
# Oxidative Radical Cyclisations for Total Synthesis

Steven J. Ferrara

Somerville College

University of Oxford

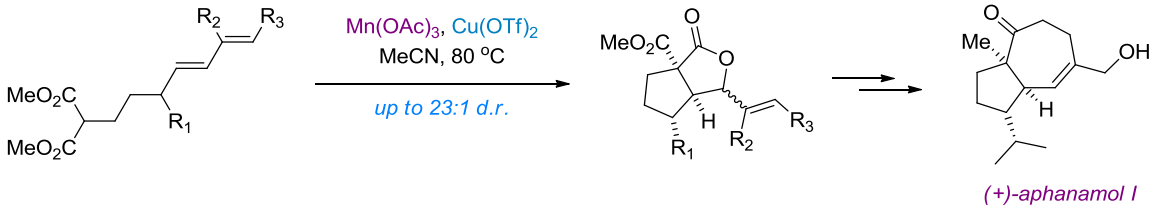
Hilary 2013

A thesis submitted in partial fulfilment of the requirements for the degree of

Doctor of Philosophy (D.Phil)

# Abstract

Manganese(III) acetate mediated radical cyclisations provide a mild and powerful tool in the construction of complex bicyclic systems. This thesis focuses on the formation of a number of alkenyl substituted [3.3.0]-bicyclic *γ*-lactones utilising a manganese(III) acetate/copper(II) triflate induced radical cyclisation. The methodology was then applied to a short catalytic and enantioselective synthesis of (+)-aphanamol I and related natural products.




*(+)-aphanamol I*

Chapter 1 presents a summary of the theories and methodology which will be utilised in this work. In particular, a key focus will revolve around oxidative radical cyclisations and how manganese(III) acetate has become a vital oxidant in such areas.

Chapter 2 details a catalytic and asymmetric total synthesis of (+)-aphanamol I. Following an overview of the natural product and its previous total synthesis, a racemic and asymmetric total synthesis is presented which utilises a manganese(III) acetate mediated radical cyclisation and a Claisen ring expansion as key steps.

Chapter 3 reports the synthesis and subsequent cyclisation of a wide range of dienyl malonate substrates. Variation of the γ-substituent is first explored, demonstrating the effect that substituent size has on the diastereoselectivity of the cyclisation. Following this, the synthesis of [2.3.0]-, [4.3.0]- and [5.3.0]- bicyclic *γ*-lactones are investigated.

Chapter 4 describes studies towards the total synthesis of a dolabellane natural product. Investigations into substrate synthesis which can be used in a RCM will be presented.

Full experimental details and spectral data, with select NMR spectra are also provided.

# Declaration

The work described in this thesis is entirely the work of the author except where specifically indicated and does not include any collaborative research.

This thesis has not been previously submitted for a degree, diploma, or any other qualification at the University of Oxford or elsewhere.

Steven J. Ferrara

January 2013

# Acknowledgments

Firstly, I would like to thank Dr Jonathan Burton for providing me with the opportunity to work in his research group over the past three years. The constant support, enthusiasm and commitment you have shown to both me and the wider group may at times be taken for granted, but I can assure you we are all appreciative of this.

I would also like to thank all the members of the Burton group both past and present who I have shared this experience with for making G4 such an enjoyable place to be. In particular I must thank Gus and Wilfried for all the insightful discussions and advice they have provided me with. Thanks are also extended to Jon, Gus and Emma for kindly taking the time to proof read this thesis – any mistakes which remain are of course, entirely my fault.

Thanks are extended to all the CRL support staff in particular the analytical staff. Whilst it is all to easy to undervalue their input into our projects, they provide and maintain vital resources, without which this project will have not been possible.

Thank you to all my friends both in and outside Oxford or their support, laughter and memories they have bought – I cannot express my gratitude enough.

Finally, I must thank my parents Karen and Giuseppe who have provided all the support, encouragement and assistance when needed. Fifteen years you gave up everything so that Steph and I could realise everything we wanted to. I hope we have and continue to make you proud parents with our achievements. Steph we may fight and argue all the time, but I couldn't and wouldn't ask for any other Sister if I had the choice. To my granddad David, whilst you may not have had the chance to go to University, you are still an extremely inspirational man who I admire and look up to. Hopefully you have been able to live the experience through me.

I guess what I really want to say is "You guys are all great!" and I wish you all the best in the future!

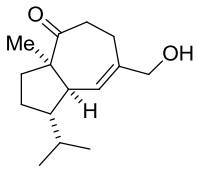
# Abbreviations

| | |
|---|---|
| **°C** | Degree(s) Celsius |
| **$\delta_C$** | $^{13}C$ chemical shift |
| **$\delta_H$** | $^{1}H$ chemical shift |
| **Ac** | Acetyl |
| **AIBN** | Azobisisobutyronitrile |
| **Ar** | Aryl |
| **aq.** | Aqueous |
| **BAIB** | bisacetoxyiodobenzene |
| **Bn** | Benzyl |
| **BINAP** | 2,2'-bis-1,1'-binaphthyl |
| **Bu** | Butyl |
| **CD** | Circular dichroism spectroscopy |
| **$cm^{-1}$** | Per centimetre |
| **COSY** | Correlation spectroscopy |
| **Cp** | Cyclopentadienyl |
| **d.r.** | Diastereomeric ratio |
| **DCM** | Dichloromethane |
| **DiBAl-H** | Diisobutylaluminium hydride |
| **DMF** | Dimethylformamide |
| **DMM** | Dimethyl malonate |
| **DMSO** | Dimethyl sulfoxide |
| **ee** | Enantiomeric excess |
| **$ESI^+$** | Electrospray ionisation (positive mode) |
| **Et** | Ethyl |
| **FGI** | Functional Group Interconversion |
| **FI** | Field ionisation |
| **h** | Hour(s) |
| **HPLC** | High-performance liquid chromatography |
| **HRMS** | High resolution mass spectrometry |
| **HSQC** | Heteronuclear single quantum coherence spectroscopy |
| **Hz** | Hertz |
| **IBX** | 2-Iodoxybenzoic acid |

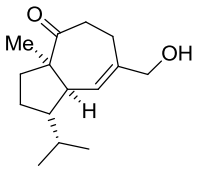
| | |
|---|---|
| **IR** | Infrared |
| **L** | Litre(s) |
| **LIDAKOR** | LDA/Bu$^t$OK |
| **LRMS** | Low resolution mass spectrometry |
| **M** | Molar |
| ***m/z*** | Mass to charge ratio |
| **Me** | Methyl |
| **min** | Minute(s) |
| **mol** | Mole(s) |
| **m.p.** | Melting Point |
| **Ms** | Methanesulfonyl |
| **NMR** | Nuclear magnetic resonance |
| **nOe** | Nuclear overhauser effect |
| **PG** | Protecting group |
| **PMB** | 4-Methoxybenzyl |
| **Ppm** | Parts per million |
| **Pr** | Propyl |
| ***quant.*** | Quantative yield |
| **R** | Alkyl (not H unless specified otherwise) |
| **RCM** | Ring-closing metathesis |
| $R_f$ | Retention factor |
| **RT** | Room temperature |
| **sat.** | Saturated |
| **SET** | Single electron transfer |
| **SOMO** | Singly occupied molecular orbital |
| t | *tert-* |
| **TBS** | *tert*-Butyldimethylsilyl |
| **TBDPS** | *tert*-Butyldiphenylsilyl |
| **TEMPO** | (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl |
| **THF** | Tetrahydrofuran |
| **TIPS** | Triisopropylsilyl |
| **TMS** | Trimethylsilyl |
| **TS** | 4-methylbenzenesulfonyl |
| $\nu_{max}$ | Absorption maxima |
| **µ** | Micro- |

# Stereochemistry

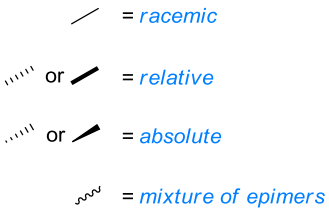
Due to the nature of the work presented in this thesis, the following representations will be used to indicate stereochemistry. All stereocenters which are racemic will be represented by a solid bond. In the case of the racemic bicyclic systems, hashed and bold bonds will be used to indicate relative configuration, but does not represent any stereochemistry at that stereocenter. When a mixture of diastereoisomers is presented a wavy bond will be used to indicate a mixture of epimers at that stereocentre relative to other stereocenters. All enantio enriched material will be represented by a wedged bond which infers the absolute configuration at that stereocenter. So for example in (±)-aphanamol I, hashed bonds are used to indicate the relative stereochemistry at the three stereocenters despite it being racemic. However in (+)-aphanamol I, a hashed wedge bond indicates the absolute configuration at that stereocenter.




*(±)-aphanamol I*




*(+)-aphanamol I*



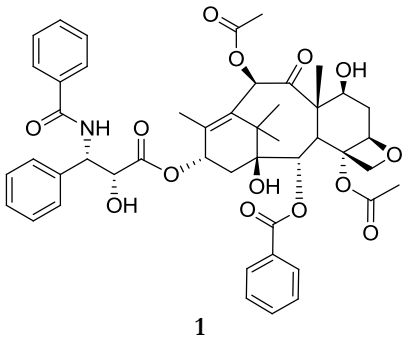
# Table of Contents

# CHAPTER 1: Introduction

The purpose of this thesis is to further explore the manganese(III) acetate-mediated oxidative radical cyclisation of alkenyl malonates for the synthesis of bicyclic *γ*-lactones, which have been shown to be useful synthetic building blocks applicable in natural product synthesis. The development of such methodology and its application in the total synthesis of several terpenoid natural products, including (+)-aphanamol I will be presented and discussed. This chapter will focus on the importance of natural product synthesis and how free radicals can play a key role in complex ring formation, specifically the use of manganese(III) acetate in such transformations.

## 1.1. Natural products

The synthesis of complex organic structures isolated from nature has played a critical role in advancing our understanding of synthetic organic chemistry. These relatively small molecules continue to be one of the major sources of inspiration in drug discovery, with many FDA pharmaceuticals derived from biologically active natural products.[1] For example, Paclitaxel (1) [**Figure 1.1**] which was isolated for its medicinal properties from the pacific yew tree *Taxus brevifolia*,[2] is a mitotic inhibitor considered the gold standard for the treatment of breast, colon, lung and ovarian cancers.[3]




**1**

**Figure 1.1: Structure of Paclitaxel, a natural product of key synthetic interest.**

The motivation behind the total synthesis of such natural products has traditionally revolved around further understanding their biological action, however in the case of Paclitaxel, an efficient total/partial synthesis also comes with great commercial benefit. As a result, there are thousands of reported total syntheses of organic structures found in nature, which are generally categorised according to their structural type such as the alkaloids, carbohydrates, flavonoids, steroids and terpenoids to name but a few.

### 1.1.1. Terpene natural product family

Originally named after turpentine, a volatile oil isolated from pine trees, the terpene natural product family is a large and diverse class of complex organic compounds isolated from a wide variety of organisms.[4] A common feature of all terpenes is an aliphatic core with a scattering of double bonds and rings, few functional groups and an abundance of methyl groups. Early on Wallach, a pioneer in terpene synthesis, recognised that the majority of isolated terpene natural products appeared to be multiples of a common $C_5$ precursor.[5] Thus, it was suggested that biosynthetically terpenes might arise from repeat units of isoprene, termed the "isoprene rule". Whilst of great value in structure determination, isoprene itself is not the biological building block used in the construction of terpenes. In 1955, $^{14}C$ labelling experiments showed that the steroid skeleton of cholesterol was constructed from repeat units of acetic acid, with mevalonic acid formally identified as the common building block. Accordingly, Ruzicka proposed a biosynthetic pathway which utilised mevalonic acid as a starting precursor for terpene synthesis [**Figure 1.2**].[6] The primary alcohol of mevalonic acid (2) is pyrophosphorylated by adenosine triphosphate (ATP) to give pyrophosphate 3. Subsequent elimination of carbon dioxide and the tertiary alcohol leads to isopentenyl pyrophosphate (IPP, 4) which can equilibrate to dimethylallyl pyrophosphate (DMAPP, 5) by a simple allylic proton transfer. Nucleophilic attack of IPP (4) onto the more electrophilic DMAPP (5) generates geranyl pyrophosphate (GPP, 6) which is a common building block for all monoterpenes. For example, GPP (6) can be cyclised to give the monoterpenoid

limonene (9), found in the rind of various citrus fruits.[7] However, GPP itself cannot be the cyclisation precursor as it has a *trans* double bond. Thus, GPP (6) undergoes an isomerisation to give tertiary pyrophosphate 7 *via* an allylic rearrangement, which now allows for free rotation about the single bond. Subsequent cyclisation of 7 in the presence of limonene synthase gives carbocation 8, which can lose a proton to give the *exo*-alkene found in limonene.

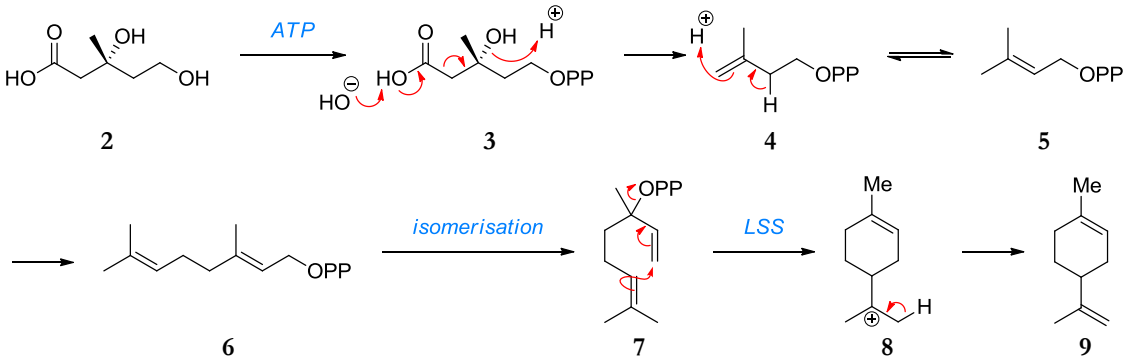


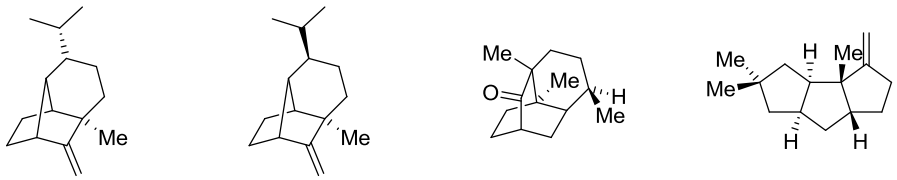

**Figure 1.2: Biosynthetic pathway involved in the synthesis of limonene.**

As chains of recurring isoprene units are built up, the resulting terpenes are classified sequentially by size as hemiterpenes, monoterpenes, sesquiterpenes and diterpenes to name but a few. The prefix in the name refers to the number of terpene units needed to assemble the molecule i.e. humulene, a member of the sesquiterpene family, is constructed from one and a half terpene units i.e. three isoprene units.

## 1.2. Radical based cyclisation reactions

As stated above, a common feature of terpene natural products is the presence of aliphatic cores, in particular complex polycyclic cores. The construction of such ring systems is one of the more challenging and intriguing aspects of synthetic organic synthesis. Historically, radical cyclisation methodology has played an important role in the synthesis of carbo- and heterocyclic systems.[8] As shown [**Figure 1.3**], some early examples of syntheses in which a radical cyclisation was utilised as a key step in natural product synthesis include Bazuki's synthesis of sativene (**10**) and capacamphene (**11**),[9] Stork's synthesis of norseychellanone (**12**)[10] and Curran's synthesis of

hirsutene (**13**).[11] Prime motivations for the use of free radicals include the inherently high reactivity of carbon radicals and low susceptibility to steric interactions.



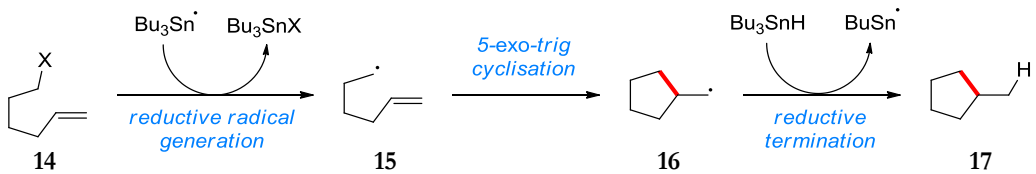

**10** **11** **12** **13**

**Figure 1.3: Examples of natural products synthesised utilising a radical cyclisation as a key step.**

Generally, radical cyclisations involve the intramolecular attack of a free radical onto an alkene, forming a cyclic compound from an acyclic precursor. The three main categories of radical cyclisation are reductive, atom transfer and oxidative. For the purpose of this thesis, a brief overview will be given of both reductive and atom transfer radical cyclisations, whilst a more detailed review of oxidative radical cyclisations will be carried out.

### 1.2.1. Reductive cyclisation

The majority of radical cyclisations reported in the literature involve the formal reduction of a C-X bond (see **14**) [**Figure 1.4**], typically by a trialkyl tin radical generated *in-situ* by a radical initiator such as AIBN, peroxide or UV light.[12] Radical **15** then undergoes a 5-*exo*-trig cyclisation in accordance with Baldwin's rules,[13] to give primary radical **16**. Subsequent hydrogen abstraction from another trialkyl stannane gives cyclopentane **17** and regenerates the tin radical. Other methods for radical generation have also been developed, most notably the use of silicon hydrides, although these methods tend to be less used due to the high reliability of the tin hydride method.[14]




**14** **15** **16** **17**

**Figure 1.4: Reductive radical cyclisation using tributyl stannane.**

In addition to using an extremely toxic organotin species in stoichiometric quantities, reductive radical cyclisations have two significant drawbacks. Firstly, the radical precursor

(halogen) has been replaced with hydrogen in the cyclised product with one equivalent of $Bu_3SnX$ produced as a waste by-product, which is atom uneconomical.[15] Secondly, the oxidation level of cyclopentane **17** has been reduced relative to alkene **14**, which is seen to be undesirable if such chemistry is to be used in a multi-step synthesis and is not in keeping with the principle of redox economy.[16] Thus, reductive radical cyclisations do not meet such criteria when designing efficient multi-step syntheses, as the functionality of **17** has been reduced with respect to **14**.

### 1.2.2. Atom transfer cyclisation

Atom transfer cyclisations provide a convenient method for the construction of ring systems with a wide range of metal catalysts reported,[17] in particular copper(I) based halogen complexes.[18] Atom transfer cyclisations rely on redox reactions between copper(I) and copper(II) oxidation states [**Figure 1.5**]. Thus, radical generation is reductive in nature as chlorine abstraction from halide **18** to give radical **15** oxidises copper(I) to copper(II). After cyclisation to give primary radical **16**, oxidative termination forms halide **19** and reduces copper(II) back to copper(I) rendering the reaction catalytic in copper. Although such transformations are catalytic in metal, refunctionalisation of radical **16** as the halide is required, which limits the possible termination pathways of the cyclisation.

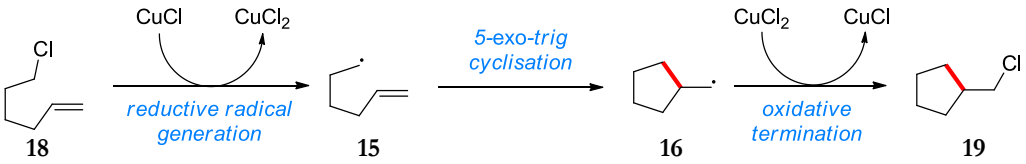



**Figure 1.5: Atom transfer radical cyclisation.**

### 1.2.3. Oxidative radical cyclisation

Alternatively, the required radical for cyclisation can be formed oxidatively through the loss of a hydrogen atom, or more practically *via* the loss of a proton followed by oxidation of the resulting anion [**Figure 1.6**].[19] Hydrogen abstraction from the relatively unfunctionalised alkene **20**, gives radical **15**, which can cyclise to give adduct radical **16**. Although reductive termination to give

cyclopentane **17** is possible (typically through hydrogen abstraction from the solvent), oxidative termination generally provides structurally more useful intermediates. Thus, primary radical **16** can be further oxidised to the formal carbocation **21**, which can either be trapped by a nucleophile to give **22** or eliminate a proton to generate *exo*-alkene **23**. In contrast to the overall two electron reduction of a reductive cyclisation, such oxidative radical cyclisations result in a two electron oxidation, producing a product which is more highly functionalised then the substrate.

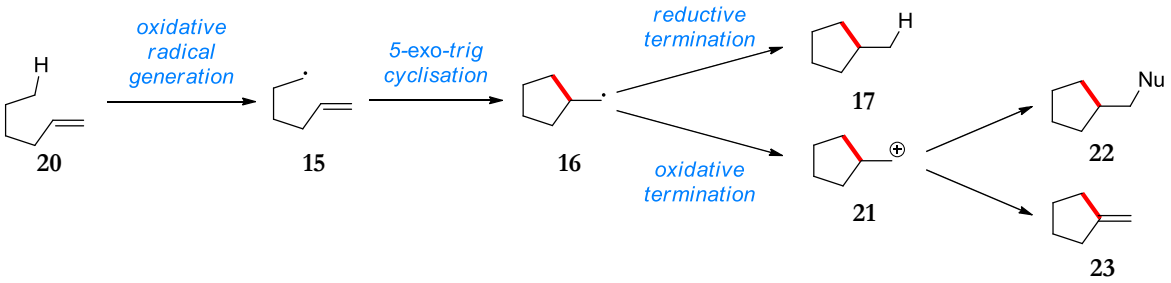



**Figure 1.6: Oxidative radical cyclisation.**

The first example of an oxidative radical cyclisation was reported by Julia in 1971, who carried out cyclisations of a number 1-substituted 5-hexenyl radicals [**Figure 1.7**].[20] For example, heating *β*-nitrile **24** in the presence of benzoyl peroxide or di-*tert*-butyl peroxide (*via* the corresponding carboxy radical) oxidatively generates radical **25**, which after a 5-*exo*-trig cyclisation gives cyclopentyl radical **26**. As there is no corresponding oxidant for radical **26**, hydrogen abstraction from the solvent (cyclohexane) proceeds to give cyclopentane **27** (reductive termination) – overall the formation of **27** is redox neutral.

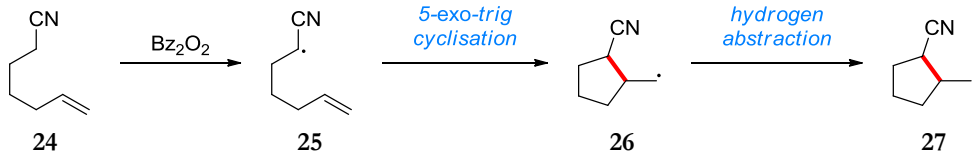



**Figure 1.7: Oxidative radical cyclisation of a 1-substituted 5-hexenyl radical.**

As mentioned above, oxidative termination provides structurally more useful intermediates. Whilst benzoyl peroxide can serve as a practical oxidative radical initiator, it does not generally act as an oxidative terminator. Instead, oxidative termination is most often achieved *via* a transition metal. For example, Breslow *et al.* found that copper(II) benzoate could be used as a terminal

oxidant in the cascade cyclisation of farnesyl acetate [**Figure 1.8**].[21] Here farnesyl acetate (**28**) undergoes a cascade radical cyclisation to give bicyclic radical **29**. Oxidative termination is then induced by copper(II) benzoate producing *exo*-alkene **30**.

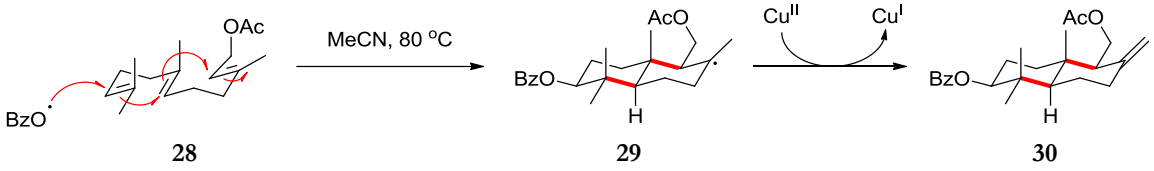



**Figure 1.8: Oxidative cascade cyclisation of farnesyl acetate.**

### 1.2.4. Regio- and stereoselectivity of 5-hexenyl radicals

In the majority of 5-hexenyl cyclisations, the reaction characteristically proceeds through adduct radical **15** [**Figure 1.9**], which typically undergoes a 5-*exo*-trig cyclisation to give cyclopentane **16**. However, it is not apparent why the irreversible 5-*exo* mode of cyclisation is preferred over the 6-*endo* cyclisation, despite radical **31** being thermodynamically more stable. Experimentally, the rate of cyclisation for the 5-*exo* product **16** is ~50 times faster[22] than that of the alternative 6-*endo* product **31**, most likely due to better orbital overlap between the SOMO and $\pi$-system of the alkene in the transition state of the 5-*exo* mode of cyclisation.

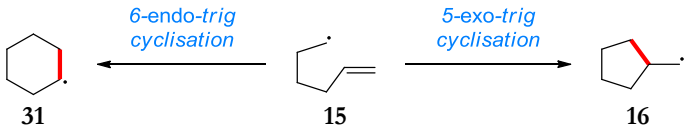



**Figure 1.9: Possible cyclisation pathways resulting in either 5- or 6-membered cyclic products.**

The experimental results were explained computationally by Beckwith *et al.*[23] and later expanded on by Houk *et al.*[24], who found the observed preference towards the 5-*exo* cyclic product **16**, to be as a result of stereoelectronic effects rather than thermodynamics [**Figure 1.10**]. In the transition state **33**, it was found that there is an effective overlap between the SOMO and the alkene $\pi/\pi^*$ molecular orbital. On the contrary, the 6-*endo* transition state **32** suffered from poor orbital overlap due to bond length constraints, which as a result placed extra strain on the system in obtaining the necessary arrangement for cyclisation. The difference in energies between the two

transition states was found to be 7.1 kJmol$^{-1}$ (Beckwith) or 10.0 kJmol$^{-1}$ (Houk) in favour of the 5-*exo*-trig mode of cyclisation.

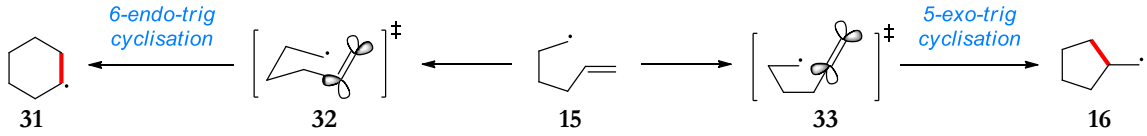



**Figure 1.10: Associated transition structures for *exo* and *endo* cyclisations.**

The real power of these models reported by Beckwith and Houk however lies in the ability to predict stereochemical outcome of such radical cyclisations. For example, cyclisation of a *β*-substituted hexenyl radical **36**, can occur through two possible diastereomeric transition states [**Figure 1.11**]. It was found that the lowest energy transition state had the the *β*-substituent in the *pseudo*-equatorial position (**37**) resulting in formation of diastereoisomer **38** as the major product. The corresponding cis-diastereoisomer **34** would arise from the transition state **35**, were the *β*-substituent is placed *pseudo*-axial. Such orientation is highly unfavourable due to 1,3-allylic and 1,3-dixial steric interactions present in the transition state. Beckwith calculated the difference in activation energies between these two transition states to be 4.6 kJmol$^{-1}$ in favour of **37**. This suggests that steric constraints could be utilised to exert a degree of stereochemical control in the final product. This model is now widely accepted as a means to explain and predict the outcome of such radical cyclisations.

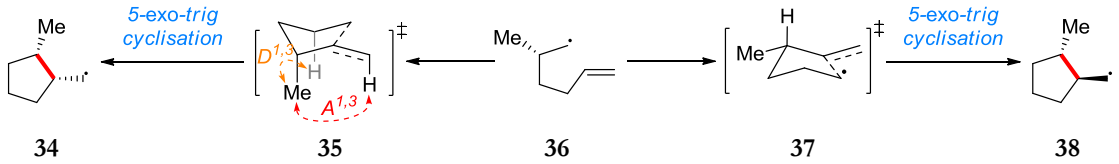



**Figure 1.11: Stereochemical outcome of a 5-*exo*-trig cyclisation.**

## 1.3. Manganese(III) acetate

Manganese(III) acetate has been extensively used a single electron oxidant to promote radical cyclisations.[19] In the solid state, manganese(III) acetate is an oxo-centred trimer of manganese atoms with bridging acetate ligands – typical of many transition metal acetates.[25] Whilst

the crystal structure has been determined [**Figure 1.12**],[26] it is not known if this structure is maintained in solution, but most proposed mechanisms assume that the trimeric structure does exist in solution. Manganese(III) acetate is therefore not a simple metal acetate ionic compound nor does the actual structure of it reflect the simple "$Mn(OAc)_3$" chemical formula that is commonly given and will be used in this thesis. Experimentally, manganese(III) acetate is generally used as the dihydrate in synthesis which is the form used throughout the work reported in this thesis.

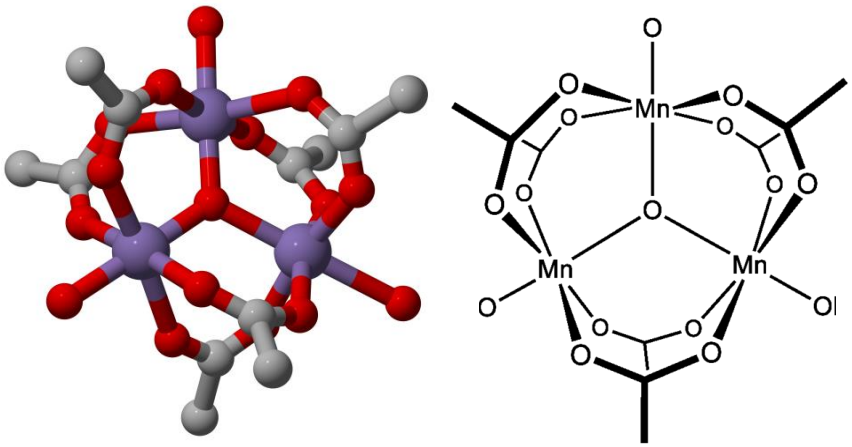
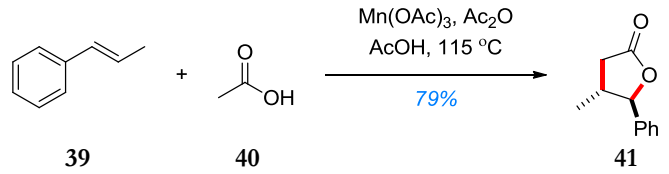



**Figure 1.12: Crystal structure of manganese(III) acetate.[26]**

### 1.3.1. Synthesis of γ-lactones

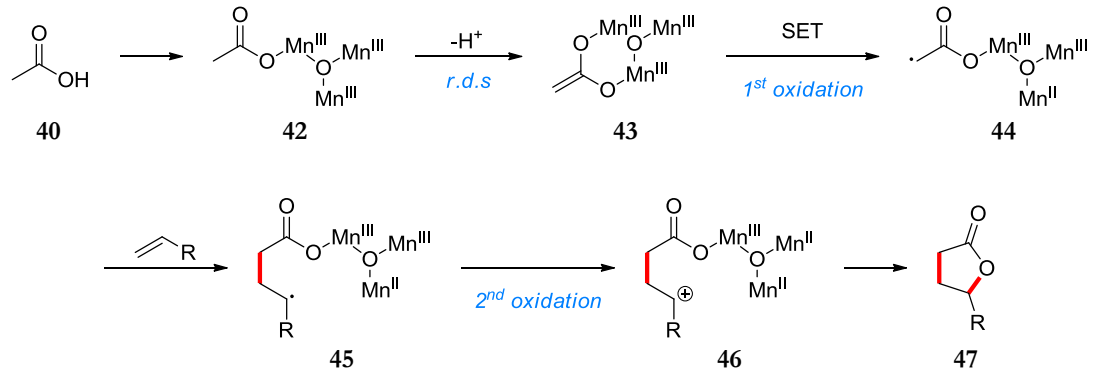
The use of manganese(III) acetate as a single electron oxidant was independently reported in 1968 by Bush *et al.*[27] and Heiba *et al.*[28] [**Scheme 1.1**]. It was shown that subjecting a number of substituted styrenes, such as **39** to acetic acid (**40**) in the presence of manganese(III) acetate, gave the corresponding *γ*-lactones **41** in good yields *via* an overall oxidative transformation. It must be noted that the reported yields are based on manganese(III) acetate, as both the styrene (5 eq.) and acid (solvent) are used in excess.




39 40 41

**Scheme 1.1: Oxidative addition of acetic acid to various substituted styrenes.**[27]

As shown in **Figure 1.13**, Hieba proposed a mechanism for the oxidative addition of acetic acid to an alkene. The reaction was thought to proceed through complexation of manganese(III) acetate to acetic acid (**40**) to give complex **42**. Subsequent deprotonation to give enolate **43** (experimentally shown to be the rate limiting step by carrying the reaction out in HOAc/DOAc-$d_4$ and monitoring H/D exchange)[29] followed by a rapid single electron transfer (SET) gives acetate radical **44**. Addition of the resulting radical **44** to an olefin, gives the more stable secondary radical **45**, which then undergoes a second oxidation by manganese(III) acetate to give the formal cation **46**. Carbocation **46** is then trapped by oxygen to give the corresponding $\gamma$-lactone **47**.




40 42 43 44 45 46 47

**Figure 1.13: Reaction mechanism proposed by Hieba for the oxidative addition of acetic acid to an olefin.**

However, formation of carbocation **46** is highly unlikely, unless R is a strong cation stabilising group such as phenyl. For example, Fristad *et al.* found that subjecting norbornene to manganese(III) acetate in acetic acid, did not give any rearranged products which would result from migration to further stabilise the 2-norbornyl cation.[30] It is also known that manganese(III) acetate does not oxidise isolated primary or secondary radicals to their corresponding cations. Yet experimentally, a number of $\gamma$-lactones have been synthesised irrespective of the nature of the carboxy radical (i.e. primary, secondary or tertiary). Thus, Fristad proposed that a different mode

of cyclisation must be occurring which would avoid the formation of the formal carbocation [**Figure 1.14**]. They proposed that *γ*-carboxy radical **45** undergoes a 5-*endo*-trig cyclisation onto the carbonyl oxygen to give **48**, which is then oxidised with the loss of manganese(II) to give *γ*-lactone **47**.

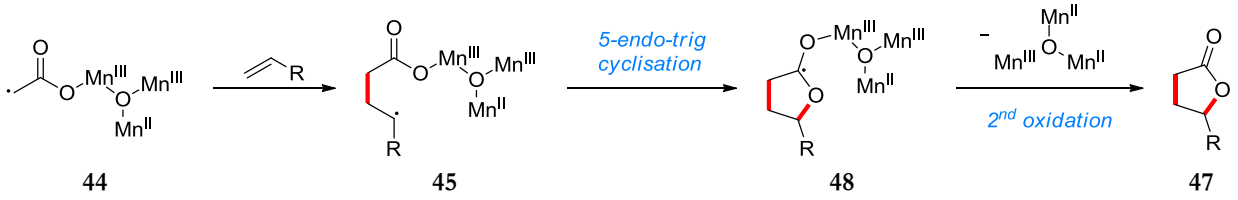



**Figure 1.14: Mechanism proposed by Fristad *et al.* accounting for observed experimental results.**

However, computational studies of such mechanism showed that a 5-*endo*-trig cyclisation of a carboxy radical onto the carbonyl functionality to be highly unfavourable.[31] This was shown to be due to poor orbital overlap between the radical SOMO and the carbonyl π-system. With this information to hand, Snider *et al.* proposed a third possible mode of cyclisation [**Figure 1.15**].[32] It was suggested that reaction of the *γ*-carboxy radical **45** might proceed *via* an intermediate metallocycle such as **49**. Subsequent reductive elimination would give the *γ*-lactone **47**. The precise mechanism for the formation of *γ*-lactones using manganese(III) acetate and alkenes is still not known.

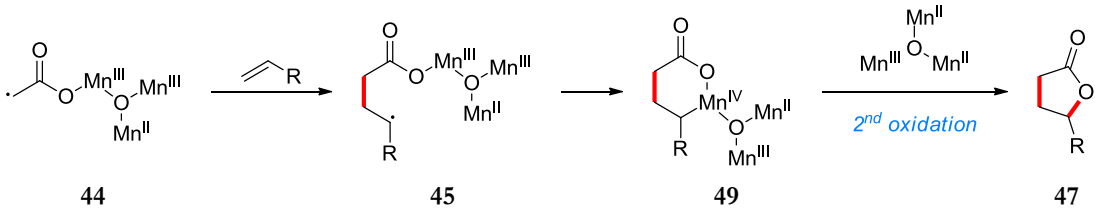



**Figure 1.15: Alternative mechanism for lactonisation as proposed by Snider *et al.*[32]**

### 1.3.2. Oxidative termination using copper(II) salts as a co-oxidant

Because of the inability of manganese(III) acetate to oxidise some radical types, the use of copper(II) salts as a co-oxidant has been found to be of advantage in oxidative termination. In 1971, Heiba and Dessau investigated the relative rates for the oxidation of a secondary radical by manganese(III), cerium(IV) and copper(II) [**Figure 1.16**].[33] By comparing the yields of reduced

product **53** to that of oxidised product **54** in the course of varying metal salt concentration, they found the relative rates of oxidation by manganese(III), cerium(IV) and copper(II) to be 1:12:350.

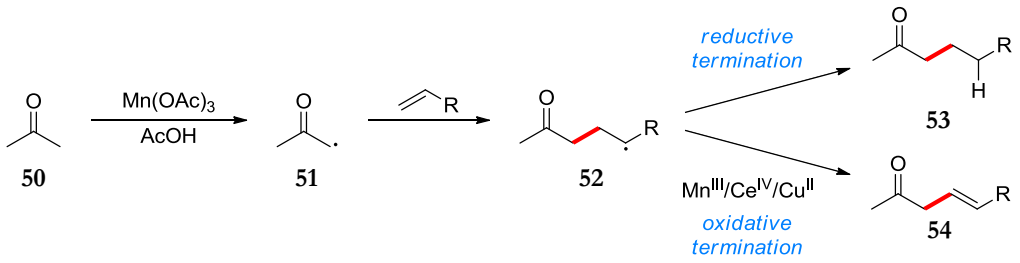



**Figure 1.16: Investigating the relative rates of oxidation by manganese(III), cerium(IV) and copper(II).**

Whilst copper(II) is the weakest oxidant out of manganese(III), cerium (IV) and copper(II) [**Equation 1.1**], the rate of oxidation for alkyl radical **52** was found to be much higher, with reaction rates of the much more strongly oxidising metals manganese(III) and cerium (IV) being much slower. Kochi *et al.* have shown that alkyl radicals react with copper(II) salts with a bimolecular rate constant of $\approx 10^6$ $M^{-1}s^{-1}$.[34]

$$Mn^{3+} + e^- \rightarrow Mn^{2+} \; E^o = +1.51\,V$$

$$Ce^{4+} + e^- \rightarrow Ce^{3+} \; E^o = +1.44\,V$$

$$Cu^{2+} + e^- \rightarrow Cu^{+} \; E^o = +0.16\,V$$

**Equation 1.1: Electrode potentials of manganese(III), cerium (IV) and copper(II).**

The most common choice of copper(II) salt as a co-oxidant for use with manganese(III) acetate has traditionally been copper(II) acetate. However work by Kochi *et al.* on the oxidation of radicals by transition metal salts, in particular copper(II) salts, found that the predominant pathway of termination can be tuned by choice of copper(II) ligand.[35] Kochi states that there are three possible oxidative outcomes for an alkyl radical in the presence of various copper(II) salts [**Figure 1.17**].[36] In each case, organocopper species **56** is formed, which may either undergo a *β*-hydrogen elimination to give alkene **57**, be oxidised to the corresponding carbocation **58** or undergo reductive elimination/ligand transfer to give alkyl halide **59**.

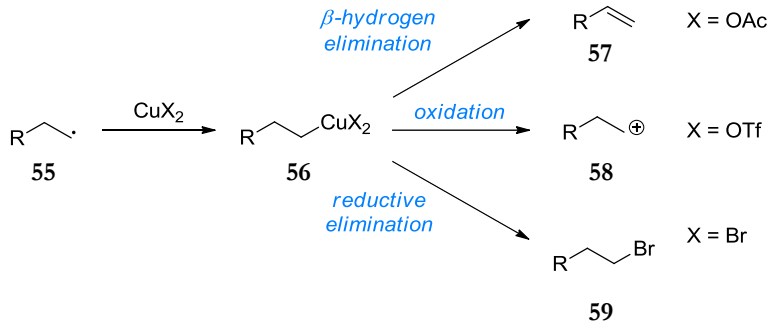



**Figure 1.17: Oxidative termination by various copper(II) salts.**

The various copper(II) salts are thought to play a role in product distribution due to the nature of the ligands attached to copper. When copper(II) acetate is used, the copper(III) species **60** may lose a *β*-hydrogen *via* a pericyclic elimination to give alkene **57** [**Figure 1.18**].[37] This is because copper(II) acetate exists largely as an inner sphere complex where the ligand is predominantly associated with the copper cation rendering intermediates such as **61** disfavoured.

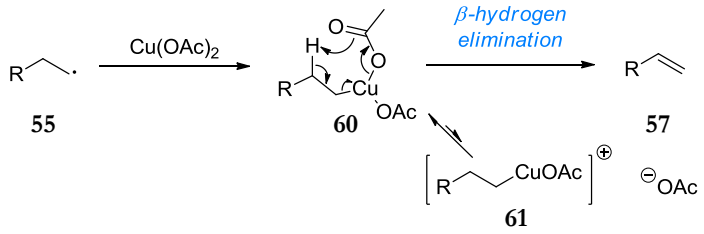



**Figure 1.18: Undissociated copper complex resulting in β-hydrogen elimination.**

Conversely, copper(II) salts with charge stabilising ligands such as triflate, tend to favour substitution over elimination [**Figure 1.19**]. Copper(II) triflate is an outer-sphere complex where one (or both) ligand(s) can become ionised from the metal centre. This leads to a greater degree of dissociation in the organocopper species **63** over the undissociated species **62**, largely due to the stability of the counter anion. Greater dissociation of the ligand promotes the formation of carbocation **58**, which can be trapped with various nucleophiles to give the substituted product **64**.[38]

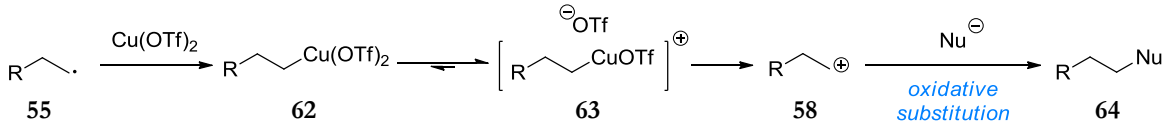



**Figure 1.19: Dissociated copper complex resulting in substitution.**

Another benefit of using copper(II) salts as a co-oxidant is that the copper(I) produced during the oxidation of radical **55** can be oxidised to copper(II) by manganese(III) acetate due to its low oxidation potential [**Equation 1.1**]. In principle, the use of copper(II) salts under such reaction conditions could be rendered catalytic in copper. In practice however, stoichiometric copper is generally used with an extra equivalent of manganese(III) acetate used to equate for the oxidation of copper(I) back to copper(II).

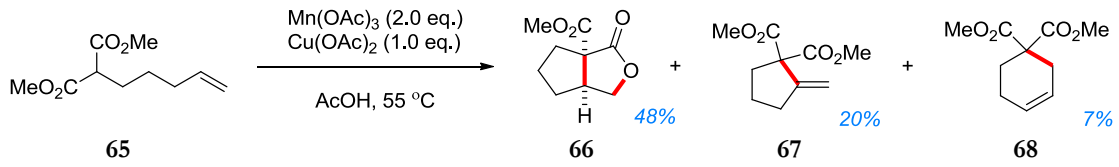
## 1.4. Cyclisation of 1,3-dicarbonyl compounds

As discussed in **Section 1.3.1**, the rate of enolisation of acetic acid has been shown to be the rate determining step in the oxidative addition of acetic acid to an olefin. Additionally it has been shown that the rate of reaction, relative to acetic acid is $\log(k_{rel}) = 0.344 \times \Delta pK_a$[I] for acetic acid derivatives featuring an electron withdrawing group (e.g. $XCH_2CO_2H$ with X = Cl, $PhSO_2$, $MeO_2C$, $HO_2C$ and NC).[39] As electron withdrawing groups enhance the rate of reaction, 1,3-dicarbonyl compounds have been widely used and studied under manganese(III) acetate conditions. For the purpose of this thesis, the use of malonates will be discussed further, although *β*-keto esters,[40] *β*-keto acids,[41] 1,3-diketones[40] and the equivalent *β*-keto sulfoxides,[42] *β*-keto sulfones[42] and *β*-nitro ketones[43] have also been studied.

### 1.4.1. Cyclisation of alkenyl malonates

Although many of the initial studies for the cyclisation of a 1,3-dicarbonyl compounds using manganese(III) acetate mediated conditions have been carried out with *β*-keto esters and *β*-keto acids, alkenyl malonates have also been shown to be suitable substrates [**Scheme 1.2**]. In 1991, Snider *et al.* reported the cyclisation of 4-pentenyl malonate (**65**) using manganese(III) acetate and copper(II) acetate in acetic acid, which gave bicyclic *γ*-lactone **66**, cyclopentane **67** and cyclohexene **68**.[44]

I $\Delta pK_a$ = $pK_a$ (acetic acid) - $pK_a$ (substituted acid)




65 66 67 68

**Scheme 1.2: Manganese(III) acetate and copper(II) acetate mediated cyclisation of 4-pentenyl malonate.[44]**

The product distribution for the cyclisation of malonate **65** can be explained using the mechanisms discussed in **Section 1.2.4**. Thus, a likely mechanism for the formation of cyclic products **66-68** is shown in **Figure 1.20**. Coordination of manganese(III) acetate to malonate **65** followed by enolisation gives **69**, which then undergoes a single electron transfer to give adduct radical **70**. Subsequent cyclisation either *via* a 5-*exo*-trig or 6-*endo*-trig mode gives the corresponding 5- (**72**) or 6-membered (**71**) rings respectively. Reaction of the primary radical with copper(II) acetate gives the corresponding copper(III) species, which may either undergo a *β*-hydrogen elimination to give cyclopentane **67** or an oxidative displacement by the ester to give oxonium ion **73**, which upon hydrolysis gives bicyclic γ-lactone **66**. The organocuprate formed from the secondary radical **71** can only undergo a *β*-hydrogen elimination to give cyclohexene **68**.

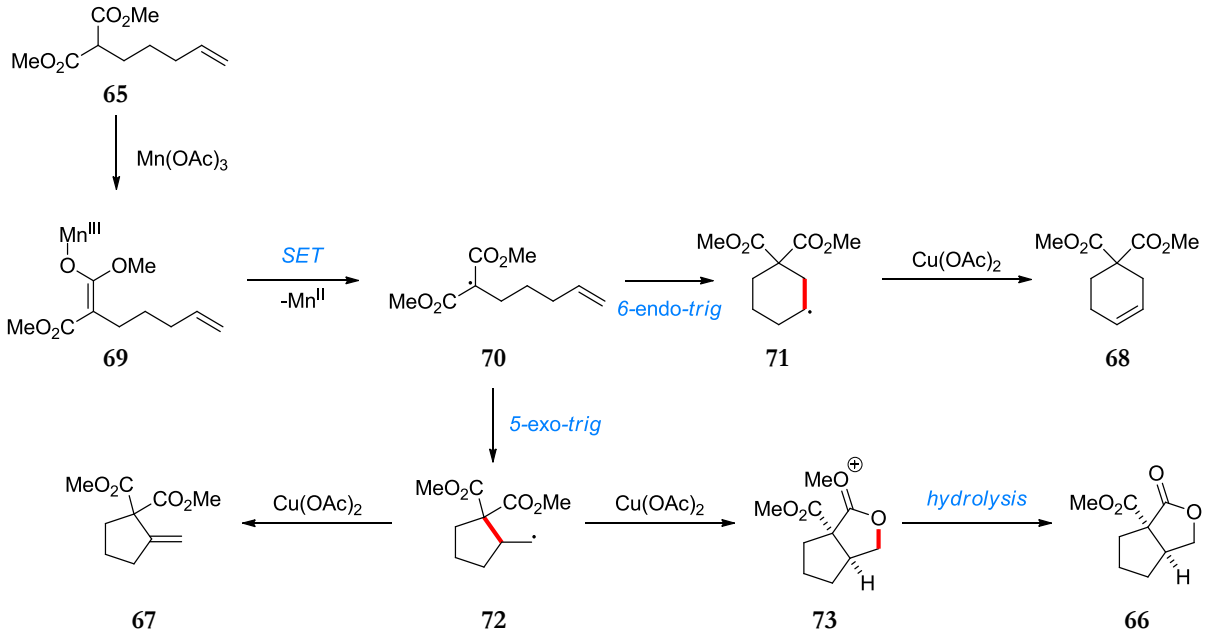
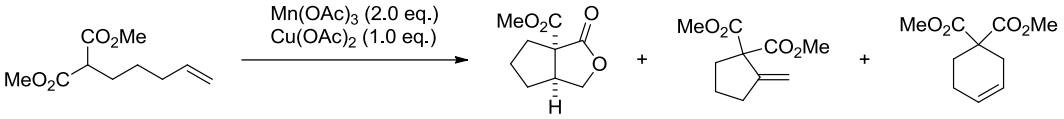



**Figure 1.20: Mechanistic explanation for the product distribution observed by Snider.[44]**

When Snider treated 4-pentenyl malonate **65** with manganese(III) acetate in the absence of copper(II) acetate, polymeric materials were obtained, with neither bicyclic *γ*-lactone **66** or

cyclopentane **67** observed. This would suggest the initial cyclisation is reversible in the absence of copper(II) salts, which is likely to be due to the stabilising effect of the two ester groups on radical **70**. Even more interesting was the influence of the solvent on both yield and product distribution [**Table 1.1**].[45] In particular, Snider found that the use of dimethylsulfoxide (entry 5) resulted in a 11:1 selectivity towards the *exo*-alkene **67** over bicyclic *γ*-lactone **66**. Changing to acetonitrile (entry 6) reversed product selectivity and instead favoured the formation of bicyclic *γ*-lactone **66** in 5:1 selectivity over **67**. The authors did not seek to propose an explanation for this observed selectivity, which would have been unexpected as both solvents are similar in character.

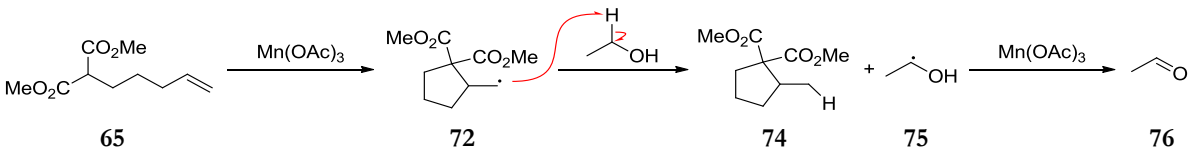



**65** **66** **67** **68**

| Entry | Solvent | Temp/ | 66 | 67 | 68 | Ratio 66 : 67 |
|---|---|---|---|---|---|---|
| 1 | AcOH | 55 | 48% | 20% | 7% | 2.4:1 |
| 2 | EtOH | 60 | 14% | 22% | 4% | 1:1.6 |
| 3 | MeOH | 70 | 17% | 35% | 5% | 1:2.0 |
| 4 | DMF | 75 | 17% | 32% | 5% | 1:1.9 |
| 5 | DMSO | 75 | 5% | 53% | 2% | 1:10.6 |
| 6 | MeCN | 55 | 38% | 8% | 3% | 4.7:1 |

**Table 1.1: Importance of solvent in product distribution for the cyclisation of 65 reported by Snider.[45]**

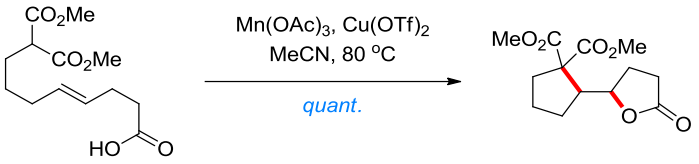
The lower yields of **66** and **67** observed using alcohol as the solvent (entry 2 and 3) are due to a competing reductive termination reaction taking place [**Figure 1.21**]. Abstraction of a hydrogen atom from the solvent (ethanol) leads to the stabilised radical **75** and the reduced cyclopentane **74**. Radical **75** is then oxidised to acetaldehyde (**76**) by manganese(III) acetate. Carrying the reaction out on malonate **65** which featured an *α*-deuterium, gave cyclopentane **74** without deuterium incorporation, suggesting that the origin of the hydrogen atom to be most likely from the solvent.




65 72 74 75 76

**Figure 1.21: Formation of cyclopentane 74 through hydrogen abstraction from the solvent**

As discussed previously [**Section 1.3.2**], copper(II) salts which favour a dissociated transition state (e.g. copper(II) triflate) should promote oxidative substitution over *β*-hydrogen elimination. In 2004, Burton *et al.* reported the cyclisation of malonate **77** in the presence manganese(III) acetate and copper(II) triflate, to give lactone **78** as a mixture of diastereoisomers in excellent yield [**Scheme 1.3**].[46] In the absence of a copper(II) salt, lactone **78** was not detected and where copper(II) acetate was used instead, lactone **78** was only obtained in 33% yield.

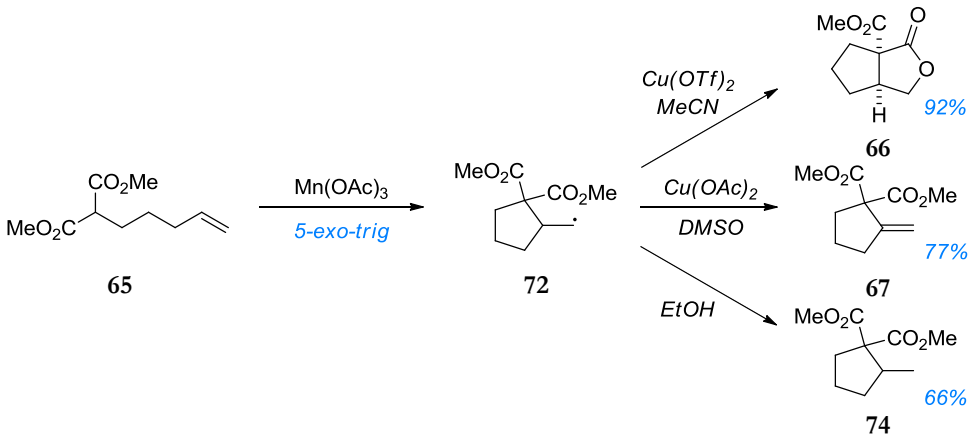



77 78

**Scheme 1.3: Application of copper(II) triflate as a co-oxidant to promote lactonisation reported by Burton.[46]**

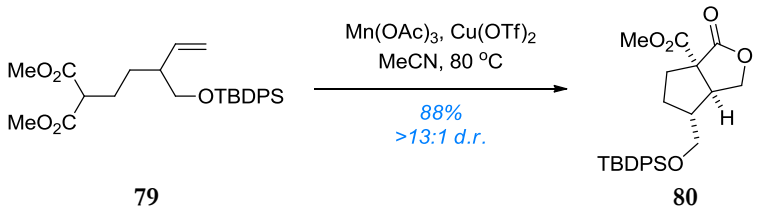
Following on from these results, the cyclisation of 4-pentenyl malonate (**65**) (as reported by Snider *et al.*) was investigated further in which Burton reported selective formation of the three cyclic products observed [**Scheme 1.4**].[47] Treatment of malonate **65** with manganese(III) acetate and copper(II) triflate in acetonitrile (0.2 M) exclusively gave [3.3.0]-bicyclic *γ*-lactone **66** in excellent yield (92%). Conversely using copper(II) acetate as the co-oxidant in dimethylsulfoxide (0.2 M) gave *exo*-methylene cyclopentane **67** in good yield (77%). Finally, using ethanol as the solvent (0.02 M) in the absence of a copper(II) salt, gave cyclopentane **74** in modest yield. It was found that the use of nitrogen sparged solvent was essential, as residual oxygen can also react with radical intermediates. The high yielding formation of **66** and **67** at high oxidant concentration can be explained by an increase in rate of reaction between radical intermediate **72** and copper(II) over other reaction pathways. The varied copper(II) ligand allows for selective tuning of the oxidative termination pathway and hence controls product distributions. Likewise, the formation of **74** at

low oxidant concentrations is a result of reduction by solvent competing with the other possible oxidative termination pathways as the effective concentration of proton sources (solvent) relative to substrate is high.




**Scheme 1.4: Highly selective cyclisation conditions reported by Burton.[47]**

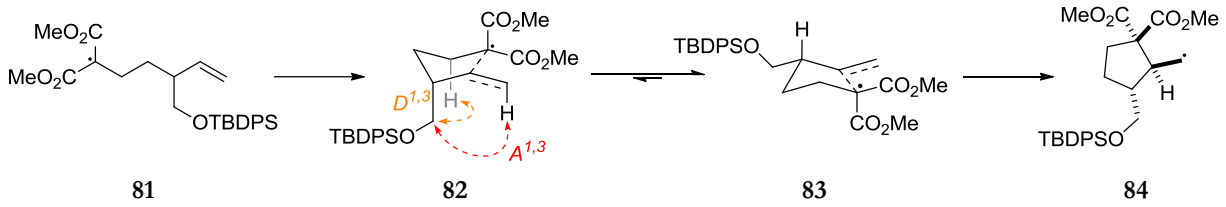
Burton further expanded the substrate scope by subjecting a number of substituted alkenyl malonates to the manganese(III) acetate methodology [**Scheme 1.5**]. For example, subjecting alkenyl malonate **79** to manganese(III) acetate and copper(II) triflate in acetonitrile (0.2 M) at 80 °C, gave the corresponding [3.3.0]-bicyclic *γ*-lactone **80** in excellent yield (88%) and good diastereoselectivity (*d.r.* >13:1).




**Scheme 1.5: Cyclisation of a *γ*-substituted malonate under optimised cyclisation conditions.**

The diastereoselectivity of the reaction can be explained using the models of Beckwith and Houk as discussed in **Section 1.2.4**. Of the two possible chair transition states [**Figure 1.22**], placing the substituent in a *pseudo*-equatorial position (**83**) would minimises the steric strain placed on the forming ring. The corresponding transition state **82** in which the substituent is *pseudo*-axial, results in 1,3-diaxial and 1,3-allylic steric clashes which are highly unfavourable. Thus transition

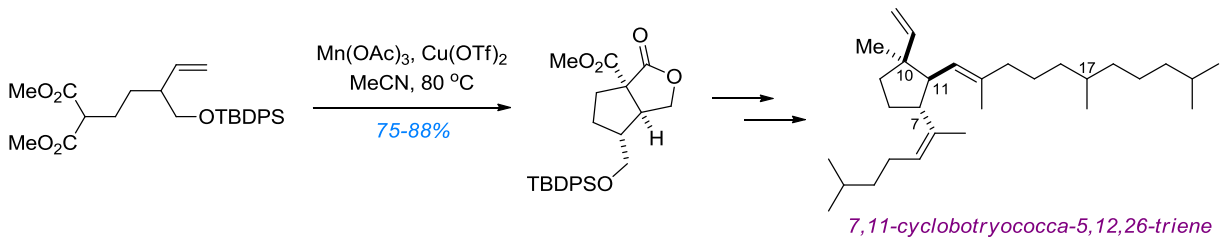
state **83** is favoured, which gives rise to the *trans*-cyclopentane **84** and upon lactonisation generates the *cis*-fused bicyclic *γ*-lactone **80**.




**81** **82** **83** **84**

**Figure 1.22: Stereochemical explanation for the high diastereoselectivity observed for the cyclisation of 79.**

This demonstrates the power of radical chemistry, as a highly sterically constrained product has been created from a simple acyclic precursor. The creation of contiguous tertiary, tertiary, quaternary stereocentres with excellent diastereocontrol can be difficult *via* more traditional methods. Another useful feature of such bicyclic *γ*-lactones is the presence of differentiated oxygen functionality. This would allow for such molecules to be utilised as highly functionalised intermediates in natural product synthesis. The generation of molecular complexity with high levels of regio- and stereoselectivity is of key importance, for natural product synthesis to be of practical use. In 2010, Burton *et al.* utilised a manganese(III) acetate mediated radical cyclisation as a key step in the total synthesis of the triterpene 7,11-cyclobotryococca-5,12,26-triene [**Scheme 1.6**].[48] Lactone **80** was functionalised at C-7, 10 and 11 to give racemic 7,11-cyclobotryococca-5,12,26-triene (**85**) in 23 steps and an overall yield of 1.0%. The total synthesis of 7,11-cyclobotryococca-5,12,26-triene proved that the natural product was indeed isolated as a mixture of C-17 diastereoisomers as originally postulated in the isolation paper.[49]



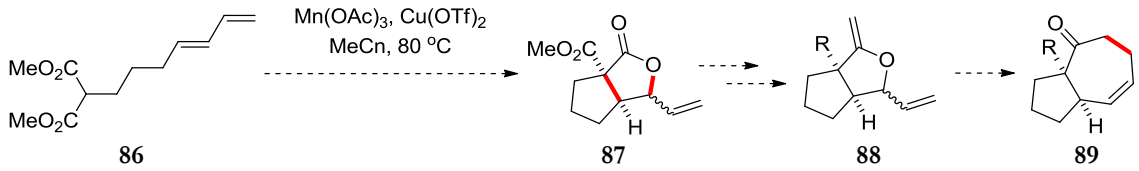

**79** **80** **85**

**Scheme 1.6: Application of manganese(III) acetate mediated radical cyclisation as a key step in the total synthesis 7,11-cyclobotryococca-5,12,26-triene.[48]**

## 1.5. Summary and project aims

Manganese(III) acetate mediated oxidative radical cyclisations can provide access to complex cyclic backbones, with at least three adjacent stereocentres in good yields and with good to high stereocontrol. The Beckwith and Houk models allow for the stereoselectivity of such reactions to be predicted with confidence, a key step when planning a multistep synthesis such as those required in complex molecule synthesis. This makes the methodology well suited for application in natural product synthesis, largely due to the countless number of natural products which bear a highly congested cyclopentane ring.

The aim of this project is to further develop the group's understanding of a manganese(III) acetate mediated oxidative radical cyclisation by applying it to the cyclisation of a dienyl malonate [**Figure 1.23**]. For example, subjecting 1,3-diene **86** to manganese(III) acetate in the presence of copper(II) triflate should give alkenyl substituted [3.3.0]-bicyclic *γ*-lactone **87**. Complementary methodology will then be developed to allow for such lactones to be converted to the corresponding [3.3.0]-bicyclic enol ether **88**, which upon heating should undergo a Claisen ring expansion to give [5.3.0]-bicyclic ketone **89**. Such molecular motif is a key scaffold found in a family of natural products which feature an hydroazulene type skeleton. Once the methodology has been established, it will be demonstrated in the total synthesis of (+)-aphanamol I and some structurally related natural products. Other aspects of manganese(III) acetate mediated cyclisations to form [3.3.0]-bicyclic *γ*-lactones will also form part of this thesis.




**86** **87** **88** **89**

**Figure 1.23: Project aims.**

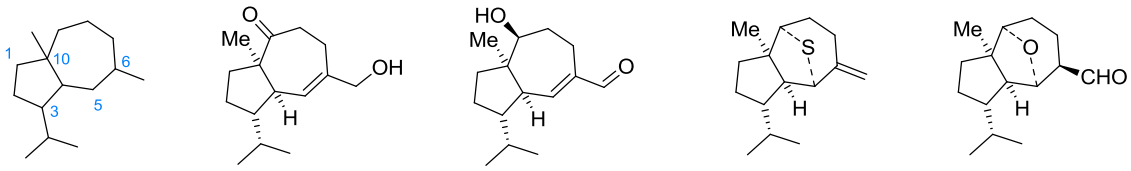
# CHAPTER 2: Total synthesis of (+)-aphanamol I

Chapter 2 will focus on the total synthesis of (+)-aphanamol I. Firstly a brief introduction to (+)-aphanamol I and related natural products will be discussed followed by a proposed biosynthesis of this natural product family. The retrosynthesis of (+)-aphanamol I based on a Claisen ring expansion of a vinyl substituted [3.3.0]-bicyclic *γ*-lactone will be presented along with methodology based on the proposed disconnections applied to a model system. After such methodology has been established, it is then applied to the total synthesis of (±)-aphanamol I, followed by a catalytic enantioselective total synthesis of (+)-aphanamol I utilising a rhodium(I) catalysed 1,4-conjugate addition to establish the asymmetry. The synthesis of several other related natural products will then be presented which further validates the absolute configuration of (+)-aphanamol I and II.

## 2.1. (+)-Aphanamol I and II

The rare sesquiterpenoid hydroazulene-type isodaucane skeleton **90** was first identified in 1979 by Yoshida *et al.* [**Figure 2.1**].[50] During studies into the chemical components of peppermint oil, Yoshida isolated a novel sulphur-containing sesquiterpene **93** and determined the structure and stereochemistry by X-ray crystallography. Following the identification of (-)-mintsulphide, several related natural products featuring an isodaucane skeleton have been identified. In 1984 Nishizawa *et al.* isolated (+)-aphanamol I (**91**) and II (**92**) from the Javan tree *Aphanamixis grandifolia,*[51] the fruits of which have traditionally been used by indigenous Indonesian tribes as fish or dart arrow poisons.[52] Analysis of the extracts of this fruit peel identified three active constituents to be responsible for the biological activity. The major toxic constituent was identified to be that of the known triterpenoid aphanamixin, which had been previously isolated from a related species, *A. polystachya*.[53] The other two active constituents were identified as the novel sesquiterpenoids (+)-aphanamol I or II by extensive spectroscopic analysis. The absolute configuration of

(+)-aphanamol I or II was assigned by comparison with the absolute configuration of (-)-mintsulphide. To date, numerous natural products featuring an isodaucane skeleton have been isolated, with saniculamoid (**94**) identified most recently in 2011 from the tree *Sanicula lamelligera*.[54]

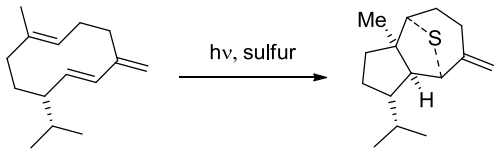



*isodaucane skeleton* **90** | *(+)-aphanamol I* **91** | *(+)-aphanamol II* **92** | *(-)-mintsulfide* **93** | *saniculamoid* **94**

**Figure 2.1: Examples of some natural products featuring a hydroazulene core.**

### 2.1.1. Proposed biosynthesis of (+)-aphanamol I

Biosynthetically, the isodaucane skeleton of (+)-aphanamol I most likely arises from (-)-germacrene D in accordance with the biomimetic synthesis of (-)-mintsulfide reported by Yoshida [**Scheme 2.1**].[50] To determine the absolute configuration of **93**, Yoshida photochemically converted (-)-germacrene D (**95**) in the presence of sulfur into (-)-mintsulfide which had been identified as a metabolite in plants producing **93**.[55]

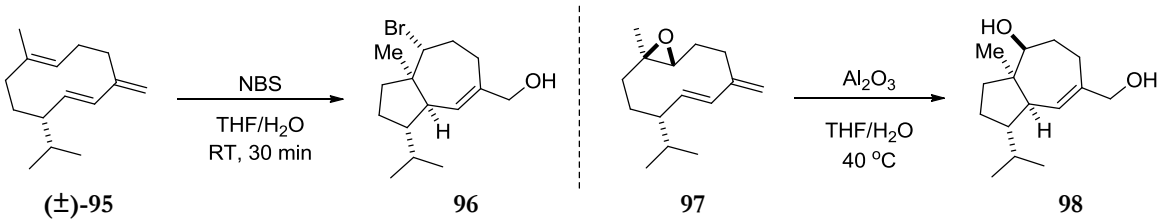



**95** **93**

**Scheme 2.1: Biomimetic synthesis of (-)-mintsulfide reported by Yoshida.**

Following this, Yamura *et al.* investigated the biomimetic synthesis of several natural products including (+)-aphanamol II [**Scheme 2.2**].[56] Treatment of racemic germacrene D (**95**) with aqueous *N*-bromosuccinimide gave a variety of gave a variety of bicyclic bromo compounds one of which featured a *cis*-fused isodaucane skeleton **96**. However despite considerable effort, Yamura was unable to convert **96** into either (+)-aphanamol I or II. On the other hand, Yamura was able to convert epoxygermacrene D (**97**) to isodauc-5-ene-2,12-diol **98** in 5.4% yield upon

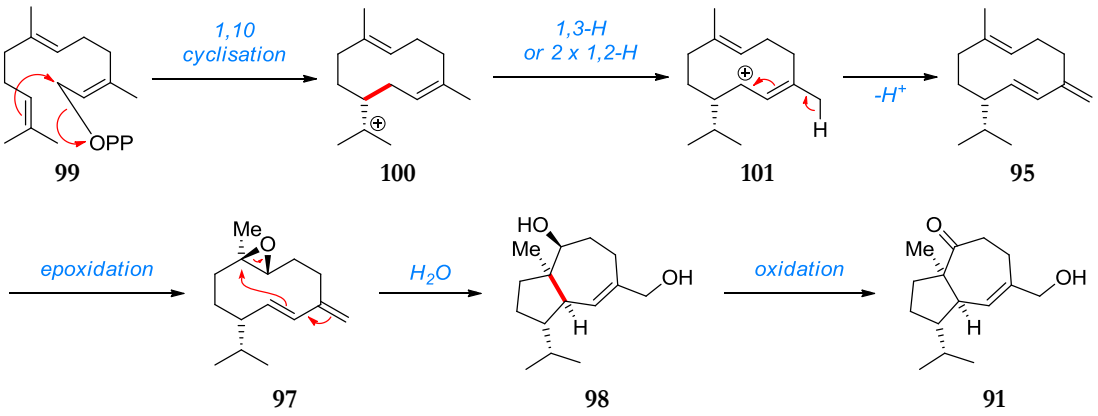
exposure to aqueous activated aluminium(III) oxide at 40 °C. Subsequent exposure of diol **98** to manganese dioxide gave (±)-aphanamol II in 43% yield.




(±)-95 96 97 98

**Scheme 2.2: Biomimetic synthesis of (±)-aphanamol II from epoxygermacrene D.**

To date more than 200 different sesquiterpene skeletons have been isolated, which are most likely biosynthesised from farnesyl pyrophosphate (FPP, **99**) as a common acyclic precursor by enzymatic cyclizations and further transformations.[57] Based on the biomimetic reports by Yoshida and Yamura we propose the following biosynthesis of (+)-aphanamol I [**Figure 2.2**]. Thus a 1,10-cyclisation of FPP (**99**) gives macrocycle **100** which after a hydride shift producing allyl cation **101**, loses a proton to give (-)-germacrene D (**95**).[58] Following epoxidation of **95** to give epoxygermacrene D (**97**), a transannular cyclisation followed by trapping with water gives diol **98**, an intermediate of Yamura's biomimetic synthesis of (±)-aphanamol II. Finally, oxidation of diol **98** generates the ketone of (+)-aphanamol I or the aldehyde found in (+)-aphanamol II.




99 100 101 95 97 98 91

**Figure 2.2: Proposed biosynthesis of (+)-aphanamol I.**

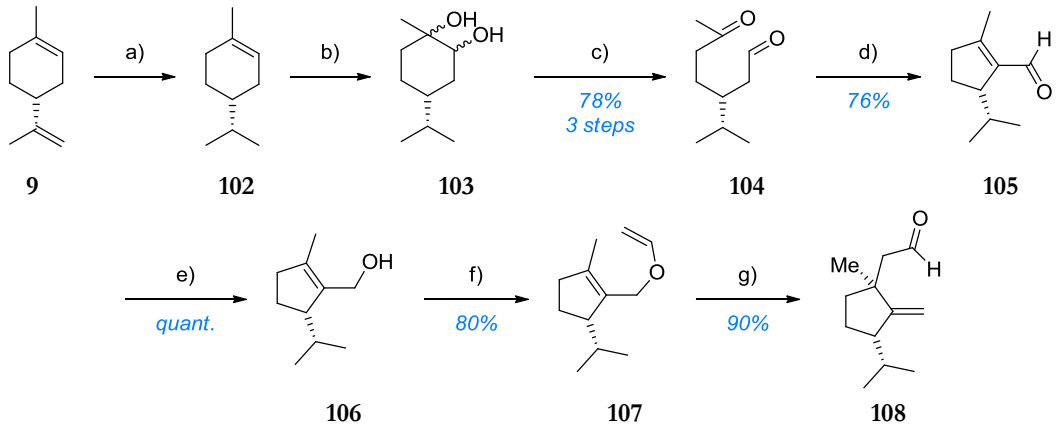
## 2.2. Previous total syntheses of aphanamol I

Owing to its structural complexity and biological activity, aphanamol I (**91**) has been the subject of several total syntheses. The main synthetic challenge has resided in the formation of the

adjacent quaternary-tertiary-tertiary stereocentres with diastereocontrol. Another issue has been the introduction of the desired configuration at C-3 (isopropyl stereocentre). To date, all asymmetric syntheses have relied on chirons derived synthetically from (*R*)-limonene. Whilst utilising the chiral pool can be an excellent source for enantiopure starting materials, the limited functionality of (*R*)-limonene has required at least three manipulations to gain access to material which bears the desired functional handles required for the total synthesis.

### 2.2.1. The Mehta synthesis (1991)

In 1991, Mehta *et al.* utilised a common chiral bifunctional derivative (**108**) in the construction of several 5,6-, 5,7- and 5,8-fused bicyclic systems present in various terpene natural products.[59] Mehta synthesised this versatile intermediate from (*R*)-limonene using standard procedures [**Scheme 2.3**]. Thus, catalytic hydrogenation of (*R*)-limonene (9) selectively reduced the *exo*-alkene to give (+)-*p*-menth-1-ene (**102**), which was converted by performic acid into a mixture of *trans*-*p*-menthane-l,2-diols (**103**) upon workup with potassium hydroxide.

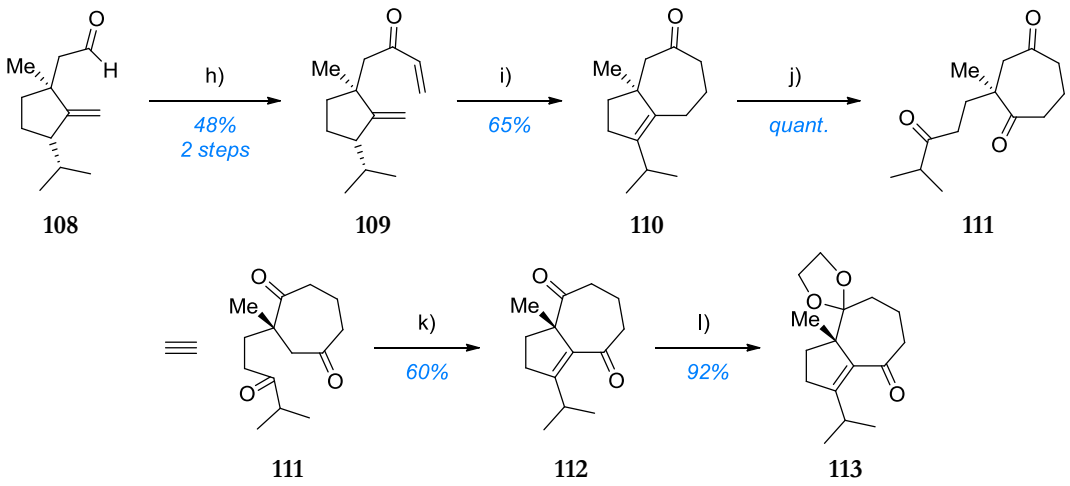



**Scheme 2.3: Synthesis of key chiral bifunctional derivative 108.**

**Reagents and conditions: a) 5% Pt/C, $H_2$; b) performic acid followed by ethanolic KOH; c) periodic acid, pyridine; d) AcOH, piperidine, benzene, reflux; e) $NaBH_4$, $CeCl_3 \bullet 7H_2O$, MeOH, 0 °C, 0.5 h; f) $CH_2=CHOCH_2CH_3$, $Hg(OAc)_2$, 30 °C, 20 h; g) sealed tube, 200 °C, 6 h.**

Oxidative cleavage of 1,2-diol **103** with periodic acid in aqueous pyridine gave 1,6-dicarbonyl compound **104**, which underwent an aldol reaction in the presence of acetic acid and piperidine to give *a,β*-unsaturated aldehyde **105** in 59% yield over four steps.[60] Subsequent 1,2-

reduction under Luche conditions[61] gave allylic alcohol **106**, which was transformed into vinyl ether **107** through a mercury-catalysed transetherification. Finally, a diastereoselective Claisen rearrangement of *a,β*-enol ether **107**, gave key chiron **108** in excellent yield (90%). Alkylation of aldehyde **108** with vinylmagnesium bromide followed by oxidation of the ensuing alcohol to the corresponding aldehyde, gave *a,β*-unsaturated enone **109** in 48% yield [**Scheme 2.4**]. A subsequent acid catalysed Prins-type cyclisation of **109** proceeded smoothly to give 5,7-fused bicycle **110** in good yield (65%). The tetrasubstituted double bond was cleaved using a ruthenium tetroxide catalyst following the procedure of Sharpless *et al.*,[62] to give trione **111**, which then underwent a base catalysed aldol cyclisation-elimination to give bicyclic enedione **112** in 60% yield over two steps. A chemoselective protection of **112** to the monoacetal **113**, allowed for functionalisation of the unprotected ketone in subsequent steps.



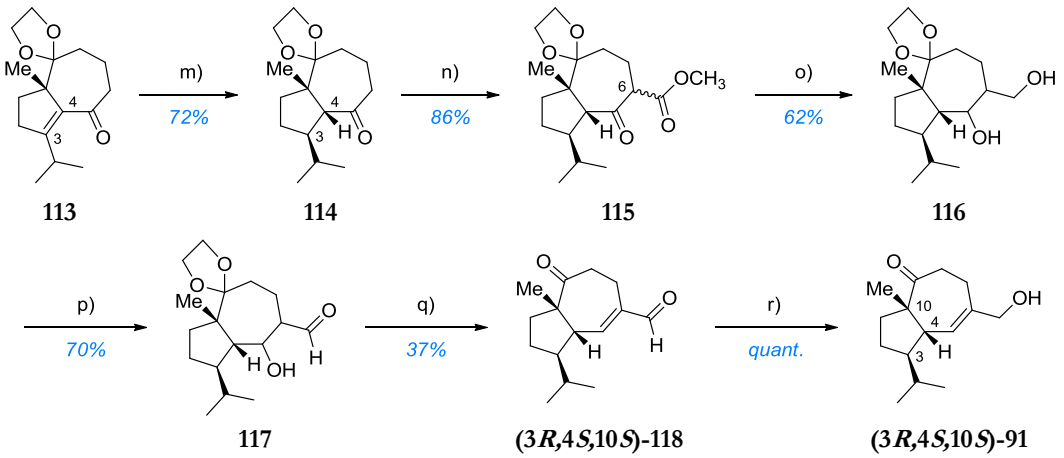

**Scheme 2.4: Key cyclisation followed by key functional group installation.**

**Reagents and conditions: h) (i) $CH_2$=CHBr, Mg, THF, 30 °C, 30 min; (ii) PCC, DCM, molecular sieves, 30 °C, 1 h; i) catalytic $HClO_4$-$(CH_3CO)_2O$, EtOAc, 30 °C, 25 min; j) $RuO_2$-$NaIO_4$, MeCN/$CCl_4$/$H_2O$, 30 °C, 1 h; k) 5% KOH, MeOH, Δ, 30 min; l) $(CH_2OH)_2$, *p*-TSA, benzene, Δ.**

The required configuration at C-3 and C-4[II] was generated by a Birch reduction of **113**, which after oxidation gave ketoacetal **114** (72% yield) as a 7.5:1 mixture of separable diastereomers at C-4 [**Scheme 2.5**]. Kinetic deprotonation of ketone **114** followed by acylation with methyl

[II] Mehta uses alternative numbering to those used by Nishizawa in the isolation paper. For clarity, Nishizawa's numbering system of (+)-aphanamol I will be used throughout the thesis (see **Figure 2.1**)

chloroformate gave *a*-ketoester **115** in excellent yield (86%) as a mixture of C-6 diastereoisomers. Subsequent reduction of ketoester **115** with sodium borohydride gave diol **116**, which was then oxidised selectively under Swern conditions[63] to hydroxyaldehyde **117** in modest yield over two steps (43%). Exposure of hydroxyaldehyde **117** to *p*-toluenesulfonic acid, resulted in dehydration and removal of the acetal protecting group to give *a,β*-unsaturated aldehyde **118**, which was reduced under Luche conditions to give (+)-aphanamol I ($[\alpha]_D$ +10.0 (*c* 0.70, $CHCl_3$)(lit.[51] $[\alpha]_D^{18}$ +13.8 (*c* 0.29, $CHCl_3$))). Direct comparisons of various spectroscopic data of Mehta's synthetic (+)-aphanamol I to those reported by Nishizawa confirmed the isodaucane skeleton previously proposed. Furthermore, with an optical rotation in accordance with the figure reported for natural (+)-aphanamol I in the isolation paper, Mehta assigned the absolute configuration of (+)-aphanamol I to be (3*R*,4*S*,10*S*) – opposite to that of Nishizawa. As (+)-aphanamol II has been synthetically directly correlated to (+)-aphanamol I, the stereochemistry of (+)-aphanamol II was also assigned as (3*R*,4*S*,10*S*).



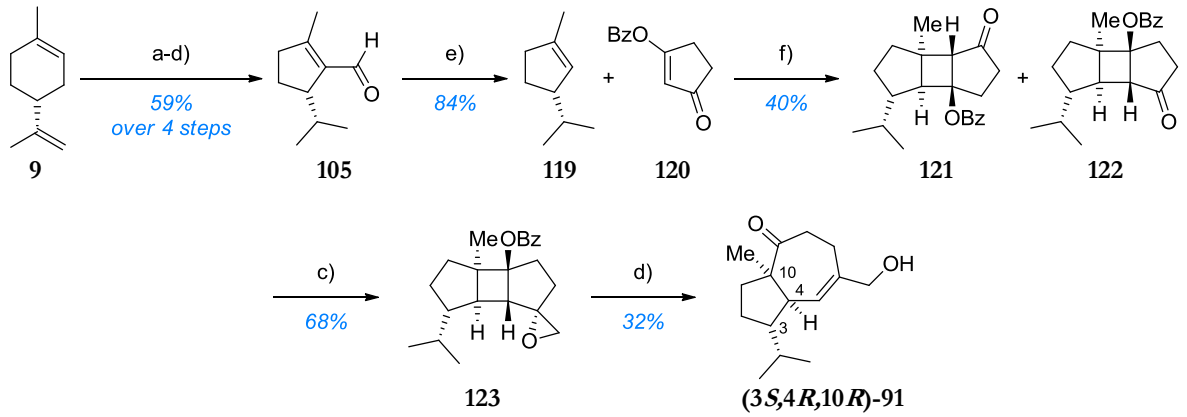

**Scheme 2.5: Functional group manipulation and completion of (+)-aphanamol I.**

**Reagents and conditions: m) (i) Li-$NH_3$ (Liq); (ii) PCC, THF/MeOH/DCM, molecular sieves; n) LiHMDS, THF, $ClCO_2CH_3$, -78 °C; o) $NaBH_4$, MeOH, 0 °C; p) $(COCl_2)_2$, $NEt_3$, DMSO, -60 °C; q) *p*-TSA, benzene, Δ; r) $NaBH_4$, $CeCl_3 \bullet 7H_2O$, MeOH, -5 °C.**

### 2.2.2. The Wickberg synthesis (1992)

A year after Mehta's synthesis, Wickberg *et al.* reported the total synthesis of (+)-aphanamol I utilising the same common intermediate **105** prepared from (*R*)-limonene, as

reported by Mehta [**Scheme 2.6**].[64] Subsequent decarbonylation of **105** using stoichiometric Wilkinson's catalyst in benzonitrile gave cyclopentene **119** in 84% yield. A [2+2] photocycloaddition of cyclopentene **119** to enone **120** gave a 1:1 mixture of regioisomers **121** and **122** in 40% overall yield. Reaction of ketone **122** with trimethylsulfonium methyl sulfate derived methylide gave *endo*-epoxide **123** as a single diastereoisomer. The selectivity was attributed to the steric hindrance present on the bottom face of ketone **122** from the methyl and isopropyl groups. Hydrolysis of the benzoate group in epoxide **123** with refluxing methanolic potassium methoxide gave (+)-aphanamol I ($[\alpha]_D^{20}$ +23.0 (*c* 2.00, $CHCl_3$)(lit.[51] $[\alpha]_D^{18}$ +13.8 (*c* 0.29, $CHCl_3$))) *via* a Grob-type fragmentation in eight steps and an overall yield of 2.5%. Wickberg assigned the configuration of (+)-aphanamol I as (3*S*,4*R*,10*R*) partly based on the optical rotation of his synthetic material which was in conflict to that assigned by Mehta. Thus, Wickberg carried out further studies to establish the absolute configuration of (+)-aphanamol I, which will be discussed in greater detail in **Section 2.2.5**.



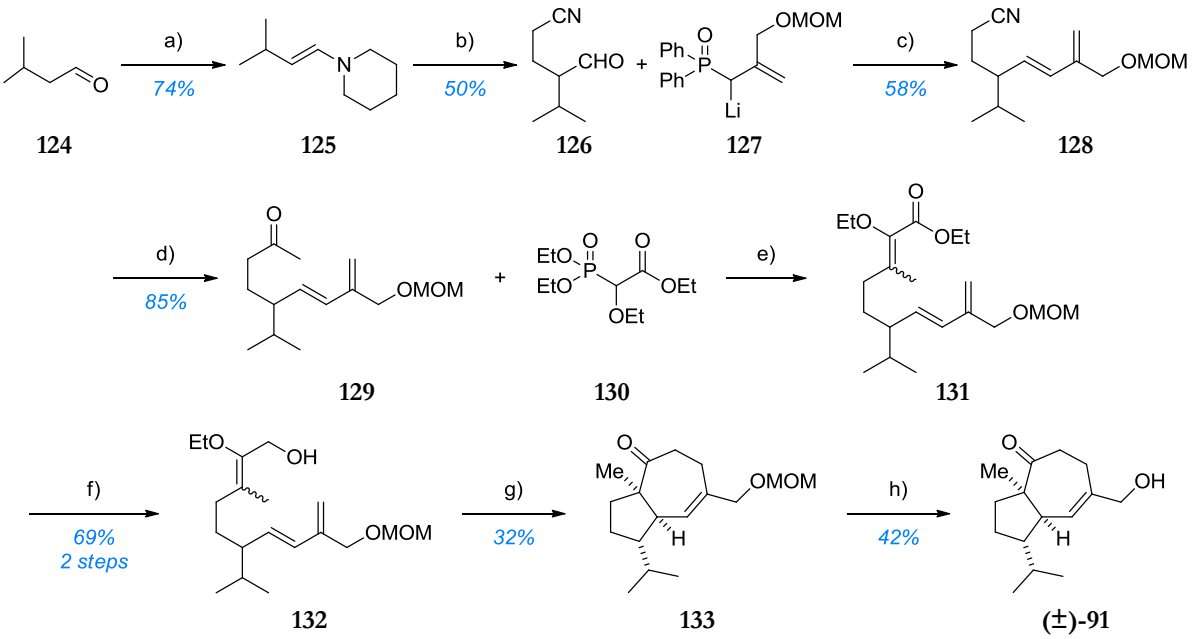

**Scheme 2.6: Wickberg *et al.* total synthesis of (+)-aphanamol I.**

**Reagents and conditions: a) 5% Pt/C, $H_2$; b) performic acid followed by ethanolic KOH; c) periodic acid, pyridine; d) AcOH, piperidine, benzene, reflux; e) $(PhP)_3RhCl$, benzonitrile, 130 °C; f) hν, MeCN, RT; c) $Me_2S(O)=CH_2$, THF, RT; d) KOH, MeOH, reflux.**

### 2.2.3. The Harmata synthesis (1997)

Harmata *et al.* took a more direct approach to the formation of the seven-membered ring by utilising a [4+3] cycloaddition previously developed within the group as a key step in the total

synthesis of (±)-aphanamol I [**Scheme 2.7**].[65] Isovaleraldehyde **124** was alkylated with acrylonitrile to give **126** *via* the corresponding enamine **125** in modest yield over two steps (37%) following standard literature procedures.[66] A subsequent Wittig-Horner reaction between lithiated phosphine oxide **127** and aldehyde **126**, gave *E*-diene **128** in 50% yield as a single geometric isomer. Alkylation of nitrile **128** with methylmagnesium iodide, followed by hydrolysis of the imine on work-up gave ketone **129** in excellent yield (85%). Horner-Wadsworth-Emmons homologation of **129** with phosphonate **130**, followed by reduction of ethyl ester **131** with lithium aluminium hydride, gave allylic alcohol **132** as a 1:1 mixture of inseparable geometric isomers. Treatment of alcohol **132** with triflic anhydride in the presence of 2,6-lutidine, gave cycloadduct **133** in modest yield, which after deprotection gave (±)-aphanamol I in eight steps and an overall yield of 1.7%.

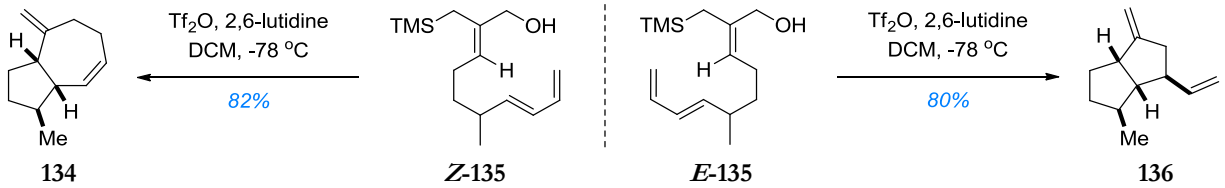



**Scheme 2.7: Harmata's total synthesis of (±)-aphanamol I**

**Reagents and conditions: a) piperidine, $K_2CO_3$, 0 °C; b) acrylonitrile, aq. work-up; c) THF; d) MeMgI, THF, reflux; e) LDA, THF; f) $LiAlH_4$, $Et_2O$; g) $Tf_2O$, 2,6-lutidine, DCM, -78 °C; h) $H_3O^+$.**

An interesting observation was made in the cyclisation of **132** to give cycloadduct **133**. Whilst only the [4+3] cycloadduct was obtained, **132** could also undergo a [3+2] cyclisation. In fact, Giguere *et al.* have reported a highly regioselective and high yielding piece of methodology for the cyclisation of *E* and *Z* isomers of alcohol **135** [**Scheme 2.8**].[67] Giguere found that exposure of

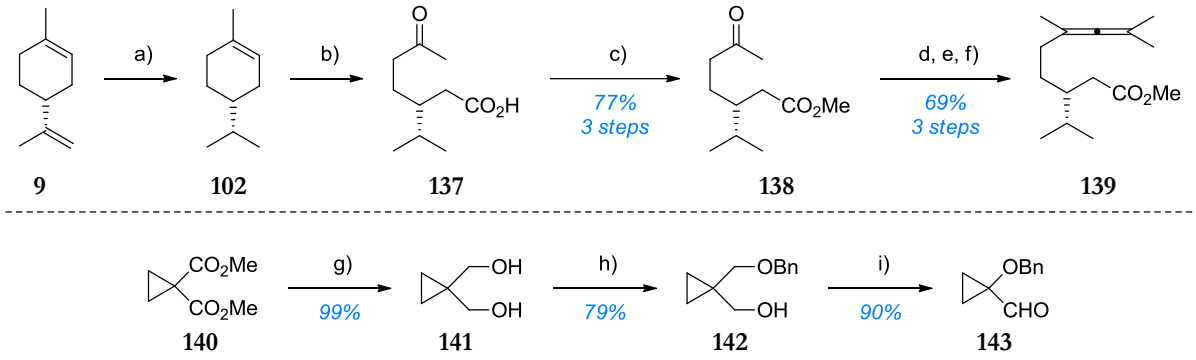
(*Z*)-**135** to triflic anhydride gave the [4+3] cycloadduct **134** in excellent yield (82%). On the other hand, (*E*)-**135** gave the alternative [3+2] cycloadduct **136** under the same conditions. Given these data, it is remarkable that although **132** is a 1:1 mixture of geometric isomers, Harmata does not report any [3+2] cycloadduct.




**Scheme 2.8 Regioselective cyclisation of 1,3-diene 135 reported by Giguere.**

### 2.2.4. The Wender synthesis (2000)

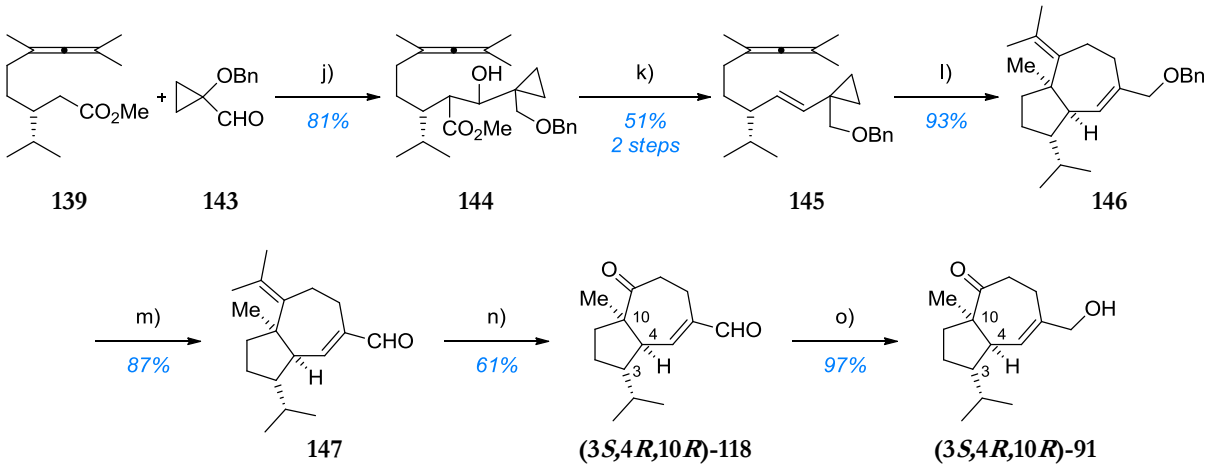
In 2000, Wender *et al.* reported the total synthesis of (+)-aphanamol I in which a novel metal catalysed [5+2] cycloaddition gave access to the [5.3.0]-bicyclic core of the isodaucane natural products.[68] It was proposed that the key cyclisation precursor would arise from cyclopropanecarboxaldehyde **143** and ketoester **139**, with the later derived from (*R*)-limonene [**Scheme 2.9**]. Hydrogenation of (*R*)-limonene (8) selectively reduced the *exo*-alkene to give **102**, which after ozonolysis with an oxidative workup using Jones' reagent gave keto acid **137**. Subsequent esterification of **137** with diazomethane provided keto ester **138** in 77% yield over three steps.[69] Treatment of ketone **138** with 1-propynyllithium,[70] gave the corresponding tertiary propargylic alcohol, which was acylated with acetic anhydride. Subsequent methylation using Gilman's reagent gave allene ester **139** *via* an $S_N2$' reaction in 69% yield over three steps. The coupling partner **143** was prepared in three steps from the corresponding diester **140** which was reduced with lithium aluminium hydride to give diol **141**. Subsequent mono benzyl protection of **141** and oxidation of the unprotected primary alcohol gave **143** in good yield (70% over three steps).




**Scheme 2.9: Synthesis of key coupling partners.**

**Reagents and conditions: a) 5% Pt/C, $H_2$; b) (i) ozone (ii) Jones reagent; c) $CH_2N_2$; d) 1-bromopropene, $^n$BuLi, THF, -78 °C; e) $Ac_2O$, $NEt_3$, cat. DMAP, DCM, RT; f) $Me_2CuLi$, THF, -78 °C; g) $LiAlH_4$, THF, reflux; h) NaH, BnBr, DMF, -10 °C; i) $(COCl)_2$, DMSO, $NEt_3$, DCM, -78 °C.**

Ester **139** was deprotonated with lithium diisopropylamide and added to aldehyde **143** to give alcohol **144** as a mixture of diastereoisomers [**Scheme 2.10**]. Decarboxylative dehydration was achieved by firstly converting alcohol **144** to the corresponding acetate and then heating in the presence of sodium cyanide to give the key cyclisation substrate **145**. Subjecting **145** to $[Rh(CO)_2Cl]_2$ (previously identified as a catalyst for such cyclisations[71]) gave cycloadduct **146** in excellent yield (93%) and as a single stereoisomer. Cleavage of the *exo*-cyclic double bond proved problematic, with direct ozonolysis of **146** cleaving the less hindered *endo*-cyclic bond selectively.




**Scheme 2.10: Key [5+2] cyclisation and completing the synthesis of (+)-aphanamol I.**

**Reagents and conditions: j) 1.2 eq. LDA, THF, -78 °C; k) (i) $Ac_2O$, $NEt_3$, DMAP, DCM, RT; (ii) NaCN, DMSO, 130 °C; l) 0.5 mol% $[Rh(CO)_2Cl]_2$, toluene, 110 °C; m) 5 eq. DDQ, DCM:$H_2O$ (10:1), RT; n (i) $O_3$, DCM, -78 °C; (ii) $Me_2S$; o) $NaBH_4$, $CeCl_3 \bullet 7H_2O$, 0 °C.**

This problem was solved by first oxidising the allylic benzyl ether to the corresponding *a,β*-unsaturated aldehyde **147**. Ozonolysis of **147** then allowed for the selective removal of the *exo*-cyclic double bond to give ketone (3*S*,4*R*,10*R*)-**118**. Subsequent selective 1,2-reduction of *a,β*-unsaturated aldehyde (3*S*,4*R*,10*R*)-**118** under Luche conditions, gave (+)-aphanamol I ($[\alpha]_D^{20}$ +23.0 (*c* 0.4, $CHCl_3$)(lit.[51] $[\alpha]_D^{18}$ +13.8 (*c* 0.29, $CHCl_3$))) in 13.4% yield over thirteen steps. Wender attributed the stereochemical outcome of the metal catalysed cycloaddition to be in accordance with a previously described mechanistic hypothesis [**Figure 2.3**]. Reversible oxidative addition of rhodium(I) to the alkene (**145**) π-face gives *cis*-fused metallocyclopentane **148**, with the isopropyl substituent placed on the less hindered *exo*-face. Subsequent cyclopropane cleavage generates **149**, which undergoes reductive elimination to give the observed stereoisomer **146**.

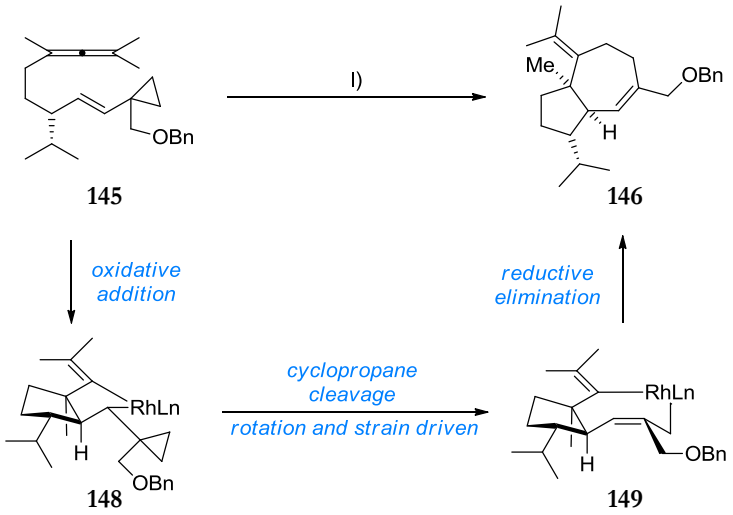



**Figure 2.3: Proposed mechanism accounting for the stereochemical outcome in the cyclisation of 145. Adapted from Wender's paper.[68]**

### 2.2.5. Absolute configuration of (+)-aphanamol I

As is apparent from the three syntheses of (+)-aphanamol I, there is a disagreement in the absolute configuration of the natural product [**Table 2.1**]. Whilst all three optical rotations were in accordance with natural (+)-aphanamol, Wender and Wickberg synthesised the (3*S*,4*R*,10*R*)-enantiomer and Mehta reported a synthesis for the opposite (3*R*,4*S*,10*S*)-enantiomer. Wickberg accounted for the difference in their observed specific rotation to that of natural (+)-aphanamol I

to be most likely due to the fact that it is not uncommon for terpenoids isolated from nature to exist as a mixture of enantiomers. For example turpentine, the distilled resin from pine trees, contains *a*-pinene in approximately 30% enantiomeric excess.[72]

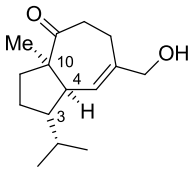
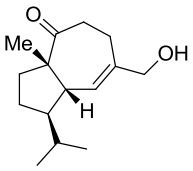
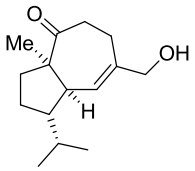
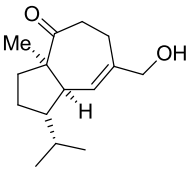
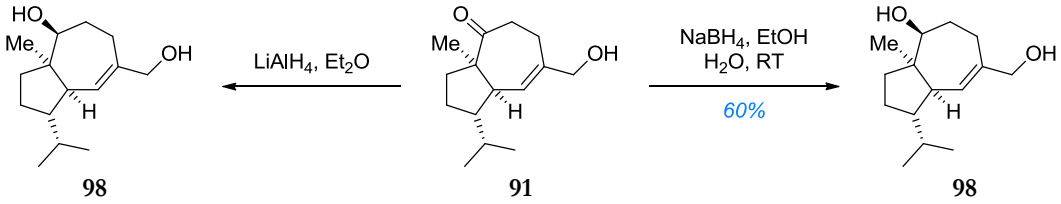
| Natural | Mehta | Wickberg | Wender |
|---|---|---|---|
|  |  |  |  |
| (3*S*,4*R*,10*R*)-**91** | (3*R*,4*S*,10*S*)-**91** | (3*S*,4*R*,10*R*)-**91** | (3*S*,4*R*,10*R*)-**91** |
| $[\alpha]_D^{18}$ +13.8 (*c* 0.29, $CHCl_3$) | $[\alpha]_D$ +10.0 (*c* 0.70, $CHCl_3$) | $[\alpha]_D^{20}$ +23.0 (*c* 2.00, $CHCl_3$) | $[\alpha]_D^{20}$ +23.0 (*c* 0.40, $CHCl_3$) |

**Table 2.1: Observed optical rotations of synthetic (+)-aphanamol I compared to natural.**

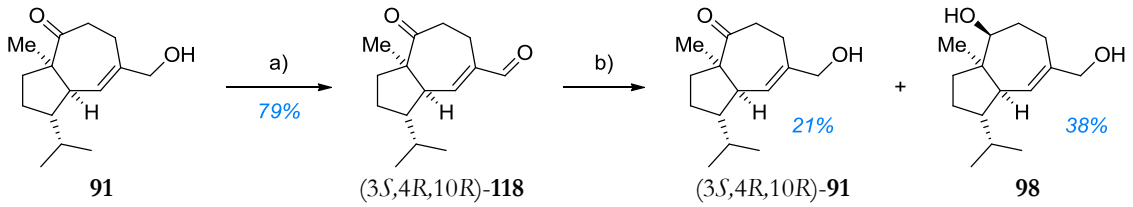
In the original isolation paper, to further aid in the structural assignment, Nishizawa treated (+)-aphanamol I with lithium aluminium hydride to give diol **98** ($[\alpha]_D^{15}$ +21.2 (*c* 0.25, $CHCl_3$)) [**Scheme 2.11**]. Accordingly, Wickberg treated synthetic (3*S*,4*R*,10*R*)-**91** with sodium borohydride to give **98** which exhibited an optical rotation of ($[\alpha]_D^{20}$ +40.0 (*c* 0.80, $CHCl_3$)). On the basis of the difference in optical rotations observed diol **98** and (+)-aphanamol I, Wickberg postulated that natural (+)-aphanamol I was isolated with an enantiomeric excess *ca.* 50%.




**Scheme 2.11: Reduction of (+)-aphanamol to the corresponding diol 98.**

This however, does not resolve the conflicting stereochemistry present in Mehta's synthetic (+)-aphanamol I. Thus, Wickberg carried out further experimental and spectroscopic studies to determine definitively the absolute configuration of (+)-aphanamol I [**Scheme 2.12**]. Subjecting their synthetic (+)-aphanamol I (**91**) to a perruthenate catalysed oxidation gave keto aldehyde

(3*S*,4*R*,10*R*)-**118** ($[\alpha]_D^{20}$ -5.9 (*c* 0.76, $CDCl_3$)), which was an intermediate in Mehta's synthesis ( $[\alpha]_D^{20}$ +33.0 (*c* 0.50, $CHCl_3$)). The sign and numerical difference of Mehta's keto aldehyde **118** cannot be explained in terms of enantiomeric excess. Wickberg was able to obtain the optical rotation data of natural aldehyde **118** isolated by Jackupovic from *C. Laevigate*,[III] which had an optical rotation of $[\alpha]_D^{20}$ -7.0, suggesting that Mehta's synthetic (+)-aphanamol might be the opposite enantiomer. Furthermore, upon reduction of aldehyde **118**, Wickberg obtained (+)-aphanamol I ($[\alpha]_D^{20}$ +18.0) together with diol ($[\alpha]_D^{20}$ +44.0). Wickberg also prepared, albeit in a less pure form, a sample of (-)-aphanamol I ((3*R*,4*S*,10*S*)-**91**) which had an optical rotation of $[\alpha]_D^{20}$ -22.0 (*c* 0.30, $CDCl_3$).



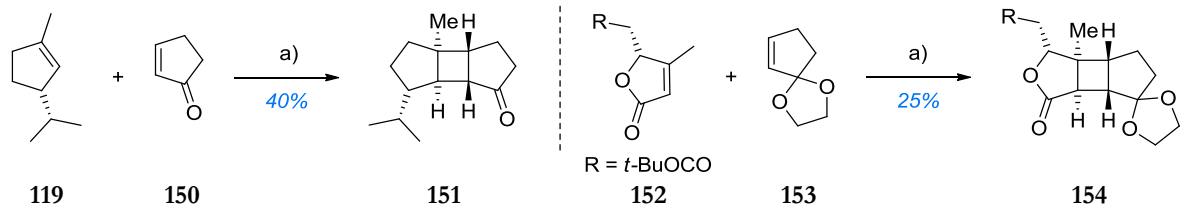

**91** (3*S*,4*R*,10*R*)-**118** (3*S*,4*R*,10*R*)-**91** **98**

**Scheme 2.12: Further experimental studies carried out by Wickberg.**

**Reagents and conditions: a) 4-methylmorpholine *N*-oxide, DCM, RT; b) $NaBH_4$, $CeCl_3 \bullet 7H_2O$, MeOH, RT.**

Wickberg also correlated cyclopentene **119** following a known procedure[73] to (-)-norbourbonone (**151**) ($[\alpha]_D^{20}$ -182 (*c* 0.50, $CHCl_3$)) which has had its absolute configuration confirmed [**Scheme 2.13**]. Koga *et al.* completed the total synthesis of (-)-*β*-bourbonene and (-)-norbourbonone in which they established the absolute configuration of lactone **152**. [74] Following a [2+2] photocycloaddition of **152** to acetal **153**, tricyclic lactone **154** was obtained in 25% yield after recrystallisation. Koga went on to complete the total synthesis of (-)-norbourbonone reporting an optical rotation of ($[\alpha]_D^{22}$ -193 (*c* 0.38, $CHCl_3$)) which matches well to the value obtained by Wickberg.

[III] Private communication between Wickberg and Jackupovic, see original publication.[64]




**119** **150** **151** **152** **153** **154**

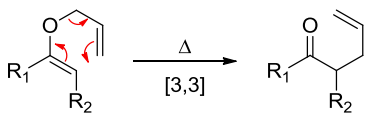
**Scheme 2.13: Wickberg's synthesis of (-)-nobourbonone to confirm the absolute configuration of 119.**

**Reagents and conditions: a) hν, benzonitrile, MeCN, RT.**

Finally, Wickberg carried out CD studies to determine the absolute configuration of an intermediate and their synthetic (-)-aphanamol I. Applying the octant rule to (+)-**122**, the model found the steric bulk of the rigid tricyclic ketone to sit in the positive quadrant, which was confirmed experimentally to have a positive $\theta$ value (+740 at 301 nm). However, the octant model of (-)-aphanamol I was found to occupy both positive and negative octants, making the predictions inconclusive. With the internal consistency of Wickberg's results combined with Wender's total synthesis, the absolute configuration of (+)-aphanamol I is (3*S*,4*R*,10*R*)-**91** and that the enantiomer synthesised by Mehta must then correspond to (-)-aphanamol I.

## 2.3. Synthesis of [5.3.0]-bicyclic ketones through a Claisen ring expansion

An attractive aspect of the [5.3.0]-bicyclic ketone core present in (+)-aphanamol I is the *γ,δ*-unsaturated relationship. One possible route to such a structure could be through a [3,3]-sigmatropic rearrangement of an allyl vinyl ether [**Figure 2.4**]. In a series of landmark papers, Claisen *et al.* developed a thermal [3,3]-sigmatropic rearrangement of various allyl vinyl ethers which is now known as the Claisen rearrangement.[75]

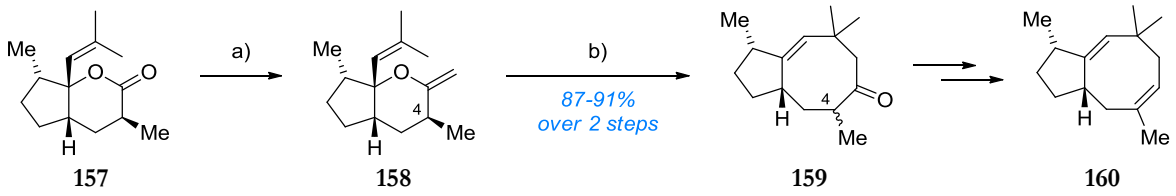



**155** **156**

**Figure 2.4: Claisen rearrangement of an allyl vinyl ether to the corresponding *γ,δ*-unsaturated carbonyl.**

Expanding on Claisen's work, Paquette *et al.* found that vinylic lactones underwent a "Claisen ring expansion", *via* the corresponding enol ether to give medium ring carbocycles.[76] For

example, Paquette applied a thermally induced Claisen ring expansion as the pivotal step in the total synthesis of precapnelladiene [**Scheme 2.14**].[76a] Treatment of bicyclic lactone **157** with Tebbe reagent, gave enol ether **158**. Subsequently, heating of allyl vinyl ether **158** in a base-washed sealed tube, to prevent enol ether hydrolysis, gave [6.3.0]-cyclooctenone **159** in excellent yield over two steps (up to 91%). The bicyclic ketone **159** was isolated as a mixture of C-4 diastereomers, most likely due to epimerisation under the basic conditions, however this stereocentre was destroyed at a later stage of the synthesis. Paquette also postulated that traces of Lewis acid impurities from the Tebbe reagent might catalyse the subsequent Claisen ring expansion, though the effect or nature of the Lewis acid is not clear. Completion of the total synthesis, gave precapnelladiene **160** in ten steps with an overall yield of 8.1%.

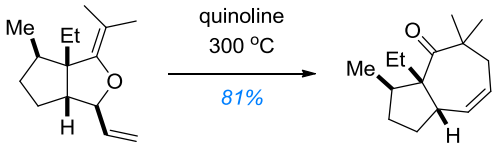



**157** **158** **159** **160**

**Scheme 2.14: Synthesis of precapnelladiene using a ring expansion Claisen as a key step.**

**Reagents and conditions: a) $Cp_2TiCl(CH_2)AlMe_3$; b) 200 °C, 87-91% yield over 2 steps.**

Although rare, Claisen ring expansions of 5-membered cyclic allyl vinyl ethers have been reported. For example, during studies into [4+3] cycloadditions, Harmata *et al.* utilised a Claisen ring expansion to verify the relative stereochemistry of such reactions [**Scheme 2.15**].[77] Heating vinyl ether **161** at 300 °C in quinoline, gave the corresponding [5.3.0]-bicyclic ketone **162** in excellent yield (81%).




**161** **162**

**Scheme 2.15: Claisen ring expansion to synthesise a [5.3.0]-bicyclic ketone, a key structural motif found in (+)-aphanamol.**

## 2.4. Retrosynthetic analysis of (+)-aphanamol I

Our retrosynthetic strategy for (+)-aphanamol I was designed to investigate the possibilty of utilising a Claisen ring expansion as well as our manganese(III) acetate/copper(II) triflate mediated oxidative radical cyclisation [**Figure 2.5**]. Thus, a [3,3]-sigmatropic rearrangement of allyl vinyl ether **163** would give the all carbon [5.3.0]-bicyclic core of (+)-aphanamol I. Enol ether **163**, in turn, could be obtained by an olefination of lactone **164** using either the Tebbe reagent or Petasis reagent. The bridgehead methyl would be introduced through a selective lithium enolate alkylation of **165**, which would be obtained *via* a Krapcho decarboxylation of methyl ester **166**. [3.3.0] Bicyclic *γ*-lactone **166** would arise from an oxidative radical cyclisation of dienyl malonate **167**, which would form the desired adjacent quaternary-tertiary-tertiary stereocentres as previously described in **Section 1.4.1**.

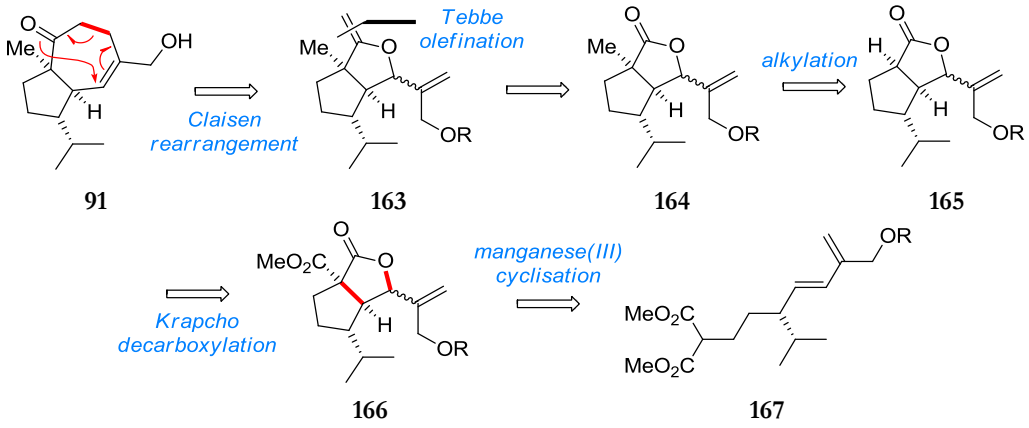
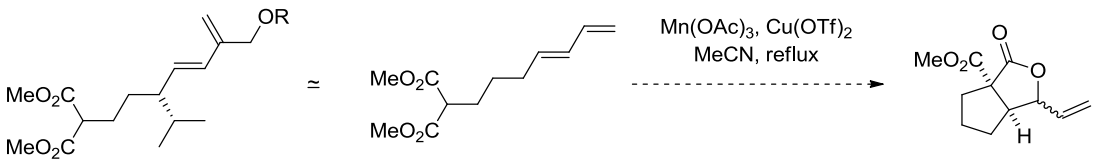



**Figure 2.5: Retrosynthesis of (+)-aphanamol I to key cyclisation precursor.**

## 2.5. Cyclisation of a simple dienyl malonate

To date, there have been no previous reports for the cyclisation of a dienyl malonate to give an allyl substituted [3.3.0]-bicyclic *γ*-lactone such as **166**, under manganese(III) acetate mediated oxidative radical conditions. Thus, an initial study of the proposed cyclisation system was carried out on a model substrate **86**, a simple variant of the key acyclic structure **167** proposed in our retrosynthesis [**Figure 2.6**]. Since this substrate is directly analogous to that of 4-pentenyl malonates previously studied in the group, the reaction was expected to follow a similar pathway.

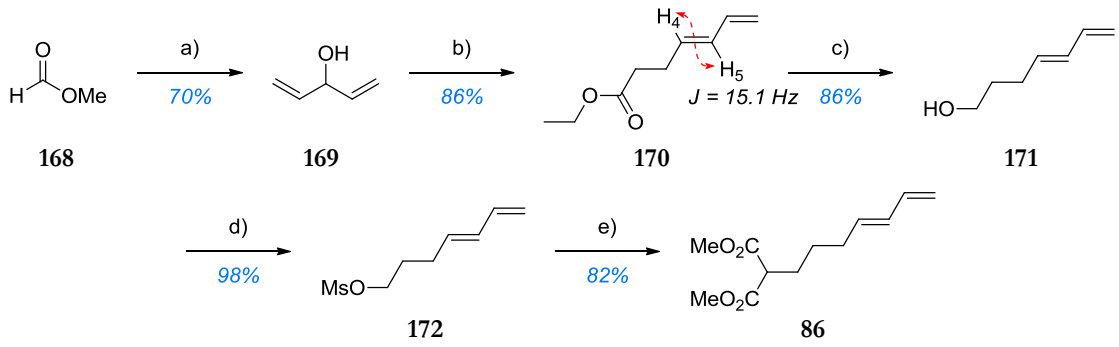



**167** **86** **87**

**Figure 2.6: Simple dienyl malonate based on the acyclic structure 167 proposed retrosynthetically.**

### 2.5.1. Simple dienyl malonate synthesis

The model cyclisation substrate, dienyl malonate **86**, was synthesised from methyl formate in five steps using standard procedures [**Scheme 2.16**]. Exposure of methyl formate **168** to two equivalents of vinylmagnesium bromide gave divinyl carbinol **169** in good yield (86%) according to the procedure of Hudlicky.[78] Maintaining an internal temperature of around 2 °C was found to give best reaction yields. A Johnson-Claisen rearrangement[79] of alcohol **169** using triethyl orthoacetate gave known ethyl ester **170** as a >20:1 *E*:*Z* mixture of geometric isomers. The major regioisomer was identified as the *E*-isomer due to a large coupling constant observed between H-4 and H-5 ($J$ = 15.1 Hz). Subsequent reduction of ester **170** using a suspension of lithium aluminium hydride in diethyl ether gave dienyl alcohol **171** in a combined yield of 71%. Mesylation of **171** with methanesulfonyl chloride gave mesylate **172** in excellent yield, which without further purification was alkylated with the anion of dimethyl malonate to give malonic ester **86** in an overall yield of 41% from methyl formate **168**.




**168** **169** **170** **171** **172** **86**

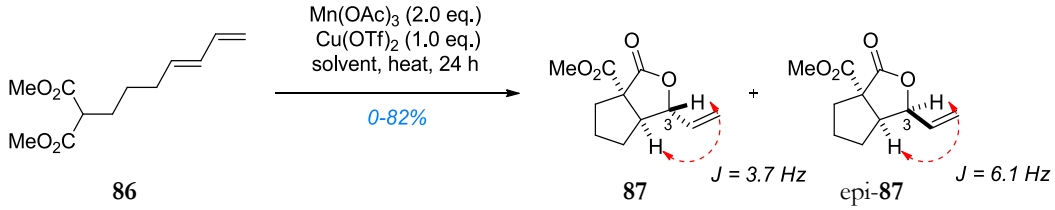
**Scheme 2.16: Synthesis of a simple dienyl malonate.**

**Reagents and conditions: a) vinylmagnesium bromide, THF, 0 °C, 2 h, 70%; b) propionic acid, triethyl orthoacetate, reflux, 18 h, 86%; c) $LiAlH_4$, $Et_2O$, 0 °C-RT, 1 h, 86%; d) methanesulfonyl chloride, triethylamine, DCM, 0 °C-RT, 1.5 h, 98%; e) NaH, dimethyl malonate, KI, DMF/THF, reflux, 18 h, 82%.**

### 2.5.2. Oxidative radical cyclisation of dienyl malonate 86

Previous studies within the group in the formation of bicyclic *γ*-lactones under oxidative radical conditions have shown that yield and selectivity are highly dependent on concentration, temperature and solvent. Therefore a screen of reaction conditions was carried out as such substrates have previously not been cyclised under manganese(III) acetate conditions [**Table 2.2**]. Dienyl malonate **86**, was initially subjected to a variety of solvents which have been shown to be compatible with manganese(III) acetate mediated radical cyclisations (entries 1-5). Acetonitrile (entry 1) and dimethoxyethane (entry 5) were found to promote formation of [3.3.0]-bicyclic *γ*-lactone **87** as an inseparable mixture of diastereoisomers at the vinylic stereocentre in good yield. Bicyclic *γ*-lactone **87** was identified by characteristic carbonyl stretching frequencies for a *γ*-lactone ($\nu_{max}$ 1775 $cm^{-1}$) and an aliphatic ester ($\nu_{max}$ 1740 $cm^{-1}$) in the IR. In the proton NMR, two terminal vinyl groups were identified by two single proton double double doublets at $\delta_H$ 5.94 ($J$ = 17.1, 10.4, 6.2 Hz) and $\delta_H$ 5.83 ($J$ = 17.1, 10.4, 6.3 Hz) assigned to the separate diastereoisomers. Two lactone protons at C-3 were observed as a double doublet $\delta_H$ 5.18 ($J$ = 6.2, 6.1 Hz) and $\delta_H$ 4.53 ($J$ = 6.3, 3.7 Hz). Based on the coupling constant observed between the lactone proton (H-3) and the bridgehead proton (H-3a) and previous work in the group, the major diastereoisomer was assigned as **87**. Acetic acid, ethanol and dimethyl sulfoxide favoured polymerisation predominantly over cyclisation as identified by mass spec and multiple methyl ester peaks in the crude proton NMR. Although slightly improved diastereoselectivity was observed in dimethoxyethane, acetonitrile was chosen for further optimisation. As polymerisation was observed in all solvents, it was postulated that polymerisation could be minimised by modifying reaction concentration, which proved to be the case. Higher concentrations of malonate **86** (entry 6 and 7) gave an increase in polymeric material, whilst lower concentrations (entries 8-10) gave good to excellent yields of the [3.3.0]-bicyclic *γ*-lactone **87**. The lower yield observed at 0.05 M concentration (entry 10) was due to incomplete consumption of malonate **86**, which could easily be overcome by increased reaction times. Finally temperature studies (entries 11-14) found that temperature did not play a critical role

in either yield or stereoselectivity of such cyclisations. Whilst reactions at 80 °C were typically complete in 1 h, room temperature reactions typically took 48 h with incomplete conversion still observed. Whilst minimal stereoselectivity at the lactone stereocentre (C-3) was observed in the cyclisation of malonate **86**, this was not of importance as this stereocentre would be destroyed in the forthcoming Claisen ring expansion.



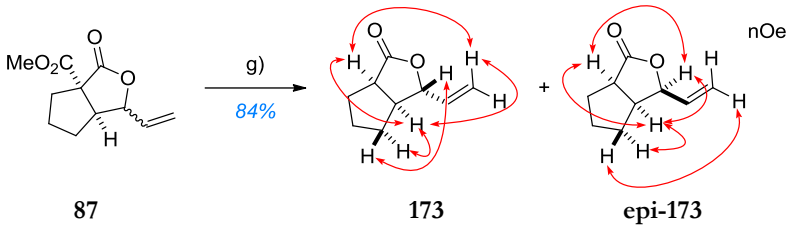

| Entry | Solvent | Conc. (mol/L) | Temp (°C) | Yield (%)[a] | *d.r.*[b] |
|---|---|---|---|---|---|
| 1 | MeCN | 0.3 | 80 | 75 | 1.3:1 |
| 2 | AcOH | 0.3 | 80 | 34 | 1.1:1 |
| 3 | EtOH | 0.3 | 80 | 3 | 1:1 |
| 4 | DMSO | 0.3 | 80 | n.d | n.d |
| 5 | DME | 0.3 | 80 | 70 | 1.4:1 |
| 6 | MeCN | 0.6 | 80 | 44 | 1.3:1 |
| 7 | MeCN | 0.4 | 80 | 62 | 1.3:1 |
| **8** | **MeCN** | **0.2** | **80** | **82** | **1.3:1** |
| 9 | MeCN | 0.1 | 80 | 79 | 1.3:1 |
| 10 | MeCN | 0.05 | 80 | 72 | 1.3:1 |
| 11 | MeCN | 0.2 | 60 | 79 | 1.3:1 |
| 13 | MeCN | 0.2 | 40 | 75 | 1.3:1 |
| 14 | MeCN | 0.2 | 20 | 69 | 1.4:1 |

**[a] Reactions carried out on 0.2 mmol of substrate. [b] *d.r.* measured by crude $^1$H NMR**

**Table 2.2: Optimisation of the $Mn(OAc)_3$ mediated cyclisation of dienyl malonate.**

The optimised cyclisation conditions proved to be highly reproducible in large scale reactions (up to 13 mmol), with yields only slightly lower (74-80%) then those carried out on small scale (82%, entry 8). At this point it was not possible to separate diastereomer **87** from epi-**87** by

high-performance liquid chromatography (HPLC). Thus, the mixture of diastereoisomers was decarboxylated under Krapcho conditions to give a separable mixture of lactones **173** and epi-**173** in excellent yield (84%) [**Scheme 2.17**]. Proton NMR nOe studies confirmed the major diastereomer to be **173** as postulated with [3.3.0]-bicyclic *γ*-lactone **87**, in which the vinyl group is placed on the less hindered *exo*-face.




**87** **173** **epi-173**

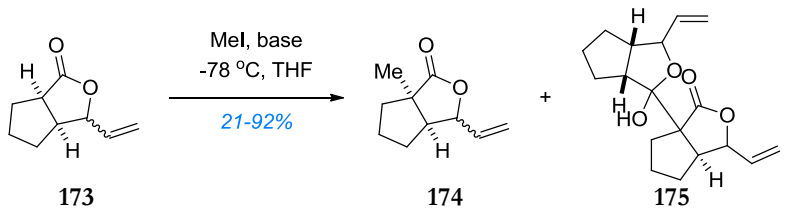
**Scheme 2.17: Decarboxylation of ester 87under Krapcho conditions and key proton nOe data**

**Reagents and conditions: g) LiCl, $H_2O$, DMSO, 195 °C, 84%.**

### 2.5.3. Alkylation of lactone 173 to introduce the bridgehead methyl

Introduction of the required bridgehead methyl group proved to be problematic [**Table 2.3**]. Deprotonation of lactone **173** with lithium bis(trimethylsilyl)amide followed by trapping of the enolate with methyl iodide (entry 1) gave a poor yield of alkylated lactone **174**. The side product was identified by extensive NMR and IR analysis as dimer **175** (HRMS found 327.1564, $C_{18}H_{24}NaO_4$ requires 327.1567), likely formed by a Claisen condensation. In the carbon NMR a resonance at $\delta_C$ 182.8 indicated a lactone carbonyl, whilst a resonance at $\delta_C$ 108.0 indicated the presence of a lactol carbon. In the IR, an alcohol stretch was observed at $\nu_{max}$ 3470 $cm^{-1}$ whilst the lactone carbonyl stretch was observed at $\nu_{max}$ 1738 $cm^{-1}$. The reason the stretch appears at a lower wavenumber compared to a normal lactone is likely due to a hydrogen bond between the carbonyl and the alcohol weakening the C=O double bond. A decrease in reaction concentration was postulated to help prevent dimerisation (entry 2 and 3). Whilst a slight increase in yield was observed at lower concentrations, the alkylation still did not give acceptable yields, nor were these results reproducible with yields varying by up to 20%. The enolate formation was investigated further, as using different bases and counterions can influence the metal aggregate formed in

solution.[80] Sodium bis(trimethylsilyl)amide (entry 4) gave comparable yields to lithium bis(trimethylsilyl)amide, whilst potassium bis(trimethylsilyl)amide (entry 5) favoured dimer formation further. Lithium diisopropylamide (entry 6), which tends to favour dimeric aggregates in solution,[81] gave a slight increase in yield of **174** over lithium bis(trimethylsilyl)amide but still favoured dimerisation over alkylation. The solvent was changed to toluene (entry 7) to further aid in the formation of dimeric aggregates - tetrahydrofuran favours monomeric aggregates as the oxygen lone pair disrupts dimeric aggregation. Unfortunately toluene did not provide any benefit over THF in yield of alkylated material. At this point it was postulated that dimerisation could be prevented by having the desired electrophile (methyl iodide) present in the reaction medium during deprotonation (entry 8). Thus deprotonation of **173** in the presence of 5 equivalents of methyl iodide gave lactone **174** in excellent yield (92%) with minimal dimer **175** observed.




**173** **174** **175**

| Entry | Base | Solvent | Conc. (mol/L) | 174 yield (%) |
|---|---|---|---|---|
| 1 | LiHMDS | THF | 0.2 | 21 |
| 2 | LiHMDS | THF | 0.1 | 27 |
| 3 | LiHMDS | THF | 0.05 | 34 |
| 4 | NaHMDS | THF | 0.05 | 32 |
| 5 | KHMDS | THF | 0.05 | 26 |
| 6 | LDA | THF | 0.05 | 36 |
| 7 | LiHMDS | toluene | 0.05 | 33 |
| **8** | **LiHMDS** | **THF** | **0.05** | **92[a]** |

**[a] Electrophile present in the reaction mixture.**

**Table 2.3: Introduction of the bridgehead methyl.**

### 2.5.4. Olefination of lactone 174 followed by a Claisen ring expansion

Typically, titanium based carbenoids are commonly used in the preparation of enol ethers from ketones and lactones over more traditional olefination methods. There are two main titanium carbenoids which have been extensively studied in the literature [**Figure 2.7**]. Titanium-aluminium complex **176**, now termed the Tebbe reagent, was first reported in 1978 as a reagent which methylenates carbonyl groups in the presence of a Lewis base.[82] The Petasis reagent (**177**) was developed as an alternative to the Tebbe reagent, as dimethyl titanocene is relatively air and moisture stable compared with **176**.[83] Typically the titanium carbene **178** is produced by either decomposition of **176** with pyridine[84] or by thermal decomposition of **177** *via* *a*-methane elimination.[83] Subsequent reaction of the carbonyl with carbene **178** gives metallocyclobutane intermediate **179**, which collapses to give alkene **180** and titanium oxide **181**. The driving force of the transformation is the formation of the strong Ti-O double bound.

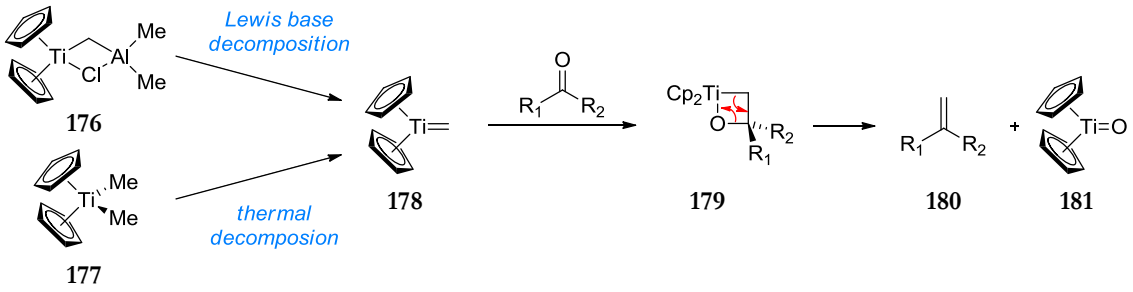
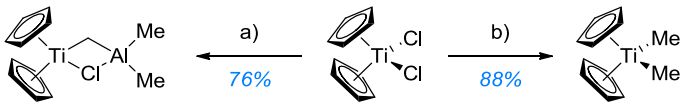



**Figure 2.7: Alkenylation of a carbonyl using the Tebbe or Petasis reagent.**

The titanium carbenoids **176** and **177** were prepared following standard literature procedures [**Scheme 2.18**]. Titanocene dichloride (**182**) was treated with trimethylaluminium over a 3 day period, to give the Tebbe reagent **176**, which was recrystallised from pentane.[85] Due to the reported in-stability of the Tebbe reagent, all procedures were carried out in a Schlenk tube to minimise water and air contact. The Petasis reagent was prepared by reacting titanocene dichloride (**182**) with two equivalents of methyl lithium and then recrystallising from pentane to give **177** as orange crystals. Both reagents were stored in brown glass bottles at -20 °C as 0.5 M (Tebbe reagent) and 0.25 M (Petasis reagent) solutions in toluene.[86]

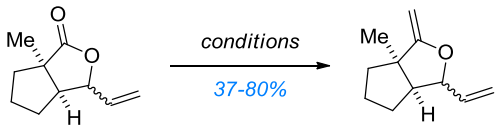



**176** **182** **177**

**Scheme 2.18: Preparation of the Tebbe and Petasis reagents.**

**Reagents and conditions: a) $AlMe_3$, toluene, RT, 3 days, 76%; b) MeLi, $Et_2O$, 88%.**

With both methylenation reagents in hand, conversion of lactone **174** to enol ether **183** was investigated [**Table 2.4**]. Subjecting lactone **174** (mixture of diastereoisomers) to the Tebbe reagent under conditions reported by Tebbe *et al.* (entry 1), gave enol ether **183** in 47% yield. The *exo*-alkene was identified by the disappearance of the lactone carbonyl IR stretch ($\nu_{max}$ 1767 $cm^{-1}$) and the presence of a characteristic enol ether alkene stretch at $\nu_{max}$ 1666 $cm^{-1}$ ($OC=CH_2$) and $\nu_{max}$ 1005 $cm^{-1}$ ($O\text{-}CCH_2$). In the proton NMR, the enol ether was identified by the presence of two diastereotopic terminal alkene protons $\delta_H$ 4.63-4.62 (m) and $\delta_H$ 3.99-3.98 (m). As discussed previously, enol ethers such as **183** are prone to hydrolysis under acidic conditions, hence reactions were carried out in base washed glassware and purified on deactivated silica (1% triethylamine). Other compatible solvents (entry 2 and 3) were tested, both of which resulted in a decrease in yield of enol ether **183**. Utilising a different Lewis base (entry 4) also gave a decrease in isolated yield of **183**. Unable to increase the yield of **183** using the Tebbe reagent, the Petasis reagent was investigated. Subjecting lactone **174** to conditions reported by Petasis *et al.* (entry 5) gave a minimal amount of olefin **183**. Throughout the reaction, the mixture remained orange suggesting thermolysis of the Petasis reagent to give the active carbene had not taken place. Increasing the temperature to 110 °C (entry 6) gave the desired enol ether **183** in good to excellent yield (61-80%). The variability in yield can be attributed to the loss of product through hydrolysis of the enol ether and possible volatility of the product. Finally, catalytic titanocene dichloride (entry 7) was added to the reaction mixture, as Payack *et al.* demonstrated using titanocene dichloride (**182**) as an additive gave cleaner and higher yielding olefinations.[87] However, in this case the addition of **182** gave a lower yield of the desired olefin **183**.

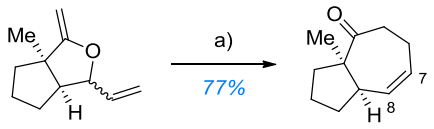



**174** **183**

| Entry | Titanium carbenoid | Solvent | Additive | Temp (°C) | Yield (%) |
|---|---|---|---|---|---|
| 1 | Tebbe | toluene | pyridine | -15 | 47 |
| 2 | Tebbe | THF | pyridine | -15 | 45 |
| 3 | Tebbe | DME | pyridine | -15 | 37 |
| 4 | Tebbe | toluene | DMAP | -15 | 40 |
| 5 | Petasis | toluene | - | 60 | 0 |
| **6** | **Petasis** | **toluene** | **-** | **110** | **61-80** |
| 7 | Petasis | toluene | $Cp_2TiCl_2$ | 110 | 44 |

**Table 2.4: Olefination optimisation utilising the Tebbe and the Petasis reagent.**

Pleasingly enol ether **183** readily underwent a Claisen ring expansion when heated in xylene at reflux to give [5.3.0]-bicyclic ketone **184** in 77% yield [**Scheme 2.19**]. In the carbon NMR, the ketone carbon was identified at δ 214.8 (7 ring ketone), whilst in the IR, a carbonyl stretch was identified at $\nu_{max}$ 1698 $cm^{-1}$ indicating the presence of an aliphatic ketone. In the proton NMR, the internal alkene was identified by a single proton multiplet at $\delta_H$ 5.62-5.54 (C-7) and a single proton multiplet at $\delta_H$ 5.49-5.45 (C-8).




**183** **184**

**Scheme 2.19: Claisen ring expansion of enol ether 183.**

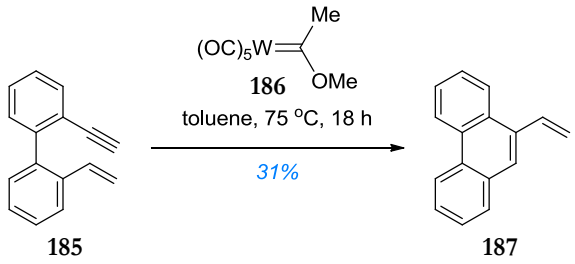
**Reagents and conditions: a) xylene, 150 °C, 24 h, 77%.**

## 2.6. Total synthesis of (±)-aphanamol I

With a robust route developed which demonstrates a Claisen ring expansion of a vinylic [3.3.0]-bicyclic *γ*-lactone, work turned to developing a synthetic route to (±)-aphanamol I. As identified retrosynthetically [**Figure 2.5**], the key cyclic material **166** would arise from a cyclisation of 1,3-diene **167**. Conjugated dienes are important building blocks in organic synthesis and polymer chemistry and hence have been of key synthetic interest. One such way of constructing the structural motif is *via* an enyne cross metathesis.

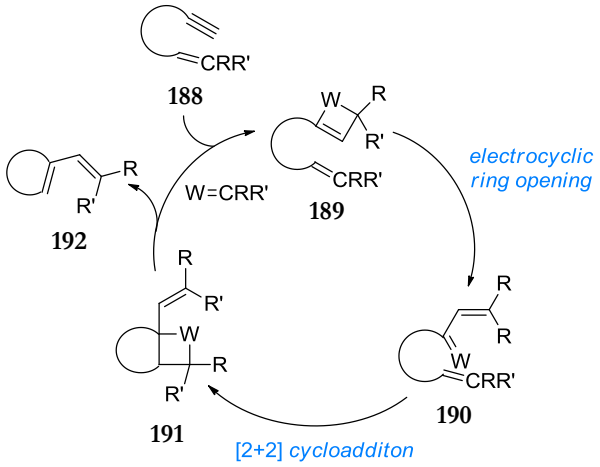
### 2.6.1. Enyne cross metathesis to form dienes

In 1985 Katz *et al.* reported a novel π-bond reorganisation in which a stabilised tungsten carbene combined a terminal acetylene with an olefin in an intramolecular enyne cross metathesis [**Scheme 2.20**].[88] For example, treatment of enyne **185** with a catalytic amount of tungsten carbene complex **186** (1 mol%) in toluene at 75 °C gave diene **187** in 31% yield. Following the report by Katz, Hoye *et al.* further extended the scope of tungsten carbene catalysed enyne metathesis and also found chromium carbenes to be applicable in such transformations.[89]



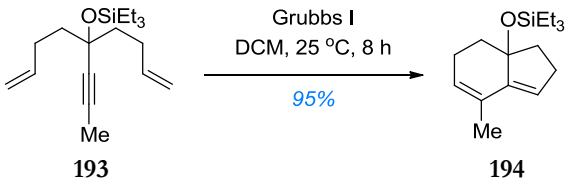

**Scheme 2.20: First example of an enyne metathesis using a tungsten carbene.**

Mechanistically, Katz proposed the metathesis reaction to proceed by a [2+2] cycloaddition of alkyne **188** to the tungsten carbene which would generate metallocyclobutene **189** [**Scheme 2.21**]. Subsequent electrocyclic ring opening of **189** produces vinyl substituted carbenoid **190**, which then undergoes an intramolecular [2+2] cycloaddition to the alkene to give metallocyclobutane **191**. Finally intermediate **191** collapses *via* an electrocyclic ring opening, to give cyclic 1,3-diene **192** and regenerates the active tungsten carbene catalyst.




**Scheme 2.21: Proposed mechanism for a tungsten catalysed enyne metathesis.**

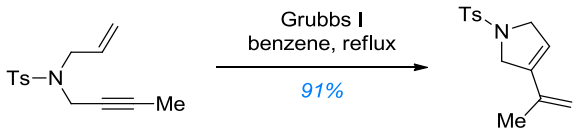
However, low yields and multiple reaction pathways restricted the synthetic applicability of Fischer carbenes in enyne cross metathesis. Although other transition metals have been shown to be applicable to enyne cross metathesis, most notably palladium and platinum,[90] the discovery of ruthenium based carbenes by Grubbs *et al.* revolutionised metathesis chemistry.[91] Even though Grubbs catalysts were developed for alkene cross metathesis, Grubbs found them to be applicable to enyne cross metathesis [**Scheme 2.22**]. For example using Grubbs I, dienyne **193** underwent an enyne/ring closing metathesis to give fused bicycle **194** in excellent yield (95%). Furthermore, Grubbs found that sterically differentiated olefins gave access to several bicyclic ring systems ([4.3.0]-, [5.4.0]-, [4.4.0]-, and [5.3.0]-bicyclic systems)




**Scheme 2.22: Application of Grubbs' catalyst in an enyne/ring closing metathesis**

Following on from his work which utilised a chromium carbene complex to synthesis a variety of heterocyclic dienes,[92] Mori *et al.* found that Grubbs catalysts were as efficient at inducing an enyne ring closing metathesis [**Scheme 2.23**].[93] For example, treatment of enyne **195** with catalytic Grubbs I (1 mol%) gave cyclic diene **196** in excellent yield (91%). Mori found that an

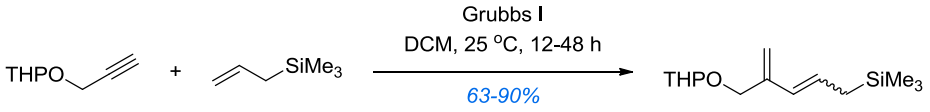
electron rich alkyne was beneficial, as the corresponding terminal alkyne gave much lower yields of the corresponding cyclic product (36%). Another benefit highlighted by Mori was the large functional group tolerance which in accordance with Grubbs's work had not previously been seen with other metal carbenes.




**195** **196**

**Scheme 2.23: Use of Grubbs catalyst in an enyne ring closing metathesis**

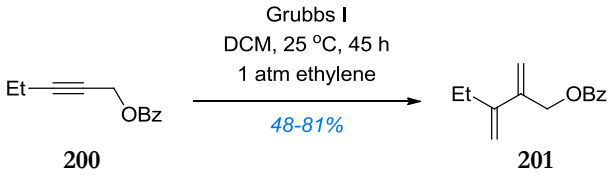
Initially enyne metathesis was limited to intramolecular cyclisations, due to multiple reaction pathways possible in an intermolecular reaction. Such a transformation is complicated to control, as there are three kinds of metathesis which can occur: 1) intermolecular diene metathesis; 2) intermolecular alkyne metathesis; 3) intermolecular enyne metathesis. Generally this leads to a complex mixture of alkene, alkyne and polymeric products, making such reactions seemingly impossible in organic synthesis.[94] A significant breakthrough in such transformation was made in 1997, when Blechert *et al.* reported a highly selective enyne metathesis [**Scheme 2.24**].[95] Blechert found that treatment of a protected propargylic alcohol **197** with Grubbs I in the presence of an excess of alkene **198** (2-3.0 eq.), gave 1,3-diene **199** in good to excellent yields (63-90%). One drawback of the methodology was the inability to control olefin geometry. In most cases, the dienes were produced as a 1:1 mixture of *E*/*Z* diastereomers, with a maximum selectivity of 3:1 observed (entry 3). Equimolar mixtures of alkyne and alkene gave the desired 1,3-diene, however yields were much lower. Interestingly, Blechert does observe un-wanted metathesis by-products such as polymer, but only to a minimal extent.




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

**Scheme 2.24: Intermolecular enyne cross metathesis of an alkyne to an alkene.**

Concurrently, More *et al.* reported an intermolecular enyne cross metathesis of an alkyne to ethylene [**Scheme 2.25**].[96] For example, alkyne **200** in the presence of Grubbs I catalyst under an ethylene atmosphere, gave simple 2,3-substituted diene **201** in modest yield (62%).




**200** **201**

**Scheme 2.25: Intermolecular enyne cross metathesis using ethylene.**

Although Mori mainly focussed on internal alkynes, one terminal alkyne was used to give a 1,3-diene in 81% yield. The use of an ethylene atmosphere was also found to be applicable in standard ring closing metathesis.[97] The reasons for the "ethylene effect" are mechanistically unclear; however, the use of ethylene has become widely used in the literature.[98]

### 2.6.1.1. Proposed mechanism of a ruthenium catalysed enyne cross metathesis

Mechanistically, two pathways have been proposed for a Grubbs mediated enyne metathesis [**Figure 2.8**]. The first (Pathway A) in a similar fashion to that proposed by Katz for tungsten carbenes, sees alkyne **203** react with ruthenium carbene **202** to give metallocyclobutene **204**. Subsequent electrocyclic ring opening gives carbenoid **205** which then undergoes a [2+2] cycloaddition to alkene **206** to give metallocyclobutane **207**. Finally ring opening gives the desired diene **208** and regenerates the active catalyst. Support for pathway A was reported by Mori *et al.* using competitive *inter*- and *intra*molecular reactions who found the alkyne to react with Grubbs catalyst at a faster rate compared to the alkene.[99] Alternatively (Pathway B), addition of ruthenium carbenoid **209**, in which the alkene is already attached, to alkyne **203** gives metallocyclobutene **210**. Following an electrocyclic ring opening of **210**, addition of alkene **206** to carbenoid **211** produces 1,3 diene **208** and continues the catalytic cycle. NMR studies by Hoye *et al.* found the presence of two distinct carbene proton resonances attributed to **209** and **211**.[100] Whilst both findings provide a

mechanistic insight into the reaction, neither disproves the other suggesting both pathways are likely active.

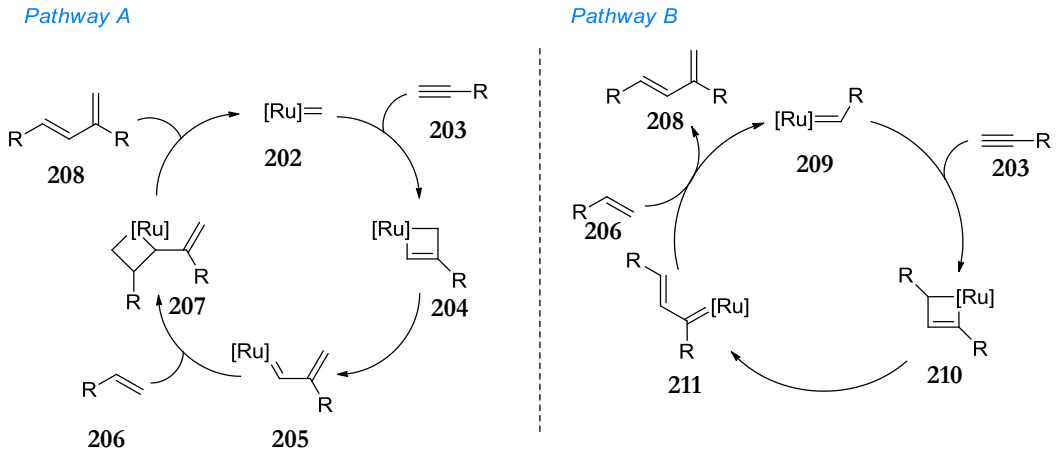



**Figure 2.8: Proposed mechanisms for a Grubbs mediated enyne cross metathesis.**

Finally, in 2005 Lloyd-Jones *et al.* provided experimental evidence in support of Pathway B.[101] Using $^{2}H$ and $^{13}C$ labelling studies of a ruthenium catalysed enyne ring closing metathesis Lloyd-Jones obtained metathesis products which were not compatible with Pathway A, but could be accounted for by Pathway B. This suggests that metathesis of the ruthenium carbene to the alkene must occur first followed by addition to the alkyne.

### 2.6.2. Retrosynthesis utilising an enyne cross metathesis to form the key diene 167

With the power of an enyne cross metathesis apparent, it was envisaged that key diene **167** could be synthesised by an enyne cross metathesis of alkene **212** with alkyne **213** [**Figure 2.9**]. Malonate **212** in turn could be synthesised from alcohol **214**, through a mesylation of **214** followed by a displacement with dimethyl malonate. Alcohol **214** would result from a lithium aluminium hydride reduction of ethyl ester **215**, which in turn would arise from a Johnson-Claisen rearrangement of allylic alcohol **216**. A chemoselective Luche reduction of commercially available 4-methyl-pentenal would give alcohol **217**.

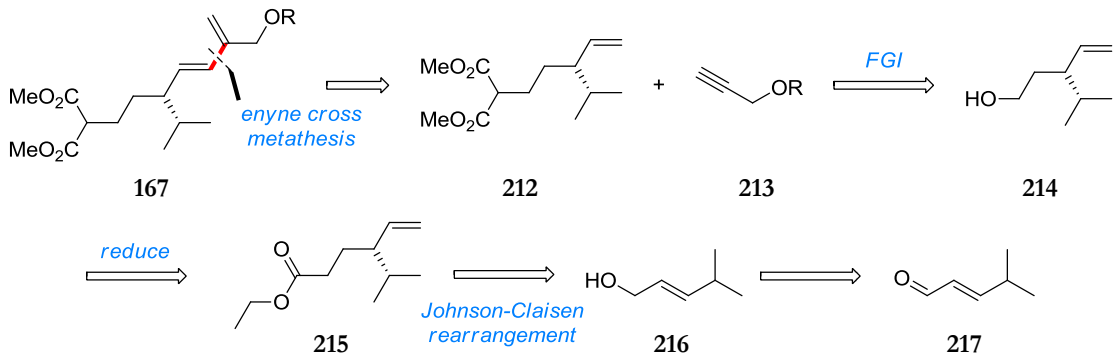
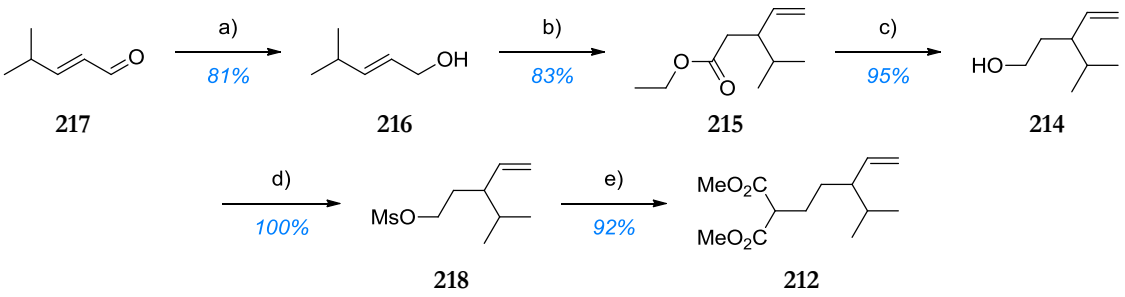



**Figure 2.9: Retrosynthesis of cyclisation precursor 167 utilising a enyne cross metathesis.**

### 2.6.3. Synthesis of enyne cross metathesis precursors 212 and 213

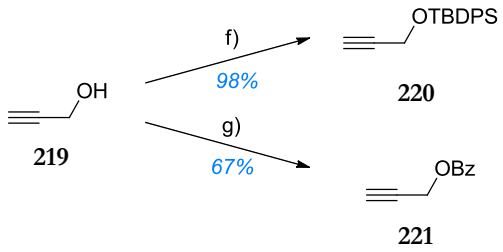
A chemoselective 1,2-reduction of 4-methyl-pentenal (**217**) under Luche conditions,[61] gave alcohol **216** in excellent yield (81%) [**Scheme 2.26**]. Subsequent reaction of allyl alcohol **216** with triethyl orthoacetate in the presence of propionic acid gave *γ,δ*-unsaturated ester **215** in 83% yield. Distillative removal of ethanol ensured that the reaction went to completion. Reduction of ethyl ester **215** using a suspension of lithium aluminium hydride in diethyl ether gave the corresponding alcohol **214**, which was mesylated with methanesulfonyl chloride in the presence of triethylamine to give mesylate **218** in 95% yield over two steps. Without further purification mesylate **218** was alkylated by the pre-formed anion of dimethyl malonate utilising catalytic potassium iodide to give malonate **212** in an overall yield of 59% over five steps. Whilst the addition of potassium iodide is not required, the alkylation of **218** proceeded more cleanly with reaction times reduced from typically 24 hours to 2 hours at 80 °C




**Scheme 2.26: Synthesis of alkenyl malonate 212 identified retrosynthetically as a metathesis partner.**

**Reagents and Conditions: a) $CeCl_3 \bullet 7H_2O$, $NaBH_4$, MeOH, 0 °C-RT, 1 h, 81%; b) triethyl orthoacetate, propionic acid, 138 °C, 18 h, 83%; c) $LiAlH_4$, ether, 0 °C-RT, 1 h, 95%; d) methanesulfonyl chloride, triethylamine, DCM, 0 °C-RT, 1.5 h, 100%; e) NaH, dimethyl malonate, KI, DMF/THF, reflux, 2 h, 92%.**

The metathesis partner, alkyne **213** was prepared by protecting propargyl alcohol [**Scheme 2.27**]. Protection helps guard against unwanted chelation to metal alkylidenes which may decelerate or shut down catalysis.[102] Thus, alcohol **219** was protected as the *tert*-butyldiphenylsilyl ether using standard procedures, which gave **220** in good yield (98%) In 2000, Diver *et al.* utilised benzyl and benzoyl protected propargylic alcohols during studies of an alkyne to ethylene enyne cross metathesis.[103] Therefore it was decided to synthesis the benzoyl ester as an alternative protected propargylic alcohol. The benzoyl protecting group was selected over benzyl as it can be removed with simple acid or base hydrolysis. Removal of a benzyl group is typically achieved by hydrogenation (although other procedures have been reported); however, such a transformation would not be possible in the final product due to the presence of an alkene in (+)-aphanamol I. Reaction of **219** with benzoic anhydride, gave benzoyl protected alkyne **221** in 67% yield.



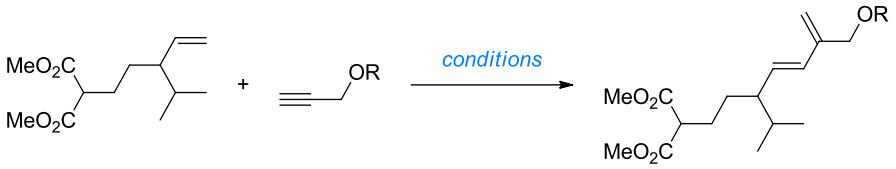

**Scheme 2.27: Synthesis of protected alkyne 213 identified retrosynthetically as a metathesis partner.**

**Reagents and conditions: f) TBDPSCl, imidazole, DMF, RT, 1.5 h, 98%; g) benzoic anhydride, DMAP, triethylamine, DCM, 0 °C-RT, 3 h, 67%.**

### 2.6.4. Enyne cross metathesis

With both metathesis partners in hand, the enyne cross metathesis of alkyne was investigated. As discussed in **Section 2.6.1**, a variety of conditions and catalysts has been reported for a enyne cross metathesis and as a result a screen of various conditions was carried out [**Table 2.5**]. Thus treatment of a solution of alkene **212** and silyl protected alkyne **220** in toluene at 40 °C with Grubbs I catalyst (10 mol%) under a nitrogen atmosphere (entry 1) saw no reaction take place with only starting materials identified by crude proton NMR. Changing to the more reactive Grubbs II catalyst still did not induce enyne metathesis between **212** and **220**. Subjecting the

benzoyl protected alkyne **221** to the same conditions as silyl protected alkyne **220** (entry 3 and 4) still gave no reaction in toluene. Changing the solvent to DCM (entry 4 and 6), which has also been used in enyne metathesis, yet again did not produce any 1,3-diene **167** with only starting material identified in the crude proton NMR. At this point it was decided to attempt the reactions under an atmosphere of ethylene due to the ethylene effect previously discussed. Consequently treatment of alkene **212** and alkyne **220** with Grubbs II in ethylene sparged toluene at 40 °C (entry 7) did not produce any 1,3-diene **167**. However, in the crude proton NMR enyne metathesis had occurred between alkyne **220** and ethylene to give the corresponding terminal 1,3-diene. The same product was observed when benzoyl protected alkyne **221** was subjected to the same reaction conditions (entry 8) whilst 1,3-diene **167** was not observed.



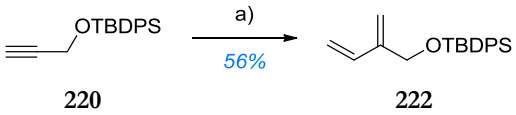

**212** **220/221** **167**

| Entry | R | Catalyst | Solvent | Atmosphere | Yield (%) |
|---|---|---|---|---|---|
| 1 | TBDPS | Grubbs I | Toluene | Nitrogen | N/R |
| 2 | TBDPS | Grubbs II | Toluene | Nitrogen | N/R |
| 3 | Benzoyl | Grubbs I | Toluene | Nitrogen | N/R |
| 4 | Benzoyl | Grubbs II | Toluene | Nitrogen | N/R |
| 5 | TBDPS | Grubbs II | DCM | Nitrogen | N/R |
| 6 | Benzoyl | Grubbs II | DCM | Nitrogen | N/R |
| 7 | TBDPS | Grubbs II | Toluene | Ethylene | 0 |
| 8 | Benzoyl | Grubbs II | Toluene | Ethylene | 0 |

**Table 2.5: Catalyst, solvent and atmosphere screen for a enyne metathesis of 212 to 213.**

From the crude NMR, for the enyne metathesis of alkene **212** with silyl protected **220** under an ethylene atmosphere, it appeared the metathesis of **220** with ethylene had taken place to

give the corresponding 1,3-diene. To confirm this, alkyne **220** was subjected to standard metathesis conditions under an ethylene atmosphere which resulted in diene **222** being produced in 56% yield [**Scheme 2.28**].

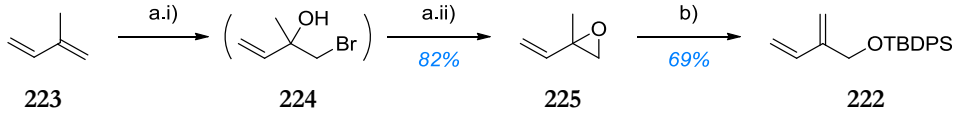



**220** **222**

**Scheme 2.28: Enyne cross metathesis of 220 with ethylene to give 1,3-diene 222.**

**Reagents and conditions: a) Grubbs II, ethylene (1 atm) toluene, 40 °C, 24 h, 56%.**

It was postulated that synthesis of 1,3-diene **167** might be possible by cross metathesis of alkene **212** to 1,3-diene **222** instead of alkyne **220**. Nishikawa *et al.* have reported the synthesis of **222** in four steps from isoprene [**Scheme 2.29**].[104] Following Nishikawa's procedure, treatment of isoprene **223** with *N*-bromosuccinimide in water gave the corresponding bromohydrin intermediate **224**, which was exposed to aqueous sodium hydroxide to give isoprene monoxide **225** in excellent yield (82%) after distillation. Base-promoted isomerisation of **225** using LiHMDS gave the corresponding allylic alcohol which was protected with *tert*-butyldiphenylsilyl chloride to give silyl ether **222** in 56% overall yield.

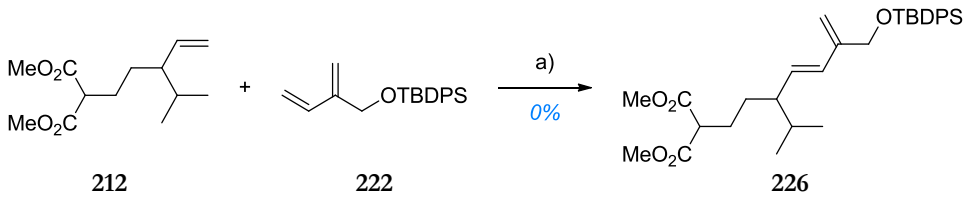



**223** **224** **225** **222**

**Scheme 2.29: Preparation of the enyne metathesis product of 220 to ethylene.**

**Reagents and conditions: a) (i) NBS, $H_2O$, 1 h; (ii) 30% aq. NaOH, 1 h, 82%; b) (i) LiHMDS, $Et_2O$, 40 °C, 24 h; (ii) TBDPSCl, imidazole, DMF, RT, 69%.**

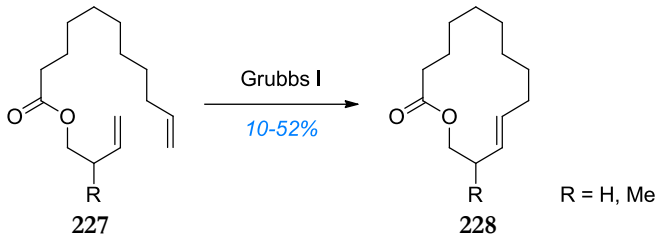
Finally, an enyne cross metathesis of alkene **212** with 1,3-diene **222** was investigated [**Scheme 2.30**]. A solution of **212** and **222** in the presence of Grubbs I was heated at 40 °C for 24 h. Proton NMR analysis showed only starting materials present in the crude reaction mixture, with no obvious resonances present to suggest **226** had been produced.




**Scheme 2.30: Enyne metathesis using 1,3-conjugate diene 222 as the metathesis partner.**

**Reagents and conditions: a) Grubbs II, ethylene (1 atm) toluene, 40 °C, 24 h.**

The reason the enyne cross metathesis between **212** and **213** could not be realised, is most likely due to steric clashes between the isopropyl functional group and the bulky ligands present on ruthenium. Whilst no such example of a substituent close to an olefin has been reported in an enyne metathesis, several examples do exist in ring closing metathesis [**Scheme 2.31**].[105] For example, **227** (where R = hydrogen) underwent a ring closing metathesis to give macrocycle **228** in 52% yield. The corresponding macrocycle **228**, where R = methyl was only obtained in 10% yield. Due to the bulky nature of the Grubbs catalyst, Furstner reasoned that bulky substituents close to the olefin resulted in unfavourable interactions between the catalyst and substrate. This is likely the case with alkene **212**, as no metathesis products were observed experimentally in which the alkene had been involved as a reactant.

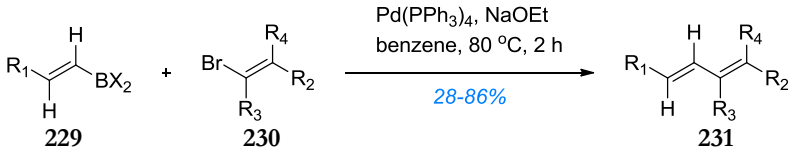



**Scheme 2.31: Ring closing metathesis of a structure bearing a substituent close to the olefin.**

### 2.6.5. Suzuki cross coupling to form dienes

After exhaustive attempts to synthesis key diene **167** *via* an enyne cross metathesis failed, a new route was investigated into the formation of the desired C-C bond. In 1979, Suzuki *et al.* reported in a series of papers, a novel cross-coupling reaction of 1-alkenylboranes to aryl and vinyl halides in the presence of a palladium catalyst and strong base.[106] Of particular interest to this

thesis was the synthesis of a number of conjugated dienes [**Scheme 2.32**]. For example, subjecting alkenylborons **229** and vinyl halides **230** to a catalytic amount of tetrakis(tri-phenylphosphine)palladium under basic conditions, gave the corresponding 1,3-dienes **231** in up to 86% yield.




**Scheme 2.32: Suzuki cross coupling of an alkenylboron to a vinyl halide.**

Mechanistically, the Suzuki cross coupling is best viewed from the perspective of the palladium catalyst which has been suggested to be involved in four distinct steps [**Figure 2.10**].[107] In the first step, an oxidative addition of palladium to halide **232** forms organopalladium species **233**. The relative reactivity of leaving groups is generally I>OTf>Br>>Cl. Oxidative addition has also been shown to proceed with retention of configuration when vinyl halides are used, whilst inversion occurs with allylic and benzylic halides.[108]

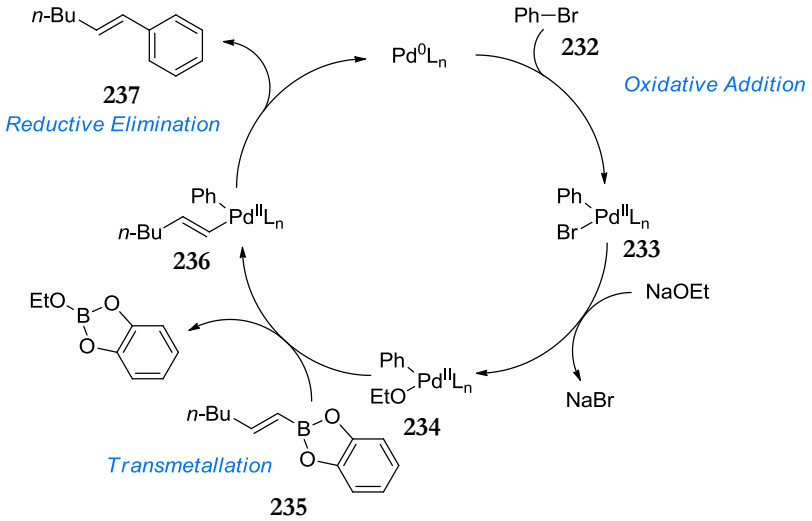


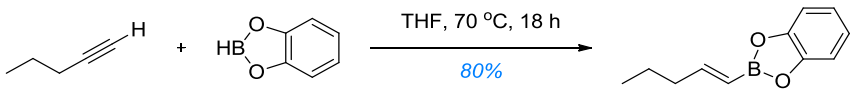

**Figure 2.10: Proposed Suzuki cross coupling mechanism.**

Subsequent reaction of **233** with base gives complex **234**, which *via* transmetallation with organo boronate **235** gives intermediate **236**. Organoboron compounds are highly covalent in character, and do not undergo transmetallation readily in the absence of base. However, the role of

the base during transmetallation is still unresolved. Boronate complexes, formed *via* quaternisation of the boron with a negatively charged base, are frequently invoked in the literature.[109] Reductive elimination of the desired product **237** regenerates the active catalyst rendering the reaction catalytic in palladium. Using deuterium-labelling, Ridgway *et al.* have shown that reductive elimination proceeds with retention of configuration.[110]

### 2.6.5.1. Synthesis of alkyl boranes from a terminal alkyne

A variety of organoboranes including vinyl boranes have been used to affect the transfer of the organic coupling partner to the reactive palladium centre *via* transmetallation. Frequently vinyl boranes are prepared by hydroboration of an alkyne, which is typically carried out selectively by using a bulky dialkyl borane to prevent double addition [**Scheme 2.33**].[111]. For example, treatment of 1-pentyne (**238**) with catecholborane (**239**) in refluxing tetrahydrofuran gives vinyl boronate **240** in excellent yield (80%). The addition of the B-H bond to the alkyne is generally regioselective, with boron adding to the less hindered end of the alkyne *via* a concerted four-membered transition state (i.e. anti-Markovnikov). Typically hydroboration of an alkyne can be carried out with 9-borabicyclo[3.3.1]nonane, pinacolborane and catecholborane.[112]




**238** **239** **240**

**Scheme 2.33: Gupta *et al.* hydroboration of a terminal alkyne.[113]**

### 2.6.6. Retrosynthesis utilising a Suzuki cross coupling to form the key acyclic diene 167

It is clear that Suzuki couplings provide a powerful method for synthesising 1,3-dienes from simple coupling partners readily prepared. Thus, a Suzuki cross-coupling of alkyne **241** *via* the subsequent boronic ester to vinyl halide **242**, should form the key 1,3-diene **167** indentified retrosynthetically in **Section 2.4** [**Figure 2.11**]. Vinyl halide **242** would arise from electrophilic addition of hydrogen iodide to the corresponding propargylic alcohol using standard literature procedures. Alkyne **241** would be synthesised from alcohol **243**, through mesylation followed by

displacement of the mesylate with dimethyl malonate. Alcohol **243** would result from a lithium aluminium hydride reduction of methyl ester **244**, prepared by a Krapcho decarboxylation of malonic ester **245**. Finally, a 1,4-conjugate addition of a protected acetylene to *a,β*-unsaturated enone **246** would give malonic ester **245**.

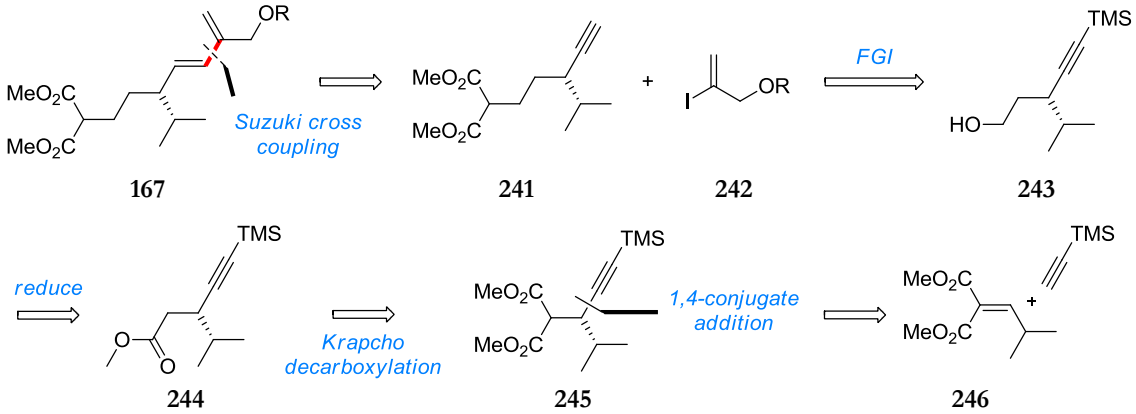
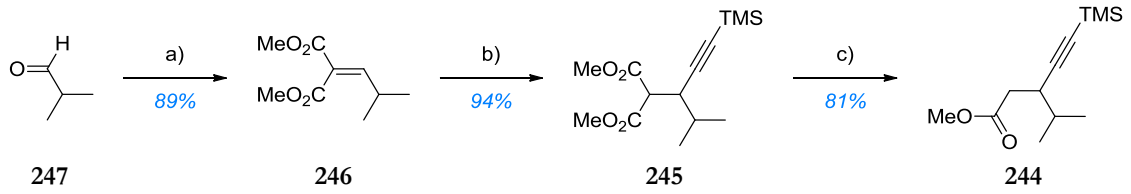



**Figure 2.11: Synthesis of key cyclisation precursor utilising a Suzuki cross coupling as the key step.**

### 2.6.7. Synthesis of alkynyl malonate 241

It was proposed that *a,β*-unsaturated enone **246** could be synthesised by a Knoevenagel condensation of isobutyraldehyde with dimethyl malonate in the presence of a weakly basic amine.[114] This reaction has been widely studied under a variety of conditions, and is generally catalysed by a base or Lewis acid. Following Cardillo's methodology for the synthesis of alkylidene and arylidene malonates,[115] freshly distilled isobutyraldehyde (**247**) was condensed with dimethyl malonate, utilising L-proline as an organocatalyst, which gave *a,β*-unsaturated enone **246** in excellent yield (89%) [**Scheme 2.34**]. Molecular sieves were added to the reaction mixture to absorb the water eliminated as a result of dehydration and drive the reaction to completion. A subsequent 1,4-conjugate addition of trimethylsilylacetylene to **246** in the presence of 0.1 mol% copper(I) chloride, gave alkynyl malonate **245** in 84% yield.[116] Rapid addition of **246** to the anion of trimethylsilylacetylene was found to increase the selectivity of the reaction, giving exclusively 1,4-product. Initially, malonic ester **245** was decarboxylated under the Krapcho conditions used in **Section 2.5.3** (LiCl, $H_2O$, DMSO, 195 °C), however only a poor yield (37%) of methyl ester **244**

was obtained. Reducing the temperature to 150 °C and changing the solvent to DMF allowed for methyl ester **244** to be synthesised in excellent yield (81%).

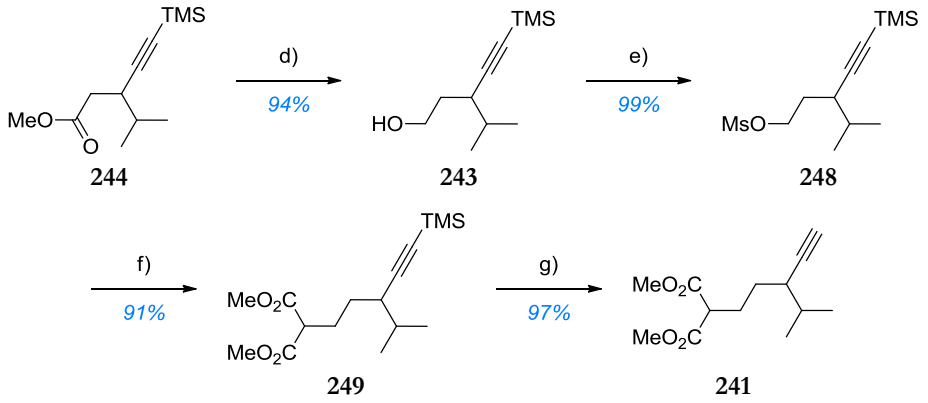



**247** **246** **245** **244**

**Scheme 2.34: Synthesis of ester 244 identified retrosynthetically.**

**Reagents and conditions: a) L-Proline, dimethyl malonate, DMSO, RT, 14 h, 89%; b) ethynyltrimethylsilane, EtMgBr, CuCl, THF, RT-0 °C, 94%; c) LiCl, $H_2O$, DMF, 150 °C, 1.5 h, 81%.**

Dropwise addition of methyl ester **244** to a stirred suspension of lithium aluminium hydride in dry diethyl ether gave the corresponding alcohol **243** in 94% yield [**Scheme 2.35**]. Subsequent mesylation of alcohol **243** with methanesulfonyl chloride gave mesylate **248**, which without further purification was alkylated with dimethyl malonate to give malonate **249** in 90% yield over two steps. Finally, removal of the trimethylsilyl protecting group using tetrabutylammonium fluoride gave the corresponding terminal alkyne **241** in 56% yield over seven steps.




**244** **243** **248** **249** **241**

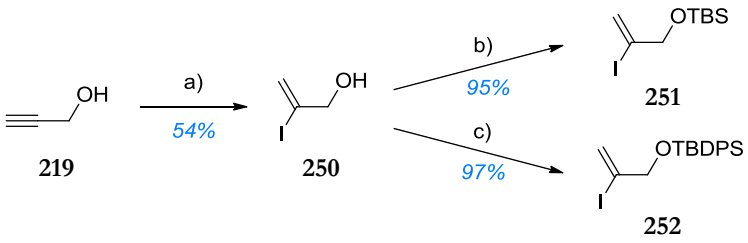
**Scheme 2.35: Synthesis of alkynyl malonate 241, a coupling partner for the Suzuki coupling.**

**Reagents and conditions: d) $LiAlH_4$, $Et_2O$, 0 °C-RT, 1 h, 93%; e) methanesulfonyl chloride, triethylamine, DCM, 0 °C-RT, 1.5 h, 99%; f) NaH, dimethyl malonate, KI, DMF/THF, 80 °C, 14 h, 91%; g) 1 M TBAF, THF, RT, 1.5 h, 97%.**

### 2.6.8. Synthesis of alkenyl iodide 242

Electrophilic addition of hydrogen halides to unsaturated linkages such as alkynes is one of the classical reactions of organic chemistry, having served as the basis of Markovnikoff's well-

known rule for regioselectivity of electrophilic additions.[117] The traditional synthesis of alkyl iodides by addition of hydrogen iodide to a double or triple bond, often leads to low yields and side reactions.[118] Consequently, several alternative approaches to hydroiodination have been developed which generate hydrogen iodide *in-situ* such as chlorotrimethylsilane/sodium iodide/water,[119] iodine/alumina,[120] borane-*N,N*-diethylaniline complex/iodine/acetic acid,[121] iodotrimethylsilane/alumina and aluminium triiodide/water.[122] According to the procedure reported by Ishii *et al.*,[119] propargylic alcohol (**219**) was hydroiodinated using chlorotrimethylsilane/sodium iodide/water to generate hydrogen iodide *in-situ* to give vinyl iodide **250** in modest yield (54%) [**Scheme 2.36**]. Allylic alcohol was subsequently converted to the corresponding silyl ethers **251** and **252** in excellent yield using standard procedures. Different silyl protecting groups were chosen, as the acidic conditions present in a manganese(III) acetate mediated cyclisation have been known to slowly remove silyl protecting groups over the course of the reaction.



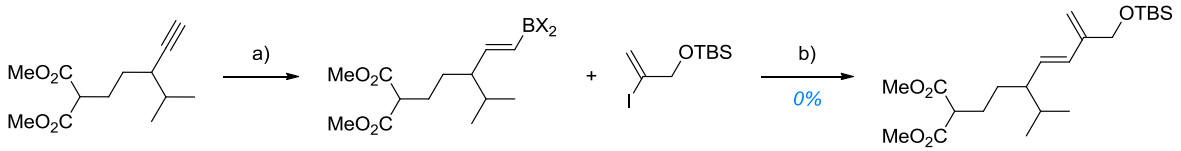

**Scheme 2.36: Synthesis of iodo alkene 242.**

**Reagents and conditions: a) sodium iodide, trimethylsilyl chloride, $H_2O$, MeCN, 0 °C-RT, 6 h, 54%; b) imidazole, *tert*-butyldimethylsilyl chloride, DMF, 0 °C-RT, 14 h, 95%; c) imidazole, *tert*-butyl diphenylchlorosilane, DMF, 0 °C-RT, 14 h, 97%.**

### 2.6.9. Suzuki cross coupling

With both key coupling partners in hand, the cross coupling of alkynyl malonate **241** to vinyl iodide **242** was investigated. As discussed in **Section 2.6.5**, a variety of sterically bulky organoboranes have been used to affect the transfer of the coupling partner, thus a screen of various boranes was investigated [**Table 2.6**]. Whilst catecholborane and pinacolborane are commercially available, disiamylborane was prepared *in-situ* by reacting borane tetrahydrofuran

complex with 2.2 equivalents of 2-methyl-2-butene. Because of the alkyl branching, only two alkenes add to a $BH_3$ moiety (due to steric hindrance), leaving one B-H covalent bond available for reaction with an alkyne. Thus, alkyne **241** was hydroborated under standard hydroboration conditions to give organoboron **253**. Attempts were made to isolate the corresponding boronic acid, by subjecting **253** (X = catecholborane) to aqueous sodium hydroxide, but no such material could be obtained. As a result of this, the crude reaction mixture was used directly in the Suzuki coupling. Tetrakis(triphenylphosphine)palladium is widely used as a catalyst for cross coupling reactions, but he compound is sensitive to air and therefore a palladium precatalyst was made *in-situ* by reacting palladium(II) acetate with 4 equivalents of triphenyl phosphine. Consequently, a solution of organoboron **253** and vinyl iodide **251** was added to the freshly made palladium(0), followed by the addition of aqueous 2 M sodium ethoxide. Unfortunately, no cross coupling of alkyne **241** to vinyl iodide **251** could be realised. The failure of this reaction was likely due to the acidic proton present in the malonate reacting with the borane, during the hydroboration.




**241** **253** **251** **167**

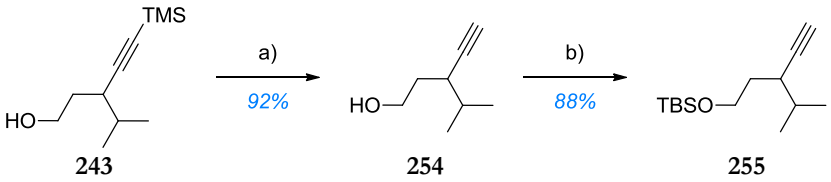
**Reagents and conditions: a) $HBX_2$, THF, 70 °C, 18 h; b) (i) $Pd(OAc)_2$, $PPh_3$, THF, RT, 20 min; (ii) 2 M NaOEt, THF, 40 °C, 4 h, 0%.**

| Entry | $HBX_2$ | Yield (%) |
|---|---|---|
| 1 | catecholborane | - |
| 2 | pinacolborane | - |
| 3 | disiamylborane | - |

**Table 2.6: Failed Suzuki cross coupling of alkene 241 to iodo alkene 251.**

As we believed the malonate to be the reason for the Suzuki cross coupling not working, it was decided to form the 1,3-diene at an earlier stage in the synthesis. Thus it was envisaged that a Suzuki cross coupling of the protected alcohol **255** should circumvent the problem observed in

**Table 2.6**. Thus, deprotection of protected alkynyl alcohol **243** using tetrabutylammonium fluoride gave terminal alkyne **254** in 92% yield [**Scheme 2.37**]. Protection of alcohol **254** with *tert*-butyldimethylsilyl chloride gave the corresponding silyl ether **255** in good yield (88%).



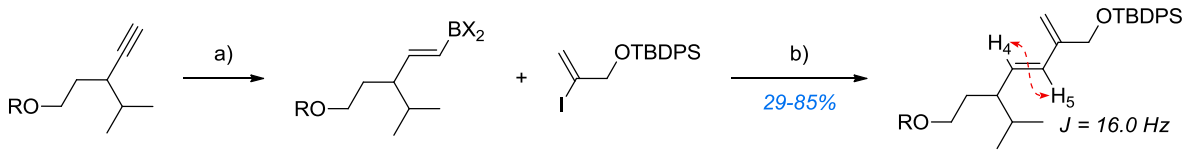

**243** **254** **255**

**Scheme 2.37: Synthesis of a new cross coupling partner.**

**Reagents and conditions: a) 1 M TBAF, THF, RT, 1.5 h, 92%; b) imidazole, *tert*-butyldimethylsilyl chloride, DMF, 0 °C-RT, 14 h, 88%.**

With alkynyl alcohol **254** and protected alkyne **255** in hand, further studies were carried out investigating the formation of the key C-C bond of the desired diene **167** [**Table 2.7**]. Pleasingly hydroboration of alkynyl alcohol **254** with catecholborane (entry 1), followed by cross coupling with vinyl iodide **252** gave 1,3-diene **257** in modest yield (34%). In the proton NMR of **257**, an *E*-alkene was identified by a large coupling constant between H-4 and H-5 ($J$ = 16.0 Hz), whilst a terminal olefin was identified by two one-proton singlets at $\delta_H$ 5.62 and $\delta_H$ 5.22. In the IR, characteristic alkene stretching frequencies were observed at $\nu_{max}$ 1649 $cm^{-1}$ (w, *trans*-RHC=CHR) and $\nu_{max}$ 1609 $cm^{-1}$ (w, $R_2C=CH_2$), while the primary hydroxyl was identified by the broad OH stretch at $\nu_{max}$ 3326 $cm^{-1}$. These data strongly supported the presence of 1,3-diene **257** as a product from the cross coupling of alkyne **254** to vinyl iodide **252**, however the low yield meant further optimisation was required. Unfortunately, hydroboration of **254** with disiamylborane and pinacolborane (entry 2 and 3) gave little increase in yield over catecholborane (entry 1). The poor yield of **257** is most likely due to a competitive reaction occurring between the free hydroxyl and the hydroborating agent. Borane is known to react with free hydroxyl groups to give the corresponding alkoxyborane with loss of hydrogen.[123] Consequently, an oxidative workup was attempted, which would hydrolyse the B-O bond. Subjecting the crude reaction mixture to an aqueous solution of hydrogen peroxide ($H_2O_2$) and sodium hydroxide, however led to

decomposition of **257** most likely due to oxidation of the 1,3-diene. Hydroboration of **254** with catecholborane (entry 4) followed by a cross coupling to vinyl iodide **252** gave 1,3-diene **258** in good yield (76%). Again, disiamylborane and pinacolborane (entry 5 and 6) gave little benefit over catecholborane in the hydroboration step, hence catecholborane was selected as the hydroborating reagent of choice from this stage on. Various aqueous bases have been shown to be applicable in the Suzuki cross coupling. Hydroxide bases (entry 7 and 8), in particular lithium hydroxide, gave a ~10% yield increase of **258** over sodium ethoxide, whilst potassium bicarbonate gave a~40% yield decrease of **258**.




**254;** R = H
**255;** R = TBS

**256**

**252**

**257;** R = H
**258;** R = TBS

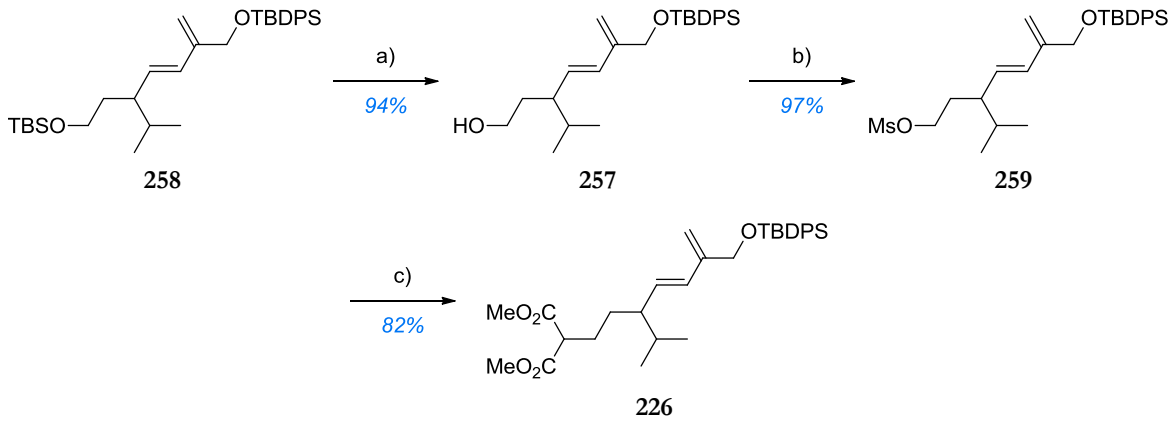
**Reagents and conditions: a) $HBX_2$, THF, 70 °C, 18 h; b) (i) $Pd(OAc)_2$, $PPh_3$, THF, RT, 20 min; (ii) 2 M base, THF, 40 °C, 4 h, 29-85%.**

| Entry | R | $HBX_2$ | Base | Yield (%) |
|---|---|---|---|---|
| 1 | H | catecholborane | NaOEt | 34 |
| 2 | H | disiamylborane | NaOEt | 29 |
| 3 | H | pinacolborane | NaOEt | 32 |
| 4 | TBS | catecholborane | NaOEt | 76 |
| 5 | TBS | disiamylborane | NaOEt | 64 |
| 6 | TBS | pinacolborane | NaOEt | 72 |
| **7** | **TBS** | **catecholborane** | **LiOH** | **85** |
| 8 | TBS | catecholborane | NaOH | 81 |
| 9 | TBS | catecholborane | $KHCO_3$ | 43 |

**Table 2.7: Suzuki cross coupling optimisation.**

In order to alkylate bis-protected diene **258** with dimethyl malonate, a selective deprotection of the TBS protecting group was required in the presence of a TBDPS protecting

group. Many procedures have been reported for the selective removal of a silyl ether in the presence of another.[124] As the TBS can be differentiated from the TBDPS silyl ether on the basis of sterics, an acid deprotection should selectively remove the TBS protecting group. Thus treatment of 1,3-diene **258** with 10 mol% camphor sulfonic acid in DCM/MeOH gave dienyl alcohol **257** in excellent yield (94%) [**Scheme 2.38**]. Mesylation of **257** with methanesulfonyl chloride gave mesylate **259** in 97% yield, which was then alkylated with the anion of dimethyl malonate to give dienyl malonate **226** in good yield over three steps (75%).

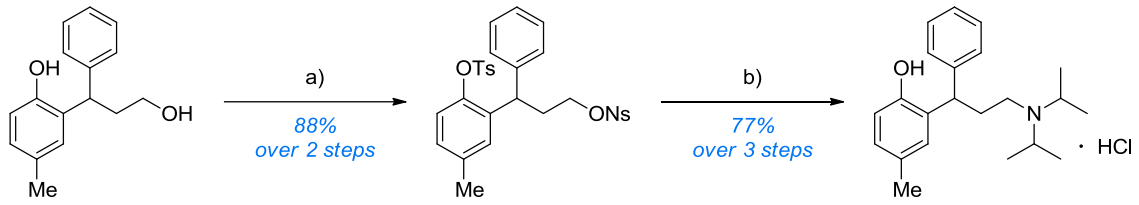



**258** **257** **259** **226**

**Scheme 2.38: Synthesis of diene 226 by mono deprotection of 258 followed by mesylation and alkylation.**

**Reagents and conditions: a) 10 mol% CSA, 1:1 MeOH:DCM, 0 °C, 2; b) methanesulfonyl chloride, triethylamine, DCM, 0 °C-RT, 1.5 h, 97%; c) NaH, dimethyl malonate, KI, DMF/THF, reflux, 18 h, 82%.**

As discussed in **Section 1.2.1**, atom efficiency plays an important role in constructing an elegant multistep synthesis of natural products. Whilst a protecting group is required to enable the Suzuki cross coupling to take place efficiently, two extra steps have been added to the overall synthesis. In 2007, Rhee *et al.* demonstrated that a tosyl functionality could be utilised as an alcohol protecting group, during their process synthesis of the commercial drug Tolterodine [**Scheme 2.39**].[125] The phenol in diol **260** was firstly protected as the tosylate followed by subsequent nosylation of the free primary alcohol to give **261** in 87% yield. Displacement of the resulting nosylate with diisopropylamine followed by removal of the tosylate by displacement with hydroxide and conversion to the HCl salt gave racemic Tolterodine **262**, which can be resolved using L-tartaric acid.

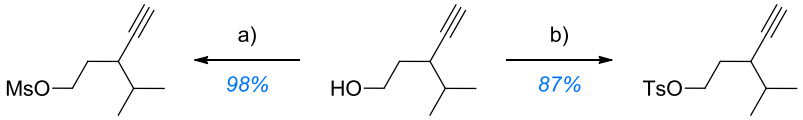



**260** **261** **262**

**Scheme 2.39: Use of a tosylate as a protecting group in the synthesis of Tolterodine.**

**Reagents and conditions: a) (i) TsCl, NaOH, $H_2O$, $CH_2Cl_2$, 40 °C, 1 h, (ii) NsCl, $NEt_3$, 0 °C, 2 h; b) (i) $NH^iPr_2$, $CH_3CN$, reflux, 12 h, (ii) NaOH, MeOH, reflux, 4 h, (iii) HCl, $CH_2Cl_2$, RT, 1 h.**

Thus we investigated whether alcohol **254** could be protected as the mesylate/tosylate, which would remove the need for the extra protection/deprotection steps, as the sulfonate could simply be displaced with dimethylmalonate at a later stage. Alkynyl alcohol **254** was protected as the mesylate **263** (98%) and the tosylate **264** (87%) following standard procedures [**Scheme 2.40**].




**263** **254** **264**

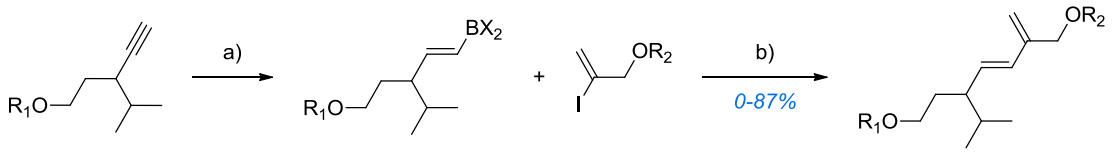
**Scheme 2.40: Mesylation and tosylation of alcohol 254.**

**Reagents and conditions: a) methanesulfonyl chloride, triethylamine, DCM, 0 °C-RT, 1.5 h, 98%; b) *p*-toluenesulfonyl chloride, pyridine, DCM, RT, 6 h, 87%.**

### 2.6.9.1. Suzuki cross coupling of a sulfonyl protected alkyne

Using mesylate **263** (entry 2, **Table 2.8**) and subjecting it to the best conditions established in **Table 2.7**, 1,3-diene **259** was obtained in modest yield (61%). Pleasingly, tosylate **264** (entry 3) gave comparable yields to the TBS protected alkyne (entry 1), with 1,3-diene **265** obtained in excellent yield (84%). A downside of the cross coupling so far however has been the requirement to use the alkyne in excess. Thus, a screen was carried out which reduced the equivalents of alkyne present in the reaction (entries 4-7). Decreasing the alkyne equivalents to 1.2 (entry 4) had a minor impact on overall yield of 1,3-diene **265** (82%), but increased the yield with respect to alkyne by ~8%. A 1:1 mixture of alkyne **264** to vinyl iodide **252** (entry 5) gave a decrease in overall yield

(73%), but a minor increase in yield with respect to alkyne (73%), whilst using vinyl iodide **252** in excess (entry 6) gave a significant reduction in overall yield (62%).




**255**; R = TBS
**263**; R = Ms
**264**; R = Ts

**256**

**250**; R = H
**251**; R = TBS
**252**; R = TBDPS

**258**; $R_1$ = TBS, $R_2$ = TBDPS
**259**; $R_1$ = Ms, $R_2$ = TBDPS
**265**; $R_1$ = Ts, $R_2$ = TBDPS
**266**; $R_1$ = Ts, $R_2$ = TBS

**Reagents and conditions: a) $HBX_2$, THF, 70 °C, 18 h; b) (i) $Pd(OAc)_2$, $PPh_3$, THF, RT, 20 min; (ii) 2 M base, THF, 40 °C, 4 h, 0-87%.**

| Entry | $R_1$ | Alkyne eq. | $R_2$ | $HBX_2$ | Yield (wrt alkyne) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | TBS | 1.4 | TBDPS | catecholborane | 61 | 85 |
| 2 | Ms | 1.4 | TBDPS | catecholborane | 43 | 61 |
| 3 | Ts | 1.4 | TBDPS | catecholborane | 60 | 84 |
| 4 | Ts | 1.2 | TBDPS | catecholborane | 68 | 82 |
| 5 | Ts | 1.0 | TBDPS | catecholborane | 73 | 73 |
| 6 | Ts | 0.8 | TBDPS | catecholborane | 62 | 62 |
| **7** | **Ts** | **1.1** | **TBDPS** | **catecholborane** | **79** | **87** |
| 8 | Ts | 1.1 | TBS | catecholborane | 65 | 71 |
| 9 | Ts | 1.1 | TBDPS | disiamylborane | 56 | 62 |
| 10 | Ts | 1.1 | TBDPS | pinacolborane | 69 | 76 |
| 11 | Ts | 1.1 | H | catecholborane | 0 | 0 |

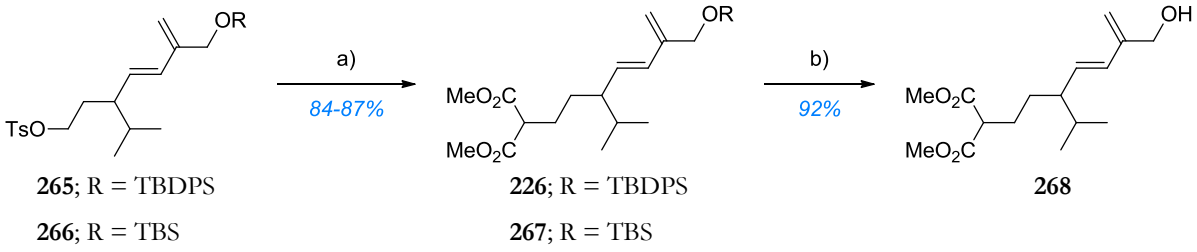
**Table 2.8: Suzuki cross coupling with a sulfonate.**

Optimal results were found to use 1.1 equivalents of alkyne **264** to vinyl iodide **252** (entry 7) which gave 1,3-diene **265** in excellent overall yield (87%) and the highest yield with respect to alkyne (79%). Changing to the TBS protected vinyl iodide **251** (entry 8) gave a slight decrease in yield (71%) when compared to the TBDPS protected vinyl iodide **252** (entry 7). Changing the hydroborating reagent to disiamylborane (entry 9) and pinacolborane (entry 10) failed to further

increase the yield of 1,3-diene **265**. Finally, alcohol **250** was subjected to the optimised conditions (entry 11) to see if it would be possible to synthesis the corresponding 1,3-diene protecting group free, however decomposition was observed.

### 2.6.10. Synthesis of the cyclisation precursor and subsequent cyclisation

With various 1,3-dienes in hand, work turned to investigating the cyclisation of such structures using manganese(III) acetate. Thus, using standard conditions 1,3-diene **265** was alkylated with dimethyl malonate to give dienyl malonate **226** in excellent yield (84%) [**Scheme 2.41**]. The corresponding TBS protected 1,3-diene **267** was likewise obtained in 87% yield. Subsequent treatment of dienyl malonate **226** with tetrabutylammonium fluoride gave dienyl alcohol **268** in excellent yield (92%).




**265**; R = TBDPS
**266**; R = TBS

**226**; R = TBDPS
**267**; R = TBS

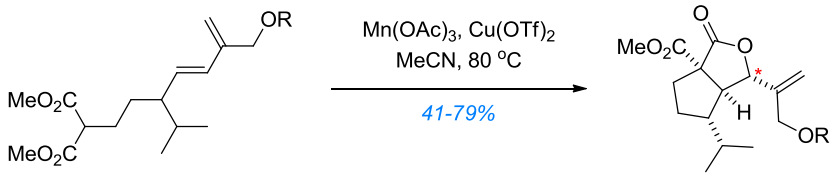
**268**

**Scheme 2.41: Synthesis of the manganese(III) acetate cyclisation precursors.**

**Reagents and conditions: a) NaH, dimethyl malonate, KI, DMF/THF, reflux, 18 h, 84-87%; b) 1 M TBAF, THF, 1.5 h, 92%.**

With three different dienyl malonates in hand, work turned to the manganese(III) acetate mediated cyclisation using the optimised conditions established in the model system [**Table 2.9**]. Pleasingly, treatment of dienyl malonate **267** (entry 1) with manganese(III) acetate and copper(II) triflate in acetonitrile (0.2 M) at 80 °C gave [3.3.0]-bicyclic *γ*-lactone **166a** in modest yield (41%) as a 8.0:1 mixture of diastereoisomers at the lactone stereocentre. [3.3.0]-Bicyclic *γ*-lactone **166a** was identified by characteristic carbonyl stretching frequencies for a *γ*-lactone ($\nu_{max}$ 1773 $cm^{-1}$) and an aliphatic ester ($\nu_{max}$ 1736 $cm^{-1}$) in the IR. In the proton NMR, the lactone proton was observed as a doublet at $\delta_H$ 5.18 ($J$ = 3.5 Hz). Based on the small coupling observed in **166a** and the data obtained from the model system, the major diastereomer was assigned as shown in which all four

substituents are placed on the outside face of the bicyclic system. A significant amount of [3.3.0]-bicyclic *γ*-lactone **166c** was also isolated (25%, most likely through loss of the protecting group under the acidic conditions of the reaction mixture. Exposure of TBDPS protected dienyl malonate **226** (entry 2) to the same conditions gave [3.3.0]-bicyclic *γ*-lactone **166b** in a slightly improved yield of 64%, however deprotection was still observed with **166c** isolated in 12% yield as well. Therefore, it was decided to see if the free hydroxyl group in dienyl malonate **268** was compatible to the cyclisation conditions which when treated with manganese(III) acetate did in fact give [3.3.0]-bicyclic *γ*-lactone **166c** in good yield (76%).




**167** **166a-c**

| Entry | Starting material | R | Time (h) | Product | Yield (%) | *d.r. | $J_{H3C-CH3a}$ (Hz) |
|---|---|---|---|---|---|---|---|
| 1 | **267** | TBS | 18 | **166a** | 41 | 8.0:1 | 3.5 |
| 2 | **226** | TBDPS | 18 | **166b** | 64 | 6.9:1 | 3.7 |
| 3 | **268** | H | 18 | **166c** | 76 | 12.1:1 | 4.8 |
| 4 | **267** | TBS | 4 | **166a** | 68 | 7.6:1 | 3.5 |
| **5** | **226** | **TBDPS** | **4** | **166b** | **79** | **7.2:1** | 3.7 |
| 6 | **268** | H | 4 | **166c** | 75 | 12.4:1 | 4.8 |

**Table 2.9: Manganese(III) acetate mediated cyclisation of a dienyl malonate to give the required [3.3.0]-bicyclic *γ*-lactone – major diastereomer shown.**

Upon closer monitoring of the reaction mixtures, deprotection of [3.3.0]-bicyclic *γ*-lactone **166a** and **166b** appeared to be much slower than the actual cyclisation. Thus it was envisaged that, if the reaction was stopped upon cyclisation, minimal material could be lost through deprotection. Indeed this was the case (entry 4 and 5) as both [3.3.0]-bicyclic *γ*-lactone **166a** and **166b** were obtained in significantly greater yields with 4 h reaction times when compared to the reactions over an 18 h period. For reasons highlighted in the model system, the diastereoselectivity at C-3 in

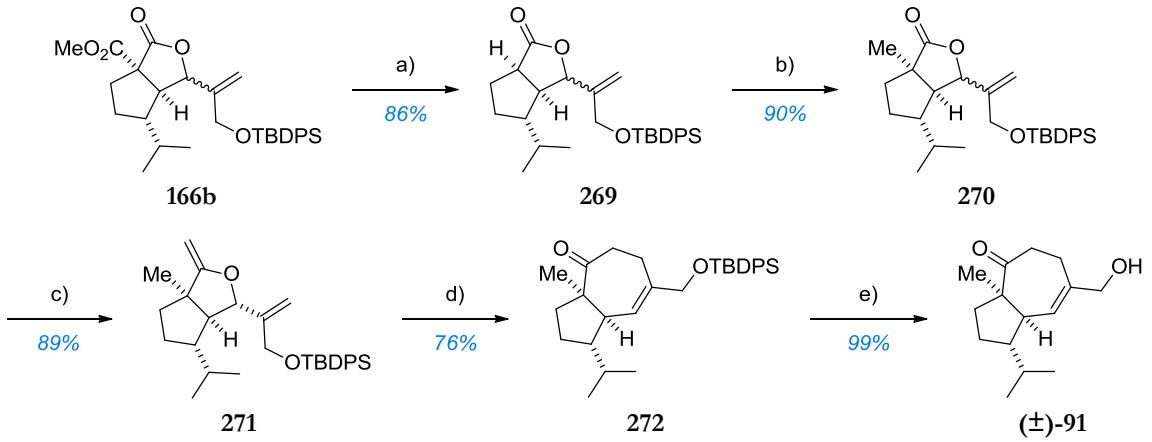
[3.3.0]-bicyclic *γ*-lactone **166a-c** is not critical as this stereocentre is destroyed in the Claisen ring expansion. In all of the above cases, the observed diastereoselectivity at C-4 (isopropyl stereocentre) was >23:1

### 2.6.11. Completion of the total synthesis of (±)-aphanamol I

With the desired [3.3.0]-bicyclic *γ*-lactone in hand, the total synthesis of (±)-aphanamol I was completed using reactions analogous to those developed in the model system [**Scheme 2.42**]. After some experimentation, it was found that the Krapcho decarboxylation of ester **166b** to give [3.3.0]-bicyclic *γ*-lactone **269** was best achieved in using lithium chloride in dimethylformamide at 150 °C. Decarboxylation under the conditions developed in the model system (LiCl, DMSO, 195 °C) gave [3.3.0]-bicyclic *γ*-lactone **269**, albeit in a lower yield (73%). At this point it was possible to separate the two diastereomers, with proton NMR nOe studies confirming the major diastereomer to be the diastereoisomer in which all four substituents are placed on the outside face of the bicyclic system. For clarity reasons, the mixture of diastereomers will be presented in the total synthesis of (±)-aphanamol I, however both the major and minor diastereomer were individually converted to (±)-aphanamol I using the same reactions.[IV] [3.3.0]-Bicyclic *γ*-lactone **269** was alkylated with methyliodide to introduce the bridgehead methyl group, producing lactone **270** in excellent yield (90%) Subsequent exposure of **270** to the Petasis reagent, gave the corresponding enol ether **271** in excellent yield (84%), which when heated in refluxing xylene gave [5.3.0]-bicyclic ketone **272** in 77% yield. Finally the total synthesis of (±)-aphanamol was completed by subjecting ketone **272** to TBAF buffered with acetic acid to give (±)-aphanamol I (**91**) in quantitative yield. Initially the deprotection of **272** was carried out using TBAF with no acid present, however (±)-**91** was only obtained in 54% with 40% starting material recovered. The likely reason for the increase in yield is due to protonation of silyl ether **272**, making it a better leaving group in what is otherwise a very sterically hindered environment. The spectroscopic data of (±)-aphanamol I

[IV] The data presented in the experimental section represents the individual diastereoisomers, whilst yields reported in the discussion refer to the mixture of diastereoisomers.

matched that of the natural product well; see **Section 2.8** for a more detailed analysis of the spectroscopic data.

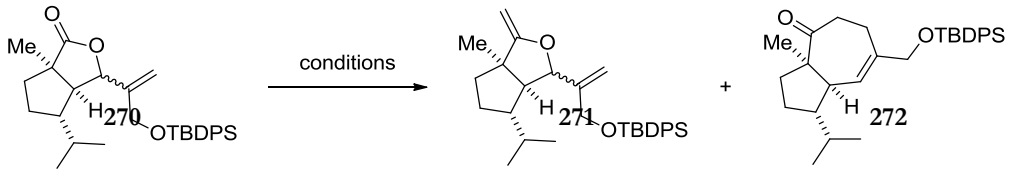



**Scheme 2.42: Completion of the total synthesis of (±)-aphanamol I.**

**Reagents and conditions: a) LiCl, $H_2O$, DMF, 150 °C, 6 h, 86%; b) 1 M LiHMDS in toluene, MeI, -78 °C, 30 min, 90%; c) the Petasis reagent, toluene, 110 °C, 30 min, 89%; d) xylene. 150 °C, 24 h, 76%; e) 1 M TBAF, AcOH, THF, 0 °C-RT, 24 h, 99%.**

During the olefination of [3.3.0]-Bicyclic *γ*-lactone **270** to give enol ether **271**, a small amount of [5.3.0]-bicyclic ketone **272** was isolated (3%). Consequently, it was decided to investigate whether the olefination/Claisen ring expansion steps could be combined into a single one -pot step [**Table 2.10**]. Increasing the reaction time to 24 h (entry 2) gave a slight increase of ketone **272** (12%), however increasing the time by another 24 h to 48 h (entry 3) resulted in minimal increase in ketone **272**, with significant decomposition of **271** observed. As the Claisen ring expansion occurs in refluxing xylene, the temperature was increased to 150 °C using a sealed tube (entry 4). Unfortunately the increased temperature gave no significant increase in ketone **272**, with decomposition of **271** still observed. We believed that the excess Petasis reagent present in the reaction mixture to be the reason for low combined isolated yields of **271** and **272**. Accordingly, after olefination of **271** had occurred (entry 5), the excess Petasis reagent was destroyed using hexane and Celite®. The temperature of the mixture was then increased to 150 °C and stirred for 24 h, resulting in excellent yield of ketone **272** with minimal enol ether **271** isolated. Leaving the

mixture for a further 12 h (entry 6) gave no further conversion of **271** to ketone **272**.




| Entry | Conditions | Yield 271 (%) | Yield 272 (%) |
|---|---|---|---|
| 1 | the Petasis reagent, toluene, 110 °C, 30 min | 84 | 3 |
| 2 | the Petasis reagent, toluene, 110 °C, 24 h | 63 | 12 |
| 3 | the Petasis reagent, toluene, 110 °C, 48 h | 38 | 15 |
| 4 | the Petasis reagent, toluene, 150 °C, 24 h | 49 | 13 |
| **5** | **i) the Petasis reagent, toluene, 110 °C, 30 min; ii) Celite®, 150 °C, 24 h** | **6** | **84** |
| 6 | i) the Petasis reagent, toluene, 110 °C, 30 min; ii) Celite®, 150 °C, 36 h | 2 | 81 |

**Table 2.10: One-pot olefination/Claisen rearrangement of 270 to give ketone 272.**

## 2.7. Total synthesis of (+)-aphanamol I

With the optimised total synthesis of (±)-aphanamol I completed in 12 steps and an overall yield of 20.8%, work now turned to investigating an asymmetric synthesis of (+)-aphanamol I based on the racemic route. As shown in **Figure 2.12**, an interesting aspect of our synthesis of (±)-aphanamol is the 1,4-relationship of the alkyne to the alcohol present in intermediate **243**. The corresponding aldehyde **273** of alcohol **243** lends itself to a 1,4-conjugate addition of a protected acetylene (**274**) to an *a,β*-unsaturated enone **217**.

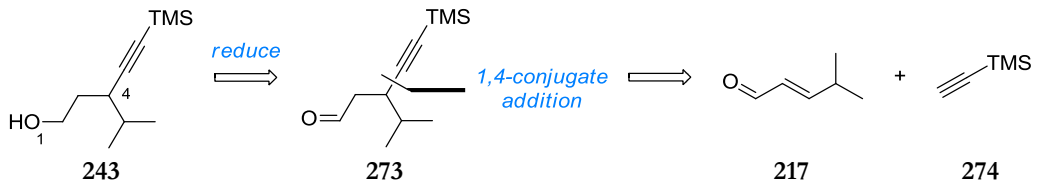


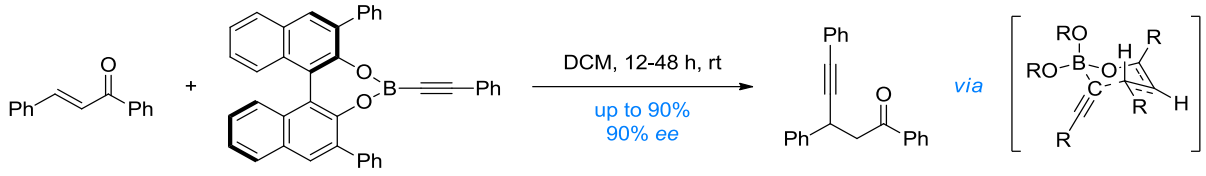

**Figure 2.12: Retrosynthesis utilising the 1,4-realtionship to synthesise enantioenriched 243.**

Enantioenriched alkynyl alcohols and amines play a critical role as building blocks in organic synthesis. Over the last 10 years significant advances have been made in the direct

enantioselective addition of a terminal alkyne into a pro-chiral carbonyl compound, realising high atom efficiency.[126] Whilst direct 1,2-additions of an alkyne to an aldehyde, ketone or imine are well established, asymmetric 1,4-conjugate addition still remains a difficult synthetic challenge.

### 2.7.1. Enantioselective addition of alkyne nucleophiles to *α,β*-unsaturated carbonyls

Of the various transition metal catalysed methods for the addition of an alkyne to an *a,β*-unsaturated carbonyl, those involving copper(I) are most advanced in the literature.[127] However additions using copper(I) have proven to be troublesome, due to the strong Cu-C bond formed in the copper acetylide.[128] Thus, the first reported example of a 1,4-conjugate addition relied on a alkynyl borane as the alkyne source [**Scheme 2.43**].[129] Chong *et al.* reported the conjugate addition of alkynyl boronate **276** to *a,β*-unsaturated ketone **275** to give **277** in 90% yield with good enantiocontrol observed (up to 90% *ee*). Chong suggested the asymmetric induction to arise from six-membered transition state (**278**) in which the chirality of BINOL dictates the facial selectivity of the addition. This proposal was further confirmed by the fact that Chong found cyclohexenone to be unreactive under the reaction conditions as it is not able to adopt an s-*cis* relationship in the transition state. One drawback of the methodology was the stoichiometric use of BINOL, although Chong later overcame this by taking advantage of the readily exchanged alkoxy ligands on boron, rendering the reaction catalytic in BINOL.[130]

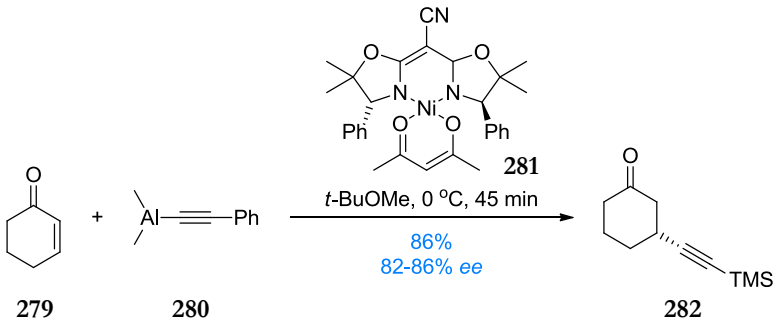



**275** **276** **277** **278**

**Scheme 2.43: First example of an enantioselective conjugate addition of an alkyne.[129]**

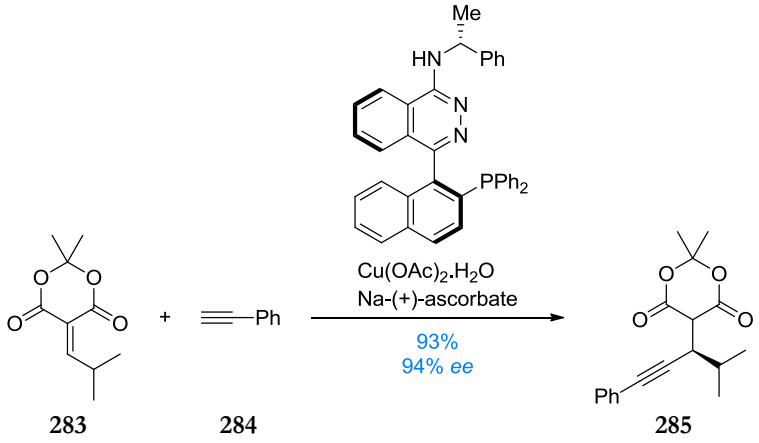
The asymmetric 1,4-conjugate addition of an alkyne to cyclic enones still remains a difficult problem in organic synthesis. This type of addition can be achieved in a non-stereoselective manner most notably with zinc[131] or aluminium acetylides.[132] Corey *et al.* were the first to report an enantioselective conjugate addition to a cyclic enone using a nickel complex [**Scheme 2.44**].[133]

Using cyano bis-oxazoline nickel complex **281**, the addition of alane **280** to cyclohexenone **279** gave *β*-alkynyl ketone **282** in excellent yield (86%) with 82-88% enantiomeric excess.




**Scheme 2.44: Corey's enantioselective conjugate addition to a cyclic enone.**[133]

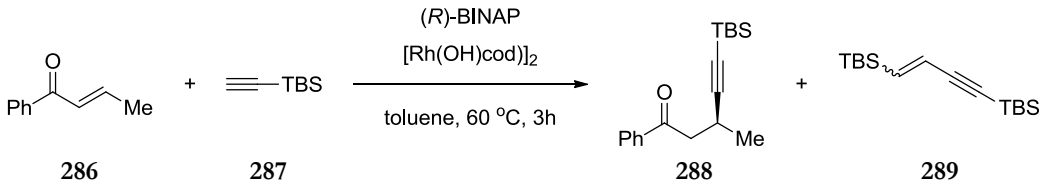
Although copper acetylides are considered to be inert due to the strong copper-alkyne bond, utilising a stronger Michael acceptor, such as a Meldrum's acid derivative, has been shown to be applicable in 1,4-conjugate additions [**Scheme 2.45**]. Carreira *et al.* found that alkylidene **283** readily underwent a 1,4-conjugate addition of a copper acetylide (formed form **284**) in the presence of PINAP and sodium ascorbate, to give **285** in excellent yield (93%) and 94% enantiomeric excess.[134]




**Scheme 2.45: Copper catalysed enantioselective conjugate alkynylation of alkylidene-Meldrum's acid.**[134]

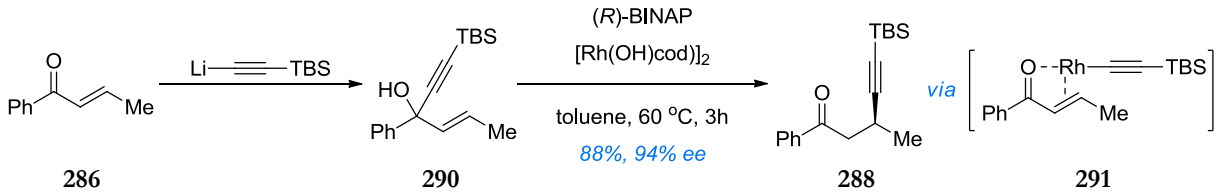
The use of rhodium catalysed conjugate addition of an alkenyl/aryl group to an *α,β*-unsaturated carbonyl is widely recognised as an efficient way of synthesising enantioenriched ketones. However, initially 1,4-conjuagte additions of an acetylene to a *β*-unsubstituted enone was limited due to undesirable side reactions [**Scheme 2.46**]. Under standard conditions for rhodium

catalysed 1,2-addition, the addition of TBS-acetylene **287** to ketone **286** typically gave a low yield of conjugate product **288** (6%) and instead dimer **289** was isolate as the major product (68%). This is because the likely alkynyl rhodium species formed in the reaction mixture is more reactive towards the acetylene favouring dimerisation over addition to the enone.




**Scheme 2.46: Standard Rh catalysed conjugate addition resulting in dimerisation**

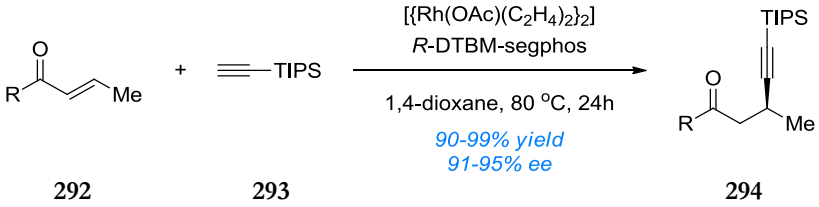
In a series of papers, Nishimura, Hayashi and co-workers have now established suitable conditions which overcome the dimerisation issues previously reported. Initially, they sought to render the reaction intramolecular *via* a 1,3 rearrangement of an alkynyl group [**Scheme 2.47**].[135] It was postulated dimerisation could be prevented by removing free alkyne from the reaction medium. Thus, treatment of alkynyl alcohol **290** (obtained by 1,2-addition of a lithium acetylide to enone **286**) with catalytic rhodium(I) in toluene gave *β*-alkynyl ketone **288** in excellent yield (88%) and enantioenrichment (94%). It was proposed that the reaction might proceed *via* a *β*-alkynyl elimination to form chiral rhodium complex **291** in which both enone and alkyne are bound to the catalyst.




**Scheme 2.47: Rh catalysed 1,3 rearrangement to give the conjugate addition product.[135]**

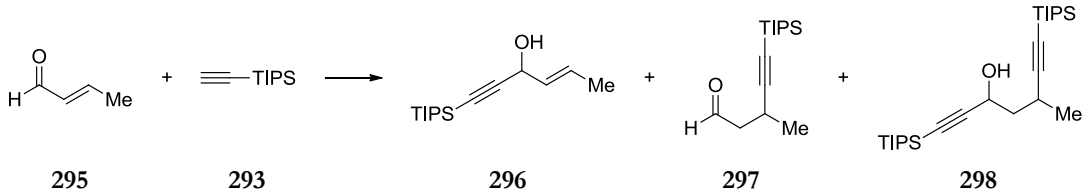
A significant breakthrough was made by Nishimura and Hayashi in 2008, allowing for the bimolecular addition of an alkyne to an *a,β*-unsaturated ketone [**Scheme 2.48**].[136] By carefully tuning the steric bulk present on the catalyst and the alkyne, it was possible to suppress alkyne dimerisation. As a result, subjecting enone **292** to a rhodium(I) catalyst featuring a bulky

phosphine ligand in the presence of TIPS-acetylene (**293**) gave the desired *β*-alkynyl ketone **294** in high yield (90-99%) and up to 95% enantiomeric excess. Smaller protected alkynes, such as TMS-acetylene were compatible with the reaction conditions, however significantly lower asymmetric induction was observed.



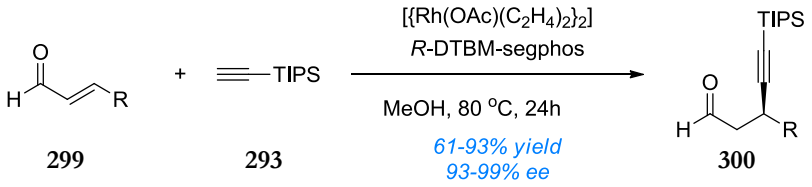

**Scheme 2.48: Rh catalysed conjugate addition of a alkyne to an enone.**[136]

Nishimura and Hayashi then sought to apply such 1,4-conjugate addition to an *a,β*-unsaturated aldehyde [**Scheme 2.49**]. However the addition proved difficult to realise, due to several possible addition pathways. In applying the optimised conditions from the ketone series, Hayashi observed a mixture of 1,2-adduct **296**, 1,4-adduct **297** and the double addition product **298**.




**Scheme 2.49: Selectivity issues for an alkynylation of a *α,β*-unsaturated aldehyde.**

The chemoselectivity issues observed were overcome after a wide temperature and solvent screen. By reducing the temperature and changing the solvent, they were able to selectively add an alkyne to an *a,β*-unsaturated aldehyde by a 1,4-conjugate addition [**Scheme 2.50**].[137] The reaction of alkyne **293** with a number *a,β*-unsaturated enals (**299**) in the presence of a catalytic rhodium(I) complex gave the corresponding *β*-alkynyl aldehydes **300**, in good yield (61-93%) and excellent enantioenrichment (up to 99% *ee*). The transformation tolerated a wide range of functional groups, of particular interest to this thesis was where R = isopropyl (88% yield, 99% *ee*).




**Scheme 2.50: Scope of rhodium catalysed asymmetric conjugate alkynylation of enals.**[137]

Mechanistically, Nishimura and Hayashi proposed the catalytic cycle to involve the insertion of an alkynyl-rhodium species into the enal **299** in accordance with the mechanism proposed in the ketone series. The enantioenrichment of the reaction was thought to arise from a model proposed by Hayashi for transition metal complexes coordinated to BINAP [**Figure 2.13**].[138] Accordingly, the olefinic bond of the enal preferentially coordinates to rhodium with the aldehyde placed in the open space at the lower part of the vacant coordination site **301**. The opposite coordination complex **302** would result in an unfavourable interaction between the ligand and the aldehyde as the upper face is blocked by a phenyl ring. As a result of this steric clash, the α-*Re* face is attacked by the alkyne to give the desired new stereocentre in **303**. Finally, elimination gives *β*-alkynyl aldehyde **297** which Hayashi confirmed the absolute configuration to be (*S*).

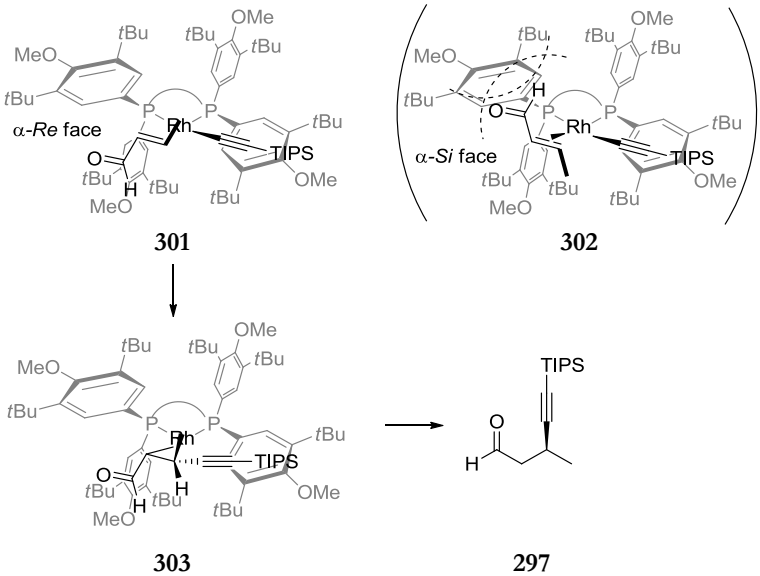


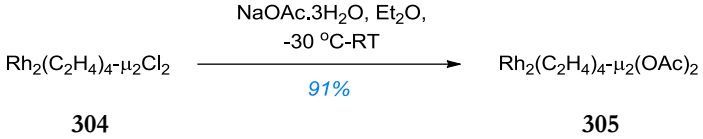

**Figure 2.13: Stereochemical pathway adapted from Nishimura and Hayashi.**[137]

### 2.7.2. Conjugate addition of TIPS-acetylene to 4-methyl-2-pentenal

With the conjugate addition of an alkyne to a *a,β*-unsaturated aldehyde providing access to an intermediate identified in our retrosynthesis, such a transformation appeared extremely attractive for the planned asymmetric synthesis. However, in order to be of use as an early step in the total synthesis of (+)-aphanamol I, the methodology would need to be scaleable. Nishimura and Hayashi reported the desired transformation but only on 0.2 mmol scale which would not provide enough material for a multi step synthesis. Additionally, the pre-catalyst is not commercially available and needs to be synthesised using Schlenk techniques. Nonetheless, it was decided to investigate Nishimura and Hayashi's methodology firstly at the reported scale and if successful look into scaling up the reaction which could then be applied in the total synthesis of (+)-aphanamol I.

#### 2.7.2.1. Preparation of rhodium(I) pre-catalyst

As the catalyst is extremely air sensitive, standard Schlenk techniques were employed under an argon atmosphere.[V] Thus, following the modified method of Werner *et al.*,[139] chlorobis(ethylene)rhodium(I) dimer **304** was treated with sodium acetate at 0 °C, under heterogeneous conditions, to give acetate dimer **305** [**Scheme 2.51**]. As the acetate complex is soluble in the reaction medium, filtration *via* cannula into a second Schlenk tube allowed for the removal of the insoluble inorganic salts. Subsequent concentration and recrystallisation from pentane gave the pre-catalyst **305** as red crystals. Unfortunately, all attempts to gain spectroscopic data on the catalyst were unsuccessful due to its instability.

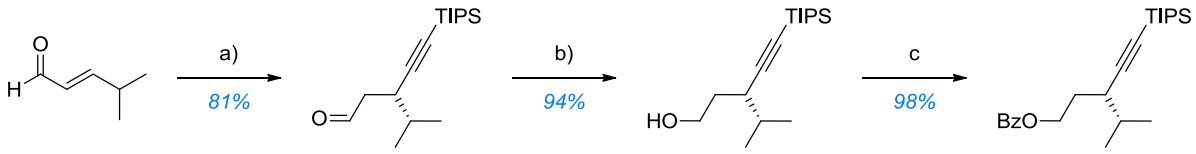



**Scheme 2.51: Synthesis of Rh(I) catalyst used in Hayashi's methodology.**

[V] We are grateful to Dr Adrian Chaplin in the Weller group for advice in the pre-catalyst preparation.

### 2.7.2.2. Conjugate addition repeating Hayashi's methodology.

As mentioned previously, Hayashi applied the methodology to 4-methyl-2-pentenal, albeit to give the opposite enantiomer (*R*)-**306** in excellent yield (88%). Thus, using the opposite enantiomer of ligand, (*S*)-DTBM-SEGPHOS, 4-methyl-2-pentenal **200** was subjected to the optimised conditions reported by Hayashi *et al.* [**Scheme 2.52**]. Pleasingly, *β*-alkynyl aldehyde (*S*)-**306** ($[\alpha]_D^{20}$ -28.7 (*c* 1.00, $CHCl_3$)(lit. enantiomer[137] $[\alpha]_D^{20}$ +30.0 (*c* 0.95, $CHCl_3$) for (*R*))) was obtained in 81% yield with all data in accordance to the opposite enantiomer reported by Hayashi. As aldehyde (*S*)-**306** does not feature a chromophore, Hayashi converted it into the corresponding benzoyl ether to carry out chiral HPLC analysis. Therefore, exposure of (*S*)-**306** to sodium borohydride gave alcohol (*S*)-**307** ($[\alpha]_D^{20}$ -8.5 (*c* 1.02, $CHCl_3$), which was benzoylated with benzoic anhydride to give benzoyl ester (*S*)-**308** ($[\alpha]_D^{20}$ -66.0 (*c* 1.00, $CHCl_3$)(lit.[137] $[\alpha]_D^{20}$ +51.0 (*c* 0.98, $CHCl_3$) for (*R*))) in 92% yield over two steps.



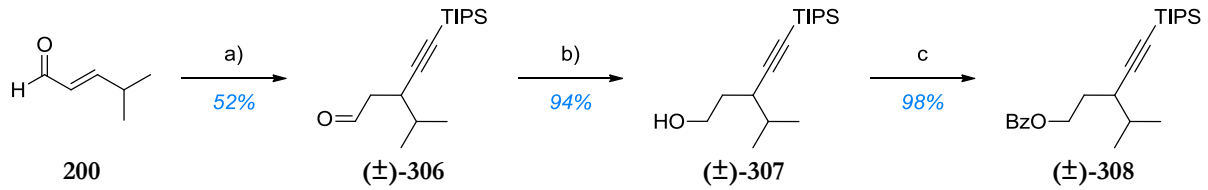

**200** (*S*)-**306** (*S*)-**307** (*S*)-**308**

**Scheme 2.52: Asymmetric 1,4 conjugate addition of TIPS-acetylene to 200.**

**Reagents and conditions: a) i) 2.5 mol% chlorobis(ethylene)rhodium(I) dimer, sodium acetate trihydrate, $Et_2O$, -30 °C-RT, 1 h; ii) 6 mol% (*S*)-(+)-DTBM-SEGPHOS, (triisopropylsilyl)acetylene, MeOH, 40 °C, 24 h, 81%; b) $LiAlH_4$, $Et_2O$, 0 °C-RT, 1 h, 94%; c) benzoic anhydride, DMAP, DCM, RT, 24 h, 98%.**

### 2.7.2.3. Preparation of (±)-308

In order to ensure the enantiomeric enrichment of the preceding alcohol **307** by HPLC analysis, a racemic standard was prepared. Thus, (±)-**308** was prepared *via* a 1,4-conjugate addition of the pre-formed copper acetylide to 4-methyl-2-pentenal (**200**) [**Scheme 2.53**]. As discussed previously, a mixture of 1,4-adduct (±)-**306** and 1,2-adduct (±)-**306b** were obtained from the reaction. Subsequent reduction of aldehyde (±)-**306** with sodium borohydride gave alcohol (±)-**307** in 94% yield, which was protected as the benzoyl ester to give (±)-**308**.




**200** **(±)-306** **(±)-307** **(±)-308**

**Scheme 2.53: Racemic 1,4 conjugate addition of TIPS-acetylene to 200.**

**Reagents and conditions: a) (triisopropylsilyl)acetylene, EtMgBr, CuCl, THF, 0 °C-RT, 52%; b) $LiAlH_4$, $Et_2O$, 0 °C-RT, 1 h, 94%; c) benzoic anhydride, DMAP, DCM, RT, 24 h, 98%.**

With both racemic and asymmetric **308** in hand, the enantiomeric excess was determined by chiral HPLC studies. Hayashi was able to separate the two enantiomers using a Chiralcel OG column, with retention times of $t_1$ = 15.5 min (*R*) and $t_2$ = 18.0 min (*S*).[VI] Whilst we did not have access to an OG column, separation of the enantiomers was also possible using a Chiralcel OD column [**Figure 2.14**]. The retention times for racemic **308** were found to be $t_1$ = 25.1 min (*S*) and $t_2$ = 26.9 min (*R*).[VII] Enantioenriched **308** gave a single peak in the UV trace at $t_1$ = 25.1 min.[VII] With an optical rotation within 5% error and displaying the opposite sign to Hayashi's reported data, the absolute configuration of aldehyde **306** was assigned as (*S*). The HPLC trace of the corresponding benzoyl ether **308** suggested the conjugate addition proceeded with >99% enantioenrichment giving aldehyde **306** as a single diastereomer. Finally, a 1:1 mixture of asymmetric **308** spiked with racemic **308** gave a UV trace of $t_1$ = 25.1 min (*S*, 75%) and $t_2$ = 26.9 min (*R*, 25%).[VII]

[VI] Chiralcel OG column, flow 0.5 mL/min, hexane, 254 nm
[VII] Chiralcel OD column, flow 0.6 mL/min, 0.2% IPA/hexane, 230 nm

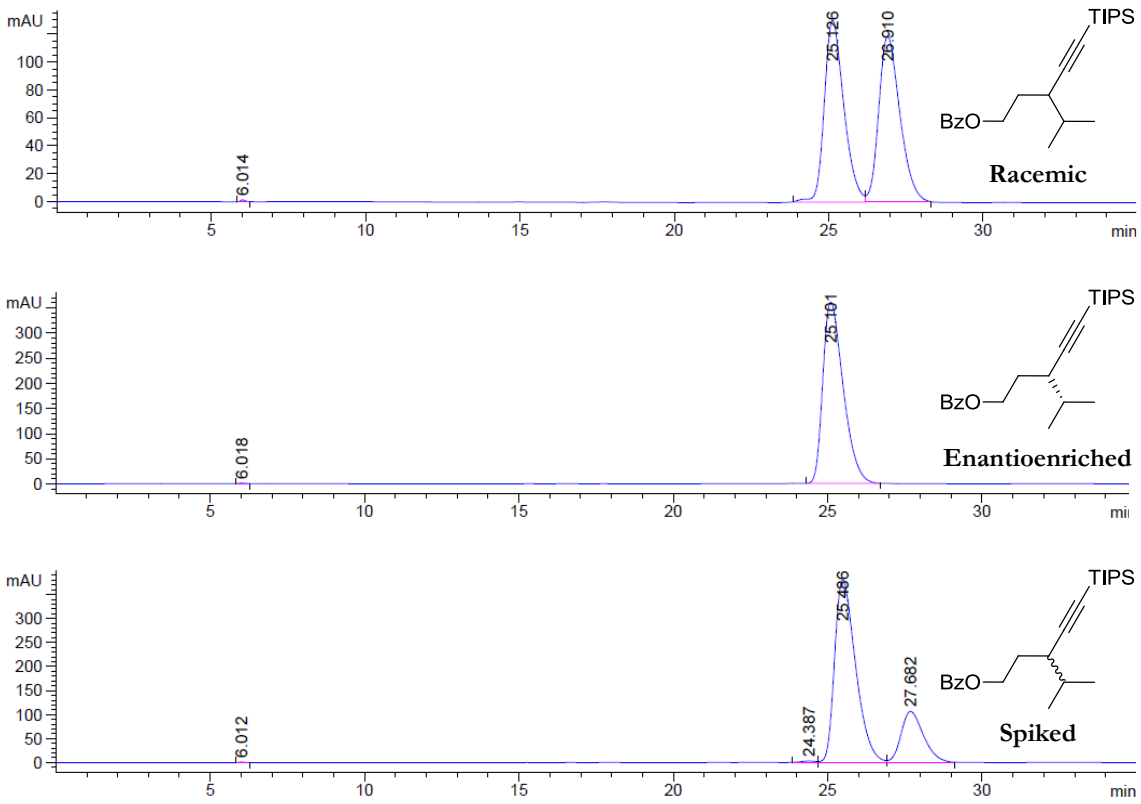
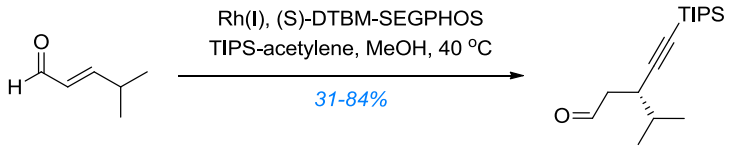



**Figure 2.14: HPLC UV traces for racemic, asymmetric and spiked 308.**

### 2.7.2.4. Large scale conjugate addition of TIPS-acetylene to 4-methyl-2-pentenal

Confident in our results, which suggested (*S*)-**306** was obtained as a single enantiomer, work was now focussed on applying the methodology on a larger scale [**Table 2.11**]. In the original paper, Hayashi synthesised 49 mg of (*R*)-**306** (0.2 mmol scale). Pleasingly increasing the amount of substrate **200** incrementally by a factor of three (entries 1-4) gave no significant decrease in yield of (*S*)-**306**. However, one drawback of using bulky phosphine ligands in asymmetric catalysis is the high molecular mass of the ligand ((*S*)-DTBM-SEGPHOS = 1179). Whilst the reaction is catalytic in rhodium and ligand, the mass of ligand required is similar to that of substrate used, making the reaction expensive to carry out on large scale. Catalyst loading was thus investigated (entry 5). Unfortunately, lowering the catalyst loading gave incomplete conversion of **200** after 3 days, with only 31% of (*S*)-**306** obtained. Recovery of the ligand by column chromatography was attempted, however clean ligand could not be obtained.




**200** (*S*)-**306**

| Entry | Scale (mmol) | Catalyst loading (mol%) | Yield (%) | $[\alpha]_D^{20}$ (*S*)-**306** |
|---|---|---|---|---|
| 1 | 0.2 | 5 | 81 | -28.7 (*c* 1.01, $CHCl_3$) |
| 2 | 0.6 | 5 | 84 | -29.6 (*c* 0.97, $CHCl_3$) |
| 3 | 1.8 | 5 | 82 | -26.1 (*c* 0.98, $CHCl_3$) |
| 4 | 5.4 | 5 | 79 | -31.6 (*c* 1.04, $CHCl_3$) |
| 5 | 5.4 | 1 | 31[a] | -29.9 (*c* 1.00, $CHCl_3$) |

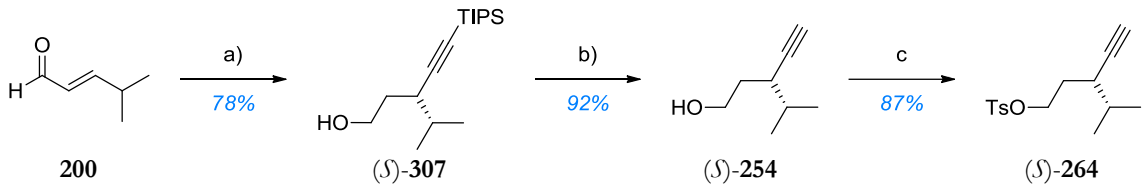
**[a] 3 days, incomplete conversion observed.**

**Table 2.11: Large scale rhodium catalysed asymmetric conjugate addition.**

### 2.7.3. Application of Hayashi's methodology in the total synthesis of (+)-aphanamol I

Having shown Hayashi's work to be scalable, this methodology was applied in the total synthesis of (+)-aphanamol I. Thus, a 1,4-conjugate addition of TIPS-acetylene to 4-methyl-2-pentenal (**200**) (7.30 mmol) followed by a reductive workup with sodium borohydride gave alcohol (*S*)-**307** in good yield (78%) ($[\alpha]_D^{20}$ -8.5 (*c* 0.97, $CHCl_3$) in >99% *ee* based on (*S*)-**308**) [**Scheme 2.54**]. Deprotection of (*S*)-**307** with TBAF gave alkyne (*S*)-**254** ($[\alpha]_D^{20}$ -23.7 (*c* 1.02, $CHCl_3$) for >99% *ee*) which was protected with tosyl chloride to give tosylate (*S*)-**264** ($[\alpha]_D^{20}$ -50.9 (*c* 1.01, $CHCl_3$) for >99% *ee*) in 80% yield over two steps. The enantiomeric excess of tosylate (*S*)-**264** was confirmed to ensure no optical purity had been lost. Pleasingly, the UV trace of (±)-**264** showed two peaks at $t_1$ = 28.4 min (*S*) and $t_2$ = 29.9 min (*R*) whilst tosylate (*S*)-**264** showed a single peak at $t_1$ = 28.5 min (*S*).[VIII]

[VIII] Chiralcel OD column, flow 0.6 mL/min, 0.5% IPA/hexane, 230 nm.




**200** (*S*)-**307** (*S*)-**254** (*S*)-**264**

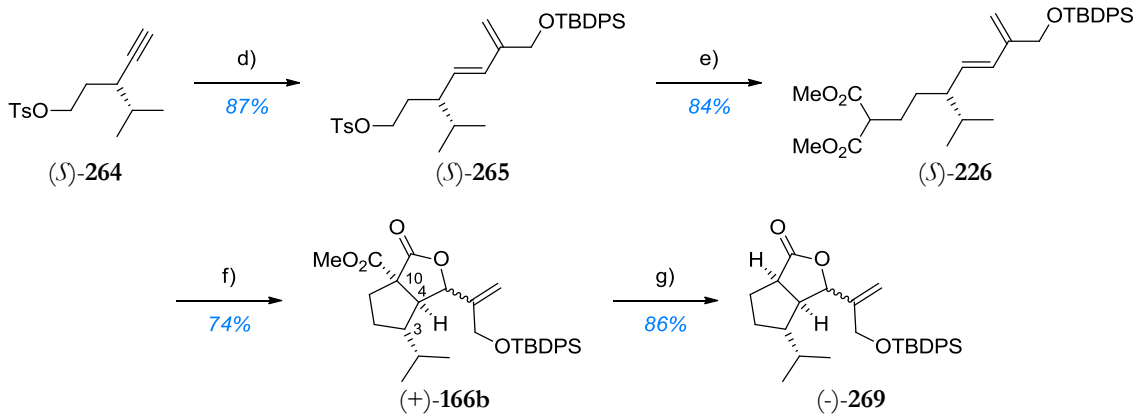
**Scheme 2.54: Large scale conjugate addition of TIPS-acetylene to 200.**

**Reagents and conditions: a) i) 2.5 mol% chlorobis(ethylene)rhodium(I) dimer, sodium acetate trihydrate, $Et_2O$, -30 °C-RT, 1 h; ii) 6 mol% (*S*)-(+)-DTBM-SEGPHOS, (triisopropylsilyl)acetylene, MeOH, 40 °C, 24 h; iii) $NaBH_4$, MeOH, RT, 30 min, 78%; b) 1 M TBAF, THF, RT, 18 h, 92%; c) *p*-toluenesulfonyl chloride, pyridine, DCM, RT, 18 h, 87%.**

Confident tosylate (*S*)-**264** was still a single enantiomer, it was cross coupled to vinyl iodide **252** to give 1,3-diene (*S*)-**265** ($[\alpha]_D^{20}$ -5.0 (*c* 1.02, DCM) for >99% *ee* based on (*S*)-**264**) in excellent yield (87%) [**Scheme 2.55**]. Subsequent displacement of the tosylate with the anion of dimethylmalonate gave dienyl malonate (*S*)-**226** ($[\alpha]_D^{20}$ -0.2 (*c* 1.01, DCM) for >99% *ee*) in 84% yield. Concerned about the low value observed for the optical rotation of (*S*)-**226**, further studies were carried out to confirm dienyl malonate (*S*)-**226** was still a single enantiomer. Unfortunately, it was not possible to separate the enantiomers by HPLC due to instability of (*S*)-**226** most likely due to the diene. However using a mercury lamp, a larger optical rotation was observed ($[\alpha]_{354}^{20}$ +10.1 (*c* 1.01, DCM) for >99% ee) confirming (*S*)-**226** was not racemic. Subjecting dienyl malonate (*S*)-**226** to the optimised cyclisation conditions gave [3.3.0]-bicyclic *γ*-lactone (+)-**166b**[IX] ($[\alpha]_D^{20}$ +1.3 (*c* 0.98, $CHCl_3$), $[\alpha]_{354}^{20}$ +2.6 (*c* 0.98, $CHCl_3$) for >99% *ee* and a diastereomeric ratio of 6:1.) in good yield (74%) as a 6:1 mixture of diastereomers at C-5. Still concerned about the low optical rotations observed in (+)-**166b**, further HPLC studies were carried out. The UV trace of (±)-**166b** showed four peaks (major and minor diastereoisomer at C-4 of each enantiomer) with retention times of $t_1$ = 8.4 (minor 3*S*,4*S*,5*R*,10*R*), 9.6 min (major 3*S*,4*S*,4*S*,10*R*) and $t_2$ = 9.6 (minor 3*R*,4*S*,5*R*,10*R*), 10.6 min (major 3*R*,4*S*,5*S*,10*R*) whilst (3*S*,4*S*,10*R*)-**166b** showed two peaks at $t_1$ = 8.5 (minor 3*S*,4*S*,5*R*,10*R*), 9.7 min (major 3*S*,4*S*,5*S*,10R). Whilst dienyl malonate (*S*)-**226** and

[IX] For clarity reasons the numbering system assigned to (+)-aphanamol I will be used which is not the same as the systematic numbering assigned in the experimental.

[3.3.0]-bicyclic γ-lactone (+)-**166b** display small optical rotations, HPLC studies of (+)-**166b** confirmed it to still be a single enantiomer. Decarboxylation of methyl ester (+)-**166b** under Krapcho conditions gave a separable mixture of (-)-**269** ($[\alpha]_D^{20}$ -6.6 (*c* 0.96, $CHCl_3$) for >99% ee) and (-)-**269** ($[\alpha]_D^{20}$ -23.0 (*c* 1.00, $CHCl_3$) for >99% *ee*) in 86% combined yield.

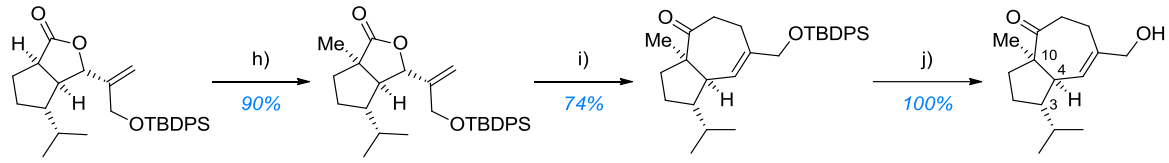



**Scheme 2.55: Cyclisation of diene (*S*)-226 to give (3*S*,4*S*,10*R*)-166b as a 6:1 mixture of diastereomers.**

**Reagents and conditions: d) (i) catecholborane, THF, 70 °C; (ii) 5 mol% palladium (II) acetate, 20 mol% triphenylphosphine, *tert*-butyl((2-iodoallyl)oxy)diphenylsilane, THF, 40 °C, 87%; e) (i) NaH, dimethyl malonate, DMF, 0 °C; (ii) KI, THF, 80 °C, 1.5 h, 84%; f) $Mn(OAc)_3$, $Cu(OTf)_2$, MeCN, 80 °C, 30 min, 74%; g) LiCl, $H_2O$, DMF, 150 °C, 6 h, 86%.**

From this point for clarity reasons only the transformations carried on the (3*S*,4*S*,5*S*,10*R*)-**269** (Major diastereomer) will be presented in the total synthesis of (+)-aphanamol I. The minor diastereomer (3*S*,4*S*,5*R*,10*R*)-**269** was also converted to (+)-aphanamol I using analogous reactions. Thus, exposure of (3*S*,4*S*,5*S*,10*R*)-**269** to lithium bis(trimethylsilyl)amide in the presence of methyl iodide introduced the bridgehead methyl group to give lactone (-)-**270** ($[\alpha]_D^{20}$ -7.5 (*c* 1.00, $CHCl_3$) for >99% *ee*) in 90% yield [**Scheme 2.56**]. Pleasingly using the one-pot procedure, subjecting (-)-**270** to the Petasis reagent followed by quenching and heating overnight gave [5.3.0]-bicyclic ketone (+)-**272** ($[\alpha]_D^{20}$ +22.9 (*c* 1.00, $CHCl_3$) for >99% *ee*) in good yield (74%). The isolated intermediate enol ether (-)-**271** ($[\alpha]_D^{20}$ -3.2 (*c* 1.00, $CHCl_3$) for >99% *ee*) also underwent a Claisen ring expansion to give (+)-**272** ($[\alpha]_D^{20}$ +22.1 (*c* 0.96, $CHCl_3$) for >99% *ee*) in 65% yield over two steps. Final HPLC studies confirmed [5.3.0]-bicyclic ketone (+)-**272** to be a single enantiomer as the UV trace

showed a single pick at $t_1$ = 15.1 min (3*S*,4*R*,10*R*) whilst (±)-**272** had two peaks at $t_1$ = 15.2 min (3*S*,4*R*,10*R*) and $t_2$ = 16.5 min (3*R*,4*R*,10*R*).[X] Finally, deprotection of (+)-**272** using acetic acid buffered tetrabutylammonium fluoride completed the total synthesis of (+)-aphanamol I in 19.3% overall yield and in ten linear steps ($[\alpha]_D^{20}$ +23.3 (*c* 0.40, $CHCl_3$) for >99% *ee*, [lit.[51] $[\alpha]_D^{18}$ +13.8 (*c* 0.29, $CHCl_3$)]).




(-)-**269** (-)-**270** (+)-**272** (3*S*,4*R*,10*R*)-**91**

**Scheme 2.56: Asymmetric total synthesis of (+)-aphanamol I.**

**Reagents and conditions: h) 1 M LiHMDS in toluene, MeI, -78 °C, 30 min, 90%; i) (i) the Petasis reagent, toluene, 110 °C, 30 min; (ii) Celite, hexane, 150 °C; j) 1 M TBAF, AcOH, THF, 0 °C-RT, 24 h, 100%.**

## 2.8. Spectroscopic analysis of (+)-aphanamol I

The proton [**Table 2.12**] and carbon [**Table 2.13**] NMR data of (3*S*,4*R*,10*R*)-**91** were in good accordance with those reported by Nishizawa. The ketone was identified by a peak in the carbon NMR at δ 214.8 (7 ring ketone), whilst in the IR, a carbonyl stretch was identified at $\nu_{max}$ 1698 $cm^{-1}$ indicating the presence of an aliphatic ketone. In the proton NMR, the internal alkene was identified by a single proton doublet at $\delta_H$ 5.53 (*J* = 4.5 Hz) identified as C-5 due to a coupling with the C-4 bridgehead proton.

[X] Chiralcel OD column, flow 0.6 mL/min, 1.0% IPA/hexane, 230 nm

| $\delta_H$ Natural | $\delta_H$ Synthetic |
|---|---|
| 5.52 (1H, d, J = 4.1 Hz, | 5.53 (1H, d, *J* = 4.5 Hz) |
| 4.03 (2H, s), | 4.03 (2H, d, *J* = 2.3 Hz) |
| 2.86–2.79 (1H, m) | 2.83 (1H, ddd, *J* = 14.6, 5.8, 3.8 Hz, |
| 2.61–2.37 (2H, m) | 2.60–2.51 (1H, m)<br>2.43 (1H, ddd, *J* = 14.6, 11.8, 5.8 Hz) |
| 2.35–2.27 (2H, m) | 2.32–2.25 (2H, m) |
| 2.18–2.02 (1H, m) | 2.14–2.05 (1H, m) |
| 1.84–1.71 (1H, m) | 1.85–1.75 (1H, m) |
| | 1.71–1.63 (1H, m) |
| 1.69-1.40 (4H, m) | 1.63–1.53 (1H, m) |
| | 1.42–1.29 (3H, m) |
| 1.22 (3H, s), | 1.27 (3H, s) |
| 0.91 (3H, d, *J* = 7.0 Hz) | 0.92 (3H, d, *J* = 6.5 Hz) |
| 0.90 (3H, d, *J* = 7.0 Hz) | 0.91 (3H, d, *J* = 6.5 Hz) |

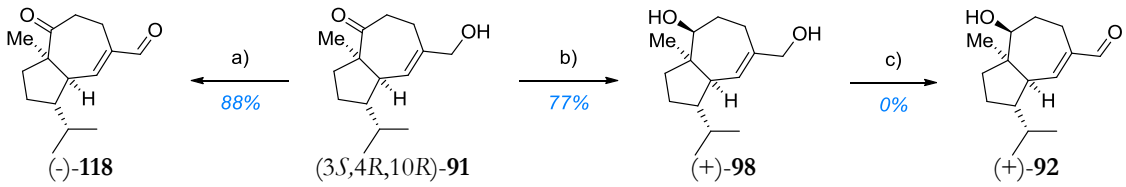
**Table 2.12: Proton NMR data for synthetic and natural (+)-aphanamol I**

| $\delta_C$ Natural | $\delta_C$ Synthetic | $\Delta\delta_{C\ ppm}$ | $\delta_C$ Natural | $\delta_C$ Synthetic | $\Delta\delta_{C\ ppm}$ |
|---|---|---|---|---|---|
| 213.7 | 213.6 | -0.1 | 34.5 | 34.5 | - |
| 141.7 | 141.6 | -0.1 | 33.0 | 33.0 | - |
| 132.9 | 132.9 | - | 27.1 | 27.0 | -0.1 |
| 67.1 | 67.1 | - | 24.9 | 24.9 | - |
| 58.9 | 58.9 | - | 24.7 | 24.7 | - |
| 56.0 | 56.0 | - | 22.1 | 22.0 | -0.1 |
| 51.4 | 51.4 | - | 19.9 | 19.9 | - |
| 39.9 | 39.9 | - | | | |

**Table 2.13: Carbon NMR data for synthetic and natural (+)-aphanamol I**

## 2.9. Synthesis of other natural products related to (+)-aphanamol I

With a synthetic sample of (+)-aphanamol I in hand work turned to validating the absolute configuration studies that were carried out by Wickberg *et al.* [**Scheme 2.57**]. Thus, a Swern oxidation of (+)-aphanamol I gave (-)-2-oxoisodauc-5-en-12-al (-)-**118** in 88% yield ($[\alpha]_D^{20}$ -6.8 (*c* 0.48, $CHCl_3$) for >99% *ee* [lit.[64] $[\alpha]_D^{20}$ -5.9 (*c* 0.76, $CDCl_3$)]). The aldehyde was identified by a carbonyl peak in the carbon NMR at δ 192.7, whilst in the IR, a carbonyl stretch was identified at $\nu_{max}$ 1686 $cm^{-1}$ indicating the presence of an *a,β*-unsaturated aldehyde. Alternatively, treatment of (+)-aphanamol I with sodium borohydride reduced the ketone to give isodauc-5-ene-2,12-diol (+)-**98** in good yield. ($[\alpha]_D^{20}$ +41.6 (*c* 0.34, $CHCl_3$) for >99% *ee* [lit.[51] $[\alpha]_D^{15}$ +21.2 (*c* 0.25, $CHCl_3$)]). Following a method reported by Piancatelli *et al.* for the selective oxidation of a primary alcohol in the presence of a secondary alcohol,[140] exposure of diol **98** to a TEMPO/BAIB oxidation did not produce (+)-aphanamol II (**92**) with decomposition of starting material observed.




**Scheme 2.57: Synthesis of (-)-2-oxoisodauc-5-en-12-al, isodauc-5-ene-2,12-diol and (+)-aphanamol II.**

**Reagents and conditions: a) $(COCl)_2$, triethylamine, DMSO, DCM, -78 °C-RT, 1 h, 88%; b) $NaBH_4$, $H_2O$, EtOH, RT, 1 h, 77%; c) TEMPO, BAIB, DCM, RT, 3 h, 0%.**

## 2.10. Summary

In summary, methodology has been developed which can be used in the synthesis of a variety of [5.3.0]-bicyclic ketones. This methodology has been applied in the total synthesis of (+)-aphanamol I which was completed in 10 steps and 19.3% overall yield. Synthesis of other related natural products has validated the studies carried out by Wickberg *et al.* in assigning the absolute configuration of (+)-aphanamol I and II.

# CHAPTER 3: Methodology scope

Chapter 3 will discuss efforts towards demonstrating a manganese(III) acetate mediated oxidative radical cyclisation of various substituted dienyl malonates. Firstly, the effect of various *γ*-substituted dienyl malonates will be investigated to determine the effect that substituent size has on the diastereoselectivity of the manganese(III) acetate mediated cyclisation. Following this, work will focus on applying the methodology in the synthesis of [2.3.0]-, [4.3.0]- and [5.3.0]-bicyclic *γ*-lactones which could be used as intermediates in the total synthesis of natural products which feature contiguous stereocentres.

## 3.1. Investigating the diastereocontrol of *γ*-substituents

As demonstrated in the total synthesis of (+)-aphanamol I, the isopropyl functionality directs the formation of the three new stereogenic centres in accordance with the Beckwith and Houk models [**Figure 3.1**]. Thus following a single electron oxidation by manganese(III) acetate, substrate **309** must cyclise *via pseudo*-chair transition state **310**, with the isopropyl group *pseudo*-equatorial to minimise 1,3-diaxial and 1,3-allylic interactions. The result of a 5-*exo*-trig cyclisation would give adduct radical **311** with the isopropyl group and the allyl radical on opposite faces of the cyclopentane **311**. Subsequent oxidation to the formal allylic carbocation **312** by copper(II) triflate, followed by trapping with one of the diastereotopic esters sets the final two stereogenic centres. The *cis*-fused bicycle **313** is formed due to better orbital overlap with the ester on the same side resulting in a lower energy transition state. The diastereoselectivity observed at C-6, in which the vinyl substituent is placed on the outside face of the bicyclic bowl preferentially (*pseudo*-equatorial), is again minimising 1,3-diaxial interactions with the ring system.

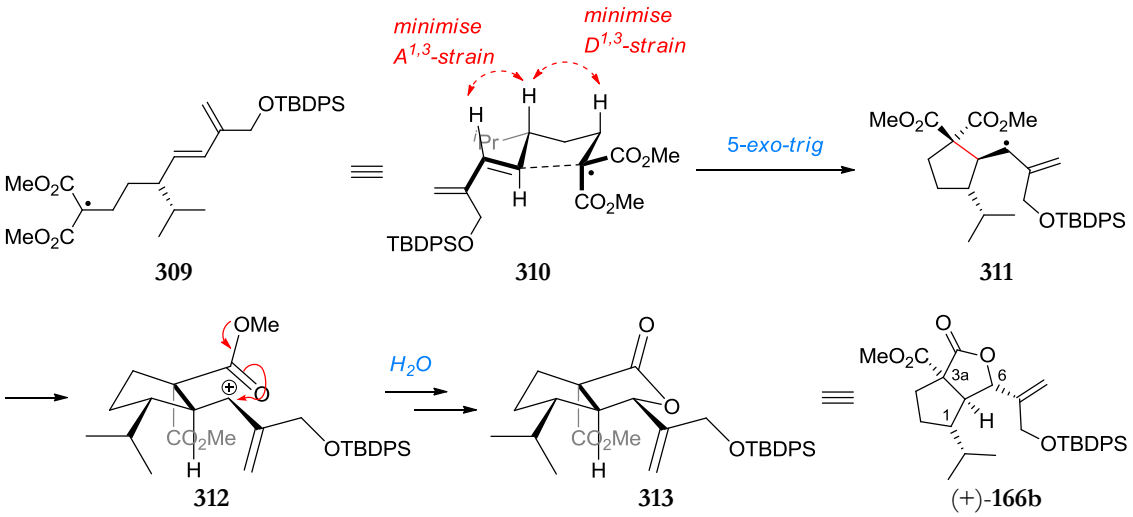



**Figure 3.1: Mechanistic explanation for the observed diastereoselectivity of the manganese(III) acetate cyclisation in the total synthesis of (+)-aphanamol I**

Whilst it is expected that the presence of a bulky isopropyl group would favour transition state **310**, it is not obvious whether other functional groups might cyclise with similar diastereoselectivities. Therefore it was decided to investigate the effect *γ*-substituent size plays on cyclisation diastereoselectivity, with a variety of substituents [**Figure 3.2**]. Different sized alkyl substituents were investigated as well as synthetically more useful phenyl, benzyl, vinyl and heteroatom substituents.

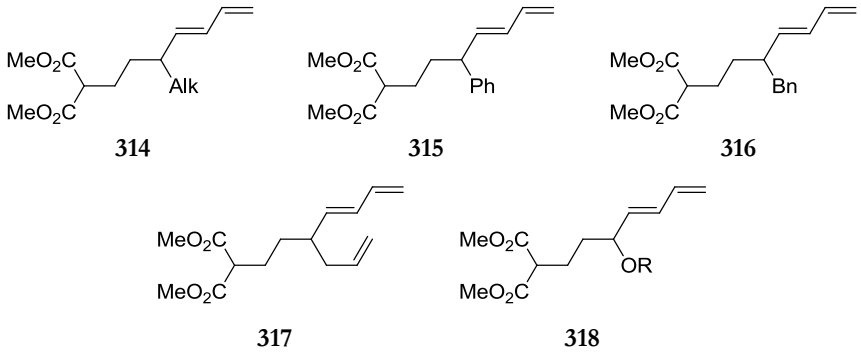
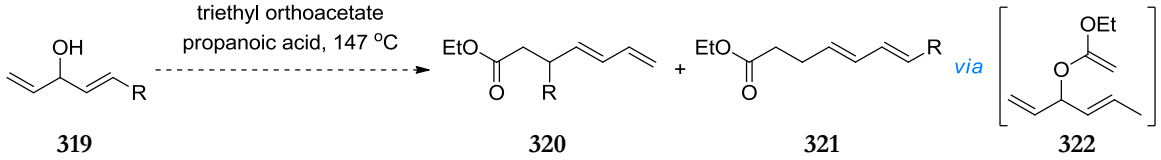



**Figure 3.2: Dienyl malonates featuring different *γ*-substituted functional groups.**

As mentioned previously, the synthesis of dienes remains a challenge to synthetic organic chemists. Whilst it was possible to synthesise a simple dienyl ester (**169**) through a Johnson-Claisen rearrangement of divinyl alcohol **170** (**Section 2.5.1**), such rearrangement could not be applied in the synthesis of *γ*-substituted 1,3-diene [**Scheme 3.1**]. This is because the required allylic alcohols

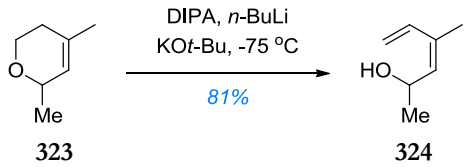
(**319**) are no longer symmetrical and would likely give a mixture of substituted dienyl ester products **320** and **321** due to rearrangement of intermediate **322** at either alkenyl group.




**Scheme 3.1: Mixture of substituted dienes likely formed from a Johnson-Claisen rearrangement of 319.**

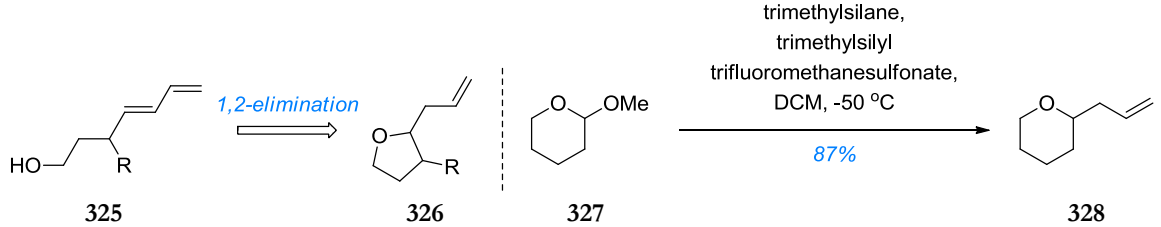
### 3.1.1. Alternative routes to *γ*-substituted dienes

In 1990, Schlosser *et al.* reported the synthesis of various substituted dienes via a 1,2-elimination of a homoallyl ether [**Scheme 3.2**].[141] For example, treatment of pyran **323** with a super basic mixture of lithium diisopropylamide and catalytic potassium *tert*-butoxide (termed LIDAKOR) gave dienyl alcohol **324** in excellent yield (81%).




**Scheme 3.2: Intramolecular *β*-elimination of a homoallyl ether to generate a dienyl alcohol.**

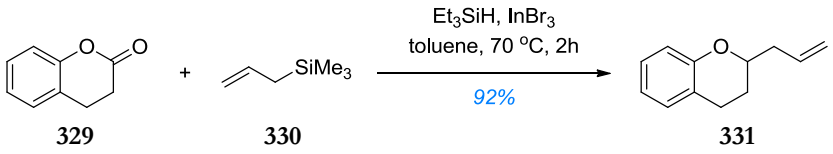
Using Schlosser's methodology, the desired dienyl alcohols (**325**) would arise from 5-membered cyclic homoallyl ethers such as **326** *via* a 1,2-elimination [**Scheme 3.3**]. In 1983, Noyori *et al.* reported the synthesis of homoallyl ether **328** in 87% yield, by treating methoxy pyran **327** with allyl trimethylsilane in the presence of catalytic trimethylsilyl trifluoromethanesulfonate.[142]




**Scheme 3.3: Intermediate required to utilise Schlosser's methodology and a possible preparation.**

However due to the limited availability of substituted methoxy ethers, such methodology has been limited in its application. Noyori tried to apply the methodology to the corresponding

lactones, but this failed to give the allylation product. The breakthrough came in 2010, when Wilkinson *et al.* reported the reductive allylation of aliphatic and alicyclic esters in the presence of catalytic indium(III) bromide [**Scheme 3.4**].[143] For example, treatment of lactone **329** and allyltrimethylsilane (**330**) with triethylsilane and 10 mol% indium(III) bromide gave homoallyl ether **331** in excellent yield (92%).




**Scheme 3.4: Reductive allylation of a *γ*-lactone using indium(III) bromide.**

The main benefit of Wilkinson's methodology is the ability to synthesise a number of substituted lactones as shown retrosynthetically [**Figure 3.3**]. Thus, a reductive allylation of substituted lactone **332** would give homoallyl ether **326**. Lactone **332** would in turn arise from an alkylation of butyrolactone (**333**) by quenching the pre-formed enolate with a variety of electrophiles (**334**).

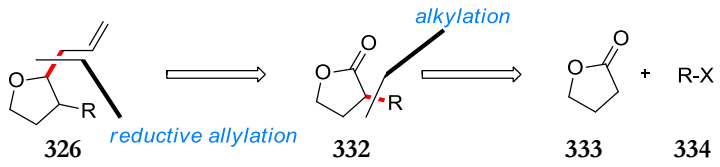
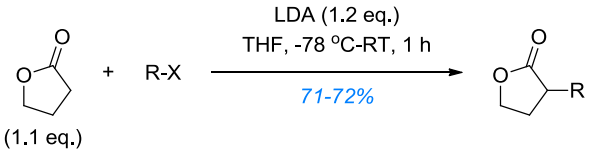



**Figure 3.3: Retrosynthesis of the desired homoallyl ether 326.**

### 3.1.2. Synthesis of simple *γ*-substituted alkyl and heteroatom dienyl malonates

As proposed above, butyrolactone **333** was alkylated with several alkyl halides to give the corresponding substituted lactones in good yield [**Table 3.1**]. Treatment of **333** with lithium diisopropylamide to form the corresponding enolate followed by quenching with a variety of alkyl halides (entry 1-3) gave substituted lactones **332a-c** in modest to excellent yield (57-72%). Unfortunately treatment of the enolate with cyclohexyl iodide (entry 4) did not give **332d**, even at reflux, most likely due to the steric bulk hindering the approach of the incoming nucleophile. As substitution reactions at sterically hindered alkyl halides and aryl halides are difficult, the remaining

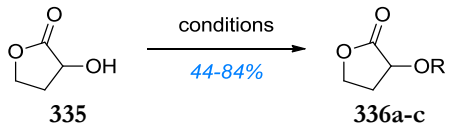
substrates were synthesised using methodology similar to that applied in the total synthesis of (±)-aphanamol I which will be presented in **Section 3.1.3**.




| Entry | RX | Product | Yield (%) |
|---|---|---|---|
| 1 | methyl iodide | **332a** | 71 |
| 2 | benzyl bromide | **332b** | 72 |
| 3 | allyl bromide | **332c** | 57 |
| 4 | cyclohexyl iodide | **332d** | N/R |

**Table 3.1: Alkylation of γ-butyrolactone with various electrophiles.**

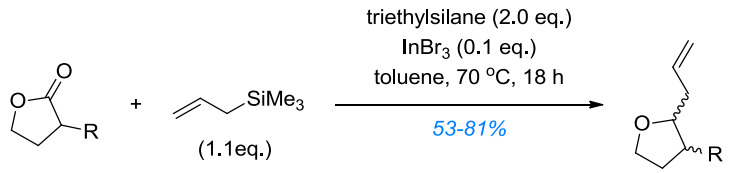
The corresponding oxygen-substituted lactone **335**, whilst commercially available, requires differentiated oxygen functionality for the subsequent malonate alkylation step and hence was protected [**Table 3.2**]. Exposure of lactone **335** to standard conditions for the formation of silyl ethers gave TBS-ether **336a** (entry 1) and TBDPS-ether **336b** (entry 2) in good yield. As deprotection was observed in the cyclisation of **267** [**Table 2.9**], a benzyl protecting group (entry 3) was also used which is acid stable and likely to be stable under the manganese(III) acetate conditions.




| Entry | Conditions | Product | R | Yield (%) |
|---|---|---|---|---|
| 1 | TBSCl, imidazole, THF, 0 °C-RT, 6 h | **336a** | TBS | 84 |
| 2 | TBDPSCl, imidazole, DMF, 0 °C-RT, 16 h | **336b** | TBDPS | 78 |
| 3 | Benzyl bromide, NaH, THF/DMF, 0 °C-RT, 48 h | **336c** | Bn | 44 |

**Table 3.2: Protection of α-hydroxy-γ-butyrolactone with various protecting groups.**

With a variety of substituted lactones in hand, the reductive allylation step was investigated [**Table 3.3**]. Pleasingly treatment of methyl substituted lactone **332a** to Wilkinson's conditions (entry 1) gave homoallyl ether **326a** in excellent yield (81%) as a 3:1 mixture of diastereomers. The allyl functionality was identified in the proton NMR as a one proton multiplet at $\delta_H$ 5.92–5.79 ($CH_2C\mathbf{H}=CH_2$) and a terminal $CH_2$ multiplet at $\delta_H$ 5.14–5.07 ($CH=CH_Z\mathbf{H_E}$) and 5.07–5.02 ($CH=C\mathbf{H_Z}H_E$). In the IR, the disappearance of the *γ*-lactone stretch at $\nu_{max}$ 1762 $cm^{-1}$ (C=O) and 1172 $cm^{-1}$ (C-O) and appearance of a cyclic ether stretch at $\nu_{max}$ 1077 $cm^{-1}$ (asymmetrical C-O-C) indicated the product to be **326a**. Reductive allylation of benzyl lactone **332b** (entry 2) gave homoallyl ether **326b** in good yield (76%) as a 7:1 mixture of diastereomers, however allyl lactone **332c** (entry 3) decomposed under the reaction conditions. Treatment of silyl ethers **336a** (entry 4) and **336b** (entry 5) under the reductive allylation conditions gave homoallyl ether **326d** and **326e** in modest yield (53% and 64% respectively) as a 1:1 mixture of diastereoisomers. The corresponding benzyl ether **336c** (entry 6) gave **326f** in 61% yield as a 1.8:1 mixture of diastereoisomers.



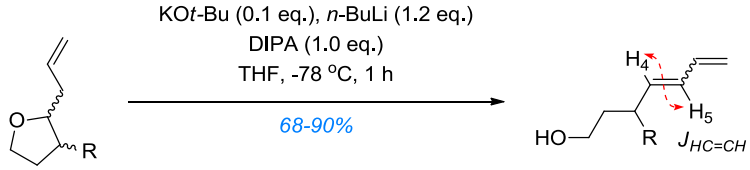

**332/336** **330** **326a-f**

| Entry | Starting material | R | Product | Yield (%) | *dr* |
|---|---|---|---|---|---|
| 1 | **332a** | Me | **326a** | 81 | 3:1 |
| 2 | **332b** | Bn | **326b** | 76 | 7:1 |
| 3 | **332c** | allyl | **326c** | 0% | -[a] |
| 4 | **336a** | OTBS | **326d** | 64 | 1.2:1 |
| 5 | **336b** | OTBDPS | **326e** | 53 | 1.1:1 |
| 6 | **336c** | OBn | **326f** | 61 | 1.8:1 |

[a] Decomposition of starting material observed.

**Table 3.3: Reductive allylation of various *α*-substituted *γ*-butyrolactones.**

Whilst a mixture of diastereoisomers was obtained, the following *β*-elimination destroys the stereogenic centre at C-2 [**Table 3.4**]. Thus, exposure of homoallyl ether **326a** (entry 1) to lithium diisopropylamine, butyl lithium and catalytic potassium *tert*-butoxide at -78 °C gave methyl substituted dienyl alcohol **337a** in excellent yield (90%) as a 10:1 mixture of geometric isomers. The major regioisomer was identified as the *E*-isomer due to a large coupling constant observed between H-4 and H-5 ($J$ = 15.2 Hz). Treatment of benzyl **326b** to the same conditions gave dienyl alcohol **337b** in 82% yield as a 17:1 mixture of regioisomers. A 1,2-elimination of the corresponding protected alcohols **326d-f** (entry 3-5) gave dienyl alcohols **337c-f** in good to excellent yields (68-83%) and as single geometric isomers. The regioselectivity of the elimination was found to be highly dependent on the rate of addition of LIDAKOR and maintaining efficient cooling of the reaction mixture.



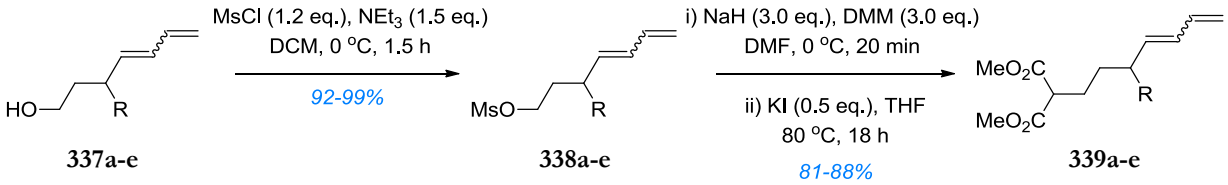

**326a-f** **337a-e**

| Entry | Starting material | R | Product | Yield (%) | *E*:*Z* ratio[a] | $J_{HC=CH}$ (Hz) |
|---|---|---|---|---|---|---|
| 1 | **326a** | Me | **337a** | 90 | 10:1 | 15.2 |
| 2 | **326b** | Bn | **337b** | 82 | 17:1 | 15.3 |
| 3 | **326d** | OTBS | **337c** | 83 | >99:1 | 15.2 |
| 4 | **326e** | OTBDPS | **337d** | 68 | >99:1 | 15.3 |
| 5 | **326f** | OBn | **337e** | 77 | >99:1 | 15.2 |

[a] Determined by analysis of crude proton NMR.

**Table 3.4: *β*-elimination to give various substituted dienyl alcohols.**

Finally, substituted dienyl alcohols **337a-e** were treated with methanesulfonyl chloride to give mesylates **338a-e** in excellent yield (92-97%) [**Table 3.5**]. Following purification, subsequent displacement with the pre-formed anion of dimethyl malonate gave the desired dienyl malonates **339a-e** in good to excellent yield (81-88%).




**337a-e** **338a-e** **339a-e**

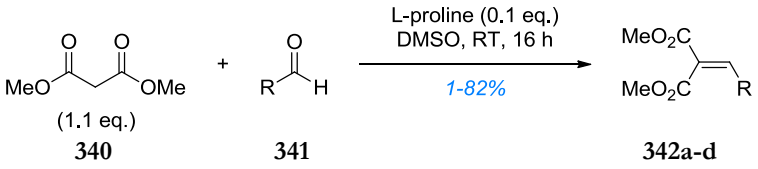
| Entry | Starting material | R | Product | Yield (%) | Product | Yield (%) | *E*:*Z* ratio[a] |
|---|---|---|---|---|---|---|---|
| 1 | **337a** | Me | **338a** | 92 | **339a** | 86 | 10:1 |
| 2 | **337b** | Bn | **338b** | 94 | **339b** | 81 | 17:1 |
| 3 | **337c** | OTBS | **338c** | 99 | **339c** | 86 | >99:1 |
| 4 | **337d** | OTBDPS | **338d** | 92 | **339d** | 83 | >99:1 |
| 5 | **337e** | OBn | **338e** | 97 | **339e** | 88 | >99:1 |

[a] As carried forward from the *β*-elimination of **326a-f**

**Table 3.5: Mesylation and alkylation of alcohols 337a-e to give dienyl malonates 339a-e.**

### 3.1.3. Synthesis of more complex *γ*-substituted alkyl and heteroatom dienyl malonates

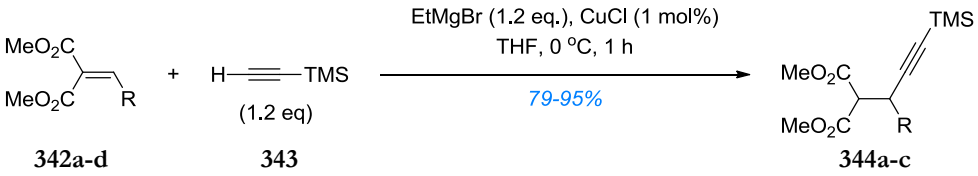
As highlighted in **Section 3.1.2**, the alkylation of butyrolactone with cyclohexyl iodide most likely failed due to sterics hindering the nucleophilic attack of the enolate. The introduction of the even more sterically hindered functional groups such as *tert*-butyl is also not possible *via* $S_N2$ nucleophilic attack for the same reason. The introduction of the phenyl substituent is also not possible *via* nucleophilic attack in either $S_N2$ of $S_N1$ fashion, firstly due to ring repulsion of the approaching nucleophile and secondly because of the strong aryl-halide bond. Therefore it was decided to synthesise the more sterically demanding and aryl substituents *via* the same route as that employed in the total synthesis of (±)-aphanamol I [**Table 3.6**]. Thus, a Knoevenagel condensation of dimethyl malonate with a variety of aldehydes (entries 1-3) gave the corresponding *α,β*-unsaturated enones **342a-c** in modest to excellent yield (59-82%). Unfortunately condensation of pivaldehyde with dimethyl malonate (entry 4) gave only a low yield of **342d**.




| Entry | R | Product | Yield (%) |
|---|---|---|---|
| 1 | $C_5H_{11}$ | **342a** | 59 |
| 2 | cyclohexane | **342b** | 79 |
| 3 | Ph | **342c** | 82 |
| 4 | *t*-butyl | **342d** | ~1 |

**Table 3.6: Knoevenagel condensation of various aldehydes with dimethyl malonate.**

Subsequent 1,4-conjugate addition of TMS-acetylene to *a,β*-unsaturated enones **342a-d** gave the corresponding alkynyl malonates **344a-c** in good to excellent yield (79-95%) [**Table 3.7**]. Unfortunately the conjugate addition of TMS-acetylene to *tert*-butyl substituted malonate **342d** (entry 4) was unsuccessful with no reaction taking place as confirmed by mass spectroscopy and proton NMR of the crude reaction mixture. Due to the low yield of **342d** from the Knoevenagel condensation and the failed conjugate addition, it was decided to abandon the *tert*-butyl substrate as this would likely cause complications due to the steric bulk at later stages in the synthesis.

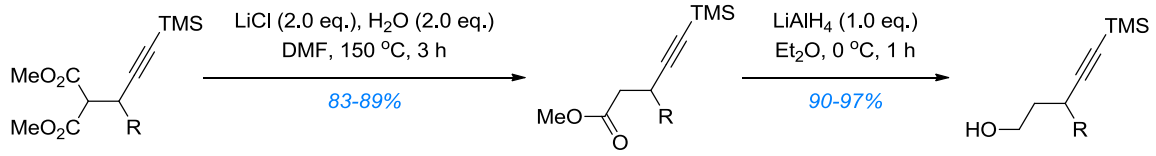



| Entry | Starting material | R | Product | Yield (%) |
|---|---|---|---|---|
| 1 | **342a** | $C_5H_{11}$ | **344a** | 79 |
| 2 | **342b** | cyclohexane | **344b** | 95 |
| 3 | **342c** | Ph | **344c** | 81 |
| 4 | **342d** | *t*-butyl | **344d** | N/R[a] |

[a] Starting materials recovered

**Table 3.7: 1,4-conjugate addition of TMS-acetylene to *α,β*-unsaturated enones 344a-c.**

A Krapcho decarboxylation of *β*-alkynyl malonates **344a-c** using the reduced temperature conditions found earlier, gave *β*-alkynyl esters **345a-c** in good to excellent yield (79-95%) [**Table 3.8**]. Esters **345a-c** were then treated with a stirred suspension of lithium aluminium hydride in anhydrous diethyl ether to give alkynyl alcohols **346a-c** in excellent yield (90-97%).

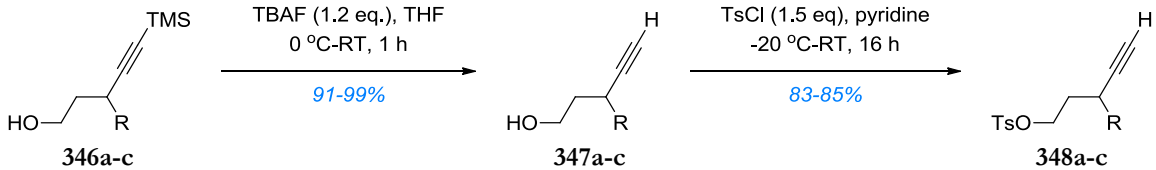



**344a-c** **345a-c** **346a-c**

| Entry | Starting material | R | Product | Yield (%) | Product | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | **344a** | $C_5H_{11}$ | **345a** | 89 | **346a** | 97 |
| 2 | **344b** | cyclohexane | **345b** | 83 | **346b** | 93 |
| 3 | **344c** | Ph | **345c** | 87 | **346c** | 90 |

**Table 3.8: Krapcho decarboxylation of malonates 344a-c followed by reduction to give alkynyl alcohol 344a-c.**

Treatment of alkynyl alcohols **346a-c** with a 1 M solution of TBAF in THF removed the trimethylsilyl protecting group to give terminal alkynes **347a-c** in excellent yield (91-99%) [**Table 3.9**]. Subsequent exposure of alcohols **347a-c** to tosyl chloride in pyridine gave the corresponding tosylates **348a-c** in excellent yield (83-85%).



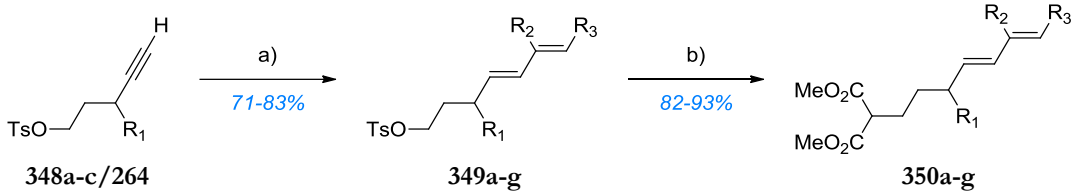

**346a-c** **347a-c** **348a-c**

| Entry | Starting material | R | Product | Yield (%) | Product | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | **346a** | $C_5H_{11}$ | **347a** | 99 | **348a** | 83 |
| 2 | **346b** | cyclohexane | **347b** | 98 | **348b** | 85 |
| 3 | **346c** | Ph | **347c** | 91 | **348c** | 85 |

**Table 3.9: Deprotection and tosylation of alkynyl alcohols 346a-c.**

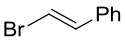
With tosyl alkynes **348a-c** in hand, work turned to synthesising the desired dienyl malonates [**Table 3.10**]. Pentyl-substituted tosylate **348a** was cross-coupled to 2-bromopropene

(entry 1) to give 1,3-diene **349a** in excellent yield (83%). The diene was identified as the *E*-isomer due to a large coupling constant observed between H-4 and H-5 ($J$ = 15.6 Hz), whilst the terminal alkene was identified as two proton singlets at $\delta_H$ 4.95 (1H, s, C=C**H**$_2$) and 4.92 (1H, s, C=C**H**$_2$). A Suzuki cross coupling of 2-bromopropene to cyclohexyl substituted tosylate **348b** (entry 2) and phenyl substituted tosylate **348c** (entry 3) gave 1,3-dienes **349b** and **349c** in 82% and 79% yield respectively.




**348a-c/264** **349a-g** **350a-g**

**Reagents and conditions: a) (i) catecholborane (1.3 eq.), THF, 70 °C; (ii) 5 mol% palladium(II) acetate, 20 mol% triphenylphosphine, RBr, THF, 40 °C; b) (i) NaH (3.0 eq.), dimethyl malonate (3.0 eq), DMF, 0 °C; (ii) KI (0.5 eq.), THF, 80 °C, 1.5 h.**

| Entry | Starting material | $R_1$ | RBr | Product | $R_2$ | $R_3$ | Yield (%) | Product | Yield (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **348a** | $C_5H_{11}$ |  | **349a** | Me | H | 83 | **350a** | 93 |
| 2 | **348b** | cyclohexane |  | **349b** | Me | H | 82 | **350b** | 91 |
| 3 | **348c** | Ph |  | **349c** | Me | H | 79 | **350c** | 90 |
| 4 | **264** | *i*-Pr |  | **349d** | H | H | 71 | **350d** | 88 |
| 5 | **264** | *i*-Pr |  | **349e** | H | Me | 80[a] | **350e** | 82[a] |
| 6 | **264** | *i*-Pr |  | **349f** | Me | H | 81 | **350f** | 86 |
| 7 | **264** | *i*-Pr |  | **349g** | H | Ph | 82 | **350g** | 82 |

[a] Isolated as a 1:1 mixture of regioisomers

**Table 3.10: Suzuki cross coupling of alkyne 348a-c followed by displacement with dimethyl malonate.**

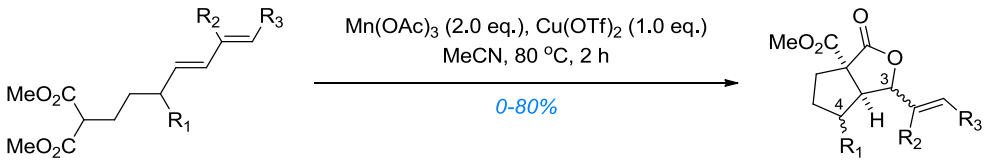
At this point, it was decided to also investigate the effect substitution on the diene plays on the diastereoselectivity at the alkenyl stereocentre during cyclisation to form the [3.3.0]-bicyclic $\gamma$-lactone products. Therefore a range of substituted vinyl bromides were coupled to isopropyl tosylate **264** (entries 4-7). A Suzuki cross coupling of **264** to vinyl bromide (entry 4) gave terminal 1,3-conjugate diene **349d** in modest yield (71%). 1,3-Diene **349e** (entry 5) was isolated as a 1:1

mixture of regioisomers, as commercially available 1-bromopropene is sold as a mixture of *cis* and *trans* isomers. Finally, displacement of the tosylate in dienes **349a-g** with the pre-formed anion of dimethyl malonate gave the corresponding dienyl malonates **350a-g** in excellent yield (82-93%).

### 3.1.4. Cyclisation

With all the key *γ*-substituted dienyl malonates in hand, work turned to cyclising these substrates under the optimised radical cyclisation conditions developed in the total synthesis of (+)-aphanamol I [**Table 3.11**]. Treatment of the alkyl substituted dienyl malonates **339a** (entry 1) and **350a** (entry 2) gave the corresponding [3.3.0]-bicyclic *γ*-lactones **351a** and **351b** in good yield (76% and 72% respectively). The diastereoselectivity observed for the [3.3.0]-bicyclic *γ*-lactone **351a** was found to be 4.2:2.8:1.0 by crude NMR analysis. Based on the diastereoselectivity observed in the total synthesis of (+)-aphanamol I, this suggests that the two major diastereoisomers are likely to be epimers at C-3 and hence the diastereoselectivity at C-4 for **351a** is 7.0:1.0. Likewise the diastereoselectivity at C-4 in [3.3.0]-bicyclic *γ*-lactone **351b** 11.1:1 in which in which the pentyl substituent is on the same face as the cis fused ring substituents. Cyclisation of cyclohexyl substituted dienyl malonate **350b** (entry 3) gave [3.3.0]-bicyclic *γ*-lactone **351c** in 73% yield as a 19.3:1 mixture of diastereoisomers at C-4. Unfortunately phenyl substituted **350c** (entry 4) gave a modest yield of cyclic product **351d** (52%), however excellent diastereoselectivity was observed at C-4 (23.1:1 *d.r.*). The corresponding benzyl substituted **339b** (entry 5) gave [3.3.0]-bicyclic *γ*-lactone **351e** in excellent yield (80%) and as an 11.1:1.0 mixture of diastereoisomers at C-4. The effects of substituents on the terminal alkene were then investigated. Cyclisation of simple 1,3-diene **350d** (entry 6) gave [3.3.0]-bicyclic *γ*-lactone **351f** in good yield (72%) as a 12.3:7.9 mixture of diastereoisomers at C-3. Cyclisation of the corresponding methyl substituted dienes **350e** (entry 7) and **350f** (entry 8) gave the corresponding [3.3.0]-bicyclic *γ*-lactones **351g** and **351h** in good yield (73% and 77% respectively). Unfortunately the diastereoselectivity of **351g** could not be determined due to the complex mixture of diastereomers observed as a result of **350e** being a

mixture of regioisomers. The diastereoselectivity observed in **351h** (17.1:2.8) was similar to those results observed in the cyclohexyl substituted lactone **351c** (entry 3). Finally, treatment of phenyl substituted 1,3-diene **350g** (entry 9) with manganese(III) acetate decomposed the starting material to give a complex mixture of what appeared to be polymeric material by proton NMR analysis. Cyclisation of the corresponding oxygen substituted dienyl malonates **339c-e** gave mostly decomposed starting material although the desired [3.3.0]-bicyclic *γ*-lactones **351j-l** were detected in the crude mass spectrum as a minor component.




**339a-e/350a-g** **351a-l**

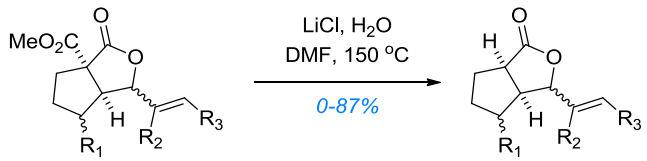
| Entry | Starting material | $R_1$ | $R_2$ | $R_3$ | Product | Yield (%) | *d.r.* |
|---|---|---|---|---|---|---|---|
| 1 | **339a** | Me | H | H | **351a** | 76 | 4.2:2.8:1.0 |
| 2 | **350a** | $C_5H_{11}$ | Me | H | **351b** | 72 | 9.0:2.1:1.0 |
| 3 | **350b** | cyclohexane | Me | H | **351c** | 73 | 16.6:2.7:1.0 |
| 4 | **350c** | Ph | Me | H | **351d** | 52 | 17.5:5.6:1.0 |
| 5 | **339b** | Bn | H | H | **351e** | 80 | 6.3:4.8:1.0 |
| 6 | **350d** | *i*-Pr | H | H | **351f** | 72 | 12.3:7.9:1.0 |
| 7 | **350e** | *i*-Pr | H | Me | **351g** | 73 | n/d[a] |
| 8 | **350f** | *i*-Pr | Me | H | **351h** | 77 | 17.1:2.8:1.0 |
| 9 | **350g** | *i*-Pr | H | Ph | **351i** | 0 | - |
| 10 | **339c** | OTBS | H | H | **351j** | trace | n/d |
| 11 | **339d** | OTBDPS | H | H | **351k** | trace | n/d |
| 12 | **339e** | OBn | H | H | **351l** | trace | n/d |

**[a] diastereomeric ratio unable to be determined due to 350e being a mixture of regioisomers.**

**Table 3.11: Cyclisation of various substituted dienyl malonates using manganese(III) acetate.**

To verify the proposed diastereomeric ratios observed at C-4, three of the substrates were decarboxylated under Krapcho conditions [**Table 3.12**]. Decarboxylation of **351a** (entry 1) and

**351h** (entry 3) proceeded smoothly to give [3.3.0]-bicyclic *γ*-lactones **352a** and **352c** in excellent yield (80% and 87% respectively). Unfortunately the benzyl substituted [3.3.0]-bicyclic *γ*-lactone **351e** (entry 2) decomposed under the reaction conditions. Whilst it was possible to separate the two major diastereomers in the decarboxylation of **351a**, proton NMR nOe studies could not distinguish the required protons to definitively assign the stereochemistry in the products.

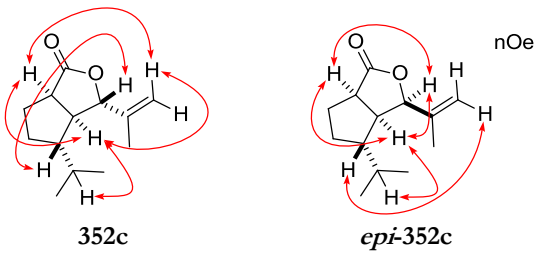



**351a,e,h** **352a-c**

| Entry | Starting material | $R_1$ | $R_2$ | $R_3$ | Product | Yield (%) | *d.r.* |
|---|---|---|---|---|---|---|---|
| 1 | **351a** | Me | H | H | **352a** | 80 | 4.2:2.8:1.0 |
| 2 | **351e** | Bn | H | H | **352b** | 0 | n/d |
| 3 | **351h** | *i*-Pr | Me | H | **352c** | 87 | 17.1:2.8:1.0 |

**Table 3.12: Krapcho decarboxylation to confirm the diastereoselectivity at C-4.**

Pleasingly, it was possible to carry out proton NMR nOe studies on the two major diastereoisomers isolated from the decarboxylation of **351h** [**Figure 3.4**]. This confirmed that the two major diastereoisomers **352c** and *epi*-**352c** were indeed the predicted products in which the substituent at C-4 is place on the same face as ring junction substituents.

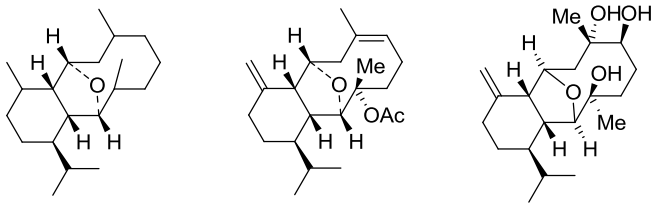



**352c** ***epi*-352c**

**Figure 3.4: Proton nOe studies to identify the two major diastereoisomers of 351h.**

## 3.2. Ring size

Whilst work in the group has typically focussed around applying the manganese(III) acetate mediated cyclisation to natural products which feature a congested cyclopentane ring, numerous other ring sizes occur in natural products. For example, the cladiellin skeleton (**353**) which features an oxatricyclic scaffold has been identified in over 100 isolated natural products [**Figure 3.5**].[144] First identified in (-)-cladiellin (**354**),[145] the family of natural products has been of critical interest to synthetic chemists due to the wide range of biological activities. For example, sclerophytin A (**355**), isolated in 1988 from the soft coral *Sclerophytum capitalis*, has been shown to be cytotoxic to L1210 cells (mouse lymphocytic leukaemia cells) with an $IC_{50}$ of 3 nM.[146] Because of the structural complexity and the potent biological activity of **355**, there have been several reported total syntheses to date.[147]

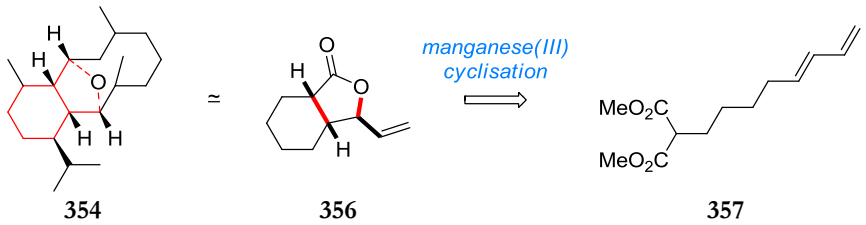



*cladiellin skeleton* **353** | *(-)-cladiellin* **354** | *sclerophytin A* **355**

**Figure 3.5: Natural products which feature an oxatricyclic [6.6.1.0]-pentadecane scaffold.**

As demonstrated in the total synthesis of (+)-aphanamol I and discussed in **Section 1.4.1**, the generation of contiguous stereocentres such as those present in the cladiellin family of natural products is well suited to a manganese(III) acetate radical cyclisation. It was envisaged that the fused cyclohexane core of **354** may be constructed through cyclisation of an acyclic precursor. To develop such a synthesis, a model system was devised which tested the ability to synthesise the [4.3.0]-bicyclic core found in **354** [**Figure 3.6**]. Thus, a manganese(III) acetate mediated cyclisation of dienyl malonate **357** would give [4.3.0]-bicyclic *γ*-lactone **356** which could be further functionalised at the lactone to generate the final macrocyclic ring. At the same time it was decided

to investigate the formation of the corresponding [2.3.0]- and [5.3.0]-bicyclic *γ*-lactones which would may also have application in natural product synthesis.

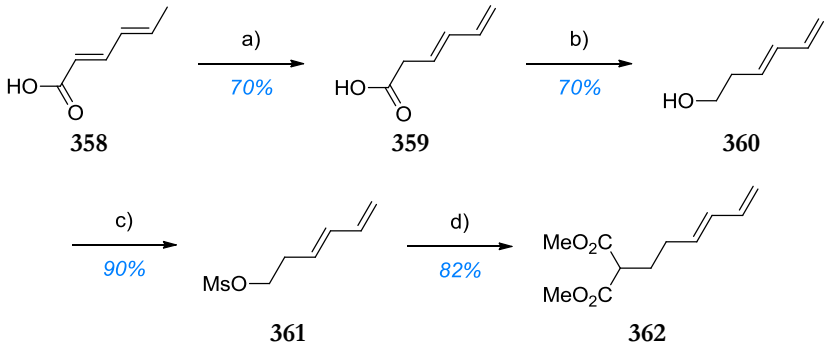



354 356 357

**Figure 3.6: Model system devised to synthesis [4.3.0]-bicyclic *γ*-lactone 371 which may be applicable in the synthesis of the cladiellin family of natural products.**

### 3.2.1. [2.3.0]-Bicyclic *γ*-lactone acyclic precursor synthesis

It was shown that the acyclic precursor to the [2.3.0]-bicyclic *γ*-lactone could be synthesised in four steps from commercially available sorbic acid [**Scheme 3.5**]. Thus, deprotonation of acid **358** using lithium diisopropylamide at -10 °C followed by kinetic protonation on workup gave the 1,3-diene **359** in 70% yield.[148] The *β,γ*-unsaturated diene was confirmed by proton NMR in which a terminal alkene was identified as a two single proton double doublets at $\delta_H$ 5.20 ($J$ = 16.8, 0.4 Hz) and $\delta_H$ 5.10 ($J$ = 10.2, 0.4 Hz). Acid **359** was then reduced to the alcohol **360** using a suspension of lithium aluminium hydride in anhydrous diethyl ether. Subsequent exposure of alcohol **360** to methanesulfonyl chloride and triethylamine gave mesylate **361** which was then alkylated with dimethyl malonate to give dienyl malonate **362** in 36% yield form sorbic acid.



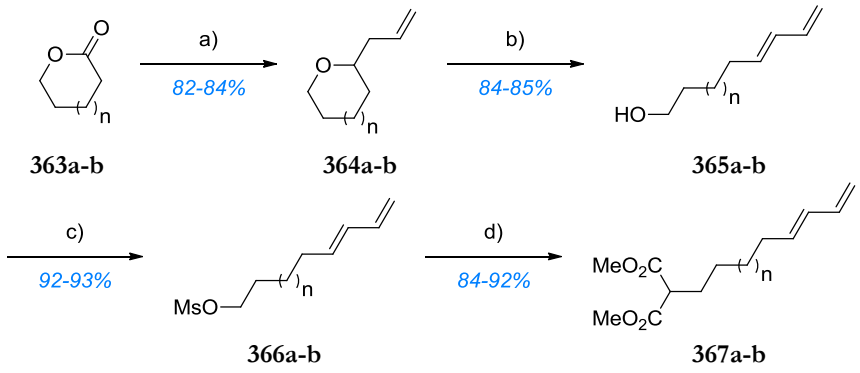

358 359 360 361 362

**Scheme 3.5: Synthesis of the [2.3.0]-bicyclic *γ*-lactone acyclic precursor 362.**

**Reagents and conditions: a) diisopropylamine, *n*-BuLi, -10 °C-RT, 1 h; b) $LiAlH_4$, $Et_2O$, 0 °C, 30 min, 70%; c) methanesulfonyl chloride, triethylamine, DCM, 0 °C-RT, 1.5 h, 90%; d) (i) NaH, dimethyl malonate, DMF, 0 °C; (ii) KI, THF, 80 °C, 1.5 h, 82%.**

### 3.2.2. [4.3.0]- and [5.3.0]-bicyclic *γ*-lactone acyclic precursor synthesis

The synthesis of long chain acyclic terminal dienyl alcohols such as those required in the synthesis of [4.3.0]-bicyclic *γ*-lactone and [5.3.0]-bicyclic *γ*-lactone are synthetically challenging. As presented in the synthesis of various substituted dienyl alcohols, a possible route to the required substrates might be through a *β*-elimination of a homoallylic ether [**Table 3.13**]. Thus treatment of *δ*-valerolactone (**363a**) (entry 1) to Wilkinson's conditions gave homoallyl ether **364a** in excellent yield (84%). Reductive allylation of *ε*-caprolactone (**363b**) (entry 2) also proceeded smoothly to give homoallyl ether **364b** in 82% yield. Subsequent treatment of **364a-b** with LIDAKOR induced a *β*-elimination to give dienyl alcohol **365a** (16: 1 mixture of regioisomers) and dienyl alcohol **365b** (17:1 mixture of regioisomers) in excellent yield. Mesylation of **365a-b** to give mesylates **366a-b**, followed by alkylation with dimethyl malonate gave dienyl malonates **367a-b** in good yield over four steps. (53-61%)



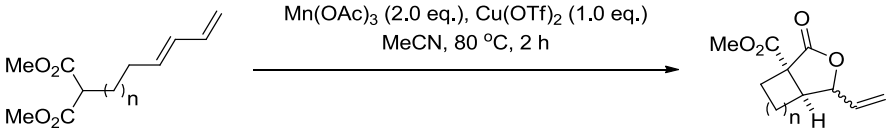

**Reagents and conditions: a) trimethylsilyl trifluoromethanesulfonate, allyltrimethylsilane $InBr_3$, DCM, -50 °C-RT, 2 h, 84%; b) *n*-BuLi, *t*-BuOK, diisopropylamine, THF, -70 °C-RT, 4 h, 84-85%; methanesulfonyl chloride, triethylamine, DCM, 0 °C-RT, 1.5 h, 93%; d) (i) NaH, dimethyl malonate, DMF, 0 °C; (ii) KI, THF, 80 °C, 1.5 h, 92%.**

| Entry | n | Product | Yield (%) | Product | Yield (%) | Product | Yield (%) | Product | Yield (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 1 | **364a** | 84 | **365a** | 85 | **366a** | 93 | **367a** | 92 |
| 2 | 2 | **364b** | 82 | **365b** | 84 | **366b** | 92 | **367b** | 84 |

**Table 3.13: Synthesis of the acyclic precursors to the [4.3.0]- and [5.3.0]-bicyclic *γ*-lactones.**

### 3.2.3. Cyclisation

With all the key acyclic dienyl malonates required to investigate the synthesis of different bicyclic systems in hand, work turned to developing cyclisation conditions [**Table 3.14**]. Exposure of dienyl malonate **362** (entry 2) and **367b** (entry 3) to the optimised cyclisation conditions developed in **Section 2.5.2** gave polymeric material with none of the desired bicyclic material **368a** or **368c** detected in the crude mass spectrum. Treatment of dienyl malonate **367a** (entry 2) with manganese(III) acetate again predominately gave polymeric material, however a trace of the [3.3.0]-bicyclic *γ*-lactone **368b** was identified by crude mass spectroscopy (*m*/*z* (ESI$^+$) 225 ([M+H]$^+$, 12%)). It was then attempted to reduce polymerisation by decreasing reaction concentration (entries 4-6). Unfortunately, this did not improve the results when compared to the reactions at 0.2 M (entries 1-3). As polymerisation would appear not to be concentration dependent, no further action was taken in attempting to form the desired [2.3.0]-, [4.3.0]- and [5.3.0]-bicyclic systems.




**362 or 367a-b** **368a-c**

| Entry | Starting material | n | Conc. (mol/L) | Yield (%) |
|---|---|---|---|---|
| 1 | **362** | 1 | 0.2 | - |
| 2 | **367a** | 3 | 0.2 | trace[a] |
| 3 | **367b** | 4 | 0.2 | - |
| 4 | **362** | 1 | 0.05 | - |
| 5 | **367a** | 3 | 0.05 | trace[a] |
| 6 | **367b** | 4 | 0.05 | - |

[a] **trace detected by mass spectroscopy.**

**Table 3.14: Cyclisation of different length dienyl malonates.**

## 3.3. Summary

It has been shown that the cyclisation of a variety of alkyl substituted dienyl malonates proceeds well under manganese(III) acetate conditions with diastereoselectivities of up to 23:1 observed. Unfortunately, substituents which modify the electronics of the diene such as oxygen or phenyl have a dramatic effect on the yield. Increasing steric bulk around the terminal alkene was also shown to increase the diastereoselectivity at the alkenyl stereocentre. Finally, the cyclisation of different length dienyl malonates was found to be incompatible to manganese(III) acetate with only polymeric material obtained.

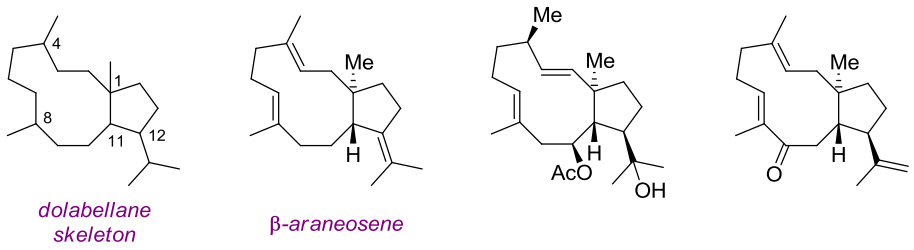
# CHAPTER 4: Towards the dolabellane diterpenoids

Chapter 4 will focus on efforts towards the total synthesis of a dolabellane diterpenoid isolated in 2010. An overview of the natural product family and some representative structures will be given followed by a proposed biosynthesis to the [9.3.0]-bicyclic core and how such structures are present in other related natural product families. Following the introduction to the dolabellanes, the various ring closing methods utilised in the total synthesis of such natural products will be discussed, including work within the group looking into a ruthenium catalysed ring closing metathesis. A retrosynthesis will then be proposed which utilises our manganese(III) acetate mediated radical cyclisation and a ring closing metathesis as key steps in forming the [9.3.0]-bicyclic core. Investigative work towards the total synthesis of the identified dolabellane diterpenoid will then be presented.

## 4.1. Dolabellane family of natural products

The dolabellanes, a diterpenoid class of natural products, typically feature a *trans*-[9.3.0]-bicyclic skeleton (**369**) and have been isolated from a variety of marine and terrestrial organisms [**Figure 4.1**]. The first such structure was isolated in 1975 by Borshberg who identified *β*-araneosene (**370**) as a constituent of the mould *Sordaria araneosa*.[149] Whilst Borshberg suggested that natural products featuring a [9.3.0]-bicyclic core similar to *β*-araneosene should fall under the araneosene natural product family, the isolation of 10-acetoxy-18-hydroxy-2,7-dolabelladiene (**371**) from the opisthobranch mollusc *Dolabella californica* led to the family being termed the "dolabellanes".[150] In 1998, Rodriguez *et al.* published a full summary of all isolated natural products bearing a [9.3.0]-bicyclic skeleton, with a total of 134 dolabellanes identified.[151] Since then, a further 35 dolabellanes have been identified, bringing the family size to 169 compounds.[152] Of particular interest to this thesis is the dolabellane **372** recently isolated in 2010 from the octocoral

*Convexella magellhaenica*, which was shown to have selective cytotoxicity to human pancreatic adenocarcinoma cells.[152e]

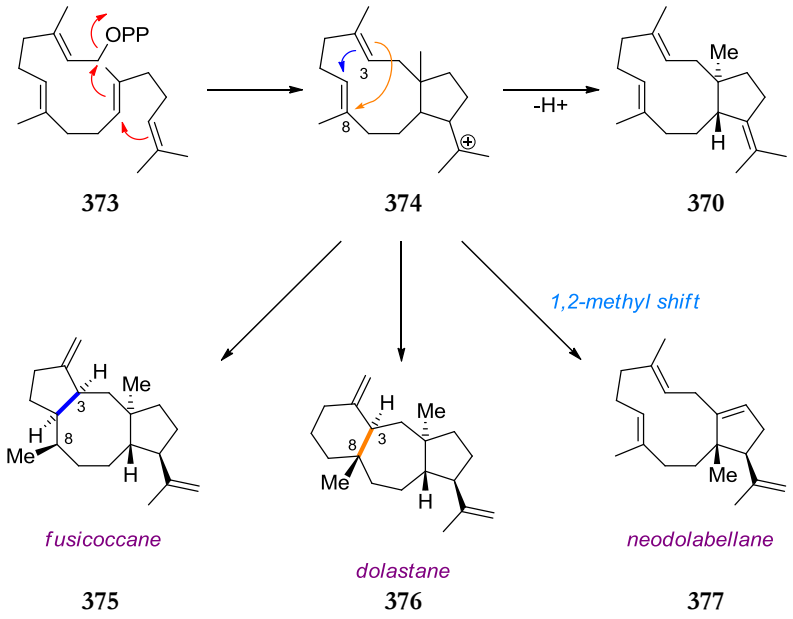



**369** **370** **371** **372**

**Figure 4.1: Some examples of natural products belonging to the dolabellane family.**

### 4.1.1. Biosynthesis

As a member of the terpenoid class of natural products, the dolabellanes most likely arise in accordance with the hypotheses discussed in **Section 1.1.1**. Thus, it is widely accepted in the literature that the biosynthesis of all diterpenes starts with geranylgeranyl pyrophosphate (GGPP) [**Figure 4.2**].[151,153] A simple cascade macrocyclisation of GGPP (**373**) gives the dolabellane skeleton **374** which after proton loss gives the diterpene *β*-araneosene (**370**) or *via* various oxidations gives other diterpenoids which feature the *trans*-[9.3.0]-tetradecane core.




**373** **374** **370**

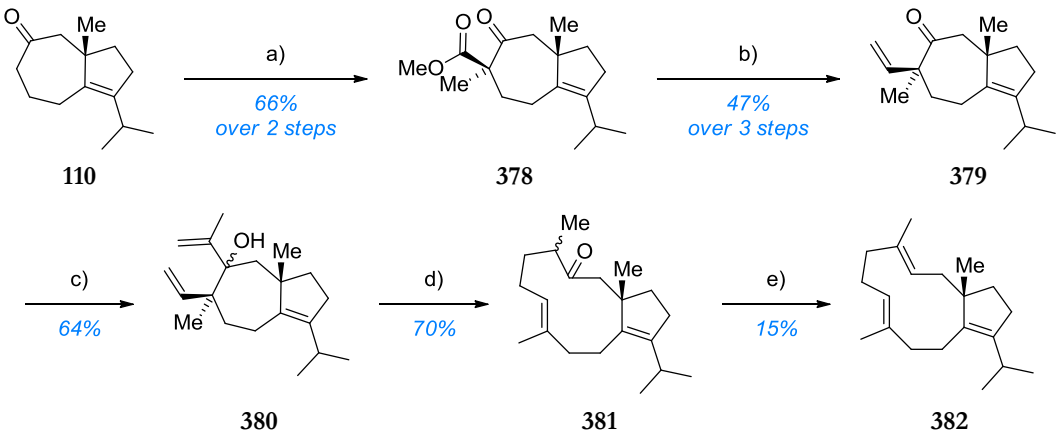
**375** **376** **377**

**Figure 4.2: Proposed biosynthetic pathways leading to the dolabellane, fusicoccane, dolastane, and neodolabellane skeletons.**

It is also believed that **374** might serve as a biosynthetic precursor to several tricyclic diterpene natural product families as presented by Bowden *et al.*[154] For instance, fusicoccane (**375**) and dolastane (**376**) are postulated to arise from a stereocontrolled transannulation of dolabellane **374**. On the other hand, neodolabellane (**377**) is the result of a 1,2-methyl migration resulting in a rearranged structural isomer of *β*-araneosene. Experimental evidence further supports this hypothesis as a number of fusicoccanes and dolastanes have been synthesised from isolated natural dolabellanes.[151]

## 4.2. Dolabellane total synthesis

Due to a wide array of densely functionalised structures and a diverse biological activity, the dolabellane natural product family has been of synthetic interest to chemists, with eleven total syntheses completed to date. The first total synthesis of a dolabellane natural product was reported in 1990 by Mehta *et al.* in which they built on the idea of a common building block for application in terpene synthesis (as discussed in **Section 2.2.1**) in the total synthesis of *δ*-araneosene [**Scheme 4.1**].[155] Thus, subjecting 5,7-fused bicycle **110** to a regioselective carbomethoxylation followed by alkylation with iodomethane gave ester **378** as the major diastereoisomer in 66% yield.




**Scheme 4.1: Mehta's total of *δ*-araneosene.**

**Reagents and conditions: a) (i) NaH, $(CH_3O)_2CO$, heat, 6 h, 78%; (ii) $K_2CO_3$, acetone, MeI, heat, 24 h, 85%; b) (i) $LiAlH_4$, $Et_2O$, RT, 1 h, 65%; (ii) $(COCl)_2$, DMSO, DCM, $NEt_3$, -60 °C; (iii) $Ph_3P^+$-$CH_3Br^-$, sodium *tert*-amyloxide, RT, 10 min, 72%; c) isopropenyl magnesium bromide, THF, heat, 30 min, 64%; d) sealed tube, 170 °C, 1 h, 70%; e) (i) $LiAlH_4$, $Et_2O$, RT, 1 h, 100%; (ii) MsCl, pyridine, DCM, 20 h, 15%.**

Ester **378** was then transformed into vinyl ketone **379** in modest yield (47%) over 3 steps, which was subsequently alkylated with isopropenyl magnesium bromide to give diene **380**. Thermal activation caused **380** to undergo an oxy-Cope rearrangement to give a 1:1 mixture of epimeric ketones **381** in good yield (70%). Finally reduction and elimination gave *δ*-araneosene (**382**) in 0.3% overall yield and 17 steps from (*R*)-limonene. The low yield was due to a wide range of transannular side products formed during the final step.

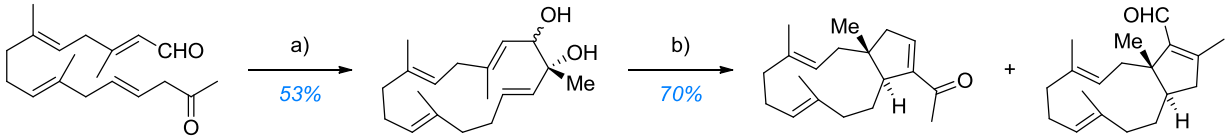
### 4.2.1. Ring closing methods used in the total synthesis of dolabellane natural products

One of the synthetic challenges encountered during the synthesis of the [9.3.0]-tetradecane core has resided in the formation of the 11-membered ring. This is largely due to transannular strain which is present in rings containing 8-11 carbons. For example, Illuminati *et al.* have studied the kinetics of 5-10 membered cyclic ether formation from ortho-bromoalkylphenoxides.[156] It was found that increasing the number of carbons also increased the enthalpy of activation, suggesting the strain within the cyclic transition state must increase with more carbons. As transannular strain is the largest source of strain present in medium rings, Illuminati concludes that the larger enthalpies resulting in slower cyclisation are as a result of transannular strain. As a result of this problem, there has been no definitive way of synthesising medium sized ring such as the 11-membered ring found in the dolabellanes. Thus a variety of methods have been used in the construction of the 11 membered ring, which can be loosely grouped into rearrangements and ring closing.

#### 4.2.1.1. Rearrangements

As discussed previously, Mehta utilised a oxy-Cope rearrangement of a 1,5-diene *via* a ring expansion to give the 11-membered ring in their total synthesis of *δ*-araneosene. Corey *et al.* reported the racemic total synthesis of (±)-palominol and (±)-dolabellatrienone using a dianion accelerated oxy-Cope ring contraction as the key step [**Scheme 4.2**].[157] A Pinacol cyclisation of keto aldehyde **383** gave a separable mixture of 1,2-diols **384** (2.1:1) in 53% yield. Subsequent

exposure to potassium hydride caused diol **384** to undergo an oxy-Cope rearrangement followed by a spontaneous aldol condensation to give a 1:1 mixture of [9.3.0]-bicyclic **385** and **386** (70% overall). Ketone **385** was then utilised in the total synthesis of (±)-palominol in 11 steps (5.3% overall) and (±)-dolabellatrienone in 12 steps (3.8% overall) from farnesyl acetate.



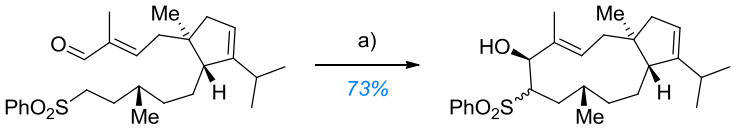

**383** **384** **385** **386**

**Scheme 4.2: Corey's total synthesis of (±)-palominol and (±)-dolabellatrienone.**

**Reagents and conditions: a) $TiCl_3$-DME, Cu/Zn, DME, -55 °C, 32 h, 53%; b) KH, THF, 45 °C, 1.5 h.**

### 4.2.1.2. Ring closing

The other types of 11-membered ring formation revolve around ring closing a long acyclic chain. Utilising Yoshii's macrocyclisation reported in the total synthesis of tetronolide,[158] Williams *et al.* used an intramolecular Julia condensation as a key step in the synthesis of various dolabellane intermediates [**Scheme 4.3**].[159] Using sodium *tert*-amylate, the *a*-sulfonyl carbanion of **387** underwent addition to the aldehyde, which gave *β*-hydroxy sulfone **388** as a mixture of diastereomers.



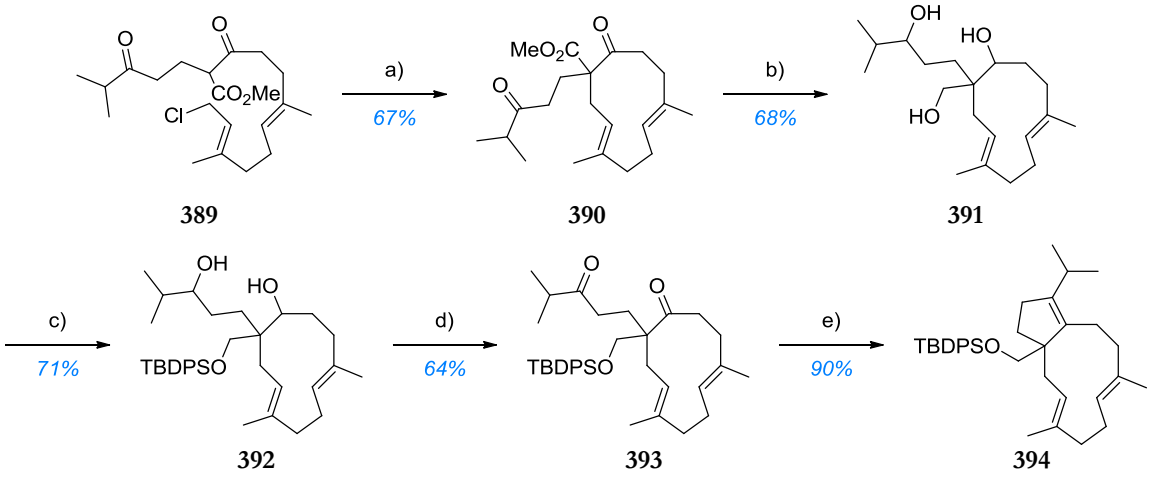

**387** **388**

**Scheme 4.3: Williams's synthesis of intermediate dolabellane structures.**

**Reagents and conditions: a) sodium *tert*-amylate, benzene, 35 °C, 73%.**

Alternatively, Boshberg reported an intramolecular alkylation as a key step in the total synthesis of (±)-*δ*-araneosene [**Scheme 4.4**].[160] After optimisation, exposure of *β*-ketoester **389** to cesium carbonate under dilute reaction conditions gave macrocycle **390** in good yield (67%). At higher concentrations dimerisation of **389** was found to take preference over cyclisation. The 5-membered ring was then synthesised *via* a McMurry cyclisation.[161] Thus, macrocycle **390** was

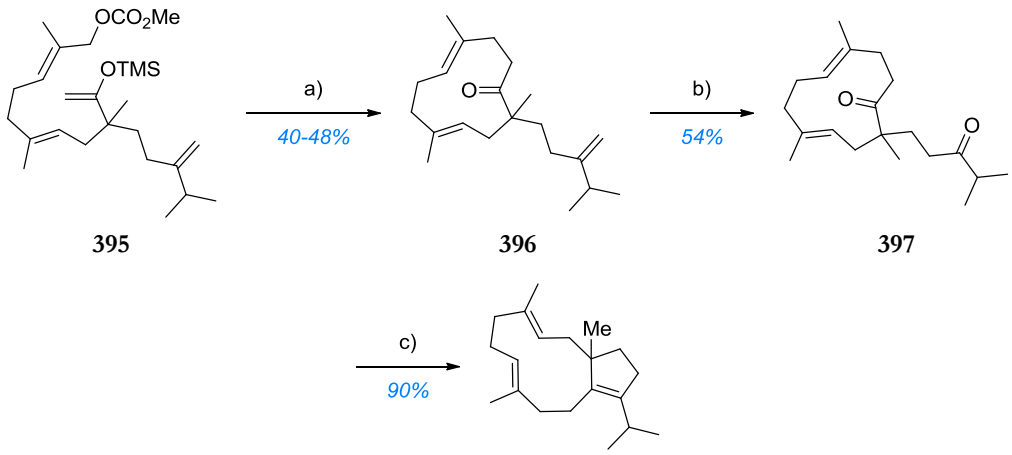
reduced with diisobutylaluminium hydride to give triol **391**, which was selectively protected at the primary alcohol to give diol **392** in modest yield over 2 steps (48%). Oxidation of diol **392** using a *tert*-butoxy-modified Dess-Martin periodinane gave 1,5-dicarbonyl **393**, which underwent a reductive coupling to give [9.3.0]-bicyclic core **394** in 90% yield. Borshberg completed the total synthesis of (±)-*δ*-araneosene in 16 steps and 0.8% overall yield.




**Scheme 4.4: Boshberg's synthesis of (±)-*δ*-araneosene.**

**Reagents and conditions: a) $Cs_2CO_3$, DMF, 25 °C, 30 h, 67%; b) DIBAL-H, DCM, 25 °C, 2 h, 68%; c) *t*-Bu(Ph)$_2$SiCl, pyridine, 25 °C, 5 d, 71%; d) modified Dess-Martin, 64%; e) $TiCl_3$, Zn/Cu, DME, 90%.**

Both the previous two syntheses have relied on a base promoted attack of an anion onto an electrophilic centre. In 2002 Corey *et al.* reported the first application of metal catalysed cyclisation in the total synthesis of (±)-*δ*-araneosene [**Scheme 4.5**].[162] Based on palladium mediated ring closure developed in the total synthesis of antheliolide A,[163] treatment of allylic carbonate **395** (prepared in 3 steps, 74%) with 10 mol% palladium complex in refluxing THF gave 11-membered ketone **396** in 40-48% yield. Selective ozonolysis of macrocycle **396** converted the *exo*-alkene into the ketone to give diketone **397**, which was transformed by a McMurry cyclisation into (±)-*δ*-araneosene in six steps and an overall yield of 14%.



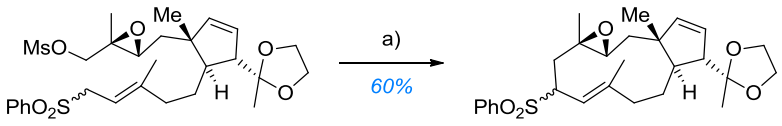

**395** **396** **397**

**382**

**Scheme 4.5: Corey's synthesis of (±)-δ-araneosene.**

**Reagents and conditions: a) $Pd_2(dba)_3$, dppf, THF, 70 °C , 1 h, 40-48%; b) $O_3$, $Me_2S$, DCM, 54% based on recovered starting material; c) $TiCl_3$, Zn/Cu, DME, 90%.**

Yamada *et al.* reported the total synthesis of claenone, palominol and dolabellatrienone in which an intramolecular nucleophilic substitution of a sulfone was used in the macrocyclisation step [**Scheme 4.6**].[164] Treatment of sulfone **398** with KHMDS gave [9.3.0]tetradecane **399** in 60% yield based on recovered starting material. Yamada completed the synthesis of claenone using macrobicyclic **399** in 41 steps and 1.8% overall. The total synthesis of palominol and dolabellatrienone were completed in 39 steps (2.6% overall) and 40 steps (1.6% overall) respectively using an intermediate along the claenone route.



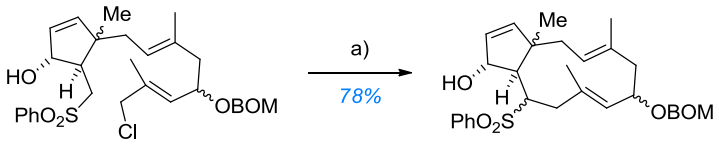

**398** **399**

**Scheme 4.6: Yamada's macrocyclisation in the total synthesis of claenone, palominol and dolabellatrienone.**

**Reagents and conditions: a) KHMDS, THF, 45 °C, 60%.**

Simultaneously, Whitby *et al.* reported the total synthesis of (±)-acetoxyodontoschismenol, which also featured an intramolecular nucleophilic substitution using a sulfone similar to Yamada [**Scheme 4.7**].[165] Addition of sulfone **400** to LiHMDS in refluxing THF gave macrocycle **401** in

78% yield as a mixture of eight diastereoisomers. Whitby went on to complete the total synthesis of (±)-acetoxyodontoschismenol in twelve steps and 3.5% overall yield.

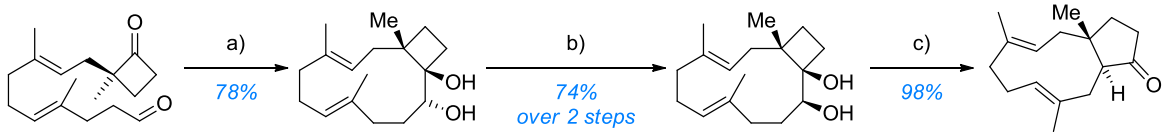



**400** **401**

**Scheme 4.7: Whitby's macrocyclisation in the total synthesis of acetoxyodontoschismenol.**

**Reagents and conditions: LiHMDS, THF, reflux, 5 h, 78%.**

In 2005, Corey *et al.* reported the total synthesis of *β*-araneosene and isoedunol, which utilised a Pinacol coupling followed by a ring expansion to form the dolabellane core [**Scheme 4.8**].[166] Slow addition of keto-aldehyde **402** to a solution of samarium(II) iodide in refluxing THF gave *trans* diol **403** as a single diastereoisomer. A subsequent oxidation/reduction sequence gave the required *syn*-diol **404**, which after mesylation of the secondary alcohol underwent a ring expansion to give 5,11-bicyclic ketone **405** in excellent yield (98%).



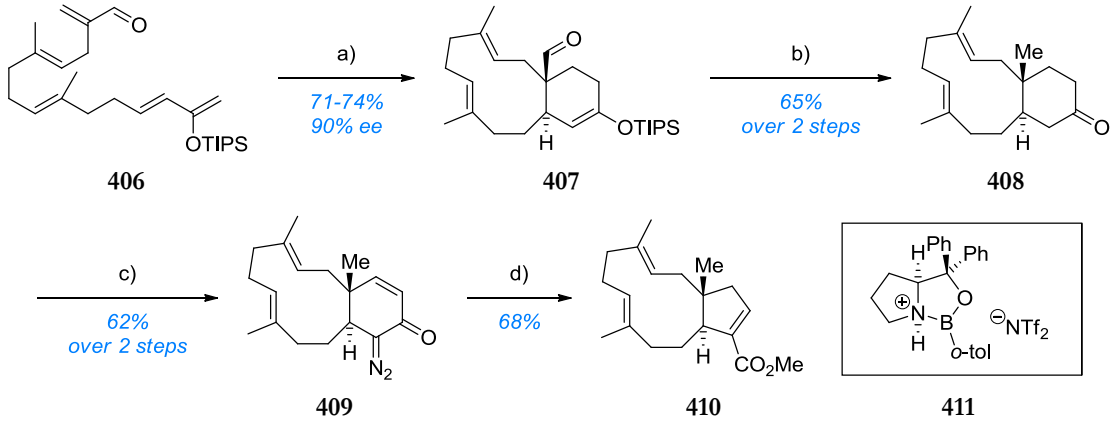

**402** **403** **404** **405**

**Scheme 4.8: Towards the total synthesis of *β*-araneosene and isoedunol reported by Corey.**

**Reagents and conditions: a) $SmI_2$, THF, 67 °C, 78%; b) (i) Swern oxidation; (ii) $LiAlH_4$, THF, 67 °C, 15 min, 74% over 2 steps; c) MsCl, $Et_3N$, DCM, -30 °C-4 °C, 72 h, 98%.**

Following the total synthesis of *β*-araneosene and isoedunol, Corey *et al.* demonstrated a Diels-Alder macrocyclisation as a key step in the total synthesis of palominol, dolabellatrienone, *β*-araneosene, and isoedunol [**Scheme 4.9**].[167] Treatment of silyl enol ether **406** with 20 mol% of (*S*)-oxazaborolidinium (**411**) gave macrocycle **407** in 74% yield and 90% enantioenrichment, with the absolute configuration confirmed by X-ray crystallographic studies on the corresponding tosylhydrazone derivative. Conversion of the aldehyde to the dithiane and treatment with deactivated Raney nickel gave ketone **408** in 65% yield. Finally a Wolff rearrangement of **409**

(synthesised by a *a,β*-desaturation followed by diazo-transfer reaction) induced a ring contraction to give *a,β*-unsaturated ester **410**, a key intermediate for the total synthesis of palominol and dolabellatrienone, which were completed in 13 (12.3% overall) and 14 steps (8.3% overall) respectively from known intermediates. Corey converted ester **410** to the corresponding ketone **405** (51% over 3 steps), an intermediate previously reported in the total syntheses *β*-araneosene and isoedunol.

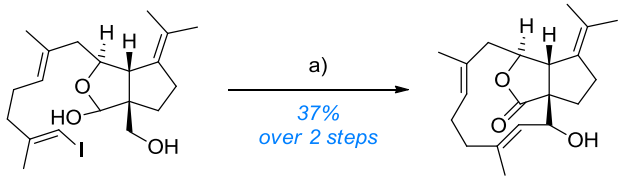



**406** **407** **408** **409** **410** **411**

**Scheme 4.9: Cory's total synthesis of palominol, dolabellatrienone, *β*-araneosene, and isoedunol.**

**Reagents and conditions: a) chiral *cis*-fused oxazaborolidinium cation, -95 °C, 3 h then -78 °C for 10 h, 71-74%; b) (i) $Me_2AlSCH_2CH_2SAlMe_2$, $ClCH_2CH_2Cl$, TBAF, THF, 60 °C, 12 h; (ii) Raney Ni, THF, 25 °C, 10 h, 65% over 2 steps; c) (i) NaHMDS, TMSCl, IBX.MPO, DMSO; (ii) Trisyl azide, 18-Crown-6, $BnEt_3NCl$, aq. KOH, benzene, 40 °C, 62% over 2 steps; d) hν, MeOH, 25 °C, 2 h then DBU, 115 °C, 18 h, 68%.**

Finally, Ready *et al.* utilised a intramolecular Nozaki-Hiyama-Kishi cyclisation to form the 11-membered ring in the total synthesis of nigellamine $A_2$ [**Scheme 4.10**].[168] Firstly the lactol **412** was oxidised to the corresponding lactone using pyridinium chlorochromate. Subsequent exposure to chromium(II) chloride in the presence of catalytic nickel(II) formed the 11-membered **413** *via* nucleophilic addition of the alkenyl group to the aldehyde.



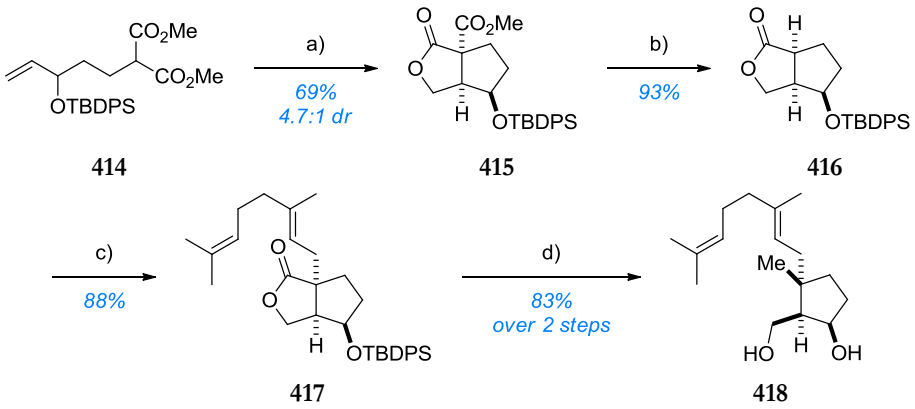

**412** **413**

**Scheme 4.10: Ready's macrocyclisation in the total synthesis of nigellamine $A_2$.**

**Reagents and conditions: a) (i) PCC, 50%; (ii) $CrCl_2$, $Ni(acac)_2$, sonication, 73%.**

### 4.2.2. Application of a manganese(III) acetate cyclisation in dolabellane synthesis

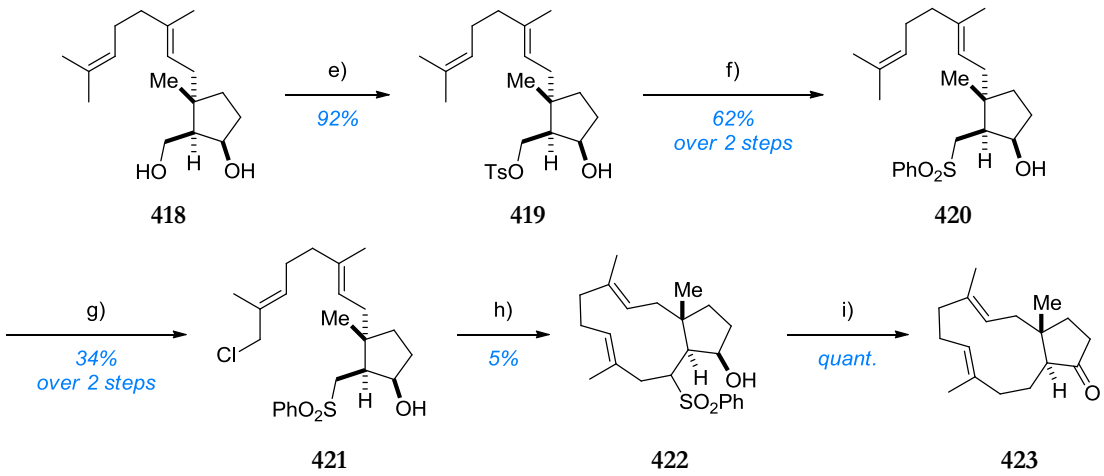
As the dolabellane natural product family generally feature a fused cyclopentane with contiguous quaternary, tertiary, tertiary stereocentres, Burton *et al.* have investigated the application of a manganese(III) acetate mediated radical cyclisation in their total synthesis. In 2011, Hallside reported the formal synthesis of *β*-araneosene and isoedunol in which a manganese(III) acetate mediated radical cyclisation featured as a key step in the formation of the required stereocentres [**Scheme 4.11**].[169] Subjecting alkenyl malonate **414** to manganese(III) acetate gave [3.3.0]-bicyclic *γ*-lactone **415** in good yield (69%). Interestingly, a *trans*-relationship was observed between the protected alcohol and the ring junction instead of the *cis*-relationship previously observed within the group. It was proposed that having an oxygen atom directly attached to C-4 led to an "inside alkoxy" effect,[170] such that the preferential transition state discussed in **Section 1.2.4** is destabilised by a $\pi \rightarrow \sigma^*_{CO}$ electronic interaction leading to the formation of the more sterically disfavoured bicyclic *γ*-lactone **415**. Subsequent decarboxylation of ester **415** followed by alkylation with geranyl bromide installed the required alkyl chain to give **417** which would be cyclised at a later stage to form the 11-membered ring. Reduction of lactone **417** with diisobutylaluminium hydride gave the corresponding lactol, which upon exposure to Wolff-Kishner conditions gave diol **418** as a result of deprotection of the secondary alcohol under the strongly basic reaction conditions.




**Scheme 4.11: Manganese(III) acetate cyclisation used in the formal synthesis of *β*-araneosene and isoedunol.**

**Reagents and conditions: a) $Mn(OAc)_3$, $Cu(OTf)_2$, MeCN, 80 °C, 69%; b) LiCl, $H_2O$, DMSO, 195 °C, 93%; c) LiHMDS, geranyl bromide, THF, -78 °C, 88%; d) (i) DIBAL-H, DCM, -78 °C, 92%; (ii) KOH, $N_2H_4$, ethylene glycol, 170 °C, 90%**

Hallside chose to use a similar route to Whitby in constructing the 11-membered ring in which a nucleophilic substitution using a sulfone was utilised [**Scheme 4.12**]. Thus the primary alcohol in diol **418** was selectively tosylated to give tosylate **419**, which after displacement with thiophenol and oxidation gave sulfone **420** in good yield over three steps (57%). Subsequent exposure to selenium dioxide caused **420** to undergo a Sharpless allylic oxidation,[171] which after mesylation was displaced with lithium chloride to give chloride **421**. Subsequent treatment of **421** with LiHMDS gave macrocycle **422** in poor yield (5%). The formal synthesis of *β*-araneosene and isoedunol was completed by firstly reducing the sulfonyl group and oxidising the secondary alcohol with Dess-Martin periodinane to give [9.3.0]-bicyclic ketone **423** in excellent yield over two steps. Spectroscopic data of **423** were in good accordance with the data published by Corey, however clearly further optimisation was required in the macrocyclisation.



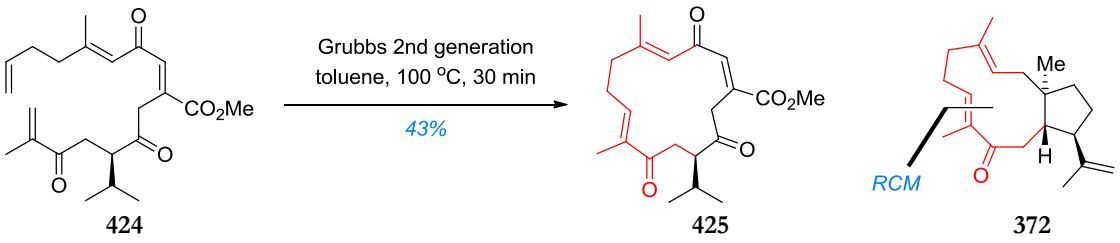

**Scheme 4.12: Construction of the 11-membered ring in the formal synthesis of *β*-araneosene and isoedunol.**

**Reagents and conditions: e) TsCl, DMAP, pyridine, 92%; f) (i) HSPh, *t*-BuOK, 80%; (ii) $H_2O_2$, $(NH_4)_6Mo_7O_{24}$, 78%; g) (i) $SeO_2$, *t*-BuOOH, salicyclic acid, 50%; (ii) MsCl, LiCl, 68%; h) LiHMDS, 5%; i) (i)Mg, MeOH, quant.; (ii) DMP, DCM, RT, quant.**

### 4.2.2.1. Alternative ring closing method

With the manganese(III) acetate mediated cyclisation providing access to a key [3.3.0]-bicyclic *γ*-lactone with good diastereocontrol, what was required was an alternative macrocyclisation route. Surprisingly, a ring closing metathesis (RCM) is yet to be reported in the total synthesis of a dolabellane diterpenoid, despite such methodology being ideally suited to the

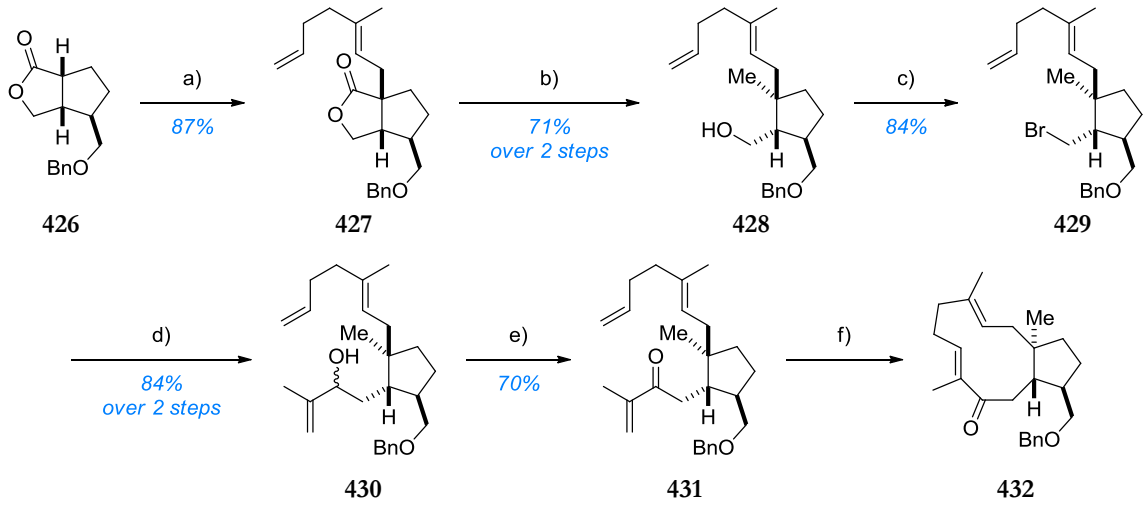
synthesis of large rings.[172] In particular, RCM has been found to be a useful macrocyclisation step in natural product synthesis due to the large number of natural products which feature medium and large rings with internal alkenes.[173] Of particular interest to this thesis is the RCM utilised by Nakata *et al.* in the total synthesis of methyl sarcophytoate [**Scheme 4.13**].[174] Treating vinyl ketone **424** with stoichiometric Grubbs 2nd generation catalyst in refluxing toluene caused a ring closing of the terminal alkene onto the vinyl ketone to give macrocycle **425** in 43% yield. Nakata noted that RCM was only observed between the terminal alkenes and that no "back-biting" was observed onto the internal alkene.




**Scheme 4.13: Utilisation of a ring closing metathesis in the total synthesis of methyl sarcophytoate.**

Whilst not directly analogous to dolabellane **372**, the presence of an *a,β*-unsaturated ketone does suggest a RCM could be applied in the construction of the 11-membered ring as a complementary step to the manganese(III) acetate cyclisation demonstrated by Hallside. Thus, Lua sought to investigate the possibility of utilising a RCM in the total synthesis of dolabellane **372** [**Scheme 4.14**].[175] Bicyclic *γ*-lactone **426** (prepared in 7 steps, 28% overall) was alkylated to give lactone **427**, which featured the desired functionality required for a RCM to form the 11-membered ring. Subsequent reduction of lactone **427** with diisobutylaluminium hydride gave the corresponding lactol, which was reduced under Wolff-Kishner conditions to give alcohol **428** in 71% yield over two steps. Conversion of **428** into alkyl bromide **429** was achieved in excellent yield (84%) by exposing alcohol **428** to methanesulfonyl chloride followed by displacement of the mesylate with bromide. Following a lithium-halogen exchange, **428** underwent a nucleophilic addition to methacrolein to give vinyl alcohol **430**, which was oxidised to ketone **431** using 2-iodoxybenzoic acid. Having synthesised the key macrocyclisation precursor **431** identified from

Nakata's report, Lua attempted a RCM using such methodology. Exposing **431** to stoichiometric Grubbs 2nd generation catalyst in refluxing toluene gave macrocycle **432** as identified by NMR and HRMS. Whilst Lua was unable to obtain a pure sample of **432**, comparisons of the alkene shifts present in the product to those of the natural product suggested the presence of the desired macrocycle.




**Scheme 4.14: Studies investigating a RCM as a complimentary step to manganese(III) acetate cyclisation.**

**Reagents and conditions: a) alkyl bromide, LiHMDS, THF, -78 °C, 87%; b) (i) DIBAL-H, DCM, -60 °C, 90%; (ii) $N_2H_2$, KOH, 180 °C, 79%; c) MsCl, $Et_3N$, THF, 0 °C, then LiBr, 84%; d) (i) *t*-BuLi, THF, -78 °C; (ii) methacrolein, THF, -78 °C, 61%; e) IBX, DMSO, THF, 70%; f) Grubbs 2nd generation catalyst, toluene, 100 °C, 30 min.**

## 4.3. Retrosynthesis

Having successfully demonstrated the macrocyclisation of **431**, our retrosynthetic strategy of dolabellane **372** was therefore designed to utilise the RCM demonstrated by Lua as a complementary step to the manganese(III) acetate mediated oxidative radical cyclisation [**Figure 4.3**]. Thus, a disconnection of the *a*,*β*-unsaturated ketone present in dolabellane **372** would give the key macrocyclisation precursor **433**. *a*,*β*-Unsaturated ketone **433** in turn could be synthesised by reduction of the acid to the methyl group and alkylation of the nitrile with isopropenylmagnesium bromide from **434**, which would result from a ring opening of lactone **435** with cyanide. The bridging alkyl chain would be introduced through a lithium enolate alkylation of lactone **437**, which would be obtained as a result of a Krapcho decarboxylation of methyl ester **438**.

An oxidative radical cyclisation of 1,4-diene **439** using manganese(III) acetate would give [3.3.0]-bicyclic *γ*-lactone **438**

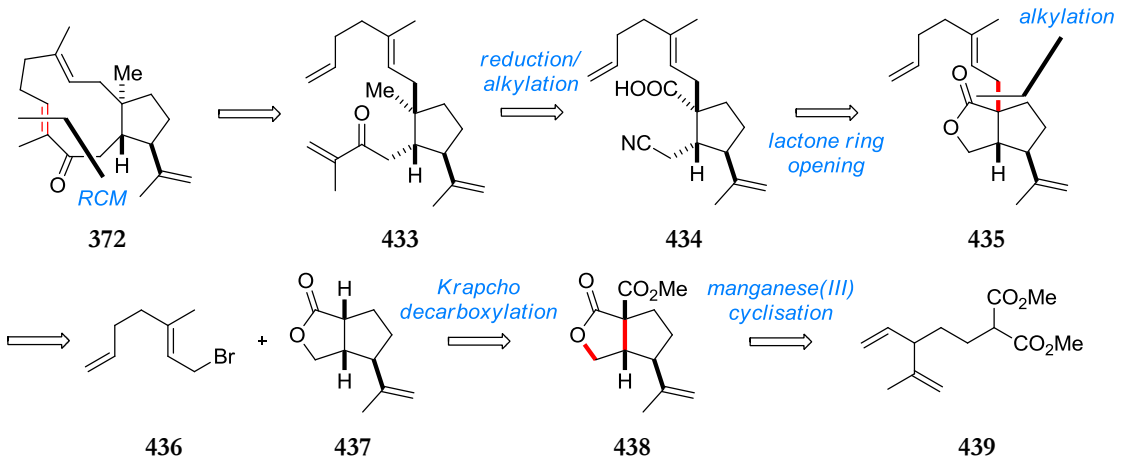



**Figure 4.3: Retrosynthesis of dolabellane 372 utilising a RCM and radical cyclisation as key steps.**

## 4.4. Towards the dolabellane diterpenoids

To date, there have been no previous reports for the cyclisation/preparation of 1,4-diene **439**. Thus it was envisaged retrosynthetically that **439** might arise from 1,3-diene **442** [**Figure 4.4**]. Therefore, malonate **439** would be synthesised from alcohol **440** *via* mesylation followed by displacement of the mesylate with dimethyl malonate as reported previously. Reduction of ethyl ester **441** would give alcohol **440**, with the former arising from a Johnson-Claisen rearrangement of known alcohol **442**.

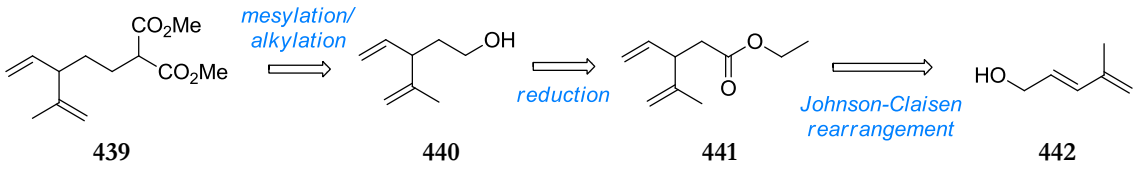
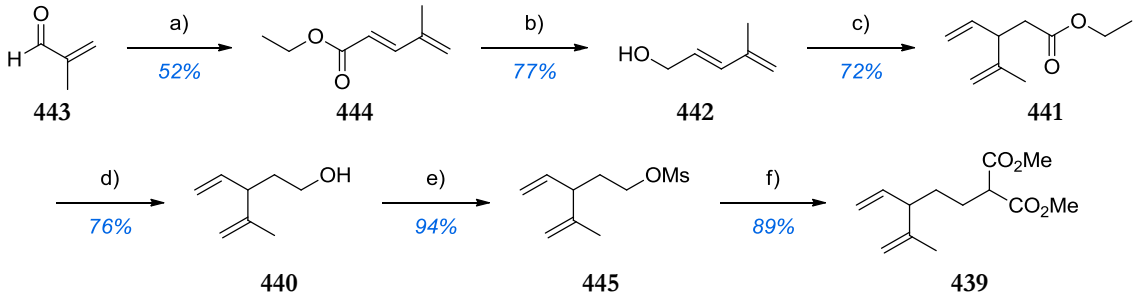



**Figure 4.4: Retrosynthesis of radical cyclisation precursor 439.**

### 4.4.1. Synthesis of alkenyl malonate 439

Following literature procedures known alcohol **442** was synthesised in two steps from methacrolein [**Scheme 4.15**]. Treatment of methacrolein (**443**) with (carbethoxymethylene)-triphenylphosphorane gave conjugate diene **444** in modest yield (52%). Subsequent exposure of

ethyl ester **444** to a stirred suspension of lithium aluminium hydride in anhydrous diethyl ether gave alcohol **442** in 40% over 2 steps. Pleasingly, upon exposure to refluxing triethyl orthoacetate with catalytic acid, alcohol **442** underwent a Johnson-Claisen rearrangement to give 1,4-diene **441** in good yield (72%) after distillation. The 1,4-diene was identified by the presence of two structurally differentiated alkenes in the proton NMR. The terminal linear alkene was identified by a single proton double double doublets at $\delta_H$ 5.71 ($J$ = 17.4, 10.1, 7.6 Hz, $CH_ZH_E$=C**H**CH) and two double doublet single *E*- and *Z*-alkene protons at $\delta_H$ 5.06 ($J$ = 17.4 Hz, CH=$CH_Z$**$H_E$**) and $\delta_H$ 5.03 ($J$ = 10.1 Hz, CH=C**$H_Z$**$H_E$), whilst the isolated alkene was identified by two single proton peaks at $\delta_H$ 4.79 and $\delta_H$ 4.76. In the IR, an ester was identified at $\nu_{max}$ 1736 $cm^{-1}$ (aliphatic C=O) and $\nu_{max}$ 1159 $cm^{-1}$ (aliphatic C-O). Ensuing reduction of ethyl ester **441** with lithium aluminium hydride gave alcohol **440** in good yield (76%). Mesylation of **440** with methanesulfonyl chloride gave mesylate **445**, which without further purification was alkylated with the pre-formed anion of dimethylmalonate to give 1,4-dienyl malonate **439** in 6 steps and 18% overall yield from methacrolein.



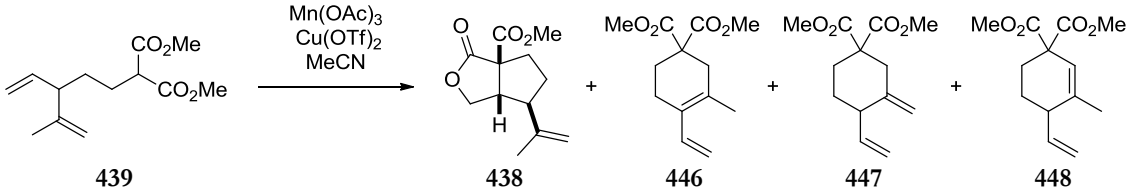

**Scheme 4.15: Synthesis of key alkenyl malonate 439.**

**Reagents and conditions: a) (carbethoxymethylene)triphenylphosphorane, DCM, 60 °C, 2 h, 52%; b) $LiAlH_4$, $Et_2O$, 0 °C, 30 min, 77%; c) triethyl orthoacetate, propionic acid, 138 °C, 4 h, 72%; d) $LiAlH_4$, $Et_2O$, 0 °C, 30 min, 76%; e) methanesulfonyl chloride, triethylamine, DCM, 0 °C-RT, 1.5 h, 94%; f) (i) NaH, dimethyl malonate, DMF, 0 °C; (ii) KI, THF, 80 °C, 1.5 h, 89%.**

### 4.4.2. Cyclisation of 439

With 1,4-dieneyl malonate **439** in hand, work then turned to developing cyclisation conditions for such substrates [**Table 4.1**]. Treatment of **439** with the optimised conditions utilised in the total synthesis of (+)-aphanamol I (entry 1) gave [3.3.0]-bicyclic *γ*-lactone **438** in 31%

yield. The *γ*-lactone was identified by a lactone carbonyl stretch in the IR at $\nu_{max}$ 1775 $cm^{-1}$ whilst in the proton NMR, diastereotopic lactone protons at C-3 were identified as two double doublets at $\delta_H$ 4.47 ($J$ = 9.3, 6.5 Hz) and $\delta_H$ 4.15 ($J$ = 9.3, 1.0 Hz). Unfortunately, the major product of the cyclisation appeared to be a mixture of other cyclic products **446**-**448** as a result of a 6-*endo*-cyclisation. Whilst a pure sample of any of these products could not be obtained, the presence of a terminal olefin was obvious by crude proton NMR analysis. In accordance with previous work in the cyclisation of a simple dienyl malonate, it was decided to investigate the effect of concentration and temperature on the selectivity of the reaction. Varying the reaction concentration (entries 2-4) gave comparable yields of **438** to 0.2 M (27-32%). Reduction of the temperature (entry 5 and 6) gave increased reactions times, but again had little effect on the selectivity of the cyclisation with **438** still isolated in similar yields (23-27%).




**439** **438** **446** **447** **448**

| Entry | Conc. (mol/L) | $Cu(OTf)_2$ (eq.) | Temp (°C) | 438 Yield (%)[a] | *d.r.* |
|---|---|---|---|---|---|
| 1 | 0.2 | 1.0 | 80 | 31 | >25:1 |
| 2 | 0.4 | 1.0 | 80 | 27 | >25:1 |
| 3 | 0.1 | 1.0 | 80 | 29 | >25:1 |
| 4 | 0.05 | 1.0 | 80 | 32 | >25:1 |
| 5 | 0.2 | 1.0 | 60 | 27 | >25:1 |
| 6 | 0.2 | 1.0 | 40 | 23 | >25:1 |
| 7 | 0.2 | 2.0 | 80 | 30 | >25:1 |

[a] **Reactions carried out on 0.5 mmol of substrate.**

**Table 4.1: Optimisation of the $Mn(OAc)_3$ mediated cyclisation of dienyl malonate.**

Mechanistically, the products formed form the cyclisation of **439** can be explained as follows. After a single electron oxidation be manganese(III) acetate, radical **450** can undergo four

possible modes of cyclisation. Firstly we can rule out a 5-*exo*-trig cyclisation onto the 1,1-disubstituted alkene to give cyclopentane **449**, as the competing 5-*exo*-trig cyclisation onto the 1,1-disubstituted alkene should take preference due to sterics [**Figure 4.5**]. Secondly, although a 6-*endo*-trig cyclisation onto the terminal alkene to give cyclo hexyl radical **451** cannot be ruled out a 5-*exo*-trig cyclisation is more likely.

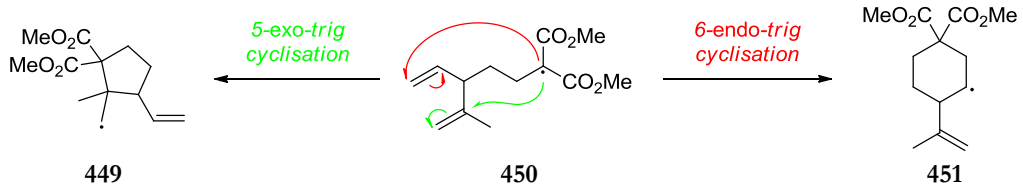



**Figure 4.5: Unlikely products formed by the cyclisation of 439.**

As a result of this, the observed products can be explained by the other two possible cyclisation modes [**Figure 4.6**]. A 5-*exo*-trig cyclisation of **450** gives cyclopentenyl radical **452**, which following a second oxidation by copper(II) triflate gives [3.3.0]bicyclic *γ*-lactone **438**. Unfortunately, whilst kinetically a 6-*endo*-trig cyclisation onto the 1,1-disubstituted alkene to give cyclopentyl radical **453** should be slower, thermodynamically the tertiary radical is much more favourable. Subsequent oxidative termination *via* three possible routes gives the observed products **446**-**448**.

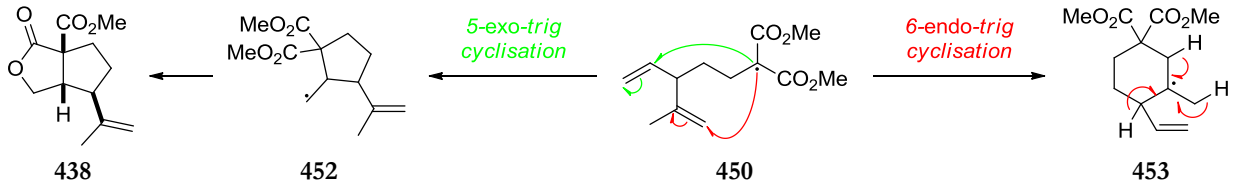



**Figure 4.6: Mechanistic explanation for the observed cyclic products in the cyclisation of 439.**

As both the 5-*exo*-trig and 6-*endo*-trig cyclisations are likely to be reversible due to the stabilised adduct radical present in **450**, interconversion between the 5- and 6-cyclic products is highly likely in the reaction medium. Thus, it was postulated that increasing the loading of copper(II) triflate in the reaction mixture might allow for favourable trapping of cyclopentyl radical **452** and as a result increase the yield of [3.3.0]bicyclic *γ*-lactone **438**. Unfortunately, increasing the

loading of copper(II) triflate to 2.0 eq. did not increase the overall yield of [3.3.0]bicyclic *γ*-lactone **438**, with similar yields observed to 1.0 eq. copper(II) triflate (entry 1).

### 4.4.3. Alternative route towards dolabellane 372

Due to the low yields of **438**, it was decided to explore a new route towards the synthesis of dolabellane **372** which utilised known [3.3.0]-bicyclic *γ*-lactone **80** [**Figure 4.7**]. The desired isopropenyl functionality could then be installed by deprotection of **80** to give primary alcohol **454**. Subsequent homologation using Ohira-Bestmann reagent[176] either *via* the aldehyde or in one-pot using a procedure reported by Taylor *et al.*[177] would give alkyne **455**. Finally, using a carboalumination reported by Negishi *et al.*,[178] alkyne **455** could be alkylated with trimethylaluminium to give isopropenyl **456**.

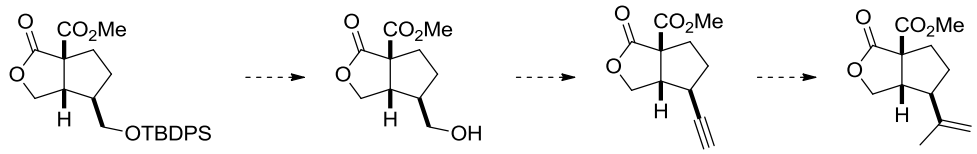
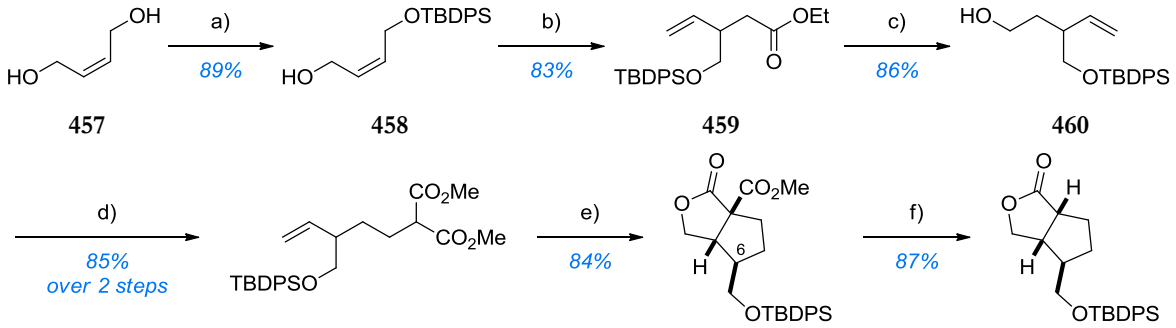



**Figure 4.7: Alternative route towards dolabellane 372 in which the isopropenyl functionality is installed after cyclisation.**

#### 4.4.3.1. Synthesis of [3.3.0]-bicyclic *γ*-lactone 80

Following procedures previously reported in the group, known bicyclic *γ*-lactone **462** was synthesised in seven steps from 1,4-butenediol [**Scheme 4.16**].[48] Diol **457**, in accordance with a protection method reported by Hu *et al.,* was monoprotected with *tert*-butylchlorodiphenylsilane to give silyl ether **458** in 89% yield.[179] The selectivity of the protection is attributed to the biphasic system formed maintaining a constant concentration of base in the DMF layer, although the author states the exact cause of selectivity is not known. A Johnson-Claisen rearrangement of **458** using triethyl orthoacetate gave ethyl ester **459**, which was then reduced to the corresponding alcohol **460** using a suspension lithium aluminium hydride powder in diethyl ether in a combined yield of 71%. Previous work in the group had shown the Johnson-Claisen rearrangement of mono-protected alcohol **459** also produced a large amount of unwanted acetate, however simply driving the reaction

to completion prevented this product forming. Subsequent mesylation of **460** with methanesulfonyl chloride gave the corresponding mesylate **461** in excellent yield, which without further purification was alkylated with the anion of dimethyl malonate to give malonic ester **79** in 85% over 2 steps. Treatment of malonate **79** with standard cyclisation conditions (2.0 eq. manganese(III) acetate, 1.0 eq. copper(II) triflate, MeCN (0.2 M), 80 °C) gave bicyclic *γ*-lactone **80** in 84% yield as a 16:1 mixture of diastereoisomers at C-6, as determined by crude NMR. The [3.3.0]-bicycle *γ*-lactone **80** was identified by the presence of a *γ*-lactone IR stretch at $\nu_{max}$ 1775 $cm^{-1}$ (lactone C=O) and $\nu_{max}$ 1241 $cm^{-1}$ (lactone C-O) and a aliphatic ester stretch at $\nu_{max}$ 1743 $cm^{-1}$ (ester C=O) and $\nu_{max}$ 1159 $cm^{-1}$ (ester C-O). In the proton NMR, diastereotopic lactone protons were identified as double doublets at $\delta_H$ 4.50 ($J$ = 9.2, 7.0 Hz, CHC**H'**HOC) and $\delta_H$ 4.26 ($J$ = 9.2, 1.3 Hz, CHCH'**H**OC). Finally, lactone **80** was decarboxylated under Krapcho conditions to give lactone **462** in 39% overall yield over seven steps.



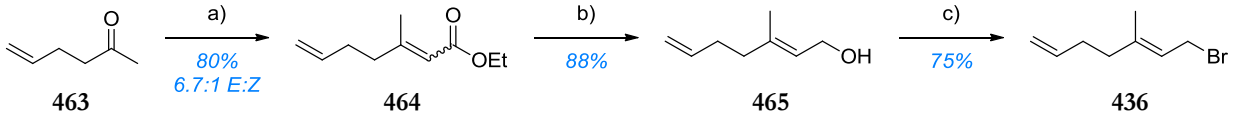

**Scheme 4.16: Synthesis of [3.3.0]-bicyclic *γ*-lactone 462 identified retrosynthetically.**

**Reagents and conditions: a) TBDPSCl, DIPEA, DMF, RT, 1 h, 89%; b) triethyl orthoacetate, propionic acid, 138 °C, 18 h, 83%; c) $LiAlH_4$, $Et_2O$, 0 °C, 30 min, 86%; d) (i) methanesulfonyl chloride, triethylamine, DCM, 0 °C-RT, 1.5 h, 96%; (ii) dimethyl malonate, NaH, DMF/THF, 80 °C, 2 h, 88%; e) $Mn(OAc)_3$, $Cu(OTf)_2$, MeCN, 80 °C, 3 h, 84%; f) LiCl, $H_2O$, DMF, 150 °C, 2 h, 87%.**

### 4.4.4. Synthesis of the required dienyl side chain

As shown retrosynthetically in **Section 4.3**, the acyclic chain which would form the 11-membered ring would come from an alkylation of lactone **435** with allylic bromide **436**. Following reported literature procedures and previous work in the group,[175] **436** was synthesised in 3 steps from 5-hexen-2-one [**Scheme 4.17**]. Thus, ketone **463** was olefinated with the pre-formed

phosphonate-stabilised carbanion of triethyl phosphonoacetate to give ethyl ester **464** in 80% yield as a 6.7:1 mixture of separable geometric isomers. Whilst only a minor separation of the isomers was observed by TLC (retention factor $Z$ = 0.36; $E$ = 0.33 (5% $Et_2O$/pentane)), elution using pentane over petrol 30-40 was found to effectively separate the two geometric isomers, with the major isomer identified as $E$ by proton NMR nOe studies. Subsequent reduction of $E$-**464** using a solution of diisobutylaluminium hydride gave alcohol **465** in excellent yield (88%). Initially ester **464** was reduced using a suspension lithium aluminium hydride in dry diethyl ether, however inconsistent yields were obtained (31-74%). Finally alcohol **465** was converted to the allylic bromide by firstly treating with methanesulfonyl chloride followed by displacement with lithium bromide to give **436** in good yield (75%). Unfortunately **436** could not be purified by column chromatography due to instability, hence was used without purification.

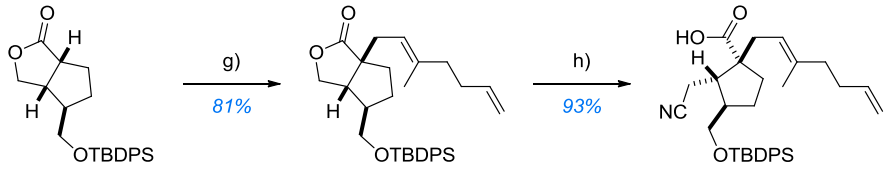



**Scheme 4.17: Synthesis of allylic bromide 436 identified retrosynthetically.**

**Reagents and conditions: a) triethyl phosphonoacetate, *n*-BuLi, THF, -78 °C-RT, 80%; b) DIBAL-H, DCM, -78 °C-RT, 88%; c) methanesulfonyl chloride, triethylamine, LiBr, THF, 0 °C, 2 h, 75%.**

### 4.4.5. Studies towards the 11-membered ring

With both lactone **462** and allylic bromide **436** in hand, work turned to developing the 11-membered ring required in the natural product. Lithium enolate alkylation of lactone **462** with allylic bromide **436** introduced the bridgehead alkyl chain to give lactone **466** in 81% yield [**Scheme 4.18**]. Pleasingly, treatment of lactone **466** with potassium cyanide in refluxing DMSO gave cyano acid **467** in excellent yield (93%). The nitrile was identified by a characteristic carbon shift in the carbon NMR at $\delta_C$ 118.9 (R-**C**≡N) and an IR stretch at $\nu_{max}$ 2247 $cm^{-1}$ (RC≡N).

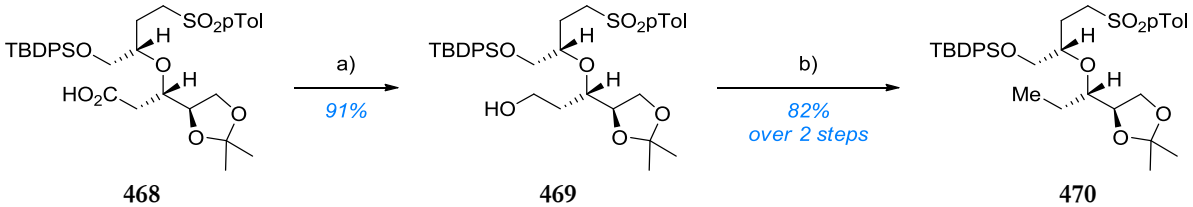



**Scheme 4.18: Synthesis of nitrile acid 467 - an intermediate towards the total synthesis of dolabellane 372.**

**Reagents and conditions: g) (*E*)-7-bromo-5-methylhepta-1,5-diene (436), LiHMDS, THF, -78 °C, 2.5 h, 81%; h) KCN, DMSO, 185 °C, 1.5 h, 93%.**

### 4.4.5.1. Reduction of the carboxylic acid to a methylene

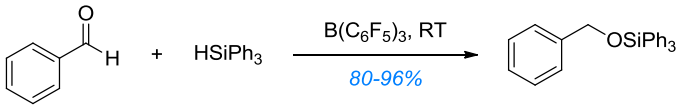
Direct conversion of a carboxylic acid to a methyl group remains a difficult challenge in organic synthesis. Typically an aldehyde or ketone can be reduced to the methylene group by a Clemmensen[180] or Wolff-Kishner reduction.[181] However both transformations rely on strong acid/basic conditions respectively to effect the reduction, limiting the functional group compatibility, in particular silyl protecting groups such as that present in acid (**467**). To overcome these compatibility issues, multistep procedures have been developed in which the acid is reduced to the alcohol, followed by transformation of the primary alcohol to a better leaving group such as tosylate or halide followed by reduction.[182] For example, during studies towards cyclic ether natural products such as obtusenyne, Palenzuela *et al.* fully reduced a carboxylic acid to the corresponding methyl [**Scheme 4.19**].[183] Acid **468** was firstly reduced to alcohol **469** using diisobutylaluminium hydride followed by tosylation under standard conditions to give the corresponding tosylate. Subsequent treatment with lithium aluminium hydride reduced the tosylate to give ethyl **470** in 74% over 3 steps.




**Scheme 4.19: Stepwise reduction of a carboxylic acid to a methyl.**

**Reagents and conditions: a) DIBAL-H, $Et_2O$, -60 °C, 91%; b) (i) TsCl, DMAP, TEA, RT; (ii) ii) $LiAlH_4$, $Et_2O$, reflux, 82% over 2 steps.**

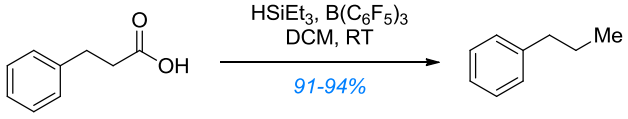
Alternatively, over the past decade or so, reduction of carbonyl derivatives by catalytic hydrosilylation in the presence of a strong Lewis acid has seen significant advancements.[184] In 1996, Piers *et al.* reported a tris(pentafluorophenyl)boron catalysed hydrosilylation of carbonyl derivatives to give the corresponding silyl ethers [**Scheme 4.20**].[185] Tris(pentafluorophenyl)borane is a convenient, commercially available Lewis acid of comparable strength to boron trifluoride.[186] Piers hydrosilylated various aromatic aldehydes, ketones, and esters at room temperature in the presence of 1-4 mol % tris(pentafluorophenyl)boron and 1 equivalent of triphenylsilane. The substrates employed in terms of yield and selectivity compared well to previous methods reported.




**471** **472** **473**

**Scheme 4.20: Hydrosilylation of aldehyde using catalytic tris(pentafluorophenyl)boron.**

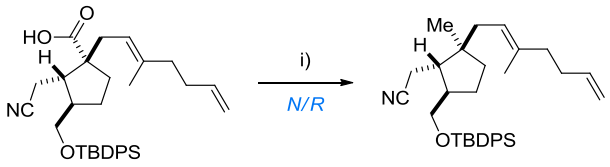
Following this breakthrough, Yamamoto *et al.* reported the reduction of various primary alcohols to the corresponding alkanes using triethylsilane in the presence of tris(pentafluorophenyl)boron.[187] Keen to combine their methodology with that reported by Piers, Yamamoto sought to develop a direct reduction of aliphatic aldehydes, acid chlorides, carboxylic acids and esters into the corresponding methyl group. Finally in 2000, Yamamoto *et al.* reported conditions, which successfully reduced a aliphatic carboxylic acid to the methyl group by exposure to triethylsilane in the presence of catalytic tris(pentafluorophenyl)boron [**Scheme 4.21**].[188]




**474** **475**

**Scheme 4.21: Direct reduction of a carboxylic acid to the corresponding methyl.**

Thus exposing acid **467** to the optimised conditions reported by Yamamoto was attempted [**Scheme 4.22**]. Unfortunately no reaction appeared to have taken place with both mass spectroscopy and the proton NMR indicating only starting material and none of reduced product **476** present in the crude mixture.



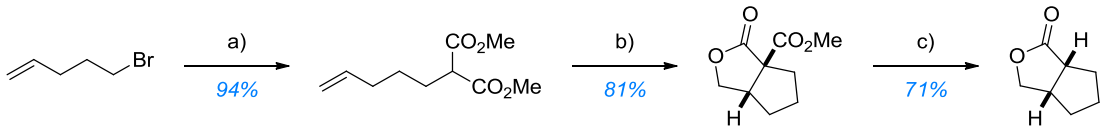

**467** **476**

**Scheme 4.22: Reduction of acid 467 using a direct hydrosilylation reduction.**

**Reagents and conditions: i) $HSiEt_3$ (3.0 eq.), $B(C_6F_5)_3$ (5 mol%), DCM, RT, 24 h, N/R.**

### 4.4.6. Model system

It was apparent that optimisation was required in the reduction of acid **467** to the corresponding methyl functionality, and hence a previously used model system was synthesised in which the methodology could be developed on [**Scheme 4.23**].[169] 5-Bromopentene (**477**) was alkylated with dimethyl malonate to give alkenyl malonate **65** in excellent yield (84%). Subsequent treatment of malonate **65** with manganese(III) acetate gave [3.3.0]-bicyclic *γ*-lactone **66**, which was decarboxylated under Krapcho conditions to give lactone **478** in 58% yield over 2 steps.

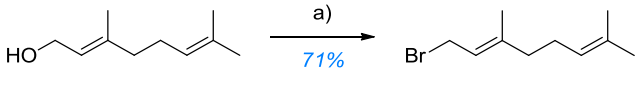



**477** **65** **66** **478**

**Scheme 4.23: Synthesis of model [3.3.0]-bicyclic *γ*-lactone 478.**

**Reagents and conditions: a) (i) NaH, dimethyl malonate, DMF, 0 °C; (ii) THF, 80 °C, 1.5 h, 94%; b) $Mn(OAc)_3$, $Cu(OTf)_2$, MeCN, 80 °C, 3 h, 81%; c) LiCl, $H_2O$, DMF, 150 °C, 2 h, 71%.**

It was decided to use geraniol as the side chain, as it features the same substituted alkenes present in allyl bromide **436**, but has the added benefit of being commercially available [**Scheme 4.24**]. Thus, geraniol (**479**) was converted to the alkyl bromide **480** using phosphorous tribromide and pyridine in modest yield (71%). As allyl bromide **436** was unstable to column chromatography, it was decided to use bromide **480** without further purification.

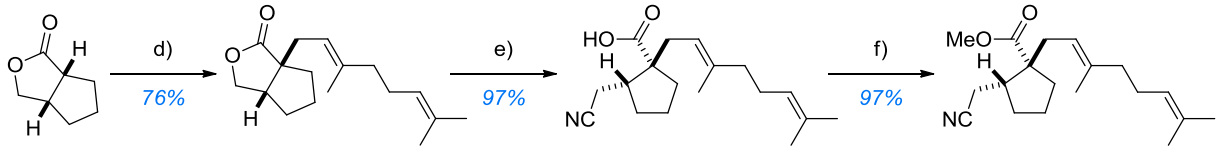



479 480

**Scheme 4.24: Synthesis of geranyl bromide 480.**

**Reagents and conditions: a) $PBr_3$, pyridine, $Et_2O$, hexane, 0 °C, 1 h, 71%**

Subsequent alkylation of lactone **478** with geranyl bromide introduced the bridgehead alkyl chain to give **481** in 76% yield [**Scheme 4.25**]. Treatment of lactone **481** with potassium cyanide caused ring opening at the lactone to give nitrile **482**, which was esterified with trimethylsilyldiazomethane[189] to give methyl ester **483** in 94% yield over two steps.



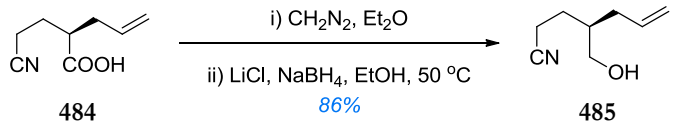

478 481 482 483

**Scheme 4.25: Synthesis of acid 482 to develop reduction conditions.**

**Reagents and conditions: d) (*E*)-1-bromo-3,7-dimethylocta-2,6-diene (480), LiHMDS, THF, -78 °C, 2.5 h, 76%; e) KCN, DMSO, 185 °C, 1.5 h, 97%; f) (trimethylsilyl)diazomethane, toluene, MeOH, RT, 30 min, 97%.**

### 4.4.7. Reduction of a carboxylic acid in the presence of a nitrile

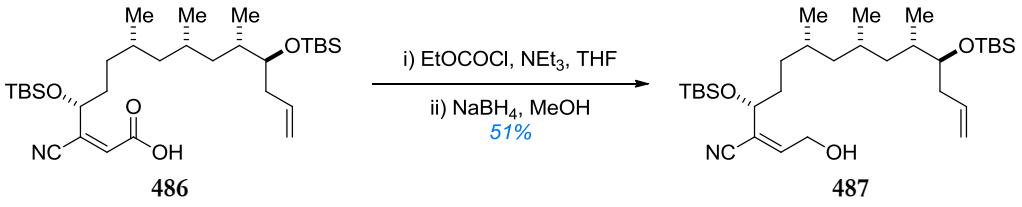
It was decided to first reduce the carboxylic acid in **482** stepwise before attempting the one-pot reduction. Typically a carboxylic acid is reduced to the corresponding alcohol using lithium aluminium hydride or complexes of borane. This is due to the fact that carboxylic acids and esters are less reactive towards nucleophiles when compared to aldehydes and ketones, hence the requirement for stronger reducing agents. However, lithium aluminium hydride has also been shown to reduce nitriles to primary amines,[190] whilst diisobutylaluminium hydride reduces nitriles to the imine, which hydrolyses to the aldehyde on workup.[191] However there are several reports for the reduction of a carboxylic acid or derivative to the alcohol in the presence of a nitrile. In 1991, Oda *et al.* reduced a carboxylic acid via the *in-situ* generated ester using lithium borohydride [**Scheme 4.26**].[192] In the same paper, exposure of **484** to diisobutylaluminium hydride selectively reduced the nitrile, which was converted to the alcohol using sodium borohydride.




484 485

**Scheme 4.26: Reduction of an acid *via* the ester in the presence of a nitrile.**

Alternatively, during their total synthesis of (-)-borrelidin, Hanessian *et al.* reduced a carboxylic acid *via* the mixed anhydride [**Scheme 4.27**].[193] Treatment of **486** with ethyl chloroformate followed by addition of sodium borohydride gave vinyl alcohol **487** in 51% yield, with the nitrile untouched.

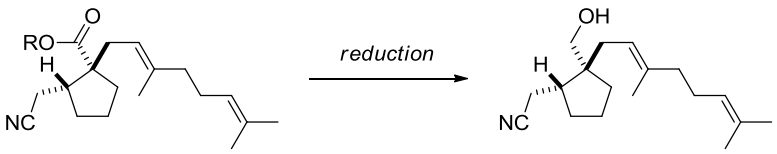



486 487

**Scheme 4.27: Reduction of a mixed anhydride to the alcohol in the presence of a nitrile.**

With a variety of conditions reported for the reduction of a carboxylic acid in the presence of a nitrile, a screen of conditions was carried out [**Table 4.2**]. Unfortunately, treatment of acid **482** with borane dimethyl sulfide complex (entry 1) led to decomposition of the starting material. This is possibly due to competing hydroboration of the carbon-carbon double bonds present in the alkyl chain, which was confirmed by the absence of alkene peaks in the crude proton NMR. Treatment of acid **482** with lithium borohydride (entry 2) gave no reaction with only starting material recovered. Unable to reduce the acid, work then turned to reducing the corresponding methyl ester **483**. Subjecting **483** to a suspension of lithium borohydride in ethanol at room temperature (entry 3) gave a trace of alcohol **488** identified by M+H in the crude mass spec (found $[M+H]^+$, 276). Increasing the temperature to 50 °C (entry 4) gave no significant increase in the desired alcohol **488** with only a trace detected by mass spectrometry. It was postulated that reaction of ethanol with the hydride source over prolonged reaction times was destroying the lithium borohydride, however changing the solvent to THF (entry 5) gave no reaction with only starting material recovered. Finally, the more reactive mixed anhydride was synthesised by

exposing acid **482** to methyl chloroformate followed by addition of the hydride source (entry 6 and 7). Whilst the mixed anhydride was identified by mass spec (found $[M+Na]^+$, 370), no reaction was observed when treated with sodium borohydride (entry 6) or lithium borohydride (entry 7). On workup, starting material was recovered as a result of hydrolysis of the mixed anhydride. Despite precedence in the literature supporting the selective reduction of an acid in the presence of a nitrile, no such reaction could be realised on **482**. This is possibly due to steric congestion present at the carbocyclic acid quaternary stereocentre.




**482/483** **488**

| Entry | R | Conditions | Yield (%) |
|---|---|---|---|
| 1 | H | $BH_3.SMe_2$, THF, 65 °C, 1 h | 0 |
| 2 | H | $LiBH_4$, EtOH, RT, 24 h | N/R |
| 3 | Me | $LiBH_4$, EtOH, RT, 24 h | trace[a] |
| 4 | Me | $LiBH_4$, EtOH, 50 °C, 24 h | trace[a] |
| 5 | Me | $LiBH_4$, THF, 50 °C, 24 h | N/R |
| 6 | $MeO_2C$ | $MeO_2CCl$, $NEt_3$, THF then $NaBH_4$ | N/R |
| 7 | $MeO_2C$ | $MeO_2CCl$, $NEt_3$, THF then $NaBH_4$ | N/R |

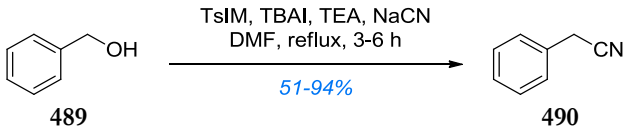
[a] trace of **488** detected by mass spec

**Table 4.2: Condition screen for the synthesis of alcohol 488 by reduction of 482.**

### 4.4.8. Wolff-Kishner reduction of lactone 481

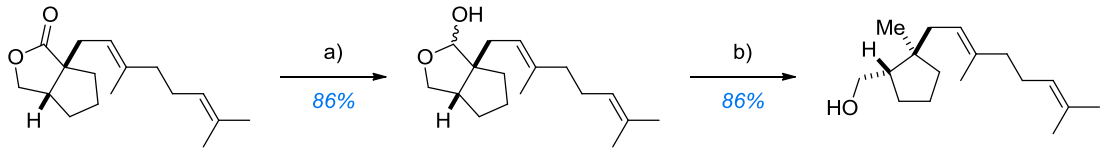
As Hallside[169] and Lua[175] had demonstrated a Wolff-Kishner reduction of a lactol to the corresponding alkane, it was decided to investigate the application of a Wolff-Kishner reduction of the lactol derived from lactone **481** followed by displacement of the resulting alcohol with cyanide. Whilst many one-pot procedures for the conversion of an alcohol to a nitrile have been reported,[194] the use of tosylimidazole is the most attractive [**Scheme 4.28**]. Rad *et al.* reported in 2007 that a

variety of primary, secondary and tertiary alcohols could be converted to the corresponding nitriles *via* tosylation and displacement with sodium cyanide.[195]




**Scheme 4.28: One-pot conversion of an alcohol to a nitrile.**

Thus lactone **481** was reduced using diisobutylaluminium hydride to give lactol **491** as a 1.3:1 mixture of diastereoisomers at C-1 [**Scheme 4.29**]. The lactol was identified in the IR by a broad alcohol stretch at $\nu_{max}$ 3396 $cm^{-1}$ (RO-H) and the absence of a lactone carbonyl stretch. In the proton NMR spectrum, two diastereotopic doublets were identified as the major and minor lactol proton at $\delta_H$ 3.96 ($J$ = 3.4 Hz) and $\delta_H$ 3.78 ($J$ = 3.0 Hz). Subsequent exposure to Huang-Minlon's modified Wolff-Kishner conditions,[196] lactol **491** was reduced to give alcohol **492** in 86% yield. Reduction of **491** was confirmed to have taken place due to the presence of an isolated three proton singlet at $\delta_H$ 3.78.

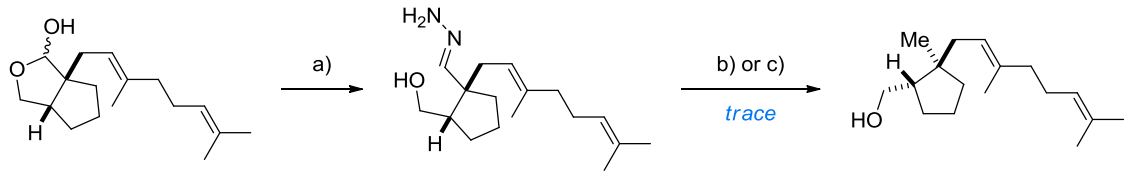



**Scheme 4.29: Wolff-Kishner reduction of 481 *via* the corresponding lactol.**

**Reagents and conditions: a) DIBAL-H, DCM, -78 °C, 1 h, 86%; b) Hydrazine monohydrate, KOH, diethylene glycol, 180 °C, 3.5 h.**

Whilst the Wolff-Kishner reduction of lactol **491** gave alcohol **492** in excellent yield, such conditions were not transferrable to the real system. This is because lactone **466** features a *tert*-butyldiphenylsilyl protecting group, which is unstable to the base at temperatures greater than 100 °C as mentioned previously. In 1962, Cram *et al.* reported a Wolff-Kishner conducted at room temperature.[197] Cram found that slow addition of pre-formed hydrazones of aldehydes and ketones to a solution of *tert*-butoxide in anhydrous dimethyl sulfoxide at 25 °C gave the corresponding hydrocarbon in 60-90% yields. Following this, Scott *et al.* found that aliphatic

hydrazones also decomposed when treated with *tert*-butoxide in refluxing toluene.[198] In light of these reports and the mild conditions described therein, a two-step Wolff-Kishner was attempted using these procedures. [**Scheme 4.30**]. Subjecting lactol **491** to hydrazine monohydrate in refluxing ethanol gave hydrazone **493** as confirmed by mass spectroscopy. After concentration the crude hydrazone was stirred with *tert*-butoxide at room temperature for 24 h in anhydrous dimethyl sulfoxide. The crude NMR indicated a trace of alcohol **492**, with mainly decomposition observed. Similarly, hydrazone **493** was subjected to Scott's conditions again resulting in decomposition of starting material.

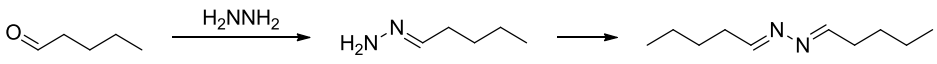



**491** **493** **492**

**Scheme 4.30: Alternative Wolff-Kishner conditions.**

**Reagents and conditions: a) $N_2H_4.H_2O$, EtOH, 100 °C, 16 h; b) KO*t*-Bu, DMSO, RT, 24 h, trace; c) KO*t*-Bu, toluene, 110 °C, 24 h, trace.**

The likely reason for decomposition of **491** under either Cram's or Scott's modified Wolff-Kishner conditions is due to dimerisation of hydrazone **493**. It is well precedented in the literature that the synthesis of hydrazones, in particular those of aldehydes, are complicated by dimerisation of the hydrazone to the corresponding azine [**Scheme 4.31**].[199] For example, the pentanal hydrazone **495** self condenses so rapidly that it is not possible to analyse **496** before decomposition.[199d]

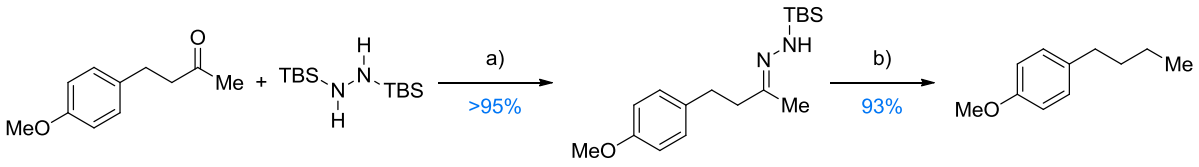



**494** **495** **496**

**Scheme 4.31: Azine formation of pentanal upon treatment with hydrazine.**

In 2004 using a modified hydrazine derivative, Myers *et al.* reported the preparation of *N*-*tert*-butyldimethylsilyl hydrazones and their application in modified Wolff-Kishner reductions and in the synthesis of vinyl halides and *gem*-dihalides [**Scheme 4.32**].[200] Treatment of neat ketone **497**

with 1,2-bis(*tert*-butyldimethylsilyl)hydrazine (**498**) in the presence of catalytic scandium(III) triflate gave hydrazone **499** in excellent yield (>95%). The benefit of using **498** is that hydrazone **499** can be isolated and purified, something previously not possible for hydrazine derived hydrazones.

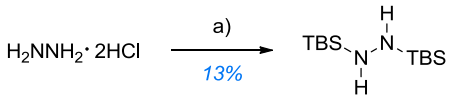



**497** **498** **499** **500**

**Scheme 4.32: Wolff-Kishner type reduction of a carbonyl reported by Myers.**

**Reagents and conditions: a) 0.01 mol% $Sc(OTf)_3$, neat, 0-23 °C; b) KO*t*-Bu, HO*t*-Bu, DMSO, RT.**

Following removal of *tert*-butyldimethylsilanol impurity, Myers found that treatment of **499** with a solution of potassium *tert*-butoxide and *tert*-butanol in dimethylsulfoxide at room temperature induced a Wolff-Kishner reduction to alkane **500** in 93% yield. Unfortunately **498** is not commercially available and requires preparation from hydrazine [**Scheme 4.33**]. Thus hydrazine dihydrochloride (**501**) in the presence of triethylamine and *tert*-butyldimethylsilyl chloride was heated at 110 °C for 4.5 hours. The crude hydrazine was purified by firstly trituration and filtration of the hydrochloride salts from pentane, followed by removal of the volatiles by high vacuum to give **498** in 13% yield.



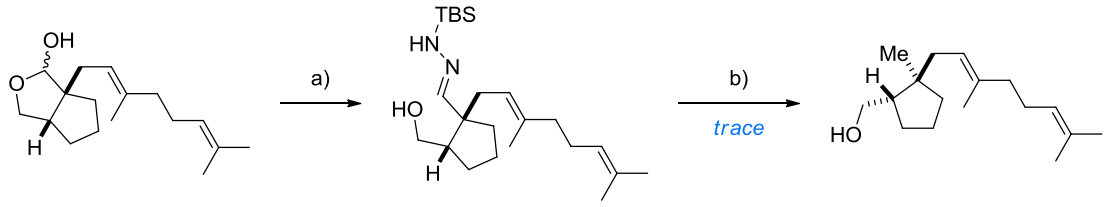

**501** **498**

**Scheme 4.33: Synthesis of 1,2-bis(*tert*-butyldimethylsilyl)hydrazine from hydrazine.**

**Reagents and conditions: a) TBSCl, triethylamine, 100 °C, 4.5 h, 13%.**

With hydrazine **498** in hand, work turned to investigating the application of Myers conditions in the reduction of lactol **491** [**Scheme 4.34**]. Treatment of lactol **491** with 1,2-bis(*tert*-butyldimethylsilyl)hydrazine (**498**) in the presence of catalytic scandium(III) triflate appeared by mass spectroscopy to produce hydrazone **502**, however upon treatment with a solution of potassium *tert*-butoxide and *tert*-butanol in dimethylsulfoxide only a trace of alcohol **492** was

detected in the crude reaction mixture. Due to time constraints no further optimisation was carried out in optimising Meyers reaction conditions.




**491** **502** **492**

**Scheme 4.34: Wolf-Kishner reduction of 491 using 1,2-bis(*tert*-butyldimethylsilyl)hydrazine.**

**Reagents and conditions: a) 1,2-bis(*tert*-butyldimethylsilyl)hydrazine (498), 0.01 mol% $Sc(OTf)_3$, neat, 0-23 °C; b) KO*t*-Bu, HO*t*-Bu, DMSO, RT, 24 h.**

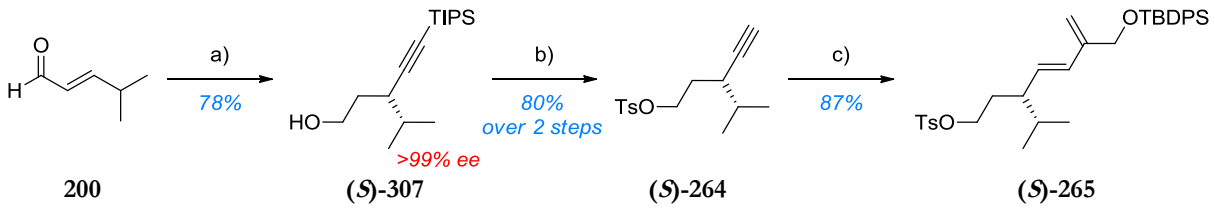
## 4.5. Summary

Significant progress has been made in the total synthesis of dolabellane **372**. Unfortunately, the key cyclisation of an alkenyl malonate which featured the required isopropenyl functionality displayed poor selectivity. Further studies are still required in designing the substrate needed for a ring closing metathesis, which includes investigating a mild Wolff-Kishner reduction, the possibilty of directly reducing a carboxylic acid to a methyl group. If such a transformation can be realised then the total synthesis of dolabellane **372** should be fairly straightforward which will make use of the proposed ring closing metathesis to form the 11-membered ring. Following this, slight modifications to the synthetic route are expected to give rise to other dolabellanes.

# CHAPTER 5: Impact and future work

Overall, manganese(III) acetate mediated radical cyclisations have been shown to provide a powerful transformation in the total synthesis of highly congested all carbon bicyclic systems. The ability to form contiguous stereocentres with good diastereocontrol from simple acyclic precursors makes such methodology well suited to multistep syntheses. With countless natural products isolated built around a cyclopentane framework, manganese(III) acetate mediated cyclisations provide a strong tool for application in their total synthesis.

In Chapter 2, we established conditions for the cyclisation of a simple dienyl malonate to give an alkenyl substituted [3.3.0]-bicyclic *γ*-lactone. Following three simple transformations, such a structure can be converted into a [5.3.0]-bicyclic ketone which is the core of the isodaucane natural product family. The applicability of the methodology in total synthesis was demonstrated in the racemic and asymmetric total synthesis of (+)-aphanamol I in ten steps and an overall yield of 19.7%. The key 1,3-diene (*S*)-**265** was constructed *via* a Suzuki cross coupling of alkyne (*S*)-**264** to vinyl iodide **252** with the former constructed using a rhodium(I) catalysed conjugate addition reported by Nishimura and Hayashi [**Scheme 5.1**].

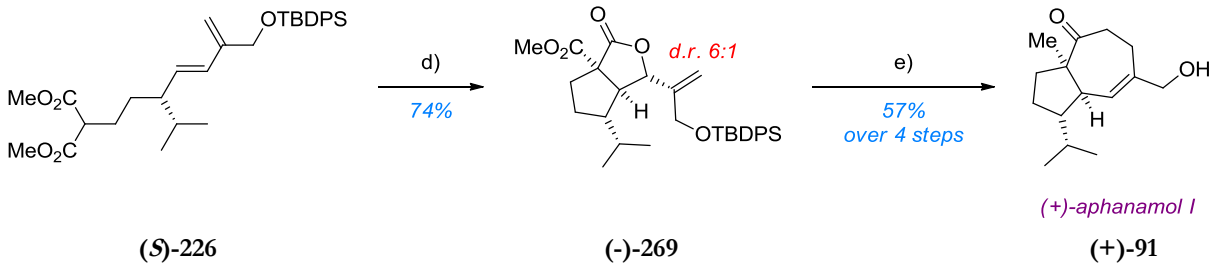



**Scheme 5.1: Synthesis of key 1,3-diene for use in the total synthesis of (+)-aphanamol I.**

**Reagents and conditions: a) (i) 2.5 mol% chlorobis(ethylene)rhodium(I) dimer, sodium acetate trihydrate, $Et_2O$, -30 °C-RT, 1 h; ii) 6 mol% (*S*)-(+)-DTBM-SEGPHOS, (triisopropylsilyl)acetylene, MeOH, 40 °C, 24 h; iii) $NaBH_4$, MeOH, RT, 30 min, 78%; b.i) 1 M TBAF, THF, RT, 18 h, 92%; (ii) *p*-toluenesulfonyl chloride, pyridine, DCM, RT, 18 h, 87%; c) (i) catecholborane, THF, 70 °C; (ii) 5 mol% palladium (II) acetate, 20 mol% triphenylphosphine, *tert*-butyl((2-iodoallyl)oxy)diphenylsilane, THF, 40 °C, 87%**

Following cyclisation of dienyl malonate (*S*)-**226** to give [3.3.0]-bicyclic *γ*-lactone, analogous reactions to those developed in the model system converted (-)-**269** into (+)-aphanamol I [**Scheme**

**5.2**]. Simple transformations of (+)-**91** gave two other closely related natural products, which further validated Wickberg's investigations into the absolute configuration of (+)-aphanamol I and II.

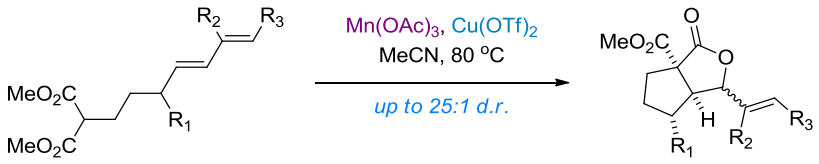



**(*S*)-226** **(-)-269** **(+)-91**

**Scheme 5.2: Total synthesis of (+)-aphanamol I.**

**Reagents and conditions: d) $Mn(OAc)_3$, $Cu(OTf)_2$, MeCN, 80 °C, 30 min, 74%; e.i) LiCl, $H_2O$, DMF, 150 °C, 6 h, 86%; (ii) 1 M LiHMDS in toluene, MeI, -78 °C, 30 min, 90%; (iii) (i) the Petasis reagent, toluene, 110 °C, 30 min; (ii) Celite, hexane, 150 °C; iv) 1 M TBAF, AcOH, THF, 0 °C-RT, 24 h, 100%.**

The general applicability of the methodology was then demonstrated in Chapter 3 [**Scheme 5.3**]. A variety of alkyl substituted dienyl malonates were shown to cyclise with good to excellent diastereoselectivity at C-4. Increasing steric bulk around the 1,3 diene also increases the diastereoselectivity at the lactone stereocentre when compared to the unsubstituted 1,3-diene due to a more favoured transition state in which the substituents are placed on the same face to minimise steric interactions.

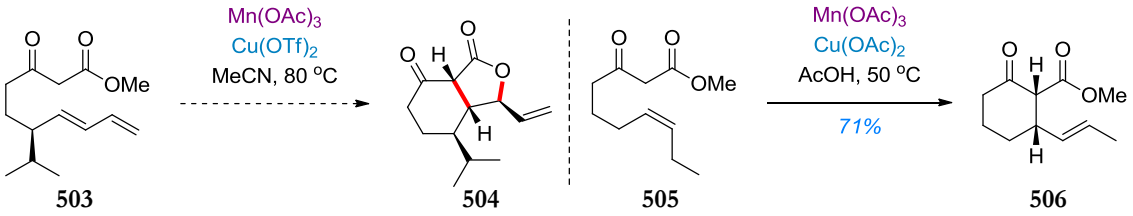



**350** **351**

**Scheme 5.3: Diastereoselective cyclisation of *γ*-substituted dienyl malonates.**

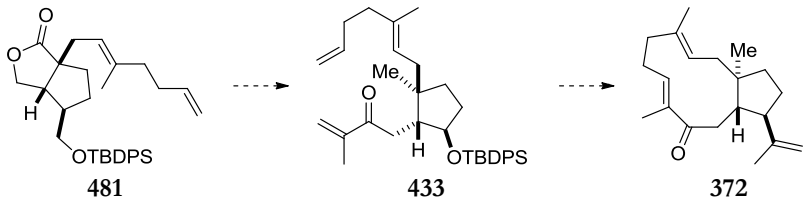
The utilisation of manganese(III) acetate in the cyclisation of different length dienyl malonates was found not to be applicable, most likely due to the slow rate of cyclisation in forming highly strained ring systems. Alternatively, the cyclisation of a dienyl *β*-ketoester (**503**) may allow access to the desired [4.3.0]-bicyclic *γ*-lactone. There is strong precedence reported in the literature for the cyclisation of a *β*-ketoester (**505**) using manganese(III) acetate to form cyclohexane **506** as

reported by Snider *et al.*[40] If such a cyclisation could be realised, then a manganese(III) acetate mediated cyclisation may be applicable to the cladiellin natural product family.




**Scheme 5.4: Proposed alternative route to the cladiellin natural product family.**

Finally, significant advances in the total synthesis of the dolabellane natural product **372** were reported in Chapter 4 [**Scheme 5.5**]. An advanced intermediate (**481**) was achieved which relied on a manganese(III) acetate mediated cyclisation to install the desired stereocentres found in the natural product. Further work is still required to gain access to key intermediate **433**, which will then be ring closed using Grubbs catalyst to form the 11-membered ring. Due to the diverse nature of the dolabellane natural product family, intermediate **433** could be utilised as a precursor to a number of other natural products by simple modifications.




**Scheme 5.5: Towards the total synthesis of the dolabellanes.**

# CHAPTER 6: Experimental

## 6.1. General Experimental

**$^{1}$H and $^{13}$C NMR spectra** were recorded at 25 °C on a Bruker AV-500 (500/125 MHz), Bruker AV-400 (400/100 MHz) or Bruker DPX-400 (400 MHz) spectrometer. Proton ($\delta_H$) and carbon ($\delta_C$) chemical shifts are quoted in ppm and are internally referenced to the residual protonated solvent signal. Assignments were made on the basis of chemical shifts, coupling constants, COSY, DEPT, HSQC data and comparison with spectra of related compounds. Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), sept (septet), m (multiplet), dd (double doublet) and so on. Coupling constants (J) are given in Hz and are rounded to the nearest 0.1 Hz. H and H' refer to diastereotopic protons attached to the same carbon and imply no particular stereochemistry. When an inseparable mixture of diastereoisomers is produced, data will be reported for each diastereomer wherever possible with the following labeling $D_1$, $D_2$ etc used to represent each diastereomer. The lowest number will represent the major diastereomer e.g. $D_1$ = major, $D_2$ = minor. The ratio of diastereomers is measured on the crude material to ensure as accurate a representation.

**High resolution mass spectra** were recorded by the Mass Spectrometry Service, at the University of Oxford Chemical Research Laboratory. Mass values ($m/z$) are reported in Daltons, with their percentage abundances and the relevant fragment ions in parentheses. High resolution values are calculated to four decimal places from the molecular formula, with all found values reported within a tolerance of 5 ppm. **Low resolution mass spectra** were recorded on a Fisons Platform spectrometer (ES).

**Infrared spectra** were recorded using a Bruker Tensor 27 Fourier Transform spectrophotometer using thin films on NaCl plates using diamond ATR. Absorption maxima ($\nu_{max}$)

are classified as strong (s), medium (m), weak (w) and broad (br) and are quoted in wavenumbers ($cm^{-1}$).

**Optical rotations** were measured using a Perkin-Elmer 241 polarimeter in a cell of 1 dm path length (l). The concentration (c) is expressed in g/0.1 $dm^3$ (equivalent to mg/0.1 $cm^3$). Specfic rotations denoted as $[\alpha]_D^T$ (T = temperature in °C, D refers to the D line of a sodium lamp, where the wavelength of light = 589 nm unless otherwise stated) imply units of $°dm^2g^{-1}$ and are calculated according to the equation below where α is the observed rotation:

$$[\alpha]_D^T = \frac{100 \propto}{lc}$$

**Melting points** were determined using a Leica Galen III Compound Microscope and are uncorrected.

**Analytical TLC** was performed on Merck DC-Alufolien 60 $F_{254}$ 0.2 mm precoated plates and visualised using acidic vanillin or basic potassium permanganate dips. Retention factors ($R_f$) are reported with the solvent system used in parentheses. **Flash column chromatography** was performed on Merck 60 silica (particle size 40–63 μm, pore diameter 60 Å) and the solvent system used is recorded in parentheses.

**HPLC** was carried out on an Agilent 1200 Series fitted with either a Zorbax Rx-SIL column measuring 9.4 × 250 mm (packed with 5 $\mu$m beads), a Chiralcel OD column measuring 4.6 × 250 mm (packed with 10 $\mu$m beads) or a Chiralpak AD-H column measuring 4.6 × 250 mm (packed with 5 $\mu$m beads) with flow rate, solvents and retention times recorded in parentheses.

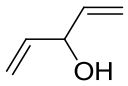
All non-aqueous reactions were carried out in oven-dried glassware sealed with rubber septa under a positive pressure of dry nitrogen or argon from a manifold or balloon during the course of the reaction. Reactions were stirred using Teflon-coated magnetic stir bars. Elevated temperature reactions were maintained using a Thermowatch-controlled DrySyn heating block. Reagents were purchased from commercial suppliers and used without further purification, unless

otherwise stated. Dry solvents were purified using standard techniques. Water used experimentally was deionised. Organic solutions were concentrated using a Büchi rotary evaporator with a water bath temperature of 30 °C. Brine refers to a saturated solution of sodium chloride in water. 'Petrol' refers to the fraction of light petroleum ether boiling in the range of 30-40 or 40-60 °C as stated. Compound names are as generated by ChemBioDraw Ultra 12.0, with NMR assignments based on either the proton/carbon environments or numbering as per compound name. Compounds titled in italics are novel. All compounds are isolated in >97% purity as determined by $^1$H NMR unless otherwise stated (e.g. mixture of diastereoisomers). All experimental data checked for consistency using the experimental data checker published by Goodman *et al.*[201]

## 6.2. Experimental Procedures

### 6.2.1. Compound Synthesis

**Penta-1,4-dien-3-ol (169)**

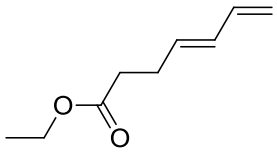



Prepared according to the procedure reported by Mulzer *et al.*[78] To a stirred solution of 1 M vinylmagnesium bromide in THF (44.0 mL, 44.0 mmol, 2.2 eq.) cooled to 0 °C in an ice/water bath, was carefully added methyl formate (**168**) (1.20 g, 20.0 mmol, 1.0 eq.) dropwise over a period of 2 h, keeping the internal temperature below 2 °C. After complete addition the mixture was stirred for a further 10 min. Sat. aq. $NH_4Cl$ solution (60 mL) was added to the mixture and extracted with $Et_2O$ (3 × 20 mL). The combined organic extracts were sequentially washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by short path fractional distillation under reduced pressure (80.0 mmHg) heating at 75°C to afford penta-1,4-dien-3-ol (**169**) as a colourless oil (1.18 g, 14.0 mmol, 70%). $R_f$ = 0.34 (30% EtOAc/petrol 40-60); *b.p.* 56–58 °C at 80 mmHg (lit.[202] 56 °C at 80 mmHg); $\delta_H$ (400 MHz, $CDCl_3$) 5.90 (2H, ddd, *J* = 16.9, 10.2, 5.9 Hz, $CH_2$=C**H**CH(OH)), 5.29 (2H, dd, *J* = 16.9, 0.8 Hz,

$CH_Z\mathbf{H_E}$=CH), 5.16 (2H, dd, *J* = 10.2, 0.8 Hz, $C\mathbf{H_Z}H_E$=CH), 4.63 (1H, td, *J* = 5.9, 0.8 Hz, =CHC**H(**OH)CH=), 1.83 (1H, s, CH(O**H**)); $\delta_C$ (100 MHz, $CDCl_3$) 139.2 (2C, $CH_2$=**C**HCH(OH)), 115.3 (2C, $\mathbf{C}H_ZH_E$=CH), 74.0 (=CH**C**H**(**OH)CH=); LRMS *m*/*z* ($ESI^+$) 102 ($[M+NH_4]^+$, 100%); $\nu_{max}$ (film)/$cm^{-1}$ 3367 (br, OH), 2922 (m, CH), 1724 (w), 1639 (m, C=C), 993 (s, C=$CH_2$), 919 (s, C=$CH_2$).

Data are consistent with literature values.[78]

**(*E*)-Ethyl hepta-4,6-dienoate (170)**

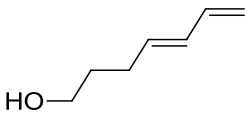


Prepared according to the procedure reported by Ghosh *et al.*[203] To a stirred solution of penta-1,4-dien-3-ol (**169**) (1.14 g, 13.6 mmol, 1.0 eq.) in triethyl orthoacetate (17.0 mL) at room temperature was added propionic acid (101 mg, 1.36 mmol, 0.1 eq.). The resulting mixture was heated at 143 °C for 18 h and cooled to room temperature. The mixture was carefully poured into 1 M HCl (20 mL), stirred for 30 min and extracted with DCM (3 × 20 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (60 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (5% $Et_2O$/petrol 30-40) to afford (*E*)-ethyl hepta-4,6-dienoate (**170**) as a colourless oil (1.75 g, 11.7 mmol, 86%). $R_f$ = 0.20 (5% $Et_2O$/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 6.29 (1H, dt, *J* = 16.9, 10.2 Hz, =CHC**H=**$CH_2$), 6.09 (1H, dd, *J* = 15.1, 10.2 Hz, CH=C**H**CH=), 5.73–5.65 (1H, m, $CH_2$C**H**=CH), 5.11 (1H, d, *J* = 16.9 Hz, CH=$CH_Z\mathbf{H_E}$), 4.99 (1H, d, *J* = 10.2 Hz, CH=$C\mathbf{H_Z}H_E$), 4.14 (2H, q, *J* = 7.1 Hz, $CH_3C\mathbf{H_2}O$), 2.42–2.39 (4H, m, C(=O)$C\mathbf{H_2}CH_2$ and $CH_2C\mathbf{H_2}$CH=), 1.26 (3H, t, *J* = 7.1 Hz, $C\mathbf{H_3}CH_2O$); $\delta_C$ (100 MHz, $CDCl_3$) 173.0 (C=O), 136.8 (=CH**C**H**=**$CH_2$), 132.6 (CH=**C**HCH=), 131.9 ($CH_2$**C**H=CH), 115.7 (CH=$\mathbf{C}H_ZH_E$), 60.4 ($CH_3\mathbf{C}H_2O$), 33.8 (C(=O)$C\mathbf{H_2}CH_2$), 27.8 ($CH_2C\mathbf{H_2}$CH=), 14.2 ($C\mathbf{H_3}CH_2O$); LRMS *m*/*z* ($ESI^+$) 175 (100%); $\nu_{max}$

(film)/$cm^{-1}$ 2982 (m, CH), 1736 (s, C=O), 1653 (m, C=C), 1603 (m, C=C), 1180 (m, C-O), 1006 (s, $CH=CH_2$), 953 (m, $C=CH_2$), 901(m, $C=CH_2$).

Data are consistent with literature values.[203]

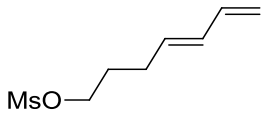
**(*E*)-Hepta-4,6-dien-1-ol (171)**




To a stirred suspension of $LiAlH_4$ (209 mg, 5.51 mmol, 1.0 eq.) in anhydrous $Et_2O$ (9.1 mL) cooled to 0 °C in an ice/water bath, was added dropwise a solution of (*E*)-ethyl hepta-4,6-dienoate (**170**) (850 mg, 5.51 mmol, 1.0 eq.) in anhydrous $Et_2O$ (9.1 mL). The mixture was warmed to room temperature and stirred for 1 h. Water (0.21 mL) was added to the mixture followed by 10% aqueous NaOH (0.21 mL) and stirred for a further 5 min. Additional water (0.42 mL) was added, then dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (30% EtOAc/petrol 40-60) to afford (*E*)-hepta-4,6-dien-1-ol (**171**) as a colourless oil (532 mg, 4.73 mmol, 86%). $R_f$ = 0.20 (30% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 6.31 (1H, dt, *J* = 16.9, 10.2 Hz, =CHC**H**=$CH_2$), 6.08 (1H, dd, *J* = 15.0, 10.2 Hz, CH=C**H**CH=), 5.71 (1H, dt, *J* = 15.0, 7.2 Hz, $CH_2$C**H**=CH), 5.10 (1H, d, *J* = 16.9 Hz, $CH=CH_Z\mathbf{H_E}$), 4.98 (1H, d, *J* = 10.2 Hz, $CH=C\mathbf{H_Z}H_E$), 3.66 (2H, t, *J* = 6.5 Hz, HOC$\mathbf{H_2}CH_2$), 2.19 (2H, q, *J* = 7.2 Hz, $CH_2C\mathbf{H_2}CH=$), 1.70–1.64 (2H, m, $OCH_2C\mathbf{H_2}CH_2$), 1.59 (1H, s, **H**$OCH_2$); $\delta_C$ (100 MHz, $CDCl_3$) 137.0 (=CH**C**H=$CH_2$), 134.3 (CH=**C**HCH=), 131.5 ($CH_2$**C**H=CH), 115.1 ($CH=\mathbf{C}H_ZH_E$), 62.3 (HO**C**$H_2CH_2$), 32.0 ($OCH_2\mathbf{C}H_2CH_2$), 28.8 ($CH_2C\mathbf{H_2}CH=$); LRMS *m*/*z* ($ESI^+$) 112 ($[M+NH_4]^+$, 23%), 413 (100%); $\nu_{max}$ (film)/$cm^{-1}$ 3337 (br, OH), 3087 (w, $=CH_2$), 2936 (s, CH), 2874 (m, CH), 1651 (m, C=C), 1602 (m, C=C), 1057 (m, C-O), 1003 (s, $CH=CH_2$), 951 (m, $C=CH_2$), 898 (m, $C=CH_2$).

Data are consistent with literature values.[204]

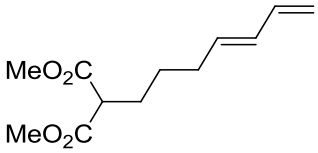
**(*E*)-Hepta-4,6-dien-1-yl methanesulfonate (172)**




To a stirred solution of (*E*)-hepta-4,6-dien-1-ol (**171**) (400 mg, 3.56 mmol, 1.0 eq.) in anhydrous DCM (11.9 mL) cooled to 0 °C in an ice/water bath, was added triethylamine (540 mg, 5.34 mmol, 1.5 eq.) followed by dropwise addition of methanesulfonyl chloride (489 mg, 1.48 mmol, 1.2 eq.). The resulting mixture was warmed to room temperature and stirred for 1.5 h. 1 M HCl (20 mL) was added to the mixture and extracted with DCM (3 × 20 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (50 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford (*E*)-hepta-4,6-dien-1-yl methanesulfonate (**172**) as a pale yellow oil (668 mg, 3.52 mmol, 98%). $R_f$ = 0.27 (30% EtOAc/Petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 6.31 (1H, dt, *J* = 16.9, 10.2 Hz, =CHC**H**=$CH_2$), 6.09 (1H, dd, *J* = 15.0, 10.2 Hz, CH=C**H**CH=), 5.66 (1H, dt, *J* = 15.0, 7.1 Hz, $CH_2$C**H**=CH), 5.13 (1H, d, *J* = 16.9 Hz, CH=$CH_Z$**H**$_E$), 5.01 (1H, d, *J* = 10.2 Hz, CH=C**H**$_Z$$H_E$), 4.23 (2H, t, *J* = 6.4 Hz, MsOC**H**$_2$$CH_2$), 3.00 (3H, s, $SO_2$C**H**$_3$), 2.23 (2H, q, *J* = 7.1 Hz, $CH_2$C**H**$_2$CH=), 1.90–1.83 (2H, m, $OCH_2$C**H**$_2$$CH_2$); $\delta_C$ (100 MHz, $CDCl_3$) 136.7 (=CH**C**H=$CH_2$), 132.5 (CH=**C**HCH=), 132.4 (CH=**C**H$CH_2$), 115.9 (CH=**C**$H_Z$$H_E$), 69.3 (MsO**C**$H_2$$CH_2$), 37.4 ($SO_2$**C**$H_3$), 28.5 ($OCH_2$**C**$H_2$$CH_2$), 28.3 ($CH_2$C**H**$_2$CH=); LRMS *m*/*z* (ESI$^+$) 213 ([M+Na]$^+$, 75%), 347 (100%); $\nu_{max}$ (film)/cm$^{-1}$ 2941 (m, CH), 1650 (w, C=C), 1603 (w, C=C), 1352 (s, $SO_2$), 1174 (s, $SO_2$), 1006 (m, CH=$CH_2$), 972 (m, C=$CH_2$), 944 (m, C=$CH_2$).

Data are consistent with literature values.[205]

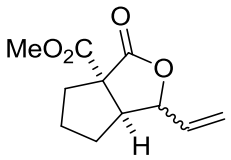
**(*E*)-Dimethyl 2-(hepta-4,6-dien-1-yl)malonate (86)**




To a stirred suspension of hexane washed NaH (1.19 g, 49.8 mmol, 3.0 eq.) in anhydrous DMF (41.5 mL) cooled to 0 °C in an ice/water bath, was carefully added dropwise dimethyl malonate (6.58 g, 49.8 mmol, 3.0 eq.). The resulting mixture was stirred for 20 min at this temperature, after which a solution of (*E*)-hepta-4,6-dien-1-yl methanesulfonate (**172**) (3.15 g, 16.6 mmol, 1.0 eq.) in anhydrous THF (41.5 mL) was added *via* cannula followed by potassium iodide (1.38 g, 8.30 mmol, 0.5 eq.). The mixture was warmed to room temperature, and then heated at 80 °C for 15 h, then cooled to room temperature. Sat. aq. $NH_4Cl$ solution (80 mL) was added to the mixture and extracted with $Et_2O$ (3 × 80 mL). The combined organic extracts were sequentially washed with water (200 mL), brine (200 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/petrol 40-60) to afford (*E*)-dimethyl 2-(hepta-4,6-dien-1-yl)malonate (**86**) as a colourless oil (3.08 g, 13.6 mmol, 82%). $R_f$ = 0.30 (20% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 6.29 (1H, dt, *J* = 16.9, 10.2 Hz, =CHC**H**=$CH_2$), 6.05 (1H, dd, *J* = 15.0, 10.2 Hz, CH=C**H**CH=), 5.65 (1H, dt, *J* = 15.0, 7.1 Hz, $CH_2$C**H**=CH), 5.09 (1H, d, *J* = 16.9 Hz, CH=$CH_Z$**H**$_E$), 4.97 (1H, d, *J* = 10.2 Hz, CH=C**H**$_Z$$H_E$), 3.74 (6H, s, OC**H**$_3$), 3.36 (1H, t, *J* = 7.4 Hz, $(MeO_2C)_2$C**H**$CH_2$), 2.12 (2H, q, *J* = 7.1 Hz, $CH_2$C**H**$_2$CH=), 1.94–1.88 (2H, m, $(MeO_2C)_2$CHC**H**$_2$$CH_2$), 1.45–1.38 (2H, m, $CHCH_2$C**H**$_2$$CH_2$); $\delta_C$ (100 MHz, $CDCl_3$) 169.8 (2C, C=O), 137.1 (=CH**C**H=$CH_2$), 134.0 (CH=**C**H$CH_2$), 131.6 (CH=**C**HCH=), 115.2 (CH=**C**H$_Z$$H_E$), 52.5 (O**C**H$_3$), 51.5 ($(MeO_2C)_2$**C**H$CH_2$), 32.0 ($CH_2$**C**H$_2$CH=), 28.3 ($(MeO_2C)_2$CH**C**H$_2$$CH_2$), 26.8 ($CHCH_2$**C**H$_2$$CH_2$); LRMS *m*/*z* (ESI$^+$) 249 ([M+Na]$^+$, 100%); $\nu_{max}$ (film)/cm$^{-1}$ 3004 (m, CH), 2954 (m, CH), 1739 (s C=O), 1651 (w, C=C), 1603 (w, C=C), 1438 (m), 1343 (m), 1155 (s, C-O), 1007 (m, CH=$CH_2$), 955 (m, C=$CH_2$), 901 (m, C=$CH_2$).

Data are consistent with literature values.[206]

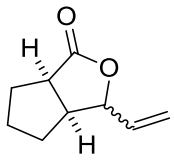
***(3aS*,6aR*)-6a-Methyl-3-vinylhexahydro-1H-cyclopenta[c]furan-1-one (87)***




A mixture of manganese(III) acetate (7.24 g, 27.0 mmol, 2.0 eq.) and copper(II) triflate (4.88 g, 13.5 mmol, 1.0 eq.) were pre heated to 80 °C, after which a solution of (*E*)-dimethyl 2-(hepta-4,6-dien-1-yl)malonate (**86**) (3.06 g, 13.5 mmol, 1.0 eq.) in Ar sparged acetonitrile (67.5 mL) was rapidly added. The resulting mixture was heated at 80 °C for 16 h and then cooled to room temperature. Water (100 mL) and $Et_2O$ (100 mL) were added and stirred for 10 min. The organic layer was separated and the aq. layer was further extracted with $Et_2O$ (2 × 100 mL). The combined organic layers were sequentially washed with brine (300 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (30% EtOAc/petrol 40-60) to afford (3*aS**,6*aR**)-6*a*-methyl-3-vinylhexahydro-1*H*-cyclopenta[*c*]furan-1-one (**87**, diastereomeric ratio = 1.3:1) as a colourless oil (2.38 g, 11.34 mmol, 84%). Characterisation is reported for the major and minor epimer where possible of an inseparable mixture of diastereoisomers. $R_f$ = 0.23 (30% EtOAc/Petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 5.94 (1H, ddd, *J* = 17.1, 10.4, 6.2 Hz, CHC**H**=$CH_2$), 5.83 (1H, ddd, *J* = 17.1, 10.4, 6.3 Hz, CHC**H'**=$CH_2$), 5.45 (1H, d, *J* = 17.1 Hz, CH=$CH_Z$**H**$_E$), 5.35 (1H, d, *J* = 17.1 Hz, CH=$CH_Z$**H'**$_E$), 5.34 (1H, d, *J* = 10.4 Hz, CH=C**H**$_Z$$H_E$), 5.24 (1H, d, *J* = 10.4 Hz, CH=C**H'**$_Z$$H_E$), 5.18 (1H, dd, *J* = 6.2, 6.1 Hz, CHC**H**(CH=)O), 4.53 (1H, dd, *J* = 6.3, 3.7 Hz, CHC**H'**(CH=)O), 3.79 (3H, s, OC**H**$_3$), 3.76 (3H, s, OC**H'**$_3$), 3.10–3.04 (1H, m, $CH_2$C**H**(C)CHO), 2.93–2.90 (1H, m, $CH_2$C**H'**(C)CHO), 2.45–2.33 (2H, m, C**H**$_2$), 2.33–2.21 (2H, m, C**H'**$_2$), 2.09–1.96 (1H, m, C**H**$_2$), 1.93–1.82 (1H, m, C**H'**$_2$), 1.82–1.69 (3H, m, C**H**$_2$), 1.69–1.56 (3H, m, C**H'**$_2$); $\delta_C$ (100 MHz, $CDCl_3$) 175.7 (**C**$O_2$Me), 175.7 (**C'**$O_2$Me), 170.8 (**C**=O), 170.3 (**C'**=O), 135.8 (CH**C**H=$CH_2$), 132.1 (CH**C'**H=$CH_2$), 118.4 (CH=**C**$H_Z$$H_E$), 117.5 (CH=**C**H'$_Z$$H_E$), 85.8 (CH**C**H(CH=)O), 81.0 (CH**C'**H(CH=)O), 63.4 ($CH_2$**C**($CO_2$Me)C), 61.9 ($CH_2$**C'**($CO_2$Me)C), 53.1 (O**C**$H_3$), 53.1 (O**C'**$H_3$), 51.3 ($CH_2$**C**H(C)CHO),

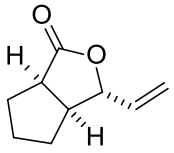
50.3 ($CH_2$**C'**H(C)CHO), 35.4 (**C**$H_2$), 34.3 (**C**$H_2$), 33.6 (**C**$H_2$), 28.1 (**C**$H_2$), 26.1 (**C**$H_2$), 25.7 (**C**$H_2$); LRMS *m*/*z* (ESI$^+$) 233 ([M+Na]$^+$, 100%), 443 ([2M+Na]$^+$, 46%); HRMS *m*/*z* (ESI$^+$) found 233.0784; $C_{11}H_{14}NaO_4$ requires 233.0784; $\nu_{max}$ (film)/cm$^{-1}$ 2958 (m, CH), 1775 (s, C=O), 1740 (s, C=O), 1436 (m), 1257 (m), 1142 (m), 990 (m), 937 (m).

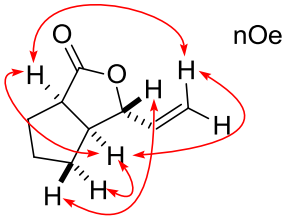
***(3*aS*,6*aR*)-3-Vinylhexahydro-1*H*-cyclopenta[*c*]furan-1-one (173)***



To a stirred solution of (3*aR**,6*aS**)-methyl 3-oxo-1-vinylhexahydro-1*H*-cyclopenta[*d*]furan-3*a*-carboxylate (**87**, diastereomeric ratio = 1.3:1) (795 mg, 3.78 mmol, 1.0 eq.) in DMSO (12.6 mL) was added water (123 mg, 7.56 mmol, 2.0 eq.) followed by LiCl (321 mg, 7.56 mmol, 2.0 eq.). The resulting mixture was heated under reflux (195 °C) for 4 h and then cooled to room temperature. Sat. aq. $NH_4Cl$ solution (50 mL) was added to the mixture and extracted with $Et_2O$ (3 × 50 mL). The combined organic extracts were sequentially washed with water (150 mL), brine (150 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/petrol 40-60) to afford (3*aS**,6*aR**)-3-vinylhexahydro-1*H*-cyclopenta[*d*]furan-1-one (**173**) (diastereomeric ratio = 1.3:1) as a colourless oil (482 mg, 3.18 mmol, 84%). Characterisation is reported for the major and minor epimers as separated by flash column chromatography.

***(3*R*,3*aS*,6*aR*)-3-Vinylhexahydro-1*H*-cyclopenta[*c*]furan-1-one (173)***

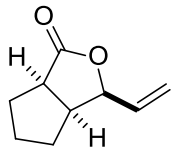


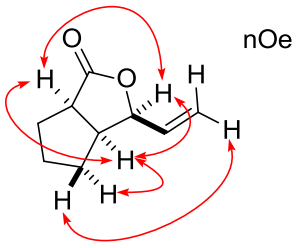



Major Epimer: $R_f$ = 0.39 (30% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 5.87 (1H, ddd, *J* = 17.0, 10.5, 5.9 Hz, C**H**=$CH_2$), 5.30 (1H, d, *J* = 17.0 Hz, CH=$CH_Z$**H**$_E$), 5.18 (1H, d, *J* = 10.5 Hz,

CH=C**H**$_Z$H$_E$), 4.55–4.50 (1H, m, C**H**CH=CH$_2$), 3.03 (1H, ddd, *J* = 9.4, 9.4, 2.6 Hz CH$_2$C**H**C=O), 2.70–2.62 (1H, m, CH$_2$C**H**CH), 2.12–2.02 (1H, m, C**H$_2$**), 1.96-1.83 (2H, m, C**H$_2$**), 1.78–1.63 (2H, m, C**H$_2$**), 1.62–1.49 (1H, m, C**H$_2$**); $\delta_C$ (100 MHz, $CDCl_3$) 180.4 (**C**=O), 136.5 (**C**H=CH$_2$), 116.2 (CH=**C**H$_2$), 85.5 (**C**HCH=CH$_2$), 45.5 (CH$_2$**C**HCH), 44.4 (CH$_2$**C**HC=O), 32.9 (**C**H$_2$), 30.5 (**C**H$_2$), 25.4 (**C**H$_2$); LRMS *m*/*z* (ESI$^+$) 175 ([M+Na]$^+$, 100%), 327 ([2M+Na]$^+$, 39); HRMS *m*/*z* (ESI$^+$) found ([M+Na]$^+$ 175.0737; $C_9H_{12}NaO_2$ requires 175.0730; $\nu_{max}$ (film)/cm$^{-1}$ 2956 (m, CH), 1770 (s, C=O), 1191 (m), 988 (m), 939 (m).

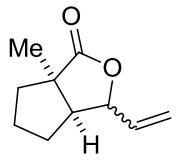
***(3S*,3aS*,6aR*)-3-Vinylhexahydro-1H-cyclopenta[c]furan-1-one (epi-173)***



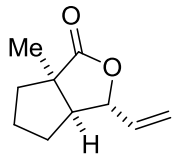

Minor Epimer: *R*$_f$ = 0.32 (30% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 5.84 (1H, ddd, *J* = 16.7, 10.7, 5.9 Hz, C**H**=CH$_2$), 5.40 (1H, d, *J* = 17.2 Hz, CH=CH$_Z$**H$_E$**), 5.29 (1H, d, *J* = 10.7 Hz, CH=C**H$_Z$**H$_E$), 5.02 (1H, dd, *J* = 6.25, 6.25 Hz, C**H**CH=CH$_2$), 3.12 (1H, ddd, *J* = 8.9, 8.9, 3.1 Hz CH$_2$C**H**C=O), 2.93–2.84 (1H, m, CH$_2$C**H**CH), 2.10–2.01 (1H, m, C**H$_2$**), 2.01-1.90 (1H, m, C**H$_2$**), 1.68–1.54 (4H, m, C**H$_2$**); $\delta_C$ (100 MHz, $CDCl_3$) 180.4 (**C**=O), 133.0 (**C**H=CH$_2$), 117.6 (CH=**C**H$_2$), 81.2 (**C**HCH=CH$_2$), 46.4 (CH$_2$**C**HCH), 44.3 (CH$_2$**C**HC=O), 29.4 (**C**H$_2$), 27.4 (**C**H$_2$), 26.0 (**C**H$_2$); LRMS *m*/*z* (ESI$^+$) 175 ([M+Na]$^+$, 100%), 327 ([2M+Na]$^+$, 39); HRMS *m*/*z* (ESI$^+$) found ([M+Na]$^+$ 175.0737; $C_9H_{12}NaO_2$ requires 175.0730; $\nu_{max}$ (film)/cm$^{-1}$ 2961 (m, CH), 1770 (s, C=O), 1179 (m), 1178 (m) , 933 (m), 939 (m).

***(3*aS*,6*aR*)-6*a*-Methyl-3-vinylhexahydro-1H-cyclopenta[*c*]furan-1-one (174)***




To a stirred solution of (3*aS**,6*aR**)-3-vinylhexahydro-1*H*-cyclopenta[*c*]furan-1-one (**173**, diastereomeric ratio = 1.3:1) (370 mg, 2.43 mmol, 1.0 eq.) in anhydrous THF (47.8 mL) cooled to -78 °C in a dry ice/acetone bath, was added iodomethane (1.72 g 12.2 mmol, 5.0 eq.), followed by dropwise addition of a 1 M solution of LiHMDS in toluene (12.2 mL, 12.2 mmol, 5.0 eq.). The mixture was slowly warmed to room temperature and stirred for 12 h. Sat. aq. $NH_4Cl$ solution (50 mL) was added to the mixture and extracted with $Et_2O$ (3 × 50 mL). The combined organic layers were sequentially washed with brine (200 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60) to afford (3*aS**,6*aR**)-6*a*-methyl-3-vinylhexahydro-1*H*-cyclopenta[*c*]furan-1-one (**174**) (diastereomeric ratio = 1.3:1) as a colourless oil (371 mg, 2.24 mmol, 92%). Characterisation is reported for the major and minor epimers as separated by semi-preparative HPLC (Zorbax Rx-SIL column, flow 2.5 mL/min, 10.0% IPA/hexane, 230 nm, $t_1$ = 6.24 min (major), $t_2$ = 6.48 min (minor).

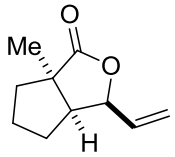
***(3R*,3aS*,6aR*)-6a-Methyl-3-vinylhexahydro-1H-cyclopenta[c]furan-1-one (174)***




Major Epimer: $R_f$ = 0.29 (20% EtOAc/petrol 40-60); $\delta_H$ (500 MHz, $CDCl_3$) 5.89 (1H, ddd, $J$ = 17.0, 10.5, 5.9 Hz, C**H**=$CH_2$), 5.34 (1H, dt, $J$ = 17.0, 1.3 Hz, CH=$CH_Z$**H**$_E$), 5.20 (1H, dt, $J$ = 10.5, 1.3 Hz, CH=C**H**$_Z$$H_E$), 4.49–4.44 (1H, m, C**H**CH=$CH_2$), 2.33–2.28 (1H, m, $CH_2$C**H**CH), 2.22–2.15 (1H, m, C**H**$_2$), 2.02–1.97 (1H, m, C**H**$_2$), 1.83–1.70 (2H, m, C**H**$_2$), 1.66–1.54 (2H, m, C**H**$_2$), 1.35

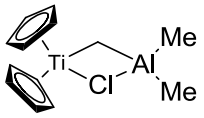
(3H, s, CC**H**$_3$); $\delta_C$ (125 MHz, $CDCl_3$) 182.6 (**C**=O), 136.8 (**C**H=$CH_2$), 116.3 (CH=**C**$H_2$), 84.5 (**C**HCH=$CH_2$), 52.5 (**C**$CH_3$), 51.4 ($CH_2$**C**HCH), 39.6 (**C**$H_2$), 33.1 (**C**$H_2$), 25.5 (**C**$H_2$), 23.9 (C**C**$H_3$); LRMS *m/z* ($ESI^+$) 167 ($[M+H]^+$, 20%), 189 ($[M+Na]^+$, 98), 355 ($[2M+Na]^+$, 100); LRMS *m/z* ($ESI^+$) 167 ($[M+H]^+$, 20%), 189 ($[M+Na]^+$, 98), 355 ($[2M+Na]^+$, 100); HRMS *m/z* ($ESI^+$) found ($[M+Na]^+$ 189.0895; $C_9H_{12}NaO_2$ requires 189.0886; $\nu_{max}$ (film)/$cm^{-1}$ 2959 (m, CH) 2872 (m), 1767 (s, C=O), 1453 (m, $CH_3$), 1215 (m), 1144 (m), 985 (m), 932 (m).

***(3S*,3aS*,6aR*)-6a-Methyl-3-vinylhexahydro-1H-cyclopenta[c]furan-1-one (epi-174)***




Minor Epimer: $R_f$ = 0.29 (20% EtOAc/petrol 40-60); $\delta_H$ (500 MHz, $CDCl_3$) 5.85 (1H, ddd, *J* = 17.0, 10.5, 5.8 Hz, C**H**=$CH_2$), 5.42 (1H, dt, *J* = 17.0, 1.4 Hz, CH=$CH_Z$**H**$_E$), 5.31 (1H, dt, *J* = 10.5, 1.3 Hz, CH=C**H**$_Z$$H_E$), 5.03–4.99 (1H, m, C**H**CH=$CH_2$), 2.48 (1H, dd, *J* = 14.5, 7.3 Hz, $CH_2$C**H**CH), 2.25–2.19 (1H, m, C**H**$_2$), 1.74-1.68 (2H, m, C**H**$_2$), 1.65–1.54 (3H, m, C**H**$_2$), 1.40 (3H, s, CC**H**$_3$); $\delta_C$ (125 MHz, $CDCl_3$) 182.8 (**C**=O), 133.0 (**C**H=$CH_2$), 117.6 (CH=**C**$H_2$), 79.8 (**C**HCH=$CH_2$), 53.1 (**C**$CH_3$), 50.7 ($CH_2$**C**HCH), 38.3 (**C**$H_2$), 28.0 (**C**$H_2$), 25.6 (**C**$H_2$), 21.8 (C**C**$H_3$); LRMS *m/z* ($ESI^+$) 167 ($[M+H]^+$, 20%), 189 ($[M+Na]^+$, 98), 355 ($[2M+Na]^+$, 100); HRMS *m/z* ($ESI^+$) found ($[M+Na]^+$ 189.0895; $C_{10}H_{14}NaO_2$ requires 189.0886; $\nu_{max}$ (film)/$cm^{-1}$ 2959 (m, CH), 2872 (m), 1767 (s, C=O), 1453 (m, $CH_3$), 1215 (m), 1144 (m), 985 (m), 932 (m).

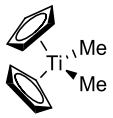
**The Tebbe Reagent (176)**




Prepared according to the procedure reported by Pine *et al.*[85] To a stirred suspension of titanocene dichloride (**182**) (2.49 g, 10.0 mmol, 1.0 eq.) in Ar sparged anhydrous toluene (1 mL) at room temperature, was added dropwise a 2.0 M solution of trimethylaluminium in toluene (10.0 mL,

20.0 mmol, 2.0 eq.). The resulting mixture was stirred at room temperature in the dark for 3 days and then concentrated under reduced pressure (no heating). The red solid was immediately dissolved in pentane (65 mL) and stored at -20 °C (freezer) for 16 h. The solution was further cooled to -78 °C and allowed to stand for 1 h. The mother liquor was removed by filtration (cannula) and the resulting solid was dried under reduced pressure to give the Tebbe reagent (**176**), as red crystals (2.39 g, 7.62 mmol, 76%). The reagent was stored as a 150 mg/mL (~0.50 M) solution in anhydrous toluene at -20 °C in a brown glass bottle. No spectral data was obtained due to the instability of the reagent.

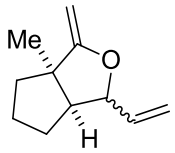
**The Petasis Reagent (177)**




Prepared according to the procedure reported by Payack *et al.*[86] To a stirred suspension of titanocene dichloride (**182**) (2.49 g, 10.0 mmol, 1.0 eq.) in anhydrous $Et_2O$ (50 mL) at 10 °C, was added dropwise a 1.6 M solution of methyllithium in $Et_2O$ (13.4 mL, 21.5 mmol, 2.15 eq.). The resulting solution was stirred for 10 min, after which the mixture was poured onto an ice slurry (100 mL). The organic layer was separated and the aqueous layer was extracted with $Et_2O$ (2 × 100 mL). The combined organic layers were successively washed with brine (200 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure (no heat) to give an orange solid (air and light sensitive). The solid was immediately dissolved in pentane (65 mL) and stored at -20 °C (freezer) for 16 h. The solution was further cooled to -78 °C and allowed to stand for 1 h. The bulk solvent was decanted off, and all residual solvent was removed under reduced pressure to afford the Petasis reagent (**177**), as orange crystals (1.84 g, 8.80 mmol, 88%). The reagent was stored as a 50 mg/mL (~0.24 M) solution in anhydrous toluene at -20 °C in a brown glass bottle. $\delta_H$ (400 MHz, $CDCl_3$) 6.08 (10H, s, Cp), -0.14 (6H, s, C**H**$_3$); $\delta_C$ (50 MHz, $CDCl_3$) 113.5 (10C, Cp), 45.9 (2C, **C**$H_3$); LRMS $m/z$ (ESI$^+$) 209 ([M+H]$^+$, 100%).

Data are consistent with literature values.[86]

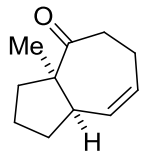
***(3aR*,6aS*)-3a-Methyl-3-methylene-1-vinylhexahydro-1H-cyclopenta[c]furan (183)***




A sealed tube was charged with ((3aS*,6aR*)-6a-methyl-3-vinylhexahydro-1H-cyclopenta[c]furan-1-one (**174**, diastereomeric ratio = 1.3:1) (166 mg, 1.00 mmol, 1.0 eq.) and a 0.24 M solution of the Petasis reagent in toluene (12.5 mL, 3.00 mmol, 3.0 eq.). The resulting mixture was heated in the dark at 110 °C for 1 h and then cooled to room temperature. Hexane (10 mL) and Celite were added to the mixture and stirred for 30 min, then filtered through a Celite plug washing with hexane (2 × 10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (5% $Et_2O$/petrol 40-60 with 1% triethylamine) to afford (3a*R**,6a*S**)-3a-methyl-3-methylene-1-vinylhexahydro-1*H*-cyclopenta[*c*]furan (**183**) as a pale orange oil (132 mg, 0.80 mmol, 80%). $R_f$ = 0.30 (20% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $C_6D_6$) 5.85 (1H, ddd, *J* = 17.1, 10.4, 6.0 Hz, CHC**H**=$CH_2$), 5.83 (1H, ddd, *J* = 17.2, 10.4, 5.5 Hz, CHC**H'**=$CH_2$), 5.45 (1H, dt, *J* = 17.2, 1.7 Hz, CH=$CH_Z$**H'$_E$**), 5.31 (1H, dt, *J* = 17.1, 1.5 Hz, CH=$CH_Z$**H$_E$**), 5.17 (1H, dt, *J* = 10.4, 1.7 Hz, CH=C**H'$_Z$**$H_E$), 5.05 (1H, dt, *J* = 10.4, 1.6 Hz, CH=C**H$_Z$**$H_E$), 4.63–4.62 (2H, m, C=C**H$_2$'**), 4.61–4.59 (1H, m, CHC**H'**(CH=)O), 4.22 (1H, tt, *J* = 6.0, 1.5 Hz, CHC**H**(CH=)O), 3.99 (1H, d, *J* = 1.5 Hz, C=C**H$_2$**), 3.98 (1H, d, *J* = 1.5 Hz, C=C**H$_2$**), 2.04–1.84 (4H, m, $CH_2$C**H**CH, $CH_2$C**H'**CH, C**H$_2$** and C**H'$_2$**), 1.72–1.38 (10H, m, C**H$_2$** and C**H'$_2$**), 1.25 (3H, s, CC**H'$_3$**), 1.24 (3H, s, CC**H'$_3$**); $\delta_C$ (100 MHz, $C_6D_6$) 173.1 (C**C**(=$CH_2$)O), 172.8 (C**C'**(=$CH_2$)O), 138.9 (CHC**H**=$CH_2$), 135.6 (CHC**H'**=$CH_2$), 115.9 (CH=**C'**$H_Z$$H_E$), 114.8 (CH=**C**$H_Z$$H_E$), 87.3 (CH**C**H(CH=)O), 81.9 (CH**C'**H(CH=)O), 78.0 (C=**C**$H_2$), 78.0 (C=**C'**$H_2$), 56.0 ($CH_2$**C**HCH), 54.4 ($CH_2$**C**($CH_3$)C), 53.6 ($CH_2$**C'**HCH), 53.6 ($CH_2$**C'**($CH_3$)C), 42.2 (**C**$H_2$), 41.9 (**C'**$H_2$), 31.1 (**C**$H_2$), 27.4 (**C'**$H_2$), 27.3 (C**C**$H_3$), 26.6 (C**C'**H'$_3$), 25.7 (**C'**$H_2$), 25.6 (**C**$H_2$); HRMS *m*/*z* ($FI^+$) found 164.1205, $C_{11}H_{16}O$ requires 164.1201; $\nu_{max}$ (film)/$cm^{-1}$ 3112 (w, =$CH_2$), 3084 (w,

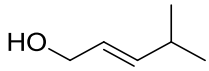
=$CH_2$), 2956 (s, CH), 2868 (m, CH), 1666 (s, C=C), 1602 (m, C=C), 1450 (m), 1374 (m), 1220 (m), 1184 (m), 1028 (s, CH=$CH_2$), 1005 (s, C-O), 987 (s).

***(3aR*,8aR*)-3a-Methyl-1,3,3a,5,6,8a-hexahydroazulen-4(2H)-one (184)***




A stirred solution of (3a*R**,6a*S**)-3a-methyl-3-methylene-1-vinylhexahydro-1*H*-cyclopenta[*d*]furan (**183**, diastereomeric ratio = 1.3:1) (164 mg, 1.00 mmol, 1.0 eq.) in anhydrous xylene (10.0 mL) was heated at 150 °C for 18 h, then cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/petrol 40-60) to afford (3a*R**,8a*R**)-3a-methyl-1,3,3a,5,6,8a-hexahydroazulen-4(2*H*)-one as a colourless oil (**184**) (126 mg, 0.77 mmol, 77%). $R_f$ = 0.29 (20% EtOAc/petrol 40-60); $\delta_H$ (500 MHz, $CDCl_3$) 5.62–5.54 (1H, m, CH=C**H**$CH_2$), 5.49 –5.45 (1H, m, CHC**H**=CH), 3.07–3.01 (1H, m, C(=O)C$\mathbf{H_2}CH_2$), 2.71 (1H, ddd, *J* = 9.4, 4.7, 2.4 Hz, $CH_2$C**H**(C)CH=), 2.49–2.40 (2H, m, $CH_2C\mathbf{H_2}$CH= and C(=O)C$\mathbf{H_2}CH_2$), 2.35–2.26 (1H, m, $CH_2C\mathbf{H_2}$CH=), 3.70 (1H, ddd, *J* = 13.2, 9.1, 7.7 Hz, $CH_2C\mathbf{H_2}$C(Me)), 2.10–2.02 (1H, m, $CH_2C\mathbf{H_2}$CH), 1.77–1.64 (2H, m, $CH_2C\mathbf{H_2}$CH), 1.61–1.54 (1H, m, $CH_2C\mathbf{H_2}$CH), 1.42 (1H, ddd, *J* = 13.2, 8.0, 5.4 Hz, $CH_2C\mathbf{H_2}$C(Me)), 1.24 (1H, s, CC$\mathbf{H_3}$); $\delta_C$ (125 MHz, $CDCl_3$) 214.8 (**C**=O), 135.0 (CH**C**H=CH), 128.8 (CH=**C**H$CH_2$), 61.5 ($CH_2$**C**(Me)CO), 46.3 ($CH_2$**C**H(C)CH=), 38.2 (C(=O)**C**$H_2CH_2$), 33.6 ($CH_2$**C**$H_2$C(Me)), 33.3 ($CH_2$**C**$H_2CH_2$), 26.6 ($CH_2$**C**$H_2$CH=), 25.3 ($CH_2$**C**$H_2$CH), 22.6 (C**C**$H_3$); LRMS *m*/*z* ($ESI^+$) 187 ($[M+Na]^+$, 100%); HRMS *m*/*z* ($ESI^+$) found 187.1092, $C_{11}H_{16}NaO$ requires 187.1093; $\nu_{max}$ (film)/$cm^{-1}$ 3071 (w, =CH), 3049 (w, =CH), 2956 (s, CH), 2858 (s, CH), 1698 (s, C=O), 1462 (m), 1428 (m), 1369 (w), 1254 (w), 1062 (m), 915 (m, C=C-H).

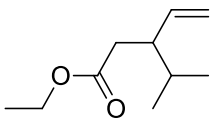
**(*E*)-4-Methylpent-2-en-1-ol (216)**



Prepared according to the procedure reported by Corey *et al.*[207] To a stirred solution of (*E*)-4-methylpent-2-enal (**217**) (3.94 g, 40.0 mmol, 1.0 eq.) in MeOH (100 mL) at 0 °C, was added cerium trichloride heptahydrate (17.9 g, 48.0 mmol, 1.2 eq.) followed by careful addition of $NaBH_4$ (1.82 g, 48.0 mmol, 1.2 eq.) over a period of 15 min. The mixture was warmed to room temperature and stirred for 45 min. Water (100 mL) was added to the mixture and extracted with $Et_2O$ (3 × 100 mL). The combined organic layers were sequentially washed with brine (300 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (60% $Et_2O$/petrol 30–40) to afford (*E*)-4-methylpent-2-en-1-ol (**216**) as a colourless oil (3.25 g, 32.4 mmol, 81%). $R_f$ = 0.30 (60% $Et_2O$/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 5.66 (1H, dd, *J* = 15.5, 6.1 Hz, CH=C**H**CH), 5.57 (1H, dt, *J* = 15.5, 5.5 Hz,$CH_2$C**H**=CH), 4.07 (2H, d, *J* = 5.5 Hz, HOC**H**$_2$CH=), 2.36–2.21 (1H, m, CHC**H**$(CH_3)_2$), 1.72 (1H, s, **H**O$CH_2$), 0.99 (6H, d, *J* = 6.8 Hz, CH(C**H**$_3)_2$); $\delta_C$ (100 MHz, $CDCl_3$) 140.2 (CH=**C**HCH), 125.9 ($CH_2$**C**H=CH), 63.8 (HO**C**$H_2$CH=), 30.6 (CHCH$(CH_3)_2$), 22.18 (2C, CH(**C**$H_3)_2$); $\nu_{max}$ (film)/$cm^{-1}$ 3337 (s, OH), 2961 (s, CH), 2870 (s, CH), 1668 (w), 1462 (m), 1076 (m), 1013 (m), 973 (s $CH_2O$).

Data are consistent with literature values.[207]

**Ethyl 3-isopropylpent-4-enoate (215)**

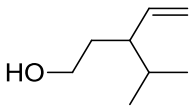


To a stirred solution of (*E*)-4-methylpent-2-en-1-ol (**216**) (2.32 g, 23.1 mmol, 1.0 eq.) in triethyl orthoacetate (26.2 mL, 162 mmol, 7.0 eq.), was added in one portion propionic acid (103 mg, 1.39 mmol, 0.06 eq.). The resulting mixture was heated at 138 °C for 18 h, under conditions for distillative removal of ethanol and then cooled to room temperature. 1 M HCl was carefully added

to the mixture (200 mL) and extracted with $Et_2O$ (3 × 50 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (200 mL), brine (200 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% $Et_2O$/petrol 30–40) to afford ethyl 3-isopropylpent-4-enoate (**215**) as a colourless oil (3.27 g, 19.2 mmol, 83%). $R_f$ = 0.38 (60% DCM/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 5.64 (1H, ddd, *J* = 17.0, 10.4, 8.6 Hz, CHC**H**=$CH_2$), 5.02 (1H, dd, *J* = 10.4, 1.6 Hz, CH=$CH_Z$C**H**$_E$), 5.00 (1H, dd, *J* = 17.0, 1.6 Hz, CH=C**H**$_Z$$CH_E$), 4.10 (2H, q, *J* = 7.1 Hz, $CH_3$C**H**$_2$O), 2.45–2.34 (2H, m, OC(=O)C**H**$_2$CH), 2.31–2.22 (1H, m, $CH_2$C**H**(CH)CH=), 1.64 (1H, oct, *J* = 6.8 Hz, CHC**H**$(CH_3)_2$), 1.23 (3H, t, *J* = 7.1 Hz, C**H**$_3$$CH_2$O), 0.89 (3H, d, *J* = 6.8 Hz, CH(C**H**$_3$$)_2$), 0.85 (3H, d, *J* = 6.8 Hz, CH(C**H**$_3$$)_2$); $\delta_C$ (100 MHz, $CDCl_3$) 172.9 (C=O), 138.7 (CH**C**H=$CH_2$), 115.9 (CH=**C**$H_Z$$CH_E$), 60.1 ($CH_3$**C**$H_2$O), 46.7 ($CH_2$**C**H(CH)CH=), 37.5 (OC(=O)**C**$H_2$CH), 31.3 (CH**C**H$(CH_3)_2$), 20.2 (CH(**C**$H_3$$)_2$), 18.8 (CH(**C**$H_3$$)_2$), 14.2 (**C**$H_3CH_2O$); LRMS *m*/*z* (ESI$^+$) 193 ([M+Na]$^+$, 56%), 413 (100%); $\nu_{max}$ (film)/cm$^{-1}$ 3078 (w, =$CH_2$), 2964 (m, CH), 1738 (s, C=O), 1640 (m, C=C), 1180 (m, C-O), 1115 (m, C-O), 1034 (m, CH=$CH_2$), 918 (m, C=$CH_2$) 858 (m).

Data are consistent with literature values.[208]

**3-Isopropylpent-4-en-1-ol (214)**

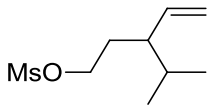



To a stirred suspension of $LiAlH_4$ (591 mg, 15.6 mmol, 1.0 eq.) in anhydrous $Et_2O$ (15.6 mL) cooled to 0 °C in a ice/water bath, was added dropwise a solution of ethyl 3-isopropylpent-4-enoate (**215**) (2.65 g, 15.6 mmol, 1.0 eq.) in anhydrous $Et_2O$ (15.6 mL). The resulting mixture was stirred at 0 °C for 30 min. Water (0.59 mL) was carefully added dropwise, followed by addition of a 10% NaOH solution (0.59 mL) and water (1.18 mL). The mixture was stirred for 5 min, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash

column chromatography (60% $Et_2O$/petrol 30–40) to afford 3-isopropylpent-4-en-1-ol (**214**) as a colourless oil (1.89 g, 14.8 mmol, 95%). $R_f$ = 0.32 (60% $Et_2O$/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 5.60 (1H, dt, *J* = 17.1, 10.0 Hz, CHC**H**=$CH_2$), 5.04 (1H, dd, *J* = 10.0, 1.9 Hz, CH=C$\mathbf{H_Z}CH_E$), 4.99 (1H, dd, *J* = 17.1, 1.9 Hz, CH=$CH_ZC\mathbf{H_E}$), 3.70–3.50 (2H, m, HOC$\mathbf{H_2}CH_2$), 1.97–1.88 (1H, m, $CH_2C\mathbf{H}$(CH)CH=), 1.76–1.44 (4H, m, $CH_2C\mathbf{H_2}CH$, **H**O$CH_2$ and CHC**H**$(CH_3)_2$), 0.89 (3H, d, *J* = 6.8 Hz, CH(C$\mathbf{H_3}$)$_2$), 0.84 (3H, d, *J* = 6.8 Hz, CH(C$\mathbf{H_3}$)$_2$); $\delta_C$ (100 MHz, $CDCl_3$) 140.5 (CH**C**H=$CH_2$), 115.8 (CH=**C**$H_ZCH_E$), 61.6 (HO**C**$H_2CH_2$), 47.5 ($CH_2$**C**H(CH)CH=), 34.8 ($CH_2$**C**$H_2$CH), 31.8 (CH**C**H$(CH_3)_2$), 20.4 (CH(**C**$H_3$)$_2$), 18.9 (CH(**C**$H_3$)$_2$); LRMS *m*/*z* (ESI$^+$) 413 (100%); $\nu_{max}$ (film)/cm$^{-1}$ 3337 (br, OH), 3075 (w, C=$CH_2$), 2960 (s, CH), 2876 (m, CH), 1639 (w, C=C), 1052 (m, C-O), 1001 (m, CH=$CH_2$), 959 (m, C=$CH_2$) 914 (s, C=$CH_2$).

Data are consistent with literature values.[209]

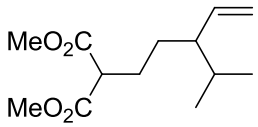
***3-Isopropylpent-4-en-1-yl methanesulfonate (218)***




To a stirred solution of 3-isopropylpent-4-en-1-ol (**214**) (1.77 g, 13.8 mmol, 1.0 eq.) in anhydrous DCM (46.0 mL) cooled to 0 °C in a ice water bath, was added triethylamine (2.09 g, 20.7 mmol, 1.5 eq.) followed by dropwise addition of methansulfonyl chloride (1.90 g, 16.5 mmol, 1.2 eq.). The resulting mixture was warmed to room temperature and stirred for 1.5 h. 1 M HCl (70 ml) was added to the mixture and extracted with DCM (3 × 20 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (100 mL), dried ($MgSO_4$) and filtered through a silic plug eluting with DCM (200 mL). The filtrate was concentrated under reduced pressure to afford 3-isopropylpent-4-en-1-yl methanesulfonate (**218**) as a colourless oil (2.64 g, 12.8 mmol, 93%). $R_f$ = 0.40 (60% $Et_2O$/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 5.34 (1H, dt, *J* = 17.1, 10.0 Hz, CHC**H**=$CH_2$), 5.10 (1H, dd, *J* = 10.0, 1.6 Hz, CH=C$\mathbf{H_Z}CH_E$), 5.01 (1H, dd, *J* = 17.1, 1.6 Hz, CH=$CH_ZC\mathbf{H_E}$), 4.29–4.10 (2H, m, MsOC$\mathbf{H_2}CH_2$), 2.98 (3H, s, $SO_2C\mathbf{H_3}$), 2.01–1.89 (2H, m,

$CH_2CH(CH)CH=$ and $CHCH(CH_3)_2$), 1.68–1.54 (2H, m, $OCH_2CH_2CH$), 0.89 (3H, d, $J$ = 6.8 Hz, $CH(CH_3)_2$), 0.85 (3H, d, $J$ = 6.8 Hz, $CH(CH_3)_2$); $\delta_C$ (100 MHz, $CDCl_3$) 138.8 ($CHCH=CH_2$), 117.1 ($CH=CH_ZCH_E$), 69.0 ($MsOCH_2CH_2$), 46.7 ($CH_2CH(CH)CH$), 37.2 ($SO_2CH_3$), 31.7 ($CHCH(CH_3)_2$), 31.2 ($OCH_2CH_2CH$), 20.3 ($CH(CH_3)_2$), 18.8 ($CH(CH_3)_2$); LRMS $m/z$ ($ESI^+$) 229 ($[M+Na]^+$, 100%), 435 ($[2M+Na]^+$, 69%); HRMS $m/z$ ($ESI^+$) found 229.0869, $C_9H_{18}NaO_3S$ requires 229.0869; $\nu_{max}$ (film)/$cm^{-1}$ 3075 (w, $C=CH_2$), 2962 (s, CH), 2877 (m, CH), 1639 (w, C=C), 1467 (w), 1355 (s, $SO_2$), 1175 (s, $SO_2$), 975 (m, $C=CH_2$), 915 (m, $C=CH_2$).

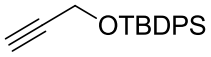
***3-Dimethyl 2-(3-isopropylpent-4-en-1-yl)malonate (212)***




To a stirred suspension of hexane washed NaH (991 mg, 41.3 mmol, 3.0 eq.), in anhydrous DMF (34.5 mL) cooled to 0 °C in an ice/water bath, was carefully added dropwise dimethyl malonate (5.46 g, 41.3 mmol, 3.0 eq.). The resulting mixture was stirred for 20 min at 0 °C, after which a solution of 3-isopropylpent-4-en-1-yl methanesulfonate (**218**) (2.84 g, 13.8 mmol, 1.0 eq.) in anhydrous THF (34.5 mL) was added *via* cannula followed by potassium iodide (1.14 g, 6.88 mmol, 0.5 eq.). The mixture was heated at 80 °C for 1.5 h and then cooled to room temperature. Sat. aq. $NH_4Cl$ solution (100 mL) was added to the mixture and extracted with EtOAc (3 × 50 mL). The combined organic extracts were sequentially washed with water (200 mL), brine (200 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (15% EtOAc/petrol 40–60) to afford dimethyl 2-(3-isopropylpent-4-en-1-yl)malonate (**212**) as a colourless oil (3.03 g, 12.7 mmol, 92%). $R_f$ = 0.31 (15% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 5.52 (1H, dt, $J$ = 17.1, 10.0 Hz, $CHCH=CH_2$), 5.04 (1H, dd, $J$ = 10.0, 1.9 Hz, $CH=CH_ZCH_E$), 4.96 (1H, dd, $J$ = 17.1, 1.9 Hz, $CH=CH_ZCH_E$), 3.73 (6H, s, $OCH_3$), 3.34 (1H, t, $J$ = 7.6 Hz, $(MeO_2C)_2CHCH_2$), 1.96–1.88 (1H, m, $CH_2CH(CH)CH=$), 1.83–1.72 (2H, m, $CHCH_2CH_2$), 1.57 (1H, oct, $J$ = 6.8, Hz, $CHCH(CH_3)_2$), 1.46–1.37 (1H, m, $CHCH_2CH_2CH$), 1.30–

1.19 (1H, m, $CHCH_2C\mathbf{H_2}CH$), 0.85 (3H, d, $J$ = 6.8 Hz, $CH(C\mathbf{H_3})_2$), 0.81 (3H, d, $J$ = 6.8 Hz, $CH(C\mathbf{H_3})_2$); $\delta_C$ (100 MHz, $CDCl_3$) 169.9 (**C**=O), 169.8 (**C**=O), 139.9 ($CH\mathbf{C}H=CH_2$), 116.1 ($CH=\mathbf{C}H_ZCH_E$), 52.4 (2C, $O\mathbf{C}H_3$), 51.7 ($(MeO_2C)_2\mathbf{C}HCH_2$), 50.3 ($CH_2\mathbf{C}H(CH)CH=$), 31.5 ($CH\mathbf{C}H(CH_3)_2$), 29.5 ($CHCH_2\mathbf{C}H_2CH$), 27.0 ($CH\mathbf{C}H_2CH_2$), 20.5 ($CH(\mathbf{C}H_3)_2$), 18.8 ($CH(\mathbf{C}H_3)_2$); LRMS $m/z$ ($ESI^+$) 265 ($[M+Na]^+$, 100%), 507 ($[2M+Na]^+$, 83%); HRMS $m/z$ ($ESI^+$) found 265.1410, $C_{13}H_{22}NaO_4$ requires 265.1410; $\nu_{max}$ (film)/$cm^{-1}$ 3074 (w, $C=CH_2$), 2959 (s, CH), 2874 (m, CH), 1741 (s, C=O), 1639 (w, C=C), 1438 (m), 1342 (m), 1226 (m, C-O), 1155 (m, C-O), 1005 (m, $CH=CH_2$), 915 (m, m, $C=CH_2$).

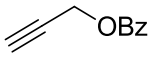
***tert*-Butyldiphenyl(prop-2-yn-1-yloxy)silane (220)**




To a stirred solution of propargyl alcohol (**219**) (1.40 g, 25.0 mmol 1.0 eq.) in anhydrous DMF (25.0 mL) was added imidazole (3.74 g, 55.0 mmol, 2.2 eq.) and stirred for 5 min. *tert*-Butyl diphenylchlorosilane (7.56 g, 27.5 mmol, 1.1 eq.) was added dropwise over a period of 1 h and then stirred for a further 30 min. Sat. aq. $NH_4Cl$ solution (100 mL) was added to the mixture and extracted with $Et_2O$ (2 × 100 mL). The combined organic layers were sequentially washed with water (200 mL), brine (200 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (2% EtOAc/petrol 40–60) to afford *tert*-butyldiphenyl(prop-2-yn-1-yloxy)silane (**220**) as a colourless oil (7.24 g, 24.5 mmol, 98%). $R_f$ = 0.63 (30% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 7.77–7.72 (4H, m, Ar**H**), 7.50–7.39 (6H, m, Ar**H**), 4.34 (2H, d, $J$ = 2.2 Hz, $\equiv CC\mathbf{H_2}OTBDPS$), 2.41 (1H, t, $J$ = 2.2 Hz, **H**C≡C), 1.10 (9H, s, $C(C\mathbf{H_3})_3$); $\delta_C$ (100 MHz, $CDCl_3$) 135.6 (4C, **Ar**), 132.9 (2C, **Ar**), 129.8 (2C, **Ar**), 127.7 (4C, **Ar**), 82.0 (HC≡**C**), 73.0 (H**C**≡C), 52.5 ($\equiv C\mathbf{C}H_2OTBDPS$), 26.7 (3C, $SiC(\mathbf{C}H_3)_3$), 19.2 ($Si\mathbf{C}(CH_3)_3$); LRMS $m/z$ ($ESI^+$) 317 ($[M+Na]^+$, 100%); $\nu_{max}$ (film)/$cm^{-1}$ 3928 (m), 3069 (m), 2935 (m), 2860 (m), 1469 (m), 1428 (m), 1371 (m), 1262 (w), 1105 (s), 1001 (w), 934 (w), 820 (m), 741 (m), 703 (s).

Data are consistent with literature values.[210]

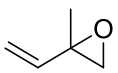
**Prop-2-yn-1-yl benzoate (221)**




To a stirred solution of propargyl alcohol (**219**) (560 mg, 10.0 mmol, 1.0 eq.) and benzoic anhydride (2.71 g, 12.0 mmol, 1.2 eq.) in anhydrous DCM (25.0 mL) cooled to 0 °C in an ice/water bath was added DMAP (122 mg, 1.00 mmol, 0.1 eq.) followed by triethylamine (3.04 g, 30.0 mmol, 3.0 eq.). The resulting mixture was warmed to room temperature and stirred for 3 h. The mixture was poured onto sat. aq. $NH_4Cl$ solution (30 ml), the organic layer separated and the aqueous layer further extracted with DCM (2 × 25 mL). The combined organic extracts were washed sequentially with sat. aq. $NaHCO_3$ solution (75 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% $Et_2O$/petrol 30–40) to afford prop-2-yn-1-yl benzoate (**221**) as a colourless oil (1.07 g, 6.69 mmol, 67%). $R_f$ = 0.34 (10% $Et_2O$/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 8.11–8.06 (2H, m, Ar**H**), 7.61–7.56 (1H, m, Ar**H**), 7.49–7.43 (2H, m, Ar**H**), 4.94 (2H, d, $J$ = 2.5 Hz, C$\mathbf{H_2}$OBz), 2.53 (1H, t, $J$ = 2.5 Hz, **H**C≡C$CH_2$); $\delta_C$ (100 MHz, $CDCl_3$) 165.8 (C=O), 133.3 (**Ar**), 129.8 (2C, **Ar**), 128.4 (2C, **Ar**), 77.7 (HC≡**C**), 75.0 (H**C**≡C), 52.4 (**C**$H_2$OBz); LRMS $m/z$ (ESI$^+$) 183 ([M+Na]$^+$, 19%), 413 (100%); $\nu_{max}$ (film)/cm$^{-1}$ 3295 (s, HC≡C), 3067 (w), 2947 (w), 2129 (w, C≡C), 1725 (S, C=O), 1600 (m), 1491 (m), 1448 (m), 1268 (s, $CH_2O$), 1176 (m), 1105 (s, $CH_2O$), 981 (m), 928 (m), 711 (s).

Data are consistent with literature values.[211]

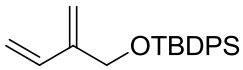
**2-Methyl-2-vinyloxirane (225)**




To a vigorously stirred solution of freshly distilled isoprene (**223**) (2.72 g, 40.0 mmol, 1.0 eq.) in water (10.0 mL) cooled to 0 °C in an ice/water bath was added portionwise, whilst maintaining an internal temperature <5 °C, *N*-bromosuccinimide (14.2 g, 80.0 mmol, 2.0 eq.). The resulting mixture was stirred at 0 °C for 1 h after which a 30% aqueous solution of NaOH (4.4 mL, 1.2 eq.)

was added dropwise. The mixture was warmed to room temperature and stirred for a further 1 h. The mixture was poured onto water (50 ml) and extracted with $Et_2O$ (3 × 50 mL). The combined organic extracts were washed sequentially with brine (150 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by fractional distillation under reduced pressure (760-230 mmHg) heating at 75 °C to afford 2-methyl-2-vinyloxirane (**225**) as a colourless oil (2.75 g, 32.8 mmol, 82%). *b.p.* 29-31 °C at 200 mbar; $R_f$ = 0.23 (30% EtOAc/petrol 40-60).

***tert*-Butyl((2-methylenebut-3-en-1-yl)oxy)diphenylsilane (222)**

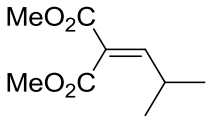



To a stirred solution of 2-methyl-2-vinyloxirane (**225**) (2.70 g, 32.0 mmol, 1.0 eq.) in anhydrous $Et_2O$ (22.9 mL) was added dropwise a 1 M solution of LiHMDS in toluene (41.6 mL, 41.6 mmol, 1.3 eq.). The resulting mixture was heated at 40 °C for 24 h and then cooled to room temperature. The mixture was poured onto 2 M HCl (50 mL) and extracted with $Et_2O$ (3 × 50 mL). The combined organic extracts were washed sequentially with sat. aq. $NaHCO_3$ solution (150 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure (no heating, 300 mbar). To a stirred solution of crude isoprenol in DMF (64.0 mL) was added imidazole (6.53 g, 96.0 mmol, 3.0 eq.) and stirred for 5 min. *tert*-Butyl diphenylchlorosilane (11.0 g, 40.0 mmol, 1.25 eq.) was added dropwise over a period of 1 h and then stirred for a further 30 min. Sat. aq. $NH_4Cl$ solution (100 ml) was added to the mixture and extracted with extracted with $Et_2O$ (3 × 50 mL). The combined organic extracts were washed sequentially with water (150 mL), brine (150 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60) to afford *tert*-butyl((2-methylenebut-3-en-1-yl)oxy)diphenylsilane (**222**) as a colourless oil (7.12 g, 22.1 mmol, 69%). $R_f$ = 0.21 (10% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 7.74–7.66 (4H, m, Ar**H**), 7.48–7.33 (6H, m, Ar**H**), 6.38 (1H, dd, *J* = 18.1, 10.9 Hz, $CH_2$=C**H**C), 5.50-5.49 (1H, m, C(=C$\mathbf{H_2}$)), 5.17–5.18 (1H, m,

C(=C**H**$_2$)), 5.05 (1H, d, *J* = 18.1 Hz, CH$_Z$**H**$_E$=CH), 4.99 (1H, d, *J* = 10.9 Hz, C**H**$_Z$H$_E$=CH), 4.39–4.35 (2H, m, CC**H**$_2$O), 1.05 (9H, s, C(C**H**$_3$)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 144.7 (CH**C**(=CH)CH$_2$), 136.5 (CH$_2$=**C**HC), 135.6 (4C, **Ar**), 133.6 (2C, **Ar**), 129.8 (2C, **Ar**), 127.8 (4C, **Ar**), 114.9 (**C**H$_Z$H$_E$=CH), 113.2 (C(=**C**H$_2$)), 62.9 (C**C**H$_2$O), 26.7 (3C, SiC(**C**H$_3$)$_3$), 19.1 (Si**C**(CH$_3$)$_3$); LRMS *m*/*z* (ESI$^+$) 345 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 345.1645, $C_{21}H_{26}NaOSi$ requires 345.1645; $\nu_{max}$ (film)/cm$^{-1}$ 3072 (m), 2931 (m), 2858 (m), 1597 (m), 1473 (m), 1428 (s), 1391 (s), 1113 (s), 902 (s).

Data are consistent with literature values.[104]

**Dimethyl 2-(2-methylpropylidene)malonate (246)**

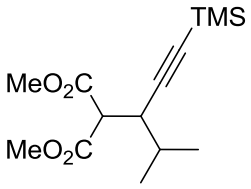



Prepared according to the procedure reported by Cardillo *et al.*[115] To a stirred solution of freshly distilled isobutyraldehyde (**247**) (2.16 g, 30.0 mmol, 1.0 eq.) in anhydrous DMSO (10 mL) containing 3Å molecular sieves was added L-proline (569 mg, 3.00 mmol, 0.1 eq.) and stirred for 5 min. To this mixture was rapidly added dimethyl malonate (4.36 g, 33.0 mmol, 1.1 eq.), and the resulting mixture was stirred at room temperature for 14 h. The precipitate and molecular sieves were removed by filtration. Water (50 mL) was added to the filtrate and extracted with EtOAc (3 × 50 mL). The combined organic extracts were sequentially washed with water (150 ml), brine (150 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/petrol 40-60) to afford dimethyl 2-(2-methylpropylidene)malonate (**246**) as a colourless oil (4.97 g, 26.7 mmol, 89%). $R_f$ = 0.28 (20% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 6.81 (1H, d, *J* = 10.6 Hz, C=C**H**CH), 3.81 (3H, s, OC**H**$_3$), 3.77 (3H, s, OC**H**$_3$), 2.67 (1H, dsept, *J* = 10.6, 6.6 Hz, CHC**H**(CH$_3$)$_2$), 1.06 (6H, d, *J* = 6.6 Hz, CH(C**H**$_3$)$_2$); $\delta_C$ (100 MHz, $CDCl_3$) 166.0 (C=O), 164.5 (C=O), 155.8 (C=**C**HCH), 125.8 ((MeO$_2$C)$_2$**C**=CH), 52.3 (O**C**H$_3$), 52.2 (O**C**H$_3$), 29.5 (CH**C**H(CH$_3$)$_2$), 21.8 (CH(**C**H$_3$)$_2$); LRMS *m*/*z* (ESI$^+$) 209 ([M+Na]$^+$, 100%), 395 ([2M+Na]$^+$, 11%); HRMS *m*/*z* (ESI$^+$) found 209.0784,

$C_9H_{14}NaO_4$ requires 209.0784; $\nu_{max}$ (film)/$cm^{-1}$ 2962 (m, CH), 2784 (w), 1731 (s, C=O), 1645 (m, C=C), 1438 (m), 1367 (m), 1325 (m), 1258 (s), 1224 (s), 1150 (m), 1058 (m).

Data are consistent with literature values.[115]

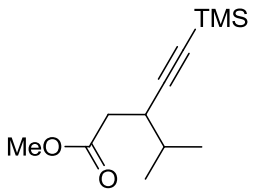
***Dimethyl 2-(4-methyl-1-(trimethylsilyl)pent-1-yn-3-yl)malonate (245)***




To a vigorously stirred solution of ethynyltrimethylsilane (0.92 g, 10.0 mmol, 1.0 eq.) in anhydrous THF (12.5 mL) at room temperature was added a 1 M solution of ethylmagnesium bromide in THF (10.0 mL, 10.0 mmol, 1.0 eq.). The resulting mixture was stirred for 2 h and then cooled to 0 °C in an ice/water bath. Copper(I) chloride (10.0 mg, 0.10 mmol, 1.0 mol%) was added followed by rapid addition of a solution of dimethyl 2-(2-methylpropylidene)malonate (**246**) (1.86 g, 10.0 mmol, 1.0 eq.) in THF (12.5 mL) *via* cannula. The mixture was warmed to room temperature and stirred for 30 min. The reaction was quenched with 1 M HCl (30.0 ml) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (100 ml), brine (100 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% $Et_2O$/petrol 30-40) to afford dimethyl 2-(4-methyl-1-(trimethylsilyl)pent-1-yn-3-yl)malonate (**245**) as a colourless oil (2.68 g, 9.43 mmol, 94%). $R_f$ = 0.25 (20% $Et_2O$/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 3.75 (3H, s, OC**H**$_3$), 3.73 (3H, s, OC**H**$_3$), 3.54 (1H, d, $J$ = 10.9 Hz, $(MeO_2C)_2C$**H**CH), 3.18 (1H, dd, $J$ = 10.9, 3.7, CHC**H**(CH)C≡), 1.73 (1H, septd, $J$ = 6.7, 3.7 Hz, CHC**H**$(CH_3)_2$), 1.03 (3H, d, $J$ = 6.7 Hz, CH(C**H**$_3)_2$), 0.93 (3H, d, $J$ = 6.7 Hz, CH(C**H**$_3)_2$), 0.13 (9H, s, Si(C**H**$_3)_3$); $\delta_C$ (100 MHz, $CDCl_3$) 186.1 (C=O), 167.9 (C=O), 103.2 (C≡**C**TMS), 89.1 (CHC≡C), 54.9 ($(MeO_2C)_2$**C**HCH), 52.6 (O**C**$H_3$), 52.5 (O**C**$H_3$), 39.6 (CH**C**H(CH)C≡), 28.7 (CH**C**H$(CH_3)_2$), 21.6 (CH(**C**$H_3)_2$), 16.7 (CH(**C**$H_3)_2$), -0.01 (3C, Si(**C**$H_3)_3$); LRMS $m/z$ (ESI$^+$) 285 ([M+H]$^+$, 45%), 307 ([M+Na]$^+$, 100), 591

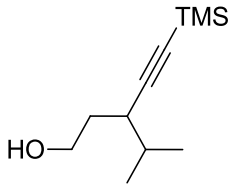
([2M+Na]$^+$, 72%); HRMS *m/z* (ESI$^+$) found 307.1334, $C_{14}H_{24}NaO_4Si$ requires 307.1336; $\nu_{max}$ (film)/cm$^{-1}$ 2962 (m, CH), 2878 (w), 2846 (w), 2174 (m, C≡C), 1744 (s, C=O), 1437 (m), 1321 (m), 1253 (m), 1159 (m), 1009 (m), 848 (s, $Si(CH_3)_3$).

***Methyl 3-isopropyl-5-(trimethylsilyl)pent-4-ynoate (244)***



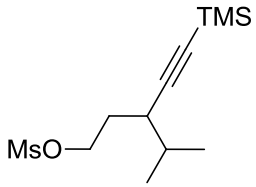

To a stirred solution of 2-(4-methyl-1-(trimethylsilyl)pent-1-yn-3-yl)malonate (**245**) (2.84 g, 10.0 mmol, 1.0 eq.) in anhydrous DMF (20.0 mL) was added water (360 mg, 20 mmol, 2.0 eq.) followed by lithium chloride (845 mg, 20.0 mmol, 2.0 eq.). The resultant mixture was heated under reflux (150° C) for 1.5 h and then cooled to room temperature. Water (30 mL) was added to the mixture and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed sequentially with water (100 mL), brine (100 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (6% $Et_2O$/petrol 30-40) to afford methyl 3-isopropyl-5-(trimethylsilyl)pent-4-ynoate (**244**) as a colourless oil (1.84 g, 8.14 mmol, 81%). $R_f$ = 0.34 (10% $Et_2O$/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 3.69 (3H, s, OC**H**$_3$), 2.82 (1H, ddd, *J* = 8.1, 7.1, 4.8 Hz, $CH_2C$**H**(CH)C≡), 2.50 (1H, dd, *J* = 15.2, 8.1 Hz, OC(=O)C**H**$_2$CH), 2.44 (1H, dd, *J* = 15.2, 7.1 Hz, OC(=O)C**H**$_2$CH), 1.72 (1H, septd, *J* = 6.7, 4.8 Hz, CHC**H**$(CH_3)_2$), 0.99 (3H, d, *J* = 6.7 Hz, CH(C**H**$_3)_2$), 0.95 (3H, d, *J* = 6.7 Hz, CH(C**H**$_3)_2$), 0.13 (9H, s, Si(C**H**$_3)_3$); $\delta_C$ (100 MHz, $CDCl_3$) 172.3 (C=O), 106.7 (C≡**C**TMS), 87.0 (CH**C**≡C), 51.6 (O**C**$H_3$), 37.8 (OC(=O)**C**$H_2$CH), 35.9 ($CH_2$**C**H(CH)C≡), 30.9 (CH**C**H$(CH_3)_2$), 20.9 (CH(**C**$H_3)_2$), 17.8 (CH(**C**$H_3)_2$), 0.10 (3C, Si(**C**$H_3)_3$); LRMS *m/z* (ESI$^+$) 227 ([M+H]$^+$, 23%), 249 ([M+Na]$^+$, 100%); HRMS *m/z* (ESI$^+$) found 249.1283, $C_{12}H_{22}NaO_2Si$ requires 249.1281; $\nu_{max}$ (film)/cm$^{-1}$ 2962 (m, CH), 2898 (w), 2877 (w), 2171 (m, C≡C), 1744 (s, C=O), 1437 (m), 1359 (m), 1253 (m, CO-O), 1164 (m, C-O-C), 1017 (m), 896 (m), 845 (s, $Si(CH_3)_3$), 760 (m).

***3-Isopropyl-5-(trimethylsilyl)pent-4-yn-1-ol (243)***



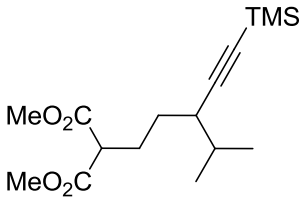

To a stirred suspension of $LiAlH_4$ (281 mg, 7.40 mmol, 1.0 eq.) in anhydrous $Et_2O$ (7.40 mL) cooled to 0 °C in an ice/water bath, was added dropwise a solution of methyl 3-isopropyl-5-(trimethylsilyl)pent-4-ynoate (**244**) (1.68 g, 7.40 mmol, 1.0 eq.) in anhydrous $Et_2O$ (7.40 mL). The resulting mixture was stirred at 0 °C for 30 min. Water (0.28 mL) was carefully added dropwise, followed by addition of a 10% NaOH solution (0.28 mL) and water (0.56 mL). The mixture was stirred for 5 min, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (25% EtOAc/petrol 40–60) to afford 3-isopropyl-5-(trimethylsilyl)pent-4-yn-1-ol (**243**) as a colourless oil (1.47 g, 6.90 mmol, 93%). $R_f$ = 0.31 (30% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 3.81 (2H, m, HOC**H**$_2$CH$_2$), 2.41 (1H, td, $J$ = 9.6, 5.5 Hz, CH$_2$C**H**(CH)C≡), 1.93 (1H, s, **H**OCH$_2$), 1.75–1.61 (3H, m, OCH$_2$C**H**$_2$CH and CHC**H**(CH$_3$)$_2$), 0.99 (3H, d, $J$ = 6.8 Hz, CH(C**H**$_3$)$_2$), 0.96 (3H, d, $J$ = 6.8 Hz, CH(C**H**$_3$)$_2$), 0.15 (9H, s, Si(C**H**$_3$)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 108.6 (C≡**C**TMS), 87.4 (CH**C**≡C), 61.7 (HOC**H**$_2$CH$_2$), 36.6 (CH$_2$**C**H(CH)C≡), 35.2 (OCH$_2$**C**H$_2$CH), 31.7 (CH**C**H(CH$_3$)$_2$), 20.8 (CH(**C**H$_3$)$_2$), 18.5 (CH(**C**H$_3$)$_2$), 0.14 (3C, Si(**C**H$_3$)$_3$); LRMS $m/z$ (ESI$^+$) 199 ([M+H]$^+$, 19%), 221 ([M+Na]$^+$, 100%); HRMS $m/z$ (ESI$^+$) found 221.1333, $C_{11}H_{22}NaOSi$ requires 221.1332; $\nu_{max}$ (film)/cm$^{-1}$ 3326 (br, OH), 2961 (s, CH), 2880 (m), 2361 (w), 2166 (m, C≡C), 1773 (w), 1684 (br), 1466 (w), 1400 (w), 1251 (m), 845 (s, Si(CH$_3$)$_3$), 758 (m).

***3-Isopropyl-5-(trimethylsilyl)pent-4-yn-1-yl methanesulfonate (248)***




To a stirred solution of 3-isopropyl-5-(trimethylsilyl)pent-4-yn-1-ol (**243**) (1.34 g, 6.75 mmol, 1.0 eq.) in anhydrous DCM (22.5 mL) cooled to 0 °C in an ice/water bath was added triethylamine (1.02 g, 10.1 mmol, 1.5 eq.) followed by dropwise addition of methanesulfonyl chloride (851 mg, 7.43 mmol, 1.1 eq.). The resulting mixture was warmed to room temperature and stirred for 1.5 h. 1 M HCl (70 ml) was added to the mixture and extracted with DCM (3 × 20 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (100 mL), dried ($MgSO_4$) and filtered through a silica plug eluting with DCM (200 mL). The filtrate was concentrated under reduced pressure to afford 3-isopropyl-5-(trimethylsilyl)pent-4-yn-1-yl methanesulfonate (**248**) as a colourless oil (1.87 g, 6.68 mmol, 99%). $R_f$ = 0.40 (30% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 4.45–4.36 (2H, m, MsOC**H**$_2$CH$_2$), 3.03 (3H, s, $SO_2$C**H**$_3$), 2.44 (1H, td, $J$ = 11.1, 4.5 Hz, CH$_2$C**H**(CH)C≡), 1.91 (1H, septd, $J$ = 6.7, 4.5 Hz, CHC**H**(CH$_3$)$_2$), 1.80–1.64 (2H, m, OCH$_2$C**H**$_2$CH), 0.99 (3H, d, $J$ = 6.7 Hz, CH(C**H**$_3$)$_2$), 0.97 (3H, d, $J$ = 6.7 Hz, CH(C**H**$_3$)$_2$), 0.15 (9H, s, Si(C**H**$_3$)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 106.6 (C≡**C**TMS), 88.2 (CH**C**≡C), 68.9 (MsO**C**H$_2$CH$_2$), 37.1 ($SO_2$**C**H$_3$), 35.8 (CH$_2$**C**H(CH)C≡), 31.8 (OCH$_2$CH$_2$CH), 31.5 (CH**C**H(CH$_3$)$_2$), 20.8 (CH(**C**H$_3$)$_2$), 18.4 (CH(**C**H$_3$)$_2$), 0.12 (3C, Si(**C**H$_3$)$_3$); LRMS $m/z$ (ESI$^+$) 299 ([M+Na]$^+$, 100%), 575 ([2M+Na]$^+$, 19%); HRMS $m/z$ (ESI$^+$) found 299.1102, $C_{12}H_{24}NaO_3SSi$ requires 299.1108; $\nu_{max}$ (film)/cm$^{-1}$ 2963 (s, CH), 2878 (m), 2167 (m, C≡C), 1467 (w), 1415 (s, $SO_2$), 1250 (m), 1210 (s $SO_2$), 968 (m), 913 (m), 846 (s, Si(CH$_3$)$_3$), 761 (m).

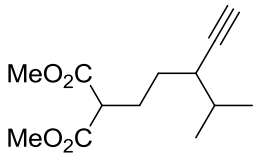
***Dimethyl 2-(3-isopropyl-5-(trimethylsilyl)pent-4-yn-1-yl)malonate (249)***




To a stirred suspension of hexane washed NaH (469 mg, 19.5 mmol, 3.0 eq.), in anhydrous DMF (16.0 mL) cooled to 0 °C in an ice/water bath was carefully added dropwise dimethyl malonate (2.58 g, 19.5 mmol, 3.0 eq.). The resulting mixture was stirred for 20 min at this temperature, after which a solution of 3-isopropyl-5-(trimethylsilyl)pent-4-yn-1-yl methanesulfonate (**248**) (1.80 g, 6.51 mmol, 1.0 eq.) in anhydrous THF (16.0 mL) was added *via* cannula followed by potassium iodide (541 mg, 3.26 mmol, 0.5 eq.). The mixture was warmed to room temperature, and then heated at 80 °C for 14 h. The mixture was cooled to room temperature, after which sat. aq. $NH_4Cl$ solution (50.0 mL) was added and extracted with $Et_2O$ (3 × 50 mL). The combined organic extracts were washed sequentially with water (200 mL), brine (200 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (15% EtOAc/petrol 40–60) to afford dimethyl 2-(3-isopropyl-5-(trimethylsilyl)pent-4-yn-1-yl)malonate (**249**) as a colourless oil (1.84 g, 5.92 mmol, 91%). $R_f$ = 0.35 (20% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 3.74 (6H, s, OC**H**$_3$), 3.41 (1H, t, $J$ = 7.5 Hz, $(MeO_2C)_2C\mathbf{H}CH$), 2.26–2.20 (1H, m, $CH_2C\mathbf{H}(CH)C\equiv$), 2.17–2.06 (1H, m, $CHC\mathbf{H}_2CH_2$), 2.03–1.92 (1H, m, $CHC\mathbf{H}_2CH_2$), 1.66 (1H, septd, $J$ = 6.7, 1.4 Hz, $CHC\mathbf{H}(CH_3)_2$), 1.43 (2H, q, $J$ = 7.8, Hz, $CH_2C\mathbf{H}_2CH$), 0.95 (3H, d, $J$ = 6.7 Hz, $CH(C\mathbf{H}_3)_2$), 0.93 (3H, d, $J$ = 6.7 Hz, $CH(C\mathbf{H}_3)_2$), 0.14 (9H, s, $Si(C\mathbf{H}_3)_3$); $\delta_C$ (100 MHz, $CDCl_3$) 169.8 (C=O), 169.7 (C=O), 108.1 (C≡**C**TMS), 87.0 (CH**C**≡C), 52.4 (O**C**$H_3$), 51.4 ($(MeO_2C)_2\mathbf{C}HCH$), 39.4 ($CH_2\mathbf{C}H(CH)C\equiv$), 31.2 ($CH\mathbf{C}H(CH_3)_2$), 30.0 ($CH_2\mathbf{C}H_2CH$), 27.0 ($CH\mathbf{C}H_2CH_2$), 20.9 ($CH(\mathbf{C}H_3)_2$), 18.3 ($CH(\mathbf{C}H_3)_2$), 0.17 (3C, $Si(\mathbf{C}H_3)_3$); LRMS $m/z$ ($ESI^+$) 335 ($[M+Na]^+$, 100%), 647 ($[2M+Na]^+$, 20%); HRMS $m/z$ ($ESI^+$) found 335.1644, $C_{16}H_{28}NaO_4Si$

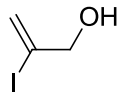
requires 335.1649; $\nu_{max}$ (film)/cm$^{-1}$ 2961 (s, CH), 2873 (w), 2166 (m, C≡C), 1741 (s, C=O), 1439 (m), 1347 (w), 1285 (m), 1154 (m), 1009 (w), 845 (s, Si(CH$_3$)$_3$), 760 (m).

***Dimethyl 2-(3-isopropylpent-4-yn-1-yl)malonate (241)***




To a stirred solution of dimethyl 2-(3-isopropyl-5-(trimethylsilyl)pent-4-yn-1-yl)malonate (**249**) (1.81 g, 5.79 mmol, 1.0 eq.) in anhydrous THF (16.0 mL) cooled to 0 °C in an ice/water bath, was carefully added dropwise, a 1 M solution of TBAF in THF (6.95 mL, 6.95 mmol, 1.2 eq.). After complete addition, the mixture was warmed to room temperature and stirred for 1.5 h. Sat. aq. $NH_4Cl$ solution (30 mL) was added and extracted with $Et_2O$ (3 × 30 mL). The combined organic extracts were successively washed with water (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40–60) to afford dimethyl 2-(3-isopropylpent-4-yn-1-yl)malonate (**241**) as a colourless oil (1.35 g, 5.61 mmol, 97%). $R_f$ = 0.22 (10% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 3.74 (6H, s, OC**H$_3$**), 3.39 (1H, t, *J* = 7.5 Hz, (MeO$_2$C)$_2$C**H**CH$_2$), 2.26–2.19 (1H, m, CH$_2$C**H**(CH)C≡), 2.19–2.10 (1H, m, CHC**H$_2$**CH$_2$), 2.06 (1H, d, *J* = 6.7 Hz, CHC≡C**H**), 2.02–1.91 (1H, m, CHC**H$_2$**CH$_2$), 1.69 (1H, septd, *J* = 6.7, 1.3 Hz, CH**C**H(CH$_3$)$_2$), 1.50–1.41 (2H, m, CH$_2$C**H$_2$**CH), 0.97 (3H, d, *J* = 6.7 Hz, CH(C**H$_3$**)$_2$), 0.94 (3H, d, *J* = 6.7 Hz, CH(C**H$_3$**)$_2$); $\delta_C$ (100 MHz, $CDCl_3$) 169.7 (C=O), 169.7 (C=O), 85.2 (CH**C**≡CH), 70.8 (CHC≡**C**H), 52.5 (2C, O**C**H$_3$), 51.5 ((MeO$_2$C)$_2$**C**HCH$_2$), 38.3 (CH$_2$**C**H(CH)C≡), 31.1 (CH**C**H(CH$_3$)$_2$), 30.1 (CH$_2$**C**H$_2$CH), 26.9 (CH**C**H$_2$CH$_2$), 20.9 (CH(**C**H$_3$)$_2$), 18.3 (CH(**C**H$_3$)$_2$); LRMS *m*/*z* (ESI$^+$) 263 ([M+Na]$^+$, 100%), 503 ([2M+Na]$^+$, 15%); HRMS *m*/*z* (ESI$^+$) found 263.1249, $C_{13}H_{20}NaO_4$ requires 263.1254; $\nu_{max}$ (film)/cm$^{-1}$ 3290 (m, ≡C-H), 2961 (m, CH), 2873 (m), 2109 (w, C≡C), 1738 (s, C=O), 1439 (m), 1347 (m), 1290 (m), 1225 (m), 1202 (m), 1155 (m, C-O), 903 (w), 859 (w), 803 (w), 639 (br, ≡C-H).

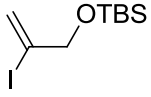
**2-Iodoprop-2-en-1-ol (250)**




Prepared according to the procedure reported by Ishii *et al.*[119] To a stirred a stirred solution of sodium iodide (7.19 g, 48.0 mmol, 1.2 eq.) in acetonitrile (80.0 mL) cooled to 0 °C in an ice/water bath was added trimethylsilyl chloride (5.21 g, 48.0 mmol, 1.2 eq.) and stirred for 15 min. To this mixture was then added water (432 mg, 24.0 mmol, 0.6 eq.) followed by rapid dropwise addition of propargyl alcohol (**219**) (2.24 g, 40.0 mmol, 1.0 eq.). After complete addition, the mixture was warmed to room temperature and stirred for 6 h. Sat. aq. $NaHCO_3$ solution (100 mL) was added to the mixture and extracted with $Et_2O$ (3 × 100 mL). The combined organic extracts were sequentially washed with 1 M NaOH (300 mL), sat. aq. sodium thiosulfate solution (300 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% $Et_2O$/petrol 30-40) to afford 2-iodoprop-2-en-1-ol (**250**) as a colourless oil (3.97 g, 21.6 mmol, 54%). $R_f$ = 0.30 (50% $Et_2O$/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 6.38 (1H, q, $J$ = 1.3 Hz, C=C**H**$_2$), 5.85 (1H, q, $J$ = 1.3 Hz, =C**H**$_2$), 4.15 (2H, dt, $J$ = 6.6, 1.3 Hz, C**H**$_2$OH), 3.03 (1H, t, $J$ = 6.6, Hz, $CH_2O$**H**); $\delta_C$ (100 MHz, $CDCl_3$) 124.5 (C=**C**$H_2$), 110.4 (**C**=$CH_2$), 70.9 (**C**$H_2$OH); HRMS $m/z$ ($FI^+$) found 183.9386, $C_3H_5IO$ requires 183.9385; $\nu_{max}$ (film)/$cm^{-1}$3305 (br, OH), 2910 (m), 2856 (m), 1808 (w, =$CH_2$ overtone), 1624 (m, C=C), 1443 (m), 1399 (m), 1229 (m), 1143 (m), 1028 (s), 976 (m), 899 (s, C=C-H), 643 (m, C-I).

Data are consistent with literature value.[119]

***tert*-Butyl((2-iodoallyl)oxy)dimethylsilane (251)**

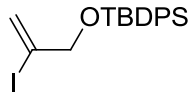



To a stirred a stirred solution of 2-iodoprop-2-en-1-ol (**250**) (860 mg, 4.67 mmol, 1.0 eq.) in anhydrous DMF (16.0 mL) cooled to 0 °C in an ice/water bath was added imidazole (795 mg,

11.7 mmol, 2.5 mmol) followed by dropwise addition *tert*-butyldimethylsilyl chloride (775 mg, 5.14 mmol, 1.1 eq.). After complete addition the mixture was warmed to room temperature and stirred for 14 h. Sat. aq. $NH_4Cl$ solution (15 mL) was added to the mixture and stirred for 5 min and then extracted with $Et_2O$ (3 × 15 mL). The combined organic extracts were successively washed with water (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (2% $Et_2O$/petrol petrol 30-40) to afford *tert*-butyl((2-iodoallyl)oxy)dimethylsilane (**251**) as a colourless oil (1.39 g, 4.44 mmol, 95%). $R_f$ = 0.53 (2% $Et_2O$/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 6.43 (1H, d, $J$ = 1.4 Hz, C=C**H**$_2$), 5.82 (1H, d, $J$ = 1.4 Hz, C=C**H**$_2$), 4.19 (2H, d, $J$ = 1.4 Hz, C**H**$_2$OTBS), 0.93 (9H, s, SiC(C**H**$_3$)$_3$), 0.11 (6H, s, SiC**H**$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 122.9 (C=**C**H$_2$), 109.7 (**C**=CH$_2$), 71.1 (**C**H$_2$OTBDPS), 25.8 (3C, SiC(**C**H$_3$)$_3$), 18.3 (Si**C**(CH$_3$)$_3$), -5.4 (2C, Si**C**H$_3$); LRMS $m/z$ (FI) found 298.0304, $C_9H_{19}IOSi$ requires 298.0250; $\nu_{max}$ (film)/cm$^{-1}$ 3248 (br), 2928 (m), 2855 (m), 2724 (m), 1684 (m, C=C), 1597 (m), 1521 (m), 1334 (m), 1252 (s), 1110 (m), 1032 (m), 902 (m, C=C-H), 844 (m), 784 (m), 728 (s, Si-C), 642 (m, C-I).

Data are consistent with literature values.[212]

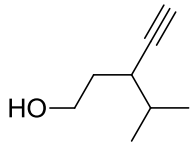
**tert-*Butyl((2-iodoallyl)oxy)diphenylsilane (252)***




To a stirred solution of 2-iodoprop-2-en-1-ol (**250**) (3.40 g, 18.5 mmol, 1.0 eq.) in anhydrous DMF (61.7 mL) cooled to 0 °C in an ice/water bath was added imidazole (3.15 g, 46.3 mmol, 2.5 eq.) followed by dropwise addition *tert*-butyl diphenylchlorosilane (5.59 g, 20.3 mmol, 1.1 eq.). After complete addition, the mixture was warmed to room temperature and stirred for 14 h. Sat. aq. $NH_4Cl$ solution (70 mL) was added to the mixture and extracted with EtOAc (3 × 70 mL). The combined organic extracts were sequentially washed with water (200 mL), brine (200 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash

column chromatography (0-4% gradient EtOAc/petrol 40-60) to afford *tert*-butyl((2-iodoallyl)oxy)diphenylsilane (**252**) as a colourless oil (7.56 g, 17.9 mmol, 97%). $R_f$ = 0.57 (2% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 7.75–7.72 (4H, m, Ar**H**), 7.52–7.41 (6H, m, Ar**H**), 6.62 (1H, q, *J* = 1.8 Hz, C=C**H**$_2$), 5.92 (1H, q, *J* = 1.8 Hz, C=C**H**$_2$), 4.28 (2H, t, *J* = 1.8 Hz, C**H**$_2$OTBDPS), 1.15 (9H, s, SiC(C**H**$_3$)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 135.5 (4C, **Ar**), 133.0 (2C, **Ar**), 129.9 (2C, **Ar**), 127.9 (4C, **Ar**), 123.3 (C=**C**H$_2$), 108.9 (**C**=CH$_2$), 71.4 (**C**H$_2$OTBDPS), 26.8 (3C, SiC(**C**H$_3$)$_3$), 19.4 (Si**C**(CH$_3$)$_3$); LRMS *m*/*z* (ESI$^+$) 423 ([M+H]$^+$, 50%), 445 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 445.0455, $C_{19}H_{23}INaOSi$ requires 445.0455; $\nu_{max}$ (film)/cm$^{-1}$ 3071 (w), 2957 (m), 2933 (m), 2890 (m), 2856 (m), 1960 (w, Ph overtone), 1893 (w, Ph overtone), 1823 (w, Ph overtone), 1625 (m, C=C), 1468 (m), 1427 (m), 1393 (m), 1364 (m), 1260 (m), 1188 (m), 1108 (m), 1076 (s, Si-O-C), 1002 (m), 899 (m, C=C-H), 818 (m), 739 (s, Si-C).

**3-Isopropylpent-4-yn-1-ol (254)**

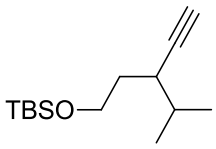



To a stirred solution of 3-isopropyl-5-(trimethylsilyl)pent-4-yn-1-ol (**243**) (5.74 g, 28.9 mmol, 1.0 eq.) in anhydrous THF (72.0 mL) cooled to 0 °C in an ice/water bath was added dropwise a 1 M solution of TBAF in THF (34.7 mL, 34.7 mmol, 1.2 eq.). After complete addition the mixture was warmed to room temperature and stirred for 1.5 h. Sat. aq. $NH_4Cl$ (100 mL) was added to the mixture and extracted with $Et_2O$ (3 × 100 mL). The combined organic extracts were successively washed with 1 M HCl (300 mL), water (300 ml), brine (300 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% $Et_2O$/petrol 40-60) to afford 3-isopropylpent-4-yn-1-ol (**254**) as a colourless oil (3.34 g, 26.6 mmol, 92%). $R_f$ = 0.24 (50% $Et_2O$/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 3.87–3.75 (2H, m, HOC**H**$_2$CH$_2$), 2.43 (1H, dtd, *J* = 7.5, 5.0, 2.5 Hz, CH$_2$C**H**(CH)C≡CH), 2.08 (1H, d, *J* = 2.5 Hz, CHC≡C**H**), 1.91 (1H, t, *J* = 5.4 Hz, **H**OCH$_2$CH$_2$), 1.78–1.61 (3H, m, CH$_2$C**H**$_2$CH and

CH**C**H(CH$_3$)$_2$), 1.00 (3H, d, *J* = 6.7 Hz, CH(C**H$_3$**)$_2$), 0.97 (3H, d, *J* = 6.7 Hz, CH(C**H$_3$**)$_2$); $\delta_C$ (100 MHz, $CDCl_3$) 85.6 (CH**C**≡CH), 70.8 (CHC≡**C**H), 61.3 (HO**C**H$_2$CH$_2$), 35.2 (CH$_2$**C**H$_2$CH), 35.1 (CH$_2$**C**H(CH)C≡CH), 31.5 (CH**C**H(CH$_3$)$_2$), 20.8 (CH(**C**H$_3$)$_2$), 18.3 (CH(**C**H$_3$)$_2$); HRMS *m*/*z* (FI$^+$) found 127.1117, $C_8H_{15}O$ requires 127.1123; $\nu_{max}$ (film)/cm$^{-1}$ 3303 (br, OH), 2961 (s, CH), 2876 (m), 2110 (w, C≡C), 1466 (m), 1387 (w), 1370 (w), 1045 (s), 629 (s).

Data are consistent with literature value.[213]

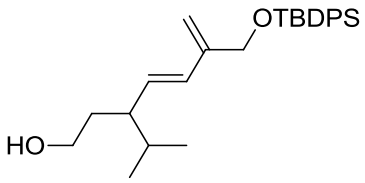
**tert-*Butyl((3-isopropylpent-4-yn-1-yl)oxy)dimethylsilane (255)***




To a stirred solution of 3-isopropylpent-4-yn-1-ol (**254**) (735 mg, 5.82 mmol, 1.0 eq.) and imidazole (994 mg, 14.6 mmol, 2.0 eq.) in anhydrous DMF (9.50 mL) cooled to 0 °C in an ice/water bath was added dropwise a solution of *tert*-butyldimethylsilyl chloride (9.66 g, 6.41 mmol, 1.2 eq.) in anhydrous DMF (9.50 mL). After complete addition the mixture was warmed to room temperature and stirred for 14 h. Sat. aq. $NH_4Cl$ (30 mL) was added to the mixture and extracted with $Et_2O$ (3 × 30 mL). The combined organic extracts were successively washed with water (100 ml), brine (100 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (5% $Et_2O$/petrol 30-40) to afford *tert*-butyl((3-isopropylpent-4-yn-1-yl)oxy)dimethylsilane (**255**) as a colourless oil (1.23 g, 5.12 mmol, 88%). $R_f$ = 0.69 (30% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 3.83–3.71 (2H, m, TBSOC**H$_2$**CH$_2$), 2.43 (1H, dtd, *J* = 7.2, 4.7, 2.4 Hz, CH$_2$C**H**(CH)C≡CH), 2.03 (1H, d, *J* = 2.4 Hz, CHC≡C**H**), 1.77–1.58 (3H, m, OCH$_2$C**H$_2$**CH and CHC**H**(CH$_3$)$_2$), 1.01 (3H d, *J* = 6.7 Hz, CH(C**H$_3$**)$_2$), 0.97 (3H, d, *J* = 6.7 Hz, CH(C**H$_3$**)$_2$), 0.91 (9H, s, SiC(C**H$_3$**)$_3$), 0.74 (3H, s, SiC**H$_3$**), 0.70 (3H, s, SiC**H$_3$**); $\delta_C$ (100 MHz, $CDCl_3$) 85.8 (CH**C**≡CH), 70.2 (CHC≡**C**H), 61.2 (TBSO**C**H$_2$CH$_2$), 35.6 (OCH$_2$**C**H$_2$CH), 34.6 (CH$_2$**C**H(CH)C≡CH), 31.2 (CH**C**H(CH$_3$)$_2$), 25.9 (3C, SiC(**C**H$_3$)$_3$), 20.9 (CH(**C**H$_3$)$_2$), 18.3

(Si**C**$(CH_3)_3$), 18.2 (CH(**C**$H_3)_2$), -5.3 (2C, Si**C**$H_3$); LRMS *m/z* (ESI$^+$) 241 ([M+H]$^+$, 80%), 263 ([M+Na]$^+$, 100%); HRMS *m/z* (FI$^+$) found 241.1992, $C_{14}H_{29}OSi$ requires 241.1988; $\nu_{max}$ (film)/cm$^{-1}$ 2957 (m, CH), 2878 (m), 2110 (w, C≡C), 1730 (m), 1464 (m), 1215 (m), 1101 (m), 923 (m), 748 (s), 668 (m).

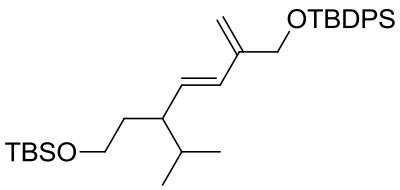
***(E)-6-(((tert-Butyldiphenylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-ol (257)***




To a stirred solution of 3-isopropylpent-4-yn-1-ol (**254**) (126 mg, 1.00 mmol, 1.4 eq.) in freeze-thaw degassed anhydrous THF (1.00 mL) was added dropwise catecholborane (144 mg, 1.20 mmol, 1.7 eq.). The resulting mixture was heated under reflux (70 °C) for 14 h and cooled to room temperature. The mixture was concentrated under reduced pressure to afford the crude boronate ester as a cloudy oil. Palladium(II) acetate (7.86 mg, 0.05 mmol, 5 mol%) and triphenylphosphine (36.7 mg, 0.20 mmol, 20 mol%) were dissolved in freeze-thaw degassed anhydrous THF (2.50 mL) and stirred at room temperature for 20 min. To the yellow solution was then added dropwise a solution of *tert*-butyl((2-iodoallyl)oxy)diphenylsilane (**252**) (296 mg, 0.70 mmol, 1.0 eq.) and crude boronate ester in freeze-thaw degassed anhydrous THF (2.50 mL). After complete addition, freeze-thaw degassed aq. 2 M LiOH (2.50 ml) was added to the mixture and stirred at 40 °C for 3 h. Water (10 mL) was added to the mixture and extracted with $Et_2O$ (3 × 10 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/petrol 30-40) to afford (*E*)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-ol (**257**) as a colourless oil (99.2 mg, 0.336 mmol, 34%). $R_f$ = 0.26 (20% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $C_6D_6$) $R_f$ = 0.26 (20% EtOAc/petrol); $\delta_H$ (400 MHz, $C_6D_6$) 7.94–7.88 (4H, m, Ar**H**), 7.35–7.29 (6H, m, Ar**H**), 6.16 (1H,

d, *J* = 16.0, Hz, CH=C**H**C(=$CH_2$)), 5.62 (1H, s, C=C**H**$_2$), 5.49 (1H, dd, *J* = 16.0, 9.5 Hz, CH(CH)C**H**=CH), 5.22 (1H, s, C=C**H**$_2$), 4.63 (2H, s, C(=$CH_2$)C**H**$_2$OTBDPS), 3.54–3.39 (2H, m, HOC**H**$_2$$CH_2$), 2.01–1.91 (1H, m, $CH_2$C**H**(CH)CH=), 1.67–1.58 (1H, m, $OCH_2$C**H**$_2$CH), 1.49 (1H, oct, *J* = 6.7, Hz, CHC**H**($CH_3$)$_2$), 1.35–1.26 (1H, m, $OCH_2$C**H**$_2$$CH_2$), 1.29 (9H, s, SiC(C**H**$_3$)$_3$), 1.05 (1H, s, **H**O$CH_2$), 0.91 (3H, d, *J* = 6.7, Hz, CH(C**H**$_3$)$_2$), 0.84 (3H, d, *J* = 6.7, Hz, CH(C**H**$_3$)$_2$); $\delta_C$ (100 MHz, $C_6D_6$) 144.7 (**C**=$CH_2$), 135.9 (4C, **Ar**), 133.9 (2C, **Ar**), 132.2 (CH(CH)**C**H=CH), 131.3 (CH=**C**HC(=$CH_2$)), 130.0 (2C, **Ar**), 128.1 (4C,**Ar**), 113.6 (C=**C**$H_2$), 64.4 (C(=$CH_2$)**C**$H_2$OTBDPS), 61.1 (HO**C**$H_2$$CH_2$), 46.8 ($CH_2$**C**H(CH)CH=), 35.4 ($OCH_2$**C**$H_2$CH), 32.4 (CH**C**H($CH_3$)$_2$), 27.0 (3C, SiC(**C**$H_3$)$_3$), 20.7 (CH(**C**$H_3$)$_2$), 19.5 (Si**C**($CH_3$)$_3$), 19.3 (CH(**C**$H_3$)$_2$); *m*/*z* (ESI$^+$) 445 ([M+Na]$^+$ 100%); HRMS *m*/*z* (ESI$^+$) found 445.2526, $C_{27}H_{38}NaO_2Si$ requires 445.2533; $\nu_{max}$ (film)/cm$^{-1}$ 3326 (br, OH), 2957 (s, CH), 2931 (s, CH), 2858 (s, CH), 1889 (w, Ph overtone), 1823 (w, Ph overtone), 1778 (w, Ph overtone), 1609 (w), 1590 (w), 1463 (m), 1428 (m), 1387 (m), 1367 (m), 1157 (s, C-O), 999 (m, CH=$CH_2$), 969 (m, C=$CH_2$).

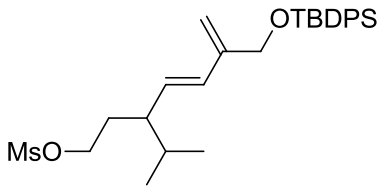
***(E)-9-Isopropyl-2,2,13,13,14,14-hexamethyl-6-methylene-3,3-diphenyl-4,12-dioxa-3,13-disilapentadec-7-ene (258)***




To a stirred solution of *tert*-butyl((3-isopropylpent-4-yn-1-yl)oxy)dimethylsilane (**255**) (200 mg, 0.83 mmol, 1.4 eq.) in freeze-thaw degassed anhydrous THF (0.42 mL) was added dropwise catecholborane (120 mg, 1.00 mmol, 1.5 eq.). The resulting mixture was heated under reflux (70 °C) for 16 h and cooled to room temperature. The mixture was concentrated under reduced pressure to afford the crude boronate ester as a cloudy oil. Palladium(II) acetate (6.74 mg, 0.04 mmol, 5 mol%) and triphenylphosphine (34.1 mg, 0.16 mmol, 20 mol%) were dissolved in freeze-thaw degassed anhydrous THF (2.50 mL) and stirred at room temperature for 20 min. To

the yellow solution was then added dropwise a solution of *tert*-butyl((2-iodoallyl)oxy)diphenylsilane (**252**) (279 mg, 0.66 mmol, 1.0 eq.) and crude boronate ester in freeze-thaw degassed anhydrous THF (2.50 mL). After complete addition, freeze-thaw degassed aq. 2 M LiOH (2.50 ml) was added to the mixture and stirred at 40 °C for 18 h. Water (10 mL) was added to the mixture and extracted with $Et_2O$ (3 × 10 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (2% EtOAc/petrol 30-40) to afford (*E*)-9-isopropyl-2,2,13,13,14,14-hexamethyl-6-methylene-3,3-diphenyl-4,12-dioxa-3,13-disilapentadec-7-ene (**258**) as a colourless oil (294 mg, 0.689 mmol, 83%). $R_f$ = 0.21 (2% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 7.76–7.72 (4H, m, Ar**H**), 7.48–7.39 (6H, m, Ar**H**), 6.03 (1H, d, *J* = 16.1, Hz, CH=C**H**C(=$CH_2$)), 5.40–5.32 (2H, m, CH(CH)C**H**=CH and C=C**H$_2$**), 5.07 (1H, s, C=C**H$_2$**), 4.38 (2H, s, C(=$CH_2$)C**H$_2$**OTBDPS), 3.61–3.54 (1H, m, TBSOC**H$_2$**$CH_2$), 3.52–3.44 (1H, m, TBSOC**H$_2$**$CH_2$), 1.97–1.89 (1H, m, $CH_2$C**H**(CH)CH=), 1.75–1.65 (1H, m, $OCH_2$C**H$_2$**CH), 1.63–1.51 (1H, m, CHC**H**($CH_3$)$_2$), 1.45–1.35 (1H, m, $OCH_2$C**H$_2$**CH), 1.10 (9H, s, SiC(C**H$_3$**)$_3$), 0.91 (9H, s, SiC(C**H$_3$**)$_3$), 0.87 (3H, d, *J* = 6.8, Hz, CH(C**H$_3$**)$_2$), 0.81 (3H, d, *J* = 6.8, Hz, CH(C**H$_3$**)$_2$), 0.04 (6H, s, SiC**H$_3$**); $\delta_C$ (100 MHz, $CDCl_3$) 144.4 (**C**=$CH_2$), 135.5 (4C, **Ar**), 133.6 (2C, **Ar**), 131.7 (CH(CH)**C**H=CH), 130.8 (CH=**C**HC(=$CH_2$)), 129.6 (2C, **Ar**), 127.6 (4C,**Ar**), 112.7 (C=**C**$H_2$), 64.6 (C(=$CH_2$)**C**$H_2$OTBDPS), 61.6 (TBSO**C**$H_2CH_2$), 46.2 ($CH_2$**C**H(CH)CH=), 35.2 ($OCH_2$**C**$H_2$CH), 32.1 (CH**C**H($CH_3$)$_2$), 26.8 (3C, SiC(**C**$H_3$)$_3$), 26.0 (3C, SiC(**C**$H_3$)$_3$), 20.6 (CH(**C**$H_3$)$_2$), 19.3 (Si**C**($CH_3$)$_3$), 19.2 (CH(**C**$H_3$)$_2$), 18.3 (Si**C**($CH_3$)$_3$), -5.3 (2C, Si**C**$H_3$); *m*/*z* (ESI$^+$) 559 ([M+Na]$^+$ 100%); HRMS *m*/*z* (ESI$^+$) found 559.3386, $C_{33}H_{52}NaO_2Si_2$ requires 559.3398; $\nu_{max}$ (film)/cm$^{-1}$ 3072 (w, =$CH_2$), 3051 (w, =CH), 2956 (s, CH), 2932 (s, CH), 2858 (s, CH), 1960 (w, Ph overtone), 1892 (w, Ph overtone), 1821 (w, Ph overtone), 1649 (w, C=C),1609 (w, C=C), 1467 (m), 1427 (m), 1387 (m), 1363 (m), 1190 (s, C-O), 1254 (m), 1105 (SiO) 1006 (m, CH=$CH_2$), 969 (m, C=$CH_2$), 934 (m, C=$CH_2$).

***(E)-6-(((tert-Butyldiphenylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-yl methanesulfonate (259)***




**Mesylation**

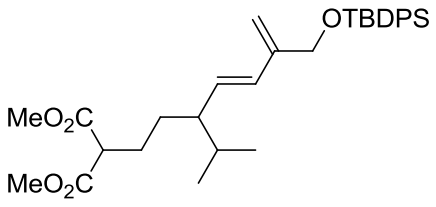
To a stirred solution of (*E*)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-ol (**257**) (276 mg, 0.65 mmol, 1.0 eq.) in anhydrous DCM (2.2 mL) cooled to 0 °C in an ice/water bath was added triethylamine (98.7 mg, 0.98 mmol, 1.5 eq.) followed by dropwise addition of methanesulfonyl chloride (81.9 mg, 0.72 mmol, 1.1 eq.). The resulting mixture was warmed to room temperature and stirred for 1.5 h. 1 M HCl (10 mL) was added to the mixture and stirred for 5 min. The organic layer was separated and the aqueous layer was further extracted with DCM (2 × 10 mL). The combined organic layers were successively washed with sat. aq. $NaHCO_3$ solution (40 mL), brine (40 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (40% $Et_2O$/petrol 40–60) to afford (*E*)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-yl methanesulfonate (**259**) as a colourless oil (316 mg, 0.63 mmol, 97%).

**Suzuki cross coupling**

To a stirred solution of 3-isopropylpent-4-yn-1-yl methanesulfonate (**263**) (204 mg, 1.00 mmol, 1.4 eq.) in freeze-thaw degassed anhydrous THF (1.00 mL) was added dropwise catecholborane (144 mg, 1.20 mmol). The resulting mixture was heated under reflux (70 °C) for 14 h and cooled to room temperature. The mixture was concentrated under reduced pressure to afford the crude boronate ester as a cloudy oil. Palladium(II) acetate (7.86 mg, 0.03 mmol, 5 mol%) and triphenylphosphine (36.7 mg, 0.12 mmol, 20 mol%) were dissolved in freeze-thaw degassed anhydrous THF (2.50 mL) and stirred at room temperature for 20 min. To the yellow solution was

then added dropwise a solution of *tert*-butyl((2-iodoallyl)oxy)diphenylsilane (**252**) (296 mg, 0.70 mmol) and crude boronate ester in freeze-thaw degassed anhydrous THF (2.50 mL). After complete addition, freeze-thaw degassed aq. 2 M LiOH (2.50 ml) was added to the mixture and stirred at 40 °C for 2 h. Water (10 mL) was added to the mixture and extracted with $Et_2O$ (3 × 10 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (40% $Et_2O$/petrol 40–60) to afford (*E*)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-yl methanesulfonate (**259**) as a colourless oil (225 mg, 0.45 mmol, 64%). $R_f$ = 0.37 (50% $Et_2O$/petrol 40–60); $\delta_H$ (400 MHz, $C_6D_6$) 7.92–7.86 (4H, m, Ar**H**), 7.35–7.30 (6H, m, Ar**H**), 6.10 (1H, d, *J* = 16.0, Hz, CH=C**H**C(=$CH_2$)), 5.59 (1H, s, C=C**H$_2$**), 5.29 (1H, dd, *J* = 16.0, 9.6 Hz, CH(CH)C**H**=CH), 5.19 (1H, s, C=C**H$_2$**), 4.57 (2H, s, C(=$CH_2$)C**H$_2$**OTBDPS), 4.02–3.96 (1H, m, MsOC**H$_2$**$CH_2$), 3.94–3.87 (1H, m, MsOC**H$_2$**$CH_2$), 2.34 (3H, s, $SO_2$C**H$_3$**), 1.91–1.81 (1H, m, $CH_2$C**H**(CH)CH=), 1.71 (1H, dddd, *J* = 13.9, 8.7, 7.0, 3.6 Hz, $OCH_2$C**H$_2$**CH), 1.42–1.30 (1H, m, CHC**H**($CH_3$)$_2$), 1.26 (9H, s, SiC(C**H$_3$**)$_3$), 1.26–1.15 (1H, m, $OCH_2$C**H$_2$**CH), 0.82 (3H, d, *J* = 6.8, Hz, CH(C**H$_3$**)$_2$), 0.75 (3H, d, *J* = 6.8, Hz, CH(C**H$_3$**)$_2$); $\delta_C$ (100 MHz, $C_6D_6$) 144.4 (**C**=$CH_2$), 135.8 (4C, **Ar**), 133.8 (2C, **Ar**), 132.3 (CH=**C**HC(=$CH_2$)), 130.4 (CH(CH)**C**H=CH), 130.1 (2C, **Ar**), 128.5 (4C,**Ar**), 114.3 (C=**C**$H_2$), 68.5 (MsO**C**$H_2CH_2$), 64.2 (C(=$CH_2$)**C**$H_2$OTBDPS), 46.3 ($CH_2$**C**H(CH)CH=), 36.6 ($SO_2$**C**$H_3$), 32.2 (CH**C**H($CH_3$)$_2$), 31.7 ($OCH_2$**C**$H_2CH$), 26.9 (3C, SiC(**C**$H_3$)$_3$), 20.5 (CH(**C**$H_3$)$_2$), 19.5 (Si**C**($CH_3$)$_3$), 19.2 (CH(**C**$H_3$)$_2$); *m*/*z* (ESI$^+$) 501 ([M+H]$^+$ 13%), 523 ([M+Na]$^+$ 100%); HRMS *m*/*z* (ESI$^+$) found 523.2299 $C_{28}H_{40}NaO_4SSi$ requires 523.2309; $\nu_{max}$ (film)/cm$^{-1}$ 2957 (m, CH), 2864 (m), 1889 (w, Ph overtone), 1823 (w, Ph overtone), 1778 (w, Ph overtone), 1604 (w), 1466 (m), 1428 (m), 1354 (s, R-$SO_2$-R), 1259 (w), 1174 (s, R-$SO_2$-R), 1105 (s), 959 (m), 909 (m), 819 (s), 741 (m), 701 (s).

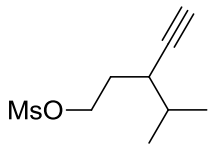
***(E)-Dimethyl 2-(6-(((tert-butyldiphenylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-yl)malonate (226)***




To a stirred suspension of hexane washed NaH (67.7 mg, 2.82 mmol, 3.0 eq.), in anhydrous DMF (2.35 mL) cooled to 0 °C in an ice/water bath, was carefully added dropwise dimethyl malonate (373 mg, 2.82 mmol, 3.0 eq.). The resultant mixture was stirred for 20 min at this temperature, after which a solution of (*E*)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-yl 4-methylbenzenesulfonate (**259**) (542 mg, 0.94 mmol, 1.0 eq.) in anhydrous THF (2.35 mL) was added *via* cannula followed by potassium iodide (78.0 mg, 0.47 mmol, 0.5 eq.). The mixture was warmed to room temperature, and then heated at 80 °C for 18 h. The mixture was cooled to room temperature, after which sat. aq. $NH_4Cl$ solution (5 mL) was added and extracted with $Et_2O$ (3 × 5 mL). The combined organic extracts were sequentially washed with water (15 mL), brine (15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 30–40) to afford (*E*)-dimethyl 2-(6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-yl)malonate (**226**) as a colourless oil (385 mg, 0.71 mmol, 76%). $R_f$ = 0.36 (20% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $C_6D_6$) 7.91 (4H, dd, *J* = 6.0, 2.6 Hz, Ar**H**), 7.35–7.29 (6H, m, Ar**H**), 6.15 (1H, d, *J* = 16.0 Hz, CH=C**H**C(=$CH_2$)), 5.60 (1H, s, C=C$\mathbf{H_2}$), 5.50 (1H, dd, *J* = 16.0, 9.4 Hz, CH(CH)C**H**=CH), 5.21 (1H, s, C=C$\mathbf{H_2}$), 4.62 (2H, s, C(=$CH_2$)C$\mathbf{H_2}$OTBDPS), 3.41 (1H, t, *J* = 7.5 Hz, ($MeO_2C$)$_2$C**H**$CH_2$), 3.40 (3H, s, OC$\mathbf{H_3}$), 3.39 (3H, s, OC$\mathbf{H_3}$), 2.18–1.96 (2H, m, CHC$\mathbf{H_2}CH_2$), 1.82–1.73 (1H, m, $CH_2$C**H**(CH)CH=), 1.57–1.44 (2H, m, CHC**H**($CH_3$)$_2$ and $CH_2$C$\mathbf{H_2}$CH), 1.34–1.25 (1H, m, $CH_2$C$\mathbf{H_2}$CH), 1.29 (9H, s, SiC(C$\mathbf{H_3}$)$_3$), 0.89 (3H, d, *J* = 6.7, Hz, CH(C$\mathbf{H_3}$)$_2$), 0.79 (3H, d, *J* = 6.7, Hz, CH(C$\mathbf{H_3}$)$_2$); $\delta_C$ (100 MHz, $C_6D_6$) 169.6 (**C**=O), 169.5 (**C**=O), 144.6 (**C**=$CH_2$), 135.9 (4C, Ar),

133.9 (2C, Ar), 131.7 (CH(CH)**C**H=CH), 131.6 (CH=**C**HC(=$CH_2$)), 130.0 (2C, Ar), 128.1 (4C, Ar), 113.7 (C=**C**$H_2$), 64.4 (C(=$CH_2$)**C**$H_2$OTBDPS), 51.9 (($MeO_2C)_2$**C**H$CH_2$), 51.8 (2C, O**C**$H_3$), 50.0 ($CH_2$**C**H(CH)CH=), 32.0 (CH**C**H$(CH_3)_2$), 30.2 (CH**C**$H_2CH_2$), 27.4 ($CH_2C$**H$_2$**CH), 26.9 (3C, SiC(**C**$H_3)_3$), 20.8 (CH(**C**$H_3)_2$), 19.5 (Si**C**$(CH_3)_3$), 19.1 (CH(**C**$H_3)_2$); LRMS *m*/*z* ($ESI^+$) 559 ($[M+Na]^+$ 100%); HRMS *m*/*z* ($ESI^+$) found 559.2838, $C_{32}H_{44}NaO_5Si$ requires 559.2850; $\nu_{max}$ (film)/$cm^{-1}$ 2955 (m, CH), 2863 (m, CH), 1966 (w), 1896 (w), 1742 (s, C=O), 1605 (w), 1460 (m), 1436 (m), 1136 (m), 1248 (m), 1152 (m, C-O), 1106 (s), 1009 (m), 970 (m), 898 (m), 820 (s), 747 (m), 701 (s).

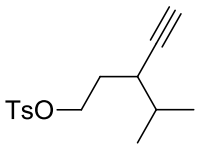
***3-Isopropylpent-4-yn-1-yl methanesulfonate (263)***




To a stirred solution of 3-isopropylpent-4-yn-1-ol (**254**) (631 mg, 5.00 mmol, 1.0 eq.) in anhydrous DCM (17.0 mL) cooled to 0 °C in an ice/water bath was added triethylamine (759 mg, 7.50 mmol, 1.5 eq.) followed by dropwise addition of methanesulfonyl chloride (630 mg, 5.50 mmol, 1.1 eq.). The resulting mixture was warmed to room temperature and stirred for 1.5 h. 1 M HCl (20 mL) was added to the mixture and stirred for 5 min. The organic layer was separated and the aqueous layer was further extracted with DCM (2 × 20 mL). The combined organic layers were successively washed with sat. aq. $NaHCO_3$ solution (60 mL), brine (60 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% $Et_2O$/petrol 30–40) to afford 3-isopropylpent-4-yn-1-yl methanesulfonate (**263**) as a colourless oil (1.00 g, 4.89 mmol, 98%). $R_f$ = 0.26 (50% $Et_2O$/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 4.46–4.35 (2H, m, MsOC**H$_2$**$CH_2$), 3.02 (3H, s, SC**H$_3$**), 2.45 (1H, dtd, *J* = 7.1, 4.6, 2.5 Hz, $CH_2$C**H**(CH)C≡CH), 2.1 (1H, d, *J* = 2.5 Hz, CHC≡C**H**), 1.98–1.88 (1H, m, O$CH_2$C**H$_2$**CH), 1.84–1.66 (2H, m, O$CH_2$C**H$_2$**CH and CHC**H**$(CH_3)_2$), 1.01 (3H, d, *J* = 6.7 Hz, CH(C**H$_3$**$)_2$), 0.98 (3H, d, *J* = 6.7 Hz, CH(C**H$_3$**$)_2$); $\delta_C$ (100 MHz, $CDCl_3$) 83.9 (CH**C**≡CH), 71.7 (CHC≡**C**H), 68.6 (MsO**C**$H_2CH_2$), 37.2 (S**C**$H_3$), 34.7 ($CH_2$**C**H(CH)C≡CH), 31.8 (O$CH_2$**C**$H_2$CH), 31.4

(CH**C**H($CH_3$)$_2$), 20.7 (CH(**C**H$_3$)$_2$), 18.3 (CH(**C**H$_3$)$_2$); LRMS *m*/*z* (ESI$^+$) 227 ([M+Na]$^+$ 100%); HRMS *m*/*z* (ESI$^+$) found 227.0708, $C_9H_{16}NaO_3S$ requires 227.0712; $\nu_{max}$ (film)/cm$^{-1}$ 3287 (m, ≡C-H), 2964 (m, CH), 2883 (m), 2111 (C≡C), 1467 (m), 1347 (s, R-$SO_2$-R), 1173 (s, R-$SO_2$-R), 962 (s), 913 (s), 844 (m), 809 (m), 645 (br, ≡C-H).

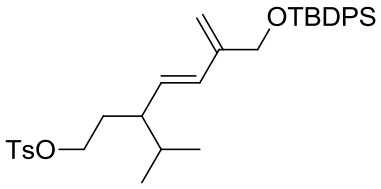
***3-Isopropylpent-4-yn-1-yl 4-methylbenzenesulfonate (264)***




To a stirred solution of 3-isopropylpent-4-yn-1-ol (**254**) (631 mg, 5.00 mmol, 1.0 eq.) in anhydrous DCM (5.0 mL) cooled to 0 °C in an ice/water bath was added pyridine (791 mg, 10.0 mmol, 2.0 eq.) followed by portionwise addition of *p*-toluenesulfonyl chloride (1.43g, 7.50 mmol, 1.5 eq.). After complete addition, the mixture was warmed to room temperature and stirred for 6 h. 1 M HCl (20 mL) was added to the mixture and stirred for 5 min. The organic layer was separated and the aqueous layer was further extracted with DCM (2 × 20 mL). The combined organic layers were washed sequentially with sat. aq. $NaHCO_3$ solution (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (30% $Et_2O$/petrol 30–40) to afford 3-isopropylpent-4-yn-1-yl 4-methylbenzenesulfonate (**264**) as a colourless oil (1.22 g, 4.35 mmol, 87%). $R_f$ = 0.30 (30% $Et_2O$/petrol 30–40); $\delta_H$ (400 MHz, $CDCl_3$) 7.80 (2H, d, *J* = 8.4 Hz, Ar**H**), 7.35 (2H, d, *J* = 8.4 Hz, Ar**H**), 4.27–4.14 (2H, m, TsOC**H**$_2$CH$_2$), 2.45 (3H, s, ArC**H**$_3$), 2.36 (1H, dtd, *J* = 7.1, 4.6, 2.4 Hz, $CH_2$C**H**(CH)C≡CH), 1.97 (1H, d, *J* = 2.4 Hz, CHC≡C**H**), 1.86–1.78 (1H, m, $OCH_2$C**H**$_2$CH), 1.73–1.59 (2H, m, $OCH_2$C**H**$_2$CH and CHC**H**($CH_3$)$_2$), 0.95 (3H, d, *J* = 6.7 Hz, CH(C**H**$_3$)$_2$), 0.92 (3H, d, *J* = 6.7 Hz, CH(C**H**$_3$)$_2$); $\delta_C$ (100 MHz, $CDCl_3$) 144.7 (Ar), 133.0 (Ar), 129.1 (2C, Ar), 127.9 (2C, Ar), 83.9 (CH**C**≡CH), 71.4 (CHC≡**C**H), 68.9 (TsO**C**$H_2CH_2$), 34.6 ($CH_2$**C**H(CH)C≡CH), 31.8 ($OCH_2$**C**$H_2$CH), 31.2 (CH**C**H($CH_3$)$_2$), 21.6 (Ar**C**$H_3$), 20.7 (CH(**C**H$_3$)$_2$), 18.1 (CH(**C**H$_3$)$_2$); LRMS *m*/*z* (ESI$^+$) 281 ([M+H]$^+$, 20%), 303 ([M+Na]$^+$, 95%), 583 ([2M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 303.1015,

$C_{15}H_{20}NaO_3S$ requires 303.1025; $\nu_{max}$ (film)/$cm^{-1}$ 3290 (m, ≡C-H), 2964 (m, CH), 2883 (m), 2112 (C≡C), 1599 (m), 1467 (m), 1357 (s, R-$SO_2$-R), 1177 (s, R-$SO_2$-R), 1095 (m), 984 (s), 909 (s), 814 (m), 777 (m), 660 (br, ≡C-H).

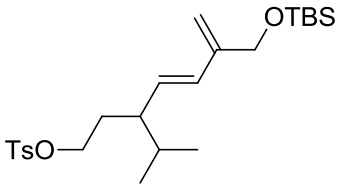
***(E)-6-(((tert-Butyldiphenylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-yl 4-methylbenzenesulfonate (265)***




To a stirred solution of 3-isopropylpent-4-yn-1-yl 4-methylbenzenesulfonate (**264**) (280 mg, 1.00 mmol, 1.1 eq.) in freeze-thaw degassed anhydrous THF (1.00 mL) was added dropwise catecholborane (144 mg, 1.20 mmol, 1.3 eq.). The resulting mixture was heated under reflux (70 °C) for 14 h and cooled to room temperature. The mixture was concentrated under reduced pressure to afford the crude boronate ester as a cloudy oil. Palladium (II) acetate (7.86 mg, 0.03 mmol, 5 mol%) and triphenylphosphine (36.7 mg, 0.12 mmol, 20 mol%) were dissolved in freeze-thaw degassed anhydrous THF (2.50 mL) and stirred at room temperature for 20 min. To the yellow solution was then added dropwise a solution of *tert*-butyl((2-iodoallyl)oxy)diphenylsilane (**252**) (384 mg, 0.91 mmol, 1.0 eq.) and crude boronate ester in freeze-thaw degassed anhydrous THF (2.50 mL). After complete addition, freeze-thaw degassed aq. 2 M LiOH (2.50 ml) was added to the mixture and stirred at 40 °C for 2 h. Water (10 mL) was added to the mixture and extracted with $Et_2O$ (3 × 10 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% $Et_2O$/petrol 40–60) to afford (E)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-yl 4-methylbenzenesulfonate (**265**) as a colourless oil (457 mg, 0.79 mmol, 87%). $R_f$ = 0.28 (20% $Et_2O$/petrol 40–60); $\delta_H$ (400 MHz, $C_6D_6$) 7.90–7.84 (4H, m, Ar**H**), 7.84 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.35–7.30 (6H, m, Ar**H**),

6.89 (2H,d, *J* = 8.2 Hz, Ar**H**), 5.92 (1H, d, *J* = 16.1 Hz, CH=C**H**C(=$CH_2$)), 5.56 (1H, d, *J* = 1.6 Hz, C=C$\mathbf{H_2}$), 5.19 (1H, dd, *J* = 16.1, 9.5 Hz, CH(CH)C**H**=CH), 5.09 (1H, d, *J* = 1.6 Hz, C=C$\mathbf{H_2}$), 4.49 (2H, s, C(=$CH_2$)C$\mathbf{H_2}$OTBDPS), 4.05–3.98 (1H, m, TsOC$\mathbf{H_2}CH_2$), 3.89 (1H, td, *J* = 9.3, 5.5 Hz, TsOC$\mathbf{H_2}CH_2$), 2.03 (3H, s, ArC$\mathbf{H_3}$), 1.87–1.77 (1H, m, $CH_2$C**H**(CH)CH=), 1.72–1.63 (1H, m, $OCH_2$C$\mathbf{H_2}$CH), 1.35–1.24 (1H, m, CHC**H**$(CH_3)_2$), 1.24 (9H, s, SiC(C$\mathbf{H_3}$)$_3$), 1.22–1.07 (1H, m, $OCH_2$C$\mathbf{H_2}$CH), 0.77 (3H, d, *J* = 6.8, Hz, CH(C$\mathbf{H_3}$)$_2$), 0.69 (3H, d, *J* = 6.8, Hz, CH(C$\mathbf{H_3}$)$_2$); $\delta_C$ (100 MHz, $C_6D_6$) 144.3 (Ar), 144.2 (**C**=$CH_2$), 135.8 (4C, Ar), 134.3 (Ar), 133.8 (Ar), 133.7 (Ar), 132.2 (CH=**C**HC(=$CH_2$)), 130.3 (CH(CH)**C**H=CH), 130.1 (Ar), 130.1 (Ar), 129.9 (2C, Ar), 128.2 (2C, Ar), 128.1 (2C, Ar), 128.1 (2C, Ar), 114.0 (C=**C**$H_2$), 69.0 (TsO**C**$H_2CH_2$), 64.1 (C(=$CH_2$)**C**$H_2$OTBDPS), 46.1 ($CH_2$**C**H(CH)CH=), 32.1 (CH**C**H$(CH_3)_2$), 31.5 ($OCH_2$**C**$H_2$CH), 26.9 (3C, SiC(**C**$H_3$)$_3$), 21.2 (Ar**C**$H_3$), 20.5 (CH(**C**$H_3$)$_2$), 19.5 (Si**C**$(CH_3)_3$), 19.1 (CH(**C**$H_3$)$_2$); *m/z* (ESI$^+$) 599 ([M+Na]$^+$ 100%); HRMS *m/z* (ESI$^+$) found 599.2618 $C_{34}H_{44}NaO_4SSi$ requires 599.2622; $\nu_{max}$ (film)/cm$^{-1}$ 3061 (w, =$CH_2$), 2957 (m, CH), 2863 (m, CH), 1901 (w, Ph overtone), 1815 (w, Ph overtone), , 1600 (w, C=C), 1464 (m), 1431 (m), 1359 (s, R-$SO_2$-R), 1179 (s, R-$SO_2$-R), 1103 (s, SiO), 959 (m, C=$CH_2$), 909 (m, C=$CH_2$).

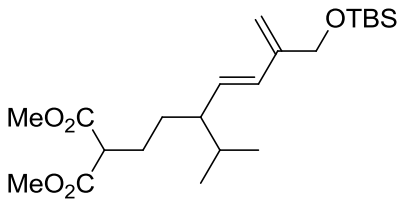
***(E)-6-(((tert-Butyldimethylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-yl 4-methylbenzenesulfonate (266)***




To a stirred solution of 3-isopropylpent-4-yn-1-yl 4-methylbenzenesulfonate (**264**) (280 mg, 1.00 mmol, 1.1 eq.) in freeze-thaw degassed anhydrous THF (1.00 mL) was added dropwise catecholborane (144 mg, 1.20 mmol, 1.3 eq.). The resulting mixture was heated under reflux (70 °C) for 14 h and cooled to room temperature. The mixture was concentrated under reduced pressure to afford the crude boronate ester as a cloudy oil. Palladium(II) acetate (7.86 mg,

0.03 mmol, 5 mol%) and triphenylphosphine (36.7 mg, 0.12 mmol, 20 mol%) were dissolved in freeze-thaw degassed anhydrous THF (2.50 mL) and stirred at room temperature for 20 min. To the yellow solution was then added dropwise a solution of *tert*-butyl((2-iodoallyl)oxy)dimethylsilane (**251**) (271 mg, 0.91 mmol, 1.0 eq.) and crude boronate ester in freeze-thaw degassed anhydrous THF (2.50 mL). After complete addition, freeze-thaw degassed aq. 2 M LiOH (2.50 ml) was added to the mixture and stirred at 40 °C for 2 h. Water (10 mL) was added to the mixture and extracted with $Et_2O$ (3 × 10 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (15% $Et_2O$/petrol 30–40) to afford (*E*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-yl 4-methylbenzenesulfonate (**266**) as a colourless oil (292 mg, 0.65 mmol, 71%). $R_f$ = 0.34 (20% $Et_2O$/petrol 40–60); $\delta_H$ (400 MHz, $C_6D_6$) 7.87 (2H, d, *J* = 8.0 Hz, Ar**H**), 6.83 (2H, d, *J* = 8.0 Hz, Ar**H**), 5.95 (1H, d, *J* = 16.0 Hz, CH=C**H**C(=$CH_2$)), 5.40 (1H, s, C=C**H$_2$**), 5.39 (1H, dd, *J* = 16.0, 9.6 Hz, CH(CH)C**H**=CH), 5.04 (1H, s, C=C**H$_2$**), 4.37 (2H, d, *J* = 2.6 Hz, C(=$CH_2$)C**H$_2$**OTBS), 4.12–4.05 (1H, m, TsOC**H$_2$**$CH_2$), 3.96 (1H, td, *J* = 9.3, 5.7 Hz, TsOC**H$_2$**$CH_2$), 1.97 (3H, s, ArC**H$_3$**), 1.94–1.84 (1H, m, $CH_2$C**H**(CH)CH=), 1.80–1.69 (1H, m, $OCH_2$C**H$_2$**CH), 1.41 (1H, oct, *J* = 6.8, Hz, CHC**H**($CH_3$)$_2$), 1.36–1.25 (1H, m, $OCH_2$C**H$_2$**CH), 1.08 (9H, s, SiC(C**H$_3$**)$_3$), 0.84 (3H, d, *J* = 6.8, Hz, CH(C**H$_3$**)$_2$), 0.79 (3H, d, *J* = 6.8, Hz, CHC**H**($CH_3$)$_2$), 0.16 (6H, s, SiC**H$_3$**); $\delta_C$ (100 MHz, $C_6D_6$) 144.8 (**C**=$CH_2$), 144.0 (**Ar**), 134.6 (**Ar**), 132.3 (CH=**C**HC(=$CH_2$)), 130.3 (CH(CH)**C**H=CH), 129.8 (4C, **Ar**), 128.1 (4C, **Ar**), 113.8 (C=**C**$H_2$), 68.9 (TsO**C**$H_2CH_2$), 63.5 (C(=$CH_2$)**C**$H_2$OTBS), 46.1 ($CH_2$**C**H(CH)CH=), 32.2 (CH**C**H($CH_3$)$_2$), 31.7 ($OCH_2$**C**$H_2$CH), 26.0 (3C, SiC(**C**$H_3$)$_3$), 21.1 (Ar**C**$H_3$), 20.5 (CH(**C**$H_3$)$_2$), 18.9 (CH(**C**$H_3$)$_2$), 18.4 (Si**C**($CH_3$)$_3$), -5.3 (2C, Si**C**$H_3$); *m*/*z* (ESI$^+$) 475 ([M+Na]$^+$ 97%), 927 ([2M+Na]$^+$ 100%); HRMS *m*/*z* (ESI$^+$) found 475.2298, $C_{24}H_{40}NaO_4SSi$ requires 475.2309; $\nu_{max}$ (film)/cm$^{-1}$ 2957 (m, CH), 2931 (m), 2857 (m), 1599 (m), 1497 (w), 1467 (m), 1386 (m), 1363 (s, R-$SO_2$-R), 1306 (w), 1292 (w), 1254 (m), 1176 (s, R-$SO_2$-R), 1099 (s, Si-O), 1010 (m), 968 (m), 911 (m).

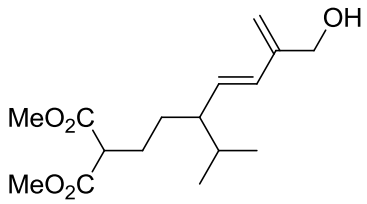
***(E)-Dimethyl 2-(6-(((tert-butyldimethylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-yl)malonate (267)***




To a stirred suspension of hexane washed NaH (17.5 mg, 0.729 mmol, 3.0 eq.), in anhydrous DMF (0.63 mL) cooled to 0 °C in an ice/water bath, was carefully added dropwise dimethyl malonate (96.4 mg, 0.729 mmol, 3.0 eq.). The resultant mixture was stirred for 20 min at this temperature, after which a solution of (*E*)-6-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-yl 4-methylbenzenesulfonate (**266**) (110 mg, 0.24 mmol, 1.0 eq.) in anhydrous THF (0.63 mL) was added *via* cannula followed by potassium iodide (21.6 mg, 0.12 mmol, 0.5 eq.). The mixture was warmed to room temperature, and then heated at 80 °C for 18 h. The mixture was cooled to room temperature, after which sat. aq. $NH_4Cl$ solution (3 mL) was added and extracted with $Et_2O$ (3 × 3 mL). The combined organic extracts were sequentially washed with water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% $Et_2O$/petrol 30–40) to afford (*E*)-dimethyl 2-(6-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-yl)malonate (**267**) as a colourless oil (86.1 mg, 0.21 mmol, 87%). $R_f$ = 0.29 (20% $Et_2O$/petrol 40–60); $\delta_H$ (400 MHz, $C_6D_6$) 6.16 (1H, d, *J* = 16.0 Hz, CH=C**H**C(=$CH_2$)), 5.66 (1H, dd, *J* = 16.0, 9.4 Hz, CH(CH)C**H**=CH), 5.43 (1H, s, C=C$\mathbf{H_2}$), 5.14 (1H, s, C=C$\mathbf{H_2}$), 4.47 (2H, s, C(=$CH_2$)C$\mathbf{H_2}$OTBS), 3.46 (1H, t, *J* = 7.4 Hz, ($MeO_2C$)$_2$C**H**$CH_2$), 3.41 (6H, s, OC$\mathbf{H_3}$), 2.26–2.00 (2H, m, CHC$\mathbf{H_2}CH_2$), 1.89–1.80 (1H, m, $CH_2$C**H**(CH)CH=), 1.65–1.50 (2H, m, CHC**H**($CH_3$)$_2$ and $CH_2$C$\mathbf{H_2}$CH), 1.47–1.35 (1H, m, $CH_2$C$\mathbf{H_2}$CH), 1.09 (9H, s, SiC(C$\mathbf{H_3}$)$_3$), 0.95 (3H, d, *J* = 6.7, Hz, CH(C$\mathbf{H_3}$)$_2$), 0.91 (3H, d, *J* = 6.7, Hz, CH(C$\mathbf{H_3}$)$_2$), 0.16 (6H, s, Si(C$\mathbf{H_3}$)); $\delta_C$ (100 MHz, $C_6D_6$) 169.6 (**C**=O), 169.5 (**C**=O), 145.1 (**C**=$CH_2$), 131.7 (CH(CH)**C**H=CH), 131.7 (CH=**C**HC(=$CH_2$)), 113.6 (C=**C**$H_2$), 63.7

(C**C**$H_2$OTBS), 52.0 (($MeO_2C)_2$**C**$HCH_2$), 51.8 (2C, O**C**$H_3$), 50.0 ($CH_2$**C**H(CH)CH=), 32.2 (CH**C**H$(CH_3)_2$), 30.4 (CH**C**$H_2CH_2$), 27.5 ($CH_2$**C**$H_2$CH), 26.0 (3C, SiC(**C**$H_3)_3$), 20.9 (CH(**C**$H_3)_2$), 19.0 (CH(**C**$H_3)_2$), 18.4 (Si**C**$(CH_3)_3$), -5.3 (2C, Si**C**$H_3$); LRMS *m*/*z* ($ESI^+$) 435 ($[M+Na]^+$ 100%); HRMS *m*/*z* ($ESI^+$) found 435.2522 $C_{22}H_{40}NaO_5Si$ requires 435.2537; $\nu_{max}$ (film)/$cm^{-1}$ 2955 (m, CH), 2930 (m), 2858 (m), 2280 (m), 1756 (s), 1738 (s, C=O), 1618 (w), 1455 (m), 1435 (m), 1387 (w), 1361 (w), 1330 (m), 1253 (m), 1154 (m, C-O), 1109 (m), 1083 (m), 1009 (w), 970 (m), 939 (w), 897 (m), 837 (s), 812 (s), 77 (s), 669 (m).

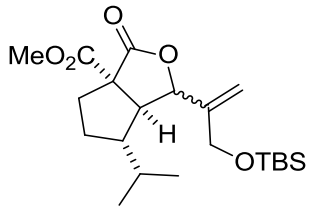
***(E)-Dimethyl 2-(6-(hydroxymethyl)-3-isopropylhepta-4,6-dien-1-yl)malonate (268)***




To a stirred solution of (*E*)-dimethyl 2-(6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-yl)malonate (**226**) (320 mg, 0.59 mmol, 1.0 eq.) in anhydrous THF (1.50 mL) cooled to 0 °C in an ice/water bath was a added dropwise a 1 M solution of TBAF in THF (0.72 mL, 0.72 mmol, 1.2 eq.). After complete addition, the mixture was warmed to room temperature and stirred for 1.5 h. Sat. aq. $NH_4Cl$ solution (3 mL) was added to the mixture and extracted with $Et_2O$ (3 × 3 mL). The combined organic extracts were sequentially washed with 1 M HCl (10 mL), water (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (40% EtOAc/petrol 30-40) to afford (*E*)-dimethyl 2-(6-(hydroxymethyl)-3-isopropylhepta-4,6-dien-1-yl)malonate (**268**) as a colourless oil (164 mg, 0.55 mmol, 92%). $R_f$ = 0.35 (40% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $C_6D_6$) 6.10 (1H, d, *J* = 16.0 Hz, CH=C**H**C(=$CH_2$)), 5.56 (1H, dd, *J* = 16.0, 9.4 Hz, CH(CH)C**H**=CH), 5.28 (1H, s, C=C**H$_2$**), 5.08 (1H, s, C=C**H$_2$**), 4.22 (2H, s, C(=$CH_2$)C**H$_2$**OH), 3.46 (1H, t, *J* = 7.4 Hz, ($MeO_2C)_2$C**H**$CH_2$), 3.42 (3H, s, OC**H$_3$**), 3.41 (3H, s, OC**H$_3$**), 2.23–1.96 (2H, m, CHC**H$_2$**$CH_2$), 1.85–1.76 (1H, m, $CH_2$C**H**(CH)CH=), 1.61–1.50 (2H, m, CHC**H**$(CH_3)_2$ and $CH_2$C**H$_2$**CH), 1.48

(1H, s, $CH_2O\mathbf{H}$), 1.43–1.31 (1H, m, $CH_2C\mathbf{H_2}CH$), 0.92 (3H, d, $J$ = 6.7, Hz, $CH(C\mathbf{H_3})_2$), 0.88 (3H, d, $J$ = 6.7, Hz, $CH(C\mathbf{H_3})_2$); $\delta_C$ (100 MHz, $C_6D_6$) 169.7 (**C**=O), 169.7 (**C**=O), 145.6 (**C**=$CH_2$), 132.0 (CH(CH)**C**H=CH), 131.6 (CH=**C**HC(=$CH_2$)), 113.3 (C=**C**$H_2$), 63.0 (C(=$CH_2$)**C**$H_2$OH), 52.0 ($(MeO_2C)_2\mathbf{C}HCH_2$), 51.9 (2C, O**C**$H_3$), 50.0 ($CH_2\mathbf{C}H(CH)CH=$), 32.2 (CH**C**$H(CH_3)_2$), 30.3 (CH**C**$H_2CH_2$), 27.4 ($CH_2\mathbf{C}H_2CH$), 20.8 ($CH(\mathbf{C}H_3)_2$), 19.1 ($CH(\mathbf{C}H_3)_2$); LRMS $m/z$ ($ESI^+$) 305 ($[M+Li]^+$ 97%), 321 ($[M+Na]^+$ 40%), 571 (100%), 603 ($[2M+Li]^+$ 55%); HRMS $m/z$ ($ESI^+$) found 321.1671, $C_{16}H_{26}NaO_5$ requires 321.1672; $\nu_{max}$ (film)/$cm^{-1}$ 3234 (w, OH), 2956 (m, CH), 2871 (m), 2280 (s), 1755 (s, C=O), 1737 (s, C=O), 1618 (m), 1454 (m), 1435 (m), 1387 (w), 1330 (s), 1219 (m), 1157 (m), 1059 (m, C-O), 1025 (m), 970 (m),897 (m), 812 (s), 665 (w).

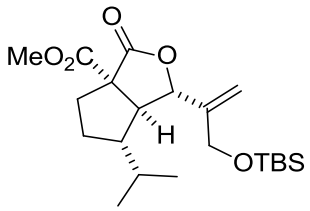
***(3aR*,6S*,6aS*)-Methyl 1-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-2-yl)-6-isopropyl-3-oxohexahydro-1H-cyclopenta[c]furan-3a-carboxylate (166a)***




A mixture of manganese(III) acetate (84.5 mg, 0.32 mmol, 2.0 eq.) and copper(II) triflate (56.8 mg, 0.16 mmol, 1.0 eq.) were pre heated to 80 °C, after which a solution of (*E*)-dimethyl 2-(6-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-yl)malonate (**267**) (64.8 mg, 0.16 mmol, 1.0 eq.) in nitrogen sparged acetonitrile (0.79 mL, 0.2 M) was rapidly added *via* cannula. The resulting mixture was heated at 80 °C for 1 h, after which water (2 mL) and $Et_2O$ (2 mL) were added and stirred for 30 min. The organic layer was separated and the aqueous layer was further extracted with $Et_2O$ (2 × 2 mL). The combined organic layers were sequentially washed with sat. aq. $NaHCO_3$ solution (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% $Et_2O$/petrol 30–40) to afford (3a*R**,6*S**,6a*S**)-methyl 1-(3-((*tert*-butyldimethylsilyl)oxy)prop-1-en-2-yl)-6-isopropyl-3-oxohexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate (**166a**) (diastereomeric ratio = 6:1)

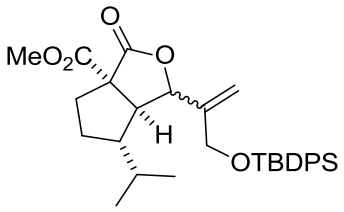
as a colourless oil (30.0 mg, 0.08 mmol, 47%). Characterisation is reported for the major epimer of an inseparable mixture of diastereoisomers.

***(1S*,3aR*,6S*,6aS*)-Methyl 1-(3-((tert-butyldimethylsilyl)oxy)prop-1-en-2-yl)-6-isopropyl-3-oxohexahydro-1H-cyclopenta[c]furan-3a-carboxylate***



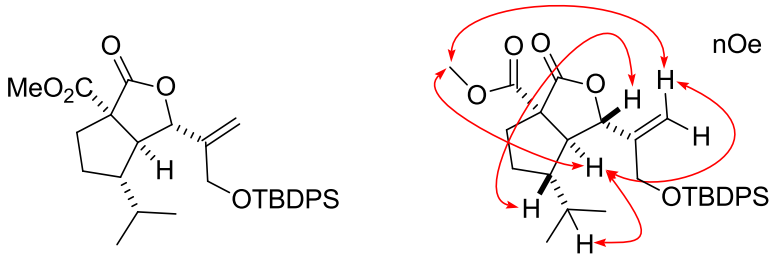

Major Epimer. $R_f$ = 0.21 (10% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 5.25 (1H, d, $J$ = 0.8 Hz, C=C**H**$_2$), 5.17 (1H, d, $J$ = 0.8 Hz, C=C**H**$_2$), 4.76 (1H, d, $J$ = 3.5 Hz, CHC**H**(C=)O), 4.29–4.16 (2H, m, C(=$CH_2$)C**H**$_2$OTBS), 3.73 (3H, s, OC**H**$_3$), 2.98–2.94 (1H, m, CHC**H**CHO), 2.52–2.44 (1H, m, $CH_2$C**H**$_2$CC(=O)), 2.17–2.08 (1H, m, $CH_2$C**H**$_2$CC(=O)), 1.90–1.81 (1H, m, $CH_2$C**H**$_2$CH), 1.79–1.66 (2H, m, $CH_2$C**H**$_2$CH and $CH_2$C**H**(CH)CH), 1.66–1.55 (1H, m, CHC**H**$(CH_3)_2$), 0.93 (3H, d, $J$ = 6.8 Hz, CH(C**H**$_3)_2$), 0.91 (9H, s, SiC(C**H**$_3)_3$), 0.90 (3H, d, $J$ = 6.8 Hz, CH(C**H**$_3)_2$), 0.08 (6H, s, SiC**H**$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 175.7 (**C**=O), 171.1 (**C**$O_2$Me), 145.3 (**C**=$CH_2$), 111.8 (C=**C**$H_2$), 84.5 (CH**C**H(C=)O), 62.7 (C(=$CH_2$)**C**$H_2$OTBS), 61.6 ($CH_2$**C**($CO_2$Me)C), 54.7 ($CH_2$**C**H(CH)CH), 54.1 (CH**C**HCHO), 53.0 (O**C**$H_3$), 34.3 ($CH_2$**C**$H_2$CC(=O)), 30.3 (CH**C**H$(CH_3)_2$), 29.6 ($CH_2$**C**$H_2$CH), 25.8 (3C, SiC(**C**$H_3)_3$), 21.7 (CH(**C**$H_3)_2$), 19.9 (CH(**C**$H_3)_2$), 18.3 (Si**C**$(CH_3)_3$), -5.4 (Si**C**$H_3$), -5.5 (Si**C**$H_3$); LRMS $m/z$ (ESI$^+$) 419 ([M+Na]$^+$, 60%), 556 (100%), 815 ([2M+Na]$^+$, 31%); HRMS $m/z$ (ESI$^+$) found 419.2224, $C_{21}H_{36}NaO_5Si$ requires 419.2224; $\nu_{max}$ (film)/cm$^{-1}$ 2957 (m, CH), 2858 (m, CH), 1773 (s, C=O), 1736 (s, C=O), 1254 (m, C-O), 1109 (s, Si-O-C), 905 (s, C=$CH_2$), 837 (m, Si-O-C).

***(3aR*,6S*,6aS*)-Methyl 1-(3-((tert-butyldiphenylsilyl)oxy)prop-1-en-2-yl)-6-isopropyl-3-oxohexahydro-1H-cyclopenta[c]furan-3a-carboxylate (166b)***



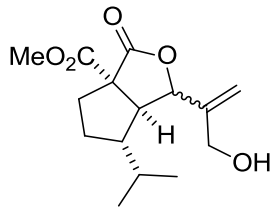

A mixture of manganese(III) acetate (219 mg, 0.86 mmol, 2.0 eq.) and copper(II) triflate (148 mg, 0.43 mmol, 1.0 eq.) were pre heated to 80 °C, after which a solution of (*E*)-dimethyl 2-(6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-yl)malonate (**226**) (231 mg, 0.43 mmol, 1.0 eq.) in nitrogen sparged acetonitrile (2.15 mL, 0.2 M) was rapidly added *via* cannula. The resulting mixture was heated at 80 °C for 1 h, after which water (3 mL) and $Et_2O$ (3 mL) were added and stirred for 30 min. The organic layer was separated and the aqueous layer was further extracted with $Et_2O$ (2 × 3 mL). The combined organic layers were sequentially washed with sat. aq. $NaHCO_3$ solution (10 mL), brine (10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60) to afford (3*aR*,6S*,6aS**)-methyl 1-(3-((*tert*-butyldiphenylsilyl)oxy)prop-1-en-2-yl)-6-isopropyl-3-oxohexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate (**166b**) (diastereomeric ratio = 6:1) as a colourless oil (176 mg, 0.34 mmol, 79%). Characterisation is reported for the major epimer of an inseparable mixture of diastereoisomers.

***(1S*,3aR*,6S*,6aS*)-Methyl 1-(3-((tert-butyldiphenylsilyl)oxy)prop-1-en-2-yl)-6-isopropyl-3-oxohexahydro-1H-cyclopenta[c]furan-3a-carboxylate***



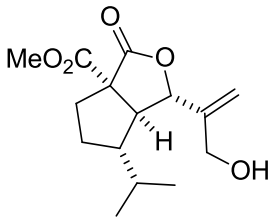

Major Epimer: $R_f$ = 0.21 (10% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 7.70–7.65 (4H, m, Ar**H**), 7.47–7.37 (6H, m, Ar**H**), 5.38 (1H, d, *J* = 0.8 Hz, C=C**H**$_2$), 5.24 (1H, d, *J* = 0.8 Hz, C=C**H**$_2$), 4.76 (1H, d, *J* = 3.7 Hz, CHC**H**(C=)O), 4.26 (2H, s, C(=CH$_2$)C**H**$_2$OTBDPS), 3.55 (3H, s, OC**H**$_3$), 2.84 (1H, dd, *J* = 5.3, 3.7 Hz, CHC**H**CHO), 2.48 (1H, dt, *J* = 13.0, 6.5 Hz, CH$_2$C**H**$_2$CC(=O)), 2.14–2.05 (1H, m, CH$_2$C**H**$_2$CC(=O)), 1.90–1.79 (1H, m, CH$_2$C**H**$_2$CH), 1.76–1.65 (2H, m, CH$_2$C**H**$_2$CH and CH$_2$C**H**(CH)CH), 1.55 (1H, dsept, *J* = 6.8, 6.8 Hz, CHC**H**(CH$_3$)$_2$), 1.08 (9H, s, SiC(C**H**$_3$)$_3$), 0.88 (3H, d, *J* = 6.8 Hz, CH(C**H**$_3$)$_2$), 0.86 (3H, d, *J* = 6.8 Hz, CH(C**H**$_3$)$_2$); $\delta_C$ (100 MHz, $CDCl_3$) 175.6 (**C**=O), 171.0 (**C**O$_2$Me), 144.9 (**C**=CH$_2$), 135.5 (2C, Ar), 135.4 (2C, Ar), 133.2 (Ar), 133.0 (Ar), 129.8 (2C, Ar), 127.8 (4C, Ar), 112.1 (C=**C**H$_2$), 84.7 (CH**C**H(C=)O), 63.2 (C(=CH$_2$)**C**H$_2$OTBDPS), 61.6 (CH$_2$**C**(CO$_2$Me)C), 55.0 (CH$_2$**C**H(CH)CH), 54.3 (CH**C**HCHO), 52.8 (O**C**H$_3$), 34.2 (CH$_2$**C**H$_2$CC(=O)), 30.3 (CH**C**H(CH$_3$)$_2$), 29.6 (CH$_2$**C**H$_2$CH), 26.7 (3C, SiC(**C**H$_3$)$_3$), 21.7 (CH(**C**H$_3$)$_2$), 19.9 (CH(**C**H$_3$)$_2$), 19.2 (Si**C**(CH$_3$)$_3$); LRMS *m*/*z* (ESI$^+$) 543 ([M+Na]$^+$, 50%), 580 (100%); HRMS *m*/*z* (ESI$^+$) found 543.2528, $C_{31}H_{40}NaO_5Si$ requires 543.2537; $\nu_{max}$ (film)/cm$^{-1}$ 3073 (w, =CH$_2$), 2959 (m, CH), 2932 (m, CH), 2859 (m, CH), 1776 (s, C=O), 1739 (s, C=O), 1239 (m, C-O), 1111 (s, Si-O-C), 907 (s, C=CH$_2$), 823 (m, Si-O-C).

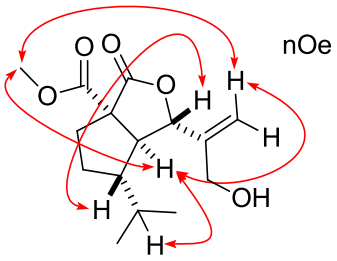
***(3aR*,6S*,6aS*)-Methyl 1-(3-hydroxyprop-1-en-2-yl)-6-isopropyl-3-oxohexahydro-1H-cyclopenta[c]furan-3a-carboxylate (166c)***




A mixture of manganese(III) acetate (177 mg, 0.65 mmol, 2.0 eq.) and copper(II) trifilate (119 mg, 0.33 mmol, 1.0 eq.) were pre heated to 80 °C, after which a solution of (*E*)-dimethyl 2-(6-(hydroxymethyl)-3-isopropylhepta-4,6-dien-1-yl)malonate (**268**) (97.0 mg, 0.33 mmol, 1.0 eq.) in nitrogen sparged acetonitrile (1.65 mL) was rapidly added *via* cannula. The resulting mixture was heated at 80 °C for 1 h. The mixture was cooled to room temperature, after which water (2 mL) and $Et_2O$ (2 mL) were added and stirred for 30 min. The organic layer was separated and the aqueous layer was further extracted with $Et_2O$ (2 × 3 mL). The combined organic layers were sequentially washed with brine (300 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (40% EtOAc/petrol 40–60) to afford (3a*R**,6*S**,6a*S**)-methyl 1-(3-hydroxyprop-1-en-2-yl)-6-isopropyl-3-oxohexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate (**166c**) (diastereomeric ratio = 9:1) as a colourless oil (66.0 mg, 0.24 mmol, 73%). Characterisation is reported for the major epimer of an inseparable mixture of diastereoisomers.

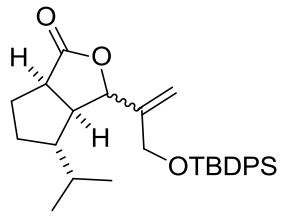
***(1S*,3aR*,6S*,6aS*)-Methyl 1-(3-hydroxyprop-1-en-2-yl)-6-isopropyl-3-oxohexahydro-1H-cyclopenta[c]furan-3a-carboxylate***



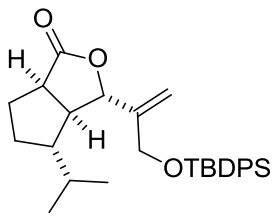

Major Epimer: $R_f$ = 0.26 (40% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 5.29 (1H, d, *J* = 1.2 Hz, C=C**H**$_2$), 5.24 (1H, d, *J* = 1.2 Hz, C=C**H**$_2$), 4.79 (1H, d, *J* = 4.8 Hz, CHC**H**(C=)O), 4.26 (2H, d, *J* = 4.3 Hz, C(=$CH_2$)C**H**$_2$OH), 3.76 (3H, s, OC**H**$_3$), 3.03 (1H, dd, *J* = 5.7, 3.8 Hz, CHC**H**CHO), 2.53–2.45 (1H, m, $CH_2$C**H**$_2$CC(=O)), 2.19–2.10 (2H, m, $CH_2$C**H**$_2$CC(=O) and $CH_2$O**H**), 1.91–1.83 (1H, m, $CH_2$C**H**$_2$CH), 1.81–1.72 (1H, m, $CH_2$C**H**(CH)CH), 1.72–1.64 (1H, m, $CH_2$C**H**$_2$CH), 1.64–1.56 (1H, m, CHC**H**($CH_3$)$_2$), 0.95 (3H, d, *J* = 6.7 Hz, CH(C**H**$_3$)$_2$), 0.92 (3H, d, *J* = 6.7 Hz, CH(C**H**$_3$)$_2$); $\delta_C$ (100 MHz, $CDCl_3$) 175.7 (**C**=O), 171.2 (**C**$O_2$Me), 145.5 (**C**=$CH_2$), 113.5 (C=C**H**$_2$), 84.9 (CH**C**H(C=)O), 62.6 (C(=$CH_2$)**C**$H_2$OH), 54.9 ($CH_2$**C**H(CH)CH), 54.1 (CH**C**HCHO), 53.1 (O**C**$H_3$), 34.4($CH_2$**C**$H_2$CC(=O)), 30.3 (CH**C**H($CH_3$)$_2$), 29.6 ($CH_2$**C**$H_2$CH), 21.6 (CH(**C**$H_3$)$_2$)), 19.9 (CH(**C**$H_3$)$_2$)); LRMS *m*/*z* ($ESI^+$) 305 ($[M+Na]^+$, 100%), 587 ($[2M+Na]^+$, 90%); HRMS *m*/*z* ($ESI^+$) found 282.12466, $C_{15}H_{22}NaO_5$ requires 282.1467; $\nu_{max}$ (film)/$cm^{-1}$ 3501 (br, OH), 2959 (m, CH), 2874 (m, CH), 1771 (C=O), 1736 (C=O), 1236 (s, C-O), 915 (s, C=$CH_2$).

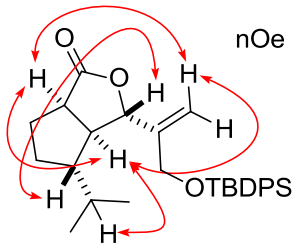
***(3aS*,4S*,6aR*)-3-(3-((tert-Butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropylhexahydro-1H-cyclopenta[c]furan-1-one (269)***




To a stirred solution of (3a*R**,6*S**,6a*S**)-methyl 1-(3-((*tert*-butyldiphenylsilyl)oxy)prop-1-en-2-yl)-6-isopropyl-3-oxohexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate (**166b**) (103 mg, 0.20 mmol, 1.0 eq.) in dry DMF (2.00 mL) was added water (7.20 mg, 0.40 mmol, 2.0 eq.) and lithium chloride (16.7 mg, 0.40 mmol, 2.0 eq.). The resulting mixture was heated at 150 °C for 6 h and cooled to room temperature. Sat. aq. $NH_4Cl$ solution (2 mL) was added and extracted with $Et_2O$ (3 × 2 mL). The combined organic extracts were sequentially washed with water (10 mL), brine (10 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40–60) to afford (3a*S**,4*S**,6a*R**)-3-(3-((*tert*-butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropylhexahydro-1*H*-cyclopenta[*c*]furan-1-one (**269**) (diastereomeric ratio = 6:1) as a colourless oil (80.0 mg, 0.17 mmol, 86%). Characterisation is reported for the major and minor epimer as separated by flash column chromatography.

***(3S*,3aS*,4S*,6aR*)-3-(3-((tert-Butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropylhexahydro-1H-cyclopenta[c]furan-1-one***

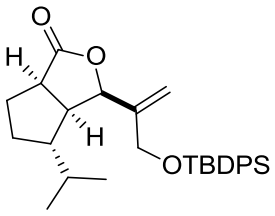


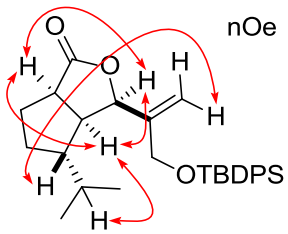




Major Epimer: $R_f$ = 0.23 (10% EtOAc/petrol 40–60); $\delta_H$ (500 MHz, $CDCl_3$) 7.69–7.65 (4H, m, Ar**H**), 7.47–7.42 (2H, m, Ar**H**), 7.42–7.37 (4H, m, Ar**H**), 5.28 (1H, s, C=C**H**$_2$), 5.16 (1H, s,

C=C**H**$_2$), 4.77 (1H, d, *J* = 2.6 Hz, CHC**H**(C=)O), 4.24 (1H, d, *J* = 13.9 Hz, C(=CH$_2$)C**H**$_2$OTBDPS), 4.18 (1H, d, *J* = 13.9 Hz, C(=CH$_2$)C**H**$_2$OTBDPS), 2.98 (1H, dt, *J* = 9.6, 4.9 Hz, CH$_2$C**H**C=O), 2.46 (1H, ddd, *J* = 9.6, 7.2, 2.6 Hz, CHC**H**CHO), 2.11–2.03 (1H, m, CH$_2$C**H**$_2$CHC=O), 1.93–1.86 (1H, m, CH$_2$C**H**$_2$CHC=O), 1.86–1.78 (1H, m, Hz, CH$_2$C**H**$_2$CH(*i*-Pr)), 1.66–1.59 (1H, m, CH$_2$C**H**(*i*-Pr)CH), 1.55 (1H, dsept, *J* = 6.7, 6.7 Hz, CHC**H**(CH$_3$)$_2$), 1.47–1.39 (1H, m, CH$_2$C**H**$_2$CH(*i*-Pr)), 1.07 (9H, s, SiC(C**H**$_3$)$_3$), 0.91 (3H, d, *J* = 6.7, Hz, CH(C**H**$_3$)$_2$), 0.86 (3H, d, *J* = 6.7, Hz, CH(C**H**$_3$)$_2$); $\delta_C$ (125 MHz, $CDCl_3$) 180.6 (**C**=O), 145.8 (**C**=CH$_2$), 135.5 (2C, Ar), 135.4 (2C, Ar), 134.8 (Ar), 133.1 (Ar), 132.9 (Ar), 129.8 (Ar), 127.7 (2C, Ar), 127.7 (2C, Ar), 111.7 (C=**C**H$_2$), 84.5 (CH**C**H(C=)O), 63.5 (C(=CH$_2$)**C**H$_2$OTBDPS), 53.4 (CH$_2$**C**H(*i*-Pr)CH), 49.1 (CH**C**HCHO), 44.4 (CH$_2$**C**HC=O), 30.9 (CH**C**H(CH$_3$)$_2$), 29.6 (CH$_2$**C**H$_2$CH(*i*-Pr)), 28.3 (**C**H$_2$CHC=O), 26.7 (3C, SiC(**C**H$_3$)$_3$), 21.7 (CH(**C**H$_3$)$_2$), 19.9 (CH(**C**H$_3$)$_2$), 19.2 (Si**C**(CH$_3$)$_3$); LRMS *m*/*z* (ESI$^+$) 331 (100%), 485 ([M+Na]$^+$, 80%), 947 ([2M+Na]$^+$, 65%); HRMS *m*/*z* (ESI$^+$) found 485.2485 $C_{29}H_{38}NaO_3Si$ requires 485.2482; $\nu_{max}$ (film)/cm$^{-1}$ 3071 (w, =CH$_2$), 2958 (m, CH), 2931 (m, CH), 2858 (m, CH), 1772 (s, C=O), 1257 (m, C-O), 1111 (s, Si-O-C), 915 (m, C=CH$_2$).

***(3R*,3aS*,4S*,6aR*)-3-(3-((tert-Butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropylhexahydro-1H-cyclopenta[c]furan-1-one***

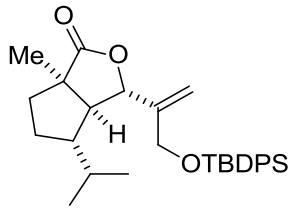



Minor Epimer: $R_f$ = 0.16 (10% EtOAc/petrol 40–60); $\delta_H$ (500 MHz, $CDCl_3$) 7.70–7.64 (4H, m, Ar**H**), 7.48–7.43 (2H, m, Ar**H**), 7.42–7.38 (4H, m, Ar**H**), 5.39 (1H, s, C=C**H**$_2$), 5.29 (1H, s, C=C**H**$_2$), 5.09 (1H, d, *J* = 6.4 Hz, CHCHC**H**O), 4.16 (1H, d, *J* = 13.8 Hz, CC**H**$_2$OTBDPS), 4.10 (1H, d, *J* = 13.8 Hz, CC**H**$_2$OTBDPS), 3.09 (1H, ddd, *J* = 8.6, 8.6, 2.2 Hz, CH$_2$C**H**C=O), 2.56 (1H, ddd, *J* = 8.2, 6.4, 2.2 Hz, CHC**H**CHO), 2.07–2.00 (1H, m, CH$_2$C**H**$_2$CHC(=O)), 1.90–1.80 (1H, m,

$CH_2C\mathbf{H_2}CHC(=O)$), 1.78–1.71 (1H, m, $CH_2C\mathbf{H}(i\text{-Pr})CH$), 1.57–1.36 (3H, m, $CH_2C\mathbf{H_2}CH(i\text{-Pr})$ & $CHC\mathbf{H}(CH_3)_2$), 1.08 (9H, s, $SiC(C\mathbf{H_3})_3$), 0.76 (3H, d, $J$ = 6.8, Hz, $CH(C\mathbf{H_3})_2$), 0.69 (3H, d, $J$ = 6.8, Hz, $CH(C\mathbf{H_3})_2$); $\delta_C$ (125 MHz, $CDCl_3$) 180.3 (**C**=O), 142.7 (**C**=$CH_2$), 135.5 (2C, Ar), 135.5 (2C, Ar), 133.1 (Ar), 132.9 (Ar), 129.9 (2C, Ar), 127.8 (2C, Ar), 127.8 (2C, Ar), 110.8 (C=**C**$H_2$), 80.0 (CHCH**C**HO), 64.2 (C**C**$H_2$OTBDPS), 47.5 ($CH_2$**C**HC=O), 46.5 ($CH_2$**C**H($i$-Pr)CH), 45.3 (CH**C**HCHO), 29.7 ($CH$**C**$H(CH_3)_2$), 28.4 ($CH_2$**C**$H_2CHC(=O)$), 26.8 (3C, $SiC(\mathbf{C}H_3)_3$), 26.3 ($CH_2$**C**$H_2CH(i\text{-Pr})$), 22.0 ($CH(\mathbf{C}H_3)_2$), 19.2 (Si**C**$(CH_3)_3$), 17.2 ($CH(\mathbf{C}H_3)_2$); LRMS $m/z$ ($ESI^+$) 485 ($[M+Na]^+$, 60%), 947 ($[2M+Na]^+$, 100%); HRMS $m/z$ ($ESI^+$) found 485.2478, $C_{29}H_{38}NaO_3Si$ requires 485.2482; $\nu_{max}$ (film)/$cm^{-1}$ 3071 (w, =$CH_2$), 2958 (m, CH), 2931 (m, CH), 2858 (m, CH), 1774 (s, C=O), 1660 (w), 1589 (w), 1471 (m), 1428 (m), 1389 (m), 1363 (m), 1257 (m, C-O), 1112 (s, Si-O-C), 1017 (m), 911 (m, C=$CH_2$), 823 (m, Si-O-C).

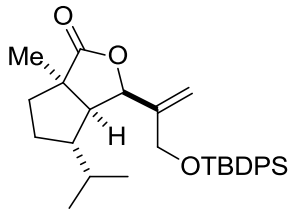
***(3S*,3aS*,4S*,6aR*)-3-(3-((tert-Butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropyl-6a-methylhexahydro-1H-cyclopenta[c]furan-1-one (270)***




To a stirred solution of (3*S**,3a*S**,4*S**,6a*R**)-3-(3-((*tert*-butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropylhexahydro-1*H*-cyclopenta[*c*]furan-1-one (**269**) (320 mg, 0.69 mmol, 1.0 eq.) in anhydrous THF (13.8 mL) cooled to -78 °C in a acetone/dry ice bath was added methyl iodide (491 mg, 3.46 mmol, 5.0 eq.) followed by dropwise addition of a 1 M solution of LiHMDS in toluene (3.46 mL, 3.46 mmol, 5.0 eq.). After complete addition the mixture was stirred for a further 30 min at -78 °C. Sat. aq. $NH_4Cl$ solution (10 mL) was added to the mixture and extracted with $Et_2O$ (3 × 10 mL). The combined organic extracts were sequentially washed brine (30 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40–60) to afford (3*S**,3a*S**,4*S**,6a*R**)-3-(3-((*tert*-

butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropyl-6a-methylhexahydro-1*H*-cyclopenta[*c*]furan-1-one (**270**) as a colourless oil (296 mg, 0.62 mmol, 90%). $R_f$ = 0.30 (10% EtOAc/petrol 40–60); $\delta_H$ (500 MHz, $CDCl_3$) 7.70–7.65 (4H, m, Ar**H**), 7.47–7.36 (6H, m, Ar**H**), 5.33 (1H, s, C=C$\mathbf{H_2}$), 5.22 (1H, s, C=C$\mathbf{H_2}$), 4.65 (1H, d, *J* = 3.9 Hz, CHC**H**(C)O), 4.21 (2H, s, CC$\mathbf{H_2}$OTBDPS), 2.17–2.14 (1H, m, CHC**H**(C)CHO), 2.01 (1H, ddd, *J* = 13.1, 8.7, 7.0 Hz, $CH_2C\mathbf{H_2}$C(Me)), 1.81–1.74 (1H, m, $CH_2C\mathbf{H_2}$CH(*i*-Pr)), 173–1.64 (2H, m, $CH_2C\mathbf{H_2}$C(Me) & $CH_2C\mathbf{H}$(*i*-Pr)CH), 1.59–1.49 (2H, m, $CH_2C\mathbf{H_2}$CH(*i*-Pr) & CHC**H**$(CH_3)_2$), 1.25 (3H, s, C(C$\mathbf{H_3}$)), 1.08 (9H, s, SiC(C$\mathbf{H_3}$)$_3$), 0.87 (3H, d, *J* = 6.7 Hz, CH(C$\mathbf{H_3}$)$_2$), 0.84 (3H, d, *J* = 6.7 Hz, CH(C$\mathbf{H_3}$)$_2$); $\delta_C$ (125 MHz, $CDCl_3$) 182.6 (C=O), 145.9 (**C**=$CH_2$), 135.5 (2C, Ar), 135.4 (2C, Ar), 133.1 (Ar), 133.0 (Ar), 129.8 (2C, Ar), 127.8 (2C, Ar), 127.7 (2C, Ar), 111.2 (C=**C**$H_2$), 84.0 (CH**C**H(C)O), 63.4 (C**C**$H_2$OTBDPS), 55.5 ($CH_2$**C**H(*i*-Pr)CH), 55.1 (CH**C**H(C)CHO), 51.1 ($CH_2$**C**(Me)C), 37.8 ($CH_2$**C**$H_2$C(Me)), 30.8 (CH**C**H$(CH_3)_2$), 29.0 ($CH_2$**C**$H_2$CH(*i*-Pr)), 26.7 (3C, SiC(**C**$H_3$)$_3$), 24.2 (C(**C**$H_3$)), 21.8 (CH(**C**$H_3$)$_2$), 19.9 (CH(**C**$H_3$)$_2$), 19.2 (Si**C**$(CH_3)_3$); LRMS *m*/*z* ($ESI^+$) 499 ($[M+Na]^+$, 49%), 975 ($[2M+Na]^+$, 100%); HRMS *m*/*z* ($ESI^+$) found 499.2636, $C_{30}H_{40}NaO_3Si$ requires 499.2639; $\nu_{max}$ (film)/$cm^{-1}$ 3071 (w, =$CH_2$), 2958 (s, CH), 2932 (m, CH), 2858 (m, CH), 1771 (s, C=O), 1658 (w), 1590 (w), 1471 (m), 1428 (m), 1389 (m), 1374 (m), 1337 (w), 1307 (w), 1255 (w), 1209 (w), 1162 (w, C-O), 1110 (s, Si-O-C), 1056 (m), 1010 (m), 914 (m, C=$CH_2$), 823 (m, Si-O-C), 741 (m), 702 (s).

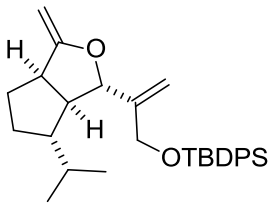
***(3*R**,3a*S**,4*S**,6a*R**)-3-(3-((tert-Butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropyl-6a-methylhexahydro-1H-cyclopenta[c]furan-1-one (270)***

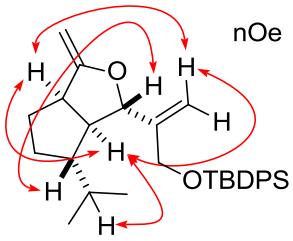



To a stirred solution of (3*R**,3*aS**,4*S**,6*aR**)-3-(3-((*tert*-butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropylhexahydro-1*H*-cyclopenta[*c*]furan-1-one (**269**) (57.0 mg, 0.12 mmol, 1.0 eq.) in anhydrous THF (2.40 mL) cooled to -78 °C in a acetone/dry ice bath was added methyl iodide (87.5 mg,

0.62 mmol, 5.0 eq.) followed by dropwise addition of a 1 M solution of LiHMDS in toluene (0.62 mL, 0.62 mmol, 5.0 eq.). After complete addition the mixture was stirred for a further 30 min at -78 °C. Sat. aq. $NH_4Cl$ solution (10 mL) was added to the mixture and extracted with $Et_2O$ (3 × 10 mL). The combined organic extracts were sequentially washed brine (30 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60) to afford (3*R**,3a*S**,4*S**,6a*R**)-3-(3-((*tert*-butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropyl-6a-methylhexahydro-1*H*-cyclopenta[*d*]furan-1-one (**270**) as a colourless oil (48.7 mg, 0.10 mmol, 85%). $R_f$ = 0.30 (10% EtOAc/petrol 40-60); $\delta_H$ (500 MHz, $CDCl_3$) 7.70–7.64 (4H, m, Ar**H**), 7.48–7.37 (6H, m, Ar**H**), 5.34 (1H, s, C=C$\mathbf{H_2}$), 5.30 (1H, s, C=C$\mathbf{H_2}$), 5.10 (1H, d, *J* = 6.1 Hz, CHC**H**(C)O), 4.16 (1H, d, *J* = 13.8 Hz, CC$\mathbf{H_2}$OTBDPS), 4.10 (1H, d, *J* = 13.8 Hz, CC$\mathbf{H_2}$OTBDPS), 2.17–2.10 (2H, m, $CH_2C\mathbf{H_2}C$(Me) & CHC**H**(C)CHO), 1.85–1.78 (1H, m, $CH_2C\mathbf{H}$(*i*-Pr)CH), 1.57–1.49 (2H, m, $CH_2C\mathbf{H_2}CH$(*i*-Pr) & $CH_2C\mathbf{H_2}C$(Me)), 1.47–1.33 (2H, m, $CH_2C\mathbf{H_2}CH$(*i*-Pr) & CHC**H**$(CH_3)_2$), 1.35 (3H, s, C(C$\mathbf{H_3}$)), 1.09 (9H, s, SiC(C$\mathbf{H_3}$)$_3$), 0.75 (3H, d, *J* = 6.8 Hz, CH(C$\mathbf{H_3}$)$_2$), 0.69 (3H, d, *J* = 6.8 Hz, CH(C$\mathbf{H_3}$)$_2$); $\delta_C$ (125 MHz, $CDCl_3$) 182.6 (**C**=O), 142.7 (**C**=$CH_2$), 135.5 (2C, Ar), 135.5 (2C, Ar), 133.0 (Ar), 132.9 (Ar), 129.9 (Ar), 129.9 (Ar), 127.8 (2C, Ar), 127.8 (2C, Ar), 110.9 (C=**C**$H_2$), 78.7 (CH**C**H(C)O), 64.2 (C**C**$H_2$OTBDPS), 54.0 ($CH_2$**C**(Me)C), 53.4 (CHC**H**(C)CHO), 45.9 ($CH_2$**C**H(*i*-Pr)CH), 37.3 ($CH_2$**C**$H_2$C(Me)), 30.5 (CH**C**H$(CH_3)_2$), 26.8 (3C, SiC(**C**$H_3$)$_3$), 25.9 ($CH_2$**C**$H_2$CH(*i*-Pr)), 21.8 (CH(**C**$H_3$)$_2$), 21.2 (C(**C**$H_3$)), 19.2 (Si**C**$(CH_3)_3$), 17.5 (CH(**C**$H_3$)$_2$); LRMS *m*/*z* (ESI$^+$) 499 ([M+Na]$^+$, 44%), 975 ([2M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 499.2635, $C_{30}H_{40}NaO_3Si$ requires 499.2639; $\nu_{max}$ (film)/cm$^{-1}$ 3071 (w, =$CH_2$), 2958 (s, CH), 2931 (m, CH), 2859 (m, CH), 1774 (s, C=O), 1660 (w), 1590 (w), 1471 (m), 1428 (m), 1389 (m), 1363 (m), 1329 (w), 1307 (w), 1272 (w), 1162 (m, C-O), 1112 (s, Si-O-C), 1074 (m), 1014 (m), 913 (m, C=$CH_2$), 824 (m, Si-O-C), 741 (m), 703 (s).

**tert-*Butyl((2-((1S*,3aR*,6S*,6aS*)-6-isopropyl-3a-methyl-3-methylenehexahydro-1H-cyclopenta[c]furan-1-yl)allyl)oxy)diphenylsilane (271)***

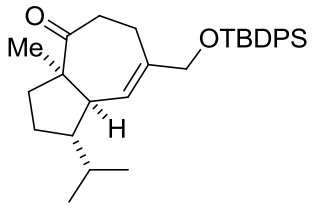



To (3*S**,3a*S**,4*S**,6a*R**)-3-(3-((*tert*-butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropyl-6a-methylhexahydro-1*H*-cyclopenta[*c*]furan-1-one (**270**) (141 mg, 0.30 mmol, 1.0 eq.) was added a 0.24 M solution of the Petasis reagent in toluene (3.06 mL, 153 mg, 0.73 mmol, 2.4 eq.). The resulting mixture was covered and heated at 110 °C for 30 min. The mixture was concentrated under reduced pressure to afford a red oil which was suspended in hexane (10 mL). Celite (5.00 g) was added to the mixture and stirred for 30 min. The mixture was filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40–60 with 1% triethylamine) to afford *tert*-butyl((2-((1*S**,3a*R**,6*S**,6a*S**)-6-isopropyl-3a-methyl-3-methylenehexahydro-1*H*-cyclopenta[*c*]furan-1-yl)allyl)oxy)diphenylsilane (**271**) as a colourless oil (122 mg, 0.26 mmol, 89%). $R_f$ = 0.25 (10% EtOAc/petrol 40–60); $\delta_H$ (500 MHz, $C_6D_6$) 7.93–7.88 (4H, m, Ar**H**), 7.36–7.30 (6H, m, Ar**H**), 5.61 (1H, dd, *J* = 3.0, 1.4 Hz, CHC(=C**H**$_2$)CH$_2$), 5.43 (1H, dt, *J* = 3.0, 1.4 Hz, CHC(=C**H**$_2$)CH$_2$), 4.60 (1H, d, *J* = 1.4 Hz, CC(=C**H**$_2$)O), 4.56 (1H, d, *J* = 5.1 Hz, CHC**H**(C)O), 4.51 (1H, t, *J* = 1.4 Hz, CC**H**$_2$OTBDPS), 4.49 (1H, t, *J* = 1.4 Hz, CC**H**$_2$OTBDPS), 3.96 (1H, d, *J* = 1.4 Hz, CC(=C**H**$_2$)O), 2.05 (1H, dd, *J* = 5.1, 5.1 Hz, CHC**H**(C)CHO), 1.92 (1H, ddd, *J* = 12.5, 10.1, 6.8 Hz, (C)C**H**$_2$CH$_2$CH), 1.75 (1H, dddd, *J* = 12.5, 6.8, 6.8, 4.0 Hz, (C)CH$_2$C**H**$_2$CH), 1.62 (1H, ddd, *J* = 12.5, 6.8, 4.0 Hz, (C)C**H**$_2$CH$_2$CH), 1.55–1.48 (1H, m, CH$_2$C**H**(*i*-Pr)CH), 1.44–1.34 (2H, m, CHC**H**(CH$_3$)$_2$ and (C)CH$_2$C**H**$_2$CH), 1.29 (9H, s, SiC(C**H**$_3$)$_3$), 1.23 (3H, s, C(C**H**$_3$)), 0.88 (3H, d, *J* = 6.6 Hz, CH(C**H**$_3$)$_2$), 0.86 (3H, d, *J* = 6.6 Hz, CH(C**H**$_3$)$_2$); $\delta_C$ (125 MHz, $C_6D_6$) 173.1 (C**C**(=CH$_2$)O), 148.3 (CHC(=**C**H$_2$)CH$_2$), 135.9 (2C, Ar), 135.9 (2C, Ar), 133.9 (Ar), 133.7 (Ar), 130.1 (2C, Ar), 128.3 (Ar), 128.1 (2C, Ar), 127.9 (Ar), 110.6

(CHC(=**C**H$_2$)CH$_2$), 87.8 (CH**C**H(C)O), 78.1 (CHC(=**C**H$_2$)CH$_2$), 63.9 (C**C**H$_2$OTBDPS), 58.7 (CH**C**H(C)CHO), 54.6 (CH$_2$**C**H(*i*-Pr)CH), 53.8 (CH$_2$**C**(Me)C), 41.6 ((C)**C**H$_2$CH$_2$CH), 32.1 (CH**C**H(CH$_3$)$_2$), 30.5 ((C)CH$_2$**C**H$_2$CH), 27.1 (C(**C**H$_3$)), 27.0 (3C, SiC(**C**H$_3$)$_3$), 22.2 (CH(**C**H$_3$)$_2$), 20.3 (CH(**C**H$_3$)$_2$), 19.5 (Si**C**(CH$_3$)$_3$); LRMS *m*/*z* (ESI$^+$) 475 ([M+H]$^+$, 35%), 497 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 497.2845, $C_{31}H_{42}NaO_2Si$ requires 497.2846; $\nu_{max}$ (film)/cm$^{-1}$ 3235 (w), 2958 (m, CH), 2859 (m, CH), 2280 (s, C=CH2)1667 (m, C=CH$_2$), 1618 (m), 1453 (m), 1428 (m), 1390 (w), 1330 (s), 1162 (w), 1112 (m, Si-O-C), 1053 (w), 914 (w), 812 (s, Si-O-C), 741 (m), 704 (s).

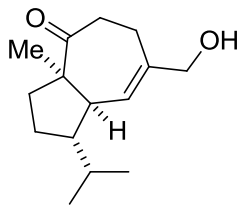
***(1S*,3aR*,8aR*)-7-(((tert-Butyldiphenylsilyl)oxy)methyl)-1-isopropyl-3a-methyl-1,3,3a,5,6,8a-hexahydroazulen-4(2H)-one (272)***




A solution of *tert*-butyl((2-((1*S**,3*a*R*,6*S**,6*a*S*)-6-isopropyl-3a-methyl-3-methylenehexahydro-1*H*-cyclopenta[*c*]furan-1-yl)allyl)oxy)diphenylsilane (**271**) (104 mg, 0.21 mmol, 1.0 eq.) in anhydrous xylene (4.20 mL) was heated at 150 °C for 16 H and then concentrated under reduced pressure. The residue was purified by flash column chromatography (5% EtOAc/petrol 40–60) to afford (1*S**,3*a*R*,8*a*R*)-7-(((*tert*-butyldiphenylsilyl)oxy)methyl)-1-isopropyl-3a-methyl-1,3,3a,5,6,8a-hexahydroazulen-4(2*H*)-one (**272**) as a colourless oil (78 mg, 0.16 mmol, 76%). $R_f$ = 0.21 (5% EtOAc/petrol 40–60); $\delta_H$ (500 MHz, $CDCl_3$) 7.68–7.64 (4H, m, Ar**H**), 7.46–7.35 (6H, m, Ar**H**), 5.56 (1H, d, *J* = 4.2 Hz, CHC**H**=C), 4.08 (2H, s, CC**H**$_2$OTBDPS), 2.80–2.74 (1H, m, C(=O)C**H**$_2$CH$_2$), 2.54–2.37 (2H, m, =C(CH$_2$)C**H**$_2$CH$_2$ & C(=O)C**H**$_2$CH$_2$), 2.32–2.27 (1H, m, CHC**H**CH=), 2.22–2.15 (1H, m, =C(CH$_2$)C**H**$_2$CH$_2$), 2.15–2.07 (1H, m, CH$_2$C**H**$_2$C(Me)), 1.84–1.76 (1H, m, CH$_2$C**H**$_2$CH(*i*-Pr)), 1.69–1.61 (1H, m, CH$_2$C**H**(*i*-Pr)CH), 1.61–1.53 (1H, m, CHC**H**(CH$_3$)$_2$), 1.42–1.29 (2H, m, CH$_2$C**H**$_2$C(Me) & CH$_2$C**H**$_2$CH(*i*-Pr)), 1.27 (3H, s, C(C**H**$_3$)), 1.06 (9H, s, SiC(C**H**$_3$)$_3$), 0.93 (3H, d, *J* = 6.6 Hz, CH(C**H**$_3$)$_2$), 0.91 (3H, d, *J* = 6.6 Hz, CH(C**H**$_3$)$_2$); $\delta_C$

(125 MHz, $CDCl_3$) 213.5 (**C**=O), 140.7 (CH=**C**(C)$CH_2$), 135.5 (4C, Ar), 133.6 (CH**C**H=C), 131.0 (2C, Ar), 129.6 (2C, Ar), 127.6 (4C, Ar), 67.3 (C**C**$H_2$OTBDPS), 58.8 ($CH_2$**C**($CH_3$)C=O), 56.0 ($CH_2$**C**H(*i*-Pr)CH), 51.3 (CH**C**HCH=), 39.6 (C(=O)**C**$H_2CH_2$), 34.7 ($CH_2$**C**$H_2$C(Me)), 33.1 (CH**C**H($CH_3$)$_2$), 27.1 ($CH_2$**C**$H_2$CH(*i*-Pr)), 26.8 (3C, SiC(**C**H$_3$)$_3$), 24.8 (=C($CH_2$)**C**$H_2CH_2$), 24.7 (C(**C**$H_3$)), 22.0 (CH(**C**H$_3$)$_2$), 20.0 (CH(**C**H$_3$)$_2$), 19.2 (Si**C**($CH_3$)$_3$); LRMS *m*/*z* ($ESI^+$) 497 ([M+Na]$^+$, 97%), 971 ([2M+Na]$^+$, 100%); HRMS *m*/*z* ($ESI^+$) found 497.2851, $C_{31}H_{42}NaO_2Si$ requires 497.2846; $\nu_{max}$ (film)/$cm^{-1}$ 3071 (w, =CH), 3049 (w, =CH), 2956 (s, CH), 2858 (s, CH), 1959 (w, Ph overtone), 1891 (w, Ph overtone), 1824 (w, Ph overtone), 1699 (s, C=O), 1462 (m), 1428 (m), 1369 (w), 1254 (w), 1111 (s, Si-O-C), 1062 (m), 915 (m, C=C-H), 823 (m, Si-O-C).

**(±)-Aphanamol-I (91)**




To a stirred solution of (1*S**,3*aR**,8*aR**)-7-(((*tert*-butyldiphenylsilyl)oxy)methyl)-1-isopropyl-3a-methyl-1,3,3a,5,6,8a-hexahydroazulen-4(2*H*)-one (**272**) (47.4 mg, 0.10 mmol, 1.0 eq.) in anhydrous THF (0.50 mL) cooled to 0 °C in a ice/water bath was added acetic acid (24.0 mg, 0.40 mmol, 4.0 eq.) followed by dropwise addition of a 1 M solution of TBAF in THF (0.20 mL, 0.20 mmol, 2.0 eq.). The resulting mixture was warmed to room temperature and stirred for 4 h. Sat. aq. $NH_4Cl$ solution (10 mL) was added and extracted with EtOAc (3 × 10 mL). The combined organic extracts were sequentially washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (40% EtOAc/petrol 40–60) to afford (±)-aphanamol-I (**91**) as a colourless oil (23.5 mg, 0.10 mmol, 100%). $R_f$ = 0.25 (40% EtOAc/petrol 40–60); $\delta_H$ (500 MHz, $CDCl_3$) 5.53 (1H, d, *J* = 4.5 Hz, C(H)C**H**=C), 4.03 (2H, d, *J* = 2.3 Hz, CC**H**$_2$OH), 2.83 (1H, ddd, *J* = 14.6, 5.8, 3.8 Hz, C(=O)C**H**$_2CH_2$), 2.60–2.51 (1H, m, =C($CH_2$)C**H**$_2CH_2$), 2.43 (1H, ddd, *J* = 14.6, 11.8, 5.8 Hz,

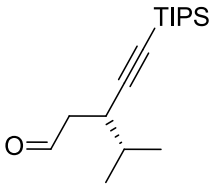
C(=O)C**H**$_2$CH$_2$), 2.32–2.25 (2H, m, =C(CH$_2$)C**H**$_2$CH$_2$ & CHC**H**CH=), 2.14–2.05 (1H, m, CH$_2$C**H**$_2$C(Me)), 1.85–1.75 (1H, m, CH$_2$C**H**$_2$CH(*i*-Pr)), 1.71–1.63 (1H, m, CH$_2$C**H**(CH)CH), 1.63–1.53 (1H, m, CHC**H**(CH$_3$)$_2$), 1.42–1.29 (3H, m, CH$_2$C**H**$_2$C(Me), CH$_2$O**H** & CH$_2$C**H**$_2$CH(*i*-Pr)), 1.27 (3H, s, C(C**H**$_3$)), 0.92 (3H, d, *J* = 6.5 Hz, CH(C**H**$_3$)$_2$), 0.91 (3H, d, *J* = 6.5 Hz, CH(C**H**$_3$)$_2$); $\delta_C$ (125 MHz, $CDCl_3$) 213.6 (**C**=O), 141.6 (CH=**C**(C)CH$_2$), 132.9 (C(H)**C**H=C), 67.1 (C**C**H$_2$OH), 58.9 (CH$_2$**C**(CH$_3$)C=O), 56.0 (CH$_2$**C**H(CH)CH), 51.4 (CH**C**HCH=), 39.9 (C(=O)**C**H$_2$CH$_2$), 34.5 (CH$_2$**C**H$_2$C(Me)), 33.0 (CH**C**H(CH$_3$)$_2$), 27.0 (CH$_2$**C**H$_2$CH(*i*-Pr)), 24.9 (=C(CH$_2$)**C**H$_2$CH$_2$), 24.7 (C(**C**H$_3$)), 22.0 (CH(**C**H$_3$)$_2$), 19.9 (CH(**C**H$_3$)$_2$); LRMS *m*/*z* (ESI$^+$) 259 ([M+Na]$^+$, 60%), 495 ([2M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 259.1670, $C_{15}H_{24}NaO_2$ requires 259.1669; $\nu_{max}$ (film)/cm$^{-1}$ 3418 (br, OH), 2960 (m, CH), 2872 (m, CH), 1691 (s, C=O), 1463 (m), 1420 (w), 1386 (w), 1374 (w), 1255 (w), 1174 (w), 1075 (m), 1000 (m).

Data are consistent with literature values.[51]

**[Rh(*μ*-O$_2$CCH$_3$)(C$_2$H$_4$)$_2$]$_2$ (305)**

Prepared accoriding to the procedure of Werner *et al.*[139] To a vigorously stirred solution of chlorobis(ethylene)rhodium(I) dimer (**304**) (13.0 mg, 33.4 μmol, 2.5 mol%) in Ar sparged $Et_2O$ (3.30 mL) cooled to -30 °C was added in one portion sodium acetate trihydrate (25.9 mg, 0.19 mmol, 0.15 eq.). The resulting yellow mixture was slowly warmed to room temperature over 1 h and then filtered *via* a cannula fitted with a glass filter paper. The filtrate was concentrated under reduced pressure then recrystallised from Ar sparged pentane to afford [Rh(*μ*-O$_2$CCH$_3$)(C$_2$H$_4$)$_2$]$_2$ (**305**) as a orange/red solid.

**(*S*)-3-Isopropyl-5-(triisopropylsilyl)pent-4-ynal ((*S*)-306)**

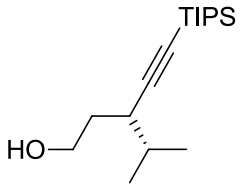



**Racemic**: To a stirred solution of TIPS-acetylene (729 mg, 4.00 mmol, 1.0 eq.) in dry THF (5.0 mL) was added dropwise a 3 M solution of EtMgBr in $Et_2O$ (1.30 mL, 4.00 mmol, 1.0 eq.). The resulting mixture was stirred at room temperature for 2 h then cooled to 40 °C in a ice/water bath. Copper(I) chloride (3.96 mg, 0.04 mmol, 0.01 eq.) was added to the mixture followed by rapid addition 4-methyl-2-pentenal (**200**) (393 mg, 4.00 mmol, 1.0 eq.) *via* cannula. The mixture was stirred at 0 °C for 30 min. 1 M HCl (20 mL) was added to the mixture and extracted with EtOAc (3 × 10 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (50 mL), brine (50 mL), dried ($MgSO_4$) filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (5% EtOAc/petrol 40-60) to afford 3-isopropyl-5-(triisopropylsilyl)pent-4-ynal ((±)-**306**) as a colourless oil (583 mg, 2.08 mmol, 52%).

**Asymmetric**: To a stirred solution of $[Rh(\mu\text{-}O_2CCH_3)(C_2H_4)_2]_2$ (13.0 mg, 33.4 μmol, 2.5 mol%) in Ar sparged anhydrous MeOH (2.64 mL), was added (S)-(+)-DTBM-SEGPHOS (93 mg, 79.0 μmol, 6.0 mol%) and stirred at room temperature for 15 min. 4-Methyl-2-pentenal (**200**) (130 mg, 1.32 mmol, 1.0 eq.) and (triisopropylsilyl)acetylene (481 mg, 2.64 mmol, 2.0 eq.) were added and the mixture was heated at 40°C for 24 h, then cooled to room temperature. Water (10 mL) was added to the mixture and extracted with DCM (3 × 10 mL). The combined organic extracts were sequentially washed with water (30 ml), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (5% EtOAc/petrol 40-60) to afford (*S*)-3-isopropyl-5-(triisopropylsilyl)pent-4-ynal ((*S*)-**306**)as a colourless oil (302 mg, 1.07 mmol, 81%, >99% *ee* (*S*)). The *ee* of (*S*)-**306** was determined by chiral HPLC analysis of the corresponding benzoyl protected alcohol (*S*)-**308**. $[\alpha]_D^{20}$ -28.7 (*c* 1.00, $CHCl_3$) for >99% *ee* [lit.

enantiomer[137] $[\alpha]_D^{20}$ +30.0 (*c* 0.95, $CHCl_3$) for (*R*)]; $R_f$ = 0.37 (10% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 9.83 (1H, t, *J* = 2.2 Hz, $CH_2C\mathbf{H}O$), 2.85 (1H, dt, *J* = 9.1, 5.2 Hz, $CH_2C\mathbf{H}(CH)C$), 2.57 (1H, ddd, *J* = 16.1, 9.1, 2.2 Hz, $CHC\mathbf{H_2}CH$), 2.47 (1H, ddd, *J* = 16.1, 5.2, 2.2 Hz, $CHC\mathbf{H_2}CH$), 1.74 (1H, septd, *J* = 6.7, 5.2 Hz, $CHC\mathbf{H}(CH_3)_2$), 1.06 (3H, s, $Si(C\mathbf{H}(i\text{-}Pr)_3)$), 1.05 (18H, s, $Si(CH(C\mathbf{H_3})_2)_3$), 1.03 (3H, d, *J* = 6.7 Hz, $CH(C\mathbf{H_3})_2$), 0.99 (3H, d, *J* = 6.7 Hz, $CH(C\mathbf{H_3})_2$); $\delta_C$ (100 MHz, $CDCl_3$) 201.6 (**C**=O), 107.9 (C≡**C**TIPS), 83.9 (CH**C**≡C), 46.6 ($CH\mathbf{C}H_2CH$), 34.0 ($CH_2\mathbf{C}H(CH)C$), 31.5 ($CH\mathbf{C}H(CH_3)_2$), 20.8 ($CH(\mathbf{C}H_3)_2$), 18.6 (6C, $Si(CH(\mathbf{C}H_3)_2)_3$), 18.1 ($CH(\mathbf{C}H_3)_2$), 11.2 (3C, $Si(\mathbf{C}H(i\text{-}Pr)_3)$); HRMS *m/z* ($FI^+$) found 280.2213, $C_{17}H_{32}OSi$ requires 280.2223; $\nu_{max}$ (film)/$cm^{-1}$ 2959 (s, CH), 2892 (m, CH), 2865 (s, CH), 2167 (m, C≡C), 1728 (s, C=O), 1463 (s), 1386 (m), 1350 (m), 1288 (m), 1243 (m), 1071 (m), 1017 (m), 882 (s).

***(S)-3-Isopropyl-5-(triisopropylsilyl)pent-4-yn-1-ol ((S)-307)***

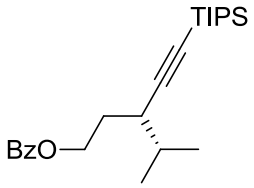



**Racemic**: To a stirred suspension of $LiAlH_4$ (251 mg, 6.60 mmol, 1.0 eq.) in anhydrous $Et_2O$ (11.0 mL) cooled to 0 °C in an ice/water bath, was added dropwise a solution of methyl 3-isopropyl-5-(triisopropylsilyl)pent-4-ynoate (±)-**308** (2.05 g, 6.60 mmol, 1.0 eq.) in anhydrous $Et_2O$ (11.0 mL). The mixture was warmed to room temperature and stirred for 2 h. Water (0.25 mL) was carefully added dropwise to the mixture followed by 10% aq. NaOH solution (0.25 mL) and stirred for 5 min. Additional water (0.50 mL) was added, after which the mixture was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/petrol 40-60) to afford 3-isopropyl-5-(triisopropylsilyl)pent-4-yn-1-ol ((±)-**307**) as a colourless oil (1.75 g, 5.92 mmol, 94%).

**Asymmetric**: To a vigorously stirred solution of chlorobis(ethylene)rhodium(I) dimer (70.7 mg, 0.18 mmol, 2.5 mol%) in Ar sparged $Et_2O$ (18.2 mL) cooled to -30 °C was added in one portion

sodium acetate trihydrate (150 mg, 1.10 mmol, 0.15 eq.). The resulting yellow mixture was slowly warmed to room temperature over 1 h and then filtered *via* a cannula fitted with a glass filter paper. The filtrate was concentrated under reduced pressure to afford an orange/red solid. The residue was re-suspended in Ar sparged anhydrous MeOH (14.6 mL), after which (S)-(+)-DTBM-SEGPHOS (517 mg, 0.44 mmol, 6.0 mol%) was added and stirred at room temperature for 15 min. 4-Methyl-2-pentenal (**200**) (716 mg, 7.30 mmol, 1.0 eq.) and (triisopropylsilyl)acetylene (2.66 g, 14.6 mmol, 2.0 eq.) were added and the mixture was heated at 40°C for 24 h, then cooled to room temperature. Sodium borohydride (11.0 g, 29.2 mmol, 4.0 eq.) was then carefully added portionwise and stirred for a further 30 min. Water (20 mL) was added to the mixture and extracted with DCM (3 × 20 mL). The combined organic extracts were sequentially washed with water (30 ml), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (5-20% gradient EtOAc/petrol 40-60) to afford (*S*)-3-isopropyl-5-(triisopropylsilyl)pent-4-yn-1-ol (*S*)-**307** as a yellow oil (1.60 g, 5.69 mmol, 78%, >99% *ee* (*S*)). The *ee* of (*S*)-**307** was determined by chiral HPLC analysis of the corresponding benzoyl protected alcohol (*S*)-**308**. $[\alpha]_D^{20}$ -8.5 (*c* 0.97, $CHCl_3$) for >99% *ee*; $R_f$ = 0.30 (20% EtOAc/petrol 40-60); $\delta_H$ (500 MHz, $CDCl_3$) 3.85 (2H, td, *J* = 6.3, 2.8 Hz, HOC**H**$_2$CH$_2$), 2.51–2.45 (1H, m, CH$_2$C**H**(CH)C≡), 1.75–1.67 (4H, m, **H**OCH$_2$, OCH$_2$C**H**$_2$CH & CHC**H**(CH$_3$)$_2$), 1.08 (3H, s, Si(C**H**(*i*-Pr)$_3$)), 1.07 (18H, s, Si(CH(C**H**$_3$)$_2$)$_3$), 1.02 (3H, d, *J* = 6.7 Hz, CH(C**H**$_3$)$_2$), 0.99 (3H, d, *J* = 6.7 Hz, CH(C**H**$_3$)$_2$); $\delta_C$ (125 MHz, $CDCl_3$) 110.1 (C≡**C**TIPS), 83.2 (CH**C**≡C), 61.9 (HOC**H**$_2$CH$_2$), 36.7 (CH$_2$**C**H(CH)C≡), 35.6 (OCH$_2$**C**H$_2$CH), 31.9 (CH**C**H(CH$_3$)$_2$), 21.1 (CH(**C**H$_3$)$_2$), 18.6 (6C, Si(CH(**C**H$_3$)$_2$)$_3$), 18.2 (CH(**C**H$_3$)$_2$), 11.3 (3C, Si(**C**H(CH$_3$)$_2$)$_3$); LRMS *m*/*z* (ESI$^+$) 283 ([M+H]$^+$, 18%), 305 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 305.2271, $C_{17}H_{34}NaOSi$ requires 305.2271; $\nu_{max}$ (film)/cm$^{-1}$ 3323 (br, OH), 2958 (s), 2942 (s), 1891 (m), 2865 (s), 2164 (m, C≡C), 1463 (m), 1385 (w), 1367 (w), 1044 (m), 1016 (m), 996 (m), 882 (s), 665 (s).

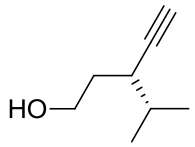
***(S)-3-Isopropyl-5-(triisopropylsilyl)pent-4-yn-1-yl benzoate ((S)-308)***




To a stirred solution of (*S*)-3-isopropyl-5-(triisopropylsilyl)pent-4-yn-1-ol ((*S*)-**307**) (56.4 mg, 0.20 mmol, 1.0 eq.) in anhydrous DCM (10.0 mL) at room temperature, was added DMAP (224 mg, 2.00 mmol, 10.0 eq.) and benzoic anhydride (294 mg, 1.30 mmol, 6.5 eq.). The resulting mixture was stirred at room temperature for 24 h. Sat. aq. $NH_4Cl$ solution (10 mL) was added to the mixture and the organic layer was separated. The aq. layer was further extracted with DCM (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (5% EtOAc/petrol 40-60) to afford (*S*)-3-isopropyl-5-(triisopropylsilyl)pent-4-yn-1-yl benzoate ((*S*)-**308**) as a colourless oil (76.0 mg, 0.19 mmol, 98%, >99% *ee* (*S*)). The *ee* was measured by HPLC (Chiralcel OD column, flow 0.6 mL/min, 0.2% IPA/hexane, 230 nm, $t_1$ = 18.9 min (*S*), $t_2$ = 20.5 min (*R*); $[\alpha]_D^{20}$ -66.0 (*c* 0.96, $CHCl_3$) for >99% ee, [lit. enantiomer[137] $[\alpha]_D^{20}$ +51 (*c* 0.98, $CHCl_3$) for (*R*)]; $R_f$ = 0.31 (5% EtOAc/petrol 40-60); $\delta_H$ (500 MHz, $CDCl_3$) 8.09–8.04 (2H, m, Ar**H**), 7.59–7.54 (1H, m, Ar**H**), 7.48–7.42 (2H, m, Ar**H**), 4.57 (1H, ddd, *J* = 11.1, 6.8, 4.9 Hz, OC$\mathbf{H_2}$CH$_2$), 4.47 (1H, ddd, *J* = 11.1, 8.3, 6.4 Hz, OC$\mathbf{H_2}$CH$_2$), 2.56 (1H, dt, *J* = 10.0, 4.8 Hz, CH$_2$C**H**(CH)C≡), 2.00–1.82 (2H, m, CH$_2$C$\mathbf{H_2}$CH), 1.77 (1H, septd, *J* = 6.7, 4.8 Hz, CHC**H**(CH$_3$)$_2$), 1.09 (3H, s, Si(C**H**(*i*-Pr)$_3$)), 1.08 (18H, s, Si(CH(C$\mathbf{H_3}$)$_2$)$_3$), 1.06 (3H, d, *J* = 6.7 Hz, CH(C$\mathbf{H_3}$)$_2$), 1.03 (3H, d, *J* = 6.7 Hz, CH(C$\mathbf{H_3}$)$_2$); $\delta_C$ (125 MHz, $CDCl_3$) 166.5 (**C**=O), 132.8 (Ar), 130.4 (Ar), 129.6 (2C, Ar), 128.3 (2C, Ar), 109.0 (C≡**C**TIPS), 83.1 (CH**C**≡C), 63.6 (OC$\mathbf{H_2}$CH$_2$), 36.5 (CH$_2$**C**H(CH)C≡), 32.0 (OCH$_2$**C**H$_2$CH), 31.6 (CH**C**H(CH$_3$)$_2$), 21.2 (CH(**C**H$_3$)$_2$), 18.6 (6C, Si(CH(**C**H$_3$)$_2$)$_3$), 18.1 (CH(**C**H$_3$)$_2$), 11.3 (3C, Si(**C**H(CH$_3$)$_2$)$_3$); LRMS *m*/*z* (ESI$^+$) 387 ([M+H]$^+$, 17%), 409 ([M+Na]$^+$, 100), 795 ([2M+Na]$^+$, 30); HRMS *m*/*z* (ESI$^+$) found 409.2525, $C_{24}H_{38}NaO_2Si$ requires 409.2533; $\nu_{max}$ (film)/cm$^{-1}$ 2959 (s, CH),

2942 (s, CH), 2891 (m, CH), 2865 (s, CH), 2166 (m, C≡C), 1722 (s, C=O), 1463 (m), 1269 (s), 1176 (m), 1114 (s), 1070 (m), 1013 (m), 883 (s).

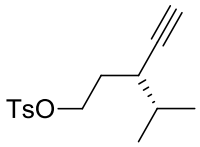
***(S)-3-Isopropylpent-4-yn-1-ol ((S)-254)***




To a stirred solution of (*S*)-3-isopropyl-5-(triisopropylsilyl)pent-4-yn-1-ol ((*S*)-**307**) (1.59 g, 5.65 mmol, 1.0 eq.) in anhydrous THF (22.6 mL) cooled to 0 °C in an ice/water bath was added dropwise a 1 M solution of TBAF in THF (11.3 mL, 11.3 mmol, 2.0 eq.). After complete addition the mixture was warmed to room temperature and stirred for 16 h. 1 M HCl (40 mL) was added to the mixture and extracted with $Et_2O$ (3 × 20 mL). The combined organic extracts were sequentially washed with sat. aq. $NH_4Cl$ solution (100 mL), brine (100 ml), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% $Et_2O$/petrol 30-40) to afford (*S*)-3-isopropylpent-4-yn-1-ol ((*S*)-**254**) as a colourless oil (656 mg, 5.20 mmol, 92%, >99% *ee* (*S*)). The *ee* of (*S*)-**254** was determined by chiral HPLC analysis of the corresponding tosyl alcohol (*S*)-**264**. $[\alpha]_D^{20}$ -23.7 (*c* 1.02, $CHCl_3$) for >99% ee; $R_f$ = 0.24 (50% $Et_2O$/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 3.87–3.75 (2H, m, HOC**H**$_2$CH$_2$), 2.43 (1H, dtd, *J* = 7.5, 5.0, 2.5 Hz, CH$_2$C**H**(CH)C≡CH), 2.08 (1H, d, *J* = 2.5 Hz, CHC≡C**H**), 1.91 (1H, t, *J* = 5.4 Hz, **H**OCH$_2$CH$_2$), 1.78–1.61 (3H, m, CH$_2$C**H**$_2$CH and CH**C**H(CH$_3$)$_2$), 1.00 (3H, d, *J* = 6.7 Hz, CH(C**H**$_3$)$_2$), 0.97 (3H, d, *J* = 6.7 Hz, CH(C**H**$_3$)$_2$); $\delta_C$ (100 MHz, $CDCl_3$) 85.6 (CH**C**≡CH), 70.8 (CHC≡**C**H), 61.3 (HO**C**H$_2$CH$_2$), 35.2 (CH$_2$**C**H$_2$CH), 35.1 (CH$_2$**C**H(CH)C≡CH), 31.5 (CH**C**H(CH$_3$)$_2$), 20.8 (CH(**C**H$_3$)$_2$), 18.3 (CH(**C**H$_3$)$_2$); HRMS *m*/*z* (FI$^+$) found 127.1117, $C_8H_{15}O$ requires 127.1123; $\nu_{max}$ (film)/cm$^{-1}$ 3303 (br, OH), 2961 (s, CH), 2876 (m), 2110 (w, C≡C), 1466 (m), 1387 (w), 1370 (w), 1045 (s), 629 (s).

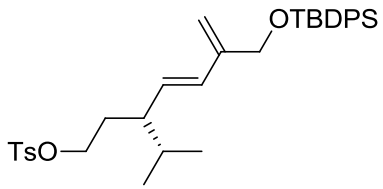
Data are consistent with racemic literature value.[213]

***(S)-3-Isopropylpent-4-yn-1-yl 4-methylbenzenesulfonate ((S)-264)***




To a stirred solution of (*S*)-3-isopropylpent-4-yn-1-ol ((*S*)-**254**) (480 mg, 3.80 mmol, 1.0 eq.) in pyridine (3.80 mL) cooled to -20 °C in a dry ice/acetone bath was added *p*-toluenesulfonyl chloride (1.08 g, 5.70 mmol, 1.5 eq.) portionwise. The resulting mixture was slowly warmed to room temperature and stirred for 18 h. 1 M HCl (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were sequentially washed water (50 mL), brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60) to afford (*S*)-3-isopropylpent-4-yn-1-yl 4-methylbenzenesulfonate ((*S*)-**264**) as a colourless oil (927 mg, 3.31 mmol, 87%, >99% *ee* (*S*)). The ee was measured by HPLC (Chiralcel OD column, flow 0.6 mL/min, 0.5% IPA/hexane, 230 nm, $t_1$ = 28.4 min (*S*), $t_2$ = 29.9 min (*R*); $[\alpha]_D^{20}$ -50.9 (*c* 1.01, $CHCl_3$) for >99% *ee*. $R_f$ = 0.23 (10% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 7.80 (2H, d, *J* = 8.4 Hz, Ar**H**), 7.35 (2H, d, *J* = 8.4 Hz, Ar**H**), 4.27–4.14 (2H, m, TsOC$\mathbf{H_2}$$CH_2$), 2.45 (3H, s, ArC$\mathbf{H_3}$), 2.36 (1H, dtd, *J* = 7.1, 4.6, 2.4 Hz, $CH_2$C**H**(CH)C≡CH), 1.97 (1H, d, *J* = 2.4 Hz, CHC≡C**H**), 1.86–1.78 (1H, m, $OCH_2$C$\mathbf{H_2}$CH), 1.73–1.59 (2H, m, $OCH_2$C$\mathbf{H_2}$CH and CHC**H**$(CH_3)_2$), 0.95 (3H, d, *J* = 6.7 Hz, CH(C$\mathbf{H_3}$)$_2$), 0.92 (3H, d, *J* = 6.7 Hz, CH(C$\mathbf{H_3}$)$_2$); $\delta_C$ (100 MHz, $CDCl_3$) 144.7 (Ar), 133.0 (Ar), 129.1 (2C, Ar), 127.9 (2C, Ar), 83.9 (CH**C**≡CH), 71.4 (CHC≡**C**H), 68.9 (TsO**C**$H_2CH_2$), 34.6 ($CH_2$**C**H(CH)C≡CH), 31.8 ($OCH_2$**C**$H_2$CH), 31.2 (CH**C**H$(CH_3)_2$), 21.6 (Ar**C**$H_3$), 20.7 (CH(**C**$H_3)_2$), 18.1 (CH(**C**$H_3)_2$); LRMS *m*/*z* (ESI$^+$) 281 ([M+H]$^+$, 20%), 303 ([M+Na]$^+$, 95%), 583 ([2M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 303.1015, $C_{15}H_{20}NaO_3S$ requires 303.1025; $\nu_{max}$ (film)/cm$^{-1}$ 3290 (m, ≡C-H), 2964 (m, CH), 2883 (m), 2112 (C≡C), 1599 (m), 1467 (m), 1357 (s, R-$SO_2$-R), 1177 (s, R-$SO_2$-R), 1095 (m), 984 (s), 909 (s), 814 (m), 777 (m), 660 (br, ≡C-H).

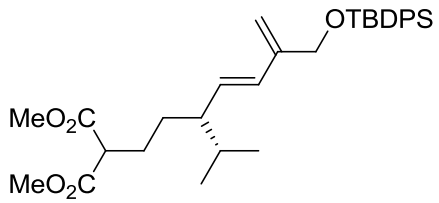
***(S,E)-6-(((tert-Butyldiphenylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-yl 4-methylbenzenesulfonate ((S)-265)***




To a stirred solution of (*S*)-3-isopropylpent-4-yn-1-yl 4-methylbenzenesulfonate ((*S*)-**264**) (920 mg, 3.28 mmol, 1.1 eq.) in Ar sparged anhydrous THF (3.28 mL) was added dropwise catecholborane (472 mg, 3.93 mmol, 1.3 eq.). The resulting mixture was heated at 70 °C for 18 h and cooled to room temperature. The mixture was concentrated under reduced pressure to afford the crude boronate ester, as a pale yellow cloudy oil. Palladium(II) acetate (33.4 mg, 0.15 mmol, 5 mol%) and triphenylphosphine (156 mg, 0.60 mmol, 20 mol%) were suspended in Ar sparged THF (8.20 mL) and stirred at room temperature for 20 min. To the yellow solution was added dropwise a solution of *tert*-butyl((2-iodoallyl)oxy)diphenylsilane (**252**) (1.26 g, 2.98 mmol, 1.0 eq.) and crude boronate ester in Ar sparged anhydrous THF (8.20 mL). After complete addition, Ar sparged aq. 2 M LiOH (8.20 ml, 5.5 eq.) was added to the mixture and then heated at 40 °C for 4 h. Water (20 mL) was added to the mixture and extracted with EtOAc (3 × 10 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (50 mL), brine (50 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60 with 1% triethylamine) to afford (*S,E*)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-yl 4-methylbenzenesulfonate ((*S*)-**265**) as a pale yellow oil (1.50 g, 2.85 mmol, 87%, >99% *ee* (*S*)). $[\alpha]_D^{20}$ -5.0 (*c* 1.02, DCM) for >99% *ee*; $R_f$ = 0.28 (20% $Et_2O$/petrol 40-60); $\delta_H$ (400 MHz, $C_6D_6$) 7.90–7.84 (4H, m, Ar**H**), 7.84 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.35–7.30 (6H, m, Ar**H**), 6.89 (2H,d, *J* = 8.2 Hz, Ar**H**), 5.92 (1H, d, *J* = 16.1 Hz, CH=C**H**C(=$CH_2$)), 5.56 (1H, d, *J* = 1.6 Hz, C=C$\mathbf{H}_2$), 5.19 (1H, dd, *J* = 16.1, 9.5 Hz, CH(CH)C**H**=CH), 5.09 (1H, d, *J* = 1.6 Hz, C=C$\mathbf{H}_2$), 4.49 (2H, s, C(=$CH_2$)C$\mathbf{H}_2$OTBDPS), 4.05–

3.98 (1H, m, TsOC**H**$_2$CH$_2$), 3.89 (1H, td, *J* = 9.3, 5.5 Hz, TsOC**H**$_2$CH$_2$), 2.03 (3H, s, ArC**H**$_3$), 1.87–1.77 (1H, m, CH$_2$C**H**(CH)CH=), 1.72–1.63 (1H, m, OCH$_2$C**H**$_2$CH), 1.35–1.24 (1H, m, CHC**H**(CH$_3$)$_2$), 1.24 (9H, s, SiC(C**H**$_3$)$_3$), 1.22–1.07 (1H, m, OCH$_2$C**H**$_2$CH), 0.77 (3H, d, *J* = 6.8, Hz, CH(C**H**$_3$)$_2$), 0.69 (3H, d, *J* = 6.8, Hz, CH(C**H**$_3$)$_2$); $\delta_C$ (100 MHz, $C_6D_6$) 144.3 (Ar), 144.2 (**C**=CH$_2$), 135.8 (4C, Ar), 134.3 (Ar), 133.8 (Ar), 133.7 (Ar), 132.2 (CH=**C**HC(=CH$_2$)), 130.3 (CH(CH)**C**H=CH), 130.1 (Ar), 130.1 (Ar), 129.9 (2C, Ar), 128.2 (2C, Ar), 128.1 (2C, Ar), 128.1 (2C, Ar), 114.0 (C=**C**H$_2$), 69.0 (TsO**C**H$_2$CH$_2$), 64.1 (C(=CH$_2$)**C**H$_2$OTBDPS), 46.1 (CH$_2$**C**H(CH)CH=), 32.1 (CH**C**H(CH$_3$)$_2$), 31.5 (OCH$_2$**C**H$_2$CH), 26.9 (3C, SiC(**C**H$_3$)$_3$), 21.2 (Ar**C**H$_3$), 20.5 (CH(**C**H$_3$)$_2$), 19.5 (Si**C**(CH$_3$)$_3$), 19.1 (CH(**C**H$_3$)$_2$); *m*/*z* (ESI$^+$) 599 ([M+Na]$^+$ 100%); HRMS *m*/*z* (ESI$^+$) found 599.2618, $C_{34}H_{44}NaO_4SSi$ requires 599.2622; $\nu_{max}$ (film)/cm$^{-1}$ 3061 (w, =CH$_2$), 2957 (m, CH), 2863 (m, CH), 1901 (w, Ph overtone), 1815 (w, Ph overtone), 1600 (w, C=C), 1464 (m), 1431 (m), 1359 (s, R-SO$_2$-R), 1179 (s, R-SO$_2$-R), 1103 (s, SiO), 959 (m, C=CH$_2$), 909 (m, C=CH$_2$).

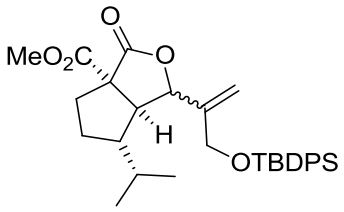
***(S,E)-Dimethyl 2-(6-(((tert-butyldiphenylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-yl)malonate ((S)-226)***




To a stirred suspension of hexane washed NaH (180 mg, 7.54 mmol, 3.0 eq.), in anhydrous DMF (6.28 mL) cooled to 0 °C in an ice/water bath, was carefully added dropwise dimethyl malonate (996 mg, 7.54 mmol, 3.0 eq.). The resulting mixture was stirred for 20 min at 0 °C, after which a solution of (S,*E*)-6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-yl 4-methylbenzenesulfonate ((*S*)-**265**) (1.45 g, 2.51 mmol, 1.0 eq.) in anhydrous THF (6.28 mL) was added *via* cannula followed by potassium iodide (208 mg, 1.26 mmol, 0.5 eq.). The mixture was heated at 80 °C for 1.5 h and then cooled to room temperature. Sat. aq. $NH_4Cl$ solution (20 mL)

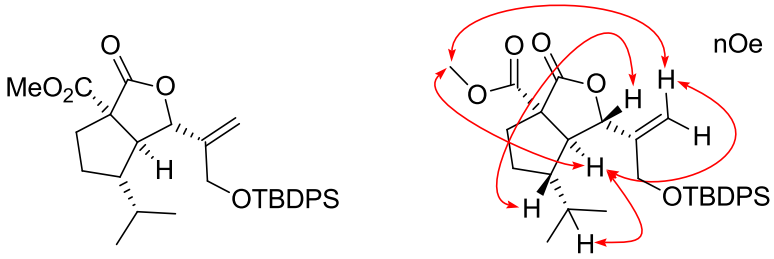
was added to the mixture and extracted with EtOAc (3 × 20 mL). The combined organic extracts were sequentially washed with water (60 mL), brine (60 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60 with 1% triethylamine) to afford (S,*E*)-dimethyl 2-(6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-yl)malonate ((*S*)-**226**) as a colourless oil (1.12 g, 2.11 mmol, 84%, >99% *ee* (*S*)). $[\alpha]_D^{20}$ -0.2 (*c* 1.01, DCM), $[\alpha]_{354}^{20}$ +10.1 (*c* 1.01, DCM) for >99% ee; $R_f$ = 0.29 (15% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $C_6D_6$) 7.91 (4H, dd, *J* = 6.0, 2.6 Hz, Ar**H**), 7.35–7.29 (6H, m, Ar**H**), 6.15 (1H, d, *J* = 16.0 Hz, CH=C**H**C(=$CH_2$)), 5.60 (1H, s, C=C$\mathbf{H_2}$), 5.50 (1H, dd, *J* = 16.0, 9.4 Hz, CH(CH)C**H**=CH), 5.21 (1H, s, C=C$\mathbf{H_2}$), 4.62 (2H, s, C(=$CH_2$)C$\mathbf{H_2}$OTBDPS), 3.41 (1H, t, *J* = 7.5 Hz, $(MeO_2C)_2$C**H**$CH_2$), 3.40 (3H, s, OC$\mathbf{H_3}$), 3.39 (3H, s, OC$\mathbf{H_3}$), 2.18–1.96 (2H, m, CHC$\mathbf{H_2}CH_2$), 1.82–1.73 (1H, m, $CH_2$C**H**(CH)CH=), 1.57–1.44 (2H, m, CHC**H**$(CH_3)_2$ and $CH_2$C$\mathbf{H_2}$CH), 1.34–1.25 (1H, m, $CH_2$C$\mathbf{H_2}$CH), 1.29 (9H, s, SiC(C$\mathbf{H_3}$)$_3$), 0.89 (3H, d, *J* = 6.7, Hz, CH(C$\mathbf{H_3}$)$_2$), 0.79 (3H, d, *J* = 6.7, Hz, CH(C$\mathbf{H_3}$)$_2$); $\delta_C$ (100 MHz, $C_6D_6$) 169.6 (**C**=O), 169.5 (**C**=O), 144.6 (**C**=$CH_2$), 135.9 (4C, Ar), 133.9 (2C, Ar), 131.7 (CH(CH)**C**H=CH), 131.6 (CH=**C**HC(=$CH_2$)), 130.0 (2C, Ar), 128.1 (4C, Ar), 113.7 (C=**C**$H_2$), 64.4 (C(=$CH_2$)**C**$H_2$OTBDPS), 51.9 ($(MeO_2C)_2$**C**H$CH_2$), 51.8 (2C, O**C**$H_3$), 50.0 ($CH_2$**C**H(CH)CH=), 32.0 (CH**C**H$(CH_3)_2$), 30.2 (CH**C**$H_2CH_2$), 27.4 ($CH_2$C$\mathbf{H_2}$CH), 26.9 (3C, SiC(**C**$H_3$)$_3$), 20.8 (CH(**C**$H_3$)$_2$), 19.5 (Si**C**$(CH_3)_3$), 19.1 (CH(**C**$H_3$)$_2$); LRMS *m*/*z* ($ESI^+$) 559 ($[M+Na]^+$ 100%); HRMS *m*/*z* ($ESI^+$) found 559.2838, $C_{32}H_{44}NaO_5Si$ requires 559.2850; $\nu_{max}$ (film)/$cm^{-1}$ 2955 (m, CH), 2863 (m, CH), 1966 (w), 1896 (w), 1742 (s, C=O), 1605 (w), 1460 (m), 1436 (m), 1136 (m), 1248 (m), 1152 (m, C-O), 1106 (s), 1009 (m), 970 (m), 898 (m), 820 (s), 747 (m), 701 (s).

***(3aR,6S,6aS)-Methyl 1-(3-((tert-butyldiphenylsilyl)oxy)prop-1-en-2-yl)-6-isopropyl-3-oxohexahydro-1H-cyclopenta[c]furan-3a-carboxylate ((+)-166b)***



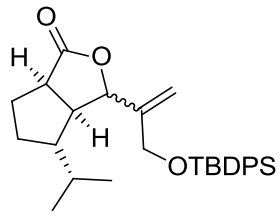

A mixture of manganese(III) acetate (1.00 g, 3.76 mmol, 2.0 eq.) and copper(II) triflate (681 mg, 1.88 mmol, 1.0 eq.) were pre heated to 80 °C, after which a solution of (*S,E*)-dimethyl 2-(6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-yl)malonate ((*S*)-**226**) (1.01 g, 1.88 mmol, 1.0 eq.) in Ar sparged acetonitrile (9.40 mL) was rapidly added. The resulting mixture was heated at 80 °C for 30 min and then cooled to room temperature. Water (10 mL) and $Et_2O$ (10 mL) were added and stirred for 10 min. The organic layer was separated and the aq. layer was further extracted with $Et_2O$ (2 × 10 mL). The combined organic layers were sequentially washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60) to afford (3*a*R,6*S*,6*a*S)-methyl 1-(3-((*tert*-butyldiphenylsilyl)oxy)prop-1-en-2-yl)-6-isopropyl-3-oxohexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate ((+)-**166b**, diastereomeric ratio = 6:1) as a colourless oil (720 mg, 1.39 mmol, 74%, >99% *ee* (*S*)). The *ee* was measured by HPLC (Chiralpak AD-H column, flow 0.6 mL/min, 1.0% IPA/hexane, 230 nm, $t_1$ = 8.4 (minor *S*) and 9.6 min (major *S*), $t_2$ = 9.6 (minor *R*) and 10.6 min (major *R*); $[\alpha]_D^{20}$ +1.3 (*c* 0.98, $CHCl_3$), $[\alpha]_{354}^{20}$ +2.6 (*c* 0.98, $CHCl_3$) for >99% *ee* and a diastereomeric ratio of 6:1. Characterisation is reported for the major epimer of an inseparable mixture of diastereoisomers.

***(1S,3aR,6S,6aS)-Methyl 1-(3-((tert-butyldiphenylsilyl)oxy)prop-1-en-2-yl)-6-isopropyl-3-oxohexahydro-1H-cyclopenta[c]furan-3a-carboxylate***



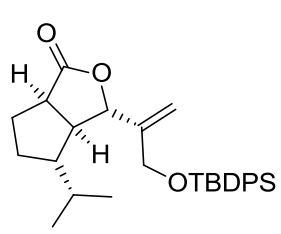

Major Epimer: $R_f$ = 0.21 (10% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 7.70–7.65 (4H, m, Ar**H**), 7.47–7.37 (6H, m, Ar**H**), 5.38 (1H, d, *J* = 0.8 Hz, C=C**H**$_2$), 5.24 (1H, d, *J* = 0.8 Hz, C=C**H**$_2$), 4.76 (1H, d, *J* = 3.7 Hz, CHC**H**(C=O), 4.26 (2H, s, C(=$CH_2$)C**H**$_2$OTBDPS), 3.55 (3H, s, OC**H**$_3$), 2.84 (1H, dd, *J* = 5.3, 3.7 Hz, CHC**H**CHO), 2.48 (1H, dt, *J* = 13.0, 6.5 Hz, $CH_2$C**H**$_2$CC(=O)), 2.14–2.05 (1H, m, $CH_2$C**H**$_2$CC(=O)), 1.90–1.79 (1H, m, $CH_2$C**H**$_2$CH), 1.76–1.65 (2H, m, $CH_2$C**H**$_2$CH and $CH_2$C**H**(CH)CH), 1.55 (1H, dsept, *J* = 6.8, 6.8 Hz, CHC**H**$(CH_3)_2$), 1.08 (9H, s, SiC(C**H**$_3)_3$), 0.88 (3H, d, *J* = 6.8 Hz, CH(C**H**$_3)_2$), 0.86 (3H, d, *J* = 6.8 Hz, CH(C**H**$_3)_2$); $\delta_C$ (100 MHz, $CDCl_3$) 175.6 (**C**=O), 171.0 (**C**$O_2$Me), 144.9 (**C**=$CH_2$), 135.5 (2C, Ar), 135.4 (2C, Ar), 133.2 (Ar), 133.0 (Ar), 129.8 (2C, Ar), 127.8 (4C, Ar), 112.1 (C=**C**$H_2$), 84.7 (CH**C**H(C=O), 63.2 (C(=$CH_2$)**C**$H_2$OTBDPS), 61.6 ($CH_2$**C**($CO_2$Me)C), 55.0 ($CH_2$**C**H(CH)CH), 54.3 (CH**C**HCHO), 52.8 (O**C**$H_3$), 34.2 ($CH_2$**C**$H_2$CC(=O)), 30.3 (CH**C**H$(CH_3)_2$), 29.6 ($CH_2$**C**$H_2$CH), 26.7 (3C, SiC(**C**$H_3)_3$), 21.7 (CH(**C**$H_3)_2$), 19.9 (CH(**C**$H_3)_2$), 19.2 (Si**C**$(CH_3)_3$); LRMS *m*/*z* ($ESI^+$) 543 ($[M+Na]^+$, 50%), 580 (100%); HRMS *m*/*z* ($ESI^+$) found 543.2528, $C_{31}H_{40}NaO_5Si$ requires 543.2537; $\nu_{max}$ (film)/$cm^{-1}$ 3073 (w, =$CH_2$), 2959 (m, CH), 2932 (m, CH), 2859 (m, CH), 1776 (s, C=O), 1739 (s, C=O), 1239 (m, C-O), 1111 (s, Si-O-C), 907 (s, C=$CH_2$), 823 (m, Si-O-C).

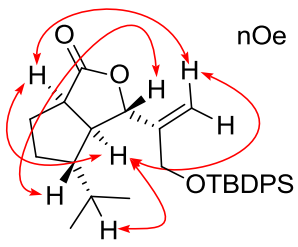
***(3aS,4S,6aR)-3-(3-((tert-Butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropylhexahydro-1H-cyclopenta[c]furan-1-one ((-)-269)***




To a stirred solution of (3a*R*,6*S*,6a*S*)-methyl 1-(3-((*tert*-butyldiphenylsilyl)oxy)prop-1-en-2-yl)-6-isopropyl-3-oxohexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate ((+)-**166b**, diastereomeric ratio = 6:1) (702 mg, 1.35 mmol, 1.0 eq.) in anhydrous DMF was added water (48.6 mg, 2.70 mmol, 2.0 eq.) and lithium chloride (114 mg, 2.70 mmol, 2.0 eq.). The resulting mixture was heated at 150 °C for 6 h then cooled to room temperature. Sat. aq. $NH_4Cl$ solution (20 mL) was added to the mixture and extracted with $Et_2O$ (3 × 10 mL). The combined organic extracts were sequentially washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10-20% gradient EtOAc/petrol 40-60) to afford (3a*S*,4*S*,6a*R*)-3-(3-((*tert*-butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropylhexahydro-1*H*-cyclopenta[*c*]furan-1-one ((-)-**269**, diastereomeric ratio = 6:1) as a colourless oil (541 mg, 1.16 mmol, 86%, >99% *ee* (*S*)). Characterisation is reported for the major and minor epimers as separated by flash column chromatography.

***(3S,3aS,4S,6aR)-3-(3-((tert-Butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropylhexahydro-1H-cyclopenta[c]furan-1-one***

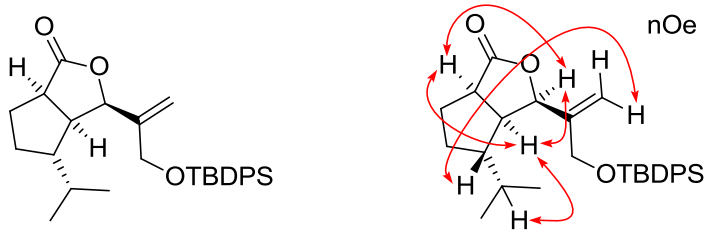



Major Epimer (465 mg, 1.00 mmol, 75%, >99% *ee* (*S*)): $[\alpha]_D^{20}$ -6.6 (*c* 0.96, $CHCl_3$), $[\alpha]_{354}^{20}$ -20.4 (*c* 0.96, $CHCl_3$) for >99% ee; $R_f$ = 0.38 (20% EtOAc/petrol 40-60); $\delta_H$ (500 MHz, $CDCl_3$) 7.69–7.65

(4H, m, Ar**H**), 7.47–7.42 (2H, m, Ar**H**), 7.42–7.37 (4H, m, Ar**H**), 5.28 (1H, s, C=C**H**$_2$), 5.16 (1H, s, C=C**H**$_2$), 4.77 (1H, d, *J* = 2.6 Hz, CHC**H**(C=)O), 4.24 (1H, d, *J* = 13.9 Hz, C(=CH$_2$)C**H**$_2$OTBDPS), 4.18 (1H, d, *J* = 13.9 Hz, C(=CH$_2$)C**H**$_2$OTBDPS), 2.98 (1H, dt, *J* = 9.6, 4.9 Hz, CH$_2$C**H**C=O), 2.46 (1H, ddd, *J* = 9.6, 7.2, 2.6 Hz, CHC**H**CHO), 2.11–2.03 (1H, m, CH$_2$C**H**$_2$CHC=O), 1.93–1.86 (1H, m, CH$_2$C**H**$_2$CHC=O), 1.86–1.78 (1H, m, Hz, CH$_2$C**H**$_2$CH(*i*-Pr)), 1.66–1.59 (1H, m, CH$_2$C**H**(*i*-Pr)CH), 1.55 (1H, dsept, *J* = 6.7, 6.7 Hz, CHC**H**(CH$_3$)$_2$), 1.47–1.39 (1H, m, CH$_2$C**H**$_2$CH(*i*-Pr)), 1.07 (9H, s, SiC(C**H**$_3$)$_3$), 0.91 (3H, d, *J* = 6.7, Hz, CH(C**H**$_3$)$_2$), 0.86 (3H, d, *J* = 6.7, Hz, CH(C**H**$_3$)$_2$); $\delta_C$ (125 MHz, $CDCl_3$) 180.6 (**C**=O), 145.8 (**C**=CH$_2$), 135.5 (2C, Ar), 135.4 (2C, Ar), 134.8 (Ar), 133.1 (Ar), 132.9 (Ar), 129.8 (Ar), 127.7 (2C, Ar), 127.7 (2C, Ar), 111.7 (C=**C**H$_2$), 84.5 (CH**C**H(C=)O), 63.5 (C(=CH$_2$)**C**H$_2$OTBDPS), 53.4 (CH$_2$**C**H(*i*-Pr)CH), 49.1 (CH**C**HCHO), 44.4 (CH$_2$**C**HC=O), 30.9 (CH**C**H(CH$_3$)$_2$), 29.6 (CH$_2$**C**H$_2$CH(*i*-Pr)), 28.3 (**C**H$_2$CHC=O), 26.7 (3C, SiC(**C**H$_3$)$_3$), 21.7 (CH(**C**H$_3$)$_2$), 19.9 (CH(**C**H$_3$)$_2$), 19.2 (Si**C**(CH$_3$)$_3$); LRMS *m*/*z* ($ESI^+$) 331 (100%), 485 ($[M+Na]^+$, 80%), 947 ($[2M+Na]^+$, 65%); HRMS *m*/*z* ($ESI^+$) found 485.2485 $C_{29}H_{38}NaO_3Si$ requires 485.2482; $\nu_{max}$ (film)/$cm^{-1}$ 3071 (w, =CH$_2$), 2958 (m, CH), 2931 (m, CH), 2858 (m, CH), 1772 (s, C=O), 1257 (m, C-O), 1111 (s, Si-O-C), 915 (m, C=CH$_2$), 823 (m, Si-O-C).

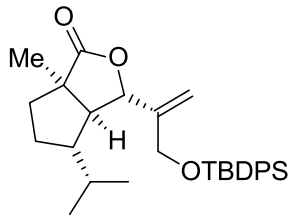
***(3R,3aS,4S,6aR)-3-(3-((tert-Butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropylhexahydro-1H-cyclopenta[c]furan-1-one***




Minor Epimer (76 mg, 0.16 mmol, 12%, >99% *ee* (*S*)): $[\alpha]_D^{20}$ -23.0 (*c* 1.00, $CHCl_3$), $[\alpha]_{354}^{20}$ -76.9 (*c* 1.00, $CHCl_3$) for >99% ee; $R_f$ = 0.31 (20% EtOAc/petrol 40-60); $\delta_H$ (500 MHz, $CDCl_3$) 7.70–7.64 (4H, m, Ar**H**), 7.48–7.43 (2H, m, Ar**H**), 7.42–7.38 (4H, m, Ar**H**), 5.39 (1H, s, C=C**H**$_2$), 5.29

(1H, s, C=C**H**$_2$), 5.09 (1H, d, *J* = 6.4 Hz, CHCHC**H**O), 4.16 (1H, d, *J* = 13.8 Hz, CC**H**$_2$OTBDPS), 4.10 (1H, d, *J* = 13.8 Hz, CC**H**$_2$OTBDPS), 3.09 (1H, ddd, *J* = 8.6, 8.6, 2.2 Hz, CH$_2$C**H**C=O), 2.56 (1H, ddd, *J* = 8.2, 6.4, 2.2 Hz, CHC**H**CHO), 2.07–2.00 (1H, m, CH$_2$C**H**$_2$CHC(=O)), 1.90–1.80 (1H, m, CH$_2$C**H**$_2$CHC(=O)), 1.78–1.71 (1H, m, CH$_2$C**H**(*i*-Pr)CH), 1.57–1.36 (3H, m, CH$_2$C**H**$_2$CH(*i*-Pr) & CHC**H**(CH$_3$)$_2$), 1.08 (9H, s, SiC(C**H**$_3$)$_3$), 0.76 (3H, d, *J* = 6.8, Hz, CH(C**H**$_3$)$_2$), 0.69 (3H, d, *J* = 6.8, Hz, CH(C**H**$_3$)$_2$); $\delta_C$ (125 MHz, $CDCl_3$) 180.3 (**C**=O), 142.7 (**C**=CH$_2$), 135.5 (2C, Ar), 135.5 (2C, Ar), 133.1 (Ar), 132.9 (Ar), 129.9 (2C, Ar), 127.8 (2C, Ar), 127.8 (2C, Ar), 110.8 (C=**C**H$_2$), 80.0 (CHCH**C**HO), 64.2 (C**C**H$_2$OTBDPS), 47.5 (CH$_2$**C**HC=O), 46.5 (CH$_2$**C**H(*i*-Pr)CH), 45.3 (CH**C**HCHO), 29.7 (CH**C**H(CH$_3$)$_2$), 28.4 (CH$_2$**C**H$_2$CHC(=O)), 26.8 (3C, SiC(**C**H$_3$)$_3$), 26.3 (CH$_2$**C**H$_2$CH(*i*-Pr)), 22.0 (CH(**C**H$_3$)$_2$), 19.2 (Si**C**(CH$_3$)$_3$), 17.2 (CH(**C**H$_3$)$_2$); LRMS *m*/*z* (ESI$^+$) 485 ([M+Na]$^+$, 60%), 947 ([2M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 485.2478, $C_{29}H_{38}NaO_3Si$ requires 485.2482; $\nu_{max}$ (film)/cm$^{-1}$ 3071 (w, =CH$_2$), 2958 (m, CH), 2931 (m, CH), 2858 (m, CH), 1774 (s, C=O), 1660 (w), 1589 (w), 1471 (m), 1428 (m), 1389 (m), 1363 (m), 1257 (m, C-O), 1112 (s, Si-O-C), 1017 (m), 911 (m, C=CH$_2$), 823 (m, Si-O-C).

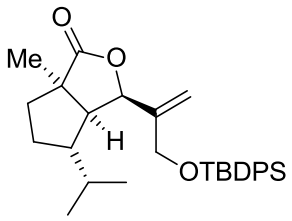
***(3S,3aS,4S,6aR)-3-(3-((tert-Butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropyl-6a-methylhexahydro-1H-cyclopenta[c]furan-1-one ((-)-270)***




To a vigorously stirred solution of (3*S*,3a*S*,4*S*,6a*R*)-3-(3-((*tert*-butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropylhexahydro-1*H*-cyclopenta[*c*]furan-1-one ((3*S*,4*S*,5*S*,10*R*)-**269**) (450 mg, 0.97 mmol, 1.0 eq.) in anhydrous THF (19.4 mL) cooled to -78 °C in a dry ice/acetone bath was added methyl iodide (691 mg, 4.86 mmol, 5.0 eq.) followed by dropwise addition of a 1 M solution of LiHMDS in toluene (4.86 mL, 4.86 mmol, 5.0 eq.). The resulting mixture was stirred for 30 min at -78 °C. Sat. aq. $NH_4Cl$ solution (20 mL) was added to the mixture and extracted with $Et_2O$ (3 × 10 mL).

The combined organic extracts were sequentially washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60) to afford (3*S*,3a*S*,4*S*,6a*R*)-3-(3-((*tert*-butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropyl-6a-methylhexahydro-1*H*-cyclopenta[*c*]furan-1-one ((-)-**270**) as a colourless oil (414 mg, 0.87 mmol, 90%, >99% *ee* (*S*)). The *ee* was measured by HPLC (Chiralcel OD column, flow 0.6 mL/min, 1.0% IPA/hexane, 230 nm, $t_1$ = 15.2 min (*S*), $t_2$ = 16.5 min (*R*); $[\alpha]_D^{20}$ -7.5 (*c* 1.00, $CHCl_3$), $[\alpha]_{354}^{20}$ -23.3 (*c* 1.00, $CHCl_3$) for >99% ee; $R_f$ = 0.21 (10% EtOAc/petrol 40-60); $\delta_H$ (500 MHz, $CDCl_3$) 7.70–7.65 (4H, m, Ar**H**), 7.47–7.36 (6H, m, Ar**H**), 5.33 (1H, s, C=C$\mathbf{H_2}$), 5.22 (1H, s, C=C$\mathbf{H_2}$), 4.65 (1H, d, *J* = 3.9 Hz, CHC**H**(C)O), 4.21 (2H, s, CC$\mathbf{H_2}$OTBDPS), 2.17–2.14 (1H, m, CHC**H**(C)CHO), 2.01 (1H, ddd, *J* = 13.1, 8.7, 7.0 Hz, $CH_2C\mathbf{H_2}$C(Me)), 1.81–1.74 (1H, m, $CH_2C\mathbf{H_2}$CH(*i*-Pr)), 173–1.64 (2H, m, $CH_2C\mathbf{H_2}$C(Me) & $CH_2C\mathbf{H}$(*i*-Pr)CH), 1.59–1.49 (2H, m, $CH_2C\mathbf{H_2}$CH(*i*-Pr) & CHC**H**$(CH_3)_2$), 1.25 (3H, s, C(C$\mathbf{H_3}$)), 1.08 (9H, s, SiC(C$\mathbf{H_3}$)$_3$), 0.87 (3H, d, *J* = 6.7 Hz, CH(C$\mathbf{H_3}$)$_2$), 0.84 (3H, d, *J* = 6.7 Hz, CH(C$\mathbf{H_3}$)$_2$); $\delta_C$ (125 MHz, $CDCl_3$) 182.6 (C=O), 145.9 (**C**=$CH_2$), 135.5 (2C, Ar), 135.4 (2C, Ar), 133.1 (Ar), 133.0 (Ar), 129.8 (2C, Ar), 127.8 (2C, Ar), 127.7 (2C, Ar), 111.2 (C=**C**$H_2$), 84.0 (CH**C**H(C)O), 63.4 (C**C**$H_2$OTBDPS), 55.5 ($CH_2\mathbf{C}$H(*i*-Pr)CH), 55.1 (CH**C**H(C)CHO), 51.1 ($CH_2\mathbf{C}$(Me)C), 37.8 ($CH_2\mathbf{C}H_2$C(Me)), 30.8 (CH**C**H$(CH_3)_2$), 29.0 ($CH_2\mathbf{C}H_2$CH(*i*-Pr)), 26.7 (3C, SiC(**C**$H_3$)$_3$), 24.2 (C(**C**$H_3$)), 21.8 (CH(**C**$H_3$)$_2$), 19.9 (CH(**C**$H_3$)$_2$), 19.2 (Si**C**$(CH_3)_3$); LRMS *m*/*z* ($ESI^+$) 499 ($[M+Na]^+$, 49%), 975 ($[2M+Na]^+$, 100%); HRMS *m*/*z* ($ESI^+$) found 499.2636, $C_{30}H_{40}NaO_3Si$ requires 499.2639; $\nu_{max}$ (film)/$cm^{-1}$ 3071 (w, =$CH_2$), 2958 (s, CH), 2932 (m, CH), 2858 (m, CH), 1771 (s, C=O), 1658 (w), 1590 (w), 1471 (m), 1428 (m), 1389 (m), 1374 (m), 1337 (w), 1307 (w), 1255 (w), 1209 (w), 1162 (w, C-O), 1110 (s, Si-O-C), 1056 (m), 1010 (m), 914 (m, C=$CH_2$), 823 (m, Si-O-C), 741 (m), 702 (s).

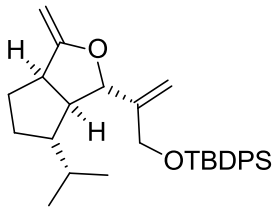
***(3*R*,3a*S*,4*S*,6a*R*)-3-(3-((tert-Butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropyl-6a-methylhexahydro-1H-cyclopenta[c]furan-1-one ((-)-270)***

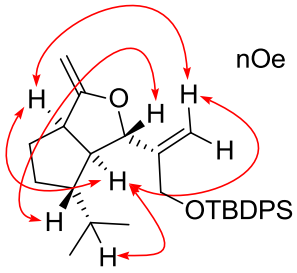



To a vigorously stirred solution of (3*R*,3*aS*,4*S*,6*aR*)-3-(3-((*tert*-butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropylhexahydro-1*H*-cyclopenta[*c*]furan-1-one ((3*S*,4*S*,5*R*,10*R*)-**269**) (69.0 mg, 0.15 mmol, 1.0 eq.) in anhydrous THF (3.0 mL) cooled to -78 °C in a dry ice/acetone bath was added methyl iodide (106 mg, 0.75 mmol, 5 eq.) followed by dropwise addition of a 1 M solution of LiHMDS in toluene (0.75 mL, 0.75 mmol, 5.0 eq.). The resulting mixture was stirred for 30 min at -78 °C. Sat. aq. $NH_4Cl$ solution (20 mL) was added to the mixture and extracted with $Et_2O$ (3 × 10 mL). The combined organic extracts were sequentially washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60) to afford (3*R*,3a*S*,4*S*,6a*R*)-3-(3-((*tert*-butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropyl-6a-methylhexahydro-1*H*-cyclopenta[*c*]furan-1-one ((3*S*,4*S*,5*R*,10*R*)-**270**) as a colourless oil (53.3 mg, 0.11 mmol, 75%, >99% *ee* (*S*)). $[\alpha]_D^{20}$ -15.3 (*c* 1.00, $CHCl_3$) for >99% ee; $R_f$ = 0.30 (10% EtOAc/petrol 40-60); $\delta_H$ (500 MHz, $CDCl_3$) 7.70–7.64 (4H, m, Ar**H**), 7.48–7.37 (6H, m, Ar**H**), 5.34 (1H, s, C=C**H**$_2$), 5.30 (1H, s, C=C**H**$_2$), 5.10 (1H, d, *J* = 6.1 Hz, CHC**H**(C)O), 4.16 (1H, d, *J* = 13.8 Hz, CC**H**$_2$OTBDPS), 4.10 (1H, d, *J* = 13.8 Hz, CC**H**$_2$OTBDPS), 2.17–2.10 (2H, m, $CH_2$C**H**$_2$C(Me) & CHC**H**(C)CHO), 1.85–1.78 (1H, m, $CH_2$C**H**(*i*-Pr)CH), 1.57–1.49 (2H, m, $CH_2$C**H**$_2$CH(*i*-Pr) & $CH_2$C**H**$_2$C(Me)), 1.47–1.33 (2H, m, $CH_2$C**H**$_2$CH(*i*-Pr) & CHC**H**$(CH_3)_2$), 1.35 (3H, s, C(C**H**$_3$)), 1.09 (9H, s, SiC(C**H**$_3$)$_3$), 0.75 (3H, d, *J* = 6.8 Hz, CH(C**H**$_3$)$_2$), 0.69 (3H, d, *J* = 6.8 Hz, CH(C**H**$_3$)$_2$); $\delta_C$ (125 MHz, $CDCl_3$) 182.6 (**C**=O), 142.7 (**C**=$CH_2$), 135.5 (2C, Ar), 135.5 (2C, Ar), 133.0 (Ar), 132.9 (Ar), 129.9 (Ar), 129.9 (Ar), 127.8 (2C, Ar), 127.8 (2C, Ar), 110.9 (C=**C**$H_2$), 78.7 (CH**C**H(C)O), 64.2 (C**C**$H_2$OTBDPS), 54.0

($CH_2$**C**(Me)C), 53.4 (CHC**H**(C)CHO), 45.9 ($CH_2$**C**H(*i*-Pr)CH), 37.3 ($CH_2$**C**$H_2$C(Me)), 30.5 (CH**C**H($CH_3$)$_2$), 26.8 (3C, SiC(**C**$H_3$)$_3$), 25.9 ($CH_2$**C**$H_2$CH(*i*-Pr)), 21.8 (CH(**C**$H_3$)$_2$), 21.2 (C(**C**$H_3$)), 19.2 (Si**C**($CH_3$)$_3$), 17.5 (CH(**C**$H_3$)$_2$); LRMS *m*/*z* (ESI$^+$) 499 ([M+Na]$^+$, 44%), 975 ([2M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 499.2635, $C_{30}H_{40}NaO_3Si$ requires 499.2639; $\nu_{max}$ (film)/cm$^{-1}$ 3071 (w, =$CH_2$), 2958 (s, CH), 2931 (m, CH), 2859 (m, CH), 1774 (s, C=O), 1660 (w), 1590 (w), 1471 (m), 1428 (m), 1389 (m), 1363 (m), 1329 (w), 1307 (w), 1272 (w), 1162 (m, C-O), 1112 (s, Si-O-C), 1074 (m), 1014 (m), 913 (m, C=$CH_2$), 824 (m, Si-O-C), 741 (m), 703 (s).

**tert-*Butyl((2-((1S,3aR,6S,6aS)-6-isopropyl-3a-methyl-3-methylenehexahydro-1H-cyclopenta[c]furan-1-yl)allyl)oxy)diphenylsilane ((-)-271)***

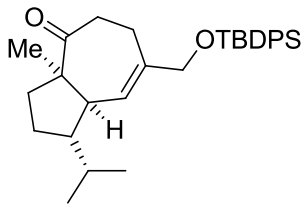



A sealed tube was charged with (3*S*,3*aS*,4*S*,6*aR*)-3-(3-((*tert*-butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropyl-6a-methylhexahydro-1*H*-cyclopenta[*c*]furan-1-one ((-)-**270**) (47.7 mg, 0.10 mmol, 1.0 eq.) and a 0.24 M solution of the Petasis reagent in toluene (1.25 mL, 0.30 mmol, 3.0 eq.). The resulting mixture was covered and heated at 110 °C for 1 h, then cooled to room temperature. Hexane (10 mL) and Celite were added to the mixture and stirred for 30 min, then filtered through a Celite plug washing with hexane (2 × 10 mL). The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (0-15% EtOAc/petrol 40-60 with 1% triethylamine) to afford *tert*-butyl((2-((1*S*,3a*R*,6*S*,6a*S*)-6-isopropyl-3a-methyl-3-methylenehexahydro-1*H*-cyclopenta[*c*]furan-1-yl)allyl)oxy)diphenylsilane ((-)-**271**) as a pale orange oil (39.9 mg, 0.08 mmol, 84%, >99% ee (*S*)). $[\alpha]_D^{20}$ -3.2 (*c* 1.00, $CHCl_3$) for >99% ee; $R_f$ = 0.15 (10% EtOAc/petrol 40-60); $\delta_H$ (500 MHz, $C_6D_6$) 7.93–7.88 (4H, m, Ar**H**), 7.36–7.30 (6H, m, Ar**H**), 5.61 (1H, dd, *J* = 3.0, 1.4 Hz, CHC(=C**H**$_2$)$CH_2$), 5.43 (1H, dt, *J* = 3.0, 1.4 Hz,

CHC(=C**H**$_2$)CH$_2$), 4.60 (1H, d, *J* = 1.4 Hz, CC(=C**H**$_2$)O), 4.56 (1H, d, *J* = 5.1 Hz, CHC**H**(C)O), 4.51 (1H, t, *J* = 1.4 Hz, CC**H**$_2$OTBDPS), 4.49 (1H, t, *J* = 1.4 Hz, CC**H**$_2$OTBDPS), 3.96 (1H, d, *J* = 1.4 Hz, CC(=C**H**$_2$)O), 2.05 (1H, dd, *J* = 5.1, 5.1 Hz, CHC**H**(C)CHO), 1.92 (1H, ddd, *J* = 12.5, 10.1, 6.8 Hz, (C)C**H**$_2$CH$_2$CH), 1.75 (1H, dddd, *J* = 12.5, 6.8, 6.8, 4.0 Hz, (C)CH$_2$C**H**$_2$CH), 1.62 (1H, ddd, *J* = 12.5, 6.8, 4.0 Hz, (C)C**H**$_2$CH$_2$CH), 1.55–1.48 (1H, m, CH$_2$C**H**(*i*-Pr)CH), 1.44–1.34 (2H, m, CHC**H**(CH$_3$)$_2$ and (C)CH$_2$C**H**$_2$CH), 1.29 (9H, s, SiC(C**H**$_3$)$_3$), 1.23 (3H, s, C(C**H**$_3$)), 0.88 (3H, d, *J* = 6.6 Hz, CH(C**H**$_3$)$_2$), 0.86 (3H, d, *J* = 6.6 Hz, CH(C**H**$_3$)$_2$); $\delta_C$ (125 MHz, $C_6D_6$) 173.1 (C**C**(=CH$_2$)O), 148.3 (CHC(=**C**H$_2$)CH$_2$), 135.9 (2C, Ar), 135.9 (2C, Ar), 133.9 (Ar), 133.7 (Ar), 130.1 (2C, Ar), 128.3 (Ar), 128.1 (2C, Ar), 127.9 (Ar), 110.6 (CHC(=**C**H$_2$)CH$_2$), 87.8 (CH**C**H(C)O), 78.1 (CHC(=**C**H$_2$)CH$_2$), 63.9 (C**C**H$_2$OTBDPS), 58.7 (CH**C**H(C)CHO), 54.6 (CH$_2$**C**H(*i*-Pr)CH), 53.8 (CH$_2$**C**(Me)C), 41.6 ((C)**C**H$_2$CH$_2$CH), 32.1 (CH**C**H(CH$_3$)$_2$), 30.5 ((C)CH$_2$**C**H$_2$CH), 27.1 (C(**C**H$_3$)), 27.0 (3C, SiC(**C**H$_3$)$_3$), 22.2 (CH(**C**H$_3$)$_2$), 20.3 (CH(**C**H$_3$)$_2$), 19.5 (Si**C**(CH$_3$)$_3$); LRMS *m*/*z* (ESI$^+$) 475 ([M+H]$^+$, 35%), 497 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 497.2845, $C_{31}H_{42}NaO_2Si$ requires 497.2846; $\nu_{max}$ (film)/cm$^{-1}$ 3235 (w), 2958 (m, CH), 2859 (m, CH), 2280 (s, C=CH$_2$)1667 (m, C=CH$_2$), 1618 (m), 1453 (m), 1428 (m), 1390 (w), 1330 (s), 1162 (w), 1112 (m, Si-O-C), 1053 (w), 914 (w), 812 (s, Si-O-C), 741 (m), 704 (s).

***(1S,3aR,8aR)-7-(((tert-Butyldiphenylsilyl)oxy)methyl)-1-isopropyl-3a-methyl-1,3,3a,5,6,8a-hexahydroazulen-4(2H)-one ((+)-272)***



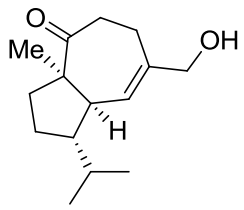

A stirred solution of *tert*-butyl((2-((1*S*,3*aR*,6*S*,6*aS*)-6-isopropyl-3a-methyl-3-methylenehexahydro-1*H*-cyclopenta[*c*]furan-1-yl)allyl)oxy)diphenylsilane ((-)-**271**) (35.0 mg, 0.07 mmol, 1.0 eq.) in anhydrous xylene (1.47 mL) was heated at 150 °C for 18 h, then cooled to room temperature. The mixture was concentrated under reduced pressure. The residue was purified by flash column

chromatography (10% EtOAc/petrol 40-60) to afford (1*S*,3*a*R,8*a*R)-7-(((*tert*-butyldiphenylsilyl)oxy)methyl)-1-isopropyl-3a-methyl-1,3,3a,5,6,8a-hexahydroazulen-4(2*H*)-one ((+)-**274**) as a colourless oil (25.7 mg, 0.05 mmol, 77%, >99% *ee* (*S*)).

**One-pot:** A sealed tube was charged with 3*S*,3a*S*,4*S*,6a*R*)-3-(3-((*tert*-butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropyl-6a-methylhexahydro-1*H*-cyclopenta[*c*]furan-1-one ((-)-**270**) (23.8 mg, 0.05 mmol, 1.0 eq.) and a 0.24 M solution of the Petasis reagent in toluene (0.65 mL, 0.15 mmol, 3.0 eq.). The resulting mixture was covered and heated at 110 °C for 1 h, then cooled to room temperature. Celite and a few drops of hexane were added to the mixture to destroy residual Petasis reagent. The resulting mixture was then heated at 150 °C for 18 h and cooled to room temperature and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60) to afford (1*S*,3*a*R,8*a*R)-7-(((*tert*-butyldiphenylsilyl)oxy)methyl)-1-isopropyl-3a-methyl-1,3,3a,5,6,8a-hexahydroazulen-4(2*H*)-one ((+)-**272**) as a colourless oil (17.6 mg, 0.03 mmol, 74%, >99% *ee* (*S*)). The *ee* was measured by HPLC (Chiralcel OD column, flow 0.6 mL/min, 1.0% IPA/hexane, 230 nm, $t_1$ = 15.2 min (*S*), $t_2$ = 16.5 min (*R*); $[\alpha]_D^{20}$ +22.9 (*c* 1.00, $CHCl_3$) for >99% *ee*; $R_f$ = 0.28 (10% EtOAc/petrol 40-60); $\delta_H$ (500 MHz, $CDCl_3$) 7.68–7.64 (4H, m, Ar**H**), 7.46–7.35 (6H, m, Ar**H**), 5.56 (1H, d, *J* = 4.2 Hz, CHC**H**=C), 4.08 (2H, s, CC**H**$_2$OTBDPS), 2.80–2.74 (1H, m, C(=O)C**H**$_2$CH$_2$), 2.54–2.37 (2H, m, =C(CH$_2$)C**H**$_2$CH$_2$ & C(=O)C**H**$_2$CH$_2$), 2.32–2.27 (1H, m, CHC**H**CH=), 2.22–2.15 (1H, m, =C(CH$_2$)C**H**$_2$CH$_2$), 2.15–2.07 (1H, m, CH$_2$C**H**$_2$C(Me)), 1.84–1.76 (1H, m, CH$_2$C**H**$_2$CH(*i*-Pr)), 1.69–1.61 (1H, m, CH$_2$C**H**(*i*-Pr)CH), 1.61–1.53 (1H, m, CHC**H**(CH$_3$)$_2$), 1.42–1.29 (2H, m, CH$_2$C**H**$_2$C(Me) & CH$_2$C**H**$_2$CH(*i*-Pr)), 1.27 (3H, s, C(C**H**$_3$)), 1.06 (9H, s, SiC(C**H**$_3$)$_3$), 0.93 (3H, d, *J* = 6.6 Hz, CH(C**H**$_3$)$_2$), 0.91 (3H, d, *J* = 6.6 Hz, CH(C**H**$_3$)$_2$); $\delta_C$ (125 MHz, $CDCl_3$) 213.5 (**C**=O), 140.7 (CH=**C**(C)CH$_2$), 135.5 (4C, Ar), 133.6 (CH**C**H=C), 131.0 (2C, Ar), 129.6 (2C, Ar), 127.6 (4C, Ar), 67.3 (C**C**H$_2$OTBDPS), 58.8 (CH$_2$**C**(CH$_3$)C=O), 56.0 (CH$_2$**C**H(*i*-Pr)CH), 51.3 (CH**C**HCH=), 39.6 (C(=O)**C**H$_2$CH$_2$), 34.7 (CH$_2$**C**H$_2$C(Me)), 33.1 (CH**C**H(CH$_3$)$_2$), 27.1 (CH$_2$**C**H$_2$CH(*i*-Pr)), 26.8

(3C, SiC(**C**$H_3$)$_3$), 24.8 (=C($CH_2$)**C**$H_2CH_2$), 24.7 (C(**C**$H_3$)), 22.0 (CH(**C**$H_3$)$_2$), 20.0 (CH(**C**$H_3$)$_2$), 19.2 (Si**C**$(CH_3)_3$); LRMS *m*/*z* (ESI$^+$) 497 ([M+Na]$^+$, 97%), 971 ([2M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 497.2851, $C_{31}H_{42}NaO_2Si$ requires 497.2846; $\nu_{max}$ (film)/cm$^{-1}$ 3071 (w, =CH), 3049 (w, =CH), 2956 (s, CH), 2858 (s, CH), 1959 (w, Ph overtone), 1891 (w, Ph overtone), 1824 (w, Ph overtone), 1699 (s, C=O), 1462 (m), 1428 (m), 1369 (w), 1254 (w), 1111 (s, Si-O-C), 1062 (m), 915 (m, C=C-H), 823 (m, Si-O-C).

**(+)-Aphanamol I ((3*S*,4*R*,10*R*)-91)**

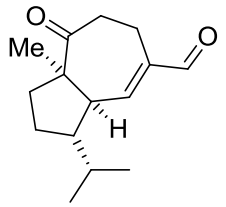



To a stirred solution of (1*S*,3*aR*,8*aR*)-7-(((*tert*-butyldiphenylsilyl)oxy)methyl)-1-isopropyl-3a-methyl-1,3,3a,5,6,8a-hexahydroazulen-4(2*H*)-one ((3*S*,4*R*,10*R*)-**272**) (14.2 mg, 0.03 mmol, 1.0 eq.) in anhydrous THF (0.50 mL) cooled to 0 °C in a ice/water bath was added acetic acid (7.81 mg, 0.13 mmol, 4.0 eq.) followed by dropwise addition of a 1 M solution of TBAF in THF (60.0 μL, 0.06 mmol, 2.0 eq.). The resulting mixture was warmed to room temperature and stirred for 24 h. 1 M HCl (10 mL) was added to the mixture and extracted with $Et_2O$ (3 × 10 mL). The combined organic extracts were sequentially washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (40% EtOAc/petrol 40-60) to afford (+)-aphanamol I ((3*S*,4*R*,10*R*)-**91**) as a colourless oil (7.1 mg, 0.03 mmol, 100%, >99% *ee* (*S*)). $[\alpha]_D^{20}$ +23.3 (*c* 0.40, $CHCl_3$) for >99% *ee*, [lit.[51] $[\alpha]_D^{18}$ +13.8 (*c* 0.29, $CHCl_3$)]; $R_f$ = 0.22 (40% EtOAc/petrol 40-60); $\delta_H$ (500 MHz, $CDCl_3$) 5.53 (1H, d, *J* = 4.5 Hz, C(H)C**H**=C), 4.03 (2H, d, *J* = 2.3 Hz, CC**H**$_2$OH), 2.83 (1H, ddd, *J* = 14.6, 5.8, 3.8 Hz, C(=O)C**H**$_2CH_2$), 2.60–2.51 (1H, m, =C($CH_2$)C**H**$_2CH_2$), 2.43 (1H, ddd, *J* = 14.6, 11.8, 5.8 Hz, C(=O)C**H**$_2CH_2$), 2.32–2.25 (2H, m, =C($CH_2$)C**H**$_2CH_2$ & CHC**H**CH=), 2.14–2.05 (1H, m, $CH_2$C**H**$_2$C(Me)), 1.85–1.75 (1H, m, $CH_2$C**H**$_2$CH(*i*-Pr)), 1.71–1.63 (1H, m, $CH_2$C**H**(CH)CH), 1.63–

1.53 (1H, m, CHC**H**$(CH_3)_2$), 1.42–1.29 (3H, m, $CH_2C\mathbf{H_2}C$(Me), $CH_2O\mathbf{H}$ & $CH_2C\mathbf{H_2}CH$(*i*-Pr)), 1.27 (3H, s, C(C$\mathbf{H_3}$)), 0.92 (3H, d, *J* = 6.5 Hz, CH(C$\mathbf{H_3}$)$_2$), 0.91 (3H, d, *J* = 6.5 Hz, CH(C$\mathbf{H_3}$)$_2$); $\delta_C$ (125 MHz, $CDCl_3$) 213.6 (**C**=O), 141.6 (CH=**C**(C)$CH_2$), 132.9 (C(H)**C**H=C), 67.1 (C**C**$H_2$OH), 58.9 ($CH_2$**C**($CH_3$)C=O), 56.0 ($CH_2$**C**H(CH)CH), 51.4 (CH**C**HCH=), 39.9 (C(=O)**C**$H_2CH_2$), 34.5 ($CH_2$**C**$H_2$C(Me)), 33.0 (CH**C**H$(CH_3)_2$), 27.0 ($CH_2$**C**$H_2$CH(*i*-Pr)), 24.9 (=C($CH_2$)**C**$H_2CH_2$), 24.7 (C(**C**$H_3$)), 22.0 (CH(**C**$H_3)_2$), 19.9 (CH(**C**$H_3)_2$); LRMS *m*/*z* (ESI$^+$) 259 ([M+Na]$^+$, 60%), 495 ([2M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 259.1670, $C_{15}H_{24}NaO_2$ requires 259.1669; $\nu_{max}$ (film)/cm$^{-1}$ 3418 (br, OH), 2960 (m, CH), 2872 (m, CH), 1691 (s, C=O), 1463 (m), 1420 (w), 1386 (w), 1374 (w), 1255 (w), 1174 (w), 1075 (m), 1000 (m).

Data are consistent with literature values.[51]

**(-)-2-Oxoisodauc-5-en-12-al ((3*S*,4*R*,10*R*)-118)**

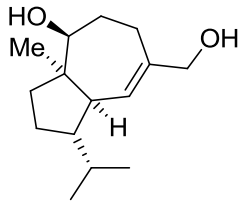



To a vigorously stirred solution of oxalyl chloride (10.6 mg, 0.08 mmol, 1.1 eq.) in anhydrous DCM (0.15 mL) cooled to -78 °C in a dry ice/acetone bath was added dropwise, a solution of DMSO (11.7 mg, 0.15 mmol, 2.2 eq.) in anhydrous DCM (0.10 mL). The resulting mixture was stirred for 2 min followed by dropwise addition of a solution of (+)-aphanamol-I ((3*S*,4*R*,10*R*)-**91**) (17.6 mg, 0.07 mmol, 1.0 eq.) in anhydrous DCM (0.10 mL) and then stirred for 15 min. Triethylamine (35.4 mg, 0.35 mmol, 5.0 eq.) was added to the mixture, warmed to room temperature and stirred for 1 h. Water (10 mL) and DCM (10 mL) was added to the mixture and the organic layer was separated. The aq. layer was further extracted with DCM (2 × 10 mL). The combined organic extracts were washed with water (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 30-40) to afford (-)-2-oxoisodauc-5-en-12-al ((3*S*,4*R*,10*R*)-**118**) as a colourless oil (15.6 mg, 0.06 mmol, 88%).

$[\alpha]_D^{20}$ -6.8 (*c* 0.48, $CHCl_3$) for >99% *ee* [lit.[64] $[\alpha]_D^{20}$ -5.9 (*c* 0.76, $CDCl_3$)]; $R_f$ = 0.24 (10% EtOAc/petrol 40-60); $\delta_H$ (500 MHz, $CDCl_3$) 9.36 (1H, s, CC**H**O), 6.64 (1H, d, *J* = 4.8 Hz, CHC**H**=C), 2.84–2.70 (2H, m, C(=O)C**H**$_2$CH$_2$ & =C(CH$_2$)C**H**$_2$CH$_2$), 2.57–2.40 (3H, m, CH**C**HCH=, =C(CH$_2$)C**H**$_2$CH$_2$ & C(=O)C**H**$_2$CH$_2$), 2.27–2.17 (1H, m, CH$_2$C**H**$_2$CH(*i*-Pr)), 1.91–1.79 (2H, m, CH$_2$C**H**$_2$C(Me) & CH$_2$C**H**(*i*-Pr)CH), 1.66 (1H, dq, *J* = 6.7 Hz, CHC**H**(CH$_3$)$_2$), 1.50–1.39 (2H, m, CH$_2$C**H**$_2$C(Me) & CH$_2$C**H**$_2$CH(*i*-Pr)), 1.33 (3H, s, C(C**H**$_3$)), 0.95 (6H, d, *J* = 6.7 Hz, CH(C**H**$_3$)$_2$); $\delta_C$ (125 MHz, $CDCl_3$) 212.2 (**C**=O), 192.7 (C**C**HO), 158.6 (CHC**H**=C), 143.8 (CH=**C**(C)CH$_2$), 59.6 (CH$_2$**C**(CH$_3$)C=O), 55.4 (CH$_2$**C**H(*i*-Pr)CH), 53.1 (CH**C**HCH=), 38.9 (C(=O)**C**H$_2$CH$_2$), 35.1 (CH$_2$**C**H$_2$CH(*i*-Pr)), 32.4 (CH**C**H(CH$_3$)$_2$), 26.8 (CH$_2$**C**H$_2$C(Me)), 25.0 (C(**C**H$_3$)), 21.9 (CH(**C**H$_3$)$_2$), 19.6 (=C(CH$_2$)**C**H$_2$CH$_2$), 19.5 (CH(**C**H$_3$)$_2$); LRMS *m*/*z* (ESI$^+$) 257 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 257.1509, $C_{15}H_{22}NaO_2$ requires 257.1512; $\nu_{max}$ (film)/cm$^{-1}$ 2957 (s), 2872 (m), 2717 (w), 1686 (s, C=O), 1634 (m, C=O), 1460 (m), 1370 (w), 1313 (w), 1252 (w), 1175 (w), 1072 (w), 945 (w), 916 (w), 794 (w).

Data are consistent with literature values.[64]

**(1*R*,2*S*,7*R*,8*S*)-Isodauc-5-ene-2,12-diol (98)**

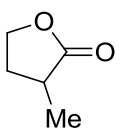



To a stirred solution of (+)-aphanamol-I ((3*S*,4*R*,10*R*)-**91**) (23.6 mg, 0.10 mmol, 1.0 eq.) in ethanol (1.4 mL) was added water (0.6 mL) and $NaBH_4$ (15 mg, 0.40 mmol, 4.0 eq.). The resulting mixture was stirred at room temperature for 1 h. Water (10 mL) was added to the mixture and extracted with DCM (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (60% EtOAc/petrol 40–60) to afford (1*R*,2*S*,7*R*,8*S*)-Isodauc-5-ene-2,12-diol (**98**) as a colourless oil

(18.3 mg, 0.08 mmol, 77%). $[\alpha]_D^{20}$ +41.6 (*c* 0.34, $CHCl_3$) for >99% *ee* [lit.[51] $[\alpha]_D^{15}$ +21.2 (*c* 0.25, $CHCl_3$)]; $R_f$ = 0.25 (60% EtOAc/petrol 40-60); $\delta_H$ (500 MHz, $CDCl_3$) 5.59 (1H, d, *J* = 4.2 Hz, CHC**H**=C), 4.06 (2H, s, CC$\mathbf{H_2}$OH), 3.55–3.49 (1H, m, CC**H**(OH)$CH_2$), 2.41 (1H, ddd, *J* = 12.9, 12.9, 7.4 Hz, =C($CH_2$)C$\mathbf{H_2}$$CH_2$), 2.25 (1H, d, *J* = 7.9 Hz, CH(O**H**)), 2.22–2.11 (2H, m, CHC**H**CH= & $CH_2$C$\mathbf{H_2}$CH(*i*-Pr)), 2.11–2.03 (2H, m, =C($CH_2$)C$\mathbf{H_2}$$CH_2$ & CH(OH)C$\mathbf{H_2}$$CH_2$), 1.98–1.89 (2H, m, CCH2O**H** & CH(OH)C$\mathbf{H_2}$$CH_2$), 1.76–1.63 (2H, m, $CH_2$C$\mathbf{H_2}$C(Me) & $CH_2$C**H**(*i*-Pr)CH), 1.58 (1H, dsept, *J* = 6.7, 6.7 Hz, CHC**H**($CH_3$)$_2$), 1.40–1.30 (1H, m, $CH_2$C$\mathbf{H_2}$C(Me)), 1.22 (1H, dd, *J* = 12.5, 6.3 Hz, $CH_2$C$\mathbf{H_2}$CH(*i*-Pr)), 1.07 (3H, s, C(C$\mathbf{H_3}$)), 0.92 (3H, d, *J* = 6.7 Hz, CH(C$\mathbf{H_3}$)$_2$), 0.89 (3H, d, *J* = 6.7 Hz, CH(C$\mathbf{H_3}$)$_2$); $\delta_C$ (125 MHz, $CDCl_3$) 142.1 (CH=**C**(C)$CH_2$), 133.0 (CH**C**H=C), 76.6 (C**C**H(OH)$CH_2$), 67.5 (C**C**$H_2$OH), 56.8 ($CH_2$**C**H(*i*-Pr)CH), 49.8 (CH**C**HCH=), 48.5 ($CH_2$**C**(Me)CH), 35.8 ($CH_2$**C**$H_2$CH(*i*-Pr)), 32.3 (CH**C**H($CH_3$)$_2$), 30.5 (CH(OH)**C**$H_2$$CH_2$), 27.2 (C(**C**$H_3$)), 26.7 ($CH_2$**C**$H_2$C(Me)), 25.3 (=C($CH_2$)**C**$H_2$$CH_2$), 22.3 (CH(**C**$H_3$)$_2$), 19.4 (CH(**C**$H_3$)$_2$); LRMS *m*/*z* (ESI$^+$) 261 ([M+Na]$^+$, 100%), 499 ([2M+Na]$^+$, 32%); HRMS *m*/*z* (ESI$^+$) found 261.1827, $C_{15}H_{26}NaO_2$ requires 261.1825; $\nu_{max}$ (film)/cm$^{-1}$ 3357 (br, OH), 2952 (s, CH), 2869 (s, CH), 1663 (w), 1562 (m), 1462 (s), 1367 (m), 1291 (m), 1248 (m), 1016 (s, $CH_2$-OH), 926 (w), 850 (w), 726 (w).

Data are consistent with literature values.[51]

**3-Methyldihydrofuran-2(3*H*)-one (332a)**

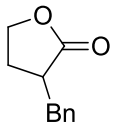



Prepared according to the procedure reported by Breit *et al.*[214] To a stirred solution of diisopropylamine (4.45 g, 44.0 mmol, 1.1 eq.) in anhydrous THF (20.0 mL) cooled to -78 °C in a dry ice/acetone bath was added dropwise a 2.5 M solution of n-BuLi in hexane (19.2 mL, 48.0 mmol, 1.2 eq.). The resulting mixture was stirred for 20 min at -78 °C after which a solution of

butyrolactone (**333**) (3.44 g, 40.0 mmol, 1.0 eq.) in anhydrous THF (20.0 mL) was added dropwise. After a further 20 min, a solution of methyl iodide (6.81 g, 48.0 mmol, 1.2 eq.) in anhydrous THF (20.8 mL) was added dropwise and then warmed slowly to room temperature. Sat. aq. $NH_4Cl$ solution (100 mL) was added to the mixture and extracted with $Et_2O$ (3 × 40 mL). The combined organic layers were washed sequentially with water (120 mL), brine (120 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by short path fractional distillation under reduced pressure (10.0 mmHg) heating at 110°C to afford 3-methyldihydrofuran-2(3*H*)-one (**332a**) as a colourless oil (2.85 g, 28.4 mmol, 71%). $R_f$ = 0.17 (30% EtOAc/petrol 40–60); *b.p.* 78–80 °C at 10.0 mmHg; $\delta_H$ (400 MHz, $CDCl_3$) 4.24 (1H, td, *J* = 8.6, 2.7 Hz, OC**H**$_2$CH$_2$), 4.09 (1H, ddd, *J* = 9.8, 9.1, 6.6 Hz, OC**H**$_2$CH$_2$), 2.52 (1H, ddt, *J* = 10.4, 8.5, 7.1 Hz, CH$_2$C**H**(Me)C=O), 2.36 (1H, dddd, *J* = 12.5, 9.1, 6.6, 2.7 Hz, CH$_2$C**H**$_2$CH(Me)), 1.83 (1H, dddd, *J* = 12.5, 10.1, 8.6, 8.5Hz, CH$_2$C**H**$_2$CH(Me)), 1.18 (3H, d, *J* = 7.1 Hz, CH(C**H**$_3$)); $\delta_C$ (100 MHz, $CDCl_3$) 180.2 (C=O), 66.3 (O**C**H$_2$CH$_2$), 34.0 (CH$_2$**C**H(Me)C=O), 30.6 (CH$_2$**C**H$_2$CH(Me)), 15.1 (CH(**C**H$_3$)); HRMS *m/z* (FI$^+$) found 100.0526, $C_5H_8O_2$ requires 100.0524; $\nu_{max}$ (film)/cm$^{-1}$ 2977 (m, CH), 2937 (m, CH), 2882 (m, CH), 1762 (s, C=O), 1172 (s, C-O), 1019 (s).

Data are consistent with literature values.[214]

**3-Benzyldihydrofuran-2(3*H*)-one (332b)**

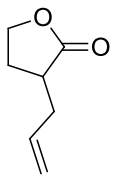



Prepared according to the procedure reported by Miao *et al.*[215] To a stirred solution of butyrolactone (**333**) (473 mg, 5.50 mmol, 1.1 eq.) in anhydrous THF (25.0 mL) cooled to -78 °C in a acetone/dry ice bath was added benzyl bromide (855 mg, 5.00 mmol, 1.0 eq.) followed by dropwise addition of a 1 M solution of LiHMDS in toluene (6.00 mL, 6.00 mmol, 1.2 eq.). The resulting mixture was stirred at -78 °C for 30 min, removed from the bath and quenched with sat. aq. $NH_4Cl$ solution (20 mL) and $Et_2O$ (10 mL). The organic layer was separated and the aqueous

layer was further extracted with $Et_2O$ (2 × 10 mL). The combined organic extracts were sequentially washed brine (30 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/petrol 40–60) to afford 3-benzyldihydrofuran-2(3*H*)-one (**332b**) as a colourless oil (635 mg, 3.61 mmol, 72%). $R_f$ = 0.24 (20% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 7.35–7.29 (2H, m, Ar**H**), 7.27–7.19 (3H, m, Ar**H**), 4.26–4.19 (1H, m, OC**H**$_2$CH$_2$), 4.18–4.10 (1H, m, OC**H**$_2$CH$_2$), 3.25 (1H, dd, *J* = 13.6, 4.0 Hz, CHC**H**$_2$Ph), 2.90-2.80 (1H, m, CH$_2$C**H**(Bn)C=O), 2.76 (1H, dd, *J* = 13.6, 9.2 Hz, CHC**H**$_2$Ph), 2.25 (1H, dddd, *J* = 12.5, 8.4, 6.7, 3.1 Hz, ), 2.05-1.93 (1H, m, CH$_2$C**H**$_2$CH(Bn)); $\delta_C$ (100 MHz, $CDCl_3$) 178.7 (**C**=O), 138.4 (Ar), 128.9 (2C, Ar), 128.7 (2C, Ar), 126.7 (Ar), 66.6 (O**C**H$_2$CH$_2$), 41.1 (CH$_2$**C**H(Bn)C=O), 36.1 (CH**C**H$_2$Ph), 28.0 (CH$_2$**C**H$_2$CH(Bn)); LRMS *m*/*z* (ESI$^+$) 199 ([M+Na]$^+$, 100%); $\nu_{max}$ (film)/cm$^{-1}$ 2988 (m, CH), 2914 (m, CH), 1763 (s, C=O), 1496 (m), 1454 (m), 1375 (m), 1203 (m), 1184 (m), 1146 (s, C-O), 1021 (s), 958 (m).

Data are consistent with literature values.[215]

**3-Allyldihydrofuran-2(3*H*)-one (332c)**

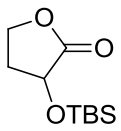


Prepared according to the procedure reported by Ciufolini *et al.*[216] To a stirred solution of butyrolactone (**333**) (473 mg, 5.50 mmol, 1.1 eq.) in anhydrous THF (25.0 mL) cooled to -78 °C in a acetone/dry ice bath was added allyl bromide (605 mg, 5.00 mmol, 1.0 eq.) followed by dropwise addition of a 1 M solution of LiHMDS in toluene (6.00 mL, 6.00 mmol, 1.2 eq.). The resulting mixture was stirred at -78 °C for 1 h, removed from the bath and quenched with sat. aq. $NH_4Cl$ solution (20 mL) and $Et_2O$ (10 mL). The organic layer was separated and the aqueous layer was further extracted with $Et_2O$ (2 × 10 mL). The combined organic extracts were sequentially washed brine (30 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was

purified by flash column chromatography (20% EtOAc/petrol 40–60) to afford 3-allyldihydrofuran-2(3*H*)-one (**332c**) as a colourless oil (362 mg, 2.85 mmol, 57%). $R_f$ = 0.22 (20% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 5.82–5.71 (1H, m, $CH_2C\mathbf{H}=CH_2$), 5.12 (1H, d, $J$ = 17.0 Hz, $CH=CH_Z\mathbf{H_E}$), 5.09 (1H, d, $J$ = 10.1 Hz, $CH=C\mathbf{H_Z}H_E$), 4.35–4.27 (1H, m, $OC\mathbf{H_2}CH_2$), 4.19 (1H, dddd, $J$ = 9.3, 9.3, 6.9, 1.0 Hz, $OC\mathbf{H_2}CH_2$), 2.68–2.54 (2H, m, $CH_2C\mathbf{H}(CH_2)CO$ and $CHC\mathbf{H_2}CH=$), 2.40–2.30 (1H, m, $CH_2C\mathbf{H_2}CH$), 2.30–2.20 (1H, m, $CHC\mathbf{H_2}CH=$), 2.05–1.92 (1H, m, $CH_2C\mathbf{H_2}CH$); $\delta_C$ (100 MHz, $CDCl_3$) 178.3 (**C**=O), 134.4 ($CH_2\mathbf{C}H=CH_2$), 117.7 ($CH=CH_ZH_E$), 66.6 ($O\mathbf{C}H_2CH_2$), 38.8 ($CH_2\mathbf{C}H(CH_2)CO$), 34.3 ($CH\mathbf{C}H_2CH=$), 27.8 ($CH_2\mathbf{C}H_2CH$); LRMS $m/z$ ($ESI^+$) 149 ($[M+Na]^+$, 100%); $\nu_{max}$ (film)/$cm^{-1}$ 3080 (w, C=C), 2983 (m, CH), 2913 (m, CH), 1763 (s, C=O), 1642 (m, C=C), 1375 (m), 1212 (m), 1164 (s, C-O), 1021 (s), 999 (m).

Data are consistent with literature values.[216]

**3-((*tert*-Butyldimethylsilyl)oxy)dihydrofuran-2(3*H*)-one (336a)**

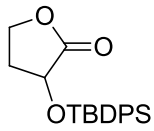



Prepared according to the procedure reported by Altmann *et al.*[217] To a stirred solution of *a*-hydroxy-*γ*-butyrolactone (**335**) (510 mg, 5.00 mmol, 1.0 eq.) and imidazole (511 mg, 7.50 mmol, 1.5 eq.) in anhydrous THF (10.0 mL) cooled to 0 °C in a ice/water bath was added *tert*-butyldimethylsilyl chloride (829 mg, 5.50 mmol, 1.1 eq.) portionwise. The resulting mixture was warmed to room temperature and stirred for 6 h. Sat. aq. $NH_4Cl$ solution (20 mL) was added and extracted with EtOAc (3 × 10 mL). The combined organic extracts were sequentially washed brine (30 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (15% EtOAc/petrol 40–60) to afford 3-((*tert*-butyldimethylsilyl)oxy)dihydrofuran-2(3*H*)-one (**336a**) as a colourless oil (908 mg, 4.20 mmol, 84%). $R_f$ = 0.34 (20% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 4.44–4.35 (2H, m, $CH_2C\mathbf{H}$(OTBS)C=O and $OC\mathbf{H_2}CH_2$), 4.19 (1H, ddd, $J$ = 9.1, 9.1, 6.4 Hz, $OC\mathbf{H_2}CH_2$), 2.46 (1H,

dddd, *J* = 12.8, 7.7, 6.4, 3.3 Hz, $CH_2C\mathbf{H_2}CH(OTBS)$), 2.22 (1H, dddd, *J* = 12.8, 9.1, 8.4, 8.4 Hz, $CH_2C\mathbf{H_2}CH(OTBS)$), 0.91 (9H, s, $SiC(C\mathbf{H_3})_3$), 0.17 (3H, s, $SiC\mathbf{H_3}$), 0.15 (3H, s, $SiC\mathbf{H_3}$); $\delta_C$ (100 MHz, $CDCl_3$) 175.9 (C=O), 68.2 ($CH_2\mathbf{C}H(OTBS)C=O$), 64.7 ($O\mathbf{C}H_2CH_2$), 32.3 ($CH_2\mathbf{C}H_2CH(OTBS)$), 25.6 (3C, $SiC(\mathbf{C}H_3)_3$), 18.2 ($Si\mathbf{C}(CH_3)_3$), -4.7 ($Si\mathbf{C}H_3$), -5.3 ($Si\mathbf{C}H_3$); LRMS *m/z* ($ESI^+$) 239 ($[M+Na]^+$, 100%); $\nu_{max}$ (film)/$cm^{-1}$ 2930 (m, CH), 2857 (m, CH), 1784 (s, C=O), 1149 (s, Si-O-C), 837 (s, Si-O-C), 779 (s, $SiCH_3$).

Data are consistent with literature values.[217]

**3-((*tert*-Butyldiphenylsilyl)oxy)dihydrofuran-2(3*H*)-one (336b)**

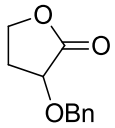



Prepared according to the procedure reported by Mulzer *et al.*[218] To a stirred solution of *a*-hydroxy-*γ*-butyrolactone (**335**) (1.02 g, 10.0 mmol, 1.0 eq.) and imidazole (1.70 g, 25.0 mmol, 2.5 eq.) in anhydrous DMF (40.0 mL) cooled to 0 °C in a ice/water bath was added dropwise *tert*-butyl diphenylchlorosilane (4.12 g, 15.0 mmol, 1.5 eq.). The resulting mixture was warmed to room temperature and stirred for 16 h. Sat. aq. $NH_4Cl$ solution (20 mL) was added and extracted with EtOAc (3 × 20 mL). The combined organic extracts were sequentially washed with water (60 mL), brine (60 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/petrol 40–60) to afford 3-((*tert*-butyldiphenylsilyl)oxy)dihydrofuran-2(3*H*)-one (**336b**) as a white solid (2.66 g, 7.80 mmol, 78%). $R_f$ = 0.33 (20% EtOAc/petrol 40–60); *m.p.* 104–106 °C; $\delta_H$ (400 MHz, $CDCl_3$) 7.85–7.81 (2H, m, Ar**H**), 7.74–7.70 (2H, m, Ar**H**), 7.51–7.39 (6H, m, Ar**H**), 4.39 (1H, dd, *J* = 9.5, 8.1 Hz, $CH_2C\mathbf{H}(OTBDPS)C=O$), 4.35–4.29 (1H, m, $OC\mathbf{H_2}CH_2$), 4.01 (1H, td, *J* = 9.5, 6.4 Hz, $OC\mathbf{H_2}CH_2$), 2.32–2.14 (2H, m, $CH_2C\mathbf{H_2}CH(OTBDPS)$), 1.13 (9H, s, $SiC(C\mathbf{H_3})_3$); $\delta_C$ (100 MHz, $CDCl_3$) 175.5 (**C**=O), 136.0 (2C, Ar), 135.7 (2C, Ar), 133.2 (Ar), 132.1 (Ar), 130.1 (2C, Ar), 127.9 (2C, Ar), 127.8 (2C, Ar), 68.6 ($CH_2\mathbf{C}H(OTBDPS)C=O$), 64.3 ($O\mathbf{C}H_2CH_2$), 32.2

($CH_2\mathbf{C}H_2CH(OTBDPS)$), 26.7 (3C, $SiC(\mathbf{C}H_3)_3$), 19.2 ($Si\mathbf{C}(CH_3)_3$); LRMS *m*/*z* ($ESI^+$) 363 ($[M+Na]^+$, 93%), 703 ($[2M+Na]^+$, 100%); $\nu_{max}$ (film)/$cm^{-1}$ 3058 (w), 2958 (m, CH), 2929 (m, CH), 2857 (m, CH), 1781 (s, C=O), 1427 (m), 1355 (m), 1220 (m), 1153 (s, Si-O-C), 1107 (s), 1023 (m), 999 (m), 842 (s, Si-O-C), 747 (s, $SiCH_3$).

Data are consistent with literature values.[218]

**3-(Benzyloxy)dihydrofuran-2(3*H*)-one (336c)**

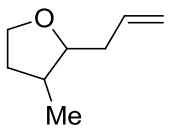



Prepared according to the procedure reported by Shiina *et al.*[219] To a stirred suspension of 60% NaH (480 mg, 12.0 mmol, 1.2 eq.) in anhydrous THF (6.0 mL) cooled to 0 °C in a ice/water bath was added a solution of *a*-hydroxy-*γ*-butyrolactone (**335**) (1.02 g, 10.0 mmol, 1.0 eq.) in anhydrous THF (4.0 mL). The resulting mixture was warmed to room temperature and stirred for 15 min, after which a solution of benzyl bromide (2.22 g, 13.0 mmol, 1.3 eq.) in dry DMF (1.0 mL) was added dropwise. The resulting mixture was stirred for 48 h at room temperature. Sat. aq. $NH_4Cl$ solution (20 mL) was added and extracted with EtOAc (3 × 20 mL). The combined organic extracts were sequentially washed with water (60 mL), brine (60 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (30% EtOAc/petrol 40–60) to afford 3-(benzyloxy)dihydrofuran-2(3*H*)-one (**336c**) as a colourless oil (843 mg, 4.39 mmol, 44%). $R_f$ = 0.19 (30% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 7.41–7.30 (5H, m, Ar**H**), 4.94 (1H, d, *J* = 11.8 Hz, $OC\mathbf{H}_2Ph$), 4.74 (1H, d, *J* = 11.8 Hz, $OC\mathbf{H}_2Ph$), 4.41 (1H, ddd, *J* = 9.1, 8.1, 4.2 Hz, $OC\mathbf{H}_2CH_2$), 4.25–4.16 (2H, m, $OC\mathbf{H}_2CH_2$ & $CH_2C\mathbf{H}(OBn)C{=}O$), 2.51–2.41 (1H, m, $OCH_2C\mathbf{H}_2CH$), 2.34–2.23 (1H, m, $CH_2C\mathbf{H}_2CH$); $\delta_C$ (100 MHz, $CDCl_3$) 175.1 (**C**=O), 137.0 (Ar), 128.5 (2C, Ar), 128.2 (2C, Ar), 128.1 (Ar), 72.5 ($CH_2\mathbf{C}H(OBn)C{=}O$), 72.1 ($O\mathbf{C}H_2Ph$), 65.5 ($O\mathbf{C}H_2CH_2$), 29.8 ($OCH_2C\mathbf{H}_2CH$); HRMS *m*/*z* ($FI^+$) found 192.0783, $C_{11}H_{12}O_3$ requires 192.0786; $\nu_{max}$ (film)/$cm^{-1}$ 3064 (w), 3032 (w), 2995 (m, CH), 2917 (m, CH), 2873 (m, CH),

1775 (s, C=O), 1497 (m), 1454 (m), 1343 (m), 1219 (s), 1172 (s), 1135 (s), 1112 (s), 1014 (s), 948 (m).

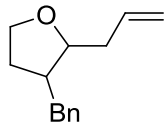
Data are consistent with literature values.[219]

***2-Allyl-3-methyltetrahydrofuran (326a)***



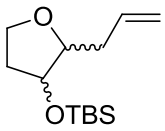

To a stirred solution of 3-methyldihydrofuran-2(3*H*)-one (**332a**) (2.00 g, 20.0 mmol, 1.0 eq.), triethylsilane (2.56 g, 22.0 mmol, 1.1 eq.) and allyltrimethylsilane (4.57 g, 40.0 mmol, 2.0 eq.) in anhydrous toluene (60.0 mL) at 70 °C was added in one portion indium(III) bromide (709 mg, 2.00 mmol, 0.1 eq.). The resulting mixture was heated at 70 °C for 5 h, and then cooled to room temperature. The mixture was filtered through a silica plug eluting with petrol 30–40 (200 mL) followed by 10% $Et_2O$/petrol 30–40 (500 mL) and concentrated under reduced pressure. The residue was purified by short path fractional distillation under reduced pressure (19.3 mmHg) heating at 72°C to afford 2-allyl-3-methyltetrahydrofuran (**326a**) (diastereomeric ratio = 3:1) as a colourless oil (2.05 g, 16.2 mmol, 81%). Characterisation is reported for the major epimer of an inseparable mixture of diastereoisomers. $R_f$ = 0.23 (5% $Et_2O$/petrol 40–60); *b.p.* 44–46 °C at 19.3 mmHg; $\delta_H$ (400 MHz, $CDCl_3$) 5.92–5.79 (1H, m, $CH_2C\mathbf{H}=CH_2$), 5.14–5.07 (1H, m, $CH=CH_Z\mathbf{H_E}$), 5.07–5.02 (1H, m, $CH=C\mathbf{H_Z}H_E$), 3.95–3.67 (2H, m, $OC\mathbf{H_2}CH_2$), 3.37 (1H, dt, $J$ = 7.4, 4.6 Hz, $CHC\mathbf{H}(CH_2)O$), 2.39–2.16 (2H, m, $CHC\mathbf{H_2}CH=$), 2.11–2.03 (1H, m, $CH_2C\mathbf{H_2}CH(Me)$), 1.91–1.79 (1H, m, $CH_2C\mathbf{H}(Me)CH$), 1.62–1.58 (1H, m, $CH_2C\mathbf{H_2}CH(Me)$), 1.02 (3H, d, $J$ = 6.7 Hz, $CH(C\mathbf{H_3})$); $\delta_C$ (100 MHz, $CDCl_3$) 135.3 ($CH_2\mathbf{C}H=CH_2$), 116.6 ($CH=\mathbf{C}H_ZH_E$), 85.0 ($CH\mathbf{C}H(CH_2)O$), 66.8 ($O\mathbf{C}H_2CH_2$), 38.6 ($CH\mathbf{C}H_2CH=$), 38.4 ($CH_2\mathbf{C}H(Me)CH$), 34.6 ($CH_2\mathbf{C}H_2CH(Me)$), 17.2 ($CH(\mathbf{C}H_3)$); HRMS $m/z$ ($FI^+$) found 126.1049, $C_8H_{14}O$ requires 126.1045; $\nu_{max}$ (film)/$cm^{-1}$ 2963 (m, CH), 2874 (w, CH), 1077 (m, C-O), 955 (w, $C=CH_2$), 904 (s, $C=CH_2$), 726 (s).

***2-Allyl-3-benzyltetrahydrofuran (326b)***



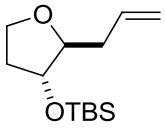

To a stirred solution of 3-benzyldihydrofuran-2(3*H*)-one (**332b**) (3.59 g, 20.4 mmol, 1.0 eq.), triethylsilane (2.61 g, 22.4 mmol, 1.1 eq.) and allyltrimethylsilane (4.65 g, 40.7 mmol, 2.0 eq.) in anhydrous toluene (68.0 mL) at 70 °C, was added in one portion indium(III) bromide (723 mg, 2.04 mmol, 0.1 eq.). The resulting mixture was heated at 70 °C for 18 h, and then cooled to room temperature. EtOAc (20 mL) and water (1 mL) was added to the mixture, stirred for 5 min then dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (15% $Et_2O$/petrol 30–40) to afford 2-allyl-3-benzyltetrahydrofuran (**326b**) (diastereomeric ratio = 7:1) as a colourless oil (3.14 g, 15.5 mmol, 76%). Characterisation is reported for the major epimer of an inseparable mixture of diastereoisomers. $R_f$ = 0.32 (15% $Et_2O$/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 7.34–7.28 (2H, m, Ar**H**), 7.25–7.17 (3H, m, Ar**H**), 5.92–5.79 (1H, m, $CH_2C\mathbf{H}=CH_2$), 5.12–5.05 (2H, m, $CH=C\mathbf{H_Z}\mathbf{H_E}$), 3.87–3.82 (2H, m, $OC\mathbf{H_2}CH_2$), 3.64 (1H, td, *J* = 7.1, 4.7 Hz, $CHC\mathbf{H}(CH_2)O$), 2.80 (1H, dd, *J* = 13.5, 6.0 Hz, $CHC\mathbf{H_2}Ph$), 2.59 (1H, dd, *J* = 13.5, 9.0 Hz, $CHC\mathbf{H_2}Ph$), 2.35-2.10 (3H, m, $CHC\mathbf{H_2}CH=$ & $CH_2C\mathbf{H}(Bn)CH$ ), 2.04–1.94 (1H, m, $CH_2C\mathbf{H_2}CH(Bn)$), 1.72–1.62 (1H, m, $CH_2C\mathbf{H_2}CH(Bn)$); $\delta_C$ (100 MHz, $CDCl_3$) 140.6 ($CH_2\mathbf{C}H=CH_2$), 135.1 (Ar), 128.8 (2C,Ar), 128.4 (2C, Ar), 126.1 (Ar), 116.8 ($CH=\mathbf{C}H_ZH_E$), 83.3 ($CH\mathbf{C}H(CH_2)O$), 66.9 ($O\mathbf{C}H_2CH_2$), 45.4 ($CH_2\mathbf{C}H(Bn)CH$), 39.2 ($CH\mathbf{C}H_2Ph$), 38.9 ($CH\mathbf{C}H_2CH=$), 32.5 ($CH_2\mathbf{C}H_2CH(Bn)$); LRMS *m/z* ($ESI^+$) 225 ($[M+Na]^+$, 55%), 371 (100%); HRMS *m/z* ($ESI^+$) found 225.1256; $C_{14}H_{18}NaO$ requires 225.1250; $\nu_{max}$ (film)/$cm^{-1}$ 3064 (w), 3026 (w), 2926 (m, CH), 2854 (m, CH), 1946 (w, Ph overtone), 1807 (w, Ph overtone), 1738 (w, Ph overtone), 1641 (m, $C=CH_2$), 1603 (m), 1496 (m), 1454 (m), 1077 (s, C-O-C), 1056 (s), 999 (s, $C=CH_2$), 911 (s, $C=CH_2$).

***(2-Allyltetrahydrofuran-3-yl)oxy)(*tert*-butyl)dimethylsilane (326d)***




To a stirred solution of 3-((*tert*-butyldimethylsilyl)oxy)dihydrofuran-2(3*H*)-one (**336a**) (3.55 g, 16.4 mmol, 1.0 eq.), triethylsilane (2.09 g, 18.0 mmol, 1.1 eq.) and allyltrimethylsilane (3.75 g, 32.8 mmol, 2.0 eq.) in anhydrous toluene (54.6 mL) at 70 °C, was added in one portion indium(III) bromide (581 mg, 1.64 mmol, 0.1 eq.). The resulting mixture was heated at 70 °C for 24 h, and then cooled to room temperature. EtOAc (20 mL) and water (1 mL) was added to the mixture, stirred for 5 min then dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% $Et_2O$/petrol 30–40) to afford (2-allyltetrahydrofuran-3-yl)oxy)(*tert*-butyl)dimethylsilane (**326d**) (diastereomeric ratio = 1.2:1) as a colourless oil (2.53 g, 10.5 mmol, 64%). Characterisation is reported for the major and minor epimer as separated by flash column chromatography.

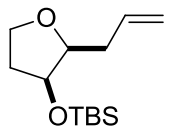
***(((2S*,3R*)-2-Allyltetrahydrofuran-3-yl)oxy)(*tert*-butyl)dimethylsilane***




Major Epimer: $R_f$ = 0.38 (10% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 5.84 (1H, ddt, *J* = 17.1, 10.2, 6.9 Hz, $CH_2C\mathbf{H}{=}CH_2$), 5.14–5.05 (2H, m, $CH{=}C\mathbf{H_Z}\mathbf{H_E}$), 4.00 (1H, dt, *J* = 6.6, 3.5 Hz, $CHC\mathbf{H}(CH_2)O$), 3.95–3.86 (2H, m, $OC\mathbf{H_2}CH_2$), 3.69 (1H, ddd, *J* = 6.6, 5.9, 3.5 Hz, $CH_2C\mathbf{H}(OTBS)CH$), 2.33–2.18 (2H, m, $CHC\mathbf{H_2}CH{=}$), 2.02 (1H, dtd *J* = 12.6, 8.3, 6.6 Hz, $CH_2C\mathbf{H_2}CH(OTBS)$), 1.81–1.74 (1H, m, $CH_2C\mathbf{H_2}CH(OTBS)$), 0.88 (9H, s, $SiC(C\mathbf{H_3})_3$), 0.06 (6H, s, $SiC\mathbf{H_3}$); $\delta_C$ (100 MHz, $CDCl_3$) 134.8 ($CH_2\mathbf{C}H{=}CH_2$), 116.9 ($CH{=}\mathbf{C}H_ZH_E$), 85.2 ($CH_2\mathbf{C}H(OTBS)CH$), 75.7 ($CH\mathbf{C}H(CH_2)O$), 66.6 ($O\mathbf{C}H_2CH_2$), 37.9 ($CH\mathbf{C}H_2CH{=}$), 35.3 ($CH_2\mathbf{C}H_2CH(OTBS)$), 25.7 (3C, $SiC(\mathbf{C}H_3)_3$), 17.9 ($Si\mathbf{C}(CH_3)_3$), -4.6 ($Si\mathbf{C}H_3$), -4.7 ($Si\mathbf{C}H_3$); LRMS

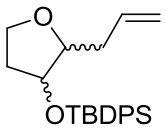
*m/z* (ESI$^+$) 265 ([M+Na]$^+$, 100%); HRMS *m/z* (ESI$^+$) found 265.1594, $C_{13}H_{26}NaO_2Si$ requires 265.1594; $\nu_{max}$ (film)/cm$^{-1}$ 3078 (w), 2954 (m, CH), 2930 (s, CH), 2886 (m, CH), 2858 (s, CH), 1642 (w, C=$CH_2$), 1472 (m), 1463 (m), 1409 (m), 1388 (m), 1361 (m), 1253 (s), 1111 (s), 1054 (s), 1006 (m, C=$CH_2$), 914 (s, C=$CH_2$), 834 (s, Si-O-C), 774 (s, $SiCH_3$).

***(((2S*,3S*)-2-Allyltetrahydrofuran-3-yl)oxy)(*tert*-butyl)dimethylsilane***



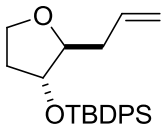

Minor Epimer: $R_f$ = 0.28 (10% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 5.87 (1H, ddt, *J* = 17.1, 10.2, 6.9 Hz, $CH_2C\mathbf{H}=CH_2$), 5.12 (1H, dd, *J* = 17.1, 1.8 Hz, $CH=CH_Z\mathbf{H_E}$), 5.05 (1H, dd, *J* = 10.2, 1.8 Hz, $CH=C\mathbf{H_Z}H_E$), 4.26 (1H, ddd, *J* = 5.2, 3.7, 2.1 Hz, $CHC\mathbf{H}(CH_2)O$), 4.01 (1H, dt, *J* = 15.5, 8.4 Hz, $OC\mathbf{H_2}CH_2$), 3.77 (1H, ddd, *J* = 8.4, 8.2, 4.3 Hz, $OC\mathbf{H_2}CH_2$), 3.69 (1H, ddd, *J* = 8.0, 5.4, 3.7 Hz, $CH_2C\mathbf{H}(OTBS)CH$), 2.43–2.29 (2H, m, $CHC\mathbf{H_2}CH=$), 2.09 (1H, dtd, *J* = 13.4, 8.4, 5.4 Hz, $CH_2C\mathbf{H_2}CH(OTBS)$), 1.90–1.83 (1H, m, $CH_2C\mathbf{H_2}CH(OTBS)$), 0.90 (9H, s, $SiC(C\mathbf{H_3})_3$), 0.08 (3H, s, $SiC\mathbf{H_3}$), 0.07 (3H, s, $SiC\mathbf{H_3}$); $\delta_C$ (100 MHz, $CDCl_3$) 135.7 ($CH_2\mathbf{C}H=CH_2$), 116.4 ($CH=\mathbf{C}H_ZH_E$), 82.6 ($CH_2\mathbf{C}H(OTBS)CH$), 72.7 ($CH\mathbf{C}H(CH_2)O$), 65.9 ($O\mathbf{C}H_2CH_2$), 36.1 ($CH_2\mathbf{C}H_2CH(OTBS)$), 34.0 ($CH\mathbf{C}H_2CH=$), 25.8 (3C, $SiC(\mathbf{C}H_3)_3$), 18.1 ($Si\mathbf{C}(CH_3)_3$), -4.5 ($Si\mathbf{C}H_3$), -5.0 ($Si\mathbf{C}H_3$); LRMS *m/z* (ESI$^+$) 265 ([M+Na]$^+$, 100%); HRMS *m/z* (ESI$^+$) found 265.1593, $C_{13}H_{26}NaO_2Si$ requires 265.1594; $\nu_{max}$ (film)/cm$^{-1}$ 3078 (w), 2954 (m, CH), 2930 (s, CH), 2886 (m, CH), 2858 (s, CH), 1642 (w, C=$CH_2$), 1472 (m), 1463 (m), 1388 (m), 1361 (m), 1253 (s), 1111 (s), 1054 (s), 1006 (m, C=$CH_2$), 914 (s, C=$CH_2$), 834 (s, Si-O-C), 774 (s, $SiCH_3$).

***((2-Allyltetrahydrofuran-3-yl)oxy)(*tert*-butyl)diphenylsilane (326e)***




To a stirred solution of 3-((*tert*-butyldiphenylsilyl)oxy)dihydrofuran-2(3*H*)-one (**336b**) (2.41 g, 7.08 mmol, 1.0 eq.), triethylsilane (905 mg, 7.79 mmol, 1.1 eq.) and allyltrimethylsilane (1.63 g, 14.2 mmol 2.0 eq.) in anhydrous toluene (24.0 mL) at 70 °C, was added in one portion indium(III) bromide (251 mg, 0.71 mmol, 0.1 eq.). The resulting mixture was heated at 70 °C for 16 h, and then cooled to room temperature. EtOAc (20 mL) and water (0.7 mL) was added to the mixture, stirred for 5 min then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (5-10% EtOAc/petrol 40–60 gradient) to afford ((2-allyltetrahydrofuran-3-yl)oxy)(*tert*-butyl)diphenylsilane (**326e**) (diastereomeric ratio = 1.1:1) as a colourless oil (1.38 g, 3.75 mmol, 53%). Characterisation is reported for the major and minor epimer as separated by flash column chromatography.

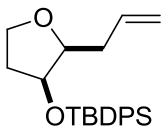
***(((2S*,3R*)-2-Allyltetrahydrofuran-3-yl)oxy)(*tert*-butyl)diphenylsilane***




Minor Epimer: $R_f$ = 0.35 (10% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 7.71–7.66 (4H, m, Ar**H**), 7.49–7.37 (6H, m, Ar**H**), 5.61 (1H, ddt, *J* = 17.1, 10.3, 7.0 Hz, $CH_2C\mathbf{H}=CH_2$), 4.96–4.87 (2H, m, $CH=C\mathbf{H_Z}\mathbf{H_E}$), 4.08 (1H, dt, *J* = 5.9, 2.9 Hz, $CHC\mathbf{H}(CH_2)O$), 4.02–3.94 (1H, m, $OC\mathbf{H_2}CH_2$), 3.94–3.88 (1H, m, $OC\mathbf{H_2}CH_2$), 3.85 (1H, ddd, *J* = 7.2, 5.6, 2.9 Hz, $CH_2C\mathbf{H}$(OTBDPS)CH), 2.05–1.90 (2H, m, $CHC\mathbf{H_2}CH=$), 1.90–1.79 (2H, m, $CH_2C\mathbf{H_2}$CH(OTBDPS)), 1.09 (9H, s, $SiC(C\mathbf{H_3})_3$); $\delta_C$ (100 MHz, $CDCl_3$) 135.9 (2C, Ar), 135.8 (2C, Ar), 134.6 ($CH_2\mathbf{C}H=CH_2$), 133.9 (Ar), 133.8 (Ar), 129.8 (Ar), 129.7 (Ar), 127.7 (4C, Ar), 116.8 ($CH=\mathbf{C}H_ZH_E$), 85.9 ($CH_2\mathbf{C}H$(OTBDPS)CH), 76.8 ($CH\mathbf{C}H(CH_2)O$), 66.9 ($O\mathbf{C}H_2CH_2$), 37.9

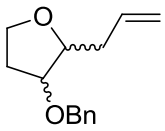
(CH**C**$H_2$CH=), 35.2 ($CH_2$**C**$H_2$CH(OTBDPS)), 26.9 (3C, SiC(**C**$H_3$)$_3$), 19.1 (Si**C**$(CH_3)_3$); LRMS *m/z* (ESI$^+$) 389 ([M+Na]$^+$, 100%), 755 ([2M+Na]$^+$, 75%); HRMS *m/z* (ESI$^+$) found 389.1909, $C_{23}H_{30}NaO_2Si$ requires 389.1907; $\nu_{max}$ (film)/cm$^{-1}$ 3071 (w), 3050 (w), 2931 (m, CH), 2892 (m, CH), 2858 (s, CH), 1961 (w, Ph overtone), 1891 (w, Ph overtone), 1825 (w, Ph overtone), 1641 (w, C=$CH_2$), 1590 (w), 1472 (m), 1427 (s), 1390 (w), 1362 (w), 1159 (w), 1106 (s), 1052 (s), 968 (m), 914 (s, C=$CH_2$).

***(((2S*,3S*)-2-Allyltetrahydrofuran-3-yl)oxy)(*tert*-butyl)diphenylsilane***



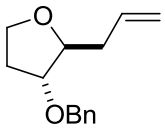

Major Epimer: $R_f$ = 0.29 (10% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 7.73–7.68 (4H, m, Ar**H**), 7.49–7.38 (6H, m, Ar**H**), 5.91 (1H, ddt, *J* = 17.1, 10.2, 6.9 Hz, $CH_2$C**H**=$CH_2$), 5.15 (1H, ddd, *J* = 17.1, 3.4, 1.6 Hz, CH=$CH_Z$**H$_E$**), 5.10–5.15 (1H, m, CH=C**H$_Z$**$H_E$), 4.39 (1H, dt, *J* = 4.4, 3.9 Hz, CHC**H**$(CH_2)$O), 4.06–3.99 (1H, m, OC**H$_2$**$CH_2$), 3.72–3.64 (2H, m, OC**H$_2$**$CH_2$ & $CH_2$C**H**(OTBDPS)CH), 2.58–2.49 (1H, m, CHC**H$_2$**CH=), 2.47–2.39 (1H, m, CHC**H$_2$**CH=), 1.88–1.77 (2H, m, $CH_2$C**H$_2$**CH(OTBDPS)), 1.11 (9H, s, SiC(C**H$_3$**)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 136.0 ($CH_2$**C**H=$CH_2$), 135.9 (2C, Ar), 135.8 (2C, Ar), 134.3 (Ar), 133.5 (Ar), 129.8 (Ar), 129.7 (Ar), 127.7 (2C, Ar), 127.6 (2C, Ar), 116.4 (CH=**C**$H_Z$$H_E$), 82.4 ($CH_2$**C**H(OTBDPS)CH), 74.1 (CH**C**H$(CH_2)$O), 65.8 (O**C**$H_2CH_2$), 35.3 ($CH_2$**C**$H_2$CH(OTBDPS)), 34.3 (CH**C**$H_2$CH=), 26.9 (3C, SiC(**C**$H_3$)$_3$), 19.4 (Si**C**$(CH_3)_3$); LRMS *m/z* (ESI$^+$) 389 ([M+Na]$^+$, 100%), 755 ([2M+Na]$^+$, 13%); HRMS *m/z* (ESI$^+$) found 389.1907, $C_{23}H_{30}NaO_2Si$ requires 389.1907; $\nu_{max}$ (film)/cm$^{-1}$ 3072 (w), 3050 (w), 2931 (m, CH), 2890 (m, CH), 2857 (m, CH), 1965 (w, Ph overtone), 1890 (w, Ph overtone), 1825 (w, Ph overtone), 1641 (w, C=$CH_2$), 1589 (w), 1472 (m), 1427 (s), 1394 (w), 1362 (w), 1189 (w), 1111 (s), 1050 (s), 997 (m), 971 (m), 910 (s, C=$CH_2$).

***2-Allyl-3-(benzyloxy)tetrahydrofuran (326f)***




To a stirred solution of 3-(benzyloxy)dihydrofuran-2(3*H*)-one (**336c**) (874 mg, 4.5 mmol, 1.0 eq.), triethylsilane (581 mg, 5.0 mmol, 1.1 eq.) and allyltrimethylsilane (1.04 g, 9.1 mmol, 2.0 eq.) in anhydrous toluene (15.0 mL) at 70 °C, was added in one portion indium(III) bromide (160 mg, 0.45 mmol, 0.1 eq.). The resulting mixture was heated at 70 °C for 16 h, and then cooled to room temperature. EtOAc (10 mL) and water (0.45 mL) was added to the mixture, stirred for 5 min then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (15% EtOAc/petrol 40–60) to afford 2-allyl-3-(benzyloxy)tetrahydrofuran (**326f**) (diastereomeric ratio = 1.8:1) as a colourless oil (596 mg, 2.75 mmol, 61%). Characterisation is reported for the major and minor epimer as separated by flash column chromatography.

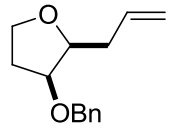
***(2S*,3R*)-2-Allyl-3-(benzyloxy)tetrahydrofuran***




Minor Epimer: $R_f$ = 0.33 (15% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 7.40–7.28 (5H, m, Ar**H**), 5.85 (1H, ddt, *J* = 17.2, 10.2, 7.0 Hz, $CH_2C\mathbf{H}{=}CH_2$), 5.15–5.02 (2H, m, $CH{=}C\mathbf{H_Z H_E}$), 4.55 (1H, d, *J* = 11.8 Hz, $OC\mathbf{H_2}Ph$), 4.50 (1H, d, *J* = 11.8 Hz, $OC\mathbf{H_2}Ph$), 3.01–3.88 (3H, m, $OC\mathbf{H_2}CH_2$ & $CHC\mathbf{H}(CH_2)O$), 3.87–3.83 (1H, m, $CH_2C\mathbf{H}(OBn)CH$), 2.33–2.28 (2H, m, $CHC\mathbf{H_2}CH{=}$), 2.05–1.99 (2H, m, $CH_2C\mathbf{H_2}CH$); $\delta_C$ (100 MHz, $CDCl_3$) 138.2 (Ar), 134.5 ($CH_2\mathbf{C}H{=}CH_2$), 128.4 (2C, Ar), 127.7 (3C, Ar), 117.2 ($CH{=}\mathbf{C}H_ZH_E$), 83.2 ($CH\mathbf{C}H(CH_2)O$), 82.5 ($CH_2\mathbf{C}H(OBn)CH$), 71.3 ($O\mathbf{C}H_2Ph$), 66.9 ($O\mathbf{C}H_2CH_2$), 38.3 ($CH\mathbf{C}H_2CH{=}$), 32.1 ($CH_2\mathbf{C}H_2CH$); LRMS *m*/*z* ($ESI^+$) 241 ($[M+Na]^+$, 100%); HRMS *m*/*z* ($ESI^+$) found 241.1201, $C_{14}H_{18}NaO_2$ requires 241.1199; $\nu_{max}$

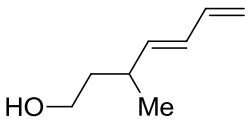
(film)/cm$^{-1}$ 3067 (w), 3031 (w), 2977 (m, CH), 2933 (m, CH), 2865 (m, CH), 1813 (w, Ph overtone), 1641 (m, C=$CH_2$), 1497 (m), 1454 (s), 1340 (m), 1205 (m), 1107 (s), 1064 (s).

***(2S*,3S*)-2-Allyl-3-(benzyloxy)tetrahydrofuran***




Major Epimer: $R_f$ = 0.27 (15% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 7.37–7.27 (5H, m, Ar**H**), 5.88 (1H, ddt, *J* = 17.1, 10.2, 6.9 Hz, $CH_2C\mathbf{H}=CH_2$), 5.16 (1H, dd, *J* = 17.1, 1.4 Hz, $CH=CH_Z\mathbf{H_E}$), 5.07 (1H, dd, *J* = 10.2, 1.4 Hz, $CH=C\mathbf{H_Z}H_E$), 4.63 (1H, d, *J* = 12.0 Hz, $OC\mathbf{H_2}Ph$), 4.45 (1H, d, *J* = 12.0 Hz, $OC\mathbf{H_2}Ph$), 4.09–4.00 (2H, m, $OC\mathbf{H_2}CH_2$ & $CH_2C\mathbf{H}(OBn)CH$), 3.83-3.74 (2H, m, $OC\mathbf{H_2}CH_2$ & $CHC\mathbf{H}(CH_2)O$), 2.53-2.48 (2H, m, $CHC\mathbf{H_2}CH=$), 2.16-2.00 (2H, m, $CH_2C\mathbf{H_2}CH$); $\delta_C$ (100 MHz, $CDCl_3$) 138.4 (Ar), 135.5 ($CH_2\mathbf{C}H=CH_2$), 128.3 (2C, Ar), 127.6 (Ar), 127.5 (2C, Ar), 116.6 ($CH=\mathbf{C}H_ZH_E$), 81.9 ($CH\mathbf{C}H(CH_2)O$), 78.8 ($CH_2\mathbf{C}H(OBn)CH$), 71.1 ($O\mathbf{C}H_2Ph$), 66.0 ($O\mathbf{C}H_2CH_2$), 33.7 ($CH\mathbf{C}H_2CH=$), 31.8 ($CH_2\mathbf{C}H_2CH$); LRMS *m*/*z* (ESI$^+$) 241 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 241.1200, $C_{14}H_{18}NaO_2$ requires 241.1199; $\nu_{max}$ (film)/cm$^{-1}$ 3067 (w), 3031 (w), 2976 (m, CH), 2941 (m, CH), 2865 (m, CH), 1812 (w, Ph overtone), 1641 (m, C=$CH_2$), 1497 (m), 1454 (s), 1348 (m), 1206 (m), 1120 (s), 1066 (s).

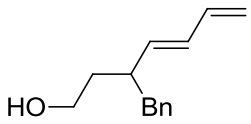
***(E)-3-Methylhepta-4,6-dien-1-ol (337a)***




To a vigorously stirred suspension of potassium *tert*-butoxide (41.5 mg, 0.37 mmol, 0.1 eq.) in a 2.5 M solution of n-BuLi in hexane (1.77 mL, 4.42 mmol, 1.2 eq.) cooled to -78 °C in a dry ice/acetone bath was added dropwise a solution of diisopropylamine (372 mg, 3.68 mmol, 1.0 eq.) and 2-allyl-3-methyltetrahydrofuran (**326a**) (465 mg, 3.68 mmol, 1.0 eq.) in anhydrous THF (5.59 mL). After complete addition the mixture was warmed to -50 °C and stirred for 1 h at this

temperature. Sat. aq. $NH_4Cl$ solution (10 mL) was added to the mixture and extracted with $Et_2O$ (3 × 4 mL). The combined organic layers were washed sequentially with brine (12 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% $Et_2O$/petrol 30–40) to afford (*E*)-3-methylhepta-4,6-dien-1-ol (**337a**) (*E*:*Z* = 10:1) as a colourless oil (381 mg, 2.16 mmol, 90%). Characterisation is reported for the major epimer of an inseparable mixture of regioisomers. $R_f$ = 0.31 (50% $Et_2O$/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 6.30 (1H, dt, *J* = 17.0, 10.2 Hz, =CHC**H**=$CH_2$), 6.05 (1H, dd, *J* = 15.2, 10.2 Hz, CH=C**H**CH=), 5.59 (1H, dd, *J* = 15.2, 8.1 Hz, CH(Me)C**H**=CH), 5.09 (1H, dd, *J* = 17.0, 0.8 Hz, CH=$CH_Z$**H**$_E$), 4.96 (1H, d, *J* = 10.2, 0.8 Hz, CH=C**H**$_Z$$H_E$), 3.64 (2H, t, *J* = 5.4 Hz, HOC**H**$_2$$CH_2$), 2.40–2.31 (1H, m, $CH_2$C**H**(Me)CH=), 1.65 (1H, s, **H**O$CH_2CH_2$), 1.62–1.54 (2H, m, $CH_2$C**H**$_2$CH(Me)), 1.04 (3H, d, *J* = 6.8 Hz, CH(C**H**$_3$)); $\delta_C$ (100 MHz, $CDCl_3$) 140.3 (CH(Me)**C**H=CH), 137.1 (=CH**C**H=$CH_2$), 129.7 (CH=**C**HCH=), 115.3 (CH=**C**$H_Z$$H_E$), 61.0 (HO**C**$H_2CH_2$), 39.6 ($CH_2$**C**$H_2$CH(Me)), 33.6 ($CH_2$**C**H(Me)CH=), 20.6 (CH(**C**$H_3$)); HRMS *m*/*z* ($FI^+$) found 126.1042, $C_8H_{14}O$ requires 126.1045; $\nu_{max}$ (film)/$cm^{-1}$ 3328 (br, OH), 3086 (w, =$CH_2$), 2959 (s, CH), 2928 (s, CH), 2872 (m, CH), 1650 (m, C=C), 1604 (m, C=C), 1050 (m, C-O), 1002 (s, CH=$CH_2$), 952 (m, C=$CH_2$), 897 (s, C=$CH_2$).

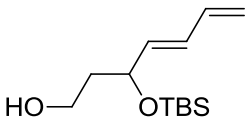
***(E)-3-Benzylhepta-4,6-dien-1-ol (337b)***




To a vigorously stirred suspension of potassium *tert*-butoxide (73 mg, 0.65 mmol, 0.1 eq.) in anhydrous THF (11 mL) cooled to -78 °C in a dry ice/acetone bath was added dropwise a 1.6 M solution of *n*-BuLi in hexane (8.9 mL, 14.3 mmol, 1.2 eq.). To this mixture was added dropwise a solution of diisopropylamine (658 mg, 6.50 mmol, 1.0 eq.) and 2-allyl-3-benzyltetrahydrofuran (**326b**) (1.32 g, 6.50 mmol, 1.0 eq.) in anhydrous THF (11 mL) *via* cannula. The resulting mixture was stirred at -78 °C for 1 h, Sat. aq. $NH_4Cl$ solution (40 mL) was added to the mixture and

extracted with EtOAc (3 × 20 mL). The combined organic layers were washed sequentially with brine (100 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (30% EtOAc/petrol 40–60) to afford (*E*)-3-benzylhepta-4,6-dien-1-ol (**337b**) (*E*:*Z* = 17:1) as a colourless oil (1.08 g, 5.33 mmol, 82%). Characterisation is reported for the major isomer. $R_f$ = 0.29 (30% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 7.32–7.26 (2H, m, Ar**H**), 7.24–7.14 (3H, m, Ar**H**), 6.31 (1H, dt, *J* = 17.0, 10.2 Hz, =CHC**H**=$CH_2$), 6.01 (1H, dd, *J* = 15.3, 10.2 Hz, CH=C**H**CH=), 5.56 (1H, dd, *J* = 15.3, 8.9 Hz, CH(Bn)C**H**=CH), 5.10 (1H, dd, *J* = 17.0, 0.8 Hz, CH=$CH_Z\mathbf{H_E}$), 5.00 (1H, dd, *J* = 10.2, 0.8 Hz, CH=C$\mathbf{H_Z}H_E$), 3.70–3.53 (2H, m, HOC$\mathbf{H_2}CH_2$), 2.72 (1H, dd, *J* = 13.5, 7.3 Hz, CHC$\mathbf{H_2}$Ph), 2.67 (1H, dd, *J* = 13.5, 6.9 Hz, CHC$\mathbf{H_2}$Ph), 2.59–2.48 (1H, m, $CH_2$C**H**(Bn)CH=), 1.85–1.69 (1H, m, $CH_2$C$\mathbf{H_2}$CH(Bn)), 1.57–1.47 (2H, m, **H**O$CH_2CH_2$ & $CH_2$C$\mathbf{H_2}$CH(Bn)); $\delta_C$ (100 MHz, $CDCl_3$) 139.9 (CH(Bn)**C**H=CH), 137.9 (=CH**C**H=$CH_2$), 136.9 (Ar), 131.5 (CH=**C**HCH=), 129.3 (2C, Ar), 128.2 (2C, Ar), 126.0 (Ar), 115.7 (CH=**C**$H_ZH_E$), 61.0 (HO**C**$H_2CH_2$), 42.2 (CH**C**$H_2$Ph), 41.3 ($CH_2$**C**H(Bn)CH=), 37.0 ($CH_2$**C**$H_2$CH(Bn)); HRMS *m*/*z* ($FI^+$) found 202.1353, $C_{14}H_{18}O$ requires 202.1358; $\nu_{max}$ (film)/$cm^{-1}$ 3337 (br, OH), 3085 (w, =$CH_2$), 3062 (w), 2962 (s, CH), 1944 (w, Ph overtone), 1804 (w, Ph overtone), 1650 (m, C=C), 1602 (m, C=C), 1495 (s), 1453 (s), 1052 (m, C-O), 1031 (m), 1003 (s, CH=$CH_2$), 952 (m, C=$CH_2$), 898 (s, C=$CH_2$).

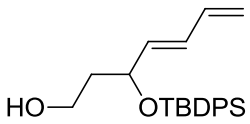
***(E)-3-((tert-Butyldimethylsilyl)oxy)hepta-4,6-dien-1-ol (337c)***




To a vigorously stirred suspension of potassium *tert*-butoxide (102 mg, 0.91 mmol, 0.1 eq.) in anhydrous THF (15 mL) cooled to -78 °C in a dry ice/acetone bath was added dropwise a 1.6 M solution of *n*-BuLi in hexane (6.8 mL, 10.9 mmol, 1.2 eq.). To this mixture was added dropwise a solution of diisopropylamine (917 mg, 9.07 mmol, 1.0 eq.) and (2-allyltetrahydrofuran-3-yl)oxy)(*tert*-butyl)dimethylsilane (**326d**) (2.20 g, 9.07 mmol, 1.0 eq.) in anhydrous THF (15 mL) *via* cannula.

The resulting mixture was stirred at -78 °C for 1 h, Sat. aq. $NH_4Cl$ solution (50 mL) was added to the mixture and extracted with $Et_2O$ (3 × 30 mL). The combined organic layers were washed sequentially with brine (100 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (30% $Et_2O$/petrol 30–40) to afford (*E*)-3-((*tert*-butyldimethylsilyl)oxy)hepta-4,6-dien-1-ol (**337c**) as a colourless oil (1.83 g, 7.53 mmol, 83%). $R_f$ = 0.20 (30% $Et_2O$/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 6.32 (1H, dt, *J* = 16.8, 10.2 Hz, =CHC**H**=$CH_2$), 6.18 (1H, d, *J* = 15.2, 10.2 Hz, CH=C**H**CH=), 5.70 (1H, dd, *J* = 15.2, 6.4 Hz, CH(OTBS)C**H**=CH), 5.19 (1H, dd, *J* = 16.8, 1.1 Hz, CH=$CH_Z\mathbf{H_E}$), 5.08 (1H, dd, *J* = 10.2, 1.1 Hz, CH=C$\mathbf{H_Z}H_E$), 4.48–4.42 (1H, m, $CH_2$C**H**(OTBS)CH=), 3.85–3.75 (1H, m, HOC$\mathbf{H_2}CH_2$), 3.75–3.66 (1H, m, HOC$\mathbf{H_2}CH_2$), 2.54 (1H, s, **H**O$CH_2$), 1.89–1.80 (1H, m, $CH_2$C$\mathbf{H_2}$CH(OTBS)), 1.78–1.69 (1H, m, $CH_2$C$\mathbf{H_2}$CH(OTBS)), 0.91 (9H, s, SiC(C$\mathbf{H_3}$)$_3$), 0.09 (3H, s, SiC$\mathbf{H_3}$), 0.05 (3H, s, SiC$\mathbf{H_3}$); $\delta_C$ (100 MHz, $CDCl_3$) 136.3 (CH(OTBS)**C**H=CH), 136.2 (=CH**C**H=$CH_2$), 130.5 (CH=**C**HCH=), 117.2 (CH=$\mathbf{C}H_ZH_E$), 72.4 ($CH_2$**C**H(OTBS)CH=), 60.1 (HO**C**$H_2CH_2$), 39.5 ($CH_2$**C**$H_2$CH(OTBS)), 25.8 (3C, SiC(**C**$H_3$)$_3$), 18.1 (Si**C**$(CH_3)_3$), -4.4 (Si**C**$H_3$), -5.0 (Si**C**$H_3$); LRMS *m*/*z* (ESI$^+$) 265 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 265.1593, $C_{13}H_{26}NaO_2Si$ requires 265.1594; $\nu_{max}$ (film)/cm$^{-1}$ 3344 (br, OH), 3087 (w, =$CH_2$), 3041 (w), 2956 (m, CH), 2931 (m, CH), 2885 (m, CH), 2858 (m, CH), 1605 (m, C=C), 1472 (m), 1362 (m), 1255 (s), 1054 (s, C-O), 1004 (s, CH=$CH_2$), 952 (m, C=$CH_2$), 836 (s, Si-O-C), 777 (s, Si$CH_3$).

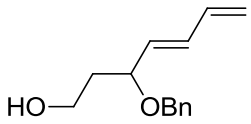
***(E)-3-((tert-Butyldiphenylsilyl)oxy)hepta-4,6-dien-1-ol (337d)***




To a vigorously stirred suspension of potassium *tert*-butoxide (34 mg, 0.30 mmol, 0.1 eq.) in anhydrous THF (5 mL) cooled to -78 °C in a dry ice/acetone bath was added dropwise a 1.6 M solution of *n*-BuLi in hexane (2.27 mL, 3.63 mmol, 1.2 eq.). To this mixture was added dropwise a solution of diisopropylamine (306 mg, 3.02 mmol, 1.0 eq.) and ((2-allyltetrahydrofuran-3-

yl)oxy)(*tert*-butyl)diphenylsilane (**326e**) (1.11 g, 3.02 mmol, 1.0 eq.) in anhydrous THF (5 mL) *via* cannula. The resulting mixture was stirred at -78 °C for 2 h, Sat. aq. $NH_4Cl$ solution (20 mL) was added to the mixture and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed sequentially with brine (60 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (15% EtOAc/petrol 40–60) to afford (*E*)-3-((*tert*-butyldiphenylsilyl)oxy)hepta-4,6-dien-1-ol (**337d**) as a colourless oil (752 mg, 2.05 mmol, 68%). $R_f$ = 0.21 (15% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 7.73–7.69 (2H, m, Ar**H**), 7.69–7.65 (2H, m, Ar**H**), 7.48–7.34 (6H, m, Ar**H**), 6.21 (1H, dt, *J* = 16.8, 10.2 Hz, =CHC**H=**$CH_2$), 5.90 (1H, dd, *J* = 15.3, 10.2 Hz, CH=C**H**CH=), 5.67 (1H, dd, *J* = 15.3, 6.8 Hz, CH(OTBDPS)C**H**=CH), 5.10–5.00 (2H, m, CH=C$\mathbf{H_Z H_E}$), 4.49–4.43 (1H, m, $CH_2$C**H**(OTBDPS)CH=), 3.81–3.72 (1H, m, HOC$\mathbf{H_2}CH_2$), 3.70–3.61 (1H, m, HOC$\mathbf{H_2}CH_2$), 1.91 (1H, t, *J* = 5.2 Hz, **H**O$CH_2$), 1.88–1.79 (1H, m, $CH_2$C$\mathbf{H_2}$CH(OTBDPS)), 1.77–1.68 (1H, m, $CH_2$C$\mathbf{H_2}$CH(OTBDPS)), 1.09 (9H, s, SiC(C$\mathbf{H_3}$)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 136.2 (=CH**C**H**=**$CH_2$), 136.0 (2C, Ar), 135.9 (2C, Ar), 135.3 (CH(OTBDPS)**C**H=CH), 133.7 (Ar), 133.6 (Ar), 131.1 (CH=**C**HCH=), 129.8 (Ar), 129.7 (Ar), 127.6 (2C, Ar), 127.5 (2C, Ar), 117.3 (CH=**C**$H_Z H_E$), 72.7 ($CH_2$**C**H(OTBDPS)CH=), 59.6 (HO**C**$H_2CH_2$), 39.7 ($CH_2$**C**$H_2$CH(OTBDPS)), 27.0 (3C, SiC(**C**$H_3$)$_3$), 19.3 (Si**C**$(CH_3)_3$); HRMS *m/z* ($FI^+$) found 366.2029, $C_{23}H_{30}O_2Si$ requires 366.2015; $\nu_{max}$ (film)/$cm^{-1}$ 3351 (br, OH), 3072 (w, =$CH_2$), 3047 (w), 3015 (w), 2999 (m, CH), 2931 (m, CH), 2889 (m, CH), 2857 (m, CH), 1959 (w, Ph overtone), 1890 (w, Ph overtone), 1821 (w, Ph overtone), 1604 (m, C=C), 1589 (m, C=C), 1472 (m), 1361 (m), 1047 (s, C-O), 1001 (s, CH=$CH_2$), 951 (m, C=$CH_2$), 857 (s, Si-O-C).

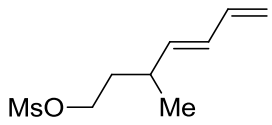
***(E)-3-(Benzyloxy)hepta-4,6-dien-1-ol (337e)***




To a vigorously stirred suspension of potassium tert-butoxide (27 mg, 0.24 mmol, 0.1 eq.) in anhydrous THF (3.97 mL) cooled to -78 °C in a dry ice/acetone bath was added dropwise a 1.6 M solution of *n*-BuLi in hexane (1.80 mL, 2.86 mmol, 1.2 eq.). To this mixture was added dropwise a solution of diisopropylamine (241 mg, 2.38 mmol, 1.0 eq.) and 2-allyl-3-(benzyloxy)tetrahydrofuran (**326f**) (520 mg, 2.38 mmol, 1.0 eq.) in anhydrous THF (3.97 mL) *via* cannula. The resulting mixture was stirred at -78 °C for 2 h, Sat. aq. $NH_4Cl$ solution (20 mL) was added to the mixture and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed sequentially with brine (60 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (30% EtOAc/petrol 40-60) to afford (*E*)-3-(benzyloxy)hepta-4,6-dien-1-ol (**337e**) as a colourless oil (402 mg, 1,83 mmol, 77%). $R_f$ = 0.28 (30% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 7.40–7.26 (5H, m, Ar**H**), 6.39 (1H, dt, *J* = 16.8, 10.2 Hz, =CHC**H**=$CH_2$), 6.26 (1H, dd, *J* = 15.2, 10.2 Hz, CH=C**H**CH=), 5.67 (1H, dd, *J* = 15.2, 8.1 Hz, CH(OBn)C**H**=CH), 5.27 (1H, d, *J* = 16.8 Hz, CH=$CH_Z\mathbf{H_E}$), 5.17 (1H, d, *J* = 10.2 Hz, CH=C$\mathbf{H_Z}H_E$), 4.63 (1H, d, *J* = 11.8 Hz, OC$\mathbf{H_2}$Ph), 4.37 (1H, d, *J* = 11.8 Hz, OC$\mathbf{H_2}$Ph), 4.08 (1H, td, *J* = 8.1, 4.5 Hz, $CH_2$C**H**(OBn)CH=), 3.83–3.70 (2H, m, HOC$\mathbf{H_2}CH_2$), 2.45 (1H, s, **H**O$CH_2$), 1.96-1.84 (1H, m, $CH_2$C$\mathbf{H_2}$CH(OBn)), 1.85-1.76 (1H, m, $CH_2$C$\mathbf{H_2}$CH(OBn)); $\delta_C$ (100 MHz, $CDCl_3$) 138.2 (Ar), 136.1 (=CH**C**H=$CH_2$), 133.5 (CH=**C**HCH=), 133.4 (CH(OBn)**C**H=CH), 128.5 (2C, Ar), 127.8 (2C, Ar), 127.7 (Ar), 118.1 (CH=**C**$H_ZH_E$), 78.9 ($CH_2$**C**H(OBn)CH=), 70.3 (O**C**$H_2$Ph), 60.5 (HO**C**$H_2CH_2$), 38.0 ($CH_2$**C**$H_2$CH(OBn)); HRMS *m/z* ($FI^+$) found 218.1307, $C_{14}H_{18}O_2$ requires 218.1307; $\nu_{max}$ (film)/$cm^{-1}$ 3385 (br, OH), 3087 (w, =$CH_2$), 3064 (w), 3032 (w), 2944 (m, CH), 2867 (m, CH), 1953 (w, Ph overtone), 1812 (w, Ph overtone), 1604 (m, C=C), 1496

(m), 1454 (m), 1418 (m), 1391 (m), 1345 (m), 1205 (m), 1050 (s, C-O), 1004 (s, CH=$CH_2$), 954 (m, C=$CH_2$), 904 (s).

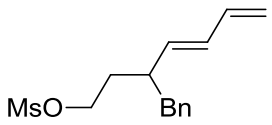
***(E)-3-Methylhepta-4,6-dien-1-yl methanesulfonate (338a)***




To a stirred solution of (*E*)-3-methylhepta-4,6-dien-1-ol (**337a**) (355 mg, 2.81 mmol, 1.0 eq.) in anhydrous DCM (9.36 mL) cooled to 0 °C in an ice/water bath was added triethylamine (427 mg, 4.22 mmol, 1.5 eq.) followed by dropwise addition of methanesulfonyl chloride (354 mg, 3.09 mmol, 1.1 eq.). After complete addition the mixture was warmed to room temperature and stirred for 1.5 h. The mixture was poured over 1 M HCl (10 mL), the organic layer separated and the aqueous layer was further extracted with DCM (2 × 10 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (30 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% $Et_2O$/petrol 30–40) to afford (*E*)-3-methylhepta-4,6-dien-1-yl methanesulfonate (**338a**) (*E*:*Z* = 10:1) as a colourless oil (528 mg, 2.59 mmol, 92%). Characterisation is reported for the major epimer of an inseparable mixture of regioisomers. $R_f$ = 0.35 (50% $Et_2O$/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 6.29 (1H, dt, *J* = 17.0, 10.2 Hz, =CHC**H**=$CH_2$), 6.06 (1H, ddd, *J* = 15.2, 10.2, 0.7 Hz, CH=C**H**CH=), 5.52 (1H, dd, *J* = 15.2, 8.3 Hz, CH(Me)C**H**=CH), 5.13 (1H, dd, *J* = 17.0, 0.9 Hz, CH=$CH_Z$**H**$_E$), 5.01 (1H, d, *J* = 10.2, 0.8 Hz, CH=C**H**$_Z$$H_E$), 4.27–4.15 (2H, m, MsOC**H**$_2$$CH_2$), 2.98 (3H, s, $SO_2$C**H**$_3$), 2.44–2.32 (1H, m, $CH_2$C**H**(Me)CH=), 1.85–1.65 (2H, m, $CH_2$C**H**$_2$CH(Me)), 1.06 (3H, d, *J* = 6.8 Hz, CH(C**H**$_3$)); $\delta_C$ (100 MHz, $CDCl_3$) 138.5 (CH(Me)**C**H=CH), 136.8 (=CH**C**H=$CH_2$), 130.7 (CH=**C**HCH=), 116.0 (CH=**C**$H_ZH_E$), 68.4 (MsO**C**$H_2CH_2$), 37.3 ($SO_2$**C**$H_3$), 35.8 ($CH_2$**C**H(Me)CH=), 33.3 ($CH_2$**C**H(Me)CH=), 20.4 (CH(**C**$H_3$)); LRMS *m*/*z* (ESI$^+$) 227 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 227.0713, $C_9H_{16}NaO_3S$ requires 227.0712; $\nu_{max}$ (film)/cm$^{-1}$ 3086 (w, =$CH_2$), 2965 (m, CH), 2939 (m, CH),

2872 (M, CH), 1650 (w, C=C), 1604 (w, C=C), 1351 (s, $SO_2$), 1171 (s, $SO_2$), 1007 (m, $CH=CH_2$), 972 (m, $C=CH_2$), 938 (s, $C=CH_2$).

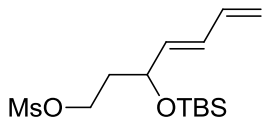
***(E)-3-Benzylhepta-4,6-dien-1-yl methanesulfonate (338b)***




To a stirred solution of (*E*)-3-benzylhepta-4,6-dien-1-ol (**337b**) (2.24 g, 11.0 mmol, 1.0 eq.) in anhydrous DCM (36.7 mL) cooled to 0 °C in an ice/water bath was added triethylamine (1.68 g, 16.7 mmol, 1.5 eq.) followed by dropwise addition of methanesulfonyl chloride (1.40 g, 12.2 mmol, 1.1 eq.). After complete addition the mixture was warmed to room temperature and stirred for 1 h. The mixture was poured over 1 M HCl (50 mL), the organic layer separated and the aqueous layer was further extracted with DCM (2 × 50 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (100 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford (*E*)-3-benzylhepta-4,6-dien-1-yl methanesulfonate (**338b**) (*E*:*Z* = 17:1) as a colourless oil (2.91 g, 10.3 mmol, 94%). Characterisation is reported for the major epimer of an inseparable mixture of regioisomers. $R_f$ = 0.36 (30% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 7.32–7.26 (2H, m, Ar**H**), 7.24–7.20 (1H, m, Ar**H**), 7.17–7.12 (2H, m, Ar**H**), 6.29 (1H, dt, *J* = 17.0, 10.2 Hz, $=CHC\mathbf{H}=CH_2$), 6.02 (1H, dd, *J* = 15.2, 10.2 Hz, $CH=C\mathbf{H}CH=$), 5.50 (1H, dd, *J* = 15.2, 9.0 Hz, $CH(Bn)C\mathbf{H}=CH$), 5.12 (1H, dd, *J* = 17.0, 0.8 Hz, $CH=CH_Z\mathbf{H_E}$), 5.03 (1H, d, *J* = 10.2, 0.8 Hz, $CH=C\mathbf{H_Z}H_E$), 4.24 (1H, ddd, *J* = 9.8, 7.0, 5.1 Hz, $MsOC\mathbf{H_2}CH_2$), 4.14 (1H, ddd, *J* = 9.8, 8.2, 6.2 Hz, $MsOC\mathbf{H_2}CH_2$), 2.93 (3H, s, $SO_2C\mathbf{H_3}$), 2.74 (1H, dd, *J* = 13.5, 7.2 Hz, $CHC\mathbf{H_2}Ph$), 2.67 (1H, dd, *J* = 13.5, 7.0 Hz, $CHC\mathbf{H_2}Ph$), 2.60–2.49 (1H, m, $CH_2C\mathbf{H}(Bn)CH=$), 1.95 (1H, dddd, *J* = 14.3, 8.2, 7.0, 4.0 Hz, $CH_2C\mathbf{H_2}CH(Bn)$), 1.66 (1H, dddd, *J* = 14.3, 10.5, 6.2, 5.1 Hz, $CH_2C\mathbf{H_2}CH(Bn)$); $\delta_C$ (100 MHz, $CDCl_3$) 139.2 (Ar), 136.5 ($=CH\mathbf{C}H=CH_2$), 136.1 ($CH(Bn)\mathbf{C}H=CH$), 132.5 ($CH=\mathbf{C}HCH=$), 129.3 (2C, Ar), 128.3 (2C, Ar), 126.2 (Ar), 116.4 ($CH=\mathbf{C}H_ZH_E$), 68.4 ($MsO\mathbf{C}H_2CH_2$), 41.9 ($CH\mathbf{C}H_2Ph$), 40.9 ($CH_2\mathbf{C}H(Bn)CH=$), 37.3 ($SO_2\mathbf{C}H_3$),

33.3 ($CH_2$**C**$H_2$CH(Bn)); HRMS *m*/*z* ($FI^+$) found 280.1138, $C_{15}H_{20}O_3S$ requires 280.1133; $\nu_{max}$ (film)/$cm^{-1}$ 3085 (w, =$CH_2$), 3027 (m, CH), 2937 (m, CH), 1650 (m, C=C), 1602 (m, C=C), 1495 (m), 1454 (m), 1352 (s, $SO_2$), 1171 (s, $SO_2$), 1007 (s, CH=$CH_2$), 970 (s, C=$CH_2$), 951 (s, C=$CH_2$).

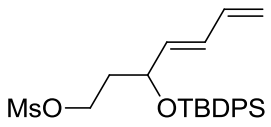
***(E)-3-((tert-Butyldimethylsilyl)oxy)hepta-4,6-dien-1-yl methanesulfonate (338c)***




To a stirred solution of (*E*)-3-((*tert*-butyldimethylsilyl)oxy)hepta-4,6-dien-1-ol (**337c**) (1.78 g, 7.34 mmol, 1.0 eq.) in anhydrous DCM (24.5 mL) cooled to 0 °C in an ice/water bath was added triethylamine (1.11 g, 11.0 mmol, 1.5 eq.) followed by dropwise addition of methanesulfonyl chloride (925 mg, 8.07 mmol, 1.2 eq.). After complete addition the mixture was warmed to room temperature and stirred for 1.5 h. The mixture was poured over 1 M HCl (40 mL), the organic layer separated and the aqueous layer was further extracted with DCM (2 × 25 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (75 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford (*E*)-3-((*tert*-butyldimethylsilyl)oxy)hepta-4,6-dien-1-yl methanesulfonate (**338c**) as a colourless oil (2.34 g, 7.27 mmol, 99%). $R_f$ = 0.22 (30% $Et_2O$/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 6.32 (1H, dt, *J* = 16.8, 10.2 Hz, =CHC**H**=$CH_2$), 6.18 (1H, dd, *J* = 15.1, 10.2 Hz, CH=C**H**CH=), 5.63 (1H, dd, *J* = 15.1, 6.7 Hz, CH(OTBS)C**H**=CH), 5.20 (1H, dd, *J* = 16.8, 0.8 Hz, CH=$CH_Z$**H**$_E$), 5.10 (1H, dd, *J* = 10.2, 0.8 Hz, CH=C**H**$_Z$$H_E$), 4.37–3.25 (3H, m, $CH_2$C**H**(OTBS)CH= & MsOC**H**$_2$$CH_2$), 2.99 (3H, s, $SO_2$C**H**$_3$), 2.00-1.86 (2H, m, $CH_2$C**H**$_2$CH(OTBS)), 0.89 (9H, s, SiC(C**H**$_3$)$_3$), 0.07 (3H, s, SiC**H**$_3$), 0.03 (3H, s, SiC**H**$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 136.1 (=CH**C**H=$CH_2$), 135.7 (CH(OTBS)**C**H=CH), 131.0 (CH=**C**HCH=), 117.6 (CH=**C**$H_Z$$H_E$), 69.2 ($CH_2$**C**H(OTBS)CH=), 66.8 (MsO**C**$H_2$$CH_2$), 37.5 ($CH_2$**C**$H_2$CH(OTBS)), 37.3 ($SO_2$**C**$H_3$), 25.8 (3C, SiC(**C**$H_3$)$_3$), 18.1 (Si**C**$(CH_3)_3$), -4.3 (Si**C**$H_3$), -5.0 (Si**C**$H_3$); LRMS *m*/*z* ($ESI^+$) 343 ($[M+Na]^+$, 100%), 663 ($[2M+Na]^+$, 38%); HRMS *m*/*z* ($ESI^+$) found 343.1365, $C_{14}H_{28}NaO_4SSi$ requires 343.1370; $\nu_{max}$ (film)/$cm^{-1}$ 3088 (w, =$CH_2$), 2955 (m, CH), 2930 (m, CH),

2837 (m, CH), 2858 (m, CH), 1605 (m, C=C), 1472 (m), 1356 (s, $SO_2$), 1253 (m), 1175 (s, $SO_2$), 1089 (m), 1003 (s, $CH=CH_2$), 970 (s, $C=CH_2$), 955 (s, $C=CH_2$), 835 (s, Si-O-C), 777 (s, $SiCH_3$).

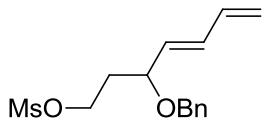
***(E)-3-((tert-Butyldiphenylsilyl)oxy)hepta-4,6-dien-1-yl methanesulfonate (338d)***




To a stirred solution of (*E*)-3-((*tert*-butyldiphenylsilyl)oxy)hepta-4,6-dien-1-ol (**337d**) (736 mg, 2.00 mmol, 1.0 eq.) in anhydrous DCM (6.66 mL) cooled to 0 °C in an ice/water bath was added triethylamine (305 mg, 3.01 mmol, 1.5 eq.) followed by dropwise addition of methanesulfonyl chloride (253 mg, 2.21 mmol, 1.2 eq.). After complete addition the mixture was warmed to room temperature and stirred for 2 h. The mixture was poured over 1 M HCl (20 mL), the organic layer separated and the aqueous layer was further extracted with DCM (2 × 10 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (40 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford (*E*)-3-((*tert*-butyldiphenylsilyl)oxy)hepta-4,6-dien-1-yl methanesulfonate (**338d**) as a colourless oil (821 mg, 1.84 mmol, 92%). $R_f$ = 0.45 (100% DCM); $\delta_H$ (400 MHz, $CDCl_3$) 7.71–7.66 (2H, m, Ar**H**), 7.66–7.62 (2H, m, Ar**H**), 7.48–7.35 (6H, m, Ar**H**), 6.21 (1H, dt, *J* = 17.0, 10.3 Hz, =CHC**H**=$CH_2$), 5.91 (1H, dd, *J* = 15.3, 10.3 Hz, CH=C**H**CH=), 5.61 (1H, dd, *J* = 15.3, 7.0 Hz, CH(OTBDPS)C**H**=CH), 5.09 (1H, d, *J* = 17.0 Hz, $CH=CH_Z\mathbf{H_E}$), 5.06 (1H, d, *J* = 10.3 Hz, $CH=C\mathbf{H_Z}H_E$), 4.41–4.32 (1H, m, $CH_2C\mathbf{H}$(OTBDPS)CH=), 4.31–3.20 (2H, m, $MsOC\mathbf{H_2}CH_2$), 2.87 (3H, s, $SO_2C\mathbf{H_3}$), 2.05–1.85 (2H, m, $CH_2C\mathbf{H_2}CH$(OTBDPS)), 1.09 (9H, s, $SiC(C\mathbf{H_3})_3$); $\delta_C$ (100 MHz, $CDCl_3$) 136.0 (=CH**C**H=$CH_2$), 135.9 (2C, Ar), 135.8 (2C, Ar), 134.5 (CH(OTBDPS)**C**H=CH), 133.8 (Ar), 133.5 (Ar), 131.8 (CH=**C**HCH=), 129.8 (Ar), 129.7 (Ar), 127.7 (2C, Ar), 127.5 (2C, Ar), 117.9 ($CH=\mathbf{C}H_ZH_E$), 70.6 ($CH_2\mathbf{C}H$(OTBDPS)CH=), 66.6 ($MsO\mathbf{C}H_2CH_2$), 37.2 ($SO_2\mathbf{C}H_3$), 37.0 ($CH_2\mathbf{C}H_2CH$(OTBDPS)), 27.0 (3C, $SiC(\mathbf{C}H_3)_3$), 19.3 ($Si\mathbf{C}(CH_3)_3$); LRMS *m/z* ($ESI^+$) 467 ($[M+Na]^+$, 100%); HRMS *m/z* ($ESI^+$) found 467.1677, $C_{24}H_{32}NaO_4SSi$ requires 467.1677; $\nu_{max}$ (film)/$cm^{-1}$ 3072 (w, $=CH_2$), 3045

(w, =$CH_2$), 2959 (m, CH), 2932 (m, CH), 2893 (m, CH), 2858 (m, CH), 1967 (w, Ph overtone), 1826 (w, Ph overtone), 1605 (m, C=C), 1472 (m), 1428 (m), 1356 (s, $SO_2$), 1267 (m), 1174 (s, $SO_2$), 1111 (s), 1082 (s), 1003 (s, CH=$CH_2$), 954 (s, C=$CH_2$), 867 (s, Si-O-C).

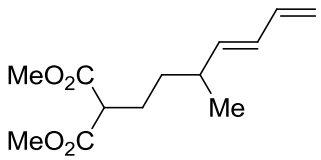
***(E)-3-(Benzyloxy)hepta-4,6-dien-1-yl methanesulfonate (338e)***




To a stirred solution of (*E*)-3-(benzyloxy)hepta-4,6-dien-1-ol (**337e**) (262 mg, 1.20 mmol, 1.0 eq.) in anhydrous DCM (4.0 mL) cooled to 0 °C in an ice/water bath was added triethylamine (182 mg, 1.80 mmol, 1.5 eq.) followed by dropwise addition of methanesulfonyl chloride (151 mg, 1.32 mmol, 1.2 eq.). After complete addition the mixture was warmed to room temperature and stirred for 1.5 h. The mixture was poured over 1 M HCl (10 mL), the organic layer separated and the aqueous layer was further extracted with DCM (2 × 10 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (30 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure to afford (*E*)-3-(benzyloxy)hepta-4,6-dien-1-yl methanesulfonate (**338e**) as a colourless oil (346 mg, 1.16 mmol, 97%). $R_f$ = 0.38 (30% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 7.39–7.26 (5H, m, Ar**H**), 6.45–6.24 (2H, m, =CHC**H**=$CH_2$ & CH=C**H**CH=), 5.62 (1H, dd, *J* = 15.1, 8.0 Hz, CH(OBn)C**H**=CH), 5.29 (1H, dd, *J* = 16.8, 1.5 Hz, CH=$CH_Z$**H**$_E$), 5.18 (1H, dd, *J* = 10.3, 1.5 Hz, CH=C**H**$_Z$$H_E$), 4.61 (1H, d, *J* = 11.6 Hz, OC**H**$_2$Ph), 4.43–4.36 (1H, m, MsOC**H**$_2$$CH_2$), 4.35 (1H, d, *J* = 11.6 Hz, OC**H**$_2$Ph), 4.34–3.26 (1H, m, MsOC**H**$_2$$CH_2$), 4.01 (1H, td, *J* = 8.1, 4.9 Hz, $CH_2$C**H**(OBn)CH=), 2.93 (3H, s, $SO_2$C**H**$_3$), 2.10–1.93 (2H, m, $CH_2$C**H**$_2$CH); $\delta_C$ (100 MHz, $CDCl_3$) 138.2 (Ar), 135.9 (=CH**C**H=$CH_2$), 134.1 (CH=**C**HCH=), 132.8 (CH(OBn)**C**H=CH), 128.4 (2C, Ar), 127.9 (2C, Ar), 127.7 (Ar), 118.5 (CH=**C**$H_Z$$H_E$), 75.4 ($CH_2$**C**H(OBn)CH=), 70.4 (O**C**$H_2$Ph), 66.8 (MsO**C**$H_2$$CH_2$), 37.2 ($SO_2$**C**$H_3$), 35.3 ($CH_2$**C**$H_2$CH); LRMS *m*/*z* (ESI$^+$) 319 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 319.0975, $C_{15}H_{20}NaO_4S$ requires 319.0975; $\nu_{max}$ (film)/cm$^{-1}$ 3088 (w, =$CH_2$), 3031 (w, =$CH_2$),

2939 (m, CH), 2866 (m, CH), 1819 (w, Ph overtone), 1604 (m, C=C), 1497 (m), 1454 (m), 1352 (s, $SO_2$), 1175 (s, $SO_2$), 1095 (s), 1006 (s, $CH=CH_2$), 970 (s, $C=CH_2$).

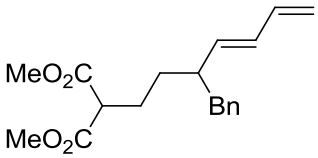
***(E)-dimethyl 2-(3-methylhepta-4,6-dien-1-yl)malonate (339a)***




To a stirred suspension of hexane washed NaH (174 mg, 7.28 mmol, 3.0 eq.) in anhydrous DMF (6.08 mL) cooled to 0 °C in an ice/water bath, was carefully added dropwise dimethyl malonate (962 mg, 7.28 mmol, 3.0 eq.). The resulting mixture was stirred for 20 min at this temperature, after which a solution of (*E*)-3-methylhepta-4,6-dien-1-yl methanesulfonate (**338a**) (496 mg, 2.43 mmol, 1.0 eq.) in anhydrous THF (6.08 mL) was added *via* cannula followed by potassium iodide (202 mg, 1.22 mmol, 0.5 eq.). The mixture was warmed to room temperature, and then heated at 80 °C for 1.5 h. The mixture was cooled to room temperature, after which sat. aq. $NH_4Cl$ solution (10 mL) was added and extracted with $Et_2O$ (3 × 10 mL). The combined organic extracts were sequentially washed with water (30 mL), brine (30 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% $Et_2O$/petrol 30–40) to afford (*E*)-dimethyl 2-(3-methylhepta-4,6-dien-1-yl)malonate (**339a**) (*E*:*Z* = 10:1) as a colourless oil (503 mg, 2.09 mmol, 86%). Characterisation is reported for the major epimer of an inseparable mixture of regioisomers. $R_f$ =0.26 (20% $Et_2O$/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 6.28 (1H, dt, *J* = 17.0, 10.2 Hz, =CHC**H**=$CH_2$), 6.02 (1H, dd, *J* = 15.3, 10.2 Hz, CH=C**H**CH=), 5.54 (1H, dd, *J* = 15.3, 7.9 Hz, CH(Me)C**H**=CH), 5.10 (1H, d, *J* = 17.0 Hz, $CH=CH_Z\mathbf{H_E}$), 4.97 (1H, d, *J* = 10.2 Hz, $CH=C\mathbf{H_Z}H_E$), 3.73 (6H, s, $OC\mathbf{H_3}$), 3.33 (1H, t, *J* = 7.5 Hz, $(MeO_2C)_2C\mathbf{H}CH_2$), 2.24–2.11 (1H, m, $CH_2C\mathbf{H}(Me)CH=$), 1.92–1.84 (2H, m, $CHC\mathbf{H_2}CH_2$), 1.35–1.27 (2H, m, $CH_2C\mathbf{H_2}CH(Me)$), 1.01 (3H, d, *J* = 6.7 Hz, $CH(C\mathbf{H_3})$); $\delta_C$ (100 MHz, $CDCl_3$) 169.8 (C=O), 169.8 (C=O), 139.9 (CH(Me)**C**H=CH), 137.2 (=CH**C**H**=**$CH_2$), 129.8 (CH=**C**HCH=), 115.2

(CH=**C**$H_ZH_E$), 52.4 (2C, O**C**$H_3$), 51.7 ((MeO$_2$C)$_2$**C**HCH$_2$), 36.5 (CH$_2$**C**H(Me)CH=), 34.3 (CH$_2$**C**H$_2$CH(Me)), 26.7 (CH**C**H$_2$CH$_2$), 20.3 (CH(**C**H$_3$)); LRMS *m*/*z* (ESI$^+$) 263 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 263.1253, $C_{13}H_{20}NaO_4$ requires 263.1254; $\nu_{max}$ (film)/cm$^{-1}$ 3086 (w, =CH$_2$), 2956 (m, CH), 2869 (m, CH), 1735 (s C=O), 1650 (w, C=C), 1604 (w, C=C), 1435 (m), 1152 (s, C-O), 1007 (m, CH=CH$_2$), 959 (m, C=CH$_2$), 902 (m, C=CH$_2$).

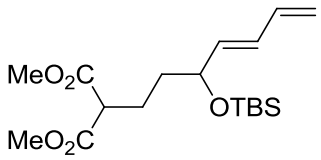
***(E)-Dimethyl 2-(3-benzylhepta-4,6-dien-1-yl)malonate (339b)***




To a stirred suspension of hexane washed NaH (731 mg, 30.5 mmol, 3.0 eq.) in anhydrous DMF (25.5 mL) cooled to 0 °C in an ice/water bath, was carefully added dropwise dimethyl malonate (4.03 g, 30.5 mmol, 3.0 eq.). The resulting mixture was stirred for 20 min at this temperature, after which a solution of (*E*)-3-benzylhepta-4,6-dien-1-yl methanesulfonate (**338b**) (2.85 g, 10.2 mmol, 1.0 eq.) in anhydrous THF (25.5 mL) was added *via* cannula followed by potassium iodide (847 mg, 5.10 mmol, 0.5 eq.). The mixture was warmed to room temperature, and then heated at 80 °C for 16 h. The mixture was cooled to room temperature, after which sat. aq. $NH_4Cl$ solution (100 mL) was added and extracted with EtOAc (3 × 50 mL). The combined organic extracts were sequentially washed with water (150 mL), brine (150 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/petrol 30–40) to afford (*E*)-dimethyl 2-(3-benzylhepta-4,6-dien-1-yl)malonate (**339b**) (*E*:*Z* = 17:1) as a colourless oil (2.62 g, 8.26 mmol, 81%). Characterisation is reported for the major epimer of an inseparable mixture of regioisomers. $R_f$ = 0.32 (20% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 7.29–7.24 (2H, m, Ar), 7.21–7.15 (1H, m, Ar), 7.14–7.10 (2H, m, Ar), 6.29 (1H, dt, *J* = 17.0, 10.2 Hz, =CHC**H**=CH$_2$), 5.96 (1H, dd, *J* = 15.3, 10.2 Hz, CH=C**H**CH=), 5.51 (1H, dd, *J* = 15.3, 8.7 Hz, CH(Bn)C**H**=CH), 5.08 (1H, dd, *J* = 17.0, 1.5 Hz, CH=CH$_Z$**H**$_E$), 4.98 (1H, dd,

*J* = 10.2, 1.5 Hz, CH=C**H**$_Z$H$_E$), 3.70 (3H, s, OC**H**$_3$), 3.70 (3H, s, OC**H**$_3$), 3.31 (1H, t, *J* = 7.8 Hz, (MeO$_2$C)$_2$C**H**CH$_2$), 2.66 (1H, d, *J* = 2.5 Hz, CHC**H**$_2$Ph), 2.64 (1H, d, *J* = 1.9 Hz, CHC**H**$_2$Ph), 2.40–2.30 (1H, m, CH$_2$C**H**(Bn)CH=), 1.97 (1H, dddd, *J* = 13.5, 11.3, 7.8, 4.9 Hz, CHC**H**$_2$CH$_2$), 1.87–1.76 (1H, m, CHC**H**$_2$CH$_2$), 1.50–1.40 (1H, m, CH$_2$C**H**$_2$CH(Bn)), 1.33 (1H, dddd, *J* = 13.9, 11.1, 9.3, 4.9 Hz, CH$_2$C**H**$_2$CH(Bn)); $\delta_C$ (100 MHz, $CDCl_3$) 169.8 (**C**=O), 169.7 (**C**=O), 139.9 (Ar), 137.5 (CH(Bn)**C**H=CH), 137.0 (=CH**C**H=CH$_2$), 131.7 (CH=**C**HCH=), 129.2 (2C, Ar), 128.1 (2C, Ar), 125.9 (Ar), 115.5 (CH=**C**H$_Z$H$_E$), 52.4 (O**C**H$_3$), 52.4 (O**C**H$_3$), 51.6 ((MeO$_2$C)$_2$**C**HCH$_2$), 44.2 (CH$_2$**C**H(Bn)CH=), 41.8 (CH**C**H$_2$Ph), 31.7 (CH$_2$**C**H$_2$CH(Bn)), 26.7 (CH**C**H$_2$CH$_2$); LRMS *m*/*z* (ESI$^+$) 339 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 339.1568, $C_{19}H_{24}NaO_4$ requires 339.1567; $\nu_{max}$ (film)/cm$^{-1}$ 3085 (w, =CH$_2$), 3027 (w), 3002 (m), 2953 (m, CH), 2922 (m, CH), 2853 (m, CH), 1751 (s C=O), 1733 (s, C=O), 1650 (w, C=C), 1602 (m, C=C), 1495 (m), 1435 (s), 1284 (m), 1196 (m), 1148 (s, C-O),1006 (s, CH=CH$_2$), 954 (m, C=CH$_2$), 901 (m, C=CH$_2$).

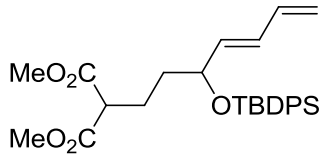
***(E)-Dimethyl 2-(3-((tert-butyldimethylsilyl)oxy)hepta-4,6-dien-1-yl)malonate (339c)***




To a stirred suspension of hexane washed NaH (513 mg, 21.4 mmol, 3.0 eq.) in anhydrous DMF (17.9 mL) cooled to 0 °C in an ice/water bath, was carefully added dropwise dimethyl malonate (2.83 g, 21.4 mmol, 3.0 eq.). The resulting mixture was stirred for 20 min at this temperature, after which a solution of (*E*)-3-((*tert*-butyldimethylsilyl)oxy)hepta-4,6-dien-1-yl methanesulfonate (**338c**) (2.29 g, 7.14 mmol, 1.0 eq.) in anhydrous THF (17.9 mL) was added *via* cannula followed by potassium iodide (593 mg, 3.57 mmol, 0.5 eq.). The mixture was warmed to room temperature, and then heated at 80 °C for 18 h. The mixture was cooled to room temperature, after which sat. aq. $NH_4Cl$ solution (50 mL) was added and extracted with EtOAc (3 × 25 mL). The combined organic extracts were sequentially washed with water (100 mL), brine (100 mL), dried ($Na_2SO_4$), filtered and

concentrated under reduced pressure. The residue was purified by flash column chromatography (15% EtOAc/petrol 40–60) to afford (*E*)-dimethyl 2-(3-((*tert*-butyldimethylsilyl)oxy)hepta-4,6-dien-1-yl)malonate (**339c**) as a colourless oil (2.20 g, 6.14 mmol, 86%). $R_f$ = 0.38 (20% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 6.30 (1H, dt, *J* = 16.8, 10.2 Hz, =CHC**H**=$CH_2$), 6.14 (1H, dd, *J* = 15.2, 10.2 Hz, CH=C**H**CH=), 5.62 (1H, dd, *J* = 15.2, 6.4 Hz, CH(OTBS)C**H**=CH), 5.17 (1H, dd, *J* = 16.8, 1.3 Hz, CH=$CH_Z$**H**$_E$), 5.05 (1H, dd, *J* = 10.2, 1.3 Hz, CH=C**H**$_Z$$H_E$), 4.20–4.13 (1H, m, $CH_2$C**H**(OTBS)CH=), 3.72 (6H, s, OC**H**$_3$), 3.36 (1H, t, *J* = 7.5 Hz, $(MeO_2C)_2$C**H**$CH_2$), 2.04–1.85 (2H, m, CHC**H**$_2$$CH_2$), 1.55–1.48 (2H, m, $CH_2$C**H**$_2$CH(OTBS)), 0.89 (9H, s, SiC(C**H**$_3$)$_3$), 0.05 (3H, s, SiC**H**$_3$), 0.02 (3H, s, SiC**H**$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 169.8 (**C**=O), 169.7 (**C**=O), 136.5 (CH(OTBS)**C**H=CH), 136.4 (=CH**C**H=$CH_2$), 130.4 (CH=**C**HCH=), 116.9 (CH=**C**H$_Z$$H_E$), 72.4 ($CH_2$**C**H(OTBS)CH=), 52.4 (2C, O**C**$H_3$), 51.5 ($(MeO_2C)_2$**C**H$CH_2$), 35.5 ($CH_2$**C**H$_2$CH(OTBS)), 25.8 (3C, SiC(**C**$H_3$)$_3$), 24.5 (CH**C**H$_2$$CH_2$), 18.2 (Si**C**$(CH_3)_3$), -4.4 (Si**C**$H_3$), -4.90 (Si**C**$H_3$); LRMS *m/z* (ESI$^+$) 379 ([M+Na]$^+$, 100%), 735 ([2M+Na]$^+$, 37%); HRMS *m/z* (ESI$^+$) found 379.1915, $C_{18}H_{32}NaO_5Si$ requires 379.1911; $\nu_{max}$ (film)/cm$^{-1}$ 2954 (m, CH), 2930 (m, CH), 2888 (m, CH), 2853 (m, CH), 1754 (s C=O), 1736 (s, C=O), 1605 (m, C=C), 1472 (m), 1435 (s), 1346 (m), 1252 (m), 1152 (s, C-O), 1083 (m), 1004 (s, CH=$CH_2$), 954 (m, C=$CH_2$), 903 (m, C=$CH_2$), 834 (s, Si-O-C), 775 (s, Si$CH_3$).

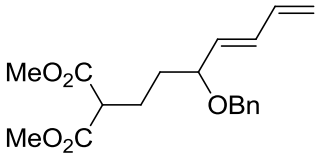
***(E)-Dimethyl 2-(3-((tert-butyldiphenylsilyl)oxy)hepta-4,6-dien-1-yl)malonate (339d)***




To a stirred suspension of hexane washed NaH (125 mg, 5.22 mmol, 3.0 eq.) in anhydrous DMF (4.35 mL) cooled to 0 °C in an ice/water bath, was carefully added dropwise dimethyl malonate (689 mg, 5.22 mmol, 3.0 eq.). The resulting mixture was stirred for 20 min at this temperature, after which a solution of (*E*)-3-((*tert*-butyldiphenylsilyl)oxy)hepta-4,6-dien-1-yl methanesulfonate (**338d**)

(774 mg, 1.74 mmol, 1.0 eq.) in anhydrous THF (4.35 mL) was added *via* cannula followed by potassium iodide (144 mg, 0.87 mmol, 0.5 eq.). The mixture was warmed to room temperature, and then heated at 80 °C for 16 h. The mixture was cooled to room temperature, after which sat. aq. $NH_4Cl$ solution (20 mL) was added and extracted with EtOAc (3 × 10 mL). The combined organic extracts were sequentially washed with water (50 mL), brine (50 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60) to afford (*E*)-dimethyl 2-(3-((*tert*-butyldiphenylsilyl)oxy)hepta-4,6-dien-1-yl)malonate (**339d**) as a colourless oil (690 mg, 1.44 mmol, 83%). $R_f$ = 0.32 (15% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 7.70–7.66 (2H, m, Ar**H**), 7.66–7.62 (2H, m, Ar**H**), 7.46–7.33 (6H, m, Ar**H**), 6.22 (1H, dt, *J* = 17.0, 10.3 Hz, =CHC**H=**$CH_2$), 5.89 (1H, dd, *J* = 15.3, 10.3 Hz, CH=C**H**CH=), 5.61 (1H, dd, *J* = 15.3, 6.8 Hz, CH(OTBDPS)C**H**=CH), 5.07 (1H, dd, *J* = 17.0, 1.3 Hz, CH=$CH_Z$**H**$_E$), 5.02 (1H, dd, *J* = 10.3, 1.3 Hz, CH=C**H**$_Z$$H_E$), 4.26–4.19 (1H, m, $CH_2$C**H**(OTBDPS)CH=), 3.71 (3H, s, OC**H**$_3$), 3.70 (3H, s, OC**H**$_3$), 3.25 (1H, t, *J* = 7.5 Hz, $(MeO_2C)_2$C**H**$CH_2$), 1.96–1.82 (2H, m, CHC**H**$_2$$CH_2$), 1.60–1.45 (2H, m, $CH_2$C**H**$_2$CH(OTBDPS)), 1.08 (9H, s, SiC(C**H**$_3$)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 169.7 (2C, **C**=O), 136.4 (=CH**C**H**=**$CH_2$), 136.0 (2C, Ar), 135.9 (2C, Ar), 135.5 (CH(OTBDPS)**C**H=CH), 134.1 (Ar), 133.9 (Ar), 131.3 (CH=**C**HCH=), 129.6 (Ar), 129.5 (Ar), 127.5 (2C, Ar), 127.4 (2C, Ar), 117.1 (CH=**C**$H_ZH_E$), 73.2 ($CH_2$**C**H(OTBDPS)CH=), 52.4 (2C, O**C**$H_3$), 51.5 ($(MeO_2C)_2$**C**H$CH_2$), 35.2 ($CH_2$**C**$H_2$CH(OTBDPS)), 27.0 (3C, SiC(**C**$H_3$)$_3$), 24.0 (CH**C**$H_2$$CH_2$), 19.3 (Si**C**$(CH_3)_3$); LRMS *m/z* (ESI$^+$) 503 ([M+Na]$^+$, 100%), 983 ([2M+Na]$^+$, 94%); HRMS *m/z* (ESI$^+$) found 503.2213, $C_{28}H_{36}NaO_5Si$ requires 503.2224; $\nu_{max}$ (film)/cm$^{-1}$ 3071 (w, =$CH_2$), 3000 (w, =$CH_2$), 2953 (m, CH), 2932 (m, CH), 2892 (m, CH), 2858 (m, CH), 1754 (s C=O), 1736 (s, C=O), 1605 (m, C=C), 1472 (m), 1428 (s), 1347 (m), 1257(m), 1152 (s, C-O), 1082 (m), 1004 (s, CH=$CH_2$), 952 (m, C=$CH_2$), 904 (m, C=$CH_2$), 852 (s, Si-O-C).

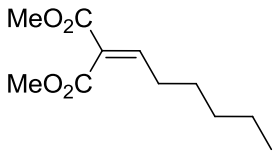
***(E)-Dimethyl 2-(3-(benzyloxy)hepta-4,6-dien-1-yl)malonate (339e)***




To a stirred suspension of hexane washed NaH (69 mg, 2.87 mmol, 3.0 eq.) in anhydrous DMF (2.40 mL) cooled to 0 °C in an ice/water bath, was carefully added dropwise dimethyl malonate (379 mg, 2.87 mmol, 3.0 eq.). The resulting mixture was stirred for 20 min at this temperature, after which a solution of (*E*)-3-(benzyloxy)hepta-4,6-dien-1-yl methanesulfonate (**338e**) (284 mg, 0.96 mmol, 1.0 eq) in anhydrous THF (2.40 mL) was added *via* cannula followed by potassium iodide (79.7 mg, 0.48 mmol, 0.5 eq.). The mixture was warmed to room temperature, and then heated at 80 °C for 16 h. The mixture was cooled to room temperature, after which sat. aq. $NH_4Cl$ solution (10 mL) was added and extracted with EtOAc (3 × 5 mL). The combined organic extracts were sequentially washed with water (20 mL), brine (20 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/petrol 40-60) to afford (*E*)-dimethyl 2-(3-(benzyloxy)hepta-4,6-dien-1-yl)malonate (**339e**) as a colourless oil (280 mg, 0.84 mmol, 88%). $R_f$ = 0.29 (20% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 7.38–7.29 (5H, m, Ar**H**), 6.37 (1H, dt, *J* = 16.8, 10.2 Hz, =CHC**H**=$CH_2$), 6.22 (1H, dd, *J* = 15.3, 10.2 Hz, CH=C**H**CH=), 5.60 (1H, dd, *J* = 15.3, 8.0 Hz, CH(OBn)C**H**=CH), 5.25 (1H, dd, *J* = 16.8, 1.0 Hz, CH=$CH_Z\mathbf{H_E}$), 5.14 (1H, dd, *J* = 10.2, 1.0 Hz, CH=C$\mathbf{H_Z}H_E$), 4.58 (1H, d, *J* = 11.8 Hz, OC$\mathbf{H_2}$Ph), 4.34 (1H, d, *J* = 11.8 Hz, OC$\mathbf{H_2}$Ph), 3.85–3.78 (1H, m, $CH_2$C**H**(OBn)CH=), 3.73 (6H, s, OC$\mathbf{H_3}$), 3.37 (1H, t, *J* = 7.6 Hz, $(MeO_2C)_2$C**H**$CH_2$), 2.11–1.99 (1H, m, CHC$\mathbf{H_2}CH_2$), 1.99–1.89 (1H, m, CHC$\mathbf{H_2}CH_2$), 1.75–1.64 (1H, m, $CH_2$C$\mathbf{H_2}$CH), 1.62–1.52 (1H, m, $CH_2$C$\mathbf{H_2}$CH); $\delta_C$ (100 MHz, $CDCl_3$) 169.7 (**C**=O), 169.7 (**C**=O), 138.5 (Ar), 136.1 (=CH**C**H=$CH_2$), 133.8 (CH=**C**HCH=), 133.6 (CH(OBn)**C**H=CH), 128.3 (2C, Ar), 127.7 (2C, Ar), 127.5 (Ar), 117.9 (CH=**C**$H_ZH_E$), 78.9 ($CH_2$**C**H(OBn)CH=), 70.1 (O**C**$H_2$Ph), 52.5 (2C, O**C**$H_3$), 51.4 ($(MeO_2C)_2$**C**H$CH_2$), 33.2 ($CH_2$**C**$H_2$CH), 24.9 (CH**C**$H_2CH_2$); LRMS *m*/*z* (ESI$^+$) 355 ([M+Na]$^+$,

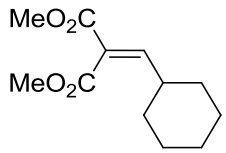
100%); HRMS *m/z* (ESI$^+$) found 355.1519, $C_{19}H_{24}NaO_5$ requires 355.1516; $\nu_{max}$ (film)/cm$^{-1}$ 3088 (w, =$CH_2$), 3031 (w), 3003 (w, =$CH_2$), 2953 (m, CH), 2861 (m, CH), 1751 (s C=O), 1733 (s, C=O), 1604 (m, C=C), 1454 (m), 1435 (m), 1346 (m), 1257(m), 1150 (s, C-O), 1093 (m), 1005 (s, CH=$CH_2$), 956 (m, C=$CH_2$), 907 (m, C=$CH_2$).

***Dimethyl 2-hexylidenemalonate (342a)***




To a stirred solution of freshly distilled hexanal (4.00 g, 40.0 mmol, 1.0 eq.) in anhydrous DMSO (13.3 mL) over 3Å molecular sieves was added L-proline (759 mg, 4.00 mmol, 0.1 eq.) and stirred for 5 min. To this mixture was rapidly added dimethyl malonate (5.81 g, 44.0 mmol, 1.1 eq.), and the resulting mixture was stirred at room temperature for 14 h. The precipitate and molecular sieves were removed by filtration. Water (100 mL) was added to the filtrate and extracted with EtOAc (3 × 50 mL). The combined organic extracts were sequentially washed with water (150 ml), brine (150 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60) to afford dimethyl 2-hexylidenemalonate (**342a**) as a colourless oil (5.08 g, 23.7 mmol, 59%). $R_f$ = 0.24 (10% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 7.02 (1H, t, *J* = 7.9 Hz, C=C**H**$CH_2$), 3.81 (3H, s, OC**H**$_3$), 3.76 (3H, s, OC**H**$_3$), 2.27 (2H, ddd, *J* = 7.6 Hz, =CC**H**$_2$$CH_2$), 1.52–1.41 (2H, m, $CH_2$C**H**$_2$$CH_2$), 1.33–1.25 (4H, m, $CH_2$C**H**$_2$$CH_2$ & $CH_2$C**H**$_2$$CH_3$), 0.87 (3H, t, *J* = 6.7 Hz, $CH_2$C**H**$_3$); $\delta_C$ (125 MHz, $CDCl_3$) 165.9 (C=O), 164.4 (C=O), 150.6 (C=**C**H$CH_2$), 127.8 ((MeO$_2$C)$_2$**C**=CH), 52.2 (O**C**H$_3$), 52.1 (O**C**H$_3$), 31.3 ($CH_2$**C**H$_2$$CH_2$), 29.7 (=C**C**H$_2$$CH_2$), 27.9 ($CH_2$**C**H$_2$$CH_2$), 22.3 ($CH_2$**C**H$_2$$CH_3$), 13.8 ($CH_2$**C**H$_3$); LRMS *m/z* (ESI$^+$) 215 ([M+H]$^+$, 13%), 237 ([M+Na]$^+$, 100%), 451 ([2M+Na]$^+$, 90%); HRMS *m/z* (ESI$^+$) found 237.1104, $C_{11}H_{18}NaO_4$ requires 237.1097; $\nu_{max}$ (film)/cm$^{-1}$ 2955 (m, CH), 2931 (m, CH), 2861 (m, CH), 1725 (s, C=O), 1646 (m, C=C), 1436 (s) 1371 (m), 1259 (s), 1221 (s), 1199 (s), 1143 (m), 1062 (s), 911 (s), 729 (s).

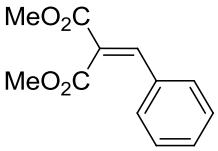
**Dimethyl 2-(cyclohexylmethylene)malonate (342b)**




To a stirred solution of freshly distilled cyclohexanecarboxaldehyde (2.24 g, 20.0 mmol, 1.0 eq.) in anhydrous DMSO (6.7 mL) over 3Å molecular sieves was added L-proline (230 mg, 2.0 mmol, 0.1 eq.) and stirred for 5 min. To this mixture was rapidly added dimethyl malonate (2.91 g, 22.0 mmol, 1.1 eq.), and the resulting mixture was stirred at room temperature for 18 h. The precipitate and molecular sieves were removed by filtration. Water (40 mL) was added to the filtrate and extracted with EtOAc (3 × 20 mL). The combined organic extracts were sequentially washed with water (60 ml), brine (60 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20-30% gradient EtOAc/petrol 40-60) to afford dimethyl 2-(cyclohexylmethylene)malonate (**342b**) as a colourless oil (3.55 g, 15.8 mmol, 79%). $R_f$ = 0.25 (10% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 6.82 (1H, d, $J$ = 10.5 Hz, C=C**H**CH), 3.80 (3H, s, OC$\mathbf{H_3}$), 3.75 (3H, s, OC$\mathbf{H_3}$), 2.35 (1H, ddddd, $J$ = 10.6, 10.6, 10.6, 3.3, 3.3 Hz, =CHC**H**$(CH_2)_2$), 1.76–1.60 (5H, m, C$\mathbf{H_2}$), 1.32–1.08 (5H, m, C$\mathbf{H_2}$); $\delta_C$ (100 MHz, $CDCl_3$) 166.1 (C=O), 164.6 (C=O), 154.5 (C=**C**HCH), 126.0 ($(MeO_2C)_2$**C**=CH), 52.2 (O**C**$H_3$), 52.2 (O**C**$H_3$), 39.0 (=CH**C**H$(CH_2)_2$), 31.6 (2C, **C**$H_2$), 25.5 (**C**$H_2$), 25.1 (2C, **C**$H_2$); LRMS $m/z$ ($ESI^+$) 249 ($[M+Na]^+$, 100%), 475 ($[2M+Na]^+$, 45%); HRMS $m/z$ ($ESI^+$) found 249.1099, $C_{12}H_{18}NaO_4$ requires 249.1097; $\nu_{max}$ (film)/$cm^{-1}$ 2999 (w), 2928 (s, CH), 2853 (m, CH), 1724 (s, C=O), 1643 (m, C=C), 1436 (s), 1374 (m), 1307 (m), 1259 (s), 1233 (s), 1211 (s), 1149 (m), 1103 (m), 1060 (s), 991 (m).

Data are consistent with literature values.[220]

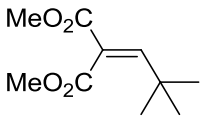
**Dimethyl 2-benzylidenemalonate (342c)**




To a stirred solution of freshly distilled benzaldehyde (2.12 g, 20.0 mmol, 1.0 eq.) in anhydrous DMSO (6.7 mL) over 3Å molecular sieves was added L-proline (230 mg, 2.0 mmol, 0.1 eq.) and stirred for 5 min. To this mixture was rapidly added dimethyl malonate (2.91 g, 22.0 mmol, 1.1 eq.), and the resulting mixture was stirred at room temperature for 18 h. The precipitate and molecular sieves were removed by filtration. Water (40 mL) was added to the filtrate and extracted with EtOAc (3 × 20 mL). The combined organic extracts were sequentially washed with water (60 ml), brine (60 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20-30% EtOAc/petrol 40-60 gradient) to afford dimethyl 2-benzylidenemalonate (**342c**) as white needle crystals (3.97 g, 18.0 mmol, 90%). $R_f$ = 0.24 (20% EtOAc/petrol 40-60); *m.p.* 38.6–40.2 °C; $\delta_H$ (400 MHz, $CDCl_3$) 7.77 (1H, s, ArC**H**=C), 7.45–7.35 (5H, m, Ar**H**), 3.84 (6H, s, OC$\mathbf{H}_3$); $\delta_C$ (125 MHz, $CDCl_3$) 167.1 (C=O), 164.5 (C=O), 142.9 (Ar**C**H=C), 132.7 (Ar), 130.7 (Ar), 129.4 (2C, Ar), 128.8 (2C, Ar), 125.5 ($(MeO_2C)_2$**C**=CH), 52.7 (2C, O**C**$H_3$); LRMS *m*/*z* ($ESI^+$) 243 ($[M+Na]^+$, 100%), 463 ($[2M+Na]^+$, 15%); HRMS *m*/*z* ($ESI^+$) found 243.0626, $C_{12}H_{12}NaO_4$ requires 243.0628; $\nu_{max}$ (film)/$cm^{-1}$ 3003 (w), 2953 (m), 2847 (w), 1724 (s, C=O), 1627 (s, C=C), 1435 (s), 1260 (s), 1181 (s), 1063 (s).

Data are consistent with literature values.[220]

**Dimethyl 2-(2,2-dimethylpropylidene)malonate (342d)**

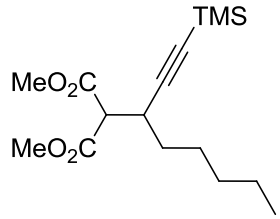



To a stirred solution of freshly distilled pivaldehyde (1.72 g, 20.0 mmol, 1.0 eq.) in anhydrous DMSO (6.7 mL) over 3Å molecular sieves was added L-proline (230 mg, 2.0 mmol, 0.1 eq.) and

stirred for 5 min. To this mixture was rapidly added dimethyl malonate (2.91 g, 22.0 mmol, 1.1 eq.), and the resulting mixture was stirred at room temperature for 18 h. The precipitate and molecular sieves were removed by filtration. Water (40 mL) was added to the filtrate and extracted with EtOAc (3 × 20 mL). The combined organic extracts were sequentially washed with water (60 ml), brine (60 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/petrol 40-60) to afford Dimethyl 2-(2,2-dimethylpropylidene)malonate (**342d**) as a colourless oil (37.8 mg, 0.19 mmol, 1%). $R_f$ = 0.28 (20% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 6.86 (1H, s, C=C**H**C$(CH_3)_3$), 3.84 (3H, s, OC**H**$_3$), 3.81 (3H, s, OC**H**$_3$), 1.20 (9H, s, C(C**H**$_3)_3$); $\delta_C$ (100 MHz, $CDCl_3$) 166.0 (C=O), 164.5 (C=O), 155.8 (C=**C**HCH), 125.2 ($(MeO_2C)_2$**C**=CH), 52.3 (O**C**$H_3$), 52.2 (O**C**$H_3$), 34.2 (CH**C**$(CH_3)_3$), 29.5 (3C, C(**C**$H_3)_3$); LRMS $m/z$ (ESI$^+$) 223 ([M+Na]$^+$, 100%); $\nu_{max}$ (film)/cm$^{-1}$ 2962 (m, CH), 2784 (w), 1731 (s, C=O), 1645 (m, C=C), 1438 (m), 1367 (m), 1325 (m), 1258 (s), 1224 (s), 1150 (m), 1058 (m).

Data are consistent with literature values.[221]

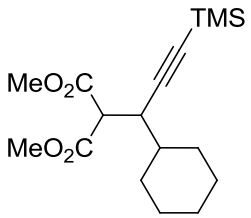
***Dimethyl 2-(1-(trimethylsilyl)oct-1-yn-3-yl)malonate (344a)***




To a vigorously stirred solution of trimethylsilylacetylene (2.68 g, 27.3 mmol, 1.2 eq.) in anhydrous THF (28.4 mL) at room temperature was added a 3 M solution of ethylmagnesium bromide in $Et_2O$ (9.1 mL, 27.3 mmol, 1.2 eq.). The resulting mixture was stirred for 2 h and then cooled to 0 °C in an ice/water bath. Copper(I) chloride (22.8 mg, 0.23 mmol, 1.0 mol%.) was added followed by rapid addition of a solution of dimethyl 2-hexylidenemalonate (**342a**) (4.87 g, 22.7 mmol, 1.0 eq.) in THF (28.4 mL) *via* cannula, after which the mixture was stirred at 0 °C for 1 h. 1 M HCl (70 ml) was added to the mixture and extracted with EtOAc (3 × 50 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (150 ml), brine (150 ml), dried

($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60) to afford dimethyl 2-(1-(trimethylsilyl)oct-1-yn-3-yl)malonate (**344a**) as a colourless oil (5.46 g, 21.5 mmol, 79%). $R_f$ = 0.28 (10% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 3.73 (3H, s, OC**H**$_3$), 3.73 (3H, s, OC**H**$_3$), 3.45 (1H, d, *J* = 9.6 Hz, $(MeO_2C)_2$C**H**CH), 3.15 (1H, ddd, *J* = 9.6, 9.3, 3.5 Hz, CHC**H**(*n*-Hex)C≡), 1.60–1.34 (4H, m, CHC**H**$_2$CH$_2$ & CH$_2$C**H**$_2$CH$_2$), 1.34–1.20 (4H, m, CH$_2$C**H**$_2$CH$_2$ & CH$_2$C**H**$_2$CH$_3$), 0.88 (3H, t, *J* = 6.7 Hz, CH$_2$C**H**$_3$), 0.11 (9H, s, Si(C**H**$_3$)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 167.9 (C=O), 167.8 (C=O), 105.6 (C≡**C**TMS), 87.7 (CH**C**≡C), 56.5 ($(MeO_2C)_2$**C**HCH), 52.5 (O**C**H$_3$), 52.4 (O**C**H$_3$), 32.9 (CH**C**H(*n*-Hex)C≡), 32.3 (**C**H$_2$), 31.2 (**C**H$_2$), 26.5 (**C**H$_2$), 22.4 (**C**H$_2$), 13.9 (CH$_2$**C**H$_3$), 0.0 (3C, Si(**C**H$_3$)$_3$); LRMS *m*/*z* (ESI$^+$) 313 ([M+H]$^+$, 59%), 335 ([M+Na]$^+$, 100%), 647 ([2M+Na]$^+$, 83%); HRMS *m*/*z* (ESI$^+$) found 335.1645, $C_{16}H_{28}NaO_4Si$ requires 335.1649; $\nu_{max}$ (film)/cm$^{-1}$ 2956 (m, CH), 2932 (m, CH), 2861 (m, CH), 2173 (m, C≡C), 1759 (C=O), 1741 (s, C=O), 1435 (m), 1342 (m), 1249 (s), 1196 (m), 1149 (m), 1018 (m), 840 (s).

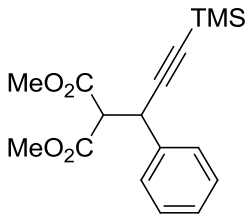
***Dimethyl 2-(1-cyclohexyl-3-(trimethylsilyl)prop-2-yn-1-yl)malonate (344b)***




To a vigorously stirred solution of trimethylsilylacetylene (1.83 g, 18.6 mmol, 1.2 eq.) in anhydrous THF (19.4 mL) at room temperature was added a 3 M solution of ethylmagnesium bromide in $Et_2O$ (5.68 mL, 17.1 mmol, 1.1 eq.). The resulting mixture was stirred for 2 h and then cooled to 0 °C in an ice/water bath. Copper(I) chloride (15.8 mg, 0.16 mmol, 1.0 mol%.) was added followed by rapid addition of a solution of dimethyl 2-(cyclohexylmethylene)malonate (**342b**) (3.50 g, 15.5 mmol, 1.0 eq.) in THF (19.4 mL) *via* cannula, after which the mixture was stirred at 0 °C for 1 h. 1 M HCl (50 ml) was added to the mixture and extracted with EtOAc (3 × 20 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (100 ml), brine

(100 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60) to afford dimethyl 2-(1-cyclohexyl-3-(trimethylsilyl)prop-2-yn-1-yl)malonate (**344b**) as a colourless oil (4.78 g, 14.7 mmol, 95%). $R_f$ = 0.27 (10% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 3.73 (6H, s, OC**H**$_3$), 3.58 (1H, d, $J$ = 10.6 Hz, $(MeO_2C)_2$C**H**CH), 3.14 (1H, dd, $J$ = 10.6, 2.6 Hz, CHC**H**(CH)C≡), 1.79–1.55 (5H, m, C**H**$_2$), 1.40–1.26 (2H, m, CHC**H**$(CH_2)_2$ & C**H**$_2$), 1.26–1.05 (4H, m, C**H**$_2$), 0.11 (9H, s, Si(C**H**$_3)_3$); $\delta_C$ (100 MHz, $CDCl_3$) 168.1 (C=O), 168.0 (C=O), 104.0 (C≡**C**TMS), 88.9 (CH**C**≡C), 54.1 ($(MeO_2C)_2$**C**HCH), 52.6 (O**C**$H_3$), 52.5 (O**C**$H_3$), 39.0 (CH**C**H(CH)C≡), 38.6 (CH**C**H$(CH_2)_2$), 31.8 (**C**$H_2$), 27.4 (**C**$H_2$), 26.3 (**C**$H_2$), 26.1 (**C**$H_2$), 26.0 (**C**$H_2$), 0.0 (3C, Si(**C**$H_3)_3$); LRMS $m/z$ ($ESI^+$) 325 ($[M+H]^+$, 35%), 347 ($[M+Na]^+$, 100%), 671 ($[2M+Na]^+$, 53%); HRMS $m/z$ ($ESI^+$) found 347.1649, $C_{17}H_{28}NaO_4Si$ requires 347.1649; $\nu_{max}$ (film)/$cm^{-1}$ 2954 (m, CH), 2928 (m, CH), 2854 (m, CH), 2170 (m, C≡C), 1759 (C=O), 1740 (s, C=O), 1435 (m), 1373 (m), 1339 (m), 1249 (s), 1196 (m), 1145 (m), 1022 (m), 840 (s).

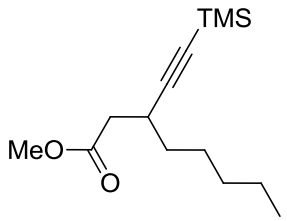
***Dimethyl 2-(1-phenyl-3-(trimethylsilyl)prop-2-yn-1-yl)malonate (344c)***




To a vigorously stirred solution of trimethylsilylacetylene (7.87 g, 80.2 mmol, 1.2 eq.) in anhydrous THF (83.5 mL) at room temperature was added a 3 M solution of ethylmagnesium bromide in $Et_2O$ (24.5 mL, 73.5 mmol, 1.1 eq.). The resulting mixture was stirred for 2 h and then cooled to 0 °C in an ice/water bath. Copper(I) chloride (66.3 mg, 0.67 mmol, 1.0 mol%.) was added followed by rapid addition of a solution of dimethyl 2-benzylidenemalonate (**342c**) (14.7 g, 66.8 mmol, 1.0 eq.) in THF (83.5 mL) *via* cannula, after which the mixture was stirred at 0 °C for 1 h. 1 M HCl (100 ml) was added to the mixture and extracted with EtOAc (3 × 20 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (300 ml), brine (300 ml), dried

($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (15% EtOAc/petrol 40-60) followed by recrystallisation from hot hexane (100 ml) to afford dimethyl 2-(1-phenyl-3-(trimethylsilyl)prop-2-yn-1-yl)malonate (**344c**) as white needle crystals (17.2 g, 53.9 mmol, 81%). $R_f$ = 0.29 (15% EtOAc/petrol 40-60); *m.p.* 54.4–56.5 °C; $\delta_H$ (400 MHz, $CDCl_3$) 7.38 (2H, d, *J*= 7.2 Hz, Ar**H**), 7.31 (2H, t, *J* = 7.2 Hz, Ar**H**), 7.26 (1H, t, *J* = 7.2 Hz, Ar**H**), 4.44 (1H, d, *J* = 10.6 Hz, CHC**H**(Ar)C≡), 3.79 (3H, s, OC$\mathbf{H_3}$), 3.77 (1H, d, *J* = 10.6 Hz, $(MeO_2C)_2C\mathbf{H}CH$), 3.53 (3H, s, $(MeO_2C)_2C\mathbf{H}CH$), 0.15 (9H, s, $Si(C\mathbf{H_3})_3$); $\delta_C$ (100 MHz, $CDCl_3$) 167.4 (C=O), 166.9 (C=O), 137.7 (Ar), 128.6 (2C, Ar), 128.2 (2C, Ar), 127.7 (Ar), 104.3 (C≡**C**TMS), 89.0 (CH**C**≡C), 59.5 ($(MeO_2C)_2\mathbf{C}HCH$), 52.7 (O**C**$H_3$), 52.5 (O**C**$H_3$), 38.7 (CH**C**H(Ar)C≡), -0.1 (3C, $Si(\mathbf{C}H_3)_3$); LRMS *m/z* ($ESI^+$) 341 ($[M+Na]^+$, 100%), 659 ($[2M+Na]^+$, 19%); HRMS *m/z* ($ESI^+$) found 341.1179, $C_{17}H_{22}NaO_4Si$ requires 341.1179; $\nu_{max}$ (film)/$cm^{-1}$ 3066 (w), 3036 (w), 2954 (m, CH), 2899 (w, CH), 2175 (m, C≡C), 1747 (C=O), 1735 (s, C=O), 1497 (m), 1433 (s), 1319 (m), 1249 (s), 1151 (s), 1009 (s), 840 (s).

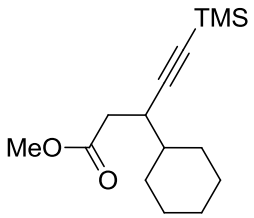
***Methyl 3-((trimethylsilyl)ethynyl)octanoate (345a)***




To a stirred solution of dimethyl 2-(1-(trimethylsilyl)oct-1-yn-3-yl)malonate (**344a**) (5.00 g, 16.0 mmol, 1.0 eq.) in anhydrous DMF (32.0 mL) was added water (576 mg, 32.0 mmol, 2.0 eq.) followed by lithium chloride (1.36 g, 32.0 mmol, 2.0 eq.). The resulting mixture was heated at 150° C for 3 h and then cooled to room temperature. Sat. aq. $NH_4Cl$ solution (50 mL) was added to the mixture and extracted with $Et_2O$ (3 × 50 mL). The combined organic extracts were sequentially washed with water (150 mL), brine (150 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (5% EtOAc/petrol 40–60) to afford methyl 3-((trimethylsilyl)ethynyl)octanoate (**345a**) as a colourless

oil (3.62 g, 14.2 mmol, 89%). $R_f$ = 0.31 (5% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 3.68 (3H, s, OC**H**$_3$), 2.90–2.80 (1H, m, $CH_2$C**H**(*n*-Hex)C≡), 2.51 (1H, dd, *J* = 15.2, 7.3 Hz, CC**H**$_2$CH), 2.41 (1H, dd, *J* = 15.2, 7.3 Hz, $O_2$CC**H**$_2$CH), 1.54–1.20 (8H, m, 4 × C**H**$_2$), 0.88 (3H, t, *J* = 6.8 Hz, $CH_2$C**H**$_3$), 0.12 (9H, s, Si(C**H**$_3$)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 172.0 (C=O), 108.5 (C≡**C**TMS), 85.8 (CH**C**≡C), 51.5 (O**C**H$_3$), 39.9 (C**C**H$_2$CH), 34.3 (**C**H$_2$), 31.4 (**C**H$_2$), 29.2 ($CH_2$**C**H(*n*-Hex)C≡), 26.6 (**C**H$_2$), 22.4 (**C**H$_2$), 13.9 ($CH_2$**C**H$_3$), 0.1 (3C, Si(**C**H$_3$)$_3$); LRMS *m*/*z* (ESI$^+$) 255 ([M+H]$^+$, 25%), 277 ([M+Na]$^+$, 100%), 531 ([2M+Na]$^+$, 30%); HRMS *m*/*z* (ESI$^+$) found 277.1595, $C_{14}H_{26}NaO_2Si$ requires 277.1594; $\nu_{max}$ (film)/cm$^{-1}$ 2957 (m, CH), 2931 (m, CH), 2860 (m, CH), 2170 (m, C≡C), 1742 (s, C=O), 1437 (m), 1359 (m), 1249 (s), 1161 (s), 839 (s).

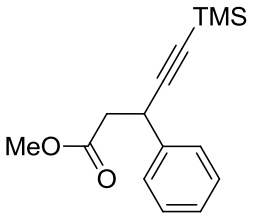
***Methyl 3-cyclohexyl-5-(trimethylsilyl)pent-4-ynoate (345b)***




To a stirred solution of dimethyl 2-(1-cyclohexyl-3-(trimethylsilyl)prop-2-yn-1-yl)malonate (**344b**) (4.72 g, 14.5 mmol, 1.0 eq.) in anhydrous DMF (28.0 mL) was added water (524 mg, 29.1 mmol, 2.0 eq.) followed by lithium chloride (1.23 g, 29.1 mmol, 2.0 eq.). The resulting mixture was heated at 150° C for 3 h and then cooled to room temperature. Sat. aq. $NH_4Cl$ solution (50 mL) was added to the mixture and extracted with EtOAc (3 × 50 mL). The combined organic extracts were sequentially washed with water (150 mL), brine (150 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (5% EtOAc/petrol 40-60) to afford methyl 3-cyclohexyl-5-(trimethylsilyl)pent-4-ynoate (**345b**) as a colourless oil (3.20 g, 12.0 mmol, 83%). $R_f$ = 0.31 (5% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 3.68 (3H, s, C**H**$_3$O), 2.81–2.74 (1H, m, $CH_2$C**H**(CH)C≡), 2.47 (2H, d, *J* = 7.7 Hz, CC**H**$_2$CH), 1.80–1.69 (4H, m, C**H**$_2$), 1.69–1.60 (2H, m, C**H**$_2$), 1.40–1.30 (1H, m, CHC**H**$(CH_2)_2$), 1.26–1.08 (4H, m, C**H**$_2$), 0.12 (9H, s, Si(C**H**$_3$)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 172.4 (**C**=O), 107.3 (C≡**C**TMS), 86.9

(CH**C**≡C), 51.6 (**C**H$_3$O), 40.6 (CH**C**H(CH$_2$)$_2$), 37.5 (C**C**H$_2$CH), 35.2 (CH$_2$**C**H(CH)C≡), 31.2 (**C**H$_2$), 28.6 (**C**H$_2$), 26.3 (2C, **C**H$_2$), 26.1 (**C**H$_2$), 0.1 (3C, Si(**C**H$_3$)$_3$); LRMS *m*/*z* (ESI$^+$) 267 ([M+H]$^+$, 20%), 289 ([M+Na]$^+$, 100%), 555 ([2M+Na]$^+$, 41%); HRMS *m*/*z* (ESI$^+$) found 289.1594, $C_{15}H_{26}NaO_2Si$ requires 289.1594; $\nu_{max}$ (film)/cm$^{-1}$ 2927 (m, CH), 2854 (m, CH), 2169 (m, C≡C), 1741 (C=O), 1450 (m), 1437 (m), 1354 (m), 1308 (m), 1249 (s), 1160 (s), 1020 (m), 998 (m), 839 (s).

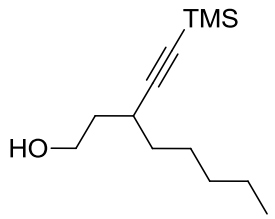
***Methyl 3-phenyl-5-(trimethylsilyl)pent-4-ynoate (345c)***




To a stirred solution of dimethyl 2-(1-phenyl-3-(trimethylsilyl)prop-2-yn-1-yl)malonate (**344c**) (17.0 g, 53.5 mmol, 1.0 eq.) in anhydrous DMF (107 mL) was added water (1.93 g, 107 mmol, 2.0 eq.) followed by lithium chloride (4.54 g, 107 mmol, 2.0 eq.). The resulting mixture was heated at 150° C for 2 h and then cooled to room temperature. Sat. aq. $NH_4Cl$ solution (100 mL) was added to the mixture and extracted with EtOAc (3 × 100 mL). The combined organic extracts were sequentially washed with water (300 mL), brine (300 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60) to afford methyl 3-phenyl-5-(trimethylsilyl)pent-4-ynoate (**345c**) as a colourless oil (12.1 g, 46.6 mmol, 87%). $R_f$ = 0.34 (10% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 7.40 (2H, d, *J* = 7.2 Hz, Ar**H**), 7.34 (2H, t, *J* = 7.2 Hz, Ar**H**), 7.26 (1H, t, *J* = 7.2 Hz, Ar**H**), 4.24–4.18 (1H, m, CH$_2$C**H**(Ar)C≡), 3.68 (3H, s, C**H$_3$**O), 2.83 (1H, dd, *J* = 15.2, 8.2 Hz, CC**H$_2$**CH), 2.73 (1H, dd, *J* = 15.2, 7.1 Hz, CC**H$_2$**CH), 0.19 (9H, s, Si(C**H$_3$**)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 171.2 (**C**=O), 140.1 (Ar), 128.6 (2C, Ar), 127.4 (2C, Ar), 127.2 (Ar), 106.4 (C≡**C**TMS), 87.8 (CH**C**≡C), 51.7 (**C**H$_3$O), 43.3 (C**C**H$_2$CH), 35.1 (CH$_2$**C**H(Ar)C≡), 0.0 (3C, Si(**C**H$_3$)$_3$); LRMS *m*/*z* (ESI$^+$) 283 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 283.1128, $C_{15}H_{20}NaO_2Si$ requires 283.1125; $\nu_{max}$ (film)/cm$^{-1}$ 3064 (w, CH), 3030 (w, CH), 2956 (m, CH), 2900 (w, CH), 2176 (m, C≡C), 1740 (s,

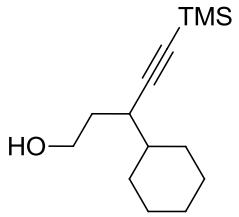
C=O), 1602 (w), 1494 (m), 1453 (m), 1437 (m), 1352 (m), 1249 (s), 1152 (s), 1065 (m), 1023 (s), 839 (S).

***3-((Trimethylsilyl)ethynyl)octan-1-ol (346a)***



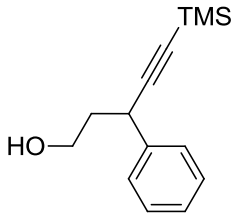

To a stirred suspension of $LiAlH_4$ (544 mg, 14.2 mmol, 1.0 eq.) in anhydrous $Et_2O$ (23.8 mL) cooled to 0 °C in an ice/water bath, was added dropwise a solution of methyl 3-((trimethylsilyl)ethynyl)octanoate (**345a**) (3.65 g, 14.2 mmol, 1.0 eq.) in anhydrous $Et_2O$ (23.8 mL). The mixture was warmed to room temperature and stirred for 1 h. Water (0.54 mL) was carefully added dropwise to the mixture followed by 10% aq. NaOH solution (0.54 mL) and stirred for 5 min. Additional water (1.08 mL) was added, after which the mixture was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/petrol 40-60) to afford 3-((trimethylsilyl)ethynyl)octan-1-ol (**346a**) as a colourless oil (3.16 g, 13.9 mmol, 97%). $\delta_H$ (400 MHz, $CDCl_3$) 3.79 (2H, t, $J$ = 6.0 Hz, HOC**H**$_2$CH$_2$), 2.55–2.45 (1H, m, CH$_2$C**H**(*n*-Hex)C≡), 2.06 (1H, s, **H**OCH$_2$), 1.78–1.58 (2H, m, CH$_2$C**H**$_2$CH), 1.55–1.20 (8H, m, 4 × C**H**$_2$), 0.89 (3H, t, $J$ = 6.5 Hz, CH$_2$C**H**$_3$), 0.14 (9H, s, Si(C**H**$_3$)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 110.3 (C≡**C**TMS), 86.3 (CH**C**≡C), 61.3 (HO**C**H$_2$CH$_2$), 37.6 (CH$_2$**C**H$_2$CH), 35.0 (**C**H$_2$), 31.5 (**C**H$_2$), 29.7 (CH$_2$**C**H(*n*-Hex)C≡), 26.7 (**C**H$_2$), 22.5 (**C**H$_2$), 14.0 (CH$_2$**C**H$_3$), 0.1 (3C, Si(**C**H$_3$)$_3$); LRMS $m/z$ (ESI$^+$) 249 ([M+Na]$^+$, 100%); HRMS $m/z$ (ESI$^+$) found 249.1640, $C_{13}H_{26}NaOSi$ requires 249.1645; $\nu_{max}$ (film)/cm$^{-1}$ 3325 (br, OH), 2957 (m, CH), 2931 (m, CH), 2859 (m, CH), 2166 (m, C≡C), 1466 (m), 1379 (m), 1341 (m), 1249 (s), 1055 (m), 838 (s).

***3-Cyclohexyl-5-(trimethylsilyl)pent-4-yn-1-ol (346b)***



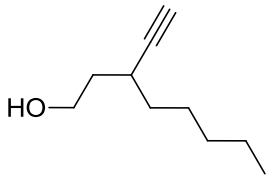

To a stirred suspension of $LiAlH_4$ (454 mg, 11.9 mmol, 1.0 eq.) in anhydrous $Et_2O$ (19.8 mL) cooled to 0 °C in an ice/water bath, was added dropwise a solution of methyl 3-cyclohexyl-5-(trimethylsilyl)pent-4-ynoate (**345b**) (3.19 g, 11.9 mmol, 1.0 eq.) in anhydrous $Et_2O$ (19.8 mL). The mixture was warmed to room temperature and stirred for 1 h. Water (0.45 mL) was carefully added dropwise to the mixture followed by 10% aq. NaOH solution (0.45 mL) and stirred for 5 min. Additional water (0.91 mL) was added, after which the mixture was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/petrol 40-60) to afford 3-cyclohexyl-5-(trimethylsilyl)pent-4-yn-1-ol (**346a**) as a colourless oil (2.63 g, 11.0 mmol, 93%). $R_f$ = 0.27 (20% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 3.82–3.77 (2H, m, HOC**H**$_2$CH$_2$), 2.39 (1H, dt, $J$ = 10.3, 5.3 Hz, CH$_2$C**H**(CH)C≡), 2.04 (1H, s, **H**OCH$_2$), 1.84–1.61 (7H, m, C**H**$_2$), 1.38–1.06 (6H, m, CHC**H**(CH$_2$)$_2$ and C**H**$_2$), 0.14 (9H, s, Si(C**H**$_3$)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 109.1 (C≡**C**TMS), 87.3 (CH**C**≡C), 61.7 (HO**C**H$_2$CH$_2$), 41.4 (CH**C**H(CH$_2$)$_2$), 35.9 (CH$_2$**C**H(CH)C≡), 34.8 (**C**H$_2$), 31.2 (**C**H$_2$), 29.2 (**C**H$_2$), 26.4 (2C, **C**H$_2$), 26.3 (**C**H$_2$), 0.2 (3C, Si(**C**H$_3$)$_3$); LRMS $m/z$ (ESI$^+$) 239 ([M+H]$^+$, 50%), 261 ([M+Na]$^+$, 100%); HRMS $m/z$ (ESI$^+$) found 261.1652, $C_{14}H_{26}NaOSi$ requires 261.1645; $\nu_{max}$ (film)/cm$^{-1}$ 3325 (br, OH), 2925 (m, CH), 2853 (m, CH), 2165 (m, C≡C), 1450 (m), 1248 (s), 1057 (m), 838 (s).

***3-Phenyl-5-(trimethylsilyl)pent-4-yn-1-ol (346c)***



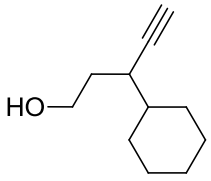

To a stirred suspension of $LiAlH_4$ (1.59 g, 42.0 mmol, 1.0 eq.) in anhydrous $Et_2O$ (70.0 mL) cooled to 0 °C in an ice/water bath, was added dropwise a solution of 3-phenyl-5-(trimethylsilyl)pent-4-ynoate (**345c**) (11.0 g, 42.0 mmol, 1.0 eq.) in anhydrous $Et_2O$ (70.0 mL). The mixture was warmed to room temperature and stirred for 1 h. Water (1.59 mL) was carefully added dropwise to the mixture followed by 10% aq. NaOH solution (1.59 mL) and stirred for 5 min. Additional water (3.18 mL) was added, after which the mixture was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (25-30% gradient EtOAc/petrol 40-60) to afford 3-phenyl-5-(trimethylsilyl)pent-4-yn-1-ol (**346c**) as a colourless oil (8.82 g, 37.8 mmol, 90%). $R_f$ = 0.33 (30% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 7.39 (2H, d, *J* = 7.4 Hz, Ar**H**), 7.34 (2H, t, *J* = 7.4 Hz, Ar**H**), 7.26 (1H, t, *J* = 7.4 Hz, Ar**H**), 3.94–3.81 (2H, m, HOC**H**$_2$CH$_2$ & CH$_2$C**H**(Ar)C≡), 3.76 (1H, dt, *J* = 11.1, 5.7 Hz, HOC**H**$_2$CH$_2$), 2.07–1.93 (3H, m, CH$_2$C**H**$_2$CH & **H**OCH$_2$), 0.22 (9H, s, Si(C**H**$_3$)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 141.2 (Ar), 128.6 (2C, Ar), 127.4 (2C, Ar), 126.8 (Ar), 107.8 (C≡**C**TMS), 88.1 (CH**C**≡C), 60.8 (HOC**H**$_2$CH$_2$), 41.1 (CH$_2$**C**H$_2$CH), 35.5 (CH$_2$**C**H(Ar)C≡), 0.1 (3C, Si(**C**H$_3$)$_3$); LRMS *m*/*z* (ESI$^+$) 255 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 255.1179, $C_{14}H_{20}NaOSi$ requires 255.1176; $\nu_{max}$ (film)/cm$^{-1}$ 3329 (br, OH), 3063 (w, CH), 3030 (w, CH), 2957 (m ,CH), 2897 (w, CH), 2170 (m, C≡C), 1602 (w), 1494 (m), 1453 (m), 1249 (s), 1043 (s), 981 (m), 838 (s).

***3-Ethynyloctan-1-ol (347a)***




To a stirred solution of 3-((trimethylsilyl)ethynyl)octan-1-ol (**346a**) (3.15 g, 13.9 mmol, 1.0 eq.) in anhydrous THF (55.6 mL) cooled to 0 °C in an ice/water bath was added dropwise a 1 M solution of TBAF in THF (16.7 mL, 16.7 mmol, 1.2 eq.). After complete addition the mixture was warmed to room temperature and stirred for 30 min. 1 M HCl (40 mL) was added to the mixture and extracted with $Et_2O$ (3 × 20 mL). The combined organic extracts were successively washed with sat. aq. $NH_4Cl$ solution (100 mL), brine (100 ml), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% $Et_2O$/petrol 30-40) to afford 3-ethynyloctan-1-ol (**347a**) as a colourless oil (2.09 g, 13.8 mmol, 99%). $R_f$ = 0.31 (50% $Et_2O$/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 3.78 (2H, t, $J$ = 6.2 Hz, HOC**H**$_2$$CH_2$), 2.55–2.43 (1H, m, $CH_2$C**H**(*n*-Hex)C≡), 2.21 (1H, s, **H**O$CH_2$), 2.07 (1H, d, $J$ =2.3 Hz, C≡C**H**), 1.77–1.58 (2H, m, $CH_2$C**H**$_2$CH), 1.55–1.20 (8H, m, 4 × C**H**$_2$), 0.87 (3H, t, $J$ = 6.8 Hz, $CH_2$C**H**$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 86.3 (CH**C**≡C), 69.8 (C≡**C**H), 60.8 (HO**C**$H_2CH_2$), 37.5 ($CH_2$**C**$H_2$CH), 35.0 (**C**$H_2$), 31.6 (**C**$H_2$), 28.2 ($CH_2$**C**H(*n*-Hex)C≡), 26.8 (**C**$H_2$), 22.5 (**C**$H_2$), 14.0 ($CH_2$**C**$H_3$); HRMS *m/z* ($FI^+$) found 155.1433, $C_{10}H_{19}O$ requires 155.1436; $\nu_{max}$ (film)/$cm^{-1}$ 3310 (br, OH and ≡C-H), 2955 (m, CH), 2930 (m, CH), 2859 (m, CH), 2112 (w, C≡C), 1466 (m), 1379 (m), 1343 (m), 1053 (s).

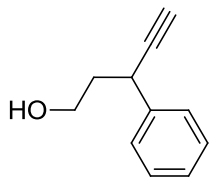
***3-Cyclohexylpent-4-yn-1-ol (347b)***




To a stirred solution of 3-cyclohexyl-5-(trimethylsilyl)pent-4-yn-1-ol (**346b**) (2.63 g, 11.0 mmol, 1.0 eq.) in anhydrous THF (44.0 mL) cooled to 0 °C in an ice/water bath was added dropwise a

1 M solution of TBAF in THF (13.2 mL, 13.2 mmol, 1.2 eq.). After complete addition the mixture was warmed to room temperature and stirred for 30 min. 1 M HCl (40 mL) was added to the mixture and extracted with $Et_2O$ (3 × 50 mL). The combined organic extracts were successively washed with sat. aq. $NH_4Cl$ solution (200 mL), brine (200 ml), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% $Et_2O$/petrol 30-40) to afford 3-cyclohexylpent-4-yn-1-ol (**347b**) as a colourless oil (1.79 g, 10.8 mmol, 98%). $R_f$ = 0.25 (50% $Et_2O$/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 3.84–3.74 (2H, m, HOC**H**$_2$CH$_2$), 2.39 (1H, dtd, *J* = 10.0, 5.0, 2.4 Hz, CH$_2$C**H**(CH)C≡), 2.18 (1H, s, **H**OCH$_2$), 2.08 (1H, d, *J* = 2.4 Hz, CHC≡C**H**), 1.83–1.60 (7H, m, C**H**$_2$), 1.37–1.28 (1H, m, CHC**H**(CH$_2$)$_2$), 1.28–1.06 (5H, m, C**H**$_2$); $\delta_C$ (100 MHz, $CDCl_3$) 86.1 (CH**C**≡C), 70.8 (CHC≡**C**H), 61.1 (HO**C**H$_2$CH$_2$), 41.2 (CH**C**H(CH$_2$)$_2$), 34.8 (**C**H$_2$), 34.4 (CH$_2$**C**H(CH)C≡), 31.2 (**C**H$_2$), 28.9 (**C**H$_2$), 26.3 (2C, **C**H$_2$), 26.2 (**C**H$_2$); HRMS *m*/*z* (FI$^+$) found 167.1434, $C_{11}H_{19}O$ requires 167.1436; $\nu_{max}$ (film)/cm$^{-1}$ 3307 (br, OH), 2924 (s, CH), 2853 (m, CH), 2109 (m, C≡C), 1450 (m), 1056 (m), 1036 (m).

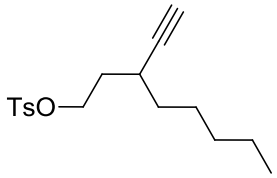
***3-Phenylpent-4-yn-1-ol (347c)***




To a stirred solution of 3-phenyl-5-(trimethylsilyl)pent-4-yn-1-ol (**346c**) (8.78 g, 37.8 mmol, 1.0 eq.) in anhydrous THF (151 mL) cooled to 0 °C in an ice/water bath was added dropwise a 1 M solution of TBAF in THF (45.4 mL, 45.4 mmol, 1.2 eq.). After complete addition the mixture was warmed to room temperature and stirred for 30 min. 1 M aq. HCl (150 mL) was added to the mixture and extracted with EtOAc (3 × 100 mL). The combined organic extracts were successively washed with sat. aq. $NH_4Cl$ solution (300 mL), brine (300 ml), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (30% EtOAc/petrol 40-60) to afford 3-phenylpent-4-yn-1-ol (**347c**) as a colourless oil (5.49 g,

34.4 mmol, 91%). $R_f$ = 0.27 (30% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 7.41 (2H, d, *J* = 7.3 Hz, Ar**H**), 7.36 (2H, t, *J* = 7.3 Hz, Ar**H**), 7.27 (1H, t, *J* = 7.3 Hz, Ar**H**), 3.92–3.82 (2H, m, HOC**H**$_2$CH$_2$ & CH$_2$C**H**(Ar)C≡), 3.74 (1H, dt, *J* = 11.1, 5.7 Hz, HOC**H**$_2$CH$_2$), 2.32 (1H, d, *J* = 2.3 Hz, CHC≡C**H**), 2.18–2.10 (1H, m, **H**OCH$_2$), 2.54–1.99 (2H, m, CH$_2$C**H**$_2$CH); $\delta_C$ (100 MHz, $CDCl_3$) 141.0 (Ar), 128.7 (2C, Ar), 127.4 (2C, Ar), 127.0 (Ar), 85.5 (CH**C**≡C), 71.5 (CHC≡**C**H), 60.4 (HOC**H**$_2$CH$_2$), 40.7 (CH$_2$**C**H$_2$CH), 34.1 (CH$_2$**C**H(Ar)C≡); HRMS *m*/*z* (FI$^+$) found 160.0890, $C_{11}H_{12}O$ requires 160.0888; $\nu_{max}$ (film)/cm$^{-1}$ 3291 (br, OH), 3062 (w, CH), 3029 (w, CH), 2950 (m ,CH), 2883 (w, CH), 2114 (w, C≡C), 1600 (w), 1493 (m), 1453 (m), 1040 (s).

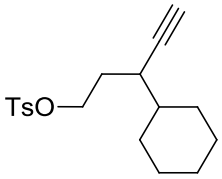
***3-Ethynyloctyl 4-methylbenzenesulfonate (348a)***




To a stirred solution of 3-ethynyloctan-1-ol (**347a**) (2.07 g, 13.4 mmol, 1.0 eq.) in pyridine (13.4 mL) cooled to -20 °C in a dry ice/acetone bath was added portionwise *p*-toluenesulfonyl chloride (3.84 g, 20.1 mmol, 1.5 eq.). The resulting mixture was slowly warmed to room temperature and stirred for 16 h. 1 M HCl (50 mL) was added to the mixture and extracted with EtOAc (3 × 50 mL). The combined organic extracts were sequentially washed water (150 mL), brine (150 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (15% EtOAc/petrol 40-60) to afford 3-ethynyloctyl 4-methylbenzenesulfonate (**348a**) as a colourless oil (3.31 g, 11.1 mmol, 83%). $R_f$ = 0.29 (15% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 7.79 (2H, d, *J* = 8.2 Hz, Ar**H**), 7.34 (2H, d, *J* = 8.2 Hz, Ar**H**), 4.22–4.17 (2H, m, TsOC**H**$_2$CH$_2$), 2.44 (3H, s, ArC**H**$_3$), 2.44–2.39 (1H, m, CH$_2$C**H**(*n*-Hex)C≡), 1.97 (1H, d, *J* = 2.4 Hz, C≡C**H**), 1.89–1.79 (1H, m, CH$_2$C**H**$_2$CH), 1.72–1.62 (1H, m, CH$_2$C**H**$_2$CH), 1.50–1.06 (8H, m, 4 × C**H**$_2$), 0.88 (3H, t, *J* = 7.0 Hz, CH$_2$C**H**$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 144.7 (Ar), 133.0 (Ar), 129.8 (2C, Ar), 127.9 (2C, Ar), 85.6 (CH**C**≡C), 70.3 (C≡**C**H), 68.5

(TsO**C**$H_2CH_2$), 34.6 (**C**$H_2$), 34.0 ($CH_2$**C**$H_2$CH), 31.5 (**C**$H_2$), 27.8 ($CH_2$**C**H(*n*-Hex)C≡), 26.7 (**C**$H_2$), 22.5 (**C**$H_2$), 21.6 (Ar**C**$H_3$), 14.0 ($CH_2$**C**$H_3$); LRMS *m/z* (ESI$^+$) 331 ([M+Na]$^+$, 100%); HRMS *m/z* (ESI$^+$) found 331.1342, $C_{17}H_{24}NaO_3S$ requires 331.1338; $\nu_{max}$ (film)/cm$^{-1}$ 3289 (m, ≡C-H), 2956 (m, CH), 2930 (m, CH), 2859 (m, CH), 2113 (w, C≡C), 1598 (m), 1466 (m), 1361 (s, R-$SO_2$-R), 1189 (s), 1175 (s, R-$SO_2$-R), 1097 (m), 961 (m), 908 (s).

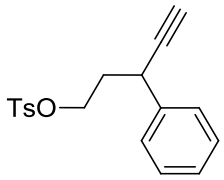
***3-Cyclohexylpent-4-yn-1-yl 4-methylbenzenesulfonate (348b)***




To a stirred solution of 3-cyclohexylpent-4-yn-1-ol (**347b**) (1.73 g, 10.4 mmol, 1.0 eq.) in pyridine (10.4 mL) cooled to -20 °C in a dry ice/acetone bath was added portionwise *p*-toluenesulfonyl chloride (2.98 g, 15.6 mmol, 1.5 eq.). The resulting mixture was slowly warmed to room temperature and stirred for 18 h. 1 M aq. HCl (50 mL) was added to the mixture and extracted with EtOAc (3 × 50 mL). The combined organic extracts were sequentially washed water (150 mL), brine (150 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60) to afford 3-cyclohexylpent-4-yn-1-yl 4-methylbenzenesulfonate (**348b**) as a colourless oil (2.84 g, 8.84 mmol, 85%). $R_f$ = 0.23 (10% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 7.79 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.34 (2H, d, *J* = 8.1 Hz, Ar**H**), 4.26–4.14 (2H, m, TsOC**H**$_2$$CH_2$), 2.44 (3H, s, ArC**H**$_3$), 2.33 (1H, dtd, *J* = 6.6, 4.7, 2.5 Hz, $CH_2$C**H**(CH)C≡), 1.96 (1H, d, *J* = 2.5 Hz, CHC≡C**H**), 1.84 (1H, tdt, *J* = 8.9, 6.6, 4.4 Hz, CHC**H**$(CH_2)_2$), 1.75–1.58 (6H, m, C**H**$_2$), 1.30–1.02 (6H, m, C**H**$_2$); $\delta_C$ (100 MHz, $CDCl_3$) 144.7 (Ar), 133.0 (Ar), 129.8 (2C, Ar), 127.9 (2C, Ar), 84.3 (CH**C**≡C), 71.3 (CHC≡**C**H), 68.9 (TsO**C**$H_2CH_2$), 40.8 (CH**C**H$(CH_2)_2$), 33.8 ($CH_2$**C**H(CH)C≡), 31.3 (**C**$H_2$), 31.3 (**C**$H_2$), 28.8 (**C**$H_2$), 26.2 (2C, **C**$H_2$), 26.1 (**C**$H_2$), 21.6 (Ar**C**$H_3$); LRMS *m/z* (ESI$^+$) 343 ([M+Na]$^+$, 100%), 663 ([2M+Na]$^+$, 90%); HRMS *m/z* (ESI$^+$) found 343.1334, $C_{18}H_{24}NaO_3S$ requires 343.1338; $\nu_{max}$ (film)/cm$^{-1}$ 3285 (m, ≡C-H),

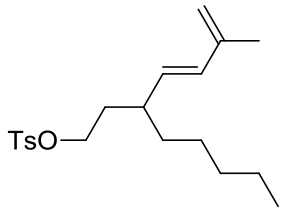
2925 (s, CH), 2853 (m, CH), 2110 (w, C≡C), 1598 (m), 1360 (s, R-$SO_2$-R), 1174 (s, R-$SO_2$-R), 1096 (s).

***3-Phenylpent-4-yn-1-yl 4-methylbenzenesulfonate (348c)***




To a stirred solution of 3-phenylpent-4-yn-1-ol (**347c**) (5.29 g, 33.0 mmol, 1.0 eq.) in pyridine (33.0 mL) cooled to -20 °C in a dry ice/acetone bath was added portionwise *p*-toluenesulfonyl chloride (9.44 g, 49.5 mmol, 1.5 eq.). The resulting mixture was slowly warmed to room temperature and stirred for 18 h. 1 M aq. HCl (100 mL) was added to the mixture and extracted with EtOAc (3 × 100 mL). The combined organic extracts were sequentially washed water (300 mL), brine (300 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/petrol 40-60) to afford 3-phenylpent-4-yn-1-yl 4-methylbenzenesulfonate (**348c**) as a colourless oil (8.73 g, 28.1 mmol, 85%). $R_f$ = 0.27 (20% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 7.81 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.36 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.33–7.22 (5H, m, Ar**H**), 4.25 (1H, ddd, *J* = 10.0, 7.9, 5.3 Hz, TsOC**H**$_2$$CH_2$), 4.10 (1H, ddd, *J* = 10.0, 5.4, 5.4 Hz, TsOC**H**$_2$$CH_2$), 3.78 (1H, ddd, *J*= 8.8, 6.3, 2.4 Hz, $CH_2$C**H**(Ph)C≡CH), 2.46 (3H, s, ArC**H**$_3$), 2.22 (1H, d, *J* = 2.4 Hz, CH(Ph)C≡C**H**), 2.15–2.99 (2H, m, $CH_2$C**H**$_2$CH); $\delta_C$ (100 MHz, $CDCl_3$) 144.8 (Ar), 139.7 (Ar), 132.9 (Ar), 129.9 (2C, Ar), 128.7 (2C, Ar), 128.0 (2C, Ar), 127.3 (2C, Ar), 127.2 (Ar), 83.9 (CH(Ph)**C**≡CH), 72.0 (C≡**C**H), 67.9 (TsO**C**$H_2CH_2$), 37.1 ($CH_2$**C**$H_2$CH), 33.6 ($CH_2$**C**H(Ph)C≡CH), 21.6 (Ar**C**$H_3$); LRMS *m*/*z* ($ESI^+$) 337 ($[M+Na]^+$, 100%); HRMS *m*/*z* ($ESI^+$) found 337.0861, $C_{18}H_{18}NaO_3S$ requires 337.0869; $\nu_{max}$ (film)/$cm^{-1}$ 3287 (s, ≡C-H), 3062 (w, C-H), 3030 (w, C-H), 2961 (w, C-H), 2115 (w, C≡C), 1598 (m), 1359 (s, R-$SO_2$-R), 1173 (s, R-$SO_2$-R), 1096 (s).

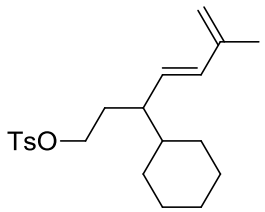
***(E)-3-(3-Methylbuta-1,3-dien-1-yl)octyl 4-methylbenzenesulfonate (349a)***




To a stirred solution of 3-ethynyloctyl 4-methylbenzenesulfonate (**348a**) (1.29 g, 4.18 mmol, 1.1 eq.) in Ar sparged anhydrous THF (4.20 mL) was added dropwise catecholborane (592 mg, 4.94 mmol, 1.3 eq.). The resulting mixture was heated at 70 °C for 18 h and cooled to room temperature. The mixture was concentrated under reduced pressure to afford the crude boronate ester, as a pale yellow cloudy oil. Palladium(II) acetate (42.7 mg, 0.19 mmol, 5 mol%) and triphenylphosphine (199 mg, 0.76 mmol, 20 mol%) were suspended in Ar sparged THF (10.5 mL) and stirred at room temperature for 20 min. To the yellow solution was added dropwise a solution of crude boronate ester and 2-bromopropene (440 mg, 3.64 mmol, 1.0 eq.) in Ar sparged anhydrous THF (10.5 mL). After complete addition, Ar sparged aq. 2 M LiOH (10.5 ml, 5.5 eq.) was added to the mixture and then heated at 40 °C for 4 h. Water (40 mL) was added to the mixture and extracted with EtOAc (3 × 20 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (60 mL), brine (60 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60 with 1% triethylamine) to afford (*E*)-3-(3-methylbuta-1,3-dien-1-yl)octyl 4-methylbenzenesulfonate (**349a**) as a pale yellow oil (1.10 g, 3.15 mmol, 83%). $R_f$ = 0.27 (10% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 7.86 (2H, d, *J* = 8.2 Hz, Ar**H**), 6.83 (2H, d, *J* = 8.2 Hz, Ar**H**), 6.06 (1H, d, *J* = 15.6 Hz, CH=C**H**C), 5.18 (1H, dd, *J* = 15.6, 9.2 Hz, CHC**H**=CH), 4.95 (1H, s, C=C$\mathbf{H_2}$), 4.92 (1H, s, C=C$\mathbf{H_2}$), 4.10–3.92 (2H, m, TsOC$\mathbf{H_2}CH_2$), 2.15–2.05 (1H, m, $CH_2$C**H**(*n*-Hex)C≡), 1.96 (3H, s, ArC$\mathbf{H_3}$), 1.77 (3H, s, C(=$CH_2$)C$\mathbf{H_3}$), 1.74–1.63 (1H, m, $CH_2$C$\mathbf{H_2}$CH), 1.37–1.10 (9H, m, C$\mathbf{H_2}$), 0.95 (3H, t, *J* = 7.0 Hz, $CH_2$C$\mathbf{H_3}$); $\delta_C$ (100 MHz, $CDCl_3$) 144.1 (Ar), 141.7 (**C**=$CH_2$), 134.4 (Ar), 134.3 (CH=**C**HC), 133.1 (CH**C**H=CH), 129.8 (2C, Ar),

128.1 (2C, Ar), 115.4 (C=**C**$H_2$), 68.6 (TsO**C**$H_2$$CH_2$), 39.5 ($CH_2$**C**H(*n*-Hex)C≡), 35.5 ($CH_2$**C**$H_2$CH), 34.5 (**C**$H_2$), 32.1 (**C**$H_2$), 27.1 (**C**$H_2$), 22.9 (**C**$H_2$), 21.1 (Ar**C**$H_3$), 18.7 (C(=$CH_2$)**C**$H_3$), 14.2 ($CH_2$**C**$H_3$); LRMS *m/z* ($ESI^+$) 373 ($[M+Na]^+$, 100%); HRMS *m/z* ($ESI^+$) found 373.1805, $C_{20}H_{30}NaO_3S$ requires 373.1808; $\nu_{max}$ (film)/$cm^{-1}$ 2956 (w, CH), 2926 (s, CH), 2857 (m, CH), 1599 (m), 1456 (m), 1362 (s, R-$SO_2$-R), 1188 (s), 1175 (s. R-$SO_2$-R), 1097 (s), 961 (s), 911 (s, CH=$CH_2$).

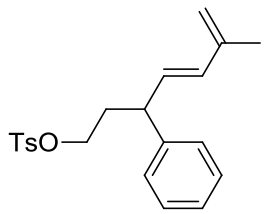
***(E)-3-Cyclohexyl-6-methylhepta-4,6-dien-1-yl 4-methylbenzenesulfonate (349b)***




To a stirred solution of 3-cyclohexylpent-4-yn-1-yl 4-methylbenzenesulfonate (**348b**) (1.34 g, 4.18 mmol, 1.1 eq.) in Ar sparged anhydrous THF (4.18 mL) was added dropwise catecholborane (592 mg, 4.94 mmol, 1.3 eq.). The resulting mixture was heated at 70 °C for 18 h and cooled to room temperature. The mixture was concentrated under reduced pressure to afford the crude boronate ester, as a pale yellow cloudy oil. Palladium (II) acetate (42.7 mg, 0.19 mmol, 5 mol%) and triphenylphosphine (199 mg, 0.76 mmol, 20 mol%) were suspended in Ar sparged THF (10.5 mL) and stirred at room temperature for 20 min. To the yellow solution was added dropwise a solution of crude boronate ester and 2-bromopropene (483 mg, 3.80 mmol, 1.0 eq.) in Ar sparged anhydrous THF (10.5 mL). After complete addition, Ar sparged aq. 2 M LiOH (10.5 ml, 5.5 eq.) was added to the mixture and then heated at 40 °C for 4 h. Water (40 mL) was added to the mixture and extracted with EtOAc (3 × 20 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (60 mL), brine (60 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60 with 1% triethylamine) to afford (*E*)-3-cyclohexyl-6-methylhepta-4,6-dien-1-yl 4-methylbenzenesulfonate (**349b**) as a pale yellow oil (1.12 g, 3.11 mmol, 82%). $R_f$ = 0.26 (10% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $C_6D_6$) 7.87 (2H, d, *J* = 8.1 Hz, Ar**H**), 6.83 (2H, d, *J* =

8.1 Hz, Ar**H**), 6.02 (1H, d, *J* = 15.6 Hz, CH=C**H**C), 5.22 (1H, dd, *J* = 15.6, 9.6 Hz, CHC**H**=CH), 4.95 (1H, s, C=C$\mathbf{H_2}$), 4.93 (1H, s, C=C$\mathbf{H_2}$), 4.09 (1H, ddd, *J* = 9.6, 6.5, 4.7 Hz, TsOC$\mathbf{H_2}$CH$_2$), 3.95 (1H, ddd, *J* = 9.6, 9.2, 5.8 Hz, TsOC$\mathbf{H_2}$CH$_2$), 1.96 (3H, s, ArC$\mathbf{H_3}$), 1.95–1.87 (1H, m, CH$_2$C**H**(CH)CH=), 1.84–1.62 (3H, m, C$\mathbf{H_2}$), 1.77 (3H, s, C(=CH$_2$)C$\mathbf{H_3}$), 1.62–1.50 (2H, m, C$\mathbf{H_2}$), 1.37–1.26 (1H, m, C$\mathbf{H_2}$), 1.25–1.01 (5H, m, C$\mathbf{H_2}$ and CHC**H**(CH$_2$)$_2$), 1.62–1.50 (2H, m, C$\mathbf{H_2}$); $\delta_C$ (100 MHz, $C_6D_6$) 144.1 (Ar), 141.7 (**C**=CH$_2$), 135.1 (CH=**C**HC), 134.4 (Ar), 131.3 (CH**C**H=CH), 129.8 (2C, Ar), 128.1 (2C, Ar), 115.3 (C=**C**H$_2$), 69.1 (TsO**C**H$_2$CH$_2$), 45.0 (CH$_2$**C**H(CH)CH=), 42.2 (CH**C**H(CH$_2$)$_2$), 31.6 (**C**H$_2$), 31.2 (**C**H$_2$), 29.8 (**C**H$_2$), 26.8 (**C**H$_2$), 26.8 (**C**H$_2$), 26.7 (**C**H$_2$), 21.1 (Ar**C**H$_3$), 18.8 (C(=CH$_2$)**C**H$_3$); LRMS *m*/*z* (ESI$^+$) 385 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 385.1796, $C_{21}H_{30}NaO_3S$ requires 385.1808; $\nu_{max}$ (film)/cm$^{-1}$ 3079 (w, CH), 2923 (s, CH), 2851 (m, CH), 1598 (m), 1449 (m), 1361 (s, R-SO$_2$-R), 1187 (s), 1175 (s. R-SO$_2$-R), 1097 (m), 967 (s), 911 (s, CH=CH$_2$).

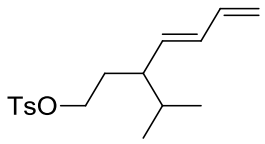
***(E)-6-Methyl-3-phenylhepta-4,6-dien-1-yl 4-methylbenzenesulfonate (349c)***




To a stirred solution of 3-phenylpent-4-yn-1-yl 4-methylbenzenesulfonate (**348c**) (1.26 g, 4.00 mmol, 1.1 eq.) in Ar sparged anhydrous THF (4.00 mL) was added dropwise catecholborane (504 mg, 4.20 mmol, 1.15 eq.). The resulting mixture was heated at 70 °C for 18 h and cooled to room temperature. The mixture was concentrated under reduced pressure to afford the crude boronate ester, as a pale yellow cloudy oil. Palladium (II) acetate (40.4 mg, 0.18 mmol, 5 mol%) and triphenylphosphine (191 mg, 0.73 mmol, 20 mol%) were suspended in Ar sparged THF (10.0 mL) and stirred at room temperature for 20 min. To the yellow solution was added dropwise a solution of crude boronate ester and 2-bromopropene (462 mg, 3.64 mmol, 1.0 eq.) in Ar sparged anhydrous THF (10.0 mL). After complete addition, Ar sparged aq. 2 M LiOH (10.0 ml, 5.5 eq.)

was added to the mixture and then heated at 40 °C for 4 h. Water (40 mL) was added to the mixture and extracted with EtOAc (3 × 20 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (60 mL), brine (60 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (15% EtOAc/petrol 40-60 with 1% triethylamine) to afford (*E*)-6-methyl-3-phenylhepta-4,6-dien-1-yl 4-methylbenzenesulfonate (**349c**) as a pale yellow oil (1.02 g, 2.88 mmol, 79%). $R_f$ = 0.35 (20% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $C_6D_6$) 7.81 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.17 (2H, t, *J* = 7.2 Hz, Ar**H**), 7.11 (1H, t, *J* = 7.2 Hz, Ar**H**), 7.01 (2H, d, *J* = 7.2 Hz, Ar**H**), 6.81 (2H, d, *J* = 8.1 Hz, Ar**H**), 6.13 (1H, d, *J* = 15.7 Hz, CH=C**H**C), 5.61 (1H, dd, *J* = 15.7, 7.8 Hz, CHC**H**=CH), 4.95 (2H, s, C=C$\mathbf{H_2}$), 4.00–3.86 (2H, m, TsOC$\mathbf{H_2}$$CH_2$), 3.43 (1H, ddd, *J* = 7.8 Hz, $CH_2$C**H**(Ph)CH=), 1.96 (3H, s, ArC$\mathbf{H_3}$), 1.91–1.83 (2H, m, $CH_2$C$\mathbf{H_2}$CH), 1.72 (3H, s, C(=$CH_2$)C$\mathbf{H_3}$); $\delta_C$ (100 MHz, $C_6D_6$) 144.1 (Ar), 143.2 (Ar), 141.8 (**C**=$CH_2$), 134.2 (Ar), 133.5 (CH=**C**HC), 132.5 (CH**C**H=CH), 129.8 (2C, Ar), 128.9 (2C, Ar), 128.1 (2C, Ar), 127.8 (2C, Ar), 126.7 (Ar), 116.1 (C=**C**$H_2$), 68.2 (TsO**C**$H_2CH_2$), 44.7 ($CH_2$**C**H(Ph)CH=), 34.9 ($CH_2$**C**$H_2$CH), 21.1 (Ar**C**$H_3$), 18.6 (C(=$CH_2$)**C**$H_3$); LRMS *m*/*z* ($ESI^+$) 379 ($[M+Na]^+$, 100%); HRMS *m*/*z* ($ESI^+$) found 379.1333, $C_{21}H_{24}NaO_3S$ requires 379.1338; $\nu_{max}$ (film)/$cm^{-1}$ 3062 (w, CH), 3028 (w, CH), 2956 (w, CH), 2921 (w, CH), 1599 (m), 1453 (m), 1359 (m), 1307 (s, R-$SO_2$-R), 1174 (s, R-$SO_2$-R), 1096 (s).

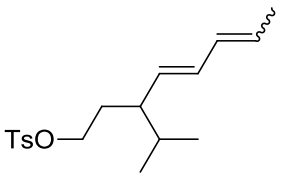
***(E)-3-Isopropylhepta-4,6-dien-1-yl 4-methylbenzenesulfonate (349d)***




To a stirred solution of 3-isopropylpent-4-yn-1-yl 4-methylbenzenesulfonate (**264**) (308 mg, 1.10 mmol, 1.1 eq.) in Ar sparged anhydrous THF (1.10 mL) was added dropwise catecholborane (158 mg, 1.32 mmol, 1.3 eq.). The resulting mixture was heated at 70 °C for 16 h and cooled to room temperature. The mixture was concentrated under reduced pressure to afford the crude boronate ester, as a pale yellow cloudy oil. Palladium (II) acetate (11.2 mg, 0.05 mmol, 5 mol%) and

triphenylphosphine (52.4 mg, 0.20 mmol, 20 mol%) were suspended in Ar sparged THF (2.75 mL) and stirred at room temperature for 20 min. To the yellow solution was added dropwise a solution of crude boronate ester and vinyl bromide (107 mg, 1.00 mmol, 1.0 eq.) in Ar sparged anhydrous THF (2.75 mL). After complete addition, Ar sparged aq. 2 M LiOH (2.75 ml, 5.5 eq.) was added to the mixture and then heated at 40 °C for 4 h. Water (20 mL) was added to the mixture and extracted with $Et_2O$ (3 × 20 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (60 mL), brine (60 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60 with 1% triethylamine) to afford (*E*)-3-isopropylhepta-4,6-dien-1-yl 4-methylbenzenesulfonate (**349d**) as a pale yellow oil (219 mg, 0.71 mmol, 71%). $R_f$ = 0.25 (10% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $C_6D_6$) 7.86 (2H, d, *J* = 8.1 Hz, Ar**H**), 6.84 (2H, d, *J* = 8.1 Hz, Ar**H**), 6.24 (1H, ddd, *J* = 17.0, 10.3, 10.3 Hz, =CHC**H**=$CH_2$), 5.85 (1H, dd, *J* = 15.2, 10.3 Hz, CH=C**H**CH=), 5.13 (1H, dd, *J* = 15.2, 9.7 Hz, CHC**H**=CH), 5.06 (1H, d, *J* = 17.0 Hz, CH=$CH_Z$**H**$_E$), 4.99 (1H, d, *J* = 10.3 Hz, CH=C**H**$_Z$$H_E$), 4.04 (1H, ddd, *J* = 9.9, 6.6, 4.8 Hz, TsOC**H**$_2$$CH_2$), 3.89 (1H, ddd, *J* = 9.9, 9.3, 5.9 Hz, TsOC**H**$_2$$CH_2$), 1.97 (3H, s, ArC**H**$_3$), 1.90–1.80 (1H, m, $CH_2$C**H**(CH)CH=), 1.75–1.65 (1H, m, $CH_2$C**H**$_2$CH), 1.44–1.30 (1H, m, CHC**H**$(CH_3)_2$), 1.30–1.19 (1H, m, $CH_2$C**H**$_2$CH), 0.79 (3H, d, *J* = 6.8 Hz, CH(C**H**$_3)_2$), 0.73 (3H, d, *J* = 6.8 Hz, CH(C**H**$_3)_2$); $\delta_C$ (100 MHz, $C_6D_6$) 144.1 (Ar), 137.1 (=CH**C**H=$CH_2$), 135.1 (CH**C**H=CH), 134.3 (Ar), 133.5 (CH=**C**HCH=), 129.8 (2C, Ar), 128.1 (2C, Ar), 115.6 (CH=C**H**$_Z$$H_E$), 68.9 (TsO$CH_2CH_2$), 45.3 ($CH_2$**C**H(CH)CH=), 32.1 (CH**C**H$(CH_3)_2$), 31.6 ($CH_2$**C**$H_2$CH), 21.1 (Ar**C**$H_3$), 20.5 (CH(**C**$H_3)_2$), 18.8 (CH(**C**$H_3)_2$); LRMS *m*/*z* ($ESI^+$) 331 ($[M+Na]^+$, 100%); HRMS *m*/*z* ($ESI^+$) found 331.1326, $C_{17}H_{24}NaO_3S$ requires 331.1338; $\nu_{max}$ (film)/$cm^{-1}$ 2959 (w, CH), 2873 (w, CH), 1599 (m), 1466 (m), 1291 (s, R-$SO_2$-R), 1175 (s, R-$SO_2$-R), 1097 (s).

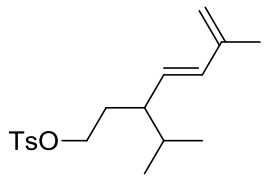
***(4E)-3-Isopropylocta-4,6-dien-1-yl 4-methylbenzenesulfonate (349e)***




To a stirred solution of 3-isopropylpent-4-yn-1-yl 4-methylbenzenesulfonate (**264**) (1.17 g, 4.18 mmol, 1.1 eq.) in Ar sparged anhydrous THF (4.18 mL) was added dropwise catecholborane (592 mg, 4.94 mmol, 1.3 eq.). The resulting mixture was heated at 70 °C for 18 h and cooled to room temperature. The mixture was concentrated under reduced pressure to afford the crude boronate ester, as a pale yellow cloudy oil. Palladium (II) acetate (42.7 mg, 0.19 mmol, 5 mol%) and triphenylphosphine (199 mg, 0.76 mmol, 20 mol%) were suspended in Ar sparged THF (10.5 mL) and stirred at room temperature for 20 min. To the yellow solution was added dropwise a solution of crude boronate ester and 1-bromopropene (483 mg, 3.80 mmol, 1.0 eq.) in Ar sparged anhydrous THF (10.5 mL). After complete addition, Ar sparged aq. 2 M LiOH (10.5 ml, 5.5 eq.) was added to the mixture and then heated at 40 °C for 4 h. Water (40 mL) was added to the mixture and extracted with EtOAc (3 × 20 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (60 mL), brine (60 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60 with 1% triethylamine) to afford (4*E*)-3-isopropylocta-4,6-dien-1-yl 4-methylbenzenesulfonate (**349e**, 1:1 mixture of diastereoisomers) as a pale yellow oil (980 mg, 3.04 mmol, 80%). $R_f$ = 0.27 (10% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $C_6D_6$) 7.86 (4H, d, *J* = 8.1 Hz, Ar**H**), 6.83 (4H, d, *J* = 8.1 Hz, Ar**H**), 6.36 (1H, dd, *J* = 15.1 Hz, 11.0 Hz, CHC**H**=CHMe, $D_E$), 6.05 (1H, dd, *J* = 11.4, 10.2 Hz, CHC**H**=CH, $D_Z$), 6.00–5.92 (1H, m, C**H**=CHCH), 5.86 (1H, dd, *J* = 14.9, 10.4 Hz, C**H**=CHCH), 5.54–5.39 (2H, m, CH=C**H**$CH_3$), 5.19 (1H, dd, *J* = 15.1, 9.6 Hz, CHC**H**=CH), 5.04 (1H, dd, *J* = 14.9, 9.6 Hz, CHC**H**=CH), 4.12–3.90 (4H, m, TsOC**H$_2$**$CH_2$, $D_E$ and $D_Z$), 1.97 (6H, s, ArC**H$_3$**, $D_E$ and $D_Z$), 1.95–1.82 (2H, m, $CH_2$C**H**(CH)CH=, $D_E$ and $D_Z$), 1.78–1.65 (2H, m, $CH_2$C**H$_2$**CH, $D_E$ and $D_Z$), 1.69 (6H, d, *J* = 5.8 Hz, =CHC**H$_3$**, $D_E$ and $D_Z$), 1.45–

1.35 (2H, m, CHC**H**$(CH_3)_2$, $D_E$ and $D_Z$), 1.34–1.22 (2H, m, $CH_2C\mathbf{H_2}CH$, $D_E$ and $D_Z$), 0.83 (6H, d, *J* = 6.8 Hz, CH(C**H**$_3)_2$, $D_E$ and $D_Z$), 0.82 (3H, d, *J* = 6.8 Hz, CH(C**H**$_3)_2$, $D_Z$), 0.72 (3H, d, *J* = 6.8 Hz, CH(C**H**$_3)_2$, $D_E$); $\delta_C$ (100 MHz, $C_6D_6$) 144.1 (Ar), 144.0 (Ar), 134.4 (2C, Ar), 134.2 (CH**C**H=CH), 133.1 (CH=**C**HCH), 131.8 (CH=**C**HCH), 131.5 (CH**C**H=CH), 129.7 (4C, Ar), 129.7 (CH**C**H=CH), 128.1 (4C, Ar), 128.1 (CH**C**H=CH), 127.5 (CH=**C**$HCH_3$), 124.7 (CH=**C**$HCH_3$), 69.1 (TsO**C**$H_2CH_2$), 69.1 (TsO**C**$H_2CH_2$), 45.6 ($CH_2$**C**H(CH)CH=), 45.4 ($CH_2$**C**H(CH)CH=), 32.3 (CH**C**H$(CH_3)_2$), 32.1 (CH**C**H$(CH_3)_2$), 31.8 ($CH_2$**C**$H_2$CH), 31.7 ($CH_2$**C**$H_2$CH), 21.1 (2C, Ar**C**$H_3$), 20.6 (CH(**C**$H_3)_2$), 20.5 (CH(**C**$H_3)_2$), 18.9 (CH(**C**$H_3)_2$), 18.8 (CH(**C**$H_3)_2$), 18.0 (=CH**C**$H_3$), 13.4 (=CH**C**$H_3$); LRMS *m*/*z* ($ESI^+$) 345 ($[M+Na]^+$, 100%); HRMS *m*/*z* ($ESI^+$) found 345.1484, $C_{18}H_{26}NaO_3S$ requires 345.1495; $\nu_{max}$ (film)/$cm^{-1}$ 3018 (w, CH), 2959 (m, CH), 2930 (m, CH), 2873 (m, CH), 1599 (m), 1466 (m), 1292 (s, R-$SO_2$-R), 1175 (s, R-$SO_2$-R), 1097 (s).

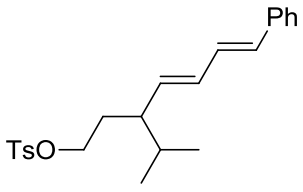
***(E)-3-Isopropyl-6-methylhepta-4,6-dien-1-yl 4-methylbenzenesulfonate (349f)***




To a stirred solution of 3-isopropylpent-4-yn-1-yl 4-methylbenzenesulfonate (**264**) (1.12 g, 4.00 mmol, 1.1 eq.) in Ar sparged anhydrous THF (4.00 mL) was added dropwise catecholborane (576 mg, 4.80 mmol, 1.3 eq.). The resulting mixture was heated at 70 °C for 18 h and cooled to room temperature. The mixture was concentrated under reduced pressure to afford the crude boronate ester, as a pale yellow cloudy oil. Palladium (II) acetate (40.9 mg, 0.18 mmol, 5 mol%) and triphenylphosphine (191 mg, 0.73 mmol, 20 mol%) were suspended in Ar sparged THF (10.0 mL) and stirred at room temperature for 20 min. To the yellow solution was added dropwise a solution of crude boronate ester and 2-bromopropene (440 mg, 3.64 mmol, 1.0 eq.) in Ar sparged anhydrous THF (10.0 mL). After complete addition, Ar sparged aq. 2 M LiOH (10.0 ml, 5.5 eq.) was added to the mixture and then heated at 40 °C for 4 h. Water (40 mL) was added to the

mixture and extracted with EtOAc (3 × 40 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (150 mL), brine (150 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (8% EtOAc/petrol 40-60 with 1% triethylamine) to afford (*E*)-3-isopropyl-6-methylhepta-4,6-dien-1-yl 4-methylbenzenesulfonate (**349f**) as a pale yellow oil (951 mg, 2.95 mmol, 81%). $R_f$ = 0.35 (10% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $C_6D_6$) 7.86 (2H, d, *J* = 8.1 Hz, Ar**H**), 6.83 (2H, d, *J* = 8.1 Hz, Ar**H**), 6.02 (1H, d, *J* = 15.7 Hz, CH=C**H**C), 5.20 (1H, dd, *J* = 15.7, 9.5 Hz, CHC**H**=CH), 4.95 (1H, s, C=C**H**$_2$), 4.92 (1H, s, C=C**H**$_2$), 4.07 (1H, ddd, *J* = 9.6, 6.6, 4.7 Hz, TsOC**H**$_2$CH$_2$), 3.93 (1H, ddd, *J* = 9.6, 9.2, 5.8 Hz, TsOC**H**$_2$CH$_2$), 1.96 (3H, s, ArC**H**$_3$), 1.95–1.85 (1H, m, CH$_2$C**H**(CH)CH=), 1.81–1.69 (1H, m, CH$_2$C**H**$_2$CH), 1.75 (3H, s, C(=CH$_2$)C**H**$_3$), 1.47–1.36 (1H, m, CHC**H**(CH$_3$)$_2$), 1.35–1.25 (1H, m, CH$_2$C**H**$_2$CH), 0.82 (3H, d, *J* = 6.8 Hz, CH(C**H**$_3$)$_2$), 0.77 (3H, d, *J* = 6.8 Hz, CH(C**H**$_3$)$_2$); $\delta_C$ (100 MHz, $C_6D_6$) 144.1 (Ar), 141.7 (**C**=CH$_2$), 135.4 (CH=**C**HC), 134.4 (Ar), 130.6 (CH**C**H=CH), 129.8 (2C, Ar), 128.1 (2C, Ar), 115.4 (C=**C**H$_2$), 69.0 (TsO**C**H$_2$CH$_2$), 45.6 (CH$_2$**C**H(CH)CH=), 32.2 (CH**C**H(CH$_3$)$_2$), 31.8 (CH$_2$**C**H$_2$CH), 21.1 (Ar**C**H$_3$), 20.5 (CH(**C**H$_3$)$_2$), 18.9 (CH(**C**H$_3$)$_2$), 18.7 (C(=CH$_2$)**C**H$_3$); LRMS *m*/*z* (ESI$^+$) 345 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 345.1488, $C_{18}H_{26}NaO_3S$ requires 345.1495; $\nu_{max}$ (film)/cm$^{-1}$ 3080 (w, CH), 2959 (m, CH), 2873 (w, CH), 1599 (m), 1465 (m), 1291 (s, R-SO$_2$-R), 1175 (s, R-SO$_2$-R), 1097 (s).

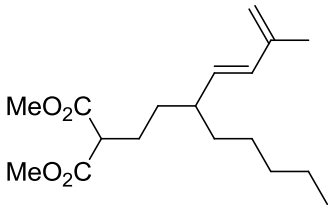
***(4E,6E)-3-Isopropyl-7-phenylhepta-4,6-dien-1-yl 4-methylbenzenesulfonate (349g)***




To a stirred solution of 3-isopropylpent-4-yn-1-yl 4-methylbenzenesulfonate (**264**) (1.03 g, 3.67 mmol, 1.1 eq.) in Ar sparged anhydrous THF (3.67 mL) was added dropwise catecholborane (521 mg, 4.34 mmol, 1.3 eq.). The resulting mixture was heated at 70 °C for 16 h and cooled to room temperature. The mixture was concentrated under reduced pressure to afford the crude

boronate ester, as a pale yellow cloudy oil. Palladium (II) acetate (37.5 mg, 0.17 mmol, 5 mol%) and triphenylphosphine (175 mg, 0.67 mmol, 20 mol%) were suspended in Ar sparged THF (9.20 mL) and stirred at room temperature for 20 min. To the yellow solution was added dropwise a solution of crude boronate ester and bromostyrene (611 mg, 3.34 mmol, 1.0 eq.) in Ar sparged anhydrous THF (9.20 mL). After complete addition, Ar sparged aq. 2 M LiOH (9.2 ml, 5.5 eq.) was added to the mixture and then heated at 40 °C for 4 h. Water (20 mL) was added to the mixture and extracted with EtOAc (3 × 10 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (50 mL), brine (50 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10-15% gradient, EtOAc/petrol 40-60 with 1% triethylamine) to afford (4*E*,6*E*)-3-isopropyl-7-phenylhepta-4,6-dien-1-yl 4-methylbenzenesulfonate (**349g**) as a pale yellow oil (1.05 g, 3.01 mmol, 82%). $R_f$ = 0.18 (10% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $C_6D_6$) 7.88 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.37 (2H, d, *J* = 7.5 Hz, Ar**H**), 7.26 (2H, t, *J* = 7.5 Hz, Ar**H**), 7.16 (1H, t, *J* = 7.5 Hz, Ar**H**), 6.81 (2H, d, *J* = 8.1 Hz, Ar**H**), 6.65 (1H, dd, *J* = 15.7, 10.4 Hz, =CHC**H**=CH), 6.36 (1H, d, *J* = 15.7 Hz, CH=C**H**Ph), 5.99 (1H, dd, *J* = 15.1, 10.4 Hz, CH=C**H**CH=), 5.23 (1H, dd, *J* = 15.1, 9.7 Hz, CHC**H**=CH), 4.12 (1H, ddd, *J* = 9.6, 6.5, 4.5 Hz, TsOC**H**$_2$CH$_2$), 3.95 (1H, ddd, *J* = 9.6, 9.3, 5.6 Hz, TsOC**H**$_2$CH$_2$), 2.01–1.92 (1H, m, CH$_2$C**H**(CH)CH=), 1.91 (3H, s, ArC**H**$_3$), 1.82–1.72 (1H, m, CH$_2$C**H**$_2$CH), 1.50–1.36 (1H, m, CHC**H**(CH$_3$)$_2$), 1.36–1.26 (1H, m, CH$_2$C**H**$_2$CH), 0.86 (3H, d, *J* = 6.8 Hz, CH(C**H**$_3$)$_2$), 0.81 (3H, d, *J* = 6.8 Hz, CH(C**H**$_3$)$_2$); $\delta_C$ (100 MHz, $C_6D_6$) 144.1 (Ar), 137.9 (Ar), 135.2 (CH**C**H=CH), 134.3 (Ar), 133.2 (CH=**C**HCH=), 131.3 (CH=**C**HPh), 129.8 (2C, Ar), 129.1 (=CH**C**H=CH), 128.6 (2C, Ar), 128.2 (2C, Ar), 127.6 (Ar), 126.6 (2C, Ar), 68.9 (TsO**C**H$_2$CH$_2$), 45.7 (CH$_2$C**H**(CH)CH=), 32.3 (CH**C**H(CH$_3$)$_2$), 31.8 (CH$_2$**C**H$_2$CH), 21.1 (Ar**C**H$_3$), 20.6 (CH(**C**H$_3$)$_2$), 18.9 (CH(**C**H$_3$)$_2$); LRMS *m*/*z* (ESI$^+$) 407 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 407.1639, $C_{23}H_{28}NaO_3S$ requires 407.1651; $\nu_{max}$ (film)/cm$^{-1}$ 3024 (w, CH), 2959 (m, CH), 2873 (w, CH), 1598 (m), 1449 (m), 1363 (s), 1291 (s, R-SO$_2$-R), 1188 (s), 1176 (s, R-SO$_2$-R), 1097 (m).

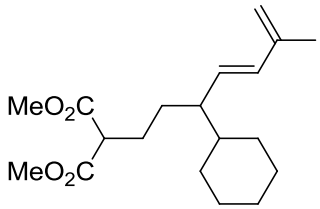
***(E)-Dimethyl 2-(3-(3-methylbuta-1,3-dien-1-yl)octyl)malonate (350a)***




To a stirred suspension of hexane washed NaH (175 mg, 7.27 mmol, 3.0 eq.), in anhydrous DMF (6.10 mL) cooled to 0 °C in an ice/water bath, was carefully added dropwise dimethyl malonate (960 mg, 7.27 mmol, 3.0 eq.). The resulting mixture was stirred for 20 min at 0 °C, after which a solution of (*E*)-3-(3-methylbuta-1,3-dien-1-yl)octyl 4-methylbenzenesulfonate (**349a**) (850 mg, 2.42 mmol, 1.0 eq.) in anhydrous THF (6.10 mL) was added *via* cannula followed by potassium iodide (201 mg, 1.21 mmol, 0.5 eq.). The mixture was heated at 80 °C for 1.5 h and then cooled to room temperature. Sat. aq. $NH_4Cl$ solution (40 mL) was added to the mixture and extracted with EtOAc (3 × 20 mL). The combined organic extracts were sequentially washed with water (60 mL), brine (60 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60 with 1% triethylamine) to afford dimethyl (*E*)-dimethyl 2-(3-(3-methylbuta-1,3-dien-1-yl)octyl)malonate (**350a**) as a colourless oil (671 mg, 2.25 mmol, 93%). $R_f$ = 0.42 (100% DCM); $\delta_H$ (400 MHz, $CDCl_3$) 6.28 (1H, d, $J$ = 15.6 Hz, CH=C**H**C), 5.46 (1H, dd, $J$ = 15.6, 9.1 Hz, CHC**H**=CH), 5.02 (1H, s, C=C**H$_2$**), 4.97 (1H, s, C=C**H$_2$**), 3.46 (1H, t, $J$ = 7.5 Hz, $(MeO_2C)_2C\mathbf{H}CH_2$), 3.41 (6H, s, 2 × OC**H$_3$**), 2.25–2.00 (3H, m, CHC**H$_2$**$CH_2$ & $CH_2C\mathbf{H}$(*n*-Hex)CH=), 1.86 (3H, s, C(=$CH_2$)C**H$_3$**), 1.59–1.63 (1H, m, $CH_2C\mathbf{H}_2CH$), 1.45–1.20 (9H, m, C**H$_2$**), 0.97 (3H, t, $J$ = 6.9 Hz, $CH_2C\mathbf{H}_3$); $\delta_C$ (100 MHz, $CDCl_3$) 169.6 (**C**=O), 169.6 (**C**=O), 142.0 (**C**=$CH_2$), 134.5 (CH**C**H=CH), 133.8 (CH=**C**HC), 115.1 (C=**C**$H_2$), 52.0 ($(MeO_2C)_2\mathbf{C}HCH_2$), 51.8 (2C, O**C**$H_3$), 43.3 ($CH_2\mathbf{C}H$(*n*-Hex)CH=), 35.6 (**C**$H_2$), 33.4 (**C**$H_2$), 32.2 (**C**$H_2$), 27.2 (**C**$H_2$), 27.2 (**C**$H_2$), 22.9 (**C**$H_2$), 18.8 (C(=$CH_2$)**C**$H_3$), 14.3 ($CH_2\mathbf{C}H_3$); LRMS $m/z$ ($ESI^+$) 333 ($[M+Na]^+$, 100%); HRMS $m/z$ ($ESI^+$) found 333.2034, $C_{18}H_{30}NaO_4$ requires 333.2036; $\nu_{max}$ (film)/$cm^{-1}$ 3081 (w, =$CH_2$), 2954 (m, CH), 2626 (s, CH), 2856 (m, CH), 1754 (s, C=O), 1736 (s,

C=O), 1608 (w, C=C), 1455 (s), 1435 (s), 1345 (m), 1197 (m), 1151 (s, C-O), 1019 (w), 967 (s), 852 (s).

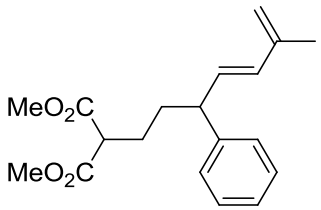
***(E)-Dimethyl 2-(3-cyclohexyl-6-methylhepta-4,6-dien-1-yl)malonate (350b)***




To a stirred suspension of hexane washed NaH (216 mg, 9.02 mmol, 3.0 eq.), in anhydrous DMF (7.50 mL) cooled to 0 °C in an ice/water bath, was carefully added dropwise dimethyl malonate (1.19 g, 9.02 mmol, 3.0 eq.). The resulting mixture was stirred for 20 min at 0 °C, after which a solution of (*E*)-3-cyclohexyl-6-methylhepta-4,6-dien-1-yl 4-methylbenzenesulfonate (**349b**) (1.09 g, 3.01 mmol, 1.0 eq.) in anhydrous THF (7.50 mL) was added *via* cannula followed by potassium iodide (250 mg, 1.50 mmol, 0.5 eq.). The mixture was heated at 80 °C for 1.5 h and then cooled to room temperature. Sat. aq. $NH_4Cl$ solution (40 mL) was added to the mixture and extracted with EtOAc (3 × 20 mL). The combined organic extracts were sequentially washed with water (60 mL), brine (60 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60 with 1% triethylamine) to afford (*E*)-dimethyl 2-(3-cyclohexyl-6-methylhepta-4,6-dien-1-yl)malonate (**350b**) as a colourless oil (843 mg, 2.74 mmol, 91%). $R_f$ = 0.31 (10% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $C_6D_6$) 6.24 (1H, d, $J$ = 15.6 Hz, CH=C**H**C), 5.50 (1H, dd, $J$ = 15.6, 9.5 Hz, CHC**H**=CH), 5.03 (1H, s, C=C$\mathbf{H_2}$), 4.98 (1H, s, C=C$\mathbf{H_2}$), 3.47 (1H, t, $J$ = 7.5 Hz, $(MeO_2C)_2C\mathbf{H}CH_2$), 3.41 (3H, s, OC$\mathbf{H_3}$), 3.40 (3H, s, OC$\mathbf{H_3}$), 2.27–2.16 (1H, m, CHC$\mathbf{H_2}CH_2$), 2.11–2.00 (1H, m, CHC$\mathbf{H_2}CH_2$), 1.94–1.85 (1H, m, $CH_2C\mathbf{H}(CH)CH$=), 1.86 (3H, s, C(=$CH_2$)C$\mathbf{H_3}$), 1.80–1.55 (6H, m, C$\mathbf{H_2}$), 1.47–1.36 (1H, m, C$\mathbf{H_2}$), 1.32–0.92 (6H, m, C$\mathbf{H_2}$ and CHC$\mathbf{H}(CH_2)_2$); $\delta_C$ (100 MHz, $C_6D_6$) 169.6 (**C**=O), 169.6 (**C**=O), 142.0 (**C**=$CH_2$), 134.6 (CH=**C**HC), 132.7 (CH**C**H=CH), 115.0 (C=**C**$H_2$), 52.0 ($(MeO_2C)_2\mathbf{C}HCH_2$), 51.8 (O**C**$H_3$), 51.8 (O**C**$H_3$), 49.1 ($CH_2\mathbf{C}H(CH)CH$=), 42.4 (CH**C**H$(CH_2)_2$), 31.5 (**C**$H_2$), 30.2 (**C**$H_2$), 30.0

(**C**$H_2$), 27.5 (**C**$H_2$), 26.9 (2C, **C**$H_2$), 18.9 (C(=$CH_2$)**C**$H_3$); LRMS *m*/*z* (ESI$^+$) 345 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 345.2031, $C_{19}H_{30}NaO_4$ requires 345.2036; $\nu_{max}$ (film)/cm$^{-1}$ 3080 (w, CH), 2923 (s, CH), 2852 (m, CH), 1754 (s), 1736 (s, C=O), 1608 (w, C=C), 1435 (s), 1345 (m), 1197 (m), 1150 (s, C-O), 968 (s).

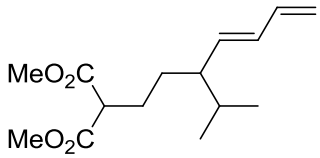
***(E)-Dimethyl 2-(6-methyl-3-phenylhepta-4,6-dien-1-yl)malonate (350c)***




To a stirred suspension of hexane washed NaH (237 mg, 8.58 mmol, 3.0 eq.), in anhydrous DMF (5.72 mL) cooled to 0 °C in an ice/water bath, was carefully added dropwise dimethyl malonate (1.13 g, 8.58 mmol, 3.0 eq.). The resulting mixture was stirred for 20 min at 0 °C, after which a solution of (*E*)-6-methyl-3-phenylhepta-4,6-dien-1-yl 4-methylbenzenesulfonate (**349c**) (1.02 g, 2.86 mmol, 1.0 eq.) in anhydrous THF (5.72 mL) was added *via* cannula followed by potassium iodide (237 mg, 1.43 mmol, 0.5 eq.). The mixture was heated at 80 °C for 1.5 h and then cooled to room temperature. Sat. aq. $NH_4Cl$ solution (40 mL) was added to the mixture and extracted with EtOAc (3 × 20 mL). The combined organic extracts were sequentially washed with water (60 mL), brine (60 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60 with 1% triethylamine) to afford (*E*)-dimethyl 2-(6-methyl-3-phenylhepta-4,6-dien-1-yl)malonate (**350c**) as a colourless oil (814 mg, 2.57 mmol, 90%). $R_f$ = 0.39 (100% DCM); $\delta_H$ (400 MHz, $C_6D_6$) 7.28–7.22 (2H, m, Ar**H**), 7.20–7.12 (3H, m, Ar**H**), 6.29 (1H, d, *J* = 15.7 Hz, CH=C**H**C), 5.82 (1H, dd, *J* = 15.7, 7.9 Hz, CHC**H**=CH), 5.00 (1H, s, C=C**H**$_2$), 4.97 (1H, s, C=C**H**$_2$), 3.43 (1H, t, *J* = 7.4 Hz, ($MeO_2C$)$_2$C**H**$CH_2$), 3.37 (3H, s, OC**H**$_3$), 3.36 (3H, s, OC**H**$_3$), 3.34–3.27 (1H, m, $CH_2$C**H**(Ph)CH=), 2.22–2.16 (1H, m, CHC**H**$_2$$CH_2$), 2.10–1.98 (1H, m, CHC**H**$_2$$CH_2$), 1.90–1.82 (2H, m, $CH_2$C**H**$_2$CH), 1.78 (3H, s, C(=$CH_2$)C**H**$_3$); $\delta_C$ (100 MHz, $C_6D_6$) 169.5 (**C**=O), 169.4 (**C**=O), 144.3 (Ar), 142.0

(**C**=$CH_2$), 133.7 (CH=**C**HC), 133.1 (CH**C**H=CH), 128.9 (2C, Ar), 127.8 (2C, Ar), 126.6 (Ar), 115.8 (C=**C**$H_2$), 51.8 (3C, $(MeO_2C)_2$**C**$HCH_2$ and O**C**$H_3$), 49.1 ($CH_2$**C**H(CH)CH=), 33.7 ($CH_2$**C**$H_2$CH), 27.4 (CH**C**$H_2CH_2$), 18.7 (C(=$CH_2$)**C**$H_3$); LRMS *m/z* ($ESI^+$) 339 ($[M+Na]^+$, 100%); HRMS *m/z* ($ESI^+$) found 339.1557, $C_{19}H_{24}NaO_4$ requires 339.1567; $\nu_{max}$ (film)/$cm^{-1}$ 3082 (w, CH), 3026 (m, CH), 2953 (m, CH), 1751 (s), 1731 (s, C=O), 1607 (w, C=C), 1435 (s), 1345 (m), 1197 (m), 1148 (s, C-O), 966 (s).

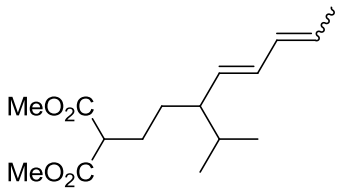
***(E)-Dimethyl 2-(3-isopropylhepta-4,6-dien-1-yl)malonate (350d)***




To a stirred suspension of hexane washed NaH (249 mg, 10.4 mmol, 3.0 eq.), in anhydrous DMF (8.68 mL) cooled to 0 °C in an ice/water bath, was carefully added dropwise dimethyl malonate (1.37 g, 10.4 mmol, 3.0 eq.). The resulting mixture was stirred for 20 min at 0 °C, after which a solution of (*E*)-3-isopropylhepta-4,6-dien-1-yl 4-methylbenzenesulfonate (**349d**) (1.07 g, 3.47 mmol, 1.0 eq.) in anhydrous THF (8.68 mL) was added *via* cannula followed by potassium iodide (289 mg, 1.74 mmol, 0.5 eq.). The mixture was heated at 80 °C for 2 h and then cooled to room temperature. Sat. aq. $NH_4Cl$ solution (30 mL) was added to the mixture and extracted with EtOAc (3 × 30 mL). The combined organic extracts were sequentially washed with water (100 mL), brine (100 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (8% EtOAc/petrol 40-60 with 1% triethylamine) to afford (*E*)-dimethyl 2-(3-isopropylhepta-4,6-dien-1-yl)malonate (**350d**) as a colourless oil (822 mg, 3.05 mmol, 88%). $R_f$ = 0.28 (10% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $C_6D_6$) 6.37 (1H, ddd, *J* = 17.0, 10.4, 10.0 Hz, =CHC**H**=$CH_2$), 6.07 (1H, dd, *J* = 15.2, 10.4 Hz, CH=C**H**CH=), 5.43 (1H, dd, *J* = 15.2, 9.5 Hz, CHC**H**=CH), 5.15 (1H, d, *J* = 17.0 Hz, CH=$CH_Z$**H**$_E$), 5.02 (1H, d, *J* = 10.0 Hz, CH=C**H**$_Z$$H_E$), 3.43 (1H, t, *J* = 7.6 Hz, $(MeO_2C)_2$C**H**$CH_2$),

3.41 (6H, s, OC**H**$_3$), 2.20–2.10 (1H, m, CHC**H**$_2$CH$_2$), 2.05–1.94 (1H, m, CHC**H**$_2$CH$_2$), 1.85–1.75 (1H, m, CH$_2$C**H**(CH)CH=), 1.60–1.47 (2H, m, CH$_2$C**H**$_2$CH and CHC**H**(CH$_3$)$_2$), 1.41–1.30 (1H, m, CH$_2$C**H**$_2$CH), 0.90 (3H, d, *J* = 6.8 Hz, CH(C**H**$_3$)$_2$), 0.85 (3H, d, *J* = 6.8 Hz, CH(C**H**$_3$)$_2$); $\delta_C$ (100 MHz, $C_6D_6$) 169.6 (**C**=O), 169.6 (**C**=O), 137.4 (=CH**C**H=CH$_2$), 136.5 (CH=**C**HCH=), 133.0 (CH**C**H=CH), 115.2 (C=**C**H$_2$), 52.0 ((MeO$_2$C)$_2$**C**HCH$_2$), 51.8 (2C, O**C**H$_3$), 49.3 (CH$_2$**C**H(CH)CH=), 32.1 (CH**C**H(CH$_3$)$_2$), 30.3 (CH$_2$C**H**$_2$CH), 27.4 (CH**C**H$_2$CH$_2$), 20.8 (CH(**C**H$_3$)$_2$), 18.9 (CH(**C**H$_3$)$_2$); LRMS *m*/*z* (ESI$^+$) 291 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 291.1568, $C_{15}H_{24}NaO_4$ requires 291.1567; $\nu_{max}$ (film)/cm$^{-1}$ 3086 (w, CH), 2956 (m, CH), 2872 (m, CH), 1753 (s), 1735 (s, C=O), 1603 (w, C=C), 1435 (s), 1345 (m), 1148 (s, C-O), 969 (s).

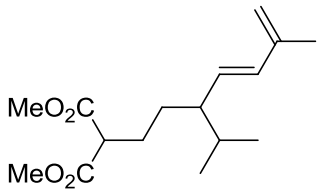
***Dimethyl 2-((4E)-3-isopropylocta-4,6-dien-1-yl)malonate (350e)***




To a stirred suspension of hexane washed NaH (195 mg, 8.11 mmol, 3.0 eq.), in anhydrous DMF (6.80 mL) cooled to 0 °C in an ice/water bath, was carefully added dropwise dimethyl malonate (1.07 g, 8.11 mmol, 3.0 eq.). The resulting mixture was stirred for 20 min at 0 °C, after which a solution of (4*E*)-3-isopropylocta-4,6-dien-1-yl 4-methylbenzenesulfonate (**349e**, 1:1 mixture of diastereoisomers) (872 mg, 2.70 mmol, 1.0 eq.) in anhydrous THF (6.80 mL) was added *via* cannula followed by potassium iodide (224 mg, 1.35 mmol, 0.5 eq.). The mixture was heated at 80 °C for 1.5 h and then cooled to room temperature. Sat. aq. $NH_4Cl$ solution (40 mL) was added to the mixture and extracted with EtOAc (3 × 20 mL). The combined organic extracts were sequentially washed with water (60 mL), brine (60 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60 with 1% triethylamine) to afford dimethyl 2-((4*E*)-3-isopropylocta-4,6-dien-1-yl)malonate (**350e**, 1:1 mixture of diastereoisomers) as a colourless oil (623 mg, 2.21 mmol, 82%). $R_f$ = 0.49

(100% DCM); $\delta_H$ (400 MHz, $C_6D_6$) 6.47 (1H, dd, *J* = 15.0, 11.0 Hz, CHC**H**=CH, $D_E$), 6.15 (1H, dd, *J* = 11.9, 10.4 Hz, CHC**H**=CH, $D_Z$), 6.12–6.02 (2H, m, C**H**=CHCH, $D_E$ and $D_Z$), 5.61–5.50 (1H, m, CH=C**H**$CH_3$), 5.50–5.40 (2H, m, CH=C**H**$CH_3$ and CHC**H**=CH), 5.37–5.29 (1H, m, CHC**H**=CH), 3.45 (1H, t, *J* = 7.5 Hz, $(MeO_2C)_2C\mathbf{H}CH_2$, $D_E$), 3.44 (1H, t, *J* = 7.2 Hz, $(MeO_2C)_2C\mathbf{H}CH_2$, $D_Z$), 3.41 (12H, s, O**C**$\mathbf{H_3}$), 2.25–2.13 (2H, m, CHC$\mathbf{H_2}CH_2$, $D_E$ and $D_Z$), 2.09–1.97 (2H, m, CHC$\mathbf{H_2}CH_2$, $D_E$ and $D_Z$), 1.92–1.77 (2H, m, $CH_2C\mathbf{H}$(CH)CH=, $D_E$ and $D_Z$), 1.71 (3H, d, *J* = 7.2 Hz, =CHC$\mathbf{H_3}$, $D_E$), 1.69 (3H, d, *J* = 6.7 Hz, =CHC$\mathbf{H_3}$, $D_Z$), 1.62–1.49 (4H, m, $CH_2C\mathbf{H_2}$CH and CHC**H**$(CH_3)_2$, $D_E$ and $D_Z$), 1.45–1.32 (2H, m, $CH_2C\mathbf{H_2}$CH, $D_E$ and $D_Z$), 0.94 (6H, d, *J* = 6.8 Hz, CH(C$\mathbf{H_3}$)$_2$, $D_E$ and $D_Z$), 0.89 (3H, d, *J* = 6.8 Hz, CH(C$\mathbf{H_3}$)$_2$, $D_Z$), 0.87 (3H, d, *J* = 6.8 Hz, CH(C$\mathbf{H_3}$)$_2$, $D_E$); $\delta_C$ (100 MHz, $C_6D_6$) 169.7 (**C**=O), 169.6 (**C**=O), 169.6 (**C**=O), 169.6 (**C**=O), 135.7 (CH**C**H=CH), 133.0 (CH**C**H=CH), 132.5 (**C**H=CHCH), 132.2 (**C**H=CHCH), 130.0 (CH**C**H=CH), 127.3 (CH**C**H=CH), 127.0 (CH=**C**H$CH_3$), 124.2 (CH=**C**H$CH_3$), 52.0 (2C, $(MeO_2C)_2\mathbf{C}HCH_2$), 51.8 (4C, O**C**$H_3$), 49.6 ($CH_2\mathbf{C}H$(CH)CH=), 49.4 ($CH_2\mathbf{C}H$(CH)CH=), 32.3 (CH**C**H$(CH_3)_2$), 32.1 (CH**C**H$(CH_3)_2$), 30.5 ($CH_2C\mathbf{H_2}CH$), 30.4 ($CH_2C\mathbf{H_2}CH$), 27.5 (CH**C**$H_2CH_2$), 27.5 (CH**C**$H_2CH_2$), 20.9 (CH(**C**$H_3)_2$), 20.8 (CH(**C**$H_3)_2$), 19.0 (CH(**C**$H_3)_2$), 18.9 (CH(**C**$H_3)_2$), 18.8 (=CH**C**$H_3$), 13.3 (=CH**C**$H_3$); LRMS *m*/*z* ($ESI^+$) 305 ($[M+Na]^+$, 100%); HRMS *m*/*z* ($ESI^+$) found 305.1718, $C_{16}H_{26}NaO_4$ requires 305.1723; $\nu_{max}$ (film)/$cm^{-1}$ 3016 (w, CH), 2956 (m, CH), 2871 (m, CH), 1754 (s), 1736 (s, C=O), 1435 (s), 1368 (m), 1345 (m), 1199 (m), 1151 (s, C-O).

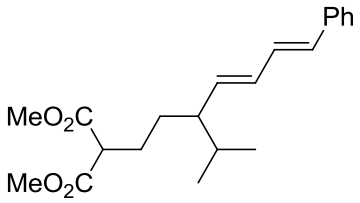
***(E)-Dimethyl 2-(3-isopropyl-6-methylhepta-4,6-dien-1-yl)malonate (350f)***




To a stirred suspension of hexane washed NaH (212 mg, 8.84 mmol, 3.0 eq.), in anhydrous DMF (7.38 mL) cooled to 0 °C in an ice/water bath, was carefully added dropwise dimethyl malonate (1.17 g, 8.84 mmol, 3.0 eq.). The resulting mixture was stirred for 20 min at 0 °C, after which a

solution of (*E*)-3-isopropyl-6-methylhepta-4,6-dien-1-yl 4-methylbenzenesulfonate (**349f**) (950 mg, 2.95 mmol, 1.0 eq.) in anhydrous THF (7.38 mL) was added *via* cannula followed by potassium iodide (189 mg, 1.14 mmol, 0.5 eq.). The mixture was heated at 80 °C for 2 h and then cooled to room temperature. Sat. aq. $NH_4Cl$ solution (40 mL) was added to the mixture and extracted with EtOAc (3 × 40 mL). The combined organic extracts were sequentially washed with water (100 mL), brine (100 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (8% EtOAc/petrol 40-60 with 1% triethylamine) to afford (*E*)-dimethyl 2-(3-isopropyl-6-methylhepta-4,6-dien-1-yl)malonate (**350f**) as a colourless oil (715 mg, 2.53 mmol, 86%). $R_f$ = 0.31 (10% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $C_6D_6$) 6.23 (1H, d, *J* = 15.6 Hz, CH=C**H**C), 5.48 (1H, dd, *J* = 15.6, 9.4 Hz, CHC**H**=CH), 5.01 (1H, s, C=C**H$_2$**), 4.97 (1H, s, C=C**H$_2$**), 3.45 (1H, t, *J* = 7.5 Hz, $(MeO_2C)_2C\mathbf{H}CH_2$), 3.41 (6H, s, O**H$_3$**), 2.23–2.12 (1H, m, CHC**H$_2$**$CH_2$), 2.09–1.97 (1H, m, CHC**H$_2$**$CH_2$), 1.92–1.83 (1H, m, $CH_2C\mathbf{H}(CH)CH$=), 1.85 (3H, s, C(=$CH_2$)C**H$_3$**), 1.64–1.51 (2H, m, $CH_2C\mathbf{H_2}CH$ and $CHC\mathbf{H}(CH_3)_2$), 1.45–1.34 (1H, m, $CH_2C\mathbf{H_2}CH$), 0.93 (3H, d, *J* = 6.8 Hz, $CH(C\mathbf{H_3})_2$), 0.89 (3H, d, *J* = 6.8 Hz, $CH(C\mathbf{H_3})_2$); $\delta_C$ (100 MHz, $C_6D_6$) 169.6 (**C**=O), 169.5 (**C**=O), 142.0 (**C**=$CH_2$), 134.9 (CH=**C**HC), 132.0 (CH**C**H=CH), 115.1 (C=**C**$H_2$), 52.0 ($(MeO_2C)_2\mathbf{C}HCH_2$), 51.8 (O**C**$H_3$), 51.8 (O**C**$H_3$), 49.5 ($CH_2\mathbf{C}H(CH)CH$=), 32.2 ($CH\mathbf{C}H(CH_3)_2$), 30.4 ($CH_2\mathbf{C}H_2CH$), 27.5 ($CH\mathbf{C}H_2CH_2$), 20.8 ($CH(\mathbf{C}H_3)_2$), 19.0 ($CH(\mathbf{C}H_3)_2$), 18.8 (C(=$CH_2$)**C**$H_3$); LRMS *m*/*z* ($ESI^+$) 305 ($[M+Na]^+$, 100%); HRMS *m*/*z* ($ESI^+$) found 305.1718, $C_{16}H_{26}NaO_4$ requires 305.1723; $\nu_{max}$ (film)/$cm^{-1}$ 3081 (w, CH), 2956 (m, CH), 2871 (m, CH), 1755 (s), 1737 (s, C=O), 1609 (w, C=C), 1435 (s), 1344 (m), 1199 (m), 1152 (s, C-O), 970 (s).

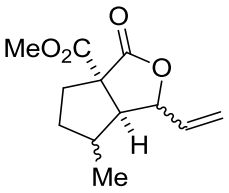
***Dimethyl 2-((4E,6E)-3-isopropyl-7-phenylhepta-4,6-dien-1-yl)malonate (350g)***




To a stirred suspension of hexane washed NaH (164 mg, 6.84 mmol, 3.0 eq.), in anhydrous DMF (5.70 mL) cooled to 0 °C in an ice/water bath, was carefully added dropwise dimethyl malonate (904 mg, 6.84 mmol, 3.0 eq.). The resulting mixture was stirred for 20 min at 0 °C, after which a solution of (4*E*,6*E*)-3-isopropyl-7-phenylhepta-4,6-dien-1-yl 4-methylbenzenesulfonate (**349g**) (877 mg, 2.28 mmol, 1.0 eq.) in anhydrous THF (5.70 mL) was added *via* cannula followed by potassium iodide (189 mg, 1.14 mmol, 0.5 eq.). The mixture was heated at 80 °C for 1.5 h and then cooled to room temperature. Sat. aq. $NH_4Cl$ solution (20 mL) was added to the mixture and extracted with EtOAc (3 × 20 mL). The combined organic extracts were sequentially washed with water (60 mL), brine (60 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/petrol 40-60 with 1% triethylamine) to afford dimethyl 2-((4*E*,6*E*)-3-isopropyl-7-phenylhepta-4,6-dien-1-yl)malonate (**350g**) as a colourless oil (643 mg, 1.87 mmol, 82%). $R_f$ = 0.32 (20% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $C_6D_6$) 7.37 (2H, d, *J* = 7.4 Hz, Ar**H**), 7.25 (2H, t, *J* = 7.4 Hz, Ar**H**), 7.15 (1H, t, *J* = 7.4 Hz, Ar**H**), 6.78 (1H, dd, *J* = 15.6, 10.4 Hz, =CHC**H**=CH), 6.45 (1H, d, *J* = 15.6 Hz, CH=C**H**Ph), 6.20 (1H, dd, *J* = 15.1, 10.4 Hz, CH=C**H**CH), 5.54 (1H, dd, *J* = 15.1, 9.5 Hz, CHC**H**=CH), 3.48 (1H, t, *J* = 7.5 Hz, $(MeO_2C)_2C\mathbf{H}CH_2$), 3.43 (3H, s, OC$\mathbf{H_3}$), 3.42 (3H, s, OC$\mathbf{H_3}$), 2.27–2.16 (1H, m, CHC$\mathbf{H_2}CH_2$), 2.10–2.00 (1H, m, CHC$\mathbf{H_2}CH_2$), 1.94–1.85 (1H, m, $CH_2C\mathbf{H}(CH)CH$=), 1.66–1.53 (2H, m, $CH_2C\mathbf{H_2}CH$ and $CHC\mathbf{H}(CH_3)_2$), 1.49–1.38 (1H, m, $CH_2C\mathbf{H_2}CH$), 0.96 (3H, d, *J* = 6.8 Hz, $CH(C\mathbf{H_3})_2$), 0.91 (3H, d, *J* = 6.8 Hz, $CH(C\mathbf{H_3})_2$); $\delta_C$ (100 MHz, $C_6D_6$) 169.7 (**C**=O), 169.6 (**C**=O), 138.0 (Ar), 136.7 (CH**C**H=CH), 132.7 (CH=**C**HCH), 131.0 (CH=**C**HPh), 129.5 (=CH**C**H=CH), 128.8 (2C, Ar), 127.4 (Ar), 126.6 (2C, Ar), 52.1 ($(MeO_2C)_2\mathbf{C}HCH_2$), 51.9 (O**C**$H_3$), 51.9 (O**C**$H_3$),

49.7 ($CH_2$**C**H(CH)CH=), 32.3 (CH**C**H($CH_3$)$_2$), 30.5 ($CH_2$**C**$H_2$CH), 27.6 (CH**C**$H_2$$CH_2$), 20.9 (CH(**C**$H_3$)$_2$), 19.0 (CH(**C**$H_3$)$_2$); LRMS *m*/*z* (ESI$^+$) 367 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 367.1868, $C_{21}H_{28}NaO_4$ requires 367.1880; $\nu_{max}$ (film)/cm$^{-1}$ 3022 (w, CH), 2955 (m, CH), 2871 (m, CH), 1752 (s), 1734 (s, C=O), 1434 (s), 1345 (m), 1196 (m), 1152 (s, C-O), 990 (s).

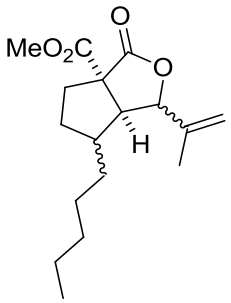
***(3aR*,6aS*)-Methyl 6-methyl-3-oxo-1-vinylhexahydro-1H-cyclopenta[c]furan-3a-carboxylate (351a)***




A mixture of manganese(III) acetate (1.08 g, 4.00 mmol, 2.0 eq.) and copper(II) triflate (725 mg, 2.00 mmol, 1.0 eq.) were pre heated to 80 °C, after which a solution of (*E*)-dimethyl 2-(3-methylhepta-4,6-dien-1-yl)malonate (**339a**) (482 mg, 2.00 mmol, 1.0 eq.) in Ar sparged acetonitrile (10.0 mL) was rapidly added. The resulting mixture was heated at 80 °C for 1 h and then cooled to room temperature. Water (10 mL) and $Et_2O$ (10 mL) were added and stirred for 10 min. The organic layer was separated and the aq. layer was further extracted with $Et_2O$ (2 × 10 mL). The combined organic layers were sequentially washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/petrol 40-60) to afford (3a*R**,6a*S**)-methyl 6-methyl-3-oxo-1-vinylhexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate (**351a**, diastereomeric ratio = 4.2:2.8:1.0) as a colourless oil (342 mg, 1.52 mmol, 76%). Characterisation is reported for the three epimers where possible of an inseparable mixture of diastereoisomers. $R_f$ = 0.28 (20% EtOAc/Petrol 40-60); $\delta_H$ (500 MHz, $CDCl_3$) 5.97–5.85 (3H, m, CHC**H**=$CH_2$ ($D_3$), CHC**H**=$CH_2$ ($D_2$) and CHC**H**=$CH_2$ ($D_1$)), 5.49 (1H, d, *J* = 17.2 Hz, CH=$CH_Z$**H**$_E$ ($D_2$)), 5.37 (1H, d, *J* = 10.1 Hz, CH=C**H**$_Z$$H_E$ ($D_2$)), 5.35 (1H, d, *J* = 17.2 Hz, CH=$CH_Z$**H**$_E$ ($D_3$)), 5.34 (1H, d, *J* = 16.9 Hz, CH=$CH_Z$**H**$_E$ ($D_1$)), 5.25 (1H, d, *J* = 10.7 Hz, CH=C**H**$_Z$$H_E$ ($D_3$)), 5.24 (1H, d, *J* = 10.5 Hz, CH=C**H**$_Z$$H_E$ ($D_1$)), 5.18 (1H, dd, *J* = 6.4, 6.3 Hz,

CHC**H**(CH=)O ($D_2$)), 4.78 (1H, dd, *J* = 6.2, 5.2 Hz, CHC**H**(CH=)O ($D_3$)), 4.64 (1H, ddd, *J* = 6.5, 2.6, 1.3 Hz, CHC**H**(CH=)O ($D_1$)), 3.79 (3H, s, OC**H**$_3$ ($D_2$)), 3.77 (3H, s, OC**H**$_3$ ($D_3$)), 3.76 (3H, s, OC**H**$_3$ ($D_1$)), 2.89 (1H, dd, *J* = 7.5, 5.2 Hz, CHC**H**(C)CHO ($D_3$)), 2.61–2.51 (3H, m, C**H**$_2$ ($D_1$), CHC**H**(C)CHO ($D_1$) and C**H**$_2$ ($D_2$)), 2.48 (1H, dd, *J* = 6.3, 2.8 Hz, CHC**H**(C)CHO ($D_2$)), 2.42 (1H, ddd, *J* = 13.5, 12.7, 6.9 Hz, C**H**$_2$ ($D_3$)), 2.36–2.25 (2H, m, $CH_2$C**H**(Me)CH ($D_3$) and C**H**$_2$ ($D_3$)), 2.20–2.10 (2H, m, C**H**$_2$ ($D_1$) and C**H**$_2$ ($D_2$)), 2.10–1.99 (2H, m, $CH_2$C**H**(Me)CH ($D_2$) and $CH_2$C**H**(Me)CH ($D_1$)), 1.95–1.83 (3H, m, C**H**$_2$ ($D_3$), C**H**$_2$ ($D_1$) and C**H**$_2$ ($D_2$)), 1.53 (1H, dddd, *J* = 12.9, 7.6, 7.6, 7.6 Hz, C**H**$_2$ ($D_1$)), 1.45 (1H, dddd, *J* = 18.0, 12.0, 9.4, 9.4 Hz, C**H**$_2$ ($D_2$)), 1.33 (1H, dddd, *J* = 12.5, 12.5, 12.5, 7.2 Hz, C**H**$_2$ ($D_3$)), 1.09 (3H, d, *J* = 6.9 Hz, CHC**H**$_3$ ($D_3$)), 1.08 (3H, d, *J* 6.8 Hz, CHC**H**$_3$ ($D_1$)), 1.03 (3H, d, *J* = 6.5 Hz, CHC**H**$_3$ ($D_2$)); $\delta_C$ (125 MHz, $CDCl_3$) 176.0 (**C**=O ($D_1$)), 175.9 (**C**=O ($D_3$)), 175.8 (**C**=O ($D_2$)), 171.2 (**C**=O ($D_1$)), 170.8 (**C**=O ($D_3$)), 170.5 (**C**=O ($D_2$)), 136.4 (CH**C**H=$CH_2$ ($D_3$)), 136.0 (CH**C**H=$CH_2$ ($D_1$)), 131.8 (CH**C**H=$CH_2$ ($D_2$)), 118.8 (CH=**C**$H_ZH_E$ ($D_2$)), 117.4 (CH=**C**$H_ZH_E$ ($D_3$)), 117.3 (CH=**C**$H_ZH_E$ ($D_1$)), 84.4 (CH**C**H(CH=)O ($D_1$)), 80.9 (CH**C**H(CH=)O ($D_2$)), 79.0 (CH**C**H(CH=)O ($D_3$)), 63.8 ($CH_2$**C**($CO_2$Me)C ($D_2$)), 62.1 ($CH_2$**C**($CO_2$Me)C ($D_3$)), 61.5 ($CH_2$**C**($CO_2$Me)C ($D_1$)), 59.4 (CH**C**H(C)CHO ($D_1$)), 57.8 (CH**C**H(C)CHO ($D_2$)), 54.8 (CH**C**H(C)CHO ($D_3$)), 53.2 (O**C**$H_3$ ($D_1$)), 53.1 (2C, O**C**$H_3$ ($D_2$) and O**C**$H_3$ ($D_3$)), 41.2 ($CH_2$**C**H(Me)CH ($D_1$)), 38.2 ($CH_2$**C**H(Me)CH ($D_3$)), 36.0 ($CH_2$**C**H(Me)CH ($D_2$)), 35.2 (**C**$H_2$ ($D_2$)), 34.5 (**C**$H_2$ ($D_3$)), 34.2 (**C**$H_2$ ($D_1$)), 33.9 (**C**$H_2$ ($D_1$)), 32.9 (**C**$H_2$ ($D_3$)), 32.3 (**C**$H_2$ ($D_2$)), 19.4 (CH**C**$H_3$ ($D_2$)), 18.6 (CH**C**$H_3$ ($D_1$)), 14.1 (CH**C**$H_3$ ($D_3$)); LRMS *m*/*z* ($ESI^+$) 247 ($[M+Na]^+$, 100%); HRMS *m*/*z* ($ESI^+$) found 247.0934, $C_{12}H_{16}NaO_4$ requires 247.0941; $\nu_{max}$ (film)/$cm^{-1}$ 2958 (m, CH), 2874 (m, CH), 1772 (s, C=O), 1739 (s, C=O), 1459 (m), 1435 (m), 1242 (m), 1203 (m), 1167 (m, C-O), 1138 (m), 986 (s), 910 (s).

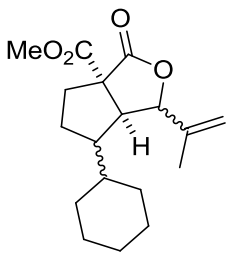
***(3aR*,6aS*)-Methyl 3-oxo-6-pentyl-1-(prop-1-en-2-yl)hexahydro-1H-cyclopenta[c]furan-3a-carboxylate (351b)***




A mixture of manganese(III) acetate (1.12 g, 4.18 mmol, 2.0 eq.) and copper(II) triflate (756 mg, 2.09 mmol, 1.0 eq.) were pre heated to 80 °C, after which a solution of dimethyl (*E*)-dimethyl 2-(3-(3-methylbuta-1,3-dien-1-yl)octyl)malonate (**350a**) (620 mg, 2.09 mmol, 1.0 eq.) in Ar sparged acetonitrile (10.5 mL) was rapidly added. The resulting mixture was heated at 80 °C for 1 h and then cooled to room temperature. Water (10 mL) and $Et_2O$ (10 mL) were added and stirred for 10 min. The organic layer was separated and the aq. layer was further extracted with $Et_2O$ (2 × 10 mL). The combined organic layers were sequentially washed with brine (30 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (15% EtOAc/petrol 40-60) to afford (3a*R**,6a*S**)-methyl 3-oxo-6-pentyl-1-(prop-1-en-2-yl)hexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate (**351b**, diastereomeric ratio = 9.0:2.1:1.0) as a colourless oil (422 mg, 1.50 mmol, 72%). Characterisation is reported for the two major epimers where possible of an inseparable mixture of three diastereoisomers. $R_f$ = 0.27 (15% EtOAc/Petrol 40-60); $\delta_H$ (500 MHz, $CDCl_3$) 5.17 (1H, s, C=C**H**$_2$ ($D_2$)), 5.06 (1H, d, *J* = 6.3 Hz, CHC**H**(C)O ($D_2$)), 5.04 (2H, s, C=C**H**$_2$ ($D_2$) and C=C**H**$_2$ ($D_1$)), 4.93 (1H, s, C=C**H**$_2$ ($D_1$)), 4.53 (1H, d, *J* = 3.8 Hz, CHC**H**(C)O ($D_1$)), 3.80 (3H, s, OC**H**$_3$ ($D_2$)), 3.75 (3H, s, OC**H**$_3$ ($D_1$)), 2.71 (1H, dd, *J* = 6.3, 5.4 Hz, CHC**H**(C)CHO ($D_2$)), 2.66 (1H, dd, *J* = 4.5, 3.8 Hz, CHC**H**(C)CHO ($D_1$)), 2.52 (1H, ddd, *J* = 13.8, 7.4, 6.9 Hz, C**H**$_2$ ($D_1$)), 2.46–2.35 (1H, m, C**H**$_2$ ($D_2$)), 2.33–2.23 (1H, m, C**H**$_2$ ($D_2$)), 2.18 (1H, ddd, *J* = 13.8, Hz C**H**$_2$ ($D_1$)), 1.99–1.87 (3H, m, C**H**$_2$ ($D_1$), $CH_2$C**H**($CH_2$)CH ($D_2$) and $CH_2$C**H**($CH_2$)CH ($D_1$)), 1.78 (3H, s, C(=$CH_2$)C**H**$_3$ ($D_1$)), 1.75 (3H, s, C(=$CH_2$)C**H**$_3$ ($D_2$)), 1.70–

1.56 (2H, m, C**H**$_2$ ($D_1$) and C**H**$_2$ ($D_2$)), 1.51 (1H, dddd, $J$ = 12.8, 7.7, 5.0, 5.0 Hz, C**H**$_2$ ($D_2$)), 1.48-1.16 (16H, m, C**H**$_2$ ($D_1$) and C**H**$_2$ ($D_2$)), 0.89 (3H, t, $J$ = 6.8 Hz, $CH_2C$**H**$_3$ ($D_1$)), 0.87 (3H, t, $J$ = 7.0 Hz, $CH_2C$**H**$_3$ ($D_2$)); $\delta_C$ (125 MHz, $CDCl_3$) 175.9 (**C**=O ($D_1$)), 175.7 (**C**=O ($D_2$)), 171.3 (**C**=O ($D_1$)), 170.3 (**C**=O ($D_2$)), 142.0 (**C**=$CH_2$ ($D_1$)), 138.5 (**C**=$CH_2$ ($D_2$)), 112.3 (C=**C**H$_2$ ($D_1$)), 111.7 (C=**C**H$_2$ ($D_2$)), 86.6 (CH**C**H(CH=)O ($D_1$)), 82.5 (CH**C**H(CH=)O ($D_2$)), 63.8 ($CH_2$**C**($CO_2$Me)C ($D_2$)), 61.4 ($CH_2$**C**($CO_2$Me)C ($D_1$)), 56.5 (CH**C**H(C)CHO ($D_1$)), 54.8 (CH**C**H(C)CHO ($D_2$)), 53.1 (O**C**H$_3$ ($D_2$)), 53.0 (O**C**H$_3$ ($D_1$)), 47.7 ($CH_2$**C**H($CH_2$)CH ($D_1$)), 40.3 ($CH_2$**C**H($CH_2$)CH ($D_2$)), 35.1 (**C**H$_2$ ($D_2$)), 34.2 (**C**H$_2$ ($D_1$)), 33.5 (**C**H$_2$ ($D_1$)), 32.5 (**C**H$_2$ ($D_2$)), 31.8 (**C**H$_2$ ($D_1$)), 31.7 (**C**H$_2$ ($D_1$)), 31.6 (**C**H$_2$ ($D_2$)), 31.0 (**C**H$_2$ ($D_2$)), 27.6 (**C**H$_2$ ($D_1$)), 27.6 (**C**H$_2$ ($D_2$)), 22.5 (2C, **C**H$_2$ ($D_1$) and **C**H$_2$ ($D_2$)), 19.6 (C(=$CH_2$)**C**H$_3$ ($D_2$)), 17.6 (C(=$CH_2$)**C**H$_3$ ($D_1$)), 14.0 (2C, $CH_2$**C**H$_3$ ($D_1$) and $CH_2$**C**H$_3$ ($D_2$)); LRMS $m/z$ ($ESI^+$) 317 ($[M+Na]^+$, 100%); HRMS $m/z$ ($ESI^+$) found 317.1721, $C_{17}H_{26}NaO_4$ requires 317.1723; $\nu_{max}$ (film)/$cm^{-1}$ 2955 (m, CH), 2936 (m, CH), 2857 (m, CH), 1775 (s, C=O), 1739 (s, C=O), 1656 (w, C=C), 1453 (m), 1436 (m), 1239 (m), 1160 (m, C-O), 1118 (m), 953 (m), 903 (m).

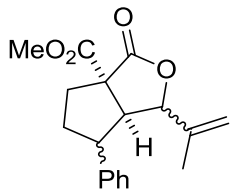
***(3aR*,6aS*)-Methyl 6-cyclohexyl-3-oxo-1-(prop-1-en-2-yl)hexahydro-1H-cyclopenta[c]furan-3a-carboxylate (351c)***




A mixture of manganese(III) acetate (1.38 g, 5.14 mmol, 2.0 eq.) and copper(II) triflate (929 mg, 2.57 mmol, 1.0 eq.) were pre heated to 80 °C, after which a solution of (*E*)-dimethyl 2-(3-cyclohexyl-6-methylhepta-4,6-dien-1-yl)malonate (**350b**) (794 mg, 2.57 mmol, 1.0 eq.) in Ar sparged acetonitrile (12.9 mL) was rapidly added. The resulting mixture was heated at 80 °C for 1 h and then cooled to room temperature. Water (30 mL) and EtOAc (30 mL) were added and stirred for 10 min. The organic layer was separated and the aq. layer was further extracted with EtOAc

(2 × 30 mL). The combined organic layers were sequentially washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (15% EtOAc/petrol 40-60) to afford (3a*R**,6a*S**)-methyl 6-cyclohexyl-3-oxo-1-(prop-1-en-2-yl)hexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate (**351c**, diastereomeric ratio = 16.6:2.7:1.0) as a colourless oil (574 mg, 1.88 mmol, 73%). Characterisation is reported for the major and minor epimer where possible of an inseparable mixture of diastereoisomers. $R_f$ = 0.25 (15% EtOAc/Petrol 40-60); $\delta_H$ (500 MHz, $CDCl_3$) 5.16 (1H, s, C=C**H**$_2$ ($D_2$)), 5.08 (1H, d, *J* = 6.1 Hz, CHC**H**(C)O ($D_2$)), 5.04 (1H, s, C=C**H**$_2$ ($D_2$) and C=C**H**$_2$ ($D_1$)), 4.96 (1H, s, C=C**H**$_2$ ($D_1$)), 4.55 (1H, d, *J* = 4.2 Hz, CHC**H**(C)O ($D_1$)), 3.80 (3H, s, OC**H**$_3$ ($D_2$)), 3.75 (3H, s, OC**H**$_3$ ($D_1$)), 2.94 (1H, dd, *J* = 6.1, 5.2 Hz, CHC**H**(C)CHO ($D_2$)), 2.89 (1H, dd, *J* = 5.2, 4.2 Hz, CHC**H**(C)CHO ($D_1$)), 2.48 (1H, ddd, *J* = 13.0, 6.7, 5.7 Hz, C**H**$_2$ ($D_1$)), 3.31–2.25 (2H, m, C**H**$_2$ ($D_2$)), 2.09 (1H, ddd, *J* = 13.0, 8.4, 7.1 Hz, C**H**$_2$ ($D_1$)), 1.91–1.84 (2H, m, $CH_2$C**H**(*i*Pr)CH ($D_2$) and C**H**$_2$ ($D_1$)), 1.80 (3H, s, C(=$CH_2$)C**H**$_3$ ($D_2$)), 1.79 (3H, s, C(=$CH_2$)C**H**$_3$ ($D_2$)), 1.77–1.55 (14H, m, C**H**$_2$ ($D_1$) and C**H**$_2$ ($D_2$)), 1.26–1.08 (9H, m, C**H**$_2$ ($D_1$), C**H**$_2$ ($D_2$), CHC**H**($CH_2$)$_2$ ($D_1$) and CHC**H**($CH_2$)$_2$ ($D_2$)), 0.97–0.85 (4H, m, C**H**$_2$ ($D_1$) and C**H**$_2$ ($D_2$)); $\delta_C$ (125 MHz, $CDCl_3$) 175.6 (**C**=O ($D_2$)), 175.5 (**C**=O ($D_1$)), 171.1 (**C**=O ($D_1$)), 170.3 (**C**=O ($D_2$)), 141.6 (**C**=$CH_2$ ($D_1$)), 138.6 (**C**=$CH_2$ ($D_2$)), 113.6 (C=**C**$H_2$ ($D_1$)), 112.0 (C=**C**$H_2$ ($D_2$)), 87.9 (CH**C**H(CH=)O ($D_1$)), 82.9 (CH**C**H(CH=)O ($D_2$)), 63.9 ($CH_2$**C**($CO_2$Me)C ($D_2$)), 61.8 ($CH_2$**C**($CO_2$Me)C ($D_1$)), 53.9 ($CH_2$**C**H($CH_2$)CH ($D_1$)), 53.7 (CH**C**H(C)CHO ($D_1$)), 53.1 (O**C**$H_3$ ($D_2$)), 53.0 (O**C**$H_3$ ($D_1$)), 51.8 (CH**C**H(C)CHO ($D_2$)), 45.7 ($CH_2$**C**H($CH_2$)CH ($D_2$)), 40.7 (CH**C**H($CH_2$)$_2$ ($D_2$)), 40.5 (CH**C**H($CH_2$)$_2$ ($D_1$)), 34.4 (**C**$H_2$ ($D_1$)), 33.5 (**C**$H_2$ ($D_2$)), 32.6 (**C**$H_2$ ($D_2$)), 32.2 (**C**$H_2$ ($D_1$)), 30.7 (2C, **C**$H_2$ ($D_1$) and **C**$H_2$ ($D_2$)), 30.1 (2C, **C**$H_2$ ($D_1$) and **C**$H_2$ ($D_2$)), 26.6 (**C**$H_2$ ($D_2$)), 26.4 (**C**$H_2$ ($D_2$)), 26.4 (**C**$H_2$ ($D_2$)), 26.3 (**C**$H_2$ ($D_1$)), 26.3 (**C**$H_2$ ($D_1$)), 26.1 (**C**$H_2$ ($D_1$)), 19.6 (C(=$CH_2$)**C**$H_3$ ($D_2$)), 17.4 (C(=$CH_2$)**C**$H_3$ ($D_1$)); LRMS *m*/*z* ($ESI^+$) 329 ($[M+Na]^+$, 100%); HRMS *m*/*z* ($ESI^+$) found 329.17, $C_{18}H_{26}NaO_4$ requires 329.1723; $\nu_{max}$ (film)/$cm^{-1}$ 2955 (m, CH), 2936 (m, CH), 2857 (m, CH), 1775 (s, C=O), 1739 (s, C=O), 1656 (w, C=C), 1453 (m), 1436 (m), 1239 (m), 1160 (m, C-O), 1118 (m), 953 (m), 903 (m).

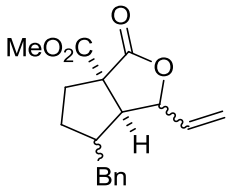
***(3aR*,6aS*)-Methyl 3-oxo-6-phenyl-1-(prop-1-en-2-yl)hexahydro-1H-cyclopenta[c]furan-3a-carboxylate (351d)***




A mixture of manganese(III) acetate (1.19 g, 4.44 mmol, 2.0 eq.) and copper(II) triflate (803 mg, 7.04 mmol, 1.0 eq.) were pre heated to 80 °C, after which a solution of (*E*)-dimethyl 2-(6-methyl-3-phenylhepta-4,6-dien-1-yl)malonate (**350c**) (703 mg, 2.22 mmol, 1.0 eq.) in Ar sparged acetonitrile (11.1 mL) was rapidly added. The resulting mixture was heated at 80 °C for 1 h and then cooled to room temperature. Water (20 mL) and $Et_2O$ (20 mL) were added and stirred for 10 min. The organic layer was separated and the aq. layer was further extracted with $Et_2O$ (2 × 20 mL). The combined organic layers were sequentially washed with brine (60 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (15% EtOAc/petrol 40-60) to afford (3a*R**,6a*S**)-methyl 3-oxo-6-phenyl-1-(prop-1-en-2-yl)hexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate (**351d**, diastereomeric ratio = 17.5:5.6:1.0) as a colourless oil (346 mg, 1.15 mmol, 52%). Characterisation is reported for the two major epimers where possible of an inseparable mixture of three diastereoisomers. $R_f$ = 0.28 (15% EtOAc/Petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 7.38–7.14 (10H, m, Ar**H**), 5.27 (1H, s, C=C**H**$_2$ ($D_2$)), 5.07 (1H, d, *J* = 5.8 Hz, CHC**H**(C)O ($D_2$)), 4.99 (1H, s, C=C**H**$_2$ ($D_1$)), 4.94 (1H, s, C=C**H**$_2$ ($D_2$)), 4.86 (1H, s, C=C**H**$_2$ ($D_1$)), 4.65 (1H, d, *J* = 2.4 Hz, CHC**H**(C)O) ($D_1$), 3.85 (3H, s, OC**H**$_3$ ($D_2$)), 3.76 (3H, s, OC**H**$_3$ ($D_1$)), 3.32 (1H, dd, *J* = 9.0, 5.8 Hz, CHC**H**(C)CHO ($D_2$)), 3.12 (1H, dd, *J* = 8.4, 2.4 Hz, CHC**H**(C)CHO ($D_1$)), 3.10–3.02 (2H, m, $CH_2$C**H**(Ph)CH ($D_1$) and $CH_2$C**H**(Ph)CH ($D_2$)), 2.72 (1H, ddd, *J* = 13.5, 8.6, 4.6 Hz, C**H**$_2$ ($D_2$)), 2.67–2.59 (1H, m, C**H**$_2$ ($D_1$)), 2.34–2.18 (3H, m, C**H**$_2$ ($D_1$), C**H**$_2$ ($D_1$) and C**H**$_2$ ($D_2$)), 2.12–2.02 (2H, m, C**H**$_2$ ($D_1$) and C**H**$_2$ ($D_2$)), 1.94–1.83 (1H, m, C**H**$_2$ ($D_2$)), 1.50 (3H, s, C(=$CH_2$)C**H**$_3$ ($D_1$)), 1.11 (3H, s, C(=$CH_2$)C**H**$_3$ ($D_2$)); $\delta_C$ (100 MHz, $CDCl_3$) 175.6

(**C**=O ($D_1$)), 175.5 (**C**=O ($D_2$)), 171.2 (**C**=O ($D_1$)), 170.2 (**C**=O ($D_2$)), 142.6 (**C**=$CH_2$ ($D_2$)), 141.6 (**C**=$CH_2$ ($D_1$)), 140.9 (Ar ($D_1$)), 138.3 (Ar ($D_2$)), 128.9 (2C, Ar ($D_1$)), 128.6 (2C, Ar ($D_2$)), 127.7 (2C, Ar ($D_2$)), 127.2 (3C, Ar ($D_1$)), 126.7 (Ar ($D_2$)), 111.7 (C=**C**$H_2$ ($D_2$)), 111.5 (C=**C**$H_2$ ($D_1$)), 85.1 (CH**C**H(CH=)O ($D_1$)), 81.7 (CH**C**H(CH=)O ($D_2$)), 64.0 ($CH_2$**C**($CO_2$Me)C ($D_2$)), 61.0 ($CH_2$**C**($CO_2$Me)C ($D_1$)), 58.0 (CH**C**H(C)CHO ($D_1$)), 56.1 (CH**C**H(C)CHO ($D_2$)), 53.7 ($CH_2$**C**H(Ph)CH ($D_1$)), 53.4 (O**C**$H_3$ ($D_2$)), 53.1 (O**C**$H_3$ ($D_1$)), 47.1 ($CH_2$**C**H(Ph)CH ($D_2$)), 36.9 (**C**$H_2$ ($D_2$)), 35.7 (**C**$H_2$ ($D_1$)), 34.9 (**C**$H_2$ ($D_1$)), 32.8 (**C**$H_2$ ($D_2$)), 19.0 (C(=$CH_2$)**C**$H_3$ ($D_2$)), 17.8 (C(=$CH_2$)**C**$H_3$ ($D_1$)); LRMS *m*/*z* ($ESI^+$) 301 ($[M+H]^+$, 100%); HRMS *m*/*z* ($ESI^+$) found 323.1253, $C_{18}H_{20}NaO_4$ requires 323.1254; $\nu_{max}$ (film)/$cm^{-1}$ 2958 (m, CH), 2874 (m, CH), 1773 (s, C=O), 1748 (s, C=O), 1450 (m), 1436 (m), 1263 (m), 1234 (m), 1162 (m, C-O), 1121 (m), 957 (m), 912 (m).

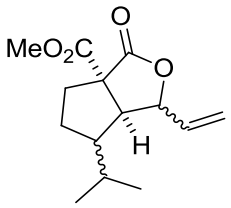
***(3aR*,6aS*)-Methyl 6-benzyl-3-oxo-1-vinylhexahydro-1H-cyclopenta[c]furan-3a-carboxylate (351e)***




A mixture of manganese(III) acetate (3.78 g, 14.1 mmol, 2.0 eq.) and copper(II) triflate (2.55 mg, 7.04 mmol, 1.0 eq.) were pre heated to 80 °C, after which a solution of (*E*)-dimethyl 2-(3-benzylhepta-4,6-dien-1-yl)malonate (**339b**) (2.23 g, 7.04 mmol, 1.0 eq.) in Ar sparged acetonitrile (35.0 mL) was rapidly added. The resulting mixture was heated at 80 °C for 2 h and then cooled to room temperature. Water (50 mL) and $Et_2O$ (50 mL) were added and stirred for 10 min. The organic layer was separated and the aq. layer was further extracted with $Et_2O$ (2 × 50 mL). The combined organic layers were sequentially washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/petrol 40-60) to afford (3a*R**,6a*S**)-Methyl 6-benzyl-3-oxo-1-vinylhexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate (**351e**, diastereomeric ratio = 6.3:4.8:1.0) as a colourless oil

(1.69 g, 5.63 mmol, 80%). Characterisation is reported for the two major epimers where possible of an inseparable mixture of three diastereoisomers. $R_f$ = 0.25 (20% EtOAc/Petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 7.34-7.08 (10H, m, Ar**H** ($D_1$) and Ar**H** ($D_2$)), 5.84 (1H, ddd, *J* = 17.0, 10.7, 6.0 Hz, CHC**H**=$CH_2$ ($D_2$)), 5.69 (1H, ddd, *J* = 17.1, 10.6, 6.4 Hz, CHC**H**=$CH_2$ ($D_1$)), 5.48 (1H, dt, *J* = 17.0, 1.2 Hz, CH=$CH_Z$**H**$_E$ ($D_2$)), 5.39 (1H, dt, *J* = 10.7, 1.2 Hz, CH=C**H**$_Z$$H_E$ ($D_2$)), 5.21–5.16 (1H, m, CHC**H**(CH=)O ($D_2$)), 5.08 (1H, dt, *J* = 10.6, 1.0 Hz, CH=C**H**$_Z$$H_E$ ($D_1$)), 5.04 (1H, dd, *J* = 17.1, 1.0 Hz, CH=$CH_Z$**H**$_E$ ($D_1$)), 4.38–4.34 (1H, m, CHC**H**(CH=)O ($D_1$)), 3.80 (3H, s, OC**H**$_3$ ($D_2$)), 3.76 (3H, s, OC**H**$_3$ ($D_1$)), 2.87–2.75 (3H, m, C**H**$_2$ ($D_1$), C**H**$_2$ ($D_2$) and CHC**H**(C)CHO ($D_2$)), 2.65–2.55 (3H, m, C**H**$_2$ ($D_1$), C**H**$_2$ ($D_2$) and CHC**H**(C)CHO ($D_1$)), 2.55–2.48 (2H, m, C**H**$_2$ ($D_1$) and C**H**$_2$ ($D_2$)), 2.41–2.23 (2H, m, $CH_2$C**H**(Bn)CH ($D_2$) and $CH_2$C**H**(Bn)CH ($D_1$)), 2.20–2.10 (2H, m, C**H**$_2$ ($D_1$) and C**H**$_2$ ($D_2$)), 1.96–1.87 (1H, m, C**H**$_2$ ($D_1$)), 1.75–1.61 (2H, m, C**H**$_2$ ($D_1$) and C**H**$_2$ ($D_2$)), 1.61–1.50 (1H, m, C**H**$_2$ ($D_2$)); $\delta_C$ (100 MHz, $CDCl_3$) 175.8 (**C**=O ($D_1$)), 175.5 (**C**=O ($D_2$)), 171.2 (**C**=O ($D_1$)), 170.3 (**C**=O ($D_2$)), 139.8 (CH**C**H=$CH_2$ ($D_2$)), 139.6 (CH**C**H=$CH_2$ ($D_1$)), 135.5 (Ar ($D_1$)), 131.9 (Ar ($D_2$)), 128.8 (4C, Ar ($D_2$) and Ar ($D_1$)), 128.7 (2C, Ar($D_1$)), 128.5 (2C, Ar ($D_2$)), 126.5 (Ar ($D_1$)), 126.4 (Ar ($D_2$)), 118.6 (CH=**C**$H_Z$$H_E$ ($D_2$)), 117.2 (CH=**C**$H_Z$$H_E$ ($D_1$)), 84.4 (CH**C**H(CH=)O), 80.9 (CH**C**H(CH=)O ($D_2$)), 63.5 ($CH_2$**C**($CO_2$Me)C ($D_2$)), 61.5 ($CH_2$**C**($CO_2$Me)C ($D_1$)), 57.3 (CH**C**H(C)CHO ($D_1$)), 55.1 (CH**C**H(C)CHO ($D_2$)), 53.2 (O**C**$H_3$ ($D_2$)), 53.1 (O**C**$H_3$ ($D_1$)), 49.4 ($CH_2$**C**H(Bn)CH ($D_1$)), 42.7 ($CH_2$**C**H(Bn)CH ($D_2$)), 40.6 (**C**$H_2$ ($D_2$)), 40.0 (**C**$H_2$ ($D_1$)), 33.8 (**C**$H_2$ ($D_1$)), 32.6 (**C**$H_2$ ($D_1$)), 32.4 (**C**$H_2$ ($D_2$)), 32.0 (**C**$H_2$ ($D_2$)); LRMS *m*/*z* ($ESI^+$) 323 ($[M+Na]^+$, 100%); HRMS *m*/*z* ($ESI^+$) found 323.1252, $C_{18}H_{20}NaO_4$ requires 323.1254; $\nu_{max}$ (film)/$cm^{-1}$ 3062 (w, CH), 3027 (w, CH), 2954 (m, CH), 2870 (m, CH), 1771 (s, C=O), 1738 (s, C=O), 1603 (m), 1495 (m), 1453 (m), 1434 (m), 1242 (s), 1202 (m), 1198 (m, C-O), 1138 (s), 986 (s).

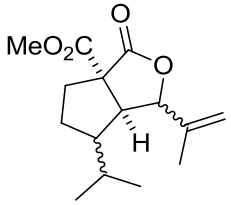
***(3aR*,6aS*)-Methyl 6-isopropyl-3-oxo-1-vinylhexahydro-1H-cyclopenta[c]furan-3a-carboxylate (351F)***




A mixture of manganese(III) acetate (1.51 g, 5.63 mmol, 2.0 eq.) and copper(II) triflate (1.02 g, 2.81 mmol, 1.0 eq.) were pre heated to 80 °C, after which a solution of dimethyl (*E*)-dimethyl 2-(3-isopropylhepta-4,6-dien-1-yl)malonate (**350d**) (755 mg, 2.81 mmol, 1.0 eq.) in Ar sparged acetonitrile (14.1 mL) was rapidly added. The resulting mixture was heated at 80 °C for 2 h and then cooled to room temperature. Water (30 mL) and EtOAc (30 mL) were added and stirred for 10 min. The organic layer was separated and the aq. layer was further extracted with EtOAc (2 × 30 mL). The combined organic layers were sequentially washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (15% EtOAc/petrol 40-60) to afford (3a*R**,6a*S**)-methyl 6-isopropyl-3-oxo-1-vinylhexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate (**351f**, diastereomeric ratio = 12.3:7.9:1.0) as a colourless oil (509 mg, 2.02 mmol, 72%). Characterisation is reported for the two major epimers where possible of an inseparable mixture of three diastereoisomers. $R_f$ = 0.18 (15% EtOAc/Petrol 40-60); $\delta_H$ (500 MHz, $CDCl_3$) 5.94 (1H, ddd, *J* = 17.2, 10.4, 7.0 Hz, CHC**H**=$CH_2$ ($D_1$)), 5.85 (1H, ddd, *J* = 17.0, 10.8, 6.2 Hz, CHC**H**=$CH_2$ ($D_2$)), 5.47 (1H, d, *J* = 17.1 Hz, CH=$CH_Z$**H**$_E$ ($D_2$)), 5.36 (1H, d, *J* = 10.8 Hz, CH=C**H**$_Z$$H_E$ ($D_2$)), 5.35 (1H, d, *J* = 17.0 Hz, CH=$CH_Z$**H**$_E$ ($D_1$)), 5.27 (1H, d, *J* = 10.4 Hz, CH=C**H**$_Z$$H_E$ ($D_1$)), 5.21 (1H, dd, *J* = 6.4, 6.2 Hz, CHC**H**(CH=)O ($D_2$)), 4.68 (1H, dd, *J* = 7.0, 3.1 Hz, CHC**H**(CH=)O ($D_1$)), 3.80 (3H, s, OC**H**$_3$ ($D_2$)), 3.77 (3H, s, OC**H**$_3$ ($D_1$)), 2.86 (1H, dd, *J* = 6.4, 6.4 Hz, CHC**H**(C)CHO ($D_2$)), 2.68 (1H, dd, *J* = 7.1, 3.1 Hz, CHC**H**(C)CHO ($D_1$)), 2.57 (1H, ddd, *J* = 13.5, 7.4, 3.6 Hz, C**H**$_2$ ($D_1$)), 2.38 (1H, ddd, *J* = 13.3, 8.1, 8.1 Hz, C**H**$_2$ ($D_2$)), 2.19 (1H, ddd, *J* = 13.3, 6.5, 6.5 Hz, C**H**$_2$ ($D_2$)), 2.05 (1H,

ddd, *J* = 13.5, 10.0, 6.8 C**H**$_2$ (D$_1$)), 2.03–1.95 (1H, m, CH$_2$C**H**(*i*Pr)CH (D$_2$)), 1.94 (1H, dddd, *J* = 12.6, 6.8, 6.4, 3.6 Hz, C**H**$_2$ (D$_1$)), 1.75-1.76 (1H, m, CH$_2$C**H**(*i*Pr)CH (D$_1$)), 1.76–1.61 (3H, m, CHC**H**(CH$_3$)$_2$ (D$_2$) and C**H**$_2$ (D$_2$)), 1.61–1.53 (2H, m, C**H**$_2$ (D$_1$) and CHC**H**(CH$_3$)$_2$ (D$_1$)), 0.94 (3H, d, *J* = 6.7 Hz, CH(C**H**$_3$)$_2$ (D$_1$)), 0.92 (3H, d, *J* = 6.7 Hz, CH(C**H**$_3$)$_2$ (D$_1$)), 0.88 (3H, d, *J* = 6.7 Hz, CH(C**H**$_3$)$_2$ (D$_2$)), 0.84 (3H, d, *J* = 6.7 Hz, CH(C**H**$_3$)$_2$ (D$_2$)); $\delta_C$ (125 MHz, $CDCl_3$) 175.7 (**C**=O (D$_1$)), 175.6 (**C**=O (D$_2$)), 171.1 (**C**=O (D$_1$)), 170.3 (**C**=O (D$_2$)), 135.4 (CH**C**H=CH$_2$ (D$_1$)), 132.2 (CH**C**H=CH$_2$ (D$_2$)), 118.5 (CH=**C**H$_Z$H$_E$ (D$_2$)), 118.0 (CH=**C**H$_Z$H$_E$ (D$_1$)), 85.6 (CH**C**H(CH=)O (D$_1$)), 81.4 (CH**C**H(CH=)O (D$_2$)), 63.8 (CH$_2$**C**(CO$_2$Me)C (D$_2$)), 61.8 (CH$_2$**C**(CO$_2$Me)C (D$_1$)), 56.3 (CH**C**H(C)CHO (D$_1$)), 55.1 (CH$_2$**C**H(*i*Pr)CH (D$_1$)), 53.1 (2C, O**C**H$_3$ (D$_2$) and O**C**H$_3$ (D$_1$)), 53.1 (CH**C**H(C)CHO (D$_2$)), 46.4 (CH$_2$**C**H(*i*Pr)CH (D$_2$)), 34.1 (**C**H$_2$ (D$_1$)), 32.9 (**C**H$_2$ (D$_2$)), 31.9 (CH**C**H(CH$_3$)$_2$ (D$_1$)), 31.3 (**C**H$_2$ (D$_1$)), 30.0 (CH**C**H(CH$_3$)$_2$ (D$_2$)), 27.4 (**C**H$_2$ (D$_2$)), 21.7 (CH**C**H(CH$_3$)$_2$), 21.4 (CH**C**H(CH$_3$)$_2$ (D$_2$)), 20.8 (CH**C**H(CH$_3$)$_2$ (D$_1$)), 18.1 (CH**C**H(CH$_3$)$_2$ (D$_2$)); LRMS *m*/*z* (ESI$^+$) 275 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 275.1249, $C_{14}H_{20}NaO_4$ requires 275.1254; $\nu_{max}$ (film)/cm$^{-1}$ 2958 (m, CH), 2874 (m, CH), 1774 (s, C=O), 1740 (s, C=O), 1464 (m), 1435 (m), 1249 (m), 1202 (m), 1166 (m, C-O), 1135 (m), 987 (s), 934 (m).

***(3aR*,6aS*)-Methyl 6-isopropyl-3-oxo-1-(prop-1-en-2-yl)hexahydro-1H-cyclopenta[c]furan-3a-carboxylate (351h)***

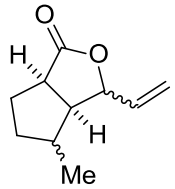



A mixture of manganese(III) acetate (1.26 g, 4.68 mmol, 2.0 eq.) and copper(II) triflate (846 mg, 2.34 mmol, 1.0 eq.) were pre heated to 80 °C, after which a solution of (*E*)-dimethyl 2-(3-isopropyl-6-methylhepta-4,6-dien-1-yl)malonate (**350f**) (661 mg, 2.34 mmol, 1.0 eq.) in Ar sparged acetonitrile (11.7 mL) was rapidly added. The resulting mixture was heated at 80 °C for 2 h and then cooled to room temperature. Water (30 mL) and EtOAc (30 mL) were added and stirred for

10 min. The organic layer was separated and the aq. layer was further extracted with EtOAc (2 × 30 mL). The combined organic layers were sequentially washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (15% EtOAc/petrol 40-60) to afford (3a*R**,6a*S**)-methyl 6-isopropyl-3-oxo-1-(prop-1-en-2-yl)hexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate (**351h**, diastereomeric ratio = 17.1:2.8:1.0) as a colourless oil (479 mg, 1.80 mmol, 77%). Characterisation is reported for the two major epimers where possible of an inseparable mixture of three diastereoisomers. $R_f$ = 0.22 (15% EtOAc/Petrol 40-60); $\delta_H$ (500 MHz, $CDCl_3$) 5.17 (1H, s, C=C**H**$_2$ ($D_2$)), 5.08 (1H, s, C=C**H**$_2$ ($D_2$)), 5.04 (1H, s, C=C**H**$_2$ ($D_1$)), 4.96 (1H, s, C=C**H**$_2$ ($D_1$)), 4.77 (1H, d, *J* = 5.6 Hz, CHC**H**(C)O ($D_2$)), 4.56 (1H, d, *J* = 4.2 Hz, CHC**H**(C)O ($D_1$)), 3.80 (3H, s, OC**H**$_3$ ($D_2$)), 3.75 (3H, s, OC**H**$_3$ ($D_1$)), 2.89 (1H, dd, *J* = 6.4, 5.6 Hz, CHC**H**(C)CHO ($D_2$)), 2.87 (1H, dd, *J* = 5.1, 4.2 Hz, CHC**H**(C)CHO ($D_1$)), 2.50 (1H, ddd, *J* = 13.7, 6.7, 6.1 Hz, C**H**$_2$ ($D_1$)), 3.35–2.24 (2H, m, C**H**$_2$ ($D_2$)), 2.11 (1H, ddd, *J* = 13.7, 8.1, 7.4 Hz, C**H**$_2$ ($D_1$)), 1.93–1.85 (2H, m, C**H**$_2$ ($D_1$) and $CH_2$C**H**(*i*Pr)CH ($D_2$)), 1.81 (3H, s, C(=$CH_2$)C**H**$_3$ ($D_2$)), 1.79 (3H, s, C(=$CH_2$)C**H**$_3$ ($D_1$)), 1.76–1.66 (3H, m, C**H**$_2$ ($D_1$), $CH_2$C**H**(*i*Pr)CH ($D_1$) and C**H**$_2$ ($D_2$)), 1.61–1.46 (3H, m, CHC**H**($CH_3$)$_2$ ($D_1$), CHC**H**($CH_3$)$_2$ ($D_2$) and C**H**$_2$ ($D_2$)), 0.92 (3H, d, *J* = 6.7 Hz, CH(C**H**$_3$)$_2$ ($D_1$)), 0.90 (3H, d, *J* = 6.7 Hz, CH(C**H**$_3$)$_2$ ($D_1$)), 0.89 (3H, d, *J* = 6.8 Hz, CH(C**H**$_3$)$_2$ ($D_2$)), 0.85 (3H, d, *J* = 6.8 Hz, CH(C**H**$_3$)$_2$ ($D_2$)); $\delta_C$ (125 MHz, $CDCl_3$) 175.7 (**C**=O ($D_2$)), 175.5 (**C**=O ($D_1$)), 171.1 (**C**=O ($D_1$)), 170.3 (**C**=O ($D_2$)), 141.6 (**C**=$CH_2$ ($D_1$)), 138.6 (**C**=$CH_2$ ($D_2$)), 113.5 (C=**C**$H_2$ ($D_1$)), 112.0 (C=**C**$H_2$ ($D_2$)), 87.7 (CH**C**H(CH=)O ($D_1$)), 82.7 (CH**C**H(CH=)O ($D_2$)), 64.0 ($CH_2$**C**($CO_2$Me)C ($D_2$)), 61.8 ($CH_2$**C**($CO_2$Me)C ($D_1$)), 54.8 ($CH_2$**C**H(*i*Pr)CH ($D_1$)), 54.0 (CH**C**H(C)CHO ($D_1$)), 53.1 (O**C**$H_3$ ($D_2$)), 53.0 (O**C**$H_3$ ($D_1$)), 52.3 (CH**C**H(C)CHO ($D_2$)), 46.2 ($CH_2$**C**H(*i*Pr)CH ($D_2$)), 34.3 (**C**$H_2$ ($D_1$)), 33.3 (**C**$H_2$ ($D_2$)), 30.5 (CH**C**H($CH_3$)$_2$ ($D_1$)), 30.1 (CH**C**H($CH_3$)$_2$ ($D_2$)), 30.0 (**C**$H_2$ ($D_1$)), 26.6 (**C**$H_2$ ($D_2$)), 22.0 (CH**C**H($CH_3$)$_2$), 21.6 (CH**C**H($CH_3$)$_2$ ($D_1$)), 20.1 (CH**C**H($CH_3$)$_2$ ($D_1$)), 19.6 (CH**C**H($CH_3$)$_2$ ($D_2$)), 17.7 (C(=$CH_2$)**C**$H_3$ ($D_2$)), 17.4 (C(=$CH_2$)**C**$H_3$ ($D_1$)); LRMS *m*/*z* ($ESI^+$) 289 ($[M+Na]^+$, 100%); HRMS *m*/*z* ($ESI^+$) found 289.1405, $C_{15}H_{22}NaO_4$ requires 289.1410; $\nu_{max}$ (film)/$cm^{-1}$ 2958 (m, CH),

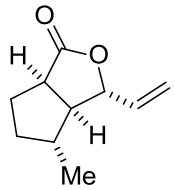
2874 (m, CH), 1773 (s, C=O), 1748 (s, C=O), 1450 (m), 1436 (m), 1263 (m), 1234 (m), 1162 (m, C-O), 1121 (m), 957 (m), 912 (m).

***(3aS*,6aR*)-4-Methyl-3-vinylhexahydro-1H-cyclopenta[c]furan-1-one (352a)***




To a stirred solution of (3a*R**,6a*S**)-methyl 6-methyl-3-oxo-1-vinylhexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate (**351a**) (176 mg, 0.78 mmol, 1.0 eq.) in anhydrous DMF (8.45 mL) was added water (31.2 mg, 1.73 mmol, 2.0 eq.) and lithium chloride (73.2 mg, 1.73 mmol, 2.0 eq.). The resulting mixture was heated at 150 °C for 5 h then cooled to room temperature. Sat. aq. $NH_4Cl$ solution (10 mL) was added to the mixture and extracted with $Et_2O$ (3 × 10 mL). The combined organic extracts were sequentially washed with water (15 mL), brine (15 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/petrol 40-60) to afford (3a*S**,6a*R**)-4-methyl-3-vinylhexahydro-1*H*-cyclopenta[*c*]furan-1-one (**352a**, diastereomeric ratio = 4.2:2.8:1.0) as a colourless oil (103 mg, 0.63 mmol, 80%). Characterisation is reported for the two major epimers as separated by flash column chromatography.

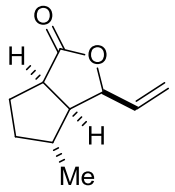
***(3S*,3aS*,4S*,6aR*)-4-Isopropyl-3-(prop-1-en-2-yl)hexahydro-1H-cyclopenta[c]furan-1-one***




Major epimer (53.0 mg, 0.32 mmol, 41%): $R_f$ = 0.35 (20% EtOAc/petrol 40-60); $\delta_H$ (500 MHz, $CDCl_3$) 5.88 (1H, ddd, *J* = 17.0, 10.5, 5.6 Hz, CHC**H**=$CH_2$), 5.33 (1H, d, *J* = 17.0 Hz, CH=$CH_Z$**H**$_E$), 5.20 (1H, d, *J* = 10.5 Hz, CH=C**H**$_Z$$H_E$), 4.67–4.64 (1H, m, CHC**H**(CH=)O), 3.07 (1H, ddd, *J* = 10.1, 9.2, 4.1 Hz, $CH_2$C**H**C=O), 2.20–2.11 (2H, m, CHC**H**CHO and

$CH_2C\mathbf{H_2}CHC=O$), 2.00–1.83 (3H, m, $CH_2C\mathbf{H_2}CHC=O$, $CH_2C\mathbf{H}(Me)CH$ and $CH_2C\mathbf{H_2}CH(Me)$), 1.36 (1H, dddd, $J$ = 15.1, 11.7, 7.6, 7.1 Hz, $CH_2C\mathbf{H_2}CH(Me)$), 1.07 (3H, d, $J$ = 6.6 Hz, $CHC\mathbf{H_3}$); $\delta_C$ (125 MHz, $CDCl_3$) 180.7 (**C**=O), 136.6 ($CH\mathbf{C}H=CH_2$), 116.0 ($CH=\mathbf{C}H_ZH_E$), 83.5 ($CH\mathbf{C}H(CH=)O$), 53.9 ($CH\mathbf{C}HCHO$), 43.7 ($CH_2\mathbf{C}HC=O$), 40.4 ($CH_2\mathbf{C}H(Me)CH$), 34.2 ($CH_2\mathbf{C}H_2CH(Me)$), 28.1 ($\mathbf{C}H_2CHC=O$), 18.6 ($CH\mathbf{C}H_3$); LRMS $m/z$ ($ESI^+$) 189 ($[M+Na]^+$, 100%); HRMS $m/z$ ($ESI^+$) found 189.0884, $C_{10}H_{14}NaO_2$ requires 189.0886; $\nu_{max}$ (film)/$cm^{-1}$ 3088 (w, $=CH_2$), 2956 (m, CH), 2872 (m, CH), 1766 (s, C=O), 1646 (w, C=C), 1460 (m), 1379 (m), 1314 (m), 1249 (m), 1154 (m, C-O), 1098 (m), 983 (m), 927 (m, $C=CH_2$).

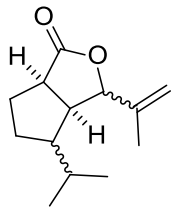
***(3S*,3aS*,4R*,6aR*)-4-Isopropyl-3-(prop-1-en-2-yl)hexahydro-1H-cyclopenta[c]furan-1-one***




Minor epimer (36.0 mg, 0.22 mmol, 28%): $R_f$ = 0.28 (20% EtOAc/petrol 40-60); $\delta_H$ (500 MHz, $CDCl_3$) 5.91 (1H, ddd, $J$ = 17.1, 10.6, 6.4 Hz, $CHC\mathbf{H}=CH_2$), 5.45 (1H, d, $J$ = 17.1 Hz, $CH=CH_Z\mathbf{H_E}$), 5.33 (1H, d, $J$ = 10.6 Hz, $CH=C\mathbf{H_Z}H_E$), 5.02 (1H, dd, $J$ = 6.6, 6.4 Hz, $CHC\mathbf{H}(CH=)O$), 3.17 (1H, ddd, $J$ = 9.7, 9.2, 4.2 Hz, $CH_2C\mathbf{H}C=O$), 2.40 (1H, ddd, $J$ = 9.2, 8.4, 6.6 Hz, $CHC\mathbf{H}CHO$), 2.10 (1H, dddd, $J$ = 13.4, 9.7, 8.8, 3.9 Hz, $CH_2C\mathbf{H_2}CHC=O$), 2.00–1.90 (2H, m, $CH_2C\mathbf{H_2}CHC=O$ and $CH_2C\mathbf{H}(Me)CH$), 1.90–1.82 (1H, m, $CH_2C\mathbf{H_2}CH(Me)$), 1.31 (1H, dddd, $J$ = 17.7, 12.3, 8.6, 8.6 Hz, $CH_2C\mathbf{H_2}CH(Me)$), 1.01 (3H, d, $J$ = 6.5 Hz, $CHC\mathbf{H_3}$); $\delta_C$ (125 MHz, $CDCl_3$) 180.5 (**C**=O), 132.7 ($CH\mathbf{C}H=CH_2$), 117.9 ($CH=\mathbf{C}H_ZH_E$), 81.0 ($CH\mathbf{C}H(CH=)O$), 52.0 ($CH\mathbf{C}HCHO$), 46.9 ($CH_2\mathbf{C}HC=O$), 35.4 ($CH_2\mathbf{C}H_2CH(Me)$), 34.9 ($CH_2\mathbf{C}H(Me)CH$), 27.3 ($\mathbf{C}H_2CHC=O$), 19.5 ($CH\mathbf{C}H_3$); LRMS $m/z$ ($ESI^+$) 189 ($[M+Na]^+$, 100%); HRMS $m/z$ ($ESI^+$) found 189.0883, $C_{10}H_{14}NaO_2$ requires 189.0886; $\nu_{max}$ (film)/$cm^{-1}$ 3088 (w, $=CH_2$), 2957 (m, CH), 2931 (m,

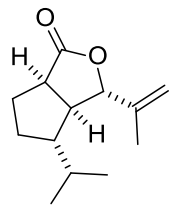
CH), 2873 (m, CH), 1762 (s, C=O), 1647 (w, C=C), 1461 (m), 1379 (m), 1325 (m), 1272 (m), 1183 (m, C-O), 1110 (m), 985 (m), 948 (m, $C=CH_2$).

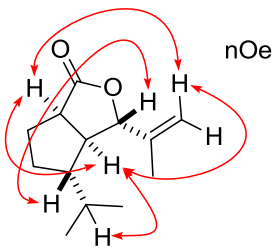
***(3aS*,6aR*)-4-Isopropyl-3-(prop-1-en-2-yl)hexahydro-1H-cyclopenta[c]furan-1-one (352c)***



To a stirred solution of (3a*R**,6a*S**)-methyl 6-isopropyl-3-oxo-1-(prop-1-en-2-yl)hexahydro-1*H*-cyclopenta[*d*]furan-3a-carboxylate (**351h**) (450 mg, 1.69 mmol, 1.0 eq.) in anhydrous DMF (8.45 mL) was added water (60.9 mg, 3.38 mmol, 2.0 eq.) and lithium chloride (143 mg, 3.38 mmol, 2.0 eq.). The resulting mixture was heated at 150 °C for 3 h then cooled to room temperature. Sat. aq. $NH_4Cl$ solution (20 mL) was added to the mixture and extracted with EtOAc (3 × 10 mL). The combined organic extracts were sequentially washed with water (40 mL), brine (40 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10-15% gradient EtOAc/petrol 40-60) to afford (3a*S**,6a*R**)-4-isopropyl-3-(prop-1-en-2-yl)hexahydro-1*H*-cyclopenta[*d*]furan-1-one (**352c**, diastereomeric ratio = 17.1:2.8:1.0) as a colourless oil (307 mg, 1.45 mmol, 87%). Characterisation is reported for the two major epimers as separated by flash column chromatography.

***(3S*,3aS*,4S*,6aR*)-4-Isopropyl-3-(prop-1-en-2-yl)hexahydro-1H-cyclopenta[c]furan-1-one***

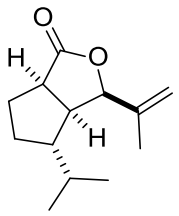


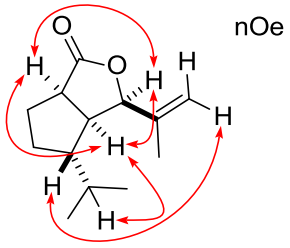



Major epimer (256 mg, 1.22 mmol, 72%): $R_f$ = 0.28 (15% EtOAc/petrol 40-60); $\delta_H$ (500 MHz, $CDCl_3$) 5.01 (1H, s, C=C**H**$_2$), 4.92 (1H, s, C=C**H**$_2$), 4.64 (1H, d, *J* = 2.7 Hz, CHC**H**(C=)O), 3.06 (1H, ddd, *J* = 9.8, 9.7, 5.0 Hz, $CH_2$C**H**C=O), 2.41 (1H, ddd, *J* = 9.7, 7.2, 2.7 Hz, CHC**H**CHO),

2.17–2.07 (1H, m, $CH_2C\mathbf{H}_2CHC{=}O$), 1.95–1.83 (2H, m, $CH_2C\mathbf{H}_2CHC{=}O$ and $CH_2C\mathbf{H}_2CH(i\text{-Pr})$), 1.77 (3H, s, $C(=CH_2)C\mathbf{H}_3$), 1.70–1.62 (1H, m, $CH_2C\mathbf{H}(i\text{-Pr})CH$), 1.62–1.54 (1H, m, $CHC\mathbf{H}(CH_3)_2$), 1.52–1.42 (1H, m, $CH_2C\mathbf{H}_2CH(i\text{-Pr})$), 0.97 (3H, d, $J$ = 6.6, Hz, $CH(C\mathbf{H}_3)_2$), 0.92 (3H, d, $J$ = 6.6, Hz, $CH(C\mathbf{H}_3)_2$); $\delta_C$ (125 MHz, $CDCl_3$) 181.1 (**C**=O), 143.1 (**C**=$CH_2$), 113.2 (C=**C**$H_2$), 88.0 (CH**C**H(C=)O), 54.2 ($CH_2$**C**H(*i*-Pr)CH), 49.4 (CH**C**HCHO), 45.1 ($CH_2$**C**HC=O), 31.6 (CH**C**H$(CH_3)_2$), 30.5 ($CH_2$**C**$H_2$CH(*i*-Pr)), 29.0 (**C**$H_2$CHC=O), 22.2 (CH(**C**$H_3)_2$), 20.6 (CH(**C**$H_3)_2$), 18.0 (C(=$CH_2$)**C**$H_3$); LRMS $m/z$ ($ESI^+$) 231 ($[M+Na]^+$, 100%), 439 ($[2M+Na]^+$, 45%); HRMS $m/z$ ($ESI^+$) found 231.1354 $C_{13}H_{20}NaO_2$ requires 231.1356; $\nu_{max}$ (film)/$cm^{-1}$ 3082 (w, =$CH_2$), 2959 (m, CH), 2872 (m, CH), 1768 (s, C=O), 1654 (w, C=C), 1466 (m), 1450 (m), 1369 (m), 1300 (m), 1255 (m), 1162 (m, C-O), 1105 (m), 903 (m, C=$CH_2$).

***(3R*,3aS*,4S*,6aR*)-4-Isopropyl-3-(prop-1-en-2-yl)hexahydro-1H-cyclopenta[c]furan-1-one***

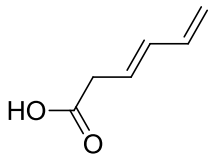



Minor epimer (51.0 mg, 0.24 mmol, 14%): $R_f$ = 0.19 (15% EtOAc/petrol 40-60); $\delta_H$ (500 MHz, $CDCl_3$) 5.14 (1H, s, C=C**H**$_2$), 5.01 (1H, s, C=C**H**$_2$), 4.93 (1H, d, $J$ = 6.5 Hz, CHC**H**(C=)O), 3.14 (1H, ddd, $J$ = 8.6, 8.4, 2.4 Hz, $CH_2$C**H**C=O), 2.74 (1H, ddd, $J$ = 8.4, 6.5, 6.0 Hz, CHC**H**CHO), 2.06 (1H, dddd, $J$ = 13.1, 7.3, 4.5, 2.4 Hz, $CH_2C\mathbf{H}_2CHC{=}O$), 1.89 (1H, dddd, $J$ = 17.7, 13.1, 8.9, 8.6 Hz, $CH_2C\mathbf{H}_2CHC{=}O$), 1.81 (1H, dddd, $J$ = 11.3, 8.0, 6.0, 5.6 Hz, $CH_2C\mathbf{H}(i\text{-Pr})CH$), 1.76 (3H, s, $C(=CH_2)C\mathbf{H}_3$), 1.62–1.46 (3H, m, $CHC\mathbf{H}(CH_3)_2$ and $CH_2C\mathbf{H}_2CH(i\text{-Pr})$), 0.89 (3H, d, $J$ = 6.8, Hz, $CH(C\mathbf{H}_3)_2$), 0.83 (3H, d, $J$ = 6.8, Hz, $CH(C\mathbf{H}_3)_2$); $\delta_C$ (125 MHz, $CDCl_3$) 180.4 (**C**=O), 139.3 (**C**=$CH_2$), 111.5 (C=**C**$H_2$), 82.9 (CH**C**H(C=)O), 47.4 ($CH_2$**C**HC=O), 46.3 (CH**C**HCHO), 45.5 ($CH_2$**C**H(*i*-Pr)CH), 29.9 (CH**C**H$(CH_3)_2$), 28.4 (**C**$H_2$CHC=O), 26.6 ($CH_2$**C**$H_2$CH(*i*-Pr)), 22.1

($CH(\mathbf{C}H_3)_2$), 19.7 ($C(=CH_2)\mathbf{C}H_3$), 17.5 ($CH(\mathbf{C}H_3)_2$); LRMS *m*/*z* ($ESI^+$) 231 ($[M+Na]^+$, 100%); HRMS *m*/*z* ($ESI^+$) found 231.1356 $C_{13}H_{20}NaO_2$ requires 231.1356; $\nu_{max}$ (film)/$cm^{-1}$ 2961 (m, CH), 2875 (m, CH), 1763 (s, C=O), 1657 (w, C=C), 1466 (m), 1450 (m), 1370 (m), 1242 (m), 1179 (m, C-O), 904 (m, $C=CH_2$).

**(*E*)-Hexa-3,5-dienoic acid (359)**

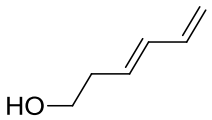



Prepared according to the procedure reported by Giguere *et al.*[148] To a stirred solution of diisopropylamine (2.02 g, 20.0 mmol) in anhydrous THF (20.0 mL) cooled to -10 °C in a dry ice/acetone bath was added dropwise a 2.5 M solution of *n*-BuLi in hexane (8.00 mL, 20.0 mmol). The resulting mixture was stirred at -10 °C for 30 min after which a solution of sorbic acid (**358**) (998 mg, 8.90 mmol) in anhydrous THF (2.00 mL) was added dropwise *via* cannula. After complete addition, the mixture was warmed to room temperature and stirred for 1 h. After this time the mixture was cooled to 0 °C in an ice/water bath, quenched with 3 M HCl (30 mL) and extracted with $Et_2O$ (3 × 30 mL). The combined organic extracts were washed with brine (100 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by short path fractional distillation under reduced pressure (1.50 mmHg) heating at 110°C to afford (*E*)-hexa-3,5-dienoic acid (**359**) as a colourless oil (695 mg, 6.19 mmol, 70%). $R_f$ = 0.27 (50% EtOAc/petrol 40-60); *b.p.* 79–81 °C at 1.50 mmHg; $\delta_H$ (400 MHz, $CDCl_3$) 11.70 (1H, s, $\mathbf{H}OC(=O)CH_2$), 6.35 (1H, dt, *J* = 16.8, 10.2 Hz, $=CHC\mathbf{H}=CH_ZH_E$), 6.22–6.14 (1H, m, $CH=C\mathbf{H}CH=C$), 5.78 (1H, dtd, *J* = 15.1, 7.2, 0.4 Hz, $CH_2C\mathbf{H}=CHC$), 5.20 (1H, dd, *J* = 16.8, 0.4 Hz, $CHCH=CH_Z\mathbf{H_E}$), 5.10 (1H, dd, *J* = 10.2, 0.4 Hz, $CHCH=C\mathbf{H_Z}H_E$), 3.18 (2H, dd, *J* = 7.2, 1.1 Hz, $HO_2CC\mathbf{H_2}CH=$); $\delta_C$ (100 MHz, $CDCl_3$) 178.3 ($HO\mathbf{C}(=O)CH_2$), 136.1 ($=CH\mathbf{C}H=CH_ZH_E$), 134.9 ($CH=\mathbf{C}HCH=C$), 124.5 ($CH_2\mathbf{C}H=CHC$), 117.4 ($CHCH=\mathbf{C}H_ZH_E$), 37.6 ($HO_2CC\mathbf{H_2}CH=$); HRMS *m*/*z* ($FI^+$) found

112.0524 $C_6H_8O_2$ requires 112.0524; $\nu_{max}$ (film)/$cm^{-1}$ 3023 (br, OH and CH), 1704 (s, C=O), 1652 (m, C=C), 1602 (m, C=C), 1002 (s, CH=$CH_2$), 952 (m, C=$CH_2$), 903 (s, C=$CH_2$).

Data are consistent with literature values.[148]

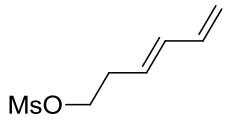
**(*E*)-Hexa-3,5-dien-1-ol (360)**




To a stirred suspension of $LiAlH_4$ (188 mg, 4.95 mmol, 1.0 eq.) in dry $Et_2O$ (15.0 mL) cooled to 0 °C in an ice/water bath was added dropwise a solution of (*E*)-hexa-3,5-dienoic acid (**359**) (555 mg, 4.95 mmol, 1.0 eq.) in dry $Et_2O$ (1.50 mL). After complete addition, the mixture was warmed to room temperature and stirred for 30 min. Water (0.19 mL) was carefully added dropwise to the mixture followed by 10% aq. NaOH solution (0.19 mL) and stirred for 5 min. Additional water (0.38 mL) was added, after which the mixture was dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by short path fractional distillation under reduced pressure (19.0 mmHg) heating at 105°C to afford (*E*)-hexa-3,5-dien-1-ol (**360**) as a colourless oil (340 mg, 3.43 mmol, 70%). $R_f$ = 0.28 (30% EtOAc/petrol 40-60); *b.p.* 72–74 °C at 19.0 mmHg; $\delta_H$ (400 MHz, $CDCl_3$) 6.31 (1H, dt, *J* = 16.9, 10.1 Hz, =CHC**H**=$CH_ZH_E$), 6.18–6.10 (1H, m, CH=C**H**CH=C), 5.67 (1H, dt, *J* = 15.2, 7.2 Hz, $CH_2$C**H**=CHC), 5.13 (1H, dd, *J* = 16.9, 0.5 Hz, CHCH=$CH_Z$**H**$_E$), 5.10 (1H, dd, *J* = 10.1, 0.5 Hz, CHCH=C**H**$_Z$$H_E$), 3.66 (2H, t, *J* = 6.4 Hz, HOC**H**$_2$$CH_2$), 3.34 (2H, dtd, *J* = 7.2, 6.4, 1.0 Hz, HO$CH_2$C**H**$_2$CH=), 2.06 (1H, s, **H**O$CH_2$); $\delta_C$ (100 MHz, $CDCl_3$) 136.8 (=CH**C**H=$CH_ZH_E$), 133.6 (CH=**C**HCH=C), 130.6 ($CH_2$**C**H=CHC), 115.9 (CHCH=**C**$H_ZH_E$), 61.8 (HO**C**$H_2CH_2$), 35.9 (HO$CH_2$**C**$H_2$CH=); HRMS *m*/*z* ($FI^+$) found 98.0732 $C_6H_{10}O$ requires 98.0732; $\nu_{max}$ (film)/$cm^{-1}$ 3346 (br, OH), 3087 (w, =$CH_2$), 3038 (w, =CH), 3011 (w, =CH), 2932 (CH), 2881 (CH), 1652 (m, C=C), 1603 (m, C=C), 1043 (s, $CH_2$-OH), 1002 (s, CH=$CH_2$), 952 (m, C=$CH_2$), 904 (s, C=$CH_2$).

Data are consistent with literature values.[222]

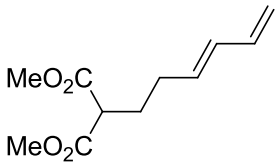
**(*E*)-Hexa-3,5-dien-1-yl methanesulfonate (361)**




To a stirred solution of (*E*)-hexa-3,5-dien-1-ol (**360**) (236 mg, 2.40 mmol, 1.0 eq.) in anhydrous DCM (8.00 mL) cooled to 0 °C in an ice/water bath was added triethylamine (365 mg, 3.61 mmol, 1.5 eq.) followed by dropwise addition of methanesulfonyl chloride (304 mg, 2.65 mmol, 1.1 eq.). After complete addition the mixture was warmed to room temperature and stirred for 1.5 h. The mixture was poured over 1M HCl (10 mL), the organic layer separated and the aqueous layer was further extracted with DCM (2 × 5 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (30 mL), brine (30 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (60% $Et_2O$/petrol 30-40) to afford (*E*)-hexa-3,5-dien-1-yl methanesulfonate (**361**) as a colourless oil (381 mg, 2.16 mmol, 90%). $R_f$ = 0.30 (30% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 6.31 (1H, dt, $J$ = 16.8, 10.2 Hz, =CHC**H**=$CH_ZH_E$), 6.21–6.12 (1H, m, CH=C**H**CH=C), 5.64 (1H, dt, $J$ = 15.2, 7.3 Hz, $CH_2$C**H**=CHC), 5.17 (1H, dd, $J$ = 16.8, 1.0 Hz, CHCH=$CH_Z$**H**$_E$), 5.10 (1H, dd, $J$ = 10.2, 1.0 Hz, CHCH=C**H**$_Z$$H_E$), 3.66 (2H, t, $J$ = 6.7 Hz, MsOC**H**$_2$$CH_2$), 3.00 (3H, s, $SO_2$C**H**$_3$), 2.57–2.50 (2H, m, MsOCH$_2$C**H**$_2$CH=); $\delta_C$ (100 MHz, $CDCl_3$) 136.6 (=CH**C**H=$CH_ZH_E$), 134.5 (CH=**C**HCH=C), 127.8 ($CH_2$**C**H=CHC), 116.9 (CHCH=**C**$H_ZH_E$), 68.9 (MsO**C**$H_2CH_2$), 37.5 ($SO_2$**C**$H_3$), 32.3 (HOCH$_2$**C**$H_2$CH=); LRMS $m/z$ (ESI$^+$) 199 ([M+Na]$^+$, 100%); HRMS $m/z$ (ESI$^+$) found 199.0400 $C_7H_{12}NaO_3S$ requires 199.0399; $\nu_{max}$ (film)/cm$^{-1}$ 3089 (w, =$CH_2$), 3018 (w, =CH), 2975 (CH), 2903 (CH), 1654 (m, C=C), 1604 (m, C=C), 1356 (s, $SO_2$), 1175 (s, $SO_2$) 1042 (s, $CH_2$-OH), 1005 (s, CH=$CH_2$), 955 (m, C=$CH_2$), 905 (s, C=$CH_2$).

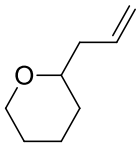
Data are consistent with literature values.[223]

***(E)-Dimethyl 2-(hexa-3,5-dien-1-yl)malonate (362)***




To a stirred suspension of hexane washed NaH (137 mg, 5.72 mmol, 3.0 eq.) in anhydrous DMF (4.78 mL) cooled to 0 °C in an ice/water bath, was carefully added dropwise dimethyl malonate (756 mg, 5.72 mmol, 3.0 eq.). The resulting mixture was stirred for 20 min at this temperature, after which a solution of (*E*)-hexa-3,5-dien-1-yl methanesulfonate (**361**) (336 mg, 1.91 mmol, 1.0 eq.) in anhydrous THF (4.78 mL) was added *via* cannula followed by potassium iodide (159 mg, 0.955 mmol, 0.5 eq.). The mixture was warmed to room temperature, and then heated at 80 °C for 14 h. The mixture was cooled to room temperature, after which sat. aq. $NH_4Cl$ solution (10 mL) was added and extracted with $Et_2O$ (3 × 10 mL). The combined organic extracts were sequentially washed with water (30 mL), brine (30 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% $Et_2O$/petrol 30-40) to afford (*E*)-dimethyl 2-(hexa-3,5-dien-1-yl)malonate (362) as a colourless oil (334 mg, 1.57 mmol, 82%). $R_f$ = 0.30 (20% $Et_2O$/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 6.28 (1H, dt, *J* = 17.0, 10.2 Hz, =CHC**H**=$CH_2$), 6.06 (1H, dd, *J* = 15.2, 10.2 Hz, CH=C**H**CH=), 5.65 (1H, dt, *J* = 15.2, 7.4 Hz, $CH_2$C**H**=CH), 5.11 (1H, d, *J* = 17.0 Hz, CH=$CH_Z$**H**$_E$), 4.99 (1H, d, *J* = 10.2 Hz, CH=C**H**$_Z$$H_E$), 3.73 (6H, s, OC**H**$_3$), 3.38 (1H, t, *J* = 7.3 Hz, $(MeO_2C)_2$C**H**$CH_2$), 2.13 (2H, dt, *J* = 7.3, 7.2 Hz, CHC**H**$_2$$CH_2$), 2.02 (2H, dt, *J* = 7.4, 7.2 Hz, $CH_2$C**H**$_2$CH=); $\delta_C$ (100 MHz, $CDCl_3$) 169.7 (2C, C=O), 136.8 (=CH**C**H=$CH_2$), 132.6 ($CH_2$**C**H=CH), 132.3 (CH=**C**HCH=), 115.7 (CH=**C**$H_Z$$H_E$), 52.5 (2C, O**C**$H_3$), 50.9 ($(MeO_2C)_2$**C**H$CH_2$), 30.1 (CH**C**$H_2$$CH_2$), 28.2 ($CH_2$**C**$H_2$CH=); LRMS *m*/*z* (ESI$^+$) 235 ([M+Na]$^+$, 100%); *m*/*z* (ESI$^+$) found 235.0940, $C_{11}H_{16}NaO_4$ requires 235.0941; $\nu_{max}$ (film)/cm$^{-1}$ 3007 (m, CH), 2955 (m, CH), 2847 (m, CH), 1732 (s C=O), 1653 (w, C=C), 1603 (w, C=C), 1156 (s, C-O), 1005 (m, CH=$CH_2$), 953 (m, C=$CH_2$), 905 (m, C=$CH_2$).

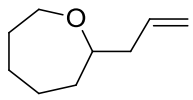
**2-Allyltetrahydro-2*H*-pyran (364a)**



To a stirred solution of trimethylsilyl trifluoromethanesulfonate (113 mg, 0.50 mmol) and allyltrimethylsilane (628 mg, 5.50 mmol), in dry DCM (0.50 mL) cooled to -50 °C in an acetone/dry ice bath, was added dropwise *via* cannula a solution 2-methoxytetrahydropyran (581 mg, 5.00 mmol) in dry DCM (2.00 mL). The resulting mixture was kept at -50 °C for 15 min and then warmed to -40 °C. After 2 h at -40 °C the mixture was further warmed to 0 °C and stirred for 1 h. The mixture was pored over sat. aq. $NaHCO_3$ solution (10 mL) and then extracted with $Et_2O$ (3 × 10 mL). The combined organic extracts were sequentially washed with brine (10 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (5% $Et_2O$/petrol 30-40) to afford 2-allyltetrahydro-2*H*-pyran (**364a**) as a colourless oil (631 mg, 4.20 mmol, 84%). $R_f$ = 0.30 (5% $Et_2O$/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 5.82 (1H, ddt, *J* = 17.2, 10.2, 7.0 Hz, $CH_2C\mathbf{H}=CH_2$), 5.10–5.04 (1H, m, $CH=CH_Z\mathbf{H_E}$), 5.05–5.01 (1H, m, $CH=C\mathbf{H_Z}H_E$), 4.00–3.94 (1H, m, $OC\mathbf{H_2}CH_2$), 3.41 (1H, dt, *J* = 11.6, 11.5, 2.6 Hz, $OC\mathbf{H_2}CH_2$), 3.35–3.27 (1H, m, $CHC\mathbf{H}(CH_2C=)O$), 2.31–2.23 (1H, m, $CHC\mathbf{H_2}CH=$), 2.21–2.12 (1H, m, $CHC\mathbf{H_2}CH=$), 1.85–1.78 (1H, m, $CH_2C\mathbf{H_2}CH_2CH$), 1.64–1.40 (4H, m, $CH_2C\mathbf{H_2}CH$, $OCH_2C\mathbf{H_2}CH_2$ and $CH_2C\mathbf{H_2}CH_2CH$), 1.32–1.20(1H, m, $CH_2C\mathbf{H_2}CH$); $\delta_C$ (100 MHz, $CDCl_3$) 135.1 ($CH_2\mathbf{C}H=CH_2$), 116.5 ($CH=\mathbf{C}H_ZH_E$), 77.3 ($CH\mathbf{C}H(CH_2C=)O$), 68.6 ($O\mathbf{C}H_2CH_2$), 41.1 ($CHC\mathbf{H_2}CH=$), 31.4 ($CH_2\mathbf{C}H_2CH$), 26.0 ($OCH_2\mathbf{C}H_2CH_2$), 23.5 ($CH_2\mathbf{C}H_2CH_2CH$); HRMS *m*/*z* ($FI^+$) found 126.1045, $C_8H_{14}O$ requires 126.1045; $\nu_{max}$ (film)/$cm^{-1}$ 2939 (m, CH), 2849 (m, CH), 1642 (w, C=C), 1088 (m, C-O), 1048 (m), 904 (s, $CH=CH_2$).

No spectral data reported in the literature.[224]

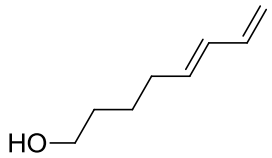
**2-Allyloxepane (364b)**



To a stirred solution of ε-caprolactone (**363b**) (1.11 g, 10.0 mmol, 1.0 eq.), triethylsilane (1.28 g, 11.0 mmol, 1.1 eq,) and allyltrimethylsilane (2.29 g, 20.0 mmol, 2.0 eq.) in anhydrous toluene (30.0 ml) heated to 70 °C, was added in one portion indium(III) bromide (355 mg, 1.00 mmol, 0.1 eq.). The resulting mixture was heated at 70 °C for 2 h, and then cooled to room temperature. The mixture was filtered through a silica plug eluting with petrol 30–40 (100 mL) followed by 10% $Et_2O$/petrol 30-40 (200 mL). The filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography (5% $Et_2O$/petrol 30–40) to afford 2-allyloxepane (**364b**) as a colourless oil (1.15 g, 8.20 mmol, 82%). $R_f$ = 0.32 (5% $Et_2O$/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 5.84 (1H ddt, $J$ = 17.2, 10.1, 7.0 Hz, $CH_2C\mathbf{H}=CH_2$), 5.10–5.03 (1H, m, $CH=CH_Z\mathbf{H_E}$), 5.05–5.00 (1H, m, $CH=C\mathbf{H_Z}H_E$), 3.90–3.82 (1H, m, $OC\mathbf{H_2}CH_2$), 3.57–3.48 (2H, m, $OC\mathbf{H_2}CH_2$ and $CHC\mathbf{H}(CH_2C=)O$), 2.33–2.24 (1H, m, $CHC\mathbf{H_2}CH=$), 2.20–2.11 (1H, m, $CHC\mathbf{H_2}CH=$), 1.83–1.56 (6H, m, $OCH_2C\mathbf{H_2}CH_2$, $CH_2C\mathbf{H_2}CH$, $CH_2C\mathbf{H_2}CH_2CH$, and $OCH_2CH_2C\mathbf{H_2}CH_2$), 1.56–1.43 (2H, m, $OCH_2C\mathbf{H_2}CH_2$ and $OCH_2CH_2C\mathbf{H_2}CH_2$); $\delta_C$ (100 MHz, $CDCl_3$) 135.8 ($CH_2\mathbf{C}H=CH_2$), 116.2 ($CH=\mathbf{C}H_ZH_E$), 79.2 ($CH\mathbf{C}H(CH_2C=)O$), 68.6 ($O\mathbf{C}H_2CH_2$), 41.3 ($CH\mathbf{C}H_2CH=$), 35.4 ($OCH_2\mathbf{C}H_2CH_2$), 30.9 ($CH_2\mathbf{C}H_2CH$), 26.7 ($CH_2\mathbf{C}H_2CH_2CH$), 25.7 ($OCH_2CH_2\mathbf{C}H_2CH_2$); HRMS $m/z$ ($FI^+$) found 140.1202, $C_9H_{16}O$ requires 140.1201; $\nu_{max}$ (film)/$cm^{-1}$ 2930 (m, CH), 2857 (w, CH), 1108 (m, C-O-C), 955 (w, $C=CH_2$), 906 (s, $C=CH_2$), 728 (s).

Data are consistent with literature values.[225]

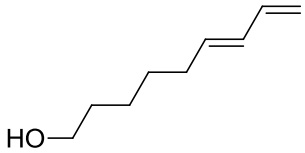
**(*E*)-Octa-5,7-dien-1-ol (365a)**




To a vigorously stirred 2.5 M solution of *n*-BuLi in hexane (1.52 mL, 3.80 mmol, 1.0 eq.) cooled to -70 °C in an acetone/dry ice bath was added dropwise a suspension of potassium *tert*-butoxide (43 mg, 0.380 mmol, 0.1 eq.), diisopropylamine (384 mg, 3.80 mmol, 1.0 eq.) and 2-allyltetrahydro-2*H*-pyran (**364a**) (480 mg, 3.80 mmol, 1.0 eq.) in anhydrous THF (1.50 mL). After complete addition the mixture was slowly warmed to -50 °C and stirred at this temp for 4 h. The mixture was then slowly warmed to room temperature. Water (10 mL) was added to the mixture and extracted with $Et_2O$ (3× 10 mL). The combined organic extracts were sequentially washed with brine (30 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% $Et_2O$/petrol 30–40) to afford (*E*)-octa-5,7-dien-1-ol (**365a**) (trans :cis = 16:1) as a colourless oil (407 mg, 3.23 mmol, 85%). $R_f$ = 0.24 (50% $Et_2O$/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 6.31 (1H, dt, *J* = 16.9, 10.2 Hz, =CHC**H**=$CH_2$), 6.06 (1H, dd, *J* = 15.2, 10.2 Hz, CH=C**H**CH=), 5.70 (1H, dt, *J* = 15.2, 7.2 Hz, $CH_2$C**H**=CH), 5.09 (1H, d, *J* = 16.9 Hz, CH=$CH_Z$**H**$_E$), 4.96 (1H, d, *J* = 10.2 Hz, CH=C**H**$_Z$$H_E$), 3.64 (2H, t, *J* = 6.2 Hz, HOC**H**$_2$$CH_2$), 2.12 (2H, dt, *J* = 7.2, 7.1 Hz, $CH_2$C**H**$_2$CH=), 1.61–1.55 (3H, m, $OCH_2$C**H**$_2$$CH_2$ and **H**$OCH_2$), 1.52–1.45 (2H, m, $CH_2$C**H**$_2$$CH_2$CH=); $\delta_C$ (100 MHz, $CDCl_3$) 137.2 (=CH**C**H=$CH_2$), 134.9 ($CH_2$**C**H=CH), 131.2 (CH=**C**HCH=), 114.9 (CH=**C**$H_Z$$H_E$), 62.7 (HO**C**$H_2$$CH_2$), 32.2 ($CH_2$**C**$H_2$CH=), 32.2 ($OCH_2$**C**$H_2$$CH_2$), 25.3 ($CH_2$**C**$H_2$$CH_2$CH=); HRMS *m*/*z* ($FI^+$) found 126.1049, $C_8H_{14}O$ requires 126.1045; $\nu_{max}$ (film)/$cm^{-1}$ 3337 (br, OH), 3086 (w, =$CH_2$), 2933 (s, CH), 2861 (m, CH), 1652 (m, C=C), 1602 (m, C=C), 1059 (m, C-O), 1002 (s, CH=$CH_2$), 950 (m, C=$CH_2$), 896 (s, C=$CH_2$).

Data are consistent with literature values.[226]

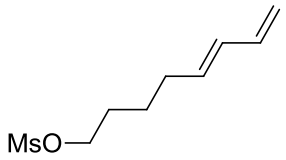
**(*E*)-Nona-6,8-dien-1-ol (365b)**




To a vigorously stirred suspension of potassium *tert*-butoxide (58.3 mg, 0.520 mmol, 0.1 eq.) in a 2.5 M solution of n-BuLi in hexane (2.50 mL, 6.25 mmol, 1.2 eq.) cooled to -78 °C in a dry ice/acetone bath was added dropwise a solution of diisopropylamine (526 mg, 5.20 mmol, 1.0 eq.) and 2-allyloxepane (**364b**) (750 mg, 5.20 mmol, 1.0 eq.) in anhydrous THF (7.90 mL). After complete condition the mixture was warmed to -50 °C and stirred for 1 h at this temperature. Sat. aq. $NH_4Cl$ solution (10 mL) was added to the mixture and extracted with $Et_2O$ (3 × 5 mL). The combined organic layers were washed sequentially with brine (15 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% $Et_2O$/petrol 30–40) to afford (*E*)-nona-6,8-dien-1-ol (**365b**) (trans :cis = 17:1) as a colourless oil (614 mg, 4.37 mmol, 84%). $R_f$ = 0.23 (50% $Et_2O$/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 6.30 (1H, dt, *J* = 16.9, 10.2, Hz, CHC**H**=$CH_2$), 6.04 (1H, dd, *J* = 15.0, 10.2 Hz, CH=C**H**CH=), 5.70 (1H, dt, *J* = 15.0, 7.0 Hz, $CH_2$C**H**=CH), 5.08 (1H, dd, *J* = 16.9, 0.5 Hz, CH=$CH_Z$**H**$_E$), 4.95 (1H, dd, *J* = 10.2, 0.5 Hz, CH=C**H**$_Z$$H_E$), 3.62 (2H, t, *J* = 6.5 Hz, HOC**H**$_2$$CH_2$), 2.09 (2H, dt, *J* = 7.0, 6.8 Hz, $CH_2$C**H**$_2$CH=), 1.76 (1H, s, **H**O$CH_2$), 1.61–1.52 (2H, m, O$CH_2$C**H**$_2$$CH_2$), 1.46–1.31 (4H, m, O$CH_2CH_2$C**H**$_2$$CH_2$ and $CH_2$C**H**$_2$$CH_2$CH=); $\delta_C$ (100 MHz, $CDCl_3$) 137.3 (CH**C**H=$CH_2$), 135.2 ($CH_2$**C**H=CH), 131.1 (CH=**C**HCH=), 114.7 (CH=**C**$H_Z$$H_E$), 62.7 (HO**C**$H_2$$CH_2$), 32.6 (O$CH_2$**C**$H_2$$CH_2$), 32.4 ($CH_2$**C**$H_2$CH=), 28.9 ($CH_2$**C**$H_2$$CH_2$CH=), 25.3 (O$CH_2CH_2$**C**$H_2$$CH_2$); HRMS *m*/*z* ($FI^+$) found 140.1205, $C_9H_{16}O$ requires 140.1201; $\nu_{max}$ (film)/$cm^{-1}$ 3359 (br, OH), 2932 (m, CH), 2858 (m, CH), 1652 (w, C=C), 1602 (w, C=C), 1052 (m, C-O), 1004 (m, $CH=CH_2$), 950 (m, $C=CH_2$), 905 (s, $C=CH_2$), 729 (s).

Data are consistent with literature values.[227]

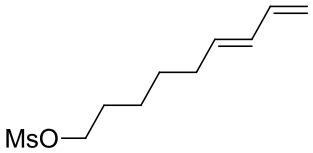
**(*E*)-Octa-5,7-dien-1-yl methanesulfonate (366a)**




To a stirred solution of (*E*)-octa-5,7-dien-1-ol (**365a**) (360 mg, 2.85 mmol, 1.0 eq.) in anhydrous DCM (9.50 mL) cooled to 0 °C in an ice/water bath was added triethylamine (433 mg, 4.28 mmol, 1.5 eq.) followed by dropwise addition of methanesulfonyl chloride (359 mg, 3.13 mmol, 1.1 eq.). After complete addition the mixture was warmed to room temperature and stirred for 1.5 h. The mixture was poured over 1 M HCl (10 mL), the organic layer separated and the aqueous layer was further extracted with DCM (2 × 10 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (30 mL), brine (30 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% $Et_2O$/petrol 30–40) to afford (*E*)-octa-5,7-dien-1-yl methanesulfonate (**366a**) (trans :cis = 16:1) as a colourless oil (542 mg, 2.40 mmol, 93%). $R_f$ = 0.27 (50% $Et_2O$/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 6.30 (1H, dt, *J* = 16.9, 10.2 Hz, =CHC**H**=$CH_2$), 6.06 (1H, dd, *J* = 15.2, 10.2 Hz, CH=C**H**CH=), 5.67 (1H, dt, *J* = 15.2, 7.2 Hz, $CH_2$C**H**=CH), 5.10 (1H, d, *J* = 16.9, Hz, CH=$CH_Z$**H**$_E$), 4.98 (1H, d, *J* = 10.2 Hz, CH=C**H**$_Z$$H_E$), 4.22 (2H, t, *J* = 6.6 Hz, MsOC**H**$_2$$CH_2$), 3.00 (3H, s, $SO_2$C**H**$_3$), 2.12 (2H, dt, *J* = 7.2, 7.1 Hz, $CH_2$C**H**$_2$CH=), 1.81–1.72 (2H, m, $OCH_2$C**H**$_2$$CH_2$), 1.57–1.48 (2H, m, $CH_2$C**H**$_2$$CH_2$CH=); $\delta_C$ (100 MHz, $CDCl_3$) 136.9 (=CH**C**H=$CH_2$), 133.9 ($CH_2$**C**H=CH), 131.7 (CH=**C**HCH=), 115.3 (CH=**C**$H_Z$$H_E$), 69.9 (MsO**C**$H_2$$CH_2$), 37.3 ($SO_2$**C**$H_3$), 31.7 ($CH_2$**C**$H_2$CH=), 28.5 ($CH_2$**C**$H_2$$CH_2$CH=), 24.9 ($OCH_2$**C**$H_2$$CH_2$); LRMS *m*/*z* ($ESI^+$) 227 ($[M+Na]^+$, 100%); HRMS *m*/*z* ($ESI^+$) found 227.0719 $C_9H_{16}NaO_3S$ requires 227.0712; $\nu_{max}$ (film)/$cm^{-1}$ 2940 (m, CH), 2861 (w, CH), 1651 (w, C=C), 1602 (w, C=C), 1352 (s, $SO_2$), 1173 (s, $SO_2$) 1059 (m, C-O), 1006 (m, CH=$CH_2$), 972 (m, C=$CH_2$), 907 (s, C=$CH_2$), 728 (s, S-O).

No spectral data reported in the literature.[228]

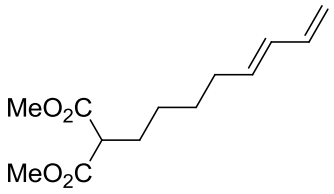
**(*E*)-Nona-6,8-dien-1-yl methanesulfonate (366b)**




To a stirred solution of (*E*)-nona-6,8-dien-1-ol (**365b**) (519 mg, 3.70 mmol, 1.0 eq.) in anhydrous DCM (12.3 mL) cooled to 0 °C in an ice/water bath was added triethylamine (562 mg, 5.55 mmol, 1.5 eq.) followed by dropwise addition of methanesulfonyl chloride (466 mg, 4.07 mmol, 1.1 eq.). After complete addition the mixture was warmed to room temperature and stirred for 1.5 h. The mixture was poured over 1 M HCl (10 mL), the organic layer separated and the aqueous layer was further extracted with DCM (2 × 10 mL). The combined organic extracts were washed sequentially with sat. aq. $NaHCO_3$ solution (30 mL), brine (30 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% $Et_2O$/petrol 30–40) to afford (*E*)-nona-6,8-dien-1-yl methanesulfonate (**366b**) (trans :cis = 17:1) as a colourless oil (743 mg, 3.40 mmol, 92%). $R_f$ = 0.32 (50% $Et_2O$/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 6.28 (1H, dt, *J* = 17.0, 10.2 Hz, CHC**H**=$CH_2$), 6.03 (1H, dd, *J* = 15.0, 10.2 Hz, CH=C**H**CH=), 5.67 (1H, dt, *J* = 15.0, 6.8 Hz, $CH_2$C**H**=CH), 5.08 (1H, dd, *J* = 17.0, 0.9 Hz, CH=$CH_Z$**H**$_E$), 4.95 (1H, dd, *J* = 10.2, 0.9 Hz, CH=C**H**$_Z$$H_E$), 4.20 (2H, t, *J* = 6.6 Hz, MsOC**H**$_2$$CH_2$), 2.98 (3H, s, $SO_2$C**H**$_3$), 2.08 (2H, dt, *J* = 6.8, 6.6 Hz, $CH_2$C**H**$_2$CH=), 1.79–1.70 (2H, m, $OCH_2$C**H**$_2$$CH_2$), 1.45–1.39 (4H, m, $OCH_2CH_2$C**H**$_2$$CH_2$ and $CH_2$C**H**$_2$$CH_2$CH=); $\delta_C$ (100 MHz, $CDCl_3$) 137.1 (CH**C**H=$CH_2$), 134.6 ($CH_2$**C**H=CH), 131.3 (CH=**C**HCH=), 115.0 (CH=**C**$H_2$$H_E$), 70.1 (MsO**C**$H_2$$CH_2$), 37.3 ($SO_2$**C**$H_3$), 32.2 ($CH_2$**C**$H_2$CH=), 28.9 ($CH_2$**C**$H_2$$CH_2$CH=), 28.5 ($OCH_2$**C**$H_2$$CH_2$), 24.9 ($OCH_2CH_2$**C**$H_2$$CH_2$); LRMS *m*/*z* (ESI$^+$) 241 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 241.0873, $C_{10}H_{18}NaO_3S$ requires 241.0869; $\nu_{max}$ (film)/cm$^{-1}$ 2939 (m, CH), 2860 (w, CH), 1651 (w, C=C), 1602 (w, C=C), 1353 (s, $SO_2$), 1174 (s, $SO_2$) 1060 (m, C-O), 1006 (m, CH=$CH_2$), 973 (m, C=$CH_2$), 906 (s, C=$CH_2$), 726 (s, S-O).

No spectral data reported in the literature.[229]

***(E)-Dimethyl 2-(octa-5,7-dien-1-yl)malonate (367a)***

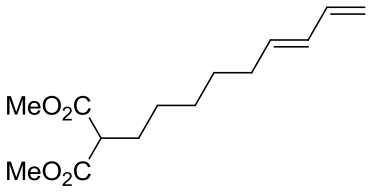



To a stirred suspension of hexane washed NaH (176 mg, 7.34 mmol, 3.0 eq.), in anhydrous DMF (6.13 mL) cooled to 0 °C in an ice/water bath, was carefully added dropwise dimethyl malonate (970 mg, 7.34 mmol, 3.0 eq.). The resultant mixture was stirred for 20 min at this temperature, after which a solution of (*E*)-octa-5,7-dien-1-yl methanesulfonate (**366a**) (500 mg, 2.45 mmol, 1.0 eq.) in anhydrous THF (6.13 mL) was added *via* cannula followed by potassium iodide (204 mg, 1.23 mmol). The mixture was warmed to room temperature, and then heated at 80 °C for 14 h. The mixture was cooled to room temperature, after which sat. aq. $NH_4Cl$ solution (10 mL) was added and extracted with $Et_2O$ (3 × 10 mL). The combined organic extracts were sequentially washed with water (30 mL), brine (30 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% $Et_2O$/petrol 30–40) to afford (*E*)-dimethyl 2-(octa-5,7-dien-1-yl)malonate (**367a**) (trans :cis = 16:1) as a colourless oil (541 mg, 2.25 mmol, 92%). $R_f$ = 0.31 (20% $Et_2O$/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 6.28 (1H, dt, *J* = 16.9, 10.2 Hz, =CHC**H**=$CH_2$), 6.03 (1H, dd, *J* = 15.2, 10.2 Hz, CH=C**H**CH=), 5.66 (1H, dt, *J* = 15.2, 7.2 Hz, $CH_2$C**H**=CH), 5.08 (1H, dd, *J* = 16.9, 1.1 Hz, CH=$CH_Z$**H**$_E$), 4.94 (1H, dd, *J* = 10.2, 1.1 Hz, CH=C**H**$_Z$$H_E$), 3.72 (6H, s, OC**H**$_3$), 3.35 (1H, t, *J* = 7.6 Hz, $(CO_2Me)_2$C**H**$CH_2$), 2.08 (2H, dt, *J* = 7.2, 7.0 Hz, $CH_2$C**H**$_2$CH=), 1.89 (2H, dt, *J* = 7.9, 7.6 Hz, CHC**H**$_2$$CH_2$), 1.47–1.37 (2H, m, $CH_2$C**H**$_2$$CH_2$CH=), 1.36–1.27 (2H, m, $CHCH_2$C**H**$_2$$CH_2$); $\delta_C$ (100 MHz, $CDCl_3$) 169.8 (2C, C=O), 137.1 (=CH**C**H=$CH_2$), 134.7 ($CH_2$**C**H=CH), 131.2 (CH=**C**HCH=), 114.8 (CH=**C**H$_Z$$H_E$), 52.4 (2C, O**C**H$_3$), 51.6 ($(CO_2Me)_2$**C**H$CH_2$), 32.1 ($CH_2$**C**$H_2$CH=), 28.6 (CH**C**$H_2$$CH_2$), 28.6 ($CH_2$**C**$H_2$$CH_2$CH=), 26.8 ($CHCH_2$**C**$H_2$$CH_2$); LRMS *m/z*

(ESI$^+$) 263 ([M+Na]$^+$, 100%); HRMS *m/z* (ESI$^+$) found 263.1250, $C_{13}H_{20}NaO_4$ requires 263.1254; $\nu_{max}$ (film)/cm$^{-1}$ 3086 (w, =$CH_2$), 3005 (m, CH), 2953 (m, CH), 2859 (m, CH), 1734 (s, C=O), 1652 (m, C=C), 1602 (m, C=C), 1053 (s, C-O), 1005 (s, CH=$CH_2$), 953 (m, C=$CH_2$), 899 (m, C=$CH_2$).

Data are consistent with literature values.[230]

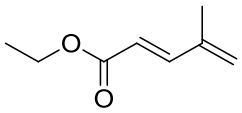
***(E)-Dimethyl 2-(nona-6,8-dien-1-yl)malonate (367b)***




To a stirred suspension of hexane washed NaH (221 mg, 9.23 mmol, 3.0 eq.), in anhydrous DMF (7.70 mL) cooled to 0 °C in an ice/water bath, was carefully added dropwise dimethyl malonate (1.21 g, 9.23 mmol, 3.0 eq.). The resultant mixture was stirred for 20 min at this temperature, after which a solution of (*E*)-nona-6,8-dien-1-yl methanesulfonate (**366b**) (671 mg, 3.08 mmol) in anhydrous THF (7.70 mL) was added *via* cannula followed by potassium iodide (256 mg, 1.54 mmol). The mixture was warmed to room temperature, and then heated at 80 °C for 14 h. The mixture was cooled to room temperature, after which sat. aq. $NH_4Cl$ solution (10 mL) was added and extracted with $Et_2O$ (3 × 10 mL). The combined organic extracts were washed sequentially with water (30 mL), brine (30 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% $Et_2O$/petrol 30–40) to afford (*E*)-dimethyl 2-(nona-6,8-dien-1-yl)malonate (**367b**) (trans :cis = 17:1) as a colourless oil (782 mg, 2.59 mmol, 84%). $R_f$ = 0.30 (20% $Et_2O$/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 6.28 (1H, dt, *J* = 17.0, 10.2 Hz, =CHC**H**=$CH_2$), 6.01 (1H, dd, *J* = 15.2, 10.2 Hz, CH=C**H**CH=), 5.66 (1H, dt, *J* = 15.2, 7.2 Hz, $CH_2$C**H**=CH), 5.06 (1H, d, *J* = 17.0 Hz, CH=$CH_Z$**H**$_E$), 4.93 (1H, d, *J* = 10.2, Hz, CH=C**H**$_Z$$H_E$), 3.72 (6H, s, OC**H**$_3$), 3.34 (1H, t, *J* = 7.4 Hz, $(CO_2Me)_2$C**H**$CH_2$), 2.05 (2H, dt, *J* = 7.2, 7.0 Hz, $CH_2$C**H**$_2$CH=), 1.91–1.84 (2H, m, CHC**H**$_2$$CH_2$), 1.42–1.25 (6H, m, $CHCH_2$C**H**$_2$$CH_2$, $CHCH_2CH_2$C**H**$_2$$CH_2$ and $CH_2$C**H**$_2$$CH_2$CH=);

$\delta_C$ (100 MHz, $CDCl_3$) 169.9 (2C, C=O), 137.2 (=CH**C**H=$CH_2$), 135.1 ($CH_2$**C**H=CH), 131.0 (CH=**C**HCH=), 114.7 (CH=**C**$H_Z H_E$), 52.4 (2C, O**C**$H_3$), 51.6 (($CO_2Me)_2$**C**H$CH_2$), 32.3 ($CH_2$**C**$H_2$CH=), 28.7 (CH**C**$H_2CH_2$), 28.7 ($CH_2$**C**$H_2CH_2$CH=), 28.6 (CH$CH_2CH_2$C**H$_2$**$CH_2$), 27.1 (CH$CH_2$**C**$H_2CH_2$); LRMS *m*/*z* ($ESI^+$) 277 ($[M+Na]^+$, 100%); HRMS *m*/*z* ($ESI^+$) found 277.1407, $C_{14}H_{22}NaO_4$ requires 277.1410; $\nu_{max}$ (film)/$cm^{-1}$ 2954 (m, CH), 2930 (m, CH), 2858 (m, CH), 1734 (s, C=O), 1651 (m, C=C), 1602 (m, C=C), 1257 (s, C-O), 1153 (s, C-O), 1005 (s, CH=$CH_2$), 952 (m, C=$CH_2$), 907 (s, C=$CH_2$).

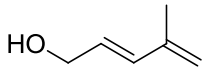
**(*E*)-Ethyl 4-methylpenta-2,4-dienoate (444)**



Prepared according to the procedure reported by Sundberg *et al.*[231] To a stirred solution of (carbethoxymethylene)triphenylphosphorane (27.9 g, 80.0 mmol, 1.0 eq.) in anhydrous DCM (300 mL) was added dropwise a solution of freshly distilled methacrolein (**443**) (5.61 g, 80.0 mmol, 1.0 eq.) in anhydrous DCM (20 mL). The resulting mixture was heated at 60 °C for 2 h, cooled to room temperature and then concentrated under reduced pressure. The residue was purified by fractional distillation under reduced pressure (20 mbar) heating at 100 °C to afford (*E*)-ethyl 4-methylpenta-2,4-dienoate (**444**) as a colourless oil (5.80 g, 41.4 mmol, 52%). $R_f$ = 0.62 (15% EtOAc/petrol 40–60); *b.p.* 74–76 °C at 20 mbar (lit.[231] 81–83 °C at 17 mmHg); $\delta_H$ (400 MHz, $CDCl_3$) 7.34 (1H, d, *J* = 15.8 Hz, CH=C**H**C), 5.85 (1H, d, *J* = 15.8 Hz, CC**H**=CH), 5.33 (1H, s, C=C**H$_2$**), 5.31 (1H, s, C=C**H$_2$**), 4.20 (2H, q, *J* = 7.1 Hz, $CH_3$C**H$_2$**O), 1.86 (3H, s, CC**H$_3$**), 1.28 (3H, t, *J* = 7.1 Hz, C**H$_3$**$CH_2$O); $\delta_C$ (100 MHz, $CDCl_3$) 167.1 (**C**=O), 146.9 (CH=**C**HC), 140.5 (CH**C**(=$CH_2$)$CH_3$), 124.2 (C=**C**$H_2$), 118.7 (C**C**H=CH), 60.3 ($CH_3$**C**$H_2$O), 18.0 (C**C**$H_3$), 14.2 (**C**$H_3CH_2$O); HRMS *m*/*z* ($FI^+$) found 140.0831, $C_8H_{12}O_2$ requires 140.0837; $\nu_{max}$ (neat)/$cm^{-1}$ 3088 (m, =$CH_2$), 2981 (m, CH), 1711 (s, C=O), 1632 (s, C=C), 1606 (s, C=C), 1452 (m), 1366 (m), 1306 (s), 1267 (m), 1164 (s, C-O), 1037 (s), 981 (s, C=C), 907 (s, C=$CH_2$), 864 (s, C=$CH_2$).

Data are consistent with literature values.[231]

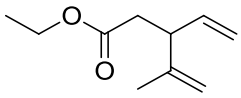
**(*E*)-4-Methylpenta-2,4-dien-1-ol (442)**




Prepared according to the procedure reported by Sutherland *et al.*[232] To a stirred suspension of $LiAlH_4$ (1.56 g, 41.1 mmol, 1.0 eq.) in anhydrous $Et_2O$ (41.1 mL) cooled to 0 °C in a ice/water bath, was added dropwise a solution of (*E*)-ethyl 4-methylpenta-2,4-dienoate (**444**) (5.76 g, 41.1 mmol, 1.0 eq.) in anhydrous $Et_2O$ (41.1 mL). The resulting mixture was stirred at 0 °C for 30 min. Water (1.56 mL) was carefully added dropwise, followed by addition of a 10% NaOH solution (1.56 mL) and water (3.12 mL). The mixture was stirred for 5 min, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by fractional distillation under reduced pressure (20 mbar) heating at 100 °C to afford (*E*)-4-methylpenta-2,4-dien-1-ol (**442**) as a colourless oil (3.11 g, 31.6 mmol, 77%). $R_f$ = 0.10 (15% EtOAc/petrol 40–60); *b.p.* 74–76 °C at 20 mbar (lit.[232] 90 °C at 50 mmHg); $\delta_H$ (400 MHz, $CDCl_3$) 6.32 (1H, d, $J$ = 15.7 Hz, CH=C**H**C), 5.78 (1H, dt, $J$ = 15.7, 5.8 Hz, $CH_2C$**H**=CH), 4.97 (2H, s, C=C$\mathbf{H_2}$), 4.19 (2H, d, $J$ = 5.8 Hz, HOC$\mathbf{H_2}$CH=), 2.33 (1H, s, **H**O$CH_2$), 1.84 (3H, s, CC$\mathbf{H_3}$); $\delta_C$ (100 MHz, $CDCl_3$) 141.3 (CH**C**(=$CH_2$)$CH_3$), 133.9 (CH=**C**HC), 128.4 ($CH_2$**C**H=CH), 116.7 (C=**C**$H_2$), 63.3 (HO**C**$H_2$CH=), 18.5 (C**C**$H_3$); HRMS $m/z$ ($FI^+$) found 98.0732, $C_6H_{10}O$ requires 98.0732; $\nu_{max}$ (neat)/$cm^{-1}$ 3311 (br, OH), 3082 (m, =$CH_2$), 3029 (m, =CH), 2973 (m, CH), 2944 (m, CH), 2920 (m, CH), 2861 (m, CH), 1610 (s, C=C), 1453 (m), 1437 (m), 1095 (s, $CH_2$-OH), 1029 (s), 965 (s, trans C=C), 885 (s, C=$CH_2$).

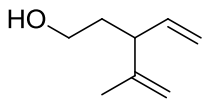
Data are consistent with literature values.[232]

***Ethyl 4-methyl-3-vinylpent-4-enoate (441)***



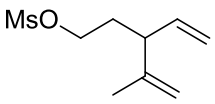
To a stirred solution of (*E*)-4-methylpenta-2,4-dien-1-ol (**442**) (2.80 g, 28.5 mmol, 1.0 eq.) in triethyl orthoacetate (36.6 mL, 199 mmol, 7.0 eq.), was added in one portion propionic acid (127 mg, 1.71 mmol, 0.06 eq.). The resulting mixture was heated at 138 °C for 4 h, under conditions for distillative removal of ethanol and then cooled to room temperature. 1 M HCl was carefully added to the mixture (200 mL) and extracted with $Et_2O$ (3 × 50 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (200 mL), brine (200 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by fractional distillation under reduced pressure (20 mbar) heating at 105 °C to afford ethyl 4-methyl-3-vinylpent-4-enoate (**441**) as a colourless oil (3.42 g, 20.5 mmol, 72%). $R_f$ = 0.51 (15% EtOAc/petrol 40-60); *b.p.* 79-81 °C at 20 mbar; $\delta_H$ (400 MHz, $CDCl_3$) 5.71 (1H, ddd, *J* = 17.4, 10.1, 7.6 Hz, CHC**H**=$CH_2$), 5.06 (1H, d, *J* = 17.4 Hz, CH=$CH_Z$**H**$_E$), 5.03 (1H, d, *J* = 10.1 Hz, CH=C**H**$_Z$$H_E$), 4.79 (1H, s, C=C**H**$_2$), 4.76 (1H, s, C=C**H**$_2$), 4.10 (2H, q, *J* = 7.1 Hz, $CH_3$C**H**$_2$O), 3.21 (1H, q, *J* = 7.6 Hz, $CH_2$C**H**(C)CH=), 2.52 (1H, dd, *J* = 14.8, 7.6 Hz, CC**H**$_2$CH), 2.45 (1H, dd, *J* = 14.8, 7.6 Hz, CC**H**$_2$CH), 1.70 (3H, s, C**H**$_3$C(C)=), 1.26 (3H, t, *J* = 7.1 Hz, C**H**$_3$$CH_2$O); $\delta_C$ (100 MHz, $CDCl_3$) 172.1 (**C**=O), 145.8 ($CH_3$**C**(C)=$CH_2$), 139.1 (CH**C**H=$CH_2$), 115.3 (CH=**C**H$_2$), 111.0 (C=**C**H$_2$), 60.3 ($CH_3$**C**H$_2$O), 47.2 ($CH_2$**C**H(C)CH=), 37.9 (C**C**H$_2$CH), 20.4 (**C**H$_3$C(C)=), 14.2 (**C**H$_3$$CH_2$O); HRMS *m*/*z* (FI$^+$) found 168.1146, $C_{10}H_{16}O_2$ requires 168.1150; $\nu_{max}$ (neat)/cm$^{-1}$ 3082 (m, =$CH_2$), 2980 (m, CH), 2940 (m, CH), 1736 (s, C=O), 1647 (m, C=C), 1636 (m, C=C), 1446 (m), 1370 (m), 1303 (m), 1256 (m), 1159 (s, C-O), 1033 (s), 993 (s, C=C), 917 (s, C=$CH_2$) 893, (s, C=$CH_2$).

***4-Methyl-3-vinylpent-4-en-1-ol (440)***




To a stirred suspension of $LiAlH_4$ (722 mg, 19.0 mmol, 1.0 eq.) in anhydrous $Et_2O$ (19.0 mL) cooled to 0 °C in a ice/water bath, was added dropwise a solution of ethyl 4-methyl-3-vinylpent-4-enoate (**441**) (3.20 g, 19.0 mmol, 1.0 eq.) in anhydrous $Et_2O$ (19.0 mL). The resulting mixture was stirred at 0 °C for 30 min. Water (0.72 mL) was carefully added dropwise, followed by addition of a 10% NaOH solution (0.72 mL) and water (1.44 mL). The mixture was stirred for 5 min, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by fractional distillation under reduced pressure (20 mbar) heating at 105 °C to afford 4-methyl-3-vinylpent-4-en-1-ol (**440**) as a colourless oil (1.82 g, 14.4 mmol, 76%). $R_f$ = 0.24 (15% EtOAc/petrol 40-60); *b.p.* 81-83 °C at 20 mbar; $\delta_H$ (400 MHz, $CDCl_3$) 5.71 (1H, ddd, *J* = 17.4, 10.1, 7.6 Hz, CHC**H**=$CH_2$), 5.05 (1H, d, *J* = 17.4 Hz, CH=$CH_Z$**H**$_E$), 5.02 (1H, d, *J* = 10.1 Hz, CH=C**H**$_Z$$H_E$), 4.77 (2H, s, C=C**H**$_2$), 3.61 (2H, td, *J* = 6.6, 1.4 Hz, HOC**H**$_2$$CH_2$), 2.84 (1H, q, *J* = 7.6 Hz, $CH_2$C**H**(C)CH=), 2.14 (1H, s, **H**O$CH_2$), 1.85–1.63 (2H, m, $CH_2$C**H**$_2$CH), 1.68 (3H, s, C**H**$_3$C(C)=); $\delta_C$ (100 MHz, $CDCl_3$) 147.1 ($CH_3$**C**(C)=$CH_2$), 140.6 (CH**C**H=$CH_2$), 114.8 (CH=**C**$H_2$), 110.8 (C=**C**$H_2$), 61.0 (HO**C**$H_2CH_2$), 47.9 ($CH_2$**C**H(C)CH=), 34.9 ($CH_2$**C**$H_2$CH), 19.9 (**C**$H_3$C(C)=); HRMS *m*/*z* ($FI^+$) found 126.1047, $C_8H_{14}O$ requires 126.1045; $\nu_{max}$ (neat)/$cm^{-1}$ 3329 (br, OH), 3077 (m, =$CH_2$), 2970 (m, CH), 2940 (m, CH), 2879 (m, CH), 1634 (s, C=C), 1436 (m), 1374 (m), 1051 (s, $CH_2$-OH), 913 (s, C=C), 889 (s, C=$CH_2$).

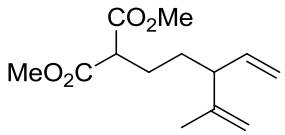
***4-Methyl-3-vinylpent-4-en-1-yl methanesulfonate (445)***




To a stirred solution of 4-methyl-3-vinylpent-4-en-1-ol (**440**) (1.74 g, 13.8 mmol, 1.0 eq.) in anhydrous DCM (46.0 mL) cooled to 0 °C in a ice water bath, was added triethylamine (2.09 g,

20.7 mmol, 1.5 eq.) followed by dropwise addition of methanesulfonyl chloride (1.90 g, 16.5 mmol, 1.2 eq.). The resulting mixture was warmed to room temperature and stirred for 1.5 h. 1 M HCl (70 ml) was added to the mixture and extracted with DCM (3 × 20 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (100 mL), dried ($MgSO_4$) and filtered through a silica plug eluting with DCM (200 mL). The filtrate was concentrated under reduced pressure to afford 4-methyl-3-vinylpent-4-en-1-yl methanesulfonate (**445**) as a colourless oil (2.65 g, 13.0 mmol, 94%). $R_f$ = 0.33 (20% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 5.67 (1H, ddd, *J* = 17.4, 10.2, 7.8 Hz, CHC**H**=$CH_2$), 5.08 (1H, d, *J* = 10.2 Hz, CH=C$\mathbf{H_Z}H_E$), 5.08 (1H, d, *J* = 17.4 Hz, CH=$CH_Z\mathbf{H_E}$), 4.83 (1H, s, C=C$\mathbf{H_2}$), 4.78 (1H, s, C=C$\mathbf{H_2}$), 4.20 (2H, t, *J* = 6.6 Hz, MsOC$\mathbf{H_2}CH_2$), 2.99 (3H, s, $SO_2C\mathbf{H_3}$), 2.84 (1H, q, *J* = 7.8 Hz, $CH_2C\mathbf{H}$(C)CH=), 2.03–1.82 (2H, m, $CH_2C\mathbf{H_2}CH$), 1.68 (3H, s, $C\mathbf{H_3}C$(C)=); $\delta_C$ (100 MHz, $CDCl_3$) 145.6 ($CH_3\mathbf{C}$(C)=$CH_2$), 139.3 (CH**C**H=$CH_2$), 115.9 (CH=**C**$H_2$), 111.6 (C=**C**$H_2$), 68.3 (MsO**C**$H_2CH_2$), 47.1 ($CH_2\mathbf{C}$H(C)CH=), 37.2 ($SO_2\mathbf{C}H_3$), 31.3 ($CH_2\mathbf{C}H_2CH$), 19.9 (**C**$H_3$C(C)=); LRMS *m/z* ($ESI^+$) 227 ($[M+Na]^+$, 100%); HRMS *m/z* ($ESI^+$) found 227.0715, $C_9H_{16}NaO_3S$ requires 227.0712; $\nu_{max}$ (neat)/$cm^{-1}$ 3080 (m, =$CH_2$), 3028 (m, =CH), 2974 (m, CH), 2942 (m, CH), 1646 (m, C=C), 1636 (m, C=C), 1455 (m), 1351 (s, $RSO_2R$), 1333 (s, $RSO_2R$), 1171 (s, $RSO_2R$), 972 (s), 954 (s), 913 (s), 816 (s, S-O).

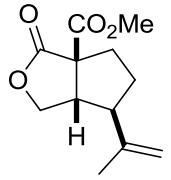
***Dimethyl 2-(4-methyl-3-vinylpent-4-en-1-yl)malonate (439)***




To a stirred suspension of hexane washed NaH (916 mg, 38.2 mmol, 3.0 eq.), in anhydrous DMF (31.8 mL) cooled to 0 °C in an ice/water bath, was carefully added dropwise dimethyl malonate (5.03 g, 38.2 mmol, 3.0 eq.). The resulting mixture was stirred for 20 min at 0 °C, after which a solution of 4-methyl-3-vinylpent-4-en-1-yl methanesulfonate (**445**) (2.60 g, 12.7 mmol, 1.0 eq.) in anhydrous THF (31.8 mL) was added *via* cannula followed by potassium iodide (1.05 g, 6.35 mmol, 0.5 eq.). The mixture was heated at 80 °C for 1.5 h and then cooled to room temperature. Sat. aq.

$NH_4Cl$ solution (100 mL) was added to the mixture and extracted with EtOAc (3 × 50 mL). The combined organic extracts were sequentially washed with water (200 mL), brine (200 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (15% EtOAc/petrol 40-60) to afford dimethyl 2-(4-methyl-3-vinylpent-4-en-1-yl)malonate (**439**) as a colourless oil (2.71 g, 11.3 mmol, 89%). $R_f$ = 0.31 (15% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 5.67 (1H, ddd, *J* = 17.2, 10.4, 7.7 Hz, CHC**H**=$CH_2$), 5.02 (1H, d, *J* = 17.2 Hz, CH=$CH_Z$**H**$_E$), 5.01 (1H, d, *J* = 10.4 Hz, CH=C**H**$_Z$H$_E$), 4.76 (1H, s, C=C**H**$_2$), 4.74 (1H, s, C=C**H**$_2$), 3.72 (6H, s, OC**H**$_3$), 3.35 (1H, t, *J* = 7.5 Hz, $(MeO_2C)_2$C**H**$CH_2$), 2.65 (1H, q, *J* = 7.5 Hz, $CH_2$C**H**(C)CH=), 1.90–1.79 (2H, m, CHC**H**$_2$$CH_2$), 1.64 (3H, s, C**H**$_3$C(C)=), 1.56–1.37 (2H, m, $CH_2$C**H**$_2$CH); $\delta_C$ (100 MHz, $CDCl_3$) 169.8 (2C, **C**=O), 146.5 ($CH_3$**C**(C)=$CH_2$), 140.3 (CH**C**H=$CH_2$), 114.9 (CH=**C**H$_Z$H$_E$), 111.1 (C=**C**H$_2$), 52.4 (2C, O**C**H$_3$), 51.5 ($(MeO_2C)_2$**C**H$CH_2$), 51.0 ($CH_2$**C**H(C)CH=), 29.7 ($CH_2$**C**H$_2$CH), 26.8 (CH**C**H$_2$CH$_2$), 19.7 (**C**H$_3$C(C)=); LRMS *m/z* (ESI$^+$) 263 ([M+Na]$^+$, 100%); HRMS *m/z* (ESI$^+$) found 263.1245, $C_{13}H_{20}NaO_4$ requires 263.1254; $\nu_{max}$ (neat)/cm$^{-1}$ 3077 (m, =$CH_2$), 2955 (m, CH), 2865 (m, CH), 1752 (s, C=O), 1734 (s, C=O), 1635 (m, C=C), 1435 (s), 1374 (m), 1345 (m), 1288 (m), 1219 (m, C-O), 1199 (m, C-O), 1151 (s), 996 (m, CH=$CH_2$), 913 (s, C=$CH_2$), 893 (s, C=$CH_2$).

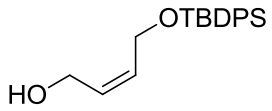
***(3aR*,6R*,6aS*)-Methyl 3-oxo-6-(prop-1-en-2-yl)hexahydro-1H-cyclopenta[c]furan-3a-carboxylate (438)***




A mixture of manganese(III) acetate (268 mg, 1.00 mmol, 2.0 eq.) and copper(II) triflate (181 mg, 0.50 mmol, 1.0 eq.) were pre heated to 80 °C, after which a solution of dimethyl 2-(4-methyl-3-vinylpent-4-en-1-yl)malonate (**439**) (120 mg, 0.50 mmol, 1.0 eq.) in Ar sparged acetonitrile (2.50 mL) was rapidly added. The resulting mixture was heated at 80 °C for 4 h and then cooled to

room temperature. The reaction mixture was passed through a silica plug eluting with $Et_2O$ (100 mL) and then concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60) to afford (3a*R**,6*R**,6a*S**)-methyl 3-oxo-6-(prop-1-en-2-yl)hexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate (**438**) as a colourless oil (34.9 mg, 0.16 mmol, 31%). $R_f$ = 0.23 (20% EtOAc/Petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 4.08 (1H, s, C=C**H**$_2$), 4.74 (1H, s, C=C**H**$_2$), 4.47 (1H, dd, *J* = 9.3, 6.5 Hz, OC**H**$_2$CH), 4.15 (1H, dd, *J* = 9.3, 1.0 Hz, OC**H**$_2$CH), 3.77 (3H, s, OC**H**$_3$), 2.89 (1H, ddd, *J* = 9.5, 6.5, 1.0 Hz, OCH$_2$C**H**CH), 2.64 (1H, ddd, *J* = 13.8, 8.4, 2.8 Hz, CC**H**$_2$CH$_2$), 2.39 (1H, ddd, *J* = 10.3, 9.5, 6.2 Hz, CHC**H**(C=)CH$_2$), 2.10 (1H, ddd, *J* = 13.8, 10.3, 2.1 Hz, CC**H**$_2$CH$_2$), 1.99–1.85 (1H, m, CHC**H**$_2$CH$_2$), 1.74–1.65 (1H, m, CHC**H**$_2$CH$_2$), 1.70 (3H, s, CC**H**$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 176.5 (**C**O$_2$Me), 170.3 (**C**=O), 143.7 (**C**=CH$_2$), 112.0 (C=**C**H$_2$), 70.5 (O**C**H$_2$CH), 60.8 (C**C**(CO$_2$Me)CCH$_2$), 53.8 (CH**C**H(C=)CH$_2$), 53.2 (O**C**H$_3$), 50.4 (OCH$_2$**C**HCH), 32.5 (C**C**H$_2$CH$_2$), 32.0 (CH**C**H$_2$CH$_2$), 20.1 (C**C**H$_3$); LRMS *m*/*z* (ESI$^+$) 247 ([M+Na]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 247.0939, $C_{12}H_{16}NaO_4$ requires 247.0941; $\nu_{max}$ (film)/cm$^{-1}$ 2958 (m, CH), 1775 (s, C=O), 1740 (s, C=O), 1436 (m), 1257 (m), 1142 (m), 990 (m), 937 (m).

**(*Z*)-4-((*tert*-Butyldiphenylsilyl)oxy)but-2-en-1-ol (458)**

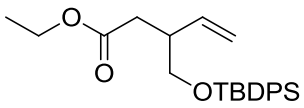



Prepared according to the procedure reported by Hu *et al.*[179] To a stirred solution of (*Z*)-but-2-ene-1,4 diol (**457**) (3.52 g, 40.0 mmol, 1.0 eq.) in dry DMF (133 mL) was added *N*,*N*-diisopropylethylamine (51.7 g, 400 mmol, 10 eq.) forming a biphasic mixture. *tert*-Butyl diphenylchlorosilane (11.5 g, 42.0 mmol, 1.05 eq.) was added dropwise whilst the mixture was gently stirred to avoid mixing the layers together. After complete addition the mixture was stirred for 1 h at room temperature. Ice water (400 ml) was added to the mixture and extracted with EtOAc (3 × 80 mL). The combined organic extracts were sequentially washed with 1 M HCl

(200 mL), sat. aq. $NH_4Cl$ solution (200 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (25-30% EtOAc/petrol 40-60 gradient) to afford (*Z*)-4-((*tert*-butyldiphenylsilyl)oxy)but-2-en-1-ol (**458**) as a colourless oil (6.36 g, 19.6 mmol, 49%). $R_f$ = 0.35 (30% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 7.75–7.69 (4H, m, Ar**H**), 7.50–7.39 (6H, m, Ar**H**), 5.74 (1H, dt, *J* = 11.5, 5.8 Hz, CH=C**H**$CH_2$), 5.65 (1H, dt, *J* = 11.5, 6.2 Hz, $CH_2$C**H**=CH), 4.29 (2H, d, *J* = 5.8 Hz, =CHC**H**$_2$O), 4.03 (2H, d, *J* = 6.2 Hz, OC**H**$_2$CH=), 1.86 (1H, s, **H**O$CH_2$), 1.09 (9H, s, SiC(C**H**$_3$)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 135.6 (4C, Ar), 133.0 (2C, Ar), 130.9 (CH=**C**H$CH_2$), 129.9 ($CH_2$**C**H=CH), 129.8 (2C, Ar), 127.7 (4C, Ar), 60.2 (=CH**C**$H_2$O), 58.7 (O**C**$H_2$CH=), 26.8 (3C, SiC(**C**$H_3$)$_3$), 19.1 (Si**C**$(CH_3)_3$); LRMS *m*/*z* (ESI$^+$) 349 ([M+Na]$^+$, 100%); $\nu_{max}$ (film)/cm$^{-1}$ 3339 (br, OH), 3071 (w, CH), 3050 (w, CH), 3023 (w, CH), 2958 (m, CH), 2931 (m, CH), 2891 (m, CH), 2857 (m, CH), 1891 (w), 1769 (w), 1697 (w, C=C), 1589 (w), 1472 (m), 1427 (s), 1391 (m), 1361 (m), 1330 (m), 1261 (m), 1222 (m), 1188 (m), 1109 (s, Si-O-C), 1078 (s), 1025 (m), 998 (m), 974 (m), 939 (m), 700 (s, *Z* CH=CH).

Data are consistent with literature values.[179]

**Ethyl 3-(((*tert*-butyldiphenylsilyl)oxy)methyl)pent-4-enoate (459)**

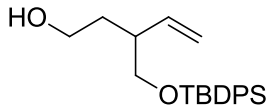



To a stirred solution of (*Z*)-4-((*tert*-butyldiphenylsilyl)oxy)but-2-en-1-ol (**458**) (1.63 g, 5.00 mmol, 1.0 eq.) in triethyl orthoacetate (6.42 mL, 35.0 mmol, 7.0 eq.), was added in one portion propionic acid (22.2 mg, 0.30 mmol, 0.06 eq.). The resulting mixture was heated at 138 °C for 18 h, under conditions for distillative removal of ethanol and then cooled to room temperature. 1 M HCl was carefully added to the mixture (50 mL) and extracted with EtOAc (3 × 20 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (5-10% EtOAc/petrol 40-60 gradient) to afford ethyl 3-(((*tert*-

butyldiphenylsilyl)oxy)methyl)pent-4-enoate (**459**) as a colourless oil (1.64 g, 4.15 mmol, 83%). $R_f$ = 0.26 (5% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 7.70–7.64 (4H, m, Ar**H**), 7.47–7.36 (6H, m, Ar**H**), 5.79 (1H, ddd, *J* = 17.3, 10.4, 7.9 Hz, CHC**H**=$CH_2$), 5.11 (1H, d, *J* = 17.3 Hz, CH=$CH_Z$**H**$_E$), 5.08 (1H, d, *J* = 10.4 Hz, CH=C**H**$_Z$$H_E$), 4.14 (2H, q, *J* = 7.1 Hz, $CH_3C$**H**$_2$O), 3.69 (1H, dd, *J* = 9.9, 5.2 Hz, CHC**H**$_2$OTBDPS), 3.60 (1H, dd, *J* = 9.9, 6.7 Hz, CHC**H**$_2$OTBDPS), 2.90–2.80 (1H, m, $CH_2$C**H**($CH_2$)CH=), 2.71 (1H, dd, *J* 15.2, 5.7 Hz, CC**H**$_2$CH), 2.39 (1H, dd, *J* = 15.2, 8.6 Hz, CC**H**$_2$CH), 1.26 (3H, t, *J* = 7.1 Hz, C**H**$_3$$CH_2$), 1.08 (9H, s, SiC(C**H**$_3$)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 172.6 (**C**=O), 138.0 (CH**C**H=$CH_2$), 135.6 (4C, Ar), 133.5 (2C, Ar), 129.7 (2C, Ar), 127.7 (4C, Ar), 116.2 (CH=**C**$H_Z$$H_E$), 66.4 (CH**C**$H_2$OTBDPS), 60.3 ($CH_3$**C**$H_2$O), 42.6 ($CH_2$**C**H($CH_2$)CH=), 36.2 (C**C**$H_2$CH), 26.8 (3C, SiC(**C**$H_3$)$_3$), 19.3 (Si**C**($CH_3$)$_3$), 14.3 (**C**$H_3CH_2$); LRMS *m*/*z* (ESI$^+$) 419 ([M+Na]$^+$, 100%); $\nu_{max}$ (film)/cm$^{-1}$ 3072 (w, =$CH_2$), 3050 (w, =$CH_2$), 2959 (m, CH), 2932 (m, CH), 2895 (m, CH), 2858 (m, CH), 1734 (s, C=O), 1642 (w, C=C), 1590 (w, C=C), 1472 (m), 1446 (m), 1390 (s), 1251 (m, C-O), 1178 (m), 1107 (s, Si-O-C), 1031 (m), 998 (m), 918 (m, CH=$CH_2$).

Data are consistent with literature values.[48]

**3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)pent-4-en-1-ol (460)**

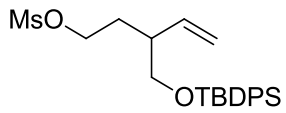



To a stirred suspension of $LiAlH_4$ (362 mg, 9.53 mmol, 1.0 eq.) in anhydrous $Et_2O$ (9.53 mL) cooled to 0 °C in a ice/water bath, was added dropwise a solution of 3-(((*tert*-butyldiphenylsilyl)oxy)methyl)pent-4-enoate (**459**) (3.78 g, 9.53 mmol, 1.0 eq.) in anhydrous $Et_2O$ (9.53 mL). The resulting mixture was stirred at 0 °C for 30 min. Water (0.36 mL) was carefully added dropwise, followed by addition of a 10% NaOH solution (0.36 mL) and water (0.72 mL). The mixture was stirred for 5 min, dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/petrol 40-60) to

afford 3-(((*tert*-butyldiphenylsilyl)oxy)methyl)pent-4-en-1-ol (**460**) as a colourless oil (2.90 g, 8.19 mmol, 86%). $R_f$ = 0.24 (20% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 7.67 (4H, d, *J* = 6.9 Hz, Ar**H**), 7.49–7.38 (6H, m, Ar**H**), 5.72 (1H, ddd, *J* = 17.0, 10.6, 8.7 Hz, CHC**H**=$CH_2$), 5.08 (1H, d, *J* = 17.0 Hz, CH=$CH_Z$**H**$_E$), 5.07 (1H, d, *J* = 10.6 Hz, CH=C**H**$_Z$$H_E$), 3.77–3.59 (4H, m, HOC**H**$_2$$CH_2$ & CHC**H**$_2$OTBDPS), 2.47–2.37 (1H, m, $CH_2$C**H**($CH_2$)CH=), 1.96 (1H, s, **H**O$CH_2$), 1.90–1.80 (1H, m, $CH_2$C**H**$_2$CH), 1.71–1.61 (1H, m, $CH_2$C**H**$_2$CH), 1.09 (9H, s, SiC(C**H**$_3$)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 139.6 (CH**C**H=$CH_2$), 135.6 (4C, Ar), 133.5 (2C, Ar), 129.6 (2C, Ar), 127.7 (4C, Ar), 116.0 (CH=**C**$H_Z$$H_E$), 67.4 (CH**C**$H_2$OTBDPS), 61.2 (HO**C**$H_2$$CH_2$), 43.8 ($CH_2$**C**H($CH_2$)CH=), 34.4 ($CH_2$**C**$H_2$CH), 26.9 (3C, SiC(**C**$H_3$)$_3$), 19.3 (Si**C**($CH_3$)$_3$); LRMS *m*/*z* (ESI$^+$) 377 ([M+Na]$^+$, 100%); $\nu_{max}$ (film)/cm$^{-1}$ 3333 (br, OH), 3072 (w, =$CH_2$), 3050 (w, =$CH_2$), 2999 (m, CH), 2931 (m, CH), 2893 (m, CH), 2858 (m, CH), 1891 (w), 1825 (w), 1641 (w, C=C), 1589 (w, C=C), 1472 (m), 1427 (m), 1390 (w), 1110 (s, Si-O-C), 1050 (m), 997 (m), 915 (m, CH=$CH_2$).

Data are consistent with literature values.[48]

**3-(((*tert*-Butyldiphenylsilyl)oxy)methyl)pent-4-en-1-yl methanesulfonate (461)**

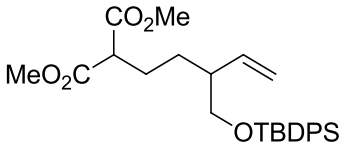



To a stirred solution of 3-(((*tert*-butyldiphenylsilyl)oxy)methyl)pent-4-en-1-ol (**460**) (2.09 g, 5.89 mmol, 1.0 eq.) in anhydrous DCM (19.6 mL) cooled to 0 °C in a ice water bath, was added triethylamine (894 mg, 8.84 mmol, 1.5 eq.) followed by dropwise addition of methanesulfonyl chloride (808 mg, 7.07 mmol, 1.2 eq.). The resulting mixture was warmed to room temperature and stirred for 1.5 h. 1 M HCl (50 ml) was added to the mixture and extracted with DCM (3 × 20 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was passed through a silica plug eluting with DCM (200 mL). The filtrate was concentrated under reduced pressure to afford 3-(((*tert*-butyldiphenylsilyl)oxy)methyl)pent-4-en-1-yl methanesulfonate (**461**) as a colourless

oil (2.45 g, 5.65 mmol, 96%). $R_f$ = 0.53 (100% DCM); $\delta_H$ (400 MHz, $CDCl_3$) 7.70 (4H, d, $J$ = 6.7 Hz, Ar**H**), 7.49–7.38 (6H, m, Ar**H**), 5.68 (1H, ddd, $J$ = 17.3, 10.0, 8.7 Hz, CHC**H**=$CH_2$), 5.14 (1H, d, $J$ = 10.0 Hz, CH=C**H**$_Z$H$_E$), 5.11 (1H, d, $J$ = 17.3 Hz, CH=CH$_Z$**H**$_E$), 4.33–4.19 (2H, m, MsOC**H**$_2$CH$_2$), 3.66 (1H, dd, $J$ = 9.9, 5.3 Hz, CHC**H**$_2$OTBDPS), 3.61 (1H, dd, $J$ = 9.9, 6.4 Hz, CHC**H**$_2$OTBDPS), 2.98 (3H, s, $SO_2C$**H**$_3$), 2.47–2.37 (1H, m, $CH_2C$**H**($CH_2$)CH=), 2.16–2.06 (1H, m, $CH_2C$**H**$_2$CH), 1.81–1.70 (1H, m, $CH_2C$**H**$_2$CH), 1.08 (9H, s, SiC(C**H**$_3$)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 138.0 (CH**C**H=$CH_2$), 135.6 (4C, Ar), 133.5 (2C, Ar), 129.7 (2C, Ar), 127.7 (4C, Ar), 117.4 (CH=**C**H$_Z$H$_E$), 68.4 (MsO**C**H$_2$CH$_2$), 66.9 (CH**C**H$_2$OTBDPS), 42.8 ($CH_2$**C**H($CH_2$)CH=), 37.3 ($SO_2$**C**H$_3$), 30.3 ($CH_2$**C**H$_2$CH), 26.9 (3C, SiC(**C**H$_3$)$_3$), 19.3 (Si**C**($CH_3$)$_3$); LRMS $m/z$ (ESI$^+$) 455 ([M+Na]$^+$, 100%); $\nu_{max}$ (film)/cm$^{-1}$ 3071 (w, =$CH_2$), 2957 (m, CH), 2932 (m, CH), 2895 (m, CH), 2858 (m, CH), 1827 (w), 1642 (w, C=C), 1589 (w, C=C), 1472 (m), 1428 (m), 1390 (s), 1175 (s), 1110 (s, Si-O-C), 1030 (m), 998 (m), 921 (m, CH=$CH_2$).

Data are consistent with literature values.[48]

**Dimethyl 2-(3-(((*tert*-butyldiphenylsilyl)oxy)methyl)pent-4-en-1-yl)malonate (79)**

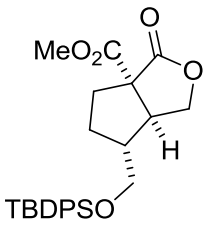



To a stirred suspension of hexane washed NaH (399 mg, 16.6 mmol, 3.0 eq.), in anhydrous DMF (13.9 mL) cooled to 0 °C in an ice/water bath, was carefully added dropwise dimethyl malonate (2.19 g, 16.6 mmol, 3.0 eq.). The resulting mixture was stirred for 20 min at 0 °C, after which a solution of 3-(((*tert*-butyldiphenylsilyl)oxy)methyl)pent-4-en-1-yl methanesulfonate (**461**) (2.40 g, 5.55 mmol, 1.0 eq.) in anhydrous THF (13.9 mL) was added *via* cannula followed by potassium iodide (461 mg, 2.78 mmol, 0.5 eq.). The mixture was heated at 80 °C for 1.5 h and then cooled to room temperature. Sat. aq. $NH_4Cl$ solution (50 mL) was added to the mixture and extracted with EtOAc (3 × 20 mL). The combined organic extracts were sequentially washed with water (100 mL), brine (100 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The

residue was purified by flash column chromatography (15% EtOAc/petrol 40-60) to afford dimethyl 2-(3-(((*tert*-butyldiphenylsilyl)oxy)methyl)pent-4-en-1-yl)malonate (**79**) as a colourless oil (2.30 g, 4.88 mmol, 88%). $R_f$ = 0.31 (15% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 7.67 (4H, d, *J* = 6.6 Hz, Ar**H**), 7.47–7.37 (6H, m, Ar**H**), 5.64 (1H, ddd, *J* = 17.2, 10.2, 8.8 Hz, CHC**H**=$CH_2$), 5.08 (1H, d, *J* = 10.2 Hz, CH=C**H**$_Z$$H_E$), 5.06 (1H, d, *J* = 17.2 Hz, CH=$CH_Z$**H**$_E$), 3.74 (6H, s, 2 × O**C**$H_3$), 3.61 (1H, dd, *J* = 9.9, 5.9 Hz, CHC**H**$_2$OTBDPS), 3.56 (1H, dd, *J* = 9.9, 6.7 Hz, CHC**H**$_2$OTBDPS), 3.36 (1H, t, *J* = 7.6 Hz, $(MeO_2C)_2$C**H**$CH_2$), 2.30–2.19 (1H, m, $CH_2$C**H**$(CH_2)$CH=), 2.04–1.92 (1H, m, CHC**H**$_2$$CH_2$), 1.90–1.79 (1H, m, CHC**H**$_2$$CH_2$), 1.69–1.58 (1H, m, $CH_2$C**H**$_2$CH), 1.36–1.25 (1H, m, $CH_2$C**H**$_2$CH), 1.06 (9H, s, SiC(C**H**$_3$)$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 169.9 (**C**=O), 169.8 (**C**=O), 139.1 (CH**C**H=$CH_2$), 135.6 (4C, Ar), 133.7 (2C, Ar), 129.6 (2C, Ar), 127.6 (4C, Ar), 116.5 (CH=**C**$H_Z$$H_E$), 67.0 (CH**C**$H_2$OTBDPS), 52.4 (2C, O**C**$H_3$), 51.8 ($(MeO_2C)_2$**C**H$CH_2$), 46.3 ($CH_2$**C**H$(CH_2)$CH=), 28.4 ($CH_2$**C**$H_2$CH), 26.8 (3C, SiC(**C**$H_3$)$_3$), 26.5 (CH**C**$H_2$$CH_2$), 19.3 (Si**C**$(CH_3)_3$); LRMS *m*/*z* (ESI$^+$) 491 ([M+Na]$^+$, 100%); $\nu_{max}$ (film)/cm$^{-1}$ 3072 (w, =$CH_2$), 2999 (w), 2954 (m, CH), 2932 (m, CH), 2858 (m, CH), 1893 (w), 1754 (s, C=O), 1736 (s, C=O), 1641 (w, C=C), 1589 (w, C=C), 1472 (m), 1457 (s), 1429 (m), 1390 (s), 1224 (m), 1153 (m), 1109 (s, Si-O-C), 998 (m), 917 (m, CH=$CH_2$).

Data are consistent with literature values.[48]

**(3a*R**,6*R**,6a*S**)-Methyl 6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-oxohexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate (80)**

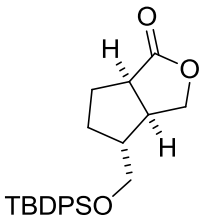



To a mixture of manganese(III) acetate (2.41 g, 9.00 mmol, 2.0 eq.) and copper(II) triflate (1.63 g, 4.50 mmol, 1.0 eq.) under an Ar atmosphere was added a 0.2 M solution of dimethyl 2-(3-(((*tert*-

butyldiphenylsilyl)oxy)methyl)pent-4-en-1-yl)malonate (**79**) (2.11 g, 4.50 mmol, 1.0 eq.) in Ar sparged acetonitrile (22.5 mL). The resulting mixture was heated at 80 °C for 3 h and then cooled to room temperature. The mixture was filtered through a silica plug eluting with $Et_2O$ (200 mL) and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/petrol 40-60) to afford (3a*R**,6*R**,6a*S**)-methyl 6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-oxohexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate (**80**) (diastereomeric ratio = 16:1) as a colourless oil (1.70 g, 3.78 mmol, 84%). Characterisation is reported for the major epimer of an inseparable mixture of diastereoisomers. $R_f$ = 0.31 (20% EtOAc/Petrol 40-60); $\delta_H$ (500 MHz, $CDCl_3$) 7.65–7.60 (4H, m, Ar**H**), 7.48–7.43 (2H, m, Ar**H**), 7.43–7.38 (4H, m, Ar**H**), 4.50 (1H, dd, *J* = 9.2, 7.0 Hz, CHC**H**$_2$O), 4.26 (1H, dd, *J* = 9.2, 1.3 Hz, CHC**H**$_2$O), 3.77 (3H, s, OC**H**$_3$), 3.70 (1H, dd, *J* = 10.3, 5.6 Hz, TBDPSOC**H**$_2$CH), 3.56 (1H, dd, *J* = 10.3, 7.4 Hz, TBDPSOC**H**$_2$CH), 2.86 (1H, td, *J* = 7.0, 1.3 Hz, CHC**H**CH$_2$), 2.55 (1H, ddd, *J* = 13.8, 8.2, 5.5 Hz, CH$_2$C**H**$_2$C), 2.20–2.10 (2H, m, CH$_2$C**H**$_2$C & CH$_2$C**H**(CH$_2$)CH), 1.79 (1H, dtd, *J* = 12.9, 7.1, 5.5 Hz, CH$_2$C**H**$_2$CH), 1.59 (1H, ddt, *J* = 16.7, 12.9, 8.2 Hz, CH$_2$C**H**$_2$CH), 1.06 (9H, s, SiC(C**H**$_3$)$_3$); $\delta_C$ (125 MHz, $CDCl_3$) 176.5 (**C**=O), 170.3 (**C**=O), 135.5 (2C, Ar), 135.5 (2C, Ar), 133.2 (Ar), 133.1 (Ar), 129.9 (2C, Ar), 127.8 (2C, Ar), 127.8 (2C, Ar), 72.0 (CH**C**H$_2$O), 65.7 (TBDPSO**C**H$_2$CH), 61.4 (CH$_2$**C**(CO$_2$Me)C), 53.1 (O**C**H$_3$), 50.0 (CH**C**HCH$_2$), 49.5 (CH$_2$**C**H(CH$_2$)CH), 32.7 (CH$_2$**C**H$_2$C), 29.1 (CH$_2$**C**H$_2$CH), 26.8 (3C, SiC(**C**H$_3$)$_3$), 19.1 (Si**C**(CH$_3$)$_3$); LRMS *m*/*z* (ESI$^+$) 475 ([M+Na]$^+$, 100%); $\nu_{max}$ (film)/cm$^{-1}$ 3071 (w, CH), 3049 (w, CH), 2955 (m, CH), 2932 (m, CH), 2858 (m, CH), 1775 (s, C=O), 1743 (s, C=O), 1589 (w), 1472 (m), 1428 (s), 1389 (m), 1375 (m), 1241 (s, CO-O), 1159 (s, CO-O), 1105 (s, Si-O-C), 1089 (s), 970 (m), 938 (m), 905 (m).

Data are consistent with literature values.[48]

**(3a*S**,4*R**,6a*R**)-4-(((*tert*-Butyldiphenylsilyl)oxy)methyl)hexahydro-1*H*-cyclopenta[*c*]furan-1-one (462)**

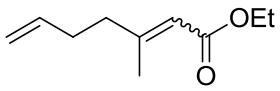



To a stirred solution of (3a*R**,6*R**,6a*S**)-methyl 6-(((*tert*-butyldiphenylsilyl)oxy)methyl)-3-oxohexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate (**80**) (1.56 g, 3.45 mmol, 1.0 eq.) in dry DMF (6.90 mL) was added water (124 mg, 6.90 mmol, 2.0 eq.) and lithium chloride (292 mg, 6.90 mmol, 2.0 eq.). The resulting mixture was heated at 150 °C for 2 h and then cooled to room temperature. Sat. aq. $NH_4Cl$ solution (50 mL) was added to the mixture and extracted with EtOAc (3 × 20 mL). The combined organic extracts were sequentially washed with water (100 mL), brine (100 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (40% EtOAc/petrol 30–40) to afford (3a*S**,4*R**,6a*R**)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)hexahydro-1*H*-cyclopenta[*c*]furan-1-one (**462**) (diastereomeric ratio = 16:1) as a colourless oil (1.18 g, 3.00 mmol, 87%). Characterisation is reported for the major epimer of an inseparable mixture of diastereoisomers. $R_f$ = 0.37 (50% $Et_2O$/Petrol 40–60); $\delta_H$ (500 MHz, $CDCl_3$) 7.66–7.63 (4H, m, Ar**H**), 7.48–7.43 (2H, m, Ar**H**), 7.43–7.38 (4H, m, Ar**H**), 4.40 (1H, dd, *J* = 9.4, 7.2 Hz, CHC**H**$_2$O), 4.19 (1H, dd, *J* = 9.4, 2.3 Hz, CHC**H**$_2$O), 3.68 (1H, dd, *J* = 10.2, 5.8 Hz, TBDPSOC**H**$_2$CH), 3.54 (1H, dd, *J* = 10.2, 7.2 Hz, TBDPSOC**H**$_2$CH), 3.01 (1H, td, *J* = 9.4, 4.2 Hz, $CH_2$C**H**(CH)$CO_2$), 2.69 (1H, dtd, *J* = 9.4, 7.2, 2.3 Hz, CHC**H**(CH)$CH_2$), 2.13–2.03 (2H, m, $CH_2$C**H**$_2$C & $CH_2$C**H**($CH_2$)CH), 1.98 (1H, dtd, *J* = 11.7, 7.4, 4.2 Hz, $CH_2$C**H**$_2$CH$CO_2$), 1.81–1.73 (1H, m, $CCH_2$C**H**$_2$CHCH), 1.56–1.47 (1H, m, $CCH_2$C**H**$_2$CHCH), 1.07 (9H, s, SiC(C**H**$_3$)$_3$); $\delta_C$ (125 MHz, $CDCl_3$) 181.0 (**C**=O), 135.5 (2C, Ar), 135.5 (2C, Ar), 133.3 (Ar), 133.3 (Ar), 129.8 (2C, Ar), 127.7 (4C, Ar), 72.4 (CH**C**$H_2$O), 65.9 (TBDPSO**C**$H_2$CH), 48.9 ($CH_2$**C**H($CH_2$)CH), 44.5 ($CH_2$**C**H(CH)$CO_2$), 43.5 (CH**C**H(CH)$CH_2$), 29.1 ($CCH_2$**C**$H_2$CHCH), 28.4 ($CH_2$**C**$H_2$CH$CO_2$), 26.8

(3C, SiC(**C**$H_3)_3$), 19.2 (Si**C**$(CH_3)_3$); LRMS $m/z$ (ESI$^+$) 417 ([M+Na]$^+$, 100%); $\nu_{max}$ (film)/cm$^{-1}$ 3073 (w, CH), 3032 (w, CH), 2999 (w, CH), 2949 (m, CH), 2929 (m, CH), 2856 (m, CH), 1760 (s, C=O), 1589 (w), 1482 (m), 1455 (m), 1428 (m), 1379 (m), 1375 (m), 1253 (s, CO-O), 1130 (s), 1104 (s, Si-O-C), 1009 (s), 966 (m), 944 (m), 909 (m).

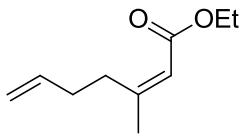
Data are consistent with literature values.[48]

**Ethyl 3-methylhepta-2,6-dienoate (464)**




Prepared according to the procedure reported by Marko *et al.*[233] To a stirred solution of triethyl phosphonoacetate (12.3 g, 55.0 mmol, 1.0 eq.) in anhydrous THF (125 mL) cooled to -78 °C in a dry ice/acetone bath, was added dropwise a 2.5 M solution of *n*-BuLi in hexanes (24.0 mL, 60.0 mmol, 1.2 eq.). The resulting mixture was warmed to room temperature and stirred for 2 h. After cooling back to -78 °C, a solution of 5-hexen-2-one (**463**) (4.91 g, 50.0 mmol, 1.0 eq.) in anhydrous THF (22.1 mL) was added to the mixture *via* cannula. The resulting mixture was warmed to room temperature and stirred for 20 h. Sat. aq. $NH_4Cl$ solution (100 mL) was added to the mixture and extracted with $Et_2O$ (3 × 100 mL). The combined organic extracts were sequentially washed with brine (300 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure (no heating). The residue was purified by flash column chromatography (2% $Et_2O$/pentane) to afford dimethyl (*E*)-ethyl 3-methylhepta-2,6-dienoate (**464**) (diastereomeric ratio = 6.7:1) as a colourless oil (6.70 g, 39.8 mmol, 80%). Characterisation is reported for the major and minor epimers as partially separated by flash column chromatography.

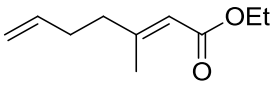
**(*Z*)-Ethyl 3-methylhepta-2,6-dienoate ((*Z*)-464)**




Minor Epimer: $R_f$ = 0.36 (5% $Et_2O$/pentane); $\delta_H$ (400 MHz, $CDCl_3$) 5.83 (1H, ddt, *J* = 17.0, 10.2, 6.7 Hz, $CH_2$=C**H**$CH_2$), 5.66 (1H, s, C=C**H**$CO_2Et$), 5.03 (1H, dd, *J* = 17.0, 1.7 Hz, $CH_Z\mathbf{H_E}$=CH), 4.94 (1H, dd, *J* = 10.2, 1.7 Hz, $\mathbf{H_Z}H_E$=CH), 4.12 (2H, q, *J* = 7.1 Hz, O$\mathbf{H_2}CH_3$), 2.70 (2H, t,, *J* = 7.5 Hz, $CH_2C\mathbf{H_2}C$), 2.26–2.19 (2H, m, =CHC$\mathbf{H_2}CH_2$), 1.87 (3H, d, *J* = 1.3 Hz, CC$\mathbf{H_3}$), 1.25 (3H, t, *J* = 7.1 Hz, $CH_2C\mathbf{H_3}$); $\delta_C$ (100 MHz, $CDCl_3$) 166.2 (**C**=O), 159.5 ($CH_2$**C**($CH_3$)=CH), 137.9 ($CH_2$=**C**H$CH_2$), 116.5 (C=**C**H$CO_2Et$), 114.8 (**C**$H_ZH_E$=CH), 59.4 (O**C**$H_2CH_3$), 32.6 ($CH_2$**C**$H_2$C), 32.2 (C**C**$H_2CH_2$), 25.2 (C**C**$H_3$), 14.3 ($CH_2$**C**$H_3$); HRMS *m*/*z* ($FI^+$) found 168.1149, $C_{10}H_{16}O_2$ requires 168.1150; $\nu_{max}$ (neat)/$cm^{-1}$ 3079 (w, =$CH_2$), 2979 (m, CH), 2935 (m, CH), 2874 (m, CH), 1712 (s, C=O), 1648 (s, C=C), 1445 (m), 1327 (w), 1222 (s, C-O), 1144 (s, C-O), 1097 (m), 1047 (s), 995 (s, CH=$CH_2$).

Data are consistent with literature values.[234]

**(*E*)-Ethyl 3-methylhepta-2,6-dienoate ((*E*)-464)**

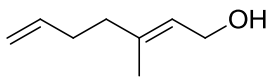



Major Epimer: $R_f$ = 0.33 (5% $Et_2O$/pentane); $\delta_H$ (400 MHz, $CDCl_3$) 5.82–5.70 (1H, m, $CH_2$=C**H**$CH_2$), 5.61 (1H, s, C=C**H**$CO_2Et$), 5.02 (1H, d, *J* = 17.6 Hz, $CH_Z\mathbf{H_E}$=CH), 4.97 (1H, d, *J* = 9.9 Hz, $\mathbf{H_Z}H_E$=CH), 4.13 (2H, q, *J* = 7.1 Hz, O$\mathbf{H_2}CH_3$), 2.24–2.20 (4H, m, 2 × C$\mathbf{H_2}$), 2.15 (3H, d, *J* = 1.1 Hz, CC$\mathbf{H_3}$), 1.26 (3H, t, *J* = 7.1 Hz, $CH_2C\mathbf{H_3}$); $\delta_C$ (100 MHz, $CDCl_3$) 166.7 (**C**=O), 159.0 ($CH_2$**C**($CH_3$)=CH), 137.2 ($CH_2$=**C**H$CH_2$), 115.9 (C=**C**H$CO_2Et$), 115.2 (**C**$H_ZH_E$=CH), 59.4 (O**C**$H_2CH_3$), 40.1 ($CH_2$**C**$H_2$C), 31.5 (C**C**$H_2CH_2$), 18.7 (C**C**$H_3$), 14.3 ($CH_2$**C**$H_3$); HRMS *m*/*z* ($FI^+$) found 168.1153, $C_{10}H_{16}O_2$ requires 168.1150; $\nu_{max}$ (neat)/$cm^{-1}$ 3079 (w, =$CH_2$), 2981 (m, CH), 2938

(m, CH), 1714 (s, C=O), 1647 (s, C=C), 1445 (m), 1327 (w), 1220 (s, C-O), 1144 (s, C-O), 1111 (m), 1097 (m), 1042 (s), 994 (s, CH=$CH_2$).

Data are consistent with literature values.[235]

**(*E*)-3-Methylhepta-2,6-dien-1-ol (465)**

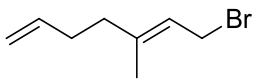



To a stirred solution of (*E*)-ethyl 3-methylhepta-2,6-dienoate ((*E*)-**464**) (2.13 g, 12.7 mmol, 1.0 eq.) in dry DCM (42.3 mL) cooled to -78 °C in a dry ice/acetone bath, was added dropwise over 1.5 h a 1 M solution of DIBAL-H in hexanes (27.8 mL, 27.8 mmol, 2.2 eq.). After complete addition, the mixture was stirred at -78 °C for 1 h, then warmed to 0 °C in a ice/water bath. Methanol (3.37 mL, 83.8 mmol, 6.6 eq.) was carefully added dropwise, followed by addition of a water (1.51 mL. 83.8 mmol, 6.6 eq.) and 0.5 M HCl (6.35 mL, 3.18 mmol, 25 mol%.) and then stirred for 1 h at room temperature. Water (100 mL) was added to the mixture and extracted with $Et_2O$ (3 × 100 mL). The combined organic extracts were sequentially washed with brine (300 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure (no heating). The residue was purified by flash column chromatography (40-50% $Et_2O$/petrol 30–40 gradient) to afford (*E*)-3-methylhepta-2,6-dien-1-ol (**465**) as a colourless oil (2.30 g, 4.88 mmol, 88%). $R_f$ = 0.36 (50% $Et_2O$/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 5.78 (1H, ddt, *J* = 17.0, 10.1, 6.3 Hz, $CH_2$=C**H**$CH_2$), 5.40 (1H, td, *J* = 6.9, 1.0 Hz, C=C**H**$CH_2$), 5.00 (1H, dd, *J* = 17.0, 1.6 Hz, $CH_Z$**H**$_E$=CH), 4.94 (1H, dd, *J* = 10.1, 1.6 Hz, C**H**$_Z$$H_E$=CH), 4.12 (2H, d, *J* = 6.9 Hz, =CHC**H**$_2$OH), 2.21–2.13 (2H, m, =CHC**H**$_2$$CH_2$), 2.12–2.06 (2H, m, $CH_2$C**H**$_2$C), 1.87 (1H, s, $CH_2$O**H**), 1.66 (3H, s, CC**H**$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 138.9 ($CH_2$**C**($CH_3$)=CH), 138.2 ($CH_2$=**C**H$CH_2$), 123.7 (C=**C**H$CH_2$), 114.6 (**C**$H_Z$$H_E$=CH), 59.2 (=CH**C**$H_2$OH), 38.8 ($CH_2$**C**$H_2$C), 31.9 (=CH**C**$H_2$$CH_2$), 16.2 ($CH_2$**C**$H_3$); HRMS *m*/*z* (FI$^+$) found 126.1048, $C_8H_{14}O$ requires 126.1045; $\nu_{max}$ (neat)/cm$^{-1}$ 3323 (br, OH), 3078

(m, $=CH_2$), 2978 (m, CH), 2930 (s, CH), 2851 (m, CH), 1669 (m, $CH=CH_2$), 1641 (s, $C=CH_2$), 1439 (s), 1382 (s), 1299 (w), 1237 (w), 1179 (w), 1082 (w), 993 (s, $CH=CH_2$), 908 (s, $CH=CH_2$).

Data are consistent with literature values.[236]

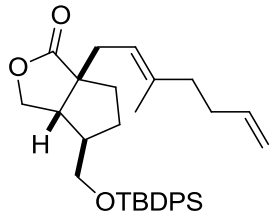
**(*E*)-7-Bromo-5-methylhepta-1,5-diene (436)**




Prepared according to the procedure reported by Gagne *et al.*[237] To a stirred solution of (*E*)-3-methylhepta-2,6-dien-1-ol ((*E*)-**465**) (3.78 g, 30.0 mmol, 1.0 eq.) in anhydrous THF (100 mL) cooled to 0 °C in a ice/water bath, was added triethylamine (6.37 g, 63.0 mmol, 2.1 eq.) followed by dropwise addition of methanesulfonyl chloride (4.79 g, 41.9 mmol, 1.4 eq.). The resulting mixture was stirred at 0 °C for 2 h, after which lithium bromide (13.0 g, 150 mmol, 5.0 eq.) was added portionwise. Sat. aq. $NH_4Cl$ solution (100 mL) was added to the mixture and extracted with $Et_2O$ (3 × 100 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (150 mL), brine (150 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure (no heating) to afford (*E*)-7-Bromo-5-methylhepta-1,5-diene (**436**) as pale yellow oil (4.26 g, 22.5 mmol, 75%). The crude bromide was used without further purification as it was found to be unstable to column chromatography. $R_f$ = 0.63 (50% $Et_2O$/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 5.79 (1H, ddt, $J$ = 17.0, 10.4, 6.3 Hz, $CH_2=C\mathbf{H}CH_2$), 5.55 (1H, t, $J$ = 8.3 Hz, $C=C\mathbf{H}CH_2$), 5.03 (1H, ddt, $J$ = 17.0, 1.8, 1.4 Hz, $CH_Z\mathbf{H_E}=CH$), 4.97 (1H, ddt, $J$ = 10.4, 1.8, 1.0 Hz, $C\mathbf{H_Z}H_E=CH$), 4.03 (2H, d, $J$ = 8.3 Hz, $=CHC\mathbf{H_2}Br$), 2.25–2.10 (4H, m, $=CHC\mathbf{H_2}CH_2$ & $CH_2C\mathbf{H_2}C$), 1.74 (3H, d, $J$ = 1.2 Hz, $CC\mathbf{H_3}$); $\delta_C$ (100 MHz, $CDCl_3$) 143.0 ($CH_2\mathbf{C}(CH_3)=CH$), 137.8 ($CH_2=\mathbf{C}HCH_2$), 120.8 ($C=\mathbf{C}HCH_2$), 114.9 ($\mathbf{C}H_ZH_E=CH$), 38.8 ($CH_2\mathbf{C}H_2C$), 31.8 ($=CH\mathbf{C}H_2Br$), 29.5 ($=CH\mathbf{C}H_2CH_2$), 15.9 ($C\mathbf{C}H_3$); HRMS $m/z$ ($FI^+$) found 188.0200, $C_8H_{13}{}^{77}Br$ requires 188.0201 and 190.0182, $C_8H_{13}{}^{79}Br$ requires 190.0181; $\nu_{max}$ (film)/$cm^{-1}$ 3078 (m, $=CH_2$), 2976 (s, CH), 2933 (s, CH), 2852 (m, CH), 1656 (s, C=CH), 1641 (m, $CH=CH_2$), 1446 (s), 1379 (m), 1362 (m).

Data are consistent with literature values.[237]

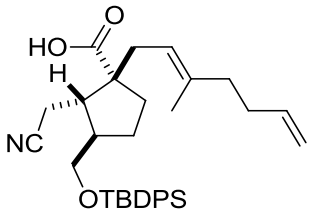
***(3aS*,4R*,6aS*)-4-(((tert-Butyldiphenylsilyl)oxy)methyl)-6a-((E)-3-methylhepta-2,6-dien-1-yl)hexahydro-1H-cyclopenta[c]furan-1-one (466)***




To a stirred solution of (3a*S**,4*R**,6a*R**)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)hexahydro-1*H*-cyclopenta[*c*]furan-1-one (**462**) (3.35 g, 8.50 mmol, 1.0 eq.) in anhydrous THF (150 mL) cooled to -78 °C in a dry ice/acetone bath, was added a solution of (*E*)-7-bromo-5-methylhepta-1,5-diene (3.21 g, 17.0 mmol, 2.0 eq.) in anhydrous THF (20 mL) followed by dropwise addition of a 1 M solution of LiHMDS in toluene (17.0 mL, 17.0 mmol, 2.0 eq.) over a 2 h period. After complete addition, the mixture was stirred at -78 °C for a further 30 min. The reaction mixture was pored over sat. aq. $NH_4Cl$ solution (300 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were sequentially washed with brine (300 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60) to afford (3a*S**,4*R**,6a*S**)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-6a-((*E*)-3-methylhepta-2,6-dien-1-yl)hexahydro-1*H*-cyclopenta[*c*]furan-1-one (**466**) as a colourless oil (3.46 g, 6.89 mmol, 81%). $R_f$ = 0.23 (10% EtOAc/petrol 40–60); $\delta_H$ (500 MHz, $CDCl_3$) 7.66–7.62 (4H, m, Ar**H**), 7.48–7.43 (2H, m, Ar**H**), 7.42–7.38 (4H, m, Ar**H**), 5.77 (1H, ddt, *J* = 17.0, 10.1, 6.3 Hz, $CH_2C\mathbf{H}=CH_2$), 5.11 (1H, td, *J* = 7.6, 1.0 Hz, $CH_2C\mathbf{H}=C(CH_3)C$), 5.01 (1H, dd, *J* = 17.0, 1.6 Hz, $CH=CH_Z\mathbf{H_E}$), 4.94 (1H, dd, *J* = 10.1, 1.6 Hz, $CH=C\mathbf{H_Z}H_E$), 4.25 (1H, dd, *J* = 9.3, 7.0 Hz, $OC\mathbf{H_2}CH$), 4.09 (1H, dd, *J* = 9.3, 1.6 Hz, $OC\mathbf{H_2}CH$), 3.66 (1H, dd, *J* = 10.2, 5.8 Hz, $CHC\mathbf{H_2}$OTBDPS), 3.54 (1H, dd, *J* = 10.2, 7.2 Hz, $CHC\mathbf{H_2}$OTBDPS), 2.47 (1H, dd, *J* = 14.2, 7.6 Hz, $CC\mathbf{H_2}CH=$), 2.37 (1H, ddd, *J* = 7.0, 7.0, 1.6 Hz, $CH_2C\mathbf{H}(C)CH$), 2.25 (1H, dd, *J* = 14.2, 7.6 Hz, $CC\mathbf{H_2}CH=$), 2.19–2.00 (6H, m, 2 × $C\mathbf{H_2}$ side chain, $CHC\mathbf{H}(CH_2)CH_2$ & $C\mathbf{H_2}$ ring), 1.80–1.65

(2H, m, C**H**$_2$ ring), 1.62 (3H, s, CC**H**$_3$), 1.54–1.46 (1H, m, C**H**$_2$ ring), 1.06 (9H, s, SiC(C**H**$_3$)$_3$); $\delta_C$ (125 MHz, $CDCl_3$) 183.0 (**C**=O), 140.0 ($CH_2$**C**H=$CH_2$), 138.2 (CH=**C**($CH_3$)$CH_2$), 135.5 (2C, Ar), 135.5 (2C, Ar), 133.4 (Ar), 133.3 (Ar), 129.8 (2C, Ar), 127.7 (2C, Ar), 127.7 (2C, Ar), 118.7 ($CH_2$**C**H=C($CH_3$)C), 114.6 (CH=**C**$H_ZH_E$), 71.8 (O**C**$H_2$CH), 65.8 (CH**C**$H_2$OTBDPS), 55.7 ($CH_2$**C**$(C)_2CO_2$), 50.3 (CH**C**H($CH_2$)$CH_2$), 47.2 ($CH_2$**C**H(C)CH), 39.2 (**C**$H_2$ side chain), 35.4 (**C**$H_2$ ring), 34.7 (C**C**$H_2$CH=), 32.2 (**C**$H_2$ side chain), 28.5 (**C**$H_2$ ring), 26.8 (3C, SiC(**C**$H_3$)$_3$), 19.2 (Si**C**($CH_3$)$_3$), 16.3 (C**C**$H_3$); LRMS *m*/*z* ($ESI^+$) 503 ($[M+H]^+$, 100%); HRMS *m*/*z* ($ESI^+$) found 525.2795, $C_{32}H_{42}NaO_3Si$ requires 525.2795; $\nu_{max}$ (neat)/$cm^{-1}$ 3072 (m, =$CH_2$), 2931 (m, CH), 2858 (m, CH), 2247 (w, C≡N), 1695 (s, C=O), 1471 (m), 1389 (s), 1362 (m), 1253 (m), 1110 (s), 997 (m), 909 (m).

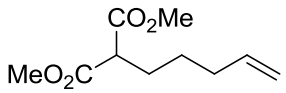
***(1S*,2S*,3R*)-3-(((tert-Butyldiphenylsilyl)oxy)methyl)-2-(cyanomethyl)-1-((E)-3-methylhepta-2,6-dien-1-yl)cyclopentanecarboxylic acid (467)***




To a stirred solution of (3a*S**,4*R**,6a*S**)-4-(((*tert*-butyldiphenylsilyl)oxy)methyl)-6a-((*E*)-3-methylhepta-2,6-dien-1-yl)hexahydro-1*H*-cyclopenta[*c*]furan-1-one (**466**) (42.1 mg, 0.08 mmol, 1.0 eq.) in anhydrous DMSO (1.60 mL), was added in one portion potassium cyanide (26.0 mg, 0.40 mmol, 5.0 eq.). The resulting mixture was heated at 185 °C for 1.5 h, then cooled to room temperature. Sat. aq. $NH_4Cl$ solution (10 mL) was added to the mixture followed by 1 M HCl (10 mL) and then extracted with EtOAc (3 × 10 mL). The combined organic extracts were sequentially washed with brine (30 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (2–4% MeOH/DCM gradient) to afford (1*S**,2*S**,3*R**)-3-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-(cyanomethyl)-1-((*E*)-3-methylhepta-2,6-dien-1-yl)cyclopentanecarboxylic acid (**467**) as a colourless oil (40.2 mg,

0.08 mmol, 95%). $R_f$ = 0.39 (4% MeOH/DCM); $\delta_H$ (500 MHz, $CDCl_3$) 7.67–7.64 (4H, m, Ar**H**), 7.48–7.38 (6H, m, Ar**H**), 5.76 (1H, ddt, *J* = 17.0, 10.1, 6.3 Hz, $CH_2C\mathbf{H}{=}CH_2$), 5.14 (1H, t, *J* = 7.4 Hz, $CH_2C\mathbf{H}{=}C(CH_3)C$), 4.99 (1H, dd, *J* = 17.0, 1.7 Hz, $CH{=}CH_Z\mathbf{H_E}$), 4.93 (1H, dd, *J* = 10.1, 1.7 Hz, $CH{=}C\mathbf{H_Z}H_E$), 3.71 (1H, dd, *J* = 10.4, 4.3 Hz, $CHC\mathbf{H_2}OTBDPS$), 3.65 (1H, dd, *J* = 10.4, 5.1 Hz, $CHC\mathbf{H_2}OTBDPS$), 2.71 (1H, dd, *J* = 14.4, 7.4 Hz, $CC\mathbf{H_2}CH{=}$), 2.61 (1H, dd, *J* = 17.1, 5.4 Hz, $CHC\mathbf{H_2}CN$), 2.54 (1H, dd, *J* = 17.1, 7.0 Hz, $CHC\mathbf{H_2}CN$), 2.24 (1H, dd, *J* = 14.4, 7.4 Hz, $CC\mathbf{H_2}CH{=}$), 2.20–2.03 (7H, m, 2 × $C\mathbf{H_2}$ side chain, $CH_2C\mathbf{H}(CH_2)CH$, $CHC\mathbf{H}(C)CH_2$ & $C\mathbf{H_2}$ ring), 1.98–1.89 (1H, m, $C\mathbf{H_2}$ ring), 1.63 (3H, s, $CC\mathbf{H_3}$), 1.62–1.50 (2H, m, $C\mathbf{H_2}$ ring), 1.08 (9H, s, $SiC(C\mathbf{H_3})_3$); $\delta_C$ (125 MHz, $CDCl_3$) 179.6 (**C**=O), 138.4 ($CH{=}\mathbf{C}(CH_3)CH_2$), 138.3 ($CH_2\mathbf{C}H{=}CH_2$), 135.6 (4C, Ar), 133.3 (Ar), 133.2 (Ar), 129.8 (Ar), 129.8 (Ar), 127.8 (2C, Ar), 127.7 (2C, Ar), 119.4 ($CH_2\mathbf{C}H{=}C(CH_3)C$), 118.9 ($CH_2\mathbf{C}N$), 114.5 ($CH{=}\mathbf{C}H_ZH_E$), 65.5 ($CH\mathbf{C}H_2OTBDPS$), 57.1 ($CH_2\mathbf{C}(C)_2CO_2$), 46.1 ($CH\mathbf{C}H(C)CH_2$), 46.0 ($CH_2\mathbf{C}H(CH_2)CH$), 39.2 ($=C(CH_3)\mathbf{C}H_2CH_2$), 35.5 ($C\mathbf{C}H_2CH{=}$), 33.3 ($\mathbf{C}H_2$ ring), 32.2 ($CH_2\mathbf{C}H_2CH{=}$), 26.9 (3C, $SiC(\mathbf{C}H_3)_3$), 26.0 ($\mathbf{C}H_2$ ring), 19.2 ($Si\mathbf{C}(CH_3)_3$), 18.1 ($CH\mathbf{C}H_2CN$), 16.3 ($C\mathbf{C}H_3$); LRMS *m/z* ($ESI^-$) 528 ($[M\text{-}H]^-$, 100%); HRMS *m/z* ($ESI^+$) found 552.2895, $C_{33}H_{43}NNaO_3Si$ requires 552.2904; $\nu_{max}$ (neat)/$cm^{-1}$ 3072 (m, $=CH_2$), 2931 (m, CH), 2858 (m, CH), 2247 (w, C≡N), 1695 (s, C=O), 1471 (m), 1389 (s), 1362 (m), 1253 (m), 1110 (s), 997 (m), 909 (m).

**Dimethyl 2-(pent-4-en-1-yl)malonate (65)**

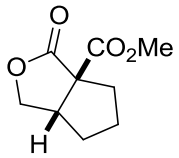



To a stirred suspension of hexane washed NaH (2.16 g, 90.0 mmol, 3.0 eq.), in anhydrous DMF (75.0 mL) cooled to 0 °C in an ice/water bath, was carefully added dropwise dimethyl malonate (11.9 g, 90.0 mmol, 3.0 eq.). The resulting mixture was stirred for 20 min at 0 °C, after which a solution of 5-bromo-1-pentene (**477**) (4.47 g, 30.0 mmol, 1.0 eq.) in anhydrous THF (75.0 mL) was added *via* cannula. The mixture was heated at 80 °C for 1.5 h and then cooled to room

temperature. Sat. aq. $NH_4Cl$ solution (100 mL) was added to the mixture and extracted with EtOAc (3 × 100 mL). The combined organic extracts were sequentially washed with water (300 mL), brine (300 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10-15% EtOAc/petrol 40-60 gradient) to afford dimethyl 2-(pent-4-en-1-yl)malonate (**65**) as a colourless oil (5.65 g, 28.2 mmol, 94%). $R_f$ = 0.21 (10% EtOAc/petrol 40-60); $\delta_H$ (500 MHz, $CDCl_3$) 5.74 (1H, ddt, $J$ = 17.0, 10.2, 6.6 Hz, CHC**H**=$CH_2$), 4.99 (1H, ddt, $J$ = 17.0, 2.0, 1.5 Hz, CH=$CH_Z$**H**$_E$), 4.93 (1H, ddt, $J$ = 10.2, 2.0, 1.2 Hz, CH=C**H**$_Z$$H_E$), 3.71 (6H, s, OC**H**$_3$), 3.34 (1H, t, $J$ = 7.5 Hz, $(MeO_2C)_2$C**H**$CH_2$), 2.08–2.02 (2H, m, $CH_2$C**H**$_2$CH=), 1.92–1.85 (2H, m, CHC**H**$_2$$CH_2$), 1.43–1.34 (2H, m, $CH_2$C**H**$_2$$CH_2$); $\delta_C$ (125 MHz, $CDCl_3$) 169.9 (**C**=O), 137.8 (CH**C**H=$CH_2$), 115.0 (CH=**C**$H_Z$$H_E$), 52.4 (2C, O**C**$H_3$), 51.5 ($(MeO_2C)_2$**C**H$CH_2$), 33.2 ($CH_2$**C**$H_2$CH=), 28.2 (CH**C**$H_2$$CH_2$), 26.5 ($CH_2$**C**$H_2$$CH_2$); LRMS *m/z* (ESI$^+$) 201 ([M+H]$^+$, 38%), 223 ([M+Na]$^+$, 100%); $\nu_{max}$ (film)/cm$^{-1}$ 3078 (w, =$CH_2$), 2955 (m, CH), 2863 (m, CH), 1733 (s, C=O), 1641 (m, C=C), 1435 (s), 1344 (m), 1286 (m), 1243 (m), 1217 (m), 1199 (m), 1151 (s), 1122 (m), 1056 (m).

Data are consistent with literature values.[169]

**(3a*R**,6a*S**)-Methyl 3-oxohexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate (66)**

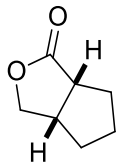



To a mixture of manganese(III) acetate (15.1 g, 56.3 mmol, 2.0 eq.) and copper(II) triflate (10.1 g, 28.1 mmol, 1.0 eq.) under an Ar atmosphere was added a 0.2 M solution of dimethyl 2-(pent-4-en-1-yl)malonate (**65**) (5.64 g, 28.1 mmol, 1.0 eq.) in Ar sparged acetonitrile (140.5 mL). The resulting mixture was heated at 80 °C for 8 h and then cooled to room temperature. 1 M HCl (100 mL) was added to the mixture and extracted with EtOAc (3 × 100 mL). The combined organic extracts were sequentially washed with sat. aq. $NaHCO_3$ solution (300 mL), brine (300 mL), dried ($Na_2SO_4$),

filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20-30% EtOAc/petrol 40-60 gradient) to afford (3a*R**,6a*S**)-methyl 3-oxohexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate (**66**) as a colourless oil (3.46 g, 6.89 mmol, 81%). $\delta_H$ (400 MHz, $CDCl_3$) 4.54 (1H, dd, *J* = 9.2, 7.6 Hz, OC**H**$_2$CH), 4.06 (1H, dd, *J* = 9.2, 2.5 Hz, OC**H**$_2$CH), 3.75 (3H, s, OC**H**$_3$), 3.11–3.04 (1H, m, $CH_2$C**H**(C)$CH_2$), 2.34 (1H, ddd, *J* = 13.3, 9.3, 7.3 Hz, CC**H**$_2$$CH_2$), 2.25–2.18 (1H, m, CC**H**$_2$$CH_2$), 2.09–1.97 (1H, m, CHC**H**$_2$$CH_2$), 1.85–1.74 (1H, m, $CH_2$C**H**$_2$$CH_2$), 1.69–1.53 (2H, m, CHC**H**$_2$$CH_2$ & $CH_2$C**H**$_2$$CH_2$); $\delta_C$ (100 MHz, $CDCl_3$) 176.4 (**C**=O), 170.4 (**C**=O), 73.0 (O$CH_2$CH), 61.5 ($CH_2$**C**($CO_2$Me)C), 53.1 (O**C**$H_3$), 45.5 ($CH_2$**C**H(C)$CH_2$), 34.6 (C**C**$H_2$$CH_2$), 34.0 (CH**C**$H_2$$CH_2$), 25.8 ($CH_2$**C**$H_2$$CH_2$); LRMS *m*/*z* (ESI$^+$) 207 ([M+Na]$^+$, 100%); $\nu_{max}$ (neat)/cm$^{-1}$ 2957 (m, CH), 2916 (m, CH), 2874 (m, CH), 1768 (s, C=O), 1738 (s, C=O), 1477 (m), 1449 (m), 1435 (m), 1379 (m), 1253 (s), 1203 (m), 1169 (m), 1143 (m), 1114 (m), 1054 (m), 1010 (m).

Data are consistent with literature values.[169]

**(3a*S**,6a*R**)-Hexahydro-1*H*-cyclopenta[*c*]furan-1-one (478)**

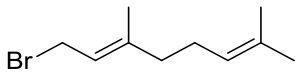



To a stirred solution of (3a*R**,6a*S**)-methyl 3-oxohexahydro-1*H*-cyclopenta[*c*]furan-3a-carboxylate (**66**) (4.19 g, 22.7 mmol, 1.0 eq.) in dry DMF (45.4 mL) was added water (819 mg, 45.5 mmol, 2.0 eq.) and lithium chloride (1.93 g, 45.5 mmol, 2.0 eq.). The resulting mixture was heated at 150 °C for 2 h and then cooled to room temperature. Sat. aq. $NH_4Cl$ solution (50 mL) was added to the mixture and extracted with $Et_2O$ (3 × 50 mL). The combined organic extracts were sequentially washed with water (200 mL), brine (200 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (50% $Et_2O$/petrol 30–40) to afford (3a*S**,6a*R**)-hexahydro-1*H*-cyclopenta[*c*]furan-1-one (**478**) as a

colourless oil (2.03 g, 16.1 mmol, 71%). $R_f$ = 0.24 (50% $Et_2O$/Petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 4.45 (1H, dd, *J* = 9.4, 7.8 Hz, OC**H**$_2$CH), 3.97 (1H, dd, *J* = 9.4, 3.2 Hz, OC**H**$_2$CH),, 2.99 (1H, td, *J* = 9.1,. 2.5 Hz, $O_2$CC**H**$CH_2$), 2.97–2.88 (1H, m, $CH_2$C**H**(C)$CH_2$), 2.11–2.02 (1H, m, CHC**H**$_2$$CH_2$), 1.95–1.84 (2H, m, CHC**H**$_2$$CH_2$ & CHC**H**$_2$$CH_2$), 1.75–1.66 (1H, m, $CH_2$C**H**$_2$$CH_2$), 1.63–1.48 (2H, m, $CH_2$C**H**$_2$$CH_2$ & CHC**H**$_2$$CH_2$); $\delta_C$ (100 MHz, $CDCl_3$) 181.2 (**C**=O), 73.6 (O**C**$H_2$CH), 44.5 ($O_2$C**C**H$CH_2$), 38.9 ($CH_2$**C**H(C)$CH_2$), 33.8 (CH**C**$H_2CH_2$), 30.7 ($CH_2$**C**$H_2CH_2$), 25.5 (CH**C**$H_2CH_2$); LRMS *m*/*z* (ESI$^+$) 149 ([M+Na]$^+$, 100%); $\nu_{max}$ (neat)/cm$^{-1}$ 2958 (s, CH), 2909 (m, CH), 2871 (m, CH), 1757 (s, C=O), 1438 (m), 1451 (m), 1377 (s), 1140 (s), 1099 (s), 1061 (m), 1028 (m), 1010 (m), 969 (s), 932 (s).

Data are consistent with literature values.[169]

**(*E*)-1-Bromo-3,7-dimethylocta-2,6-diene (480)**

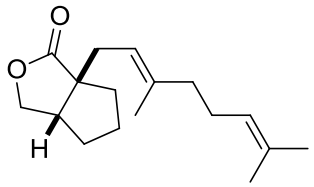



To a stirred solution of geraniol (**479**) (4.63 g, 30.0 mmol, 1.0 eq.) in anhydrous $Et_2O$ (36.0 mL) and hexane (10.3 mL) was added dropwise pyridine (237 mg, 3.00 mmol, 0.1 eq.). The resulting mixture was cooled to 0 °C in an ice/water bath, after which phosphorus tribromide (3.09 g, 11.4 mmol, 0.4 eq.) was added dropwise over a 30 min period. After complete addition, the mixture was stirred at 0 °C for 1 h. Water (50 mL) was added to the mixture and extracted with $Et_2O$ (3 × 50 mL). The combined organic extracts were sequentially washed with brine (150 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure (no heating) to afford (*E*)-1-bromo-3,7-dimethylocta-2,6-diene (**480**) as pale yellow oil (4.66 g, 21.5 mmol, 71%). The crude bromide was used without further purification as it was found to be unstable to column chromatography. $R_f$ = 0.81 (50% $Et_2O$/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 5.53 (1H, t, *J* = 8.4 Hz, $CH_2$C**H**=C($CH_3$)C), 5.11–5.04 (1H, m, $CH_2$C**H**=C($CH_3$)$_2$), 4.03 (2H, d, *J* = 8.4 Hz, BrC**H**$_2$CH=), 2.15–2.02 (4H, m, CC**H**$_2$$CH_2$ & $CH_2$C**H**$_2$CH=), 1.73 (3H, s, C**H**$_3$), 1.69 (3H, s, C**H**$_3$), 1.61 (3H, s,

C**H**$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 143.5 (CH=**C**($CH_3$)$CH_2$), 131.9 (CH=**C**($CH_3$)$_2$), 123.5 ($CH_2$**C**H=C($CH_3$)$_2$), 120.5 ($CH_2$**C**H=C($CH_3$)C), 39.5 ($CH_2$**C**$H_2$CH=), 29.6 (Br**C**$H_2$CH=), 26.1 (C**C**$H_2CH_2$), 25.6 (**C**$H_3$), 17.7 (**C**$H_3$), 15.9 (**C**$H_3$); HRMS *m*/*z* ($FI^+$) found 216.0521, $C_{10}H_{17}{}^{79}Br$ requires 216.0514; $\nu_{max}$ (neat)/$cm^{-1}$ 2968 (m, CH), 2916 (m, CH), 2855 (m, CH), 1655 (m, C=C), 1445 (s), 1377 (m), 1200 (s), 1108 (m).

Data are consistent with literature values.[238]

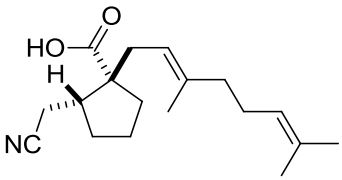
***(3aS*,6aS*)-6a-((E)-3,7-Dimethylocta-2,6-dien-1-yl)hexahydro-1H-cyclopenta[c]furan-1-one (481)***




To a stirred solution of (3a*S**,6a*R**)-hexahydro-1*H*-cyclopenta[*c*]furan-1-one (**478**) (1.34 g, 10.6 mmol, 1.0 eq.) in anhydrous THF (200 mL) cooled to -78 °C in a dry ice/acetone bath, was added a solution of (*E*)-1-bromo-3,7-dimethylocta-2,6-diene (4.61 g, 21.2 mmol, 2.0 eq.) in anhydrous THF (12 mL) followed by dropwise addition of a 1 M solution of LiHMDS in toluene (21.2 mL, 21.2 mmol, 2.0 eq.) over a 2 h period. After complete addition, the mixture was stirred at -78 °C for a further 5 min. The reaction mixture was pored over sat. aq. $NH_4Cl$ solution (200 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were sequentially washed with brine (300 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60) to afford (3a*S**,6a*S**)-6a-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)hexahydro-1*H*-cyclopenta[*c*]furan-1-one (**481**) as a colourless oil (2.11 g, 8.04 mmol, 76%). $R_f$ = 0.27 (10% EtOAc/petrol 40–60); $\delta_H$ (500 MHz, $CDCl_3$) 5.12 (1H, t, *J* = 7.6 Hz, $CH_2$C**H**=C), 5.06 (1H, t, *J* = 6.7 Hz, $CH_2$C**H**=C), 4.36–4.31 (1H, m, OC**H**$_2$CH), 3.91 (1H, dd, *J* = 9.3, 3.2 Hz, OC**H**$_2$CH), 2.61 (1H, dddd, *J* = 11.4, 8.0, 3.2, 3.2 Hz, $CH_2$C**H**(C)$CH_2$), 2.51 (1H, dd, *J* = 14.2, 6.9 Hz, CC**H**$_2$CH=), 2.29 (1H, dd, *J* = 14.2, 8.2 Hz,

CC**H**$_2$CH=), 2.14–2.10 (5H, m, C**H**$_2$), 1.99–1.90 (1H, m, C**H**$_2$), 1.75–1.50 (4H, m, $CH_2$), 1.68 (3H, s, C**H**$_3$), 1.64 (3H, s, C**H**$_3$), 1.60 (3H, s, C**H**$_3$); $\delta_C$ (125 MHz, $CDCl_3$) 183.4 (**C**=O), 139.7 (CH=**C**($CH_3$)$CH_2$), 132.1 (CH=**C**($CH_3$)$_2$), 124.4 ($CH_2$**C**H=C), 119.2 ($CH_2$**C**H=C), 73.3 (O**C**$H_2$CH), 56.3 ($CO_2$**C**(C)$_2CH_2$), 43.3 ($CH_2$**C**H(C)$CH_2$), 40.3 (**C**$H_2$), 38.0 (**C**$H_2$), 35.0 (**C**$H_2$), 34.6 (C**C**$H_2$CH=), 26.9 (**C**$H_2$), 26.1 (=C(**C**$H_3$)$_2$), 25.9 (**C**$H_2$), 28.1 (=C(**C**$H_3$)$_2$), 16.7 (C**C**$H_3$); LRMS *m/z* (ESI$^+$) 263 ([M+H]$^+$, 19%), 285 ([M+Na]$^+$, 100%); HRMS *m/z* (ESI$^+$) found 285.1824, $C_{17}H_{26}NaO_2$ requires 285.1825; $\nu_{max}$ (neat)/cm$^{-1}$ 2960 (m, CH), 2911 (m, CH), 2868 (m, CH), 1762 (s, C=O), 1668 (w, C=C), 1449 (m), 1377 (m), 1202 (m), 1169 (m, C-O), 1142 (m), 1108 (m), 1058 (m), 1011 (m), 978 (m).

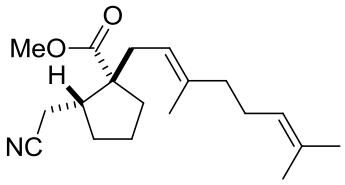
***(1S*,2R*)-2-(Cyanomethyl)-1-((E)-3,7-dimethylocta-2,6-dien-1-yl)cyclopentanecarboxylic acid (482)***




To a stirred solution of (3a*S**,6a*S**)-6a-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)hexahydro-1*H*-cyclopenta[*d*]furan-1-one (**481**) (787 mg, 3.00 mmol, 1.0 eq.) in anhydrous DMSO (60.0 mL), was added in one portion potassium cyanide (977 mg, 15.0 mmol, 5.0 eq.). The resulting mixture was heated at 185 °C for 3 h, then cooled to room temperature. Sat. aq. $NH_4Cl$ solution (100 mL) was added to the mixture followed by 1 M HCl (100 mL) and then extracted with EtOAc (3 × 50 mL). The combined organic extracts were sequentially washed with water (150 mL), brine (150 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (30% EtOAc/petrol 40-60 with 1% AcOH) to afford (1*S**,2*R**)-2-(cyanomethyl)-1-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)cyclopentanecarboxylic acid (**482**) as a colourless oil (843 mg, 2.91 mmol, 97%). $R_f$ = 0.27 (30% EtOAc/petrol 40-60 with 1% AcOH); $\delta_H$ (500 MHz, $CDCl_3$) 5.10 (1H, dd, *J* = 7.4 Hz, $CH_2$C**H**=C), 5.06 (1H, t, *J* = 6.7 Hz, $CH_2$C**H**=C),

2.62 (1H, dd, *J* = 16.8, 4.4 Hz, CHC**H**$_2$CN), 2.57 (1H, dd, *J* = 14.4, 7.3 Hz, (C)C**H**$_2$CH=C), 2.40 (1H, dd, *J* = 16.8, 9.7 Hz, CHC**H**$_2$CN), 2.27–2.19 (2H, m, C**H**$_2$), 2.18–2.00 (6H, m, C**H**$_2$ and $CH_2$C**H**(C)$CH_2$)), 1.91–1.80 (1H, m, C**H**$_2$)1.74–1.61 (3H, m, C**H**$_2$), 1.68 (3H, s, C**H**$_3$), 1.63 (3H, s, C**H**$_3$), 1.61 (3H, s, C**H**$_3$); $\delta_C$ (125 MHz, $CDCl_3$) 181.9 (**C**=O), 139.5 (CH=**C**($CH_3$)$CH_2$), 132.0 (CH=**C**($CH_3$)$_2$), 124.4 ($CH_2$**C**H=C), 119.5 ($CH_2$**C**N), 119.4 ($CH_2$**C**H=C), 56.7 ($CO_2$**C**(C)$_2CH_2$), 45.3 ($CH_2$**C**H(C)$CH_2$), 40.4 (**C**H$_2$), 35.5 (**C**H$_2$), 34.2 (**C**H$_2$), 31. (**C**H$_2$), 26.9 (**C**H$_2$), 26.1 (C**C**H$_3$), 22.3 (**C**H$_2$), 19.5 (**C**H$_2$), 18.1 (=C(**C**H$_3$)$_2$), 16.7 (=C(**C**H$_3$)$_2$); LRMS *m*/*z* (ESI$^+$) 288 ([M-H]$^-$, 100%); HRMS *m*/*z* (ESI$^+$) found 312.1929, $C_{18}H_{27}NNaO_2$ requires 285.1825; $\nu_{max}$ (neat)/cm$^{-1}$ 2960 (m, CH), 2911 (m, CH), 2868 (m, CH), 1762 (s, C=O), 1668 (w, C=C), 1449 (m), 1377 (m), 1202 (m), 1169 (m, C-O), 1142 (m), 1108 (m), 1058 (m), 1011 (m), 978 (m).

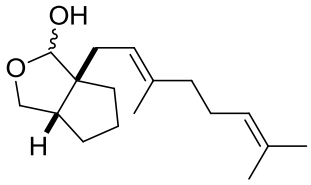
***(1S*,2R*)-Methyl 2-(cyanomethyl)-1-((E)-3,7-dimethylocta-2,6-dien-1-yl)cyclopentanecarboxylate (483)***




To a stirred solution of (1*S**,2*R**)-2-(cyanomethyl)-1-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)cyclopentanecarboxylic acid (**482**) (145 mg, 0.50 mmol, 1.0 eq.) in anhydrous toluene (10 mL) and MeOH (2.5 mL) was added dropwise a 2 M solution of (trimethylsilyl)diazomethane in $Et_2O$ (0.25 mL, 0.50 mmol, 1.0 eq.). The resulting mixture was stirred at room temperature for 30 min, then concentrated under reduced pressure. The residue was purified by flash column chromatography (10% EtOAc/petrol 40-60) to afford (1*S**,2*R**)-methyl 2-(cyanomethyl)-1-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)cyclopentanecarboxylate (**483**) as a colourless oil (146 mg, 0.48 mmol, 97%). $R_f$ = 0.19 (10% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $CDCl_3$) 5.06–4.98 (2H, m, $CH_2$C**H**=C & $CH_2$C**H**=C), 3.67 (3H, s, C**H**$_3$O), 2.55 (1H, dd, *J* = 14.2, 7.4 Hz, CC**H**$_2$CH=), 2.52 (1H, dd, *J* = 16.7, 4.6 Hz, CH(C)C**H**$_2$CN), 2.28 (1H, dd, *J* = 16.7, 9.4 Hz, CH(C)C**H**$_2$CN), 2.22–

1.95 (8H, m, C**H**$_2$, CC**H**$_2$CH= & CH$_2$C**H**(C)CH$_2$), 1.88–1.77 (1H, m, C**H**$_2$), 1.70–1.50 (3H, m, C**H**$_2$), 1.67 (3H, s, C**H**$_3$), 1.60 (3H, s, C**H**$_3$), 1.59 (3H, s, C**H**$_3$); $\delta_C$ (100 MHz, $CDCl_3$) 175.2 (**C**=O), 138.5 (CH=**C**(CH$_3$)CH$_2$), 131.5 (CH=**C**(CH$_3$)$_2$), 124.0 (CH$_2$**C**H=C), 119.3 (CH$_2$**C**H=C), 119.2 (CH$_2$**C**N), 56.5 (CO$_2$**C**(C)$_2$CH$_2$), 51.7 (**C**H$_3$O), 45.0 (CH$_2$**C**H(C)CH$_2$), 39.9 (**C**H$_2$), 35.5 (C**C**H$_2$CH=), 33.5 (**C**H$_2$), 30.9 (**C**H$_2$), 26.4 (**C**H$_2$), 25.7 (=C(**C**H$_3$)$_2$), 21.8 (**C**H$_2$), 19.2 (CH(C)**C**H$_2$CN), 17.7 (=C(**C**H$_3$)$_2$), 16.2 (C**C**H$_3$); LRMS *m*/*z* (ESI$^+$) 304 ([M+H]$^+$, 100%); HRMS *m*/*z* (ESI$^+$) found 326.2089, $C_{19}H_{29}NNaO_2$ requires 326.2091; $\nu_{max}$ (neat)/cm$^{-1}$ 2963 (m, =CH$_2$), 2917 (m, CH), 2248 (w, C≡N), 1694 (s, C=O), 1449 (m), 1377 (s), 1238 (m), 1163 (m), 1107 (m), 1015 (m).

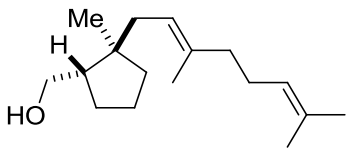
***(3aS*,6aS*)-6a-((E)-3,7-Dimethylocta-2,6-dien-1-yl)hexahydro-1H-cyclopenta[c]furan-1-ol (491)***




To a stirred solution of (3a*S**,6a*S**)-6a-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)hexahydro-1*H*-cyclopenta[*d*]furan-1-one (**481**) (262 mg, 1.00 mmol, 1.0 eq.) in anhydrous DCM (10.0 mL) cooled to -78 °C in a dry ice/acetone bath, was added dropwise a 1 M solution of DIBAL-H in hexanes (1.10 mL, 1.10 mmol, 1.1 eq.) over a 30 min period. After complete addition the mixture was stirred at -78 °C for 1 h. Methanol (0.13 mL, 3.3 eq.) was carefully added dropwise to the mixture followed by a sat. aq. solution of Rochelle's salt (10 mL) and $Et_2O$ (10 mL). The resulting mixture was vigorously stirred at room temperature for 1 h. The organic layer was separated and the aq. layer was further extracted with $Et_2O$ (2 × 10 mL). The combined organic extracts were sequentially washed with brine (50 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/petrol 40-60) to afford (3a*S**,6a*S**)-6a-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)hexahydro-1*H*-cyclopenta[*d*]furan-1-ol

(**491**) (diastereomeric ratio = 1.3:1) as a colourless oil (227 mg, 0.86 mmol, 86%). Characterisation is reported for both epimers of an inseparable mixture of diastereoisomers. $R_f$ = 0.29 (20% EtOAc/petrol 40–60); $\delta_H$ (400 MHz, $C_6D_6$) 5.57–5.50 (1H, m, $CH_2C\mathbf{H}$=C), 5.44–5.27 (1H, m, CH2C**H**'=C), 5.34–5.27 (2H, m, $CH_2C\mathbf{H}$=C & $CH_2C\mathbf{H}$'=C), 4.34 (1H, t, *J* = 8.5 Hz, O**C$H_2$**CH), 4.06 (1H, t, *J* = 8.5 Hz, O**C$H_2$**'CH), 3.96 (1H, d, *J* = 3.4 Hz, OC**H**'(OH)C), 3.78 (1H, d, *J* = 3.0 Hz, OC**H**(OH)C), 3.67 (1H, dd, *J* = 8.5, 7.3 Hz, O**C$H_2$**'CH), 3.47 (1H, dd, *J* = 8.5, 3.2 Hz, O**C$H_2$**CH), 2.65 (1H, dd, *J* = 14.1, 6.4 Hz, CC**$H_2$**CH=), 2.48–2.14 (14H, m, CC**$H_2$**CH=, CC**$H_2$**'CH=, C**$H_2$**, C**$H_2$**', $CH_2C\mathbf{H}$(C)$CH_2$ & $CH_2C\mathbf{H}$'(C)$CH_2$), 2.08–1.95 (1H, m, C**$H_2$**), 1.90–1.32 (12H, m, C**$H_2$** & C**$H_2$**'), 1.79 (3H, s, C**$H_3$**'), 1.78 (3H, s, C**$H_3$**), 1.73 (6H, s, C**$H_3$** & C**$H_3$**'), 1.66 (6H, s, C**$H_3$** & C**$H_3$**'); $\delta_C$ (100 MHz, $C_6D_6$) 137.0 (CH=**C**'($CH_3$)$CH_2$), 136.2 (CH=**C**($CH_3$)$CH_2$), 131.2 (CH=**C**'($CH_3$)$_2$), 131.1 (CH=**C**($CH_3$)$_2$), 124.9 ($CH_2\mathbf{C}$H=C), 124.8 ($CH_2\mathbf{C}$'H=C), 123.0 ($CH_2\mathbf{C}$H=C), 121.8 ($CH_2\mathbf{C}$'H=C), 104.8 (O**C**H(OH)C), 104.1 (O**C**'H(OH)C), 73.1 (O**C**$H_2$CH), 71.6 (O**C**'$H_2$CH), 59.4 ($CO_2\mathbf{C}$(C)$_2CH_2$), 59.4 ($CO_2\mathbf{C}$'(C)$_2CH_2$), 49.9 ($CH_2\mathbf{C}$'H(C)$CH_2$), 48.4 ($CH_2\mathbf{C}$H(C)$CH_2$), 40.4 (**C**$H_2$), 40.3 (**C**$H_2$'), 38.0 (**C**$H_2$'), 36.4 (**C**$H_2$), 34.0 (**C**$H_2$), 33.3 (**C**$H_2$), 32.6 (**C**$H_2$'), 31.3 (**C**$H_2$'), 27.7 (**C**$H_2$'), 27.1 (**C**$H_2$), 27.0 (**C**$H_2$'), 25.9 (**C**$H_2$), 25.9 (**C**$H_3$'), 25.8 (**C**$H_3$), 17.7 (2C, **C**$H_3$ & **C**$H_3$'), 16.3 (**C**$H_3$'), 16.3 (**C**$H_3$); LRMS *m*/*z* ($ESI^+$) 287 ($[M+Na]^+$, 100%); HRMS *m*/*z* ($ESI^+$) found 287.1976, $C_{17}H_{28}NaO_2$ requires 287.1982; $\nu_{max}$ (neat)/$cm^{-1}$ 3396 (br, OH), 2930 (s, CH), 2865 (m, CH), 1668 (w, C=C), 1448 (s), 1376 (m), 1108 (m), 1077 (m), 1054 (s), 1001 (s), 915 (s).

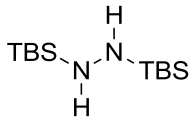
***((1S*,2R*)-2-((E)-3,7-Dimethylocta-2,6-dien-1-yl)-2-methylcyclopentyl)methanol (492)***




A stirred solution of (3a*S**,6a*S**)-6a-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)hexahydro-1*H*-cyclopenta[*d*]furan-1-ol (**491**) (52.9 mg, 0.20 mmol, 1.0 eq.) in diethylene glycol (1.00 mL) was degassed under high vacuum for 45 min, then placed under a argon atmosphere. Hydrazine

monohydrate (250 mg, 1.00 mmol, 1.0 eq.) was added to the mixture and heated at 130 °C for 1 h, then cooled to room temperature. Crushed KOH pellets (56.1 mg, 1.00 mmol, 1.0 eq.) was added in one portion and the resulting mixture was heated at 180 °C for 3.5 h then cooled to room temperature. Water (10 mL) was added to the mixture and extracted with $Et_2O$ (3 × 10 mL). The combined organic extracts were sequentially washed with brine (50 mL), dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (20% EtOAc/petrol 40-60) to afford ((1*S**,2*R**)-2-((*E*)-3,7-dimethylocta-2,6-dien-1-yl)-2-methylcyclopentyl)methanol (**492**) as a colourless oil (43.1 mg, 0.17 mmol, 86%). $R_f$ = 0.27 (20% EtOAc/petrol 40-60); $\delta_H$ (400 MHz, $CDCl_3$) 5.22 (1H, t, *J* = 7.6 Hz, $CH_2C\mathbf{H}$=C), 5.09 (1H, t, *J* = 6.7 Hz, $CH_2C\mathbf{H}$=C), 3.72 (1H, dd, *J* = 10.4, 5.6 Hz, HOC$\mathbf{H_2}$CH), 3.46 (1H, dd, *J* = 10.4, 8.3 Hz, HOC$\mathbf{H_2}$CH), 2.16 (1H, dd, *J* = 14.1, 8.0 Hz, CC$\mathbf{H_2}$CH=), 2.12–1.86 (6H, m, CC$\mathbf{H_2}$CH= & C$\mathbf{H_2}$), 1.81–1.71 (1H, m, $CH_2C\mathbf{H}(C)CH_2$), 1.70–1.50 (3H, m, C$\mathbf{H_2}$), 1.67 (3H, d, *J* = 1.0 Hz, C$\mathbf{H_3}$), 1.60 (6H, s, C$\mathbf{H_3}$), 1.46 (1H, s, $\mathbf{H}OCH_2$), 1.45–1.32 (2H, m, C$\mathbf{H_2}$), 0.81 (3H, s, $C\mathbf{H_3}C(C)_3$); $\delta_C$ (100 MHz, $CDCl_3$) 136.4 (CH=$\mathbf{C}(CH_3)CH_2$), 131.3 (CH=$\mathbf{C}(CH_3)_2$), 124.4 ($CH_2\mathbf{C}H$=C), 121.6 ($CH_2\mathbf{C}H$=C), 64.7 (O$\mathbf{C}H_2CH$), 49.8 ($CH_2\mathbf{C}H(C)CH_2$), 44.1 ($CH_3\mathbf{C}(C)_3$), 40.1 (C$\mathbf{C}H_2CH$=), 39.8 ($\mathbf{C}H_2$), 39.7 ($\mathbf{C}H_2$), 28.7 ($\mathbf{C}H_2$), 26.6 ($\mathbf{C}H_2$), 25.7 ($\mathbf{C}H_3$), 21.8 ($\mathbf{C}H_2$), 20.4 ($\mathbf{C}H_3$), 17.7 ($\mathbf{C}H_3$), 16.1 ($\mathbf{C}H_3C(C)_3$); LRMS *m*/*z* ($ESI^+$) 251 ($[M+H]^+$, 100%); HRMS *m*/*z* ($ESI^+$) found 273.2176, $C_{17}H_{30}NaO$ requires 273.2189; $\nu_{max}$ (neat)/$cm^{-1}$ 3328 (br, OH), 2954 (s, CH), 2925 (s, CH), 2872 (s, CH), 1668 (w, C=C), 1448 (s), 1376 (m), 1108 (m), 1072 (m), 1034 (s), 1013 (s).

**1,2-Bis(*tert*-butyldimethylsilyl)hydrazine (498)**




Prepared according to the procedure reported by Feringa *et al.*[239] To a stirred mixture of hydrazine dihydrochloride (**501**) (1.05 g, 10.0 mmol, 1.0 eq.) and *tert*-butyldimethylsilyl chloride (3.01 g, 20.0 mmol, 2.0 eq.) at room temperature was carefully added triethylamine (5.00 mL). The resulting

mixture was heated at 110 °C for 4.5 h with additional triethylamine (4 × 2 mL) added every 30 min. Pentane (20 mL) was added to the mixture, cooled to -20 °C (freezer) for 3 h, filtered to remove the precipitate and concentrated under reduced pressure to afford 1,2-Bis(*tert*-butyldimethylsilyl)hydrazine (**498**) as a colourless oil (349 mg, 1.34 mmol, 13%). The crude hydrazine was used without further purification and stored at -20 °C (freezer). $\delta_H$ (300 MHz, $CDCl_3$) 2.34 (2H, s, N**H**), 0.88 (18H, s, SiC(C**H**$_3$)$_3$), -0.02 (12H, s, SiC**H**$_3$); $\delta_C$ (75 MHz, $CDCl_3$) 26.9 (6C, SiC(**C**H$_3$)$_3$), 18.1 (2C, Si**C**(CH$_3$)$_3$), -5.6 (4C, Si**C**H$_3$).

Data are consistent with literature values.[239]

# CHAPTER 7: References


1. D. J. Newman, G. M. Cragg, *J. Nat. Prod.,* **2007**, *70,* 461-477.

2. M. C. Wani, H. L. Taylor, M.E. Wall, P. Coggon, A. T. McPhali, *J. Am. Chem. Soc.*, **1971**, *93*, 2325-2327.

3. M. W. Saville, J. Lietzau, J. M. Pluda, W. H. Wilson, R. W. Humphrey, E. Feigel, S. M. Steinberg, S. Broder, R. Yarchoan, *Lancet.*, **1995**, *346*, 26-28.

4. J. Gershenzon, N. Dudareva, *Nature Chemical Biology*, **2007**, *3*, 408-414.

5. L. Ruzicka, *J. Chem. Soc.*, **1932**, 1582-1597.

6. L. Ruzicka, *Cell. Mol. Life Sci.*, **1953**, *9*, 357-367.

7. O. Wallach, *Liebigs Annalen*, **1888**, *246*, 221-239.

8. a) P. Renaud, M. P. Sibi, *Radicals in Organic Synthesis*; Wiley-VCH, 2001.; b) B. Giese, B. Kopping, T. Gobel, J. Dickhaut, G. Thoma, K. Kulicke, F. Trach, In *Organic Reactions*; John Wiley & Sons, Inc., 2004; Vol. 48, pp 301-856.

9. P. Bakuuzis, O. O. S. Campos, M. L. F. Bakuzi, *J. Org. Chem.*, **1976**, *41*, 3261-3264.

10. G. Stork, N. H. Baine, *Tetrahedron Lett.*, **1985**, *26*, 5927-5930.

11. D. P. Curran, D. M. Rakiewicz, *J. Am. Chem. Soc.*, **1985**, *107*, 1448-1449.

12. C. P. Jasperse, D. P. Curran, T. L. Fevig, *Chem. Rev.*, **1991**, *91*, 1237-1286.

13. J. E. Baldwin, *J. Chem. Soc., Chem. Commun.,* **1976**, 734-736.

14. a) P. A. Baguley, J. C. Walton, *Angew. Chem. Int. Ed.,* **1998**, *37*, 3072-3082.; b) D. M. Smith, M. E. Pulling, J. R. Norton, *J. Am. Chem. Soc.,* **2007**, *129*, 770-771.; c) C. Chatgilialoglu, *Chem. Eur. J.,* **2008**, *14*, 2310-2320.

15. B. M. Trost, *Angew. Chem. Int. Ed.,* **1995**, *34*, 259-281.

16. N. Z. Burns, P. S. Baran, R. W. Hoffmann, *Angew. Chem. Int. Ed.,* **2009**, *48*, 2854-2867.

17. a) J. Boivin, M. Yousfi, S. Z. Zard, *Tetrahedron Lett.*, **1994**, *35*, 5629-5632.; b) H. Nagashima, H. Wakamatsu, K. Itoh, Y. Tomo, J. Tsuji, *Tetrahedron Lett.*, **1983**, *24*, 2395-2398.

18. A Clark, *J. Chem. Soc. Rev.*, **2002**, *31*, 1-11.

19. B. B. Snider, *Chem. Rev.*, **1996**, *96*, 339-363.

20. M. Julia, *Acc. Chem. Res.,* **1971**, *4*, 386-392.

21. a) R. Breslow, J. Groves, S. S. Olin, *Tetrahedron Lett.,* **1966**, *7*, 4717-4719; b) R. Breslow, S. S. Olin, J. T. Groves, *Tetrahedron Lett.,* **1968**, *9*, 1837-1840.

22. A. L. J. Beckwith, I. A. Blair, G. Phillipou, *Tetrahedron Lett.*, **1974**, *26*, 2251-2254.

23. A. L. J. Beckwith, C. H. Schiesser, *Tetrahedron*, **1985**, *41*, 3925-3941.

24. D. C. Spellmeyer, K. N. Houk, *J. Org. Chem.*, **1987**, *52*, 959-974.

25. a) L. W. Hessel, C. Romers, *Recueil des Travaux Chimiques des Pays-Bas,* **1969**, *88*, 545-552.; b) V. Amani, N. Safari, H. R. Khavasi, *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy,* **2012**, *85*, 17-24.; c) M. Eshel, A. Bino, *Inorg. Chim. Acta.,* **2001**, *320*, 127-132.

26. L. W. Hessel, C. Romers, *Recl. Trav. Chim. Pays-Bas,* **1969**, *88*, 545-552.

27. J. B. Bush, H. Finkbeiner, *J. Am. Chem. Soc.*, **1968**, *90*, 5903-5904

28. E. I. Heiba, R. M. Dessau, W. J. Koehl, *J. Am. Chem. Soc.*, **1968**, *90*, 5905-5906

29. W. E. Fristad, J. R. Peterson, A. B. Ernst, G. B. Urbi, *Tetrahedron,* **1986**, *42*, 3429-3442.

30. W. E Fristad, J. R. Peterson, *J. Org. Chem.,* **1985**, *50*, 10-18.

31. Y. Yamamoto, M. Ohno, S. Eguchi, *J. Org. Chem.,* **1996**, *61*, 9264-9271.

32. B. B. Snider; In *Radicals in Organic Synthesis*, P. Renaud, M. P. Sibi, Eds. Wiley VCH, New York, **2001**; Vol 1, 198-216.

33. a) E. I Heiba, R. M. Dessau, *J. Am. Chem. Soc.*, **1971**, *93*, 524-527.; b) E. I Heiba, R. M. Dessau, *J. Am. Chem. Soc.*, **1972**, *94*, 2888-2889.

34. J. K. Kochi, *J. Am. Chem. Soc.,* **1965**, *87*, 3609-3619.

35. J. K. Kochi, R. V. Subramanian, *J. Am. Chem. Soc.,* **1965**, *87*, 4855-4866.

36. J. K. Kochi, *Acc. Chem. Res.* **1974**, *7*, 351-360.

37. A. L. J. Beckwith, A. A. Zavitsas, *J. Am. Chem. Soc.,* **1986**, *108*, 8230-8234.

38. J. K. Kochi. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, **1973**; Vol. 1, Chapter 11.

39. W. E. Fristad, J. R. Peterson, *J. Org. Chem.,* **1985**, *50*, 10-18.

40. S. A. Kates, M. A. Dombroski, B. B. Snider, *J. Org. Chem.*, **1990**, *55*, 2427-2436.

41. E. J. Corey, M. C. Kang, *J. Am. Chem. Soc.*, **1984**, *106*, 5384-5385.

42. B. B. Snider, B. Y. F. Wan, B .O. Buckman, B. M. Foxman, *J. Org. Chem.*, **1991**, *56*, 328-334.

43. R. Warsinsky, E. Steckhan, *J. Chem. Soc., Perkin Trans. 1*, **1994**, 2027-2037.

44. B. B. Snider**,** J. E. Merritt**,** M. A. Dombroski**,** B. O. Buckman, *J. Org. Chem.*, **1991**, *56*, 5544-5553.

45. B. B. Snider, B. A. McCarthy, *J. Org. Chem.*, **1993**, *58*, 6217-6223.

46. D. G. Hulcoop, H. M. Sheldrake, J. W. Burton, *Org. Bio. Chem.,* **2004**, *2*, 965-967.

47. L. H. Powell, P. H. Docherty, D. G. Hulcoop, P. D. Kemmitt, J. W. Burton, *Chem. Commun.,* **2008**, 2559–2561.

48. J. J. Davies, T. M. Krulle, J. W. Burton, *Org. Lett.*, **2010**, *12*, 2738-2741.

49. A. Behrens, P. Schaeffer, S. Bernasconi, P. Albrecht, *Org. Lett.*, **2000**, *2*, 1271-1274.

50. T. Yoshida, S. Muraki, K. Takahashi, T. Kato, C. Kabuto, T. Suzuki, T. Uyehara, T. Ohnuma, *J. Chem. Soc., Chem. Commun.*, **1979**, 512-513.

51. M. Nishizawa, A. Inoue, Y. Hayashi, S. Satrapradja, S. Kosela, T. Iwashita, *J. Org. Chem.,* **1984**, *49*, 3660-3662.

52. a) M. Nishizawa, H. Nishide, Y. Hayashi, S. Kosela, *Tetrahedron Lett.*, **1982**, *23*, 1349-1350.; b) M. Nishizawa, A. Inoue, S. Sastrapradja, Y. Hayashi, Phytochemistry, **1983**, *22*, 2083-2085.; c) M. Nishizawa, H. Nishide, Y. Hayashi, S. Kosela, *J. Org. Chem.*, **1983**, *48*, 4462-4466.

53. A. Chatterjee, A. B. Kundu, *Tetrahedron Lett.*, **1967**, *16*, 1471-1476.

54. X. Li, X. Zhou, X. Zhang, J. Su, X. Li, Y. Yan, Y. Zheng, Y. Li, L. Yang Y. Cheng, *J. Nat. Prod.*, **2011**, *74*, 1521-1525.

55. M. Niwa, M. Iguchi, S. Yamamura, *Tetrahedron Lett.*, **1978**, *19*, 4043-4046.

56. Y. Shizuri, S. Yamaguchi, Y. Terada, S. Yamamura, *Tetrahedron Lett.*, **1986**, *27*, 57-60.

57. D. E. Crane, *Chem. Rev.*, **1990**. *90*, 1089-1103.

58. P. Steliopoulos, M. Wust, K.-P. Adamb, A. Mosandl, *Phytochemistry*, **2002**, *60*, 13-20.

59. G. Mehta, N. Krishnamurthy, S. R. Karra, *J. Am. Chem. Soc.,* **1991**, *113*, 5765-5775.

60. G. L. Lange, E. E. Neindert, W. J. Orrom, D. J. Wallace, *Can. J. Chem.,* **1978**, *56*, 1628-1633.

61. A. L. Gemal, J.-L. Luch, *J. Am. Chem. Soc.*, **1981**, *103*, 5454-5459.

62. P. H. Carlson, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.,* **1981**, *46*, 3936-3938.

63. K. Omura, D. Swern, *Tetrahedron,* **1978**, *34*, 1651-1660.

64. T. Hanssen, B. Wickberg, *J. Org. Chem.,* **1992**, *57*, 5370-5376.

65. M. Harmata, K. W. Carter, *Tetrahedron Lett.,* **1997**, *38*, 7985-7988.

66. a) G. Stork, A. Brizzolaras, H. Landesmann, J. Szmuszkovicz, R Terrell, *J. Am. Chem. Soc.*, **1963**, *85*, 207-222.; b)R. R. Johnson, J. A. Nicholson, *J. Org. Chem.*, **1965**, *30*, 2918-2921.

67. a) R. J. Giguere, S. M. Duncan, J. M. Bean, L. Purvis, *Tetrahedron Lett.*, **1988**, 29, 6071-6073.; b) R. J. Giguere, S. M. Tassely, M. I. Rose, V. V. Krishnamurthy, *Tetrahedron Lett.*, **1990**, 31, 4577-4580.

68. P. A. Wender, L. Zhang, *Org. Lett.,* **2000**, *15*, 2323-2326.

69. T. Kitahara K. Mori, *J. Org. Chem.*, **1984**, *49*, 3281-3285.

70. J. Suffert, D. Toussaint, *J. Org. Chem.*, **1995**, *60*, 3550-3553.

71. P. A. Wender, D. Sperandio, *J. Org. Chem.*, **1998**, *63*, 4164-4165.

72. P. M. Dewick, Medicinal Natural Products: A Biosynthetic Approach. John Wiley & Sons, Inc., New York, **1997**, 166.

73. J. D. White, D. N. Gupta, *J. Am. Chem. Soc.*, **1968**, *90*, 6171-6177.

74. K. Tomioka, M. Tanaka, K. Koga, *Chem. Pharm. Bull.*, **1989**, *37*, 1201-1207.

75. a) L. Claisen, *Chem. Ber.,* **1912**, *45*, 3157-3166.; b) L. Claisen, E. Tietze, *Chem. Ber.,* **1925**, *58*, 275-281.; c) L. Claisen, E. Tietze, *Chem. Ber.,* **1926**, *59*, 2344-2351.

76. a) W. A. Kinney, M. J. Coghlan, L. A. Paquette, *J. Am. Chem. Soc.*, **1984**, *106*, 6868-6870.; b) W. A. Kinney, M. J. Coghlan, L. A. Paquette, *J. Am. Chem. Soc.*, **1985**, *107*, 7352-7360.; c) H. J. Kang, L. A. Paquette, *J. Am. Chem. Soc.*, **1990**, *112*, 3252-3253,; d) L. A. Paquette, T. J. Sweeney, *J. Org. Chem.,* **1990**, *55*, 1703-1704.; e) L. A. Paquette, T. J. Sweeney, *Tetrahedron*, **1990**, *46*, 4487-4502.; f) H. J. Kang, L. A. Paquette, *J. Am. Chem. Soc.*, **1991**, *113*, 2610-2621.; g) L. A. Paquette, D. Friedrich, R. D. Rogers, *J. Org. Chem.,* **1991**, *56*, 3841-3849.

77. M. Harmata, C. B. Gamlath, C. L. Barnes, D. E. Jones, *J. Org. Chem.*, **1995**, *60*, 5077-5092.

78. T. Hudlicky, F. J. Koszyk, T. Kutchan, J. P. Sheth, *J. Org. Chem.*, **1980**, *45*, 5020-5027.

79. W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, M. R. Petersen, *J. Am. Chem. Soc.*, **1970**, *92*, 741-743.

80. H. O. House, M. Gall, H. D. Olmstead, *J. Org. Chem.*, **1971**, *36*, 2361-2371.

81. D. Seebach, *Angew. Chem., Int. Ed.,* **1988**, *27,* 1624-1654.

82. F. N. Tebbe, G. W. Parshall, G. S. Reddy, *J. Am. Chem. Soc.,* **1978**, *100*, 3611-3613.

83. N. A. Petasis, E. I. Bzowej, *J. Am. Chem. Soc.*, **1990**, *112*, 6392-6394.

84. K. A. Brown-Wensley, S. L. Buchwald, L. Cannizzo, L. Clawson, S. Ho, D. Meinhardt, J. R. Stille, D. Straus, R. H. Grubbs, *Pure Appl. Chem.,* **1983,** *55*, 1733-1744.

85. S. H. Pine, G. Kim, V. Lee, *Org. Synth.*, **1990**, *69*, 72-79.

86. J. F. Payack, D. L. Hughes, D. Cai, I. F. Cottrell, T. R. Verhoeven, *Org. Synth.*, **2002**, *79*, 19-26.

87. J. F. Payack, M. A. Huffman, D. Cai, D. L. Hughes, P. C. Collins, B. K. Johnson, I. F. Cottrell, L. D. Tuma, *Org. Process Res. Dev.* **2004**, *8*, 256-259.

88. T. J. Katz, T. M. Sivavec, *J. Am. Chem. Soc.*, **1985**, *107*, 737-738.

89. P. F. Korkowski, T. R. Hoye, D. B. Rydberg, *J. Am. Chem. Soc.,* **1988**, *110*, 2676-2678.

90. a) B. M. Trost, G. J. Tanoury, *J. Am. Chem. Soc.,* **1988**, *110*, 1636-1638.; b) N. Chatani, N. Furukawa, H. Sakurai, S. Murai, *Organometallics,* **1996**, *15*, 901-903.

91. G. C. Fu, S. T. Nguyen, R. H. Grubbs, *J. Am. Chem. Soc.*, **1993**, *115*, 9856-9857.

92. a) S. Watanuki, N. Ochifuji, M. Mori, *Organometallics*, **1995**, *14*, 5062-5067.; b) S. Watanuki, N. Mori, *Organometallics*, **1995**, *14*, 5054-5061.

93. A. Kinoshita, M Mori, *Synlett,* **1994**, 1020-1022.

94. M. Mori, *Top. Organomet. Chem.,* **1998**, *1*, 133-154.

95. a) R. Stragies, M. Schuster, S. Blechert, *Angew. Chem., Int. Ed.,* **1997**, *36,* 2518–2520.

96. A. Kinoshita, N. Sakakibara, M. Mori, *J. Am. Chem. Soc.,* **1997**, *119,* 12388–12389.

97. M. Mori, N. Sakakibara, A. Kinoshita, *J. Org. Chem.,* **1998**, *63*, 6082-6083.

98. S. T. Diver, A. J. Giessert, *Chem. Rev.*, **2004**, *104*, 1317-1382.

99. A. Kinoshita, M. Mori, *Synlett,* **1994**, 1020-1022.

100. T. R. Hoye, S. M. Donaldson, T. J. Vos, *Org. Lett.,* **1999**, *2*, 277-279.

101. G. C. Lloyd-Jones, R. G. Margue, J. G. de Vries, *Angew. Chem. Int. Ed.*, **2005**, *44*, 7442-7447.

102. A. Fürstner, K. Langemann, *J. Am. Chem. Soc.*, **1997**, *119*, 9130-9136.

103. J. A. Smulik, S. T. Diver, *Org. Lett.*, **2000**, *2,* 2271-2274.

104. Y. Satake, T. Nishikawa, T. Hiramatsu, H. Araki, M. Isobe, *Synthesis*, **2010**, *12*, 1992-1998.

105. A. Fürstner, K. Langemann, *J. Org. Chem.,* **1996**, *61*, 3942-3943.

106. a) N. Miyaura, K. Yamada, A. Suzuki, *Tetrahedron Lett.*, **1979**, 20, 3437-3440.; b) N. Miyaura, A. Suzuki, *J. Chem. Soc. Chem. Commun.*, **1979**, 866-867.

107. A. Suzuki, *Pure & Appl. Chem.*, **1985**, *57*, 1749–1758.

108. J. K. Stille, K. S. Y. Lau, *Acc. Chem. Res.*, **1977**, *10*, 434-442.

109. K. Matos, J. A. Soderquist, *J. Org. Chem.*, **1998**, *63*, 461-470.

110. B. H. Ridgway, K. A. Woerpel, *J. Org. Chem.,* **1998**, *63*, 458-460.

111. H. C. Brown, *Tetrahedron*, **1961**, *12*, 117-138.

112. N. Miyaura, A. Suzuki, *Chem. Rev.*, **1995**, *95*, 2457-2483.

113. H. C. Brown, S. K. Gupta, *J. Am. Chem. Soc.*, **1972**, *94*, 4370-4371.

114. E. Knoevenagel, *Berichte der deutschen chemischen Gesellschaft*, **1898**, *3*, 2596-2619.

115. G. Cardillo, S. Fabbroni, L. Gentilucci, M. Gianotti, A. Tolomelli, *Synthetic Communications*, **2006**, *33*, 1587-1594.

116. H. Ohno, Y. Takeoka, Y. Kadoh, K. Miyamura, T. Tanaka, *J. Org. Chem.*, **2004**, *69*, 4541-4544.

117. V. Markovnikoff, *Compr. Rend.*, **1875**, *81*, 668-671.

118. H. Ston, H. Shechier, *Org. Synth. Coll.*, **1963**, *4*, 543.

119. S. Irifune, T. Kibayashi, Y. Ishii, M. Ogawa, *Synthesis*, **1988**, *5*, 366-369.

120. R. M. Pagni, G. W. Kabalka, R. Boothe, K. Gaetano, L. J. Stewart, R. Conaway, C. Dial, D. Gray, S. Larson, T. Luidhart, *J. Org. Chem.* **1988**, *53*, 4477-4482.

121. C. K. Reddy, M. Periasamy, *Tetrahedron Lett.,* **1990**, *31*, 1919-1920.

122. P. J. Kropp, K. A. Daus, M. T. Tubergen, K. D. Kepler, V. P. Wilson, S. L. Craig, M. M. Baillargeon, G. W. Breton, *J. Am. Chem. Soc.*, **1993**, *115*, 3071-3079.

123. T. P. Fehlner, *Inorg. Chem.*, **1973**, *12*, 98-102.

124. a) T. D. Nelson, R. D. Crouch, *Synthesis*, **1996**, *9*, 1031-1069; b) R. D. Crouch, *Tetrahedron*, **2004**, *60*, 5833-5871.

125. K. A. De Castro, J. Ko, D. Park, S. Park, H. Rhee, *Org. Process Res. Dev.*, **2007**, *11*, 918-921.

126. a) B. M. Trost, A. H. Weiss, *Adv. Synth. Catal.* **2009**, *351*, 963-983.; b) S. Fujimori, T. F. Knopfel, P. Zarotti, T. Ichikawa, D. Boyall, E. M. Carreira, *Bull. Chem. Soc. Jpn.*, **2007**, *80*, 1635-1657.

127. a) N. Krause and S. Thorand, *Inorg. Chim. Acta*, **1999**, *296*, 1-11.; b) A. G. Csaky, G. Herran, M. C. Murcia, *Chem. Soc. Rev.*, **2010**, *39*, 4080-4102.

128. H. O. House, W. F. Fischer, *J. Org. Chem.*, **1969**, *34*, 3615-3618.

129. J. M. Chong, L. Shen, N. J. Taylor, *J. Am. Chem. Soc.*, **2000**, *122*, 1822-1823.

130. T. R. Wu, J. M. Chong, *J. Am. Chem. Soc.*, **2005**, *127*, 3244-3245.

131. S. Kim, J. M. Lee, *Tetrahedron Lett.*, **1990**, *31*, 7627-7630.

132. J. Schwartz, D. B. Carr, R. T. Hansen, F. M. Dayrit, *J. Org. Chem.*, **1980**, *45*, 3053-3061.

133. Y. S. Kwak, E. J. Corey, *Org. Lett.*, **2004**, *6*, 3385-3388,

134. T. F. Knçpfel, P. Zarotti, T. Ichikawa, E. M. Carreira, *J. Am. Chem. Soc.*, **2005**, *127*, 9682-9683.

135. T. Nishimura, T. Katoh, K. Takatsu, R. Shintani, T. Hayashi, *J. Am. Chem. Soc.*, **2007**, *129*, 14158-14159.

136. T. Nishimura, X. Guo, N. Uchiyama, T. Katoh, T. Hayashi, *J. Am. Chem. Soc.*, **2008**, *130*, 1576-1577.

137. T. Nishimura, T. Sawano, T. Hayashi, *Angew. Chem. Int. Ed.*, **2009**, *48*, 8057-8059.

138. Y. Takaya, M. Ogasawara, T. Hayashi, *J. Am. Chem. Soc.*, **1998**, *120*, 5579-5580.

139. H. Werner, S. Poelsma, M. E. Schneider, B. Windmiiller, D. Barth, *Chem. Ber.*, **1996**, *129*. 647-652.

140. A. De Mico, R. Margarita, L. Parlanti, A. Vescovi, G. Piancatelli, *J. Org. Chem.*, **1997**, *62*, 6974-6977.

141. C. Margot, M. Rizzolio, M. Schlosser, *Tetrahedron,* **1990**, *46*, 2411-2424.

142. R. Noyori, S. Murata, M. Suzuki, *Tetrahedron*, **1981**, *31*, 3899-3910.

143. R. Lagoutte, J. A. Wilkinson, *Tetrahedron Lett.*, **2010**, *51*, 6942-6944.

144. A. J. Welford, I. Collins, *J. Nat. Prod.* **2011**, *74*, 2318-2328.

145. R. Kazlauskas, P. T. Murphy, R. J. Wells, P. Schonholzer, *Tetrahedron Lett.*, **1977**, *18*, 4643-4646.

146. P. Sharma, M. Alam, *J. Chem. Soc., Perkin Trans. 1*, **1988**, 2537-2540.

147. a) L. A. Paquette, O. M. Moradei, P. Bernardelli, T. Lange, *Org. Lett.* **2000**, *2*, 1875-1878.; b) L. E. Overman, L. D. Pennington, *Org. Lett.,* **2000**, *2*, 2683-2686.; c) D. W. C. MacMillan, L. E. Overman, L. D. Pennington, *J. Am. Chem. Soc.*, **2001**, *123*, 9033-9044.; d) P. Bernardelli, O. M. Moradei, D. Friedrich, J. Yang, F. Gallou, B. P. Dyck, R. W. Doskotch, T. Lange, L. A. Paquette, *J. Am. Chem. Soc.*, **2001**, *123*, 9021-9032.; e) F. Gallou, D. W. C. MacMillan, L. E. Overman, L. A. Paquette, L. D. Pennington, J. Yang, *Org. Lett.*, **2001**, *3*, 135-137.; f) B. Wang, A. P. Ramirez, J. J. Slade, J. P. Morken, *J. Am. Chem. Soc.*, **2010**, *132*, 16380-16382.

148. M. A. Brodney, J. P. O'Leary, J. A. Hansen, R. J. Giguere, *Synth. Commun.*, **1995**, *25*, 521-531.

149. H.-J. Borschberg, Ph.D. Thesis, Eidenøssischen Technischen Hochschule (ETH) Zurich, No. 5578, **1975**.

150. C. Ireland, D. J. Faulkner, J. Finer, J. Clardy, *J. Am. Chem. Soc.*, **1976**, *98*, 4664-4665.

151. A. D. Rodriguez, E. Gonzlez, C. RamIrez, *Tetrahedron*, **1998**, *54*, 11683-11729.

152. a) M. Hiersemann, H. Helmboldt, *Top. Curr. Chem.*, volume 243. Springer-Verlag, 2005.; b) X.-J. Hao, J Zhou, X.-D. Luo, X.-H. Cai, *Helv. Chim. Acta*, **2005**, *88*, 2938-2943.; c) Y Wang, L. J. Harrison, B. C. Tan, *Tetrahedron*, **2009**, *65*, 4035-4043.; d) Y. Viano, D. Bonhomme, M. Camps, J.-F. Briand, A. Ortalo-Magne, Y. Blache, L. Piovetti, G. Culioli, *J. Nat. Prod.*, **2009**, *72*, 1299-1304.; e) X.-H. Cai, Y.-Y. Wang, P.-J. Zhao, Y. Li, X.-D. Luo, *Phytochemistry*, **2010**, *71*, 1020-1024.; f) M. T. Rojo de Almeida, G. E. Siless, C. D. Perez, M. J. Veloso, L. Schejter, L. Puricelli, J. A. Palermo, *J. Nat. Prod.*, **2010**, *73*, 1714-1717.

153. T. Toyomasu, M. Tsukahara, H. Kenmoku, M. Anada, H. Nitta, J. Ohkanda, W. Mitsuhashi, T. Sassa, N. Kato, N. *Org. Lett.*, **2009**, *11*, 3044-3047.

154. B. F. Bowden, J.-C. Braekman, J. C. Coll, S. J. Mitchell, *Aust. J. Chem.*, **1980**, *33*, 927-932.

155. G. Mehta, *Pure Appl. Chem.*, **1990**, *62*, 1263-1268.

156. G. Illuminati, L. Mandolini, B. Masci, *J. Am. Chem. Soc.,* **1975**, *97*, 4960-4966.

157. E. Corey, R. S. Kania, *Tetrahedron Lett.*, **1998**, *39*, 741-744.

158. a) E. Yoshii K. Talceda, M. Urahata, H. Takayanagi, H. Ogura, *J. Org Chem.*, **1986**, *51*, 4735-4737.; b) E. Yoshii, H. Nakamura, E. Kawanisht, K. Takeda, *Tetrahedron Lett.,* **1991**, 32, 4925-4928.

159. D. R. Williams, P. J. Coleman, C. R. Nevill, L. A. Robinson, *Tetrahedron Lett.*, **1993**, *34*, 7895-7898.

160. L. Jenny, H.-J. Borschberg, *Helv. Chim. Acta*, **1995**, *78*, 715-731.

161. a) J. E. McMurry, K. L. Kees, *J. Org. Chem.*, **1977**, *42*, 2655-2656.; b) J. E. McMurry, T. Lectka, J G. Rico, *J. Org. Chem.*, **1989**, *54*, 3748-3749.; c) J. E. McMurry, *Chem. Rev.*, **1989**, *89*, 1513-1524.

162. T. Hu, E. J. Corey, *Org. Lett.*, **2002**, *4*, 2441-2443.

163. a) E. J. Corey, S. Lin, *J. Am. Chem. Soc.*, **1996**, *118*, 8765-8766.; b) E. J. Corey, S. Lin, G. Luo, G. *Tetrahedron Lett.*, **1997**, *38*, 5771-5774.

164. H. Miyaoka, Y. Isaji, H. Mitome, Y. Yamada, *Tetrahedron*, **2003**, *59*, 61-75.

165. I. R. Baldwin, R. J. Whitby, *Chem. Commun.*, **2003**, 2786-2787.

166. J. Kingsbury, E. Corey, *J. Am. Chem. Soc.*, **2005**, *127*, 13813-13815.

167. S. Snyder, E. Corey, *J. Am. Chem. Soc.*, **2006**, *128*, 740-742.

168. J. Bian, M. Van Wingerden, J. M. Ready, *J. Am. Chem. Soc.*, **2006**, *128*, 7428-7429.

169. M. S. Hallside, D.Phil. Thesis, University of Oxford, **2011**.

170. K. N. Houk, S. R. Moses, Y.-D. Wu, N. G. Rondan, V. Jager, R. Schohe, F. R. Fronczekl, *J. Am. Chem. Soc.*, **1984**, *106*, 3880-3882.

171. M. A. Umbreit, K. B. Sharpless, *J. Am. Chem. Soc.*, **1977**, *99*, 5526-5528.

172. M. E. Maier, *Angew. Chem. Int. Ed.,* **2000**, *39*, 2073-2077.

173. A. Gardillas, J. Perez-Castells, *Angew. Chem. Int. Ed.,* **2006**, 45, 6086-6101.

174. T. Ichige, Y. Okano, N. Kanoh, M. Nakata, *J. Org. Chem.*, **2009**, *74*, 230-243.

175. J. S. J. Lua, Part II Thesis, University of Oxford, **2012**.

176. a) S. Ohira, *Synth. Commun.*, **1989**, *19*, 561-564.; b) S. Müller, B. Liepold, G. J. Roth, H. J. Bestmann, *Synlett*, **1996**, *6*, 521-522.; c) G. Roth, B. Liepold, S. Müller, H. J. Bestmann, *Synthesis*, **2004**, 1, 59-62.

177. E. Quesada, R. J. K. Taylor, *Tetrahedron Lett.*, **2005**, *46*, 6473-6476.

178. D. E. Van Horn, E. Negishi, *J. Am. Chem. Soc.*, **1978**, 100, 2252-2254.

179. C. Yu, B. Liu, L. Hu, *Tetrahedron Lett.*, **2000**, *41*, 4281-4285.

180. a) E. Clemmensen, *Ber. Dtsch. Chem. Ges.*, **1914**, *47*, 51-63.; b) E. Clemmensen, *Ber. Dtsch. Chem. Ges.*, **1914**, *47*, 681-687.; c) E. Vedejs, *Org. React.*, **1975**, *22*, 401-415.

181. a) J. Kishner, *J. Russ. Phys. Chem. Soc.* **1911**, *43*, 582-595.; b) C. Wolff, *Justus Liebigs Ann. Chem.*, **1912**, *394*, 86-108.; c) Huang-Minlon, *J. Am. Chem. Soc.*, **1946**, *68*, 2487-2488.; d) D. Todd, *Org. React.*, **1948**, *4*, 378-422.

182. a) R. A. Benkeser, K. M. Foley, F. M. Gaul, G. S. Li, *J. Am. Chem. Soc.*, **1970**, *92*, 3232-3233.; b) G. S. Li, D. F. Ehler, R. A. Benkeser, *Org. Synth.*, **1988**, *50*, 747.; c) J Seyden-Penne, Reductions by the Alumino- and Borohydrides in Organic Synthesis; Wiley-VCH: Weinheim, **1997**, Chap. 2.

183. M. T. Mujica, M. M. Afonso, A. Galindo, J. A, Palenzuela, *J. Org. Chem.*, **1998**, *63*, 9728-9738.

184. D. Addis, S. Das, K. Junge, M. Beller, *Angew. Chem. Int. Ed.*, **2011**, *50*, 6004-6011.

185. D. J. Parks, W. E. Piers, *J. Am. Chem. Soc.*, **1996**, *118*, 9440-9441.

186. L. Luo, T. J. Marks, *Top. Catal.*, **1999**, *7*, 97-106.

187. a) V. Gevorgyan, J.-X. Liu, M. Rubin, S. Benson, Y. Yamamoto, *Tetrahedron Lett.*, **1999**, *40*, 8919-8922.; b) V. Gevorgyan, M. Rubin, S. Benson, J.-X. Liu, Y. Yamamoto, *J. Org. Chem.*, **2000**, *65*, 6179-6186.

188. a) V. Gevorgyan, M. Rubin, J.-X. Liu, Y. Yamamoto, *J. Org. Chem.*, **2001**, *66*, 1672-1675.; b) G. B. Bajracharya, T. Nogami, T. Jin, K. Matsuda, V. Gevorgyan, Y. Yamamoto, *Synthesis*, **2004**, *2*, 308-311.

189. E. Kuhnel, D. D. P. Laffan, G. C. Lloyd-Jones, T. Martinez del Campo, I. R. Shepperson, J. L. Slaughter, *Angew. Chem. Int. Ed.*, **2007**, *46*, 7075-7078.

190. L. H. Amundsen, L. S. Nelson, *J. Am. Chem. Soc.*, **1951**, *73*, 242-244.

191. M. T. Crimmins, D. K. Jung, J. L. Gray, *J. Am. Chem. Soc.*, **1993**, *115*, 3146-3155.

192. Y. Yamamoto, A. Sakamoto, T. Nishioka, J. Oda, Y. Fukazawa, *J. Org. Chem.*, **1991**, *56*, 1112-1119.

193. S. Hanessian, Y. Yang, S. Giroux, V. Mascitti, J. Ma, F. Raeppel, *J. Am. Chem. Soc.*, **2003**, *125*, 13784-13792.

194. a) D. Brett, I. M. Dowine, J. B. Lee, *J. Org. Chem.*, **1967**, *32*, 855–856.; b) H. Loibner, E. Zbiral, *Helv. Chim. Acta*, **1976**, 59, 2100–2113.; c) A. Mizuno, Y. Hamada, T. Shioiri, *Synthesis*, **1980**, 1007–1009.; d) R. Davis, K. G. Untch, *J. Org. Chem.*, **1981**, *46*, 2985–2987.; e) K. W. Bogdan, *Synth.*

*Commun.*, **1993**, *23*, 2481–2484.; f) N. Iranpoor, H. Firouzabadi, B. Akhlaghinia, N. Nowrouzi, *J. Org. Chem.*, **2004**, *69*, 2562–2564.; g) S. Iida, H. Togo, *Synlett*, **2005**, 1456–1458.; h) S. Iida, H. Togo, *Synlett,* **2007**, 407–410.

195. M. N. S. Rad, A. Khalafi-Nezhad, S. Behrouz, M. A. Faghihi, *Tetrahedron Lett.*, **2007**, *48*, 6779-6784.

196. Huang-Minlon, *J. Am. Chem. Soc.*, **1946**, *68*, 2487-2488.

197. D. J. Cram, M. R. V. Sahyun, G. R. Knox, *J. Am. Chem. Soc.*, **1962**, *84*, 1734-1735.

198. M. F. Grundon, H. B. Henbest, M. D. Scott, *J. Chem. Soc.*, **1963**, *1*, 1855-1858.

199. a) D. H. R. Barton, R. E. O'Brien, S. Sternhell, *J. Chem. Soc.*, **1962**, 470-476; b) M. F. Grundon, H. B. Henbest, M. D. Scott, *J. Chem. Soc.*, **1963**, 1855-1858.; c) A. Pross, S. Sternhell, *Aust. J. Chem.,* **1970**, *23*, 989-1003.; d) T. L. Holton, H. Shechter, *J. Org. Chem.*, **1995**, 60, 4725-4729.; e) D. Sanz, M. A. Ponce, R. M. Claramunt, C. Fernandez-Castano, C. Foces-Foces, J. Elguero, *J. Phys. Org. Chem.*, **1999**, *12*, 455-469.

200. M. E. Furrow, A. G. Myers, , *J. Am. Chem. Soc.*, **2004**, *126*, 5436-5445.

201. S. E. Adams, J. M. Goodman, R. J. Kidd, A. D. McNaught, P. Murray-Rust, F. R. Norton, J. A. Townsend, C. A. Waudby, *Org. Biomol. Chem.*, **2004**, *2*, 3067-3070.

202. K. Schank, S. Bügler, H. Folz, N. Schott, *Helv. Chim. Acta*, **2007**, *90*, 1606-1649.

203. A. K. Ghosh, G. Gong, *J. Org. Chem.*, **2006**, *71*, 1085-1093.

204. R. W. Ware, C. S. Day, S. B. King, *J. Org. Chem.,* **2002**, *67*, 6174-6180.

205. W. D. Wulff, T. S. Powers, *J. Org. Chem.*, **1993**, *58*, 2381-2393.

206. O. Kitagawa, H. Fujiwara, T. Suzuki, T. Taguchi, M. Shiro, *J. Org. Chem.,* **2000**, *65*, 6819-6825.

207. O. V. Larionov, E. J. Corey, *J. Am. Chem. Soc.*, **2008**, *130*, 2954-2955.

208. H. Takahata, T. Takamatsu, T. Yamazaki, *J. Org. Chem.*, **1989**, *54*, 4812-4822.

209. M. T. Didiuk, C. W. Johannes, J. P. Morken, A. H. Hoveyda, *J. Am. Chem. Soc.*, **1995**, *117*, 7097-7104.

210. T. Bekele, S. R. Brunette, M. A. Lipton, *J. Org. Chem.,* **2003**, *68*, 8471-8479.

211. T. Achard, A. Lepronier, Y. Gimbert, H. Clavier, L. Giordano, A. Tenaglia, G. Buono, *Angew. Chem. Int. Ed.,* **2011**, *50*, 3552-3556.

212. M. Lai, D. Li, E. Oh, and H. Liu, *J. Am. Chem. Soc.*, **1993**, *115*, 1619-1628.

213. F. Beaufils, F. Denes, P. Renaud, *Angew. Chem. Int. Ed.*, **2005**, *44*, 5273 -5275.

214. C. U. Grunager, B. Breit, *Angew. Chem. Int. Ed.*, **2008**, *47*, 7346-7349.

215. L. Miao, I. Haque, M. R. Manzoni, W. S. Tham, S. R. Chemler, *Org. Lett.*, **2010**, *12*, 4739-4741.

216. M. A. Ciufolini, S. Zhu, M. V. Deaton, *J. Org. Chem.,* **1997**, *62*, 7806-7811.

217. R. Schiess, J. Gertsch, W. B. Schweizer, K. Altmann, *Org. Lett.*, **2011**, *13*, 1436-1439.

218. A. Ahmed, E. K. Hoegenauer, V. S. Enev, M. Hanbauer, H. Kaehlig, E. Ohler, J. Mulzer, *J. Org. Chem.*, **2003**, 68, 3026-3042.

219. I. Shiina, Y. Kawakita, R. Ibuka, K. Yokoyama, Y. Yamai, *Chem. Commun.*, **2005**, 4062-4064.

220. D. M. Nickerson, A. E. Mattson, *Chem. Eur. J.*, **2012**, *18*, 8310-8314.

221. L. Provencher, H. Wynn, J. B. Jones, *Tetrahedron: Asymmetry*, **1993**, *4*, 2025-2040.

222. C. A. Miller, R. A. Batey, *Org. Lett.*, **2004**, *6*, 699-702.

223. J. F. W. Keana, M. D. Ogan, *J. Am. Chem. Soc.*, **1986**, *108*, 7951-7957.

224. T. Tsunoda, M. Suzuki, R. Nyori, *Tetrahedron Lett.*, **1980**, *21*, 71-74.

225. K. C. Nicolaou, D. G. McGarry, P. K. Somers, B. H. Kim, W. W. Ogilvie, G. Yiannikouros, C. V. C. Prasad, C. A. Veale, R.R. Hark, *J. Am. Chem. Soc.*, **1990**, *112*, 6263-6276.

226. C. Margot, M. Rizzolio, M. Schlosser, *Tetrahedron*, **1990**, *7*, 2411-2424.

227. W. D. Wulff, T. S. Powers, *J. Org. Chem.*, **1993**, *58*, 2381-2393.

228. M. C. Clasby, D. Craig, A. M. Slawin, A. J. White, D. J. Williams, *Tetrahedron*, **1995**, *5*, 1509-1532.

229. E. Vedejs, T. H. Eberlein, R. G. Wilde, *J. Org. Chem.*, **1988**, *53*, 2220-2226.

230. B. M. Trost, G. B. Tometzki, *Synthesis*, **1991**, *12*, 1235-1245.

231. R. J. Sundberg, P. A. Bukowick, F. O. Holcombe, *J. Org. Chem.*, **1967**, *32*, 2938-2941.

232. T. Laird, W. D. Ollis, I. O. Sutherland, *J. Chem. Soc., Perkin Trans. 1*, **1980**, 2033-2048.

233. P. Wasnaire, M. Wiaux, R. Touillaux, I. E. Marko, *Tetrahedron Lett.*, **2006**, *47*, 985-989.

234. J. She, J. W. Lampe, A. B. Polianski, P. S. Watson, *Tetrahedron Lett.*, **2009**, *50*, 298-301.

235. B. B. Snider, E. Ron, B. W. Burbaum, *J. Org. Chem.*, **1987**, *52*, 5413-5419.

236. K. M Foote, C. J Hayes, M. P John, G. Pattenden, *Org. Biomol. Chem.*, **2003**, *1*, 3917-3948.

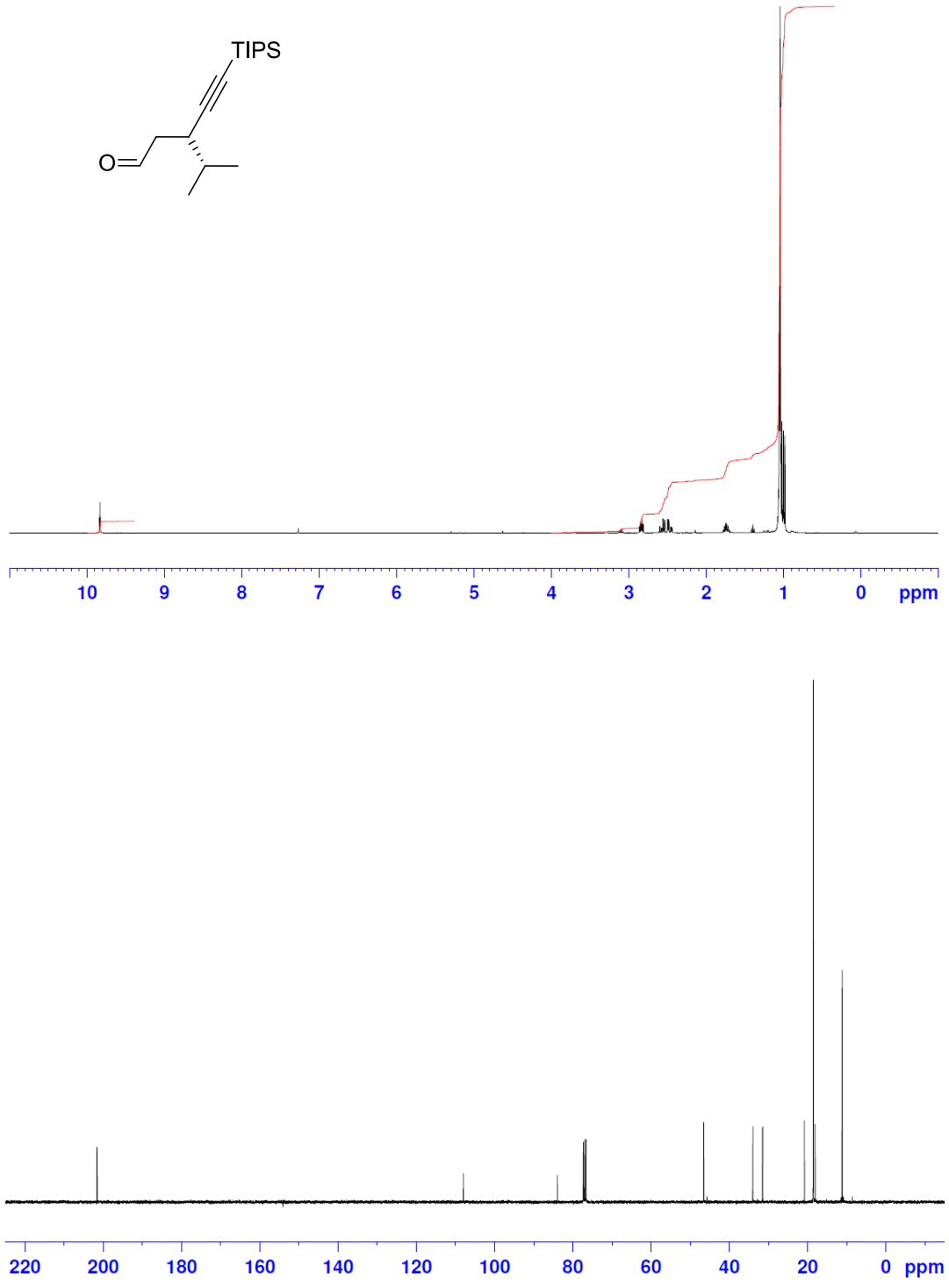
237. J. G. Sokol, C. S. Korapala, P. S. White, J. J. Becker, M. R. Gagne, *Angew. Chem. Int. Ed.*, **2011**, *50*, 5658-5661.

238. S. Nakano, S. Ohashi, T. Hoshino, *Org. Biomol. Chem.*, **2004**, *2*, 2012-2022.

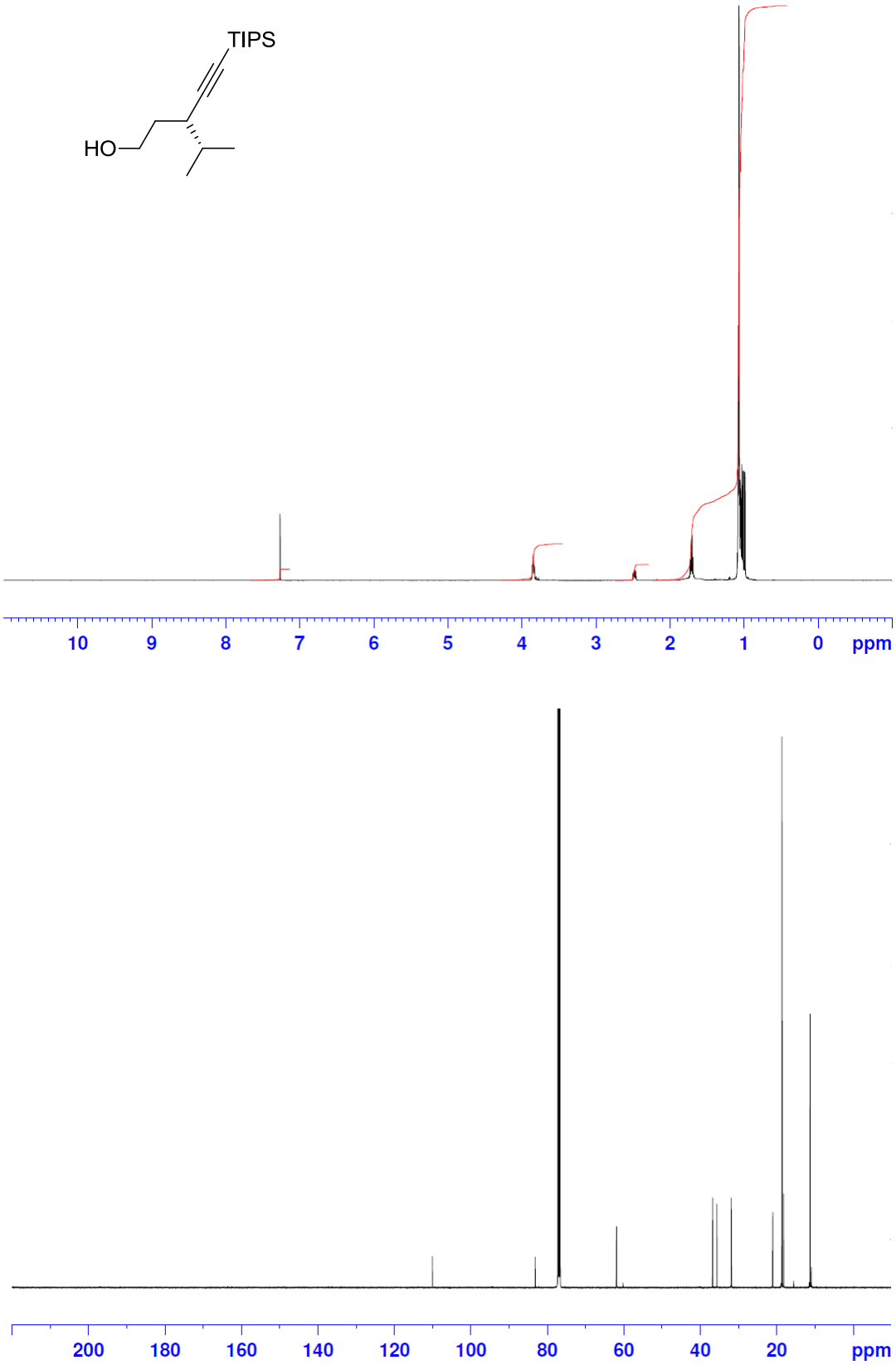
239. T. C. Pijper, D. Pijper, M. M. Pollard, F. Dumur, S. G. Davey, A. Meetsma, B. L. Feringa, *J. Org. Chem.*, **2010**, *75*, 825-838.

# Appendix 1: Selected spectra

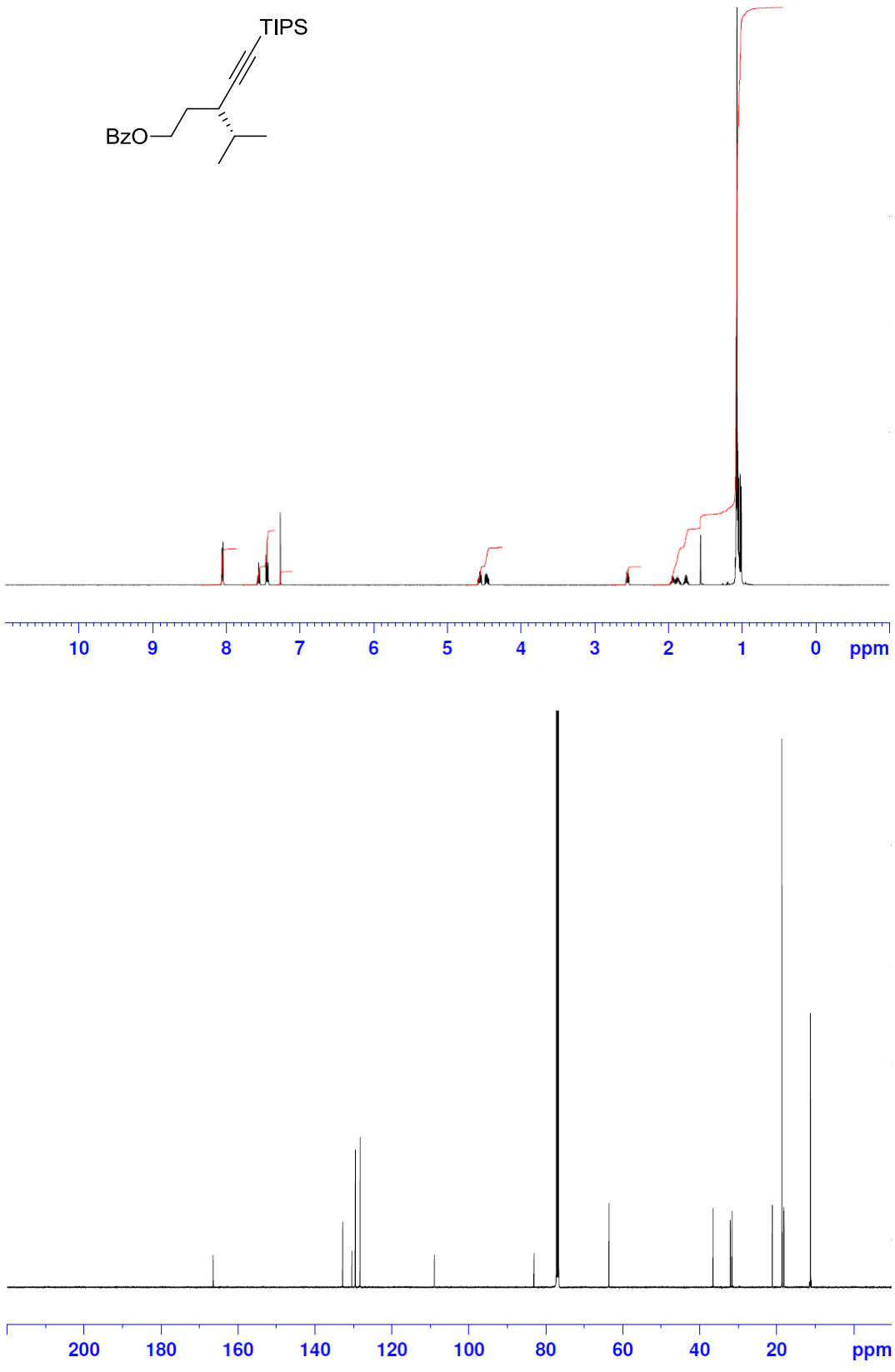
**(*S*)-3-Isopropyl-5-(triisopropylsilyl)pent-4-ynal**

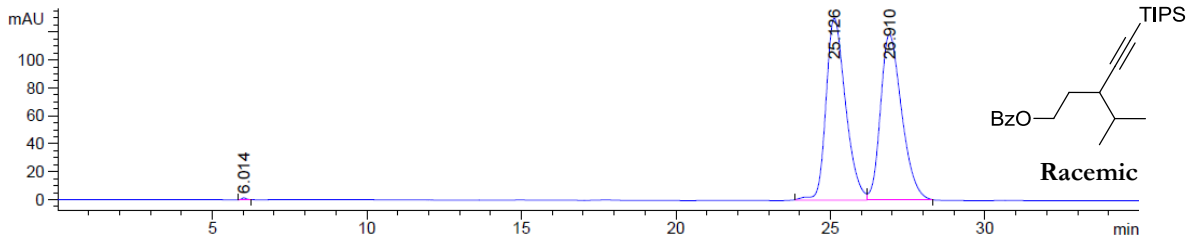


***(S)-3-Isopropyl-5-(triisopropylsilyl)pent-4-yn-1-ol***



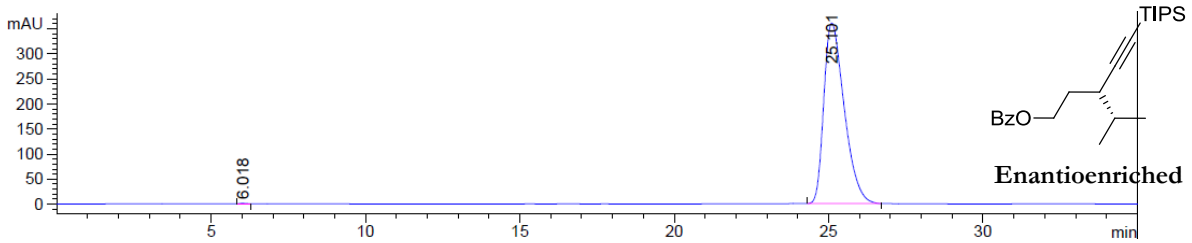
***(S)-3-Isopropyl-5-(triisopropylsilyl)pent-4-yn-1-yl benzoate***





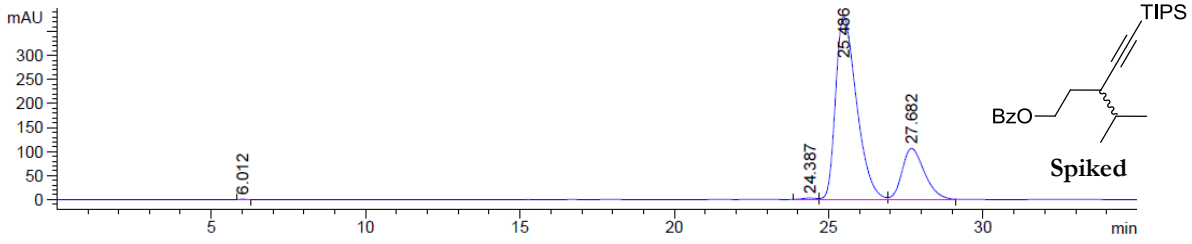

Signal 4: DAD1 D, Sig=230,16 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 6.014 | BB | 0.1530 | 12.85503 | 1.28172 | 0.1126 |
| 2 | 25.126 | BV | 0.6722 | 5736.58496 | 130.15561 | 50.2548 |
| 3 | 26.910 | VB | 0.7312 | 5665.55811 | 118.62328 | 49.6326 |
| Totals : | | | | 1.14150e4 | 250.06061 | |




Signal 4: DAD1 D, Sig=230,16 Ref=360,100

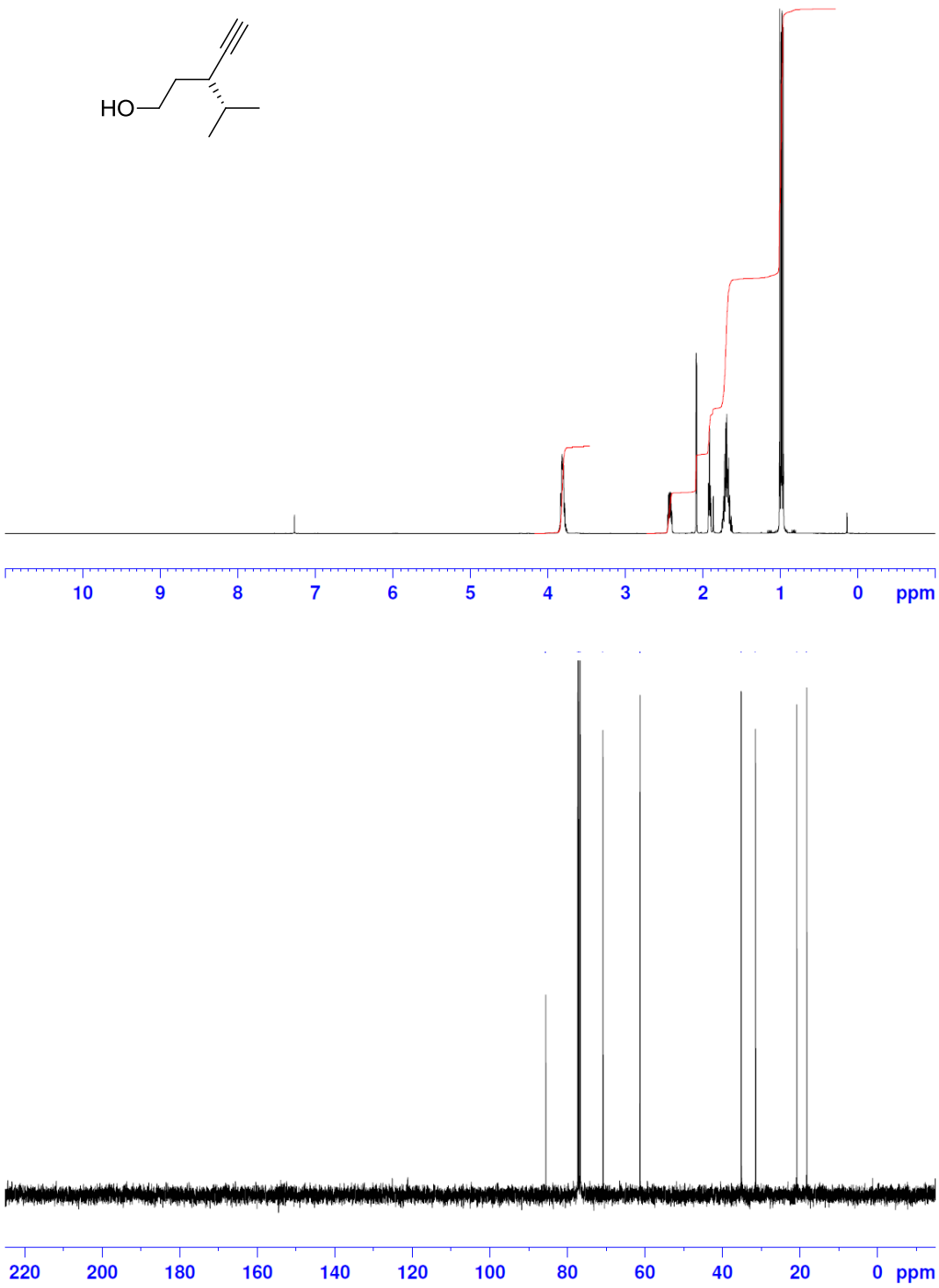
| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 6.018 | BB | 0.1525 | 13.19739 | 1.32118 | 0.0797 |
| 2 | 25.101 | BB | 0.7059 | 1.65458e4 | 360.19833 | 99.9203 |
| Totals : | | | | 1.65590e4 | 361.51952 | |



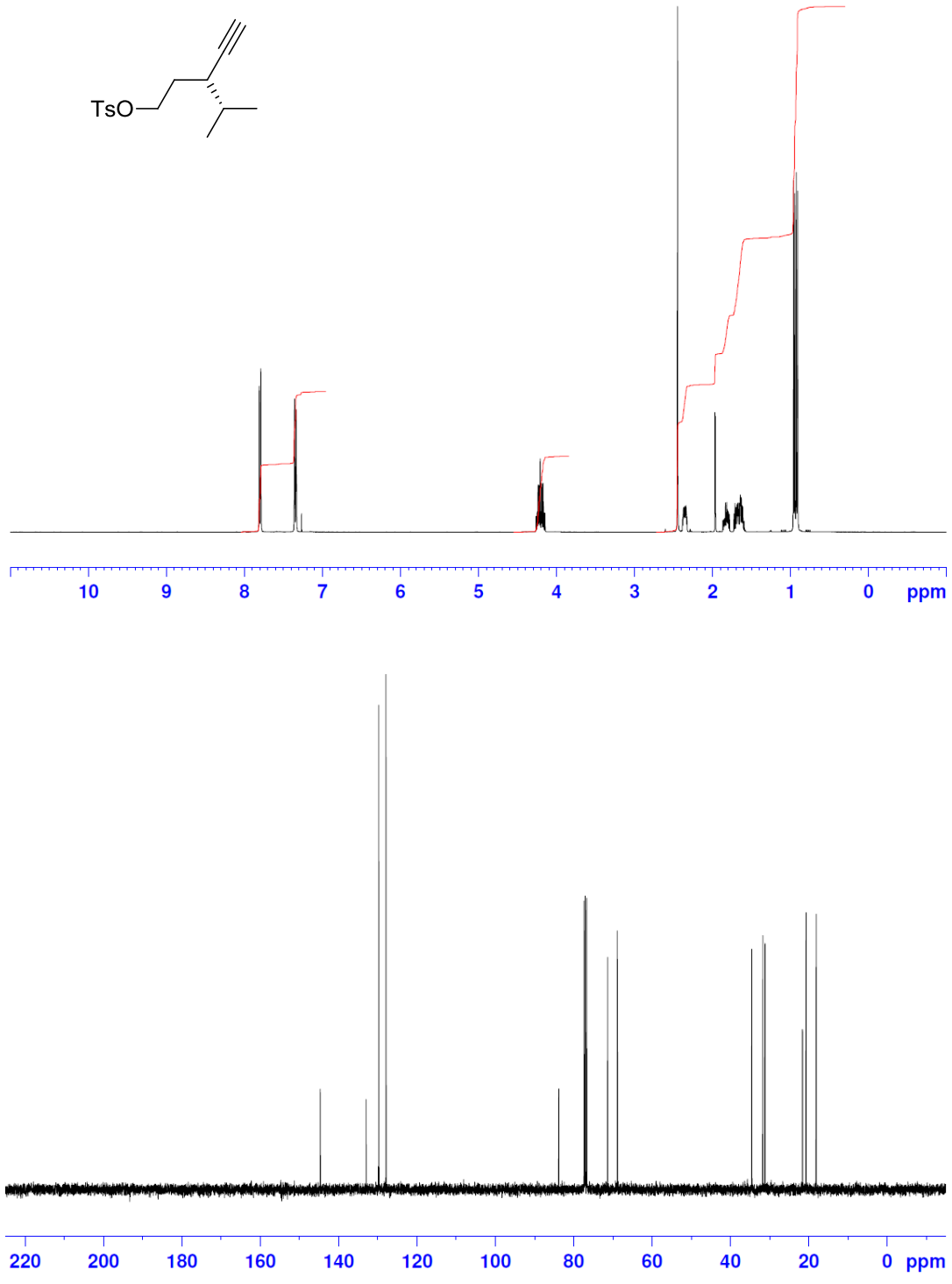

Signal 4: DAD1 D, Sig=230,16 Ref=360,100

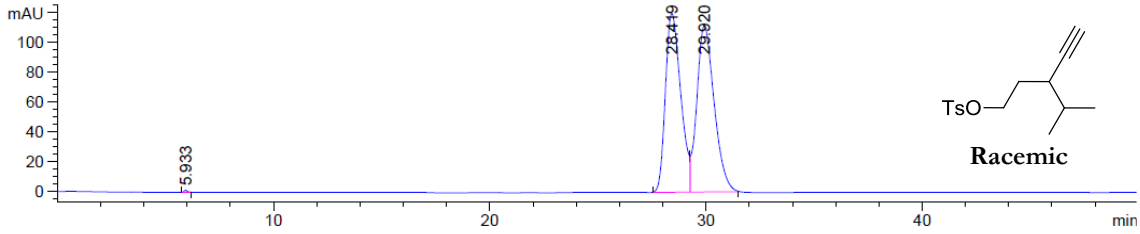
| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 6.012 | BB | 0.1553 | 12.62923 | 1.23535 | 0.0538 |
| 2 | 24.387 | BV | 0.4649 | 100.87181 | 3.08996 | 0.4301 |
| 3 | 25.486 | VB | 0.7285 | 1.79951e4 | 379.95398 | 76.7228 |
| 4 | 27.682 | BB | 0.7740 | 5346.12305 | 106.08109 | 22.7933 |
| Totals : | | | | 2.34548e4 | 490.36037 | |

***(S)-3-Isopropylpent-4-yn-1-ol***



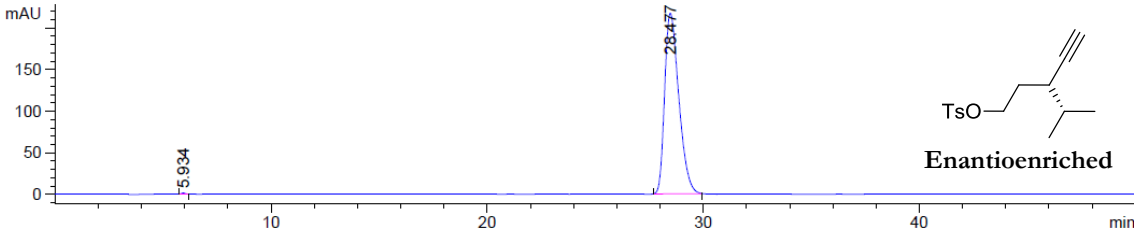
***(S)-3-Isopropylpent-4-yn-1-yl 4-methylbenzenesulfonate***





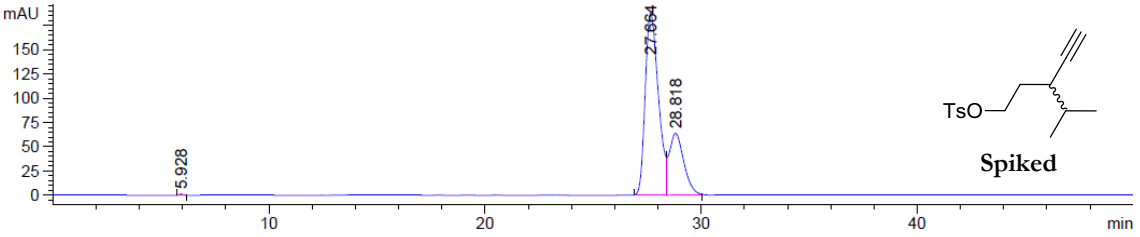

Signal 4: DAD1 D, Sig=230,16 Ref=360,100

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 5.933 | BB | 0.1505 | 13.03433 | 1.30533 | 0.1074 |
| 2 | 28.419 | BV | 0.7549 | 5891.51807 | 119.98285 | 48.5458 |
| 3 | 29.920 | VB | 0.8482 | 6231.44336 | 111.46406 | 51.3468 |
| Totals : | | | | 1.21360e4 | 232.75224 | |



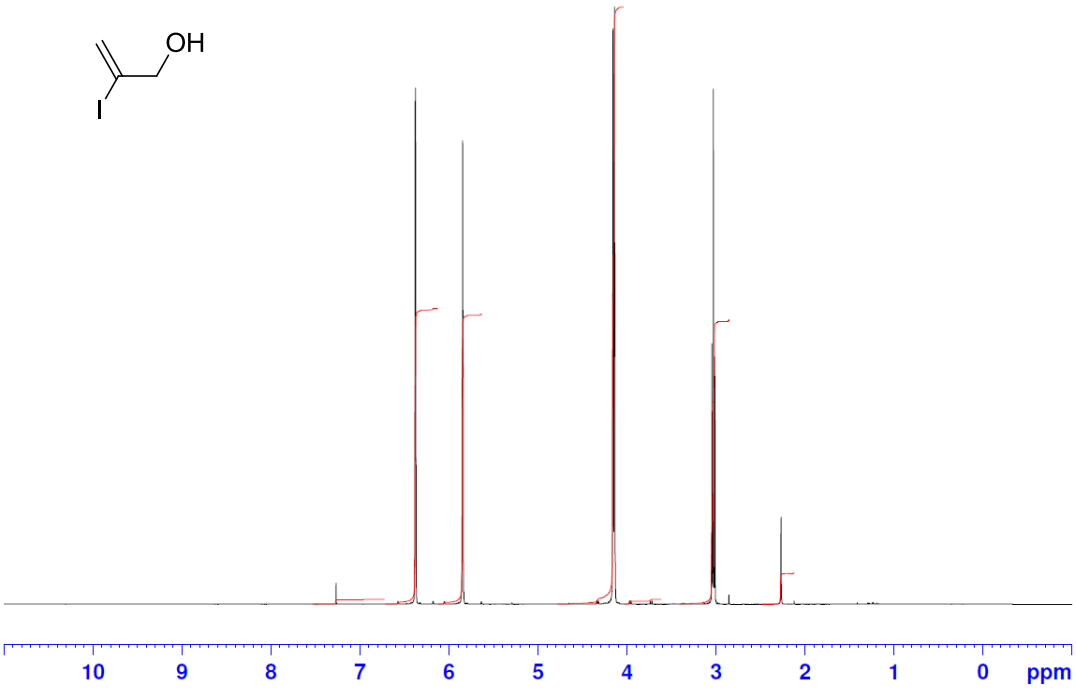

Signal 4: DAD1 D, Sig=230,16 Ref=360,100

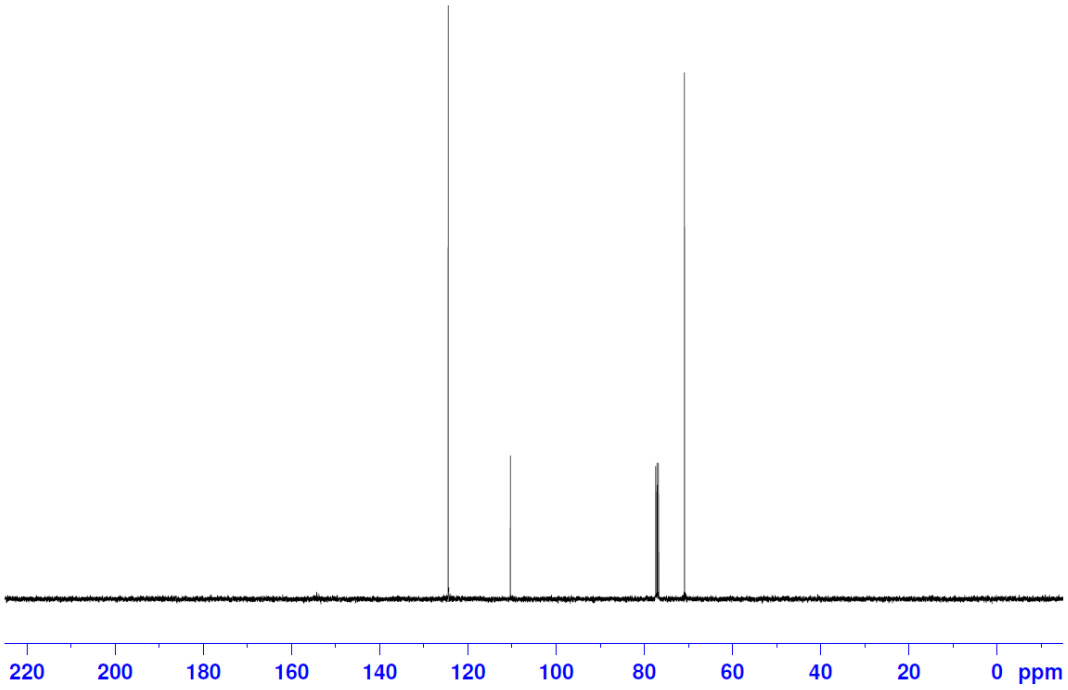
| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 5.934 | BB | 0.1507 | 12.62038 | 1.28394 | 0.1276 |
| 2 | 28.477 | BB | 0.7006 | 9878.15039 | 217.19830 | 99.8724 |
| Totals : | | | | 9890.77077 | 218.48225 | |



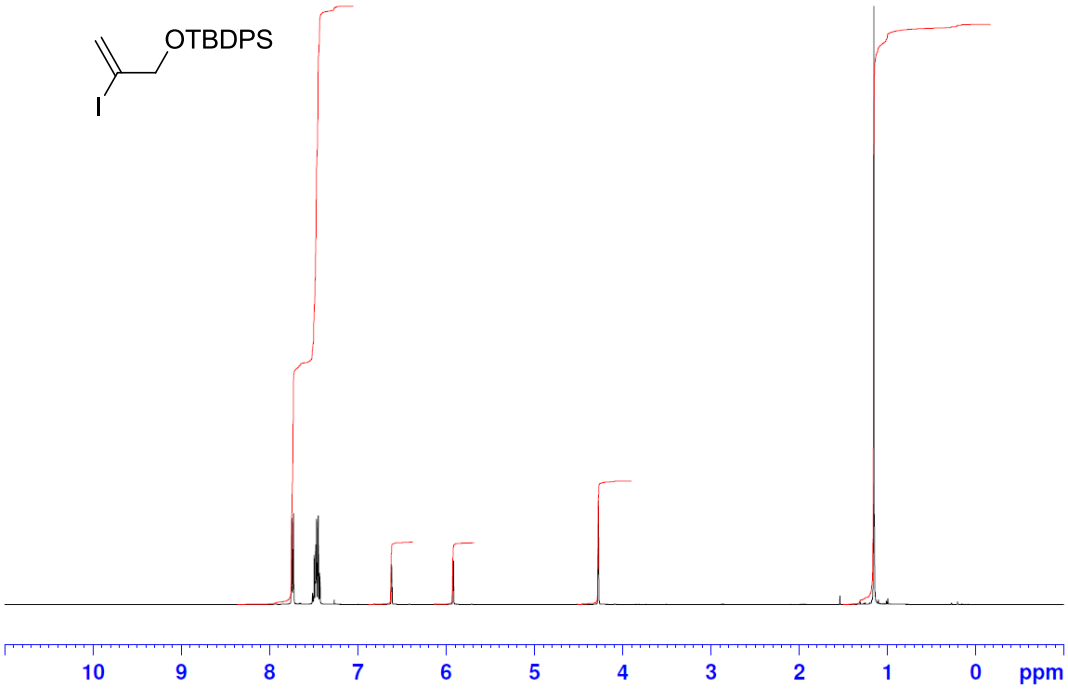

| Peak # | RetTime [min] | Type | Width [min] | Area [mAU*s] | Height [mAU] | Area % |
|---|---|---|---|---|---|---|
| 1 | 5.928 | BB | 0.1503 | 13.10849 | 1.31515 | 0.1199 |
| 2 | 27.664 | BV | 0.6572 | 7981.04053 | 187.28857 | 72.9816 |
| 3 | 28.818 | VB | 0.6917 | 2941.53638 | 63.35188 | 26.8985 |
| Totals : | | | | 1.09357e4 | 251.95561 | |

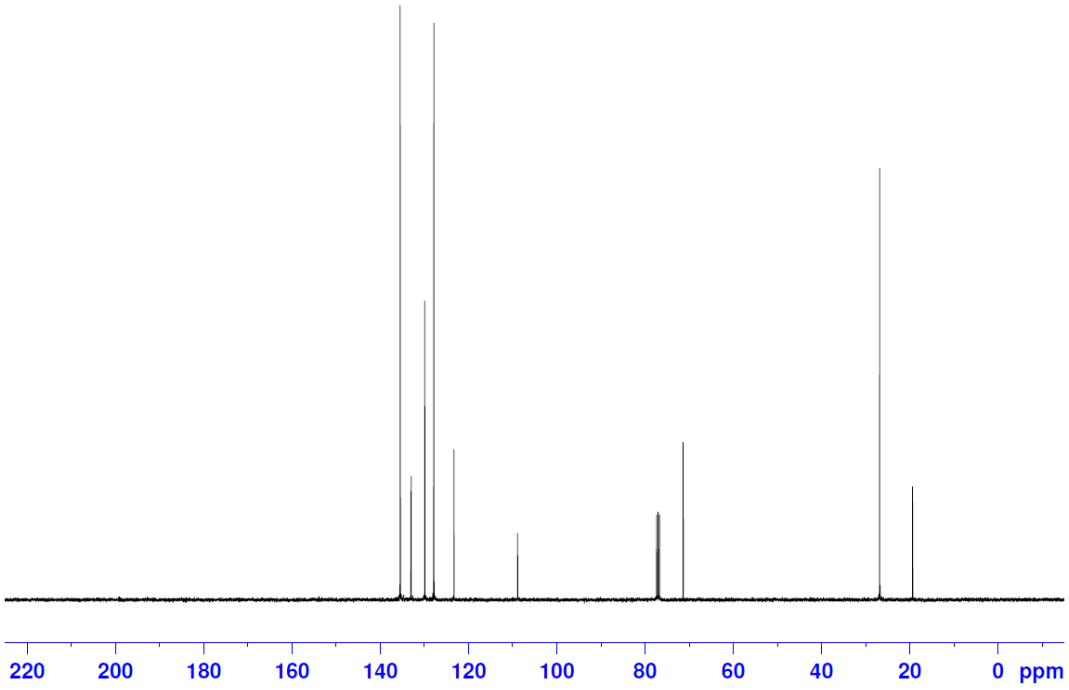
**2-Iodoprop-2-en-1-ol**



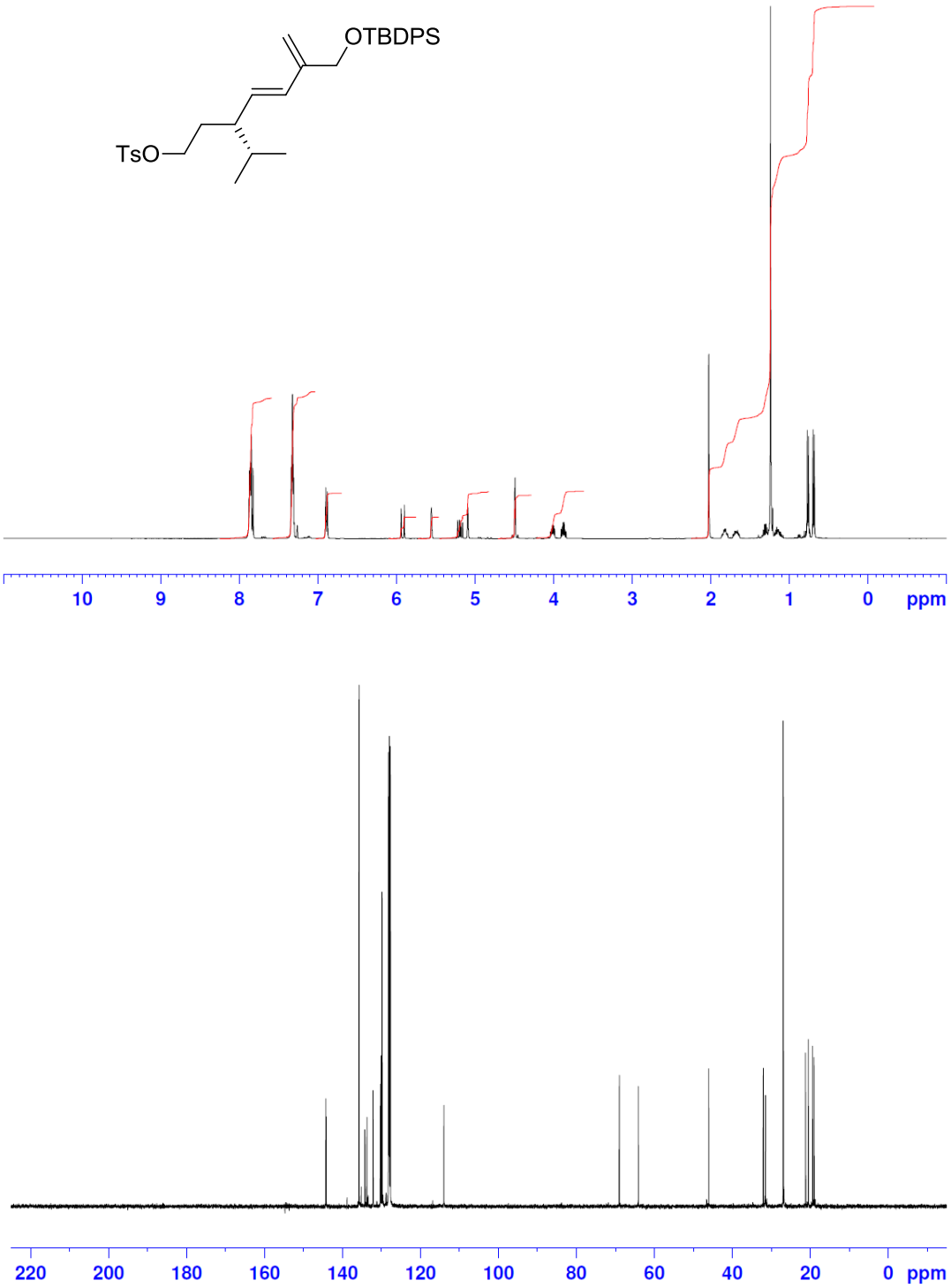



**tert-*Butyl((2-iodoallyl)oxy)diphenylsilane***

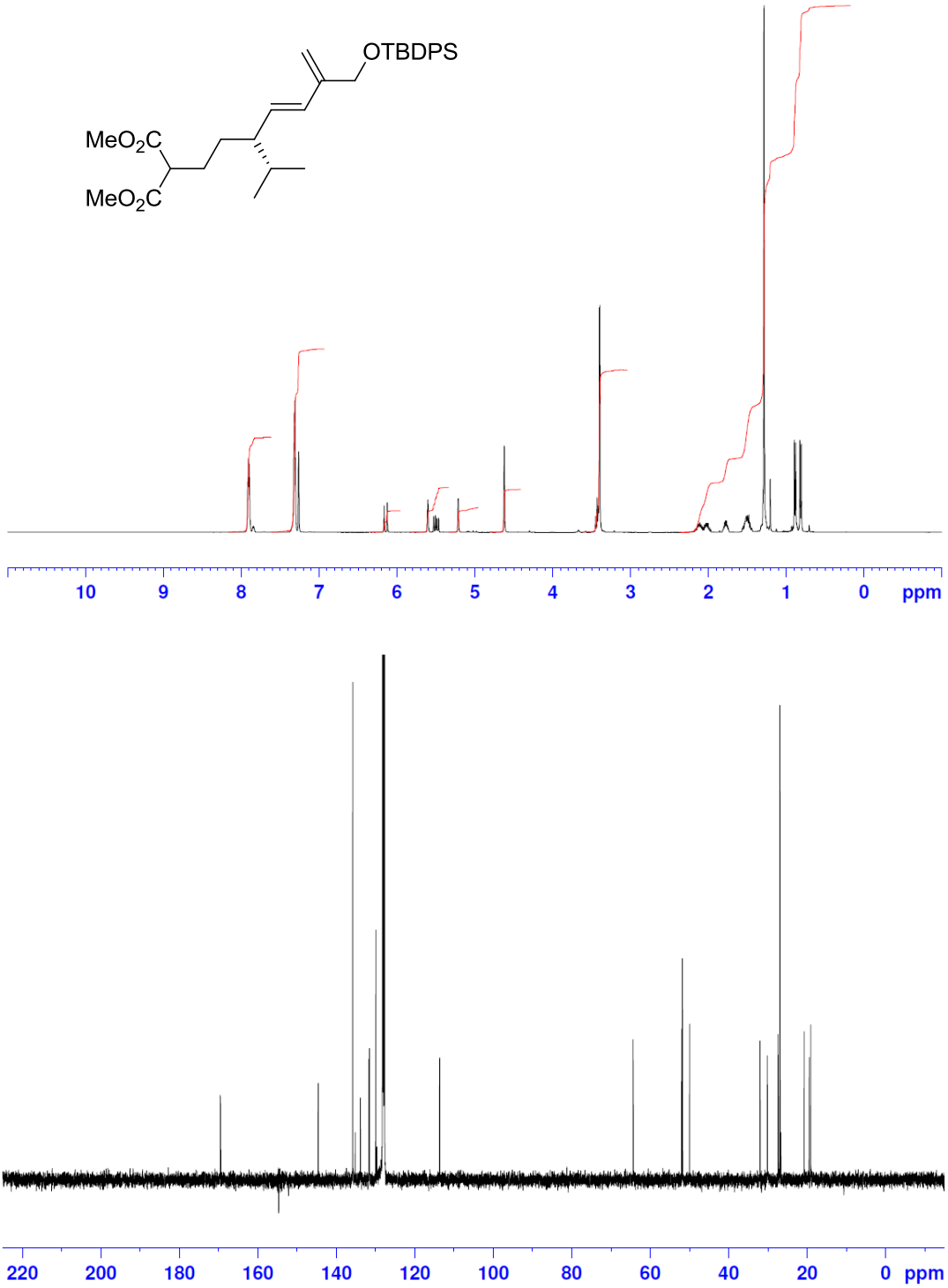


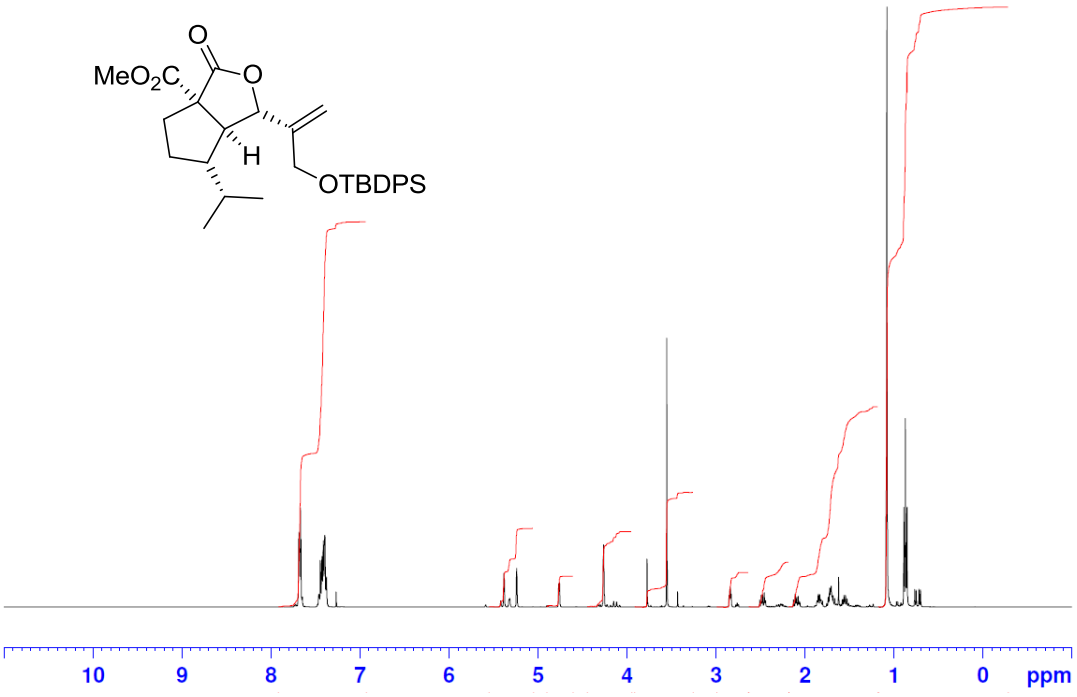
***(S,E)-6-(((tert-Butyldiphenylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-yl 4-methylbenzenesulfonate***

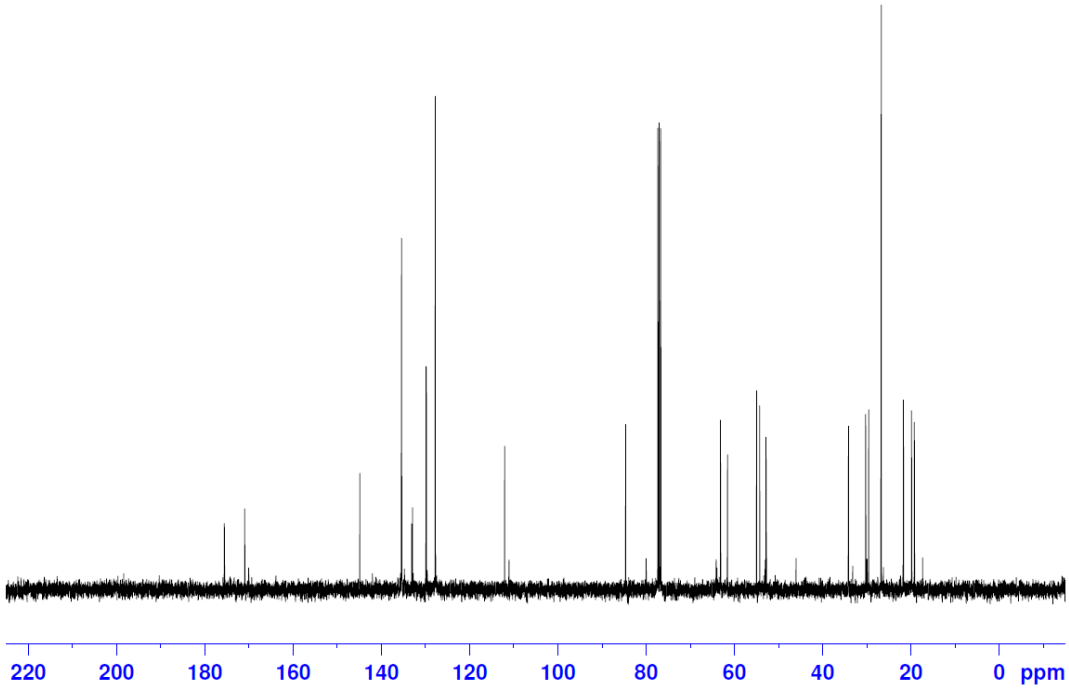


***(S,E)-Dimethyl 2-(6-(((tert-butyldiphenylsilyl)oxy)methyl)-3-isopropylhepta-4,6-dien-1-yl)malonate***

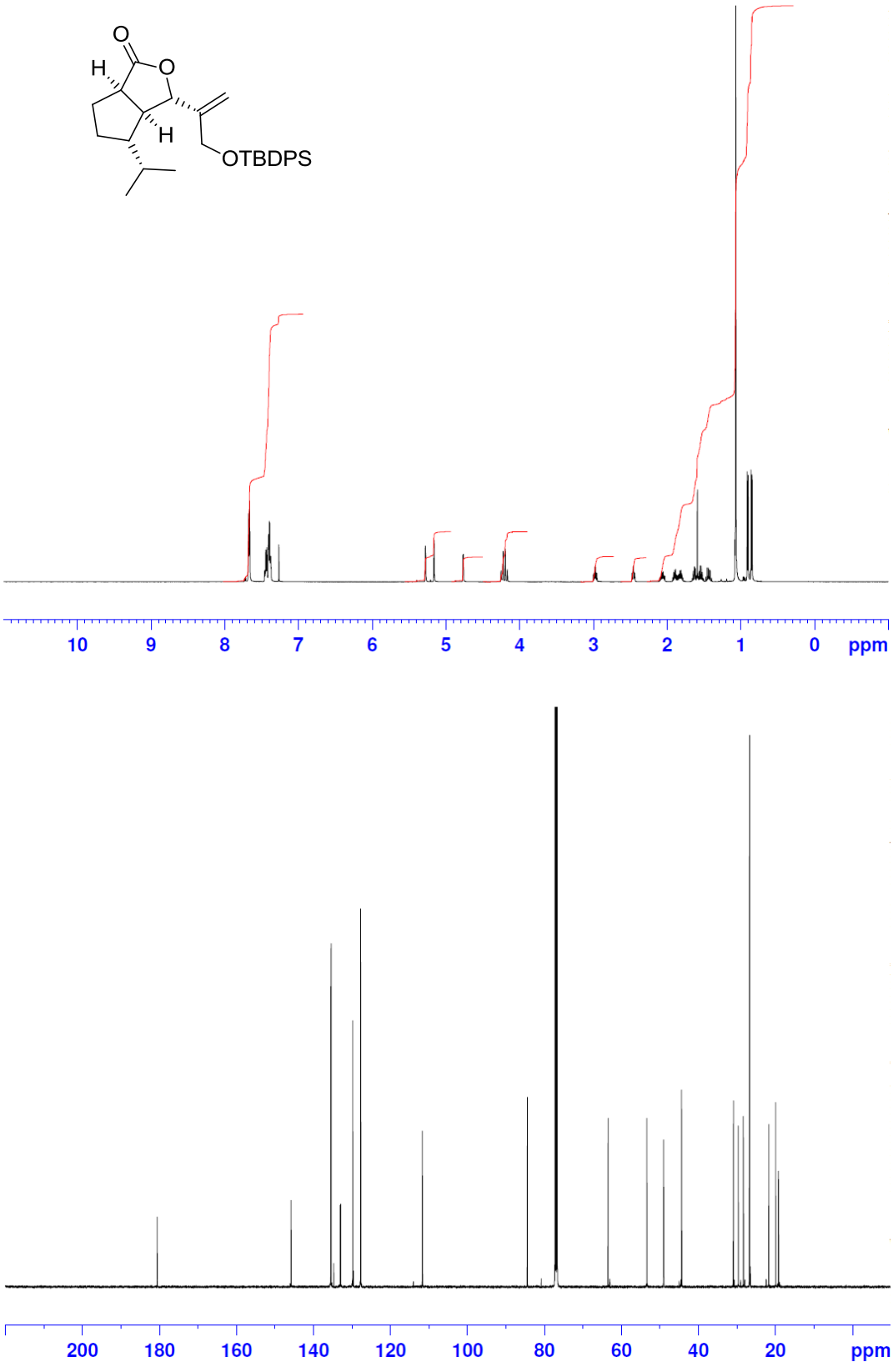


***(1S,3aR,6S,6aS)-Methyl 1-(3-((tert-butyldiphenylsilyl)oxy)prop-1-en-2-yl)-6-isopropyl-3-oxohexahydro-1H-cyclopenta[c]furan-3a-carboxylate***

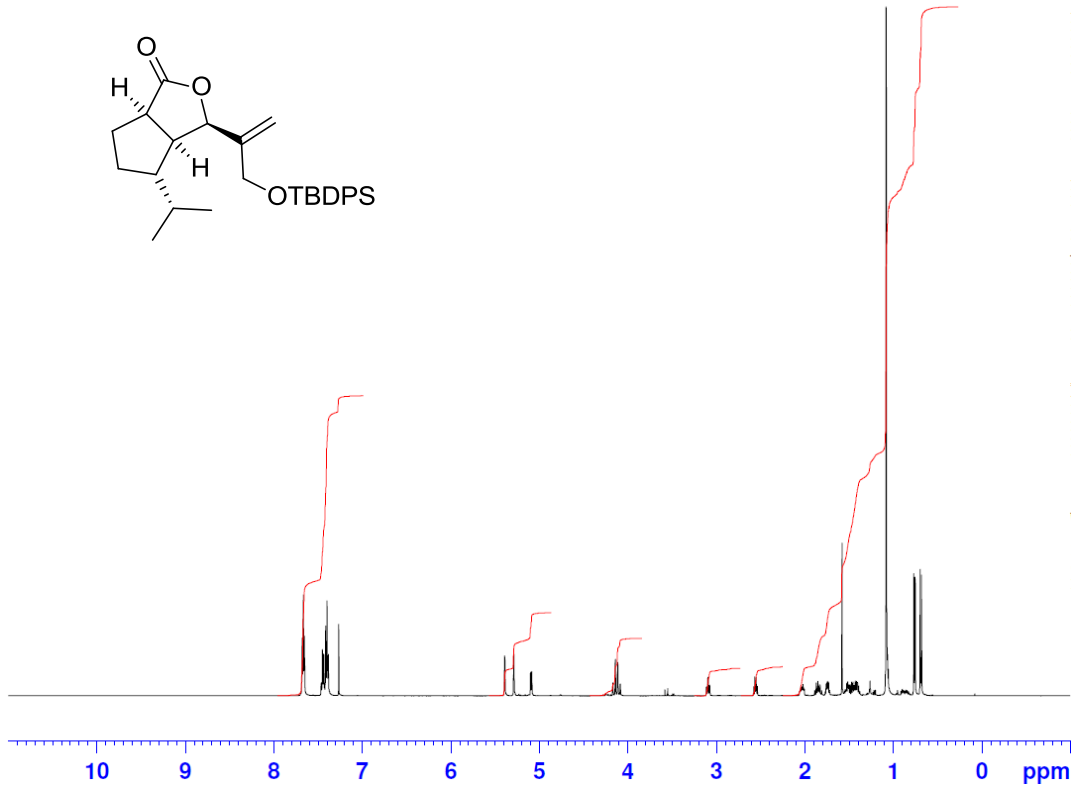


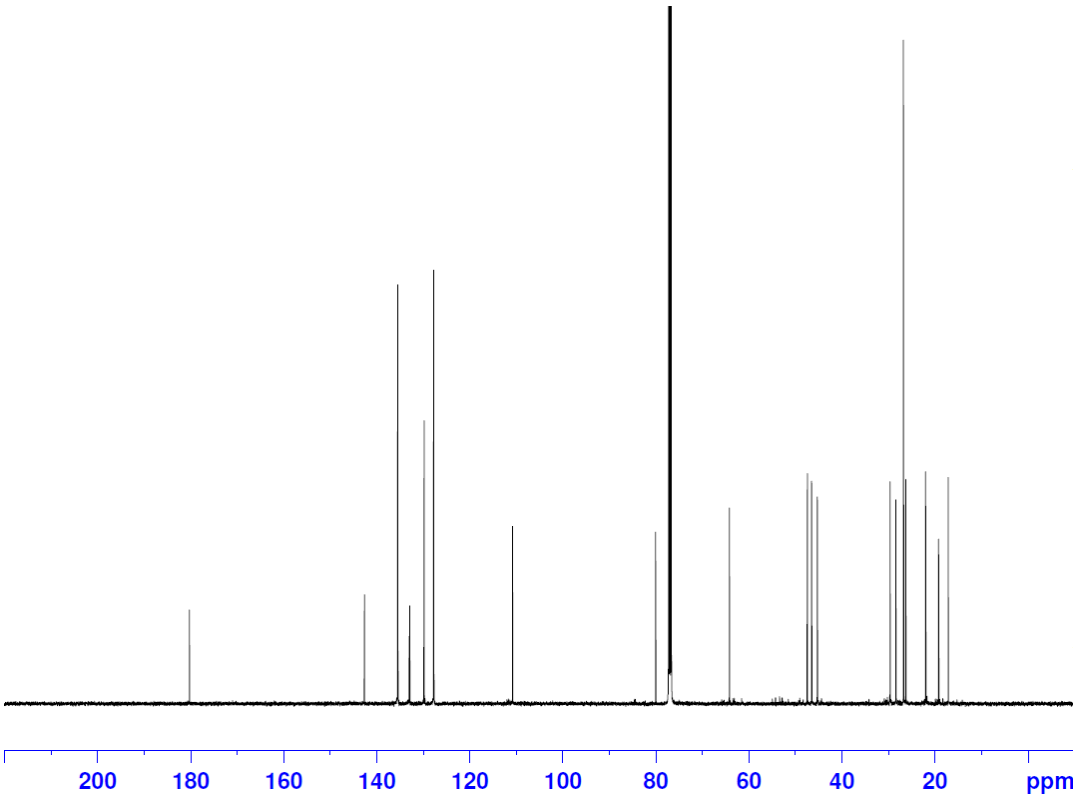



***(3S,3aS,4S,6aR)-3-(3-((tert-Butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropylhexahydro-1H-cyclopenta[c]furan-1-one***

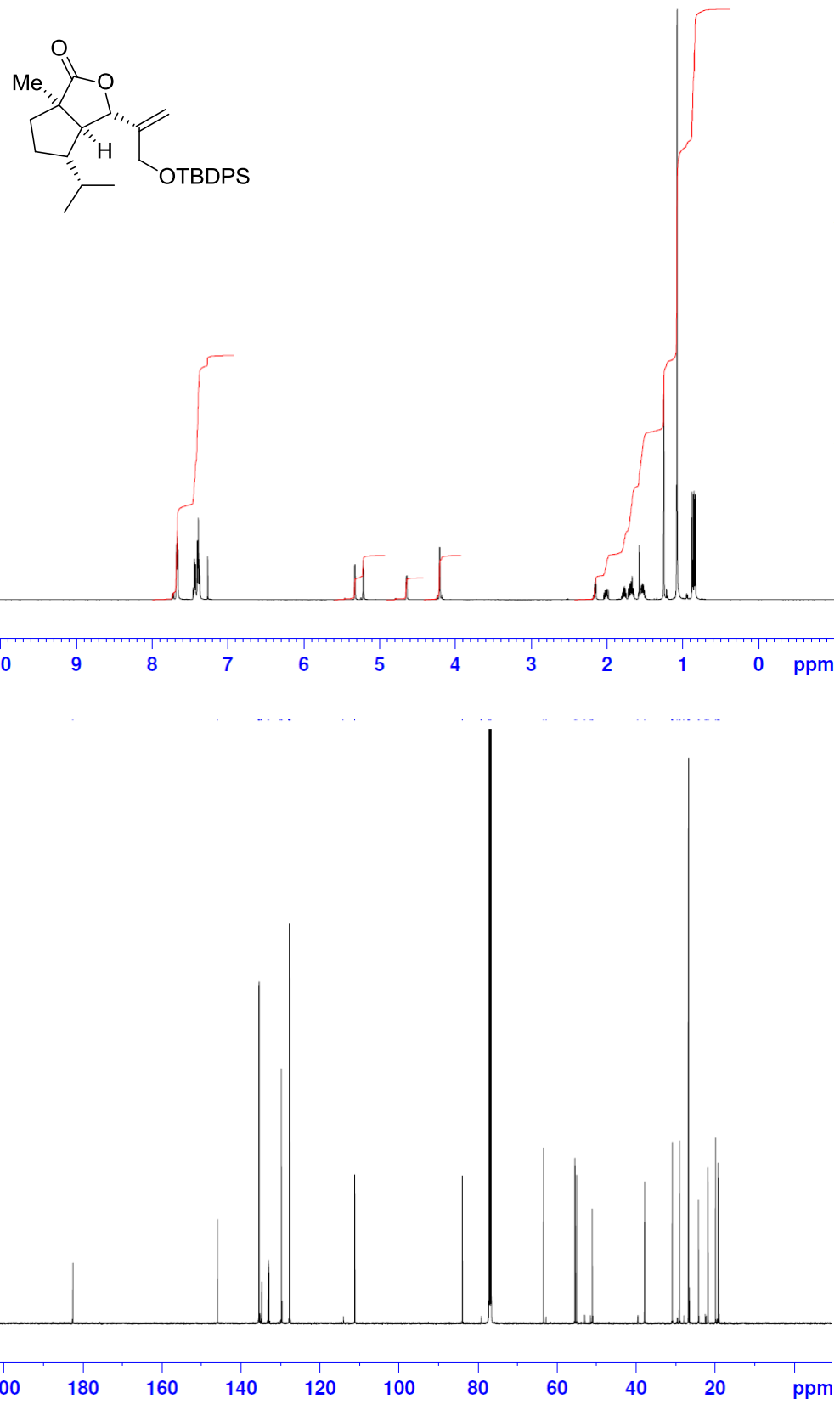


***(3R,3aS,4S,6aR)-3-(3-((tert-Butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropylhexahydro-1H-cyclopenta[c]furan-1-one***

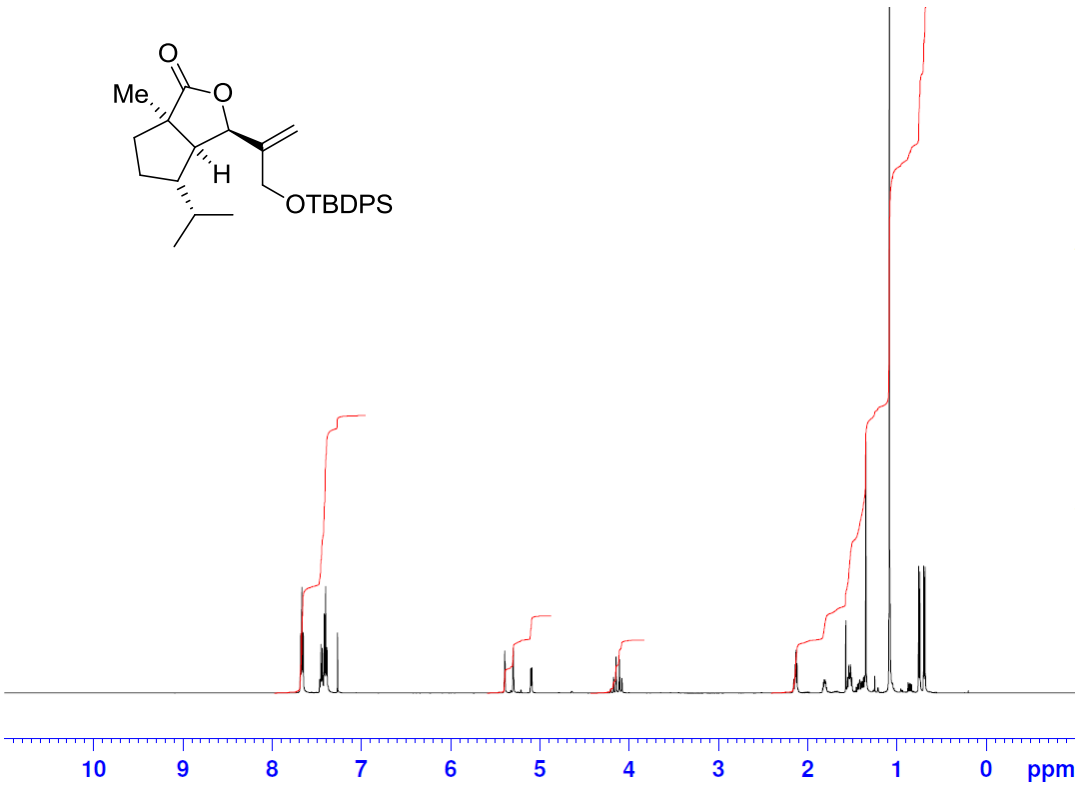


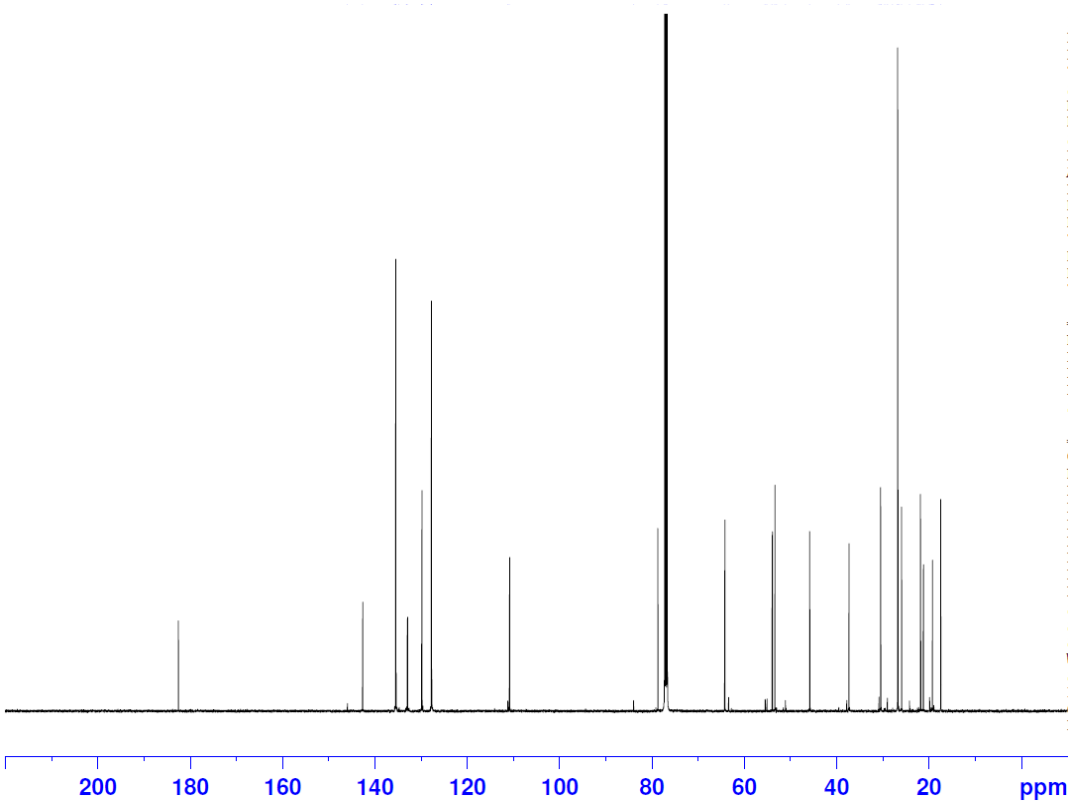



***(3S,3aS,4S,6aR)-3-(3-((tert-Butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropyl-6a-methylhexahydro-1H-cyclopenta[c]furan-1-one***

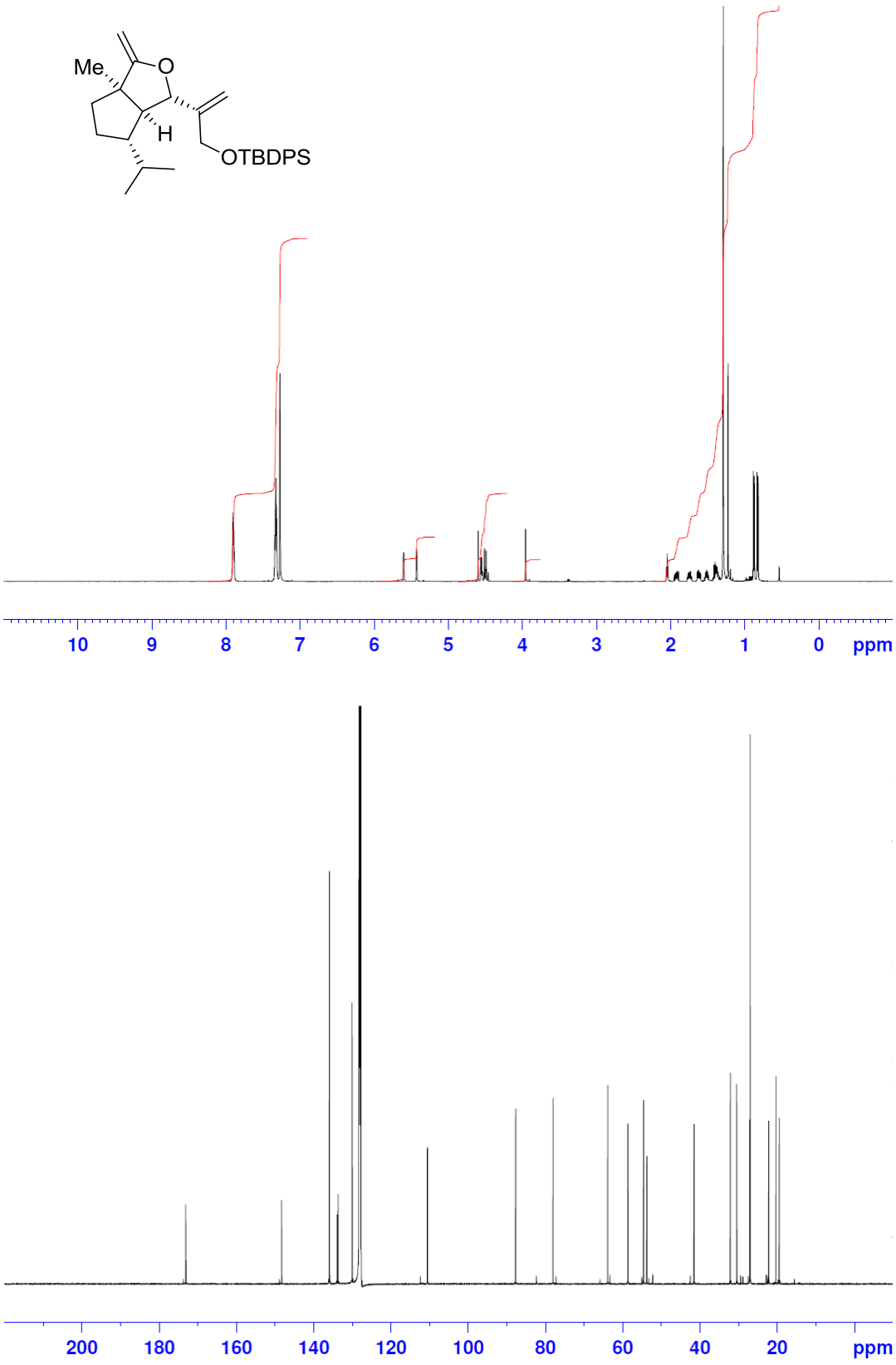


***(3R,3aS,4S,6aR)-3-(3-((tert-Butyldiphenylsilyl)oxy)prop-1-en-2-yl)-4-isopropyl-6a-methylhexahydro-1H-cyclopenta[c]furan-1-one***

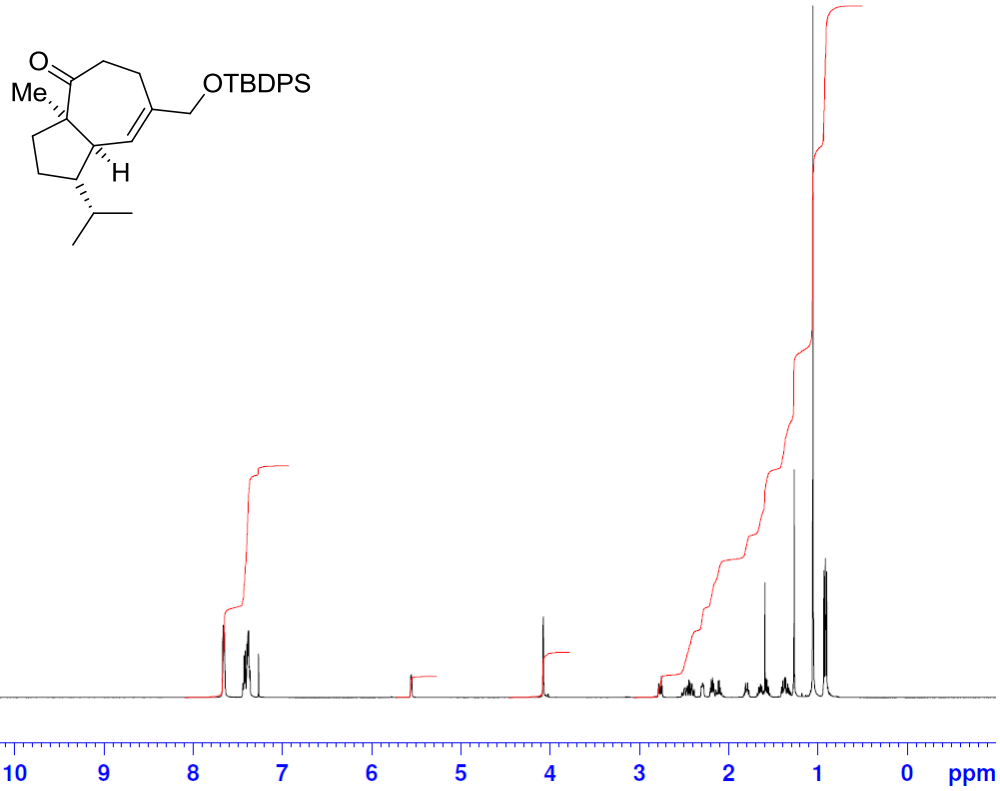


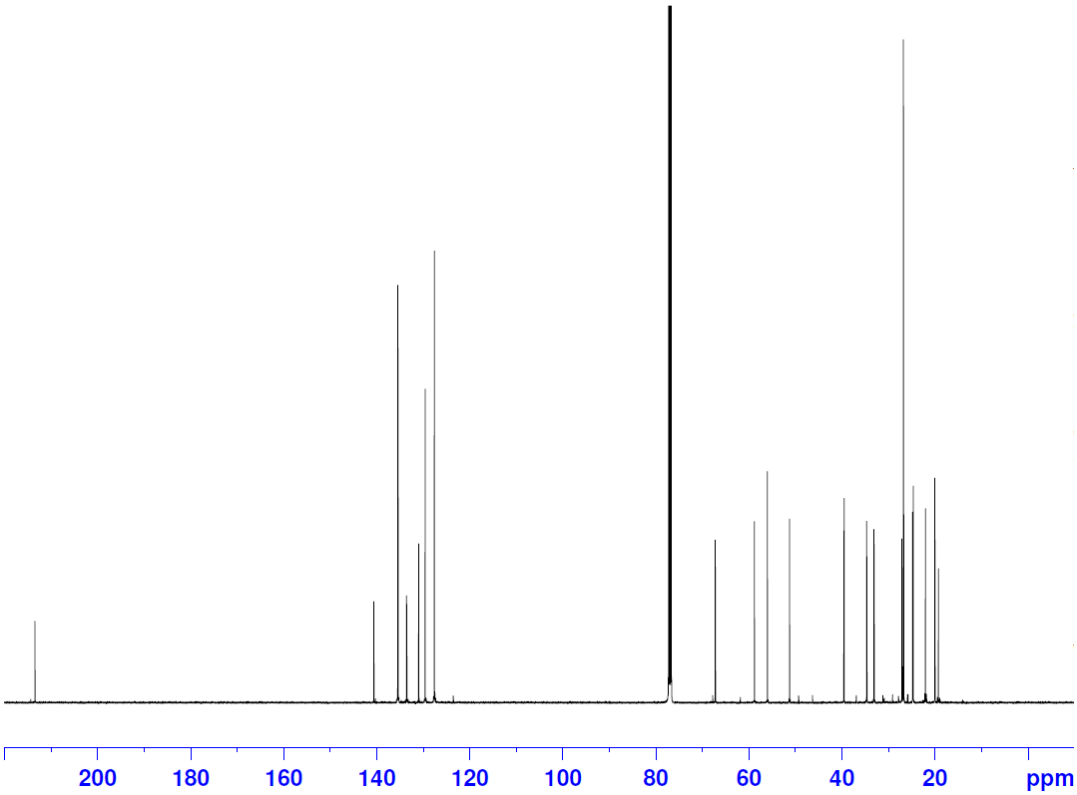



**tert-*Butyl((2-(((1*S*,3a*R*,6*S*,6a*S*)-6-isopropyl-3a-methyl-3-methylenehexahydro-1*H*-cyclopenta[*c*]furan-1-yl)allyl)oxy)diphenylsilane**

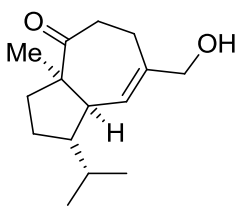


***(1S,3aR,8aR)-7-(((tert-Butyldiphenylsilyl)oxy)methyl)-1-isopropyl-3a-methyl-1,3,3a,5,6,8a-hexahydroazulen-4(2H)-one***

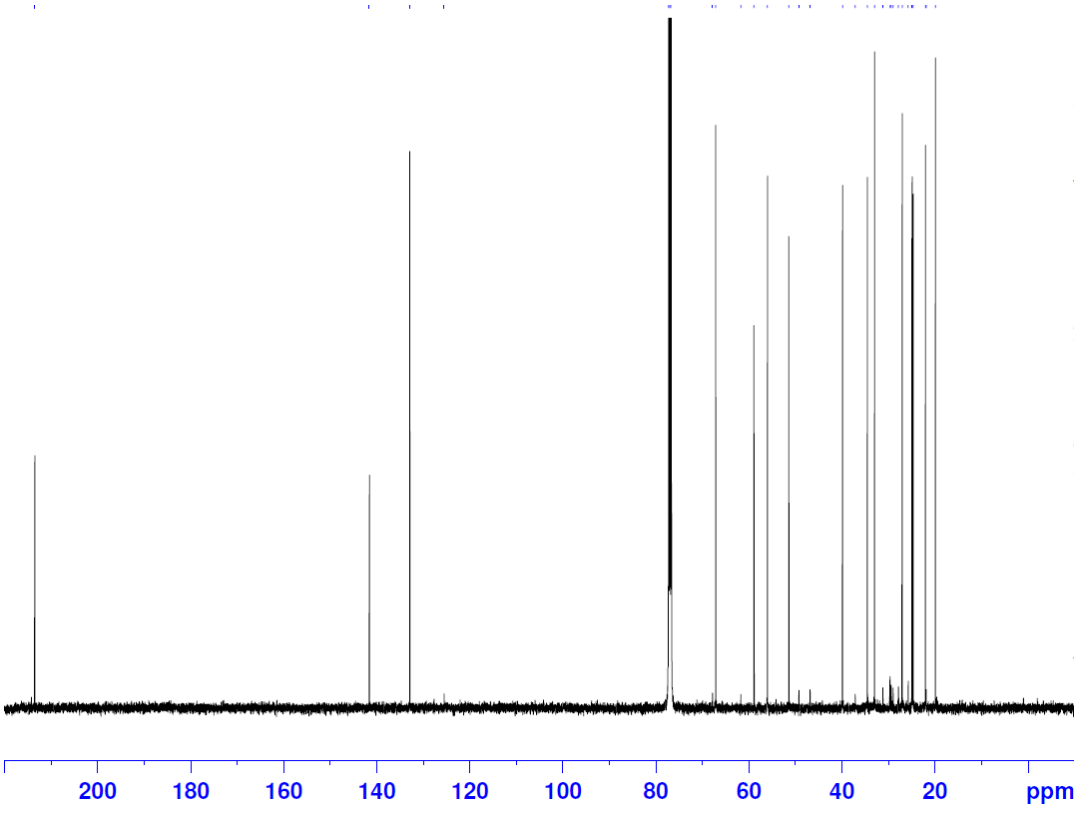


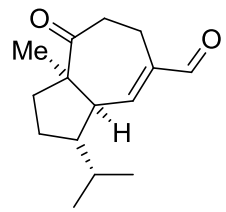
**(+)-Aphanamol-I**


O
Me
OH
H


10
9
8
7
6
5
4
3
2
1
0
ppm

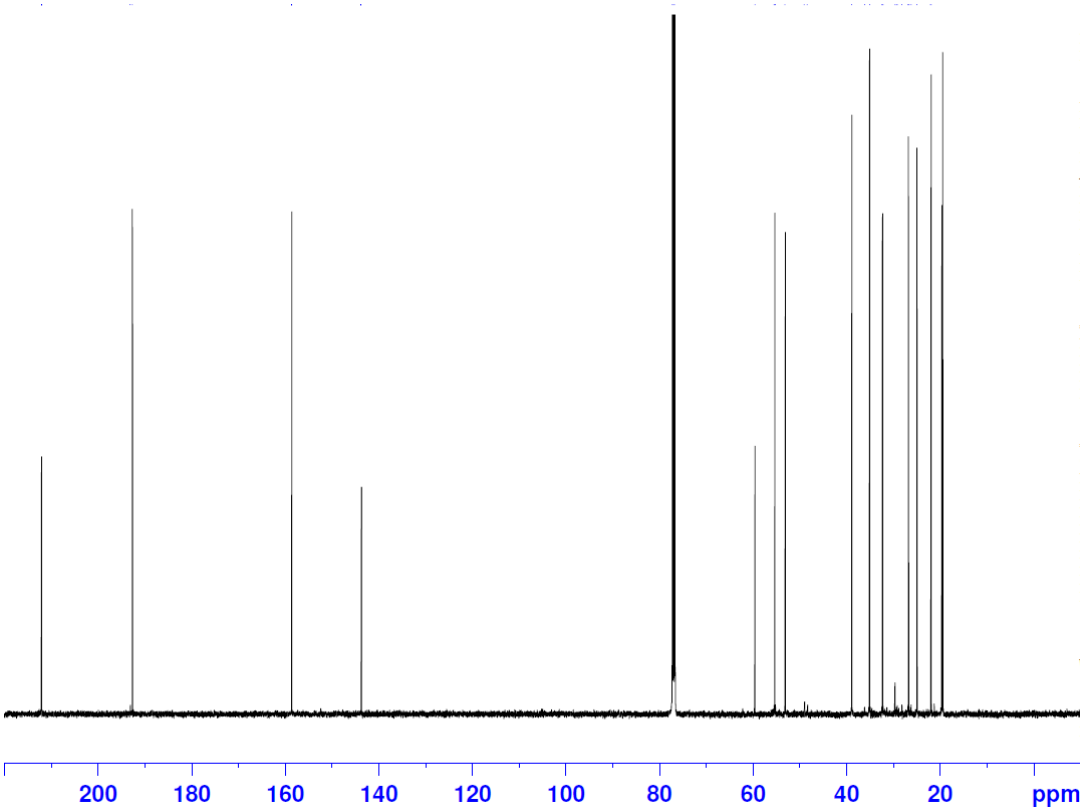

200
180
160
140
120
100
80
60
40
20
ppm

**(-)-2-Oxoisodauc-5-en-12-al**









**(1*R*,2*S*,7*R*,8*S*)-Isodauc-5-ene-2,12-diol**