UNIVERSITY OF SOUTHAMPTON

FACULTY OF ENGINEERING, SCIENCE & MATHEMATICS

School of Chemistry

Carbenoid Insertions and Cyclometallations of Zirconacycles

By Louise Daisy Norman

Thesis for the degree of Doctor of Philosophy

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ABSTRACT

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CARBENOID INSERTIONS AND CYCLOMETALLATIONS OF ZIRCONACYCLES

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The synthesis of zirconacycles and further elaborations to produce a wide variety of carbocyclic and heterocyclic systems is well established. This thesis focuses on the insertion of chloro(aryl)methyllithiums (benzyl carbenoids) into a range of zirconacyclopentenes and zirconacyclopentanes.

Benzyl carbenoid insertion into a zirconacyclopentene generated the zirconacyclohexene *via* a 1,2-metalate rearrangement. A low temperature quench afforded the expected benzyl inserted product. Quenching at higher temperatures afforded a styrene containing product. It was proposed that the styrene product was formed *via* a novel endocyclic cyclometallation to afford a zirconocene η^2-alkene complex followed by decomplexation. A wide variety of zirconacyclopentenes and benzyl carbenoids have been investigated.

A range of benzyl carbenoids were inserted into a zirconacyclopentane to afford the expected benzyl inserted product. Double benzyl carbenoid insertion was also observed and afforded a mono-alkene product. It was speculated that the bis-inserted products were formed *via* a zirconacycloheptane followed by a novel endocyclic cyclometallation.

Having shown that zirconacyclohexenes underwent an endocyclic cyclometallation to afford a zirconocene η^2-alkene complex, the concept of intramolecular trapping of the zirconocene η^2-alkene complex, to generated bicyclic compounds, was investigated.

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Declaration

This thesis is based solely on the work carried out by the author whilst registered for the degree of Doctor of Philosophy in the School of Chemistry at the University of Southampton, except where specific citations of literature examples are indicated. All computational modelling reported in this thesis was carried out by Prof. R. J. Whitby

Acknowledgements

First of all I would like to thank my supervisor Richard for all his help, encouragement and for the constant ideas. To the members of the Whitby group, Fra, Joe, Alan and Sally I would like to say thank you for helping me survive this process. I would like to say a special thank you to Sally for the endless discussions and encouragement. I would like to say thank you to all the members of lab 3003 for making the experience such good fun. To Iain and Ian I would like to thank you for ensuring there was never a dull moment in the lab and for being so supportive.

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List of Abbreviations

Techniques

EI	Electron Impact Ionisation
ES	Electrospray
GC	Gas Chromatography
GCMS	Gas Chromatography Mass Spectrometry
HRMS	High Resolution Mass Spectrometry
IR	Infra-Red Spectroscopy
LRMS	Low Resolution Mass Spectrometry
NMR	Nuclear Magnetic Resonance

Reagents

BnOH	Benzyl alcohol
$BnNH_2$	Benzyl amine
BnCl	Benzyl chloride
n-BuLi	*n*-Butyllithium
sec-BuLi	*sec*-Butyllithium
DIBAL-H	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DMSO	Dimethyl sulfoxide
EtOH	Ethanol
HMPA	Hexamethylphosphoroamide
LDA	Lithium diisopropylamide
LiTMP	Lithium 2,2,6,6-tetramethylpiperidide
MsCl	Methanesulfonyl chloride
THF	Tetrahydrofuran
TMEDA	*N*,*N*,*N*,*N*-Tetramethylethylenediamine
p-TsOH	*para*-Toluenesulfonic acid
TMS	Trimethylsilyl
TMSCl	Trimethylsilyl chloride

Chemical Groups

Ar	Aryl
Bu	Butyl
Bn	Benzyl
BOC	*tert*-Butyloxycarbonyl
Cp	Cyclopentadienyl
Et	Ethyl
Hex	Hexyl
LG	Leaving Group
Me	Methyl
Ms	Methanesulfonyl
Np	1-Napthyl
Nu	Nucleophile
Oct	Octyl
Ph	Phenyl
Pr	Propyl

Others

aq.	Aqueous
°C	Degrees Celsius
eq	Equivalent(s)
h	Hour(s)
min	Minute(s)
m/z	Mass Charge Ratio
rt	Room Temperature

1 Introduction

1.1 Overview

The results described in this thesis focus on the insertion of chloro(aryl)methyllithiums (benzyl carbenoids) into zirconacycles. Work carried out by Fillery,[1] within the Whitby group, demonstrated that benzyl carbenoids can be successfully inserted into zirconacycles. Chapter 1 gives a brief description of the formation of carbenoids, zirconacycles and elaboration of zirconacycles by inserting carbenoids. A more detailed discussion of benzyl carbenoids and previous work investigating their insertion into zirconacycles is described. The aim of the research was to extend the methodology and to gain a greater mechanistic understanding of the relevant reactions. The results of these investigations are reported in Chapters 2-4.

1.2 Background

Organozirconium chemistry has now been under investigation for over 50 years. The birth of organozirconium chemistry can be defined by the preparation of the first well characterised organozirconium compound, zirconocene dibromide ($ZrCp_2Br_2$) by Wilkinson and Birmingham in 1954.[2] This discovery was of great significance to organozirconium chemistry as around 70-80% of the known organozirconium compounds are zirconocene derivatives.[3]

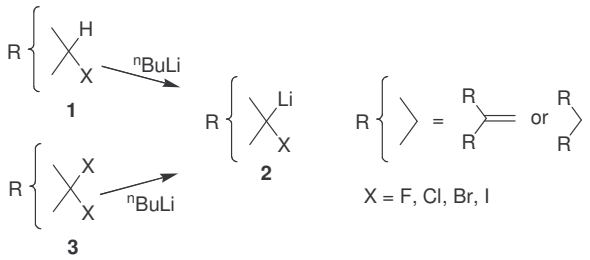
There are several favourable properties which make zirconium of interest in organic chemistry. Zirconium occurs in the lithosphere to the extent of 0.022% and therefore is roughly as abundant as carbon. It is one of the least expensive transition metals and does not appear to be associated with acute or severe toxicity.[3]

The chemistry of zirconocene complexes is dominated by the usual 16 electron configuration. The empty orbital remaining is not very Lewis acidic and therefore not filled by Lewis base coordination.[4] The oxidation state is normally +4, though a few +2 complexes are known.

1.3 Carbenoids

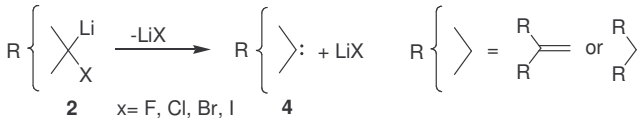
The term carbenoid was first used by Closs and Moss to describe an intermediate which exhibited properties similar to those of carbenes.[5] A carbenoid is a species which contains a metal atom (M) (or lone pair if ionised) and a leaving group (X) on the same carbon. (R'R''CMX). This section focuses on lithium halocarbons (R'R''CLiX) (hereafter referred to as carbenoids).

There are two main methods for forming carbenoids **2** (**Scheme 1**).[6-8] The easiest method is *via* deprotonation of the corresponding halogenated hydrocarbon **1** with a base.[6, 7] The optimum temperature for formation of the carbenoid **2** is between –120 and –70 °C. The temperature range is limited at the lower end by the rate of deprotonation and at the upper end by the rate of decomposition of the carbenoid. This is a major limitation of the method and many substrates will not deprotonate at the low temperatures required for stability of the carbenoid. The second method is halogen-metal exchange of the gem-dihalogen-compound **3**.[6, 7] Halogen-metal exchange is a very fast process, even at low temperatures and therefore can often be used to make carbenoids that cannot be synthesised *via* the deprotonation method. However, one limitation of this method is competing side reactions such as α-metallation.



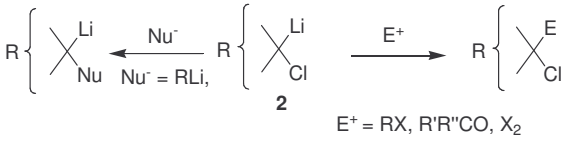
Scheme 1: Formation of carbenoids.

Carbenoids **2** are extremely thermally sensitive species. There are several pathways by which they can decompose. One important pathway is α-elimination to generate the carbene **4** (**Scheme 2**).[6]



Scheme 2: Decomposition of carbenoids to generate carbenes.

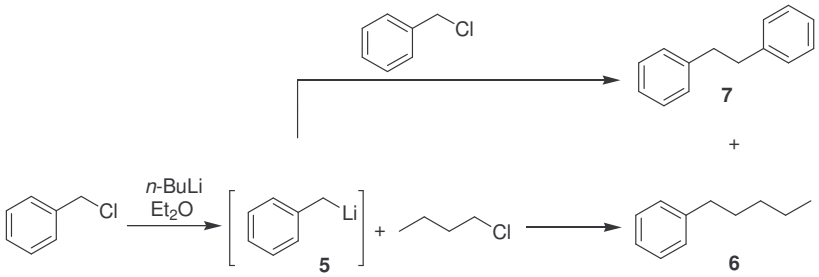
Carbenoids **2** can be described as being amphiphilic, meaning they have both nucleophilic and electrophilic properties. Nucleophilic reactions of carbenoids include alkylations, acylations and halogenations.[6-8] Electrophilic reactions of carbenoids include reactions with alkyl metals (**Scheme 3**).[6, 7, 9]



Scheme 3: Nucleophilic and electrophilic reactions of carbenoids.

1.4 Benzyl carbenoids

The reaction of benzyl chloride with *n*-BuLi is well known and is the basis for the extensively used Gilman-Haubein 'double titration' method for quantitative analysis of *n*-BuLi.[10] Gilman and Haubein suggested that the reaction proceeded *via* halogen-lithium exchange to form benzyllithium **5**, which was rapidly consumed in subsequent cross-coupling reactions to give a mixture of bibenzyl **7** and pentylbenzene **6** (**Scheme 4**).

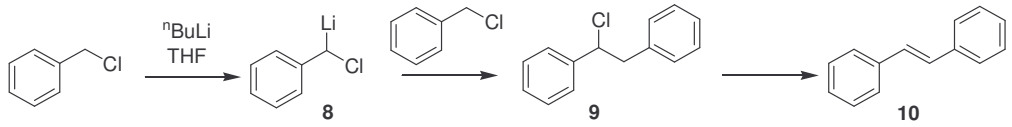


Scheme 4: Gilman-Haubein 'double titration' method for quantitative analysis of *n*-BuLi.

Evidence for the benzyllithium **5** as the intermediate was provided by the observed yellow colour, characteristic of benzyllithium and the production of phenylacetic acid when the intermediate was treated with solid carbon dioxide.[10]

Hoeg *et al.* also observed *trans*-stilbene **10**, in 20% yield, when the reaction was carried out in THF rather than diethyl ether.[11] The formation of the *trans*-stilbene **10** suggested that an alternative intermediate had formed, as **10** is unlikely to be produced from the benzyllithium intermediate.

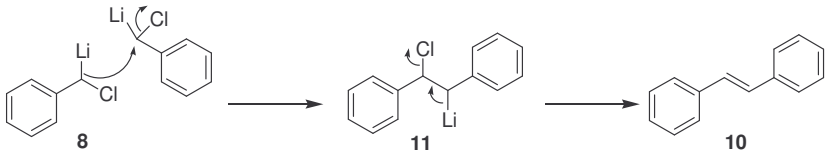
Hoeg *et al.* suggested that the mechanism was *via* α-metallation to give benzyl chloride **8**. Subsequent reaction of the benzyl carbenoid **8** with benzyl chloride gave the α-chlorobibenzyl **9** which under-went a thermal dehydrochlorination to give the *trans*-stilbene **10** (**Scheme 5**).[11]



Scheme 5: Formation of benzyl carbenoid and subsequent reaction with benzyl chloride to form *trans*-stilbene.

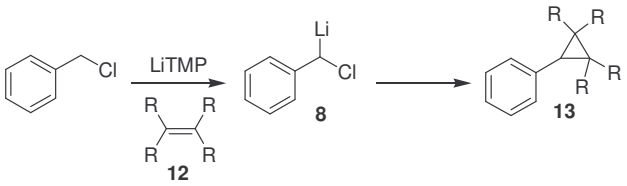
It was reported that this reaction was solvent dependant and *trans*-stilbene **10** was only observed when the reaction was carried out in THF. The yields of **10** were increased as the reaction temperature was reduced. An 80% yield is obtained when 2 equivalents of benzyl chloride and 1 equivalent of *n*-BuLi is used at –100 °C. Attempts to methylate the benzyl carbenoid after formation proved unsuccessful even at –100 °C, suggesting that the benzyl carbenoid **8** is a highly unstable species.[11]

Since carbenoids are much more electrophilic than the parent halide due to 'metal assisted ionisation',[12] it seems likely that carbenoid dimerisation to afford **11** followed by fast elimination of LiCl is occurring, to give *trans*-stilbene **10** (**Scheme 6**).



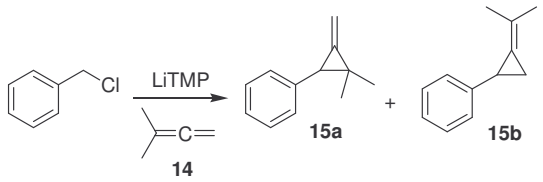
Scheme 6: Benzyl carbenoid dimerisation.

Benzyl carbenoid **8** has been used in the synthesis of arylcyclopropanes **13** (**Scheme 7**). The first published procedure was the reaction of benzyl chloride with *n*-BuLi in cyclohexene, which gave phenylnorcarane in a low 14% yield.[13] Improvements in the yield were observed when LiTMP was used as the base. A large range of alkenes **12** have been successfully trapped by benzyl carbenoids **8** to yield arylcyclopropanes **13** (50-87% yield).[14]



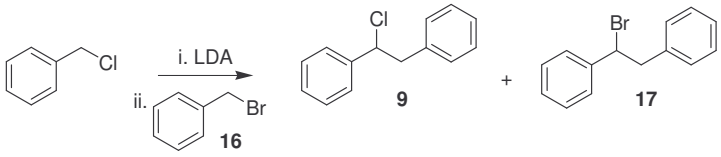
Scheme 7: Synthesis arylcyclopropanes *via* benzyl carbenoids.

The methodology was extended by trapping allene **14** with benzyl carbenoids to give arylmethylenecyclopropanes **15** (**Scheme 8**).[15]



Scheme 8: Synthesis of arylmethylenecyclopropanes.

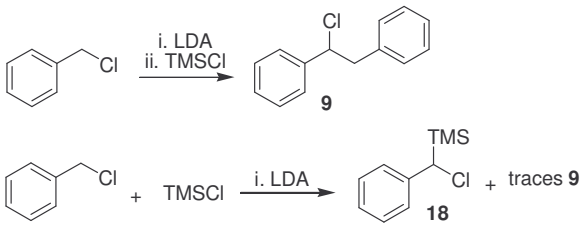
The *in situ* trapping of benzyl carbenoid **8** was investigated by Wenkert *et al.*[16] Benzyl chloride was treated with 1 equivalent of LDA at –78 °C, followed by the addition of benzyl bromide **16**. A mixture of α-chlorobiphenyl **9** and α-bromobiphenyl **17** was produced (**Scheme 9**).



Scheme 9: Self condensation of benzyl carbenoids.

Generation of the α-bromobiphenyl **17** can only occur if the deprotonation of the benzyl chloride was incomplete. Wenkert *et al.* suggested the rate of alkylation of the benzyl carbenoid was greater than the rate of deprotonation of the benzyl chloride, resulting in complete consumption of the benzyl chloride before complete α-metallation could be achieved. The benzyl bromide **16** added to the reaction mixture was α-metallated using the remaining LDA to give bromo(phenyl)methyllithium. Bromomethylphenyllithium was rapidly alkylated with the remaining benzyl bromide to give α-bromobiphenyl **17**.

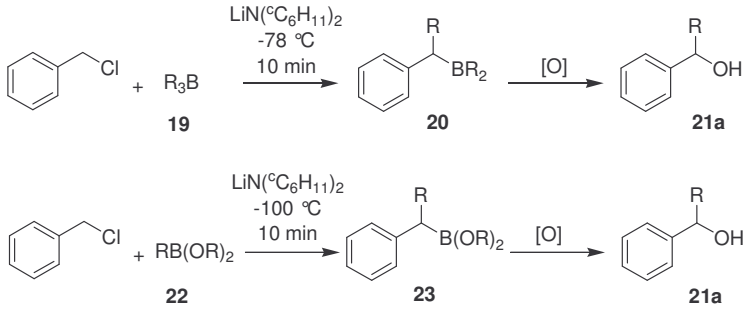
Brandsma *et al.* attempted to trap the preformed carbenoid with trimethylsilyl chloride at –100 °C, however, only the self condensation product **9** was observed (**Scheme 10**).[17]



Scheme 10: Trapping benzyl carbenoid with TMSCl.

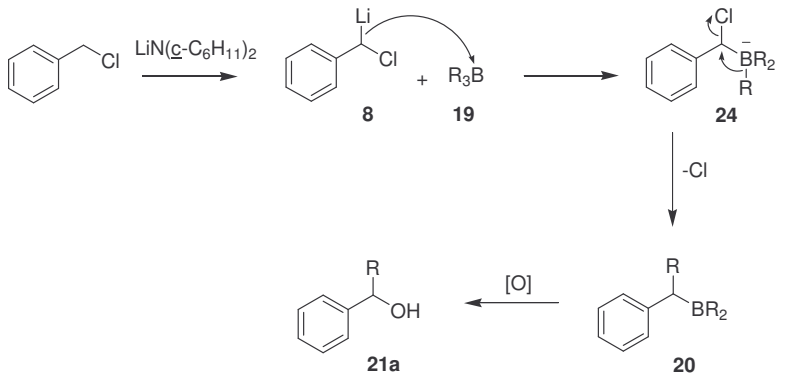
Brandsma *et al.* overcame this by adding the trimethylsilyl chloride to the benzyl chloride prior to the very slow addition of LDA at –100 °C, which gave the desired product **18** in 84% yield. Even under these conditions traces of the self condensed product **9** was observed (**Scheme 10**).

Kabalka *et al.* reported the *in situ* reaction of benzyl carbenoids with trialkylboranes **19** and alkylboronic esters **22** to give the alkylarylcarbinols **21a** in very good yield after oxidation (**Scheme 11**).[18] It was reported that the highest yields were obtained when lithium dicyclohexylamide was used as the base. For trialkylboranes **19** the optimum reaction temperature was –78 °C, whereas, for alkylboronic ester **22** the optimum reaction temperature was –100 °C.



Scheme 11: Insertion of benzyl carbenoids into trialkylboranes and alkylboronic esters.

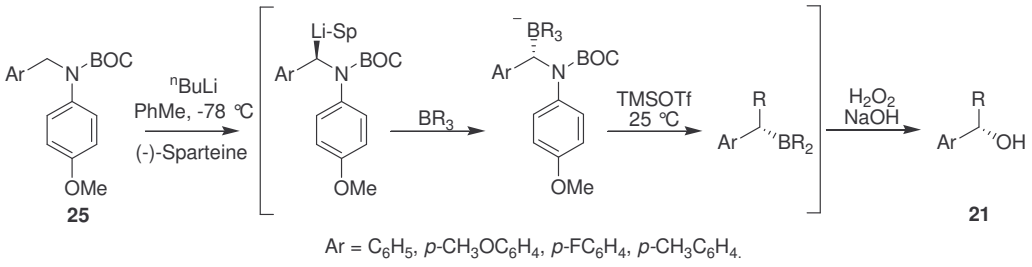
Deprotonation of the benzyl chloride generated the benzyl carbenoid **8**. The carbenoid reacts with the trialkylborane **19** to form a borate complex **24** that gives a new trialkylborane **20** *via* a 1,2-metalate rearrangement (**Scheme 12**).



Scheme 12: Mechanism of benzyl carbenoid insertion into trialkylboranes.

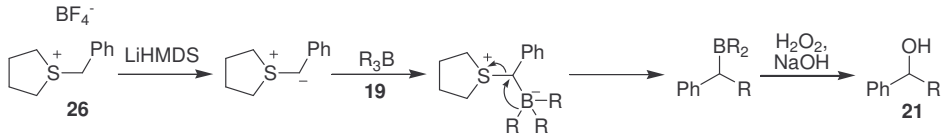
This method has been successfully applied to a wide range of trialkylboranes and alkylboronic esters and extended to included substituted benzyl chlorides. Benzyl carbenoids with *para*-methyl, methoxy and chloro substituents have all successfully inserted into trialkylboranes. Significantly lower yields were observed when benzyl bromide was used as the carbenoid precursor, which was attributed to the more facile formation and greater stability of the lithium chloro-carbenoid compared to the lithium bromo-carbenoids.

In a related publication, Aggarwal *et al.* reported the asymmetric lithiation of substituted benzylamines **25** and subsequent insertion into trialkylboranes, which after oxidation, gave the chiral secondary alcohols **21** with high enantioselectivity (**Scheme 13**).[19]



Scheme 13: Insertion of lithiated benzyl amines into trialkylboranes.

Aggarwal *et al.* has also reported the reaction of benzyl sulfonium salt **26** and trialkylboranes **19**, which after oxidation gave the secondary alcohol **21** in excellent yield (**Scheme 14**).[20]

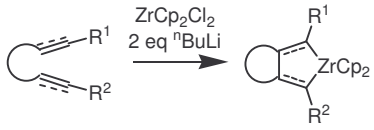


Scheme 14: Insertion of sulfonium ylides into trialkylboranes.

Chiral sulfonium salts have also been successfully reacted with trialkylboranes to generate chiral organoboranes, which after quenching with either H_2O_2 and NaOH or NH_2OSO_3H afforded the chiral secondary alcohol or amine in high enantioselectivity.[19]

1.5 Synthesis of zirconacycles

The main method employed to synthesise zirconacycles is the co-cyclisation of dienes, enynes and diynes[21, 22] using a '$ZrCp_2$' equivalent (**Scheme 15**).[3] Negishi *et al.* published the first co-cyclisation of an enyne with a '$ZrCp_2$' equivalent generated by reducing $ZrCp_2Cl_2$ with a magnesium amalgam.[23] In view of the low chemoselectivity of the magnesium and the toxicity of the mercury this method has largely been replaced with a '$ZrCp_2$' equivalent formed *in situ* by treating $ZrCp_2Cl_2$ with 2 equivalents of *n*-BuLi.[24]



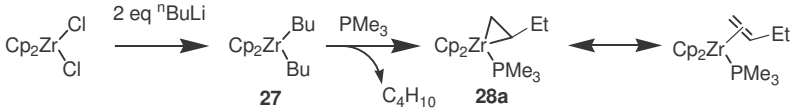
Scheme 15: Co-cyclisation using Negishi's reagent.

Examination of the reaction of $ZrCp_2Cl_2$ with *n*-BuLi by ^1H NMR at –78 °C revealed the disappearance of a cyclopentadienyl (Cp) singlet at δ_H 6.61 ppm corresponding to $ZrCp_2Cl_2$ and the appearance of a Cp singlet at δ_H 6.18 ppm, which indicated complete conversion to $ZrCp_2Bu_2$ (Negishi's reagent) **27**. Treatment of **27** with 2 equivalents of I_2, gave ^{n}Bu-I (ca. 2 equivalents) and $ZrCp_2I_2$ (ca. 1 eq) providing additional evidence of the formation of $ZrCp_2Bu_2$.[24]

Attempts to identify the actual '$ZrCp_2$' reactive species were carried out by treating $ZrCp_2Bu_2$ with two equivalents of $PMePh_2$. Negishi *et al.* suggested that the complex

formed was $Cp_2Zr(PMePh_2)_2$. Assignment was based on the presence of a triplet in the ^1H NMR spectra corresponding to the two Cp groups.[24]

However, Buchwald *et al.* reported that the treatment of $ZrCp_2Bu_2$ with 2 equivalents of PMe_3 led to the formation of Cp_2Zr(1-butene)(PMe_3) **28a** (**Scheme 16**).[25]



Scheme 16: Formation of Cp_2Zr(1-butene)(PMe_3).

Re-examination by Negishi *et al.* revealed the apparent triplet was not due to the presence of two $PMePh_2$ groups but had resulted from the chirality of the 1,2-butylidene moiety which caused the two Cp groups to be non-equivalent. Negishi *et al.* repeated the reaction of $ZrCp_2Bu_2$ with 2 equivalents of PMe_3 and proposed that the correct structures were **28b** and **28a** in a 90:10 mixture (**Figure 1**).[21] It is proposed that the dibutylzirconocene ($ZrCp_2Bu_2$) undergoes a concerted non-dissociative process to give zirconocene(1-butene) **29** as the '$ZrCp_2$' equivalent on warming (**Scheme 17**). Free '$ZrCp_2$' is believed to be too unstable to be a true intermediate.

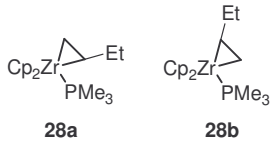
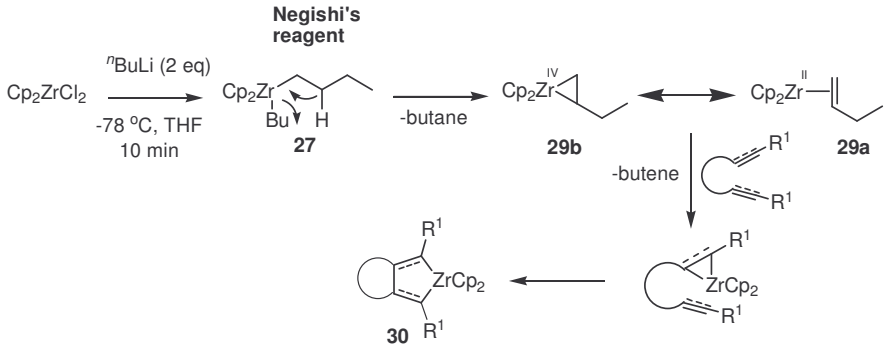


Figure 1: Isomers of $Cp_2ZrBu(PMe_3)$.

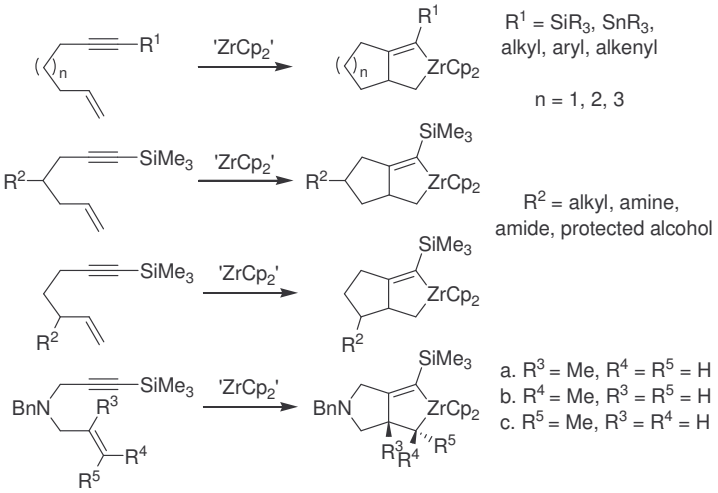
Zirconocene(1-butene) **29** can either be viewed as Cp_2Zr(II) **29a** or a Cp_2Zr(IV) **29b** species. The butene ligand is weakly bound to the zirconocene and can readily be replaced by an alkyne or alkene from the co-cyclisation substrate, followed by a concerted carbometallation to afford the zirconacycle **30** (**Scheme 17**).



Scheme 17: Zirconocene promoted intramolecular co-cyclisation using Negishi's reagent.

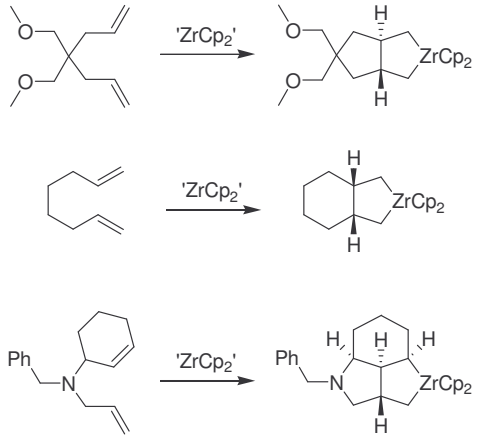
The method of zirconocene promoted intramolecular co-cyclisation has proven to be very successful and can be applied to a wide variety of diynes, enynes and dienes. The method has also been extensively applied to the synthesis of complex natural products.[26-30]

Diyne cyclisation successfully affords 4- to 8-membered fused rings.[21, 22] Enyne co-cyclisation successfully affords 5- to 8-membered fused rings (**Scheme 18**).[3, 21, 31-33] Several successful examples with ring substitutions such as alkyl,[21] protected alcohol,[32, 33] amines[32] and amides[32] are present in the literature. Examples using substrates containing substituted alkenes are known.[21] Nitrogen containing enynes with substituted alkenes are often successful, although the corresponding all carbon enynes fail to cyclise. Although terminal alkynes are incompatible with this method of zirconium promoted cyclisation, several terminally substituted alkyne derivatives, such as silicon, tin, alkyl, aryl and alkenyl, have been successfully cyclised.[21]



Scheme 18: Examples of zirconium promoted enyne co-cyclisation.

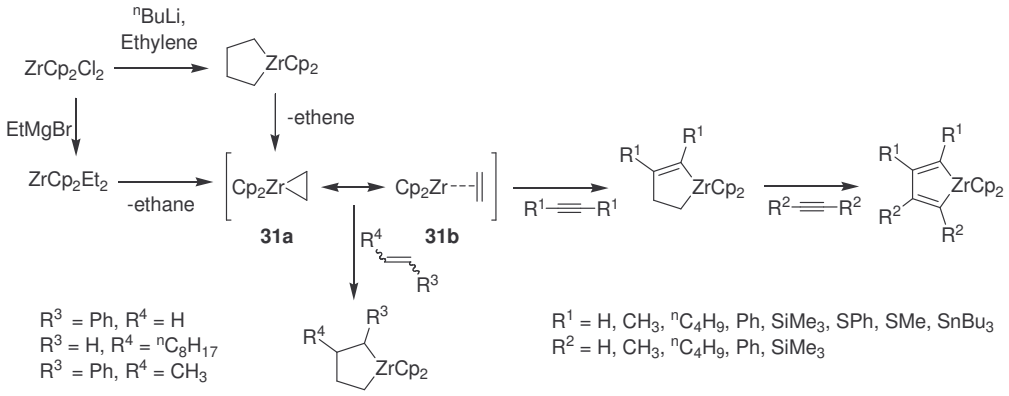
Diene co-cyclisation successfully affords 5- and 6-membered fused ring (**Scheme 19**).[34] 1,6-Heptadienes co-cyclise to give the *trans*-ring junction, whereas 1,7-octadienes co-cyclise to give the *cis*-ring junction as the kinetic product, though heating isomerises this to give the more stable *trans*-ring junction.[34] Examples of substrates containing substituted alkenes are known, however tri- and tetrasubstituted alkenes are usually not successful.[35-37] Instead of co-cyclisation, heavily substituted dienes may undergo a double bond migration to produce a conjugated diene-zirconocene complex when treated with '$ZrCp_2$'.[35] Diene co-cyclisation of substrates with ring substituents such as acetals, protected alcohols, and alkyl groups has been reported in the literature.[36, 37] Dienes with nitrogen or silicon in the chain are also known.[36, 37]



Scheme 19: Examples of zirconium promoted diene co-cyclisation.

1.6 Synthesis of monocyclic zirconacycles

The most convenient method of generating monocyclic zirconacycles is by the co-cyclisation of ethylene zirconocene **31** with either an alkyne or alkene (**Scheme 20**).[38] Ethylene zirconocene **31** can be generated by treating $ZrCp_2Cl_2$ with EtMgBr.[39] Alternatively when zirconocene(1-butene) **29** is synthesised under an atmosphere of ethylene gas zirconacyclopentane is generated which reversibly eliminates ethene to give ethylene zirconocene **31**.[40]



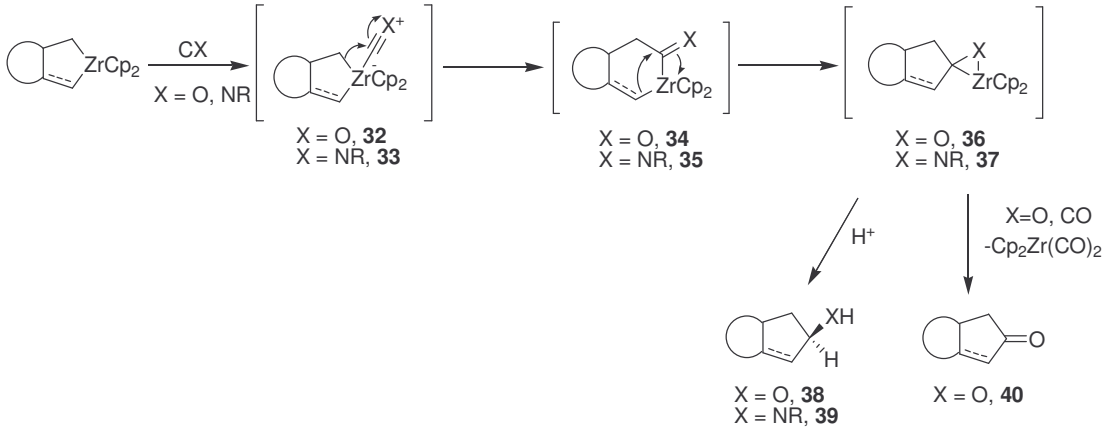
Scheme 20: Formation of monocyclic zirconacycles using ethylene zirconocene.

1.7 Elaboration of zirconacycles

There are several ways in which zirconacycles can be elaborated. These include protonation,[23] halogenolysis,[41] transmetallation,[42] metathesis to main group elements[43] and insertion of carbon monoxide, isonitriles and carbenoids.[44]

1.7.1 Carbonylation and isonitrile insertions into zirconacycles

The zirconium centre of a zirconacycle is electronically unsaturated (16 e^-) so can accept an electron pair from a donor. Carbenic species such as carbon monoxide[3, 24, 34, 44] and isonitriles readily insert (**Scheme 21**).[44, 45]

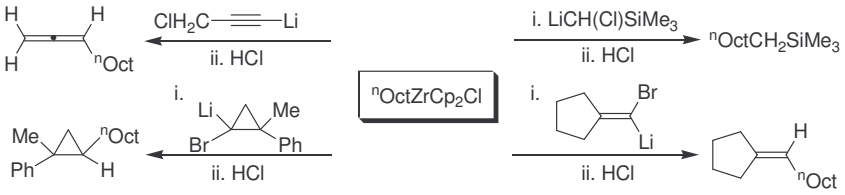


Scheme 21: Carbonylation and isonitriles insertion into zirconacycles

In carbonylation and isonitrile insertion, initial attack on the 16-electron zirconium centre produces an 18-electron complex **32** and **33**. In the case of carbonylation, a rearrangement occurs to give the acyl complex **34** which rapidly rearranges to give the η^2-ketone complex **36**. The η^2-ketone complex of zirconacyclopentanes is stable and protonation affords the alcohol **38**. When zirconacyclopentanes and pentenes are subject to prolonged exposure to carbon monoxide, the cyclic ketone **40** was generated.[24, 34, 44] In the case of isonitrile insertion, a rearrangement occurs to give the iminoacyl complex **35**, which slowly rearranges to give the η^2-imine complex **37**. Protonation of the η^2-imine complex affords the amine **39**.[44, 45]

1.7.2 Carbenoid insertion into zirconacycles

Carbenoids have similar electronic properties to carbon monoxide and isonitriles and therefore are expected to readily insert into organozirconium species. The first publication in this field was by Negishi *et al.* and involved the insertion of α- and γ-haloorganolithiums into acyclic organozirconocene derivates (**Scheme 22**).[46] Carbenoid insertion into zirconacycles has been extensively investigated by Whitby *et al.* and these will now be detailed throughout the following section.[44]

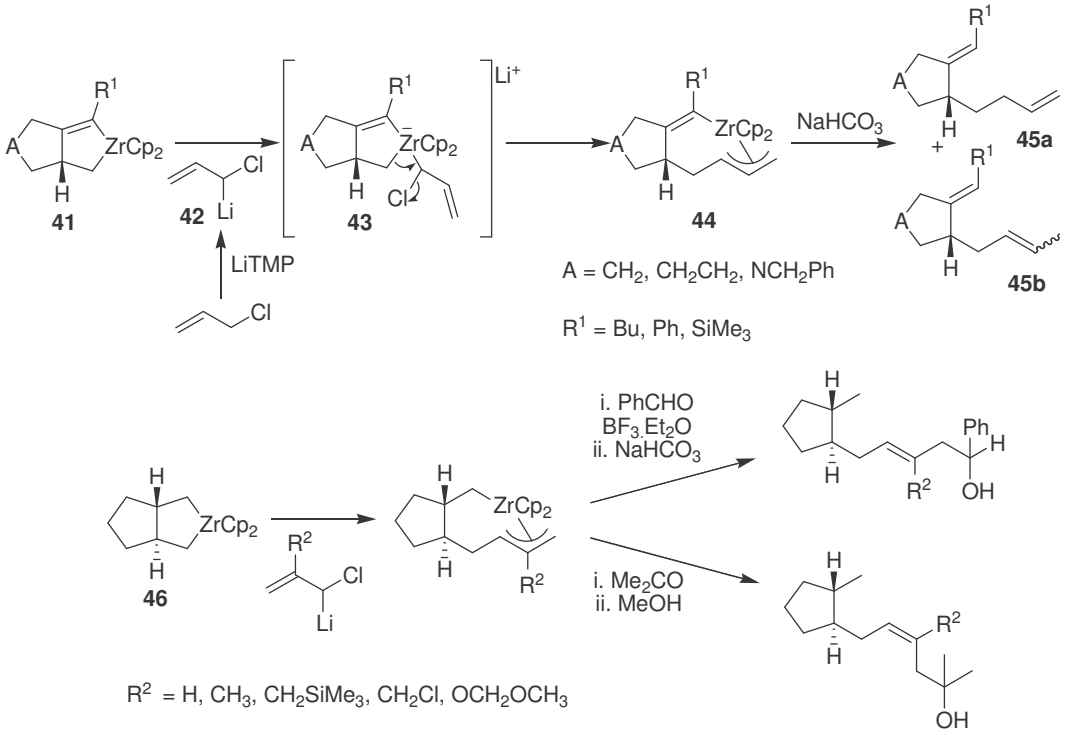


Scheme 22: Carbenoid insertion into organozirconium derivatives.

1.7.2.1 Insertion of allyl carbenoids

Allyl carbenoid **42** inserted into zirconacyclopentenes[47] **41** and pentanes[48] **46** (**Scheme 23**). Initial nucleophilic attack of the allyl carbenoid **42** generates an 18 electron 'ate' complex **43**. A 1,2-rearrangement with loss of the leaving group affords zirconium allyl complex **44**. Simple protonation of the complex affords the alkene products **45a** and **45b**. Further elaborations of the zirconium allyl complexes by the addition of an electrophile has been reported.[47-49] Various electrophiles such as aldehydes, ketones, acetals, ortho esters, iminium ions and thienium ions have all been successfully inserted into zirconium allyl species.[49] A Lewis acid was needed to catalyse the insertion of

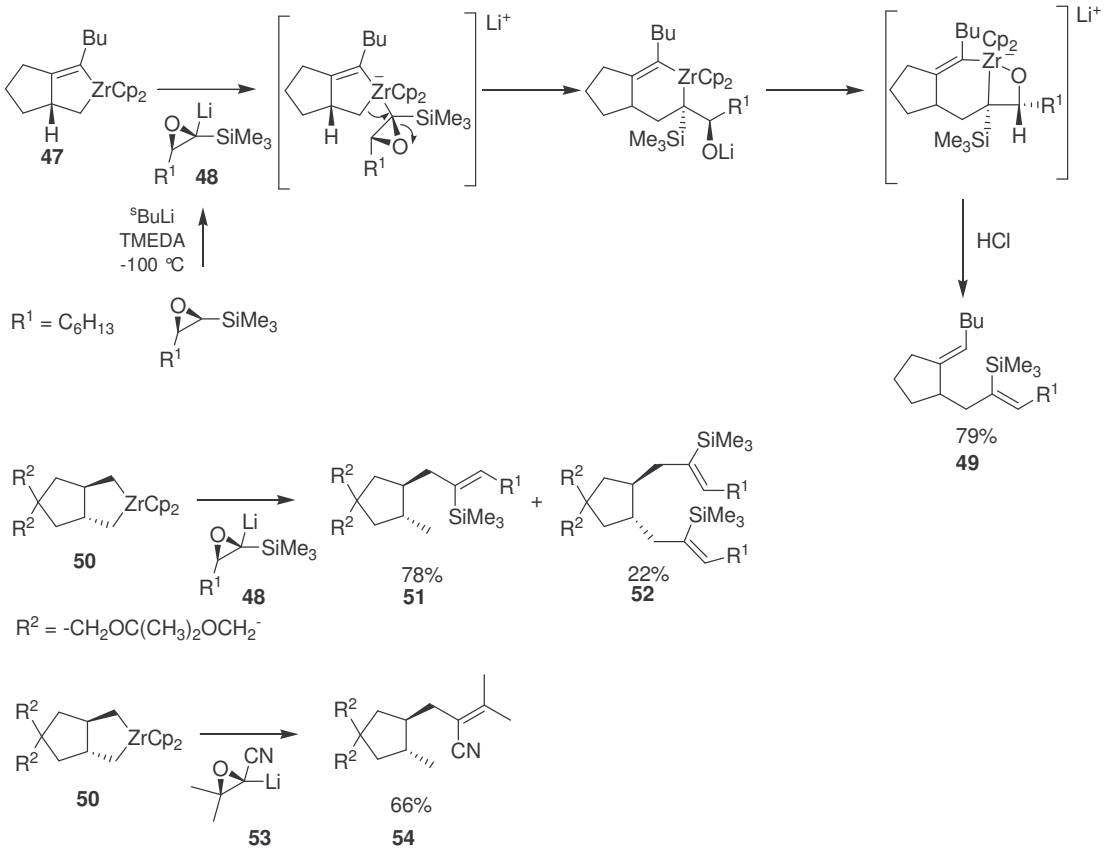
aldehydes, acetals and ortho esters into zirconium allyl complexes. Variations of the allyl carbenoid have also been reported.[50] This methodology was extended to include allyl components with carbamate and tosylate leaving groups. 2-Substituted allyl components also successfully insert. Allyl carbenoid insertion into zirconacycles has been utilised in the synthesis of several complex natural products.[51-54]



Scheme 23: Insertion of allyl carbenoids into zirconacycles.

1.7.2.2 Insertion of metalated epoxide carbenoids

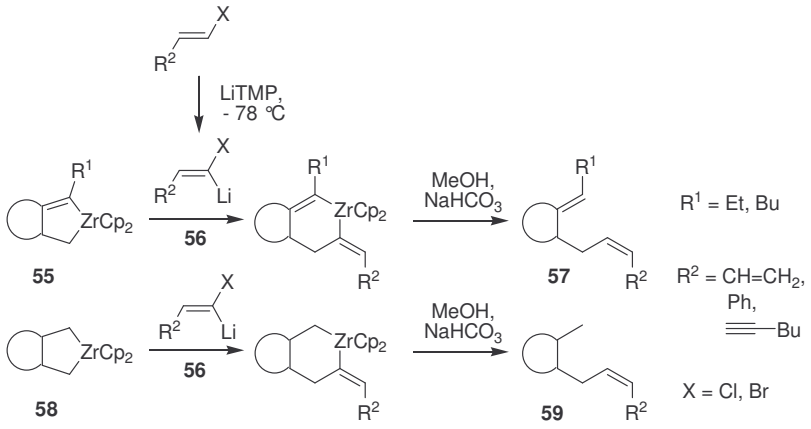
Insertion of lithiated epoxides into zirconacycles also affords substituted alkene products (**Scheme 24**).[55] Insertion of an electron-rich α-silyl-α-lithium substituted epoxide **48** into a zirconacyclopentene **47** affords **49**. Epoxide **48** inserts into zirconacyclopentane **50**, to afford a mixture of **51** and **52**. Compound **52** results from bis insertion of the carbenoid **48** into **50**. Insertion of an electron-poor α-cyano-α-lithium substituted epoxide **53** into zirconacyclopentane **50** affords **54** only. No bis-insertion was observed.



Scheme 24: Insertion of lithiated epoxides into zirconacycles.

1.7.2.3 Insertion of alkenyl carbenoids

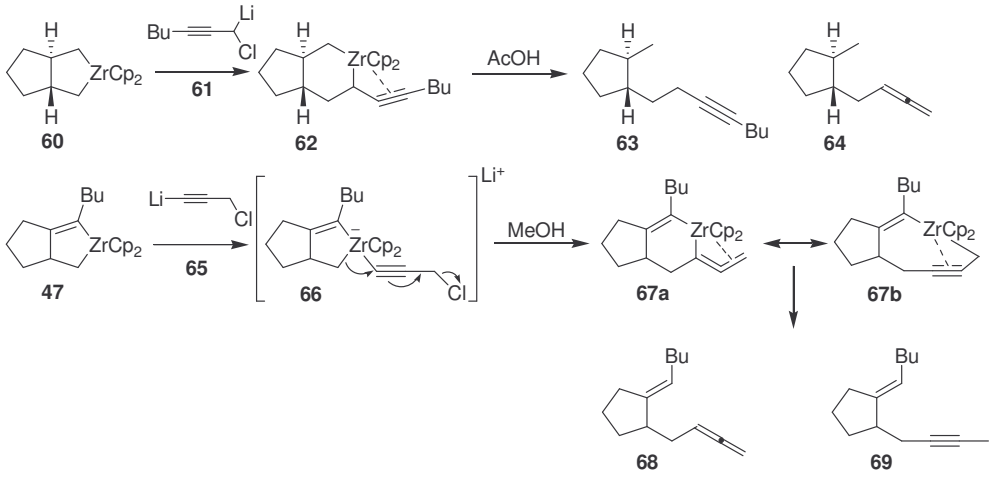
1-Lithio-1-haloalkenes insert into zirconacyclopentenes **55** and pentanes **58** to afford substituted alkene products **57** and **59**.[56, 57]



Scheme 25: Insertion of alkenyl carbenoids.

1.7.2.4 Insertion of propargyl and allenyl carbenoids

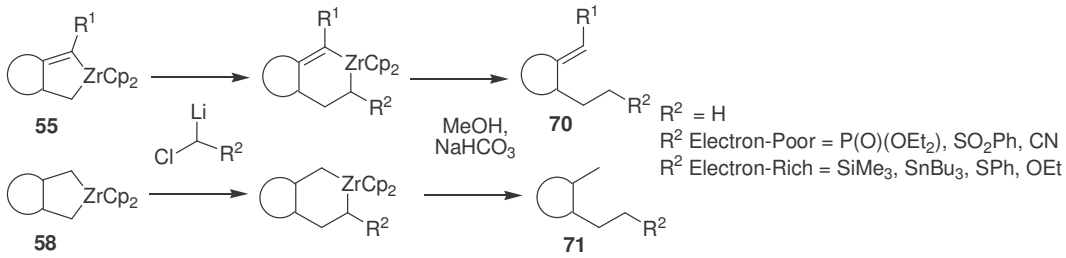
Propargyl **61** and allenyl **65** carbenoids have been successfully inserted into a range of zirconacyclopentanes and pentenes.[58, 59] An example of insertion of a propargyl carbenoid and an allenyl carbenoid are shown in **Scheme 26**. Propargyl carbenoid **61** was generated *in situ* by treating 1-chlorohept-2-yne with LiTMP at –78 °C. Insertion into zirconacyclopentane **60** gave the zirconacyclohexane **62** which, on protonation, afforded a mixture of **63** and **64**. Allenyl carbenoid **65** was generated *in situ* by treating 3-chloroprop-1-yne with LiTMP at –78 °C. Insertion into the zirconacyclopentene **47** afforded the ring expanded products **67a** and **67b** *via* the 18 electron 'ate' complex **66**. Protonation afforded a mixture of **68** and **69**. Further elaboration by tandem insertion of propargyl or allenyl carbenoids and aldehydes has also been reported.[59]



Scheme 26: Insertion of propargyl and allenyl carbenoids.

1.7.2.5 Insertion of substituted alkyl carbenoids

A wide range of substituted alkyl carbenoids have been inserted into a range of zirconacyclopentenes **55** and pentanes **58** to afford interesting functionalised products **70** and **71**.[56] Alkyl carbenoids with both electron-poor and electron-rich substituents have been reported and are highlighted in **Scheme 27**.



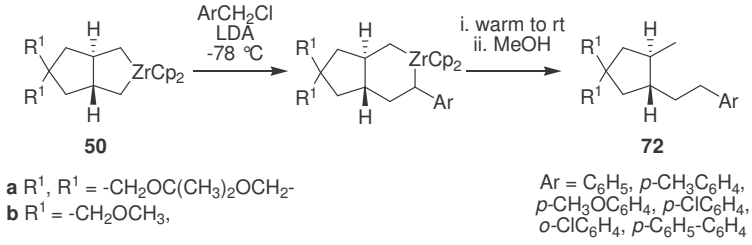
Scheme 27: Insertion of substituted alkyl carbenoids.

1.7.3 Insertion of benzyl carbenoids

Fillery demonstrated that zirconocene complexes are sufficiently reactive to trap benzyl carbenoids formed *in situ*.[1] The carbenoids were formed by treating the corresponding benzyl chloride with LDA at –78 °C.

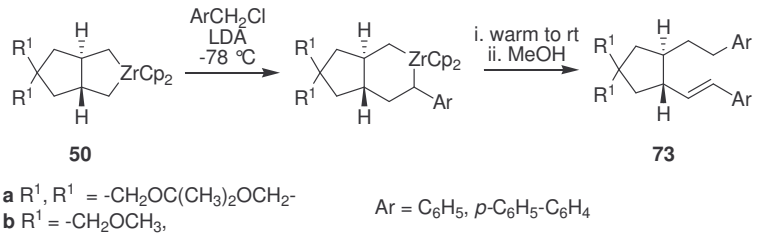
1.7.3.1 Benzyl carbenoid insertion into saturated zirconacycles

Fillery initially investigated the insertion of benzyl carbenoids into saturated zirconacycles **50**.[1] It was demonstrated that a range of commercially available benzyl chlorides could be converted to benzyl carbenoids and subsequently inserted into zirconacycles to give **72** on protonation (**Scheme 28**). The one exception was the carbenoid derived from *p*-nitrobenzyl chloride, which failed to insert. This was thought to be due to the strong electron-withdrawing effect of the nitro group making the carbenoid less nucleophilic.



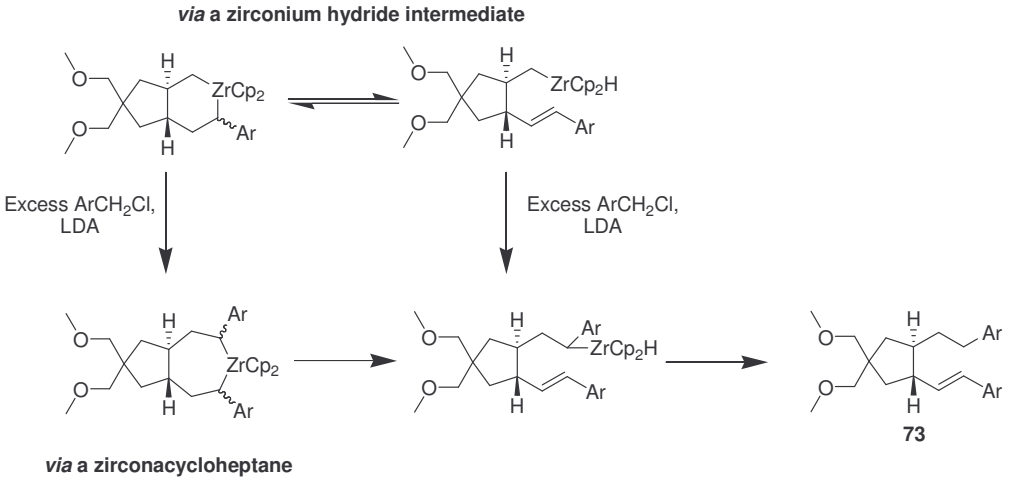
Scheme 28: Benzyl carbenoid insertion into saturated zirconacycles.

Fillery noted that in almost all cases a by-product was obtained, in no more than 5% yield, which was identified as the bis inserted product **73**.[1] If the number of equivalents of benzyl carbenoid were increased to 5 then complete conversion to the bis inserted product **73** was observed (**Scheme 29**).



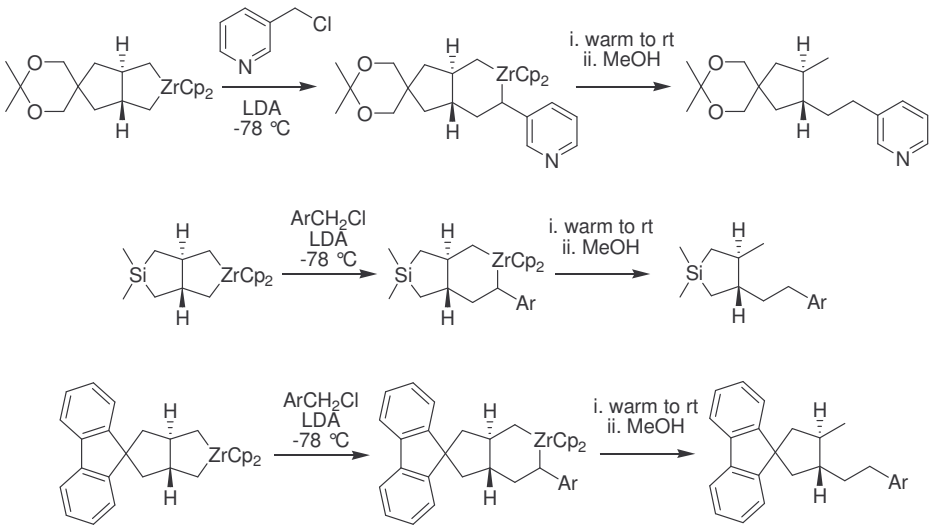
Scheme 29: Benzyl carbenoid insertion into a saturated zirconacycle to give the bis inserted product.

Fillery proposed two possible mechanisms for the formation of the bis inserted product, either *via* a zirconium hydride intermediate or *via* a zirconacycloheptane (**Scheme 30**).[1]



Scheme 30: Proposed mechanisms for the formation of the bis inserted product.

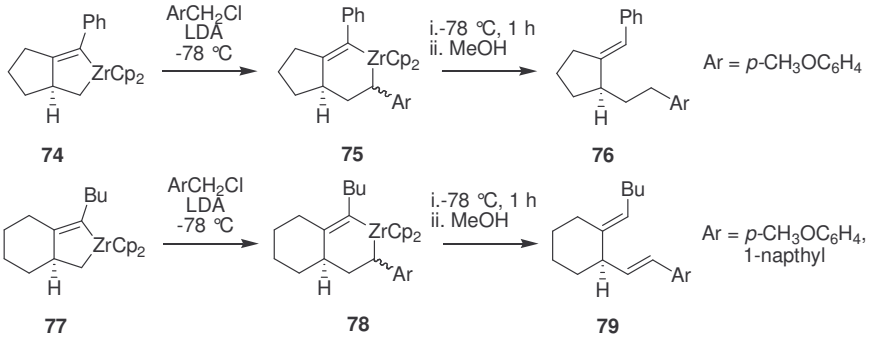
Fillery demonstrated that the general benzyl carbenoid methodology could be applied to a wide range of zirconacycles and carbenoids, including heteroaromatic carbenoids. Some examples are highlighted in **Scheme 31**.[1]



Scheme 31: Examples of benzyl carbenoid insertion into a range of zirconacycles.

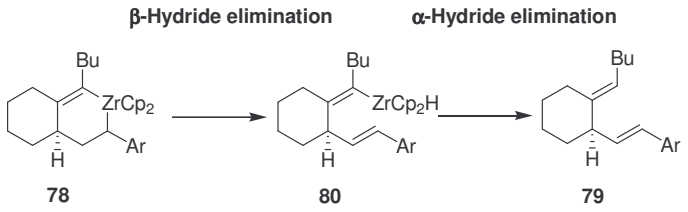
1.7.3.2 Benzyl carbenoid insertion into unsaturated zirconacycles

Fillery reported that benzyl carbenoid will insert cleanly into unsaturated zirconacycles (**Scheme 32**).[1] Benzyl carbenoid insertion into a 5-membered fused zirconacycle **74** gave **76** on protonation in 85% yield. Zirconacyclohexene **75** is formed as a 1:1 ratio of diastereoisomers and was shown to be stable at rt for several weeks or after prolonged heating to 60 °C.



Scheme 32: Benzyl carbenoid insertion into unsaturated zirconacycles.

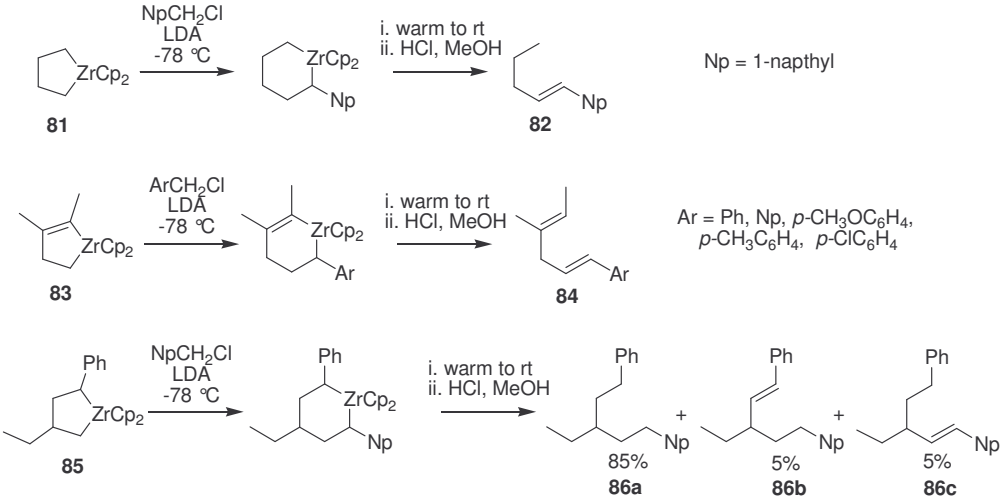
Benzyl carbenoid insertion into the 6-membered fused zirconacycle **77** afforded the skipped diene products **79**. Fillery proposed that the skipped dienes **79** were formed *via* a β-hydride elimination to afford a zirconium hydride intermediate **80** (**Scheme 33**).[1]



Scheme 33: Mechanism of formation of the skipped dienes.

1.7.3.3 Benzyl carbenoid insertion into monocyclic zirconacycles

Fillery reported the benzyl carbenoid insertion into both saturated and unsaturated monocyclic zirconacycles (**Scheme 34**).[1] Insertion of 1-(chloromethyl)naphthalene carbenoid, generated *in situ*, into monocycle **81** gave **82** in 92% yield. Insertion of benzyl carbenoids into unsaturated monocyclic zirconacycle **83** gave *E,E*–1,4-dienes **84** in excellent yield.

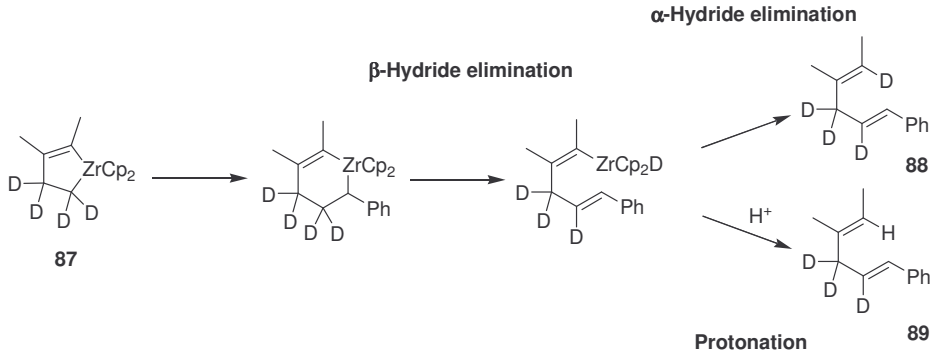


Scheme 34: Benzyl carbenoid insertion into monocyclic zirconacycles.

A mixture of products **86a**, **86b** and **86c** were produced from benzyl carbenoid insertion into zirconacycle **85**. The results indicate the aryl group does not control the β-hydride elimination as both **86b** and **86c** are observed.

Fillery proposed that the alkene products were arising from a β-hydride elimination, which accounts for the complete stereoselectivity observed in the final products.[1] However, the final step of the reaction could be occurring *via* two different

mechanisms; α-hydride elimination or protonation. Fillery investigated this by carrying out an experiment with a deuterium labelled zirconacycle **87** (**Scheme 35**).



Scheme 35: β-Hydride elimination followed by α-hydride elimination.

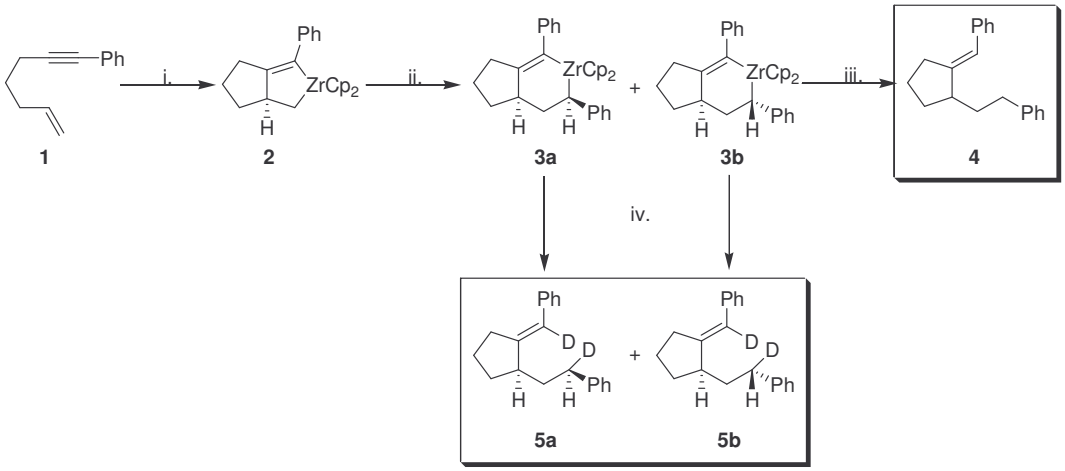
Fillery only observed **88**, suggesting that the alkene product is formed by a β-hydride elimination followed by an α-hydride elimination.

2 Insertion of benzyl carbenoids into unsaturated zirconacycles- discovery of a novel endocyclic cyclometallation

Dr S. Fillery[1] showed that benzyl carbenoids could be successfully inserted into unsaturated zirconacycles (**Chapter 1, Scheme 32**). The methodology has been extended to include a wide range of unsaturated zirconacycles and a detailed investigation of the mechanism was carried out, the results of which are reported within this chapter.

2.1 Insertion of benzyl carbenoids into zirconacyclopentenes

Intramolecular co-cyclisation of 1-phenylhept-1-yn-6-ene **1** using zirconocene(1-butene), generated *in situ* from dibutylzirconocene (Negishi's reagent),[24] afforded zirconacyclopentene **2**. Insertion of the benzyl carbenoid, generated *in situ* by treating benzyl chloride with LDA at –78 °C, afforded **4** on quenching with HCl, presumably generated *via* zirconacyclohexene **3** (**Scheme 36**).

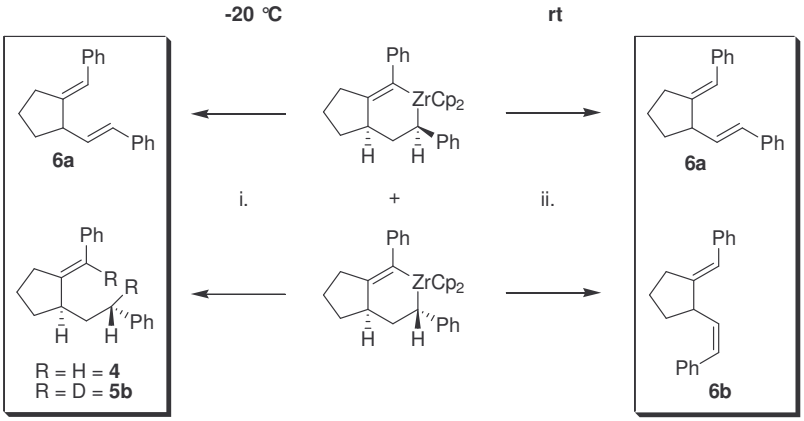


Scheme 36: *Reagents and Conditions:* i. $ZrCp_2Cl_2$, *n*-BuLi, THF, –78 °C, 30 min then warm to rt, 2 h. ii. BnCl, LDA, –78 °C, 30 min. iii. 2 M HCl in Et_2O, –78 °C - rt, 18 h, 62% iv. MeOD followed by D_2O, –78 °C - rt, 18 h.

A deuterium quench supported this assumption and produced the bis deuterated compound **5** as a 1:1 ratio of epimers at the deuterated benzyl carbon. The chemical shifts of the diastereotopic benzyl hydrogen's were identified by C-H correlation

spectroscopy in d_6 benzene, at δ_H 2.76 and 2.63 ppm, respectively, in the ^1H NMR. Relative deuteration of each epimer was also determined by ^2D NMR, which had signals at δ_D –4.64 and –4.75 ppm, which corresponded to the benzyl deuteriums (referenced to C_6H_6) and a signal at δ_D –0.92 ppm, which corresponded to the deuterated alkene. The 1,2-metalate rearrangement should occur stereospecifically with inversion so insertion of the chiral but racemic carbenoid into **2** gave rise to a 1:1 ratio of **3a** and **3b**.

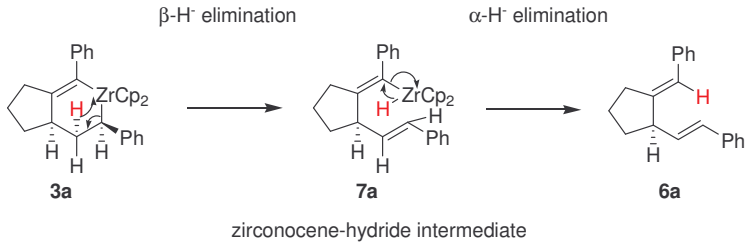
When the reaction mixture was allowed to warm to –20 °C for 1 h before a sample was quenched with HCl, producing a 1:1 mixture of the (*E*)-alkene **6a** and **4**. A sample was also quenched with MeOD followed by D_2O, which gave a 1:1 mixture of **5b** and **6a**. Epimer **5b** was characterised by the benzylic hydrogen signal at 2.63 ppm in the ^1H NMR and the benzylic deuterium at δ_D –4.64 ppm in the ^2H NMR. There was complete loss of signals corresponding to the other epimer **5a**. No deuterium incorporation into alkene **6a** was observed. If the reaction mixture was allowed to warm to reflux for 3 h (or rt for 24 h) before quenching, a 1:1 mixture of the (*E*)- and (*Z*)-alkenes **6a** and **6b** was isolated in good yield. Again no deuterium incorporation was observed in either alkene when the reaction was quenched with MeOD. This indicated one diastereoisomer produced the (*E*)-alkene **6a** where as the other diastereoisomer produced the (*Z*)-alkene **6b** (**Scheme 37**).



Scheme 37: *Reagents and conditions:* i. –20 °C, 1 h, 2 M HCl (aq) or MeOD/D_2O, 18 h. ii. Reflux, 3 h, 2 M HCl (aq), 52% or MeOD/ D_2O, 18 h,

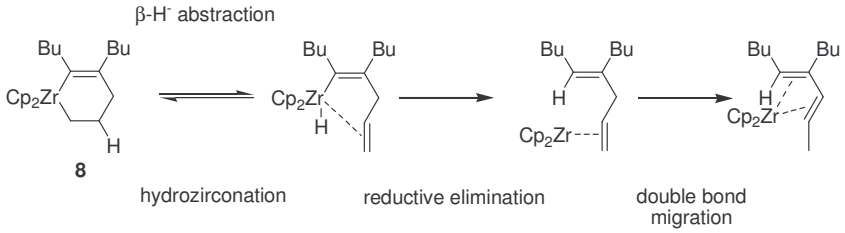
2.2 Discussion of the possible mechanisms for the formation of the alkene products

The first mechanism considered was an endocyclic β-hydride elimination to generate a zirconocene-hydride intermediate followed by an α-hydride elimination (**Scheme 38**).



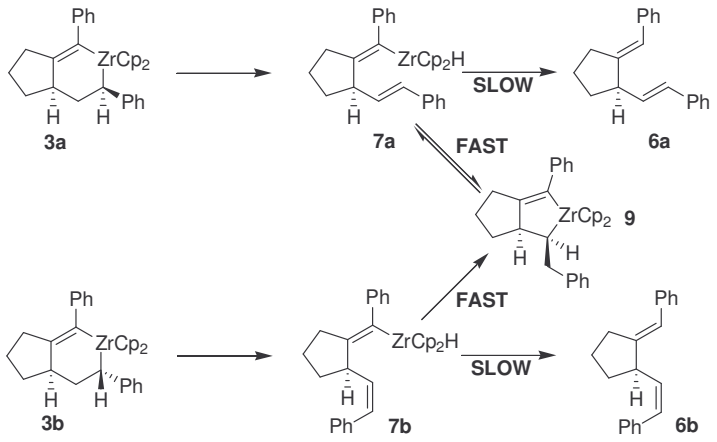
Scheme 38: β-Hydride elimination.

On first inspection this appeared to be a very attractive way to describe the transformation. This mechanism has been previously proposed by our group[44] and recently by Xi *et al.*.[60] Xi *et al.* proposed the observed decomposition of zirconacyclohexene **8** occurred *via* β-hydride abstraction followed by reductive elimination (**Scheme 39**).



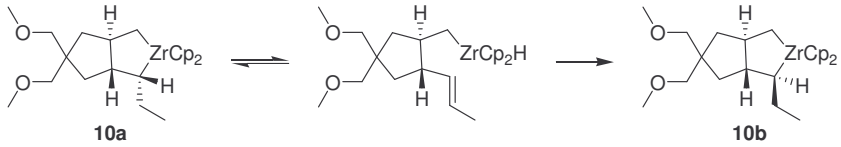
Scheme 39: Documented decomposition of zirconacyclohexenes.[60]

An essential element of our proposed mechanism is the α-hydride elimination, however this is known to be a slow process.[61] The zirconocene-hydride intermediate **7** would also be expected to undergo a fast re-addition to the alkene to afford a zirconacyclopentene **9** (**Scheme 40**).



Scheme 40: Re-addition of the zirconocene-hydride intermediate to generate zirconacyclopentenes.

Work carried out within our group[62] has previously reported the rapid isomerisation of the zirconacyclopentene **10a**, derived from the *cis*-alkene, to the zirconacyclopentene **10b**, derived from the *trans*-alkene *via* an exocyclic β-hydride elimination – re-addition process (**Scheme 41**).

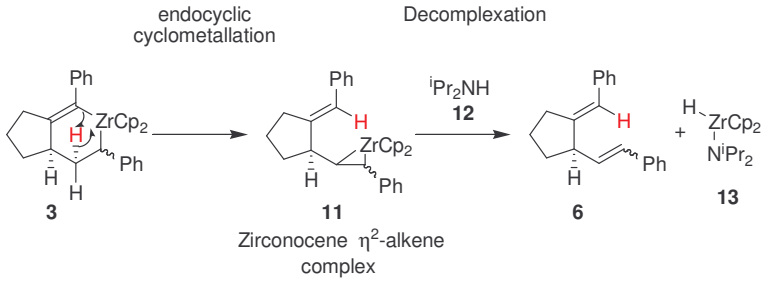


Scheme 41: Documented rapid isomerisation of the *cis*- to *trans*-zirconacyclopentane.[62]

If the mechanism of alkene formation is *via* an endocyclic β-hydride elimination one would expect to only produce the (*E*)-alkene **6a**, due to rapid isomerisation *via* the zirconacyclopentene **9** formed from re-addition of the zirconocene-hydride to the alkene. However, a 1:1 ratio of (*E*):(*Z*) alkenes **6a** and **6b** is always observed for this system.

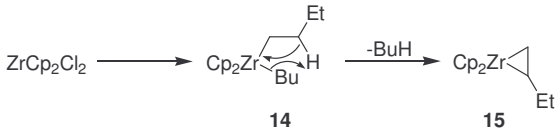
Hence an alternative mechanism was sought. It was proposed that the formation of the alkene products could be occuring *via* a novel endocyclic cyclometallation process to afford the zirconocene η^2-alkene complex (**Scheme 42**). The mechanism supports the observed 1:1 ratio of (*E*):(*Z*)-alkenes **6a** and **6b**. It is also suggested that the decomposition of zirconacycle **8**, observed by Xi *et al.*,[60] may have occurred via a endocyclic cyclometallation rather β-hydride elimination. Modelling of the cyclometallation process predicted that diastereoisomer **3a** gives the (*E*)-alkene **6a** and

diastereoisomer **3b** gives the (*Z*)-alkene. A more detailed discussion of this is given in section 2.3.



Scheme 42: Endocyclic cyclometallation.

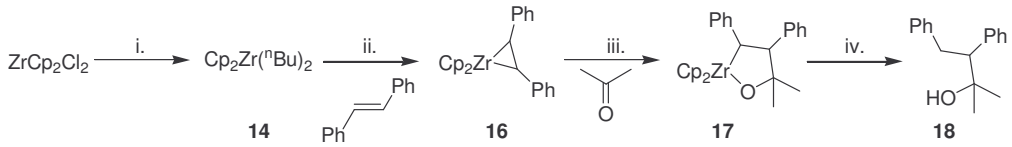
Such cyclometallation processes to afford zirconocene η^2-alkene complexes are well known.[31] One such example is the formation of zirconocene(1-butene) **15** from dibutylzirconocene (Negishi's reagent)[31] **14**, however the mechanism within this programme is the first endocyclic transfer to be proposed (**Scheme 43**).



Scheme 43: Formation of zirconocene(1-butene). A well known example of a cyclometallation.

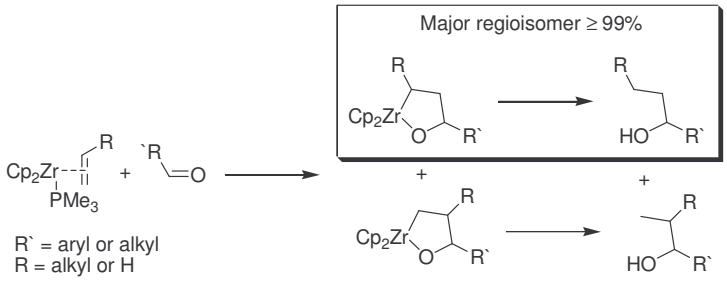
Protonolysis of the zirconocene η^2-alkene complexe **11** is expected to afford the saturated compound **4**,[24] however in this case this is not observed and instead, alkene **6** formation is observed *via* decomplexation of the zirconocene presumable aided by the presence of diisopropylamine **12**, present in the reaction from the *in situ* generation of the benzyl carbenoid from benzyl chloride and LDA. The diisopropylamine **12** may trap the zirconocene, as a zirconocene-amido hydride species **13**, though we have no direct evidence for this. This is a key step of the mechanism as zirconocene is a highly reactive species and could catalyse further reactions such as isomerisation of the alkene. It is worth noting that isomerisation is observed in the monocyclic systems, which provides further evidence for formation of a zirconocene η^2-alkene complex. This is discussed in greater detail in section 2.7.

To successfully distinguish between the two possible mechanisms, attempts were made to directly trap the intermediate zirconocene η^2-alkene complexes **11**. The concept of trapping a zirconocene η^2-alkene complex is well reported within literature.[63-65] The first example was published by Negishi *et al.* in 1987.[63] Negishi *et al.* showed that a zirconocene stilbene complex **16** could be successfully trapped with acetone to give alcohol **18** on protonolysis, which was presumably formed *via* **17** (**Scheme 44**).



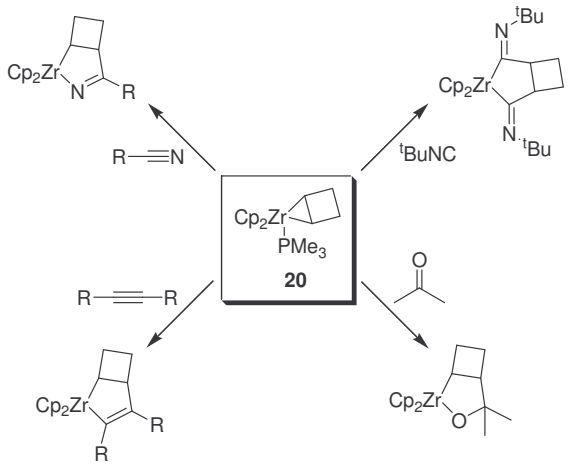
Scheme 44: *Reagents and conditions:* i. 2 eq *n*-BuLi, –78 °C. ii. 0 °C, iii. rt, 1 h, iv. 3M HCl.

Takahashi *et al.* reported the successful insertion of a range of aldehydes into a variety of zirconium alkene complexes with high (≥ 99%) regioselectivity (**Scheme 45**).[64]



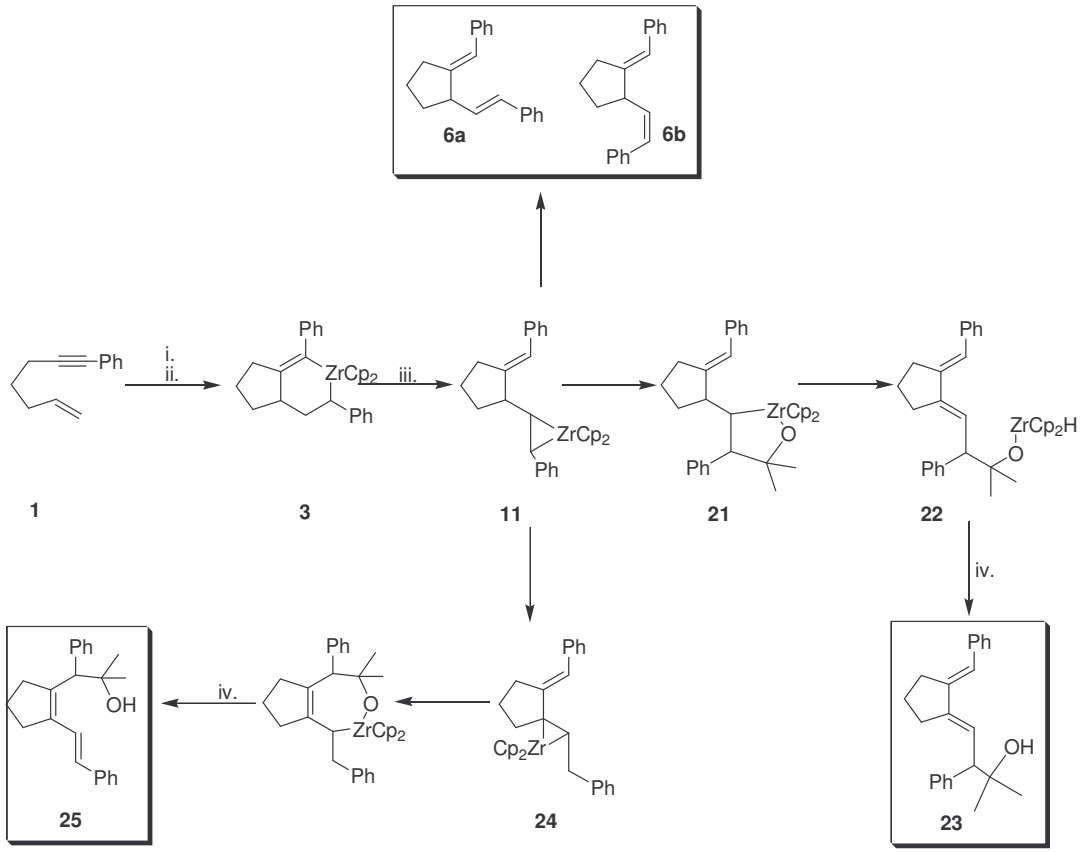
Scheme 45: Insertion of a range of aldehydes into various zirconium alkene complexes.

Buchwald *et al.* extended this methodology and demonstrated that a range of unsaturated compounds, such as ketones, nitriles, alkynes and isocyanides, could be successfully inserted into zirconocene cyclobutene complex **20** (**Scheme 46**).[65]



Scheme 46: Insertion of a range of unsaturated compounds into a zirconium-alkene complex.

An initial attempt was made to trap the zirconocene η^2-alkene complexes with 1 equivalent of acetone. Monitoring the reaction by GC and GCMS revealed small amounts of new products had been formed, presumably acetone insertion into the zirconocene η^2-alkene **11**. The reaction was repeated using 2, 3 and 5 equivalents of acetone. The most successful result was achieved with 5 equivalents of acetone. Column chromatography allowed successful separation of a mixture of the recovered alkene products (**6a** and **6b**) in 30% yield, and two acetone insertion products **23** and **25** (**Scheme 47**). Acetone insertion into the zirconocene η^2-alkene complex **11** gave intermediate **21**, followed by an exocyclic β-hydride transfer to afford **22** which on protonolysis gave alcohol **23** in 35% yield. The second acetone insertion product was identified as alcohol **25** and was isolated in 6% yield. Alcohol **25** was presumably formed by insertion of acetone into a rearranged zirconocene η^2-alkene complex **24** (**Scheme 47**). Attempts to improve the yield of **23** were not successful. This may be due to the fact that diisopropylamine present in the reaction mixture assisted in the decomplexation of the zirconocene η^2-alkene complex **11**. As a result, it would appear that acetone insertion and decomplexation are competing reactions.



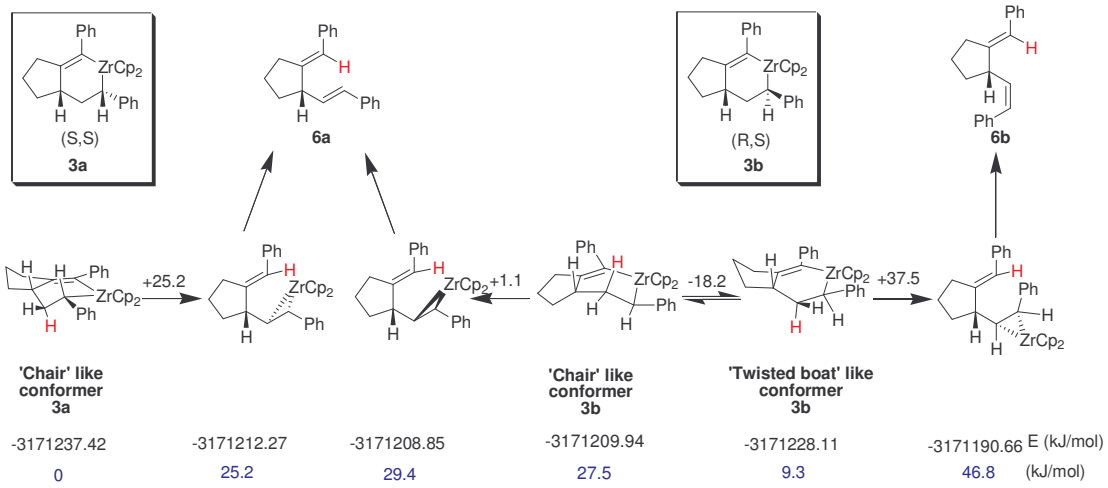
Scheme 47: *Reagents and conditions:* i. $ZrCp_2Cl_2$, *n*-BuLi, THF, –78 °C - rt, 2 h. ii. BnCl, LDA, –78 °C, 5 min. iii. Acetone, –78 °C, 30 min then warmed to rt, 20 h. iv. MeOH, $NaHCO_3$, rt, 2 h, **6a** and **6b** in 30%, **23** in 35% and **25** in 6%.

Attempts to trap the η^2-alkene zirconocene complex with benzophenone, benzylaldehyde and phenyl isocyanate were unsuccessful.

2.3 Theoretical investigation of the mechanism

Attempts to find a transition state for the β-hydride transfer mechanism (**Scheme 38**) by creating a reaction profile (using semi-empirical methods with PM3 parameters extended to cope with transition metals) by reducing the relevant hydrogen-zirconium distance gave an energy maximum. A transition state search from this point successfully converged to a structure which was characterised as a transition state through calculation of the vibrational spectrum which had a single imaginary frequency. However, inspection of the imaginary frequency (the reaction coordinate) showed it to

correspond to movement of the hydrogen between the carbon, and remote alkenyl carbon (i.e. the cyclometallation mechanism, **Scheme 42**), not to the zirconium. Unfortunately semi-empirical calculations have severe limitations in terms of giving realistic energies. Furthermore, they do not cope well with either metal-H bonds or strained rings (as the product η^2-alkene complex may be viewed). Density function theory (DFT) calculations are far more reliable, but are several orders of magnitude slower so cannot realistically be used to create reaction profiles. However, DFT calculations can be used to examine related energies of conformers.



Scheme 48: DTF relative energy calculations.[66]

The calculations predicted that the lowest energy conformation of **3a** is a 'chair' like structure and cyclometallation affords (*E*)-alkene **6a** whereas **3b** is a 'twisted boat' like conformer and cyclometallation affords (*Z*)-alkene **6b** (**Scheme 48**). This was indeed what is observed, however minimum energy calculations showed that there are two reasonable conformers of diastereoisomer **3b**. The 'twisted boat' like conformer which leads to the (*Z*)-alkene **6b** is 18.2 kJ/mol more stable than the 'chair' like conformer which leads to the (*E*)-alkene **6a**.

2.4 Kinetic studies

It has already been shown that there is a large difference in the rate of cyclometallation between diastereoisomer **3a** and **3b** (see page 34) and kinetic studies were undertaken to quantify this.

This was achieved by removing aliquots (0.1 mL) of the reaction mixture and quenching them with 2 M HCl at timed intervals. The samples were analyzed by GC for loss of product **4** and appearance of alkenes **6a** and **6b**. The rate of cyclometallation was monitored at 20 °C over 44 h. The data represented in **Figure 2** highlights the rate difference for the cyclometallation of each diastereoisomer.

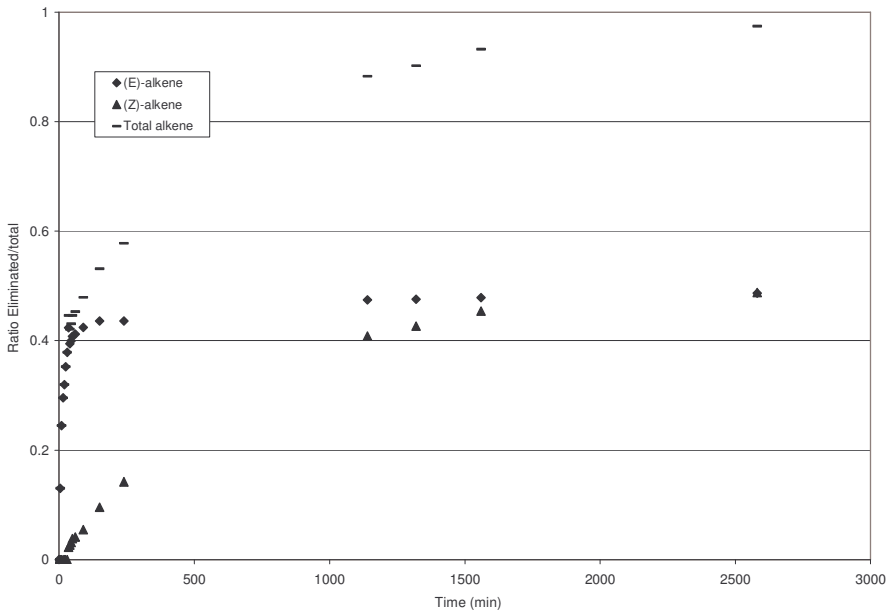


Figure 2: Reaction Profile: Cyclometallation of diastereoisomer **3a** to give the (*E*)-alkene **6a** and **3b** to give the (*Z*)-alkene **6b**.

First order rate plots were produced by plotting ln [**4**] verses time; rate constant (k) and half lives have been calculated.

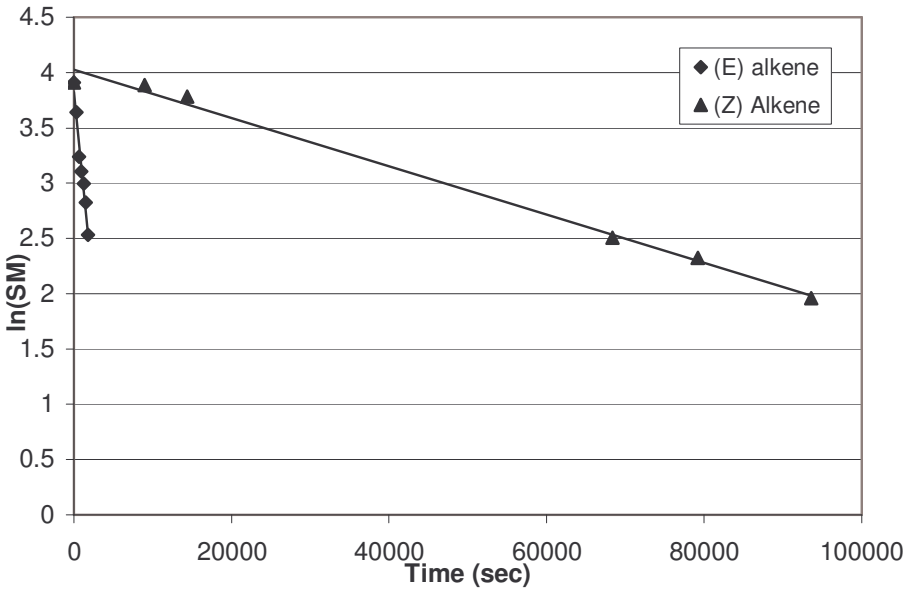


Figure 3: 1st Order Rate Plot: Cyclometallation of diastereoisomer **3a** to give the (*E*)-alkene **6a** and **3b** to give the (*Z*)-alkene **6b**.

The rate constant of cyclometallation of **3a** to give the (*E*)-alkene **6a** was 0.0007 s^{-1} with a half life of 16.5 min. The rate constant of cyclometallation of **3b** to give the (*Z*)-alkene **6b** was 0.00002 s^{-1} with a half life of 578 min. This clearly shows a large difference in the rate of cyclometallation of each diastereoisomer (**Figure 3**).

The DFT calculations (**Scheme 48**) indicate that the zirconacycle **3a** is 25.2 kJ/mol less stable than the (*E*)- η^2-alkene complex, whereas the zirconacycle **3b** is 37.5 kJ/mol less stable than the (*Z*)- η^2-alkene complex, consistent with the observed slower reaction in the later case, although it is transition state energies which are really needed.

2.5 Cyclometallation of a deuterium labelled compound

Minimum energy structures predict that the same hydrogen, relative to the ring junction, is transferred during the cyclometallation process in both diastereoisomers **3a** and **3b**. For the cyclometallation process to occur diastereoisomer **3a** must take on a chair-like confirmation whereas diastereoisomer **3b** must take on a twisted-boat-like confirmation (**Figure 4**).

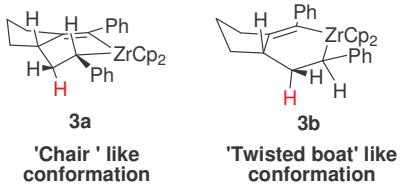


Figure 4: Conformation of diastereoisomers **3a** and **3b**.

To demonstrate the cyclometallation mechanism and to confirm that the same hydrogen is transferred in both diastereoisomers synthesis of the mono deuterium labelled compounds **26a** and **26b** was attempted (**Figure 5**).

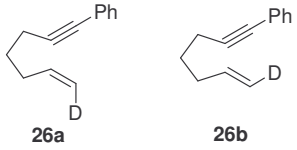
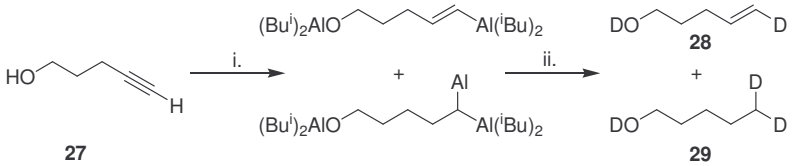


Figure 5: Deuterium labelled compounds.

The initial route to the deuterium labelled compounds was *via* stereospecific hydrometallation of alkyne **27** with a D_2O workup to give the (*E*)-alkene **28**. Initially the reaction was carried out using 2 equivalents DIBAL-H at 50 °C. This, however, produced an inseparable mixture of the desired (*E*)-alkene **28** and the over reduced alkane **29** (**Scheme 49**).



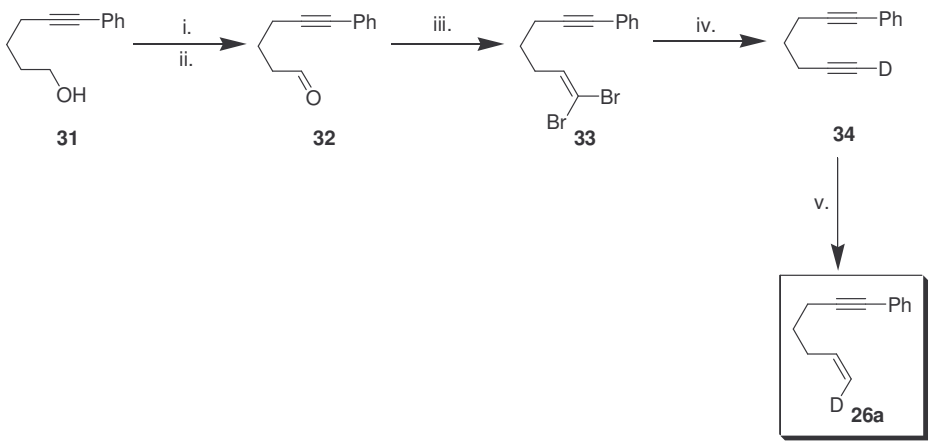
Scheme 49: *Reagents and conditions:* i. 2 eq DIBAL-H, pentane, rt - 50 °C, 3 h. ii. D_2O, rt, 18 h.

The reaction was repeated with only 1 equivalent of DIBAL-H, however, no reaction was observed even after 4.5 h at 50 °C. This is due to the fact that DIBAL-H will react with the alcohol preferentially over the alkyne unit. A second equivalent of DIBAL-H was added and the reaction was monitored by GC. Before complete disappearance of the alkyne **27**, alkane product **29** was also observed. However, after 2 h complete disappearance of the alkyne **27** was observed. The total amount of hyrdometallation was greater than the number of DIBAL-H equivalents used. It was suggested that elimination of one of the ^{i}butyl groups had occurred to generate an additional aluminium-hydride. The rate of reduction of the alkenyl aluminium must be comparable to the rate of reduction of the alkyne. Below 40 °C no reduction is observed, however above 40 °C alkane product **29** is always observed before complete disappearance of starting alkyne **27**. Attempts to separate the alkene **28** from the alkane **29** using 5% silver nitrate doped silica gel proved unsuccessful.

Attempts to hydrozirconate the alkyne **27** with Schwartz reagent also proved to be unsuccessful. No over reduction was observed, however, complete reduction to the alkene **28** was not observed even with 2.2 equivalents of Schwartz reagent. A mixture of the starting alkyne **27** and alkene **28** were produced. This was most likely due to the quality of the Schwartz reagent. Further investigations into this route were not carried out due to the high cost of the Schwartz reagent and the large quantity required due to this being the first step of the sequence.

Although there are several examples of reducing an alkyne to an alkene selectively using reducing agents such as DIBAL-H,[67] Schwartz reagent[68] and boranes,[69] caution should be taken as several examples convert the alkene to the epoxide prior to separating, providing a successful method of isolating the alkene from the alkane.[67]

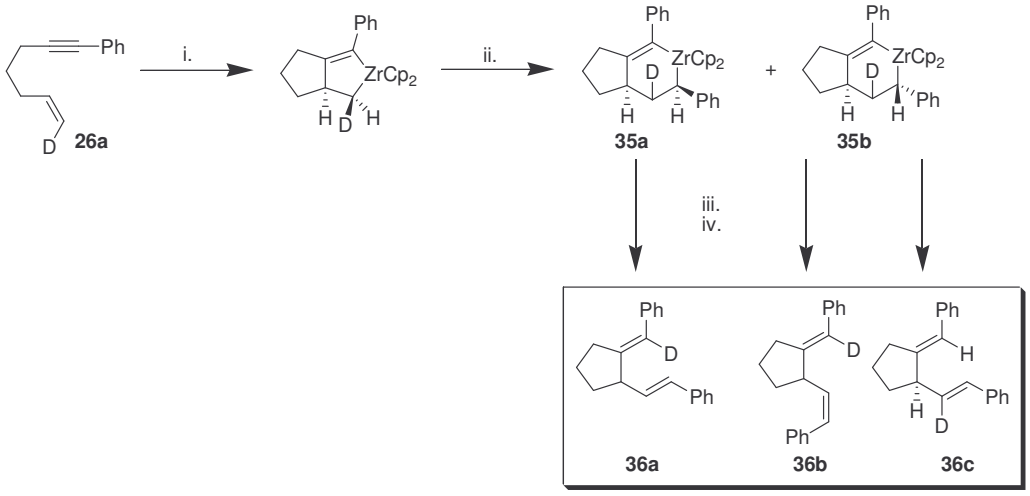
The focus was changed to the synthesis of the (*Z*)-alkene **26a** (**Scheme 50**) as the modelling (**Scheme 48**) predicted the deuterium in this isomer was positioned to be transferred during the cyclometallation process in both diastereoisomers of the intermediate zirconacyclohexene.



Scheme 50: *Reagents and Conditions:* i. $(COCl)_2$, DMSO, CH_2Cl_2, –78 °C, 1 h. ii. Et_3N, –78 °C – rt, 1 h, 96%. iii. PPh_3, CBr_4, CH_2Cl_2, rt, 30 min, 70%. iv. *n*-BuLi, THF, –78 °C, 30 min then D_2O, –78 °C - rt, 1 h, 83%. v. $ZrCp_2HCl$ (prepared by treating $ZrCp_2Cl_2$ with DIBAL-H, 0 °C), THF, rt, then potassium sodium tartrate, 18 h, rt, 48%.

Swern oxidation of alcohol **31** gave **32** in 96% yield.[70] The aldehyde **32** was successfully converted to the dibromide **33**, *via* the Corey-Fuchs reaction, in 70% yield.[71] The dibromide **33** was treated with 2 equivalents of *n*-BuLi, and quenched with D_2O to give to deuterated alkyne **34** in 83% yield with ≥ 99% deuterium incorporation. Alkyne **34** was then selectively hydrozirconated to give the alkene **26a** in 48% yield. Previously it was shown that over hydrometallation was not observed when Schwartz reagent was used, however, complete reduction was also not observed. This was attributed to the quality of the Schwartz reagent. $ZrCp_2HCl$ formed *in situ*, by treating $ZrCp_2Cl_2$ with DIBAL-H at 0 °C, was used in preference to commercially available Schwartz reagent.[72] Several equivalents of $ZrCp_2HCl$ were prepared and aliquots were added until complete disappearance of the alkyne **34** was observed by GC analysis. It was estimated that 1.5 equivalents of the $ZrCp_2HCl$ mixture was required to achieve complete hydrometallation of the alkyne **34**.

Intramolecular co-cyclisation of enyne **26a** with zirconocene(1-butene) followed by insertion of the benzyl carbenoid (**Scheme 51**) occurred cleanly and the reaction mixture was warmed to rt for 72 h. Purification by column chromatography yielded an inseparable mixture of (*E*)-alkene **36a**, (*Z*)-alkene **36b** and (*E*)-alkene **36c** in a ratio of 2:1:1 (**Figure 6**). Also observed was an impurity which may have arisen due to isomerisation of the alkene by "$ZrCp_2$" (**Figure 6**). There is a large decrease in the rate of cyclometallation when the hydrogen atom is replaced with a deuterium atom; as the reaction time was increased from 24 h to 72 h.



Scheme 51: *Reagents and conditions:* i. $ZrCp_2Cl_2$, *n*-BuLi, THF, –78 °C - rt, 2.5 h. ii. BnCl, LDA, –78 °C, 30 min. iii. Warm to rt for 72 h. iv. 2 M HCl (aq), 18 h, rt, 72%.

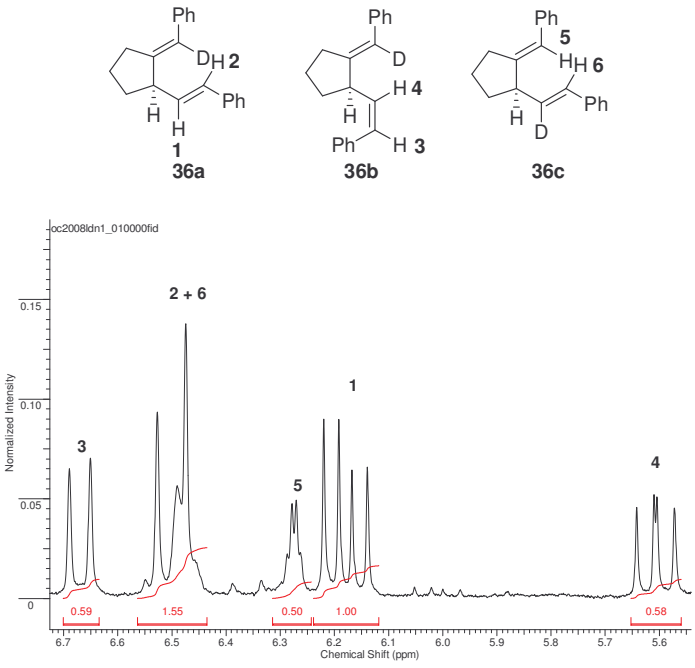
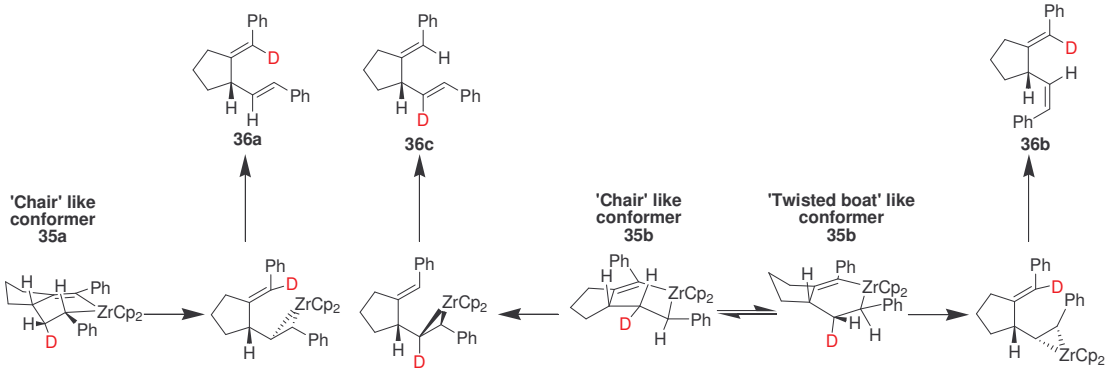


Figure 6: ^{1}H NMR (300 MHz, $CDCl_3$) alkene region of **36a**, **36b** and **36c**.

A 1:1 mixture of **36a** and **36b** was predicted. The observation of **36c** was unexpected and implies that diastereoisomer **35b** gave an equal mixture of **36b** and **36c**. From **Scheme 52** it can be seen that there is a route to the (*E*)-alkene **36c** via a higher energy conformation. It is proposed that migration of a deuterium rather than a hydrogen adds significantly to the activation energy of conversion of **35b** to **36b**, therefore migration of the hydrogen to give **36c** becomes competitive.



Scheme 52: Routes to alkenes **36a**, **b**, **c**.[66]

The differences between the deuterated and non deuterated analogues were attributed to the kinetic isotope effect, as it takes more energy to break a C-D bond than a C-H bond. It has been observed that replacing the hydrogen atom with a deuterium atom caused a large kinetic isotope effect.

The kinetic isotope effect was calculated by carrying out a reaction containing a 1:1 mixture of enyne **1** (non deuterated analogue) and enyne **26a** (deuterated analogue). As diastereoisomer **35b** cyclometallates to give two alkene products **36b** and **36c**, the kinetic isotope effect was only calculated for the diastereoisomer **35a**. The kinetic isotope effect was calculated from the ratio of **6a:36a** ((*E*)-alkene of the non-deuterated analogue:(*E*)-alkene of the deuterated analogue) at the initial point of cyclometallation. This was obtained from the GCMS and the results are reported in **Table 1**.

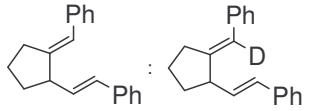
Time (min)	 **6a** : **36a**	Kinetic Isotope Effect
10	48.4 : 15.1	3.2
20	52.7 : 13.5	3.9
30	42.2 : 13.3	3.2
Average		3.4
Standard Error		±0.25

Table 1: Kinetic isotope effect.

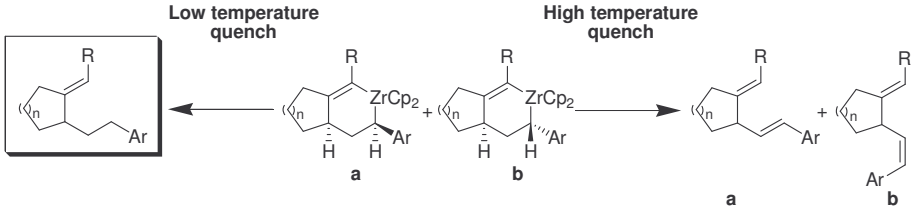
The kinetic isotope effect for the (*E*)-alkene was estimated from the GCMS, which showed that the rate of cyclometallation was 3.4 times greater (± 0.25) when a C-H bond is broken rather than the C-D bond.

In conclusion, it has been shown that the same hydrogen is transferred in both diastereoisomers (**3a** and **3b**) to give a 1:1 ratio of (*E*)-alkene **6a** and (*Z*)-alkenes **6b**. When the hydrogen is replaced with a deuterium a kinetic isotope effect was observed. A 2:1:1 ratio of (*E*)-alkene **36a**, (*Z*)-alkene **36b** and (*E*)-alkene **35c** is observed.

2.6 Benzyl carbenoid insertion into a range of zirconacycles

The insertions of a range of benzyl carbenoids into a range of unsaturated zirconacycles was examined in order to investigate the scope of the reaction and gain further insight into the proposed novel endocyclic cyclometallation that has been proposed.

In all cases, protonation at low temperature (–78 °C) gave the benzyl inserted product generated *via* the zirconacyclohexene. The cyclometallation was observed in all systems to afford the styrene product, but the ratios of (*E*):(*Z*) alkenes produced and temperature of this process varied widely. The large difference in rate of cyclometallation of each diastereoisomer was observed in all examples (**Table 2**).



n=1, Ar=Ph, R=Ph **4**
n=1, Ar=*p*-MeOC$_6$H$_4$, R=Ph **38**
n=1, Ar=*p*-ClC$_6$H$_4$, R=Ph **41**
n=1, Ar=Ph, R=Bu, **44**
n=2, Ar=Ph, R=Ph, **47**
n=2, Ar=Ph, R=Bu, **50**

n=1, Ar=Ph, R=Ph **3**
n=1, Ar=*p*-MeOC$_6$H$_4$, R=Ph **37**
n=1, Ar=*p*-ClC$_6$H$_4$, R=Ph **40**
n=1, Ar=Ph, R=Bu, **43**
n=2, Ar=Ph, R=Ph, **46**
n=2, Ar=Ph, R=Bu, **49**

n=1, Ar=Ph, R=Ph **6**
n=1, Ar=*p*-MeOC$_6$H$_4$, R=Ph **39**
n=1, Ar=*p*-ClC$_6$H$_4$, R=Ph **42**
n=1, Ar=Ph, R=Bu, **45**
n=2, Ar=Ph, R=Ph, **48**
n=2, Ar=Ph, R=Bu, **51**

Low temperature quench (Yield %)	High temperature quench (Yield %)	**Temperature of cyclometallation °C**[a]	**Half life (min)**[a]	**K (s^1)** [a]
4	**6a + b**	20	16.5	7 x10^{-4}
(62)	(52)		578	2 x10^{-5}
	1:1 (*E*):(*Z*)			
38	**39a + b**	20	6.4	2 x10^{-3}
(63)	(48)		385	3 x10^{-5}
	1:1 (*E*):(*Z*)			
41	**42a + b**	20	19	6 x10^{-4}
(88)	(50)		578	2 x10^{-5}
	1:1 (*E*):(*Z*)			
44	**45a + b**	20	< 4	
(59)	(53%)		28	4 x10^{-4}
	3:1 (*E*):(*Z*)			
47	**48a**	–60	< 10	
(53)	(65)	–10	12.8	9 x10^{-4}
	1:0 (*E*):(*Z*)			
50 (55)	**51a**	–60	< 10	
+ 51 (6)	(72)		< 10	
	1:0 (*E*):(*Z*)			

Table 2: Benzyl carbenoid insertion into a range of unsaturated zirconacycles.

a. Half lives and rates are presented in the order of diasterisomer a then b.

The first noteworthy observation is the effect of changing the aromatic carbenoid. In all cases a 1:1 ratio of (*E*):(*Z*) alkenes (**6a/b**, **39a/b** and **42a/b**) were produced as expected, however, the rate of cyclometallation varied slightly with the choice of carbenoid. An electron-withdrawing subsituent on the phenyl, i.e. chlorine, had little effect on the rate of cyclometallation whereas an electron-donating subsituent, i.e. methoxy resulted in a small increase in the rate of cyclometallation.

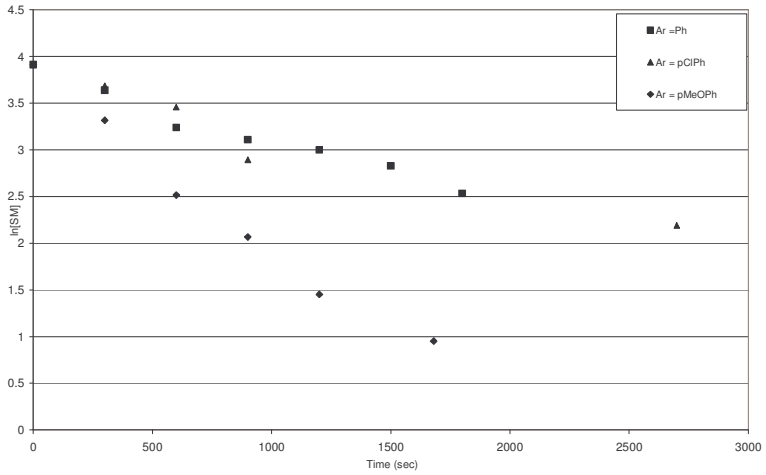


Figure 7: 1st Order rate plot. The effect of different carbenoids on the rate of cyclometallation of zirconacyclohexanes, **3a**, **37a** and **40a**, to give the (*E*)-alkenes**, 6b**, **39b** and **42b**.

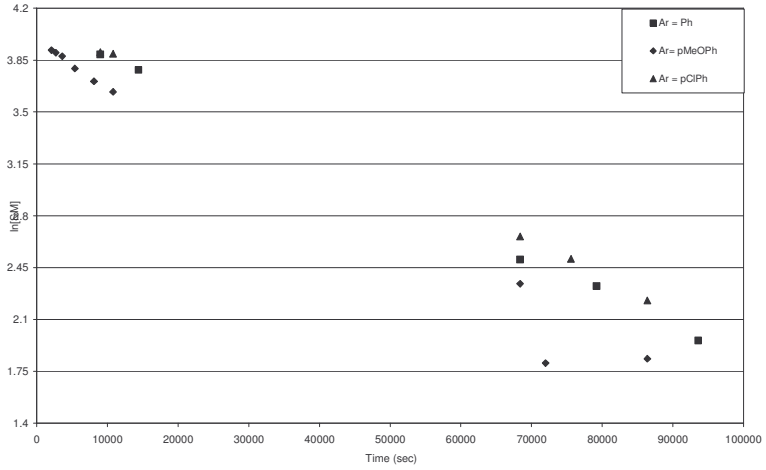


Figure 8: 1st Order rate plot. The effect of different carbenoids on the rate of cyclometallation of zirconacyclohexanes, **3b**, **37b** and **40b**, to give the (*E*)-alkenes, **6a**, **39a** and **42b**.

In all cases there is a large difference in the rate of cyclometallation of each diastereoisomer. The half lives varied from 6.4 - 19.0 minutes for zirconacyclohexenes **3a**, **37a** and **40a** to 385 - 578 minutes for diastereoisomer **3b**, **37b** and **40b** at 20 °C (**Figure 7** and **Figure 8**).

The effect of the zirconacycle was also investigated. The first consideration was the effect of the alkene subsituent (R) on the rate of cyclometallation. The phenyl group was replaced with a butyl group. The first important observation is that a 1:1 (*E*):(*Z*) was not obtained as expected and instead a 3:1 (*E*):(*Z*) was observed. By following the

reaction at –10 °C it was concluded that **43a** behaves as expected and only gave the (*E*)-alkene. Cyclometallation of diastereoisomer **43b** afforded a roughly equal mixture of the (*E*)- and (*Z*)-alkene. Several factors were considered for why this ratio of (*E*):(*Z*) olefins was obtained. One suggestion was that LDA was epimerising the two zirconacyclohexenes so that there was not a 1:1 ratio of the two diastereoisomers **43a** and **43b** prior to cyclometallation. This was considered as it has been found that the zirconacyclohexanes undergoes isomerisation in the presence of excess LDA (**Chapter 3**). The reaction was carried out with an excess of LDA, however, this had no effect on the reaction and again a 3:1 (*E*):(*Z*) mixture was observed. This suggested that epimerisation is not observed in the zirconacyclohexenes as the alkene substituent blocks nucleophilic addition into the vacant zirconium orbital (**Figure 9**) (see Chapter 3).

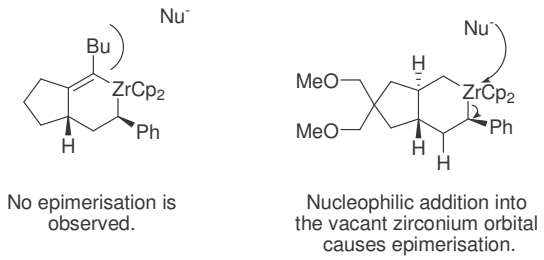
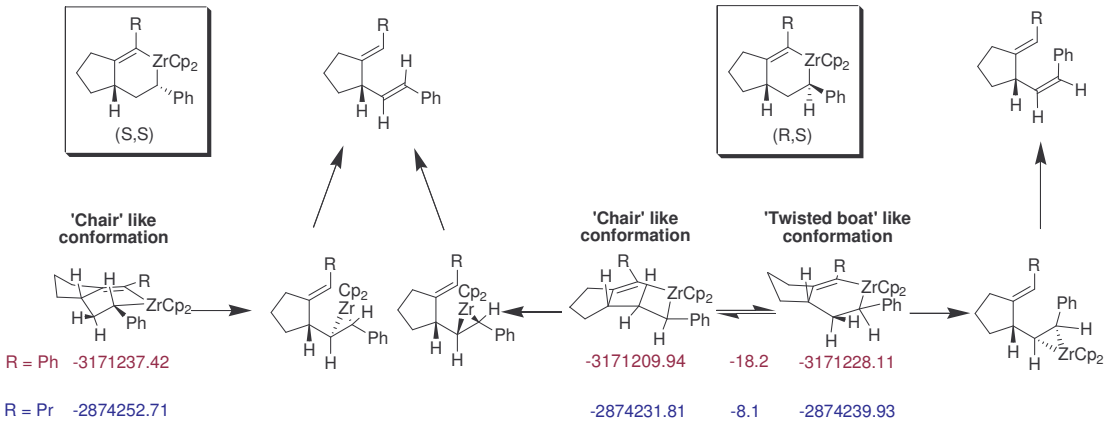


Figure 9: Epimerisation *via* nucleophilic addition.

One other possibility was that zirconocene generated in the reaction isomerised the double bond. The reaction was carried out in the presence of 4-octyne as a zirconocene trap. Again the 3:1 (*E*):(*Z*) ratio was produced. It was concluded that the 3:1 (*E*):(*Z*) ratio was produced by the cyclometallation of diastereoisomer **43b** occurring *via* two pathways as observed in the deuterium labelled system (**Scheme 51**).

Minimum energy calculations were carried out on these systems.[66] As shown previously (**Scheme 48**), there are too possible conformers of diastereoisomers **3b**. When R = Ph the 'twisted boat' like conformer, which leads to the (*Z*)-alkene is 18.2 kJ/mol more stable than the 'chair' like conformer, which leads to the (*E*)-alkene; diastereoisomer **3b** only cyclometallates to give the (*Z*)-alkene. However, when the calculations were repeated with a propyl group (model for R=Bu stystem) the energy difference between the 'twisted boat' like conformer and the 'chair' like conformer is reduced to 8.1

kJ/mol, which is consistent with the observation that diastereoisomer **43b** can cyclometallate to give both the (*E*)- and (*Z*)-alkenes (**Scheme 53**).



Scheme 53: DFT relative energy calculations.

The other noteworthy observation is that changing the alkene subsituent (R) from a phenyl group to a butyl group greatly increased the rate of cyclometallation with half lives calculated as <4 minutes for diastereoisomer **43a** and 28 minutes for diastereoisomer **43b** at 20 °C.

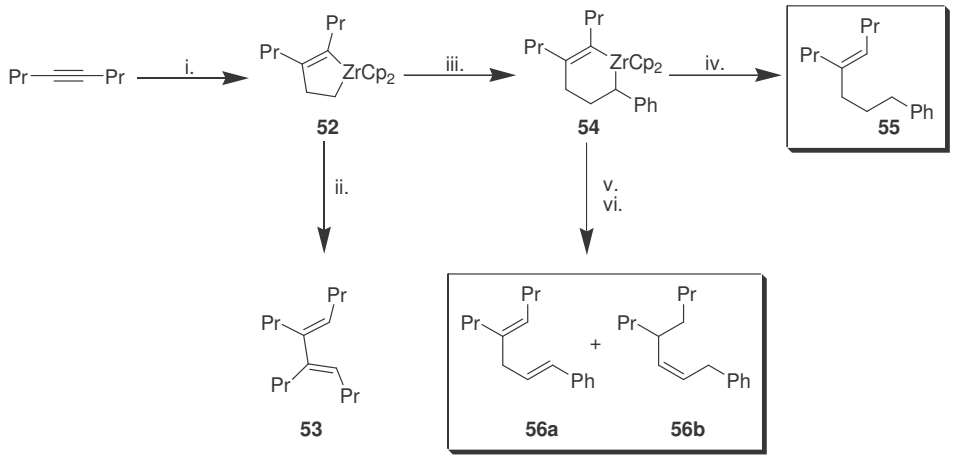
The next consideration was the size of the ring fused to the zirconacycle. Increasing the fused ring from a 5 to a 6 membered ring had a dramatic effect on the outcome of the reaction. When R was either phenyl or butyl only the (*E*)-alkene is produced. As expected the zirconacyclohexene **46a** and **49a** undergoes the cyclometallation to give the (*E*)-alkene, however, zirconacyclohexenes **46b** and **49b** also gave the (*E*)-alkene. Minimum energy calculations predicted that the 'chair' like conformer of diastereoisomer **46b** is 15.3 kJ/mol more stable than the 'twisted boat' like conformer. When the calculations were repeated with a methyl group (model for the R = Bu system) replacing the phenyl group, it was predicted that the 'chair' like conformer is 14.4 kJ/mol more stable than the 'twisted boat' like conformer. These calculations support the fact that both diastereoisomers cyclometallate to give the (*E*)-alkene when the fused ring is a 6-membered ring.[66]

Increasing the size of the ring from a 5-membered ring to a 6-membered ring caused a dramatic reduction in the temperature at which the zirconacyclohexenes underwent the cyclometallation. In the example with the phenyl subsituent **46**, the first diastereoisomer **46a** has a half life estimated as <10 minutes at –60 °C and 12.8 minutes at –10 °C for diastereoisomer **46b**. In the case with the butyl subsituent **49**, the half lives of both diastereoisomers were estimated at <10 minutes at –60 °C.

In summary, only a small difference in the rate of cyclometallation is observed when varying the aromatic carbenoid used. However, very dramatic effects are observed with different zirconacycles. Changing the R substituent and size of the fused ring greatly increases the rate of cyclometallation and alters the (*E*):(*Z*) ratio of the products.

2.7 Benzyl carbenoid insertion into monocyclic zirconacycles

Formation of the monocyclic zirconacycle **52** was achieved by the co-cyclisation of 4-octyne with ethylene zirconocene, generated from zirconocene dichloride treated with 2 equivalents of EtMgBr.[73] Temperature control was essential when forming monocycle **52**. Ensuring the reaction mixture was not warmed above 0 °C prevented formation of the alkyne dimer **53**. Insertion of the benzyl carbenoid was facile but the reaction needed to be quenched very rapidly at –78 °C to afford alkene **55**, in 57% yield (**Scheme 54**).

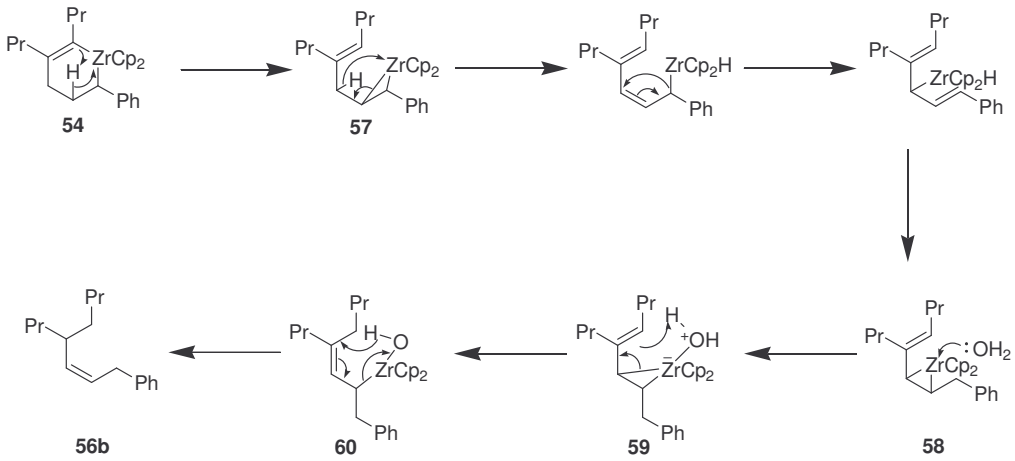


Scheme 54: *Reagents and conditions:* i. $ZrCp_2Cl_2$, EtMgBr, THF, –78 - 0 °C, 4 h. ii. warmed to rt, 2 M HCl (aq). iii. BnCl, LDA, –78 °C, 10 min. iv. 2 M HCl in Et_2O, –78 °C - rt, 1 h, 57% v. warm to rt, 30 min. vi. MeOH, sat $NaHCO_3$ (aq), rt, 1 h, **56a** in 47% and **56b** in 14%.

When the reaction mixture was warmed to rt before quenching with 2 M HCl (aq) and MeOH, the expected diene **56a** and the unexpected alkene **56b** were isolated in 47% and 14% yield respectively (**Scheme 54**). The unexpected alkene product was identified by a characteristic double triple doublet at δ_H 5.50 ppm and double double triplet δ_H 5.25 ppm in the ^{1}H NMR spectrum. The benzylic protons were observed as a doublet at 3.32 ppm. In addition GCMS analysis assisted in confirming the identity of alkene **56b** with the molecular ion observed at 230 m/z.

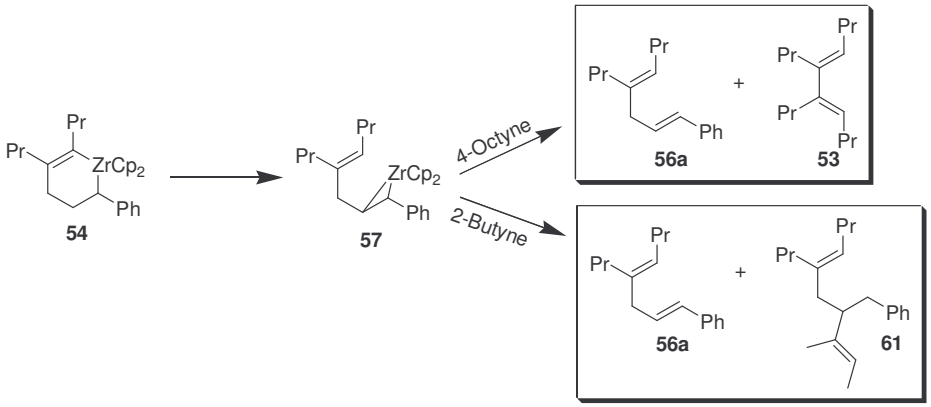
It was proposed that alkene **56b** was formed by isomerisation of the initial zirconocene η^2-alkene complex **57** to give zirconocene η^2-alkene complex **58 (Scheme 55)**. On work-up insertion of water into the 16-electron complex **58** gave the 18-electron zirconium complex **59**. A proton transfer of **59** generated the 16-electron complex **60**

which underwent a final proton transfer to give the alkene product **56b**. Complete isomerisation was not observed as the majority of zirconocene η^2-alkene complex **57** was successfully trapped by the diisopropylamine present in the reaction mixture. A rearrangement analogous to **54** to **57** did not occur with bicyclic zirconacycles, probably because the initial hydride migration to zirconium is sterically hindered.



Scheme 55: Proposed mechanism for the formation of alkene **56b**.

To obtain alkene products cleanly it appeared that it was essential to trap the zirconocene produced in the cyclometallation-decomplexation process. The reaction was first attempted with an excess of 4-octyne, which successfully trapped the zirconocene, evident by the formation of dimer **53**, which was formed by 2 equivalents of 4-octyne co-ordinating to zirconocene (**Scheme 56**). However, diene **56a** could not be separated from diene **53** by column chromatography.



Scheme 56: Effects of adding alkyne traps to prevent formation of the rearranged product.

The reaction was also repeated in the presence of 2-butyne. 2-Butyne should trap the zirconocene as successfully as 4-octyne but would be more easily separated from the reaction mixture as any dimer formed should be much more volatile. When the reaction was carried out diene **56a** and diene **61** were isolated as an inseparable mixture (**Scheme 56**). Diene **61** was formed by 2-butyne inserting into zirconocene η^2-alkene complex **57**. The structure of diene **61** was deduced by NMR and GCMS analysis. The NMR data confirmed a mixture of two compounds. The most interesting new peaks in the ^{1}H NMR spectra were a triplet at δ_H 5.13 ppm and a quartet at δ_H 5.05 ppm characteristic of diene **61** (**Figure 10**). Two products were detected by GCMS analysis: one with a retention time of 8.6 minutes, molecular ion at 228, corresponded to diene **56a** and the other at 9.0 minutes, molecular ion at 284, which corresponded to diene **61**.

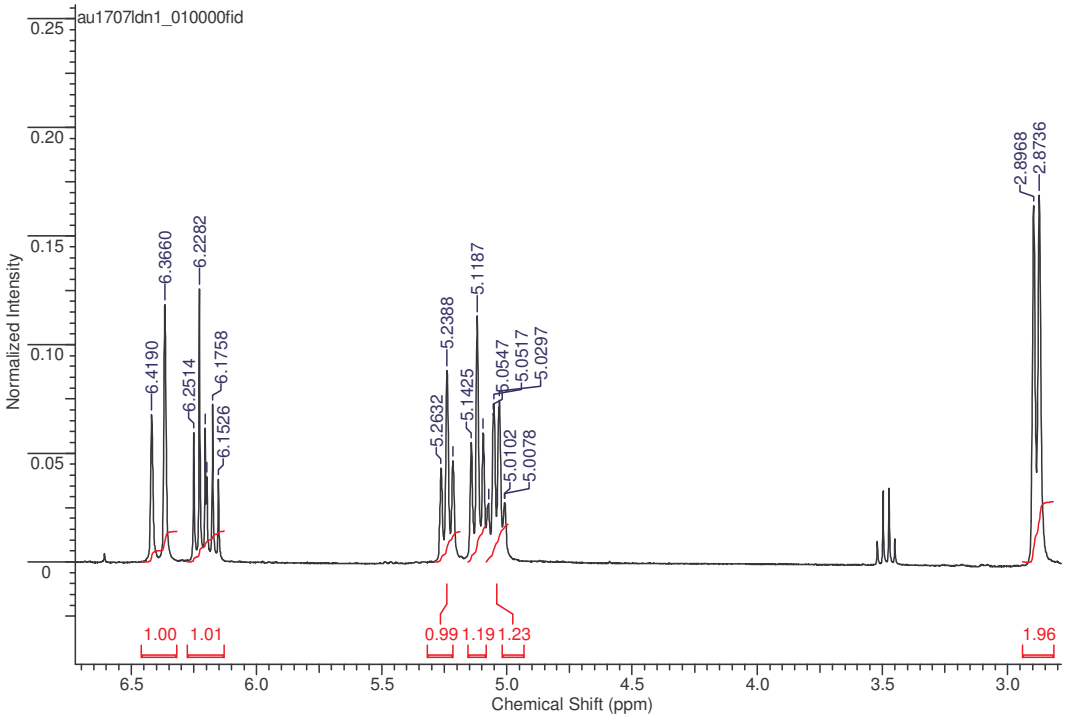
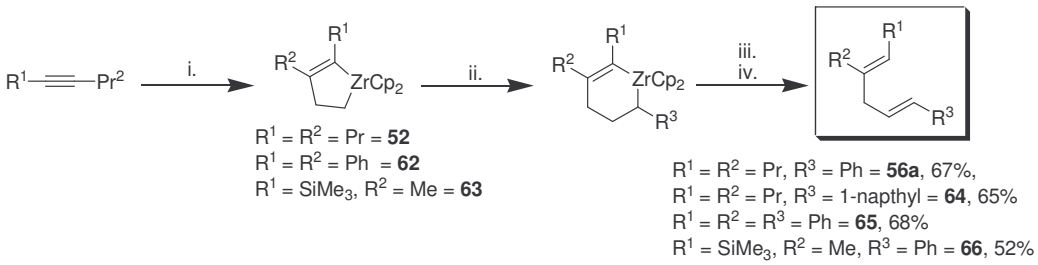


Figure 10: ^{1}H NMR of diene **56a** and **61**.

Further investigations were carried out in order to find a suitable trap. Cleaner reactions were obtained when either butylamine or CH_2Cl_2 were used, and it was concluded that the cleanest reaction occurred when CH_2Cl_2 was added as a trap. Work carried out

within our group by Norton demonstrated that zirconocene reacts with CH_2Cl_2. When a zirconocene mediated cyclisation was carried out in the presence of CH_2Cl_2 no cyclisation was observed, as the zirconocene(1-butene) reacted preferentially with the carbon-chlorine bond of the CH_2Cl_2.[74]

The scope of the reaction was examined by insertion of a range of benzyl carbenoids into a range of zirconacycles (**52**, **62** and **63**) (**Scheme 57**).



Scheme 57: *Reagents and conditions:* i. $ZrCp_2Cl_2$, EtMgBr, THF, –78 - 0 °C, 4 h. ii. ArCl, LDA, –78 °C, 5 min. iii. CH_2Cl_2, –78 °C, 30 min then warmed to rt, 30 min, iv. 2 M HCl (aq), rt, 18 h.

Zirconacycle **63** is formed in greater than 99% regioselectivity when trimethyl(prop-1-ynyl)silane was used as the precursor.[40] Successful insertion of the carbenoids and subsequent cyclometallations occurred cleanly, when CH_2Cl_2 was added to trap the zirconocene, affording skipped dienes **56a**, **64**, **65** and **66** in good yields (52-68%).

2.8 Conclusion

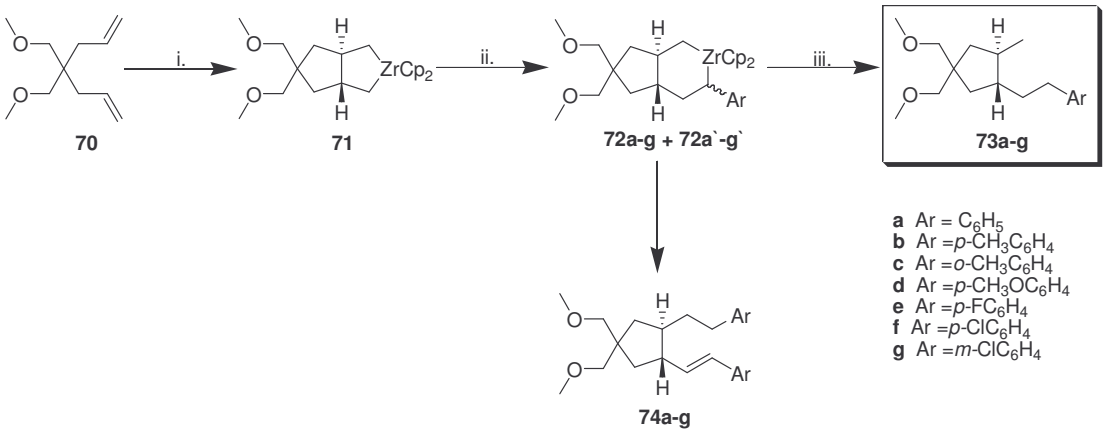
A range of benzyl carbenoids have been successfully inserted into a range of zirconacyclopentenes to afford zirconacyclohexenes. A novel endocyclic cyclometallation of zirconacyclohexenes to afford zirconocene η^2-alkene complexes has been reported. The mechanism and scope of this reaction has been thoroughly investigated.

3 Insertion of benzyl carbenoids into saturated zirconacycles

Fillery[1] showed that benzyl carbenoids could be successfully inserted into saturated zirconacycles to give the expected benzyl carbenoid inserted product (**Chapter 1, Scheme 28**) together with a small amount of an alkene product (**Chapter 1, Scheme 29**) resulting from bis-insertion of the carbenoid.

3.1 Mono-insertion of benzyl carbenoids into zirconacyclopentanes

This methodology was extended by inserting a large range of benzyl carbenoids into a saturated zirconacycle. The results are highlighted in **Scheme 58** and **Table 3**. Intramolecular co-cyclisation of 4,4-bis(methoxymethyl)hepta-1,6-diene **70** with zirconocene(1-butene) generated *in situ* from dibutylzirconocene (Negishi's reagent)[24] afforded the zirconacyclopentane **71**. Benzyl carbenoid insertion was achieved by treating the corresponding benzyl chloride with LDA *in situ* followed by TMEDA. Quenching with MeOH and $NaHCO_3$ gave **73a-g** generated *via* the zirconacyclohexanes **72a-g** and **72a`-g`** (` used to differentiate between the two zirconacyclohexane diastereoisomers). Fillery[1] reported that bis-insertion is observed even when only 1 equivalent of carbenoid is used. It was found that adding TMEDA limited the amount of bis-insertion product **74a-g** to <5%. The effect of TMEDA on the reaction is not understood.



Scheme 58: *Reagents and conditions:* i. $ZrCp_2Cl_2$, *n*-BuLi, THF, –78 °C - rt, 2 h. ii. $ArCH_2Cl$, LDA, TMEDA –78 °C, 1 h. iii. MeOH, $NaHCO_3$, –78 °C - rt, 18 h.

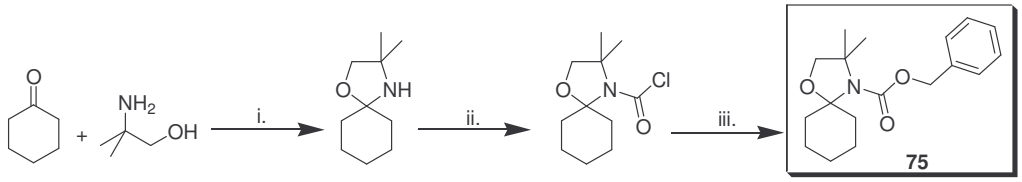
Product	Ar	Isolated Yield (%)
73a	C_6H_5	75
73b	*p*-$CH_3C_6H_4$	46
73c	*o*-$CH_3C_6H_4$	46
73d	*p*-$CH_3OC_6H_4$	37
73e	*p*-FC_6H_4	47
73f	*p*-ClC_6H_4	30
73g	*m*-ClC_6H_4	61
73h	*p*-CNC_6H_4	0
73i	*p*-$CH_3OOCC_6H_4$	0

Table 3: Benzyl carbenoid insertion into zirconacyclopentane **71**.

A range of benzyl carbenoids were successfully inserted into the saturated zirconacycle **71** (**Table 3**). The notable exceptions are the benzyl carbenoids with cyano- and ester-substituents. The failure could be due to the electron withdrawing nature of the *p*-cyano- and *p*-ester-substituent making the carbenoid less nucleophilic preventing formation of a zirconate complex. Alternatively the zirconate complex might form, but not rearrange. If the later was true it would prevent other carbenoids attacking the zirconium. To attempt to distinguish between the hypotheses a reaction was carried out where 2 equivalents of LDA was added to a mixture of 1 equivalent of the zirconacycle **71**, 1 equivalent of benzyl chloride and 1 equivalent of *p*-cyano-benzyl chloride. GC showed complete insertion of benzyl carbenoid into the zirconacycle suggesting that the failure of the *p*-cyano-benzyl carbenoid to insert was due to poor nucleophilicity of the electron-poor carbenoid.

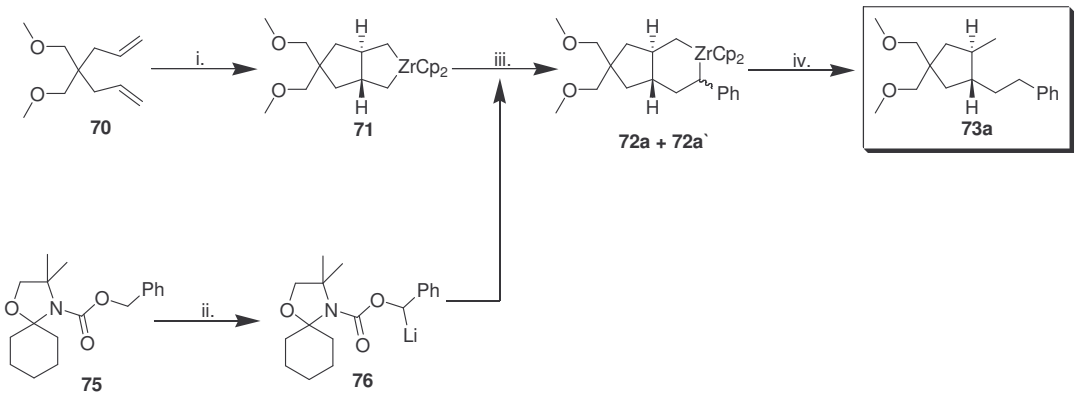
There was no evidence that that zirconacyclohexanes **72a** and **72a`** underwent a cyclometallation process to afford the alkene product, analogous to those observed in the unsaturated system (**Chapter 2**), even on prolonged heating. Zirconacyclohexanes **72a** and **72a`** are stable at 66 °C for 2 days. Slow decompostion of zirconacyclohexanes **72a** and **72a`** was observed when heating at 66 °C was continued for longer than 2 days.

The methodology was extended to show that benzyl carbamates could be used as precursors for the carbenoids. The benzyl carbamate **75** was prepared according to a known procedure (**Scheme 59**).[1] A basic work up was used in each step rather than the acid work up, as previously reported, as this was found to be essential for high yields.



Scheme 59: *Reagents and conditions:* i. *p*-TsOH, reflux, 4 days, 80%; ii. Triphosgene, Et_3N, benzene, reflux, 20 h, 82%; iii. NaH, BnOH, 0 °C - rt, 18 h, 58%.

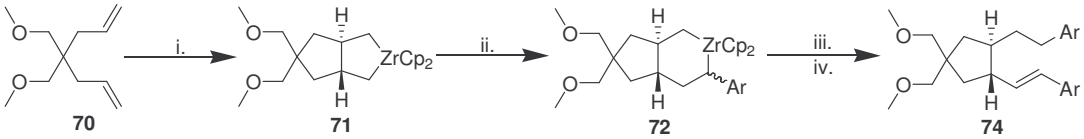
Benzyl carbamate carbenoids **76** can be generated in two ways: *in situ,* by treating with LDA or by pre-forming, by treating benzyl carbamate **75** with *sec*-BuLi and TMEDA. The *in situ* method gave **73a**, in 40% yield, with the low yield being due to incomplete carbenoid insertion. GC analysis revealed benzyl carbamate **75** and zirconacyclopentane **71** remaining even after several hours at –78 °C. Next, the benzyl carbamate carbenoid **76** was preformed by adding an equivalent of *sec*-BuLi to a solution of the benzyl carbamate **75** and TMEDA in THF at –78 °C for 30 minutes. The solution was then added to the zirconacyclopentane **71**, which had been formed using standard co-cyclisation conditions. After stirring for 3 h at –78 °C and quenching with MeOH and $NaHCO_3$ the desired product **73a** was produced in 60% yield. The low yield was again due to incomplete insertion of the carbamate (**Scheme 60**). Again, GC analysis revealed benzyl carbamate **75** and zirconacyclopentane **71** remaining even after several hours at –78 °C. It was suggested that complete insertion was not observed as either the benzyl carbamate **75** was not completely deprotonated or benzyl carbamate carbenoid **76** decomposes before it inserts into the zirconacyclopentane **71**.



Scheme 60: *Reagents and conditions:* i. $ZrCp_2Cl_2$, *n*-BuLi (2 eq), THF, –78 °C - rt, 2 h. ii. *sec*-BuLi, TMEDA, THF –78 °C, 30 min. iii. 3 h, –78 °C, iv. MeOH, $NaHCO_3$ (aq), –78 °C - rt, 18 h, 60%.

3.2 Bis-insertion of benzyl carbenoids into zirconacyclopentanes.

Filery demonstrated that complete conversion to the bis-inserted products could be achieved if a large excess of benzyl carbenoid was used (**Chapter 1, Scheme 29**).[1] To extend this methodology a range of different benzyl carbenoids were inserted (**Scheme 61** and **Table 3**).



Scheme 61: *Reagents and conditions:* i. $ZrCp_2Cl_2$, *n*-BuLi, THF, –78 °C - rt, 2 h. ii. $ArCH_2Cl$, LDA, –78 °C. iii. $ArCH_2Cl$, LDA, –78 °C. iii. MeOH, $NaHCO_3$ (aq) or HCl (aq), –78 °C – rt, 18 h.

Product	Eq. carbenoid	Ar	Yield (%)
74a	5	C_6H_5	50[a]
74b	3	*p*-$CH_3C_6H_4$	48[b]
74f	5	*p*-ClC_6H_4	43[a]

Table 4: Benzyl carbenoid bis-insertion into zirconacyclopentane 71.
a. reaction quenched with MeOH/NaHCO3 (aq). b. reaction quenched with 2M HCl (aq)

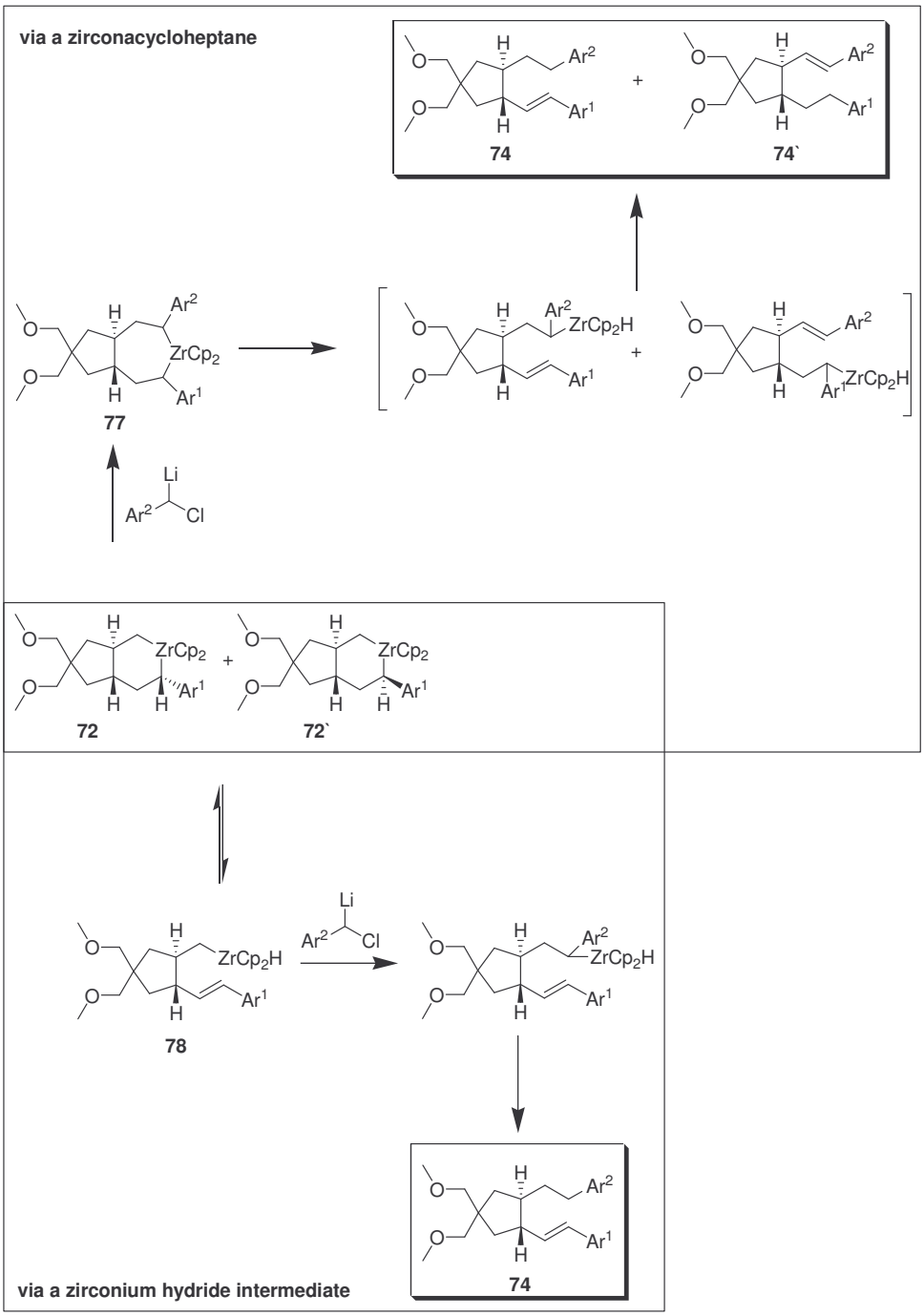
The benzyl carbenoids were formed *in situ* by treating the corresponding benzyl chloride with LDA at –78 °C. Each equivalent of carbenoid was added sequentially until there was complete loss of the mono-inserted product observed by GC.

Purification by column chromatography of the bis-inserted products from co-formed benzyl carbenoid polymers was difficult and resulted in only modest yields of the bis-inserted products (**Table 4**).

3.3 Discussion of the possible mechanism of bis-insertion of benzyl carbenoids into zirconacylcopentanes

Fillery proposed two mechanisms of bis-insertion of benzyl carbenoids into zirconacyclopentanes (**Scheme 62**);[1] *via* zirconacycloheptane **77** or *via* zirconium hydride intermediate **78**.

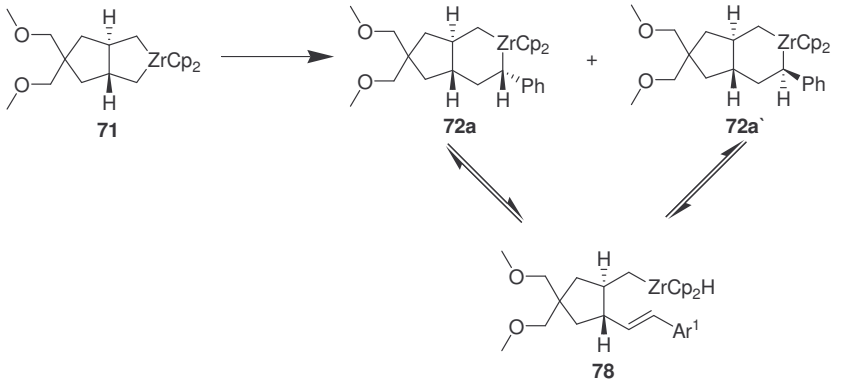
If the mechanism is *via* zirconacycloheptane **77**, if Ar^1 and Ar^2 are different, two different products **74** and **74`** would be expected. If the mechanism was *via* the zirconium hydride intermediate **78**, then only the alkene **74** would be expected.



Scheme 62: Proposed mechanisms for bis-benzyl carbenoid insertion.

Fillery suggested that the mechanism of bis-insertion was *via* zirconium hydride intermediate **78**.[1] This was supported by the observation that zirconacyclohexane **72a`** epimerised to give zirconacyclohexane **72a**. Initially, as expected, a 1:1 diastereoisomer mixture of zirconacyclohexanes **72a** and **72a`** was observed. The 1:1 mixture arises as

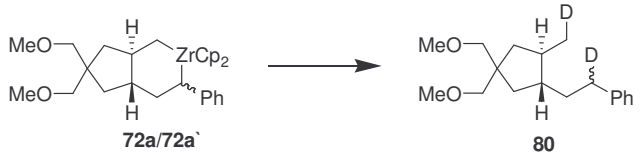
the 1,2-metallate rearrangements occurs stereospecifically with inversion, of the chiral but racemic carbenoid. However, Fillery reported that, on warming, epimerisation of the less stable diastereoisomer **72a`** occurred to afford zirconacyclohexane **72a**. This process took several hours at rt or a few minutes at 60 °C. DFT calculations indicate that **72a** is 13 kJ/mol more stable than **72a`**. Fillery proposed that epimerisation was occurring *via* a zirconium hydride intermediate **78** (**Scheme 63**).



Scheme 63: Proposed mechanism for epimerisation of the zirconacyclohexanes.

Further work into the mechanism of epimerisation was required as work carried out within the group by Dixon[62] (**Scheme 41**) suggested that the zirconocene hydride intermediate **78** would close to form a zirconacyclopentane.

The positions of the diastereotopic benzyl hydrogen's of **73a** were identified, by C-H correlation spectroscopy in $CDCl_3$, at δ_H 2.70 and 2.50 ppm respectively in the ^1H NMR spectra. Relative deuteration of the diastereotopic benzyl hydrogen position was confirmed by loss of the signal in the ^1H NMR. The loss of the signal in the ^1H NMR was used to calculate the ratio of diastereoisomers (**Scheme 64**).



Scheme 64: Quenching the zirconacyclohexane with DCl in D_2O affords the bis deuterium compound **80**.

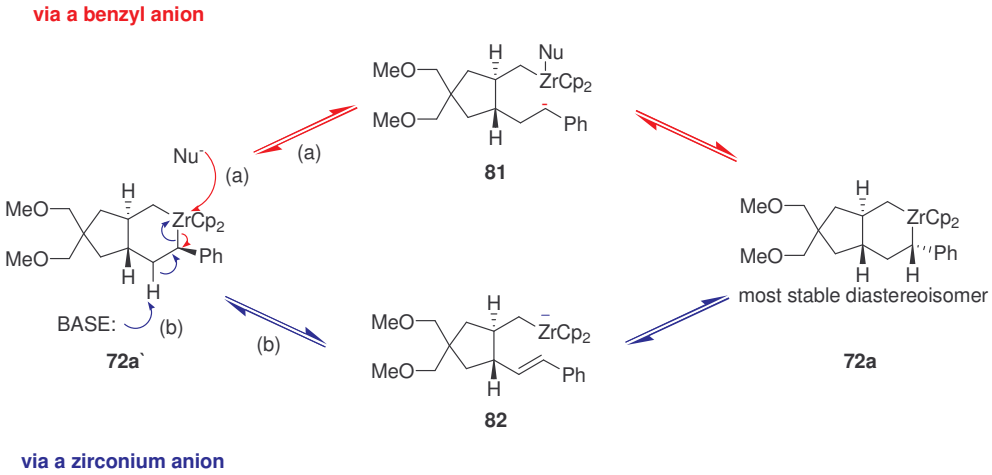
Initial studies confirmed that the zirconacyclohexanes **72a** and **72a`** were produced as a 1:1 diastereotopic mixture, and this ratio was maintained if the reaction mixture was not

warmed above –10 °C. However, interesting results were obtained when the reaction mixture was allowed to warm to 0 °C. Study A clearly showed epimerisation of diastereoisomer **72a`** to **72a**, whereas no epimerisation was observed in study B even though both reactions were carried out under seemingly the same conditions (**Table 5**).

Time after benzyl carbenoid insertion (min)	A		B	
	72a (%)	**72a`** (%)	**72a** (%)	**72a`** (%)
0	51	49	50	50
10	65	35	50	50
30	74	26	50	50
90	77	23	50	50

Table 5: The ratio of diastereoisomers of zirconacyclohexane **72a** at 0 °C. Study A and B were carried out under the same conditions. (*Reagents and conditions*): i. $ZrCp_2Cl_2$, *n*-BuLi, THF, –78 °C - rt, 2 h. ii. BnCl, LDA, –78 °C, 5 min. iii. Warm to 0 °C and samples (1 mL) removed at timed intervals and quenched with 2M DCl in D_2O.

It was proposed that an excess of base could be catalysing the epimerisation. Two possible mechanisms for base epimerisation of the zirconacyclohexane **72a`** were proposed. The first was that the epimerisation was catalysed by the nucleophilic addition of LDA into the vacant zirconium orbital to generate benzyl anion **81**. The second mechanism proposed was that LDA deprotonated the zirconacyclohexane **72a`** to generate zirconocene anion **82** (**Scheme 65**).

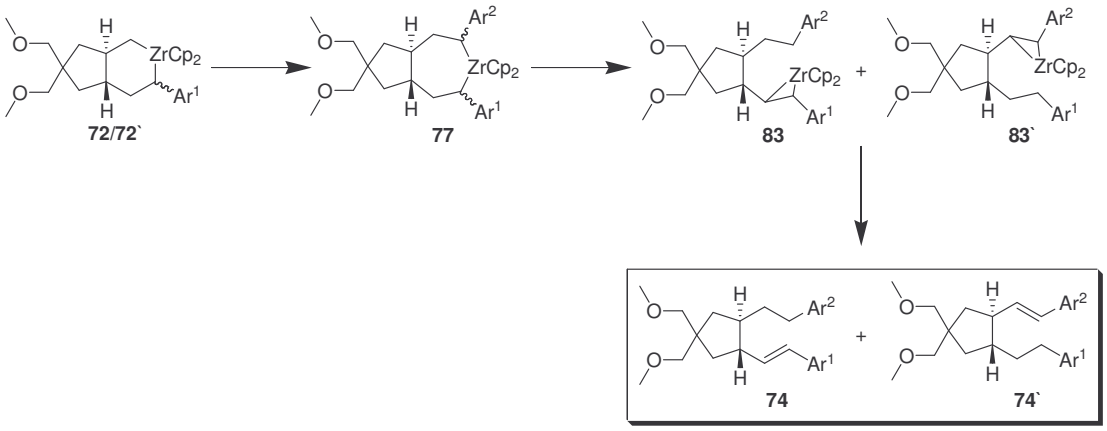


Scheme 65: Proposed mechanisms of epimerisation.

This process was investigated by carrying out an experiment where initially only 0.75 equivalents of LDA was added to ensure that there was no excess of base present. A 1:1 ratio of diastereoisomers was observed, and this was maintained even when held at 0 °C for 2 h. The addition of a further 0.5 equivalents of LDA catalysed the rapid epimerisation to give only diastereoisomer **72a** in 30 minutes at 0 °C. This demonstrates that the epimerisation is being catalysed by LDA. When the reaction was repeated with LiTMP as the base, no epimerisation was observed, even with a large excess of base. This led to the conclusion that epimerisation is catalysed by nucleophilic addition of the LDA in to the vacant zirconium orbital.

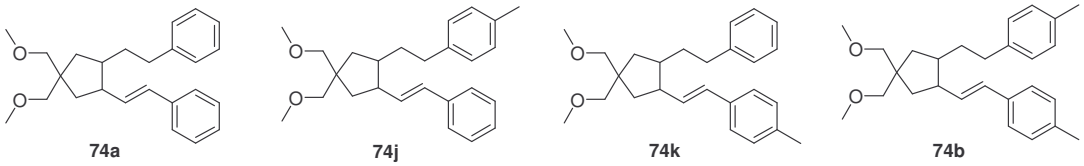
As it was concluded that epimerisation was occurring *via* a nucleophilic catalysed process, rather than *via* a zirconium hydride intermediate, further investigation of the mechanism of bis-insertion was required.

Taking into account the discovery of the endocyclic cyclometallation process that occurred in the unsaturated systems to give the alkene products (**Chapter 2**), the following bis-insertion mechanism was proposed. The second equivalent of benzyl carbenoid inserts into the zirconacyclohexane **72** and **72`** to afford a zirconacycloheptane **77**. A subsequent cyclometallation afford the zirconocene $\eta^2$-alkene complexes **83** and **83`**, which on decomplexation affords alkenes **74** and **74`** (**Scheme 66**).



Scheme 66: Proposed mechanism of bis-insertion into a saturated zirconacycle.

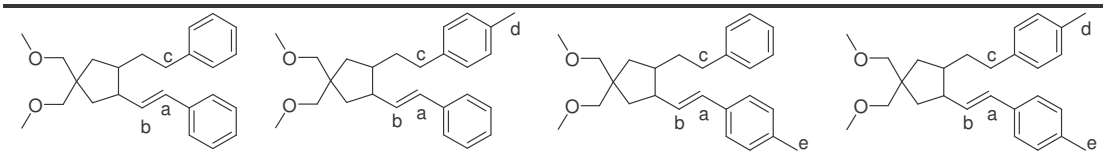
As the mechanism proceeds *via* a zirconacycloheptane **77**, the order of addition should have no effect on the outcome of the reaction. The mechanism of bis-insertion into saturated zirconacycles was investigated by sequentially adding two different benzyl carbenoids that were electronically very similar. As a result, benzyl chloride and *para*-methylbenzyl chloride were selected as the carbenoid precursors. Two experiments were carried out in a deficiency of base, to ensure the second equivalent of carbenoid was added to a 1:1 diastereotopic mixture of **72** and **72`** and two were carried out with an excess of base, to ensure that the second equivalent of carbenoid was added to only the most stable diastereoisomer **72**. The results are highlighted in **Table 6**.



	1st carbenoid precursor	2nd carbenoid precursor	Excess of base added	**74a**	**74j**	**74k**	**74b**
1	BnCl	*p*-CH_3BnCl	No	2	4	3	0
2	*p*-CH_3BnCl	BnCl	No	0	2	10	3
3	BnCl	*p*-CH_3BnCl	Yes	4	20	1	0
4	*p*-CH_3BnCl	BnCl	Yes	0	1	40	8

Table 6: Ratio of products from the bis-insertion reactions.

Structural determinations of the bis-inserted products was achieved by comparing ^{1}H and ^{13}C NMR of the two bis-insertion products with **74a** and **74b**. Clear correlations were observed and are highlighted in **Table 7** and **Table 8**. One notable observation is that there is no deuterium incorporation into the bis-inserted compound on a 1 M DCl in D_2O quench.



74a		**74j**		**74k**		**74b**	
δ (ppm)	Assign	δ (ppm)	Assign	Δ (ppm)	Assign	δ (ppm)	Assign
6.35	Ha	6.35	Ha	6.32	Ha	6.31	Ha
6.04	Hb	6.04	Hb	5.98	Hb	5.98	Hb
2.67	Hc	2.65	Hc	2.68	Hc	2.65	Hc
2.53	Hc	2.49	Hc	2.53	Hc	2.49	Hc
-	-	-	-	2.33	He	2.33	He
-	-	2.31	Hd	-	-	2.31	Hd

Table 7: ^{1}H NMR (300 MHz, $CDCl_3$) assignments of the bis inserted products.

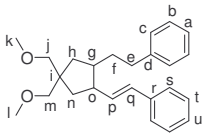
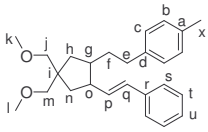
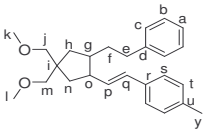
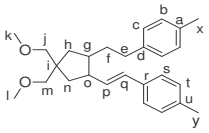
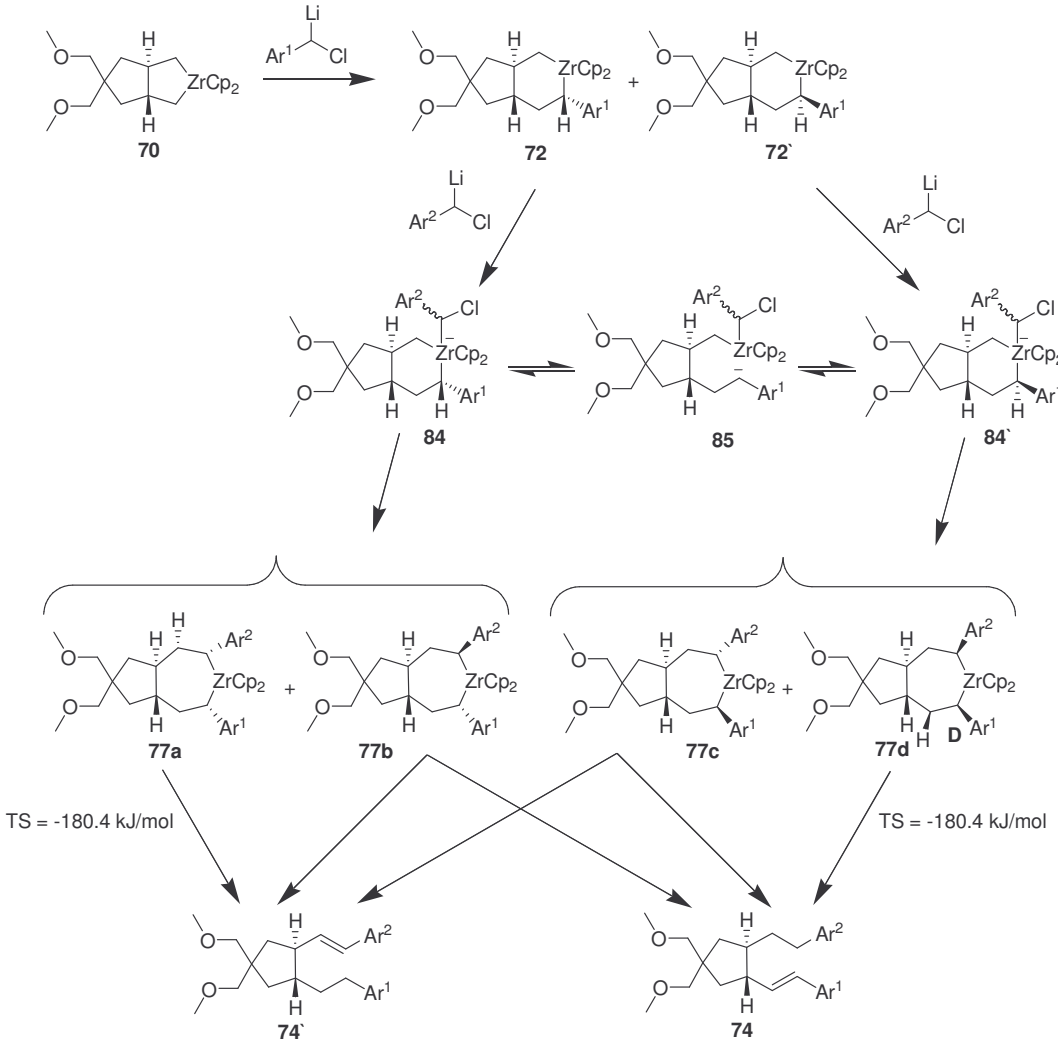
Assign	Mult.	 **74a**	 **74j**	 **74k**	 **74b**
Ca	C/CH	125.88	134.98	125.56	134.93
Cb	CH	128.29/ 128.24	128.92/ 128.14	128.29/ 128.22	128.91/ 128.14
Cc	CH	128.29/ 128.24	128.92/ 128.14	128.29/ 128.22	128.92/ 128.14
Cd	C	142.82	139.73	142.82	139.75
Ce	CH_2	35.94	36.14	35.95	36.14
Cf	CH_2	34.72	34.27	34.72	34.27
Cg	CH	45.26	45.24	45.26	45.24
Ch	CH_2	40.02/ 39.15	39.95/39.12	40.00/39.12	40.00/ 39.12
Ci	C	45.84	45.72	45.70	45.72
Cj	CH_2	77.92	77.86/ 77.82	77.87/ 77.84	77.88/ 77.84
Ck	CH_3	59.28	59.29	59.29	59.27
Cl	CH_3	59.28	59.29	59.29	59.27
Cm	CH_2	77.92	77.86/ 77.82	77.87/ 77.84	77.88/ 77.84
Cn	CH_2	40.02/ 39.15	39.95/39.12	40.00/39.12	40.00/ 39.12
Co	CH	49.85	49.87	49.88	49.85
Cp	**CH**	**133.79**	**133.72**	**132.67**	**132.70**
Cq	**CH**	**129.81**	**129.77**	**129.62**	**129.58**
Cr	C	137.77	137.69	136.57	136.52
Cs	**CH**	**126.00**	**125.97**	**125.87**	**125.86**
Ct	**CH**	**128.44**	**128.44**	**129.14**	**129.12**
Cv	C/CH	126.84	126.82	134.90	134.93
Cx	CH_3	-	20.96	-	20.96
Cy	CH_3	-	-	21.12	21.11

Table 8: ^{13}C NMR (300 MHz, $CDCl_3$) assignments of the bis inserted products.

As expected two different alkene products are produced during the reaction, however, the ratios of the two cross-over products are not as predicted. The most interesting result is when the zirconacyclohexane is epimerised prior to insertion of the second carbenoid. In both cases the reaction is almost entirely selective, preferring the alkene to be positioned next to the aromatic group that was inserted first (entry 3 and 4, **Table 6**).

When a deficiency of base was used insertion of the first carbenoid afforded the zirconacyclohexanes **72** and **72`** in a 1:1 ratio of diastereoisomers. In the same way

insertion of the second benzyl carbenoid would be expected to lead to a 1:1:1:1 mixture of **77a-d**. However, it is possible that epimerisation of **72`** to **72** could occur during the second insertion, either due to the LDA present, or at the 'ate' complex stage **84** and **84`** (via **85**) leading to an imbalance between **77a** and **77b** and between **77c** and **77d**. It is also possible that insertion of the second carbenoid is influenced by the stereochemistry of the zirconacyclohexane i.e. **72** and **72`** might select between the two available enantiomers of the carbenoid either at the initial addition stage, or via reversible formation of the 'ate' complex leading to an imbalance between **77a** and **77b** and between **77c** and **77d**. If **72`** is epimerised to **72** before addition of the second carbenoid then only **77a** and **77b** can be formed and although a 1:1 mixture might be expected, an imbalance is possible for the reasons outlined above.



Scheme 67: Proposed mechanism of bis-insertion.

If Ar^1 and Ar^2 are electronically similar then **77b** and **77c** must give equal amounts of **74** and **74'** by symmetry. **77a** and **77d** may produce different ratios of **74** and **74'** but by symmetry the ratio's must be equal and opposite. The energies of the transition states for the cyclometallation of **77a/d** (Ar^1=Ar^2=Ph so they are the same) were modelled using semi empirical (PM3) calculations[66] (**Scheme 67**) and predict that **77a** will give **74'** and **77d** will give **74**. Therefore if we start with a 1:1:1:1 mix of **77a-d** we would expect, by symmetry to get a 1:1 mixture of **74** and **74'**. If we start with a 1:1 mixture of **77a** and **77b** (initial empimerisation of **72`** to **72**) we would expect to get a 3:1 mixture of **74'** to **74**. If the second benzyl carbenoid insertion is influenced by the structure of the zirconacyclohexane we could conceivable get only **77a** (giving **74'**) or **77b** (giving 1:1 **74'** and **74**). In practice we observe good selectivity for **74** in this case (alkene next to aryl group from the first benzyl carbenoid inserted – Ar^1). Although transition states were found using semi empirical (PM3) calculations, the energies are not reliable. A more conclusive way would be to model the reaction profile using DFT calculations. Density function theory (DFT) calculations are far more reliable, but are several orders of magnitude slower so cannot realistically be used to create reaction profiles. Never the less, these calculations do cast doubt over the mechanism of bis-insertion being *via* a zirconacycloheptane. However, an alternative mechanism that explains the observed results is yet to be found.

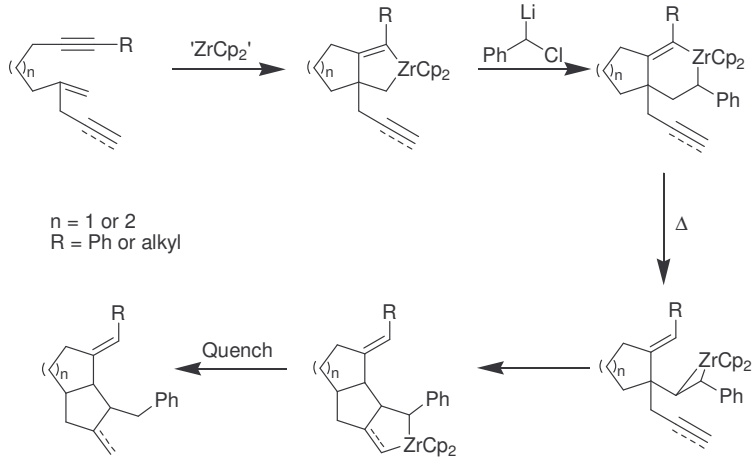
3.4 Conclusions

A range of benzyl carbenoids, with exception of those with strongly electron-withdrawing substituents, have been successfully inserted into saturated zirconacycles. Bis-insertion of benzyl carbenoids into saturated zirconacycles affords the mono-alkene product. It was speculated that the mechanism of bis-insertion is *via* a zirconacycloheptane followed by an endocyclic cyclometallation to afford a zirconocene η^2-alkene complex, which on decomplexation gave the mono-alkene product.

4 Intramolecular trapping of zirconocene η^2-alkene complexes to generate bicyclic compounds

4.1 Introduction to the concept

It has been shown that zirconium η^2-alkene complexes, generated by a novel endocyclic cyclometallation, can be successfully trapped with species such as acetone and alkynes (Chapter 2). This led to the concept of intramolecular trapping of the zirconocene η^2-alkene complex being proposed (**Scheme 68**). Trapping of the η^2-alkene complex with a pendant alkene or alkyne species would lead to interesting bicyclic compounds in a one pot tandem reaction sequence.

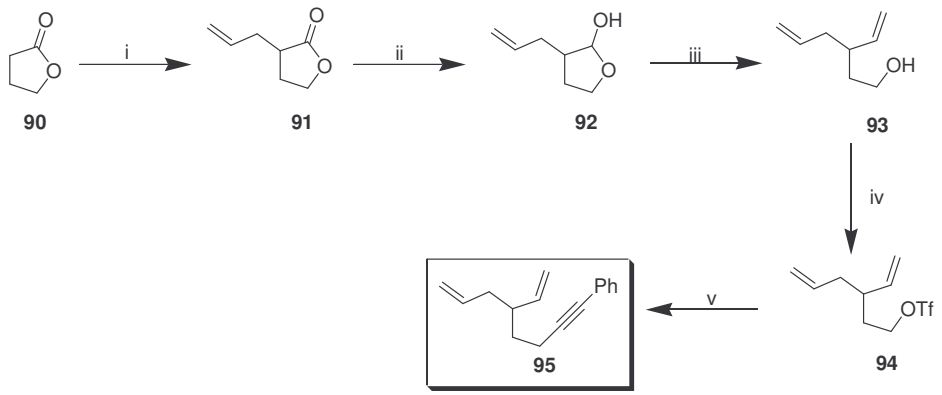


Scheme 68: Intramolecular trapping of zirconium η^2-alkene complexes with alkenes or alkynes.

4.2 β-Branched systems

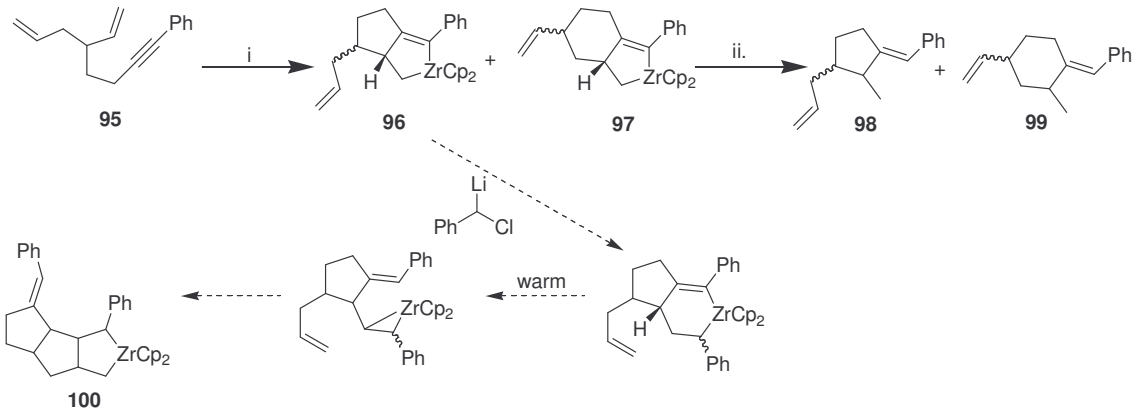
Enyne **95** was selected as a suitable substrate to investigate the concept of intramolecular trapping of zirconocene η^2-alkene complexes. The synthesis of enyne **95** is highlighted in **Scheme 69**. Alkylation of lactone **90** with allylbromide yielded the lactone **91** in 41% yield.[75] Lactone **91** was reduced with DIBAL-H to afford lactol **92** which was used crude in the subsequent reaction.[75] Wittig olefination of **92** afforded alcohol **93**, in 41% yield over the two steps.[76] Conversion of alcohol **93** to the corresponding triflate **94** was carried out using standard conditions.[77] Triflate **94** was used crude in the subsequent alkylation reaction to give the desired substrate **95** in 41%

yield. Parallel alkylation reactions were carried either in the presence or absence of HMPA. No improvement of yield was observed with the presence of HMPA and the low yield is believed to be due to the instability of triflate **94**. The corresponding alkylation reaction with the more stable mesylate was unsuccessful.



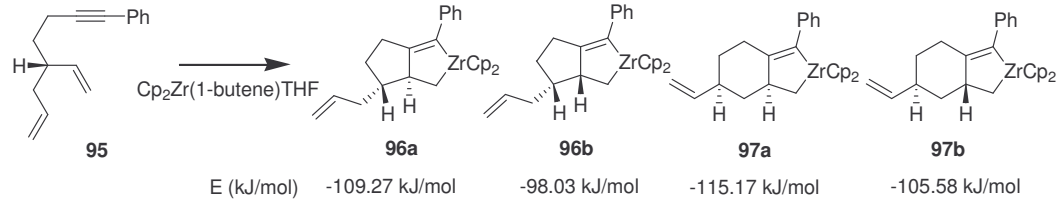
Scheme 69: *Reagent and condition:* i. LDA, HMPA, allyl bromide, THF, –78 ºC, 2 h, 41%. ii. DIBAL-H, toluene, –78 ºC, 30 min. iii. CH_3PPh_3, KHMDS, THF, 0 ºC, 15 min then rt 1 h, 41% over the two steps. iv. Triflic anhydride, pyridine, CH_2Cl_2, 0 ºC, 15 min, 97%. v. Phenylacetylene, *n*-BuLi, THF, –78 ºC – rt, 18 h, 41%.

Attempted co-cyclisation of **95** using zirconocene(1-butene), generated *in situ* from dibutylzirconocene (Negishi's reagent)[24] afforded a 1:1 mixture of the dienes **98** and **99**, presumably generated *via* zirconacyclopentenes **96** and **97** (**Scheme 70**). Formation of **96** and **97** was determined by removing a small amount of the reaction mixture and quenching with HCl. Analysis of the crude NMR revealed a triplet of double doublets at δ_H 5.78 ppm, a characteristic signal of the terminal alkene of **98**, overlapping with a double double doublet at 5.69 ppm, a characteristic signal of the terminal alkene of **99**. Both products were produced in a 9:1 mixture of diastereoisomers, determined by GC analysis. No further work was carried out on this system due to the conclusions drawn from the DFT calculation given below (**Scheme 71** and **Scheme 72**).



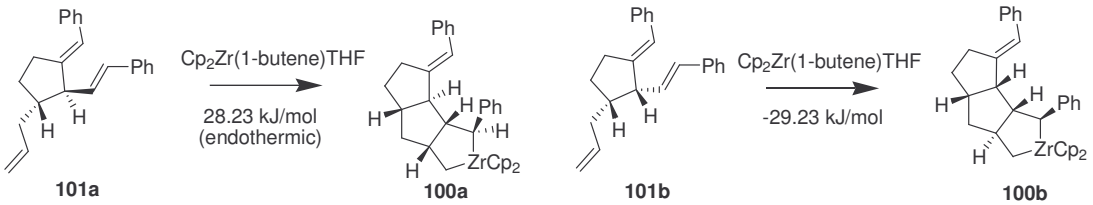
Scheme 70: *Reagents and conditions:* i. $ZrCp_2Cl_2$, *n*-BuLi, THF, –78 °C - rt, 2 h. ii. 2 M HCl (aq), 2 h, rt.

DFT relative energy calculations predicted that the zirconacyclopentene **97a** should be the most stable from the possible isomers shown (**Scheme 71**).[66] It is speculated that isomerisation of zirconacyclopentene **96a** to only give **97a** would have been observed if the reaction mixture had been left for longer. The calculations also predicted that the initial cyclisation should be stereospecific, if under thermodynamic control, supporting the 9:1 diastereotopic ratio observed.



Scheme 71: DFT calculation of the zirconocene mediated co-cyclisation of enyne 95.

At this point DFT relative energy calculations were also carried out on the desired final co-cyclisation to form **100**. For simplicity the co-cyclisation of diene **101** with zirconocene(1-butene) was modelled (**Scheme 72**). The calculations predicted that cyclisation of diene **101a** to afford **100a** was an unfavourable, endothermic, process, whereas cyclisation of diene **101b** to afford **100b** was a favourable process. Co-cyclisation of **101a** is unfavourable as it involved the formation of a *trans*-fused 5,5 ring system. Therefore the final co-cyclisation was unlikely to be successful as the major diastereoisomer of the desired zirconacyclopentene **96a** of the first co-cyclisation would have afforded **100a** in the second co-cyclisation.



Note in each case cyclisation is shown to the most stable of the 4 possible isomeric products.

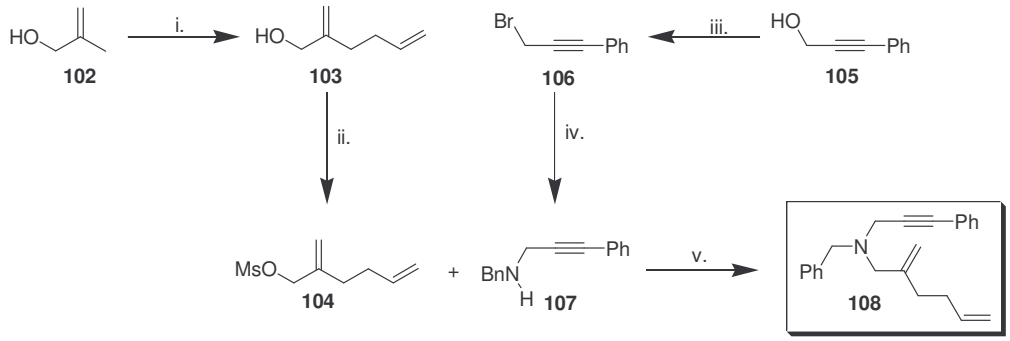
Scheme 72: DFT calculations of the zirconocene mediated co-cyclisation of diene **101a**.

4.3 α-Branched systems

By moving the alkene pendant to the α-position, several problems highlighted in the system above were overcome. It was speculated that only the desired co-cyclisation should occur as a 5-membered enyne co-cyclisation should be more favourable than an 8-membered co-cyclisation. The final product would be a spirocyclic product rather than a fused cyclic product and therefore the issue of forming unfavoured 5,5 *trans* ring junctions would be overcome.

4.3.1 Nitrogen system

A nitrogen containing substrate was chosen for ease of synthesis. Substrate **108** was synthesised under the following conditions (**Scheme 73**).



Scheme 73: *Reagents and Conditions:* i. TMEDA, *n*-BuLi, Et_2O, –78 °C - rt, 20 h, followed by allyl bromide, –78 °C, 2 h, then warmed rt, 2 h, 57%. ii. MsCl, Et_3N, CH_2Cl_2, –10 - 0 °C, 30 min, 98%. iii. PPh_3, Br_2, CH_2Cl_2, 0 °C, 1 h, 71%. iv. $BnNH_2$, Et_2O, rt, 18 h, 53%. v. THF, 10% LiI, rt, 18 h, 57%.

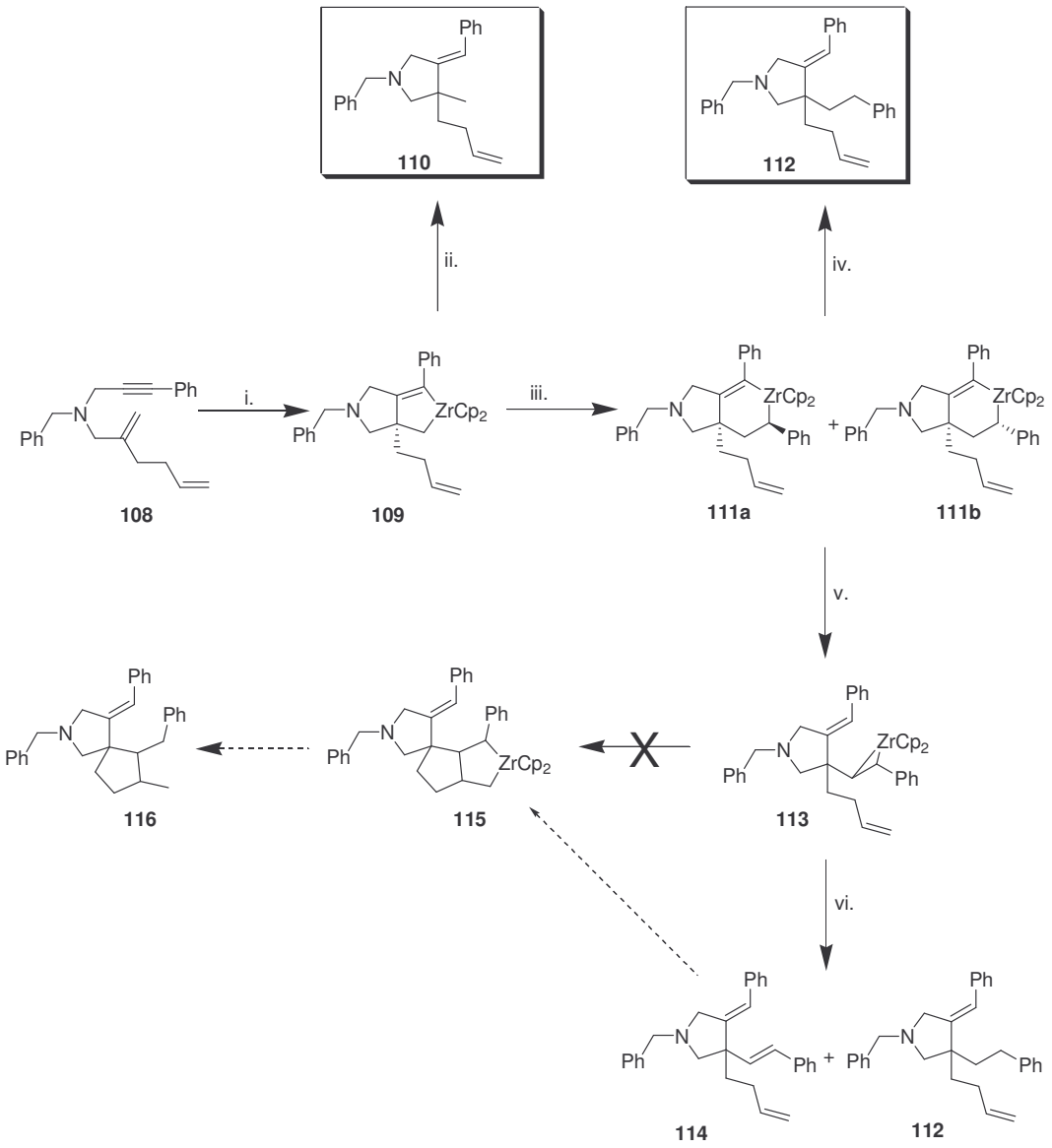
Treatment of 2-methyl-2-propen-1-ol **102** with a preformed mixture of TMEDA and *n*-BuLi afforded the dianion.[78] Alkylation with allyl bromide gave **103**, in 57% yield.[78] Amine **107** was produced by treating benzylamine with bromide[79] **106** in Et_2O. The

mesylate **104** was used crude in the subsequent alkylation of **107** catalysed by 10% LiI to produce the desired substrate **108** in 57% yield.

Intramolecular co-cyclisation of **108** using zirconocene(1-butene) afforded the zirconacyclopentene **109**, which on quenching with HCl gave **110** in 72% yield. Insertion of the benzyl carbenoid, generated *in situ* by treating benzyl chloride with LDA at –78 °C, into zirconacyclopentene **109** afforded **112** on quenching with HCl in Et_2O, generated *via* zirconacyclohexene **111** (**Scheme 74**).

Initial attempts to effect the synthesis of spirocyclic compound **115** were carried out by warming the zirconacyclohexene **111** to rt for 18 h. The mixture was quenched with MeOH/$NaHCO_3$ for 66 h and produced an inseparable 1:1 mixture of **112** and the triene **114**. When the reaction was repeated but was only allowed to quench for 18 h an interesting result was observed. The ^{1}H NMR spectrum revealed signals at δ_H 6.27 and 5.77 ppm, characteristic of the cyclopentadienes of the zirconocene. That suggested that the reaction mixture had not been completely quenched.

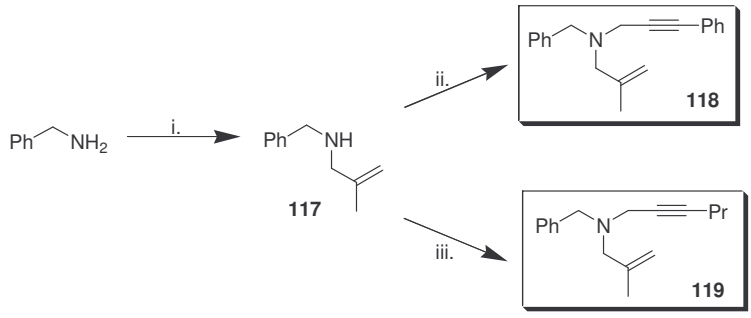
It was apparent that the reaction mixture required harsh quenching conditions. A range of different quenches were investigated. It was found that KOH/MeOH effectively quenched the reaction mixture in 6 h, 2 M HCl (aq) in 18 h and MeOH/$NaHCO_3$ required 66 h. It was concluded that the most practical quench was 2M HCl (aq) for 18 h. With all intermediates quenched the crude ^{1}H NMR suggested a 1:1 mixture of **112** and triene **114** had been produced. The mixture was not purified.



Scheme 74: *Reagents and conditions:* i. $ZrCp_2Cl_2$, *n*-BuLi, THF, –78 °C - rt, 2 h. ii. 2 M HCl (aq), rt 18 h, 72%. iii. BnCl, LDA, –78 °C, 30 min. iv. 2 M HCl in Et_2O, –78 °C - rt, 18 h, 79%. v. Warm to rt, 18 h. vi. 2 M HCl (aq), rt 18 h.

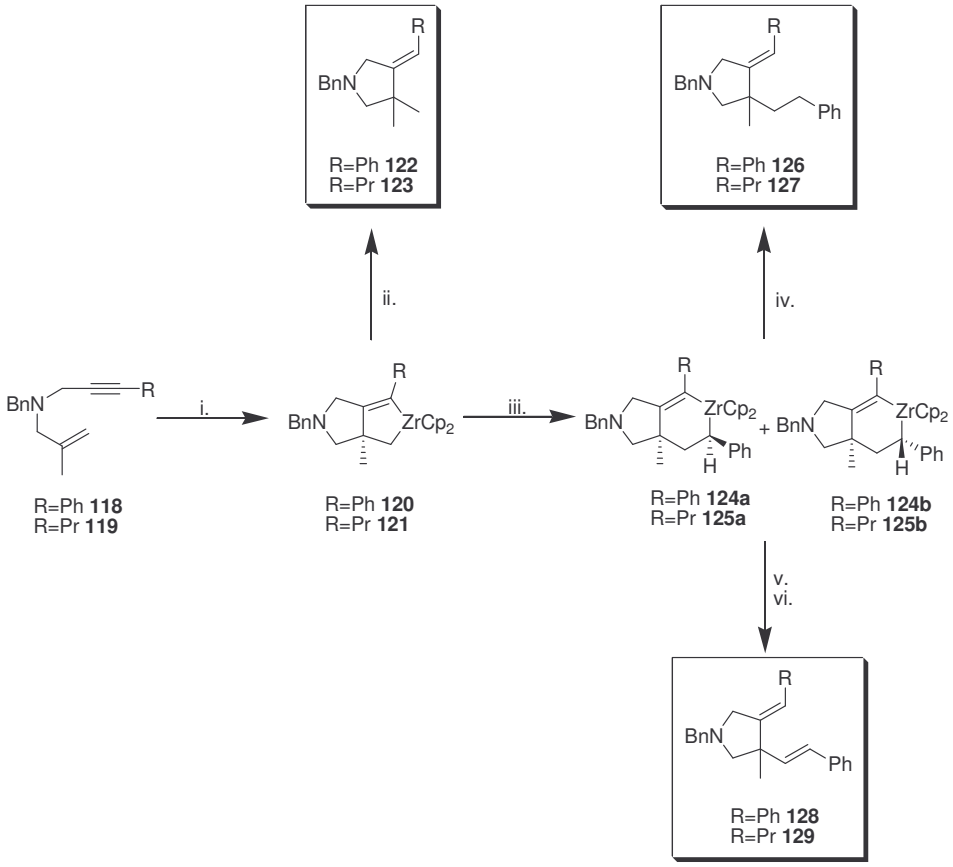
Initial reactions indicated that the cyclometallation of **111** to afford zirconocene η^2-alkene complex **113** is very slow, after 18 h a 1:1 mixture of **112** and (*E*)-alkene **114** is afforded. This indicated that only one diastereoisomer had undergone the cyclometallation. As the cyclometallation process has never been studied on systems containing nitrogen or systems with a substituent in the α position, model studies were conducted.

Alkylation of benzylamine with 3-chloro-2-methylprop-1-ene in H_2O gave *N*-benzyl-2-methylprop-2-en-1-amine **117** in 62% yield.[80] Enyne **118** was synthesised in 93% yield *via* the Mannich reaction of **117** and phenyl acetylene (**Scheme 75**).[81] Enyne **119** was synthesised in 51% yield by alkylation of **117** with 1-bromohex-2-yne.



Scheme 75: *Reagents and conditions:* i. 3-chloro-methylprop-1-ene, $NaHCO_3$, H_2O, 90 °C, 18 h, 62%. ii. Phenylacetylene, formaldehyde, DMSO, rt, 20 h, 93%. iii. 1-bromohex-2-yne, K_2CO_3, MeCN, rt, 18 h, 51%.

In both cases intramolecular co-cyclisation with zirconocene(1-butene) yielded the expected zirconacyclopentenes **120** and **121**, which on quenching yielded **122** and **123** in 85% and 70% yields respectively. Benzyl carbenoid insertion occurred cleanly and a low temperature quench gave **126** and **127** in 72% and 75% yield respectively, generated *via* zirconacyclohexenes **124** and **125**. On warming the zirconacyclohexenes **124** or **125** to reflux for 12 h, (*E*)-alkenes **128** and **129** were afforded in 55% and 53% yield respectively.



Scheme 76: *Reagents and conditions.* i. $ZrCp_2Cl_2$, *n*-BuLi, THF, –78 °C - rt, 2 h. ii. 2 M HCl (aq), rt 18 h, R=Ph 85%, R=Pr 70%. iii. BnCl, LDA, –78 °C, 10 min. iv. 2 M HCl in Et_2O, –78 °C – rt, 20 h, R=Ph 72%, R=Pr 75%. v. Warm to reflux, 12 h. vi. 2 M HCl (aq), rt 18 h, R=Ph 55%, R=Pr 53%.

Kinetic studies were carried out by removing aliquots of the reaction mixture and quenching them with 2 M HCl at timed intervals. The samples were analyzed by GC for loss of **126/127** and appearance of the alkene **128/129** to produce first order rate plots. The outcomes of these reactions are highlighted in **Table 9**.

Zirconacyclohexene	Temp of Cyclometallation (°C)	Half Life (min)	K (s^{-1})
124a	20	11.6	0.0019
124b	66	115.5	0.0001
125a	0	11.6	0.0019
125b	66	57.8	0.0002

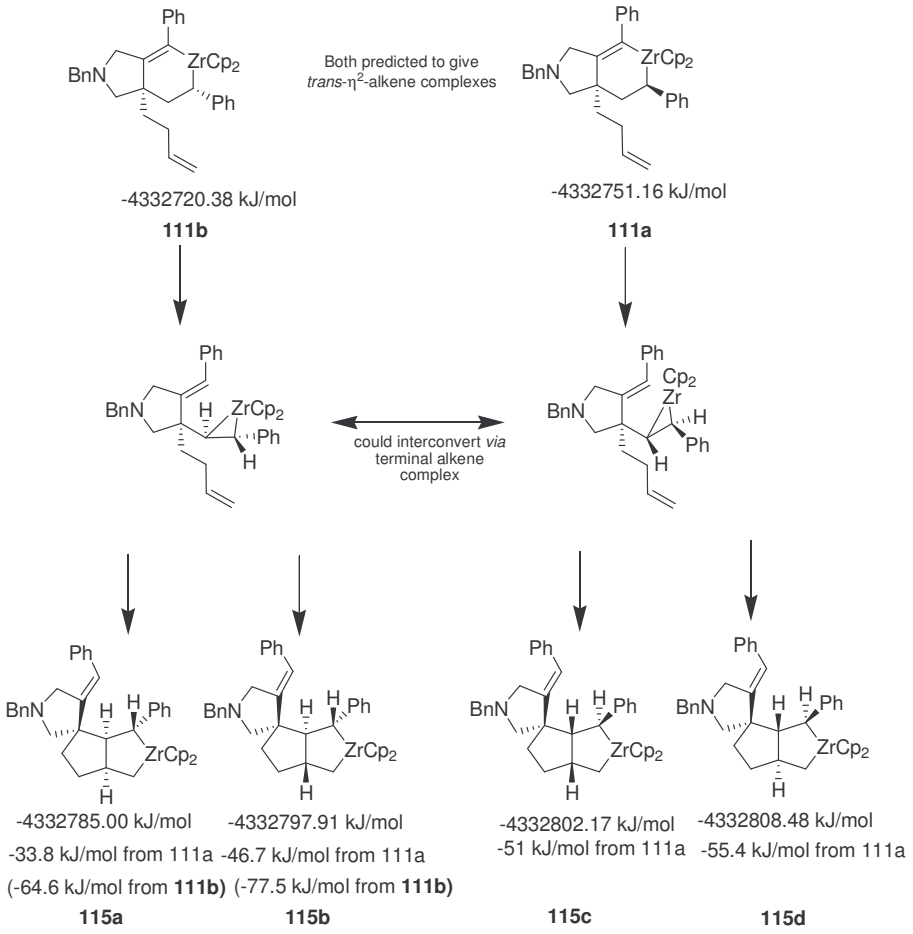
Table 9: Summary of kinetic studies.

As observed in similar systems (**Chapter 2**) diastereoisomer **124b/125b** cyclometallates at a much slower rate than the alternative diastereoisomer **124a/125a**. Diastereoisomers **124b/125b** cyclometallate at a much slower rate than the systems studies in **Chapter 2**. No cyclometallation of diastereoisomers **124b/125b** was observed when the reaction mixture was monitored for 24 h at 20 °C. The slow rate of cyclometallation was attributed to the α-branch.

It was concluded that a 1:1 mixture of **112** and (*E*)-alkene **114** was observed due to the fact that the cyclometallation of diastereoisomer **111b** was much slower than predicted. However, why was the (*E*)-alkene **114** observed and not the desired spirocycle **116**? One possible explanation is the final co-cyclisation may be hindered; therefore the rate of decomplexation may be greater than the rate of co-cyclisation. Another possible explanation is the zirconocene η^2-alkene complex **113** may have been stabilised by the nitrogen.

One way to determine whether the final cyclisation is feasible or not, would be to carry out a co-cyclisation of alkene **114** using Negishi's reagent, which should yield the desired spirocycle **116**. Attempted synthesis of the alkene **114** was carried out as before but with the presence of CH_2Cl_2[74] to aid decomplexation and the reaction mixture was warmed to reflux to increase the rate of cyclometallation. After 48 h the cyclometallation was incomplete and the mixture had started to decompose.

DFT relative energy calculations[66] predict that the final co-cyclisation should be a favourable process (**Scheme 77**).



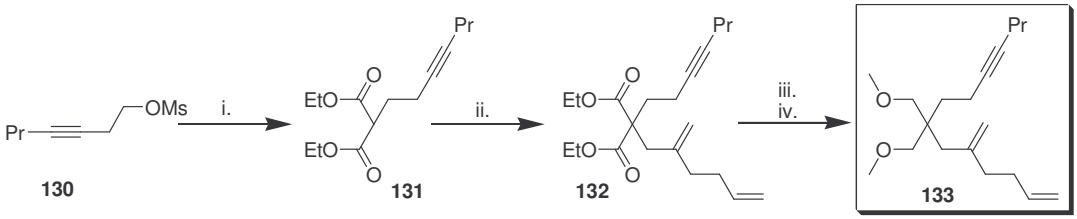
Scheme 77: DFT calculations.

Several points can be concluded, the first noteworthy observation was that the rate of cyclometallation was very slow and therefore did not go to completion. There could be several reasons why the zirconocene η^2-alkene complex formed failed to undergo the final cyclisation. The zirconocene η^2-alkene complex may have existed as the nitrogen complex, preventing co-ordination of the alkene. The rate of decomplexation of the zirconocene η^2-alkene complex, aided by diisopropylamine may have been greater than the rate of cyclisation.

4.3.2 6-Membered system

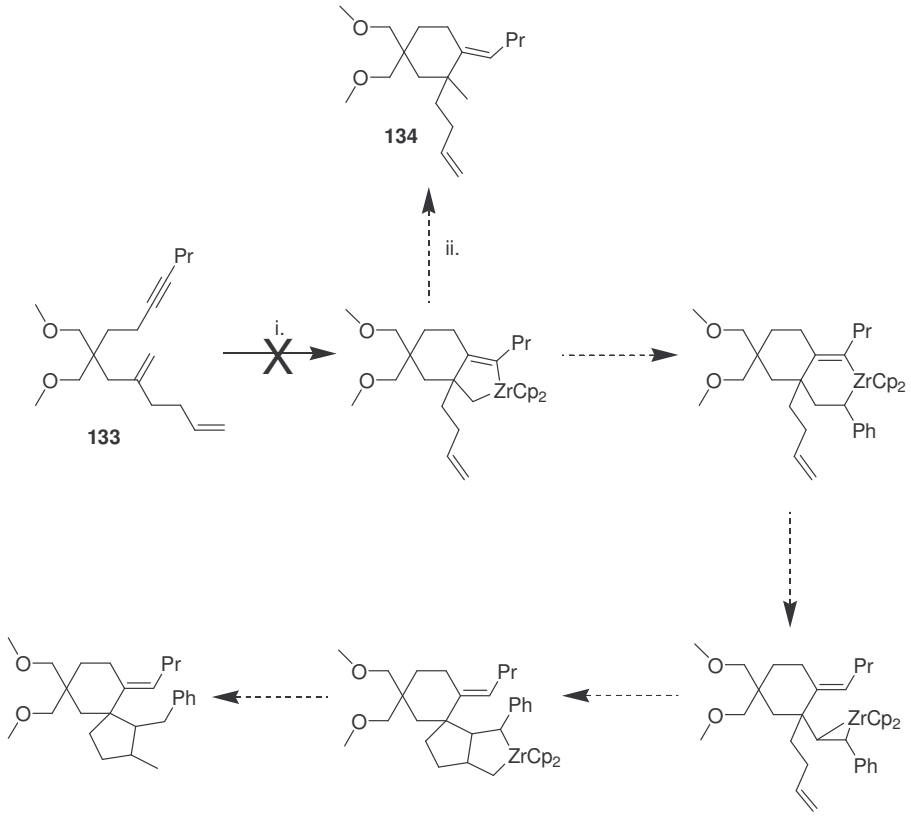
The studies on the nitrogen system showed that an α-substituent drastically decreases the rate of cyclometallation. Previous work carried out showed that the rate of cyclometallation was greater in a system with a 6-membered fused ring than a 5-

membered fused ring. The rate of cyclometallation was also greater in a system with an alkyl substituent rather than a phenyl substituent. Therefore, substrate **133** was synthesised (**Scheme 78**).



Scheme 78: *Reagents and conditions*: i. Diethyl malonate, Na, 10% NaI, EtOH, 0°C - rt, 18 h, 20%. ii. 2-methylenehex-5-enyl methanesulfonate **104**, 10% NaH, NaI, THF, 0 °C - rt, 24 h, 58%. iii. $LiAlH_4$, Et_2O, 0 °C - rt, 4 h, 99%, iv. NaH, MeI, THF, 0 °C - rt, 5 h, 85%.

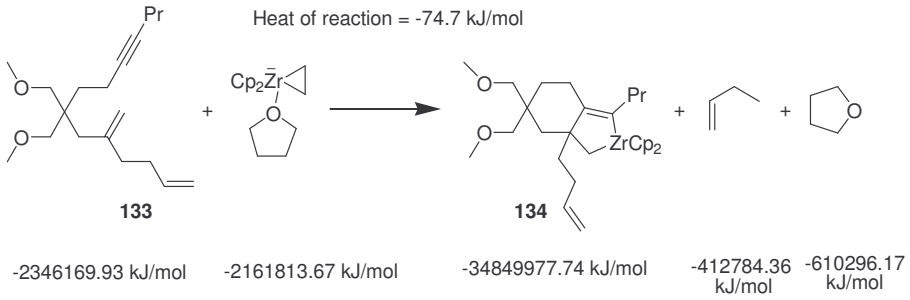
Alkylation of diethyl malonate with hept-3-ynyl methanesulfonate **130** gave the desired mono-alkylated product **131** in only 20% yield. This was due to the fact that the hept-3-ynyl methanesulfonate **130** readily eliminates mesyic acid. A subsequent alkylation of **131** gave **132** in 58% yield. Reduction of **132** and methylation of the resulting diol using standard conditions gave the desired substrate **133** in 85% yield.



Scheme 79: *Reagents and conditions:* i. $ZrCp_2Cl_2$, *n*-BuLi, THF, –78 °C – rt, 2 h. ii. 2 M HCl (aq), 2 h.

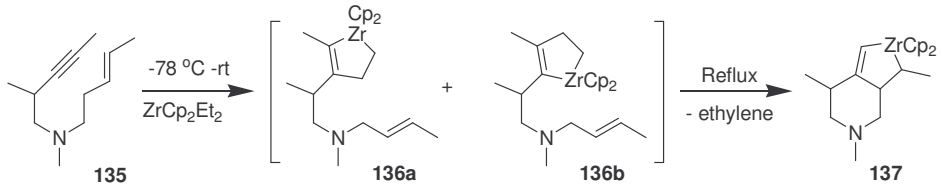
The co-cyclisation of **133** using zirconocene(1-butene) was attempted, but protonation gave no product which could be characterised as the alkene **134** expected therefore, benzyl carbenoid insertion was not pursued.

DFT relative energy calculations[66] show that the co-cyclisation is thermodynamically allowed. However, the alkene is hindered and therefore the intramolecular co-cyclisation may be kinetically unfavoured (**Scheme 80**).



Scheme 80: DFT calculations.

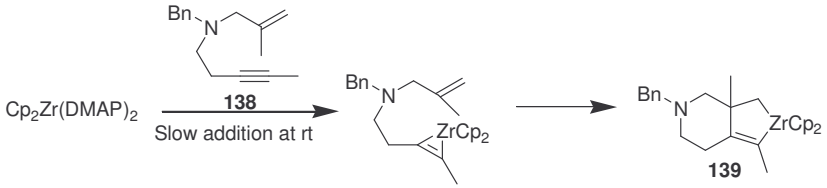
The literature reveals two methods for the co-cyclisation of unfavorable enyne systems. The first method involves the co-cyclisation of the hindered enyne **135** with zirconocene(ethylene)[39](**Scheme 81**). The first step of the reaction involves the zirconocene(ethylene) undergoing a co-cyclisation with the alkyne to form a zirconacyclopentene complex **136**. This first step occurs at low temperature (–78 °C - rt) and it is only on warming to reflux that the alkene displaces the ethylene to give the desired zirconacyclopentene **137**.[26]



Scheme 81: Co-cyclisation of a hindered enyne with zirconocene(ethylene).

The second method illustrated in (**Scheme 82**) involved the co-cyclisation of the hindered enyne **138** with a preformed solution of $Cp_2Zr(DMAP)_2$. $Cp_2Zr(DMAP)_2$ is a

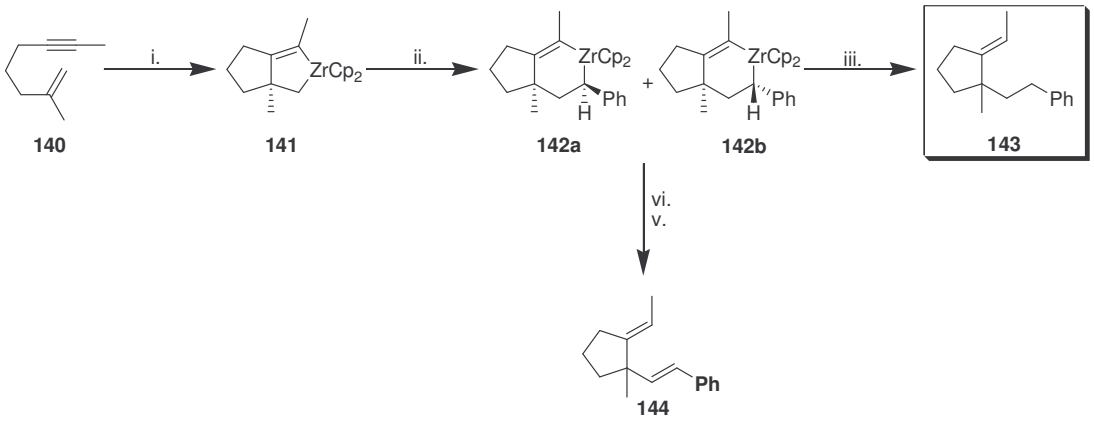
thermally more stable zirconocene(II) equivalent.[82] The hindered enyne is added dropwise to a solution of $Cp_2Zr(DMAP)_2$ at rt. As the concentration of enyne **138** remains low at all times intramolecular co-cyclisation is favoured over intermolecular dimerisation to afford the desired zirconacyclopentene **139**.[27]



Scheme 82: Co-cyclisation of a hindered enyne with zirconocene-DMAP complex.

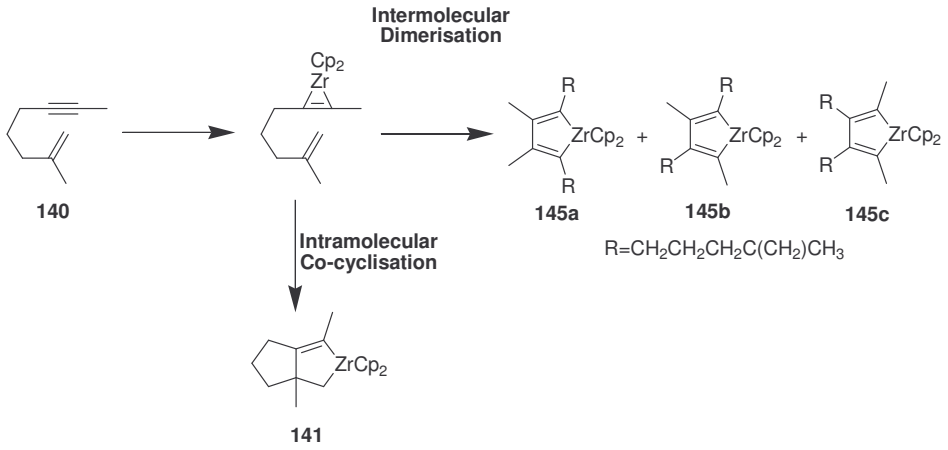
To ensure cyclisation and benzyl carbenoid insertion would be successful under the alternative conditions, the following model system was investigated. This system was chosen as the enyne has an α-substituent and was conveniently available.

Initial reactions carried out showed that the intramolecular co-cyclisation of enyne **140** with $Cp_2Zr(DMAP)_2$ afforded the expected zirconacyclopentane **141**. Benzyl carbenoid insertion occurred cleanly to give **143**, in 73% yield, on quenching with HCl, *via* the zirconacyclohexene **142**. On warming to room temperature, cyclometallation took place to afford the (*E*)-alkene **144** in 53% yield (**Scheme 83**).



Scheme 83: *Reagents and conditions:* i.$ZrCp_2Cl_2$, *n*-BuLi, DMAP, THF, –78 °C - rt, ii. BnCl, LDA, –78 °C, 10 min. iii. 2 M HCl in Et_2O, –78 °C - rt, 18 h, 73%, vi. Warm to rt, 5 h. v. 2 M HCl (aq), rt, 18 h, 53%.

One notable observation was that the initial co-cyclisation was variable. Sometimes it occurred cleanly to give the desired zirconacyclopentene **141** whilst at other times significant amounts of the intermolecular dimerisation products **145** were observed.



Scheme 84: Intramolecular co-cyclisation and intermolecular dimerisation.

In all cases, no excess of enyne **140** had been added which led to the hypothesis that the enyne co-cyclisation is a reversible process. **Table 10** shows the outcome of the co-cyclisation under a range of different conditions.

Time of Sampling	Enyne added at 0 °C	Enyne added at 20 °C (A)	Enyne added at 20 °C (B)
	140: **141**: **145**	**140**: **141**: **145**	**140**: **141**: **145**
½ Enyne added	0.07 : 1 : 0	0 : 1 : 0	0 : 1 : 0
All Enyne added	0.80 : 1 : 0.04	0.11 : 1 : 0.10	0 : 1 : 0.02
1 h	0.28 : 1 : 0.27	0 : 1 : 0.27	0 : 1 : 0.02
21 h	0 : 1 : 0.97	0 : 1 : 0.34	0 : 1 : 0.17

Table 10: Optimisation of intramolecular co-cyclisation with $Cp_2Zr_2(DMAP)_2$. In reaction (A) an excess of enyne **140** was added where as in reaction (B) a deficiency of enyne **140** was used.

In all cases no dimerisation took place when only ½ the enyne had been added. Results showed that the reaction should not be carried out 0 °C as the rate of co-cyclisation is significantly reduced, resulting in a build up of the enyne **140** which leads to

dimerisation. The most interesting observation is that the amount of dimerisation observed increases with time. This is even observed in the reaction which had a deficiency of enyne **140**. This shows that the enyne co-cyclisation must be a reversible process.

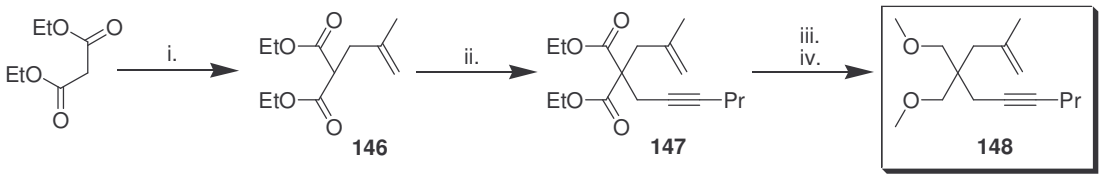
These observations led to the conclusion that the optimum co-cyclisation conditions were at 20 °C (rt) with a slight deficiency of enyne. The resulting zirconacyclopentene should be used immediately.

Intramolecular co-cyclisation of enyne **133** with $Cp_2Zr(DMAP)_2$ proved to be unsuccessful even under the optimal conditions described above. Even with very slow addition (1.5 h), significant amounts of the products of dimerisation were observed in the NMR spectra. Due to time constraints no other methods of co-cyclisation were attempted.

4.3.3 5-Membered system

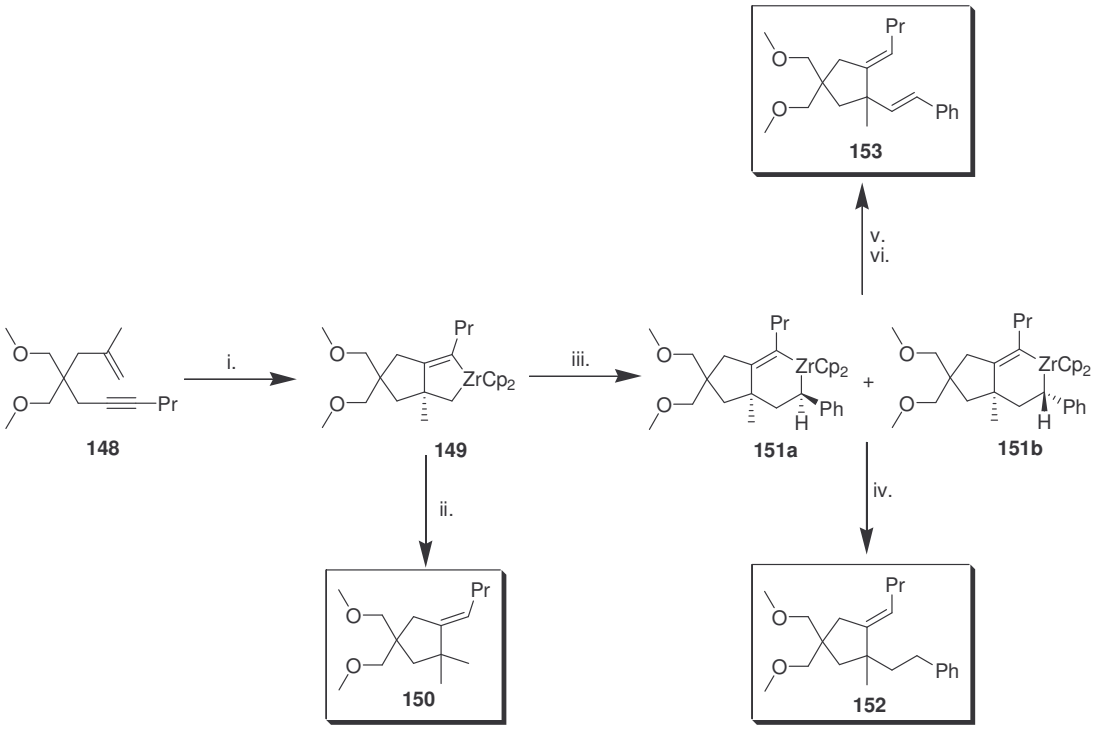
Although several interesting mechanistic observations have been observed, attempts to develop a system capable of intramolecular trapping of zirconium η^2-alkene complexes to give interesting bicyclic compounds have proved unsuccessful. Based on the conclusion drawn from those experiments a 5-membered all carbon system was proposed.

In an attempt to identify potential issues with the system as early as possible the following model system was studied. Synthesis of **148** was achieved by alkylating diethyl malonate with methylallyl chloride to afford **146**.[83] Alkylation of **146** with 1-bromohex-2-yne afforded **147**.[84] Enyne **147** was reduced to give the corresponding diol. Methylation of this diol gave the desired enyne **148** in 73% yield (**Scheme 85**).



Scheme 85: *Reagents and conditions:* i.Methylallyl chloride, NaH, THF, 0 °C - rt, 72 h, 27% yield. ii. 1-bromohex-2-yne, Na, EtOH, 0 °C - rt, 18 h, 87%, iii. $LiAlH_4$, Et_2O, 0 °C - rt, 18 h, 89%, iv. NaH, MeI, THF, 0 °C - rt, 18 h, 73%.

Intramolecular co-cyclisation of enyne **148** with zirconocene(1-butene) gave zirconacyclopentene **149**, which on quenching with HCl (aq) afforded **150** in 70% yield. Benzyl carbenoid insertion afforded zirconacyclohexene **151**, which on quenching with HCl in Et_2O at –78 °C afforded **152** in 65% yield. Warming of zirconacyclohexene **151** to rt afforded the (*E*)-alkene **153** in 86% yield (**Scheme 86**).



Scheme 86: *Reagents and conditions:* i. $ZrCp_2Cl_2$, *n*-BuLi, THF, –78 °C - rt, 2 h. ii. 2 M HCl (aq), rt 18 h, 70% iii. BnCl, LDA, –78 °C, 5 min. iv. 2 M HCl in Et_2O, –78 °C - rt, 18 h, 65%. v. Warm to rt, 24 h. vi. 2 M HCl (aq), rt, 18 h, 86%.

Kinetic studies were carried out to gain greater insight into the cyclometallation process in systems with α-substituents. The results are highlighted **Table 11**.

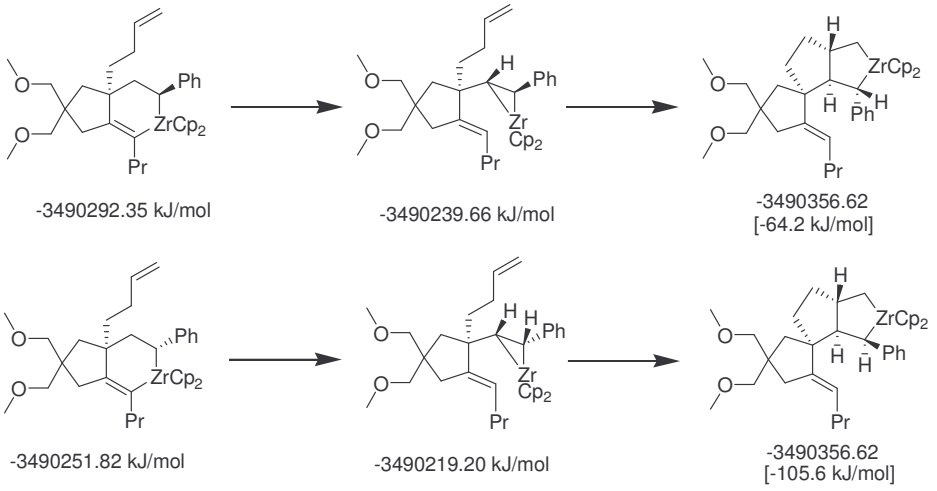
Zirconacyclohexene	Temp of cyclometallation (°C)	Half Life (min)	K (s^{-1})
151a	–5	14.4	0.0008
151b	20	577	0.00002

Table 11: Summary of kinetic study.

As observed in the nitrogen system, diastereoisomer **151b** cyclometallates at a much slower rate than diastereoisomer **151a**. The rate of cyclometallation in the all carbon system **151** is comparable to the rate of cyclometallation in the nitrogen system **125**.

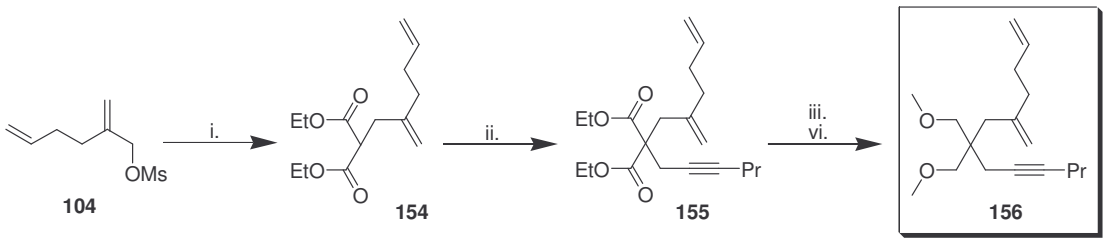
These results show that both diastereoisomers undergo the cyclometallation process to give the (*E*)-alkene. As observed in the nitrogen series, having an α-substituent dramatically decreases the rate of cyclometallation of diastereoisomer **151b**.

The results from this model system provided good evidence that the initial cyclisation and cyclometallation process should be successful. DFT relative energy calculations also predicted that the final co-cyclisation is a favourable process (**Scheme 87**).



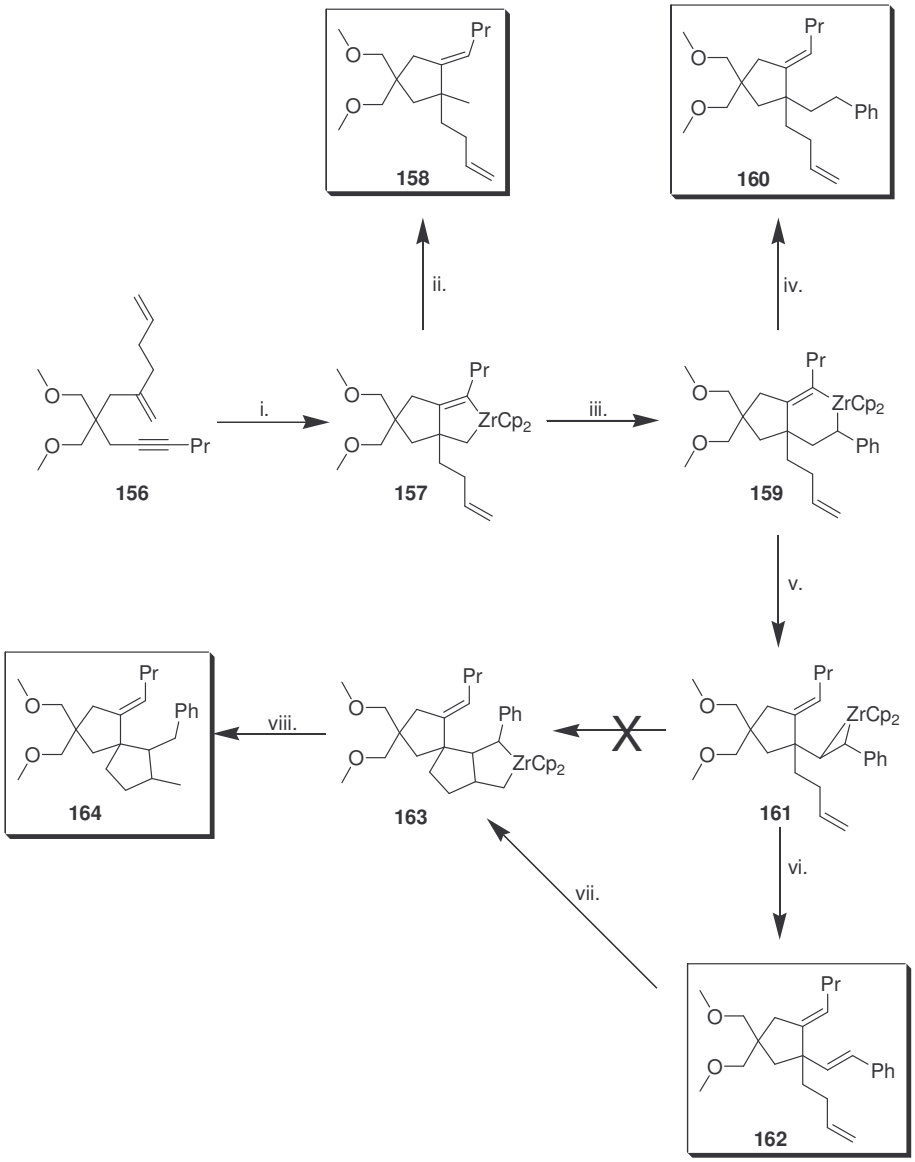
Scheme 87: DFT calculations.

The proposed substrate was synthesised by the following route (**Scheme 88**). Alkylation of diethyl malonate with 2-methylenehex-5-enyl methanesulfonate **104** yielded **154** in 37% yield. Subsequent alkylation of **154** gave **155** in 72% yield. Reduction to the diol followed by methylation occurred cleanly to give **156** in 88% overall yield.



Scheme 88: *Reagents and condition:* i. Diethyl malonate, EtOH, Na, 20% NaI, EtOH, 0 °C - rt, 3 h, 37%. ii. hex-2-ynyl methanesulfonate, NaH, 20% NaI, THF, 0 °C - rt, 24 h, 72%. iii. $LiAlH_4$, Et_2O, 0 °C - rt, 3 h, 94%, iv. NaH, MeI, THF, 0 °C - rt, 4 h, 88%.

Intramolecular co-cyclisation of enyne **156** with zirconocene(1-butene) gave zirconacyclopentane **157**, which afforded **158** on quenching with HCl (aq). Benzyl carbenoid insertion gave **160** on quenching, generated *via* zirconacyclohexene **159**. Warming to rt for 24 h before quenching yielded an inseparable mixture of **160** and **162**. To discover whether the final cyclisation was viable, it was decided to try and isolate the (*E*)-alkene **162** and then co-cyclise with zirconocene(1-butene) in a stepwise process. The (*E*)-alkene **162** was synthesised by adding 2-butyne to the reaction mixture to ensure rapid decomplexation of the zirconocene η^2-alkene complex. The isolated (*E*)-alkene **162** was successfully co-cyclised with zirconocene(1-butene) to give the desired spirocyclic compound **164**, in 68% yield as a 1:1 mixture of diastereoisomers. The two diastereoisomers were successfully separated by preparative HPLC.



Scheme 89: *Reagents and conditions:* i. $ZrCp_2Cl_2$, *n*-BuLi, THF, –78 °C - rt, 2 h. ii. 2 M HCl (aq), rt, 18 h, 93%. iii. BnCl, LDA, –78 °C, 5 min. iv. 2 M HCl in Et_2O, –78 °C - rt, 20 h, 78%. v. 2-Butyne, warm to rt, 24 h. vi. 2 M HCl (aq), rt, 18 h, 30%. vii. $ZrCp_2Cl_2$, *n*-BuLi, THF, –78 °C - rt, 3 h. viii. MeOH, sat $NaHCO_3$ (aq), rt, 20 h, 68%.

Following the successful stepwise synthesis of the spirocyclic compound **164** it was speculated that the reason the final cyclisation failed in the tandem reaction sequence was due the diisopropylamine rapidly decomplexing the zirconocene η^2-alkene complex before the final cyclisation could occur. Closer inspection of GC traces taken during initial reactions showed that a small amount of the spirocyclic compound **164** was present in the reaction mixture, supporting the speculation. 2,2,6,6-Tetramethyl

piperidine is a bulky amine, unlike diisopropylamine, and therefore should not decomplex the zirconocene η^2-alkene complex **161** as rapidly. Therefore the benzyl carbenoid was generated with LiTMP rather than LDA.

After 3 h at rt a 1:2 mixture of (*E*)-alkene **162** and spirocyclic compound **164** was observed. The spirocyclic compound was initially formed as a 1:1 mixture of two diastereoisomers. After 24 h, epimerisation of the spirocyclic compound had occurred to only give one diastereoisomer. Separation of (*E*)-alkene **162** and spirocyclic compound **164** by column chromatography and preparative HPLC proved to be unsuccessful. NMR and GC confirmed a 2:1 mixture of **164** and **162**.

4.4 Further work

Changing the base from LDA to LiTMP had a dramatic effect on the outcome of the reaction. It demonstrates that the amines are greatly aiding decomplexation of the zirconocene η^2-alkene complex. This leads us to consider other bases to form the carbenoids. Nucleophilic bases, such as BuLi, cannot be used as these will react with the zirconacycle. One way that these problems maybe overcome would be to use a benzyl carbamate instead of benzyl chloride to form the benzyl carbenoid. It was shown in Chapter 2 that benzyl carbamate carbenoids can be successfully inserted into zirconacycles. The literature reveals the benzyl carbamate carbenoids are much more stable than the carbenoid derived from benzyl chloride. In fact the benzyl carbamate carbenoids can be preformed by treating with ^{sec}BuLi and are stable at –78 °C. The preformed carbenoid could then be added to the zirconacycle. As a non amine base will be used, hopefully the rate of the final cyclisation will be greater than the rate of decomplexation.

4.5 Conclusions

Several attempted intramolecular trappings of zirconocene η^2-alkene complexes have been reported. The most successful system was the all carbon system **156**. It was shown that the concept of intramolecular trapping of zirconocene η^2-alkene complexes is feasible, however further work is needed to optimise this process. Further investigations of the endocyclic cyclometallation process to afford zirconocene η^2-alkene complexes

were carried out. It was concluded that α-substituents decrease the rate of cyclometallation.

5 Experimental

5.1 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 a hot oven (>140 ºC, for at least 12 hours) and cooled in a sealed desiccator over silica gel.

Unless otherwise stated, reagents were obtained from commercial suppliers and if necessary dried and distilled before use. Solvents for air or moisture sensitive reactions were prepared in the following ways. THF and diethyl ether were freshly distilled from sodium benzophenone ketyl under argon. Dichloromethane was freshly distilled over CaH_2 under argon. *n*-Butyllithium was used as a 2.5 M solution in hexanes, stored in Schlenk stock bottles under argon. Lithium diisopropylamide was used as a 1.8 M solution, stored in stock bottles under argon. DIBAL-H was used as a 1 M solution in hexanes or a 1 M solution in toluene, stored in stock bottles under argon. Potassium bis(trimethylsilyl)amide was used as a 0.5 M solution in toluene, stored in stock bottles under argon. Lithium 2,2,6,6-tetramethylpiperidide was prepared from 2,2,6,6-tetramethylpiperidine (distilled, stored over 4Å sieves under argon) in THF by addition of 1 equivalent of *n*-BuLi at 0 ºC and stirring for 20 minutes.

NMR spectra were recorded on Bruker AV300, AM300 or DPX400 spectrometers. The chemical shifts, δ, were recorded as values in ppm referenced to the $C\underline{H}Cl_3$ peak at 7.27 ppm for ^1H spectra and to the $C\underline{D}Cl_3$ central peak of a 1:1:1 triplet at 77.00 ppm for ^{13}C spectra or to the $C_6\underline{H}D_5$ peak at 7.16 ppm for ^1H spectra and to the $C_6\underline{D}_6$ central peak of a 1:1:1 triplet at 128.1 ppm for ^{13}C spectra. ^2H spectra were referenced to the $C_6H_5\underline{D}$ peak at 0 ppm. The following abbreviations were used to denote multiplicity and may be compounded: s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, sxt = sextet, m = multiplet. Coupling constants, *J*, are measured in hertz (Hz). ^{13}C spectra were proton decoupled. DEPT, COSY and ^1H-^{13}C correlation experiments were used to aid assignment of spectra.

Electron impact ionisation mass spectra (EI) were recorded on a ThermoQuest TraceMS GCMS. Electrospray mass spectra (ES) were recorded using a VG platform quadrupole spectrometer. All electrospray spectra were ES^+ unless otherwise stated. All values of *m/z* are reported in atomic mass units and the peak intensity relative to the base peak is reported in parenthesis. Only the most abundant isotope is reported for compounds containing chlorine. Accurate mass spectra were recorded on a VG analytical 70-250-SE double focusing mass spectrometer using electron impact ionisation (EI) at 70eV or a Bruker Apex III using electrospray ionisation.

Infra-red spectra were run as neat films on a Thermo Mattson FTIR Golden Gate spectrometer and a Thermo Nicolet 380 FT-IR spectrometer with a Smart Orbit Goldengate attachment. Absorptions are given in wavenumbers (cm^{-1}) and the following abbreviations used to denote peak intensities: s = strong, m = medium, w = weak.

Thin layer chromatography was carried out on aluminium backed silica plates and spots visualized by UV (254 nm lamp), phosphomolybdic acid or permanganate stains. Flash column chromatography on silica gel was performed on Kieselgel 60 (230-400 mesh) silica gel. Columns were packed and run under light pressure. Solvent compositions are described as ratios prior to mixing.

Gas chromatography was performed on a Hewlett Packard HP 6890 series GC system, using a HP-5 (cross-linked 5% Ph Me siloxane) 30 m column, with a film thickness of 0.25 μm and 0.32 mm internal diameter. The carrier gas was helium and the flow rate was 2.7 mL min^{-1}. Peak areas were determined using the standard intergrator in Chem Station 6.

GC Method A	**GC Method B**
Injector temperature: 200 °C	Injector temperature: 200 °C
Initial temperature: 80 °C	Initial temperature: 80 °C
Ramp: 25 °C per min	Ramp: 25 °C per min
Final temperature: 250 °C held for 4 min	Final temperature: 300 °C held for 5 min

The following compounds were prepared according to literature procedures: 1-(hept-6-en-1-ynyl)benzene **1**,[21] undec-1-en-6-yne,[21] 1-(oct-7-en-1-ynyl)benzene,[21] dodec-1-en-7-yne,[21] 6-phenylpent-5-yn-1-ol **31**,[85] 4,4-bis(methoxymethyl)hepta-1,6-diene **70**,[36] benzyl 3,3-dimethyl-1-oxa-4-azaspiro[4.5]decane-4-carboxylate **75**,[1] and 2-methyloct-1-en-6-yne **140**.[21]

5.2 Kinetic experiments

General Procedure

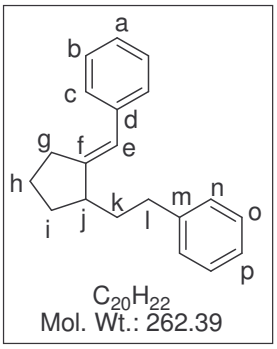
To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 30 min before dropwise addition of a solution of enyne (1.0 mmol) in THF (2 mL). After stirring for a further 30 min at –78 °C the solution was warmed to rt and stirred for a further 2 h. The solution was re-cooled to –78 °C followed by dropwise addition of the benzyl chloride derviative (1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). The solution continued to stir for 15 min at –78 °C before being warmed to the required temperature. Samples (0.1 mL) were removed from the reaction mixture and quenched with 2 M HCl (aq) (1.5 mL) at timed intervals. Et_2O (1 mL) was added to the quenched sample. The Et_2O layer was separated and passed through a short plug of $MgSO_4$ in Pasteur pipette. The samples were analysed by GC.

GC retention times and experimental conditions

Zirconacycle	GC retention time (min) (compound numbers in brackets)			Temperature of cyclometallation (°C)	GC method
	Quenched zirconacycle	(*E*)-alkene	(*Z*)-alkene		
3	7.89 (**4**)	8.22 (**6a**)	7.74 (**6b**)	20	A
37	9.72 (**38**)	10.52 (**39a**)	9.50 (**39b**)	20	A
40	9.03 (**41**)	9.49 (**42a**)	8.70 (**42b**)	20	A
43	6.18 (**44**)	6.38 (**45a**)	6.07 (**45b**)	20	A
46	7.85 (**47**)	8.32 (**48a**)	-	–60[a] –10[b]	A
49	6.37 (**50**)	6.64 (**51a**)	-	–60	A
124	10.35 (**126**)	10.63 (**128**)	-	20[a] 66[b]	B
125	8.34 (**127**)	8.50 (**129**)	-	20[a] 66[b]	B
151	7.73 (**152**)	7.85 (**153**)	-	–5[a] 20[b]	A

Fotenote: a. Temperature of cyclometallation of diastereoisomer a. b. Temperature of cyclometallation of diastereoisomer b.

5.3 (*E*)-2-(2-Benzylidenecyclopentyl)ethyl)benzene **4**



To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 30 min before dropwise addition of a solution of 1-(hept-6-en-1-ynyl)benzene (0.170 g, 1.0 mmol) in THF (2 mL). After stirring for a further 30 min at –78 °C the solution was warmed to rt and stirred for a further 2 h. The solution was re-cooled to –78 °C before the dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). The solution continued to stir for a further 30 min before the addition of 2 M HCl in Et_2O (5 mL). The mixture was stirred for a further 18 h while warming to rt. The mixture was diluted with Et_2O (10 mL), washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compound (0.162 g, 0.62 mmol, 62%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-7.08 (10H, m, **Ar-H**), 6.25 (1H, apparent q, *J* = 2.2 **He**), 2.79-2.49 (5H, m), 2.07-1.79 (3H, m), 1.71-1.54 (2H, m), 1.39 (1H, m) ppm.

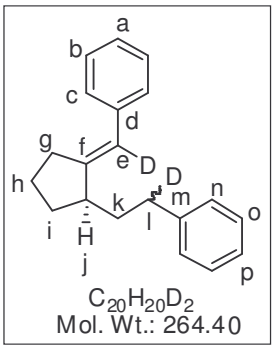
^{13}C NMR (75 MHz, $CDCl_3$): δ 150.21 (C, **Cf**), 142.70 (C, **Cm**), 138.83 (C, **Cd**), 128.38 (CHx2), 128.32 (CHx2), 128.14 (CHx2), 128.13 (CHx2), 125.69 (CH), 125.67 (CH), 120.82 (CH, **Ce**), 45.87 (CH, **Cj**), 36.66 (CH_2), 34.09 (CH_2), 31.75 (CH_2), 31.53 (CH_2), 24.88 (CH_2, **Ch**) ppm.

IR ν_{max}/cm^{-1} (film): 1600 (m), 1490 (m), 1450 (m), 745 (m), 693 (s).

LRMS (EI, CH_2Cl_2): m/z 262 ([$M^{+\cdot}$], 15%), 158 (40%), 129 (65%), 91 (100%).

HRMS (EI): $C_{20}H_{22}$ [$M^{+\cdot}$] calculated 262.1722, found 262.1727.

When the reaction mixture was quenched with MeOD (3 mL) followed by D_2O (3 mL) the following bis-deuterated compound **5** was produced. The following changes in the ^{1}H and ^{13}C NMR were observed.

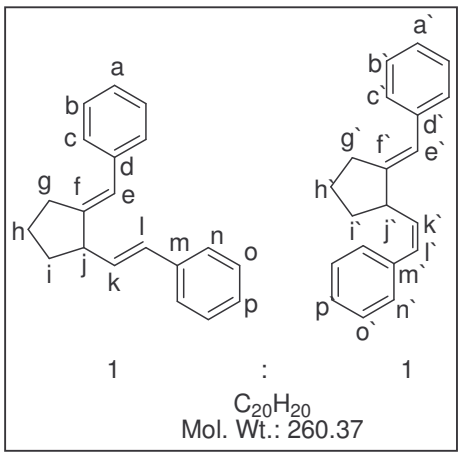


^{1}H NMR (300 MHz, C_6D_6): δ 2.76 (0.5H, m, **Hl**), 2.63 (0.5H, m, **Hl**) ppm.

^{13}C NMR (75 MHz, C_6D_6): δ 120.95 (C, t, *J* = 23.0, **Ce**), 33.82 (CH, t, *J* = 19.4, **Cl**) ppm.

^{2}H NMR (61 MHz, C_6H_6): δ -0.92 (**De**), -4.64 (**Dl**), -4.75 (**Dl**) ppm.

5.4 1-((*E*)-2-((*E*)-2-Benzylidenecyclopentyl)vinyl)benzene **6a** and 1-((*Z*)-2-((*E*)-2-Benzylidenecyclopentyl)vinyl)benzene **6b**



To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 30 min before dropwise addition of a solution of 1-(hept-6-en-1-ynyl)benzene (0.170 g, 1.0 mmol) in THF (2 mL). After stirring for a further 30 min at –78 °C the solution was warmed to rt and stirred for a further 2 h. The solution was re-cooled to –78 °C followed by dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). The solution continued to stir for 15 min at –78 °C before being warmed to reflux. The solution was stirred for a further 3 h before cooling to rt and the addition of 2 M HCl (aq) (5 mL). The mixture was stirred for 18 h before being extracted with Et_2O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: hexane) yielded a 1:1 mixture of the title compounds (0.135 g, 0.52 mmol, 52%) as a colourless oil. NMR of the crude product showed a 1:1 ratio of the (*E*)- and (*Z*)-isomers.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.09 (20H, m, **Ar-H**), 6.59 (1H, d, *J* = 11.5, **Hl`**), 6.58 (1H, d, *J* = 15.9, **Hl**), 6.25 (1H, apparent q, *J* = 2.4, **He**), 6.21 (1H, apparent q, *J* = 2.4, **He`**), 6.11 (1H, dd, *J* = 15.7, 8.4, **Hk**), 5.53 (1H, dd, *J* = 11.5, 9.9, **Hk`**), 3.66 (1H, m, **Hj** ), 3.27 (1H, m, **Hj`**), 2.73-2.25 (4H, m), 2.07-1.85 (4H, m), 1.71-1.37 (4H, m) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 148.70 (C, **Cf/Cf`**), 148.58, (C. **Cf/Cf`**), 138.57 (C, **Cd/Cd`**), 138.50 (C, **Cd/Cd`**), 137.62 (C, **Cm/Cm`**), 137.51 (C, **Cm/Cm`**), 134.75 (CH, **Ck`**), 133.06 (CH, **Ck**), 130.57 (CH, **Cl**), 129.86 (CH, **Cl`**), 128.50 (CHx2), 128.36 (CHx2), 128.25 (CHx2), 128.18 (CHx4), 128.10 (CHx4), 127.00 (CH), 126.78

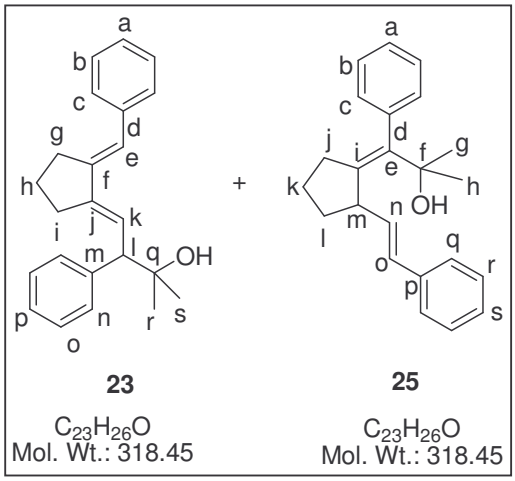
(CH), 126.12 (CHx2), 125.91 (CHx2), 122.85 (CH, **Ce/Ce`**), 122.23 (CH, **Ce/Ce`**), 51.00 (CH, **Cj**), 46.26 (CH, **Cj`**), 34.14 ($CH_2$, **Cg/Cg`**), 33.64 (CH_2, **Cg/Cg`**), 31.58 ($CH_2$, **Ch/Ch`**), 31.31 (CH_2, **Ch/Ch`**), 25.4 ($CH_2$, **Ci/Ci`**), 25.3 (CH_2, **Ci/Ci`**) ppm.

IR ν_{max}/cm^{-1} (film): 1600 (w), 1490 (m), 1446 (m), 745 (s), 691 (s).

LRMS (EI, CH_2Cl_2): m/z 260 ([$M^{+\cdot}$], 35%), 169 (55%), 141 (90%), 115 (90%), 91 (80%).

HRMS (EI): $C_{20}H_{20}$ [$M^{+\cdot}$] calculated 260.1565, found 260.1563.

5.5 (4*E*)-4-((*E*)-2-Benzylidenecyclopentylidene)-2-methyl-3-phenylbutan-2-ol **23** and 2-Methyl-1-phenyl-1-(2-(*E*)-styrylcyclopent-1-enyl)propan-2-ol **25**



$C_{23}H_{26}O$
Mol. Wt.: 318.45

$C_{23}H_{26}O$
Mol. Wt.: 318.45

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (2.0 mmol, 0.80 mL) dropwise over 2 min. After 30 min a solution of 1-(hept-6-en-1-ynyl)benzene (0.172 g, 1.0 mmol) was added dropwise. After 30 min the reaction mixture was warmed to rt for 2 h. The solution was re-cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 1.0 mmol) followed by LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). The reaction mixture was stirred for 5 min at -78 °C before the addition of acetone (0.290 g, 5.0 mmol). The reaction mixture was stirred for a further 30 min at -78 °C before warming to rt for 20 h. The reaction mixture was quenched with MeOH (5 mL) and sat $NaHCO_3$ (aq) (5 mL) and stirred for 2 h. The resulting mixture was diluted with Et_2O (30 mL), washed with H_2O (3 x 50 mL) and brine (3 x 50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 15% Et_2O in hexane) gave firstly the title compound (0.112 g, 0.35 mmol, 35%) as a colourless oil followed by **25** (0.019 g, 0.06 mmol, 6%) and an inseperable mixture of **6a** and **6b** (0.078 g, 0.3 mmol, 30%).

Data for compound **23**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.17 (10H, m, **Ar-H**), 6.88 (1H, s, **He**), 6.50 (1H, d, *J* = 10.0, **Hk**), 3.55 (1H, d, *J* = 10.0, **Hl**), 2.72-2.65 (2H, m), 2.49 (1H, m), 2.29 (1H, m), 1.81-1.63 (2H, m), 1.56 (1H, s, **OH**), 1.28 (3H, s, **Hr/s**), 1.22 (3H, s, **Hr/s**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 144.46 (C), 143.03 (C), 141.51 (C), 138.27 (C), 129.36 (CHx2), 128.75 (CHx2), 128.22 (CHx2), 128.19 (CHx2), 126.57 (CH, **Ca/p**), 126.21 (CH, **Ca/p**), 118.66 (CH, **Ce/k**), 118.40 (CH, **Ce/k**), 73.20 (C, **Cq**), 57.12 (CH, **Cl**),

32.66 (CH_2, **Cg/ i**), 29.69 (CH_2, **Cg/i**), 28.24 (CH_3, **Cr/s**), 27.54 (CH_3, **Cr/s**), 24.22 (CH_2, **Ch**) ppm.

IR ν_{max}/cm^{-1} (film): 3445 (br), 1595 (w), 1489 (w), 1444 (w), 907 (s), 726 (s), 692 (s).

LRMS (ES, H_2O): m/z 341 ($[M + Na]^+$, 100%).

HRMS (ES): $C_{23}H_{26}NaO$ $[M + Na]^+$ calculated 341.1876, found 341.1871.

Data for compound **25**.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42-7.13 (4H, m, **Ar-H**), 7.29-7.13 (7H, m, **Ar-H + Hn**), 6.43 (1H, d, *J* = 15.9, **Ho**), 3.92 (1H, s, **He**), 2.89 (1H, m, **Hj**), 2.60-2.45 (3H, m, **Hj, Hl**), 1.84-1.65 (2H, m, **Hk**), 1.44 (1H, s, **OH**), 1.23 (3H, s, **Hh/g**), 1.16 (3H, s, **Hh/g**) ppm.

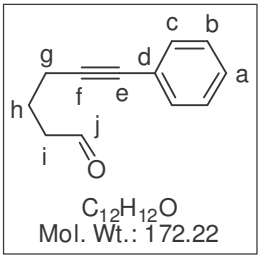
^{13}C NMR (75 MHz, $CDCl_3$): δ 142.84 (C), 140.85 (C), 138.17 (C), 137.37 (C), 129.72 (CHx2), 129.28 (CH, **Co**), 128.60 (CHx2), 128.23 (CHx2), 127.15 (CH), 126.44 (CH), 126.30 (CHx2), 123.23 (CH, **Cn**), 73.97 (C, **Cf**), 55.66 (CH, **Ce**), 36.59 (CH_2, **Cj**), 32.85 (CH_2, **Cl**), 29.85 (CH_3, **Ch/g**), 29.56 (CH_3, **Ch/g**), 22.17 (CH_2, **Ck**) ppm.

IR ν_{max}/cm^{-1} (film): 3489 (br), 1622 (w), 1486 (m), 1448 (m), 952 (s), 756 (s), 688 (s).

LRMS (ES, H_2O): m/z 341 ($[M + Na]^+$, 100%).

HRMS (ES): $C_{23}H_{26}NaO$ $[M + Na]^+$ calculated 341.1876, found 341.1872.

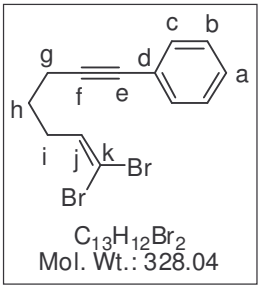
5.6 1-(7,7-Dibromohept-6-en-1-ynyl)benzene **33**



Synthesis of 6-Phenylhex-5-ynal 32: Synthesis was carried out using a procedure published by Tanaka *et al.*[70] A solution of DMSO (3.3 mL, 46.5 mmol) in CH_2Cl_2 (20 mL) was added to a solution of oxalyl chloride (2.93 g, 23.1 mmol) at –78 °C. The resulting mixture was stirred at –78 °C for 15 min before the addition of 6-phenylhex-5-yn-1-ol (3.06 g, 17.6 mmol). The reaction mixture was stirred for a further 1 h at –78 °C before the addition of Et_3N (18.3 mL, 132 mmol). The solution was warmed to rt for 1 h before being quenched by the addition of H_2O (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed sat NH_4Cl (aq) (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (eluent: 20% Et_2O in hexane) yielded the title compound (2.92 g, 16.9 mmol, 96%) as a colourless oil. The compound was immediately used in the next reaction. ^{1}H NMR data was consistent with published data.[70]

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.82 (1H, t, *J* = 1.3, **Hj**), 7.37 (2H, m, **Ar-H**), 7.29-7.24 (3H, m, **Ar-H**), 2.64 (2H, td, *J* = 7.2, 1.3, **Hi**), 2.49 (2H, t, *J* = 6.9, **Hg**), 1.92 (2H, quin, *J* = 7.0, **Hh**) ppm.

Synthesis of 1-(7,7-Dibromohept-6-en-1-ynyl)benzene 33: Synthesis was carried out using a procedure published by Uenishi *et al.*[71] To a stirred solution of CBr_4 (4.64 g, 14 mmol) in CH_2Cl_2 (20 ml) at 0 °C was added PPh_3 (7.34 g, 28 mmol) in CH_2Cl_2 (20 mL). The resulting solution was warmed to rt for 1 h before the addition of 6-phenylhex-5-ynal (1.32 g, 7 mmol) in CH_2Cl_2 (20 mL). The resulting solution was stirred for 30 min and the solvent removed *in vacuo*. Purification by column chromatography (eluent: hexane) yielded the title compound (1.605 g, 4.9 mmol, 70%) as a colourless oil.



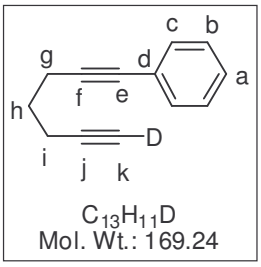
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39 (2H, m, **Ar-H**), 7.28-7.24 (3H, m, **Ar-H**), 6.44 (1H, t, *J* = 7.3, **Hj**), 2.44 (2H, t, *J* = 7.0, **Hg**), 2.28 (2H, q, *J* = 7.5, **Hi**), 1.73 (2H, quin, *J* = 7.2, **Hh**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 137.74 (CH, **Cj**), 131.54 (CHx2, **Cc**), 128.19 (CHx2, **Cb**), 127.65 (CH, **Ca**), 123.73 (C, **Cd**), 89.54 (C, **Ck**), 89.04 (C, **Cf**), 81.39 (C, **Ce**), 32.24 (CH_2, **Ci**), 26.50 (CH_2, **Ch**), 18.80 (CH_2, **Cg**) ppm.

IR ν_{max}/cm^{-1} (film):1597 (w), 755 (s), 692 (s).

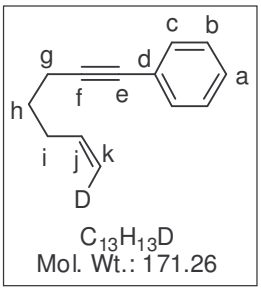
LRMS (EI, CH_2Cl_2): m/z 328 ([$M^{+\cdot}$], 2% ($C_{13}H_{12}{}^{79}Br\,{}^{81}Br$)), 168 (72%), 168 (100%), 115 (80%).

5.7 (6*Z*)-(7-$^2H_1$)Hept-6-en-1-yn-1-ylbenzene **26a**



Synthesis of (7-^{2}H)hepta-1,6-diyn-1-ylbenzene 34: To a stirred solution of 1-(7,7-dibromohept-6-en-1-ynyl)benzene (0.984 g, 3 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (2.4 mL, 6 mmol). The solution was stirred for 30 min at –78 °C before the dropwise addition of D_2O (1 mL). The solution was warmed to rt for 1 h before being extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the compound (0.420 g, 2.5 mmol, 83%) as a colourless oil. The compound was used without any further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.34 (3H, m, **Ar-H**), 7.24 (2H, m, **Ar-H**), 2.51 (2H, t, *J* = 7.0, **Hg**), 2.34 (2H, t, *J* = 7.0, **Hi**), 1.80 (2H, quin, *J* = 7.0, **Hh**) ppm.



Synthesis of (6*Z*)-(7-$^2H_1$)hept-6-en-1-yn-1-ylbenzene 26a: Synthesis was carried out following a procedure by Negishi *et al*.[72] A solution of $ZrCp_2HCl$ was prepared by treating $ZrCp_2Cl_2$ (1.46 g, 5 mmol) in THF (5 mL) with DIBAL-H (1 M in hexanes) (5 mL, 5 mmol), at 0 °C for 30 min. The resulting mixture was added portionwise to a solution of diyne **34** (0.419 g, 2.5 mmol) in THF (5 mL) at rt and monitored by GC until hydrozirconation was complete. The mixture was poured onto saturated sodium potassium tartrate solution (50 mL), stirred for 18 h at rt then extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography (eluent: hexane) yielded the title compound (0.197 g, 1.2 mmol, 48%) as a colourless oil.

Data was consistent with known un-deuterated compound.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.36 (2H, m, **Ar-H**), 7.26-7.23 (3H, m, **Ar-H**), 5.81 (1H, m, **Hj**), 4.99 (1H, d, *J* = 10.3, **Hk**), 2.42 (2H, t, *J* = 7.1, **Hg**), 2.23 (2H, q, *J* = 7.1, **Hi**), 1.71 (2H, quin, *J* = 7.1, **Hh**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 137.79 (CH, **Cj**), 131.52 (CHx2, **Cc**), 128.16 (CHx2, **Cb**), 127.49 (CH, **Ca**), 123.98 (C, **Cd**), 114.90 (CH_2, t, *J* = 23.8, **Ck**), 89.93 (C, **Cf**), 80.85 (C, **Ce**), 32.79 (CH_2, **Ci**), 27.91 (CH_2, **Ch**), 18.80 (CH_2, **Cg**) ppm.

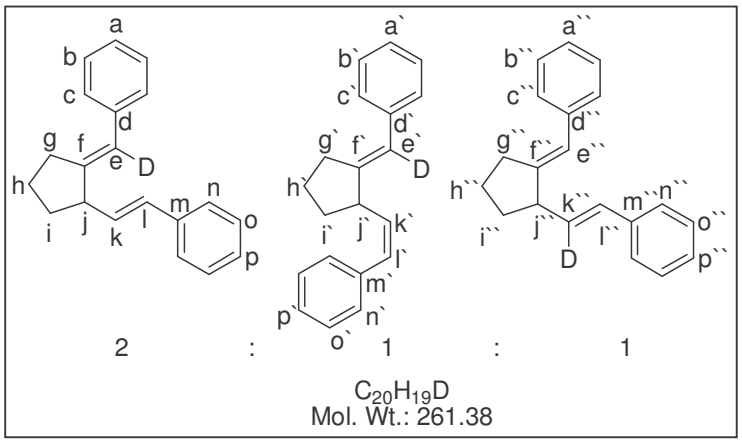
IR ν_{max}/cm^{-1} (film): 1617 (w), 1598 (w), 1489 (m), 799 (s), 753 (s), 690 (s).

LRMS (EI, CH_2Cl_2): m/z 171 ([$M^{+\cdot}$], 12%), 143 (60%), 115 (100%).

HRMS (EI): $C_{13}H_{13}D$ [$M^{+\cdot}$] calculated 171.1158, found 171.1159.

GC (Method A): **34** – 4.36 min and **26a** – 4.22 min

5.8 ((*E*)-2-((*E*)-2-Phenylethenyl)cyclopentylidene)(^{2}H)methyl) benzene **36a**, ((*E*)-2-((*Z*)-2-Phenylethenyl)cyclopentylidene) (^{2}H)methyl)benzene **36b** and ((*E*)-2-((2*E*)-2-Benzylidenecyclopentyl)(2-^{2}H)ethenyl)benzene **36c**



To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 30 min before dropwise addition of a solution of enyne **26a** (0.171 g, 1.0 mmol) in THF (2 mL). After stirring for a further 30 min at –78 °C the solution was warmed to rt and stirred for a further 2 h. The solution was re-cooled to –78 °C followed by dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). After 30 min at –78 °C the reaction mixture was warmed to rt. The reaction mixture was stirred for 72 h at rt before being quenched with 2 M HCl (aq) (5 mL). The reaction mixture was stirred for 18 h at rt before being extracted with Et_2O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compounds (0.188 g, 0.72 mmol, 72%) as a colourless oil. The compounds were isolated as an inseparable 2:1:1 mixture of isomers determined from the NMR of the crude compounds.

The following differences were observed in the ^{1}H NMR when compared with compounds **6a** and **6b** data.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.65 (1H, d, *J* = 11.5, **Hl`**), 6.51-6.44 (3H, m, **Hl + Hl``**), 6.25 (1H, apparent q, *J* = 2.4, **He``**), 6.17 (2H, dd, *J* = 15.8, 8.4, **Hk**), 5.60 (1H, dd, *J* = 11.5, 9.9, **Hk`**) ppm.

GCMS (EI, CH_2Cl_2): (*Z*)-alkene - 9.85 min: 261 (40%), 91 (100%) and (*E*)-alkene 10.07 min: 261 (20%), 91 (100%).

5.9 Kinetic isotope experiment

To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 30 min before dropwise addition of a solution of 1-(hept-6-en-ynyl)benzene (0.085 g, 0.5 mmol) and enyne **26a** (0.0.86 g, 0.5 mmol) in THF (2 mL). After stirring for a further 30 min at –78 °C the solution was warmed to rt and stirred for a further 2 h. The solution was re-cooled to –78 °C followed by dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). After 10 min at –78 °C the reaction mixture was warmed to 20 °C by placing in a water bath. Samples (0.2 mL) were removed from the reaction mixture and quenched with 2 M HCl (aq) (1.5 mL) and timed intervals. Et_2O (1 mL) was added added to the quenched sample. The Et_2O layer was separated and passed through a short plug of $MgSO_4$ in Pasteur pipette. The samples were analysed by GCMS.

GCMS conditions:

Gas chromatography was performed on a ThermoQuest trace MS, using a Zebron 30 m column, with a film thickness of 0.25 μm and 0.25 mm internal diameter. The carrier gas was helium and the flow rate was 1 mL min^{-1}.

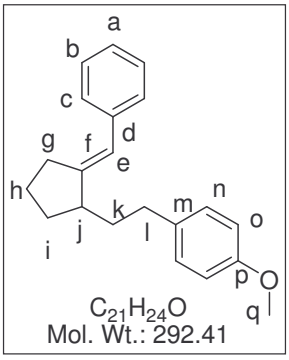
Injector Temperature: 220 °C

Initial Temperature: 60 °C

Ramp: 40 °C per min

Final Temperature: 320 °C held for 6 min

5.10 (*E*)-1-(2-(2-Benzylidenecyclopentyl)ethyl)-4-methoxybenzene **38**



The following compound was prepared using the same method as for compound **4** but using *p*-methoxybenzyl chloride (0.156 g, 1 mmol) in place of benzyl chloride. Purification by column chromatography on silica gel (eluent: 5% EtOAc in hexane) yielded the title compound (0.184 g, 0.63 mmol, 63%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.32 (4H, m, **Ar-H**), 7.23-7.15 (3H, s, **Ar-H**), 6.88-6.84 (2H, m, **Ar-H**), 6.29 (1H, apparent q, *J* = 2.3, **He**), 3.81 (3H, s, **Hq**), 2.78-2.55 (5H, m), 2.19-2.07 (3H, m), 1.70-1.58 (2H, m), 1.41 (1H, m) ppm.

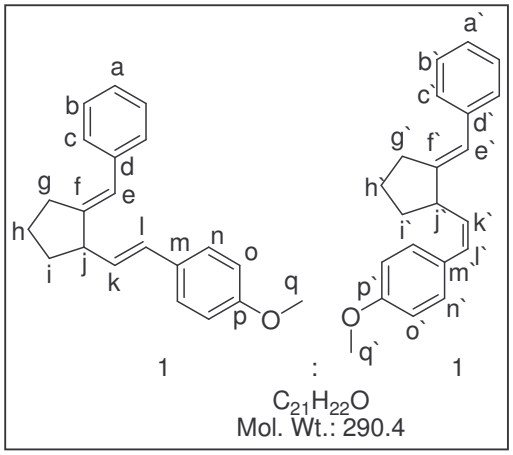
^{13}C NMR (75 MHz, $CDCl_3$): δ 157.66 (C, **Cp**), 150.32 (C, **Cf**), 138.82 (C, **Cd**), 134.76 (C, **Cm**), 129.23 (CHx2), 128.12 (CHx4), 125.66 (CH, **Ca**), 120.71 (CH, **Ce**), 113.74 (CHx2, **Co**), 55.25 (CH_3, **Hq**), 45.81 (CH, **Cj**), 36.90 (CH_2), 33.15 (CH_2), 31.75 (CH_2), 31.56 (CH_2), 24.89 (CH_2, **Ch**) ppm.

IR ν_{max}/cm^{-1} (film): 1610 (w), 1580 (w), 1510 (m), 1490 (m), 1440 (m).

LRMS (EI, CH_2Cl_2): m/z 292 ([$M^{+\cdot}$], 5%), 207 (20%), 134 (90%), 121 (100%).

HRMS (EI): $C_{21}H_{24}O$ [$M^{+\cdot}$] calculated 292.1827, found 292.1833.

5.11 1-((*E*)-2-((*E*)-2-Benzylidenecyclopentyl)vinyl)-4-methoxybenzene **39a** and 1-((*Z*)-2-((*E*)-2-Benzylidenecyclopentyl)vinyl)-4-methoxybenzene **39b**



To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 5 min before dropwise addition of a solution of 1-(hept-6-en-1-ynyl)benzene (0.170 g, 1.0 mmol) in THF (2 mL). After stirring for a further 30 min at –78 °C the solution was warmed to rt and stirred for a further 2 h. The solution was re-cooled to –78 °C followed by the dropwise addition of *p*-methoxybenzyl chloride (0.156 g, 0.14 mL, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). The solution was stirred for 3 min before the addition of CH_2Cl_2 (0.2 mL, 3 mmol). The solution continued to stir for 15 min at –78 °C before being warmed to rt. The solution was stirred for a further 24 h before the addition of 2 M HCl (aq) (5 mL). The mixture was stirred for 18 h before being extracted with Et_2O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed in vacuo. Purification by column chromatography on silica gel (eluent: hexane - 5% Et_2O in hexane) yielded a 1:1 mixture of the title compounds (0.140 g, 0.48 mmol, 48%) as a colourless oil. NMR of the crude product showed a 1:1 ratio of the (*E*)- and (*Z*)-isomers

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.26 (12H, m, **Ar-H**), 7.20-7.17 (2H, m, **Ar-H**), 6.90-6.86 (4H, m, **Ar-H**), 6.60 (1H, d, *J* = 11.3, **Hl`**), 6.43 (1H, d, *J* = 15.6, **Hl**), 6.30 (1H, q, *J* = 2.3 **He**), 6.26 (1H, q, *J* = 2.3, **He`**), 6.02 (1H, dd, *J* = 15.8, 8.3, **Hk**), 5.51 (1H, dd, *J* = 11.3, 9.8, **Hk`**), 3.82 (6H, s, **Hq, q`**), 3.71 (1H, m), 3.32 (1H, m), 2.82-2.73 (2H, m), 2.69-2.59 (2H, m), 2.06-1.93 (4H, m), 1.76-1.66 (2H, m), 1.59-1.40 (2H, m) ppm.

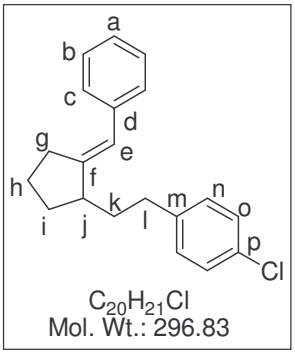
^{13}C NMR (100 MHz, $CDCl_3$): δ 158.81 (C, **Cp/p`**), 158.50 (C, **Cp/p`**), 148.87 (C, **Cf/f`**), 148.78 (C, **Cf/f`**), 138.63 (C, **Cd/d`**), 138.56 (C, **Cd/d`**), 133.32 (CH), 130.94 (C, **Cm/m`**), 129.94 (C, **Cm/m`**), 129.53 (CH), 129.33 (CH), 128.18 (CHx5), 128.08 (CHx4), 127.21 (CHx4), 125.88 (CHx2), 122.68 (CH, **Ce/e`**), 122.08 (CH, **Ce/e`**), 113.95 (CHx2, **Co/o`**), 113.70 (CHx2, **Co/o`**), 55.32 (CH_3, **Cq/q`**), 55.26 ($CH_3$, **Cq/q`**), 51.05 (CH, **Cj/j`**), 46.35 (CH, **Cj/j`**), 34.19 (CH_2), 33.74 (CH_2), 31.56 (CH_2), 31.31 (CH_2), 25.41 (CH_2), 25.30 (CH_2) ppm.

IR ν_{max}/cm^{-1} (film): 1606 (m), 1509 (s), 1301 (s), 1248 (s).

LRMS (EIMS, CH_2Cl_2): m/z 290 ([$M^{+\cdot}$], 80%), 121 (100%).

HRMS (EI): $C_{21}H_{24}O$ [$M^{+\cdot}$] calculated 290.1671, found 290.1670.

5.12 (*E*)-1-(2-(2-Benzylidenecyclopentyl)ethyl)-4-chlorobenzene **41**



The following compound was prepared using the same method as for compound **4** but using *p*-chlorobenzyl chloride (0.160 g, 1 mmol) in place of benzyl chloride. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compound (0.233 g, 0.88 mmol, 88%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.31 (4H, m **Ar-H**), 7.28-7.26 (2H, m, **Ar-H**), 7.19-7.15 (3H, m, **Ar-H**), 6.26 (1H, apparent q, *J* = 2.4, **He**), 2.80-2.54 (5H, m), 2.05-1.85 (3H, m), 1.70-1.60 (2H, m), 1.40 (1H, m) ppm.

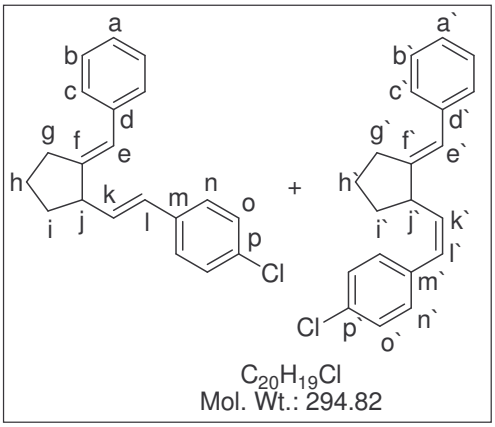
^{13}C NMR (100 MHz, $CDCl_3$): δ 150.01 (C, **Cf**), 141.10 (C, **Cm**), 138.71 (C, **Cd**), 131.37 (C, **Cp**), 129.72 (CHx2), 128.41 (CHx2), 128.16 (CHx4), 125.77 (CH), 120.91 (CH, **Ce**), 45.75 (CH, **Cj**), 36.56 (CH_2), 33.42 (CH_2), 31.72 (CH_2), 31.52 (CH_2), 24.89 (CH_2, **Ch**) ppm.

IR ν_{max}/cm^{-1} (film): 1713 (m), 1588 (w) 1491 (s), 1447 (m), 1081 (s), 1014 (s), 695 (s).

LRMS (EI, CH_2Cl_2): m/z 296 ([$M^{+\cdot}$], 20%), 158 (30%), 158 (70%), 129 (80%), 91 (100%).

HRMS (EI): $C_{20}H_{21}{}^{35}Cl$ [$M^{+\cdot}$] calculated 296.1332, found 296.1331.

5.13 1-((*E*)-2-((*E*)-2-Benzylidenecyclopentyl)vinyl)-4-chlorobenzene **42a** and 1-((*Z*)-2-((*E*)-2-Benzylidenecyclopentyl)vinyl)-4-chlorobenzene **42b**



The following compound was prepared using the same method as for compound **39** but using *p*-methoxybenzyl chloride (0.160 g, 1 mmol) in place of *p*-chlorobenzyl chloride. Purification by column chromatography on silica gel (eluent: hexane) yielded a 1:1 mixture of the title compounds (0.148 g, 0.50 mmol, 50%) as a colourless oil. NMR of the crude product showed a 1:1 ratio of the (*E*)- and (*Z*)-isomers

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.12 (18H, m, **Ar-H**), 6.56 (1H, d, *J* = 11.4, **Hl`**), 6.41 (1H, d, *J* = 15.7, **Hl**), 6.25-6.21 (2H, m, **He, e`**), 6.11 (1H, dd, *J* = 15.7, 8.4, **Hk**), 5.59 (1H, dd, *J* = 11.4, 9.8, **Hk`**), 3.62 (1H, m, **Hj`**), 3.52 (1H, m, **Hj**), 2.80-2.54 (4H, m), 2.03-1.89 (4H, m), 1.72-1.38 (4H, m) ppm.

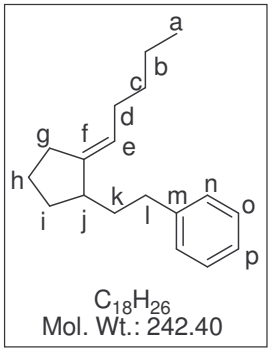
^{13}C NMR (100 MHz, $CDCl_3$): δ 148.42 (C, **Cf/ f`**), 148.39 (C, **Cf/ f`**), 138.46 (C, **Cd/ d`**), 138.37 (C, **Cd/d`**), 136.08 (C, **Cm/m`**), 135.58 (C, **Cm/m`**), 135.41 (CH), 133.81 (CH), 132.54 (Cx2, **Cp, p`**), 129.64 (CH), 129.33 (CH), 128.70 (CHx2), 128.61 (CHx4), 128.41 (CHx4), 128.17 (CHx4), 128.08 (CHx2), 127.31 (CH), 126.02 (CH), 122.94 (CH, **Ce/e`**), 122.27 (CH, **Ce/e`**), 50.91 (CH, **Cj**), 46.24 (CH, **Cj`**), 34.06 (CH_2, **Cg`**), 33.58 ($CH_2$, **Cg**), 31.56 ($CH_2$, **Ch**), 31.26 ($CH_2$, **Ch`**), 25.45 (CH_2, **Ci**), 25.32 (CH_2, **Ci`**) ppm.

IR ν_{max}/cm^{-1} (film): 1602 (w), 1459 (m), 1378 (m), 722 (m).

LRMS (EI, CH_2Cl_2): m/z 294 ([$M^{+\cdot}$], 50%), 196 (100%), 141 (90%), 115 (80%), 91 (70%).

HRMS (EI): $C_{20}H_{19}{}^{35}Cl$ [$M^{+\cdot}$] calculated 294.1175, found 294.1166.

5.14 (*E*)-(2-(2-Pentylidenecyclopentyl)ethyl)benzene **44**



The following compound was prepared using the same method as for compound **4** but using undec-1-en-6-yne (0.150 g, 1 mmol) in place of 1-(hept-6-en-1-ynyl)benzene. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compound (0.144 g, 0.59 mmol, 59%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.27 (2H, m, **Ar-H**), 7.23-7.16 (3H, m, **Ar-H**), 5.19 (1H, tq, *J* = 7.4, 2.3, **He**), 2.72 (1H, ddd, *J* = 13.7, 10.6, 5.3, **Hl**), 2.60 (1H, ddd, *J* = 13.7, 10.3, 6.4, **Hl**), 2.33-2.16 (3H, m), 2.03-1.86 (4H, m), 1.77 (1H, m), 1.62-1.45 (2H, m), 1.39-1.25 (5H, m), 0.91 (3H, t, *J* = 6.8, **Ha**) ppm.

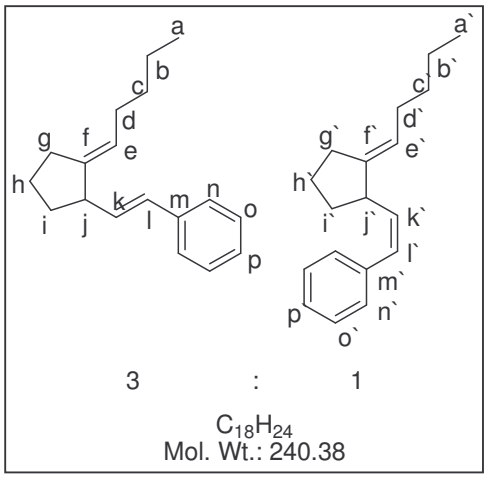
^{13}C NMR (75 MHz, $CDCl_3$): δ 146.08 (C, **Cf**), 143.05 (C, **Cm**), 128.36 (CHx2), 128.25 (CHx2), 125.54 (CH), 120.21 (CH, **Ce**), 43.85 (CH, **Cj**), 36.57 (CH_2), 34.16 (CH_2), 32.77 (CH_2), 31.97 (CH_2), 29.12 (CH_2x2), 24.14 (CH_2), 22.39 (CH_2), 14.05 (CH_3, **Ca**) ppm.

IR ν_{max}/cm^{-1} (film): 1597 (w), 1491 (m), 1450 (m), 690 (s).

LRMS (EI, CH_2Cl_2): m/z 242 ([$M^{+\cdot}$], 20%), 138 (90%), 91 ([$C_6H_7^+$], 100%).

HRMS (EI): $C_{18}H_{26}$ [$M^{+\cdot}$] calculated 242.2035, found 242.2030.

5.15 1-((*E*)-2-((*E*)-2-Pentylidenecyclopentyl)vinyl)benzene **45a** and 1-((*Z*)-2-((*E*)-2-Pentylidenecyclopentyl)vinyl)benzene **45b**



To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 10 min before dropwise addition of a solution of undec-1-en-6-yne (0.150 g, 1.0 mmol) in THF (2 mL). After stirring for a further 10 min at –78 °C the solution was warmed to rt and stirred for a further 2 h. The solution was re-cooled to –78 °C followed by the dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). The solution continued to stir for 15 min at –78 °C before being warmed to rt. The solution was stirred for a further 3 h before the addition of 2 M HCl (aq) (5 mL). The mixture was stirred for 18 h before being extracting with Et_2O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: hexane) yielded a 3:1 mixture of the title compounds (0.128 g, 0.53 mmol, 53%) as a colourless oil. ^{1}H NMR of the crude product showed a 3:1 ratio of the (*E*)- and (*Z*)-isomers. HPLC purification (eluent: hexane) isolated the (*E*)- isomer.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.28 (4H, m, **Ar-H**), 7.21 (1H, m, **Ar-H**), 6.38 (1H, d, *J* = 15.7, **Hl**), 6.10 (1H, dd, *J* = 15.8, 8.3, **Hk**), 5.17 (1H, tq, *J* = 7.2, 2.4, **He**), 3.09 (1H, q, *J* = 8.1), 2.41-2.23 (2H, m), 2.01-1.92 (3H, m), 1.84 (1H, m), 1.69-1.44 (2H, m), 1.37-1.27 (4H, m), 0.90 (3H, t, *J* = 6.8, **Ha**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 144.84 (C, **Cf**), 137.83 (C, **Cm**), 133.81 (CH, **Ck**), 129.72 (CH, **Cl**), 128.45 (CHx2, **Co**), 126.78 (CH, **Cp**), 126.01 (CHx2, **Cn**), 122.63 (CH, **Ce**), 48.98 (CH, **Cj**), 34.39 (CH_2), 31.79 (CH_2), 29.32 (CH_2), 28.91 (CH_2), 24.66 (CH_2), 22.44 (CH_2), 14.04 (CH_3, **Ca**) ppm.

IR ν_{max}/cm^{-1} (film): 1600 (w), 1448 (m), 962 (s), 743 (s), 692 (s).

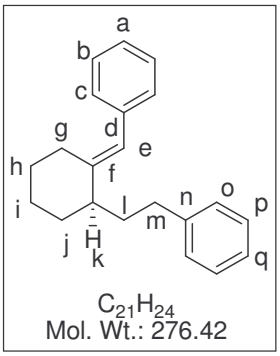
LRMS (EI, CH_2Cl_2): m/z 240 ([$M^{+\cdot}$], 50%), 91 ([$C_6H_7^+$], 100%).

HRMS (EI): $C_{18}H_{24}$ [$M^{+\cdot}$] calculated 240.1878, Found 240.1880.

The ^{1}H NMR of the 3:1 mixture of the (*E)*- and (*Z)*-alkenes revealed the following peaks which are characteristic of the (*Z)*- isomer.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.53 (1H, d, *J* = 11.5, **Hl`**), 5.46 (1H, dd, *J* = 11.4, 9.8, **Hk`**), 5.17 (1H, m, **He`**) ppm.

5.16 (*E*)-(2-(2-Benzylidenecyclohexyl)ethyl)benzene **47**



$C_{21}H_{24}$
Mol. Wt.: 276.42

To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 10 min before dropwise addition of a solution of 1-(oct-7-en-1-ynyl)benzene (0.184 g, 1.0 mmol) in THF (2 mL). After stirring for a further 10 min at –78 °C the solution was warmed to rt and stirred for a further 2 h. The solution was re-cooled to –78 °C followed by the dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). The solution continued to stir for a further 5 min before the addition of 2 M HCl in Et_2O (5 mL). The mixture was stir for a further 14 h while warming to rt. The mixture was diluted with Et_2O (50 mL) and washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compound (0.147 g, 0.53 mmol, 53%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34-7.18 (10H, m, **Ar-H**), 6.28 (1H, s, **He**), 2.67 (2H, t, *J* = 8.1, **Hm**), 2.45-2.24 (3H, m), 2.07 (1H, ddd, *J* = 8.0, 7.7, 13.5, **Hg**), 1.90-1.46 (7H, m) ppm.

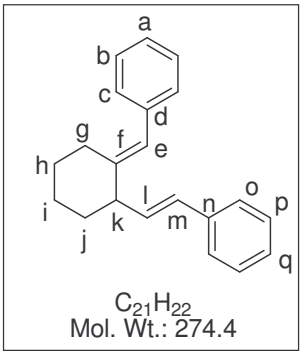
^{13}C NMR (75 MHz, $CDCl_3$): δ 145.55 (C, **Cf**), 142.89 (C, **Cn**), 138.49 (C, **Cd**), 128.98 (CHx2), 128.42 (CHx2), 128.30 (CHx2), 127.99 (CHx2), 125.81 (CH), 125.62 (CH), 121.85 (CH, **Ce**), 44.57 (CH, **Hk**), 34.12 (CH_2), 34.01 (CH_2), 33.72 (CH_2), 28.30 (CH_2), 27.12 (CH_2), 23.27 (CH_2) ppm.

IR ν_{max}/cm^{-1} (film): 1648 (w), 1599 (m), 1444 (m), 692 (s).

LRMS (EI, CH_2Cl_2): m/z 276 ([$M^{+\cdot}$], 40%), 185 (50%), 171 (90%), 117 (100%), 91 (100%).

HRMS (EI): $C_{21}H_{24}$ [$M^{+\cdot}$] calculated 276.1878, found 276.1886.

5.17 1-((*E*)-2-((*E*)-2-Benzylidenecyclohexyl)vinyl)benzene **48a**



To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 5 min before dropwise addition of a solution of 1-(oct-7-en-1-ynyl)benzene (0.184 g, 1.0 mmol) in THF (2 mL). After stirring for a further 10 min at –78 °C the solution was warmed to rt and stirred for a further 18 h. The solution was re-cooled to –78 °C followed by dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). The solution continued to stir for 30 min at –78 °C before being warmed to rt. The solution was stirred for a further 4 h before addition of 2 M HCl (aq) (5 mL). The mixture was stirred for 18 h before being extracted with Et_2O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compound **48a** (0.177 g, 0.65 mmol, 65%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (2H, d, *J* = 7.5, **Ar-H**), 7.35-7.24 (5H, m, **Ar-H**), 7.22-7.19 (3H, m, **Ar-H**), 6.47 (1H, d, *J* = 16.0, **Hm**), 6.41 (1H, dd, *J* = 15.8, 6.8, **Hl**), 6.29 (1H, s, **He**), 3.06 (1H, m), 2.72 (1H, m), 2.16 (1H, m), 1.95 (1H, m), 1.84 (1H, m), 1.72-1.57 (4H, m) ppm.

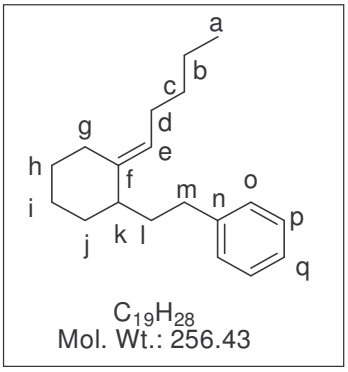
^{13}C NMR (100 MHz, $CDCl_3$): 145.10 (C, **Cf**), 138.38 (C, **Cd**), 137.78 (C, **Cn**), 133.06 (CH, **Cl**), 130.13 (CH, **Cm**), 128.98 (CHx2), 128.52 (CHx2), 127.98 (CHx2), 127.01 (CH, **Ca/q**), 126.11 (CHx2), 125.91 (CH, **Ca/q**), 122.52 (CH, **Ce**), 48.15 (CH, **Ck**), 34.43 (CH_2), 28.61 (CH_2), 27.81 (CH_2), 24.87 (CH_2) ppm.

IR ν_{max}/cm^{-1} (film): 1492 (m), 1106 (s), 812 (m).

LRMS (EI, CH_2Cl_2): m/z 274 ([$M^{+\cdot}$], 50%), 183 (60%), 141 (100%), 115 (70%), 91 (100%).

HRMS (EI): $C_{21}H_{22}$ [$M^{+\cdot}$] calculated 274.1722, found 274.1721.

5.18 (*E*)-(2-(2-Pentylidenecyclohexyl)ethyl)benzene **50**



To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 10 min before dropwise addition of a solution of dodec-1-en-7-yne (0.164 g, 1.0 mmol) in THF (2 mL). After stirring for a further 10 min at –78 °C the solution was warmed to rt and stirred for a further 2 h. The reaction mixture was re-cooled to –78 °C followed by the dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) in THF (2 mL) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). The solution continued to stir for a further 5 min before the addition of 2 M HCl in Et_2O (5 mL). The mixture was stir for a further 18 h while warming to rt. The mixture was diluted with Et_2O (50 mL) and washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: hexane) yielded a mixture of the title compound **50** and (0.157 g, 0.55 mmol, 55%) and 1-((*E*)-2-((*E*)-2-pentylidenecyclohexyl)vinyl)benzene **51a** (0.015 g, 0.06 mmol, 6%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.26 (2H, m, **Ar-H**), 7.23-7.15 (3H, m, **Ar-H**), 5.12 (1H, t, *J* = 7.2, **He**), 2.56 (2H, t, *J* = 8.4, **Hm**), 2.16-1.90 (6H, m), 1.71-1.41 (7H, m), 1.36-1.28 (4H, m), 0.94-0.89 (3H, m) ppm.

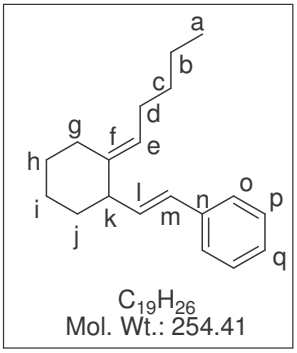
^{13}C NMR (75 MHz, $CDCl_3$): δ 143.20 (C, **Cf**), 141.36 (C, **Cn**), 128.38 (CHx2), 128.21 (CHx2), 125.48 (CH), 121.35 (CH, **Ce**), 44.25 (CH, **Ck**), 34.06 (CH_2x2), 33.91 (CH_2), 32.51 (CH_2), 28.24 (CH_2), 26.79 (CH_2), 26.41 (CH_2), 23.63 (CH_2), 22.32 (CH_2), 14.03 (CH_3, **Ca**) ppm.

IR ν_{max}/cm^{-1} (film): 1498 (m), 1453 (m), 746 (s), 696 (s).

LRMS (EI, CH_2Cl_2): m/z 256 ([$M^{+\cdot}$], 10%), 152 (805), 95 (100%).

HRMS (EI): $C_{19}H_{28}$ [$M^{+\cdot}$] calculated 256.2191, found 256.2193.

5.19 1-((*E*)-2-((*E*)-2-Pentylidenecyclohexyl)vinyl)benzene **51a**



To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 10 min before dropwise addition of a solution of dodec-1-en-7-yne (0.164 g, 1.0 mmol) in THF (2 mL). After stirring for a further 10 min at –78 °C the solution was warmed to rt and stirred for a further 2 h. The reaction mixture was re-cooled to –78 °C followed by the dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). The solution continued to stir for 20 min at –78 °C before being warmed to rt. The solution was stirred for a further 30 min before the addition of 2 M HCl (aq) (5 mL). The mixture was stirred for 18 h at rt before being extracted with Et_2O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compound **51a** (0.183 g, 0.72 mmol, 72%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.18 (5H, m, **Ar-H**), 6.33 (1H, dd, *J* = 16.7, 6.0, **Hl**), 6.28 (1H, d, *J* = 16.7, **Hm**), 5.13 (1H, t, *J* = 7.3, **He**), 2.84 (1H, m, **Hk**), 2.44 (1H, m), 2.05-1.19 (3H, m), 1.84-1.71 (2H, m), 1.65-1.41 (4H, m), 2.34-1.26 (4H, m), 0.89 (3H, t, *J* =7.0, **Ha**) ppm.

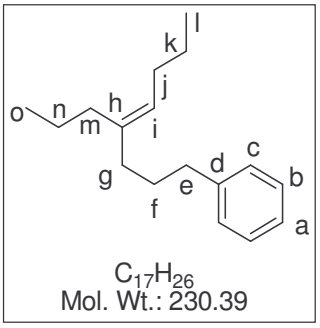
^{13}C NMR (75 MHz, $CDCl_3$): δ 141.08, (C, **Cf**), 137.95 (C, **Cn**), 133.72 (CH, **Cl**), 129.42 (CH, **Cm**), 128.41 (CHx2), 126.77 (CH, **Cq**), 126.00 (CHx2), 122.22 (CH, **Ce**), 47.77 (CH, **Ck**), 34.39 (CH_2), 32.37 (CH_2), 27.68 (CH_2x2), 26.91 (CH_2), 24.96 (CH_2), 22.63 (CH_2), 14.01 (CH_3, **Ca**) ppm.

IR ν_{max}/cm^{-1} (film): 1600 (w), 1448 (m), 746 (s), 693 (s).

LRMS (EI, CH_2Cl_2): m/z 254 ([$M^{+\cdot}$], 20%), 197 (100%), 149 (30%), 91 (40%).

HRMS (EI): $C_{19}H_{26}$ [$M^{+\cdot}$] calculated 254.2035, found 254.2037.

5.20 (*E*)-(4-Propyloct-4-enyl)benzene **55**



$C_{17}H_{26}$
Mol. Wt.: 230.39

To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added EtMgBr (1 M solution in THF) (2 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 1 h before dropwise addition of 4-octyne (0.110 g, 0.15 mL, 1.0 mmol). After stirring for a further 10 min at –78 °C the solution was warmed to slowly to 0 °C over 4 h. The reaction mixture was re-cooled to –78 °C before the dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). The reaction mixture continued to stir for a further 10 min before the addition of 2 M HCl in Et_2O (5 mL). The reaction mixture was stirred for a further 1 h while warming to rt before being poured onto $NaHCO_3$ (aq) (10 mL). The mixture was extracted with Et_2O (50 mL) and washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compound (0.130 g, 0.57 mmol, 57%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.27 (2H, m, **Ar-H**), 7.21-7.17 (3H, m, **Ar-H**), 5.17 (1H, t, *J* = 7.0, **Hi**), 2.61 (2H, t, *J* = 7.7, **Hg**), 2.07-1.97 (6H, m), 1.79-1.69 (2H, m, **Hf**), 1.46-1.32 (4H, m), 0.92 (3H, t, *J* = 7.3, **Hl/o**), 0.89 (3H, t, *J* = 7.3, **Hl/o**) ppm.

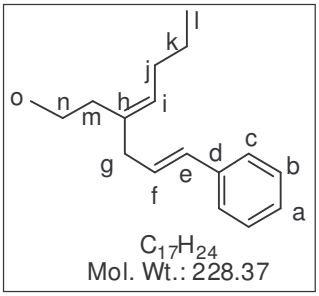
^{13}C NMR (75 MHz, $CDCl_3$): δ 142.82 (C, **Cd**), 138.88 (C, **Ch**), 128.41 (CHx2), 128.21 (CHx2), 125.57 (CH), 125.26 (CH, **Ci**), 36.54 (CH_2), 35.68 (CH_2), 32.12 (CH_2), 30.08 (CH_2), 29.84 (CH_2), 23.26 (CH_2), 21.61 (CH_2), 14.20 (CH_3, **Cl/o**), 13.88 (CH_3, **Cl/o**) ppm

IR ν_{max}/cm^{-1} (film): 1454 (m), 744 (m), 697 (s).

LRMS (EI, CH_2Cl_2): m/z 230 ([$M^{+\cdot}$], 25%), 156 (35%), 135 (40%), 115 (30%), 73 (100%).

HRMS (EI): $C_{17}H_{26}$ [$M^{+\cdot}$] calculated 230.2035, found 230.2033.

5.21 ((1*E*,4*E*)-4-Propylocta-1,4-dien-1-yl)benzene **56a** and (*E*)-(4-Propyloct-2-enyl)benzene **56b**



To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added EtMgBr (1 M solution in THF) (2 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 1 h before dropwise addition of 4-octyne (0.110g, 0.15 mL, 1.0 mmol). After stirring for a further 10 min at –78 °C the solution was warmed to slowly to 0 °C over 4 h. The solution was re-cooled to –78 °C before the dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). The reaction mixture was stirred for a further 10 min at –78 °C before being warmed to rt. The reaction mixture continued to stir for a further 30 min before the addition of MeOH (5 mL) and sat $NaHCO_3$ (aq) (5 mL). The mixture was stirred for a further 1 h before being extracted with Et_2O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: hexane) yielded **56b** (0.03 g, 0.14 mmol, 14%) followed by **56a** (0.108 g, 47 mmol, 47%) as a colourless oils.

Data for coumpound 56a

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.19 (5H, m, **Ar-H**), 6.40 (1H, d, *J* = 15.8, **He**), 6.21 (1H, dt, *J* = 15.8, 6.8, **Hf**), 5.25 (1H, t, *J* = 7.1, **Hi**), 2.90 (2H, d, *J* = 6.8, **Hg**), 2.08-1.99 (4H, m, **Hj, m**), 1.51-1.33 (4H, m, **Hk, n**), 0.93 (3H, t, *J* = 7.1, **Hl/o**), 0.90 (3H, t, *J* = 7.1, **Hl/o**), ppm.

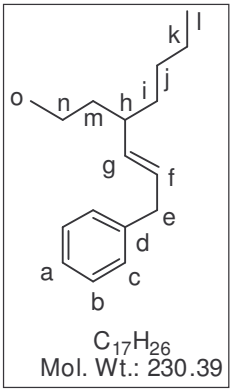
^{13}C NMR (75 MHz, $CDCl_3$): δ 137.80 (Cx2, **Ch, Cd**), 130.68 (CH, **Ce**), 129.53 (CH, **Cf**), 128.43 (CHx2), 126.82 (CH), 126.47 (CH), 126.00 (CHx2), 40.62 (CH_2, **Cg**), 32.30 (CH_2), 29.98 (CH_2), 23.16 (CH_2), 21.47 (CH_2), 14.13 (CH_3, **Cl/o**), 13.93 (CH_3, **Cl/o**) ppm.

IR ν_{max}/cm^{-1} (film): 1598 (w), 1445 (m), 964 (s), 746 (s), 691 (s).

LRMS (EI, CH_2Cl_2): m/z 228 ([$M^{+\cdot}$], 30%), 185 (60%), 143 (60%), 129 (50%), 115 (50%), 91 ([Bn^+], 100%).

HRMS (EI): $C_{17}H_{24}$ [$M^{+\cdot}$] calculated 228.1878, found 228.1873.

(*E*)-(4-Propyloct-2-enyl)benzene **56b**



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.19-7.13 (5H, m, **Ar-H**), 5.50 (1H, dtd, *J* = 15.2, 6.8, 0.7, **Hf**), 5.25 (1H, ddt, *J* = 15.2, 8.8, 1.2, **Hg**), 3.32 (2H, br d, *J* = 6.8, **He**), 1.95 (1H, m, **Hh**), 1.36-1.20 (10H, m, **Hi, j, k, m, n**), 0.91-0.87 (6H, m, **Hl, o**) ppm.

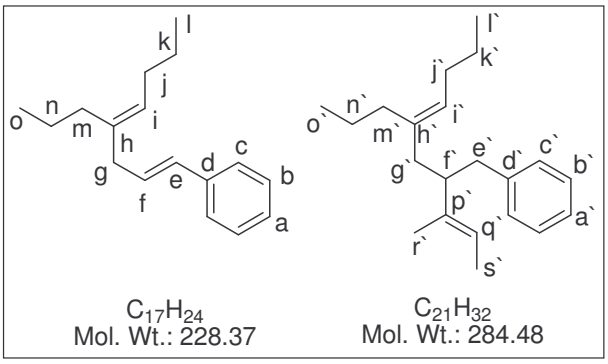
^{13}C NMR (75 MHz, $CDCl_3$): δ 141.31 (C, **Cd**), 136.93 (CH), 128.47 (CHx2), 128.27 (CHx2), 128.22 (CH), 125.78 (CH), 42.46 (CH, **Ch**), 39.10 (CH_2, **Ce**), 37.74 (CH_2), 35.14 (CH_2), 29.55 (CH_2), 22.80 (CH_2), 20.39 (CH_2), 14.19 (CH_3, **Cl/o**), 14.12 (CH_3, **Cl/o**) ppm.

IR ν_{max}/cm^{-1} (film): 1604 (w), 1453 (m), 733 (s), 697 (s).

LRMS (EI, CH_2Cl_2): m/z 230 ([$M^{+\cdot}$], 20%), 131 (60%), 117 (100%), 91 ([Bn^{+}], 90%).

HRMS (EI): $C_{17}H_{26}$ [$M^{+\cdot}$] calculated 230.2035, found 230.2030.

5.22 ((1*E*,4*E*)-4-Propylocta-1,4-dien-1-yl)benzene **56a** and 1-((4*E*)-2-((*E*)-But-2-en-2-yl)-4-propyloct-4-enyl)benzene **61**



To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added EtMgBr (1 M solution in THF) (2 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 1 h before dropwise addition of 4-octyne (0.110g, 0.15 mL, 1.0 mmol). After stirring for a further 10 min at –78 °C the solution was warmed to slowly to 0 °C over 4 h. The solution was re-cooled to –78 °C before the dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). After 5 min at –78 °C 2-butyne (0.24 mL, 3.0 mmol) was added. The reaction mixture was stirred for a further 30 min at –78 °C before being warmed to rt. The solution continued to stir for a further 30 min before the addition of 2 M HCl (aq) (5 mL) The mixture was stirred for a further 18 h before being extracted with Et_2O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compounds as an inseparable 1:1 mixture (0.142 g, 0.56 mmol, 56%).

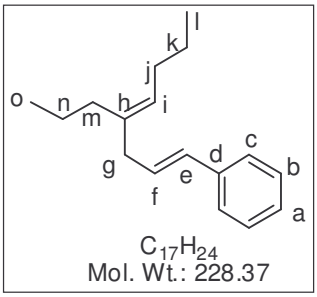
^{1}H NMR (300 MHz, $CDCl_3$): 7.39-7.09 (10H, m, **Ar-H**), 6.39 (1H, d, *J* = 15.8, **He**), 6.20 (1H, dt, *J* = 15.8, 6.8, **Hf**), 5.25 (1H, t, *J* = 7.1, **Hi**), 5.13 (1H, t, *J* = 7.3, **Hi`**), 5.05 (1H, q, *J* = 6.6, **Hq`**), 2.90 (2H, d, *J* = 6.6, **Hg**), 2.70 -2.53 (2H, m), 2.44 (1H, quin, *J* = 7.3, **Hf`**), 2.08-1.93 (11H, m), 1.49-1.29 (14H, m), 0.96-0.85 (12H, m) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): 141.64 (C, **Cp`**), 137.80 (Cx2, **Cd, h**), 137.61 (C, **Cd`/h`**), 136.79 (C, **Cd`/h`**), 130.71 (CH, **Ce**), 129.51 (CH, **Cf**), 128.97 (CHx4), 128.44 (CHx2), 127.86 (CHx2), 126.84 (CH), 126.49 (CH), 125.99 (CHx2), 125.41 (CH), 120.13 (CH, **Ci`**), 49.06 (CH, **Cf`**), 40.86 ($CH_2$, **Cg`**), 40.62 (CH_2, **Cg**), 39.60 (CH_2, **Ce`**), 32.30 (CH_2), 31.46 (CH_2), 29.98 (CH_2), 29.78 (CH_2), 23.22 (CH_2), 23.17 (CH_2),

21.47 (CH_2), 21.35 (CH_2), 14.13 (CH_3x2), 13.91 (CH_3), 13.71 (CH_3), 13.08 (CH_3), 12.14 (CH_3) ppm.

GCMS (EI, CH_2Cl_2): 8.63 min: 228 ([$M^{+\cdot}$], 50%), 185 (100%), 143 (90%), 115 (70%), 91 (70%). 9.01 min: 284 ([$M^{+\cdot}$], 5%), 241 (30%), 193 (95%), 150 (80%), 117 (100%), 91 (70%).

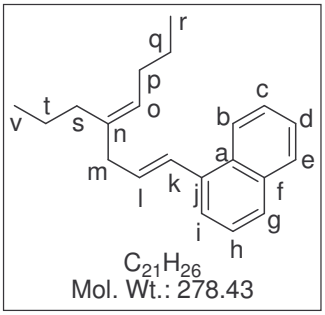
5.23 ((1*E*,4*E*)-4-Propylocta-1,4-dien-1-yl)benzene **56a**



To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added was added EtMgBr (1 M solution in THF) (2 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 1 h before dropwise addition of 4-octyne (0.110g, 0.15 mL, 1.0 mmol). After stirring for a further 10 min at –78 °C the solution was warmed to slowly to 0 °C over 4 h. The solution was re-cooled to –78 °C before the dropwise addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). After 5 min at –78 °C CH_2Cl_2 (0.3 mL, 2.0 mmol) was added. The reaction mixture was stirred for a further 30 min at –78 °C before being warmed to rt. The solution continued to stir for a further 30 min before the addition of 2 M HCl (aq) (5 mL). The mixture was stirred for a further 18 h before being extracted with Et_2O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compound (0.1517 g, 0.67 mmol, 67%) as a colourless oil.

See experiment 5.21 for data for **56a**

5.24 1-((1*E*,4*E*)-4-Propylocta-1,4-dien-1-yl)naphthalene **64**



The following compound was prepared using the same method as for compound **56a** as described in experiment 5.23 but using 1-(chloromethyl)naphthalene (0.176g, 1 mmol) in place of benzyl chloride. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compound (0.178 g, 0.65 mmol, 65%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (1H, d, *J* = 9.5 , **Ar-H**), 7.86 (1H, m, **Ar-H**), 7.76 (1H, d, *J* = 8.2, **Ar-H**), 7.59-7.42 (4H, m, **Ar-H**), 7.14 (1H, d, *J* = 15.6, **Hk**), 6.23 (1H, dt, *J* = 15.5, 7.0, **Hl**), 5.31 (1H, t, *J* = 7.2 **Ho**), 3.02 (2H, d, *J* = 7.0, **Hm**), 2.15-2.02 (4H, m, **Hp, s**), 1.56-1.35 (4H, m, **Hq, t**), 0.95 (3H, t, *J* = 7.3, **Hr/v**), 0.94 (3H, t, *J* = 7.32, **Hr/r**) ppm.

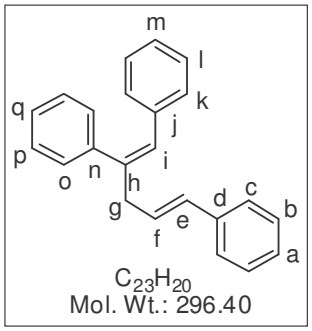
^{13}C NMR (75 MHz, $CDCl_3$): δ 137.82 (C, **Cn**), 135.65 (C, **Cj**), 133.59 (C, **Cf**), 132.81 (CH), 131.13 (C, **Ca**), 128.42 (CH), 127.91 (CH), 127.25 (CH), 126.66 (CH), 125.78 (CH), 125.65 (CH), 125.60 (CH), 123.94 (CH), 123.56 (CH, **Co**), 41.04 (CH_2, **Cm**), 32.40 (CH_2), 30.01 (CH_2), 23.18 (CH_2), 21.53 (CH_2), 14.18 (CH_3, **Cr/v**), 13.93 (CH_3, **Cr/v**) ppm.

IR ν_{max}/cm^{-1} (film): 1591 (w), 1456 (m), 968 (m), 775 (s).

LRMS (EI, CH_2Cl_2): m/z: 278 ([$M^{+\cdot}$], 80%), 235 (80%), 193 (60%), 165 (100%), 141 (80%).

HRMS (EI): $C_{21}H_{26}$ [$M^{+\cdot}$] calculated 278.2035, found 278.2032.

5.25 (1*Z*,4*E*)-1,2,5-Triphenylpenta-1,4-diene **65**



To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added EtMgBr (1 M solution in THF) (2 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 1 h before dropwise addition of diphenylacetylene (0.178 g, 1.0 mmol) in THF (3 mL). After stirring for a further 10 min at –78 °C the solution was warmed slowly to 0 °C over 4 h. The solution was re-cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). After 5 min at –78 °C CH_2Cl_2 (0.3 mL, 2.0 mmol) was added. The solution was stirred for a further 30 min at –78 °C before being warmed to rt. The solution continued to stir for a further 30 min before the addition of 2 M HCl (aq) (5 mL). The solution was stirred for a further 18 h before being extracted with Et_2O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by recrystalisation (hexane) yielded the title compound (0.201 g, 0.68 mmol, 68%) as a white crystalline solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.22 (10H, m, **Ar-H**), 7.12-7.10 (3H, m, **Ar-H**), 6.99-6.96 (2H, m, **Ar-H**), 6.53 (1H, s, **Hi**), 6.49 (1H, d, *J* = 15.8, **He**), 6.32 (1H, dt, *J* = 15.8, 6.8, **Hf**), 3.41 (2H, d, *J* = 6.8, **Hg**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 141.33 (C, **Ch/n**), 141.28 (C, **Ch/n**), 137.55 (C, **Cd/j**), 137.24 (C, **Cd/j**), 131.85 (CH, **Ce**), 129.02 (CHx2), 128.52 (CHx6), 127.82 (CHx2), 127.59 (CH), 127.23 (CH), 127.09 (CH), 127.00 (CH), 126.29 (CH, **Ci**), 126.12 (CHx2), 43.83 (CH_2, **Cg**) ppm.
Tentative assignments based on ^{13}C NMR intergration.

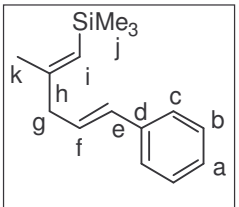
IR ν_{max}/cm^{-1} (film): 1597 (w), 1491 (m), 1443 (m), 700 (s), 690 (s).

LRMS (EI, CH_2Cl_2): m/z 296 ([$M^{+\cdot}$], 80%), 205 (100%), 178 (55%), 115 (30%).

HRMS (EI): $C_{23}H_{20}$ [$M^{+\cdot}$] calculated 296.1565, found 296.1557.

M.p: 67-70 °C.

5.26 Trimethyl((1*E*,4*E*)-2-methyl-5-phenylpenta-1,4-dienyl)silane **66**



$C_{15}H_{22}Si$
Mol. Wt.: 230.42

To a stirred solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (5 mL) at –78 °C was added was added EtMgBr (1 M solution in THF) (2 mL, 2.0 mmol) dropwise over 2 min. The solution was stirred at –78 °C for a further 1 h before dropwise addition of (trimethylsilyl)propyne (0.15 mL, 0.112 g, 1.0 mmol) in THF (3 mL). After stirring for a further 10 min at –78 °C the solution was warmed to slowly to 0 °C over 4 h. The solution was re-cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). After 5 min at –78 °C CH_2Cl_2 (0.3 mL, 2.0 mmol) was added. The solution was stirred for a further 30 min at –78 °C before being warmed to rt. The solution continued to stir for a further 30 min before the addition of 2 M HCl (aq) (5 mL). The mixture was stirred for a further 18 h before being extracted with Et_2O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compound (0.092 g, 0.52 mmol, 52%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41-7.20 (5H, m, **Ar-H**), 6.42 (1H, d, *J* = 15.7, **He**), 6.24 (1H, dt, *J* = 15.7, 7.0, **Hf**), 5.31 (1H, s, **Hi**), 2.97 (2H, d, *J* = 7.1, **Hg**), 1.84 (3H, s, **Hk**), 0.13 (9H, s, **Hj**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 153.30 (C, **Ch**), 137.66 (C, **Cd**), 131.38 (CH, **Ce**), 128.48 (CHx2), 128.38 (CH, **Cf**), 126.99 (CH), 126.07 (CHx2), 124.52 (CH, **Ci**), 46.07 (CH_2, **Cg**), 21.76 (CH_3, **Ck**), 0.07 (CH_3x3, **Cj**) ppm.

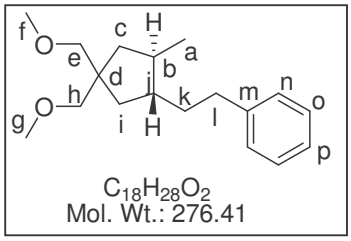
IR ν_{max}/cm^{-1} (film): 1617 (m), 836 (s), 747 (s), 690 (s).

LRMS (EI, CH_2Cl_2): m/z 230 ([$M^{+\cdot}$], 30%), 156 (30%), 135 (30%), 73 (100%).

HRMS (EI): $C_{15}H_{22}Si$ [$M^{+\cdot}$] calculated 230.1491, found 230.1485.

5.27 *rac*-(2-((1*R*,2*R*)-4,4-Bis(methoxymethyl)-2-methylcyclopentyl) ethyl)benzene **73a**

Method A



$C_{18}H_{28}O_2$
Mol. Wt.: 276.41

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 4,4-bis(methoxymethyl)-1,6-heptadiene (0.184 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The reaction mixture was cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) followed by TMEDA (0.15 mL, 0.116 g, 1 mmol) dropwise. The reaction mixture was quenched after 1 h at –78 °C with MeOH (5 mL) and sat $NaHCO_3$ (aq) (5 mL) then allowed to warm to rt with stirring for 18 h. The resulting mixture was diluted with Et_2O (100 mL), washed with H_2O (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% EtOAc in hexane) gave the title compound (0.206 g, 0.75 mmol, 75%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.22 (2H, m, **Hn**), 7.16-7.14 (3H, m, **Ho, p**), 3.36 (6H, s, **Hf, g**), 3.25 (2H, dd, *J* = 9.0, 4.0, **He/h**), 3.20 (2H, dd, *J* = 9.2, 4.4, **He/h**), 2.70 (1H, ddd, *J* = 13.9, 11.0, 4.8, **Hl**), 2.50 (1H, ddd, *J* = 13.7, 10.2, 6.4, **Hl**), 1.95-1.86 (2H, m, **Hc/i, j**), 1.75 (1H, dd, *J* = 12.8, 7.0, **Hc/i**), 1.51 (1H, m, **Hb/k**), 1.40-1.26 (2H, m, **Hb/k**), 1.10 (1H, dd, *J* = 13.0, 10.2, **Hc/i**), 1.01 (1H, dd, *J* = 13.0, 11.0, **Hc/i**), 0.95 (3H, d, *J* = 6.4, **Ha**) ppm.

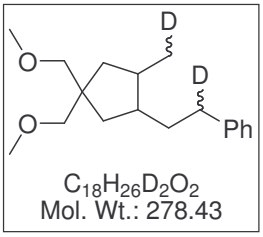
^{13}C NMR (75 MHz, $CDCl_3$): δ 143.04 (C, **Cm**), 128.23 (CHx4, **Cn, o**), 125.54 (CH, **Cp**), 88.0 (CH_2, **Ce/h**), 77.87 (CH_2, **Ce/h**), 59.22 (CH_3x2, **Cf, g**), 46.45 (CH, **Cj**), 45.28 (C, **Cd**), 41.85 (CH_2), 39.82 (CH, **Cb**), 39.45 (CH_2), 35.97 (CH_2), 34.76 (CH_2), 18.05 (CH_3, **Ca**) ppm.

IR ν_{max}/cm^{-1} (film): 1500 (m), 1450 (m), 1105 (s), 698 (s).

LRMS (EI, CH_2Cl_2): *m/z* 276 ([$M^{+\cdot}$], 30%), 212 (60%), 143 (60%), 91 ([$C_7H_7^+$], 100%).

HRMS (EI): $C_{18}H_{28}O_2$ [$M^{+\cdot}$] calculated 276.2089, found 276.2086.

When a sample of the reaction mixture was quenched with 2 M DCl in D_2O the bis-deuterated compound **80** was produced. The following changes in the ^1H and ^{13}C NMR were observed.



^{1}H NMR (300 MHz, $CDCl_3$): δ 2.66 (0.5 H, m, **CHD**), 2.48 (0.5H, m, **CHD**), 0.91 (2H, d, *J* = 6.4, **CH_2D**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 34.8 (CH_2, t, *J* = 58.0, **CHD**), 18.0 (CH_3, t, *J* = 58.0, **CH_2D**) ppm.

Epimerisation experiment

Following the above procedure for the preparation of the benzyl carbenoid inserted zirconacycle. The reaction mixture was warmed to 0 °C and samples of the reaction mixture (1 mL) were removed at timed intervals and quenched with 2 M DCl in D_2O (2 mL). The samples were stirred for 2 h before being diluted with Et_2O (5 mL), washed with H_2O (3 x 5 mL) and brine (5 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The ratio of diastereoisomers was determined from the ^1H NMR spectra.

Synthesis of 73a using benzyl carbamate carbenoid:

Method B

In situ formation of benzyl carbenoid carbamate.

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 4,4-bis(methoxymethyl)-1,6-heptadiene (0.184 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The reaction mixture was cooled to –78 °C before the addition of carbamate **75** (0.303g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. The reaction mixture was quenched after 3 h at –78 °C with MeOH (5 mL) and sat $NaHCO_3$ (aq) (5 mL) then allowed to warm to rt with stirring for 18 h. The resulting mixture was diluted with Et_2O (100 mL), washed with H_2O (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% EtOAc in hexane) gave the title compound (0.111 g, 0.40 mmol, 40%) as a colourless oil.

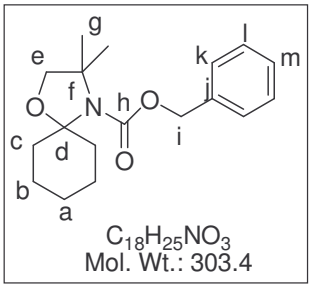
Method C

Preforming benzyl carbamate carbenoid method.

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 4,4-bis(methoxymethyl)-1,6-heptadiene (0.184 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The reaction mixture was cooled to –78 °C before the addition of benzyl carbamate carbenoid **76**, preformed by treating a solution of benzyl carbamate **75** (0.303 g, 1.0 mmol) and TMEDA (0.15 mL, 0.116 g, 1 mmol) in THF (5 mL) at -78 °C with *sec*-BuLi (0.80 M in cyclohexane) (1.25 mL, 1 mmol) for 30 min. The reaction mixture was quenched after 3 h at –78 °C with MeOH (5 mL) and sat $NaHCO_3$ (aq) (5 mL) then allowed to warm to rt with stirring for 18 h. The resulting mixture was diluted with Et_2O (100 mL), washed with H_2O (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% EtOAc in hexane) gave the title compound (0.166 g, 0.60 mmol, 60%) as a colourless oil.

GC (Method A): **71** – 2.72 min, **73a** – 6.26 min and **75** – 5.01 min.

5.28 Benzyl 3,3-dimethyl-1-oxa-4-aza-[4.5]-spirodecane-4-carboxylate **75**



Synthesis of 3,3-dimethyl-1-oxa-4-aza-[4.5]-spirodecane: Cyclohexanone (52 mL, 49 g, 0.50 mol) and 2-amino-2-methyl-1-propanol (47.0 mL, 44.60g, 0.5 mol) were refluxed neat under a Dean and Stark apparatus with *para*-toluene sulfonic acid (100 mg) for 4 days. After this time the reaction mixture was diluted with pentane (500 ml), washed with $NaHCO_3$ (3 x 100ml), dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude compound was purified by distillation (bp 105-118°C, 0.1 mmHg) to yield the 3,3-dimethyl 1-oxa-4-aza-[4.5]-spirodecane (68.0 g, 0.4 mol, 80%).

Synthesis of 3,3-dimethyl-1-oxa-4-aza-[4.5]spirodecane-4-carbonyl chloride: To a solution of triphosgene (5.0 g, 16.8 mmol) in benzene (60 mL) was added 3,3-dimethyl-1-oxa-4-aza-[4.5]-spirodecane (8.50 g, 51 mmol) in benzene (20 mL) followed by Et_3N (7.4 mL, 5.37 g, 53 mmol) dropwise. The mixture was refluxed for 20 h and then cooled and poured onto $NaHCO_3$ (aq) (250 mL). The reaction mixture was extracted with Et_2O (3 x 250 mL), dried ($MgSO_4$) and the solvent was removed *in vacuo* to yield 3,3-dimethyl-1-oxa-4-aza-[4.5]spirodecane-4-carbonyl chloride (9.56 g, 41 mmol, 82%). The compound was used without further purification.

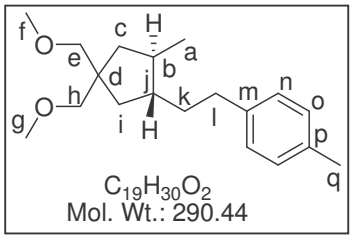
Synthesis of benzyl 3,3-dimethyl-1-oxa-4-aza-[4.5]-spirodecane-4-carboxylate: To sodium hydride (60% solution in mineral oil) (2.3 g 57.5 mmol) suspended in Et_2O (200 mL) was added dropwise benzyl alcohol (5.70 mL, 5.96 g, 55 mmol) at 0 °C. The mixture was stirred at rt for 1 h before the dropwise addition of a solution of 3,3-dimethyl-1-oxa-4-aza-[4.5]spirodecane-4-carbonyl chloride (11.58 g, 50 mmol) in Et_2O (80 mL). The mixture was stirred at rt for 18 h before being poured onto water (100 mL). The water layer was then separated and extracted with Et_2O (3 x 100 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et_2O in hexane) yielded the title compound (8.81 g, 29 mmol, 58%) as a low melting solid.

Data was consistent with published data.[1]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.31 (5H, m, Ar-H), 5.13 (2H, s, **Hi**), 3.70 (2H, s, **He**), 2.45-2.17 (2H, m), 1.62-1.34 (14H, m) ppm.

IR ν_{max}/cm^{-1} (film): 1694 (s), 1610 (m), 1600 (m), 1600 (w), 1520 (w), 1500 (m), 1440 (w), 950 (m), 900 (m).

5.29 *rac*-1-(2-((1*R*,2*R*)-4,4-Bis(methoxymethyl)-2-methylcyclopentyl) ethyl)-4-methylbenzene **73b**



The title compound was prepared using the same method as for compound **73a** (Method A) but *p*-methylbenzyl chloride (0.140 g, 1 mmol) replaced benzyl chloride. Purification by column chromatography on silica gel (eluent: 5% EtOAc in hexane) gave the title compound (0.133 g, 0.46 mmol, 46%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.11-7.05 (4H, m, **Hn, o**), 3.36 (6H, s, **Hf, g**), 3.24 (2H, dd, *J* = 8.8, 3.1, **He/h**), 3.20 (2H, dd, *J* = 4.0, 8.6, **He/h**), 2.66 (1H, ddd, *J* = 14.0, 10.8, 4.3, **Hl**), 2.47 (1H, ddd, *J* = 13.8, 10.3, 6.3, **Hl**), 2.32 (3H, s, **Hq**), 1.92-1.82 (2H, m, **Hc/i, j**), 1.74 (1H, dd, *J* = 13.1, 7.1, **Hc/i**) 1.56-1.22 (3H, m, **Hb, k**), 1.09 (1H, dd, *J* = 13.0, 10.4, **Hc/i**), 1.01 (1H, dd, *J* = 13.0, 11.1, **Hc/i**), 0.94 (3H, d, *J* = 6.2, **Ha**) ppm.

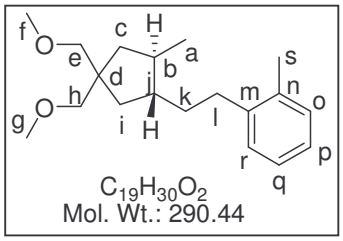
^{13}C NMR (75 MHz, $CDCl_3$): δ 139.97 (C, **Cp**), 134.94 (C, **Cm**), 128.93 (CHx2), 128.10 (CHx2), 78.98 (CH_2, **Ce/h**), 77.85 (CH_2, **Ce/h**), 59.24 (CH_3x2, **Cf, g**), 46.44 (CH, **Cj**), 45.23 (C, **Cd**), 41.85 (CH_2), 39.83 (CH, **Cb**), 39.47 (CH_2), 36.15 (CH_2), 34.32 (CH_2), 20.98 (CH_3, **Cq**), 18.05 (CH_3, **Ca**) ppm.

IR ν_{max}/cm^{-1} (film): 1515 (m), 1448 (m), 1105 (s) 806 (m).

LRMS (ES, MeCN): *m/z* 313 ($[M + Na]^+$, 100%).

HRMS (ES): $C_{19}H_{30}NaO_2$ $[M + Na]^+$ calculated 313.2138, found 313.2134.

5.30 *rac*-1-(2-((1*R*,2*R*)-4,4-Bis(methoxymethyl)-2-methylcyclopentyl) ethyl)-2-methylbenzene **73c**



$C_{19}H_{30}O_2$
Mol. Wt.: 290.44

The title compound was prepared using the same method as for compound **73a** (Method A) but *o*-methylbenzyl chloride (0.140 g, 1 mmol) replaced benzyl chloride. Purification by column chromatography on silica gel (eluent: 5% EtOAc in hexane) gave the title compound (0.133 g, 0.46 mmol, 46%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.14-7.11 (4H, m, **Ar-H**), 3.37 (3H, s, **Hf/g**), 3.36 (3H, s, **Hf/g**), 3.24 (4H, dd, *J* = 11.5, 8.8, **He, h**), 2.67 (1H, ddd, *J* = 13.7, 11.9, 4.9, **Hl**), 2.50 (1H, ddd, *J* = 13.6, 11.2, 5.5, **Hl**), 2.31 (3H, s, **Hs**), 1.93 (1H, dd, *J* = 12.9, 6.9, **Hc/i**), 1.85 (1H, m, **Hj**) 1.76 (1H, dd, *J* = 12.9, 10.5, **Hc/i**), 1.53-1.20 (3H, m, **Hb, k**), 1.03 (1H, dd, *J* = 13.0, 10.5, **Hc/i**), 0.96 (1H, dd, *J* = 13.0, 11.0, **Hc/i**), 0.96 (3H, d, *J* = 6.2, **Ha**) ppm.

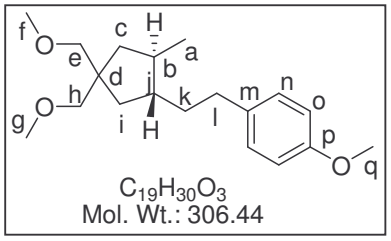
^{13}C NMR (75 MHz, $CDCl_3$): δ 141.24 (C, **Cm**), 135.71 (C, **Cn**), 130.08 (CH), 128.57 (CH), 125.89 (CH), 125.72 (CH), 78.02 (CH_2, **Ce/h**), 77.89 (CH_2, **Ce/h**), 59.26 (CH_3x2, **Cf/g**), 46.94 (CH, **Cj**), 45.32 (C, **Cd**), 41.83 (CH_2), 39.78 (CH, **Cb**), 39.50 (CH_2), 34.65 (CH_2), 32.19 (CH_2), 19.26 (CH_3, **Cs**), 18.11 (CH_3, **Ca**) ppm.

IR ν_{max}/cm^{-1} (film): 1493 (m), 1458 (m), 1104 (s), 736 (s).

LRMS (ES, MeCN): *m/z* 313 ($[M + Na]^+$, 100%).

HRMS (ES): $C_{19}H_{30}NaO_2$ $[M + Na]^+$ calculated 313.2138, found 313.2132.

5.31 *rac*-1-(2-((1*R*,2*R*)-4,4-Bis(methoxymethyl)-2-methylcyclopentyl) ethyl)-4-methoxybenzene **73d**



The title compound was prepared using the same method as for compound **73a** (Method A) but *p*-methoxybenzyl chloride (0.156 g, 1 mmol) replaced benzyl chloride. Purification by column chromatography on silica gel (eluent: 15% EtOAc in hexane) gave the title compound (0.113 g, 0.37 mmol, 37%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.10 (2H, d, *J* = 8.6, **Hn**), 6.83 (2H, d, *J* = 8.6, **Ho**), 3.80 (3H, s, **Hq**), 3.36 (6H, s, **Hf, g**), 3.24 (2H, dd, *J* = 8.8, 3.5, **He/h**), 3.19 (2H, dd, *J* = 8.8, 4.6, **He/h**) 2.64 (1H, ddd, *J* = 14.5, 10.9, 4.3, **Hl**), 2.45 (1H, ddd, *J* = 16.3, 10.0, 6.3, **Hl**), 2.0-1.81 (2H, m, **Hc/i, j**), 1.74 (1H, dd, *J* = 12.2, 6.9, **Hc/i**), 1.51 (1H, m, **Hb/k**), 1.39-1.22 (2H, m, **Hb/k**), 1.08 (1H, dd, *J* = 13.0, 10.4, **Hc/i**), 1.0 (1H, dd, *J* = 13.0, 11.0, **Hc/i**), 0.94 (3H, d, *J* = 6.4, **Ha**) ppm.

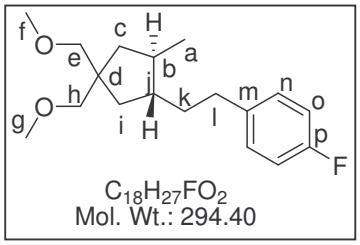
^{13}C NMR (75 MHz, $CDCl_3$): δ 157.58 (C, **Cp**), 135.15 (C, **Cm**), 129.07 (CHx2, **Co**), 113.68 (CHx2, **Cn**), 78.97 (CH_2, **Ce/h**), 77.84 (CH_2, **Ce/h**), 59.24 (CH_3x2, **Cf, g**), 55.24 (CH_3, **Cq**), 46.36 (CH, **Cj**), 45.23 (C, **Cd**), 41.84 (CH_2), 39.82 (CH, **Cb**), 39.45 (CH_2), 36.22 (CH_2), 33.82 (CH_2), 18.06 (CH_3, **Ca**) ppm.

IR ν_{max}/cm^{-1} (film): 1511 (s), 1457 (m) 1233 (s), 1104 (s).

LRMS (EI, CH_2Cl_2): *m/z* 306 ([$M^{+\cdot}$], 80%), 185 (15%), 121 (100%).

HRMS (EI): $C_{19}H_{30}O_3$ [$M^{+\cdot}$]calculated 306.2195, found 306.2198.

5.32 *rac*-1-(2-((1*R*,2*R*)-4,4-Bis(methoxymethyl)-2-methylcyclopentyl) ethyl)-4-fluorobenzene **73e**



$C_{18}H_{27}FO_2$
Mol. Wt.: 294.40

The title compound was prepared using the same method as for compound **74a** (Method A) but *p*-fluorobenzyl chloride (0.144 g, 1 mmol) replaced benzyl chloride. Purification by column chromatography on silica gel (eluent: 10% EtOAc in hexane) gave the title compound (0.140 g, 0.47 mmol, 47%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (2H, dd, *J* = 8.7, 5.6, **Hn**), 6.96 (2H, t, *J* = 8.8, **Ho**), 3.36 (3H, s, **Hf/g**), 3.35 (3H, s, **Hf/g**), 3.26-3.17 (4H, m, **He, h)**, 2.67 (1H, ddd, *J* = 14.4, 10.6, 4.5, **Cl**), 2.49 (1H, ddd, *J* = 14.0, 10.0, 6.6, **Cl**), 1.87 (2H, dd, *J* = 16.3, 6.7, **Hc/i, j**), 1.75 (1H, dd, *J* = 13.0, 7.1, **Hc/i**), 1.51 (1H, m, **Hb/k**), 1.38-1.20 (2H, m, **Hb/k**), 1.10 (1H, dd, *J* = 13.0, 10.4, **Hc/i**), 1.02 (1H, dd, *J* = 13.0, 11.0, **Hc/i**), 0.94 (3H, d, *J* = 6.2, **Ha**) ppm.

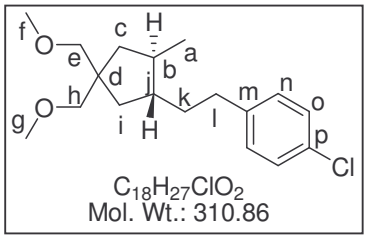
^{13}C NMR (100 MHz, $CDCl_3$): δ 161.09 (C, d, *J* = 242, **Cp**), 138.53 (C, d, *J* = 2.8, **Cm**), 129.45 (CHx2, d, *J* = 7.7, **Cn**), 114.87 (CHx2, d, *J* = 20.9, **Co**), 77.96 (CH_2, **Ce/h**), 77.84 (CH_2, **Ce/Ch**), 59.17 (CH_3x2, **Cf, g**) 46.26 (CH, **Cj**), 45.26 (C, **Cd**), 41.8 (CH_2), 38.78 (CH, **Cb**), 39.38 (CH_2), 36.01 (CH_2), 33.88 (CH_2), 18.00 (CH_3, **Ca**) ppm.

IR ν_{max}/cm^{-1} (film): 1600 (m), 1510 (s), 1460 (m), 1160 (s).

LRMS (ES, MeCN): *m/z* 317 ($[M + Na]^+$, 100%).

HRMS (ES): $C_{18}H_{27}FNaO_2$ $[M + Na]^+$ calculated 317.1887, found 317.1883.

5.33 *rac*-1-(2-((1*R*,2*R*)-4,4-Bis(methoxymethyl)-2-methylcyclopentyl) ethyl)-4-chlorobenzene **73f**



The title compound was prepared using the same method as for compound **74a** (Method A) but *p*-chlorobenzyl chloride (0.160 g, 1 mmol) replaced benzyl chloride. Purification by column chromatography on silica gel (eluent: 5% EtOAc in hexane) gave the title compound (0.094 g, 0.30 mmol, 30%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (2H, d, *J* = 8.4, **Ho**), 7.10 (2H, d, *J* = 8.4, **Hn**), 3.36 (3H, s, **Hf/g**), 3.35 (3H, s, **Hf/g**), 3.23 (2H, dd, *J* = 8.8, 4.9, **He/h**), 3.20 (2H, dd, *J* = 8.8, 4.6, **He/h**), 2.66 (1H, ddd, *J* = 14.0, 10.9, 4.5, **Hl**), 2.48 (1H, ddd, *J* = 13.8, 10.2, 6.7, **Hl**), 1.90-1.82 (2H, m, **Hc/i, j**), 1.74 (1H, dd, 13.0, 7.0, **Hc/i**), 1.52 (1H, m, **Hb/k**), 1.37-1.24 (2H, m, **Hb/k**), 1.09 (1H, dd, *J* = 13.0, 10.4, **Hc/i**), 1.02 (1H, dd, *J*= 13.0, 11.0, **Hc/i**), 0.94 (3H, d, *J* = 7.4, **Ha**) ppm.

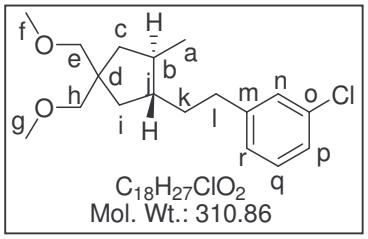
^{13}C NMR (75 MHz, $CDCl_3$): δ 141.42 (C, **Cp**), 131.26 (C, **Cm**), 129.58 (CHx2), 128.32 (CHx2), 78.00 (CH_2, **Ce/h**), 77.89 (CH_2, **Ce/h**), 59.24 (CH_3x2, **Cf, g**), 46.29 (CH, **Cb**), 45.28 (C, **Cd**), 41.82 (CH_2), 39.83 (CH, **Cj**), 39.41 (CH_2), 35.81 (CH_2), 34.09 (CH_2), 18.04 (CH_3, **Ca**) ppm.

IR ν_{max}/cm^{-1} (film): 1492 (m), 1458 (m), 1106 (s) 812 (m).

LRMS (ES, MeCN): *m/z* 333 ($[M + Na]^+$, 100%).

HRMS (ES): $C_{18}H_{27}{}^{35}ClNaO_2$ $[M + Na]^+$ calculated 333.1592, found 333.1586.

5.34 *rac*-1-(2-((1*R*,2*R*)-4,4-Bis(methoxymethyl)-2-methylcyclopentyl) ethyl)-3-chlorobenzene **73g**



$C_{18}H_{27}ClO_2$
Mol. Wt.: 310.86

The title compound was prepared using the same method as for compound **73a** (Method A) but *m*-chlorobenzyl chloride (0.160 g, 1 mmol) replaced benzyl chloride. Purification by column chromatography on silica gel (eluent: 5% EtOAc in hexane) gave the title compound (0.189 g, 0.61 mmol, 61%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23-7.13 (4H, m, **Ar-H**), 6.29 (6H, s, **Hf, g**), 3.24 (2H, dd, *J* = 8.8, 4.2 Hz, **He/h**), 3.19 (2H, dd, *J* = 8.8, 3.3, **He/h**), 2.67 (1H, ddd, *J* = 14.1, 11.3, 4.8, **Hl**), 2.49 (1H, ddd, *J* = 13.7, 10.1, 6.4, **Hl**), 1.91-1.83 (2H, m, **Hc/i, j**), 1.75 (1H, dd, *J*= 7.1, 13.0, **Hc/i**), 1.62-1.25 (3H, m, **Hb, k**), 1.09 (1H, dd, *J* = 13.0, 10.4, **Hc/i**), 1.09 (1H, dd, *J* = 13.0, 11.0, **Hc/i**), 1.02 (3H, d, *J* = 6.4, **Ha**) ppm.

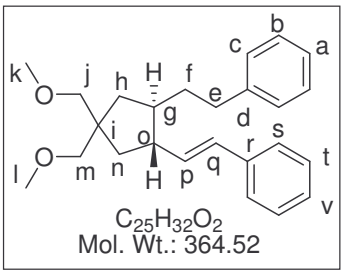
^{13}C NMR (75 MHz, $CDCl_3$): δ 145.06 (C, **Cm**), 140.0 (C, **Co**), 129.48 (CH), 128.38 (CH), 126.44 (CH), 125.76 (CH), 78.0 (CH_2, **Ce/h**), 77.89 (CH_2, **Ce/h**), 59.24 (CH_3x2, **Cg, f**), 46.34 (CH, **Cb**), 45.28 (C, **Cd**), 41.80 (CH_2), 39.83 (CH, **Cj**), 39.93 (CH_2), 35.46 (CH_2), 34.45 (CH_2), 18.04 (CH_3, **Ca**) ppm.

IR ν_{max}/cm^{-1} (film): 1515 (w), 1475 (m), 1448 (m), 1106 (s).

LRMS (ES, MeCN): *m/z* 333 ($[M + Na]^+$, 100%).

HRMS (ES): $C_{18}H_{27}{}^{35}ClNaO_2$ $[M + Na]^+$ calculated 333.1592, found 333.1591.

5.35 *rac*-(2-((1*R*,2*R*)-4,4-Bis(methoxymethyl)-2-((*E*)-styryl)cyclopentyl) ethyl)benzene **74a**



To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 4,4-(bis(methoxymethyl)-1,6-heptadiene (0.184 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The reaction mixture was cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. The reaction mixture was stirred at –78 °C for 40 min before the addition of a further equivalent of benzyl carbenoid (benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol)). Addition of further equivalents of carbenoid was repeated until a total of 5 equivalents had been added. The reaction mixture was quenched with MeOH (5 mL) and sat $NaHCO_3$ (aq) (5 mL) then allowed to warm to rt with stirring for 18 h. The resulting mixture was diluted with Et_2O (100 mL), washed with H_2O (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% EtOAc in hexane) gave the title compound (0.181 g, 0.50 mmol, 50%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30-7.09 (10H, m, **Ar-H**), 6.35 (1H, d, *J* = 15.8, **Hq**), 6.04 (1H, dd, *J* = 15.8, 8.4, **Hp**), 3.38 (6H, s, **Hk, l**), 3.30-3.23 (4H, m, **Hj, m**), 2.67 (1H, ddd, *J* = 13.6, 11.3, 5.3, **He**), 2.53 (1H, ddd, *J* = 13.6, 10.5, 6.3, **He**), 2.28 (1H, m, **Ho**), 1.98-1.87 (2H, m), 1.77 (1H, dd, *J* = 13.2, 7.3), 1.71 (1H, m), 1.45-1.34 (2H, m), 1.20 (1H, t, *J* = 12.0, CH_2) ppm.

^{13}C NMR (300 MHz, $CDCl_3$): δ 142.82 (C, **Cd**), 137.77 (C, **Cr**), 133.79 (CH, **Cp**), 129.81 (CH, **Cq**), 128.44 (CHx2), 128.29 (CHx2), 128.24 (CHx2), 126.84 (CH, **Cv**), 126.0 (CHx2), 125.88 (CH, **Ca**), 77.92 (CH_2, **Cj/m**), 77.89 (CH_2, **Cj/m**), 59.28 (CH_3x2, **Ck, l**), 49.85 (CH, **Co**), 45.84 (C, **Ci**), 45.26 (CH, **Cg**), 40.02 (CH_2), 39.15 (CH_2), 35.94 (CH_2), 34.72 (CH_2) ppm.

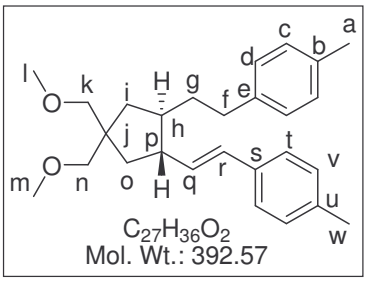
IR ν_{max}/cm^{-1} (film): 1600 (w), 1495 (m), 1475 (m), 1448 (m), 1104 (s), 963 (s), 745 (s), 693 (s).

LRMS (ES, MeCN): *m/z* 387 ([M+Na]$^+$, 100%).

HRMS (ES): $C_{25}H_{32}NaO_2$ [M+Na]$^+$ calculated 387.2295, found 387.2288.

GC (Method B): 9.06 min (**73a** – 6.26 min).

5.36 *rac*-1-(2-((1*R*,2*R*)-4,4-Bis(methoxymethyl)-2-((*E*)-4-methylstyryl) cyclopentyl)ethyl)-4-methylbenzene **74b**



To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 4,4-(bismethoxymethyl)-1,6-heptadiene (0.184 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The reaction mixture was cooled to –78 °C before the addition of *p*-methylbenzyl chloride (0.13 mL, 0.140 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. After 20 min at –78 °C a further 2 eq of *p*-methylbenzyl chloride (0.26 mL, 0.280 g, 2.0 mmol) and LDA (1.8 M solution in THF) (1.2 mL, 2.0 mmol) was added dropwise. After a further 20 min the reaction mixture was quenched with 2 M HCl (aq) (5 mL) then allowed to warm to rt with stirring for 18 h. The resulting mixture was diluted with Et_2O (100 mL), washed with H_2O (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et_2O in hexane) gave the title compound (0.188 g, 0.48 mmol, 48%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (2H, d, *J* = 8.2, **Ar-H**), 7.11-7.02 (6H, m, **Ar-H**), 6.31 (1H, d, *J* = 15.9, **Hr**), 5.98 (1H, dd, *J* = 15.7, 8.4, **Hq**), 3.38 (6H, s, **Hl, m**), 3.31-3.22 (4H, m, **Hk, n**), 2.65 (1H, ddd, *J* = 13.5, 11.2, 4.9, **Hf**), 2.49 (1H, ddd, *J* = 13.7, 10.6, 6.4, **Hf**), 2.33 (3H, s, **Ha/w**), 2.31 (3H, s, **Ha/w**), 2.18 (1H, m, **Ho**), 1.95 (1H, dd, *J* = 13.2, 7.5, CH_2), 1.86 (1H, m), 1.81 (1H, dd, *J* = 13.3, 7.3), 1.70 (1H, m), 1.43-1.32 (2H, m), 1.18 (1H, dd, *J* = 12.9, 11.1) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 139.75 (C, **Cb**), 136.52 (C, **Cs**), 134.93 (Cx2, **Ce, u**), 132.70 (CH), 129.58 (CH), 129.12 (CHx2), 128.91 (CHx2), 128.14 (CHx2), 125.86 (CHx2), 77.88 (CH_2, **Ck/n**), 77.84 (CH_2, **Ck/n**), 59.27 (CH_3x2, **Cl, m**), 49.85 (CH, **Cp**), 47.72 (C, **Cj**), 45.24 (CH, **Ch**), 40.00 (CH_2), 39.12 (CH_2), 36.12 (CH_2), 34.26 (CH_2), 21.11 (CH_3), 20.96 (CH_3) ppm.

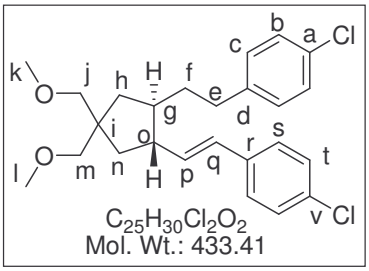
IR ν_{max}/cm^{-1} (film): 1514 (m), 1475 (m), 1447 (m), 1104 (s), 964 (s) 849(m).

LRMS (ES, MeCN): *m/z* 415 ([M+Na]$^+$, 100%).

HRMS (ES): $C_{27}H_{36}NaO_2$ [M+Na]$^+$ calculated 415.2608, found 415.2598.

GC (Mehtod B): 9.76 min (**73b** – 6.64 min).

5.37 *rac*-1-Chloro-4-((*E*)-2-((1*R*,2*R*)-2-(4-chlorophenethyl)-4,4-bis(methoxymethyl)cyclopentyl)vinyl)benzene **74f**



The title compound was prepared using the same method as for compound **74a** but *p*-chlorobenzyl chloride (0.800 g, 5 mmol) replaced benzyl chloride. Purification by column chromatography on silica gel (eluent: 5% EtOAc in hexane) gave the title compound (0.184 g, 0.43 mmol, 43%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29-7.23 (6H, m, **Ar-H**), 7.10-7.08 (2H, d, *J* = 8.3, **Ar-H**), 6.31 (1H, d, *J* = 15.8, **Hq**), 6.01 (1H, dd, *J* = 15.8, 8.5, **Hp**), 3.39 (6H, s, **Hk, l**), 3.31-3.22 (4H, m, **Hm, j**), 2.67 (1H, ddd, *J* = 14.1, 10.8, 4.8, **He**), 2.51 (1H, ddd, *J* = 13.6, 10.2, 6.5, **He**), 2.28 (1H, m, **Ho**), 1.95 (1H, dd, *J* = 13.1, 7.5, CH_2), 1.91-1.80 (2H, m, CH_2/CH), 1.69 (1H, m, CH_2), 1.44-1.36 (2H, m, CH_2), 1.21 (1H, dd, *J* = 12.8, 11.3, CH_2) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 141.10 (C, **Cd**), 136.08 (C, **Cr**), 134.33 (CH, **Cp**), 132.45 (C, **Cv**), 131.32 (C, **Ca**), 129.61 (CHx2), 128.58 (CH, **Cq**), 128.57 (CHx2), 128.33 (CHx2), 127.17 (CHx2), 77.88 (CH_2, **Cj/m**), 77.85 (CH_2, **Cj/m**), 59.29 (CH_3x2, **Ck, l**), 49.89 (CH, **Co**), 45.78 (C, **Ci**), 45.07 (CH, **Cg**), 39.91 (CH_2), 39.06 (CH_2), 35.78 (CH_2), 34.01 (CH_2) ppm.

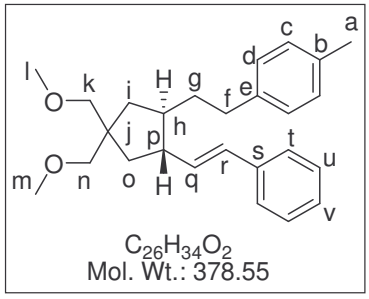
IR ν_{max}/cm^{-1} (film): 1490 (s), 1104 (s), 965 (s).

LRMS (ES, MeCN): *m/z* 455 ($[M+Na]^+$, 100%).

HRMS (ES): $C_{25}H_{30}{}^{35}Cl_2NaO_2$ $[M+Na]^+$ calculated 455.1515, found 455.1508.

GC (Method B): 10.45 min (**73f** – 10.45 min).

5.38 *rac*-1-(2-((1*R*,2*R*)-4,4-Bis(methoxymethyl)-2-((*E*)-styryl) cyclopentyl)ethyl)-4-methylbenzene **74j**



$C_{26}H_{34}O_2$
Mol. Wt.: 378.55

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 4,4-(bismethoxymethyl)-1,6-heptadiene (0.184 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The reaction mixture was cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. After 40 min at –78 °C the reaction mixture was warmed to rt for 40 min before being cooled to 0 °C and LDA (1.8 M solution in THF) (0.3 mL, 0.5 mmol) added dropwise. A sample was removed (0.5 mL) and quenched with 1 M DCl in D_2O (1 mL) to confirm the diastereotopic ratio of the mono-inserted product. The reaction mixture was cooled to –78 °C before the addition of *p*-methylbenzyl chloride (0.13 mL, 0.140 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). After a further 20 min the reaction mixture was quenched with 1 M DCl in D_2O (5 mL) then allowed to warm to rt with stirring for 18 h. The resulting mixture was diluted with Et_2O (100 mL), washed with H_2O (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica (eluent: 5% Et_2O in hexane) yielded a mixture of mono-inserted (**73a**), bis-inserted (**74a**, cross over bis-inserted (**74j**) and cross over bis-inserted (**74k**) in a ratio of 8:4:20:1. The yield was not calculated as the reaction was carried out as part of a mechanistic study and several samples were removed from the reaction mixture during the course of the reaction. The crossover products were observed as a ratio of 20:1 (title compound (**74j**): minor (**74k**)). Further purification by prep HPLC (eluent: hexane) was carried out to give a pure sample of the title compound as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.17 (5H m, **Ar-H**), 7.09-7.03 (4H, m, **Ar-H**), 6.35 (1H, d, *J* = 15.9, **Hr**), 6.04 (1H, dd, *J* = 15.9, 8.5, **Hq**), 3.38 (6H, s, **Hl, m**), 3.31-3.23 (4H, m, **Hk, n**), 2.65 (1H, ddd, *J* = 13.5, 11.0, 5.1, **Hf**), 2.49 (1H, ddd, *J* = 13.5,

10.6, 6.3, **Hf**), 2.31 (3H, s, **Ha**), 2.27 (1H, m, **Hp**), 1.95 (1H, dd *J* = 13.0, 7.5 Hz, CH_2), 1.90 (1H, m, CH), 1.82 (1H, dd, *J* = 13.4, 7.3, CH_2), 1.71 (1H, m, CH_2), 1.44-1.27 (2H, m, CH_2), 1.19 (1H, dd, *J* = 12.9, 11.1, CH_2) ppm.

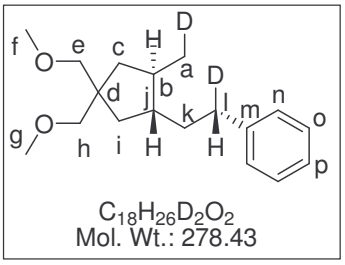
^{13}C NMR (100 MHz, $CDCl_3$): δ 139.73 (C, **Cb**), 137.69 (C, **Cs**), 134.98 (C, **Ce**), 133.72 (CH, **Cq**), 129.77 (CH, **Cr**), 128.92 (CHx2), 128.44 (CHx2, **Cu**), 128.14 (CHx2), 126.82 (CH, **Cv**), 125.92 (CHx2, **Ct**), 77.86 (CH, **Ck/h**), 77.82 (CH, **Ck/h**), 59.29 (CH_3x2, **Cl, m**), 49.87 (CH, **Cp**), 45.72 (C, **Cj**), 45.24 (CH, **Ch**), 39.95 (CH_2), 39.12 (CH_2), 36.14 (CH_2), 34.27 (CH_2), 20.96 (CH_3, **Ca**) ppm.

IR ν_{max}/cm^{-1} (film): 1514 (w), 1494 (w), 1448 (m), 1104 (s), 963 (s), 746 (s).

LRMS (ES, MeCN): *m/z* 401 ($[M+Na]^+$, 100%).

HRMS (ES): $C_{26}H_{34}NaO_2$ $[M+Na]^+$ calculated 401.2451, found 401.2443.

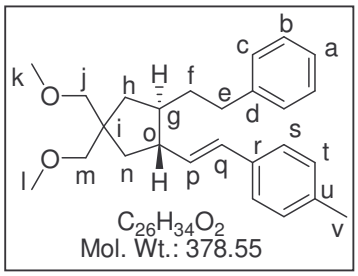
NMR analysis of the mono inserted product prior to insertion of the second benzyl carbenoid revealed that there was only one diastereoisomer.



$C_{18}H_{26}D_2O_2$
Mol. Wt.: 278.43

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.18 (5H, m, **Ar-H**), 3.36 (6H, s, **Hf, g**), 3.26-3.17 (4H, m, **He, h**), 2.67 (1H, m, **Hl**), 1.92-1.85 (2H, m, **Hc/i, b**), 1.74 (1H, dd, *J* = 13.0, 6.9, **Hc/i**), 1.52-1.27 (3H, m, **Hj, k**), 1.10 (1H, dd, *J* = 13.0, 10.4, **Hc/i**), 1.01 (1H, dd, *J* = 13.0, 11.2, **Hc/i**), 0.92 (2H, d, *J* = 6.0, **Ha**) ppm.

5.39 *rac*-1-((*E*)-2-((1*R*,2*R*)-4,4-Bis(methoxymethyl)-2-phenethylcyclopentyl)vinyl)-4-methylbenzene **74k**



To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 4,4-(bismethoxymethyl)-1,6-heptadiene (0.184 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The reaction mixture was cooled to –78 °C before the addition of *p*-methylbenzyl chloride (0.13 mL, 0.140 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. After 40 min at –78 °C the reaction mixture was warmed to rt for 40 min before being cooled to 0 °C and LDA (1.8 M solution in THF) (0.3 mL, 0.5 mmol) added dropwise. A sample was removed (0.5 mL) and quenched with 1 M DCl in D_2O (1 mL) to confirm the diastereotopic ratio of the mono-inserted product. The reaction mixture was cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol). After a further 20 min the reaction mixture was quenched with 1 M DCl in D_2O (5 mL) then allowed to warm to rt with stirring for 18 h. The resulting mixture was diluted with Et_2O (100 mL), washed with H_2O (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et_2O in hexane) yielded a mixture of mono-inserted (**73b**), bis-inserted (**74b**), cross over bis-inserted (**74k**) and cross over bis-inserted (**74j**) in a ratio of 40:8:40:1. The yield was not calculated as the reaction was carried out as part of a mechanistic study and several samples were removed from the reaction mixture during the course of the reaction. The crossover products were observed as a ratio of 40:1 (title compound (**74k**): minor (**74j**)). Further purification by prep HPLC (eluent: hexane) was carried out to give a pure sample of the title compound as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25-7.09 (9H, m, **Ar-H**), 6.32 (1H, d, *J* = 15.7, **Hq**), 5.98 (1H, dd, *J* = 15.7, 8.4, **Hp**), 3.38 (6H, s, **Hk, l**), 3.32-3.22 (4H, m, **Hj, m**), 2.68 (1H, ddd, *J* = 13.5, 11.0, 4.9, **He**), 2.53 (1H, ddd, *J* = 13.6, 10.6, 6.2, **He**), 2.33 (3H, s,

Hu), 2.26 (1H, m, **He**), 1.95 (1H, dd, *J* = 13.0, 7.3, CH_2), 1.87 (1H, m, CH_2), 1.81 (1H, dd *J* = 13.4, 7.3, CH_2), 1.70 (1H, m CH_2), 1.45 (2H, m, CH_2), 1.19 (1H, dd, *J* = 12.9, 11.1, CH_2) ppm.

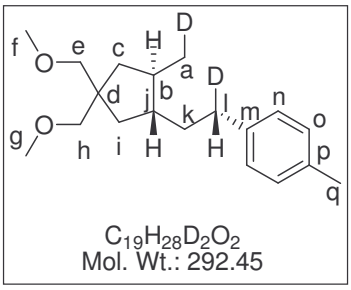
^{13}C NMR (100 MHz, $CDCl_3$): δ 142.84 (C, **Cd**), 136.57 (C, **Cr**), 134.90 (C, **Cv**), 132.67 (CH, **Cp**), 129.62 (CH, **Cq**), 129.14 (CHx2, **Ct**), 128.29 (CHx2), 128.22 (CHx2), 125.87 (CHx2, **Cs**), 125.56 (CH, **Ca**), 77.87 (CH_2, **Cj/m**), 77.84 (CH_2, **Cj/m**), 59.29 (CH_3x2, **Ck, l**), 49.88 (CH, **Co**), 45.70 (C, **Ci**), 45.26 (CH, **Cg**), 40.00 (CH_2), 39.12 (CH_2), 35.97 (CH_2), 34.72 (CH_2), 21.12 (CH_3, **Cu**) ppm.

IR ν_{max}/cm^{-1} (film): 1513 (m), 1496 (w), 1453 (m), 1104 (s), 964 (s), 699 (s).

LRMS (ES, MeCN): *m/z* 401 ($[M+Na]^+$, 100%).

HRMS (ES): $C_{26}H_{34}NaO_2$ $[M+Na]^+$ calculated 401.2451, found 401.2444.

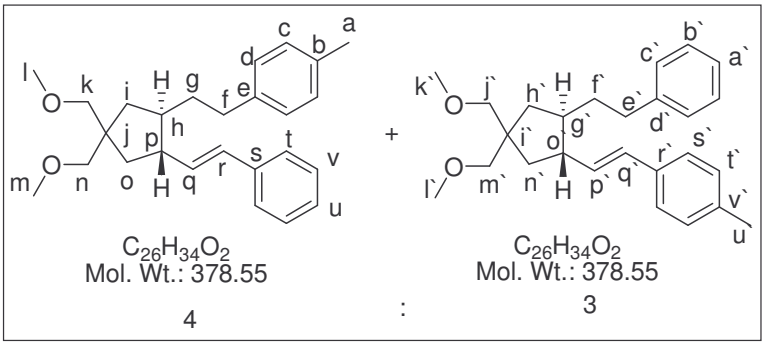
NMR analysis of the mono-inserted product prior to insertion of the second benzyl carbenoid revealed that there was only one diastereoisomer.



$C_{19}H_{28}D_2O_2$
Mol. Wt.: 292.45

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09 (4H, s, **Ar-H**), 3.36 (6H, s, **Hf, g**), 3.26-3.18 (4H, m, **He, h**), 2.64 (1H, m, **Hl**), 2.33 (3H, s, **Hq**) 1.91-1.83 (2H, m, **Hc/i, b**), 1.74 (1H, dd, *J* = 13.0, 7.0, **Hc/i**), 1.39-1.22 (3H, m, **Hj, k**), 1.10 (1H, dd, *J* = 12.8, 10.3, **Hc/i**), 1.01 (1H, dd, *J* = 12.8, 11.6, **Hc/i**), 0.91 (2H, d, *J* = 6.0, **Ha**) ppm.

5.40 *rac*-1-(2-((1*R*,2*R*)-4,4-Bis(methoxymethyl)-2-((*E*)-styryl) cyclopentyl)ethyl)-4-methylbenzene **74j** and *rac*-1-((*E*)-2-((1*R*,2*R*)-4,4-Bis(methoxymethyl)-2-phenethylcyclopentyl)vinyl)-4-methylbenzene **74k**

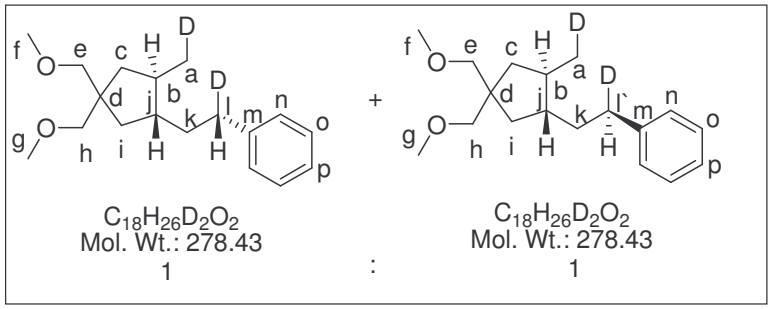


To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 4,4-bis(methoxymethyl)-1,6-heptadiene (0.184 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The reaction mixture was cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. After 40 min as –78 °C the reaction mixture was warmed to rt for 40 min. A sample was removed (0.5 mL) and quenched with 1 M DCl in D_2O (1 mL) to confirm the diastereotopic ratio of the mono-inserted product. The reaction mixture was cooled to –78 °C before the addition of *p*-methylbenzyl chloride (0.13 mL, 0.140 g, 1.0 mmol) and LDA (0.6 mL of 1.8 M solution in THF, 1.0 mmol). After a further 20 min the reaction mixture was quenched with 1 M DCl in D_2O (5 mL) then allowed to warm to rt with stirring for 18 h. The resulting mixture was diluted with Et_2O (100 mL), washed with H_2O (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et_2O in hexane) yielded a mixture of mono-inserted (**73a**), bis-inserted (**74a**), cross over bis-inserted (**74j**) and cross over bis-inserted (**74k**) in a ratio of 1:2:4:3.

^{13}C NMR (75 MHz, $CDCl_3$): δ 142.82 (C, **Cd`**), 139.72 (C, **Cb**), 137.68 (C, **Cs**), 136.54 (C, **Cr`**), 134.96 (C, **Cu`**), 134.89 (C, **Ce**), 133.72 (CH, **Cq**), 129.76 (CH, **Cr**), 129.12 (CH), 128.91 (CH), 128.43 (CH), 128.29 (CH), 128.22 (CH), 128.14 (CH), 126.82 (CH, **Cu**), 125.97 (CH, **Cv**), 125.86 (CH), 77.86 ($CH_2$), 77.82 ($CH_2$), 59.27 ($CH_3$), 49.87 (CH, C**p, o`**), 45.72 (C, **Cj, Ci`**), 45.34 (CH, **Ch, g`**), 39.95 (CH_2), 39.11

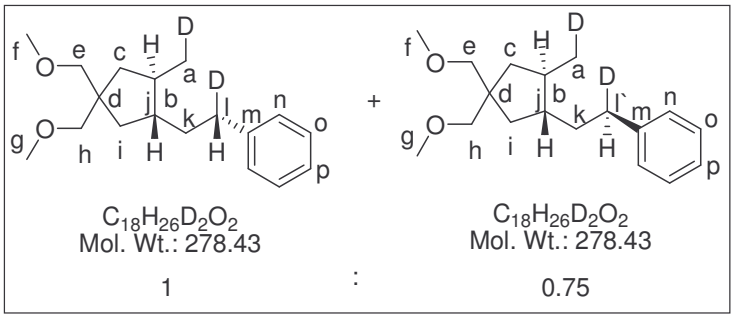
(CH_2), 36.13 (CH_2), 35.97 (CH_2), 34.72 (CH_2), 34.25 (CH_2), 21.11 (CH_3, **Cu`**), 20.96 (CH_3, **Ca**) ppm.

NMR analysis of the mono inserted product prior to insertion of the second benzyl carbenoid revealed a 1:1 ratio of diastereoisomers



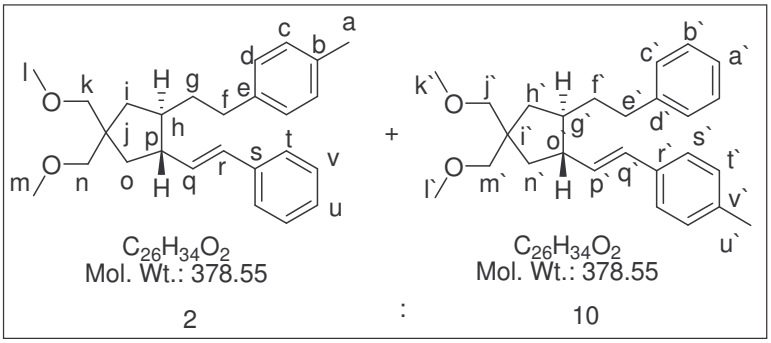
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.18 (5H, m, **Ar-H**), 3.36 (6H, s, **Hf, g**), 3.26-3.17 (4H, m, **He, h**), 2.68 (0.5H, m, **Hl`**), 2.50 (0.5H, m, **Hl**), 1.91-1.85 (2H, m, **Hc/i, b**), 1.74 (1H, dd, *J* = 13.0, 7.0, **Hc/i**), 1.42-1.19 (3H, m, **Hj, k**), 1.10 (1H, dd, *J* = 12.7, 10.2, **Hc/i**), 1.01 (1H, dd, *J* = 13.0, 11.1, **Hc/i**), 0.92 (2H, d, *J* = 5.9, **Ha**) ppm.

NMR analysis of the mono inserted product remaining after the insertion of the second benzyl carbenoid revealed a 1:0.75 ratio of diastereoisomers.



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.15 (5H, m, **Ar-H**), 3.36 (6H, s, **Hf, g**), 3.26-3.17 (4H, m, **He, h**), 2.70 (0.57H, m, **Hl`**), 2.50 (0.43H, m, **Hl**), 1.90-1.84 (2H, m, **Hc/i, b**), 1.73 (1H, dd, *J* = 13.0, 7.4, **Hc/i**), 1.52-1.26 (3H, m, **Hj, k**), 1.09 (1H, dd, *J* = 13.1, 10.4, **Hc/i**), 1.01 (1H, dd, *J* = 12.8, 11.2, **Hc/i**), 0.92 (2H, d, *J* = 6.0, **Ha**) ppm.

5.41 *rac*-1-((*E*)-2-((1*R*,2*R*)-4,4-Bis(methoxymethyl)-2-phenethylcyclopentyl)vinyl)-4-methylbenzene **74k** and *rac*-1-(2-((1*R*,2*R*)-4,4-Bis(methoxymethyl)-2-((*E*)-styryl)cyclopentyl)ethyl)-4-methylbenzene **74j**

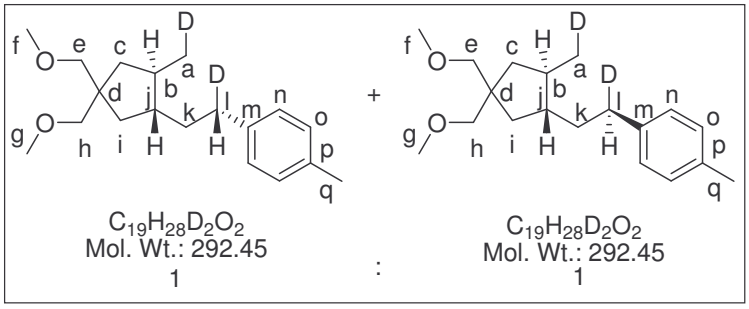


To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 4,4-bis(methoxymethyl)-1,6-heptadiene (0.184 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The reaction mixture was cooled to –78 °C before the addition of *p*-methylbenzyl chloride (0.13 mL, 0.140 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. After 40 min as –78 °C the reaction mixture was warmed to rt for 40 min. A sample was removed (0.5 mL) and quenched with 1 M DCl in D_2O (1 mL) to confirm the diastereotopic ratio of the mono-inserted product. The reaction mixture was cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (0.6 mL of 1.8 M solution in THF, 1.0 mmol). After a further 20 min the reaction mixture was quenched with 1 M DCl in D_2O (5 mL) then allowed to warm to rt with stirring for 18 h. The resulting mixture was diluted with Et_2O (100 mL), washed with H_2O (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et_2O in hexane) yielded a mixture of mono-inserted (**73b**), bis-inserted (**74b**), cross over bis-inserted **(74j**) and cross over bis-inserted (**74k**) in a ratio of 4:3:2:10.

^{13}C NMR (75 MHz, $CDCl_3$): δ 142.87 (C, **Cd`**), 136.59 (C, **Cr`**), 134.94 (C, **Cu`**), 133.77 (CH, **Cr**), 132.71 (CH, **Cp`**), 129.65 (CH, **Cq`**), 129.17 (CH), 128.95 (CH, **Ce**), 128.47 (CH, **Ct**), 128.26 (CH), 128.19 (CH, **Cd**), 126.86 (CH, **Cu**), 125.90 (CH, **Cv**), 125.60 (CH, **Ca**), 77.91 (CH_2), 77.88 (CH_2), 59.32 (CH_3), 49.91 (CH), 45.75 (C), 45.29

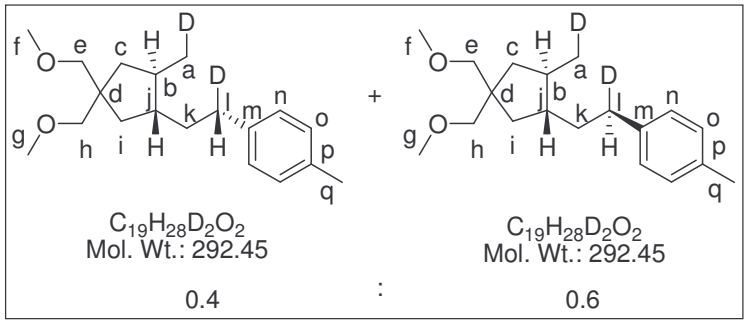
(CH), 40.03 (CH_2), 39.16 (CH_2), 39.01 (CH_2), 34.77 (CH_2), 34.31 (CH_2), 21.16 (CH_3, **Cu`**), 21.60 (CH_3, **Ca**) ppm.

NMR analysis of the mono inserted product prior to insertion of the second benzyl carbenoid revealed a 1:1 ratio of diastereoisomers.



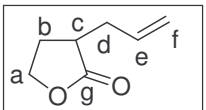
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09 (4H, s, **Ar-H**), 3.36 (6H, s, **Hf, g**), 3.27-3.18 (4H, m, **He, h**), 2.64 (0.5H, m, **Hl**), 2.42 (0.5H, m, **Hl**) 2.33 (3H, s, **Hq**) 1.91-1.85 (2H, m, **Hc/i, b**), 1.74 (1H, dd, *J* = 13.0, 6.9, **Hc/i**), 1.55-1.24 (3H, m, **Hj, k**), 1.09 (1H, dd, *J* = 13.0, 10.4, **Hc/i**), 1.01 (1H, dd, *J* = 13.1, 11.5, **Hc/i**), 0.92 (2H, d, *J* = 6.0, **Ha**) ppm.

NMR analysis of the mono inserted product remaining after the insertion of the second benzyl carbenoid revealed a 0.4:0.6 ratio of diastereoisomers.



^{1}H NMR (300 MHz, $CDCl_3$): δ 7.09 (4H, s, **Ar-H**), 3.36 (6H, s, **Hf, g**), 3.26-3.17 (4H, m, **He, h**), 2.63 (0.6H, m, **Hl**), 2.42 (0.4H, m, **Hl**) 2.33 (3H, s, **Hq**) 1.90-1.84 (2H, m, **Hc/i, b**), 1.73 (1H, dd, *J* = 13.0, 7.4, **Hc/i**), 1.55-1.24 (3H, m, **Hj, k**), 1.09 (1H, dd, *J* = 13.0, 10.4, **Hc/i**), 1.01 (1H, dd, *J* = 13.1, 11.3, **Hc/i**), 0.92 (2H, d, *J* = 6.0, **Ha**) ppm.

5.42 3-Allyldihydrofuran-2(3*H*)-one **91**



$C_7H_{10}O_2$
Mol. Wt.: 126.15

Synthesis was carried out using a procedure published by Walton and Fraser-Reid.[75] *n*-BuLi (2.5 M solution in hexanes) (14.0 mL, 34.9 mmol) was added to a solution of distilled diisopropylamine (4.9.0 mL, 34.9 mmol) in THF (250 mL) at 0 ºC and then cooled to –78 ºC. A solution of the dihydrofuran-2(3*H*)-one (2.50 g, 29 mmol) in THF (25 mL) was added dropwise. After 30 min HMPA (7.6 mL, 43.6 mmol) was added followed by allyl bromide (2.8 mL, 31. 9 mmol). The mixture was stirred for 2 h at –78 ºC and quenched with sat NH_4Cl (aq) (25 mL) before being warmed to rt. The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 20 % EtOAc in hexane) to yield the title compound (1.47 g, 12 mmol, 41%) as a colourless oil.

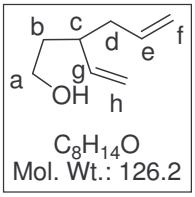
Data was consisitent with published data[75].

^{1}H NMR (400 MHz, $CDCl_3$): 5.78 (1H, tdd, *J* = 7.0, 10.0, 17.1, **Hf**), 5.15-5.09 (2H, m, **He**), 4.32 (1H, ddd, *J* = 3.3, 9.0, 12.0, **Ha**), 4.19 (1H, ddd, *J* = 7.0, 9.3, 16.3, **Ha**), 2.68-2.57 (2H, m), 2.40-2.22 (2H, m), 1.99 (1H, tt, *J* = 6.9, 9.5, **Hc**) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 178.72 (C=O, **Cg**), 134.35 (CH, **Ce**), 117.65 (CH_2, **Cf**), 66.49 (CH_2, **Ca**), 38.79 (CH, **Cc**), 34.29 (CH_2), 27.76 (CH_2) ppm.

IR ν_{max}/cm^{-1} (film):.1761 (s), 1642 (w), 1440 (w), 1374 (w) 1163 (s), 916 (m).

5.43 3-Vinylhex-5-en-1-ol **93**



Synthesis was carried out using a procedure published by Walton and Fraser-Reid.[75] To a solution of 3-allyldihydrofuran-2(3*H*)-one (1.26 g, 10 mmol) in toluene (50 mL) at –78 ºC was added DIBAL-H (1M solution in toluene) (40 mL, 40 mmol). After 30 min at –78 ºC the mixture was quenched by dropwise addition of MeOH (20 mL). Sat potassium sodium tartrate (aq) (30 mL) and sat NH_4Cl (aq) (20 mL) was added and the reaction mixture was stirred for 3 h until the organic layer was clear. The reaction mixture was diluted with EtOAc (100 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo* to give 3-allyltetrahydrofuran-2-ol **92** (0.72 g) which was used directly in the next reaction.

Wittig olefination was carried out using a procedure published by Bailey *et al.*[76] To a solution methyltriphenylphosphonium bromide (5.36 g, 15 mmol) in THF (50 mL) at 0 ºC was added KHMDS (0.5 M solution in toluene) (30 mL, 15 mmol). The resulting yellow suspension was stirred at 0 ºC for 15 min before warming to rt for 1 h. The mixture was then recooled to 0 ºC and a solution of 3-allyltetrahydrofuran-2-ol **92** (0.72 g) in THF (5 mL) was added slowly over 40 min. The mixture was stirred for a further 1 h at rt, poured onto 2 M HCl (aq) (75 mL) and extracted with Et_2O (1 x 50 mL). The combined organic extracts were washed with sat $NaHCO_3$ (aq) (50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 25 % EtOAc in hexane) yielded the title compound (0.51 g, 4.1 mmol, 41%) as a colourless oil.

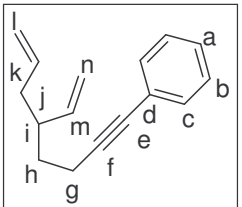
Data was consistent with published data[76].

^{1}H NMR (300 MHz, $CDCl_3$): 5.66 (1H, tdd, *J* = 6.9, 10.4, 17.4, **He**), 5.52 (1H, br dd, *J* = 8.4, 17.6, **Hg**), 4.96-4.90 (4H, m, **Hf, h**), 3.64-3.50 (2H, m), 2.18-2.00 (2H, m), 1.95 (1H, br s, OH), 1.63 (1H, m, **Hc**), 1.46-1.36 (2H, m) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 142.12 (CH_2, **f/h**), 136.51 (CH_2, **Cf/h**), 116.06 (CH, **Cg/e**), 114.90 (CH, **Cg/e**), 61.08 (CH_2, **Ca**), 40.69 (CH, **Cc**), 39.61 (CH_2), 36.93 (CH_2) ppm.

IR ν_{max}/cm^{-1} (film): 3328 (br s), 1640 (m), 1440 (w), 1419 (w), 1050 (m), 992 (s), 999 (s).

5.44 1-(5-Vinyloct-7-en-1-ynyl)benzene **95**



$C_{16}H_{18}$
Mol. Wt.: 210.31

Standard procedure was published by Baum *et al.*[77] A solution of 3-vinylhex-5-en-1-ol (0.81 g, 6.4 mmol), pyridine (0.52 mL, 6.4 mmol) and CH_2Cl_2 (2 mL) was added dropwise over 15 min to a solution of triflic anhydride (2.08 g, 7.4 mmol) in CH_2Cl_2 (5 mL) at 0 ºC. After 15 min the solution was diluted with CH_2Cl_2 (50 mL), washed with water (3 x 50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to give 3-vinylhex-5-enyl trifluoromethanesulfonate **94** (1.50 g, 6.2 mmol, 97%) which was used directly in the next reaction.

To a stirred solution of phenylacetylene (0.29 mL, 2.7 mmol) in THF (10 mL) at –78 ºC was added *n*-BuLi (2.5 M solution in THF) (1.1 mL, 2.8 mmol) dropwise. After 30 min at –78 ºC a solution of 3-vinylhex-5-enyl trifluoromethanesulfonate **94** (0.774 g, 3.2 mmol) in THF (2 mL) was added and the mixture was allowed to warm to rt for 18 h. The reaction mixture was quenched with sat NH_4Cl (aq) (20 mL) and extracted with Et_2O (10 mL). The aqueous layer was separated and re-extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 10 % EtOAc in hexane) yielded the title compound (0.268 g, 1.1 mmol, 41%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): 7.33-7.30 (2H, m, **Ar-H**), 7.20-7.18 (3H, m, **Ar-H**), 5.71 (1H, tdd, *J* = 17.4, 10.5, 7.1, **Hk**), 5.52 (1H, ddd, *J* = 18.0, 9.6, 8.4, **Hm**), 5.02-4.91 (4H, m, **Hl, n**), 2.41-2.18 (3H, m), 2.11-2.04 (2H, m), 1.69 (1H, m), 1.45 (1H, m) ppm.

^{13}C NMR (75 MHz, CDCl3): 141.38 (CH, **Cm/k**), 136.57 (CH, **Cm/k**), 131.51 (CHx2), 128.16 (CHx2), 127.48 (CH), 124.02 (C, **Cd**), 116.01 (CH_2, **Cn/l**), 115.35 (CH_2, **Cn/l**), 90.08 (C, **Ce/f**), 80.90 (C, **Ce/f**) 42.84 (CH, **Ci**), 39.26 (CH_2), 32.98 (CH_2), 17.20 (CH_2, **Cg**) ppm.

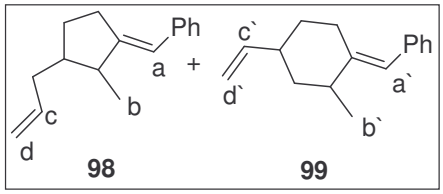
IR ν_{max}/cm^{-1} (film): 1640 (w), 1598 (w),1489 (m), 993 (m), 911 (s), 754 (s), 690 (s).

LRMS (EI, CH_2Cl_2): 210 ([$M^{+\cdot}$], 2%), 169 (100%), 141 (60%), 115 (100%).

HRMS (ES): $C_{16}H_{18}$ [$M^{+\cdot}$] calculated 210.1409, found 210.1413.

5.45 Attempted zirconocene mediated co-cyclisation of 1-(5-Vinyloct-7-en-1-ynyl)benzene.

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 1-(5-Vinyloct-7-en-1-ynyl)benzene **95** (0.210 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. A sample (1 mL) was removed, quenched with 2 M HCl (aq) (1 mL) and stirred for 2 h. The reaction mixture was extracted with Et_2O (5 mL), washed with water (3 x 5 mL) and brine (5 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*.

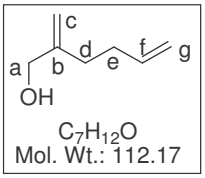


Analysis of the crude ^{1}H NMR revealed the following peaks which are characteristic of a 1:1 mixture of **98** and **99**.

^{1}H NMR (300 MHz, $CDCl_3$): 6.17 (1H, s, **Ha/a`**), 6.16 (1H, s, **Ha/a`**), 5.78 (1H, tdd, *J* = 7.0, 9.6, 17.3, **Hc**), 5.69 (1H, ddd, *J* = 7.5, 10.2, 17.5, **Hc`**), 5.03-4.84 (4H, m, **Hd, d`**), 1.13 (3H, d, *J* = 11.3, **Hb/b`**), 1.12 (3H, d, *J* = 11.9, **Hb/b`**) ppm.

GC (method B): 8.62 and 8.86 min.

5.46 2-Methylenehex-5-en-1-ol **103**



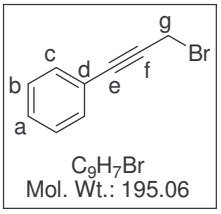
Synthesis was carried out using a procedure published by Trost *et al*.[78] To a solution of *n*-BuLi (2.5 M in hexanes) (320 ml, 800 mmol) at –78 °C was added TMEDA (121 mL, 800 mmol) dropwise. Et_2O (160 mL) was added to the reaction mixture. 2-Methyl-2-propen-1-ol (34 mL, 400 mmol) was added and the solution was warmed to rt for 20 h. The solution was cooled to –78 °C before the dropwise addition of allyl bromide (25.4 mL, 300 mmol) in Et_2O (40 mL). The solution was stirred for 2 h at –78 °C and then warmed to rt for a further 2 h. The reaction mixture was quenched with sat NH_4Cl (aq) (50 mL) and extracted with Et_2O (3 x 400 mL). The combined organic layers were washed with $CuSO_4$ (aq) (3 x 400 mL) and brine (2 x 400 mL), dried ($MgSO_4$) and the solvent removed by distillation to yield the title compound (19.2 g, 170 mmol, 57%) as a pale yellow oil. The compound was used crude without any further purification.
Data was consistent with published data.[78]

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.81 (1H, ddd, *J* = 16.2, 10.2, 6.3, **Hf**), 5.06-4.87 (4H, m, **Hg, c**), 4.05 (2H, s, **Ha**), 2.27-2.14 (4H, m, **Hd, e**) 1.73 (1H, s, **OH**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 148.26 (C, **Cb**), 138.08 (CH, **Cf**), 114.71 (CH_2, **Cg/Cc**), 109.44 (CH_2, **Cg/Cc**), 65.67 (CH_2, **Ca**), 32.12 (CH_2), 31.82 (CH_2) ppm.

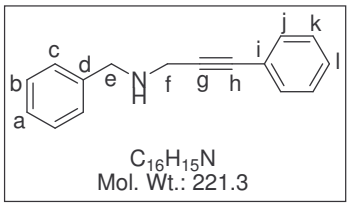
IR ν_{max}/cm^{-1} (film): 3336 (br), 1641 (m), 1449 (m), 1023 (m), 993 (m), 899 (s).

5.47 *N*-Benzyl-3-phenylprop-2-yn-1-amine **107**



Synthesis of (3-bromoprop-1-ynyl)benzene **106** was carried out following a procedure published by Chan *et al.*[79] To a solution of PPh_3 (9.43 g, 38 mmol) in CH_2Cl_2 (150 mL) at 0 °C was added bromine (1.95 mL, 6.07 g, 38 mmol) dropwise. The solution was stirred for 30 min before the addition of 3-phenyl-2-propyne-1-ol (5 g, 38.0 mmol). The solution was stirred for 1 h before the addition of hexane (600 mL). The resulting suspension was passed through a short silica pad. The solvent was removed *in vacuo* to yield the title compound (5.30 g, 27 mmol, 71%) as a colourless oil. Alkyne **106** was used crude without any further purification. Data was consistent with published data.[79]

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (2H, m, **Ar-H**), 7.35-7.32 (3H, m, **Ar-H**), 4.18 (2H, s, **Hg**) ppm.



Synthesis of *N*-benzyl-3-phenylprop-2-yn-1-amine **107:** To a solution of benzylamine (11.5 g, 48 mmol) in Et_2O (10 mL) at 0 °C was added (3-bromoprop-1-ynyl)benzene (5.3 g, 24 mmol) and the mixture was stirred at rt for 18 h. The reaction mixture was poured onto H_2O (100 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et_3N, 10% Et_2O in hexane) yielded the title compound (2.82 g, 12.7 mmol, 53%) as a colourless oil.

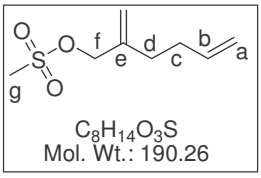
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (2H, m, **Ar-H**), 7.38 (2H, d, *J* = 8.1, **Ar-H**), 7.27-7.16 (3H, m, **Ar-H**), 7.09-7.06 (3H, m, **Ar-H**). 3.80 (2H, s, **He**), 3.47 (2H, s. **Hf**), 1.05 (1H, br s, **NH**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 140.42 (C, **Cd**), 132.0 (CHx2, **Cj**), 128.67 (CHx2), 128.61 (CHx2), 128.58 (CHx2), 128.13 (CH), 127.22 (CH), 124.21 (C, **Ci**), 88.72 (C, **Cg/h**), 83.94 (C, **Cg/h**), 52.62 (CH_2, **Ce**), 38.39 (CH_2, **Ch**) ppm

IR ν_{max}/cm^{-1} (film): 1599 (m), 1486 (m) 756 (s), 733 (s), 688 (s).

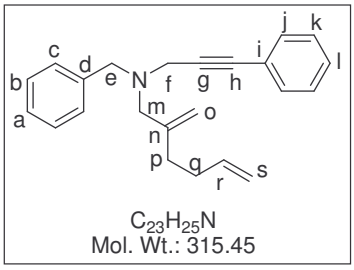
LRMS (ES, MeCN): *m/z* 222 ($[M + H]^+$, 100%).

5.48 *N*-Benzyl-2-methylene-*N*-(3-phenylprop-2-ynyl)hex-5-en-1-amine **108**



Synthesis of 2-methylenehex-5-enyl methanesulfonate **104**: To a stirred solution of 2-methylenehex-5-en-1-ol **103** (4.0 g, 35.7 mmol) and Et_3N (5.5 g, 54 mmol) in CH_2Cl_2 (100 mL) at –10 °C was added MsCl (3.3 mL, 42 mmol) dropwise maintaining the temperature between –10 - 0 °C. The solution was warmed to rt and stirred for 30 min before being poured onto H_2O (50 mL). The organic layer was separated. The aqueous layer was re-extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with 2 M HCl (aq) (50 mL), H_2O (50 mL), sat $NaHCO_3$ (aq) (50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to yielded 2-methylenehex-5-enyl methanesulfonate **104** (6.65g, 35 mmol, 98%) as a pale yellow oil. The compound was used crude without any further purification.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.89-5.75 (1H, m, **Hb**), 5.21-4.99 (4H, m, **Ha, f**), 4.67 (2H, s, **Hg**), 3.03 (3H, s, **Hh**), 2.25 (4H, m, **Hd, c**) ppm.



Synthesis of *N*-benzyl-2-methylene-*N*-(3-phenylprop-2-ynyl)hex-5-en-1-amine **108**: To a stirred solution of amine **107** (3.32 g, 15 mmol) and LiI (0.40 g, 3 mmol) in THF (30 mL) at 0 °C was added 2-methylenehex-5-enyl methanesulfonate **104** (2.85 g, 15 mmol) in THF (5 ml) dropwise. The solution was warmed to rt and stirred for 18 h before being poured onto H_2O (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et_3N, 10% Et_2O in hexane) yielded the title compound (2.68 g, 8.5 mmol, 57%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.51-7.23 (10H, m, **Ar-H**), 5.84 (1H, m, **Hr**), 5.10-4.94 (4H, m, **Ho, s**), 3.69 (2H, s, **He**), 3.60 (2H, s, **Hf**), 3.17 (2H, s, **Hm**), 2.28-2.19 (4H, m, **Hp, q**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 146.24 (C, **Cn**), 139.10 (C, **Cd**), 138.57 (CH, **Cr**), 131.72 (CHx2, **Cj**), 129.01 (CHx2), 138.24 (CHx4), 127.91 (CH), 127.01 (CH), 123.44

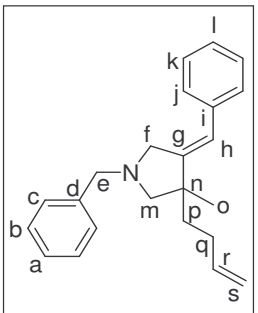
(C, **Ci**), 114.46 (CH_2, **Cs**), 112.94 (CH_2, **Co**), 85.56 (C, **Cg/h**), 84.61 (C, **Cg/h**), 58.85 (CH_2, **Cm**), 57.49 (CH_2, **Ce**), 42.17 (CH_2, **Cf**), 33.37 (CH_2, **Cp**), 31.86 (CH_2, **Cq**) ppm.

IR ν_{max}/cm^{-1} (film): 2359 (w), 1641 (m), 1489 (m), 904 (s), 754 (s), 690 (s).

LRMS (ES, MeCN): *m/z* 316 ($[M + H]^+$, 100%).

HRMS (ES): $C_{23}H_{26}N$ $[M + H]^+$ calculated 316.2060, found 316.2066.

5.49 (*Z*)-1-Benzyl-4-benzylidene-3-(but-3-en-1-yl)-3-methylpyrrolidine **110**



To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of *N*-benzyl-2-methylene-*N*-(3-phenylprop-2-ynyl)hex-5-en-1-amine **108** (0.315 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. 2 M HCl (aq) (5 mL) was added and the mixture was stirred for 18 h before neutralising with 2 M NaOH (aq) (5 mL). The reaction mixture was extracted with Et_2O (50 mL), washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et_2O in hexane) yielded the title compound (0.229 g, 0.72 mmol, 72%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.14 (10H, m, **Ar-H**), 6.14 (1H, s, **Hh**), 5.84 (1H, tdd, *J* = 17.0, 10.1, 6.4, **Hr**), 5.02 (1H, dd, *J* = 17.0, 1.3, **Hs**), 4.93 (1H, dd, *J* = 10.1, 1.3, **Hs**), 3.69 (2H, s), 3.60 (2H, s), 2.60 (1H, d, *J* = 8.7, **Hm**), 2.42 (1H, d, *J* = 8.7, **Hm**), 2.25-1.92 (2H, m, **Hq**), 1.72-1.62 (2H, m, **Hp**), 1.24 (3H, s, **Ho**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 150.56 (C, **Cg**), 139.35 (CH, **Cr**), 139.31 (C), 138.09 (C), 128.37 (CHx2), 128.27 (CHx2), 128.22 (CHx2), 127.95 (CHx2), 126.82 (CH), 126.04 (CH), 119.64 (CH, **Cn**), 113.98 (CH_2, **Cs**), 65.10 (CH_2), 60.32 (CH_2), 58.91 (CH_2), 46.22 (C, **Cn**), 40.18 (CH_2, **Cp**), 29.53 (CH_2, **Cq**), 26.09 (CH_3, **Co**) ppm.

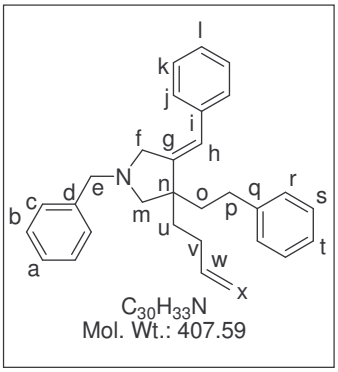
IR ν_{max}/cm^{-1} (film): 1639 (w), 1539 (m), 1494 (m), 907 (s), 736 (s), 694 (s).

LRMS (ES, MeCN): *m/z* 318 ($[M + H]^+$, 100%).

HRMS (ES): $C_{23}H_{28}N$ $[M + H]^+$ calculated 318.2216, found 318.2222.

5.50 (*Z*)-1-Benzyl-4-benzylidene-3-(but-3-en-1-yl)-3-phenethylpyrrolidine

112



To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.8 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of N-benzyl-2-methylene-N-(3-phenylprop-2-ynyl)hex-5-en-1-amine **108** (0.315 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The solution was re-cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. The solution continued to stir for a further 30 min before the addition of 2 M HCl (aq) in Et_2O (5 mL). The solution was stirred for a further 18 h while warming to rt. The mixture was neutralised with 2 M NaOH (aq) (5 mL) before being extracted with Et_2O (50 mL), washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 10% Et_2O in hexane) yielded the title compound (0.320 g, 0.79 mmol, 79%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.16 (15H, m, **Ar-H**), 6.17 (1H, s, **Hh**), 5.83 (1H, tdd, *J* = 16.9, 10.3, 6.6, **Hw**), 5.01 (1H, dd, *J* = 16.9, 1.8, **Hx**), 4.93 (1H, dd, *J* = 10.3, 1.8, **Hx**), 3.70 (2H, s, **He**), 3.62 (2H, m, **Hf**), 2.78-2.54 (4H, m), 2.27-2.03 (2H, m), 1.96 (1H, ddd, *J* = 14.4, 13.5, 5.1, **Hp**), 1.86-1.74 (2H, m), 1.66 (1H, ddd, *J* = 17.0, 12.2, 5.1, **Hp**) ppm.

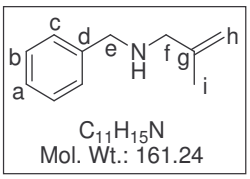
^{13}C NMR (75 MHz, $CDCl_3$): δ 148.46 (C, **Cg**), 143.12 (C, **Cq**), 139.33 (CH, **Cw**), 139.28 (C), 137.99 (C), 128.40 (CHx8), 128.27 (CHx2), 128.06 (CHx2), 126.87 (CH), 126.81 (CH), 125.62 (CH), 120.49 (CH, **Ch**), 114.09 (CH_2, **Cx**), 63.29 (CH_2), 60.44 (CH_2), 59.32 (CH_2), 49.52 (C, **Cn**), 41.88 (CH_2), 38.84 (CH_2), 31.40 (CH_2), 29.23 (CH_2) ppm.

IR ν_{max}/cm^{-1} (film): 1639 (m), 1494 (m), 907 (s), 733 (s), 695 (s).

LRMS (ES, MeCN): *m/z* 408 ($[M + H]^+$, 100%).

HRMS (ES): $C_{30}H_{34}N$ $[M + H]^+$ calculated 408.2686, found 408.2679.

5.51 *N*-Benzyl-2-methylprop-2-en-1-amine **117**



$C_{11}H_{15}N$
Mol. Wt.: 161.24

Synthesis of *N*-benzyl-2-methylprop-2-en-1-amine was carried out using a procedure published by Itoh *et al.*[80] To a stirred solution of benzylamine (22.0 mL, 22.0 g, 200 mmol) and $NaHCO_3$ (5.50 g, 65 mmol) in H_2O (200 mL) was added 3-chloro-2-methylprop-1-ene (4.90 mL, 4.50 g, 50 mmol) dropwise. The mixture was heated to 90 °C and stirred for 18 h. The mixture was cooled to rt and the organic layer was separated. The aqueous layer was extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with H_2O (3 x 100 mL) and brine (100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 50% Et_2O in hexane) yielded the title compound (4.97 g, 31 mmol, 62%) as a pale yellow oil.

Data was consistent with published data.[80]

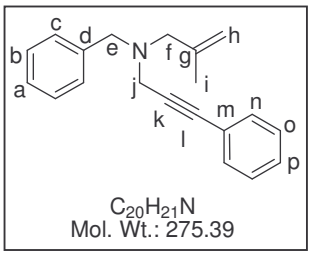
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.21 (5H, m, **Ar-H**), 4.89 (1H, s, **Hh**), 4.84 (1H, s, **Hh**), 3.75 (2H, s, **He**), 3.18 (2H, s, **Hf**), 1.75 (3H, s, **Hi**), 1.44 (1H, br, **NH**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 143.87 (C), 140.46 (C), 128.32 (CHx2), 128.10 (CHx2), 126.84 (CH, **Ca**), 110.73 (CH_2, **Ch**), 54.97 (CH_2), 53.05 (CH_2), 20.76 (CH_3, **Ci**) ppm.

IR ν_{max}/cm^{-1} (film): 1652 (w), 1452 (m), 883 (m), 734 (s), 696 (s).

LRMS (ES, MeCN): *m/z* 162 ($[M + H]^+$, 100%)

5.52 *N*-Benzyl-2-methyl-*N*-(3-phenylprop-2-ynyl)prop-2-en-1-amine **118**



Synthesis of *N*-benzyl-2-methyl-*N*-(3-phenylprop-2-ynyl)prop-2-en-1-amine was carried out using a procedure published by Bieber *et al*.[81] CuI (0.04 g, 0.2 mmol) was placed in a flask wrapped in foil. To this a solution of *N*-benzyl-2-methylprop-2-en-1-amine **117** (2.0 g, 12.4 mmol) in DMSO (25 mL) was added followed by phenyl acetylene (1.1 mL, 1.05 g, 10.3 mmol) and formaldehyde (37 % solution in H_2O) (11.7 mL, 144.2 mmol). The resulting mixture was stirred at rt for 20 h. The reaction mixture was quenched with sat NH_4Cl (aq) (50 mL) before being extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with H_2O (3 x 30 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et_2O in hexane) yielded the title compound (2.64 g, 9.6 mmol, 93%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50-7.23 (10H, m, **Ar-H**), 5.04 (1H, s, **Hh**), 4.92 (1H, s, **Hh**), 3.70 (2H, s, **He**), 3.50 (2H, s, **Hj**), 3.15 (2H, s, **Hf**), 1.82 (3H, s, **Hi**) ppm.

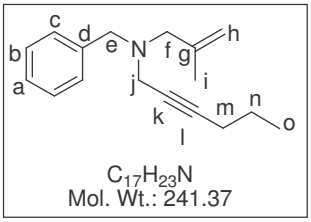
^{13}C NMR (75 MHz, $CDCl_3$): δ 142.11 (C, **Cg**), 139.13 (C, **Cd**), 131.73 (CHx2), 128.98 (CHx2), 128.25 (CHx4), 127.91 (CH), 126.98 (CH), 123.46 (C, **Cm**), 113.3 5 (CH_2, **Cn**), 85.54 (C, **Ck/l**) 84.60 (C, **Ck/l**), 60.45 (CH_2), 57.24 (CH_2), 42.12 (CH_2), 20.75 (CH_3, **Ci**) ppm.

IR ν_{max}/cm^{-1} (film): 1652 (w), 1489 (m), 1442 (m), 754 (s), 740 (s), 689 (s).

LRMS (ES, MeCN): *m/z* 276 ($[M + H]^+$, 100%).

HRMS (ES): $C_{20}H_{22}N$ $[M + H]^+$ calculated 276.1747, found 276.1750.

5.53 *N*-Benzyl-*N*-(2-methylallyl)hex-2-yn-1-amine **119**



$C_{17}H_{23}N$
Mol. Wt.: 241.37

To a stirred suspension of K_2CO_3 (6.40 g, 46.5 mmol) in MeCN (45 mL) was added *N*-benzyl-2-methylprop-2-en-1-amine **117** (2.50 g, 15.5 mmol) in MeCN (5 mL) dropwise. After 30 min 1-bromohex-2-yne (3.72 g, 23.3 mmol) in MeCN (5 mL) was added dropwise. The resulting mixture was stirred at rt for 18 h. The reaction mixture was quenched with sat $NaHCO_3$ (aq) (50 mL) and extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with H_2O (3 x 30 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent 5% Et_2O in Hexane) yielded the title compound (1.93 g, 8.0 mmol, 51%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.22 (5H, m. **Ar-H**), 4.98 (1H, s, **Hh**), 4.89 (1H, s, **Hh**), 3.61 (2H, s, **He**), 3.26 (2H, t, *J* = 2.2, **Hj**), 3.06 (2H, s, **Hf**), 2.23 (2H, tt, *J* = 7.0, 2.2, Hm), 1.71 (3H, s, **Hi**), 1.59 (2H, sxt, *J* = 7.2, **Hh**), 1.05 (3H, t, *J* = 7.3 **Ho**) ppm.

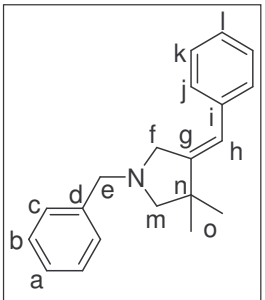
^{13}C NMR (75 MHz, $CDCl_3$): δ 143.33 (C, **Cg**), 139.34 (C, **Cd**), 128.94 (CHx2), 128.10 (CHx2), 126.84 (CH, **Ca**), 113.05 (CH_2, **Ch**), 85.37 (C, **Cl**), 74.66 (C, **Ck**), 60.26 (CH_2, **Ce/f**), 56.99 (CH_2, **Ce/f**), 44.75 (CH_2, **Cj**), 22.55 (CH_2, **Cn**), 20.74 (CH_2, **Ci**), 20.74 (CH_3, **Ci**), 13.56 (CH_3, **Co**) ppm.

IR ν_{max}/cm^{-1} (film): 1652 (w), 1454 (m), 1431 (m), 897 (s), 738 (s), 696 (s).

LRMS (ES, MeCN): *m/z* 242 ($[M + H]^+$, 100%).

HRMS (ES): $C_{17}H_{24}N$ $[M + H]^+$ calculated 242.1903, found 242.1905.

5.54 (*Z*)-1-Benzyl-4-benzylidene-3,3-dimethylpyrrolidine **122**



$C_{20}H_{23}N$
Mol. Wt.: 277.4

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of *N*-benzyl-2-methyl-*N*-(3-phenylprop-2-ynyl)prop-2-en-1-amine **118** (0.275 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h before being quenched with 2 M HCl (aq) (5 mL). The reaction mixture was stirred for 18 h before being neutralised with 2 M NaOH (aq) (5 mL). The reaction mixture was extracted with Et_2O (50 mL), washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et_2O in hexane) yielded the title compound (0.236 g, 0.85 mmol, 85%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (10H, m, **Ar-H**), 6.19 (1H, t, *J* = 2.5, **Hh**), 3.72 (2H, s, **He**), 3.64 (2H, d, *J* = 2.5, **Hf**), 2.5 (2H, s, **Hm**), 1.27 (6H, s, **Ho**) ppm.

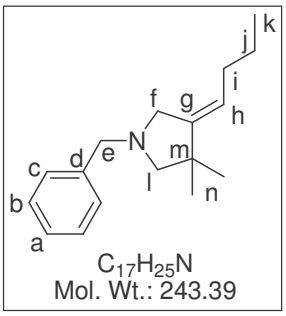
^{13}C NMR (75 MHz, $CDCl_3$): δ 151.62 (C, **Cg**), 139.32 (C, **Cd**), 138.16 (C, **Ci**), 128.42 (CHx2), 128.27 (CHx2), 128.22 (CHx2), 127.89 (CHx2), 126.80 (CH), 125.97 (CH), 118.91 (CH, **Ch**), 67.43 (CH_2), 60.28 (CH_2), 58.78 (CH_2), 43.16 (C, **Cn**), 28.09 (CH_3x2, **Co**) ppm.

IR ν_{max}/cm^{-1} (film): 1597 (w), 1494 (m), 1447 (m), 737 (s), 693(s).

LRMS (ES, MeCN): *m/z* 278 ($[M + H]^+$, 100%).

HRMS (ES): $C_{20}H_{24}N$ $[M + H]^+$ calculated 2778.1903, found 278.1899.

5.55 (*Z*)-1-Benzyl-4-butylidene-3,3-dimethylpyrrolidine **123**



To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of *N*-benzyl-*N*-(2-methylallyl)hex-2-yn-1-amine **119** (0.241 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h before being quenched with 2 M HCl (aq) (5 mL). The reaction mixture was stirred for 18 h before being neutralised with 2 M NaOH (aq) (5 mL). The reaction mixture was extracted with Et_2O (50 mL), washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et_2O in hexane) yielded the title compound (0.170 g, 0.70 mmol, 70%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.21 (5H, m, **Ar-H**), 5.08 (1H, tt, *J* = 7.3, 2.6, **Hh**), 3.62 (2H, s, **He**), 3.24-3.23 (2H, m, **Hf**), 2.40 (2H, s, **Hl**), 1.86 (2H, q, *J* = 7.3, **Hi**), 1.35 (2H, sxt, *J* = 7.3, **Hj**), 1.12 (6H, s, **Hn**), 0.87 (3H, t, *J* = 7.3, **Hk**) ppm.

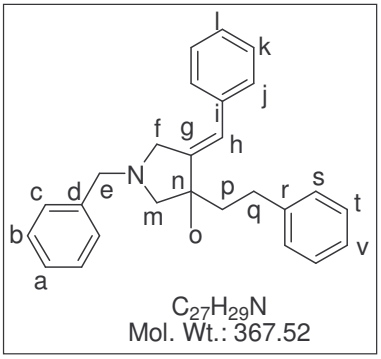
^{13}C NMR (75 MHz, $CDCl_3$): δ 148.43 (C, **Cg**), 139.53 (C, **Cd**), 128.50 (CHx2), 128.15 (CHx2), 126.71 (CH, **Ca**), 118.04 (CH, **Ch**), 68.39 (CH_2), 60.53 (CH_2), 57.02 (CH_2, **Cf**), 41.35 (C, **Cm**), 31.32 (CH_2, **Ci**), 28.20 (CH_3x2, **Cn**), 22.71 (CH_2, **Cj**), 13.71 (CH_3, **Ck**) ppm.

IR ν_{max}/cm^{-1} (film): 1495 (m), 1454 (m), 738 (m), 697(s).

LRMS (ES, MeCN): *m/z* 244 ($[M + H]^+$, 100%).

HRMS (ES): $C_{17}H_{26}N$ $[M + H]^+$ calculated 244.2060, found 244.2056.

5.56 (*Z*)-1-Benzyl-4-benzylidene-3-methyl-3-phenethylpyrrolidine **126**



To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of *N*-benzyl-2-methyl-*N*-(3-phenylprop-2-ynyl)prop-2-en-1-amine **118** (0.275 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The solution was re-cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. The solution continued to stir for a further 10 min before the addition of 2 M HCl in Et_2O (5 mL). The mixture was stirred for a further 20 h while warming to rt. The mixture was neutralised with 2 M NaOH (aq) (5 mL) before being extracted with Et_2O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et_2O in hexane) yielded the title compound (0.264 g, 0.72 mmol, 72%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (15H, m, **Ar-H**), 6.19 (1H, t, *J* = 2.4, **Hh**), 3.72 (2H, s, **He**), 3.60-3.63 (2H, m, **Hf**), 2.79-2.67 (2H, m, **Hm, q**), 2.63-2.46 (2H, m, **Hm, q**), 1.89 (2H, dd, *J* = 9.7, 7.7, **Hp**), 1.31 (3H, s, **Ho**) ppm.

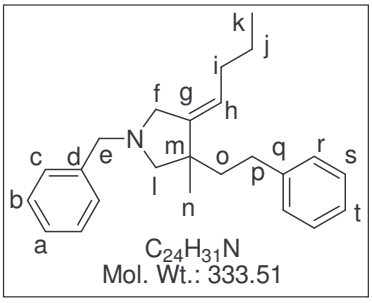
^{13}C NMR (75 MHz, $CDCl_3$): δ 150.45 (C, **Cg**), 143.06 (C, **Cr**), 139.32 (C, **Cd**), 138.08 (C, **Ci**), 128.38 (CHx2), 128.31 (CHx8), 127.97 (CHx2), 126.85 (CH, **Ca**), 126.08 (CH, **Cl**), 125.85 (CH, **Cv**), 119.72 (CH, **Ch**), 65.02 (CH_2, **Cm**), 60.03 (CH_2, **Ce**), 58.95 (CH_2, **Cf**), 46.64 (C, **Cn**), 43.28 (CH_2), 31.70 (CH_2), 26.17 (CH_3, **Co**) ppm.

IR ν_{max}/cm^{-1} (film): 1603 (w), 1495 (m), 1455 (m), 1028 (m), 694 (s).

LRMS (ES, MeCN): *m/z* 368 ($[M + H]^+$, 100%).

HRMS (ES): $C_{27}H_{30}N$ $[M + H]^+$ calculated 368.2373, found 368.2379.

5.57 (*Z*)-1-Benzyl-4-butylidene-3-methyl-3-phenethylpyrrolidine **127**



To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of *N*-benzyl-*N*-(2-methylallyl)hex-2-yn-1-amine **119** (0.241 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The solution was re-cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. The solution continued to stir for a further 10 min before the addition of 2 M HCl in Et_2O (5 mL). The mixture was stirred for a further 20 h while warming to rt. The mixture was neutralised with 2 M NaOH (aq) (5 mL) before being extracted with Et_2O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et_2O in hexane) yielded the title compound (0.250 g, 0.75 mmol, 75%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.17 (10H, m, **Ar-H**), 5.11 (1H, tt, *J* = 7.1, 2.4, **Hh**), 3.65 (2H, s, **He**), 3.33-3.22 (2H, m, **Hf**), 2.68 (1H, ddd, *J* = 13.4, 11, 5.6, **Hp**), 6.23 (1H, d, *J* = 8.6, **Hl**), 2.52 (1H, ddd, *J* = 13.4, 10.8, 5.6, **Hp**), 2.41 (1H, d, *J* = 8.6, **Hl**), 1.92 (2H, apparent q, *J* = 7.2, **Hi**), 1.80-1.73 (2H, m, **Ho**), 1.39 (2H, sxt, *J* = 7.3, **Hj**), 1.18 (3H, s, **Hn**), 0.90 (3H, t, *J* = 7.3, **Hk**) ppm.

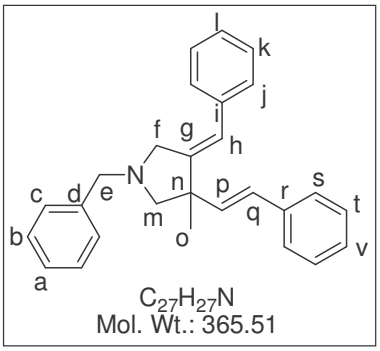
^{13}C NMR (75 MHz, $CDCl_3$): δ 147.18 (C, **Cg**), 143.38 (C, **Cq**), 139.56 (C, **Cd**), 128.45 (CHx2), 128.34 (CHx2), 128.27 (CHx2), 128.19 (CHx2), 126.76 (CH, **Ca**), 125.49 (CH, **Ct**), 119.13 (CH, **Ch**), 66.11 (CH_2, **Cl**), 60.53 (CH_2, **Ce**), 57.23 (CH_2, **Cf**), 44.72 (C, **Cm**), 43.32 (CH_2, **Co**), 31.72 (CH_2), 31.38 (CH_2), 26.09 (CH_2, **Cj**), 22.77 (CH_3, **Cn**), 13.78 (CH_3, **Ck**) ppm.

IR ν_{max}/cm^{-1} (film): 1495 (m), 1453 (m), 839 (m), 696 (s).

LRMS (ES, MeCN): *m/z* 343 ($[M + H]^+$, 100%).

HRMS (ES): $C_{24}H_{32}N$ $[M + H]^+$ calculated 234.2529, found 234.2524.

5.58 (4*Z*)-1-Benzyl-4-benzylidene-3-methyl-3-(*E*)-styrylpyrrolidine **128**



To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.8 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of *N*-benzyl-2-methyl-*N*-(3-phenylprop-2-ynyl)prop-2-en-1-amine **118** (0.275 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The solution was re-cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. The solution continued to stir for a further 10 min before being warmed to reflux. The solution was stirred for 12 h at reflux before cooling to rt. The reaction mixture was quenched 2 M HCl in Et_2O (5 mL) before being stirred for a further 18 h at rt. The mixture was neutralised with 2 M NaOH (aq) (5 mL) before being extracted Et_2O (50 mL), washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et_2O in hexane) yielded the title compounds (0.201 g, 0.55 mmol, 55%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (15H, m, **Ar-H**), 6.51 (1H, d, *J* = 16.1, **Hp**), 6.37 (1H, d, *J* = 16.1, **Hq**), 6.16 (1H, s, **Hh**), 3.78-3.57 (4H, m, **He, m**), 2.70 (1H, d, *J* = 8.8, Hf), 2.64 (1H, d, *J* = 8.8, **Hf**), 1.48 (3H, s, **Ho**) ppm.

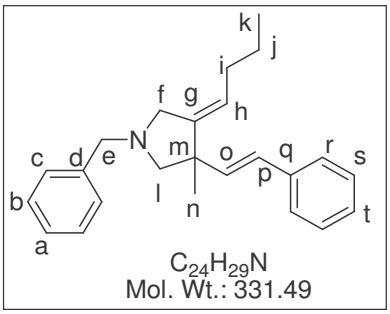
^{13}C NMR (75 MHz, $CDCl_3$): δ 149.06 (C, **Cg**), 139.06 (C, **Cr**), 137.82 (C, **Cd**), 137.66 (C, **Ci**), 136.93 (CH, **Cp**), 128.47 (CHx2), 128.45 (CHx2), 128.31 (CHx2), 128.27 (CHx2), 127.98 (CHx2), 127.00 (CH), 126.94 (CH), 126.91 (CH), 126.26 (CH), 126.20 (CHx2), 121.65 (CH, **Ch**), 66.29 (CH_2, **Cm**), 60.29 (CH_2, **Ce**), 58.39 (CH_2, **Cf**), 49.30 (C, **Cm**), 24.93 (CH_3, **Co**) ppm.

IR ν_{max}/cm^{-1} (film): 1493 (m), 1447 (m), 744 (s), 692 (s).

LRMS (ES, MeCN): *m/z* 366 ($[M + H]^+$, 100%).

HRMS (ES): $C_{27}H_{28}N$ $[M + H]^+$ calculated 366.2216, found 366.2218.

5.59 (4*Z*)-1-Benzyl-4-butylidene-3-methyl-3-(*E*)-styrylpyrrolidine **129**



To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of *N*-benzyl-*N*-(2-methylallyl)hex-2-yn-1-amine **119** (0.241 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The solution was re-cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. The solution continued to stir for a further 10 min before being warmed to reflux. The solution was stirred for 12 h at reflux before cooling to rt. The reaction mixture was quenched with 2 M HCl in Et_2O (5 mL) before being stirred for a further 18 h at rt. The mixture was neutralised with 2 M NaOH (aq) (5 mL) before being extracted with Et_2O (50 mL), washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et_2O in hexane) yielded the title compound (0.176 g, 0.53 mmol, 53%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.16 (10H, m, **Ar-H**), 6.41 (1H, d, *J* = 16.0, **Hp**), 6.28 (1H, d, *J* = 16.0, **Ho**), 5.11 (1H, tt, *J* = 7.5, 2.4, **Hh**), 3.72-3.62 (2H, m, **He**), 3.37 (1H, d, *J*= 13.7, **Hf**), 3.24 (1H, d, *J*= 13.7, **Hf**), 2.66 (1H, d, *J* = 8.7, **Hl**), 2.56 (1H, d, *J* = 8.7, **Hl**), 1.93-1.84 (2H, m, **Hi**), 1.39-1.24 (5H, m, **Hj, n**), 0.87 (3H, t, *J* = 7.5, **Hk**) ppm.

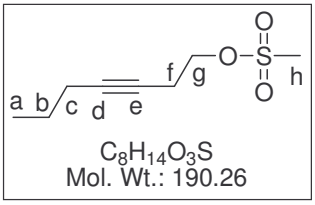
^{13}C NMR (75 MHz, $CDCl_3$): δ 145.95 (C, **Cg**), 139.18 (C, **Cq**), 137.89 (C, **Cd**), 137.69 (CH, **Co**), 128.56 (CHx2), 128.42 (CHx2), 128.21 (CHx2), 126.85 (CH, **Ca**), 126.80 (CH, **Ct**), 126.25 (CH, **Cp**), 126.12 (CHx2), 121.27 (CH, **Ch**), 67.09 (CH_2, **Cl**), 60.35 (CH_2, **Ce**), 56.61 (CH_2, **Cf**), 47.55 (C, **Cm**), 31.47 (CH_2, **Ci**), 25.09 (CH_2, **Cj**), 22.59 (CH_3, **Cn**), 13.76 (CH_3, **Ck**) ppm.

IR ν_{max}/cm^{-1} (film): 1495 (m), 1455 (m), 1028 (m), 694 (s).

LRMS (ES, MeCN): *m/z* 332 ($[M + H]^+$, 100%).

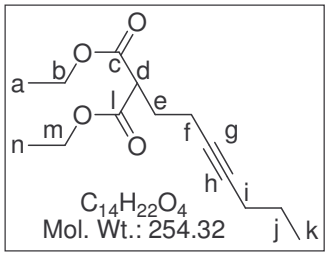
HRMS (ES): $C_{24}H_{30}N$ $[M + H]^+$ calculated 332.2373, found 332.2371.

5.60 Diethyl 2-(hept-3-ynyl)malonate **131**



Synthesis of hept-3-ynyl methanesulfonate **130**: To a stirred solution of hept-3-yn-1-ol (5.60 g, 50 mmol) and triethylamine (10.4 mL, 7.6 g, 75 mmol) in CH_2Cl_2 (120 mL) at –10 °C was added methanesulfonyl chloride (6.84 g, 4.60 mL, 60 mmol) dropwise. After 30 min at –10 °C the reaction mixture was poured onto H_2O (50 mL). The aqueous layer was separated and re-extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with 2M HCl (aq) (50 mL), H_2O (50 mL), $NaHCO_3$ (50 mL) and brine (50 mL). The organic layer was dried ($MgSO_4$) and solvent removed *in vacuo* to yield hept-3-ynyl methanesulfonate **130** (9.14 g, 48.0 mmol, 96%) No further purification was required.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.26 (2H, t, *J* = 6.6, **Hg**), 3.04 (3H, s, **Hh**), 2.64-2.60 (2H, m, **Hf**), 2.14 -2.08 (2H, m, **Hc**), 1.54-1.44 (2H, m, **Hb**), 0.96 (3H, t, *J* = 7.2, **Ha**) ppm.



Synthesis of diethyl 2-(hept-3-ynyl)malonate **131**: Sodium (1.4 g, 60 g-atom) was added portion wise to ethanol (100 mL) at 0 °C. Once complete dissolution was observed a solution of diethyl malonate (12 g, 75 mmol) in ethanol (10 ml) was added dropwise and the solution was stirred for 15 min at 0 °C. A solution of mesylate **130** (9.5 g, 50 mmol) in ethanol (50 mL) and 10% NaI (0.75 g, 5 mmol) in ethanol (5 mL) was added before being warmed to rt and stirred for a further 18 h. The reaction mixture was poured onto H_2O (500 mL) and extracted with Et_2O (3 x 200 mL). The combined organic extracts were washed with H_2O (3 x 100 mL) and brine (100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 10% Et_2O in hexane) yielded the title compound **131** (2.57 g, 10 mmol, 20%) as a colourless oil.

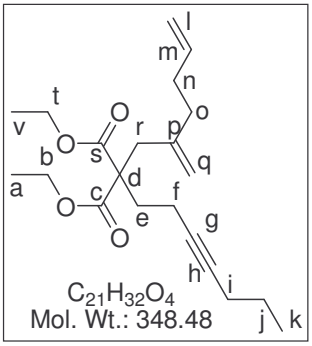
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.21 (2H, q, *J* = 7.2, **Hb/ m**), 4.20 (2H, q, *J* = 7.2, **Hb/ m**), 3.57 (1H, t, *J* = 7.3, **Hd**), 2.28-2.26 (2H, m, **He**), 2.13-2.05 (4H, m, **Hf, i**), 1.50 (2H, sxt, *J* = 7.3, **Hj**), 1.28 (6H, t, *J* = 7.2, **Ha, n**), 0.97 (3H, t, *J* = 7.3, **Hk**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 169.21 (Cx2, **Cc, l**) 81.64 (C, **Cg/h**), 78.09 (C, **Cg/h**), 61.36 (CH_2x2, **Cb, m**), 50.74 (CH, **Cd**), 28.08 (CH_2, **Ce**), 22.39 (CH_2), 20.72 (CH_2), 16.77 (CH_2), 14.05 (CH_3x2, **Ca, n**), 13.43 (CH_3, **Ck**) ppm.

IR ν_{max}/cm^{-1} (film): 1748 (s), 1730 (s), 1151(s), 1022 (m).

LRMS (ES, MeCN): *m/z* 277 ([M + Na]$^+$, 100%).

5.61 Diethyl 2-(hept-3-yn-1-yl)-2-(2-methylenehex-5-en-1-yl)malonate **132**



To a stirred suspension of NaH (60% suspension in mineral oil) (4.80 g, 12.5 mmol) in THF (20 mL) at 0 °C was added malonate **131** (2.57 g, 10 mmol) in THF (10 mL) dropwise. The solution was stirred for a further 15 min before the addition of mesylate **104** (2.28 g, 12 mmol) in THF (10 mL) and NaI (0.37 g, 2.4 mmol) in THF (10 mL). The solution was warmed to rt and stirred for 24 h. The reaction mixture was quenched by the dropwise addition of sat NH_4Cl (aq) (50 mL) before being extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent gradient: 0 - 10% Et_2O in hexane) yielded the title compound (2.0 g, 5.8 mmol, 58%) as a colourless oil.

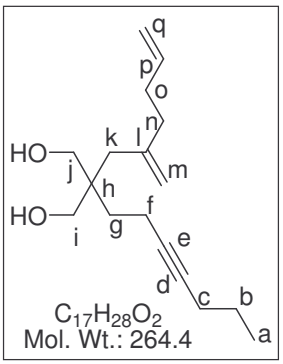
^{1}H NMR (300 MHz, $CDCl_3$): δ 5.87 (1H, ddt, *J* = 16.8, 10.4, 6.8, **Hm**), 5.03-4.94 (4H, m, **Hl, q**), 4,17 (4H, q, *J* = 6.8, **Cb, t**), 2.71 (2H, s, **Hr**), 2.18-2.23 (8H, m, **CH_2**), 2.03-1.99 (2H, m, **CH_2**), 1.49 (2H, sxt, *J* = 7.2, **Hj**), 1.25 (6H, t, *J* = 7.2, **Ha, n**), 0.96 (3H, t, *J* = 7.2, **Hk**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.15 (Cx2, **Cc, s**), 143.70 (C, **Cp**), 138.0 (CH, **Cm**), 115.04 (CH_2, **Cq/l**), 114.61 (CH_2, **Cq/l**), 80.53 (C, **Cg/h**), 78.88 (C, **Cg/h**), 61.28 (CH_2x2, **Cb, t**), 56.62 (C, **Cd**), 38.22 (CH_2), 35.77 (CH_2), 32.10 (CH_2x2), 22.37 (CH_2, **Ci**), 20.67 (CH_2, **Cj**), 14.29 (CH_2, **Cf**), 13.97 (CH_3x2, **Ca, v**), 13.46 (CH_3, **Ck**) ppm.

IR ν_{max}/cm^{-1} (film): 1729 (s), 1238 (s), 1178 (s), 1082 (m).

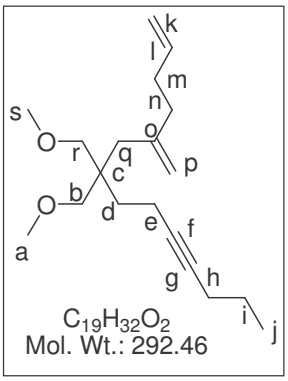
LRMS (ES, MeCN): *m/z* 371 ([M + Na]$^+$, 100%).

5.62 7,7-Bis(methoxymethyl)-5-methylenetetradec-1-en-10-yne **133**



Synthesis of 2-(hept-3-yn-1-yl)-2-(2-methylenehex-5-en-1-yl)propane-1,3-diol: To a stirred suspension of $LiAlH_4$ (0.66 g, 17.4 mmol) in Et_2O (40 mL) at 0 °C was added malonate **132** (2.0g, 5.8 mmol) in Et_2O (10 mL). The solution was warmed to rt and stirred for 4 h before the dropwise addition of 2 M NaOH (aq) (5 mL) followed by water (20 mL). The mixture was poured onto 2 M HCl (aq) (20 mL) and extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with H_2O (3 x 50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the title compound (1.56, 5.8 mmol, 99%) as a colourless oil. No further purification was required.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.82 (1H, ddt, *J* = 16.4, 10.4, 6.0, **Hp**), 5.06-4.79 (4H, m, **Hq/m**), 3.62 (2H, s, **Ci/j**), 3.61 (2H, s, **Ci/j**), 2.42 (2H, br s, **OH**), 2.27-2.19 (4H, m), 2.16-2.11 (4H, m), 2.03 (2H, s, **Ck**), 1.65 (2H, t, *J* = 6.8), 1.51 (2H, sxt, *J* = 7.2, **Hb**), 0.97 (3H, t, *J* = 7.2, **Ha**) ppm



Synthesis of 7,7-bis(methoxymethyl)-5-methylenetetradec-1-en-10-yne **133**: To a stirred suspension of NaH (60% suspension in mineral oil) (0.67 g, 17.4 mmol) in THF (40 mL) at 0 °C was added the 2-(hept-3-ynyl)-2-(2-methylenehex-5-enyl)propane-1,3-diol (1.56 g, 5.8 mmol) in THF (10 mL) dropwise. After 30 min MeI (1.25 g, 8.7 mmol) in THF (5 mL) was added and the solution was stirred at 0 °C for 30 min. The remaining MeI (1.25 g, 8.7 mmol) in THF (5 mL) was added and the solution was warmed to rt and stirred for 5 h. The reaction mixture was quenched with the dropwise addition on MeOH (10 mL) poured onto H_2O (50 mL) and extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent gradient: 5% Et_2O in hexane) yielded the title compound (2.15 g, 7.4 mmol, 85%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.81 (1H, ddt, *J* = 16.5, 10.2, 6.3, **Hl**), 5.06-4.77 (4H, m, **Hk, p**), 3.29 (6H, s, **Ha, s**), 3.15 (4H, s, **Hb, r**), 2.25-2.09 (8H, m), 2.05 (2H, s, **Hq**), 1.60-1.55 (2H, m), 1.50 (2H, sxt, *J* = 7.2, **Hi**), 0.97 (3H, t, *J* = 7.2 **Hj**) ppm.

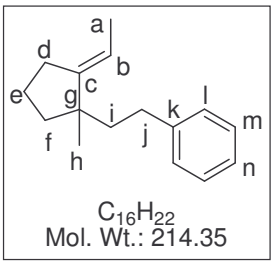
^{13}C NMR (75 MHz, $CDCl_3$): δ 145.53 (C, **Co**), 138.60 (CH, **Cl**), 114.37 (CH_2, **Cp/k**), 113.93 (CH_2, **Cp/k**), 80.63 (C, **Cf/g**), 79.79 (C, **Cf/g**), 75.07 (CH_2, **Cb/r**), 74.95 (CH_2, **Cb/r**), 58.83 (CH_3x2, **Ca, s**), 41.88 (C, **Cc**), 37.87 (CH_2), 37.20 (CH_2), 32.82 (CH_2), 32.58 (CH_2), 22.50 (CH_2), 20.82 (CH_2), 13.50 (CH_2, **Ci**), 13.35 (CH_3, **Cj**) ppm.

IR ν_{max}/cm^{-1} (film): 1639 (m), 1449 (m), 1104 (s).

LRMS (ES, MeCN): *m/z* 315 ($[M + Na]^+$, 100%).

HRMS (ES): $C_{19}H_{32}NaO_2$ $[M + Na]^+$ calculated 315.2295, found 315.2290.

5.63 (*E*)-(2-(2-Ethylidene-1-methylcyclopentyl)ethyl)benzene **143**



$C_{16}H_{22}$
Mol. Wt.: 214.35

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of DMAP (0.268 g, 2.2 mmol) in THF (5 mL) was added. The solution was warmed to rt and stirred for a further 1 h before a solution of 2-methylhept-1-en-5-yne (0.116 g, 0.95 mmol) in THF (2 mL) was added dropwise over 1 h. The solution was re-cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. The solution continued to stir for a further 10 min at –78 °C before the addition of 2 M HCl in Et_2O (5 mL). The solution was stirred for a further 18 h while warming to rt before being diluted with Et_2O (50 mL). The reaction mixture was washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compound (0.156 g, 0.73 mmol, 73%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-7.15 (5H, m, **Ar-H**), 5.16 (1H, qt, *J* = 16.8, 2.6, **Hb**), 2.62-2.46 (2H, m, **Hj**), 2.41 (1H, m, **Hd**), 2.25 (1H, m, **Hd**), 1.73-1.45 (9H, m), 1.07 (3H, s, **Hh**) ppm.

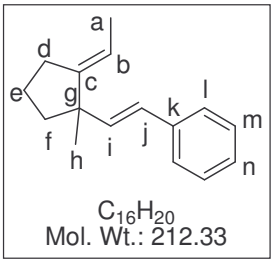
^{13}C NMR (75 MHz, $CDCl_3$): δ 150.92 (C, **Cc**), 143.53 (C, **Ck**), 128.24 (CHx4), 125.43 (CH, **Cn**), 113.17 (CH, **Cb**), 44.99 (C, **Cg**), 43.24 (CH_2), 39.47 (CH_2), 31.48 (CH_2, **Cj**), 29.30 (CH_2, **Cd**), 26.67 (CH_2, **Ce**), 22.31 (CH_3, **Ch**), 14.63 (CH_2, **Ca**) ppm.

IR ν_{max}/cm^{-1} (film): 1603 (w), 1495 (m), 1454 (m), 748 (m), 697 (s).

LRMS (EI, CH_2Cl_2): 214 ([$M^{+\cdot}$], 20%), 109 (100%).

HRMS (EI): $C_{16}H_{22}$ [$M^{+\cdot}$] calculated, 214.1722 found 214.1715.

5.64 ((*E*)-2-((*E*)-2-Ethylidene-1-methylcyclopentyl)vinyl)benzene **144**



To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of DMAP (0.268 g, 2.2 mmol) in THF (5 mL) was added. The solution was warmed to rt and stirred for a further 1 h before a solution of 2-methylhept-1-en-5-yne (0.116 g, 0.95 mmol) in THF (2 mL) was added dropwise over 1 h. The solution was re-cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. The solution continued to stir for a further 10 min before warming to rt. The solution was stirred for a further 5 h before the addition of 2 M HCl (aq) in Et_2O (5 mL). The reaction mixture was stirred for a further 18 h at rt, extracted with Et_2O (50 mL), washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: hexane) yielded the title compound (0.112 g, 0.53 mmol, 53%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.14 (5H, m, **Ar-H**), 6.30 (1H, d, *J* = 15.9, **Hj**), 6.17 (1H, d, *J* = 16.2, **Hi**), 5.21 (1H, m, **Hb**), 2.35-2.33 (2H, m, CH_2), 1.80-1.47 (7H, m, CH_2, CH_3), 1.21 (3H, s, **Hh**) ppm

^{13}C NMR (75 MHz, $CDCl_3$): δ 148.41 (C, **Cc**), 139.53 (CH, **Ci**), 138.02 (C, **Ck**), 128.41 (CHx2, **Cm**), 126.66 (CH, **Cj**), 126.03 (CHx3, **Cl, n**), 115.51 (CH, **Cb**), 48.26 (C, **Cg**), 41.28 (CH_2, **Cf**), 28.84 (CH_2, **Cd**), 25.61 (CH_3, **Ch**), 22.44 (CH_2, **Ce**), 14.69 (CH_3, **Ca**) ppm.

IR ν_{max}/cm^{-1} (film): 1600 (w), 1495 (m), 1447 (m), 966 (s), 745 (s), 691 (s).

LRMS (EI, CH_2Cl_2): 212 ([$M^{+\cdot}$], 100%), 91 (90%).

HRMS (EI): $C_{16}H_{20}$ [$M^{+\cdot}$] calculated 212.1565, found 212.1556.

5.65 Optimisation of the zirconene mediated co-cylcisation of 2-methylhept-1-en-5-yne

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of DMAP (0.268 g, 2.2 mmol) in THF (5 mL) was added. The solution was warmed to x °C (see table for temperature) and stirred for a further 1 h before a solution of 2-methylhept-1-en-5-yne (see table for amount) in THF (2 mL) was added dropwise over 1 h. Samples (0.1 mL) were removed from the reaction mixture and quenched with 2 M HCl (aq) (1.5 mL) at timed intervals. Et_2O (1 mL) was added to the quenched sample. The Et_2O layer was separated and passed through a short plug of $MgSO_4$ in Pasteur pipette. The samples were analysed by GC.

Experiment	**1**	**2**	**3**
Enyne amount	0.122 g, 1 mmol	0.134 g, 1.1 mmol	0.110 g, 0.9 mmol
Temperature °C	0	20	20

GC conditions and retention times

Standard GC conditions and column – see general experimental for details.

GC method:

Injector temperature: 200 °C

Initial temperature: 40 °C held for 2 min

Ramp 1: 10 °C per min to 70 °C

Ramp 2: 25 °C per min

Final temperature: 250 °C held for 4 min

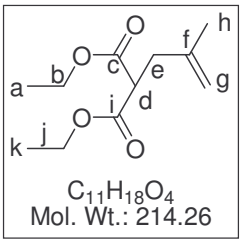
Retention times:

Quenched zirconacycle **141** – 5.01 min

Starting enyne **140** – 6.27 min

Intermolecular cyclisation products **145a-c** – 8.40 min, 8.52 min and 8.63 min

5.66 Diethyl 2-(2-methylallyl)malonate **146**



$C_{11}H_{18}O_4$
Mol. Wt.: 214.26

Synthesis of **146** was carried out using a procedure published by Begley *et al.*[83] To a stirred suspension of NaH (60% suspension in mineral oil) (2.40 g, 60 mmol) in THF (100 mL) at 0 °C was added methylallyl chloride (5.40 g, 60 mmol) in THF (10 mL) dropwise. The resulting solution was stirred at rt for 72 h before being quenched with H_2O (50 mL) and extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with H_2O (3 x 50 mL), brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 10% Et_2O in hexane) yielded the title compound (3.47 g, 16 mmol, 27%) as a colourless oil.

All data was consistent with published data.[83]

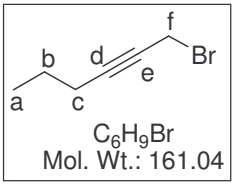
^{1}H NMR (300 MHz, $CDCl_3$): δ 4.78 (1H, s, **Hg**), 4.73 (1H, s, **Hg**), 4.19 (4H, q, *J* = 6.9, **Hb, j**), 3.57 (1H, t, *J* = 7.8, **Hd**), 2.62 (2H, d, *J* = 7.5, **He**), 1.75 (3H, s, **Hh**), 1.26 (6H, t, *J* = 6.9, **Ha, k**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 169.07 (Cx2, **Cc, i**), 141.66 (C, **Cf**), 112.23 (CH_2, **Cg**), 61.36 (CH_2x2, **Cb, j**), 50.52 (CH, **Cd**), 36.46 (CH_2, **Ce**), 22.52 (CH_3, **Ch**), 14.04 (CH_3x2, **Ca, k**) ppm.

IR ν_{max}/cm^{-1} (film): 1731 (s), 1652 (w), 1446 (m), 1147 (s), 1048 (s), 1028 (s).

LRMS (ES, MeCN): *m/z* 237 ($[M + Na]^+$, 100%).

5.67 Diethyl 2-(hex-2-ynyl)-2-(2-methylallyl)malonate **147**

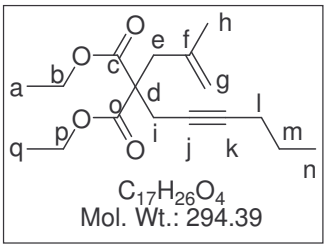


Synthesis of 1-bromohex-2-yne was carried out using a procedure published by Lu *et al.*[84] PPh_3 (13.4 g, 51 mmol) was dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C before bromine (2.6 mL, 8.2 g, 51 mmol) was added dropwise. The resulting solution was stirred for 30 min at 0 °C. Hex-2-yn-1-ol (5.6 mL, 5.0 g, 51 mmol) was added dropwise at 0 °C and stirred for a further 1 h before the addition of pentane (300 mL). The resulting suspension was passed through a short silica pad and washed with pentane (50 mL). The solvent was removed *in vacuo* to yield the compound (7.1 g, 44 mmol, 86%) as a colourless oil.

Data was consistent with published data.[84]

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.93 (2H, t, *J* = 2.2, **Hf**), 2.22 (2H, tt, *J* = 7.0, 2.2, **Hc**), 1.58-1.54 (2H, m, **Hb**), 0.99 (3H, t, *J* = 7.4, **Ha**) ppm.

IR ν_{max}/cm^{-1} (film): 2232 (m), 1642 (m), 1206 (m), 606 (s).



Synthesis of diethyl 2-(hex-2-ynyl)-2-(2-methylallyl) malonate **147**: Sodium (0.83 g, 36 g-atom) was added portion-wise to ethanol (20 mL) at 0 °C. Once complete dissolution was observed a solution of the substituted diethyl malonate **146** (3.47 g, 16 mmol) in ethanol (5 mL) was added dropwise and the solution was stirred for 15 min at 0 °C. A solution of 1-bromohex-2-yne (3.20 g, 20 mmol) in ethanol (5 mL) was added dropwise and the reaction mixture was warmed to rt and stirred for a further 18 h. The reaction mixture was poured onto H_2O (50 mL) and extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with H_2O (3 x 50 mL), brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 10% Et_2O in hexane) yielded the title compound (4.07 g, 13.9 mmol, 87%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.89 (1H, m, **Hg**), 4.84 (1H, m, **Hg**), 4.27-4.11 (4H, m, **Hb, p**), 2.82 (2H, s, **He**), 2.79 (2H, t, *J* = 2.4, **Hi**), 2.10 (2H, tt, *J* = 6.0, 2.4, Hl), 1.68

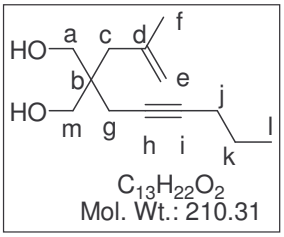
(3H, s, **Hh**), 1.48 (2H, sxt, *J* = 7.2, **Hm**), 1.25 (6H, t, *J* = 7.2, **Ha, q**), 0.95 (3H, t, *J* = 7.5, **Hn**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.41 (Cx2, **Cc, o**), 140.27 (C, **Cf**), 115.86 (CH_2, **Cg**), 83.61 (C, **Ck**), 74.83 (C, **Cj**), 61.41 (CH_2x2, **Cb, p**), 56.75 (C, **Cd**), 39.31 (CH_2, **Ce**), 23.35 (CH_3, **Ch**), 22.91 (CH_2), 22.33 (CH_2), 20.66 (CH_2), 13.99 (CH_3x2, **Ca, q**), 13.38 (CH_3, **Cn**) ppm.

IR ν_{max}/cm^{-1} (film): 1732 (s),1646 (w), 1202 (s), 1180 (s), 107 (m), 1058 (m).

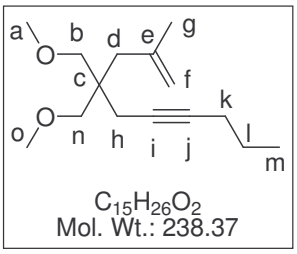
LRMS (ES, MeCN): *m/z* 317 ($[M + Na]^+$, 100%).

5.68 4,4-Bis(methoxymethyl)-2-methyldec-1-en-6-yne **148**



Synthesis of 2-(hex-2-ynyl)-2-(2-methylallyl)propane-1,3-diol: To a stirred suspension of $LiAlH_4$ (1.82 g, 48 mmol) in Et_2O (100 mL) at 0 °C was added substituted malonate **147** (4.06 g, 13.8 mmol) in Et_2O (20 mL). The solution was warmed to rt and stirred for 18 h before the dropwise addition of 2 M NaOH (aq) (10 mL) followed by water (20 mL). The mixture was poured onto 2 M HCl (aq) (30 mL) and extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with H_2O (3 x 50 mL) brine (50 ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the 2-(hex-2-ynyl)-2-(2-methylallyl)propane-1,3-diol as a colourless oil (2.59 g, 12.3 mmol, 89%). No further purification was required.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.19 (1H, m, **He**), 4.80 (1H, m, **He**), 3.68-3.58 (4H, m, **Ha, m**), 2.76 (2H, s, **OH**), 2.23 (2H, s, **Hc**), 2.17-2.08 (4H, m, **Hg, j**), 1.81 (3H, s, **Hf**), 1.51 (2H, sxt, *J* = 7.3, **Hk**), 0.97 (3H, t, *J* = 7.3, **Hl**) ppm.



Synthesis of 4,4-bis(methoxymethyl)-2-methyldec-1-en-6-yne **148:** To a stirred suspension of NaH (60% suspension in mineral oil) (1.48 g, 37 mmol) in THF (80 ml) at 0 °C was added the2-(hex-2-ynyl)-2-(2-methylallyl)propane-1,3-diol (2.59 g, 12.3 mmol) in THF (10 mL) dropwise. After 30 min MeI (1.15 mL, 2.63 g, 18.5 mmol) in THF (5 mL) was added and the solution was stirred at 0 °C for 30 min. The remaining MeI (1.15 mL, 2.63 g, 18.5 mmol) in THF (5 mL) was added and the solution was warmed to rt and stirred for 18 h. The reaction mixture was quenched with the dropwise addition of MeOH (10 mL) poured onto H_2O (50 mL) and extracted with Et_2O (3 x 70 mL). The combined organic extracts were washed with H_2O (3 x 50 mL), brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent gradient: 5 - 10% Et_2O in hexane) yielded the title compound (2.14 g, 9.0 mmol, 73%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.90 (1H, s, **Hf**), 4.77 (1H, s, **Hf**), 3.32 (6H, s, **Ha, o**), 3.26-3.20 (4H, m, **Hb, n**), 2.17-2.13 (6H, m, **Hd, h, k**), 1.78 (3H, s, **Hg**), 1.53 (2H, sxt, *J* = 7.0, **Hi**), 0.99 (3H, t, *J* = 7.3, **Hm**) ppm.

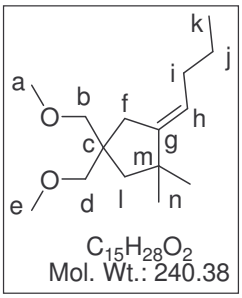
^{13}C NMR (75 MHz, $CDCl_3$): δ 142.11 (C, **Ce**), 114.74 (CH_2, **Cf**), 82.36 (C, **Cj**), 76.81 (C, **Ci**), 74.37 (CH_2x2, **Cb, n**), 59.05 (CH_3x2, **Ca, o**), 42.45 (C, **Cc**), 38.30 (CH_2), 25.02 (CH_3, **Cg**), 22.64 (CH_2x2), 20.84 (CH_2), 13.53 (CH_3, **Cm**) ppm.

IR ν_{max}/cm^{-1} (film): 1641 (w), 1456 (m), 1103 (s), 896 (m).

LRMS (ES, MeCN): *m/z* 261 ($[M + Na]^+$, 100%).

HRMS (ES): $C_{15}H_{26}NaO_2$ $[M + Na]^+$ calculated 261.1825, found 261.182530.

5.69 (*E*)-2-Butylidene-4,4-bis(methoxymethyl)-1,1-dimethylcyclopentane **150**



To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 4,4-bis(methoxymethyl)-2-methyldec-1-en-6-yne **148** (0.238 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h before being quenched with 2 M HCl (aq) (5 mL). The reaction mixture was stirred for 18 h before being extracted with Et_2O (50 mL), washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et_2O in hexane) yielded the title compound (0.167 g, 0.70 mmol, 70%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.11 (1H, tt, *J* = 7.3, 2.2, **Hh**), 3.32 (6H, s, **Ha, e**), 3.22 (4H, q, *J* = 8.8, **Hb, d**), 2.25-2.24 (2H, m, **Hf**), 1.94 (2H, q, *J* = 7.3, **Hi**), 1.48 (2H, s, **Hl**), 1.34 (2H, sxt, *J* = 7.3 **Hj**), 1.07 (6H, s, **Hn**), 0.87 (3H, t, *J* = 7.3, **Hk**) ppm.

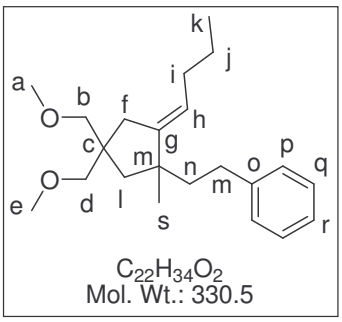
^{13}C NMR (75 MHz, $CDCl_3$): 150.40 (C, **Ch**), 119.19 (CH, **Cg**), 76.74 (CH_2x2, **Cb, d**), 59.16 (CH_3x2, **Ca, e**), 46.82 (CH_2, **Cl**), 45.24 (C, **Cc**), 40.85 (C, **Cm**), 35.40 (CH_2, **Cf**), 31.20 (CH_2, **Ci**), 31.10 (CH_3x2, **Cn**), 22.96 (CH_2, **Cj**), 13.64 (CH_3, **Ck**) ppm.

IR ν_{max}/cm^{-1} (film): 1454 (m), 1104 (s), 966 (m).

LRMS (ES, MeCN): *m/z* 263 ($[M + Na]^+$, 100%).

HRMS (ES): $C_{15}H_{28}NaO_2$ $[M + Na]^+$ calculated 263.1982, found 263.1985.

5.70 (*E*)-(2-(2-Butylidene-4,4-bis(methoxymethyl)-1-methylcyclopentyl)ethyl)benzene **152**



$C_{22}H_{34}O_2$
Mol. Wt.: 330.5

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 4,4-bis(methoxymethyl)-2-methyldec-1-en-6-yne **148** (0.238 g, 1.0 mmol) in THF (2 mL) was added dropwise. After a further 10 min the reaction mixture was warmed to rt for 2 h. The solution was re-cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. The solution continued to stir for a further 5 min at -78 °C before before the addition of 2 M HCl in Et_2O (5 mL). The solution was stirred for a further 18 h while warming to rt before being diluted with Et_2O (50 mL). The reaction mixture was washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et_2O in hexane) yielded the title compounds (0.215 g, 0.65 mmol, 65%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): 7.28-7.13 (5H, m, **Ar-H**), 5.13 (1H, tt, *J* = 7.3, 2.2, **Hh**), 3.33 (3H, s, **Ha/e**), 3.32 (3H, s, **Ha/e**), 3.29-3.16 (4H, m, **Hb,d**), 2.61-2.44 (2H, m, **Hm**), 2.34 (1H, d, *J* = 15.7), 2.14 (1H, d, *J* = 15.7), 1.96 (2H, q, *J* = 7.3, **Hi**), 1.71-1.54 (3H, m), 1.44 (1H, d, *J* = 13.4), 1.35 (2H, sxt, *J* = 7.3, **Hj**), 1.12 (3H, s, **Hs**), 0.87 (3H, t, *J* = 7.3, **Hk**) ppm.

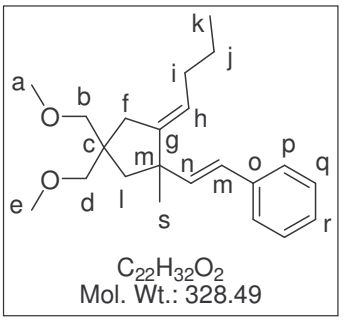
^{13}C NMR (75 MHz, $CDCl_3$): 148.90 (C, **Cg**), 143.36 (C, **Co**), 128.34 (CHx2, **Cp/q**), 128.28 (CHx2, **Cp/q**), 125.49 (CH, **Cr**), 120.58 (CH, **Ch**), 77.181 (CH_2, **Cb/d**), 76.39 (CH_2, **Cb/d**), 59.23 (CH_3, **Ca/e**), 59.20 (CH_3, **Ca/e**), 45.62 (CH_2, **Cl**), 45.16 (C, **Cc**), 44.37 (CH_2), 44.30 (C, **Cm**), 35.86 (CH_2), 31.57 (CH_2), 31.31 (CH_2), 28.37 (CH_3, **Cs**), 23.04 (CH_2), 13.75 (CH_3, **Ck**) ppm.

IR ν_{max}/cm^{-1} (film): 1456 (m), 1104 (s), 698 (s).

LRMS (ES, MeCN): *m/z* 353 ($[M + Na]^+$, 100%).

HRMS (ES): $C_{22}H_{34}NaO_2$ $[M + Na]^+$ calculated 353.2457, found 353.2457.

5.71 ((*E*)-2-((*E*)-2-Butylidene-4,4-bis(methoxymethyl)-1-methylcyclopentyl)vinyl)benzene **153**



$C_{22}H_{32}O_2$
Mol. Wt.: 328.49

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 4,4-bis(methoxymethyl)-2-methyldec-1-en-6-yne **148** (0.238 g, 1.0 mmol) in THF (2 mL) was added dropwise. After a further 10 min the reaction mixture was warmed to rt for 2 h. The solution was re-cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. The solution continued to stir for a further 10 min before warming to rt. The solution was stirred for 24 h at rt before the addition of 2 M HCl (aq) (5 mL).The reaction mixture was stirred for a further 18 h at rt before being extracted with Et_2O (50 mL), washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et_2O in hexane) yielded the title compound (0.282 g, 0.86 mmol, 86%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): 7.37-7.16 (5H, m, **Ar-H**), 6.33 (1H, d, *J* = 16.0, **Hm**), 6.22 (1H, d, *J* = 16.0, **Hn**), 5.21 (1H, tt, *J* = 7.3, 2.0, **Hh**), 3.36 (3H, s, **Ha/ e**), 3.30 (3H, s, **Ha/e**), 3.28-3.21 (4H, m, **Hb/d**), 2.34 (1H, d, *J* = 16.4, CH_2), 2.23 (1H, d, *J* = 16.4, CH_2), 2.01 (2H, q, *J* = 7.3, **Hi**), 1.91 (1H, d, *J* = 16.4, CH_2), 1.54 (1H, d, *J* = 16.4, **CH_2**), 1.40 (2H, sxt, *J* = 7.3, **Hj**), 1.26 (3H, s, **Hs**), 0.91 (3H, t, *J* = 7.3, **Hk**) ppm.

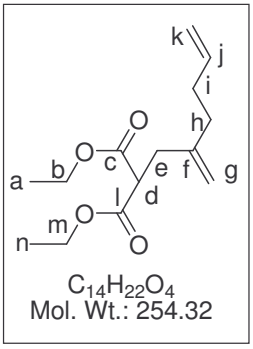
^{13}C NMR (75 MHz, $CDCl_3$): 147.42 (C, **Cg**), 140.60 (C, **Co**), 137.98 (CH, **Cn**), 128.45 (CHx2, **Cq**), 126.74 (CH, **Cm**), 126.08 (CHx2, **Cp**), 125.40 (CH, **Cr**), 122.57 (CH, **Ch**), 77.07 (CH_3, **Cb/d**), 76.03 (CH_3, **Cb/d**), 59.24 (CH_2, **Ca/e**), 59.17 (CH_2, **Ca/e**), 47.44 (C, **Cm**), 45.58 (CH_2, **Cl**), 45.58 (C, **Cc**), 35.61 (CH_2), 31.37 (CH_2), 28.11 (CH_3, **Cs**), 22.91 (CH_2, **Cj**), 13.79 (CH_3, **Ck**) ppm.

IR ν_{max}/cm^{-1} (film): 1447 (m), 1103 (s), 966 (s), 747 (s), 693 (s).

LRMS (ES, MeCN): *m/z* 351 ($[M + Na]^+$, 100%).

HRMS (ES): $C_{22}H_{32}NaO_2$ $[M + Na]^+$ calculated 351.2295, found 351.2292.

5.72 Diethyl 2-(2-methylenehex-5-enyl)malonate **154**



$C_{14}H_{22}O_4$
Mol. Wt.: 254.32

Sodium (1.3 g, 53.4 g-atom) was added portion-wise to ethanol (100 mL) at 0 °C. Once complete dissolution was observed a solution of diethyl malonate (6.5 mL, 42.7 mmol) was added dropwise and the solution was stirred for 15 min at 0 °C. A solution of 2-methylenehex-5-enyl methanesulfonate **104** (6.8 g, 35.6 mmol) in ethanol (50 mL) and 20% NaI (1.04 g, 7 mmol) in ethanol (5 mL) was added. The solution was warmed to rt and stirred for a further 3 h before being poured onto H_2O (500 mL) and extracted with Et_2O (3 x 200 mL). The combined organic extracts were washed with H_2O (3 x 100 mL), brine (2 x 100 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 10% Et_2O in hexane) yielded the title compound (3.2 g, 13 mmol, 37%).

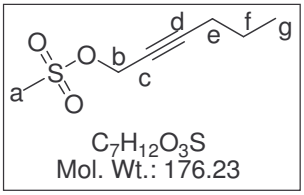
^{1}H NMR (300 MHz, $CDCl_3$): δ 5.81 (1H, ddt , *J* = 16.3, 10.2, 5.9, **Hj**), 5.06-4.81 (4H, m, **Hk, g**), 4.19 (4H, q, *J* = 7.1, **Hb, m**), 3.58 (1H, t, *J* = 7.8, **Hd**), 2.63 (2H, d, *J* = 7.8, **He**), 2.22-2.12 (4H, m, **Hh, i**), 1.26 (6H, t, *J* = 7.1, **Ha, n**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 169.07 (Cx2, **Cc, l**), 145.00 (C, **Cf**), 137.97 (CH, **Cj**), 114.78 (CH_2, **Ck**), 111.27 (CH_2, **Cg**), 61.39 (CH_2x2, **Cb, m**), 50.59 (CH_2, **Cd**), 35.23 (CH_2), 34.77 (CH_2), 31.78 (CH_2), 14.05 (CH_3x2, **Ca, n**) ppm.

IR ν_{max}/cm^{-1} (film): 1731 (s), 1642 (w), 14456 (m), 1147 (s).

LRMS (ES, MeCN): 277 ([M+Na$^+$], 100%).

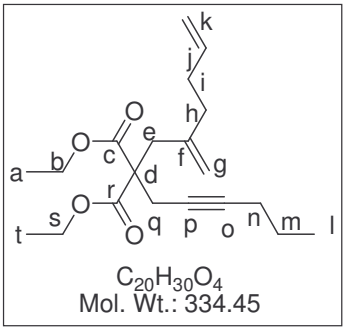
5.73 Diethyl 2-(hex-2-yn-1-yl)-2-(2-methylenehex-5-en-1-yl)malonate **155**



$C_7H_{12}O_3S$
Mol. Wt.: 176.23

Synthesis of hex-2-ynyl methanesulfonate: To a stirred solution of hex-2-yn-1-ol (1.66 g, 17 mmol) and triethylamine (3.6 mL, 2.6 g, 26 mmol) in CH_2Cl_2 (40 mL) at –10 °C was added methanesulfonyl chloride (2.4 g, 1.6 mL, 20 mmol) dropwise. After 30 min at –10 °C the reaction mixture was poured onto H_2O (30 mL). The aqueous layer was separated and re-extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed with 2M HCl (aq) (30 mL), H_2O (30 mL), $NaHCO_3$ (30 mL) and brine (30 mL). The organic layer was dried ($MgSO_4$) and solvent removed in *vacuo* to yield hex-2-ynyl methanesulfonate (2.82 g, 16 mmol, 94%). No further purification was required.

^{1}H NMR (300 MHz, $CDCl_3$): 4.85 (2H, s, **Hb**), 3.11 (3H, s, **Ha**), 2.23 (2H, t, *J* = 7.2, **He**), 1.56 (2H, sextet, *J* = 7.2, **Hf**), 0.99 (3H, t, *J* = 7.2, **Hg**) ppm.



$C_{20}H_{30}O_4$
Mol. Wt.: 334.45

Synthesis of diethyl 2-(hex-2-yn-1-yl)-2-(2-methylenehex-5-en-1-yl)malonate **155**: To a stirred suspension of NaH (60% suspension in mineral oil) (0.626 g, 16.3 mmol) in THF (30 mL) at 0 °C was added malonate **154** (1.74 g, 13 mmol) in THF (10 mL) dropwise. The solution was stirred for a further 15 min before the addition of hex-2-ynyl methanesulfonate (2.82 g, 16 mmol) in THF (10 mL) and NaI (0.51 g, 3.4 mmol) in THF (10 mL). The solution was warmed to rt and stirred for 24 h before being quenched by the dropwise addition of NH_4Cl (50 mL). The reaction mixture was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent gradient: 0-10% Et_2O in hexane) yielded the title compound (3.13 g, 9.4 mmol, 72%) as a colourless oil.

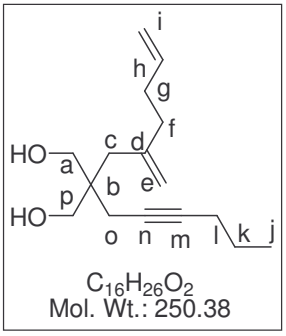
^{1}H NMR (300 MHz, $CDCl_3$): δ 5.78 (1H, ddt, *J* = 16.8, 10.2, 6.3, **Hj**), 5.04-4.89 (4H, m, **Hg, k**), 4.27-4.10 (4H, m, **Hb, s**), 2.83 (2H, s, **Hq**), 2.79 (2H, t, *J* = 2.1, **He**), 2.23-2.00 (6H, m, **CH_2**), 1.48 (2H, sxt, *J* = 7.5, **Hm**), 1.25 (6H, t, *J* = 7.2, **Ha, t**), 0.96 (3H, t, *J* = 7.5, **Hl**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.83 (Cx2, **Cc, r**), 143.64 (C, **Cf**), 130.08 (CH, **Cj**), 114.94 (CH_2, **Ck**), 114.59 (CH_2, **Cg**), 83.74 (C, **Cp/o**), 74.85 (C, **Cp/o**), 61.43 (CH_2x2, **Cb, s**), 56.97 (C, **Cd**), 37.09 (CH_2) 35.94 (CH_2), 32.18 (CH_2), 22.88 (CH_2), 22.32 (CH_2), 20.66 (CH_2), 13.98 (CH_3x2, **Ca, t**), 13.39 (CH_3, **Cl**) ppm.

IR ν_{max}/cm^{-1} (film): 1733 (s), 1641 (w), 1445 (m), 1180 (s), 1096 (s), 1051 (s), 905 (s).

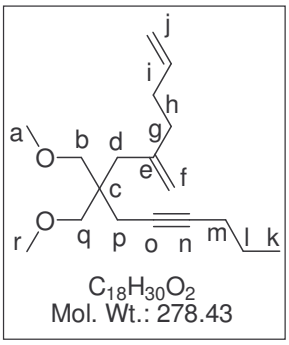
LRMS (ES, MeCN): *m/z* 357 ([M + Na]$^+$, 100%).

5.74 7,7-Bis(methoxymethyl)-5-methylenetridec-1-en-9-yne **156**



Synthesis of 2-(hex-2-yn-1-yl)-2-(2-methylenehex-5-en-1-yl)propane-1,3-diol: To a stirred suspension of $LiAlH_4$ (1.1 g, 18.2 mmol) in Et_2O (50 mL) at 0 °C was added malonate **155** (3.12 g, 9.4 mmol) in Et_2O (10 mL). The solution was warmed to rt and stirred for 3 h before the dropwise addition of 2 M NaOH (aq) (5 mL) followed by water (20 mL). The mixture was poured onto 2 M HCl (aq) (20 mL) and extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with H_2O (3 x 50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the compound as a colourless oil (2.2 g, 8.8 mmol, 94%). No further purification was required.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.88-5.75 (1H, m, **Hh**), 5.06-4.89 (4H, m, **He, i**), 3.69-3.59 (4H, m, **Ha, p**), 2.52 (2H, t, *J* = 5.7, **Hc**), 2.24-2.15 (8H, m), 2.13 (2H, br s, **OH**), 1.52 (2H, sxt, *J* = 7.2, **Hk**), 0.98 (3H, t, *J* = 7.2, **Hl**) ppm.



Synthesis of 7,7-bis(methoxymethyl)-5-methylenetridec-1-en-9-yne **156**: To a stirred suspension of NaH (60% suspension in mineral oil) (1.1 g, 28.2 mmol) in THF (80 ml) at 0 °C was added the diol (2.2 g, 8.8 mmol) in THF (10 mL) dropwise. After 30 min MeI (1.62 g, 14.1 mmol) in THF (5 mL) was added and the solution was stirred at 0 °C for 30 min. The remaining MeI (1.62 g, 14.1 mmol) in THF (5 mL) was added and the solution was warmed to rt and stirred for 4 h. The solution was quenched with the dropwise addition of MeOH (20 mL) poured onto H_2O (50 mL) before being extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et_2O in hexane) yielded the title compound (2.15 g, 7.7 mmol, 88%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.83 (1H, ddt, *J* = 16.5, 10.2, 6.0, **Hi**), 5.05-4.84 (4H, m, **Hf, j**), 3.31 (6H, s, **Ha, r**), 3.25-3.18 (4H, m, **Hb, q**), 2.19-2.12 (10H, m), 1.52 (2H, sxt, *J* = 7.2, **Hl**), 0.99 (3H, t, *J* = 7.2, **Hk**) ppm.

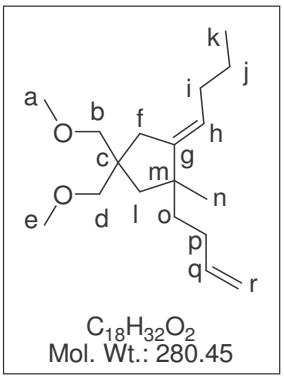
^{13}C NMR (75 MHz, $CDCl_3$): δ 145.34 (C, **Ce**), 138.62 (CH, **Ci**), 114.32 (CH_2, **Cj**), 113.95 (CH_2, **Cf**), 82.41 (C, **Co/n**) 76.81 (C, **Co/n**), 74.20 (CH_2x2, **Cb,q**), 59.0 (CH_3x2, **Ca, r**), 42.55 (C, **Cc**), 37.14 (CH_2), 36.23 (CH_2), 32.64 (CH_2), 22.57 (CH_2), 22.51 (CH_2), 20.83 (CH_2), 13.55 (CH_3, **Ck**) ppm.

IR ν_{max}/cm^{-1} (film): 1733 (s), 1639 (w), 1445 (m), 1180 (s), 1096 (s), 1051 (s), 905 (s).

LRMS (ES, MeCN): *m/z* 301 ([M + Na]$^+$, 100%).

HRMS (ES): $C_{18}H_{30}NaO_2$ [M + Na]$^+$ calculated 301.2138, found 301.2142.

5.75 (*E*)-1-(But-3-en-1-yl)-2-butylidene-4,4-bis(methoxymethyl)-1-methylcyclopentane **158**



$C_{18}H_{32}O_2$
Mol. Wt.: 280.45

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 7,7-bis(methoxymethyl)-5-methylenetridec-1-en-9-yne **156** (0.278 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h before being quenched with 2 M HCl (aq) (5 mL). The reaction mixture was was stirred for 18 h at rt before being extracted with Et_2O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et_2O in hexane) yielded the title compound (0.259 g, 0.93 mmol, 93%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.82 (1H, ddt, *J* = 17.0, 10.3, 6.5, **Hq**), 5.09 (1H, tt, *J* = 7.3, 2.2, **Hh**), 5.0-4.89 (2H, m, **Hr**), 3.35 (3H, s, **Ha/e**), 3.33 (3H, s, **Ha/e**), 3.28-3.15 (4H, m, **Hb, d**), 2.33 (1H, m), 2.12 (1H, m), 2.02-1.93 (4H, m), 1.61 (1H, m), 1.51-1.30 (5H, m), 1.06 (3H, s, **Hn**), 0.88 (3H, t, *J* = 7.3, **Hk**) ppm.

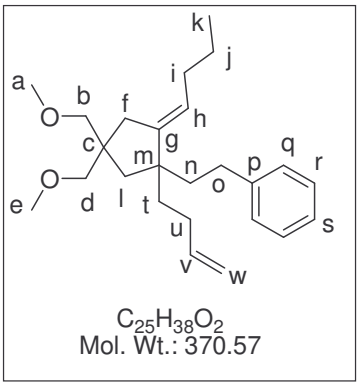
^{13}C NMR (75 MHz, $CDCl_3$): δ 148.95 (C, **Cg**), 139.64 (CH, **Cq**), 120.43 (CH, **Ch**), 113.74 (CH_2, **Cr**), 77.22 (CH_2, **Cb/d**), 76.30 (CH_3, **Cb/d**) 59.23 (CH_3, **Ca/e**), 59.18 (CH_3, **Ca/e**), 45.09 (C, **Cc**), 44.41 (CH_2, **Cl**), 44.05 (C, **Cm**), 42.54 (CH_2, **Co**), 35.82 (CH_2, **Cf**), 31.26 (CH_2), 29.42 (CH_2), 28.32 (CH_2), 23.00 (CH_3, **Cn**), 13.71 (CH_3, **Ck**) ppm.

IR ν_{max}/cm^{-1} (film): 1640 (w), 1456 (m), 1105 (s).

LRMS (ES, MeCN): *m/z* 303 ($[M + Na]^+$, 100%).

HRMS (ES): $C_{18}H_{32}NaO_2$ $[M + Na]^+$ calculated 303.2295, found 303.2295.

5.76 (*E*)-(2-(1-(But-3-en-1-yl)-2-butylidene-4,4-bis(methoxymethyl) cyclopentyl)ethyl)benzene **160**



$C_{25}H_{38}O_2$
Mol. Wt.: 370.57

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 7,7-bis(methoxymethyl)-5-methylenetridec-1-en-9-yne **156** (0.278 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The solution was re-cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. The solution continued to stirred for a further 5 min at –78 °C before the addition of 2 M HCl in Et_2O (5 mL). The solution was stirred for a further 20 h while warming to rt before being diluted with Et_2O (50 mL). The reaction mixture was washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et_2O in hexane) yielded the title compound (0.288 g, 0.78 mmol, 78%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.26 (2H, m, **Ar-H**), 7.20-7.16 (3H, m, **Ar-H**), 5.85 (1H, ddt, *J* = 17.0, 10.3, 6.5, **Hv**), 5.14 (1H, tt, *J* = 7.3, 2.0, **Hh**), 5.06-4.93 (2H, m, **Hw**), 3.37 (3H, s, **Ha/e**), 3.35 (3H, s, **Ha/e**), 3.29-3.20 (4H, m, **Hb, d**), 2.56-2.50 (2H, m, **Ho**), 2.26 (2H, br s), 2.06-1.95 (4H, m), 1.81-1.55 (5H, m), 1.45-1.36 (3H, m), 0.92 (3H, t, *J* = 7.3, **Hk**) ppm.

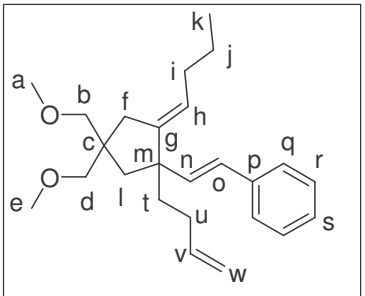
^{13}C NMR (75 MHz, $CDCl_3$): 146.47 (C, **Cg**), 143.30 (C, **Cp**), 139.45 (CH, **Cv**), 128.33 (CHx4), 125.56 (CH), 121.64 (CH, **Ch**), 113.95 (CH_2, **Cw**), 76.90 (CH_2, **Cb/d**), 76.79 (CH_2, **Cb/d**), 59.19 (CH_3x2, **Ca/e**), 47.61 (C, **Cc**), 44.71 (C, **Cm**), 42.71 (CH_2), 41.95 (CH_2), 38.85 (CH_2), 35.92 (CH_2), 31.31 (CH_2), 31.23 (CH_2), 29.11 (CH_2), 23.08 (CH_2), 13.79 (CH_3, **Ck**) ppm.

IR ν_{max}/cm^{-1} (film): 1640 (w), 1454 (m), 1104 (s), 698 (s).

LRMS (ES, MeCN): *m/z* 393 ($[M + Na]^+$, 100%).

HRMS (ES): $C_{25}H_{38}NaO_2$ $[M + Na]^+$ calculated 393.2764, found 393.2760.

5.77 ((*E*)-2-((*E*)-1-(But-3-en-1-yl)-2-butylidene-4,4-bis(methoxymethyl) cyclopentyl)vinyl)benzene **162**



$C_{25}H_{36}O_2$
Mol. Wt.: 368.55

To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 7,7-bis(methoxymethyl)-5-methylenetridec-1-en-9-yne **156** (0.278 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The solution was re-cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LDA (1.8 M solution in THF) (0.6 mL, 1.0 mmol) dropwise. After 5 min at –78 °C 2-butyne (0.16 mL, 2 mmol) was added. The solution continued to stir for a further 10 min before warming to rt. The solution was stirred for 24 h at rt before the addition of 2 M HCl (aq) (5 mL). The reaction mixture was stirred for a further 18 h at rt before being extracted with Et_2O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et_2O in hexane) yielded the title compound (0.110 g, 0.30 mmol, 30%) as a colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.28 (3H, m, **Ar-H**), 7.23-7.14 (2H, m, **Ar-H**), 6.37 (1H, d, *J* = 16.1, **Ho**), 6.23 (1H, d, *J* = 16.1, **Hn**), 5.82 (1H, tdd, *J* = 16.8, 10.6, 6.6, **Hv**), 5.28 (1H, tt, *J* = 7.1, 2.4, **Hh**), 5.04-4.90 (2H, m, **Hw**), 3.37 (3H, s, **Ha/e**), 3.33-3.21 (7H, m, **Ha/e, b, d**), 2.25 (2H, br s), 2.10-1.98 (5H, m), 1.76-1.53 (3H, m), 1.46-1.38 (2H, m), 0.93 (3H, t, *J* = 7.3, **Hk**) ppm.

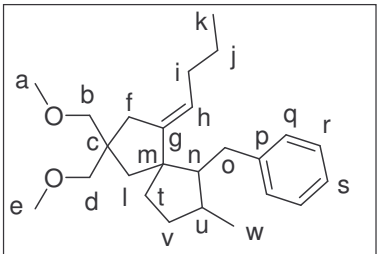
^{13}C NMR (75 MHz, $CDCl_3$): δ 146.73 (C, **Cg**), 139.28 (CH), 139.10 (CH), 137.97 (C, **Cp**), 128.48 (CHx2), 126.80 (CH), 126.43 (CH), 126.11 (CHx2), 122.82 (CH, **Ch**), 114.00 (CH_2, **Cw**), 77.28 (CH_2, **Cb/d**), 77.38 (CH_2, **Cb/d**), 59.28 (CH_3, **Ca/e**), 59.08 (CH_3, **Ca/e**), 50.66 (C, **Cm**), 45.42 (C, **Cc**), 41.36 (CH_2), 41.26 (CH_2), 36.08 (CH_2), 31.42 (CH_2), 29.45 (CH_2), 22.91 (CH_2, **Cj**), 13.83 (CH_3, **Ck**) ppm.

IR ν_{max}/cm^{-1} (film): 1640 (w), 1495 (m), 1448 (m), 1103 (s), 693 (s).

LRMS (ES, MeCN): *m/z* 391 ([M + Na]$^+$, 100%).

HRMS (ES): $C_{25}H_{36}NaO_2$ [M + Na]$^+$ calculated 391.2608, found 391.2607.

5.78 (*E*)-1-Benzyl-6-butylidene-8,8-bis(methoxymethyl)-2-methylspiro [4.4]nonane **164**



$C_{25}H_{38}O_2$
Mol. Wt.: 370.57

To a stirred solution of zirconocene dichloride (0.164 g, 0.56 mmol) in THF (2 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.45 mL, 1.12 mmol) dropwise over 5 min. After 10 min a solution of **162** (0.103 g, 0.28 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 3 h before being quenched with MeOH (2 mL) followed by sat $NaHCO_3$ (aq) (2 mL). The reaction mixture was stirred for a further 20 h at rt. The reaction mixture was extracted with Et_2O (50 mL). The combined organic layers were washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et_2O in hexane) yielded the title compounds (0.071 g, 0.19 mmol, 68%) as a colourless oil. NMR revealed that the title compound had been formed in a 1:1 ratio of diastereoisomers. Separation of the 2 diastereoisomers was achieved by preparative HPLC.

Diastereoisomer A:

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26-7.14 (5H, m, **Ar-H**), 5.31 (1H, tt, *J* = 17.3, 2.0, Hh), 3.37 (3H, s, **Ha/ e**), 3.35 (3H, s, **Ha/ e**), 3.32-3.21 (4H, m, **Hb, d**), 2.57-2.55 (2H, m **CH_2**), 2.30-2.23 (2H, m), 2.07-1.90 (5H, m), 1.79 (2H, m), 1.62-1.51 (2H, m, **CH_2**), 1.39 (2H, sxt, *J* = 7.53, **Hj**), 1.29 (1H, m), 0.93-0.89 (6H, m, **Hk, w**) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ 149.32 (C, **Cg**), 142.36 (C, **Cp**), 128.70 (CHx2), 128.11 (CHx2), 125.40 (CH), 119.91 (CH, **Ch**), 77.48 (CH_2, **Cb/d**), 75.32 (CH_2, **Cb/d**), 59.33 (CH_3, **Ca/e**), 59.14 (CH_3, **Ca/e**), 54.79 (C, **Cm**), 54.73 (CH, **Cn**), 46.11 (C, **Cc**), 43.82 (CH_2), 39.62 (CH_2), 36.99 (CH_2), 32.74 (CH_2), 32.44 (CH, **Cu**), 32.25 (CH_2), 31.48 (CH_2), 23.06 (CH_2, **Cj**), 18.07 (CH_3, **Cw**), 13.78 (CH_3, **Ck**) ppm.

IR ν_{max}/cm^{-1} (film): 1640 (w), 1495 (m), 1455 (m), 1103 (s), 699 (s).

LRMS (ES, MeCN): *m/z* 393 ($[M + Na]^+$, 100%).

HRMS (ES): $C_{25}H_{38}NaO_2$ $[M + Na]^+$ calculated 393.2764, found 393.2764.

Diastereoisomer B:

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24-7.13 (5H, m, **Ar-H**), 5.29 (1H, tt, *J* = 7.3, 2.3, **Hh**), 3.36 (3H, s, **Ha/e**), 3.34 (3H, s, **Ha/e**), 3.31-3.21 (4H, m, **Hb, d**), 2.71 (1H, dd, *J* = 13.4, 3.4), 2.42 (1H, dd, *J* = 13.6, 8.5), 2.26 (1H, d, *J* = 16.3), 2.02-1.87 (4H, m), 1.72-1.58 (5H, m),1.47 (1H, d, *J* = 13.8), 1.37 (2H, sxt, *J* = 7.3, **Hj**), 1.91 (1H, m), 0.90 (3H, t, *J* = 7.3, **Hk**), 0.65 (3H, d, *J* = 6.27, **Hw**) ppm.

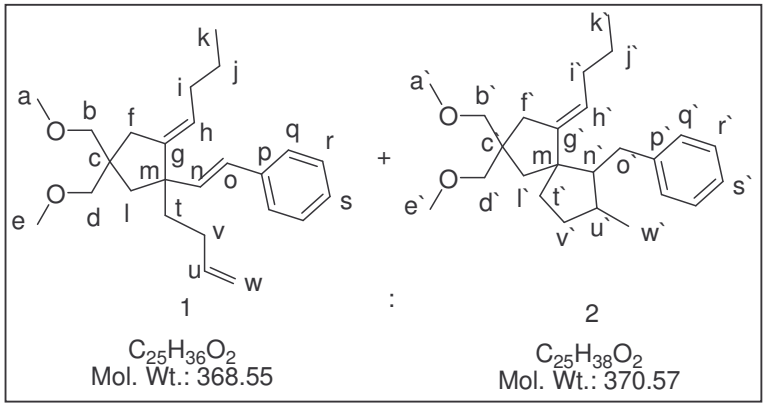
^{13}C NMR (75 MHz, $CDCl_3$): δ 147.73 (C, **Cg**), 142.53 (C, **Cp**), 129.06 (CHx2), 127.93 (CHx2), 125.39 (CH), 120.31 (CH, **Ch**), 77.21 (CH_2, **Cb/d**), 75.56 (CH_2, **Cb/d**), 59.31 (CH_3, **Ca/e**), 59.15 (CH_3, **Ca/e**), 59.15 (CH, **Cn**), 56.59 (C, **Cm**), 45.59 (C, **Cc**), 42.15 (CH_2), 38.78 (CH, **Cu**), 37.80 (CH_2), 37.20 (CH_2), 36.77 (CH_2), 31.90 (CH_2), 31.40 (CH_2), 22.50 (CH_2, **Cj**), 21.21 (CH_3, **Cw**), 13.78 (CH_3, **Ck**) ppm.

IR ν_{max}/cm^{-1} (film): 1640 (w), 1495 (m), 1455 (m), 1103 (s), 698 (s).

LRMS (ES, MeCN): *m/z* 393 ($[M + Na]^+$, 100%).

HRMS (ES): $C_{25}H_{38}NaO_2$ $[M + Na]^+$ calculated 393.2764, found 393.2764.

5.79 (*E*)-1-Benzyl-6-butylidene-8,8-bis(methoxymethyl)-2-methylspiro [4.4]nonane **164** and ((*E*)-2-((*E*)-1-(But-3-en-1-yl)-2-butylidene-4,4-bis(methoxymethyl)cyclopentyl)vinyl)benzene **162**



To a stirred solution of zirconocene dichloride (0.293 g, 1.0 mmol) in THF (5 mL) at –78 °C was added *n*-BuLi (2.5 M solution in hexanes) (0.80 mL, 2.0 mmol) dropwise over 5 min. After 10 min a solution of 7,7-bis(methoxymethyl)-5-methylenetridec-1-en-9-yne **156** (0.278 g, 1.0 mmol) in THF (2 mL) was added dropwise. After 10 min the reaction mixture was warmed to rt for 2 h. The solution was re-cooled to –78 °C before the addition of benzyl chloride (0.12 mL, 0.126 g, 1.0 mmol) and LiTMP (formed by treating 2,2,6,6-tetramethylpiperidine (0.22 mL, 0.184 g, 1.3 mmol) in THF (2 mL) at 0 °C with *n*-BuLi (2.5 M solution in hexanes) (0.52 mL, 1.3 mmol) dropwise). The solution continued to stir for 10 min at –78 °C before being warmed to rt. The solution was stirred for 24 h at rt before the addition of 2 M HCl (aq) (5 mL). The reaction mixture was stirred for a further 18 h at rt before being extracted with Et_2O (50 mL). The organic layer was washed with water (3 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by column chromatography on silica gel (eluent: 5% Et_2O in hexane) yielded the title compounds (0.259 g, 0.70 mol, 70%) as an inseparable mixture of spirocycle **164** and alkene **162** in a 2:1 ratio. Only diasterisomer A of spirocycle **164** was isolated.

For alkene **162** data analysis see experimental 5.75.

For spirocycle **164** data analysis see experimental 5.76.

6 References

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