UNIVERSITY OF SOUTHAMPTON

Carbenoid Insertion into Zirconacycles

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Doctor of Philosophy

School of Chemistry

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Abstract

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A wide range of zirconacycles can be formed, with a variety of elaboration methods discovered to date. In recent years, the insertion of carbenoids into zirconacycles has been investigated, with a range of reactions now available to the synthetic chemist. The above area has been reviewed herein, followed by discussion of new discoveries found during research for this thesis.

Insertion of *E*-1,2-dihalo-1-lithioethene into zirconacyclopentenes formed methylenecyclopentenes. The mechanism proposed involves initial formation of an alkyne that then inserts intramolecularly into a carbon-zirconocenium bond. Stable alcohol products have been formed from hydroboration of the exocyclic double bond followed by basic peroxide quench. The same methylenecyclopentenes were formed from insertion of 1-lithio-2-haloethynes *via* a novel zirconocene vinylidene. Insertion of the carbenoid into a zirconacyclopentane formed an alkyne, but also showed for the first time that a neutral zirconium species will rearrange to incorporate a carbenoid fragment at room temperature, in this case forming a bis-insertion product.

Intramolecular carbenoid insertion was attempted, but the area of research failed to give positive results. Some substrates with carbon-chlorine bonds were found to be incompatible with the zirconium cyclisation method.

The range of vinyl carbenoids inserted into zirconacyclopentanes and –enes has been extended. Novel polyinsertion of vinyl carbenoids into the same side of zirconacyclopentanes has been discovered, revealing the fluxionality of the intermediate zirconate species. A novel rearrangement of zirconacyclohexenes to form phenyl substituted methylenecyclopentenes has also been discovered.

The first insertion of carbon monoxide into a zirconacyclohexane to form a cyclohexanone is reported. The insertion of phenylsulfone or vinyl carbenoids followed by butyl isocyanide has been found to form functionalised cyclohexanones after acidic quench. The 'one pot' formation of a bicyclic cycloheptanone from an acyclic precursor, with five new regioselectively formed carbon-carbon bonds, was discovered; thus revealing the degree of elaboration possible with organozirconium chemistry.

Acknowledgements

I would firstly like to thank Richard Whitby for his ideas, enthusiasm and support over the last 3 years, as well as the odd group BBQ. Thanks also to my CASE supervisor Ed Griffen for his help and advice with the chemistry, as well as a few chats about medicinal chemistry and careers in the industry. Everyone in the lab at AstraZeneca was also very helpful and welcoming – specific thanks to Shaun and Pauline. I am also indebted to AstraZeneca for making the last three years more enjoyable financially.

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However, there are no two people I need to thank anywhere near as much as Mum and Dad for your inexhaustible support over the last 7 years at University (plus a few before that of course...). Don't worry, I'm finally getting a job!!

Finally, I would like to dedicate this thesis to my late grandfather, Reg.

Abbreviations

Techniques

NMR	Nuclear Magnetic Resonance
DEPT	Distortionless Enhancement by Polarisation Transfer
GOESY	Gradient enhanced Nuclear Overhauser Effect Spectroscopy
COSY	Correlation Spectroscopy
GC	Gas Chromatography
GCMS	Gas Chromatography Mass Spectrometry
LRMS	Low Resolution Mass Spectrometry
HRMS	High Resolution Mass Spectrometry
TLC	Thin Layer Chromatography
IR	Infra-red spectroscopy

Reagents

n-BuLi	*n*-Butyllithium
s-BuLi	*sec*-Butyllithium
t-BuLi	*tert*-Butyllithium
DMPU	*N*,*N*'-Dimethylpropyleneurea
LiTMP	Lithium 2,2,6,6-tetramethylpiperidide
LDA	Lithium diisopropylamide
TBAF	Tetrabutylammonium fluoride
AcOH	Acetic acid
9-BBN	9-Borabicyclo[3.3.1]nonane
HMPA	Hexamethylphosphoramide
TMEDA	*N*,*N*,*N*',*N*'-Tetramethylethylenediamine
THF	Tetrahydrofuran
NBS	*N*-Bromosuccinimide

Chemical groups

Cp	Cyclopentadienyl
Alk	Alkyl
Ar	Aryl
Me	Methyl
Et	Ethyl
Pr	*n*-Propyl
Bu	*n*-Butyl
Hex	*n*-Hexyl
Oct	*n*-Octyl
Cy	Cyclohexyl
Bn	Benzyl
TBDMS	*tert*-Butyldimethylsilyl
DMPS	Dimethylphenylsilyl
Ms	Methanesulfonyl

Miscellaneous

Hr(s)	Hour(s)
Min	Minute(s)
r.t.	Room temperature
HOMO	Highest Occupied Molecular Orbital
m.p.	Melting Point

Contents

Chapter 1. Introduction

1.1 Aim of the PhD and thesis overview

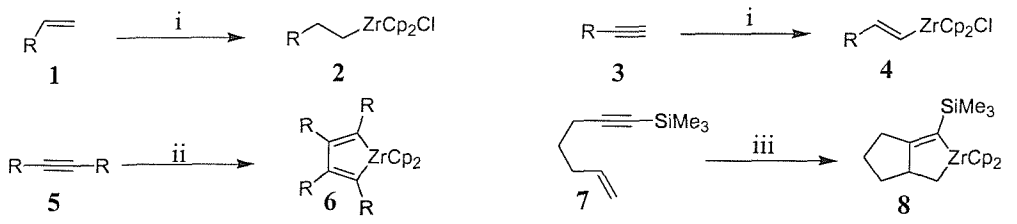
At the outset, the aim of the PhD was to investigate the insertion of carbenoids into zirconacycles to increase the current knowledge of this reaction type and discover new synthetic methodology in this area. The aim was also to enhance the synthetic utility of the reactions by developing methods for further elaboration of the zirconacycles after carbenoid insertion.

In this thesis, zirconacycle formation and examples of current methodology for further elaboration are discussed. The chemistry of carbenoids is then briefly reviewed before the subject of carbenoid insertion into organozirconium bonds is explained in more detail. The following chapters then describe the results obtained. Firstly, the insertion of 1,2-dihalo-1-lithioethenes and the subsequent rearrangements observed are discussed. Application of intramolecular carbenoid insertion is then followed by studies of vinyl carbenoids. Lastly, the use of carbon monoxide and isocyanide to elaborate zirconacyclohexanes is explained. The experimental section then details the methods used and characterisation of products.

1.2 Organozirconium chemistry.

1.2.1 Formation of carbon-zirconium bonds

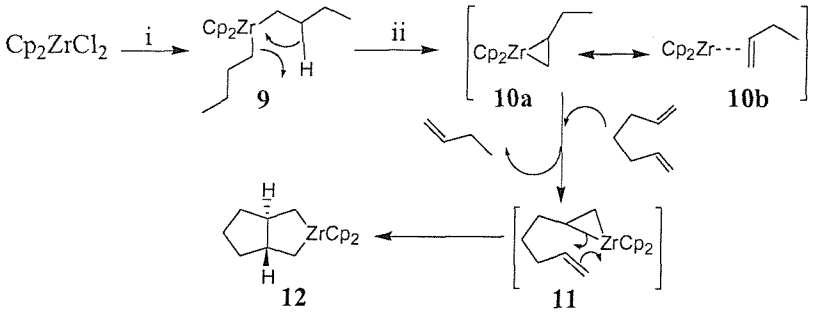
The use of organozirconium chemistry in organic synthesis originated in the early 1970's and has since been shown to effect a wide range of transformations, often with high regio- and stereocontrol and with substrates that are unreactive to traditional electrophiles and nucleophiles. The formation of acyclic organozirconium species **2** and **4** is achieved by hydrozirconation of alkenes or alkynes with Cp_2ZrHCl.[1,2] These species can be functionalised in a number of ways[2-4], including halogenation[5-7] and carbonylation.[6,8,9] Various methods of zirconacycle formation from alkenes and alkynes were initially presented.[3,10-12] However, the best results were obtained from the formation of the 14-electron species zirconocene with Mg/Hg amalgams.[13,14] Example cyclisations performed with this method are shown in Scheme 1.1.



Reagents and Conditions: i, Cp_2ZrHCl, THF, 20 °C; ii, Cp_2ZrCl_2 (0.25 eq.), $HgCl_2$ (0.25 eq.), Mg (1.25 eq.), THF; iii, Cp_2ZrCl_2 (1.0 eq.), $HgCl_2$ (1.0 eq.), Mg (10 eq.), THF

Scheme 1.1

A more experimentally facile process avoiding the toxicity of mercury was developed[15], which is still used most commonly today. Instead of forming the 14-electron zirconocene 'Cp_2Zr' directly, a zirconocene equivalent is formed from addition of two equivalents of *n*-butyllithium to zirconocene dichloride[16]. Initially, dibutyl zirconocene **9** is formed, but β-hydrogen abstraction causes loss of a butane molecule and formation of the active zirconocene (1-butene) **10**. The 1-butene ligand is loosely bound to zirconium and is easily displaced by another alkene or alkyne.[17] In the case of a diene, there is then cyclisation with the second unsaturated bond to give a zirconacycle **12**.

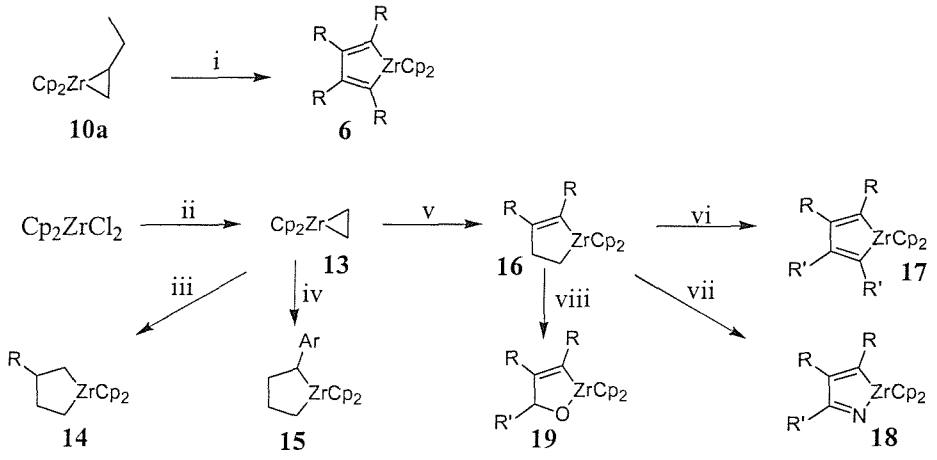


Reagents and Conditions: i, *n*-BuLi (2.0 eq.), -78 °C; ii, -78 °C - r.t.

Scheme 1.2

A range of 1,n-dienes, -enynes and –diynes can be cyclised by the above method to give zirconabicycles.[18-20] Monocycles can also be readily formed.[21] Whilst reaction of zirconocene (1-butene) with alkenes gives a mixture of products, with partial incorporation of the butene ligand, reaction with alkynes gives only zirconacyclopentadienes **6**. The methodology for monocycle formation was extended by replacement of zirconocene (1-butene) with zirconocene ethylene.[22] The latter complex is formed either by reaction of zirconocene (1-butene) with ethene, or

directly by reaction of zirconocene dichloride with an ethyl Grignard reagent. One ethene molecule remains bound when reaction with alkenes or alkynes occurs, so that specific monocycles **14**, **15** and **16** can be formed. Heating the resulting monocycle with further alkynes, nitriles or aldehydes then forms unsymmetrical zirconamonocycles[23] such as **17**, **18** and **19**.



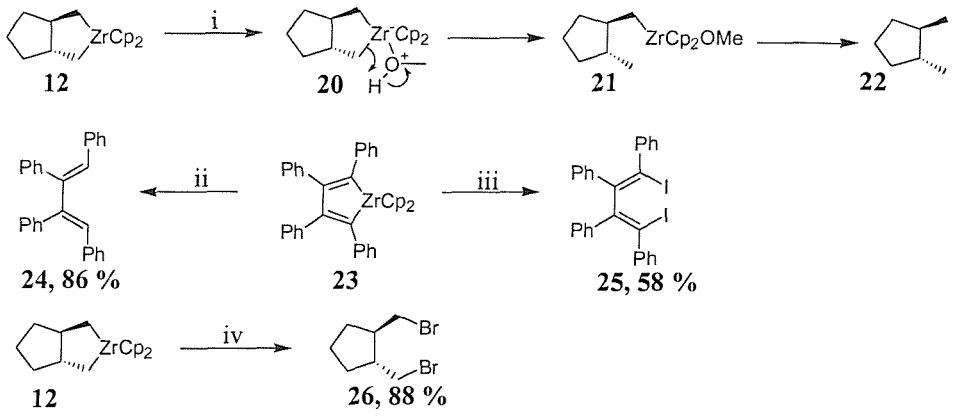
Reagents and Conditions: i, RCCR, 0 °C; ii, EtMgCl (2.0 eq.), -78 - 0 °C; iii, $RCHCH_2$, 0 °C; iv, H_2CCHAr, 0 °C; v, RCCR, 0 °C; vi, R'CCR', 50 °C; vii, R'CN, 25 °C; viii, R'CHO, 50 °C.

Scheme 1.3

A great advantage of organozirconium chemistry it that as well as the large range of zirconacycles that can be formed, there are many methods of elaboration available to the synthetic chemist. A number of the methods are described in the following sections.

1.2.2 Protonation and halogenation of zirconacycles

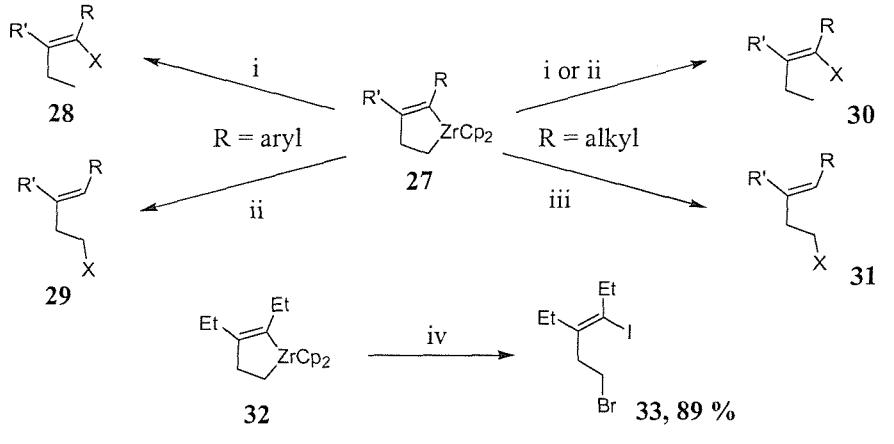
The simplest method of obtaining an organic product from a zirconacycle is protonation, which can be achieved with HCl, aqueous $NaHCO_3$ or methanol. Hence the quenching conditions can be chosen depending on the acid/base stability of the products. If present, the stereochemistry of the zirconacycle ring junction is retained[24], as is the alkene geometry of alkenyl-zirconium bonds.[25] The probable mechanism of protonation involves initial coordination to the zirconium to form a zirconate complex such as **20**, followed by protonation of the carbon-zirconium bond.



Reagents and Conditions: i, MeOH; ii, HCl (aq., 2M); iii, I_2; iv, Br_2

Scheme 1.4

Halogenation of zirconacycles occurs in the same manner, for example, to give diiodide **25** and dibromide **26**. Methodology for the selective monohalogenation of zirconacycles[26] has also been established. In particular, chemoselective halogenation of zirconacyclopentenes is possible, with reaction of either the alkyl- or alkenyl-zirconium bond, depending on the reagents used.[27,28] The methodology available is summarised in Scheme 1.5.[29]



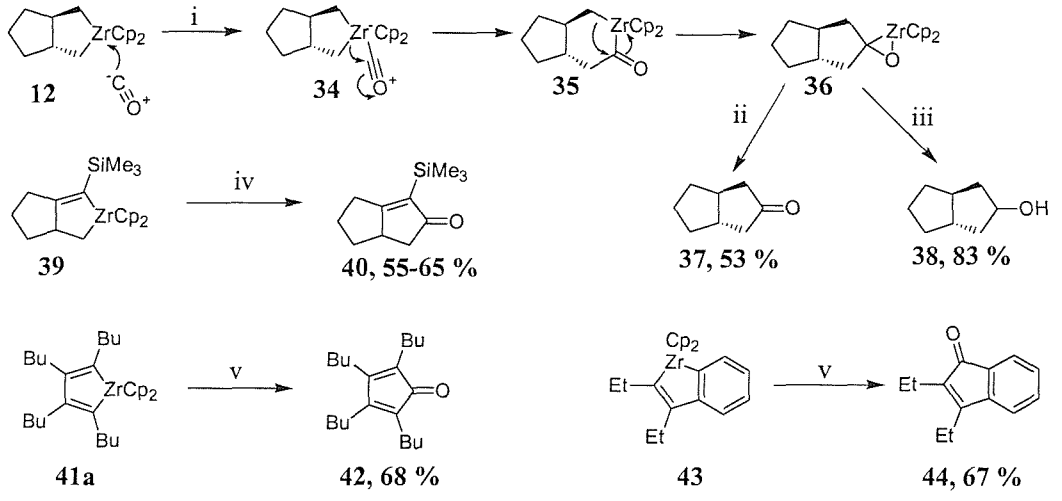
Reagents and Conditions: i, excess MeOH then I_2; ii, Br_2, I_2 or NBS (1.0 eq.); iii, CBr_4 or CCl_3Br; iv, CCl_3Br then I_2

Scheme 1.5

1.2.3 Carbonylation and isocyanide insertion

Some of the earliest zirconacycles formed were found to react with carbon monoxide[12,14] to give cyclopentenone products such as **40**. Initial coordination of a CO molecule with the zirconium forms a zirconate **34**, which is activated towards 1,2-

addition to the coordinated CO. Rearrangement to the η^2-ketone complex **36** then follows.[30] Hydrolysis at low temperature yields the alcohol **38**, whilst warming under CO or oxidative quench with iodine gives the cyclopentanone **37**.



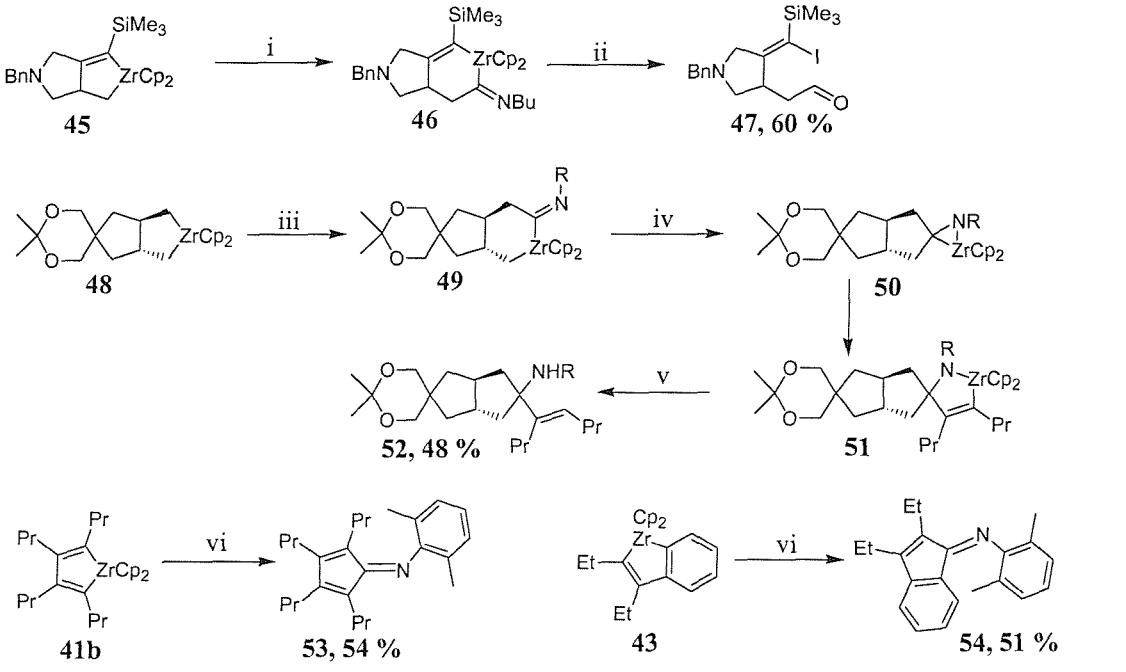
Reagents and Conditions: i, CO, -78 °C; ii, r.t., I_2; iii, HCl (3M); iv, CO, 0 °C, 1 hr; v, CO, $NiCl_2(PPh_3)_2$ (1.0 eq.), r.t., 6 hrs.

Scheme 1.6

It was considered for some time, that carbonylation of zirconacyclopentadienes did not occur. However, recent research by Takahashi has shown that it can be promoted by use of nickel to give cyclopentadienones[31], examples of which are shown in Scheme 1.6. It has also been discovered that direct carbonylation is actually possible[32], depending on the zirconacycle structure, although one of the double bonds is lost to form cyclopentenones.

Since isocyanides are isoelectronic with carbon monoxide, they undergo similar insertion into zirconacycles, although the analogous rearrangement to **35** does not occur as readily. The first isocyanide insertion was into zirconacyclopentene[33] **45**. No rearrangement of the η^1-imine **46** occurred, so after iodinolysis and protonolysis, the aldehyde **47** was formed. Insertion of *t*-butyl[34] isocyanide into zirconayclopentanes was successful, but no rearrangement was observed. However, on heating η^1-imines such as **49** from insertion of *n*-butyl[35], cyclohexyl[35], phenyl[34], trimethylsilyl[36] and benzyl[35] isocyanides, rearrangement to the η^2-imines **50** was observed. The resulting imines were then trapped by various alkynes and alkenes to form highly elaborated products such as **52**. Isocyanide insertion into

zirconacyclopentadienes has recently been achieved by a copper-mediated reaction to give iminocyclopentadienes **53** and **54** as products.[31]

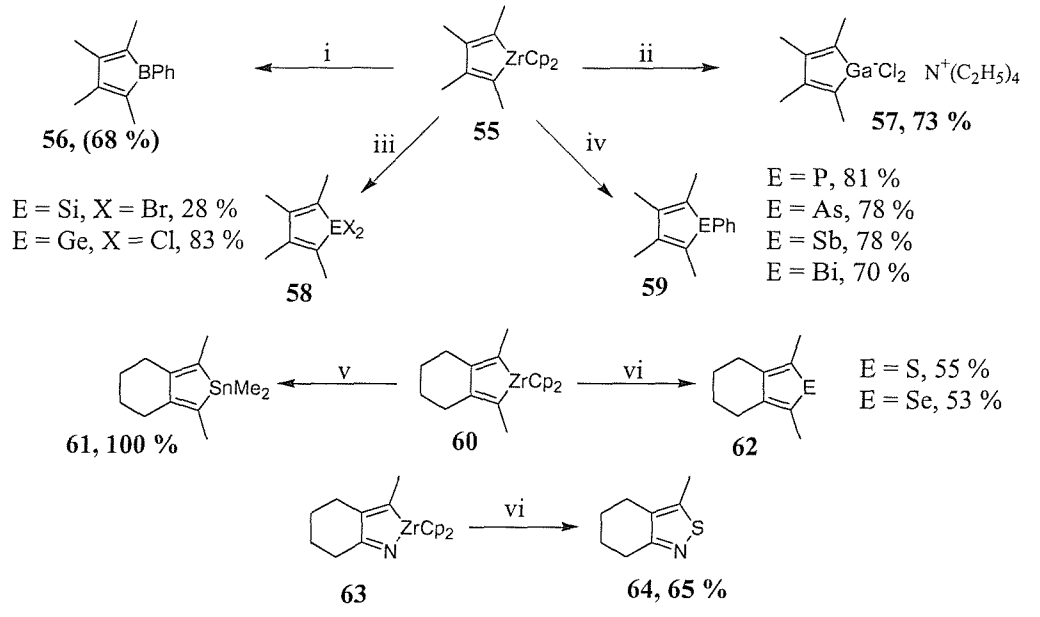


Reagents and Conditions: i, BuNC; ii, I_2 (1.2 eq.), -78 °C, 1 hr then HCl (3M); iii, RNC (1.0 eq.); iv, 4-octyne (1.25 eq.), reflux, 3 hrs; v, MeOH; vi, 2,6-dimethylphenyl isocyanide (2.0 eq.), r.t., 3 hrs, then CuCl (2.0 eq.), air

Scheme 1.7

1.2.4 Metathesis to main group elements

A considerable range of heterocycles can be formed from zirconacycles by reaction with halides of main group elements.[24,37-39] For group III elements, the borole **56** can be synthesised, but then forms a Diels-Alder dimer, whereas the gallole salt **57** is stable. Heterocycles for groups IV (**58** and **61**), V (**59**), and VI (**62**) can also be synthesised as shown in Scheme 1.8. Isothiazoles **64** can also be synthesised from the relevant azazirconacycle precursor **63**. Products shown are all from zirconacyclopentadienes, but zirconacyclopentanes and –enes also undergo similar reactions.

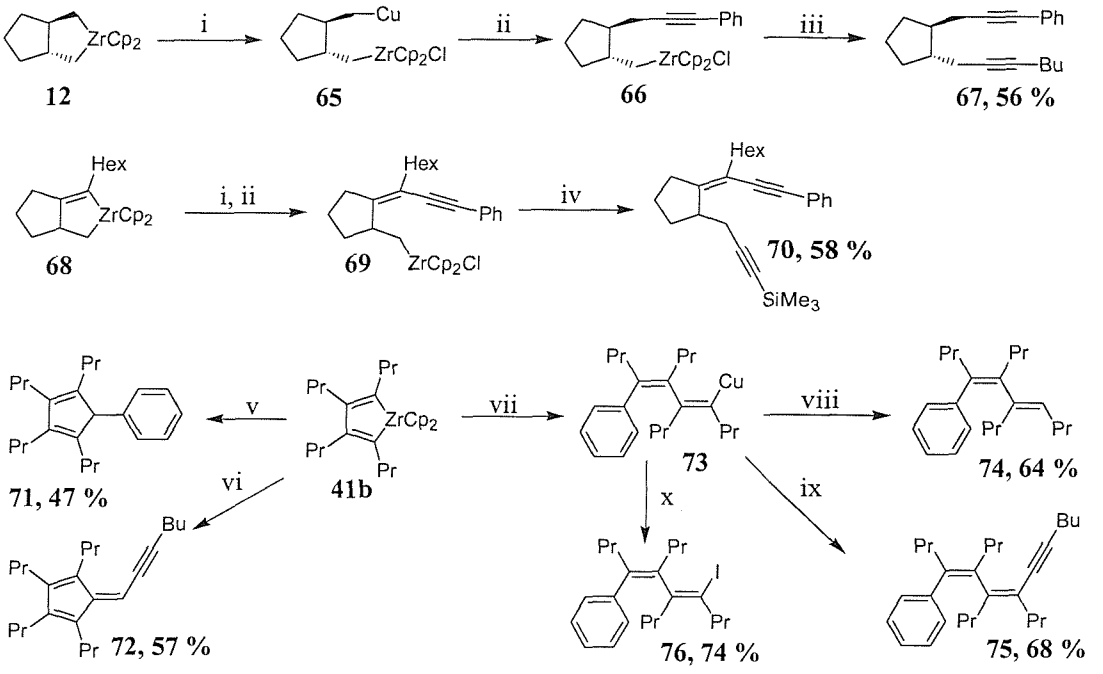


Reagents and Conditions: i, $PhBCl_2$, 25 °C, 1 hr; ii, $GaCl_3$, 25 °C, 5 min then $(C_2H_5)_4N^+Cl$; iii, For Si: $SiBr_4$ (neat), 150 °C, 2 days; for Ge: $GeCl_4$, 25 °C, 2 min; iv, For P, As: $PhECl_2$, 25 °C; for Sb, Bi: ECl_3, 25 °C then PhLi; v, Me_2SnBr_2 25 °C, 2 days; vi, E_2X_2, 25 °C, 1 hr.

Scheme 1.8

1.2.5 Transmetallation to copper

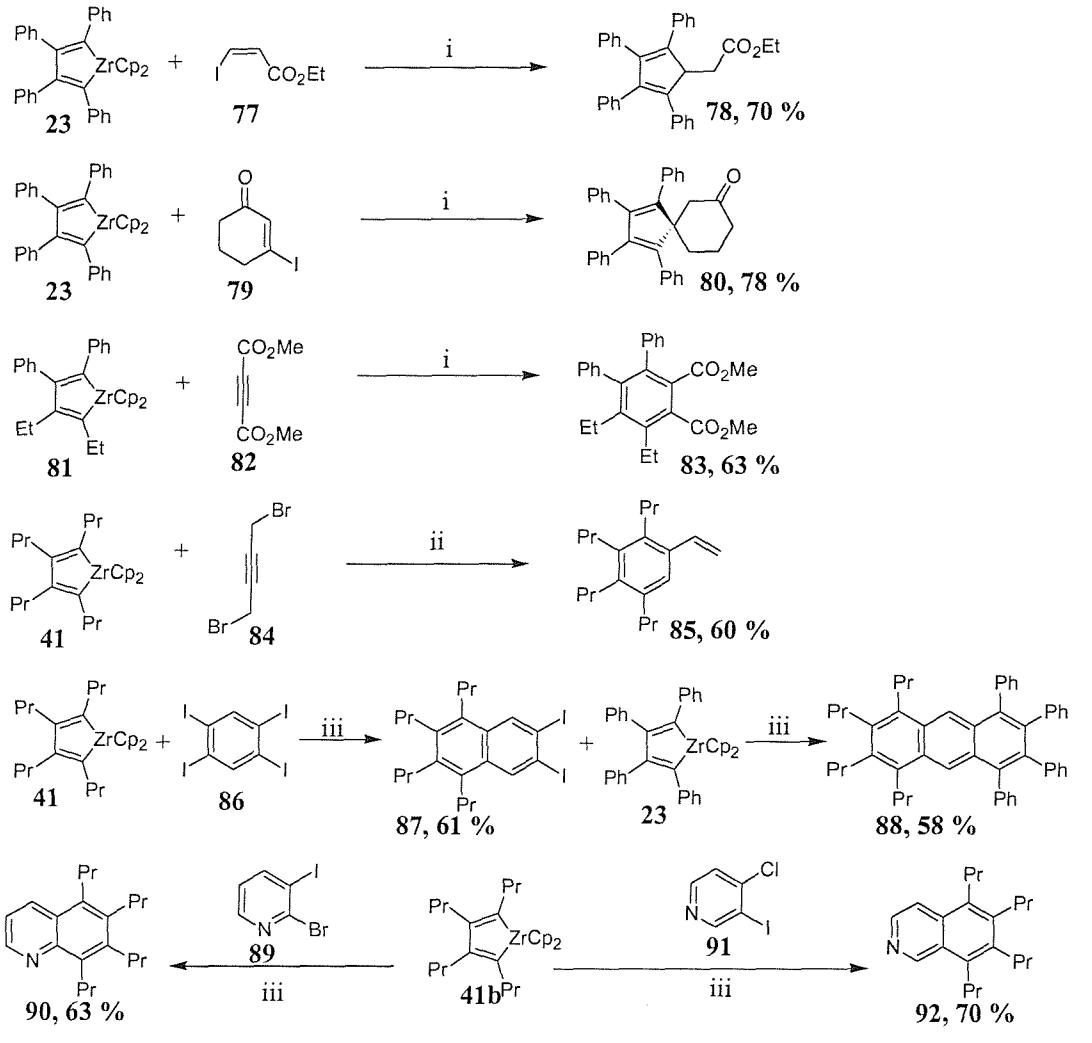
In the last five years, Takahashi has developed a wide range of copper-mediated couplings of zirconacycles, which provide high degrees of elaboration.[40,41] The work in this area has greatly increased the scope of zirconacycle chemistry providing access to highly substituted cyclic compounds.[42] It would not be appropriate to cover the area in detail here, but examples of the reactions possible are shown. Reaction of a zirconacycle with CuCl initially transmetallates one of the carbon-zirconium bonds to give **65** and the carbon-copper bond can be reacted with an alkynyl halide.[43] Addition of a second equivalent of CuCl followed by a second alkynyl halide allows a different alkyne group to be added to the other side of the zirconacycle to form **67**. In the case of zirconacyclopentenes, the first cupration is selective for the alkenyl-zirconium bond, so unsymmetrical zirconacycles can be used to give products such as **70**. Coupling with 1,1-dihalo compounds[44] leads to cyclised products **71** and **72**. Aryl iodides also react with the organocopper bonds[45] to give **73** with various methods available for quenching the remaining organocuprate.



Reagents and Conditions: i, CuCl (1.0 eq.); ii, phenylethynylbromide (1.0 eq.) 0°C, 1 hr; iii, CuCl (1.0 eq), hexynyl bromide (1.0 eq.), 20 °C, 12 hrs; iv, CuCl (1.0 eq.), trimethylsilylethynylbromide (1.0 eq.), 0 °C, 3 hrs; v, CuCl (2.0 eq.), DMPU (2.5 eq.), benzal chloride (1.0 eq.), 50 °C, 12 hrs; vi, CuCl (2.0 eq.), DMPU (2.5 eq.), 1,1-dibromooct-1-ene-3-yne (1.0 eq.), 50 °C, 12 hrs; vii, CuCl (2.0 eq.), DMPU (2.5 eq.), iodobenzene (1.0 eq.), 50 °C, 1 hr; viii, HCl (3M): ix, hexynyl iodide (1.0 eq.); x, I_2

Scheme 1.9

Organocopper reagents are known to undergo 1,4-addition to enones, which has been used to form cyclic products by reaction of zirconacycles with iodoenones as shown in Scheme 1.10. The first organocuprate bond couples to the halide and then 1,4-addition of the second organocopper bond to the enone causes cyclisation to occur to give **78**.[46] With cyclic iodoenones such as **79**, spirocycles **80** can be formed.[47] Copper-mediated reaction of zirconacyclopentadienes with dimethylacetylene dicarboxylate **82**[48] efficiently forms very highly substituted benzene derivatives **83**. A wide range of zirconacyclopentadienes can be used for this chemistry, making this a very useful reaction. Other aromatic compounds can also be formed. Reaction of zirconacyclopentadienes with 1,4-dibromo-2-butyne forms substituted styrenes[49] such as **85**. Various 1,2-dihaloaryl compounds can also be coupled[50] to form naphthalenes **87**, anthracenes **88**, quinolines **90** and isoquinolines **92**.

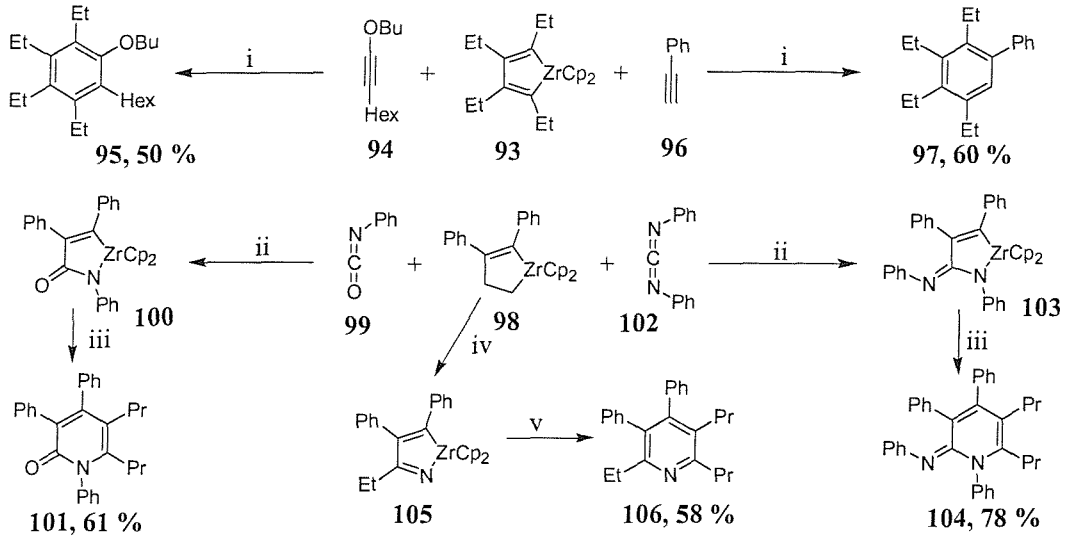


Reagents and Conditions: i, CuCl (2.0 eq.), r.t.; ii, CuCl (2.0 eq.), 50 °C; iii, CuCl (2.0 eq.), DMPU (3 eq.), 50 °C

Scheme 1.10

1.2.6 Transmetallation to nickel

The formation of polysubstituted benzenes such as **83** with copper chemistry requires the use of electron-withdrawing groups on the acetylene. However, this limitation can be overcome by use of a nickel mediated coupling instead of copper. Hence a range of benzene[51] **95** and **97**, pyridinone[52] **101**, iminopyridine[52] **104** and pyridine[53] **106** molecules can be synthesised as shown in Scheme 1.11.

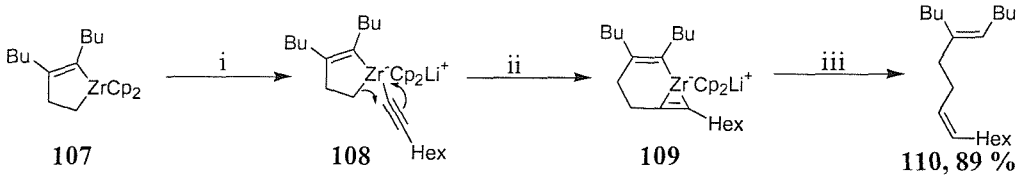


Reagents and Conditions: i, $NiBr_2(PPh_3)_2$ (1.0 eq.), 20 °C; ii, 50 °C; iii, $NiCl_2(PPh_3)_2$ (1.0 eq.), 4-octyne (1.0 eq.), 20 °C; iv, EtCN; v, $NiCl_2(PPh_3)_2$ (1.0 eq.), 4-octyne (1.0 eq.), 50 °C

Scheme 1.11

1.2.7 Reaction with metallated alkynes

Negishi has shown that elaboration of zirconacyclopentenes is possible with alkynyl metals containing lithium or magnesium.[54] Initial coordination of the metal alkyne at –78 °C is followed by rearrangement at room temperature, as shown, to give the zirconate complex **109**. Protonation then stereospecifically gives the 1,5-diene **110**.

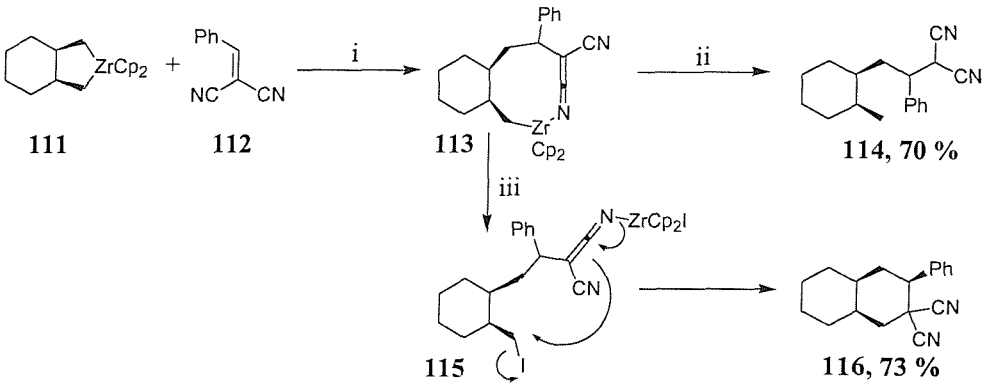


Reagents and Conditions: i, lithium-1-octyne, -78 °C; ii, -78 °C - r.t.; iii, HCl (3M)

Scheme 1.12

1.2.8 Direct addition to activated alkenes

Addition of a carbon-zirconium bond has been shown to occur directly to alkenes with two electron-withdrawing groups.[55] Protonolysis of the resulting complex **113** gives the simple addition product **114**, whereas reaction with iodine affords carbocyclic products **116**.

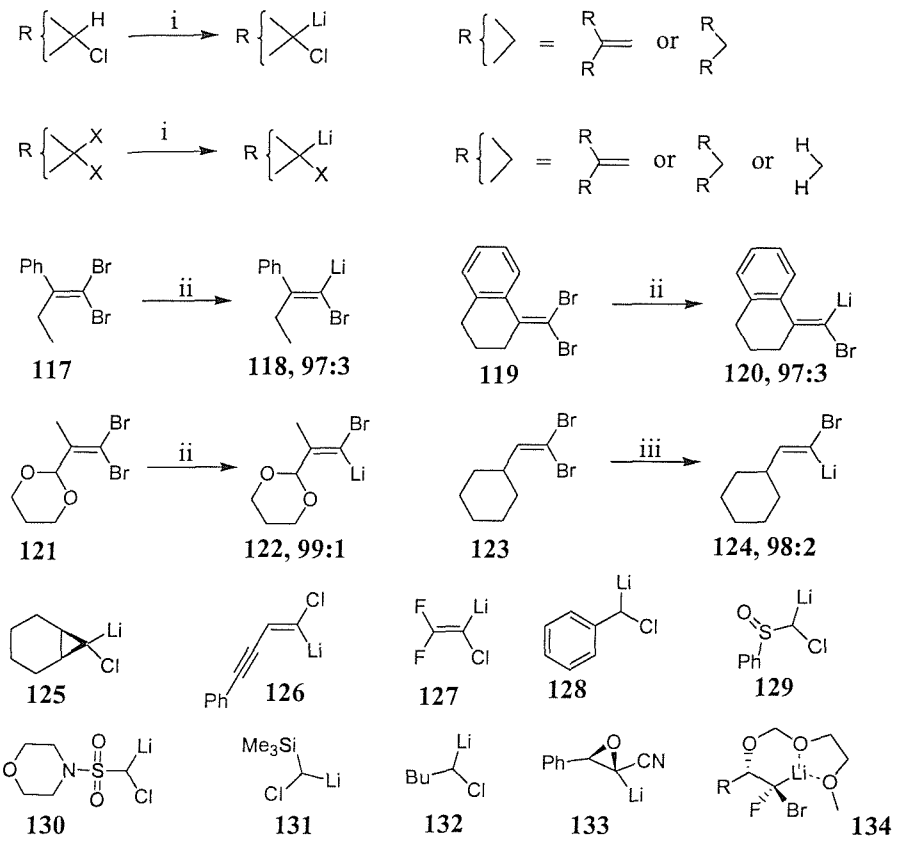


Reagents and Conditions: i, -20 °C; ii, HCl (3M); iii, I_2

Scheme 1.13

1.3 Lithium carbenoids

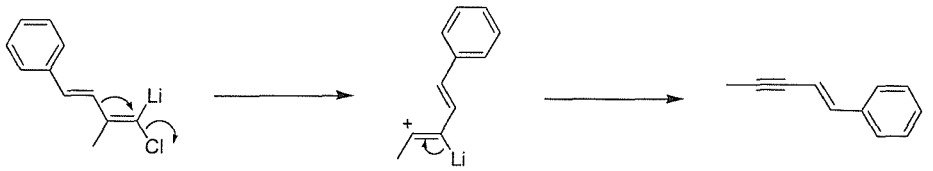
Carbenoids are thermolabile species that contain an anion and a leaving group on the same carbon and are useful synthetic tools. Carbenoids are formed at temperatures generally lower than –80 °C by either deprotonation or halogen-lithium exchange. Deprotonation with an alkyllithium or lithium amide base next to a halide or other heteroatom generates the carbenoid molecule. The early research in this area by Köbrich used deprotonation to form the carbenoids investigated.[56] Alternatively, halogen-lithium exchange of a dihalide leads to the same structure type. For 1,1-dihaloalkenes, halogen-lithium exchange can be selective depending on the groups β to the site of lithiation.[57,58] Generally, the halogen-lithium exchange occurs *cis* to a large group β to the gem-dihalide. Scheme 1.14 shows the methods of carbenoid formation, the selectivity of halogen-lithium exchange (with the dominant product shown) and also a range of carbenoids available to the synthetic chemist.[59-68]



Reagents and Conditions: i, *n*-BuLi, THF; ii, *n*-BuLi, THF, -95 °C; iii, MeLi, THF, -105 °C

Scheme 1.14

Carbenoids are inherently unstable at temperatures higher than –70 °C and undergo various reaction or degradation pathways. The primary routes of degradation are α-elimination and, for vinyl carbenoids, the Fritsch-Buttenberg-Wiechell rearrangement.[69] α-Elimination of lithium halide yields the free carbene, a highly reactive species, which can be trapped by double bonds. However, the Fritsch-Buttenberg-Wiechell rearrangement can be synthetically useful to form substituted alkynes. The requirement is that a β substituent has a π system in conjugation with the metallated alkene.[56] Migration of the substituent can then occur to displace the halide as in **135**, followed by trap of the resulting carbenium ion **136** with the remaining carbanion, as shown in Scheme 1.15. If there are two groups that could migrate, then transfer of the group *trans* to the halide is favoured.

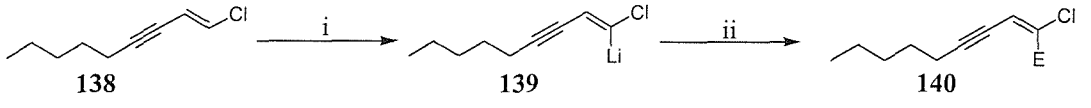


Scheme 1.15

Carbenoids have both nucleophilic and electrophilic properties and generally undergo three main types of reaction[70]:

1. Reactions with electrophiles, where the configuration at the carbenoid centre is retained.
2. Strong nucleophiles can displace the leaving group with formation of another organolithium compound and inversion of configuration.
3. Insertion into bonds such as alkenes, ketones or organometallic bonds by combined nucleophilic and electrophilic reaction paths or by degradation to the carbene.

Much of the early work by Köbrich involved formation of carbenoids followed by trap with electrophiles such as carbon dioxide. A range of electrophiles can be used, as shown by a more recent example in Scheme 1.16 and Table 1.1.[60]



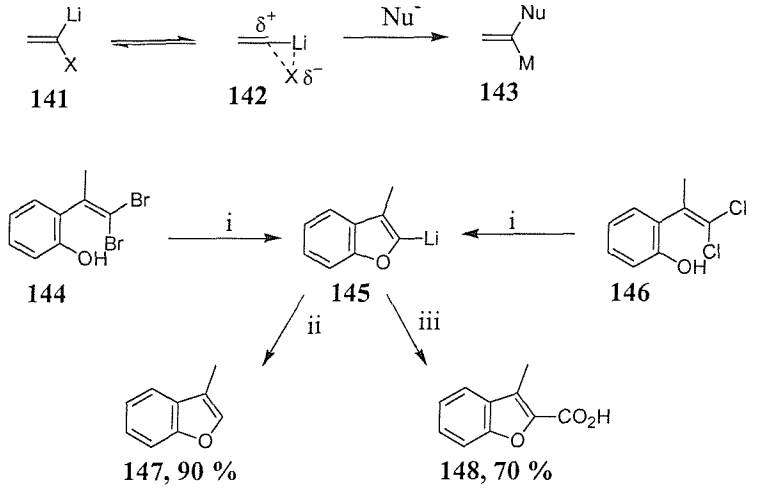
Reagents and Conditions: i, *n*-BuLi, THF/Et_2O/pentane, -100 °C; ii, electrophile, -100 °C.

Scheme 1.16

Table 1.1 *Electrophiles used to trap carbenoid **139** and the yields of **140***

Electrophile	E	Isolated yield of **140**, %
ClCOOEt	COOEt	78
PhCHO	CH(OH)Ph	85
Et_2CO	$C(OH)Et_2$	91
PhNCO	CONHPh	71
Bu_3SnCl	$SnBu_3$	87
Me_3SiCl	$SiMe_3$	85
Ph_2PCl	PPh_2	70

Carbenoids can be more powerful electrophiles[71] than the halide precursors to carbenoid formation due to metal assisted ionisation as in **142**. A good example of this is the formation of heterocycles by nucleophilic attack upon a vinyl carbenoid[72], as shown in Scheme 1.17.



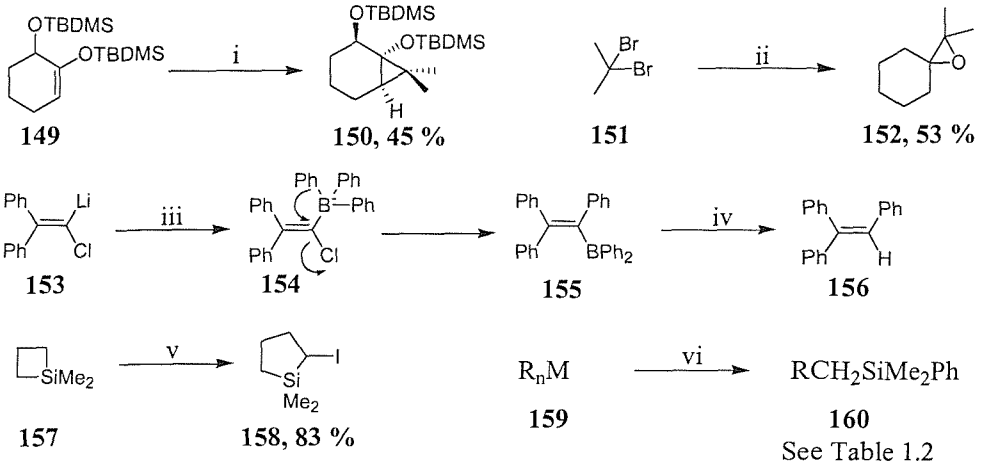
Reagents and Conditions: i, *n*-BuLi (2.0 eq.), THF, -70 °C; ii, MeOH; iii, CO_2 then H^+

Scheme 1.17

Carbenoids can also be used to insert into suitable bonds. Insertion into alkenes gives cyclopropanes[73] such as **150**, whilst insertion into ketones forms epoxides[74] such as **152**. Köbrich[75] discovered carbenoid insertion into organo-boron bonds in 1967, where initial coordination of the carbenoid to the boron in **154** is followed by 1,2-migration of an activated carbon-boron bond to displace the chloride. Such 1,2-metallate rearrangements have also been observed into carbon-silicon bonds[76] and Negishi discovered that reaction occurred with organoaluminium, -zinc, -magnesium and -cadmium species[77], as well as transition metal complexes[78] such as organozirconium, -hafnium, -vanadium, -chromium and -manganese. The above reactions are shown in Scheme 1.18, with yields for Negishi's work shown in Table 1.2.

Table 1.2 Yields for carbenoid insertion into various organometal bonds.

Organometal **159**	Product **160**	GLC Yield, %
i-Bu_3Al	*i*-$BuCH_2SiMe_2Ph$	80
Me_3Al	$MeCH_2SiMe_2Ph$	83
n-Bu_2Mg	*n*-$BuCH_2SiMe_2Ph$	72
n-Bu_2Zn	*n*-$BuCH_2SiMe_2Ph$	61
n-Bu_2Cd	*n*-$BuCH_2SiMe_2Ph$	55



Reagents and Conditions: i, $(CH_3)_2CBr_2$, *n*-BuLi, pentane, -78 °C, 3 hrs; ii, *s*-BuLi, LiBr (1.0 eq.), THF/Et_2O/pentane, -115 °C then cyclohexanone; iii, BPh_3; iv, H^+; v, diiodomethane, LDA, , THF, -78 °C; vi, $LiCH(Cl)SiMe_2Ph$ then H_2O

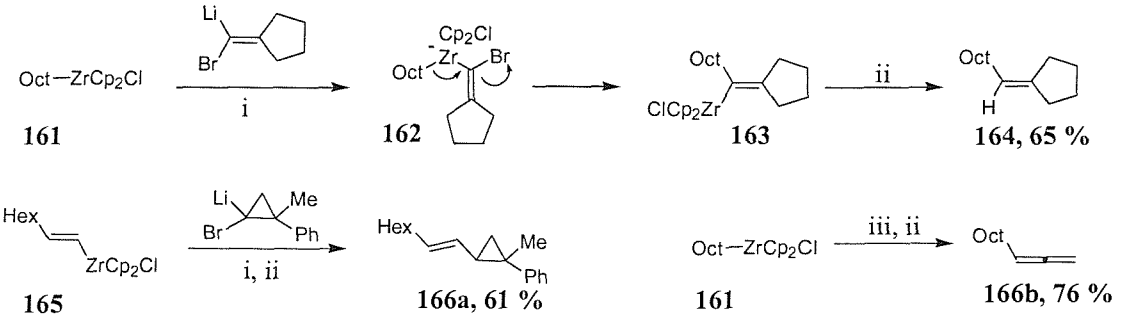
Scheme 1.18

The remainder of this introductory chapter will focus on the insertion of carbenoids into organozirconium bonds.

1.4 Carbenoid insertion into organozirconium bonds.

1.4.1 Carbenoid insertion into acyclic organozirconium bonds.

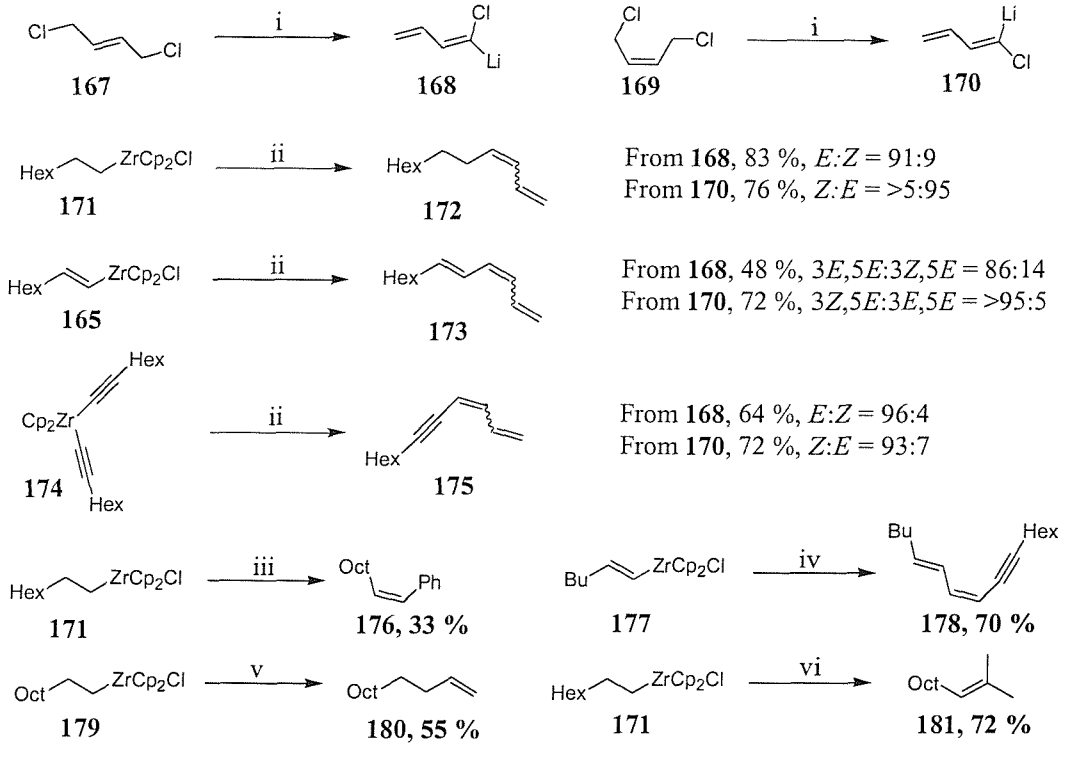
Carbenoid insertion into organozirconium bonds was introduced by Negishi[78] in 1989. Hydrozirconation of relevant alkenes and alkynes provided the templates for a variety of carbenoid insertions as shown in Scheme 1.19. Retention of configuration was obtained with the alkenyl-zirconocene **165** and the use of a γ-haloorganolithium as a carbenoid was observed in the formation of the allene **166b**.



Reagents and Conditions: i, THF, -78 °C; ii, HCl; iii, $LiCCCH_2Cl$, THF, -78 °C

Scheme 1.19

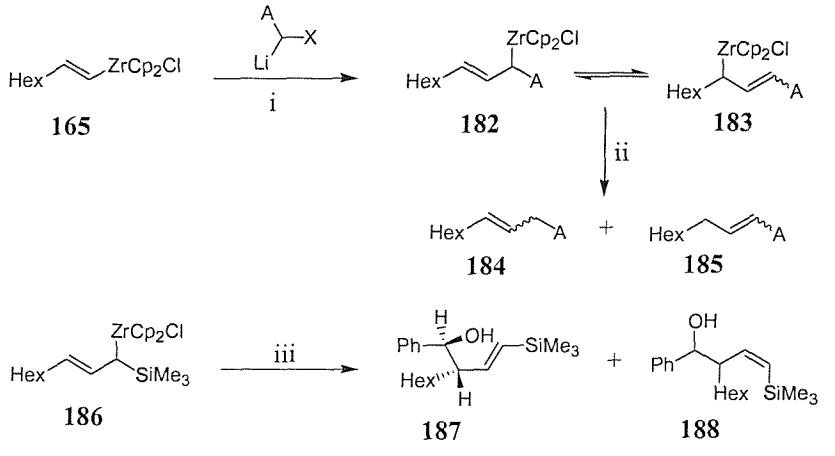
Kasatkin and Whitby extended the above methodology with the insertion of a wide range of carbenoids into acyclic organozirconium species. The insertion of vinyl carbenoids has received considerable attention.[79,80] Formation of the butadiene carbenoids **168** and **170** can be achieved by addition of two equivalents of base to the dichlorides **167** and **169,** respectively. Insertion of these carbenoids into the relevant alkyl, alkenyl and alkynyl zirconium species led to the synthesis of dienes **172,** trienes **173** and dienynes **175** with good levels of stereoselectivity. Other examples of mono-substituted carbenoids stereospecifically gave products **176** and **178.** The unsubstituted ethenyl carbenoid was generated from 1,2-dichloroethane with two equivalents of base and successfully inserted into an alkyl-zirconium bond to give **180.** A dimethyl substituted carbenoid was also inserted into an alkyl-zirconium bond to give **181.** Carbenoids with two different β-substituents were successfully inserted into alkyl-zirconcocenes, but the stereoselectivity was partially lost due to fast isomerisation of the carbenoid.



Reagents and Conditions: i, LiTMP (2.0 eq.), THF, -90 °C; ii, **168** or **170** at -90 °C then HCl; iii, *E*-bromostyrene (1.3 eq.), LiTMP (1.3 eq.), -90 °C then HCl; iv, *E*-1-chlorodec-1-en-3-yne (1.3 eq.), LiTMP (1.3 eq.), -90 °C then HCl; v, 1,2-dichloroethane (1.3 eq.), LiTMP (2.6 eq.), -90 °C then HCl; vi, 1-chloro-2-methylpropene (1.3 eq.), LiTMP (1.3 eq.), -90 °C.

Scheme 1.20

A range of lithium alkyl carbenoids have also been inserted into alkenylzirconocenes to synthesise functionalised allylmetallics.[81,82] The general reaction is shown in Scheme 1.21, with the carbenoid structures and yields shown in Table 1.3. Isomerisation of the allylmetallic led to a mixture of the two products **184** and **185** after protonation, although generally with good selectivity. The resulting organometallic products **182/183** could be reacted with electrophiles as shown for **186**, which proceeded with 97:3 *anti:syn* diastereoselectivity for **187**.



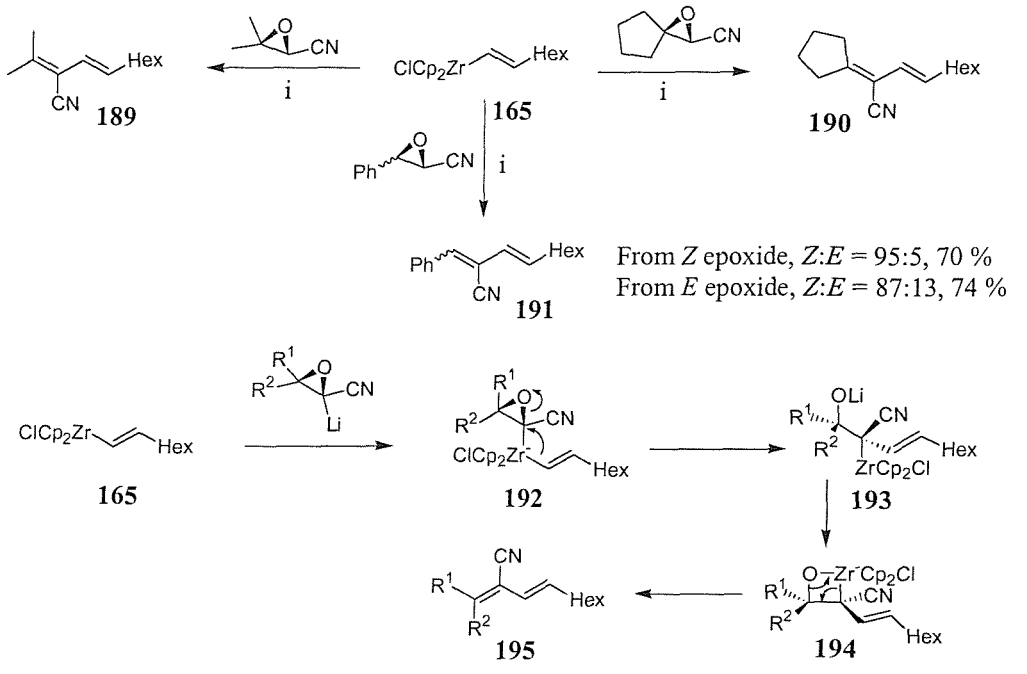
Reagents and Conditions: i, THF, -100 - -60 °C over 1 hr; ii, H_2O; iii, PhCHO (1.3 eq.), $BF_3.Et_2O$ (1.3 eq.), -78 - 20 °C then 20 °C, 18 hrs

Scheme 1.21

Table 1.3 *Protonation products from allylzirconocenes **182** and **183***

A	X	Ratio of **184**:**185**	Yield
OMe	Cl	>95:5	42
$O(CH_2)_2OMe$	Cl	80:20	59
OMe	SO_2Ph	93:7	78
SO_2Ph	Cl	>95:5	48
$P(O)(OEt)_2$	Cl	>95:5	64
CN	Cl	>95:5	73
$SiMe_3$	Cl	89:11	73

Finally, a range of metallated epoxynitriles have been inserted into organozirconocenes[67], with the epoxide oxygen acting as the leaving group of the carbenoid. Some examples plus the mechanism of reaction are shown in Scheme 1.22. Elimination of zirconconene oxide in **194** then led to the synthesis of 2-cyano-1,3-dienes.

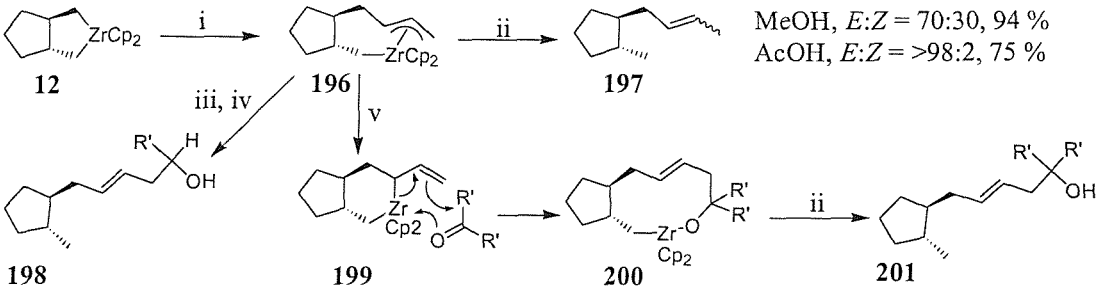


Reagents and Conditions: i, epoxide (1.3 eq.), LDA (1.3 eq.), THF, -90 °C, warm to -60 °C over 1 hr then HCl (2M)

Scheme 1.22

1.4.2 Carbenoid insertion into zirconacycles

A wide range of carbenoids has now also been inserted into zirconacyles.[83,84] The first examples were allyl and propargyl carbenoids. Whilst the 16-electron zirconacyclopentanes are generally unreactive to conventional electrophiles, the 18-electron allyl-zirconocenes **196** from allyl carbenoid insertion reacted with aldehydes and ketones as shown below and in Table 1.4.



Reagents and Conditions: i, CH_2CHCH_2Cl (1.1 eq.), LiTMP (1.1 eq.), -78 °C - r.t., THF; ii, MeOH or AcOH, 16 hrs, r.t.; iii, R'CHO, (1.1 eq.), $BF_3.Et_2O$ (1.1 eq.), -40 - 20 °C, 3 hrs; iv, MeOH/$NaHCO_3$ (aq.), 12 hrs, r.t.; v, Me_2CO, benzene, 80 °C *or* Ph_2CO or cyclohexanone, toluene, 48 hrs, 110 °C

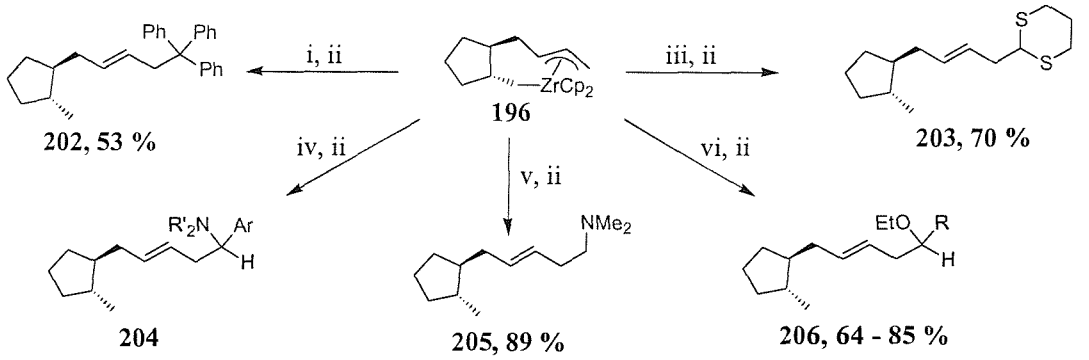
Scheme 1.23

Table 1.4 *Yields and diastereoisomer ratios for products* ***198*** *and* ***201***

Product	R'	Yield, %	Diastereomer ratio
198	Ph	90	2.9:1
198	2,4-(MeO)C_6H_3	60	3.1:1
198	$CHMe_2$	90	1.3:1
198	$(CH_2)_2Me$	95	1.5:1
201	Me	54	-
201	Ph	57	-
201	$-(CH_2)_5-$	56	-

The variation of allyl carbenoid structure compatible with this chemistry was investigated.[85] The leaving groups permitted in place of chloride were bromide, tosylate and diisopropyl carbamate. Phenoxide, ethoxide, sulfide and sulfone leaving groups were not successful in significant yield. 2-Substituted allyl carbenoids were generally tolerated with products obtained in yields greater than 75 %. These substituents were methyl, methylsilane, methyl chloride and $-OCH_2OMe$ groups. However, substituents in the 3-position were generally found to suppress carbenoid insertion and also led to mixtures of isomers.

The allyl-zirconocene **196** was also found to react with a variety of electrophiles[86] yielding the products shown in Scheme 1.24.



204
Ar = Ph, R',R' = $-(CH_2)_5-$, 95 %
Ar = p-Cl-C_6H_4-, R' = Me, 92 %

205, 89 %

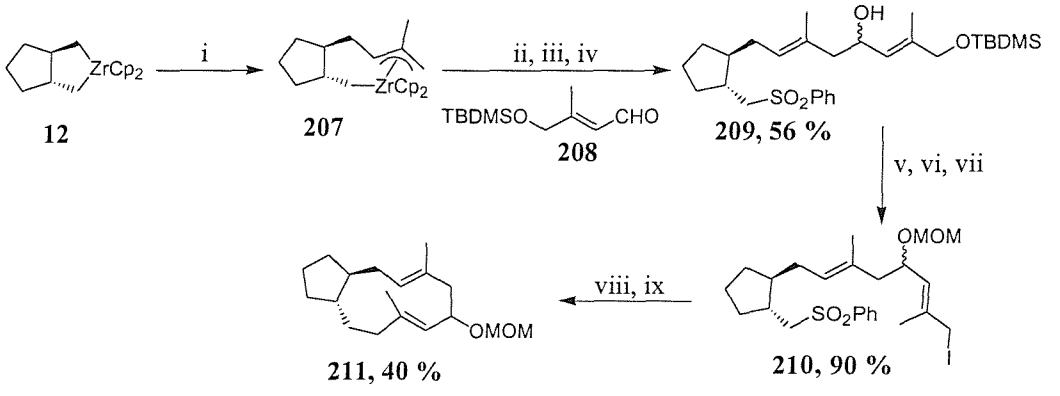
206, 64 - 85 %
R = Ph, Me, Et, $CH=CH_2$, OEt

Reagents and Conditions: i, $Ph_3C^+BF_4^-$ (1.3 eq.), -78 °C - r.t., 1.5 hrs; ii, MeOH then $NaHCO_3$ (aq.), 12 hrs, r.t.; iii, 1,3-ditheniumtetrafluoroborate (2.0 eq.), -78 °C - r.t., 1.5 hrs; iv, $ArCH(NR'_2)(OBu)$ (1.5 eq.), $BF_3.Et_2O$ (1.5 eq.), -78 °C - r.t., 2 hrs; v, $[CH_2=NMe_2]^+I^-$ (1.3 eq.), -78 °C - r.t., 1.5 hrs; vi, $RCH(OEt)_2$, $BF_3.Et_2O$, -78 °C - r.t., 2 hrs

Scheme 1.24

For the reactions with iminium ions to give **204** and acetals to give **206**, no significant diastereoselectivity was observed. Electrophiles with less cationic character than those shown in Scheme 1.24, failed to react with the allyl zirconocene.

The insertion of allyl chloride carbenoids has also been applied to the synthesis of the carbon skeletons of natural products[87] such as the dolabellane skeleton **211**.[88] Insertion of methallyl chloride into zirconacyle **12** was followed by addition of aldehyde **208**. From these zirconium steps, all the carbons required for the final product were present.

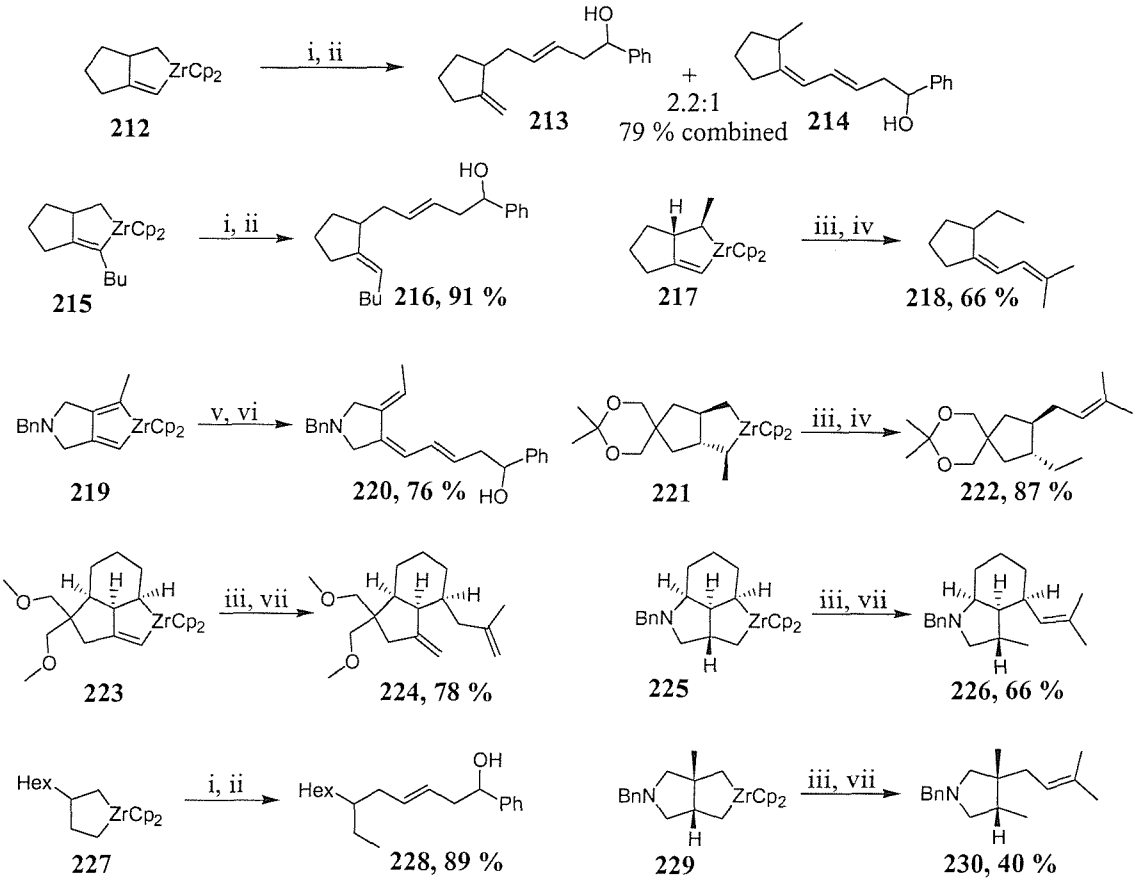


Reagents and Conditions: i, CH_2=C(Me)CH_2Cl, LiTMP, -78 °C; ii, $BF_3.Et_2O$, -78 °C - r.t.; iii, I_2, -78 - 0 °C, 45 min; iv, $NaSO_2Ph$, 45 °C, 2 hrs; v, MOMCl, $^iPr_2EtN$, 0 °C - r.t., 9 hrs; vi, TBAF, 1 hr; vii, PPh_3, imidazole, I_2, 0 °C, 1 hr; viii, LiHMDS, 0 °C - r.t.; ix, Mg/MeOH

Scheme 1.25

Insertion of allyl chloride carbenoids into substituted zirconacyclopentenes was found to be completely regioselective, with insertion into the alkyl-zirconium bond.[89] Further work on the regiochemistry of allyl carbenoids into unsymmetrical zirconacycles[90] provided an insight into how this chemistry can be controlled. The only example found to give a mixture of regioisomers was for the unsubstituted zirconabicyclooctene **212**, which gave a 2.2:1 mixture of isomers favouring insertion into the alkyl-zirconium bond. However, the presence of an α-substituent directed insertion into the unsubstituted side in the majority of cases. This was expected to be due to the blocking of the carbenoid approach. An exception to this rule was the fused ring system in **223** and **225**; in this case the insertion occurs exclusively into the substituted side. Furthermore, a β-substituent was found to direct insertion into the same side of the zirconacycle, as in **228** and **230**. A possible explanation proposed[90]

was that insertion of the carbenoid occurred primarily by the carbenoid acting as an electrophile, and reaction with the larger HOMO occurred. Molecular modelling and calculations suggested that for the fused cyclohexyl system, the HOMO was much larger on the side into which insertion occurred. Results explained in Chapter 4 of this thesis throw further light on the possible mechanism.

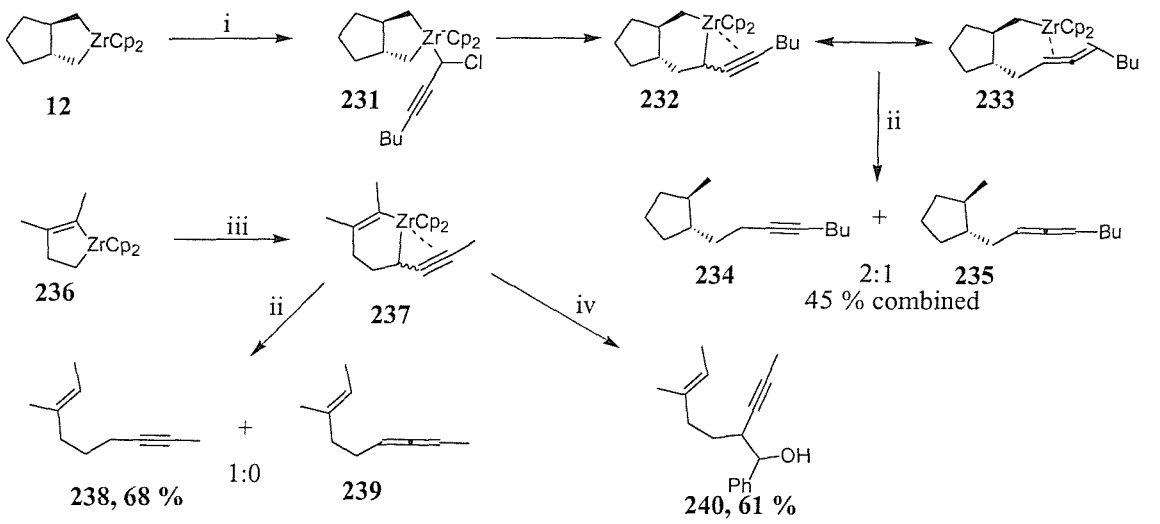


Reagents and Conditions: i, lithium chloroallylide (1.5 eq.), -78 - -30 °C.; ii, benzaldehyde (2.0 eq.), $BF_3.Et_2O$ (2.0 eq.), -30 °C - r.t. then $MeOH/NaHCO_3$; iii, lithium chloromethallylide (1.5 eq.), -78 °C - r.t.; iv, AcOH; v, lithium chloroallylide (5.0 eq.), -78 - -30 °C; vi, benzaldehyde (5.0 eq.), $BF_3.Et_2O$ (5.0 eq.), -30 °C - r.t. then $MeOH/NaHCO_3$; vii, $MeOH/NaHCO_3$

Scheme 1.26

With a good understanding of allyl carbenoid insertion into zirconacycles, attention was drawn to use of other carbenoids. Insertion of prop-2-ynyl carbenoids[91] into zirconacycle **12** was found to give cyclic zirconocene η^3-prop-2-ynyl and allenyl complexes such as **232** and **233**. Quench of these complexes gave a 2:1 mixture of the alkyne **234** and the allene **235**. Protonolysis of the alkyne complex **237** was, however, selective for the alkyne **238**, whilst aldehyde addition gave the alcohol **240**.

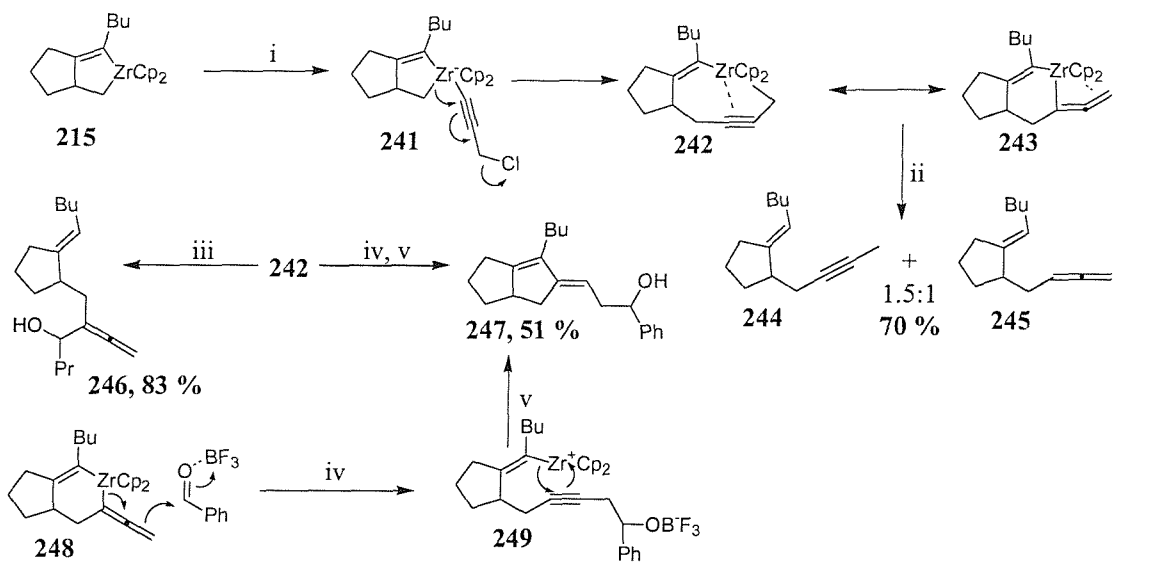
The opposite regiochemistry of aldehyde addition was observed compared to the products of allyl carbenoid addition.



Reagents and Conditions: i, $BuCCCH_2Cl$, LiTMP, -78 °C - r.t.; ii, AcOH; iii, $MeCCCH_2Cl$, LiTMP, -78 °C - r.t.; iv, PhCHO, $BF_3.Et_2O$, r.t., 10 hrs; v, $NaHCO_3$ (aq.)

Scheme 1.27

Insertion of 1-lithio-3-chloroprop-1-yne[92] also gave a mixture of alkyne and allene complexes with 1,4-displacement of the chloride as shown in Scheme 1.28.



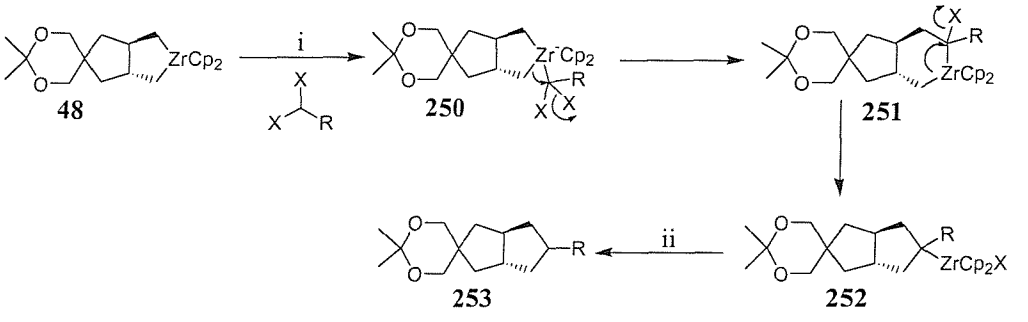
Reagents and Conditions: i, Propargyl chloride, LiTMP, -78 °C; ii, MeOH, r.t.; iii, PrCHO, $BF_3.Et_2O$, -78 °C - r.t., 2 hrs then $NaHCO_3$ (aq.); iv, PhCHO, $BF_3.Et_2O$, -78 °C - r.t.; $NaHCO_3$ (aq.)

Scheme 1.28

Addition to alkyl aldehydes to **242** gave addition products such as **246**, similar to those in Scheme 1.27. However, addition of aryl aldehydes gave cyclopentene

products such as **247** after intramolecular insertion of the alkyne into the resulting carbon-zirconocenium bond in **249**.

Carbocyclic products were formed from insertion of 1,1-dihalo-1-lithio carbenoids[93] by the mechanism shown in Scheme 1.28. After initial insertion of the carbenoid to give the zirconacyclohexane **251**, the second halide is displaced to yield the bicyclo[3.3.0]octane system **252**. The yields from insertion of various 1,1-dihalocarbenoids are shown in Table 1.5.



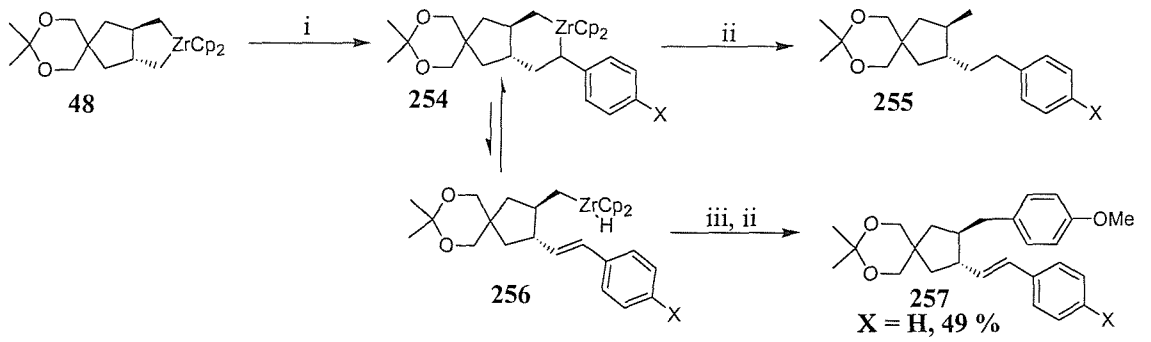
Reagents and Conditions: i, 1,1-dihalo compound (1.5 eq.), LDA (1.7 eq.), -78 - -55 °C over 2hrs; ii MeOH, $NaHCO_3$, r.t., 16 hrs.

Scheme 1.28

Table 1.5 *Yields of carbocycles **253** after insertion of 1,1-dihalo-1-lithiospecies*

R	X	Yield of **253**, %
H	Cl	15
Pr	Br	66
OMe	Cl	68
$SiMe_2Ph$	Cl	71
CN	Cl	48

A range of benzyl carbenoids has been inserted into zirconacyclopentanes and –enes to give mono- or bis-insertion products.[94] Addition of 1.1 equivalents of the carbenoid yielded the mono-insertion products **255** as shown in Scheme 1.29 and Table 1.6. A small proportion of β-hydride elimination was proposed to give the more reactive intermediate **256**, followed by the favoured second carbenoid insertion into the carbon-zirconium hydride bond to give bis-insertion products such as **257**.



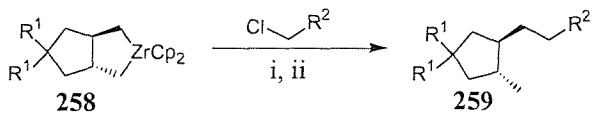
Reagents and Conditions: i, X-substituted benzyl chloride (1.1 eq.), LDA (1.1 eq.), -78 °C.; ii, warm to r.t. then MeOH; iii, 30 min at -78°C then 4-methoxy benzyl chloride (3.0 eq.), LDA (3.0 eq.)

Scheme 1.29

Table 1.6 *Yields of mono-insertion products* ***255*** *after benzyl carbenoid insertion*

X	Yield of **255**, %
H	84
Me	79
MeO	83
Cl	80

A range of other carbenoids has also been inserted into zirconacyclopentanes and –enes.[84] Carbenoids with silicon, tin, sulphur and oxygen groups were found to insert, along with electron-withdrawing groups such as phosphonate and nitrile groups. The reaction and results are shown in Scheme 1.30 and Table 1.7.



Reagents and Conditions: i, LDA or LiTMP, -78 °C; MeOH/$NaHCO_3$

Scheme 1.30

Table 1.7 *Yields of* ***259*** *from insertion of various carbenoids into zirconacycle* ***258***

R^1, R^1	R^2	Yield of **259**, %
$-CH_2OCMe_2OCH_2-$	$SiMe_3$	78
$-CH_2OCMe_2OCH_2-$	$SiMe_2Ph$	77
$-CH_2OMe, -CH_2OMe$	$SnBu_3$	11
$-CH_2OCMe_2OCH_2-$	SPh	77
$-CH_2OCMe_2OCH_2-$	OEt	45
$-CH_2OMe, -CH_2OMe$	$P(O)(OEt)_2$	74
$-CH_2OMe, -CH_2OMe$	CN	24

As explained, a range of carbenoids has been inserted into zirconacycles to date and the reactions show considerable elaboration from the starting dienes or enynes. The regiochemistry of carbenoid insertion has also been investigated for allyl carbenoids, and the results found to be relevant for other carbenoids as well. The following chapters discuss further work in the area of carbenoid insertion into zirconacycles.

1.5 References

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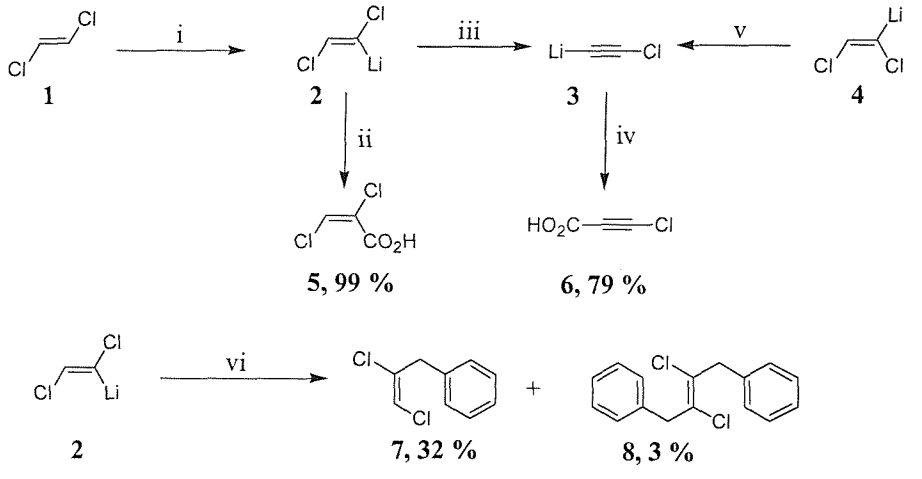
Chapter 2. Insertion of *E*-1,2-dihalo-1-lithioethene and 1-lithio-2-haloethyne into zirconacycles

2.1 Introduction to research area

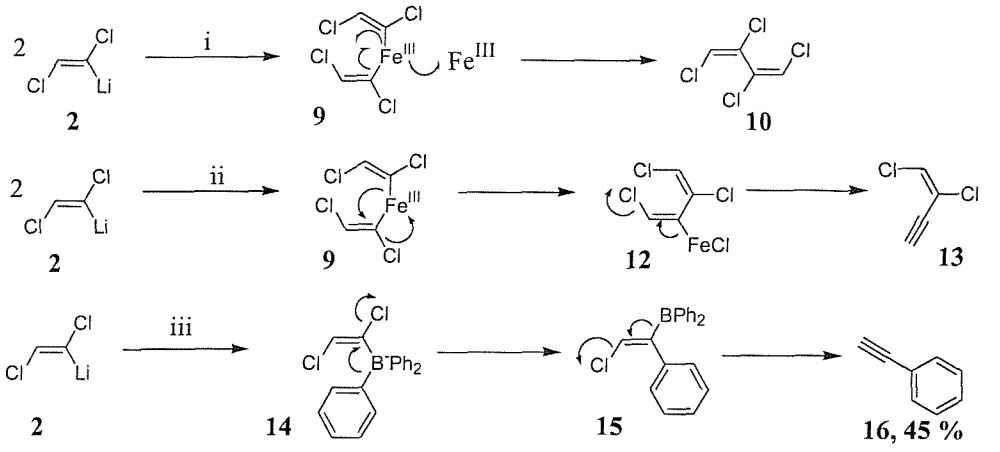
The carbenoid *E*-1,2-dichloro-1-lithioethene **2** was first reported in 1966 by Köbrich[1] and was found to be stable in the temperature range –110 - -83 °C. The carbenoid was trapped by carbon dioxide to give the acid **5** in almost quantitative yield. Slow warming of the carbenoid to –20 °C caused elimination to form **3**. The *cis*-isomer **4**, however, was never trapped and instead underwent immediate elimination of chloride, with subsequent lithiation to give **3**. Carbenoid **2** has also been trapped by benzyl bromide[2] to give the elaborated product **7**, with partial metalation of the product observed, which led to formation of **8**.



Reagents and Conditions: i, *n*-BuLi (1.0 eq.), THF, Et_2O, pentane (4:1:1), -110 °C; ii, CO_2 then H^+; iii, slow warm to -20 °C; iv, CO_2 then H^+; v, -110 °C; vi, Benzyl bromide, -100 °C, warm to r.t. over 16 hrs.

Scheme 2.1

Addition of carbenoid **2** to an excess of $FeCl_3$ to give an organoiron species **9** was followed by oxidative coupling to give the dimer **10**.[2,3] Further reaction of these products allowed generation of specific oligomers of the *trans*-dichloroethene sub-unit. If a deficiency of the iron was used, the reaction followed a different pathway where one carbenoid unit inserted into another by a 1,2-metallate rearrangement, leading to elimination of iron choride in **12** to give **13**.

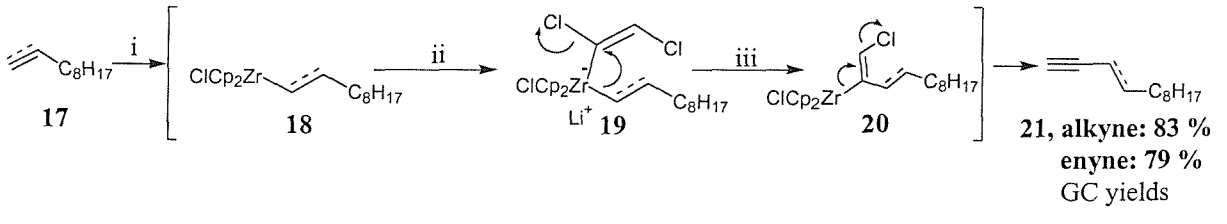


Reagents and Conditions: i, $FeCl_3$ (2.0 eq.), ii, $FeCl_3$ (0.25 eq.); iii, BPh_3, -105 °C - r.t., 2 hrs.

Scheme 2.2

Carbenoid insertion of **2** into an organoborane has also been observed by Köbrich[3-5], whereby addition of the carbenoid to triphenylborane led to an intermediate boronate complex **14**. The 1,2-rearrangement was then observed, placing the boron antiperiplanar to the chloride in **15**. β-Elimination then gave phenylacetylene in 45 % yield. The above result set suitable precedent for the insertion of carbenoid **2** into an organozirconocene, due to the similarities between the chemistry of organozirconium and organoboron complexes.

The insertion of *E*-1,2-dichloro-1-lithioethene **2** into an acyclic organozirconium bond has recently been reported by Kasatkin and Whitby.[6] Initial insertion of the carbenoid into the organozirconium bond of **18** led to a chlorine in an antiperiplanar position to the zirconium in **20**, analogous to **15**. Subsequent elimination of chloride led to the alkyne product **21**.



Reagents and Conditions: i, Cp_2ZrHCl (1.15 eq.), THF, 20 °C, 1hr; ii, *E*-1,2-dichloroethene (1.3 eq.), LiTMP (1.3 eq.), -80 °C; iii, -15 - 20 °C for 2 hrs.

Scheme 2.3

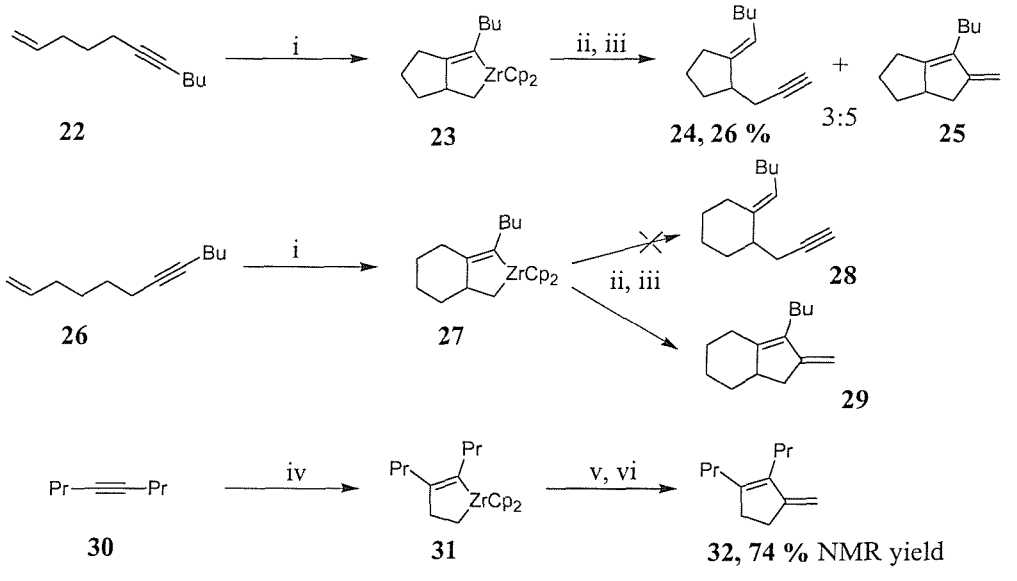
The initial aim of this project was to insert *E*-1,2-dichloro-1-lithioethene **2** into zirconacycles to see if the same elimination as in **20** occurred to give an alkyne. It was

then hoped that further elaboration of the remaining carbon-zirconium bond would be possible, so that methodology towards multi-component couplings could be invented.

2.2 Insertion into zirconacyclopentenes

2.2.1 Initial results

The carbenoid *E*-1,2-dichloro-1-lithioethene **2** was first inserted into zirconacycle **23** formed from enyne **22**. The expected enyne product **24** was indeed formed, but GC analysis showed a second product that was found to be the methylenecyclopentene **25** after further investigation. The ratio of GC peaks was 3:5 for **24**:**25**. Purification on silica yielded **24** in a 26 % yield, but **25** was not recovered due to instability to the acidic media. Even purification on neutral alumina was unsuccessful. Insertion of the carbenoid into zirconacycle **27**, however, provided none of the expected enyne **28**, but instead showed clean insertion to give only the methylenecyclopentene **29**. The crude ^{1}H NMR of **29** showed two distinct singlets at 4.6 ppm (in $CDCl_3$) that corresponded to a less well resolved peak at 4.6 ppm in the ^{1}H NMR of the crude mixture of **24** and **25**. These peaks were typical for an exocyclic alkene, which led to the hypothesis of the structures of **25** and **29**.



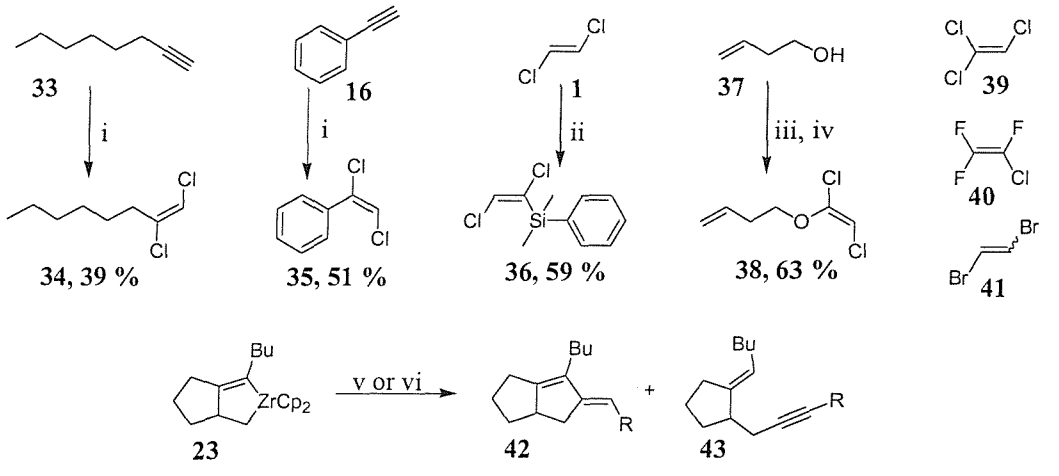
Reagents and Conditions: i, Cp_2ZrCl_2 (1.0 eq.), *n*-BuLi (2.0 eq.), THF, -78 °C - r.t.; ii, *E*-1,2-dichloroethene (2.0 eq.), LDA (2.0 eq.), -78 °C; iii, MeOH/$NaHCO_3$; iv, Cp_2ZrCl_2 (1.0 eq.), nBuLi (2.0 eq.), ethene, THF, -78 °C - r.t., then **30**; v, *E*-1,2-dichloroethene (1.0 eq.), LDA (1.0 eq.), -78 °C; vi, MeOH/$NaHCO_3$

Scheme 2.4

Insertion of the carbenoid into the monocycle **31** proceeded to completion with a single equivalent of carbenoid compared to the optimal two equivalents for the two zirconabicycles. Only the methylenecyclopentene **32** was formed and a cleaner crude NMR was obtained. Whilst purification was still found to be impossible, the yield was obtained by NMR using anisole as an internal standard.

2.2.2 Insertion of other *E*-1,2-dihalides

A range of alternative substituted carbenoid precursors were synthesised to insert into zirconacycle **23**. It was hoped that substituent groups might provide extra stability to the alkylidenecyclopentenes formed, or indeed cause a different course of reaction.



Reagents and Conditions: i, $CuCl_2$ (40 eq.), LiCl (40 eq.), MeCN; ii, LiTMP (1.0 eq.), DMPS-Cl (0.8 eq.), THF; iii, NaH (1.0 eq.), THF; iv, trichloroethene, reflux, 20 hrs; v, **34**, **35**, **36**, **38**, **39**, **41**, LDA, -78 °C; vi, **40**, *t*-BuLi, -90 °C.

Scheme 2.5

Carbenoid precursors **34** and **35** were formed from the corresponding alkynes.[7] *E*-1,2-dichloroethene **1** was lithiated in the presence of DMPS-Cl to give the alkene **36**, but this was not obtained in a pure form since further lithiation of **36** caused elimination of chloride to give the corresponding chloroalkyne. 3-Buten-1-ol **37** was deprotonated and then heated to reflux with trichloroethene to give **38**.[8,9]

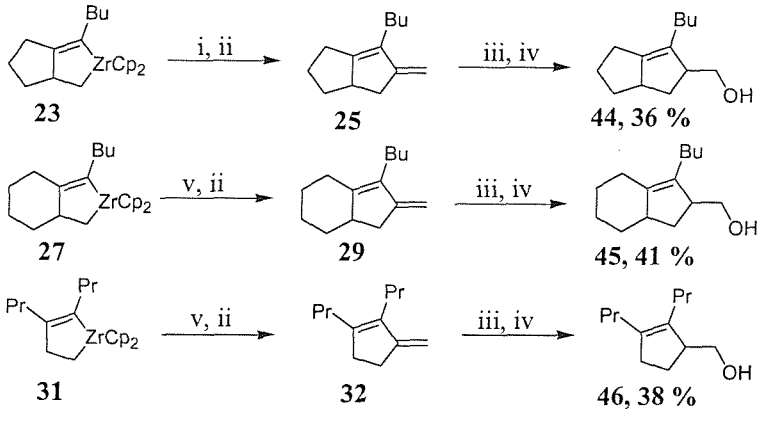
Unfortunately, none of the synthesised carbenoids inserted into zirconacycle **23**. Instead, the carbenoids degraded by elimination of chloride to yield a chloroalkyne, as identified for **34**, **35** and **36**. Metalated **39** was also inert to insertion, as was the product of chlorine-lithium exchange of **40**.[10] These results therefore did not provide

much information, except that substituted carbenoids did not react with the zirconacycle.

However, insertion of 1,2-dibromoethene **41** (1:2 mixture of *E*:*Z*) did not only go to completion with two equivalents of the carbenoid, but complete selectivity was observed for the methylenecyclopentene **42** (R = H, i.e. **25**).

2.2.3 Synthesis of stable reaction products.

Since for all cyclisation substrates so far described, the methylenecyclopentene products could now be selectively synthesised, full characterisation of the products was required. The NMR spectra for **25** and **32** were clean enough for assignment, but were not analytically pure. Full characterisation of the products was obtained by hydroboration of the crude methylenecyclopentenes with 9-BBN followed by reaction with basic peroxide, to form stable alcohols **44**, **45** and **46**.



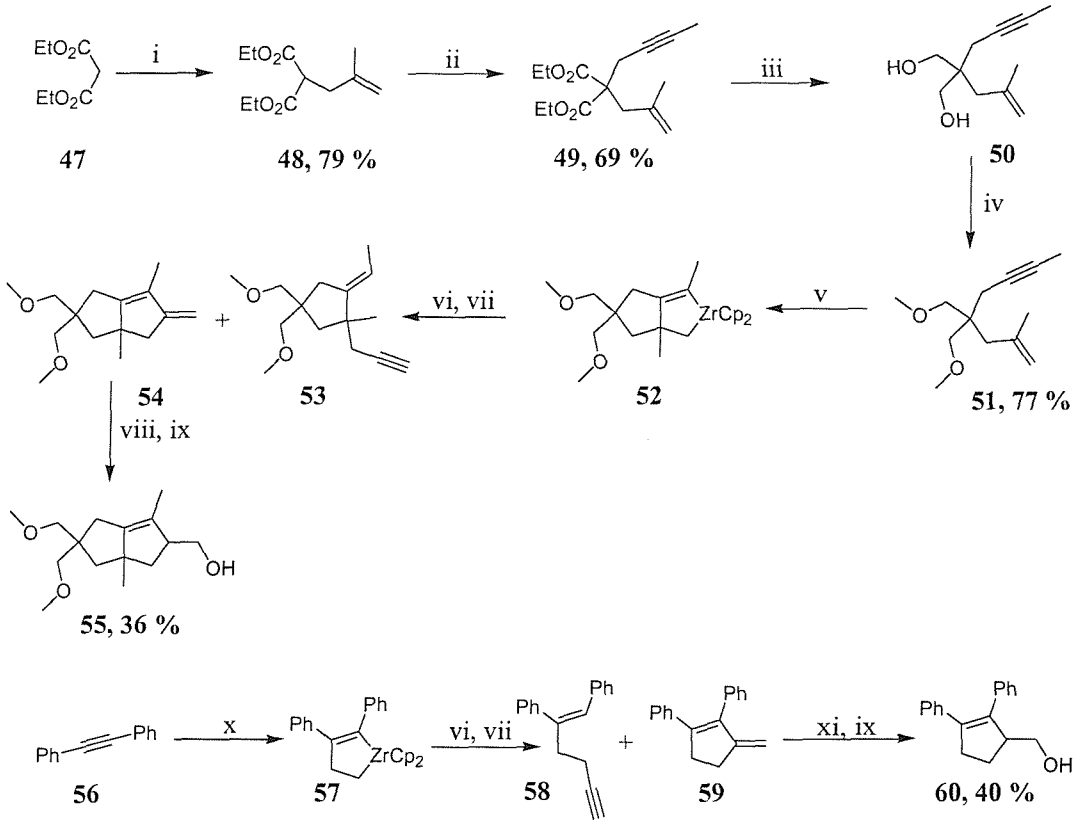
Reagents and Conditions: i, 1,2-dibromoethene (2.0 eq.), LDA (2.0 eq.), -78 °C; ii, MeOH/$NaHCO_3$, 16 hrs; iii, 9-BBN, (1.0 eq.) THF, 0 °C - r.t., 30-45 min; iv, H_2O_2 (aq., 35 %), NaOH (aq., 2.5 M); v, *E*-1,2-dichloroethene (2.0 eq.), LDA (2.0 eq.), -78 °C

Scheme 2.6

Whilst the yields of the alcohols obtained were modest, they are with respect to the acyclic hydrocarbons prior to zirconium cyclisation. Therefore, the yields were considered reasonable considering the three synthetic steps involved and the degree of elaboration obtained.

2.2.4 Carbenoid insertion into other zirconacycles.

Further synthetic examples of the methylenecyclopentenes were required and hence the enyne precursor **51** was synthesised as shown in Scheme 2.7 using malonate chemistry. Phenylacetylene and an ethyl Grignard reagent were also used to form a suitable zirconamonocycle **57**. Insertion of both the dichloro- and dibromoethenes was then performed into zirconacycles **52** and **57** to give mixtures of the corresponding enynes and methylenecyclopentenes. Yields are shown in Table 2.1. Hydroborations of the methylenecyclopentenes were also performed to give the alcohol products **55** and **60** from insertion of the 1,2-dibromoethene **41**.



Reagents and Conditions: i, NaOEt/EtOH then 3-chloro-2-methyl-1-propene; ii, NaOEt/EtOH then but-2-ynyl methanesulfonate; iii, $LiAlH_4$, Et_2O; iv, NaH (3.0 eq.), MeI (3.0 eq.) (yield over 2 steps); v, Cp_2ZrCl_2 (1.0 eq.), *n*-BuLi (2.0 eq), THF, -78 °C - r.t.; vi, 1,2-dihaloethene (2.0 eq.), LDA (2.0 eq.), -78 °C; vii, MeOH/$NaHCO_3$; viii, 9-BBN (1.0 eq.), THF, 0 °C - r.t., 45 min; ix, H_2O_2 (aq., 35 %), NaOH (aq., 2.5 M); x, Cp_2ZrCl_2 (1.0 eq.), EtMgCl (2.0 eq.), -78 °C - r.t. then **56**; xi, $BH_3.SMe_2$ (0.5 eq.), THF, 30 min.

Scheme 2.7

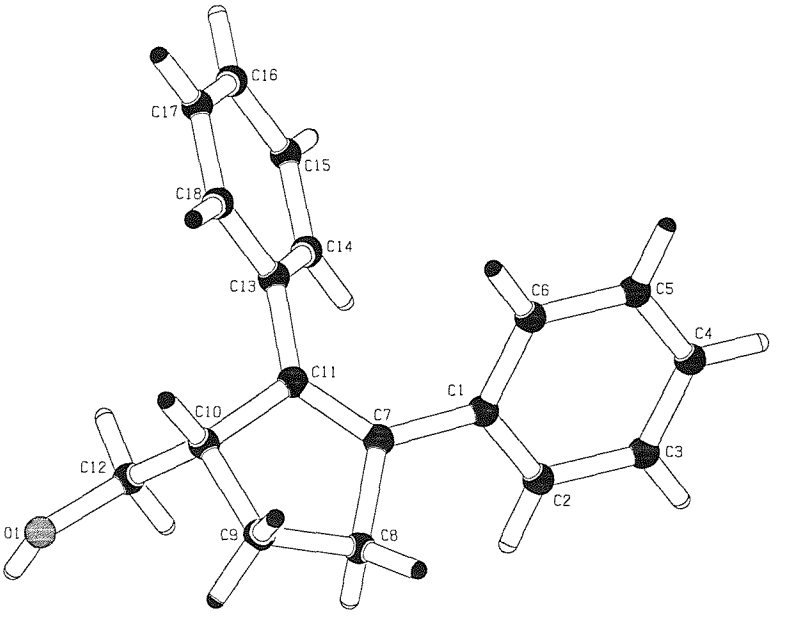
Table 2.1 *Yields of enynes* ***53*** *and* ***58*** *and methylenecyclopentenes (mcp)* ***54*** *and* ***59****.*

Zirconacycle	Carbenoid precursor	Ratio of enyne:mcp (GC)	Isolated yield of enyne, %	Isolated yield of mcp, %
52	Dichloride **1**	2:3	27	17
52	Dibromide **41**	1:22	-	66
57	Dichloride **1**	1:3	33	38
57	Dibromide **41**	1:7	15	24

Clearly, the ratio of enyne to methylenecyclopentene is substrate dependent, but the use of the dibromide increased the proportion of the latter as previously seen. The good yield of **54** from insertion of the dibromide **41** suggests a much more stable methylenecyclopentene was formed. The presence of a methyl group on the ring junction appears to provide extra stability to the molecule. Unfortunately the recovery of the same product from insertion of the dichloride **1** was not as successful.

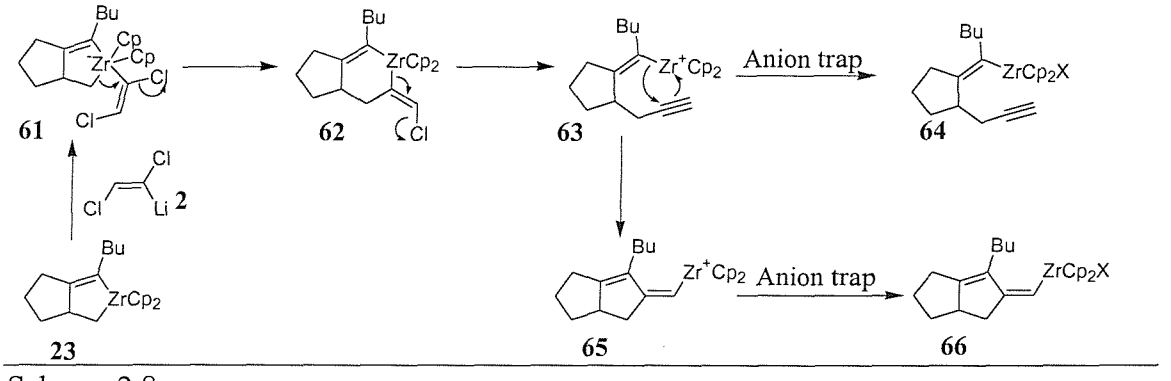
Enyne **58** and methylenecyclopentene **59** were fortunately separable and both were fully characterised. Fortuitously, the alcohol product **60** was crystalline and hence an x-ray structure could be obtained for confirmation of structure, as shown in Figure 2.1.

Figure 2.1 *X-Ray structure of alcohol* ***60***



2.2.5 Mechanism of methylenecyclopentene formation.

The proposed mechanism for insertion of *E*-1,2-dichloro-1-lithioethene **2** is shown in Scheme 2.8. Stereoselective insertion of the carbenoid would give the expected zirconacyclohexene **62** and in an analogous way to the acyclic work (Scheme 2.3), the zirconium is left anti-periplanar to the remaining chloride. Hence the chloride is eliminated to give the alkyne **63**. The latter intermediate now contains a zirconocenium ion, which is set up for insertion of the alkyne into the carbon-metal bond to form **65**. However, if the rate of anion trap of the zirconocenium ion was competitive with the rate of the cyclisation process, a mixture of **64** and **66** would be formed. A similar intramolecular cyclisation was observed when η^3-propargyl-zirconacycles were reacted with aldehydes and $BF_3.Et_2O$ (Chapter 1, Scheme 1.28).[11]



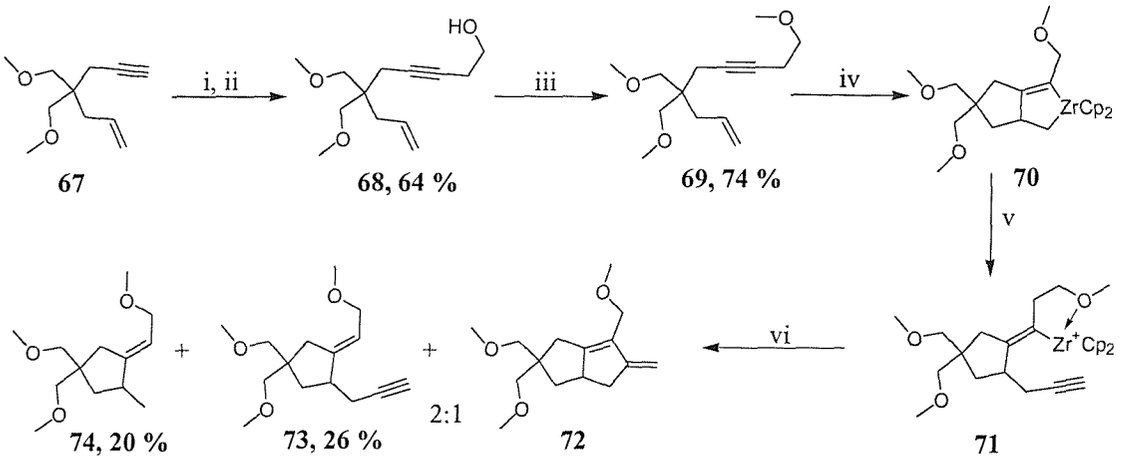
Scheme 2.8

Ring strain in bicyclo[3.3.0]octene systems **65** and the corresponding intermediate in formation of **54** reduced the amount of these products being formed and hence some anion trap of the zirconocenium ion **63** was observed. However, in methylenecyclopentenes **29** and **32** the same strain is not present and the extra flexibility allows reaction to form the cyclopentene. A logical explanation for the sole formation of the methylenecyclopentenes in the bicyclo[3.3.0]octene systems when 1,2-dibromoethene is inserted is that the bromide ion or further 1,2-dibromo-1-lithioethene does not trap the zirconocenium ion as rapidly as the corresponding chloride and carbenoid. However, an alternative explanation will be covered in a later section of this chapter.

The suppression of the cyclisation to form **65** was attempted by inclusion of suitable anions in the reaction mixture to trap the positive ion generated. Reagents used included further LiCl, lithium butoxide, lithium diethylamide and lithium pyrollidide,

but none of these altered the ratio of products. The only effect observed was a reduction of carbenoid insertion.

Suppression of the methylenecyclopentene was only achieved by the presence of a pendant methoxy group that could donate an electron pair to stabilise the zirconocenium ion in **71**. Firstly, the cyclisation precursor **69** was synthesised by lithiation of enyne **67** and reaction with ethylene oxide followed by methylation of the resulting alcohol.



Reagents and Conditions: i, *n*-BuLi (1.0 eq.), HMPA (1.0 eq.), THF, -70 - -20 °C; ii, ethylene oxide, -20 °C - r.t., 16 hrs; iii, NaH (1.5 eq.), THF, then MeI (1.5 eq.); iv, Cp_2ZrCl_2 (1.0 eq.), *n*-BuLi (2.0 eq.), THF, -78 °C - r.t.; v, *E*-1,2-dichloroethene (2.0 eq.), LDA (2.0 eq.), -78 °C; vi, $MeOH/NaHCO_3$

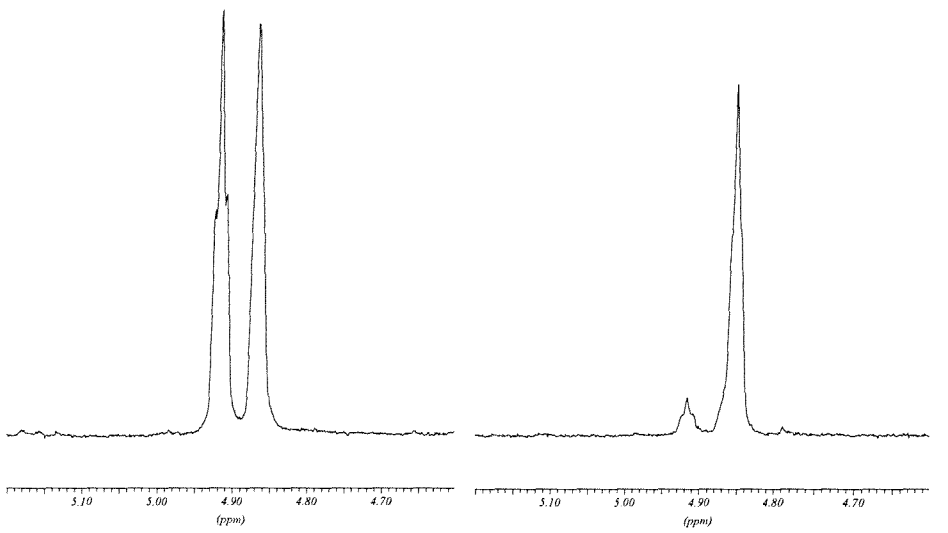
Scheme 2.9

The presence of the methoxy group was successful in suppressing the cyclisation as the ratio of enyne **73** to methylenecyclopentene **72** was 2:1, respectively, by GC. The methylenecyclopentene was unstable to chromatography, but the enyne **73** was isolated in a low 26 % yield. The low yield was due to incomplete carbenoid insertion as the pendant methoxy group clearly inhibited this step of the reaction as well. The cyclised product without carbenoid insertion, **74**, was recovered in 20 % yield.

Further evidence of the mechanism of reaction was sought through deuteration experiments in conjunction with GOESY NMR experiments to show the presence and stereochemistry of the zirconium. The substrate of choice was the monocycle **32** since the reaction was known to be the cleanest and the best crude NMR spectra had been obtained for this product. Quench of the organozirconium **75** with $MeOD/D_2O$ gave a

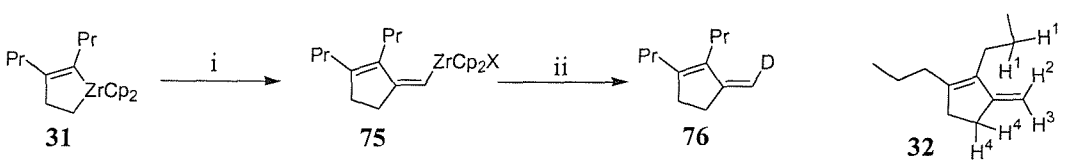
very clean ^{1}H NMR spectrum that clearly showed deuterium incorporation at only one of the vinyl positions (Figure 2.2).

Figure 2.2 *^{1}H NMR spectra showing monodeuterated product* ***76*** *(solvent C_6D_6)*



32 **76**

The above result in conjunction with a GOESY NMR experiment showed the position of the deuterium, and hence the position of the zirconium in the pre-quench reaction product, to be that shown in **76**. A through space correlation of 1 % from the peak diminished in the above NMR spectrum, H^2, was observed to the alkyl protons H^1 in Scheme 2.10. A COSY experiment also showed ^{1}H-^{1}H correlations between H^4 and both H^2 and H^3 and hence this result was eliminated from the GOESY experiment. This proof of the zirconium position strongly supports the proposed mechanism of methylenecyclopentene formation.



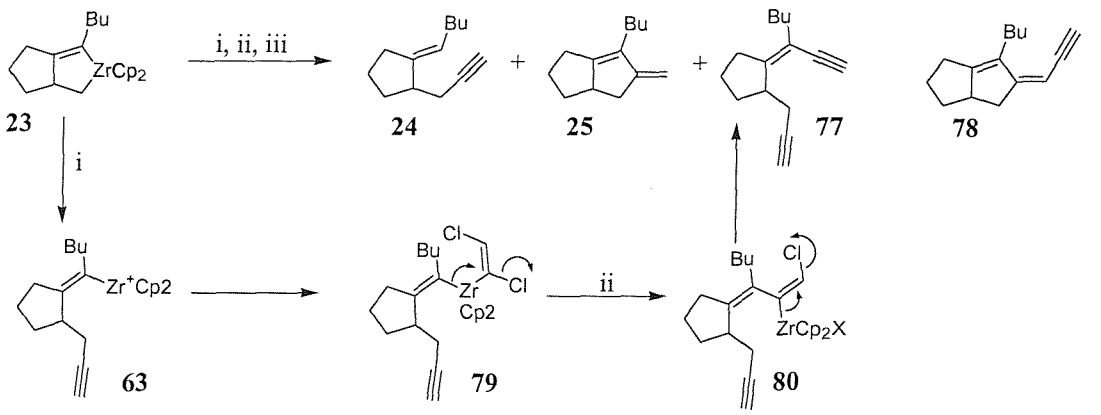
31 **75** **76** **32**

Reagents and Conditions: i, *E*-1,2-dichloroethene 1.0 eq.), LDA (1.0 eq.), -78 °C; ii, MeOD/D_2O, r.t., 16 hrs.

Scheme 2.10

2.2.6 Course of reaction with warming to room temperature

When the carbenoid **2** was inserted into zirconacycle **23** and the reaction warmed to room temperature, a bis-insertion product was observed by GC, with the correct mass peak for **77** or **78**. This showed that a further carbenoid molecule was trapping the intermediate zirconocenium ion. Because the resulting species **79** was neutral and not a zirconate species, it was not activated towards insertion of the carbenoid fragment into the carbon-zirconium bond and required the higher temperature for the reaction to occur. Once insertion had occurred, elimination of the zirconium chloride would be rapid as before. It was important to determine whether the observed peak was indeed **77** or **78**. Isolation of the products was very difficult, since on warming to room temperature, the reaction mixture became a black sludge. However, use of the GC to give GC yields was successful and the results are shown in Table 2.2. Dodecane was used as an internal standard.



Reagents and Conditions: i, *E*-1,2-dichloroethene (2.0 eq.), LDA (2.0 eq.), -78 °C; ii, -78 °C - r.t.; iii, MeOH/$NaHCO_3$

Scheme 2.11

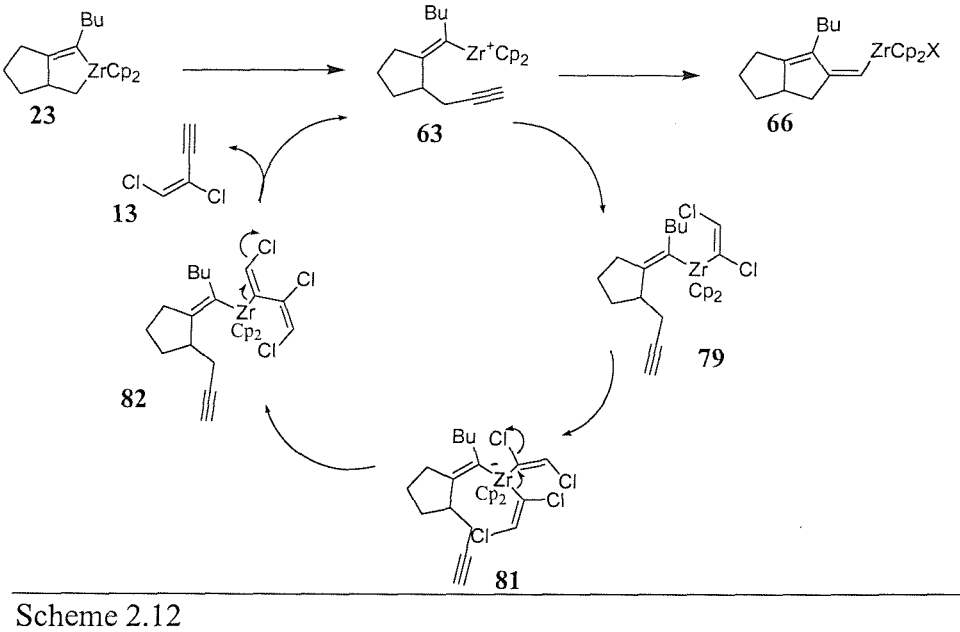
Table 2.2 *GC yields of products on warming to room temperature.*

	Yield **24**, %	Yield **25**, %	Yield **77**, %
After insertion, -78 °C	22	33	-
1 hr. at r.t.	24	16	4
3 hrs. at r.t.	16	15	11
20 hrs. at r.t.	7	15	20

Whilst a large drop in yield of the methylenecyclopentene was observed initially on warming to room temperature, the amount remained constant once at 20 °C. However, once at room temperature, the yield of **24** was reduced in an almost identical amount to the increase in **77**. Hence, the peak observed by GC was probably **77**. The initial drop in yield of **25** may have been due to the formation of **78**, which was then unstable, but this could not be proven.

2.2.7 Course of reaction with excess carbenoid

Initially it was expected that use of a large excess of carbenoid might allow a higher proportion of **24** to be synthesised, since it was known that carbenoid trapped the intermediate **63**. However, the opposite result was observed and the reaction was quite selective for the methylenecyclopentene **25**, with a 1:10 ratio of **24**:**25** observed by GC. This result can be explained by the mechanism shown in Scheme 2.12.



Scheme 2.12

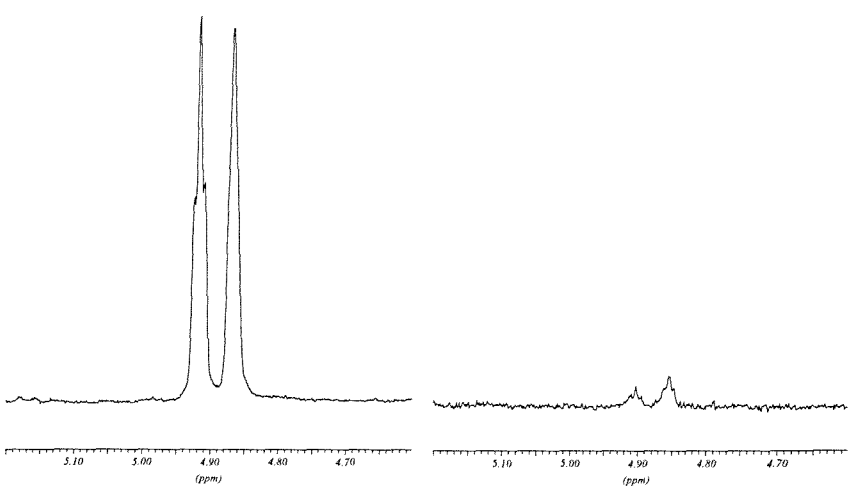
Once the zirconocenium ion in **63** is trapped, a neutral zirconium is formed. However, with a large excess of carbenoid present, coordination of a second carbenoid is possible. Once this occurs, one carbenoid fragment can insert into the other as shown in **81**. When elimination of chloride follows in **82**, the zirconocenium ion is regenerated. Every time **63** is regenerated, a proportion will cyclise to **66** and hence as further cycles

are completed, a higher proportion of **66** will be formed. The zirconium in the above mechanism is performing the same role as the iron in Scheme 2.2. The by-product **13** was synthesised by the same method as in Scheme 2.2 and the same peak was indeed observed by GC when excess carbenoid was inserted into zirconacycle **23**.

2.2.8 Alternative route to methylenecyclopentenes *via* 1-lithio-2-haloethyne

Whilst there is clear evidence of the carbenoid insertion mechanism to form methylenecyclopentenes and a logical explanation has been given for the improvement of selectivity to this product by insertion of 1,2-dibromo-1-lithioethene, the latter reagent has been found to react *via* a different mechanism. The 1,2-dibromoethene reagent used was a mixture of *E* and *Z* isomers in a 1:2 ratio, respectively, and the *Z* isomer would be expected to eliminate bromide upon lithiation to give bromoethyne. Furthermore, deuteration of the reaction products showed depletion of both vinyl peaks, rather than the one observed from insertion of the carbenoid *E*-1,2-dichloro-1-lithioethene **2**.

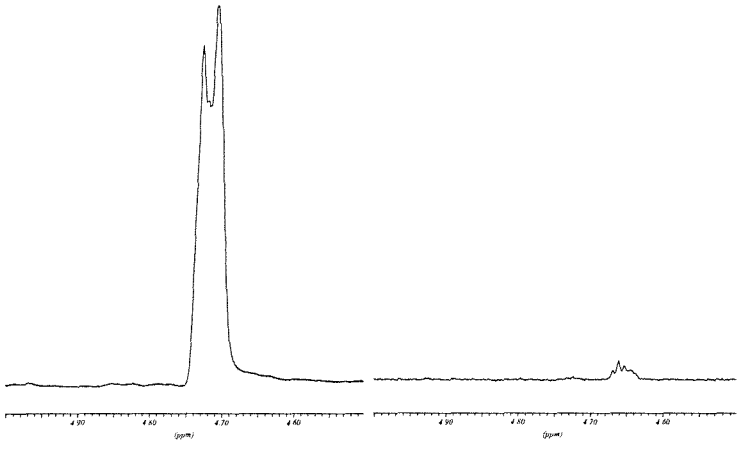
Figure 2.3 *NMR results from deuteration of reaction product of '1,2-dibromo-1-lithioethene' insertion (solvent C_6D_6)*



32 Bis-deuterated product

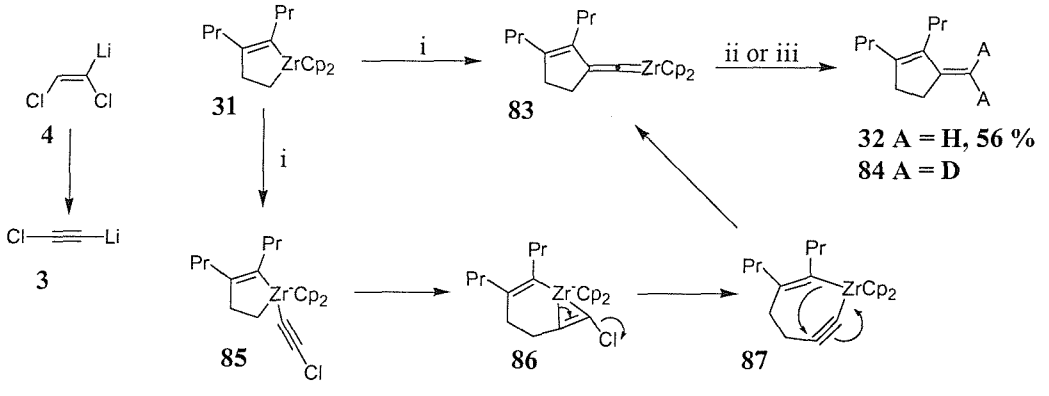
The same result was observed when *Z*-1,2-dichloroethene was deprotonated in the presence of zirconacycle **31** and the products deuterated, as shown in Figure 2.4.

Figure 2.4 *NMR results from deuteration of reaction product of Z-1,2-dichloro-1-lithioethene insertion (solvent $CDCl_3$)*



32 Bis-deuterated, **84**

The bis-deuteration results suggested the unusual zirconocene vinylidene **83** as the reaction product, since deuteration of **83** would yield **84**. A mechanism for this reaction is proposed below, involving 1-lithio-2-chloroethyne as the active reagent.



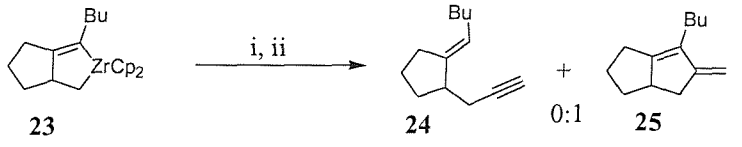
Reagents and Conditions: i, *Z*-1,2-dichloroethene (1.0 eq.), LDA (2.0 eq.), -78 °C; ii, $MeOH/NaHCO_3$; $MeOD/D_2O$

Scheme 2.13

Coordination of the anion to the zirconium would form **85**, which would rearrange to give **86**. This type of rearrangement has been shown to occur by Negishi (Chapter 1, Section 1.2.7), but usually requires time at room temperature to proceed. However, the facile loss of chloride as shown in **86** could enable the reaction to occur at low temperature. The product from loss of chloride, **87**, could be a possible intermediate, the long carbon-zirconium bonds making this structure possible. The cyclic intermediate **87** could then undergo rearrangement to the vinylidene **83**. This formation

of zirconocene vinylidenes is extremely novel. The yield of protonated **32** was found to be 56 %, as measured by NMR using anisole as the internal standard. This showed the reaction to be lower yielding than the equivalent reaction *via* carbenoid.

The rearrangement of **87** to **83** must be very favourable, since insertion of the same reagent, **3**, into zirconacycle **23** yielded methylenecyclopentene **25** as the sole product. If the corresponding zirconacycloalkyne was present in the reaction mixture at the time of quench, some of the enyne **24** would have been formed, but none was observed by GC.



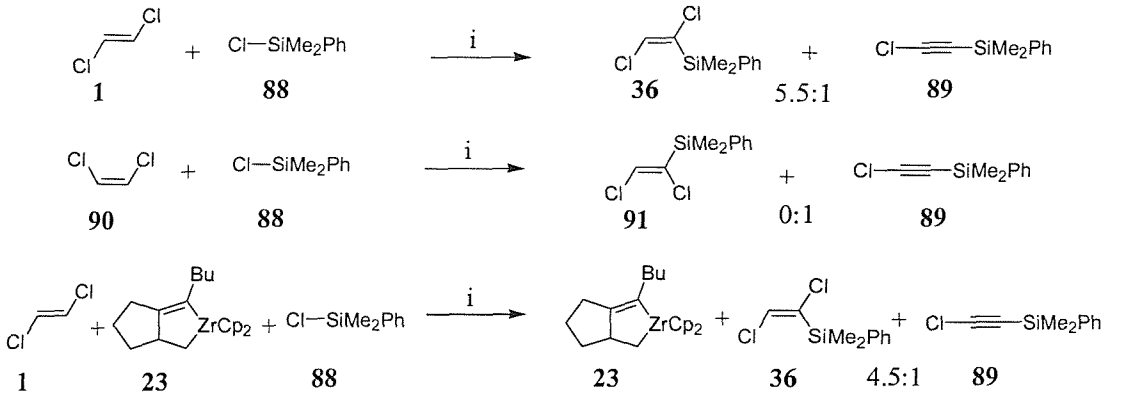
23 **24** **25**

Reagents and Conditions: i, *Z*-1,2-dichloroethene (1.0 eq.), LDA (2.0 eq.), -78 °C; ii, MeOH/$NaHCO_3$

Scheme 2.14

Therefore, the results previously obtained where insertion of 1,2-dibromoethene improved the ratio of methylenecyclopentene to enyne were due to the reaction proceeding *via* 1-lithio-2-bromoethyne and the mechanism shown in Scheme 2.13 instead of the carbenoid insertion mechanism.

To verify further that the reacting species was the lithioalkyne rather than the carbenoid, a series of reactions were performed. Firstly, the product of lithiation of both *E* and *Z* 1,2-dichloroethenes were trapped by silicon as shown in Scheme 2.15. As can be seen from the ratios shown, none of the *Z*-1,2-dichloro-1-lithioethene was trapped, but the *E* isomer was found to be relatively stable. A competition experiment also showed that trap by silicon was much faster than trap by zirconacycle. These combined results confirmed the reactive species was the lithioethyne **3**.

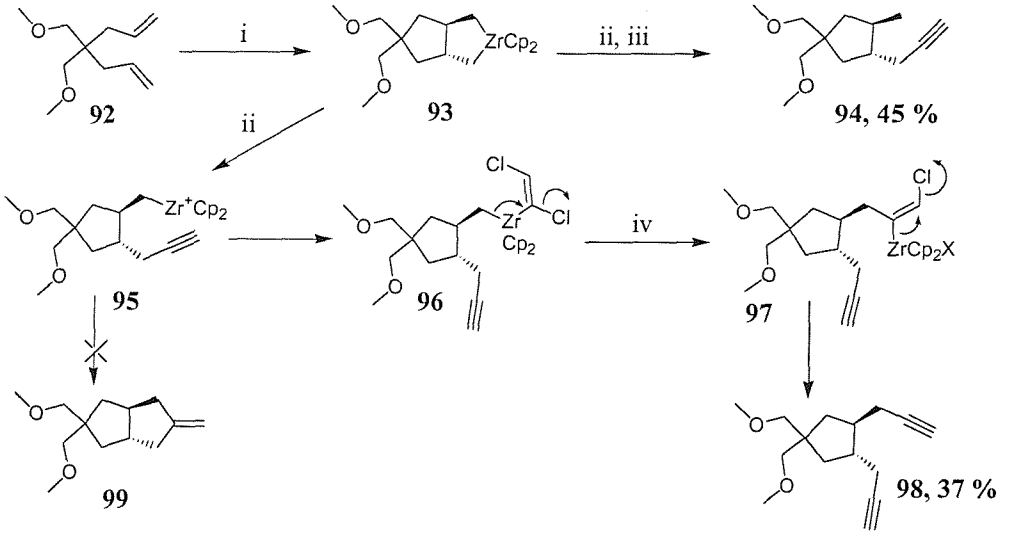


Reagents and Conditions: LDA (1.0 eq.), THF, -78 °C

Scheme 2.15

2.3 Insertion into a zirconacyclopentane

Insertion of carbenoid **2** into zirconacyclopentane **93** proceeded as originally expected to give the monoalkyne product **94** in a moderate 45 % yield when the reaction was quenched at -50 °C. Surprisingly, no formation of alkene **99** was observed, as might have been expected from the zirconacyclopentene results.



Reagents and Conditions: i, Cp_2ZrCl_2 (1.0 eq.), *n*-BuLi (2.0 eq.), THF, -78 °C - r.t.; ii, *E*-1,2-dichloroethene (2.0 eq.), LDA (2.0 eq.); iii, MeOH/$NaHCO_3$; iv, r.t., 1 hr.

Scheme 2.16

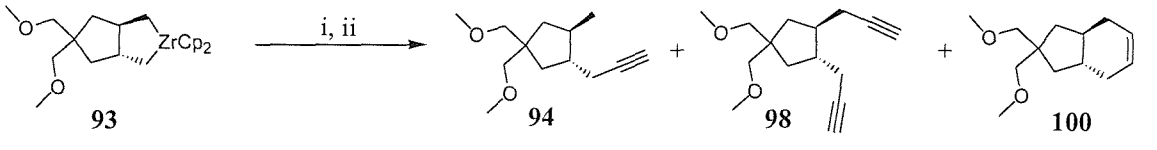
Warming the reaction to room temperature after carbenoid insertion resulted in the formation of the diyne **98** in a low 37 % yield. This result confirmed the trap of the resulting zirconocenium ion **95** by a further carbenoid molecule and rearrangement of

the neutral zirconium species **96** at higher temperature. The ratios of products as the temperature of reaction increased can be seen from the GC results detailed in Table 2.3. This shows the need to warm the reaction to –50 °C to get good levels of carbenoid insertion, and the need to warm to 18 °C to observe conversion to the diyne **98**.

Table 2.3 *Ratio of products from insertion of E-1,2-dichloro-1-lithioethene into* ***93***

Temperature (°C)	**93**		Alkyne **94**		Diyne **98**
-75 (before insertion)	1.0	:	0	:	0
-75 (after insertion)	10.4	:	10.6	:	1.0
-50	2.2	:	18.0	:	1.0
-30	1.0	:	19.0	:	1.1
0	1.0	:	17.7	:	1.8
18	1.0	:	13.0	:	6.6
18 after 45 min	1.0	:	4.1	:	13.7
18 overnight	1.0	:	2.3	:	11.8

Attempting to force the formation of the alkene **99**, an excess of carbenoid was added to zirconacycle **93**. However, small amounts of the cyclohexene **100** were formed instead. The cyclohexene could not be isolated pure, but the GC yields are shown for formation of products in Table 2.4.



93 **94** **98** **100**

Reagents and Conditions: i, *E*-1,2-dichloroethene (5.0 eq.), LDA (5.0 eq.), -78 ^{o}C; ii, MeOH/$NaHCO_3$

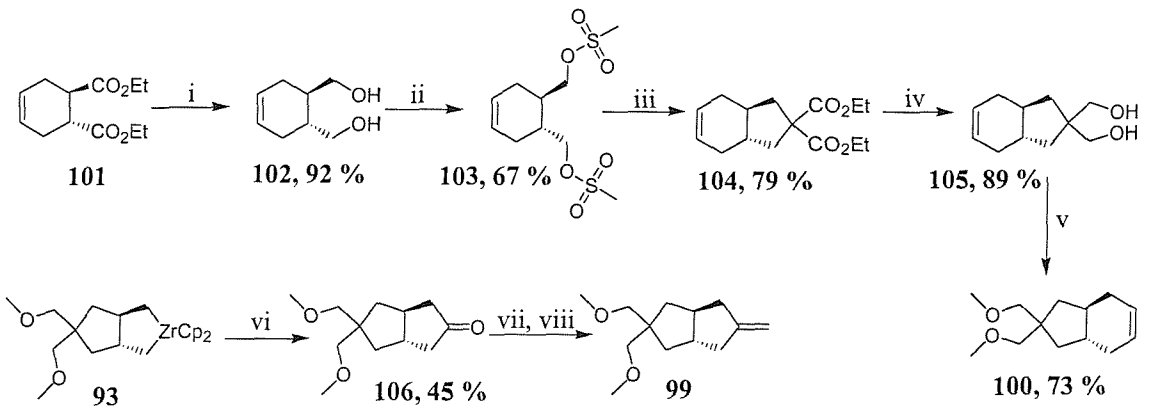
Scheme 2.17

Table 2.4 *GC yields of products from insertion into* ***93*** *(Tridecane internal standard)*

Conditions	Yield **94**, %	Yield **98**, %	Yield **100**, %
2.0 eq. carbenoid, quench –50 °C	44	7	0
2.0 eq. carbenoid, quench 20 °C	11	49	0
5.0 eq. carbenoid, quench –70 °C	17	4	25
5.0 eq. carbenoid, quench 20 °C	0	15	28

The structure of cyclohexene **100** was confirmed by independent synthesis. Reduction of the diester **101**[12] followed by mesylation[13] of the diol gave the stable dimesylate **103**. The key step was the displacement of the mesylate groups by malonate anion[14], which proceeded in good yield. Then reduction and methylation afforded the cyclohexene

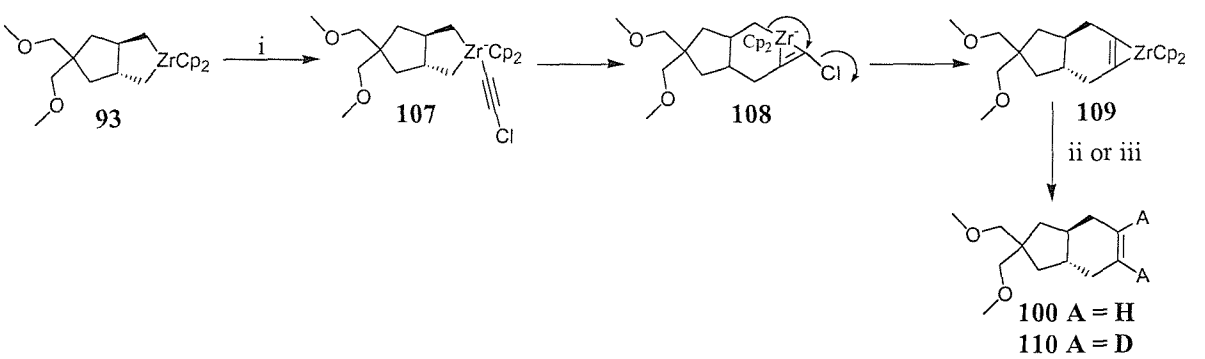
100, with the NMR data in good agreement with those obtained *via* the zirconium route. Alkene **99** was also furnished by independent synthesis to ensure it had not been formed. Initial carbon monoxide insertion into zirconacycle **93** was followed by the Petasis reaction[15] to yield **99**. The final product could not be obtained pure, but was clearly not the same product observed from the reaction in Scheme 2.17.



Reagents and Conditions: i, $LiAlH_4$, THF; ii, MsCl, triethylamine, pyridine; iii, Diethyl malonate, KI, NaOEt/EtOH, reflux 2 hrs; iv, $LiAlH_4$, THF; v, NaH then MeI, THF; vi, CO, -0 °C, then I_2; vii, Cp_2TiCl_2 (2.0 eq.), MeLi (4.0 eq.), -78 °C - r.t.; viii, ketone **106**, reflux 60 hrs.

Scheme 2.18

A mechanism of formation for cyclohexene **100** could be *via* the 1-lithio-2-chloroethyne generated from decomposition of the carbenoid as shown in Scheme 2.19.



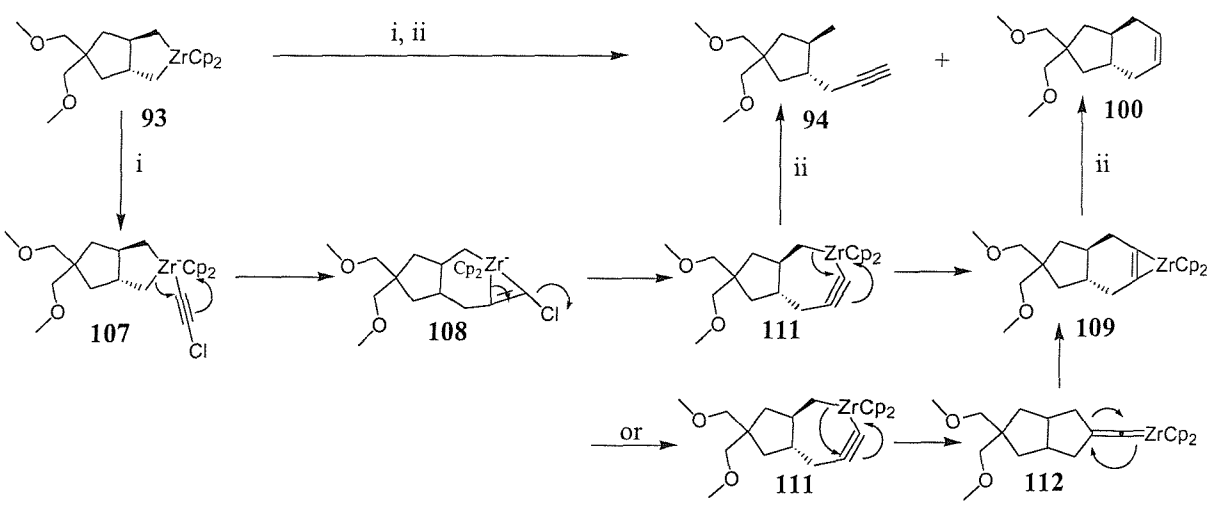
Reagents and Conditions: i, *E*-1,2-dichloroethene (5.0 eq.), LDA (5.0 eq.), -78 °C; ii, MeOH/$NaHCO_3$ for **100**; MeOD/D_2O for **110**

Scheme 2.19

Instead of elimination of chloride in the way seen for zirconacyclopentenes, the chloride could be displaced as in **108**, which would lead to the zirconocene product

109. Corroborating evidence for this mechanism was found from deuteration of the reaction products, as the bis-deuterated cyclohexene **110** was formed.

Selective formation of the cyclohexene was then expected if the 1-lithio-2-chloroethyne was generated from *Z*-1,2-dichloroethene, but surprisingly the same enyne product **94** was dominant in 41 % GC yield with 16 % yield of the cyclohexene **100**. However, on warming to room temperature, there was no conversion to diyne **98** observed. This suggests that the mechanism of reaction with the 1-lithio-2-chloroalkyne may in fact follow the same course as that for zirconacyclopentenes. The cyclic alkyne complex **111** may be more stable without the extra double bond from the cyclopentene series and therefore less likely to rearrange. The rearrangements shown from **111** may be potential routes to the cyclohexene **100**. The direct rearrangement to **109** looks unlikely, but it is similar to the known rearrangement in **107**. The alternative route, *via* the vinylidene **112** is analogous to the cyclopentene series, although the product from quench of **112** was never observed. The reason for the higher conversion to the cyclohexene in the reaction in Scheme 2.19 may have been due to the large excess of carbenoid/anion present, which is required to activate the complex **111** for rearrangement to occur.

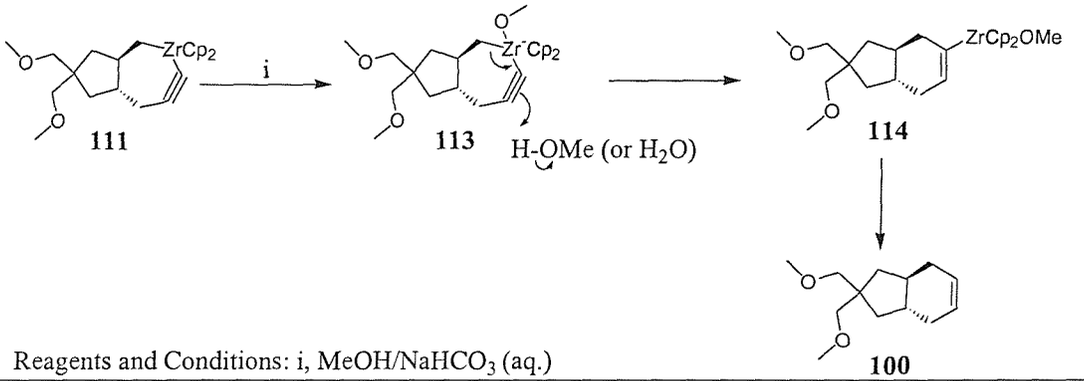


Reagents and Conditions: i, *Z*-1,2-dichloroethene (2.0 eq.), LDA (4.0 eq.), -78 °C; ii, MeOH/$NaHCO_3$

Scheme 2.20

Yet another possibility is that the cyclic zirconocene species **111** is the only species in solution, and that formation of the cyclohexene **100** occurs on quench of the reaction mixture. This is the favoured explanation since the ratio of **94**:**100** does not change

significantly with reaction time. The mechanism proposed for this is shown in Scheme 2.21. Activation of the zirconocene bonds on quench could cause the rearrangement of **113** to **114**, followed by protonation of the remaining carbon-zirconium bond. Therefore, the ratio of **94** to **100** is simply determined by the rates of the rearrangement to the rate of direct quench of the carbon-metal bonds in **111**.



Reagents and Conditions: i, MeOH/$NaHCO_3$ (aq.)

Scheme 2.21

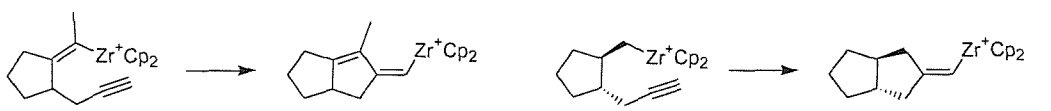
2.4 Comparison of reaction courses with energy calculations

The zirconacyclopentene and zirconacyclopentane systems followed different courses of reaction with both carbenoid and chloroethyne anion reactions. Comparing these observations with energy calculations is a useful aid to supporting the mechanisms proposed. Calculations were carried out by Professor Whitby using Spartan 02 Windows from Wavefunction Inc.

Searches for minimum energy conformations were carried out using both Molecular mechanics (MMFF94[16] force field extended to handle transition metals and cyclopentadienyl ligands) and semi-empirical (using the PM3(tm)[17] model) methods. Transition states were found and characterised (single imaginary vibration) using PM3(tm) method.

Density Function Theory[18] using the B3LYP[19] model and 6-31G*[20] basis set[21] was used to minimise and provide structures and energies for proposed intermediates (the energies are far more reliable than those from semi-empirical methods[22]). A pseudopotential was used to replace the all electron basis set for the non-valence electrons of zirconium.[21]

The cyclisation shown in Scheme 2.22 was observed for zirconacyclopentenes, but no methylenecyclopentane was formed in the same reaction conditions with carbenoid insertion into the zirconacyclopentane investigated. As can be seen from Table 2.5, the transition state for the saturated system was found to be a much higher energy level than that for the unsaturated system, likely to be the reason for the lack of cyclisation observed in the experiments. The PM3 calculations for the saturated system also showed the cyclised product to be of very similar energy to the starting molecule, suggesting little driving force for the reaction to occur. The DFT calculations, however, did show a decrease in energy on product formation.



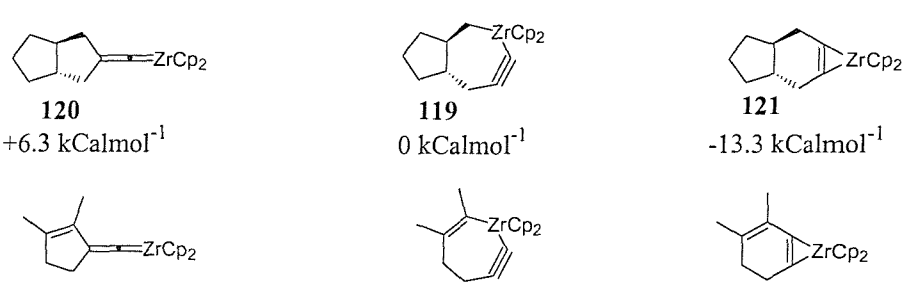
115 **116** **117** **118**

Scheme 2.22

Table 2.5 *Energy calculations for reactions in Scheme 2.22*

Reaction	Method of calculation	Uncyclised, kCal/mol (set to 0)	Relative energy of Transition state, $kCalmol^{-1}$	Relative energy of Cyclised product, $kCal/mol^{-1}$
115 to **116**	PM3	0	+7.0	-19.8
115 to **116**	DFT	0	-	-30.3
117 to **118**	PM3	0	+14.9	-0.1
117 to **118**	DFT	0	-	-18.5

For the reaction with 1-lithio-2-haloethyne, the energies (from DFT) of the expected zirconacycloalkyne intermediates **119** and **122** have been compared with the zirconocene vinylidene products **120** and **123** and the cyclohexene products **121** and **124**.



120 +6.3 $kCalmol^{-1}$ **119** 0 $kCalmol^{-1}$ **121** -13.3 $kCalmol^{-1}$

123 -14.9 $kCalmol^{-1}$ **122** 0 $kCalmol^{-1}$ **124** -22.7 $kCalmol^{-1}$

Scheme 2.23

For the cycloheptenyne system **122**, formation of both reaction products is shown to be a favourable process, suggesting the activation energy for formation of the zirconocene vinylidine **123** is lower than for the cyclohexadiene **124**, since this is the only course of reaction observed. However, for the cycloheptyne system **119**, formation of the vinylidine **120** is accompanied by an increase in energy, fitting the observation that no methylenecyclopentane is formed in the reaction. Since this course of reaction is not available, it fits that some of the intermediate **119** is able to rearrange to give **121**, since this is a thermodynamically favoured process.

2.5 Conclusions

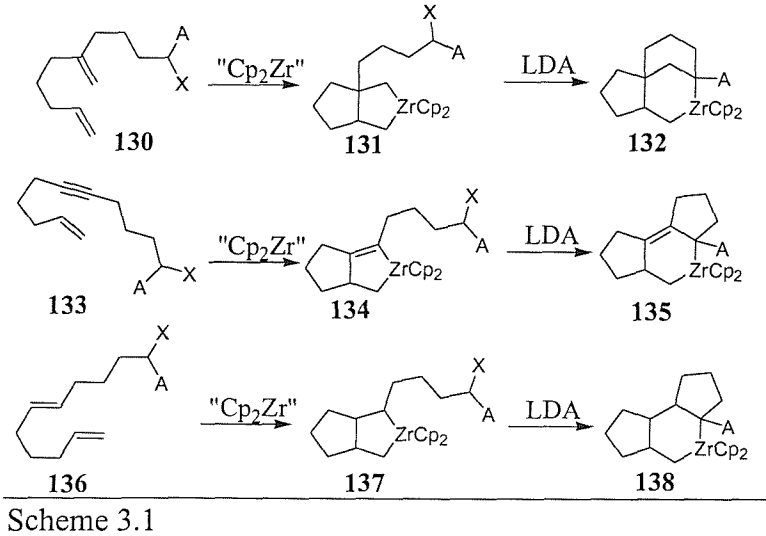
The insertion of *E*-1,2-dihalo-1-lithioethenes into zirconacyclopentenes has been found to produce methylenecyclopentenes. The mechanism of this reaction has been probed and stable alcohol products formed after hydroboration and oxidation. The same methylenecyclopentenes have been formed from insertion of 1-lithio-2-haloethynes *via* a novel method of formation of a zirconocene vinylidine. Insertion of the carbenoid into a zirconacyclopentane was found to give an alkyne, but also showed that rearrangement of a neutral zirconium species to yield a bis-insertion product can occur at room temperature. Insertion of 1-lithio-2-haloethynes also yielded the alkyne and has also been proposed as the reactive species in a side reaction to form a cyclohexene.

Chapter 3. Intramolecular carbenoid insertion into zirconacycles

3.1 Introduction to research area.

A natural progression of any methodology developed for intermolecular reactions is to consider the possibilities of applying the methodology in an intramolecular fashion. This often leads to the possibility of forming rings, which is particularly useful in organic synthesis and natural product synthesis. Despite the range of lithium carbenoids that have now been investigated for insertion into carbon-zirconium bonds, the intramolecular case with the carbenoid precursor already present in the zirconacycle molecule has not been investigated to date. This chapter details the initial investigations into achieving intramolecular carbenoid insertion and the potential scope of this area of research.

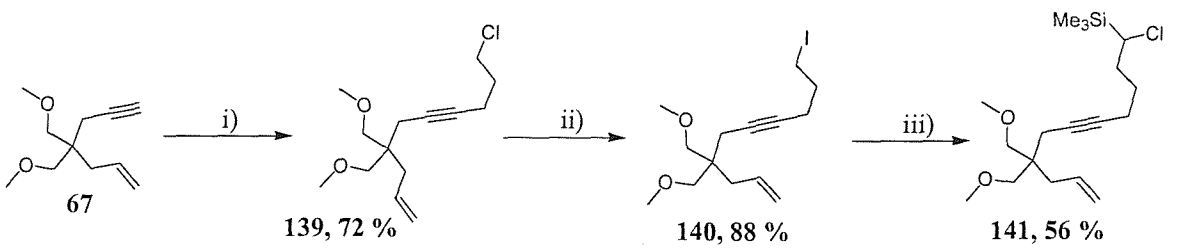
Three general precursor structures were initially considered (Scheme 3.1). From the point of view of facile carbenoid insertion, a chain *beta* to the zirconium that contained the carbenoid precursor, such as **131**, would be most appropriate due to the known preference of attack on the carbon-zirconium bond with a group in this position (see Chapter 1, Scheme 1.26). However, synthesis of such compounds would be much more problematic than of those with the group *alpha* to zirconium. Hence initial attention was drawn to examples such as **134** as alkylation of an alkyne would lead to rapid synthesis of initial test cyclisation precursors, **133**.



Scheme 3.1

3.2 Results and discussion

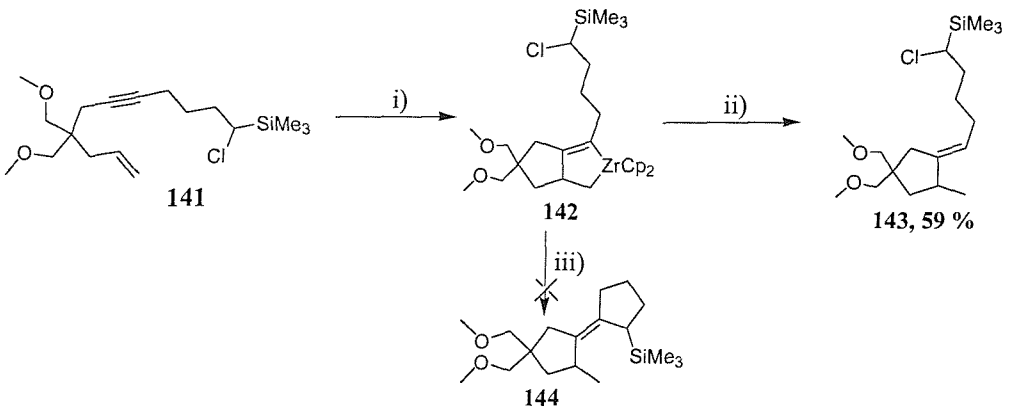
The initial carbenoid of choice was based on chloromethyltrimethylsilane, since this was known to insert cleanly into zirconacycles[23], including zirconacyclopentadienes[24]. Enyne **67** was synthesised using malonate chemistry and used as the starting material for all precursor syntheses. Lithiation of the alkyne followed by alkylation with 1-bromo-3-chloropropane showed preferential displacement of the bromide to give chloride **139**, which was then converted to the iodide[25] **140** to allow facile displacement of the halide. Initially, the use of *t*-BuLi and HMPA to deprotonate chloromethyltrimethylsilane failed and the product of the reaction was chloride **139**. This showed halogen-lithium exchange was occurring instead of deprotonation. However, use of *s*-BuLi in the presence of TMEDA was successful at deprotonation and the enyne **141** was synthesised in moderate yield.



Reagents and conditions: i) *n*-BuLi, HMPA, THF, -78 °C, then 1-bromo-3-chloropropane; ii) NaI (3 eq.), acetone, reflux; iii) chloromethyltrimethylsilane, *s*-BuLi, TMEDA, -78 °C, then add iodide **140.**

Scheme 3.2

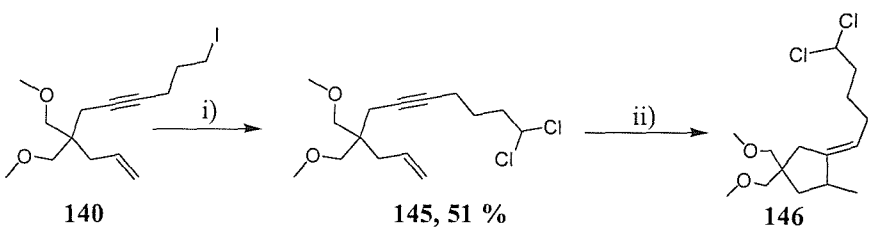
Zirconium mediated cyclisation of enyne **141** proceeded successfully and cyclised product **143** was isolated in 59 % yield. The ^{13}C NMR showed two diastereoisomers were formed, but the spectral data were so similar, the ratio could not be determined. Addition of LDA to zirconacycle **142** at –78 °C showed no reaction by GC, even on warming to room temperature overnight in the cool bath. Further addition of *t*-BuLi, once cooled to –78 °C, resulted in partial conversion to another product, but GCMS showed this to be due to chlorine-lithium exchange and quench rather than insertion of the carbenoid. Separately, deprotonation was attempted using *s*-BuLi and TMEDA, but still no reaction occurred. Since in the latter case **143** was still observed after addition of base, it suggested the carbenoid precursor was not being deprotonated, as if the carbenoid was formed, it would at least be expected to insert intermolecularly.



Reagents and Conditions: i) Cp_2ZrCl_2, *n*-BuLi (2 eq.), THF, -78 °C - r.t.; ii) MeOH/$NaHCO_3$ (aq.); iii) LDA, -78 °C.

Scheme 3.3

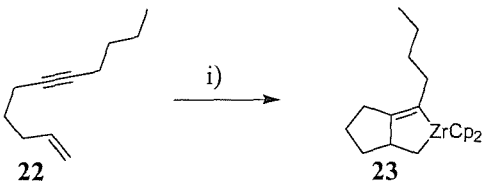
Since the above system did not prove successful, a different carbenoid precursor was investigated. The dichloride **145** was synthesised using the same procedure as for **141**. However, a more substantial problem was encountered as only partial zirconium cyclisation occurred with this enyne, suggesting the carbenoid precursor was not compatible with the cyclisation. Not only was there partial cyclisation, but GC showed a number of impurity peaks, the dominant peak showed loss of both chlorides by GCMS.



Reagents and Conditions: i) CH_2Cl_2, *s*-BuLi, TMEDA,-90 °C, then add **140**, r.t.; ii) Cp_2ZrCl_2, *n*-BuLi (2 eq.), THF, -78 °C - r.t.

Scheme 3.4

At this stage it was important to determine whether various carbenoid precursors were compatible with the cyclisation step. Therefore, cyclisations of enyne **22** in the presence of CH_2Cl_2, benzyl chloride and *E*-1,2-dichloroethene were performed. The results are summarised in Table 1.



22 **23**

Reagents and Conditions: i) Cp_2ZrCl_2, *n*-BuLi (2 eq.), THF, -78 °C - r.t., 5 hrs

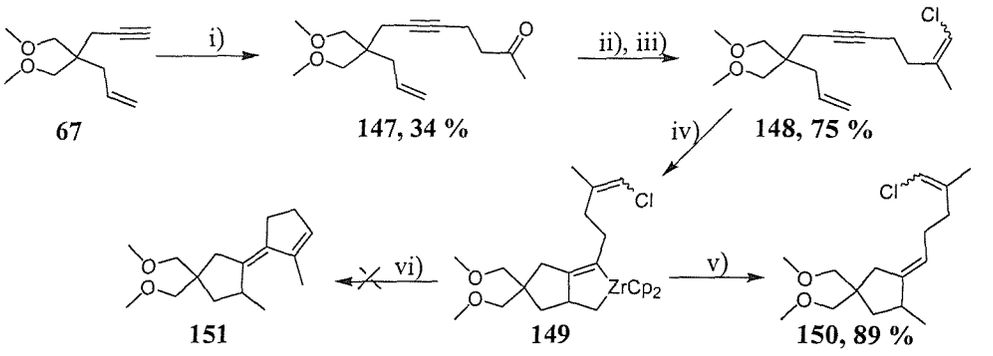
Scheme 3.5

Table 1. *Cyclisation of enyne* ***22*** *in the presence of potential carbenoid precursors*

Carbenoid precursor	Number of equivalents	Ratio of **22**:**23** by GC
CH_2Cl_2	0 (control)	0:1
CH_2Cl_2	1	1:1
CH_2Cl_2	10	1:0
Benzyl chloride	0 (control)	0:1
Benzyl chloride	1	7:3
Benzyl chloride	10	1:0
E-1,2-dichloroethene	0 (control)	0:1
E-1,2-dichloroethene	1	0:1
E-1,2-dichloroethene	10	0:1

From the results above, it was clear that cyclisations in the presence of geminal dihalide or benzyl chloride moieties would not be successful. With one equivalent of carbenoid precursor in solution, partial cyclisation was observed, but with ten equivalents to mimic an intramolecular case, there was no cyclisation. The zirconocene (1-butene) reacted preferentially with the carbon-chlorine bonds of the carbenoid precursors. These results clearly limited the possibilities for this area of work, although cyclisations were possible in the presence of *E*-1,2-dichloroethene, which was present to mimic vinyl chloride carbenoid precursors. A starting enyne containing a vinyl chloride functionality was therefore synthesised.

The ruthenium catalysed coupling[26] of enyne **67** with methyl vinyl ketone proceeded successfully to give ketone **147**, although in low yield. A Wittig reaction[27] then gave the vinyl chloride precursor **148** in good yield as a mixture of diastereoisomers. The vinyl carbenoids derived from such precursors as **148** are known to be configurationally labile[6,28-30] and hence the geometry did not have to be fixed at this stage, as only one isomer would be expected to react.



Reagents and Conditions: i) methyl vinyl ketone (3 eq.), $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), pyrollidine (0.2 eq.), benzene, 65 °C,16 hrs; ii) $Ph_3P^+CH_2ClCl^-$ (1.5 eq.), piperidine (1.5 eq), *n*-BuLi (1.5 eq.), Et_2O, 2 hrs; iii) add ketone **147**, reflux, 16 hrs; iv) Cp_2ZrCl_2, *n*-BuLi (2 eq.), THF, -78 °C - r.t., 5 hrs; v) $MeOH/NaHCO_3$; vi) LDA, -78 °C, then $MeOH/NaHCO_3$.

Scheme 3.6

Zirconium mediated cyclisation of enyne **148** was very clean and afforded the cyclised product **150** in 89 % yield. However, addition of LDA to zirconacycle **149** at –78 °C did not cause any reaction to occur and the two isomers of **150** remained in solution, as shown by GC. Even 5 eq. of LDA left for 4 hrs at –78 °C was unsuccessful and **150** was still the only product observed.

3.3 Conclusions

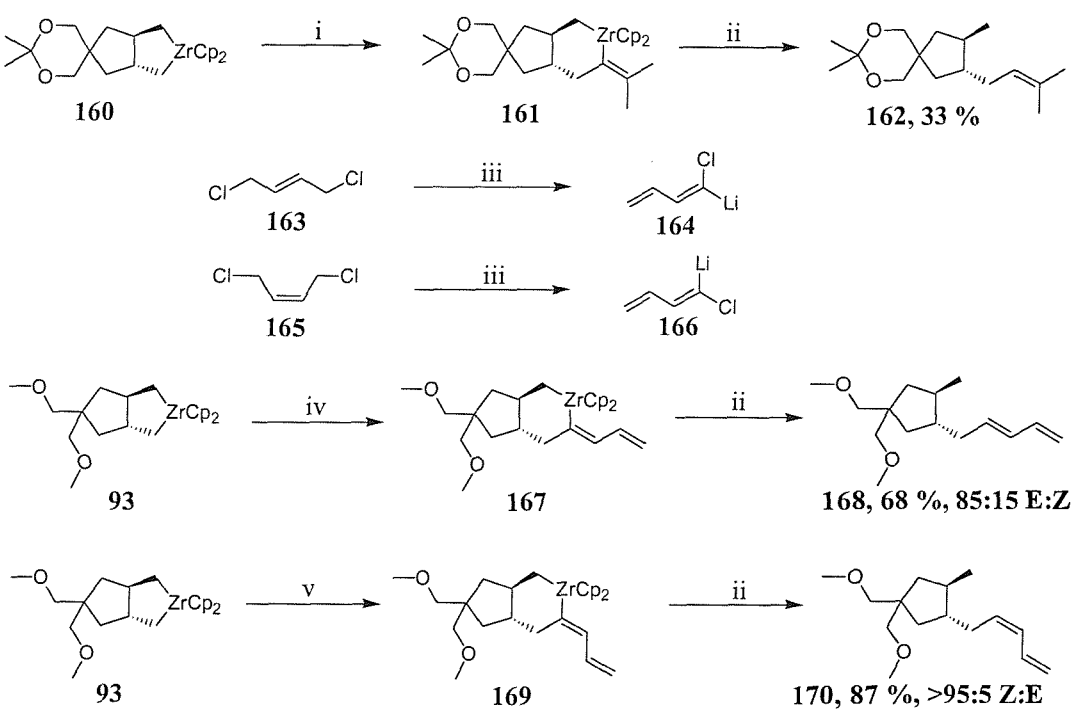
The area of intramolecular carbenoid insertion has been shown to be unsuccessful. Not only have carbenoids failed to insert once zirconacycles have been formed, but the cyclisations have been inhibited by some carbenoid precursor moieties. The zirconacycles tested may not have been the ideal examples, but synthesis of other examples with the pendant chain *beta* to the zirconium would be more complicated and this coupled with the limited scope of carbenoid types available makes the project unattractive as an area of research. This is an unfortunate limitation on the methodology available for carbenoid insertion into zirconacycles, but the limitation must be known. It is also worthy of note that limitations on precursors for zirconium mediated cyclisations have been discovered.

Chapter 4. Insertion of vinyl carbenoids into zirconacycles

4.1 Introduction to research area

The chemistry of vinyl carbenoids is well documented and a number of these reagents have been inserted into acyclic organozirconium species as described in Chapter 1. A smaller number have also been inserted into zirconacycles, but the area of work was not comprehensive. Further investigation was required for a paper on the area of carbenoid insertion that is in press at the time of writing. The aim of the work in this chapter was therefore to increase the range of carbenoids inserted into both zirconacyclopentanes and zirconacyclopentenes. Whilst investigating this area, some new discoveries were made that have shed light on the nature of carbenoid insertion and also the structure and reactivity of the resulting zirconacycles.

Before the work described in this chapter, three types of vinyl carbenoids had been inserted into zirconacyclopentanes[31] as shown in Scheme 4.1.

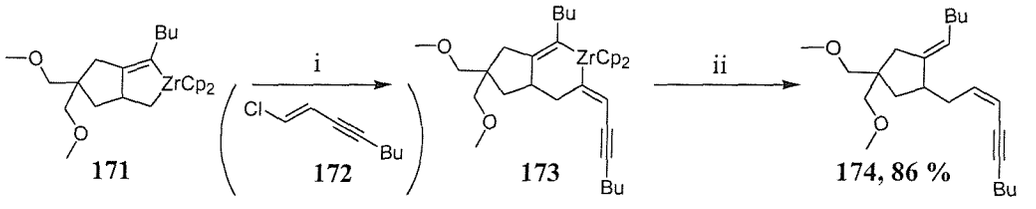


Reagents and Conditions: i, 1-chloro-2-methylpropene (5 eq.), LiTMP (5 eq.), -90 °C; ii, MeOH, 5-24 hrs; iii, LiTMP (2 eq.), -90 °C; iv, **164** (3.1 eq.), LDA (6.2 eq.), -90 °C, 1 hr; **166** (3.1 eq.), LDA (6.2 eq.), -90 °C, 1 hr.

Scheme 4.1

Formation of the trisubstituted alkene **162** required five equivalents of carbenoid for sufficient conversion, but the yield was still low from this reaction. Addition of two equivalents of base to dichlorides **163** and **165** is known to give the stereoisomeric carbenoids **164** and **166**, respectively.[6,32] Insertion of these carbenoids into zirconacycle **93** then gave **168** and **170** regioselectively and in good to excellent yield.

A chloroenyne carbenoid, generated from lithiation of **172** has also been inserted into zirconacyclopentene **171** to provide the elaborated product **174** in excellent yield[33].



Reagents and Conditions: i, *E*-1-chloro-oct-1-en-3-yne **172** (1.1 eq.), LiTMP (1.1 eq.), -78 °C; ii, MeOH/$NaHCO_3$

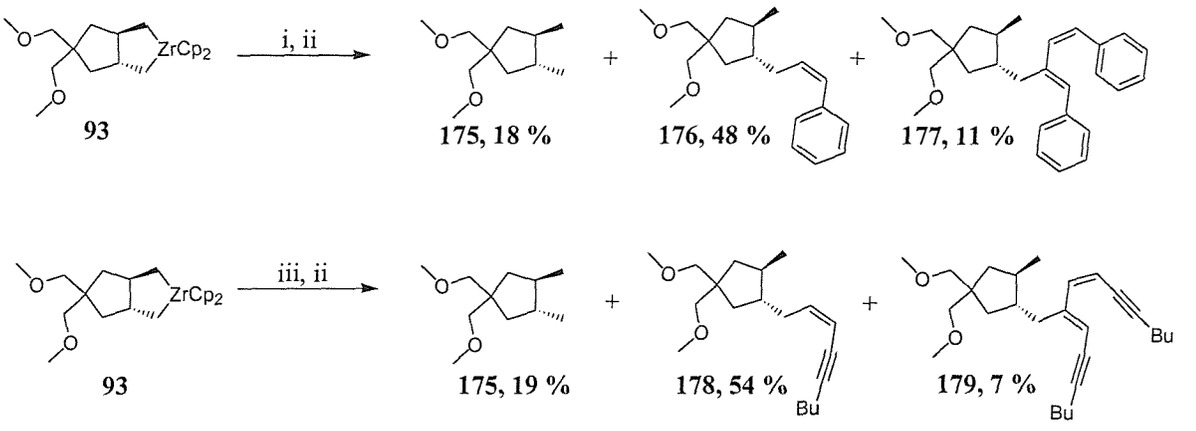
Scheme 4.2

4.2 Insertion into zirconacyclopentanes

4.2.1 Results

It is known that vinyl carbenoids are generally stabilised by a substituent *cis* to the lithium.[34] Hence, *E*-β-bromostyrene was considered a suitable carbenoid precursor and was purified from a commercial source of a mixture of *E* and *Z* isomers.[35] The chloroenyne **172** was also available after synthesis by a previous student.[33] The carbenoids generated from these precursors were then inserted into zirconacycle **93**.

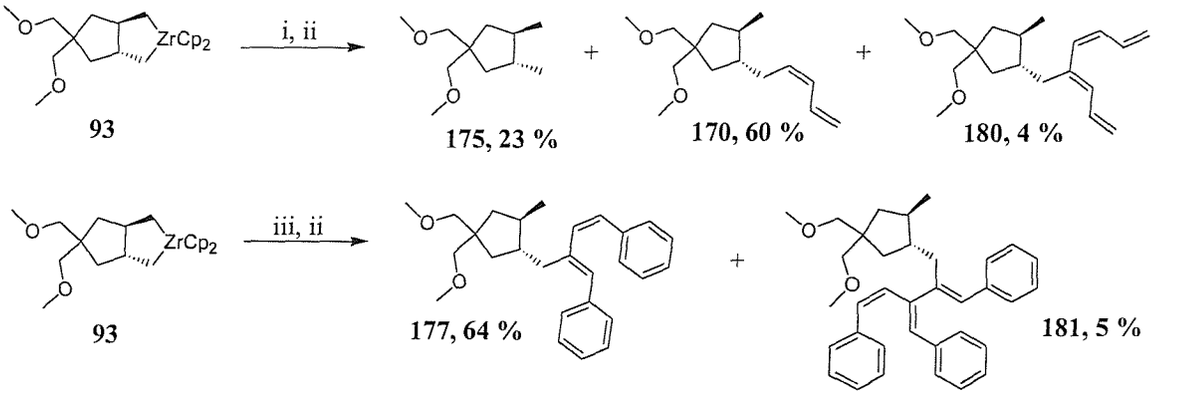
The *E*-β-bromostyrene carbenoid was found to insert cleanly and rapidly into the zirconacycle and the mass recovery of the reaction was good. However, not only was the mono-inserted product **176** observed and isolated, but also the unexpected bis-inserted product **177** was isolated. Since only one equivalent of carbenoid had been used, the insertion of the second equivalent of carbenoid was also a rapid process that competed in rate with the mono-insertion. It is not only unusual to observe bis-insertion, but this is the first example of bis-insertion into the same side of the zirconacycle. The same result was observed with the chloroenyne carbenoid, although the bis-insertion was not quite as prevalent.



Reagents and Conditions: i, *E*-bromostyrene (1.0 eq.), LDA (1.0 eq.), -90°C, 25 min; ii, MeOH/$NaHCO_3$; iii, chloroenyne **172** (1.0 eq.), LDA (1.0 eq.), -78 °C, 55 min.

Scheme 4.3

Comparison of these results with those of the dienyl carbenoids **164** and **166** showed an anomaly. In the prior work[31], 3 equivalents of the carbenoid were used with excellent yields obtained, but the above results suggest poly-insertion would occur under these conditions. Indeed, this was found to be the case as addition of 3 equivalents of dienyl carbenoid **166** to zirconacycle **93** was found to give a number of peaks in two batches on GC. These were shown by GCMS to correspond to bis- and tris-inserted products. However, use of one equivalent of carbenoid gave predominantly mono-insertion with a yield of 60 % (Scheme 4.4), showing the previous work on these carbenoids to be incorrectly reported.



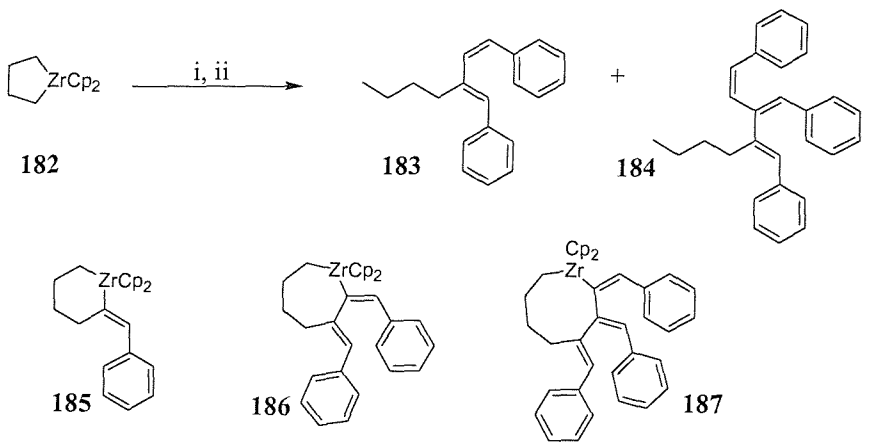
Reagents and conditions: i, *Z*-1,4-dichloro-2-butene (1.0 eq.), LDA (2.0 eq.), -90 °C, 50 min; ii, MeOH/$NHCO_3$; iii, *E*-bromostyrene (2.0 eq.), LDA (2.0 eq.), -78 °C, 70 min.

Scheme 4.4

Purposeful bis-insertion of *E*-β-bromostyrene into **93** using two equivalents of carbenoid successfully gave the bis-styrene **177** in good yield and interestingly a small

amount of the tris-inserted product **181** was also formed. Unfortunately, whilst insertion of two equivalents of carbenoid to preferentially give **179** and **180** gave the correct masses by GCMS, a number of peaks were formed, and isolation of the products by chromatography was unsuccessful. Instability of the products due to the number of unsaturated bonds in conjugation was the main obstacle to product isolation.

To investigate the potential extent of polyinsertion, the simplest possible zirconacycle **182** was synthesised from reaction of zirconocene 1-butene with ethene. Curiously, no mono-insertion product was observed, but the dominant products were those of bis- and tris-insertion in the yields shown in Table 4.1.



Reagents and Conditions: i, *E*-bromostyrene, LDA, -78 °C; ii, MeOH/$NaHCO_3$

Scheme 4.5

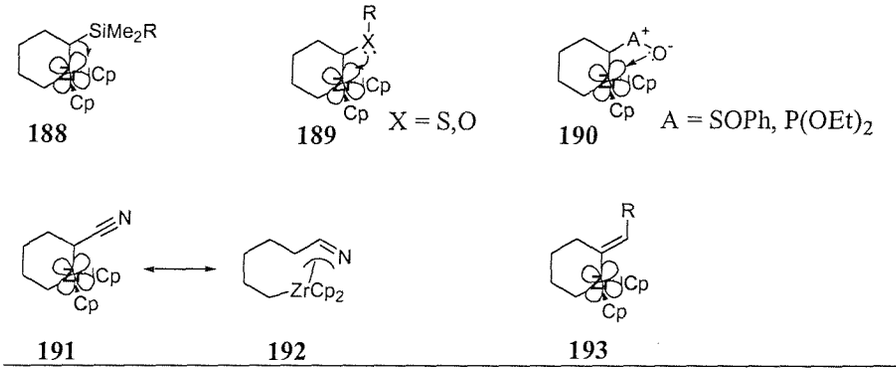
Table 4.1. *Isolated yields of **183** and **184**.*

No. of carbenoid eq.	Isolated **183**, %	Isolated **184**, %
1	16	12
2	16	28
5	8	48

As no mono-insertion product was observed even with one equivalent of carbenoid, it shows the rate of carbenoid insertion into the resulting zirconacyclohexane **185** is faster than the rate of insertion into **182**. However, there was no sign of any tetra-substituted product with 5 equivalents of carbenoid, even in the crude NMR spectrum, suggesting that expansion of the zirconacyclooctane **187** to a zirconacyclononane was unfavourable.

4.2.2 Rationalisation of polyinsertion and regiochemistry of insertion

Bis-insertion into zirconacyclopentanes has previously been observed with benzyl chloride[31] and chloroacetonitrile[23] derived carbenoids, although in each case the second carbenoid insertion occurred on the opposite side of the zirconacycle. Also, with benzyl carbenoids the second insertion is thought to occur into a zirconium hydride moiety after β-hydride elimination and not directly into the zirconacyclohexane (Chapter 1, Scheme 1.29). To date, all other carbenoids investigated have shown distinct mono-insertion. The reason for this is most likely to be due to electron donation from the carbenoid fragment to the empty zirconium orbital, preventing coordination of a second carbenoid molecule to the zirconium, as shown in Scheme 4.6.

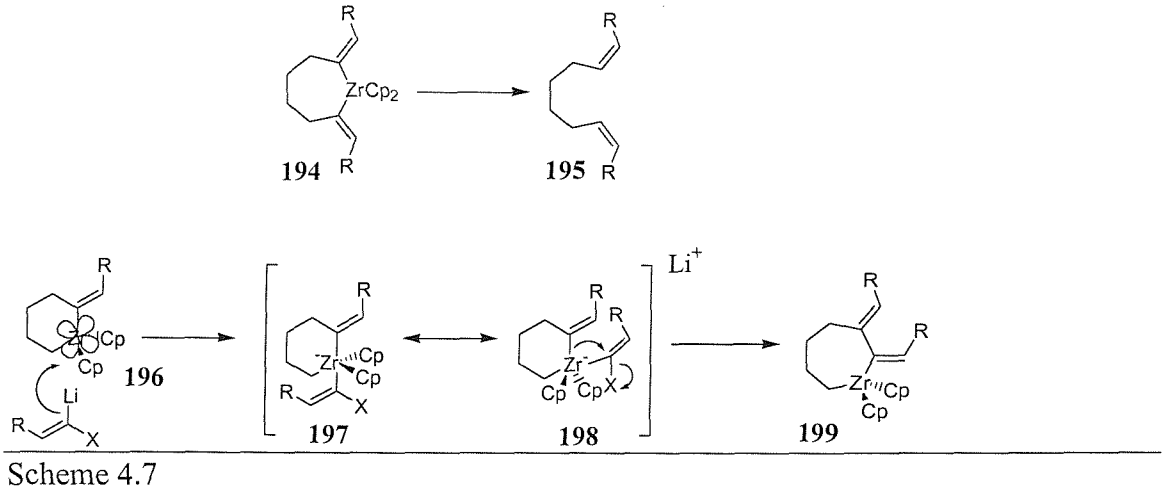


Scheme 4.6

Even with 10 equivalents of a chloromethylsilane carbenoid, only mono-insertion was observed.[31] It is well known that a carbon-silicon bond affords stabilisation of a β-carbenium ion and it can be envisaged that the same donation of electron density to the zirconium empty orbital would prevent further carbenoid attack. Likewise, in structures **189** and **190**, electron lone pairs are available to coordinate to the zirconium. Conversely, after chloroacetonitrile insertion to give zirconacycle **191**, the electron density of the cyanide group is not suitably positioned to donate into the empty orbital, allowing coordination of a second carbenoid molecule. In the latter example, isomerisation to the η^3-bonded structure **192** would be possible, but this is an 18-electron complex into which carbenoid insertion could not occur, suggesting **191** is the more favoured isomer. From these arguments, it can also be seen that after vinyl carbenoid insertion to give **193**, the electron density of the double bond lies

orthogonally to the zirconium empty orbital and hence there is no hindrance to further carbenoid insertion. This explanation appears to fit all the examples so far investigated.

The second observation that requires explanation is the regiochemistry of the second carbenoid insertion. As explained in Chapter 1, carbenoid insertion is dominantly observed into the unhindered side of a zirconacycle. If this were the case for the second insertion, then the bis-insertion product **195** would be expected. In zirconacycle **196**, the empty orbital on the metal lies in the plane of the carbon-zirconium bonds and, hence from the orbital alignment, approach of the carbenoid from the hindered side does not look possible, especially when the other 'CH_2' side is very unhindered. However, it could be visualised that after coordination of the carbenoid, the resulting zirconate complex **197** is fluxional, and could isomerise to **198**. If this occurs, then insertion of the carbenoid could occur on the hindered side of the zirconium. If this is the case it suggests two things: firstly, isomerisation of the zirconate complex **197** is faster than insertion into the unhindered side of the zirconacycle. Secondly, either isomer **198** is more energetically favourable than **197**, or migration of the alkenyl-zirconium bond in **198** is favoured over migration of the alkyl-zirconium bond in **197**.

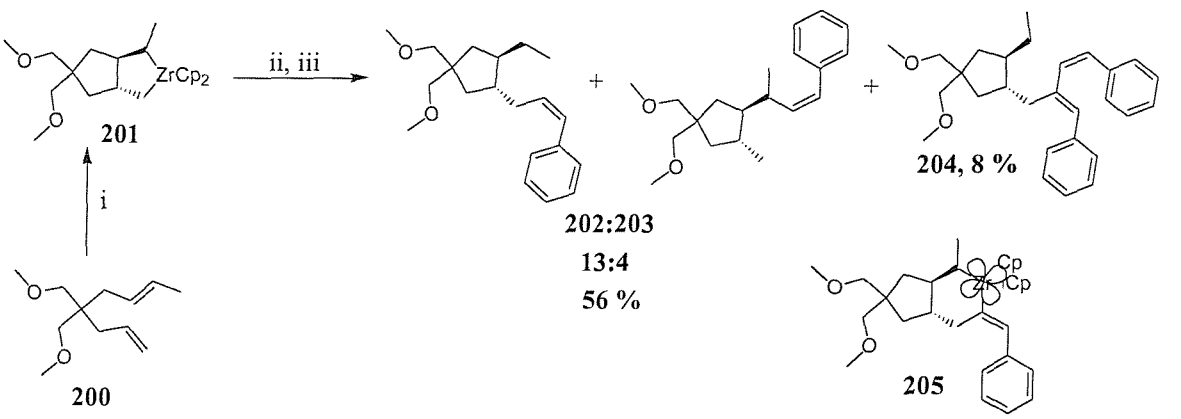


Scheme 4.7

Isomerisation of **197** could occur by two different mechanisms. Loss and then readdition of cyclopentadienide is a possibility, but the favoured explanation is the Berry pseudorotation, which is known to be very rapid and facile in some systems.[36] Here, the complex is thought to exist as the trigonal bipyramid, but slight deformation of this structure leads to the square-based pyramid and return back to the trigonal bipyramid can lead to isomerisation as shown below.

Scheme 4.8

It was realised that if the explanation for bis-insertion was correct, then blocking carbenoid attack on the previously unhindered side of the zirconium would decrease the amount of bis-insertion observed. To this end, cyclisation of diene **200** to give zirconacycle **201** was followed by insertion of one equivalent followed by a second equivalent of carbenoid (Scheme 4.9).



Reagents and Conditions: i, Cp_2ZrCl_2 (1.0 eq.), *n*-BuLi (2.0 eq.), THF, -78 °C - r.t.; ii, *E*-bromostyrene (2.0 eq.), LDA (2.0 eq.), -78 °C; iii, MeOH/$NaHCO_3$

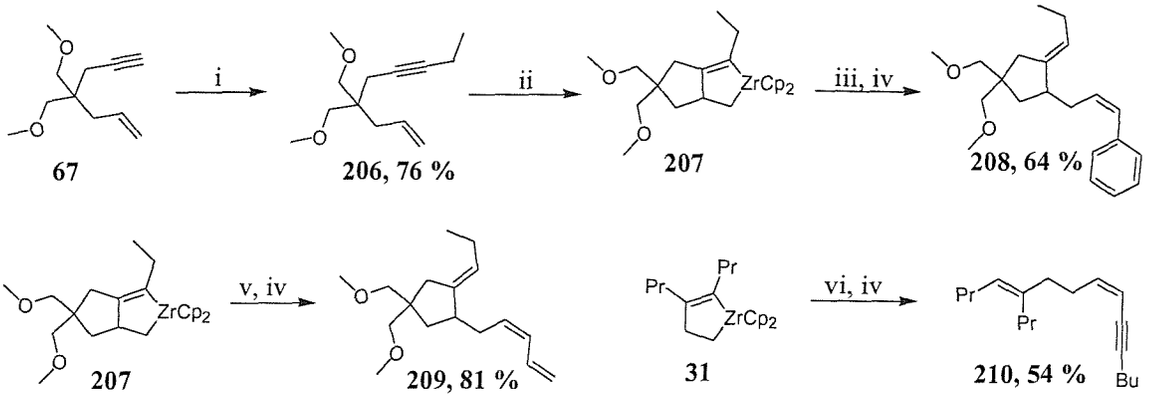
Scheme 4.9

Rather unexpectedly, a mixture of mono-insertion products was obtained, suggesting the methyl group was not large enough to ensure that only insertion on the unhindered side would occur. However, most importantly for this work, the mono-insertion products were dominant, even after addition of 2 equivalents of carbenoid. This showed a distinct difference to insertion into **93**. Therefore, the methyl group did block attack of the second carbenoid molecule in **205** and bis-insertion was suppressed.

4.3 Insertion into zirconacyclopentenes

To extend the knowledge of vinyl carbenoid insertion into zirconacycles, examples of insertion into zirconacyclopentenes were required. Synthesis of a suitable enyne precursor **206** was followed by zirconium mediated cyclisation to give zirconacycle **207**. The *E*-β-bromostyrene and dienyl **166** carbenoids were inserted into zirconacycle

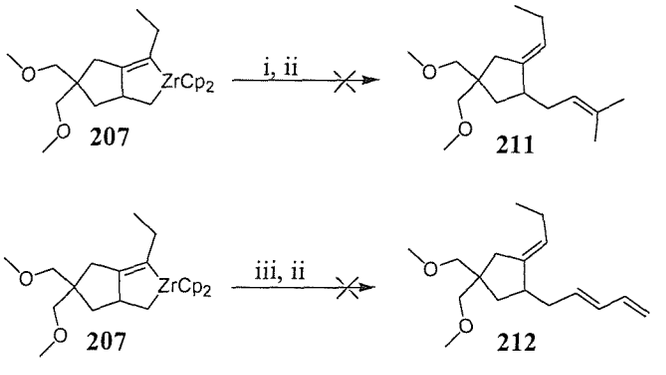
207, whilst the carbenoid derived from chloroenyne **172** was inserted into the monocycle **31**. All reactions proceeded in good yield to give the expected mono-insertion products, with none of the potential bis-inserted products formed.



Reagents and Conditions: i, *n*-BuLi (1.1 eq.), HMPA (1.1 eq.), THF, -78 - -30 °C, then EtBr (1.1 eq.); ii, Cp_2ZrCl_2 (1.0 eq.), *n*-BuLi (2.0 eq.), THF, -78 °C - r.t.; iii, *E*-bromostyrene (2.0 eq.), LDA (2.0 eq.), -78 °C; iv, MeOH/$NaHCO_3$; v, Z-1,4-dichloro-2-butene (3.0 eq.), LDA (6.0 eq.), -90 °C; vi, **172** (1.1 eq.), LDA (1.1 eq.), -90 °C.

Scheme 4.10

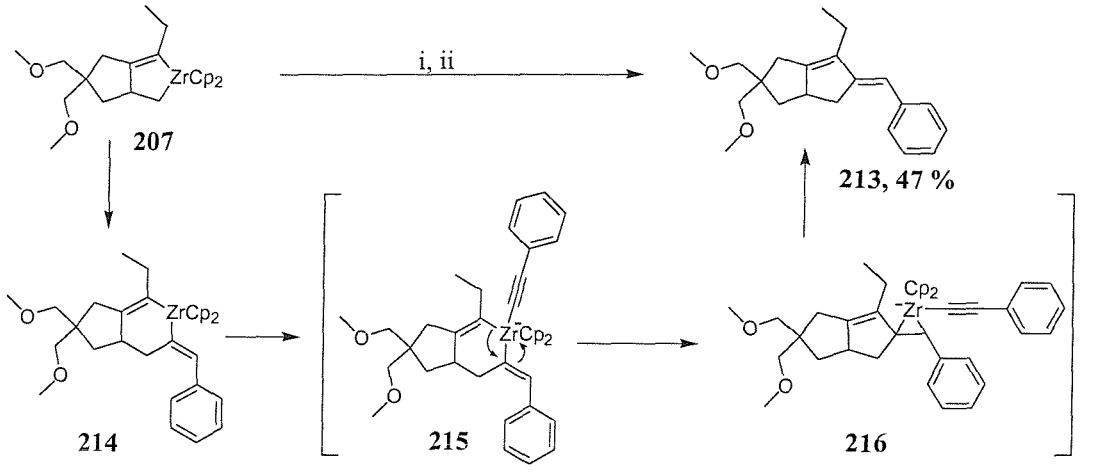
Insertion of two other carbenoids was attempted into zirconacycle **207** (Scheme 4.11). Formation of **211** was monitored by GC, but the product peak only increased to 14 % of the starting material peak and then degraded on warming to room temperature. Also, insertion of dienyl carbenoid **164** was attempted, but 7 product peaks were shown by GC and hence the reaction was abandoned. This latter result threw further doubt on the validity of the results shown in Scheme 4.1.



Reagents and Conditions: i, 1-chloro-2-methylpropene (3.0 eq.), LDA (3.0 eq.), -90 °C; ii, MeOH/$NaHCO_3$; iii, *E*-1,4-dichloro-2-butene (3.0 eq.), LDA (6.0 eq.), -90 °C.

Scheme 4.11

To ensure bis-insertion of vinyl carbenoid into zirconacyclopentene **207** did not occur, 5 equivalents of carbenoid were added. No bis-insertion was observed, however an unexpected cyclisation occurred on warming to room temperature to give a [3.3.0] bicyclic system **213**.



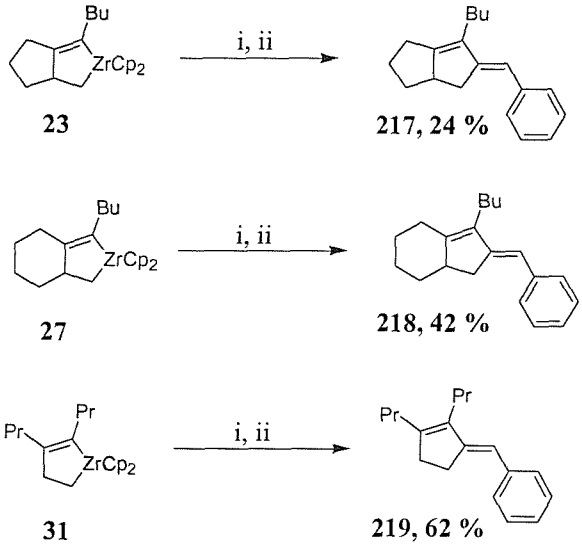
Reagents and Conditions: i, *E*-bromostyrene (5.0 eq.), LDA (5.0 eq.), -78 °C - r.t.; ii, MeOH/$NaHCO_3$

Scheme 4.12

The proposed mechanism for this reaction is shown above. Initial carbenoid insertion gives zirconacyclohexane **214** and then, when further carbenoid molecules have degraded to lithiated phenylacetylide, coordination to the zirconium promotes the rearrangement of **215** as shown. The resulting structure **216** is most likely to decomplex to give the diene **213**. The cyclisation did not occur when only 1 equivalent of carbenoid was used. However, rearrangement occurred when lithiated phenylacetylide was added to **214** at low temperature and the reaction then warmed to room temperature. Addition of just lithiated phenylacetylide to zirconacycle **207** resulted, on warming to room temperature, in the expected 'mono-insertion' product **208** from the Negishi coupling of a lithiated alkyne with a zirconacycle.[37] Therefore, it is clear that the sequential reaction of a carbenoid followed by a lithiated alkyne is necessary for formation of the diene **213**.

Evidence for the decomplexation of zirconium from **216** was obtained from a deuteration quench that provided an identical set of NMR data to the protonated product. Also, an attempt to react zirconacycle **207** with the carbenoid derived from chloroenyne **172** and then addition of lithiated phenylacetylide was unsuccessful in yielding a product with a different carbenoid fragment.

Further examples of this unusual cyclisation were obtained using the zirconacycles shown (Scheme 4.13). Yields were generally low to moderate as the reactions were not as clean as desired – a number of small impurity peaks were visible by GC. The strained diene structure of the product is known to be relatively unstable (c.f. Chapter 2). However, diene **219** was obtained in good yield.



Reagents and Conditions: i, *E*-bromostyrene (5.0 eq.), LDA (5.0 eq.), -78 °C - r.t.; ii, $MeOH/NaHCO_3$

Scheme 4.13

4.4 Conclusions

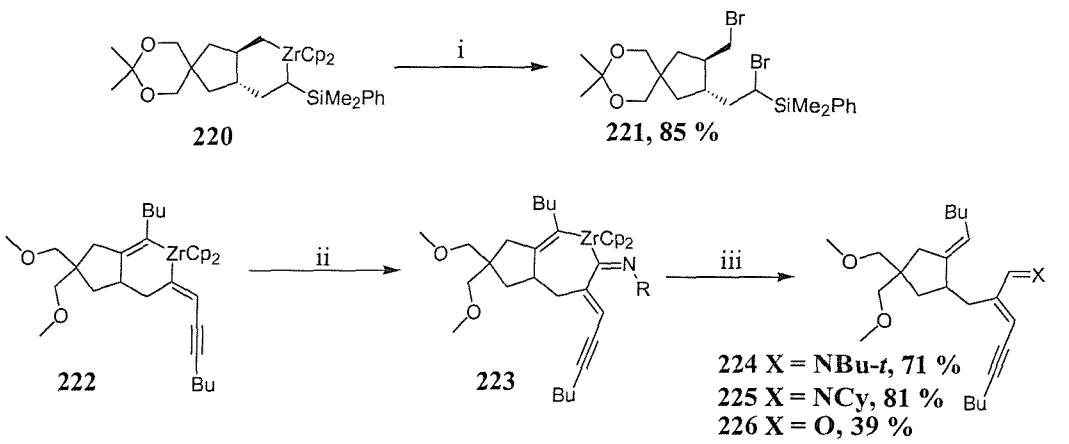
In this chapter, the range of vinyl carbenoids inserted into both zirconacyclopentanes and zirconacyclopentenes has been extended. Insertion into zirconacyclopentanes has shown that poly-insertion of carbenoids into zirconacycles occurs readily if there is no means of electron density donation to the zirconium empty orbital. The fluxionality of the resulting zirconacyclohexanes has also been discovered, exposed by the regiochemistry of the second carbenoid insertion. A novel rearrangement of zirconacyclohexenes to form phenyl substituted methylenecyclopentenes has also been discovered.

Chapter 5. Elaboration of zirconacyclohexanes with carbon monoxide and butyl isocyanide to form cyclohexanones

5.1 Introduction to research area

In Chapter 1 the range of carbenoids that have been inserted into zirconacycles was discussed and then this work extended in Chapters 2 and 4. Since the main aim of research to date has been to investigate the carbenoid insertion itself, in the majority of cases the carbon-zirconium bonds formed have simply been protonated. However, a wide range of elaboration methods are known for zirconacyclopentanes that have so far not been extended to the zirconacyclohexanes formed after carbenoid insertion. Indeed, the carbonylation of a zirconacycle to produce a cyclopentenone was discovered by Negishi in 1985[38] and reported in the same paper as the discovery of the cyclisation of enynes with zirconocene. However, the analogous carbonylation of zirconacyclohexanes has not been developed. Published elaboration methods so far, have all been related to allyl and propargyl carbenoid insertions, after which the resulting 18-electron zirconium complexes react with electrophiles such as aldehydes, as described in Chapter 1.

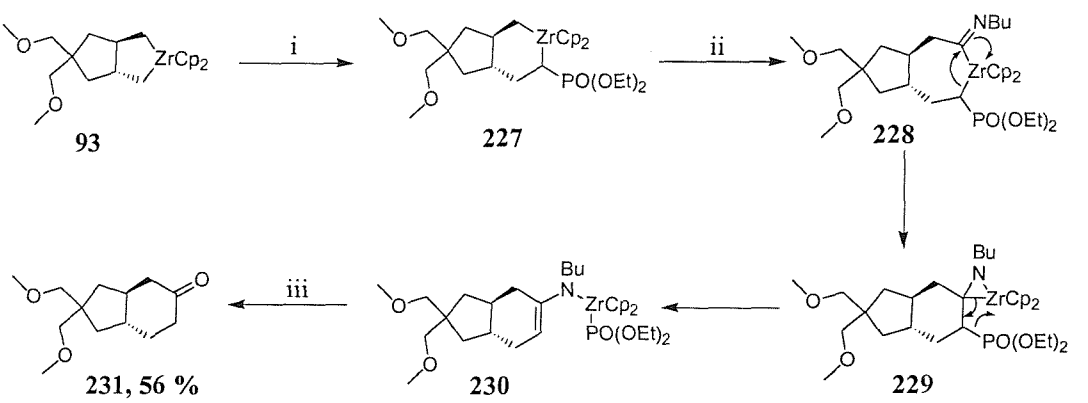
Examples of elaboration of 6-member zirconacycles containing a 16-electron zirconium have been limited to dibromination and insertion of isocyanides. The sole example of dibromination is the addition of bromine to zirconacycle **220** to give the dibromide **221** in excellent yield.[31] Insertion of cyclohexyl isocyanide and *t*-butyl isocyanide into zirconacyclopentene **222**[33] was successful to give the zirconacycloheptene **223**. If the latter zirconacycle was quenched carefully with methanol and aqueous sodium bicarbonate, the corresponding imines were formed. The isocyanides used were known not to rearrange to give η^2-imine complexes of zirconium, so cyclisation of **223** was not observed. Acidic quench of the same zirconacycles caused hydrolysis of the imines to give an α,β-unsaturated aldehyde as the product.



Reagents and Conditions: i, Br_2; ii, *t*-BuNC or CyNC; iii, MeOH/$NaHCO_3$ for **224** and **225**, AcOH (1M) for **226**

Scheme 5.1

Further work so far unpublished, involved the initial insertion of a chloromethylphosphonate and then insertion of *n*-butyl isocyanide.[39] The product of *n*-butyl isocyanide, **228**, was found to rearrange to give an intermediate η^2-imine **229**. Conserted elimination of the phosphonate formed **230** and acid quench yielded the hexanone **231**.



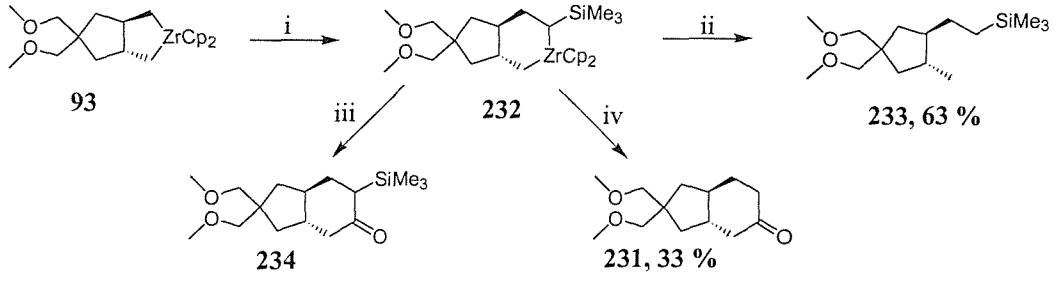
Reagents and Conditions: i, diethyl chloroethylphosphonate (1.3 eq.), LDA (1.3 eq.), -90 - -40 °C; ii, BuNC (1.3 eq.), -40 °C - r.t., 16 hrs; iii, $AcOH/H_2O$, 2 hrs.

Scheme 5.2

The aim of the work in this chapter was to further the methodology of isocyanide insertion and to investigate the use of carbon monoxide, with the target of forming cyclohexanones such as **231**. The chapter is divided into sections by the type of carbenoid inserted into the initial zirconacycle.

5.2 Chloromethylsilane derived carbenoid

Initial attention was drawn to use of chloromethyltrimethylsilane as the carbenoid precursor, as this was known to insert cleanly to give a stable zirconacycle.[23] Insertion into zirconacycle **93** gave the monoinsertion product **233** in 63 % yield.



Reagents and Conditions: i, chloromethyltrimethylsilane (1.1 eq.), LDA (1.1 eq.), -78 °C - r.t. over 16 hrs; ii, MeOH/$NaHCO_3$, 6 hrs; iii, CO, 20 hrs r.t. then I_2; iv, CO, 20 hrs r.t. then MeOH, 16 hrs.

Scheme 5.3

Initially, zirconacycle **232** was placed under an atmosphere of CO at –78 °C and warmed to 0 °C over 6 hrs. Despite the known rapid insertion of CO into zirconacyclopentanes at –78 °C, no reaction was observed by GC. However, after stirring at room temperature overnight, complete insertion was observed, although the reaction was not very clean. Initial quench of a GC sample with MeOH and aqueous $NaHCO_3$ showed the silylated ketone **234** as the major product. GCMS showed the correct M^+ peak at 298 amu. However, treatment of the reaction mixture with the same quench conditions overnight produced the desilylated ketone **231** in a low 23 % yield instead.

Some alternative quenches were investigated: $NaHCO_3$ (aq.) alone gave a mixture of **234** and **231**. Methanol quench gave the desilylated ketone **231** in a slightly higher 33 % yield. Conversely, quench with I_2 and then immediate work up gave only **234**, but after purification the product was not pure and obtained in only 8 % yield.

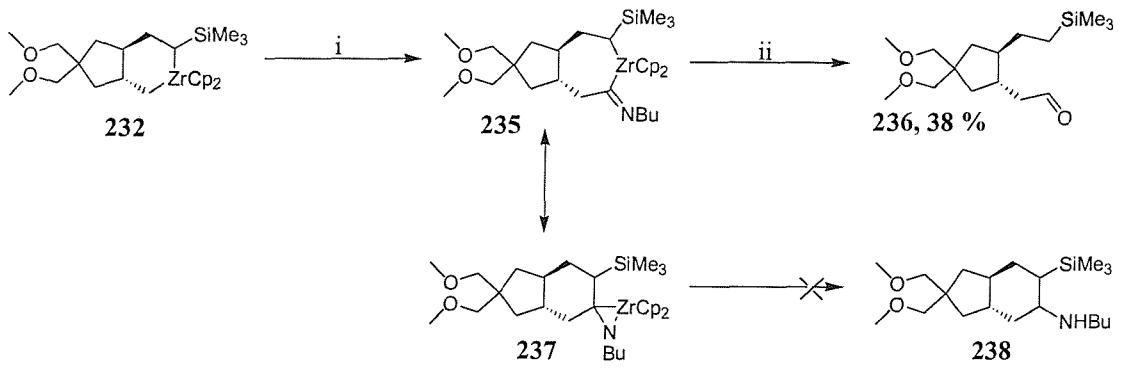
Since the quench of the reaction appeared to have a considerable effect on the outcome, a reaction was split into 15 different flasks and different quenches applied. The reactions were then monitored by GC, with an internal standard of dodecane. The GC yields of the different quench conditions are shown in Table 5.1.

Table 1. *GC yields of cyclohexanone **231** after various quenching conditions.*

Reaction quench conditions	GC yield of **231**, % (dodecane internal standard)
MeOH	30
MeOH and $NaHCO_3$ (aq.)	28
$NaHCO_3$ (aq.)	18
NaOH (aq., 2M)	28
H_2O_2 (aq., 35 %)	29
HCl (aq., 2M)	36
HCl (dioxane, 2M)	20
AcOH (MeOH, 2M)	23
AcOH (THF 2M)	- (32 % for **234**)
AcOH (H_2O, 2M)	33
TBAF (THF, 1M)	0
TBAF (aq., 2M)	30
I_2 (THF)	- (27 % for **234**, immediate work-up)
NBS (THF, 2M)	0
KF (aq., 2M)	29

The results from the above experiment confirmed the low yields obtained from the previous preparative reactions. Whilst the yield from aq. HCl quench was slightly higher, the reaction was not as clean by GC and hence a preparative reaction was not carried out. Curiously, quench with acetic acid in THF did not desilylate the product, but a preparative scale reaction was not successful with low mass recovery and an impure product.

Whilst the above work is the first example of carbonylation of a zirconacyclohexane to give a cyclohexanone, the highest yield obtained was only 33 %. Since the reaction did not prove to be high yielding, attention was diverted to insertion of butyl isocyanide. The reaction between zirconacycle **232** and the isocyanide proceeded to completion within an hour at room temperature to give the aldehyde **236** after acid quench. It was hoped rearrangement to **237** would occur and then quench would proceed to give amine **238**. Leaving zirconacycle **235** at room temperature overnight did show partial conversion to a peak of slightly higher retention time on GC. However, this product remained in the ether layer in acidic conditions, suggesting it was not an amine. Also, the product diminished with further time, leaving **236** as the only observed product. Due to the low yield of product in the first place and only partial conversion to another product, the reaction was not investigated any further.



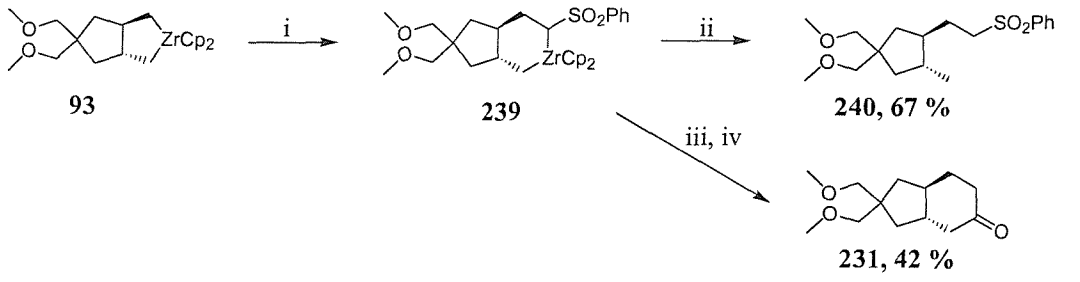
Reagents and Conditions: i, BuNC (1.1 eq.), -5 °C - r.t., 1 hr; ii, HCl (aq., 2M)

Scheme 5.4

Whilst both carbon monoxide and isocyanide inserted into zirconacycle **232**, the results were not very high yielding. Comparison to results from the chloromethyl phosphonate insertion (Scheme 5.2) showed that a lack of trap for the η^2-imine **237** (or η^2-ketone from CO) might be the reason for low yields of cyclised products.

5.3 Chloromethylsulfone carbenoid

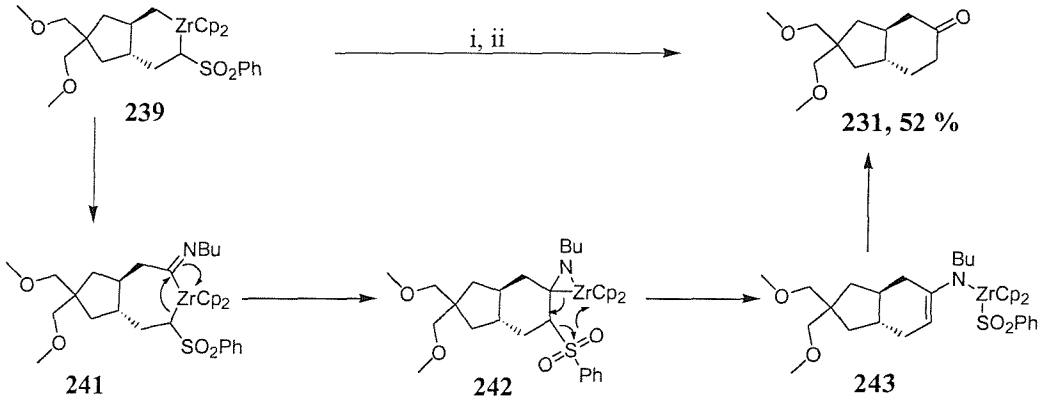
A functional group to act in a similar manner to the phosphonate was sought and to this end insertion of the chloromethylphenylsulphone moiety was found to be successful. Insertion of this carbenoid has previously been performed into an acyclic organozirconocene.[40] However, insertion of the carbenoid into a zirconacycle was itself novel and proceeded in good yield, although 3 or 4 equivalents were required for maximum yields. Two equivalents of carbenoid gave only a 42 % yield. An attempt at carbonylation of zirconacyclohexane **239** was unsuccessful as the GC trace was very messy with some material carbonylated without elimination of sulfone, along with **240** and **231** present. A switch to BuNC was much more successful, with **231** isolated in 42 % overall yield after acetic acid quench.



Reagents and Conditions: i, chloromethylphenyl sulfone (4 eq.), LDA (4 eq.), -78 °C - r.t. over 12 hrs; ii, MeOH/$NaHCO_3$, 20 hrs; iii, BuNC (1.1 eq.), 16 hrs; iv, AcOH (aq., 50 %), 20 hrs.

Scheme 5.5

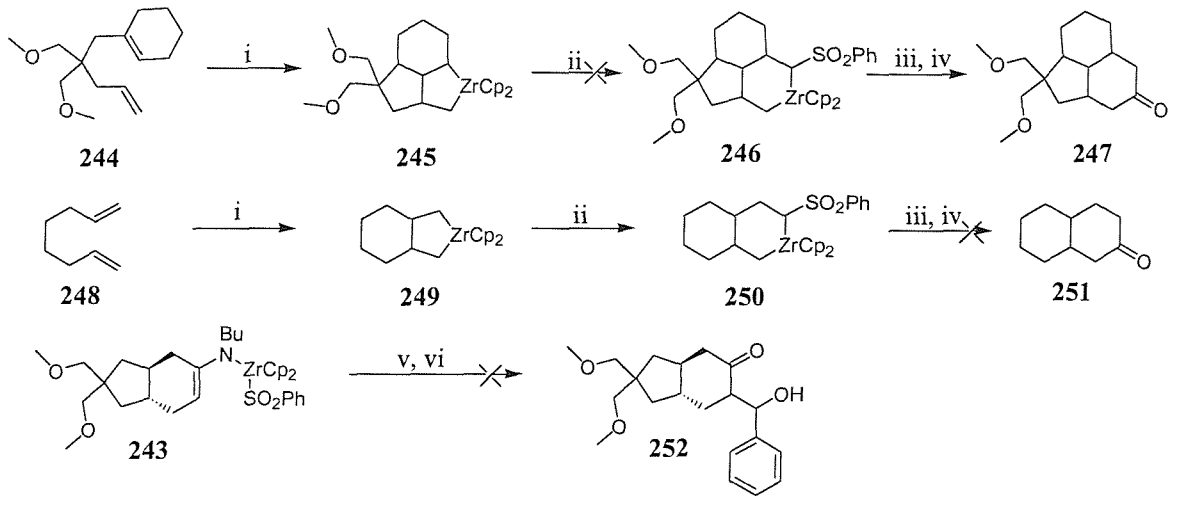
Whilst repeating the experiment to form **231** to improve the yield, it was found that a MeOH/$NaHCO_3$ quench showed a higher ratio of product than the acetic acid quench. Hence the reaction was quenched in this manner to give a higher 52 % yield as shown in Scheme 5.6, along with the proposed mechanism of reaction.



Reagents and Conditions: i, BuNC (1.1 eq.), r.t., 24 hrs; ii, MeOH/$NaHCO_3$, 24 hrs

Scheme 5.6

The above chemistry was attempted with two other substrates and **243** was reacted with benzaldehyde in an attempt to obtain the addition product **252** on work-up. However, all these reactions were unfortunately unsuccessful. Carbenoid insertion into **245** simply did not occur, even once warmed to room temperature. Carbenoid insertion into **249** did occur, but three products were visible by GC and on addition of isocyanide, further by-products could be seen. Purification was also made difficult by there being no clear product spot visible by TLC. With the attempted aldehyde addition to **243**, no reaction was observed by GC.



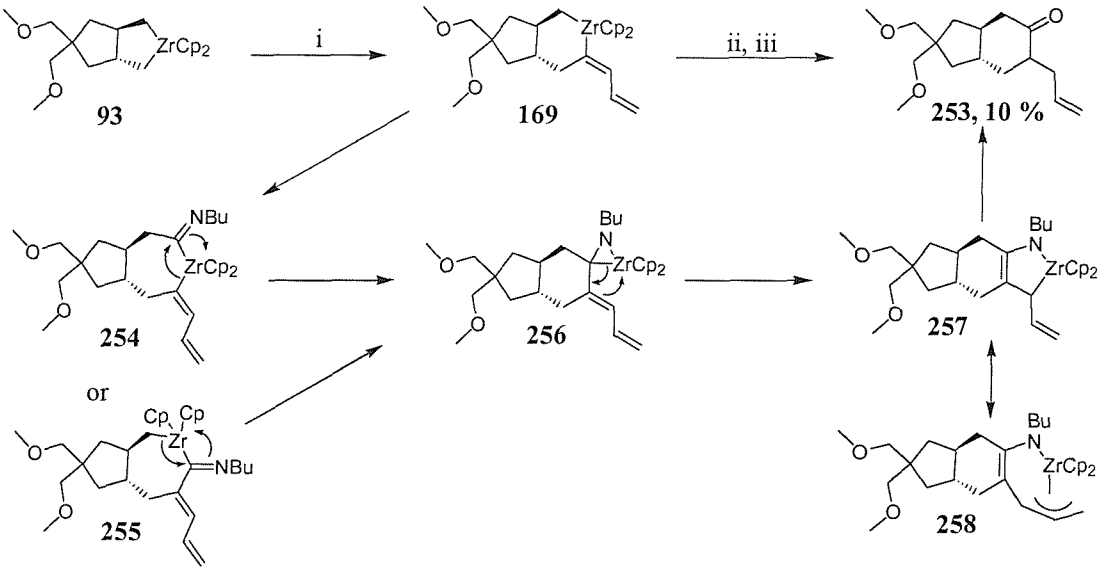
Reagents and Conditions: i, Cp_2ZrCl_2 (1.0 eq.), *n*-BuLi (2.0 eq.), THF, -78 °C - r.t.; ii, chloromethylphenylsulfone (3.0 eq.), LDA (3.0 eq.), -78 °C; iii, BuNC (1.1. eq.), 24 hrs; iv, MeOH/$NaHCO_3$; v, benzaldehyde (2.0 eq.), $BF_3.Et_2O$ (2.0 eq.), vi, AcOH/H_2O

Scheme 5.7

Whilst the chemistry in this section has been shown to be satisfactory for the initial substrate, the methodology was unfortunately not compatible with the other substrates chosen. The choice of substrate is clearly important and it is likely that the methodology would work with other zirconacycles.

5.4 Vinyl carbenoids

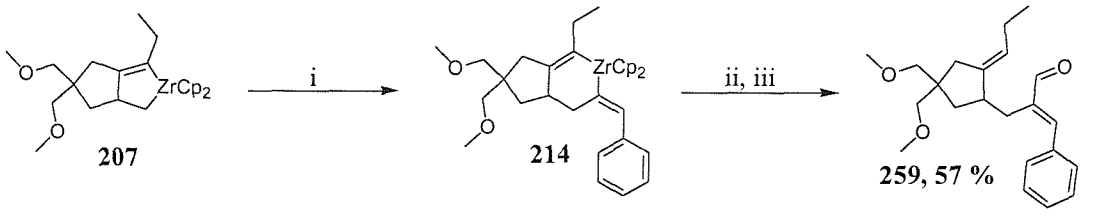
Due to the range of work discovered in the last chapter, the zirconacyclohexanes formed from vinyl carbenoid insertion were investigated for isocyanide insertion. Initially, zirconacycle **169** was chosen since the amount of bis-insertion of the carbenoid was lower than others in the chapter. Fortunately, zirconacycle **169** reacted rapidly with butyl isocyanide, with complete conversion once warmed to –40 °C. The functionalised cyclohexanone **253** was then isolated after acid quench as a single diastereoisomer. The reason for the rapid conversion to product is expected to be the trap of the η^2-imine **256** to the more favoured tricyclic structure **257**. Unfortunately, the yield of **253** was extremely low, which was unexpected from analysis of the GC trace. However, it must be noted that the species expected to be in solution, i.e. **257**, would exist as an allyl zirconocene **258**. This 18-electron species appears to be too resistant to the quenching conditions.



Reagents and Conditions: i, *Z*-1,4-dichloro-2-butene (1.0 eq.), LDA (2.0 eq.), -90 °C; ii, BuNC (1.1 eq.), -90 °C 30 min. - r.t. 16 hrs; iii, HCl (aq., 2M), 24 hrs.

Scheme 5.8

To avoid problems with the quench of the intermediate zirconacycle, the next carbenoid studied was that formed from *E*-β-bromostyrene. Firstly, insertion into zirconacyclopentene **207** was followed by insertion of butyl isocyanide. It was known that cyclohexyl and *t*-butyl isocyanides did not rearrange to η^2-imines under these conditions (Scheme 5.1) and despite the lower steric hindrance from the *n*-butyl group, only the aldehyde **259** was isolated with no rearrangement observed.

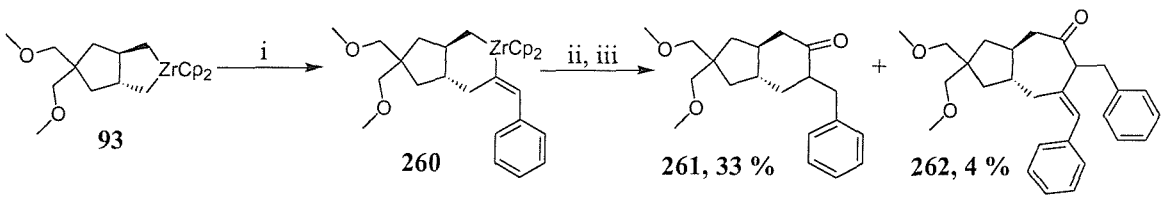


Reagents and Conditions: i, *E*-bromostyrene (1.1 eq.), LDA (1.1 eq.), -78 °C; ii, BuNC (1.1 eq.), -78 °C - r.t., 16 hrs.; iii, AcOH (aq., 50 %), 24 hrs.

Scheme 5.9

Insertion of butyl isocyanide into zirconacyclohexane **260**, however, was consistent with the insertion into **169**. Both cyclohexanone **261** and cycloheptanone **262** were synthesised, the latter from the bis-insertion of the carbenoid. Since there were two diastereoisomers of both products, separation was a problem. Two batches from column chromatography were purified separately by radial chromatography, which

provided one of the diastereoisomers of **261** in a pure form for attainment of analytical data. However, the yields shown were calculated from ratios of products in the ^1H NMR spectra obtained from the batches of fractions collected. The two diastereoisomers of **261** were obtained in an 11:2 ratio.

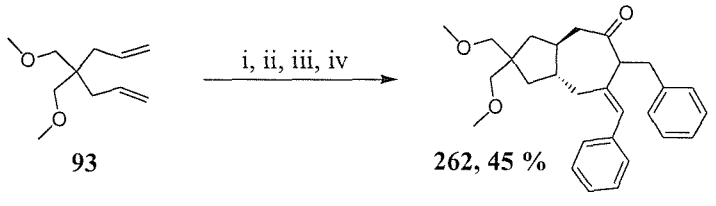


93 **260** **261, 33 %** **262, 4 %**

Reagents and Conditions: i, *E*-bromostyrene (1.0 eq.), LDA (1.0 eq.), -90 °C; ii, BuNC (1.1 eq.), -90 °C - r.t., 16 hrs.; iii, AcOH (aq., 50 %), 24 hrs.

Scheme 5.10

Clearly the bis-insertion of carbenoid was a hindrance to the above reaction to form the cyclohexanone. However, since it was known that intentional bis-insertion of this carbenoid was higher yielding, formation of the cycloheptanone **262** was attempted.



93 **262, 45 %**

Reagents and Conditions: i, Cp_2ZrCl_2 (1.0 eq.), *n*-BuLi (2.0 eq.), THF, -78 °C - r.t.; ii, *E*-bromostyrene (2.0 eq.), LDA (2.0 eq.), -90 °C, 1 hr.; iii, BuNC (1.1 eq.), -90 °C - r.t., 16 hrs.; iii, AcOH (aq., 50 %), 24 hrs.

Scheme 5.11

In the above scheme the overall reaction is shown to emphasise the degree of elaboration attained from such a simple starting structure. Whilst the overall yield is moderate, it is considered an excellent result since 5 carbon-carbon bonds were formed in one 'pot', regiospecifically in a truly multi-component reaction as four molecules have been brought together. The two diastereoisomers were obtained in a 5:2 ratio and were separated.

5.5 Conclusions

In this chapter, the first carbon monoxide insertion into a zirconacyclohexane has been reported. Insertion of butyl isocyanide into zirconacyclohexanes has been shown to successfully form cyclohexanones. Different limitations to the chemistry have unfortunately been found with the different carbenoids employed. Whilst yields may generally be low, the degree of elaboration from the simple diene precursors is considerable, suggesting that further research in this field to overcome some of the limitations would be worthwhile. Finally, the regioselective formation of a bicyclic cycloheptanone from a simple acyclic precursor perhaps provides a glimpse as to what may be possible with zirconium chemistry in the future.

Chapter 6. Experimental

6.1 General Experimental

All reactions involving air or moisture sensitive compounds were carried out under an argon atmosphere using standard Schlenk equipment and syringe techniques. All glassware was dried in an oven at >140 °C and cooled in a sealed desiccator over silica gel.

Unless otherwise stated, reagents were obtained from commercial suppliers and used without further purification. THF used in air-sensitive reactions was freshly distilled from a purple solution of sodium benzophenone ketal under argon. 2,2,6,6-tetramethylpiperidine was distilled and stored over 4Å sieves under argon, diisopropylamine was distilled and stored over KOH. *E*-1,2-dichloroethene was dried ($MgSO_4$), distilled and stored under argon. *n*-Butyllithium was used as a 2.5 mol dm^{-3} solution in hexanes, stored in stock bottles under argon.

Thin layer chromatography was carried out on aluminium backed silica plates and the spots visualised by UV (254 nm lamp), phosphomolybdic acid, sulfuric acid or permanganate stains. Column chromatography on silica was performed on Kieselgel 60 (230-400 mesh) silica gel. Columns were packed and run under light pressure. Solvent compositions are described as % volumes prior to mixing. Petroleum ether 40/60 was distilled before use.

Infra-red spectra were run as neat filmsor solids on a Bio-Rad or Thermo Mattson FTIR Golden Gate instrument. Absorptions are given in wavenumbers (cm^{-1}) and the following abbreviations used to denote peak intensity: s (strong), m (medium), w (weak), br (broad).

Mass spectra were recorded using GC-CI or GC-EI methods on a Finnegan Trace GCMS quodrupole instrument with autosampler. Electrospray mass spectra were recorded using a VG Platform quodrupole spectrometer. M/z signals are reported in

atomic mass units followed in brackets by the peak intensity relative to the base peak. HRMS spectra were obtained using a VG70-SE instrument.

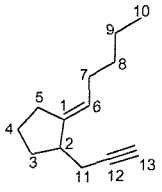
Gas chromatography was performed on a Hewlett Packard HP 6890 Series machine with an HP5 (crosslinked 5 % phenyl methyl siloxane) 30 m column with a film thickness of 0.25 μm. The carrier gas was helium with a flow rate of 2.7 mL/min.

^{1}H and ^{13}C NMR spectra were recorded on Bruker AC300, AM300 and DPX400 spectrometers. The chemical shifts, δ, are recorded as values in ppm referenced to the chloroform peaks at 7.26 ppm for ^{1}H spectra and 77.16 ppm for ^{13}C spectra. For ^{1}H spectra, the following abbreviations are used to denote multiplicity and may be compounded: s = singlet, d = doublet, t = triplet, q = quartet, br = broad, fs = fine splitting. Coupling constants, J, are measured in Hertz (Hz). ^{13}C spectra were proton decoupled and the signals reported as s, d, t, q depending on the number of directly attached protons (0, 1, 2 or 3 respectively), this having been determined by DEPT experiments. ^{1}H-^{13}C correlation and COSY experiments were used to aid assignment of spectra. In some instances, the abbreviations M and m are used to define Major and minor isomers respectively.

6.2 Detailed Experimental

6.2.1 Experimental for Chapter 2

Preparation of 1-Pent-(*E*)-ylidene-2-prop-2-ynylcyclopentane, 24



To a solution of zirconocene dichloride (584 mg, 2.0 mmol, 1.0 eq.) in THF (10 mL) at –78 °C under argon was added *n*-BuLi (1.60 mL, 4.0 mmol, 2.0 eq.) and stirred for 30 min before 1-undecen-6-yne (301 mg, 2 mmol, 1.0 eq.) was added and the reaction stirred at room temperature for 20 hrs. At –78 °C *E*-1,2-dichloroethene (380 mg, 0.30 mL, 4.0 mmol, 2.0 eq.) was added, followed by LDA (4.0 mmol in 8 mL THF, 2.0 eq.) dropwise over 5 min. After 10 min the reaction was allowed to warm to room temperature and was stirred for 1 hr. MeOH (10 mL) was added, followed by saturated $NaHCO_3$ (10 mL) and the reaction was stirred for 16 hrs. Pentane (40 mL) was added before the mixture was filtered and then the layers separated. The aqueous was extracted with pentane (20 + 10 mL). The combined pentane layer was washed with brine (2 × 20 mL) before it was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to reveal a black oil. The crude product was purified by flash silica chromatography (eluent petroleum ether 40/60) to afford the title compound (92 mg, 26 %) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.24 (1H, tq, J = 7.2, 2.4 Hz, H-6), 2.51 (1H, m, H-2), 2.40 (1H, ddd, J = 16.5, 5.2, 2.6 Hz, H-11a), 2.30-2.20 (2H, m, H-5), 2.15 (1H, ddd, J = 16.5, 8.5, 2.6 Hz, H-11b), 2.00-1.93 (2H, m, H-7), 1.96 (1H, m, H-3a), 1.92 (1H, t, J = 2.6 Hz, H-13), 1.74 (1H, m, H-4a), 1.56 (1H, m, H-4b), 1.49 (1H, m, H-3b), 1.36-2.26 (4H, m, H-8 + H-9), 0.90 (3H, t, J = 7.0 Hz, H-10) ppm.

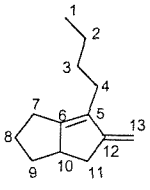
^{13}C NMR (100 MHz, $CDCl_3$) δ = 144.60 (s, C-1), 121.43 (d, C-6), 84.11 (s, C-12), 68.50 (d, C-13), 43.14 (d, C-2), 32.71 (t, C-3), 31.95 (t, C-8 or C-9), 29.37 (t, C-5 or C-7), 29.31 (t, C-5 or C-7), 23.99 (t, C-4 or C-11), 23.69 (t, C-4 or C-11), 22.51 (C-8 or C-9), 14.20 (q, C-10) ppm.

IR (neat film): 3312 (m), 2954 (s), 2952 (s), 2870 (s), 2858 (s), 2118 (w), 1671 (w), 1450 (m), 1238 (w) cm^{-1}.

LRMS (GC-CI): 194 ($M+NH_4^+$, 10 %), 177 ($M+H^+$, 40 %), 119 ($M-Bu^+$, 60 %), 95 (84 %), 81 (100 %).

HRMS (EI): Found: M^+, 176.1574; $C_{13}H_{20}$, requires M^+, 176.1565.

Preparation of 6-butyl-5-methylene-1,2,3,3a,4,5-hexahydropentalene, 25



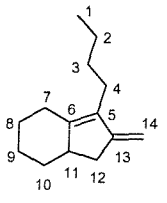
To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and stirred for 30 min. 1-undecen-6-yne (150 mg, 1.0 mmol, 1.0 eq.) in THF (2 mL) was added and the reaction stirred at room temperature for 5 hrs. The reaction was cooled to –78 °C and 1,2-dibromoethene (370 mg, 0.17 mL, 2.0 mmol, 2 eq., mixture of *E* and *Z*) was added, followed by LDA (2.0 mmol, 2 eq. in 4 mL THF) dropwise over 2 min. After 10 min, MeOH (5 mL) was added and the cool bath was removed. Saturated $NaHCO_3$ (5 mL) was added and the reaction stirred at r.t. for 16 hrs. Pentane was added (20 mL) and the layers separated. The pentane layer was then washed with H_2O (2 × 30 mL) and brine (30 mL) and dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to reveal a dark brown oil (126 mg, 0.71 mmol, 71 % crude material). Estimated purity from ^1H NMR, 50 %.

^1H NMR (400 MHz, $CDCl_3$) δ = 4.61 (2H, s, H-13), 2.81 (1H, m, H-10), 2.72 (1H, dd, J = 15.6, 7.0 Hz, H-11a), 2.28-2.20 (2H, m, H-7), 2.17 (1H, m, H-11b), 2.15-2.10 (2H, m, H-4), 2.02-1.97 (2H, m, H-8), 1.91 (1H, m, H-9a), 1.49-1.41 (2H, m, H-3), 1.35-1.27 (2H, m, H-2), 1.02 (1H, m, H-9b), 0.91 (3H, t, J = 7.3 Hz, H-1) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 160.36 (s, C-5 or C-6), 158.72 (s, C-5 or C-6), 133.32 (s, C-12), 97.37 (t, C-13), 49.41 (d, C-10), 37.27 (t, C-11), 31.96 (t, C-9), 30.60 (t, C-3), 27.64 (t, C-8), 25.91 (t, C-4), 23.40 (t, C-7), 23.00 (t, C-2), 14.15 (q, C-1) ppm.

LRMS (GC-CI): 177 ($M+H^+$, 100 %), 161 (6 %), 147 ($M-Et^+$ 24 %), 133 ($M-Pr^+$ 10 %), 119 ($M-Bu^+$ 14 %).

Preparation of 3-Butyl-2-methylene-2,4,5,6,7,7a-hexahydro-1H-indene, 29

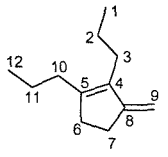


To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and stirred for 30 min. 1-dodecen-7-yne (164 mg, 1.0 mmol, 1.0 eq.) in THF (2 mL) was added and the reaction stirred at room temperature for 5 hrs. The reaction was cooled to –78 °C and *E*-1,2-dichloroethene (190 mg, 0.15 mL, 2.0 mmol, 2.0 eq.) was added, followed by LDA (2.0 mmol in 4 mL THF, 2.0 eq.) dropwise over 5 min. After 10 min, MeOH (5 mL) was added and the cool bath was removed. Saturated $NaHCO_3$ (5 mL) was added and the reaction stirred at r.t. for 16 hrs. Pentane was added (20 mL) and the layers separated. The pentane layer was then washed with H_2O (2 × 30 mL) and brine (30 mL) and dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to reveal a dark brown oil (155 mg, 0.81mmol, 81 % crude material). Estimated purity from ^1H NMR, 50 %.

^1H NMR (300 MHz, $CDCl_3$) δ = 4.68 (1H, s, H-14a), 4.64 (1H, s, H-14b), 2.73 (1H, ddt, J = 16.2, 7.3, 2.0 Hz, H-12a), 2.59 (1H, m), 2.45 (1H, m), 2.0-0.80 (17H, m) ppm.

LRMS (GC-EI): 190 (M^+, 54 %), 161 (22 %), 147 (100 %), 133 (37 %), 105 (76 %).

Preparation of 3-methylene-1,2-dipropylcyclopentene, 32



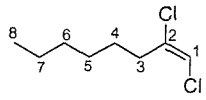
To a solution of zirconocene dichloride (292 mg, 1.0 mmol, 1.0 eq.) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and the reaction stirred for 30 min. Ethene was then flushed through the reaction vessel for 5 min before the reaction was left under ethene. The reaction was warmed to r.t. and 4-octyne (110 mg, 1.0 mmol, 1.0 eq.) in THF (2 mL) was added. The reaction was stirred for 2 hrs before the orange solution was cooled to –78 °C and *E*-1,2-dichloroethene (0.15 mL, 2.0 mml, 2.0 eq.) was added followed by LDA (2.0 mmol, 2.0 eq. in 4 mL THF) dropwise over 3 min. The reaction was stirred for 15 min before MeOH (5 mL) was added and the cool bath removed. Saturated $NaHCO_3$ (5 mL) was then added whilst the reaction was warming to r.t. and the quench stirred for 20 hrs. Et_2O (20 mL) was added and the layers separated before the aqueous layer was extracted with Et_2O (20 mL). The combined organic phase was washed with brine (20 mL) before it was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude title compound as a pale yellow oil (170 mg, 103 %). Estimated purity by ^1H NMR, 70 %. NMR yield 74 %, referenced to anisole.

^1H NMR (400 MHz, $CDCl_3$) δ = 4.69 (1H, s, H-9a), 4.66 (1H, s, H-9b), 2.54-2.49 (2H, m, H-7), 2.37-2.32 (2H, m, H-6), 2.20-2.10 (4H, m, H-3 and H-10), 1.50-1.37 (4H, m, H-2 and H-11), 0.91 (6H, t, J = 7.5 Hz, H-1 and H-12) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 156.57 (s, C4, C-5 or C-8), 148.60 (s, C-4, C-5 or C-8), 137.91 (s, C-4, C-5 or C-8), 97.66 (t, C-9), 32.92 (t, C-6), 31.85 (t, C-3 or C-10), 29.34 (t, C-7), 26.97 (t, C-3 or C-10), 22.12 (t, C-2 or C-11), 21.37 (t, C-2 or C-11), 14.54 (q, C-1 or C-12), 14.35 (q, C-1 or C-12) ppm.

LRMS (GC-CI): 165 ($M+H^+$, 100 %), 149 (M^+-Me, 22 %), 135 (M^+-Et, 10 %), 121 (M^+-Pr, 20 %), 107 (6 %).

Preparation of (*E*)-1,2-dichloro-1-octene, 34



A mixture of LiCl (33.6 g, 0.80 mol, 40 eq.), $CuCl_2$ (107 g, 0.80 mol, 40 eq.) and 1-octyne (2.95 mL, 20.0 mmol, 1 eq.) in acetonitrile (300 mL) was heated to reflux for 24 hrs. The reaction mixture was poured onto H_2O (1.4 L) and Et_2O (300 mL) was added. The layers were separated and the aqueous layer extracted with more Et_2O (300 mL) before the combined organic phase was washed with H_2O (3 × 500 mL) and brine (200 mL) and then dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to reveal a yellow oil. The crude product was Kugelrohr distilled (125 °C, 50 mm Hg) to afford a colourless oil (1.40 g, 7.7 mmol, 39 %). ^{1}H NMR data consistent with the literature (1H singlet at 6.15 ppm)[1].

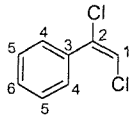
^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.14 (1H, s, H-1), 2.51 (2H, t, J = 7.4 Hz, H-3), 1.61-1.52 (2H, m, H-4), 1.38-1.25 (6H, m, H-5, H-6 and H-7), 0.89 (3H, t, J = 6.8 Hz, H-8) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 136.74 (s, C-2), 113.65 (d, C-1), 33.30, 31.65, 28.31, 26.44, 22.67 (all t, C-3, C-4, C-5, C-6 and C-7), 14.20 (q, C-8) ppm.

LRMS (GC-CI): 180 (M^+, 2 %), 162 (14 %), 144 (M^+-HCl, 18 %), 109 (M^+-HCl-Cl, 100 %), 88 (56 %).

IR (neat film): 3087 (w), 2956 (m), 2928 (m), 2859 (m), 1578 (w), 1432 (m), 1125 (m), 813 (s), 792 (s) cm^{-1}.

Preparation of [(*E*)-1,2-dichlorovinyl]benzene, 35



A mixture of LiCl (33.6 g, 0.80 mol, 40 eq.), $CuCl_2$ (107 g, 0.80 mol, 40 eq.) and phenylacetylene (2.20 mL, 20.0 mmol, 1.0 eq.) in acetonitrile (300 mL) was refluxed

for 72 hrs. The reaction mixture was poured onto H_2O (1.5 L) and extracted with Et_2O (2 × 250 mL). The combined organic phase was washed with H_2O (3 × 500 mL) and brine (200 mL) before it was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to reveal a yellow oil. The crude product was purified by flash silica chromatography (eluent petroleum ether) to yield the *E* isomer as a colourless oil (1.781 g, 10.3 mmol, 51 %). A mixture of *E* and *Z* isomers was also obtained (0.548 g, 3.2 mmol, 16 %) along with some pure *Z* isomer (0.069 g, 0.40 mmol, 2 %). ^1H NMR consistent with literature[1].

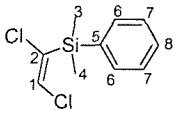
For *E* isomer:
^1H NMR (300 MHz, $CDCl_3$) δ = 7.61 (2H, dd, J = 7.9, 2.0 Hz, H-4), 7.45-7.38 (3H, m, H-5 and H-6), 6.51 (1H, s, H-1) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 134.51 (s, C-2 or C-3), 132.62 (s, C-2 or C-3), 129.64 (d, C-6), 129.05 (d, C-5), 128.34 (d, C-4), 114.38 (d, C-1) ppm.

LRMS (GC-CI): 174 (M^+, 66 %), 172 (M^+, 100 %), 137 (M-Cl^+, 27 %), 117 (6 %), 102 (M^+-2Cl, 50 %).

IR (neat film): 3081 (m), 1602 (w), 1583 (w), 1489 (m), 1444 (m), 1172 (m), 927 (m), 816 (s), 760 (s) cm^{-1}.

Preparation of [(*E*)-1,2-dichlorovinyl](dimethyl)phenylsilane, 36



A solution of *E*-1,2-dichloroethene (2.31 mL, 30.0 mmol) and chlorodimethylphenylsilane (4.0 mL, 24.0 mmol, 0.8 eq.) in THF (20 mL) was cooled to –95 °C. A freshly prepared solution of LiTMP (30 mmol in 25 mL THF) was added dropwise in 10 mL aliquots. The cool bath was allowed to warm to room temperature over a period of 72 hrs. The reaction was quenched with NH_4Cl (30 mL, aq.) and the organic layer washed with H_2O (2 × 100 mL) and brine (30 mL) before it was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to reveal a yellow oil.

The crude product was purified by flash silica chromatography (eluent petroleum ether) to afford the title product as a colourless oil (4.50 g, 19.4 mmol, 81 %). This oil was a mixture of the title product plus Cl-C≡C-$SiMe_2Ph$ in a ratio of 11:5 respectively. The IR spectrum for Cl-C≡C-$SiMe_2Ph$ fits the literature[2] - C≡C stretch at 2140 cm^{-1}.

For title compound **36**:

^1H NMR (300 MHz, $CDCl_3$) δ = 7.63-7.57 (2H, m, H-6), 7.43-7.36 (3H, m, H-7 + H-8), 6.90 (1H, s, H-1), 0.61 (6H, s, H-3 + H-4) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 134.04 (d, C-6), 129.90 (d, C-8), 129.79 (s, C-2 or C-5), 128.61 (d, C-1), 128.06 (d, C-7), -2.02 (q, C-3 and C-4) ppm. C-2 or C-5 not observed.

For impurity Cl-^1C≡^2C-Si^3Me_2Ph

^1H NMR (300 MHz, $CDCl_3$) δ = 7.60 (2H, m), 7.40 (3H, m), 0.45 (6H, s) ppm.

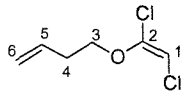
^{13}C NMR (75 MHz, $CDCl_3$) δ = 136.9 (s), 133.8 (d), 126.6 (d), 128.1 (d), 113.8 (s, C-1), -1.0 (q, C-3) ppm. C-2 not observed.

LRMS: Title compound (GC-EI): 215 (M-Me^+, 12 %), 195 (M-Cl^+, 44 %), 179 (M-Me-HCl^+, 32 %), 155 (100 %), 135 (89 %).

LRMS: Impurity (GC-EI): 179 (M-Me^+, 100 %), 145 (4 %), 129 (10 %), 103 (14 %), 63 (17 %).

IR (neat film): 3070 (w), 2960 (w), 2143 (m), 1546 (m), 1428 (m), 1251 (s), 1112 (s), 836 (s), 808 (s), 778 (s), 730 (s) cm^{-1}.

Preparation of 4-{[(*E*)-1,2-dichlorovinyl]oxy}but-1-ene, 38



Pentane washed NaH (1.92g, 48 mmol, 60 % suspension in oil) was suspended in THF (35 mL) before 3-butene-1-ol (3.61 g, 4.30 mL, 50 mmol) was added in THF (15 mL) and the reaction stirred for 3 hrs. Trichloroethene (6.00g, 4.13 mL, 46 mmol) was added and the reaction heated to reflux for 20 hrs. The reaction was quenched with MeOH (25 mL) and then H_2O (30 mL) and Et_2O (50 mL) were added. The aqueous layer was extracted with Et_2O (2 × 30 mL) before the combined organic phase was washed with brine (15 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to reveal an orange oil. The crude product was purified by flash silica chromatography (eluent 0-5 % Et_2O in petroleum ether) to afford the title compound as a pale yellow oil (4.83 g, 29 mmol, 63 %). Data consistent with literature[3].

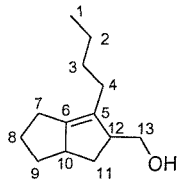
^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.87 (1H, ddt, J = 17.3, 10.3, 6.6 Hz, H-5), 5.51 (1H, s, H-1), 5.18 (1H, ddt, J = 17.3, 1.5, 1.3 Hz, H-6a), 5.13 (1H, ddt, J = 10.3, 1.5, 1.3 Hz, H-6b), 4.08 (2H, t, J = 6.6 Hz, H-3), 2.48 (2H, tdt, J = 6.6, 6.6, 1.3 Hz, H-4) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 143.65 (s, C-2), 133.50 (d, C-1), 117.81 (t, C-6), 98.11 (d, C-5), 71.11 (t, C-3), 33.38 (t, C-4) ppm.

LRMS (GC-CI): 167 ($M+H^+$, 8 %), 131 ($M+H^+$ - HCl, 8 %), 55 (butene, 100 %).

IR (neat film): 3109 (w), 2954 (w), 1627 (m), 1467 (w), 1430 (w), 1274 (m), 1082 (s), 987 (m), 918 (m), 822 (s), 742 (m) cm^{-1}.

Preparation of (3-butyl-1,2,4,5,6,6a-hexahydropentalen-2-yl)methanol, 44



To a freshly prepared sample of crude diene **25** (144 mg, about 0.8 mmol) under argon was added 9-BBN (1.70 mL, 0.85 mmol, 0.5 M in THF) and stirred for 30 min. NaOH (4 mL, 2.5 M) was then added, followed by cold H_2O_2 (4 mL, 35 % in water) and the reaction stirred for 16 hrs. Et_2O (10 mL) was added and the layers separated. The Et_2O layer was washed with H_2O (3 × 20 mL) before it was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to reveal a yellow oil. The crude material was purified by flash silica chromatography (eluent 10-50 % Et_2O in petroleum ether 40/60) to afford the title compound as a pale yellow oil (69 mg, 0.36 mmol, 36 % from starting enyne).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.68-3.58 (2H, m, H-13), 3.16 (1H, m, H-12), 2.71 (1H, m, H-10), 2.15 (1H, m, H-11a), 2.2-1.9 (2H, m, H-7), 2.1-1.9 (2H, m, H-4), 2.0-1.8 (2H, m, H-8), 1.9-1.8 (1H, m, H-9a), 1.4-1.2 (2H, m, H-2 or H-3), 1.35-1.25 (2H, m, H-2 or H-3), 1.2 (1H, m, H-11b), 0.97 (1H, m, H-9b), 0.87 (3H, t, J = 7.0 Hz, H-1) ppm.

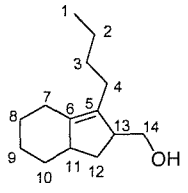
^{13}C NMR (100 MHz, $CDCl_3$) δ = 149.44 (s, C-6), 129.67 (s, C-5), 64.94 (t, C-13), 54.82 (d, C-12), 50.53 (d, C-10), 34.11 (t, C-11), 32.48 (t, C-9), 30.54 (t, C-3), 28.32 (t, C-8), 27.31 (t, C-4), 22.76 (t, C-2 or C-7), 22.73 (t, C-2 or C-7), 0.87 (q, C-1) ppm.

LRMS (GC-EI): 194 (M^+, 26 %), 176 (M^+-H_2O, 6 %), 163 (M^+-CH_2OH, 100 %), 147 (M^+-H_2O-Et, 10 %), 133 (M^+-H_2O-Pr, 20 %), 121 (M^+-OH-Bu, 48 %), 107 (M^+-CH_2OH-Bu, 56 %), 91 (84 %).

IR (neat film): 3600-3200 (m), 2950 (s), 2924 (s), 2856 (s), 1654 (w), 1447 (m), 1376 (m), 1207 (w), 1078 (m), 1024 (s) cm^{-1}.

HRMS (EI): Found: M^+, 194.1671; $C_{13}H_{22}O$ requires M^+, 194.1671.

Preparation of (3-butyl-2,4,5,6,7,7a-hexahydro-1*H*-inden-2-yl)methanol, 45



To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and stirred for 30 min. 1-dodecen-7-yne (164 mg, 1.0 mmol, 1.0 eq.) in THF (2 mL) was added and the reaction stirred at room temperature for 5 hrs. The reaction was cooled to –78 °C and *E*-1,2-dichloroethene (190mg, 0.15 mL, 2.0 mmol, 2 eq.) was added, followed by LDA (2.0 mmol, 2 eq. in 4 mL THF) dropwise over 2 min. After 10 min, MeOH (5 mL) was added and the cool bath was removed. Saturated $NaHCO_3$ (5 mL) was added and the reaction stirred at r.t. for 16 hrs. Pentane was added (20 mL) and the layers separated. The pentane layer was then washed with H_2O (2 × 30 mL) and brine (30 mL) and dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to reveal a dark brown oil. To the crude diene (160 mg, about 0.8 mmol) under argon was added 9-BBN (1.70 mL, 0.85 mmol, 0.5 M in THF) and stirred for 16 hrs. NaOH (3 mL, 2.5 M) was then added, followed by cold H_2O_2 (3 mL, 35 % in H_2O) and the reaction stirred for 24 hrs. Et_2O (15 mL) and water were added and the layers separated. The Et_2O layer was washed with H_2O (2 × 20 mL) before it was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to reveal a colourless oil. The crude material was purified by flash silica chromatography (eluent 10-40 % Et_2O in petroleum ether 40/60) to afford the title compound as a colourless oil (85 mg, 0.41 mmol, 41 % from starting enyne). Ratio of diastereoisomers, 5.8:1 (determined by GC).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.70-3.58 (2H, m, H-14), 2.84 (1H, m, H-13), 2.51 (1H, d, J = 15.5 Hz, H-7, H-8 or H-9), 2.35 (1H, m, H-11), 2.25-2.10 (2H, m, H-4a and H-12a), 2.0-1.8 (2H, m, H-4b and H-10a), 1.8-1.7 (2H, m, H-7, H-8 or H-9), 1.22-1.12 (1H, m, H-12b), 1.40-1.10 (7H, m, H-2, H-3 + H-7, H-8 or H-9), 1.00-0.90 (1H, m, H-10b), 0.88 (3H, t, J = 6.8 Hz, H-1) ppm.

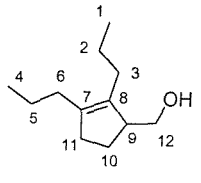
^{13}C NMR (100 MHz, $CDCl_3$) δ = 141.84 (s, C-6), 131.06 (s, C-5), 64.93 (t, C-14), 48.69 (d, C-13), 45.58 (d, C-11), 36.28 (t, C-10), 33.19 (t, C-12), 30.71 (t, C-3), 27.05 (t, C-7, C-8 or C-9), 26.63 (t, C-7, C-8 or C-9), 26.34 (t, C-7, C-8 or C-9), 25.65 (t, C-4), 22.74 (t, C-2), 14.10 (q, C-1) ppm.

LRMS (GC-EI): 208 (M^+, 12 %), 177 (M^+-CH_2OH, 100 %), 135 (20 %), 121 (M^+-CH_2OH-Bu, 96 %), 91 (82 %).

IR (neat film): 3600-3200 (m), 2921 (s), 2850 (s), 1654 (w), 1444 (m), 1376 (m), 1239 (w), 1028 (s), 940 (m) cm^{-1}.

HRMS (EI): Found: M^+, 208.1825; $C_{14}H_{24}O$ requires M^+, 208.1827.

Preparation of (2,3-dipropylcyclopent-2-en-1-yl)methanol, 46



Diene **32** was placed under argon before 9-BBN (2.0 mL, 0.5M in THF, 1.0 mmol, 1.0 eq.) was added. After 40 min the reaction was cooled to 0 °C and NaOH (3 mL, 10 % solution in H_2O) was added followed by H_2O_2 (3 mL, 35 % solution in H_2O). The quench was stirred for 20 hrs before H_2O (10 mL) and Et_2O (20 mL) were added and the layers separated. The aqueous layer was extracted with Et_2O (2 × 10 mL) before the combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a pale yellow oil. The crude product was purified by flash silica chromatography (eluent 20-60 % Et_2O in petroleum ether 40/60) to give a pale yellow oil (69 mg, 0.38 mmol, 38 % from 4-octyne).

^1H NMR (400 MHz, $CDCl_3$) δ = 3.62 (1H, ddd, J = 10.4, 7.3, 3.5 Hz, H-12a), 3.56 (1H, ddd, J = 10.4, 7.3, 3.5 Hz, H-12b), 2.83 (1H, m, H-9), 2.32 (1H, m, H-11a), 2.21 (1H, ddd, J = 15.3, 9.7, 5.4 Hz, H-11b), 2.12 (1H, m, H-3a or H6a), 2.05 (2H, t, J = 7.7 Hz, H-3 or H-6), 1.95 (1H, m, H-10a), 1.88 (1H, m, H-3b or H-6b), 1.70 (1H, ddd, J = 17.8, 9.2, 4.7, Hz, H-10b), 1.46 (1H, m, H-2a or H-5a), 1.39 (2H, tq, J = 7.5, 7.5

Hz, H-2 or H-5), 1.29 (1H, m, H-2b or H-5b), 1.18 (1H, m, -OH), 0.88 (3H, t, J = 7.3 Hz, H-1 or H-4), 0.87 (3H, t, J = 7.4 Hz, H-1 or H-4) ppm.

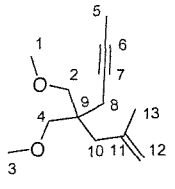
^{13}C NMR (100 MHz, $CDCl_3$) δ = 139.80 (s, C-8), 134.36 (s, C-7), 64.90 (t, C-12), 49.93 (d, C-9), 34.48 (t, C-11), 30.80 (t, C3 or C-6), 28.59 (t, C-3 or C-6), 25.82 (t, C-10), 21.76 (t, C-2 or C-5), 21.50 (t, C-2 or C-5), 14.28 (q, C-1 or C-4), 14.20 (q, C-1 or C-4) ppm.

LRMS (GC-CI): 200 ($M+NH_4^+$, 4 %), 183 ($M+H^+$, 10 %), 165 ($M-OH^+$, 36 %), 151 ($M-MeO^+$, 100 %), 135 (4 %).

IR (neat film): 3560-3050 (br, m), 2955 (s), 2930 (s), 2869 (s), 2843 (s), 1458 (m), 1377 (m), 1051 (m), 1021 (s) cm^{-1}.

HRMS (EI): Found: M^+, 182.1669; $C_{12}H_{22}O$ requires M^+, 182.1671.

Preparation of 4,4-Bis-methoxymethyl-2-methyl-oct-1-en-6-yne, 51



The known diester **49** was synthesised using malonate chemistry as shown in Scheme 2.7. Diester **49** (6.25 g, 23.0 mmol) was then added to a suspension of $LiAlH_4$ (5.24 g, 138 mmol, 6.0 eq.) in Et_2O (70 mL) at 0 °C. The reaction was stirred at r.t. for 2 hrs before it was quenched with HCl (40 mL, 2M, aq.). The layers were separated and the aqueous layer extracted with Et_2O (100 mL). The combined organic phase was then washed with H_2O (50 mL) and brine (2 × 60 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a clear oil. The crude diol was then added in THF (20 mL) to a suspension of NaH (2.76 g, 60 % in oil, 69.0 mmol, 3.0 eq.) in THF (60 mL). After 15 min, MeI (5.0 g, 2.20 mL, 35.0 mmol, 1.5 eq.) was added and the reaction stirred for 30 min before a second aliquot of MeI (5.0 g, 2.20 mL, 35.0 mmol, 1.5 eq.) was added. The reaction was stirred for 16 hrs before H_2O (70 mL) and Et_2O (100 mL) were added. The layers were separated and the aqueous layer

extracted with Et_2O (120 mL). The combined organic phase was washed with H_2O (100 mL), NH_4Cl (2 × 100 mL, sat.) and brine (2 × 100 mL) before it was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil. The crude product was purified by flash silica chromatography (eluent 3 % Et_2O in petroleum ether 40/60) to give a colourless oil (3.75 g, 17.8 mmol, 78 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.89 (1H, m, H-12a), 4.76 (1H, m, H-12b), 3.31 (6H, s, H-1 and H-3), 3.23 (2H, d, J = 9.0 Hz, H-2a and H-4a), 3.20 (2H, d, J = 9.0 Hz, H-2b and H-4b), 2.14 (2H, q, J = 2.60 Hz, H-8), 2.11 (2H, s, H-10), 1.80 (3H, t, J = 2.60 Hz, H-5), 1.77 (3H, s, H-13) ppm.

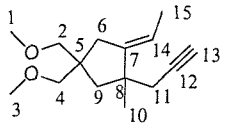
^{13}C NMR (75 MHz, $CDCl_3$) δ = 142.27 (s, C-11), 114.92 (t, C-12), 77.73 (s, C-6 or C-7), 75.94 (s, C-6 or C-7), 74.49 (t, C-2 and C-4), 59.22 (q, C-1 and C-3), 42.55 (s, C-9), 38.48 (t, C-10), 25.18 (q, C-13), 22.79 (t, C-8), 3.72 (q, C-5) ppm.

LRMS (GC-CI): 211 ($M+H^+$, 5 %), 179 ($M+H-MeOH^+$, 10 %), 147 ($M+H-2MeOH^+$, 44 %), 133 ($M+H-MeOH-CH_2OMe^+$, 49 %), 105 (50 %).

IR (neat film): 2979 (w), 2920 (m), 2888 (m), 2809 (w), 1478 (w), 1448 (m), 1195 (m), 1103 (s), 965 (m), 896 (m) cm^{-1}.

HRMS (EI): Found: M^+ (self CI), 211.1696; $C_{13}H_{23}O_2$ requires M^+, 211.1698.

Preparation of (2*E*)-2-ethylidene-4,4-bismethoxymethyl-1-methyl-1-prop-2-ynylcyclopentane, 53



To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and the reaction stirred for 30 min. 4,4-Bis-methoxymethyl-2-methyl-oct-1-en-6-yne (210 mg, 1.0 mmol, 1.0 eq.) in THF (2 mL) was added and the reaction allowed to warm to r.t. before it was stirred for 16 hrs. The solution was cooled to –78 °C and *E*-1,2-dichloroethene (0.15

mL, 2.0 mmol, 2 eq.) was added followed by LDA (2.0 mmol in 4 mL THF) in two equal batches, each over 3 min. The reaction was stirred for 20 min before MeOH (5 mL) was added, the cool bath removed and then $NaHCO_3$ (5 mL) added. The quench was stirred for 16 hrs before the mixture was poured onto H_2O (20 mL) and Et_2O (20 mL) was added. The layers were separated and the aqueous layer extracted with Et_2O (2 × 30 mL). The combined organic phase was washed with H_2O (2 × 20 mL) and brine (2 × 20 mL) before it was dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to give a yellow oil. The crude product was purified by flash alumina chromatography (eluent 3-10 % Et_2O in petroleum ether 40/60) to afford the title product as a yellow oil (64 mg, 0.27 mmol, 27 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.23 (1H, qt, J = 6.6, 2.2 Hz, H-14), 3.33 (3H, s, H-1 or H-3), 3.32 (3H, s, H-1 or H-3), 3.24 (2H, s, H-2 or H-4), 3.23 (1H, d, J = 8.8 Hz, H-2a or H-4a), 3.16 (1H, d, J = 8.8 Hz, H-2b or H-4b), 2.32 (1H, d, J = 16.2 Hz, H-6a), 2.20 (1H, d, J = 16.2 Hz, H-6b), 2.19 (2H, d, J = 2.6 Hz, H-11), 1.91 (1H, t, J = 2.6 Hz, H-13), 1.77 (1H, d, J = 14.0 Hz, H-9a), 1.58 (3H, dt, J = 6.6, 1.3 Hz, H-15), 1.50 (1H, d, J = 14.0 Hz, H-9b), 1.16 (3H, s, H-10) ppm.

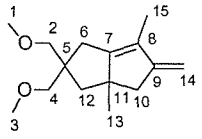
^{13}C NMR (75 MHz, $CDCl_3$) δ = 148.62 (s ,C-7), 115.22 (d ,C-14), 83.27 (s ,C-12), 77.09 (t ,C-2 or C-4), 76.45 (t ,C-2 or C-4), 69.16 (d ,C-13), 59.37 (q ,C-1 or C-3), 59.33 (q ,C-1 or C-3), 45.24 (s ,C-5 or C-8), 44.35 (t ,C-9), 44.00 (s ,C-5 or C-8), 35.70 (t ,C-6 or C-11), 33.01 (t ,C-6 or C-11) 28.17 (q ,C-10), 14.64 (q ,C-15) ppm.

LRMS (GC-CI): 237 ($M+H^+$, 20 %), 205 ($M-MeO^+$, 61%), 173 (100 %), 159 (34 %), 133 (38 %).

IR (neat film): 3298 (w), 2922 (m), 2874 (m), 2824 (m), 2115 (w), 1449 (m), 1375 (w), 1197 (m), 1103 (s), 963 (m) cm^{-1}.

HRMS (EI): Found: M^+, 136.1786; $C_{15}H_{24}O_2$ requires M^+, 236.1776.

Preparation of 2,2-bismethoxymethyl-3a,6-dimethyl-5-methylene-1,2,3,3a,4,5-hexahydropentalene, 54



To a solution of zirconocene dichloride (292 mg, 1.0 mmol, 1.0 eq.) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and the reaction stirred for 30 min. 4,4-Bis-methoxymethyl-2-methyl-oct-1-en-6-yne (210 mg, 1.0 mmol, 1.0 eq.) in THF (2 mL) was added and the reaction allowed to warm to r.t. before it was stirred for 5.5 hrs. The solution was cooled to –78 °C and 1,2-dibromoethene (mixture of *E* and *Z*) (0.17 mL, 2.0 mmol, 2.0 eq.) was added followed by LDA (2.0 mmol in 4 mL THF) in two equal batches, each over 4 min. The reaction was stirred for 20 min before MeOH (5 mL) was added, the cool bath removed and then $NaHCO_3$ (5 mL) added. The quench was stirred for 16 hrs before the mixture was poured onto H_2O (5 mL) and Et_2O (20 mL) was added. The layers were separated and the aqueous layer extracted with Et_2O (2 × 15 mL). The combined organic phase was washed with H_2O (20 mL) and brine (20 mL) before it was dried (Na_2SO_4), filtered and the solvent removed *in vacuo* to give a yellow oil. The crude product was purified by flash silica chromatography (eluent 3 % Et_2O in petroleum ether 40/60) to afford the title product as a pale yellow oil (156 mg, 0.66 mmol, 66 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.65 (1H, s, H-14a), 4.61 (1H, s, H-14b), 3.40 (1H, d, J = 8.8 Hz, H-2a or H-4a), 3.37 (3H, s, H-1 or H-3), 3.36 (1H, d, J = 8.8 Hz, H-2b or H-4b), 3.29 (3H, s, H-1 or H-3), 3.08 (1H, d, J = 8.8 Hz, H-2a or H-4a), 3.02 (1H, d, J = 8.8 Hz, H-2b or H-4b), 2.48-2.39 (2H, m, H-6), 2.22 (1H, d, J = 15.5 Hz, H-10a), 2.11 (1H, d, J = 15.5 Hz, H-10b), 1.66 (3H, d, J = 1.5 Hz, H-15), 1.57 (1H, d, J = 13.6, H-12a), 1.20 (1H, d, J = 13.6 Hz, H-12b), 1.06 (3H, s, H-13) ppm.

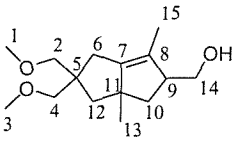
^{13}C NMR (75 MHz, $CDCl_3$) δ = 158.96 (s, C-9), 128.84 (s, C-8), 98.81 (t, C-14), 77.61 (t, C-2 or C-4), 76.86 (t, C-2 or C-4), 59.41 (q, C-1 or C-3), 59.32 (q, C-1 or C-3), 51.18 (s, C-5 or C-11), 49.76 (s, C-5 or C-11), 47.79 (t, C-12), 44.38 (t, C-10), 30.22 (t, C-6), 27.34 (q, C-13), 10.82 (q, C-15) ppm. C-7 not observed.

LRMS (GC-EI): 236 (M^+, 32 %), 205 (M-MeO^+, 50 %), 191 (M-$MeOCH_2^+$, 90 %), 159 (100 %), 129 (58 %).

IR (neat film): 3078 (w), 2920 (m), 2876 (m), 2823 (m), 2732 (w), 1626 (m), 1450 (m), 1198 (m), 1104 (s), 963 (m), 847 (m) cm^{-1}.

HRMS (EI): Found: M^+, 236.1772. $C_{15}H_{24}O_2$ requires M^+, 236.1776

Preparation of [5,5-bis(methoxymethyl)-3,6a-dimethyl-1,2,4,5,6,6a-hexahydropentalen-2-yl]methanol, 55



The crude diene **54** (211 mg, 0.89 mmol) was placed under argon and 9-BBN (1.80 mL, 0.5 M in THF, 0.89 mmol, 1.0 eq.) was added. The reaction was stirred for 45 min before it was cooled to 0 °C and NaOH (4.0 mL, 2.5 M in H_2O) was added, followed by H_2O_2 (4.0 mL, 35 % in H_2O). The cool bath was removed and the reaction stirred for 24 hrs. Et_2O (20 mL) and H_2O (10 mL) were added and the layers separated. The aqueous layer was extracted with Et_2O (3 × 20 mL) before the combined organic phase was washed with brine (2 × 10 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil. The crude product was purified by flash silica chromatography (eluent 50 % Et_2O in petroleum ether 40/60) to afford the title compound as a viscous yellow oil (91 mg, 0.36 mmol, 36 % from starting enyne).

^1H NMR (300 MHz, $CDCl_3$) δ = 3.69-3.57 (2H, m, H-14), 3.34 (3H, s, H-1 or H-3), 3.34 (1H, d, J = 9.0 Hz, H-2a or H-4a), 3.29 (1H, d, J = 9.0 Hz, H-2b or H-4b), 3.29 (3H, s, H-1 or H-3), 3.12 (1H, d, J = 9.0 Hz, H-2a or H-4a), 3.09, (1H, d, J = 9.0 Hz, H-2b or H-4b), 3.05 (1H, m, H-9), 2.12 (1H, d, J = 14.4 Hz, H-6a), 1.93 (1H, d, J = 14.4 Hz, H-6b), 1.89 (1H, dd, J = 12.0, 6.7 Hz, H-10a), 1.58 (3H, s, H-15), 1.51 (1H, d, J = 12.0 Hz, H-10b), 1.48 (1H, 13.5 Hz, H-12a), 1.40 (1H, m, O<u>H</u>), 1.27 (1H, d, J = 13.5 Hz, H-12b), 1.04 (3H, s, H-13) ppm.

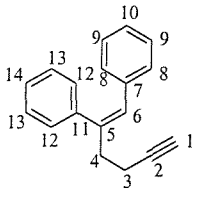
^{13}C NMR (75 MHz, $CDCl_3$) δ = 150.25 (C-7, s), 125.86 (C-8, s), 78.33 (C-2 or C-4, t), 77.60 (C-2 or C-4, t), 64.84 (C-14, t), 59.38 (C-1 or C-3, q), 59.36 (C-1 or C-3, q), 53.09 (C-9, d), 52.43 (C-5 or C-11, s), 49.76 (C-5 or C-11, s), 45.36 (C-12, t), 43.85 (C-10, t), 30.28 (C-6, t), 26.46 (C-13, q), 12.47 (C-15, q) ppm.

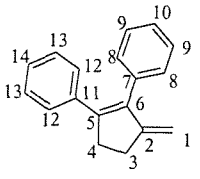
LRMS (GC-EI): 254 (M^+, 2 %), 222 (M-$MeOH^+$, 12 %), 191 (M-MeOH-MeO^+, 85 %), 159 (M-2MeOH-MeO^+, 100 %).

IR (neat film): 3558-3172 (m, br), 2921 (m), 2860 (m), 1448 (m), 1380 (m), 1197 (m), 1104 (s), 963 (m), 911 (m), 731 (s) cm^{-1}.

HRMS (EI): Found: M^+, 254.1877; $C_{15}H_{26}O_3$ requires M^+, 254.1882.

Preparation of [(1*Z*)-1-benzylidenepent-4-ynyl]benzene 58 and (3-methylene-2-phenylcyclopent-1-en-1-yl)benzene, 59





To a solution of zirconocene dichloride (292 mg, 1.0 mmol, 1.0 eq.) in THF (5 mL) at –78 °C under argon was added EtMgCl (1.0 mL, 2.0 mmol, 2.0 eq., 2.0 M in Et_2O), and the reaction stirred for 30 min. Diphenylacetylene (178 mg, 1.0 mmol, 1.0 eq.) in THF (2 mL) was added and the reaction allowed to warm to –30 °C over 2 hrs. The cool bath was removed and the reaction stirred at r.t. for 3 hrs. The reaction was cooled to –78 °C and *E*-1,2-dichloroethene (0.15 mL, 2.0 mmol, 2.0 eq.) was added, followed by LDA (2.0 mmol in 4 mL THF, 2.0 eq.) over 3 min. The reaction was stirred for 25 min before it was quenched with MeOH (5 mL), the cool bath removed and then $NaHCO_3$ (5 mL) was added. The quench was stirred for 24 hrs before the mixture was poured onto H_2O (30 mL) and Et_2O (30 mL) was added. The layers were separated and the aqueous phase extracted with Et_2O (30 mL). The combined organic phase was then washed with H_2O (2 × 30 mL) and brine (30 mL) before it was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a viscous yellow oil. The crude product was purified by flash alumina chromatography to

afford the title enyne as a yellow oil (76 mg, 0.33 mmol, 33 %) and the title diene as a white solid (88 mg, 0.38 mmol, 38 %).

For enyne **58**:

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.5-6.9 (10H, m, Ar-H), 6.53 (1H, s, H-6), 2.75 (2H, td, J = 7.4, 1.1 Hz, H-4), 2.29 (2H, td, J = 7.4, 2.6 Hz, H-3), 2.01 (1H, t, J = 2.6 Hz, H-1) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 140.99 (C-5, C-7 or C-11, s), 140.32 (C-5, C-7 of C-11, s), 137.14 (C-5, C-7 of C-11, s), 129.17 (C-8, C-9, C-12 or C-13, d) 128.79 (C-8, C-9, C-12 or C-13, d), 128.74 (C-8, C-9, C-12 or C-13, d), 127.98 (C-8, C-9, C-12 or C-13, d), 127.80 (C-6, C-10 or C-14, d), 127.30 (C-6, C-10 or C-14, d), 126.52 (C-6, C-10 or C-14, d), 83.86 (C-2, s), 69.08 (C-1, d), 39.67 (C-4, t), 17.63 (C-3, t) ppm.

LRMS (GC-EI): 232 (M^+, 52 %), 217 (22 %), 193 (M-CH_2CCH^+, 36 %), 178 (M-$HCH_2CH_2CCH^+$), 165 (20 %), 128 (33 %).

IR (neat film): 3294 (m), 3052 (w), 3022 (w), 2912 (w), 2117 (w), 1598 (m), 1441 (m), 1025 (w), 916 (w), 693 (s) cm^{-1}.

HRMS (EI): Found: M^+, 232.1254; $C_{18}H_{16}$ requires M^+, 232.1252.

For diene **59**:

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.4-7.1 (10H, m, Ar-H), 4.91 (1H, s, H-1a), 4.69 (1H, s, H-1b), 3.05-2.98 (2H, m, H-3 or H-4), 2.90-2.82 (2H, m, H-3 or H-4) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 157.40 (C-2, s), 145.38 (C-5, C-6, C-7 or C-1, s), 141.36 (C-5, C-6, C-7 or C-1, s), 137.06 (C-5, C-6, C-7 or C-1, s), 136.65 (C-5, C-6, C-7 or C-1, s), 129.77 (C-8, C-9, C-12 or C-13, d), 128.65 (C-8, C-9, C-12 or C-13, d), 128.07 (C-8, C-9, C-12 or C-13, d), 127.97 (C-8, C-9, C-12 or C-13, d), 127.27

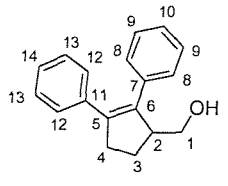
(C-10 or C-14, d), 127.18 (C-10 or C-14, d), 103.41 (C-1, t), 34.22 (C-4, t), 29.56 (C-3, t) ppm.

LRMS (GC-EI): 232 (M^+, 68 %), 215 (28 %), 202 (17 %), 189 (7 %), 128 (11 %), 115 (24 %).

IR (neat film): 3088 (w), 3047 (m), 2923 (m), 2840 (m), 1945 (w), 1891 (w), 1616 (m), 1600 (w), 1570 (w), 1494 (m), 1443 (m), 1354 (m) cm^{-1}.

HRMS (EI): Found: M^+, 232.1251; $C_{18}H_{16}$ requires M^+, 232.1252.

Preparation of (2,3-diphenylcyclopent-2-en-1-yl)methanol, 60



To a crude mixture of diene **59** (184 mg, 0.79 mmol) in THF (3 mL) was added $BH_3.SMe_2$ complex (30 mg, 0.04 mL, 0.40 mmol, 0.5 eq.). The reaction was complete after 30 min and was quenched with NaOH (3 mL) and H_2O_2 (3 mL) for 16 hrs. The mixture was diluted with H_2O (10 mL) and Et_2O (10 mL) and the aqueous layer extracted with Et_2O (2 × 10 mL). The combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow viscous oil. The crude product was purified by flash silica chromatography (eluent 5-40 % Et_2O in petroleum ether 40/60) to give a white solid recrystallised from acetonitrile (100 mg, 0.40 mmol, 40 %).

^1H NMR (400 MHz, $CDCl_3$) δ = 7.3-7.1 (10H, m, Ar-H), 3.66 (1H, dd, J = 11.0, 4.0 Hz, H-1a), 3.59 (1H, dd, J = 11.0, 6.0 Hz, H-1b), 3.46 (1H, m, H-2), 3.15 (1H, dddd, J = 16.0, 9.0, 6.6, 3.0 Hz, H-4a), 2.76 (1H, dddd, J = 16.0, 9.5, 5.0, 1.5 Hz), 2.31 (1H, dddd, J = 18.5, 9.5, 9.0, 6.6 Hz, H-3a), 2.07 (1H, ddd, J = 18.5, 9.0, 5.0 Hz, H-3b) 1.40 (1H, s, O<u>H</u>) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 139.95 (s, C-5, C-6, C-7 or C-8), 138.28 (s, C-5, C-6, C-7 or C-8), 137.81 (s, C-5, C-6, C-7 or C-8), 137.73 (s, C-5, C-6, C-7 or C-8), 128.80 (d, C-8, C-9, C-10 or C-11), 138.71 (d, C-8, C-9, C-10 or C-11), 128.25 (d, C-8, C-9, C-10 or C-11), 128.13 (d, C-8, C-9, C-10 or C-11), 127.10 (d, C-10 or C-11), 126.93 (d, C-10 or C-11), 65.84 (t, C-1), 53.63 (d, C-2), 37.04 (t, C-4), 25.90 (t, C-3) ppm.

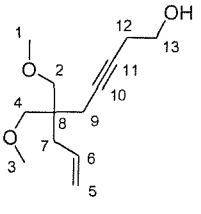
IR (neat film): 3500-3200 (m) 3079 (w), 3026 (w), 2953 (m), 2929 (m), 2914 (m), 2862 (w), 2846 (w), 1598 (w), 1574 (w), 1489 (m), 1443 (s), 1060 (m), 1023 (s) cm^{-1}.

LRMS (GC-EI): 250 (M^+, 20 %), 219 (M-CH_2OH^+, 100 %), 202 (22 %), 178 (14 %), 141 (28 %).

m.p. (from acetonitrile) 86-88 °C

CHN: Found, C(86.62), H(7.29); calculated for $C_{18}H_{18}O$, C(86.36), H(7.25).

Preparation of 6,6-bismethoxymethylnon-8-en-3-yn-1-ol, 68



Enyne **67** (0.73 g, 4.0 mmol) was dissolved in THF (15 mL) and the solution cooled to –70 °C before *n*-BuLi (1.60 mL, 4.0 mmol, 1.0 eq.) was added. The reaction was stirred for 15 min and HMPA (0.70 mL, 4.0 mmol, 1.0 eq.) was added. The solution was warmed to –20 °C before ethylene oxide (240 mL gas, about 12 mmol, 3 eq.) was added. The reaction was stirred for 1 hr to 0 °C and then r.t. for 16 hrs. NH_4Cl (10 mL) and Et_2O (20 mL) were added and the layers separated. The aqueous layer was extracted with Et_2O (2 × 20 mL) before the combined organic phase was washed with brine (2 × 20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to reveal a yellow oil. The crude product was purified by flash silica chromatography (eluent 10-60 % Et_2O in petroleum ether 40/60) to give the title product as a colourless oil

(575 mg, 2.5 mmol, 64 %). Unreacted starting material (101 mg, 0.55 mmol, 14 %) was also recovered.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.78 (1H, ddt, J = 16.5, 10.6, 7.6 Hz, H-6), 5.08 (1H, d, J = 16.5 Hz, H-5a), 5.06 (1H, d, J = 10.6 Hz, H-5b), 3.68 (2H, dt, J = 6.2 Hz, H-13), 3.31 (6H, s, H-1 and H-3), 3.25 (2H, d, J = 9.2 Hz, H-2a and H-4a), 3.22 (2H, d, J = 9.2 Hz, H-2b and H-4b), 2.44 (2H, tt, J = 6.2, 2.5 Hz, H-12), 2.17 (2H, t, J = 2.5 Hz, H-9), 2.14 (2H, d, J = 7.6 Hz, H-7), 2.08 (1H, t, J = 6.2 Hz, OH) ppm.

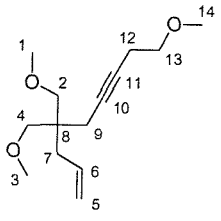
^{13}C NMR (75 MHz, $CDCl_3$) δ = 134.01 (d, C-6), 118.17 (t, C-5), 79.53 (s, C-10 or C-11), 78.52 (s, C-10 or C-11), 74.89 (t, C-2 and C-4), 61.52 (t, C-13), 59.47 (q, C-1 and C-3), 41.94 (s, C-8), 36.63 (t, C-7), 23.41 (t, C-9 or C-12), 22.78 (t, C-9 or C-12) ppm.

LRMS (GC-CI): 227 ($M+H^+$, 100 %), 195 ($M+H-MeOH^+$, 18 %), 181 ($M-CH_2MeO^+$, 6 %), 163 ($M+H-2MeOH^+$, 23 %), 149 (12 %).

IR (neat film): 3600-3100 (br, m), 3075 (w), 2979 (w), 2921 (m), 2879 (m), 2811 (m), 1639 (w), 1439 (m), 1198 (m), 1105 (s), 1044 (s), 916 (m) cm^{-1}.

HRMS (EI): Found: $M+H^+$ (self-CI), 227.1647; $C_{13}H_{23}O_3$ requires $M+H^+$, 227.1647.

Preparation of 9-methoxy-4,4-bismethoxymethylnon-1-en-6-yne, 69



Sodium hydride (144mg, 60 % dispersion in oil, 3.6 mmol, 1.5 eq.) was suspended in THF (5 mL) under argon and alcohol **68** (550 mg, 2.4 mmol, 1.0 eq.) was added. After 15 min, MeI (0.51 g, 0.22mL, 3.6 mmol, 1.5 eq.) was added and the reaction stirred for 3 hrs. The mixture was quenched with H_2O (20 mL) and Et_2O (10 mL) was added. The layers were separated and the aqueous layer extracted with Et_2O (2 × 20

mL) before the combined organic phase was washed with brine (2 × 15 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to reveal a pale yellow oil. The crude product was purified by flash silica chromatography (eluent 10-15 % Et_2O in petroleum ether 40/60) to give the title compound as a colourless oil (424 mg, 1.76 mmol, 74 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.79 (1H, ddt, J = 17.1, 10.1, 7.5 Hz, H-6), 5.07 (1H, d, J = 17.1 Hz, H-5a), 5.05 (1H, d, J = 10.1 Hz, H-5b), 3.48 (2H, t, J = 7.0 Hz, H-13), 3.36 (3H, s, H-14), 3.31 (6H, s, H-1 and H-3), 324 (2H, d, J = 9.0 Hz, H-2a and H-4a), 3.20 (2H, d, J = 9.0 Hz, H-2b and H-4b), 2.45 (2H, tt, J = 7.0, 2.5 Hz, H-12), 2.14 (2H, t, J = 2.5 Hz, H-9), 2.13 (2H, d, J = 7.5 Hz, H-7) ppm.

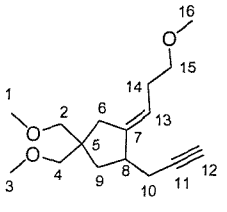
^{13}C NMR (75 MHz, $CDCl_3$) δ = 134.16 (s, C-6), 117.99 (s, C-5), 78.73 (s, C-10 or C-11), 77.87 (s, C-10 or C-11), 74.55 (t, C-2 and C-4), 71.51 (t, C-13), 59.42 (q, C-1 and C-3), 58.72 (q, C-14), 41.98 (s, C-8), 36.35 (t, C-7), 22.39 (t, C-9 or C-12), 20.16 (t, C-9 or C-12) ppm.

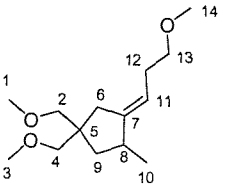
LRMS (GC-CI): 241 ($M+H^+$, 62 %), 209 ($M+H-MeOH^+$, 18 %), 195 ($M-CH_2OMe^+$, 8 %), 177 ($M+H-2MeOH^+$, 18 %), 145 ($M+H-3MeOH^+$, 22 %).

IR (neat film): 2980 (w), 2923 (m), 2876 (m), 1478 (w), 1450 (m), 1197 (m), 1105 (s), 967 (m), 916 (m) cm^{-1}.

HRMS (EI): Found: $M-Me^+$, 225.1494; $C_{13}H_{21}O_3$ requires $M-Me^+$, 225.1491.

Preparation of (3*E*)-1,1-bismethoxymethyl-3-(3-methoxypropylidene)-4-prop-2-ynylcyclopentane 73 and (3*E*)-1,1-bismethoxymethyl-3-(3-methoxypropylidene)-4-methylcyclopentane, 74





To a solution of zirconocene dichloride (146 mg, 0.5 mmol, 1.0 eq.) in THF (3 mL) at –78 °C under argon was added *n*-BuLi (0.40 mL, 1.0 mmol, 2.0 eq.) and the reaction stirred for 30 min. Enyne **69** (240 mg, 1.0mmol, 1.0 eq.) in THF (2 mL) was added and the reaction allowed to warm to r.t. before it was stirred for 4 hrs. The solution was cooled to –78 °C and *E*-1,2-dichloroethene (0.15 mL, 2.0 mmol, 4 eq.) was added followed by LDA (1.0 mmol in 2 mL THF) over 3 min. The reaction was stirred for 4 hrs, with the temperature increasing slowly to –50 °C before MeOH (5 mL) was added, the cool bath removed and then $NaHCO_3$ (5 mL) added. The quench was stirred for 16 hrs before the mixture was poured onto H_2O (5 mL) and Et_2O (20 mL) was added. The layers were separated and the aqueous layer extracted with Et_2O (2 × 15 mL). The combined organic phase was washed with H_2O (20 mL) and brine (20 mL) before it was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil. The crude product was purified by flash silica chromatography (eluent 10-15 % Et_2O in petroleum ether 40/60) to afford the title product **73** as a colourless oil (35 mg, 0.13 mol, 26 %). Cyclised product **74** without carbenoid insertion was also isolated as a colourless oil (23 mg, 0.10 mmol, 20 %).

For **73**:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.25 (1H, ttd, J = 7.0, 2.4. 2.4 Hz, H-13), 3.37 (2H, t, J = 7.0 Hz, H-15), 3.34 (3H, s, H-1, H-3 or H-16), 3.33 (6H, s, H-1, H-3 or H-16), 3.30 (1H, d, J = 9.0 Hz, H-2a or H-4a), 3.26 (1H, d, J = 9.0 Hz, H-2b or H-4b), 3.20 (2H, s, H-2 or H-4), 2.69 (1H, m, H-8), 2.44 (1H, ddd, J = 16.7, 5.3, 2.6 Hz, H-10a), 2.3-2.2 (4H, m, H-6 and H-14), 2.18 (1H, ddd, J = 16.7, 8.1, 2.6 Hz, H-10b), 1.98 (1H, dd, J = 13.1, 7.7 Hz, H-9a), 1.92 (1H, t, J = 2.6 Hz, H-12), 1.31 (1H, dd, J = 13.1, 10.5 Hz, H-9b) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.44 (s, C-7), 117.77 (d, C-13), 83.46 (s, C-11), 77.49 (t, C-2 or C-4), 75.31 (t, C-2 or C-4), 72.38 (t, C-15), 68.90 (d, C-12), 59.44 (q, C-1 or C-3), 59.43 (q, C-1 or C-3), 58.69 (q, C-16), 45.81 (s, C-5), 40.93 (d, C-8), 37.77 (t, C-9), 36.07 (t, C-6), 29.89 (t, C-14), 23.54 (t, C-10) ppm.

LRMS (GC-CI): 235 (5 %, M-MeO^+), 221 (7 %, M-$MeOCH_2^+$), 203 (13 %), 157 (46 %), 131 (56 %).

IR (neat film): 3300-3100 (w), 2976 (w), 2922 (m), 2872 (m), 2824 (m), 2116 (w), 1458 (m), 1382 (m), 1197 (m), 1102 (s), 960 (m) cm^{-1}.

HRMS (EI): Found: M^+, 266.1870; $C_{16}H_{26}O_3$ requires M^+, 266.1882.

For uninserted product **74**:

^1H NMR (300 MHz, $CDCl_3$) δ = 5.13 (1H, tq, J = 7.0, 2.4 Hz, H-11), 3.37 (2H, t, J = 7.0 Hz, H-13), 3.34 (1H, m, H-1, H-3 + H-14), 3.28 (1H, d, J = 8.8 Hz, H-2a or H-4a), 3.23 (1H, d, J = 8.8 Hz, H-2b or H-4b), 3.22 (2H, s, H-2 or H-4), 2.52 (1H, m, H-8), 2.25 (2H, dtd, J = 7.0, 7.0, 1.5 Hz, H-12), 2.18 (2H, brs, H-6), 1.85 (1H, dd, J = 12.7, 7.9 Hz, H-9a), 1.04 (3H, d, J = 6.6 Hz, H-10), 1.03 (1H, m H-9b) ppm.

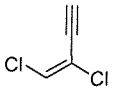
^{13}C NMR (75 MHz, $CDCl_3$) δ = 148.48 (s, C-7), 115.99 (d, C-11), 77.77 (t, C-2 or C-4), 75.54 (t, C-2 or C-4), 72.61 (t, C-14), 59.43 (q, C-1 + C-3), 58.69 (q, C-14), 45.68 (s, C-5), 40.56 (t, C-9), 36.70 (d, C-8), 35.96 (t, C-6), 29.82 (t, C-12), 18.75 (q, C-10) ppm.

LRMS (GC-CI): 243 (M+H^+, 26 %), 211 (M+H-$MeOH^+$, 70 %), 179 (M+H-2$MeOH^+$, 100 %), 165 (M+H-2MeOH-CH_2^+, 29 %), 147 (M+H-3$MeOH^+$, 56 %).

IR (neat film): 2955 (m), 2923 (m), 2870 (m), 2823 (m), 1451 (m), 1382 (w), 1197 (m), 1105 (s), 963 (m) cm^{-1}.

HRMS (EI): Found: M-$MeOH^+$, 210.1616; $C_{13}H_{22}O_2$ requires M-$MeOH^+$, 210.1620.

Preparation of (*E*)-1,2-Dichloro-but-1-en-3-yne, 13

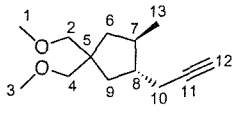


To a solution of *E*-1,2-dichloroethene (0.15 mL, 2.0 mmol) in Trapp solvent (5 mL, 4:3:3 THF:Et_2O:petane) at –110 °C was added *n*-BuLi (0.80 mL, 2.0 mmol, 1.0 eq.) dropwise over 30 min. After 1 hr at –110 °C, $FeCl_3$ (108 mg, 0.67 mL, 0.3 eq.) was added in Et_2O (1 mL) over 15 min. The reaction was stirred for 30 min at –110 °C and then warmed to r.t. over 2 hrs. The reaction was stirred at r.t. for 16 hrs before it was quenched with HCl (5mL, 2M in H_2O). The mixture was separated and the organic phase washed with H_2O (2 × 10 mL), $NaHCO_3$ (2 × 10 mL) and brine (10 mL) before it was dried ($MgSO_4$) and kept as a solution.

GC (30 – 50 °C at 40 °C/min then 250 °C at 25 °C/min): retention time = 1.87 min

LRMS (GC-EI): 120 (M^+, 64 %), 122 (M^+, 40 %), 124 (M^+, 8 %), 85 (M-Cl^+, 100 %), 87 (M-Cl^+, 34 %), 50 (M-2Cl^+, 42 %).

Preparation of rac-(3*R*,4*R*)-1,1-bis(methoxymethyl)-3-methyl-4-prop-2-ynylcyclopentane, 94



To a solution of zirconocene dichloride (321 mg, 1.1 mmol, 1.1 eq.) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.88 mL, 2.2 mmol, 2.2 eq.) and stirred for 30 min before 4,4-bis-methoxymethyl-hepta-1,6-diene (184 mg, 1.0 mmol, 1.0 eq.) was added and the reaction allowed to warm to r.t. and then stirred for 5 hrs. At –78 °C *E*-1,2-dichloroethene (0.15 mL, 2.0 mmol, 2.0 eq.) was added, followed by LDA (2.0 mmol in 4 mL THF, 2.0 eq.) dropwise over 5 min. After 30 min and warming to –50 °C, MeOH (5 mL) was added, followed by saturated $NaHCO_3$ (5 mL) and the reaction allowed to warm to room temperature before stirring for 16 hrs. The mixture was poured onto H_2O (5 mL) and Et_2O (10 mL) was added. The layers were separated

and the aqueous layer extracted with Et_2O (2 × 10 mL). The combined organic layer was washed with brine (2 × 10 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil. The crude product was purified by flash silica chromatography (eluent 2 % Et_2O in petroleum ether) to afford the title compound as a colourless oil (95 mg, 0.45 mmol, 45 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.33 (6H, s, H-1 + H-3), 3.18-3.09 (4H, m, H-2 + H-4), 2.35 (1H, ddd, J = 16.7, 4.0, 2.6 Hz, H-10a), 2.10 (1H, ddd, J = 16.7, 7.0, 2.6 Hz, H-10b), 1.92 (1H, t, J = 2.6 Hz, H-12), 1.81 (1H, dd, J = 13.2, 7.2 Hz, H-6a or H-9a), 1.76 (1H, dd, J = 12.5, 6.8 Hz, H-6a or H-9a), 1.71-1.50 (2H, m, H-7 + H-8), 1.26 (1H, dd, J = 13.2, 10.7 Hz, H-6b or H-9b), 1.05 (1H, dd, J = 12.5, 10.7 Hz, H6b or H9b), 0.95 (3H, d, J = 6.3 Hz, H-13) ppm.

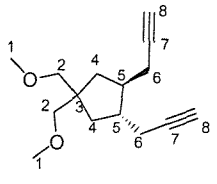
^{13}C NMR (75 MHz, $CDCl_3$) δ = 83.22 (s, C-11), 77.93 (t, C-2 or C-4), 77.70 (t, C-2 or C-4), 69.01 (d, C-12), 59.34 (q, C-1 + C-3), 45.06 (d, C-7 or C-8), 41.70 (t, C-6 or C-9), 38.78 (t, C-6 or C-9), 38.52 (d, C-7 or C-8), 21.56 (t, C-10), 17.93 (q, C-13) ppm. C-5 not observed

IR (neat film): 3307 (w), 2951 (m), 2922 (m), 2870 (m), 2824 (m), 2117 (w), 1459 (m), 1198 (m), 1104 (s), 964 (m) cm^{-1}.

LRMS (GC-CI): 211 ($M+H^+$,14 %), 177 (5 %), 163 (10 %), 135 (82 %), 105 (44 %)

HRMS (CI): Found: M^+, 211.1693; $C_{13}H_{23}O_2$ requires $M+H^+$, 211.1698.

Preparation of rac-(3*R*,4*R*)-1,1-bis(methoxymethyl)-3,4-diprop-2-ynylcyclopentane, 98



To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and the reaction stirred

for 30 min. 4,4-di(methoxymethyl)-1,6-heptadiene (184 mg, 1.0 mmol, 1.0 eq.) was then added in THF (2 mL) and the reaction allowed to warm to r.t. and stirred for 5 hrs. The reaction was cooled to –78 °C before *E*-1,2-dichloroethene (190mg, 0.15 mL, 2.0 mmol, 2.0 eq.) was added followed by a freshly prepared solution of LDA (2.0 mmol in 4 mL THF) dropwise over 3 min. After 30 min the cool bath was removed and the reaction stirred for 1 hr at r.t. The reaction was quenched by addition of MeOH (5 mL) and $NaHCO_3$ (5 mL) and stirred for 16 hrs. Pentane (20 mL) and H_2O (10 mL) were added, the layers separated and the aqueous layer extracted with pentane (10 mL). The combined organic phase was then washed with H_2O (2 × 20 mL) and brine (20 mL) before it was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to reveal a dark orange oil. The crude product was purified by flash silica chromatography (eluent 5 % Et_2O in petroleum ether) to afford the title product as a cream white solid (87 mg, 0.37 mmol, 37 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.34 (6H, s, H-1), 3.22 (4H, s, H-2), 2.38 (2H, dt, J = 16.5, 2.9, 2.9 Hz, H-6a), 2.19 (2H, ddd, J = 16.5, 5.5, 2.9 Hz, H-6b), 1.95 (2H, t, J = 2.9 Hz, H-8), 1.9-1.8 (4H, m, H-4a + H-5), 1.4-1.2 (2H, m, H-4b) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 82.74 (s, C-7), 77.47 (t, C-2), 69.45 (d, C-8), 59.40 (q, C-1), 44.95 (s, C-3), 41.94 (d, C-5), 38.57 (t, C-4), 21.69 (t, C-6) ppm.

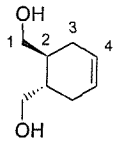
LRMS (GC-CI): 235 ($M+H^+$, 100 %), 203 ($M-OMe^+$, 8 %), 163 (16 %), 129 (29 %), 91 (40 %).

IR (neat film): 3285 (m), 3228 (m), 2933 (m), 2887 (m), 2110 (w), 1443 (m), 1097 (s) cm^{-1}.

m.p. (from pentane) 45-46 °C

CHN: Found, C(76.65), H(9.26); calculated for $C_{15}H_{22}O_2$, C(76.88), H(9.46).

Preparation of rac-[(1*R*,6*R*)-6-(hydroxymethyl)cyclohex-3-en-1-yl]methanol, 102



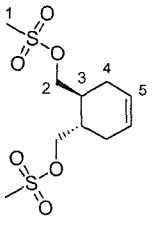
Procedure taken from literature[4]. The diol was obtained as a colourless syrup (2.48 g, 18 mmol, 92 %). Data consistent with literature[4].

^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.68-5.60 (2H, m, H-4), 3.71 (2H, brd, J = 11.2 Hz, H-2a), 3.57 (2H, ddd, J = 11.2, 5.9, 4.4 Hz, H = 2b), 3.40 (2H, t, J = 4.4 Hz, -OH), 2.20 (2H, dfs, J = 15.4 Hz, H-3a), 1.84 (2H, dfs, J = 15.4 Hz, H-3b), 1.70-1.62 (2H, m, H-2) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 126.18 (d. C-4), 66.34 (t, C-1), 39.88 (d, C-2), 28.66 (t, C-3) ppm.

IR (neat film): 3600-3000 (s), 3023 (w), 2890 (m), 2844 (m), 1435 (m), 1066 (s), 1055 (s), 1022 (s) cm^{-1}.

Preparation of rac-((1*R*,6*R*)-6-{[(methylsulfonyl)oxy]methyl}cyclohex-3-en-1-yl)methyl methanesulfonate, 103



Procedure taken from literature[5]. The dimesylate was obtained as a white solid (1.81 g, 6.1 mmol, 66 %). Data consistent with literature.[6]

^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.63 (2H, s, H-5), 4.28 (2H, dd, J = 9.9, 5.2 Hz, H-2a), 4.22 (2H, dd, J = 9.9, 5.2 Hz, H-2b), 3.03 (6H, s, H-1), 2.30-2.10 (4H, m, H-3 or H-4), 2.10-2.00 (2H, m, H-3 or H-4) ppm.

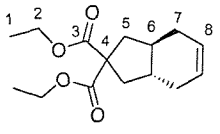
^{13}C NMR (75 MHz, $CDCl_3$) δ = 124.85 (d, C-5), 70.81 (t, C-2), 37.30 (q, C-1), 33.57 (d, C-3), 25.86 (t, C-4) ppm.

IR (neat film): 3025.59 (w), 2939 (w), 2900 (w), 2848 (w), 1488 (w), 1466 (w), 1443 (w), 1412 (w), 1336 (s), 1170 (s), 1060 (m), 972 (m), 920 (s), 836 (s) cm^{-1}.

LRMS (GC-CI): 316 ($M+NH_4^+$, 100 %), 302 (12%), 256 (16 %), 220 ($M+H-SO_2Me^+$, 10 %), 149 (36 %).

m.p. (from CH_2Cl_2/^{i}hexane): 53-55 °C.

Preparation of rac-diethyl (3a*S*,7a*S*)-1,3,3a,4,7,7a-hexahydro-2*H*-indene-2,2-dicarboxylate, 104



Adapted from literature procedure[7]. Sodium (53 mg, 2.3 mmol, 2.3 eq.) was dissolved in dry EtOH (5 mL) before diethylmalonate (1.52 mL, 10.0 mmol, 10 eq.) and KI (100 mg) were added. The mixture was heated to reflux and dimesylate **103** (298 mg, 1.0 mmol, 1.0 eq.) was added in small batches over 2 hrs before the reaction was left at reflux for 16 hrs. The reaction was quenched with H_2O (10 mL), and the mixture extracted with Et_2O (3 × 10 mL). The combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a pale yellow oil. The crude product was purified by flash silica chromatography (eluent 5-7.5 % Et_2O in isohexane) to give a colourless oil (211 mg, 0.79 mmol, 79 %).

^1H NMR (300 MHz, $CDCl_3$) δ = 5.68-5.64 (2H, m, H-8), 4.18 (2H, dq, J = 10.7, 7.4 Hz, H-2a), 4.14 (2H, dq, J = 10.7, 7.4 Hz, H-2b), 2.63 (2H, dd, J = 13.1, 6.1 Hz, H-7a), 2.26 (2H, dfs, J = 13.1 Hz, H-7b), 1.90-1.50 (6H, m, H-5 + H-6), 1.24 (6H, t, J = 7.2 Hz, H-1) ppm.

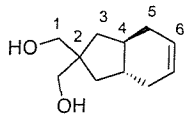
^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.16 (s, C-3), 126.80 (d, C-8), 61.45 (t, C-2), 58.39 (s, C-4), 41.24 (d, C-6), 40.70 (t, C-7), 31.38 (t, C-5), 14.19 (q, C-1) ppm.

IR (neat film): 3022 (w), 2979 (w), 2907 (w), 2834 (w), 1726 (s), 1443 (m), 1337 (m), 1246 (s), 1178 (s), 1098 (m), 1060 (m) cm^{-1}.

LRMS (GC-EI): 266 (M^+, 46 %), 221 (M-OEt^+, 78 %), 202 (20 %), 173 (91 %), 119 (100 %)

HRMS (EI): Found: M^+, 266.1520; $C_{15}H_{22}O_4$ requires M^+, 266.1518.

Preparation of rac-[(3a*S*,7a*S*)-2-(hydroxymethyl)-2,3,3a,4,7,7a-hexahydro-1*H*-inden-2-yl]methanol, 105



To a solution of diester **104** (210 mg, 0.79 mmol) in THF (2 mL) under nitrogen at 0 °C was added $LiAlH_4$ (1.60 mL, 1M in THF, 1.60 mmol, 2.0 eq.). After 10 min the cool bath was removed and the reaction stirred for 2 hrs. The solution was quenched with NaOH (2M in H_2O) until a white precipitate formed, which was removed by filtration. The solvent was removed in vacuo and the white solid recrystallised from Et_2O/hexane to give white crystals (127 mg, 0.70 mmol, 89 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.71-5.63 (2H, m, H-6), 3.65 (2H, dd, J = 10.3, 5.1 Hz, H-1a), 3.59 (2H, dd, J = 10.3, 5.1 Hz, H-1b), 2.31 (2H, t, J = 5.1 Hz, -OH), 2.25 (2H, brd, J = 14.7 Hz, H-5a), 1.83 (2H, dd, J = 13.2, 6.6 Hz, H-3a), 1.79 (2H, dfs, J = 14.7 Hz, H-5b), 1.57-1.43 (2H, m, H-4), 0.98 (2H, dd, J = 13.2, 11.0 Hz, H-3b) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 127.09 (d, C-6), 71.54 (t, C-1), 46.89 (s, C-2), 40.45 (d, C-4), 38.50 (t, C-5), 32.03 (t, C-3) ppm.

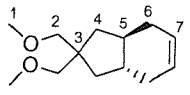
IR (neat film): 3500-3100 (m), 3025 (w), 2937 (m), 2911 (m), 2859 (m), 2833 (m), 1424 (m), 1378 (m), 1222 (w), 1157 (w), 1133 (w), 1083 (w), 1027 (s) cm^{-1}.

LRMS (ES^-): 217 ($M+Cl^-$, 100 %), 219 ($M+Cl^-$, 33 %).

m.p. (Et_2O/hexane) = 47-48 °C

CHN: Found, C(72.17), H(9.91); calculated for $C_{11}H_{18}O_2$, C(72.49), H(9.95).

Preparation of rac-(3a*S*,7a*S*)-2,2-bismethoxymethyl-2,3,3a,4,7,7a-hexahydro-1*H*-indene, 100



To a suspension of NaH (83 mg, 60 % dispersion in oil, 2.1 mmol, 3.0 eq.) in THF (2 mL) was added a solution of diol **105** (127 mg, 0.7 mmol, 1 eq.) in THF (2 mL). After 10 min MeI (0.07 mL, 1.1 mmol, 1.5 eq.) was added, the reaction stirred for 15 min and then MeI (0.07 mL, 1.1 mmol, 1.5 eq.) added. The reaction was stirred for 16 hrs before it was quenched with NH_4Cl (aq., 5mL) and Et_2O (10 mL) was added. The layers were separated and the aqueous layer extracted with Et_2O (2 × 10 mL). The combined organic phase was washed with brine (10 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to reveal a pale yellow oil. The crude product was purified by flash silica chromatography (eluent 4 % Et_2O in petroleum ether 40/60) to give a colourless oil (107 mg, 0.51 mmol, 73 %).

^1H NMR (400 MHz, $CDCl_3$) δ = 5.68-5.62 (2H, m, H-7), 3.34 (6H, s, H-1), 3.24 (2H, d, J = 8.8 Hz, H-2a), 3.20 (2H, d, J = 8.8 Hz, H-2b), 2.22 (2H, dfs, J = 16.3 Hz, H-a), 1.81 (2H, dd, J = 12.8, 6.5 Hz, H-4a), 1.78-1.70 (2H, m, H-6b), 1.52-1.45 (2H, m, H-5), 1.01 (2H, dd, J = 12.8, 11.3 Hz, H-4b) ppm.

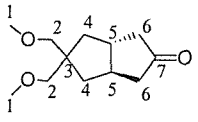
^{13}C NMR (100 MHz, $CDCl_3$) δ = 127.22 (d, C-7), 78.28 (t, C-2), 59.38 (q, C-1), 45.94 (s, C-3), 40.83 (d, C-5), 39.41 (t, C-4), 32.16 (t, C-6) ppm.

IR (neat film): 3020 (w), 2880 (m), 2828 (m), 1448 (m), 1387 (w), 1197 (m), 1104 (s) 965 (m) cm^{-1}.

LRMS (GC-EI): 210 ($M+H^+$, 5 %), 178 ($M-MeOH^+$, 10 %), 146 (50 %), 131 (26 %), 105 (30 %), 91 (100%).

HRMS (EI): Found: M^+, 210.1617; $C_{13}H_{22}O_2$ requires M^+, 210.1620.

Preparation of rac-(3a*S*,6a*S*)-5,5-bismethoxymethylhexahydropentalen-2(1*H*)-one, 106



To a solution of zirconocene dichloride (877 mg, 3.0 mmol) in THF (15 mL) at –78 °C under argon was added *n*-BuLi (2.40 mL, 6.0 mmol, 2.0 eq.) and the reaction stirred for 30 min. 4,4-bis-methoxymethyl-hepta-1,6-diene (553 mg, 3.0 mmol, 1.0 eq.) was then added in THF (5 mL) and the reaction allowed to warm to r.t. and stirred for 24 hrs. The reaction was then cooled to 0 °C and carbon monoxide was passed through the vessel for 3 min and the reaction left under slight positive pressure (balloon) for 2 hrs. A solution of iodine (512 mg, 2.0 mmol, 0.7 eq.) in THF (5 mL) was added until the iodine colour remained in the reaction mixture. The reaction mixture was washed with sodium thiosulphate (2 × 30 mL, sat. solution in H_2O), H_2O (2 × 30 mL) and brine (2 × 30 mL) before the organic phase was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give an orange oil. The crude product was purified by flash silica chromatography (eluent 10-30 % Et_2O in petroleum ether) to afford the title product as a pale yellow oil (285mg, 1.34 mmol, 45 %).

^1H NMR (300 MHz, $CDCl_3$) δ = 3.34 (6H, s, H-1), 3.27 (4H, s, H-2), 2.10-2.32 (2H, m, 6a), 1.90-1.75 (6H, m, H-4a, H-5 and H-6b), 0.97 (2H, m, H-4b) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 220.53 (C-7, s), 78.17 (C-2, t), 59.40 (C-1, q), 50.90 (C-3, s), 47.54 (C-5, d), 43.97 (C-6, t), 35.24 (C-4, t) ppm.

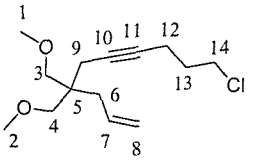
LRMS (GC-CI): 213 ($M+H^+$, 100 %), 181 ($M-OMe^+$, 38 %), 148 (40 %), 135 (5 %), 120 (15 %).

IR (neat film): 2924 (m), 2872 (m), 2823 (m), 1741 (s), 1450 (m), 1388 (m), 1198 (m), 1101 (s), 960 (m) cm^{-1}.

HRMS (EI): Found: M^+, 212.1409; $C_{12}H_{20}O_3$ requires M^+, 212.1412.

6.2.2 Experimental for Chapter 3

Preparation of 10-chloro-4,4-bis(methoxymethyl)dec-1-en-6-yne, 139



To a solution of 4,4-bis-methoxymethyl-hept-1-en-6-yne **67** (1.82 g, 10.0 mmol) in THF (30 mL) at –78 °C under argon was added *n*-BuLi (4.0 mL, 10.0 mmol, 1.0 eq.). After 1 hr, HMPA (1.74 mL, 10.0 mmol, 1.0 eq.) was added and the temperature raised to –25 °C. After 20 min 1-bromo-3-chloropropane (1.57 g, 0.99 mL, 10.0 mmol, 1.0 eq.) was added, the reaction stirred for 30 min and then the temperature was raised to 0 °C. The reaction was stirred for 3 hrs at this temperature and then at r.t. for 16 hrs. The reaction was quenched with NH_4Cl (aq., 10 mL). H_2O (20 mL) and Et_2O (30 mL) were added and the layers separated. The aqueous phase was washed with Et_2O (30 mL) before the combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a pale yellow oil. The crude product was purified by flash silica chromatography (eluent 3 % Et_2O in petroleum ether 40/60) to give a colourless oil (1.87 g, 7.2 mmol, 72%).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.79 (1H, ddt, J = 16.6, 10.3, 7.4 Hz, H-7), 5.08 (1H, d with fine splitting, J = 16.6 Hz, H-8a), 5.06 (1H, d with fine splitting, J = 10.3 Hz, H-8b), 3.67 (2H, t, J = 6.6 Hz, H-14), 3.32 (6H, s, H-1 + H-2), 3.24 (2H, d, J = 9.2 Hz, H-3a + H-4a), 3.21 (2H, d, J = 9.2 Hz, H-3b + H-4b), 2.37 (2H, tt, J = 6.6, 2.2 Hz, H-12), 2.14 (2H, t, J = 2.2 Hz, H-9), 2.13 (2H, d with fine splitting, J = 7.4 Hz, H-6), 1.94 (2H, tt, J = 6.6, 6.6 Hz, H-13) ppm.

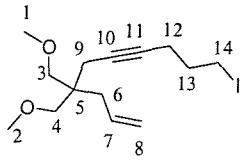
^{13}C NMR (75 MHz, $CDCl_3$) δ = 134.09 (d, C-7), 118.07 (t, C-8), 80.13 (s, C-10 or C-11), 77.90 (s, C10 or C-11), 74.58 (t, C-3 + C-4), 59.44 (q, C-1 + C-2), 43.92 (t, C-14), 41.98 (s, C-5), 36.43 (t, C-6), 31.87 (t, C-13), 22.37 (t, C-9), 16.38 (t, C-12) ppm.

IR (neat film): 3074 (w), 2979 (w), 2920 (m), 2876 (m), 2809 (m), 1638 (w), 1438 (m), 1290 (m), 1197 (m), 1104 (s), 915 (m) cm^{-1}.

LRMS (GC-CI): 259 ($M+H^+$, 100 %), 227 ($M-MeOH^+$, 14 %), 195 ($M-CH_2CH_2Cl^+$, 12 %), 145 (12 %), 117 (10 %).

HRMS (CI): Found: $M+H^+$, 259.1470; $C_{14}H_{24}O_2{}^{35}Cl$ requires $M+H^+$, 259.1465.

Preparation of 10-iodo-4,4-bis(methoxymethyl)dec-1-en-6-yne, 140



A mixture of chloroenyne **139** (4.66 g, 18.0 mmol) and sodium iodide (8.0 g, 54 mmol, 3.0 eq.) was heated to reflux in dry acetone for 20 hrs. The solvent was removed *in vacuo* and the residue taken up in Et_2O (20 mL) and H_2O (20 mL). The aqueous layer was extracted with Et_2O (20 mL) before the combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to reveal a colourless oil. The crude product was purified by flash silica chromatography (eluent 3-10 % Et_2O in petroleum ether 40/60) to give a colourless oil (5.54 g, 15.8 mmol, 88 %).

^1H NMR (300 MHz, $CDCl_3$) δ = 5.79 (1H, ddt, J = 16.9, 10.3, 7.4 Hz, H-7), 5.08 (1H, d with fine splitting, J = 16.9 Hz, H-8a), 5.07 (1H, d with fine splitting, J = 10.3 Hz, H-8b), 3.32 (6H, s, H-1 + H-2), 3.32 (2H, t, J = 6.6 Hz, H-14), 3.23 (2H, d, J = 8.8 Hz, H-3a + H-4a), 3.20 (2H, d, J = 8.8 Hz, H-3b + H-4b), 2.32 (2H, tt, J = 6.6, 2.6 Hz, H-12), 2.14 (2H, t, J = 2.6 Hz, H-9), 2.13 (2H, d with fine splitting, J = 7.4 Hz, H-6), 1.96 (2H, tt, J = 6.6, 6.6 Hz, H-13) ppm.

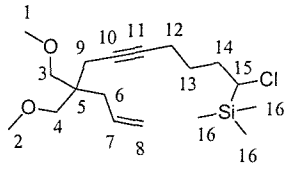
^{13}C NMR (75 MHz, $CDCl_3$) δ = 134.13 (d, C-7), 118.13 (t, C-8), 79.86 (s, C-10 or C-11), 78.16 (s, C10 or C-11), 74.64 (t, C-3 + C-4), 59.51 (q, C-1 + C-2), 42.04 (s, C-5), 36.50 (t, C-6), 32.54 (t, C-13), 22.45 (t, C-9), 20.02 (t, C-12), 5.94 (t, C-14) ppm.

IR (neat film): 3073 (w), 2978 (w), 2919 (m), 2808 (m), 1638 (w), 1431 (m), 1265 (w), 1221 (m), 1197 (m), 1103 (s), 966 (m), 915 (m) cm^{-1}.

LRMS (GC-CI): 351 ($M+H^+$, 24 %), 319 (M+H-MeOH, 4 %), 225 ($M+H-I^+$, 100 %), 193 (M+H-I-MeOH, 28 %), 161 (M+H-I-2MeOH, 28 %).

HRMS (CI): Found: $M+H^+$, 351.0822; $C_{14}H_{24}O_2I$ requires $M+H^+$, 351.0821

Preparation of (1-Chloro-8,8-bismethoxymethylundec-10-en-5-ynyl)-trimethylsilane, 141



To a solution of chloromethyltrimethylsilane (0.59g, 0.67 mL, 4.8 mmol, 1.1 eq.) in THF (20 mL) under argon at –78 °C was added *s*-BuLi (3.46 mL, 1.4 M in cyclohexane, 4.8 mmol, 1.1 eq.), and TMEDA (0.56 g, 0.73 mL, 4.8 mmol, 1.1 eq.). After 45 min, alkyl iodide **140** (1.55 g, 4.4 mmol, 1.0 eq.) was added and the reaction stirred at –78 °C for 2 hrs. The cool bath was removed and the reaction was quenched with NH_4Cl (aq., 20 mL) before H_2O (20 mL) and Et_2O (20 mL) were added. The layers were separated, the aqueous layer extracted with Et_2O (20 mL) and then the combined organic phase was washed with HCl (2M, 20 mL), $NaHCO_3$ (20 mL), H_2O (20 mL) and brine (20 mL), was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to reveal a colourless oil. The crude product was purified by flash silica chromatography (eluent 3-4 % Et_2O in petroleum ether 40/60) to give a colourless oil (845 mg, 2.45 mmol, 56 %).

^1H NMR (300 MHz, $CDCl_3$) δ = 5.79 (1H, ddt, J = 16.2, 10.3, 7.4 Hz, H-7), 5.08 (1H, d with fine splitting, J = 16.2 Hz, H-8a), 5.06 (1H, d with fine splitting, J = 10.3 Hz, H-8b), 3.32 (6H, s, H-1 + H-3), 3.26 (2H, d, J = 9.2 Hz, H-2a + H-4a), 3.23 (1H, t, J = 8.8 Hz, H-15), 3.21 (2H, d, J = 9.2 Hz, H-2b + H-4b), 2.25-2.19 (2H, m, H-12), 2.13 (2H, t, J = 2.21 Hz, H-9), 2.13 (2H, dd, J = 7.4, 1.1 Hz, H-6), 1.95-1.85 (2H, m, H-13a + H-14a), 1.71 (1H, m, H-14b), 1.59 (1H, m, H-13b), 3.23 (9H, s, H-16) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 134.12 (d, C-7), 118.0 (t, C-8), 81.59 (s, C-10 or C-11), 74.56 (t, C-2 + C-4), 59.43 (q, C-1 + C-3), 51.46 (d, C-15), 41.99 (s, C-5), 36.35

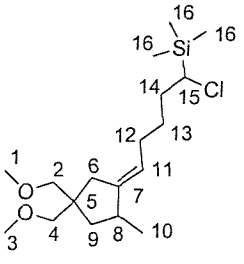
(t, C-6), 32.27 (t, C-14), 27.30 (t, C-13), 22.34 (t, C-9), 18.09 (t, C-12), -3.39 (q, C-16) ppm. C-10 or C-11 not observed.

IR (neat film): 3075 (w), 2922 (m), 2891 (m), 2809 (m), 1639 (w), 1449 (m), 1250 (m), 1106 (s), 864 (s), 836 (s) cm^{-1}.

LRMS (GC-CI): 345 ($M+H^+$, 60 %), 309 ($M-Cl^+$, 26 %), 277 ($M-Cl-MeOH^+$, 22 %), 263 ($M-Cl-MeOH-Me^+$, 10 %), 173 (38 %).

HRMS (CI): Found: $M+H^+$, 345.2025; $C_{18}H_{34}O_2{}^{35}ClSi$ requires $M+H^+$, 345.2017

Preparation of {5-[4,4-Bismethoxymethyl-2-methylcyclopent-(*E*)-ylidene]-1-chloropentyl}-trimethylsilane, 143



To zirconocene dichloride (146 mg, 0.5 mmol, 1.0 eq.) in THF (3 mL) at –78 °C under argon was added *n*-BuLi (0.40 mL, 1.0 mmol, 2.0 eq.) and stirred for 30 min before enyne **141** (173 mg, 0.5 mmol, 1.0 eq.) was added and the reaction stirred at room temperature for 5 hrs. MeOH (5mL) and $NaHCO_3$ (aq., 5 mL) were added and the quench stirred for 16 hrs. The mixture was poured onto H_2O (10 mL) and Et_2O (10 mL) was added before the layers were separated and the aqueous layer extracted with Et_2O (10 mL). The combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to reveal a pale yellow oil. The crude product was purified by flash silica chromatography (eluent 3 % Et_2O in petroleum ether 40/60) to give a colourless oil (103 mg, 0.30 mmol, 59%). The product was obtained as a mixture of two diastereoisomers.

^1H NMR (400 MHz, $CDCl_3$) δ = 5.10 (1H, tdt, J = 7.2, 2.3, 2.3 Hz, H-11), 3.34 (3H, s, H-1 or H-2), 3.33 (3H, s, H-1 or H-2), 3.28 (1H, d, J = 8.8 Hz, H-3a or H-4a), 3.25-

3.20 (4H, m, H-3, H-4 + H-15), 2.51 (1H, m, H-8), 2.16 (2H, s, H-6), 1.99 (2H, m, H-12), 1.86 (1H, dd, J = 12.8, 7.8 Hz, H-a), 1.75-1.68 (2H, m, H-13a +H-14a), 1.62 (1H, m, H-14b), 1.45 (1H, m, H-13b), 1.04 (3H, d, J = 6.5 Hz, H-10), 1.02 (1H, dd, J = 12.8, 11.0 Hz, H-9b), 0.10 (9H, s, H-16) ppm.

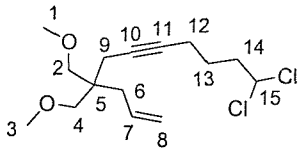
^{13}C NMR (100 MHz, $CDCl_3$) δ = 146.71 (s, C-7), 119.83 (d, C-11), 77.86 (t, C-3 or C-4), 75.86, 75.84 (t, C-3 or C-4), 59.69 (q, C-1 + C-2), 52.24, 52.21 (d, C-15), 45.79, 45.76 (s, C-5), 40.64, 40.60 (t, C-9), 36.58, 36.57 (d, C-8), 36.01 (t, C-6), 32.90, 32.85 (t, C-14), 28.65, 28.61 (t, C-12), 28.01, 27.98 (t, C-13), 19.00, 18.97 (q, C-10), -3.33 (q, C-16) ppm.

IR (neat film): 2954 (m), 2924 (m), 2870 (m), 1450 (m), 1249 (m), 1105 (s), 965 (m), 865 (m), 837 (s) cm^{-1}.

LRMS (GC-CI): 347 ($M+H^+$, 4 %), 315 ($M-OMe^+$, 22 %), 311 ($M-Cl^+$, 20 %), 279 ($M-Cl-MeOH^+$, 34 %), 175 (100 %).

HRMS (CI): Found: $M+H^+$, 347.2176; $C_{18}H_{36}O_2{}^{35}ClSi$ requires $M+H^+$, 347.2173.

Preparation of 11,11-dichloro-4,4-bis(methoxymethyl)undec-1-en-6-yne, 145



To a solution of CH_2Cl_2 (0.64 mL, 10.0 mmol, 2.0 eq.) in THF (15 mL), at –90 °C under argon was added *s*-BuLi (5.34 mL, 1.4 M in cyclohexane, 7.5 mmol, 1.5 eq.) and TMEDA (0.87 g, 1.13 mL, 7.5 mmol, 1.5 eq.). After 20 min, alkyl iodide **140** (1.75 g, 5.0 mmol) was added before the reaction was stirred at –80 °C for 1 hr and then allowed to warm to r.t. over 16 hrs. The reaction was not complete so the mixture was added by canular to a second solution of lithiated CH_2Cl_2. The reaction was quenched with $NHCl_4$ (aq., 10 mL) before H_2O (20 mL) and Et_2O (20 mL) were added and the layers separated. The aqueous layer was extracted with Et_2O (20 mL)

before the combined organic phase was washed with H_2O (20 mL) and brine (2 × 20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to reveal an orange oil. The crude product was purified by flash silica chromatography (eluent 3 % Et_2O in petroleum ether 40/60) to give a colourless oil (783 mg, 2.54 mmol, 51 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.81 (1H, t, J = 5.9 Hz, H-15), 5.79 (1H, ddt, J = 16.9, 10.6, 7.4 Hz, H-7), 5.08 (1H, dfs, J = 16.9 Hz, H-8a), 5.07 (1H, dfs, J = 10.6 Hz, H-8b), 3.32 (6H, s, H-1 + H-3), 3.24 (2H, d, J = 9.0 Hz, H-2a + H-4a), 3.21 (2H, d, J = 9.0 Hz, H-2b + H-4b), 2.38-2.30 (2H, m, H-14), 2.25 (2H, tt, J = 6.8, 2.6 Hz, H-12), 2.15 (2H, t, J = 2.6 Hz, H-9), 2.14 (2H, dfs, J = 7.4 Hz, H-6), 1.75 (2H, tt, J = 6.8, 6.8 Hz, H-13) ppm.

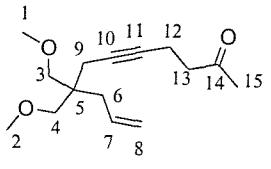
^{13}C NMR (75 MHz, $CDCl_3$) δ = 134.09 (d, C-7), 118.09 (t, C-8), 80.63 (s, C-10 or C-11), 78.04 (s, C-10 or C-11), 74.60 (t, C-3 + C-4), 73.30 (d, C-15), 59.49 (q, C-1 + C-3), 42.71 (t, C-14), 41.98 (s, C-5), 36.46 (t, C-6), 25.39 (t, C-13), 22.40 (t, C-9), 18.00 (t, C-12) ppm.

IR (neat film): 3075 (w), 2979 (w), 2920 (m), 2875 (m), 2809 (m), 1638 (w), 1438 (m), 1197 (m), 1104 (s), 966 (m), 915 (m), 750 (m) cm^{-1}.

LRMS (GC-CI): 307 ($M+H^+$, 1 %), 261 ($M-CH_2OMe^+$, 4 %), 229 ($M-CH_2OMe$-MeOH, 4 %), 157 (14 %), 117 (28 %).

HRMS (EI): Found: $M-CH_2OMe^+$, 261.0801; $C_{13}H_{19}O^{35}Cl_2$ requires $M-CH_2OMe^+$, 261.0813.

Preparation of 8,8-bis(methoxymethyl)undec-10-en-5-yn-2-one, 147



Dichloro(p-cymene) ruthenium (II) dimer (306 mg, 0.50 mmol, 5 mol%) and pyrrolidine (142 mg, 0.17 mL, 2.0 mmol, 0.2 eq.) were stirred at r.t. in benzene (40

mL) under argon for 15 min. Methyl vinyl ketone (2.10 g, 2.50 mL, 30 mmol, 3.0 eq.) and enyne **67** (1.82 g, 10.0 mmol, 1.0 eq.) were added and the mixture heated to 65 °C for 16 hrs. The solvent was removed *in vacuo* and the mixture taken up in Et_2O (30 mL) and H_2O (20 mL). The layers were separated and the organic phase washed with H_2O (2 × 20 mL) and brine (2 × 20 mL) before it was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a dark brown oil. The crude product was purified by flash silica chromatography (eluent 20-25 % Et_2O in petroleum ether 40/60) to give a pale yellow oil (854 mg, 3.38 mmol, 34 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.76 (1H, ddt, J = 16.7, 10.5, 7.4 Hz, H-7), 5.06 (1H, d with fine splitting, J = 16.7, H-8a), 5.04 (1H, d with fine splitting, J = 10.5 H, H-8b), 3.30 (6H, s, H-1 + H-3), 3.21 (2H, d, J = 9.2 Hz, H-2a + H-4a), 3.18 (2H, d, J = 9.2 Hz, H-2b + H-4b), 2.63 (2H, t, J = 7.4 Hz, H-13), 2.42 (2H, tt, J = 7.4, 2.6 Hz, H-12), 2.16 (3H, s, H-15), 2.10 (2H, t, J = 2.6 Hz, H-9), 2.10 (2H, d, J = 7.4 Hz, H-6) ppm.

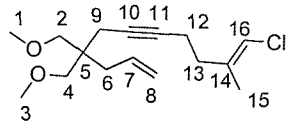
^{13}C NMR (75 MHz, $CDCl_3$) δ = 207.14 (s, C-14), 134.11 (d, C-7), 118.03 (t, C-8), 80.57 (s, C-10 or C-11), 77.35 (s, C-10 or C-11), 74.51 (t, C-2 + C-4), 59.43 (q, C-1 + C-3), 43.12 (t, C-13), 41.96 (s, C-5), 36.35 (t, C-6), 30.04 (q, C-15), 22.31 (t, C-9), 13.67 (t, C-12) ppm.

IR (neat film): 3074 (w), 2920 (m), 2889 (m), 2810 (m), 1718 (s), 1638 (w), 1438 (m), 1364 (m), 1197 (m), 1364 (m), 1197 (m), 1103 (s) cm^{-1}.

LRMS (GC-CI): 253 ($M+H^+$, 1 %), 237 ($M-Me^+$, 1 %), 207 ($M-CH_2OMe^+$, 10 %), 175 ($M-CH_2OMe-MeOH^+$, 15 %), 117 (14 %).

HRMS (EI): Found: M^+, 252.1722; $C_{15}H_{24}O_3$ requires M^+, 252.1725.

Preparation of 1-chloro-8,8-bis(methoxymethyl)-2-methylundeca-1,10-dien-5-yne, 148



To a suspension of (chloromethyl)triphenylphosphonium chloride (1.66 g, 4.8 mmol, 1.5 eq.) in piperidine (0.41 g, 0.47 mL, 4.8 mmol, 1.5 eq.) and Et_2O (8 mL) was added *n*-BuLi (1.91 mL, 4.8 mmol, 1.5 eq.) and the reaction stirred for 2 hrs. Ketone **147** (802 mg, 3.2 mmol, 1.0 eq.) was added and the reaction heated to reflux for 16 hrs. The suspension was filtered, washed with Et_2O (5 mL) and then the filtrate was washed with $NaHCO_3$ (aq., 10 mL) and brine (10 mL) before it was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to reveal a yellow oil. The crude product was purified by flash silica chromatography (eluent 4 % Et_2O in petroleum ether 40/60) to give a colourless oil (679mg, 2.38 mmol, 75 %). The product was obtained as a mixture of two regioisomers.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.88, 5.83 (1H, m, H-16), 5.78 (1H, m, H-7), 5.11 – 5.04 (2H, m, H-8), 3.32 (6H, s, H-1 + H-3), 3.24, 3.23 (2H, d, J = 8.8 Hz, H-2a + H-4a), 3.21, 3.20 (2H, d, J = 8.8 Hz, H-2b + H-4b), 2.45 – 2.21 (4H, m, H-12 + H-13), 2.15 – 2.10 (4H, m, H-6 + H-9), 1.80 (3H, s, H-15) ppm.

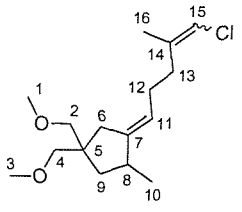
^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.29 (s, C-14), 134.21, 134.15 (d, C-7), 118.03, 117.99 (t, C-8), 113.33, 112.78 (d, C-16), 81.03, 80.63 (s, C10 or C-11), 77.86, 77.20 (s, C-10 or C-11), 74.55, 74.52, 74.49 (t, C-2 + C-4), 59.44, 59.42 (q, C-1 + C-3), 41.95 (s, C-5), 36.59, 36.31 (t, C-6), 31.42 (t, C-13), 22.38, 22.34 (t, C-9), 20.91 (q, C-15), 17.63 (t, C-12), 16.62 (t, C-13), 16.23 (q, C-15) ppm.

IR (neat film): 3074 (w), 2978 (w), 2918 (m), 2876 (m), 2809 (m), 1639 (w), 1438 (m), 1197 (m), 1104 (s), 915 (m) cm^{-1}.

LRMS (GC-CI): 285 ($M+H^+$, 100 %), 269 ($M-Me^+$, 6 %), 249 ($M-Cl^+$, 23 %), 217 ($M-Cl-MeOH^+$, 32 %), 185 ($M-Cl-2MeOH^+$, 55 %).

HRMS (EI): Found: M-Me^+, 269.1316; $C_{15}H_{22}O_2{}^{35}Cl$ requires M-Me^+, 269.1308.

Preparation of (3*E*)-3-[5-chloro-4-methylpent-4-enylidene]-1,1-bis(methoxymethyl)-4-methylcyclopentane, 150



To zirconocene dichloride (146 mg, 0.5 mmol, 1.0 eq.) in THF (3 mL) at –78 °C under argon was added *n*-BuLi (0.40 mL, 1.0 mmol, 2.0 eq.) and stirred for 20 min before enyne **148** (142 mg, 0.5 mmol, 1.0 eq.) was added and the reaction stirred at room temperature for 16 hrs. MeOH (5mL) and $NaHCO_3$ (aq., 5 mL) were added and the quench stirred for 6 hrs. The mixture was poured onto H_2O (10 mL) and Et_2O (15 mL) was added before the layers were separated and the aqueous layer extracted with Et_2O (15 mL). The combined organic phase was washed with brine (15 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to reveal a pale yellow oil. The crude product was purified by flash silica chromatography (eluent 4-5 % Et_2O in petroleum ether 40/60) to give a colourless oil (127 mg, 0.44 mmol, 88 %). The product was obtained as a 7:13 ratio (by GC) of two stereoisomers.

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.77 (2H, s, H-15 M+m), 5.11 (1H, tq, J = 7.0, 2.5 Hz, H-11 m), 5.06 (1H, m, H-11 M), 3.34 (6H, s, H-1 or H-3 M+m), 3.33 (6H, s, H-1 or H-3 M+m), 3.30-3.20 (8H, m, H-2 + H-4 M+m), 2.55-2.45 (2H, m, H-8 M+m), 2.20-2.05 (12H, m, H-6 M+m, H-12 M+m, H-13 M+m), 1.85 (2H, dd, J = 12.8, 7.8 Hz, H-9a M+m), 1.77 (3H, d, J = 1.3 Hz, H-16 M), 1.73 (3H, d, J = 1.5 Hz, H-16 m), 1.04 (3H, d, J = 6.8 Hz, H-10 m), 1.07-1.02 (2H, m, H-9b M+m), 1.02 (3H, d, J = 6.5 Hz, H-10 M) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 147.29 (s, C-7 M), 146.97 (s, C-7 m), 138.62 (s, C-14 M), 138.60 (s, C-14 m), 119.17 (d, C-11 m), 118.89 (d, C-11 M), 112.12 (d, C-15 M), 111.73 (d, C-15 m), 77.77 (t, C-2 or C-4 m), 77.76 (t, C-2 or C-4 M), 75.53 (t, C-2 or C-4 m), 75.51 (t, C-2 or C-4 M), 59.42 (q, C-1 or C-3 M+m), 59.41 (q, C-1 or C-3

M+m), 45.71 (s, C-5 M+m), 40.55 (t, C-9 M), 40.52 (t, C-9 m), 37.15 (t, C-13 M), 36.59 (d, C-8 M+m), 35.86 (t, C-6 M), 35.77 (t, C-6 m), 32.00 (t, C-13 m), 27.50 (t, C-12 M), 26.70 (t, C-12 m), 21.09 (q, C-16 m), 18.94 (C-10 M), 18.86 (q, C-10 m), 16.66 (q, C-16 M) ppm.

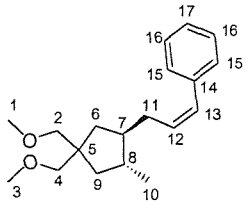
IR (neat film): 2955 (m), 2922 (m), 2872 (m), 1476 (w), 1450 (m), 1377 (w), 1198 (m), 1105 (s), 965 (m) cm^{-1}.

LRMS (GC-CI): 255 ($M\text{-}MeO^+$, 4 %), 219 (M-Cl-MeOH, 19 %), 187 (M-Cl-2MeOH), 173 (M-Cl-MeOH-CH_2OMe^+), 133 (82 %).

HRMS (EI): Found: M^+, 286.1699; $C_{16}H_{27}O_2{}^{35}Cl$ requires M^+, 286.1700.

6.2.3 Experimental for Chapter 4

Preparation of rac-{(1*Z*)-3-[(1*R*,2*R*)-4,4-bis(methoxymethyl)-2-methyl cyclopentyl]prop-1-enyl}benzene, 176



To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and stirred for 30 min before 4,4-bis-methoxymethyl-hepta-1,6-diene (184 mg, 1.0 mmol, 1.0 eq.) was added and the reaction stirred at room temperature for 3 hrs. The solution was cooled to –78 °C and *E*-*β*-bromostyrene (183 mg, 0.13 mL, 1.0 mmol, 1.0 eq.) was added, followed by LDA (1.0 mmol in 2 mL THF) dropwise over 20 min. The reaction was stirred at –78 °C for 5 min before it was quenched with MeOH (5 mL) and $NaHCO_3$ (aq, 5 mL) and stirred for 16 hrs. The reaction mixture was poured onto H_2O (10 mL) and Et_2O (30 mL) was added. The aqueous phase was extracted with Et_2O (2 × 30 mL) before the combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil. The crude product was purified by flash silica chromatography (eluent 4 % Et_2O in petroleum ether 40/60) to give the title product as a colourless oil (138 mg, 0.48 mmol, 48 %) and bis-inserted product **177** (43 mg, 0.11 mmol, 11 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.32 (2H, t, J = 7.5 Hz, H-16), 7.27 (2H, d, J = 7.5 Hz, H-15), 7.21 (1H, t, J = 7.5 Hz, H-17), 6.41 (1H, d, J = 11.5 Hz, H-13), 5.68 (1H, dt, J = 11.5, 7.3 Hz, H-12), 3.34 (3H, s, H-1 or H-3), 3.31 (3H, s, H-1 or H-3), 3.21 (1H, d, J = 9.0 Hz, H-2a or H-4a), 3.19 (1H, d, J = 9.0 Hz, H-2a or H-4a), 3.18 (1H, d, J = 9.0 Hz, H-2b or H-4b), 3.16 (1H, d, J = 9.0 Hz, H-2b or H-4b), 2.61 (1H, m, H-11a), 2.08 (1H, ddd, J = 15.0, 7.5, 7.5 Hz, H-11b), 1.82 (1H, dd, J = 13.0, 7.0 Hz, H-6a), 1.74 (1H, dd, J = 13.0, 7.0 Hz, H-9a), 1.6-1.5 (1H, m, H-8), 1.5-1.4 (1H, m, H-7), 1.05 (1H, dd, J = 10.1, 7.0 Hz, H-6b), 1.02 (1H, dd, J = 10.1, 7.0 Hz, H-9b), 0.95 (3H, d, J = 6.0 Hz, H-10) ppm.

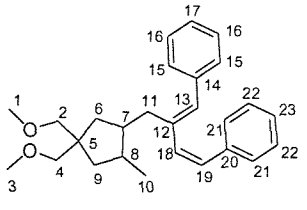
^{13}C NMR (100 MHz, $CDCl_3$) δ = 137.97 (s, C-14), 132.05 (d, C-12), 129.18 (d, C-13), 128.97 (d, C-15), 128.21 (d, C-16), 126.53 (d, C-17), 78.10 (t, C-2 or C-4) 77.98 (t, C-2 or C-4), 59.39 (q, C-1 or C-3), 59.37 (q, C-1 or C-3), 47.27 (d, C-7), 45.33 (s, C-5), 41.87 (t, C-9), 39.78 (d, C-8), 39.47 (t, C-6), 32.55 (t, C-11), 18.52 (q, C-10) ppm.

IR (neat film): 2945 (m), 2922 (m), 2870 (m), 2824 (m), 1600 (w), 1494 (w), 1475 (w), 1447 (m), 1388 (w), 1198 (m), 1105 (s), 934 (m), 768 (m) cm^{-1}.

LRMS (GC-EI): 288 (M^+, 12 %), 256 (M-$MeOH^+$, 30 %), 211 (M-Ph, 38 %), 152 (25 %), 137 (68 %).

HRMS (EI): Found: M^+, 288.2092; $C_{19}H_{28}O_2$ requires M^+, 288.2089.

Preparation of {(1*Z*)-3-[rac-(1*R*,2*R*)-4,4-bis(methoxymethyl)-2-methyl cyclopentyl]-2-[(*Z*)-2-phenylethenyl]prop-1-enyl}benzene, 177



To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and stirred for 30 min before 4,4-bis-methoxymethyl-hepta-1,6-diene (184 mg, 1.0 mmol, 1.0 eq.) was added and the reaction stirred at room temperature for 4 hrs. The solution was cooled to –78 °C and *E*-β-bromostyrene (366 mg, 0.26 mL, 2.0 mmol, 2.0 eq.) was added, followed by LDA (2.0 mmol in 2 mL THF) dropwise over 20 min. The reaction was stirred at –78 °C for 50 min before it was quenched with MeOH (5 mL) and $NaHCO_3$ (aq, 5 mL) and stirred for 16 hrs. The reaction mixture was poured onto H_2O (10 mL) and Et_2O (30 mL) was added. The aqueous phase was extracted with Et_2O (2 × 30 mL) before the combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil. The crude

product was purified by flash silica chromatography (eluent 4 % Et_2O in petroleum ether 40/60) to give a colourless oil (250 mg, 0.64 mmol, 64 %).

^1H NMR (400 MHz, $CDCl_3$) δ = 7.56 (2H, d, J = 7.5 Hz, H-15 or H-21), 7.45-7.35 (4H, m, Ar-H), 4.35-4.25 (4H, m, Ar-H), 6.67 (1H, s, H-13), 6.56 (1H, d, J = 12.2 Hz, H-18 or H-19), 6.35 (1H, d, J = 12.2 Hz, H-18 or H-19), 3.42 (3H, s, H-1 or H-3), 3.39 (3H, s, H-1 or H-3), 3.27 (1H, d, J = 8.5 Hz, H-2a or H-4a), 3.23 (1H, d, J = 8.5 Hz, H-2b or H-4b), 3.23 (1H, d, J = 9.0 Hz, H-2a or H-4a), 3.20 (1H, d, J = 9.0 Hz, H-2b or H-4b), 2.79 (1H, dd, J = 13.6, 3.5 Hz, H-11a), 2.23 (1H, dd, J = 13.6, 10.0 Hz, H-11b), 1.86 (1H, dd, J = 13.1, 7.0 Hz, H-6a), 1.78 (1H, dd, J = 13.1, 7.3 Hz, H-9a), 1.68 (1H, m, H-7), 1.50 (1H, m, H-8), 1.08 (1H, dd, J = 13.1, 10.5 Hz, H-6b), 1.05 (1H, dd, J = 13.1, 10.5 Hz, H-9b), 0.91 (3H, d, J = 6.0 Hz, H-10) ppm.

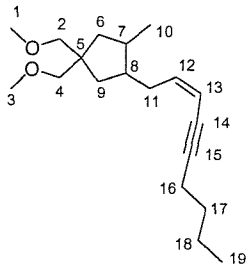
^{13}C NMR (100 MHz, $CDCl_3$) δ = 139.27 (s, C-12, C-14 or C-20), 130.0 (s, C-12, C-14 or C-20), 137.92 (s, C-12, C-14 or C-20), 134.03 (d, C-18 or C-19), 130.38 (d, C-13), 129.43 (d, C-18 or C-19), 129.04 (d, Ar-C, multiple peak), 129.01 (d, Ar-C, multiple peak), 128.20 (d, Ar-C, multiple peak), 78.03 (t, C-2 or C-4), 77.90 (t, C-2 or C-4), 59.36 (q, C-1 or C-3), 59.32 (q, C-1 or C-3), 45.80 (d, C-7), 45.30 (s, C-5), 41.69 (t, C-9), 40.23 (d, C-8), 39.77 (t, C-6), 34.90 (t, C-11), 18.01 (q, C-10) ppm.

IR (neat film): 2949 (m), 2923 (m), 2871 (m), 2824 (m), 1598 (w), 1491 (w), 1475 (w), 1447 (m), 1388 (w), 1198 (m), 1105 (s), 963 (m), 910 (m), 732 (s) cm^{-1}.

LRMS (GC-EI): 390 (M^+, 8 %), 358 (M-$MeOH^+$, 6 %), 326 (M-2$MeOH^+$, 5 %), 218 (55 %), 129 (100 %).

HRMS (EI): Found: M^+, 390.2553; $C_{27}H_{34}O_2$ requires M^+, 390.2559.

Preparation of rac-(3*R*,4*R*)-1,1-Bismethoxymethyl-3-methyl-4-((*Z*)-non-2-en-4-ynyl)cyclopentane, 178



To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and stirred for 30 min before 4,4-bis-methoxymethyl-hepta-1,6-diene (184 mg, 1.0 mmol, 1.0 eq.) was added and the reaction stirred at room temperature for 4 hrs. The solution was cooled to –78 °C and 1-chloro-oct-1-en-3-yne (327 mg, 2.0 mmol, 2.0 eq.) was added, followed by LDA (1.0 mmol in 2 mL THF) dropwise over 15 min. The reaction was stirred at –78 °C for 40 min before it was quenched with MeOH (5 mL) and $NaHCO_3$ (aq, 5 mL) and stirred for 16 hrs. The reaction mixture was poured onto H_2O (10 mL) and Et_2O (30 mL) was added. The aqueous phase was extracted with Et_2O (2 × 30 mL) before the combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil. The crude product was purified by flash silica chromatography (eluent 3 % Et_2O in petroleum ether 40/60) to give a colourless oil (158 mg, 0.54 mmol, 54 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.82 (1H, dt, J = 10.7, 7.5 Hz, H-12), 5.43 (1H, dtt, J = 10.7, 2.1, 1.4 Hz, H-13), 3.33 (3H, s, H-1 or H-3), 3.32 (3H, s, H-1 or H-3), 3.22-3.17 (4H, m, H-2 + H-4), 2.52 (1H, dddd, J = 14.1, 7.5, 4.3, 1.4 Hz, H-11a), 2.34 (2H, td, J = 6.9, 2.1 Hz, H-16), 2.09 (1H, dddd, J = 14.1, 8.8, 7.5, 1.4 Hz, H-11b), 1.75 (1H, dd, J = 13.3, 3.8 Hz, H-6a or H-9a), 1.73 (1H, dd, J = 13.1, 3.8 Hz, H-6a or H-9a), 1.60-1.40 (6H, m, H-7, H-8, H-17 + H-18), 1.10 (1H, dd, J = 13.3, 10.8 Hz, H-6b or H-9b), 1.00 (1H, dd, J = 13.0, 11.0 Hz, H-6b or H-9b), 0.98 (3H, d, J = 6.3 Hz, H-10), 0.92 (3H, t, J = 7.3 Hz, H-19) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 141.19 (d, C-12), 109.96 (d, C-13), 94.63 (s, C-15), 78.04 (t, C-2 or C-4), 77.93 (t, C-2 or C-4), 77.61 (s, C-14), 59.34 (q, C-1 + C-3),

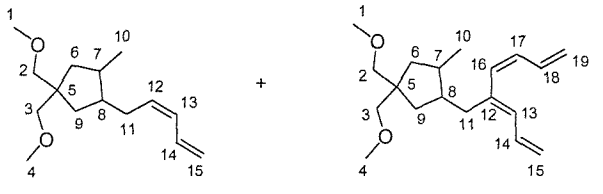
46.54 (d, C-7), 45.32 (s, C-5), 41.78 (t, C-6 or C-9), 39.60 (d, C-8), 39.22 (t, C-6 or C-9), 33.85 (t, C-11), 31.9 (t, C-17), 22.08 (t, C-18), 19.34 (t, C-16), 18.24 (q, C-10), 13.72 (q, C-19) ppm.

IR (neat film): 2952 (m), 2926 (m), 2871 (m), 2824 (w), 1458 (m), 1388 (w), 1325 (w), 1198 (m), 1107 (s), 964 (m), 737 (m) cm^{-1}.

LRMS (GC-EI): 292 (M^+, 1 %), 260 (M-$MeOH^+$, 12 %), 247 (8 %), 215 (35 %), 171 (16 %).

HRMS (EI): Found: M^+, 292.2403; $C_{19}H_{32}O_2$ requires M^+, 292.2402.

Preparation of rac-(3*R*,4*R*)-1,1-Bis-methoxymethyl-3-methyl-4-((*Z*)-penta-2,4-dienyl)-cyclopentane, 170 and rac-(3*R*,4*R*)-1,1-Bis-methoxymethyl-3-methyl-4-[(*Z*)-2-prop-2-en-(*E*)-ylidene-hexa-3,5-dienyl]-cyclopentane, 180



To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and stirred for 30 min before 4,4-bis-methoxymethyl-hepta-1,6-diene (184 mg, 1.0 mmol, 1.0 eq.) was added and the reaction stirred at room temperature for 4 hrs. The solution was cooled to –90 °C and *Z*-1,4-dichlorobut-2-ene (125 mg, 0.08 mL, 1.0 mmol, 1.0 eq.) was added, followed by LDA (1.0 mmol in 2 mL THF) dropwise over 15 min. The reaction was stirred at –90 °C for 35 min before it was quenched with MeOH (5 mL) and $NaHCO_3$ (aq, 5 mL) and stirred for 16 hrs. The reaction mixture was poured onto H_2O (10 mL) and Et_2O (30 mL) was added. The aqueous phase was extracted with Et_2O (2 × 30 mL) before the combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a pale yellow oil. The crude product was purified by flash silica chromatography ($AgNO_3$ doped silica, eluent 4-50 % Et_2O in petroleum ether 40/60) to give **170** as a colourless oil (143 mg,

0.60 mmol, 60 %), bis-insertion product **180** as a colourless oil (11 mg, 0.04 mmol, 4 %) and non-inserted product **175** (43 mg, 0.23 mmol, 23 %).

Data for mono-insertion product **170**

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.64 (1H, dt, J = 16.6, 10.5 Hz, H-14), 6.00 (1H, t, J = 10.5 Hz, H-13), 5.46 (1H, dt, J = 10.5, 7.5 Hz, H-12), 5.17 (1H, d, J = 16.6 Hz, H-15a), 5.07 (1H, d, J = 10.5 Hz, H-15b), 3.33 (3H, s, H-1 or H-3), 3.32 (3H, s, H-1 or H-3), 3.20-3.15 (4H, m, H-2 and H-4), 2.42 (1H, m, H-11a), 1.98 (1H, dt, J = 14.1, 7.5 Hz, H-11b), 1.74 (2H, dd, J = 13.1, 7.0 Hz, H-6a + H-9a), 1.54 (1H, m, H-7), 1.41 (1H, m, H-8), 1.04 (1H, dd, J = 13.1, 11.0, H-6b or H-9b), 1.02 (1H, dd, J = 13.1, 2.0 Hz, H-6b or H-9b), 0.96 (3H, d, J = 6.5 Hz, H-10) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 131.46 (d, C-14), 130.68 (d, C-12), 128.67 (d, C-13), 115.91 (t, C-15), 77.07 (t, C-2 or C-4), 76.97 (t, C-2 or C-4), 58.36 (q, C-1 + C-3), 45.94 (d, C-8), 44.24 (s, C-5), 40.83 (t, C-6 or C-9), 38.55 (d, C-7), 38.31 (t, C-6 or C-9), 30.48 (t, C-11), 17.25 (q, C-10) ppm.

IR (neat film): 2250 (m), 2923 (m), 2870 (m), 2824 (m), 1644 (w), 1593 (w), 1475 (w), 1449 (m), 1388 (w), 1198 (m), 1106 (s), 964 (m), 901 (m) cm^{-1}.

LRMS (GC-EI): 238 (M^+, 10 %), 206 (M-$MeOH^+$, 8 %), 174 (M-2$MeOH^+$, 8 %), 159 (M-2MeOH-Me^+, 20 %), 137 (36 %).

HRMS (EI): Found: M^+, 238.1931; $C_{15}H_{26}O_2$ requires M^+, 238.1933.

Data for bis-insertion product **180**

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.80 (1H, ddd, J = 17.1, 10.0, 10.0 Hz, H-18), 6.67 (1H, ddd, J = 17.1, 10.0, 10.0 Hz, H-14), 6.07 (1H, d, J = 10.0 Hz, H-13), 6.06 (1H, dd, J = 11.5, 10.0 Hz, H-17), 5.84 (1H, d, J = 11.5 Hz, H-16), 5.28 (1H, d, J = 17.1 Hz, H-19a), 5.23 (1H, d, J = 17.1 Hz, H-15a), 5.13 (1H, d, J = 10.0 Hz, H-19b), 5.12 (1H, d, J = 10.0 Hz, H-15b), 3.33 (3H, s, H-1 or H-3), 3.29 (3H, s, H-1 or H-3), 3.19 (1H, d, J = 9.0 Hz, H-2a or H-4a), 3.17 (1H, d, J = 9.0 Hz, H-2b or H-4b), 3.14 (1H, d, J = 9.0 Hz, H-2a or H-4a), 3.12 (1H, d, J = 9.0 Hz, H-2a or H-4a), 2.44 (1H, dd, J = 13.1, 4.3 Hz, H-11a), 2.11 (1H, dd, J = 13.1, 9.0 Hz, H-11b), 1.75 (1H, dd, J = 13.1,

7.0 Hz, H-6a or H-9a), 1.65 (1H, dd, J = 13.1, 7.0 Hz, H-6a or H-9a), 1.60-1.40 (2H, m, H-7 + H-8), 1.03 (1H, dd, J = 13.1, 10.5 Hz, H-6b or H-9b), 0.98 (1H, m, H-6b or H-9b), 0.97 (3H, d, J = 6.5 Hz, H-10) ppm.

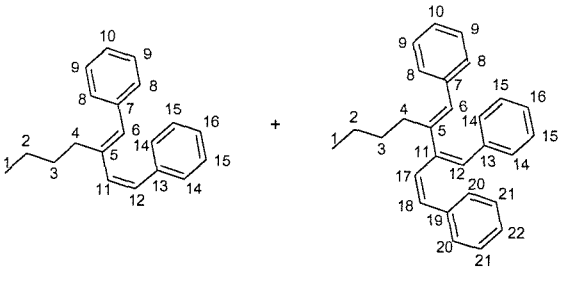
^{13}C NMR (100 MHz, $CDCl_3$) δ = 139.13 (s, C-12), 134.14 (d, C-18), 133.81 (d, C-16), 133.04 (d, C-14), 131.24 (d, C-13), 130.36 (d, C-17), 118.40 (t, C-15 or C-19), 117.70 (t, C-15 or C-19), 77.95 (t, C-2 or C-4), 77.91 (t, C-2 or C-4), 59.39 (q, C-1 or C-3), 59.36 (q, C-1 or C-3), 46.27 (d, C-8), 45.10 (s, C-5), 41.87 (t, C-6 or C-9), 40.06 (d, C-7), 39.52 (t, C-6 or C-9), 35.15 (t, C-11), 18.24 (q, C-10) ppm.

IR (neat film): 2949 (m), 2923 (m), 2871 (m), 2824 (w), 1448 (m), 1388 (w), 1198 (m), 1106 (s), 986 (m), 903 (s) cm^{-1}.

LRMS (GC-EI): 290 (M^+, 2 %), 258 (M-$MeOH^+$, 2 %), 211 (4 %), 138 (13 %), 107 (4 %).

HRMS (EI): Found: M^+, 290.2245; $C_{19}H_{30}O_2$ requires 290.2246.

Preparation of *Z*-1-phenyl-2-(*Z*-2-phenylethenyl)hex-1-ene, 183 and *Z*-1-phenyl-2-[*Z*-2-phenyl-1-(*Z*-2-phenylethenyl)-ethenyl]hex-1-ene, 184



To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and stirred for 20 min before the reaction was placed under an ethene atmosphere. The reaction was warmed to r.t. and stirred for 30 min before it was recooled to –78 °C. *E*-β-bromostyrene (183 mg, 0.13 mL, 1.0 mmol, 1.0 eq.) was added, followed by LDA (1.0 mmol in 2 mL THF) dropwise over 10 min. The reaction was stirred at –78 °C for 25 min before it was quenched with MeOH (5 mL) and $NaHCO_3$ (aq, 5 mL) and stirred for 16 hrs. The reaction mixture was poured onto H_2O (10 mL) and Et_2O (30

mL) was added. The aqueous phase was extracted with Et_2O (2 × 30 mL) before the combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil. The crude product was purified by flash silica chromatography (eluent petroleum ether 40/60) to give pale yellow oils of **183** (41 mg, 0.16 mmol, 16 %) and **184** (42 mg, 0.12 mmol, 12 %).

With further equivalents of carbenoid, the yields obtained were as follows:
2 eq.: **183** (41 mg, 0.16 mmol, 16 %), **184** (103 mg, 0.28 mmol, 28 %)
5 eq.: **183** (21 mg, 0.08 mmol, 8%), **184** (175 mg, 0.48 mmol, 48 %)

Data for **183**:
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.47 (2H, d, J = 7.5 Hz, C-8 or C-14), 7.35-7.15 (8H, m, Ar-H), 6.53 (1H, s, H-6), 6.47 (1H, d, J = 12.1 Hz, H-12), 6.20 (1H, d, J = 12.1 Hz, H-11), 2.40 (1H, t, J = 8.1 Hz, H-4a), 2.35 (1H, t, J = 8.1 Hz, H-4b), 1.52 (2H, m, H-3), 1.25 (2H, tq, J = 7.4, 7.4 Hz, H-2), 0.86 (3H, t, J = 7.4 Hz, H-1) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.79 (d, C-5), 137.91 (d, C-7 or C-13), 137.74 (d, C-7 or C-13), 133.85 (d, C-11), 129.70 (d, C-12), 129.44 (d, C-6), 128.95 (d, C-8, C-9, C-14 or C-15), 128.72 (d, C-8, C-9, C-14 or C-15), 128.27 (d, C-8, C-9, C-14 or C-15), 128.25 (d, C-8, C-9, C-14 or C-15), 126.94 (d, C-10 or C-16), 126.55 (d, C-10 or C-16), 31.14 (t, C-3 or C-4), 30.93 (t, C-3 or C-4), 23.00 (t, C-2), 14.0 (q, C-1) ppm.

IR (neat film): 3079 (w), 3055 (w), 3022 (w), 3001 (w), 2956 (m), 2926 (m), 2858 (m), 1597 (w), 1491 (m), 1446 (m), 1378 (w), 1073 (w), 1028 (w), 920 (m), 750 (s) cm^{-1}.

LRMS (GC-CI): 262 (M^+, 22 %), 205 (M-Bu^+, 100 %), 178 (8 %), 141 (6 %), 115 (12 %).

HRMS (EI): Found: M^+, 262.1720; $C_{20}H_{22}$ requires M^+, 262.1722.

Data for **184**:

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.52 (2H, d, J = 7.4 Hz, Ar-H), 7.41 (2H, d, J = 7.4 Hz, Ar-H), 7.35-7.15 (9H, m, Ar-H), 7.10 (2H, d, J = 7.4 Hz, Ar-H), 6.64 (1H, brs, H-6 or H-12), 6.57 (1H, brs, H-6 or H-12), 6.53 (1H, d, J = 12.1 Hz, H-18), 6.25 (1H, dd, J = 12.1, 1.1 Hz, H-17), 2.28 (1H, t, J = 8.1 Hz, H-4a), 2.22 (1H, t, J = 8.1 Hz, H-4b), 1.48 (2H, tt, J = 8.1, 7.4 Hz, H-3), 1.23 (2H, tq, J = 7.4, 7.4 Hz, H-2), 0.81 (3H, t, J = 7.4 Hz, H-1) ppm.

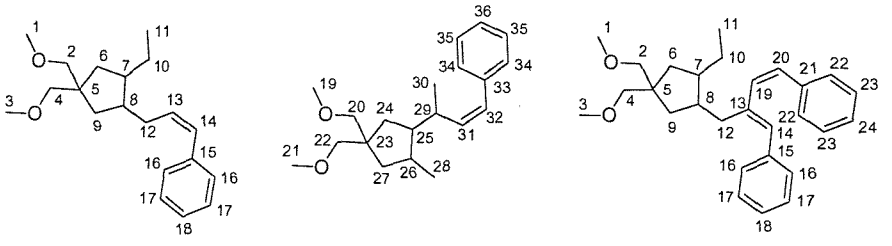
^{13}C NMR (75 MHz, $CDCl_3$) δ = 141.20 (s, C-5 or C-11), 140.92 (s, C-5 or C-11), 137.90 (s, C-7, C-13 or C-19), 137.46 (s, C-7, C-13 or C-19), 137.32 (s, C-7, C-13 or C-19), 133.48 (d, C-6, C-12, C-17 or C-18), 130.78 (d, C-6, C-12, C-17 or C-18), 130.75 (d, C-6, C-12, C-17 or C-18), 130.41 (d, C-6, C-12, C-17 or C-18), 129.25 (d, C-9, C-15 or C-21), 129.08 (d, C-9, C-15 or C-21), 128.76 (d, C-9, C-15 or C-21), 128.21 (d, C-8, C-14 or C-20), 128.15 (d, C-8, C-14 or C-20), 128.08 (d, C-8, C-14 or C-20), 127.02 (d, C-10, C-16 or C-22), 126.95 (d, C-10, C-16 or C-22), 126.55 (d, C-10, C-16 or C-22), 30.67 (t, C-3 or C-4), 30.51 (t, C-3 or C-4), 23.17 (t, C-2), 13.99 (q, C-1) ppm.

IR (neat film): 3077 (w), 3054 (w), 3021 (w), 2955 (m), 2927 (m), 2858 (w), 1597 (w), 1491 (s), 1445 (s), 1378 (w), 1074 (m), 1029 (m), 918 (s) cm^{-1}.

LRMS (GC-CI): 364 (M^+, 55 %), 307 (M-Bu^+, 59 %), 229 (M-Bu-Ph^+, 100 %), 215 (88 %), 202 (29 %).

HRMS (EI): Found: M^+, 364.2191; $C_{28}H_{28}$ requires M^+, 364.2191.

Preparation of [(*Z*)-3-(rac-(1*R*,2*R*)-2-Ethyl-4,4-bis-methoxymethyl-cyclopentyl)-propenyl]-benzene, 202, [(*Z*)-3-(rac-(1*R*,2*R*)-4,4-Bis-methoxymethyl-2-methyl-cyclopentyl)-but-1-enyl]-benzene, 203 and [(*Z*)-3-(rac-(1*R*,2*R*)-4,4-Bis-methoxymethyl-2-methyl-cyclopentyl)-2-((*Z*)-2-phenylethenyl)-but-1-enyl]-benzene, 204



To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and stirred for 20 min before diene **200** (198 mg, 1.0 mmol, 1.0 eq.) was added and the reaction stirred at room temperature for 4 hrs. The solution was cooled to –78 °C and *E*-β-bromostyrene (366 mg, 0.26 mL, 2.0 mmol, 2.0 eq.) was added, followed by LDA (2.0 mmol in 2 mL THF) dropwise over 20 min. The reaction was stirred at –78 °C for 50 min before it was quenched with MeOH (5 mL) and $NaHCO_3$ (aq, 5 mL) and stirred for 16 hrs. The reaction mixture was poured onto H_2O (10 mL) and Et_2O (30 mL) was added. The aqueous phase was extracted with Et_2O (2 × 30 mL) before the combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil. The crude product was purified by flash silica chromatography (eluent 3-5 % Et_2O in petroleum ether 40/60) to give a mixture of **202** + **203** in a 13:4 ratio (NMR) as a colourless oil (169 mg, 0.56 mmol, 56 %). Bis-insertion product **204** was obtained as a pale yellow oil (33 mg, 0.08 mmol, 8 %), in 90 % purity (estimated by NMR).

Data for mono-insertion products **202** and **203**:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.24 (4H, t, J = 7.5 Hz, H-17 + H-35), 7.18 (4H, d, J = 7.5 Hz, H-16 + H-34), 7.13 (2H, t, J = 7.5 Hz, H-18 + H-36), 6.33 (1H, d, J = 11.7 Hz, H-14), 6.25 (1H, d, J = 17.7 Hz, H-32), 5.60 (1H, dt, J = 11.7, 7.3 Hz, H-13), 5.43 (1H, dd, J = 11.7, 10.8 Hz, H-31), 3.33 (6H, s, H-1 or H-3 + H-19 or H-21), 3.32 (6H, s, H-1 or H-3 + H-19 or H-21), 3.15-3.05 (8H, m, H-2, H-4, H-20 + H-22), 2.75 (1H, ddq, J = 10.8, 6.5, 6.5 Hz, H-29), 2.55 (1H, dddd, J = 15.1, 7.3, 4.0, 2.0 Hz, H-12a),

2.00 (1H, dddd, J = 15.1, 9.0, 7.3, 1.8 Hz, H-12b), 1.74 (1H, dd, J = 13.1, 13.1 Hz, H-6a or H-9a), 1.72 (1H, dd, J = 13.1, 13.1 Hz, H-6a or H-9a), 1.65-1.42 (4H, m, H-7 or H-8, H-10a, H-24a + H-27a), 1.40-1.27 (3H, m, H-7 or H-8 + H-25 + H-26), 1.15 (1H, dd, J = 13.1, 11.0 Hz, H-24b or H-27b), 1.02-0.90 (4H, m, H-6b, H-9b, H-10b + H-24b or H-27b), 0.90 (3H, d, J = 6.3 Hz, H-28 or H-30), 0.88 (3H, d, J = 6.8 Hz, H-28 or H-30), 0.79 (3H, t, J = 7.3 Hz, H-11) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.20 (d, C-31), 138.03 (s, C-33), 137.90 (s, C-15), 132.00 (d, C-13), 129.14 (d, C-14), 128.91 (d, C-16), 128.72 (d, C-34 or C-35), 128.25 (C-34 or C-35), 128.19 (d, C-17), 126.78 (d, C-32), 126.50 (d, C-18), 126.49 (d, C-36), 77.89 (t, C-2 or C-4), 77.87 (t, C-2 or C4), 77.63 (t, C-20 or C-22), 59.38 (q, C-1 or C-3 + C-19 or C-21), 59.35 (q, C-1 or C-3 + C-19 or C-21), 51.47 (d, C-26), 46.70 (d, C-7 or C-8), 45.41 (d, C-7 or C-8), 45.18 (s, C-5), 44.83 (s, C-23), 42.02 (t, C-24 or C-27), 39.31 (t, C-6 or C-9), 38.80 (t, C-6 or C-9), 37.27 (d, C-25), 35.59 (t, C-24 or C-27), 34.35 (d, C-29), 32.72 (t, C-12), 26.67 (t, C-10), 19.23 (q, C-28 or C-30), 17.31 (q, C-28 or C-30), 12.71 (q, C-11) ppm. C-20 or C-22 not separated from C-2 or C-4 peak.

IR (neat film): 2956 (m), 2921 (m), 2872 (m), 2823 (m), 1447 (m), 1376 (w), 1199 (m), 1106 (s), 963 (m) cm^{-1}.

LRMS (GC-EI): 302 (M^+, 7 %), 270 (M-$MeOH^+$, 22 %), 257 (M-CH_2OMe^+, 26 %), 225 (M-Ph^+, 36 %), 209 (M-Et-2$MeOH^+$, 25 %), 151 (48 %).

HRMS (EI): Found: M^+, 302.2241; $C_{20}H_{30}O_2$ requires M^+, 302.2246.

Data for bis-insertion product **204**:

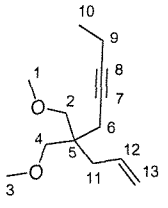
^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.36 (2H, d, J = 7.0 Hz, Ar-H), 7.25-7.15 (4H, m, Ar-H), 7.15-7.10 (4H, m, Ar-H), 6.48 (1H, s, H-14), 6.36 (1H, d, J = 12.6 Hz, H-20), 6.15 (1H, d, J = 12.6 Hz, H-19), 3.22 (3H, s, H-1 or H-3), 3.19 (3H, s, H-1 or H-3), 3.06 (1H, d, J = 9.0 Hz, H-2a or H-4a), 3.04 (1H, d, J = 9.0 Hz, H-2b or H-4b), 3.03 (1H, d, J = 8.5 Hz, H-2a or H-4a), 3.00 (1H, d, J = 8.5 Hz, H-2b or H-4b), 2.59 (1H, dd, J = 13.6, 3.3 Hz, H-12a), 2.05 (1H, dd, J = 13.6, 10.0 Hz, H-12b), 1.70-1.60 (2H,

m, H-6a + H-9a), 1.57 (1H, m, H-8), 1.41-1.32 (2H, m, H-10), 1.17 (1H, m, H-7), 0.87 (1H, dd, J = 12.6, 10.5 Hz, H-6b or H-9b), 0.83 (1H, dd, J = 13.1, 10.5 Hz, H-6b or H-9b), 0.70 (3H, t, J= 7.0 Hz, H-11) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 139.22 (s, C-14), 137.96 (s, C-15 or C-21), 137.85 (s, C-15 or C-21), 133.97 (d, C-19), 130.34 (d, C-14), 129.39 (d, C-20), 129.02 (d, Ar-C), 129.00 (d, Ar-C), 128.18 (d, Ar-C, multiple peak), 126.96 (d, C-18 or C-24), 126.53 (d, C-18 or C-24), 77.83 (t, C-2 + C-4), 59.38 (q, C-1 or C-3), 59.34 (q, C-1 or C-3), 47.23 (d, C-7), 45.19 (s, C-5), 43.97 (d, C-8), 39.56 (t, C-6 or C-9), 38.66 (t, C-6 or C-9), 35.09 (t, C-12), 26.46 (t, C-10), 12.71 (q, C-11) ppm.

LRMS (GC-EI): 404 (M^+, 4 %), 372 (M-$MeOH^+$, 5 %), 340 (M-2$MeOH^+$, 2 %), 218 (42 %), 205 (24 %).

Preparation of 4,4-Bis-methoxymethyl-non-1-en-6-yne, 206



To a solution of enyne **67** (5.0 g, 27.0 mmol) in THF (50 mL) at –78 °C under argon was added *n*-BuLi (12.0 mL, 30.0 mmol, 1.1 eq.) followed by HMPA (5.41 g, 5.25 mL, 30.0 mmol, 1.1 eq.). The reaction was warmed to –30 °C before ethyl bromide (3.29 g, 2.25 mL, 30.0 mmol, 1.1 eq.) was added and the reaction was allowed to warm to r.t. in the cool bath and stirred for 16 hrs. The reaction was quenched with aqueous NH_4Cl (20 mL) and Et_2O (60 mL) was added. The layers were separated and the aqueous layer extracted with Et_2O (2 × 30 mL). The combined organic phase was washed with H_2O (40 mL) and brine (40 mL) before it was dried ($MgSO_4$), filtered and the solvent was removed *in vacuo* to give a yellow oil. The crude product was purified by flash silica chromatography (eluent 4 % Et_2O in petroleum ether 40/60) to give a colourless oil (4.29 g, 20.4 mmol, 76 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.80 (1H, ddt, J = 16.9, 10.3, 7.7 Hz, H-12), 5.10 (1H, dfs, J = 10.3 Hz, H-13a), 5.08 (1H, dfs, J = 16.9 Hz, H-13b), 3.32 (6H, s, H-1 + H-3), 3.25 (2H, d, J = 9.2 Hz, H-2a + H-4a), 3.21 (2H, d, J = 9.2 Hz, H-2b + H-4b), 2.22-2.10 (6H, m, H-6, H-9 + H-11), 1.13 (3H, t, J = 7.4 Hz, H-10) ppm.

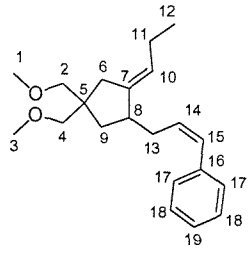
^{13}C NMR (75 MHz, $CDCl_3$) δ = 134.25 (d, C-12), 117.96 (d, C-13), 83.77 (s, C-8), 75.91 (s, C-7), 74.60 (t, C-2 + C-4), 59.45 (q, C-1 + C-3), 41.99 (s, C-5), 36.36 (t, C-11), 22.34 (t, C-6), 14.59 (q, C-10), 12.63 (t, C-9) ppm.

IR (neat film): 2976 (m), 2920 (m), 2877 (m), 2809 (m), 1477 (m), 1439 (m), 1320 (m), 1198 (m), 1106 (s) 915 (m) cm^{-1}.

LRMS (GC-CI): 211 ($M+H^+$, 100 %), 179 ($M+H-MeOH^+$, 25 %), 165 ($M+H-CH_2OMe$, 14 %), 147 ($M+H-2MeOH^+$, 24 %), 133 ($M+H-2CH_2OMe^+$, 26 %).

HRMS (EI): Found: M^+, 181.1229; $C_{11}H_{17}O_2$ requires M^+, 181.1229.

Preparation of {(*Z*)-3-[4,4-Bismethoxymethyl-2-prop-(*E*)-ylidenecyclopentyl]-propenyl}benzene, 208



To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and stirred for 30 min before 4,4-bis-methoxymethyl-non-1-en-6-yne **206** (210 mg, 1.0 mmol, 1.0 eq.) was added and the reaction stirred at room temperature for 4 hrs. The solution was cooled to –78 °C and *E*-β-bromostyrene (366 mg, 0.26 mL, 2.0 mmol, 2.0 eq.) was added, followed by LDA (2.0 mmol in 4 mL THF) dropwise over 15 min. The reaction was stirred at –78 °C for 30 min before it was quenched with MeOH (5 mL) and $NaHCO_3$ (aq, 5 mL) and stirred for 16 hrs. The reaction mixture was poured onto H_2O (10 mL)

and Et_2O (30 mL) was added. The aqueous phase was extracted with Et_2O (2 × 30 mL) before the combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil. The crude product was purified by flash silica chromatography (eluent 4 % Et_2O in petroleum ether 40/60) to give a colourless oil (200 mg, 0.64 mmol, 64 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 (2H, dd, J = 7.5, 7.5 Hz, H-18), 7.24 (2H, d, J = 7.5 Hz, H-17), 7.18 (1H, t, J = 7.5 Hz, H-19), 6.41 (1H, d, J = 11.6 Hz, H-15), 5.66 (1H, dt, J = 11.6, 7.0 Hz, H-14), 5.19 (1H, t, J = 7.0 Hz, H-10), 3.30 (3H, s, H-1 or H-3), 3.28 (3H, s, H-1 or H-3), 3.23 (1H, d, J = 9.0 Hz, H-2a or H-4a), 3.19 (1H, d, J = 9.0 Hz, H-2b or H-4b), 3.18 (2H, s, H-2 or H-4), 2.66 (1H, ddd, J = 14.0, 7.0, 7.0 Hz, H-13a), 2.57 (1H, m, H-8), 2.24 (1H, ddd, J = 14.0, 7.0, 7.0 Hz, H-13b), 2.18 (1H, d, J = 16.8 Hz, H-6a), 2.06 (1H, d, J = 16.8 Hz, H-6b), 1.94 (2H, dq, J = 7.5, 7.5 Hz, H-11), 1.86 (1H, dd, J = 12.8, 8.0 Hz, H-9a), 1.10 (1H, dd, J = 12.8, 10.5 Hz, H-9b), 0.90 (3H, t, J = 7.5 Hz, H-12) ppm.

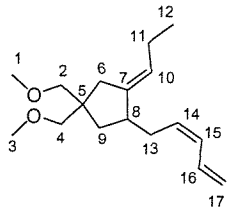
^{13}C NMR (100 MHz, $CDCl_3$) δ = 143.58 (s, C-7), 137.96 (s, C-16), 131.57 (d, C-14), 129.57 (d, C-15), 128.94 (d, C-17), 128.23 (d, C-18), 126.55 (d, C-19), 123.21 (d, C-10), 77.71 (t, C-2 or C-4), 75.46 (t, C-2 or C-4), 59.42 (q, C-1 or C-3), 59.39 (q, C-1 or C-3), 45.90 (s, C-5), 42.22 (d, C-8), 37.85 (t, C-9), 35.88 (t, C-6), 33.50 (t, C-13), 22.67 (t, C-11), 14.33 (q, C-12) ppm.

IR (neat film): 2959 (m), 2921 (m), 2872 (m), 2825 (m), 1493 (w), 1475 (w), 1448 (m), 1390 (w), 1197 (m), 1109 (s), 963 (m), 769 (m) cm^{-1}.

LRMS (GC-EI): 282 ($M\text{-}MeOH^+$, 10 %), 237 ($M\text{-}Ph^+$, 5 %), 197 ($M\text{-}PhCHCHCH_2^+$, 10 %), 165 (32 %), 117 (35 %).

HRMS (EI): Found: M^+, 314.2245; $C_{21}H_{30}O_2$ requires M^+, 314.2246.

Preparation of 1,1-Bismethoxymethyl-3-((*Z*)-penta-2,4-dienyl)-4-prop-(*E*)-ylidenecyclopentane, 209



To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and stirred for 30 min before 4,4-bis-methoxymethyl-non-1-en-6-yne **206** (210 mg, 1.0 mmol, 1.0 eq.) was added and the reaction stirred at room temperature for 4 hrs. The solution was cooled to –90 °C and *Z*-1,4-dichloro-2-butene (375 mg, 0.25 mL, 3.0 mmol, 3.0 eq.) was added, followed by LDA (6.0 mmol in 6 mL THF) dropwise over 25 min. The reaction was stirred at –90 °C for 30 min before it was quenched with MeOH (5 mL) and $NaHCO_3$ (aq, 5 mL) and stirred for 16 hrs. The reaction mixture was poured onto H_2O (10 mL) and Et_2O (30 mL) was added. The aqueous phase was extracted with Et_2O (2 × 30 mL) before the combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give an orange oil. The crude product was purified by flash silica chromatography ($AgNO_3$ doped silica, eluent 3-50 % Et_2O in petroleum ether 40/60) to give a pale yellow oil (213 mg, 0.81 mmol, 81 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.61 (1H, ddd, J = 17.1, 10.5, 10.5 Hz, H-16), 6.03 (1H, t, J = 10.5 Hz, H-15), 5.47 (1H, dt, J = 10.5, 7.5 Hz, H-14), 5.19 (1H, m, H-10), 5.17 (1H, d, J = 17.1 Hz, H-17a), 5.08 (1H, d, J = 10.5 Hz, H-17b), 3.34 (3H, s, H-1 or H-3), 3.32 (3H, s, H-1 or H-3), 3.28 (1H, d, J = 8.7 Hz, H-2a or H-4a), 3.24 (1H, d, J = 8.7 Hz, H-2b or H-4b), 3.19 (2H, s, H-2 or H-4), 2.58-2.47 (2H, m, H-8 + H-13a), 2.20 (1H, d, J = 16.6 Hz, H-6a), 2.12 (1H, d, J = 16.6 Hz, H-6b), 2.12 (1H, m, H-13b), 1.98 (2H, dq, J = 7.5, 7.5 Hz, H-11), 1.83 (1H, dd, J = 13.1, 7.5 Hz, H-9a), 1.11 (1H, dd, J = 13.1, 10.5 Hz, H-9b), 0.94 (3H, t, J = 7.5 Hz, H-12) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 143.52 (s, C-7), 132.58 (d, C-16), 131.35 (d, C-14), 129.95 (d, C-15), 123.14 (d, C-10), 117.00 (t, C-17), 77.70 (t, C-2 or C-4), 75.35 (t,

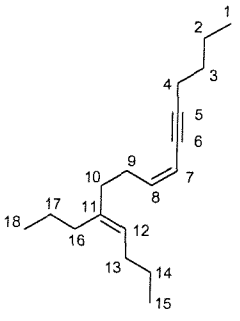
C-2 or C-4), 59.43 (q, C-1 or C-3), 59.42 (q, C-1 or C-3), 45.81 (s, C-5), 41.81 (d, C-8), 37.75 (t, C-9), 35.86 (t, C-6), 32.64 (t, C-13), 22.67 (t, C-11), 14.44 (q, C-12) ppm.

IR (neat film): 2260 (m), 2922 (m), 2873 (m), 2825 (w), 1458 (m), 1390 (w), 1259 (w), 1198 (m), 1113 (s), 997 (m), 963 (m), 901 (m) cm^{-1}.

LRMS (GC-EI): 264 (M^+, 2 %), 232 (M-$MeOH^+$, 23 %), 187 (26 %), 165 (40 %), 133 (44 %).

HRMS (EI): Found: M-$MeOH^+$, 232.1830; $C_{16}H_{24}O$ requires M-$MeOH^+$, 232.1827.

Preparation of (4*E*,8*Z*)-5-Propyl-pentadeca-4,8-dien-10-yne, 210



To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and stirred for 20 min before the reaction was placed under an ethene atmosphere. The reaction was warmed to r.t. and 4-octyne (110 mg, 1.0 mmol, 1.0 eq.) was added and the reaction stirred for 3 hrs. The solution was cooled to –78 °C and 1-chloro-oct-1-en-3-yne (157 mg, 1.1 mmol, 1.1 eq.) was added, followed by LDA (1.1 mmol in 2 mL THF) dropwise over 15 min. The reaction was stirred at –78 °C for 45 min before it was quenched with MeOH (5 mL) and $NaHCO_3$ (aq, 5 mL) and stirred for 16 hrs. The reaction mixture was poured onto H_2O (10 mL) and Et_2O (30 mL) was added. The aqueous phase was extracted with Et_2O (2 × 30 mL) before the combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil. The crude product was purified by flash silica chromatography (eluent petroleum ether 40/60) to give a colourless oil (134 mg, 0.54 mmol, 54 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.81 (1H, dt, J = 10.5, 7.5 Hz, H-8), 5.42 (1H, dt, J =10.5, 2.0 Hz, H-7), 5.16 (1H, t, J = 7.0 Hz, H-12), 2.39 (2H, dt, J = 7.5 Hz, H-9), 2.34 (2H, td, J = 7.0, 2.0 Hz, H-4), 2.07 (2H, t, J = 7.5 Hz, H-10), 2.04-1.94 (4H, m, H-13 + H-16), 1.53 (2H, m, H-3), 1.45-1.30 (6H, m, H-2, H-14 + H-17), 0.92 (3H, t, J = 7.5 Hz, H-1, H-15 or H-18), 0.90 (6H, t, J = 7.5 Hz, H-1, H-15 or H-18) ppm.

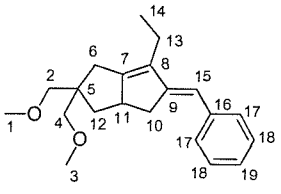
^{13}C NMR (75 MHz, $CDCl_3$) δ = 142.48 (d, C-8), 138.59 (s, C-11), 125.56 (d, C-12), 109.44 (d, C-7), 94.70 (s, C-5 or C-6), 77.47 (s, C-5 or C-6), 36.08 (t, C-10), 32.18 (t, C-13 or C-16), 31.11 (t, C-3), 29.96 (t, C-13 or C-16), 29.02 (t, C-9), 23.38 (t, C-2, C-14 or C-17), 22.11 (t, C-2, C-14 or C-17), 21.71 (t, C-2, C-14 or C-17), 19.37 (t, C-4), 14.35 (q, C-1, C-15 or C-18), 14.02 (q, C-1, C-15 or C-18), 13.78 (q, C-1, C-15 or C-18) ppm.

IR (neat film): 3021 (w), 2962 (s), 2930 (s), 2871 (m), 1456 (m), 1396 (w), 1378 (m), 1327 (m), 892 (m), 734 (s) cm^{-1}.

LRMS (GC-EI): 246 (M^+, 15 %), 217 (M-Et^+, 18 %), 203 (M-Pr^+, 95 %), 189 (M-Bu^+, 25 %), 147 (53 %).

HRMS (EI): Found: M^+, 246.2346; $C_{18}H_{30}$ requires M^+, 246.2348.

Preparation of 6-Ethyl-2,2-bis-methoxymethyl-5-[1-phenyl-meth-(*E*)-ylidene]-1,2,3,3a,4,5-hexahydro-pentalene, 213



To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and stirred for 30 min before 4,4-bis-methoxymethyl-hepta-1,6-diene **206** (184 mg, 1.0 mmol, 1.0 eq.) was added and the reaction stirred at room temperature for 4 hrs. The solution was cooled

to –78 °C and *E*-β-bromostyrene (915 mg, 0.64 mL, 5.0 mmol, 5.0 eq.) was added, followed by LDA (5.0 mmol in 5 mL THF) dropwise over 15 min. The reaction was allowed to warm to r.t. in the cool bath and was stirred for 16 hrs before it was quenched with MeOH (5 mL) and $NaHCO_3$ (aq, 5 mL) and stirred for 20 hrs. The reaction mixture was poured onto H_2O (10 mL) and Et_2O (30 mL) was added. The aqueous phase was extracted with Et_2O (2 × 30 mL) before the combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a brown oil. The crude product was purified by flash silica chromatography (eluent petroleum ether 40/60) to give a colourless oil (147 mg, 0.47 mmol, 47 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.31 (2H, d, J = 7.5 Hz, H-17), 7.25 (2H, t, J = 7.5 Hz, H-18), 7.07 (1H, t, J = 7.5 Hz, H-19), 6.07 (1H, s, H-15), 3.32 (3H, s, H-1 or H-3), 3.32-3.29 (2H, m, H-2 or H-4), 3.28 (3H, s, H-1 or H-3), 3.19-3.15 (2H, m, H-2 or H-4), 3.10-3.00 (2H, m, H-10a + H-11), 2.40 (1H, m, H-10b), 2.25 (1H, d, J = 16.6 Hz, H-6a), 2.24-2.15 (2H, m, H-13), 2.08 (1H, d, J = 16.6 Hz, H-6b), 1.90 (1H, dd, J = 12.6, 7.8 Hz, H-12a), 1.05 (3H, t, J = 7.5 Hz, H=14), 0.91 (1H, dd, J = 12.6, 10.4 Hz, H-12b) ppm.

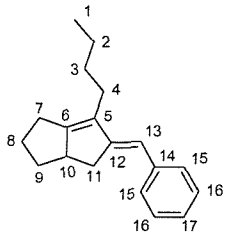
^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.31 (s, C-7 or C-9), 152.84 (s, C-7 or C-9), 139.17 (s, C-8 or C-16), 136.89 (s, C-8 or C-16), 128.39 (d, C-18), 127.98 (d, C-17), 125.37 (d, C-16), 115.38 (d, C-15), 77.77 (t, C-2 or C-4), 76.82 (t, C-2 or C-4), 59.41 (q, C-1 or C-3), 59.37 (q, C-1 or C-3), 51.26 (s, C-5), 47.78 (d, C-11), 38.12 (t, C-12), 37.37 (t, C-10), 31.44 (t, C-6), 19.30 (t, C-13), 13.43 (q, C-14) ppm.

IR (neat film): 2959 (m), 2923 (m), 2873 (m), 1619 (w), 1596 (w), 1490 (w), 1447 (m), 1388 (w), 1198 (m), 1106 (s), 962 (m), 907 (s), 731 (s) cm^{-1}.

LRMS (GC-EI): 312 (M^+, 79 %), 280 (M-MeOH$^+$, 66 %), 267 (M-CH_2OMe^+, 48 %), 235 (M-Ph^+, 100 %), 219 (M-2MeOH-Et^+, 32 %).

HRMS (EI): Found: M^+, 312.2088; $C_{21}H_{28}O_2$ requires M^+, 312.2089.

Preparation of 6-Butyl-5-[1-phenyl-meth-(*E*)-ylidene]-1,2,3,3a,4,5-hexahydro-pentalene, 216



To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and stirred for 30 min before 1-undecen-6-yne (150 mg, 1.0 mmol, 1.0 eq.) was added and the reaction stirred at room temperature for 4 hrs. The solution was cooled to –78 °C and *E*-β-bromostyrene (915 mg, 0.64 mL, 5.0 mmol, 5.0 eq.) was added, followed by LDA (5.0 mmol in 5 mL THF) dropwise over 15 min. The reaction was allowed to warm to r.t. in the cool bath and was stirred for 16 hrs before it was quenched with MeOH (5 mL) and $NaHCO_3$ (aq, 5 mL) and stirred for 20 hrs. The reaction mixture was poured onto H_2O (10 mL) and Et_2O (30 mL) was added. The aqueous phase was extracted with Et_2O (2 × 30 mL) before the combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a brown oil. The crude product was purified by flash silica chromatography (eluent petroleum ether 40/60) to give a colourless oil (61 mg, 0.24 mmol, 24 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 (2H, d, J = 7.5 Hz, H-15), 7.21 (2H, t, J = 7.5 Hz, H-16), 7.03 (1H, t, J = 7.5 Hz, H-17), 6.03 (1H, s, H-13), 3.00 (1H, ddd, J = 16.1, 7.0, 1.5 Hz, H-11a), 2.82 (1H, m, H-10), 2.40 (1H, dt, J = 16.1, 3.5 Hz, H-11b), 2.30-2.10 (4H, m, H-4 + H-7), 2.00-1.80 (3H, m, H-8 + H-9a), 1.43 (2H, tt, J = 7.5, 7.5 Hz, H-3), 1.28 (2H, tq, J = 7.5, 7.5 Hz, H-2), 0.99 (1H, m, H-9b), 0.86 (3H, t, J = 7.5 Hz, H-1) ppm.

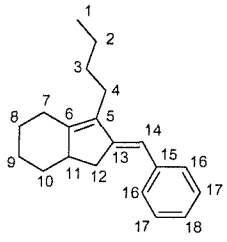
^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.52 (s, C-6 or C-12), 154.22 (s, C-6 or C-12), 139.36 (s, C-5 or C-13), 134.73 (s, C-5 or C-13), 128.38 (d, C-16), 127.97 (d, C-15), 125.28 (d, C-17), 115.16 (d, C-13), 50.43 (d, C-10), 36.79 (t, C-11), 31.97 (t, C-9), 30.73 (t, C-3), 27.74 (t, C-8), 26.10 (t, C-4), 23.55 (t, C-7), 23.04 (t, C-2), 14.19 (q, C-1) ppm.

IR (neat film): 2954 (m), 2934 (m), 2862 (w), 1494 (w), 1449 (m), 1203 (w), 1013 (m), 907 (s), 730 (s) cm^{-1}.

LRMS (GC-EI): 252 (M^+, 100 %), 237 (M-Me^+, 6 %), 223 (M-Et^+, 32 %), 209 (M-Pr^+, 35 %), 195 (M-Bu^+, 87 %).

HRMS (EI): Found: M^+, 252.1883; $C_{19}H_{24}$ requires M^+, 252.1878.

Preparation of 3-Butyl-2-[1-phenyl-meth-(*E*)-ylidene]-2,4,5,6,7,7a-hexahydro-1*H*-indene, 218



To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and stirred for 30 min before 1-dodecen-7-yne (164 mg, 1.0 mmol, 1.0 eq.) was added and the reaction stirred at room temperature for 4 hrs. The solution was cooled to –78 °C and *E*-β-bromostyrene (915 mg, 0.64 mL, 5.0 mmol, 5.0 eq.) was added, followed by LDA (5.0 mmol in 5 mL THF) dropwise over 15 min. The reaction was allowed to warm to r.t. in the cool bath and was stirred for 16 hrs before it was quenched with MeOH (5 mL) and $NaHCO_3$ (aq, 5 mL) and stirred for 20 hrs. The reaction mixture was poured onto H_2O (10 mL) and Et_2O (30 mL) was added. The aqueous phase was extracted with Et_2O (2 × 30 mL) before the combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a brown oil. The crude product was purified by flash silica chromatography (eluent petroleum ether 40/60) to give a colourless oil (111 mg, 0.42 mmol, 42 %).

^1H NMR (400 MHz, $CDCl_3$) δ = 7.30 (2H, d, J = 7.5 Hz, H-16), 7.23 (2H, t, J = 7.5 Hz, H-17), 7.04 (1H, t, J = 7.5 Hz, H-18), 6.10 (1H, s, H-14), 2.98 (1H, ddd, J = 17.1, 7.5, 2.0 Hz, H-12a), 2.58 (1H, dfs, J = 13.6 Hz, H-7a), 2.49 (1H, m, H-11), 2.28 (1H,

dt, J = 17.1, 2.5 Hz, H-12b), 2.19 (2H, t, J = 7.5 Hz, H-4), 2.00-1.90 (1H, m, H-10a), 1.90-1.86 (1H, m, H-7b), 1.85-1.75 (1H, m, H-8a), 1.75-1.67 (1H, m, H-9a), 1.43-1.30 (3H, m, H-3 + H-9b), 1.28 (2H, tq, J = 7.5, 7.5 Hz, H-2), 1.14 (1H, ddt, J = 25.6, 12.6, 4.0 Hz, H-8b), 0.94 (1H, ddd, J = 25.1, 12.6, 3.5 Hz, H-10b), 0.86 (3H, t, J = 7.5 Hz, H-1) ppm.

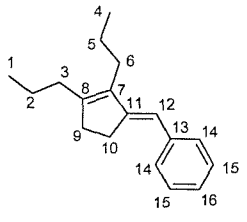
^{13}C NMR (100 MHz, $CDCl_3$) δ = 150.56 (s, C-6 or C-13), 149.17 (s, C-6 or C13), 139.49 (s, C-5 or C-15), 135.97 (s, C-5 or C-15), 128.37 (d, C-17), 128.07 (d, C-16), 125.21 (d, C-18), 115.19 (d, C-14), 45.26 (d, C-11), 37.10 (t, C-12), 35.88 (t, C-10), 31.31 (t, C-3), 27.59 (t, C-7 or C-8), 27.38 (t, C-7 or C-8), 26.28 (t, C-9), 24.21 (t, C-4), 22.97 (t, C-2), 14.22 (q, C-1) ppm.

IR (neat film): 2954 (m), 2921 (s), 2850 (m), 1619 (m), 1593 (m), 1488 (w), 1443 (m), 1238 (w), 906 (w), 855 (s) cm^{-1}.

LRMS (GC-EI): 266 (M^+, 100 %), 237 (M-Et^+, 22 %), 223 (M-Pr^+, 58 %), 209 (M-Bu^+, 90 %), 175 (86 %).

HRMS (EI): Found: M^+, 266.2033; $C_{20}H_{26}$ requires M^+, 266.2035.

Preparation of [2,3-Dipropyl-cyclopent-2-en-(*E*)-ylidenemethyl]-benzene, 219



To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and stirred for 20 min before the reaction was placed under an ethene atmosphere. The reaction was warmed to r.t. and 4-octyne (110 mg, 1.0 mmol, 1.0 eq.) was added and the reaction stirred for 3 hrs. The solution was cooled to –78 °C and *E*-β-bromostyrene (915 mg, 0.64 mL, 5.0 mmol, 5.0 eq.) was added, followed by LDA (5.0 mmol in 5 mL THF) dropwise over 15 min. The reaction was allowed to warm to r.t. in the cool bath and was stirred for 16 hrs before it was quenched with MeOH (5 mL) and $NaHCO_3$ (aq., 5

mL) and stirred for 20 hrs. The reaction mixture was poured onto H_2O (10 mL) and Et_2O (30 mL) was added. The aqueous phase was extracted with Et_2O (2 × 30 mL) before the combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a brown oil. The crude product was purified by flash silica chromatography (eluent petroleum ether 40/60) to give a colourless oil (149 mg, 0.62 mmol, 62 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 (2H, d, J = 7.5 Hz, H-14), 7.33 (2H, t, J = 7.5 Hz, H-15), 7.15 (1H, t, J = 7.5 Hz, H-16), 6.21 (1H, s, H-12), 2.90-2.85 (2H, m, H-10), 2.55-2.50 (2H, m, H-9), 2.29 (2H, t, J = 7.5 Hz, H-3 or H-6), 2.27 (2H, t, J = 7.5 Hz, H-3 or H-6), 1.52 (4H, tq, J = 7.5, 7.5 Hz, H-2 + H-5), 0.98 (3H, t, J = 7.5 Hz, H-1 or H-4), 0.96 (3H, t, J = 7.5 Hz, H-1 or H-4) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 149.61 (s, C-8 or C-11), 147.20 (s, C-8 or C-11), 138.49 (s, C-7 or C-13), 138.28 (s, C-7 or C-13), 127.37 (d, C-14 or C-15), 127.08 (d, C-14 or C-15), 124.21 (d, C-16), 114.28 (d, C-12), 32.98 (t, C-9), 30.87 (t, C-3 or C-6), 28.38 (t, C-10), 26.07 (t, C-3 or C-6), 21.21 (t, C-2 or C-5), 20.56 (t, C-2 or C-5), 13.59 (q, C-1 or C-4), 13.38 (q, C-1 or C-4) ppm.

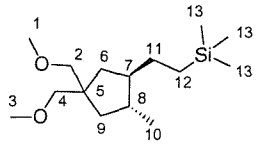
IR (neat film): 3021 (w), 2956 (s), 2930 (s), 2870 (m), 1617 (m), 1594 (m), 1495 (w), 1445 (s), 1377 (w), 1084 (w), 855 (m), 754 (s) cm^{-1}.

LRMS (GC-EI): 240 (M^+, 100 %), 225 (M-Me^+, 15 %), 211 (M-Et^+, 83 %), 197 (M-Pr^+, 81 %), 155 (55 %).

HRMS (EI): Found: M^+, 240.1876; $C_{18}H_{24}$ requires M^+, 240.1878.

6.2.4 Experimental for Chapter 5

Preparation of rac-[2-((1*S*,2*R*)-4,4-Bis-methoxymethyl-2-methyl-cyclopentyl)-ethyl]-trimethyl-silane[8], 233



To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and stirred for 30 min before 4,4-bis-methoxymethyl-hepta-1,6-diene (184 mg, 1.0 mmol, 1.0 eq.) was added and the reaction stirred at room temperature for 4 hrs. The solution was cooled to –78 °C and chloromethyltrimethylsilane (0.135 mg, 0.15 mL, 1.1 mmol, 1.1 eq.) was added, followed by LDA (1.1 mmol in 2 mL THF) dropwise over 10 min. The reaction was allowed to warm to r.t. with a cool bath and stirred for 16 hrs before it was quenched with MeOH (5 mL) and $NaHCO_3$ (aq., 5 mL) for 6 hrs. The reaction was poured onto H_2O (10 mL) and Et_2O (30 mL) was added. The layers were separated and the aqueous layer extracted with Et_2O (2 × 30 mL) before the combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil. The crude product was purified by flash silica chromatography (eluent 4 % Et_2O in petroleum ether 40/60) to give a colourless oil (171 mg, 0.63 mmol, 63 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.33 (6H, s, H-1 + H-3), 3.21 (2H, d, J = 8.8 Hz, H-2a + H-4a), 317 (2H, d, J = 8.8 Hz, H-2b + H-4b), 1.77 (1H, dd, J = 12.9, 7.2 Hz, H-6a or H-9a), 1.71 (1H, dd, J = 12.9, 7.2 Hz, H-6a or H-9a), 1.58 (1H, m, H-7, H-8 or H-11a), 1.42 (1H, m, H-7, H-8 or H-11a), 1.25 (1H, m, H-7, H-8 or H-11a), 1.05-0.95 (3H, m, H-6b, H-9b + H-11b), 0.92 (3H, d, J = 6.3 Hz, H-10), 0.54 (1H, ddd, J = 14.0, 12.5, 4.4 Hz, H-12a), 0.37 (1H, ddd, J = 14.0, 12.5, 5.2 Hz, H-12b), -0.05 (9H, s, H-13) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 78.13 (t, C-2 or C-4), 77.99 (t, C-2 or C-4), 59.38 (q, C-1 + C-3), 49.67 (d, C-7 or C-8), 45.00 (s, C-5), 42.15 (t, C-6 or C-9), 39.46 (d, C-7

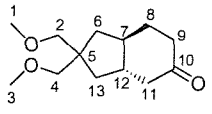
or C-8), 39.34 (t, C-6 or C-9), 27.62 (t, C-11), 18.29 (q, C-10), 14.94 (t, C-12), -1.59 (q, C-13) ppm.

IR (neat film): 2951 (m), 2911 (m), 2871 (m), 1450 (w), 1247 (m), 1198 (m), 1108 (s), 965 (m), 861 (s), 834 (m), 753 (m) cm^{-1}.

LRMS (GC-EI): 273 ($M+H^+$ self CI, 8 %), 257 ($M-Me^+$, 2 %), 240 (M-MeOH, 33 %), 225 ($M-MeOH-Me^+$, 35 %), 208 ($M-2MeOH^+$, 45 %), 195 (66 %)

HRMS (EI): Found: M^+, 272.2179; $C_{15}H_{32}O_2Si$ requires M^+, 272.2172.

Preparation of rac-(3a*S*,7a*R*)-2,2-Bismethoxymethyloctahydroinden-5-one, 231



From chloromethyltrimethylsilane carbenoid:

To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and stirred for 30 min before 4,4-bis-methoxymethyl-hepta-1,6-diene (184 mg, 1.0 mmol, 1.0 eq.) was added and the reaction stirred at room temperature for 3 hrs. The solution was cooled to –78 °C and chloromethyltrimethylsilane (135 mg, 0.15 mL, 1.1 mmol, 1.1 eq.) was added, followed by LDA (1.1 mmol in 2 mL THF) dropwise over 10 min. The reaction was allowed to warm to r.t. with a cool bath and stirred for 12 hrs. The reaction was then placed under an atmosphere of carbon monoxide (balloon) at r.t. and stirred for 20 hrs. The reaction was then quenched with MeOH (10 mL) for 24 hrs. Most of the solvent was removed *in vacuo* before the residue was taken up in Et_2O (30 mL) and H_2O (20 mL). The layers were separated and the aqueous layer extracted with Et_2O (2 × 30 mL) before the combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil. The crude product was purified by flash silica chromatography (eluent 20 % Et_2O in petroleum ether 40/60) to give a pale yellow oil (76 mg, 0.33 mmol, 33 %).

From chloromethylphenylsulphone carbenoid:

To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and stirred for 20 min before 4,4-bis-methoxymethyl-hepta-1,6-diene (184 mg, 1.0 mmol, 1.0 eq.) was added and the reaction stirred at room temperature for 3 hrs. The solution was cooled to –78 °C and chloromethylphenylsulphone (572 mg, 3.0 mmol, 3.0 eq.) in THF (2 mL) was added, followed by LDA (3.0 mmol in 3 mL THF) dropwise over 20 min. The reaction was allowed to warm to r.t. with a cool bath and stirred for 16 hrs. The reaction was then cooled to 0 °C and n-butyl isocyanide (91mg, 0.11 mL, 1.1 mmol, 1.1 eq.) was added. After 30 min the cool bath was removed and the reaction stirred for 24 hrs. The reaction was then quenched with MeOH (5 mL) and $NaHCO_3$ (aq., 5 mL) for 24 hrs. The reaction was poured onto H_2O (10 mL) and Et_2O (30 mL) was added. The layers were separated and the aqueous layer extracted with Et_2O (2 × 30 mL) before the combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a yellow oil. The crude product was purified by flash silica chromatography (eluent 5-7.5 % EtOAc in CH_2Cl_2) to give a pale yellow oil (117 mg, 0.52 mmol, 52 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 3.35 (3H, s, H-1 or H-3), 3.32 (3H, s, H-1 or H-3), 3.27 (1H, d, J = 9.0 Hz, H-2a or H-4a), 3.23 (1H, d, J = 9.0 Hz, H-2b or H-4b), 3.21 (1H, d, J = 9.0 Hz, H-2a or H-4a), 3.18 (1H, d, J = 9.0 Hz, H-2b or H-4b), 2.51 (1H, ddd, J = 14.0, 4.0, 2.0 Hz, H-11a), 2.38 (1H, dddd, J = 15.0, 5.0, 2.0, 2.0 Hz, H-9a), 2.27 (1H, ddd, J = 15.0, 13.0, 6.5 Hz, H-9b), 2.11 (1H, dd, J = 14.0, 14.0 Hz, H-11b), 2.10-2.05 (1H, m, H-8a), 1.80-1.60 (4H, m, H-6a, H-13a, H-7 + H-12), 1.39 (1H, m, H-8b), 1.17 (1H, dd, J = 12.6, 11.0 Hz, H-6b or H-13b), 1.06 (1H, dd, J = 12.0, 10.5 Hz, H-6b or H-13b) ppm.

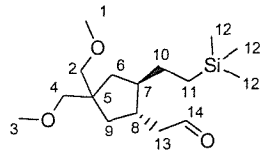
^{13}C NMR (100 MHz, $CDCl_3$) δ = 211.87 (s, C-10), 78.23 (t, C-2 or C-4), 78.16 (t, C-2 or C-4), 59.40 (q, C-1 or C-3), 59.37 (q, C-1 or C-3), 47.49 (s, C-5), 47.35 (t, C-11), 45.79 (d, C-7 or C-12), 44.00 (d, C-7 or C-12), 40.96 (t, C-9), 39.09 (t, C-6 or C-13), 39.72 (C-6 or C-13), 29.69 (t, C-8) ppm.

IR (neat film): 2925 (m), 2869 (m), 2824 (m), 1711 (s), 1452 (m), 1388 (w), 1318 (w), 1196 (m), 1104 (s), 963 (m) cm^{-1}.

LRMS (GC-EI): 227 ($M+H^+$, self CI, 8 %), 208 ($M-H_2O^+$, 16 %), 194 ($M-MeOH^+$, 73 %), 162 ($M-2MeOH^+$, 83 %), 149 (69 %).

HRMS (EI): Found: M^+, 226.1577; $C_{13}H_{22}O_3$ requires M^+, 226.1569.

Preparation of [(1*S*,2*S*)-4,4-Bis-methoxymethyl-2-(2-trimethylsilanyl-ethyl)-cyclopentyl]-acetaldehyde, 236



To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and stirred for 30 min before 4,4-bis-methoxymethyl-hepta-1,6-diene (184 mg, 1.0 mmol, 1.0 eq.) was added and the reaction stirred at room temperature for 3 hrs. The solution was cooled to –78 °C and chloromethyltrimethylsilane (110 mg, 0.15 mL, 1.1 mmol, 1.1 eq.) was added, followed by LDA (1.1 mmol in 2mL THF) dropwise over 5 min. The reaction was allowed to warm to r.t. slowly with the cool bath and stirred for 12 hrs. The reaction was cooled to –5 °C and n-butyl isocyanide (91mg, 0.11 mL, 1.1 mmol, 1.1 eq.) was added, the cool bath removed and the reaction stirred for 1 hr before it was quenched with HCl (2M aq., 10 mL) for 6 hrs. The reaction was poured onto H_2O (10 mL), Et_2O (20 mL) was added and the aqueous phase was extracted with Et_2O (2 × 30 mL) before the combined organic phase was washed with $NaHCO_3$ (20 mL) and brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a red oil. The crude product was purified by flash silica chromatography (eluent 20 % Et_2O in petroleum ether 40/60) to give a colourless oil (114 mg, 0.38 mmol, 38 %).

^1H NMR (400 MHz, $CDCl_3$) δ = 9.75 (1H, t, J = 2.5 Hz, H-14), 3.32 (3H, s, H-1 or H-3), 3.31 (3H, s, H-1 or H-3), 3.20 (1H, d, J = 8.8 Hz, H-2a or H-4a), 3.19 (1H, d, J = 8.8 Hz, H-2a or H-4a), 3.17 (1H, d, J = 8.8 Hz, H-2b or H-4b), 3.15 (1H, d, J = 8.8 Hz, H-2b or H-4b), 2.58 (1H, ddd, J = 16.1, 3.8, 2.5 Hz, H-13a), 2.20 (1H, ddd, J = 16.1, 9.3, 2.5 Hz, H-13b), 1.88 (1H, m, H-7), 1.86 (1H, dd, J = 15.3, 7.5 Hz, H-6a or

H-9a), 1.80 (1H, dd, J = 13.1, 7.2 Hz, H-6a or H-9a), 1.55-1.40 (2H, m, H-8 and 10a), 1.09 (1H, dd, J = 15.3, 13.3 Hz, H-6b or H-9b), 1.04 (1H, m, H-10b), 1.01 (1H, dd, J = 13.1, 11.0 Hz, H-6b or H-9b), 0.53 (1H, ddd, J = 14.3, 12.4, 4.5 Hz, H-11a), 0.36 (1H, ddd, J = 14.3, 12.4, 5.0 Hz, H-11b), -0.60 (9H, s, H-12) ppm.

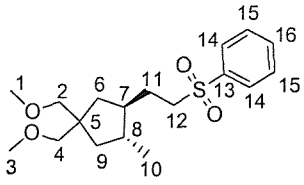
^{13}C NMR (100 MHz, $CDCl_3$) δ = 202.79 (d, C-14), 79.91 (t, C-2 + C-4), 59.35 (q, C-1 or C-3), 59.33 (q, C-1 or C-3), 48.49 (t, C-13), 48.17 (d, C-7), 45.49 (s, C-5), 39.54 (t, C-6 or C-9), 39.25 (d, C-8), 38.56 (t, C-6 or C-9), 27.54 (t, C-10), 14.80 (t, C-11), -1.63 (q, C12) ppm.

IR (neat film): 2951 (m), 2910 (m), 2875 (m), 2824 (m), 1725 (s), 1449 (w), 1389 (w), 1247 (s), 1198 (m), 1106 (s), 861 (s), 833 (s) cm^{-1}.

LRMS (GC-CI): 301 ($M+H^+$, 40 %), 282 (8 %), 266 (16 %), 237 (10 %), 147 (25 %).

HRMS (EI): Found: $M\text{-}MeOH^+$, 268.1859; $C_{15}H_{28}O_2Si$ requires $M\text{-}MeOH^+$, 268.1859.

Preparation of [2-(rac-(1*S*,2*R*)-4,4-Bismethoxymethyl-2-methylcyclopentyl)-ethanesulfonyl]benzene, 240



To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and stirred for 30 min before 4,4-bis-methoxymethyl-hepta-1,6-diene (184 mg, 1.0 mmol, 1.0 eq.) was added and the reaction stirred at room temperature for 3 hrs. The solution was cooled to –78 °C and chloromethylphenylsulphone (763 mg, 4.0 mmol, 4.0 eq.) was added, followed by LDA (4.0 mmol in 4 mL THF) dropwise over 10 min. The reaction was allowed to warm to r.t. with a cool bath and stirred for 12 hrs. The reaction was quenched with MeOH (5 mL) and $NaHCO_3$ (aq, 5 mL) and stirred for 20 hrs. The reaction mixture was poured onto H_2O (10 mL) and Et_2O (30 mL) was added. The

aqueous phase was extracted with Et_2O (2 × 30 mL) before the combined organic phase was washed with brine (20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give a brown oil. The crude product was purified by flash silica chromatography (eluent 40-50 % Et_2O in petroleum ether 40/60) to give a pale yellow oil (228 mg, 0.67 mmol, 67 %).

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.86 (2H, d, J = 7.0 Hz, H-14), 7.60 (1H, t, J = 7.0 Hz, H-16), 7.53 (2H, t, J = 7.0 Hz, H-15), 3.26 (6H, s, H-1 and H-3), 3.1-2.9 (6H, m, H-2, H-4 and H-12), 2.00 (1H, m, H-11a), 1.68 (1H, dd, J = 12.5, 7.0 Hz, H-6a or H-9a), 1.63 (1H, dd, J = 12.5, 6.6 Hz, H-6a or H-9a), 1.5-1.2 (3H, m, H-7, H-8 and H-11b), 0.99 (1H, dd, J = 12.5, 11.0 Hz, H-6b or H-9b), 0.91 (1H, dd, J = 12.5, 10.3 Hz, H-6b or H-9b), 0.87 (3H, d, J = 6.3 Hz, H-10) ppm.

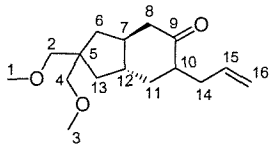
^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.22 (s, C-13), 133.71 (d, C-16), 129.31 (d, C-15), 128.04 (d, C-14), 77.77 (t, C-2 or C-4), 77.73 (t, C-2 or C-4), 59.25 (q, C-1 or C-3), 59.23 (q, C-1 or C-3), 53.38 (t, C-12), 45.27 (d, C-7 or C-8), 45.18 (s, C-5), 41.57 (t, C-6 or C-9), 39.84 (d, C-7 or C-8), 38.81 (t, C-6 or C-9), 26.21 (t, C-11), 17.89 (q, C-10) ppm.

IR (neat film): 2925 (m), 2871 (m), 2824 (m), 1447 (m), 1305 (s), 1199 (w), 1147 (s), 1104 (s), 1087 (s), 915 (m), 730 (s) cm^{-1}.

LRMS (GC-EI): 341 ($M+H^+$, self CI, 1 %), 308 ($M-MeOH^+$, 1 %), 276 ($M-2MeOH^+$, 5 %), 166 ($M-MeOH-HSO_2Ph^+$, 16 %), 134 ($M-2MeOH-HSO_2Ph^+$, 100 %).

HRMS (EI): Found: M^+, 340.1698; $C_{18}H_{28}O_4S$ requires M^+, 340.1708.

Preparation of rac-(3a*S*,7a*R*)-6-Allyl-2,2-bismethoxymethyloctahydroinden-5-one, 253



To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and stirred for 30 min before 4,4-bis-methoxymethyl-hepta-1,6-diene (184 mg, 1.0 mmol, 1.0 eq.) was added and the reaction stirred at room temperature for 4 hrs. The solution was cooled to –90 °C and *Z*-1,4-dichlorobut-2-ene (125 mg, 0.08 mL, 1.0 mmol, 1.0 eq.) was added, followed by LDA (1.0 mmol in 2 mL THF) dropwise over 15 min. The reaction was stirred at –90 °C for 30 min before n-butyl isocyanide (83 mg, 0.11 mL, 1.1 mmol, 1.1 eq.) was added and the reaction allowed to warm to r.t. in the cold bath and stirred for 16 hrs. The reaction was quenched with HCl (8 mL, aq., 2M) for 24 hrs before the mixture was added to H_2O (20 mL) and Et_2O (20 mL) was added. The layers were separated and the aqueous layer extracted with Et_2O (2 × 20 mL). The combined organic phase was washed with NaOH (20 mL, aq., 2.5 M) and brine (2 × 20 mL) before it was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give an orange oil. The crude product was purified by flash silica chromatography (eluent 15-20 % Et_2O in petroleum ether 40/60) to give a colourless oil (25 mg, 0.10 mmol, 10 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ = 5.75 (1H, dddd, J = 16.8, 10.3, 7.5, 6.5 Hz, H-15), 5.01 (1H, dfs, J = 16.8 Hz, H-16a), 4.49 (1H, dfs, J = 10.3 Hz, H-16b), 3.27 (3H, s, H-1 or H-3), 3.26 (3H, s, H-1 or H-3), 3.23 (1H, d, J = 8.8 Hz, H-2a or H-4a), 3.21 (1H, d, J = 8.8 Hz, H-2b or H-4b), 3.20 (1H, d, J = 9.0 Hz, H-2a or H-4a), 3.18 (1H, d, J = 9.0 Hz, H-2b or H-4b), 2.55 (1H, m, H-14a), 2.52 (1H, dd, J = 13.1, 3.8 Hz, H-8a), 2.29 (1H, m, H-10), 2.19 (1H, ddd, J = 11.9, 5.8, 3.0 Hz, H-11a), 2.14 (1H, dd, J = 13.1, 13.1 Hz, H-8b), 2.08 (1H, dt, J = 14.3, 7.5 Hz, H-14b), 1.80 (1H, m, H-12), 1.77 (1H, m, H-13a), 1.71 (1H, dd, J = 12.1, 6.5 Hz, H-6a), 1.63 (1H, m, H-7), 1.18 (1H, dd, J = 12.1, 11.5 Hz, H-6b), 1.08 (1H, dd, J = 11.9, 11.9 Hz, H-11b), 1.03 (1H, dd, J = 11.9, 11.3 Hz, H-13b) ppm.

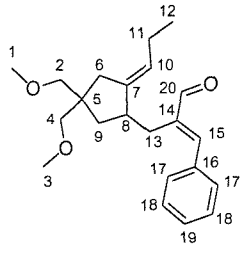
^{13}C NMR (75 MHz, $CDCl_3$) δ = 211.94 (s, C-9), 136.76 (d, C-15), 116.38 (t, C-16), 78.17 (t, C-2 or C-4), 78.10 (t, C-2 or C-4), 59.40 (q, C-1 or C-3), 59.36 (q, C-1 or C-3), 49.04 (d, C-10), 47.48 (s, C-5), 47.39 (t, C-8), 4.68 (d, C-7), 44.30 (d, C-12), 38.39 (t, C-6), 37.57 (t, C-13), 36.00 (t, C-11), 33.75 (t, C-14) ppm.

IR (neat film): 2923 (m), 2871 (m), 2826 (m), 1708 (s), 1450 (m), 1388 (w), 1195 (m), 1105 (s), 913 (m), 733 (m) cm^{-1}.

LRMS (GC-EI): 266 (M^+, 14 %), 222 (20 %), 190 (50 %), 161 (18 %), 145 (65 %).

HRMS (EI): Found: M^+, 266.1882 $C_{16}H_{26}O_3$ requires M^+, 266.1882.

Preparation of (*E*)-2-[4,4-Bismethoxymethyl-2-prop-(*E*)-ylidene-cyclopentylmethyl]-3-phenylpropenal, 259



To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and stirred for 30 min before 4,4-bis-methoxymethyl-non-1-en-6-yne (210 mg, 1.0 mmol, 1.0 eq.) was added and the reaction stirred at room temperature for 4 hrs. The solution was cooled to –78 °C and *E*-β-bromostyrene (200 mg, 0.14 mL, 1.1mmol, 1.1 eq.) was added, followed by LDA (1.1 mmol in 2 mL THF) dropwise over 15 min. The reaction was stirred at –78 °C for 30 min before n-butyl isocyanide (83 mg, 0.11 mL, 1.1 mmol, 1.1 eq.) was added and the reaction allowed to warm to r.t. in the cold bath and stirred for 16 hrs. The reaction was quenched with AcOH (8 mL, 50% in H_2O) for 24 hrs before the mixture was added to H_2O (20 mL) and Et_2O (20 mL) was added. The layers were separated and the aqueous layer extracted with Et_2O (2 × 20 mL). The combined organic phase was washed with NaOH (20 mL, aq., 2.5 M) and brine (2 × 20 mL) before it was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give an orange oil. The crude product was purified by flash silica chromatography

(eluent 25 % Et_2O in petroleum ether 40/60) to give a colourless oil (195 mg, 0.57 mmol, 57 %).

^1H NMR (400 MHz, $CDCl_3$) δ = 9.48 (1H, s, H-20), 7.44 (2H, d, J = 7.5 Hz, H-17), 7.35 (2H, t, J = 7.5 Hz, H-18), 7.30 (1H, t, H-19), 7.17 (1H, brs, H-15), 5.12 (1H, tq, J = 7.0, 2.5 Hz, H-10), 3.20 (3H, s, H-1 or H-3), 3.17 (3H, s, H-1 or H-3), 3.14 (1H, d, J = 8.8 Hz, H-2a or H-4a), 3.10 (1H, d, J = 8.8 Hz, H-2b or H-4b), 3.03 (1H, d, J = 9.0 Hz, H-2a or H-4a), 3.00 (1H, d, J = 9.0 Hz, H-2b or H-4b), 2.76 (1H, dd, J = 12.8, 5.4 Hz, H-13a), 2.65 (1H, m, H-8a), 2.50 (1H, dd, J = 12.8, 9.3 Hz, H-13b), 2.09 (1H, d, J = 16.7 Hz, H-6a), 2.03 (1H, d, J = 16.7 Hz, H-6b), 1.88 (2H, dq, J = 7.5, 7.5 Hz, H-11), 1.57 (1H, dd, J = 12.8, 7.8 Hz, H-9a), 1.00 (1H, dd, J = 12.8, 9.6 Hz, H-9b), 0.83 (3H, t, J = 7.5 Hz, H-12) ppm.

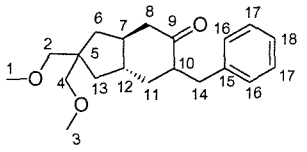
^{13}C NMR (100 MHz, $CDCl_3$) δ = 195.77 (d, C-20), 150.62 (d, C-15), 143.49 (s, C-7 or C-14), 142.29 (s, C-7 or C-14), 135.20 (s, C-16), 129.77 (d, C-17), 129.58 (d, C-19), 128.86 (d, C-18), 123.44 (d, C-10), 77.61 (t, C-2 or C-4), 75.17 (t, C-2 or C-4), 59.33 (q, C-1 or C-3), 59.31 (q, C-1 or C-3), 45.82 (s, C-5), 40.42 (d, C-8), 37.82 (t, C-9), 35.53 (t, C-6), 29.54 (t, C-13), 22.64 (t, C-11), 14.26 (q, C-12) ppm.

IR (neat film): 2959 (m), 2923 (m), 2873 (m), 2826 (m), 1680 (s), 1450 (m), 1374 (w), 1300 (w), 1198 (m), 1106 (s), 963 (m), 911 (m), 732 (s) cm^{-1}.

LRMS (GC-EI): 342 (M^+, 5 %), 324 (M-H_2O^+, 14 %), 279 (79 %), 265 (M-Ph^+, 65 %), 247 (M-Ph-H_2O^+, 82 %).

HRMS (EI): Found: M^+, 342.2192; $C_{22}H_{30}O_3$ requires M^+, 342.2195.

Preparation of rac-(3a*S*,7a*R*)-6-Benzyl-2,2-bis-methoxymethyl-octahydro-inden-5-one



To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and stirred for 30 min before 4,4-bis-methoxymethyl-hepta-1,6-diene (184 mg, 1.0 mmol, 1.0 eq.) was added and the reaction stirred at room temperature for 4 hrs. The solution was cooled to –90 °C and *E*-β-bromostyrene (183 mg, 0.13 mL, 1.0 mmol, 1.0 eq.) was added, followed by LDA (1.0 mmol in 2 mL THF) dropwise over 15 min. The reaction was stirred at –90 °C for 20 min before n-butyl isocyanide (83 mg, 0.11 mL, 1.1 mmol, 1.1 eq.) was added and the reaction allowed to warm to r.t. in the cold bath and stirred for 16 hrs. The reaction was quenched with AcOH (8 mL, 50% in H_2O) for 24 hrs before the mixture was added to H_2O (20 mL) and Et_2O (20 mL) was added. The layers were separated and the aqueous layer extracted with Et_2O (2 × 20 mL). The combined organic phase was washed with NaOH (20 mL, aq., 2.5 M) and brine (2 × 20 mL) before it was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give an orange oil. The crude product was purified by flash silica chromatography (eluent 20 % Et_2O in petroleum ether 40/60) to give two batches further purified by radial chromatography (eluent 15 % Et_2O in petroleum ether 40/60). From ^{1}H NMR analysis of chromatography fractions, cyclohexanone **260** was obtained in 33 % yield in an 11:2 ratio of diastereoisomers. Cycloheptanone **262** was also obtained in 4 % yield.

Main distereoisomer of **260**:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27 (2H, t, J = 7.0 Hz, H-17), 7.18 (1H, t, J = 7.0 Hz, H-18), 7.14 (2H, d, J = 7.0 Hz, H-16), 3.37 (3H, s, H-1 or H-3), 3.36 (3H, s, H-1 or H-3), 3.27 (1H, dd, J = 14.1, 4.5 Hz, H-14a), 3.24-3.15 (4H, m, H-2 + H-4), 2.58 (1H, dd, J = 13.1, 3.4 Hz, H-8a), 2.51 (1H, m, H-10), 2.38 (1H, dd, J = 14.1, 9.0 Hz, H-14b), 2.18 (1H, dd, J = 13.1, 12.8 Hz, H-8b), 2.05 (1H, ddd, J = 12.3, 5.5, 2.8 Hz, H-11a), 1.75-1.60 (4H, m, H-6a, H-7, H-9a + H-12), 1.17 (1H, dd, J = 11.8, 11.8 Hz,

H-6b or H-9b), 1.09 (1H, ddd, J = 12.3, 12.3, 12.3 Hz, H-11b), 1.02 (1H, dd, J = 11.3, 11.3 Hz, H-6b or H-9b) ppm.

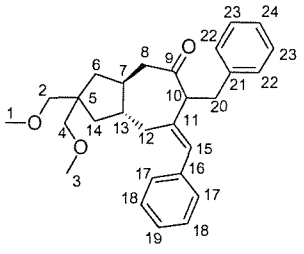
^{13}C NMR (75 MHz, $CDCl_3$) δ = 210.94 (s, C-9), 139.68 (s, C-15), 128.28 (d, C-16), 127.42 (d, C-17), 125.06 (d, C-18), 77.24 (t, C-2 or C-4), 77.19 (t, C-2 or C-4), 58.39 (q, C-1 or C-3), 58.37 (q, C-1 or C-3), 50.39 (d, C-10), 46.54 (s, C-5), 46.47 (t, C-8), 45.86 (d, C-7 or C-12), 43.38 (d, C-7 or C-12), 37.96 (t, C-6 or C-9), 36.55 (t, C-6 or C-9), 35.03 (t, C-11), 34.54 (t, C-14) ppm.

IR (neat film): 2922 (m), 2867 (m), 2835 (m), 1703 (s), 1496 (w), 1476 (w), 1455 (m), 1201 (m), 1099 (s), 1030 (w), 983 (m) cm^{-1}.

LRMS (GC-EI): 316 (M^+, 26 %), 284 (M-$MeOH^+$, 6 %), 239 (M-Ph^+, 8 %), 146 (26 %), 117 (34 %).

HRMS (EI): Found: M^+, 316.2043: $C_{16}H_{26}O_3$ requires M^+, 316.3038.

Preparation of rac-(3a*S*,8a*R*)-6-Benzyl-2,2-bismethoxymethyl-7-[1-phenylmeth-(*E*)-ylidene]octahydroazulen-5-one, 262



To a solution of zirconocene dichloride (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C under argon was added *n*-BuLi (0.80 mL, 2.0 mmol, 2.0 eq.) and stirred for 15 min before 4,4-bis-methoxymethyl-hepta-1,6-diene (184 mg, 1.0 mmol, 1.0 eq.) was added and the reaction stirred at room temperature for 4 hrs. The solution was cooled to –90 °C and *E*-β-bromostyrene (366 mg, 0.26 mL, 2.0 mmol, 2.0 eq.) was added, followed by LDA (2.0 mmol in 4 mL THF) dropwise over 15 min. The reaction was stirred at –90 °C for 1 hr before n-butyl isocyanide (83 mg, 0.11 mL, 1.1 mmol, 1.1 eq.) was added and the reaction allowed to warm to r.t. in the cold bath and stirred for 16 hrs. The reaction was quenched with AcOH (8 mL, 50% in H_2O) for 24 hrs before

the mixture was added to water (20 mL) and Et_2O (20 mL) was added. The layers were separated and the aqueous layer extracted with Et_2O (2 × 20 mL). The combined organic phase was washed with NaOH (20 mL, aq., 2.5 M) and brine (2 × 20 mL) before it was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give an orange oil. The crude product was purified by flash silica chromatography (eluent 25 % Et_2O in petroleum ether 40/60) to give a colourless oil (188 mg, 0.45 mmol, 45 %) as a mixture of two diastereoisomers in a 5:2 ratio by NMR. Further purification by radial chromatography afforded pure samples of each diastereoisomer for separate characterisation.

Diastereoisomer A:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 (2H, t, J = 7.5 Hz, H-18 or H-23), 7.26 (2H, t, J = 7.5 Hz, H-18 or H-23), 7.23-7.16 (2H, m, H-19 + H-24), 7.11 (2H, d, J = 7.5 Hz, H-17 or H-22), 7.00 (2H, d, J = 7.5 Hz, H-17 or H-22), 6.00 (1H, s, H-15), 3.51 (1H, dd, J = 13.6, 5.0 Hz, H-20a), 3.40 (1H, dd, J = 9.5, 5.0 Hz, H-10), 3.34 (3H, s, H-1 or H-3), 3.31 (3H, s, H-1 or H-3), 3.26 (1H, d, J = 9.0 Hz, H-2a or H-4a), 3.23 (1H, d, J = 9.0 Hz, H-2b or H-4b), 3.23 (1H, d, J = 8.5 Hz, H-2a or H-4a), 3.17 (1H, d, J = 8.5 Hz, H-2b or H-4b), 2.78 (1H, d, J = 11.0 Hz, H-12a), 2.73 (1H, dd, J= 13.6, 9.5 Hz, H-20b), 2.59 (1H, dd, J = 12.1, 2.5 Hz, H-8a), 2.52 (1H, dd, J = 12.1, 12.1 Hz, H-8b), 1.90 (1H, m, H-13), 1.88-1.77 (3H, m, H-12b, H-6a + H-14a), 1.67 (1H, m, H-7), 1.22 (1H, dd, J = 24.6, 12.1 Hz, H-6b), 1.15 (1H, dd, J = 13.1, 11.0 Hz, H-14b) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 210.64 (s, C-9), 140.24 (s, C-11), 137.55 (s, C-16 or C-21), 137.33 (s, C-16 or C-21), 131.40 (d, C-15), 129.48 (d, C-17, C-18, C-22 or C-23), 128.64 (d, C-17, C-18, C-22 or C-23), 128.33 (d, C-17, C-18, C-22 or C-23), 128.28 (d, C-17, C-18, C-22 or C-23), 126.69 (d, C-19 or C-24), 126.16 (d, C-19 or C-24), 78.00 (t, C-2 or C-4), 77.80 (t, C-2 or C-4), 63.78 (d, C-10), 59.43 (q, C-1 or C-3), 59.36 (q, C-1 or C-3), 48.69 (t, C-8), 47.81 (d, C-13), 45.33 (s, C-5), 43.12 (d, C-7), 40.61 (t, C-6), 39.90 (t, C-14), 35.76 (t, C-20), 33.43 (t, C-12) ppm.

IR (neat film): 3025 (w), 2923 (m), 2873 (m), 2825 (m), 1698 (s), 1494 (w), 1451 (m), 1199 (m), 1105 (s), 963 (w), 910 (s), 730 (s) cm^{-1}.

LRMS (GC-EI): 418 (M^+, 14 %), 327 (M-CH_2Ph^+, 18 %), 295 (M-MeOH-CH_2Ph^+, 8 %), 263 (M-2MeOH-CH_2Ph^+, 10 %), 129 (44 %).

HRMS (EI): Found: M^+, 418.2514; $C_{28}H_{34}O_3$ requires M^+, 418.2508.

Diastereoisomer B:

^1H NMR (400 MHz, $CDCl_3$) δ = 7.32 (2H, t, J = 7.5 Hz, 7.30-7.15 (6H, m, Ar-H), 7.13 (2H, d, J = 7.5 Hz, H-17 or H-22), 6.45 (1H, s, H-15), 3.73 (1H, t, J = 7.3 Hz, H-10), 3.46 (1H, dd, J = 14.1, 7.3 Hz, H-20a), 3.34 (3H, s, H-1 or H-3), 333 (3H, s, H-1 or H-3), 3.22-3.16 (4H, m, H-2 or H-4), 3.15 (1H, dd, J = 12.2, 3.8 Hz, H-12a), 2.98 (1H, dd, H = 14.1, 7.3 Hz, H-20b), 2.62 (1H, ddd, J = 14.8, 8.8, 8.8 Hz, H-8a), 2.30-2.20 (2H, m, H-8b + H-7), 1.85 (1H, dd, J = 13.3, 2.8 Hz, H-6a or H-14a), 1.83 (1H, dd, J = 13.3, 2.0 Hz, H-6a or H-14a), 1.74 (1H, dd, J = 12.2, 12.2 Hz, H-12b), 1.60 (1H, m, H-13), 1.22 (1H, dd, J = 13.3, 11.3 Hz, H-14b), 1.14 (1H, dd, J = 13.3, 10.8 Hz, H-6b) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 208.72 (s, C-9), 140.65 (s, C-11), 138.05 (s, C-16 or C-21), 137.41 (s, C-16 or C-21), 129.18 (d, C-17, C-18, C-22 or C-23), 128.75 (d, C-17, C-18, C-22 or C-23), 128.40 (d, C-17, C-18, C-22 or C-23), 128.36 (d, C-17, C-18, C-22 or C-23), 128.08 (d, C-15), 126.83 (d, C-19 or C-24), 126.14 (d, C-19 or C-24), 78.05 (t, C-2 or C-4), 78.84 (t, C-2 or C-4), 60.72 (d, C-10), 59.41 (q, C-1 or C-3), 59.39 (q, C-1 or C-3), 47.33 (t, C-8), 47.25 (d, C-13), 44.82 (s, C-5), 41.10 (t, C-6 or C-14), 40.90 (t, C-6 or C-14), 40.36 (d, C-7), 39.77 (t, C-12), 34.54 (t, C-20) ppm.

IR (neat film): 2922 (m), 2876 (m), 2827 (m), 1702 (s), 1495 (w), 1449 (m), 1266 (m), 1199 (m), 1106 (s), 963 (w) cm^{-1}.

LRMS (GC-EI): 418 (M^+, 17 %), 327 (M-CH_2Ph^+, 18 %), 295 (M-MeOH-CH_2Ph^+, 6 %), 263 (M-2MeOH-CH_2Ph^+, 11 %), 129 (42 %).

HRMS (EI): Found: M^+, 418.2516; $C_{28}H_{34}O_3$ requires M^+, 418.2508.

Chapter 7. Appendix and References

7.1 Appendix – X-ray data

University of Southampton · Department of Chemistry

EPSRC National Crystallography Service

Table 1. Crystal data and structure refinement.

Identification code	**03sot121**	
Empirical formula	$C_{18}H_{18}O$	
Formula weight	250.32	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 13.2247(6) Å	α = 90°
	b = 5.24860(10) Å	β = 96.261(2)°
	c = 19.7455(9) Å	γ = 90°
Volume	1362.38(9) Å^3	
Z	4	
Density (calculated)	1.220 Mg / m^3	
Absorption coefficient	0.074 mm^{-1}	
F(000)	536	
Crystal	Rod; colourless	
Crystal size	0.32 × 0.12 × 0.08 mm^3	
θ range for data collection	3.54 – 27.48°	
Index ranges	$-15 \le h \le 17$, $-6 \le k \le 6$, $-25 \le l \le 25$	
Reflections collected	15132	
Independent reflections	3102 [R_{int} = 0.0848]	
Completeness to θ = 27.48°	99.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9941 and 0.9768	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3102 / 0 / 174	
Goodness-of-fit on F^2	1.020	
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0492, $wR2$ = 0.1173	
R indices (all data)	$R1$ = 0.0826, $wR2$ = 0.1334	
Extinction coefficient	0.019(3)	
Largest diff. peak and hole	0.375 and −0.263 e Å^{-3}	

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit* sphere). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Structure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Structure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details:

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

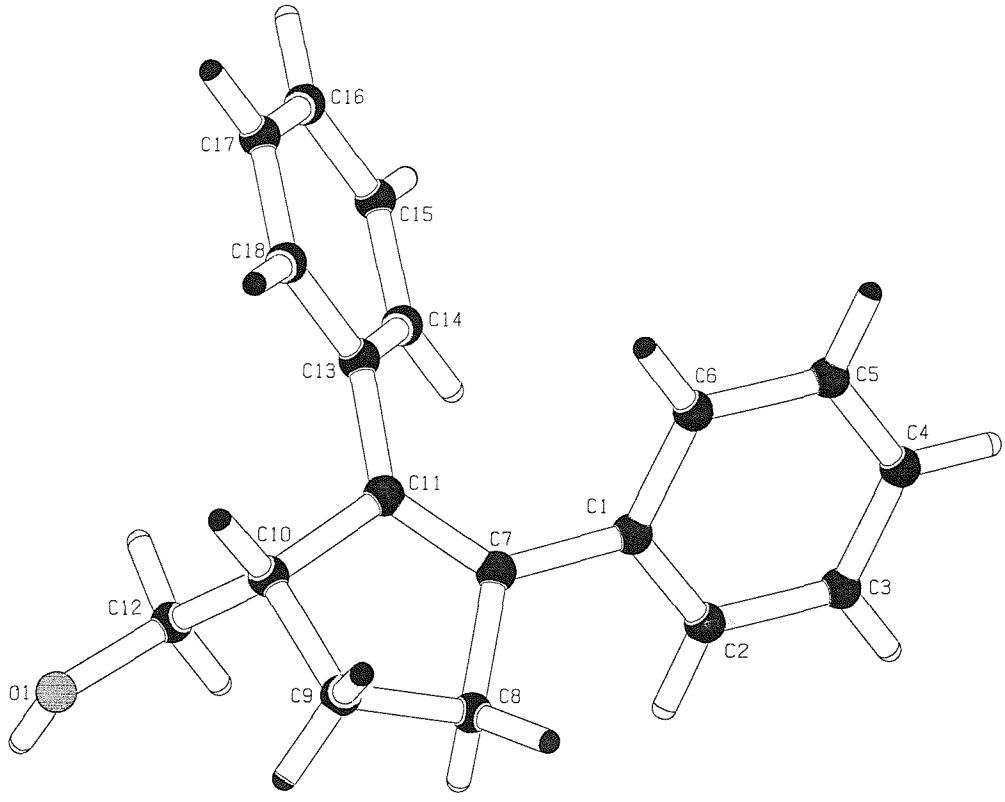
Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	697(1)	8644(3)	1169(1)	21(1)	1
C2	40(1)	6609(3)	998(1)	24(1)	1
C3	−860(1)	6358(3)	1291(1)	25(1)	1
C4	−1127(1)	8151(3)	1752(1)	24(1)	1
C5	−483(1)	10172(3)	1929(1)	24(1)	1
C6	420(1)	10411(3)	1642(1)	22(1)	1
C7	1636(1)	8977(3)	837(1)	21(1)	1
C8	1613(1)	8625(3)	74(1)	30(1)	1
C9	2597(1)	9930(4)	−86(1)	32(1)	1
C10	3304(1)	9744(3)	578(1)	23(1)	1
C11	2571(1)	9603(3)	1118(1)	20(1)	1
C12	3958(1)	7360(3)	614(1)	26(1)	1
C13	2951(1)	9824(3)	1848(1)	20(1)	1
C14	2688(1)	8036(3)	2322(1)	22(1)	1
C15	3075(1)	8207(3)	2999(1)	26(1)	1
C16	3733(1)	10148(3)	3221(1)	28(1)	1
C17	4009(1)	11921(3)	2758(1)	29(1)	1
C18	3626(1)	11753(3)	2078(1)	25(1)	1
O1	4695(1)	7483(2)	138(1)	37(1)	1

Table 3. Bond lengths [Å] and angles [°].

C1–C6	1.393(2)	C10–C11	1.518(2)
C1–C2	1.394(2)	C10–C12	1.519(2)
C1–C7	1.477(2)	C10–H10	1.0000
C2–C3	1.386(2)	C11–C13	1.479(2)
C2–H2	0.9500	C12–O1	1.4271(18)
C3–C4	1.381(2)	C12–H12A	0.9900
C3–H3	0.9500	C12–H12B	0.9900
C4–C5	1.381(2)	C13–C18	1.393(2)
C4–H4	0.9500	C13–C14	1.397(2)
C5–C6	1.383(2)	C14–C15	1.380(2)
C5–H5	0.9500	C14–H14	0.9500
C6–H6	0.9500	C15–C16	1.380(2)
C7–C11	1.339(2)	C15–H15	0.9500
C7–C8	1.514(2)	C16–C17	1.381(2)
C8–C9	1.533(2)	C16–H16	0.9500
C8–H8A	0.9900	C17–C18	1.386(2)
C8–H8B	0.9900	C17–H17	0.9500
C9–C10	1.529(2)	C18–H18	0.9500
C9–H9A	0.9900	O1–H1	0.8400
C9–H9B	0.9900		
C6–C1–C2	118.04(13)	C11–C10–C9	103.14(12)
C6–C1–C7	120.91(13)	C12–C10–C9	112.56(13)
C2–C1–C7	120.99(13)	C11–C10–H10	110.5
C3–C2–C1	120.81(14)	C12–C10–H10	110.5
C3–C2–H2	119.6	C9–C10–H10	110.5
C1–C2–H2	119.6	C7–C11–C13	128.56(13)
C4–C3–C2	120.23(15)	C7–C11–C10	110.68(12)
C4–C3–H3	119.9	C13–C11–C10	120.28(12)
C2–C3–H3	119.9	O1–C12–C10	111.04(12)
C3–C4–C5	119.67(14)	O1–C12–H12A	109.4
C3–C4–H4	120.2	C10–C12–H12A	109.4
C5–C4–H4	120.2	O1–C12–H12B	109.4
C4–C5–C6	120.13(14)	C10–C12–H12B	109.4
C4–C5–H5	119.9	H12A–C12–H12B	108.0
C6–C5–H5	119.9	C18–C13–C14	117.82(13)
C5–C6–C1	121.11(14)	C18–C13–C11	120.89(13)
C5–C6–H6	119.4	C14–C13–C11	121.21(13)
C1–C6–H6	119.4	C15–C14–C13	120.87(14)
C11–C7–C1	128.94(13)	C15–C14–H14	119.6
C11–C7–C8	111.02(13)	C13–C14–H14	119.6
C1–C7–C8	120.03(13)	C14–C15–C16	120.63(14)
C7–C8–C9	103.06(13)	C14–C15–H15	119.7
C7–C8–H8A	111.2	C16–C15–H15	119.7
C9–C8–H8A	111.2	C15–C16–C17	119.35(15)
C7–C8–H8B	111.2	C15–C16–H16	120.3
C9–C8–H8B	111.2	C17–C16–H16	120.3
H8A–C8–H8B	109.1	C16–C17–C18	120.24(15)
C10–C9–C8	104.30(12)	C16–C17–H17	119.9
C10–C9–H9A	110.9	C18–C17–H17	119.9
C8–C9–H9A	110.9	C17–C18–C13	121.07(14)
C10–C9–H9B	110.9	C17–C18–H18	119.5
C8–C9–H9B	110.9	C13–C18–H18	119.5
H9A–C9–H9B	108.9	C12–O1–H1	109.5
C11–C10–C12	109.38(12)		

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	21(1)	22(1)	18(1)	2(1)	0(1)	4(1)
C2	28(1)	23(1)	21(1)	−3(1)	1(1)	3(1)
C3	29(1)	23(1)	24(1)	1(1)	0(1)	−3(1)
C4	21(1)	27(1)	24(1)	4(1)	2(1)	0(1)
C5	24(1)	24(1)	24(1)	−2(1)	4(1)	3(1)
C6	22(1)	21(1)	23(1)	0(1)	0(1)	1(1)
C7	23(1)	21(1)	19(1)	0(1)	3(1)	4(1)
C8	29(1)	40(1)	20(1)	−1(1)	2(1)	5(1)
C9	32(1)	43(1)	23(1)	6(1)	7(1)	6(1)
C10	24(1)	23(1)	22(1)	2(1)	7(1)	1(1)
C11	24(1)	17(1)	20(1)	1(1)	4(1)	4(1)
C12	25(1)	27(1)	28(1)	0(1)	10(1)	3(1)
C13	17(1)	22(1)	21(1)	−1(1)	4(1)	4(1)
C14	20(1)	24(1)	23(1)	0(1)	3(1)	−1(1)
C15	24(1)	30(1)	23(1)	4(1)	5(1)	0(1)
C16	25(1)	36(1)	21(1)	−2(1)	−1(1)	2(1)
C17	27(1)	29(1)	31(1)	−4(1)	0(1)	−5(1)
C18	26(1)	23(1)	26(1)	1(1)	3(1)	−2(1)
O1	36(1)	37(1)	42(1)	−1(1)	24(1)	9(1)



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16. MMFF. The Merck Molecular Force Field. A molecular mechanics model.
17. PM3. Parameterization Method 3. A semi-empirical molecular orbital method. So named as considerd the third version of the MNDO (modified neglect of differential overlap) method (AM1 is the second). PM3(tm). A semi-empirical method for transition metals to be used in conjunction with the PM3 method.
18. Density Functional. A class of methods in which the energy is written as a function of the electron density. Many electron effects (Electron Correlation) are taken into account explicitly by incorporating into the Hamiltonian terms which derive from exact solutions of "idealized" many electron systems.
19. B3LYP: uses Becke's exchange functional with the LYP gradient-corrected correlation functional of Lee, Yang and Parr (Becke, A. D.; *J. Chem. Phys.*, **1993**, *98*, 5648 and Lee, C.; Yang, W; Parr, R. G.; *Phys. Rev. B*, **1988**, *37*, 785).
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