# Synthetic Approaches to the Cladiellin Diterpenes

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**at**

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**Declaration**

This work has not previously been accepted in substance for any degree and is not being concurrently submitted for candidature for any degree.

Signed …… (Natalie Laura Hewitt)

Date……

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This thesis is the result of my own investigations, except where otherwise stated. Other sources are acknowledged by footnotes giving explicit references. A bibliography is appended.

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**Abstract**

This thesis describes the result of synthetic efforts to apply a novel desymmetrisation process to the cladiellin diterpenes, an important group of natural products. The aim is to use the novel Prins-Wagner-Meerwein desymmetrisation of cyclohexa-1,4-dienes to prepare octahydroisobenzofuran structures that are closely related to the cladiellin diterpenes.

Chapter 1 presents a short review of the 2,11-cyclised cembranoids including the cladiellin diterpene structures and previous synthetic efforts, followed by a brief discussion of the Prins cyclisation. This is followed by a description of previous work carried out within the Elliott group on the Prins desymmetrisation of cyclohexa-1,4-dienes that sets the stage for the work described in chapters 2 – 5.

Chapter 2 describes the alkylation of cyclohexa-1,4-dienes using *n*-BuLi and TMEDA to give a direct and highly diastereoselective route to the corresponding 4-substituted products in which the alkyl group introduced is *trans* to the carboxylic acid.

Chapter 3 describes the attempted application of Prins cyclisation/rearrangement methodology to the core of the cladiellin diterpenes. This was successful for a model compound containing a 6-membered ring, but when applied to compounds containing 7- and 9-membered rings, macrocyclic dimeric products were obtained.

Chapter 4 describes an alternative synthetic strategy from that attempted in Chapter 3, to construct the cladiellin diterpene framework using a 6,5-fused system and cleaving of this to give a 9-membered ring system.

Chapter 5 describes the successful synthesis of a model compound containing a fused aromatic ring using the strategy developed in Chapter 4.

**Acknowledgements**

Firstly, I would like to thank my son Tyler-Jay for allowing me to write my thesis, even though he would much prefer me to be in the garden playing ball, I'm sure he will realise one day that I did this for him. I would like to thank my husband Liam for giving me the courage and support to succeed during the good and bad times.

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I'd also like to thank Steven Raw at AstraZeneca for his input into the project and for his help while I was on placement.

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Finally, I'd like to thank AstraZeneca and the EPSRC for providing the funding for this project.

**Dedication**

*I dedicate this thesis to my son Tyler-Jay Hewitt. Without him this wouldn't be possible.*

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**Abbreviations**

| | |
|---|---|
| Ac | Acetyl |
| acac | Acetylacetonate |
| AIBN | 2,2'-Azobisisobutyronitrile |
| APCl | Atmospheric Pressure Chemical Ionisation |
| AP | Atmospheric Pressure |
| Bn | Benzyl |
| Bz | Benzoyl |
| Cbz | Benzyloxycarbonyl |
| 9-BBN | 9-Borabicyclo[3.3.1]nonane |
| *n*-Bu | *n*-Butyl |
| *t*-Bu | *t*-Butyl |
| *m*-CPBA | *m*-Chloroperoxybenzoic acid |
| COSY | Correlation Spectroscopy |
| cAMP | Cyclic adenosine monophosphate |
| DCM | Dichloromethane |
| d.r. | Diastereomeric ratio |
| 4-DMAP | 4-Dimethylaminopyridine |
| DMF | *N,N*-Dimethylformamide |
| DMP | Dess-Martin periodinane |
| DMS | Dimethylsulfide |
| DMSO | Dimethylsulfoxide |
| EI | Electron Impact |
| ES | Electrospray |
| e.e. | Enantiomeric excess |
| equiv. | Equivalents |
| Et | Ethyl |
| EDTA | Ethylenediaminetetraacetic Acid |
| HMBC | Heteronuclear Multiple Bond Correlation |
| HMPA | Hexamethylphosphoramide |
| HSQC | Heteronuclear Single Quantum Correlation |
| IR | Infra-red |
| *i*Pr | Isopropyl |
| LHMDS | Lithium bis(trimethylsilyl)amide |

| | |
|---|---|
| LDA | Lithium diisopropylamide |
| *m*-CPBA | *meta*-Chloroperoxybenzoic acid |
| MS | Mass Spectrometry |
| Men | Menthyl |
| PMB | *p*-Methoxybenzyl |
| Me | Methyl |
| NMR | Nuclear Magnetic Resonance |
| nOe | Nuclear Overhauser Effect |
| NOESY | Nuclear Overhauser Enhancement Spectroscopy |
| PG | Protecting group |
| Ph | Phenyl |
| PDC | Pyridinium dichromate |
| PPTS | Pyridinium *p*-toluenesulfonate |
| Pv | Pivaloyl |
| Py | Pyridine |
| Boc | *tert*-Butoxycarbonyl |
| TBS | *tert*-Butyldimethylsilyl |
| TBDMSOTf | *tert*-butyldimethylsilyl trifluoromethanesulfonate |
| TBDPS | *tert*-Butyldiphenylsilyl |
| TBAF | Tetrabutylammonium fluoride |
| TBSOTf | *tert*-butyldimethylsilyl triflate |
| TES | Triethylsilyl |
| THF | Tetrahydrofuran |
| TMCDA | *rac-trans-N,N,N'',N''*-tetramethyl-1,2-diaminocyclohexane |
| TMEDA | *N*,*N*,*N*',*N*'-Tetramethylethylenediamine |
| TFA | Trifluoroacetic acid |
| Tf | Trifluoromethanesulfonyl |
| TIPS | Triisopropylsilyl |
| TMS | Trimethylsilyl |
| TOF $AP^+$ | Time of flight atmospheric pressure ionisation |

# Chapter 1

# Introduction

### 1.1. Introducing the 2,11-cyclised cembranoids

The 2,11-cyclised cembranoids are isolated from marine invertebrates of *Octocorallia* species. The 2,11-cyclised cembranoids fall into three categories of related structures; cladiellins, asbestinins and briarellins, sharing a common heterocyclic framework (**Figure 1**).[1] The cladiellins (**1**), briarellins (**2**) and asbestinins (**3**) are all comprised primarily of a rare oxatricyclic ring system, made up of octahydroisobenzofuran and oxacyclononane moieties. The briarellins and asbestinins also feature an additional 7-membered ether bridge between C-3 and C-16.[2]

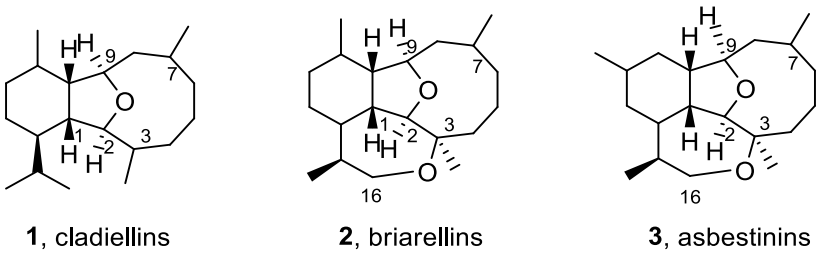
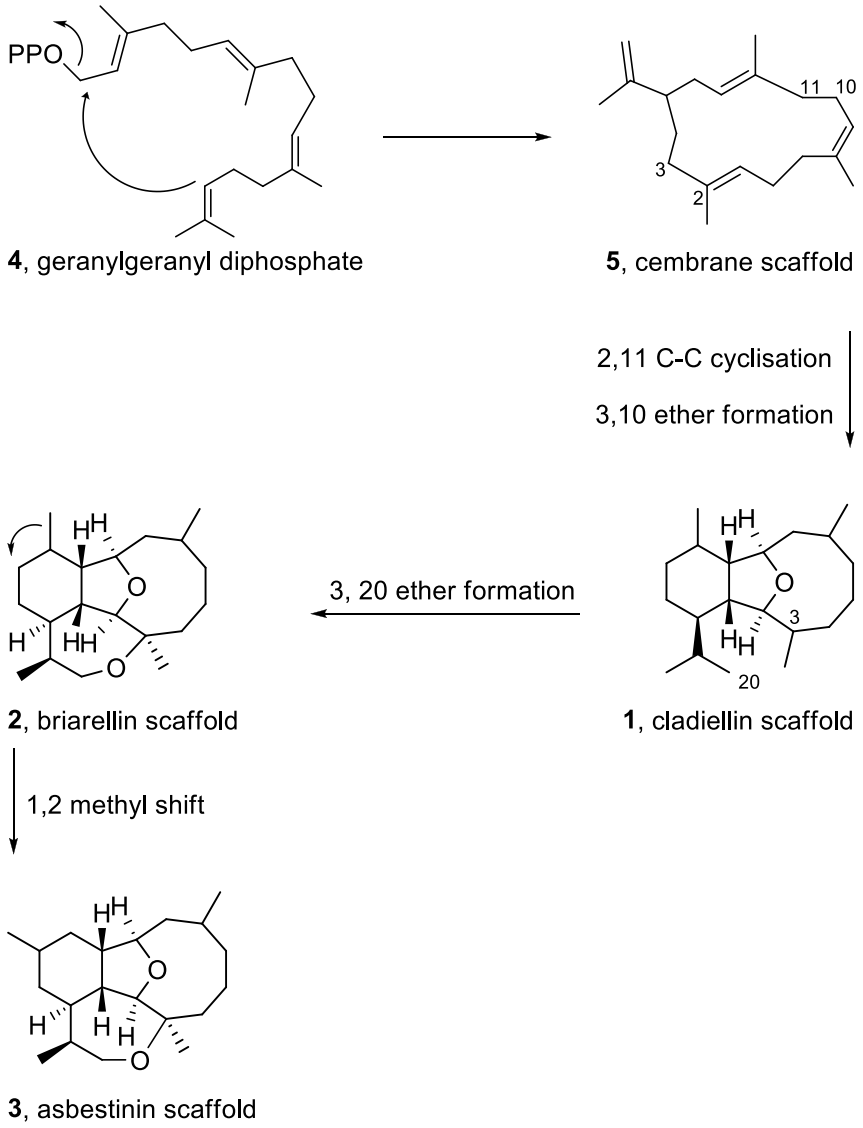



**Figure 1.** General framework of the cladiellins, briarellins and asbestinins

It is believed that 2,11-cyclised cembranoids originated from cembranoids that are biosynthesised by the macrocyclisation of geranylgeranyl diphosphate (**Scheme 1**).[1] A carbon-carbon bond-forming cyclisation takes place between C-2 and C-11. The tricyclic cladiellin structure is seen upon ether formation between C-3 and C-10. The tetracyclic briarellin structure is formed upon further ether formation between C-3 and C-20, which could then undergo a 1,2-methyl shift to give the asbestinin structure, **Scheme 1**.

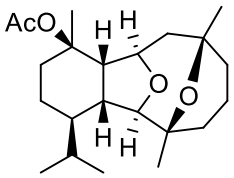



**Scheme 1.** Proposed biosynthetic pathway to 2,11-cyclised cembranoids

The cembranoid natural products are known for their protective biological activities. These include ichthyotoxic, molluscicidial and gastropod-repellent activities, as well as lethalities to brine shrimp and the ability to inhibit the cell division of starfish eggs at low concentration.[1]

The relative configuration of the 2,11-cyclised cembranoids has been assigned by various NMR techniques and X-ray crystallography. The earliest attempt to assign the absolute configuration was made in 1988, using circular dichroism methods.[3] As a result of this, and supported by subsequent total syntheses, the absolute stereochemical configuration of these natural products is as shown above.[2] The only exception to this is Polyanthellin A (**6**)

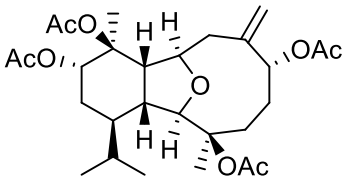
(**Figure 2**). Polyanthellin A was first isolated in 1989, with a positive specific rotation ($[\alpha]^{25}_{D}$ = +8.9°, c. 0.22, $CHCl_3$),[4] which agrees with a sample isolated in 2010 with a similar specific rotation ($[\alpha]^{25}_{D}$ = +8.0°, c. 0.73, $CHCl_3$).[5] However, in 2003 an otherwise identical sample was isolated with the opposite specific rotation ($[\alpha]^{25}_{D}$ = -9.9°, c. 1.0, $CHCl_3$),[6] which suggests that Polyanthellin A may be biosynthesised as both enantiomers.




**6**

**Figure 2.** Polyanthellin A

The cladiellins represent the most abundant class of the 2,11-cyclised cembranoids, and a member of the cladiellin family was the first of the cembranoids isolated. Eunicellin (**7**) (**Figure 3**) was isolated in 1968 by Kennard *et al.* after extraction of a species of gorgonian coral called *Eunicella stricta* off the coast of Banylus-sur-Mer in France.[7] Now there are over 100 examples known and a wide range of biological activity has been demonstrated.[1] Owing to their intriguing structure and interesting pharmacological activity, the cladiellins have seen a wide interest from a number of research groups, especially the groups of Overman,[8,9] Paquette,[9,10] Molander,[11] Kim,[12] Crimmins,[13] Hoppe,[14] Clark[15] and Johnson.[16]




**7**

**Figure 3.** Eunicellin

A prime example, which has prompted much synthetic interest, is Sclerophytin A (**Figure 4**). Sclerophytin A (**10**) shows very potent cytoxic activity against L1210 Leukaemia cells.[17] However, the structural analysis of Sclerophytin A was ambiguous. Sharma and Alam presented the structure as compound **8** following the isolation of the natural product.[17] Overman[8c] and Paquette[10a] independently reassigned the structure with a less strained arrangement of the ether bridge as shown in compound **9**. However, after completing total syntheses of compound **9**, the spectroscopic data were not identical with those of the natural product. Following this, upon re-examination of the closely related natural product Sclerophytin B (**11**), Overman and Paquette assigned the actual structure of Sclerophytin A as structure **10** (**Figure 4**) without the presence of the second ether bridge. In 2001 they confirmed this assignment by the independent total synthesis of Sclerophytin A (**10**). The compound has also shown anti-invasive and antimetastatic activities towards PC-3 human prostate cancer[5] and has shown to be a cAMP phosphodiesterase inhibitor providing anti-inflammatory activity.[2] Other cladiellins have also shown antibacterial properties.[18]

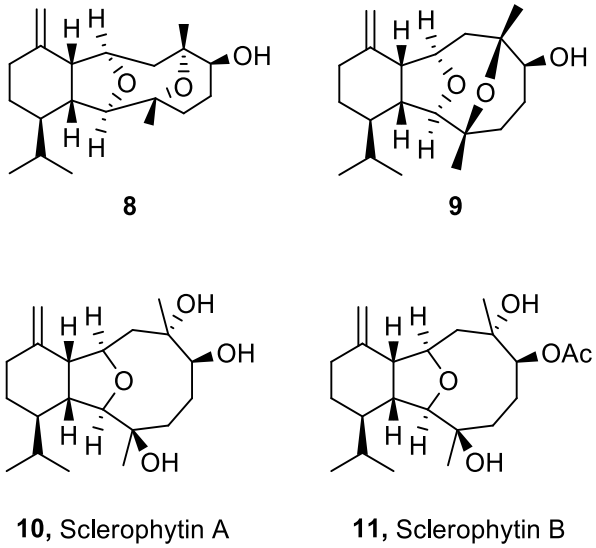
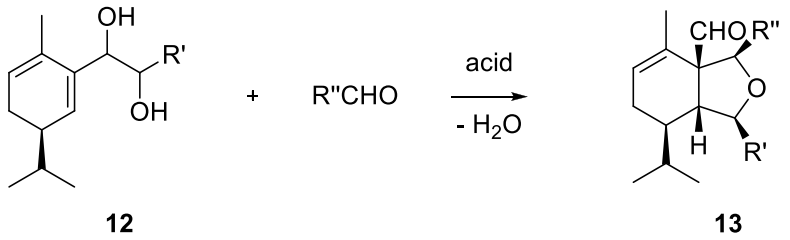



**Figure 4.** Revised structures of Sclerophytin A (**10**) and B (**11**)

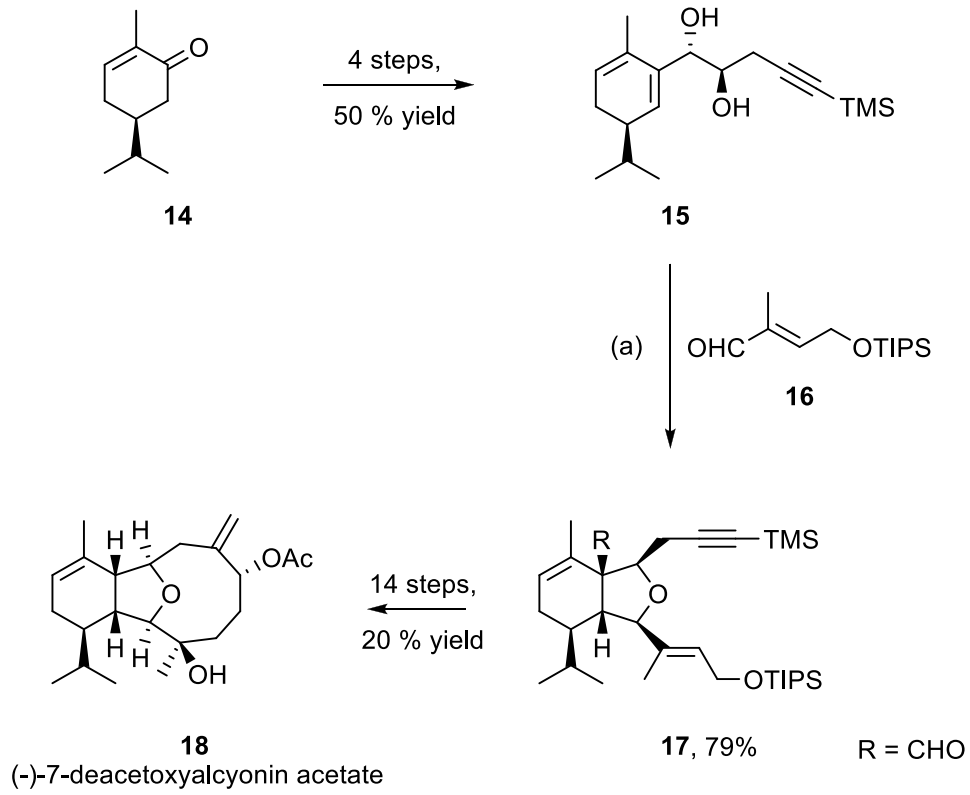
### 1.2. Synthetic approaches to the Cladiellin Diterpenes

The first synthesis of a cladiellin diterpene was that of (-)-7-deacetoxyalcyonin acetate (**18**), reported by Overman in 1995.[8a] The key reaction used by Overman *et al.* for the total synthesis of compound **18** was their stereoselective Prins-pinacol condensation-rearrangement[19] of a dienyl diol with an aldehyde to give the 2-oxabicyclo-[4.3.0]non-4-ene **13** (the isobenzofuran core) as shown in **Scheme 2**.



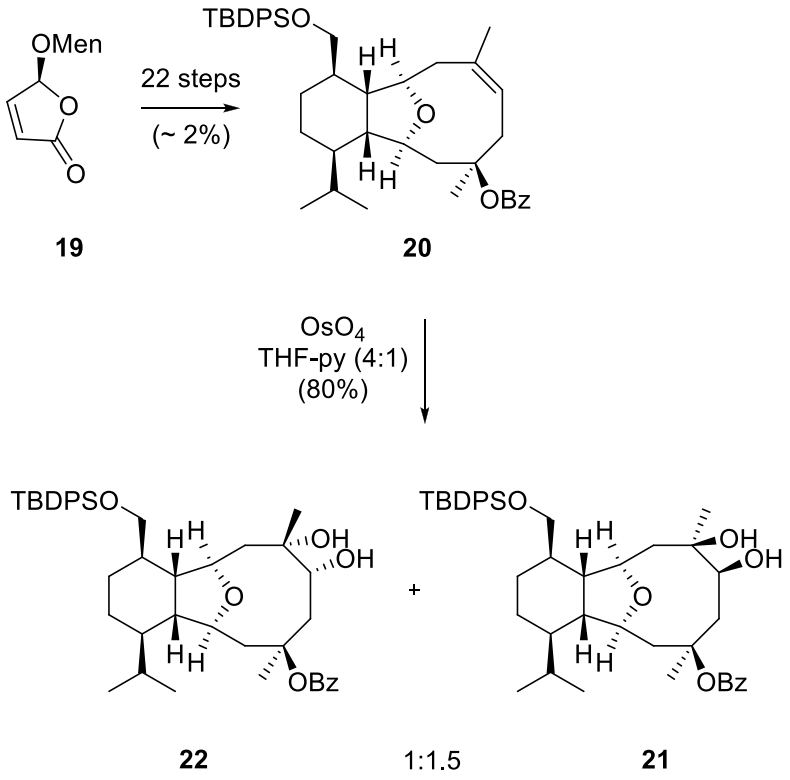

**Scheme 2.** The Prins-pinacol reaction

An enantioselective total synthesis of (-)-7-deacetoxyalcyonin acetate **18** (**Scheme 3**) was then achieved in a further 14 steps.[8a] This total synthesis confirmed the relative and absolute stereochemical configuration of (-) -7-deacetoxyalcyonin acetate **18** as reported by Uchio and co-workers.[20]



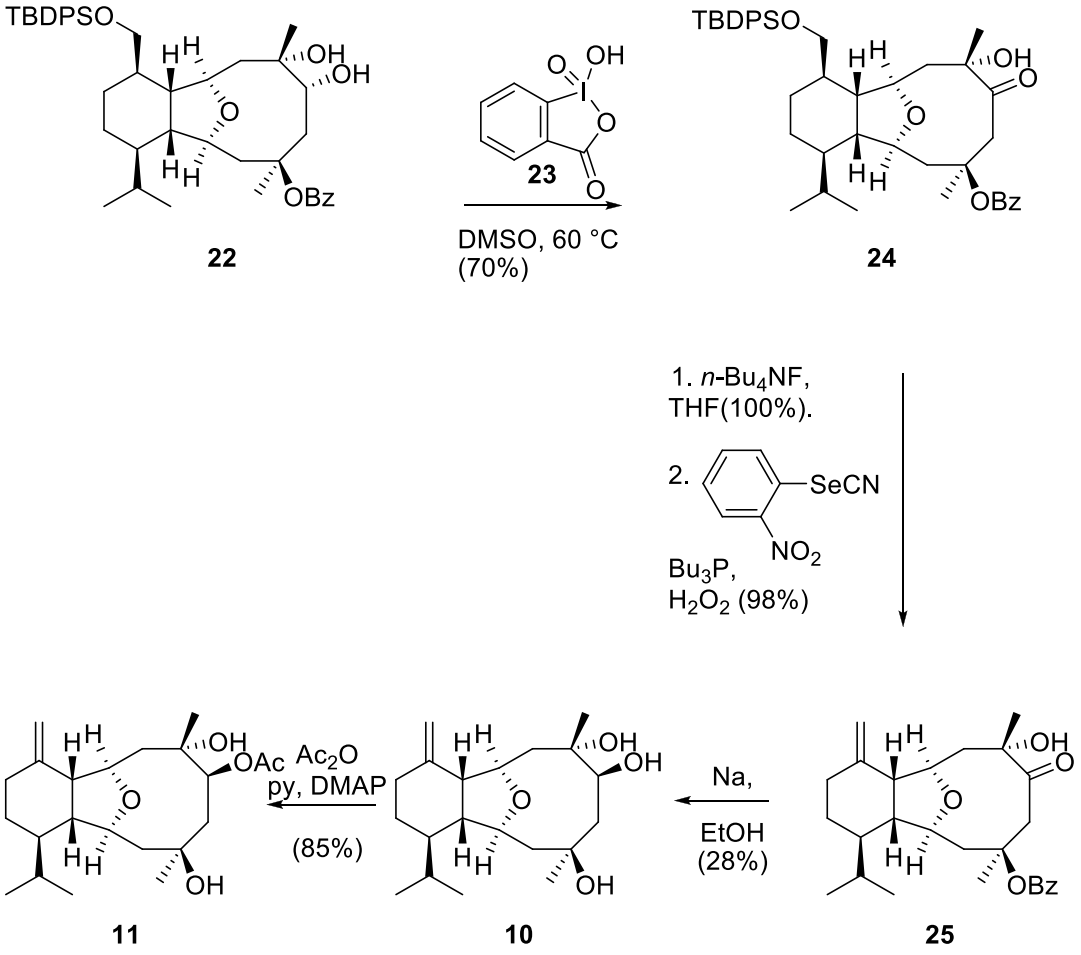

**Scheme 3.** Enantioselective total synthesis of (-)-7-deacetoxyalcyonin acetate (**18)** by Overman.[8a] *Reagents and conditions*: (a) $BF_3.OEt_2$, $CH_2Cl_2$, -55 °C to -20 °C

Both Overman and Paquette reported a total synthesis of Sclerophytin A (**10**) in 2001. [8c,9,10a] For the Overman group, the synthesis of Sclerophytin A (**10**) will be discussed later (page 23)**.** The Paquette group's syntheses of Sclerophytins A (**10**) and B (**11**) are illustrated in **Schemes 4** and **5**. Compound **20**, a substantially functionalised cyclodecene, was obtained from compound **19** in 22 steps and *ca.* 2% yield. Dihydroxylation of compound **20** gave a 1:1.5 mixture of compound **21** and **22** (**Scheme 4**).




**Scheme 4.** Dihydroxylation of compound **20** to give a 1:1.5 mixture of compounds **21** and **22**[9, 10a]

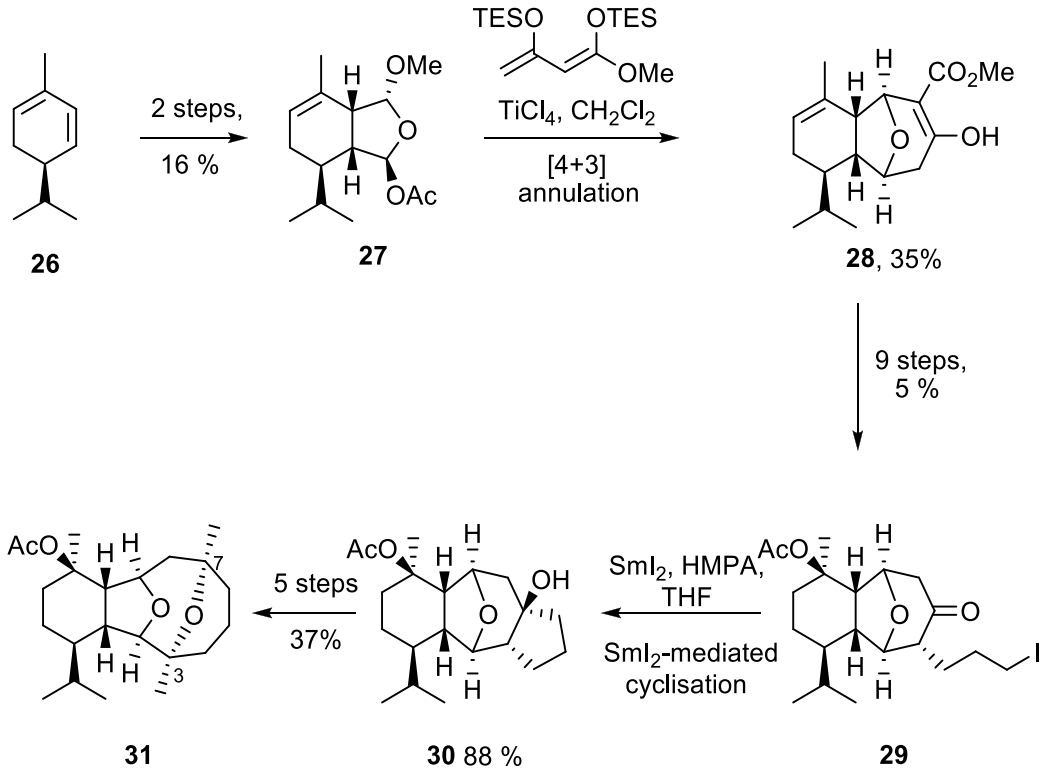
Oxidation of **22** using *o*-iodoxybenzoic acid gave **24**, the double bond in compound **25** was formed by de-silylation and elimination via the *o*-nitroselenocyanate, and then reduction of **25** using sodium in ethanol formed Sclerophytin A (**10**). Subsequent acetylation of Sclerophytin A gave Sclerophytin B (**11**).[10a]




**Scheme 5.** Total synthesis of Sclerophytin A (**10**) and B (**11**)[9, 10a]

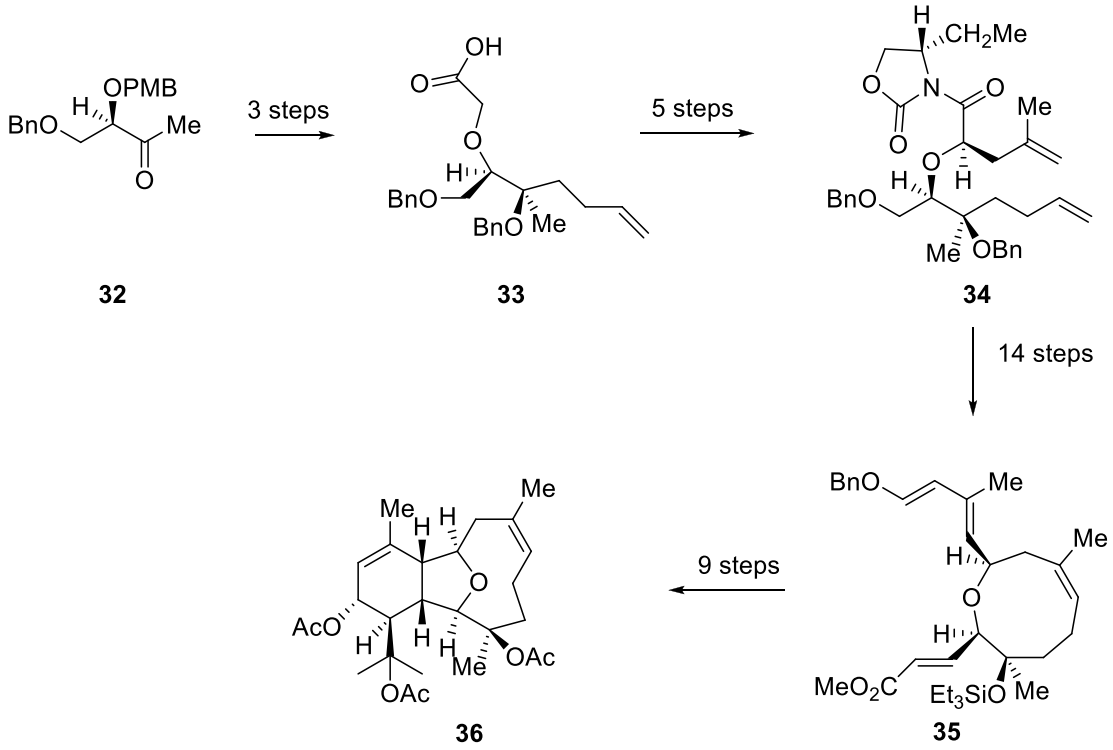
The spectroscopic data of synthetic **10** were identical to those of natural Sclerophytin A (**10**), confirming the structural revision.

Construction of medium-sized rings in compounds can be problematic. The Molander group devised a concise route for the synthesis of the cladiellin skeleton. A [4 + 3] annulation method was employed for the construction of the octahydroisobenzofuran moiety (**28**), with use of an $SmI_2$-mediated cyclisation reaction to create the medium-sized oxacyclononane subunit (**30**).[11b] The cladiellin skeleton was synthesised without the use of protecting groups in only 14 steps, from (*R*)-(-)-α-phellandrene **26**, (**Scheme 6**). A further 5 steps gave **31**, the 3,7-diastereoisomer of polyanthellin A.



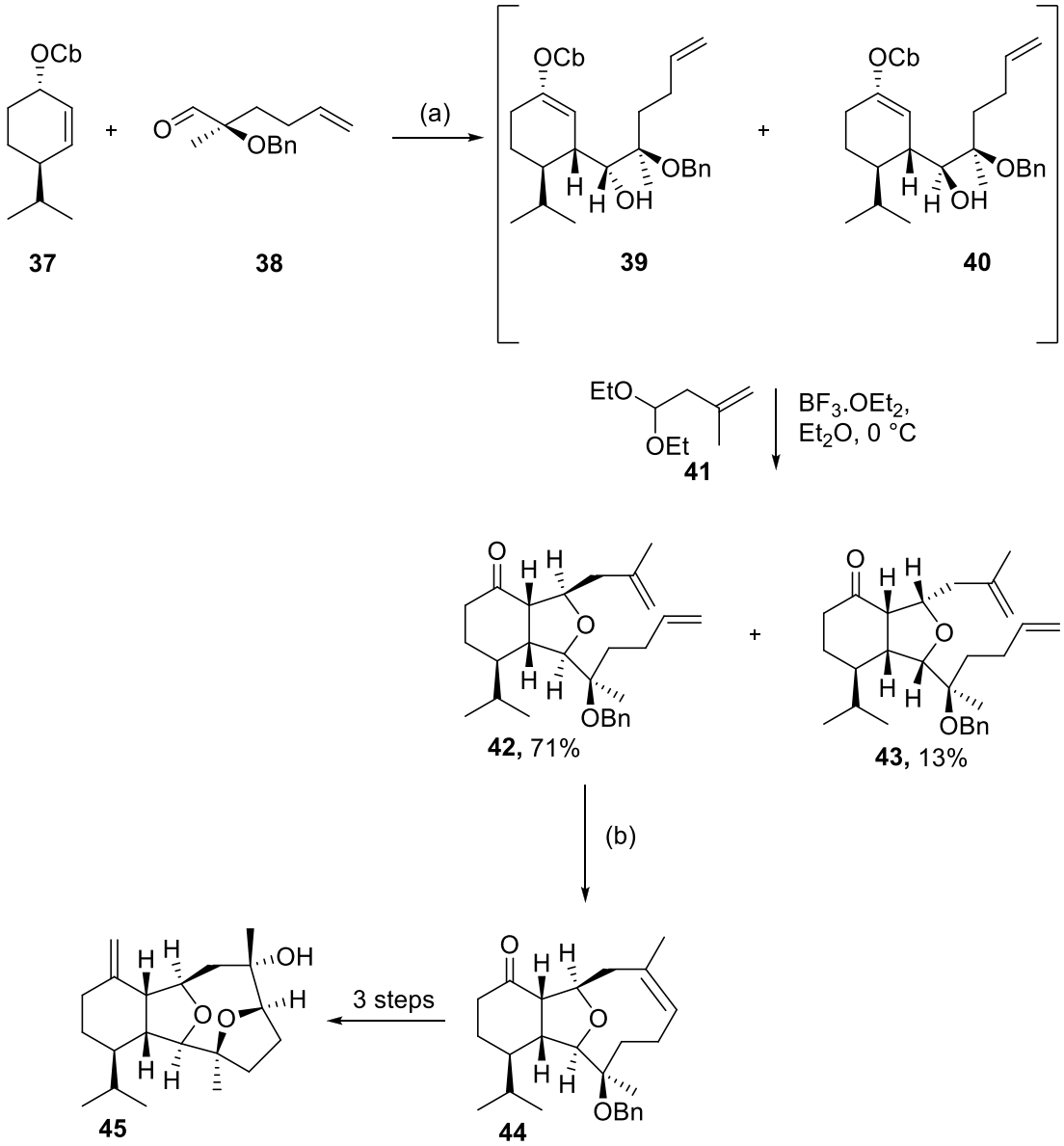

**Scheme 6.** Synthetic route towards the cladiellin skeleton (**31)** by Molander *et al*[11b]

In 2004, Crimmins and co-workers reported an enantioselective total synthesis of Ophirin B (**36**) using an intramolecular Diels-Alder strategy.[13b, 13e] Other research groups have also utilised this approach including Holmes[21] and more recently by Kim *et al.*[12] Precursor **33** was formed in 3 steps from the methyl ketone **32**. A further 5 steps gave diene **34**, which then underwent ring closure of the oxonene ring to give Diels-Alder substrate **35**. Ophirin B (**36**) was then synthesised in a further 7 steps, **Scheme 7**.



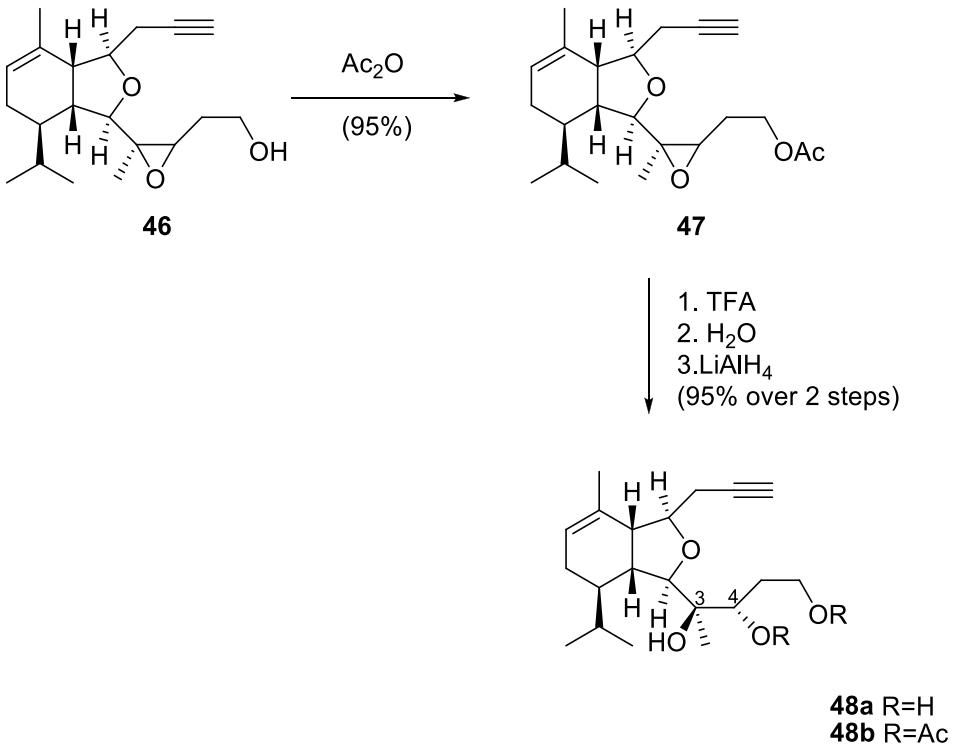

**Scheme 7**. Synthesis of Ophirin B (**36**) by Crimmins and Brown[13e]

In 2008, Hoppe *et al.* reported the total synthesis of (+)-vigulariol (**45**), using a short synthetic route from simple enantiomerically-pure starting materials.[14] The synthesis of (+)-vigulariol (**45**) was centred around three key steps; an asymmetric homoaldol reaction of carbamate **37** with α-stereogenic enal **38**, followed by Kramer THF synthesis with acetal **41**, and ring-closing metathesis of the diene **42** (**Scheme 8**).




**Scheme 8**: Synthetic route to (+)-vigulariol **45** by Hoppe *et al.*[14] *Reagents and conditions*: (a) (i) *sec*-BuLi/ TMCDA, $Et_2O$, -78 °C, (ii) $ClTi(O\textit{i}\text{-}Pr)_3$, -78 °C, (iii) **38**, -78 °C to 22 °C, (b) benzene, reflux

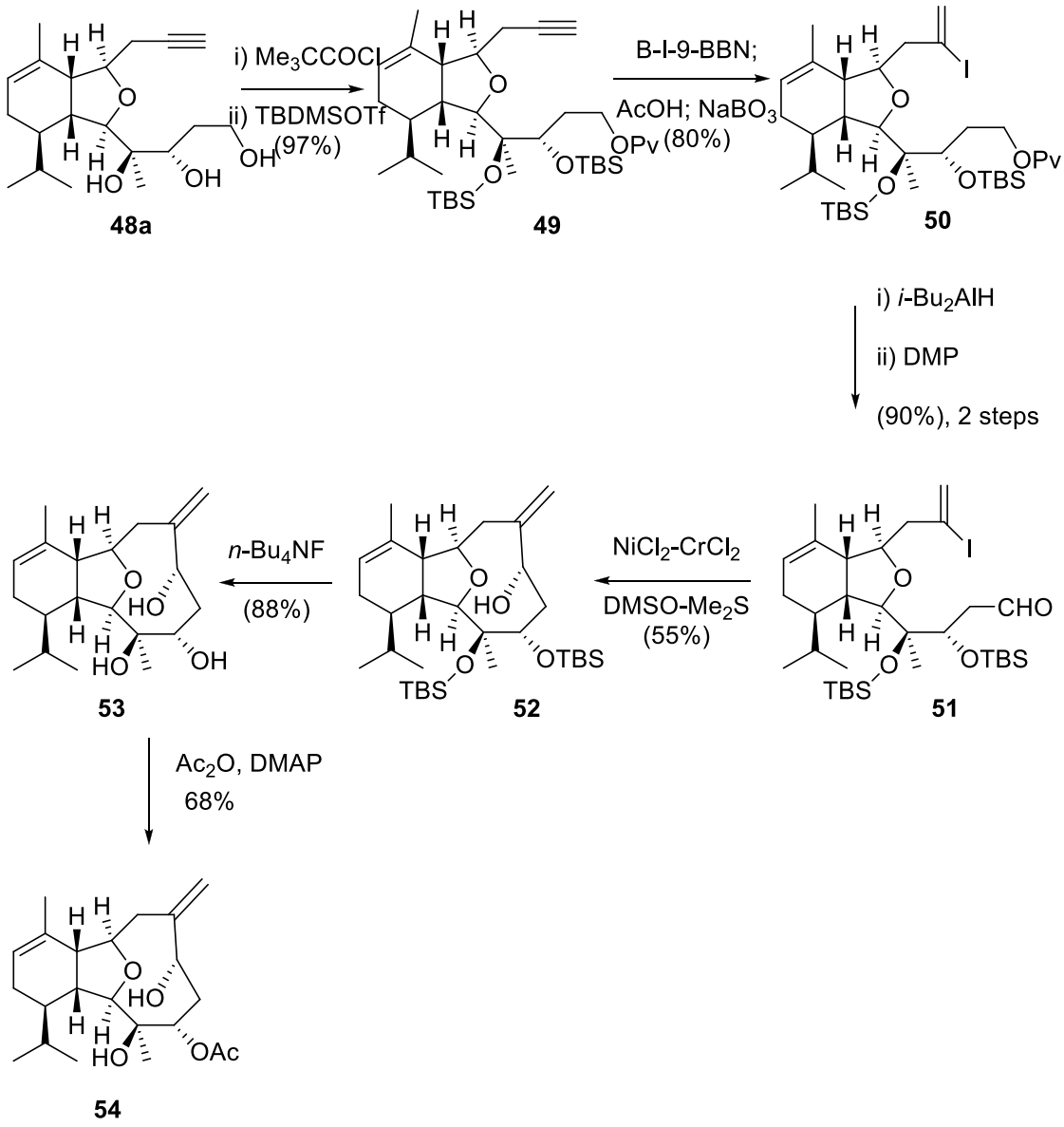
In 2003, the Overman group reported the total synthesis of the proposed structure **54** of the cladiellin diterpene alcyonin.[8g] This structure was revised in 2009, confirming the structure of the natural product as compound **55**.[8e] A nine-step synthesis starting from (*S*)-dihydrocarvone gave cis-3,4-epoxy alcohol **46** in 14% yield. Acylation of the hydroxy group in compound **46** gave epoxy ester **47** (**Scheme 9**). Epoxy ester **47** was treated with trifluoroacetic acid using the method of Giner,[22] to open the epoxide, which gave a mixture of primary and secondary acetates. The crude reaction mixture of the acetates was reduced using $LiAlH_4$ to give triol **48a.** Acetylation of **48a** at room temperature gave compound **48b**.




**Scheme 9:** Epoxy ester rearrangement and confirmation of the relative configuration at C3 and C4[8e]

Triol **48a** was then selectively protected using pivaloyl chloride and TBDMSOTf to give protected triol **49**. Iodoboration of compound **49** using *B*-iodo-9-borabicyclo[3.3.1]nonane in hexane and treatment of the resulting intermediate with acetic acid at -78 °C, followed by an oxidative work up, gave compound **50**. The pivaloyl group in compound **50** was then

cleaved with *i*-$Bu_2AlH$ and the resulting primary alcohol was oxidised with Dess-Martin periodinane to give vinyl iodide aldehyde **51**. The oxacyclononane ring in compound **51** was then closed to give compound **52** using Nozaki-Hiyama-Kishi cyclisation. The silyl protecting group of compound **52** was then removed using n-$Bu_4NF$ at room temperature and then selective acylation of the C4 alcohol of compound **53** gave compound **54**, **Scheme 10**.




**Scheme 10:** Synthesis of compound **54** by Overman and co-workers[8e]

After comparison of NMR data the Overman group noticed that the NMR data for their synthesised compound (**54**) did not resemble those for natural alcyonin.[23] After careful comparison of data along with chemical transformations of compound **54** and natural alcyonin (**55**), the Overman group concluded the revised structure of alcyonin as allylic hydroperoxide **55**, which was supported by comparison of $^{1}H$ and $^{13}C$ NMR data reported for cladiellisin (**57**) and cladiellaperoxide **56**,**Figure 5**.

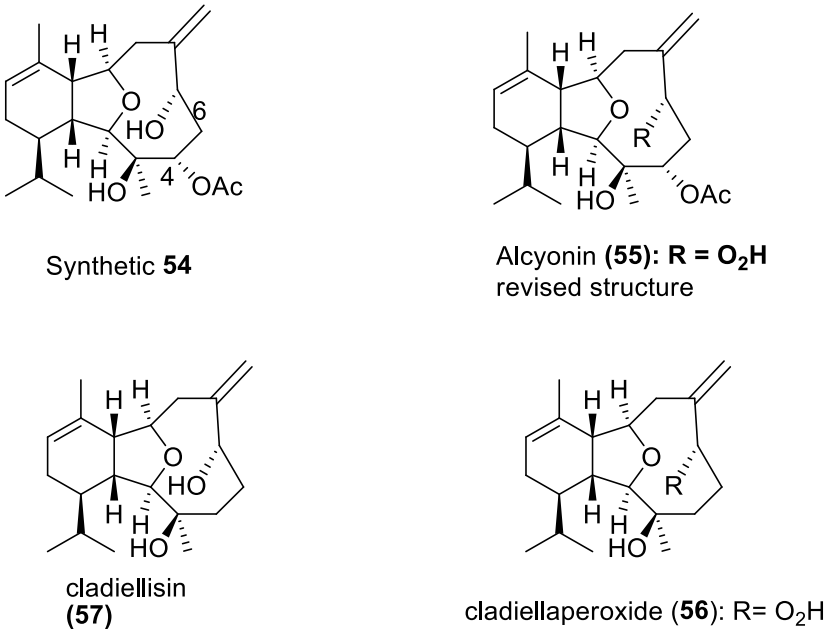
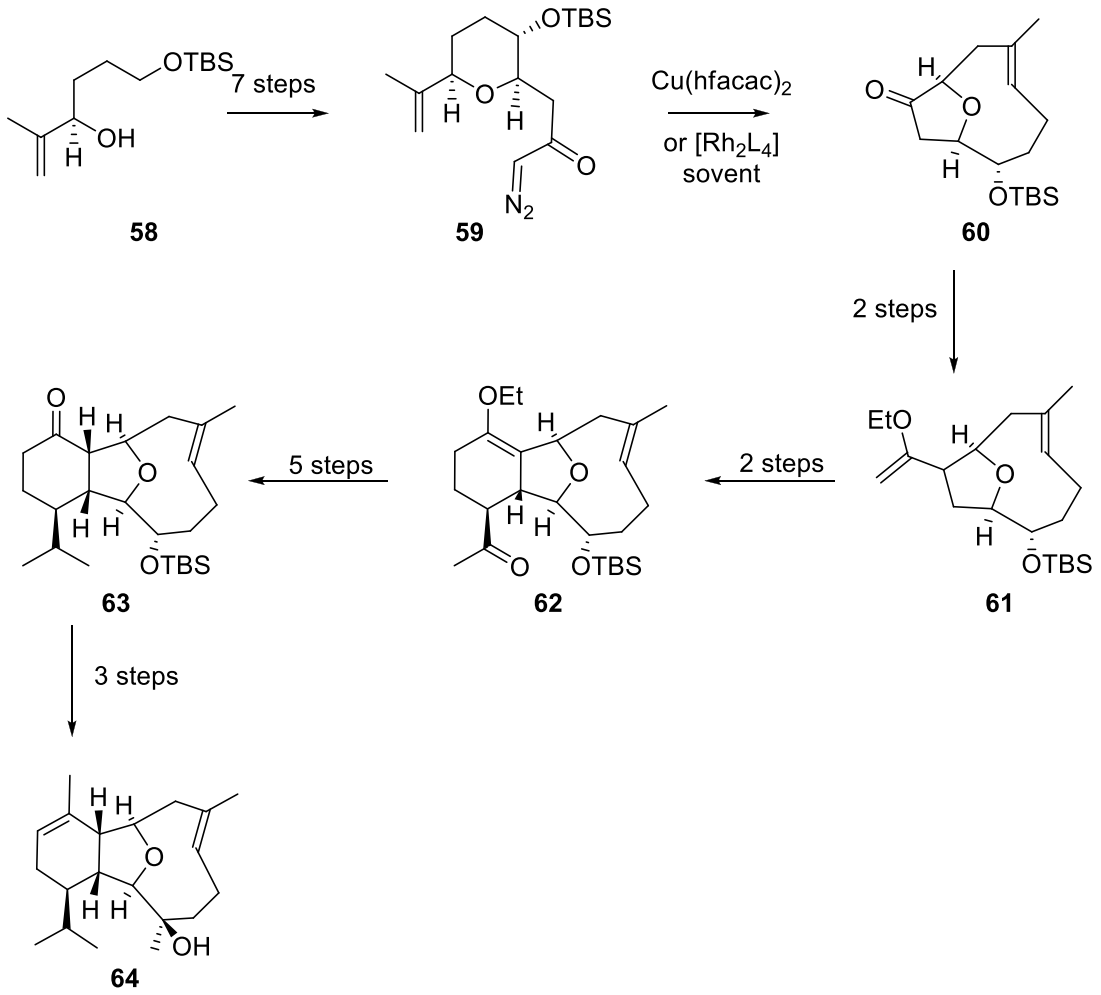


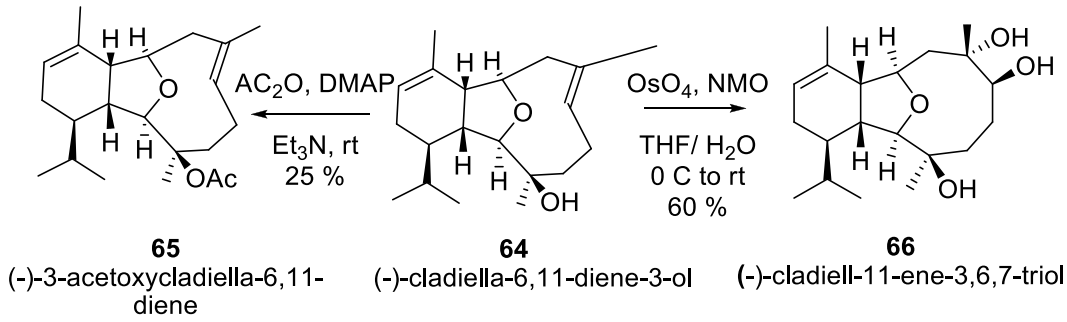

**Figure 5.** Revised structure of Alcyonin (**55**) by Corminboeuf *et al.*[8e]

In 2010 Clark *et al.* reported a general strategy for the synthesis of cladiellins possessing a (6*E*)-configuration.[15] They showed that it was possible to guide a reaction to give predominantly the *E* isomer using rhodium(II) triphenylacetate as the catalyst. This is shown through the synthesis of cladiella-6, 11-dien-3-ol (**64**, **Scheme 11**).




**Scheme 11.** Synthesis of cladiella-6,11-dien-3-ol (**64**) by Clark *et al* [15]

They then showed that cladiella-6,11-dien-3-ol (**64**) could be converted into several other cladiellin natural products, for example (-)-3-acetoxycladiella-6,11-diene (**65, Scheme 12**). This synthetic strategy that was devised by Clark *et al.* could be applied to virtually any member of the cladiellin family of marine diterpenes and is one of the two general routes to this group of natural products.




**65**
(-)-3-acetoxycladiella-6,11-diene

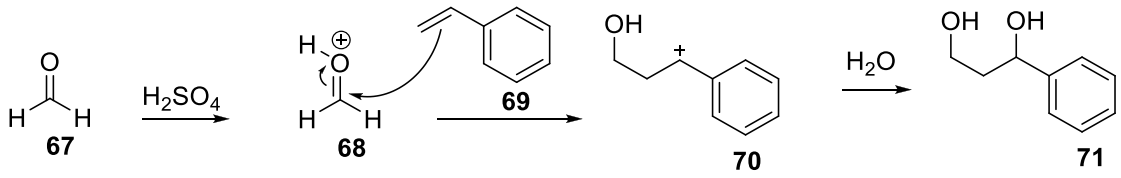
**64**
(-)-cladiella-6,11-diene-3-ol

**66**
(-)-cladiell-11-ene-3,6,7-triol

**Scheme 12.** Synthesis of (-)-3acetoxycladiella-6,11-diene and (-)-cladiell-11-ene-3,6,7-triol by Clark *et al* [15]

### 1.3. The Prins Reaction

As reported in 1919,[24] the Prins reaction is the acid-mediated addition of an alkene to an aldehyde (**Scheme 13**). The resulting carbocation **70** can react with a nucleophile to form a substitution product or lose a proton to form a homoallylic alcohol. Since 1919, the Prins reaction has broadened significantly; the nucleophile is now considered to be any π-nucleophile and the electrophile component has come to include oxocarbenium ions.[25]

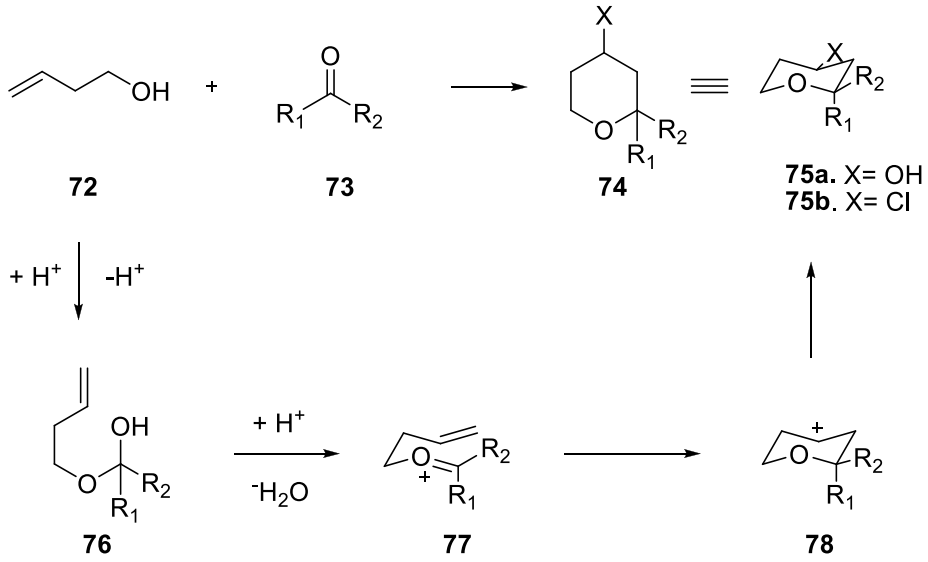



**Scheme 13.** Classical Prins reaction

In recent years, the Prins reaction has emerged as a successful strategy in natural product synthesis. The Prins reaction combines C-O and C-C bond formation and provides a selective method of forming tetrahydropyran-containing macrocyclic rings of varying sizes.[26] The yields for Prins cyclisation reactions range from good to excellent and a high degree of functionality is tolerated within the molecule. This strategy overcomes many reactivity issues associated with creating macrocyclic oxocarbenium ions and has been applied to a range of natural products.[26]

### 1.3.1. Syntheses of tetrahydropyran rings

The first synthesis of a tetrahydropyran ring using a Prins reaction was reported in 1955 by Hanschke.[27] This involved combining 3-buten-1-ol (**72**) with a variety of aldehydes or ketones in the presence of an acid (**Scheme 14**). When different acids were employed, this resulted in different products; hydrochloric acid resulted in the formation of **75b,** whilst sulfuric acid gave **75a**.

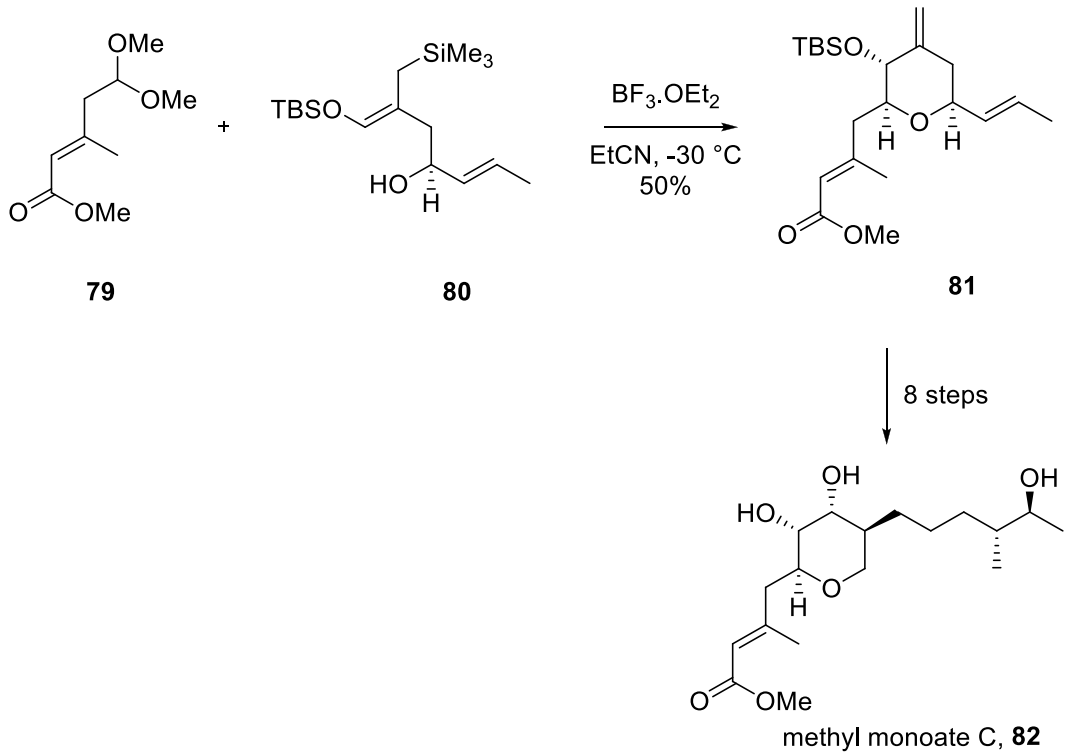



**Scheme 14.** The first report and syntheses of a tetrahydropyran ring by Prins reaction[27]

The mechanism begins with the condensation of the alcohol **72** and aldehyde **73** to give the hemiacetal intermediate **76**. The oxocarbenium ion **77** is the next intermediate, formed by acid-catalysed loss of hydroxide. The alkene then attacks the oxocarbenium ion to give a tetrahydropyranyl carbocation (**78**), which usually exists in the chair conformation. A nucleophile (chloride or water) then attacks the carbocation to give the tetrahydropyran product (**74**).

### 1.3.2. Applications in Natural Product Synthesis

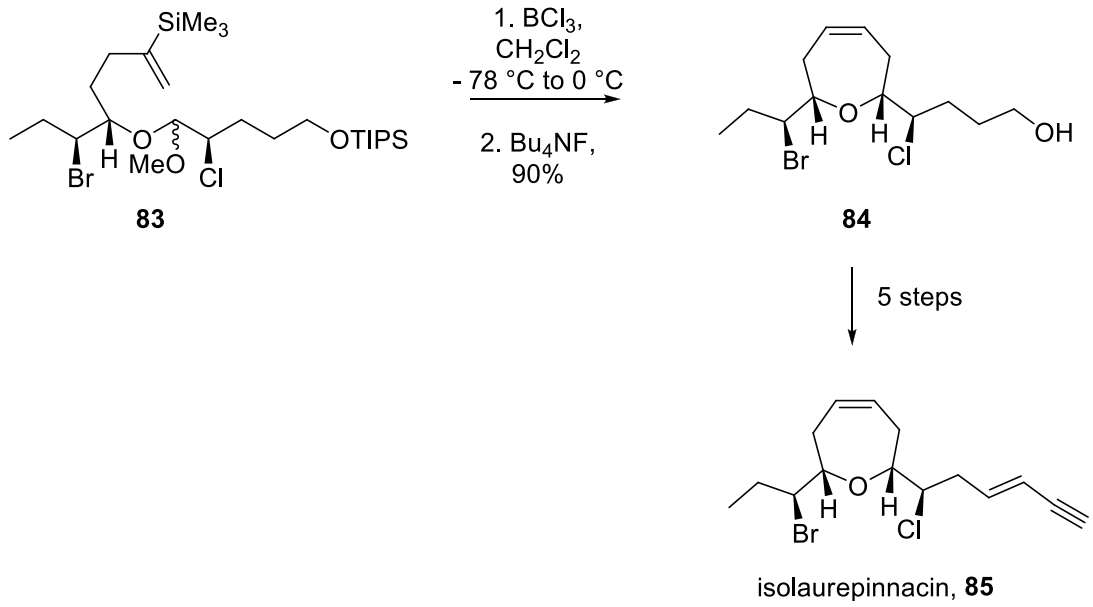
The synthesis of methyl monoate C (**82**, **Scheme 15**), an analogue of the antibiotic pseudomonic acid C, was reported by Marko and co-workers,[28] thus showing that oxygen substituents can be incorporated into Prins-type cyclisations. The reaction takes place by the $BF_3.OEt_2$-mediated condensation reaction of acetal **79** with alcohol **80**. Tetrahydropyran **81** was then produced in 50% yield after a 5 day reaction.




**79** **80** **81**

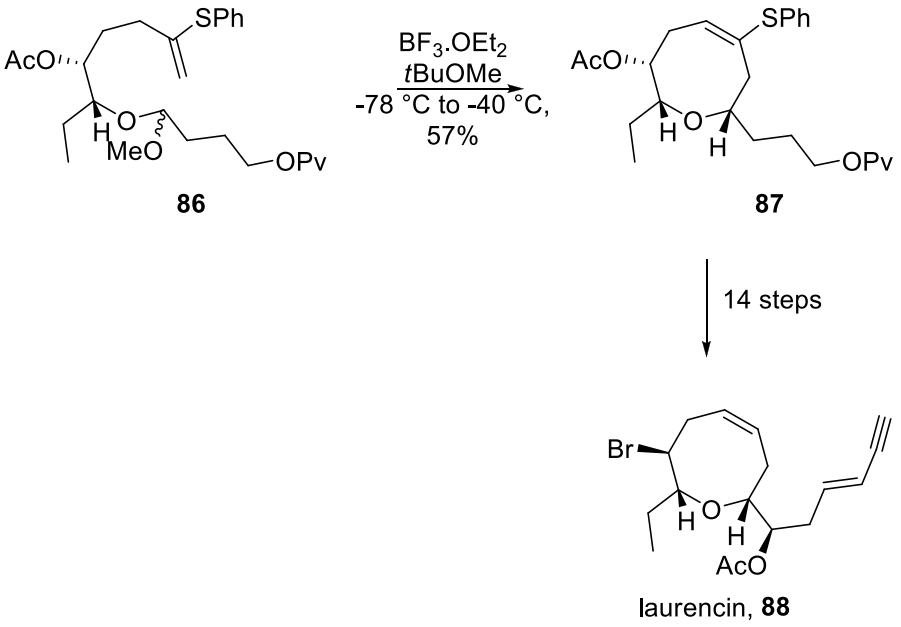
**Scheme 15.** Synthesis of methyl monoate C by Marko and co-workers[28]

Overman and co-workers reported the synthesis of isolaurepinnacin, using a Prins-type cyclisation (**Scheme 16**).[29] Oxepane **84** was produced as a single stereoisomer upon treatment of compound **83** with $BCl_3$ in dichloromethane at -78 °C, followed by $Bu_4NF$.




**Scheme 16.** Synthesis of isolaurepinnacin (**85**) by Overman and co-workers[29]

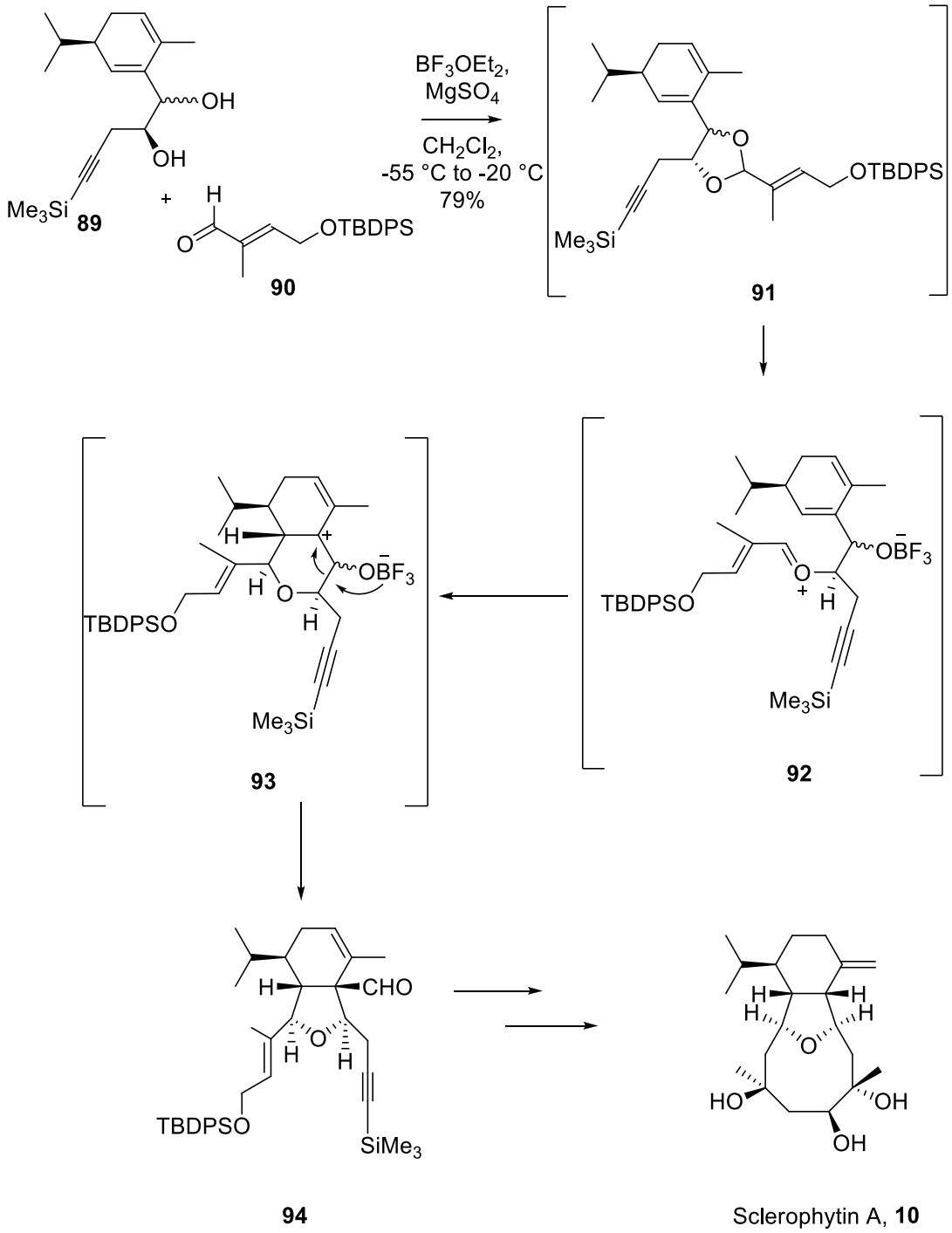
The Overman group then used a similar approach towards the total synthesis of laurencin (**88**) (**Scheme 17**).[30] Synthesis of the 8-membered ring was enhanced by the using a vinyl sulphide, **86**, as the nucleophile rather than a vinylsilane. A $BF_3OEt_2$-mediated ionisation of mixed acetal **86** gave oxecene **87** in 57% yield.




**Scheme 17.** A $BF_3OEt_2$-mediated ionisation of mixed acetal **86** in the synthesis of Laurencin (**88**)[30]

### 1.3.3. The Prins-pinacol rearrangement

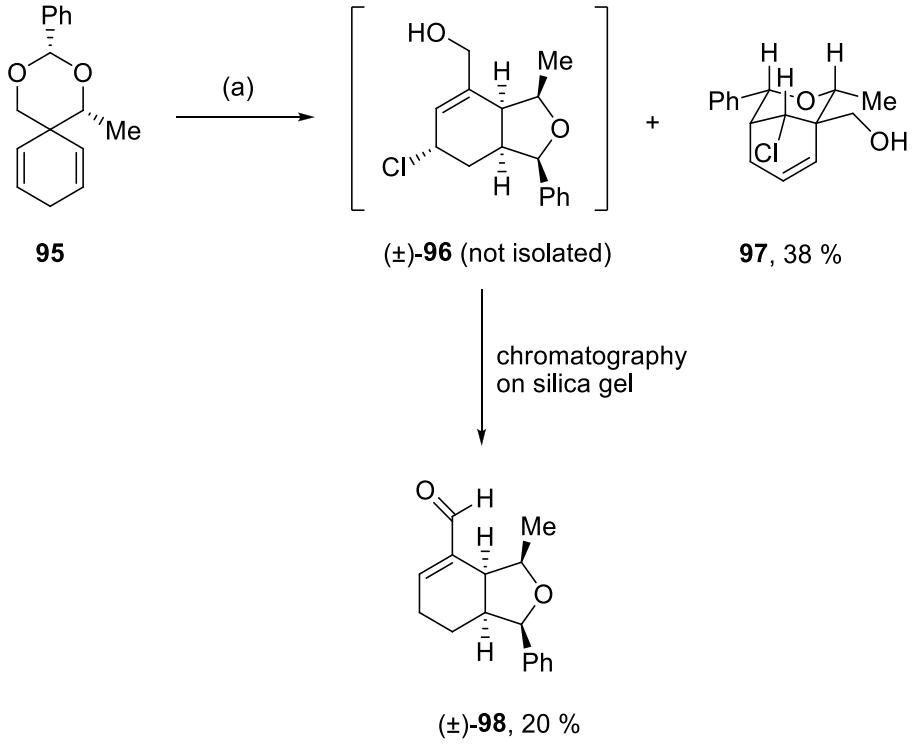
Over the years the Overman group have studied a variety of Prins cyclisation reactions, including the Prins-pinacol rearrangement used for the synthesis of Sclerophytin A[8c] (**Scheme 18**), as mentioned previously (page 8). The sequence begins with the condensation reaction of diol **89** with aldehyde **90** to give acetal **91**, which is then ionised to form oxocarbenium ion **92**. Ring-closing metathesis gave the carbocation **93** and then the Prins-pinacol rearrangement of **93** gave aldehyde **94** in 79% yield. These processes begin with simple structures and end with finished products with a major increase in molecular complexity. Also, the use of a migration reaction to quench the tetrahydropyranyl cation results in a highly atom-economical process. The Prins-pinacol reaction has been used in several other natural-product syntheses.[8c]




**Scheme 18.** Synthesis of Sclerophytin A (**10**) by Overman and co-workers using the Prins-pinacol sequence[8c]

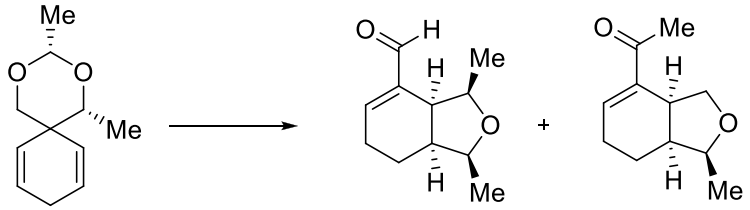
### 1.4. Diastereoselective Prins-mediated Desymmetrisation of Cyclohexa-1,4-dienes

In recent years, the Elliott group has established methodology for the desymmetrisation of cyclohexa-1,4-dienes-derived *via* a diastereoselective Prins reaction.[31] Chiral cyclohexa-1,4-diene derived acetals can be treated with a Lewis acid catalyst to effect cyclisation reactions with very high levels of stereocontrol. An example of this is the treatment of acetal **95** with $TiCl_4$ which resulted in the formation of the cyclisation products, **96** and **97**. Compound **96** was not isolated, however compound **96** was presumably converted into compound **98** upon purification (**Scheme 19**).




**Scheme 19.** The desymmetrisation of cyclohexa-1,4-diene-derived acetal **95** *via* a diastereoselective Prins reaction. *Reagents and conditions*: (a) $TiCl_4$, $CH_2Cl_2$, -78 °C, 2 h

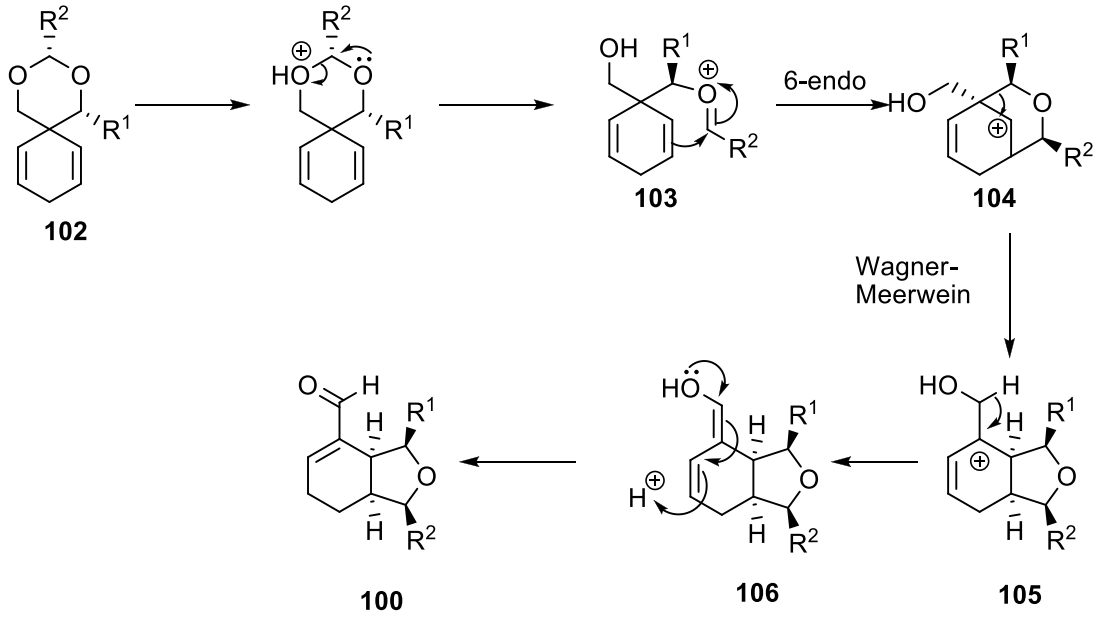
This reaction was highly diastereoselective. However the low selectivity for any one product posed a problem for any subsequent application of its methodology. This problem was overcome by the use of an acid catalyst with a non-nucleophilic counter-ion.[32] Triflic acid was used as a replacement for $TiCl_4$. As a result of this, acetal **99** gave predominantly aldehyde **100** along with small amounts of ketone **101,** both as single diastereoisomers (**Scheme 20**).




**99** **100**, 66% **101**, 6%

**Scheme 20.** Prins cyclisation/ rearrangement of cyclohexa-1,4-diene-derived acetal **99**. *Reagents and conditions*: (a) TfOH (1.6 equiv.), $CH_2Cl_2$, room temperature, 15 min

The proposed mechanism, shown in **Scheme 21**, explains the formation of compound **100.** Protonation of the least hindered oxygen atom of the acetal, followed by ring-opening of acetal, gives oxocarbenium ion **103**. A 6-*endo* cyclisation onto one of the diastereotopic double bonds then proceeds, followed by a Wagner-Meerwein shift to give the more stable tertiary allylic cation **105**. Deprotonation to give conjugated enol, followed by keto-enol tautomerisation, gives the aldehyde **100**. The ketone **101** arises from protonation of the more hindered oxygen atom of the acetal followed by a similar sequence.




**Scheme 21.** Proposed mechanism of Prins cyclisation and rearrangement

The outcome of this reaction shows that the size of the acid cation plays an important role in the regioselectivity. As the size of the acid is reduced from $TiCl_4$ to triflic acid ($H^+$), the regioselectivity of the acetal opening is also reduced. This is the reason for the production of small amounts of ketone **101** in the triflic acid-mediated reactions.

The major product of these Prins cyclisation/rearrangement is a hexahydroisobenzofuran, which is similar in structure to the core of the cladiellin diterpenes, for example Sclerophytin A (**10**). One major discrepancy between compound **100** and Sclerophytin is the relative stereochemical configuration. Instead of the *anti-syn-anti* relationship observed between the ring junction protons in the cladiellins (Sclerophytin), the opposite *syn* configuration is obtained in compound **100** (**Figure 6**).

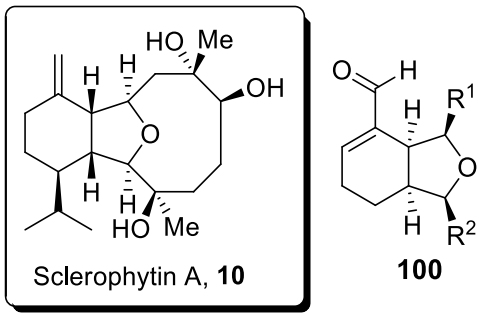
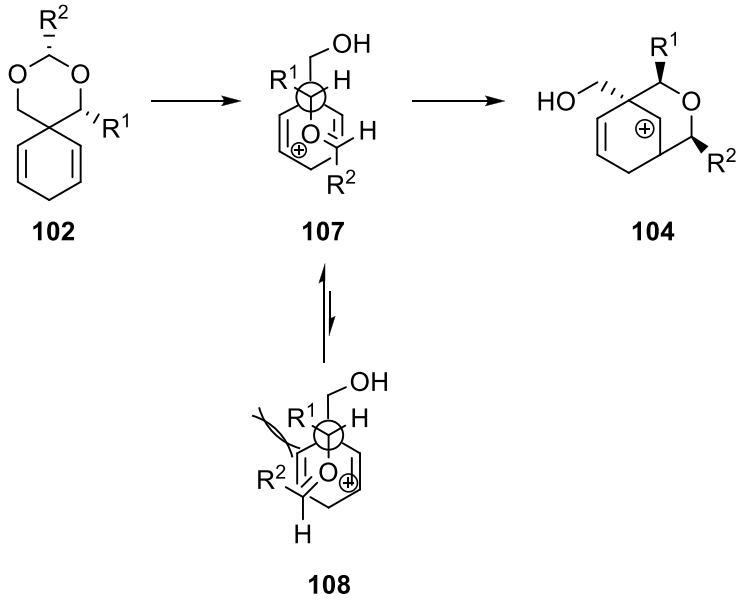


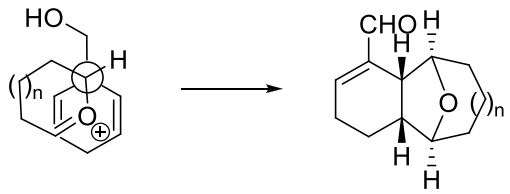

**Figure 6:** The stereochemical configuration observed between the ring-junction protons in the cladiellin, Sclerophytin A (**10**) and compound **100**

The configuration of compound **100** is determined by minimisation of $A^{1,3}$ strain in the transition state shown (**Scheme 22**).[31,32] The explanation for the stereochemical outcome is that the transition state will prefer the conformation in which $R^1$ and $R^2$ are furthest away from each other as in conformer **107**, minimising steric interactions.




**Scheme 22.** Origin of the stereochemical outcome of the Prins cyclisation/rearrangement

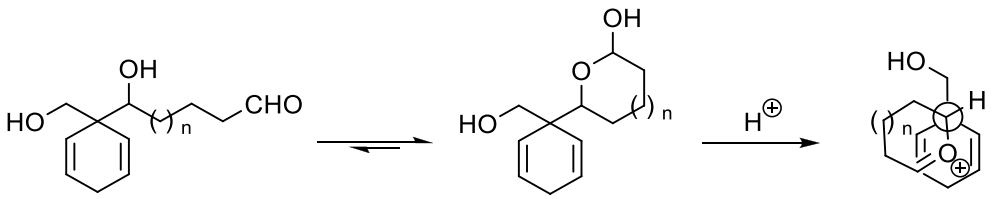
The group then proposed that the stereochemical outcome of the reaction could be reversed by tethering the $R^1$ and $R^2$ groups, as shown in **Scheme 23**. The oxocarbenium ion generated would preferentially adopt the near-attack conformation **109** rather than the alternative in which the two six-membered rings would be fully eclipsed. This would then generate the desired cladiellin stereochemistry. Also the presence of the tethering chain would also have the additional benefit of introducing an extra ring into the product **110**, as required for the natural products.




**109** **110**

**Scheme 23.** Stereochemical outcome of the reaction reversed by use of a cyclic oxocarbenium ion

To support and test this theory, the Elliott group needed to devise a suitable substrate. They considered that a compound **111**, which could actually exist as the lactol **112** should, once treated with an acid catalyst such as triflic acid, give the desired oxocarbenium ion **113**, as shown in **Scheme 24**.

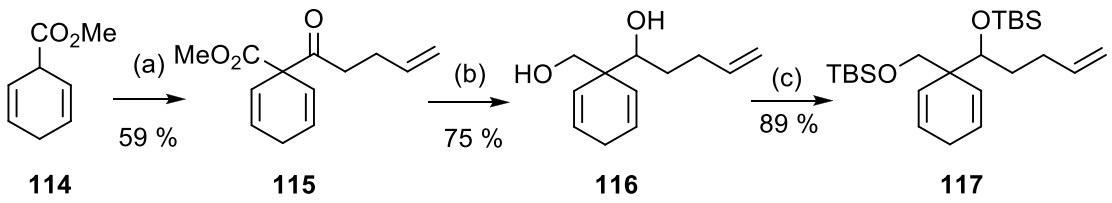



**111** **112** **113**

(n = 1)

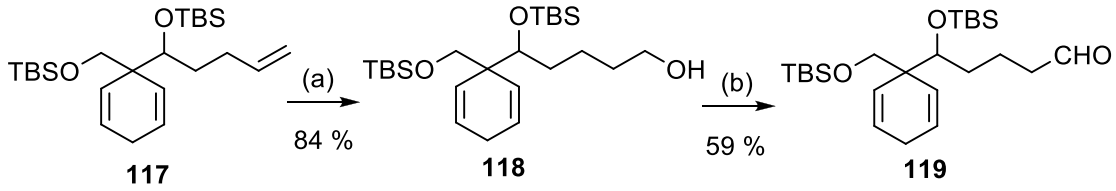
**Scheme 24.** Treatment of proposed Prins substrate **111** with triflic acid to give the desired oxocarbenium ion **113**

With the knowledge that the anion derived from ester **114** could be readily acylated with acid chlorides,[33] the Elliott group installed the alkenyl side-chain with 4-pentenoyl chloride, following a known literature procedure from 4-pentenoic acid.[34] Reaction of ester **114** with LDA and 4-pentenoyl chloride gave compound **115.** Reduction of the β-keto-ester (**115)** with $LiAlH_4$ gave diol **116,** which was then treated with TBSOTf to protect the free hydroxy groups as silyl ethers (**Scheme 25**).



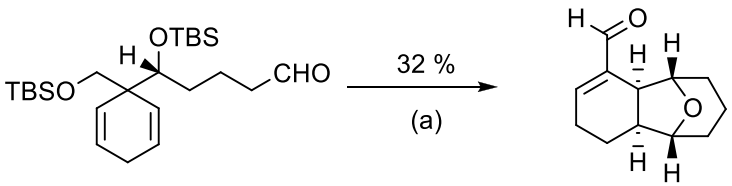

**Scheme 25.** Synthesis of substrate **117**. *Reagents and conditions:* (a) LDA, THF, -78 °C then 4-pentenoyl chloride, (b) $LiAlH_4$, THF; (c) TBSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C to room temperature

Compound **117** was treated with 9-BBN in THF, and a hydrogen peroxide work-up gave the bis-protected triol **118.** Then oxidation of compound **118** using PDC gave aldehyde **119**, (**Scheme 26**).




**Scheme 26.** Synthesis of aldehyde **119**. *Reagents and conditions:* (a) 9-BBN, THF, 18 h then $H_2O_2$, NaOH, (b) PDC, $CH_2Cl_2$, 18 h

Compound **119** was treated with 1 equivalent of triflic acid in dichloromethane for 20 minutes at room temperature. This gave compound **120** as a single diastereoisomer, (**Scheme 27**).

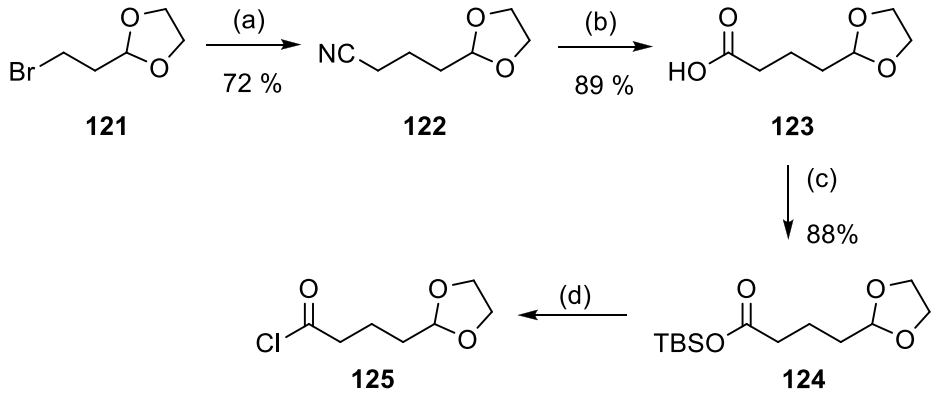



(±)-**119** (±)-**120**

**Scheme 27.** Prins cyclisation/ rearrangement of aldehyde **119**. *Reagents and conditions*: (a) TfOH (1 equiv.), $CH_2Cl_2$, 0 °C to room temperature, 20 minutes

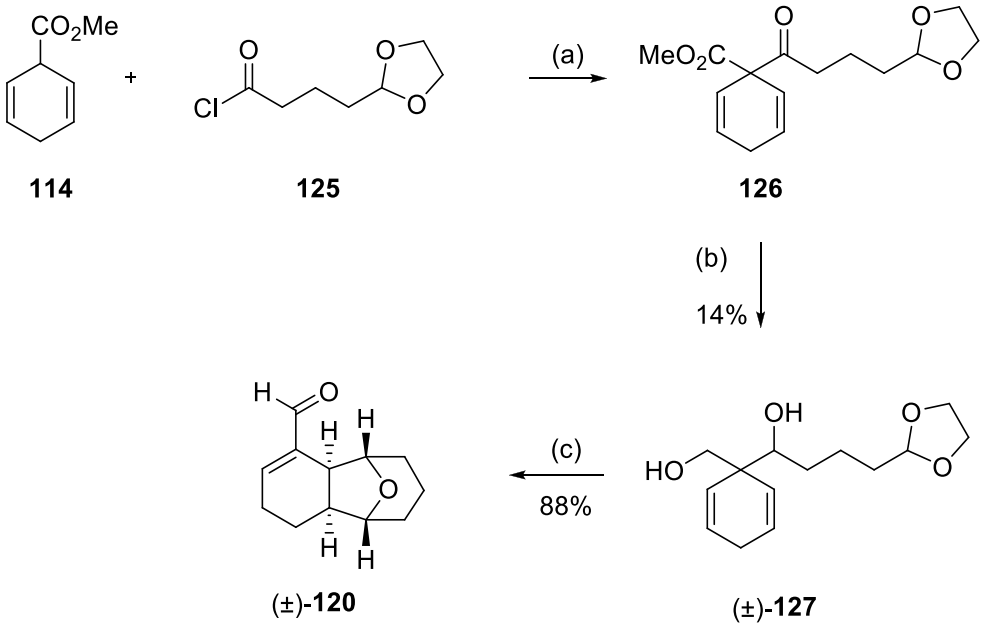
Attempts were made to improve the overall efficiency and yield of the process by initial deprotection of compound **119**, but this made no improvements. Aldehyde **119** was treated with TBAF in THF to give a complex mixture of products. In an attempt to overcome this problem they endeavoured to synthesise a substrate for the key step, similar to compound **119**, but without the use of silyl protecting groups, in order to reduce the complexity of the reaction pathway and to improve the yield of the reaction.[35]

Compound **125** was prepared from 2-(2-bromoethyl)-1,3-dioxolane (**121**); a two-carbon homologation was performed with acetonitrile to give nitrile **122**. Then hydrolysis of compound **122** with KOH in EtOH/$H_2O$ (2:1) gave acid **123**. The acid was converted into the corresponding *tert*-butyldimethylsilyl ether, which was then treated with oxalyl chloride and catalytic DMF at room temperature to give the acyl chloride (compound **125, Scheme 28)**.



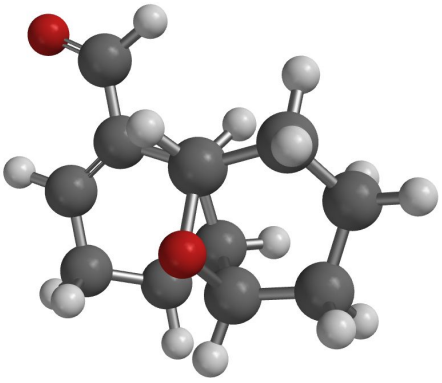

**Scheme 28.** Preparation of compound **125**. *Reagents and conditions*: (a) LDA, MeCN, THF, -78 °C to room temperature, 18 h; (b) KOH, EtOH/$H_2O$ (2:1), reflux, 16 h, (c) TBS-Cl, imidazole, 4-DMAP, $CH_2Cl_2$, 30 minutes; (d) $(COCl)_2$, DMF (cat.), $CH_2Cl_2$, 0 °C to room temperature, 2 h

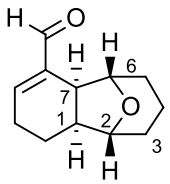
The acyl chloride **125** was relatively unstable and, as a result, it was used directly in subsequent reactions. Acylation of ester **114** with acid chloride **125** proceeded smoothly to give keto-ester **126** which was immediately reduced into the corresponding diol **127** using $LiAlH_4$. Treatment of compound **127** with triflic acid gave compound **120** as a single diastereoisomer in 88 % yield, **Scheme 29**.




**Scheme 29.** Synthesis of compound **120** *via* Prins desymmetrisation reaction. *Reagents and conditions*: (a) LDA, THF, -78 °C (b) $LiAlH_4$, THF, (c) TfOH (1 equiv.), $CH_2Cl_2$, 0 °C to room temperature, 20 minutes

Confirming the stereochemical configuration of compound **120** was not straightforward for the Elliott group as there were no diagnostic cross-peaks observed in the NOESY NMR spectrum. However, based on molecular modelling of the two possible diastereoisomers, the observed $^{1}$H NMR coupling constants were more compatible with compound **120**. For example the signal for H-7 in the $^{1}$H NMR spectrum appeared as a doublet of *J* 8.6 Hz and H-1 showed an 8.6 Hz coupling, which they presumed was to H-7. H-7 would be expected to show coupling to both H-1 and H-6. However, molecular modelling of diastereoisomer **120** showed that the dihedral angle between H-6 and H-7 was close to 90°, as illustrated in **Figure 7.** As such, a coupling constant of close to 0 Hz would be expected between these two protons, so it was feasible that the signal of H-7 would appear as a doublet of *J* 8.6 Hz in the $^{1}$H NMR spectrum of this diastereoisomer.

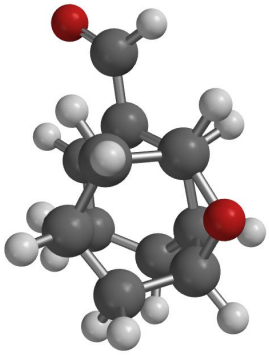


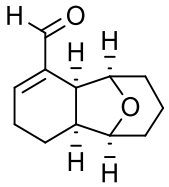



**120**

**Figure 7.** Spartan 10[36] representation of diastereoisomer **120**

For the alternative diastereoisomer **128**, molecular modelling showed that the dihedral angle between H-6 and H-7 was approaching 20°, as illustrated in **Figure 8**. Hence for this diastereoisomer, a somewhat larger coupling constant (*ca.* 6 Hz) would be expected between these two protons, so a more complex coupling pattern would be expected for H-7 than was observed.






**128**

**Figure 8.** Spartan 10[36] representation of diastereoisomer **128**.

Due to this evidence and mechanistic reasoning, the Elliott group was confident in the stereochemical assignment of compound **120**.

This result showed that the Prins cyclisation/rearrangement methodology developed within the Elliott group had the potential to provide rapid access to the cladiellin diterpenes. The successful synthesis of a model (**120**) for the hydroisobenzofuran core of the cladiellin diterpene therefore gave us a clear starting point. The oxacyclic component in compound **120** contains a 6-membered ring whereas the cladiellin core as shown in **Figure 9** contains a 9-membered ring.

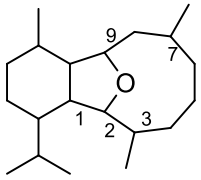



**Figure 9:** Cladiellin skeleton

### 1.5. Conclusion

The cladiellin diterpenes are synthetically-challenging natural products with a fascinating range of useful biological activity and are therefore important target compounds. Owing to their intriguing structure and interesting pharmacological activity, the cladiellins have seen a wide interest from a number of research groups, especially the groups of Overman,[8,9] Paquette,[9,10] Molander,[11] Kim,[12] Crimmins,[13] Hoppe,[14] Clark,[15] and Johnson.[16]

In recent years, the Prins reaction has emerged as a successful strategy in natural product synthesis. The Overman group have studied a variety of Prins cyclisation reactions, including the Prins-pinacol rearrangement used for the synthesis of Sclerophytin A[8c] (**Scheme 19**), as mentioned previously (page 8).

Recent studies from Cardiff have established a new tandem Prins-Wagner-Meerwein approach to partially reduce benzo[*c*]furans and, model studies have shown that this process can be used to prepare model compounds related to the cladiellin diterpenes. The Elliott group generated a model (**120**) for the hydroisobenzofuran core of the cladiellin diterpenes as a single diastereoisomer, using a Prins cyclisation reaction. These results obtained within the group provide scope for access to the cladiellin diterpenes, and knowing this process works for a simple model compound, our aim would be to extend this approach and evaluate the scope for more complex targets.

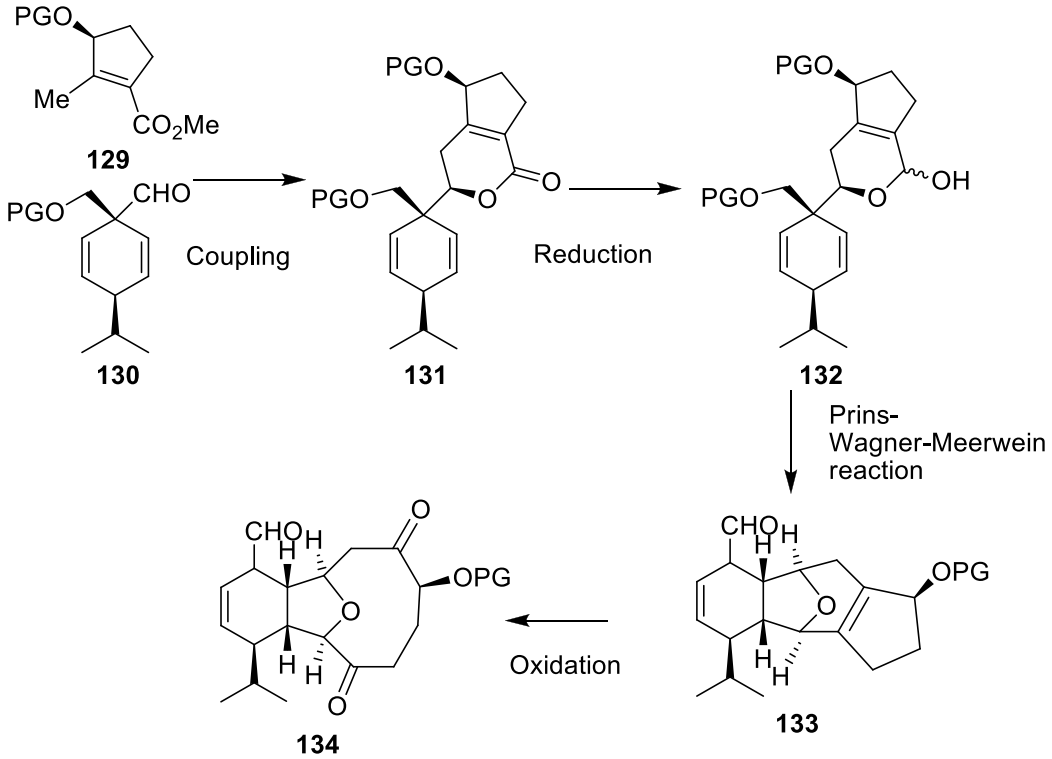
# Chapter 2

# Aims and Objectives

**2.1. Aims and Objectives**

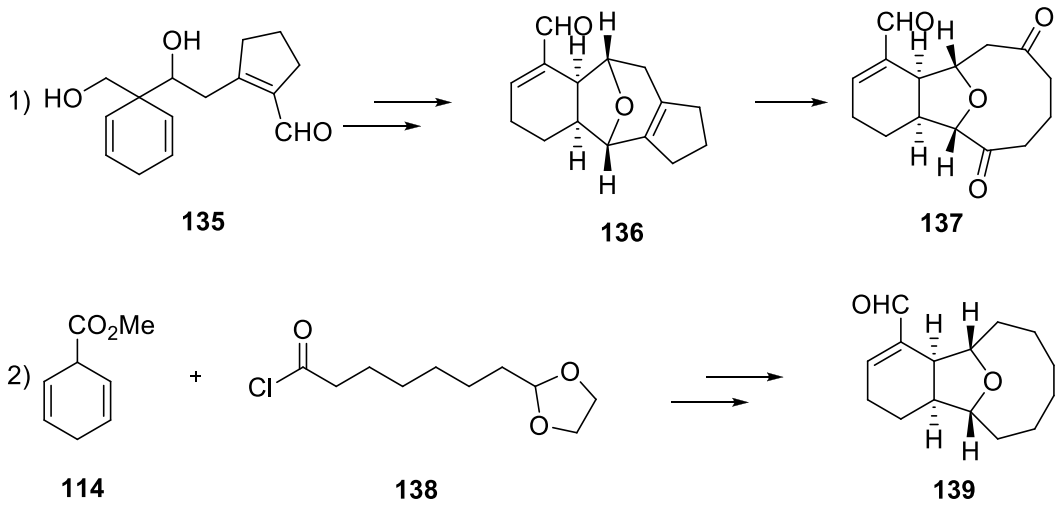
The aim is to apply the Prins rearrangement/ cyclisation methodology developed within the Elliott group to a synthesis of one or more analogues of the cladiellin diterpenes.

The Prins-Wagner-Meerwein approach will be used. This approach has been discovered to provide access to partly-reduced hexahydroisobenzofurans which are analogues of the known cladiellin diterpenes. Model studies have shown that this process can be used to prepare model compounds related to the cladiellin diterpenes.[31,32] A complete synthesis would require an aldehyde such as compound **130** and a multi-functional 5-membered ring (compound **129**, **Scheme 30**). A coupling reaction between compound **129** and **130** would give compound **131**. Then, reduction of compound **131** to give compound **132**, followed by a Prins cyclisation/rearrangement, would give compound **133.** Oxidation of compound **133** would allow formation of compound **134**, a structure which resembles the framework of the desired cladiellin diterpene skeleton.




**Scheme 30.** Potential route to access the core of the cladiellin diterpenes

To synthesise analogues of the cladiellin diterpenes there are two strategies (**Scheme 31**). The first strategy will initially involve the synthesis of compound **135** with the intention of incorporating a fused ring into the Prins precursor, with the aim to expand the ring at the end. The second will involve the investigation of a new synthesis using the same method conditions as previous members of the Elliott group[35] (page 34), but starting with a longer carbon chain as in compound **138**.




**Scheme 31**. Synthetic pathways towards a model system of the hydroisobenzofuran core of the cladiellin diterpenes

The cladiellin diterpene skeleton also contains a 6-membered ring with an isopropyl group or a similar alkyl substituent attached at the 14-position, as highlighted in **Figure 10**. This approach to the cladiellin framework does not directly involve the isopropyl group. A method of introducing the isopropyl group at the 14-position is also investigated with alkylation as the main focus of the study.

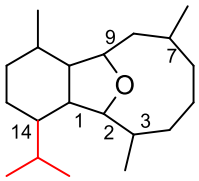



**Figure 10.** Cladiellin skeleton with the substituent at the 14-position highlighted

# Chapter 3

# Alkylation of Cyclohexa-1,4-dienes

### 3.1. Introduction

A method of introducing an isopropyl group at the 4-position of the 6-membered ring is required, as shown in the structure of the cladiellin framework in **Figure 11**. Our approach involves alkylation of cyclohexa-1,4-dienes.

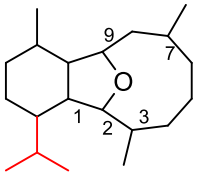
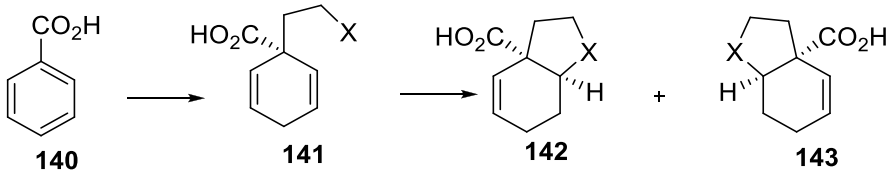



**Figure 11:** Cladiellin Diterpene framework

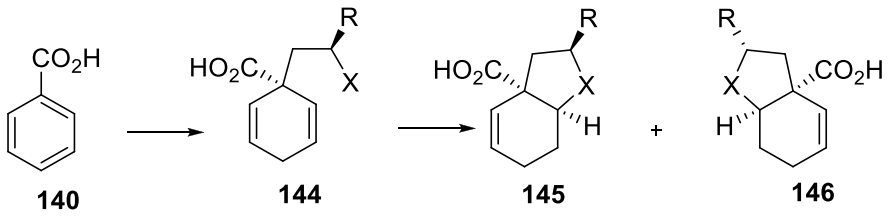
Cyclohexa-1,4-dienes are versatile intermediates in synthetic organic chemistry, most commonly prepared by various methods of the Birch reduction.[37] In particular, with appropriate substitution patterns, the two double bonds are either enantiotopic (achiral cyclohexadienes), **Scheme 32** or diastereotopic (chiral cyclohexadienes), **Scheme 33** and therefore their elaboration can lead to the formation of one or more new stereogenic centres either using inter-[38] or intramolecular[39] transformations.




**Scheme 32.** Desymmetrisation of 1,1-disubstituted-2,5-cyclohexadiene

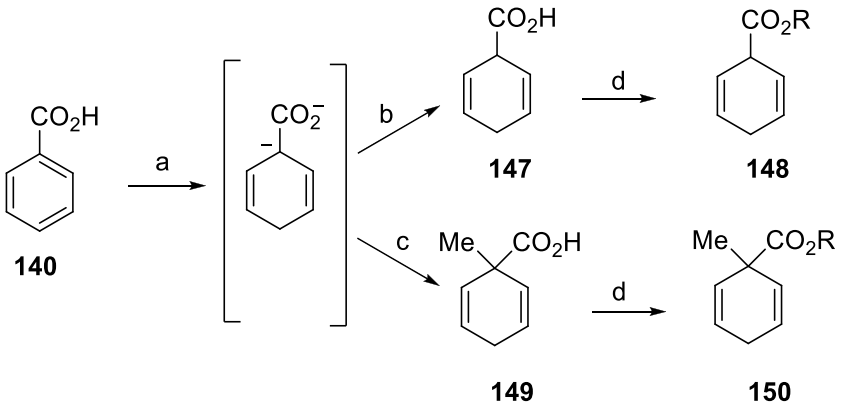
Birch reduction/alkylation gives 1,1-disubstituted cyclohexa-2,5-dienes such as **141** which contains enantiotopic double-bonds. Transformation of one of the double bonds will result in a loss of symmetry. One or two stereogenic centres will typically be formed directly as a result of the alkene functionalisation and one of the stereogenic centres is quaternary, so that this method is extremely powerful.

Such enantioselective transformations require the use of a chiral catalyst or reagent. By incorporating a stereogenic centre prior to desymmetrisation as in **144**, the substrate is now able to control which of the now diastereotopic double-bonds are involved in the reaction. Since the products are diastereoisomers they are easily differentiated and often separable by flash column chromatography. The success of the transformation is therefore straightforward to determine with a racemic substrate, while still allowing for asymmetric synthesis by use of a chiral alkylating reagent following the Birch reduction to give a single enantiomer.



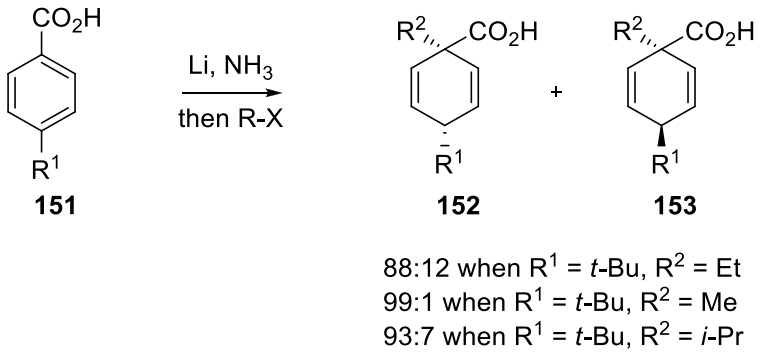

**Scheme 33.** Desymmetrisation by diastereotopic group selectivity

Desymmetrisation reactions of cyclohexa-1,4-dienes have considerable synthetic potential for preparation of fused carbocyclic and heterocyclic systems.[40] Landais and co-workers reported extensively on the use of asymmetric dihydroxylation reactions for the selective oxidation of such systems.[41] These reactions have been used for the preparation of a number of biologically important carbocyclic sugar analogues.[42] The desymmetrisation reactions of cyclohexa-1,4-dienes also have significant potential in natural product synthesis, particularly where a quaternary stereogenic centre is introduced by way of a Birch reduction/alkylation approach**.** These approaches generally make use of derivatives of 1-alkylcyclohexa-2,5-diene-1-carboxylic acids, although their potential is severely limited by the lack of availability of methods for the stereoselective introduction of substituents at the 4-position (**Scheme 34**).[43]



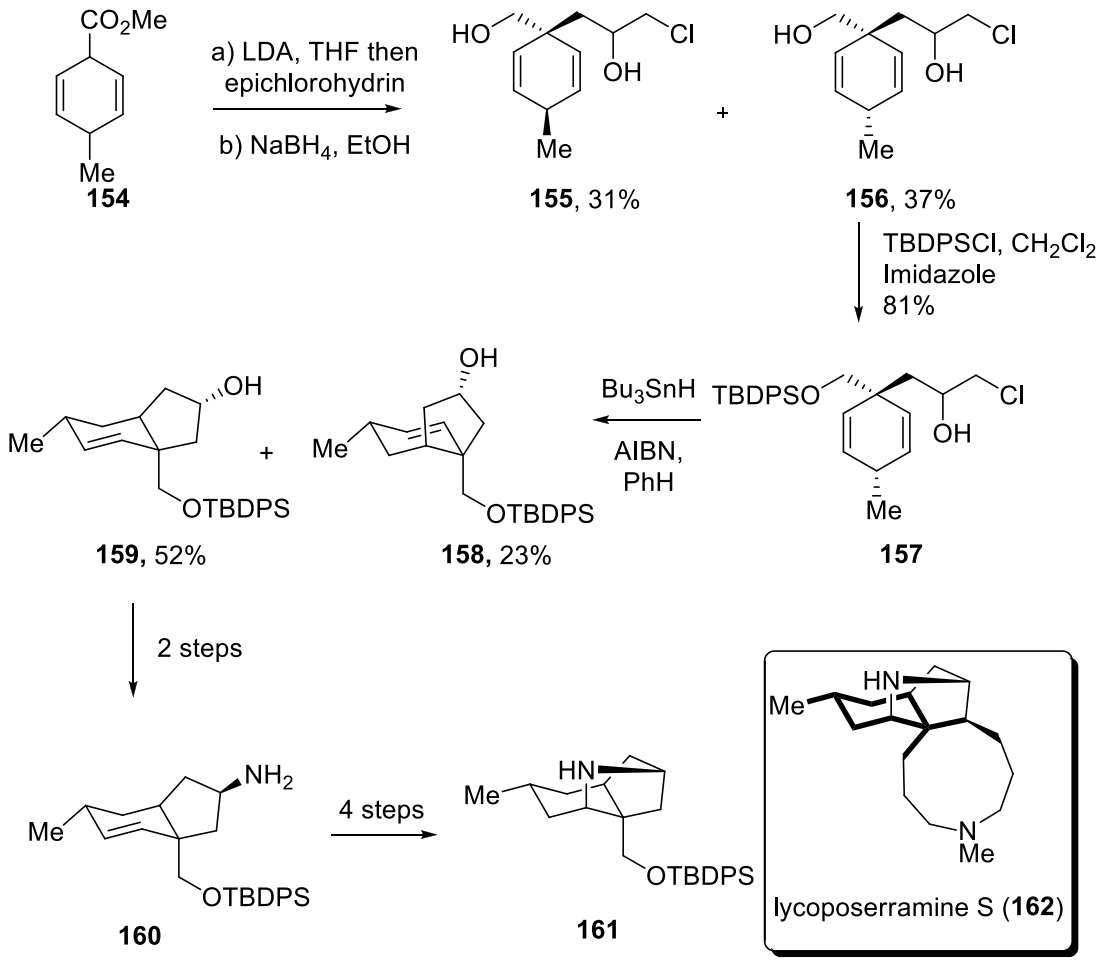

**Scheme 34.** Synthesis of 1-alkylcyclohexa-2,5-diene carboxylic acid *via* Birch reduction.
*Reagents and conditions:* (a) Li/ $NH_3$, (b), $NH_4Cl$, (c) MeI, (d) $(COCl)_2$/ $Et_2O$ then ROH/ py

When applied to 4-alkylbenzoic acid derivatives, poor stereocontrol is observed at the 4-position, unless the alkyl group is particularly bulky. In 1971, van Bekkum *et al.* conducted a study which led to the development of a convenient method of preparing alkylcyclohexa-2,5-diene-1-carboxylic acids.[44] Using Birch reduction conditions starting with benzoic acids with methyl or *t*-butyl groups in the 4-position (**Scheme 35**) resulted in almost complete conversion but gave a mixture of *cis* and *trans* isomers (**152** and **153**). However as the size of the $R^2$ group increased, it was found that the formation of the product with the *t*-butyl and carboxyl group in the *cis*-position was preferred. However it is not clear how this stereochemical assignment was made. The authors did indicate that this would be the subject of a future publication. However, it would appear that the basis of the stereochemical assignment was never published.



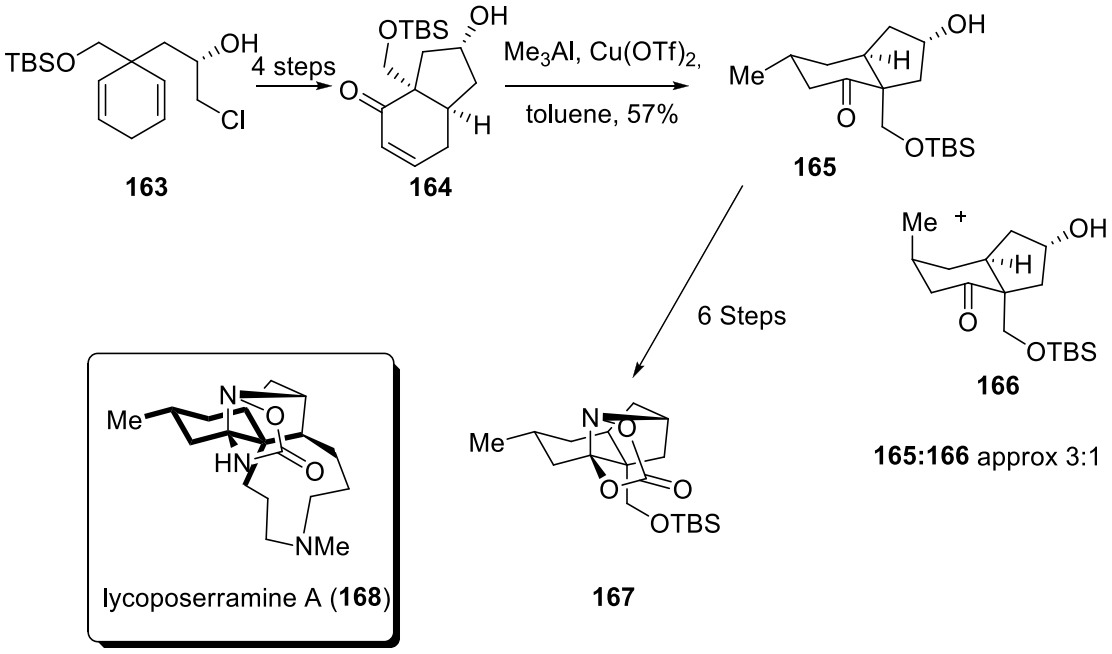

**Scheme 35.** Birch reduction of Compound **151** to give a mixture of **152** and **153**

In 2008, the Elliott group reported the synthesis of the tricyclic core of lycoposerramine S (**162**) by free-radical cyclisation of a symmetrical cyclohexadiene precursor. The synthesis of compound **162** began with a known cyclohexadiene **154**, which was previously reported as prepared from toluic acid.[45] Compound **154** was then deprotonated and treated with epichlorohydrin to give an approximately 1:1 mixture of diastereoisomers **155** and **156**. The group managed to isolate compound **156** in 37% yield (**Scheme 36**), however the stereochemical assignment of compound **155** or **156** was not possible until the cyclisation to give **159** had been carried out. The lack of stereocontrol at the 4-position is once again highlighted here. Since many of the target compounds that may be synthesised by desymmetrisation of cyclohexadienes contain substituents that would need to be present at this position, there is a need for a method for the stereoselective formation of these compounds.



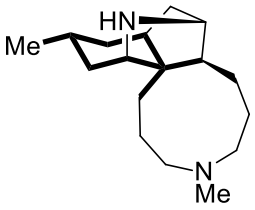

**Scheme 36.** Synthesis of the tricyclic core of lycoposerramine S (**162**)

To avoid such a poor level of stereoselectivity in the introduction of the methyl group, in a related approach to lycoposerramine A (**168**), four steps were required from the cyclohexadiene **163** to give compound **164**, which then underwent a conjugate addition of trimethylaluminium to give a 3:1 mixture of compounds **165** and **166**. Then a further two steps gave a model for the tetracyclic core (**167**) of lycoposerramine A (**168**).[46]

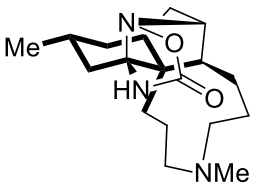



**Scheme 37.** Late introduction of methyl group to the formation of a key intermediate **165** and then formation of the tetracyclic core (**167**) of lycoposerramine A (**168**)

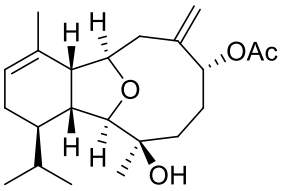
Similarly, previous members of the Elliott group have reported[32] an approach towards the core of the cladiellin diterpenes, such as 7-deacetoxyalcyonin acetate (**18**), which requires introduction of an isopropyl group at the 4-position. Numerous other important targets exist which could readily be prepared using cyclohexadiene desymmetrisation methodology, for example faurinone (**169**)[47] and the aglycon of dendronobiloside A (**170**),[48] as shown in **Figure 14**.



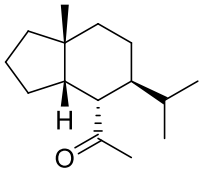

lycoposerramine S (**162**)



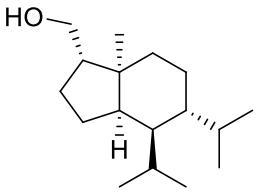

lycoposerramine A **(168**)




(-)-7-deacetoxyalcyonin acetate (**18**)



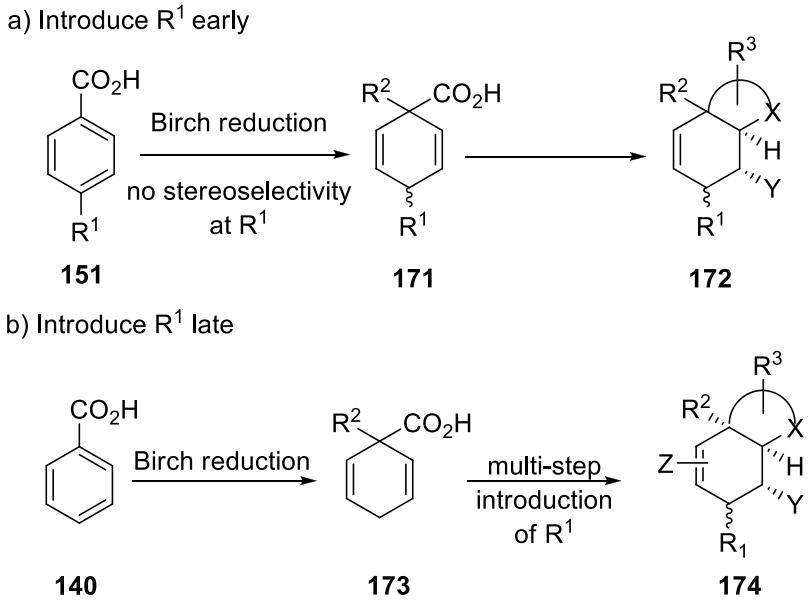

faurinone, **169**




dendronobiloside A aglycon, **170**

**Figure 14**. Actual and potential targets for cyclohexadiene desymmetrisation methodology

Therefore we can see the methods for the stereoselective introduction of substituents at this 4-position are very much needed. If the substituent is present at the start ($R^1$ in structure **151**), the Birch reduction/alkylation proceeds with little stereocontrol to form **171**. The only exception to this is if $R^1$ and $R^2$ are bulky.[45] However, late introduction of this substituent can require multiple steps as shown above (**Scheme 38**, route b).

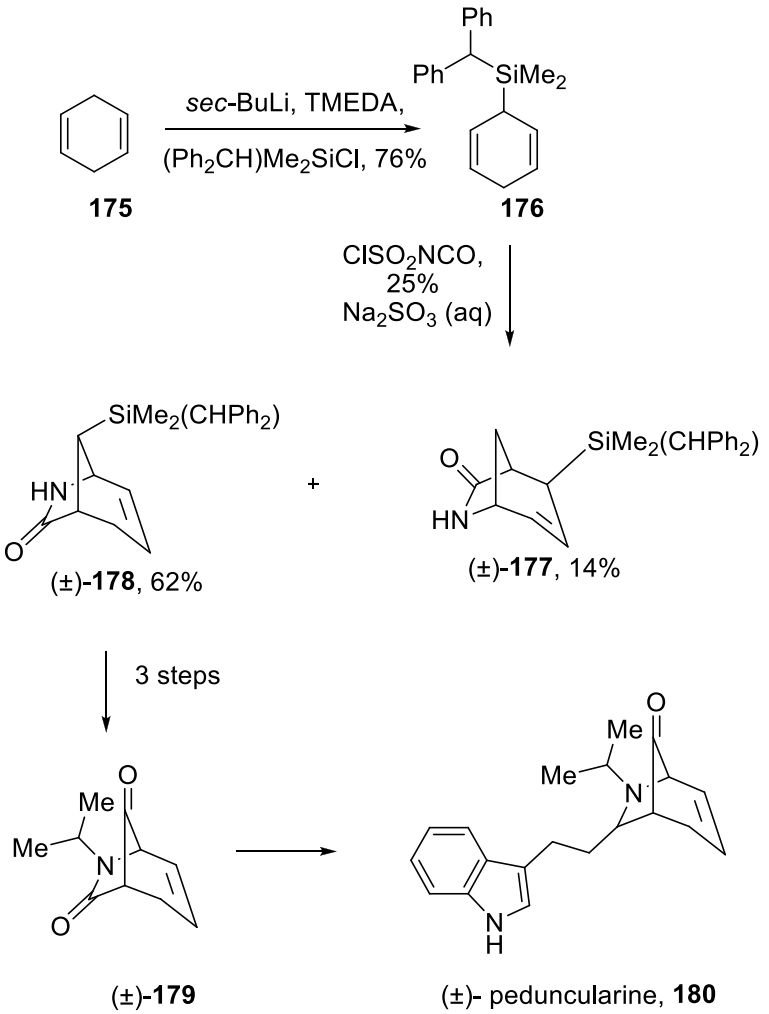



**Scheme 38.** Difficulties in introducing substituents at the 4-position of 1-alkylcyclohexa-2,5-diene-1-carboxylic acids, either late or early in a sequence.

Early introduction of $R^1$ would be the preferred method, since the desymmetrisation process to form compound **172** can proceed with selective formation of four stereogenic centres in a single step which is controlled by a stereogenic substituent $R^3$. In fact, by using a desymmetrisation process which gives reaction at both cyclohexadiene double bonds, it is possible to form up to six contiguous stereogenic centres with complete stereoselectivity in a single step using this approach.[49] The ideal method therefore features the stereoselective formation of compounds such as **171.** Since this cannot be accomplished by a stereocontrolled Birch reduction, another method for the formation of these types of compounds would involve the deprotonation and alkylation of a compound of the general structure **173**. It is therefore clear that the potential utility of cyclohexadiene desymmetrisation reactions will be greatly enhanced by the availability of a versatile method for the stereoselective formation of 1,4-dialkyl cyclohexa-2,5-diene-1-carboxylic acids.

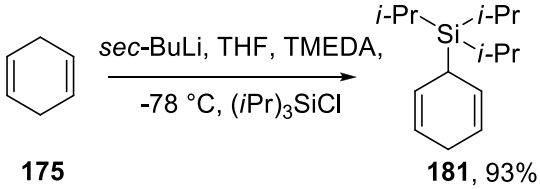
A number of groups have reported the direct deprotonation/alkylation of cyclohexa-1,4-dienes,[50,41b] while others have alkylated substituted cyclohexa-1,4-dienes.[51]

The use of cyclohexa-1,4-dienes as substrates for cyclisation reaction have been an area explored by many. In 2000, Roberson and Woerpel reported the synthesis of alkaloid (±)-peduncularine (**180**).[50] The synthesis began with the deprotonation of 1,4-cyclohexadiene (**175**) and silylation with dimethylbenzhydrylsilyl chloride to give bis-allylic silane **176**, which was then treated with chlorosulfonyl isocyanate and 25% aqueous $Na_2SO_3$ at -40 °C to give a mixture of compounds **177** and **178**. Three further steps gave compound **179**. Then Swern oxidation of compound **179** gave peduncularine **180**.



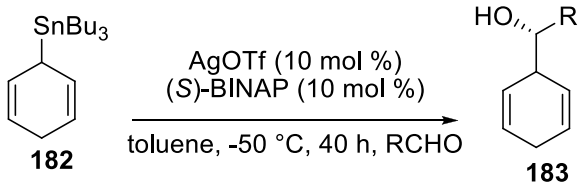

**Scheme 39**. Synthesis of alkaloid (±)-peduncularine **180**.[52]

However, when the Birch reduction was applied to arylsilanes, this process gave varying amounts of over-reduced products. Therefore arylsilanes were more conveniently prepared by metalation of cyclohexa-1,4-dienes with *sec*-BuLi and silylation of the resulting carbanion with *i*-$Pr_3SiCl$ as in **Scheme 40**.



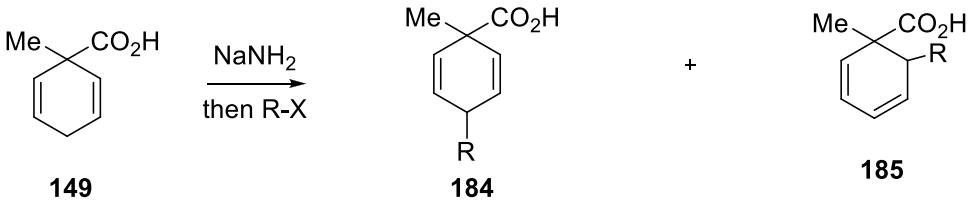

**Scheme 40**. Metalation of cyclohexa-1,4-dienes with *sec*-BuLi and silylation of the resulting carbanion with *i*-$Pr_3SiCl$[52]

More recently in 2008, Umeda and Studer reported a silver-BINAP-mediated addition of cyclohexadienylstannanes to aldehydes, **Scheme 41**.[52] This is the only asymmetric variant to date. However, this is different to the approach being investigated, since the stereochemistry is not introduced on the cyclohexadiene itself.




**Scheme 41.** Silver BINAP-mediated addition of cyclohexadienylstannanes to aldehydes[52]

In 1976, Zhurkovich and Ioffe reported[53] that the deprotonation of compound **149** with sodium amide followed by alkylation with a range of alkyl halides gave good yields but only moderate and variable stereoselectivity in the formation of the 1,4-dienes **184** (**Scheme 42**). Alkylation at the 2-position was also observed resulting in formation of the conjugated diene **185**. Zhurkovich and Ioffe stated that the reaction placed the new alkyl group trans to the carboxylic acid. However, the stereochemical outcome of these reactions was not proven. Their assignment of the cis/trans isomer of **184** were based on comparison of the relative GC retention times of the corresponding esters with data in an earlier report from van Bekkum *et al.*[45] However, that report only contained GC retention times for compounds lacking the quaternary centres, and so the relevance of the comparison is not completely clear. Furthermore, the basis of van Bekkum *et al.*'s assignment was described as "to be published" and, as mentioned previously, this work appears not to have been published. Therefore, by extending this work, it was clear that unambiguous stereochemical assignment would be required.




**149** **184** **185**

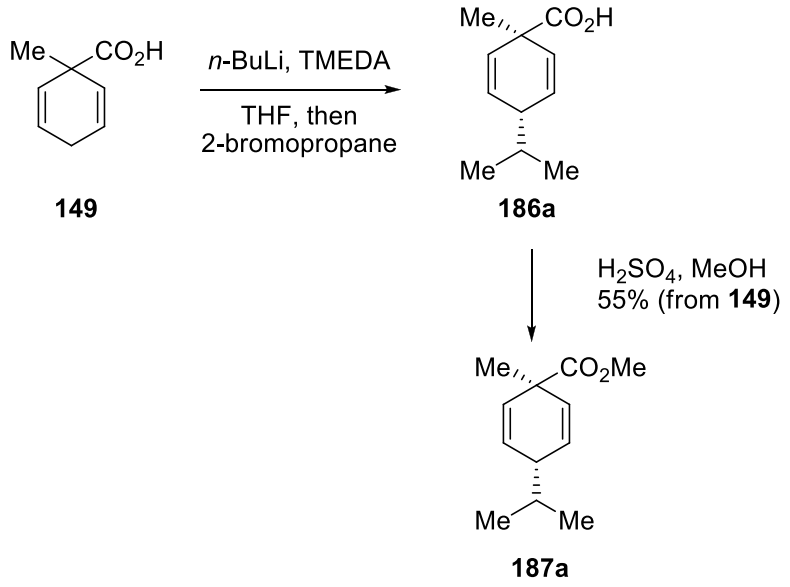
42:58 to 90:10 diastereomeric ratio

**Scheme 42**. Alkylation of 1-methylcyclohexa-2,5-diene-1-carboxylic acid reported by Zhurkovich and Ioffe[53]

The objective of this study was to investigate the deprotonation and alkylation of compounds such as **149** in order to determine conditions that could lead to high levels of stereocontrol.

### 3.2. Results and discussion

Following on from Zhurkovich and Ioffe[53] and in order to achieve high levels of stereocontrol in the deprotonation and alkylation of compounds such as **149**, certain parameters of the reaction were varied, for example; the base, solvent and the temperature. The first set of conditions to be investigated used *n*-BuLi as the base, THF as the solvent, with the reaction temperature set at -78 °C. Deprotonation at the 4-position of 1-methylcyclohexa-2,5-diene carboxylic acid **149** using *n*-BuLi/TMEDA followed by alkylation with 2-bromopropane gave high yield of a single diastereoisomer **186a** (**Scheme 43**), which was characterised upon conversion to its corresponding methyl ester **187a** (55% yield over 2 steps).



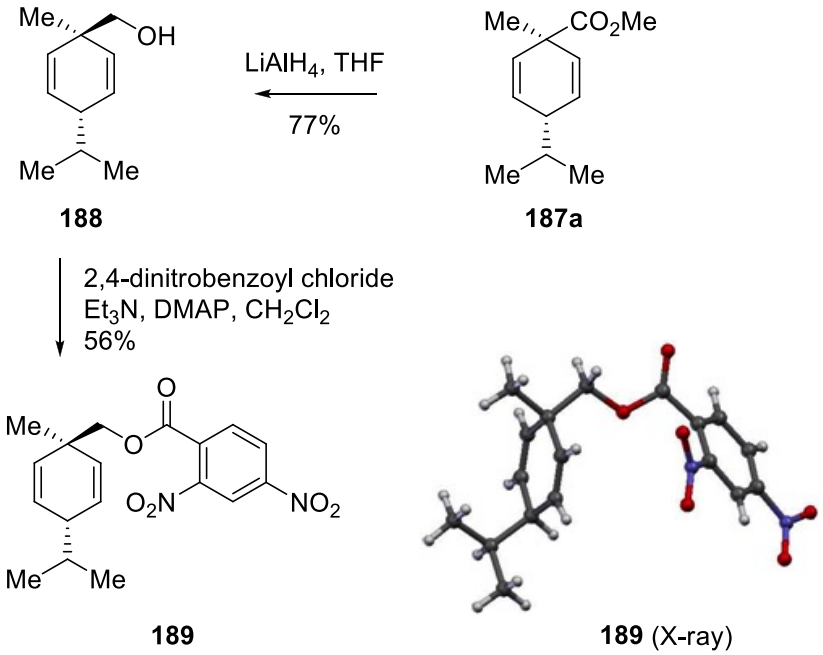

**149** **186a** **187a**

**Scheme 43.** Formation of compound **187a**

Determining the stereochemical configuration of compound **187a** was never going to be an easy task as no obvious nOe enhancements are expected in the 2D NOESY NMR spectrum of this compound, and determining the stereochemical configuration using 1D NMR spectroscopy alone was an impossible task. However, Zhurkovich and Ioffe[53] managed to report the stereochemical configuration of alkylcyclohexa-2,5-diene-1-carboxylic acids,

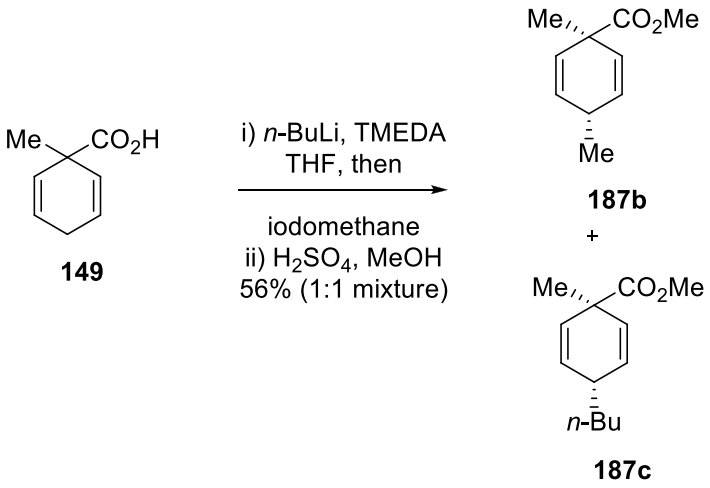
which is surprising with the instrumentation that would have been available to researchers in 1976. To solve this problem a crystalline derivative of compound **187a** was prepared.

Ester **187a** was reduced to the corresponding alcohol **188** using $LiAlH_4$. The 2,4-dinitrobenzoate ester **189** was then prepared using 2,4-dinitrobenzoyl chloride, triethylamine and catalytic 4-DMAP in dichloromethane. Formation of a single crystal of compound **189** allowed us to confirm the stereochemical configuration of the diastereoisomer as *trans* (as shown in the X-ray structure, **Scheme 44**). The stereochemical configuration of the diastereoisomer also agrees with the results reported by Zhurkovich and Ioffe, although the present conditions gave much higher levels of stereocontrol and complete regiocontrol.



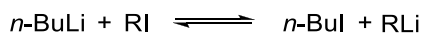

**Scheme 44.** Synthesis and stereochemical determination of compound **189**

When iodomethane was used as electrophile, the alkylation reaction also gave a single diastereoisomer of the desired product **187b**, but in this case it was contaminated with significant and variable quantities of the corresponding butyl compound **187c**, which were not completely separable during purification (**Scheme 45**).




**Scheme 45.** Methylation of 1-cyclohexa-2,5-diene-1-carboxylic acid

This is presumably formed by exchange of excess butyllithium with the methyl iodide (halogen-lithium exchange).[54] The halogen-lithium exchange is an equilibrium process favouring formation of the more stable, less basic, organolithium compound[55] (**Scheme 46**). However only a slight excess (2.2 equivalents) of butyllithium was used (where the first equivalent is used to deprotonate the acid), and could be attributed to the presence of the corresponding carboxylate salt in carboxylic acid **149** (**Scheme 46**).




**Scheme 46.** Equilibrium established upon halogen-lithium exchange

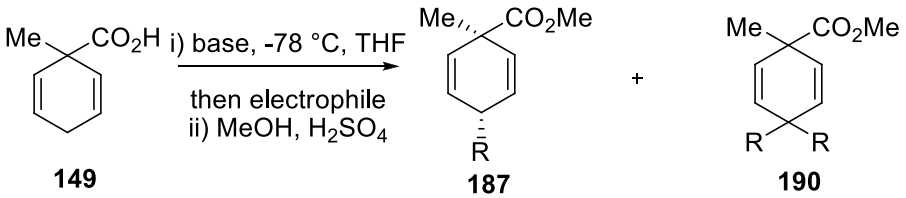
Any amount of this salt would mean that effectively a larger excess of butyllithium was being used. When less butyllithium was used, incomplete alkylation occurred, leaving some compound **149** unreacted. Initial deprotonation with NaH followed by one equivalent of

*n*-BuLi led to the formation of a complex mixture of products. Despite extensive experimentation, a reaction stoichiometry could not be found which leads to complete alkylation to give a single product in this case and without the formation of by-products. Addition of cyclohexa-1,4-diene in an attempt to quench the remaining butyllithium was also not successful, and other electrophiles (methyl triflate and dimethyl sulfate) gave a complex mixture of products or low yields.

However, other bases are effective in this transformation and the lithium-halogen exchange is not expected to be a problem with these bases but they are low yielding. For example, LIDAKOR (LDA and potassium-*tert*-butoxide) and LDA gave 53% and 37% yields, respectively, after esterification, in both cases only one diastereoisomer being formed along with a small amount of un-reacted starting material (isolated as the methyl ester). Careful examination of NMR spectra strongly suggests that the same stereoisomer was formed as when *n*-butyllithium was used as base. Using the same alkyl residue in the electrophile and alkyllithium would seem to be a logical approach for avoiding the formation of a mixture of products. Unfortunately methyllithium/TMEDA is ineffective as a base, with starting material being recovered almost quantitatively. This is a surprising result as methyllithium is slightly less basic than *n*-BuLi but more basic than LDA.

Similar complications were observed with other primary alkyl iodides (**Table 1**). With iodoethane (entry 6) an approximately 1:1 mixture of products was obtained. With 1-iodoheptane slightly less of the butyl product **187c** was obtained, and the pure heptyl product **187e** was obtained in 54% yield after esterification. However, with benzyl bromide, the butyl product was not observed, with the desired product **187g** being obtained as a single stereoisomer in 77% yield (after formation of the methyl ester).

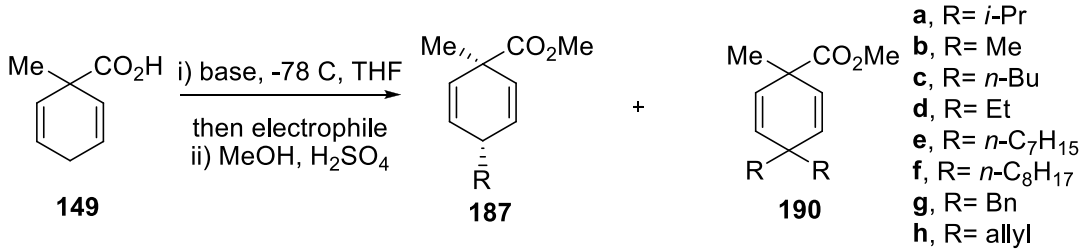
This led us to explore whether there was a difference between alkyl bromides and alkyl iodides. Deprotonation/alkylation using alkyl bromides rather than alkyl iodides appears to give the desired products in a higher yield without any of the butyl product formed from metal-halogen exchange with excess butyllithium. The rate of exchange is much higher for iodide over bromide[56] and can possibly account for the absence of halogen lithium exchange in the other lithiations/alkylations that were carried out. Unfortunately in these cases, another problem was then observed. A second alkylation took place to some extent giving a mixture of the desired mono-alkylated product **187** and doubly-alkylated products **190**, (**Scheme 17**).




**Scheme 47.** Formation of mono-alkylated (**187**) and doubly-alkylated products (**190**)

These were formed in very small quantities in most reactions (see entries 7 and 9, **Table 1**) although they were readily separated during purification. For example when bromoethane was used as the electrophile, small but variable amounts of the double alkylation product were observed in the NMR spectra of the crude reaction mixtures and was easily separated during purification. These compounds become the major products when an excess of the base/ electrophile is used (entry 12).

**Table 1.** Summary of results

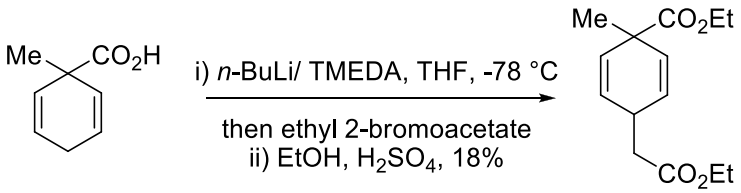



149 187 190

| Entry | Base | Electrophile | Yields (products) |
|---|---|---|---|
| 1 | *n*-BuLi/TMEDA | 2-Bromopropane | 55% (**187a**) |
| 2 | *n*-BuLi/TMEDA | Iodomethane | 58% (1:1 **187b**:**187c**) |
| 3 | LDA | Iodomethane | 53% (**187b**) |
| 4 | LIDAKOR | Iodomethane | 37% (**187b**) |
| 5 | *n*-BuLi/TMEDA | 1-Bromobutane | 64% (**187c**) + 4% (**1909c**) |
| 6 | *n*-BuLi/TMEDA | Iodoethane | 43% (1:1 **187d**:**187c**) |
| 7 | *n*-BuLi/TMEDA | Bromoethane | 51% (**187d**)[a] |
| 8 | *n*-BuLi/TMEDA | 1-Iodoheptane | 54% (**187e**) |
| 9 | *n*-BuLi/TMEDA | 1-Bromooctane | 47% (**187f**)[b] |
| 10 | *n*-BuLi/TMEDA | Benzyl bromide | 77% (**187g**) |
| 11 | *n*-BuLi/TMEDA | Allyl bromide | 54% (**187h**) |
| 12 | *n*-BuLi/TMEDA[c] | Bromoethane | 48% (**187d**) |

[a] Small but variable amounts of the double alkylation product were observed in NMR spectra of the crude reaction mixtures. This was readily removed during purification. [b] A small amount of the double-alkylation product **190f** was observed, but this was not obtained pure. [c] *n*-BuLi (5.0 equiv), TMEDA (2.5 equiv), bromoethane (3.0 equiv).

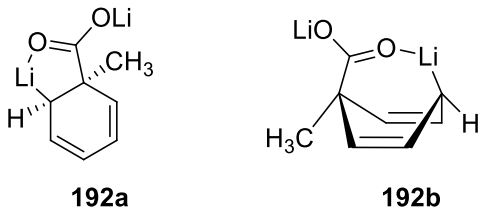
The reaction is, as shown by the examples in **Table 1**, quite general. In all cases, only a single stereoisomer was isolated, and of all the reactions that were investigated, the only electrophile that was not worthy of further consideration was ethyl 2-bromoacetate, as it gave a complex mixture of products in the first step to form the acid, resulting overall in a poor yield (**Scheme 48**).




**149** **191**

**Scheme 48**. Formation of compound **191**

When stabilised organolithium reagents react with electrophiles, the stereochemical outcome is strongly dependant on the nature of the electrophile. For example, alkyl halides tend to give inversion at the organolithium, while carbonyl electrophiles tend to give retention at the organolithium. Therefore, the observed outcome is consistent with a directed lithiation followed by alkylation with inversion.[57] In an attempt to understand this computationally, DFT calculations were carried out by Dr Simone Tomasi at AstraZeneca. DFT calculations with Gaussian 09[58] at the wB97XD/6-311++G(2df,2p)//B3LYP/6-31+G* level comparing the relative stabilities of metalated 1-methylcyclohexadienyl-1-carboxylates indicating that neither the 'annelated' intermediate **192a** nor the 'bridged' isomer **192b** are local minima. Two possible structures seemed likely for the metallated cyclohexadiene, these being compounds **192a** and **192b**. However, starting from either of these structures, minimisation led to an identical structure corresponding to $\eta_5$ coordination of the lithium to the cyclohexadienyl ligand. Saturation of the Li coordination spheres by THF or TMEDA molecules is favoured. Including thermal contributions and standard state corrections, the free energy of complexation of four THF molecules at -78 °C is -46.9 kcal $mol^{-1}$. Complexation of two molecules of TMEDA (**Figure 15**) is even more favourable at -51.5 kcal $mol^{-1}$. Therefore this should be considered to be the dominant complex of the lithiated cyclohexadiene. The presence of strongly interacting ligands that block the upper face provides a clear explanation of the observed stereoselectivity.




**192a** **192b**

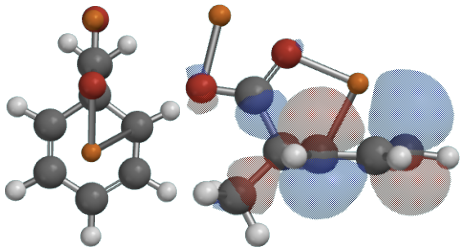


**Figure 15.** Structure of the doubly-lithiated dianion derived from compound **149**

### 3.3. Conclusion

In conclusion, deprotonation of 1-methylcyclohexa-2,5-diene-1-carboxylic acid **149** with *n*-BuLi in the presence of TMEDA, followed by alkylation, offers a direct and highly diastereoselective route to the corresponding 4-substituted products in which the alkyl group introduced is *trans* to the carboxylic acid. This is complementary to the results of van Bekkum in which a 4-substituted benzoic acid is reductively alkylated.[44] In that case, where any selectivity is observed, the alkyl group and the carboxylic acid is preferentially *cis*. This method can therefore be applied in the proposed approach to synthesise model compounds for the core of the cladiellin diterpenes.

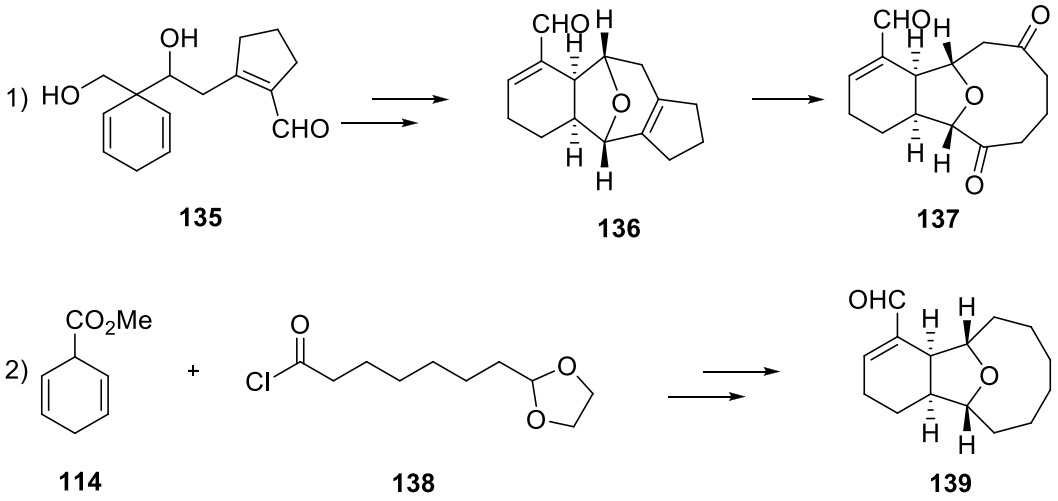
# Chapter 4

# Prins Macrocyclisation Reactions

### 4.1. Introduction

**Diastereoselective Prins-mediated Desymmetrisation of Cyclohexa-1,4-dienes**

As previously discussed, to synthesise analogues of the cladiellin diterpenes there are two strategies (**Scheme 49).** This Chapter describes attempts at synthesising analogues of the cladiellin diterpenes using route 2, **Scheme 49**.

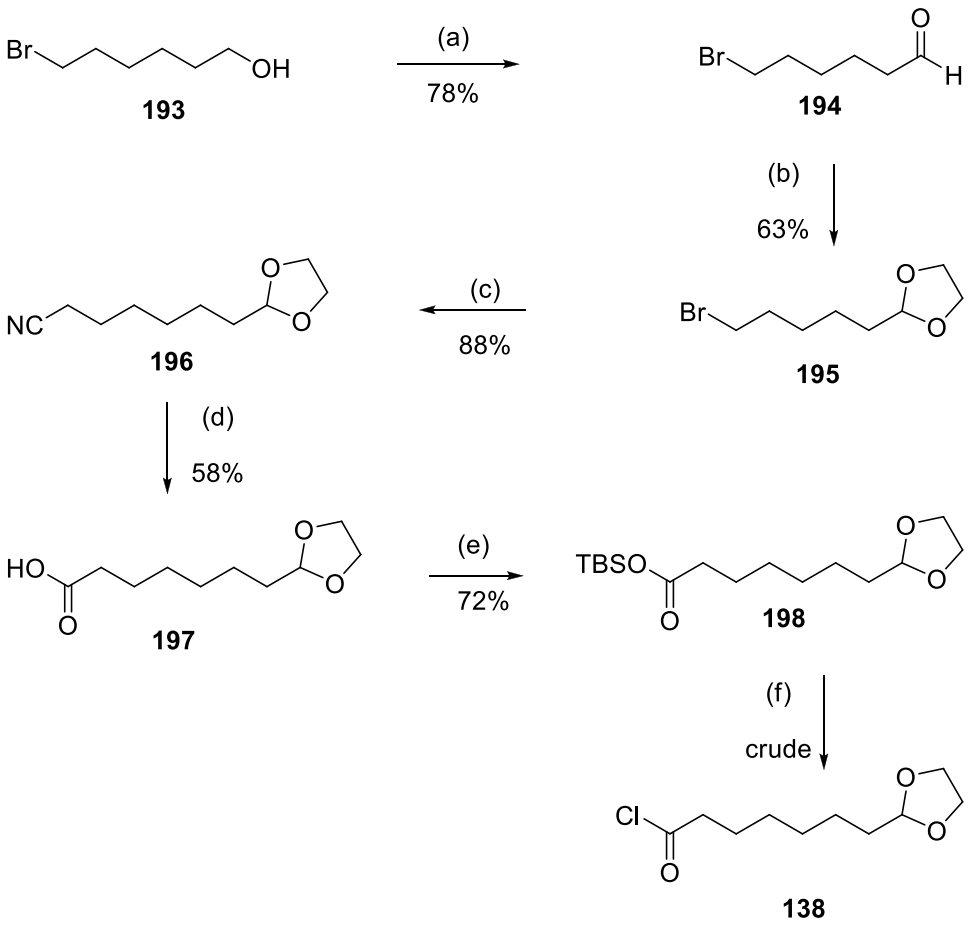



**Scheme 49**: Synthetic pathways towards a model system of the hydroisobenzofuran core of the cladiellin diterpenes

The initial decision was to extend the approach by previous members of the group[35], starting with a larger carbon chain as in compound **138**, **Scheme 49**. It was apparent that acylation of ester **114** with acid chloride **138** could potentially give a model system (**139**) for the hydroisobenzofuran core containing an oxacyclic component with an additional three carbon atoms.

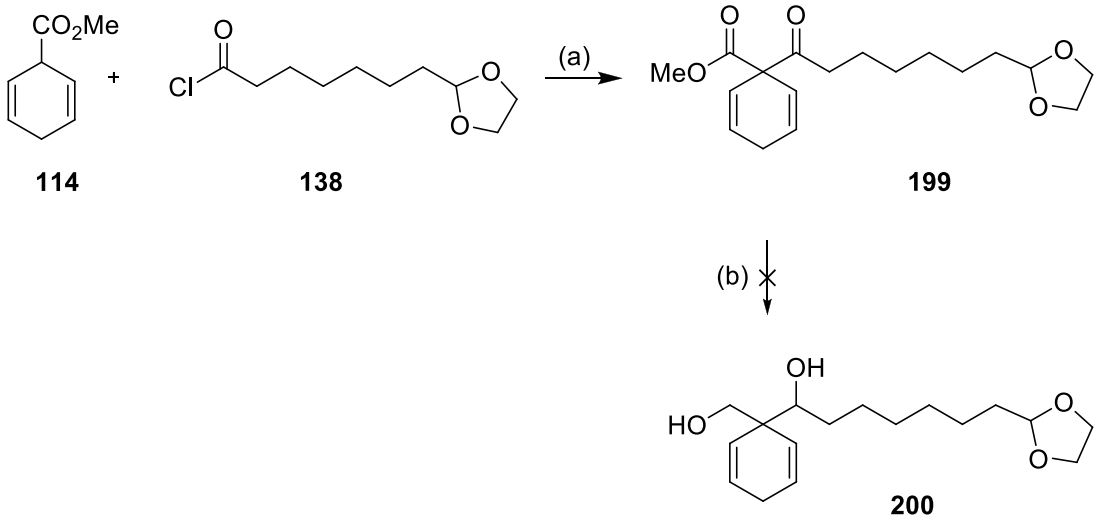
### 4.2. Results and discussion

Preparation of acid chloride **138** was accomplished as follows. Oxidation of 6-bromo-1-hexanol **193** under Swern conditions gave the corresponding aldehyde **194**. Reaction with ethylene glycol and PPTS in benzene using a Dean-Stark water separator gave dioxolane **195**. A two-carbon homologation was performed with acetonitrile to give nitrile **196** in good yield. Hydrolysis of compound **196** with KOH in water/ethanol (2:1) then gave acid **197** without loss of the sensitive dioxolane protecting group. The group of Wissner reported a strategy for forming acid chlorides from carboxylic acids containing acid-sensitive functionality.[59] The methodology involved converting the acid into the corresponding *tert*-butyldimethylsilyl ester, which was then treated with oxalyl chloride and catalytic DMF at room temperature to give the acid chloride. This enabled the formation of acid chlorides under much milder conditions than would usually be required. Applying these conditions to acid **197** gave silyl ester **198**, however, it was not a complete conversion to compound **198** as the NMR data showed that traces of the starting material **197** was still present. Compound **198** was then converted successfully into compound **138.** This compound was used crude as it was anticipated that a compound of this nature would be extremely difficult to purify by means of chromatography or distillation (**Scheme 50**).



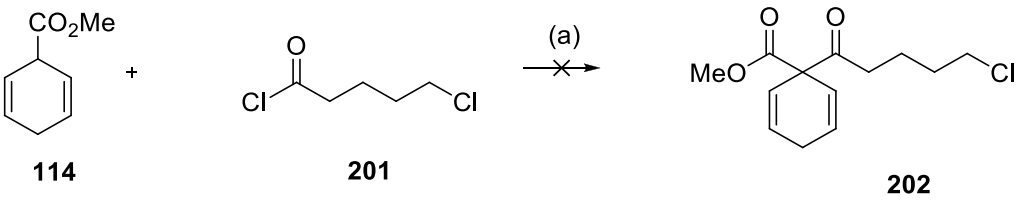

**Scheme 50.** Preparation of acid chloride **138.** *Reagents and conditions:* (a) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, -78 °C, (b) ethylene glycol, PPTS, benzene, 100 °C, 12 h, (c) LDA, MeCN, THF, -78 °C to room temperature, 18 h; (d) KOH, EtOH/$H_2O$ (2:1), reflux, 16 h, (e) TBS-Cl, imidazole, 4-DMAP, $CH_2Cl_2$, 30 min; (f) $(COCl)_2$, DMF (cat.), $CH_2Cl_2$, 0 °C to room temperature, 2 h

Acid chloride **138** was then treated with ester **114** (formed by Birch reduction of benzoic acid, then esterification upon reaction with $H_2SO_4$ in MeOH) using LDA at -78 °C. Reduction of the crude product was then attempted even though the acylation was not conclusive. However, formation of alcohol **200** using $LiAlH_4$ was not successful.



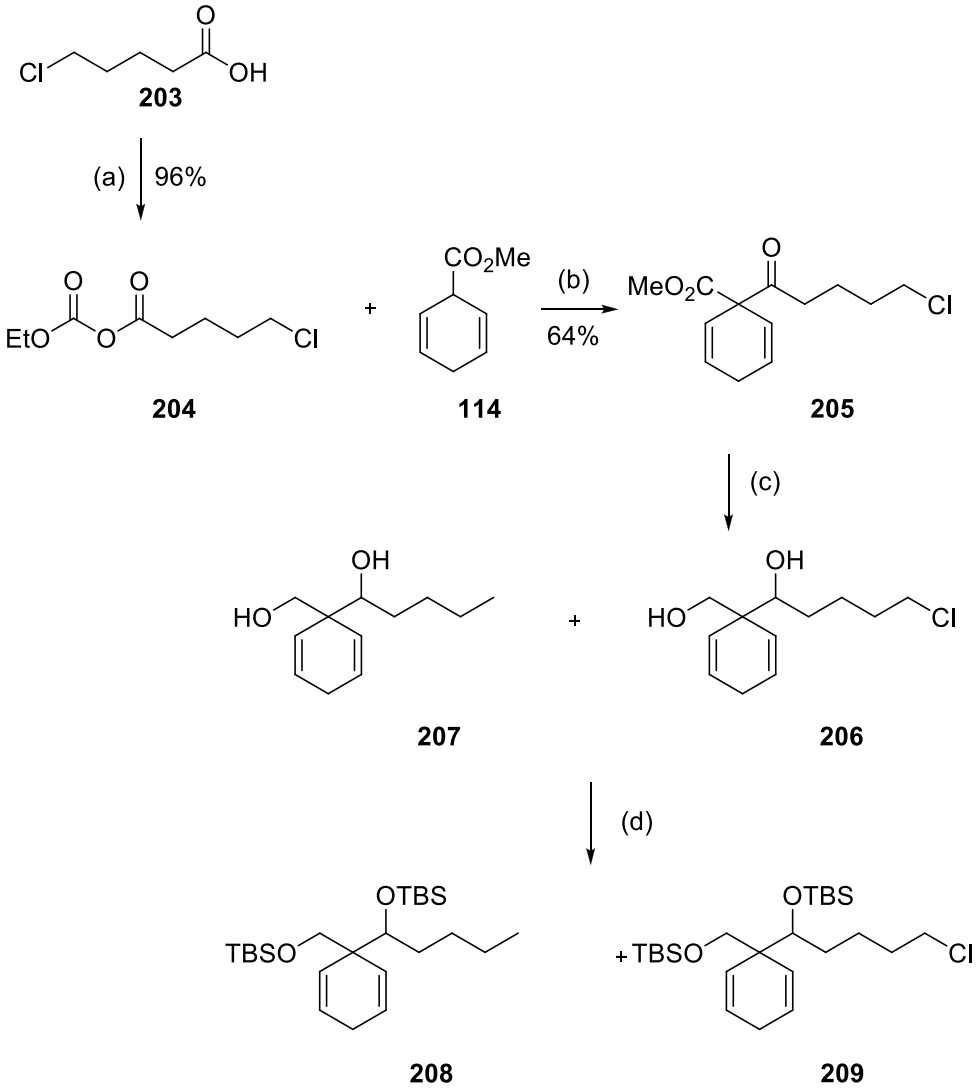

**Scheme 51.** Attempted formation of alcohol **200** *Reagents and conditions:* (a) LDA, THF, -78 °C; (b) $LiAlH_4$, THF, 25 °C, 30 min

Acylation of ester **114** with 5-chloropentanoyl chloride **201** (prepared by treatment of 5-chloropentanoic acid with oxalyl chloride and catalytic DMF in dichloromethane) was attempted, with the intention to homologate from the chloride after acylation. However formation of ester **202** was unsuccessful. In the proton NMR spectrum of the crude product, the presence of a significant amount of aromatic compounds and no cyclohexadiene indicated that decomposition of the cyclohexadiene had taken place.



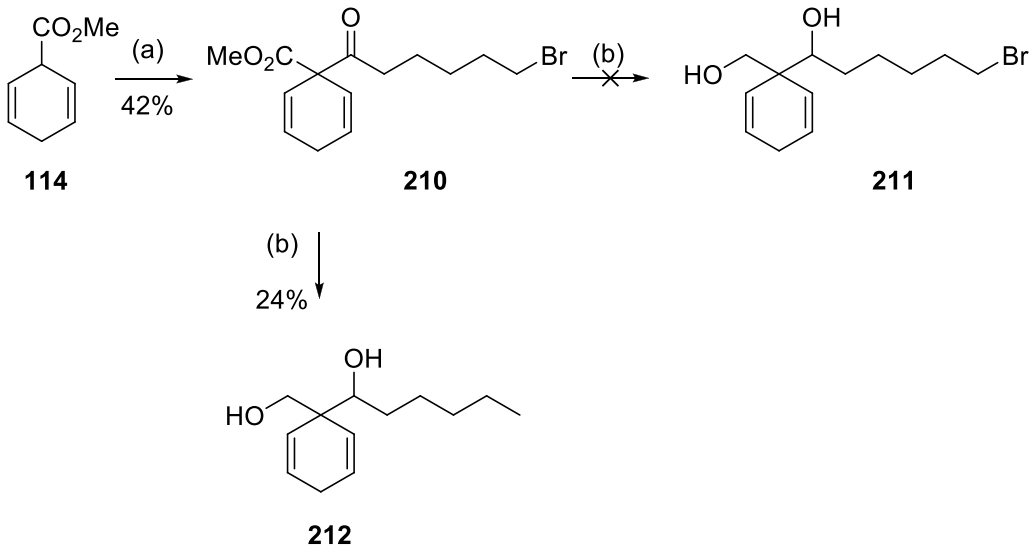

**Scheme 52.** Attempted acylation of ester **114** with 5-chloropentanoyl chloride **201** *Reagents and conditions:* (a) LDA, THF, -78 °C

Following on from this an alternative route was devised which involved mixed anhydrides[60] rather than acid chlorides. The mixed acid anhydride **204** was formed from reaction of commercially available 5-chloropentanoic acid (**203**) with ethyl chloroformate and triethylamine in THF at 0 °C (**Scheme 53**). Acylation of ester **114** with acid anhydride **203** using LDA in THF at -78 °C was successful and, after purification using flash chromatography, gave compound **205** in 64% yield. Reduction with $LiAlH_4$ at room temperature gave a mixture of compounds **206** and **207**, which could not be separated by chromatography. The inseparable mixture of **206** and **207** was treated with *tert*-butyldimethylsilyl chloride and triethylamine in THF in an attempt at protecting the diol of compound **207** as the TBS ether; this gave an inseparable mixture of compounds **208** and **209**.




**Scheme 53.** Synthesis of compound **208** and **209.** *Reagents and conditions*: (a) Ethyl chloroformate, triethylamine, THF, 0 °C (b) LDA, THF, -78 °C; (c) $LiAlH_4$, THF, 25 °C; (d) triethylamine, TBSOTf, $CH_2Cl_2$, 0 °C

The same problem was also observed with compound **210**. However, the halogen used here was bromine and there was a complete loss of the bromine during the reduction, as shown in **Scheme 54**.




**Scheme 54.** Synthesis of compound **212**. *Reagents and conditions:* (a) LDA, 6-bromohexanoyl chloride, THF, -78 °C; (b) $LiAlH_4$, THF, 25 °C, 30 min

Because of the difficulties encountered with the purification of compound **209**, this compound was used directly, (contaminated with approximately 60% of compound **208**) in the hope that the impurity could be removed at a later stage. Even though it would ultimately give a compound with the incorrect ring size (compound **213**, **Figure 16**, rather than compound **139**), a two-carbon homologation of compound **214** was used to confirm the viability of the method.

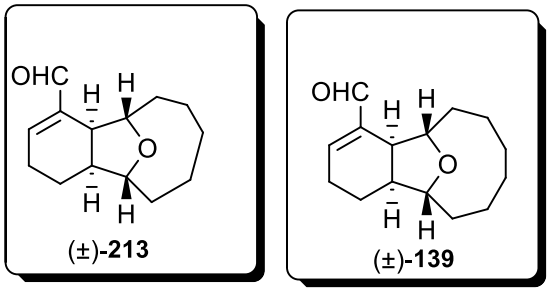
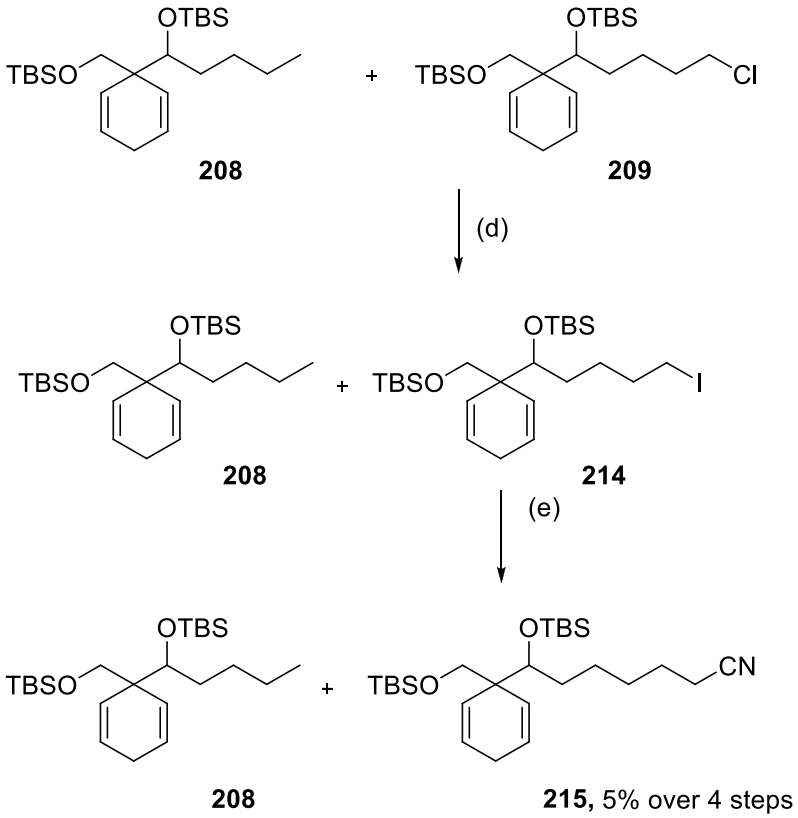


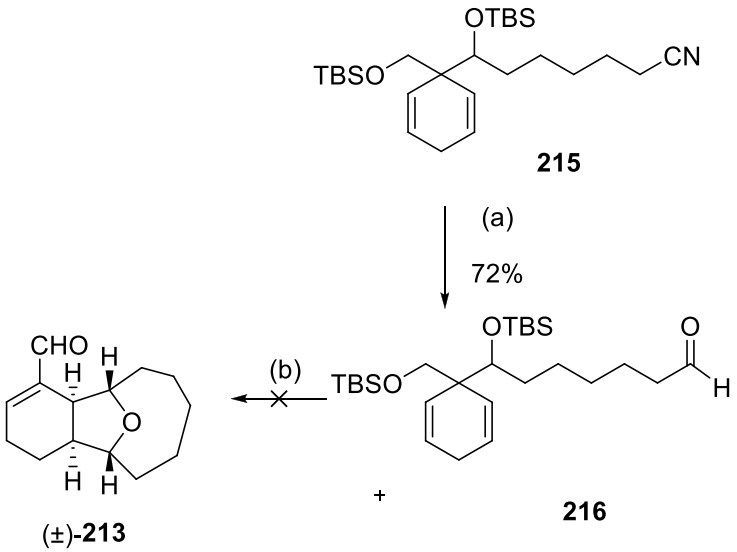

**Figure 16.** Comparison of the 8-membered ring in the proposed product (**213**) to the 9-membered ring in the desired cladiellin framework in compound **139**

Conversion of the chloride to the alkyl iodide was performed using a Finkelstein reaction with sodium iodide in acetone at 60 °C for three days. The iodide **214** (still contaminated with approximately 60% of compound **209**) was then converted into the corresponding nitrile **215**, using LDA and MeCN in THF at -78 °C (**Scheme 55**).



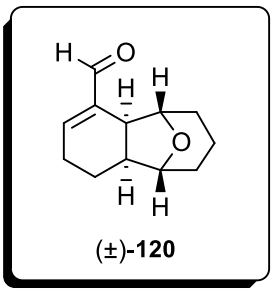

**Scheme 55.** Synthesis of compounds **208** and **215**. *Reagents and conditions:* (d) NaI, Acetone, 60 °C, 3 d; (e) LDA, MeCN, THF, -78 °C

During purification, isolation of compound **215** was successful, allowing the formation of aldehyde **216** *via* DIBAL-H reduction in $CH_2Cl_2$ at -78 °C. As this was a small-scale reaction, the crude aldehyde **216** was directly treated with trifluoromethanesulfonic acid without any further purification, in hope of deprotecting and cyclising to form the target compound **217** in one step (**Scheme 56**). This approach had previously been successful within the Elliott group for the formation of the analogous compound with a six-membered ring (compound **120**, page 34).




**Scheme 56**. Attempted synthesis of compound **213.** *Reagents and conditions:* (a) Di-isobutylaluminium hydride, $CH_2Cl_2$, -40 °C, 2 h; (b) Trifluoromethanesulfonic acid, $CH_2Cl_2$, 0 °C, 20 min

There was evidence to suggest compound **213** had been synthesised. The proton NMR spectrum of the crude product contained no cyclohexadiene peaks. Significant peaks were observed around 9.45 ppm (α,β-unsaturated aldehyde) and 7.0 ppm (alkene β-CH). Peaks in these regions of the proton NMR spectrum are indicative of Prins rearrangement products such as compound **120** (**Figure 17**) from earlier studies.



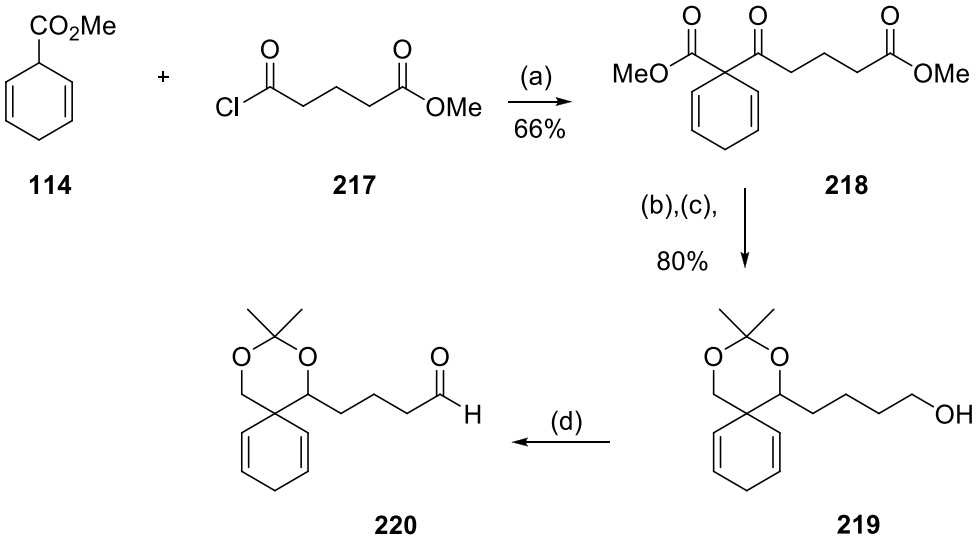

(±)-**120**

**Figure 17.** Example of a Prins cyclisation/ rearrangement product (**120**) synthesised previously in the Elliott group[35]

However, even after purification of compound **213** by chromatography, the product containing these key peaks was still very contaminated. Therefore, unfortunately, it was not possible to isolate or characterise compound **213**, and it was not possible to confirm formation of the product.

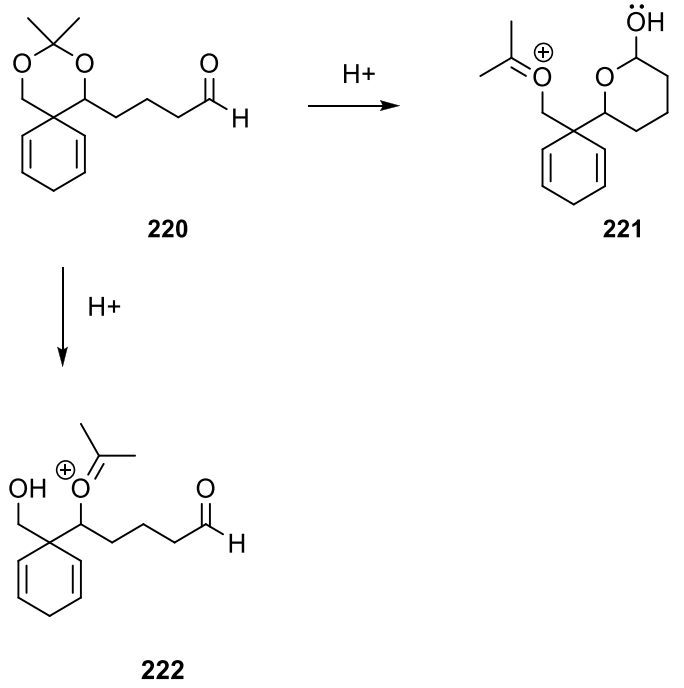
Due to these problems a new route was devised as illustrated in **Scheme 57**. This route would give a model system for the hexahydroisobenzofuran core of the cladiellin diterpene containing a 6-membered oxacyclic component (**120**) as opposed to the 9-membered oxacyclic component in the cladiellin diterpene structures. However, this could be used to test the viability of the overall approach, which could then be applied to the larger ring systems.

Commercially available methyl 5-chloro-5-oxopentanoate **217** was coupled with ester **114** using LDA to deprotonate at -78 °C. Ester (**218**) was reduced using $LiAlH_4$ in THF at 25 °C. The next stage, where protection of the 1,3-diol was required while leaving the remaining primary alcohol unprotected, was challenging. However, after investigating a number of approaches without success (including use of di-*tert*-butylsilylene protecting group, and direct oxidation of the less-hindered primary alcohol using Swern conditions without a protecting group) the 1,3-diol was protected as a ketal (**219**) using 2,2-dimethoxypropane and catalytic camphorsulfonic acid in acetone for 24 h.



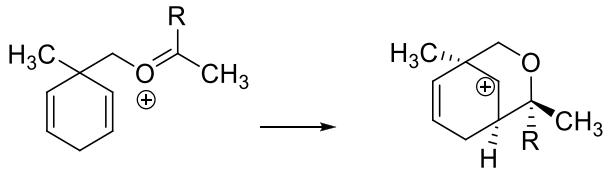

**Scheme 57.** Synthesis of compound **220**. *Reagents and conditions:* (a) LDA, THF -78 °C; (b) $LiAlH_4$, THF, 25 °C; (c) 2,2-dimethoxypropane, camphorsulfonic acid, acetone, 60 °C, 24h; (d) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, -78 °C

The advantage of this route is that it allows formation of aldehyde **220** using mild conditions. However the disadvantage is that, during the deprotection of the ketal, two possible oxocarbenium ions could be formed, depending on the direction of ring-opening (**Scheme 58**). Protonation of the aldehyde (**220**) could lead to a directed ring-opening giving compound **221** but this compound would contain an oxocarbenium ion derived from a ketone and this could also participate in a Prins reaction. In the absence of a directing effect, the expected direction of ring-opening would be governed by protonation of the least hindered oxygen as in compound **222**.




**Scheme 58:** Formation of two possible oxocarbenium ions (**221** and **222**) during Prins cyclisation of aldehyde **220**

Success of the desired cyclisation reaction of compound **220** would depend on the rate of the cyclisation of oxocarbenium ion **221**. To evaluate this possibility, semi-empirical calculations, at the PM6 level, were carried out on a simplified system where R = H (aldehyde) and R = Me (ketone) (**Scheme 59**).




**223** **224**

**Scheme 59.** Simplified system for semi-empirical calculations, at the PM6 level

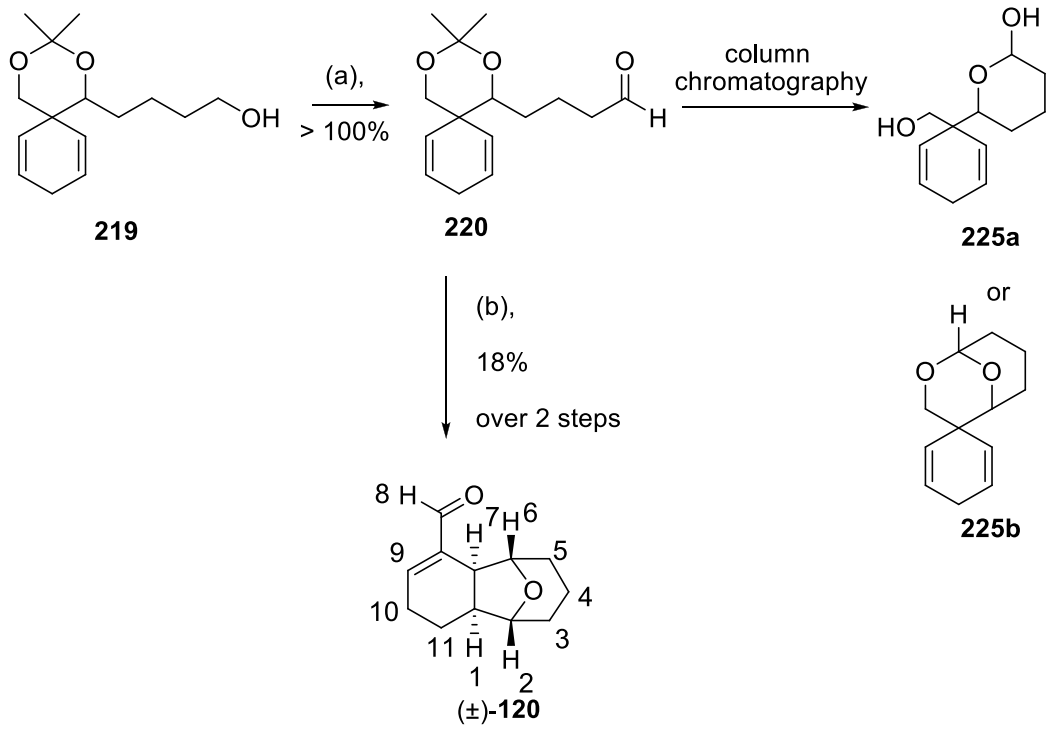
For each case, the energy of the oxocarbenium ion, the transition state for cyclisation and the cationic product was calculated. The activation energy was also calculated from the difference in energy between the starting material and the transition state. The results are as follows (**Table 2**).

| | R = H | R = Me |
|---|---|---|
| Oxocarbenium ion **223** | 593.85 | 522.97 |
| Transition state | 660.72 | 607.23 |
| Cationic product **224** | 654.01 | 605.34 |
| Activation energy | 66.87 | 84.26 |

**Table 2.** Calculated Energies (kJ $mol^{-1}$) of the oxocarbenium ion, the transition state for cyclisation and the cationic product

There are two key conclusions from these results. The main one is that the activation energy for cyclisation of the ketone oxocarbenium ion is approximately 17 kJ $mol^{-1}$ higher than for the aldehyde oxocarbenium ion. This is a significant energy difference. Secondly, there is only a small energy difference between the transition state and the carbocation product. This product is much less stable than the starting material. However, this is not so surprising, since the product is a non-stabilised secondary carbocation, where as the starting material is a relatively stable oxocarbenium ion. The results therefore show that the oxocarbenium ion that is generated from the ketal will react less readily than that from the acetal. The calculations would also indicate that the Prins cyclisation should be reversible and, at equilibrium, the oxocarbenium ion would be favoured.

Alcohol **219** was oxidised using Swern conditions to give the corresponding aldehyde **220** in crude state. However, purification of aldehyde **220** was not achieved. During purification of compound **220** using flash chromatography an unknown compound was formed. The proton NMR spectrum showed no sign of the aldehyde peak and loss of the ketal protecting group so that presumably cyclisation had taken place to give either the hemiacetal **225a** or the acetal **225b**. As a result of this, crude aldehyde **220** was treated directly with trifluoromethanesulfonic acid in $CH_2Cl_2$ for 20 minutes, and this gave the Prins cyclisation/rearrangement product **120**, **Scheme 60**.




**Scheme 60.** Prins cylisation reaction of compound **220** and formation of compound **120.**

*Reagents and conditions:* (a) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, -78 °C; (b) Trifluoromethanesulfonic acid, $CH_2Cl_2$, 0 °C, 30 min.

Compound **120** was synthesised in fewer steps than the two previous approaches within the group. During those studies, the stereochemical configuration was not confirmed. During this study, two dimensional $^{1}H$-$^{1}H$ NOESY NMR spectroscopy was carried out on compound **120** and showed a cross-peak between H-2 and one of H-10 which strongly suggests that it contains the desired stereochemical configuration, where the core is characterised by an *anti* relationship between the two pairs of ring junction protons as illustrated. The successful use of the ketal protecting group in this instance is surprising in view of the reaction mechanism. There is no water present to hydrolyse the ketal, so it is possible that protonation of the aldehyde is resulting in a directed opening of the ketal to form the desired oxocarbenium ion **225**.

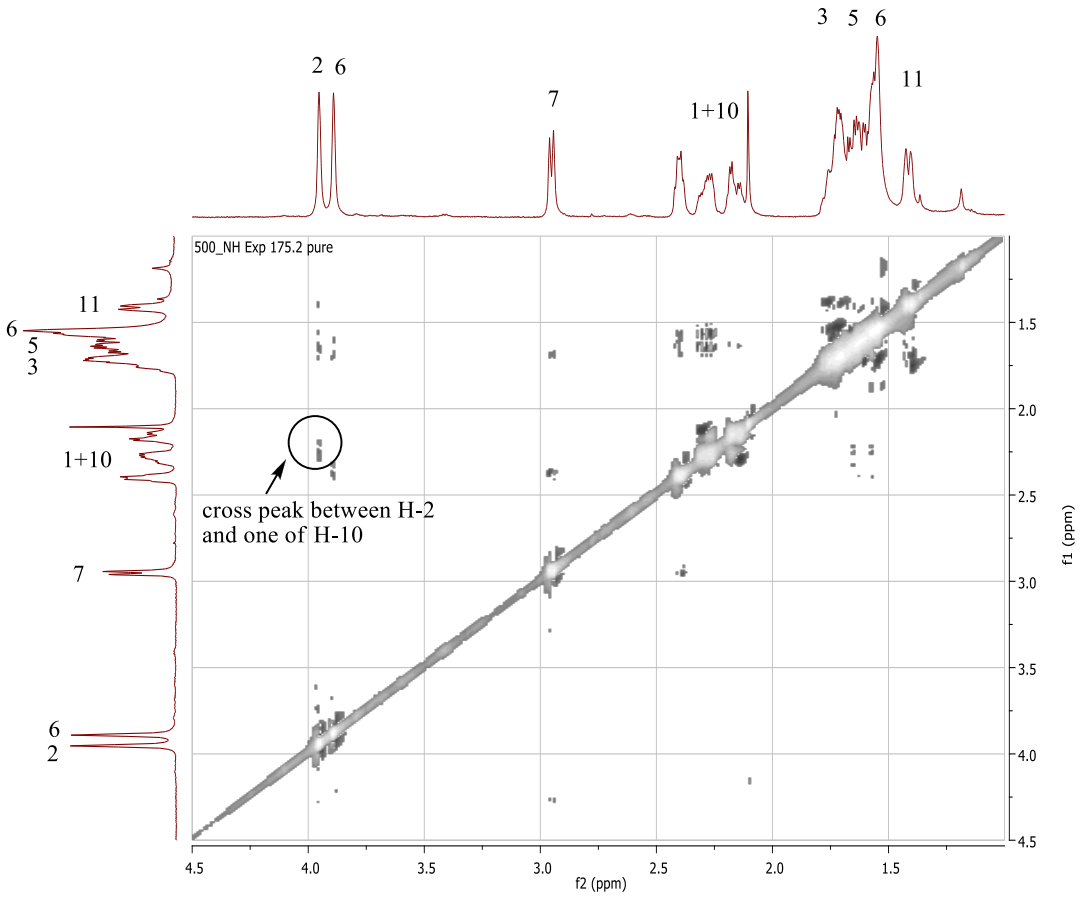
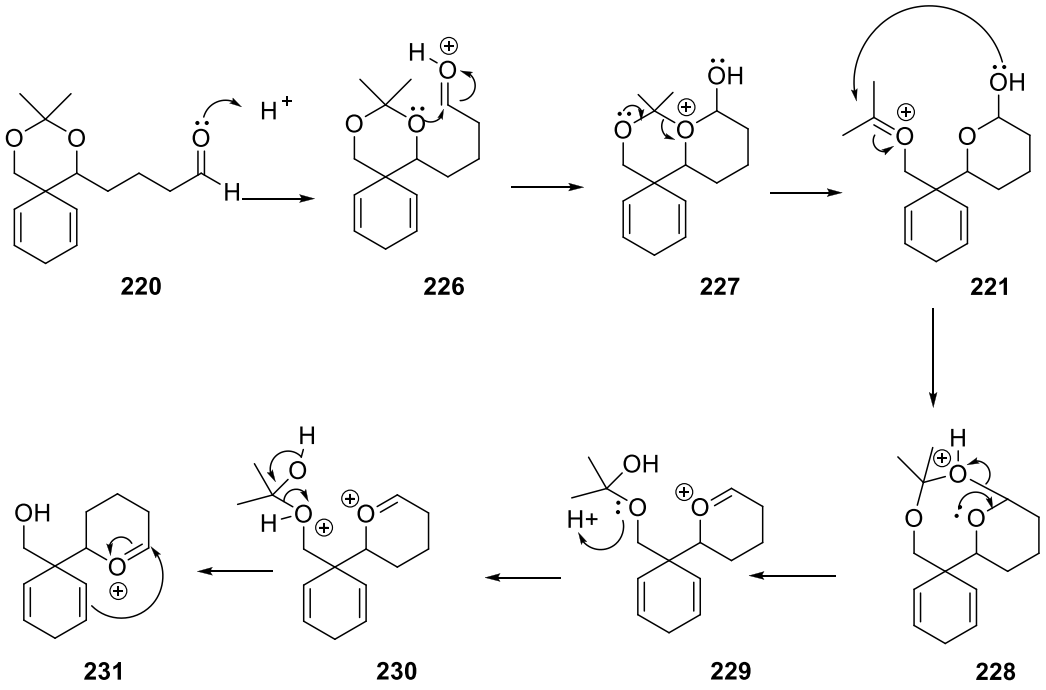



**Figure 18:** NOESY spectrum of compound **120**

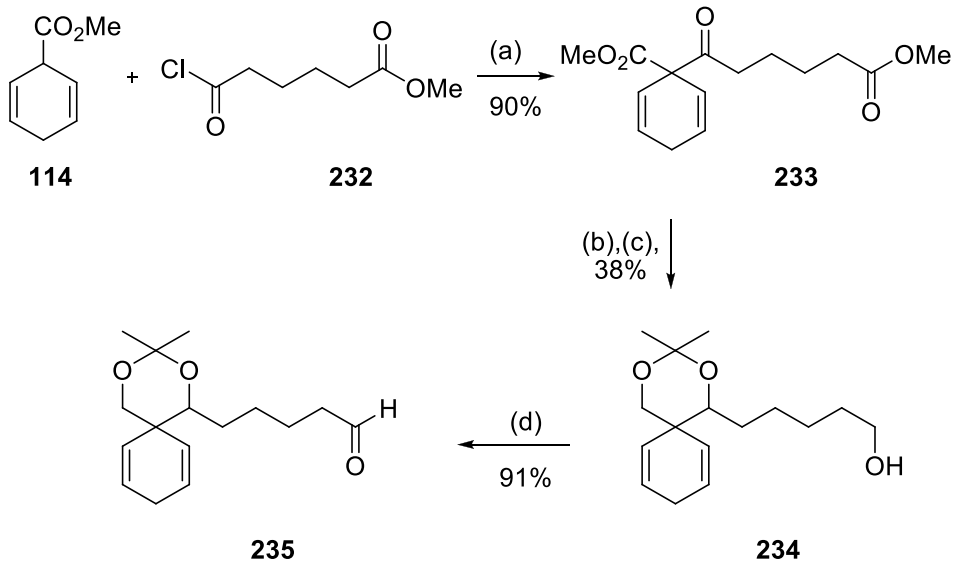
The mechanism is proposed to proceed *via* protonation of the aldehyde to form cation **226 (Scheme 61)**. From this point, attack of the ketal oxygen atom onto the protonated carbonyl group would give oxonium ion **227**. Cleavage of the ketal could give oxocarbenium ion **215**. From this point the mechanism is rather speculative, but it seems plausible that the hemiacetal OH group could attack the oxocarbenium ion to form compound **223**. Fragmentation as shown would allow eventual loss of acetone to give the key oxocarbenium ion **225,** which would then undergo the Prins-Wagner-Meerwein sequence as previously described.




**Scheme 61:** Proposed reaction mechanism for the formation of compound **231**

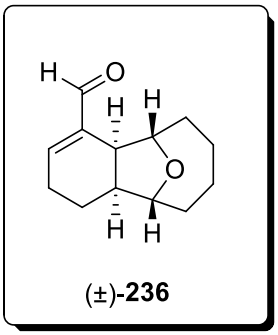
After the success of forming the 6-membered ring product **120,** the same strategy was applied to form larger ring sizes. The same method was applied in an attempt to form a 7-membered oxacyclic component and a nine-membered oxacyclic component. Formation of the 7-membered oxacyclic compound began with commercially available methyl 6-chloro-6-oxohexanoate **232** which was was coupled with ester **114** using LDA to deprotonate at -78 °C. Reduction of compound **233** using $LiAlH_4$, followed by reaction with 2,2-dimethoxypropane and catalytic camphorsulfonic acid in acetone for 24 h gave

compound **234**. This allowed oxidation of the unprotected alcohol into the corresponding aldehyde (**235**) using Swern conditions.




**Scheme 62.** Synthesis of compound **235.** *Reagents and conditions:* (a) LDA, THF -78 °C; (b) $LiAlH_4$, THF, 25 °C; (c) 2,2-dimethoxypropane, camphorsulfonic acid, acetone, 60 °C, 24h; (d) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, -78 °C

Treatment of aldehyde **235** with trifluoromethanesulfonic acid in $CH_2Cl_2$ for 20 minutes gave three distinct products that were isolated after chromatography. The NMR spectra of all of these compounds showed significant similarities with that of compound **120**. In particular, each contained an α,β-unsaturated aldehyde, two protons adjacent to oxygen and a proton in the ring junction next to the double bond. The connectivity in these compounds was confirmed by $^{1}H$-$^{1}H$ COSY NMR spectroscopy. It was therefore apparent that a Prins cyclisation reaction followed by rearrangement had indeed occurred. However, after mass spectrometric analysis of the first and second compounds eluted, the molecular ions were twice the weight of the expected product **236**, which suggested that these compounds might be dimers of the desired compound **236**. The third eluted compound appeared, by similar analysis, to be a trimer of compound **236**.

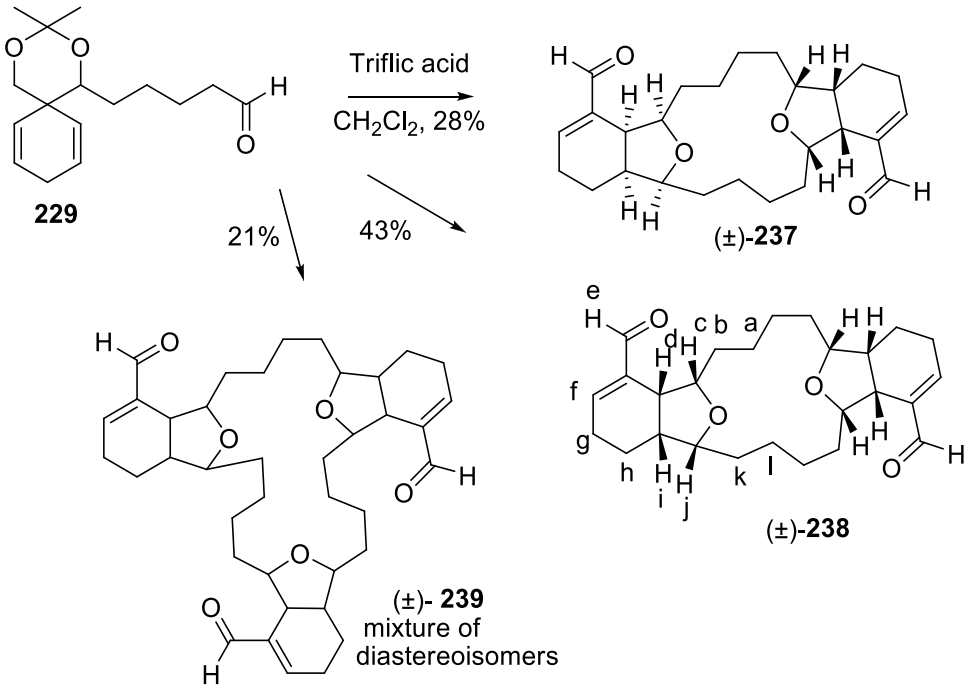



(±)-**236**

**Figure 19:** Expected product from Prins cylisation reaction of compound **235**

The structure and stereochemical configuration of the first compound was confirmed to be **237** by X-ray crystallographic analysis (**Figure 20**). Since the precursor **235** to this compound is racemic, formation of only one diastereoisomer of this structure would be remarkable. Therefore, based on the mass spectrometric data, a diastereoisomer of the dimeric compound **237** is the overwhelmingly likely structure for compound **238**. A $^{1}H$-$^{1}H$ COSY NMR spectrum confirmed the connectivity. Two dimensional NOESY NMR spectroscopy shows evidence of a cross-peak between *d* and c, *i* and *d*, *i* and *h* and no cross-peak between *j* and *g* or *j* and *c,* which confirms the stereochemistry shown, where the four hydrogen atoms on the tetrahydrofuran ring are all *cis*. Also the compound is clearly symmetrical according to the number of peaks in the $^{13}C$ NMR spectrum. This further supports the assignment of this compound as a diastereoisomer of compound **237**. The

chemical shifts and coupling patterns of compound **239** are similar to other compounds of this general structure. The $^{13}C$ NMR spectrum showed a significant number of peaks, consistent with the compound being formed as a mixture of diastereoisomers, as shown in **Scheme 63**.




**Scheme 63.** Formation of compounds **237, 238** and **239.**

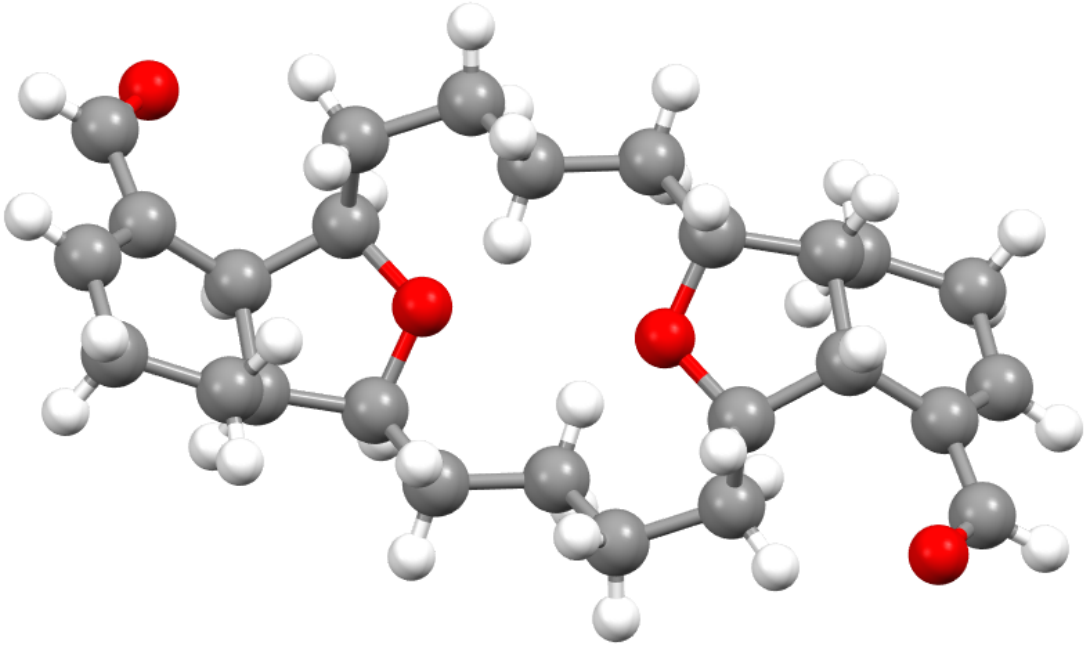
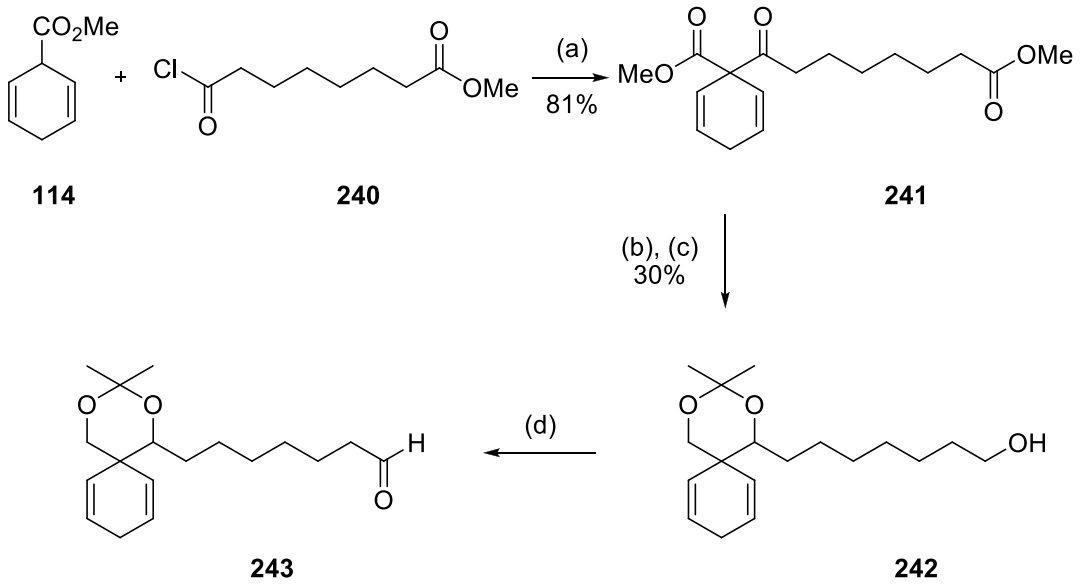


**Figure 20:** Structure of compound **237** from single-crystal X-ray diffraction data

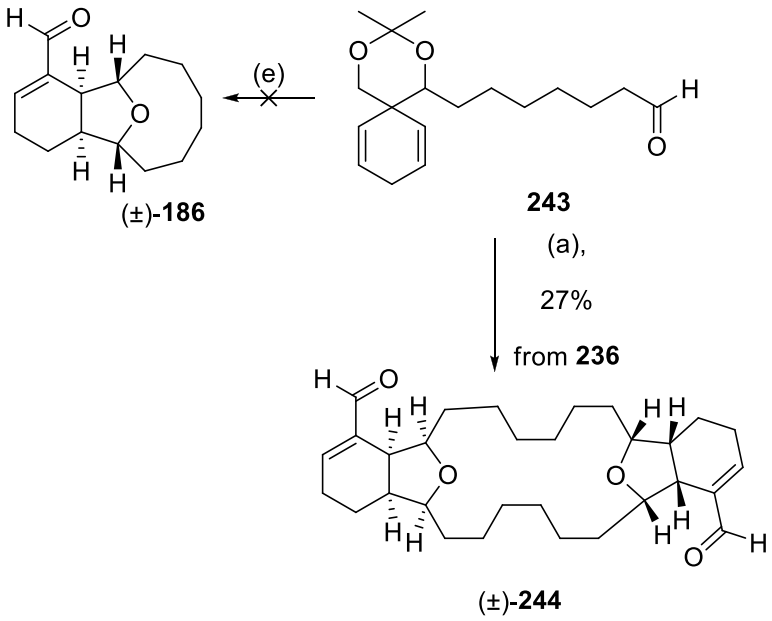
Synthesis of the nine-membered oxacyclic component began with commercially available methyl 8-chloro-8-oxooctanoate (**240**) which was coupled with ester **114** using LDA at -78 °C. Formation of a ketal **242** was achieved by reduction of ester **241** using $LiAlH_4$ in THF at 25 °C then reaction with 2,2-dimethoxypropane and catalytic camphorsulfonic acid in acetone for 24 h. This allowed oxidation of the unprotected alcohol into the corresponding aldehyde (**243**) using Swern conditions. Compared to the previous work, compounds **241** – **243** all proved very difficult to purify, and even the best samples contained significant impurities. In particular, aldehyde **243** was found to be unstable and decomposed within 24 hours, so that it had to be prepared and used promptly and without purification.




**Scheme 64.** Synthesis of compound **243.** *Reagents and conditions:* (a) LDA, THF -78 °C; (b) $LiAlH_4$, THF, 25 °C; (c) 2,2-dimethoxypropane, camphorsulfonic acid, acetone, 60 °C, 24h; (d) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, -78 °C

Treatment of aldehyde **243** with trifluoromethanesulfonic acid in $CH_2Cl_2$ gave the dimeric compound **244**. While only one diastereoisomer of this compound was obtained pure, the proton NMR spectrum of the crude reaction mixture showed two aldehyde peaks (9.44 ppm and 9.46 ppm), which would indicate that a diastereoisomer of the product was present. This product was unfortunately not obtained in pure form by chromatography.

The stereochemical configuration of **244** was confirmed by X-ray crystallographic analysis (**Figure 21**).




**Scheme 65.** Synthesis of compound **244.** *Reagents and conditions:* (a) Trifluoromethanesulfonic acid, $CH_2Cl_2$, 0 °C, 30 min

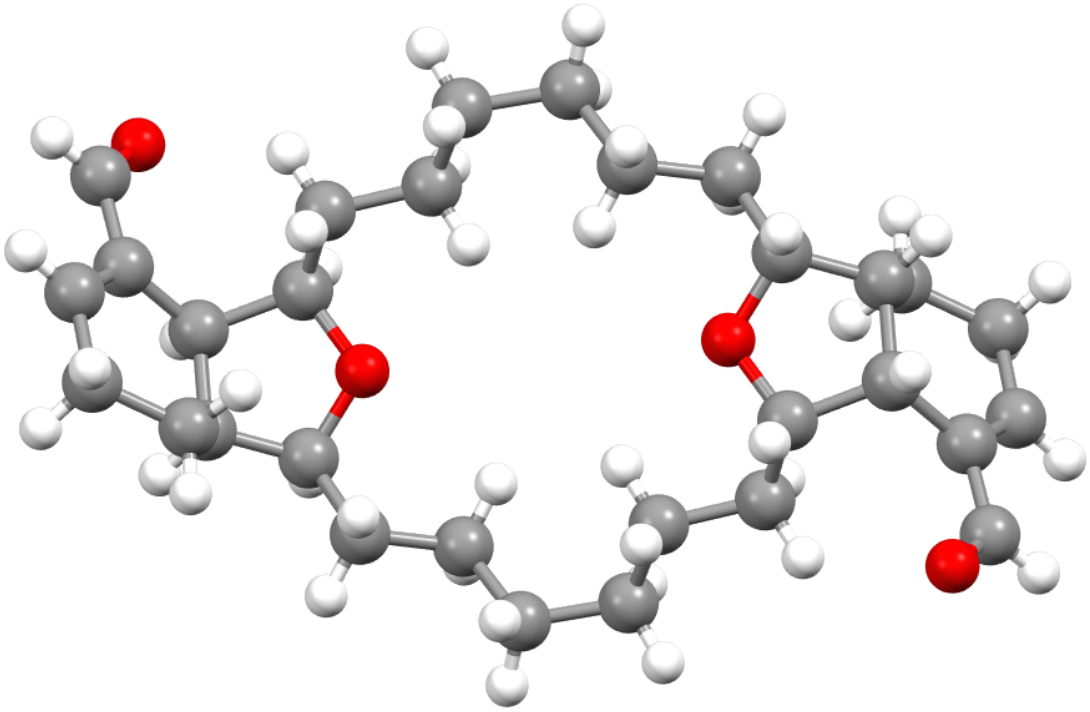
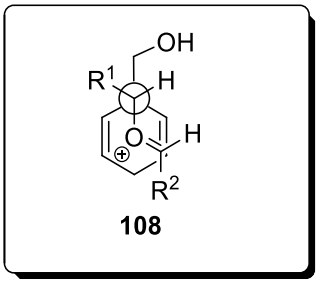


**Figure 21:** Structure of compound **244** from single-crystal X-ray diffraction data

Dimeric structures (**237**, **238**, **244**) and trimeric structure **239** were formed with the stereochemical outcome within each benzofuran sub-unit corresponding to that produced from an acyclic oxocarbenium ion **108** (**Figure 22**).[32]




**108**

**Figure 22:** Oxocarbenium ion

The starting materials **235** and **243** were racemic. The reaction proceeds with complete stereocontrol within each benzofuran sub-unit. Therefore, we can consider the array of stereocentres within each sub-unit to be either R or S as defined by the stereochemical configuration of the precursor. In this case, a dimeric product could have the stereochemical configuration RR, RS, SR or SS. RR and SS are enantiomers as shown schematically in **Figure 23**. Configurations RS and SR in this case are identical. For the trimeric product (**239**) with three sub-units, this could in principle be formed as a mixture of RRR, RRS, RSR, RSS, SRR, SRS, SSR and SSS stereoisomers. However, RRS, RSR and SRR are identical structures. These are enantiomeric with the RSS, SRS and SSR structure, which are again identical. The RRR structure is enantiomeric with the SSS structure. Therefore only two diastereoisomers are expected for both the dimer and trimer.

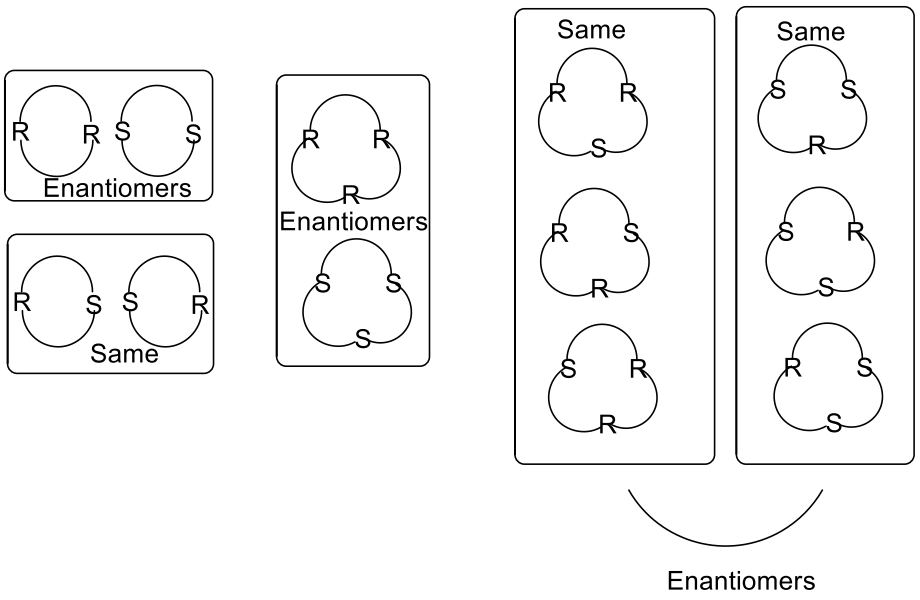



**Figure 23.** Representation of possible stereochemical configuration of dimeric structures (**237**, **238**,**244**) and trimeric structure (**239**)

What is less clear is why the macrocyclic products are formed rather than the desired compounds. Formation of 7- and 9- membered rings is often found to be difficult, and this can be explained in terms of ring strain.[61] Ring strain arises from a number of factors, in particular bond opposition forces due to imperfect staggering (Pitzer strain), deformation of ring bond angles (Baeyer strain) and transannular strain due to repulsive interactions between atoms across the ring when they are forced close to each other.[62] The energy for

the formation of medium-sized rings such as seven, eight and nine-membered is greater than the energy required for the formation of larger rings, fourteen-membered and onwards. The ring strain increases from a six-membered ring and reaches a maximum for a nine-membered ring then starts to decrease from a ten-membered ring and stays constant for a fourteen-membered ring and above. The smaller-ring systems however, such as five- and six-membered, require less energy to form due to their internal angle being close to the ideal tetrahedral angle of 109.5°. The more the angle deviates from this, the more strain there will be on the system and therefore the more energy required for the formation.

Illuminati and Mandolini carried out a study on lactone-forming reactions which showed; in 3 to 5-membered lactones the rate of cyclisation increases by five orders of magnitude. The rate decreases rapidly at the 8/9-membered rings due to the requirement of the ring size to force the ester functionality into the *cis* confirmation, and from 10-membered the rate of cyclisation gradually increases until it eventually levels off with the largest rings (**Figure 24**).[63]

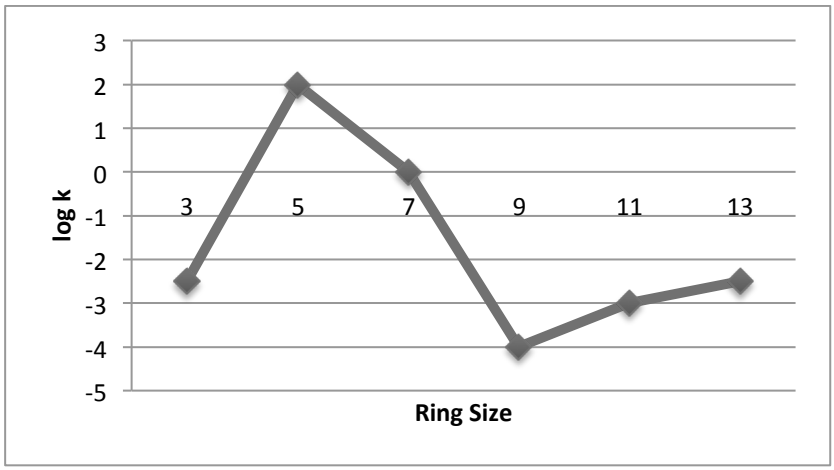
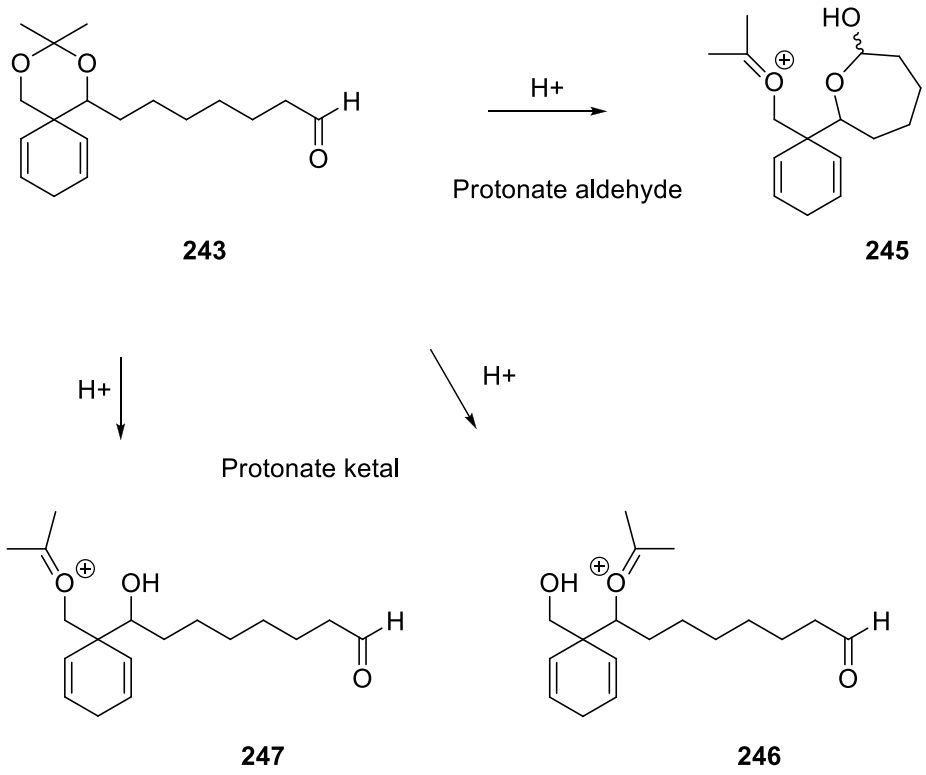



**Figure 24:** Reactivity profile for lactone formation

Formation of the macrocycles can be explained in terms of ring strain. However, in view of the reaction mechanism, the formation of macrocycles in this case is surprising. If the mechanism followed the same path as discussed earlier with the 6-membered Prins (**Scheme 61**), we might expect protonation of the aldehyde which could result in a directed opening of the ketal to form the desired oxocarbenium ion **245.** Formation of compound

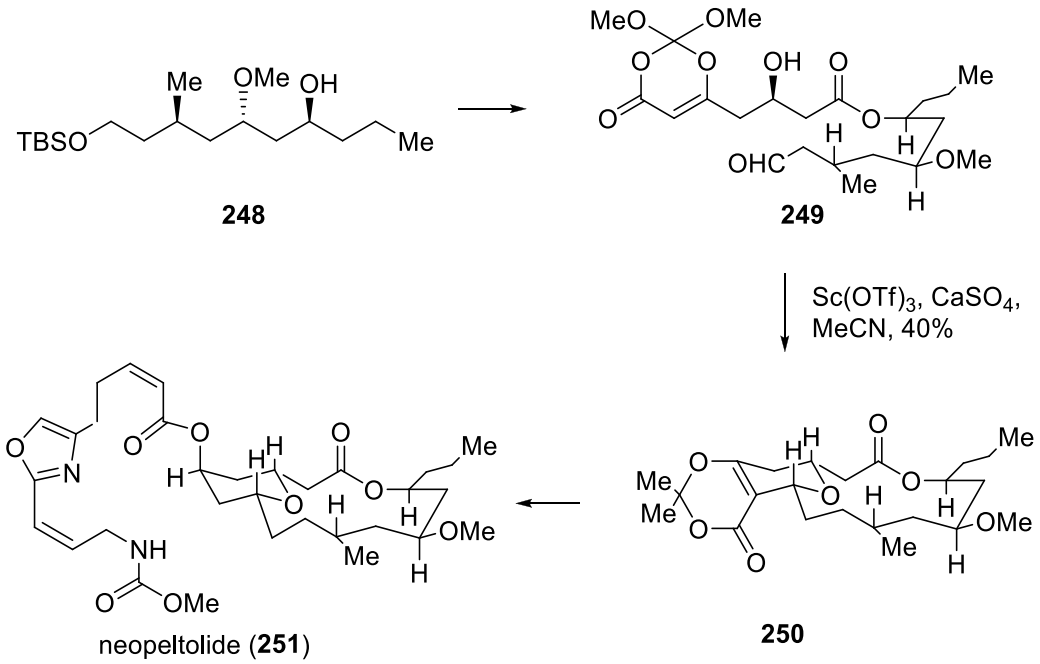
**245** would be expected which should ultimately give the desired monomer. If this applies for formation of the 14- and 18- membered rings then fundamentally one of the oxygen atoms of the ketal would react with an aldehyde from another molecule to form an oxocarbenium ion. With the ketal opening, protonation can take place in one of two positions. Protonation at the least hindered oxygen in **243** would give the expected product **247** or protonation of the more hindered oxygen would give compound **246** (**Scheme 66**). If protonation is taking place at the less hindered oxygen of the ketal then this leaves us to question how the secondary alcohol is forming an oxocarbenium ion (**Scheme 66**) but protonation of the more hindered oxygen is unexpected.




**Scheme 66.** Protonating of compound **243** during Prins cyclisation/ rearrangement

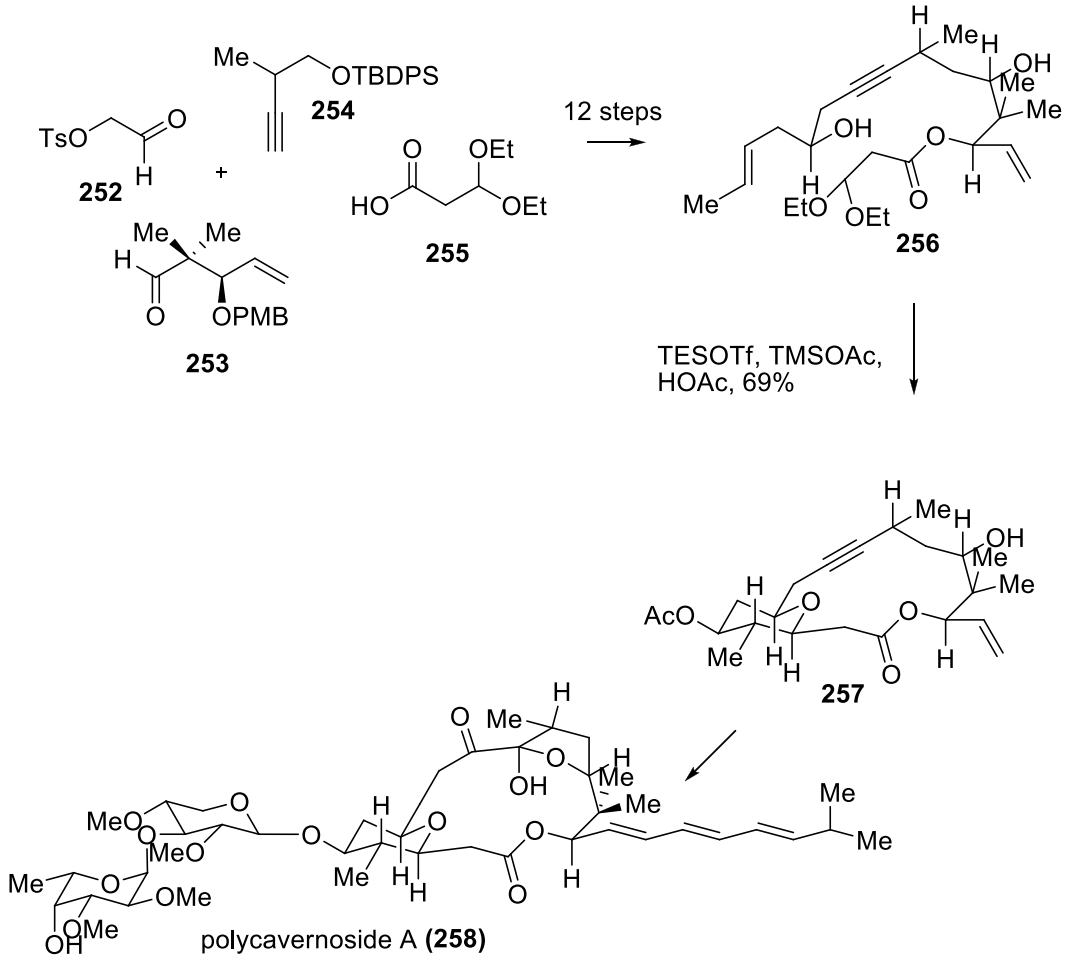
Methods to form the monomers of compounds **236** and **139** have been attempted. The Prins cyclisation/rearrangement step was repeated with varying conditions to attempt isolation of the monomer. Different acids (camphorsulfonic acid, hydrochloric acid) were used but they gave no reaction. High dilution conditions were used in an attempt to favour intramolecular oxocarbenium ion formation, but this gave no improvement - dimeric and trimeric products were still formed. Finally, quenching the reaction at varying temperatures was attempted. Quenching at 0 °C rather than 25 °C gave compound **238**. However there was no sign of the trimeric form **239**. Therefore quenching at -78 °C was attempted, but this gave no reaction; only unreacted starting material was recovered.

This is not the first time that a Prins reaction has been used to form a macrocycle. Several reactions have been reported including applications in natural product synthesis. The first example of this was the syntheses of neopeltolide, a 14-membered macrocycle with anticancer properties, by Custar *et al.*,[64] using Prins macrocyclisation to construct the macrocycle and embedded pyran ring (**Scheme 67**). Other reported syntheses of neopeltolide since then have also used the Prins macrocyclisation as a key bond-forming step.[65]




**Scheme 67.** Synthesis of Neopeltolide (**251**) by Custar *et al*[64]

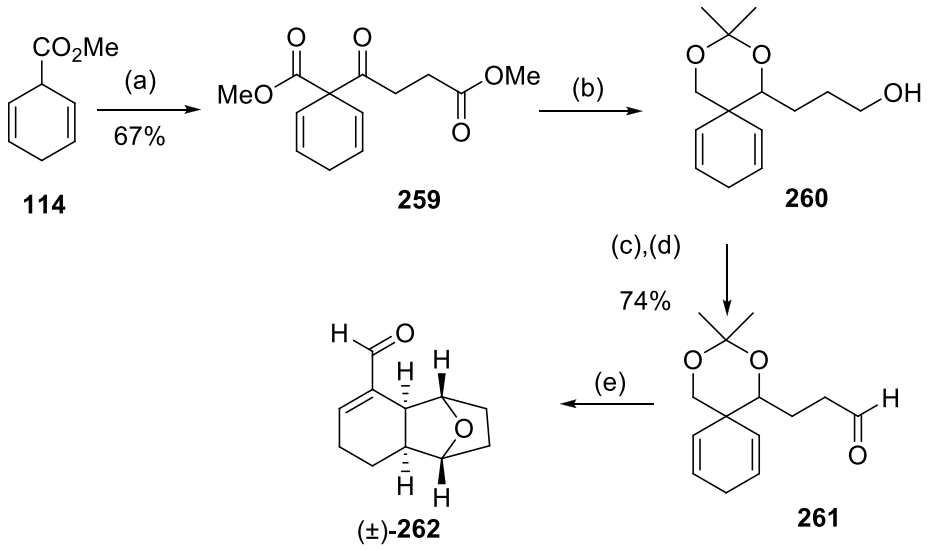
A more recent application of Prins macrocyclisation in natural product synthesis was reported by Woo and Lee in 2010 for the total synthesis of Polycavernoside A, a 16-membered macrolide containing a tetrahydropyran ring.[66] The macrocyclisation precusor **256** was formed in 12 steps and afforded the macrolide **257** in 69% yield (**Scheme 68**).




**Scheme 68.** Synthetic strategy towards Polycavernoside A by Lee and Woo[66]

After forming the six-membered oxacyclic component of the cladiellin diterpene as the monomer (**120**) and the seven and nine-membered as the dimers this theory was tested on another small ring to support the evidence that larger sizes favour the dimers and the smaller ring sizes the monomers. The next synthesis towards a model system for the cladiellin core contained a five-membered oxacyclic component (**262**), as shown in **Scheme 69**.

Commercially available methyl 4-chloro-4-oxobutanoate was coupled with ester **114** using *t*-BuLi to deprotonate at -78 °C. While LDA had been used successfully in previous cases, *t*-BuLi was found to give higher yields in this case. Other bases (*n*-BuLi, lithium bis (trimethylsilyl) amide, lithium 2,2,6,6-tetramethylpiperidide) did not perform better. Ketal **260** was fomed by reduction of ester **259** using $LiAlH_4$ in THF at 25 °C, then reaction with 2,2-dimethoxypropane and catalytic camphorsulfonic acid in acetone for 24 h. This allowed oxidation of the unprotected alcohol into the corresponding aldehyde (**261**) using Swern conditions. As reported with the earlier sequence, compounds **259** – **261** all proved very difficult to purify, and even the best samples contained significant impurities.




**Scheme 69.** Attempted synthesis of comound **262.** *Reagents and conditions:* (a) *t*-BuLi, methyl 4-chloro-4-oxobutanoate, THF, -78 °C; (b) $LiAlH_4$, THF, 25 °C; (c) 2,2-dimethoxypropane, camphorsulfonic acid, acetone, 60 °C, 24h; (d) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, -78 °C; (e) Trifluoromethanesulfonic acid, $CH_2Cl_2$, 0 °C, 30 min

There is evidence that the treatment of aldehyde **261** with trifluoromethanesulfonic acid in dichloromethane formed the desired product **262**, as there are significant peaks in the region of the proton NMR that correspond to previous products of similar structure, for example 9.43 ppm (aldehyde CH) and 7.03 ppm (alkene CH), with no evidence of any cyclohexadiene remaining. However, after extensive chromatography it was difficult to isolate compound **262**, therefore unfortunately further data could not be obtained in order to support these findings. Due to this it was impossible to determine whether any product formed was the monomer or dimer.

### 4.3. Conclusion

The Prins cyclisation/rearrangement methodology developed within the group allows access to a key fragment of the cladiellin diterpene skeleton. Three model systems of the cladiellin diterpene skeleton has been synthesised, each containing an oxacyclic component of varying sizes using this methodology. One of these (compound **120**) contained a smaller ring system than is present in the natural products but was isolated as a single diastereoisomer and was confirmed to possess the relative stereochemical configuration for the cladiellin diterpenes. Whilst the formation of the five-membered ring system **262** looked promising, however further research and analysis would be needed in order to support this.

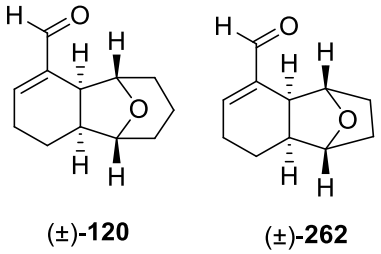



**Figure 25**. Compound **120** and compound **262**

However, when the methodology was applied to larger systems (seven- and nine-membered rings) dimeric (**237**, **238, 244**) and trimeric structures (**239**) were formed. The reason behind this could be explained in terms of ring strain, where the energy for the formation of medium size rings (seven, eight and nine) is higher than that required for larger sized rings; therefore formation of a fourteen-membered ring (**237** and **238**) rather than the required seven-membered (**236**) and an eighteen-membered ring (**244**) rather than the required nine-membered ring (**139**) would be preferred.

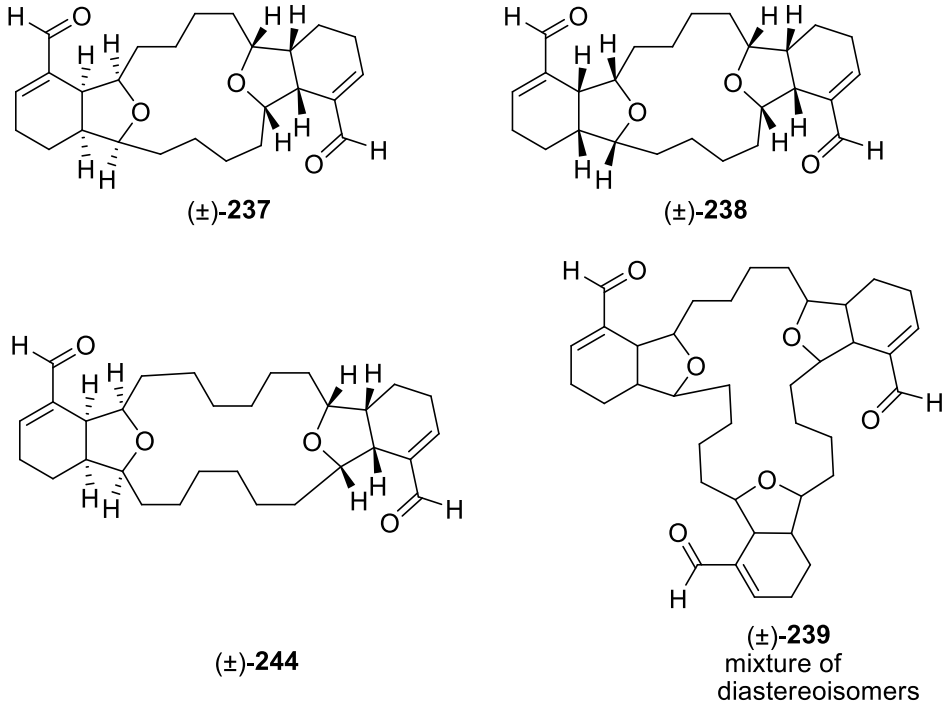



**Figure 26.** Formation of macrocyclic structures **237, 238, 244** and **239**

Even though the desired compounds **236** and **139** (**Figure 27**) were not formed, the results obtained are interesting and support the methodology for the Prins cyclisation/rearrangement. Mechanistic reasoning to explain the formation of the dimer/trimer is still being explored and would give an interesting study for future work.

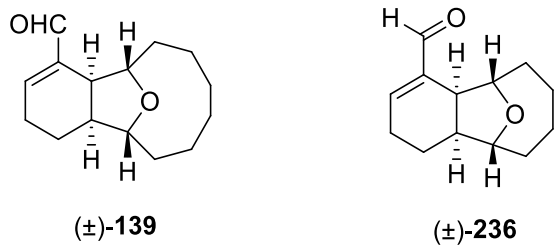


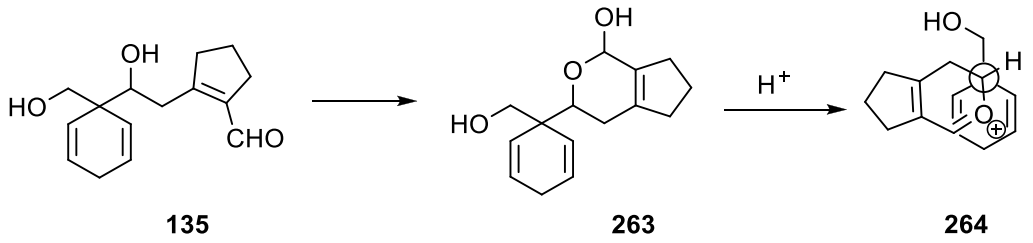

**Figure 27.** Desired compounds **139** and **236**

# Chapter 5

# Studies towards the Cladiellin Diterpene Framework

### 5.1. Introduction

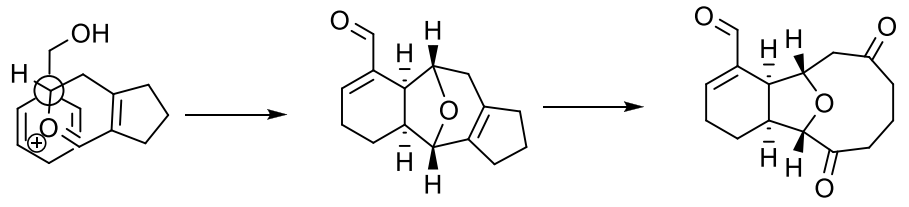
This chapter describes an alternative synthetic strategy from that attempted in **Chapter 4**, to construct the cladiellin diterpene framework using a 6,5-fused system and cleaving of this to form a 9-membered ring system. It was proposed that compound **182**, consisting of a five-membered ring, could provide a more viable route (**Scheme 70**). Formation of the corresponding oxocarbenium ion **264** also seems plausible, as the formation and successful Prins cyclisation of a six-membered cyclic oxocarbenium ion has previously been demonstrated in model studies of the cladiellin framework (compound **120,** page 80).




**135** **263** **264**

**Scheme 70.** Proposed structure **135** and treatment with acid to give intermediates **263** and **264**

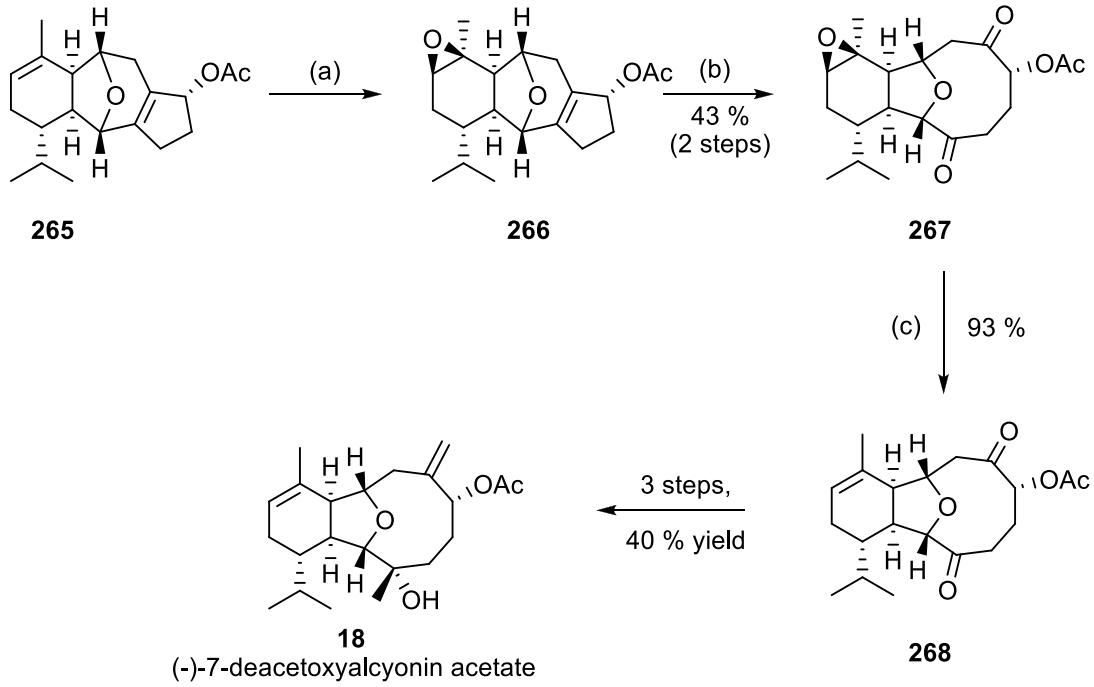
A successful Prins cyclisation/rearrangement will give compound **136** (**Scheme 73**). Molander's approach to the cladiellin skeleton could be used to open up the ring system to form the nine-membered ring.[11] This would involve selective oxidative cleavage of the tetra-substituted double-bond, to give the nine-membered ring directly,[67] as shown in **Scheme 71**.




**264** **136** **137**

**Scheme 71.** Proposed selective oxidative cleavage of compound **264**

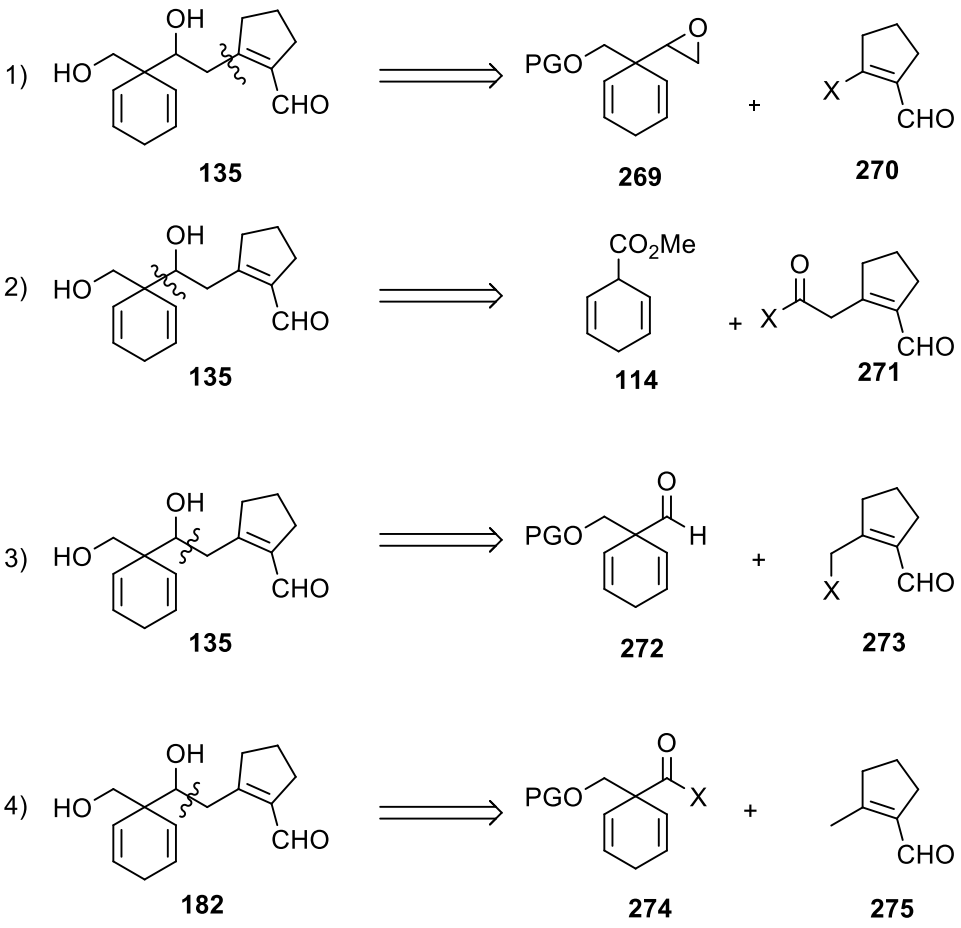
However, the Molander group were unable to achieve selective oxidative cleavage of the tetra-substituted double bond in a similar compound, during their synthesis of (-)-7-deacetoxyalcyonin acetate **18**.[11a] To overcome this problem, Molander *et al.* chemoselectively protected the tri-substituted double bond in compound **265** as the epoxide **266** before the oxidative cleavage step (**Scheme 72**). The epoxide **266** was subsequently reduced using $WCl_6$/*n*-BuLi and a further three synthetic steps led to (-)-7-deacetoxyalcyonin acetate (**18**).




**Scheme 72.** Synthesis of (-)-7-deacetoxyalcyonin acetate. *Reagents and Conditions*: (a) *m*-CPBA, 0 °C, 1 h; (b) $O_3$, -78 °C, then DMS, room temperature, 3 h; (c) $WCl_6$, *n*-BuLi (2 equiv.)

Direct selective oxidative cleavage of compound **135** might be possible, because the enal double-bond is electron-deficient. However, oxidation of the aldehyde could be a problem. If selective cleavage is not possible, both the aldehyde and alkene of the enal could be protected to allow cleavage of the desired double bond.

There are a number of possible retrosynthetic approaches to substrate **135**. Some of these are illustrated in **Scheme 73**. Approach 1 was attempted in the first instance because a previous member of the group had undertaken related work, and it gave hope that this experience would highlight opportunities to improve on the previous studies.[35] By synthesising compound **270**, where X is a halogen, the corresponding organolithium reagent could be generated *via* a lithium-halogen exchange. This could then react with the epoxide **269** to give the desired substrate **135**.

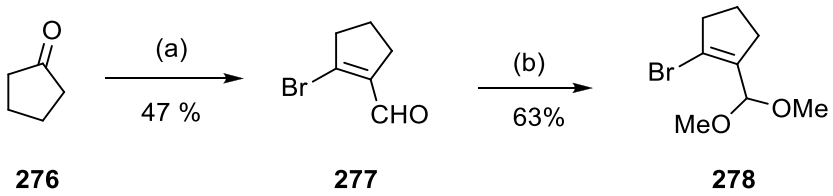



(PG = protecting group)

**Scheme 73.** Retrosyntheses for substrate **135**

### 5.1.1. Previous work within the Elliott group

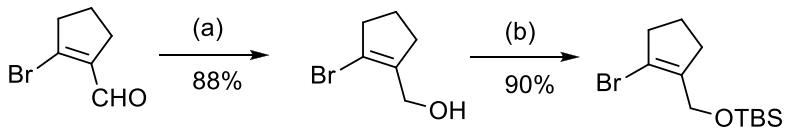
Cyclopentanone (**276**) was treated with $PBr_3$ and DMF following a known literature procedure to give compound **277**.[68] The group originally protected the aldehyde **277** functionality as an acetal **278**. However, compound **278** proved to be relatively unstable and unfortunately any attempts at effecting lithiation and subsequent reactions were unsuccessful.[35]




**276** **277** **278**

**Scheme 74.** Synthesis of compound **278.** *Reagents and Conditions*: (a) $PBr_3$, DMF, $CH_2Cl_2$, 0 °C to room temperature, 18 h; (b) $CH(OMe)_3$, MeOH, camphorsulfonic acid, 18 h

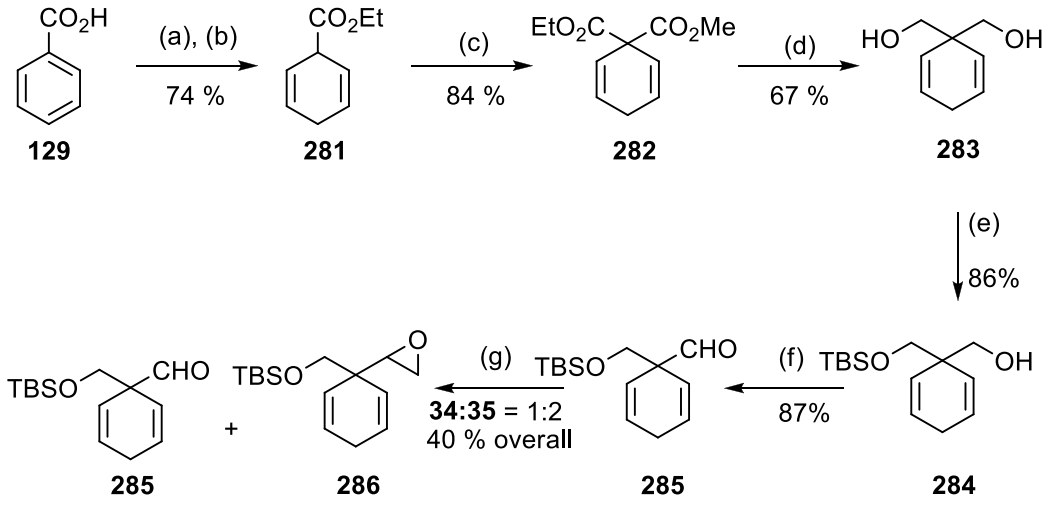
Compound **277** was then reduced to form the corresponding alcohol **279**, which was then protected as the silyl ether **280 (Scheme 75)**, in the hope that deprotection and subsequent oxidation could be achieved later on.




**277** **279** **280**

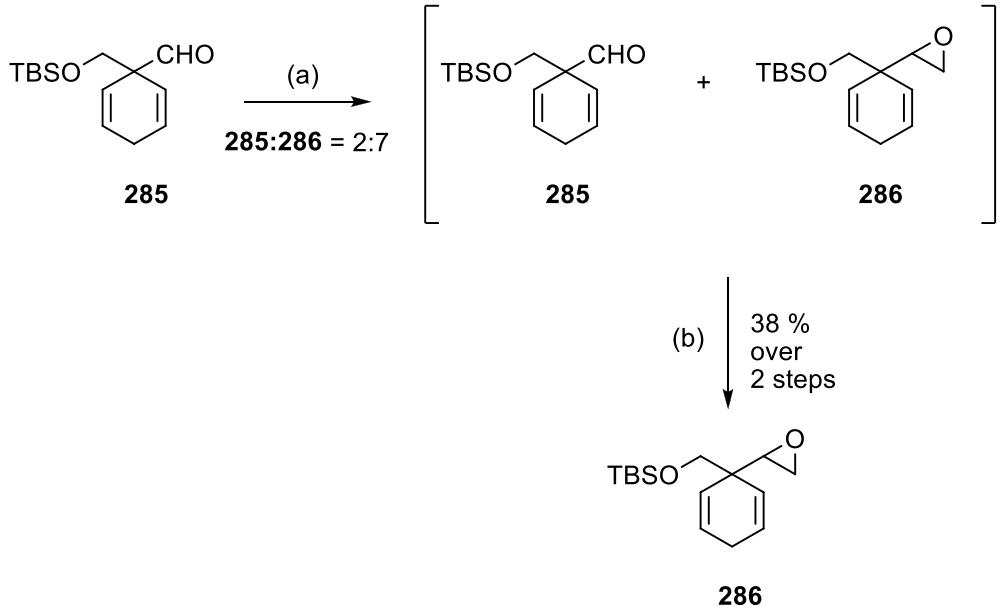
**Scheme 75.** Synthesis of compound **280.** *Reagents and Conditions*: (a) $NaBH_4$, MeOH, 0 °C to room temperature, 1 h; (b) TBSCl, imidazole, 4-DMAP, $CH_2Cl_2$, 18 h

Compound **286** was then synthesized starting with the Birch reduction of benzoic acid using sodium metal in EtOH, then esterification using $H_2SO_4$ in EtOH. Acylation of the resulting ester (**281**) with methyl chloroformate using LDA as the base resulted in formation of the diester **282**. Diester **283** was then reduced to the corresponding diol **277** using $LiAlH_4$, then mono-protected as the silyl ether **284** using *n*-BuLi to deprotonate followed by addition of *tert*-butyldimethylsilyl chloride and imidazole in THF. Oxidation of compound **284** using Swern conditions gave the corresponding aldehyde **285**. To make the epoxide **286**, aldehyde **285** was treated with dibromomethane and *n*-butyllithium. An incomplete reaction gave a 1:2 mixture of starting material (**285**) and product (**286**), which were inseparable by column chromatography (**Scheme 76**).[35]



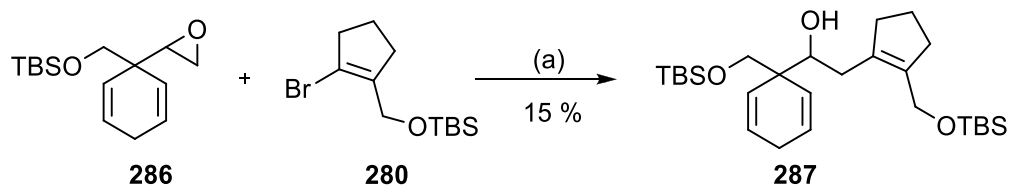

**Scheme 76:** Synthesis of compound **286** and **285**. *Reagents and Conditions*: (a) Na, $NH_3$, EtOH (4:1), -78 °C; (b) EtOH, $H_2SO_4$, 16 h; (c) LDA, THF, -78 °C, then methyl chloroformate; (d) $LiAlH_4$, THF, 2 h; (e) *n*-BuLi, -78 °C to room temperature, then TBSCl, imidazole, 16 h; (f) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, -78 °C to room temperature, 2 h; (g) *n*-BuLi, $CH_2Br_2$, THF, -78 °C to room temperature, 18 h

The group had two options; to find a way of driving the epoxide formation to completion or to separate the aldehyde **285** and epoxide **286** after the reaction. In an effort to achieve complete formation of epoxide **280**, the reaction time of the epoxide formation was increased from 18 h to 24 h. While this still gave incomplete conversion of the starting material, there was an increase in the amount of epoxide **286** formed relative to recovered aldehyde **285** (**Scheme 77**). Treatment of the mixture of compounds **285** and **286** with sodium borohydride to reduce the remaining aldehyde **285** to the alcohol **284** then allowed separation of the epoxide **286** from aldehyde **285**.[35]



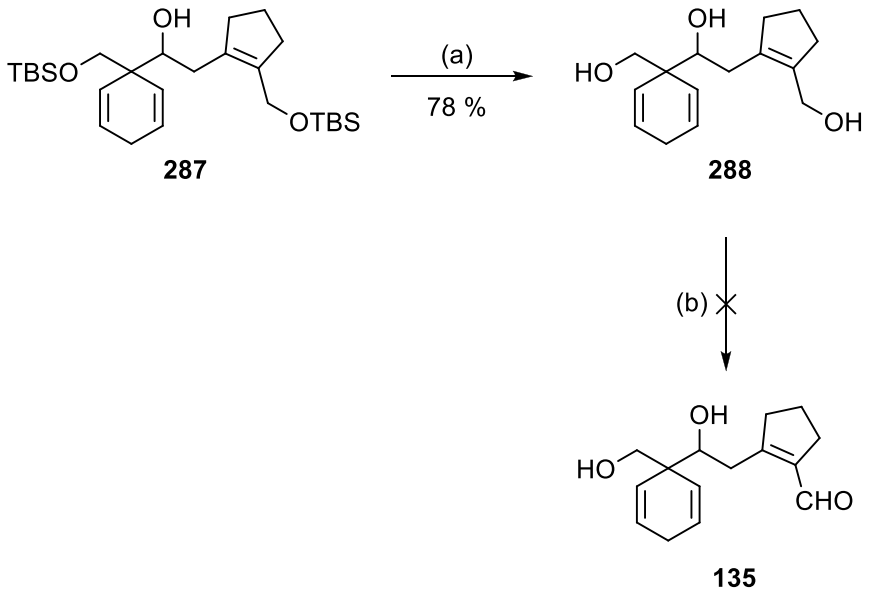

**Scheme 77.** Synthesis of compound **286.** *Reagents and Conditions*: (a) *n*-BuLi, $CH_2Br_2$, THF, -78 °C to room temperature, 24 h; (b) $NaBH_4$, MeOH, 0 °C to room temperature, 1 h

Compound **286** was treated with the organolithium reagent derived from compound **280**, which gave compound **281** (**Scheme 78**).




**Scheme 78.** Synthesis of compound **287.** *Reagents and Conditions*: (a) *t*-BuLi, $BF_3.OEt_2$, THF, -78 °C

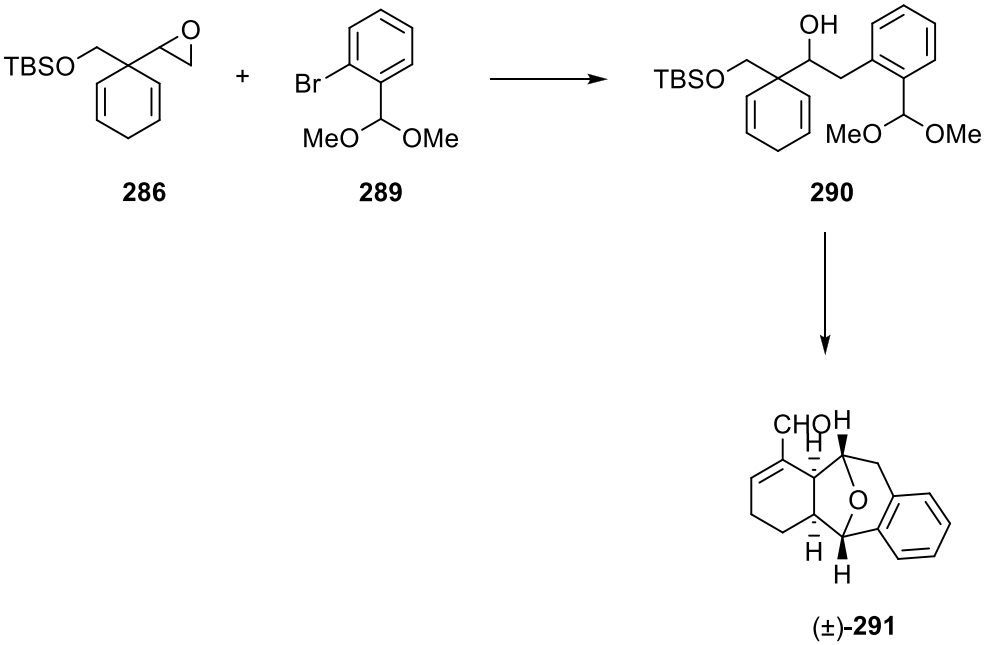
The deprotection of both primary alcohols was effective. However, attempted selective oxidation of the allylic alcohol with manganese dioxide gave a complex mixture of products (**Scheme 79**).




**287** **288** **135**

**Scheme 79.** Attempted preparation of compound **135.** *Reagents and Conditions*: (a) TBAF, THF, 18 h; (b) $MnO_2$, $CH_2Cl_2$, room temperature, 1 h

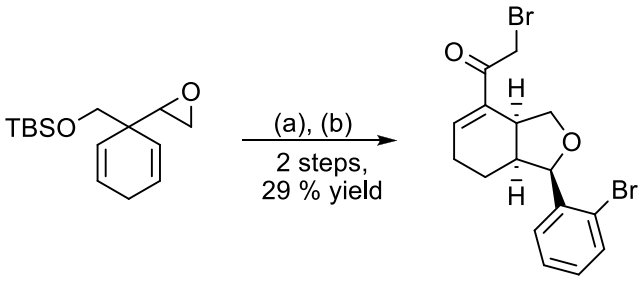
As there was only a limited amount of compound **288** remaining, the group devised a new plan rather than testing a range of different oxidising agents. They believed that an acetal, (**289**) with a benzene ring in place of the cyclopentene ring would be more stable and react more readily with epoxide **286** (**Scheme 80**). Even though the product **291** could not be further elaborated to achieve the cladiellin framework, they decided to investigate this study to provide proof of concept.




**286** **289** **290** (±)-**291**

**Scheme 80**: Proposed model study by the Elliott group

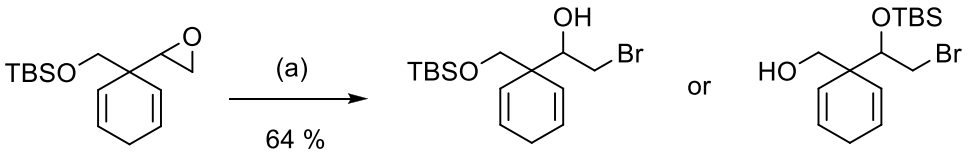
Compound **289** was treated with *t*-butyllithium, followed by epoxide **286.** Unfortunately upon reaction of the product to the Prins cyclisation conditions, this did not give the desired compound **291**. Instead, the major product of the reaction was compound **292**, as shown in **Scheme 81**.[69]




**286** **292**

**Scheme 81.** Synthesis of compound **292.** *Reagents and Conditions*: (a) *t*-BuLi, compound **289**, $BF_3.OEt_2$, THF, -78 °C; (b) TfOH (2 equiv.), $CH_2Cl_2$, 0 °C to room temperature, 25 min

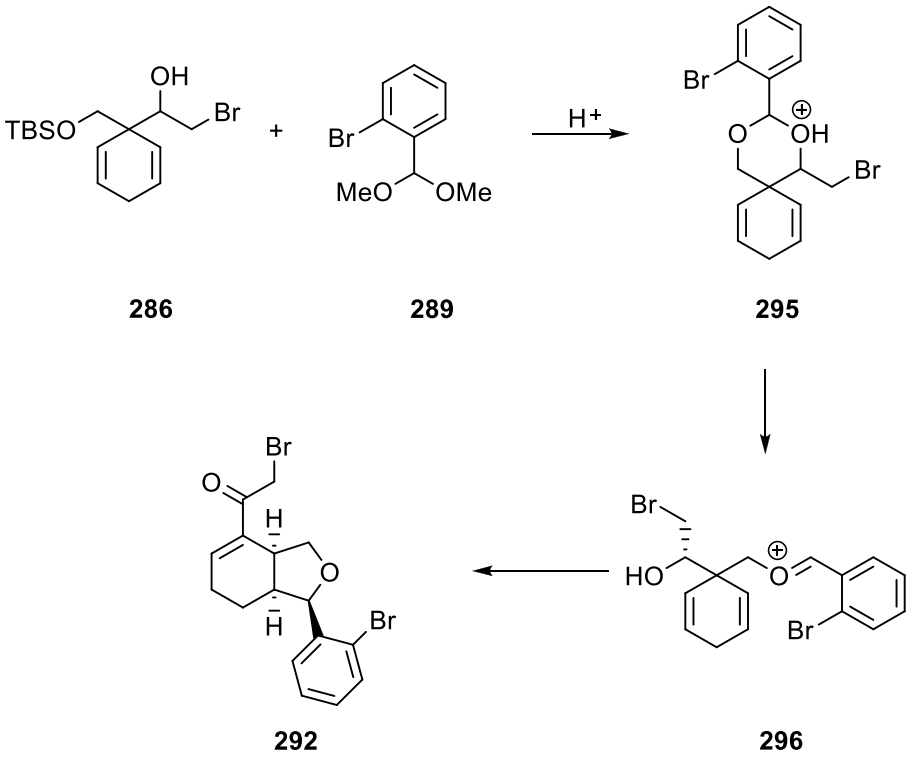
After repeating the first step and purification of the crude reaction mixture on silica gel, the group isolated one of two possible regioisomers **293** and **294**. The regiochemistry, with regards to the position of the silyl group, could not be ascertained spectroscopically. A significant amount of acetal **289** was recovered, which would suggest incomplete lithiation during the reaction.




**286** **293** **294**

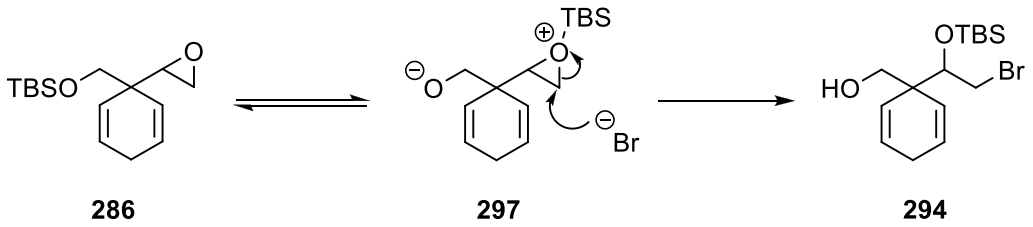
**Scheme 82.** Synthesis of compound **293** or compound **294**. *Reagents and Conditions*: (a) *t*-BuLi, **289**, $BF_3$.THF, -78 °C

Compound **292** must be formed from an oxocarbenium ion such as compound **296** (as previously discussed in the Prins cyclisation/rearrangement mechanism in **Chapter 1,** page 27). Compound **296** would have to be formed by protonation of the more hindered oxygen as in compound **295** (**Scheme 83**). This is highly unlikely. Direct formation and reaction of an oxocarbenium ion from **286** would not give product **292**. Therefore, it was proposed that the silyl group had migrated to the secondary alcohol as in compound **294** rather than staying on the primary alcohol as in compound **293**, so that oxocarbenium ion **296** has the secondary alcohol protected as the silyl ether.




**Scheme 83.** Proposed formation of compound **292**

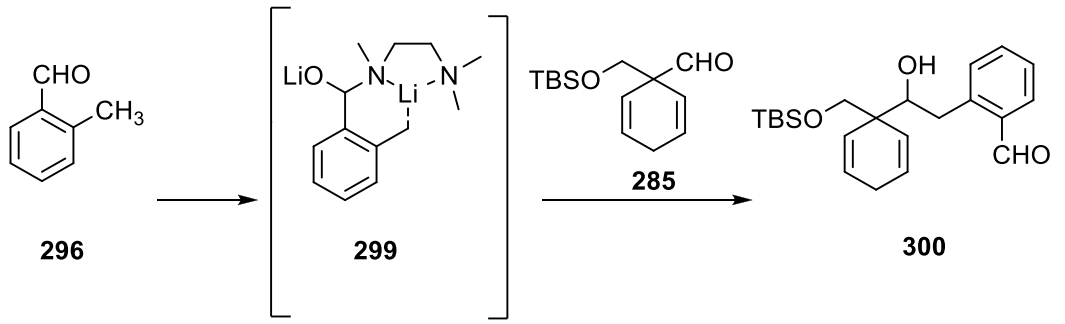
A possible mechanism for the formation of compound **294** is shown in **Scheme 84**, whereby the silyl group is removed and it coordinates directly to the oxygen atom of the epoxide, to generate oxonium ion **297**. Then ring-opening by the bromide, derived from lithium bromide, would take place to form compound **294** (**Scheme 84**).




**286** **297** **294**

**Scheme 84.** Proposed formation of compound **294**

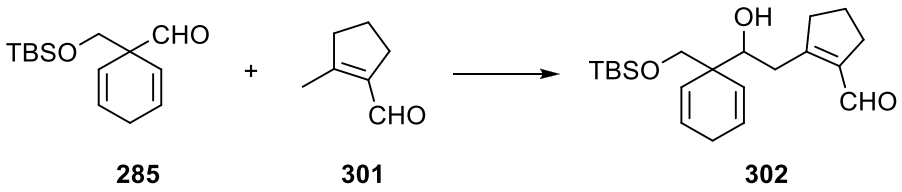
The main problem of this sequence is the formation of the silylated bromohydrin species **294** during the halogen-exchange experiments with epoxide **286**. Another problem is the reliability for the formation of epoxide **286**. Alternatively, reacting aldehyde **285** directly could be considered. Comins has described a method for directed lateral lithiation of 2-methylbenzaldehyde **298**, by forming an α-aminoalkoxide with *N,N,N'*-trimethylethylenediamine.[70] Using these conditions, it was considered that coupling of 2-methylbenzaldehyde **298** with aldehyde **285** directly could give a model substrate **300** for the Prins cyclisation (**Scheme 85**).




**296** **299** **300**

**Scheme 85.** Proposed route to compound **300**

If this approach proved successful, directed lateral lithiation of 2-methylcyclopent-1-enecarbaldehyde **301** and subsequent reaction with aldehyde **285** would be the next step (**Scheme 86**). Successful Prins cyclisation of compound **302** would provide the desired ring system for installing the oxacyclononane moiety observed in the cladiellin diterpenes.



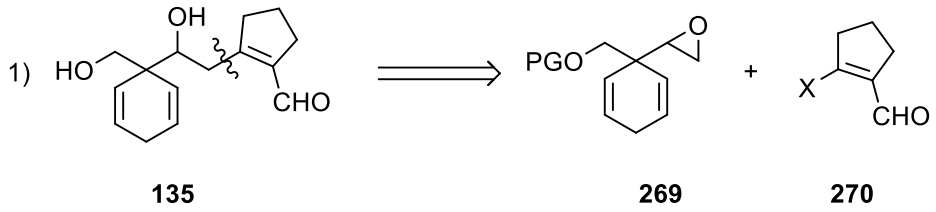

**285** **301** **302**

**Scheme 86**. Proposed route to compound **302**

## 5.2. Results and Discussion

### 5.2.1. First Retrosynthetic Approach

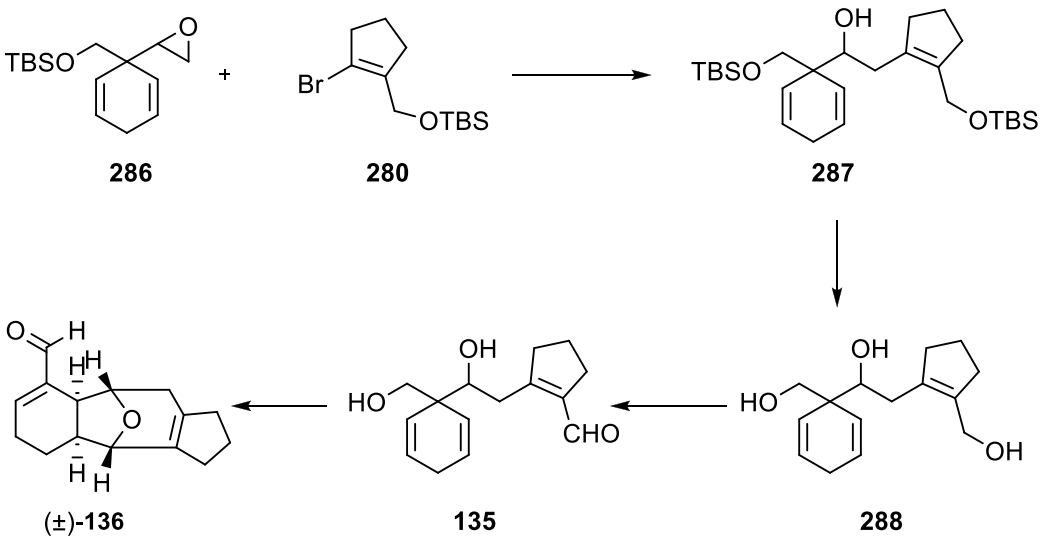
The first attempt towards synthesising the cladiellin framework began with the first retrosynthetic approach (**Scheme 87**).




**135** **269** **270**

**Scheme 87.** First retrosynthetic approach towards the synthesis of target compound **135**

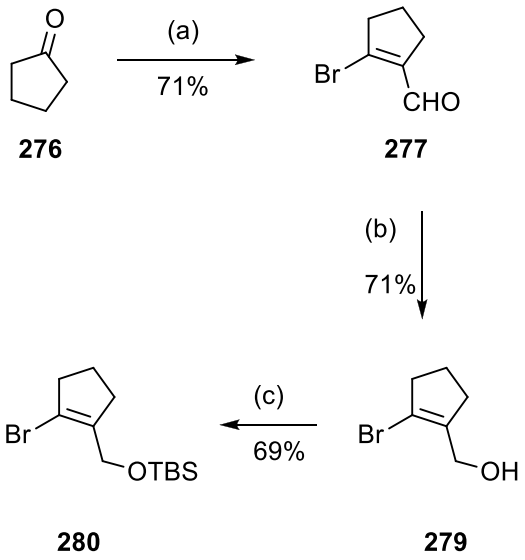
The reaction between epoxide **286** and compound **280** has previously been explored within the Elliott group.[33] However, there was still a wide range of conditions that had not been attempted. The synthesis began by adapting certain conditions. Successful coupling of epoxide **286** and compound **280** would give compound **287**, followed by removal of the TBS groups to give **288**, oxidation to form aldehyde **135** then treatment with acid to give the Prins cyclisation/ rearrangement product **135** (**Scheme 88**).




**286** **280** **287** **288** **135** (±)-**136**

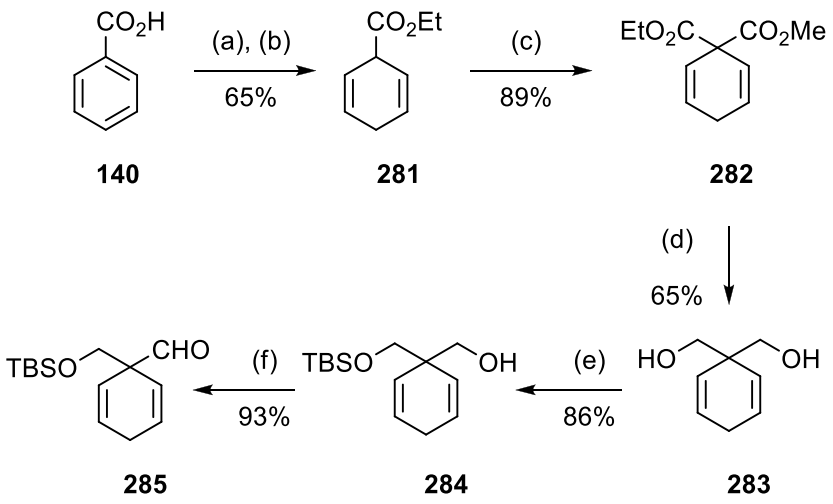
**Scheme 88.** Proposed route towards the target compound **136**

2-Bromocyclopent-1-enecarbaldehyde **277** was prepared by reaction of cyclopentanone with $PBr_3$ and DMF in dichloromethane following a literature procedure (**Scheme 89**).[71] Treatment of aldehyde **277** with sodium borohydride following a known procedure,[72] gave compound **279**, followed by protection as the corresponding silyl ether **280** by treatment with *tert*-butyldimethysilyl chloride, imidazole and 4-DMAP in dichloromethane.



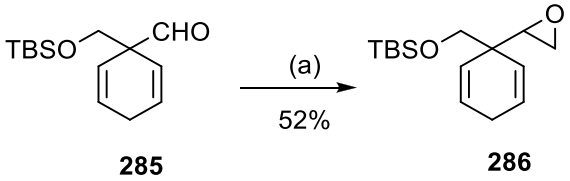

**Scheme 89.** Synthesis of compound **280**. *Reagents and Conditions*: (a) $PBr_3$, DMF, $CH_2Cl_2$, 0 °C to room temperature, 18 h. (b) $NaBH_4$, MeOH, 0 °C to room temperature, 1 h; (c) TBSCl, imidazole, 4-DMAP, $CH_2Cl_2$, 18 h

Synthesis of compound **285** (**Scheme 90**) was achieved using the same conditions as previously described (page 104).



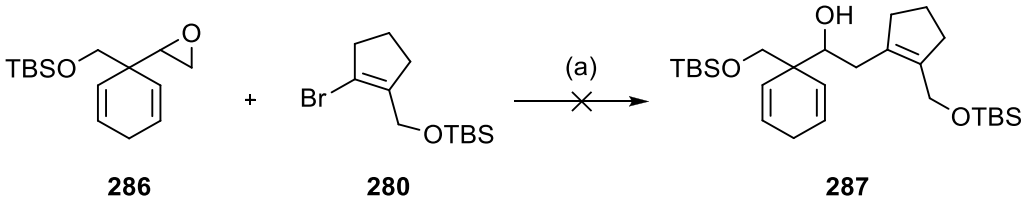

**Scheme 90.** Synthesis of compound **285.** *Reagents and Conditions*: (a) Na, $NH_3$-EtOH (4:1), -78 °C; (b) EtOH, $H_2SO_4$, 16 h; (c) LDA, THF, -78 °C, then methyl chloroformate; (d) $LiAlH_4$, THF, 2 h; (e) *n*-BuLi, -78 °C to room temperature, then TBSCl, imidazole, 16 h; (f) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, -78 °C to room temperature, 2 h

Previously in the group, problems were experienced upon formation of epoxide **286**, where an incomplete reaction gave a 1:2 mixture of starting material (**285**) and product (**286**), which were inseparable by column chromatography. However, an increase in the reaction time from 18 h to 24 h increased the amount of epoxide **286** formed relative to recovered aldehyde **285**. The synthesis was attempted and increased the reaction time to 48 h, successfully synthesising epoxide **286** without any problems (**Scheme 91**).




**Scheme 91**. Synthesis of compound **286**. (a) *n*-BuLi, $CH_2Br_2$, THF, -78 °C to room temperature, 48 h

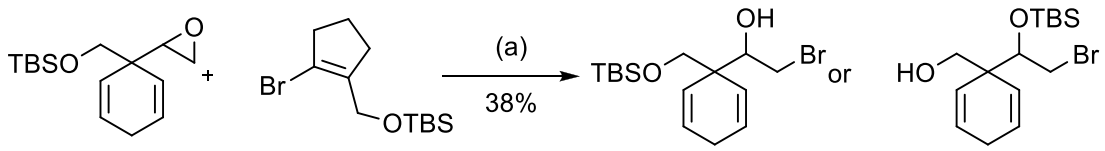
The coupling of epoxide **286** and compound **280** had previously been accomplished within the group in 15% yield, (**Scheme 79**). In our hands, the coupling reaction between epoxide **286** and compound **280** was not successful (**Scheme 92**).




**286** **280** **287**

**Scheme 92.** Attempted preparation of compound **287.** *Reagents and Conditions*: (a) *t*-BuLi (2.4 equiv.), $BF_3.OEt_2$, THF, -78 °C

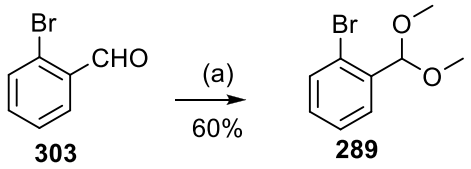
After extensive chromatography of the crude reaction mixture on silica gel, one of two possible regioisomers **293** and **294** was isolated (**Scheme 94**). However, the specific isomer that was we formed was not confirmed. A significant amount (57%) of compound **280** was also recovered during chromatography, suggesting incomplete lithiation during the reaction. However, previous work has shown that lithiation of **280** under these conditions followed by reaction with either an aldehyde or a simple epoxide gives good yields of coupled products.[35]




**286** **280** **293** **294**

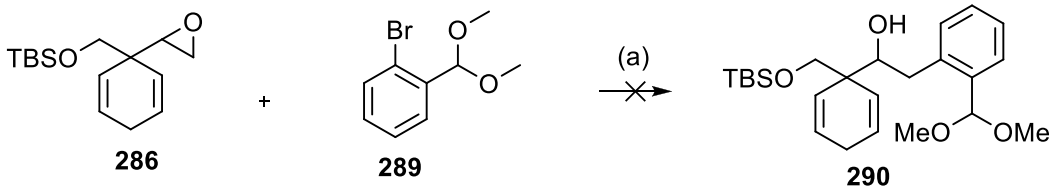
**Scheme 93.** Synthesis of compound **293** or **294.** *Reagents and Conditions*: (a) *t*-BuLi (2.4 equiv.), $BF_3.OEt_2$, THF, -78 °C

Due to these results acetal **289** was synthesized to couple with epoxide **286** as a test reaction to provide proof of concept. Compound **289** was formed by treatment of commercially available 2-bromobenzaldehyde (**303**) with trimethyl orthoformate and camphorsulfonic acid in methanol in 60% yield, following a known procedure (**Scheme 94**).[73]




**Scheme 94.** Synthesis of compound **289.** *Reagents and conditions:* (a) trimethyl orthoformate, camphorsulfonic acid, methanol, room temperature, 18 h

In previous attempts at coupling epoxide **286** with other compounds (for example compound **280**), *t*-BuLi was used with the addition of $BF_3.Et_2O$, but there was no success using these conditions. Therefore *n*-BuLi was used to test this reaction. Compound **289** was treated with *n*-BuLi in THF at -78 °C, then epoxide **286** in THF was added and the mixture was stirred for 1 h at -78 °C and then a further 1 h at room temperature. Unfortunately, treatment of compound **289** with epoxide **286** did not give the expected result (**Scheme 95**), and neither did it give the result as previous attempts within the group (**Scheme 83**). Instead it led to decomposition of epoxide **286** and deprotection of the acetal protecting group in compound **289** resulting in recovery of 2-bromobenzaldehyde.




**Scheme 95.** Attempted synthesis of compound **290**. *Reagents and conditions:* (a) *n*-BuLi, -78 °C to room temperature, 2 h

### 5.2.2. Reactivity of Aldehyde 285

The stability of compound **286** posed a problem; therefore we decided to investigate the reactivity of aldehyde **285** (**Figure 28**).

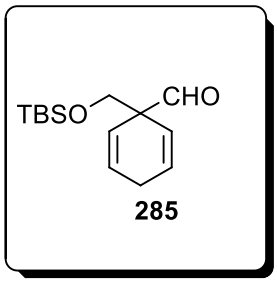
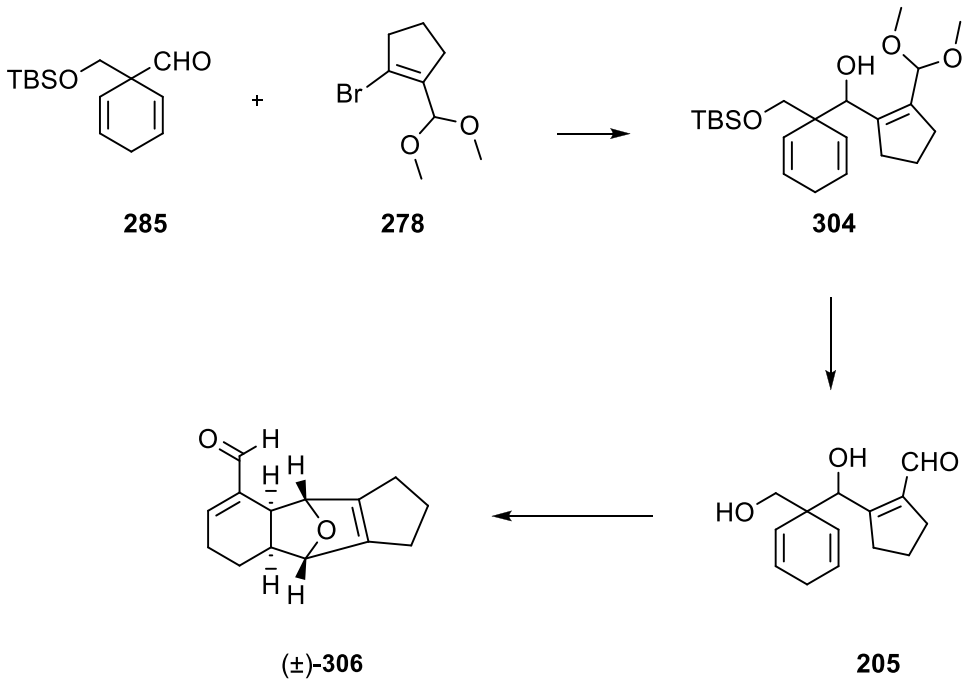


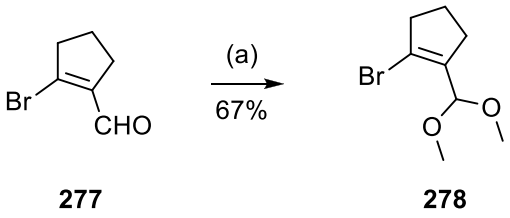

**Figure 28:** Aldehyde **285**

Although reaction of compound **285** (**Figure 28**) with compound **278** would give a product (**304**) with one carbon atom fewer than is required for the framework of the cladiellin diterpenes, it was something on which a model system could be based on (**Scheme 96**). The coupling of compound **278** with epoxide **286** was found to be ineffective.[35] However, as a model system the coupling with an aldehyde would give important information about the generation and reactivity of a nucleophile from this compound.



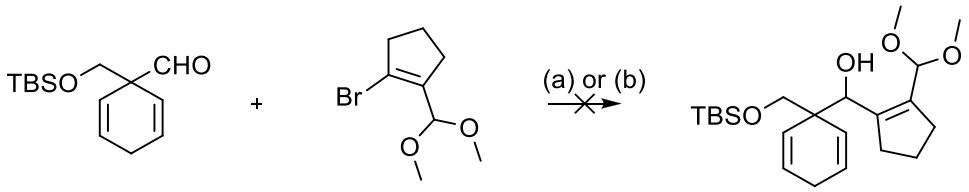

**Scheme 96**. Proposed model system towards the synthesis of compound **306**

Compound **278** was formed in 67% yield upon treatment of aldehyde **277** with trimethyl orthofomate and camphorsulfonic acid in methanol, following a known procedure (**Scheme 98**).[74]




**Scheme 97.** Synthesis of compound **278**. *Reagents and conditions:* (a) Trimethyl orthoformate, camphorsulfonic acid, methanol, room temperature, 18 h

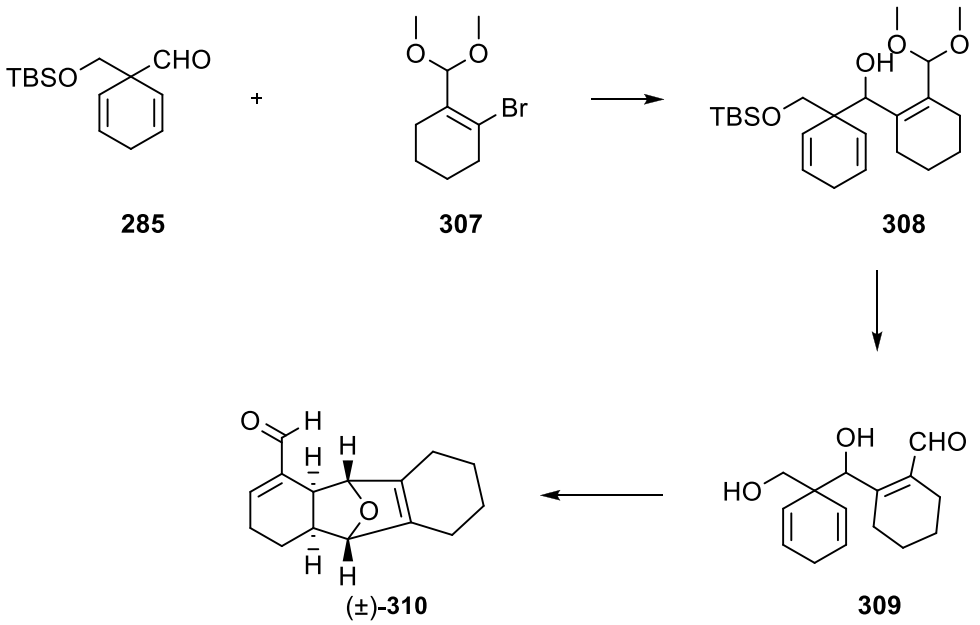
Compound **278** was treated with *t*-BuLi in THF at -78 °C and stirred for 10 minutes before addition of compound **285**. Unfortunately, this reaction only gave rise to un-reacted compound **278** and **285** (**Scheme 98**), suggesting that the lithium-halogen exchange was not taking place. The reaction was repeated using *i*-PrMgCl.LiCl but unfortunately this made no difference to the results.




**285** **278** **304**

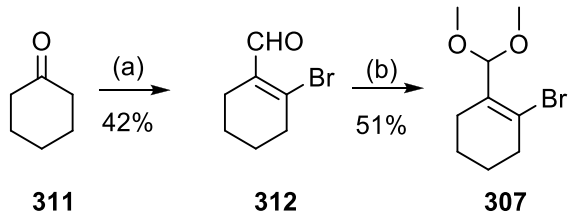
**Scheme 98.** Attempted preparation of compound **304**. *Reagents and conditions:* (a) *t*-BuLi, THF, -78 °C; (b) *i*-PrMgCl.LiCl, THF, -78 °C

Following on from this another nucleophile was used to test the reactivity of aldehyde **285**. The model system, as proposed in **Scheme 96**, could have potentially formed compound **304** and could theoretically be elaborated to give a substrate for our Prins cyclisation reaction, but it would give the wrong ring size for the cladiellin framework. Rather than pursuing further with this, attention was focused on another compound, acetal **307**, which contained a six-membered ring. Upon coupling with aldehyde **285**, the key Prins cyclisation/rearrangement step would give a product (**310**) with the correct number of carbon atoms for the cladiellin framework (**Scheme 99**). Although the attempted reaction of a 5-membered oxocarbenium ion was not successful, the presence of the double bond in this case was a novel feature.



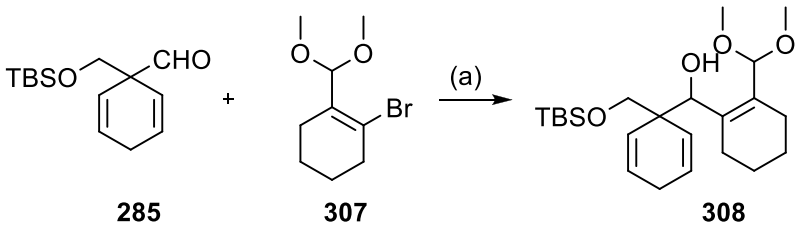

**Scheme 99.** Alternative model system towards the synthesis of compound **310**

The synthesis of compound **307** began as follows. Cyclohexanone (**311**) was treated with $PBr_3$ and DMF in dichloromethane following a known procedure[75] to give compound **312**. Compound **312** was then protected as the acetal **307** by treating with trimethyl orthoformate and camphorsulfonic acid in methanol (**Scheme 100**).




**Scheme 100.** Synthesis of compound **307.** *Reagents and Conditions*: (a) $PBr_3$, DMF, $CH_2Cl_2$, 0 °C to room temperature, 18 h; (b) Trimethyl orthoformate, camphorsulfonic acid, methanol, room temperature, 18 h

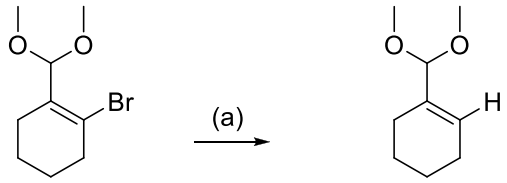
Both *n*-BuLi and *t*-BuLi are widely used for Li-halogen exchange. However, as mentioned above, the use of *t*-BuLi in reactions of compounds **285** and **307** proved unsuccessful (**Scheme 102**). In 1995, Iwata reported the lithiation of compound **307** using *n*-BuLi, followed by reaction with (-)-menthyl (S)-*p*-toluenesulfinate.[75] Therefore, compound **307** was treated with *n*-BuLi in THF at -78 °C and stirred for 2 h before adding aldehyde **285**. This was further stirred at -78 °C for 1 h then warmed and stirred at room temperature for 1 h. A small sample of the reaction was quenched with MeOD to check if the reaction had gone to completion. The proton NMR spectrum of the crude product before the work up suggested that the coupling of compound **285** with compound **307** was successful. In the proton NMR spectrum there was a new singlet at 4.47 ppm corresponding to C*H*-OH, and the $CH_3$-O peaks in the acetal region altered from a 6H singlet at 3.39 ppm in the starting material to two distinct singlets at 3.30 ppm and 3.40 ppm (which is indicative of the new diastereotopic methoxy groups). However, upon work up and purification there were no identifiable products.




**285** **307** **308**

**Scheme 101.** Attempted synthesis of compound **308.** *Reagents and conditions*: (a) *n*-BuLi, THF, -78 °C

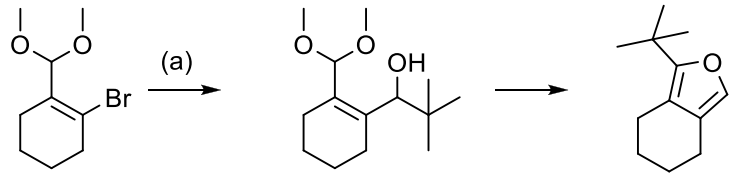
It was important to find out what was happening during this reaction. Quenching a portion of this reaction mixture with methanol gave a compound with a peak at 5.85 ppm in the $^{1}H$ NMR spectrum. This is consistent with the alkene hydrogen as illustrated in compound **313**, suggesting that the lithium-halogen exchange was working well.




**307** **313**

**Scheme 102.** Formation of compound **313**. *Reagents and conditions*: (a) *n*-BuLi, THF, MeOH, -78 °C

The coupling of compound **307** with pivalaldehyde was investigated next as a method of testing the reactivity of compound **307** with a known aldehyde. Compound **307** was treated with *n*-BuLi in THF at -78 °C and stirred for 1 h before adding pivalaldehyde. After addition of pivalaldehyde the reaction was stirred for a further 1 h at -78 °C then warmed to room temperature and stirred for a further 1 h. The proton NMR spectrum of the crude reaction mixture showed a new peak at 4.30 ppm, consistent with an allylic C*H*-OH group, and two distinct singlets at 3.35 ppm and 3.30 ppm for the two $CH_3$-O groups. However, as seen previously with compound **308** upon work up and purification of this reaction it appeared that an intramolecular condensation had taken place, resulting in the formation of compound **315** (**Scheme 103**. The data for the proposed structure **315** were comparable to the data for the corresponding *n*-propyl compound.[76]




**307** **314** **315**

**Scheme 103.** Synthesis of proposed compound **315**. *Reagents and conditions:* (a) *n*-BuLi, pivalaldehyde, THF, 1 h at -78 °C then 1 h at room temperature; (b) $NaHCO_3$/ chromatography on silica gel

Although these results were interesting, did not lead to the cladiellin framework and therefore this was not pursued any further. To summarise, it is clear that aldehyde **285** reacts with the anion formed from compound **307** but the problem is that the product is unstable. However, in the test reaction by quenching with methanol, there is evidence that the organolithium reagent might be formed. Due to these issues, our attention was directed on a different route which involved a simpler, less hindered aldehyde and different nucleophiles to help overcome these problems.

### 5.2.3. Reactivity of Aldehyde 316

Compound **316 (Figure 29)** is the simplest possible cyclohexa-1,4-diene aldehyde, so that if the proposed chemistry does not work on this aldehyde, it is clear that it will not be successful at all.

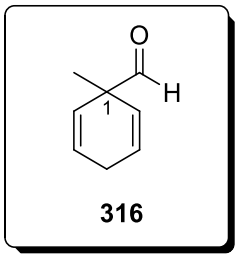
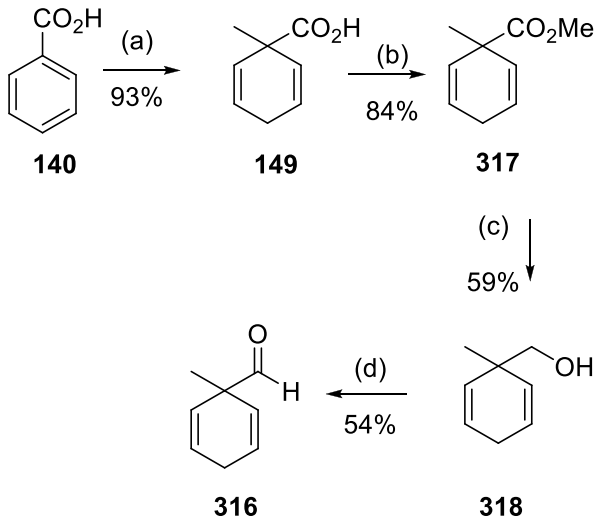



**Figure 29:** Aldehyde **316** with a smaller substituent in the 1-position

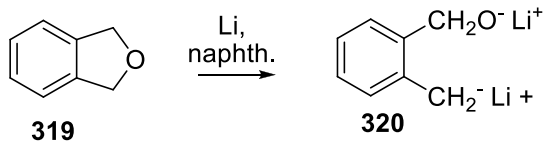
The synthesis of aldehyde **316** began by the Birch reduction of benzoic acid using liquid ammonia and lithium metal followed by addition of iodomethane, which gave compound **149** in 93% yield. Then esterification using methanol and sulfuric acid afforded the corresponding ester, **317**. This was then followed by reduction to the alcohol, **318**, using $LiAlH_4$ in THF and oxidation to the corresponding aldehyde (**316**) using Swern conditions (**Scheme 104**).




**Scheme 104.** Synthesis of compound **316.** *Reagents and conditions:* (a) Li, $NH_3$, Me-I, -78 °C; (b) MeOH, $H_2SO_4$, 40 °C, 17 h; (c) $LiAlH_4$, THF, room temperature, 2 h; (d) $(COCl)_2$, DMSO, triethylamine, $CH_2Cl_2$, -78 °C

### 5.2.3.1. Reaction with Phthalan

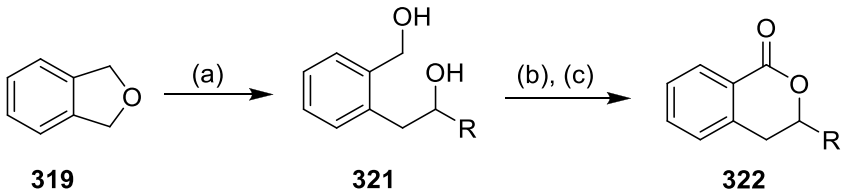
Now with a choice of aldehyde in place, a suitable nucleophile was required. As there was many concerns with the lithiation approach in our previous attempts, related ideas on simpler systems was explored next. The lithiation of phthalan (**319**) and its reactivity with aldehydes was investigated first. According to Azenna *et al.* the reaction of phthalan with lithium and a catalytic amount of naphthalene in THF led to the reductive cleavage of an aryl methyl carbon-oxygen bond with the formation of a stable dillithium compound **320** (**Scheme 105**).[77]




**319** **320**

**Scheme 105.** Formation of dilithium intermediate compound **320**

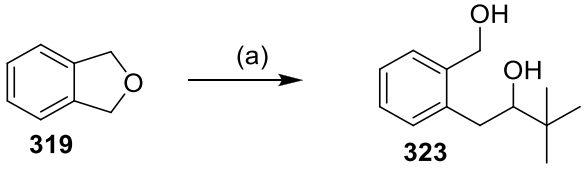
Trapping of this intermediate with several different electrophiles has already been reported.[77] Azenna *et al.* investigated the reductive cleavage of phthalan using between 2.5 and 5 equivalents of Li. It was observed that the use of a large excess of metal resulted in a shorter reaction time. They demonstrated that the addition reaction of Li carbanion **320** to the carbonyl group of non-enolizable aldehydes or ketones occurred readily at 0 °C within 1 hour. This led to the development of a simple procedure allowing the transformation of the diols (**321**) obtained by reductive lithiation of phthalan with aldehydes into 3-substituted 3,4-dihydro-1H-2-benzopyran-1-ones **322** (dihydroisocoumarins) (**Scheme 106**). Dihydroisocoumarins are a class of compounds which can be found in several plants and, due to their potential biological activity, are the subject of continuous synthetic efforts.[78,79]




**319** **321** **322**

**Scheme 106.** Transformation of diol **321** obtained by reductive lithiation of phthalan (**319**) with aldehydes into 3-substituted 3,4-dihydro-1*H*-2-benzopyran-1-ones (**322**)**.** *Reagents and conditions:* (a) Li dispersion, catalytic naphthalene and R-CHO in THF, (b) $KMnO_4$, (c) $H_3O^+$

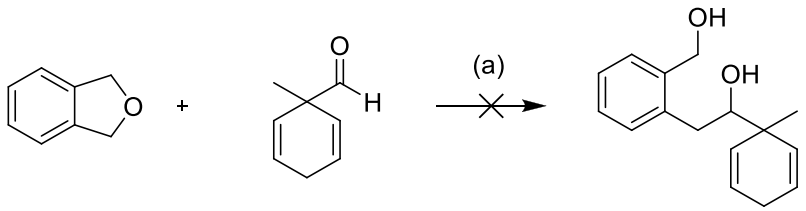
Initially the reaction of phthalan with pivalaldehyde was evaluated. Phthalan (**319**) was treated with 5 equivalents of lithium dispersion with a catalytic amount of naphthalene in THF. To this 1.2 equivalents of pivalaldehyde was added, as in the procedure reported by Azzena *et al.* and the reaction proceeded smoothly (**Scheme 107**).




**319** **323**

**Scheme 107.** Synthesis of diol **323.** *Reagents and conditions:* (a) Li dispersion, naphthalene (cat.), pivalaldehyde, THF

Unfortunately, treatment of phthalan with aldehyde **316**, using the same conditions, resulted in decomposition of the starting materials (**Scheme 108**). The same result was also observed with aldehyde **285**.

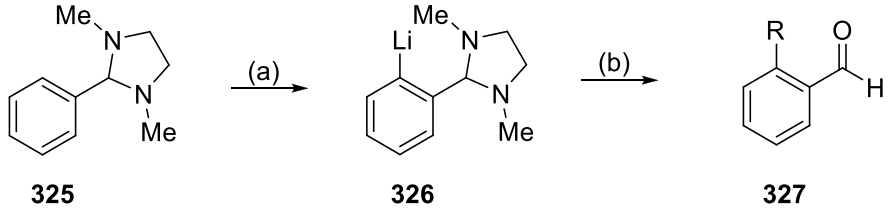



**319** **316** **324**

**Scheme 108.** Attempted synthesis of compound **324.** *Reagents and conditions:* (a) Li dispersion, naphthalene (cat.), THF

### 5.2.3.2. Reaction with a carbonyl synthon containing an imidazolidine ring

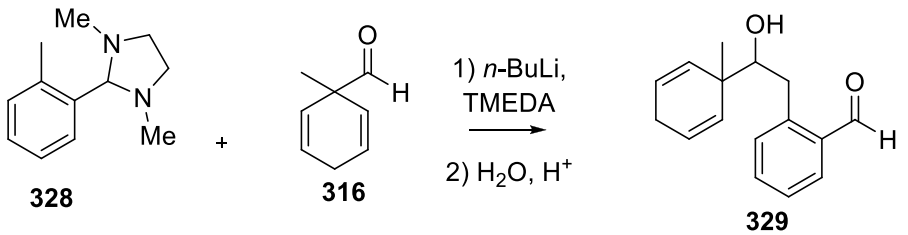
Due to the failure of phthalan to react with aldehyde **316,** a carbonyl synthon based on an imidazolidine ring (**325**) was explored as an alternative. Compound **325** has previously been reported to direct lithiation in the *ortho* position quantitatively and, after reaction with an electrophile and subsequent hydrolysis, affords the corresponding aromatic aldehyde (**327**) using mild conditions as shown in **Scheme 109**.[80]




**325** **326** **327**

**Scheme 109.** Lithiation of imidazolidine ring (**325**), followed by reaction and hydrolysis to give aldehyde (**327**). *Reagents and conditions:* (a) *n*-BuLi/ TMEDA, (b) electrophile followed by $H_2O/H^+$

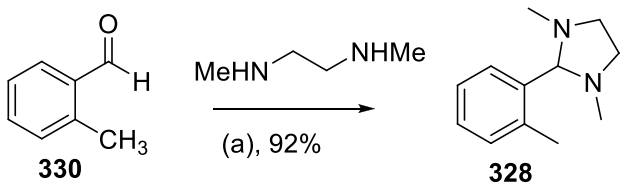
As a method for directed lateral lithiation was required, the synthesis of compound **328** and the coupling with aldehyde **316** to direct lithiation to the methyl group on the benzene ring was investigated next (**Scheme 110**).




**328** **316** **329**

**Scheme 110.** Suggested coupling of compound **328** and compound **316** towards formation of compound **329**

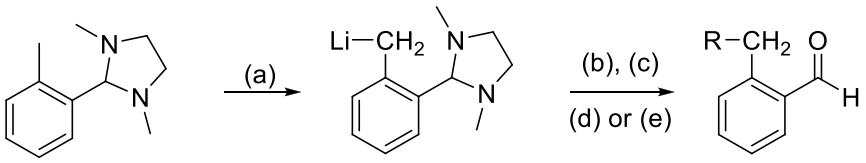
1,3-Dimethyl-2-(2-methylphenyl)imidazolidine **328** was prepared in a yield of 92% by treating *o*-tolualdehyde with *N,N*'-dimethylethylenediamine in toluene under reflux for 5 h with the removal of water *via* a Dean-Stark trap following the procedure reported by Harris and Roth (**Scheme 111**).[80]




**330** **328**

**Scheme 111.** Preparation of 1,3-Dimethyl-2--(2-methylphenyl)imidazolidine **328.** *Reagents and conditions:* (a) *p*-toluenesulfonic acid, toluene, 5 h

The *ortho*-lithiated derivative **331** was then prepared by addition of TMEDA then *n*-BuLi drop-wise in diethyl ether (**Scheme 112**).

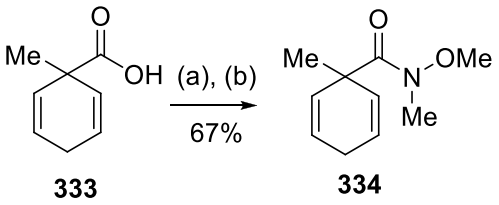



**328** **331** **332**

**332a** R= $C_3H_7$

**Scheme 112.** Attempted synthesis of compounds **332a-e.** *Reagents and conditions:* (a) TMEDA, $Et_2O$, *n*-BuLi, 2.5 h, room temperature; (b) 1-bromopropane; (c) hexanal; (d) benzoyl chloride; (e) Weinreb amide **334**

This was then quenched with a number of electrophiles: 1-bromopropane, hexanal, benzoyl chloride and Weinreb amide **334.** Preparation of Weinreb amide **334** began by the Birch reduction of benzoic acid, followed by formation of the corresponding acid chloride with oxalyl chloride and DMF in dichloromethane, then treatment with *N*,*O*-dimethylhydroxylamine (**Scheme 113**).



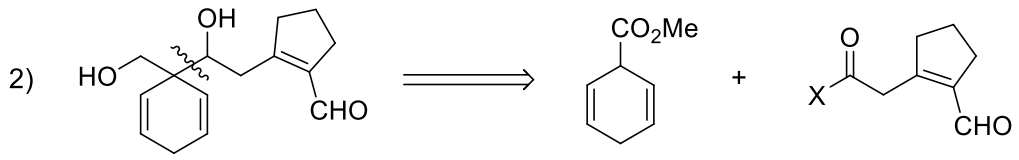

**333** **334**

**Scheme 113.** Synthesis of Weinreb amide **334.** *Reagents and conditions:* (a) $(COCl)_2$, DMF, 40 °C, 1 h, (b) *N*,*O*-dimethylhydroxylamine hydrochloride, $Na_2CO_3$, pyridine, $Et_2O$, room temperature, 24 h

Unfortunately the only electrophile that successfully reacted with compound **328** using these conditions was 1-bromopropane, which has previously been reported.[80] Reaction with the other electrophiles gave no identifiable products, and therefore it was presumed that the reaction of compound **328** with aldehyde **316** was unlikely to be successful.

### 5.2.4. Second retrosynthetic approach

An alternative approach to synthesising the cladiellin framework began with the second retrosynthetic approach (**Scheme 114**).

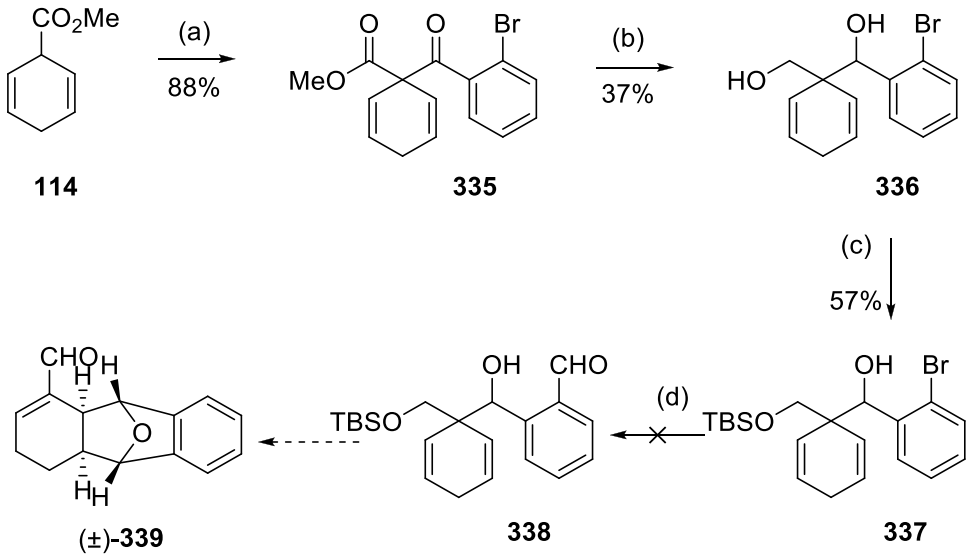



**135** **114** **271**

**Scheme 114.** Synthetic approach to formation of compound **135**

Ester **114** can easily be prepared by Birch reduction of benzoic acid followed by esterification using methanol and sulfuric acid. However, synthesising compound **271** could be challenging. In particular, it was concerning that the double-bond in compound **271** could move to the exocyclic position into conjugation with the acid chloride carbonyl group (assuming X = Cl) in the product. Furthermore, reduction to give the diol would be problematic if the aldehyde was present. A simplified model system in which the aldehyde could be introduced at the end *via* lithiation/reaction with DMF was therefore evaluated as an alternative.

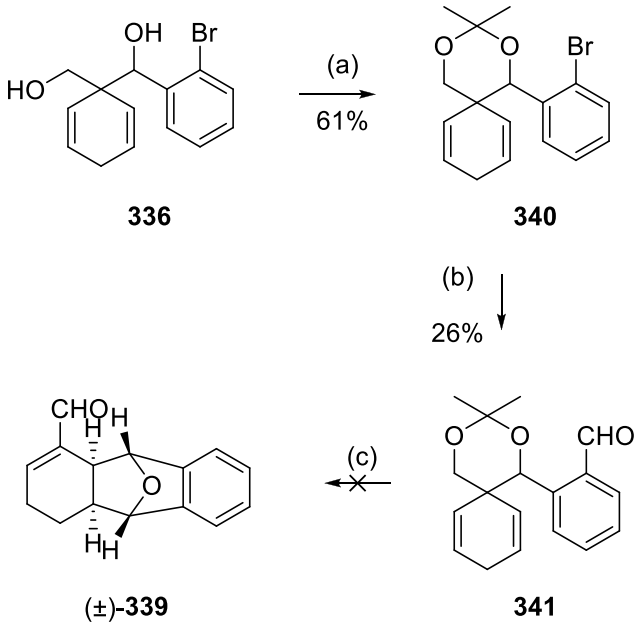
Commercially available 2-bromobenzoyl chloride was coupled with ester **114** using LDA to deprotonate at -78 °C.[81] The corresponding diol **336** was formed upon reduction of the ester using $LiAlH_4$ in THF at 25 °C. The primary alcohol was then mono-protected while leaving the secondary alcohol unprotected using *tert*-butyldimethylsilyl chloride, triethylamine and a catalytic amount of 4-DMAP in dichloromethane. This formed compound **337** in 57% yield. However, attempts at forming aldehyde **338** by reaction with *n*-BuLi (2.3 equivalents) followed by DMF in THF were unsuccessful (**Scheme 115**).




**Scheme 115.** Attempted synthesis of compound **339**. *Reagents and conditions*: (a) LDA, THF -78 °C; (b) $LiAlH_4$, THF, 25 °C; (c) *t*-butyldimethylsilylchloride, $Et_3N$, 4-DMAP, $CH_2Cl_2$, (d) *n*-BuLi, DMF, THF, -78 °C

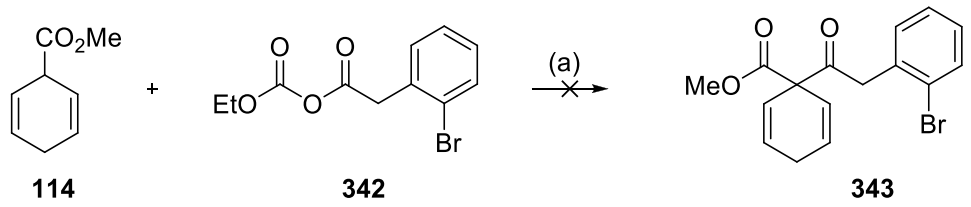
The use of a ketal as protecting group, as used in **Chapter 3**, was investigated next. Using 2,2-dimethoxypropane and catalytic camphorsulfonic acid in acetone for 24 h allowed the formation of compound **340**. Then lithium-halogen exchange using *n*-BuLi followed by DMF in THF gave slightly impure aldehyde **341** in low yield (26%). The Prins rearrangement/cyclisation step was then tested using triflic acid in dichloromethane at 0 °C. Unfortunately this did not give the desired Prins rearrangement product **339**.

As this system will inevitably give the incorrect ring size for the natural product targets and that a related 5-membered ring approach was unsuccessful in **Chapter 4** this experiment was not explored any further. It seems likely that formation of a 5-membered Prins product is beyond the limit for this type of reaction. However, the introduction of the aldehyde **341** in this manner is useful and could no-doubt be optimised on a more relevant system.




**Scheme 116.** Attempted synthesis of compound **339**. *Reagent and conditions:* (a) 2,2-dimethoxypropane, camphorsulfonic acid, acetone, 60 °C, 24 h; (b) *n*-BuLi, DMF, THF, -78 °C; (c) Trifluoromethanesulfonic acid, $CH_2Cl_2$, 0 °C, 30 min

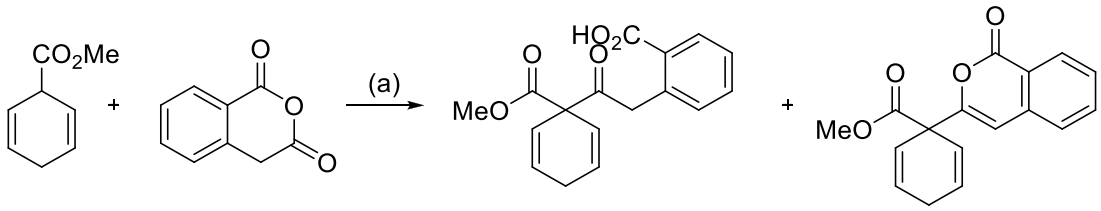
Alongside these efforts, the coupling of ester **114** with compound **343** was also attempted. Compound **342** was prepared by treating 2-bromophenylacetic acid with triethylamine and ethyl chloroformate in THF. Due to the additional $CH_2$ between the benzene ring and the carbonyl in compound **342**, successful coupling of the two would give a model compound with the correct connectivity that is required towards synthesis of the cladiellin diterpene analogues. Unfortunately, after numerous attempts, the reaction of ester **114** with compound **342** was unsuccessful (**Scheme 117**).




**114** **342** **343**

**Scheme 117.** Attempted synthesis of compound **343**. *Reagents and conditions:* (a) LDA, THF, -78 °C, 1 h then 25 °C, 18 h

Another similar reaction that was attempted involved the coupling of ester **114** with commercially-available homophthalic anhydride **345**, (**Scheme 118**). Reaction with LDA interestingly gave a 3:2 mixture of compounds **346** and **347** with some recovered starting material (**114**). Due to the poor yield of this reaction this synthesis was not pursued any further.




**114** **345** **346,** 9% **347,** 7%

**Scheme 118.** Synthesis of compounds **346** and **347**. *Reagents and conditions:* (a) LDA, THF, -78 °C for 1 h then 25 °C for 18 h

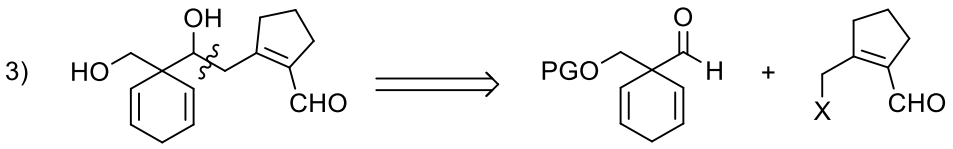
### 5.3. Conclusion

From this study, it can be concluded that the described synthetic strategy of coupling epoxide **286** with compound **280** is not ideal for approaching the cladiellin framework. The main weakness in the sequence is the use and stability of epoxide **286** as a synthetic intermediate. Formation of compound **294** appears to be the dominant process in each of the lithium-halogen exchange experiments with epoxide **286**. This process appears to be triggered by the removal of the silyl protecting group from the primary alcohol with boron trifluoride. Unfortunately, the use of boron trifluoride is necessary for activation of the epoxide, as no reaction is observed when this reagent is omitted. Whilst simply changing from a silyl protecting group might inhibit the undesired reaction process, the unreliable formation of the epoxide **286** from the aldehyde **285** still poses a significant problem.

The stability of aldehyde **285** is much greater than that of epoxide **286**. However, reacting with phthalan **320** was not successful. Nor was the reaction with an imidazolidine ring as an *ortho*-directing group. However, the development of a less bulky aldehyde **316** looked promising and the option of a new protecting group strategy seems a plausible alternative, as demonstrated in compound **272**, **Scheme 119**.

From the second retrosynthetic approach (page 134), the successful formation of compound **341**, one step away from the Prins cyclisation/rearrangement, was an achievement. However, the low yield and purity of compound **341** was a problem.

Looking back at the remaining retrosynthetic approaches (page 102), the third retrosynthetic approach was investigated next, as the first two approaches were not successful. With a compound of similar structure to compound **272** already in place to test this route, all that was needed was to devise a method of synthesizing a compound **273** or similar. The five-membered ring in compound **273** would be required for the cladiellin framework. However, as a model system, using an aromatic six-membered ring to test reactivity first could be a starting point for the next approach towards the cladiellin framework.




**135** **272** **273**

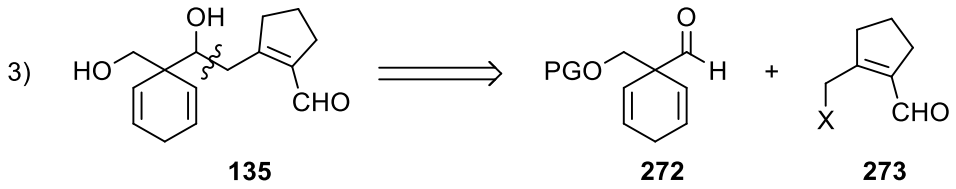
**Scheme 119.** Retrosynthetic approach towards the synthesis of compound **135**

# Chapter 6

# Development of the Cladiellin Diterpene framework

### 6.1. Introduction

An alternative approach to the cladiellin framework is investigated in this Chapter using the strategy developed in **Chapter 5.** This investigation began with retrosynthetic analysis 3 (**Scheme 120**), as discussed previously (**Chapter 5**, page 102.)




**Scheme 120.** Retrosynthetic analysis of substrate **135**

The coupling of substrate **273** (**Scheme 121**) with aldehyde **272** would give the required compound **135**. However, due to the reactivity problems of a similar aldehyde (**285**), it was considered that the bulk of the silyl ether in compound **285** was a hindrance and caused problems in its reactivity. As a result of this a simpler aldehyde (**316**) was used in a model study to verify the approach, before investigating alternative protecting group strategies.

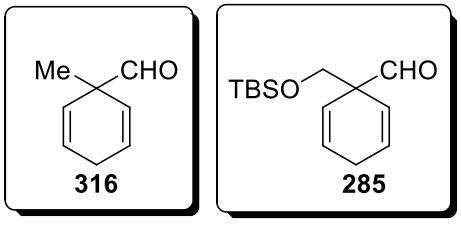
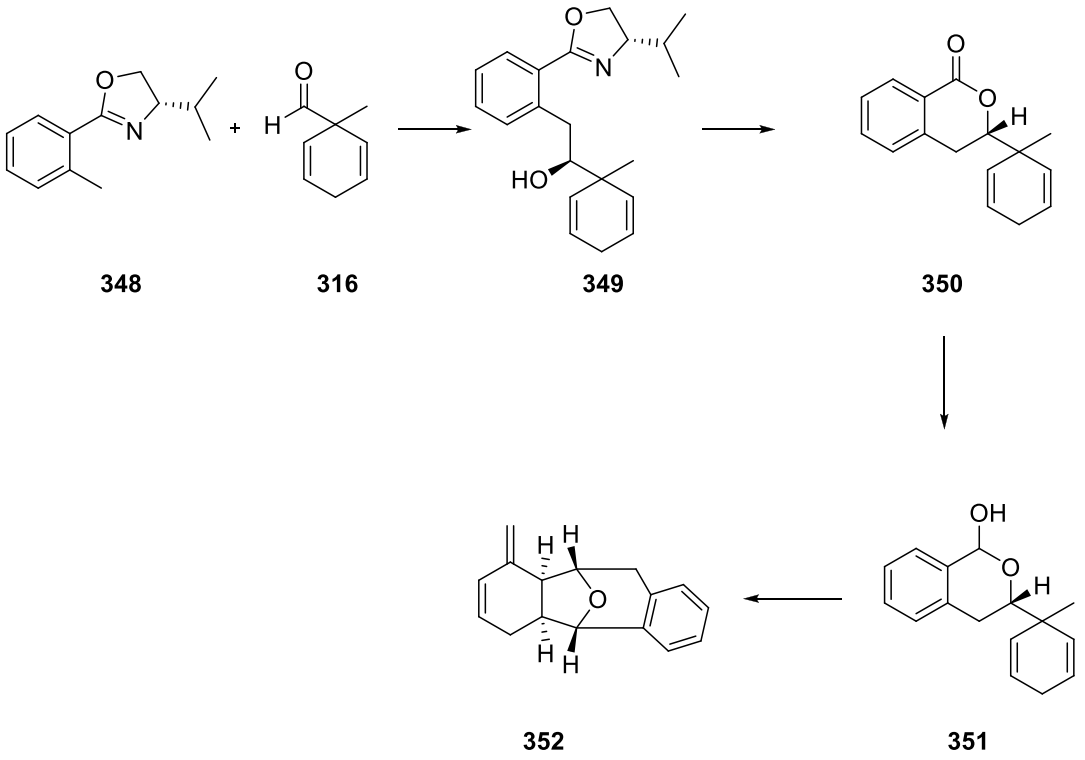



**Figure 30:** An alternative simpler aldehyde **316** as opposed to bulky aldehyde **285** used in previous studies

Before synthesising substrate **273**, an alternative approach was investigated which involved coupling of aldehyde **316** with an aromatic compound containing a lateral directing group. In **Chapter 5** other lateral directing groups were explored such as with 1,3-dimethyl-2-(*2*-methylphenyl)imidazolidine and phthalan.

Initially, the coupling of compound **348** (containing an oxazoline ring) with aldehyde **316** was examined**.** The product, **349**, would contain the correct carbon framework for the target compound, which could then be elaborated using an acid-catalysed reaction to form the lactone **350.** The formation of the corresponding lactol (**351**) was envisaged, using diisobutyl aluminium hydride in toluene and the addition of trifluoromethanesulfonic acid to compound **351** to form the model compound **352** (**Scheme 121**). However, this was only a speculation based on the likely mechanism, as the methyl substituent in compound **316** was a novel feature in the Prins reaction.

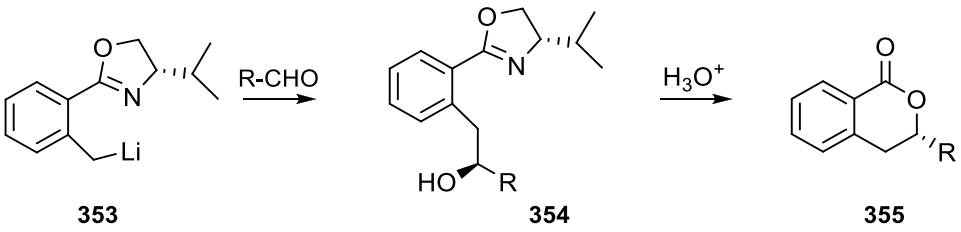



**348** **316** **349** **350** **351** **352**

**Scheme 121.** Model system towards the synthesis of compound **352**

Utilization of an oxazoline ring as a directing group in aromatic *ortho*-lithiation was demonstrated independently in 1975 by both Gschwend and Meyers.[82] In 2004, Tahara *et al.* investigated the lithiation of 4,4-dimethyl-2-(2-methylphenyl)-4,5-dihydrooxazoles and revealed that regioselectivity (whether *ortho* or lateral lithiation) could be controlled by presence/absence of TMEDA.[83] They described how the selectivity has been rationalized by steric interactions between TMEDA and C-4 substituents on the oxazoline ring in the

transition states of deprotonation and that the use of TMEDA as a ligand was vital for good selectivity. Tahara *et al.* discovered that the chirality from the 4,5-dihydrooxazole could only be transferred to a prochiral aldehyde in the presence of TMEDA and, using this information, the group synthesized 3-substituted 8-hydroxy-3,4-dihydroisocoumarins including natural products (±)-hydragenol and (±)-phyllodulcin.[84] Following on from this, Kurosaki *et al.* investigated the asymmetric synthesis of optically enriched 3-substituted 3,4-dihydroisocoumarins by stereoselective addition of laterally lithiated chiral 2-(2-methylphenyl)-4,5-dihydrooxazoles to aldehydes followed by acid-catalyzed lactonization as shown in **Scheme 122**.[85]

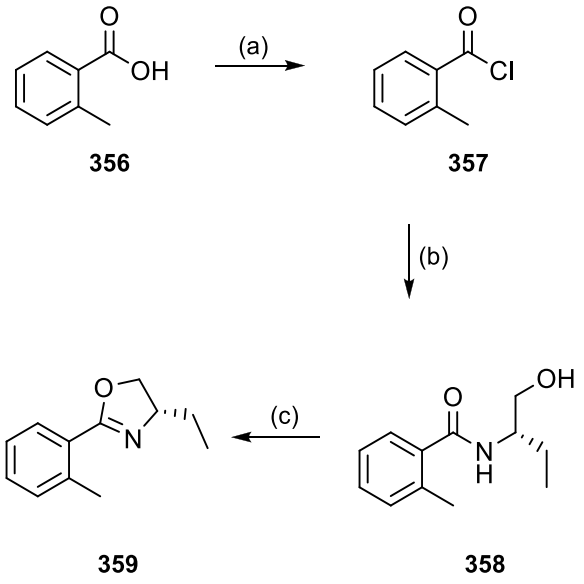



**353** **354** **355**

**Scheme 122.** Asymmetric synthesis of optically enriched 3-substituted 3,4-dihydroisocoumarins

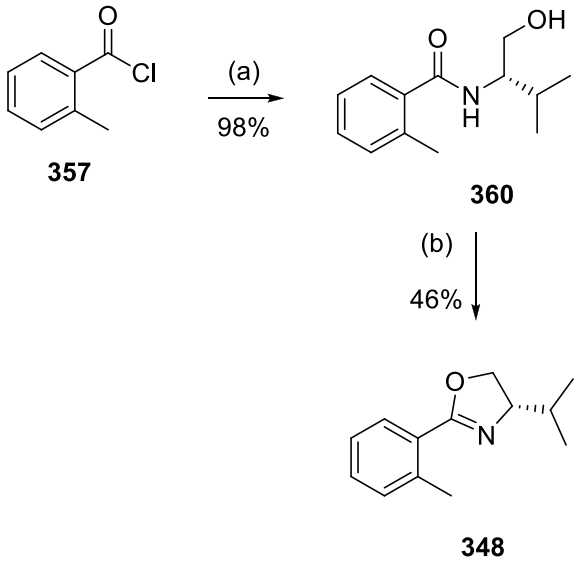
### 6.2. Results and Discussion

Oxazoline **359** was synthesized using similar conditions to that devised by Tahara *et al.*[83] The acid chloride **357** was formed by chlorination of 2-methylbenzoic acid (**356**) using oxalyl chloride and a catalytic amount of DMF at room temperature. Treatment of the resulting 2-methylbenzoyl chloride **357** with 2-amino-1-butanol and triethylamine in THF, gave the intermediate 2-methylbenzamide, **358**. This was followed by further treatment of the amide **358** with methanesulfonyl chloride and triethylamine in $CH_2Cl_2$, to give oxazoline **359**. Upon treatment of compound **359** with either pivalaldehyde and hexanal under varying conditions, for example different solvents (diethyl ether/THF), with TMEDA/without TMEDA, $N_2$ atmosphere/argon atmosphere, unfortunately resulted in a mixture of unreacted starting materials. Both pivalaldehyde and hexanal have been reported[83] to react successfully with the equivalent oxazoline with an isopropyl group, but in our hands they failed to react with compound **359** containing an ethyl substituent.




**Scheme 123.** Syntheisis of compound **359**. *Reagents and conditions.* (a) Oxalyl chloride, DMF (cat.), $CH_2Cl_2$ 25 °C; (b) (*S*)-2-aminobutan-1-ol, $Et_3N$,THF , 0 °C, 1h; (c) methanesulfonyl chloride, $Et_3N$, $CH_2Cl_2$

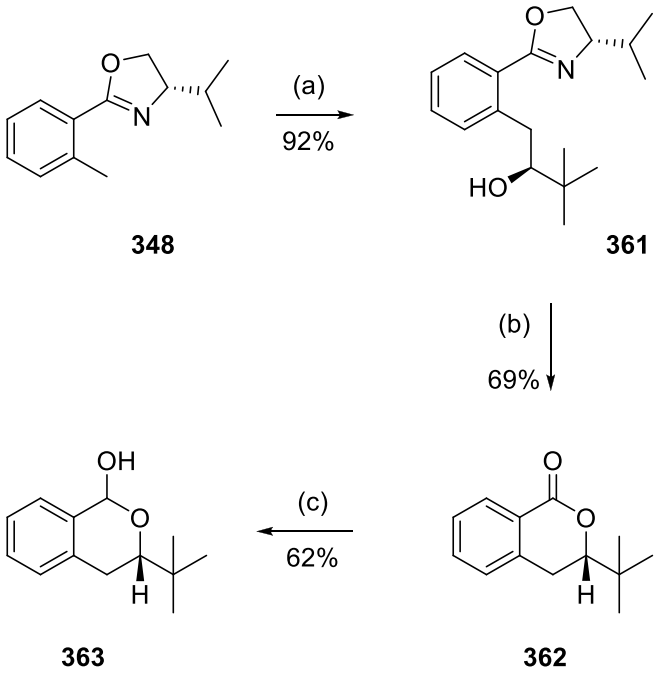
As a result of this, oxazoline substrate **348** was prepared, since the deprotonation of this compound and subsequent reaction with aldehydes had already been reported.[83,84] Treatment of 2-methylbenzoyl chloride **357** with (*S*)-(+)-2-amino-3-methyl-butanol and triethylamine in THF gave the intermediate 2-methylbenzamide, **360**. Treatment of 2-methylbenzamide **360** with thionyl chloride formed oxazoline **348** in 46% yield.




**357** **360** **348**

**Scheme 124.** Preparation of oxazoline **348.** *Reagents and conditions:* (a) (*S*)-2-Amino-3-methyl-butanol, $Et_3N$, THF, 0 °C, 1h; (b) Thionyl chloride, MeOH, 0 °C to 25 °C

Oxazoline **348** was then coupled with pivalaldehyde using *sec*-BuLi and TMEDA in diethyl ether, forming compound **361** in 92% yield. The corresponding lactone **362** was formed upon treatment of compound **361** with a mixed solution of THF-$H_2O$-TFA (10:1.5:0.5). Then, reduction of lactone **362** with diisobutyl aluminium hydride in toluene formed the corresponding lactol (**363**) in 62% yield.

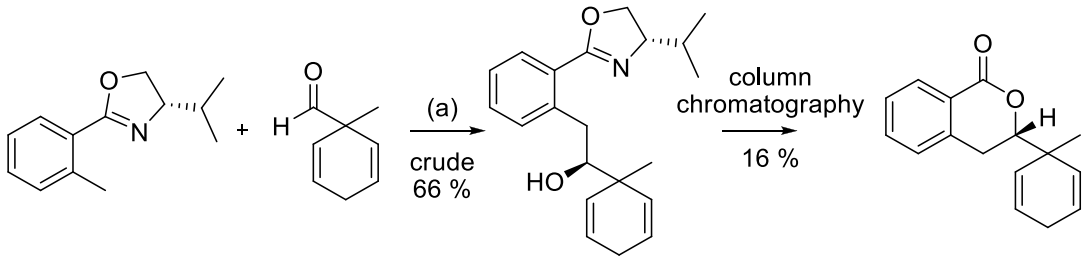



**Scheme 125**. Preparation of compound **363**. *Reagents and conditions*: (a) *sec*-BuLi, TMEDA, pivalaldehyde, $Et_2O$, -78 °C; (b) THF-$H_2O$-TFA (10:1.5:0.5), 0 °C, 24 h; (c) diisobutyl aluminium hydride, toluene, -78 °C, 30 minutes

Owing to this result, it was considered that applying the same conditions to couple aldehyde **316** with oxazoline **348** could enable the formation of a model system for the hexahydroisobenzofuran core of the cladiellin diterpenes (**352**).

Reaction of aldehyde **316** with oxazoline **348** using *sec*-BuLi and TMEDA in diethyl ether at -78 °C successfully formed compound **349** (**Scheme 126**). The stereochemical configuration of compound **349** was assumed, based on reported configurations of similar compounds formed using the same conditions.[83-85] During purification, lactone **350** formed on the column due to the acidity of the silica gel; however, this was not a concern as the

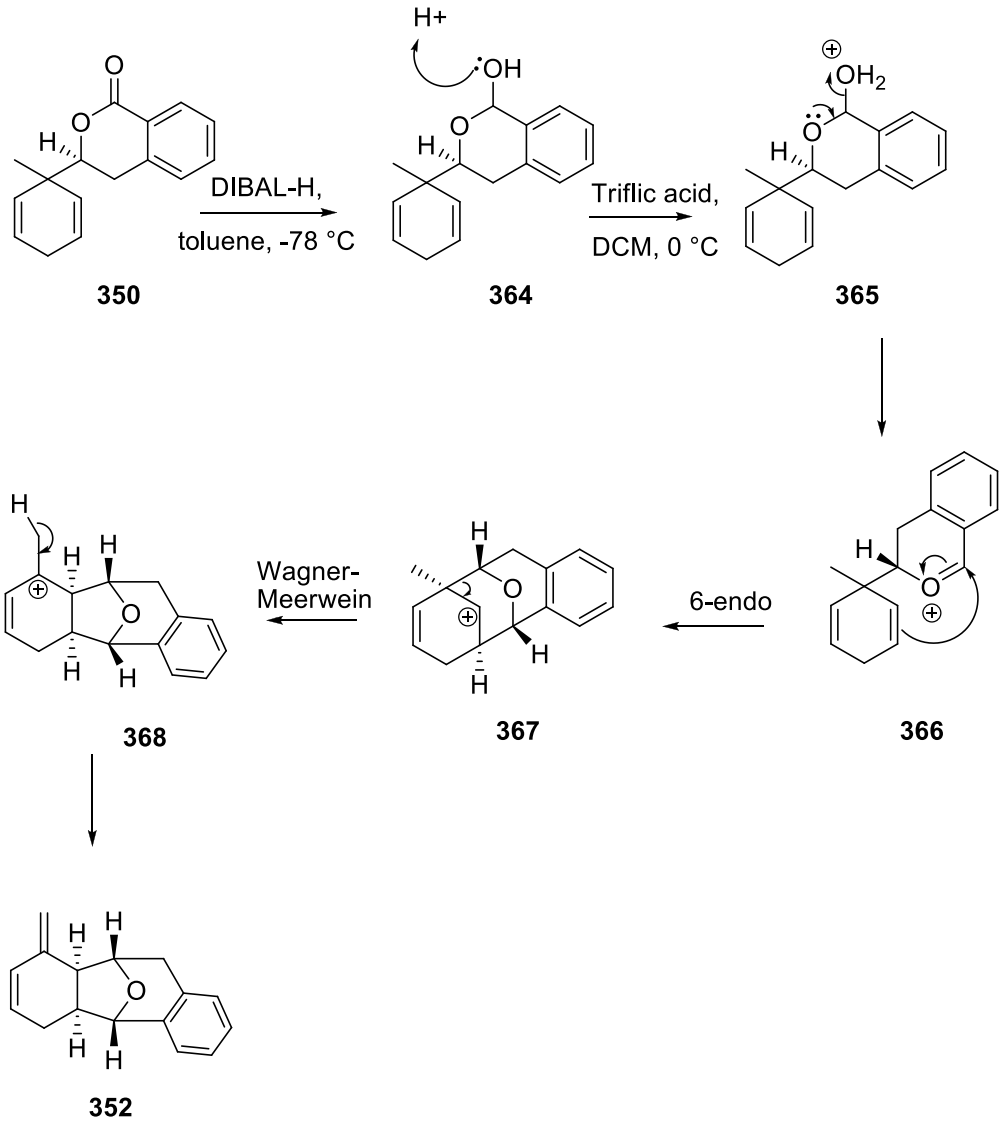
lactone was required in the next step. As a result of this, compound **349** was not characterised.




**348** **316** **349** **350**

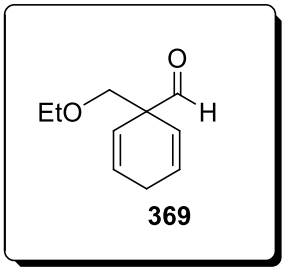
**Scheme 126.** Preparation of compound **350**. *Reagents and conditions:* (a) *sec*-BuLi, TMEDA, $Et_2O$, -78 °C

Unfortunately, formation of the corresponding lactol **364** was not possible due to the little amount of compound **350** remaining**.** With time constraints, there were two choices. One option was to synthesize more of aldehyde **316** to attempt formation of the corresponding lactol and then to apply the subsequent Prins rearrangement/cyclisation methodology (**Scheme 127**). It was proposed that protonation of the oxygen atom of the alcohol in compound **364**, followed by loss of water, would give oxocarbenium ion **366**. A 6-*endo* cyclisation onto one of the diastereotopic double bonds would then proceed, followed by a Wagner-Meerwein shift to give the allylic cation **368**. It was speculated that deprotonation of compound **368** would result in formation of the diene **352**.




**Scheme 127**. Proposed formation of compound **352** via Prins cyclisation/rearrangement methodology

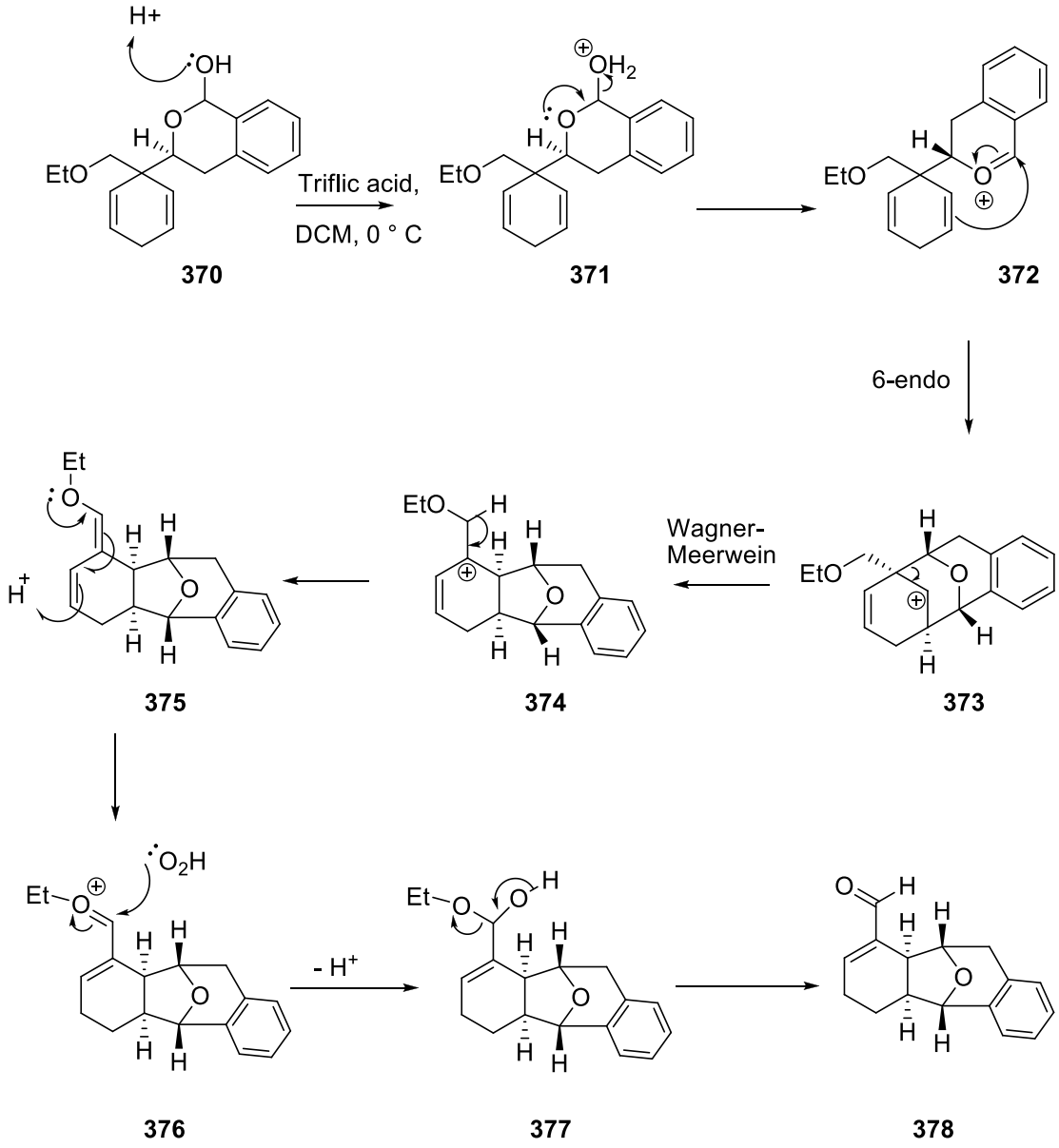
However, as described above, even if this approach were successful, it would not give us the desired compound containing an aldehyde. An alternative choice was to synthesize a novel aldehyde with the additional functionality required for the cladiellin framework (**369)**, **Figure 31**.




**369**

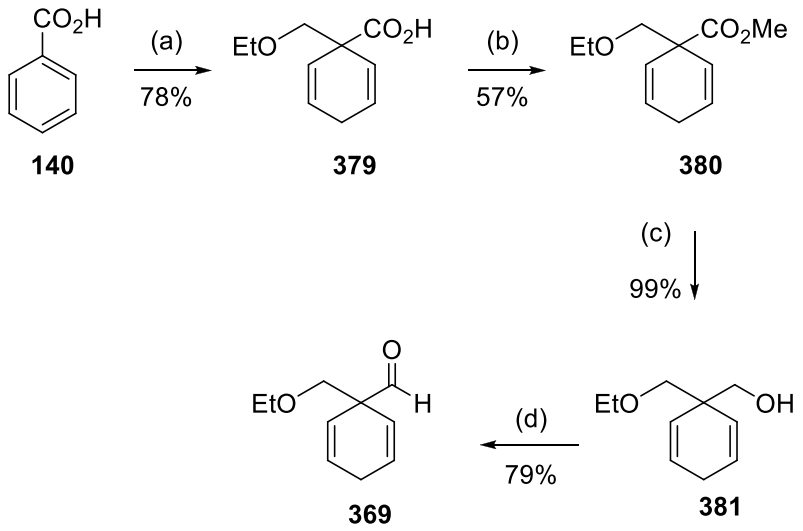
**Figure 31.** Compound **369** with a novel ethyl ether protecting group

The use of an ethyl ether as a 'protecting group' in compound **369** is a novel feature of this approach and, although it would not normally be appropriate, it was expected to be effective with the Prins mechanism, owing to the formation and hydrolysis of an enol ether (**Scheme 128**).



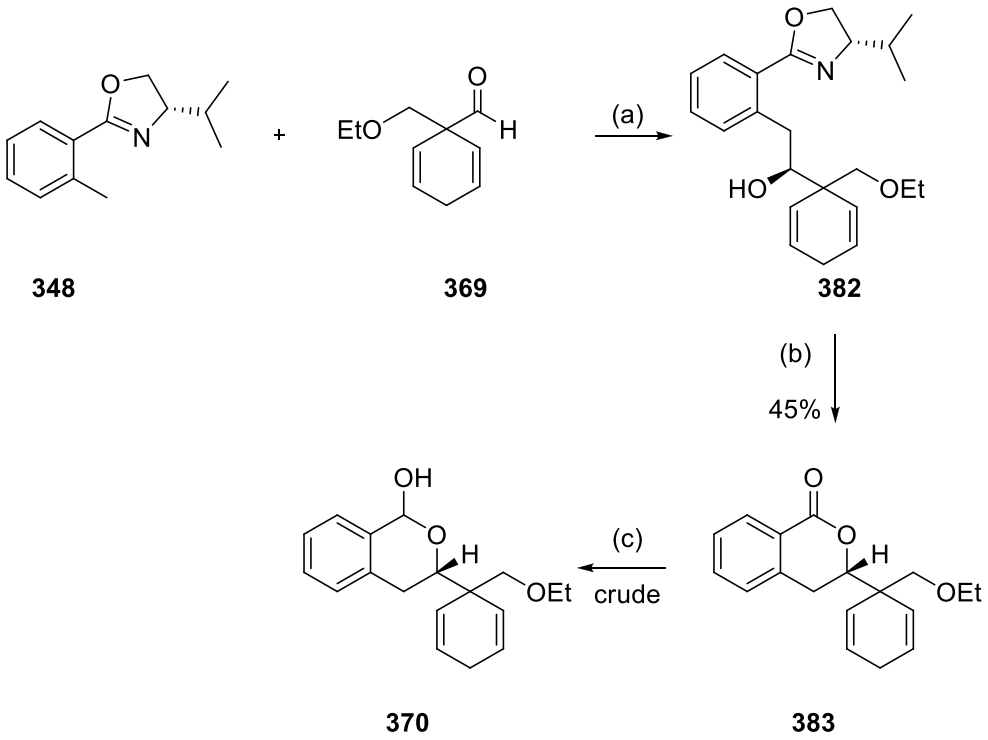

**Scheme 128.** Formation of compound **378** via Prins cyclisation/rearrangement methodology

Synthesis of compound **369** began by the Birch reduction of benzoic acid using lithium metal in ammonia followed by alkylation with chloromethyl ethyl ether to give compound **379**. Esterification of compound **379** using $H_2SO_4$ in MeOH gave ester **380**. Ester **380** was then reduced to its corresponding alcohol **381** using $LiAlH_4$. Oxidation of compound **381** using Swern conditions gave the corresponding aldehyde **369** in 79% yield (**Scheme 129**).



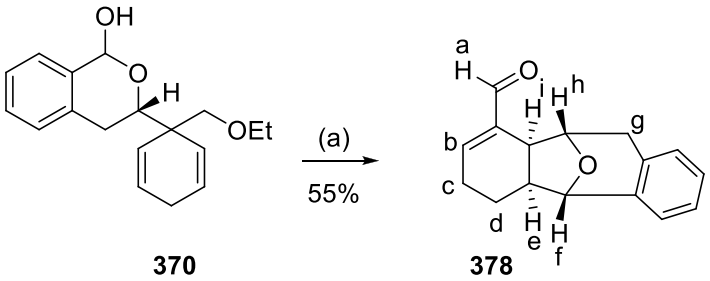

**Scheme 129.** Formation of compound **369**. *Reagents and conditions:* (a) Li, $NH_3$, chloromethyl ethyl ether, -78 °C; (b) MeOH, $H_2SO_4$, 16 h; (c) $LiAlH_4$, THF, 2 h; (d) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, -78 °C to room temperature, 2 h

Oxazoline **348** was treated with *sec*-BuLi and TMEDA in diethyl ether for 2 h at -78 °C before adding aldehyde **369** to allow formation of compound **382**. However, during purification of compound **382** the acidity of the silica gel was causing partial formation of lactone **383**. The same problem was experienced with the formation of lactone **350**. To overcome this problem, a mixture of compounds **382** and **383** was treated with a mixed solution of THF-$H_2O$-TFA (10:1.5:0.5) which resulted in complete conversion to lactone **383** with minor impurities. As a result of this, compound **382** was not characterised. Reduction of lactone **383** with diisobutyl aluminium hydride in toluene formed the corresponding lactol (**370**), (**Scheme 130**).



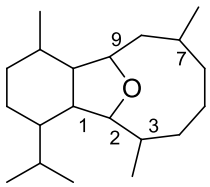

**Scheme 130.** Synthesis of compound **370**. *Reagent and conditions:* (a) *sec*-BuLi, TMEDA, pivalaldehyde, $Et_2O$, -78 ° C:, (b) THF-$H_2O$-TFA (10:1.5:0.5), 0 ° C, 24 h; (c) diisobutyl aluminium hydride, toluene, -78 ° C, 30 minutes

Gratifyingly, treatment of the crude lactol **370** with trifluoromethanesulfonic acid in dichloromethane gave compound **378** as a single diastereoisomer in 55% yield over two steps from compound **383** (**Scheme 131**).

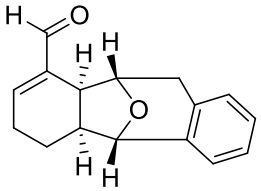



**Scheme 131.** Synthesis of compound **378**. *Reagents and conditions:* (a) Trifluoromethanesulfonic acid, $CH_2Cl_2$, 0 °C, 30 minutes

A model system for the hydroisobenzofuran core (**378**) of the cladiellin diterpenes has been synthesized as a single diastereoisomer using the Prins cyclisation/rearrangement methodology developed within the group. The NOESY NMR spectrum shows evidence of a cross-peak between one of the $H^g$ protons and $H^i$ confirming that it contains the desired configuration, and a significant cross-peak between $H^e$ and $H^i$ which confirms the ring junction configuration where the core is characterised by an *anti* relationship between the two pairs of ring junction protons as illustrated (**Figure 32**).




Cladiellin framework




**378**

**Figure 32.** Comparison of cladiellin framework to the framework of the model compound **378**

The formation of a model compound of the cladiellin core (with an additional carbon atom) as a single diastereoisomer in relatively few synthetic steps is a significant achievement and an improvement on previous attempts within the group. The proton NMR spectrum of compound **378** is shown in **Figure 33**, followed by a summary for the overall formation of compound **378** (**Scheme 132**).

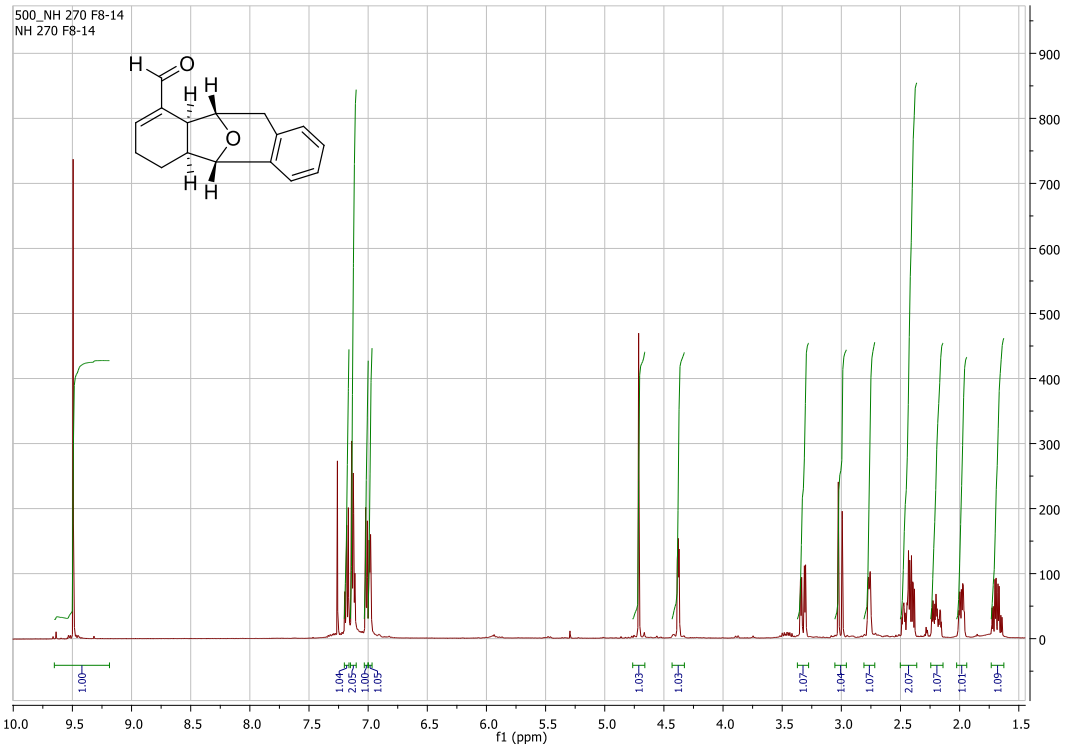
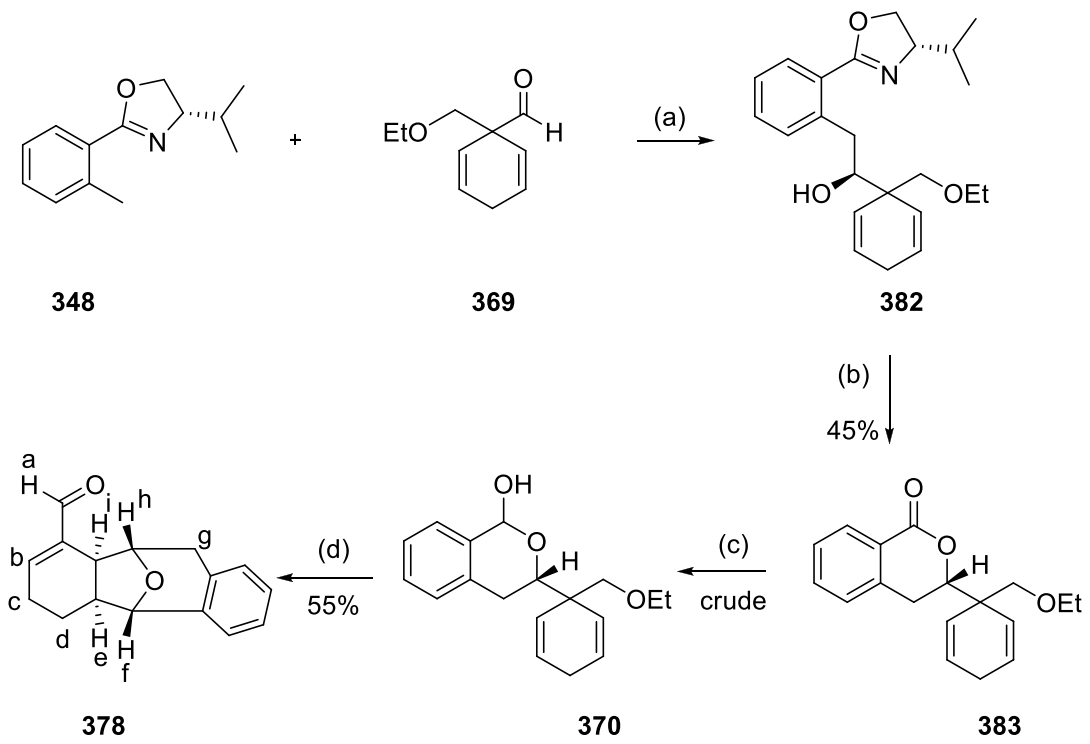


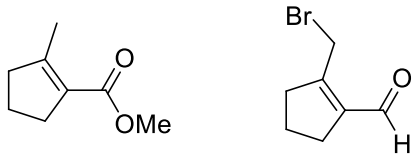

**Figure 33.** Proton NMR spectrum of compound **378**




**Scheme 132.** Summary of the overall synthesis of compound **378**

### 6.2.1. Cyclopentene-fused compounds

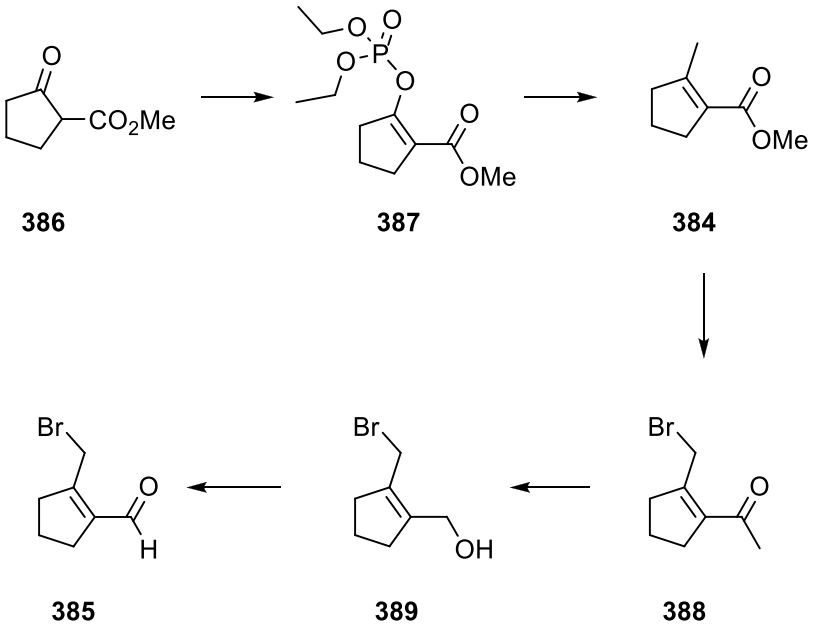
This key result gave us confidence that, once this method is applied and aldehyde **369** is coupled to a compound containing a five-membered ring (**Figure 34**), rather than a six-membered ring, a hydroisobenzofuran core resembling the exact framework of the cladiellin diterpenes could be accessed.




**384** **385**

**Figure 34.** Potential substrates for reaction with aldehyde **369**

The aim was to couple a compound of general structure **385** with compound **369**. The substrate **384** could be prepared by initially forming the enol phosphate **387** by treating commercially available methyl-2-oxocyclopentanecarboxylate **386** with sodium hydride and diethyl chlorophosphate. Then, compound **388** could be formed by treating the enol phosphate **387** with lithium dimethylcuprate, hydrochloric acid and sodium chloride in ammonia.[86] Bromination of compound **387** using *N*-bromosuccinimide and $(PhCO_2)_2$ would allow formation of compound **388**.[87] The corresponding alcohol (**389**) could then be accessed by reduction of compound **388** using $LiAlH_4$, and construction of the corresponding aldehyde **385** upon treating alcohol **389** with $MnO_2$.[88]



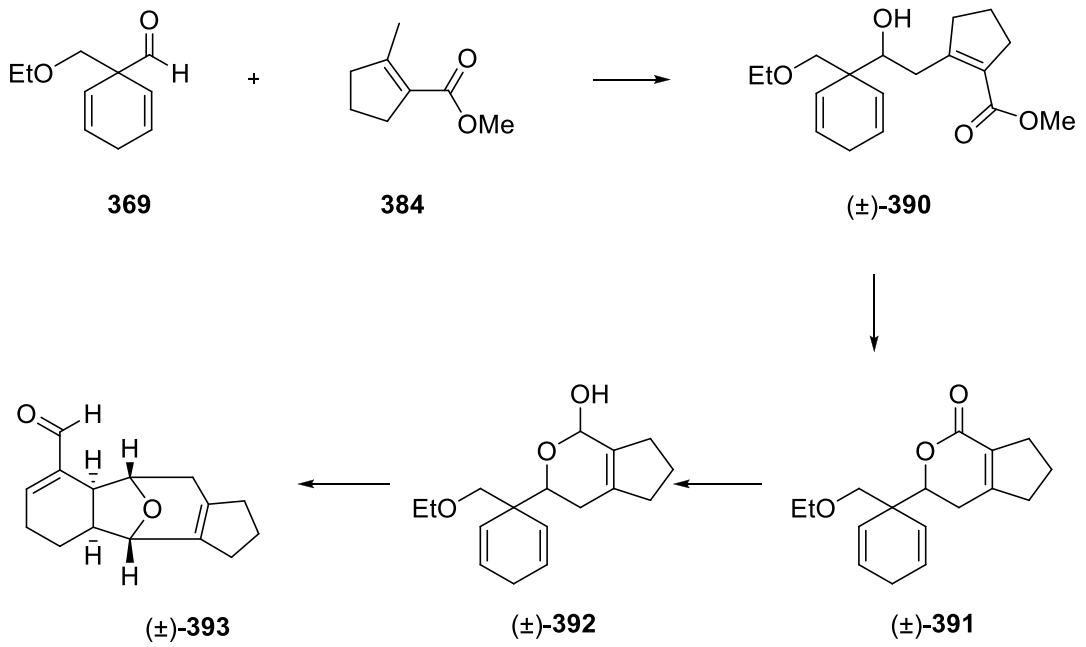

386 387 384

385 389 388

**Scheme 133.** Proposed synthesis of compound **385**

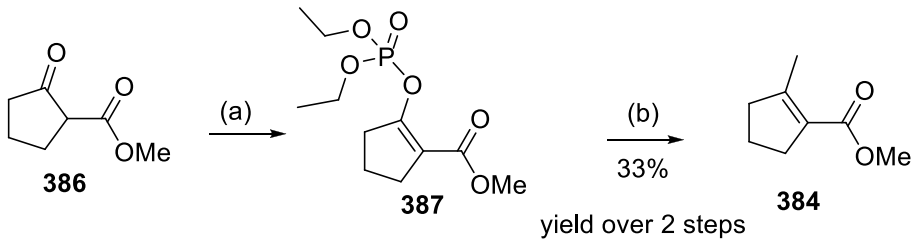
After formation of compound **385**, protection of the aldehyde or reaction at a different oxidation level such as the corresponding ester would be required, and, depending on the group, it may be possible to form the anion by lateral deprotonation of a methyl group (**384**). However, without a suitable directing group, the bromine could be used to undergo lithium-halogen exchange.

Due to time constraints, ester **384** was synthesized as an alternative to compound **385** to react directly with aldehyde **369** (**Scheme 134**).



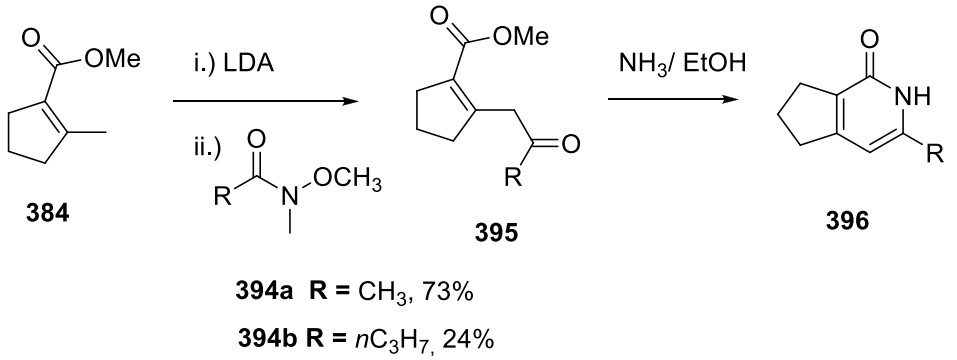

**Scheme 134.** New model system for the framework of the cladiellin diterpene

Compound **384** was synthesized as follows: commercially available methyl 2-oxocyclopentanecarboxylate (**386**) was treated with sodium hydride in diethyl ether for 30 minutes before adding diethyl chlorophosphate and further stirring for 3 h, resulting in the formation of compound **387**.[86] Compound **387** was then converted without further purification to compound **384** using copper iodide and methyllithium in diethyl ether (**Scheme 135**).[87]



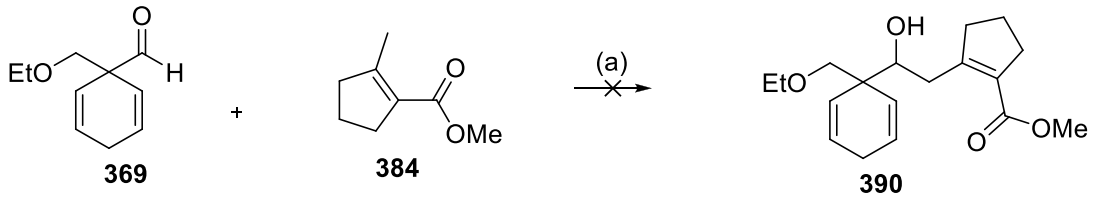

**Scheme 135.** Preparation of compound **384**. *Reagents and conditions:* (a) NaH, Diethyl chlorophosphate, $Et_2O$, 0 °C; (b) copper iodide, methyllithium, diethyl ether, 0 °C to -40 °C

Chen *et al.* reported the successful coupling of ester dienolate derived from compound **384** with Weinreb amides, and the conversion of the resulting δ-ketoacrylates into fused pyridones (**396**).[89] The reaction of the dienolate derived from **384** with *N*-methoxy-*N*-methyl acetamide or butyramide gave δ-keto esters **394a** and **394b** along with some un-reacted starting material (compound **384**). It has been reported that reaction of ester enolates with Weinreb amides are often difficult to drive to completion.[90] Heating **394a** and **394b** with ethanolic ammonia gave pyridine **396a** and **396b** in high yield (**Scheme 136**).



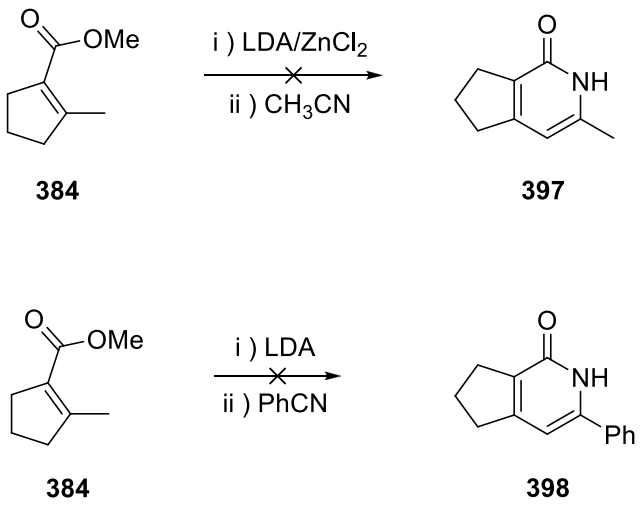

**Scheme 136.** Condensation of dienolates with enolizable Weinreb amides[91]

Owing to their success, the conditions reported by Chen *et al.* were used to deprotonate compound **384**. Compound **384** was treated with LDA in THF at -78 °C and stirred for 1.5 h before adding aldehyde **369** (**Scheme 137**).




**Scheme 137.** Attempted synthesis of compound **390**. *Reagents and conditions:* (a) LDA, THF, -78 ° C

Unfortunately this reaction was not successful. However, this is not the first time that compound **384** failed to react under these conditions. Chen *et al.* reported the failure of compound **384** to react with nitriles using similar conditions (**Scheme 138**).[89]




**Scheme 138.** Unsuccessful condensation attempts by Chen *et al*.[89]

### 6.3. Conclusion

A model for the hydroisobenzofuran core (**378**) of the cladiellin diterpenes has been synthesized as a single diastereoisomer, using Prins cyclisation/rearrangement methodology developed within the group. Although this model system has an aromatic six-membered ring in place of the desired cyclopentene ring, it is the closest our group have prepared to the core of the cladiellin diterpenes. This route is relatively straightforward, and now provides scope for access to key fragments of the cladiellin diterpenes.

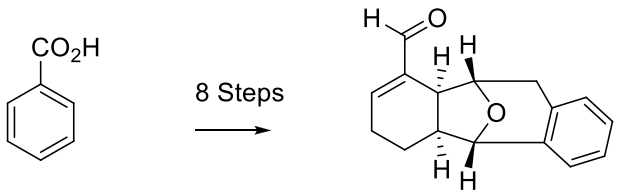
The next logical step would be to improve the conditions for the deprotonation of compound **384** to couple with compound **369**. If this proves successful then the cladiellin framework could be achieved in three further steps.

# Chapter 7

# Conclusion

### 7.1. Conclusion

Compound **378**, a model for the hydroisobenzofuran core of the cladiellin diterpenes, has been synthesised as a single diastereoisomer using Prins cyclisation/rearrangement methodology developed within the group, **Scheme 139**. Although this model system has an aromatic six-membered ring in place of the desired cyclopentene ring, it is the closest our group have prepared to the core of the cladiellin diterpenes. This route is relatively straightforward, and now provides scope for access to key fragments of the cladiellin diterpenes.




**140** **378**

**Scheme 139:** Synthesis of a model for the hydroisobenzofuran core (**378**) of the cladiellin diterpenes

The Prins cyclisation/rearrangement methodology developed within the group also provided three model systems of the cladiellin diterpene skeleton each containing an oxacyclic component of varying sizes. One of these (compound **120**) contained a smaller ring system than is present in the natural products but was isolated as a single diastereoisomer and was confirmed to possess the correct relative stereochemical configuration for the cladiellin diterpenes. The attempt to form the five-membered ring (**262**) was inconclusive, while attempts to form seven- and nine-membered rings gave macrocyclic compounds **237** and **244**, **Figure 35**.

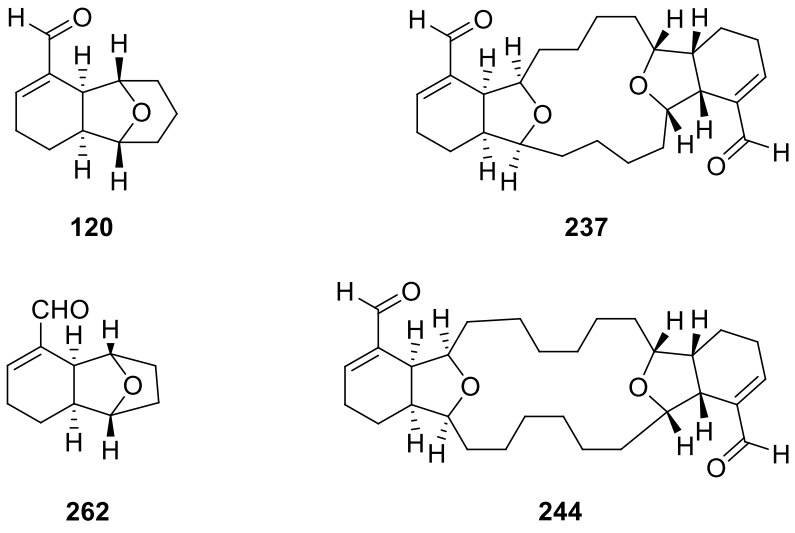
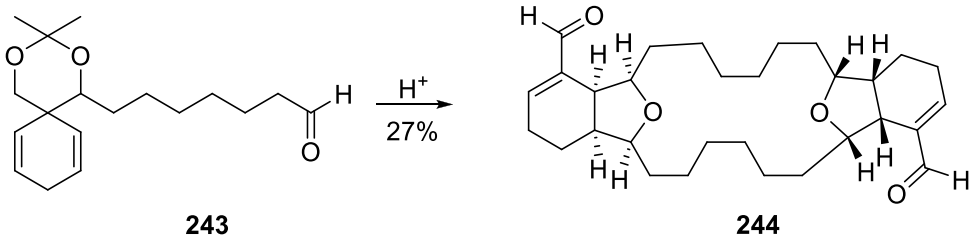



**Figure 35.** Prins cyclisation/rearrangement products.

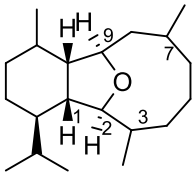
Attempts at installing the nine-membered ring directly as discussed in **Chapter 4** resulted in the formation of the dimeric compound **244**, containing an eighteen-membered ring (**Scheme 140**). Various attempts at synthesising the monomer were not successful.




**243** **244**

**Scheme 70.** Previous attempt at installing a nine-membered ring.

In addition, a method has been developed that introduces an isopropyl and similar alkyl groups at the 4-position of the 6-membered ring , as shown in the structure of the cladiellin framework in **Figure 36**.



**1**, cladiellins

**Figure 36:** Cladiellin Diterpene framework containing an isopropyl substituent at the 4-position of the 6-membered ring.

# Chapter 8

# Experimental Section

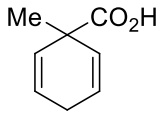
### 8.1. General Experimental Points

All starting materials, reagents and solvents were purchased from commercial suppliers and used as supplied unless otherwise stated. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. Mass spectra were recorded on a Fisons VG Platform II spectrometer and on a Micromass Q-TOF Micro spectrometer. NMR spectra were recorded on a Bruker DPX 400 spectrometer operating at 400 MHz for $^{1}H$ and at 100 MHz for $^{13}C$ at 25 °C, or 250 MHz and 62 MHz respectively on a Bruker Avance DPX 250 or on a Bruker Avance 500 spectrometer operating at 500 MHz for $^{1}H$ and 125 MHz for $^{13}C$ at 25 °C. All chemical shifts are reported in ppm downfield from TMS, or relative to residual $CHCl_3$. Coupling constants (*J*) are reported in Hz. Multiplicity in $^{1}H$-NMR is reported as singlet (s), doublet (d), double doublet (dd), double triplet (dt), double quartet (dq), triplet (t), and multiplet (m). Multiplicity in $^{13}C$-NMR was obtained using the DEPT pulse sequence. All NMR spectra were obtained in $CDCl_3$, unless otherwise noted. Flash chromatography was performed using Matrex silica 60 35 – 70 micron.

Solvents for moisture-sensitive reactions were dried by distillation; THF, benzene and toluene from sodium benzophenone ketyl and $CH_2Cl_2$ from $CaH_2$. Such reactions were conducted under an atmosphere of dry nitrogen.

## 8.2. Experimental Data for Chapter 3

### 1-Methylcyclohexa-2,5-dienecarboxylic acid (149) [43,91]



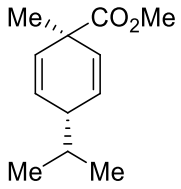

**149**

Ammonia (500 mL) was added to benzoic acid (20.0 g, 164 mmol) in a 1L multineck round-bottomed flask through a dry ice-acetone condenser. With careful stirring, Li (3.2 g, 460 mmol) was added portion-wise until a permanent blue colour was observed. After stirring for 15 mins at this temperature, iodomethane (29.0 mL, 468 mmol) was added drop-wise over a period of 30 minutes. The ammonia was left to evaporate and the residue was dissolved in iced water. Dilute sulfuric acid was added, until pH 1 – 2 was reached. The solution was then extracted with diethyl ether (3 x 200 mL). The extract was dried over $MgSO_4$ and the solvent was concentrated *in vacuo* to give the title compound (20.97 g, 93%) as a colourless oil; $\delta_H$ (400 MHz; $CDCl_3$) 5.88 – 5.83 (2H, m, 2 x alkene CH), 5.80 – 5.75 (2H, m, 2 x alkene CH), 2.69 – 2.63 (2H, m, $CH_2$) and 1.37 (3H, s, $CH_3$).

### General Procedure for the Alkylation of 1-Methylcyclohexa-2,5-diene-1-carboxylic acid (149)

A solution of *n*-butyllithium (2.0 M in cyclohexane, 1.99 mL, 3.98 mmol) was added to 1-methylcyclohexa-2,5-diene-1-carboxylic acid (**149** (0.25 g, 1.81 mmol) in THF (10 mL) at -78 °C. TMEDA (0.59 mL, 3.98 mmol) was then added and the solution was stirred for 30 minutes. The electrophile (for number of equivalents see individual compounds) was added and the reaction mixture was stirred for 10 minutes at –78 °C, then warmed to room temperature and the mixture was stirred for a further 1 h. The reaction mixture was quenched with 2 M hydrochloric acid (5 mL) and the product was extracted into $CH_2Cl_2$ (3 x 20mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo*. The resulting residue was dissolved in methanol (10 mL). Concentrated sulfuric acid (0.05 mL) was added and the solution mixture was stirred at 25 °C for 17 h. The methanol was removed *in vacuo* and saturated aqueous $NaHCO_3$ solution (5mL) was added. The organic material was extracted with $CH_2Cl_2$ (3 x 20 mL). The extract was dried over $MgSO_4$, and the solvent concentrated *in vacuo*. The crude products were purified as described below.

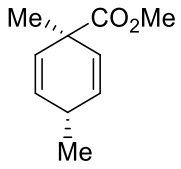
**(1*r*,4*r*)-Methyl 4-isopropyl-1-methylcyclohexa-2,5-dienecarboxylate (187a)**




**187a**

Prepared according to the general procedure, using 14.5 mmol of 1-methylcyclohexa-2,5-diene-1-carboxylic acid (**149**), and using 2-bromopropane (1.50 mL, 15.9 mmol, 1.1 equiv.) as electrophile. Purification by flash column chromatography (9:1 hexane:diethyl ether) gave the *title compound* (1.55 g, 55%) as a colourless oil (Found: $MH^+$, 195.1377. $C_{12}H_{19}O_2$ requires M, 195.1385); $\nu_{max.}$ (neat) 2961, 2875, 1734, 1250 and 1114 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 5.83 (2H, dd, *J* 10.4, 2.0, 2 x alkene CH), 5.70 (2H, dd, *J* 10.4, 3.1, alkene CH), 3.69 (3H, S, OC*H*$_3$), 2.67 (1H, app. dtt, *J* 4.0, 3.1, 2.0, CH=CH-C*H*), 1.77 (1H, septet of doublets, *J* 6.9, 4.0, CH-C*H*$(CH_3)_2$), 1.32 (3H, s, C*H*$_3$) and 0.89 (6H, d, *J* 6.9, 2 x C*H*$_3$); $\delta_C$ (125 MHz; $CDCl_3$) 175.8 (C=O), 129.4 (CH), 127.7 (CH), 52.3 ($CH_3$), 44.7 (C), 41.6 (CH), 32.0 (CH), 27.6 ($CH_3$) and 19.3 ($CH_3$); *m/z* (APCI) (%) 195 ($MH^+$, 100) and 115 (34).

**(1*r*,4*r*)-Methyl 1,4-dimethylcyclohexa-2,5-dienecarboxylate (187b)**




**187b**

Prepared according to the general procedure, using 3.6 mmol of 1-methylcyclohexa-2,5-diene-1-carboxylic acid (**149**), and using iodomethane (0.46 mL, 7.7 mmol, 2.1 equiv.) as electrophile. Purification by flash column chromatography (9:1 hexane:diethyl ether) gave the *title compound* (0.39 g, 58 %) as a pale yellow oil, approximately 1:1 ratio of **187b**:**187c** with spectroscopic data in line with those from the individual compounds as given below.

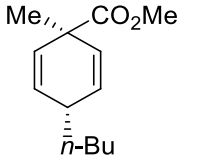
**(1*r*,4*r*)-Methyl 1,4-dimethylcyclohexa-2,5-dienecarboxylate (187b) using LDA as base**

A solution of *n*-butyllithium (2.0 M in cyclohexane, 2.80 mL, 5.60 mmol) was added to a solution of diisopropylamine (0.81 mL, 5.60 mmol) in THF (10 mL) at –78 °C. After stirring for 30 minutes, 1-methylcyclohexa-2,5-diene-1-carboxylic acid (**149**) (0.25 g, 1.81 mmol) in THF (2 mL) was added and the resulting solution was stirred for a further 30 minutes before addition of iodomethane (0.56 mL, 9.05 mmol). The solution was then stirred for 10 minutes at –78 °C, allowed to warm to room temperature and stirred for a further 1 h. The reaction mixture was quenched with 2 M hydrochloric acid (5 mL), and the product extracted into $CH_2Cl_2$ (3 x 20mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo.* The resulting residue was dissolved in methanol (10 mL). Concentrated sulfuric acid (0.05 mL) was added and the solution was stirred at 25 °C for 17 h. The methanol was removed *in vacuo* and the reaction was quenched with saturated aqueous $NaHCO_3$ solution (5mL). The organic material was extracted with $CH_2Cl_2$ (3 x 20 mL), which was then dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash column chromatography (9:1 hexane:diethyl ether) gave the *title compound* (0.16 g, 53%) as a colourless oil as an inseparable 4:1 mixture of compound **187b** and the methyl ester of carboxylic acid **149** (Found: $MH^+$, 167.1075. $C_{10}H_{15}O_2$ requires M, 167.1072); $\nu_{max.}$ (neat) 2956, 1733, 1248, 1116 and 733 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 5.67 – 5.65 (4H, m, alkene CH), 3.68 (3H, s, $CH_3O$), 2.78 – 2.70 (1H, m, CH), 1.33 (3H, s, $CH_3$) and 1.08 (3H, d, *J* 7.3, $CH_3$); $\delta_C$ (125 MHz; $CDCl_3$) 175.7 (C=O), 131.0 (CH), 127.8 (CH), 52.3 ($CH_3$), 44.3 (C), 30.4 (CH), 27.9 ($CH_3$) and 21.8 ($CH_3$); *m/z* (APCI) (%) 167 ($MH^+$, 100).

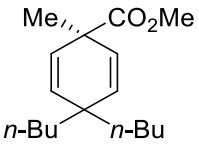
**(1*r*,4*r*)-Methyl 1,4-dimethylcyclohexa-2,5-dienecarboxylate (186b) using LIDAKOR as base**

A solution of *n*-butyllithium (2.0 M in cyclohexane, 1.53 mL, 3.05 mmol) was added to a solution of potassium *tert*-butoxide (0.36 g, 3.19 mmol) in THF (7 mL) at –78 °C, followed by diisopropylamine (0.45 mL, 3.19 mmol) and the remaining solution was stirred for 30 minutes. 1-Methylcyclohexa-2,5-diene-1-carboxylic acid (**149**) (0.20 g, 1.45 mmol) in THF (1 mL) was added and stirred for a further 30 minutes before iodomethane (0.45 mL, 7.25 mmol) was added, stirred for 10 minutes at –78 °C and then for 1 h at 25 °C. The reaction was quenched with 2 M hydrochloric acid (5 mL), and the product was extracted with $CH_2Cl_2$ (3 x 20mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo*. The residue was dissolved in methanol (10 mL), concentrated sulfuric acid (0.04 mL) was added, and the resulting solution was stirred at 25 °C for 17 h. The methanol was removed *in vacuo* and the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (5mL). The organic material was extracted with $CH_2Cl_2$ (3 x 20 mL). The extract was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (9:1 hexane:diethyl ether) gave the *title compound* (90 mg, 37%) as a colourless oil as an inseparable 4:1 mixture of **187b** and the methyl ester of carboxylic acid **149**. Spectroscopic data are as above.

**(1*r*,4*r*)-Methyl 4-butyl-1-methylcyclohexa-2,5-dienecarboxylate (187c) and methyl 4,4-dibutyl-1-methylcyclohexa-2,5-dienecarboxylate (190c)**




**187c**



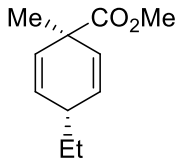

**190c**

Prepared according to the general procedure using bromobutane (0.21 mL, 1.99 mmol, 1.1 equiv.) as electrophile. Purification by flash column chromatography (20:1 hexane:diethyl ether) gave the di-butyl compound **190** (20mg, 4%) as a pale yellow oil first, and then the mono-butyl compound **187c** (240mg, 64%) as a colourless oil

Data for compound **190**: Found: $MH^+$, 265.2178. $C_{17}H_{29}O_2$ requires M, 265.2168; $\nu_{max.}$ (neat) 2956, 2929, 1735, 1238, 1112 and 800 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 5.77 (2H, d, *J* 10.2, 2 x alkene CH), 5.39 (2H, d, *J* 10.2, alkene CH), 3.67 (3H, s, $CH_3O$), 1.31 (3H, s, $CH_3$), 1.31 – 1.00 (12H, m, 6 x $CH_2$) and 0.85 (3H, t, *J* 7.0, $CH_3$) and 0.83 (3H, t, *J* 7.0, $CH_3$); $\delta_C$ (125 MHz; $CDCl_3$) 175.8 (C=O), 133.4 (CH), 128.5 (CH), 52.2 ($CH_3$), 44.6 (C), 41.6 ($CH_2$), 41.2 (C), 41.2 ($CH_2$), 27.4 ($CH_2$), 27.4 ($CH_3$), 27.1 ($CH_2$), 23.4 ($CH_2$), 23.4 ($CH_2$), 14.2 ($CH_3$) and 14.2 ($CH_3$); *m/z* (ES) (%) 265 ($MH^+$, 100), 205 (14) and 146 (14).

Data for compound **187c**: Found: $M^+$, 208.1464. $C_{13}H_{20}O_2$ requires M, 208.1458; $\nu_{max.}$ (neat) 2956, 2931, 2873, 1733, 1248, 1117, 796 and 734 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 5.81 – 5.69 (4H, m, alkene CH), 3.68 (3H, s, $CH_3O$), 2.76 – 2.67 (1H, m, CH), 1.45 – 1.38 (2H, m, $CH_2$), 1.33 (3H, s, $CH_3$), 1.32 – 1.19 (4H, m, 2 x $CH_2$) and 0.89 (3H, t, *J* 6.9, $CH_3$); $\delta_C$ (125 MHz; $CDCl_3$) 175.8 (C=O), 129.6 (CH), 128.4 (CH), 52.3 ($CH_3$), 44.5 (C), 35.4 (CH), 35.4 ($CH_2$), 28.6 ($CH_2$), 27.8 ($CH_3$), 23.0 ($CH_2$) and 14.2 ($CH_3$); *m/z* (ES) (%) 208 ($M^+$, 20), 164 (18), 149 (100), 121 (25), 105 (68) and 93 (78).

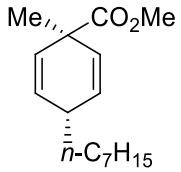
**(1*r*,4*r*)-Methyl 4-ethyl-1-methylcyclohexa-2,5-dienecarboxylate (187d)**




**187d**

Prepared according to the general procedure using bromoethane (0.15 mL, 1.99 mmol, 1.1 equiv.) as electrophile. Purification by flash column chromatography (50:1 hexane:diethyl ether) gave the *title compound* (165 mg, 51%) as a pale yellow oil (Found: $MH^+$, 181.1230. $C_{11}H_{17}O_2$ requires M, 181.1229); $\nu_{max.}$ (neat) 3023, 2965, 2931, 2875 and 1736 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 5.79 (2H, dd, *J* 10.3, 1.9, alkene CH), 5.71 (2H, dd, *J* 10.3, 3.1, alkene CH), 3.68 (3H, s, $CH_3O$), 2.73 – 2.67 (1H, m, CH), 1.47 (2H, qd, *J* 7.4, 6.0, $CH_2$), 1.33 (3H, s, $CH_3$) and 0.87 (3H, t, *J* 7.4, $CH_3$); $\delta_C$ (125 MHz; $CDCl_3$) 175.8 (C=O), 129.2 (CH), 128.7 (CH), 52.4 ($CH_3$), 44.4 (C), 36.4 (CH), 28.1 ($CH_2$), 27.8 ($CH_3$) and 10.5 ($CH_3$); *m/z* (APCI) (%) 181 ($MH^+$, 100) and 115 (62).

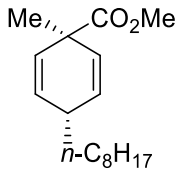
**(1*r*,4*r*)-Methyl 4-heptyl-1-methylcyclohexa-2,5-dienecarboxylate (187e)**




**187e**

Prepared according to the general procedure using 1-iodoheptane (0.59 mL, 3.62 mmol, 2.0 equiv.) as electrophile. Purification by flash column chromatography (9:1 hexane:diethyl ether) gave the *title compound* (240mg, 53%) as a colourless oil (Found: $M^+$, 250.1936. $C_{16}H_{26}O_2$ requires M, 250.1933); $\nu_{max.}$ (neat) 3026, 2955, 2927, 2856, 1735, 1240, 1114, 795 and 733 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 5.79 – 5.70 (4H, m, 4 x alkene CH), 3.68 (3H, s, $CH_3O$), 2.74 – 2.67 (1H, m, CH), 1.45 – 1.36 (2H, m, $CH_2$), 1.33 (3H, s, $CH_3$), 1.33 – 1.20 (10H, m, 5 x $CH_2$), and 0.88 (3H, t, *J* 7.0, $CH_3$); $\delta_C$ (125 MHz; $CDCl_3$) 175.6 (C=0), 129.5 (CH), 128.2 (CH), 52.2 ($CH_3$), 44.3 (C), 35.6 ($CH_2$), 35.2 (CH), 31.9 ($CH_2$), 29.8 ($CH_2$), 29.2 ($CH_2$), 27.6 ($CH_3$), 26.2 ($CH_2$), 22.6 ($CH_2$) and 14.1 ($CH_3$); *m/z* (EI) (%) 250 ($M^+$, 20), 191 (100), 105 (80) and 91 (97).

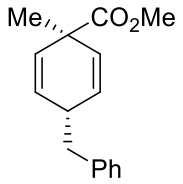
**(1*r*,4*r*)-Methyl 1-methyl-4-octylcyclohexa-2,5-dienecarboxylate (187f)**




**187f**

Prepared according to the general procedure using 1-bromooctane (0.35 mL, 1.99 mmol, 1.1 equiv.) as electrophile. Purification by flash column chromatography (9:1 hexane:diethyl ether) gave the *title compound* (226mg, 43%) as a colourless oil (Found: $MH^+$, 265.2164. $C_{17}H_{29}O_2$ requires M, 265.2168); $\nu_{max.}$ (neat) 2954, 2926, 2855, 1734, 1240, 1114, 734 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 5.76 (2H, dd, *J* 10.4, 1.5, alkene CH), 5.73 (2H, dd, *J* 10.4, 2.5, alkene CH), 3.68 (3H, s, $CH_3$), 2.74 – 2.68 (1H, m, CH), 1.44 – 1.36 (2H, m, $CH_2$), 1.32 (3H, s, $CH_3$), 1.32 – 1.20 (12H, m, 7 x $CH_2$) and 0.87 (3H, t, *J* 6.8, $CH_3$); $\delta_C$ (125 MHz; $CDCl_3$) 175.8 (C=O), 129.6 (CH), 128.4 (CH), 52.3 ($CH_3$), 44.5 (C), 35.8 ($CH_2$), 35.4 (CH), 32.0 ($CH_2$), 30.0 ($CH_2$), 29.7 ($CH_2$), 29.5 ($CH_2$), 27.8 ($CH_3$), 26.4 ($CH_2$), 22.8 ($CH_2$) and 14.2 ($CH_3$); *m/z* (APCl) (%) 265 ($MH^+$, 100). Earlier fractions contained approximately 20% of the double-octyl compound **190f**, but this was not sufficiently pure for characterisation purposes.

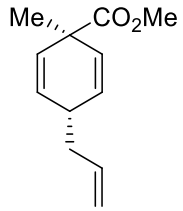
**(1*r*,4*r*)-Methyl 4-benzyl-1-methylcyclohexa-2,5-dienecarboxylate (187g)**




**187g**

Prepared according to the general procedure using benzyl bromide (0.43 mL, 3.62 mmol, 2.0 equiv.) as electrophile. Purification by flash column chromatography (50:1 hexane:diethyl ether) gave the *title compound* (340mg, 77%) as a colourless oil (Found: $MH^+$, 243.1393. $C_{16}H_{19}O_2$ requires M, 243.1385); $\nu_{max.}$ (neat) 3028, 2928, 1732, 1242, 1114, 726 and 701 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 7.28 (2H, app. tt, *J* 7.0, 1.4, aromatic CH), 7.19 (1H, app. tt, *J* 7.3, 1.4, aromatic CH), 7.17 – 7.13 (2H, m, aromatic CH), 5.78 – 5.70 (4H, m, alkene CH), 3.66 (3H, s, $OCH_3$), 3.05 – 2.99 (1H, m, C*H*Bn), 2.71 (2H, d, J 7.0, $CH_2$) and 1.14 (3H, s, $CH_3$); $\delta_C$ (125 MHz; $CDCl_3$) 175.6 (C=O), 139.3 (C), 129.5 (2 x CH), 128.9 (2 x CH), 128.7 (2 x CH), 128.2 (2 x CH), 126.3 (CH), 52.4 ($CH_3$), 44.5 (C), 42.4 ($CH_2$), 37.3 (CH) and 27.5 ($CH_3$); *m/z* (TOF $AP^+$) (%) 284 ($MH^+ + CH_3CN$, 38), 243 ($MH^+$, 100) and 115 (40).

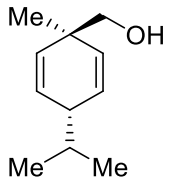
**(1*r*,4*r*)-Methyl 4-allyl-1-methylcyclohexa-2,5-dienecarboxylate (187h)**




**187h**

Prepared according to the general procedure using allyl bromide (0.31 mL, 3.62 mmol, 2.0 equiv.) as electrophile. Purification by flash column chromatography (20:1 hexane:diethyl ether) gave the *title compound* (0.19 g, 54%) as a colourless oil (Found: M – $H^+$, 191.1075. $C_{12}H_{15}O_2$ requires M, 191.1072); $\nu_{max.}$ (neat) 2953, 1732, 1244, 1115 and 734; $\delta_H$ (400 MHz; $CDCl_3$) 5.82 – 5.70 (5H, m, alkene CH), 5.08 – 5.01 (2H, m, alkene $CH_2$), 3.69 (3H, s, $OCH_3$), 2.83 – 2.76 (1H, m, CH), 2.18 (2H, app. t, *J* 6.8, $CH_2$) and 1.33 (3H, s, $CH_3$); $\delta_C$ (125 MHz; $CDCl_3$) 175.6 (C=O), 135.9 (CH), 128.9 (CH), 128.7 (CH), 116.8 ($CH_2$), 52.4 ($CH_3$), 44.4 (C), 40.1 ($CH_2$), 35.2 (CH) and 27.7 ($CH_3$); *m/z* (TOF MS $EI^+$) (%) 191 ($M^+$ – H, 32), 151 (93), 107 (78), 91 (98) and 84 (100).

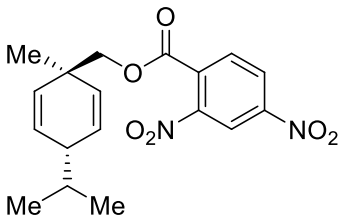
**((1*r*,4*r*)-4-Isopropyl-1-methylcyclohexa-2,5-dienyl)methanol (188)**




**188**

A solution of (1*r*,4*r*)-methyl 4-isopropyl-1-methylcyclohexa-2,5-dienecarboxylate (**187a**) (1.00 g, 5.15 mmol) in THF (2 mL) was added to a suspension of $LiAlH_4$ (0.27 g, 7.22 mmol) in THF (50 mL). The reaction mixture was stirred at 25 °C for 1 h, and then was quenched with 15% aqueous NaOH solution (0.19 mL) and water (0.6 mL). The reaction mixture was stirred for 30 minutes, then the mixture was dried over $Na_2SO_4$. The solvent was removed under reduced pressure to give the *title compound* (0.66 g, 77%) as a colourless oil (Found: $MH^+$, 167.1433. $C_{11}H_{19}O$ requires M, 167.1430); $\nu_{max.}$ (neat) 3366, 3011, 2957, 2928, 2871, 1464, 1384 and 1366 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 5.78 (2H, dd, *J* 10.4, 3.2, alkene CH), 5.51 (2H, dd, *J* 10.4, 2.0, alkene CH), 3.33 (2H, d, *J* 6.1, C*H*$_2$OH), 2.69 – 2.65 (1H, m, CH=CH-C*H)*, 1.76 (1H, septet of doublets, *J* 6.9, 4.1, C*H*$(CH_3)_2$), 1.36 (1H, t, *J* 6.1, OH), 0.99 (3H, s, $CH_3$) and 0.89 (6H, d, *J* 6.9, 2 x $CH_3$); $\delta_C$ (125 MHz; $CDCl_3$) 131.9 (CH), 129.5 (CH), 71.0 ($CH_2$), 42.1 (CH), 39.9 (C), 32.1 (CH), 24.8 ($CH_3$) and 19.3 ($CH_3$); *m/z* (ES) (%) 167 ($MH^+$, 21), 149 (100) and 115 (56).

**((1*r*,4*r*)-4-Isopropyl-1-methylcyclohexa-2,5-dienyl)methyl 2,4-dinitrobenzoate (189)**

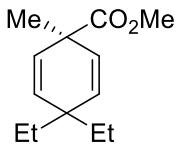


**189**

A solution of 2,4-dinitrobenzoyl chloride (0.14 g, 0.60 mmol) in $CH_2Cl_2$ (1 mL) was added to ((1*r*,4*r*)-4-isopropyl-1-methylcyclohexa-2,5-dienyl)methanol (**188**) (0.10 g, 0.60 mmol) in $CH_2Cl_2$ (10 mL). Triethylamine (0.08 mL, 0.60 mmol) and 4-DMAP (10 mg) were then added and the solution was stirred for 24 h. The reaction was quenched with water (5 mL). The solution was then extracted with $CH_2Cl_2$ (3 x 15 mL) and the extracts were dried over $Na_2SO_4$. Recrystallisation from 1:1 hexane:ethyl acetate gave the *title compound* (0.12 g, 56%) as beige crystals (Found: $MH^+$, 361.1392. $C_{18}H_{21}N_2O_6$ requires M, 361.1394); $\nu_{max.}$ (neat) 2959, 1738, 1538, 1349 and 1284 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 8.74 (1H, d, *J* 2.2, aromatic CH), 8.51 (1H, dd, *J* 8.4, 2.2, aromatic CH), 7.92 (1H, d, *J* 8.4, aromatic CH), 5.69 (2H, dd, *J* 10.4, 3.2, alkene CH), 5.55 (2H, dd, *J* 10.4, 2.0, alkene CH), 4.15 (2H, s, $CH_2O$), 2.62 – 2.58 (1H, m, C*H*), 1.75 (1H, septet of doublets, *J* 6.9, 3.9, C*H*$(CH_3)_2$), 1.09 (3H, s, C*H*$_3$) and 0.88 (6H, d, *J* 6.9, 2 x $CH_3$); $\delta_C$ (125 MHz; $CDCl_3$) 131.6 (CH), 130.8 (2 x CH), 128.7 (2 x CH), 127.4 (CH), 119.7 (CH), 74.2 ($CH_2$), 42.0 (CH), 37.6 (C), 32.1 (CH), 25.3 ($CH_3$) and 19.3 ($CH_3$) (The ester and aromatic quaternary carbon atoms are not evident); *m/z* (ES) (%) 361 ($MH^+$, 50), 163 (18) and 115 (100).

Selected crystallographic data: $C_{18}H_{20}N_2O_6$, FW = 360.36, T = 150 K, λ = 0.71073 Å, Triclinic, *P*-1, *a* = 7.6377(3) Å, *b* = 7.8225(3) Å, *c* = 32.1299(10) Å, α = 93.748(2)°, β = 91.221(2)°, γ = 109.094(2)°, V = 1808.28(11) $Å^3$, Z = 4, ρ(calc) = 1.324 $Mg/m^3$ , crystal size = 0.30 x 0.20 x 0.12 $mm^3$, reflections collected =8271, independent reflections = 6414, R(int) = 0.0393, parameters = 476, $R_1$ [$I > 2\sigma(I)$] =0.0706, $wR_2$ [$I > 2\sigma(I)$] =0.1381, $R_1$ (all data) =0.1050, $wR_2$ (all data) =0.1588. Full crystallographic data for this compound have been deposited with the CCDC, reference number 854352, and can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif

**Methyl 4,4-diethyl-1-methylcyclohexa-2,5-dienecarboxylate (190d)**

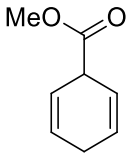



**190d**

A solution of *n*-butyllithium (2.0 M in cyclohexane, 4.52 mL, 9.05 mmol) was added to 1-methylcyclohexa-2,5-dienecarboxylic acid (**149**) (0.25 g, 1.81 mmol) in THF (10 mL) at –78 °C. TMEDA (0.68 mL, 4.53 mmol) was then added and the solution was stirred for a further 30 minutes. Bromoethane (0.41 mL, 5.43 mmol) was added, the solution was stirred for 10 minutes at –78 °C, warmed to room temperature and the reaction mixture was stirred for a further 1 h. The reaction was quenched with 2 M hydrochloric acid (5 mL) and the organic material was extracted with $CH_2Cl_2$ (3 x 20 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated *in vacuo* to give the crude alkylated carboxylic acid. This was then dissolved in methanol (10 mL), concentrated sulfuric acid (0.05 mL) was added and the resulting solution was stirred at 25 °C for 17 h. The solvent was removed *in vacuo*, saturated $NaHCO_3$ solution (5mL) was added and the product was extracted into $CH_2Cl_2$ (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Purification by flash column chromatography (20:1 hexane:diethyl ether) gave the *title compound* (181 mg, 48%) as a pale yellow oil (Found: $M^+$, 208.1469. $C_{13}H_{20}O_2$ requires M, 208.1463); $\nu_{max.}$ (neat) 2964, 2928, 1734 and 1241 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 5.83 (2H, d, *J* 10.3, 2 x alkene CH), 5.32 (2H, d, *J* 10.3, 2 x alkene CH), 3.67 (3H, s, $CH_3O$), 1.34 (2H, q, *J* 7.5, $CH_2$), 1.33 (2H, q, *J* 7.5, $CH_2$), 1.32 (3H, s, $CH_3$), 0.73 (3H, t, *J* 7.5, $CH_3$) and 0.72 (3H, t, *J* 7.5, $CH_3$); $\delta_C$ (125 MHz; $CDCl_3$) 175.8 (C=O), 132.5 (CH), 129.3 (CH), 52.2 ($CH_3$), 44.6 (C), 42.1 (C), 34.0 ($CH_2$), 33.5 ($CH_2$), 27.5 ($CH_3$), 9.5 ($CH_3$) and 9.2 ($CH_3$); *m/z* (EI) (%) 208 ($M^+$, 15), 207 (17), 179 (100), 149 (90) and 107 (100).

## 8.3. Experimental Data for Chapter 4

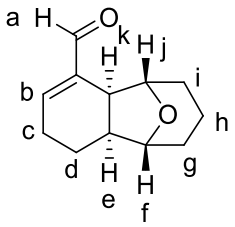
### Methyl cyclohexa-2,5-dienecarboxylate (114)[92]




**114**

Ammonia (500 mL) was added to benzoic acid (20.0 g, 164 mmol) in a 1L multineck round-bottomed flask through a dry ice-acetone condenser. With careful stirring Li (3.20 g, 460 mmol) was added portion-wise until a permanent blue colour was observed. After stirring the reaction mixture for 15 minutes at this temperature, ammonium chloride (29.2 g, 540 mmol) was added portion-wise over a period of 30 minutes. The ammonia was left to evaporate and the residue was dissolved in iced water. Dilute sulfuric acid was added, until pH 1 – 2 was reached, and then the solution was extracted with diethyl ether (3 x 200 mL). The combined organic extracts were dried over $MgSO_4$ and were concentrated *in vacuo*. The residue was re-dissolved in methanol (150 mL) and treated with concentrated $H_2SO_4$ (0.45 mL, 4.6 mmol). The reaction mixture was heated under reflux for 6 h. The solvent was removed and the residue was neutralised with saturated aqueous sodium hydrogen carbonate solution (50 mL). The solution was extracted into $CH_2Cl_2$ (3 x 100 mL) and the combined organic extracts were dried over $MgSO_4$, and concentrated *in vacuo* to give the *title compound* (14.0 g, 84 %) as a colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 5.93 – 5.78 (4H, m, 4 x alkene CH), 3.78 – 3.73 (1H, m, CH), 3.72 (3H, s, O-$CH_3$) and 2.74 – 2.65 (2H, m, $CH_2$).

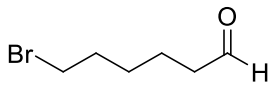
**(4a*RS*,5*RS*,9*SR*,9a*RS*)-2,4a,5,6,7,8,9,9a-Octahydro-1*H*-5,9-epoxybenzo[7]annulene-4-carbaldehyde (120)**[35]




(±)-**120**

Trifluoromethanesulfonic acid (0.08 mL, 0.88 mmol) was added drop-wise to a solution of crude 4-(3,3-dimethyl-2,4-dioxaspiro[5.5]undeca-7,10-dien-1-yl)butanal **220** (0.20 g, 0.88 mmol) in $CH_2Cl_2$ (10 mL) at 0 °C. The solution was warmed to 25 °C and the reaction mixture was stirred for 20 minutes. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (5 mL) and extracted with $CH_2Cl_2$ (3 x 15 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (1:1 hexane:diethyl ether) gave the *title compound* (80 mg, 18% from **220**) as a colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 9.43 (1H, s, CHO), 7.03 (1H, dd, *J* 5.2, 4.0, alkene CH), 4.02 (1H, s, H-CO), 3.95 (1H, s, OC-H), 3.02 (1H, d, *J* 8.7, CH), 2.47 (1H, app. dt, *J* 9.2, 5.5, ring junction CH), 2.41 – 2.30 (1H, m, one of $CH_2CH$=C), 2.28 – 2.17 (1H, m, one of $CH_2CH$=C) and 1.84 – 1.60 (8H, m, 4 x $CH_2$). The proton connectivity was confirmed by $^1H$-$^1H$ COSY NMR spectroscopy. Two-dimensional NOESY NMR spectroscopy shows evidence of a cross-peak between *f* and *c* which confirms the stereochemistry shown, where the core is characterised by an *anti* relationship between the two pairs of ring-junction protons as illustrated.

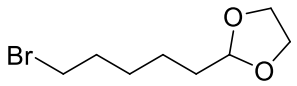
**6-Bromohexanal (194)**[93]




**194**

Dimethylsulfoxide (4.47 mL, 63.0 mmol) was added to a solution of oxalyl chloride (2.67 mL, 31.5 mmol) in dichloromethane (50 mL) at –78 °C. After 2 minutes of stirring, 6-bromo-1-hexanol (2.85 g, 15.7 mmol) was added and the mixture was stirred for 40 minutes. Triethylamine (11.0 mL, 78.7 mmol) was added and the reaction mixture was stirred at –78 °C for 10 minutes then warmed to room temperature. The reaction was quenched with water (15 mL), the organic material was extracted with dichloromethane (3 x 50 mL) and washed with brine (2 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (9:1 petroleum ether: ethyl acetate) gave the *title compound* (2.20 g, 78%) as a colourless oil; $\nu_{max}$ (neat) 2940, 2864, 1723, 1266, 1129, 734 and 646 $cm^{-1}$. $\delta_H$ (400 MHz; $CDCl_3$) 9.78 (1H, t, *J* 1.6, CHO), 3.41 (2H, t, *J* 6.7, $CH_2$-Br), 2.47 (2H, td, *J* 7.3, 1.6, C*H*$_2$-CHO), 1.95 – 1.83 (2H, m, $CH_2$), 1.72 – 1.64 (2H, m, 7.3, $CH_2$) and 1.55 – 1.42 (2H, m, $CH_2$); $\delta_C$ (125 MHz; $CDCl_3$) 201.9 (C=O), 43.6 ($CH_2$), 33.2 ($CH_2$), 32.4 ($CH_2$), 27.7 ($CH_2$) and 21.2 ($CH_2$).

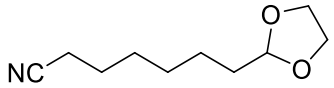
**2-(5-Bromopentyl)-1,3-dioxolane (195)**[94]




**195**

A solution of 6-bromohexanal (**194**) (1.80 g, 10.2 mmol), ethylene glycol (2.85 mL, 51.1 mmol) and PPTS (0.02 g) in benzene (150 mL) was heated to reflux using Dean-Stark conditions and stirred for 12 h. The solvent was removed *in vacuo* and the residue dissolved in diethyl ether (50 mL), washed with saturated aqueous $NaHCO_3$ (2 x 20 mL), brine (2 x 20 mL) and water (2 x 20 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo* to give the *title compound* (1.43 g, 63%) as a colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 4.85 (1H, t, *J* 4.7, CH), 4.01 – 3.91 (2H, m, dioxolane C*H*HC*H*H), 3.90 – 3.80 (2H, m, dioxolane CH*H*CH*H*), 3.41 (2H, t, *J* 6.8, $CH_2$-Br), 1.96 – 1.79 (2H, m, $CH_2$), 1.73 – 1.60 (2H, m, $CH_2$) and 1.52 – 1.37 (4H, m, 2 x $CH_2$); $\delta_C$ (125 MHz; $CDCl_3$) 104.4 (CH), 64.9 ($CH_2$), 44.9 ($CH_2$), 33.7 ($CH_2$), 32.5 ($CH_2$), 26.8 ($CH_2$) and 23.3 ($CH_2$); *m/z* (ES) (%) 250.1 (92), 215.1 (11), 173.1 (100), 159.1 (91), 145.0 (32) and 129.1 (31).

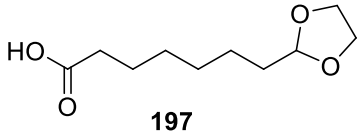
**7-(1,3-Dioxolan-2-yl)heptanenitrile (196)[95]**



**196**

*n*-Butyllithium (4.04 mL, 8.08 mmol, 2.0 M in pentane) was added to a solution of diisopropylamine (1.13 mL, 8.08 mmol) in THF (10 mL) at 0 °C and the solution was stirred for 30 minutes. The solution was cooled to –78 °C before adding acetonitrile (0.84 mL, 16.2 mmol) and the reaction mixture was further stirred for 1 h. Then 2-(5-bromopentyl)-1,3-dioxolane (**195**) (0.90 g, 4.04 mmol) was added and the reaction mixture was warmed to room temperature. The reaction mixture was stirred for a further for 18 h. The reaction was quenched with water (5 mL) and the product extracted into diethyl ether (3 x 20 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (3:1 hexane:ethyl acetate) gave the *title compound* (0.65 g, 88%) as a colourless oil (Found: $MH^+$, 184.1340. $C_{10}H_{18}NO_2$ requires M, 184.1338); $\nu_{max}$ (neat) 2939, 2246, 1642, 1412, 1136 and 1032 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 4.84 (1H, t, *J* 4.8, CH), 3.99 – 3.94 (2H, m, dioxolane C*H*HC*H*H), 3.87 – 3.82 (2H, m, dioxolane CH*H*CH*H* ), 2.33 (2H, t, *J* 7.1, $CH_2$-CN), 1.72 – 1.60 (4H, m, 2 x $CH_2$) and 1.52 – 1.31 (6H, m, 3 x $CH_2$); $\delta_C$ (125 MHz; $CDCl_3$) 120.0 (CN), 104.5 (CH), 64.9 ($CH_2$), 33.7 ($CH_2$), 28.6 ($CH_2$), 28.5 ($CH_2$), 25.2 ($CH_2$), 23.7 ($CH_2$) and 17.1 ($CH_2$); *m/z* (AP) (%) 184.1 ($MH^+$, 100), 149.2 (60) and 116.1 (47).

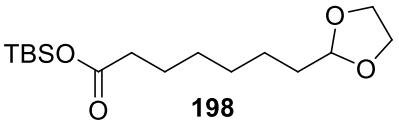
**7-(1,3-Dioxolan-2-yl)heptanoic acid (197)**



**197**

Potassium hydroxide (2.31 g, 41.3 mmol) was added to a solution of 7-(1,3-dioxolan-2-yl)heptanenitrile (**196**) (0.63 g, 3.44 mmol) in 2:1 water:ethanol (30 mL) and the solution was heated to reflux for 16 h. The reaction mixture was cooled to room temperature and acidified to pH 2 with 2 M HCl solution. The product was extracted with diethyl ether (3 x 50 mL), the combined organic extracts were dried over $Na_2SO_4$ and concentrated in *vacuo* to give *the title compound* **197** (0.40 g, 58%) as a pale oil (Found: M – $H^+$, 201.1126. $C_{10}H_{17}O_4$ requires M, 201.1127); $\nu_{max}$ (neat) 3423, 2935, 1712, 1411, 1140 and 1031 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 4.84 (1H, td, *J* 4.8, 1,4, CH), 4.00 – 3.91 (2H, m, dioxolane C*H*HC*H*H), 3.90 – 3.80 (2H, m, dioxolane CH*H*CH*H*), 2.35 (2H, app. tt, *J* 7.1, 3.7, $CH_2$), 1.77 – 1.56 (4H, m, 2 x $CH_2$) and 1.52 – 1.28 (6H, m, 3 x $CH_2$); $\delta_C$ (125 MHz; $CDCl_3$) 104.6 (CH), 64.9 ($CH_2$), 33.8 ($CH_2$), 28.9 ($CH_2$), 28.6 ($CH_2$), 25.2 ($CH_2$), 23.8 ($CH_2$) and 17.1 ($CH_2$); *m/z* (EI) (%) 201.1 (M – $H^+$, 10), 84.0 (35) and 73.0 (100).

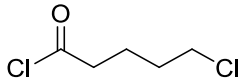
***tert*-Butyldimethylsilyl 7-(1,3-dioxolan-2-yl)heptanoate (198)**



**198**

*tert*-Butyldimethylsilyl chloride (0.33 g, 2.18 mmol), imidazole (0.30 g, 4.36 mmol) and 4-DMAP (0.01 g) was added to a solution of 7-(1,3-dioxolan-2-yl)heptanoic acid (**197**) (0.40 g, 1.98 mmol) in dichloromethane (30 mL) and the resulting solution was stirred for 30 minutes. The reaction mixture was quenched with water (5 mL) and the product was extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (3:1 hexane:ethyl acetate) gave the *title compound* (0.50 g, 72%) as a colourless oil. $\nu_{max}$ (neat) 2929, 2858, 1722, 1579, 1255 and 1032 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) (selected peaks) 4.84 (1H, td, *J* 4.8, 1.5, CH), 4.00 – 3.90 (2H, m, dioxolane C*H*HC*H*H), 3.89 – 3.80 (2H, m, dioxolane CH*H*CH*H*), 2.34 (2H, td, *J* 7.3, 5.1, $CH_2$), 1.73 – 1.56 (4H, m, 2 x $CH_2$), 1.53 – 1.29 (6H, m, 3 x $CH_2$), 0.91 (9H, s, 3 x $CH_3$) and 0.10 (6H, s, 2 x $CH_3$).

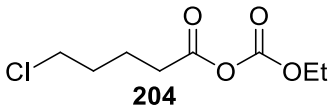
**5-Chloropentanoyl chloride (201)**[96]



**201**

Oxalyl chloride (1.35 mL, 16.1 mmol) and dimethylformamide (cat.) was added to a solution of 5-chloropentanoic acid (1.71 mL, 14.6 mmol) in dichloromethane (40 mL) and the reaction mixture was stirred for 4 h at room temperature. The solvent was then removed *in vacuo* to give the *title compound* (2.25 g, 100%) as a colourless oil. $\nu_{max}$ (neat) 2961, 2874, 1797, 1404, 1089 and 721 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 3.55 (2H, t, *J* 6.0, $CH_2$-Cl), 2.95 (2H, t, *J* 6.8, $CH_2C$=O) and 1.95 – 1.78 (4H, m, 2 x $CH_2$).

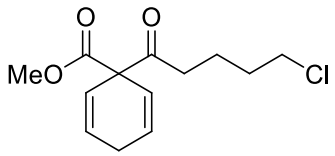
**5-Chloropentanoic (ethyl carbonic) anhydride (204)**[97]



**204**

Triethylamine (3.55 mL, 25.5 mmol) was added to a solution of 5-chloropentanoic acid (2.13 mL, 18.20 mmol) in THF (40 mL) at 0 °C and the solution was stirred for 5 minutes. Ethyl chloroformate (2.60 mL, 27.30 mmol) was then added and the reaction mixture was further stirred for 90 minutes before removing the solvent *in vacuo*. The reaction was quenched with 2 M HCl (10 mL) and diluted with diethyl ether (25 mL). The organic layer was then washed with $Na_2CO_3$ (2 x 25 mL) and water (2 x 25 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give the *title compound* (3.64 g, 96%) as a colourless oil. $\nu_{max}$ (neat) 2963, 1821, 1758, 1242, 1091 and 1033 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 4.33 (2H, q, *J* 7.1, $CH_2$-O), 3.56 (2H, t, *J* 6.1, $CH_2$-Cl), 2.52 (2H, t, *J* 7.0, $CH_2C$=O), 1.91 – 1.80 (4H, m, 2 x $CH_2$) and 1.37 (3H, t, *J* 7.1, $CH_3$); $\delta_C$ (125 MHz; $CDCl_3$) 167.5 (C=O), 149.0 (C=O), 65.7 ($CH_2$), 44.2 ($CH_2$), 33.3 ($CH_2$), 31.4 ($CH_2$), 21.6 ($CH_2$) and 13.9 ($CH_3$).

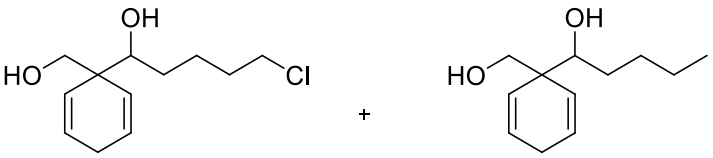
**Preparation of methyl 1-(5-chloropentanoyl)cyclohexa-2,5-dienecarboxylate (205)**




**205**

A solution of *n*-butyllithium (8.58 mL, 16.0 mmol, 2.0 M in cyclohexane) was added to a solution of diisopropylamine (2.24 mL, 16.0 mmol) in THF (40 mL) at –78 °C and the solution was stirred for 30 minutes. Methyl cyclohexa-2,5-dienecarboxylate (**114**) (2.01 g, 14.6 mmol) was added and the reaction mixture was further stirred for 30 minutes. Then 5-chloropentanoic (ethyl carbonic) anhydride (**204**) (3.64 g, 17.5 mmol) was added and the reaction mixture was further stirred for 20 minutes at –78 °C and then 10 minutes at 0 °C. The reaction was quenched with water (15 mL) and the product extracted with diethyl ether (3 x 40 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (9:1 hexane:diethyl ether) gave the *title compound* (2.41 g, 64%) as a pale yellow oil (Found: $MH^+$, 257.0938. $C_{13}H_{18}O_3{}^{35}Cl$ requires M, 257.0944); $\nu_{max}$ (neat) 2954, 1722, 1436, 1280 and 1112 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 6.07 (2H, app. ddd, *J* 6.6, 5.9, 3.3, 2 x alkene CH), 6.00 – 5.95 (2H, m, 2 x alkene CH), 3.76 (3H, s, $CH_3$-O), 3.51 (2H, t, *J* 6.3, $CH_2$-Cl), 2.84 – 2.69 (2H, m, ring $CH_2$), 2.57 (2H, t, *J* 6.7, $CH_2C$=O) and 1.85 – 1.61 (4H, m, 2 x $CH_2$); $\delta_C$ (125 MHz; $CDCl_3$) 205.5 (C=O), 171.0 (C=O), 128.1 (CH), 122.8 (CH), 62.8 (C), 52.6 ($CH_3$), 44.5 ($CH_2$), 37.3 ($CH_2$), 31.7 ($CH_2$), 26.1 ($CH_2$) and 21.0 ($CH_2$); *m/z* (AP) (%) 532.9 (100), 534.9 (96), 273.1 (10), 259.1 ($^{37}$Cl-$MH^+$, 8) 257.1 ($^{35}$Cl-$MH^+$, 27) and 214 (10).

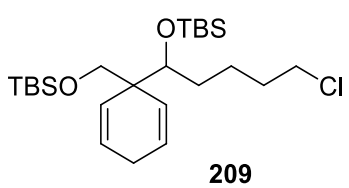
**5-Chloro-1-(1-(hydroxymethyl)cyclohexa-2,5-dienyl)pentan-1-ol** (**206**)




**206** **207**

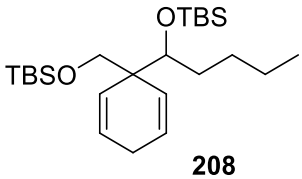
A solution of methyl 1-(5-chloropentanoyl)cyclohexa-2,5-dienecarboxylate (**205**) (2.410 g, 9.41 mmol) in THF (2 mL) was added to a suspension of $LiAlH_4$ (1.43 g, 37.7 mmol) in THF (40 mL) and the reaction mixture was stirred for 30 minutes. The reaction mixture was quenched with 2 M NaOH (aq.) (2 mL), dried over $Na_2SO_4$, filtered and the solvent was concentrated *in vacuo*. Purification by flash column chromatography (1:1 diethyl ether:hexane) gave *a mixture of compounds* **206** *and* **207** (0.95 g) as a colourless oil (Found: $MH^+$, 231.1154. $C_{12}H_{20}O_2{}^{35}Cl$ requires M, 231.1152); $\nu_{max}$ (neat) 3368, 2942, 2867, 1421, 1266, 1017 and 878 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$): 6.00 – 5.87 (4H, m, 2 x alkene CH 200 and 2 x alkene CH 201), 5.71 (2H, dd, *J* 10.3, 2.1, alkene CH 200 and alkene CH **207**), 5.37 (2H, dd, *J* 10.2, 2.1, alkene CH **206** and alkene CH **207**), 3.63 – 3.53 (6H, m, C*H*-OH + C$H_2$-OH of **206** and C*H*-OH + C$H_2$-OH of **207**), 3.50 (2H, app. td, *J* 6.6, 0.9, $CH_2$-Cl), 2.99 (2H, broad s, OH), 2.81 (2H, broad s, OH), 2.85 – 2.40 (4H, m, ring $CH_2$ of **206** and ring $CH_2$ of **207**), 1.85 – 1.69 (3H, m, $CH_2$ + 1H of $CH_2$ of compound **206**),1.68 – 1.67 (6H, m, 3 x $CH_2$ from compound **201**), 1.52 – 1.20 (3H, m, $CH_2$ + 1H of $CH_2$ compound **206**) and 1.18 (3H, t, *J* 7.0, $CH_3$ **207**); $\delta_C$ (125 MHz; $CDCl_3$) 128.1 (CH), 128.0 (CH), 127.2 (CH), 125.7 (CH), 76.6 (CH), 69.6 ($CH_2$), 46.7 (C), 45.0 ($CH_2$), 32.5 ($CH_2$), 32.2 ($CH_2$), 27.2 ($CH_2$) and 23.8 ($CH_2$); *m/z* ($AP^+$) (%) 274.1 ($^{37}$Cl-$MH^+$ + MeCN, 18), 272.1 ($^{35}$Cl-$MH^+$ + MeCN, 54), 256.1 ($^{37}$Cl-M + MeCN – $H_2O$, 8), 254.1 ($^{35}$Cl-M + MeCN – $H_2O$, 27), 233.1 ($^{37}$Cl-$MH^+$, 52), 231.1 ($^{35}$Cl-$MH^+$, 52), 215.1 ($^{35}$Cl-$MH^+$ – $H_2O$, 33), 213.1 ($^{37}$Cl-$MH^+$ – $H_2O$, 97) and 197.1 (35), 195.1 (100).

***tert*-Butyl((1-(1-(*tert*-butyldimethylsilyloxy)-5-chloropentyl)cyclohexa-2,5-dienyl)methoxy)dimethylsilane (209)/ *tert*-butyl((1-(1-(*tert*-butyldimethylsilyloxy)hexyl)cyclohexa-2,5-dienyl)methoxy)dimethylsilane (208)**




**209**

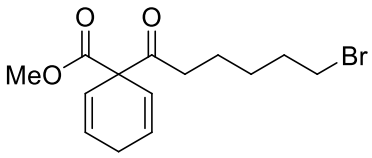
+




**208**

2,6-Dimethylpyridine (1.74 mL, 15.0 mmol) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (2.64 mL, 11.2 mmol) was added to a mixture of 5-chloro-1-(1-(hydroxymethyl)cyclohexa-2,5-dienyl)pentan-1-ol (**206**) and compound **207** (0.86 g, 3.74 mmol) in $CH_2Cl_2$ (40 mL) at 0 °C then the solution was warmed to 25 °C and the reaction mixture was stirred for 17 h. The reaction was quenched with water (10 mL) and the product extracted into $CH_2Cl_2$ (3 x 40 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (2:1 diethyl ether: hexane) gave a mixture of compounds **209** and **208** (1.35 g). $\delta_H$ (250 MHz; $CDCl_3$) 5.88 – 5.70 (2H of **208** and 2H of **209**, m, alkene CH), 3.84 – 3.74 (1H of **208** and **209**, m, C*H*-OTBS), 3.62 (1H of **208** and 1H of **209**, d, J 9.3, 1 of C$H_2$-OTBS), 3.49 (2H, t, *J* 6.6, $CH_2Cl$), 3.27 ( 1H of **208** and 1H of **209**, 2 x d, J 9.3 and 3.3 , 1 of C$H_2$-OTBS), 2.69 – 2.58 (2H of **208** and 2H of **209**, m, $CH_2$ ring), 1.91 – 1.04 (6H of **208** and 6H of **209**, m, 3 x $CH_2$), 0.95 – 0.83 (21 H of **208**, 18H of **209**, m, *t*-butyl $CH_3$ and –$CH_2$-$CH_3$) and 0.04 – 0.14 (12H of **208** and 12H of **209**, m, $CH_3$).

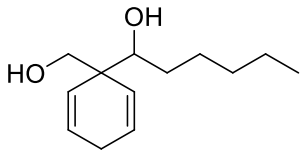
**Preparation of methyl 1-(6-bromohexanoyl)cyclohexa-2,5-dienecarboxylate (210)**




**210**

A solution of *n*-butyllithium (4.30 mL, 8.59 mmol, 2.0 M in cyclohexane) was added to a mixture of diisopropylamine (1.20 mL, 8.59 mmol) in THF (50 mL) at –78 °C and the reaction mixture was stirred for 30 minutes. Compound **114** (1.08 g, 7.81 mmol) in THF (2 mL) was added and the solution was stirred for 30 minutes. 6-Bromohexanoyl chloride (1.40 mL, 9.37 mmol) was then added and the reaction mixture was further stirred for 20 minutes at —78 °C then 10 minutes at 0 °C. The reaction was quenched with water (10 mL) and the product extracted with diethyl ether (3 x 40 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (9:1 hexane: ethyl acetate) gave the *title compound* (1.04 g, 42%) as a colourless oil (Found: $MH^+$, 315.0582. $C_{14}H_{20}O_3{}^{79}Br$ requires M, 315.0596); $\nu_{max}$ (neat) 2950, 2866, 1743, 1716, 1435, 1233 and 713 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 6.10 – 6.02 (2H, m, 2 x alkene CH), 6.00 – 5.95 (2H, m, 2 x alkene CH), 3.75 (3H, s, $CH_3$-O), 3.39 (2H, t, *J* 6.8, $CH_2$-Br), 2.84 – 2.69 (2H, m, ring $CH_2$), 2.54 (2H, t, *J* 7.1, $CH_2C$=O), 1.94 – 1.70 (2H, m, $CH_2$), 1.60 – 1.50 (2H, m, $CH_2$) and 1.44 – 1.33 (2H, m, $CH_2$); $\delta_C$ (125 MHz; $CDCl_3$) 205.7 (C=O), 170.8 (C=O), 128.0 (CH), 122.8 (CH), 62.8 (C), 52.6 ($CH_3$), 38.0 ($CH_2$), 33.5 ($CH_2$), 32.5 ($CH_2$), 27.5 ($CH_2$), 26.1 ($CH_2$) and 22.7 ($CH_2$); *m/z* (AP) (%) 318.1 (21), 317.1 $^{81}$Br-$MH^+$, 100), 316.1 (21) and 315.1 ($^{79}$Br-$MH^+$, 100).

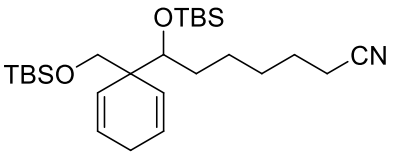
**1-(1-(Hydroxymethyl)cyclohexa-2,5-dienyl)hexan-1-ol (212)**




**212**

1-(6-Bromohexanoyl)cyclohexa-2,5-dienecarboxylate (**212**) (0.50 g, 1.59 mmol) in THF (2 mL) was added to a suspension of $LiAlH_4$ (0.18 g, 4.76 mmol) in THF (20 mL) and the reaction mixture was stirred for 30 minutes at room temperature. The reaction was quenched with aqueous 2 M NaOH solution (2 mL), dried over $Na_2SO_4$ and the solvent was concentrated *in vacuo* to give the *title compound* (0.11 g, 24%) as a colourless oil (Found: $MH^+ - H_2O$, 193.1583. $C_{13}H_{21}O$ requires M, 193.1592); $\nu_{max}$ (neat) 3342, 2930, 1455, 1021 and 715 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 6.00 – 5.80 (2H, m, 2 x alkene CH), 5.70 – 5.60 (1H, m, alkene CH), 5.40 – 5.30 (1H, m, alkene CH), 3.65 – 3.45 (3H, m, C*H*$_2$-OH + C*H*-OH), 2.65 – 2.55 (2H, m, ring $CH_2$), 2.30 – 2.10 (2H, s broad, 2 x OH), 1.50 – 1.20 (8H, m, 4 x $CH_2$) and 0.85 – 0.75 (3H, s, $CH_3$); *m/z* ($AP^+$) (%) 234.2 ($MH^+$ + Na, 20), 193.2 ($MH^+ - H_2O$, 79), 175.1 (100) and 132.1 (47).

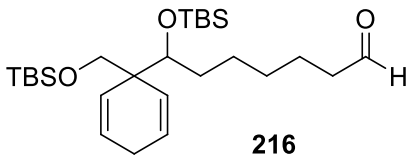
**7-(*tert*-butyldimethylsilyloxy)-7-(1-((*tert*-butyldimethylsilyloxy)methyl)cyclohexa-2,5-dienyl)heptanenitrile (215)**




**215**

Sodium iodide (0.75 g, 5.01 mmol) was added to a mixture of compounds **209** and **208** (1.35 g) in acetone (40 mL) and the solution was stirred for 3 days at 60 °C. The reaction mixture was cooled to room temperture, diluted with diethyl ether (30 mL) and was filtered. Then the reaction mixture was washed with water (2 x 30 mL) and concentrated in *vacuo* to give a crude mixture of iodide **214** and compound **208**, which was directly reacted without further purification. A solution of *n*-butyllithium (1.6 M in cyclohexane, 2.16 mL, 3.45 mmol) was added to diisopropylamine (0.48 mL, 3.45 mmol) in THF (40 mL) at 0 °C and the solution was stirred for 30 minutes. The temperature was cooled to –78 °C then acetonitrile (0.36 mL, 6.90 mmol) was added and the reaction mixture was further stirred. After 1 h the mixture of compound **214** and compound **208** (1.95 g) in THF (2 mL) was added and the reaction mixture was stirred at room temperature for 17 h. The reaction was quenched with water (5 mL) and the product extracted with diethyl ether (3 x 40 mL). The combined organic extracts was dried over $MgSO_4$ and concentrated in *vacuo*. Purification by flash column chromatography (3:1 hexane:ethyl acetate) gave the *title compound* (0.20 g, 5%, over 4 steps from compound **205** as a colourless oil (Found: $MH^+$, 464.3383. $C_{26}H_{50}NO_2Si_2$ requires M, 464.3380); $\nu_{max}$ (neat) 2955, 2929, 2857, 2253, 1472, 1255, 1086, 836 and 775 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 5.85 – 5.73 (2H, m, 2 x alkene CH), 5.62 (1H, dd, *J* 10.4, 2.0, alkene CH), 5.50 (1H, dd, *J* 10.2, 2.0, alkene CH), 3.79 (1H, dd, *J* 5.8, 3.4, C*H*-OH), 3.61 (1H, d, *J* 9.3, 1H of C$H_2$-OH), 3.26 (1H, d, *J* 9.3, 1H of C$H_2$-OH), 2.66 – 2.62 (2H, m, ring $CH_2$), 2.30 (2H, t, *J* 7.2, $CH_2$-CN), 1.78 – 1.67 (2H, m, $CH_2$), 1.53 – 1.45 (2H, m, $CH_2$), 1.37 – 1.27 (2H, m, $CH_2$), 0.90 – 0.85 (18H, s, 6 x $CH_3$) and 0.10 – 0.00 (12H, m, 4 x $CH_3$); $\delta_C$ (125 MHz; $CDCl_3$) (CN missing), 129.9 (CH), 127.3 (CH), 126.0 (CH), 124.7 (CH), 73.5 (CH), 67.9 ($CH_2$), 47.0 (C), 34.4 ($CH_2$), 29.1 ($CH_2$), 27.3 ($CH_2$), 26.0 ($CH_3$), 25.9 ($CH_2$), 25.3 ($CH_2$), 17.1 ($CH_2$) and –3.9 ($CH_3$); *m/z* (AP) (%) 465.3 (35), 464.3 ($MH^+$, 88), 333.2 (28), 332.2 (100) and 200.1 (38).

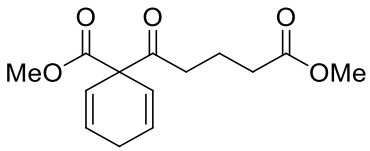
**7-(*tert*-butyldimethylsilyloxy)-7-(1-((*tert*-butyldimethylsilyloxy)methyl)cyclohexa-2,5-dienyl)heptanal (216)**




**216**

A solution of diisobutyl aluminium hydride (1.0 M, in hexane, 0.23 mL, 0.23 mmol) was added to compound **215** (0.09 g, 0.19mmol) in $CH_2Cl_2$ (5 mL) at –40 °C and the solution was stirred for 2 h. The reaction was quenched with an aqueous solution of ammonium chloride (3 mL) at –50 °C and then the reaction mixture was warmed to 25 °C before diluting with water (3 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic layers washed with brine (2 x 10 mL) then dried over $Na_2SO_4$. Purification by flash column chromatography (20:1 hexane:ethyl acetate) gave a 1:1 mixture of compounds **215**: **216** (0.023 g) as a colourless oil; $\delta_H$ (400 MHz; $CDCl_3$) 9.75 (1H, t, *J* 1.8, C*H*O **216**), 5.86 – 5.71 (4H, m, 2 x alkene CH for **215** and 2 x alkene CH for **216**), 5.63 – 5.59 (2H, m, 1x alkene CH for **215** and 1 x alkene CH **216**), 5.52 – 5.48 (2H, m, 1 x alkene CH for **215** and 1 x alkene CH for **216**), 3.80 – 3.76 (2H, m, 1H for C*H*-OH of **215** and 1H C*H*-OH for **216**), 3.61 (2H, d, *J* 9.4, 1H of C$H_2$-OH for **215** and **216**), 3.25 (2H, d, *J* 9.4, 1H of C$H_2$-OH for **215** and **216**), 2.65 – 2.61 (4H, m, ring $CH_2$ for **215** and **216**), 2.30 (2H, t, *J* 7.2, $CH_2$-CN for **215**), 2.39 (2H, td, *J* 7.4, 1.8, $CH_2$-C=O for **216**), 1.78 – 1.67 (2H, m, $CH_2$ for **215**), 1.64 – 1.58 (2H, m, CH2 for **216**), 1.53 – 1.45 (2H, m, $CH_2$ for **215**), 1.43 – 1.41 (2H, m, $CH_2$ for **216**), 1.37 – 1.27 (2H, m, $CH_2$ for **215**), 1.28 – 1.23 (4H, m, 2 x $CH_2$), 0.94 – 0.78 (36H, m, 6 x $CH_3$ for **215** and **216**) and 0.14 – 0.00 (24H, m 4 x $CH_2$ for **215** and **216**).

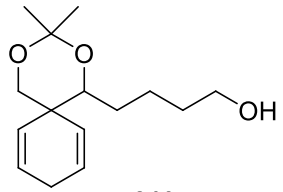
**Methyl 1-(5-methoxy-5-oxopentanoyl)cyclohexa-2,5-dienecarboxylate (218)**



**218**

A solution of *n*-butyllithium (2.0 M in cyclohexane, 13.9 mL, 27.8 mmol) was added to diisopropylamine (3.96 mL, 27.8 mmol) in THF (150 mL) at –78 °C and the resulting solution was stirred for 30 minutes. A solution of compound **114** (3.49 g, 25.3 mmol) in THF (5 mL) was added and the reaction mixture was stirred for a further 30 minutes. Methyl 5 chloro-5-oxopentanoate (4.20 mL, 30.4 mmol) was added and the solution was stirred for 1 h at -78 °C then for 17 h at 25 °C. The reaction was quenched with saturated aqueous ammonium chloride solution (20 mL) and the product extracted into diethyl ether (3 x 100 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (3:1 hexane:diethyl ether) gave the *title compound* (4.44 g, 66%) as a colourless oil (Found: M + $Na^+$, 289.1042. $C_{14}H_{18}O_5Na$ requires M, 289.1052); $\nu_{max}$ (neat) 2953, 1738, 1720, 1630, 1435 and 706 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 6.06 (2H, app. dt, *J* 10.5, 3.3, 2 x alkene CH), 5.96 (2H, dt, *J* 10.5, 1.9, 2 x alkene CH), 3.75 (3H, s, $CH_3O$), 3.66 (3H, s, $CH_3O$), 2.79 – 2.74 (2H, m, ring $CH_2$), 2.60 (2H, t, *J* 7.0, $CH_2$), 2.30 (2H, t, *J* 7.2, $CH_2$) and 1.86 (2H, app. quintet, *J* 7.2, $CH_2$); $\delta_C$ (125 MHz; $CDCl_3$) (ketone carbon not observed), 173.6 (C=O), 170.9 (C=O), 128.3 (CH), 122.9 (CH), 62.9 (C), 52.8 ($CH_3$), 51.7 ($CH_3$), 37.3 ($CH_2$), 33.0 ($CH_2$), 26.2 ($CH_2$) and 19.1 ($CH_2$); *m/z* (ES) (%) 289.1 (M + $Na^+$, 100), 269.2 (58) and 206.2 (29).

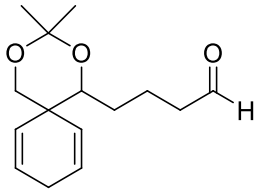
**4-(3,3-Dimethyl-2,4-dioxaspiro[5.5]undeca-7,10-dien-1-yl)butan-1-ol (219)**



**219**

A solution of methyl 1-(5-methoxy-5-oxopentanoyl)cyclohexa-2,5-dienecarboxylate (**218**) (3.20 g, 12.4 mmol) in THF (5 mL) was added to a suspension of $LiAlH_4$ (2.82 g, 73.9 mmol) in THF (100 mL) at 25 °C and the reaction mixture was stirred for 30 minutes. The reaction mixture was quenched with 15% NaOH (aq.) (0.25 mL) and water (0.55 mL). The solution was dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The resulting residue was dissolved in acetone (90 mL). Dimethoxypropane (4.76 mL, 41.0 mmol) and camphorsulfonic acid (0.02 g, cat.) was added to the reaction mixture and the solution was stirred at 60 °C for 24 h. The solvent was removed *in vacuo* and the reaction mixture was neutralised with a saturated $NaHCO_3$ (aq) solution (15 mL) and water (20 mL). The product was extracted into $CH_2Cl_2$ (3 x 50 mL) and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (2:1 hexane:diethyl ether) gave the *title compound* (1.65 g, 80%) as a colourless oil (Found: $M^+ - CH_3$, 237.1492. $C_{14}H_{21}O_3$ requires M, 237.1491); $\nu_{max}$ (neat) 3399, 2939, 2860, 1380, 1198, 1069 and 714 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 6.05 – 5.92 (1H,m *J* 10.2, 2.0, alkene CH), 5.91 – 5.83 (2H, m, 2 x alkene CH), 5.19 (1H, app. dq, *J* 10.2, 2.0, alkene CH), 3.74 (1H, d, *J* 11.3, one of $CH_2O$), 3.64 – 3.59 (3H, m, CH-O and $CH_2OH$), 3.47 (1H, d, *J* 11.3, one of $CH_2O$), 2.69 – 2.65 (2H, m, $CH_2$), 1.58 – 1.48 (4H, m, 2 x $CH_2$), 1.47 (3H, s, $CH_3$), 1.43 (3H, s, $CH_3$) and 1.35 – 1.25 (2H, m, $CH_2$); $\delta_C$ (125 MHz; $CDCl_3$) 128.5 (CH), 127.1 (CH) 127.1 (CH), 124.8 (CH), 98.8 (C), 76.1 (CH), 70.2 ($CH_2$), 63.1 ($CH_2$), 40.1 (C), 32.8 ($CH_2$), 31.0 ($CH_2$), 29.7 ($CH_3$), 27.6 ($CH_2$), 22.5 ($CH_2$) and 19.1 ($CH_3$); *m/z* (ES) (%) 237.1 ($(M - CH_3)^+$, 5), 201.2 (7), 117.1 (23), 92.1 (96) and 83.9 (100).

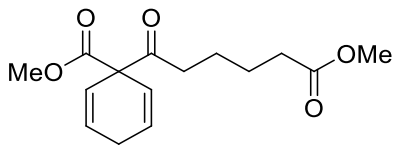
**4-(3,3-Dimethyl-2,4-dioxaspiro[5.5]undeca-7,10-dien-1-yl)butanal (220)**



**220**

Dimethylsulfoxide (2.04 mL, 26.2 mmol) was added to oxalyl chloride (1.11 mL, 13.1 mmol) in $CH_2Cl_2$ (120 mL) at –78 °C and the mixture was stirred for 2 minutes. 4-(3,3-Dimethyl-2,4-dioxaspiro[5.5]undeca-7,10-dien-1-yl)butan-1-ol (**219**) (1.65 g, 6.55 mmol) in $CH_2Cl_2$ (2 mL) was added and the solution was stirred for 40 minutes before adding triethylamine (5.57 mL, 32.8 mmol) and stirring for a further 10 minutes. The reaction mixture was warmed to room temperature, quenched with water (15 mL) and the product was extracted with $CH_2Cl_2$ (3 x 75 mL). The combined organic extracts were washed with brine (2 x 25 mL) and water (2 x 25 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the crude product **220** (2.26 g, > 100%) as a colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 9.74 (1H, t, *J* 1.7, CHO), 6.09 (1H, app. ddd, *J* 10.2, 4.1, 2.0, 1 x alkene CH), 5.91 – 5.82 (2H, m, 2 x alkene CH), 5.18 (1H, app. ddd, *J* 10.1, 4.1, 2.0, 1 x alkene CH) 3.74 (1H, d, *J* 11.4, one of $CH_2O$), 3.61 (1H, app. dd, *J* 10.0, 2.4, CH), 3.46 (1H, d, *J* 11.4, one of $CH_2O$), 2.69 – 2.64 (2H, m, $CH_2$ ring), 1.91 – 1.71 (4H, m, 2 x $CH_2$), 1.63 – 1.49 (2H, m, $CH_2$), 1.47 (3H, s, $CH_3$) and 1.43 (3H, s, $CH_3$).

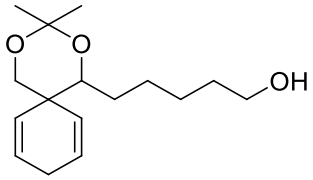
**Methyl 1-(6-methoxy-6-oxohexanoyl)cyclohexa-2,5-dienecarboxylate (233)**




**233**

A solution of *n*-butyllithium (2.0 M in cyclohexane, 5.13 mL, 10.3 mmol) was added to diisopropylamine (1.44 mL, 10.3 mmol) in THF (50 mL) at –78 °C and the resulting solution was stirred for 30 minutes. A solution of methyl cyclohexa-2,5-dienecarboxylate **114** (1.29 mL, 9.33 mmol) in THF (2 mL) was added and the reaction mixture was stirred for a further 30 minutes. Methyl 6-chloro-6-oxohexanoate (1.74 mL, 11.2 mmol) was then added and the solution further stirred for 1 h at –78 °C and 17 h at 25 °C. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (10 mL) and the product extracted into diethyl ether (3 x 50 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (20:1 hexane: diethyl ether) gave *the title compound* (2.36 g, 90%) as a pale yellow oil (Found: M + $Na^+$, 303.1206. $C_{15}H_{20}O_5Na$ requires M, 303.1208); $\nu_{max}$ (neat) 2952, 2872, 1738, 1719, 1631, 1436, 1340 and 710 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 6.09 – 6.03 (2H, m, alkene), 5.96 (2H, app. dt, *J* 10.5, 1.9, alkene), 3.75 (3H, s, $OCH_3$), 3.65 (3H, s, $OCH_3$), 2.79 – 2.74 (2H, m, ring $CH_2$), 2.54 (2H, t, *J* 6.8, $CH_2C$=O), 2.35 – 2.27 (4H, m, 2 x $CH_2$) and 1.71 – 1.62 (2H, m, $CH_2$); $\delta_C$ (125 MHz; $CDCl_3$) 205.3 (C=O), 173.6 (C=O), 170.8 (C=O), 128.0 (CH), 122.8 (CH), 62.8 (C), 52.6 ($CH_3$), 51.5 ($CH_3$), 37.8 ($CH_2$), 33.8 ($CH_2$), 26.1 ($CH_2$), 24.3 ($CH_2$) and 23.1 ($CH_2$); *m/z* ($ES^+$) (%) 304.1 (MH + $Na^+$, 21), 303.1 (100) and 269.2 (30).

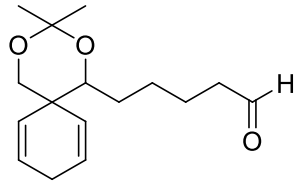
**5-(3,3-Dimethyl-2,4-dioxaspiro[5.5]undeca-7,10-dien-1-yl)pentan-1-ol (234)**




**234**

A solution of methyl 1-(6-methoxy-6-oxohexanoyl)cyclohexa-2,5-dienecarboxylate (**233**) (2.20 g, 7.86 mmol) in THF (5 mL) was added to a suspension of $LiAlH_4$ (1.79 g, 47.1 mmol) in THF (90 mL) at 25 °C and the reaction mixture was stirred for 30 minutes. The reaction mixture was quenched with 15% NaOH (aq.) (1.88 mL) and water (5.40 mL). The combined organic extracts were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The resulting residue was dissolved in acetone (80 mL). 2,2-Dimethoxypropane (4.29 mL, 35.0 mmol) and camphorsulfonic acid (cat.) was added to the reaction mixture and the solution was stirred under reflux conditions for 24 h. The solvent was removed and the reaction mixture was neutralised with a saturated aqueous solution of $NaHCO_3$ (15 mL) and water (10 mL), and the product extracted into $CH_2Cl_2$ (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (2:1 hexane:diethyl ether) gave the *title compound* (0.73 g, 39%) as a colourless oil (Found: M – $CH_3^+$, 251.1648. $C_{15}H_{23}O_3$ requires M, 251.1647); $\nu_{max}$ (neat) 3370.0, 2931, 2856, 1614.5 and 1463 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 6.(1H, app. dq, *J* 10.3, 2.0, alkene CH), 5.91 – 5.82 (2H, m, 2 x alkene CH), 5.19 (1H, app. dq, *J* 10.1, 2.1), 3.75 (1H, d, *J* 11.3, one of C*H*$_2$O), 3.62 (2H, t, *J* 6.6, $CH_2OH$), 3.60 (1H, dd, *J* 9.5, 2.6, C*H*-O), 3.46 (1H, d, *J* 11.3, one of C*H*$_2$O), 2.69 – 2.65 (2H, m, ring $CH_2$), 1.60 – 1.48 (8H, m, 4 x $CH_2$), 1.47 (3H, s, $CH_3$) and 1.43 (3H, s, $CH_3$); $\delta_C$ (125 MHz; $CDCl_3$) 128.3 (CH), 127.0 (CH), 126.9 (CH), 124.6 (CH), 98.6 (C), 75.8 (CH), 70.1 ($CH_2$), 63.0 ($CH_2$), 40.1 (C), 32.7 ($CH_2$), 31.1 ($CH_2$), 29.6 ($CH_3$), 27.4 ($CH_2$), 25.8 ($CH_2$), 25.6 ($CH_2$) and 19.0 ($CH_3$); *m/z* ($ES^+$) (%) 251.2 ((M – $CH_3$)$^+$, 59), 191.1 (92), 131.1 (32) and 92.7 (100).

**5-(3,3-Dimethyl-2,4-dioxaspiro[5.5]undeca-7,10-dien-1-yl)pentanal (235)**

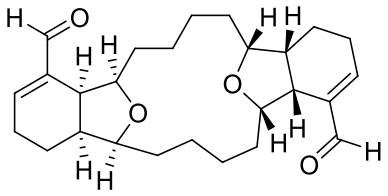


**235**

Dimethylsulfoxide (0.78 mL, 11.0 mmol) was added to a solution of oxalyl chloride (0.46 mL, 5.48 mmol) in $CH_2Cl_2$ (50 mL) at –78 °C and the resulting solution was stirred for 2 minutes, before addition of 5-(3,3-dimethyl-2,4-dioxaspiro[5.5]undeca-7,10-dien-1-yl)pentan-1-ol (**228**) (0.73 g, 2.74 mmol) in $CH_2Cl_2$ (5 mL). After 40 minutes of stirring, triethylamine (1.91 mL, 13.7 mmol) was added to the reaction mixture and stirring was continued for a further 10 minutes. The reaction mixture was warmed to room temperature, quenched with water (15 mL) and the product extracted into $CH_2Cl_2$ (3 x 50 mL). The combined organic extracts were washed with water (2 x 25 mL) and brine (2 x 25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (9:1 hexane:diethyl ether) gave the *title compound* (0.66 g, 91%) as a colourless oil (Found: $(M - CH_3)^+$, 249.1490. $C_{15}H_{21}O_3$ requires M, 249.1491); $\nu_{max}$ (neat) 2941, 2857, 1725.0, 1457 and 1380 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 9.75 (1H, t, *J* 1.8, C*H*O), 6.10 (1H, app. dq, *J* 10.2, 1.9, alkene C*H*), 5.92 – 5.81 (2H, m, 2 x alkene C*H*), 5.19 (1H, app. dq, *J* 10.2, 2.0, alkene C*H*), 3.75 (1H, d, *J* 11.3, one H of C$H_2$-O), 3.60 (1H, dd, *J* 9.3, 2.5, C*H*), 3.45 (1H, d, *J* 11.3, one H of C$H_2$-O), 2.75 – 2.59 (2H, m, $CH_2$ ring), 2.41 (2H, app. td, *J* 7.3, 1.8, C$H_2$-CHO), 1.68 – 1.16 (6H, m, 3 x $CH_2$), 1.47 (3H, s, $CH_3$) and 1.43 (3H, s, $CH_3$); $\delta_C$ (125 MHz; $CDCl_3$) 202.8 (C=O), 128.5 (CH), 126.9 (CH), 126.8 (CH), 124.7 (CH), 98.7 (C), 75.6 (CH), 70.0 ($CH_2$), 43.9 ($CH_2$), 40.0 (C), 30.9 ($CH_2$), 29.6 ($CH_3$), 27.4 ($CH_2$), 25.7 ($CH_2$), 22.0 ($CH_2$) and 18.9 ($CH_3$); *m/z* (EI) (%) 249.1 ($(M - CH_3)^+$, 52), 189.1 (41), 171.1 (25), 129.1 (33) and 92.7 (100).

**Prins reaction of 5-(3,3-dimethyl-2,4-dioxaspiro[5.5]undeca-7,10-dien-1-yl)pentanal (235)**

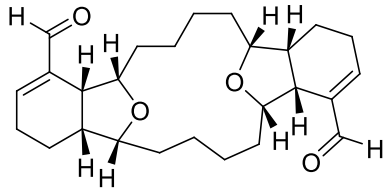
Trifluoromethanesulfonic acid (0.03 mL, 0.34 mmol) was added drop-wise to a solution of 5-(3,3-dimethyl-2,4-dioxaspiro[5.5]undeca-7,10-dien-1-yl)pentanal (**235**) (0.09 g, 0.34 mmol) in $CH_2Cl_2$ (3 mL) at 0 °C, then the mixture was warmed to 25 °C and stirred for 20 minutes. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (5 mL) and the product was extracted into $CH_2Cl_2$ (3 x 10 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (1:1 hexane:diethyl ether) gave three compounds **237** (20.1 mg, 28%), **238** (31.0 mg, 43%) and **239** (0.15 mg, 21%). The first compound was identified as dimeric structure **237** (X-ray analysis).



(±)-**237**

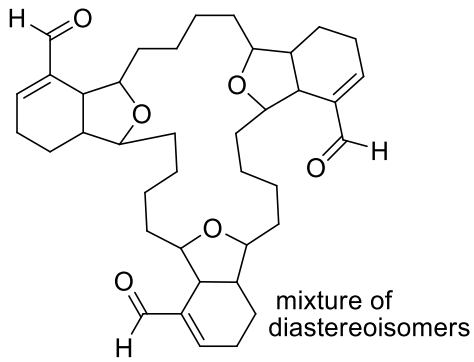
**Compound 231**: (Found: M, 412.2612. $C_{26}H_{36}O_4$ requires M, 412.2614); $\delta_H$ (400 MHz; $CDCl_3$) 9.43 (2H, s, C*H*=O), 6.96 (2H, app. broad s, alkene C*H*), 4.30 – 4.22 (2H, m, C*H*-O), 3.93 – 3.87 (2H, m, C*H*-O), 3.27 – 3.19 (2H, m, ring junction C*H*), 2.57 – 2.45 (2H, m, ring junction C*H*), 2.33 – 2.12 (4H, m, C$H_2$C=C), 2.06 – 1.90 (4H, m, C$H_2$), 1.87 – 1.62 (10H, m, 4 x C$H_2$, two of C$H_2$) and 1.51 – 1.39 (6H, m, 2 x C$H_2$ and 2H of C$H_2$); $\delta_C$ (125 MHz; $CDCl_3$) 194.0 (C=O), 152.6 (CH), 80.4 (CH), 79.6 (CH), 77.2 (CH), 40.0 (C), 39.6 (CH), 33.3 ($CH_2$), 31.3 ($CH_2$), 27.1 ($CH_2$), 26.7 ($CH_2$), 25.9 ($CH_2$) and 20.4 ($CH_2$); *m/z* (ES) (%) 412.3 ($M^+$, 100), 394.3 (14), 261.1 (8), 208.1 (10), 159.1 (13), 121.1 (17) and 107.0 (45).

Selected crystallographic data: $C_{26}H_{36}O_4$, FW = 412.55, T = 150 K, λ = 0.71073 Å, Monoclinic, *P* $2_1$/c, *a* = 7.6535(7) Å, *b* = 19.1870(16) Å, *c* = 7.8396(7) Å, α = 90.00°, β = 111.132(4)°, γ = 90.0°, V = 1073.81(16) $Å^3$, Z = 2, ρ(calc) = 1.276 $Mg/m^3$ , crystal size = 0.50 x 0.20 x 0.02 $mm^3$, reflections collected =3507, independent reflections = 2029, R(int) = 0.0535, parameters = 136, $R_1$ [$I > 2\sigma(I)$] =0.0849, $wR_2$ [$I > 2\sigma(I)$] =0.1701, $R_1$ (all data) =0.1300, $wR_2$ (all data) =0.1932.



**238**

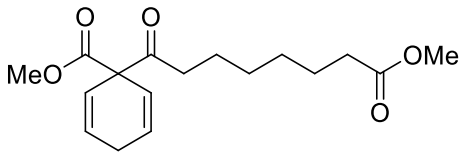
**Compound 238**: (Found: M, 412.2610. $C_{26}H_{36}O_4$ requires M, 412.2614); $\nu_{max}$ (neat) 2917, 2850, 1683 and 1641 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 9.45 (2H, s, C*H*=O), 6.95 (2H, app. t, *J* 6.6, alkene C*H*), 4.25 (2H, app. t, *J* 9.7, C*H*-O) 3.89 (2H, dd, *J* 10.2, 4.7, C*H*-O), 3.23 (2H, app. t, *J* 8.0, ring junction C*H*), 2.52 (2H, app. dt, *J* 18.7, 5.0, one of C$H_2$C=C), 2.32 – 2.08 (2H, m, C$H_2$C=C), 2.01 – 1.93 (4H, m, ring junction CH) and 1.60 – 1.38 (16H, m, 8 x C$H_2$); $\delta_C$ (125 MHz; $CDCl_3$) 194.4 (CHO), 152.0 (CH), 141.3 (C), 81.5 (CH), 80.3 (CH), 40.2 (CH), 40.0 (CH), 31.3 ($CH_2$), 28.8 ($CH_2$), 27.8 ($CH_2$), 26.1 ($CH_2$), 26.0 ($CH_2$) and 20.3 ($CH_2$); *m/z* (ES) (%) 412.2 ($M^+$, 100), 261.1 (12) and 207.0 (36). The $^1H$ and $^{13}C$ NMR spectra for this compound are broadly similar to those of compound **237**.




**239**

**Third compound 239:** (trimer) (Found: M, 618.3915. $C_{39}H_{54}O_6$ requires M, 618.3920); $\nu_{max}$ (neat) 2917, 2850, 1683 and 1641 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) All x 3 9.45 (1H, s, C*H*=O), 6.98 (1H, m, alkene C*H*), 4.19 (1 H, app. td, *J* 8.9, 2.6, C*H*-O), 3.89 – 3.77 (1H, m, C*H*-O), 3.21 (1H, d, *J* 7.0, ring junction C*H*), 2.56 – 2.42 (1H, m, one of C$H_2$C=C), 2.30 – 2.17 (1H, m, one of C$H_2$C=C), 2.03 – 1.91 (1H, m, ring junction CH) and 1.51 – 1.40 (8H, m, 4 x C$H_2$); *m/z* (ES) (%) 618.4 ($M^+$, 100), 590.4 (31), 412.3 (12), 321.2 (5) and 208.1 (18).

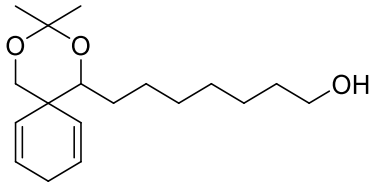
**Methyl 1-(8-methoxy-8-oxooctanoyl)cyclohexa-2,5-dienecarboxylate (241)**




**241**

A solution of *n*-butyllithium (2.0 M in cyclohexane, 1.5 mL, 3.02 mmol) was added to diisopropylamine (0.43 mL, 3.02 mmol) in THF (25 mL) at –78 °C and the resulting solution was stirred for 30 minutes. A solution of methyl cyclohexa-2,5-diene-1-carboxylate (**114**) (0.38 g , 2.74 mmol) in THF (1 mL) was added and the mixture was stirred for 30 minutes. Methyl 8-chloro-8-oxooctanoate (0.68 mL, 3.29 mmol) was added then the solution was further stirred for 1 h at –78 °C, then for 17 h at 25 °C. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (5 mL) and the product extracted with diethyl ether (3 x 30 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (3:1 hexane:diethyl ether) gave the *title compound* (0.68 g, 81%) as a colourless oil (Found: M + $Na^+$, 331.1525. $C_{17}H_{24}O_5Na$ requires M, 331.1521); $\nu_{max}$ (neat) 2951, 2861, 1735,1720, 1436, 1233 and 714 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 6.05 (2H, app. dtd, *J* 10.5, 3.2, 1.7, 2 x alkene CH), 5.97 (2H, app. dt, *J* 10.4, 1.9, 2 x alkene CH), 3.75 (3H, s, $CH_3O$), 3.66 (3H, s, $CH_3O$), 2.79 – 2.75 (2H, m, $CH_2$ ring), 2.50 (2H, t, *J* 7.2, $CH_2CO$), 2.29 (2H, t, *J* 7.5, $CH_2CO$), 1.64 – 1.48 (4H, m, 2 x $CH_2$) and 1.34 – 1.20 (4H, m, 2 x $CH_2$); $\delta_C$ (125 MHz; $CDCl_3$) 204.7 (C=O), 173.7 (C=0), 170.9 (C=O), 128.0 (CH), 122.8 (CH), 62.8 (C), 52.6 ($CH_3$), 51.5 ($CH_3$), 38.1 ($CH_2$), 34.0 ($CH_2$), 28.9 ($CH_2$), 28.6 ($CH_2$), 26.1 ($CH_2$), 24.7 ($CH_2$) and 23.4 ($CH_2$); *m/z* (ES) (%) 331.2 (M + $Na^+$, 100).

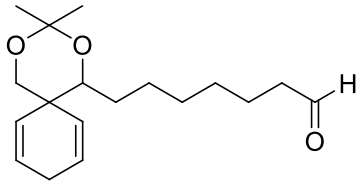
**7-(3,3-Dimethyl-2,4-dioxaspiro[5.5]undeca-7,10-dien-1-yl)heptan-1-ol (242)**




**242**

A solution of methyl 1-(8-methoxy-8-oxooctanoyl)cyclohexa-2,5-dienecarboxylate (**241**) (0.68 g, 2.21 mmol) in THF (1 mL) was added to a suspension of $LiAlH_4$ (0.50 g, 13.2 mmol) in THF (45 mL) at 25 °C and the resulting mixture was stirred for 30 minutes. The reaction was quenched with 15% aqueous NaOH solution (0.47 mL) and water (1.04 mL), dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. 2,2-Dimethoxypropane (1.04 mL, 8.46 mmol) camphorsulfonic acid (20.0 mg) was added to a mixture of the resulting residue in acetone (30 mL) and and the resulting solution was stirred at 60 °C for 24 h. The solvent was removed *in vacuo* and the reaction mixture was neutralised with saturated aqueous $NaHCO_3$ solution (10 mL) and water (15 mL). Then the product was extracted into $CH_2Cl_2$ (3 x 40 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (1:1 hexane:diethyl ether) gave the *title compound* (0.15 g, 30%) as a colourless oil (Found: $MH^+$ 295.2263. $C_{18}H_{31}O_3$ requires M, 295.2273); $\nu_{max}$ (neat) 3365, 2931, 2856, 1456, 1381, 1198, 1055 and 713 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 6.10 (1H, app dq, *J* 10.3, 2.0, alkene CH), 5.90 – 5.81 (2H, m, 2 x alkene CH), 5.29 (1H, app. dq, *J* 10.1, 1.9, alkene CH), 3.73 (1H, d, *J* 11.3, one of $CH_2O$), 3.65 – 3.59 (3H, m, OCH and $CH_2OH$), 3.45 (1H, d, *J* 11.3, one of $CH_2O$), 2.69 – 2.65 (2H, m, $CH_2$ ring), 1.65 – 1.48 (12H, m, 6 x $CH_2$), 1.47 (3H, s, $CH_3$) and 1.43 (3H, s, $CH_3$); $\delta_C$ (125 MHz; $CDCl_3$) 128.2 (CH), 127.1 (CH), 127.0 (CH), 124.5 (CH), 98.6 (C), 75.8 (CH), 70.1 ($CH_2$), 63.1 ($CH_2$), 39.9 (C), 32.8 ($CH_2$), 31.2 ($CH_2$), 29.6 ($CH_3$), 29.5 ($CH_2$), 29.4 ($CH_2$), 27.4 ($CH_2$), 26.0 ($CH_2$) and 25.7 ($CH_2$); *m/z* (TOF) (%) 296.2 (8), 295.2 ($MH^+$, 29), 237.2 (81), 219.2 (100) and 206.2 (90).

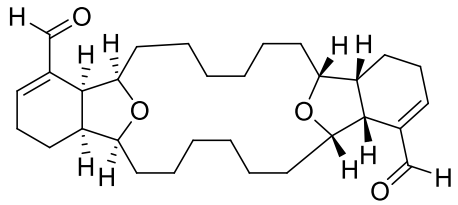
**7-(3,3-Dimethyl-2,4-dioxaspiro[5.5]undeca-7,10-dien-1-yl)heptanal (243)**



**243**

Dimethylsulfoxide (0.15 mL, 1.97 mmol) was added to oxalyl chloride (0.08 mL, 0.99 mmol) in $CH_2Cl_2$ (25 mL) at –78 °C and the solution was stirred for 2 minutes. 7-(3,3-Dimethyl-2,4-dioxaspiro[5.5]undeca-7,10-dien-1-yl)heptan-1-ol 9 (**242**) (0.15 g, 0.49 mmol) in $CH_2Cl_2$ (0.50 mL) was added and the solution was stirred for 40 minutes. Triethylamine (0.34 mL, 2.45 mmol)was added to the reaction mixture and stirring was continued for a further 10 min. The reaction mixture was warmed to room temperature, quenched with water (5 mL) and the product extracted with $CH_2Cl_2$ (3 x 30 mL). The combined organic extracts was washed with water (2 x 15 mL) and brine (2 x 15 mL), dried over $MgSO_4$ and concentrated *in vacuo,* to give crude compound **243** (0.17 g, >100%) as a colourless oil (Found: $MH^+$ 293.2126. $C_{18}H_{29}O_3$ requires M, 293.2117); $\nu_{max}$ (neat) 2939, 1723, 1436, 1382, 1026 and 735 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$)) 9.76 (1H, m, CHO), 6.11 (1H, app. ddd, *J* 10.3, 3.8, 1.9, 1 x alkene CH), 5.90 – 5.82 (2H, m, 2 x alkene CH), 5.19 (1H, app. ddd, *J* 10.1, 3.8, 2.0, 1 x alkene CH), 3.73 (1H, d, *J* 11.3, one of $CH_2$-O), 3.58 (1H, dd, *J* 9.3, 2.3, CH), 3.46 (1H, d, *J* 11.3, one of $CH_2$-O), 2.69 – 2.65 (2H, m, $CH_2$ ring), 2.49 – 2.37 (4H, m, 2 x $CH_2$), 1.74 – 1.55 (8H, m, 4 x $CH_2$), 1.47 (3H, s, $CH_3$) and 1.43 (3H, s, $CH_3$); $\delta_C$ (125 MHz; $CDCl_3$) 202.9 (C=O), 128.2 (CH), 127.0 (CH), 126.9 (CH), 124.5 (CH), 98.6 (C), 75.8 (CH), 70.0 ($CH_2$), 45.8 ($CH_2$), 43.8 ($CH_2$), 39.9 (C), 31.1 ($CH_2$), 29.5 ($CH_3$), 29.1 ($CH_2$), 27.4 ($CH_2$), 25.7 ($CH_2$) and 22.0 ($CH_2$); *m/z* (EI) (%) 293.2 ($MH^+$, 38), 284.2 (78) and 206.2 (100).

**Prins reaction of 7-(3,3-dimethyl-2,4-dioxaspiro[5.5]undeca-7,10-dien-1-yl)heptanal (243)**

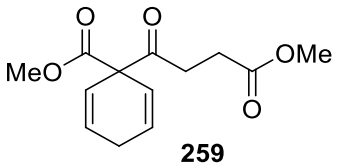


(±)-**244**

Trifluoromethanesulfonic acid (0.03 mL, 0.31 mmol) was added drop-wise to a solution of 7-(3,3-dimethyl-2,4-dioxaspiro[5.5]undeca-7,10-dien-1-yl)heptanal (**243)** (0.09 g, 0.31 mmol) in $CH_2Cl_2$ (3 mL) at 0 °C, then the solution was warmed to 25 °C and stirred for 20 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (4 mL) and the product extracted into $CH_2Cl_2$ (3 x 8 mL). The combined organic extracts was dried over $Na_2SO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (1:1 hexane:diethyl ether) gave compound **244** (21.5 mg, 27%), over two steps from **242** as a colourless solid (Found: M, 468.3228. $C_{30}H_{44}O_4$ requires M, 468.3240); $\nu_{max}$ (neat) 2932, 1681, 1260, 1031, 911 and 731 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) All x 2 9.42 (1H, m, CHO), 6.95 (1H, m, alkene CH), 4.23 – 4.11 (1H, m, CH), 3.89 – 3.79 (1H, m, CH), 3.57 – 3.44 (1H, m, CH), 3.27 – 3.17 (1H, m, CH), 2.42 – 2.45 (2H, m, $CH_2$), 2.31 – 2.24 (2H, m, $CH_2$) and 1.68 – 1.50 (12H, m, 6 x $CH_2$); $\delta_C$ (125 MHz; $CDCl_3$) 194.5 (CHO), 152.5 (CH), 126.0 (C), 81.5 (CH), 79.0 (CH), 40.0 (CH) and 39.5 (CH), 34.2 ($CH_2$), 27.7 ($CH_2$), 26.7 ($CH_2$), 25.8 ($CH_2$), 25.7 ($CH_2$), 25.4 ($CH_2$), 20.0 ($CH_2$), 19.8 ($CH_2$); *m/z* (ES) (%) 469 (31), 468 ($MH^+$, 100), 358 (48), 236 (28), 107 (62) and 91 (93).

Selected crystallographic data: $C_{30}H_{44}O_4$, FW = 468.65, T = 150 K, λ = 0.71073 Å, Monoclinic, *P* $2_1$/c, *a* = 10.4006(4) Å, *b* = 11.2635(6) Å, *c* = 11.2583(6) Å, α = 90.00°, β = 96.957(3)°, γ = 90.00°, V = 1309.17(11) $Å^3$, Z = 2, ρ(calc) = 1.189 $Mg/m^3$ , crystal size = 0.50 x 0.22 x 0.14 $mm^3$, reflections collected =4974, independent reflections = 2999, R(int) = 0.0411, parameters = 154, $R_1$ [$I > 2\sigma(I)$] =0.0595, $wR_2$ [$I > 2\sigma(I)$] =0.1231, $R_1$ (all data) =0.0973, $wR_2$ (all data) =0.1398.

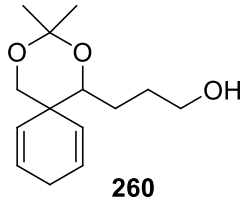
**Methyl 1-(4-methoxy-4-oxobutanoyl)cyclohexa-2,5-dienecarboxylate (259)**



**259**

A solution of *t*-butyllithium (1.7 M in pentane, 14.3 mL, 24.4 mmol) was added to methyl cyclohexa-2,5-dienecarboxylate (**114**) (3.06 g, 22.2 mmol) in THF (100 mL) at –78 °C and the resulting solution was stirred for 30 minutes. Methyl 4-chloro-4-oxobutyrate (3.27 mL, 26.6 mmol) was added and the solution was further stirred for a 1 h at –78 °C and 17 h at 25 °C. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (20 mL) and the product extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (3:1 hexane:diethyl ether) gave the *title compound* (3.70 g, 67%) as a colourless oil (Found: $[M - CH_3]^-$, 237.0759. $C_{12}H_{13}O_5$ requires M, 237.0763); $\nu_{max}$ (neat) 2954, 1732, 1719, 1641, 1436, 942, 795 and 714 $cm^{-1}$; $\delta_H$ (250 MHz; $CDCl_3$) 6.09 (2H, dt, *J* 10.7, 3.1, CH), 5.99 (2H, dt, *J* 10.4, 1.7, CH), 3.75 (3H, s, $OCH_3$), 3.66 (3H, s, $OCH_3$), 2.87 (2H, t, *J* 6.7, $CH_2$), 2.81 – 2.76 (2H, m, ring $CH_2$) and 2.55 (2H, t, *J* 6.7, $CH_2$); $\delta_C$ (100 MHz; $CDCl_3$) 204.4 (C=O), 173.0 (C=O), 128.3 (CH), 122.7 (CH), 62.4 (C), 52.7 ($CH_3$), 51.9 ($CH_3$), 33.7 ($CH_2$), 27.8 ($CH_2$) and 26.0 ($CH_2$); *m/z* (EI) (%) 237.1 ($M^+ - CH_3$, 12), 209.1 (15), 189.1 (22), 161.1 (71) and 137.1 (98).

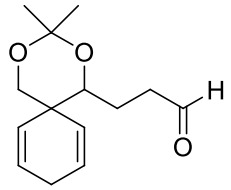
**3-(3,3-Dimethyl-2,4-dioxaspiro[5.5]undeca-7,10-dien-1-yl)propan-1-ol (260)**




**260**

A solution of methyl 1-(4-methoxy-4-oxobutanoyl)cyclohexa-2,5-dienecarboxylate (**259**) (3.65 g, 14.5 mmol) in THF (5 mL) was added to a suspension of $LiAlH_4$ (3.31 g, 87.0 mmol) in THF (100 mL) at 0 °C and then the reaction mixture was stirred for 30 minutes at 25 °C. The reaction mixture was quenched with 15% NaOH (aq) (4.20 mL) and water (7.91 mL), dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. Camphorsulfonic acid (100 mg) was added to the crude mixture in 2,2-dimethoxypropane (50 mL) and the resulting solution was heated under reflux for 24 h. The solvent was removed then the reaction mixture was neutralised with saturated aqueous $NaHCO_3$ solution (20 mL) and water (30 mL). Then the product was extracted into $CH_2Cl_2$ (3 x 60 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (20:1 hexane:diethyl ether) gave *the title compound* (0.85 g, 37%) as a colourless oil (Found: M – $CH_3^+$, 223.1338. $C_{13}H_{19}O_3$ requires M, 223.1334); $\nu_{max}$ (neat) 3400, 2991, 2942, 2860, 1455, 1380, 1207, 1055 and 714 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 6.10 (2H, app. dq, *J* 10.3 and 2.1, CH), 5.94 – 5.80 (2H, m, 2 x CH), 5.25 – 5.14 (1H, app. dq, *J* 10.1 and 2.1, CH), 3.75 (1H, d, *J* 11.4, 1H of $CH_2$), 3.70 – 3.52 (3H, m, CH and $CH_2$), 3.47 (1H, d, *J* 11.4, 1H of $CH_2$), 2.77 – 2.56 (2H, m, ring $CH_2$), 1.66 – 1.53 (4H, m, 2 x $CH_2$), 1.49 (3H, s, $CH_3$) and 1.44 (3H, s, $CH_3$); $\delta_C$ (12500 MHz; $CDCl_3$) 128.7 (CH), 126.6 (CH), 126.5 (CH), 124.8 (CH), 98.8 (C), 76.4 (CH), 69.9 ($CH_2$), 62.8 ($CH_2$), 39.9 (C), 29.9 ($CH_2$), 29.5 ($CH_3$), 28.2 ($CH_2$) and 27.4 ($CH_2$); *m/z* (EI) (%) 223.1 ((M – $CH_3$)$^+$, 26), 163.1 (78) and 92.4 (100).

**3-(3,3-Dimethyl-2,4-dioxaspiro[5.5]undeca-7,10-dien-1-yl)propanal (261)**

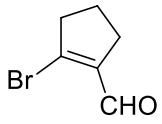


**261**

Dimethylsulfoxide (0.96 mL, 14.3 mmol) was added to oxalyl chloride (0.60 mL, 7.14 mmol) in $CH_2Cl_2$ (60 mL) at –78 °C and the solution was stirred for 2 minutes. Then 3-(3,3-dimethyl-2,4-dioxaspiro[5.5]undeca-7,10-dien-1-yl)propan-1-ol (**260**) (0.85 g, 3.57 mmol) in $CH_2Cl_2$ (2 mL) was added and the solution was stirred for 40 minutes. Triethylamine (2.49 mL, 17.9 mmol) was added and the reaction mixture was further stirred for 10 minutes. The reaction mixture was warmed to room temperature, quenched with water (25 mL) and the product extracted with $CH_2Cl_2$ (3 x 60 mL). The combined organic extracts was washed with water (2 x 30 mL) and brine (2 x 30 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give somewhat impure 3-(3,3-dimethyl-2,4-dioxaspiro[5.5]undeca-7,10-dien-1-yl)propanal (**261**) (0.63 g, 74%) as a yellow oil (Found: M – $CH_3^+$, 221.1179. $C_{13}H_{17}O_3$ requires M, 221.1178); $\nu_{max}$ (neat) 2992, 1725, 1380, 1206, 1055 and 715 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 9.71 (1H, t, *J* 1.8, CHO), 6.19 – 6.04 (1H, m, CH), 5.97 – 5.80 (2H, m, 2 x CH), 5.27 – 5.13 (1H, m, CH), 3.74 (1H, d, *J* 11.4, 1H of $CH_2$), 3.68 – 3.52 (1H, m, CH), 3.47 (1H, d, *J* 11.4, 1H of $CH_2$), 2.74 – 2.62 (2H, m, ring $CH_2$), 1.82 – 1.54 (4H, m, 2 x $CH_2$), 1.44 (3H, s, $CH_3$) and 1.41 (3H, m, $CH_3$); $\delta_C$ (125 MHz; $CDCl_3$) 202.7 (C=O), 128.8 (CH), 126.4 (CH), 126.3 (CH), 125.2 (CH), 98.8 (C), 75.0 (CH), 69.7 ($CH_2$), 62.8 ($CH_2$), 40.6 (C), 29.7 ($CH_2$), 29.5 ($CH_3$) and 24.1 ($CH_2$); *m/z* (EI) (%) 221.1 ($M^+$ – $CH_3$, 11), 161.1 (13), 117.1 (21), 104.1 (37) and 92.1 (100).

## 8.4. Experimental Data for Chapter 5

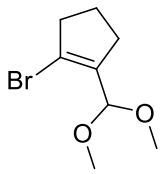
### 2-Bromocyclopent-1-enecarbaldehyde (277)[71]




**277**

$PBr_3$ (24.3 mL, 241 mmol) was added drop-wise to a solution of dimethylformamide (20.6 mL, 267.5 mmol) in dichloromethane (120 mL) at 0 °C and the solution was stirred for 60 minutes. Cyclopentanone (7.5 g, 89 mmol) was then added and the reaction mixture was stirred at this temperature for 8 h. The reaction mixture was quenched by slowly pouring into a conical flask containing iced-water (450 mL), neutralised with solid $NaHCO_3$ and the product was extracted with dichloromethane (3 x 120 mL). The combined organic extracts were washed with brine (2 x 120 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the *title compound* (11.0 g, 71%) as a colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 9.90 (1H, s, CHO), 2.91 (2H, dt, *J* 7.5, 2.3, $CH_2$), 2.53 (2H, tt, *J* 8.8, 2.3, $CH_2$) and 2.07 – 1.96 (2H, m, $CH_2$).

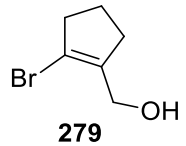
### 1-Bromo-2-(dimethoxymethyl)cyclopent-1-ene (278)[74]




**278**

Trimethyl orthoformate (10 mL) and camphorsulfonic acid (~ 10 mg) were added to a solution of 2-bromocyclopent-1-enecarbaldehyde (**277**) (0.45 g, 2.57 mmol) in methanol (10 mL) and the reaction mixture was stirred at room temperature for 18 h. The solvent was removed and the residue treated with solid potassium carbonate and filtered. Purification by flash column chromatography (1:1 hexane: dichloromethane) gave *the title compound* (0.38 g, 67%) as a colourless solid. $\delta_H$ (400 MHz; $CDCl_3$) 5.00 (1H, s, CH), 3.40 (6H, s, 2 x $CH_3$-O), 2.65 – 2.55 (2H, m, $CH_2$), 2.45 – 2.35 (2H, m, $CH_2$) and 2.00 – 1.90 (2H, m, $CH_2$).

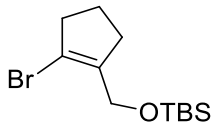
**(2-Bromocyclopent-1-enyl)methanol (279)**[72]




**279**

Sodium borohydride (2.63 g, 69.1 mmol) was added portion-wise over 10 minutes to a solution of 2-bromocyclopent-1-enecarbaldehyde (**277**) (11.0 g, 62.9 mmol) in methanol (70 mL) at 0 °C. The reaction mixture was warmed to room temperature and the solution was stirred for 1 h. The reaction mixture was quenched with water (120 mL), diethyl ether (300 mL) was added and the product was extracted with diethyl ether (3 x 150 mL). The combined organic extracts were washed with brine (2 x 150 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the *title compound* (7.88 g, 71%) as a colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 4.27 (2H, s, $CH_2OH$), 2.71 – 2.56 (2H, m, $CH_2$), 2.51 – 2.4 (2H, m, $CH_2$) and 1.91 (2H, app. q, J 7.5, $CH_2$).

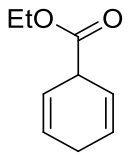
**((2-Bromocyclopent-1-enyl)methoxy)(tert-butyl)dimethylsilane (280)**[35]




**280**

*tert*-Butyldimethylsilyl chloride (1.39 g, 9.20 mmol), imidazole (1.25 g, 18.4 mmol) and 4-DMAP (~ 10 mg) were added to a solution of (2-bromocyclopent-1-enyl)methanol (**277**) (1.48 g, 8.36 mmol) in dichloromethane (25 mL) and the resulting solution was stirred at room temperature for 18 h. The reaction mixture was quenched with water (10 mL) and the product was extracted into dichloromethane (3 x 25 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (3:1 petroleum ether: diethyl ether) gave the *title compound* (1.30 g, 69%) as a colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 4.28 – 4.26 (2H, m, $CH_2OTBS$), 2.71 – 2.56 (2H, m, $CH_2$), 2.46 – 2.40 (2H, m, $CH_2$), 2.02 – 1.86 (2H, m, $CH_2$), 0.90 (9H, s, 3 x $CH_3$) and 0.08 (6H, s, 2 x $CH_3$).

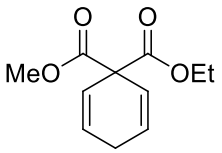
**Ethyl cyclohexa-2,5-dienecarboxylate (281)**[69]




**281**

Sodium metal (6.22 g, 270 mmol) was added portion-wise to a solution of benzoic acid (10 g, 81.9 mmol) in liquid ammonia:ethanol (4:1 500 mL) at –78 °C. After the blue colour had subsided, solid ammonium chloride (17.5 g, 330 mmol) was added and the ammonia was left to evaporate. The mixture was acidified by addition of 2 M hydrochloric acid and the aqueous layer was extracted with diethyl ether (3 x 200 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated in *vacuo*. The reside was re-dissolved in ethanol (250 mL), treated with concentrated sulfuric acid (0.50 mL, 5.10 mmol) and stirred at room temperature for 16 h. The solvent was removed and the reaction mixture was neutralised with aqueous sodium hydrogen carbonate solution and extracted with diethyl ether (3 x 200 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo* to give the *title compound* (7.99 g, 65%) as a colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 5.97 – 5.75 (4H, m, 4 x alkene CH), 4.17 (2H, q, *J* 7.1, $CH_2$), 3.72 (1H, app. ddt, *J* 10.3, 8.1, 2.4, CH), 2.73 – 2.64 (2H, m, ring $CH_2$) and 1.27 (3H, t, *J* 7.1, $CH_3$).

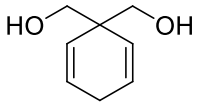
**1-Ethyl 1-methyl cyclohexa-2,5-diene-1,1-dicarboxylate (282)**[97]




**282**

A solution of *n*-butyllithium (15.45 mL, 32.9 mmol, 2.0 M in pentane) was added drop-wise to a solution of diisopropylamine in THF (50 mL) at 0 °C. The reaction mixture was stirred at this temperature for 30 minutes then cooled to –78 °C. Ethyl cyclohexa-2,5-dienecarboxylate (**281**) (5.00 g, 33.0 mmol) in THF (10 mL) was added drop-wise to the reaction mixture and stirred for 30 minutes at –78 °C. Then methyl chloroformate (2.80 mL, 36.2 mmol) was added. The reaction mixture was further stirred for 15 minutes at –78 °C. Then the reaction mixture was quenched with saturated aqueous ammonium chloride solution (20 mL) and the product extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (49:1 hexane: ethyl acetate) gave the *title compound* (6.14 g, 89%) as a colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 6.08 – 5.95 (4H, m, 4 x CH), 4.20 (2H, q, *J* 7.1, $CH_2$-O), 3.75 (3H, s, $CH_3$-O), 2.74 – 2.69 (2H, m, ring $CH_2$) and 1.27 (3H, t, *J* 7.1, $CH_3$).

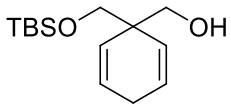
**Cyclohexa-2,5-diene-1,1-diyldimethanol (283)**[97]



**283**

To a stirred suspension of $LiAlH_4$ (2.18 g, 57.4 mmol) in dry THF (60 mL) under a nitrogen atmosphere at room temperature, was added a solution of 1-ethyl 1-methyl cyclohexa-2,5-diene-1,1-dicarboxylate (**282**) (6.14 g, 28.7 mmol) in dry THF (20 mL). The mixture was stirred at room temperature for 2 h. The reaction mixture was quenched with an aqueous solution of 15% NaOH (2.04 mL) and water (3.00 mL). Then the product was filtered and concentrated *in vacuo* to give *the title compound* as a colourless oil (2.63 g, 65%). $\delta_H$ (400 MHz; $CDCl_3$) 6.10 – 6.00 (2H, m, 2 x alkene CH), 5.58 (2H, app. dt, *J* 10.5, 2.0, 2 x alkene CH), 3.52 (4H, s, 2 x $CH_2$) and 2.71 (2H, app. tt, *J* 3.3, 2.1, ring $CH_2$).

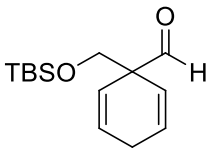
**(1-((*tert*-Butyldimethylsilyloxy)methyl)cyclohexa-2,5-dienyl)methanol (284)**[97]



**284**

A solution of *n*-butyllithium (2.40 mL, 2.0 M in pentane, 6.01 mmol) was added to a solution of cyclohexa-2,5-diene-1,1-diyldimethanol (**283**) (0.89 g, 6.33 mmol) in dry THF (15 mL) at -78 °C. The reaction mixture was warmed to room temperature for 1 h. A solution of *tert*-butyldimethylsilylchloride (0.86 g, 5.70 mmol) in THF (1 mL) was added and the reaction mixture was stirred for 30 minutes. Imidazole (10 mg) was added and the reaction mixture was further stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (10 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic extracts were dried over $Na_2SO_4$ and solvent concentrated *in vacuo*. Purification by flash column chromatography (9:1 hexane: ethyl acetate) gave the *title compound* (1.38 g, 86%) as a colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 6.07 (1H, app. dt, *J* 10.4, 3.3, alkene CH), 5.97 – 5.83 (1H, m, alkene CH), 5.71 – 5.45 (2H, m alkene 2 x CH), 3.59 (2H, s, $CH_2$-O), 3.53 (2H, s, $CH_2$-OTBS), 2.75 – 2.70 (2H, m, $CH_2$), 0.91 (9H, s, 3 x $CH_3$) and 0.10 (6H, s, 2 x $CH_3$).

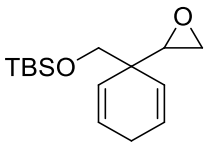
**1-((*tert*-Butyldimethylsilyloxy)methyl)cyclohexa-2,5-dienecarbaldehyde (285)**[97]




**285**

To a stirred solution of oxalyl chloride (0.59 mL, 6.89 mmol) in dry dichloromethane (20 mL) dimethylsufoxide (1.12 mL, 15.7 mmol) was added over 5 minutes. The reaction mixture was stirred at –78 °C for 10 minutes. A solution of compound **284** (0.50 g, 1.96 mmol) in dry dichloromethane (5 mL) was then added, and stirring at –78 °C was continued for 15 minutes. Triethylamine (3.57 mL, 25.6 mmol) was added and the reaction mixture was warmed to room temperature and further stirred for 2 h. The reaction mixture was quenched with a solution of saturated aqueous sodium hydrogen carbonate and the product extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (50:1 petroleum ether: diethyl ether) gave the *title compound* (0.41 g, 93%) as a pale yellow oil. $\delta_H$ (400 MHz; $CDCl_3$) 9.51 (1H, s, CHO), 5.94 – 6.01 (2H, m, alkene, 2 x CH), 5.70 – 5.63 (2H, m, alkene, 2 x CH), 3.75 (2H, s, $CH_2$-OTBS), 2.72 – 2.68 (2H, m, ring $CH_2$), 0.82 (9H, s, *t*-butyl) and 0.03 (6H, s, 2 x $CH_3$).

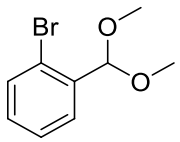
***tert*-Butyldimethyl((1-(oxiran-2-yl)cyclohexa-2,5-dienyl)methoxy)silane (286)**[97]




**286**

A solution of *n*-Butyllithium (3.82 mL, 7.64 mmol, 2.0 M in cycohexane) was added drop-wise to a solution of 1-((tert-butyldimethylsilyloxy)methyl)cyclohexa-2,5-dienecarbaldehyde (**285**) (1.75 g, 6.94 mmol) and dibromomethane (0.73 mL, 10.4 mmol) in THF (40 mL) at –78 °C. The reaction mixture was warmed to room temperature and was stirred for 48 h. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (10 mL) and the product extracted with diethyl ether (3 x 40 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (50:1 petroleum ether: diethyl ether) gave *the title compound* (0.96 g, 52 %) as a pale yellow oil. $\delta_H$ (400 MHz; $CDCl_3$) 5.93 – 5.81 (2H, m, 2 x alkene CH), 5.67 (1H, app. ddd, *J* 10.2, 4.1, 2.0, alkene CH), 5.37 (1H, app. dq, *J* 10.3, 2.0, alkene CH), 3.63 (1H, d, *J* 9.3, 1H of $CH_2$OTBS), 3.48 (1H, d, *J* 9.3 1H of $CH_2$OTBS), 3.13 (1H, dd, *J* 4.0, 2.9, epoxide CH), 2.67 – 2.63 (3H, m, $CH_2$ ring + 1H of epoxide CH), 2.60 (1H, dd, *J* 5.1, 2.9, 1H of epoxide $CH_2$), 0.90 (9H, s, 3 x $CH_3$), 0.05 (3H, s, $CH_3$) and 0.04 (3H, s, $CH_3$).

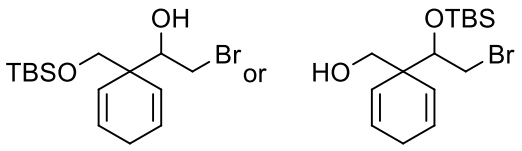
**1-Bromo-2-(dimethoxymethyl)benzene (289)**[98]




**289**

Trimethyl orthoformate (10 mL) and camphorsulfonic acid (10 mg) were added to a solution of 2-bromobenzaldehyde (0.63 mL, 5.40 mmol) in methanol (10 mL) and the solution was stirred at room temperature for 18 h. The solvent was removed and the residue was treated with solid potassium carbonate and then filtered. Purification by flash column chromatography (1:1 hexane: dichloromethane) gave the *title compound* (0.75 g, 60%) as a colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 7.63 – 7.53 (2H, m, 2 x CH aromatic), 7.37 (1H, t, *J* 7.5, CH aromatic), 7.20 (1H, td, *J* 7.6, 1.7, CH aromatic), 5.56 (1H, s, CH) and 3.39 (6H, s, 2 x $CH_3O$).

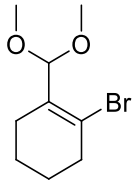
**2-Bromo-1-(1-((tert-butyldimethylsilyloxy)methyl)cyclohexa-2,5-dienyl)ethanol (293) or (1-(2-bromo-1-(tert-butyldimethylsilyloxy)ethyl)cyclohexa-2,5-dienyl)methanol (294)**




**293** **294**

A solution of *t*-butyllithium (4.98 mL, 7.22 mmol, 1.45 M in pentane) was added drop-wise to a solution of compound **289** (0.82 g, 3.61 mmol) in THF (25 mL) at –78 °C and the solution was stirred for 10 min. Epoxide (**286**) (0.96 g, 3.61 mmol) in THF (10 mL) was then added and the reaction mixture was stirred for 20 h at –78 °C then $BF_3.OEt_2$ (0.37 mL, 3.01 mmol) was added and the reaction mixture was further stirred for 1 h. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (10 mL) and the product extracted with diethyl ether (3 x 45 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* (120.0 mg, 38 %) as a yellow oil. $\delta_H$ (400 MHz; $CDCl_3$) 5.97 – 5.86 (2H, m, alkene CH), 5.81 (1H, ddd, *J* 10.3, 4.1, 2.0, alkene CH), 5.43 (1H, ddd, *J* 10.3, 4.1, 2.0, alkene CH), 4.01 (1H, app. broad d, *J* 10.5, $CH_2$OTBS), 3.70 (1H, s, OH), 3.68 (1H, d, *J* 9.5, one of $CH_2OH$), 3.58 (1H, d, *J* 9.5, one of $CH_2OH$), 3.52 (1H, ddd, *J* 1.5, 1.8. 1.1, one of $CH_2Br$), 3.27 (1H, t, *J* 10.5, one of $CH_2Br$), 2.69 – 2.63 (2H, m, ring $CH_2$), 0.90 (9H, s, *t*-Bu) and 0.06 (6H, s, 2 x $CH_3$).

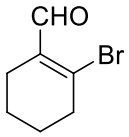
**1-Bromo-2-(dimethoxymethyl)cyclohex-1-ene (307)**[75]




**307**

Trimethyl orthoformate (35 mL) and camphorsulfonic acid (10 mg.) were added to a solution of 2-bromocyclohex-1-enecarbaldehyde (**312**) (3.5 g, 18.5 mmol) in methanol (35 mL) and the reaction mixture was stirred at room temperature for 18 h. The solvent was removed and the residue treated with solid potassium carbonate and filtered. Purification by flash column chromatography (1:1 hexane: dichloromethane) gave the *title compound* (2.3 g, 51%) as a colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 5.15 (1H, s, CH), 3.39 (6H, s, 2 x $CH_3$-O), 2.59 – 2.46 (2H, m, $CH_2$), 2.20 – 2.13 (2H, m, $CH_2$) and 1.78 – 1.58 (4H, m, 2 x $CH_2$).

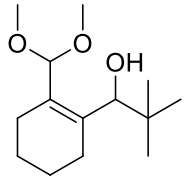
**2-Bromocyclohex-1-enecarbaldehyde (312)**[75]




**312**

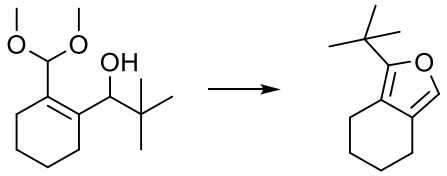
$PBr_3$ (14.4 mL, 153 mmol) was added drop-wise to a solution of dimethylformamide (10.7 mL, 138 mmol) in $CH_2Cl_2$ (80 mL) at 0 °C and the solution was stirred for 60 minutes. Cyclohexanone (5.28 mL, 50.9 mmol) was then added and the reaction mixture was stirred for 17 h. The reaction mixture was quenched by slowly pouring into a conical flask containing iced-water (300 mL), neutralised with solid $NaHCO_3$ and the product was extracted into dichloromethane (3 x 80 mL). The combined organic extracts were washed with brine (2 x 80 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (1:1 hexane: dichloromethane) gave the *title compound* (4.00 g, 42%) as a colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 10.01 (1H, s, CHO), 2.80 – 2.70 (2H, m, $CH_2$), 2.31 – 2.21 (2H, m, $CH_2$) and 1.82 – 1.62 (4H, m, 2 x $CH_2$).

**1-(2-(Dimethoxymethyl)cyclohex-1-enyl)-2-methylpropan-1-ol (314), and cyclised form 1-*tert*-butyl-4,5,6,7-tetrahydroisobenzofuran (315)**



**314**

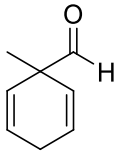
A solution of *n*-butyllithium (0.39 mL, 0.78 mmol, 2.0 M in cyclohexane) was added drop-wise to a solution of 1-bromo-2-(dimethoxymethyl)cyclohex-1-ene (**307**) (100 mg, 0.43 mmol) in THF (10 mL) at –78 °C and the solution was stirred for 2 h. Pivalaldehyde (0.12 mL, 0.39 mmol)) was then added and the reaction mixture was stirred for 1 h at –78 °C then warmed to room temperature and further stirred for 1 h. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (5 mL) and the product was extracted with ethyl acetate (3 x 15 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in *vacuo* to give the *title compound* (**314**) (160.0 mg, > 100%) as a yellow oil. $\delta_H$ (400 MHz; $CDCl_3$) 5.10 (1H, s, CH), 4.30 (1H, s, CH), 3.35 (3H, s, $CH_3$-O), 3.30 (3H, s, $CH_3$-O), 2.30 – 1.30 (8H, m, 4 x $CH_2$) and 0.99 (9H, s, 3 x $CH_3$).



**314** **315**

Purification by flash column chromatography (50:1 hexane: ethyl acetate) gave *the title compound* (**315**)(90.0 mg, > 100%) as a colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 6.95 (1H, s, furan CH), 2.75 – 2.65 (2H, m $CH_2$), 2.60 – 2.50 (2H, m, $CH_2$), 1.70 – 1.60 (4H, m, 2 x $CH_2$) and 1.25 (9H, s, 3 x $CH_3$).

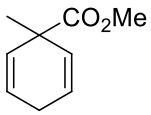
**1-Methylcyclohexa-2,5-dienecarbaldehyde (316)**[97]



**316**

To a stirred solution of oxalyl chloride (5.58 mL, 65.9 mmol) in dry dichloromethane (100 mL), dimethylsulfoxide (9.40 mL, 132 mmol) was added. The reaction mixture was stirred at –78 °C for 10 minutes, then a solution of (1-methylcyclohexa-2,5-dienyl)methanol (**318**) (6.7 g, 54.0 mmol) in dry dichloromethane (50 mL) was added, and stirring at –78 °C was continued for 15 minutes. Triethylamine (14.3 mL, 103 mmol) was added and the temperature of the reaction was warmed to room temperature then further stirred at room temperature for 1 h. The reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate (50 mL) and extracted with dichloromethane (3 x 100 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (49:1 hexane:diethyl ether) gave the *title compound* (3.50 g, 54%) as a pale yellow oil. $\delta_H$ (400 MHz; $CDCl_3$) 9.33 (1H, s, CHO), 5.99 (2H, app. dt, *J* 10.3, 3.4, 2 x alkene CH), 5.45 (2H, app. dt, *J* 10.3, 2.0, 2 x alkene CH), 2.78 – 2.70 (2H, m, ring $CH_2$) and 1.23 (3H, s, $CH_3$).

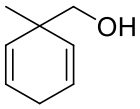
**Methyl 1-methylcyclohexa-2,5-dienecarboxylate (317)**[99]




**317**

1-Methylcyclohexa-2,5-dienecarboxylic acid (**149**) (15 g, 109 mmol) was dissolved in methanol (150 mL) and concentrated $H_2SO_4$ (0.45 mL, 4.59 mmol) was added. The mixture was heated and stirred for 6h. The solvent was removed, the residue was neutralised with saturated aqueous sodium hydrogen carbonate solution and extracted with $CH_2Cl_2$ (3 x 100 mL). The combined organic extracts was dried over $MgSO_4$ then concentrated *in vacuo* to give the *title compound* (14.0 g, 84 %) as a colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 5.85 – 5.74 (4H, m, 4 x alkene CH), 3.69 (3H, s, $OCH_3$), 2.70 – 2.61 (2H, m, $CH_2$) and 1.33 (3H, s, $CH_3$).

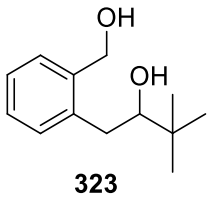
**(1-Methylcyclohexa-2,5-dienyl)methanol (318)**[101]




**318**

To a stirred suspension of $LiAlH_4$ (4.89 g, 129 mmol) in dry THF (100 mL) under a nitrogen atmosphere at 25 °C, was added a solution of methyl 1-methylcyclohexa-2,5-dienecarboxylate (**317**) (14.0 g, 92.1 mmol) in dry THF (20 mL). The reaction mixture was stirred at this temperature for 1 h, quenched with an aqueous solution of 15% NaOH (4.76 mL) and water (15.9 mL). The reaction mixture was then filtered and concentrated *in vacuo* to give the *title compound* (6.70 g, 59%) as a colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 5.95 – 5.87 (2H, m, 2 x alkene CH), 5.46 (2H, dt, *J* 10.5, 2.0, 2 x alkene CH), 3.32 (2H, s, $CH_2$) and 2.79 – 2.54 (2H, m, $CH_2$ ring).

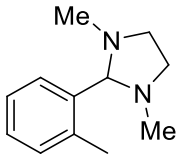
**1-(2-(Hydroxymethyl)phenyl)-3,3-dimethylbutan-2-ol (323)**[77]




**323**

Li metal (0.59 g, 21 mmol) was placed in a two-neck round-bottomed flask equipped with a reflux condenser and washed with THF (3 x 5 mL), then THF (15 mL) was added and the suspension was heated under an argon atmosphere. To the suspension, naphthalene (15.0 mg, 0.10 mmol) was added and the reaction mixture was stirred until a green colour change was observed. The reaction mixture was then cooled to 0 °C. Phthalan (0.49 mL, 4.00 mmol) was added and stirring was continued for 1.5 h. Pivalaldehyde (0.52 mL, 4.80 mmol) was added slowly and the reaction mixture was further stirred for 1 h. The reaction mixture was quenched with water (10 mL) and extracted with diethyl ether (3 x 20 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo* to give *the title compound* (0.90 g) as a beige solid. $\delta_H$ (400 MHz; $CDCl_3$) 7.33 – 7.27 (2H, m, 2 x CH), 7.24 – 7.19 (2H, m, 2 x CH), 4.84 (1H, d, *J* 11.8, CH of $CH_2$), 4.42 (1H, d, *J* 11.8, CH of $CH_2$), 3.42 (1H, dd, *J* 10.1, 2.8, C*H*-OH), 2.86 – 2.76 (2H, m, $CH_2$), 2.30 (2H, broad s, 2 x OH) and 1.02 (9H, s, 3 x $CH_3$).

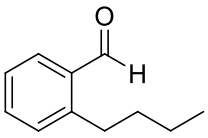
**1,3-Dimethyl-2-(2-methylphenyl)imidazolidine (328)**[80]




**328**

A solution of 2-methylbenzaldehyde (11.5 mL, 100 mmol), *N*,*N*'-dimethylenediamine (10.6 mL, 110 mmol) and *p*-toluenesulfonic acid (cat.) in toluene (300 mL) were heated under reflux for 5 h with removal of water *via* a Dean-Stark trap. The solution was cooled then the solvent removed *in vacuo*. Purification by distillation (bp 98-100 °C, 1.6 mm Hg) gave 1,3-dimethyl-2-(2-methylphenyl)imidazolidine (19.3 mL, 92%) as a colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 7.59 (1H, dd, *J* 7.3, 1.8, CH), 7.25 – 7.15 (2H, m, 2 x CH), 7.12 (1H, dd, *J* 7.3, 1.8), 3.72 (1H, s, CH), 3.41 – 3.35 (2H, m, 2 x CH cis to aryl), 2.63 – 2.57 (2H, m, 2 x CH trans to aryl), 2.41 (3H, s, $CH_3$) and 2.17 (6H, s, 2 x $CH_3$).

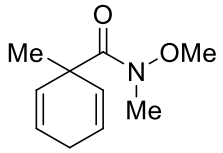
**2-Butylbenzaldehyde (332a)**[82]




**332a**

A solution of *n*-butyllithium (3.60 mL, 9.00 mmol, 2.5 M in hexane) was added to a mixture of 1,3-dimethyl-2-(2-methylphenyl)imidazolidine (**328**) (0.57 g, 3.00 mmol) and TMEDA (1.35 mL, 9.00 mmol) in diethyl ether (20 mL) and the reaction mixture was stirred for 1.5 h at 25 °C. 1-Bromopropane (0.54 mL, 6.00 mmol) was then added and the reaction mixture was further stirred for 1 h. The reaction mixture was quenched with an aqueous solution of 2M HCl (50 mL) then the solution was stirred for 10 minutes and extracted with diethyl ether (3 x 25 mL). The combined organic extract were dried over $Na_2SO_4$ and concentrated in *vacuo* to give the *title compound* (0.49 g, 100%) as a pale yellow oil. $\delta_H$ (400 MHz; $CDCl_3$) 10.3 (1H, s, CHO), 7.88 – 7.77 (1H, m, CH), 7.56 – 7.43 (1H, m, CH), 7.41 – 7.31 (2H, m, 2 x CH), 3.04 (2H, t, *J* 7.8, $CH_2$), 1.66 – 1.54 (2H, m, $CH_2$), 1.41 (2H, q, *J* 14.8, 7.4, $CH_2$) and 0.94 (3H, t, *J* 7.4, $CH_3$).

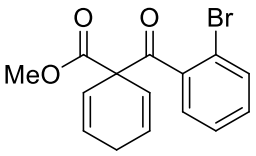
***N*-Methoxy-*N*,1-dimethylcyclohexa-2,5-dienecarboxamide (334)**




**334**

Dimethylformamide (0.5 mL) was added to a solution of oxalyl chloride (3.0 mL, 36 mmol) in dry $CH_2Cl_2$ (40 mL). After evolution of the gas had ceased, 1-methylcyclohexa-2,5-dienecarboxylic acid (**149**) (2.25 g, 16.30 mmol) in dry $CH_2Cl_2$ (10 mL) was added drop-wise and the reaction mixture was heated under reflux for 1 h. The solvent was removed *in vacuo* and the brown residue re-dissolved in dry diethyl ether (10 mL). The residue was added to a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (3.18 g, 32.6 mmol), $Na_2CO_3$ (6.18 g) and pyridine (cat.) in dry diethyl ether (40 mL). The resulting suspension was stirred for 24 h. The reaction mixture was quenched with water and extracted with diethyl ether (3 x 20 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo* to give the *title compound* (1.98 g, 67%) as a colourless oil. $\nu_{max}$ (neat) 3025, 2930, 1644, 1456 and 1421 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 5.75 – 5.69 (2H, m, 2 x alkene CH), 5.64 – 5.60 (2H, m, 2 x alkene CH), 3.57 (3H, s, $OCH_3$), 3.10 (3H, s, $NCH_3$), 2.60 (2H, m, $CH_2$), 1.25 (3H, s, $CH_3$); $\delta_C$ (100 MHz; $CDCl_3$) 174.5 (C=O) 129.1 (CH), 123.4 (CH), 60.8 ($CH_3$), 44.5 (C) 34.3 ($CH_3$), 27.5 ($CH_3$) and 26 ($CH_2$); *m/z* (ES) (%) 181 ($MH^+$, 5), 166 (5), 119 (5), 105 (100), 92 (85), 84 (75), 77 (75) and 65 (75).

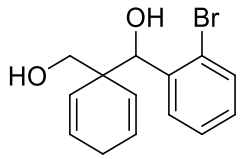
**Methyl 1-(2-bromobenzoyl)cyclohexa-2,5-dienecarboxylate (335)**[83]




**335**

A solution of *n*-butyllithium (2.09 mL, 4.18 mmol, 2.0 M in cyclohexane) was added to a solution of diisopropylamine (0.59 mL, 4.18 mmol) in THF (40 mL) at –78 °C and the reaction mixture was stirred for 30 minutes. Methyl cyclohexa-2,5-dienecarboxylate (**114**) (0.52 g, 3.80 mmol) in THF (1 mL) was added and the solution was stirred for 30 minutes. Then 2-bromobenzoyl chloride (0.59 mL, 4.52 mmol) was added and the reaction mixture was stirred for 1 h at –78 °C then 18 h at room temperature. The reaction was quenched with satuarated aqueous ammonium chloride solution (10 mL) and the product extracted into diethyl ether (3 x 40 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo* to give the *title compound* (1.27 g, 88%) as a colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 8.04 (1H, dd, *J* 8.4, 1.3, CH aromatic), 7.59 – 7.50 (2H, m, 2 x CH aromatic), 7.44 (1H, t, *J* 7.8, CH aromatic), 6.15 – 6.05 (2H, m, 2 x alkene CH), 6.00 (2H, app. dt, *J* 9.9, 3.1, 2 x alkene CH), 3.81 (3H, s, $CH_3$-O) and 2.78 – 2.45 (2H, m, $CH_2$ ring).

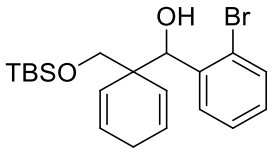
**(2-Bromophenyl)-(1-(hydroxymethyl)cyclohexa-2,5-dienyl)methanol (336)**[83]




**336**

Methyl 1-(2-bromobenzoyl)cyclohexa-2,5-dienecarboxylate (**335**) (1.26 g, 3.92 mmol) in THF (5 mL) was added to a suspension of $LiAlH_4$ (0.60 g, 15.7 mmol) in THF (40 mL) at room temperature and the solution was stirred for 30 minutes. The reaction was quenched with aqueous 2 M NaOH solution (3 mL), dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. Purification by flash column chromatography (1:1 hexane:ethyl acetate) gave *the title compound* (0.43 g, 37%) as a colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 7.55 – 7.45 (2H, m, 2 x CH aromatic), 7.31 – 7.26 (1H, m, CH aromatic), 7.14 – 7.07 (1H, m, CH aromatic), 6.12 – 6.05 (1H, m, CH alkene), 5.95 – 5.80 (2H, m, 2 x CH alkene), 5.63 (1H, app. ddd, *J* 10.3, 4.1, 2.1, CH alkene), 5.29 (1H, d, *J* 3.0 C*H*-OH), 3.86 (1H, dd, J 10.5, 5.8, 1H of C$H_2$-OH), 2.57 (1H, dd, *J* 10.5, 6.2, 1H of C$H_2$-OH), 2.65 – 2.49 (2H, m, $CH_2$ ring), 2.41 – 2.26 (1H, m, OH) and 1.88 (1H, app. broad s, OH).

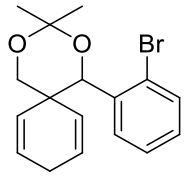
**(2-Bromophenyl)(1-((*tert*-butyldimethylsilyloxy)methyl)cyclohexa-2,5-dienyl)methanol (337)**




**337**

*tert*-Butyldimethylsilyl chloride (0.57 g, 3.80 mmol) was added to a solution of (2-bromophenyl)(1-(hydroxymethyl)cyclohexa-2,5-dienyl)methanol (**336**) (1.02 g, 3.46 mmol) in dichloromethane (40 mL). Triethylamine (0.53 mL, 3.80 mmol) was added followed by 4-DMAP (10 mg) and the reaction mixture was stirred for 24 h. The reaction was quenched with 2 M aq. HCl (15 mL) and the product extracted into dichloromethane (3 x 40 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (4:1 hexane:ethyl acetate) gave the *title compound* (0.80 g, 57%) as a colourless oil (Found: M, 409.1191. $C_{20}H_{30}O_2Si^{79}Br$ requires M, 409.1198); $\nu_{max}$ (neat) 3465, 2928, 1471, 1256, 1099, 837 and 745 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 7.53 (1H, dd, *J* 7.9, 1.7, CH aromatic), 7.44 (1H, dd, *J* 8.0, 1.2, CH aromatic), 7.25 – 7.20 (1H, m, CH aromatic), 7.09 – 7.03 (1H, m CH aromatic), 6.00 (1H, app. ddd, *J* 10.3, 3.9, 2.0, CH alkene), 5.89 (1H, dt, *J* 10.4, 3.2, CH alkene), 5.69 (1H, ddd, *J* 10.2, 3.9, 2.0, CH alkene), 5.62 – 5.54 (1H, m, CH), 5.47 (1H, s, C*H*-OH), 3.81 (1H, d, *J* 9.5, 1H of C*H*-OH), 3.74 (1H, d, *J* 9.5, 1H of C$H_2$-OH), 2.52 (1H, m, 1H of $CH_2$ ring), 2.17 – 1.99 (1H, m, 1H of $CH_2$ ring), 0.96 (9H, s, 3 x $CH_3$), 0.15 (3H, s, $CH_3$) and 0.12 (3H, s, $CH_3$); $\delta_C$ (125 MHz; $CDCl_3$) 140.5 (C), 131.9 (CH), 130.1 (CH), 128.5 (CH), 127.5 (CH), 126.6 (CH), 126.4 (CH), 126.0 (CH), 125.1 (CH), 77.9 (CH), 71.9 ($CH_2$), 46.9 (C), 26.8 ($CH_2$), 25.9 ($CH_3$) and –5.6 ($CH_3$); *m/z* ($AP^+$) (%) 412.1 (37) 411.1 ($^{81}$Br-M, 98) and 409.1 ($^{79}$Br-M, 100).

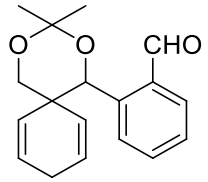
**1-(2-Bromophenyl)-3,3-dimethyl-2,4-dioxaspiro[5.5]undeca-7,10-diene (340)**[83]




**340**

2,2-Dimethoxypropane (3.22 g, 26.3 mmol) was added to a solution of (2-bromophenyl)(1-(hydroxymethyl)cyclohexa-2,5-dienyl)methanol (**337**) (1.55 g, 5.25 mmol) and camphorsulfonic acid (0.05 g, 0.21 mmol) in acetone (100 mL) and the reaction was heated for 48 h. The solvent was removed, the reaction was neutralised with saturated aqueous $NaHCO_3$ solution (20 mL) and then extracted with dichloromethane (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (20:1 hexane:diethyl ether) gave the *title compound* (1.07 g, 61%) as a colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 7.50 – 7.40 (2H, m, 2 x CH aromatic), 7.23 (1H, d, *J* 7.4, CH aromatic), 7.12 – 7.03 (1H, m, CH), 6.38 – 6.25 (1H, m, CH alkene), 5.80 – 5.56 (3H, m, 3 x CH alkene), 5.44 (1H, s, CH), 4.05 (1H, d, *J* 11.3, CH of $CH_2$), 3.64 (1H, d, *J* 11.3, CH of $CH_2$) 2.46 – 2.35 (1H, m, 1 H of $CH_2$ ring), 2.02 – 1.92 (1H, m, 1 H of $CH_2$ ring) 1.59 (3H, s, $CH_3$) and 1.56 (3H, s, $CH_3$).

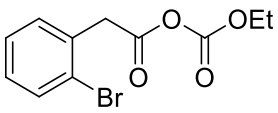
**2-(3,3-Dimethyl-2,4-dioxaspiro[5.5]undeca-7,10-dien-1-yl)benzaldehyde (341)**




**341**

A solution of *n*-butyllithium (0.59 mL, 1.18 mmol, 2.0 M in cyclohexane) was added to a solution of 1-(2-bromophenyl)-3,3-dimethyl-2,4-dioxaspiro[5.5]undeca-7,10-diene (**340**) (360 mg, 1.07 mmol) in THF (4 mL) at –78 °C and the reaction mixture was stirred for 2 h. Dimethylformamide (0.09 mL, 1.18 mmol) was added and the reaction mixture was stirred for 30 minutes at –78 °C and then warmed to room temperature. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (1 mL) and the product was extracted into dichloromethane (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (4:1 hexane:ethyl acetate) gave the *title compound* (80 mg, 26%) as a colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 10.3 (1H, s, CHO), 7.74 (1H, dd, *J* 7.7, 1.3, CH aromatic), 7.58 (1H, d, *J* 7.8, CH aromatic), 7.43 – 7.36 (2H, m, 2 x CH alkene), 6.26 – 6.15 (1H, m, CH alkene), 5.98 (1H, s, CH), 5.71 – 5.59 (2H, m, 2 x CH alkene), 5.41 (1H, dd, *J* 10.1, 1.8, CH alkene), 4.07 (1H, d, *J* 11.4, CH of $CH_2$), 3.68 (1H, d, *J* 11.4, CH of $CH_2$), 1.64 (3H, s, $CH_3$) 2.37 – 2.23 (1H, m, 1 H of $CH_2$ ring), 1.75 – 1.63 (1H, m, 1 H of $CH_2$ ring) and 1.57 (3H, s, $CH_3$). $\delta_C$ (75 MHz; $CDCl_3$) missing C=O, 156.2 (C), 131.0 (CH), 129.5 (CH), 129.0 (CH), 127.0 (CH), 126.1 (CH), 124.0 (CH), 120.7, 117.5 (CH), 116.0 (CH), 82.0 (CH), 69.5 ($CH_2$), 29.5 ($CH_3$), 26.5 ($CH_2$) and 18.0 ($CH_3$).

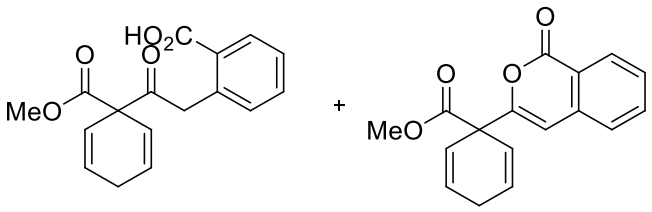
**2-(2-Bromophenyl)acetic (ethyl carbonic) anhydride (342)**




**342**

Triethylamine (0.45 mL, 3.26 mmol) was added to a stirred solution of 2-bromophenyl acetic acid (0.50 g, 2.33 mmol) in THF (40 mL) at 0 °C and the solution was stirred for 5 minutes. Ethyl chloroformate (0.33 mL, 3.50 mmol) was added and the reaction mixture was further stirred for 90 minutes. The solvent was removed *in vacuo* and diethyl ether (30 mL) was added. The reaction was quenched with 2 M HCl (10 mL). The organic layer was washed with saturated aqueous $Na_2CO_3$ solution (2 x 25 mL) and water (2 x 25 mL), dried over $MgSO_4$ and concentrated in *vacuo* to give the *title compound* (0.44 g, 67%) as a colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 7.57 (1H, d, J 7.8, CH aromatic), 7.30 – 7.27 (2H, m, 2 x CH), 7.18 – 7.11 (1H, m, CH), 4.19 (2H, q, *J* 7.1, $CH_2$-O), 3.78 (2H, s, $CH_2C$=O) and 1.27 (3H, t, *J* 7.1, $CH_3$).

**2-(2-(1-(methoxycarbonyl)cyclohexa-2,5-dienyl)-2-oxoethyl)benzoic acid (346) and methyl 1-(1-oxo-1H-isochromen-3-yl)cyclohexa-2,5-dienecarboxylate (347)**

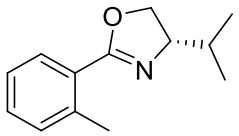



**346** **347**

*n*-Butyllithium (2.83 mL, 5.66 mmol, 2.0 M in cyclohexane) was added to a solution of diisopropylamine (0.80 mL, 5.66 mmol) in THF (50 mL) at –78 ° C and the solution was stirred for 30 minutes. Methyl cyclohexa-2,5-dienecarboxylate (**114**) (0.71 g, 5.14 mmol) in THF (2 mL) was added and the reaction mixture was further stirred for 30 minutes. Then homophthalic anhydride (1.00 g, 6.17 mmol) in THF (2 mL) was added and the reaction mixture was stirred for 1 h at –78 °C then 18 h at room temperature. The reaction mixture was quenched with saturated aqueous ammonium chloride solution (20 mL) and the product extracted into diethyl ether (3 x 40 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated in *vacuo*. Purification by flash column chromatography (4:1 hexane:ethyl acetate) gave a mixture (3:2) of compounds **346** and **347** (0.40 g) as a clear oil. $\delta_H$ (400 MHz; $CDCl_3$) 10.9 (1H, broad s, OH), 8.06 – 8.02 (1H, m, CH), 7.97 – 7.95 (1H, m, CH), 7.59 – 7.53 (3H, m, 3 x CH), 7.47 – 7.43 (2H, m, 2 x CH), 6.96 – 6.92 (1H, m, CH), 6.37 (1H, ddd, *J* 9.9, 3.5, 1.8, alkene CH **347**), 5.94 – 5.86 (4H, m, 2 x alkene CH from **346** and 2 x alkene CH from **347**), 5.85 – 5.79 (4H, m, 2 x alkene CH from **346** and 2 x alkene CH from **347**), 3.92 (2H, s, $CH_2$ from **346**), 3.72 (6H, s, $OCH_3$ from **346** and $OCH_3$ from **347**) and 2.74 (4H, m, 2 x $CH_2$ alkene from **346** and **347**).

## 8.5. Experimental Data for Chapter 6

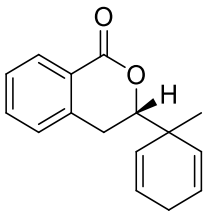
### (4*S*)-2-(2-methylphenyl)-4-(prop-2-yl)-4,5-dihydrooxazole (348)[83]



**348**

Thionyl chloride (18 mL, 248 mmol) was added drop-wise to (2*S*)-*N*-(1-hydroxy-3-methylbutan-2-yl)-2-methylbenzamide (5.70 g, 25.8 mmol) and was stirred for 1 h. Methanol (18 mL) was then added at 0 °C to decompose the thionyl chloride, then the solution was made basic with 10% aqueous KOH. The solution was further stirred for 1 h at 25 °C then extracted with dichloromethane (3 x 30 mL). The combined organic extracts were washed with brine (2 x 30 mL) and dried over $Na_2SO_4$ before being concentrating *in vacuo*. Purification by flash column chromatography (20:1 hexane:diethyl ether) gave the *title compound* (2.41 g, 46%) as a colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 7.78 (1H, d, *J* 7.8, CH), 7.36 – 7.28 (1H, m, CH), 7.25 – 7.18 (2H, m, 2 x CH), 4.38 (1H, td, *J* 7.2, 1.4, CH), 4.21 – 4.07 (2H, m, $CH_2$), 2.58 (3H, s, $CH_3$), 1.94 – 1.81 (1H, m, CH), 1.04 (3H, d, *J* 6.8, $CH_3$) and 0.96 (3H, d, *J* 6.8, $CH_3$).

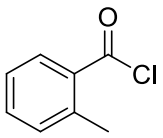
**(3*S*)-3-(1-Methylcyclohexa-2,5-dienyl)isochroman-1-one (350)**



**350**

A solution of *sec*-BuLi (1.17 mL, 1.2 M in cyclohexane, 1.40 mmol) was added to (4*S*)-4-(prop-2-yl)-2-(2-methylphenyl)-4,5-dihydrooxazole (**348**) (238 mg, 1.17 mmol) in dry diethyl ether (10 mL) at –78 °C under an argon atmosphere. After stirring for 1 h at this temperature, TMEDA (0.26 mL, 1.76 mmol) was added and the reaction mixture was stirred for another 1 h at –78 °C. Then a solution of 1-methylcyclohexa-2,5-dienecarbaldehyde (186 mg, 1.52 mmol) in dry diethyl ether (2 mL) was added and the resulting solution was further stirred for 1 h. The reaction mixture was quenched with water (10 mL) at –78 °C then warmed to room temperature. The product was extracted with diethyl ether (3 x 15 mL), dried over $Na_2SO_4$ and concentrated *in vacuo* to give (1*S*)-2-(2-((4*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)phenyl)-1-(1-methylcyclohexa-2,5-dienyl)ethanol as a pale oil. Purification by flash column chromatography (5:1 hexane: diethyl ether) gave 3-(1-methylcyclohexa-2,5-dienyl)isochroman-1-one (**350**) (281 mg, 45%) as a colourless oil (Found: $MH^+$, 241.1218. $C_{16}H_{17}O_2$ requires M, 241.1229); $\nu_{max}$ (nujol) 3024, 2962 and 1728 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 8.00 (1H, s, CH), 7.45 (1H, d, *J* 7.5, CH), 7.25 (1H, d, *J* 7.6, CH), 7.10 (1H, d, *J* 7.6, CH), 5.80 – 5.90 (2H, m, alkene, 2 x CH), 5.78 – 5.65 (1H, m, alkene, CH), 5.40 – 5.35 (1H, m, alkene, CH), 4.20 – 4.12 (1H, m, CH), 2.95 – 2.70 (2H, dd, *J* 2.8, 13.3, ring $CH_2$), 2.63 – 2.55 (2H, s, $CH_2$) and 1.20 (3H, s, $CH_3$); $\delta_C$ (100 MHz; $CDCl_3$) 165.9 (C=O) 139.4 (C), 130.2 (CH), 130.1 (CH), 128.6 (CH), 127.5 (CH), 125.7 (CH), 84.6 ($CH_2$), 29.9 (CH), 26.7 ($CH_2$) and 14.1 ($CH_3$); *m/z* (ES) (%) 481 ($2MH^+$, 8%), 242 (14), 241 ($MH^+$, 76) and 223 (100).

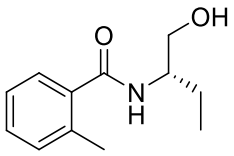
**2-Methylbenzoyl chloride (357)**[85]



**357**

Oxalyl chloride (5.12 mL, 80.8 mmol) was added drop-wise to a solution of 2-methylbenzoic acid (10.0 g, 73.5 mmol) in dry dichloromethane (100 mL) under a nitrogen atmosphere. A catalytic amount of dimethylformamide (3 drops) was added and the mixture was left to stir at room temperature for 4h. The solvent was removed under reduced pressure to give 2 methylbenzoyl chloride (11.1 g, 98%) as a pale yellow oil. $\delta_H$ (400 MHz; $CDCl_3$) 8.23 (1H, dd, *J* 8.0, 1.3, CH), 7.52 (1H td, *J* 7.5, 1.3, CH), 7.38 – 7.33 (1H, m, CH), 7.32 – 7.27 (1H, m, CH) and 2.58 (3H, s, $CH_3$).

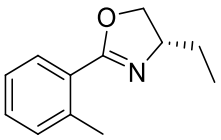
**(*S*)-*N*-(1-Hydroxybut-2-yl)-2-methylbenzamide (358)**[100]



**358**

A solution of 2-methylbenzoyl chloride (**357**) (10.0 g, 64.7 mmol) in dry THF (80 mL) was added drop-wise to a mixed solution of (*S*)-2-aminobutan-1-ol (5.50 mL, 58.3 mmol) and triethylamine (9.92 mL, 71.2 mmol) in dry THF (80 mL) at 0 °C. The mixture was stirred for 1h, then saturated aqueous sodium hydrogen carbonate (20 mL) was added and the solvent was concentrated in vacuo. The residue was extracted with dichloromethane (3 x 50 mL) and washed with brine (2 x 50 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo* to give the *title compound* (10.7 g, 80%) as a beige solid. $\delta_H$ (400 MHz; $CDCl_3$) 7.38 – 7.27 (2H, m, 2 x CH), 7.22 – 7.16 (2H, m, 2 x CH), 6.02 (1H, d, *J* 6.7, NH), 4.09 – 3.96 (1H, m, C*H*-NH), 3.76 (1H, dd, *J* 11.1, 3.5, 1H of $CH_2$), 3.65 (1H, dd, *J* 11.1, 5.5, 1H of $CH_2$), 2.60 (1H, broad s, OH), 2.43 (3H, s, $CH_3$), 1.75 – 1.49 (2H, m, $CH_2$) and 1.01 (3H, t, *J* 7.5, $CH_3$).

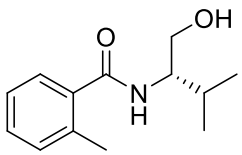
**(*S*)-4-Ethyl-2-(2-methylphenyl)4,5-dihydrooxazole (359)**



**359**

Triethylamine (2.78 mL, 20.0 mmol) and methanesulfonyl chloride (0.77 mL, 10.0 mmol) was added to a solution of (*S*)-*N*-(1-hydroxybutan-2-yl)-2-methylbenzamide (**358**) (2.00 g, 10.0 mmol) in dichloromethane (15 mL) at 25 °C and stirred for 16 h. Dichloromethane (20 mL) was added and the mixture was washed with saturated aqueous sodium hydrogen carbonate (2 x 25 mL), dried over $Na_2SO_4$ and concentrated *in vacuo* to give the *title compound* (1.91 g, 100%) as white crystals. m.p 120 – 121 °C (Found: M, 189.1151. $C_{12}H_{15}NO$ requires M, 189.1154); $\nu_{max}$ (nujol) 3062, 2963, 1645 and 775 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 7.43 – 7.22 (4H, m, 4 x CH), 4.31 – 4.41 (1H, m, CH), 3.90 – 3.72 (2H, dd, *J* 3.3, $CH_2$), 2.46 (3H, s, ring $CH_3$), 1.83 – 1.69 (2H, m, $CH_2$) and 1.10 – 1.00 (3H, t, *J* 7.4, $CH_3$); $\delta_C$ (125 MHz; $CDCl_3$), 136.3 (CH), 136.1 (C), 131.0 (CH), 130.0 (CH), 126.7 (CH), 125.8 (CH), 51.1 (CH), 47.7 ($CH_3$), 25.0 ($CH_3$), 19.8 ($CH_2$) and 10.4 ($CH_2$); *m/z* (ES) (%) 189 ($M^+$, 31), 160 (35), 132 (23), 105 (19) and 84 (100).

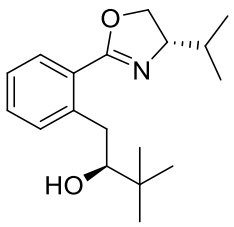
**(*S*)-*N*-(1-hydroxy-3-methylbut-2-yl)-2-methylbenzamide (360)**[85]




**360**

A solution of 2-methylbenzoyl chloride (**357**) (5 g, 32.4 mmol) in dry THF (40 mL) was added drop-wise to a mixed solution of (*S*)-2-amino-3-methyl-butan-1-ol (3.20 mL, 29.1 mmol) and triethylamine (4.96 mL, 35.6 mmol) in dry THF (40 mL) at 0 °C. The mixture was stirred for 1 h, then saturated aqueous sodium hydrogen carbonate was added and the solvent concentrated in vacuo. The residue was extracted with dichloromethane (3 x 25 mL) and washed with brine (2 x 25 mL). The combined organic extracts were dried over $Na_2SO_4$ and concentrated *in vacuo* to give *the title compound* (7.00 g, 98 %) as a white solid. $\delta_H$ (400 MHz; $CDCl_3$) 8.05 (1H, dd, *J* 7.8, 1.2, CH), 7.51 (1H, dt, *J* 7.5, 1.4, CH), 7.40 – 7.28 (2H, m, 2 x CH), 5.95 (1H, s, NH), 4.00 – 3.90 (1H, m, C*H*-NH), 3.83 (1H, dd, *J* 11.1, 3.5, 1H of $CH_2$), 3.76 (1H, dd, *J* 11.1, 6.0, 1H of $CH_2$), 2.46 (3H, s, $CH_3$), 2.03 – 1.94 (1H, m, CH), 1.04 (3H, d, *J* 6.5, $CH_3$) and 1.02 (3H, d, *J* 6.3, $CH_3$).

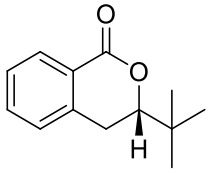
**(2*S*)-1-(2-((4*S*)-4-Isopropyl-4,5-dihydrooxazol-2-yl)phenyl)-3,3-dimethylbutan-2-ol (361)**[83]




**361**

A solution of *sec*-butyllithium (1.2 M in cyclohexane, 2.00 mL, 2.40 mmol) was added to a solution of (4*S*)-2-(2-methylphenyl)-4-(prop-2-yl)-4,5-dihydrooxazole (**348**) (0.41 g, 2.00 mmol) in dry diethyl ether (40 mL) at –78 °C and stirred for 1h. TMEDA (0.45 mL, 3.00 mmol) was then added and the reaction mixture was stirred for 1 h before adding pivalaldehyde (0.28 ml, 2.60 mmol) and stirring was continued for 1 h. The solution was quenched with water (5 mL) and the product extracted with diethyl ether (3 x 40 mL). The combined organic extracts were dried over $MgSO_4$ before concentrating *in vacuo* to give the *title compound* (0.53 g, 92 %) as a colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 7.41 (1H, app. td, *J* 7.6, 1.5, CH), 7.29 (1H, app. td, *J* 7.6, 1.3, CH), 7.25 – 7.18 (2H, m, 2 x CH), 6.43 (1H, d, *J* 5.0, OH), 4.42 (1H, dd, *J* 9.5, 8.1, CH), 4.22 (1H, ddd, *J* 9.6, 7.7, 5.5, CH), 4.13 (2H, m, $CH_2$-O), 3.43 – 3.35 (2H, m, C*H*-OH + 1H of $CH_2$), 2.77 (1H, d, *J* 10.8, 1H of $CH_2$), 1.96 – 1.80 (1H, m, CH) and 1.05 – 0.97 (15H, m, 5 x $CH_3$).

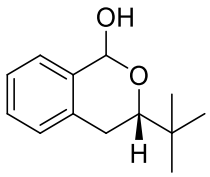
**(3*S*)-3-*tert*-butylisochroman-1-one (362)**[83]



**362**

(2*S*)-1-(2-((4*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)phenyl)-3,3-dimethylbutan-2-ol (**354**) (0.42 g, 1.45 mmol) was added to a mixed solution (18.0 mL) of (THF-$H_2O$-TFA 10:1.5:0.5) at 0 °C and stirred for 24 h. The solution was quenched with saturated aqueous $NaHCO_3$ solution (6 mL) and the product was extracted with diethyl ether (3 x 30 mL). The combined organic extracts was washed with brine (2 x 30 mL) and dried over $MgSO_4$ before concentrating *in vacuo* to give the *title compound* (0.28 g, 69 %) as a colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 8.09 (1H, dd, *J* 7.8, 1.1, CH), 7.52 (1H, td, *J* 7.5, 1.4, CH), 7.38 (1H, td, *J* 7.6, 1.0, CH), 7.27 – 7.24 (1H, m, CH), 4.17 (1H, dd, *J* 12.9, 2.7, CH), 3.02 (1H, dd, *J* 16.1, 12.9, 1H of $CH_2$), 2.84 (1H, dd, *J* 16.1, 2.7, 1H of $CH_2$) and 1.08 (9H, s, 3 x $CH_3$).

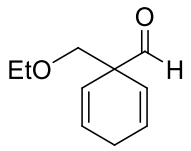
**(3*S*)-3-*tert*-butylisochroman-1-ol (363)**




**363**

A solution of diisobutyl aluminium hydride (1.0 M in hexane, 1.61 mL, 1.61 mmol) was added to a stirred solution of (3*S*)-3-*tert*-butylisochroman-1-one (**362**) (0.15 g, 0.73 mmol) in toluene (22 mL) at –78 °C and stirred for 30 minutes. The solution was quenched by slow addition of methanol (0.02 mL) and cold 10% aq. HCl (0.5 mL) and the product was extracted with diethyl ether (3 x 25 mL). The combined organic extracts was dried over $MgSO_4$ before concentrating *in vacuo* to give *the title compound* (93.1 mg, 62 %) as a colourless oil (Found: M, 206.1303. $C_{13}H_{18}O_2$ requires M, 206.1307) $\nu_{max}$ (neat) 3375, 2955, 2871, 1460, 1363, 1069 and 745 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 7.33 – 7.21 (4H, m, 4 x CH), 6.05 (1H, d, *J* 4.3, CH), 3.85 (1H, dd, *J* 11.7, 2.9, OH), 2.81 – 2.77 (1H, m, CH), 2.65 (1H, d, *J* 2.9, 1H of $CH_2$), 2.61 (1H, d, *J* 2.9, 1H of $CH_2$) and 1.01 (9H, s, 3 x $CH_3$); $\delta_C$ (125 MHz) (Missing 1 x C), 135.0 (C), 129.0 (CH), 128.7 (CH), 127.9 (CH), 127.3 (CH), 92.1 (CH), 74.5 (CH), 34.0 (C), 28.5 ($CH_2$) and 26.3 ($CH_3$); *m/z* (ES) (%) 206.1 (M, 8), 189.1 (15), 188.1 (M – $H_2O$, 100), 173.1 (100), and 155.1 (55).

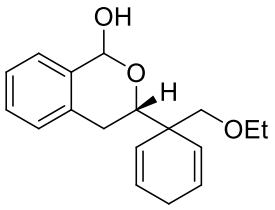
**1-(Ethoxymethyl)cyclohexa-2,5-dienecarbaldehyde (369)**




**369**

To a stirred solution of dimethyl sulphoxide (2.50 mL, 35.2 mmol) in dry dichloromethane (40 mL) at –78 °C, oxalyl chloride (1.30 mL, 15.4 mmol) was added and stirred for 10 minutes. Then a solution of (1-(ethoxymethyl)cyclohexa-2,5-dienyl)methanol (**374**) (0.74 g, 4.40 mL) in dichloromethane (2 mL) was added and stirred for a further 10 minutes before adding triethylamine (9.20 mL, 66 mmol). The solution was warmed to 25 °C and stirred for 2 h. The reaction was quenched by pouring into saturated aqueous $NaHCO_3$ solution (25 mL) and the product extracted with dichloromethane (3 x 40 mL). The combined organic extracts were washed with brine (2 x 40 mL) and dried over $MgSO_4$ before concentrating *in vacuo*. Purification by flash column chromatography (20:1 diethyl ether) gave the *title compound* (0.58 g, 79 %) as a colourless oil (Found: $M^+$, 166.0996. $C_{10}H_{14}O_2$ requires M, 166.0994); $\nu_{max}$ (neat) 2977, 2870, 1727, 1116 and 709 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 9.44 (1H, s, CHO), 6.05 (2H, dt, *J* 10.4, 3.4, 2 x alkene CH), 5.68 (2H, dt, *J* 10.4, 2.0, 2 x alkene CH), 3.60 (2H, s, $CH_2$-O), 3.49 (2H, q, *J* 7.0, $CH_2$), 2.77 – 2.73 (2H, m, $CH_2$ ring) and 1.16 (3H, t, *J* 7.0, $CH_3$); $\delta_C$ (125 MHz; $CDCl_3$) 199.6 (CHO), 128.6 (CH), 123.0 (CH), 74.0 ($CH_2$), 67.2 ($CH_2$), 54.7 (C), 26.8 ($CH_2$) and 14.9 ($CH_3$); *m/z* (ES) (%) 166.1 ($MH^+$, 7%), 136.1 (19), 120.1 (9), 107.0 (88) and 92.0 (100).

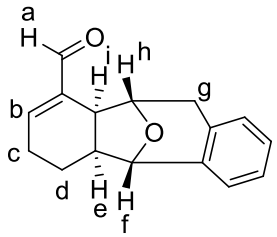
**(3*S*)-3-(1-(Ethoxymethyl)cyclohexa-2,5-dienyl)isochroman-1-ol (370)**




**370**

A solution of diisobutyl aluminium hydride (1.0 M in hexane, 0.62 mL, 0.62 mmol) was added to a stirred solution of (3*S*)-3-(1-(ethoxymethyl)cyclohexa-2,5-dienyl)isochroman-1-one (**383**) (80.0 mg, 0.28 mmol) in toluene (8.4 mL) at –78 °C and was stirred for 30 minutes. The solution was quenched by slow addition of methanol (0.01 mL) and cold 10% HCl (0.2 mL) and the product was extracted into diethyl ether (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*, to give the *title compound* (80.1 mg, 100%) as a colourless oil (Found: M – $H_2O$, 268.1461. $C_{18}H_{20}O_2$ requires M, 268.1463); $\nu_{max}$ (neat) 3399, 3027, 2866, 1112 and 736 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 7.31 – 7.25 (2H, m, CH), 7.25 – 7.19 (2H, m, 2 x CH), 6.03 (1H, s, C*H*-OH), 5.95 (2H, td, *J* 11.2, 2.2, 2 x alkene CH), 5.68 (2H, dt, *J* 10, 2.0, 2 x alkene CH), 4.33 (1H, dd, *J* 11.9, 2.9, CH), 3.65 (1H, d, *J* 8.9, 1H of $CH_2$), 3.53 (2H, q, *J* 7.0, $CH_2$), 3.40 (1H, d, *J* 8.9, 1H of $CH_2$), 2.76 – 2.70 (3H, m, $CH_2$ ring and 1H of $CH_2$), 2.55 (1H, dd, *J* 16.6, 2.9, 1H of $CH_2$) and 1.17 (3H, t, *J* 7.0, $CH_3$); $\delta_C$ (125 MHz; $CDCl_3$) 138.0 (C), 136.0 (C), 129.0 (CH), 128.4 (CH), 128.2 (CH), 127.8 (CH), 127.1 (CH), 126.8 (CH), 126.1 (CH), 125.9 (CH), 91.8 (CH), 75.0 ($CH_2$), 69.0 (CH), 67.1 ($CH_2$), 44.5 (C), 29.5 ($CH_2$), 27.2 ($CH_2$) and 15.0 ($CH_3$); *m/z* (ES) (%) 268.1 (M – $H_2O$, 57), 209.1 (100) 208.1 (60), 179.1 (88) and 178.1 (83).

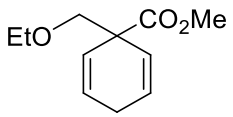
**Prins reaction of (3*S*)-3-(1-(ethoxymethyl)cyclohexa-2,5-dienyl)isochroman-1-ol (370)**




**378**

Trifluoromethanesulfonic acid (0.02 mL, 0.28 mmol) was added to a solution of (3*S*)-3-(1-(ethoxymethyl)cyclohexa-2,5-dienyl)isochroman-1-ol (**370**) (80.1 mg, 0.28 mmol) in dichloromethane (5 mL) at 0 °C and the resulting solution was stirred at 25 °C for 30 minutes. The solution was quenched with saturated aqueous $NaHCO_3$ solution (2 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (1:1 hexane: diethyl ether) gave compound **378** (34.4 mg, 55%) as a colourless oil (Found: $MH^+$, 241.1228. $C_{16}H_{17}O_2$ requires M, 241.1229); $\nu_{max}$ (neat) 2934, 1678, 1203, 912 and 732 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 9.49 (1H, s, C*H*O), 7.21 – 7.15 (1H, m, CH), 7.15 – 7.09 (2H, m, 2 x CH), 7.04 – 7.00 (1H, m, CH), 7.00 – 6.97 (1H, m, alkene CH), 4.71 (1H, app. s, C*H*O), 4.41 – 4.31 (1H, m, C*H*O), 3.32 (1H, dd, *J* 16.5, 4.8, CH of $CH_2C$=C), 3.01 (1H, d, *J* 16.5,CH of $CH_2C$=C), 2.83 – 2.69 (1H, m, ring junction CH), 2.50 – 2.37 (2H, m, ring junction CH and one of $CH_2$), 2.27 – 2.12 (1H, m, one of $CH_2$), 1.99 (1H, app. dtd, *J* 13.0, 5.1, 2.8, 1H of $CH_2$) and 1.73 – 1.64 (1H, m, one of $CH_2$); $\delta_C$ (125 MHz; $CDCl_3$) 194.5 (C=O), 151.6 (CH), 142.9 (C), 140.0 (C), 132.4 (C), 129.6 (CH), 127.3 (CH), 125.7 (CH), 124.3 (CH), 82.1 (CH), 79.8 (CH), 47.5 (CH), 39.3 (CH), 36.2 ($CH_2$), 25.3 ($CH_2$) and 24.9 ($CH_2$); *m/z* (TOF) (%) 282.1 (M + MeCN , 100) and 241.1 ($MH^+$, 12).

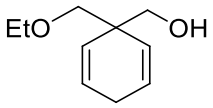
**Methyl 1-(ethoxymethyl)cyclohexa-2,5-dienecarboxylate (380)**




**380**

Ammonia (500 mL) was condensed (dry-ice/acetone condenser) into a 500 mL round bottomed flask containing benzoic acid (10.0 g, 82.0 mmol) at –78 °C. Lithium metal (1.6 g, 230 mmol) was added portion-wise to the stirred suspension until a permanent blue colour was observed and then stirring was continued for 15 minutes. Chloromethyl ethyl ether (21.7 mL, 234 mmol) was added slowly over 1 h and the ammonia was left to evaporate overnight. The residue was dissolved in ice-cold water (200 mL) and then treated with sulfuric acid (conc., approx. 100 mL) until pH 1 – 2 was reached. The product was then extracted into diethyl ether (3 x 200 mL). The combined organic extracts was dried over $MgSO_4$, filtered and concentrated *in vacuo.* The residue was re-dissolved in methanol (100 mL) and treated with concentrated sulfuric acid (0.16 mL, 3.05 mmol) and the solution was stirred at 25 °C for 17 h. The solvent was removed *in vacuo* and dichloromethane (100 mL) was added. The solution was neutralised with saturated aqueous $NaHCO_3$ solution and the aqueous layer was extracted into dichloromethane (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash column chromatography (5:1 hexane:diethyl ether) gave the *title compound* (7.18 g, 57%) as a colourless oil (Found: $MH^+$, 197.1183. $C_{11}H_{17}O_3$ requires M, 197.1178); $\nu_{max}$ (neat) 2976, 2866, 1734, 1434, 1221, 1116 and 705 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 5.92 (2H, app. dt, *J* 10.5, 3.2, 2 x alkene CH), 5.85 (2H, app. dt, *J* 10.5, 1.8, 2 x alkene CH), 3.71 (3H, s, $CH_3O$), 3.53 (2H, s, $CH_2O$), 3.48 (2H, q, *J* 7.0, $CH_2$), 2.73 – 2.65 (2H, m, ring $CH_2$) and 1.14 (3H, t, *J* 7.0, $CH_3$); $\delta_C$ (125 MHz; $CDCl_3$) 173.8 (C=O), 126.3 (CH), 125.3 (CH), 77.0 ($CH_2$), 67.0 ($CH_2$), 52.2 ($OCH_3$), 49.5 (C), 26.3 ($CH_2$) and 14.9 ($CH_3$); *m/z* (ES) (%) 197.1 ($MH^+$, 18), 133.1 (20), 132.1 (100) and 91.1 (39).

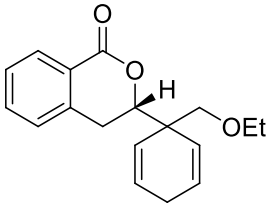
**(1-(Ethoxymethyl)cyclohexa-2,5-dienyl)methanol (381)**




**381**

A solution of methyl 1-(ethoxymethyl)cyclohexa-2,5-dienecarboxylate (**373**) (1.00 g, 5.10 mmol) in THF (5 mL) was added drop-wise to a suspension of $LiAlH_4$ (0.39 g, 10.2 mmol) in THF (20 mL) at 0 °C. The solution was stirred for 1 h at 25 °C. The reaction was then quenched with an aqueous solution of 15% NaOH (0.33 mL) and water (1.10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give the *title compound* (0.74 g, 99%) as a colourless oil. $\nu_{max}$ (neat) 3399, 2975, 2866, 1423, 1116 and 711 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 5.93 (2H, dt, *J* 10.4, 3.3, 2 x alkene CH), 5.65 (2H, dt, *J* 10.4, 2.0, 2 x alkene CH), 3.56 (2H, s, $CH_2$-O), 3.47 (2H, q, *J* 7.0, $CH_2$), 3.37 (2H, s, $CH_2$-OH), 2.65 – 2.74 (2H, app. m, $CH_2$ ring) and 1.18 (3H, t, *J* 7.0, $CH_3$); $\delta_C$ (125 MHz; $CDCl_3$) 127.5 (CH), 126.9 (CH), 77.3 ($CH_2$), 69.3 ($CH_2$), 67.2 ($CH_2$), 43.0 (C), 27.0 ($CH_2$) and 15.0 ($CH_3$).

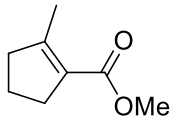
**(3*S*)-3-(1-(Ethoxymethyl)cyclohexa-2,5-dienyl)isochroman-1-one (383)**




**383**

A solution of *sec*-butyllithium (1.2 M in cyclohexane, 1.34 mL, 1.61 mmol) was added to a mixture of oxazoline (**348**) (0.27 g, 1.34 mmol) in dry diethyl ether (20 mL) at –78 °C and the resulting solution was stirred for 1 h. TMEDA (0.30 mL, 2.01 mmol) was added and the reaction mixture was stirred for 1 h before adding 1-(ethoxymethyl)cyclohexa-2,5-dienecarbaldehyde (**369**) (0.29 g, 1.75 mmol) in THF (2 mL). Then the solution was stirred for a further 1 h. The reaction mixture was warmed to 25 °C over 1 h, quenched with water (5 mL) and then the product was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$ before concentrating *in vacuo*. Purification by flash column chromatography (5:1 diethyl ether) gave a 2:1 mixture of (2*S*)-1-(1-(ethoxymethyl)cyclohexa-2,5-dienyl)-2-(2-((4*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)phenyl)-ethanol (**382**) and (3*S*)-3-(1-(ethoxymethyl)cyclohexa-2,5-dienyl)isochroman-1-one (**383**). This mixture of compounds **382** and **383** (0.19 g, 0.51 mmol) was added to a mixed solution (6.40 mL) of (THF-$H_2O$-TFA 10:1.5:0.5) at 0 °C and the resulting solution was stirred for 24 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (2 mL) and extracted with diethyl ether (3 x 10 mL). The combined organic extracts was washed with brine (2 x 10 mL) and dried over $MgSO_4$ before concentrating *in vacuo*. Purification by flash column chromatography (5:1 diethyl ether) gave the *title compound* (99.4 mg, 45%) as colourless oil (Found: $MH^+$, 285.1499. $C_{18}H_{21}O_3$ requires M, 285.1491); $\nu_{max}$ (neat) 2974, 2866, 1732, 1460, 1117 and 739 $cm^{-1}$; $\delta_H$ (400 MHz; $CDCl_3$) 8.07 (1H, dd, *J* 7.8, 1.1, CH), 7.50 (1H, app. td, *J* 7.5, 1.4, CH), 7.36 (1H, *J* 7.6, CH), 7.20 (1H, d, *J* 7.6, CH), 6.06 – 5.93 (2H, m, 2 x alkene CH), 5.78 – 5.68 (2H, m, 2 x alkene CH), 4.72 (1H, dd, *J* 13.1, 2.8, CH), 3.80 (1H, d, *J* 8.9, one of $CH_2O$), 3.53 – 3.48 (2H, m, $CH_2$-O), 3.34 (1H, d, *J* 8.9, one of $CH_2O$), 3.09 – 2.94 (2H, m, $CH_2$ ring), 2.76 – 2.71 (2H, m, $CH_2$ ring) and 1.15 (3H, t, *J* 7.0, $CH_3$); $\delta_C$ (125 MHz; $CDCl_3$) (Missing C=O and C), 140.0 (C), 133.5 (CH), 130.2 (CH), 128.1 (CH), 127.5 (CH), 127.3 (CH), 127.1 (CH), 126.9 (CH), 125.0 (CH), 79.5 (CH), 74.0 ($CH_2$), 66.9 ($CH_2$), 44.5 (C), 29.4 ($CH_2$), 27.1 ($CH_2$) and 15.1 ($CH_3$); *m/z* (ES) (%) 285.1 ($MH^+$, 20), 240.1 (22), 239.1 (100) and 221.1 (40).

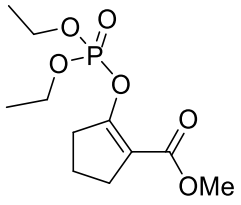
**Methyl 2-methylcyclopent-1-enecarboxylate (384)**[86]




**384**

A solution of methyllithium (24.6 mL, 39.3 mmol, 1.6 M in diethyl ether) was added to a solution of copper iodide (3.73 g, 19.6 mmol) in diethyl ether (25 mL) at 0 °C. The reaction mixture was cooled to -40 °C before adding methyl 2-(diethoxyphosphoryloxy)cyclopent-1-enecarboxylate (**387**) (3.91 g, 14.0 mmol) in diethyl ether (15 mL) drop-wise. Stirring was continued at this temperature for 3 h. The mixture was then poured into a flask containing ice-cold 5% HCl (35 mL) saturated with NaCl and stirred in an ice-bath for 5 – 10 mins. 15% Aqueous ammonia (70 mL) was then added to the grey suspension and the mixture was swirled vigorously until the organic layer turned bright blue. The product was extracted with diethyl ether (3 x 50 mL). The combined organic extracts was washed with brine (2 x 30 mL) and dried over $MgSO_4$ before concentrating *in vacuo*. Purification by flash column chromatography (1:1 hexane:dichloromethane) gave the *title compound* (0.66 g, 33 %) as colourless oil. $\delta_H$ (400 MHz; $CDCl_3$) 3.72 (3H, s, $CH_3$-O), 2.61 (2H, ddq, *J* 7.8, 6.3, 2.1, $CH_2$), 2.52 – 2.42 (2H, m, $CH_2$), 2.10 (3H, tt, *J* 2.0, 1.2, $CH_3$) and 1.88 – 1.73 (2H, m, $CH_2$).

**Methyl 2-(diethoxyphosphoryloxy)cyclopent-1-enecarboxylate (387)**[86]




**387**

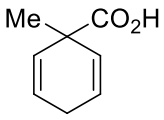
Sodium hydride (57-60%) dispersion in mineral oil (1.85 g, 30.9 mmol) was placed in a 250 mL roundbottom flask flushed with nitrogen and washed with anhydrous diethyl ether (4 x 10 mL), diluted with diethyl ether (120 mL) and cooled to 0 °C. Methyl-2-oxocyclo-pentanecarboxylate (3.47 mL, 28.1 mmol) in diethyl ether (5 mL) was added, allowing the evolution of hydrogen and then stirred for 30 minutes. Diethyl chlorophosphate (4.20 mL, 29.0 mmol) was added and stirred at 25 °C for 3 h. Solid $NH_4Cl$ (0.6 g) was then added and stirring was continued for 30 minutes. The resulting suspension was filtered and concentrated *in vacuo* to give the *title compound* (7.80 g) as a white solid. $\delta_H$ (400 MHz; $CDCl_3$) 4.40 – 4.11 (4H, m, 2 x $CH_2$-O), 3.71 (3H, s, $CH_3$-O), 2.38 – 2.19 (4H, m, 2 x $CH_2$), 1.98 – 1.79 (2H, m, $CH_2$) and 1.41 – 1.32 (6H, m, 2 x $CH_3$).

# Appendix A

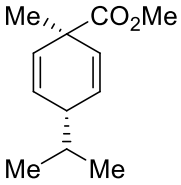
# Compound Lists

**Appendix A – Compound Lists**

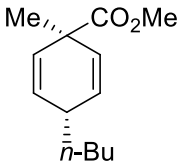
**Appendix A-1 – Compound List for Chapter 3**



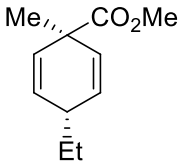
**149**



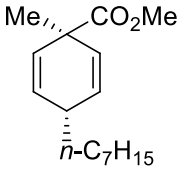
**187a**



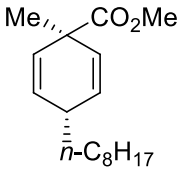
**187c**



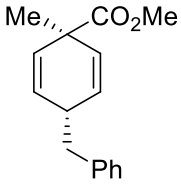
**187d**



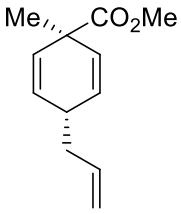
**187e**



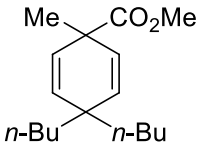
**187f**



**187g**



**187h**



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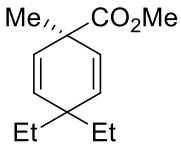
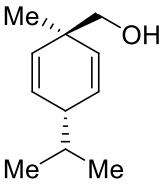
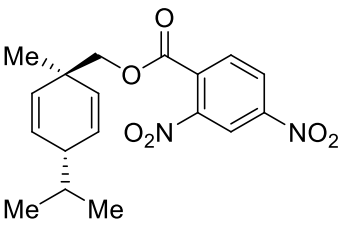


**190d**

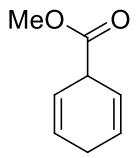


**188**

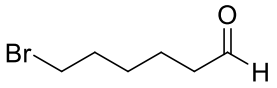


**189**

**Appendix A-2 – Compound List for Chapter 4**




**114**

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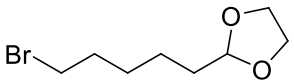


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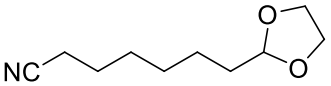


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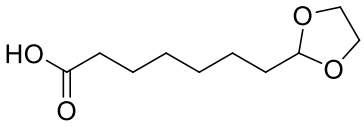
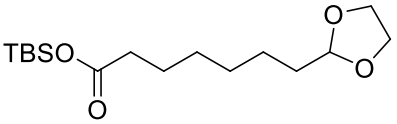



**197**

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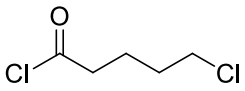


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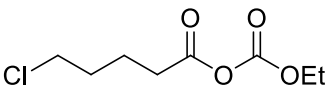


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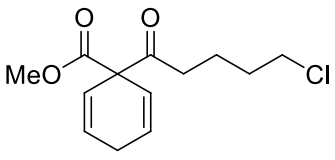


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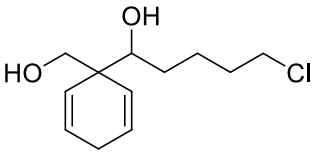


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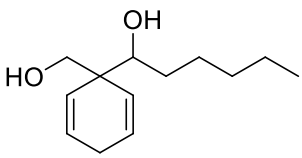


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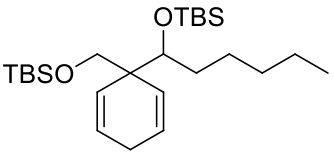


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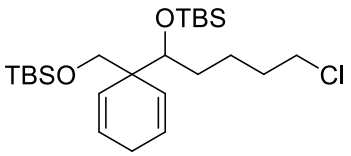


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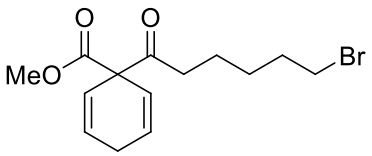


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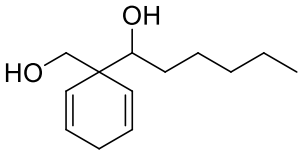


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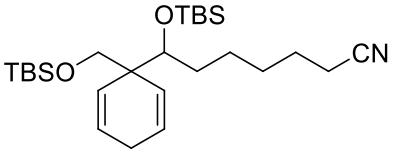


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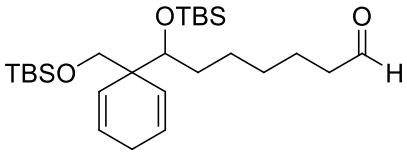


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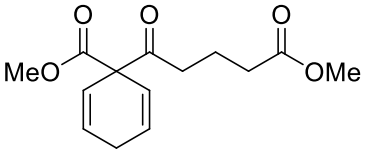


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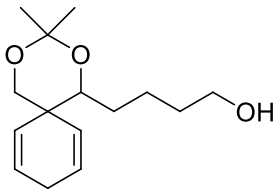


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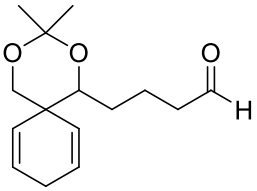


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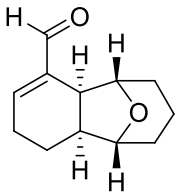


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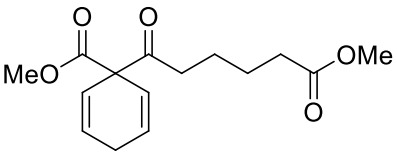


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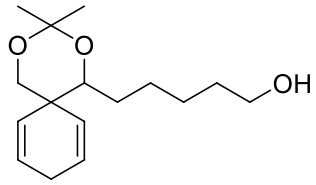

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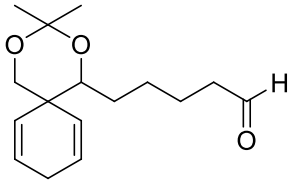

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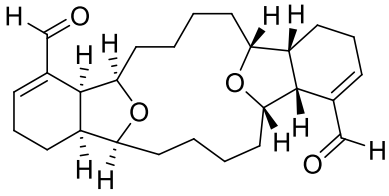

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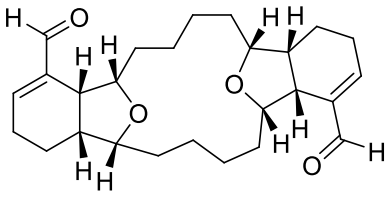

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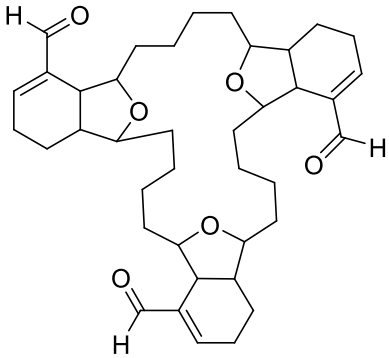

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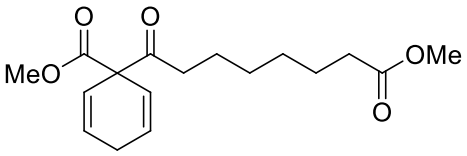

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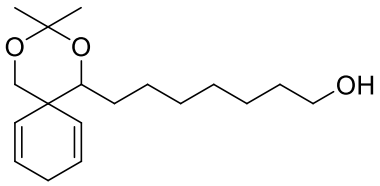

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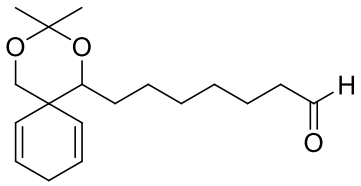

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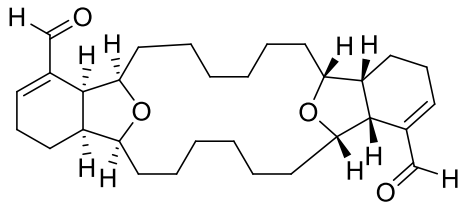

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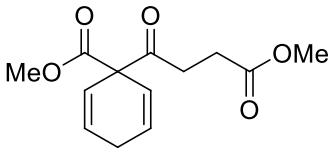

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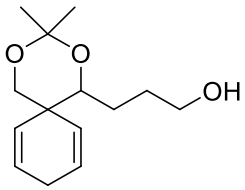

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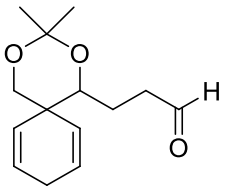
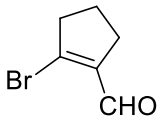


**261**

**Appendix A-3 – Compound List for Chapter 5**

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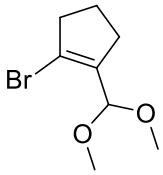


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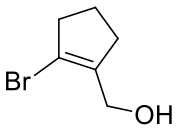


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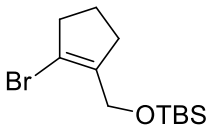


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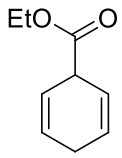


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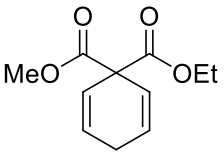


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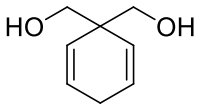
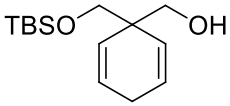
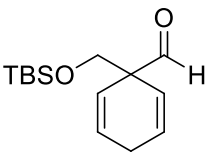



**283**




**284**

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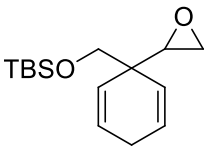


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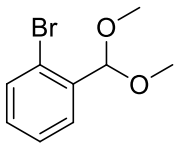


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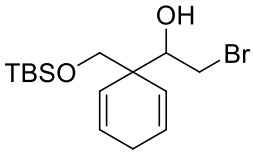


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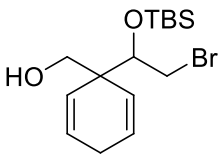


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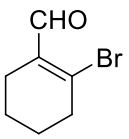


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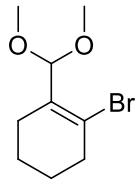


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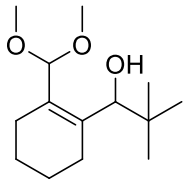


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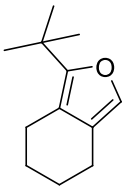


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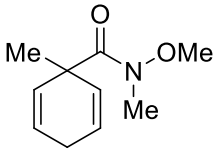


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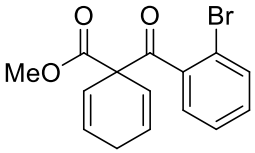


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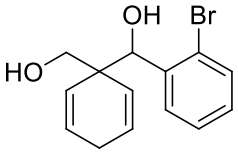


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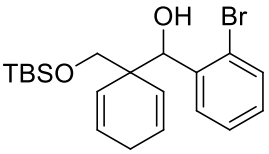


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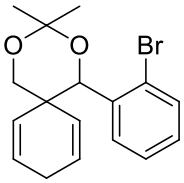


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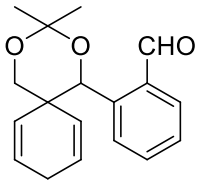


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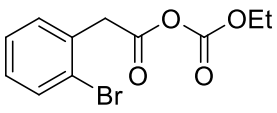


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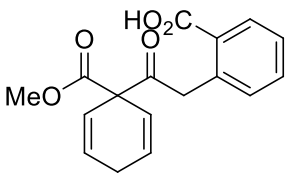


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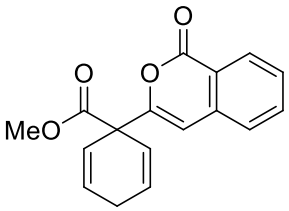


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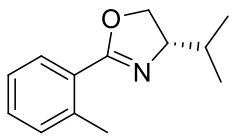
**Appendix A-4 – Compound List for Chapter 6**

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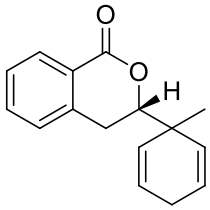


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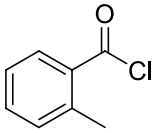


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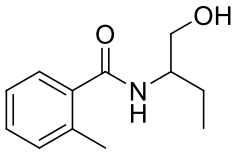


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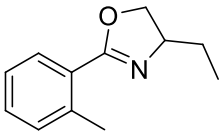


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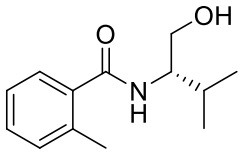


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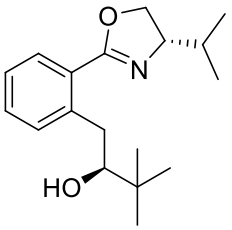


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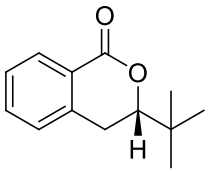


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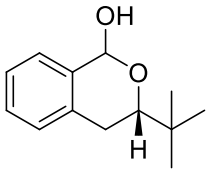


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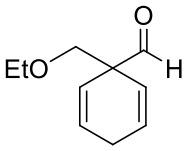


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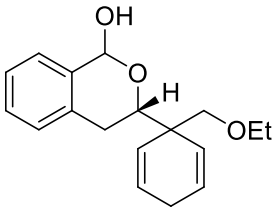


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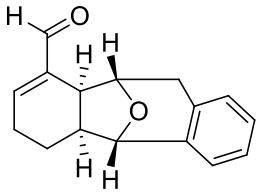


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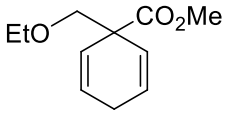


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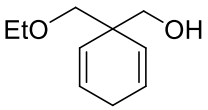


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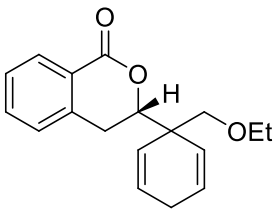


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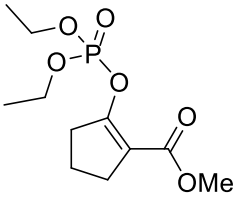


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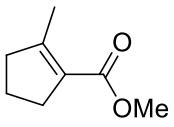


**384**

# Appendix B

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**Appendix B- References**


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