Studies Towards Efficient Synthesis
With Dendralenes

A thesis submitted in fulfilment of the requirements for admission
to the degree of

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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 July 2008 to July 2010 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 60,000 words in length.

Mehmet Fatih Saglam

12 July 2010
Dedication

This work is dedicated to my Mum Serife, Dad Mustafa, brother Hasan and my sisters Fatma and Zeynep who always support and encourage me.
Acknowledgements

Firstly, I would like to extend many thanks to my supervisor Associate Professor Mick Sherburn for his guidance, advice and patience during two years.

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Abbreviations

%  percentage yield
Δ  heat
°C  degree/s Celsius
μ  micro
δ  chemical shift
ν  absorption maxima (IR)
Ac  acetyl
aq.  aqueous
Ar  aryl or argon
aza catalyst  1-(4-methoxyphenyl)-4-phenyl-1-aza-1,3-butadiene
BHT  2,6-di-tert-butyl-4-methylphenol
Bn  benzyl
bp.  boiling point
br  broad
Bu  butyl
calcd  calculated
CAN  ceric ammonium nitrate
cm⁻¹  wave number
cod  cycloocta-1,5-diene
COSY  correlated spectroscopy
Cy  cyclohexyl
1D  one dimensional
2D  two dimensional
d  doublet/s
DA  Diels–Alder
dba  dibenzylideneacetone
DBU  1,8-diazabicyclo[5.4.0]undec-7-ene
DFT  density functional theory
d.e.  diastereomeric excess
dm  decameter
(DHQ)₂PHAL  hydroquinine 1,4-phthalazinediyl diether
(DHQD)₂PHAL  hydroquinidine 1,4-phthalazinediyl diether
DMDO  dimethylidioxirane
DMF  dimethylformamide
DMSO  dimethylsulfoxide
dppe  1,2-bis(diphenylphosphino)ethane
dppf  [1,1'-((diphenylphosphino)ferrocene]}
dppp: 1,3-bis(diphenylphosphino)propane

d.r.: diastereomeric ratio

EDG: electron donating group

ee: enantiomeric excess

EI: electron impact

Et: ethyl

ESI: electrospray ionization

eV: electron Volts

EWG: electron withdrawing group

FabF: β-ketoacyl-[acyl carrier protein] synthase II

FTIR: fourier transform infrared spectroscopy

g: gram(s)

GC: gas chromatography

GLC: gas-liquid chromatography

h: hour/s

HMBC: heteronuclear multiple bond coherence

HOMO: highest occupied molecular orbital

HPLC: high pressure liquid chromatography

HRMS: high resolution mass spectrometry

HSQC: heteronuclear single quantum coherence

Hz: Hertz

i-Pr: isopropyl

IR: infrared

J: coupling constant

kbar: kilobar

KTC: Kumada-Tamao-Corriu

L: litre/s

lit.: literature

LUMO: lowest unoccupied molecular orbital

m: multiplet or metre/s

m-CPBA: m-chloroperbenzoic acid

mM: millimolar

M: molar

M⁺: molecular ion

Me: methyl

mg: milligram/s

MHz: megahertz

min: minute

mm: millimeter/s
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Abstract

Arguably, the most important aim of modern synthetic chemistry is to synthesise target materials possessing complex structures by the shortest practicable route. By using domino reactions, such as diene-transmissive Diels-Alder reactions, the construction of molecular complexity is readily achieved.

The work detailed in the first Chapter of this report describes efforts towards this ideal: the practical synthesis of 1-alkyl-substituted [4]dendralene and examination of its reactivity in diene-transmissive Diels-Alder reactions is reported. This represents the final unexplored position of the family of alkyl-substituted [4]dendralenes. 1-(E)-Hexyl [4]dendralene was synthesised using a nickel catalysed Kumada-Tamao-Corriu cross-coupling reaction.

\[
\text{MgCl}_2 + \text{Cl} - \text{n-hex} \rightarrow \text{MgCl} + \text{Cl} - \text{n-hex}
\]

With this substituted [4]dendralene in hand, its reactivity with NMM was investigated. Under kinetically controlled conditions, 1-(E)-hexyl [4]dendralene reacted with excess of NMM to afford a mono-adduct, two bis-adducts, and two tris-adducts products. The efficient synthesis of a complex hexacyclic structure in a one pot reaction using a simple acyclic starting material, forming nine new stereocenters and six carbon-carbon bonds was achieved.

The first practical synthesis of C2 alkynyl [3]dendralene, an interesting intermediate in our studies, is reported. Its chemistry in the Diels-Alder reaction was also investigated.
Intriguingly, the site selectivity of this reaction is the reverse of that observed for all previously-investigated C2 substituted [3]dendralenes.

Again, with a view towards the rapid construction of molecular complexity, Chapter Two focused on the manipulation reaction of a readily prepared tetracycle. Formed by dimerisation of [5]dendralene via pericyclic cascade reactions, this compound was ripe for investigations of selective functionalisation.

Interesting reactivity patterns were discerned: Selective functionalisation of the vinyl group at the C/D ring junction was achieved. Diastereoselective functionalisation of both the A and B rings was possible. A framework of relevance to natural product synthesis was also prepared.

Specifically, treatment of tetracycle with epoxidizing agents, m-CPBA or DMDO afforded a single diastereomeric *bis*-epoxide and a mixture of *mono*-epoxides. The
reactions only occurred at the most electron rich endocyclic alkenes. Reaction with OsO₄ was found to take place at the less sterically hindered and electron poor alkene unit. Only two diastereomeric products were observed and their identities were confirmed by single crystal X-ray diffraction analysis. Excitingly, ozonolysis provides a tricyclic complex compound, which possesses the same tricyclic carbon skeleton as the natural product platensimycin. Finally, a cross-metathesis reaction was examined and only one trans- isomer product was isolated.
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Scheme 1.3: The reaction between 4-tert-butylcyclohexadiene 6 and succinyl anhydride 7. Product 8 (90%) is obtained.

1.1.1.2 Conservation of olefin and aldehyde components in the Diels-Alder reaction
1.1 Introduction

1.1.1 The importance of efficient synthesis in organic chemistry

Organic compounds featuring complicated skeleta and appended functionality, once considered the exclusive domain of nature, are now routinely prepared. This state of affairs has come about by the efforts of scientists working to provide new tools to construct carbon-carbon bonds and to facilitate functional group manipulations. The purpose of the work reported in this Chapter is to explore the preparation and reactivity of substrates that allow rapid construction of complex polycyclic frameworks. Diene-transmissive Diels-Alder reactions with dendralenes, prepared by cross-coupling methods, were employed to this end.

1.1.2 The Diels-Alder reaction

One of the most important and powerful organic reactions is the Diels-Alder reaction. Discovered by Otto Diels and his student Kurt Alder in 1928, its application has been of benefit to human society, resulting in the preparation of useful compounds such as the insecticide aldrin 3 (Scheme 1.1). The use of this reaction, especially in the generation of structurally-challenging natural products remains commonplace.

![Scheme 1.1: Synthesis of aldrin 3 (newly formed C-C bonds highlighted in red).](image)

1.1.2.1 The mechanism of the Diels-Alder reaction

The Diels-Alder reaction generally involves the reaction of an electron-rich diene (in the so-called s-cis conformation) unit and an electron-deficient dienophile (alkene or
alkyne) unit. These two components react via a concerted [4π+2π] cycloaddition reaction (Scheme 1.2).^f

Scheme 1.2: The Diels-Alder reaction of diene 4 and dienophile 5.

The reaction forms two new σ bonds at the expense of two π bonds. In addition, a new six-membered ring containing a double bond and up to four contiguous stereocentres are formed.

1.1.2.2 Regiochemistry in the Diels-Alder reaction

The possible formation of different regioisomers arises in the Diels-Alder reaction when both diene and dienophile are not symmetrical. For example, the reaction between terminal substituted butadiene 8 and methyl acrylate 9 preferentially affords the so-called ortho-adduct 11, rather than the meta-adduct 10 (Scheme 1.3).^f


1.1.2.3 Conservation of diene and dienophile geometries in the Diels-Alder reaction

The Diels-Alder reaction is concerted, and the stereochemistry of the diene and dienophile are conserved in the products: If substituted butadiene 12 reacts with
dienophile 13 possessing Z-geometry, the products 14 and 15 would be expected to form. If, however, the same diene 12 reacts with a dienophile 16 having E-geometry, product 17 will be formed (Scheme 1.4).

Scheme 1.4: Conservation of diene and dienophile geometries in the Diels-Alder reaction.

1.1.2.4 Endo/exo stereoselectivity in the Diels-Alder reaction

The Diels-Alder reaction can, in principle, produce so-called endo or exo products, arising from the dienophile approaching the diene in two possible orientations (Scheme 1.5). In the endo-transition state, the dienophile interacts with the diene in a relatively sterically hindered orientation. In contrast, in the exo-transition state, the dienophile interacts with the diene in a less sterically hindered orientation.
Scheme 1.5: Endo/exo selectivity in the intermolecular Diels-Alder reaction between cyclopentadiene 18 and maleic anhydride 19.

Despite this, the more compact endo-transition state is thought to be favoured by the existence of stabilising secondary orbital interactions, making it more stable than the exo-transition state.\(^7\)\(^8\) Experimentally, it is generally observed that the intermolecular Diels-Alder reaction preferentially provides the endo-product. This tendency is summarised by the so-called Alder endo rule.\(^9\) Many exceptions to this rule are known, however.

1.1.2.5 \(\pi\)-Diastereofacial selectivity in the Diels-Alder reaction

With certain diene or dienophile substitution patterns, steric or electronic effects may favour the approach of one particular reagent to a particular face of the other. For example, the cycloaddition reaction between cyclopentadiene 18 and chiral dienophile 22 afforded, in a diastereomeric ratio of 98:2, 23 (Scheme 1.6).\(^{10}\)
**Scheme 1.6**: \( \pi \)-Diastereofacial selectivity in the intermolecular Diels-Alder reaction between cyclopentadiene 18 and 5-(L-menthyloxy)-2(5\(H \))-furanone 22. **Reagents and conditions**: (a) Toluene, 110 °C, 65% yield, 98:2 d.r.

### 1.1.2.6 Site selectivity in the Diels-Alder reaction

When one of the substrates contains more than one diene or dienophile, a Diels-Alder reaction may exhibit regioselectivity for one site over the other. This type of regioselectivity is called site selectivity. For instance, when a dienophile 25 reacts with tetraene 26, the cycloaddition reaction takes place preferentially at the silyl ether activated terminal diene site (Scheme 1.7).\(^{11}\)

**Scheme 1.7**: Site selectivity in the intermolecular Diels-Alder reaction between a dienophile 25 and a multiple diene 26. **Reagents and conditions**: (a) CCl\(_4\), reflux, 55%.
Thus, the activation of one of the terminal diene units induces site selectivity. Site selectivity can also be controlled by the use of a Lewis acid catalyst. This idea will be discussed later in this Chapter (Section 1.1.6).

1.1.3 Dendralenes: multidiene units

There are four fundamental types of conjugated oligoalkenes, namely acyclic linear-conjugated alkenes (polyenes), acyclic cross-conjugated alkenes (dendralenes), cyclic linear-conjugated alkenes (annulenes), and cyclic cross-conjugated alkenes (radialenes) (Figure 1.1). The work discussed in this thesis will focus on the dendralenes.

![Figure 1.1: The family of conjugated oligoalkenes.](image)

Dendralenes, their name derived from dendron, the Greek for tree, are acyclic cross-conjugated polyenes. Cross-conjugated compounds are defined as carrying at least three alkene units, two of which are conjugated with a third alkene unit but not conjugated to each other. Dendralenes are named trivially according to the number of alkene units they contain. For example, the simplest dendralene, which contains three alkene units, is named [3]dendralene 28.

The first synthesis of a dendralene, specifically [3]dendralene 28, was independently reported by the Bailey and Blomquist groups in 1955 (Figure 1.2). Seven years later, Bailey also detailed the first synthesis of [4]dendralene 29. 

[12] This idea will be discussed later in this Chapter (Section 1.1.6).

[13] The work discussed in this thesis will focus on the dendralenes.

[14] Dendralenes are named trivially according to the number of alkene units they contain. For example, the simplest dendralene, which contains three alkene units, is named [3]dendralene 28.

[15] The first synthesis of a dendralene, specifically [3]dendralene 28, was independently reported by the Bailey and Blomquist groups in 1955 (Figure 1.2).

[16] Seven years later, Bailey also detailed the first synthesis of [4]dendralene 29.
Figure 1.2: [3]dendralene 28 and [4]dendralene 29.

Although some improvements to the synthesis of [3] and [4]dendralene on small scale were made by different groups, practical syntheses of [3] and [4]dendralene remained elusive. In 2000, Sherburn and co-workers investigated the syntheses of the [n]dendralene family, from [3]dendralene to [8]dendralene. They further studied the reactivities and properties of these [n]dendralenes. In the following years, general methods for the first practical syntheses of [n]dendralenes were developed, using cross-coupling reactions. These processes involved the use of cross-coupling reactions. Using this technology several members of the dendralene family can now be synthesised on multi-gram scales.

1.1.4 Cross-coupling reactions

The transition metal-catalysed reactions that result in the connection of two organic building blocks via the reaction between an organometallic reagent and an organic halide or triflate are known as cross-coupling reactions (Scheme 1.8). This versatile reaction group is tolerant of a wide variety of alkyl and aryl residues \( R \) and \( R' \).

\[
R-M + X-R' \xrightarrow{\text{catalyst}} R-R' + M-X
\]

Scheme 1.8: A general cross-coupling reaction. Newly formed bond in red (M=metal, X=halide or triflate).

A vast array of cross-coupling reactions using different organometallic substrates and various catalysts are known. Many named reactions, utilised the world over for synthesis including Suzuki, Negishi, Stille and Sonogashira fall into this class. These metal-catalysed cross-coupling reactions share many mechanistic similarities (Scheme 1.9).
Scheme 1.9: Generic transition metal (M) catalysed cross-coupling reaction mechanism between organometallic reagent R-M and coupling partner R'-X.

A transition metal catalyst LnM' is inserted into the R'-X bond of coupling substrate R'X. Following transmetallation, reductive elimination extrudes the newly coupled product (R-R') with concomitant regeneration of the catalyst.

Of particular utility in the synthesis of dendralenes is the Kumada-Tamao-Corriu (KTC) reaction, first reported in 1972.\textsuperscript{22,23} This nickel\textsuperscript{(0)}-catalysed reaction involves the coupling of Grignard reagents with organohalides and was used by Payne and Bradford in the formation of substituted [3]dendralenes (Scheme 1.10).\textsuperscript{19}
1.1.5 Diene-transmissive Diels-Alder reactions

Dendralenes are a family of compounds of significant synthetic utility with latent ability to form complex, polycyclic frameworks in one pot reactions. This bold statement may be justified by an examination of Scheme 1.11: One diene unit of [3]dendralene 28 may react with a dienophile 5 to provide structure 38. Note that 38 is itself possessed of a new diene unit, comprised of one unreacted double bond from the starting material and a new alkene arising from the Diels-Alder reaction.

This new semicyclic diene 38 may then undergo a second Diels-Alder reaction to form 39. Such a sequence, in which a first Diels-Alder reaction provides one alkene unit of a diene that undergoes a second Diels-Alder reaction is termed a diene-transmissive Diels-Alder reaction. Diene transmissive Diels-Alder reactions are themselves a subgroup of so-called cascade reactions, in which several bond forming events take place in a single reaction “pot”. These reactions may be ionic, pericyclic, radical-mediated or transition-metal-mediated. Such reactions are of great utility in synthetic chemistry by virtue of their atom economy, ability to install structural complexity with short synthetic sequences and concomitant economic and ecological benefits.

The work reported in this Chapter refers to the simplest members of the dendralene family. C2 substituted [3]dendralenes will be discussed, as will [4]dendralenes, substituted at the 1,2 and 4 positions (Figure 1.3).

Figure 1.3: [3]dendralene 28 and [4]dendralene 29.

1.1.6 Previous synthesis and diene-transmissive Diels-Alder reactions of C2 substituted [3]dendralenes

Although the synthesis of several C2 substituted [3]dendralenes had been reported in the literature practical, gram scale syntheses of this family remained elusive until the work of Sherburn and co-workers, published in 2007. The group also studied the
stability, reactivity and diene-transmissive Diels-Alder reactions of these compounds. 2-Methyl [3]dendralene 42 was prepared using the operationally simple, scaleable KTC cross-coupling reaction by Sherburn and coworkers in 2007 (Scheme 1.12).^{19}

\[
\text{40} \quad \text{Cl} + \quad \text{BrMg} \quad \text{41} \quad \xrightarrow{a} \quad \text{42}
\]

**Scheme 1.12:** Synthesis of 2-methyl [3]dendralene 42. *Reagents and conditions:* (a) Isopropenyl magnesium bromide 41 (1.2 mol equiv), Ni(dppp)Cl₂ (0.030 mol equiv), 0 °C, 2 h, (in 30-40 °C petrol solution, 31%).

2-Chloro [3]dendralene 37 was synthesised from the commercially available starting materials, 1,1-dichloroethylene 32 and chloroprene 40 using a Kumada-Tamao-Corriu cross-coupling reaction (Scheme 1.13). Commercially unavailable in Australia, chloroprene 40 was prepared by dehydrochlorination of 3,4-dichloro-1-butene 43 using Ca(OH)₂.\(^{31}\) This was then converted into the corresponding Grignard reagent 34 which underwent a cross-coupling reaction with 1,1-dichloroethylene 32 to form 2-chloro [3]dendralene 37 in good yield. This reaction is scaleable, allowing the formation of tens of grams of this interesting compound.

\[
\text{43} \quad \xrightarrow{a} \quad \text{40} \quad \text{Cl} \quad \xrightarrow{b} \quad \text{34} \quad \xrightarrow{c} \quad \text{37}
\]

**Scheme 1.13:** Synthesis of 2-chloro [3]dendralene 37. *Reagents and conditions:* (a) 3,4-Dichloro-1-butene (2.0 mol equiv), Ca(OH)₂ (1.0 mol equiv), ethylene glycol, 100 °C, 30 min, 74%; (b) Mg turnings (1.6 mol equiv), BrC₂H₄Br (0.30 mol equiv), ZnBr₂ (0.010 mol equiv), THF, 80 °C, 2 h, 89%; (c) 1,1-dichloroethylene 32 (5.0 mol equiv), Ni(dppe)Cl₂ (0.010 mol equiv), -20 °C, 16 h, 65%.

Using nickel catalysed KTC (Section 1.1.4) or palladium catalysed Negishi cross-coupling reactions, a variety of C₂ substituted [3]dendralene were synthesised (Figure 1.4).\(^{19}\)
Chapter 1

Figure 1.4: C2 substituted [3]dendralenes.\(^{19}\)

With a family of C2 substituted [3]dendralenes in hand, investigations into their behaviour in the Diels-Alder reaction, with particular emphasis on diene-transmissive reactions (Section 1.1.5), was undertaken. These studies employed \(N\)-methylmaleimide (NMM) \(^{49}\), a good dienophile, known to proceed with strong \textit{endo}-selectivity (Section 1.1.2.4). This material also provided adducts amenable to column chromatography, in contrast with such dienophiles as maleic anhydride \(^{19}\). Reaction of a C2 substituted [3]dendralene with an excess of NMM \(^{49}\) can, in principle, produce up to six products, arising from single and double Diels-Alder reaction (Scheme 1.14). It is important to note that exhaustive reaction of [3]dendralenes can occur with two molar equivalents of NMM \(^{49}\).
Scheme 1.14: Products arising from the addition of NMM 49 (5 mol equiv) to C2 substituted [3]dendralenes 50 at 25°C. Red arrow shows diene participating in Diels-Alder reaction.

The results of this investigation into the diene-transmissive Diels-Alder reaction of C2 substituted [3]dendralenes were quite illuminating (Table 1.1). Independent of the nature of the C2 substituent, the major isolated product was always bis-adduct 52, arising from mono-adduct 51. The next most prevalent product was generally mono-adduct 54. The remainder of material was minor bis-adduct 53, also arising from mono-adduct 51. No significant amounts of bis-adducts 55 or 56 were observed. Thus, mono-adduct 54 appears unreactive under the reaction conditions.
Table 1.1: Diels-Alder reactions of C2 substituted [3]dendralenes with NMM 49.19

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<td>37</td>
<td>Cl</td>
<td>61:12:27</td>
</tr>
<tr>
<td>2</td>
<td>44</td>
<td>Ph</td>
<td>58:6:36</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>Me</td>
<td>56:8:36</td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>p-OMePh</td>
<td>65:7:28</td>
</tr>
<tr>
<td>5</td>
<td>48</td>
<td>p-NO2Ph</td>
<td>65:7:28</td>
</tr>
<tr>
<td>6</td>
<td>46</td>
<td>OEt</td>
<td>81:10:9</td>
</tr>
<tr>
<td>7</td>
<td>47</td>
<td>CO2Me</td>
<td>68:8:24</td>
</tr>
</tbody>
</table>

The product ratio arising from the first Diels-Alder reaction of 2-chloro [3]dendralene 37 with NMM 49 to give mono-adducts 51 and 54 may be deduced to be 73:27 (Table 1.1, entry 1). Density functional theory (DFT) calculations (B3LYP/6-31G(d)) on this reaction predicted a product distribution of 88:12, in good agreement with the experimental data. The product distribution was rationalised on the basis of destabilising steric congestion in the transition state B, leading to reduced formation of mono-adduct 54, relative to mono-adduct 51 (Figure 1.5). More generally, given the similarities of the product distributions, independent of the electronic nature of the C2 substituent R (Table 1.1, entries 1-7), it appears that the steric effect described above overcomes any electronic effects of the substituents. Interestingly, the computational study showed that the unreacting diene, as well as the reacting diene in the substrate, adopts the s-cis conformation.
Lewis acids are known to often catalyse Diels-Alder reactions by reducing the LUMO energy of the dienophile to which they are complexed. Further, they have been demonstrated to sometimes influence the regioselectivities of such reactions by virtue of their effect on the magnitude of the orbital coefficients. With these effects in mind, the effect of the Lewis acid ethyl aluminium dichloride, pre-complexed to NMM 49, on the diene-transmissive Diels-Alder reaction with 2-phenyl [3]dendralene 44 was compared with the uncatalysed reaction (Scheme 1.15).
Scheme 1.15: Comparison of uncatalysed and Lewis acid-catalysed Diels-Alder reactions of 2-phenyl [3]dendralene 44 with NMM 49. Reagents and conditions: (a) NMM (5 mol equiv), CDCl₃, rt, 90%, 58:59:60 58:6:36; (b) NMM:EtAlCl₂, PhMe, -78 °C to rt, 68%, 58:59:60 25:50:25 or NMM:2EtAlCl₂, PhMe, -78 °C to rt, 67%, 58:59:60 33:67:0.

The reaction is clearly catalysed by EtAlCl₂ proceeding from -78 °C to room temperature. Further, the reaction is now completely site selective, with only bis-adducts 58 and 59 arising via Diels-Alder reaction of the mono-adduct 57 being observed.

1.1.7 Practical synthesis of [4]dendralene 29 and its Diels-Alder reactions

Initially, [4]dendralene 29 was only available in milligram quantities, with the requirement of custom-fabricated equipment impeding investigations into the chemistry of this remarkable diene. Payne surmounted this problem and synthesised [4]dendralene 29 on gram scale using the cheap starting material chloroprene 40 in 26% yield using standard laboratory equipments and methods. Tetraene 29 was synthesised in a one pot reaction (Scheme 1.16).
Scheme 1.16: The first practical synthesis of [4]dendralene 29. Reagents and conditions: (a) Mg, ZnBr₂, BrC₂H₄Br, THF; (b) CuCl, −78 °C; (c) CuCl₂·2LiCl, −78 °C, 26%.

Following formation of the Grignard reagent derived from chloroprene 40 and conversion to the organocuprate, oxidative coupling with CuCl₂·2LiCl provided [4]dendralene 29. This material can be stored as a neat liquid over several weeks with only tiny amounts of decomposition, in marked contrast to the predicted instability of this family of hydrocarbons. With [4]dendralene 29 in hand, attention next turned to exploring the chemistry of this material. Under kinetically controlled conditions at room temperature, the reaction between [4]dendralene 29 and an excess of NMM 49 in THF gives a mixture of five products, one mono-adduct, two bis-adducts and two tris-adducts (Scheme 1.17). This is quite interesting, since, in principle, one could expect, in the absence of any selectivity, many products arising from single, double and triple Diels-Alder reactions with NMM 49.
Scheme 1.17: Reactions between [4]dendralene 29 and NMM 49 under kinetically controlled conditions at room temperature. Reagents and conditions: (a) NMM (2.5 mol equiv), rt, 16 h, 95%.

From the first cycloaddition reaction, just one mono-adduct, 61, arising from a Diels-Alder reaction between NMM 49 and the internal diene, was isolated in 21% yield. In addition, Z-triene 61 does not undergo further reaction with NMM 49 under the reaction conditions. The other possible mono-adduct, terminal mono-adduct 62, arising from NMM 49 reaction with the terminal diene of [4]dendralene 29, could not be isolated. This semicyclic [3]dendralene 62 is clearly very reactive and undergoes further cycloaddition reactions with NMM 49 to give two isolable diastereomeric bis-adducts 63 and 64. On the other hand, the other possible bis-adducts 65 and 66, could not be isolated and instead underwent third cycloaddition reactions with NMM 49 to form tris-adducts 67 and 68.
The isolated product ratio of \textit{bis}-adducts 63 and 64 (4:42) is clear evidence for strong \(\pi\)-diastereofacial selectivity when the second Diels-Alder reaction takes place at the semicyclic diene of \textit{mono}-adduct 62. NMM 49 preferentially approaches the convex face of semicyclic diene 62, leading to product 64 (Scheme 1.18). The minor pathway, leading to product 63 is disfavoured by steric clashes between the approaching NMM 49 and the imide functionality incorporated into 62.

![Diagram](image)

**Scheme 1.18:** Two possible addition of NMM 49 to \textit{mono}-adduct 62 and \textit{bis}-adducts 63 and 64. Reagents and conditions: (a) NMM (2.5 mol equiv), 16 h, rt (4:5 ratio, 4\%, 42\% respectively).

In contrast, when the second Diels-Alder reaction takes place at the exocyclic diene of \textit{mono}-adduct 62 leading to \textit{bis}-adducts 65 and 66, no \(\pi\)-diastereofacial selectivity is in evidence. This statement is supported by the isolated ratio of the subsequent products 67 and 68 (14:14), arising from third cycloadditions to 65 and 66.

Although the first cycloaddition reaction product 61 does not undergo further reaction with NMM 49 under kinetically control conditions at room temperature, as described, it does react further to provide tetracycle 69 as the major product under high pressure (19 kbar) at ambient temperature (Scheme 1.19). Additionally, the \(6\pi\)-electrocyclisation reaction of 61 in toluene at reflux not only gives electrocyclisation product 70 in good
yield, but also pentacycle 71 in 70% yield, arising from further cycloaddition cascade reaction with dienophile N-phenylmaleimide (NPM) (Scheme 1.19).

Scheme 1.19: Further transformation of internal mono-adduct product 61. Reagents and conditions: (a) NMM (2 mol equiv), CH₂Cl₂, rt, 19 kbar, overnight, 69%; (b) toluene, BHT, reflux, 18 h, 72%; (c) NPM (3 mol equiv), BHT, reflux, toluene, 18 h, 70% (yield from 61, in two steps).

Further, at ambient temperature at 19 kbar, [4]dendralene 29 reacts with an excess of NMM 49 to furnish tris-adduct 72 in a one pot reaction in 34% isolated yield. Under the same conditions, the same product can be produced from the reaction of bis-adduct 64 and NMM 49 in 84% yield (Scheme 1.20), elucidating a likely pathway to this material.

Scheme 1.20: The efficient preparation of tris-adduct 72. Reagents and conditions: (a) NMM (3.6 mol equiv), CH₂Cl₂, 19 kbar, 70 °C, 2 h, then rt, 4 days, 84%; (b) NMM (9.5 mol equiv), CH₂Cl₂, 19 kbar, 70 °C, 2 h, then rt, 4 days, 34%.

Finally, site selective reactions may be achieved by simply reacting the dendralene 29 with premixed dienophile and different amounts of simple Lewis acid promoters. For example, when a 1:1 molar ratio of NMM 49 and MeAlCl₂ are used, the internal cycloaddition product 61 is formed in high selectivity in 77% yield from of
In conclusion, operationally simple conditions for the practical formation of [4]dendralene 29 were identified. By carefully controlling reaction conditions such as temperature, pressure and the presence and stoichiometry of Lewis acid catalysts, site selectivity, \( \pi \)-diastereofacial selectivity and extent of sequential pericyclic reactions may be tuned in the versatile [4]dendralene system.

### 1.1.8 Previous syntheses and diene-transmissive Diels-Alder reactions of substituted [4]dendralenes

In 2008, Visiting Fellow, Ali Reza Alborzi\(^{33}\) prepared the family of C2 and C4 substituted [4]dendralenes and examined their reactivity in the Diels-Alder reaction. Only one stereochemistry is possible for C2 substituted [4]dendralene 73 (Figure 1.6). In contrast, both (E)- and (Z)- configurations are possible for C4 substituted dendralenes.
(74 and 75, respectively). The remaining 1-(E) and (Z)-substituted [4]dendralenes 76 and 77 form the body of discussion of Sections 1.3.1 and 1.3.2 of this present report.

Figure 1.6: [4]dendralene 29 and substituted [4]dendralene family.

1.1.8.1 Synthesis and reactivity of 2-methyl [4]dendralene 78

The first substituted dendralene for us to review is 2-methyl [4]dendralene 78. A KTC coupling reaction between isopropenyl magnesium bromide 41 and 2-chloro [3]dendralene 37 (see Section 1.1.6) provides the title compound 78 in reasonable yield (Scheme 1.22).

\[
\text{37} + \text{BrMg} \rightarrow \text{a} \rightarrow \text{78}
\]

Scheme 1.22: Synthesis of 2-methyl [4]dendralene 78. Reagents and conditions: (a) Isopropenyl magnesium bromide (1.5 mol equiv), Ni(dppp)Cl2 (0.040 mol equiv), THF, 0 °C to rt, overnight, 29%.

With 2-methyl [4]dendralene 78 in hand, its exhaustive reactivity with NMM 49 was examined. It must be noted that this dendralene has three distinct diene sites available for the first Diels-Alder reaction with NMM 49. As with unsubstituted [4]dendralene 29, a terminal diene (blue) and an internal diene (green) are found. There is also a ‘substituted’ diene (red) to be found in substituted dendralene 78 (Figure 1.7).
Three molar equivalents of NMM 49 were reacted at room temperature and the products isolated by flash column chromatography (Scheme 1.23). Only a minor amount (3%) of internal mono-adduct 79 was isolated. Terminal mono-adducts 80 and 81 were not observed. Two bis-adducts, 82 and 83, were isolated in 27% and 14%, respectively, could be derived from 80 or 81. Another two bis-adducts, 84 and 85, isolated in 26% and 1%, respectively, could only be derived from mono-adduct 81. Clearly, internal mono-adduct 79 is formed in limited amount and is inert to further reaction with NMM 49.
Scheme 1.23: Diels-Alder reaction of 2-methyl [4]dendralene 78 with NMM 49. Reagents and conditions: (a) NMM (3 mol equiv), CH$_2$Cl$_2$, rt, 14 h, 71%.

It is unclear whether bis-adducts 82 and 83 are formed by reaction of a second molar equivalent of NMM 49 to mono-adduct 80 alone, mono-adduct 81 alone, or both 80 and 81 simultaneously. In any case, the terminal diene sites of 2-methyl [4]dendralene 78 are more reactive than is the internal diene site, as was observed for unsubstituted [4]dendralene 29 (Section 1.1.7). Further work is required to determine which of the terminal diene sites of 2-methyl [4]dendralene 78 is the more reactive. Specifically, the reaction with one molar equivalent of NMM 49 should be examined.

1.1.8 Synthesis and reactivity of 4-(E)-methyl [4]dendralene 86

Alborzi next examined the effect of substitution at the C4 position of [4]dendralene. Let us first discuss the formation of 4-(E)-methyl [4]dendralene 86. A disconnection to provide readily available Grignard reagent 34 was briefly examined and discarded. It was decided that the unknown and presumably highly reactive and volatile chloro-butadiene 87 would render this approach problematic.

An alternate approach was therefore examined (Scheme 1.25). Retrosynthesis of the target material provides dibromide 96, itself ultimately accessed from diester 93. Elimination of HBr to provide an alkene unit was used to great effect within the group to prepare [3]dendralene 28. Diester 93 may be obtained from alkyne diol 89 by a double Johnson-Claisen rearrangement.


In the synthesis, commercially available alkyne diol 89 was treated with triethylorthoacetate 88 and propionic acid in dry DMF under microwave irradiation (Scheme 1.26). The mechanism of the conversion of alkyne diol 89 to diester 93 involves a double Johnson-Claisen rearrangement: Following condensation of one of the alcohols to form ketene acetal 90, a [3,3] sigmatropic rearrangement occurs to form allene 91, the alcohol of which is converted to ketene acetal 92 that undergoes a second Johnson-Claisen rearrangement.

This, in turn, undergoes a second cycle of reaction to form target E-configured diester 93. The Z-configured diester 94 is also formed. This is of utility in the formation of 4-(Z)-methyl [4]dendralene 101 as will be discussed in Section 1.1.8.3.
Scheme 1.26: Preparation of E- and Z- diesters 93 and 94.\textsuperscript{35} Reagents and conditions: (a) CH\textsubscript{3}C(OEt)\textsubscript{3} (9.1 mol equiv), C\textsubscript{2}H\textsubscript{5}CO\textsubscript{2}H, DMF, 180 °C, 300 W microwave irradiation, 25 min, 73% (ratio E- to Z- isomer 93 and 94, respectively 47:53); i) acetal exchange step ii) elimination step iii) [3,3]-sigmatropic rearrangement step iv) acetal exchange step v) elimination step vi) [3,3]-sigmatropic rearrangement step.

Reduction of E- configured diester 93 was then carried out with lithium aluminium hydride to form diol 95 in excellent yield. Dehydroxylative bromination of diol 95 provided dibromide 96 following purification by flash column chromatography (Scheme 1.27). Twofold elimination of HBr from dibromide 96 provided target 4-(E)-methyl [4]dendralene 86. This was then distilled to purity from the crude reaction mixture. This reaction progressed in good yield.

Scheme 1.27: Preparation of 4-(E)-methyl [4]dendralene 86. Reagents and conditions: (a) LiAlH\textsubscript{4} (2.0 mol equiv), Et\textsubscript{2}O, 0 °C, 30 min, then rt, overnight, 97%; (b) NBS (2.0 mol equiv), PPh\textsubscript{3} (2.0 mol equiv), CH\textsubscript{2}Cl\textsubscript{2}, -78 °C to rt, overnight, 40%; (c) DBU (6.4 mol equiv), DMSO, rt, 50 mmHg, 15 min, then 15 mmHg, 2 h, 60%.
With dendralene 86 in hand, its reaction with potent dienophile NMM 49 was then examined (Scheme 1.28). Similarly to 2-methyl [4]dendralene 78 (Figure 1.7), 4-(E)-methyl [4]dendralene 86 also has three distinct diene sites available for Diels-Alder reaction (Figure 1.8).

![Diagram of 4-(E)-methyl [4]dendralene 86 with labeled diene sites]

**Figure 1.8:** The three distinct diene sites of 4-(E)-methyl [4]dendralene 86.

Internal mono-adduct 97 was formed in good yield (42%). No products arising from further reaction of this adduct were observed. No mono-adduct from Diels-Alder reaction at the substituted diene was observed, nor was bis-adducts arising from this.

![Chemical structure of mono-adduct 97 and bis-adducts 99 and 100]

**Scheme 1.28:** Diels-Alder reaction of 4-(E)-methyl [4]dendralene 86 with NMM 49. \( \text{Reagents and conditions: } (\text{a}) \text{ NMM (3 mol equiv), rt, CH}_2\text{Cl}_2, \text{ overnight, 90%}. \)

In contrast, cycloaddition at the unsubstituted terminal diene site provided mono-adduct 98, which was not isolated. Instead, it reacted on to provide mainly bis-adduct 99 (45%), with traces of bis-adduct 100 (3%). There is clear strong \( \pi \)-diastereofacial...
selectivity here, with approach of the second molar equivalent of NMM preferentially occurring from the least hindered face of the mono-adduct.

There is a dramatic enhancement of reactivity at the internal diene, compared with the parent [4]dendralene. This is clearly due to the effect of the 4-(E)-methyl substituent.


Synthetic effort now turned towards the 4-(Z)- configured analogue of 4-(E)-methyl [4]dendralene. As discussed in Section 1.1.8.2, both E- and Z-configurations of the methyl substituent on diester are available from the same reaction of alkyne diol and the yield of Z- configured diester is 38% (Scheme 1.26). This was then taken on in the same sequence as for the E-configured diester: Preparation of the Z-configured dibromide proceeded in superior yield to that of E-configured dibromide (84% and 40%, respectively). Target 4-(Z)-methyl [4]dendralene 101 was distilled from the crude reaction mixture in good yield (Scheme 1.29).

![Scheme 1.29: Preparation of 4-(Z)-methyl [4]dendralene 101. Reagents and conditions: (a) LiAlH₄ (2.0 mol equiv), Et₂O, 0 °C, 30 min, then rt, overnight, 91%; (b) NBS (2.0 mol equiv), PPh₃ (2.0 mol equiv), CH₂Cl₂, −78 °C to rt, overnight, 84%; (c) DBU (6.4 mol equiv), DMSO, rt, 50 mmHg, 15 min, then 15 mmHg, 2 h, 77%.

The reaction of 4-(Z)-methyl [4]dendralene 101 with NMM was now examined (Scheme 1.30). No products derived from reaction at the internal diene were observed. All isolated products were derived from terminal mono-adducts 104 or 105. No mono-adducts were themselves isolated, they instead underwent further cycloaddition reactions. Specifically, only two bis-adducts 106 and 107 were isolated. These must be formed from terminal mono-adduct 105. Bis-adduct 109 underwent a third cycloaddition reaction to form tris-adducts 111 and 112. While there was only one endo-adduct product 110 arising from a third Diels-Alder reaction on bis-adduct 108, probably for
steric reasons. Since an excess of NMM 49 was used, it is as yet unclear whether the first cycloaddition occurs at the substituted or unsubstituted terminal diene. Experiments with a single molar equivalent of NMM 49 would resolve this issue.

\[ \text{Scheme 1.30: Diels-Alder reaction of 4-(Z)-methyl [4]dendralene 101 with NMM 49. Reagents and conditions: (a) NMM (3 mol equiv), rt, CH}_2\text{Cl}_2, \text{overnight, 70%}. \]

In contrast with its (E)-configured analogue 86, 4-(Z)-methyl [4]dendralene 101 preferentially undergoes Diels-Alder reaction with an excess of NMM 49 to yield major products arising from reaction at the terminal dienes (Figure 1.9).

1.2 Aims

The first aim of this project involves the syntheses of 1-alkyl substituted [4]dendralenes, the remaining undescribed members of the substituted [4]dendralene family. Both (E)- and (Z)- substituted dendralenes 113 and 114 will be examined (Figure 1.10).

Figure 1.10: 1-(E)-alkyl substituted [4]dendralene 113 and 1-(Z)-alkyl substituted [4]dendralene 114.

The second aim is to investigate the site selectivity of the Diels-Alder reaction of 1-alkyl substituted [4]dendralenes with the potent dienophile NMM 49 in order to identity patterns of reactivity that may have potential synthetic applications.

1.3 Results & Discussion

1.3.1 The synthesis of 1-(E)-alkyl substituted [4]dendralene 113

The first 1-(E)-alkyl substituted [4]dendralene 113 selected for investigation was 1-(E)-methyl [4]dendralene 115. We employed cross-coupling reactions (Section 1.1.4), given their previous utility for the preparation of other dendralenes in the group. One obvious disconnection of this compound leaves us with 2-chloro [3]dendralene 37 and a
metallated alkenyl fragment 116 (Retrosynthesis One of Scheme 1.31). A similar approach was used to great effect by Alborzi to prepare 2-methyl [4]dendralene 78 (Section 1.1.8).

\[
\begin{align*}
\text{Retrosynthesis One} \\
\begin{array}{c}
\text{113} \\
\text{37} \\
\text{116}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{Retrosynthesis Two} \\
\begin{array}{c}
\text{113} \\
\text{34} \\
\text{117}
\end{array}
\end{align*}
\]

**Scheme 1.31:** Retrosynthetic analyses of 1-(E)-alkyl substituted [4]dendralene 113. (M= metallated fragment; R=Me, n-hex *vide infra*).

One may consider an alternate disconnection, to provide readily available Grignard reagent 34 derived from chloroprene 40 and an E- alkyl substituted butadienyl electrophile 117 (Retrosynthesis Two of Scheme 1.31). Let us consider the reactions associated with these two retrosynthetic analyses in turn.


The transformation to prepare 1-(E)-methyl [4]dendralene 115 from 2-chloro [3]dendralene 37 via a cross-coupling reaction could employ a variety of coupling partners. The work described in this report explored the use of organoboron species (Suzuki-Miyaura) and a Grignard reagent (Kumada-Tamao-Corriu) for the cross-coupling reactions (Scheme 1.32).
2-Chloro [3]dendralene 37 was previously synthesised within our group (Section 1.1.6) in yields around 65%. Optimisation of this procedure in our hands (reducing reaction time and increasing the amount of inexpensive and volatile coupling partner, 1,1-dichloroethylene 32 from five to eight molar equivalents) boosted the yield of this important intermediate to 85% (Scheme 1.33). Analytically pure material was available following aqueous workup of the crude reaction mixture. This operational issue is important, since it is known that 2-chloro [3]dendralene 37 is prone to undergo dimerisation via Diels-Alder reaction.19

Scheme 1.33: Improved synthesis of 2-chloro [3]dendralene 37. Reagents and conditions: (a) 1,1-dichloroethylene (7.6 mol equiv), Ni(dppe)Cl2 (0.013 mol equiv), −20 °C, 13 h, 85%.

It is well established that the order of reactivities of organohalides in the Suzuki-Miyaura cross-coupling reaction is 1 > OTf > Br >> Cl.36 To this end, we attempted the synthesis of the previously unknown 2-bromo and iodo [3]dendralene derivatives, 119 and 120, respectively. Both materials were prepared by reaction of electrophilic halide sources with the Grignard reagent 118 which is formed from 2-chloro [3]dendralene 37 (Scheme 1.34).
Reagents and conditions: (a) Magnesium powder (2.9 mol equiv), BrC₂H₄Br (0.70 mol equiv), ZnBr₂ (0.030 mol equiv), THF, reflux, 30 min, 36%; (b) NBS (3.0 mol equiv), THF, -78 °C to rt, 2.5 h, 13%; (c) I₂ (3.0 mol equiv), Et₂O, -78 °C to rt, 2.5 h, 30%.

As was the case for the chloride, both new halides were prone to decomposition, with iodo derivative 120 isolated in pure form only once and bromo derivative 119 isolated in impure form only. As an interesting aside, bromo derivative 119 was found to be contaminated with allenyl rearrangement product 122. This may or may not arise from the allenic Grignard reagent 121 (Scheme 1.35). It is unclear whether the Grignard reagent 118 is in equilibrium with its allenic form 121 or not. This type of equilibrium is discussed more fully in Section 2.3.8 of Chapter Two.

Scheme 1.35: Possible relationships between 118 and 121. Reagents and conditions: (a) NBS (3 mol equiv), THF, -78 °C, 1.5 h then to rt, 1 h, 28%, (ratio of 119:122, 45:55, isolated ratio).

Various sources of electrophilic bromine were investigated for the synthesis of 2-bromo [3]dendralene 119. No target product 119 was observed when
1,2-dibromoethane was used. When elemental bromine was used as the halogen source, the reaction resulted in a low yield (2%) of target product 119 and rearrangement by-product 122. When the source of bromine was N-bromosuccinimide (NBS), the reaction afforded compound 119 in impure form in 13% yield and the rearrangement by-product 122 in pure form in 15% yield.

Our optimised yield for 2-iodo [3]dendralene 120 (30%) was higher than that for the corresponding bromide. In addition, the target iodide 120 was extremely difficult to handle, prone to decomposition.


The Suzuki-Miyaura reaction involves the palladium-catalysed cross-coupling of organohalides (or organohalide equivalents such as triflates) with organoboron species (Scheme 1.36).36 It was anticipated that 2-chloro [3]dendralene 37 would smoothly undergo Suzuki-Miyaura cross-coupling the pinacol boronate ester of 1-(E)-propene to provide 1-(E)-methyl [4]dendralene 115.

\[
\text{R-M} + \text{X-R'} \xrightarrow{\text{catalyst}} \text{R-R'} + \text{M-X}
\]

Scheme 1.36: The Suzuki-Miyaura cross-coupling reaction. (M=boron, X=halide or triflate).36

Following a literature procedure, treatment of catechol borane 123 with ca. 1.3 mol equiv of propyne 124 at 70 °C for 12 hours,37 afforded catechol boronate 125 in 58% yield. Conversion of 125 to pinacol boronate ester 126 proceeded smoothly in ether at room temperature (Scheme 1.37).
Scheme 1.37: Synthesis of pinacol boronate ester 126. Reagents and conditions: (a) Propyne (ca. 1.3 mol equiv), -78 °C to 70 °C, THF, 12 h, 58%; (b) Pinacol (1.0 mol equiv), Et₂O, rt, 3 h, 63%.

With pinacol boronate ester 126 in-hand, its Suzuki-Miyaura cross-coupling reaction with 2-chloro [3]dendralene 37 was attempted. Traditionally, bromides and iodides are used as coupling partners in Suzuki-Miyaura reactions. Only recently have catalyst systems suitable for use with the less reactive chlorides become available. They are generally used for the coupling of aryi chlorides. Activation of the catalyst by ligand modification is known to increase substrate tolerance and reactivity in the Suzuki-Miyaura reaction.\(^\text{38}\) Among the most successful systems are those reported by the Buchwald group. We therefore employed Buchwald’s SPhos ligand 127 (Figure 1.11) in our reaction.\(^\text{39}\)

Figure 1.11: SPhos ligand 127.

Disappointingly, even with this reactive catalyst system, no evidence of cross-coupled target material 115 was observed (Scheme 1.38). Analysis of crude reaction mixtures, obtained at variety of temperatures, showed only unreacted starting material and decomposition products by \(^1\)H NMR.
Scheme 1.38: An attempt to synthesise 1-(E)-methyl [4]dendralene 115. Reagents and conditions: (a) Pinacol boranate ester (1.5 mol equiv), Pd(OAc)$_2$ (0.020 mol equiv), SPhos (0.040 mol equiv), K$_3$PO$_4$ (2.0 mol equiv), $n$-BuOH/H$_2$O (9:1), various temperatures, from rt to 50 °C, in the dark, Ar, overnight.

Kumada-Tamao-Corriu (KTC) cross-coupling between 2-chloro [3]dendralene 37 and the Grignard reagent of 1-(E)-propene 129 was also explored en route to target compound 115. Following a procedure reported in the literature,\(^\text{40}\) Grignard reagent 129 was prepared from commercially available (E)-prop-1-en-1-yl bromide 128 (Scheme 1.39). Titration with water showed the extent of conversion to be 57%.

Scheme 1.39: Preparation of Grignard reagent 129. Reagents and conditions: (a) Magnesium turnings (2.3 mol equiv), I$_2$ (one crystal), THF, -20 °C for 40 min then 0 °C for 40 min, 57%.

Once the Grignard reagent 129 was prepared, the KTC cross-coupling reaction was tried (Scheme 1.40). Gratifyingly, $^1$H NMR analysis of the crude reaction mixture strongly suggested the presence of target 1-(E)-methyl [4]dendralene 115. Unfortunately, evidence for the presence of the 1-(Z)- isomer 130 was also observed. Bulb to trap distillation provided a purified mixture of the two isomers. Frustratingly, reverse phase HPLC failed to provide target material. We ascribe this to the high volatility of the materials.

Scheme 1.40: An attempt to synthesise 1-(E)-methyl [4]dendralene 115. Reagents and conditions: (a) Grignard reagent (1.3 mol equiv), Ni(dppp)Cl$_2$ (0.10 mol equiv), PPh$_3$ (0.20 mol equiv), THF, 0 °C to rt, 5 h, (ratios 115:130, 45:55).
The presence of (Z)- isomer 130 may be due to isomerisation of initially-formed (E)-target material 115 (Scheme 1.41). There is some evidence for this process occurring under nickel-catalysed conditions. Additionally, propenyl Grignard reagent 129 has been reported to isomerise to the (Z)-isomer 131. In any case, isomerisation occurs during the KTC coupling, precluding the preparation of pure (E)- or (Z)-isomers.


Clearly, what is needed is a synthetic method that provides exclusively products with either (E)- or (Z)- configurations exclusively. This would avoid the separation problems associated with these two volatile materials. Studies next focused on the second route which involved the KTC cross-coupling reaction between the readily available Grignard reagent 34 derived from chloroprene 40 and 1-(E)-alkyl substituted 3-chloro butadiene 117 (Scheme 1.42).

1.3.1.2 1-(E)-Alkyl substituted [4]dendralenes from Grignard reagent 34

The preparation of 1-(E)-alkyl substituted [4]dendralenes 113 from Grignard reagent 34 (itself derived from chloroprene 40) via a KTC reaction requires substituted chloro-butadiene 117 as the coupling partner (Scheme 1.42). The work described in this section will detail approaches towards coupling partner 117 and subsequent KTC reaction between this coupling partner 117 and Grignard reagent 34.
Scheme 1.42: Preparation of 1-\((E)\)-alkyl substituted [4]dendralene 113 from Grignard reagent 34 and coupling partner 117. (\(R=\text{Me, } n\)-hex).

1.3.1.3 Attempted preparation of 1-\((E)\)-alkyl substituted 3-chloro butadiene 117

Although 1-\((E)\)-methyl-3-chloro-butadiene 132 first appears in the chemical literature in 1951, contaminated with 2,2-dichloropentene,\textsuperscript{42} efficient pathways to its formation have yet to be found. An obvious preparation would employ previously prepared pinacol boronate ester 126 and 1,1-dichloroethylene 32 using a Suzuki-Miyaura cross-coupling reaction (Scheme 1.43). Conditions reported by Sulikowski to be useful for the coupling of a catechol boronate and a vinyl iodide were trialled.\textsuperscript{37}

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} + \quad \text{O} \quad \text{O} \\
32 & \quad 126 & \quad a & \quad 132 & \quad 133
\end{align*}
\]

Scheme 1.43: Towards the preparation of 1-\((E)\)-methyl-3-chloro-butadiene 132. Reagents and conditions: (a) 1,1-dichloroethylene (1.2 mol equiv), Pd(PPh\textsubscript{3})\textsubscript{4} (0.020 mol equiv), Ag\textsubscript{2}CO\textsubscript{3} (2.0 mol equiv), THF, various temperature, 6 h, only starting material; (b) 1,1-dichloroethylene (1.0 mol equiv), Pd(dppf)Cl\textsubscript{2} (0.050 mol equiv), NaOH (2.0 mol equiv), sealed tube, THF, various temperatures, 8 h.

Both Pd(PPh\textsubscript{3})\textsubscript{4} and Pd(dppf)Cl\textsubscript{2} catalysts were examined, with only the latter providing any evidence of reaction at all. These reactions provided mixtures of volatile butadiene 132 and double coupling by-product 133 in THF. The handling of these materials was problematic, due to their high volatilities. It was found that the boiling points of THF and the target material 132 were almost identical, hindering effective purification.

At this stage in the research, in order to address the volatility issues, it was decided to elongate the Cl substituent alkyl chain to a C\textsubscript{6}H\textsubscript{13} unit, rather than a CH\textsubscript{3}. The associated large differences in masses of the target material 136 and the by-product
arising from double coupling 137 (Scheme 1.44) were anticipated to allow the effective isolation of pure target material from THF.

Scheme 1.44: Preparation of 1-(E)-hexyl-3-chloro-butadiene 136. Reagents and conditions: (a) Catecholborane (1.1 mol equiv), THF, 70 °C, 2 h, then pinacol (1.2 mol equiv), 3 h, rt, 49%; (b) 1,1-dichloroethylene (3.0 mol equiv), Pd(dppf)Cl₂ (0.010 mol equiv), NaOH (1.3 mol equiv), sealed tube, THF, various temperatures.

Disappointingly, it was found that the undesired double coupling by-product 137, predominated, even with extreme amounts of 1,1-dichloroethylene 32. This was done in an attempt to bias the reaction in favour of the mono-coupled product 136. Amazingly, even with 60 molar equivalents of 1,1-dichloroethylene 32, the product of double coupling predominated. Neither 136 nor 137 could be isolated in pure form from these reactions. It is clear that the mono-coupled product 136 is far more reactive in the cross-coupling reaction than is 1,1-dichloroethylene 32. In any event, 1-(E)-hexyl 3-chloro butadiene 136 is a known compound, prepared from the 1-(E)-octen-1-ylboronic acid 138, rather than the pinacol boronate ester 135. Boronic acid 138 was prepared according to a literature procedure (Scheme 1.45).

Scheme 1.45: Preparation of 1-(E)-octen-1-ylboronic acid 138. Reagents and conditions: (a) Catecholborane (1 mol equiv), 70 °C, 2 h then H₂O (excess), rt, 2 h, 39%.

The boronic acid 138 was used for the Suzuki-Miyaura cross-coupling reaction with 1,1-dichloroethylene 32 according to a slight modification of the procedure of
Barluenga and co-workers (Scheme 1.46). The cross-coupling reaction provided the target product 136 in 32% yield.

Scheme 1.46: Preparation of 1-(E)-hexyl 3-chloro butadiene 136. Reagents and conditions: (a) 1,1-Dichloroethylene (4 mol equiv), Pd2(dba)3 (0.005 mol equiv), XPhos (0.02 mol equiv), K3PO4 (2 mol equiv), toluene, 60 °C, 6 h, 32% isolated yield 136, (80:20 ratio, 136 and 137 by crude 1H NMR).

Evidently, cross-coupling under these conditions is more selective for the product of mono-coupling 136. The reasons for this are unclear, and clearly warrant further investigation. With coupling partner 136 in hand, KTC cross-coupling with the Grignard reagent 34 derived from chloroprene 40 was explored. A variety of conditions were examined, including varying the order of reagent addition, reaction temperature, reaction time and catalyst loading. To our delight, the highest yield of 1-(E)-hexyl [4]dendralene 139 was obtained from the dropwise addition of three molar equivalents of Grignard reagent 34 to coupling partner 136 with 5% catalyst loading (Scheme 1.47).

Scheme 1.47: Preparation of 1-(E)-hexyl [4]dendralene 139. Reagents and conditions: (a) Grignard reagent (3 mol equiv), PPh3 (0.05 mol equiv), Ni(dppp)Cl2 (0.05 mol equiv), THF, -12 °C to 22 °C, 5.5 h, 53%.

1.3.2 Towards the synthesis of 1-(Z)-hexyl [4]dendralene 140

Bouyed by our success with the synthesis of 1-(E)-hexyl [4]dendralene 139, it was reasonable to anticipate the synthesis of the (Z)- configured analogue 140 via 1-(Z)-hexyl 3-chloro butadiene 141 (Scheme 1.48).
1.3.2.1 Formation of \( \text{1-(Z)-hexyl [4]dendralene 140 via KTC cross-coupling} \)

The electrophilic fragment \( 141 \) may be derived by Suzuki-Miyaura cross-coupling of 1,1-dichloroethylene \( 32 \) with \( (Z) \)-boronic acid \( 142 \), as was shown for the \( (E) \)-analogue \( 138 \) (vide supra) (Scheme 1.49). A variety of conditions were explored towards the preparation of \( (Z) \)-boronic acid \( 142 \).

Standard uncatalysed hydroborations of alkynes give the \( (E) \)-boronic acid \( 138 \). Unfortunately, literature methods for producing the \( (Z) \)-boronic acid \( 142 \) do not exist. On the other hand, the preparation of \( (Z) \)-catechol boronate \( 143 \) is known. The first method employed rhodium-mediated coupling of the alkyne \( 134 \) with catecholborane \( 123 \). Hydrolysis of the initially-formed catechol boronate \( 143 \) was anticipated to provide target boronic acid \( 142 \) (Scheme 1.50). While evidence for the formation of \( (Z) \)-catechechol boronate \( 143 \) was observed with \( (E) \)-isomer \( 144 \) in 1:2 ratio, respectively, no target \( (Z) \)-product could be isolated. The presence of the \( (E) \)-isomer is presumably due to the uncatalysed background reaction. We were unable, therefore, to apply this \( (Z) \)-selective hydroboration.
Scheme 1.50: An rhodium catalysed attempt to prepare (Z)-catechol boranate 143. Reagents and conditions: (a) [Rh(cod)Cl]₂ (0.015 mol equiv), PCy₃ (0.060 mol equiv), Et₃N (1.0 mol equiv), rt, 30 min, then 1-octyne (1.2 mol equiv), rt, 2 h, 10% yield, (143:144, 1:2 ratio).

We therefore elected to use a more established route, specifically the well-known Lindlar reduction of alkynes to form (Z)-alkenes (Scheme 1.51). Reaction of 1-octyne 134 with triisopropoxy borane 145 provided boronate 146, itself used to prepare pinacol and catechol boronates 148 and 150, respectively. Attempts to perform (Z)-selective hydrogenation on these three substrates met with limited success. For instance, pinacol boronate ester 149 was formed, although contaminated with (E)-isomer. Attempted hydrolysis of the boronate esters 143 and 149 to the target material 142 also proved problematic, with only unreacted starting material returned. Reduction and hydrolysis of the diisopropyl boronate ester 146 was irreproducible.
Scheme 1.51: Hydrogenation-based methods towards (Z)-boronic acid 142. Reagents and conditions: (a) n-BuLi (1.5 M, 1.00 mol equiv), Et₂O, -78 °C, 30 min, then B(O-i-Pr)₃ (1.00 mol equiv), -78 °C, 2 h, then, HCl (2 M in Et₂O, 1.03 mol equiv), 94%; (b) Lindlar catalyst, H₂ (ca. 1 mol equiv), pyridine, 1,4-dioxane, in the dark, rt, 1.5 h, without purification; (c) H₂O, 1h, rt, 11% (over two steps); (d) Pinacol (1.05 mol equiv), Et₂O, 4 h, rt, 100%; (e) Lindlar catalyst, H₂ (ca. 1 mol equiv), pyridine, pentane, in the dark, rt, 30 min, 87% (E:Z ratio 20:80); (f) H₂O, rt, 2 h, no deprotection; (g) Catechol (1.00 mol equiv), Et₂O, rt, 4 h, 85% (without purification); (h) Lindlar catalyst, H₂ (ca. 1 mol equiv), pyridine, pentane, in the dark, rt, 3.5 h, 22%; (i) H₂O, rt, 3 h, no deprotection.

Since neither approach to (Z)-configured boronic acid 142 worked, a new synthetic route to coupling partner 141 was needed. Preparation of this critical starting material began with Sonogashira coupling of 1,1-dichloroethylene 32 and 1-octyne 134 by following a known literature procedure. Thus, reaction of 1,1-dichloroethylene 32 with 1-octyne 134 produced 151 in 63% isolated yield (75% lit.). This was followed by catalytic hydrogenation to yield a mixture of products (Scheme 1.52).
Scheme 1.52: An attempt to prepare 141. Reagents and conditions: (a) 1,1-dichloroethylene (1.5 mol equiv), Pd(PPh₃)₄ (0.030 mol equiv), toluene, seal tube, rt, 25 min, then 1-octyne (1 mol equiv), n-BuNH₂ (1.5 mol equiv), Cul (0.030 mol equiv), 40 °C, 8 h, 63%; (b) H₂, 5%Pd on BaSO₄, quinoline, methanol, rt, 72 h, 14% (ratio 141:153, 19:1) and 11% 154.

Target coupling partner 141 was observed in limited yields and, in our hands, was unable to be separated from over-reduced by-product 153. Many conditions were explored for optimisation the catalytic hydrogenation. These included varying the reaction time and solvents; toluene, methanol, EtOAc, THF, CH₂Cl₂, as well as the catalyst. Palladium poisoned with lead or quinoline, on CaCO₃ or BaSO₄ were trialled, to no avail. As an interesting aside, methyl ester 154, clearly arising from the action of methanol solvent, was isolated in pure form after further purification by flash column chromatography and was fully characterised.

1.3.2.2 Formation of 1-(Z)-hexyl [4]dendralene 140 via hydrogenation

An alternate approach to 1-(Z)-hexyl [4]dendralene 140 involves a functional group interconversion of a substituted alkyne to produce the alkene in substituted dendralene 140. The C2 alkynyl substituted [3]dendralene 155 is derived from Grignard reagent 34 and alkynyl fragment 151 via a KTC reaction (Scheme 1.53). Grignard reagent 34, derived from chloroprene 40 is readily available. In addition, halide 151 has already been synthesised (Section 1.52).
This approach was inspired by the work of Hopf and Priebe, who formed [3]dendralene 28 from alkynyl-butadiene 156 (Scheme 1.54). To our knowledge, this is the only reported example of selective hydrogenation on a cross-conjugated dieneyne. Putting the hydrogenation step at the end of the synthesis also allowed us to use our well-developed KTC methodology for construction of our requisite trieneyne 155.

Gratifyingly, the reaction between Grignard reagent 34 and chloroeneyne 151 worked well. Optimisation of the KTC coupling conditions provided a procedure that could easily be performed on gram scale in good yields (Scheme 1.55).

Various conditions were tried to synthesise the target 1-(Z)-hexyl [4]dendralene 140. Although evidence of reductions was observed, limited selectivity prevented the utility of these reactions. For instance, varying the reaction time with Lindlar catalysis showed no evidence of target material. Reduction of linear conjugated alkynylldienes to alkenes using zinc powder was reported previously, however, this type of reduction method
with a variety of alcoholic hydrogen sources provided nothing more than traces of target material for our substrates.

Scheme 1.56: An attempt for the reduction of C2 alkynyl substituted [3]dendralene 155 using Zinc. Reagents and conditions: (a) Zn powder, n-PrOH:H2O (1:1), rt, 1.5 h, 23%.

Scheme 1.56 shows a typical result: alkyne 157 was isolated and fully characterised. Interestingly, this appears to be the product of a hydrogenation event across a diene. No evidence for the presence of target material 140 was observed by ¹H NMR. Mass spectral analysis of the crude reaction mixtures were not, regrettably, carried out.

Hopf’s preparation of [3]dendralene 28 from a C2 substituted alkynyl butadiene is known to work (Scheme 1.54). The problem in our case appears to be that a 2,3-disubstituted diene is hydrogenated more rapidly than is an alkyne. This is, to the best of our knowledge, a new reactivity pattern.

It was hoped that protection of either diene would allow selective reduction of the triple bond. Dienes may be protected by complexation with an iron tricarbonyl group. Previous work in the group has demonstrated that [3] and [4]dendralene 28 and 29 are readily complexed by an iron tricarbonyl group. This was applied to C2 alkynyl substituted [3]dendralene 155 (Scheme 1.57).
Scheme 1.57: Complexation of C2 alkynyl substituted [3]dendralene 155 with iron tricarbonyl and decomplexation with CAN. Reagents and conditions: (a) Fe\(_2\)(CO)\(_9\) (1.8 mol equiv), aza catalyst 160 (0.35 mol equiv), 1,2-dimethoxyethane, THF, in the dark, 60 °C, 40 h, 158:159, 30% and 13%, isolated, respectively; (b) CAN (2 mol equiv), acetone, methanol, 0 °C, 30 min, then more CAN (2 mol equiv), 0 °C, 5 min, clean product by \(^1\)H NMR.

Following treatment of substrate 155 with Fe\(_2\)(CO)\(_9\), examination of the crude reaction mixture by \(^1\)H NMR confirmed the presence of species containing iron proximal 158 and distal 159 to the alkyne. It must be noted that in neither compound is an intact diene to be found. Oxidative deprotection with ceric ammonium nitrate (CAN) unmasked the dienes to return starting material 155.

While separation of iron complexes 158 and 159 proved challenging, both compounds were fully characterised. Encouraged, we turned our attention to hydrogenation of these protected substrates. Our first attempts involved hydrogenation of mixtures of the protected alkynes, 158 and 159 (Scheme 1.58). The mixture of products 161 and 162 proved inseparable in our hands. Attempted decomplexation of the product mixture provided complex mixtures, with no pure target 1-(Z)-hexyl [4]dendralene 140 isolated.
Scheme 1.58: Reduction of iron tricarbonyl protected mixture (158:159, 2:1 ratio). *Reagents and conditions:* (a) H₂, Lindlar catalyst, pentane, in the dark, rt, 6 h. 65% (impure).

It was hoped that the separation problem could be forestalled by the reduction of pure iron tricarbonyl adducts. Both the proximal protected diene 158 and the distal protected diene 159 were hydrogenated separately and then deprotected by the action of CAN (Scheme 1.59).

Scheme 1.59: Summary of the hydrogenation approach to 1-(Z)-hexyl [4]dendralene 140 via iron tricarbonyl protected substrates. *Reagents and conditions:* (a) Fe₂(CO)₉ (1.8 mol equiv), aza catalyst (0.35 mol equiv), 1,2-dimethoxyethane, THF, in the dark, 60 °C, 40 h, 158:159, 30% and 13%, respectively; (b) H₂, Lindlar catalyst, pentane, in the dark, rt, 6 h, 82% (impure); (c) H₂, Lindlar catalyst, pyridine, pentane, in the dark, rt, 14 h, 45% (impure); (d) CAN (2 mol equiv), acetone, methanol, 0 °C, 5 min (impure); (e) CAN (2 mol equiv), acetone, methanol, 0 °C, 1 h, then more CAN (2 mol equiv), 0 °C, 15 min (impure).

To our great frustration, all attempts at hydrogenation of both protected dienes 158 and 159 provided mixtures that were resistant to purification in our hands. CAN mediated oxidative deprotection of both substrate mixtures provided impure samples of 1-(Z)-hexyl [4]dendralene 140. A useful avenue of future work would be to determine...
the identities of the impurities for both reactions with a view to forestalling their formation.

No 1-(Z)-hexyl [4]dendralene 140 was isolated in purity sufficient for reactivity studies. Time constraints prevented further investigations, so the difficult decision to abandon this line of investigation was made. The aims of this work were to prepare novel substituted [4]dendralenes and to examine their reactivity patterns in the Diels-Alder reaction with a view to possible application in organic syntheses.

1.3.3 Diels-Alder reactions between 1-(E)-hexyl [4]dendralene 139 and NMM 49

Hundreds of milligrams of pure 1-(E)-hexyl [4]dendralene 139 were prepared via a three step synthesis. The Diels-Alder reactivity of this substrate with the dienophile NMM 49 was examined. An initial reaction screen with a single molar equivalent of NMM 49 provided a mixture of five major products: 163, 166, 167, 168 and 169 (Scheme 1.60). This is in stark contrast to the many possible products arising from single, double and triple Diels-Alder reactions. $^1$H NMR analysis of the crude reaction mixture gave the following approximate product ratio: unreacted starting material 139 (30%), internal mono-adduct 163 (20%), and bis-adducts 166 and 167 (25% and 15% respectively). Signals consistent with bis-adducts 168 and 169 were also observed (10%).
Scheme 1.60: The Diels-Alder reaction between 1-(E)-hexyl [4]dendralene 139 and one molar equivalent of NMM 49. **Reagents and conditions:** (a) NMM (1 mol equiv), CDCl₃, rt, 117 hours. Yields estimated from the crude ¹H NMR spectrum.

The reaction is clearly not selective for mono addition. Mono-adducts 164 and 165, substituted [3]dendralenes, were not observed and instead reacted on to form bis-adducts 166 and 167, respectively. 168 and 169 are also formed from these mono-adducts. This is unsurprising, since it is known that [3]dendralenes are, as a group, more reactive than [4]dendralenes. From the result of this experiment, it is clear that the first Diels-Alder reaction occurs preferentially at the terminal dienes: Only 20% of material resulting from internal mono addition, 163 is observed.

It is more difficult to ascertain which of the terminal dienes is more reactive. For instance, we observe 25% bis-adduct 166 in the crude reaction mixture. This can only be derived from substituted terminal mono-adduct 164. Similarly, 15% of 167, derived from unsubstituted terminal mono-adduct 165 is detected. In contrast, approximately 10% of material forms bis-adducts 168 and 169, which might be derived from either
substituted *mono*-adduct 164 or unsubstituted *mono*-adduct 165 or both. It is not yet known which path(s) (dotted lines in Scheme 1.60) are favoured. Careful reaction of *mono*-adducts 164 and 165 with one molar equivalent of NMM 49 would be required to answer this question.

Three molar equivalents of NMM 49 were then employed in an exhaustive Diels-Alder reaction at room temperature (Scheme 1.61). $^1$H NMR analysis of the crude reaction mixture provided the following approximate product ratio: Internal *mono*-adduct 163 (27%), *bis*-adduct 166 and 167 (27% and 15%, respectively) and *tris*-adduct 170 and 171 (15% each). No evidence of *bis*-adduct 168 or 169 was observed. These materials instead reacted on to form *tris*-adduct 170 and 171. Minor amounts (< 5%) of other materials were also observed.

The five major products were isolated by flash column chromatography: one *mono*-adduct 163, two *bis*-adducts 166 and 167 and two *tris*-adducts 170 and 171. That the isolated product ratios differ from the ratios estimated from the crude reaction mixture may be attributed to differing stabilities of these adducts during purification. The structure and stereochemistry of *bis*-adduct 166 was determined unambiguously by single crystal X-ray analysis. The structures and stereochemistries of the other adducts were determined by spectral comparison with this compound, and with products arising from the NMM 49 reaction with [4]dendralene 29 (Section 1.1.7). It is worthy of note that *bis*-adducts 168 and 169 undergo completely diastereoselective Diels-Alder reactions with NMM 49 from the less hindered face (away from the hexyl substituent) to provide 170 and 171 in comparable yields.
Scheme 1.61: The Diels-Alder reaction between 1-(E)-hexyl [4]dendralene 139 and an excess of NMM 49. Reagents and conditions: (a) NMM (3 mol equiv), CDCl₃, rt, 1 day. Crude product ratios in red text, isolated yields in black text.

Let us now compare the reactivities of the family of substituted [4]dendralenes (Figure 1.12): The Diels-Alder reaction of 1-(E)-hexyl [4]dendralene 139 with NMM 49 preferentially occurs at the terminal dienes with significant reactivity at the internal diene. This behaviour is similar to (unsubstituted) [4]dendralene 29, which shows reaction at both the terminal sites and the internal diene. 4-(Z)-Methyl [4]dendralene 101 and 2-methyl [4]dendralene 78 show reactivity predominantly at terminal diene sites. In contrast, 4-(E)-methyl [4]dendralene 86 shows reactivity at the unsubstituted...
terminal diene and the internal diene. The most significant finding from this study is that an *inside* alkyl substituent clearly disfavours Diels-Alder reaction at that diene.

It is critical to note that for all three 2-methyl and 4-methyl substituted [4]dendralenes 78, 86 and 101, experiments with NMM 49 involved exhaustive reaction with three molar equivalents of dienophile. Experiments with one molar equivalent of dienophile would be required in order to determine which terminal diene site of 78 and 101 is the more reactive. This issue is not of importance for 4-(E)-methyl [4]dendralene 86, which shows no reactivity at the diene carrying an *inside* substituent.


**1.3.4 Diels-Alder reactions between C2 alkynyl [3]dendralene 155 and NMM 49**

Alkynyl fragment 155 (Scheme 1.62) was utilised as a protected intermediate towards 1-(E)-hexyl [4]dendralene 140 (Section 1.3.2.2). Regrettably, hydrogenation of the cross-conjugated alkyne proved problematic, hence we were unable to synthesise 140. Nevertheless, since 155 was readily available, we decided to investigate this interesting compound. Study was made of its reactions with NMM 49.

![Retrosynthetic analysis of 1-(Z)-hexyl [4]dendralene 140.](image)
Reaction of NMM 49 with the dendralene 155 in a 1:1 ratio provided a mixture of compounds (Scheme 1.63). Examination of the crude reaction mixture by $^1$H NMR spectroscopy showed the following approximate product ratio: unreacted starting material 155 (10%), less substituted mono-adduct 172 (10%), more substituted mono-adduct 173 (50%) and two bis-adducts 174 and 175 (combined 30%). Slightly more material arising from reaction at the more substituted diene is observed (50%) than is observed from reaction at the less substituted diene (40%). Cross-conjugated dieneyne 172 is clearly more reactive to Diels-Alder reaction with NMM 49 than is the parent dendralene 155 or linearly conjugated diene 173, since it mainly reacts on to provide bis-adducts 174 and 175.

The products were isolated by flash column chromatography. One mono-adduct 173 (37%), two bis-adducts 174 (18%) and 175 (2%) were isolated by flash column chromatography (Scheme 1.63). That terminal mono-adduct 172 could not be isolated by flash column chromatography is perhaps, unsurprising, given its high reactivity. The difference between isolated and crude product ratios is rationalised by differing stabilities of the adducts to the isolation conditions.
Reagents and conditions: (a) NMM (1 mol equiv), CDCl₃, rt, 4.5 h. Isolated yields.

As mentioned previously, the first Diels-Alder reaction occurs with a slight preference for the more substituted diene. This is in contrast with previous work (Section 1.1.6) on [3]dendralenes substituted with both 2-aryl- and alkyl- substituents which react at the less substituted diene with good selectivity (60-70% addition at this site)
(Figure 1.13). Cross-conjugated dieneyne 172 is therefore more reactive to Diels-Alder reaction with NMM 49 than is the alkynyl dendralene 155 or linearly conjugated dieneyne 173. We have thus identified a new reactivity pattern for [3]dendralenes.

Figure 1.13: Preferred sites of reaction of NMM 49 (red arrows) for 2-octynyl [3]dendralene 155 and other substituted [3]dendralenes 50. (R = alkyl, and EDG and EWG aryl groups).
1.4 Conclusions

The first aim of this project involved the syntheses of 1-(E)- and (Z)-alkyl substituted [4]dendralenes 113 and 114, the remaining undescribed members of the substituted [4]dendralene family (Figure 1.14).

![Figure 1.14: 1-(E)- and (Z)-alkyl substituted [4]dendralenes 113 and 114.]

Evidence for the formation of a mixture of 1-(E)- and 1-(Z)-methyl [4]dendralenes 115 and 130 was observed following a KTC coupling reaction (Scheme 1.64). Frustratingly, in our hands, repeated attempts at separation of these two regioisomers met with failure.

![Scheme 1.64: An attempt to synthesise 1-(E)-methyl [4]dendralene 115. Reagents and conditions: (a) Grignard reagent (1.3 mol equiv), Ni(dppp)Cl2 (0.10 mol equiv), PPh3 (0.20 mol equiv), THF, 0 °C to rt, 5 h, (ratios 115:130, 45:55).]

The 1-(E)-hexyl analogue was successfully produced by KTC coupling with the Grignard reagent 34 derived from chloroprene 40 and chloro-substituted diene 136 (Scheme 1.65). This approach incorporated the (E)- configuration at the terminal alkene within starting diene 136.
Scheme 1.65: Preparation of 1-(E)-hexyl [4]dendralene 139. Reagents and conditions: (a) Grignard reagent (3 mol equiv), PPh₃ (0.05 mol equiv), Ni(dppp)Cl₂ (0.05 mol equiv), THF, -12 °C to 22 °C, 5.5 h, 53%.

The 1-(Z)-hexyl analogue 140 proved far more elusive, with pure (Z)-chloro-substituted diene 141 unavailable in pure form. Efforts towards this intermediate included KTC and Suzuki-Miyaura coupling based methods. Frustratingly, all met with the production of inseparable mixtures, often in low yield.

Figure 1.15: Elusive 1-(Z)-hexyl 3-chloro butadiene 141.

1-(Z)-Hexyl [4]dendralene 140 was prepared, albeit in impure form by an alternate route (Scheme 1.66). The KTC cross-coupling reaction between the Grignard reagent 34 derived from chloroprene 40 and chloro-alkyne 151 proceeded well. The subsequent hydrogenation step, however, proved unselective, with no evidence of target material observed.

Scheme 1.66: Attempted formation of 1-(Z)-hexyl [4]dendralene 140. Reagents and conditions: (a) Chloroprene Grignard reagent (3 mol equiv), PPh₃ (0.05 mol equiv), Ni(dppp)Cl₂ (0.05 mol equiv), THF, -15 °C to 0 °C, 2.5 h, 63%; (b) Various hydrogenation conditions.

The same synthetic approach, with the added step of protecting the dienes in precursor 155 was next investigated. Protection as iron tricarbonyl complexes proceeded well.
Hydrogenation and deprotection gave desired 1-(Z)-hexyl [4]dendralene 140, albeit contaminated with by-products. These proved inseparable in our hands (Scheme 1.67).

Scheme 1.67: Summary of the hydrogenation approach to 1-(Z)-hexyl [4]dendralene 140 via iron tricarbonyl protected substrates. Reagents and conditions: (a) Fe₂(CO)₉ (1.8 mol equiv), aza catalyst (0.35 mol equiv), 1,2-dimethoxyethane, THF, in the dark, 60 °C, 40 h, 158:159, 30% and 13%, respectively; (b) H₂, Lindlar catalyst, pentane, in the dark, rt, 6 h, 82% (impure); (c) H₂, Lindlar catalyst, pyridine, pentane, in the dark, rt, 14 h, 45% (impure); (d) CAN (2 mol equiv), acetone, methanol, 0 °C, 5 min (impure); (e) CAN (2 mol equiv), acetone, methanol, 0 °C, 1 h, then more CAN (2 mol equiv), 0 °C, 15 min (impure).

The second aim of the work discussed in this Chapter was to investigate the site selectivity of the Diels-Alder reaction of 1-alkyl substituted [4]dendralenes with a common dienophile NMM 49. The Diels-Alder reactions of C2 alkynyl substituted [3]dendralene, an interesting intermediate in our syntheses of 1-alkyl substituted [4]dendralene was also examined (Figure 1.16).

The behaviour of 1-(E)-hexyl [4]dendralene 139 (Scheme 1.68) with an excess of NMM 49 gave five major products, which were isolated by flash column chromatography: one mono-adduct 163, two bis-adducts 166 and 167 and two tris-adducts 170 and 171. Reaction with one molar equivalent of NMM 49 provided unreacted starting material 139, mono-adduct 163 and bis-adducts 166 and 167 (30:20:25:15), as evidenced by $^1$H NMR analysis of the crude reaction mixture. Signals consistent with bis-adducts 168 and 169 were also observed (10%).
Scheme 1.68: The Diels-Alder reaction between 1-(E)-hexyl [4]dendralene 139 and an excess of NMM 49. Reagents and conditions: (a) NMM (3 mol equiv), CDCl₃, rt, 1 day. Isolated yields shown.

2-Octynyl [3]dendralene 155 reacted with one molar equivalent of NMM 49 to provide three major products, which were isolated by flash column chromatography: one mono-adduct 173 and two bis-adducts 174 and 175 (Scheme 1.69). ¹H NMR analysis of the crude reaction mixture also indicated the presence of mono-adduct 172. The product distribution of the crude reaction mixture was estimated to be 155 (10%), 172 (10%), 173 (50%) and two 174 and 175 (combined 30%) by ¹H NMR analysis.
Scheme 1.69: Reaction of 2-octynyl [3]dendralene 155 with NMM 49. Reagents and conditions: (a) NMM (1 mol equiv), CDCl₃, rt, 4.5 h, isolated yields shown.

The first Diels-Alder reaction occurs at the more substituted diene with moderate preference. This is in marked contrast with previous work (Section 1.1.6) on C₂ substituted [3]dendralenes, substituted with both aryl- and alkyl- substituents, that found preferential reaction at the less substituted diene (Figure 1.17). Interestingly, the mono-adduct product 172, arising from reaction of NMM 49 at the unsubstituted diene is reactive enough to go on to form 174 and 175. In contrast, the analogous mono-adducts in the C₂ aryl- and alkyl- substituted [3]dendralene series (Section 1.1.6) are not. Cross-conjugated dieneyne 172 is therefore more reactive to Diels-Alder reaction with NMM 49 than is the parent dendralene 155 or linearly conjugated dieneyne 173. We have thus identified a new reactivity pattern for [3]dendralenes.
Chapter 1

1.5 Future work

The purpose of this work was to develop ways to prepare substituted [4]dendralenes and to document their reactivity in the Diels-Alder reaction with the hope of promoting synthetic applications. It is fair to say that at present, these reactions are not useful in total synthesis because of their propensity to generate complex mixtures. It has been shown that Lewis acid catalysis can promote reaction at either the terminal or internal dienes (depending on stoichiometry) of unsubstituted [4]dendralene. Future work should therefore focus on exploring this method of promoting selectivity in the reactions of substituted [4]dendralenes.

\[ \text{Figure 1.17: Preferred sites of reaction of NMM 49 (red arrows) for 2-octynyl [3]dendralene 155 and other substituted [3]dendralenes 50. R=alkyl, and EDG and EWG aryl groups.} \]
Chapter 2

2.1 Introduction

2.1.1 Synthesis of [5]dendralene 176

As mentioned in Chapter One, the dendralenes, acyclic branched oligo-alkenes, are interesting and important substances. They also have potential for the rapid synthesis of polycyclic structures.

![Figure 2.1: Some members of the dendralene family.](image)

Although studies into [3]dendralene\(^1\)\(^{15,16,47,53-56}\) 28 and [4]dendralene\(^1\)\(^{17,32,57-60}\) 29 were reported in the literature between 1955 and 1962, the synthesis of [5]dendralene 176 was not achieved until 2000.\(^1\)\(^{18}\) Its predicted instability was presumably the reason for lack of synthetic efforts towards this fascinating compound. For instance, Henning Hopf in his review said that:

"Even if [5]dendralene 176 could be obtained by a preparatively simple route, it would presumably be difficult to study its chemical properties since it is probably a very reactive substance."\(^32\)

The first general synthesis of the [n]dendralene family including [5]dendralene 176 was reported by Sherburn and co-workers in 2000.\(^1\)\(^{18}\) Taking into account the expected decomposition, the group chose a masking method: the terminal 1,3-butadiene units of [5]dendralene 176 were masked as 3-sulfolene derivatives. This synthesis, shown in Scheme 2.1, employed a double Stille cross-coupling reaction between sulfolene 178 and 1,1-dibromoethylene to prepare masked [5]dendralene 179, a stable white crystalline solid. Chelotropic elimination of sulfur dioxide affords [5]dendralene 176 in five steps from 3-sulfolene 177 in less than 2% overall yield.
Later, in 2008, the Sherburn group reported the first practical synthesis of [5]dendralene 176 using a double Kumada-Tamao-Corriu\textsuperscript{22,23} (KTC) cross-coupling reaction.\textsuperscript{20} This synthesis is more practical because it proceeds in good overall yield in only two steps from a commercially available starting material, chloroprene 40, without any protection. Thus, Grignard reagent 34, which is prepared from chloroprene 40, undergoes a double KTC cross-coupling reaction with 1,1-dichloroethylene 32, and affords [5]dendralene 176 in 65% yield (Scheme 2.1). Operational modifications allow 176 to be prepared on a scale of tens of grams.\textsuperscript{61}

\begin{center}
\begin{tikzpicture}[baseline=0pt]
\node (a) at (0,0) {177};
\node (b) at (1,0) {178};
\node (c) at (2,0) {179};
\node (d) at (3,0) {176};
\node (e) at (4,0) {34};
\node (f) at (5,0) {40};
\draw[->] (a) -- (b) node[midway,above] {\text{3 steps}};
\draw[->] (b) -- (c) node[midway,above] {a};
\draw[->] (c) -- (d) node[midway,above] {b};
\draw[->] (d) -- (e) node[midway,above] {c};
\draw[->] (e) -- (f) node[midway,above] {d};
\end{tikzpicture}
\end{center}

Scheme 2.1: Synthesis of [5]dendralene 176. Reagents and conditions: (a) CH$_2$CBr$_2$ (0.50 mol equiv), PdCl$_2$(CH$_3$CN)$_2$ (0.050 mol equiv), DMF, 40 °C, Ar, 36 h, 11%; (b) 450 °C, 65%; (c) magnesium turnings, BrC$_2$H$_4$Br, ZnBr$_2$, THF; (d) CH$_2$CCl$_2$ (1.0 mol equiv), Grignard reagent (3.5 mol equiv), Ni(dppp)$_2$Cl$_2$ (0.040 mol equiv), PPh$_3$ (0.040 mol equiv), THF, rt, 48 h, 65%.

2.1.2 Diels-Alder dimerisation of [5]dendralene 176

Dendralenes possess both diene and dienophile units within their structures. They can, therefore, dimerise via a Diels-Alder reaction. As shown in Figure 2.2, [5]dendralene 176 has two distinct diene sites (the terminal and internal 1,3-butadienes) and three potential dienophile sites (terminal alkene, internal alkene a, and internal alkene b). Neglecting stereochemistry considerations, when all combinations of these two dienes and three dienophiles are taken into account, twelve distinct Diels-Alder dimer products are possible.
The first study into Diels-Alder dimerisation of [5]dendralene 176 was conducted by Bojase. Suprisingly, the Diels-Alder dimerisation of [5]dendralene 176 in CH₂Cl₂ at room temperature for 96 hours afforded only two dimeric products, 180 and 181 (78:22 isolated product ratio) which could be separated by preparative HPLC (Scheme 2.2).

Thus, only internal alkene a acts as a dienophile, while both the terminal and internal dienes participate in Diels-Alder dimerisations of [5]dendralene 176.

It is known that the Diels-Alder reactions of non-polar precursors in aqueous and other polar solvents favour the more compact transition state, driven by the hydrophobic effect. The transition state leading to minor dimer 181 is more compact than that leading to major dimer 180. Hence, in more polar solvents, it is reasonable to anticipate that the dimerisation product ratio might change in favour of 181. In order to check this hypothesis, Kirwan studied the Diels-Alder dimerisation of [5]dendralene 176 in solvents of differing polarity, while holding concentration and temperature constant (Scheme 2.2). The product ratio was determined by HPLC analysis of crude dimer mixtures, in contrast to the aforementioned work of Bojase, who isolated pure dimeric products.
Within experimental error, identical crude product dimer ratios (180:181) of ca. 60:40 were obtained by Kirwan in solutions of hexane, toluene, diethyl ether, dichloromethane, methanol, acetonitrile and when the neat liquid [5]dendralene 176 was used. As an aside, Kirwan’s results show increased amounts of 181, relative to 180 when compared with Bojase’s isolated yields (180:181 of 78:22). We propose that this apparent discrepancy is explained by losses of 181 during the isolation process of Bojase. In any case, Kirwan’s results clearly show that solvent polarity does not significantly influence the regioselectivity of the Diels-Alder dimerisation of [5]dendralene 176.

2.1.3 Synthesis of tetracycle 183

The first synthesis of a tetracycle from [5]dendralene 176 was performed by Bojase. Upon heating Diels-Alder dimer 181 at reflux in chlorobenzene for 24 hours, tetracycle 183 was isolated in 80% yield. This remarkable reaction proceeds via a sequence of two pericyclic reactions, namely, a 6π-electrocyclisation forming intermediate 182 and an intramolecular [4+2] cycloaddition reaction resulting in tetracyclic product 183 (Scheme 2.3).

![Scheme 2.3: Synthesis of tetracycle 183 and its X-ray crystal structure. Reagents and conditions: (a) PhCl, BHT, reflux, 24 h, 80%.](image-url)
When the major dimer 180 was subjected to the same reaction conditions, only a complex mixture of products was observed (Scheme 2.4).

\[
\begin{align*}
\text{180} & \xrightarrow{a} \text{complex mixture}
\end{align*}
\]

**Scheme 2.4:** Heat treatment of the major dimer 180. *Reagents and conditions:* (a) PhCl, BHT, reflux, 24 h.

The lack of large quantities of tetracycle 183 was an impediment to further studies. Kirwan optimised the reaction conditions and synthesised larger amounts of tetracycle 183. The first improvement was the synthesis of tetracycle 183 directly from the mixture of dimers 180 and 181. Thus, treatment of a ca. 60:40 mixture of Diels-Alder dimers under the same reaction conditions as shown in Scheme 2.3 resulted in the formation of target product 183 in 7% yield with a little unreacted starting material (Scheme 2.5). When the reaction was conducted in mesitylene at reflux, it reached completion at 4.5 hours. The product 183 was isolated by flash column chromatography in 10% yield, based on a mixture of dimers 180 and 181 of [5]dendralene 176 (the yield based upon the amount of minor dimer 181 in the mixture was 25%). This sequence is clearly advantageous because it avoids HPLC separation of dimers 180 and 181.

\[
\begin{align*}
\text{180} + \text{181} & \xrightarrow{a} \text{183}
\end{align*}
\]

**Scheme 2.5:** Synthesis of tetracycle 183 from a mixture of Diels-Alder dimers of [5]dendralene 176. *Reagents and conditions:* (a) A ca. 60:40 mixture of 180 and 181, PhCl, BHT, reflux, 24 h, 7% or mesitylene, reflux, 4.5 h, 10%.

In a further improvement, [5]dendralene 176 was converted directly into tetracycle 183 in a one pot reaction. The successful reaction conditions involved heating a solution of 176 in mesitylene (200 mM) at reflux. The reaction was complete in 6 hours and the
target product 183 was isolated by flash column chromatography in 9% yield based on [5]dendralene 176 (Scheme 2.6). 1.5 g of tetracycle 183 was synthesised using this method.

Scheme 2.6: Synthesis of tetracycle 183 in one pot from [5]dendralene 176. Reagents and conditions: (a) Mesitylene, reflux, 6 h, 9%.

This spectacular result involves a cascade of three pericyclic reactions (intermolecular [4+2] cycloaddition, 6π-electrocyclisation, and intramolecular [4+2] cycloaddition) in one pot. In the tetracyclic product, five new carbon-carbon bonds and three stereocentres are generated from two molecules of a simple acyclic precursor.

In a final attempt to further extend the one pot preparation, Kirwan attempted the synthesis of tetracycle 183 directly from the commercially available starting materials, 1,1-dichloroethylene 32 and the Grignard reagent 34, derived from chloroprene 40. Unfortunately, this approach failed because the impurities arising from the first step could not be separated from the target product 183 (Scheme 2.7).

Scheme 2.7: An attempted synthesis of tetracycle 183 in a one pot reaction without purification of [5]dendralene 176. Reagents and conditions: (a) Chloroprene Grignard reagent (in a THF solution, 3.1 mol equiv), 1,1-dichloroethylene (1.0 mol equiv), PPh3 (0.050 mol equiv), Ni(dppp)Cl2 (0.020 mol equiv), 15 °C to rt, 20 h; then crude [5]dendralene 2.4, mesitylene, reflux, 16 h.
2.1.4 Natural products structurally related to tetracycle 183

While no natural product carries the exact tetracyclic framework of 183, many important natural products have three of the four carbocyclic rings of tetracycle 183. If efficient manipulations can be developed, 183 has the potential for use in short total syntheses of the natural products shown in Figure 2.3 and their analogues.

![Diagram of natural products](image)

**Figure 2.3:** Tetracycle 183 and structurally related natural products.

Platensimycin 184 is a fatty acid biosynthesis inhibitor that is selective for FabF. This natural product has activity against Gram-positive bacteria and analogues have also shown antibacterial properties. Platensimycin 184 has been the subject of much synthetic activity in recent times, with the first total syntheses of both racemic and enantiomerically pure compounds being reported by Nicolaou and co-workers (in 17 steps and 7% overall yield for the racemate, and in 17 steps and 7% overall yield for chiral-auxiliary-based asymmetric synthesis of (-)-platensimycin 184, and in 23 steps...
and 2% overall yield for catalytic enantioselective synthesis of (-)-platensimycin 184, respectively.\(^{66,67}\) This research group also reported several biologically active analogues of platensimycin.\(^{68,69}\) If the A ring of the tetracycle 183 could be removed, the core tricyclic carbon framework of platensimycin 184 would be formed.

A variety of recent studies have shown that some tricyclic trinervitane diterpenes (Figure 2.4) possess antimicrobial activities.\(^{70}\) One member of this family is a substance present in a defensive termite secretion,\(^{71}\) rippertenol 185, was first isolated in late 1970s.\(^{72}\)

\[ \text{Figure 2.4: Trinervitane carbon skeleton 189.} \]

Studies towards an enantioselective total synthesis of rippertenol 185 have been reported by Kreuzer and Metz.\(^{71}\) In principle, rippertenol 185 could be accessed from tetracycle 183 by removal of the C/D-system methylene bridge and incorporation of a new cyclopentane ring fusion between rings A and D.

Aphidicolin 186 is a fungal metabolite\(^{73}\) and potentially important drug target. Not only an antibiotic and anti-herpes agent, 186 is also a mammalian DNA polymerase inhibitor.\(^{74}\) Its activity against several cancer lines has been reported.\(^{75}\) The first enantioselective formal total synthesis of this natural product was achieved by Holton and co-workers.\(^{76}\) In 9 steps and 12% overall yield, they enantioselectively prepared an intermediate reported, in racemic form, by Corey.\(^{77}\) This intermediate is only two synthetic steps away from aphidicolin 186. If the B ring of the tetracycle 183 could be relocated, the carbocyclic skeleton of aphidicolin 186 would be formed.

The marine diterpenoid elisabethin A 187 was isolated in 1998 from the West Indian sea whip \textit{Pseodopterogorgia elisabethae}.\(^{78}\) While studies into its biological activity are incomplete, this complex natural product has been the target of several research groups
because analogues have shown interesting anti-inflammatory, antibacterial, analgesic, and cytotoxic activities. To date, however, the synthesis of elisabethin A has proven elusive. In principle, the core tricyclic carbon framework of elisabethin A could be accessed from tetracycle 183 by removal of the C ring.

Aflavinine 188 was isolated from a strain of *Aspergillus flavus*. The full biological activity of this natural product has not been investigated so far, due to its limited availability from isolation. It has potential as a drug candidate because similar indolic diterpenoids show tremorogenic properties. While a total synthesis of aflavinine 188 has not yet been achieved, the core tricyclic carbon skeleton of aflavinine 188 could be obtained from tetracycle 183 by removal of the D ring.

Another possible approach to elisabethin A 187 and aflavinine 188 is through the use of a substituted [5]dendralene 190 precursor. Thus, if dimethyl substituted [5]dendralene 190 could be prepared, its Diels-Alder dimerisation might proceed in an analogous way to the unsubstituted [5]dendralene 176. The resulting tetracyclic product 193 would have methyl substituents in the same key positions present in the A and B rings of these natural products (Scheme 2.8).
Scheme 2.8: A possible route from a dimethyl [5]dendralene 190 to elisabethin A 187 and aflavinine 188.

2.2 Aims

Tetracycle 183, derived from [5]dendralene 176, has five different alkene units; two mono-substituted alkenes, one 1,1-disubstituted alkene and two tri-substituted alkenes (Figure 2.5). The first aim of this project is to look for selectivity in the manipulation of these alkenes.
The second aim involves the synthesis of dimethyl substituted [5]dendralene 190 using the method that we have previously developed for the synthesis of [5]dendralene 176 in the group (Scheme 2.9). Subsequent transformation of 190 into tetracycle 193 will also be investigated.

These investigations will have applicability to rapid syntheses of natural products such as shown in Figure 2.6. While selective functionalisation of 183 is applicable towards all natural products in Figure 2.6, preparation of tetramethyl substituted tetracycle 193 will be of special utility for the formation of elisabethin A 187 and aflavinine 188.
2.3 Results & Discussion

2.3.1 Synthesis of tetracycle 183

[Dendralene 176 was obtained from supplies within the Sherburn group. Tetracycle 183 was synthesised in a one pot reaction from [5]dendralene 176 following Kirwan’s procedure. A 0.2 M concentration solution of [5]dendralene 176 in mesitylene was stirred at reflux for 17 hours (Scheme 2.10). Following removal of mesitylene by distillation under reduced pressure, the residue was subjected to flash column chromatography to afford tetracycle 183 as a single diastereomer in 7% yield. The identity of this material was unambiguously assigned by comparison of spectroscopic data with that of Bojase who determined the structure and stereochemistry of 183 by single crystal X-ray analysis.
Scheme 2.10: Synthesis of tetracycle 183 in one pot from [5]dendralene 176. Reagents and conditions: (a) Mesitylene, reflux, 17 h, 7%.

2.3.2 Manipulation reactions of tetracycle 183

As indicated in Section 2.1.4 and Section 2.2, while there are no known natural products carrying the tetracyclic core of 183, several natural products possess three of the four rings of tetracycle 183. The intention of the work currently being reported is to explore the chemistry of tetracycle 183, focusing on obtaining selective functionalisation.

Figure 2.7: Tetracycle 183.

The tetracycle 183 contains two tri-substituted alkenes in rings A and B, a 1,1-disubstituted alkene (exocyclic alkene) on ring D, and two mono-substituted alkenes (vinyl groups) attached to the A/D and C/D ring junctions (Figure 2.7). It was envisioned that the different steric environments and electronic properties of these five alkenes would allow selective reactions. We began by exploring oxidation protocols using OsO₄, m-chloroperbenzoic acid (m-CPBA), dimethyldioxirane (DMDO), and ozone since these methods would promote ring opening, transformations of most value.
in any proposed total synthesis. A cross-metathesis reaction using Grubbs' second-generation catalyst was also examined.

2.3.3 Dihydroxylation reaction of tetracycle 183

Dihydroxylation of alkenes is a very commonly used transformation in organic chemistry. While one of the most effective methods for dihydroxylation of alkenes involves the use of OsO$_4$ 194 alone, this volatile reagent is very toxic and expensive. Researchers at the Upjohn corporation devised a method for the catalytic dihydroxylation reaction of alkenes using a catalytic amount of OsO$_4$ 194 with a stoichiometric amount of the co-oxidant $N$-methylmorpholine $N$-oxide (NMO) 197. The mechanism of OsO$_4$/NMO dihydroxylation reaction involves a cycloaddition reaction to form osmate ester 196. It is oxidized by NMO 197 to 199, which is in turn hydrolysed to diol 200, releasing OsO$_4$ 194, which participates in the next cycle (Scheme 2.11).

Clearly, the [3+2] cycloaddition of OsO$_4$ 194 could take place at one or more of the five alkenic sites in our tetracycle 183. The rate of reaction at the different sites will depend on the steric environment and electronic properties of the alkenes in question. Osmium tetroxide 194 is the electron poor component of this cycloaddition reaction. On one
hand, the more electron donating alkyl groups are attached to the alkene, the more electronically reactive the alkene is towards OsO$_4$ 194. On the other hand, the more substituted the alkene, the greater is the steric impediment to the approach of OsO$_4$ 194. Thus, on electronic grounds, the tri-substituted alkenes are expected to be the most reactive while on steric grounds the mono-substituted alkenes are expected to be the most reactive.

Sharpless and Andersson$^{86}$ previously demonstrated that the order of reactivity for alkenes with OsO$_4$ 194 alone is tetra-substituted alkene > tri-substituted alkene > trans-1,2-di-substituted alkene > 1,1-di-substituted alkene > cis-1,2-disubstituted alkene > mono-substituted alkene. Sharpless and co-workers$^{87}$ also showed that when K$_3$Fe(CN)$_6$ is used as a stoichiometric co-oxidant in the presence of (DHQD)$_2$-PHAL 201 ligand (Figure 2.8) and OsO$_4$ 194, the order of reactivity for unsymmetrical conjugated dienes becomes tri-substituted alkene > trans-1,2-di-substituted alkene > 1,1-di-substituted alkene > mono-substituted alkene and for non-conjugated dienes is tri-substituted alkene > 1,2-di-substituted alkene > 1,1-di-substituted alkene > mono-substituted alkene. In contrast, Sclafani and co-workers$^{88}$ reported that non-conjugated dienes undergo highly regioselective dihydroxylation at the less substituted alkene when using Sharpless (DHQ)$_2$-PHAL 202 ligand (Figure 2.8). Additionally, Leahy and co-workers$^{89}$ reported that a non-conjugated diene is preferentially dihydroxylated at the less substituted alkene by OsO$_4$ 194 in the presence of NMO 197 as a stoichiometric co-oxidant. Thus, the selectivity of OsO$_4$ 194 mediated dihydroxylation of alkenes is exquisitely sensitive to co-oxidant, ligand and substrate.

![Figure 2.8: (DHQD)$_2$-PHAL 201 and (DHQ)$_2$-PHAL 202 ligands.](image-url)

Tetracycle 183 was treated with 0.04 mol equiv of OsO$_4$ 194 in the presence of 2 mol equiv of NMO 197 in THF/H$_2$O/($t$-BuOH at room temperature. The reaction was
run in the dark for 4 days. Following flash column chromatography, a mixture of diastereomers 203 and 204 (in a crude product ratio 203:204 ca. 70:30) was obtained in 30% yield (Scheme 2.12). Although these two diastereomers could not be separated by flash column chromatography on silica gel, analytical samples were obtained by normal phase preparative HPLC. The low yield for this reaction has been attributed to decomposition of the products during the purification, since the mass balance before chromatography was excellent and the $^1$H NMR spectrum of the crude product was very clean. The $^1$H NMR spectra of the products are essentially identical apart from the signals due to protons on the alcohol bearing carbons. Samples of both diastereoisomers could be crystallised and this allowed for single crystal X-ray analysis and the unambiguous assignment of structures 203 and 204.

Scheme 2.12: Dihydroxylation reaction of tetracycle 183 and single X-ray crystal structures of the dihydroxylation products 203 and 204. Reagents and conditions: (a) OsO$_4$ (0.04 mol equiv), NMO (2 mol equiv), THF/H$_2$O/i-BuOH (5:1:1 ratio), rt, 4 days, in the dark, 30%, 203:204 (ca. 70:30 ratio).

Clearly, only one of the two exocyclic mono-substituted alkenes reacts with OsO$_4$ 194. In this case steric effects outweigh electronic effects in accordance with the observation
of Sclafani\textsuperscript{88} and Leahy.\textsuperscript{89} In addition, reaction at the top face of the favoured mono-substituted alkene is twice as fast as than reaction at the bottom face. It is clear from inspection of the structure of tetracycle 183 (determined by single-crystal X-ray diffraction) that the top face of the reactive mono-substituted alkene is more accessible to an approaching OsO\textsubscript{4} 194 molecule than is the bottom face. The major product 203 is formed through reaction of tetracycle 183 at the more accessible top face of the reactive mono-substituted alkene. The minor product 204, is formed through reaction at the less accessible bottom face of the same alkene.

2.3.4 Epoxidation reactions of tetracycle 183

Epoxidation is a commonly used method for the oxidation of alkenes.\textsuperscript{82} \textit{m}-CPBA 206 is one of the most widely used reagents to effect this transformation.\textsuperscript{14} The mechanism of epoxidation with \textit{m}-CPBA 206 is shown in Scheme 2.13. An alkene’s \(\pi\)-electrons are attached to the weakly polarized O-O bond of the peracid 206. Concerted transfer of oxygen leads to the formation of epoxide 208 and \textit{m}-chlorobenzoic acid 209.

![Scheme 2.13: Epoxidation of an alkene 205 using \textit{m}-CPBA 206.\textsuperscript{5}]

A potential limitation of this epoxidation protocol is that the by-product, \textit{m}-chlorobenzoic acid 209 may participate in nucleophilic substitution reactions or even induce rearrangements.\textsuperscript{85} An alternative reagent is dimethyldioxirane (DMDO) 210 that is also used for the epoxidation of an alkene 205 (Scheme 2.14).\textsuperscript{90,91} In contrast with \textit{m}-CPBA 206, the by-product of epoxidations using DMDO 210 is relatively unreactive acetone 212.
The order of reactivity for the epoxidation of simple alkenes carrying alkyl substituents is tetra- and tri-substituted alkenes > di-substituted alkenes > mono-substituted alkenes. This is due to the electron donating nature of alkyl groups. The more alkyl substituents, the more electron rich the alkene, and the faster reacting it becomes. Thus, on the basis of this literature precedent, the most electron rich tri-substituted alkenes are expected to be epoxidised most quickly in our system.

Various reaction conditions using the two different epoxidizing reagents were tested in order to investigate which alkenic sites of tetracycle 183 would be epoxidised. Tetracycle 183 was treated with 1 mol equiv of \( \mu \)-CPBA 206 in CH\_2\_Cl\_2 at \(-20\) °C. While some starting material still remained after 21 hours, the reaction was subjected to work-up. Purification of the resultant mixture by flash column chromatography afforded a mixture of mono-epoxides (ratio 214:215, 30:70) in 28% yield, bis-epoxide 213 in 23% yield, and recovered starting material in 20% yield. The mixture of mono-epoxides 214 and 215 proved inseparable in our hands, so attention was focused on maximizing the formation of the bis-epoxide 213. For the next attempt, the tetracycle 183 was treated with 2 mol equiv of \( m \)-CPBA 206 in CH\_2\_Cl\_2 at \(-15\) °C, then allowed to warm to room temperature and stirred for 6 hours. Purification by flash column chromatography gave a mixture of mono-epoxides in 3% yield (ratio 214:215, 10:90) and bis-epoxide 213 in 29% yield (Scheme 2.15).
Scheme 2.15: Epoxidation reactions of tetracycle 183 using m-CPBA 206 or DMDO 210. Reagents and conditions: (a) m-CPBA (2 mol equiv), CH$_2$Cl$_2$, -15 °C to rt, 6 h, 29% 213 (bis-epoxide) and 3% (mono-epoxides, ratio 214:215, 10:90); (b) DMDO in acetone (2 mol equiv), rt, 2 h, 37% 213 (bis-epoxide) and 9% (mono-epoxides, ratio 214:215, 25:75).

When tetracycle 183 was treated with 1 mol equiv of freshly prepared DMDO 210 in acetone at 0 °C, much starting tetracycle 183 remained after 20 hours. In the hope of maximising the yield of mono-epoxide, a further 1.2 mol equiv DMDO 210 in acetone solution was added in three portions over the next nine hours and the reaction progress was carefully monitored by TLC analysis. Once the formation of the undesired bis-epoxide 213 was observed to significantly increase, the reaction was stopped. Purification of the resultant mixture afforded mono-epoxides in 29% yield (ratio 214:215, 10:90) and bis-epoxide 213 in 17% yield. In later experiments targeting the bis-epoxide 213, tetracycle 183 was reacted with 2 mol equiv of DMDO 210 in acetone at room temperature. The reaction was terminated once all starting material had been consumed (two hours). Flash column chromatography gave a mixture of mono-epoxides in 9% yield (ratio 214:215, 25:75) and bis-epoxide 213 in 37% yield (Scheme 2.15).

The stereochemistry of bis-epoxide 213 was assigned by 2D NMR studies. The NOESY spectrum is shown with relevant cross peaks highlighted in red in Figure 2.9.
Figure 2.9: NOESY spectrum of bis-epoxide 213. nOe cross-peaks highlighted in red are due to the spatial correlations indicated by red arrows.

Walking around the molecule, we see NOESY cross-peaks (highlighted in red in Figure 2.9) between H_t and H_j, H_j and H_z, confirming their location on the lower face of 213. HSQC cross-peaks indicate that H_z and H_k substitute the same carbon. Now, H_k and H_i show NOESY cross-peaks, as do H_i and H_y. Taken together, this unequivocally demonstrates that the epoxides on the A and B rings must be on opposite faces of the molecule.

From the outcomes of the epoxidation reactions both using m-CPBA 206 and DMDO 210, clearly, only the most electron rich tri-substituted alkenes react with the epoxidizing reagents. Although attempted purification and characterisation of
mono-epoxides failed, we can assume the stereochemistry of the mono-epoxides by analogy with the bis-epoxide 213: Only one diastereomeric bis-epoxide 213 is isolated, presumably formed via the mono-epoxides 214 and 215. It follows, therefore, that the configurations of each of the epoxides attached to the A and B rings in 214 and 215 must be the same as those of each component epoxide in 213 (Scheme 2.16).

Scheme 2.16: Proposed structures of mono-epoxides 214 and 215.

While isolation of each diastereomeric mono-epoxides eluded us, reaction conditions favouring mono-epoxidation have been identified (1 mol equiv of m-CPBA 206 in CH₂Cl₂ at -20 °C). While similar results could be achieved with prolonged reaction of more than one molar equivalent of DMDO 210 at 0 °C, it seems likely that some degradation of the reagent was taking place. A good mass balance of our crude isolate was observed and a quite clean reaction was suggested by ¹H NMR analysis. For both epoxidation reactions, however, poor mass recovery was observed following flash column chromatographic purification. We postulate that the epoxides are unstable to chromatography.

Only moderate selectivity was observed for the two epoxidations with both DMDO 210 and m-CPBA 206 (214:215, ~1:4). Also, epoxidation of one tri-substituted alkene does not significantly affect the configuration of tetracycle 183. We know this since each mono-epoxides has the same stereoselectivity. Our hopes for obtaining selective epoxidation of one tri-substituted alkene over the other are limited.
2.3.5 Ozonolysis reactions of tetracycle 183

Ozonolysis is the most useful method for cleaving alkenes.\(^\text{82}\) This reaction proceeds with formation of two oxidation products, the identities of which depend on the starting alkene. The oxidative cleavage reaction of alkenes involves two [3+2] cycloadditions, one retro-cycloaddition and a reductive elimination (Scheme 2.17).\(^\text{94}\) The first [3+2] cycloaddition reaction takes place between alkene 216 and ozone 217 to form unstable primary ozonide 218. The subsequent reverse [3+2] cycloaddition of 218 affords an aldehyde 219 and a carbonyl oxide 220. Following rotation of the aldehyde 219 through 180°, another [3+2] cycloaddition reaction forms ozonide 221. Finally, in a separate reaction, a reductive elimination to the ozonide 221 affords an aldehyde 219 and ketone 222. The last step is usually carried out with PPh\(_3\), SMe\(_2\) or Zn/HOAc.\(^\text{5,14}\)

![Scheme 2.17: The mechanism of alkene ozonolysis.\(^\text{94}\)](image)

Pryor and co-workers\(^\text{95}\) observed that ozone 217 is an electron poor reagent and more reactive towards more electron rich alkenes. Bailey and Lane\(^\text{96}\) demonstrated for sterically hindered alkenes, the approach of ozone 217 to give the first [3+2] cycloaddition reaction is not possible and instead a [2+1] cycloaddition reaction takes place to form an epoxide.

There are five different alkenes on our tetracycle 183 and ozonolysis could, in principle, take place at each of these alkenic sites. Considering electronic effects, the tri-substituted alkenes of 183 are the most electron rich and should be most reactive. On
steric grounds, both of the mono-substituted alkenes are expected to be most accessible. Thus, if electronic effects dominate, we anticipate that ozonolysis of tetracycle 183 would occur preferentially at the tri-substituted alkenes. If steric effects dominate, then the mono-substituted alkenes will be ozonolysed. If ozonolysis is controlled by a balanced of these 2 factors then perhaps the di-substituted alkene will be ozonolysed.

Tetracycle 183 was treated with an excess of ozone 217 at -78 °C (Scheme 2.18). After flash column chromatography, product 223 was isolated as a single diastereomer in 8% yield.

Scheme 2.18: Ozonolysis reaction of tetracycle 183. Reagents and conditions: (a) O3 (excess), CH2Cl2, 15 min, -78 °C, then PPh3 (6 mol equiv), -78 °C to 0 °C, 30 min, 8%.

High-resolution mass spectrometry indicated that the molecular ion of product 223 has a mass to charge ratio of 314.1529, consistent with molecular formula C19H22O4. In the 1H NMR spectrum of the product, signals associated with one mono-substituted alkene and a di-substituted alkene are still present (6.04 (1H, dd) and 5.08 (1H, s), 5.00 (1H, s) ppm, respectively) as in the starting material 183 (5.89 (IH, dd), 5.85 (1H, dd), 4.94 (1H, s), 4.82 (1H, s). While the two tertiary alkenic proton signals of 183 between 5.35 and 5.45 ppm are no longer present in the spectrum of the product, two new signals belonging to aldehyde protons appear between 9.69 and 9.48 ppm. In addition, a signal at 3.01 ppm, suggestive of an epoxide, was observed. In the 13C NMR spectrum of the product, three different signals are observed in the low field region. Two of them are associated with aldehyde carbons (201 and 200 ppm, respectively), whereas one of them is due to the resonance of a ketone carbon (208 ppm). All of 1H NMR signals were unequivocally assigned by COSY, HMBC and HSQC experiments. The stereochemistry of the compound 223 was assigned by a NOESY experiment. The NOESY cross-peaks are shown in Figure 2.10.
When exposed to ozone 217, tetracycle 183 undergoes a complex sequence of reactions. Overall, there is reaction with three of the five alkenes in the substrate. The endocyclic A-ring alkene and one terminal alkene undergo ozonolysis. The endocyclic alkene in the B-ring suffers epoxidation, a [2+1] cycloaddition, rather than the [3+2] cycloaddition leading to ozonolysis. This is presumably due to steric hindrance of the approach of ozone 217 to this alkene. As described above, epoxidation competes with ozonolysis when compounds containing sterically hindered carbon-carbon double bonds are treated with ozone 217 (Scheme 2.19).
Scheme 2.19: Proposed mechanism for epoxidation of the sterically hindered B-ring alkene during the ozonolysis.\textsuperscript{97}

We do not know the order of events and further work is needed to determine this. It is important not to over-interpret the results of the treatment of tetracycle 183 with ozone 217, since it is a very messy reaction, with only 8\% isolated yield of pure product 223. Even so, selective cleavage of the A-ring of tetracycle 183 to form tricyclic compound 223 is extremely encouraging. The tricyclic carbon skeleton of platensimycin 184 is the same as that of compound 223 and is one possible target for ambitious further investigations (Scheme 2.20).

Scheme 2.20: From tetracycle 183 to platensimycin 184.

2.3.6 Cross-metathesis reaction of tetracycle 183

Olefin metathesis (Scheme 2.21), "the metal-catalysed redistribution of carbon-carbon double bonds" was first described in 1967 by Calderon and co-workers.\textsuperscript{98} Nobel laureate Robert Grubbs prepared families of ruthenium based carbenoid catalysts for these reactions.\textsuperscript{99} The process forms two new alkenes that are often difficult to make by alternate routes. It is now a widely used method for the formation of carbon-carbon double bonds.\textsuperscript{35}
Scheme 2.21: Alkene cross-metathesis reaction: general transformation.98

The ruthenium-catalysed cross-metathesis reaction mechanism is shown in Scheme 2.22. The mechanism involves the first [2+2] cycloaddition between ruthenium carbene catalyst 224 and alkene 225 to form intermediate 226, which is converted to 228 via a reverse [2+2] cycloaddition reaction. Analogous processes between 228 and 229 afford 231.

Scheme 2.22: Mechanism of a ruthenium-catalysed alkene cross-metathesis reaction.99

By varying the steric and electronic properties of the ligands (L) appended to the ruthenium centre, various reactivity profiles have been observed.99 For instance, Grubbs's second-generation catalyst 232 (Figure 2.11), is particularly fast reacting in the cross-metathesis of alkenes.99
Figure 2.11: Grubbs’ second-generation catalyst 232.

Tetracycle 183 has five alkene units. An examination of the mechanism of cross-metathesis (Scheme 2.22) shows that the first step is [2+2] cycloaddition of one of the alkene substrates 225 to the ruthenium carbene catalyst 224. It is, therefore, expected that the cross-metathesis reaction would preferentially occur at the least sterically hindered alkene of our substrate, the vinyl group attached to the C/D ring junction. With this prediction in mind, tetracycle 183 was treated with 2 mol equiv of (Z)-but-2-ene-1,4-diyl diacetate 233 in the presence of catalytic amount of Grubbs’ second-generation catalyst 232 in CH2Cl2 at 60 °C in a sealed tube (Scheme 2.23).

Scheme 2.23: Cross-metathesis reaction of tetracycle 183. Reagents and conditions: (a) (Z)-but-2-ene-1,4-diyl diacetate (4 mol equiv), Grubbs II catalyst (0.2 mol equiv), CH2Cl2, 60 °C, sealed tube, 24 h, 13% (34% based on recovered starting material).

After 3.5 hours, the reaction was incomplete by TLC examination. It was also observed that (Z)-but-2-ene-1,4-diyl diacetate 233 was isomerised to (E)-but-2-ene-1,4-diyl diacetate. Following the addition of a further 2 mol equiv of (Z)-but-2-ene-1,4-diyl diacetate 233 and catalyst, the reaction was stirred at 60 °C for another 20.5 hours. While the reaction did not reach completion, the decision was made to subject it to work-up and purification of the resultant mixture by flash column chromatography. The major product defied isolation. Starting material 183 and one cross-metathesis product 235 were isolated. The structural identification of this product will now be discussed.
We had previously assigned the carbons of the A, C and D rings 1 through 8 of starting material \textbf{183} and may assign them by analogy to possible structures \textbf{234} and \textbf{235} (Figure 2.12).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.12}
\caption{Starting material \textbf{183} and two possible cross-metathesis products \textbf{234} and \textbf{235}.}
\end{figure}

The $^1$H NMR spectrum of starting material \textbf{183} has two double doublets at $\delta$ 5.89 and 5.85 ppm, assigned to the methine protons of the two vinyl groups of \textbf{183}. In the $^1$H NMR spectrum of the product, only one double doublet signal is present at $\delta$ 5.93 ppm. In addition, two new signals, one proton doublet at $\delta$ 5.73 ppm and one proton doublet of triplets at $\delta$ 5.55 ppm were observed. These signals are consistent with resonances of the protons substituting C9 and C10 of either structure \textbf{234} or \textbf{235}. Thus, the $^1$H NMR spectrum showed that the cross-metathesis reaction had occurred at either the vinyl group attached to the A/D ring junction of \textbf{183}, (ie compound \textbf{234}) or that attached to the C/D ring junction, (ie compound \textbf{235}). Together, these data confirm a single cross-metathesis event at one mono-substituted alkene. Additionally, the coupling constant of the two hydrogens across the new double bond ($J = 15.2$ Hz) is consistent with a trans- configuration.

In order to answer which mono-substituted alkene underwent the cross-metathesis reaction, we turned to the long range coupling information revealed by a HMBC experiment. Let us now consider the protons appended to the new double bond of either structure \textbf{234} or \textbf{235}. Cross-peaks are observed between the proton attached to C9 and the following carbon atoms: C11, methylene carbons C5 and C6 and quaternary carbon C3. In contrast, the proton substituting C12 exhibits a HMBC correlation with
methylene carbon C7 and quaternary carbons C1 and C3. These data are consistent with structure 235, but not with structure 234.

Although the compound 235 was isolated in only 13% yield, starting material 183 (62%) was also recovered (Scheme 2.23) resulting in an overall yield, based on recovered starting material 183, of 34%. Repetition of the above reaction in 1,2-dichloroethane at 85 °C afforded the compound 235 in 6% yield as a single stereoisomer with 35% recovery of starting material 183.

Despite the fact that our isolated product 235 is obtained in low yield, we may rationalise its formation rather than 234. Examination of the model arising from single crystal X-ray diffraction studies of starting tetracycle 183 allows us to analyse the steric environments of the two exocyclic alkenes.

**Figure 2.13:** Relatively sterically hindered exocyclic alkene (blue), compared with unhindered alkene (red).

The exocyclic double bond on the bottom face of 183 (blue in Figure 2.13) has the capacity to tuck under the tetracycle, *partially* impeding access to the endocyclic double bond of the B-ring from the lower face. In contrast, the exocyclic double bond pendant from the C/D ring junction (red in Figure 2.13) is sterically unhindered. It is, therefore, unsurprising that product 235 is formed.

Despite the poor isolated yield of 235, the fact that a product of selective cross-methathesis may be isolated at all is cause for optimism. Careful exploration of the system, using various conditions, especially changing the catalyst (Figure 2.14), may reasonably be anticipated to yield fruitful results.
For example, Grubbs' generation one catalyst 236 is known to be less reactive than second-generation catalyst 232, used in this present study. Invoking the reactivity-selectivity principle, perhaps we may see a single product predominating in our reaction mixture with the use of this milder catalyst. More sterically challenging olefins within the substrate 183, such as the mono-substituted alkene at the A/D ring junction, or the 1,1-disubstituted alkene at ring D, may be targeted by catalysts with relatively open space around the ruthenium core, such as catalysts 237 and 238 (Figure 2.14).

In summary, the work described in this section demonstrates selective manipulation of tetracycle 183 (Scheme 2.24), successfully achieving the first stated aim of this project. Dihydroxylation and cross-metathesis reactions proceed only at the mono-substituted alkene on C/D ring junction. While dihydroxylation reaction gives two separable stereoisomeric products, 203 and 204, the cross metathesis reaction affords only one trans-stereoisomeric product, 235. Both epoxidising agents trialled, m-CPBA 206 and DMDO 210, only react with tertiary alkene units. Both reagents afford the same single diastereomeric bis-epoxide 213 and a mixture of mono-epoxides. Reaction of 183 with excess ozone 217 gives a product 223, rich in handles for further selective functionalisation.
2.3.7 Retrosynthesis of dimethyl substituted [5]dendralene 190

As described in Scheme 2.1, [5]dendralene 176 was obtained via a double Kumada-Tamao-Corriu cross-coupling reaction between the Grignard reagent 34 derived from chloroprene 40 and 1,1-dichloroethylene 32. We proposed that if we are able to synthesise the Grignard reagent 242, dimethyl substituted [5]dendralene 190 could be obtained using analogous chemistry for a double cross-coupling reaction between the Grignard reagent 242 and 1,1-dichloroethylene 32 (Scheme 2.25). We have a need, therefore, to prepare Grignard reagent 242.

2.3.8 Synthesis of Grignard reagent 242

In order to synthesise this desired [5]dendralene precursor 190, we started from commercially available 2-methylbut-3-yn-2-ol 239. Following a procedure previously reported in the literature, dehydration of 239 gave 2-methylbut-1-en-3-yne 240 in 63% yield. HCl addition in the presence of CuCl and NH₄Cl gave 2-chloro-3-methylbuta-1,3-diene 241 in 26% yield along with 32% recovered starting material 240. In the next step, 2-chloro-3-methylbuta-1,3-diene 241 was converted to the Grignard reagent 242 in 55% yield (Scheme 2.26) after careful optimisation.

![Scheme 2.26: Synthesis of Grignard reagent 242. Reagents and conditions: (a) 2-Methyl-3-butyn-2-ol (1.0 mol equiv), Ac₂O (1.3 mol equiv), p-TsOH (0.040 mol equiv), 1 h, 63%; (b) 2-methylbut-1-en-3-yne (1.0 mol equiv), conc. HCl (1.0 mol equiv), CuCl (0.20 mol equiv), NH₄Cl (0.20 mol equiv), 20 °C, 75 min, 26%; (c) 2-chloro-3-methylbuta-1,3-diene (1.0 mol equiv), magnesium powder (2.9 mol equiv), BrC₂H₃Br (0.70 mol equiv), ZnBr₂ (0.030 mol equiv), THF, reflux, 75 min, 55%.]

A variety of reaction conditions were tested in order to synthesise pure 2-chloro-3-methylbuta-1,3-diene 241. Following attempts to force the reaction to completion, the product contained contaminants, which were inseparable in our hands. After some experimentation, it was found that the best conditions involved the treatment of 240 with 1 mol equiv of conc. HCl, 0.2 mol equiv of CuCl and 0.2 mol equiv of NH₄Cl at 20 °C for 75 min, to give the chloride 241 in 26% yield along with 32% unreacted starting material 240. Although the reaction was low yielding, ten of grams of material could be readily prepared.

After pure 2-chloro-3-methylbuta-1,3-diene 241 had been obtained, its conversion into Grignard reagent 242 was investigated. Dissappointingly, treatment of halide 241 with magnesium turnings in the presence of 1,2-dibromoethane and ZnBr₂ at reflux in THF for 2 hours did not result in the formation of the Grignard reagent 242. We were surprised by this, given that chloroprene 40 reacts smoothly under these conditions to afford the analogous Grignard reagent 34. When more 1,2-dibromoethane, ZnBr₂, and
iodine were added, the reaction was complete at 17 hours. Gratifyingly, we found that substituting magnesium powder for magnesium turnings in the presence of 1,2-dibromoethane and ZnBr₂ at reflux in THF, resulted in formation of the Grignard reagent 242 in under two hours.

In order to determine whether the Grignard reagent formation had proceeded to completion, a small amount of the reaction mixture was quenched with water, diluted with CDCl₃ and examined by ¹H NMR spectroscopy. We expected to see only one product, isoprene 243. The ¹H NMR spectrum indicated, however, the presence of another (transposition) product, 1,1-dimethyl allene 244. The ratio of 243:244, was determined by integration as 90:10 (Scheme 2.27).

Scheme 2.27: The formation of Grignard 242 reagent and its protonolysis products.
Reagents and conditions: (a) Magnesium powder (2.9 mol equiv), BrC₂H₄Br (0.70 mol equiv), ZnBr₂ (0.030 mol equiv), THF, reflux, 75 min, 55%. (b) Quenched with water and diluted with CDCl₃, (ratio 243:244, 90:10).

This result is in stark contrast to the analogous chloroprene Grignard reagent 34, which gives only butadiene 4 under these conditions (Scheme 2.28). The possibility of the formation of the allenic isomer 245 of the Grignard reagent derived from chloroprene 40 was considered by Aufdermarsh¹⁰³ as long ago as 1963 but, to the best of our knowledge, this transformation has never been observed. It is clear, therefore, that methyl substituted chloroprene 241 is not behaving in the same way as chloroprene 40.

Scheme 2.28: The formation of Grignard 34 reagent and its protonolysis product.
Reagents and conditions: (a) Magnesium turnings (1.6 mol equiv), BrC₂H₄Br (0.30 mol equiv), ZnBr₂ (0.010 mol equiv), THF, reflux, 2 h, 76%. (b) Quenched with water and diluted with CDCl₃. Also see.¹⁰³
It is, as yet, unclear why methyl substituted chloroprene 241 is behaving differently to chloroprene 40. Two general possibilities (Scheme 2.29) relate to either the existence of the Grignard reagent containing an sp² carbon-magnesium bond 242 or an sp³ carbon-magnesium bond 246. It is not clear whether or not either of these two forms exist in solution or whether they are in equilibrium.

Scheme 2.29: Possible relationships between Grignard reagents and hydrocarbons observed by 'H NMR.

Aufdermarsh demonstrated that the chloroprene Grignard reagent exists in the diene form 34 and not the allene form 247 by virtue of the lack of an allenic absorption in the infrared spectrum of the Grignard reagent derived from chloroprene (Figure 2.15). Coming back to the methyl substituted system, it is also not known whether either of these forms (242 and 246) would be expected to react exclusively to form their corresponding protonolysis products directly, without rearrangement.

Figure 2.15: Grignard reagent 34 derived from chloroprene 40 and its allenic form 247.

Clearly, with a simple quenching experiment using water, the Grignard reagent 242 derived from methyl substituted chloroprene 241 is behaving in a more complex manner than the unsubstituted chloroprene Grignard reagent 34. In light of time constraints, we
chose at this stage to continue with the synthesis of dimethyl substituted [5]dendralene 190 from this Grignard reagent, leaving an investigation into the structure and reactivity of this fascinating compound to future studies.

### 2.3.9 Towards the synthesis of dimethyl substituted [5]dendralene 190

As mentioned in Section 2.1.1, the synthesis of [5]dendralene 176 employed a double Kumada-Tamao-Corriu cross-coupling reaction between chloroprene Grignard reagent 34 and 1,1-dichloroethylene 32. Thus, an excess of (3-methylbuta-1,3-dien-2-yl) magnesium chloride 242 was treated with 1,1-dichloroethylene 32 in the presence of Ni(dppp)Cl2 and PPh3 at room temperature for 4 days, under the modified conditions of Bojase for the synthesis of [5]dendralene 176.20 1H NMR spectroscopic analysis of a sample subjected to aqueous workup indicated the presence of isoprene 243 and dimethyl allene 244, consistent with unreacted Grignard reagent 242, so additional catalyst and 1,1-dichloroethylene 32 were added and the reaction temperature was increased to 30 °C. The reaction was practically complete after 3.5 hours. Purification of the crude mixture by flash column chromatography on silica gel afforded mainly a mixture of compounds 190 and 249, a small amount of compound 248, and a tiny amount of compound 250 (Scheme 2.30). Further purification using reverse phase HPLC provided small amounts of pure compounds 190 and 248. Unfortunately, target compound 190 was lost during evaporation of the solvent and could not be fully characterised. Time constraints did not allow this synthesis to be repeated.

Scheme 2.30: Towards the synthesis of dimethyl substituted [5]dendralene 190.
Reagents and conditions: (a) (3-Methylbuta-1,3-dien-2-yl)magnesium chloride (3.0 mol equiv), 1,1-dichloroethylene (1.0 mol equiv), PPh3 (0.050 mol equiv), Ni(dppp)Cl2 (0.025 mol equiv), 15 °C to rt, 45 h.
The product 190, isolated by reverse phase HPLC, displayed a molecular ion with a mass to charge ratio of 160.1258 in mass spectrometric studies, consistent with a molecular formula of C\textsubscript{12}H\textsubscript{16}. In addition, analysis of this symmetrical compound 190 by 'H NMR spectroscopy indicated five distinct alkenic signals around 5.22-5.00 ppm associated with 10 protons and one signal at 1.97 ppm associated with six aliphatic protons.

In attempts to improve the yield of this reaction, a range of reagent ratios were investigated. Frustratingly, the target product 190 could not be isolated in pure form by flash column chromatography. As sufficient pure amounts of the desired product 190 could not be practically prepared, an alternative route was investigated.

2.3.10 Towards the synthesis of 2-chloro-4-methyl [3]dendralene 249

The problem was isolating 190 in the presence of isomeric hydrocarbons 248 and 250, and 2-chloro-4-methyl substituted [3]dendralene 249. It was proposed that 248 and 250 are the result of an initial coupling to give 251 (Figure 2.16).

![Figure 2.16: Proposed product of initial coupling between rearrangement Grignard reagent 246 and 1,1-dichloroethylene 32.](image)

Hence, an alternative approach involving the isolation of chloro [3]dendralene 249 was investigated (Scheme 2.31). According to this two-step approach, compound 249 would be first synthesised from the cross-coupling reaction between Grignard reagent 242 and 1,1-dichloroethylene 32. A second cross-coupling reaction between pure compound 249 and Grignard reagent 242 might then to result in the selective formation of target product 190.
Scheme 2.31: An alternative approach to synthesise dimethyl substituted [5]dendralene 190.

The Grignard reagent 242 was treated with an excess of 1,1-dichloroethylene 32 in the presence of Ni(dppe)Cl_2 in THF at -20 °C, following a modified procedure of Bradford. The reaction was not complete after 36 hours. More catalyst was added and the reaction stirred for a further 30 hours at the same temperature. Since only minor amounts of isoprene 243 were observed upon aqueous workup of small aliquots, consistent with minor amounts of unreacted Grignard reagent 242, the reaction was subjected to work-up. Attempted purification of the crude mixture by flash column chromatography on silica gel provided a mixture of compounds 249, 190, and 248 in low yield (Scheme 2.32).

Scheme 2.32: Towards the synthesis of 2-chloro-4-methyl substituted [3]dendralene 249. Reagents and conditions: (a) 1,1-Dichloroethylene (5 mol equiv), Ni(dppe)Cl_2 (0.01 mol equiv), -20 °C, 66 h.

At this stage, time was short. Given the propensity of Grignard reagent 242 to react with mono-adduct 249, even in the presence of an excess of 1,1-dichloroethylene 32 and our inability to separate 249 from 190, a practical synthesis of 190 remains elusive.

2.3.11 An attempt to synthesise tetracycle 193 from 190

In order to test the Diels-Alder dimerisation of dimethyl substituted [5]dendralene 190, a mixture of dimethyl substituted [5]dendralene 190 and 2-chloro-4-methyl [3]dendralene 249 in mesitylene was heated at reflux for 17 hours.
After the solvent was removed by bulb to trap distillation, purification of the resultant residue by flash column chromatography on silica gel afforded impure material that we tentatively propose to contain tetracycle 193 (8%). Disappointingly, attempted further purification failed. Analysis of the \(^1\)H NMR spectrum of the isolate indicated four alkenic singlets at 6.50 ppm (1H), 6.30 ppm (1H), 5.10 ppm (2H) and 5.00 ppm (2H), and several aliphatic signals between 1.80 ppm and 0.80 ppm. The spectrum was complicated by the appearance of signals consistent with oligomeric and polymeric material. Although time constraints prevented further purification and characterisation, we speculate that the Diels-Alder dimerisation of dimethyl substituted \([5]\)dendralene 190 proceeds in an analogous way to \([5]\)dendralene 176 via sequential pericyclic cascade reactions, namely intramolecular Diels-Alder, \(6\pi\) electrolyclication, and intermolecular Diels-Alder reaction to provide tetracycle 193 (Scheme 2.33).

![Scheme 2.33: Formation of tetracycle 193 from the Diels-Alder dimerisation of 190. Reagents and conditions: (a) Mesitylene, reflux, 17 h.](image)

2.4 Conclusions

Tetracycle 183, derived from \([5]\)dendralene 176, has five different alkenes units; two mono-substituted alkenes, one 1,1-disubstituted alkene and two tri-substituted alkenes.
The first aim of this project was to look for selectivity in the manipulation of these alkenes. This goal has clearly been achieved (Scheme 2.34).

Scheme 2.34: Summary of manipulation of tetracycle 183. (a) DMDO in acetone (2 mol equiv), rt, 2 h, 37% 213 (bis-epoxide) and 9% (mono-epoxides); (b) O₃ (excess), CH₂Cl₂, 15 min, −78 °C, then PPh₃ (6 mol equiv), −78 °C to 0 °C, 30 min, 8%; (c) OsO₄ (4.1% in H₂O solution) (0.04 mol equiv), THF/H₂O/t-BuOH (5:1:1 ratio), rt, 4 days, in the dark, 30%; (d) (Z)-But-2-ene-1,4-diyl diacetate (4 mol equiv), Grubbs II catalyst (0.2 mol equiv), CH₂Cl₂, 60 °C, 24 h, 13%.

High selectivity for the reaction of tri-substituted alkenes over mono- or di-substituted alkenes was observed. No selectivity between the two tri-substituted alkenes was observed: isolation of pure mono-epoxides was not achieved within our limited timeframe. Conditions for the isolation of pure bis-epoxide 213 were, however, identified. Both m-CPBA 206 and DMDO 210 were useful in affecting this transformation on the endocyclic alkenes on the A and B rings. A more global method of installing varying functionality at the B ring and at the less sterically hindered vinyl group attached to the C/D ring junction with concomitant cleavage of the A ring was identified by the use of ozone 217 to produce derivative 223. Selective fuctionalisation of the vinyl group attached to the C/D ring junction of 183 was achieved with both dihydroxylation and cross-metathesis reactions. These selectivities were rationalised using a combination of electronic and steric arguments.
The second aim of the work described in this report involved the synthesis of dimethyl substituted [5]dendralene 190 using the method that we have previously developed for the synthesis of [5]dendralene 176 in the group (Scheme 2.35).

Scheme 2.35: Formation of [5]dendralene 176. Reagents and conditions: (a) Grignard reagent (3.5 mol equiv), 1,1-dichloroethylene (1.0 mol equiv), Ni(dppp)Cl₂ (0.040 mol equiv), PPh₃ (0.040 mol equiv), THF, rt, 48 h, 65%.

When this method was applied, operational limitations prevented full characterisation of 190. Given the mass spectrometric, ^1H NMR and IR spectroscopic data, in comparison with known members of the dendralene family, we are, however, confident of the identity of 190 (Scheme 2.36).

Scheme 2.36: Towards the synthesis of dimethyl substituted [5]dendralene 190. Reagents and conditions: (a) (3-Methylbuta-1,3-dien-2-yl)magnesium chloride (3.0 mol equiv), 1,1-dichloroethylene (1.0 mol equiv), PPh₃ (0.050 mol equiv), Ni(dppp)Cl₂ (0.025 mol equiv), 15 °C to rt, 45 h.

It became clear during this work, that the differing behaviour of the Grignard reagent 242 to that of the Grignard 34, derived from chloroprene 40, rendered our previous method of limited use for the practical preparation of dimethyl substituted [5]dendralene 190 (Figure 2.17).
Figure 2.17: Grignard reagents 242 and 34 for the formation of dimethyl substituted [5]dendralene 190 and [5]dendralene 176, respectively.

2.5 Future work

Reaction of tetracycle 183 with excess ozone 217 resulted in cleavage of the ring A, with associated functionalisation of the B ring and of one exocylic alkene. The results of treatment with one molar equivalent of ozone 217 need to be assessed. In any case, the new tricyclic ring system of 223, formed by treatment of 183 with excess ozone 217, closely matches the carbocyclic skeleton of the topical natural product platensymicin 184. Further transformation is needed in order to manipulate this product toward platensimycin 184 (Scheme 2.37). For example, an extra heterocyclic oxo bridge needs to be incorporated across ring C and D.

Scheme 2.37: From tetracycle 183 to platensimycin 184.

Improved yields of bis-epoxide 213 (Figure 2.18) may readily be achieved by the use of excess DMDO 210. This reagent was found to be superior to m-CPBA 206 for the epoxidation of tetracycle 183. The exploration of different catalysts in the cross-methathesis reaction of tetracycle 183 and different co-oxidants in the dihydroxylation of same, is anticipated to provide improvements in yield and selectivity in the manipulations of the tetracycle.
Figure 2.18: *Bis-*epoxide 213.

The isolated yields for the products of manipulations of tetracycle 183 are generally lower than are indicated by $^1$H NMR spectral analysis of crude reaction mixtures. Clearly, further work is needed to optimise the purification protocols of our new products.

Furthermore, future work will focus on optimising (different catalysts/conditions) the yield of dimethyl substituted [5]dendralene 190. Once enough material has been synthesised, its transformation into methyl substituted tetracycle 193 will be studied (Scheme 2.38).


An alternative path towards 190 will involve cross-coupling reactions (Scheme 2.39). It was previously reported by Sherburn and co-workers$^{104}$ that the so-called “even” [4]dendralene 29 is more stable than the so-called “odd” [3]dendralene 28.

The first coupling between dihalogen 252 and methyl substituted Grignard reagent 242 will result in the formation of a derivative of [4]dendralene 253 (Scheme 2.39). The second KTC cross-coupling reaction between 253 and isopropenyl magnesium bromide 41 will afford the target product 190. In contrast, the attempted route, described in this report, results in the formation the less stable derivative of [3]dendralene 249 (Scheme 2.40).

Chapter 3

Experimental
3.1 General Methods

Reactions were performed under a positive pressure of dry argon or nitrogen. Diethyl ether and tetrahydrofuran were dried over sodium wire and distilled from sodium benzophenone ketyl. Dichloromethane was distilled from calcium hydride. Toluene was obtained from Myer solvent dispensing system. Dimethyldioxirane was prepared according to Murray and Singh\(^9\) procedure and used freshly. The dimethyldioxirane concentration was determined using a standard solution of phenyl methyl sulfide along with a standard solution of hexadecane in acetone by GLC method. Commercially available chemicals were purified by standard procedures or used as purchased. Analytical thin layer chromatography (TLC) was performed with Merck (A.T. 5554) silica gel 60 F\(_{254}\) (0.2 mm) precoated on aluminium sheets. Flash column chromatography employed Merck Kieselgel 60 (230-400 mesh) silica gel. Preparative HPLC was performed using a Waters 600 pump with a Waters 600E controller and a SunFire Prep Silica 5 µm, 150 x 19 mm column monitored by a Waters 2996 photodiode array detector. Reverse-phase preparative HPLC was performed using a Waters 600 pump with a Waters 600 controller and a Column Cronusil Triple-E C18 4 µm, 250 x 21 mm column monitored by a Waters 2996 photodiode array detector. GC measurements were recorded on an Agilent 7890A gas chromatograph with a split/splitless (split ratio 25/1) capillary inlet and FID detector. Separation was achieved at 60 °C for 5 min then 20 °C/min to 250 °C for 5.5 min with HP-5 5% phenyl methyl siloxan column (30 m x 320 µm x 0.25 µm). NMR spectra were recorded at 298 K using a Bruker Avance 800, Varian INOVA 500, Varian INOVA 400 or Varian INOVA 300 spectrometer. Residual chloroform (δ = 7.26 ppm) was used as internal reference for \(^1\)H NMR spectra measured in this solvent. The central line of the CDCl\(_3\) triplet (δ = 77.1 ppm) was used as internal reference for \(^{13}\)C NMR spectra. Assignment of proton signals was assisted by COSY and NOESY experiments where necessary. Assignment of carbon signals was assisted by DEPT experiments and HMBC, HSQC experiments where necessary. Signals are described in terms of chemical shifts, intensity and multiplicity (the following abbreviations were used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet and br, broad) and coupling constants (J). IR spectra were recorded on a Perkin-Elmer 1600 FTIR spectrometer as neat films on NaCl plates for oils or as KBr disks for solids. Mass spectra were recorded by the Mass
Spectrometry Facility of the Research School of Chemistry, Australian National University, Canberra on a Finnigan PolarisQ ion trap mass spectrometer using electron impact (EI⁺) ionization mode at 70 eV for low resolution mass spectra and VG Autospec mass spectrometer operation at 70 eV for high resolution mass spectra. Melting points were measured on a Reichert hot stage melting apparatus and are uncorrected.

3.2 Chapter 1 Experimental

Chloroprene \(40\)

The title compound \(40\) was prepared according to a patented procedure.\(^{31}\) A flame dried three-necked flask was charged with calcium hydroxide (42 g, 0.57 mol, 0.57 mol equiv), BHT (0.28 g, 1.3 mmol, 1.3 μmol equiv) and ethylene glycol (500 mL). This solution was stirred at 105 °C under a nitrogen atmosphere for 30 min. 3,4-Dichloro-1-butene (0.11 L, 1.0 mol, 1.0 mol equiv) was then added dropwise to this mixture. The product was distilled directly from the reaction mixture lit.\(^{31}\) bp. 59 °C/760 mm Hg, dried over anhydrous CaCl₂ and filtered to give the title compound \(40\) (64 g, 0.72 mol, 72%) as a colourless oil. \(^1\)H NMR data was consistent with that reported in the literature.\(^{31}\)

2-(1,3-Butadienyl)magnesium chloride \(34\)

The title compound \(34\) was prepared by modifications to the procedure reported by Nunomoto.\(^{105}\) To a stirred mixture of oven-dried magnesium turnings (7.3 g, 0.30 mol, 1.6 mol equiv) in dry THF (50 mL) at room temperature, 1,2-dibromoethane (2.3 mL, 27 mmol, 0.14 mol equiv) was added dropwise (exotherm) followed by anhydrous zinc bromide (0.44 g, 2.0 mmol, 0.010 mol equiv). Material adhering to the sides of the flask was rinsed into the reaction mixture with THF (1 mL). A solution of
chloroprene 40 (16.7 g, 189 mmol, 1.00 mol equiv) and 1,2-dibromoethane (2.6 mL, 30 mmol, 0.16 mol equiv) in THF (100 mL) was then added dropwise to this mixture which maintained reflux and the resulting mixture was stirred at reflux for 2 h. The formation of 2-(1,3-butadienyl)magnesium chloride 34 was checked by the formation of butadiene upon hydrolysis with water. Titration of the resultant Grignard reagent 34, with salicylaldehyde phenylhydrazone,\textsuperscript{106} indicated a 0.96 M solution of the \textit{title compound} 34 in THF, hence a 76% yield.

2-Chloro [3]dendralene 37

\begin{center}
\includegraphics[width=0.2\textwidth]{37.png}
\end{center}

The \textit{title compound} 37 was prepared according to a slightly modified literature procedure.\textsuperscript{19} To a stirred solution of 2-(1,3-butadienyl)magnesium chloride 34 (100 mL of a 0.96 M THF solution, 96 mmol, 1.0 mol equiv) at -20 °C, 1,1-dichloroethylene 32 (60 mL, 0.73 mol, 7.6 mol equiv) was added followed by Ni(dppe)Cl\textsubscript{2} (665 mg, 1.26 mmol, 0.013 mol equiv). The resulting mixture was stirred for 13 h at -20 °C. The reaction mixture was then poured onto a stirred biphasic cold mixture of H\textsubscript{2}O (300 mL) and 30-40 °C petrol (150 mL) and stirred for 15 minutes. Collected organic phase was then successively washed with 1 M \textit{aq.} HCl (45 mL), \textit{aq.} NaHCO\textsubscript{3} (50 mL) and \textit{aq.} NaCl (50 mL), and then dried over anhydrous MgSO\textsubscript{4}. Filtration and removal of the solvent under reduced pressure (20 mbar, 0 °C) afforded the \textit{title compound} 37 (9.36 g, 81.7 mmol, 85%) as a pale yellow oil. \textsuperscript{1}H NMR data was consistent with that reported in the literature.\textsuperscript{19}

(3-Methylene-penta-1,4-dien-2-yl)magnesium chloride 118

\begin{center}
\includegraphics[width=0.2\textwidth]{118.png}
\end{center}

The \textit{title compound} 118 was prepared according to a literature procedure.\textsuperscript{19} A dry three-neck flask was charged with oven-dried magnesium powder (0.99 g, 41 mmol, 2.9 mol equiv), THF (8 mL), and 1,2-dibromoethane (0.35 mL, 4.0 mmol, 0.30 mol equiv) (exotherm). After the reaction had subsided, ZnBr\textsubscript{2} (95 mg, 0.42 mmol, 0.030 mol equiv) was added. Material adhering to the sides of the flask was rinsed into
the reaction mixture with THF (1 mL). The reaction mixture was then heated to vigorous reflux upon which a solution of 2-chloro [3]dendralene 37 (1.6 g, 14 mmol, 1.0 mol equiv) and 1,2-dibromoethane (0.50 mL, 5.8 mmol, 0.40 mol equiv) in THF (20 mL) was added dropwise over 40 min. When the addition was complete, the reaction mixture was stirred at reflux for a further 30 min. The formation of (3-methylenepenta-1,4-dien-2-yl)magnesium chloride 118 was checked by the formation of [3]dendralene 28 upon hydrolysis with water. Titration of the resulting Grignard reagent 118, with salicylaldehyde phenylhydrazone,106 indicated a 0.22 M solution of the title compound 118 in THF, hence a 36% yield.


To a cooled suspension of freshly recrystallised NBS (0.89 g, 5.0 mmol, 3.0 mol equiv) in dry THF (5 mL) at −78 °C, a solution of (3-methylenepenta-1,4-dien-2-yl)magnesium chloride 118 (0.17 M, 10 mL, 1.7 mmol, 1.0 mol equiv) in THF was added slowly under argon gas atmosphere and stirred for 1.5 h. The reaction mixture was then poured onto sat. aq. Na₂CO₃ (50 mL) and stirred for 10 min at room temperature. After extraction with Et₂O (25 mL), the combined organic phases were dried over anhydrous MgSO₄ and filtered. The filtrate was concentrated under reduced pressure (25 mbar, 0 °C). Purification by flash column chromatography on silica gel eluting with pentane afforded compound 119 (36 mg, 0.23 mmol, 13%) and compound 122 (43 mg, 0.27 mmol, 15%) as a colourless oil.

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Rf</th>
<th>Literature Data</th>
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<tbody>
<tr>
<td>119</td>
<td>0.40 (30-40 °C petrol)</td>
<td></td>
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<tr>
<td>2-Bromo [3]dendralene 119: Rf 0.40 (30-40 °C petrol); ¹H NMR (300 MHz, CDCl₃) δ 6.38 (1H, ddd, J = 17.4, 10.8, 0.9 Hz), 5.86 (1H, d, J = 1.5 Hz), 5.72 (1H, d, J = 1.2 Hz), 5.50 (1H, ddd, J = 17.1, 1.5, 0.6 Hz), 5.44 (1H, m), 5.33 (1H, s), 5.29 (1H, m) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 134.5 (C), 129.1 (C), 120.1 (CH), 119.2 (CH₂), 118.0 (CH₂), 116.4 (CH₂) ppm; IR (thin film): νₘₐₓ = 3089, 2927, 1587, 1417 cm⁻¹;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
MS (70 eV, El): \( m/z \) (%): 143 (3) [M]\(^+\), 131 (19), 117 (38), 105 (18), 91 (44), 79 (100); HRMS: calc for \( \text{C}_9\text{H}_7\text{Br} \) [M]\(^+\): 157.9731; found 157.9736.

\[
\begin{align*}
\text{C} & \quad \text{Br} \\
\text{122}
\end{align*}
\]

3-(Bromomethyl)penta-1,2,4-triene 122: \( R_f \) 0.45 (30-40 \( ^\circ\)C petrol); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 6.18 (1H, dddd, \( J = 17.7, 11.1, 8.7 \) Hz), 5.36 (1H, dd, \( J = 17.7, 17.4 \) Hz), 5.21 (1H, dt, \( J = 10.5, 1.5 \) Hz), 5.03-5.00 (2H, m), 4.13 (2H, t, \( J = 1.5 \) Hz) ppm; \(^1^3\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 211.4 (C), 131.0 (CH), 115.0 (CH\(_2\)), 102.5 (C), 77.7 (CH\(_2\)), 29.8 (CH\(_2\)) ppm; IR (thin film): \( \nu_{\text{max}} \) = 2929, 1635, 1415 \( \text{cm}^{-1} \); MS (70 eV, El): \( m/z \) (%): 157 (19) [M]\(^+\), 143 (14), 129 (22), 57 (100); HRMS: calc for \( \text{C}_9\text{H}_7\text{Br} \) [M]\(^+\): 157.9731; found 157.9726.

2-Iodo [3]dendralene 120

\[
\begin{align*}
\text{120}
\end{align*}
\]

To a stirred solution of iodine (1.3 g, 5.0 mmol, 3.0 mol equiv) in dry Et\(_2\)O (10 mL) at -78 \( ^\circ\)C, a solution of (3-methylenepent-1,4-dien-2-yl)magnesium chloride 118 (0.17 M, 10 ml, 1.7 mmol, 1.0 mol equiv) in THF was added slowly under an argon atmosphere. After stirring for a further 1.5 h, the reaction mixture was then poured onto 5\% aq. Na\(_2\)S\(_2\)O\(_4\) (100 mL) and stirred at room temperature for 10 min. The aqueous layer was extracted with Et\(_2\)O (50 mL), and the combined organic phases were then dried over anhydrous MgSO\(_4\) and filtered. The filtrate was concentrated under reduced pressure (25 mbar, 0 \( ^\circ\)C). Purification by flash column chromatography on silica gel eluting with pentane afforded the title compound 120 (0.10 g, 0.40 mmol, 29\%) as a clear yellow oil. \( R_f \) 0.65 (30-40 \( ^\circ\)C petrol); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 6.35 (1H, dd, \( J = 17.4, 10.5 \) Hz), 6.23 (1H, d, \( J = 1.2 \) Hz), 6.00 (1H, d, \( J = 1.2 \) Hz), 5.44 (1H, ddd, \( J = 17.4, 1.2, 0.6 \) Hz), 5.34 (1H, s), 5.29-5.23 (1H, m), 5.22 (1H, s); \(^1^3\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 149.1 (C), 134.1 (CH), 129.2 (CH\(_2\)), 118.9 (CH\(_2\)), 118.1 (CH\(_2\)), 104.2 (C); IR (thin film): \( \nu_{\text{max}} \) = 2927, 1621, 1437 \( \text{cm}^{-1} \); MS (70 eV, El): \( m/z \) (%): 206 (12) [M]\(^+\), 191 (5), 179 (6), 165 (8), 127 (28), 77 (100); HRMS: calc for \( \text{C}_{10}\text{H}_{12} \) [M]\(^+\): 205.9593; found 205.9592.
(E)-2-(Prop-1-en-1-yl)benzo[d][1,3,2]dioxaborole 125

The title compound 125 was prepared according to the literature procedure. A pressure tube was charged with catecholborane (3.0 g, 25 mmol, 1.0 mol equiv) and dry THF (12.5 mL). The tube was then cooled with liquid nitrogen before propyne (ca. 2 mL, 33 mmol, 1.3 mol equiv) was condensed into the solution and the tube was then capped immediately. The resulting solution was allowed to warm to room temperature and then heated to 70 °C for 12 h. The solvent was removed in vacuo and a bulb to trap distillation of the residue afforded the title compound 125 (2.5 g, 16 mmol, 63%) as a clear colourless oil (bp. 50 °C/1 mm Hg; lit. bp. 71 °C/2 mm Hg). \(^1\)H NMR data was consistent with that reported in the literature.

(E)-4,4,5,5-Tetramethyl-2-(prop-1-en-1-yl)-1,3,2-dioxaborolane 126

This known compound has previously been made through a different procedure. (E)-2-(Prop-1-en-1-yl)benzo[d][1,3,2]dioxaborole 125 (2.0 g, 13 mmol, 1.0 mol equiv) and pinacol (1.5 g, 13 mmol, 1.0 mol equiv) in Et₂O (11 mL) were stirred at room temperature for 3 h. The solvent was removed in vacuo followed by purification by flash column chromatography on silica gel (elution with 2.5 % Et₂O: 97.5% hexane) afforded the title compound 126 (1.3 g, 7.9 mmol, 63%) as a clear colourless oil. \(^1\)H NMR data was consistent with reported in the literature.

(E)-Prop-1-en-1-ylmagnesium bromide 129

The title compound 129 was prepared according to a modified version of the literature procedure. A flame-dried two-necked flask fitted with a dry ice condenser was
charged with oven-dried magnesium turnings (0.46 g, 19 mmol, 2.3 mol equiv), THF (9 mL), and one crystal of iodine. The red reaction mixture turned to a turbid brown-red colour. The dry ice condenser was cooled to −78 °C and (E)-prop-1-en-1-yl bromide 128 (0.70 mL, 8.2 mmol, 1.0 mol equiv) was added. The reaction mixture was immediately cooled to −20 °C and stirred for 40 min. At this point, the reaction progress was checked by $^1$H NMR spectroscopy and some starting material was observed. The reaction mixture was therefore allowed to warm to 0 °C and stirred for a further 40 min. The molarity of the (E)-prop-1-en-1-ylmagnesium bromide 129 solution was measured by the formation of propene upon hydrolysis with water. Thus, gas titration indicated a 0.024 M solution of the title compound in THF (57% yield).

(E)-4,4,5,5-Tetramethyl-2-(oct-1-en-1-yl)-1,3,2-dioxaborolane 135

This known compound has previously been made through a different procedure. Catecholborane (0.6 g, 5.0 mmol, 1.1 mol equiv) was added carefully to 1-octyne (0.5 g, 4.5 mmol, 1.0 mol equiv) with stirring under a nitrogen atmosphere at room temperature and the resulting mixture was heated to 70 °C for 2h. The reaction mixture was cooled to room temperature, and THF (15 mL) was added followed by pinacol (0.64 g, 5.5 mmol, 1.2 mol equiv). This mixture was stirred at room temperature for 3 h, before it was diluted with EtOAc (15 mL). Then the resulting mixture was successively washed with H$_2$O (5 mL) and sat. aq. NaCl (5 mL). The combined organic layers were then dried over anhydrous Na$_2$SO$_4$, filtered and the solvent was removed in vacuo. Purification by flash column chromatography on silica gel (elution with 5% EtOAc: 95% hexane) afforded the title compound 135 (0.53 g, 2.2 mmol, 49%) as a colourless oil. $^1$H NMR data was consistent with that reported in the literature.

(E)-Oct-1-en-1-ylboronic acid 138

The title compound 138 was prepared according to a literature procedure. A solution of 1-octyne (2.8 g, 25 mmol, 1.0 mol equiv.) and catecholborane (3.0 g, 25 mmol,
1.0 mol equiv) was stirred under nitrogen at 70 °C for 2 h. The reaction mixture was then cooled to room temperature and diluted with H2O (25 mL). The resulting mixture was cooled to 0 °C, the precipitated solid was collected and recrystallised from hot water to give the *title compound* 138 (1.5 g, 9.8 mmol, 39%) as a white solid. 1H NMR data was consistent with that reported in the literature.110

**(E)-2-Chlorodeca-1,3-diene 136**

![Chemical structure of (E)-2-Chlorodeca-1,3-diene 136](image)

The *title compound* 136 was prepared by modifying a literature procedure.43 A small Schlenk flask was charged with XPhos (60 mg, 0.13 mmol, 0.020 mol equiv), Pd2(dba)3 (30 mg, 0.032 mmol, 0.005 mol equiv), anhydrous K3PO4 (3.0 g, 13 mmol, 2.0 mol equiv), (E)-oct-1-en-1-ylboronic acid 138 (1.0 g, 6.4 mmol, 1.0 mol equiv) and dry toluene (25 mL) under a nitrogen atmosphere. After stirring for a one minute, 1,1-dichloroethylene (2.1 mL, 26 mmol, 4.0 mol equiv) was added, the tube was sealed and heated to 60 °C for 6 h. The reaction mixture was cooled to room temperature, diluted with dry hexane (90 mL), and filtered through celite. The solvent was evaporated (20 mbar, 30 °C). The resulting crude material was diluted again with dry hexane (90 mL) and filtered through celite. After the solvent was evaporated (20 mbar, 30 °C), purification by flash column chromatography on silica gel eluting with hexane afforded the *title compound* 136 (0.35 g, 2.0 mmol, 32%) as a pale yellow oil. 1H NMR data was consistent with that reported in the literature.43

**(E)-3,4-Dimethylene-dodeca-1,5-diene 139**

![Chemical structure of (E)-3,4-Dimethylene-dodeca-1,5-diene 139](image)

Ni(dppp)Cl2 (35 mg, 0.065 mmol, 0.050 mol equiv) and PPh3 (17 mg, 0.065 mmol, 0.050 mol equiv) were added at −15 °C to a solution of (E)-2-chlorodeca-1, 3-diene 136 (0.23 g, 1.3 mmol, 1.0 mol equiv) in THF (1.5 mL). This was followed by the dropwise addition of 2-(1,3-butadienyl)magnesium chloride 34 (0.94 M, 4.2 mL, 3.9-mmol, 3 mol equiv). The reaction mixture was allowed to warm to room temperature and then stirred for 5.5 h at room temperature. The reaction mixture was poured onto a stirred
biphasic mixture of 30-40 °C petrol (10 mL) and H$_2$O (15 mL) and stirred for 15 min. 
The mixture was successively washed with 1M $aq.$ HCl (10 mL), sat. $aq.$ Na$_2$CO$_3$ (10 mL), and sat. $aq.$ NaCl (10 mL). The organic layer was then dried over anhydrous MgSO$_4$ and concentrated under reduced pressure (15 mbar, 25 °C). Purification by flash column chromatography on silica gel (eluting with 30-40 °C petrol) afforded the title compound 139 (0.13 g, 0.70 mmol, 53 %) as a colourless oil: $R_f$ 0.55 (hexane); $^1$H NMR (300 MHz, CDCl$_3$) δ 6.41 (1H, ddd, $J = 17.1, 10.2, 0.6$ Hz), 6.10 (1H, d, $J = 15.9$ Hz), 5.63 (1H, dt, $J = 15.6, 7.1$ Hz), 5.23-5.16 (1H, ddt, $J = 17.4, 1.5, 0.6$ Hz), 5.21-5.19 (1H, m), 5.12-5.06 (1H, dtd, $J = 10.5, 1.5, 0.6$ Hz), 5.11-5.09 (1H, m), 5.05-5.04 (1H, m), 4.91 (1H, d, $J = 2.4$ Hz), 2.06 (2H, dt, $J = 7.2, 6.3$ Hz), 1.40-1.22 (8H, m), 0.88 (3H, t, $J = 6.7$ Hz) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) δ 147.6 (C), 146.6 (C), 137.7 (CH), 134.2 (CH), 130.6 (CH), 117.4 (CH$_2$), 116.6 (CH$_2$), 115.1 (CH$_2$), 32.8 (CH$_2$), 31.8 (CH$_2$), 29.2 (CH$_2$), 29.0 (CH$_2$), 22.7 (CH$_2$), 14.2 (CH$_3$) ppm; IR (thin film): $\nu_{max}$ = 2958, 2926, 2855, 1585, 1466 cm$^{-1}$; MS (70 eV, El): $m/z$ (%): 190 (5), 175 (1), 161 (1), 147 (1), 133 (3), 119 (8), 105 (100); HRMS: calc for C$_{14}$H$_{22}$ [M$^+$]: 190.1722; found 190.1736.$^{111}$

Diisopropyl oct-1-yn-1-ylboronate 146

The title compound 146 was prepared according to a literature procedure.$^{111}$ A flame dried flask was charged with 1-octyne (2.2 mL, 15 mmol, 1.0 mol equiv) in dry Et$_2$O (70 mL) under an argon atmosphere and cooled to $-78$ °C. After stirring for 10 min, n-BuLi (1.5 M, 10 mL, 15 mmol, 1.0 mol equiv) was added and stirring was continued at the same temperature for a further 30 min. A solution of triisopropyl borate (3.5 mL, 15 mmol, 1.0 mol equiv) in dry Et$_2$O (50 mL) was stirred at $-78$ °C for 10 min. The octynyl-lithium reagent was added dropwise via cannula to the vigorously stirred solution at $-78$ °C and the resulting mixture was stirred at $-78$ °C for 2 h. The resultant viscous solution was warmed to room temperature. The solvent was removed under vacuo and the title compound 146 was obtained, as a clear
colourless oil (3.22 g, 13.5 mmol, 90%). $^1$H NMR data was consistent with that reported in the literature.$^{112}$

4,4,5,5-Tetramethyl-2-(oct-1-yn-1-yl)-1,3,2-dioxaborolane 148

![Molecular structure of 148](image)

This known compound has previously been made through a different procedure.$^{113}$ A solution of diisopropyl oct-1-yn-1-ylboronate 146 (1.0 g, 4.2 mmol, 1.0 mol equiv) and pinacol (520 mg, 4.40 mmol, 1.05 mol equiv) in dry Et$_2$O (7 mL) was stirred under an argon atmosphere at room temperature for 4 h. The solvent was removed under reduced pressure (9 mbar, 20 °C) to afford the title compound 148 (1.0 g, 4.2 mmol, 100%) as a clear yellow oil. $^1$H NMR data was consistent with that reported in the literature.$^{113}$

2-Chlorodec-1-en-3-yne 151

![Molecular structure of 151](image)

The title compound 151 was prepared according to a literature procedure.$^{46}$ A screw-capped pressure tube was charged with a solution of Pd(PPh$_3$)$_4$ (0.35 g, 0.30 mmol, 0.030 mol equiv) in dry toluene (15 mL) and 1,1-dichloroethylene (1.2 mL, 15 mmol, 1.5 mol equiv) was slowly added into the solution. The mixture was stirred at room temperature under argon for 25 min. To the yellow reaction mixture, a solution of 1-octyne (1.1 g, 10 mmol, 1.0 mol equiv) and n-butylamine (1.1 g, 15 mmol, 1.5 mol equiv) was transferred via cannula over 5 min. Cul (0.06 mg, 0.3 mmol, 0.03 mol equiv) was then added. Material adhering to the sides of the flask was rinsed into the reaction mixture with toluene (2 mL). The tube was sealed with a teflon cap and heated to 40 °C for 8 h. The cloudy red reaction mixture was filtered through celite and diluted with hexane (15 mL). The solvent was removed under reduced pressure (9 mbar, 33 °C). The resultant red oil was then diluted with CH$_2$Cl$_2$ (2 mL) and absorbed onto silica gel (4 g) under reduced pressure (9 mbar, 33 °C). Purification by flash column chromatography on silica gel eluting with hexane afforded the title compound 151.
(1.1 g, 6.3 mmol, 63%) as a yellow oil. \(^1\)H NMR data was consistent with that reported in the literature.\(^4\)

**Hydrogenation of 2-chlorodec-1-en-3-yne 151**

The general method reported by Overman et al.\(^{114}\) for the conversion alkynes to (Z)-alkenes was adopted. A dry two-necked flask was charged with 2-chlorodec-1-en-3-yne 151 (0.40 g, 2.3 mmol, 1.0 mol equiv), 5% Pd on BaSO\(_4\) (20 mg), quinoline (20 \(\mu\)L), and dry methanol (5 mL). The vessel was evacuated under vacuum and flushed with hydrogen gas three times. The reaction mixture was stirred at room temperature for 3 days. The resultant mixture was filtered through a pad of celite and filtercake was washed with Et\(_2\)O (5 mL). The filtrate was then washed with 1 M aq. HCl and sat. aq. NaCl. The organic layer was dried over MgSO\(_4\), filtered and the solvent was concentrated in vacuo. Purification by flash column chromatography on silica gel eluting with hexane afforded a 9:1 ratio mixture of 141 and 153 as a colourless oil (57 mg, 14%) and compound 154 (0.2 g) with some impurity. A further purification by flash column chromatography on silica gel eluting with Et\(_2\)O:hexane (2.5:97.5) afforded the *title compound* 154 (45 mg, 0.26 mmol, 11%) as a colourless oil: R\(_f\) 0.30 Et\(_2\)O:hexane (2.5:97.5); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 6.23 (1H, dt, \(J = 11.5, 7.5\) Hz), 5.76 (1H, dt, \(J = 11.5, 1.5\) Hz), 3.71 (3H, t, \(J = 0.5\)), 2.67-2.62 (2H, m), 1.47-1.40 (2H, m), 1.36-1.24 (6H, m), 0.88 (3H, t, \(J = 7.0\) Hz) ppm; \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 167.0 (C), 151.2 (CH), 119.2 (CH), 51.1 (CH\(_3\)), 31.7 (CH\(_2\)), 29.1 (CH\(_2\)) (three coincident signals), 22.7 (CH\(_2\)), 14.2 (CH\(_3\)) ppm; IR (thin film): \(\nu_{\text{max}} = 2955, 2927, 2857, 1726, 1645\) cm\(^{-1}\); MS (70 eV, El): \(m/z\) (%): 170 (19) [M]\(^+\), 155 (1), 139 (18), 127 (8), 113 (100); HRMS: calc for C\(_{10}\)H\(_{18}\)O\(_2\) [M]\(^+\): 170.1307; found 170.1302.
An oven-dried flask was charged with a solution of 2-chlorodec-1-en-3-yne 151 (2.0 g, 12 mmol, 1.0 mol equiv) in dry THF (16 mL), Ni(dppp)Cl$_2$ (0.32 g, 0.59 mmol, 0.050 mol equiv), and PPh$_3$ (0.15 g, 0.59 mmol, 0.050 mol equiv). Material adhering to the sides of the flask was rinsed into the reaction mixture with dry THF (10 mL). The mixture was cooled to -15 °C and stirred under nitrogen for 30 min. After a solution of 2-(1,3-butadienyl)magnesium chloride 34 (0.83 M, 42 mL, 35 mmol, 3.0 mol equiv) in dry THF was added dropwise, the reaction mixture was allowed to warm to 0 °C and stirred for 2.5 h. The reaction mixture was poured onto a stirred biphasic mixture of 30-40 °C petrol (100 mL) and H$_2$O (150 mL) and then allowed to stir for 15 min. Following successive washes with 1 M aq. HCl (40 mL), sat. aq. NaHCO$_3$ (50 mL) and sat. aq. NaCl (30 mL), the organic layer was dried over MgSO$_4$, filtered and the solvent was removed under reduced pressure (9 mbar, 0 °C) to give an oil. Purification by flash column chromatography on silica gel eluting with pentane afforded the title compound 155 (1.4 g, 7.3 mmol, 63%) as a clear colourless oil: R$_f$ 0.42 (pentane); $^1$H NMR (300 MHz, CDCl$_3$) δ 6.44 (1H, dd, J = 16.5, 11.7, 9.9 Hz), 5.52-5.44 (4H, m), 5.29 (1H, s), 5.18 (1H, dd, J = 10.5, 1.8 Hz), 2.34 (2H, t, J = 7.1 Hz), 1.61-1.50 (2H, m), 1.47-1.36 (2H, m), 1.36-1.24 (4H, m), 0.90 (3H, t, J = 6.8 Hz) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) δ 145.3 (C), 135.2 (CH), 130.6 (C), 121.5 (CH$_2$), 117.0 (CH$_2$), 116.3 (CH$_2$), 91.8 (C), 79.3 (C), 31.4 (CH$_2$), 28.7 (CH$_2$) (two coincident signals), 22.6 (CH$_2$), 19.4 (CH$_2$), 14.1 (CH$_3$) ppm; IR (thin film): $\nu_{\max}$ = 2928, 2857, 1996 cm$^{-1}$; MS (70 eV, EI): m/z (%): 188 (45) [M]$^+$, 173 (22), 159 (41), 145 (56), 131 (82), 117 (100); HRMS: calc for C$_{14}$H$_{20}$ [M]$^+$: 188.1565; found 188.1567.

(E)-3,4-Dimethyldec-a,1,3-dien-5-yne 157

The general method reported by Naf et al.$^{50}$ for the conversion alkynes to (Z)-alkenes was adopted. A solution of 3,4-dimethylenedodec-1-en-5-yne 155 (50 mg, 0.27 mmol,
1.0 mol equiv), Zn powder (5 g), KCN (0.2 g), H2O (6 mL), and n-PrOH (6 mL) was stirred at room temperature under an argon atmosphere in the dark for 1.5 h. The reaction mixture was poured onto a biphasic mixture of 30-40 °C petrol (50 mL) and H2O (50 mL) and the organic phase was collected. The combined organic phases were extracted with 30-40 °C petrol (50 mL) three times. The organic phase was dried over anhydrous MgSO4 and filtered. The solvent was removed under reduced pressure (25 mbar, 0 °C). Purification by flash column chromatography on silica gel eluting with pentane afforded the title compound 157 (11 mg, 0.060 mmol, 23%) as colourless oil. Rf 0.30 (pentane); 1H NMR (300 MHz, CDCl3) δ 7.16 (1H, dd, J = 17.4, 10.5 Hz), 5.21 (1H, d, J = 17.7 Hz), 5.07 (1H, d, J = 10.5 Hz), 2.37 (2H, t, J = 6.9 Hz), 1.92 (3H, s), 1.81 (3H, s), 1.61-1.49 (2H, m), 1.47-1.36 (2H, m), 1.36-1.24 (4H, m), 0.89 (3H, t, J = 6.9 Hz) ppm; 13C NMR (75 MHz, CDCl3) δ 137.9 (CH), 126.7 (C), 113.1 (CH2), 110.1 (C), 95.4 (C), 81.6 (C), 31.4 (CH2), 29.0 (CH2), 28.7 (CH2), 22.7 (CH2), 20.1 (CH3), 19.7 (CH2), 14.2 (CH3), 13.0 (CH3) ppm; IR (thin film): νmax = 2956, 2930, 2858 cm⁻¹; MS (70 eV, EI): m/z (%): 190 (9) [M]+, 175 (3), 161 (5), 147 (13), 133 (51), 119 (36), 105 (65); HRMS: calc for C14H22 [M]+: 190.1722; found 190.1719.


Protection of 155 was carried out according to the general method reported by Osinski52 was adopted. To a stirred solution of Fe2(CO)9 (2.9 g, 8.0 mmol, 1.5 mol equiv) and 1-(4-methoxyphenyl)-4-phenyl-1-aza-1,3-butadiene (0.44 g, 1.9 mmol, 0.35 mol equiv) in 1,2-dimethoxyethane (15 mL), a solution of 3,4-dimethylenedodec-1-en-5-yne 155 (1.0 g, 5.3 mmol, 1.0 mol equiv) in dry THF (11 mL) was added. The reaction mixture was stirred at 60 °C under an argon atmosphere in the dark for 20 h. At this point, the reaction progress was checked by 1H NMR and some unreacted starting material was observed. More Fe2(CO)9 (0.6 g, 1.6 mmol, 0.3 mol equiv) was added and material adhering to the sides of the flask was rinsed into the reaction mixture with 1,2-dimethoxyethane (3 mL). The reaction mixture was stirred at 60 °C under argon for another 20 h. The resulting mixture was filtered through celite and the filtercake was
rinsed with pentane (20 mL). After the solvent was removed under reduced pressure (15 mbar, 0 °C), purification by flash column chromatography on silica gel eluting with pentane afforded internal butadiene complex 158 (0.24 g, 0.72 mmol, 13%) and terminal butadiene complex 159 (0.52 g, 1.6 mmol, 30%) as clear yellow oils.

Tricarbonyl[(3-6-η)-3,4-dimethylenedodec-1-en-5-yne]iron 158 (0.24 g, 0.72 mmol, 13%): Rf 0.46 (pentane); 1H NMR (300 MHz, CDCl3) δ 7.16 (1H, dd, J = 16.8, 10.5 Hz), 5.58 (1H, d, J = 18.3 Hz), 5.24 (1H, dd, J = 10.5, 1.2 Hz), 2.36 (2H, t, J = 6.8 Hz), 2.19 (1H, d, J = 3.0 Hz), 2.00 (1H, d, J = 2.4 Hz), 1.63-1.52 (2H, m), 1.49-1.37 (2H, m), 1.37-1.23 (4H, m), 0.90 (3H, t, J = 6.8 Hz), 0.38 (1H, d, J = 2.1 Hz), 0.01 (1H, d, J = 1.2 Hz) ppm; 13C NMR (75 MHz, CDCl3) δ 210.2 (C), 135.3 (CH), 115.8 (CH2), 110.2 (C), 102.5 (C), 91.3 (C), 85.8 (C), 43.2 (CH2), 35.2 (CH2), 31.4 (CH2), 28.6 (CH2) (two coincident signals), 22.6 (CH2), 19.4 (CH2), 14.1 (CH3) ppm; IR (thin film): νmax = 2932, 2859, 2052, 1979 (br) cm⁻¹; MS (70 eV, El): m/z (%): 328 (9) [M]+, 300 (5), 272 (23), 244 (100); HRMS: calc for C17H20FeO3 [M]+: 328.0762; found 328.0762.

Tricarbonyl[(1-4-η)-3,4-dimethylenedodec-1-en-5-yne]iron 159 (0.52 g, 1.6 mmol, 30%): Rf 0.40 (pentane); 1H NMR (300 MHz, CDCl3) δ 5.83 (1H, t, J = 8.0 Hz), 5.73 (1H, d, J = 1.2 Hz), 5.42 (1H, s), 2.38 (2H, t, J = 7.1 Hz), 2.22 (1H, dd, J = 3.0, 1.8 Hz), 1.83 (1H, dd, J = 6.9, 2.4 Hz), 1.63-1.52 (2H, m), 1.48-1.36 (2H, m), 1.36-1.24 (4H, m), 0.89 (3H, t, J = 7.1 Hz), 0.29 (1H, dd, J = 9.3, 2.1 Hz), 0.11 (1H, d, J = 3.6 Hz) ppm; 13C NMR (75 MHz, CDCl3) δ 211.0 (C), 131.2 (C), 119.7 (CH), 101.2 (C), 92.7 (C), 84.9 (C), 39.8 (CH2), 38.3 (CH2) (two coincident signals), 31.4 (CH2), 28.7 (CH2) (two coincident signals), 22.6 (CH2), 19.3 (CH2), 14.1 (CH3)
A solution of \((E)-3,4\text{-dimethylenedodeca-1,5-diene}\ 139\) (0.10 g, 0.54 mmol, 1.0 mol equiv) and \(N\)-methylmaleimide \(49\) (0.18 g, 1.6 mmol, 3.0 mol equiv) in deuterochloroform (2.3 mL) was stirred at room temperature under an argon atmosphere for 24 h. The solvent was removed in \textit{vacuo}. Purification by flash column chromatography on silica gel (gradient elution 15\% EtOAc in hexane to 100\% EtOAc) afforded compounds 163 (28 mg, 0.093 mmol, 17\%) and 166 (39 mg, 0.095 mmol, 18\%) as colourless oils, and a mixture of compounds 167, 170, and 171 (88 mg). Purification of the mixture by flash column chromatography on silica gel (elution with CH\(_2\)Cl\(_2\):EtOAc (50:50)) afforded compounds 167 (6 mg, 0.015 mmol, 3\%), 170 (12 mg, 0.023 mmol, 4\%), and 171 (13 mg, 0.025 mmol, 5\%) as pale yellow oils.
(E)-3,4-Dimethylenedodeca-1,5-diene 139 internal mono-adduct 163: R_f 0.10 EtOAc:hexane (30:70); 1H NMR (300 MHz, CDCl_3) δ 6.89 (1H, dd, J = 17.1, 11.1 Hz), 6.53 (1H, d, J = 15.3 Hz), 5.84 (1H, dt, J = 15.6, 6.9 Hz), 5.21 (1H, d, J = 17.4 Hz), 5.09 (1H, d, J = 11.1 Hz), 3.14-3.09 (2H, m), 2.96 (1H, t, J = 2.7 Hz), 2.90 (3H, s), 2.39-2.26 (2H, m), 2.13 (2H, q, J = 7.3 Hz), 1.42-1.33 (2H, m), 1.33-1.22 (7H, m), 0.87 (3H, t, J = 6.6 Hz) ppm; 13C NMR (75 MHz, CDCl_3) δ 179.9 (C), 179.6 (C), 132.9 (C), 132.6 (CH), 132.0 (CH), 130.1 ((C), 125.4 (CH), 113.5 (CH_2), 39.5 (CH_2) (two coincident signals), 33.5 (CH_2), 31.8 (CH_2), 29.4 (CH_2), 29.0 (CH_2), 25.3 (CH_2), 25.0 (CH_2), 24.1 (CH_2), 22.7 (CH_3), 14.2 (CH_3) ppm; IR (thin film): ν_max = 2954, 2925, 2853, 1701 (br), 1433 cm⁻¹; MS (70 eV, EI): m/z (%): 301 (73) [M]^+ 286 (1), 272 (3), 258 (5), 244 (8), 230 (72), 216 (100); HRMS: calc for C_{19}H_{27}NO_2 [M]^+: 301.2042; found 301.2027.

(E)-3,4-Dimethylenedodeca-1,5-diene 139 bis-adduct 166 crystallized from CH_2Cl_2/hexane at room temperature as colourless needles, mp. 154-155 °C. R_f 0.05 EtOAc:hexane (30:70); 1H NMR (300 MHz, CDCl_3) δ 6.57 (1H, dd, J = 16.8, 11.1 Hz), 5.29 (1H, d, J = 17.7 Hz), 5.08 (1H, d, J = 11.1 Hz), 3.35 (1H, dd, J = 8.7, 5.1 Hz), 3.28 (1H, dd, J = 9.6, 4.8 Hz), 3.19-3.10 (3H, m), 3.06-3.10 (1H, m), 2.86 (3H, s), 2.83 (3H, s), 2.21-2.10 (1H, m), 2.05-1.86 (4H, m), 1.82-1.68 (1H, m), 1.50-1.20 (8H, m), 0.89 (3H, t, J = 7.1 Hz) ppm; 13C NMR (75 MHz, CDCl_3) δ 179.6 (C), 179.0 (C),
178.4 (C), 177.6 (C), 132.7 (C), 132.1 (C), 131.4 (CH), 114.9 (CH₂), 41.1 (CH),
40.3 (CH), 40.1 (CH), 39.9 (CH), 39.4 (CH), 34.1 (CH), 31.9 (CH₂), 29.5 (CH₂),
28.9 (CH₂), 27.1 (CH₂), 24.9 (CH₃), 24.7 (CH₃), 24.1 (CH₂), 24.0 (CH₂), 22.7 (CH₂),
14.2 (CH₃) ppm; IR (thin film): \(\nu_{\text{max}} = 2928, 2855, 1772, 1697\) (br), 1433 (br) cm\(^{-1}\);
MS (70 eV, EI): \(m/z\) (%): 412 (100) [M]**, 397 (3), 383 (6), 369 (2), 355 (7), 341 (21),
327 (51), 112 (69); HRMS: calc for C\(_{24}\)H\(_{32}\)N\(_2\)O\(_4\) [M]**: 412.2362; found 412.2370.

(\(E\))-3,4-Dimethylenedodeca-1,5-diene 139 bis-adduct 167: \(R_f\) 0.50 CH\(_2\)Cl₂:EtOAc
(50:50); \(^1\)H NMR (800 MHz, CDCl₃) \(\delta\) 6.23 (1H, d, \(J = 15.6\) Hz), 5.75 (1H, dt, \(J = 15.6,
6.9\) Hz), 3.21 (1H, ddd, \(t = 9.5, 5.5, 2.4\) Hz), 3.17 (1H, dd, \(J = 14.9, 1.9\) Hz), 3.13 (1H,
ddd, \(J = 9.5, 6.2, 1.7\) Hz), 3.11-3.06 (2H, m), 3.00 (1H, ddd, \(J = 14.2, 2.5, 2.6\) Hz),
2.92 (3H, s), 2.85 (3H, s), 2.76 (1H, td, \(J = 14.0, 5.6\) Hz), 2.37 (1H, ddd, \(J = 14.2, 4.8,
2.6\) Hz), 2.20-2.12 (2H, m), 2.08 (2H, q, \(J = 14.8, 7.4\) Hz), 1.98-1.94 (1H, m), 1.36 (2H,
m), 1.29 (2H, m), 1.28-1.23 (4H, m), 0.88 (3H, t, \(J = 7.1\) Hz) ppm; \(^{13}\)C NMR (125 MHz,
CDCl₃) \(\delta\) 180.9 (C), 179.7 (C), 179.0 (C), 178.0 (C), 132.3 (CH), 131.8 (C), 128.9 (C),
124.9 (CH), 43.5 (CH), 39.9 (CH), 39.5 (CH), 39.0 (CH), 34.4 (CH), 33.3 (CH₂),
31.8 (CH₂), 29.3 (CH₂), 29.0 (CH₃), 25.2 (CH₃), 25.1 (CH₂), 25.0 (CH₂), 23.9 (CH₂),
23.5 (CH₂), 22.7 (CH₂), 14.2 (CH₃) ppm; MS (70 eV, EI): \(m/z\) (%): 412 (100) [M]**,
397 (3), 383 (2), 369 (2), 355 (7), 341 (38), 314 (77), 301 (36), 112 (66); HRMS: calc
for C\(_{24}\)H\(_{32}\)N\(_2\)O\(_4\) [M]**: 412.2362; found 412.2358.
(E)-3,4-Dimethylenedodeca-1,5-diene 139 tris-adduct 170: Rf 0.50 CH$_2$Cl$_2$:EtOAc (50:50); $^1$H NMR (800 MHz, CDCl$_3$) $\delta$ 3.35 (1H, dd, $J = 8.3$, 5.8 Hz), 3.31 (1H, dd, $J = 9.4$, 4.9 Hz), 3.17 (1H, dd, $J = 8.7$, 6.1 Hz), 3.05-3.03 (1H, m), 2.99 (3H, s), 3.00-2.96 (2H, m), 2.85 (3H, s), 2.83 (3H, s), 2.81-2.76 (1H, m), 2.70-2.63 (2H, m), 2.60-2.34 (1H, dt, $J = 13.6$, 4.9 Hz), 2.24 (1H, q, $J = 13.2$ Hz), 2.20-2.14 (2H, m), 2.00-1.96 (1H, m), 1.90-1.83 (2H, m), 1.78 (2H, t, $J = 10.5$ Hz), 1.48-1.40 (3H, m), 1.38-1.32 (4H, m), 0.90 (3H, t, $J = 6.7$ Hz) ppm; $^{13}$C NMR (200 MHz, CDCl$_3$) $\delta$ 179.5 (C), 178.7 (C) (two coincident signals), 178.2 (C), 176.8 (C), 176.7 (C), 132.0 (C), 130.0 (C), 43.3 (CH), 40.6 (CH), 40.5 (CH) (two coincident signals), 40.0 (CH), 39.6 (CH), 39.5 (CH), 36.7 (CH), 34.4 (CH), 31.9 (CH$_2$), 29.5 (CH$_2$), 28.7 (CH$_2$), 27.1 (CH$_2$), 24.9 (CH$_3$), 24.9 (CH$_3$), 24.8 (CH$_3$), 24.7 (CH$_3$), 24.4 (CH$_2$), 23.8 (CH$_2$), 22.7 (CH$_2$), 14.2 (CH$_3$) ppm; IR (thin film): $\nu_{\text{max}} = 2926$, 1773, 1701, 1432 cm$^{-1}$; MS (70 eV, EI): $m/z$ (%): 523 (100) [M$^+$], 508 (1), 466 (1), 452 (6), 438 (22), 412 (85), 112 (60); HRMS: calc for C$_{29}$H$_{37}$N$_3$O$_6$ [M$^+$]: 523.2682; found 523.2682.

(E)-3,4-Dimethylenedodeca-1,5-diene 139 tris-adduct 171: Rf 0.20 CH$_2$Cl$_2$:EtOAc (50:50); $^1$H NMR (800 MHz, CDCl$_3$) $\delta$ 3.31 (1H, dd, $J = 8.7$, 6.0 Hz), 3.22 (1H, dd, $J = 9.2$, 4.4 Hz), 3.18-3.16 (1H, m), 3.11-3.07 (2H, m), 2.97 (1H, dd, $J = 8.7$, 6.1 Hz), 2.91-2.88 (1H, m), 2.90 (3H, s), 2.89 (3H, s), 2.85 (3H, s), 2.72-2.68 (1H, m), 2.63 (1H, td, $J = 14.0$, 5.8 Hz), 2.34 (1H, ddd, $J = 14.4$, 9.4, 2.5 Hz), 2.13-2.06 (2H, m),
1.97-1.90 (3H, m), 1.86-1.82 (1H, m), 1.73-1.68 (1H, m), 1.43-1.38 (3H, m), 1.36-1.30 (4H, m), 0.89 (3H, t, $J = 6.9$ Hz) ppm; $^{13}$C NMR (200 MHz, CDCl$_3$) δ 179.7 (C), 178.7 (C), 178.5 (C), 178.2 (C), 177.1 (C), 176.7 (C), 131.0 (C), 130.7 (C), 43.5 (CH), 40.3 (CH) (two coincident signals), 40.2 (CH), 39.6 (CH), 39.2 (CH), 38.8 (CH), 33.8 (CH), 33.6 (CH), 31.9 (CH$_2$), 29.5 (CH$_2$), 28.9 (CH$_2$), 27.1 (CH$_2$), 25.0 (CH$_3$), 24.9 (CH$_3$), 24.7 (CH$_2$), 24.7 (CH$_3$), 24.3 (CH$_2$), 23.1 (CH$_2$), 22.7 (CH$_2$), 14.2 (CH$_2$) ppm; IR (thin film): $v_{max} =$ 2928, 1696, 1434 cm$^{-1}$; MS (70 eV, EI): $m/z$ (%): 523 (100) [M]$^+$, 480 (1), 452 (3), 438 (28), 412 (32), 112 (38); HRMS: calc for C$_{29}$H$_{37}$N$_3$O$_6$ [M]$^+$: 523.2682; found 523.2682.

**Reaction of 3,4-dimethylenedodec-1-en-5-yne 155 with NMM 49**

A solution of 155 (0.21 g, 1.1 mmol, 1.0 mol equiv) and N-methylmaleimide 49 (0.12 g, 1.1 mmol, 1.0 mol equiv) in deuterochloroform (6 mL) was stirred at room temperature under an argon atmosphere for 4.5 h. The solvent was removed in vacuo. Purification by flash column chromatography on silica gel (gradient elution 85:15 (hexane:EtOAc) to 100% EtOAc) afforded a internal mono-adduct 173 (0.12 g, 0.40 mmol, 37%), two bis-adducts 174 (80 mg, 0.20 mmol, 18%), and 175 (8 mg, 0.02 mmol, 2%) as clear colourless oils.
3,4-dimethylenedodec-1-en-5-yne 155 internal mono-adduct 173: \( R_f 0.20 \) EtOAc:hexane (70:30); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 6.93 (1H, dd, \( J = 17.7, 10.5 \) Hz), 5.36 (1H, d, \( J = 17.7 \) Hz), 5.14 (1H, d, \( J = 10.8 \) Hz), 3.16-3.04 (2H, m), 2.94 (3H, s), 2.89 (1H, dd, \( J = 15.3, 3.3 \) Hz), 2.71 (1H, dd, \( J = 15.6, 3.3 \) Hz), 2.51 (1H, dd, \( J = 15.9, 6.3 \) Hz), 2.35 (2H, t, \( J = 6.9 \) Hz), 2.36-2.27 (1H, m), 1.58-1.48 (2H, m), 1.44-1.35 (2H, m), 1.35-1.22 (4H, m), 0.89 (3H, t, \( J = 6.9 \) Hz) ppm; \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 179.3 (C) (two coincident signals), 139.5 (C), 134.6 (CH), 119.2 (C), 114.4 (CH\(_2\)), 97.9 (C), 79.0 (C), 39.3 (CH), 39.2 (CH), 31.4 (CH\(_2\)), 30.3 (CH\(_3\)), 28.7 (CH\(_2\)), 28.6 (CH\(_2\)), 25.2 (CH\(_2\)), 23.0 (CH\(_2\)), 22.6 (CH\(_2\)), 19.8 (CH\(_2\)), 14.1 (CH\(_3\)) ppm; IR (thin film): \( v_{\text{max}} = 2959, 2931, 2857, 1701 \) (br), 1433 cm\(^{-1}\); MS (70 eV, EI): \( m/z \) (%) 299 (22) [M\(^+\)], 284 (4), 270 (26), 256 (54), 242 (100); HRMS: calc for C\(_{19}\)H\(_{25}\)NO\(_2\) [M\(^+\)]: 299.1885; found 299.1882.

3,4-dimethylenedodec-1-en-5-yne 155 bis-adduct 174: \( R_f 0.20 \) EtOAc:hexane (70:30); \(^1\)H NMR (800 MHz, CDCl\(_3\)) \( \delta \) 3.24 (1H, dd, \( J = 15.2, 1.8 \) Hz), 3.19 (1H, ddd, \( J = 8.6, 5.6, 2.5 \) Hz), 3.09 (1H, ddd, \( J = 9.0, 6.9, 1.7 \) Hz), 3.03 (1H, t, \( J = 7.8 \) Hz), 2.99 (1H, dd, \( J = 8.8, 5.8 \) Hz), 2.90 (3H, s), 2.87 (3H, s), 2.72 (1H, d, \( J = 15.1 \) Hz), 2.68 (1H, td, \( J = 13.9, 5.7 \) Hz), 2.33 (1H, ddd, \( J = 14.2, 4.7, 2.7 \) Hz), 2.26 (2H, t, \( J = 7.1 \) Hz), 2.20-2.16 (1H, m), 2.08-2.03 (1H, m), 1.48 (2H, m), 1.35 (2H, m), 1.31-1.20 (5H, m), 0.85 (3H, t, \( J = 7.1 \) Hz) ppm; \(^{13}\)C NMR (200 MHz, CDCl\(_3\)) \( \delta \) 179.9 (C), 179.2 (C), 178.6 (C), 177.4 (C), 139.3 (C), 117.3 (C), 95.3 (C), 77.9 (C), 43.0 (CH), 39.6 (CH),
3.4-dimethylenedodec-1-en-5-yne 155 bis-adduct 175: Rf 0.38 EtOAc:hexane (85:15); 
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 3.31 (1H, dd, $J = 14.7, 6.9$ Hz), 3.20-3.06 (1H, m), 3.00 (3H, s), 2.90 (3H, s), 3.02-2.85 (4H, m), 2.44-2.26 (4H, m), 2.07-1.94 (1H, m), 1.57-1.46 (2H, m), 1.43-1.23 (8H, m), 0.89 (3H, t, $J = 6.9$ Hz) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 179.0 (C), 178.9 (C), 178.8 (C), 177.3 (C), 140.8 (C), 116.4 (C), 95.5 (C), 78.0 (C), 77.3 (CH$_2$), 43.2 (CH), 40.1 (CH), 40.0 (CH), 38.7 (CH), 36.7 (CH), 31.4 (CH$_2$), 30.3 (CH$_2$), 28.7 (CH$_2$), 26.6 (CH$_2$), 25.1 (CH$_2$), 25.1 (CH$_3$), 25.0 (CH$_3$), 22.6 (CH$_2$), 19.7 (CH$_2$), 14.1 (CH$_3$) ppm; IR (thin film): $\nu_{max} = 2929, 2858, 1701, 1686, 1437$ cm$^{-1}$; MS (70 eV, El): $m/z$ (%): 410 (100) [M$^+$], 395 (2), 381 (8), 112 (45); HRMS: calc for C$_{24}$H$_{30}$N$_2$O$_4$ [M$^+$]: 410.2206; found 410.2205.

![175](image)

3.3 Chapter 2 Experimental

2-Methylbut-1-en-3-yne 240

The title compound 240 was prepared according to a procedure of Bradsma.$^{101}$ To a 
stirred solution of acetic anhydride (345 mL, 3.64 mol, 1.3 mol equiv) and 
p-toluenesulfonic acid monohydrate (20 g, 0.11 mol, 0.04 mol equiv) at $-20$ °C in a
three-necked flask fitted a distillation apparatus, 2-methyl-3-butyn-2-ol 239 (0.27 L, 2.8 mol, 1.0 mol equiv) was added over 40 min. After addition was complete, the reaction mixture was slowly heated and the distillate was collected over the course of one hour. The distillate was washed with cold 3 M KOH (2 x 25 mL). Redistillation over anhydrous MgSO₄ gave the title compound 240 (lit.¹¹⁵ bp. 35 °C/760 mm Hg) as a colourless oil (117 g, 1.77 mol, 63%). ¹H NMR data for this compound was consistent with that reported in the literature.¹¹⁵

2-Chloro-3-methylbuta-1,3-diene 241

![Structure of 2-Chloro-3-methylbuta-1,3-diene](image)

The title compound 241 was prepared by modifying the literature procedure.¹¹⁶ A mixture of 2-methylbut-1-en-3-yne 240 (123 g, 1.86 mol, 1.00 mol equiv), CuCl (37 g, 0.37 mol, 0.20 mol equiv), and NH₄Cl (20 g, 0.37 mol, 0.20 mol equiv) was stirred at 0 °C for 15 min. To this mixture, 12 M aq. HCl (150 mL, 1.86 mol, 1.00 mol equiv) was added dropwise. The mixture was then allowed to warm to 20 °C and stirred for 75 min. The organic layer was separated. Purification by fractional distillation afforded the title compound 241 (48.9 g, 0.477 mol, 26%) and unreacted starting material 240 (39 g, 0.60 mol, 32%): bp. 50–52 °C/175 mm Hg, lit.¹¹⁷ bp. 90–92 °C/760 mm Hg. ¹H NMR data for this compound was consistent with that reported in the literature.¹¹⁶

(3-Methylbuta-1,3-dien-2-yl)magnesium chloride 242

![Structure of (3-Methylbuta-1,3-dien-2-yl)magnesium chloride](image)

This known compound has previously been made through a different procedure.¹¹⁸ To a slurry of oven-dried magnesium powder (1.4 g, 57 mmol, 2.9 mol equiv) in dry THF (10 mL), 1,2-dibromoethane (0.50 mL, 5.8 mmol, 0.30 mol equiv) was added slowly (exotherm). After the reaction had subsided, ZnBr₂ (0.13 g, 0.59 mmol, 0.030 mol equiv) was added. Material adhering to the sides of the flask was rinsed into the reaction mixture with dry THF (2 mL). The reaction mixture was heated to reflux and at this point, a solution of 2-chloro-3-methylbuta-1,3-diene 241 (2.0 g, 0.020 mol,
1.0 mol equiv) and 1,2-dibromoethane (0.68 mL, 7.9 mmol, 0.40 mol equiv) in THF (8 mL) was added dropwise to maintain a generous reflux. After the addition was complete, the reaction mixture was stirred at reflux for 75 min. Titration of resulting Grignard reagent 242 with salicylaldehyde phenylhydrazone\textsuperscript{106} indicated a 0.74 M solution of the title compound 141 in THF (55\% yield).

Attempts to synthesis the dimethyl substituted [5]dendralene 190

\[
\begin{align*}
\text{MgCl}_2 + \text{Cl}_2 & \rightarrow \text{MgCl}_2 + \text{Cl}_2 \\
242 & \rightarrow 190 + 248 + 249
\end{align*}
\]

To a stirred solution of PPh\textsubscript{3} (70 mg, 0.26 mmol, 0.050 mol equiv), Ni(dppp)Cl\textsubscript{2} (70 mg, 0.13 mmol, 0.025 mol equiv), and (3-methylbuta-1,3-dien-2-yl)magnesium chloride 242 (0.51 M, 31 mL, 16 mmol, 3.0 mol equiv) in dry THF at 15 °C, 1,1-dichloroethylene 32 (0.42 mL, 5.2 mmol, 1.0 mol equiv) was added dropwise. After the addition was complete, the reaction mixture was warmed to room temperature and stirred for 4 days. At this point, a small amount of the reaction mixture was quenched with water, diluted CDCl\textsubscript{3}. The formation of isoprene upon hydrolysis of the Grignard reagent 242 and presence of a little amounts of 1,1-dichloroethylene 32 were indicated by \textsuperscript{1}H NMR spectroscopy. More Ni(dppp)Cl\textsubscript{2} (70 mg, 0.13 mmol, 0.025 mol equiv) and 1,1-dichloroethylene 32 (0.42 mL, 5.2 mmol, 1.0 mol equiv) were therefore added and the reaction mixture was heated to 30 °C and stirred for further 3.5 h. The reaction mixture was poured onto a stirred biphasic mixture of 30-40 °C petrol (150 mL) and H\textsubscript{2}O (300 mL) and stirred for 15 min. The resulting mixture was washed with aq. 1 M HCl (100 mL) and organic layer was collected. The combined organic layers were washed successively with sat. aq. NaHCO\textsubscript{3} (120 mL) and sat. aq. NaCl (120 mL). The solvent was removed under reduced pressure (20 mbar, 15 °C). Purification by flash column chromatography on silica gel elution with 30-40 °C petrol gave a mixture of 190 and 248 (170 mg) and a mixture of 190 and 249 (100 mg). A mixture of 248 and 190 could be separated via reverse-phase preparative HPLC (70% MeCN in H\textsubscript{2}O) and the compound 248 (13 mg, 0.080 mmol, 2 \%) was isolated as a colourless oil.
3,7-Dimethyl-5,6-dimethyleneocta-1,2,7-triene 248: $R_f = 0.60$ (30-40 °C petrol). 
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.19 (1H, s), 5.05 (1H, s), 5.01 (1H, s), 4.97 (1H, s), 4.90 (1H, s), 4.89-4.85 (3H, m), 3.19 (2H, s), 1.92 (3H, s), 1.87 (3H, s) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 210.6 (C), 145.1 (C), 142.8 (C), 139.4 (C), 113.8 (CH$_2$), 112.7 (CH$_2$), 110.8 (CH$_2$), 105.5 (C), 77.6 (CH$_2$), 34.5 (CH$_2$), 22.1 (CH$_3$), 21.3 (CH$_3$) ppm; IR (thin film): $\nu_{max} = 3092, 2924, 2853, 1599 \text{ cm}^{-1}$; MS (70 eV, EI): $m/z$ (%): 160 (3) [M$^-$], 145 (100); HRMS: calcd for C$_{11}$H$_{13}$[M$^-$]: 145.1017; found 145.1017.

2,6-Dimethyl-3,4,5-trimethylenehepta-1,6-diene 190: $R_f = 0.60$ (30-40 °C petrol). 
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 5.21 (2H, s), 5.15 (2H, d, $J = 1.8$ Hz), 5.04 (4H, s), 5.01 (2H, d, $J = 1.2$ Hz), 1.93 (6H, s) ppm; ; IR (thin film): $\nu_{max} = 3093, 2971, 1585, 1441 \text{ cm}^{-1}$; MS (70 eV, EI): $m/z$ (%): 161 (40) [M$^-$], 145 (100); HRMS: calcd for C$_{11}$H$_{13}$[M$^-$]: 160.1252; found 160.1258.

**Tetracycle 183**

The compound 183 was prepared following Kirwan’s procedure.$^{61}$ A 0.2 M solution of [5]dendralene 176 (126 mg, 0.953 mmol, 2.00 mol equiv) in mesitylene (5 mL) was stirred at reflux for 17 h. The solvent was removed under by vacuum distillation (45 °C, 0.60 mbar) to leave the crude product mixture as an oil (180 mg). Purification by flash column chromatography on silica gel elution with pentane gave the compound 183 (9 mg, 0.03 mmol, 7%) as a colourless oil. $^1$H NMR data for this compound was consistent with that reported in the literature.$^{20}$
Cross-metathesis of tetracycle 183

A flame-dried vial was charged with Grubbs’ second-generation catalyst (14 mg, 0.010 mmol, 0.10 mol equiv) under an argon atmosphere. The vessel was then evacuated under vacuum and flushed with argon three times before a solution of tetracycle 183 (42 mg, 0.16 mmol, 1.0 mol equiv) and (Z)-but-2-ene-1,4-diyli diacetate (55 mg, 0.32 mmol, 2.0 mol equiv) in CH$_2$Cl$_2$ (10 mL) was added. The mixture was subjected to a threefold freeze-pump-thaw degassing process and placed under an argon atmosphere. The mixture was stirred at reflux for 3.5 h. At this point, the reaction progress was checked by TLC analysis (10% EtOAc/hexane) and mostly unreacted starting material and E-but-2-ene-1,4-diyli diacetate were observed. Therefore, more catalyst (14 mg, 0.010 mmol, 10 mol%) and (Z)-but-2-ene-1,4-diyli diacetate (55 mg, 0.32 mmol, 2 mol equiv) were added and the flask was again subjected to a threefold freeze-pump-thaw degassing process. The reaction mixture was stirred at reflux for another 20.5 h. The reaction mixture was filtered through a plug of silica, rinsed with CH$_2$Cl$_2$ and concentrated under vacuo. Purification by flash column chromatography on silica gel (gradient elution 100% hexane to 5% EtOAc in hexane) afforded unreacted starting material 183 (26 mg, 0.10 mmol, 62%) and the compound 235 (7 mg, 0.02 mmol, 13%) as a colourless oil: R$_f$ 0.34 (10% EtOAc/hexane). $^1$H NMR (800 MHz, C$_6$D$_6$) δ 5.93 (1H, dd, J = 17.6, 11.2 Hz), 5.73 (1H, d, J = 15.2 Hz), 5.55 (1H, dt, J = 15.2, 6.4 Hz), 5.39 (1H, d, J = 5.6 Hz), 5.33 (1H, d, J = 4.0 Hz), 5.27 (1H, dd, J = 17.6, 1.6 Hz), 5.08 (1H, dd, J = 11.2, 1.6 Hz), 5.02-4.97 (1H, m), 4.96 (1H, s), 4.89 (1H, s), 4.54-4.53 (2H, m), 2.39-2.32 (1H, m), 2.28-2.23 (1H, m), 2.17-2.11 (2H, m), 2.06-1.97 (3H, m), 1.87 (1H, dd, J = 11.2, 2.4 Hz), 1.81-1.76 (1H, m), 1.76-1.66 (1H, m), 1.69 (3H, s), 1.58-1.56 (1H, m), 1.51 (1H, td, J = 12.8, 5.6 Hz), 1.45 (1H, dd, J = 13.6, 5.6 Hz) ppm; $^{13}$C NMR (200 MHz, C$_6$D$_6$) δ 169.9 (C), 164.4 (C), 145.0 (C), 141.6 (CH), 139.9 (C), 139.5 (CH), 122.6 (CH), 121.0 (CH), 119.9 (CH), 113.8 (CH$_2$), 105.5 (CH$_2$), 65.3 (CH$_2$), 52.1 (C), 51.4 (CH$_2$), 50.2 (C), 39.2 (CH$_2$), 33.5 (CH$_2$), 32.1 (CH$_2$), 31.2 (CH$_2$), 28.3 (C), 27.9 (CH$_2$), 22.9 (CH$_2$), 20.5 (CH$_3$) ppm;
IR (thin film): $v_{\text{max}} = 2929, 2853, 1742 \text{ cm}^{-1}$; MS (70 eV, EI): $m/z$ (%): 336 (75) [$M^+\$], 321 (3), 276 (45), 43 (100); HRMS: calcd for C$_{23}$H$_{28}$O$_2$ [$M^+\$]: 336.2089; found 336.2086.

**Epoxidation of tetracycle 183**

**By reaction of tetracycle 183 with m-CPBA 206**: To a stirred solution of tetracycle 183 (19 mg, 0.072 mmol, 1.0 mol equiv) in CH$_2$Cl$_2$ (0.5 mL) at $-15 \degree C$, a solution of m-CPBA 206 (25 mg, 0.14 mmol, 2.0 mol equiv) in CH$_2$Cl$_2$ (0.45 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 6 h under a nitrogen atmosphere. At this point, the reaction mixture was diluted with CH$_2$Cl$_2$ (3 mL) and then washed with sat. aq. NaHCO$_3$ (3 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 3 mL). The organic layers were combined, washed with sat. aq. NaCl (3 mL) and dried over MgSO$_4$ and filtered. The filtrate was concentrated in vacuo. Purification by flash column chromatography on silica gel (gradient elution 100% to 10% EtOAc in 30-40 °C petrol) afforded the compound 213 (6 mg, 0.02 mmol, 29%) as a colourless oil.

**By reaction of tetracycle 183 with dimethyldioxirane (DMDO) 210**: A solution of dimethyldioxirane 210 (0.040 M in acetone, 3.3 mL, 0.13 mmol, 2.0 mol equiv) was added dropwise to tetracycle 183 (17 mg, 0.066 mmol, 1.0 mol equiv) with stirring. The resulting mixture was stirred at room temperature for 2 h under nitrogen. At this point, the reaction mixture was diluted with CH$_2$Cl$_2$ (5 mL) and washed then with sat. aq. NaHCO$_3$ (5 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 5 mL). The organic layers were combined, washed again sat. aq. NaCl (5 mL), dried over MgSO$_4$ and filtered. The filtrate was concentrated in vacuo. Purification by flash column chromatography on silica gel (gradient elution 100% 30-40 °C petrol to 10% EtOAc in 30-40 °C petrol) afforded the compound 213 (7.2 mg, 0.024 mmol, 37%) as colourless oil.
Rf 0.32 (10% EtOAc/30–40 °C petrol). ¹H NMR (800 MHz, CDCl₃) δ 5.93 (1H, dd, \( J = 17.8, 11.5 \) Hz), 5.85 (1H, dd, \( J = 17.4, 10.8 \) Hz), 5.24 (1H, d, \( J = 11.2 \) Hz), 5.23 (1H, dd, \( J = 9.4, 1.2 \) Hz), 5.10 (1H, dd, \( J = 10.5, 1.4 \) Hz), 5.09 (1H, dd, \( J = 3.8, 1.4 \) Hz), 4.90 (1H, s), 4.84 (1H, s), 3.20 (1H, d, \( J = 3.8 \) Hz), 2.82 (1H, s), 2.41 (1H, ddd, \( J = 13.4, 13.3, 4.5 \) Hz), 2.17 (2H, app. ddd, \( J = 12.7, 12.7, 5.3 \) Hz), 2.11 (1H, dd, \( J = 11.9, 2.0 \) Hz), 2.02 (1H, d, \( J = 11.8 \) Hz), 1.97 (1H, app. ddd, \( J = 14.0, 5.2, 1.4 \) Hz) 1.90–1.85 (2H, m), 1.82 (1H, ddd, \( J = 15.0, 2.1, 2.1 \) Hz), 1.63–1.58 (1H, dd, \( J = 14.0, 4.8 \) Hz), 1.58–1.54 (1H, m), 1.19 (1H, dd, \( J = 14.4, 5.1 \) Hz), 1.02 (1H, dd, \( J = 14.1, 5.1 \) Hz), 0.84 (1H, ddd, \( J = 12.9, 3.0, 3.0 \) Hz ppm; ¹³C NMR (200 MHz, CDCl₃) δ 162.9 (C), 143.9 (CH), 139.7 (CH), 115.1 (CH₂), 112.8 (CH₂), 105.9 (CH₂), 64.9 (C), 63.0 (CH), 61.8 (CH), 58.2 (C), 51.6 (C), 49.8 (C), 46.6 (C), 41.2 (CH₂), 35.4 (CH₂), 31.6 (CH₂), 30.4 (CH₂), 28.0 (CH₂), 23.3 (CH₂), 21.7 (CH₂) ppm; IR (thin film): \( \nu_{\text{max}} = 2961, 2937, 1637, 1446 \) cm⁻¹; MS (70 eV, EI): \( m/z (\%) \): 296 (29) [M⁺], 268 (69), 255 (18), 227 (34), 211 (31), 197 (29), 183 (38), 169 (37), 91 (100); HRMS: calcd for C₂₀H₂₄O₂ [M⁺]: 296.1776; found 296.1773.

**Dihydroxylation of tetracycle 183**

To a stirred solution of tetracycle 183 (44 mg, 0.016 mmol, 1 mol equiv) and H₂O (0.3 mL) in THF (1.6 mL) was added OsO₄ 194 (4.1% in H₂O, 41 µL, 7.0 µmol, 0.040 mol equiv) and followed by 4-methyl morpholine-N-oxide (NMO) (39 mg, 0.33 mmol, 2.0 mol equiv). The reaction mixture was stirred at room temperature for 3 days under a nitrogen atmosphere. The resulting mixture was then cooled in an ice bath and sat. aq. sodium metabisulfite solution (5 mL) was added before it was was allowed to warm to room temperature over 45 min. The aqueous layer was separated and extracted with EtOAc (4 x 7 mL). The organic layers were combined, washed sat. aq. NaCl (10 mL), dried over Na₂SO₄ and filtered. The filtrate was concentrated in vacuo. Purification by flash column chromatography on silica gel (gradient elution 30% EtOAc to 50% EtOAc in 30–40 °C petrol) gave a mixture of the two diastereomeric
products 203 and 204 as a colourless oil (15 mg, 0.050 mmol, 30%) which were then separated using normal phase HPLC (eluting with 3% i-PrOH/hexane) to give 203 (7 mg, 0.02 mmol, 14%) and 204 (3 mg, 0.01 mmol, 6%).

The compound 203 crystallized from hexane/methanol at room temperature as colourless needles, mp. 122-124 °C and Rf 0.45 (50% EtOAc/30-40 °C petrol). $^1$H NMR (800 MHz, CDCl$_3$) δ 5.84 (1H, dd, $J = 17.8, 11.2$ Hz), 5.45 (1H, d, $J = 6.8$ Hz), 5.36 (1H, d, $J = 4.6$ Hz), 5.22 (1H, dd, $J = 17.8, 1.3$ Hz), 5.10 (1H, dd, $J = 11.2, 1.4$ Hz), 2.31-2.26 (1H, m), 2.21-2.16 (3H, m), 2.13-2.06 (5H, m), 2.05-1.99 (1H, m), 1.92-1.88 (1H, m), 1.79 (1H, ddd, $J = 13.3, 12.5, 5.8$ Hz), 1.59 (1H, d, $J = 11.4$ Hz), 1.52 (1H, ddd, $J = 12.1, 11.8, 5.8$ Hz), 1.49 (1H, dd, $J = 13.7, 5.9$ Hz), 1.41-1.37 (1H, m) ppm; $^{13}$C NMR (200 MHz, CDCl$_3$) δ 163.5 (C), 141.3 (C), 139.5 (C), 138.6 (CH), 121.3 (CH), 119.5 (CH), 114.4 (CH$_2$), 103.8 (CH$_2$), 74.2 (CH), 63.4 (CH$_2$), 51.9 (C), 51.7 (C), 49.7 (C), 44.3 (CH$_2$), 37.8 (CH$_2$), 31.7 (CH$_2$), 31.6 (CH$_2$), 30.7 (CH$_2$), 27.4 (CH$_2$), 22.6 (CH$_2$) ppm; IR (thin film): $\nu_{max} = 3427, 2928, 2840$ cm$^{-1}$; MS (70 eV, EI): $m/z$ (%): 298 (65) [M]$^+$, 281 (7), 267 (31), 249 (18), 237 (100); HRMS: calcd for C$_{20}$H$_{26}$O$_2$ [M]$^+$: 298.1933; found 298.1932.

The compound 204 crystallized from CH$_2$Cl$_2$/hexane at room temperature as colourless needles, mp. 130-132 °C and Rf 0.45 (50% EtOAc/30-40 °C petrol). $^1$H NMR (800 MHz, CDCl$_3$) δ 5.83 (1H, dd, $J = 17.7, 11.2$ Hz), 5.45 (1H, d, $J = 6.0$ Hz), 5.35 (1H, d, $J = 4.6$ Hz), 5.19 (1H, dd, $J = 17.7, 1.1$ Hz), 5.08 (1H, dd, $J = 11.2, 1.2$ Hz),
5.0 (1H, s), 4.96 (1H, s), 3.83-3.80 (2H, m), 3.54 (1H, t, J = 9.2 Hz), 2.30-2.22 (2H, m), 2.20 (1H, d, J = 3.7 Hz), 2.18 (1H, dd, J = 12.4, 5.0 Hz), 2.12-2.06 (3H, m), 2.04-1.99 (1H, m), 1.91-1.86 (3H, m), 1.84 (1H, dd, J = 11.4, 2.5 Hz), 1.81 (1H, d, J = 11.4 Hz), 1.68 (1H, dd, J = 13.4, 12.6, 5.8 Hz), 1.50 (1H, d, J = 5.8 Hz), 1.49 (1H, d, J = 5.2 Hz) ppm; $^{13}$C NMR (200 MHz, CDCl$_3$) δ 162.7 (C), 141.3 (C), 139.9 (C), 138.8 (CH$_2$), 121.0 (CH), 119.5 (CH), 114.2 (CH), 104.8 (CH$_2$), 77.3 (CH$_2$), 63.4 (CH), 52.5 (C), 50.5 (C), 49.4 (C), 45.9 (CH$_2$), 38.7 (CH$_2$), 31.9 (CH$_2$), 31.8 (CH$_2$), 30.6 (CH$_2$), 27.5 (CH$_2$), 22.6 (CH$_2$) ppm; IR (thin film): $\nu$$_{\max}$ = 3401, 2925, 2837 cm$^{-1}$; MS (70 eV, EI): m/z (%): 298 (13) [M$^+$], 281 (3), 267 (7), 249 (3), 237 (18), 223 (5), 195 (8), 84 (60), 49 (100); HRMS: calcd for C$_{20}$H$_{26}$O$_2$ [M$^+$]: 298.1933; found 298.1934.

Ozonolysis of tetracycle 183

Through a stirred solution of tetracycle 183 (53 mg, 0.17 mmol, 1 mol equiv) in CH$_2$Cl$_2$ (2 mL) at -78 °C, an excess of ozone was bubbled over 15 min, whereupon the colour of the stirred solution had turned blue. A solution of PPh$_3$ (0.31 g, 1.2 mmol, 6.0 mol equiv) in CH$_2$Cl$_2$ (3 mL) was then added dropwise at -78 °C. The resulting mixture was allowed to warm to 0 °C and stirred for 30 min. The solvent was removed in vacuo. Purification by flash column chromatography on silica gel (gradient elution 40% EtOAc to 60% EtOAc in 30-40 °C petrol) afforded the compound 223 (5 mg, 0.02 mmol, 8%) as a colourless oil: R$_f$ 0.34 (50% EtOAc/30-40 °C petrol); $^1$H NMR (800 MHz, CDCl$_3$) δ 9.69 (1H, s), 9.48 (1H, s), 6.04 (1H, dd, J = 17.6, 11.0 Hz), 5.52 (1H, d, J = 11.0 Hz), 5.33 (1H, d, J = 17.6 Hz), 5.08 (1H, s), 5.00 (1H, s), 3.15 (1H, s), 3.01 (1H, dd, J = 12.7, 2.4 Hz), 2.55-2.47 (1H, m), 2.43-2.30 (4H, m), 2.28-2.20 (2H, m), 2.01-1.95 (1H, m), 1.95-1.88 (1H, m), 1.85 (1H, td, J = 12.7, 6.5 Hz), 1.68 (1H, d, J = 12.6 Hz), 1.58-1.56 (1H, m), 1.38 (1H, dd, J = 15.4, 6.4 Hz) ppm; $^{13}$C NMR (200 MHz, CDCl$_3$) δ 207.5 (C), 201.0 (CH), 200.4 (CH), 152.7 (C), 137.5 (CH), 118.5 (CH$_2$), 114.9 (CH$_2$), 65.0 (C), 64.2 (C), 59.2 (C), 58.3 (CH), 56.0 (C), 39.3 (CH$_2$), 36.5 (CH$_2$), 33.7 (CH$_2$), 31.7 (CH$_2$), 28.7 (CH$_2$), 24.7 (CH$_2$), 22.2 (CH$_2$) ppm; IR (thin film): $\nu$$_{\max}$ = 2928, 1717, 1448 cm$^{-1}$; MS (70 eV, EI): m/z (%):
314 (3) $[M]^+$, 277 (36), 257 (31), 229 (31), 213 (26), 185 (29), 169 (25), 91 (96), 55 (100); HRMS: calcd. for C$_{19}$H$_{22}$O$_4$ $[M]^+$: 314.1518; found: 314.1529.
Appendix

X-Ray crystallography reports for compounds: 166, 203, and 204, are provided on the CD on the inside back cover of the thesis. X-Ray single crystal analyses were performed by Dr Anthony C. Willis, X-Ray Crystallographic Unit, Research School of Chemistry, Australian National University, Canberra on a Nonius Kappa CCD diffractometer.
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