leq 16$, $-8 \leq k \leq 13$, $-18 \leq l \leq 18$
Reflections collected	8896
Independent reflections	4283[R(int) = 0.0198]
Data/restraints/parameters	4283/0/260
Goodness-of-fit on F^2	1.047
Final R indexes [I>=2σ (I)]	R_1 = 0.0419, wR_2 = 0.1097
Final R indexes [all data]	R_1 = 0.0448, wR_2 = 0.1121
Largest diff. peak/hole / e Å^{-3}	0.30/-0.23

Table 2 Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($Å^2 \times 10^3$) for 119. U_{eq} is defined as 1/3 of of the trace of the orthogonalised U_{IJ} tensor.

Atom	*x*	*y*	*Z*	U(eq)
C1	5671.0(8)	5765.5(10)	7804.4(7)	12.6(2)
C2	6469.6(8)	5549.9(11)	8644.4(7)	14.1(2)
C3	7119.6(8)	6708.4(11)	8931.3(8)	15.5(2)
C4	6583.3(8)	7821.5(11)	9264.1(7)	14.5(2)
C5	6316.3(8)	8896.4(11)	8663.1(8)	15.6(2)
C6	5548.9(9)	9893.2(11)	8760.7(8)	19.2(3)
C7	4693.9(9)	9956.1(11)	7980.4(8)	20.4(3)
C8	3910.3(9)	8931.1(12)	7928.0(8)	18.4(3)
C9	3865.4(9)	7993.3(12)	7197.0(8)	18.2(3)
C10	3310.2(9)	6758.2(12)	7140.3(8)	19.9(3)
C11	3846.8(9)	5480.7(11)	7081.3(8)	16.9(2)
C12	4226.3(9)	5270.9(12)	6184.2(8)	19.1(3)
C13	5220.1(9)	5919.4(11)	6122.1(7)	16.8(2)
C14	6042.5(9)	5560.9(11)	6883.0(7)	14.5(2)
C15	4644.2(8)	5104.9(11)	7878.5(7)	14.7(2)
C16	7151.9(9)	4418.9(11)	8583.0(8)	18.7(3)
C17	8622.2(9)	4020.3(11)	9630.2(8)	19.3(3)
C18	8972.7(11)	3670.1(14)	10579.8(9)	28.5(3)
C19	6089.4(9)	7599.3(11)	10082.0(8)	18.0(2)
C20	3441.4(9)	8725.1(12)	8764.5(8)	21.4(3)
C21	6964.0(9)	6349.2(11)	6771.9(8)	17.3(2)
C22	4238.1(9)	5495.4(11)	8736.6(8)	17.0(2)
C23	4712.2(9)	3661.4(11)	7903.2(8)	20.0(3)
O1	7206.3(6)	8947.9(8)	9323.9(5)	17.40(19)
O2	3199.2(7)	9070.4(8)	7122.9(6)	22.5(2)
O3	6280.5(6)	4255.2(8)	6801.5(6)	18.2(2)
O4	7618.7(6)	4117.6(8)	9483.2(6)	20.0(2)
O5	9155.0(7)	4185.8(10)	9066.6(7)	28.8(2)

Table 3 Anisotropic Displacement Parameters ($Å^2×10^3$) for 129. The Anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U_{11}+...+2hka×b×U_{12}]$

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C1	14.5(5)	11.1(5)	12.3(5)	-0.9(4)	1.9(4)	-0.4(4)
C2	15.5(5)	13.1(5)	13.5(5)	-0.7(4)	1.6(4)	1.2(4)
C3	12.8(5)	17.1(6)	16.0(5)	-1.6(4)	-0.1(4)	0.3(4)
C4	14.3(5)	14.5(5)	14.3(5)	-2.3(4)	1.0(4)	-3.2(4)
C5	16.6(5)	15.6(5)	14.8(5)	-2.0(4)	3.2(4)	-2.0(4)
C6	22.0(6)	15.3(6)	20.7(6)	-2.7(4)	4.1(5)	1.5(5)
C7	23.7(6)	16.5(6)	21.3(6)	2.0(5)	4.1(5)	5.8(5)
C8	17.2(5)	19.7(6)	17.8(6)	1.7(5)	0.7(4)	6.8(4)
C9	17.2(5)	21.3(6)	15.7(5)	2.1(5)	0.8(4)	5.5(5)
C10	15.0(5)	26.4(7)	17.2(6)	-0.1(5)	-1.3(4)	0.4(5)
C11	15.8(5)	20.0(6)	14.4(5)	-1.8(4)	0.6(4)	-5.1(4)
C12	21.2(6)	22.3(6)	12.8(5)	-2.7(5)	-0.7(4)	-3.9(5)
C13	21.1(6)	18.0(6)	11.5(5)	-1.2(4)	3.0(4)	-1.3(4)
C14	18.0(5)	12.0(5)	13.9(5)	-1.8(4)	4.3(4)	-0.4(4)
C15	16.4(5)	14.6(6)	13.2(5)	-0.4(4)	2.2(4)	-2.5(4)
C16	22.7(6)	17.9(6)	14.6(5)	0.5(4)	0.1(4)	5.8(5)
C17	20.9(6)	12.9(5)	23.1(6)	-2.7(5)	-0.8(5)	1.3(4)
C18	28.4(7)	27.5(7)	26.8(7)	1.7(6)	-6.0(5)	2.3(6)
C19	22.3(6)	17.9(6)	14.4(5)	-1.7(4)	4.5(4)	-2.8(5)
C20	20.6(6)	24.0(6)	20.2(6)	-0.5(5)	4.5(5)	4.3(5)
C21	18.8(6)	17.1(6)	17.1(6)	-0.1(4)	5.9(4)	-1.1(4)
C22	16.8(5)	20.2(6)	14.2(5)	0.6(4)	2.5(4)	-1.6(4)
C23	24.1(6)	15.8(6)	20.6(6)	0.6(5)	5.5(5)	-4.7(5)
O1	17.5(4)	16.2(4)	18.1(4)	-1.8(3)	1.2(3)	-4.8(3)
O2	21.8(4)	25.1(5)	19.3(4)	2.2(3)	-1.4(3)	9.5(4)
O3	25.1(4)	13.1(4)	18.1(4)	-2.4(3)	9.3(3)	1.5(3)
O4	19.9(4)	22.4(5)	17.5(4)	4.2(3)	1.4(3)	6.4(3)
O5	22.0(5)	35.1(6)	29.4(5)	-2.2(4)	3.8(4)	-3.1(4)

Table 4 Bond Lengths for 129.

Atom	Atom	Length/Å	Atom	Atom	Length/Å
C1	C2	1.5658(15)	C9	C10	1.5138(17)
C1	C14	1.5614(15)	C9	O2	1.4551(14)
C1	C15	1.5736(15)	C10	C11	1.5532(17)
C2	C3	1.5441(16)	C11	C12	1.5327(16)
C2	C16	1.5298(15)	C11	C15	1.5542(16)
C3	C4	1.5141(16)	C12	C13	1.5247(16)
C4	C5	1.4779(16)	C13	C14	1.5333(16)
C4	C19	1.5040(15)	C14	C21	1.5309(16)
C4	O1	1.4637(13)	C14	O3	1.4402(14)
C5	C6	1.5071(16)	C15	C22	1.5359(15)
C5	O1	1.4539(14)	C15	C23	1.5445(16)
C6	C7	1.5341(17)	C16	O4	1.4555(14)
C7	C8	1.5169(18)	C17	C18	1.4967(18)
C8	C9	1.4873(17)	C17	O4	1.3465(15)
C8	C20	1.5081(17)	C17	O5	1.2029(16)
C8	O2	1.4505(14)			

Table 5 Bond Angles for 129.

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C2	C1	C15	112.99(9)	O2	C9	C10	112.86(10)
C14	C1	C2	115.72(9)	C9	C10	C11	122.50(10)
C14	C1	C15	113.36(9)	C10	C11	C15	117.43(9)
C3	C2	C1	114.27(9)	C12	C11	C10	113.29(10)
C16	C2	C1	114.81(9)	C12	C11	C15	111.65(10)
C16	C2	C3	109.03(9)	C13	C12	C11	113.18(9)
C4	C3	C2	116.30(9)	C12	C13	C14	113.09(10)
C5	C4	C3	119.49(10)	C13	C14	C1	110.28(9)
C5	C4	C19	122.06(10)	C21	C14	C1	112.83(9)
C19	C4	C3	115.92(10)	C21	C14	C13	107.18(9)
O1	C4	C3	111.62(9)	O3	C14	C1	108.37(9)
O1	C4	C5	59.24(7)	O3	C14	C13	108.93(9)
O1	C4	C19	113.30(9)	O3	C14	C21	109.19(9)
C4	C5	C6	126.92(10)	C11	C15	C1	110.57(9)
O1	C5	C4	59.89(7)	C22	C15	C1	111.10(9)
O1	C5	C6	114.83(9)	C22	C15	C11	107.21(9)
C5	C6	C7	114.19(10)	C22	C15	C23	106.12(9)
C8	C7	C6	116.98(10)	C23	C15	C1	113.53(9)
C9	C8	C7	118.75(10)	C23	C15	C11	108.00(9)
C9	C8	C20	123.20(11)	O4	C16	C2	107.69(9)

Atom	Atom	Atom	Angle/°	Atom	Atom	Atom	Angle/°
C20	C8	C7	115.63(10)	O4	C17	C18	110.79(11)
O2	C8	C7	110.22(10)	O5	C17	C18	125.24(12)
O2	C8	C9	59.36(7)	O5	C17	O4	123.97(11)
O2	C8	C20	114.45(10)	C5	O1	C4	60.87(7)
C8	C9	C10	126.70(11)	C8	O2	C9	61.58(7)
O2	C9	C8	59.06(7)	C17	O4	C16	117.84(9)

Table 6 Hydrogen Bonds for 129.

D	H	A	d(D-H)/Å	d(H-A)/Å	d(D-A)/Å	D-H-A/°
O3	H3	O1[1]	0.84	2.04	2.8549(12)	163.3

[1]3/2-X,-1/2+Y,3/2-Z

Table 7 Torsion Angles for 129.

A	B	C	D	Angle/°	A	B	C	D	Angle/°
C1	C2	C3	C4	65.80(13)	C10	C11	C15	C23	154.15(10)
C1	C2	C16	O4	-162.54(9)	C11	C12	C13	C14	54.86(14)
C2	C1	C14	C13	-174.74(9)	C12	C11	C15	C1	52.19(13)
C2	C1	C14	C21	-54.93(13)	C12	C11	C15	C22	173.45(10)
C2	C1	C14	O3	66.10(12)	C12	C11	C15	C23	-72.58(12)
C2	C1	C15	C11	173.26(9)	C12	C13	C14	C1	-52.75(13)
C2	C1	C15	C22	54.34(12)	C12	C13	C14	C21	-175.93(9)
C2	C1	C15	C23	-65.17(12)	C12	C13	C14	O3	66.06(12)
C2	C3	C4	C5	-101.13(12)	C14	C1	C2	C3	86.11(11)
C2	C3	C4	C19	61.21(13)	C14	C1	C2	C16	-40.94(13)
C2	C3	C4	O1	-167.06(9)	C14	C1	C15	C11	-52.57(12)
C2	C16	O4	C17	-127.24(10)	C14	C1	C15	C22	-171.49(9)
C3	C2	C16	O4	67.78(12)	C14	C1	C15	C23	69.00(12)
C3	C4	C5	C6	161.16(11)	C15	C1	C2	C3	-140.86(10)
C3	C4	C5	O1	-98.98(10)	C15	C1	C2	C16	92.09(11)
C3	C4	O1	C5	112.35(10)	C15	C1	C14	C13	52.39(12)
C4	C5	C6	C7	-119.11(13)	C15	C1	C14	C21	172.20(9)
C5	C6	C7	C8	74.55(14)	C15	C1	C14	O3	-66.77(11)
C6	C5	O1	C4	119.79(11)	C15	C11	C12	C13	-54.10(14)
C6	C7	C8	C9	-110.48(12)	C16	C2	C3	C4	-164.23(9)
C6	C7	C8	C20	52.43(14)	C18	C17	O4	C16	-178.31(10)
C6	C7	C8	O2	-175.82(9)	C19	C4	C5	C6	-0.06(18)
C7	C8	C9	C10	165.56(11)	C19	C4	C5	O1	99.81(11)
C7	C8	C9	O2	-97.66(11)	C19	C4	O1	C5	-114.60(11)
C7	C8	O2	C9	112.18(11)	C20	C8	C9	C10	4.02(18)
C8	C9	C10	C11	-120.39(13)	C20	C8	C9	O2	100.80(12)
C9	C10	C11	C12	-70.49(14)	C20	C8	O2	C9	-115.45(12)

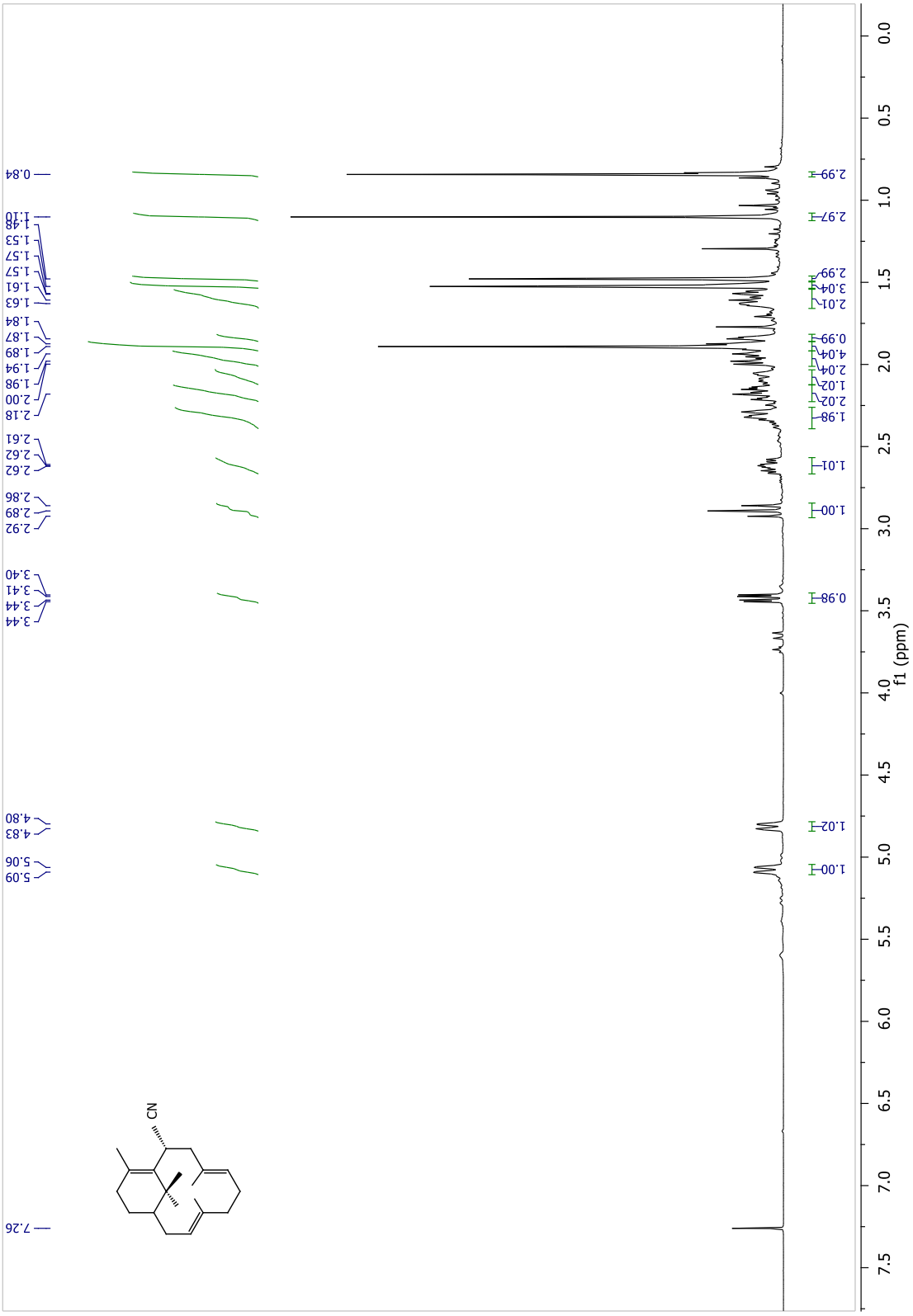
A	B	C	D	Angle/°	A	B	C	D	Angle/°
C9	C10	C11	C15	62.05(15)	O1	C4	C5	C6	-99.87(12)
C10	C9	O2	C8	120.23(11)	O1	C5	C6	C7	171.00(10)
C10	C11	C12	C13	81.18(12)	O2	C8	C9	C10	-96.78(12)
C10	C11	C15	C1	-81.07(12)	O2	C9	C10	C11	172.05(10)
C10	C11	C15	C22	40.18(13)	O5	C17	O4	C16	1.18(17)

Table 8 Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 129.

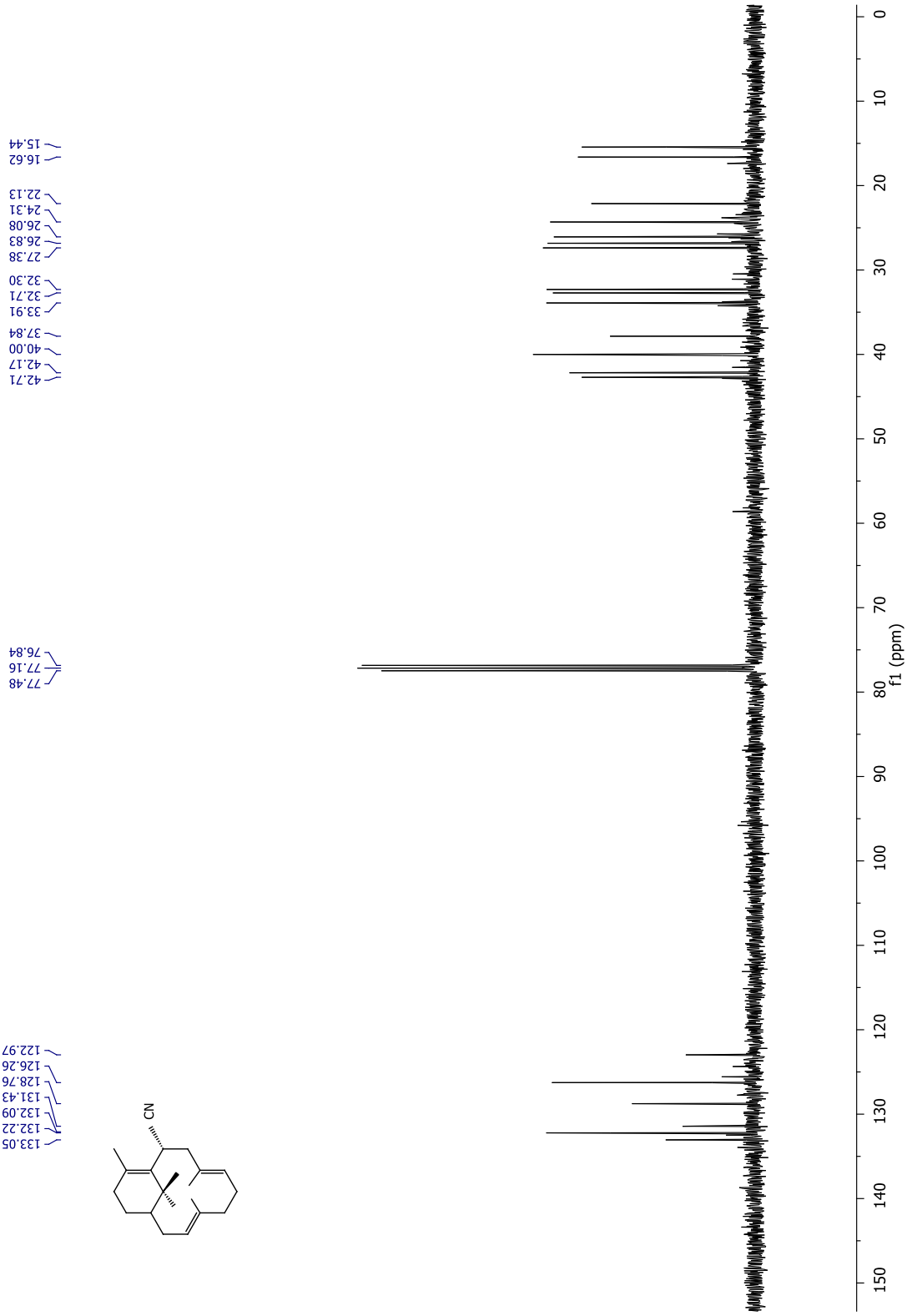
Atom	*x*	*y*	*z*	U(eq)
H1	5517	6681	7818	15
H2	6085	5369	9149	17
H3A	7657	6450	9409	19
H3B	7443	6984	8416	19
H5	6454	8765	8037	19
H6A	5888	10717	8821	23
H6B	5262	9737	9318	23
H7A	4351	10771	8010	24
H7B	4991	9946	7418	24
H9	4425	8043	6829	22
H10A	2790	6810	6612	24
H10B	2955	6714	7669	24
H11	3304	4846	7089	20
H12A	4305	4361	6092	23
H12B	3719	5585	5700	23
H13A	5119	6837	6130	20
H13B	5443	5699	5546	20
H16A	6757	3697	8319	22
H16B	7669	4619	8201	22
H18A	8708	4270	10978	43
H18B	9705	3684	10687	43
H18C	8734	2827	10696	43
H19A	6546	7135	10525	27
H19B	5476	7113	9920	27
H19C	5924	8405	10335	27
H20A	3182	9522	8958	32
H20B	3945	8397	9236	32
H20C	2892	8123	8643	32
H21A	7537	6054	7189	26
H21B	6831	7229	6896	26
H21C	7114	6268	6159	26
H22A	3540	5227	8705	26
H22B	4276	6408	8801	26
H22C	4639	5101	9252	26

Atom	*x*	*y*	*z*	U(eq)
H23A	4048	3308	7935	30
H23B	5173	3400	8428	30
H23C	4958	3360	7362	30
H3	6626	4161	6385	27

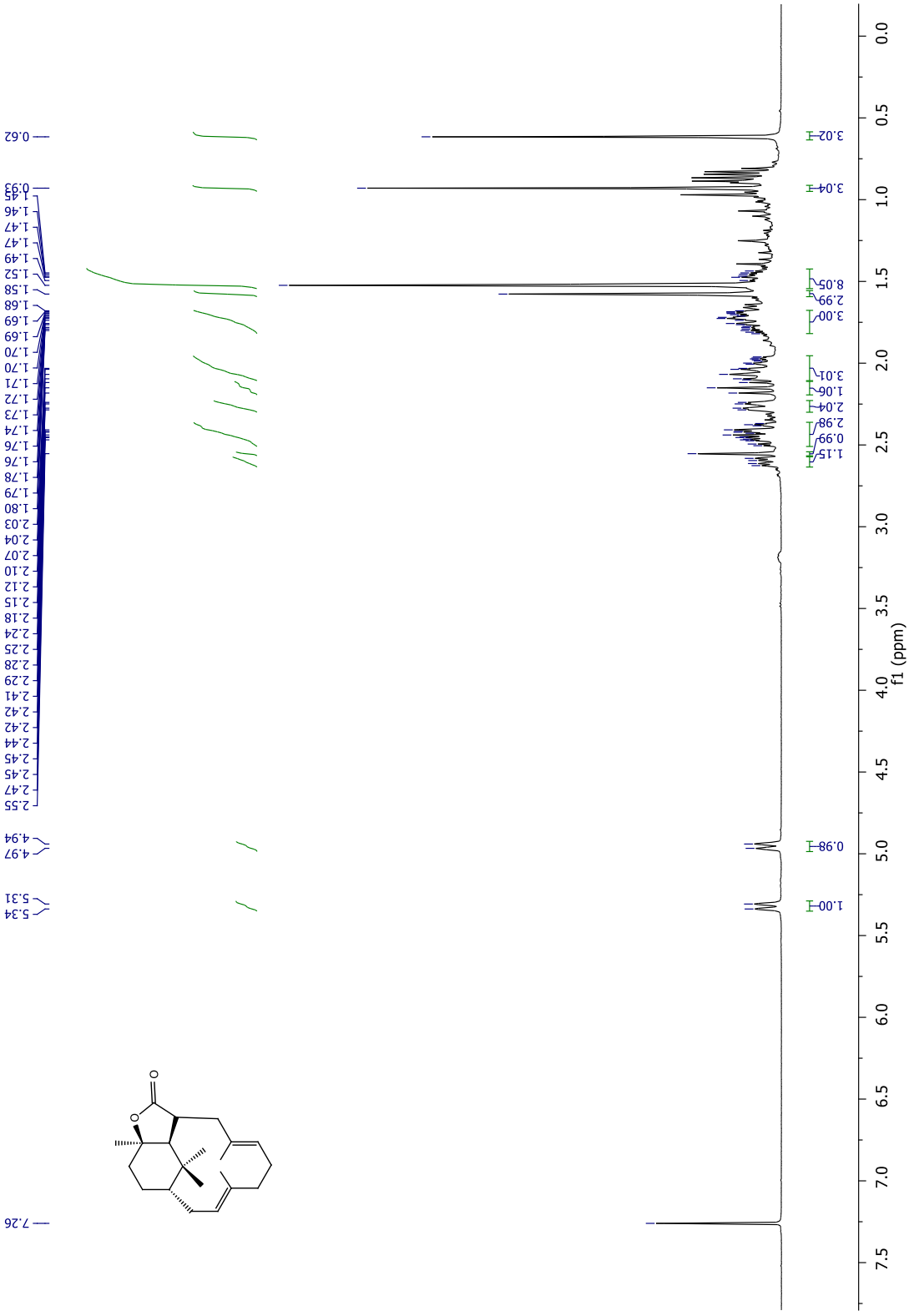
Appendix 1: ^{1}H NMR cyanoverticillene **26**



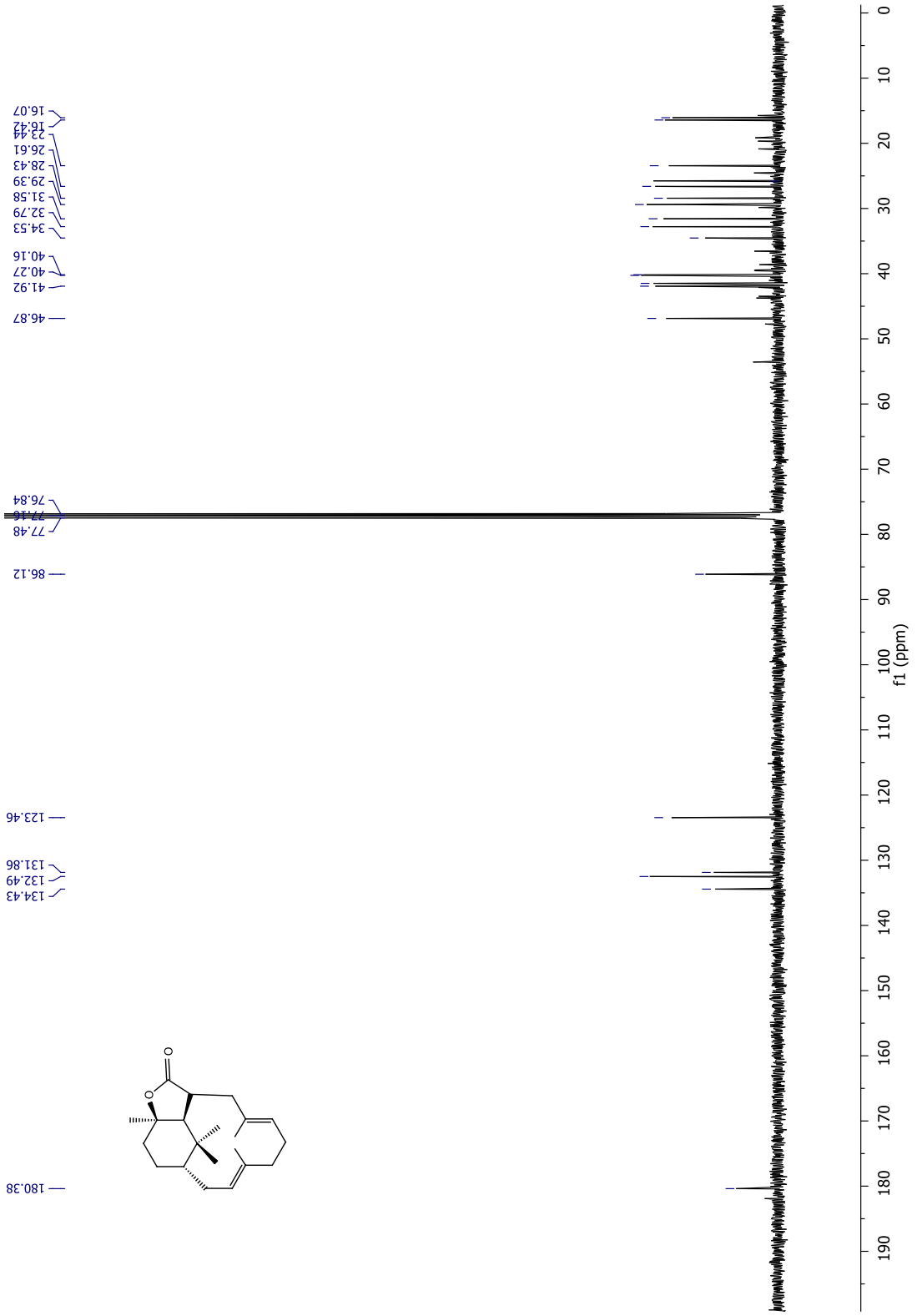
Appendix 2: ^{13}C NMR of cyanoverticillene **26**



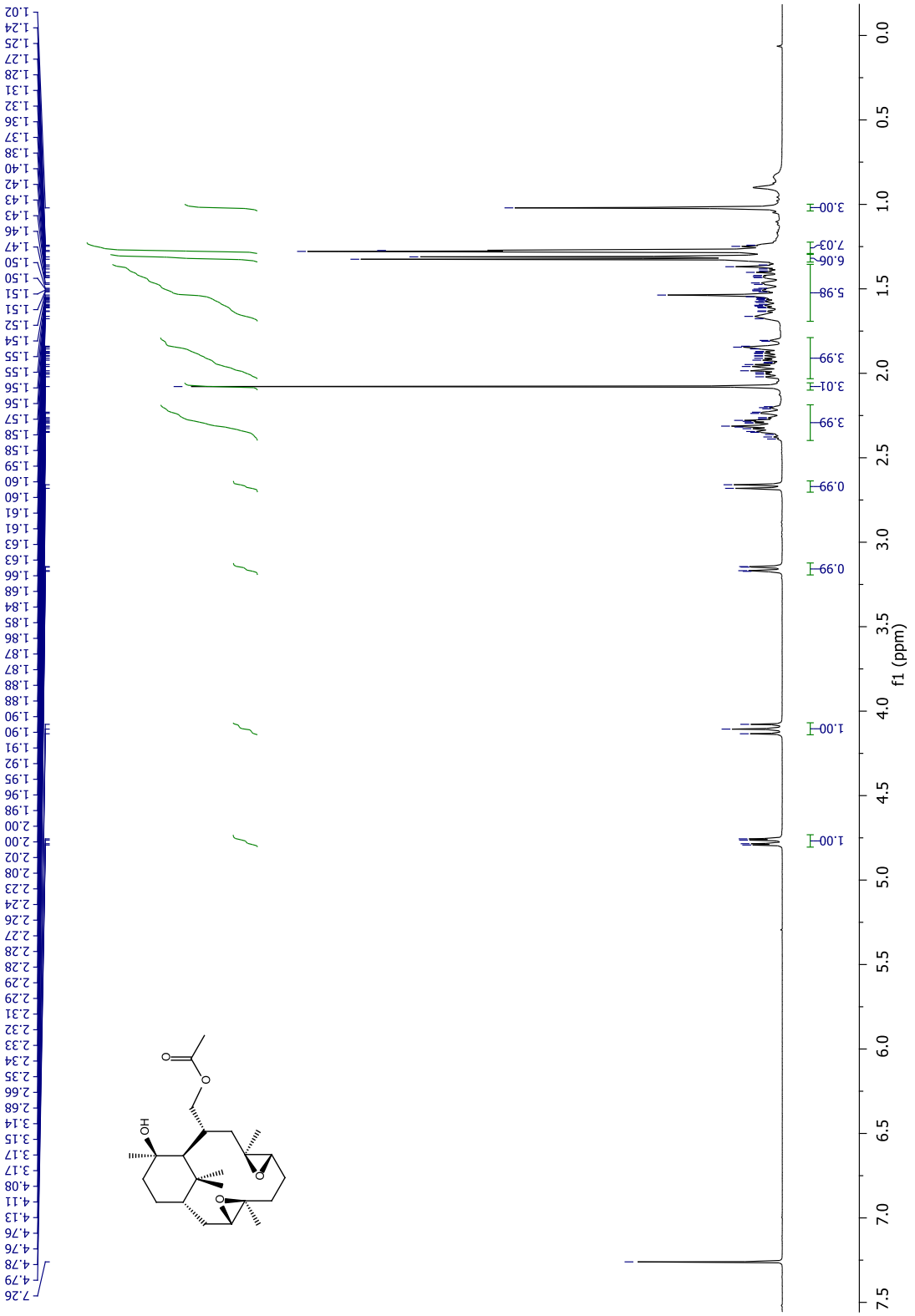
Appendix 3: ^{1}H NMR of lactone **35**



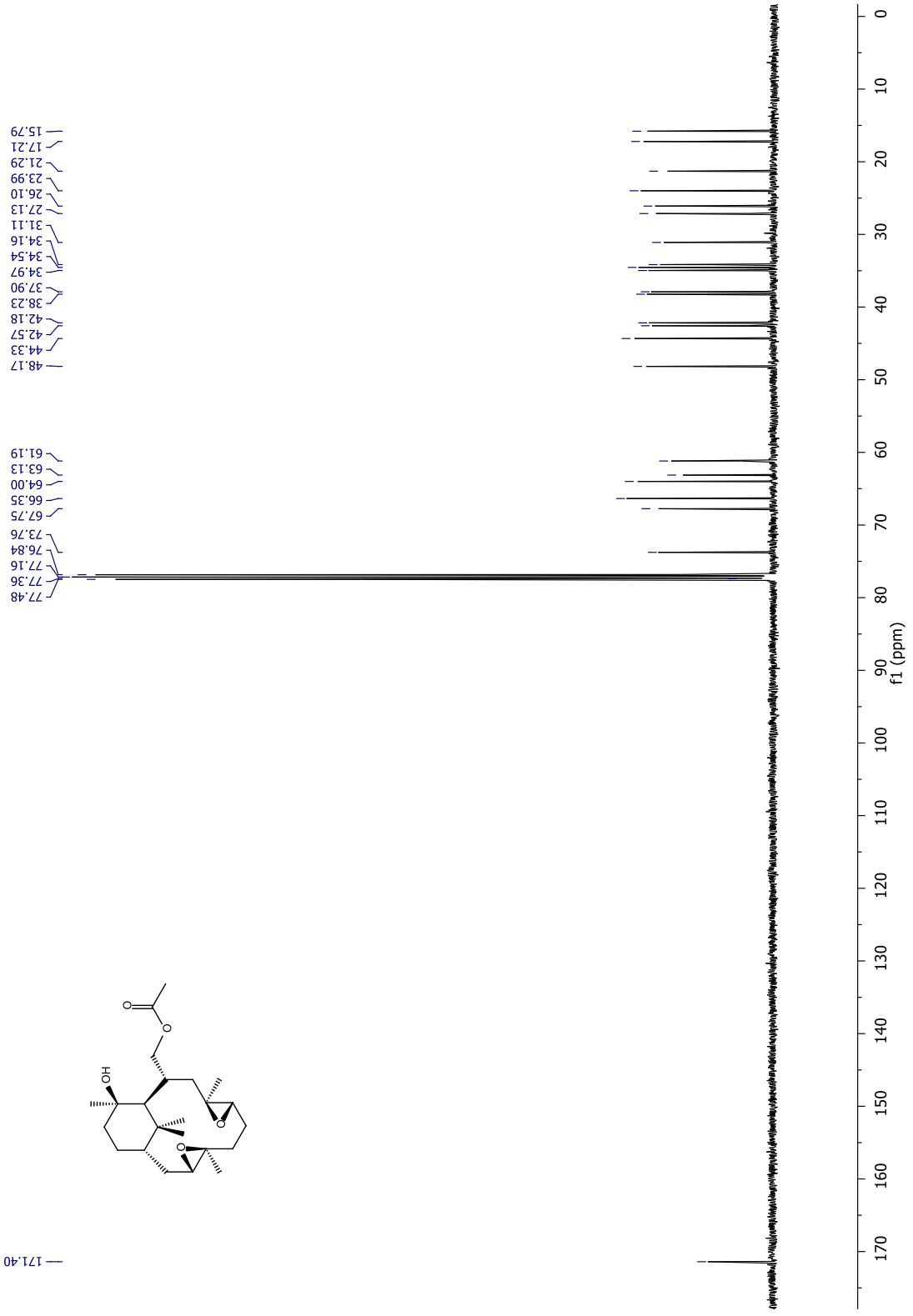
Appendix 4: ^{13}C NMR of lactone **35**



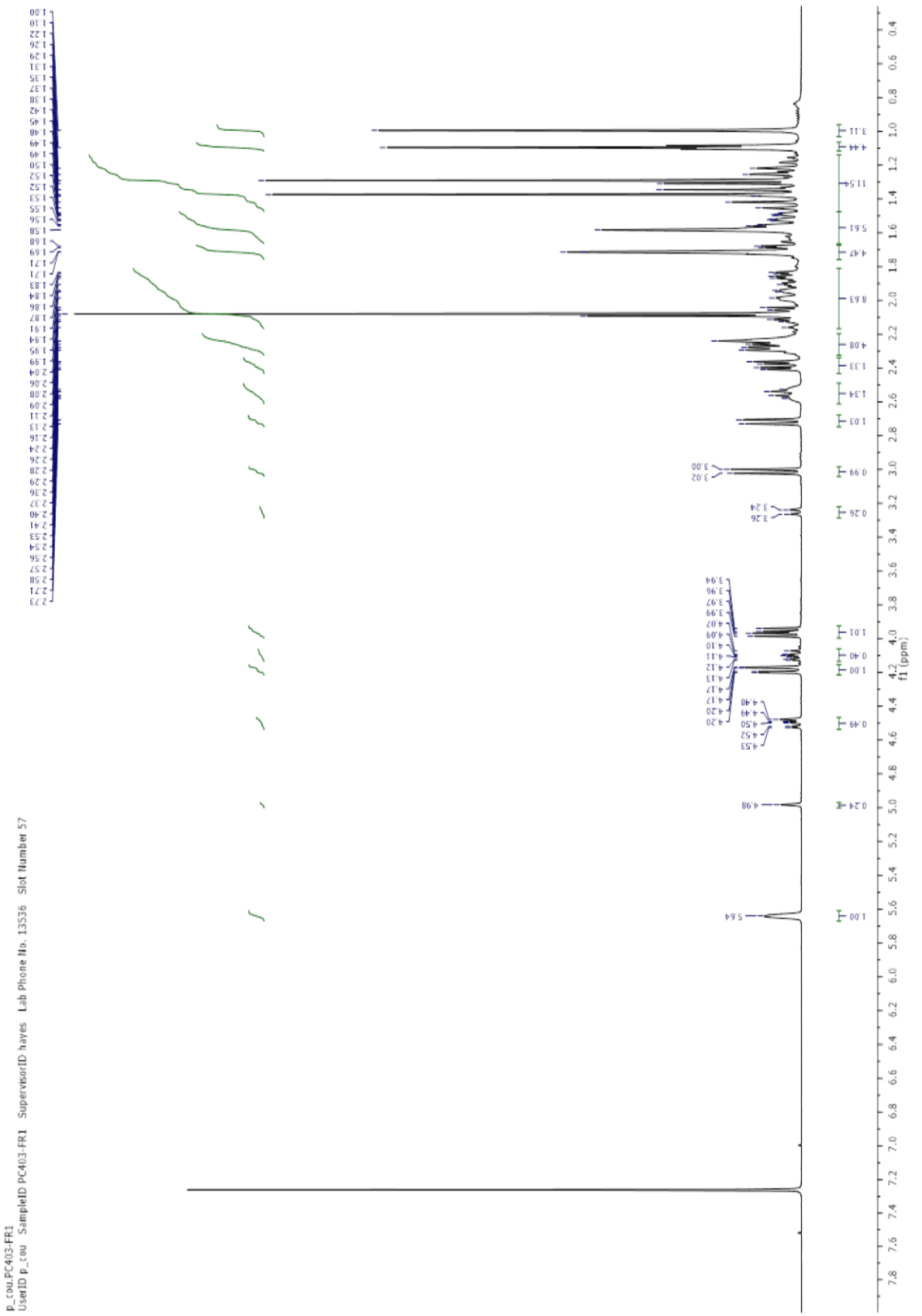
Appendix 5: ^{1}H NMR of bisepoxide **129**



Appendix 6: ^{13}C NMR of bisepoxide **129**



Appendix 7: ^{1}H NMR mixture of compound **160** and **161 (5:1)**



Appendix 8: ^{13}C NMR of mixture of compound **160** and **161 (5:1)**

