A Unified Approach to Carbocyclic Frameworks: DTDA Sequences in Total Synthesis

A thesis submitted for the degree of

Doctor of Philosophy

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Declaration

Except where specific acknowledgements of others are made, the work described in this thesis was carried out by the author during the period of March 2011 to December 2015 in the Research School of Chemistry of the Australian National University, Australia, under the supervision of Associate Professor Mick Sherburn. The material presented has not been submitted for any other degree and is less than 100,000 words in length.

Joshua Boyle

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Abbreviations

% percent
Δ heat
° C degree/s Celsius
µ micro
δ chemical shift
ν absorption maxima (IR)
Ac acetyl
aq. aqueous
Ar aryl or argon
ATPH aluminium tris(2,6-diphenylphenoxide
BHT 2,6-di-tert-butyl-4-methylphenol
BINAP 2,2′-bis(diphenylphosphino)-1-1′-binaphthyl
Bn benzyl
bp. boiling point
br broad
b.r.s.m. based on recovered starting material
Bu butyl
calcd calculated
CAN ceric ammonium nitrate
cm⁻¹ wave number
COSY correlated spectroscopy
CSA camphorsulfonic acid
Cy cyclohexyl
1D one dimensional
2D two dimensional
DBU 1,8-diazabicyclo[5.4.0]undec-7-ene
DCE dichloroethylene
DDQ 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DFT density functional theory
d.r. diastereomeric ratio
DMAD dimethyl acetylenedicarboxylate
DMAP N,N, dimethylaminopyridine
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<tr>
<td>dppe</td>
<td>1,2-bis(diphenylphosphino)ethane</td>
</tr>
<tr>
<td>dppf</td>
<td>[1,1'-(diphenylphosphino)ferrocene]</td>
</tr>
<tr>
<td>dppp</td>
<td>1,3-bis(diphenylphosphino)propane</td>
</tr>
<tr>
<td>DTDA</td>
<td>diene transmissive Diels–Alder</td>
</tr>
<tr>
<td>er</td>
<td>enantiomeric ratio</td>
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</tr>
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<td>heteronuclear multiple bond coherence</td>
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<tr>
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<tr>
<td>IR</td>
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<td>J</td>
<td>coupling constant</td>
</tr>
<tr>
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<td>kilobar</td>
</tr>
<tr>
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<td>litre/s</td>
</tr>
<tr>
<td>LUMO</td>
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</tr>
<tr>
<td>m</td>
<td>multiplet or metre/s</td>
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<tr>
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Abstract

[3]Dendralene is a small π-rich hydrocarbon that is capable of taking part in a wide range of chemical reactions, not least of which is the diene transmissive Diels–Alder (DTDA) reaction sequence. Unfortunately, the synthesis of this molecule relies on highly toxic and commercially unavailable intermediates, namely chloroprene. **Chapter 1** of this thesis details a new synthetic approach to [3]dendralene via a double cross coupling reaction beginning with 1,1-dichloroethylene and vinyl magnesium bromide. This work was extended to the synthesis of a variety of symmetrically substituted [3]dendralenes.

**Chapter 2** details the exploration of the Diels–Alder reactivity of [3]dendralene. While there has been some experimental work examining [3]dendralene in DTDA sequences, these have tended to focus on symmetrical and highly reactive dienophiles. This chapter describes the use of unsymmetrical dienophiles, which are either cyclic or acyclic in nature. This enables the synthesis of a range of polycyclic frameworks in just two steps. Through this methodology, the synthesis of bicyclic, linear tricyclic, angular tricyclic and angular tetracyclic structures is possible.

The angular tetracyclic framework mentioned above is present in a number of natural products, including marine sponge derived compounds xestoquinone and halenaquinone. **Chapter 3** presents a comprehensive review into previous
syntheses of these two natural products as well as briefly examining work towards related natural products.

Finally, **Chapter 4** details our attempts to apply a DTDA reaction sequence beginning with [3]dendralene to the total synthesis of the natural product xestoquinone. [3]dendralene was reacted sequentially with two carbocyclic dienophiles before a series of functional group manipulations led to an advanced precursor of the targeted natural product.
A UNIFIED APPROACH TO CARBOCYCLIC FRAMEWORKS: DTDA SEQUENCES
IN TOTAL SYNTHESIS

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3. ABBREVIATIONS

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Chapter 1: A New and Improved Synthesis of [3]Dendralene

1.1 Introduction to [3]Dendralene

1.1.1 Classes of Conjugated Hydrocarbons

There are four fundamental classes of conjugated hydrocarbons (Figure 1).[1] These classes can contain through-conjugation, such as the acyclic polyenes and the cyclic annulenes, or cross-conjugation, as observed in the acyclic dendralenes and the cyclic radialenes. While the chemical and physical properties of the linearly conjugated polyenes and annulenes have been well documented, much less is known about the cross-conjugated classes of hydrocarbons, namely the dendralenes[2] and the radialenes.[3]

![Figure 1: The four classes of fundamental hydrocarbons](image)

The dendralenes, like dendrimers, derive their name from the Greek word for tree (dendron) because of their branched nature. The structure of the family as a whole is easy to derive. For example, [4]dendralene, the next higher member of the
dendralene family, can be formed by replacing a non-terminal hydrogen of [3]dendralene with a vinyl group. This process can be repeated indefinitely to give the higher analogues of the family. The naming of the dendralenes is trivial; the number of alkene units in the molecule is placed in square brackets before the word dendralene. Thus, [4]dendralene has four cross-conjugated alkene units, [5]dendralene has five alkene units and so on (Figure 2). [3]Dendralene, the smallest member of the cross-conjugated acyclic dendralenes, is the main focus of this chapter.

![Figure 2: Three members of the dendralene family](image)

### 1.1.2 Previous Syntheses of [3]Dendralene

[3]Dendralene was once perceived to be an extremely unstable molecule,[4] yet it has long been a target of interest for organic synthesis because of its wide ranging synthetic utility. Many of the early syntheses of [3]dendralene relied on elimination reactions or thermal rearrangements, and often required harsh reaction conditions in order for these reactions to occur. Flash vacuum pyrolysis (FVP) for example, was often employed in the formation of this compound. The first reported synthesis of [3]dendralene appeared in 1955 when Blomquist and Verdol synthesised diacetoxyalkene 3 in two steps from commercially available 2-methyl propene (2) (Scheme 1).[5] Heating diacetoxyalkene 3 to 485 °C then caused the thermal elimination of two equivalents of acetic acid to form [3]dendralene in 50%
yield. In a separate study published later that year, Bailey and co-workers showed that triacetate 5, which could be synthesised in three steps from aconitic acid (4), underwent conversion to [3]dendralene under FVP conditions in 47% yield.\[^{[6]}\] This approach was repeated and optimised by Koeplinger and co-workers some 36 years later.\[^{[7]}\] Martin and co-workers prepared [3]dendralene via a three-fold Hoffman elimination of tri-ammonium salt 7, again under FVP conditions in 1980,\[^{[8,9]}\] however, very little experimental information about this reaction was included and no yields were reported. One slightly different approach to [3]dendralene was published by the Vdovin group. Methylene cyclobutane 8, the synthesis of which was not discussed, was transformed into vinylcyclobutene 9 over two steps. Subjecting this vinylcyclobutene to 335 °C led to a retro 4π electrocyclisation to form [3]dendralene, although the isolated yield of the reaction was not mentioned.\[^{[10]}\]

A novel, yet important route to [3]dendralene which also employed FVP, was developed by Cadogen and co-workers in 1991 in which 3-sulfolene was used as a masked butadiene unit. Vinyl sulfolene 11, which is a stable, white crystalline solid at room temperature, was prepared in five steps from 3-sulfolene (10). Upon heating to 550 °C, vinyl sulfolene 11 underwent cheletropic elimination of SO\(_2\) gas to give [3]dendralene in 87% yield. Finally, Hopf and co-workers synthesised dienyne 13 over two steps via a copper catalysed dimerisation/rearrangement sequence starting from propargyl bromide 12. Partial hydrogenation of dienyne 13 using Lindlar’s catalyst then gave [3]dendralene in 60% yield.\[^{[11,12]}\]
Scheme 1: Early approaches towards [3]dendralene

While all of the syntheses mentioned so far were successful in synthesising [3]dendralene, mostly by elimination or thermal rearrangement reactions, only the Sherburn group have used direct cross-coupling reactions to form these π-bond rich hydrocarbons.\cite{13} Realising the potential of the sulfolene based approach towards [3]dendralene published from the Cadogan group, vinyl stannane 15 was coupled with iodide 14, itself available in four steps from 3-sulfolene, under Pd(0)-catalysed conditions to form vinyl sulfolane 11 in 92% yield. Cheletropic elimination of SO\textsubscript{2} then gave the desired [3]dendralene in 89% yield (Scheme 2). By altering the reagents used, this strategy was then employed to generate the [3]-[8]dendralenes, most on multigram scale, by using appropriate cross-coupling partners. This in turn allowed for an in depth study of the dendralene family’s physical and chemical properties for the first time.
While successful in synthesising [3]dendralene, the reliance on FVP meant that this sequence was not possible without the use of specialist equipment. With this in mind, the Sherburn group devised a more direct cross-coupling approach to access [3]dendralene (Scheme 3).\(^\text{[14]}\)

Chloroprene, (16), which had previously been used in the synthesis of [4]dendralene,\(^\text{[15]}\) was coupled with vinyl magnesium bromide (17) under nickel-catalysed conditions, to yield [3]dendralene as a THF solution in 30% yield. Additionally, by varying the substitution patterns on the cross-coupling partner, a number of 2-substituted [3]dendralenes were also accessed. One major drawback
to this synthesis was that [3]dendralene could only be accessed as a dilute THF solution, and so, in 2009, Sherburn and co-workers published a revised cross-coupling approach towards [3]dendralene that allowed access to neat [3]dendralene.\[16\] To achieve this, the chloroprene derived Grignard reagent 18 was coupled with iodide 19 in the presence of Li₂CuCl₄ to give alcohol 20, which was subsequently converted into bromide 21 under Appel conditions.\[17\] Treatment with the bulky amine base DBU caused the elimination of hydrogen bromide and formed [3]dendralene. The target hydrocarbon was then distilled out of solution under reduced pressure and collected in a cold trap to give the desired cross-conjugated compound as a colourless liquid in 79% yield.

### 1.1.3 Physical Properties of [3]Dendralene

As mentioned previously, [3]dendralene was originally thought to be an extremely unstable compound. Indeed, the initial reports of Blomquist describe the compound as being “extremely prone to undergo dimerization and polymerization.”\[4\] Early characterisation data collected on [3]dendralene consisted only of UV and IR spectra. It wasn’t until the work of Sherburn in 2005\[15\] and subsequent studies carried out in 2008\[18\] and 2010\[16\] that the physical and chemical properties of not only [3]dendralene, but the [3]–[8] dendralenes were studied in detail for the first time. It was found that contrary to popular belief, [3]dendralene was in fact a reasonably stable compound which possessed a half-life of ten hours when stored neat at 25 °C.\[16\] Studies also showed that [3]dendralene was relatively stable when stored at –20 °C as a 1 M solution in common organic solvents (<10% decomposition over a twelve month period). From the present work, we now know that [3]dendralene can be stored neat at –80 °C without any signs of
degradation. The major path of decomposition of [3]dendralene was shown to be a Diels–Alder dimerisation which proceeds through a concerted bispericyclic transition state that has biradicaloid character (Figure 3).[^19]

![Bispericyclic transition state for the Diels–Alder dimerisation of [3]dendralene](image)

**Figure 3:** Bispericyclic transition state for the Diels–Alder dimerisation of [3]dendralene

### 1.1.4 Chemical Reactivity of [3]Dendralene

Perhaps the most powerful of the transformations that [3]dendralene can undergo is that of the diene transmissive Diels–Alder (DTDA) reaction sequence (Scheme 4). In this sequence of reactions, one of the 1,3-butadiene units of [3]dendralene reacts with a dienophile in a Diels–Alder reaction to form a six membered ring. At the same time, olefinic character is ‘transmitted’ to a different part of the molecule. This newly formed diene is then able to participate in a second Diels–Alder reaction. The synthetic utility of this DTDA reaction sequence has been extensively studied and will be discussed in more detail in the following chapter. With this in mind, this next section will examine reactions that [3]dendralene can participate in that are not Diels–Alder reactions.
Scheme 4: [3]Dendralene is capable of undergoing a DTDA sequence of reactions to form four new carbon-carbon bonds.

In 2010, Sherburn and co-workers showed that [3]dendralene could undergo an exhaustive cyclopropanation reaction under Shi cyclopropanation conditions to give [3]ivyane (22) in 46% isolated yield (Scheme 5). While [3]ivyane was shown to be acid sensitive, a characteristic reflected in the relatively low yields associated with its synthesis, the higher ivyanes, synthesised from exhaustive cyclopropanation of the higher dendralenes, were shown to be stable under ambient conditions. The National Aeronautics and Space Administration (NASA) then investigated these compounds as potential rocket fuel additives due to the record breaking high heats of combustion of these compounds.

Scheme 5: [3]Dendralene is capable of undergoing exhaustive cyclopropanation or dihydroxylation reactions.

In 2013, the same group performed an exhaustive dihydroxylation of [3]dendralene under Upjohn conditions to give 4 different stereoisomers (23, 24 and the two epimers of 25) of the hexahydroxylated product in 68% yield. These results were then used to reassign the structure of the natural product 3-...
(hydroxymethyl) xylitol, which was originally assigned the structure of one of the isomers of 25,[23] to that of galactitol.

While exhaustive reactions (i.e. reactions in which all three alkene bonds take part) have been discussed, the selectivity of [3]dendralene when using sub-stoichiometric amounts of reagents is problematic. For example, a one-to-one mixture of [3]dendralene and cyclopropanating reagents led only to complex mixtures of products, presumably of mono-, bis- and tri- cyclopropanated [3]dendralene.[24] This problem can be overcome through the use of iron tricarbonyl complexation. Iron tricarbonyl groups are known to form η⁴ complexes with 1,3-butadiene units and can be thought of as a protecting group for 1,3-butadienes.[25] Iron tricarbonyl-protected [3]dendralene had previously been synthesised through a Wittig reaction of 2-formyl-1,3-butadienyltricarbonyliron.[26] In 2011 however, Sherburn and co-workers showed that the naked [3]dendralene could be reacted with an iron tricarbonyl source to form the protected cross-conjugated triene 26 in 71% yield (Scheme 6).[24] Decomplexation back to the naked [3]dendralene was shown to occur quantitatively upon treatment with ceric ammonium nitrate (CAN) in acetone.

Unlike the naked [3]dendralene, the protected compound 26 selectively underwent a series of reactions at the terminal alkene of the molecule (Scheme 7).[24] Treatment
of iron tricarbonyl complex 26 under Shi cyclopropanation conditions yielded cyclopropane 27 as the sole product in 71% yield. Likewise, mono dihydroxylation was observed when complex 26 was subject to Criegee dihydroxylation conditions, to give diol 28 as a 3:1 mixture of diastereoisomers. A 3:1 mixture of diastereoisomers was also observed in the selective mono 2,3-dipolar cycloaddition between complex 26 and bromo nitrile oxide to give isoxazoline 29.

**Scheme 7:** Reactivity of iron tricarbonyl-protected [3]dendralene

Finally, cross metathesis of complex 26 using the second-generation Hoveyda–Grubbs precatalyst led to a series of (E) 1-substituted [3]dendralenes (30) in yields ranging from 70–81%.
1.2 Aims

While the current cross-coupling approach towards [3]dendralene affords neat target material in synthetically useful amounts, the approach is not ideal because of the lack of availability of certain starting materials. Both chloroprene (16) and its precursor 3,4-dichloro-1-butene, are highly carcinogenic and as a consequence, are no longer commercially available in Australia. With this in mind, the aims of this project were:

- To develop a new cross-coupling approach to [3]dendralene that would afford the target material using cheap, commercially available and less toxic starting materials

- To extend this cross-coupling approach towards the synthesis of symmetrically substituted [3]dendralenes

- To develop a new method for the synthesis of chloroprene that will allow access to this important compound in synthetically useful amounts

1.3 Results and Discussion

The commercial unavailability of both chloroprene, and its synthetic precursor 3,4-dichloro-but-1-ene, led us to attempt to develop a new cross-coupling approach towards [3]dendralene.
1.3.1 Previous Cross-Coupling Approaches to Related Dendralenes

[5]Dendralene (32), a higher member of the dendralene family, has previously been synthesised by the Sherburn group through a Ni(0)-catalysed double Tamao–Kumada–Corriu cross-coupling reaction between 2-(1,3-butadienyl)magnesium chloride (18), derived from chloroprene, and 1,1-dichloroethylene (DCE) (31) (Scheme 8).[18]

![Scheme 8: Previous synthesis of [5]dendralene](image)

With this in mind, we aimed to synthesise [3]dendralene in a similar manner, using vinyl magnesium bromide (17) as the nucleophilic cross-coupling partner (Scheme 9).

![Scheme 9: Proposed synthesis of [3]dendralene](image)

One potential limitation of this approach is the fact that vinyl magnesium bromide can only be formed as a THF solution.[27] Previous attempts to remove [3]dendralene from a THF solution have proved unsuccessful[14] so a new method for the extraction of [3]dendralene would also be required.
While cross-coupling reactions involving vinyl magnesium bromide are common,[28,29] the use of DCE as a coupling partner is much less prevalent, although not unheard of. DCE has been used in Sonagashira reactions[30-32] and cross-coupling reactions involving the formation of sp²-sp³ C-C bonds,[33-35] however, it has only been used in a handful of cases to form sp²-sp³ C-C bonds. There are only two papers apart from the previously mentioned [5]dendralene synthesis, in which DCE is used in a double cross-coupling reaction to form two sp²-sp² C-C bonds (Scheme 10).

Scheme 10: Previous examples employing DCE in double cross-coupling reactions

In 2006, Knochel and co-workers developed a diethyl phosphite/DMAP/Ni(II) system for the cross-coupling of aryl zinc species, which produced a single example of a double cross-coupling reaction with DCE to give diaryl ethylene 34 in 88% yield.[36] Meanwhile, Barluenga and co-workers detected the double cross-coupled product 37 as an unwanted side product during their work on the coupling of vinyl boron species 35 to DCE.[37] There are also a small number of papers in which a single sp²-sp³ C-C bond is formed using DCE as a cross-coupling partner.[31,38]
1.3.1.1 The Synthesis of [3]Dendralene via a Double Cross-Coupling Sequence

We began our studies towards the synthesis of [3]dendralene by attempting the conditions previously used for the synthesis of [5]dendralene. Thus Ni(dppp)Cl₂ (0.03 equiv) was added to a solution of DCE, vinyl magnesium bromide (2.2 equiv) and triphenyl phosphine (0.06 equiv) in THF at 0 °C. After two hours, the DCE had been completely consumed as monitored by GC-MS, however, upon workup, a 1:1 mixture of desired [3]dendralene (1) and 1,3-butadiene (38), the product of oxidative homo-coupling of vinyl magnesium bromide, was observed (Scheme 11).

Scheme 11: Initial attempts at synthesising [3]dendralene was accompanied by the formation of 1,3-butadiene

Oxidative homo-coupling of the organometallic cross-coupling partner was also observed in the original [5]dendralene paper (forming [4]dendralene), however in that case, the minor impurity (10%) could be easily separated from the targeted [5]dendralene via vacuum distillation. Unfortunately, attempts to separate [3]dendralene and 1,3-butadiene, either through vacuum distillation or flash column chromatography, were unsuccessful. Due to the large amounts of 1,3-butadiene being generated, and the difficulty involved with separating [3]dendralene from 1,3-butadiene, we set about optimising the cross-coupling reaction.
After observing a 1:1 ratio of [3]dendralene to 1,3-butadiene using the original Tamao–Kumada–Corriu cross-coupling reaction conditions, we observed a slight increase in selectivity when altering the order of addition. When adding DCE to the reaction last, a 3:2 mixture of [3]dendralene : butadiene was observed. The use of an internal standard showed the yield of [3]dendralene to be 27%. Using a commercial source of vinyl magnesium bromide made no difference to the selectivity or yield of the reaction, while removing the PPh₃ ligand also had no effect apart from making the reaction more atom economical. Higher catalyst loading and lower reaction temperatures both failed to have a positive impact on the selectivity of the reaction.

In an attempt to determine the source of the butadiene contaminant, vinyl magnesium bromide and DCE were combined in THF in the absence of a catalyst, however, neither [3]dendralene nor 1,3 butadiene were detected either by GC-MS or ¹H NMR. This suggests that the unwanted butadiene impurity is formed by an unwanted side reaction and is not the result of background reactions or degradation. Cross-coupling between vinyl magnesium bromide and chloroprene was attempted in order compare the amounts of homo-coupled Grignard reagent being formed. A slight increase in the ratio of [3]dendralene to oxidative homo-coupled product was observed when chloroprene was used as the electrophile; however, there was still a significant amount of the oxidative homo-coupled product present. This indicated that there was an inherent problem with the cross-coupling conditions being used.

We next turned our attention to the catalyst. The use of a range of monodentate and bidentate phosphine ligands did not increase the yield or selectivity of the
reaction. In fact when bis(diphenylphosphino)ferrocene (dppf) was used as the ligand, 1,3-butadiene was the major product formed. Switching to palladium based catalysts led only to recovery of the starting material. Our first breakthrough came when we altered the nature of the nucleophilic cross-coupling partner. When vinyl magnesium bromide was transmetalated using zinc bromide to the organozinc nucleophile, and subject to the cross-coupling reaction conditions, a greater than 19:1 ratio of [3]dendralene to 1,3-butadiene was observed, with trace amounts of chloroprene still present. When the catalyst loading was increased to 10%, full consumption of both DCE and chloroprene was observed and only minimal amounts of 1,3-butadine were detected by ¹H NMR spectroscopic analysis. After workup, the use of an internal standard showed the yield of the reaction to be 55%.

With this successful reaction in hand, another round of optimisation was undertaken. Attempts to make the reaction catalytic in regards to ZnBr₂ yielded a 1:1 mixture of [3]dendralene and 1,3-butadiene. Experimenting with the stoichiometry of the reaction allowed the catalyst loading to be dropped to 1% if the amount of organozinc species was increased slightly. Lastly, distilling the product out of the reaction mixture directly and avoiding an aqueous workup also led to an increase in yield. Thus, under optimised conditions, vinyl magnesium bromide solution (2.75 equiv) was added slowly to a solution of Ni(dppp)Cl₂ (0.01 equiv) and zinc bromide (2.75 equiv) in THF at 0 °C and the solution was left to equilibrate for 30 minutes before DCE (1 equiv) was added dropwise to the reaction mixture. Slow addition of DCE was imperative as allowing the internal temperature of the reaction to increase beyond 4 °C resulted in lower yields. After 2 hours, the reactive metal species were quenched with 1M HCl solution and the target material collected via vacuum distillation in a cold trap to give a solution of pure [3]dendralene in THF in 76% yield by comparison to an internal standard
The yield of 76% is particularly impressive because of the fact that two cross-coupling reactions are occurring. Taking this into account, the average yield for each cross-coupling step is 87%. This procedure has the added advantage of using only cheap, commercially available reagents. Starting from vinyl bromide and DCE, a price analysis of this reaction sequence reveals that the cost of all reagents, catalysts and solvents used comes to $6.61 per gram of [3]dendralene formed. This procedure has been used to prepare [3]dendralene in batches of up to 5 grams.

**Scheme 12**: Optimised conditions for the synthesis of [3]dendralene

The presumed catalytic cycle (**Scheme 13**) of this reaction begins with reduction of the Ni(II) precatalyst *via* two transmetalations of vinyl zinc bromide and subsequent reductive elimination, to give Ni(0) complex 41 and one molecule of 1,3-butadiene.\[^{[39]}\] The active Ni(0) species then oxidatively inserts into one of the carbon-chlorine bonds of DCE to give intermediate 42. Transmetalation with vinyl zinc bromide then leads to intermediate 43 which, upon reductive elimination, either regenerates the reactive Ni(0) species and forms chloroprene (16), which is free to go through another catalytic cycle (path b), or forms Ni(II) complex 44 directly (path c), which also goes on to form [3]dendralene.
A possible mechanism for the formation of 1,3 butadiene is provided (Scheme 14). Initial oxidative insertion of the active Ni(0) species (41) into one of the carbon-chlorine bonds of DCE can form Ni(II) complex 42. From here, elimination of chloroacetylene 47 (path a') or acetylene (48) (path a'') leads to Ni(II) species 46. Ni(II) complex 46 is then free to undergo a double transmetalation with vinyl magnesium bromide to form complex 49. This complex is then reduced back to Ni(0) complex 41 via an reductive elimination to generate 1,3-butadiene as a by-product.
The 1,2-elimination product (path a’) has been observed previously in cross-coupling reactions involving trans 1,2-dihaloalkenes (Scheme 15).\textsuperscript{[40]} When 4,5-dibromoocct-4-ene (50) was reacted with phenyl zinc iodide under Pd(0)-catalysed Negishii conditions, a 2:1:1 ratio of mono coupled product 52: alkyne 53: homo-coupled phenyl zinc iodide 54 was observed. It was postulated that following the oxidative insertion of the Pd(0)-species into one of the C-Br bonds, anti elimination of PdBr\textsubscript{2} led to the formation of the observed alkyne. The newly formed Pd(II)Br\textsubscript{2} species was subsequently reduced back to Pd(0) by a transmetallation/reductive elimination sequence with the organic zinc species resulting in homo-coupled product 54.

\textbf{Scheme 15:} 1,2-dibromoelimination under Negishii cross-coupling conditions

Likewise, path a’’ has also been previously observed. When 2,2-diphenyl-1,1-dibromoethylene (55) was treated with a stoichiometric amount of Pd(PPh\textsubscript{3})\textsubscript{4}, formation of alkyne 57 was observed (Scheme 16).\textsuperscript{[41]} This alkyne was thought to have formed via alpha dehalopalladation to form palladium carbenoid 56 \textit{in situ},
followed by a 1,2 hydride migration to eliminate Pd(II) chloride. While this reaction was stoichiometric with regards to palladium, regeneration of the Pd(0)-species via a transmetalation/reductive elimination sequence could, in theory, render this reaction catalytic. It is unlikely that path a’ is the cause of our oxidative homo-coupling product formation as hydrides are generally poor leaving groups. It is path a” therefore, that is the likely source of 1,3-butadiene in our reaction.

Scheme 16: Formation of carbenoid 56 through dehalopalladation of dibromoalkene 55

1.3.1.2 The Workup

With the preparation of [3]dendralene proving successful, attention was turned towards obtaining a sample of neat [3]dendralene free of THF. We hypothesised that if we could exchange the THF for either a low or high boiling solvent, selective distillation of either [3]dendralene or the solvent would lead to a neat sample of target material. In collaboration with fellow Sherburn PhD student Dr. Nicholas Green, we decided to take advantage of THF’s solubility in water and devise a continuous washing procedure that would bypass the need for multiple individual washes, by allowing a continuous flow of water to remove the THF (Figure 4).
For organic solvents that are less dense than water, the THF solution was first taken up in a small amount of the desired solvent and placed in a large separating funnel equipped with a magnetic stir bar. The separating funnel was placed on a 45° angle and the top of the funnel attached to a tap via a gas adapter and rubber tubing. Water was then poured into the vessel until the separating funnel was half full, at which time the bottom tap was opened. Water was then continuously passed through the solution at such a rate as to keep the volume constant. It was found that eight litres of water was required to remove 200 mL of THF.

In this way we were able to access [3]dendralene in a variety of solvents including pentane (b.p. 36.1 °C) and isopentane (b.p. 27.7 °C) as well as high boiling solvents decalin (b.p 187–196 °C), o dichlorobenzene (b.p. 180.5 °C) and tetralin (b.p. 207 °C). 1H NMR spectra of these solutions after subjecting them to our continuous
washing technique showed that no residual THF remained and almost no loss of [3]dendralene was observed as determined through the use of internal standards. Unfortunately, when the distillation of [3]dendralene was attempted from decalin, o-dichlorobenzene or tetralin, it was discovered that the desired product was shown to azeotrope with the solvent. This was a surprising result as [3]dendralene has been successfully distilled from solutions of DMSO without any trace of solvent present.\[16\] Work is ongoing regarding the isolation of [3]dendralene from low boiling solvents. As a result, we were not able to obtain a clean sample of neat [3]dendralene via this method. We did however show that [3]dendralene could be obtained as a solution in a number of organic solvents, providing that they have low water solubility.

1.3.2 Synthesis of Symmetrically Substituted [3]Dendralenes via a Double Cross-Coupling Sequence

With the double cross-coupling reaction between DCE and vinyl magnesium bromide optimised, we decided to investigate whether we could extend this methodology to the synthesis of symmetrically substituted [3]dendralenes. A double cross-coupling reaction has been used previously by a number of groups for the synthesis of substituted [3]dendralenes, however, the majority of these employed 2-substituted-1,1-dibromoethylenes as cross-coupling partners (Scheme 17). Shen and co-workers as part of their work on synthesising the isocoumarins, performed a successful double Stille cross-coupling reaction on dibromide 58 to form substituted [3]dendralene 59 in 92% yield.\[42\] Oh and co-workers showed that 2-phenyl-1,1-dibromoethylene (61) could undergo a double Suzuki cross-coupling sequence with a range of boronic acids to form a series of substituted
[3]dendralenes (62) in 40–60% yields.\textsuperscript{[43]} As part of a formal synthesis of the natural product triptolide,\textsuperscript{[44]} the Sherburn group formed the first ever chiral [3]dendralene (64) via a double Stille cross-coupling reaction in 61% yield.\textsuperscript{[45]} Finally, Ichikawa and co-workers synthesised the first ever fluorinated [3]dendralene by coupling organozinc species 65 with a 2-substituted 1,1-dibromoethylene species 66 to form substituted tetrafluoro[3]dendralene 67 in 70% yield.

![Scheme 17: The synthesis of substituted [3]dendralenes via a double cross-coupling reaction sequence](image)

One novel approach that employed a double cross-coupling approach towards substituted [3]dendralenes involved the use of 1,1-dimetallo ethylenes (Scheme 18). Shimizu and co-workers used substituted 1,1-diborylethylene 69 in a stepwise cross-coupling sequence to form substituted [3]dendralene 71 in 59% yield.\textsuperscript{[46]} Selective monocoupling with bromide 68 occurred \textit{trans} to the more bulky phenyl substituent, before a second cross-coupling event with iodide 70 afforded the
desired target material. The same group also showed that a one-pot double cross-coupling reaction could be used to synthesise substituted [5]dendralene 74 in 37% yield.\(^{[47]}\)

\begin{align*}
\text{Ph} \quad \text{Br} & \quad \text{C}_2\text{H}_5 \quad \text{Ph} \quad \text{Bpin} \quad \text{Bpin} \quad \text{1)} \quad \text{Pd}(\text{PPh}_3)_2, \text{KOH} \\
& \quad \text{THF, 73\%} \\
\text{Ph} \quad \text{I} & \quad \text{C}_2\text{H}_5 \quad \text{Ph} \quad \text{Bpin} \quad \text{Bpin} \quad \text{2)} \quad \text{Pd}(\text{dppf})\text{Cl}_2, \text{KOH} \\
& \quad \text{DME, 81\%} \\
\end{align*}

Scheme 18: The synthesis of substituted [3]- and [5]-dendralenes via a double cross-coupling reaction using 1,1-diborylethylene

Not mentioned here are syntheses of substituted [3]dendralenes that employ a single cross-coupling reaction for the formation of the cross-conjugated alkenes, however, selected references are provided.\(^{[48-54]}\)

For our approach, we decided to focus on the cross-coupling reaction between DCE and Grignard reagents that were either commercially available or easily accessible, and which also contained a variety of substitution patterns (Figure 5).

Figure 5: Organometallic partners used in cross-coupling experiments
We first examined the use of 2-methyl-1-propenyl magnesium bromide (75) as a cross-coupling partner. After subjecting this to our previously developed optimised reaction conditions for [3]dendralene, we observed a 53% yield of our desired substituted [3]dendralene 80, along with an 18% yield of oxidative homo-coupled butadiene 81 (Scheme 19).

![Scheme 19: Initial results using 2-methyl-1-propenyl magnesium bromide as a cross-coupling partner](image)

We decided to investigate whether we could reduce the amount of homo-coupled product present and embarked upon another round of optimisation studies. Along with the conditions seen previously in section 1.3.1, we also experimented with a range of palladium catalysts, Kumada cross-coupling conditions, and a wide range of ligands, however, regardless of the organometallic cross-coupling partner used, the use of Kumada cross-coupling conditions led predominantly to the formation of the oxidative homo-coupled product, while the use of palladium catalysts led only to the recovery of DCE, potentially indicating that oxidative insertion of the palladium catalyst into the C-Cl bond did not occur. While disappointing, this result is not surprising, as Ni(0) is known to undergo oxidative addition into C-Cl bonds at a much faster rate than its Pd(0) analogue. The optimised conditions for the cross-coupling of substituted alkenyl Grignard reagents required the use of Ni(dppe)Cl₂ and triphenylphosphine ligand in the presence of zinc bromide (Table
1). With these conditions in hand, we next attempted the synthesis of a number of symmetrically substituted [3]dendralenes.

![Chemical diagram]


<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>80</td>
<td>71%</td>
<td>95:5</td>
</tr>
<tr>
<td>82</td>
<td>86%</td>
<td>95:5</td>
</tr>
<tr>
<td>83</td>
<td>88%</td>
<td>84:16</td>
</tr>
<tr>
<td>84</td>
<td>22%</td>
<td>66:33</td>
</tr>
<tr>
<td>85</td>
<td>0%</td>
<td>0:100</td>
</tr>
</tbody>
</table>

Grignard reagents 75 and 76 both coupled well with DCE after undergoing transmetalation with zinc bromide to give dendralenes 80 and 82 in yields of 71% and 86% respectively, although dendralene 82 could only be recovered as a solution in THF and therefore an internal standard was used to determine it’s $^1$H NMR yield. In both of these reactions, almost no oxidative homo-coupling of the organozinc species was observed.

Cyclopentenyl magnesium bromide (77) also led to high yields of [3]dendralene 83, however, the bis cyclopentene homo-coupled product was present as a minor product in an 84:16 mixture. Cross-coupling with TMS substituted Grignard reagent 79 also led to large amounts of homo-coupled product being formed and
only gave the desired [3]dendralene in low yields. Surprisingly, the use of either
cyclohexenyl magnesium bromide (78) or chloroprene Grignard reagent (18) failed
to form any of the desired double cross-coupled products. Cyclohexenyl
magnesium bromide was unreactive under both Negishi and Kumada cross-
coupling conditions across a range of catalysts and ligands, leading only to the
formation of bis-cyclohexene. Interestingly, chloroprene Grignard reagent 18
formed only [4]dendralene (the oxidative homo-coupled product) under Negishi
conditions but formed [5]dendralene under Kumada cross-coupling conditions.\[18\]

The reason for the differing reactivities of the organozinc species is unknown.
Cyclopentenyl zinc bromide and cyclohexenyl zinc bromide for example, are very
similar in terms of sterics and electronics yet show a marked difference in
reactivity. We postulate that a successful cross-coupling reaction requires a fast
transmetallation step (Scheme 20). When this transmetallation step is slow, the
formation of Ni(II) complex 46 is favoured, which in turn leads to oxidative homo-
coupling of the organometallic cross-coupling partner. When the transmetalation is
fast however, Ni(II) complex 87 is formed instead, and following reductive
elimination, forms diene 88, which then goes on to participate in another cross-
coupling event.
**Scheme 20:** The first catalytic cycle in the formation of symmetrically substituted [3]dendralenes

1.3.3 The Synthesis of Unsymmetrical [3]Dendralenes via a Selective Mono Cross-Coupling Reaction

With the double cross-coupling reactions proving relatively successful we next turned our attention to mono cross-coupling reactions in the hope it would give us access to not only the now unavailable chloroprene (16), but also a series of unsymmetrical [3]dendralene products (89) (**Scheme 21**). While selective mono-cross-coupling with DCE has been observed previously,\textsuperscript{32,38} the difficulty in
separating the side products of the reaction from the target material meant that the selectivity of our cross-coupling reaction needed to be high in order to make this strategy useful.

![Scheme 21](image-url)

**Scheme 21**: Potential synthesis of unsymmetrical [3]dendralenes

We began our studies by combining a 1:1 mixture of vinyl magnesium bromide (17) and DCE under our previously optimised [3]dendralene conditions, which led to a 2:1 mixture of [3]dendralene and chloroprene as determined by proton NMR spectroscopy. This ratio was observed regardless of the reaction conditions used, as different nickel precatalysts and ligands, and various reaction temperatures were all trialed under both Negishi and Kumada cross-coupling conditions. These results have been mirrored in the literature by a number of groups who have observed double cross-coupling reactions of 1,1-dihalo-2-alkylethylenes.\[43,56,57\] In an effort to observe chloroprene as the major product, we attempted the cross-coupling reaction with a three-fold excess of DCE. Once again, however, we observed [3]dendralene 1 as the major product in a 2:1 ratio. This preference for the double cross-coupled product over the single cross-coupled product was observed for a range of organometallic cross-coupling partners. In fact, of the organometallic cross-coupling partners pictured in Figure 3, only chloroprene derived Grignard reagent 18 showed any selectivity for the formation of mono coupled product. The reason for this irregularity is still unknown.
There are three potential reasons for the observed preference for double cross-coupling reactions. The first of these could be due to the proximity of the two carbon-halogen bonds. During the reductive elimination step of the first catalytic cycle, Ni(0) is expelled in close proximity to the second carbon-chlorine bond. The Ni(0) could immediately oxidatively insert into this bond, thus initiating the second catalytic cycle. Such a mechanism was postulated by Lau and co-workers\cite{58} to rationalise the formation of fluorene 92 during the attempted mono-cross-coupling reaction of 2,2′-diiodobiphenyl 90 and phenyl acetylene (91) (Scheme 22). It was found that mono-coupling of phenylacetylene with 2,2′-diiodobiphenyl 90 was not possible, instead, an intramolecular Heck reaction occurred immediately following the first cross-coupling event due to the proximity of the C–I bond, to form fluorene 92 as the major product.

\begin{center}
\includegraphics[width=0.5\textwidth]{Scheme22.png}
\end{center}

**Scheme 22:** Unexpected formation of fluorene compounds

The second possible cause for the preference for double cross-coupling is that the product of the first cross-coupling reaction is more reactive than the starting material. The product of the first cross-coupling reaction, chloroprene (16), contains a chorine atom that is both allylic and alkenic. Allylic chlorides have been known to undergo facile cross-coupling reactions under Negishi reaction conditions\cite{59} and this added activation could be the reason the second cross-
coupling occurs preferentially. The third explanation for the selectivity of the second cross-coupling event is that the Ni(0) species could form a Ni(0)-π complex as it is being reductively eliminated from the first catalytic cycle (Scheme 13). This π-complex could then direct the oxidative insertion into the second C-Cl bond, which then participates in a second catalytic cycle to form the undesired [3]dendralene.

![Scheme 23: Intramolecular oxidative insertion promoted by the formation of a Ni(0)-π complex](image)

The observed results suggest that the second cross-coupling reaction is as fast if not faster than the first which tends to agree with the similar work published in this area. While there are some reports in the literature of 1,1-dihaloalkenes undergoing selective mono-cross-coupling reactions under Negishi conditions, [41,62] these reactions tend to be: 1) Pd(0)-catalysed, 2) substituted at the 2-position and 3) involve aryl cross-coupling partners. When alkynyl cross-coupling partners are used, for example, selective double cross-coupling was observed.[63]

### 1.4 Summary

This chapter describes the development of a one-pot synthesis of the synthetically versatile [3]dendralene via a double cross-coupling reaction using commercially available starting materials (Scheme 24). Not only does this new synthesis utilise a
less toxic precursor than previously seen, it also lowers the cost of [3]dendralene to around $6.61 a gram based on Australian chemical prices as of May 2015, thus making it a viable and inexpensive starting material for future exploration. While the cross-coupling reaction furnishes [3]dendralene as a solution in THF, we have shown that continuous extraction can be used to access [3]dendralene in a variety of solvents.

Scheme 24: A double cross-coupling reaction was used to form [3]dendralene in one pot

The double cross-coupling strategy was extended to the synthesis of a series of symmetrical [3]dendralenes by altering the substitution patterns on the organozinc cross-coupling partners (Figure 6). Substituted [3]dendralenes 80 and 82 were formed nearly exclusively, however the formation of substituted [3]dendralenes 83 and 84 was accompanied by formation of symmetrical butadienes as a result of oxidative homo-coupling of the organozinc species. Substituted [3]dendralenes 32 and 85 could not be synthesised under any of the Negishi conditions trialed. Interestingly, it has been shown previously that [5]dendralene (32) can be synthesised under Kumada cross-coupling conditions.18

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17

2.75 equiv

MgBr

Cl

Cl

31

Ni(dppp)Cl2 (0.01 equiv)

ZnBr2 (2.75 equiv)

THF, 76%

1
A New and Improved Synthesis of [3]Dendralene

Figure 6: Symmetrical [3]dendralenes was synthesised via a double cross-coupling reaction between DCE and substituted alkenyl zinc bromides

Finally, attempts at the synthesis of unsymmetrical [3]dendralenes were also made (Scheme 25). Treatment of alkenyl zinc bromides with excess DCE led to a 2:1 mixture of double: single cross-coupled products 95:88. This indicates that the second cross-coupling event is faster than the first, which in turn means that the selective formation of unsymmetrical [3]dendralenes would be difficult to control.

Scheme 25: A 2:1 ratio of dendralene 95 and diene 88 was formed when DCE was used in excess

1.5 Future Work

While we were able to access some symmetrical substituted [3]dendralenes, many of the successful cross-coupling reactions were accompanied by oxidative homo-coupled side products. The elimination of this unwanted butadiene and
subsequent optimisation of the reactions is an obvious avenue of future work. While organozinc and organomagnesium cross-coupling partners were both examined in this work, a number of other potential organometallic partners exist that have been shown to react selectively with 1,1-dihaloethylene species. Organostannanes$^{[64]}$ and organoboranes$^{[65]}$ as well as cross-couplings involving alkenylalanes$^{[66]}$ and alkenylzirconates$^{[67]}$ have all been observed previously and any of these organometallic species could potentially produce less oxidative homo-coupled products (Scheme 26).

Another possible alteration we could make to the reaction is varying the dihaloalkene electrophile. Unpublished results from within the group have successfully used 1,1-dibromoethylene in a one-pot double cross-coupling reaction with alkenic organometallic cross-coupling partners to form the higher dendralenes (Scheme 27). One advantage of this approach is that the C–Br bond is much weaker than the C–Cl bond and is more prone to oxidative insertion by transition metal catalysts.$^{[68]}$ While we have shown that only Ni(II) catalysts are suitable for double cross-coupling reactions with DCE under our conditions, changing the electrophile to 1,1-dibromoethylene could potentially open up the possibility of using palladium$^{[69]}$ or iron$^{[70]}$ catalysts, which in turn could also lead to a reduction in the amount of oxidative homo-coupled product.
Scheme 27: The use of 1,1-dibromoethylene as a cross-coupling partner could reduce the amount of oxidative homo-coupled product being formed

Alternatively, a mixed 1,1-dihaloethylene species, such as ethylene 98, could also be examined, to take advantage of the reactivity of different C-X bonds (Scheme 28).[^71] These systems, which could alternatively contain enol triflates as coupling partners, could then be used to sequentially undergo cross-coupling reactions in order to form unsymmetrical [3]dendralenes.

Scheme 28: A mixed dihalo ethylene cross-coupling partner could be used to form unsymmetrical [3]dendralenes

Finally, if we are able to develop methodology that reduces the formation of oxidative homo-coupled products, we could then broaden the study to include alkenyl cross-coupling partners with a wide array of substitution patterns. One way to form these cross-coupling partners would be to take advantage of Negishi’s ‘elementometalations’ of alkynes (Scheme 29).[^72] This facile reaction allows access...
to a range of alkenyl cross-coupling partners and could form substituted [3]dendralenes in one pot from the relevant starting alkynes.

Scheme 29: The potential use of Negishi's 'elementometalation' strategy could lead to a variety of substituted [3]dendralenes in one step from alkynes.
Chapter 2: A Unified Approach to Carbocyclic Frameworks


As mentioned in Chapter 1, [3]dendralene can participate in DTDA sequences in which, after an initial Diels–Alder reaction, diene character is transmitted to a different part of the molecule. This new diene is then free to undergo a second Diels–Alder reaction (Scheme 30). In this way, bicyclo[4.4.0]dec-1-ene (105) ring systems can be formed in just two steps. The DTDA reaction sequence can either be carried out so that the same dienophile reacts twice, or in a sequential manner in which two different dienophiles are used.

\[ \text{1st diene site} \rightarrow \text{DA} \rightarrow \text{new diene site} \rightarrow \text{DA} \rightarrow 105 \]

Scheme 30: The prototypical diene transmissive Diels–Alder sequence between [3]dendralene and two molar equivalents of ethylene

There have been a number of investigations into the Diels–Alder reactivity of [3]dendralene. For the majority of these studies, only symmetrical and highly reactive dienophiles have been examined (Scheme 31), perhaps because of the perceived instability of the parent [3]dendralene precluding less reactive
dienophiles from being used.\textsuperscript{[73]} Interestingly, with one exception, all previous works describe thermal (i.e. uncatalysed) Diels–Alder processes.

An early study by Cadogan and co-workers showed that mono Diels–Alder adducts \textbf{106, 107} and \textbf{108} were formed preferentially from 1:1 stoichiometry reactions between [3]dendralene and the dienophiles dimethyl acetylenedicarboxylate (DMAD), \textit{p}-benzoquinone and tetrachloroethylene (TCNE) respectively (\textbf{Scheme 31}).\textsuperscript{[74]}

This work demonstrates an interesting and important aspect of the reactivity of [3]dendralene, in that the first Diels–Alder reaction is faster than the second. If this were not the case, a mixture of mono- and double- Diels–Alder adducts would be observed.\textsuperscript{[74]}

The use of symmetrical dienophiles in a selective single Diels–Alder reaction with [3]dendralene gives rise to only one possible product. The use of unsymmetrical dienophiles however gives rise to the possibility of regioisomers being formed. The only example of an unsymmetrical dienophile being used in a Diels–Alder reaction with [3]dendralene comes from the Sherburn group.\textsuperscript{[16]} A series of acyclic enone dienophiles were reacted with [3]dendralene to selectively give mono cycloaddition products as single regioisomers. It was found that Lewis acids were required in order to promote the Diels–Alder reaction. In each case, the observed products followed the so called \textit{ortho-para} rule as predicted by FMO theory\textsuperscript{[75]} to give semicyclic dienes \textbf{109} in which the activating group of the original dienophile is ‘\textit{para}’ to the vinyl substituent of the [3]dendralene diene.
Scheme 31: Previous studies examining the Diels–Alder reactions of [3]dendralene with various reactive dienophiles. BQ = benzoquinone, NQ = napthoquinone, TCNE = tetrachloroethylene, PTAD = 4-phenyl-1,2,4-triazole-3,5-dione, EVK = ethyl vinyl ketone, MA = maleic anhydride, DMAD = dimethyl acetylenedicarboxylate

The regioisomer 110, in which the activating group of the dienophile is ‘meta’ to the vinyl substituent, was not observed under any circumstances. It was also found that the double cycloaddition product was not observed under these reaction conditions, even when a large excess of the dienophile was used.
While these are the only examples of selective mono additions to this cross-conjugated triene, a number of groups have worked on the one pot double Diels–Alder reaction involving [3]dendralene and a single dienophile. Bicycle 111,[76] tetracycles 112,[4] 113,[74] 114[7] and 115[16] and hexacycle 116[77] were all the products of one pot double Diels–Alder reactions involving [3]dendralene. Of these double Diels–Alder adducts, only the stereochemistry of tetracycle 115 was discussed.[16] Sherburn and co-workers proved through the use of single crystal X-ray analysis that the major product of these reactions arose from the second cycloaddition occurring at the oppose π-diastereoface to that of the first.

Finally, there are only two examples in the literature that feature two different dienophiles being used in a DTDA reaction sequence with [3]dendralene. Cadogan and co-workers demonstrated that tetracycle 117 and tricycle 118 could both be synthesised through sequential Diels–Alder reactions beginning with [3]dendralene. In each case, the reactive dienophile 4-phenyl-1,2,4-triazole-3,5-dione (PTAD) was reacted under thermal conditions with a semicyclic diene that was itself the product of a Diels–Alder reaction between [3]dendralene and p-benzoquinone or TCNE respectively.

2.2 Aims

With a couple of exceptions, the majority of the reagents that have been studied in Diels–Alder reactions with [3]dendralene have been symmetrical, highly electron deficient dienophiles that are known to react readily and predictably in Diels–Alder reactions. Studies so far have shown that the first Diels–Alder reaction of
[3]dendralene is faster and more facile than the second cycloaddition, which is reflected in the fact that the first cycloaddition has been studied more extensively. With this in mind, the aims of the work described in this chapter are:

- To examine the use of less reactive acyclic dienophiles in both the first and second Diels–Alder reaction with [3]dendralene

- To extend our knowledge of [3]dendralene chemistry by examining Diels–Alder reactions involving carbocyclic dienophiles

- To investigate the tolerance of [3]dendralene and its Diels–Alder adducts to a variety of conditions commonly used in Diels–Alder reactions, including exposure to Lewis acids, ultra high pressure and high temperatures; and

- To use a mixture of cyclic and acyclic dienophiles to develop methodology capable of synthesising a range of polycyclic products

In regards to this last point, a range of different polycycles can, in principle, be accessed through DTDA sequences beginning with [3]dendralene (Scheme 32) by varying the nature of the two dienophiles used. A single Diels–Alder reaction with an acyclic dienophile (as depicted in red) can form semicyclic diene 119. If this diene is then reacted with another acyclic dienophile (red), bicyclic compounds such as 105 can be formed. If instead, a carbocyclic dienophile is reacted with 119 (as depicted in blue), angular tricycle 120 will be formed, where the letter inside the carbocycle denotes a range of carbocyclic ring sizes. If we conversely react [3]dendralene with a carbocyclic dienophile (blue), we can access semicyclic diene
From here, reaction with an acyclic dienophile (red) leads to linear tricycle 122 while reaction with a carbocyclic dienophile (blue) forms angular tetracycle 123.

Scheme 32: The different polycyclic structures available through Diels–Alder reactions involving [3]dendralene

2.3 Results and Discussion

2.3.1 Formation of Semicyclic Dienes

In order to develop methodology capable of synthesising a library of polycyclic frameworks, we need dienophiles capable of selectively undergoing Diels–Alder reactions with [3]dendralene (Scheme 33).
Scheme 33: The selective mono addition of either acyclic or carbocyclic dienophiles leads to new semicyclic dienes

2.3.1.1 Synthesis of Mono Cyclic Dienes

The dienophiles methyl vinyl ketone (MVK), DMAD and methyl propiolate were chosen as model substrates to investigate the Diels–Alder reactivity of acyclic dienophiles with [3]dendralene in DTDA reaction sequences. The choice of MVK as an acyclic alkenic dienophile was based on a number of factors. 1) It would complement previous work performed in the group in which acrylates were shown to react selectively with [3]dendralene (Scheme 31), 2) MVK is an unsymmetrical dienophile that would allow us to explore the regioselectivity of cycloaddition reactions with both [3]dendralenes and its Diels–Alder adducts, and 3) MVK is a cheap and readily available starting material. Methyl propiolate was chosen as an alkynic equivalent to MVK for similar reasons.
Based on the group’s previous work using acrylates as dienophiles, we decided to investigate the use of aluminium-based Lewis acids in promoting the Diels–Alder reaction with [3]dendralene. After extensive optimisation, it was found that using Me₂AlCl as a reagent consistently provided superior results compared to the Lewis acids AlCl₃, Me₂AlCl₂, Me₃Al, TiCl₄ or BF₃·Et₂O. Thus, MVK (124) and a slight excess of [3]dendralene were combined in CH₂Cl₂ in the presence of Me₂AlCl (0.5 molar equiv.) to give semicyclic diene 125 in 71% yield as a single regioisomer, the structure of which was confirmed by 2D NMR spectroscopic analysis. The observed regiochemistry conformed to the ortho-para rule observed previously (Scheme 34).¹⁶

![Scheme 34: Products arising from a single Diels–Alder reaction between an acyclic dienophile and [3]dendralene](image)

The other two acyclic dienophiles that we decided to investigate were DMAD (126) and methyl propiolate (128). While the Diels–Alder reactivity of the symmetrical dienophile DMAD with [3]dendralene has been examined previously,⁷⁶ we were
interested to see if it would react in THF solution, thus making it compatible with our method development from Chapter 1. We were also interested to see how the unsymmetrical alkyne, methyl propiolate, would react in the Diels–Alder reaction with [3]dendralene, and to see if any regiochemical selectivity would be observed. We were pleased to discover that DMAD reacted cleanly with [3]dendralene in THF to give the desired triene 127 in 88% yield after 16 hours. The less activated methyl propiolate also reacted with [3]dendralene to give semicyclic diene 129 as a single isomer in 58% yield over 40 hours. In an attempt to improve the yield of the Diels–Alder reaction between [3]dendralene and methyl propiolate, Lewis acidic conditions were trialed, however, without exception, these reactions were lower yielding than the thermal Diels–Alder reaction. With the three semicyclic dienes 125, 127 and 129 in hand, we moved on to synthesising the remainder of our polycyclic library.

2.3.1.2 Synthesis of Bicyclic Dienes

2.3.1.2.1 Cyclic Enones and the Diels–Alder Reaction

With the successful synthesis of monocyclic dienes achieved, attention turned towards using carbocyclic dienophiles in Diels–Alder reactions with [3]dendralene. It was decided that the cyclic enone cyclohexenone (131) would be an ideal substrate for our optimisation studies, again due to its unsymmetrical nature and its commercial availability. Cyclic enones, such as cyclohexenone, are notoriously poor dienophiles in Diels–Alder reactions, a characteristic recently attributed to the high energies required to distort them into a conformation that maximises orbital overlap in the transition state.[78] Bartlett and co-workers showed in 1940 that
cyclohexenone required temperatures in excess of 200 °C for a period of up to four days to promote the thermal Diels–Alder reaction between cyclohexenone (131) and 2,3-dimethy butadiene (130), a reaction that formed bicycle 132 in just 20% yield (Scheme 35).[79] The low yields of this transformation were attributed to the harsh conditions required to promote the reaction. D’Angelo and co-workers later showed that ultra high pressure could be used in place of high temperature to promote Diels–Alder reactions involving cyclic enones. It was shown that at 12 kbar, cyclopentenone (134) reacted with diene 133 to form bicycle 135 in 70% yield as a single stereoisomer.[80]

![Scheme 35: High temperatures and high pressures are required for Diels–Alder reactions involving cyclic enones](image)

As both high temperatures and high pressures were likely to lead to Diels—Alder dimerisation of [3]dendralene, we decided to attempt to promote the reaction using Lewis acids, borrowing conditions from work performed in the Danishefsky group. In this work, the Diels–Alder reaction between cyclic enones and substituted 1,3-butadienes gave optimal results when MeAlCl₂ was used as a catalyst (Scheme 36).[81]
Scheme 36: Conditions developed by Danishefsky and co-workers using Me₂AlCl to promote the Diels–Alder reaction between cyclohexenone and 2,3-dimethyl-1,3-butadiene

Following Danishefsky’s experimental protocol, a large excess of [3]dendralene was combined with cyclohexenone in the presence of MeAlCl₂ at 0 °C to give an 80% yield of a Diels–Alder product as a 2:1 mixture of isomers (Table 2). The two isomers were confirmed as the regioisomers 136 and 137 through the use of 2D NMR spectroscopy and single crystal X-ray analysis. The presence of regioisomer 137 in this reaction was surprising, as all other studies examining the Diels–Alder reactivity of [3]dendralene with unsymmetrical dienophiles had previously generated exclusively a single regioisomer. It was found that lowering the number of molar equivalents of [3]dendralene from five to two led to an increase in both yield (95%) and selectivity (3:1), however, lowering the stoichiometric ratio further led to reduced yields. We next decided to examine alternative Lewis acids in an attempt to optimise the reaction further. While the use of the strong Lewis acid TiCl₄ led to a sharp decrease in selectivity (1:1 ratio), the use of the less Lewis acidic Me₂AlCl₄ led almost exclusively to the formation of a single isomer. By lowering the internal reaction temperature to −20 °C, we were able to obtain semicyclic diene 136 as the sole product in 93% yield.
With this positive result in hand, we examined the use of other cyclic enones as dienophiles under our optimised conditions (Figure 7). Cyclopentenone combined with [3]dendralene to give bicyclic diene 138 as the major product, along with its regioisomer, in a 3:1 mixture. Substitution at the C2 position of cyclohexenone with a methyl group led to diene 139 as the sole product in 64% yield, while the use of 3-methylcyclohexen-2-one led only to recovery of the starting material. The lower yields observed when 2-methyl cyclohexenone was used as the dienophile, and the complete lack of reactivity when 3-methyl cyclohexenone was used, can both be attributed to the steric bulk imposed by the methyl groups of the respective dienophiles interrupting the formation of new C–C bonds in the transition state of the reaction.\textsuperscript{[83]}

![Chemical reaction image]

**Table 2:** Optimisation of the reaction between [3]dendralene and cyclohexenone

<table>
<thead>
<tr>
<th>Entry</th>
<th>Molar equiv. of 131</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>Selectivity (136:137)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>MeAlCl(_2), CH(_2)Cl(_2), 0 °C</td>
<td>80</td>
<td>2:1</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>MeAlCl(_2), CH(_2)Cl(_2), 0 °C</td>
<td>95</td>
<td>3:1</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>MeAlCl(_2), CH(_2)Cl(_2), 0 °C</td>
<td>60</td>
<td>3:1</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>TiCl(_4), CH(_2)Cl(_2), 0 °C</td>
<td>-</td>
<td>1:1</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>Me(_2)AlCl, CH(_2)Cl(_2), 0 °C</td>
<td>90</td>
<td>10:1</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>Me(_2)AlCl, CH(_2)Cl(_2), -20 °C</td>
<td>93</td>
<td>&gt;20:1</td>
</tr>
</tbody>
</table>
2.3.1.2.2 Arynes and the Diels–Alder Reaction

A second class of carbocyclic dienophile capable of undergoing Diels–Alder reactions with 1,3-butadiene units are arynes. Arynes are reactive intermediates, formed in situ, via the elimination of two ortho substituents from an aromatic ring (Scheme 37).

\[
\begin{align*}
\text{Scheme 37:} & \text{ Benzyne is formed through the elimination of two ortho substituents from an aromatic ring} \\
\end{align*}
\]

The presence of o-benzyne (142) was first postulated by Bachmann and Clarke in 1927, however, it was not until the work of Wittig in 1942 that these reactive intermediates began to be examined in greater detail. There are a number of different substituted arenes that can lead to the formation of aryynes in situ (Scheme 38). Some of these precursors, such as haloarene 143 and 2-amino benzoic acid (145) require either high temperatures or strong bases in order to form the reactive benzyne intermediate, while organometallic arene 144 is itself a reactive species.
and is not compatible with a number of functional groups. It was not until the 1980s that a facile approach to the formation of arynes was discovered. Koboyashi and co-workers determined that treatment of ortho TMS phenol triflate 146 with a fluoride source under ambient conditions led to the formation of benzyne \textit{in situ} without the need for high temperatures or strong bases.\cite{87}

\begin{center}
\textbf{Scheme 38:} A number of precursors can lead to the generation of benzyne \textit{in situ}
\end{center}

While the use of benzynes in Diels–Alder reactions is not unknown, previous examples are mostly limited to cyclic or highly constrained dienes, with substituted furans being used most often.\cite{86} In fact, the lack of examples of acyclic dienes reacting with benzynes in the literature led Brian Stoltz to state “the use of acyclic dienes [in Diels–Alder reactions with benzynes] in natural product synthesis is still a considerable challenge and represents an underexplored area of aryne methodology.”\cite{86}

Despite this lack of precedent, it was thought that the successful Diels–Alder reaction between benzynes and [3]dendralene could be possible due to the reactive nature of [3]dendralene as a diene, and thus was worth exploring. It was decided that the symmetrical benzyne precursors 147 and 148 would be used in our initial Diels–Alder studies (\textbf{Figure 8}).
Figure 8: The symmetrical benzyne precursors used in our initial Diels–Alder studies.

Dimethoxybenzyne precursor 148 was synthesised using a modified procedure from Castedo and co-workers (Scheme 39). Baeyer–Villiger oxidation of aldehyde 149 and hydrolysis of the resulting ester led to phenol 150 in 85% yield. This phenol was then protected as a TMS ether through treatment with hexamethyldisilazane. Directed lithiation of TMS ether 151, and subsequent quenching of the resultant organolithium species with TMSCl led to arene 152. Finally, treatment of arene 152 with n-BuLi in the presence of triflic anhydride led to dimethoxybenzyne precursor 148 in 72% yield. The second benzyne precursor required for our studies, TMS triflate 147, is a commercially available compound, however, it can also be made through a similar sequence to that of the dimethoxy benzyne precursor, using 2-bromo or 2-chlorophenol as the starting material.
Treatment of ortho TMS triflate 147 with TBAF\(^{[87]}\) in the presence of [3]dendralene, led only to the isolation of a complex mixture of products. Switching to cesium fluoride led to clean formation of the desired bicyclic diene 153 as a colourless oil, which solidified when placed in the freezer (Scheme 40). The low solubility of CsF in acetonitrile\(^{[90]}\) ensures that the concentration of benzyne in solution remains low, which in turn limits the amount of unwanted side reactions.\(^{[91]}\) It was found that anhydrous conditions were required for optimal yields, as the presence of water in the reaction mixture led to the formation of phenol through the addition of water across the benzyne triple bond. Dimethoxybenzyne precursor 148 also reacted with [3]dendralene in the presence of CsF to give bicyclic diene 154 in 22\% yield (67\% based on recovered starting material). The reason for the decreased yield of bicyclic diene 154 is unknown.

Initially, we were concerned about the stability of semicyclic dienes 153 and 154 in air, as autoxidation could lead to a more stable vinyl naphthalene product,
however, minimal degradation (<10%) of these compounds was observed when stored in the freezer neat, even after 18 months.

\[
\begin{align*}
\text{Scheme 40: The Diels–Alder reaction between [3]dendralene and symmetrical benzyynes} \\
\text{TMS} & + \text{CsF} \rightarrow \text{OMe, 81\%} \\
\text{TMS} & + \text{CsF} \rightarrow \text{OMe, 22\%}
\end{align*}
\]

With the synthesis of these new semicyclic dienes successfully completed, we now had a range of compounds with which to extend our library of polycyclic structures. We next turned our attention to performing a second Diels–Alder reaction on these newly formed dienes in order to build a library of polycyclic compounds.

2.3.2 Synthesis of Bicyclic Double Diels–Alder Products

Having successfully demonstrated the mono Diels–Alder reaction between [3]dendralene and both cyclic and acyclic dienophiles, the next goal was to examine the use of acyclic dienophiles in Diels–Alder reactions with these newly formed semicyclic dienes. A successful Diels–Alder reaction between an acyclic dienophile and a monocyclic diene 119 would allow access to bicyclic compounds 105 (Scheme 41).
2.3.2.1 The Use of Acyclic Dienophiles with Mono Cyclic Dienes

The use of semicyclic dienes in Diels–Alder reactions to build complex ring systems is not a new concept. A number of studies have been carried out examining a range of unsymmetrical, acyclic dienophiles and the Diels–Alder reactivity with monocyclic dienes (Scheme 42). Inayama and co-workers showed that MVK reacts with diene 155 under thermal conditions to give a 14:5:3 mixture of isomers 156:157:158 in a 65% yield.$^{[92]}$ Two of these isomers (156 and 158) arise from transition states in which the dienophile approaches from opposite π-diastereofaces of the diene, while bicycle 157 is a regioisomer of the other two products. Bhat and co-workers demonstrated, as part of their work on the synthesis of bioactive terpenoids, that these reactions could be carried out in a regio- and stereo- selective manner through the use of Lewis acids. Decalin 160 was
obtained as a single isomer in 60% yield following the AlCl₃-promoted cycloaddition of MVK and diene 159. Finally, the Barriault group showed that the use of directing groups in conjunction with bidentate Lewis acids could be used to impart selectivity on Diels–Alder systems employing unsymmetrical dienophiles. During their synthesis of vinigrol, Barriault and co-workers combined dienol 161 with methyl acrylate (162) in the presence of magnesium bromide. The bidentate magnesium Lewis acid formed a temporary tether between the diene and dienophile that delivered methyl acrylate selectively to one face of the diene, thus forming bicycle 163 in 78% yield as a single stereoisomer.

We began our studies into the formation of bicyclic systems by examining the cycloaddition between MVK (124) and semicyclic diene 125 (Scheme 43), however, we were unsuccessful in achieving a clean Diels–Alder reaction under any of the conditions trialed.
Attempts to form bicycle 164 thermally in refluxing toluene led only to the recovery of starting material, while subjecting MVK and diene 125 to 19 kbar pressure led to a complicated mixture of decomposition products. Borrowing from the work of Barriault, we next attempted to form a temporary tether between through the use of a bidentate Lewis acid. The use of MeAlCl₂ in the presence of MVK and diene 125 appeared to promote a successful cycloaddition, however, a mixture of what appeared to be four Diels–Alder products was observed in a 3:1:1:1 ratio of isomers, however, in our hands, we could not isolate any of these isomers cleanly. Attempts to change to boron, titanium, zinc, magnesium or other aluminium based Lewis acids also proved unsuccessful in the formation of bicycle 164, as all led to a complex mixture of up to four stereoisomers.

With the Diels–Alder reaction between semicyclic diene 125 and MVK proving unsuccessful, we moved onto reactions involving diene 127. It was hoped that Diels–Alder reactions involving diene 127 would be cleaner than those involving diene 125, as the equivalency of its two \( \pi \)-diastereofaces meant less isomeric products could be formed. Unfortunately, no signs of Diels–Alder adducts were ever observed under Lewis acid conditions. One potential reason for this is the increased number of Lewis basic sites present on the diene. The Lewis acids used
in these reactions may selectively bind to the various oxygen containing functional groups of the diene, which in turn, would mean that MVK is not activated towards Diels–Alder reactions. When Lewis acid conditions proved unsuccessful, we briefly examined thermal conditions, by combining diene 127 and MVK in refluxing toluene, and high pressure conditions where diene 127 and MVK were subject to 19 kbar, however, this led to recovery of the starting material and decomposition of the diene respectively.

These results, while disappointing, mirrored previous work performed in the group examining the DTDA reaction sequence between [3]dendralene and methyl acrylate (Scheme 44).[^16] In these studies, only mono Diels–Alder products were ever isolated, despite attempts to promote the second Diels–Alder reaction by treating [3]dendralene with a large excess of the dienophile.

![Scheme 44](image.png)

**Scheme 44:** The Diels–Alder reaction between [3]dendralene and excess methyl acrylate did not yield double Diels–Alder products

With Diels–Alder reactions between monocyclic dienes and MVK proving unsuccessful, we next turned our attention towards using symmetrical DMAD as a dienophile. Combining DMAD and semicyclic diene 125 in refluxing toluene led to an 85% yield of the two isomers of bicycle 166 as a 2:1 mixture of products. As DMAD is a symmetrical alkyne, the only possible isomers for this reaction arise from addition of the dienophile from opposite π-diastereofaces of the diene. While

[^16]: Reference to additional information.
the relative stereochemistry of the different isomers was not determined, the major isomer is expected to contain both the proton at the ring junction and the acetyl group on the same face of the molecule due to the destabilising steric interactions in the transition state that would lead to the other isomer. Despite many attempts to do so, the two isomers could not be separated by column chromatography. It was therefore decided to instead aromatise the system in order to remove one of the stereocentres, hence removing the mixture of diastereomers and generate a single (racemic) product. Treatment of bicycle 166 as a 2:1 mixture of isomers with DDQ in refluxing toluene gave tetralin 167 in 66% yield as the sole product. This procedure was applied to diene 127 in a similar manner to give rise to tetra ester 111 in 78% yield, which, following DDQ oxidation, led to naphthalene 168. It was found that this two-step Diels–Alder/oxidation sequence could be carried out in one pot with no loss of yield. These results agreed with work carried out previously by Hopf and co-workers.[76]

Scheme 45: The selective formation of tetralin and naphthalene frameworks beginning from semicyclic dienes
This methodology allows for the selective synthesis of either tetralin or naphthalene systems in just three steps beginning with a DTDA sequence involving [3]dendralene and two acyclic dienophiles, followed by DDQ oxidation.

With the Diels–Alder reactivity of monocyclic dienes and acyclic dienophiles established, we next looked at the how bicyclic dienes and acyclic dienophiles would behave under similar conditions.

### 2.3.3 Synthesis of Linear Tricyclic Double Diels–Alder Products

Continuing on with the goal of synthesising a library of polycyclic compounds, we next attempted the synthesis of linearly tricyclic compounds 122 through the cycloaddition of acyclic dienophiles with bicyclic dienes 121 (Scheme 46).

![Scheme 46: Diels–Alder reactions between acyclic dienophiles and bicyclic dienes form linear tricyclic compounds](image-url)
2.3.3.1 The Use of Acyclic Dienophiles with Polycyclic Dienes

Polycyclic dienes where the diene unit is situated at the terminal end of a fused ring system, such as diene 121, are quite rare, and their participation in Diels–Alder reactions with acyclic dienophiles even more so. There are only two such examples of cycloadditions of this type appearing in the literature to date. The Sainsbury group obtained an 82% yield of pentacycle 170 as a 1:1 mixture of endo/exo isomers when methyl acrylate (162) was reacted with codeine-derived diene 169 under thermal conditions (Scheme 47). More recently, Hergenrother and co-workers showed that diene 171, which could be obtained from the natural product abietic acid in three steps, reacts with the symmetrical dienophile TCNE with complete π-diastereofacial selectivity to form tricycle 173 in a 72% yield as a single stereoisomer.

Scheme 47: Examples of Diels–Alder reactions between acyclic dienophiles and semicyclic dienes
Our own studies began by examining the thermal Diels–Alder reaction between MVK and bicyclic diene 136. In contrast to our previous unsuccessful results involving monocyclic diene 125, this led to a 2:1 mixture of isomers in a 70% overall yield. It is thought that the higher thermal stability of the larger bicyclic diene allows this reaction to proceed successfully (Scheme 48). Following flash column chromatography, the two compounds were separated and the structures were confirmed by single crystal X-ray analysis to be regioisomers 174 and 175 (Figure 9).

![Scheme 48](image)

**Scheme 48:** The thermal Diels–Alder reaction between semicyclic diene 136 and MVK led to a 2:1 mixture of regioisomers

In an attempt to improve the selectivity of the reaction, a series of optimisation studies was undertaken. A 5M solution of lithium perchlorate in diethyl ether or nitromethane is known to promote Diels–Alder reactions, either by increasing the internal pressure of the reaction mixture\(^{[97]}\) or through simple Lewis acid catalysis,\(^{[98]}\) however, in our hands, no signs of a successful Diels–Alder reaction was ever observed. Attempting the reaction in the presence of a variety of aluminium based Lewis acids, including AlCl₃, MeAlCl₂ and Me₂AlCl led to a 2:1 mixture of 174 and 175, along with trace amounts of other uncharacterised isomers. When BF₃·Et₂O was used in place of aluminium based Lewis acid analogues, the yield of the reaction increased to 85% while the selectivity of the reaction improved to 5:1 in favour of tricycle 174. Finally, when semicyclic diene 136 and MVK were
combined in CH₂Cl₂ and subjected to 19 kbar pressure for 18 hours, tricycles 174 and 175 were isolated as a 10:1 mixture of regioisomers in an 84% overall yield.

Figure 9: The single crystal X-ray structures of regioisomers 174 and 175

The π-diastereofacial selectivity of this reaction can be explained upon simple examination of the diene. Single crystal X-ray analysis of diene 136 shows a well-defined convex and concave face (Figure 10).

Figure 10: The single crystal X-ray structure of diene 136 shows the convex and concave faces of the molecule

Dienophile approach from the more sterically hindered concave face is blocked by the cyclohexanone ring, which therefore favours approach from the convex face of the molecule. The complete endo selectivity observed in the reaction is a result of the preference of endo transition states under ultra high pressure reaction
conditions.[99] The regioselectivity of the reaction can be explained by FMO theory. Houk and co-workers have shown computationally that the largest molecular orbital coefficient of 1,2-disubstituted 1,3-butadienes most often sits at the C4 position of the butadiene unit[100,101] while computational studies on the Diels–Alder reactivity of MVK have shown that the largest molecular orbital coefficient sits at the terminal end of the alkene (Figure 11).[102] In order to maximise orbital overlap, FMO theory would predict a Diels–Alder reaction where a new C–C bond is formed between these two positions, which was observed experimentally in our system with regioisomer 174 being formed as the major product.

![Predicted and Calculated Molecular Orbital Coefficients](image)

**Figure 11:** The calculated molecular orbital coefficients of diene 136 and MVK (124)

These optimised conditions were next applied to dienes 138 and 153. These reactions afforded tricyclic structures 176 and 177 as the major products in 70% and 82% yields, respectively.
In each case, minor isomers were observed, which could not be cleanly isolated or characterised.

With Diels–Alder reactions involving bicyclic dienes and MVK proving successful, attention moved to the use of DMAD as a dienophile. Exposure of diene 136 to DMAD in refluxing toluene formed tricycle 178 as a 3:1 mixture of isomers, arising from addition of DMAD to the two different π-diastereofaces of diene 136 (Scheme 49). Attempted separation of these isomers by flash column chromatography again proved unsuccessful. In order to confirm the structure of the Diels–Alder products, the 3:1 mixture of diastereoisomers was subjected to DDQ oxidation in refluxing toluene to give tricycle 179 as the sole diastereomeric product in 52% yield over two steps. These conditions were also used to form tricycles 181 and 185 in 79% and 54% yields, respectively. Aromatic ring containing diene 153 formed tricycle 182 as a single isomer, which, upon DDQ oxidation, formed anthracene 183 in 50% yield over two steps. Once again, this two-step Diels–Alder reaction/oxidation sequence could be carried out in one pot without any decrease in product yield.
Scheme 49: Formation of aromatic-containing linear tricycles

By using acyclic compounds as the second dienophile in the DTDA reaction sequence with [3]dendralene, a series of bicyclic and linear tricyclic compounds have been synthesised. It was shown that systems involving bicyclic dienes are compatible with Lewis acid, high pressure and thermally promoted reaction conditions and that reasonable selectivity can be achieved when one face of the diene is sterically encumbered. It was also shown that the use of alkynic dienophiles could lead to the formation of substituted tetralin, naphthalene and anthracene compounds. This serves to highlight the synthetic utility of [3]dendralene by way of DTDA sequences.
2.3.4 Synthesis of Angular Tricyclic Double Diels–Alder Products

With the use of acyclic dienophiles explored, we next turned our attention to the use of carbocyclic compounds as the second dienophile in DTDA sequences with [3]dendralene. A successful Diels–Alder reaction between a carbocyclic dienophile and a monocyclic diene would give rise to angular tricyclic systems such as tricycle 120 (Scheme 50).

Scheme 50: Diels–Alder reactions between cyclic dienophiles and monocyclic dienes form angular tricyclic compounds

2.3.4.1 The Use of Cyclic Enones with Mono Cyclic Dienes

Numerous groups have previously reported on the formation of angular tricyclic structures through Diels–Alder reactions as part of the synthesis of various natural products, however, successful Diels–Alder reactions often required either activated
Diels–Alder partners, or harsh reaction conditions in order to facilitate a successful cycloaddition (Scheme 51).

Scheme 51: Examples of cyclic enones acting as dienophiles in Diels–Alder reactions to form angular structures

Vanderwal and co-workers reacted substituted cyclohexenone 187 with electron rich diene 186 under Lewis acid conditions as part of a synthesis of the clionastatins.[103] When these two reagents were combined in the presence of EtAlCl₂, tricycle 188 was formed as the sole product, although no yield was reported for this individual step. Jung and co-workers required microwave heating under pressure to promote the Diels–Alder reaction between diene 189 and doubly activated dienophile 190 during their work on the synthesis of cucurbitacins B and D.[104] Combining these two compounds in CH₂Cl₂ and subjecting them to heating in a microwave reactor at 100 °C for 18 hours gave pentacyclic compound 191 as a single, albeit undesired, isomer. Finally, as part of their work on investigating the
A Unified Approach to Carbocyclic Frameworks

The synthetic usefulness of trimethyl vinyl cyclohexenone 192, the Engler group required both ZnBr₂ and high pressure conditions to promote the Diels–Alder reaction between diene 192 and the doubly activated cyclohexenone 193.¹⁰⁵ This gave tricycle 194 as the major product in 47–63% yield. Interestingly, it was shown that this reaction did not take place in the presence of alternative Lewis acids.

We decided to examine the thermal Diels–Alder reaction between monocyclic diene 125 and cyclohexenone (Scheme 52) as a starting point for our studies, despite the fact that neither the diene, nor the dienophile in this reaction are particularly activated when compared to previous literature examples.

![Scheme 52: The thermal Diels–Alder reaction between monocyclic diene 125 and cyclohexenone did not lead to a successful reaction](image)

Perhaps unsurprisingly, attempts to promote the reaction thermally were unsuccessful. Performing the reaction in refluxing toluene led to no reaction being observed, while raising the temperature to 200 °C or above in a sealed tube led only to decomposition of the starting diene. A range of Lewis acids, including TiCl₄, BF₃.EtO and AlCl₃ amongst others, were trialed in an attempt to promote the reaction, however, at best only trace amounts of potential Diels–Alder products were observed. Attempts to utilise ionic Diels–Alder conditions by preforming the ethylene ketal of cyclohexenone¹⁰⁶,¹⁰⁷ or employing LiClO₄ to promote the reaction also led only to recovery of the starting materials. Finally, the use of ultra high pressure conditions proved successful. Combining monocyclic diene 125 (0.33
mmol) and cyclohexenone (1.66 mmol) in CH₂Cl₂ and subjecting the mixture to 19 kbar for 18 hours resulted in a 2:3 mixture of Diels–Alder products and starting material (For a rationalisation of this increase in rate acceleration, and comments on the diastereoselectivity of high pressure reactions, see Chapter 4). When the reaction was left for 72 hours, complete consumption of the diene was observed and the target material was isolated in an 82% yield as a 2:1 mixture of isomers (Scheme 53).

Scheme 53: The optimised conditions for the Diels–Alder reaction between cyclohexenone and monocyclic diene 125

The two isomers could be separated by flash column chromatography and the structures were confirmed by single crystal X-ray analysis and 2D NMR spectroscopic examination to be isomers 196 and 197 respectively. These two compounds were shown to be diastereoisomers arising from addition of cyclohexenone to opposite faces of the diene.

The major cycloaddition product arose from cyclohexenone reacting from the opposite π-diastereoface to that of the acetyl group (Figure 13). In the case of both isomers, the cycloaddition occurred exclusively through an endo transition state, which agrees with the literature observation that this is the preferred reaction mode of high pressure Diels–Alder reactions, especially when cycloalkenones are being used.[108] The regiochemical outcome of the reaction can be explained through FMO theory, as maximum orbital overlap is achieved when the terminal
end of the diene reacts with the β carbon of the cyclic dienophile as discussed in section 2.3.3.1 of this chapter.\cite{109}

![Figure 13: The single crystal X-ray structure of major isomer 196](image)

Semicyclic diene 127 was also combined with cyclohexenone and subjected to 19 kbar pressure for three days to afford angular tricycle 198 as a single isomer in 72% yield (Scheme 54). This reaction was completely regioselective and proceeded exclusively through the endo transition state.

![Scheme 54: The endo selective Diels–Alder reaction between semicyclic diene 127 and cyclohexenone](image)

2.3.4.1 The Use of Arynes with Mono Cyclic Dienes

The use of benzynes in Diels–Alder reactions with our recently synthesised monocyclic dienes was also attempted. There are only two examples in the literature of benzynes reacting in Diels–Alder reactions with semicyclic dienes. Wutichai and co-workers combined semicyclic diene 199 and benzyne precursor
145 in the presence of isoamyl nitrile to give tricycle 200 in 25% yield (Scheme 55). More recently, in unpublished work from within the Sherburn group, a series of substituted benzyne precursors were reacted with semicyclic diene 201 in the presence of cesium fluoride to yield a range of tetracyclic compounds in 56–64% yield as a mixture of isomers.\cite{110}

\[ \text{Scheme 55: Examples of Diels–Alder reactions between benzenes and semicyclic dienes} \]

We began our studies by attempting the Diels–Alder reaction between monocyclic diene 125 and benzyne precursor 147. Using CsF as a fluoride source, a 2:1 mixture of Diels–Alder products was isolated in 30% overall yield. Single crystal X-ray analysis confirmed the structure of the major isomer as tricycle 204, in which the benzyne approached the diene from the opposite face to the acetyl group (Scheme 56). Monocyclic diene 127 was also treated with benzyne precursor 147 under the same conditions, however, no Diels–Alder adducts were observed.
We have examined the use of carbocyclic dienophiles in the Diels–Alder reaction with monocyclic dienes. Combining cyclic enones with monocyclic dienes under ultra high pressure conditions led to the formation of angular tricyclic compounds 196, 197 and 198 as mixtures of isomers in good yields (Scheme 53 and Scheme 54), while a successful Diels–Alder reaction using TMS triflate benzyne precursor 147 led to only the third example of a successful Diels–Alder reaction between a semicyclic diene and an aryne (Scheme 56). With these reactions proving successful, we next applied these methodologies towards the synthesis of angular tetracyclic frameworks.

**Figure 14:** The single crystal X-ray structure of major isomer 204
2.3.6 Synthesis of Angular Tetracyclic Double Diels–Alder Products

The completion of our studies into the synthesis of a polycyclic library required the use of carbocyclic dienophiles with bicyclic dienes, which, if successful, would lead to angular tetracyclic compounds 123 (Scheme 57).

Scheme 57: The synthesis of tetracyclic compounds through Diels–Alder reactions between cyclic dienophiles and bicyclic dienes

The formation of angular tetracyclic compounds of this nature via a Diels–Alder reaction between a bicyclic diene and an unsymmetrical carbocyclic dienophile has not yet been reported in the literature, although systems in which the symmetrical, nitrogen containing maleimides are used with bicyclic dienes, are known.\cite{111,112} We began our investigations by examining the Diels–Alder reactivity of the achiral diene 153. As seen in section 2.3.4.1, Diels–Alder reactions between monocyclic dienes and cyclic enones proved unsuccessful under thermal or Lewis acid promoted conditions, and this was again the case when diene 153 was used. Ultra
high pressure however, was successful in forming the desired Diels–Alder adduct 206 as a single stereoisomer in 84% yield (Scheme 58).

Scheme 58: The ultra high pressure promoted Diels–Alder reaction between cyclohexenone and diene 153

The relative stereochemistry of the sole adduct was determined by single crystal X-ray analysis, which showed that the product was formed via endo addition of the dienophile in an orientation that would be predicted by FMO theory.

With this reaction proving successful, we then went on to determine the selectivity of Diels–Alder reactions involving bicyclic dienes containing non-equivalent faces. When diene 136 and cyclohexenone were combined in CH₂Cl₂ and subject to 19 kbar for 72 hours, tetracycle 207 was formed as a single stereoisomer in 67% yield (Scheme 59). The relative stereochemistry of tetracycle was confirmed by single crystal X-ray analysis (Figure 15).
Scheme 59: The products of DTDA sequences involving [3]dendralene and two cyclic enones

This selectivity was particularly pleasing considering a total of eight possible isomers can be formed in this reaction. As seen previously when using MVK as a dienophile, the bulky cyclohexanone ring of diene 136 controls the $\pi$-diastereofacial selectivity of the reaction, directing the second Diels–Alder cycloaddition to the opposite $\pi$-diastereoface from which the first reaction occurred. The cyclohexenone dienophile again reacted with complete regioselectively through an *endo* transition state, due to the effects of the ultra high pressure conditions.

Figure 15: The single crystal X-ray structure of tetracycle 207
With this reaction proving successful, we next investigated the effect of ring size of the dienophile. Cyclopentenone (134) also reacted with diene 136 to form tetracycle 208 as a single diastereoisomer in 54% yield. This same selectivity was observed when semicyclic diene 138 was used under identical conditions. Despite the smaller ring size of diene 138, complete \( \pi \)-diastereofacial selectivity was observed with both cyclohexenone and cyclopentenone to form tetracycles 209 and 210 respectively as single stereoisomers. The stereochemistry of all tetracyclic products was confirmed by single crystal X-ray analysis.

To complete our work on our polycyclic library, we lastly looked at the tolerance for substitution of the carbocyclic dienophile, specifically at the C2 and C3 positions of the cyclic enone (Scheme 60). When 2-methyl cyclohexenone (211) was combined with semicyclic diene 138 in CH\(_2\)Cl\(_2\) and subjected to ultra high pressure conditions, a 2:1 mixture of isomers was obtained in an 83% yield. We were able to assign the stereochemistry of the major product as tetracycle 212 through the use of 2D NMR spectroscopic analysis and single crystal X-ray analysis as the product arising from addition via an endo transition state. This addition occurred on the opposite \( \pi \)-diastereoface to that of the cyclopentanone ring. While we were not able to cleanly isolate the minor isomer, we tentatively assigned its structure as exo product 213 due in part to 2D NMR spectroscopic analysis showing that the minor adduct is not a regioisomer of the major product, and because of previous work by Wenkert and co-workers detailing the tendency of 2-alkyl cyclohexenones to form endo/exo mixtures in Diels–Alder reactions.\textsuperscript{[113,114]} When 3-methylcyclohexen-2-one (214) was used as the dienophile, no Diels–Alder products were observed, even after seven days at 19 kbar. These differences in reactivity when compared to the parent cyclohexenone can be attributed to steric interactions in the transition state of the reaction. As C3 of 3-methyl cyclohexenone is involved in the shortest
forming bond of the cycloaddition, substitution at this position has a greater negative impact on the reactivity of the dienophile than substitution at the C2 position.\textsuperscript{[113,114]}

**Scheme 60:** Substitution at the C2 or C3 position of cyclic diene affects the selectivity and reactivity of the Diels–Alder reaction

Benzynes were also examined as potential dienophiles in the Diels–Alder reaction with bicyclic dienes, however, unlike the previous section, no clean Diels–Alder adducts were isolated with any of the bicyclic dienes 136 or 153, despite a number of fluoride sources and solvents being trialed (Scheme 61).

**Scheme 61:** The Diels–Alder reaction between benzynes and previously synthesised bicyclic dienes proved unsuccessful under a range of conditions
To summarise this sections main findings, we have examined the use of carbocyclic dienophiles in the Diels–Alder reaction with bicyclic dienes. The use of unsubstituted cyclic enones under high pressure conditions with bicyclic dienes led to single stereoisomers in all cases while substitution on the C2 or C3 position of the dienophile led either to a mixture of stereoisomers or no products at all. Benzyne dienophiles were also unsuccessful in forming angular tetracyclic structures.

2.4 Summary

This chapter describes work towards the development of a library of polycyclic structures through the diene transmissive Diels–Alder reaction sequence between [3]dendralene and a variety of different dienophiles. Our studies explored the reactivity and selectivity of DTDA sequences involving [3]dendralene by examining how this molecule reacts in the presence of a range of both acyclic and carbocyclic dienophiles. By mixing and matching the dienophiles used, we have been able to synthesise bicyclic (105), linear tricyclic (122), angular tricyclic (120) and angular tetracyclic (123) structures in just two steps (Scheme 62).
A unified approach to carbocyclic frameworks

Scheme 62: A DTDA reaction sequence starting with [3]dendralene led to the synthesis of a library of polycyclic compounds.

Both acyclic and carbocyclic dienophiles reacted selectively with [3]dendralene to form mono Diels–Alder products, and these newly formed semicyclic dienes were then used in further studies. The sequential use of two acyclic alkenic dienophiles proved unsuccessful in synthesising decalin structures, however, we were able to synthesise both tetralin and naphthalene frameworks through the Diels–Alder reaction of alkynic dienophiles with mono cyclic dienes, followed by DDQ oxidation (Scheme 63).

Scheme 63: The formation of tetralin and naphthalene compounds over two steps beginning with monocyclic dienes.
Monocyclic dienes proved unsuccessful in forming Diels–Alder adducts with alkenic acyclic dienophiles, however, reactions involving bicyclic dienes proved much more successful. The increased stability and steric bulk associated with these dienes meant that MVK could react under ultra high pressure conditions to give linear tricyclic compounds (Scheme 64). The use of alkynic dienophiles with bicyclic dienes also proved successful with anthracene and octahydroanthracene products being formed following oxidation of the relevant linear tricycles.

**Scheme 64:** Acyclic dienophiles react with bicyclic dienes to form linear tricyclic products

The use of carbocyclic compounds as the second dienophile in DTDA reaction sequences involving [3]dendralene was also examined. Cyclic enones reacted with monocyclic dienes under ultra high pressure conditions to form mixtures of isomers, the result of cycloaddition occurring at each of the two \( \pi \)-diastereofaces of the diene, while the use of benzyne precursor 147 with monocyclic diene 125 led to only the third reported instance of an aryne reacting with a semicyclic diene in a Diels–Alder reaction (Scheme 65).
Scheme 65: Monocyclic dienes and carbocyclic dienophiles react to form angular tricyclic compounds

Finally, bicyclic dienes were shown to react with carbocyclic dienophiles to form angular tetracyclic products (Scheme 66). Unsubstituted cyclic enones reacted with bicyclic dienes under ultra high pressure conditions with complete selectivity, forming a single diastereoisomer regardless of the ring size of the dienophile used, while substituted enones led either to endo/exo mixtures of products, or no reaction at all. Benzynes were also examined as dienophiles in this system, however, no Diels–Alder products were observed.

Scheme 66: Carbocyclic dienophiles and bicyclic dienes combined to form angular tetracyclic products

In total, over 30 polycyclic structures have been synthesised via a DTDA reaction sequence beginning with [3]dendralene. This methodology has shown that [3]dendralene is a versatile starting material that is tolerant to a variety of reaction conditions and these studies prove the feasibility of future synthetic projects utilising this fundamental hydrocarbon.
2.5 Future work

With the diastereoselectivity of the DTDA sequence between [3]dendralene and carbon-based dienophiles being thoroughly examined under a range of different reaction conditions, one obvious extension of this work is to investigate the possibility of enantioselective DTDA reaction sequences involving [3]dendralene. Sherburn and co-workers have previously showed that treatment of methyl acrylate with Corey’s tin tetrachloride activated oxazaborolidinium catalyst 219 (Ar= 3,5-dimethoxyphenyl) in the presence of [3]dendralene led to semicyclic diene 218 as the sole product with an e.r of 96:4 (Scheme 67), while the same group also showed that organocatalysts could also be used in enantioselective Diels–Alder reactions between [3]dendralene and acyclic dienophiles.

![Scheme 67](image)

**Scheme 67**: Examples of enantioselective Diels–Alder reactions between [3]dendralene and acyclic dienophiles

While previous work has shown that Diels–Alder reactions can be carried out enantioselectively with acyclic dienophiles, no work has yet been performed examining [3]dendralene and carbocyclic dienophiles.
Yamamoto and co-workers have shown that enantioselective Diels–Alder reactions are possible with carbocyclic dienophiles when they observed alpha-halo cyclohexenones such as 2-bromocyclohexenone (223) undergoing enantioselective Diels–Alder reactions with the symmetrical diene 2,3-dimethyl butadiene when treated with tin tetrachloride activated oxazaborolidine 225 (Scheme 68).[116]

![Scheme 68: Examples of enantioselective Diels–Alder reactions involving carbocyclic dienophiles](image)

The Corey group obtained similar results when they synthesised bicycle 228 in 95% yield and 90% ee during their work on using oxazaborolidine 229 to promote the Diels–Alder reaction between benzoquinone (226) and diene 227.[117]

It can be envisaged that using a similar oxazaborolidine catalysed approach to enantioselective Diels–Alder reactions between [3]dendralene and cyclic enones should be possible, which in turn would lead to the formation of enantiopure semicyclic diene 136 (Scheme 69). A second Diels–Alder reaction with
cyclohexenone would then form tetracycle 207, a two-step sequence that would install five new stereocentres and form a single enantiomer. This methodology could then be applied in the synthesis of enantiomerically pure natural products.

Scheme 69: An enantioselective Diels–Alder reaction between [3]dendralene and a cyclic enone followed by a second Diels–Alder reaction would lead to enantiopure tetracyclic compounds

Another potential area for future work is to examine the use of hetero dienophiles in Diels–Alder reactions containing [3]dendralene. Some work in this field has already been performed. Sherburn and co-workers showed in 2012 that [3]dendralene underwent selective mono Diels–Alder reaction with nitrosocarbonyl 230, formed in situ from the relevant hydroxylamine, to form diene 231 in 83% yield. This semicyclic diene was then converted into amino sugar 232 over three steps (Scheme 70). The same group also showed that the reactive diaza heterodienophile 233 reacts with [3]dendralene to form a 5:2 mixture of mono: bis Diels–Alder adducts 234:235 in 74% overall yield.
Scheme 70: Examples of Diels–Alder reactions between [3]dendralene and hetero dienophiles

An obvious extension to this work would be to examine the use of carbonyl dienophiles in Diels–Alder reactions with [3]dendralene. While there has been extensive work performed in this field using activated aldehydes such as glyoxylates\textsuperscript{[119]} or electron rich dienes,\textsuperscript{[120]} very little work has appeared in the literature reacting unactivated carbonyls with unactivated dienes. One such report from Matsubara and co-workers used cationic iron porphyrins as catalysts to promote the Diels–Alder reaction between benzaldehyde (236) and 2,3-dimethylbutadiene (130) under mild conditions (Scheme 71).\textsuperscript{[121]} We envisage that this methodology would be compatible with reactions involving [3]dendralene, which in turn could lead to pyran 239 after one Diels–Alder reaction and could potentially be used to form dipyran 241 following a second successful Diels–Alder reaction.
Scheme 71: The use of [Fe(TPP)]BF₄ as a catalyst can be used to promote the Diels–Alder reaction between benzaldehyde and dimethyl butadiene, and how it can be applied to reactions involving [3]dendralene.
Chapter 3: The Xestoquinone Family of Natural Products

3.1 Meet the Family: Structure, Isolation, Biosynthesis and Biological Activity

The marine natural product xestoquinone (242) belongs to a family of polycyclic compounds, which all contain an aromatic quinone or hydroquinone ring. These secondary metabolites possess a single, all carbon quaternary stereocenter (Figure 16) and have been isolated from a variety of tropical marine sponges. \[122-126\]

**Figure 16:** Eight related compounds from the xestoquinone family
Diversity in the family arises from a difference in the oxidation state at carbons 4, 13 and 16, substitution at carbons 14 and 15 or the oxidation state of the E ring. Halenaquinone (243) and xestoquinone, the two most abundant and well studied members of the family, were first isolated in 1983\textsuperscript{[122]} and 1985\textsuperscript{[127]} respectively from sponges of the \textit{xestospongia} genus found off the coast of Okinawa and surrounding islands. Xestoquinone and halenaquinone both show a remarkable yet vastly different range of biological activity. In cytotoxicity tests against human squamous cell carcinoma lines, xestoquinone was shown to be over 500 times more potent than halenaquinone,\textsuperscript{[128]} however, when the same compounds were tested for their antifungal properties, halenaquinone was shown to be extremely effective whereas xestoquinone displayed almost no activity. These studies suggest that oxygenation at C4 plays a large role in their biological profiles. On top of this, xestoquinone has also been shown to induce muscle relaxation\textsuperscript{[129]} as well as being a potent cardiotonic agent\textsuperscript{[130]} and importantly, has also been shown to exhibit moderate antimalarial activity.\textsuperscript{[131]}

The biosynthesis of this family of natural products has not yet been fully determined. Crews and co-workers postulated that xestoquinone could be the product of a mixed sesquiterpene/polyketide biosynthesis (\textbf{Scheme 72})\textsuperscript{[132]} The first step in Crews’ proposed biosynthesis begins with known triene farnesyl hydroquinone (250). Cyclisation in the presence of a proton source leads to the known natural product zonarol (251).\textsuperscript{[133]}
From here, the biosynthetic pathway is speculative, however, carbon–carbon bond formation between the aromatic ring and the newly formed C=C double bond could lead to tetracycle 252, the napthoquinone analogue of which has been synthesised and confirmed as the natural product (-)-cyclozonarone (262) (Scheme 73). Demethylation of tetracycle 252 would give 253 which could lead to pentacycle 254 through a series of oxidative steps in which the hydroquinone ring is converted into a quinone, three oxygen atoms are introduced and a dihydrofuran ring is formed. Pentacycle 254 was synthesised and later isolated from the *xestospongia sapra* marine sponge by Harada and co-workers who showed that this intermediate was a precursor to both xestoquinone and halenaquinone. Dehydration of the secondary alcohol and isomerisation of the resulting C=C double bond led to xestoquinone, while oxidation of the secondary alcohol, followed by aromatisation formed the closely related halenaquinone.
The absolute stereochemistry of the naturally occurring (-)-cyclozonarone (262), a potential precursor to xestoquinone, was determined following the synthesis of its enantiomer (+)-cyclozonarone (258) by Cortés and co-workers in 2001 (Scheme 73). Diene 257 was synthesised in four steps from naturally occurring (-)-polygodial (255) (A$16200/g from Sigma Aldrich as of April 2015) before a Diels–Alder reaction with benzoquinone and subsequent DDQ oxidation yielded (+)-cyclozonarone (258). This synthetic sample was identical to all characterisation data of the natural product except for the sign of its specific optical rotation. The stereochemistry of the naturally occurring enantiomer was confirmed later that year by Seifert and co-workers who followed a near identical synthesis, beginning with the natural product (+)-albicanol (260), itself the product of an eight step synthesis beginning from ketone 259. Seifert found that (-)-cyclozonarone matched perfectly with both the spectroscopic data, and the specific optical rotation of the naturally occurring product.

Scheme 73: Synthesis of the naturally occurring (-)-cyclozonarone (262) and its enantiomer (+)-cyclozonarone (258)
3.2 Previous Synthesis of the Xestoquinone Family of Natural Products

Due to the wide range of biological activity shown by the xestoquinone family of natural products, there has been a significant amount of work published on the syntheses of these compounds. There are currently 10 total or formal syntheses of the natural products xestoquinone and halenaquinone. This review will focus mainly on synthetic work on the xestoquinone family of natural products, however the more important synthetic contributions towards other closely related structures will also be highlighted. The syntheses are divided into three sections based on the final targets of the respective pieces of work, while papers with similar strategies have been grouped together.

This review is interested in all synthetic work towards halenaquinone and xestoquinone, and while model studies ‘towards’ natural products are always important, it is total synthesis that interests us more. With this in mind, all of the total syntheses of these natural products that have been published so far will be examined in detail, while model studies towards xestoquinone and halenaquinone will only be discussed briefly.

Ahn and co-workers published a synthesis of the B,C,D,E ring system of xestoquinone (Scheme 74) in which ester 263 is converted into ynal 264 over seven steps. This key intermediate undergoes an intramolecular hetero Diels–Alder reaction and, following rearrangement, gives furan 265, albeit in low yields. This furan then undergoes an intramolecular Friedel–Crafts reaction upon treatment with boron tribromide to give tetracycle 266 in 42% yield.
Nemoto and co-workers published a series of papers towards the B,C,D,E ring system of halenaquinone (Scheme 75) in 2001 and 2002.\textsuperscript{[139,140]}

Compounds 268 and 270 were synthesised in four and two steps respectively from commercially available starting materials and combined to form benzocyclobutene 271. When this compound was heated to reflux in ortho-dichlorobenzene, the cyclobutene underwent a $4\pi$ electrocyclic ring opening to form ortho-quinone-dimethide 272 \textit{in situ} before an intramolecular Diels–Alder reaction furnished dihydrofuran 273. A further 3 steps transformed this dihydrofuran into tetracycle 274, which contained both the ketone and furan functionalities present in halenaquinone.
Finally, the Wipf group published work on the synthesis of one half of the noelaquinone core (248, Figure 16) in which hydrazine 275, itself synthesised in four steps, was converted into diformamide 276 over six steps (Scheme 76). A three-step Staudinger-aza-Wittig reaction sequence formed key intermediate 277 in 40% yield before removal of the protecting groups gave the desired tricycle 278. This tricycle possessed the functionality associated with three of the rings of the natural product noelaquinone.

Scheme 76: Wipf’s work on the noelaquinone core.

We have chosen not to include in this review work on model studies of the structurally similar furanosteroids viridin[142-148] and wortmannin[149-153] but provide references for those interested.

3.2.1 Previous Syntheses of Xestoquinone

The first total synthesis of xestoquinone was completed by Harada and co-workers in 1990 (Scheme 77).[154] Starting from commercially available Wieland–Miescher ketone (279), enone 280 was accessed in 9 steps and 30% yield via installation of a protected hydroxymethyl group and a series of functional group interconversions.
Scheme 77: The first total synthesis of (+)-xestoquinone

The key bond-forming step was a Diels–Alder reaction between enone 280 and benzocyclobutane 281, a known precursor to ortho-quinone-dimethide 282. This allowed for efficient formation of the carbon framework of xestoquinone as a single isomer in 40% yield, although the exact stereochemistry of this isomer was not determined.

Oxidation of the B ring of tetracycle 283 with DDQ yielded napthalene 284 in 80% yield while a second oxidation, this time using oxygen in the presence of potassium tert-butoxide gave diosphenol 285. MOM deprotection afforded key
intermediate 286, which was transformed into furan 287 via a one-pot oxidation/cyclisation/dehydration sequence. Finally, oxidation of the 1,4-dimethoxynaphthalene to the corresponding para-napthoquinone with ceric ammonium nitrate (CAN) afforded xestoquinone in 55% yield. Overall, the total synthesis was achieved through a longest linear sequence of 15 steps from the Wieland–Miescher ketone in 1.7% overall yield.

Kanematsu and co-workers, inspired by Harada’s disconnections, built on this work in their formal synthesis of xestoquinone, which was completed in 1991 (Scheme 78). The synthesis began with what was described as a ‘furan ring transfer’ reaction in which 3,4-fused bicyclic system 289 was synthesised from 2-substituted furan 288 via an intramolecular Diels–Alder reaction between the cyclic diene and an allene formed in situ from the corresponding terminal alkyne. Hydrogenation of the cyclic alkene, followed by an Omura–Sharma–Swern oxidation of the secondary alcohol gave ketone 290 in 79% yield, which was converted into ester 291 via a series of alkylation reactions. A Cagliotti-modified Wolff–Kishner reaction afforded furan 292 over three steps, which was then cyclised via an acyl chloride intermediate to give annulated furan 293. Finally, selenylation alpha to the carbonyl group and subsequent oxidative elimination yielded enone 294. The key bond-forming step in the synthesis was once again a Diels–Alder reaction, this time between enone 294 and dibromide 295, which formed ortho-quinone-dimethide 282 in situ upon treatment with chromium(II) chloride, to give pentacycle 296 which contained the entire carbon backbone of xestoquinone.
Completion of the synthesis required two further oxidation steps to afford xestoquinone in 17% yield. Overall Kanematsu was also able to access, xestoquinone through a longest linear sequence of 14 steps beginning with the commercially available furfuryl ether (288).

Rodrigo and co-workers published a similar route to xestoquinone in 1997[156] with an improved sequence disclosed in 2001[157] in which the key bond forming step was a Diels–Alder reaction between isobenzofuran 301 and tricyclic enone 300. This strategy was successful not only in forming xestoquinone, but by altering the substitution pattern on the isobenzofuran diene, also formed the C13 and C14..
methoxy substituted analogues of xestoquinone, which themselves are natural products (Scheme 79).[158]

Scheme 79: Rodrigo’s second-generation synthesis of racemic xestoquinone

Treatment of commercially available methylguaiacol (297) with 2,4-pentadienol in the presence of PIFA led to proposed intermediate 298, which upon removal of excess diene yielded two Diels–Alder products 299 and 300 in a 7.5:1 ratio. Although the major product 299, arising from the cyclic diene reacting with the internal alkene of the pendent chain in a Diels–Alder reaction was an unwanted isomer, it was found that this could be converted into the desired isomer, tricycle 300, via a Cope rearrangement in refluxing 1,2,4-trimethylbenzene. A second Diels–Alder reaction between isobenzofuran 301, available in three steps from
commercially available starting materials,[159] and enone 300 proceeded through an exo transition state with complete facial selectivity to give compound 302 as a single stereoisomer in 78% yield. Treatment with sodium methoxide led to napthalene 303, which was converted into furan 304 upon elimination of methanol and subsequent p-chloranil oxidation in 86% yield. Hydrogenation of the cyclic alkene led to furan 287 in 97% yield, which was finally transformed into xestoquinone upon treatment with CAN. This 12-step synthesis gave xestoquinone in 18% overall yield from 4-methyl guaiacol and is currently the shortest synthesis of this natural product to date.

A unique approach towards xestoquinone was undertaken by Keay and co-workers in 1997 in which a powerful bicyclisation cascade allowed the first catalytic enantioselective synthesis of xestoquinone (Scheme 80).[160] Building on work previously published by the group,[161] acyl chloride 313 was combined with highly substituted furan 309 to form key intermediate 315, which was further elaborated into the natural product. Boronate 306, generated in situ from known furan 305,[162] was united with 2-bromopropene (307) in a Suzuki–Miyaura cross-coupling reaction to give alkenylfuran 308 in 95% yield. PDC oxidation of the primary alcohol followed by a Wittig olefination of the newly formed aldehyde yielded the desired trisubstituted furan 309 in a total of four steps. Synthesis of the requisite acyl chloride 313 began with a Diels–Alder reaction between known benzocyclobutene 310, accessible in three steps from commercially available starting materials,[163] and bromoalkyne ester 311 to give napthalene 312. A series of functional group interconversions then afforded the required cross coupling partner 313 in four steps.
Scheme 80: The first enantioselective synthesis of (+)-xestoquinone

Nucleophilic acyl substitution of the newly formed acyl chloride 313 with lithiofuran 314 (formed in situ from furan 309) gave ketone 315. Removal of both TBS protecting groups, and conversion of the newly revealed phenol (316) into a triflate gave key intermediate triflate 317. Treatment of triflate 317 with Pd:(dba)3 pre-catalyst and the chiral ligand (S)-(+)-BINAP then triggered an enantioselective bicyclisation cascade, which furnished the remaining two rings of xestoquinone in an 82% yield with 68% ee. Hydrogenation of the resulting alkene of pentacycle 304 and oxidation of the dimethoxynaphthalene with CAN finally afforded...
xestoquinone in 55% yield. Overall, this approach formed the natural product in a total of 20 steps with a 14 step longest linear sequence from dimethoxybenzocyclobutene 310 and a 4% overall yield.

Inspired by Keay’s elegant sequence, Shibasaki and co-workers published a similar synthetic route towards xestoquinone in 1998[164] where the key cyclisation cascade sequence was triggered using bromide 318 (Scheme 81), which was one of the intermediates formed in Keay’s original paper.

**Scheme 81: The key steps in the Shibasaki formal synthesis of (+)-xestoquinone**

This enantioselective reaction, which had been attempted by the Keay group, only to give an e.r of 53:47, was made possible through the use of silver salts, which have previously been shown to boost enantioselectivity in the Heck reaction.[165] Under optimised conditions, Shibasaki was able to form pentacycle 304 with 63 % ee. While this ee was comparable to that reported by Keay using a triflate as a coupling partner, the yield of this key step was only 39%.

### 3.2.2 Previous Syntheses of Halenaquinone

Halenaquinone is a pentacyclic marine based natural product identical to that of xestoquinone apart from the presence of a ketone at the C4 position. Halenaquinone has also been the subject of numerous synthetic studies. The first
The first total synthesis of (+)-halenaquinone appeared in 1988 and was again published by Harada and co-workers (Scheme 82).\cite{166}

A similar approach to the previously described synthesis of xestoquinone (Scheme 77) was undertaken, where commercially available Wieland–Miescher ketone (279) was converted into enone 319 over nine steps.

**Scheme 82**: The first total synthesis of (+)-halenaquinone

From here, the same pathway to that previously reported for xestoquinone was followed to give diosphenol 322 via intermediates 320 and 321 in comparable
yields to those seen previously. Removal of the acetonide protecting group revealed triol 323 which was transformed into halenaquinone methyl ether 324 via an Omura–Sharma–Swern oxidation/cyclisation sequence before a CAN oxidation yielded halenaquinone (243) in 55% yield. Harada was able to access the natural product in 19 steps with a longest linear sequence of 15 steps from Wieland–Miescher ketone 279.

In 2001, Rodrigo also published a synthesis of halenaquinone that borrowed heavily from his previous work (Scheme 83).[167] The synthesis required known dienol 328, which could be synthesised from propargylic alcohol (325) in five steps and 63% yield via two Stille cross coupling reactions.[168] With dienol 328 in hand, the previous synthesis of xestoquinone (Scheme 79) was followed to give furan 335, again in comparable yields to those reported by Rodrigo previously.

Oxidation of the thiophenol functional group to the required ketone gave halenaquinone methyl ether 324 in 63% yield before known CAN oxidation gave the desired natural product. Overall, Rodrigo’s synthesis of racemic halenaquinone was achieved in 16 steps with a longest linear sequence of 13 steps from propargylic alcohol and is currently the shortest synthesis of this natural product.
Scheme 83: Rodrigo’s 2001 synthesis of racemic halenaquinone

The next synthesis to be examined, published by Shibasaki in 1996, employed an intermolecular Suzuki/intramolecular Heck cross coupling sequence to enantioselectively install the sole stereogenic center of halenaquinone (Scheme 84).\textsuperscript{[169,170]} Commercially available tetralin 336 was converted into diol 337 over five steps \textit{via} a series of functional group interconversions. Treatment of diol 337 with triflic anhydride gave ditriflate 338. When this ditriflate was treated with alkylborane 342, itself available in three steps from commercially available starting
materials\textsuperscript{[171]} in the presence of palladium acetate pre-catalyst and the chiral ligand (S)-BINAP, an elegant Suzuki/Heck cascade ensured, affording the desired tricycle 339 in 80% yield but only 60:40 e.r.

\begin{center}
\begin{tikzpicture}
\node[below] at (0,0) {\textbf{Scheme 84}: Shibasaki’s enantioselective synthesis of the (+)-halenaquinone core};
\end{tikzpicture}
\end{center}

In an attempt to improve the e.r of the reaction, diol 337 was treated first with TBSCI and then triflic anhydride to give protected napthalene 340. This could be coupled with alkylborane 342 to give alkene 341 in 61% yield. Deprotection of the TBS group, followed by conversion of the newly revealed phenol to a triflate and subsequent Heck reaction under the conditions seen previously, gave the desired tricycle 339 in a lower overall yield but with an improved ee of 87%.

With the key stereocenter in place, attention then turned to the construction of the rest of the molecule (\textbf{Scheme 85}). Hydrogenation of the C=C double bond of tricycle 339 and silyl deprotection of the primary TBS ether led to alcohol 343 in 93% yield. Conversion of the alcohol into a triflate leaving group, and subsequent treatment with alkyne 349 in the presence of LDA gave ynone 344 in 68% over two steps. Protection of both the terminal alkyne and the ketone functionalities led to
protected tricycle 345 before a series of oxidation steps gave diosphenol 346 in 75% yield. A further two steps furnished iodide 347 in 95% yield which was primed to undergo the key palladium catalysed cyclisation step.

Scheme 85: Completion of Shibasaki’s synthesis of (+)-halenaquinone.

Iodide 347 underwent an intramolecular Heck reaction in which the palladium intermediate, following oxidative addition and alkyne insertion, was intercepted by the nearby alcohol functionality, to give pentacycle 348, which contained the entire halenaquinone skeleton. Desilylation followed again by CAN oxidation of the napthalene functionality yielded enantiomerically pure halenaquinone for the first time, which was accessed in a total of 26 steps with a longest linear sequence of 20 steps from the commercially available tetralin 336 and a 1.6% overall yield.
The most recent of the synthetic work towards halenaquinone that has appeared in the literature to date is Trauner’s 2008 synthesis of ent-halenaquinone.[172] The synthesis required three key building blocks (Scheme 86). Diiodofuran 352 was synthesised in two steps and 14% yield from 1,4-butyndiol (350) while known aldehyde 355 could be obtained from commercially available methacrolein (353) in 17% yield over four steps. The final building block, styrenyl stannane 358, was synthesised from commercially available dimethoxy cinnamic acid (356) via a two-step conversion to the alkenyl bromide, followed by a Stille cross coupling with hexamethyliditin.

![Scheme 86: Synthesis of the key building blocks in the Trauner synthesis of (-)-ent-halenaquinone](image)

With the three key building blocks in hand, the halenaquinone synthesis was initiated (Scheme 87). Diiodide 352 and aldehyde 355 were combined, and after oxidation of the resultant secondary alcohol to a ketone, and subsequent selective reduction with (-)-B-chlorodisopino-campheylborane ((-)-DIP-Cl), formed
enantiomerically pure furan 359 in 41% yield. Protection of the secondary alcohol and subsequent formylation gave furanaldehyde 360. An intramolecular Heck reaction then gave bicycle 361 as the major diastereoisomer (d.r = 7:1). Interestingly, the d.r. of the reaction was diminished without the formyl group at the C2 position of the furan ring present. Nucleophilic addition of the lithiated alkenyl stannane 358, to bicycle 361 gave enol 362 as an inconsequential mixture of isomers. Silyl deprotection, followed by a double Ley–Griffith oxidation of both secondary alcohols, led to key intermediate 363 in 58% yield over two steps.

Scheme 87: Trauner’s 2008 synthesis of (-)-ent-halenaquinone

Treatment of intermediate 363 with silver(II) oxide in the presence of nitric acid led to oxidative demethylation of the hydroquinone ring to form an alkenyl quinone \textit{in situ}, which underwent a thermal, inverse electron demand Diels–Alder reaction to form the halenaquinone framework, before oxidation with DDQ in the same pot.
afforded ent-halenaquinone (364) in a 12% yield. This one pot procedure could also be carried out in a stepwise manner in a 47% yield over three steps. Overall, this sequence afforded ent-halenaquinone in 0.36% overall yield from commercially available starting materials in 19 total steps with a longest linear sequence of 14 steps starting from methacrolein.

The last synthetic work we will examine in this field is the synthesis of thiohalenaquinone carried out by Wipf and co-workers in 2007 (Scheme 88).[173]

Scheme 88: Wipf’s synthesis of racemic unnatural thiohalenaquinone
In this work, the thiophene analogue of halenaquinone was synthesised in order to
determine the effect the heterocyclic ring has on the overall strain of the natural
product. In a strategy that borrowed inspiration heavily from both the Harada and
Keay syntheses of xestoquinone, the synthesis began with commercially available
3,4-dibromothiophene (365) and introduced functionality in a stepwise manner to
reach bromide 366 in 12 steps and 34% yield. Bromide 366 reacted as a dienophile
in a Diels–Alder reaction with known ortho-quinone-dimethide precursor 281 to
give napthalene 367. This key intermediate was primed for an intramolecular Heck
reaction, which proceeded under microwave conditions in the presence of
Pd(PPh₃)₄ catalyst to form tetracycle 368 in low yield. With tetracycle 368 in hand,
deprotection of the primary TBS ether and subsequent oxidation led to aldehyde
369 before addition of allyltributylstannane to the newly formed aldehyde gave
alcohol 370 as an inconsequential 6:1 mixture of isomers. Isomerisation of the
newly introduced alkene from the terminal position to the internal position gave
diene 371, before ruthenium catalyzed cross-metathesis led to thiohalenaquinol
dimethyl ether 372. Finally, DMP oxidation of the allylic alcohol, hydrogenation of
the cyclic alkene and CAN oxidation afforded thiohalenaquinone (373) in 30%
yield over three steps.

3.2.3 Previous Syntheses of Related Natural Products

While the majority of the syntheses highlighted in this review so far have looked at
synthetic work towards halenaquinone and xestoquinone, this final section will
examine studies focused on natural products that contain similar polycyclic
frameworks to that of the aforementioned compounds (Figure 17), such as
adociaquinone B (244), which contains the A,B,C,D,E framework of xestoquinone, as well as xestosaprol O (245), which contains the A,B,C and D rings.

Figure 17: Four compounds structurally similar to xestoquinone that will be covered in this review. (Red and blue colouring indicates structural homology with xestoquinone)

Studies of the furanosteroids viridin (374) and wortmannin (375) are also included because of the similarities in their structures to the B,C,D,E portion of xestoquinone.

The compounds adociaquinone A and B both contain hexacyclic backbones and have been isolated from the same marine sponge that produced xestoquinone and halenaquinone.\textsuperscript{[126]} Harada and co-workers showed that both adociaquinones A and B could be synthesised from xestoquinone in one pot\textsuperscript{[174]} and, in doing so, confirmed the absolute stereochemistry of these natural compounds (Scheme 89).
Hypotaurine (376) undergoes an aza-Michael addition to either C13 or C14 of xestoquinone (242) to form napthoquinol 377 (or its regioisomer) before oxidation, presumably with molecular oxygen, reforms napthoquinone 378 \textit{in situ}. Napthoquinone 378 then undergoes an intramolecular thia-Michael addition to form napthoquinol 379, which yields adociaquinones A and B upon a second oxidation event. This reaction gives a 7:2 ratio of the two adociaquinones in a 76% yield, with adociaquinone B (244) being the major product. Thus, any total or formal synthesis of xestoquinone is also a formal synthesis of the adociaquinones.

\textbf{Scheme 89}: The synthesis of (+)-adociaquinone B

The xestosaprols are a subgroup within the xestoquinone family that displays a diverse range of oxygenation patterns specifically on C4, C5, C6, C13 and C16 (Figure 18). [123,124,175,176]
Figure 18: Seven members of the xestosaprols. Red colouring indicates structural homology with xestoquinone

The only synthetic work towards this diverse subgroup of compounds is that of Anderson and co-workers, who synthesised deoxy analogues of both xestosaprol O and xestosaprol N in a divergent total synthesis (Scheme 90).\textsuperscript{[177]} Employing reaction conditions previously reported by Sato and co-workers,\textsuperscript{[178]} 2-bomoacetonaphthone (380) was irradiated with UV light in the presence of silver triflate to form tetracycle 383 in 40\% yield. This reaction presumably proceeds through radical 381, which would undergo addition to 1-methylcyclohexene to form tertiary radical 382. This stabilised radical could then undergo cyclisation onto the aromatic ring, and rearomatisation, to form the observed tetracycle 383. Benzylic oxidation of tetracycle 383 then led to a 1:1 mixture of regioisomers 384 and 385 in a 40\% yield. These regioisomers were separated and individually treated with \textit{tert}-butoxide and oxygen to give diosphenols 386 and 387. Condensation with hypotaurine (376) yielded both deoxy-xestosaprol O (388) and its regioisomer deoxy-xestosaprol N (389) in 42\% and 45\% yields respectively. The naturally occurring xestosaprol O and xestosaprol N both possess a hydroxyl group at the C4 position.
The furanosteroid viridin (374) is a pentacyclic natural product which contains a B,C,D,E ring system similar to that of xestoquinone. Viridin first appeared in the literature when it was isolated from the soil fungus *Gliocladium virens* in 1945.[179] While it has been the topic of a swathe of synthetic work, it only succumbed to total synthesis in 2004 following work from the Sorensen group (Scheme 91).[180]

Beginning from alcohol 390, triyne 391 was accessed over a six-step sequence in 67% yield. Treatment with [RuCl(PPh₃)₃] triggered a formal [2+2+2] alkyne cyclotrimerisation event to give benzocyclobutane 392 in 88% yield. 2-Trimethylsilyl-3-vinylfuran, which was synthesised in two steps, was combined with benzocyclobutane 392 over a three-step sequence to give tetracyclic compound 393. Upon heating to 140 °C in the presence of Hunig’s base, tetracycle 393 underwent a retro 4π electrocyclisation reaction to reveal ortho-quinone-
dimethide 394, which underwent a $6\pi$ electrocyclisation to form furanonaphthalene 395 following DDQ oxidation.

![Chemical structures and reactions]

**Scheme 91:** Sorensen’s synthesis of the furanosteroid viridin in racemic form

Deprotection of the TES group, followed by allylation of the newly revealed phenol, gave ether 396 before an aromatic para-Claisen rearrangement afforded diene 397 in 91% yield. This newly formed diene was treated with Grubbs second-generation metathesis catalyst to form pentacycle 398 and install the final ring of the viridin framework. A further 12 steps were required to introduce the correct
The Xestoquinone Family of Natural Products

oxygenation pattern and finally afforded the natural product in 21% yield. Overall, the first and only total synthesis of viridin was achieved in a longest linear sequence of 26 steps with a yield of 4.5%.

Wortmannin (375) is a heterocyclic natural product that is structurally similar to viridin. Its biological profile, however, has been studied in a lot more detail, with over 15000 references associated with the search term ‘wortmannin’ appearing on SciFinder as of May 2015. Perhaps surprisingly, only one total syntheses and one semi-synthesis of wortmannin have been reported in the literature to date. Shibasaki and co-workers published the first semi synthesis of wortmannin in 1996.181 Starting from the commercially available steroid hydrocortisone (400), tetracycle 401 was synthesised over six steps via a series of functional group interconversions (Scheme 92).

Ring opening and oxidation of the alpha hydroxy cyclohexenone ring led to tetracycle 402 before further functional group manipulations resulted in ester 403 over three steps. Epoxidation of the newly formed terminal alkene, followed by a series of further functional group interconversions, led to pentacycle 404 which, when treated with CSA, triggered a cyclisation cascade to give lactone 405 in 56% yield. With this key intermediate in hand, attention next turned to installation of the required oxygenation pattern. A series of oxidations led to epoxide 406 over six steps before a final dihydroxylation gave pentacycle 407, which contained the correct oxygenation pattern of the natural product. Twelve further steps were required to transform pentacycle 407 into the desired wortmannin (375) in 1.8% yield.
Following this synthetic achievement, Shibasaki went on to publish the first and only total synthesis of this natural product in 2002 (Scheme 93).\textsuperscript{182} Starting from the four commercially available starting materials 408, 409, 410 and 411, known tetracycle 412 was formed over a 16 step sequence using well established chemistry.\textsuperscript{183} Inversion of the secondary alcohol stereocenter and a subsequent change of protecting group gave TBS ether 413, which was converted into tris-protected triol 414 over five steps through a series of functional group interconversions. Oxidation and introduction of an allylic ether led to tetracycle 415 before a Claisen rearrangement, followed by a series of functional group interconversions, gave key aldehyde 416 as a mixture of diastereoisomers in five steps and 40% yield.
Scheme 93: The first total synthesis of racemic wortmannin.

The crucial lactone formation was achieved through the removal of the acetate protecting group and subsequent cyclisation of the alcohol to form a lactol before Ley–Griffith oxidation led to lactone 417 in 75% yield. Introduction of another allylic ether α to the lactone group, followed by protecting group manipulations and oxidation led to key intermediate pentacyle 418 as a 3:1 mixture of isomers, although the exact nature of these isomers was not discussed. Furan formation and the removal of all protecting groups led to wortmannin over six steps and 10% yield. In total, Shibasaki was able to access wortmannin in 0.01% yield in a longest linear sequence of 46 steps beginning with commercially available starting materials.
3.3 Summary and Outlook

A summary of the ten total or formal syntheses of xestoquinone and halenaquinone (Figure 19), and the four total or semi synthesis of structurally related compounds (Figure 20) examined in this review is shown below which highlights the commercially available starting materials used in each synthesis. Harada’s syntheses of xestoquinone and halenaquinone were the first, and provided original disconnections that other groups subsequently borrowed heavily from. Harada’s synthetic sequences use chiral pool precursors to introduce the required absolute stereochemistry and suffer from a reliance on protecting groups. Kanematsu designed an elegant synthesis of xestoquinone that borrowed heavily from Harada’s original disconnections. The ‘furan ring transfer’ reaction, however, which is one of the key steps of the synthesis, produces racemic products and would be difficult to develop into an enantioselective process. Likewise Rodrigo’s work on both natural products has limited scope for the synthesis of enantiomerically pure compounds. Rodrigo’s elegant synthesis of both halenaquinone and xestoquinone remain the shortest synthetic sequence to these targets. Of the syntheses that use a cross-coupling reaction as the key bond forming step, Shibasaki’s trailblazing synthesis of halenaquinone incorporated an intramolecular Heck reaction to install the quaternary center of halenaquinone selectively for the first time, however, the lengthy synthetic sequence of 26 steps has since been overtaken in terms of efficiency. Keay and Shibasaki also used this approach to form xestoquinone and while both syntheses were efficient in terms of step count (16 and 14 steps respectively), the e.r of the enantioselective reactions were only 85:15. Finally, Trauner has devised the shortest current synthesis of
enantiomerically pure ent-halenaquinone, which is only 14 steps. The syntheses highlighted in Figure 20 are the first total or semi synthesis of their respective compounds, and as such are difficult to compare, but apart from some exceptions, all suffer from containing long synthetic sequences.

While all of these strategies were successful in synthesising the targeted compounds, we believe that the step count and enantioselectivity of sequences towards these natural products can be improved on significantly. The experimental work outlined in Chapter 2 of this thesis indicates that the ABCD tetracyclic ring pattern seen in Figure 19 can be rapidly accessed through a double Diels–Alder reaction sequence, and this makes these natural products the perfect target in order to showcase the synthetic utility of [3]dendralene in total synthesis. We will specifically target xestoquinone and attempt to improve upon the current shortest step count.
Figure 19: A summary of the previous total and formal syntheses of xestoquinone and halenaquinone

If this is successful, we will move on to attempt to synthesise the synthetically more challenging furanosteroids viridin and wortmannin using a similar sequence as outlined above, again in an attempt to significantly improve the current step count.
Figure 20: A summary of the previous total and semi syntheses of compounds structurally similar to xestoquinone.
Chapter 4: Towards the Total Synthesis of (±) -Xestoquinone

The work detailed in Chapter 2 of this thesis described a methodology that allowed access to a number of different polycyclic compounds. By using two carbocyclic dienophiles in a DTDA sequence with [3]dendralene, we showed that compounds with frameworks such as tetracycle 123 could be synthesised in just two steps (Scheme 94).

```
Scheme 94: The synthesis of tetracycle 123 can be achieved through a DTDA reaction between [3]dendralene and two carbocyclic dienophiles
```

It was decided to take this methodology and apply it to total synthesis. Xestoquinone and halenaquinone (Figure 21), two pentacyclic compounds previously seen in Chapter 3, both contain a carbocyclic backbone that is amenable
to formation through a double DTDA sequence between [3]dendralene and two carbocyclic dienophiles. It was thought that by selecting appropriate functionality on the respective dienophiles, the total syntheses of these natural products could be completed in a quick and efficient manner. We decided to target xestoquinone specifically for our total synthetic studies.

![Chemical structures of xestoquinone and halenaquinone](image)

**Figure 21:** The natural products xestoquinone and halenaquinone contain tetracyclic carbon frameworks that can be accessed through a double DTDA sequence between [3]dendralene (mapped on in red) and two carbocyclic dienophiles (mapped on in blue)

### 4.1 Retrosynthetic Analysis of Xestoquinone

Previous syntheses of xestoquinone and related compounds have shown that Diels–Alder reactions are a reliable and efficient technique that can be used to install the synthetically challenging quaternary centre contained in the target molecule. Our total synthesis also makes use of the Diels–Alder reaction, however it does so in a different manner to that seen in previous syntheses. As seen in Chapter 3 of this thesis, xestoquinone has previously been accessed from dimethoxy naphthalene 287 via CAN oxidation to the corresponding ketone. We decided to use this protected form of xestoquinone as the starting point for our retrosynthetic analysis. The first disconnection made was across a C–O single bond...
to open the furan ring. This revealed bis enol 419, which can be mapped perfectly onto tetracycle 420 following some functional group manipulations. Tetracycle 420 is a DTDA sequence retron, which was disconnected back to [3]dendralene, substituted cyclohexenone 421 and dimethoxy benzyne 422, an intermediate which would have to be prepared in situ (Scheme 95). Both the regioselectivity and the π-diastereofacial selectivity of the second Diels–Alder reaction of the DTDA sequence would need to be controlled, not only to ensure the relative functional groups are delivered in the correct orientation, but also to control the absolute stereochemistry of the all carbon quaternary centre.

Scheme 95: Our initial retrosynthetic analysis of xestoquinone

Substituted cyclohexenone 421, was analysed retrosynthetically after considering substituted cyclohexene 423. This again revealed a Diels–Alder retron. A Diels–Alder transform revealed known Danishefsky-type diene 424 and methyl acrylate (162) as the required diene and dienophile respectively (Scheme 96).
4.2 Synthetic Work Towards (±)-Xestoquinone

4.2.1 Formation of the Carbon Framework of Xestoquinone

Our synthesis of xestoquinone started with a selective, single Diels–Alder reaction between [3]dendralene and 2,5-dimethoxybenzene (422), generated in situ from TMS containing triflate 148 to give diene 154 in 22% yield (Scheme 97). While this reaction gave the desired protected diene 154 in one step, the reaction is low yielding, and the synthesis of the dimethoxybenzene precursor, TMS containing triflate 148, requires four synthetic steps (Scheme 39, Chapter 2). An alternative to this one step method was devised. A Diels–Alder reaction between [3]dendralene and p-benzoquinone (226), an inexpensive and readily available starting material, followed by treatment with sodium hydride and methyl iodide, also gave the desired semicyclic diene 154 in one pot and 72% yield via intermediate 107. As well as being a higher yielding sequence, this one pot approach has the added advantage of using the new one step synthesis of [3]dendralene as outlined in Chapter 1, as both the Diels–Alder reaction and subsequent aromatisation can be carried out in THF in the same pot.
Towards the Total Synthesis of (±)-Xestoquinone

The next step in our synthetic sequence requires a selective Diels–Alder reaction between semicyclic diene 154 and substituted cyclohexenone 421. It was hoped that this key reaction would not only allow for the installation of the synthetically challenging quaternary centre, but also potentially allow for an enantioselective synthesis of xestoquinone.

The synthesis of substituted cyclohexenone 421 began according to a modified literature procedure used by Lin and coworkers to form diene 429 (Scheme 98).[^185] Methyl ethyl ketone (425) and ethyl formate (426) were combined in the presence of sodium ethoxide to give sodium enolate 427. Williamson ether synthesis with bromoethane furnished enone 428, before treatment with triethylamine in the presence of zinc chloride and trimethylsilyl chloride afforded the known Danishefsky type diene 429. A thermal Diels–Alder reaction between diene 429 and methyl acrylate (162) in refluxing toluene formed substituted cyclohexene 423 as a single isomer in 96% yield, before reduction with DIBAL-H and subsequent deprotection with HCl in one pot gave the desired substituted cyclohexenone 421 in five steps.
Scheme 98: Synthesis of substituted cyclohexenone 421

With substituted cyclohexenone 421 in hand, the key second Diels–Alder reaction was attempted. We probed the reactivity of semicyclic diene 154 in order to determine the optimum reaction conditions (Table 3). While screening these conditions, it became apparent that commercially available 2-methylcyclohexeneone (211) would be a suitable model dienophile for this reaction and therefore was used in some of the trial reactions. Attempts to promote the reaction between diene 154 and substituted cyclohexenone 421 thermally either in refluxing toluene or in DMSO at 140 °C led only to the recovery of starting material (entries 1 and 2). When higher temperatures were used, clean decomposition of semicyclic diene 154 to naphthalene 431 was observed (entries 3–5) (Scheme 99). We theorised that this decomposition could be the result of an acid-catalysed double bond isomerisation. Indeed, when the high temperature reaction was repeated in the presence of propylene oxide acting as a proton scavenger, no sign of naphthalene 431 was observed (entry 6), and instead only a complex mixture of products was isolated.
Lewis acid catalysis also proved unsuccessful in promoting the Diels–Alder reaction. Treatment of the diene and dienophile with TiCl₄ (entries 7 and 8) led only consumption of the dienophile, however, no signs of Diels–Alder adducts

<table>
<thead>
<tr>
<th>Dienophile</th>
<th>Conditions</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 421</td>
<td>PhMe, reflux, 24 hours</td>
<td>No reaction</td>
</tr>
<tr>
<td>2 421</td>
<td>DMSO, 140 °C, 24 hours</td>
<td>No reaction</td>
</tr>
<tr>
<td>3 211</td>
<td>o-DCB, sealed tube, 250 °C, 4 hours</td>
<td>Formation of 431</td>
</tr>
<tr>
<td>4 211</td>
<td>PhMe, sealed tube, 250 °C, 4 hours</td>
<td>Formation of 431</td>
</tr>
<tr>
<td>5 211</td>
<td>Ph₂O, sealed tube, 250 °C, 4 hours</td>
<td>Formation of 431</td>
</tr>
<tr>
<td>6 211</td>
<td>PhMe, BHT, propylene oxide, sealed tube, 250 °C, 4 hours</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>7 421</td>
<td>TiCl₄, CH₂Cl₂, 40 °C, overnight</td>
<td>Dienophile consumption</td>
</tr>
<tr>
<td>8 421</td>
<td>TiCl₄, CH₂Cl₂, r.t, overnight</td>
<td>Dienophile consumption</td>
</tr>
<tr>
<td>9 211</td>
<td>AlCl₃, PhMe, r.t, overnight</td>
<td>No reaction</td>
</tr>
<tr>
<td>10 211</td>
<td>Et₂AlCl, PhMe, r.t, overnight</td>
<td>No reaction</td>
</tr>
<tr>
<td>11 211</td>
<td>MeAlCl₂, PhMe, r.t, overnight</td>
<td>Formation of 431</td>
</tr>
<tr>
<td>12 211</td>
<td>CH₂Cl₂, 19 kbar, r.t, 3 days</td>
<td>9:1 mixture TM:SM</td>
</tr>
</tbody>
</table>

Table 3: Conditions trialed to promote the Diels–Alder reaction between diene 154 and substituted cyclohexenone 421. All reactions were carried out with 0.33 mmol of diene 154 and 1 mmol dienophile 211 or 421 in 1 mL of solvent. For the Lewis acid promoted reactions, 0.5 mmol of the appropriate Lewis acid was used.
were observed. The use of AlCl₃ or Et₂AlCl resulted only in recovery of the starting material (entries 9 and 10) while treatment with MeAlCl₂ (entry 11) led to formation of the previously observed naphthalene 431.

![Scheme 99: Potential pathway for the acid-catalysed degradation of diene 154 to naphthalene 431](image)

The first signs of a successful second Diels–Alder reaction came when 2-methylcyclohexenone and semicyclic diene 154 were subjected to high pressure conditions. Treatment of diene 154 with a five fold excess of 2-methyl cyclohexenone (211) at 19 kbar for three days led to a Diels–Alder product as a mixture of two diastereoisomers in a 3:2 ratio, along with 10% of the starting diene. Changing the dienophile to substituted cyclohexenone 421 showed identical levels of conversion and selectivity. Allowing the reaction to run for five days at 19 kbar led to full consumption of the semicyclic diene. It was discovered that using three molar equivalents of substituted cyclohexenone 421 also led to full conversion after five days and increased the selectivity of the reaction to a 3:1 mixture of isomers.
Using a lower stoichiometric ratio of dienophile to diene however, retarded the reaction. Thus, a 3:1 mixture of substituted cyclohexenone 421 and semicyclic diene 154 was subjected to 19 kbar for five days to give a 49% yield of diastereomeric Diels–Alder products as a 3:1 mixture of products (Scheme 100). The two diastereoisomers were separated using HPLC, and single crystal X-ray analysis confirmed that the major and minor diastereoisomers were tetracycles 435 and 436 respectively (Figure 22). This reaction was also accompanied by a large amount of what appeared to be polymerised starting material, although it was difficult to determine if this was oligomerised diene or dienophile. This polymerisation, which presumably is a result of the extreme conditions required to promote this reaction, may account for the modest yields achieved for this step.

**Scheme 100**: High pressure conditions led to the successful formation of tetracycles 435 and 436

The selectivity of this reaction deserves a brief discussion. There are eight possible isomeric products of this Diels–Alder reaction arising from 1) the orientation at which the dienophile approaches the diene, 2) whether the dienophile reacts *via* an *endo* or *exo* transition state and 3) which π-face of both the diene and the dienophile unite. Each point will be discussed separately, beginning with the regiochemistry of the reaction.
Towards the Total Synthesis of (±)-Xestoquinone

**Figure 22**: The structures of the major (435) and minor (436) isomers of the second Diels–Alder reaction were determined through the use of single crystal X-ray analysis.

Normally, predicting the regiochemical outcome of a Diels–Alder reaction is done by evoking FMO theory. However, there are examples in the literature where ultra high pressure conditions have given the opposite regiochemical outcome that would be predicted by FMO theory.\[186\] Reactions that are carried out at high pressures favour reactions that have a large negative volume of activation (–ΔV),\[99\] where the volume of activation is defined by IUPAC as the difference between the partial molar volumes of the transition state and the sums of the partial volumes of the reactants at the same temperature and pressure.\[187\] The transition state leading to the observed products potentially has a smaller volume than the transition state in which the dienophile reacts in its opposite orientation (Scheme 101) and therefore a larger –ΔV. Unfortunately, we do not have the computational capacity to measure this property.
Scheme 101: The observed (right) and unobserved (left) regiochemical outcomes of the Diels–Alder reaction between diene 154 and substituted cyclohexenone 421

With the regioselectivity of the reaction discussed, there are still four potential diastereomeric outcomes possible from this Diels–Alder reaction, however, only two of these are observed. The π-diastereofacial selectivity of this reaction is determined by the presence of the pendant hydroxy methyl chain attached to the dienophile. In the transition state of the reaction, the dienophile approaches the diene in such a way as to position the hydroxymethyl group so it is pointing away from the newly forming C-C bonds (Scheme 102). If we consider only the (S)-enantiomer of the dienophile for clarity, the major isomer of the reaction (435) is the product of an endo transition state in which the dienophile approaches the diene from the bottom π-face as shown in Scheme 10. The minor isomer (436) arises from an exo transition state in which the dienophile approaches the diene from the top π-face as drawn. This preference for the endo product over the exo product is a common trait of reactions performed under high pressure conditions, as endo transition states tend to be more compact than the exo equivalents. The other two isomers, formed through transition states in which the dienophile approaches via an exo transition state to the bottom π-face of the diene (437) or through and endo transition state to the top π-face of the diene (438), were not observed. The fact that two different isomers 435 and 436 were both isolated from the reaction is inconsequential, as only the absolute stereochemistry around the quaternary centre is retained by the final product.
Scheme 102: The possible stereoisomers arising from the Diels–Alder reaction between diene 154 and substituted cyclohexenone 421. These four diastereoisomers arise from the reaction proceeding through either an endo or exo transition state and approaching from either of the π-faces of the diene.

While we were delighted to find that the Diels–Alder reaction gave the correct regioselectivity, we were even more excited to discover that the absolute stereochemistry of substituted cyclohexenone 421 (which appears at C15 of tetracycles 435 and 436) determines the absolute stereochemistry at the C14 of the product, as both product diastereoisomers have a syn relationship between C15 and C14 substituents. While this result has no bearing on our synthesis of racemic xestoquinone, it does provide the possibility for an asymmetric synthesis of xestoquinone. If a single enantiomer of substituted cyclohexenone 421 with the correct configuration could be made, it could potentially lead to the synthesis of enantiomerically pure xestoquinone.
4.1.2 Formation of Ring E

With the challenging quaternary centre installed, we next turned our attention to deleting the now superfluous carbonyl oxygen that was necessary to activate the second dienophile. We believed that by deleting this functional group early in the synthesis, we might avoid problems later on in the sequence. We first attempted to remove the carbonyl group via a Wolff–Kishner reduction (Scheme 103). The major isomer of the second Diels–Alder reaction was isolated and subject to Huang–Minlon deoxygenation conditions\(^{189}\) using hydrazine and potassium hydroxide in ethylene glycol at 200 °C, however this led only to decomposition of the starting material. Presumably, the high pH and elevated temperatures required for this reaction were not compatible with the sensitive tetracyclic core.

![Scheme 103: Attempted Wolff–Kishner reductions of tetracycle 435](image)

We next attempted a Cagliotti modified Wolff–Kishner reaction\(^{190}\) where tosylhydrazine was condensed with tetracycle 435 in methanol to give tosylhydrazone 439 in 67% yield. Unfortunately, attempts to reduce tosylhydrazone 439 with LiAlH\(_4\)\(^{191}\) NaBH\(_4\)\(^{192}\) or NaBH\(_3\)CN\(^{193}\) led only to recovery of the starting material. We postulated that the steric bulk associated with the adjacent quaternary centre was blocking the approach of the respective reducing agents, which in turn prevented the deoxygenation reaction from occurring.
With the Wolff Kishner reduction proving unsuccessful, a radical based deoxygenation was attempted (Scheme 104).

Scheme 104: Radical deoxygenation of tetracycle 435

Again using only the major isomer of the preceding Diels–Alder reaction, the primary alcohol of tetracycle 435 was protected with TBSCI in the presence of imidazole to give silyl ether 440. This was then reduced with sodium borohydride to give alcohol 441 as a single stereoisomer. While the stereochemistry of 441 was not determined, due to the fact that it would be deleted in the deoxygenation step, we predicted that the concave face of tetracycle 440 would block approach of the
sodium borohydride from that direction, and instead the hydride source would be delivered to the convex face of the molecule. Alcohol 441 was then condensed with methyl chlorooxalate (442) to give oxalyl ester 443, a functional group that is known to be reductively removed on exposure to Bu₃SnH¹⁹⁴ even at sterically hindered positions.¹⁹⁵ Unfortunately, in our hands, treatment of oxalyl ester 443 with tributyl tin hydride in the presence of a radical initiator led only to hydrolysis of the oxalyl ester, returning alcohol 441 in 65% yield. More successful was the deoxygenation under standard Barton–McCombie conditions.¹⁹⁶ Treatment of alcohol 441 first with n-BuLi, then dimethyl sulfide and finally methyl iodide afforded xanthate ester 444, which was successfully reduced to the desired deoxygenated tetracycle 445 upon treatment with Bu₃SnH in 79% yield. Finally, TBAF desilylation of tetracycle 445 afforded the desired primary alcohol 446 in near quantitative yield.

While this 5-step protocol led to the desired compound, we were unhappy with the total step count of the sequence. Our interest was captured by work from the Arimoto group¹⁹⁷, where a modified Clemmensen reaction was carried out under mild conditions using zinc powder and trimethylsilyl chloride to deoxygenate steroid 447 and form tetracycle 448 (Scheme 105).

Scheme 105: Deoxygenation of steroid 447 under Arimoto’s modified Clemmensen conditions
This method was highly tolerant of a range of functional groups, including secondary alcohols, and if successfully applied to our synthesis, would remove the need for protecting groups. Subjecting ketone 435 to Arimoto’s deoxygenation conditions led to clean conversion to tetracycles 446 and 449 in a 3:1 mixture of products. Lowering the internal reaction temperature to 0 °C afforded the desired tetracycle 446 as the sole product in a 62% yield (Scheme 106). Apart from keeping the internal reaction temperature below 0 °C, it was also important to use a small magnetic stir bar operating at under 150 RPM. Using a large stir bar at high stirring rates led to aggregation of the solid zinc powder into large balls. This aggregation led to a smaller surface area of the zinc and in turn led to retardation of the reaction, along with the formation of higher levels of unwanted tetracycle 449.

Scheme 106: The reductive deoxygenation of ketone 435 using Arimoto’s modified Clemmensen conditions

With tetracycle 446 in hand, we next turned our attention to formation of the tetrahydrofuran E ring through C–H activation. Suarez and coworkers demonstrated in 1984 that tetrahydrofuran rings could be formed by irradiating suitable primary alcohols with visible light in the presence of iodobenzene diacetate and iodine (Scheme 107). In this work, tetracycle 451 was formed in 85% from steroid based tetracycle 450 when subjected the optimum reaction conditions. This methodology, which proceeds through an intramolecular 1,5
hydrogen atom abstraction, showed a widespread tolerance to a range of functional groups and has since been used in a number of total synthesis,\textsuperscript{[199,200]}

\begin{equation}
\text{Scheme 107: Tetrahydrofuran formation under Suarez conditions}
\end{equation}

We decided that tricycle 454, which can be formed through a reduction of the commercially available natural product podocarpic acid (452), would serve as a suitable substrate to model the reaction on (Scheme 108).

\begin{equation}
\text{Scheme 108: Synthesis of model compound 454 used for Suarez cyclisation studies}
\end{equation}

Podocarpic acid (452) was treated with methyl iodide in the presence of potassium carbonate to give phenyl protected methyl ester 453, before reduction with DIBAL-H afforded alcohol 454 in 75 % yield. With the desired model compound in hand, attention was turned to ring formation. When tricycle 454 was subjected to the original Suarez conditions, two new compounds were observed in a 60% yield along with a considerable amount of the starting material (Scheme 109).
Scheme 109: Two new products were formed when model compound 454 was subjected to typical Suarez conditions

These two new compounds were assigned as tetrahydrofuran ring containing product 455 and tricycle 456 through the use of 2D NMR spectroscopy and subsequent comparison to spectra found in the literature.[201] Tetracycle 455 is the product of a successful Suarez reaction in which a new C–O bond is formed to install the desired tetrahydrofuran ring while tricycle 456 is the product of an unwanted β-scission reaction, a tentative mechanism for which is shown in Scheme 110.

Treatment of the model compound 454 with iodine in the presence of light could form oxygen-based radical 457. β-Fragmentation of radical 457 could then form stabilised tertiary radical 458 along with one equivalent of formaldehyde. A further single electron oxidation event would form stabilised carbocation 459 before deprotonation could form the observed tricycle 456.[202]
Scheme 110: Tentative mechanism for the formation of tricycle 456

Despite the formation of an unwanted side product in our model system, we decided against optimising the reaction for this substrate. We reasoned that radical containing tetracycle 460, the product of treating tetracycle 446 with iodine in the presence of light, would not undergo β-fragmentation because the resulting secondary radical 461 would not be a stable product (Scheme 111). Mihailovic and co-workers have demonstrated that radical stability was an important factor in determining the outcome of β-scission reactions.\cite{202}

Scheme 111: β-fragmentation of radical 460 would form the unstable secondary radical 461
With this in mind, we subjected tetracycle 446 to the standard Suarez reaction conditions. Unfortunately, upon treatment with iodine and PIFA in the presence of light, only decomposition of the starting material was observed. We next attempted to alter the conditions in order to form the desired tetrahydrofuran ring. Using Pb(OAc)$_4$ as the oxidant in place of PhI(OAc)$_2$ led to a complex mixture of products,[203] as did using alternative solvents such as cyclohexane, benzene or DCM.[204,205] Finally, a range of different light sources were trialed,[206,207] however, no sign of the desired tetrahydrofuran ring formation was observed (Scheme 112).

![Scheme 112: Treatment of tetracycle 446 with iodine in the presence of an oxidant in the presence of light led only to the formation of complex mixtures](image)

### 4.1.3 A Revised Approach to Xestoquinone

With the Suarez cyclisation proving unsuccessful, we decided to revise our original retrosynthetic analysis (Scheme 113). Borrowing from Harada’s original synthesis of xestoquinone, we decided that the targeted dimethoxy naphthalene 287 was a retron of an oxidative cyclisation reaction, which led back to diosphenol 462. Disconnecting the C–O bond α to the carbonyl led to ketone 463, which is a retron for a benzylic oxidation of dimethoxy naphthalene 464. Finally, we predicted that dimethoxy naphthalene 464 could be formed via aromatisation of tetracycle 446, the product of a Clemmensen reaction seen previously (Scheme 106).
We began our new approach by attempting the aromatisation of tetracycle 446 in order to form naphthalene 464. Treatment of tetracycle 446 with DDQ in refluxing benzene,[154] led not to the expected naphthalene product, but instead formed vinyl naphthalene 465 in 58% yield (Scheme 114). This reaction not only aromatised the B ring of tetracycle 446 as planned, but also installed a double bond in conjugation with the newly formed naphthalene system. To our knowledge, this is the first example of substituted vinyl naphthalenes being formed in this way. It was found that this reaction could also be carried out on the diastereomeric mixture of tetracycle 446 in comparable yields, which in turn removes the need for HPLC separation in previous steps.

**Scheme 113**: A revised retrosynthesis of xestoquinone
This somewhat unexpected result allowed us to develop a third retrosynthetic analysis of xestoquinone that we hoped would deliver the natural product in a short and efficient sequence (Scheme 115).

### 4.1.4 Synthesis of Diosphenol 466

We again determined that the targeted dimethoxy benzene 287 was the retron of an oxidative cyclisation reaction, which led back to diosphenol 466. Considering the reduced form of diosphenol 466 led to 1,2,5-triol 467. This 1,2,5-triol is a retron for a dihydroxylation reaction, which maps perfectly onto our newly aromatised tetracycle 465. A number of different dihydroxylation conditions were examined in order to form triol 467. While the attempted dihydroxylation of tetracycle 465 with KMnO₄[288] led only to decomposition of the starting material, treatment with dimethyldioxirane (DMDO) proved more successful.[209]
Combining tetracycle 465 with an excess of DMDO in acetone formed triol 468 as a 2:1 mixture of isomers in a 36% yield after just 15 minutes (Scheme 116). Presumably, this reaction proceeds through an epoxide intermediate, before ring opening in the presence of water forms the observed triol.

Surprisingly, as well as installing the required 1,2,5-triol functionality, DMDO also oxidised the hydroquinone ring to a naphthoquinone system. While the oxidation of phenols to quinones by oxiranes is known\cite{210} there have been no reports in the literature on the oxidation of hydroquinones to quinones using DMDO.
Unfortunately, we were not able to separate and confirm the exact stereochemistry of the two isomers formed via flash column chromatography. Despite our inability to isolate and determine the stereochemistry of the two isomers, we decided to attempt a 3-fold oxidation of triol 468, as this would converge the two stereoisomers formed in the dihydroxylation step.

The oxidising agent needed for the next step had to be chosen carefully to avoid 1,2-diol cleavage, a reaction often observed with chromium metal based oxidants,$^{[211,212]}$ KMnO$_4$,$^{[213]}$ Pb(OAc)$_2$,$^{[214,215]}$ and the hypervalent iodine compounds DMP$^{[216]}$ and sodium periodate.$^{[217]}$ With this in mind, we attempted the oxidation of triol 468 under a range of conditions with limited success. Oxidations using IBX$^{[218]}$, DMDO,$^{[219]}$ TEMPO$^{[220]}$ or MnO$_2$ led only to decomposition of the starting material as did oxidations that use activated DMSO, such as the Parikh–Doering,$^{[221]}$ Swern$^{[222]}$ and Omura–Sharma–Swern$^{[223]}$ reactions. We attributed this tendency of triol 468 to decompose to the presence of the reactive naphthoquinone functionality, and therefore decided to revisit our dihydroxylation conditions in an attempt to form triol 467 without oxidising the dimethoxy naphthalene ring.

It was decided to examine Upjohn dihydroxylation conditions in an effort to introduce the vicinal diol functionality.$^{[224]}$ Both OsO$_4$ and the less toxic K$_2$OsO$_2$(OH)$_4$ were trialed under these conditions with a range of additives including citric acid, DMAP and pyridine.$^{[225]}$ Unfortunately, no triol product was observed. We attributed this lack of reactivity to a low turnover of the osmium catalyst. This theory seemed justified when we changed to Donohoe dihydroxylation conditions.$^{[226]}$ When tetracycle 465 was treated with stoichiometric amounts of OsO$_4$ in the presence of TMEDA, full conversion of the starting material to osmate ester 469 was observed in just five minutes (Scheme
Osmate ester 469 however proved difficult to cleave as both HCl\textsuperscript{[227]} and sodium sulfite\textsuperscript{[228]} were unsuccessful in facilitating this cleavage. Finally, ethylene diamine\textsuperscript{[229]} was shown to cleave osmate ester 469 to give the desired triol 470 in a 64\% yield over three days as a single stereoisomer. While the exact stereochemistry of triol 470 was not confirmed, the selectivity of Donohoe dihydroxylations in general are known to be directed by the presence of allylic or homoallylic alcohols. In our case, the presence of a homoallylic alcohol on the top face of the substituted vinyl naphthalene 465 directs the osmium tetraoxide to the top $\pi$-face of the molecule to form osmate ester 469 via a [2+3] cycloaddition before cleavage of the osmate ester forms a syn 1,2-diol.

With triol 470 in hand, we again attempted a three-fold oxidation, however, once again only decomposition of the starting material was observed under MnO$_2$\textsuperscript{[154]} IBX\textsuperscript{[218]} and TEMPO\textsuperscript{[220]} oxidation conditions. Unfortunately, by this stage, we had run out of triol 470 and all precursors leading up to this intermediate, which prevented us from completing the synthesis of (±)-xestoquinone.
4.2 Summary

This chapter describes work towards the total synthesis of (±)-xestoquinone via a DTDA reaction sequence involving [3]dendralene (Scheme 118). Our studies explored the reactivity and selectivity of [3]dendralene in Diels–Alder reactions by performing two selective cycloadditions to install the entire carbon backbone of the natural product (±)-xestoquinone in just three steps. A Diels–Alder reaction between [3]dendralene and benzoquinone (226) followed by a one-pot aromatisation/methylation sequence gave semicyclic diene 154, which underwent a second diastereoselective Diels–Alder reaction with substituted cyclohexenone 421. This also provided a potential pathway for a synthesis of enantiomerically pure xestoquinone. A deoxygenation under modified Clemmensen conditions formed tetracycle 446 before a surprising aromatisation reaction result led to the formation of vinyl napthalene 465. This unexpected result allowed for the formation of triol 470 under Donohoe dihydroxylation conditions, which has the potential to be transformed into xestoquinone in a quick and efficient manner.
Scheme 118: Synthetic work carried out towards the synthesis of (±)-xestoquinone

If this synthesis can be completed, it will represent the first time that unsubstituted [3]dendralene has been used in total synthesis. This will demonstrate the powerful synthetic utility of [3]dendralene and its DTDA capabilities, which will pave the way for further use of this fundamental hydrocarbon in total synthesis.

4.3 Future Work

Any future work carried out on this project must look at completing the total synthesis of (±)-xestoquinone. We strongly believe that under the right oxidation
conditions, triol 470 can be transformed into diosphenol 466, which in turn could be transformed into xestoquinone in just two further steps (Scheme 119).

While some oxidation conditions have already been trialed on triol 470, Parikh–Doering,[230] TPAP,[231] Swern[222,232] and Omura–Sharma–Swern[223] oxidations have not yet been attempted and remain a viable option for this oxidation. If these oxidations are not successful, a somewhat lengthier sequence could be attempted, in which the primary alcohol is protected to give diol 471, before a double oxidation of the resulting diol could be attempted to form diosphenol 472. Deprotection, oxidation and subsequent cyclisation could then lead to dimethoxy naphthalene 462, which in turn could lead to the desired target molecule (Scheme 120).
Towards the Total Synthesis of (±)-Xestoquinone

While this synthetic route, if successful, would represent the shortest current synthesis of xestoquinone, it could be improved dramatically by an improved synthesis of dienophile 421. Currently, it takes five steps to synthesise substituted cyclohexenone 421, which is nearly as many steps as is required to make the rest of the molecule. Yamamoto and coworkers have previously used the bulky Lewis acid aluminium tris(2,6-diphenylphenoxide) (ATPH) to access the kinetically unfavoured dienolate (473) of cyclohexenone (131) (Scheme 121).[233] This dienolate was then trapped with benzaldehyde, thus alkylating cyclohexenone at the 4’ position selectively over the 2’ position to give substituted cyclohexenone 474. Applied to our system, formation of the dienolate (475) of 2-methylcyclohexenone (211) and subsequent nucleophilic addition to formaldehyde, would give access to dienophile 421 in just one step from commercially available starting materials.
Scheme 121: Formation of substituted cyclohexenone 474 and a potentially similar synthesis of substituted cyclohexenone 421

Finally, we would like to examine the possibility of a synthesis of enantiomerically pure xestoquinone. As mentioned previously, the single stereocentre in this synthesis is installed during the Diels–Alder reaction between semicyclic diene 154 and substituted cyclohexenone 421, and is determined by the configuration of the hydroxymethyl group at C4 of the dienophile. If we were able to access enantiomerically pure substituted cyclohexenone 421, we should in theory be able to synthesise enantiomerically pure xestoquinone. There are two promising routes towards this outcome. Yamamoto has shown that chiral bulky Lewis acids can be used in the asymmetric alkylation of aldehydes by blocking one face of the molecule to give enantiomerically pure alcohols such as secondary alcohol 476.[234] Combination of this work with the dienolate formation methodology mentioned earlier in this section could deliver enantiomerically pure dienophile 421 in just one step via a similar pathway.
Scheme 122: The use of chiral Lewis acids in enantioselective alkylation reactions and its application towards the synthesis of enantiomerically pure substituted cyclohexenone 421

Another possibility is the use of dynamic kinetic resolution. Backvall and coworkers have shown that primary alcohols that contain a stereocentre at the β position can undergo a dynamic kinetic resolution in the presence of the enantioselective acylating lipase PS-D I, isolated from *Burkholderia cepacia*, and the racemising catalyst 482 to yield enantiomerically pure esters in good yields ([Scheme 123](#)). If this system was successfully applied to our synthetic pathway, we envisage enantiomerically pure substituted cyclohexenone 421 could be synthesised in just two additional steps to the sequence currently employed and could potentially lead to the shortest synthesis of enantiomerically pure xestoquinone.
Scheme 123: Dynamic kinetic resolution of primary alcohols with β stereocentres
Chapter 5: Experimental

5.1 General

NMR Spectra

1H NMR spectra were recorded at 400 MHz or 300 MHz using a Varian 400-MR or Varian Mercury 300 MHz spectrometer, as indicated. Residual solvent peaks were used as an internal reference for 1H NMR spectra (CDCl$_3$ δ 7.26 ppm, MeOD δ 3.31 ppm). Coupling constants (J) are quoted to the nearest 0.1 Hz. Assignment of proton signals was assisted by COSY, HSQC and HMBC experiments. 13C NMR spectra were recorded at 100 MHz using a Varian 400-MR spectrometer. Solvent peaks were used as an internal reference for 13C NMR spectra (CDCl$_3$ δ 77.16 ppm, MeOD δ 49.00 ppm). Assignment of carbon signals was assisted by HSQC and HMBC experiments. The following abbreviations (or combinations thereof) were used to describe 1H NMR multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, p = quintet, m = multiplet, br = broad.

IR Spectra

IR spectra were recorded as KBr discs (for solid samples) or thin films on NaCl plates (for oils) using a Perkin–Elmer 1600 FTIR spectrometer.
Mass Spectrometry

Low resolution EI mass spectra were recorded on an Agilent HP 6869 series mass spectrometer using electron impact (EI+) ionisation mode at 70 eV. High resolution EI mass spectra were recorded on a Waters Auto Spec Premier spectrometer operating at 70 eV. Low resolution ESI mass spectra were recorded on a ZMD Micromass spectrometer with Waters Alliance 2690 HPLC. High resolution ESI mass spectra were recorded on a Waters LCT Premier time-of-flight (TOF) mass spectrometer.

HPLC

Analytical HPLC was conducted using an Agilent 1100 quaternary pump, automatic sampler, column compartment and diode array detector. Preparative HPLC was performed using an Agilent 1100 preparative binary pump, preparative automatic sampler, and diode array detector with a preparative flow cell.

Melting Points

Melting points are uncorrected, and were measured on a Reichert melting point apparatus.

Analytical TLC

Merck silica gel plates, pre-coated with silica gel 60 F254 (0.2 mm), were used for analytical TLC. Visualisation was effected by quenching of UV fluorescence (max=...
254 nm) or by staining with p-anisaldehyde, potassium permanganate or phosphomolybdic acid TLC stain solution, followed by heating.

**Flash Chromatography**

Merck Kiesgel 60 (230 – 400 mesh) silica gel was used for flash chromatography.

**X-ray Crystallographic Data**

Single crystal X-ray analyses were performed by Dr. Anthony Willis, and are provided in a DVD inside the back cover of this thesis.

**Experimental Procedures, Reagents and Glassware**

Reactions were conducted in oven-dried glassware under a positive pressure of dry nitrogen or argon as indicated. Anhydrous solvents were dried using a purification based on that described by Grubbs and co-workers or using standard laboratory procedures. Commercially available chemicals were used as purchased, or purified by standard techniques. ‘Hexanes’ or ‘Petroleum spirits’ refers to petroleum spirits 40–60 °C unless otherwise indicated. Solutions of n-BuLi were titrated using the method of Lin and Paquette, Grignard reagents were titrated against salicylaldehyde phenylhydrazone using the procedure of Love and Jones, and solutions of DIBAL were titrated against p-methoxybenzaldehyde according to the procedure of Hoye.
5.2 Experimental Data for Chapter One

\[ \text{Ni(dppp)Cl}_2 \]

Bis(diphenylphosphino)propane (8.25 g, 20.0 mmol) was dissolved in THF (70 mL) at 60 °C and cannulated into a solution of NiCl₂.6H₂O (4.8 g, 20 mmol) in methanol (100 mL). The resulting mixture was left to stir for 30 minutes before cooling to room temperature. The resulting precipitate was collected, washed with H₂O (x3) and methanol (x3) and dried under reduced pressure to give pure target material as an orange solid (9.04 g, 16.7 mmol, 83%).

\[ \text{Vinyl magnesium bromide (17)} \]

To a 2L round bottom flask fitted with a dry ice condenser and a dropping funnel, was added Mg turnings (26.1 g, 1.19 mol), a single crystal of I₂ and dry THF (90 mL). A solution of vinyl bromide (484) (116 g, 77 mL, 1.08 mol) in dry THF (450 mL) was added at such a rate as to keep the reaction mixture at reflux. After addition was complete, the mixture was heated to 40 °C and left to stir for 2 hours. The solution was then cooled to room temperature and titrated with salicylaldehyde phenylhydrazone[230] which showed a concentration of 1.6 M of the desired Grignard reagent (75%).
[3]Dendralene (1)

\[
\begin{align*}
\text{Ni(dppp)Cl}_2 & \quad \text{ZnBr}_2 \\
\text{THF} & \\
\text{MgBr} & \quad \text{Cl} & \quad \text{Cl} & \quad \text{Ni(dppp)Cl}_2, \text{ZnBr}_2 & \quad \text{THF} & \quad 1
\end{align*}
\]

Ni(dppp)Cl₂ (5 mg, 0.01 mmol) and anhydrous ZnBr₂ solution (1.02 M in THF, 2.70 mL, 2.75 mmol) were combined in a 25 mL round bottomed flask and cooled to 8 °C. Vinyl magnesium bromide solution (1.52 M in THF, 1.80 mL, 2.75 mmol) was then added dropwise and left to stir for 30 minutes. 1,1 dichloroethylene (31) (96.9 mg, 80 µL, 1.00 mmol) was then added dropwise at such a rate as to keep the internal temperature below 10 °C. After addition was complete, the reaction was allowed to slowly warm to room temperature and stirred for two hours. After two hours, the reaction was cooled to 0 °C and quenched with a 1M HCl solution (1 mL). The reaction mixture was then distilled (0 °C, 50 mbar) and the distillate collected in a cold trap to give a pure solution of [3]dendralene in THF (0.76 mmol, 76% yield - determined by ¹H NMR analysis using durene as an internal standard)

2-Propenyl magnesium bromide (76)

\[
\begin{align*}
\text{Br} & \quad \text{Mg, DBE, THF} & \quad \text{BrMg} & \quad 76
\end{align*}
\]

1,2-Dibromoethane (6.86 g, 3.16 mL, 36.5 mmol) was added dropwise to a suspension of magnesium turnings (14.6g, 600 mmol) in dry THF (100 mL). A solution of 2-bromopropene (485) (45.4 g, 33.3 mL, 0.375 mol) in dry THF (400 mL) was then added dropwise at such a rate as to keep the reaction mixture at reflux. After addition was complete, the reaction mixture was heated to reflux and left to stir for two hours. The solution was then cooled to room temperature and titrated with salicylaldehyde phenylhydrazone[239] which showed a concentration of 0.65 M of the desired Grignard reagent (86 %).
1-Bromocyclopentene (487)

Bromine (48.9 g, 15.8 mL, 306 mmol) was added dropwise to a solution of triphenyl phosphite (86.8 g, 73.6 mL, 280 mmol) in dry CH$_2$Cl$_2$ (800 mL) at –78 °C under Ar. Dry triethylamine (34.0 g, 46.9 mL, 336 mmol) was then added dropwise followed by cyclopentanone (486) (26.9 g, 26.9 mL, 256 mmol). The resulting solution was then heated to reflux and stirred for two hours. The solvent was then removed under reduced pressure. The resulting liquid was filtered first through a plug of Celite and then through a plug of SiO$_2$ eluting with CH$_2$Cl$_2$. The solvent was removed under reduced pressure to give the crude target material as an orange liquid. The crude material was purified via vacuum distillation (50–54 °C/50 mbar) to give the desired bromide 487 as a pale yellow liquid (11.8 g, 80.3 mmol, 32%). All spectroscopic data corresponded to that quoted in the literature.[241]

Cyclopentenyl magnesium bromide (77)

1,2-Dibromoethane (1.36 g, 627 µL, 7.24 mmol) was added dropwise to a suspension of magnesium turnings (2.91, 120 mmol) in dry THF (30 mL). A solution of bromide 487 (11 g, 7.6 mL, 74 mmol) in dry THF (70 mL) was then added dropwise at such a rate as to keep the reaction mixture at reflux. After addition was complete, the reaction mixture was heated to reflux and left to stir for two hours. The solution was then cooled to room temperature and titrated with
salicylaldehyde phenylhydrazone which showed a concentration of 0.5 M of the desired Grignard reagent (66%).

1-Bromocyclohexene (489)

Bromine (48.9 g, 15.8 mL, 306 mmol) was added dropwise to a solution of triphenyl phosphite (86.8 g, 73.6 mL, 280 mmol) in dry CH₂Cl₂ (800 mL) at –78 °C under Ar. Dry triethylamine (34.0 g, 46.9 mL, 336 mmol) was then added dropwise followed by cyclohexanone (488) (24.6 g, 24.8 mL, 256 mmol). The resulting solution was then heated to reflux and stirred for two hours. The solvent was then removed under reduced pressure. The resulting liquid was filtered first through a plug of Celite and then through a plug of SiO₂, eluting with CH₂Cl₂. The solvent was removed under reduced pressure to give the desired bromide as an orange liquid. The crude material was purified via vacuum distillation (75–80 °C/50 mbar) to give the desired bromide 489 as pale yellow liquid (11.5 g, 71.4 mmol, 28%). All spectroscopic data corresponded to that quoted in the literature.[241]

Cyclohexenyl magnesium bromide (78)

1,2-Dibromoethane (1.36 g, 627 µL, 7.24 mmol) was added dropwise to a suspension of magnesium turnings (2.91, 120 mmol) in dry THF (30 mL). A solution of bromide 489 (11.2 g, 8.05 mL, 70.0 mmol) in dry THF (70 mL) was then added dropwise at such a rate as to keep the reaction mixture at reflux. After
addition was complete, the reaction mixture was heated to reflux and left to stir for two hours. The solution was then cooled to room temperature and titrated with salicylaldehyde phenylhydrazone\cite{239} which showed a concentration of 0.5 M of the desired Grignard reagent (66\%).

**Vinyl trimethylsilane (491)**

![Chemical reaction diagram]

A solution of chlorotrimethylsilane (490) (10.9 g, 12.7 mL, 0.100 mol) in dry THF (10 mL) was added dropwise over 30 minutes to a refluxing solution of vinylmagnesium bromide (17) (0.807 M in THF, 124 mL, 0.100 mol). After addition was complete, the reaction was allowed to stir at reflux for a further two hours. After allowing the reaction mixture to cool to room temperature, the flask was fixed with a distillation apparatus and the target product was carefully distilled off (55 °C). The distillate was washed with H2O (x5) to give the desired target material 491 as a colourless liquid (4.0 g, 0.040 mol, 40%). All spectroscopic data corresponded with that quoted in the literature.\cite{242}

**1-Bromo-1-trimethylsilyl ethylene (492)**

![Chemical reaction diagram]

Bromine (16.8 g, 5.40 mL, 121 mmol) was added dropwise to a flask containing vinyltrimethylsilane (491) (8.98 g, 13.1 mL, 89.5 mmol) at –78 °C over one hour. The flask was warmed to room temperature before adding diethylamine (26.3 g, 37.0 mL, 582 mmol). The reaction was then heated to reflux and left to stir for 18 hours. The reaction was allowed to cool to room temperature and then filtered, and the
collected solid washed with ether (x3). The organic layers was acidified with 2M HCl to pH~4, washed with H₂O (x3) and brine (x1) and dried over MgSO₄ before removing the solvent under reduced pressure to give the crude target material as a colourless liquid. The crude material was purified via distillation (56 °C/100 mbar) to give the desired alkenyl bromide 492 as a colourless liquid (6.73 g, 37.6 mmol, 42%). All spectroscopic data corresponded to that quoted in the literature.[242]

1-Trimethylsilyl vinylmagnesium bromide (79)

1,2-Dibromoethane (0.56 g, 0.26 mL, 3.0 mmol) was added drop-wise to a suspension of magnesium turnings (1.17 g, 48.1 mmol) in dry THF (10 mL). A solution of bromide 492 (5.41 g, 30.2 mmol) in dry THF (35 mL) was then added drop-wise at such a rate as to keep the reaction mixture at reflux. After addition was complete, the reaction mixture was heated to reflux and left to stir for two hours. The solution was then cooled to room temperature and titrated with salicylaldehyde phenylhydrazone[239] which showed a concentration of 0.4 M of the desired Grignard reagent (60%).

1,1',5,5'-Tetramethyl [3]dendralene (80)

Ni(dppe)Cl₂ (11 mg, 0.021 mmol), triphenylphosphine (10.5 mg, 0.0420 mmol) and anhydrous zinc bromide solution (1.50 M in THF, 1.83 ml, 2.75 mmol) were combined in a 25 mL round bottomed flask and cooled to 8 °C. A solution of 2-methylpropenyl-1-magnesium bromide (75) (0.41 M in THF, 6.70 ml, 2.75 mmol)
was then added dropwise and the resulting mixture was stirred for 30 minutes. 1,1-dichloroethylene (96.9 mg, 80 µL, 1.00 mmol) was then added at such a rate as to keep the internal temperature below 10 °C. After addition was complete, the reaction was allowed to slowly warm to room temperature and stirred for two hours. After two hours, the reaction was poured into a mixture of 30–40 °C petroleum spirits (5 mL) and ice water (10 mL) before adding 2M HCl solution (2 mL). The organic layer was collected, washed with saturated NaHCO₃ solution (x1), H₂O (x1) and brine (x1) before being dried over MgSO₄. The solvent was then removed under reduced pressure to give the crude target material as a yellow oil. The crude residue was taken up in pentane and pushed through a plug of SiO₂ before again removing the solvent under reduced pressure to give the desired target dendralene 80 as a colourless oil (97.2 mg, 71.4 mmol, 71 %). All characterisation data corresponded with that quoted in the literature.[243]

2,4-dimethyl [3]dendralene (82)

Ni(dppe)Cl₂ (26 mg, 0.050 mmol), triphenylphosphine (26 mg, 0.10 mmol) and anhydrous zinc bromide solution (1.5 M in THF, 4.60 ml, 6.87 mmol) were combined in a 50 mL round bottomed flask and cooled to 8 °C. A solution of 2-propenylmagnesium bromide (76) (0.6 M in THF, 11.5 ml, 6.87 mmol) was then added dropwise and the reaction mixture was stirred for 30 minutes. 1,1-dichloroethylene (242 mg, 200 µL, 2.50 mmol) was then added at such a rate as to keep the internal temperature below 10 °C. After addition was complete, the reaction was allowed to slowly warm to room temperature and stirred for two hours. After two hours, the reaction was cooled to 0 °C and quenched with a 1M
HCl solution (1 mL). The reaction mixture was then distilled (0 °C, 50 mbar) and the distillate collected in a cold trap to give a pure solution of substituted [3]dendralene 82 in THF (2.15 mmol, 86% yield - determined by \textsuperscript{1}H NMR analysis using durene as an internal standard).

**Biscyclopentenyl [3]dendralene 83**

\[
\begin{align*}
\text{MgBr}_77 & + \text{Cl} & \text{Ni(dppe)Cl} & \text{Cl} & \text{Ni(dppe)Cl} & \text{PPh}_3 & \text{ZnBr}_2 & \text{THF} \\
\text{Cl} & \text{Cl} & \text{82} & \text{493}
\end{align*}
\]

Ni(dppe)Cl\(_2\) (20 mg, 0.037 mmol), triphenylphosphine (20 mg, 0.074 mmol) and anhydrous zinc bromide solution (1.5 M in THF, 3.43 mL, 5.15 mmol) were combined in a 50 mL round bottomed flask and cooled to 8 °C. A solution of 1-cyclopentenylmagnesium bromide (77) (0.5 M in THF, 10.3 ml, 5.15 mmol) was then added dropwise and the reaction mixture was stirred for 30 minutes. 1,1-dichloroethylene (182 mg, 150 µL, 1.87 mmol) was then added at such a rate as to keep the internal temperature below 10 °C. After addition was complete, the reaction was allowed to slowly warm to room temperature and stirred for two hours. After two hours, the reaction was poured into a mixture of 30–40 °C petroleum spirits (10 mL) and ice water (20 mL) before adding 2M HCl solution (4 mL). The organic layer was collected, washed with saturated NaHCO\(_3\) solution (x1), H\(_2\)O (x1) and brine (x1) before being dried over MgSO\(_4\). The solvent was then removed under reduced pressure to give crude target material as a pale yellow oil. The crude residue was taken up in pentane and pushed through a plug of SiO\(_2\) before again removing the solvent under reduced pressure to give a 84:16 mixture of desired [3]dendralene 83 and bis cyclopentene 493 in 88% yield. A small amount of [3]dendralene 83 was isolated via distillation for characterisation purposes.
\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 5.82 (q, \(J = 2.2\) Hz, 2H), 4.97 (s, 2H), 2.58–2.53 (m, 4H), 2.45–2.40 (m, 4H), 1.93 (q, \(J = 7.6\) Hz, 4H) ppm.

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 142.8 (C\(_q\)), 142.6 (C\(_q\)), 129.1 (CH\(_2\)), 111.2 (CH\(_2\)), 34.5 (CH\(_2\)), 33.0 (CH\(_2\)), 23.2 (CH\(_2\)) ppm.

\(\text{IR: (KBr): } v_{\text{max}} = 3085, 2940, 2908, 2834, 1678, 1603\) cm\(^{-1}\).

5.3 Experimental for Chapter Two

Chloroprene (16)

\[
\begin{align*}
\text{494} & \xrightarrow{\text{Ca(OH)}_2, (HOCH}_2\text{)} \text{2} \text{16} \\
\text{Cl} & \text{Cl} & \text{Cl} \\
\end{align*}
\]

To a 3-neck round bottom flask fitted with a magnetic stirrer, pressure equalising addition funnel and a distillation apparatus was added calcium hydroxide (42.0 g, 0.57 mol) ethylene glycol (500 mL) and BHT (one spatula). The reaction mixture was heated to 105 °C and allowed to equilibrate for 30 minutes. 3,4-dichloro-1-butene (494) was added dropwise at such a rate as to keep the distillation apparatus below 62 °C. The distillate was dried over calcium chloride to yield pure chloroprene (16) as a colourless liquid (58.8 g, 0.665 mol, 67%). All characterisation data corresponded with that quoted in the literature.

Chloroprene Grignard (18)

\[
\begin{align*}
\text{16} & \xrightarrow{\text{Mg, ZnBr\(_2\), DBE, THF}} \text{18} \\
\text{Cl} & \text{Cl} & \text{MgCl} \\
\end{align*}
\]
To a 3-neck round bottom flask fitted with a magnetic stirrer, dry ice condenser and pressure equalising addition funnel was added magnesium turnings (2.43 g, 0.10 mol) followed by dry THF (20 mL). 1,2-dibromoethane (1.65 g, 0.760 ml 9.00 mmol) was then added dropwise, followed by ZnBr$_2$ solution in THF (1.3 M, 0.5 mL, 0.65 mmol). A solution of chloroprene (5.56 g, 7.32 ml, 63.0 mmol) and 1,2-dibromoethane (1.88 g, 0.87 ml, 10.0 mmol) in dry THF (35 ml) was then added via addition funnel at such a rate as to keep the reaction at reflux. After addition was complete, the reaction was heated to reflux and allowed to stir for two hours. The solution was then cooled to room temperature and titrated with salicylaldehyde phenylhydrazone$^{[239]}$ which showed a concentration of 0.48 M of the desired Grignard reagent (76 %).

**Dienol 20**

A solution of ethylene oxide (1.52 g, 1.72 ml, 34.5 mmol) in dry THF (17.5 mL) was added to a solution of LiCl (0.15g, 4.16 mmol) and anhydrous CuCl$_2$ (0.23 g, 2.82 mmol) in dry THF (25 mL) in a 2-neck round bottom flask fitted with a dry ice condenser. The solution was cooled to 0 °C and chloroprene Grignard reagent (0.48 M in THF, 40 mL, 34.7 mmol) was added via cannula at such a rate as to prevent an exotherm. After addition was complete, the reaction was allowed to slowly warm to room temperature and stirred for 16 hours. The reaction mixture was subject briefly to vacuum to remove any unreacted ethylene oxide before partitioning between ether (100 mL) and water (100 mL). The pH of the solution was adjusted to pH~4 (2 M HCl) upon which a colour change occurred. The mixture was decanted, and the aqueous layer was extracted with ether (x3). The combined
organic layers were washed with H₂O (x1) and brine (x1) and dried over MgSO₄. The solvent was removed under reduced pressure to yield the crude target material as a yellow oil (2.77 g, 28.2 mmol, 81%). All characterisation data corresponded with that quoted in the literature.[16] The crude material was used without further purification.

**Bromo-diene 21**

N-bromosuccinimide (14.14g, 79.0 mmol) was added portion wise to a solution of dienol 20 (6.5 g, 66.0 mmol) and PPh₃ (20.9 g, 79.0 mmol) in dry CH₂Cl₂ (70 mL) at –78 °C. After addition was complete, the reaction was allowed to warm to room temperature and stirred for three hours. The reaction was then slowly poured into 30–40 °C petrol (400 mL) and stirred for 30 minutes. The mixture was filtered and concentrated under reduced pressure (0 °C/80 mbar). The resulting mixture was loaded onto a short silica plug and eluted with 30–40 °C petrol. The solvent was removed under reduced pressure to yield crude target material as a colourless oil (6.87 g, 42.9 mmol, 65%). All characterisation data corresponded with that quoted in the literature.[16] The crude material was used without further purification.

**[3]dendralene (1)**

DBU (18.2 g, 18.0 ml, 119 mmol) was added dropwise to a solution of bromide 21 (6.0 g, 37.3 mmol) in DMSO (20 ml) at 0 °C. The solution was slowly allowed to warm to room temperature and stirred for 30 minutes. The reaction was cooled
back down to 0 °C and a vacuum (80 mbar) was applied for one hour. [3]dendralene (1) was collected in a cold trap as a colourless oil (2.43 g, 30.3 mmol, 81 %). All characterisation data corresponded with that quoted in the literature.[16]

**Monocyclic diene 125**

\[
\text{CH}_2\text{Cl}_2 + \text{Me}_2\text{AlCl}_2 \xrightarrow{\text{Me}_2\text{AlCl, CH}_2\text{Cl}_2} \text{Me}_2\text{AlCl}_2\text{CH}_2\text{Cl}_2
\]

Me₂AlCl (1.0M solution in hexane, 205 µL, 0.205 mmol,) was added dropwise to a solution of freshly prepared [3]dendralene (50 mg, 0.62 mmol) and methyl vinyl ketone (29 mg, 35 µL, 0.42 mmol) in dry CH₂Cl₂ (1 mL) at −20 °C under N₂. The solution was stirred for two hours before triethylamine (0.1 mL) was added. The reaction mixture was warmed to room temperature before saturated potassium sodium tartarate solution (5 mL) was added and the resulting mixture was stirred for 30 minutes. The mixture was poured into ice water (5 mL) and extracted with CH₂Cl₂ (x3). The organic layers were collected and washed with brine (x1), dried over MgSO₄ and the solvent removed under reduced pressure to give the crude product as a yellow oil. Following flash column chromatography (0–10% EtOAc in hexanes) pure product 125 was isolated as a colourless oil (44 mg, 0.29 mmol, 71%).

\[ R_f \ 0.27 \ (90:10; \text{hexanes:EtOAc}). \]

\[^1\text{H NMR}\ (400 \text{MHz, CDCl}_3): \delta 6.33 \ (\text{dd}, J = 17.6, 10.8 \text{ Hz, 1H}), 5.74 \ (\text{s, 1H}), 5.06 \ (\text{d, J = 17.6 Hz, 1H}), 4.92 \ (\text{d, J = 10.8 Hz, 1H}), 2.67–2.51 \ (\text{m, 1H}), 2.34–2.29 \ (\text{m, 3H}), 2.18 \ (\text{s, 3H}), 2.16–2.13 \ (\text{m, 1H}), 2.09–2.04 \ (\text{m, 1H}), 1.71–1.56 \ (\text{m, 1H}) \text{ ppm.} \]
\[ ^{13}C\text{ NMR}\ (100\text{ MHz, CDCl}_3): \delta\ 211.2\ (C_\text{q}),\ 139.2\ (CH),\ 135.6\ (C_\text{q}),\ 127.4\ (CH),\ 110.6\ (CH_2),\ 47.3\ (CH),\ 28.0\ (CH_3),\ 27.3\ (CH_2),\ 24.8\ (CH_2),\ 23.8\ (CH_2)\ \text{ppm.}\]

\text{IR:}\ (\text{thin film}): v_{\text{max}}\ =\ 3003,\ 2925,\ 2840,\ 1710,\ 1644,\ 1606\ \text{cm}^{-1}.

\text{LRMS:}\ (70\text{ eV, EI): m/z (%): 150.1 (80, [M+•]), 135.1 (30), 107.1 (48), 91.1 (75), 84.0 (66), 79.1 (100), 77.0 (46)}

\text{HRMS:} (70\text{ eV, EI): m/z calc. for C}_{10}\text{H}_{14}\text{O [M]••: 150.1045; found 150.1049}

\text{Monocyclic diene 127}

\text{DMAD (219 mg, 189 \mu L, 1.54 mmol) was added to a solution of [3]dendralene (136 mg, 1.70 mmol) in THF (9 mL) and stirred at 40 °C for 16 hours. After cooling to room temperature, the solvent was removed under reduced pressure to yield crude target material as a colourless oil. Following flash column chromatography (SiO}_2 10–20% EtOAc in hexanes) pure target material 127 was isolated as a colourless oil (301 mg, 1.32 mmol, 88%). All characterisation data corresponded with that quoted in the literature.\textsuperscript{[76]}

\text{Monocyclic diene 129}
Methyl propiolate (48 mg, 51 \mu L, 0.56 mmol) was added to a solution of [3]dendralene (54 mg, 0.62 mmol) in THF (5 mL) and stirred at 40 °C for 40 hours. After cooling to room temperature, the solvent was removed under reduced pressure to yield crude target material as a colourless oil. Following flash column chromatography (SiO\(_2\) 10–20% EtOAc in hexanes) pure product 129 was isolated as a colourless oil (53 mg, 0.32 mmol, 58%) 

\[ R_f \text{ 0.39 (95:5; hexanes:EtOAc).} \]

\( ^1\text{H NMR} \) (400 MHz, CDCl\(_3\)): \( \delta \) 7.06 (s, 1H), 6.42 (dd, J = 17.5, 10.7 Hz, 1H), 5.83 (s, 1H), 5.08 (d, J = 17.5 Hz, 1H), 5.02 (d, J = 10.8 Hz, 1H), 3.76 (s, 3H), 3.07–3.01 (m, 2H), 3.01–2.94 (m, 2H) ppm.

\( ^{13}\text{C NMR} \) (100 MHz, CDCl\(_3\)): \( \delta \) 167.3 (C\(_q\)), 138.4(CH), 136.2(CH), 131.4 (C\(_q\)), 127.2 (C\(_q\)), 126.1(CH), 111.4 (CH\(_2\)), 51.6 (CH\(_3\)), 26.3(CH\(_2\)), 26.1 (CH\(_2\)) ppm.

\( \text{IR} \): (thin film): \( \nu_{\text{max}} \) = 3084, 3010, 2950, 2867, 1716, 1676, 1639 cm\(^{-1}\).

\( \text{LRMS} \) (70 eV, ESI): m/z (%): 165.1 (80, [M+H]\(^+\)), 133.1 (35), 105.0 (100), 102.0 (22).

\( \text{HRMS} \) (70 eV, EI): m/z calc. for C\(_{10}\)H\(_{15}\)O\(_2\) [M+H]\(^+\): calc; 165.0916. found; 165.0924.

**Bicyclic diene 136**

![Bicyclic diene 136](image)
Me₃AlCl (1.0M solution in hexane, 310 µL, 0.310 mmol,) was added dropwise to a solution of freshly prepared [3]dendralene (100 mg, 1.25 mmol) and cyclohexenone (60 mg, 60 µL, 0.62 mmol) in dry CH₂Cl₂ (1 mL) at −78 °C under N₂. The solution was allowed to warm to −20 °C and was stirred for 18 hours then triethylamine (0.1 mL) was added. The mixture was warmed to room temperature before saturated potassium sodium tartrate solution (5 mL) was added and the resulting mixture was stirred for 30 minutes. The mixture was poured into water and extracted with CH₂Cl₂ (x3). The organic layers were collected and washed with brine (x1), dried over MgSO₄ and the solvent was removed under reduced pressure to give the crude product as a white solid. Following flash column chromatography (SiO₂, 5% EtOAc in hexanes) the pure product 136 was isolated as a white solid (101 mg, 0.573 mmol, 93%). Recrystallisation from EtOAc gave white crystals, mp 37–39 °C, which were suitable for single crystal X-ray analysis.

**R:** 0.22 (95:5; hexanes:EtOAc).

**¹H NMR** (400 MHz, CDCl₃): δ 6.33 (dd, J = 17.5, 10.8 Hz, 1H), 5.69 (s, 1H), 5.01 (d, J = 17.5 Hz, 1H), 4.89 (d, J = 10.8 Hz, 1H), 2.78–2.67 (m, 1H), 2.63 (d, J = 19.0 Hz, 1H), 2.50–2.36 (m, 2H), 2.36–2.21 (m, 1H), 2.20–2.03 (m, 3H), 1.97–1.87 (m, 3H), 1.84–1.71 (m, 1H) ppm.

**¹³C NMR** (100 MHz, CDCl₃): δ 212.3 (C₉), 139.7 (CH₂), 134.0 (C₉), 126.7 (CH), 110.1 (CH₂), 48.3 (CH), 40.2 (CH₂), 35.9 (CH), 28.8 (CH₂), 25.9 (CH₂), 24.5 (CH₂), 24.0 (CH₂) ppm.

**IR:** (KBr): \( \nu_{\text{max}} = 2928, 1708, 1645, 1606 \text{ cm}^{-1} \).
**LRMS:** (70 eV, EI): m/z (%): 176.1 (100, [M]^••), 130.1 (90), 105.1 (90), 84.0 (78)

**HRMS:** (70 eV, EI): m/z calc. for C_{12}H_{16}O [M]^••: 176.1201; found 176.1201.

**Bicyclic diene 138**

\[
\begin{align*}
134 & \quad + \quad 1 \\
\quad & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad
\end{align*}
\]

Me_{2}AlCl (1.0M solution in hexane, 310 µL, 0.310 mmol,) was added dropwise to a solution of freshly prepared [3]dendralene (100 mg, 1.25 mmol) and cyclopentenone (50 mg, 0.62 mmol) in dry CH_{2}Cl_{2} (1 mL) at –78 °C under N_{2}. The solution was allowed to warm to –20 °C and was stirred for 18 hours then triethylamine (0.1 mL) was added. The mixture was warmed to room temperature before saturated potassium sodium tartarate solution (5 mL) was added and the resulting mixture was stirred for 30 minutes. The mixture was poured into water and extracted with CH_{2}Cl_{2} (x3). The organic layers were collected and washed with brine (x1), dried over MgSO_{4} and the solvent was removed under reduced pressure to give the crude material as a colourless oil. Following flash column chromatography (SiO2 5% EtOAc in hexanes) pure product 138 was isolated as a colourless oil (76 mg, 0.47 mmol, 76%).

**Rf:** 0.18 (95:5; hexanes:EtOAc).

**1H NMR** (400 MHz, CDCl_{3}): δ 6.34 (dd, J = 17.5, 10.8 Hz, 1H), 5.69 (s, 1H), 5.06 (d, J = 17.5 Hz, 1H), 4.92 (d, J = 10.8 Hz, 1H), 2.63–2.50 (m, 2H), 2.46–2.33 (m, 3H), 2.33–
2.23 (m, 2H), 2.16–1.99 (m, 1H), 1.86 (ddt, J = 12.7, 8.0, 3.7 Hz, 1H), 1.79–1.67 (m, 1H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 219.2 (C$_q$), 139.5 (CH), 134.3 (C$_q$), 127.1 (CH), 110.2 (CH), 46.9 (CH), 34.1 (CH), 32.4 (CH$_2$), 26.5 (CH$_2$), 24.5 (CH$_2$), 22.2 (CH$_2$) ppm.

IR: (thin film): $v_{\text{max}}$ = 2927, 2835, 2880, 1732, 1645, 1606 cm$^{-1}$.

LRMS: (70 eV, EI): m/z (%): 162.1 (82, [M]$^+\ast$), 117 (100), 105.1 (90), 91.1 (78), 79.1 (50).

HRMS: (70 eV, EI): m/z calc. for C$_{11}$H$_{14}$O [M]$^{++}$: 176.1201; found 176.1201.

Bicyclic diene 139

Me$_2$AlCl (1.0M solution in hexane, 155 µL, 0.155 mmol,) was added dropwise to a solution of freshly prepared [3]dendralene (50 mg, 0.62 mmol) and 2-methyl cyclohexenone (34 mg, 36 µL, 0.31 mmol) in dry CH$_2$Cl$_2$ (1mL) at –78 °C under N$_2$. The solution was allowed to warm to –20 °C and was stirred for 20 hours then triethylamine (0.1 mL) was added. The mixture was warmed to room temperature before saturated potassium sodium tartarate solution (5 mL) was added and the resulting mixture was stirred for 30 minutes. The mixture was poured into water and extracted with CH$_2$Cl$_2$ (x3). The organic layers were collected and washed with brine (x1), dried over MgSO$_4$ and the solvent was removed under reduced pressure.
to give the crude target material as a colourless oil. Following flash column chromatography (SiO$_2$ 10% EtOAc in hexanes) pure product 139 was isolated as a colourless oil (39 mg, 0.20 mmol, 67%).

$R_f$: 0.31 (90:10; hexanes:EtOAc).

$^1$H NMR (400 MHz, CDCl$_3$): δ 6.34 (dd, $J$ = 17.6, 11.2 Hz, 1H), 5.65 (s, 1H), 5.06 (d, $J$ = 17.6 Hz, 1H), 4.92 (d, $J$ = 11.2 Hz, 1H), 2.64–2.54 (m, 2H), 2.34–2.28 (m, 2H), 2.07–2.00 (m, 2H), 1.88–1.78 (m, 2H), 1.72–1.62 (m, 3H), 1.09 (s, 3H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 212.3 (C$_q$), 139.6 (CH), 133.0 (CH), 125.1 (CH), 110.5 (CH$_2$), 47.8 (C$_q$), 41.1 (CH), 37.2 (CH$_2$), 32.1 (CH$_2$), 27.8 (CH$_2$), 26.8 (CH$_2$), 25.14 (CH$_{3}$), 20.6 (CH$_3$) ppm.

IR: (thin film): $v_{\text{max}}$ = 2931, 2865, 1703, 1676, 1646, 1607, cm$^{-1}$.

LRMS: (70 eV, EI): m/z (%): 190.1 (63, [M]$^+$); 175 (83), 147 (52), 130 (100), 91 (83).

HRMS: (70 eV, EI): m/z calc. for C$_{13}$H$_{18}$O [M]$^+$: 190.1358; found 190.1363.

2,5-dimethoxy phenol (150)

\[
\begin{align*}
\text{OMe} & & \text{OMe} \\
\text{OMe} & & \text{OMe} \\
\text{H} & & \\
\begin{array}{c}
\text{149} \\
\text{150}
\end{array}
\]

\text{CH}_2\text{Cl}_2

\text{m-CPBA}

\text{NaOH}

This compound was synthesised using a modified protocol from Michael and co-workers.$^{[244]}$ A solution of 2,5-dimethoxybenzaldehyde (20 g, 0.12 mol) in dry
CH₂Cl₂ (40 mL) was added dropwise to a solution of m-CPBA (28 g, 0.16 mol) in CH₂Cl₂ (160 mL) at 0°C. The solution was heated to reflux and left to stir for 16 hours. After cooling to room temperature, the solution was washed with saturated NaHCO₃ solution (x10) and saturated Na₂S₂O₃ (x2) and dried over MgSO₄. The solvent was removed under reduced pressure to give the crude ester as a yellow oil. This yellow oil was taken up in MeOH (100 mL) before sodium hydroxide solution (10% w/v, 100 mL) was added and the reaction mixture left to stir for three hours. The solution was acidified to pH 1 (6M HCl) and extracted with CH₂Cl₂ (x3). The solvent was removed under reduced pressure to give crude target material 150 as a yellow oil. Following flash column chromatography (SiO₂ 10% EtOAc in hexanes) pure product 150 was isolated as a colourless oil (16.05 g, 0.104 mol, 87%). All characterisation data corresponded with that quoted in the literature.[244]

2,5-dimethoxy trimethylsilane (151)

This compound was synthesised using a modified protocol from Michael and co-workers.[244] 2,5 dimethoxyphenol (16.05 g, 0.104 mol) and hexamethyldisilazane (10.11 g, 13.13 mL, 0.063 mol) were combined in a round bottom flask and heated to 70 °C. After stirring for 45 minutes, the solution was cooled to room temperature and excess hexamethyldisilazane was removed under reduced pressure to give pure target material 151 in near quantitative yield (23.5 g, 0.103 mol, 99%). All characterisation data corresponded with that quoted in the literature.[244]
2,5-dimethoxy-3-triemethyilsilyl trimethylsilane (152)

This compound was synthesised using a modified protocol from Castedo and co-workers.\textsuperscript{[88]} A solution of TMS ether 151 (4.16 g, 18.4 mmol) in dry THF (25 mL) was added dropwise to a solution of freshly prepared LDA (2.16 g, 20.2 mmol) at –78 °C under N\textsubscript{2}. The solution was warmed to room temperature and stirred for two hours. The solution was then cooled to –78 °C and freshly distilled TMSCl (2.38 g, 2.80 mL, 22.0 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred for 20 hours. The reaction was quenched with saturated NH\textsubscript{4}Cl solution (5 mL) and extracted with Et\textsubscript{2}O (x3). The organic layer was dried over MgSO\textsubscript{4} and the solvent removed under reduced pressure to give crude target material 152 as a colourless oil. The crude material was used without further purification. All characterisation data corresponded with that quoted in the literature.\textsuperscript{[88]}

2,5-dimethoxybenzyne precursor 148

This compound was synthesised using a modified protocol from Castedo and co-workers.\textsuperscript{[88]} n-BuLi (1.6M in hexanes, 11.7 mL, 18.6 mmol) was added dropwise to a solution of TMS ether 152 (5.29 g, 17.7 mmol) in dry ether (190 mL) at 0 °C under N\textsubscript{2}. The solution was warmed to room temperature and allowed to stir for four
hours. The solution was then cooled to 0 °C and triflic anhydride (10.0 g, 9.66 mL, 35.4 mmol) was added dropwise. The solution was allowed to warm to room temperature and stirred for 18 hours. The reaction was quenched with saturated NH₄Cl solution (70 mL) and extracted with Et₂O (x3). The organic layers were dried over MgSO₄ and the solvent removed under reduced pressure to give crude target material as a yellow oil. Following flash column chromatography (SiO₂ 33% CH₂Cl₂ in hexanes) pure product 148 was isolated as a colourless oil (4.56 g, 12.7 mmol, 69% over two steps). All characterisation data corresponded with that quoted in the literature.[184]

**Bicyclic diene 153**

![Chemical Structure](image)

2-(trimethylsilyl)phenyl trifluoromethanesulfonate (147) (45 mg, 37 µL, 0.15 mmol) was added dropwise to a suspension of freshly prepared [3]dendralene (50 mg, 0.61 mmol) and CsF (69 mg, 0.45 mmol) in acetonitrile (0.5 mL) and stirred at room temperature for 18 hours. The mixture was then taken up in CH₂Cl₂ (3 mL) and the solution was washed with water (x3) and brine (x1) and dried over MgSO₄. The solvent was removed under reduced pressure to give crude target material as a colourless oil. Following flash column chromatography (SiO₂ pentane) pure product 153 was isolated as a colourless oil (19 mg, 0.12 mmol, 81%).

$R_f$: 0.55 (pentane).

$^1H$ NMR (400 MHz, CDCl₃): $\delta$ 7.23–7.17 (m, 4H), 6.53 (dd, $J = 17.2$, 10.4 Hz, 1H), 5.99 (s, 1H), 5.25 (d, $J = 17.2$ Hz, 1H), 5.07 (d, 10.4 Hz, 1H), 3.64–3.45 (m, 4H) ppm.
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 138.9 (C$_q$), 134.0 (C$_q$), 133.9 (C$_q$), 133.6 (C$_q$), 128.6 (CH), 128.1 (CH), 126.6 (CH), 126.1 (CH), 126.0 (CH), 111.0 (CH$_2$), 30.7 (CH$_2$), 28.6 (CH$_2$) ppm.

IR: (thin film): $v_{\text{max}} =$ 3086, 3046, 3022, 3006, 2868, 2817, 1609, cm$^{-1}$.

LRMS: (70 eV, EI): m/z (%) : 156.1 (85, [M]$^{++}$), 155.1 (35), 141.1 (73), 28.1 (100), 115.05 (52).

HRMS: (70 eV, EI): m/z calc. for C$_{12}$H$_{12}$ [M]$^{++}$: 156.0939; found 156.0935.

Bicyclic diene 154

A solution of 3,6-dimethoxy-2-(trimethylsilyl)phenyl trifluoromethanesulfonate (148) (1.49 g, 4.16 mmol) in dry acetonitrile (2 mL) was added dropwise to a mixture of freshly prepared [3]dendralene (1.0 g, 12 mmol,), cesium fluoride (1.26 g, 8.32 mmol) and BHT (1 crystal) in dry acetonitrile (8 mL) and left to stir at room temperature. After 20 hours, the mixture was taken up in CH$_2$Cl$_2$ (20 mL) and the solution was washed with water (x3) and brine (x1) and dried over MgSO$_4$. The solvent was removed under reduced pressure to give the crude target material as a yellow solid. Following flash column chromatography (SiO$_2$ 0–10% EtOAc in hexanes) pure product 154 was isolated as a yellow solid. (199 mg, 0.920 mmol,
22% yield (67% b.r.s.m)). Recrystallisation from Et₂O/hexanes gave yellow crystals, mp. 57–59°C, which were suitable for single crystal X-ray analysis.

\[ R_f: 0.66 \text{ (90:10; hexanes:EtOAc).} \]

\[ ^1H \text{ NMR (400 MHz, CDCl}_3\text{: } \delta \text{ 6.67 (s, 2H), 6.51 (dd, } J = 17.6, 10.8 \text{ Hz, 1H), 5.95 (s, 1H), 5.30 (d, 17.6 Hz, 1H), 5.05 (d, } J = 10.8 \text{ Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.36–3.42 (m, 4H) ppm.} \]

\[ ^{13}C \text{ NMR (100 MHz, CDCl}_3\text{: } \delta \text{ 151.1 (C}_q\text{), 150.9 (C}_q\text{), 139.2 (CH), 132.6 (C}_q\text{), 125.8 (CH), 124.8 (C}_q\text{), 123.8 (C}_q\text{), 111.1 (CH}_2\text{), 106.9 (CH), 106.7 (CH), 55.6 (CH}_3\text{), 55.6 (CH}_3\text{), 25.6 (CH}_2\text{), 23.3 (CH}_2\text{) ppm.} \]

\[ IR: (KBr): v_{\text{max}} = 3085, 2994, 2935, 2896, 2831 \text{ cm}^{-1}. \]

\[ LRMS: (70 \text{ eV, ESI): m/z (%): 217.1 (100, [M+H]^{+}), 201.1 (28), 185.1 (41), 175.1 (25).} \]

\[ HRMS: (70 \text{ eV, ESI): m/z calc. for C}_{14}\text{H}_{17}\text{O}_2\text{ [M+H]}^{+}: 217.1150; \text{ found 216.1151.} \]

Bicycle 166

Semicyclic diene 124 (33 mg, 0.22 mmol) was added to a solution of DMAD (63 mg, 0.44 mmol) in toluene (1 mL) and stirred at reflux for 18 hours. After cooling to room temperature, the solvent was removed under reduced pressure to yield crude target material as a 2:1 mixture of isomers. Excess DMAD was removed
using column chromatography (SiO$_2$ 10–25% EtOAc in hexanes) to yield pure target material as a 2:1 mixture of isomers (55.1 mg, 187 mmol, 85%) The mixture was taken on without any further purification.

$R_{f}$: 0.12 (85:15; hexanes:EtOAc).

**Bicycle 167**

Diester 166 (64 mg, 0.22 mmol) and DDQ (50 mg, 0.22 mmol) were combined in toluene (1 mL) and stirred at reflux for 18 hours. The mixture was allowed to cool to room temperature and the solvent was removed under reduced pressure to give the crude material as a brown sludge. Following flash column chromatography (Al$_2$O$_3$ 20 % EtOAc in hexanes) mostly pure target material was isolated as a slightly orange solid. The solid was washed with EtOAc to yield pure target material 167 as a yellow solid (37 mg, 0.12 mmol, 56% over 2 steps) Recrystallisation from methanol gave yellow crystals mp 56–57 °C, which were suitable for single crystal X-ray analysis.

$R_{f}$: 0.10 (80:20; hexanes:EtOAc).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.76 (d, J = 8 Hz, 1H), 7.18 (d, J = 8 Hz, 1H), 3.94 (s, 3H), 3.86 (s, 3H), 2.94–2.76 (m, 5H), 2.23 (s, 3H), 2.15 (m, 1H), 1.75 (m, 1H) ppm.
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 210.0 (C$_q$), 169.8 (C$_q$), 166.1 (C$_q$), 141.8 (C$_q$), 135.8 (C$_q$), 132.5 (C$_q$), 129.7 (C$_q$), 127.4 (C$_q$), 125.8 (C$_q$), 52.7 (CH$_3$), 52.4 (CH$_3$), 47.0 (CH), 29.2 (CH$_2$), 28.3 (CH$_3$), 27.5 (CH$_2$), 24.5 (CH$_2$) ppm.

IR: (KBr): $v_{\text{max}} = 2954, 1733, 1704, 1594$ cm$^{-1}$.

LRMS: (70 eV, ESI): m/z (%): 313.4 (100, [M+Na]$^+$), 291.4 (5), 259.4 (8).

HRMS: (70 eV, ESI): m/z calc. for C$_{16}$H$_{18}$O$_5$Na [M+Na]$^+$: 313.1052; found 313.1053.

**Bicycle 111**

Semicyclic diene 127 (69 mg, 0.31 mmol) and DMAD (45 mg, 0.32 mmol) were combined in THF (0.5 mL) and heated to reflux. After stirring for 18 hours, the solution was allowed to cool to room temperature. The solvent and excess DMAD were removed under reduced pressure to give crude tetraester 111 as an orange solid. The mixture was taken on without any further purification.

**Bicycle 168**

Crude tetraester 111 (80 mg, 0.22 mmol) and DDQ (102 mg, 0.450 mmol) were combined in toluene (1 mL) and stirred at reflux for 18 hours. The mixture was allowed to cool to room temperature before the solvent was removed under
reduced pressure to give the crude material as a brown sludge. Following flash column chromatography (Al_{2}O_{3} 20 % EtOAc in hexanes) pure target material 168 was isolated as a yellow solid (50 mg, 0.19 mmol, 62% over two steps). All spectroscopic data matched with that quoted in the literature.\(^{[76]}\)

**Tricycles 174 and 175**

METHOD A: Semicyclic diene 136 (40 mg, 0.22 mmol), methyl vinyl ketone (78 mg, 93 µL, 1.1 mmol) and hydroquinone (1 crystal) were combined in CH_{2}Cl_{2} (1 mL) and subject to 19 kbar for 22 hours. The solvent and excess MVK were removed under reduced pressure to give crude product as a 10:1 mixture of isomers. Following flash column chromatography (SiO_{2} 10–25% gradient, EtOAc in hexanes) pure products 174 (42 mg, 0.17 mmol 77%) and 175 (3.5 mg, 0.014 mmol, 7.6%) were isolated as white solids as the major and minor products respectively. Recrystallisation from EtOAc/hexane gave white crystals, mp 107–109 °C and mp 93–94 °C, which were suitable for single crystal X-ray analysis.

METHOD B: A solution of methyl vinyl ketone (17 mg, 20 µL, 0.24 mmol) and freshly distilled BF_{3}•Et_{2}O (34 mg, 30 µL, 0.24 mmol) in dry CH_{2}Cl_{2} (0.75 mL) was stirred at –20 °C for 30 minutes under N_{2}. A solution of semicyclic diene 136 (40 mg, 0.22 mmol) in dry CH_{2}Cl_{2} (0.75 mL) was then added dropwise and the solution
left to stir at -20 °C for 30 minutes. Triethylamine (35 µL) was added and the solution was poured into ice water (10 ml) and ether (5 mL). The organic layer was collected and washed with brine (x2) and dried over MgSO₄. The solvent was removed under reduced pressure to give crude product as a 4:1 mixture of isomers. Following flash column chromatography (SiO₂:10–25% gradient EtOAc in hexanes) pure products 174 (43 mg, 0.173 mmol, 75%) and 175 (9.8 mg, 0.02 mmol, 10%) were isolated as yellow solids as the major and minor products respectively. Recrystallisation from EtOAc/hexane gave white crystals mp 107–109 °C, and mp 93–94 °C, which were suitable for single crystal X-ray analysis.

**Tricycle 174**

\[
\text{Rf: } 0.42 \text{ (80:20; hexanes:EtOAc).}
\]

**¹H NMR** (400 MHz, CDCl₃): δ 5.41 (d, J=5.6 Hz, 1H), 2.79–2.63 (m, 3H), 2.36 (m, 1H), 2.35 (s, 3H), 2.30–2.26 (m, 2H), 2.09–1.83 (m, 8H), 1.78–1.63 (m, 2H), 1.48 (dtd, J = 13.4, 11.6, 5.6 Hz, 1H), 1.09 (td, J = 12.4, 4.8 Hz, 1H) ppm.

**¹³C NMR** (100 MHz, CDCl₃): δ 212.5 (Cₛ), 211.6 (Cₛ), 139.8 (Cₛ), 119.4 (CH), 51.2 (CH), 49.7 (CH), 42.9 (CH), 42.0 (CH₂), 38.6 (CH₂), 34.3 (CH), 30.4 (CH₂), 28.8 (CH₃), 28.0 (CH₂), 24.7 (CH₂), 22.5 (CH₂), 18.4 (CH₂) ppm.

**IR: (KBr): v max = 2939, 2850, 1692 cm⁻¹.**
LRMS: (70 eV, EI): m/z (%): 246.2 (60, [M]+), 203.1 (80), 185.1 (100), 97.1 (83).

HRMS: (70 eV, EI): m/z calc. for C_{16}H_{22}O_{2} [M]+: 246.1620; found 246.1623.

Tricycle 176

![Chemical reaction diagram]

A solution of methyl vinyl ketone (24 mg, 29 µL, 0.34 mmol) and freshly distilled BF₃·Et₂O (49 mg, 43 µL, 0.34 mmol) in dry CH₂Cl₂ (1 mL) was stirred at −20 °C for 30 minutes under N₂. A solution of semicyclic diene 138 (50 mg, 0.31 mmol) in dry CH₂Cl₂ (0.5 mL) was then added dropwise and the solution left to stir at −20 °C for 30 minutes. Triethylamine (35 µL, ) was added and the solution was poured into ice water (10 mL) and ether (5 mL). The organic layer was washed with brine (x2) and dried over MgSO₄. The solvent was removed under reduced pressure to give crude product as a 4:1 mixture of isomers. Following flash column chromatography (10–20% gradient EtOAc in hexanes) pure tricycle 176 was isolated as a white solid. (36 mg, 0.15 mmol, 50%) Recrystallisation from EtOAc/hexane gave white crystals mp 87–90 °C, which were suitable for single crystal X-ray analysis.

Rᵋ: 0.19 (80:20; hexanes:EtOAc).

¹H NMR (400 MHz, CDCl₃): δ 5.50 (d, J = 4.5 Hz, 1H), 2.76 (ddd, J = 12.6, 5.7, 2.7 Hz, 1H), 2.51–2.29 (m, 5H), 2.25–2.17 (m, 2H), 2.15 (s, 3H), 2.11–1.68 (m, 5H), 1.56 (ddt, J = 18.5, 12.9, 5.5 Hz, 1H), 1.39–1.13 (m, 2H) ppm.
$^{13}$C NMR (100 MHz, CDCl$_3$): 220.1 (C$_q$), 210.3 (C$_q$), 135.6 (C$_q$), 121.9 (CH), 51.3 (CH), 48.6 (CH), 37.7 (CH), 37.4 (CH$_2$), 37.4 (CH$_2$), 36.9 (CH), 28.7 (CH$_3$), 26.5 (CH$_2$), 24.5 (CH$_3$), 23.9 (CH$_2$), 19.0 (CH$_2$) ppm.

**IR:** (KBr): $v_{\text{max}} = 2912, 2879, 2828, 1731, 1705$ cm$^{-1}$.

**LRMS:** (70 eV, EI): m/z (%): 232 (35 [M]$^{\cdot\cdot}$), 189 (100), 171 (52), 145 (33), 91 (52).

**HRMS:** (70 eV, EI): m/z calc. for C$_{15}$H$_{20}$O$_2$ [M]$^{\cdot\cdot}$: 232.1463: found 232.1461.

**Tricycle 177**

![Chemical Structure](image)

A solution of semicyclic diene 153 (40 mg, 0.25 mmol) and MVK (87 mg, 102 µL, 1.25 mmol) were combined in CH$_2$Cl$_2$ (2 mL) and subject to 19 kbar for 20 hours. The solvent and excess MVK was removed under reduced pressure to give crude target material as a yellow oil. Following flash column chromatography (0–10% gradient EtOAc in hexanes) pure product 177 was isolated as a white solid (46.4 mg, 0.21 mmol, 82%). Mp 86–89 °C.

**Rf:** 0.43 (90:10; hexanes:EtOAc).

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.25–6.99 (m, 4H), 5.64 (s, 1H), 3.70–3.44 (m, 1H), 3.38 (d, J = 17.4 Hz, 1H), 2.99–2.84 (m, 2H), 2.83–2.64 (m, 1H), 2.57–2.43 (m, 1H), 2.23 (s, 3H), 2.22–2.03 (m, 3H), 1.85–1.65 (m, 1H) ppm.
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 210.8 (C$_q$), 136.3 (C$_q$), 136.0 (C$_q$), 135.7 (C$_q$), 129.3 (CH), 128.5 (CH), 126.08 (CH), 125.7 (CH), 120.2 (CH), 119.0 (C$_q$), 51.0 (CH), 38.7 (CH$_2$), 35.7 (CH$_2$), 35.4 (CH$_3$), 24.7 (CH$_2$), 18.9 (CH$_2$) ppm.

IR: (KBr): $v_{\text{max}}$ = 2912, 2879, 2828, 1731 cm$^{-1}$.

LRMS: (70 eV, EI): m/z (%): 226 (59, [M]$^+$), 183 (100), 165 (48), 141 (97) 115 (42).

HRMS: (70 eV, EI): m/z calc. for C$_{16}$H$_{18}$O [M]$^+$: 226.1358: found 226.1354.

Tricycle 178

Semicyclic diene 136 (50 mg, 0.28 mmol) was added to a solution of DMAD (79 mg, 47 µL, 0.56 mmol) in toluene (1 mL) and stirred at reflux for 18 hours. After cooling to room temperature, the solvent was removed under reduced pressure to yield crude target material as a 3:1 mixture of isomers. Excess DMAD was removed using column chromatography (SiO$_2$ 10–25% EtOAc in hexanes) to yield pure target material 178 as a 3:1 mixture of isomers. (74.9 mg, 0.235 mmol, 84%) The mixture was taken on without any further purification.

Rf: 0.13 (15% EtOAc in hexanes).
Tricycle 179

Diester 178 (55 mg, 0.17 mmol) and DDQ (40 mg, 0.17 mmol) were combined in toluene (1 mL) and heated at reflux for 18 hours. After cooling to room temperature, the solvent was removed under reduced pressure to give crude target material as a brown sludge. Following flash column chromatography (Al₂O₃ 20 % EtOAc in hexanes) mostly pure target material 179 was isolated as an orange solid. The solid was washed with minimal amounts of EtOAc to yield pure target material 179 as a yellow solid. (28 mg, 0.089 mmol, 52%) Recrystallisation from methanol gave yellow crystals, mp 154–157 °C, which were suitable for single crystal X-ray analysis.

Rₚ: 0.12 (80:20; hexanes:EtOAc).

¹H NMR (400 MHz, CDCl₃): δ 7.75 (d, J = 8 Hz, 1H), 7.16 (d, J = 8 Hz, 1H), 3.97 (s, 3H), 3.86 (s, 3H), 3.11–2.81 (m, 3H), 2.75 (dd, J = 17.2, 11.6 Hz, 1H), 2.55–2.32 (m, 3H), 2.26–2.00 (m, 2H), 1.87 (qt, J = 11.7, 4.2 Hz, 1H), 1.74 (qt, J = 13.2, 4.2 Hz, 1H), 1.55 (qd, J = 13.2, 3.6 Hz, 1H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ 210.3 (Cₘ), 210.3 (Cₘ), 169.7 (Cₘ), 166.1 (Cₘ), 141.1 (Cₘ), 136.1 (Cₘ), 132.8 (Cₘ), 129.3 (CH), 127.3 (CH), 125.2 (Cₘ), 52.7 (CH₃), 52.4 (CH₃), 50.1 (CH), 41.8 (CH₃), 39.8 (CH), 32.4 (CH₂), 26.0 (CH₂), 25.5 (CH₂) ppm.

IR: (KBr): νmax = 2951, 1730, 1714, 1595, 1580 cm⁻¹.
LRMS: (70 eV, ESI): m/z (%): 339.4 (100 [M+Na]+), 337.3 (10), 317.5 (8).

HRMS: (70 eV, ESI): m/z calc. for C_{18}H_{20}O_5Na [M+Na]^+: 339.1208; found 339.1208.

Tricycle 180

Semicyclic diene 138 (40 mg, 0.24 mmol) was added to a solution of DMAD (70 mg, 60 µL, 0.49 mmol) in toluene (1.5 mL) and stirred at reflux for 18 hours. After cooling to room temperature, the solvent was removed under reduced pressure to yield crude target as a yellow oil in a 2:1 mixture of isomers. Excess DMAD was removed using column chromatography (SiO_2 10–25% EtOAc in hexanes) to yield pure target material 180 (72 mg, 0.24 mmol 100%) as a 3:1 mixture of isomers. The mixture was taken on without any further purification.

Rf: 0.22 (15% EtOAc in hexanes).

Tricycle 181

Crude diester 180 (72 mg, 0.24 mmol) and DDQ (54 mg, 0.24 mmol,) were combined in toluene (1.5 mL) and stirred at reflux for 20 hours. After cooling to room temperature, the solvent was removed under reduced pressure to give crude
target material as a brown sludge. Following flash column chromatography (Al₂O₃ 30% EtOAc in hexanes) pure product 181 was isolated as a yellow solid (57 mg, 0.19 mmol, 79% over 2 steps). Mp 131–135 °C.

$R_f$: 0.21 (70:30; hexanes:EtOAc).

$^1$H NMR (400 MHz, CDCl₃): $\delta$ 7.80 (d, $J = 7.9$ Hz, 1H), 7.23 (d, $J = 7.9$ Hz 1H), 3.97 (s, 3H), 3.87 (s, 3H), 3.27–3.06 (qd, $J = 16$, 4.8 Hz, 1H), 2.98–2.79 (m, 3H), 2.77–2.44 (m, 2H), 2.41–2.09 (m, 3H), 1.75–1.62 (m, 1H) ppm.

$^{13}$C NMR (100 MHz, CDCl₃): $\delta$ 220.0 (C$_q$), 210.3 (C$_q$), 160.4 (C$_q$), 135.5 (C$_q$), 121.9 (C$_q$), 115.4 (C$_q$), 51.3 (CH$_3$), 48.6 (CH$_3$), 37.7 (CH), 37.4 (CH$_2$), 36.9 (CH$_2$), 30.5 (CH), 28.7 (CH$_2$), 26.5 (CH$_2$), 24.5 (CH$_2$), 23.9 (CH$_2$), 19.0 (CH$_2$) ppm.

IR: (KBr): $v_{max} = 2958, 1736, 1720, 1591$, cm$^{-1}$.

**Tricycle 182**

Semicyclic diene 153 (40 mg, 0.25 mmol) was added to a solution of DMAD (73 mg, 61 µL, 0.50 mmol) in toluene (2 mL) and stirred at reflux for 18 hours. After cooling to room temperature, the solvent was removed under reduced pressure to yield crude target as a yellow oil. Excess DMAD was removed using column chromatography (SiO$_2$: 10–25% EtOAc in hexanes) to yield pure target material 182.
(75 mg, 0.25 mmol 100%) as a yellow oil. The mixture was taken on without any further purification.

*RF:* 0.19 (15% EtOAc in hexanes).

**Tricycle 182**

![Chemical structure of tricycle 182](image)

Crude diester 182 (75 mg, 0.25 mmol) and DDQ (170 mg, 0.750 mmol) were combined in toluene (1.5 mL) and stirred at reflux for 20 hours. The mixture was allowed to cool to room temperature before the solvent was removed under reduced pressure to give crude target material as a brown sludge. Following flash column chromatography (Al₂O₃ 20% EtOAc in hexanes) mostly pure product was isolated as an orange solid. The solid was washed with methanol to yield target material 183 as an orange solid (37 mg, 0.12 mmol, 50 % yield over two steps). Recrystallisation from methanol gave yellow crystals, mp 128–130 °C, which were suitable for single crystal X-ray analysis.

*RF:* 0.43 (80:20; hexanes:EtOAc).

1'H NMR (400 MHz, CDCl₃): δ 8.44 (s, 2H), 8.10 (d, J = 9.2 Hz, 1H), 8.08–8.00 (m, 2H), 7.95 (d, J = 9.2 Hz, 1H), 7.60–7.52 (m, 2H), 4.16 (s, 3H), 3.99 (s, 3H) ppm.
^13C NMR (100 MHz, CDCl3): δ 174.2 (Cq), 166.3 (Cq), 133.0 (Cq), 132.4 (Cq), 132.0 (Cq), 130.0 (CH), 128.8 (CH), 128.0 (CH), 127.1 (CH), 127.0 (Cq), 126.7 (CH), 126.4 (CH), 126.0 (Cq), 125.9 (CH), 124.2 (Cq), 123.5 (CH), 53.0 (CH₃), 52.7 (CH₃) ppm.

IR: (KBr): νₘₐₓ = 2947, 1728, 1714, 1615 cm⁻¹.

LRMS: (70 eV, ESI): m/z (%): 317.3 (100 [M+Na]⁺), 185.0 (95), 163.3 (90).

HRMS: (70 eV, ESI): m/z calc. for C₁₈H₁₄O₄Na [M+Na]⁺: 317.0790; found 317.0790.

Tricycle 184

Semicyclic diene 139 (60 mg, 0.31 mmol) was added to a solution of DMAD (65 mg, 55 µL 0.46 mmol) in toluene (1 mL) and stirred at reflux for 18 hours. After cooling to room temperature, the solvent was removed under reduced pressure to yield crude target material as a yellow oil. Excess DMAD was removed using column chromatography (SiO₂ 10–25% EtOAc in hexanes) to yield pure target material 184 (103 mg, 0.31 mmol 100%) as a yellow oil in a 3:1 mixture of isomers. The mixture was taken on without any further purification.

Rf: 0.11 (15% EtOAc in hexanes).
Tricycle 185

Crude diester 184 (103 mg, 0.310 mmol) and DDQ (140 mg, 0.620 mmol) were combined in toluene (1 mL) and heated at reflux for 20 hours. The mixture was allowed to cool to room temperature before the solvent was removed under reduced pressure to give crude target material 185 as a brown sludge. Following flash column chromatography (Al₂O₃ 20% EtOAc in hexanes) pure product 185 was isolated as a yellow solid. (51.2 mg, 0.155 mmol, 50 % yield over two steps). Recrystallisation from methanol gave yellow crystals, mp 120–123 °C, which were suitable for single crystal X-ray analysis.

R_f: 0.24 (80:20 hexanes:EtOAc)

1H NMR (400 MHz, CDCl₃): δ 7.78 (d, J = 8.1 Hz, 1H), 7.21 (d, J = 8.1 Hz, 1H), 3.93 (s, 3H), 3.88–3.85 (m, 3H), 3.18 (d, J = 17.2 Hz, 1H), 3.06 (dd, J = 17.9, 6.1 Hz, 1H), 2.69 (dd, J = 17.7, 3.3 Hz, 1H), 2.65–2.56 (m, 1H), 2.46–2.30 (m, 2H), 2.10–1.93 (m 2H), 1.86–1.44 (m, 3H), 1.15 (s, 3H) ppm.

13C NMR (100 MHz, CDCl₃): δ 214.0 (C₆), 169.7 (C₅), 166.1 (C₆), 140.0 (C₅), 135.9 (C₆), 130.7 (C₆), 130.2 (CH), 127.4 (CH), 125.4 (C₅), 52.7 (CH₃), 52.4 (CH₂), 47.8 (C₅), 41.0 (CH₂), 36.9 (CH₂), 32.6 (CH₃), 31.7 (CH₂), 27.5 (CH₂), 24.7 (CH₂), 21.1 (CH₂) ppm.

IR: (KBr): v_max = 2965, 1734, 1714, 1617 cm⁻¹.
Tricycles 196 and 197

A solution of diene 125 (50.0 mg, 0.330 mmol) and cyclohexenone (160 mg, 160 µL, 1.66 mmol) in CH₂Cl₂ (1 mL) was subject to 19 kbar for 3 days. The solvent was removed under reduced pressure to give crude product as a 2:1 mixture of isomers. Following flash column chromatography (SiO₂ 10–30% gradient EtOAc in hexanes) tricycle 196 (52.5 mg, 0.213 mmol, 65%) and tricycle 197 (13.8 mg, 0.056 mmol, 17%) were isolated as the major and minor isomers respectively as yellow solids. Recrystallisation from EtOAc gave white crystals 92–94 °C, and 87–88 °C, which were suitable for single crystal X-ray analysis.

Tricycle 196

\[ R_f: 0.21 \ (85:15 \ \text{hexanes}:\text{EtOAc}). \]

\[^1H\ \text{NMR} \ (400 \ \text{MHz, CDCl}_3): \ \delta \ 5.23 \ (dd, \ J = 5.2, 2.4 \ \text{Hz, 1H}), \ 2.89 \ (t, \ J = 4.8 \ \text{Hz, 1H}), \ 2.74 \ (t, \ J = 2.8 \ \text{Hz, 1H}), \ 2.45–2.33 \ (m, 3H), \ 2.25–2.19 \ (m, 3H), \ 2.17–2.16 \ (m, 1H), \ 2.15 \ (s, 3H), \ 2.12–2.08 \ (m, 1H), \ 2.00–1.91 \ (m, 4H), \ 1.86–1.75 \ (m, 3H), \ 1.67–1.65 \ (m, 1H) \ \text{ppm.} \]
**13C NMR** (100 MHz, CDCl₃): δ 211.9 (C₄), 211.9 (C₃), 136.4 (C₃), 117.8 (CH), 53.3 (CH), 47.4 (CH), 43.6 (CH₂), 39.8 (CH), 35.0 (CH), 30.2 (CH₂), 30.0 (CH₂), 28.0 (CH₃), 27.4 (CH₃), 26.6 (CH₂), 26.4 (CH₂), 25.3 (CH₂) ppm.

**IR:** (KBr): νₘₐₓ = 2920, 2895, 2881, 1707, 1701, cm⁻¹;

**LRMS:** (70 eV, EI): m/z (%): 246 (100, [M]⁺), 203 (85), 188 (70), 143 (27), 117 (25), 91 (47).

**HRMS:** (70 eV, EI): m/z calc for C₁₆H₂₂O₂ [M]⁺: 246.1620; found 246.1619.

Tricycle 197

![Tricycle 197](image)

**Rf:** 0.21 (85:15 hexanes:EtOAc)

**1H NMR** (400 MHz, CDCl₃): δ 5.31 (s, 1H), 2.91 (t, J = 4.7 Hz, 1H), 2.49–2.18 (m, 7H), 2.13 (s, 3H), 2.11–1.87 (m, 5H), 1.87–1.77 (m, 1H), 1.72–1.60 (m, 3H), 1.47 (m, 1H) ppm.

**13C NMR** (100 MHz, CDCl₃): δ 211.6 (C₄), 211.3 (C₃), 135.5 (C₃), 118.6 (CH), 53.2 (CH), 52.2 (CH), 43.4 (CH₂), 39.6 (CH), 38.5 (CH), 33.5 (CH₂), 30.4 (CH₂), 29.8 (CH₃), 28.3 (CH₃), 27.4 (CH₂), 26.5 (CH₂), 25.2 (CH₂) ppm.

**IR:** (KBr): νₘₐₓ = 2910, 2853, 1708, 1697, cm⁻¹:
**LRMS**: (70 eV, El): m/z (%): 246 (100, [M]+•), 230 (43), 210 (35), 203 (56), 185 (60), 91 (77).

**HRMS**: (70 eV, El) m/z calc. for C_{16}H_{22}O_2 [M]+•: 246.1620; found 246.1616.

**Tricycle 198**

A solution of diene 127 (70 mg, 0.30 mmol) and cyclohexenone (151 mg, 152 µL, 1.50 mmol) in CH_2Cl_2 (1.5 mL) was subject to 19 kbar for 72 hours. The solvent was removed under reduced pressure to give crude product 198 as a yellow oil. Following flash column chromatography (SiO_2 10–30% gradient EtOAc in hexanes, pure product 198 was isolated as a colourless oil. (69 mg, 0.22 mmol, 73%)

**Rf**: 0.18 (80:20 hexanes:EtOAc)

**_H NMR** (400 MHz, CDCl_3): δ 5.46 (s, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.17 (s, 2H), 2.99–2.95 (m, 2H), 2.52–2.50 (m, 1H), 2.41–2.32 (m, 3H), 2.25–2.21 (m, 1H), 2.02–1.95 (m, 5H), 1.75–1.63 (m, 1H) ppm.

**_C NMR** (100 MHz, CDCl_3): δ 211.1 (C=), 168.5 (C=), 168.3 (C=), 135.4 (C=), 133.5 (C=), 130.6 (C=), 120.0 (CH), 52.1 (CH_3), 52.1 (CH_3), 52.0 (CH), 43.1 (CH_2), 39.4 (CH), 35.2 (CH), 32.0 (CH_3), 29.7 (CH_2), 28.5 (CH_2), 26.7 (CH_2), 24.9 (CH_2) ppm.

**IR**: (thin film): v_{max} 2949, 1738, 1714 cm^{-1}.
Tricycle 204

2-(trimethylsilyl)phenyl trifluoromethanesulfonate (147) (178 mg, 150 µL, 0.590 mmol) was added dropwise to a solution of semicyclic diene 125 (50 mg, 0.33 mmol) and CsF (125 mg, 0.830 mmol) in acetonitrile (0.5 mL) and stirred at 40 °C for 18 hours. The mixture was then taken up in CH₂Cl₂ (3 mL) and the solution was washed with water (x3) and brine (x1) and dried over MgSO₄. The solvent was removed under reduced pressure to give crude product as a colourless oil as a complex mixture of isomers. Following flash column chromatography (SiO₂ 10% EtOAc in hexanes) tricycle 204 was isolated as a white solid (28 mg, 0.12 mmol, 38%) Recrystallisation from MeOH gave white crystals 64–66 °C which were suitable for single crystal X-ray analysis.

Rf: 0.43 (90:10; hexanes:EtOAc).

¹H NMR (400 MHz, CDCl₃): δ 7.25–6.99 (m, 4H), 5.64 (s, 1H), 3.70–3.44 (m, 1H), 3.38 (d, J = 17.4 Hz, 1H), 2.99–2.84 (m, 2H), 2.83–2.64 (m, 1H), 2.57–2.43 (m, 1H), 2.23 (s, 3H), 2.22–2.03 (m, 3H), 1.85–1.65 (m, 1H) ppm.

¹³C NMR (100 MHz, CDCl₃): δ 210.8 (Cₛ), 136.3 (Cₛ), 136.0 (Cₛ), 135.7 (Cₛ), 129.3 (CH), 128.5 (CH), 126.08 (CH), 125.7 (CH), 120.2 (CH), 119.0 (Cₛ), 51.0 (CH), 38.7 (CH₂), 35.7 (CH₂), 35.4 (CH₃), 24.7 (CH₂), 18.9 (CH₂) ppm.
IR: (KBr): $v_{\text{max}} = 2912, 2879, 2828, 1731 \text{ cm}^{-1}$.

LRMS: (70 eV, EI): m/z (%): 226 (59, [M]+), 183 (100), 165 (48), 141 (97) 115 (42).

HRMS: (70 eV, EI): m/z calc. for C$_{16}$H$_{18}$O [M]+: 226.1358: found 226.1354.

Tetracycle 206

A solution of semicyclic diene 153 (40 mg, 0.25 mmol) and cyclohexenone (123 mg, 127 µL, 1.25 mmol) in CH$_2$Cl$_2$ (1 mL) was subject to 19 kbar for 72 hours. The solvent was removed under reduced pressure to yield crude product as a yellow oil. Following flash column chromatography (SiO$_2$ 0%-10% gradient EtOAc in hexanes) pure product 206 was isolated as a white solid (54.3 mg, 0.21 mmol, 84%). Recrystallisation from EtOAc gave white crystals, mp. 91–94 °C, which were suitable for single crystal X-ray analysis.

$R_f$: 0.37 (90:10; hexanes:EtOAc).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.19–7.01 (m, 4H), 5.43 (s, 1H), 3.73–3.63 (m, 1H), 3.46–3.30 (m, 2H), 2.95 (t, $J = 4.2$ Hz, 1H), 2.65–2.55 (m, 1H), 2.50 (dd, $J = 14.1, 4.6$ Hz, 1H), 2.47–2.34 (m, 1H), 2.34–2.25 (m, 2H), 2.11–1.92 (m, 5H), 1.72 (td, $J = 11.0, 3.9$ Hz, 1H) ppm.
\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 211.4 (C\(_q\)), 139.8 (C\(_q\)), 136.9 (C\(_q\)), 134.8 (C\(_q\)), 127.2 (CH), 126.9 (CH), 126.0 (CH), 125.5 (CH), 117.4 (CH), 53.1 (CH), 43.1 (CH), 39.5 (CH\(_2\)), 38.8 (CH\(_2\)), 36.1 (CH), 33.0 (CH\(_2\)), 29.9 (CH\(_2\)), 27.3 (CH\(_2\)), 24.4 (CH\(_2\)) ppm.

**IR:** (KBr): \(v_{\text{max}} = 2959, 2926, 2858, 1720\) cm\(^{-1}\).

**LRMS:** (70 eV, EI): m/z (%): 252 (100, [M]\(^+\)), 234 (48), 207 (65), 179 (95), 141 (52), 97 (63).

**HRMS:** (70 eV, EI): m/z calc. for \(\text{C}_{18}\text{H}_{20}\text{O} [M]^{+}\): 252.1514; found 252.1514.

**Tetracycle 207**

A solution of semicyclic diene 136 (100 mg, 0.567 mmol) and cyclohexenone (274 mg, 275 µL, 2.85 mmol) in CH\(_2\)Cl\(_2\) (3 mL) was subject to 19 kbar for 72 hours. The solvent was removed under reduced pressure to yield crude product as a yellow oil. Following flash column chromatography (SiO\(_2\) 5%–20% gradient, EtOAc in hexanes) pure product 207 was isolated as a white solid (95 mg, 0.38 mmol, 67%). Recrystallisation from hot EtOAc gave white crystals, mp 155–158 °C, which were suitable for single crystal X-ray analysis.

**R:** 0.19 (85:15; hexanes:EtOAc).
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.24 (br s, 1H), 2.95 (t, $J$ = 4.8 Hz, 1H), 2.68 (t, $J$ = 4.0 Hz, 1H), 2.54–2.14 (m, 8H), 2.16–1.85 (m, 9H), 1.81–1.60 (m, 4H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 213.6 (C$_q$), 212.1 (C$_q$), 136.7 (C$_q$), 118.1 (CH), 52.9 (CH), 49.7 (CH), 43.7 (CH$_2$), 41.8 (CH$_2$), 40.4 (CH), 39.3 (CH), 35.7 (CH$_2$), 34.0 (CH), 30.3 (CH$_2$), 30.0 (CH$_2$), 26.3 (CH$_2$), 26.0 (CH$_2$), 25.5 (CH$_2$), 22.4 (CH$_2$) ppm.

IR: (KBr): $v_{\text{max}}$ = 2957, 2907, 2865, 1708, 1706 cm$^{-1}$.

LRMS: (70 eV, EI): m/z (%): 272 (100, [M]$^{+•}$), 254 (65), 236 (23), 183 (31), 91 (38).

HRMS: (70 eV, EI): m/z calc. for C$_{18}$H$_{24}$O$_2$ [M]$^{+•}$: 272.1776; found 272.1778.

Tetracycle 208

A solution of semicyclic diene 136 (60 mg, 0.31 mmol) and cyclohexenone (125 mg, 127 $\mu$L 1.55 mmol) in CH$_2$Cl$_2$ (3 mL) was subject to 19 kbar for 72 hours. The solvent was removed under reduced pressure to give crude product as a yellow oil. Following flash column chromatography (SiO$_2$ 5%–20% gradient, EtOAc in hexanes) pure product 208 was isolated as a white solid (43 mg, 0.17 mmol, 54%). Recrystallisation from EtOAc gave white crystals, mp 127–129 °C, which were suitable for single crystal X-ray analysis.

Rf: 0.27 (15% EtOAc in hexanes).
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.24 (br s, 1H), 2.71 (t, $J = 3.6$ Hz, 1H), 2.48 (t, $J = 6.9$ Hz, 1H), 2.44 – 2.26 (m, 5H), 2.26 – 2.14 (m, 3H), 2.14 – 2.02 (m, 2H), 2.02 – 1.82 (m, 6H), 1.83 – 1.63 (m, 3H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 218.4 (C$_3$), 213.1 (C$_4$), 137.6 (C$_4$), 118.3 (CH), 50.7 (CH), 49.8 (CH), 41.9 (CH$_2$), 40.2 (CH), 36.7 (CH$_2$), 35.6 (CH$_2$), 34.5 (CH), 31.9 (CH), 30.3 (CH$_2$), 26.9 (CH$_2$), 26.5 (CH$_2$), 25.7 (CH$_2$), 22.4 (CH$_2$) ppm.

IR: (KBr): $\nu_{max} =$ 2920, 2876, 2848, 1732, 1697, cm$^{-1}$.

LRMS: (70 eV, EI): m/z (%): 258 (100 [M]+•), 240 (52), 176 (70), 141 (26) 117 (26).

HRMS: (70 eV, EI): m/z calc. for C$_{17}$H$_{22}$O$_2$ [M]+•: 258.1620; found 258.1626.

**Tetracycle 209**

A solution of semicyclic diene 138 (100 mg, 0.616 mmol) and cyclohexenone (290 mg, 292 $\mu$L, 3.10 mmol) in CH$_2$Cl$_2$ (3 mL) was subject to 19 kbar for 72 hours. The solvent was removed under reduced pressure to yield crude product as a yellow oil. Following flash column chromatography (SiO$_2$ 5%-20% gradient EtOAc in hexanes) pure product 209 was isolated as a white solid (120 mg, 0.464 mmol,
Recrystallisation from EtOAc gave white crystals, mp 105–107 °C, which were suitable for single crystal X-ray analysis.

\[ R_f: 0.13 \, (85:15; \text{hexanes:EtOAc}). \]

\[ ^1H \text{ NMR} \, (400 \, \text{MHz, CDCl}_3): \delta \, 5.31 \, (\text{br s, 1H}), \, 2.91 \, (t, J = 4.8 \, \text{Hz, 1H}), \, 2.54 \, (m, 1H), \, 2.41–2.15 \, (m, 8H), \, 2.08–1.85 \, (m, 6H), \, 1.81–1.63 \, (m, 5H) \, \text{ppm.} \]

\[ ^{13}C \text{ NMR} \, (100 \, \text{MHz, CDCl}_3): \delta \, 220.0 \, (C\equiv), \, 212.0 \, (C\equiv), \, 135.5 \, (C\equiv), \, 119.1 \, (CH), \, 53.4 \, (CH), \, 49.5 \, (CH_2), \, 43.6 \, (CH), \, 39.9 \, (CH), \, 35.5 \, (CH_2), \, 35.3 \, (CH), \, 35.0 \, (CH), \, 34.8 \, (CH_2), \, 29.9 \, (CH_2), \, 26.5 \, (CH_2), \, 26.0 \, (CH_2), \, 25.4 \, (CH_2), \, 23.5 \, (CH_2) \, \text{ppm.} \]

\[ IR: \, (\text{KBr}): \, \nu_{\text{max}} = 2939, \, 2915, \, 2893, \, 2875, \, 2824, \, 1730, \, 1703 \, \text{cm}^{-1}. \]

\[ LRMS: \, (70 \, \text{eV, EI}): \, m/z \, (\%): \, 258 \, (100, [M]^+), \, 240 \, (26), \, 184 \, (26), \, 162 \, (16), \, 91 \, (29). \]

\[ HRMS: \, (70 \, \text{eV, EI}): \, m/z \, \text{calc. for C}_{17}H_{22}O_2 \, [M]^+: \, 258.1620; \, \text{found} \, 258.1622. \]

Tetracycle 210

A solution of semicyclic diene 138 (80 mg, 0.49 mmol,) and cyclopentenone (203 mg, 207 µL, 2.46 mmol) in CHCl_3 (3 mL) was subject to 19 kbar for 72 hours. The solvent was removed under reduced pressure to yield crude material as a yellow oil. Following flash column chromatography (SiO_2 5%-20% gradient of EtOAc in
hexanes) pure target material 210 was isolated as a white solid (38 mg, 0.16 mmol, 32%). Recrystallisation from EtOAc gave white crystals, mp 117–119 °C, which were suitable for single crystal X-Ray analysis.

\( R_f: 0.16 \) (85:15; hexanes:EtOAc).

\( ^1H \text{ NMR} \) (400 MHz, CDCl\(_3\)): \( \delta \) 5.42 (br s, 1H), 2.48–2.31 (m, 4H), 2.30–2.10 (m, 8H), 2.04–1.92 (m, 3H), 1.85–1.75 (m, 1H), 1.74–1.64 (m, 3H) ppm.

\( ^{13}C \text{ NMR} \) (100 MHz, CDCl\(_3\)): \( \delta \) 219.8 (C\(_q\)), 218.7 (C\(_q\)), 136.7 (C\(_q\)), 119.2 (CH), 50.2 (CH), 50.0 (CH\(_2\)), 36.8 (CH), 36.7 (CH), 36.3 (CH\(_2\)), 34.7 (CH), 34.4 (CH), 32.6 (CH\(_2\)), 26.7 (CH\(_2\)), 26.4 (CH\(_2\)), 25.7 (CH\(_2\)), 25.0 (CH\(_2\)) ppm.

\( IR: (KBr): v_{\text{max}} = 2918, 2873, 2838, 1734, 1709 \text{ cm}^{-1}. \)

\( LRMS: (70 \text{ eV, EI}): m/z (\%): 244 (100, [M]+), 226 (48), 170 (39), 131 (41). \)

\( HRMS: (70 \text{ eV, EI}): m/z \text{ calc. for } C_{16}H_{20}O_2 [M]^{+*}: 244.1463; \text{ found } 244.1453. \)

**Tetracycle 212**

\[ \begin{align*}
\text{138} & \quad + \quad \text{211} \\
& \quad \text{19 kbar, CH}_2\text{Cl}_2 \\
\rightarrow & \quad \text{212}
\end{align*} \]

A solution of semicyclic diene 138 (50 mg, 0.328 mmol) and 2-methyl cyclohexenone (180 mg, 186 \( \mu \text{L}, 1.64 \text{ mmol}) in CH\(_2\)Cl\(_2\) (1.5 mL) was subject to 19 kbar for 72 hours. The solvent was removed under reduced pressure to yield crude
product as a yellow oil. Following flash column chromatography (SiO2 5%–20% gradient EtOAc in hexanes) pure product 212 was isolated as a white solid (43 mg, 0.157 mmol, 48%). Mp 101–104 °C.

Rf: 0.28 (85:15; hexanes:EtOAc).

1H NMR (400 MHz, CDCl3): δ 5.38 (s, 1H), 2.62 (dt, J = 15.0, 7.2 Hz, 1H), 2.55–2.49 (m, 1H), 2.37 (t, J = 6.9 Hz, 1H), 2.34 (dd, J = 14.1, 5.7 Hz, 1H), 2.32–2.19 (m, 4H), 2.18–2.13 (m, 1H), 2.13–2.08 (m, 1H), 2.04–1.92 (m, 4H), 1.92–1.88 (m, 1H), 1.87–1.82 (m, 2H), 1.76–1.66 (m, 3H), 1.56 (s, 3H) ppm.

13C NMR (100 MHz, CDCl3): δ 214.6 (Cq), 214.5(Cq), 135.3(Cq), 117.4(CH), 100.0(Cq), 50.7 (CH), 50.0 (CH₂), 41.7 (CH), 40.0 (CH), 37.5 (CH₂), 36.8 (CH), 34.9 (CH₃), 27.9 (CH₂), 26.7 (CH₂), 26.2 (CH₂), 25.7 (CH₂), 24.0 (CH₂), 23.7 (CH₂) ppm.

IR: (KBr): νmax = 2928, 2875, 2841, 1735, 1696 cm⁻¹.

LRMS: (70 eV, EI): m/z (%): 272 (83, [M]⁺), 229 (100), 183 (30), 147 (82), 83 (80).

HRMS: (70 eV, EI): m/z calc. for C₁₈H₂₅O₂ [M]⁺: 272.1776; found 272.1777.
5.4 Experimental Data for Chapter Four

Semicyclic diene 107

Benzoquinone (226) (3.51 g, 32.5 mmol), was added to a solution of freshly prepared [3]dendralene (3.12 g, 38.9 mmol) in THF (145 mL) and left to stir at 40 °C for 12 hours. The solvent was removed under reduced pressure to give desired diene 107 as a yellow solid. Recrystallisation from MeOH gave pure diene 107 as yellow crystals, mp 52–54 °C (5.92g, 31.5 mmol, 97%).

$^1$H NMR (400 MHz, CDCl$_3$): δ 6.69 (s, 2H), 6.32 (dd, J = 17.6, 10.8 Hz, 1H), 5.73 (s, 1H), 5.10 (d, J = 17.6 Hz, 1H), 4.99 (d, J = 10.8 Hz, 1H), 3.30 (dd, J = 11.7, 6.4 Hz, 1H), 3.24 (dd, J = 11.5, 6.1 Hz, 1H), 2.69–2.52 (m, 2H), 2.39–2.27 (m, 2H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 199.8 (C$_q$), 199.7 (C$_q$), 139.3 (CH), 139.3 (CH), 138.4 (CH), 133.3 (C$_q$), 125.8 (CH), 111.5 (CH$_2$), 46.3 (CH), 46.2 (CH), 24.8 (CH$_2$), 23.2 (CH$_2$) ppm.

IR: (KBr): $\nu_{\text{max}}$ = 3050, 2951, 2866, 2844, 1722, 1630, 1573 cm$^{-1}$.

LRMS: (70 eV, ES): m/z (%): 188.1 (100, [M]$^{+\cdot}$), 173.1 (32), 160.1 (36), 147.0 (48), 131.0 (22).

HRMS: (70 eV, ES): m/z calc. for C$_{12}$H$_{12}$O$_2$ [M]$^{+\cdot}$: 188.0837; found 188.0837.
Semicyclic diene 154

A solution of diene 107 (7.16 g, 38.0 mmol) in dry THF (45 mL), was added slowly to a slurry of NaH (3.60 g, 152 mmol) in dry THF (10 mL) at 0 °C followed by methyl iodide (16.2g, 7.33 mL, 114 mmol). The slurry was warmed to room temperature and stirred for 18 hours. The solvent and excess methyl iodide was removed under reduced pressure. The crude residue was then taken up in ether (100 mL), washed with H$_2$O (x3) and dried over MgSO$_4$. The solvent was removed under reduced pressure to yield crude product as a viscous yellow oil. Following flash column chromatography (SiO$_2$, 10% EtOAc in hexanes) pure product 154 was isolated as a yellow solid (6.10g, 28.2 mmol, 74%). Recrystallisation from Et$_2$O/hexanes gave yellow crystals, mp. 57–59°C, which were suitable for single crystal X-ray analysis. All spectroscopic data corresponded with that reported previously in this thesis.

Sodium ethoxide (496)

Mg turnings (1.25 g, 50.0 mmol) and I$_2$ (125 mg, 5.00 mmol) were placed in a 1L round-bottomed flask fitted with a reflux condenser. Absolute ethanol (85 mL) was then added to the flask and the mixture was stirred at 60 °C until colourless. Absolute ethanol (250 mL) was then added to the flask and the mixture stirred at reflux for 2 hours. The dry ethanol was then distilled directly into a 1L 3-necked
flask fitted with a reflux condenser and heated to 40 °C. Sodium metal (16 g, 0.7 mol) was then added portionwise over three hours. The reaction vessel was stirred at 40 °C until all the sodium metal had dissolved. Excess ethanol was removed under reduced pressure to give a fine white powder that was used immediately in the next step.

**Sodium enolate 427**

![Chemical formula](image)

A solution of methyl ethyl ketone (425) (63.1 g, 78.4 mL, 0.875 mol) and ethyl formate (426) (64.1 g, 69.9 mL, 0.875 mol) in dry ether (20 mL) was added slowly to suspension of freshly prepared sodium ethoxide (59.5 g, 0.875 mol) in dry ether (600 mL) at 0 °C. The suspension was warmed to room temperature and was stirred for 18 hours. The resulting precipitate was collected via vacuum assisted filtration through a cintered funnel and washed with ether (x3) before drying under high vacuum to give sodium enolate 427 as a white powder. The resulting solid was used without further purification.

**Enone 428**

![Chemical formula](image)

Bromoethane (498) (166 g, 114 mL, 1.53 mol) was added to a solution of sodium enolate 427 (103.8 g, 0.850 mol) in dry DMF (590 mL) at room temperature. The solution was then heated to 50 °C and stirred for 18 hours. The solution was cooled to room temperature and partitioned between ether (300 mL) and H₂O (300 mL). The aqueous layer was extracted with ether (x3) and the organic layers were
combined, washed with 5% LiCl solution (x3) dried over MgSO₄ and the solvent removed under reduced pressure to give crude target material as a yellow liquid. The crude material was purified by distillation (70–72 °C, 7.8 mbar) to afford ethoxy enone 428 as a pale yellow liquid (70.0g, 0.546 mol, 64% over two steps). All spectroscopic data corresponded to that quoted in the literature.[245]

**Diene 428**

Anhydrous zinc chloride (1.1 g, 8.0 mmol) and freshly distilled triethylamine (63.5 g, 87.5 mL, 0.630 mmol) were combined in a round-bottomed flask and stirred for one hour. A solution of ethoxy enone 428 (35 g, 0.27 mol) in dry benzene (98 mL) was then added to the solution followed by trimethylsilyl chloride (490) (59.3 g, 69.3 mL, 0.546 mol). The solution was heated to 40 °C and left to stir for 18 hours. The solution was cooled to room temperature, taken up in ether (500 mL) and filtered. The filtrate was then washed with water (x3) and brine (x1) and dried over MgSO₄. The solvent was removed under reduced pressure to give the crude target material as an orange liquid. The crude material was purified via vacuum distillation (68–70 °C, 6.5 mbar) to afford target diene 429 as a pale yellow liquid (43.1 g, 0.215 mol, 80 %). All spectroscopic data corresponded to that quoted in the literature.[245]

**Cyclic ester 423**

Experimental
Diene 429 (43.0 g, 0.215 mol) and methyl acrylate (162) (37.0 g, 39.0 mL, 0.431 mol) were combined in toluene (68 mL). The solution was heated to reflux and stirred for 16 hours. The solvent was removed under reduced pressure to give pure product 423 as a pale yellow liquid that did not require any further purification (59.2 g, 0.205 mol, 96%).

$^1H$ NMR (400 MHz, CDCl₃): δ 4.15 (d, J = 5.1 Hz, 1H), 3.17 (s, 3H), 3.64–3.59 (m, 1H), 3.52 (q, J = 7.2 Hz, 2H), 2.76–2.71 (m, 2H), 2.09–2.05 (m, 2H), 1.59 (s, 3H), 1.19 (t, J = 7.2 Hz, 3H), 0.17 (s, 9H) ppm.

$^{13}$C NMR (100 MHz, CDCl₃): δ 173.7 (C₄), 147.5 (CH), 112.1 (C₆), 78.5 (C₄), 67.1 (CH₃), 51.1 (CH), 45.6 (CH₂), 29.7 (CH₃), 19.8 (CH₃), 16.1 (CH₂), 14.8 (CH₃), 0.84 (CH₃), 0.84 (CH₃), 0.84 (CH₃) ppm.

IR: (thin film): $\nu_{max}$ = 2955, 1738 cm⁻¹.

LRMS: (70 eV, EI): m/z (%): 286 (25, [M]⁺), 257 (85), 241.1 (100), 185.0 (100), 141.0 (35)

**Substituted cyclohexenone 421**

DIBAL-H (1.0 M solution in toluene, 109.1 mL, 109.1 mmol) was added dropwise to a stirred solution of ester 423 (12.5 g, 43.5 mmol) in dry CH₂Cl₂ (150 mL) at −78 °C under N₂. The reaction was then warmed to room temperature and stirred for 3 hours. The reaction was cooled down to 0 °C and a solution of THF:2M HCl (4:1,
250 mL) was added slowly. The reaction was allowed to warm to room temperature and stirred for 18 hours. The reaction was then diluted with CH₂Cl₂ (300 mL) and poured into a mixture of sat. NaHCO₃ solution (500 mL) and potassium sodium tartrate solution (500 mL) and stirred for six hours. The aqueous layer was extracted with CH₂Cl₂ (x3) and the organic layers were combined, dried over MgSO₄ and the solvent removed under reduced pressure to give crude product as a yellow oil. Following flash column chromatography (SiO₂, 50% EtOAc in hexane) pure product 421 was isolated as a yellow oil (3.16g, 22.5 mmol, 52%).

**Rf:** 0.21 (60:40 EtOAc:hexanes)

**¹H NMR** (400 MHz, CDCl₃): δ 6.72–6.70 (m, 1H), 3.67–3.62 (m, 2H), 2.57 (dd, J = 5.1, 4.8 Hz, 1H), 2.51 (dd, J = 5.1, 4.8 Hz, 1H), 2.42–2.30 (m 1H), 2.20 (br s, 1H), 2.13 – 2.03 (m, 1H), 1.77 (s, 3H), 1.81 – 1.68 (ddd, J = 17.3, 5.1, 4.8 Hz, 1H) ppm.

**¹³C NMR** (100 MHz, CDCl₃): δ 200.2 (CH), 146.5 (C₄), 136.5 (C₄), 65.7 (CH₂), 39.4 (CH), 36.9 (CH₂), 25.9 (CH₂) 16.3 (CH₃) ppm.

**IR:** (thin film): νₘₐₓ = 3423, 2950, 1672 cm⁻¹.

**LRMS:** (70 eV, EI): m/z (%): 140 (46, [M]⁺⁺), 110 (92), 95 (100), 81 (92).

**Tetracycles 435 and 436**

![Chemical structures of Tetracycles 435 and 436]
Diene 154 (2.70 g, 12.5 mmol) and substituted cyclohexenone 421 (5.25 g, 37.5 mmol) were combined in CH$_2$Cl$_2$ (9 mL) and subject to 19 kbar for 5 days. The solvent was removed under reduced pressure to give crude target material in a 3:1 mixture of isomers. Following flash column chromatography (SiO$_2$, 50% EtOAc in hexane) tetracycles 435 and 436 were isolated as a 3:1 mixture of diastereoisomers as the major and minor isomers respectively (1.98g, 5.56 mmol, 45%). The two isomers 435 and 436 were separated via normal phase preparative HPLC for characterisation purposes (Phenomenex Luna 5 µm Silica column (150 x 21.2 mm, 90:10, CH$_2$Cl$_2$:EtOAc). Recrystallisation from EtOAc/hexanes gave tetracycle 435 and tetracycle 436 as white crystals, mp 155–157 °C and mp 177–179 °C, which were suitable for single crystal X-ray analysis.

**Tetracycle 435**

![Tetracycle 435](image)

$R_f$: 0.43 (50:50 hexanes:EtOAc).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.61 (d, $J$ = 8.8 Hz, 1H), 6.57 (d, $J$ = 8.8 Hz, 1H), 5.56 (br s, 1H), 3.77 (s, 3H), 3.71 (s, 3H), 3.75–3.67 (m, 1H), 3.65–3.57 (m, 1H), 3.46–3.29 (m, 2H), 2.95 (dd, $J$ = 15.6, 5.1 Hz, 1H), 2.69 (dt $J$ = 16.8, 6.6 Hz, 1H), 2.59–2.46 (m, 2H), 2.3 (br s, 2H), 2.22–2.06 (m, 2H), 2.06–1.92 (m, 1H), 1.91–1.76 (m, 2H), 1.27 (s, 3H) ppm.

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 216.4 (C$_{q}$), 150.9 (C$_{q}$), 150.8 (C$_{q}$), 134.0 (C$_{q}$), 126.3 (C$_{q}$), 126.0 (C$_{q}$), 115.9 (CH), 107.0 (CH), 106.7 (CH), 66.0 (CH$_2$), 55.6 (CH$_3$), 55.5 (CH$_3$),
49.0 (C₆), 41.2 (CH), 39.3 (CH₂), 39.1 (CH), 36.1 (CH), 33.7 (CH₂), 30.1 (CH₂), 25.7 (CH₂), 25.3 (CH₃), 23.9 (CH₃) ppm.

**IR:** (KBr): \(v_{\text{max}} = 3456, 2914, 2892, 2834, 1672, 1601 \text{ cm}^{-1}\).

**LRMS:** (70 eV, EI): m/z (%): 356.2 (25, [M]+), 216.1 (100), 215.1 (40), 141.1 (46).


**Tetracycle 436**

\[
\text{\begin{center}
\includegraphics[width=0.5\textwidth]{tetracycle_436.png}
\end{center}}
\]

\(R_f: 0.43\) (50:50 hexanes:EtOAc).

**\(^1\)H NMR** (400 MHz, CDCl₃): \(\delta 6.64\) (d, \(J = 8.9\) Hz, 1H), 6.61 (d, \(J = 8.9\) Hz, 1H), 5.60 (s, 1H), 3.78 (s, 3H), 3.75–3.74 (m, 1H), 3.72 (s, 3H), 3.67–3.56 (m, 2H), 3.36 (d, \(J = 2.0\) Hz, 1H), 2.83–2.63 (m, 3H), 2.38 (ddd, \(J = 14.7, 5.0, 2.4\) Hz, 1H), 2.31–2.18 (m, 2H), 2.18–2.06 (m, 2H), 2.05–1.93 (m, 1H), 1.74–1.59 (m, 2H), 1.34–1.21 (m, 1H), 1.13 (s, 3H) ppm.

**\(^{13}\)C NMR** (100 MHz, CDCl₃): \(\delta 214.4\) (C₆), 150.5 (C₆), 132.7 (C₆), 127.3 (C₆), 125.5 (C₆), 117.8 (CH), 107.3 (CH), 107.3 (CH), 65.3 (CH₂), 77.2 (C₆), 55.7 (CH₃), 55.7 (CH₃), 50.5
(C₃), 44.7 (CH), 37.6 (CH), 37.1 (CH₂) 36.2 (CH), 29.7 (CH₂), 29.6 (CH₂), 23.9 (CH₂), 22.3 (CH₂), 16.2 (CH₃) ppm.

**IR**: (KBr) \( v_{\text{max}} = 3453, 2920, 2872, 1686, 1603 \text{ cm}^{-1} \).

**LRMS**: (70 eV, ESI): m/z (%): 379.5 (100, [M+Na]+), 357.5 (23), 339.5 (10).

**HRMS**: (70 eV, ESI): m/z calc. for C₂₂H₂₈O₄Na [M + Na]^+: 379.1885; found 379.1885.

**Naphthalene 431**

A solution of diene 154 (40 mg, 0.17 mmol) in toluene (2 mL) was heated to 200 °C in a sealed vessel and left to stir for two hours. After cooling to room temperature, the solvent was removed under reduced pressure to give crude target material as a colourless oil. Following flash column chromatography (SiO₂, 0–10% gradient EtOAc in hexanes) pure product 431 was isolated as a colourless oil (36.4 mg, 0.169 mmol, 99%).

**Rf**: 0.69 (90:10; hexanes:EtOAc).

**¹H NMR** (400 MHz, CDCl₃): \( \delta 8.13 \text{ (d, } J = 8.6 \text{ Hz, } 1\text{H}), 8.00 \text{ (s, } 1\text{H}), 7.38 \text{ (dd, } J = 8.6, 1.7 \text{ Hz, } 1\text{H}), 6.73–6.60 \text{ (m, } 2\text{H}), 3.96 \text{ (s, } 3\text{H}), 3.95 \text{ (s, } 3\text{H}), 2.83 \text{ (q, } J = 7.6 \text{ Hz, } 2\text{H}), 1.33 \text{ (t, } J = 7.6 \text{ Hz, } 3\text{H}) \text{ ppm.} \)
\[ ^{13}C \text{ NMR} \ (100 \text{ MHz, CDCl}_3): \delta \ 149.6 \ (C_1), \ 149.2 \ (C_4), \ 141.9 \ (C_9), \ 126.8 \ (CH), \ 126.5 \ (C_4), \ 124.7 \ (C_4), \ 121.8 \ (CH), \ 119.5 \ (CH), \ 103.2 \ (CH), \ 102.3 \ (CH), \ 55.7 \ (CH_3), \ 55.7 \ (CH_3), \ 29.3 \ (CH_3), \ 15.7 \ (CH_3) \ \text{ppm.}\]

\[ \text{IR: (KBr): } v_{\text{max}} = 2997, \ 2962, \ 2935, \ 2833, \ 1632, \ 1603 \ \text{cm}^{-1}.\]

\[ \text{LRMS: (70 eV, ESI): } m/z \ (\%): \ 216.1 \ (88, [M+Na]^+), \ 201.1 \ (100), \ 186.1 \ (15), \ 173.1 \ (44), \ 143.0 \ (35), \ 115.0 \ (33).\]

\[ \text{HRMS: (70 eV, ESI): } m/z \ \text{calc. for } C_{14}H_{16}O_2Na [M+Na]^+: 216.1150; \ \text{found } 216.1150.\]

\text{Tosylhydrazone 439}

\[ \begin{align*}
\text{p-Toluenesulfonic acid (TsOH)} & \ (6.0 \text{ mg}, \ 0.03 \text{ mmol}) \ \text{and tosyl hydrazine} \ (78 \text{ mg}, \ 0.42 \text{ mmol}) \ \text{were added to a solution of tetracycle 435} \ (100 \text{ mg}, \ 0.281 \text{ mmol}) \ \text{in dry methanol} \ (3 \text{ mL}) \ \text{at room temperature. The reaction was heated to reflux and stirred for four hours. The reaction was then cooled to room temperature and filtered through a plug of Celite (MeOH). The solvent was removed under reduced pressure to yield crude product as a white solid. Following flash column chromatography (SiO}_2, 10–20\% \ \text{gradient EtOAc in CH}_2Cl_2) \ \text{pure product 439 was isolated as a pale yellow solid} \ (85.8 \text{ mg}, \ 0.186 \text{ mmol, 67\%}). \ \text{Recrystallisation from EtOAc gave white crystals, 185–189 °C decomp, which were suitable for single crystal X-ray analysis.}\n\end{align*} \]
Experimental

31P NMR (80 MHz, CDCl$_3$): $\delta$ 26.0 (s, 1P).

IR: (KBr) $\nu_{\text{max}}$ = 3505, 3102, 2929, 2830, 1597 cm$^{-1}$.

LRMS: (70 eV, ESI): m/z (%): 547.3 (100, [M+Na$^+$]), 525.3 (20), 449 (11), 309.3 (10).

HRMS: (70 eV, ESI): m/z calc. for C$_{20}$H$_{36}$N$_2$O$_5$SNa [M+Na]$^+$: 547.2243; found 547.2249.
** tert-Butyl-dimethylsilyl ether 440**

\[
\text{TBSCI, imidazole} \quad \text{CH}_2\text{Cl}_2
\]

\[
\begin{align*}
\text{435} & \quad \rightarrow \\
\text{440}
\end{align*}
\]

tert-Butyldimethylsilyl chloride (63 mg, 0.42 mmol) was added to a solution of tetracycle 435 (100 mg, 0.281 mmol) and imidazole (57 mg, 0.84 mmol) in dry CH\(_2\text{Cl}_2\) (3 mL) and stirred for one hour. The reaction was then cooled to 0 °C and quenched with H\(_2\)O (1 mL). The mixture was then taken up in EtOAc (5 mL) and the organic layer was washed with brine (x1) and dried over MgSO\(_4\). The solvent was removed under reduced pressure to yield crude product as a colourless oil. Following flash column chromatography (SiO\(_2\), 10% EtOAc in hexane) pure product 440 was isolated as a white solid (110 mg, 0.234 mmol, 84%). Recrystallisation from EtOAc gave white crystals, mp 124–126 °C.

\(R_f: 0.29\) (90:10 hexanes:EtOAc).

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)): \(\delta 6.61\) (d, \(J = 8.8\) Hz, 1H), 6.57 (d, \(J = 8.8\) Hz, 1H), 5.54 (br s, 1H) 3.77 (s, 3H), 3.71 (s, 3H), 3.62–3.58 (m, 2H), 3.46–3.29 (m, 2H), 2.96 (dd, \(J = 15.5, 4.9\) Hz, 1H), 2.67 (ddd, \(J = 16.4, 7.7, 6.1\) Hz, 1H), 2.55–2.42 (m, 2H), 2.29–2.22 (m, 2H) 2.22–2.12 (m, 1H), 2.11–1.97 (m, 1H), 1.94–1.77 (m, 3H), 1.26 (s, 3H), 0.89 (s, 9H), 0.04 (s, 6H) ppm.

\(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)): \(\delta 217.3\) (C\(_q\)), 151.6 (C\(_q\)), 151.0 (C\(_q\)) 134.0 (C\(_q\)), 126.7 (C\(_q\)), 126.3 (C\(_q\)) 116.2 (CH), 107.1 (CH), 106.8 (CH), 66.1 (CH\(_2\)), 55.7 (CH\(_3\)) 55.7 (CH\(_3\)) 48.9 (C\(_q\)), 41.4 (CH), 39.6 (CH\(_2\)), 38.6 (CH) 36.2 (CH), 31.2 (CH\(_2\)), 31.2 (CH\(_2\)), 26.1 (CH\(_3\)),
25.8 (CH₂), 25.6 (CH), 24.06 (CH₂), 18.4 (CH₃), 18.4 (CH₂), 18.4 (CH₃), -5.3 (C₃), -5.36 (CH₃) ppm.

**IR:** (KBr): $v_{\text{max}} = 2956, 2930, 2829, 1702 \text{ cm}^{-1}$.

**LRMS:** (70 eV, ESI): m/z (%): 493.3 (100, [M+Na]⁺), 488.4 (18), 449.4 (12), 321.3 (12), 102.0 (12).

**HRMS:** (70 eV, ESI): m/z calc. for C₂₈H₄₂O₄SiNa [M+Na]⁺: 493.2750; found 493.2750.

**Tetracyclic alcohol 441**

Sodium borohydride (12 mg, 0.34 mmol) was added to a solution of tetracycle 435 (105 mg, 0.223 mmol) in THF (1 mL). MeOH (3 drops) was then added and the mixture was stirred for two hours. The reaction was cooled to 0 °C and quenched with NH₄Cl solution (200 µL). The reaction mixture was then partitioned between CH₂Cl₂ (10 mL) and water (10 mL) and the organic layer was collected. The aqueous layer was extracted with CH₂Cl₂ (x3) and the combined organic layers were washed with H₂O (x3) and brine (x1) and dried over MgSO₄. The solvent was removed under reduced pressure to give crude product as an off white solid. Following flash column chromatography (SiO₂, 10% EtOAc in hexanes) pure product 441 was isolated as a white solid (95 mg, 0.20 mmol, 91%). Mp 135–139 °C.

$R_f$: 0.1 (90:10 hexanes:EtOAc).
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 6.60 (s, 2H), 5.51 (s, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.62–3.40 (m, 4H), 3.36 (d, $J$ = 6.7 Hz, 2H), 2.67 (dd, $J$ = 14.2, 14.2 Hz, 1H), 2.33–2.07 (m, 4H), 1.98–1.85 (m, 2H), 1.80–1.65 (m, 1H), 1.39–1.22 (m, 3H), 1.15 (s, 3H), 0.87 (s, 9H), 0.01 (s, 6H) ppm.

$^{13}$C NMR: (100 MHz, CDCl$_3$) $\delta$ = 151.1 (C$_q$), 150.9 (C$_q$), 134.6 (C$_q$), 127.6 (C$_q$), 126.4 (C$_q$), 116.9 (CH), 106.7 (CH), 106.5 (CH), 79.2 (CH), 66.3 (CH$_2$), 55.6 (CH$_3$), 55.6 (CH$_3$), 40.9 (CH), 40.6 (CH), 39.6 (C$_q$), 37.1 (CH), 33.7 (CH$_2$), 31.1 (CH$_2$), 30.1 (CH$_2$) 28.5 (CH$_3$), 25.9 (CH$_3$), 25.4 (CH$_3$), 25.9 (CH$_3$), 23.5 (CH$_3$) 18.3 (CH$_3$), -5.5 (CH$_3$) -5.5 (CH$_3$) ppm.

LRMS: (70 eV, ESI): m/z (%): 495.2 (100, [M+Na]$^+$), 449.3 (22), 323.1 (19).

HRMS: (70 eV, ESI): m/z calc. for C$_{28}$H$_{44}$O$_4$SiNa [M+Na]$^+$: 495.2907; found 495.2904.

Tetracyclic xanthate ester 444

![Tetracyclic xanthate ester 444](image)

n-BuLi (1.56 M in hexane, 140 µL, 0.218 mmol,) was added to a solution of alcohol 441 (50 mg, 0.11 mmol) in dry THF (2 mL) at 0 °C. The resultant brown solution was warmed to room temperature and stirred for 60 minutes. The reaction was then cooled back to 0 °C and carbon disulfide (24 mg, 19 µL, 0.32 mmol) was added followed by methyl iodide (76 mg, 35 µL, 0.53 mmol). The reaction was again
warmed to room temperature and stirred for 60 minutes. After confirming the reaction was complete by TLC, the reaction was cooled to 0 °C and quenched carefully with NH₄Cl solution. The mixture was extracted with CH₂Cl₂ (x3) and the combined organic layers were washed with H₂O (x3) and brine (x1) and dried over MgSO₄. The solvent was removed under reduced pressure to give crude product as a pungent brown oil. Following flash column chromatography (SiO₂, 10% EtOAc in hexanes), pure product 444 was isolated as a pungent yellow solid (40.0 mg, 0.07 mmol, 67%).

**Rf**: 0.32 (90:10 hexanes:EtOAc).

**¹H NMR** (400 MHz, CDCl₃): δ = 6.63 (s, 2H), 5.63 (dd, J = 11.8, 6.1 Hz, 1H), 5.54 (s, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.63 (dd, J = 15.7, 4.8 Hz, 1H), 3.58–3.42 (m, 3H), 3.42–3.33 (m, 2H), 2.79–2.66 (m, 1H), 2.46 (s, 3H), 2.37–2.10 (m, 4H), 1.98–1.84 (m, 1H), 1.84–1.70 (m, 1H), 1.53–1.37 (m, 2H), 1.08 (s, 3H), 0.88 (s, 9H), 0.02 (s, 6H) ppm.

**¹³C NMR** (100 MHz, CDCl₃) δ = 215.4 (C₉), 151.0 (C₄), 150.9 (C₄), 134.0 (C₄), 127.4 (C₄), 126.2 (C₄), 116.6 (CH), 106.8 (CH), 106.7 (CH), 91.0 (CH), 65.9 (CH₂), 55.8 (CH₃), 55.5 (CH₃), 41.5 (CH), 41.3 (CH), 39.8 (C₃), 36.6 (CH), 33.7 (CH₂), 30.3 (CH₂), 28.4 (CH₃), 27.8 (CH₂), 26.8 (CH₂), 25.9 (CH₃), 25.9 (CH₃), 25.9 (CH₃) 23.0 (CH₂), 18.2 (CH₃), -5.46 (C₃), -5.52(CH₃), -5.52 (CH₃) ppm.

**IR**: (KBr): νₘₐₓ = 2952, 2927, 2855, 1711, 1602 cm⁻¹.

**LRMS**: (70 eV, ESI): m/z (%): 585.3 (100, [M+Na]+), 569.3 (32), 477.3 (30), 449.4 (29), 323.3 (22).
**HRMS:** (70 eV, ESI) m/z calc. for C₃₀H₄₆O₃S₂SiNa [M+Na]⁺: 585.2505; found 585.2508.

**Tetracycle 445**

A solution of xanthate ester **444** (39 mg, 0.069 mmol) in cyclohexane (3 mL) was heated to 80 °C before adding Bu₃SnH (40 mg, 37 µL, 0.14 mmol) followed by AIBN solution (1.1 mg, in 1 mL cyclohexane, 0.0070 mmol). The reaction was then heated to reflux and stirred for 16 hours. The reaction was allowed to cool to room temperature and was partitioned between CH₂Cl₂ (10 mL) and H₂O (10 mL). The organic layer was then washed with H₂O (x3) and brine (x1) and dried over MgSO₄. The solvent was then removed under reduced pressure to yield crude product as a colourless oil. Following flash column chromatography (SiO₂, 30% CH₂Cl₂ in hexanes) pure product **445** was isolated as a colourless oil (25 mg, 0.056 mmol, 79%).

**Rf:** 0.24 (70:30 hexanes:CH₂Cl₂).

**¹H NMR** (400 MHz, CDCl₃): δ 6.61 (s, 2H), 5.52 (s, 1H), 3.78 (s, 6H), 3.54 (m, 2H), 3.34 (s, 2H), 3.25 (dd, J = 15.8, 5.0 Hz, 1H), 2.57 (t, J = 14.6, 1H), 2.26 (d, J = 18.3 Hz 1H), 2.15 (d, J = 21.3 Hz, 1H), 1.96 (dd, J = 12.7, 4.1 Hz, 1H), 1.93–1.72 (m, 3H), 1.71–1.58 (m, 2H), 1.43–1.20 (m, 3H), 1.01 (s, 3H), 0.91 (s, 9H), 0.02 (s, 6H) ppm.
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 150.95$ (C), 134.36 (C), 128.15 (C), 126.59 (C), 117.23 (C), 106.80 (C), 106.80 (C), 66.88 (C), 55.78 (C), 55.59 (C), 44.71 (C), 42.22 (C), 38.87 (C), 35.99 (C), 34.42 (C), 33.06 (C), 32.18 (C), 29.05 (C), 28.79 (C), 25.98 (C), 25.98 (C), 24.54 (C), 22.25 (C), 18.36 (C), -5.37 (C), -5.40 (C), -5.40 (C) ppm.

$IR$: (KBr): $v_{\text{max}} = 2952, 2928, 2856$ cm$^{-1}$.

$LRMS$: (70 eV, ESI): m/z (%): 479.3 (100, [M+Na]$^+$), 474.4 (15), 325.2 (88), 323.3 (18).

$HRMS$: (70 eV, ESI): m/z calc. for C$_{28}$H$_{44}$O$_3$SiNa [M+Na]$^+$: 479.2957; found 479.2959.

**Tetracycle 446**

TBAF (1.0 M in THF, 131 $\mu$L, 0.131 mmol) was added to a solution of tetracycle 445 (20 mg, 0.043 mmol) in dry THF (1 mL) and left to stir at room temperature for 20 hours. The reaction mixture was partitioned between CH$_2$Cl$_2$ (5 mL) and H$_2$O (5 mL) and the organic layer was collected. The aqueous layer was extracted with CH$_2$Cl$_2$ (x2) and the combined organic layers were washed with brine (x1) and dried over MgSO$_4$. The solvent was removed under reduced pressure to give the crude product as a colourless oil. Following flash column chromatography (SiO$_2$, CH$_2$Cl$_2$) pure product 446 was isolated as a colourless oil (15 mg, 0.043 mmol, 99%).
Rf: 0.21 (CH₂Cl₂).

^1H NMR (400 MHz, CDCl₃): δ 6.55 (s, 2H), 5.47 (br s, 1H), 3.71 (s, 6H), 3.58–3.53 (m, 2H), 3.30 (s, 2H), 3.19 (dd, J = 15.8, 5.1 Hz, 1H), 2.51 (t, J = 14.4 Hz, 1H), 2.28–2.08 (m, 2H), 1.92 (d, J = 12.7 Hz, 1H), 1.87–1.68 (m, 3H), 1.69–1.54 (m, 2H), 1.37–1.17 (m, 3H), 1.06 (s, 1H), 0.96 (s, 3H) ppm.

^13C NMR (100 MHz, CDCl₃) δ 150.9 (C₄), 134.6 (C₃), 127.9 (C₄), 126.5 (C₃), 116.9 (CH), 106.9 (CH), 106.8 (CH), 67.0 (CH₂), 55.8 (CH₃), 55.6 (CH₃), 44.6 (CH), 42.3 (CH), 39.1 (CH), 35.8 (CH₂), 34.5 (CH₂), 33.0 (CH₂), 31.7 (CH₃), 29.0 (CH₂), 28.6 (CH₂), 24.6 (CH₂), 22.7 (CH₂), 22.1 (CH₂) ppm.

IR: (KBr): v_max = 3369, 2931, 1601 cm⁻¹.

LRMS: (70 eV, ESI): m/z (%): 365.3 (100, [M+Na⁺]), 325.2 (22), 279.0 (26), 84.7 (48).

HRMS: (70 eV, ESI): m/z calc. for C₂₂H₃₁O₃ [M+H⁺]: 343.2273; found 343.2276.

Tetracycle 446

A solution of tetracycle 435 (25 mg, 0.070 mmol) in MeOH:CH₂Cl₂ (3:1, 7 mL) was stirred with a small magnetic stir bar and mechanical stirrer at 160 rpm (note that slow stirring is needed for the duration of this experiment to avoid clogging of the Zn dust). The mixture was cooled to –10 °C before adding zinc powder (458 mg,
7.01 mmol) to the reaction mixture. TMSCl (751 mg, 880 µL, 7.01 mmol) was subsequently added via syringe pump at such a rate that the internal temperature of the reaction mixture was maintained below −5 °C. After addition was complete, the resulting mixture was stirred for 1 hour at −10 °C, then solid NaHCO₃ (715 mg, 8.41 mmol) was added in one portion and the cooling bath was removed. After reaching room temperature, the reaction mixture was filtered through Celite and the solvent was removed under reduced pressure. The resulting residue was taken up in CHCl₃ (3 mL) and washed with aqueous NH₄Cl solution (x1), H₂O (x1) and brine (x1) before drying over MgSO₄. The solvent was removed under reduced pressure to give the crude product as a colourless oil. Following flash column chromatography (SiO₂, CH₂Cl₂) pure product 446 was isolated as a colourless oil (15 mg, 0.043 mmol, 61%). All spectroscopic data corresponded with that quoted above.

Naphthalene 465

DDQ (320 mg, 1.41 mmol) was added to a solution of tetracycle 446 (230 mg, 0.67 mmol) in dry benzene (12 mL) and heated to reflux and stirred for four hours. The solution was allowed to cool to room temperature and the mixture was then loaded onto a small plug of Al₂O₃ and eluted with EtOAc. The solvent was removed under reduced pressure to give crude target material as an orange solid. Following flash column chromatography (SiO₂, 20% EtOAc in hexanes) pure product 465 was isolated as an off white solid (133 mg, 0.392 mmol, 58%). Recrystallisation from MeOH gave white crystals mp 144–146 °C.
**Rf:** 0.37 (70:30 hexanes:EtOAc).

$^1H\text{ NMR}$ (400 MHz, MeOD): \(\delta 8.02\, (s, 1H),\) \(7.79\, (s, 1H),\) \(6.73\, (d, J = 8.4\, \text{Hz}, 1H),\) \(6.71\, (d, J = 8.4\, \text{Hz}, 1H),\) \(6.61\, (d, J = 9.7\, \text{Hz}, 1H),\) \(6.23\, (dd, J = 9.7, 6.4\, \text{Hz}, 1H),\) \(3.95\, (s, 3H),\) \(3.93\, (s, 3H),\) \(3.62 - 3.46\, (m, 4H),\) \(2.61\, (d, J = 15.8\, \text{Hz}, 2H),\) \(1.78 - 1.65\, (m, 2H),\) \(1.63 - 1.43\, (m, 3H),\) \(1.15\, (s, 3H)\, \text{ppm}.

$^{13}C\text{ NMR}$: (100 MHz, MeOD) \(\delta\) 150.9 (C\(_q\)), \(150.7\) (C\(_q\)), \(141.2\) (C\(_q\)), \(133.2\) (CH), \(133.1\) (C\(_q\)), \(128.1\) (CH), \(127.2\) (C\(_q\)), \(126.2\) (C\(_q\)), \(120.7\) (CH), \(118.1\) (CH), \(104.4\) (CH), \(104.1\) (CH), \(66.1\) (CH\(_2\)), \(56.1\) (CH\(_3\)), \(56.1\) (CH\(_3\)), \(46.5\) (CH), \(44.6\) (CH), \(39.8\) (C\(_q\)), \(36.3\) (CH\(_2\)), \(31.8\) (CH\(_3\)), \(31.1\) (CH\(_2\)), \(23.1\) (CH\(_2\)) ppm.

**IR:** (KBr): \(v_{\text{max}} = 3444, 2960, 2923, 2854, 1737, 1596\, \text{cm}^{-1}.

**LRMS:** (70 eV, ESI): m/z (%): 361.2 (100, [M+Na\(^+\)]), 339.1 (82), 321.2 (30), 227.0 (32).

**HRMS:** (70 eV, ESI): m/z calc. for C\(_{22}\)H\(_{26}\)O\(_3\)Na [M+Na\(^+\)]: 361.1780; found 361.1781.

**Triol 470**

Osmium tetraoxide solution (0.39 M in CHCl\(_3\), 225 \(\mu\)L, 0.087 mmol) was added to a solution of TMEDA (10.5 mg, 15 \(\mu\)L, 0.09 mmol) and tetracycle 465 (30.0 mg, 0.087 mmol) in CHCl\(_3\) (3.5 mL) at room temperature. The solution was stirred for ten
minutes before adding ethylenediamine (45 mg, 50 µL, 0.7 mmol). The solution was then stirred for five days. The reaction mixture was taken up in EtOAc (3 mL) and washed with water (x3) and brine (x1). The organic layer was dried over Na₂SO₄ and the solvent removed under reduced pressure to give crude target material as a yellow oil. Following flash column chromatography (SiO₂, 100 % EtOAc) pure product 470 was isolated as an orange solid (21 mg, 0.056 mmol, 64%).

rf: 0.32 (EtOAc).

1H NMR (400 MHz, CDCl₃) δ 8.30 (s, 1H), 8.13 (s, 1H), 6.63 (d, J = 8.3 Hz, 1H), 6.60 (d, J = 8.3 Hz, 1H), 4.99 (s, 1H), 4.26 (dd, J = 7.8, 4.1 Hz, 1H), 3.94 (s, 6H), 3.87 (dd, J = 10.6, 6.9 Hz, 1H), 3.72 (dd, J = 10.6, 4.7 Hz, 1H), 2.74 (s, 2H), 2.20–2.11 (m, 1H), 2.11–2.02 (m, 1H), 2.00–1.90 (m, 1H), 1.72–1.55 (m, 5H), 1.53 (s, 3H), 1.44–1.34 (m, 1H) ppm.

13C NMR: (100 MHz, CDCl₃) δ 149.2 (C₄), 149.0 (C₃), 143.7 (C₂), 134.0 (C₃), 126.6 (C₄), 124.9 (C₃), 122.8 (CH), 119.0 (CH), 103.0 (CH), 102.4 (CH), 70.1 (CH), 69.1 (CH), 66.9 (CH₂), 55.7 (CH₃), 55.6 (CH₃), 44.8 (CH), 39.7 (CH₂), 38.5 (CH), 37.1 (Cₙ), 32.9 (CH₃), 25.8 (CH₃), 19.9 (CH₃) ppm.

IR: (KBr): v_max = 3383, 2928, 2860 cm⁻¹.

LRMS: (70 eV, ESI): m/z (%): 395.3 (100, [M+Na⁺]), 337.3 (46), 279.2 (8).

HRMS: (70 eV, ESI): m/z calc. for C₂₂H₂₈O₅Na [M+Na]⁺: 395.1834; found 395.1834.
Chapter 6: References


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