Studies Towards Efficient Synthesis With Dendralenes

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

Master of Philosophy

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Declaration

Except where specific acknowledgements of others are made, the work described in this thesis was carried out by the author during the period of 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.

I would also like to thank all past and present members of Sherburn Group, in particular Dr. Katie Cergol for teaching and encouragement in the laboratory and Dr. Nicholas Kanizaj for his assistance with proofreading. I also thank Dr. Andrew Lawrence, Thomas Fallon and Bill Lording for proofreading. Thanks to all RSC technical staff for their assistance, especially Tony Herlt with HPLC, Chris Blake with NMR and Dr. Tony Willis for single crystal X-ray analyses.

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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	dimethyldioxirane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dppf	[1,1'-(diphenylphosphino)ferrocene]

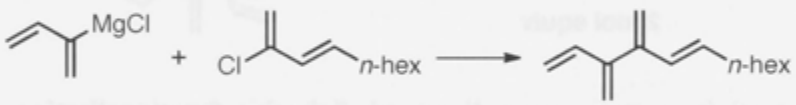
dppp	1,3-bis(diphenylphosphino)propane
d.r.	diastereomeric ratio
EDG	electron donating group
ee	enantiomeric excess
EI	electron impact
Et	ethyl
ESI	electrospray ionization
eV	electron Volts
EWG	electron withdrawing group
FabF	β-ketoacyl-[acyl carrier protein] synthase II
FTIR	fourier transform infrared 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

mm Hg	millimetres of mercury
mol	mole
mol equiv	molar equivalent/s
mp.	melting point
MS	mass spectroscopy
m/z	mass to charge ratio
NBS	*N*-bromosuccinimide
n-Bu	*n*-butyl
n-hex	*n*-hexyl
NMM	*N*-methymaleimide
NMO	4-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
nOe	nuclear overhauser effect
NOESY	nuclear overhauser and exchange spectroscopy
NPM	*N*-phenylmaleimide
p-TsOH	*para*-toluenesulfonic acid
Ph	phenyl
ppm	parts per million
q	quartet
R_f	retention factor
rt	room temperature
sat.	saturated
SM	starting material
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
t	time
t-Bu	*tert*-butyl
Tf	triflouromethanesulfonate
THF	tetrahydrofuran
TLC	thin layer chromatography
TS	transition state
XPhos	2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl
W	watt
30-40 °C petrol	30-40 °C petroleum spirit

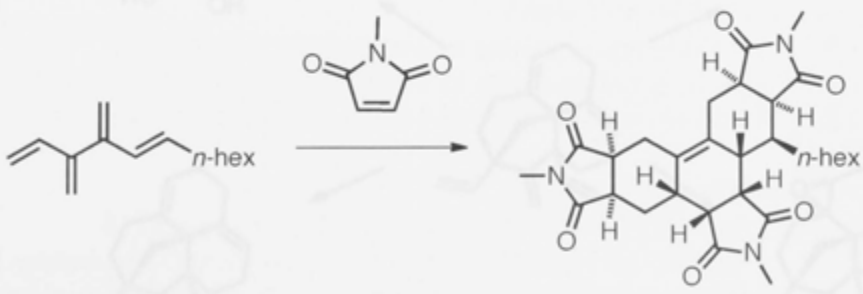
Abstract

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.

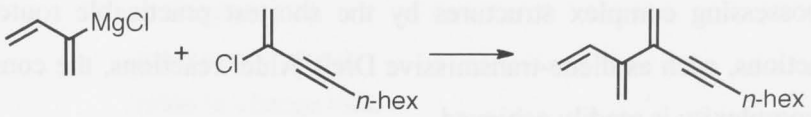


With this substituted [4]dendralene in hand, its reactivity with NMM was investigated. Under kinetically controlled conditions, 1-(*E*)-hexyl [4]dendralene reacted with excess of NMM to afford a *mono*-adduct, two *bis*-adducts, and two *tris*-adducts products. The efficient synthesis of a complex hexacyclic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



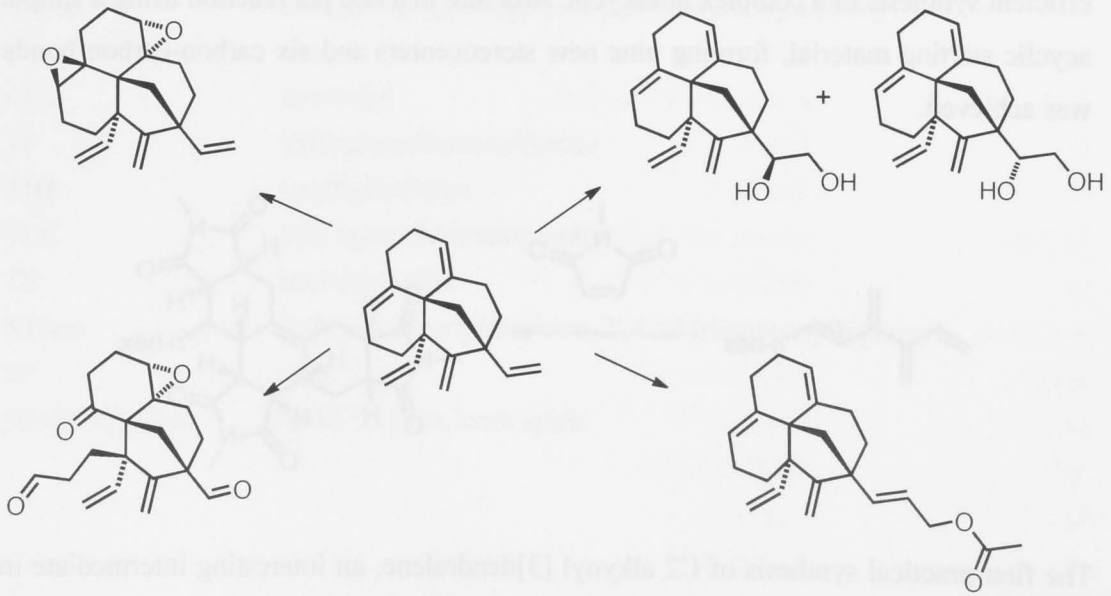
The first practical synthesis of C2 alkynyl [3]dendralene, an interesting intermediate in our studies, is reported. Its chemistry in the Diels-Alder reaction was also investigated.

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. Diastereoselecive 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 OsO_4 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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Chapter 1

The Synthesis and Diels-Alder Chemistry of 1-Hexyl [4]Dendralenes

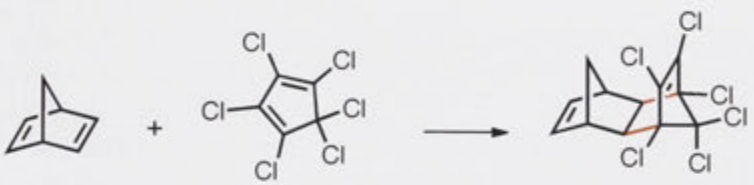
1.1 Introduction

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.[1] 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.web page[2] 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,[3] 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.[4]



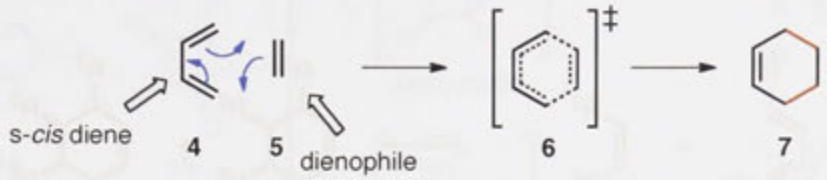
1 **2** **3**

Scheme 1.1: Synthesis of aldrin **3** (newly formed C-C bonds highlighted in red).[5]

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**).[5]

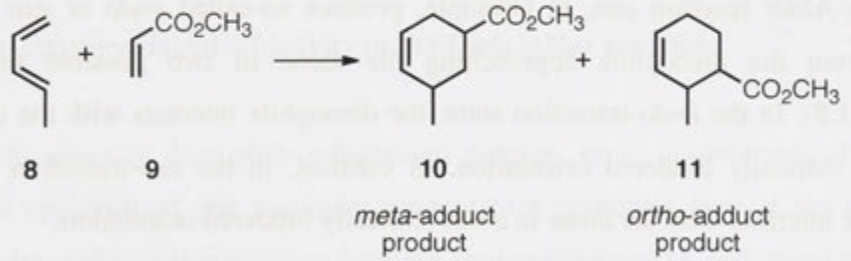


Scheme 1.2: The Diels-Alder reaction of diene **4** and dienophile **5**.

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**).[6]

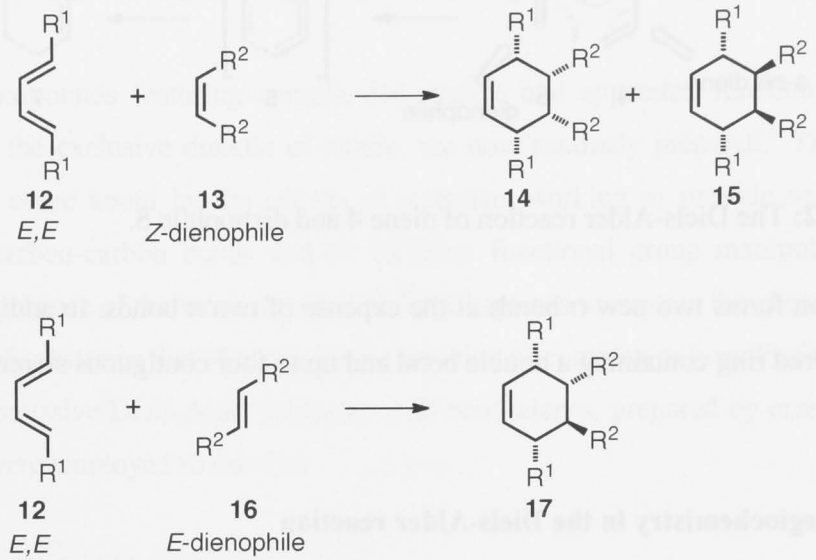


Scheme 1.3: The reaction between a terminal substituted butadiene **8** and methyl acrylate **9**. Product ratio: (10:90) (*meta*:*ortho*).

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

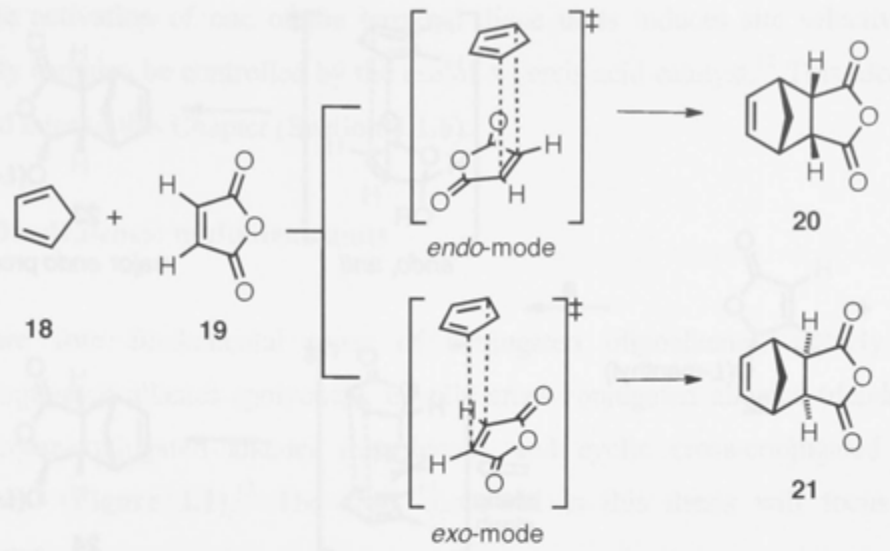
dienophile **13** possessing *Z*-geometry, the products **14** and **15** would be expected to form. If, however, the same diene **12** reacts with a dienophile **16** having *E*-geometry, product **17** will be formed (**Scheme 1.4**).



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.

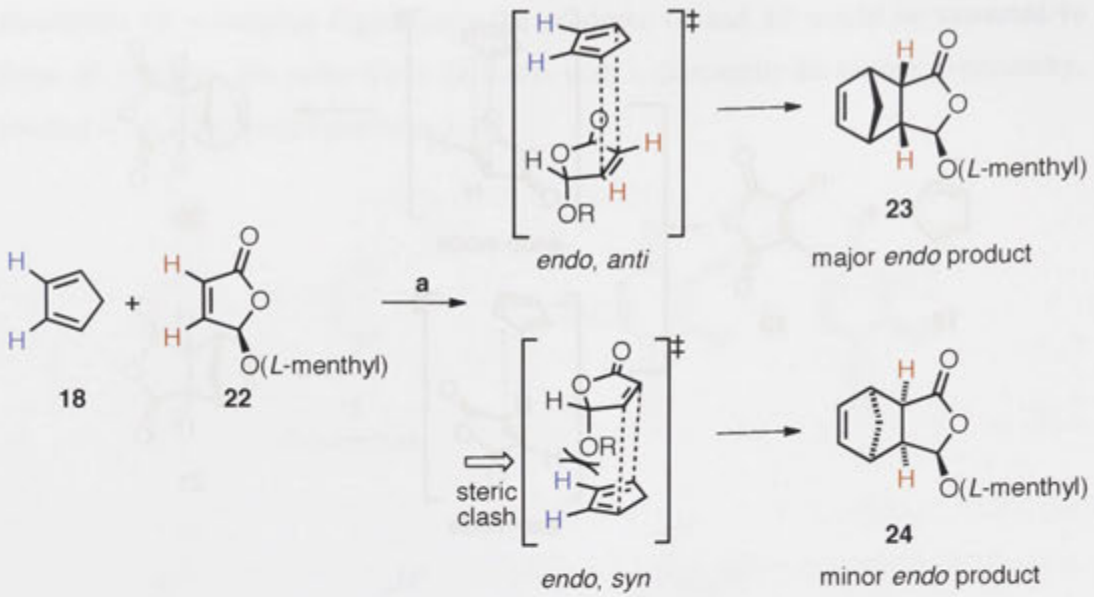


Scheme 1.5: *Endo*/*exo* selectivity in the intermolecular Diels-Alder reaction between cyclopentadiene **18** and maleic anhydride **19**.

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 π-Diastereofacial selectivity in the Diels-Alder reaction

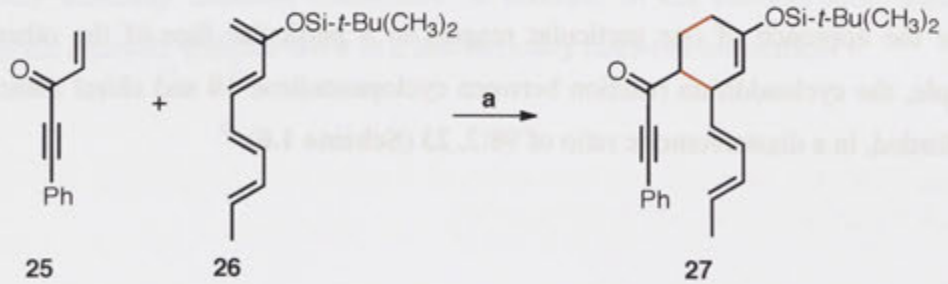
With certain diene or dienophile substitution patterns, steric or electronic effects may favour the approach of one particular reagent to a particular face of the other. For example, the cycloaddition reaction between cyclopentadiene **18** and chiral dienophile **22** afforded, in a diastereomeric ratio of 98:2, **23** (**Scheme 1.6**).[10]



Scheme 1.6: π-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.[12] 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**).[13] The work discussed in this thesis will focus on the dendralenes.

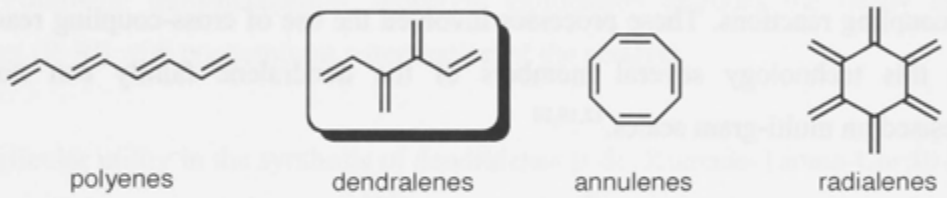


Figure 1.1: The family of conjugated oligoalkenes.

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.[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**.

The first synthesis of a dendralene, specifically [3]dendralene **28**, was independently reported by the Bailey and Blomquist groups in 1955 (**Figure 1.2**).[15,16] Seven years later, Bailey also detailed the first synthesis of [4]dendralene **29**.[17]

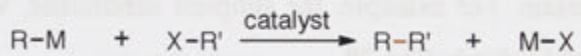
28 29

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.[18] 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.[12,19,20]

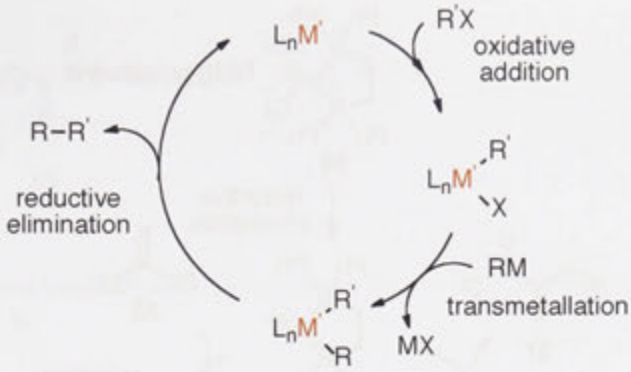
1.1.4 Cross-coupling reactions

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**).[5,14] This versatile reaction group is tolerant of a wide variety of alkyl and aryl residues R and R'.[5]



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

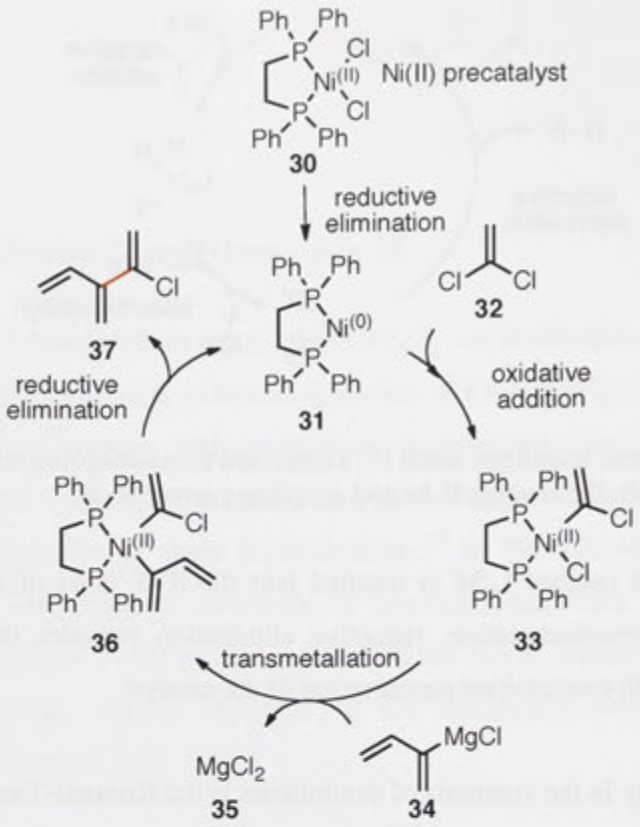
A vast array of cross-coupling reactions using different organometallic substrates and various catalysts are known. Many named reactions, utilised the world over for synthesis including Suzuki, Negishi, Stille and Sonogashira fall into this class.[21] These metal-catalysed cross-coupling reactions share 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 L_nM' 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.

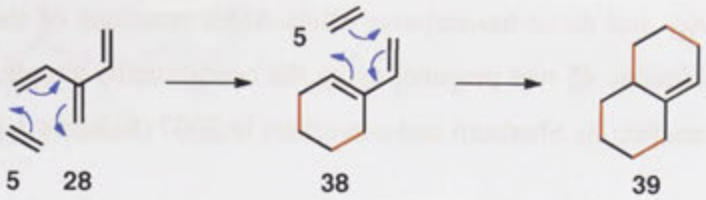
Of particular utility in the synthesis of dendralenes is the Kumada-Tamao-Corriu (KTC) reaction, first reported in 1972.[22,23] This nickel$^{(0)}$-catalysed reaction involves the coupling of Grignard reagents with organohalides and was used by Payne and Bradford in the formation of substituted [3]dendralenes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



Scheme 1.10: Formation of 2-chloro [3]dendralene **37** by KTC reaction, catalysed by Ni(dppe)Cl_2 **30**. Newly formed carbon-carbon bond in red.[22,23]

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.



Scheme 1.11: Diene-transmissive Diels-Alder reaction of unsubstituted [3]dendralene **28** with dienophile **5**.

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.[24] Diene transmissive Diels-Alder reactions are themselves a subgroup of so-called cascade reactions,[25] 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.

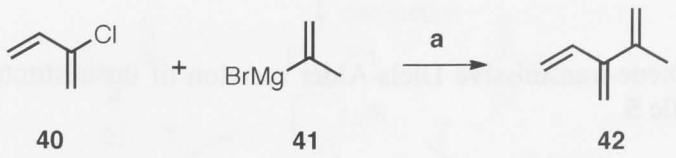
The work reported in this Chapter refers to the simplest members of the dendralene family. C2 substituted [3]dendralenes will be discussed, as will [4]dendralenes, substituted at the 1,2 and 4 positions (**Figure 1.3**).

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

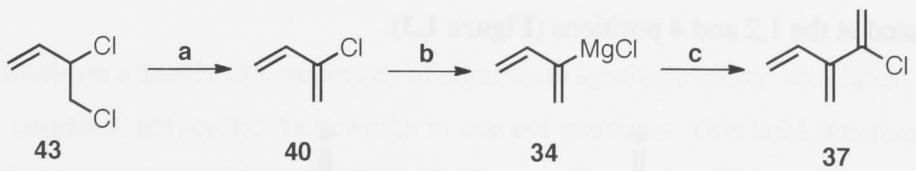
Although the synthesis of several C2 substituted [3]dendralenes had been reported in the literature[26-30] practical, gram scale syntheses of this family remained elusive until the work of Sherburn and co-workers[19], published in 2007. The group also studied the

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]



Scheme 1.12: Synthesis of 2-methyl [3]dendralene **42**. *Reagents and conditions:* (a) Isopropenyl magnesium bromide **41** (1.2 mol equiv), Ni(dppp)Cl_2 (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.



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), BrC_2H_4Br (0.30 mol equiv), $ZnBr_2$ (0.010 mol equiv), THF, 80 °C, 2 h, 89%; (c) 1,1-dichloroethylene **32** (5.0 mol equiv), Ni(dppe)Cl_2 (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]

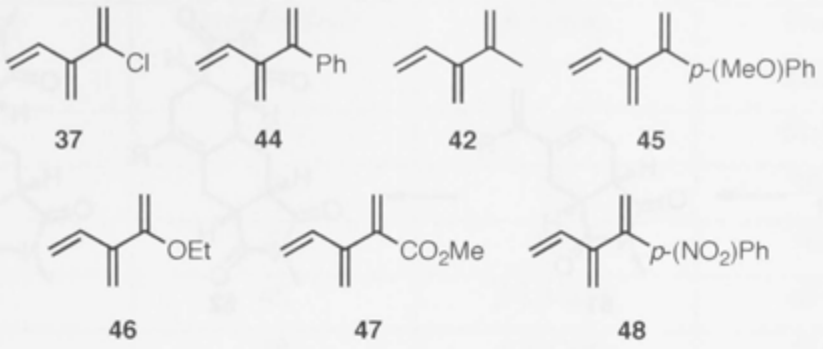
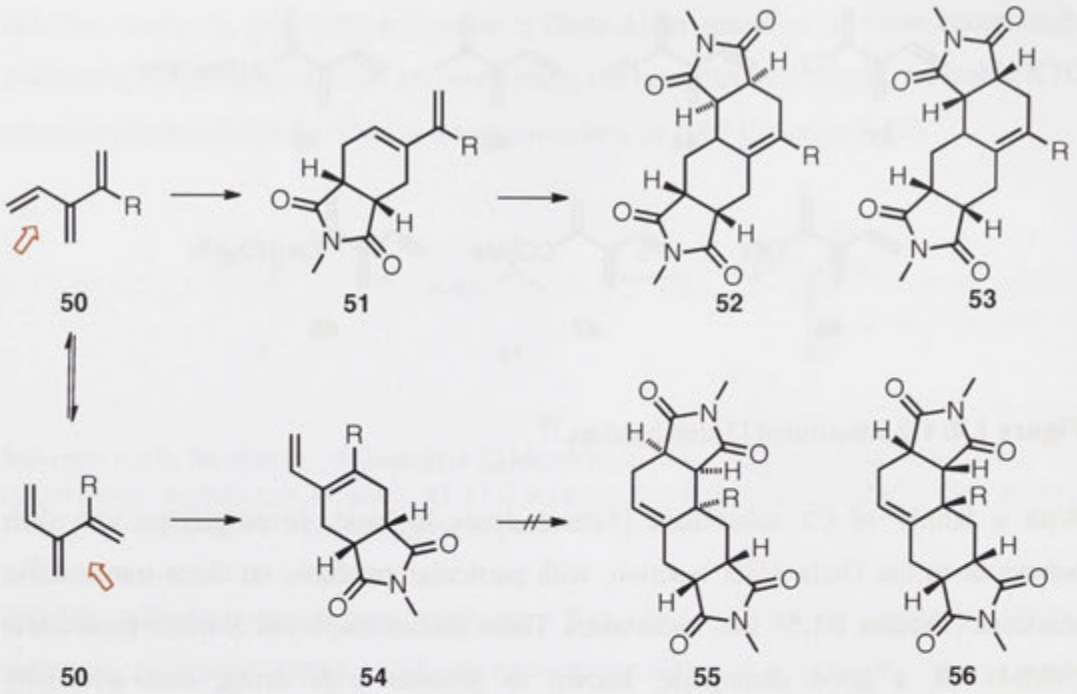


Figure 1.4: C2 substituted [3]dendralenes.[19]

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 *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.

Entry	[3]dendralene	R Group	Products **52**:**53**:**54**
1	**37**	Cl	61:12:27
2	**44**	Ph	58:6:36
3	**42**	Me	56:8:36
4	**45**	*p*-OMePh	65:7:28
5	**48**	*p*-NO_2Ph	65:7:28
6	**46**	OEt	81:10:9
7	**47**	CO_2Me	68:8:24

Table 1.1: Diels-Alder reactions of C2 substituted [3]dendralenes with NMM **49**.[19]

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,[19] 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.

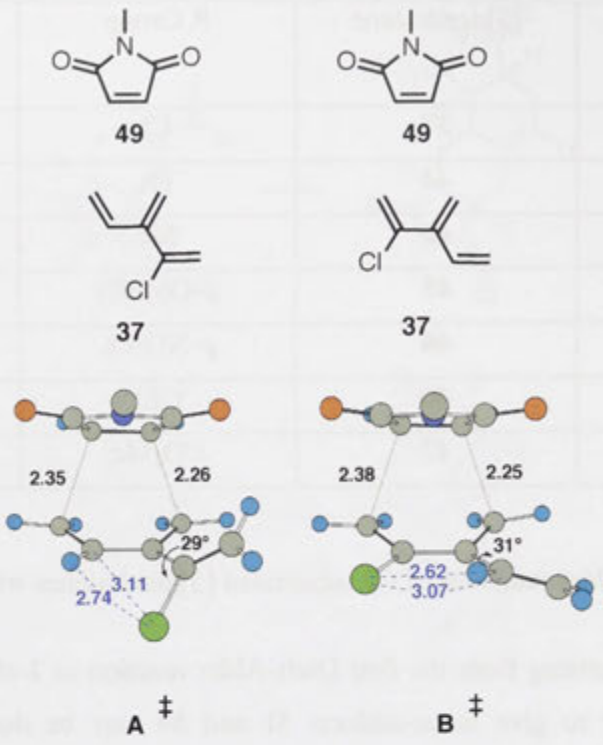
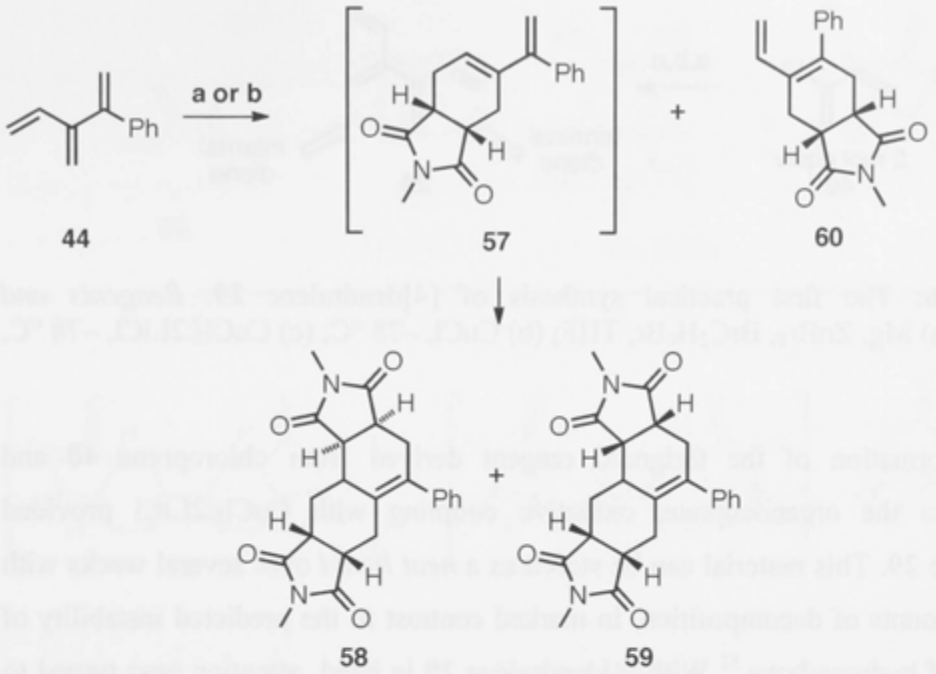


Figure 1.5: Representations of DFT optimised transition state structures for the addition of NMM **49** to 2-chloro [3]dendralene **37**. (Chemdraw structures shown above for clarity).

Lewis acids are known to often catalyse Diels-Alder reactions by reducing the LUMO energy of the dienophile to which they are complexed.[5] 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.[5] 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**).[19]

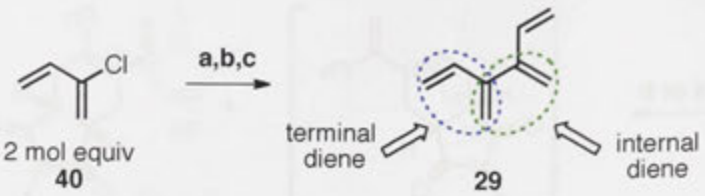


Scheme 1.15: Comparison of uncatalysed and Lewis acid-catalysed Diels-Alder reactions of 2-phenyl [3]dendralene **44** with NMM **49**. *Reagents and conditions:* (a) NMM (5 mol equiv), $CDCl_3$, rt, 90%, **58**:**59**:**60** 58:6:36; (b) NMM:$EtAlCl_2$, PhMe, –78 °C to rt, 68%, **58**:**59**:**60** 25:50:25 or NMM:$2EtAlCl_2$, PhMe, –78 °C to rt, 67%, **58**:**59**:**60** 33:67:0.

The reaction is clearly catalysed by $EtAlCl_2$ 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.

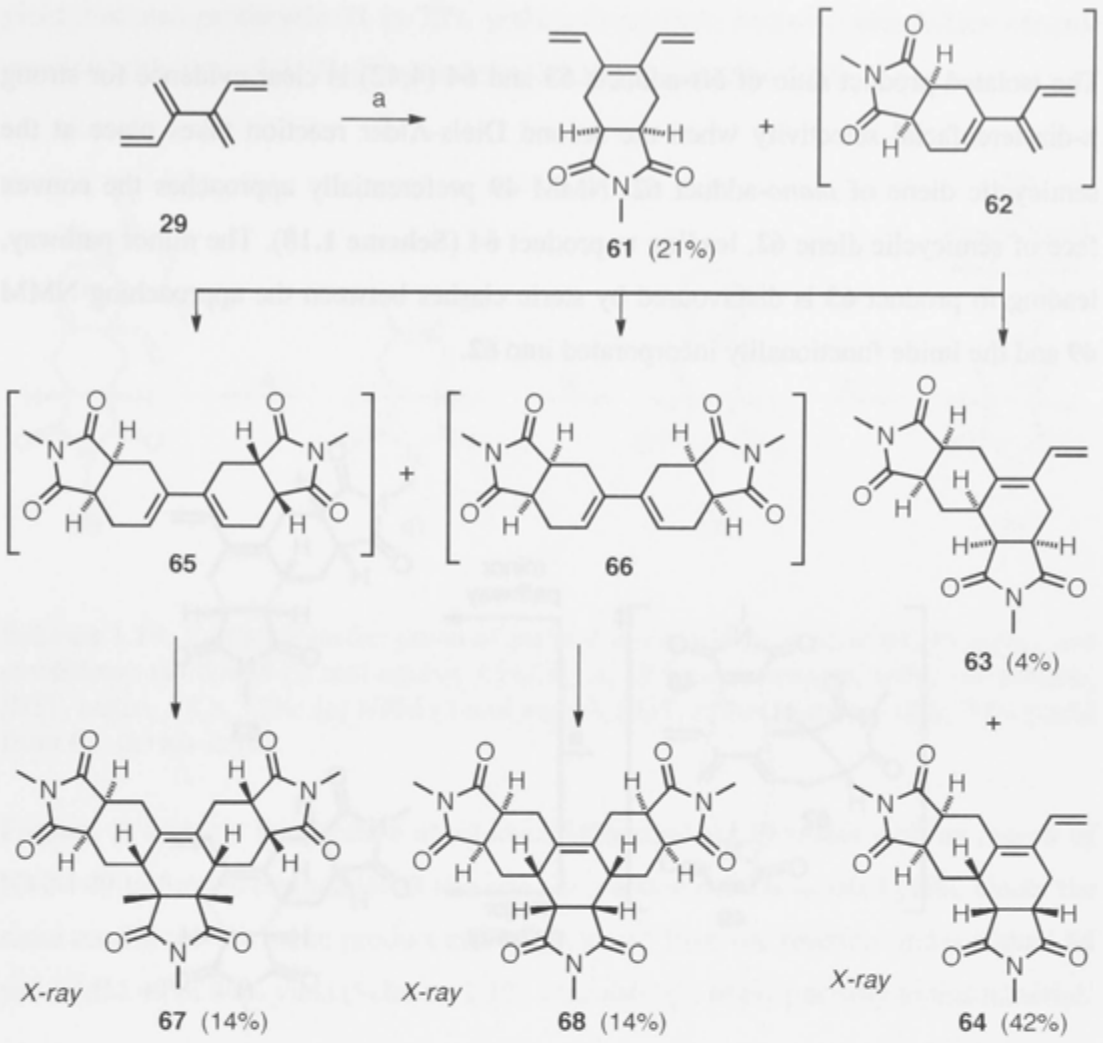
1.1.7 Practical synthesis of [4]dendralene 29 and its Diels-Alder reactions

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.[18] 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.[12] 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, $ZnBr_2$, BrC_2H_4Br, THF; (b) CuCl, –78 °C; (c) $CuCl_2$.2LiCl, –78 °C, 26%.

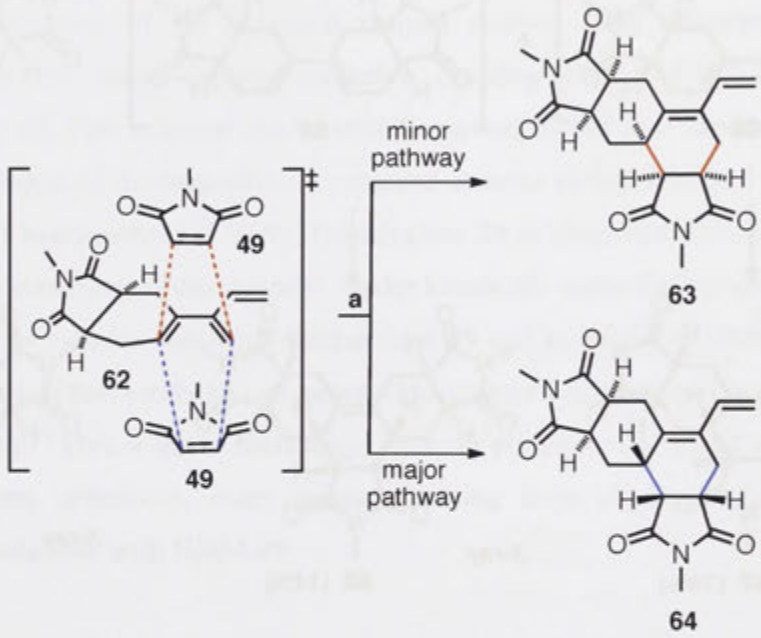
Following formation of the Grignard reagent derived from chloroprene **40** and conversion to the organocuprate, oxidative coupling with $CuCl_2$.2LiCl provided [4]dendralene **29**. This material can be stored as a *neat liquid* over several weeks with only tiny amounts of decomposition, in marked contrast to the predicted instability of this family of hydrocarbons.[32] 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**).[12] 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 *bis*-adducts **63** and **64** (4:42) is clear evidence for strong π-diastereofacial selectivity when the second Diels-Alder reaction takes place at the semicyclic diene of *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**.

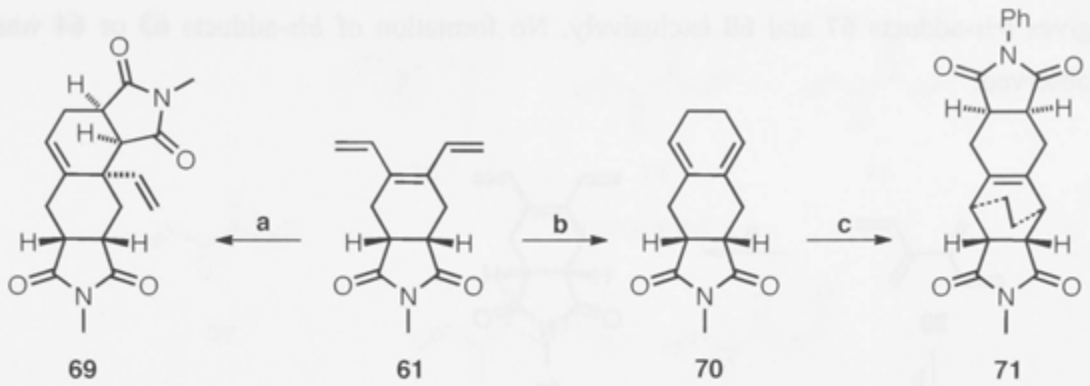


Scheme 1.18: Two possible addition of NMM **49** to *mono*-adduct **62** and *bis*-adducts **63** and **64**. *Reagents and conditions:* (a) NMM (2.5 mol equiv), 16 h, rt (**4**:**5** ratio, 4%, 42% respectively).

In contrast, when the second Diels-Alder reaction takes place at the exocyclic diene of *mono*-adduct **62** leading to *bis*-adducts **65** and **66**, no π-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**.

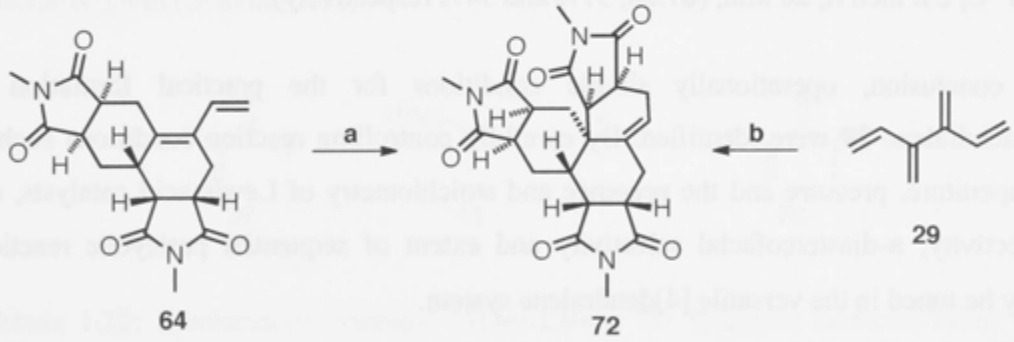
Although the first cycloaddition reaction product **61** does not undergo further reaction with NMM **49** under kinetically control conditions at room temperature, as described, it does react further to provide tetracycle **69** as the major product under high pressure (19 kbar) at ambient temperature (**Scheme 1.19**). Additionally, the 6π-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), CH_2Cl_2, 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).

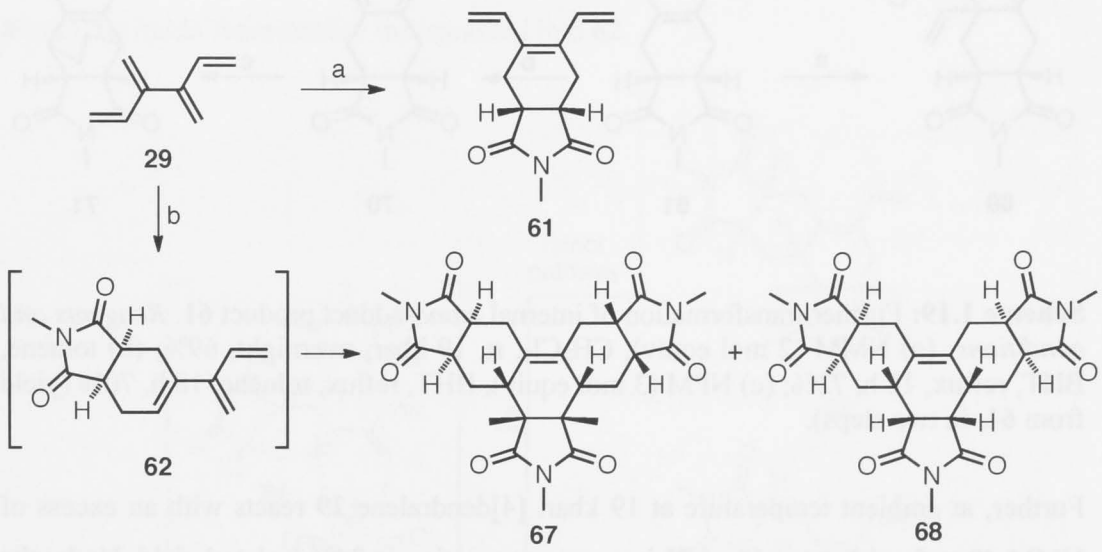
Further, at ambient temperature at 19 kbar, [4]dendralene **29** reacts with an excess of NMM **49** to furnish *tris*-adduct **72** in a one pot reaction in 34% isolated yield. Under the same conditions, the same product can be produced from the reaction of *bis*-adduct **64** and NMM **49** in 84% 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), CH_2Cl_2, 19 kbar, 70 °C, 2 h, then rt, 4 days, 84%; (b) NMM (9.5 mol equiv), CH_2Cl_2, 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 $MeAlCl_2$ are used, the internal cycloaddition product **61** is formed in high selectivity in 77% yield from of

[4]dendralene **29** (**Scheme 1.21**). In contrast, using a 1:2 molar ratio of NMM **49** and $MeAlCl_2$, the first cycloaddition reaction affords terminal *mono*-adduct **62** as the sole product. In addition, further cycloaddition reactions of **62** under the same conditions gives *tris*-adducts **67** and **68** exclusively. No formation of *bis*-adducts **63** or **64** was observed.



Scheme 1.21: Controlling the cycloaddition site selectivity with Lewis acid catalysts. *Reagents and conditions:* (a) NMM.$MeAlCl_2$ complex (2 mol equiv), toluene, –78 °C, 30 min to rt, 20 min, 77%; (b) NMM.2$MeAlCl_2$ complex (3 mol equiv), CH_2Cl_2, –78 °C, 2 h then rt, 20 min, (**67**:**68**, 37% and 34% respectively).

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, π-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.

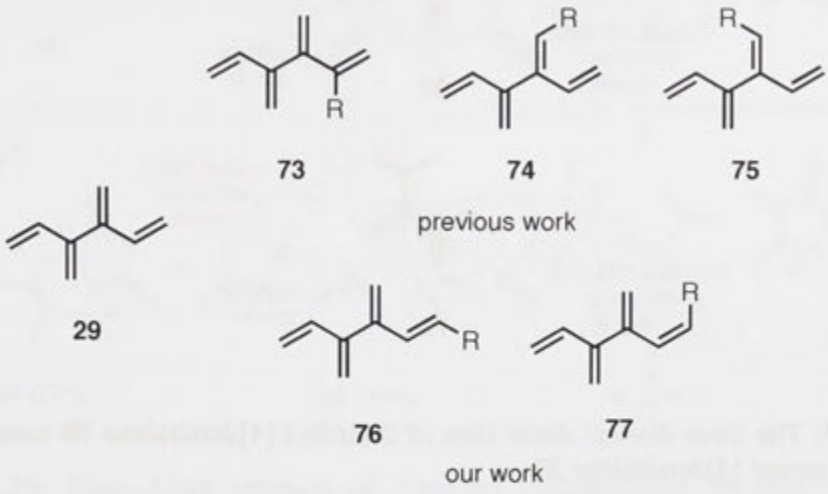
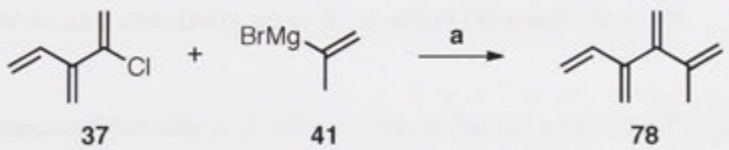


Figure 1.6: [4]dendralene **29** and substituted [4]dendralene family.

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**).



Scheme 1.22: Synthesis of 2-methyl [4]dendralene **78**. *Reagents and conditions:* (a) Isopropenyl magnesium bromide (1.5 mol equiv), $Ni(dppp)Cl_2$ (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**).

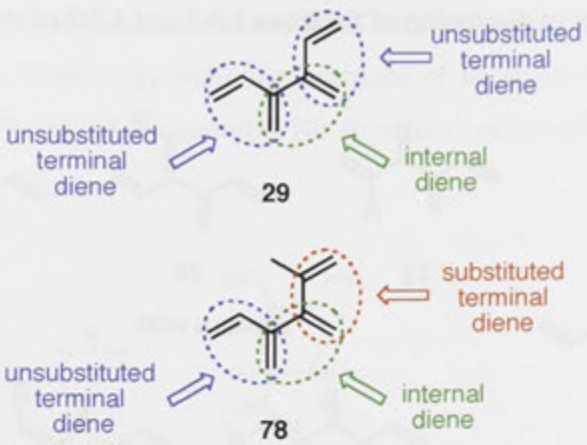
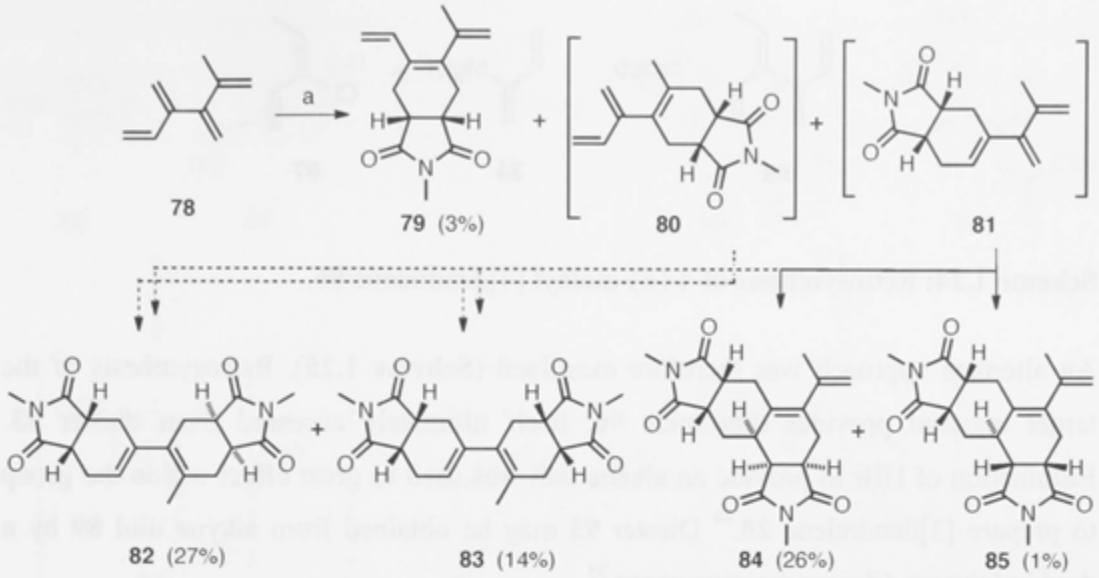


Figure 1.7: The three distinct diene sites of 2-methyl [4]dendralene **78** compared with the two of parent [4]dendralene **29**.

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**.

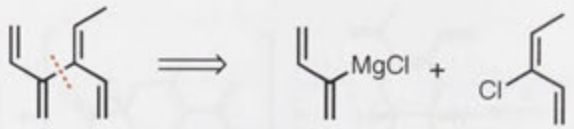


Scheme 1.23: Diels-Alder reaction of 2-methyl [4]dendralene **78** with NMM **49**. *Reagents and conditions:* (a) NMM (3 mol equiv), CH_2Cl_2, rt, 14 h, 71%.

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.

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

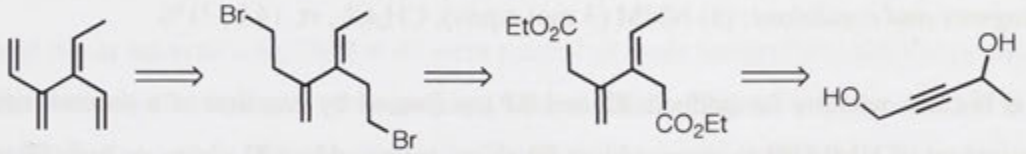
Alborzi next examined the effect of substitution at the C4 position of [4]dendralene. Let us first discuss the formation of 4-(*E*)-methyl [4]dendralene **86**. A disconnection to provide readily available Grignard reagent **34** was briefly examined and discarded. It was decided that the unknown and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



86 34 87

Scheme 1.24: Retrosynthesis of 4-(*E*)-methyl [4]dendralene **86**.

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**.[34] Diester **93** may be obtained from alkyne diol **89** by a double Johnson-Claisen rearrangement.[35]

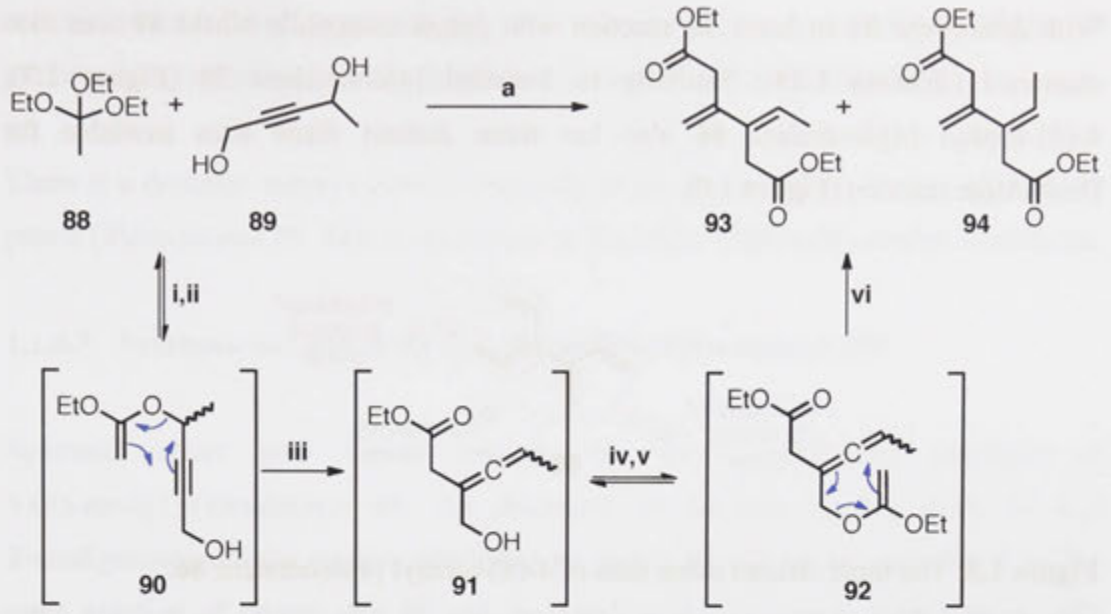


86 96 93 89

Scheme 1.25: Retrosynthesis of 4-(*E*)-methyl [4]dendralene **86**.

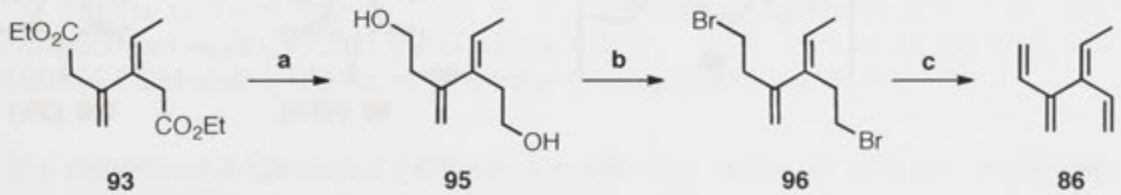
In the synthesis, commercially available alkyne diol **89** was treated with triethylorthoacetate **88** and propionic acid in dry DMF under microwave irradiation (**Scheme 1.26**). The mechanism of the conversion of alkyne diol **89** to diester **93** involves a double Johnson-Claisen rearrangement: 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**.[35] *Reagents and conditions:* (a) $CH_3C(OEt)_3$ (9.1 mol equiv), $C_2H_5CO_2H$, 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) $LiAlH_4$ (2.0 mol equiv), Et_2O, 0 °C, 30 min, then rt, overnight, 97%; (b) NBS (2.0 mol equiv), PPh_3 (2.0 mol equiv), CH_2Cl_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**).

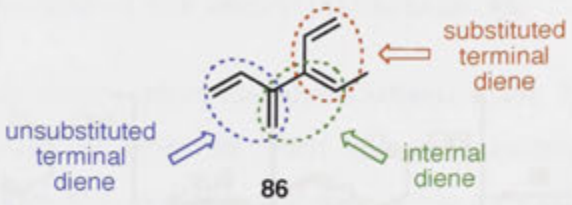
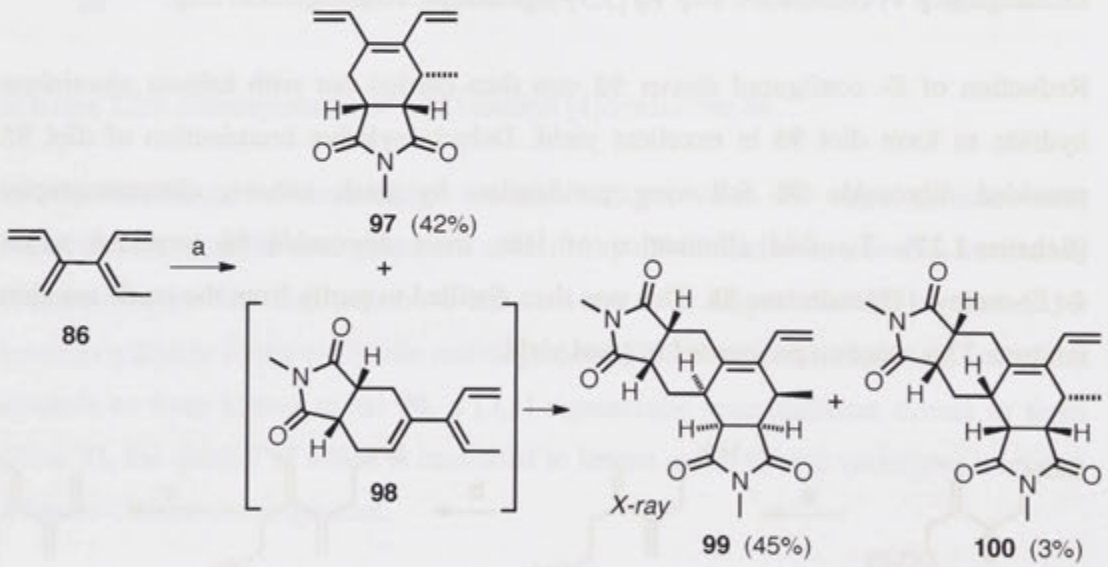


Figure 1.8: The three distinct diene sites of 4-(*E*)-methyl [4]dendralene **86**.

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.



Scheme 1.28: Diels-Alder reaction of 4-(*E*)-methyl [4]dendralene **86** with NMM **49**. *Reagents and conditions:* (a) NMM (3 mol equiv), rt, CH_2Cl_2, overnight, 90%.

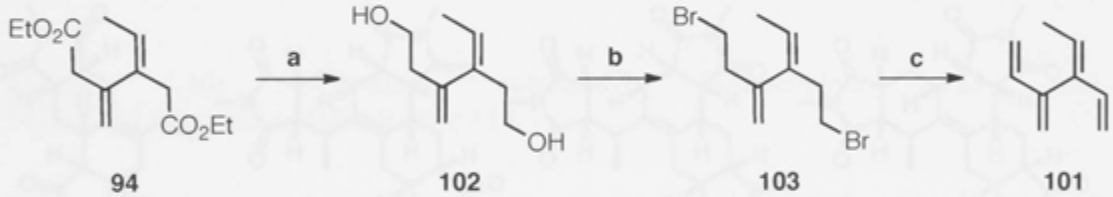
In contrast, cycloaddition at the unsubstituted terminal diene site provided *mono*-adduct **98**, which was not isolated. Instead, it reacted on to provide mainly *bis*-adduct **99** (45%), with traces of *bis*-adduct **100** (3%). There is clear strong π-diastereofacial

selectivity here, with approach of the second molar equivalent of NMM **49** preferentially occurring from the least hindered face of the *mono*-adduct **98**.

There is a dramatic enhancement of reactivity at the internal diene, compared with the parent [4]dendralene **29**. This is clearly due to the effect of the 4-(*E*)-methyl substituent.

1.1.8.3 Synthesis and reactivity of 4-(*Z*)-methyl [4]dendralene 101

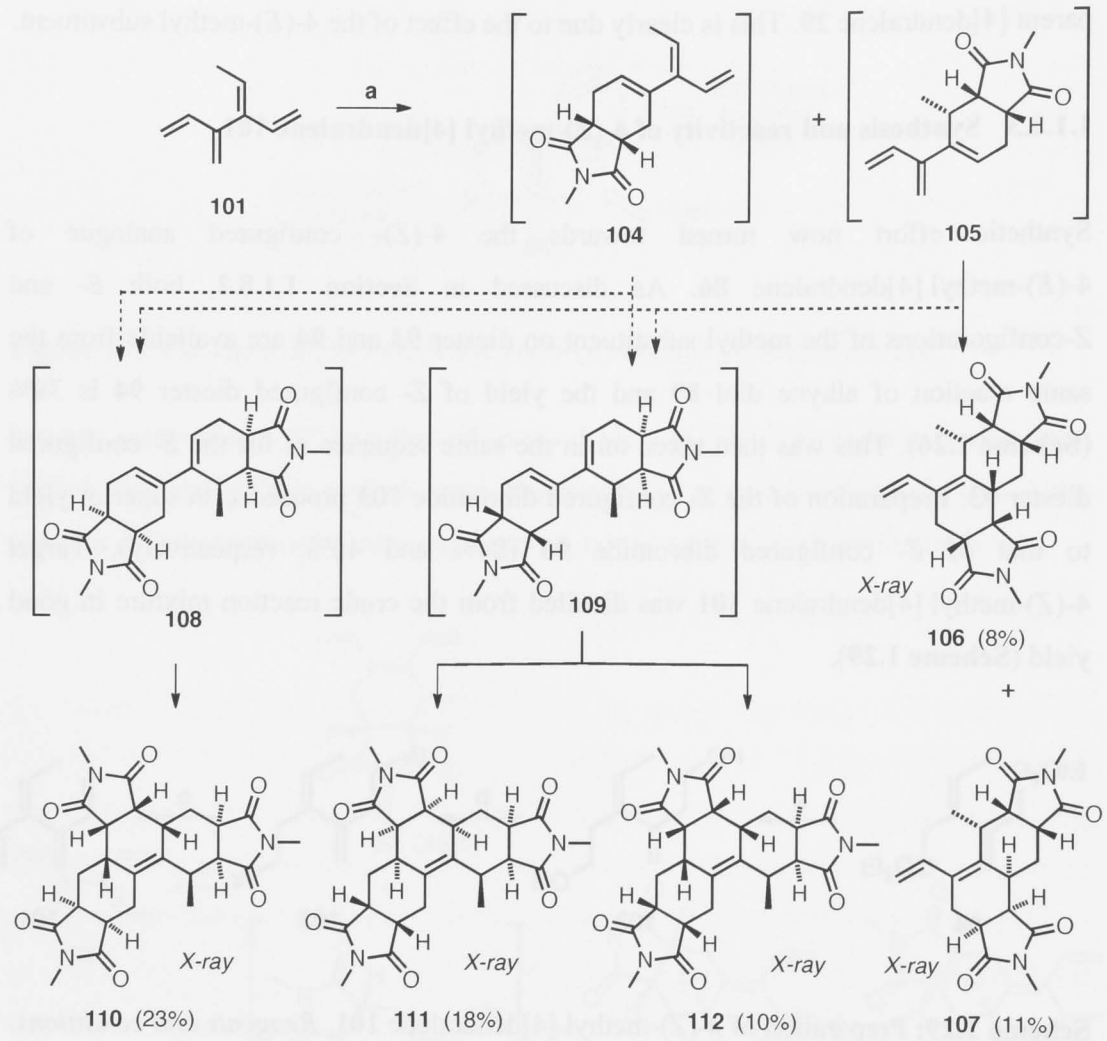
Synthetic effort now turned towards the 4-(*Z*)- configured analogue of 4-(*E*)-methyl [4]dendralene **86**. As discussed in **Section 1.1.8.2**, both *E*- and *Z*-configurations of the methyl substituent on diester **93** and **94** are available from the same reaction of alkyne diol **89** and the yield of *Z*- configured diester **94** is 38% (**Scheme 1.26**). This was then taken on in the same sequence as for the *E*- configured diester **93**: Preparation of the *Z*- configured dibromide **103** proceeded in superior yield to that of *E*- configured dibromide **96** (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) $LiAlH_4$ (2.0 mol equiv), Et_2O, 0 °C, 30 min, then rt, overnight, 91%; (b) NBS (2.0 mol equiv), PPh_3 (2.0 mol equiv), CH_2Cl_2, –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 **49** 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.



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_2Cl_2, 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**).

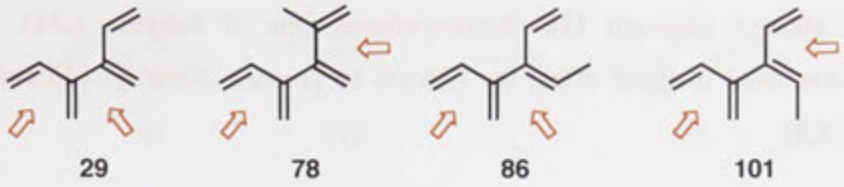


Figure 1.9: Observed site selectivies of the exhaustive Diels Alder reactions of NMM **49** with [4]dendralene **29**, 2-methyl [4]dendralene **78**, 4-(*E*)-methyl [4]dendralene **86** and 4-(*Z*)-methyl [4]dendralene **101** (red arrows).

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**).

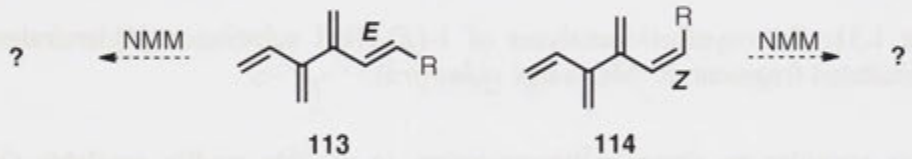


Figure 1.10: 1-(*E*)-alkyl substituted [4]dendralene **113** and 1-(*Z*)-alkyl substituted [4]dendralene **114**.

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.

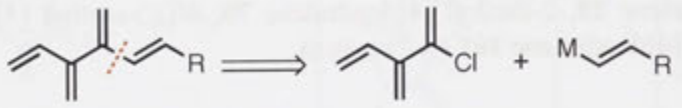
1.3 Results & Discussion

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

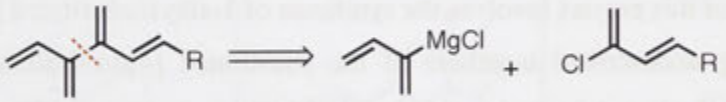
metallated alkenyl fragment **116** (Retrosynthesis One of **Scheme 1.31**). A similar approach was used to great effect by Alborzi to prepare 2-methyl [4]dendralene **78** (**Section 1.1.8**).

Retrosynthesis One



113 **37** **116**

Retrosynthesis Two



113 **34** **117**

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.

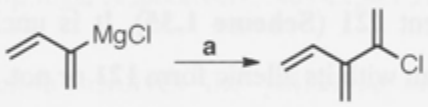
1.3.1.1 1-(*E*)-Methyl [4]dendralene 115 from 2-chloro [3]dendralene 37

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**).

37 116 115

Scheme 1.32: Preparation of 1-(*E*)-methyl [4]dendralene **115** from 2-chloro [3]dendralene **37** using transition metal catalysis (M = $B(OR)_2$ or MgBr).

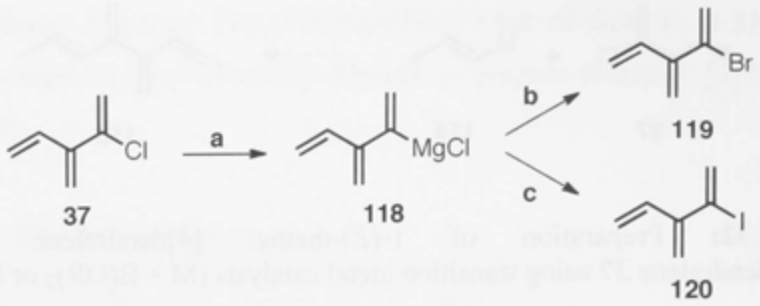
2-Chloro [3]dendralene **37** was previously synthesised within our group (**Section 1.1.6**) in yields around 65%.[19] Optimisation of this procedure in our hands (reducing reaction time and increasing the amount of inexpensive and volatile coupling partner, 1,1-dichloroethylene **32** from five to 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]



34 37

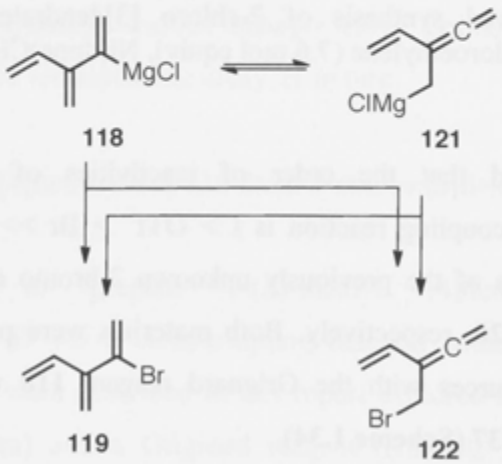
Scheme 1.33: Improved synthesis of 2-chloro [3]dendralene **37**. *Reagents and conditions:* (a) 1,1-dichloroethylene (7.6 mol equiv), $Ni(dppe)Cl_2$ (0.013 mol equiv), –20 °C, 13 h, 85%.

It is well established that the order of reactivities of organohalides in the Suzuki-Miyaura cross-coupling reaction is I > 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**).



Scheme 1.34: Preparation of 2-bromo [3]dendralene **119** and 2-iodo [3]dendralene **120**. *Reagents and conditions:* (a) Magnesium powder (2.9 mol equiv), BrC_2H_4Br (0.70 mol equiv), $ZnBr_2$ (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) I_2 (3.0 mol equiv), Et_2O, –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).

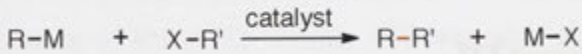
Various sources of electrophilic bromine were investigated for the synthesis of 2-bromo [3]dendralene **119**. No target product **119** was observed when

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.

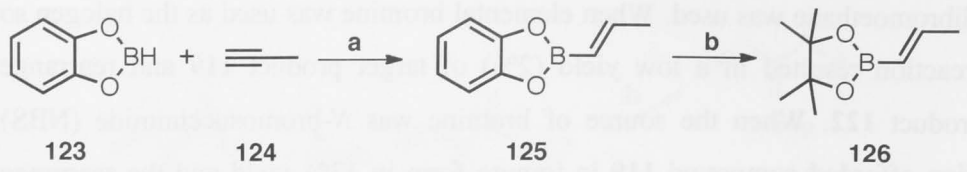
In light of the low yields for the syntheses of the 2-bromo- and iodo- [3]dendralenes **119** and **120**, coupled with their instabilities, attention returned to 2-chloro [3]dendralene **37**. We next required a convenient nucleophile to allow efficient cross-coupling for the synthesis of the target 1-(*E*)-methyl [4]dendralene **115**. The use of organoboron and organomagnesium nucleophilic fragments for use in Suzuki-Miyaura and Kumada-Tamao-Corriu couplings, respectively, was explored.

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**.



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

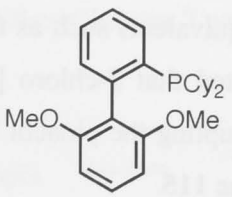
Following a literature procedure, treatment of catechol borane **123** with *ca.* 1.3 mol equiv of propyne **124** at 70 °C for 12 hours,[37] afforded catechol boronate **125** in 58% yield. Conversion of **125** to pinacol boronate ester **126** proceeded smoothly in ether at room temperature (**Scheme 1.37**).



123 124 125 126

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), Et_2O, rt, 3 h, 63%.

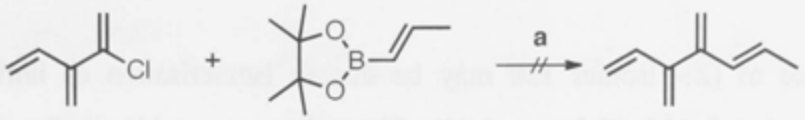
With pinacol boronate ester **126** in-hand, its Suzuki-Miyaura cross-coupling reaction with 2-chloro [3]dendralene **37** was attempted. Traditionally, bromides and iodides are used as coupling partners in Suzuki-Miyaura reactions. Only recently have catalysts systems suitable for use with the less reactive chlorides become available. They are generally used for the coupling of *aryl* chlorides. Activation of the catalyst by ligand modification is known to increase substrate tolerance and reactivity in the Suzuki-Miyaura reaction.[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.[39]



127

Figure 1.11: SPhos ligand **127**.

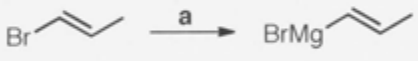
Disappointingly, even with this reactive catalyst system, no evidence of cross-coupled target material **115** was observed (**Scheme 1.38**). Analysis of crude reaction mixtures, obtained at variety of temperatures, showed only unreacted starting material and decomposition products by ^{1}H NMR.



37 126 115

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_3PO_4 (2.0 mol equiv), *n*-BuOH/H_2O (9:1), various temperatures, from rt to 50 °C, in the dark, Ar, overnight.

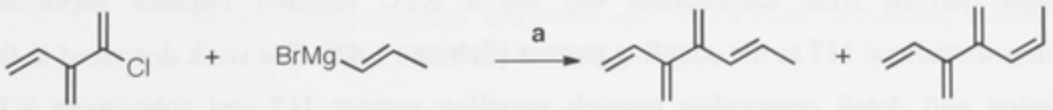
Kumada-Tamao-Corriu (KTC) cross-coupling between 2-chloro [3]dendralene **37** and the Grignard reagent of 1-(*E*)-propene **129** was also explored *en route* to target compound **115**. Following a procedure reported in the literature,[40] Grignard reagent **129** was prepared from commercially available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



128 129

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%.

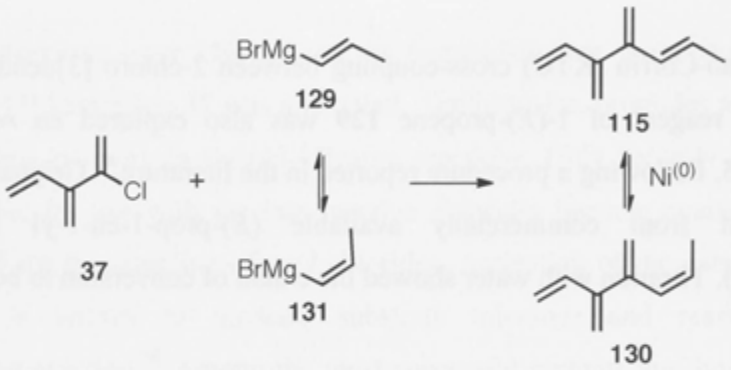
Once the Grignard reagent **129** was prepared, the KTC cross-coupling reaction was tried (**Scheme 1.40**). Gratifyingly, ^{1}H NMR analysis of the crude reaction mixture strongly suggested the presence of target 1-(*E*)-methyl [4]dendralene **115**. Unfortunately, evidence for the presence of the 1-(*Z*)- 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.



37 129 115 130

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.[41] Additionally, propenyl Grignard reagent **129** has been reported to isomerise to the (*Z*)-isomer **131**.[40] In any case, isomerisation occurs during the KTC coupling, precluding the preparation of pure (*E*)- or (*Z*)-isomers.

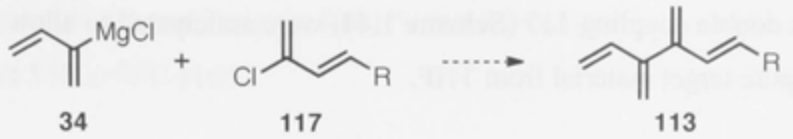


Scheme 1.41: Possible routes to the formation of 1-(*E*)-methyl [4]dendralene **115** and 1-(*Z*)-methyl [4]dendralene **130**.

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**.

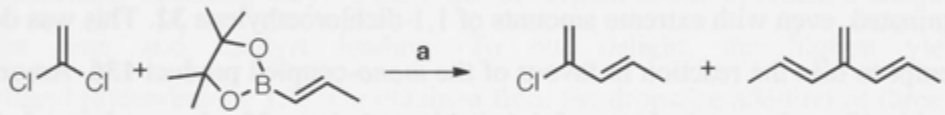


34 117 113

Scheme 1.42: Preparation of 1-(*E*)-alkyl substituted [4]dendralene **113** from Grignard reagent **34** and coupling partner **117**. (R=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,[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.[37]



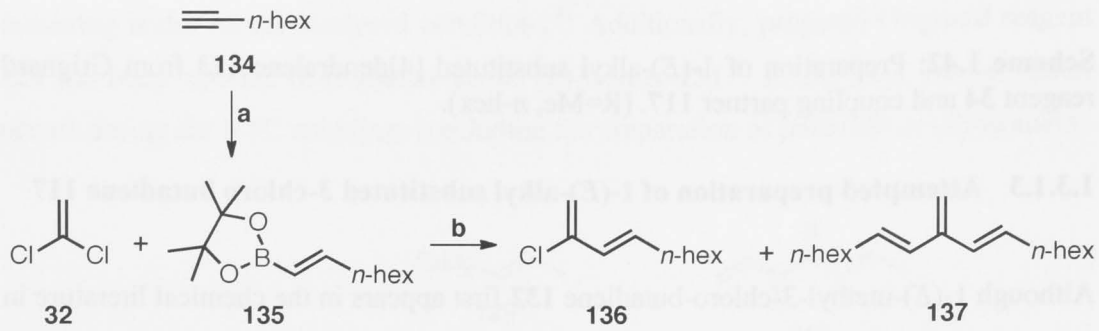
32 126 132 133

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), $Pd(PPh_3)_4$ (0.020 mol equiv), Ag_2CO_3 (2.0 mol equiv), THF, various temperature, 6 h, only starting material; (b) 1,1-dichloroethylene (1.0 mol equiv), $Pd(dppf)Cl_2$ (0.050 mol equiv), NaOH (2.0 mol equiv), sealed tube, THF, various temperatures, 8 h.

Both $Pd(PPh_3)_4$ and $Pd(dppf)Cl_2$ 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.

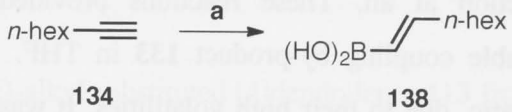
At this stage in the research, in order to address the volatility issues, it was decided to elongate the C1 substituent alkyl chain to a C_6H_{13} unit, rather than a CH_3. The associated large differences in masses of the target material **136** and the by-product

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), $Pd(dppf)Cl_2$ (0.010 mol equiv), NaOH (1.3 mol equiv), sealed tube, THF, various temperatures.

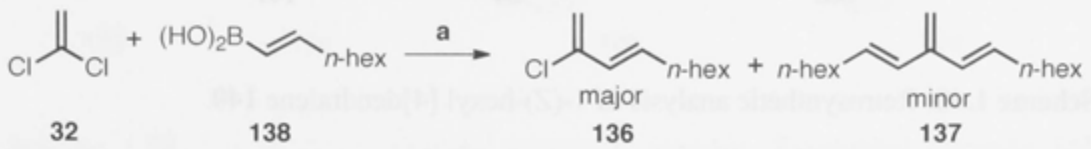
Disappointingly, it was found that the undesired double coupling by-product **137**, predominated, even with extreme amounts of 1,1-dichloroethylene **32**. This was done in an attempt to bias the reaction in favour of the *mono*-coupled product **136**. Amazingly, even with 60 molar equivalents of 1,1-dichloroethylene **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**.[43] Boronic acid **138** was prepared according to a literature procedure (**Scheme 1.45**).[44]



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 H_2O (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

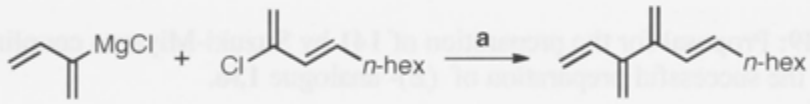
Barluenga and co-workers (**Scheme 1.46**).[43] The cross-coupling reaction provided the target product **136** in 32% yield.



32 **138** **136** **137**

Scheme 1.46: Preparation of 1-(*E*)-hexyl 3-chloro butadiene **136**. *Reagents and conditions:* (a) 1,1-Dichloroethylene (4 mol equiv), $Pd_2(dba)_3$ (0.005 mol equiv), XPhos (0.02 mol equiv), K_3PO_4 (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**).

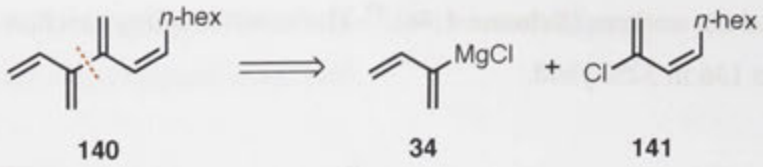


34 **136** **139**

Scheme 1.47: Preparation of 1-(*E*)-hexyl [4]dendralene **139**. *Reagents and conditions:* (a) Grignard reagent (3 mol equiv), PPh_3 (0.05 mol equiv), $Ni(dppp)Cl_2$ (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**).

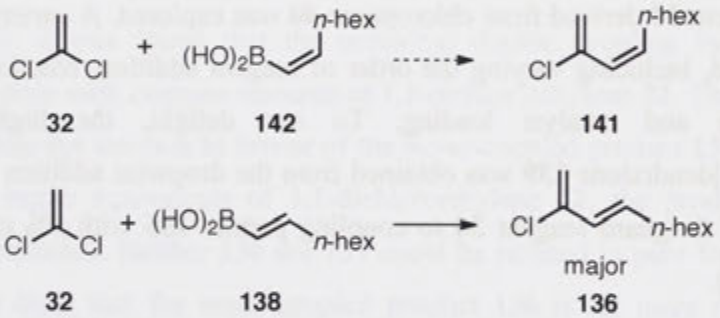


140 34 141

Scheme 1.48: Retrosynthetic analysis of 1-(*Z*)-hexyl [4]dendralene **140**.

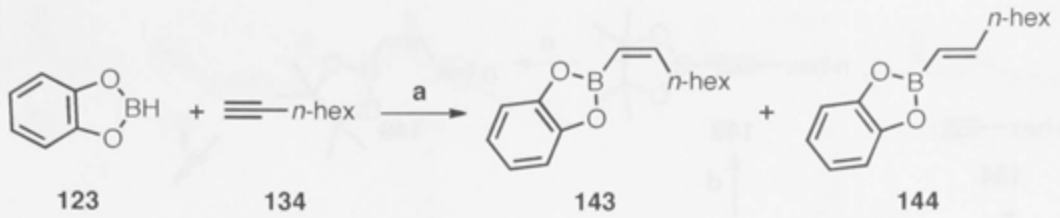
1.3.2.1 Formation of 1-(*Z*)-hexyl [4]dendralene 140 *via* KTC cross-coupling reaction

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**.



Scheme 1.49: Proposal for the preparation of **141** by Suzuki-Miyaura coupling reaction, inspired by the successful preparation of (*E*)- analogue **136**.

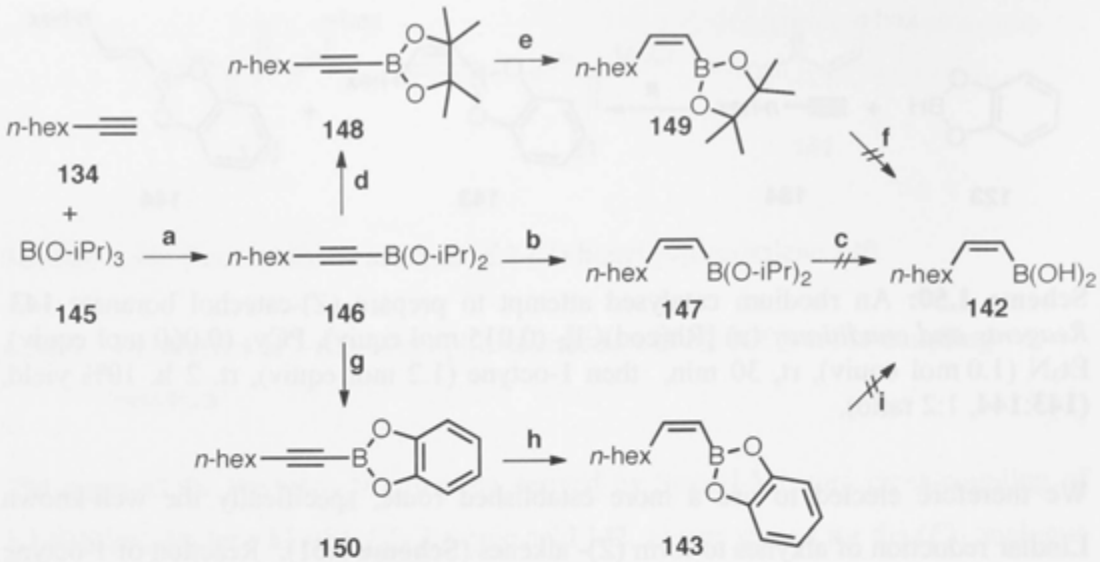
Standard uncatalysed hydroborations of alkynes give the (*E*)- boronic acid **138**.[5] Unfortunately, literature methods for producing the (*Z*)- boronic acid **142** do not exist. On the other hand, the preparation of (*Z*)-catechol boronate **143** is known. The first method employed rhodium-mediated coupling of the alkyne **134** with catecholborane **123**.[45] 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.



123 134 143 144

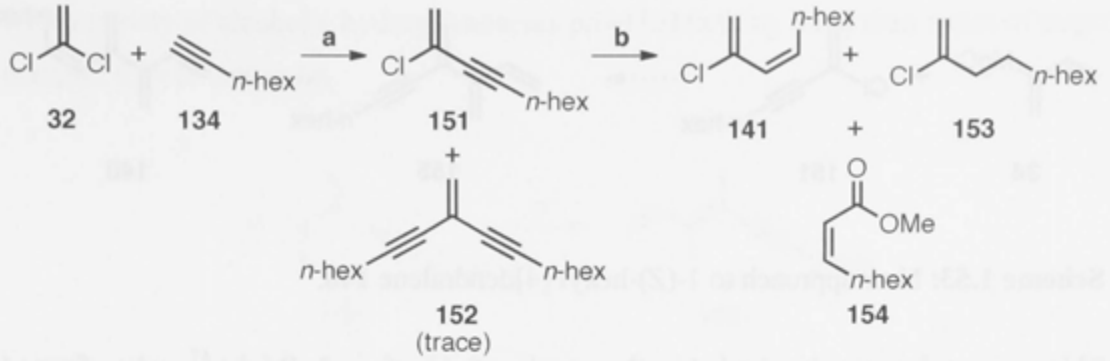
Scheme 1.50: An rhodium catalysed attempt to prepare (*Z*)-catechol boranate **143**. *Reagents and conditions:* (a) $[Rh(cod)Cl]_2$ (0.015 mol equiv), PCy_3 (0.060 mol equiv), Et_3N (1.0 mol equiv), rt, 30 min, then 1-octyne (1.2 mol equiv), rt, 2 h, 10% yield, (**143**:**144**, 1:2 ratio).

We therefore elected to use a more established route, specifically the well-known Lindlar reduction of alkynes to form (*Z*)- alkenes (**Scheme 1.51**).[5] 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), Et_2O, –78 °C, 30 min, then $B(O\text{-}i\text{-}Pr)_3$ (1.00 mol equiv), –78 °C, 2 h, then, HCl (2 M in Et_2O, 1.03 mol equiv), 94%; (b) Lindlar catalyst, H_2 (*ca.* 1 mol equiv), pyridine, 1,4-dioxane, in the dark, rt, 1.5 h, without purification; (c) H_2O, 1h, rt, 11% (over two steps); (d) Pinacol (1.05 mol equiv), Et_2O, 4 h, rt, 100%; (e) Lindlar catalyst, H_2 (*ca.* 1 mol equiv), pyridine, pentane, in the dark, rt, 30 min, 87% (*E*:*Z* ratio 20:80); (f) H_2O, rt, 2 h, no deprotection; (g) Catechol (1.00 mol equiv), Et_2O, rt, 4 h, 85% (without purification); (h) Lindlar catalyst, H_2 (*ca.* 1 mol equiv), pyridine, pentane, in the dark, rt, 3.5 h, 22%; (i) H_2O, 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.[46] 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**).

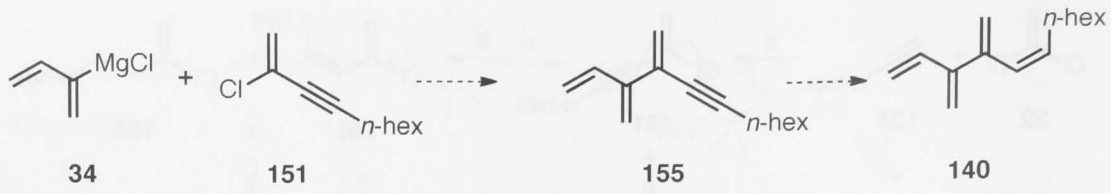


Scheme 1.52: An attempt to prepare **141**. *Reagents and conditions:* (a) 1,1-dichloroethylene (1.5 mol equiv), $Pd(PPh_3)_4$ (0.030 mol equiv), toluene, seal tube, rt, 25 min, then 1-octyne (1 mol equiv), *n*-$BuNH_2$ (1.5 mol equiv), CuI (0.030 mol equiv), 40 °C, 8 h, 63%; (b) H_2, 5%Pd on $BaSO_4$, 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, CH_2Cl_2, as well as the catalyst. Palladium poisoned with lead or quinoline, on $CaCO_3$ or $BaSO_4$ 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.

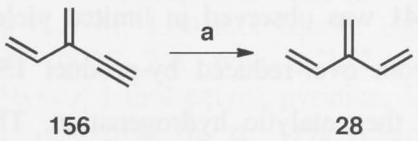
1.3.2.2 Formation of 1-(*Z*)-hexyl [4]dendralene 140 *via* hydrogenation

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**).



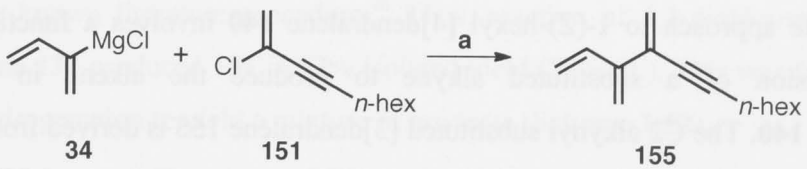
Scheme 1.53: New approach to 1-(*Z*)-hexyl [4]dendralene **140**.

This approach was inspired by the work of Hopf and Priebe,[47] 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**.



Scheme 1.54: Hopf's synthesis of [3]dendralene **28**. *Reagents and conditions:* (a) H_2, Lindlar catalyst, 60%.

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**).



Scheme 1.55: Synthesis C2 alkynyl substituted [3]dendralene **155**. *Reagents and conditions:* (a) Grignard reagent (3 mol equiv), PPh_3 (0.05 mol equiv), $Ni(dppp)Cl_2$ (0.05 mol equiv), THF, –15 °C to 0 °C, 2.5 h, 63%.

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 alkynyldienes to alkenes using zinc powder was reported previously,[48-50] however, this type of reduction method

with a variety of alcoholic hydrogen sources provided nothing more than traces of target material for our substrates.

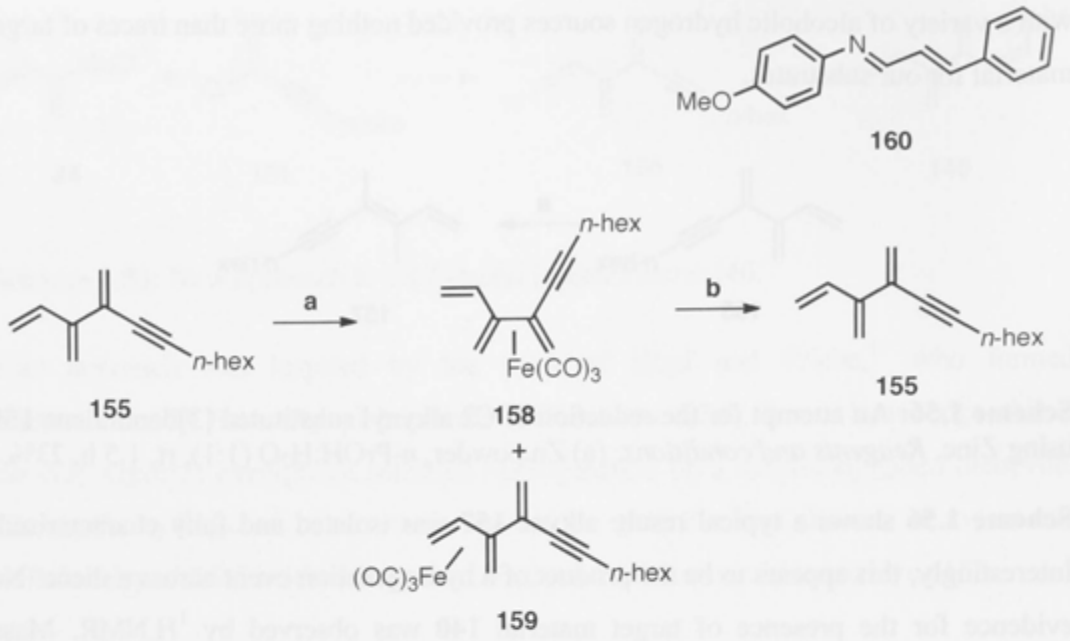
155 157

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:H_2O (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 ^{1}H 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.

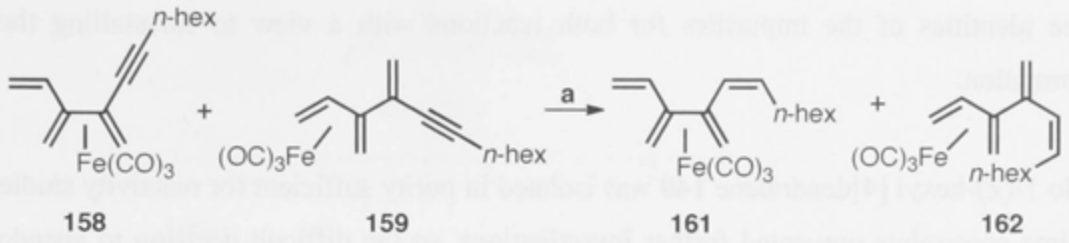
It was hoped that protection of either diene would allow selective reduction of the triple bond. Dienes may be protected by complexation with an iron tricarbonyl group.[51] Previous work in the group[52] has demonstrated that [3] and [4]dendralene **28** and **29** are readily complexed by an iron tricarbonyl 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.

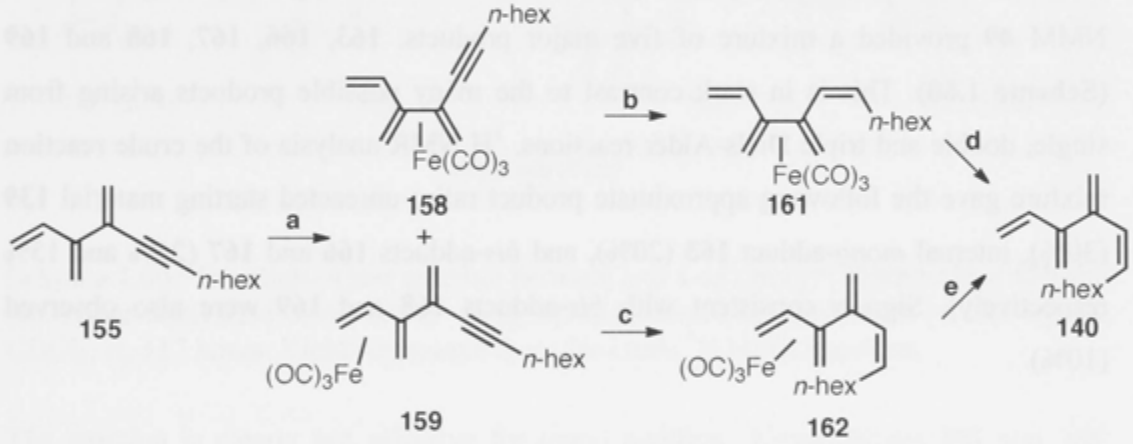
Following treatment of substrate **155** with $Fe_2(CO)_9$, examination of the crude reaction mixture by ^{1}H NMR confirmed the presence of species containing iron proximal **158** and distal **159** to the alkyne. It must be noted that in *neither* compound is an intact diene to be found. Oxidative 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) H_2, 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) $Fe_2(CO)_9$ (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) H_2, Lindlar catalyst, pentane, in the dark, rt, 6 h, 82% (impure); (c) H_2, 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).

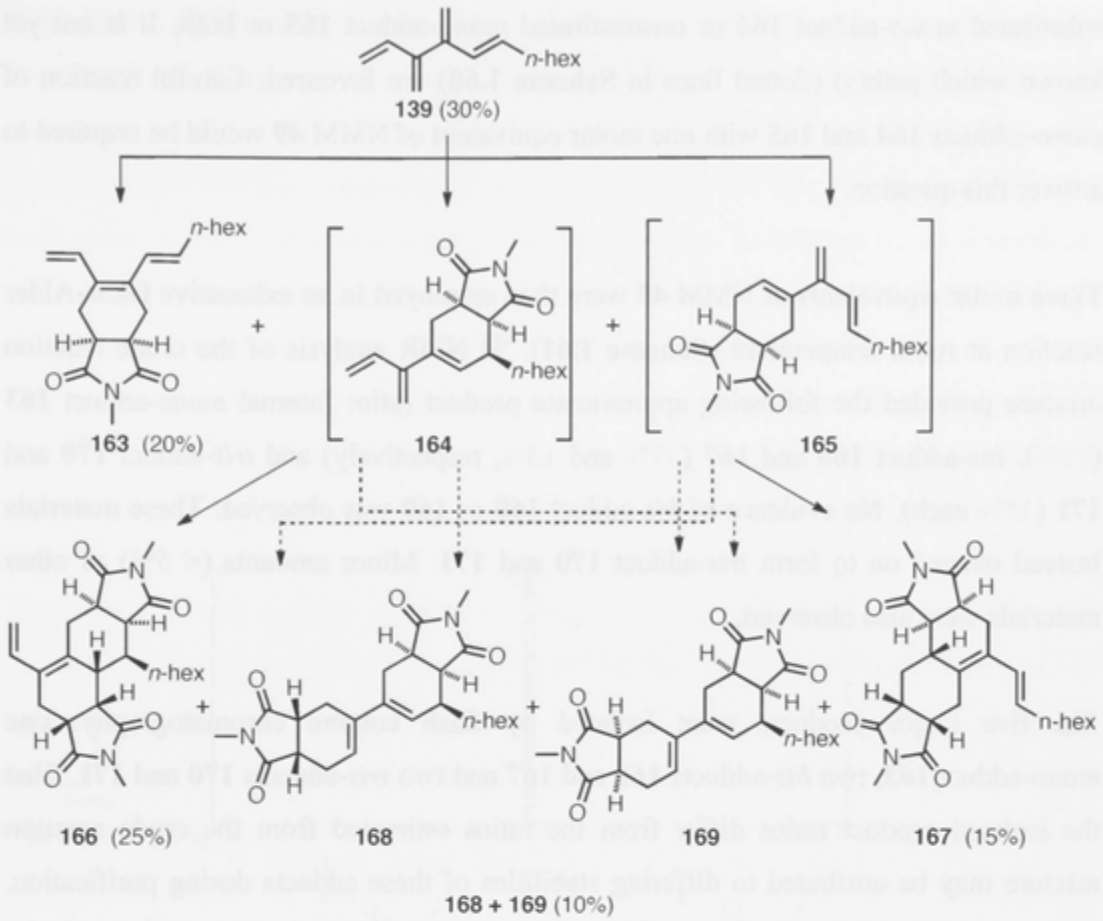
To our great frustration, all attempts at hydrogenation of both protected dienes **158** and **159** provided mixtures that were resistant to purification in our hands. CAN mediated oxidative deprotection of both substrate mixtures provided impure samples of 1-(*Z*)-hexyl [4]dendralene **140**. A useful 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 and 1-(*E*)-hexyl [4]dendralene **139** and one molar equivalent of NMM **49**. *Reagents and conditions:* (a) NMM (1 mol equiv), $CDCl_3$, rt, 117 hours. Yields estimated from the crude ^1H NMR spectrum.

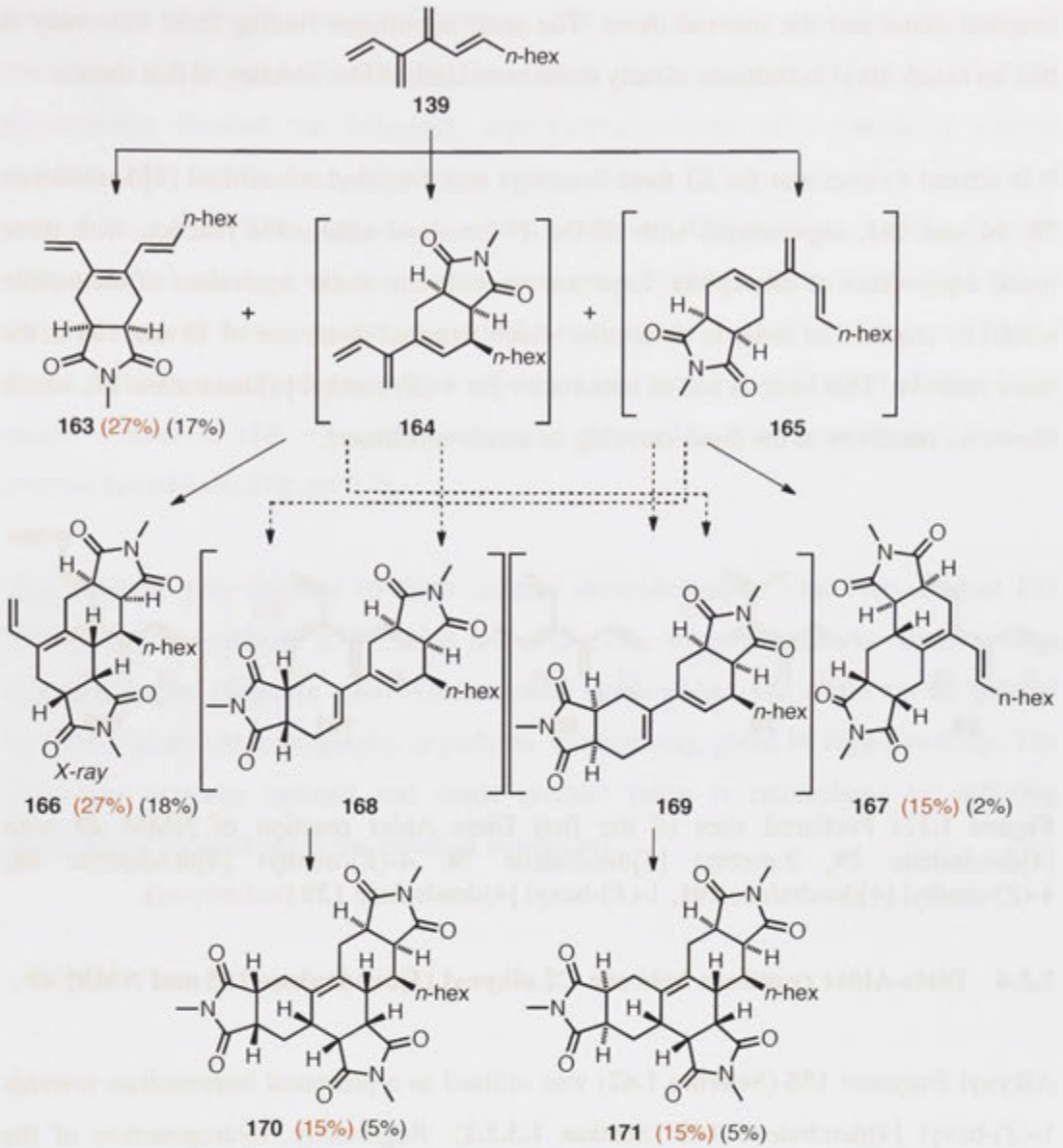
The reaction is clearly not selective for mono addition. *Mono*-adducts **164** and **165**, substituted [3]dendralenes, were not observed and instead reacted on to form *bis*-adducts **166** and **167**, respectively. **168** and **169** are also formed from these *mono*-adducts. This is unsurprising, since it is known that [3]dendralenes are, as a group, more reactive than [4]dendralenes.[34] 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 and 1-(*E*)-hexyl [4]dendralene **139** and an excess of NMM **49**. *Reagents and conditions:* (a) NMM (3 mol equiv), $CDCl_3$, 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 constrast, 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.

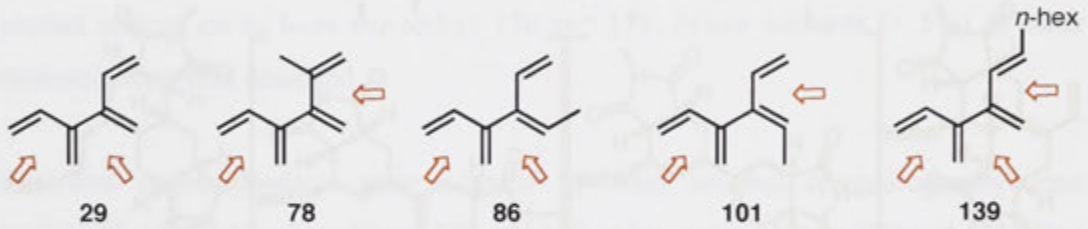
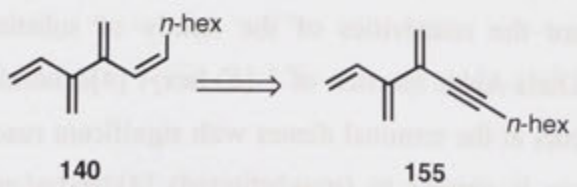


Figure 1.12: Preferred sites of the first Diels Alder reaction of NMM **49** with [4]dendralene **29**, 2-methyl [4]dendralene **78**, 4-(*E*)-methyl [4]dendralene **86**, 4-(*Z*)-methyl [4]dendralene **101**, 1-(*E*)-hexyl [4]dendralene **139** (red arrows).

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

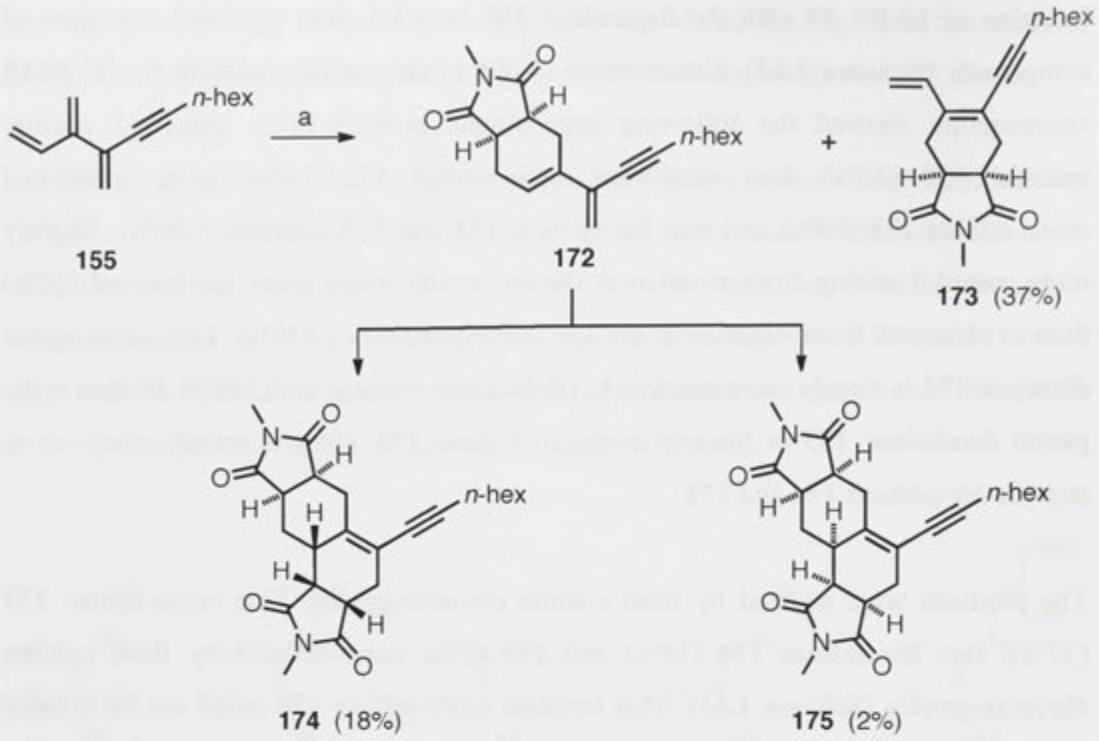
Alkynyl fragment **155** (**Scheme 1.62**) was utilised as a protected intermediate towards 1-(*Z*)-hexyl [4]dendralene **140** (**Section 1.3.2.2**). Regrettably, hydrogenation of the cross-conjugated alkyne proved problematic, hence we were unable to synthesise **140**. Nevertheless, since **155**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



Scheme 1.62: Retrosynthetic analysis of 1-(*Z*)-hexyl [4]dendralene **140**.

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.



Scheme 1.63: Diels-Alder reaction of 2-octynyl [3]dendralene **155** with NMM **49**. *Reagents and conditions:* (a) NMM (1 mol equiv), $CDCl_3$, 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)[19] (**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.

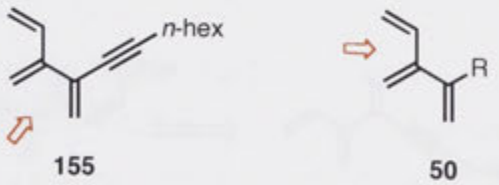
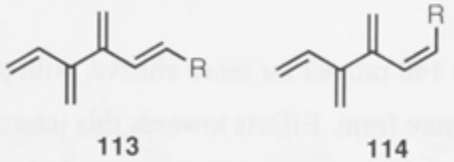


Figure 1.13: Preferred sites of reaction of NMM **49** (red arrows) for 2-octynyl [3]dendralene **155** and other substituted [3]dendralenes **50**. (R= alkyl, and EDG and EWG aryl groups).

1.4 Conclusions

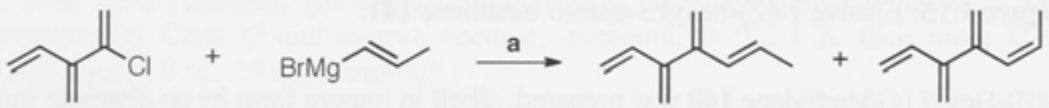
The first aim of this project involved the syntheses of 1-(*E*)- and (*Z*)-alkyl substituted [4]dendralenes **113** and **114**, the remaining undescribed members of the substituted [4]dendralene family (**Figure 1.14**).



113 **114**

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

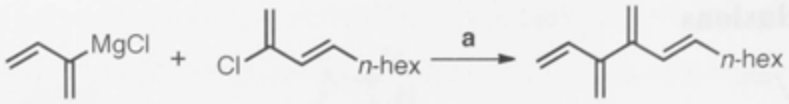
Evidence for the formation of a mixture of 1-(*E*)- and 1-(*Z*)-methyl [4]dendralenes **115** and **130** was observed following a KTC coupling reaction (**Scheme 1.64**). Frustratingly, in our hands, repeated attempts at separation of these two regioisomers met with failure.



37 **129** **115** **130**

Scheme 1.64: An attempt to synthesise 1-(*E*)-methyl [4]dendralene **115**. *Reagents and conditions:* (a) Grignard reagent (1.3 mol equiv), $Ni(dppp)Cl_2$ (0.10 mol equiv), PPh_3 (0.20 mol equiv), THF, 0 °C to rt, 5 h, (ratios **115**:**130**, 45:55).

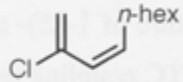
The 1-(*E*)-hexyl analogue was successfully produced by KTC coupling with the Grignard reagent **34** derived from chloroprene **40** and chloro-substituted diene **136** (**Scheme 1.65**). This approach incorporated the (*E*)- configuration at the terminal alkene within starting diene **136**.



34 136 139

Scheme 1.65: Preparation of 1-(*E*)-hexyl [4]dendralene **139**. *Reagents and conditions:* (a) Grignard reagent (3 mol equiv), PPh_3 (0.05 mol equiv), $Ni(dppp)Cl_2$ (0.05 mol equiv), THF, –12 °C to 22 °C, 5.5 h, 53%.

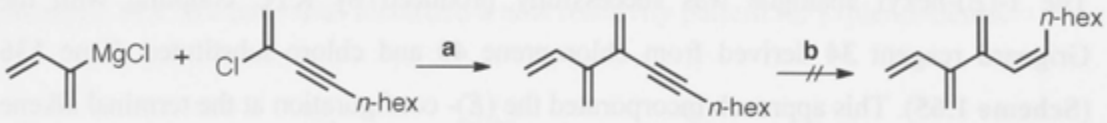
The 1-(*Z*)-hexyl analogue **140** proved far more elusive, with pure (*Z*)-chloro-substituted diene **141** unavailable in pure form. Efforts towards this intermediate included KTC and Suzuki-Miyaura coupling based methods. Frustratingly, all met with the production of inseparable mixtures, often in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



141

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.

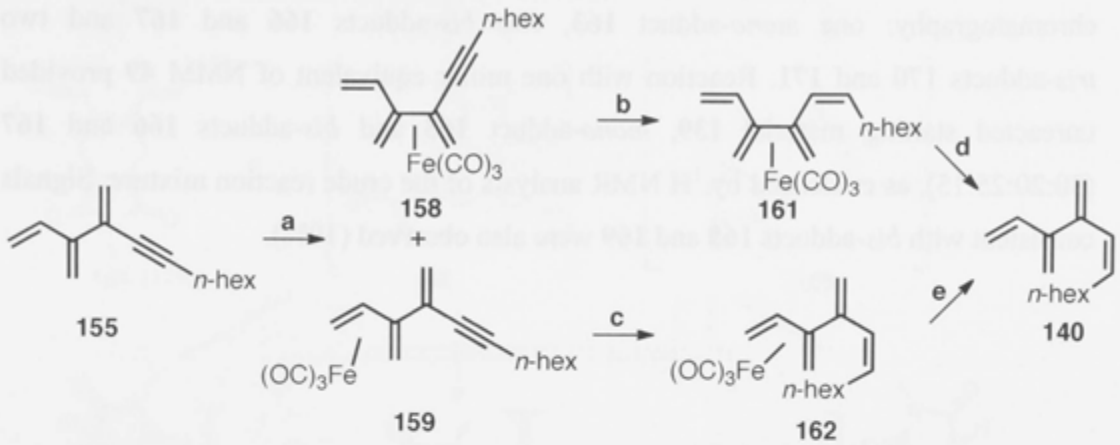


34 151 155 140

Scheme 1.66: Attempted formation of 1-(*Z*)-hexyl [4]dendralene **140**. *Reagents and conditions:* (a) Chloroprene Grignard reagent (3 mol equiv), PPh_3 (0.05 mol equiv), $Ni(dppp)Cl_2$ (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) $Fe_2(CO)_9$ (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) H_2, Lindlar catalyst, pentane, in the dark, rt, 6 h, 82% (impure); (c) H_2, 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**).

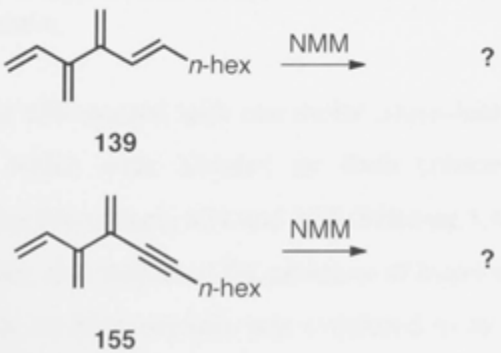
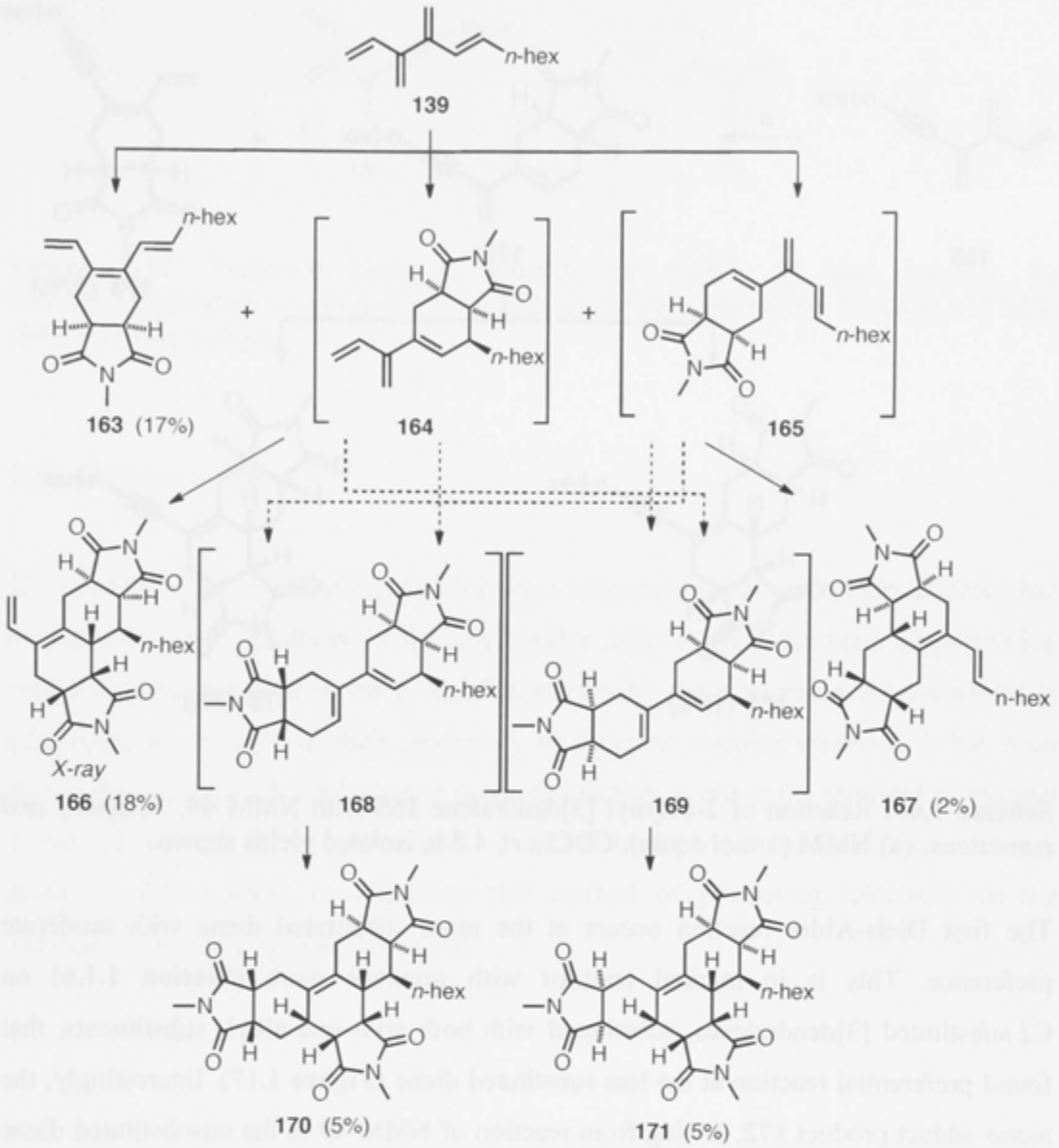


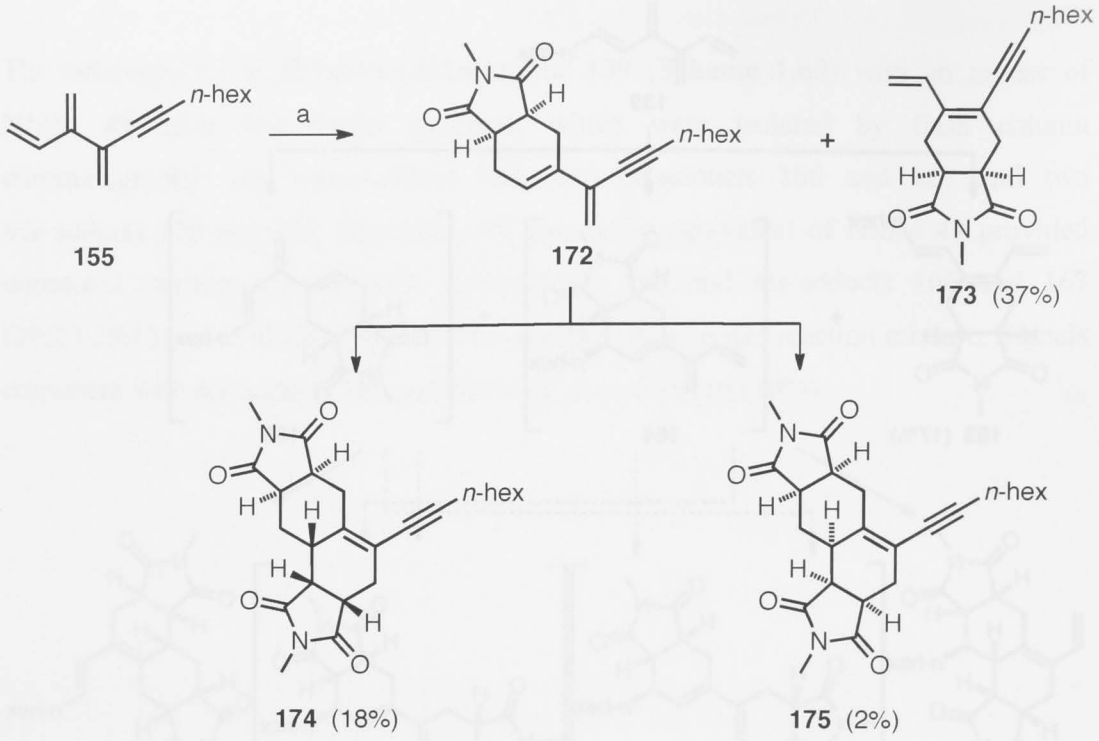
Figure 1.16: Diels-Alder reactions of 1-(*E*)-hexyl [4]dendralenes **139** and of 2-octynyl [3]dendralene **155**.

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 and 1-(*E*)-hexyl [4]dendralene **139** and an excess of NMM **49**. *Reagents and conditions:* (a) NMM (3 mol equiv), $CDCl_3$, 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**). ^{1}H NMR analysis of the crude reaction mixture also indicated the presence of *mono*-adduct **172**. The product distrubution of the crude reaction mixture was estimated to be **155** (10%), **172** (10%), **173** (50%) and two **174** and **175** (combined 30%) by ^{1}H NMR analysis.



Scheme 1.69: Reaction of 2-octynyl [3]dendralene **155** with NMM **49**. *Reagents and conditions:* (a) NMM (1 mol equiv), $CDCl_3$, 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.

155 50

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.

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.[12] Future work should therefore focus on exploring this method of promoting selectivity in the reactions of substituted [4]dendralenes.

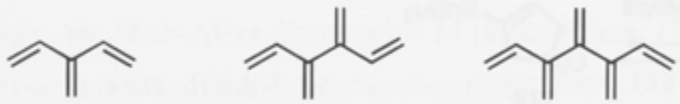
Chapter 2

Exploratory Investigations Into Total Synthesis Using [5]Dendralenes

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.



28 **29** **176**
[3]dendralene **[4]dendralene** **[5]dendralene**

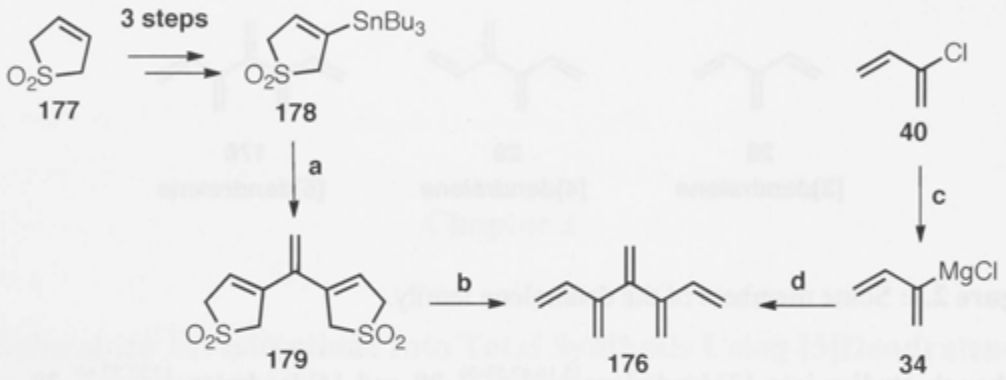
Figure 2.1: Some members of the dendralene family.

Although studies into [3]dendralene[15,16,47,53-56] **28** and [4]dendralene[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.[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.[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. Cheleotropic 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[22,23] (KTC) cross-coupling reaction.[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.[61]



Scheme 2.1: Synthesis of [5]dendralene **176**. *Reagents and conditions:* (a) CH_2CBr_2 (0.50 mol equiv), $PdCl_2(CH_3CN)_2$ (0.050 mol equiv), DMF, 40 °C, Ar, 36 h, 11%; (b) 450 °C, 65%; (c) magnesium turnings, BrC_2H_4Br, $ZnBr_2$, THF; (d) CH_2CCl_2 (1.0 mol equiv), Grignard reagent (3.5 mol equiv), $Ni(dppp)_2Cl_2$ (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.

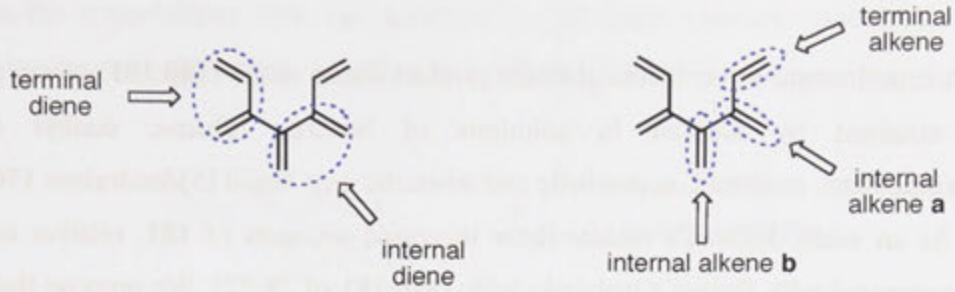
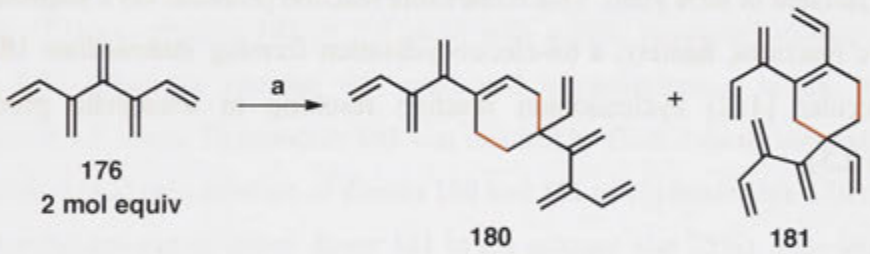


Figure 2.2: Diene and dienophile sites of [5]dendralene **176**.

The first study into Diels-Alder dimerisation of [5]dendralene **176** was conducted by Bojase.[20] Suprisingly, the Diels-Alder dimerisation of [5]dendralene **176** in CH_2Cl_2 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**.



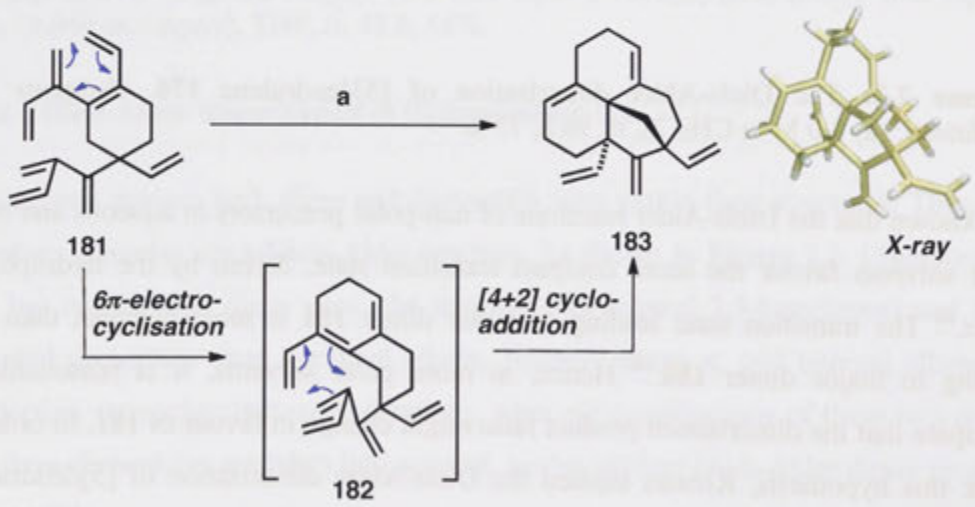
Scheme 2.2: The Diels-Alder dimerisation of [5]dendralene **176**. *Reagents and conditions*: (a) 5.0 M in CH_2Cl_2, rt, 96 h, 75%.

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.[62] The transition state leading to minor dimer **181** is more compact than that leading to major dimer **180**.[63] 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.[61]

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**.

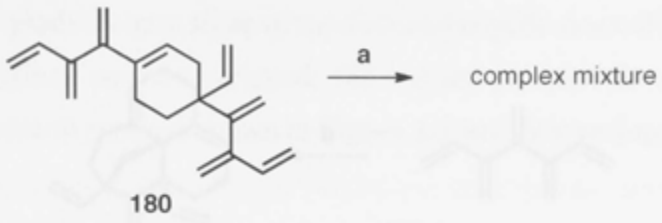
2.1.3 Synthesis of tetracycle 183

The first synthesis of a tetracycle from [5]dendralene **176** was performed by Bojase.[20] 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**).



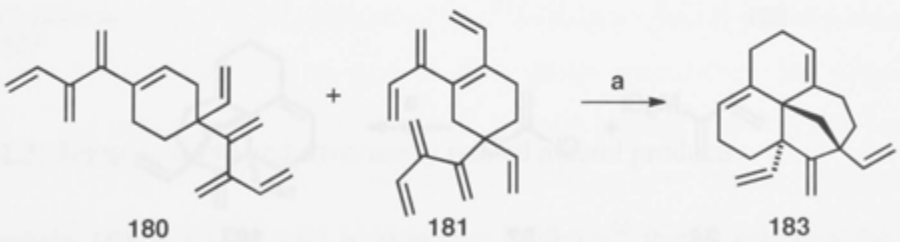
Scheme 2.3: Synthesis of tetracycle **183** and its X-ray crystal structure. *Reagents and conditions:* (a) PhCl, BHT, reflux, 24 h, 80%.

When the major dimer **180** was subjected to the same reaction conditions, only a complex mixture of products was observed (**Scheme 2.4**).



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

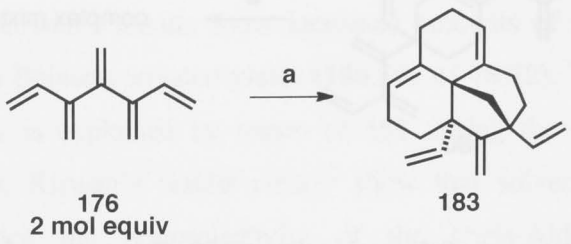
The lack of large quantities of tetracycle **183** was an impediment to further studies. Kirwan optimised the reaction conditions and synthesised larger amounts of tetracycle **183**.[61] The first improvement was the synthesis of tetracycle **183** directly from the mixture of dimers **180** and **181**. 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**.



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

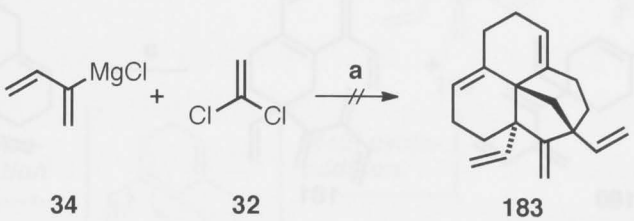
target product **183** was isolated by flash column chromatography in 9% yield based on [5]dendralene **176** (**Scheme 2.6**). 1.5 g of tetracycle **183** was synthesised using this method.



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 tetracylic 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), PPh_3 (0.050 mol equiv), $Ni(dppp)Cl_2$ (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.

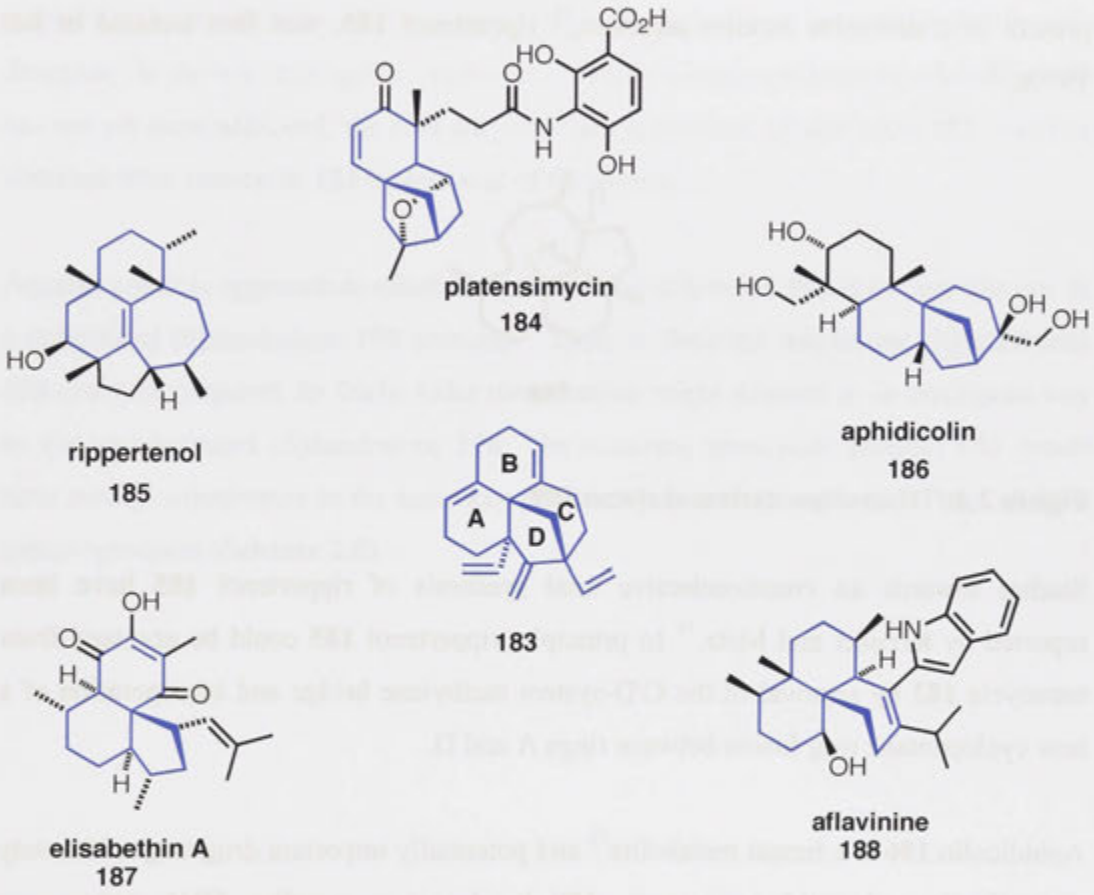
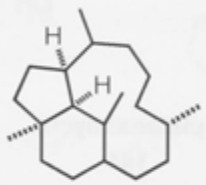


Figure 2.3: Tetracycle **183** and structurally related natural products.

Platensimycin **184** is a fatty acid biosynthesis inhibitor[64] that is selective for FabF.[65] This natural product has activity against Gram-positive bacteria and analogues have also shown antibacterial properties.[65] 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]



189

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.

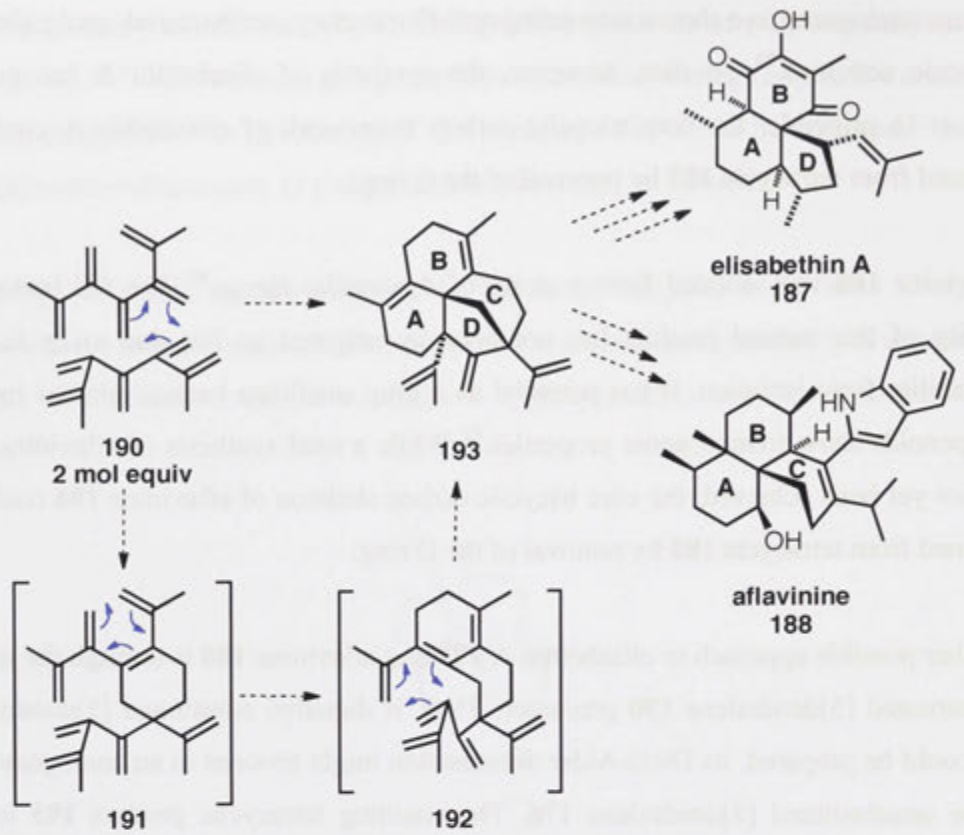
Aphidicolin **186** is a fungal metabolite[73] and potentially important drug target. Not only an antibotic and anti-herpes agent, **186** is also a mammalian DNA polymerase inhibitor.[74] Its activity against several cancer lines has been reported.[75] The first enantioselective formal total synthesis 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 *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-flammatory, antibacterial, analgesic, and cytotoxic activities.[79] 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*.[80] 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.[81] 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.

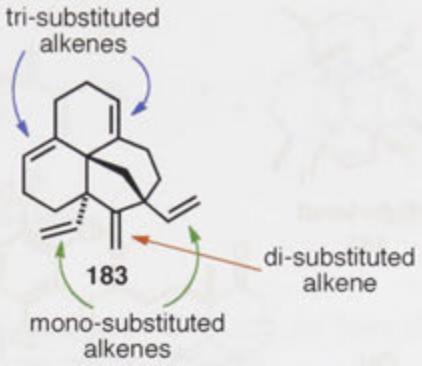
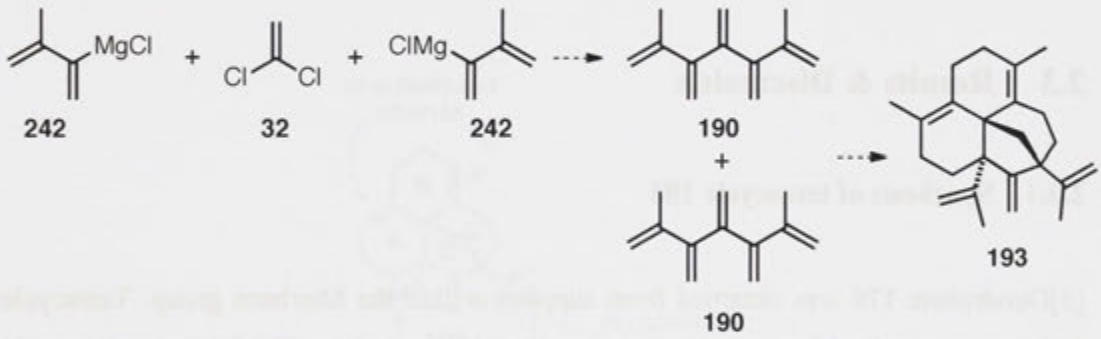


Figure 2.5: Tetracycle **183**.

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.



Scheme 2.9: Proposed synthesis of tetracycle **193**.

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**.

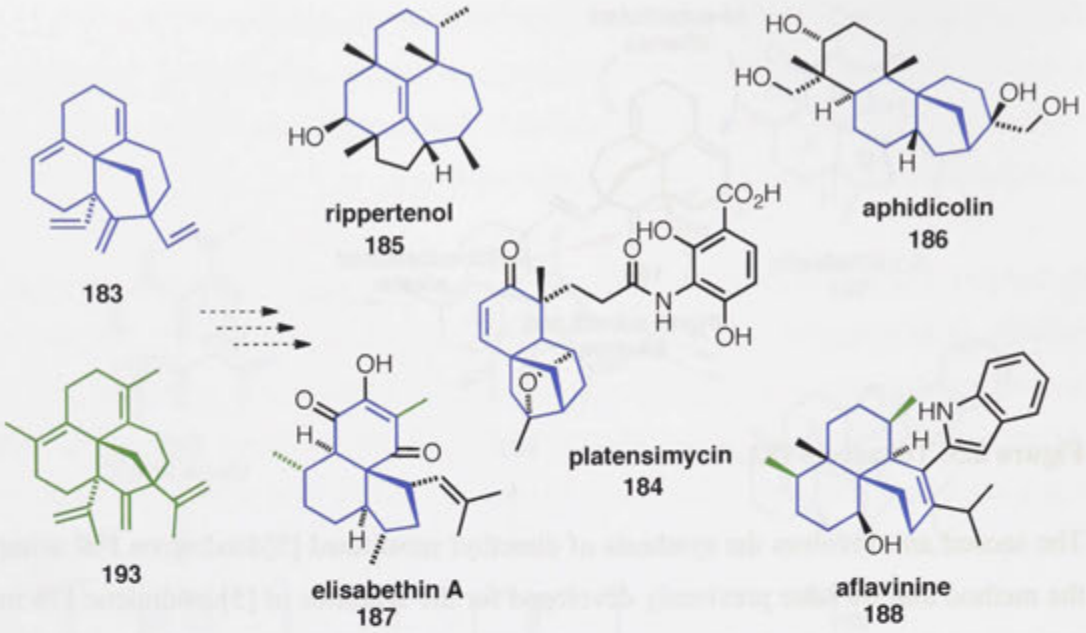
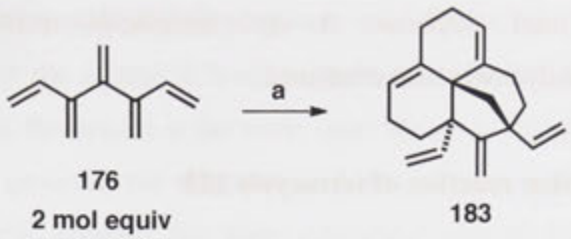


Figure 2.6: Tetracycle **183**, tetracycle **193** and structurally related natural products.

2.3 Results & Discussion

2.3.1 Synthesis of tetracycle 183

[5]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.[61] 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[20] 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.

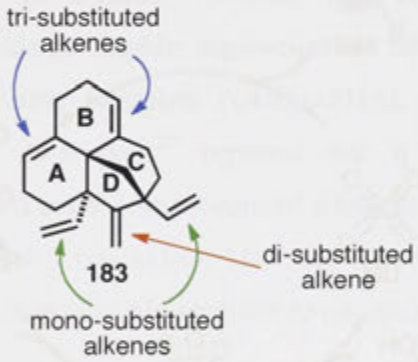


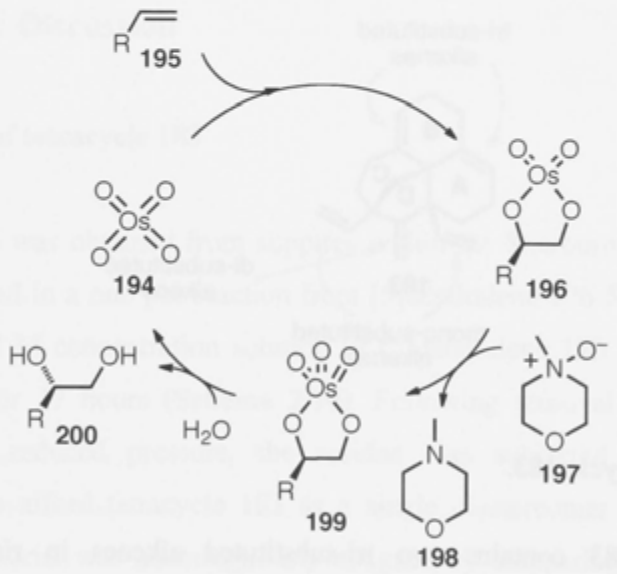
Figure 2.7: Tetracycle **183**.

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 OsO_4, *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.[5] 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.[82] 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**.[83] 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**).[84]



Scheme 2.11: Mechanism of dihydroxylation of an alkene using catalytic amounts of OsO_4 **194** with NMO **197** co-oxidant.[84]

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.[85] 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 $K_3Fe(CN)_6$ 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.

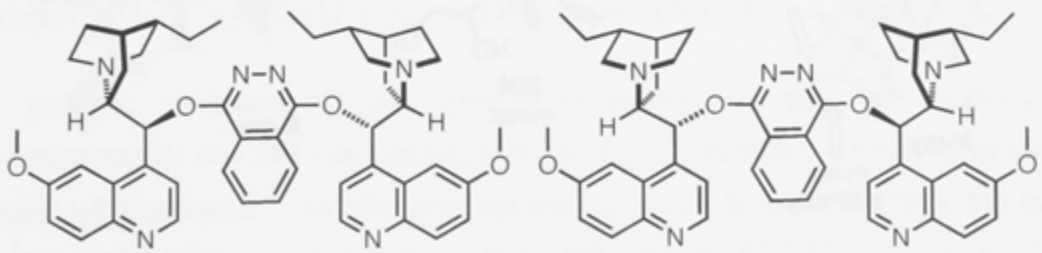
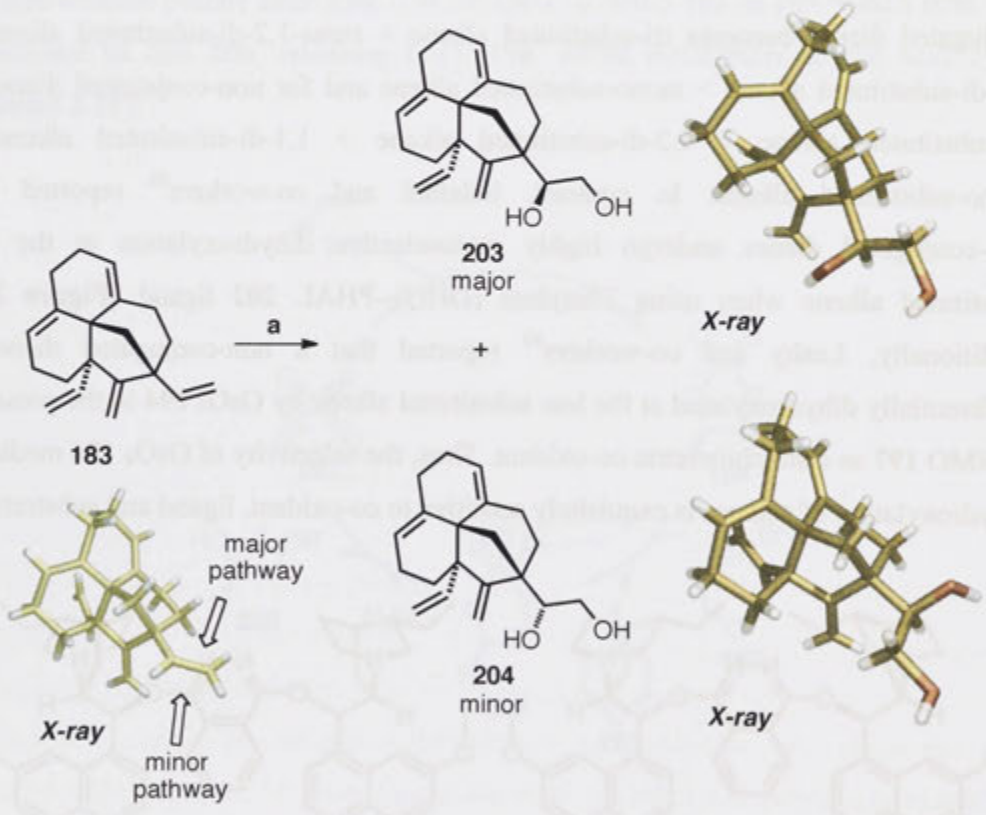


Figure 2.8: $(DHQD)_2$-PHAL **201** and $(DHQ)_2$-PHAL **202** ligands.

Tetracycle **183** was treated with 0.04 mol equiv of OsO_4 **194** in the presence of 2 mol equiv of NMO **197** in $THF/H_2O/t$-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**.



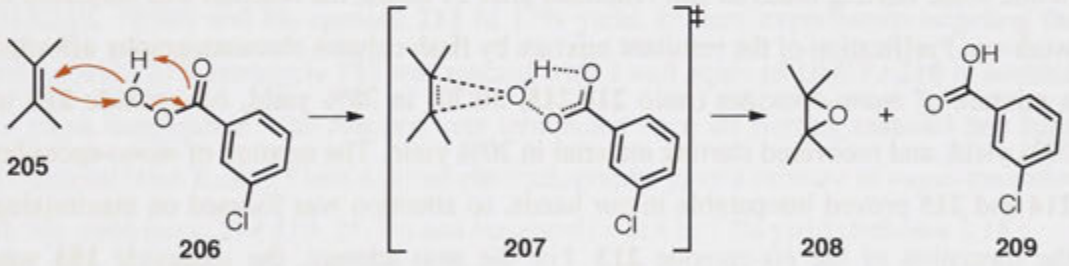
Scheme 2.12: Dihydroxylation reaction of tetracycle **183** and single X-ray crystal structures of the dihydroxylation products **203** and **204**. *Reagents and conditions:* (a) OsO_4 (0.04 mol equiv), NMO (2 mol equiv), THF/H_2O/*t*-BuOH (5:1:1 ratio), rt, 4 days, in the dark, 30%, **203**:**204** (*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[88] and Leahy.[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_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.

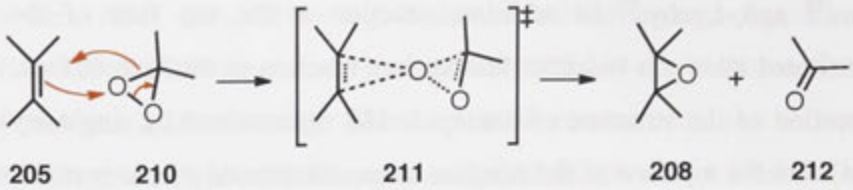
2.3.4 Epoxidation reactions of tetracycle 183

Epoxidation is a commonly used method for the oxidation of alkenes.[82] *m*-CPBA **206** is one of the most widely used reagents to effect this transformation.[14] The mechanism of epoxidation with *m*-CPBA **206** is shown in **Scheme 2.13**. An alkene's π-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 *m*-chlorobenzoic acid **209**.



Scheme 2.13: Epoxidation of an alkene **205** using *m*-CPBA **206**.[5]

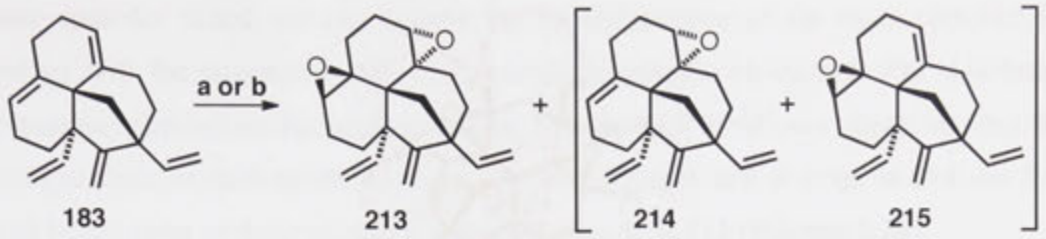
A potential limitation of this epoxidation protocol is that the by-product, *m*-chlorobenzoic acid **209** may participate in nucleophilic substitution reactions or even induce rearrangements.[85] An alternative reagent is dimethyldioxirane (DMDO) **210** that is also used for the epoxidation of an alkene **205** (**Scheme 2.14**).[90,91] In contrast with *m*-CPBA **206**, the by-product of epoxidations using DMDO **210** is relatively unreactive acetone **212**.



Scheme 2.14: Epoxidation of an alkene **205** using DMDO **210**.[91]

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.[92,93] 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.

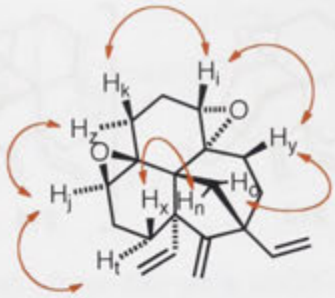
Various reaction conditions using the two different epoxidizing reagents were tested in order to investigate which alkenic sites of tetracycle **183** would be epoxidised. Tetracycle **183** was treated with 1 mol equiv of *m*-CPBA **206** in CH_2Cl_2 at –20 °C. While some starting material still remained 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_2Cl_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_2Cl_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**.



213

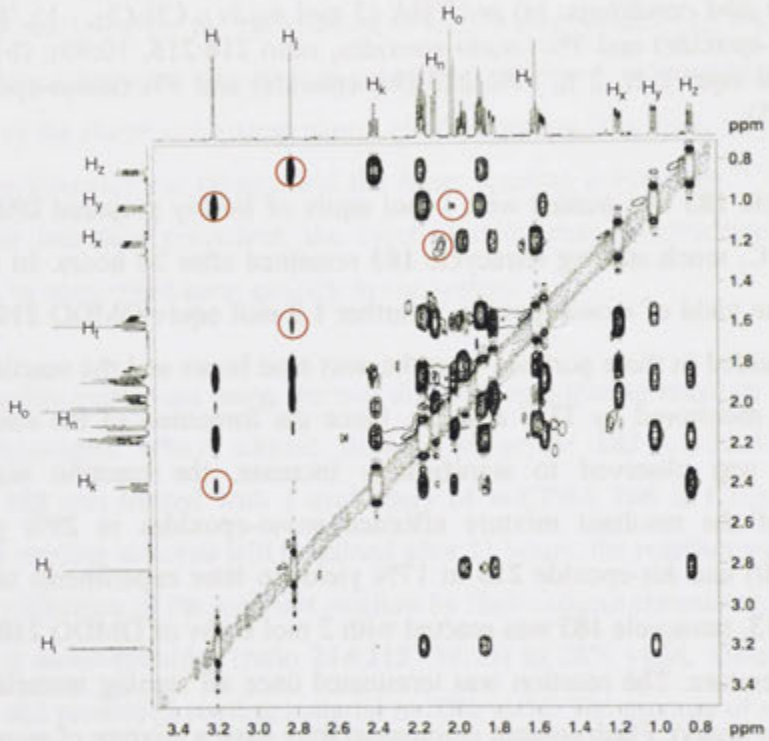
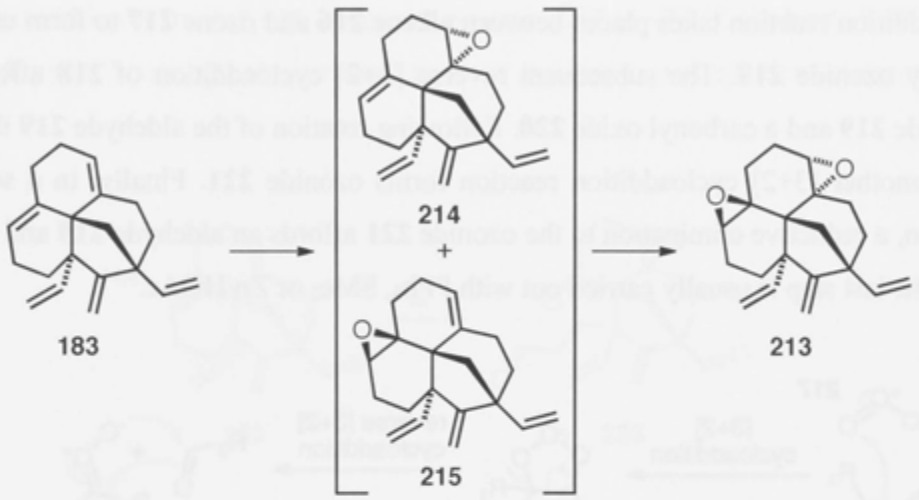


Figure 2.9: NOESY spectrum of *bis*-epoxide **213**. nOe cross-peaks highlighted in red are due to the spatial correlations indicated by red arrows.

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**).



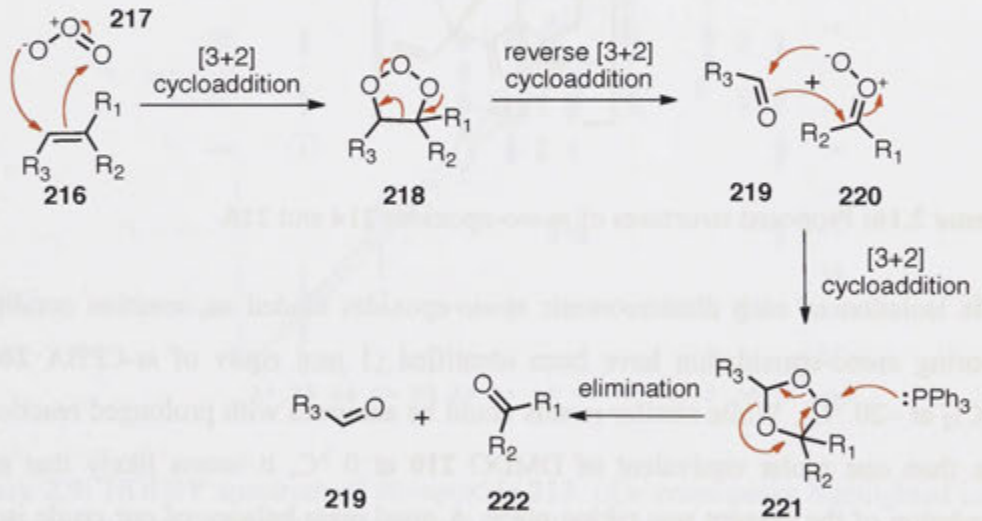
Scheme 2.16: Proposed structures of *mono*-epoxides **214** and **215**.

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 CH_2Cl_2 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 ^{1}H 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.[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**).[94] The first [3+2] cycloaddition reaction takes places 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.[5,14]



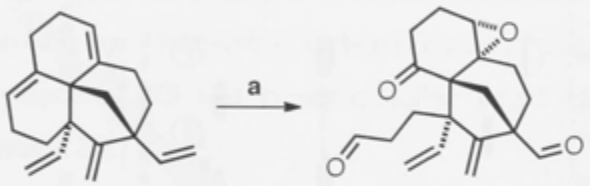
Scheme 2.17: The mechanism of alkene ozonolysis.[94]

Pryor and co-workers[95] observed that ozone **217** is an electron poor reagent and more reactive towards more electron rich alkenes. Bailey and Lane[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 tetracyle **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.

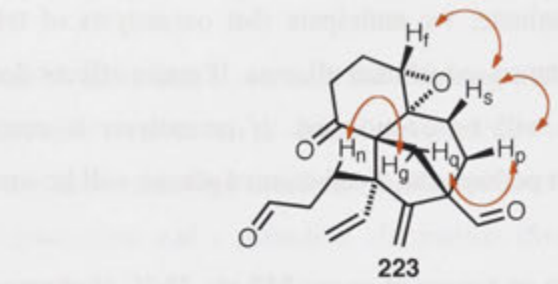
Tetracycle **183** was treated with an excess of ozone **217** at –78 °C (**Scheme 2.18**). After flash column chromatography, product **223** was isolated as a single diastereomer in 8% yield.



183 **223**

Scheme 2.18: Ozonolysis reaction of tetracycle **183**. *Reagents and conditions:* (a) O_3 (excess), CH_2Cl_2, 15 min, –78 °C, then PPh_3 (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 $C_{19}H_{22}O_4$. 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 (1H, 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 ^{13}C 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**.



223

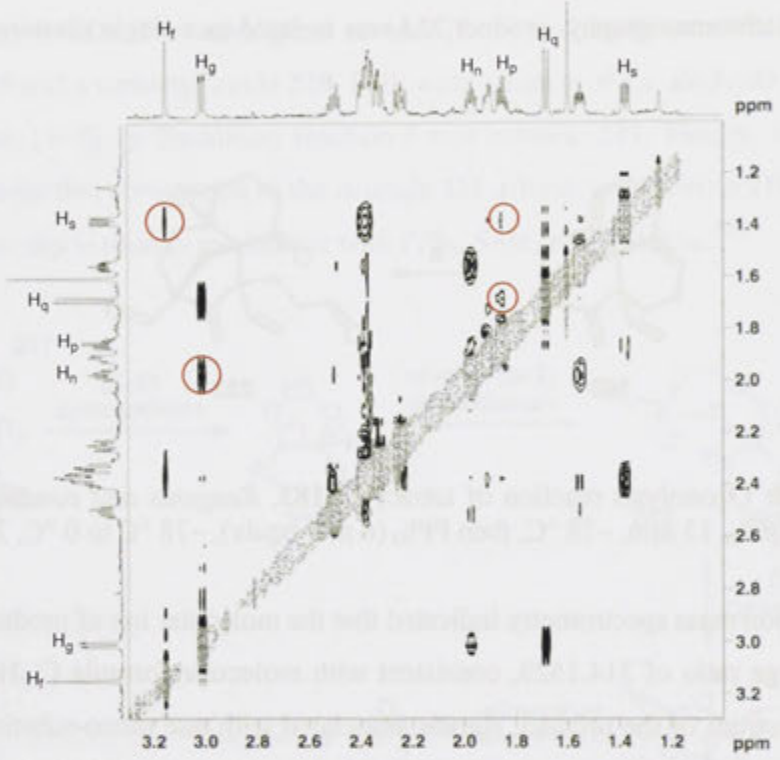
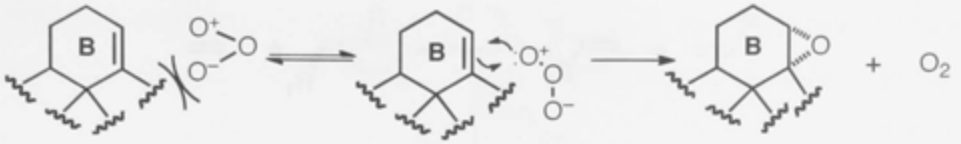


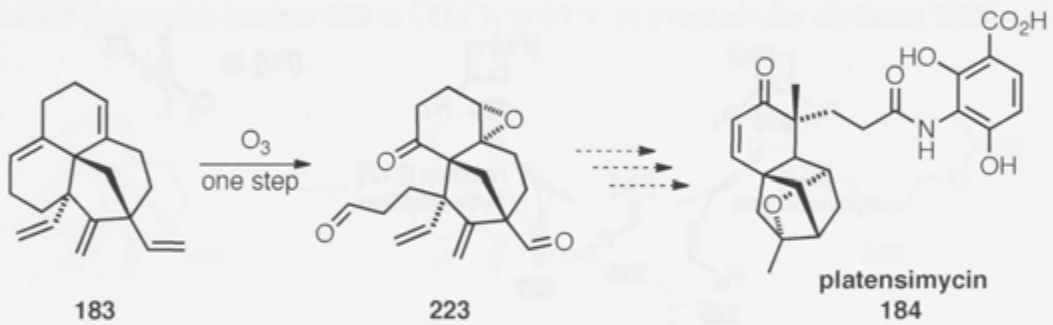
Figure 2.10: NOESY spectrum of the compound **223**. nOe cross-peaks highlighted in red are associated with the spatial correlations indicated by red arrows.

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 endocylic 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**).[97]



Scheme 2.19: Proposed mechanism for epoxidation of the sterically hindered B-ring alkene during the ozonolysis.[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**).



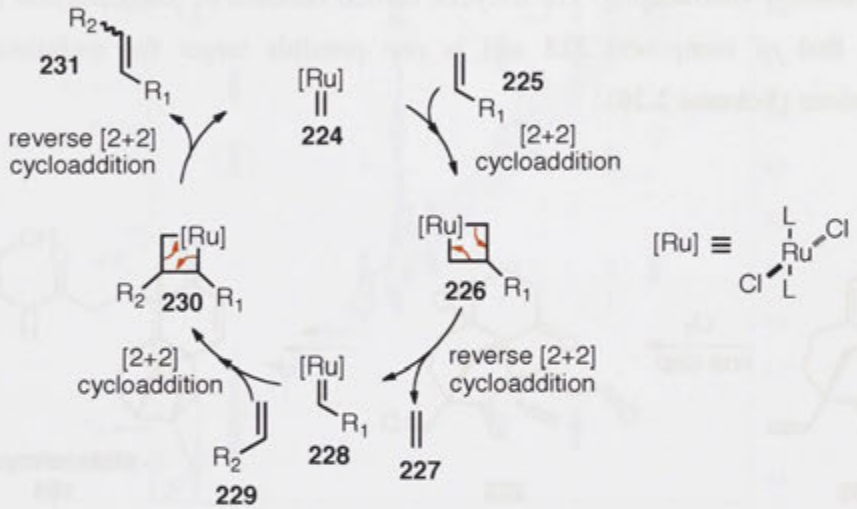
Scheme 2.20: From tetracycle **183** to platensimycin **184**.

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.[98] Nobel laureate Robert Grubbs prepared families of ruthenium based carbenoid catalysts for these reactions.[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.[35]

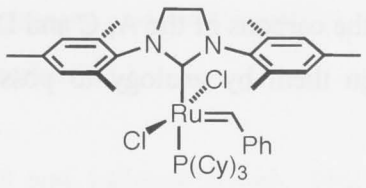
Scheme 2.21: Alkene cross-metathesis reaction: general transformation.[98]

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]

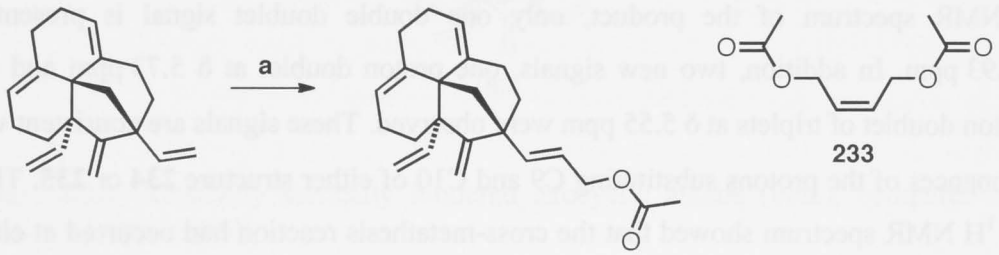
By varying the steric and electronic properties of the ligands (L) appended to the ruthenium centre, various reactivity profiles have been observed.[99] For instance, Grubbs's second-generation catalyst **232** (**Figure 2.11**), is particularly fast reacting in the cross-metathesis of alkenes.[99]



232

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 CH_2Cl_2 at 60 °C in a sealed tube (**Scheme 2.23**).



183 235 233

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), CH_2Cl_2, 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 **183** and may assign them by analogy to possible structures **234** and **235** (**Figure 2.12**).

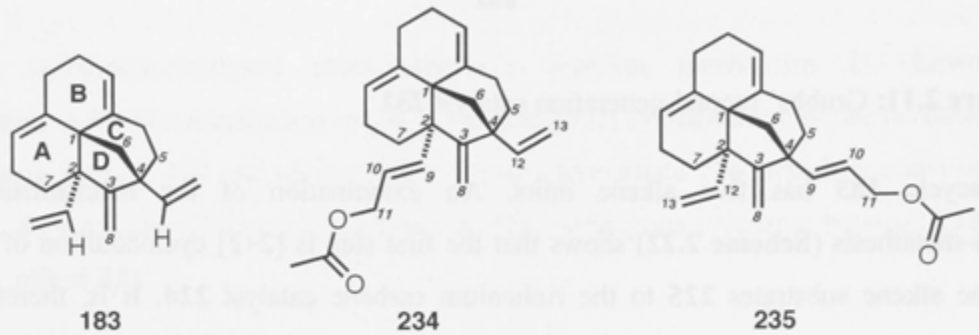


Figure 2.12: Starting material **183** and two possible cross-metathesis products **234** and **235**.

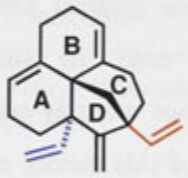
The ^{1}H NMR spectrum of starting material **183** has two double doublets at δ 5.89 and 5.85 ppm, assigned to the methine protons of the two vinyl groups of **183**. In the ^{1}H NMR spectrum of the product, only one double doublet signal is present at δ 5.93 ppm. In addition, two new signals, one proton doublet at δ 5.73 ppm and one proton doublet of triplets at δ 5.55 ppm were observed. These signals are consistent with resonances of the protons substituting C9 and C10 of either structure **234** or **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 **183**, (*ie* compound **234**) or that attached to the C/D ring junction, (*ie* compound **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 **234** or **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.

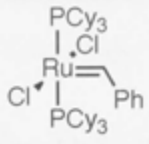


183

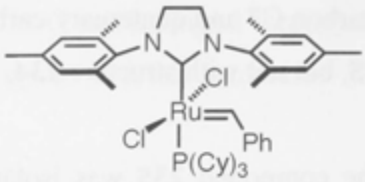
Figure 2.13: Relatively sterically hindered exocyclic alkene (blue), compared with unhindered alkene (red).

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.

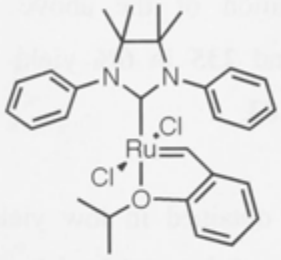
Despite the poor isolated yield of **235**, the fact that a product of selective cross-methathesis may be isolated at all is cause for optimism. Careful exploration of the system, using various conditions, especially changing the catalyst (**Figure 2.14**), may reasonably be anticipated to yield fruitful results.



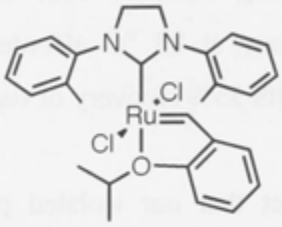
236



232



237

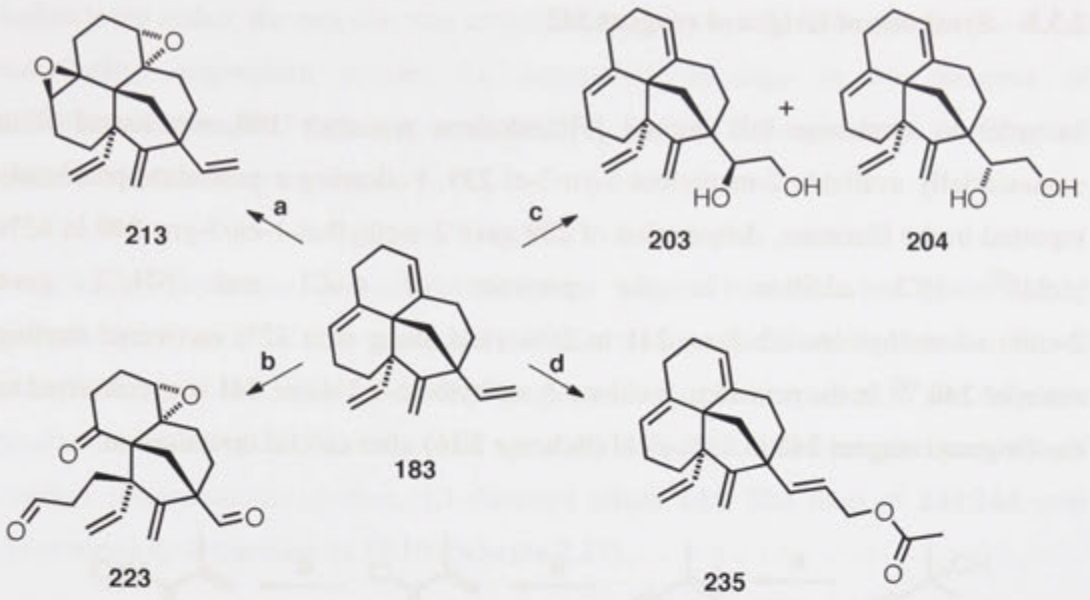


238

Figure 2.14: Candidate catalysts for the alkene cross-metathesis.[100]

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**).

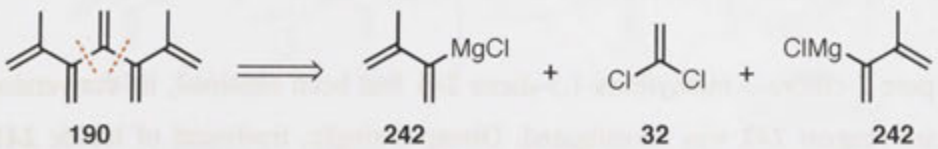
In summary, the work described in this section demonstrates selective manipulation of tetracycle **183** (**Scheme 2.24**), successfully achieving the first stated aim of this project. Dihydroxylation and cross-metathesis reactions proceed only at the *mono*-substituted alkene on C/D ring junction. While 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.



Scheme 2.24: 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) O_3 (excess), CH_2Cl_2, 15 min, –78 °C, then PPh_3 (6 mol equiv), –78 °C to 0 °C, 30 min, 8%; (c) OsO_4 (4.1% in H_2O solution) (0.04 mol equiv), THF/H_2O/*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), CH_2Cl_2, 60 °C, 24 h, 13%.

2.3.7 Retrosynthesis of dimethyl substituted [5]dendralene 190

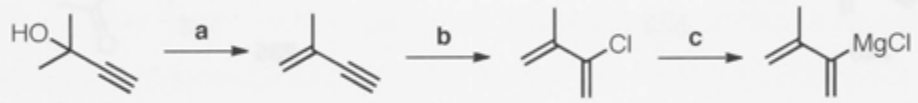
As described in **Scheme 2.1**, [5]dendralene **176** was obtained *via* a double Kumada-Tamao-Corriu cross-coupling reaction between the Grignard reagent **34** derived from chloroprene **40** and 1,1-dichloroethylene **32**. We proposed that if we are able to synthesise the Grignard reagent **242**, 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**.



Scheme 2.25: Retrosynthetic analysis of dimethyl substituted [5]dendralene **190**.

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.[101] HCl addition in the presence of CuCl and NH_4Cl gave 2-chloro-3-methylbuta-1,3-diene **241** in 26% yield along with 32% recovered starting material **240**.[102] 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.



239 **240** **241** **242**

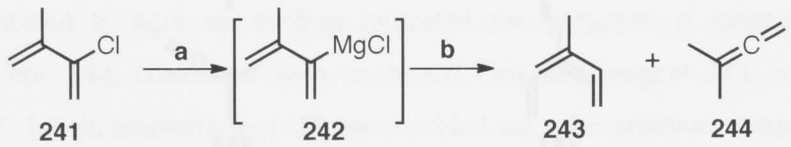
Scheme 2.26: Synthesis of Grignard reagent **242**. *Reagents and conditions*: (a) 2-Methyl-3-butyn-2-ol (1.0 mol equiv), Ac_2O (1.3 mol equiv), *p*-TsOH (0.040 mol equiv), 1 h, 63%; (b) 2-methylbut-1-en-3-yne (1.0 mol equiv), conc. HCl (1.0 mol equiv), CuCl (0.20 mol equiv), NH_4Cl (0.20 mol equiv), 20 °C, 75 min, 26%; (c) 2-chloro-3-methylbuta-1,3-diene (1.0 mol equiv), magnesium powder (2.9 mol equiv), BrC_2H_4Br (0.70 mol equiv), $ZnBr_2$ (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 NH_4Cl 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. Dissapointingly, treatment of halide **241** with magnesium turnings in the presence of 1,2-dibromoethane and $ZnBr_2$ 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**.[103] When more 1,2-dibromoethane, $ZnBr_2$, and

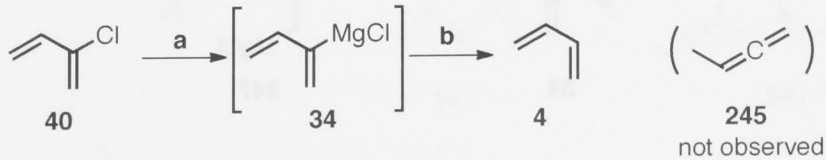
iodine were added, the reaction was complete at 17 hours. Gratifyingly, we found that substituting magnesium powder for magnesium turnings in the presence of 1,2-dibromoethane and $ZnBr_2$ at reflux in THF, resulted in formation of the Grignard reagent **242** in under two hours.

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 $CDCl_3$ 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**).



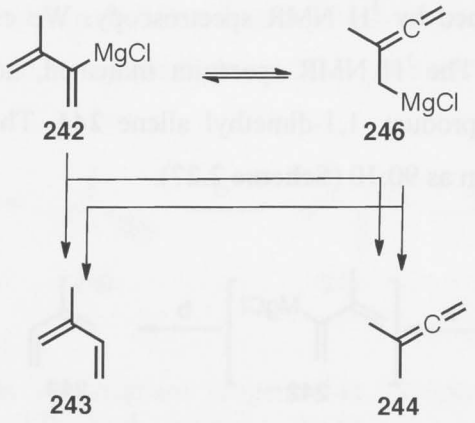
Scheme 2.27: The formation of Grignard **242** reagent and its protonolysis products. *Reagents and conditions:* (a) Magnesium powder (2.9 mol equiv), BrC_2H_4Br (0.70 mol equiv), $ZnBr_2$ (0.030 mol equiv), THF, reflux, 75 min, 55%. (b) Quenched with water and diluted with $CDCl_3$, (ratio **243**:**244**, 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 Aufdermarsh[103] 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), BrC_2H_4Br (0.30 mol equiv), $ZnBr_2$ (0.010 mol equiv), THF, reflux, 2 h, 76%. (b) Quenched with water and diluted with $CDCl_3$. 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 sp^2 carbon-magnesium bond **242** or an sp^3 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 ^1H 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.

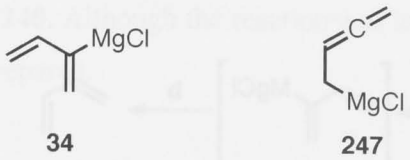


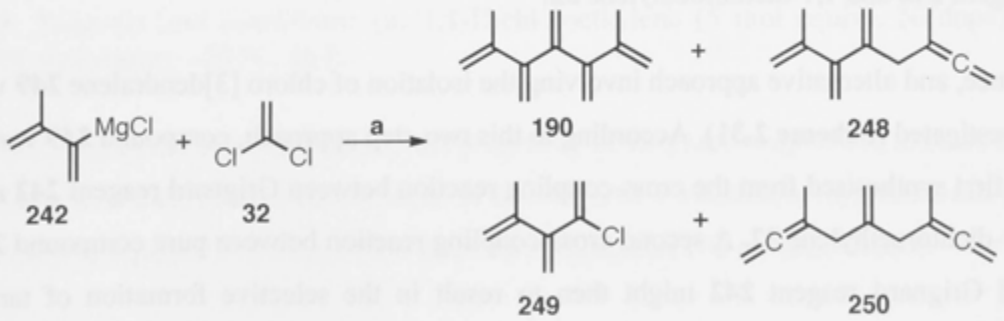
Figure 2.15: Grignard reagent **34** derived from chloroprene **40** and its allenic form **247**.

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 subtituted [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 $Ni(dppp)Cl_2$ and PPh_3 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.



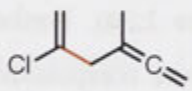
Scheme 2.30: Towards the synthesis of dimethyl substituted [5]dendralene **190**. *Reagents and conditions:* (a) (3-Methylbuta-1,3-dien-2-yl)magnesium chloride (3.0 mol equiv), 1,1-dichloroethylene (1.0 mol equiv), PPh_3 (0.050 mol equiv), $Ni(dppp)Cl_2$ (0.025 mol equiv), 15 °C to rt, 45 h.

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 $C_{12}H_{16}$. In addition, analysis of this symmetrical compound **190** by ^1H 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

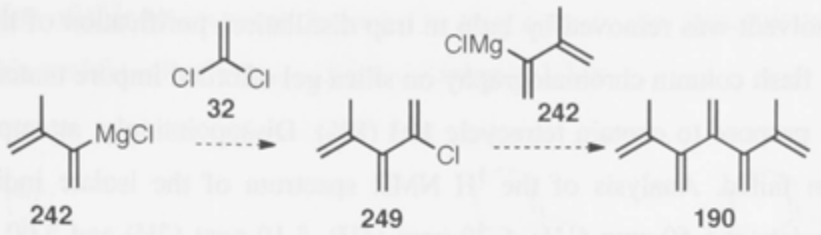
The problem was isolating **190** in the presence of isomeric hydrocarbons **248** and **250**, and 2-chloro-4-methyl substituted [3]dendralene **249**. It was proposed that **248** and **250** are the result of an initial coupling to give **251** (**Figure 2.16**).



251

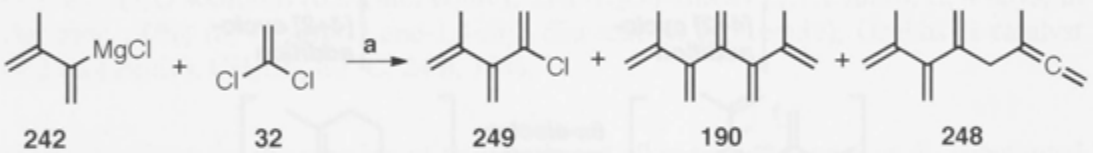
Figure 2.16: Proposed product of initial coupling between rearrangement Grignard reagent **246** and 1,1-dichloroethylene **32**.

Hence, and 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.[19] 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**).



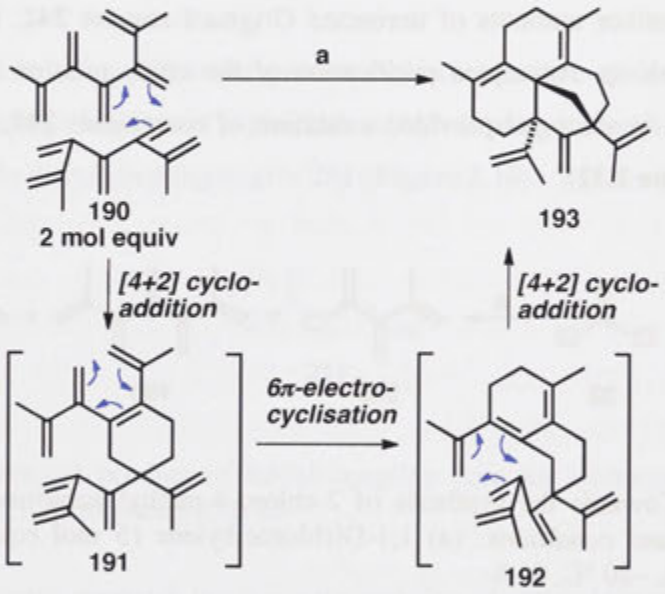
Scheme 2.32: Towards the synthesis of 2-chloro-4-methyl substituted [3]dendralene **249**. *Reagents and conditions:* (a) 1,1-Dichloroethylene (5 mol equiv), Ni(dppe)Cl_2 (0.01 mol equiv), –20 °C, 66 h.

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 bulp 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, 6π electrocyclisation, and intermolecular Diels-Alder reaction to provide tetracycle **193** (**Scheme 2.33**).

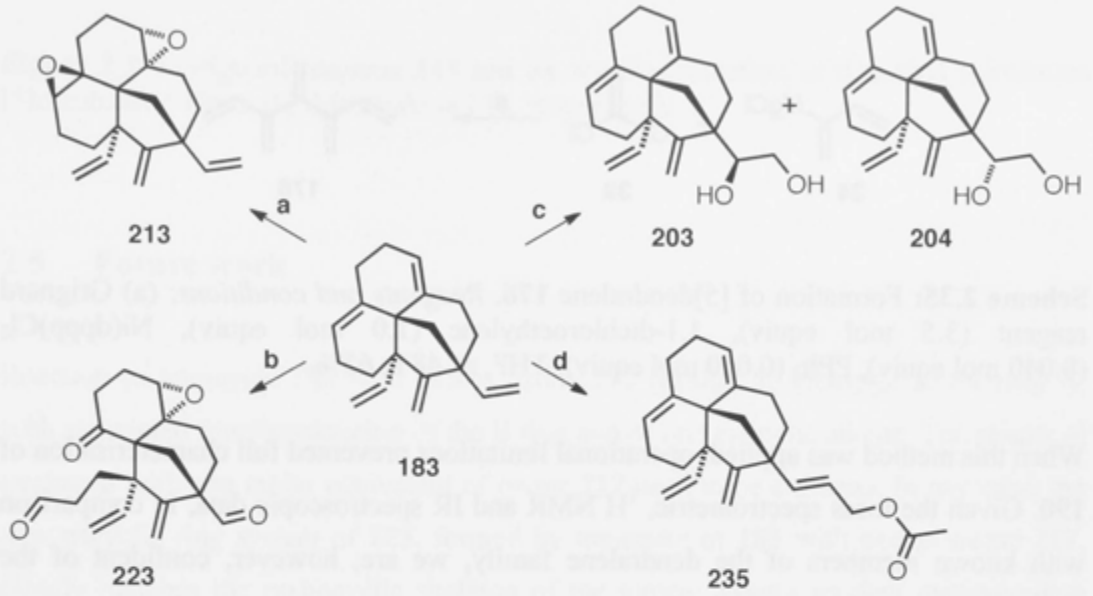


Scheme 2.33: Formation of tetracycle **193** from the Diels-Alder dimerisation of **190**. *Reagents and conditions:* (a) Mesitylene, reflux, 17 h.

2.4 Conclusions

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.

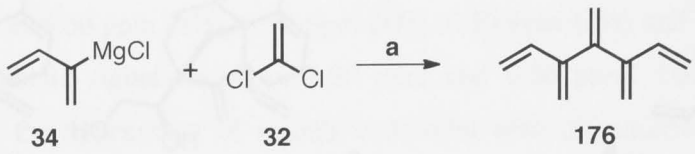
The first aim of this project was to look for selectivity in the manipulation of these alkenes. This goal has clearly been achieved (**Scheme 2.34**).



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) O_3 (excess), CH_2Cl_2, 15 min, –78 °C, then PPh_3 (6 mol equiv), –78 °C to 0 °C, 30 min, 8%; (c) OsO_4 (4.1% in H_2O solution) (0.04 mol equiv), THF/H_2O/*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), CH_2Cl_2, 60 °C, 24 h, 13%.

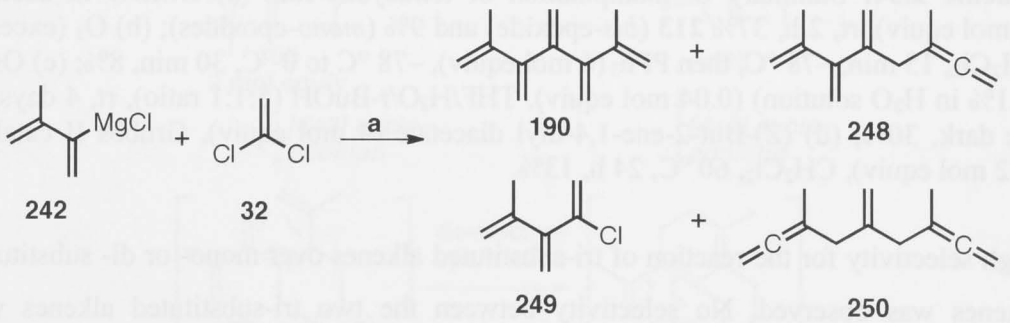
High selectivity for the reaction of tri-substituted alkenes over mono- or di- substituted alkenes was observed. No selectivity between the two tri-substituted alkenes was observed: isolation of pure *mono*-epoxides was not achieved within our limited timeframe. Conditions for the isolation of pure *bis*-epoxide **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**).



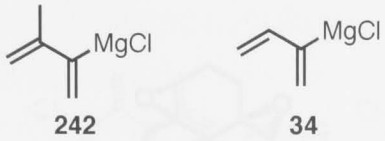
Scheme 2.35: Formation of [5]dendralene **176**. *Reagents and conditions:* (a) Grignard reagent (3.5 mol equiv), 1,1-dichloroethylene (1.0 mol equiv), $Ni(dppp)Cl_2$ (0.040 mol equiv), PPh_3 (0.040 mol equiv), THF, rt, 48 h, 65%.

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), PPh_3 (0.050 mol equiv), $Ni(dppp)Cl_2$ (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**).

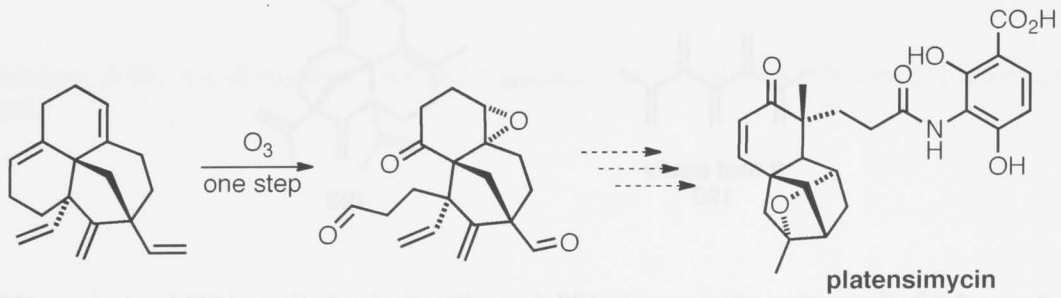


242 34

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

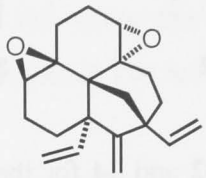
Reaction of tetracycle **183** with excess ozone **217** resulted in cleavage of the ring A, with associated functionalisation of the B ring and of one exocylic alkene. The results of treatment with one molar equivalent of ozone **217** need to be assessed. In any case, the new tricyclic ring system 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.



183 223 platensimycin 184

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.

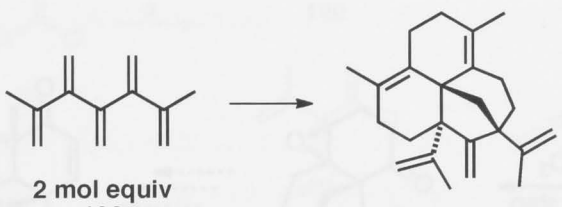


213

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**).

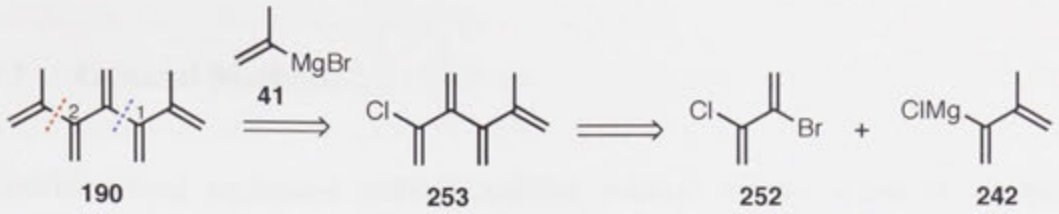


2 mol equiv
190

193

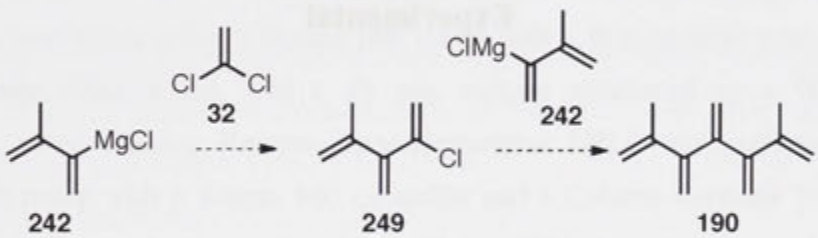
Scheme 2.38: Formation of tetracycle **193** from dimethyl substituted [5]dendralene **190**.

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**.



Scheme 2.39: Proposed retrosynthesis of dimethyl substituted [5]dendralene **190**.

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**).



Scheme 2.40: An alternative approach to synthesise dimethyl substituted [5]dendralene **190**.

Chapter 3

Experimental

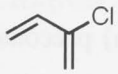
3.1 General Methods

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[90] procedure and used freshly. The dimethyldioxirane concentration was determined using a standart 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

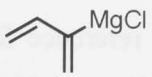
Chloroprene ***40***



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 $CaCl_2$ 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***

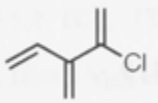


34

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,[106] indicated a 0.96 M solution of the *title compound* **34** in THF, hence a 76 % yield.

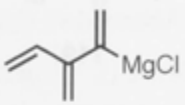
2-Chloro [3]dendralene 37



37

The *title compound* **37** was prepared according to a slightly modified literature procedure.[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_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_2O (300 mL) and 30-40 °C petrol (150 mL) and stirred for 15 minutes. Collected organic phase was then successively washed with 1 M *aq.* HCl (45 mL), sat. *aq.* $NaHCO_3$ (50 mL) and sat. *aq.* NaCl (50 mL), and then dried over anhydrous $MgSO_4$. Filtration and removal of the solvent under reduced pressure (20 mbar, 0 °C) afforded the *title compound* **37** (9.36 g, 81.7 mmol, 85 %) as a pale yellow oil. ^{1}H NMR data was consistent with that reported in the literature.[19]

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

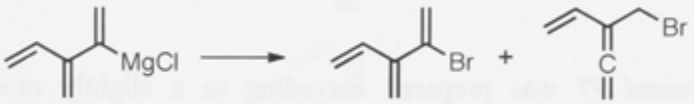


118

The *title compound* **118** was prepared according to a literature procedure.[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, $ZnBr_2$ (95 mg, 0.42 mmol, 0.030 mol equiv) was added. Material adhering to the sides of the flask was rinsed into

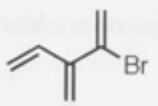
the reaction mixture with THF (1 mL). The reaction mixture was then heated to vigorous reflux upon which a solution of 2-chloro [3]dendralene **37** (1.6 g, 14 mmol, 1.0 mol equiv) and 1,2-dibromoethane (0.50 mL, 5.8 mmol, 0.40 mol equiv) in THF (20 mL) was added dropwise over 40 min. When the addition 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.

*Synthesis of 2-bromo [3]dendralene **119***



118 **119** **122**

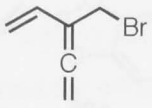
To a cooled suspension of freshly recrystalised NBS (0.89 g, 5.0 mmol, 3.0 mol equiv) in dry THF (5 mL) at –78 °C, a solution of (3-methylenepenta-1,4-dien-2-yl)magnesium chloride **118** (0.17 M, 10 mL, 1.7 mmol, 1.0 mol equiv) in THF was added slowly under argon gas atmosphere and stirred for 1.5 h. The reaction mixture was then poured onto sat. *aq.* Na_2CO_3 (50 mL) and stirred for 10 min at room temperature. After extraction with Et_2O (25 mL), the combined organic phases were dried over anhydrous $MgSO_4$ 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.



119

2-Bromo [3]dendralene **119**: R_f 0.40 (30-40 °C petrol); ^{1}H NMR (300 MHz, $CDCl_3$) 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; ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.5 (C), 129.1 (C), 120.1 (CH), 119.2 (CH_2), 118.0 (CH_2), 116.4 (CH_2) ppm; IR (thin film): ν_{max} = 3089, 2927, 1587, 1417 cm^{-1};

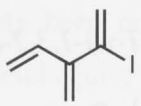
MS (70 eV, EI): *m/z* (%): 143 (3) $[M]^+$, 131 (19), 117 (38), 105 (18), 91 (44), 79 (100); HRMS: calc for C_6H_7Br $[M]^+$: 157.9731; found 157.9736.



122

3-(Bromomethyl)penta-1,2,4-triene **122**: R_f 0.45 (30-40 °C petrol); ^1H NMR (300 MHz, $CDCl_3$) δ 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; ^{13}C NMR (75 MHz, $CDCl_3$) δ 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): ν_{max} = 2929, 1635, 1415 cm^{-1}; MS (70 eV, EI): *m/z* (%): 157 (19) $[M]^+$, 143 (14), 129 (22), 57 (100); HRMS: calc for C_6H_7Br $[M]^+$: 157.9731; found 157.9726.

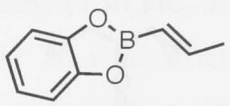
2-Iodo [3]dendralene ***120***



120

To a stirred solution of iodine (1.3 g, 5.0 mmol, 3.0 mol equiv) in dry Et_2O (10 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 an argon atmosphere. After stirring for a further 1.5 h, the reaction mixture was then poured onto 5% *aq.* $Na_2S_2O_4$ (100 mL) and stirred at room temperature for 10 min. The aqueous layer was extracted with Et_2O (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 °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 °C petrol); ^1H NMR (300 MHz, $CDCl_3$) δ 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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1 (C), 134.1 (CH), 129.2 (CH_2), 118.9 (CH_2), 118.1 (CH_2), 104.2 (C); IR (thin film): ν_{max} = 2927, 1621, 1437 cm^{-1}; MS (70 eV, EI): *m/z* (%): 206 (12) $[M]^+$, 191 (5), 179 (6), 165 (8), 127 (28), 77 (100); HRMS: calc for C_6H_7I $[M]^+$: 205.9593; found 205.9592.

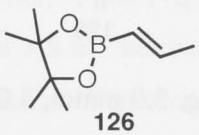
(E)-2-(Prop-1-en-1-yl)benzo[d][1,3,2]dioxaborole ***125***



125

The *title compound* **125** was prepared according to the literature procedure.[37] 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.[37] bp. 71 °C/2 mm Hg). ^{1}H NMR data was consistent with that reported in the literature.[37]

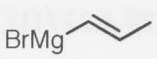
(E)-4,4,5,5-Tetramethyl-2-(prop-1-en-1-yl)-1,3,2-dioxaborolane ***126***



126

This known compound has previously been made through a different procedure.[107] (*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 Et_2O (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 % Et_2O: 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.[107]

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

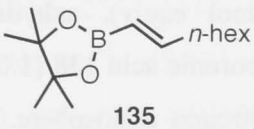


129

The *title compound* **129** was prepared according to a modified version of the literature procedure.[40] 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).

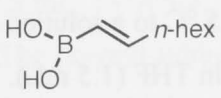
*(E)-4,4,5,5-Tetramethyl-2-(oct-1-en-1-yl)-1,3,2-dioxaborolane **135***



135

This known compound has previously been made through a different procedure.[108] 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_2O (5 mL) and sat. *aq.* NaCl (5 mL). The combined organic layers were then dried over anhydrous Na_2SO_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.[109]

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

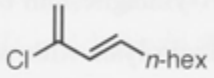


138

The *title compound* **138** was prepared according to a literature procedure.[44] 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 H_2O (25 mL). The resulting mixture was cooled to 0 °C, the precipicated 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. ^{1}H NMR data was consistent with that reported in the literature.[110]

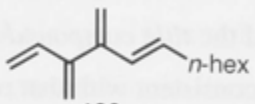
*(E)-2-Chlorodeca-1,3-diene **136***



136

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), $Pd_2(dba)_3$ (30 mg, 0.032 mmol, 0.005 mol equiv), anhydrous K_3PO_4 (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. ^{1}H NMR data was consistent with that reported in the literature.[43]

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

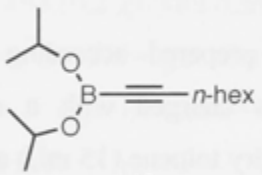


139

$Ni(dppp)Cl_2$ (35 mg, 0.065 mmol, 0.050 mol equiv) and PPh_3 (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_2O (15 mL) and stirred for 15 min. The mixture was successively washed with 1M *aq.* HCl (10 mL), sat. *aq.* Na_2CO_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 (CH2), 29.0 (CH_2), 22.7 (CH_2), 14.2 (CH_3) ppm; IR (thin film): ν_{max} = 2958, 2926, 2855, 1585, 1466 cm^{-1}; MS (70 eV, EI): *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***



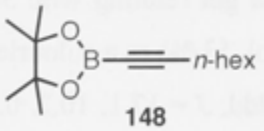
146

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_2O (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_2O (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]

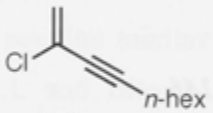
4,4,5,5-Tetramethyl-2-(oct-1-yn-1-yl)-1,3,2-dioxaborolane ***148***



148

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_2O (7 mL) was stirred under an argon atmophere 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***

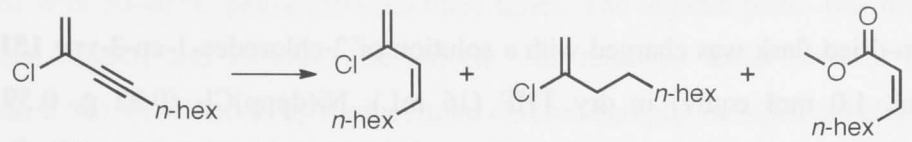


151

The *title compound* **151** was prepared according to a literature procedure.[46] A screw-capped pressre 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. CuI (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_2Cl_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.[46]

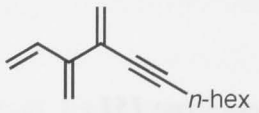
Hydrogenation of 2-chlorodec-1-en-3-yne ***151***



151 **141** **153** **154**

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 μL), 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_2O (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_2O: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_2O:hexane (2.5:97.5); ^{1}H NMR (500 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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): ν_{max} = 2955, 2927, 2857, 1726, 1645 cm^{-1}; MS (70 eV, EI): *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.

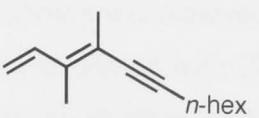
3,4-Dimethylenedodec-1-en-5-yne ***155***



155

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_2O (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): ν_{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-Dimethyldodeca-1,3-dien-5-yne ***157***

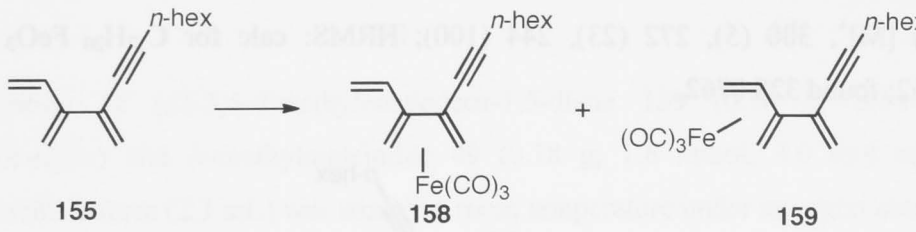


157

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,

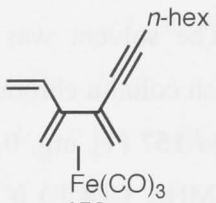
1.0 mol equiv), Zn powder (5 g), KCN (0.2 g), H_2O (6 mL), and *n*-PrOH (6 mL) was stirred at room temperature under an argon atmosphere in the dark for 1.5 h. The reaction mixture was poured onto a biphasic mixture of 30-40 °C petrol (50 mL) and H_2O (50 mL) and the organic phase was collected. The combined organic phases were extracted with 30-40 °C petrol (50 mL) three times. The organic phase was dried over anhydrous $MgSO_4$ 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. R_f 0.30 (pentane); ^{1}H NMR (300 MHz, $CDCl_3$) 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; ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9 (CH), 126.7 (C), 113.1 (CH_2), 110.1 (C), 95.4 (C), 81.6 (C), 31.4 (CH_2), 29.0 (CH_2), 28.7 (CH_2), 22.7 (CH_2), 20.1 (CH_3), 19.7 (CH_2), 14.2 (CH_3), 13.0 (CH_3) ppm; IR (thin film): ν_{max} = 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 $C_{14}H_{22}$ $[M]^+$:190.1722; found 190.1719.

Synthesis of irontricarbonyl complexes of alkynl[3]dendralene ***155***



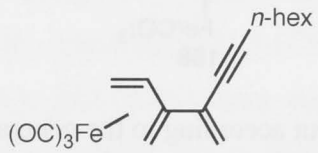
Protection of **155** was carried out according to the general method reported by Osinski[52] was adopted. To a stirred solution of $Fe_2(CO)_9$ (2.9 g, 8.0 mmol, 1.5 mol equiv) and 1-(4-methoxyphenyl)-4-phenyl-1-aza-1,3-butadiene (0.44 g, 1.9 mmol, 0.35 mol equiv) in 1,2-dimethoxyethane (15 mL), a solution 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 ^{1}H NMR and some unreacted starting material was observed. More $Fe_2(CO)_9$ (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.



158

Tricarbonyl[(3-6-η)-3,4-dimethylenedodec-1-en-5-yne]iron **158** (0.24 g, 0.72 mmol, 13%): R_f 0.46 (pentane); ^{1}H NMR (300 MHz, $CDCl_3$) 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; ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.2 (C), 135.3 (CH), 115.8 (CH_2), 110.2 (C), 102.5 (C), 91.3 (C), 85.8 (C), 43.2 (CH_2), 35.2 (CH_2), 31.4 (CH_2), 28.6 (CH_2) (two coincident signals), 22.6 (CH_2), 19.4 (CH_2), 14.1 (CH_3) ppm; IR (thin film): ν_{max} = 2932, 2859, 2052, 1979 (br) cm^{-1}; MS (70 eV, EI): *m/z* (%): 328 (9) $[M]^+$, 300 (5), 272 (23), 244 (100); HRMS: calc for $C_{17}H_{20}FeO_3$ $[M]^+$: 328.0762; found 328.0762.

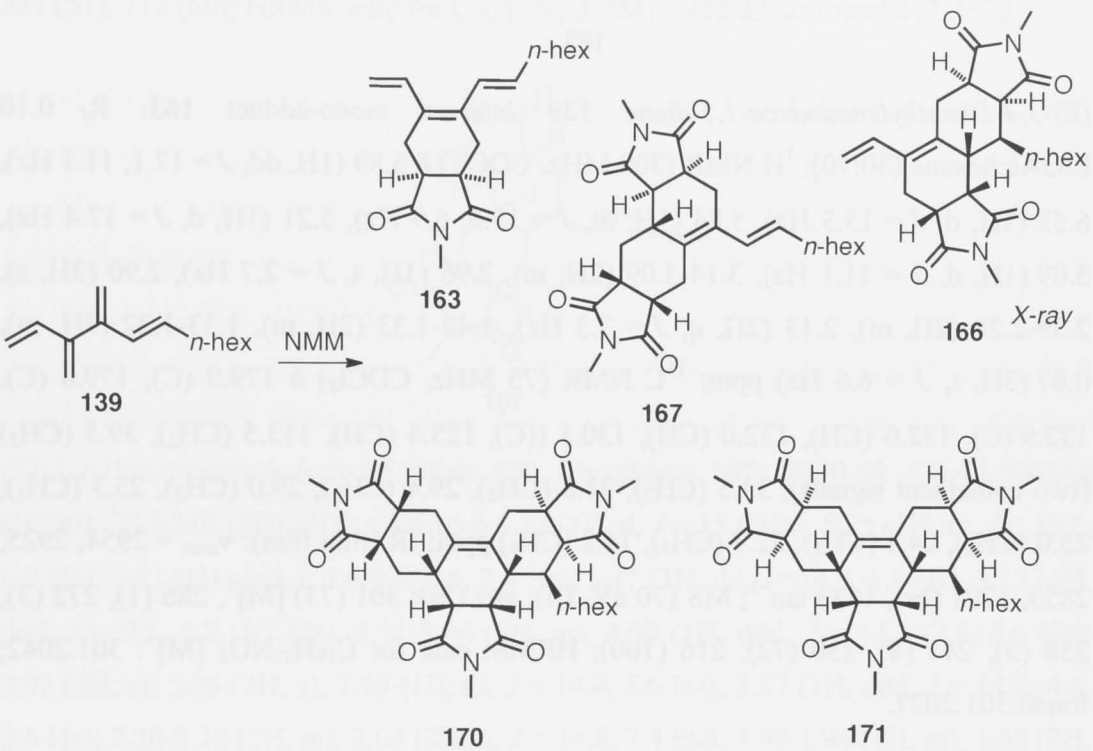


159

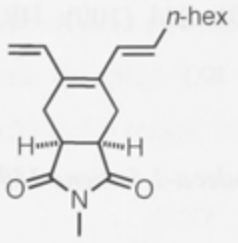
Tricarbonyl[(1-4-η)-3,4-dimethylenedodec-1-en-5-yne]iron **159** (0.52 g, 1.6 mmol, 30%): R_f 0.40 (pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (1H, t, J = 8.0 Hz), 5.73 (1H, d, J = 1.2 Hz), 5.42 (1H, s), 2.38 (2H, t, J = 7.1 Hz), 2.22 (1H, dd, J = 3.0, 1.8 Hz), 1.83 (1H, dd, J = 6.9, 2.4 Hz), 1.63-1.52 (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; ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.0 (C), 131.2 (C), 119.7 (CH), 101.2 (C), 92.7 (C), 84.9 (C), 39.8 (CH_2), 38.3 (CH_2) (two coincident signals), 31.4 (CH_2), 28.7 (CH_2) (two coincident signals), 22.6 (CH_2), 19.3 (CH_2), 14.1 (CH_3)

ppm; IR (thin film): ν_{max} = 2932, 2859, 2051, 1975 (br) cm^{-1}; MS (70 eV, EI): *m/z* (%): 328 (10) $[M]^+$, 300 (9), 272 (29), 244 (100); HRMS: calc for $C_{17}H_{20}FeO_3$ $[M]^+$: 328.0762; found 328.0763.

*Reaction of (E)-3,4-dimethylenedodeca-1,5-diene **139** with NMM **49***

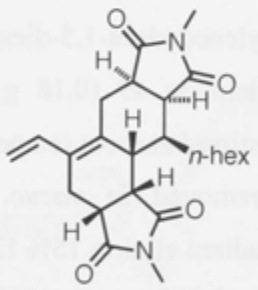


A solution of (*E*)-3,4-dimethylenedodeca-1,5-diene **139** (0.10 g, 0.54 mmol, 1.0 mol equiv) and *N*-methylmaleimide **49** (0.18 g, 1.6 mmol, 3.0 mol equiv) in deuterochloroform (2.3 mL) was stirred at room temperature under an argon atmosphere for 24 h. The solvent was removed in *vacuo*. Purification 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_2Cl_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.



163

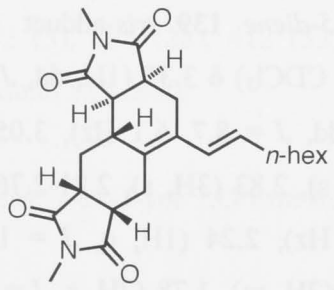
(E)-3,4-Dimethylenedodeca-1,5-diene **139** *internal mono*-adduct **163**: R_f 0.10 EtOAc:hexane (30:70); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (1H, dd, *J* = 17.1, 11.1 Hz), 6.53 (1H, d, *J* = 15.3 Hz), 5.84 (1H, dt, *J* = 15.6, 6.9 Hz), 5.21 (1H, d, *J* = 17.4 Hz), 5.09 (1H, d, *J* = 11.1 Hz), 3.14-3.09 (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; ^{13}C 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.



166 *X-ray*

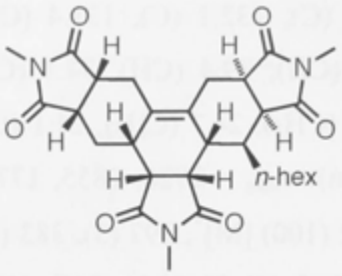
(E)-3,4-Dimethylenedodeca-1,5-diene **139** *bis*-adduct **166** crystallized from CH_2Cl_2/hexane at room temperature as colourless needles, mp. 154-155 °C. R_f 0.05 EtOAc:hexane (30:70); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.57 (1H, dd, *J* = 16.8, 11.1 Hz), 5.29 (1H, d, *J* = 17.7 Hz), 5.08 (1H, d, *J* = 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; ^{13}C 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 (CH_2), 41.1 (CH), 40.3 (CH), 40.1 (CH), 39.9 (CH), 39.4 (CH), 34.1 (CH), 31.9 (CH_2), 29.5 (CH_2), 28.9 (CH_2), 27.1 (CH_2), 24.9 (CH_3), 24.7 (CH_3), 24.1 (CH_2), 24.0 (CH_2), 22.7 (CH_2), 14.2 (CH_3) ppm; IR (thin film): ν_{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 $C_{24}H_{32}N_2O_4$ $[M]^+$: 412.2362; found 412.2370.



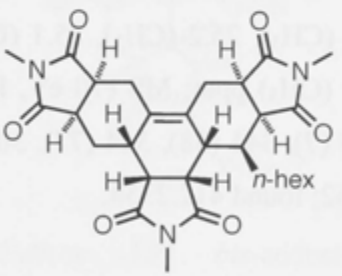
167

(E)-3,4-Dimethylenedodeca-1,5-diene **139** *bis-adduct* **167**: R_f 0.50 CH_2Cl_2:EtOAc (50:50); ^1H NMR (800 MHz, $CDCl_3$) δ 6.23 (1H, d, *J* = 15.6 Hz), 5.75 (1H, dt, *J* = 15.6, 6.9 Hz), 3.21 (1H, ddd, t, *J* = 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, $CDCl_3$) δ 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 (CH_2), 31.8 (CH_2), 29.3 (CH_2), 29.0 (CH_3), 25.2 (CH_3), 25.1 (CH_2), 25.0 (CH_2), 23.9 (CH_2), 23.5 (CH_2), 22.7 (CH_2), 14.2 (CH_3) 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 $C_{24}H_{32}N_2O_4$ $[M]^+$: 412.2362; found 412.2358.



170

(E)-3,4-Dimethylenedodeca-1,5-diene **139** *tris*-adduct **170**: R_f 0.50 CH_2Cl_2:EtOAc (50:50); ^{1}H NMR (800 MHz, $CDCl_3$) δ 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), 2.34 (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, $CDCl_3$) δ 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_2), 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): ν_{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 $C_{29}H_{37}N_3O_6$ $[M]^+$: 523.2682; found 523.2682.

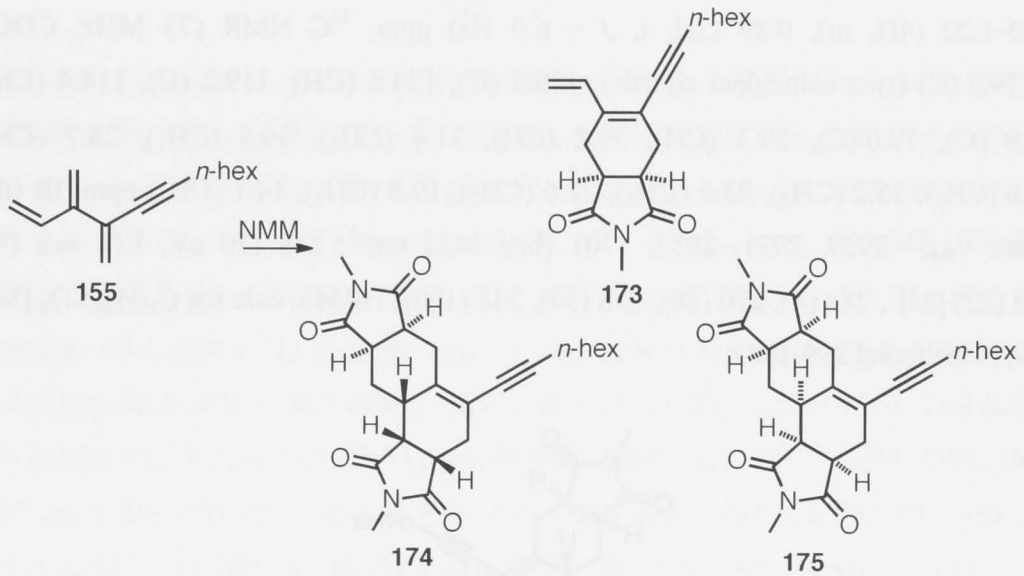


171

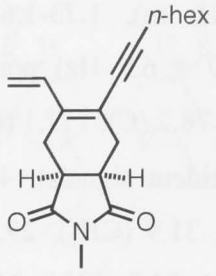
(E)-3,4-Dimethylenedodeca-1,5-diene **139** *tris*-adduct **171**: R_f 0.20 CH_2Cl_2:EtOAc (50:50); ^{1}H NMR (800 MHz, $CDCl_3$) δ 3.31 (1H, dd, *J* = 8.7, 6.0 Hz), 3.22 (1H, dd, *J* = 9.2, 4.4 Hz), 3.18-3.16 (1H, m), 3.11-3.07 (2H, m), 2.97 (1H, dd, *J* = 8.7, 6.1 Hz), 2.91-2.88 (1H, m), 2.90 (3H, 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): ν_{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 $C_{29}H_{37}N_3O_6$ $[M]^+$: 523.2682; found 523.2682.

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

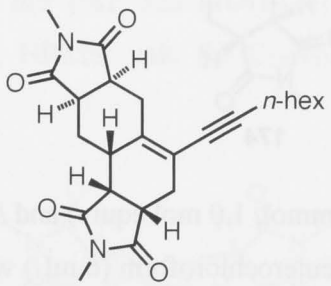


A solution of **155** (0.21 g, 1.1 mmol, 1.0 mol equiv) and *N*-methylmaleimide **49** (0.12 g, 1.1 mmol, 1.0 mol equiv) in deuterochloroform (6 mL) was stirred at room temperature under an argon atmosphere for 4.5 h. The solvent was removed in *vacuo*. Purification by flash column chromatography on 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.



173

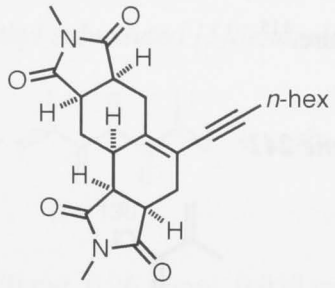
3,4-dimethylenedodec-1-en-5-yne **155** *internal mono*-adduct **173**: R_f 0.20 EtOAc:hexane (30:70); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (1H, dd, *J* = 17.7, 10.5 Hz), 5.36 (1H, d, *J* = 17.7 Hz), 5.14 (1H, d, *J* = 10.8 Hz), 3.16-3.04 (2H, m), 2.94 (3H, s), 2.89 (1H, dd, *J* = 15.3, 3.3 Hz), 2.71 (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, $CDCl_3$) δ 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): ν_{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.



174

3,4-dimethylenedodec-1-en-5-yne **155** *bis*-adduct **174**: R_f 0.20 EtOAc:hexane (70:30); ^{1}H NMR (800 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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),

39.0 (CH), 38.9 (CH), 33.7 (CH), 31.3 (CH_2), 30.0 (CH_2), 28.6 (CH_2), 28.5 (CH_2), 27.0 (CH_2), 25.0 (CH_3) (two coincident signals), 23.4 (CH_2), 22.5 (CH_2), 19.5 (CH_2), 14.0 (CH_3) ppm; IR (thin film): ν_{max} = 2930, 2857, 1697 (br), 1434 cm^{-1}; MS (70 eV, EI): *m/z* (%): 410 (100) $[M]^+$, 395 (2), 381 (8), 112 (45); HRMS: calc for $C_{24}H_{30}N_2O_4$ $[M]^+$: 410.2206; found 410.2205.

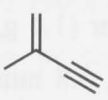


175

3,4-dimethylenedodec-1-en-5-yne **155** *bis*-adduct **175**: R_f 0.38 EtOAc:hexane (85:15); ^1H NMR (300 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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): ν_{max} = 2929, 2858, 1701, 1686, 1437 cm^{-1}; MS (70 eV, EI): *m/z* (%): 410 (100) $[M]^+$, 395 (1), 381 (3), 353 (4), 339 (19), 325 (14); HRMS: calc for $C_{24}H_{30}N_2O_4$ $[M]^+$: 410.2206; found 410.2207.

3.3 Chapter 2 Experimental

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

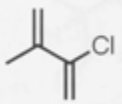


240

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, 0.040 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 $MgSO_4$ gave the *title compound* **240** (lit.[115] bp. 35 °C/760 mm Hg) as a colourless oil (117 g, 1.77 mol, 63%). ^{1}H NMR data for this compound was consistent with that reported in the literature.[115]

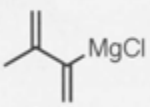
2-Chloro-3-methylbuta-1,3-diene ***241***



241

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 NH_4Cl (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. ^{1}H NMR data for this compound was consistent with that reported in the literature.[116]

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

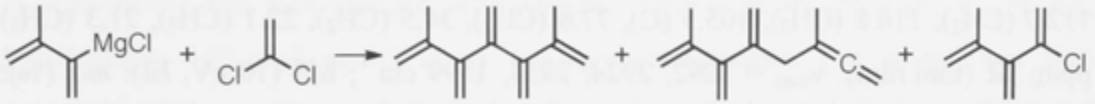


242

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, $ZnBr_2$ (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,

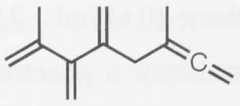
1.0 mol equiv) and 1,2-dibromoethane (0.68 mL, 7.9 mmol, 0.40 mol equiv) in THF (8 mL) was added dropwise to maintain a generous reflux. After the addition was complete, the reaction mixture was stirred at reflux for 75 min. Titration of resulting Grignard reagent **242** with salicylaldehyde phenylhydrazone[106] indicated a 0.74 M solution of the *title compound* **242** in THF (55 % yield).

*Attempts to synthesis the dimethyl substituted [5]dendralene **190***



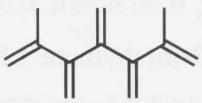
242 **32** **190** **248** **249**

To a stirred solution of PPh_3 (70 mg, 0.26 mmol, 0.050 mol equiv), Ni(dppp)Cl_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 $CDCl_3$. 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 ^{1}H NMR spectroscopy. More Ni(dppp)Cl_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_2O (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.* $NaHCO_3$ (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_2O) and the compound **248** (13 mg, 0.080 mmol, 2 %) was isolated as a colourless oil.



248

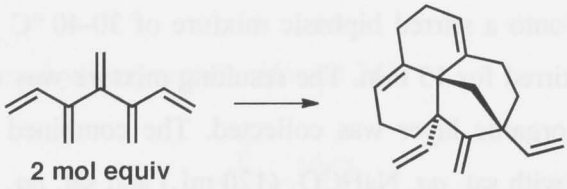
3,7-Dimethyl-5,6-dimethyleneocta-1,2,7-triene **248:** R_f = 0.60 (30-40 °C petrol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.19 (1H, s), 5.05 (1H, s), 5.01 (1H, s), 4.97 (1H, s), 4.90 (1H, s), 4.89-4.85 (3H, m), 3.19 (2H, s), 1.92 (3H, s), 1.87 (3H, s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.6 (C), 145.1 (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): ν_{max} = 3092, 2924, 2853, 1599 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.



190

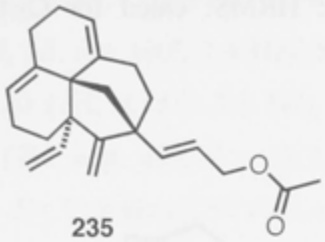
2,6-Dimethyl-3,4,5-trimethylenehepta-1,6-diene **190:** R_f = 0.60 (30-40 °C petrol). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.21 (2H, s), 5.15 (2H, d, *J* = 1.8 Hz), 5.04 (4H, s), 5.01 (2H, d, *J* = 1.2 Hz), 1.93 (6H, s) ppm; ; IR (thin film): ν_{max} = 3093, 2971, 1585, 1441 cm^{-1}; MS (70 eV, EI): *m/z* (%): 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***

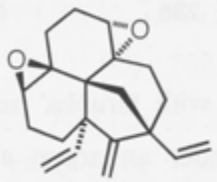


235

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-diyl diacetate (55 mg, 0.32 mmol, 2.0 mol equiv) in CH_2Cl_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-diyl diacetate were observed. Therefore, more catalyst (14 mg, 0.010 mmol, 10 mol%) and (*Z*)-but-2-ene-1,4-diyl 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_2Cl_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_6D_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_6D_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): ν_{max} = 2929, 2853, 1742 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***



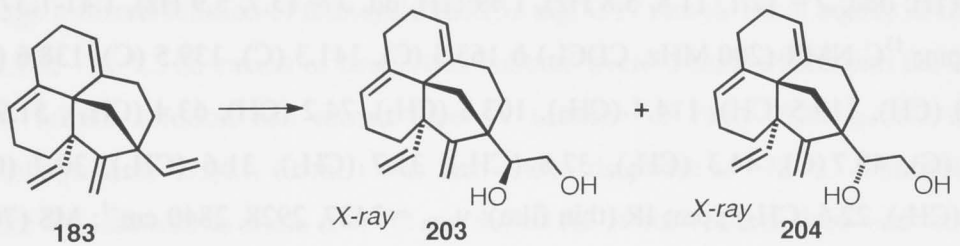
213

*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_2Cl_2 (0.5 mL) at –15 °C, a solution of *m*-CPBA **206** (25 mg, 0.14 mmol, 2.0 mol equiv) in CH_2Cl_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_2Cl_2 (3 mL) and then washed with sat. *aq.* $NaHCO_3$ (3 mL). The aqueous layer was extracted with CH_2Cl_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_2Cl_2 (5 mL) and washed then with sat. *aq.* $NaHCO_3$ (5 mL). The aqueous layer was extracted with CH_2Cl_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*. Pufication 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.

R_f 0.32 (10% EtOAc/30-40 °C petrol). ^{1}H NMR (800 MHz, $CDCl_3$) 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; ^{13}C NMR (200 MHz, $CDCl_3$) δ 162.9 (C), 143.9 (CH), 139.7 (CH), 115.1 (CH_2), 112.8 (CH_2), 105.9 (CH_2), 64.9 (C), 63.0 (CH), 61.8 (CH), 58.2 (C), 51.6 (C), 49.8 (C), 46.6 (C), 41.2 (CH_2), 35.4 (CH_2), 31.6 (CH_2), 30.4 (CH_2), 28.0 (CH_2), 23.3 (CH_2), 21.7 (CH_2) ppm; IR (thin film): ν_{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 $C_{20}H_{24}O_2$ $[M]^+$: 296.1776; found 296.1773.

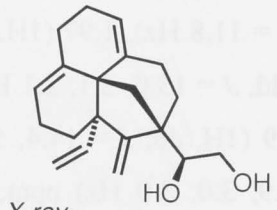
Dihydroxylation of tetracycle ***183***



183 **203** **204**

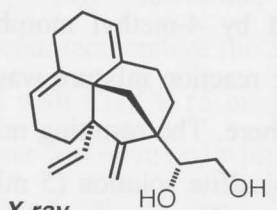
To a stirred solution of tetracycle **183** (44 mg, 0.016 mmol, 1 mol equiv) and H_2O (0.3 mL) in THF (1.6 mL) was added OsO_4 **194** (4.1% in H_2O, 41 μL, 7.0 μmol, 0.040 mol equiv) and followed by 4-methyl morpholine-*N*-oxide (NMO) (39 mg, 0.33 mmol, 2.0 mol equiv). The reaction mixture was stirred 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 Na_2SO_4 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%).



X-ray **203**

The compound **203** crystallized from hexane/methanol at room temperature as colourless needles, mp. 122-124 °C and R_f 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), 5.10 (1H, s), 4.93 (1H, s), 3.88-3.86 (1H, m), 3.78-3.75 (1H, m), 3.55-3.52 (1H, m), 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): ν_{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.

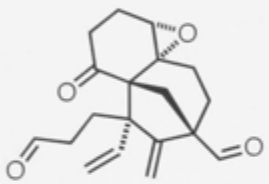


X-ray **204**

The compound **204** crystallized from CH_2Cl_2/hexane at room temperature as colourless needles, mp. 130-132 °C and R_f 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, td, 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): ν_{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***



223

Through a stirred solution of tetracycle **183** (53 mg, 0.17 mmol, 1 mol equiv) in CH_2Cl_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_2Cl_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): ν_{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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