UNIVERSITY OF SOUTHAMPTON

FACULTY OF SCIENCE
DEPARTMENT OF CHEMISTRY

CARBENOID INSERTION INTO ORGANOZIRCONIUM SPECIES'

By Sally Dixon

A thesis submitted in partial fulfilment of the requirements for
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ABSTRACT

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Zirconium-mediated synthesis of mono- and bi- cyclic zirconacyclopent-anes, -enes and –adienes is well established and the potential for their elaboration has begun to be realised in recent years by carbenoid insertion into carbon-zirconium bonds. Synthetic methods and the history of carbenoid insertion into organozirconocenes, including zirconacycles, is reviewed herein.

The novel work in this thesis is then presented in three sections. Firstly, regioselective co-cyclisation between 1-stannyl, 1-thio or 1-silyl substituted 1-propynes and zirconocene-ethene has furnished monocyclic zirconacyclopentenes with α-substituents. Subsequent insertion of allyl carbenoids into the sp^3C-Zr bond leads to cyclic zirconocene η^3-allyl species, reaction of which with aldehydes constitutes a concise route to homoallylic alcohols. The nature of the α-substitution is found to influence geometry about the alkene introduced and application specifically of α-$SnBu_3$ substituted monocyclic zirconacyclopentenes to the synthesis of naturally occurring terpenoids has been made. 9-Hydroxyfarnesoic acid, 9-hydroxyfarnesol, crinitol and 9-hydroxysargaquinone, all of which contain (E)-homoallylic alcohol functionality, are synthesised *via* this one-pot protocol followed by Stille coupling methods for functional group interconversion at the alkenyl stannyl group. In the same way, a precursor compound to β-D-galactose and –altrose linked sesquiterpenoids Moritoside and Euplexide A has been furnished.

A second area, insertion of unfunctionalised alkyl and alkenyl carbenoids into zirconacycles, demonstrates synthesis of zirconacyclohexenes bearing an α-exocyclic alkene by 1-chloro-1-lithio enyne insertion into five-membered zirconacycles. Further ring-expansion *via* isocyanide insertion yields a zirconacycloheptene-iminoacyl complex in a multi-component synthesis of α,β-unsaturated aldehydes and imines.

Finally, investigation of the regiochemistry of carbenoid insertion into non-symmetrical zirconacycles required the preparation of an α-ethyl substituted zirconacyclopentane, found to arise from either (E) or (Z) co-cyclisation precursor alkenes *via* β-H elimination and re-addition to give a five- and not six-membered zirconacycle. Ring junction stereochemistry of β-methyl substituted zirconacyclopentanes can also be predicted. The regiochemistry of insertion of 1-chlor-1-lithio enynes, 1-chloro-1-lithio-silanes and 1-chloro-1-lithio ethers into these α-alkyl and β-alkyl zirconacyclopentanes is found to be consistent, taking place exclusively or predominantly into the α-cyclohexyl and β-methyl substituted side of the zirconacycle and into the C-Zr bond opposite to an α-ethyl substituent. Discussion of the mechanism of carbenoid insertion in terms of nucleophilic attack upon zirconium and interconversion of regioisomeric zirconate complexes is made.

Contents.

Acknowledgements.

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Finally, thank you to my family for their support and encouragement, especially Tony and my Mum, for whom the thesis is written.

Abbreviations.

Techniques.

NMR	Nuclear Magnetic Resonance
COSY	COrrelation SpectroscopY
DEPT	Distortionless Enhancement by Polarisation Transfer
NOE	Nuclear Overhauser Effect
IR	InfraRed
m/z	mass of ion
EI	Electron Impact
CI	Chemical Ionisation
FAB	Fast Atom Bombardment
ES	Electrospray
GC	Gas Chromatography
LRMS	Low Resolution Mass Spectrometry
HRMS	High Resolution Mass Spectrometry
DFT	Density Functional Theory

Reagents and Solvents.

Ac	acetyl
Ar	aryl
Bn	benzyl
Bu	butyl
Cp	cyclopentadienyl
Cy	cyclohexyl
DIBAL-H	diisobutylaluminium hydride
DMF	dimethyl formamide
DMAP	4-dimethylamino pyridine
HMPA	hexamethyl phosphoramide
LDA	lithium diisopropylamide
LiTMP	lithium 2,2,6,6-tetramethyl piperidine
Ms	methanesulphonyl (mesyl)
PPTS	pyridinium *para*-toluene sulphonate

PMA	phosphomolybdic acid
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran
TMEDA	*N*, *N*, *N'*, *N'*-tetramethylethylenediamine
TMS	trimethylsilyl

Miscellaneous.

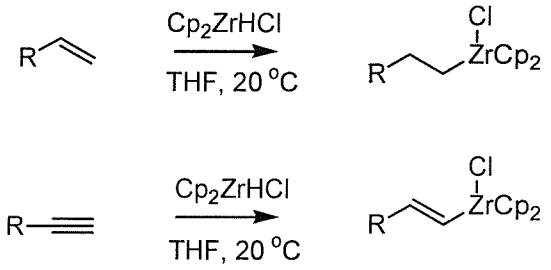
h	hour(s)
min	minute(s)
eq	equivalents

Chapter One : Current Methods for Synthesis of Organozirconium Species' and their Elaboration *via* Carbenoid Insertion.

1.0 Foreword.

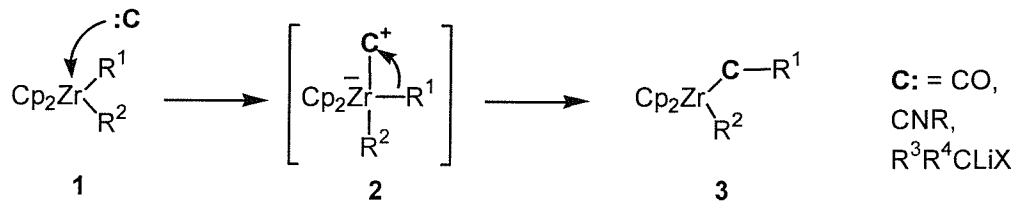
The application of stoichiometric zirconium chemistry to organic synthesis has developed rapidly over the past fifteen years. Intermediate organozirconocene chlorides and cyclic five-membered zirconacycles are formed respectively from the hydrozirconation of π-compounds with Cp_2ZrHCl[1,2](Scheme 1.1) or the co-cyclisation of alkenes and/or alkynes with a zirconocene equivalent 'Cp_2Zr' (Section 1.1)[3,4].

Scheme 1.1 Synthesis of organozirconocene chlorides by hydrozirconation of π-compounds.



Further elaboration of these organozirconium species' by iterative carbon-carbon bond formation is restricted by their lack of reactivity towards conventional electrophiles[5]. In marked contrast however, carbon monoxide is observed to insert rapidly into Cp_2ZrMe_2 at -130°C[6]. Such reactivity may be understood if we note that characteristic of organozirconocene complexes is the preferred 16 electron configuration of the metal. Essential for reactivity, the remaining empty orbital on zirconium is able to accept an electron pair to form an 18 electron zirconate species **2**, such that tandem synthesis of a zirconium species **1** followed by insertion of a carbene (such as CO), **:C**, yields products **3** following 1,2-rearrangement of the 'ate' complex. Species **3** itself possesses potential for elaboration of the two carbon-zirconium bonds (Scheme 1.2).

Scheme 1.2 Carbene insertion into organozirconocenes.



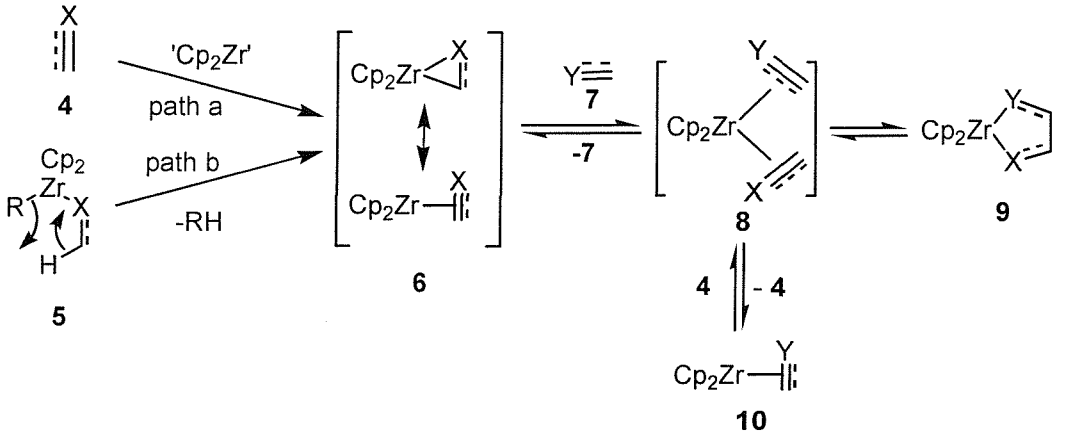
This chapter provides necessary background upon the formation of zirconacycles, followed by a brief review of insertion of carbon monoxide and the isoelectronic isonitriles into organozirconocenes. The insertion of α-halo-α-lithium species' (R^1R^2CLiX, 'carbenoids') as a means for elaboration of organozirconocenes, which may be viewed as taking place *via* a conceptually similar mechanism, is then described.

1.1 Zirconocene–Mediated Co-Cyclisation.

1.1.1 Introduction.

The formal co-cyclisation of two π-components (**4** and **7**, alkene, alkyne, allene, imine, carbonyl or nitrile) allows formation of a wide variety of five-membered zirconacycles (Scheme 1.3)[3,4,7].

Scheme 1.3 Zirconocene-mediated co-cyclisation.



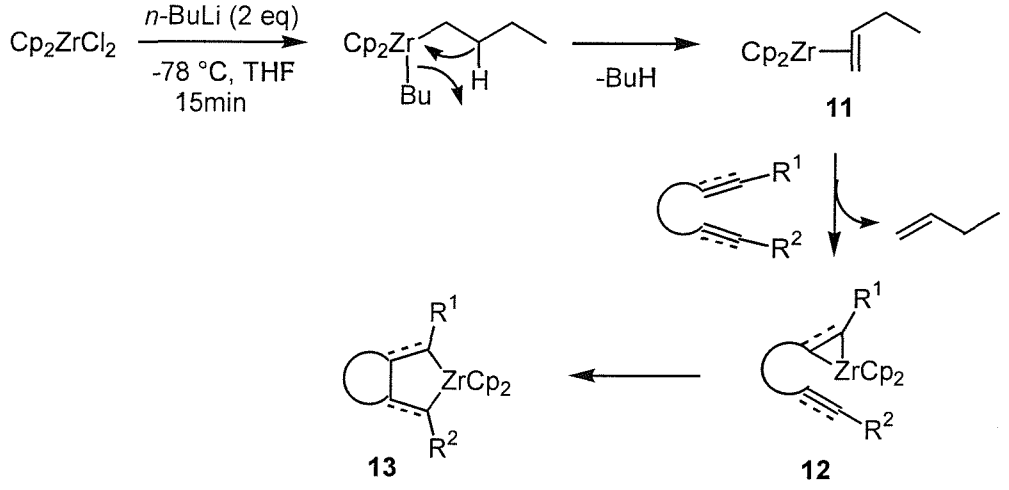
The co-cyclisation takes place *via* the η^2-complex **6** of one of the components, usually formed by complexation of **4** to a zirconocene equivalent (path a) ('Cp_2Zr' itself is probably too unstable to be a true intermediate) or by oxidation on the metal (cyclometallation / β-hydrogen elimination) (path b). Two additional routes to zirconocene η^2-complexes are by the reverse of the co-cyclisation reaction (**9** returning to **6** or **10** *via* **8**), and by rearrangement of iminoacyl complexes (see section 1.2.2 below). Direct complexation (path a) is generally only useful for intramolecular co-cyclisation (see section 1.1.2 below), when the two π-components are the same, or when dimerisation of one component is unfavourable. Co-cyclisation of the intermediate **8** is generally slow relative to the loss of one of the π-components (to return to **6**, or **10**). As a consequence, even when the starting η^2-complex **6** is formed by a path which avoids self condensation,

exchange to form **10** with liberation of **4** takes place and consequently mixtures of the desired zirconacycle **9** and products resulting from dimerisation of **4** or **7** are formed. Intermolecular co-cyclisations may be successful when cycloreversion of **8** always occurs to give **6**, not **10**. This may be because the η^2-complex **6** is much more stable than **10** (for example zirconocene η^2-imine complexes, zirconocene ethylene and some zirconocene alkyne complexes), or because the π-component **4** is very unstable (for example where **4** is a benzyne) (Section 1.1.3).

1.1.2 Zirconocene–Mediated Intramolecular Co-Cyclisation.

An important consideration in the co-cyclisation reaction is the requirement for 14 electron Cp_2Zr. Several alkene and alkyne π-complexes of zirconocene have been discovered as convenient for use as a loosely ligand-protected 16 electron Cp_2Zr equivalent[8-11], however the most commonly used is zirconocene(1-butene) **11** generated *in situ* by reduction of zirconocene dichloride (Cp_2ZrCl_2) with *n*-butyllithium[12,13]. This takes place *via* β-hydrogen elimination and Cp_2Zr(1-butene), the Negishi reagent, has found widespread use in co-cyclisation reactions by many research groups (Scheme 1.4).

Scheme 1.4 Formation and use of Negishi's reagent in intramolecular co-cyclisation.



Bicyclic zirconacyclopent –anes, -enes and –adienes **13** are therefore available from respective 1,n-diene, enyne and diyne coupling. The procedure is applicable to a wide range of carbocyclic and heterocyclic systems[3,4,14,15] and five-, six- and seven-membered rings may be fused to the zirconacycle.

Intramolecular co-cyclisation of 1,6- and 1,7-dienes to give fused five- or six-membered rings works well, although larger rings may be formed when the chain contains a nitrogen,

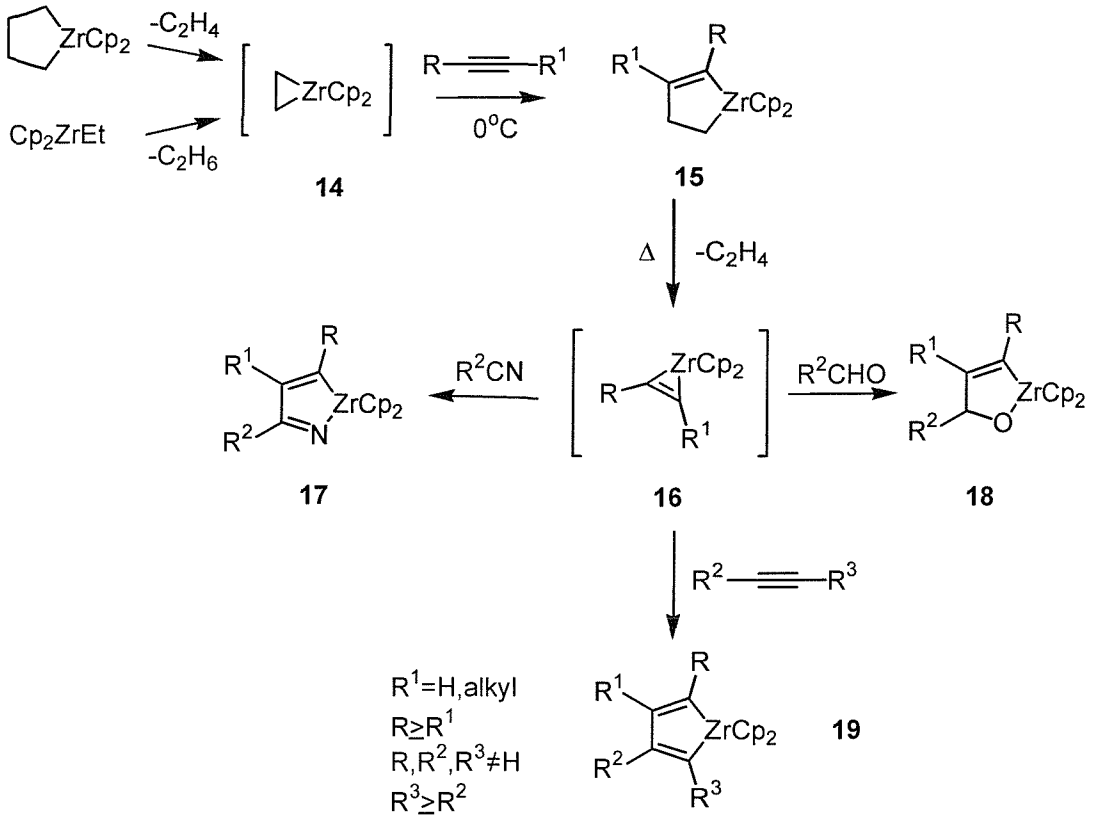
or steric constraints. Co-cyclisation of substrates containing heavily substituted alkenes (tri- or tetra-substituted) are generally not successful. In cases of enyne co-cyclisation, five- to seven-membered rings are readily formed whilst for diyne co-cyclisation four-membered to large rings are successful. Ether or alkoxide substituents are compatible, except when β-to a carbon-zirconium bond in the intermediate **12**. Carbonyl groups are usually not compatible with the cyclisation although, when remote to the metal, amide groups survive.

1.1.3 Zirconocene-Mediated Intermolecular Co-Cyclisation.

Cross-coupled monocyclic zirconium species are not generally available *via* the direct zirconocene-mediated π-component coupling described for intramolecular co-cyclisation. Homocoupled products arise from this method as established in section 1.1.1.

Pair selective monocyclisation may be achieved by reduction of alkynes with Cp_2Zr(-ethene) **14** (generated *in situ* from diethyl zirconocene *via* β-elimination or from Cp_2Zr(1-butene) under ethylene gas)[16,17]. Zirconacyclopentenes **15** are synthesised in this way and thermal elimination of ethene in the presence of a second alkyne also allows access to the zirconacyclopentadiene products **19** *via* the Cp_2Zr-alkyne complex **16**. This species is also reactive towards nitriles and aldehydes such that heteroaromatic zirconacycles **17** and **18** may be accessed (Scheme 1.5)[16,18].

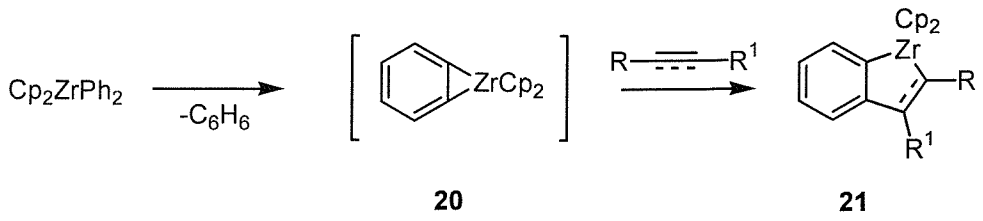
Scheme 1.5 Formation of monocyclic zirconacycles.



Variation in the nature of substitution about the monocycle is realised and the regiochemistry can be controlled to some extent by the nature of these substituents[19]; for example, silyl, sulphur or aryl substituted zirconacyclopropenes **16** yield zirconacyclopentadienes **19** with such groups positioned α to zirconium *via* chelation to the metal.

Zirconaind-ane/-ene synthesis *via* a Cp_2Zr(-benzyne) complex **20** is an analogous procedure, extensively developed and deserving of inclusion here (Scheme 1.6)[7,20-23].

Scheme 1.6 Formation of zirconaind-anes/-enes *via* zirconocene-benzyne.

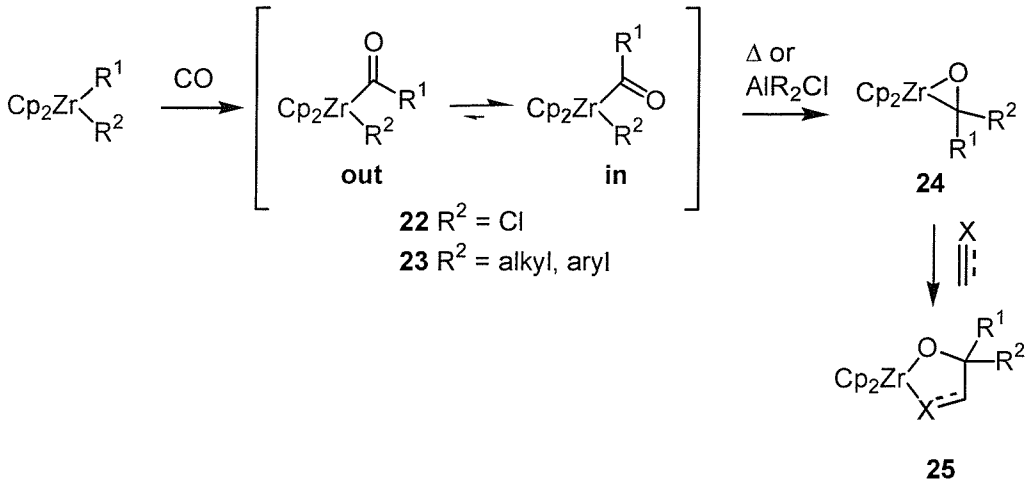


1.2 Carbonylation and Isonitrile Insertion into Organozirconium Species.

1.2.1 Insertion into Acyclic Organozirconocenes.

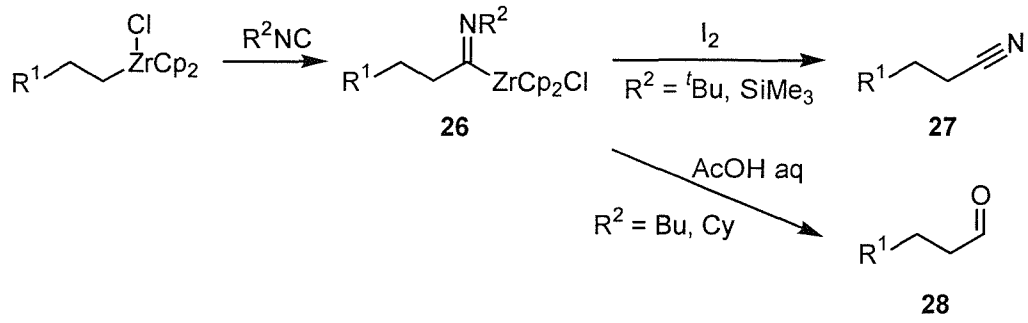
Insertion of carbon monoxide into the carbon-zirconium bond of alkyl- and alkenyl-zirconocene chlorides takes place rapidly at low temperature with retention of configuration at carbon to give acylzirconocene chlorides **22** (Scheme 1.7). Acylzirconocene chlorides have found synthetic utility in Lewis acid catalysed additions to enones, aldehydes and imines, yielding α-keto allylic alcohols, α-hydroxy ketones and α-amino ketones respectively[24] and in palladium catalysed addition to alkyl/aryl halides and α,β-ynones[25]. The acyl complex **23** formed by the insertion of carbon monoxide into dialkyl, alkylaryl, or diaryl zirconocenes may rearrange to an η^2-ketone complex **24** either thermally (particularly R^1=R^2=Ph) or on addition of a Lewis acid[6,26,27]. The rearrangement occurs through the less stable **23-out** isomer. The η^2-ketone complexes **24** insert π-components to form zirconacycles **25** (Scheme 1.7)[26,27].

Scheme 1.7 Carbonylation of organozirconocenes.



Synthesis of analogous iminoacyl complexes derived from isonitrile insertion into linear alkylzirconocene chlorides is also known. In an overall regiospecific hydrocyanation of alkenes, iminoacyls **26** derived from ^{t}BuNC or Me_3SiCN (as Me_3SiNC isomer) may be treated with I_2 to rapidly generate an imidoyl iodide and subsequently the nitrile **27**[28]. Less hindered iminoacyl complexes (for example R = Bu, Cy) may be hydrolysed to afford aldehydes **28** (Scheme 1.8)[29].

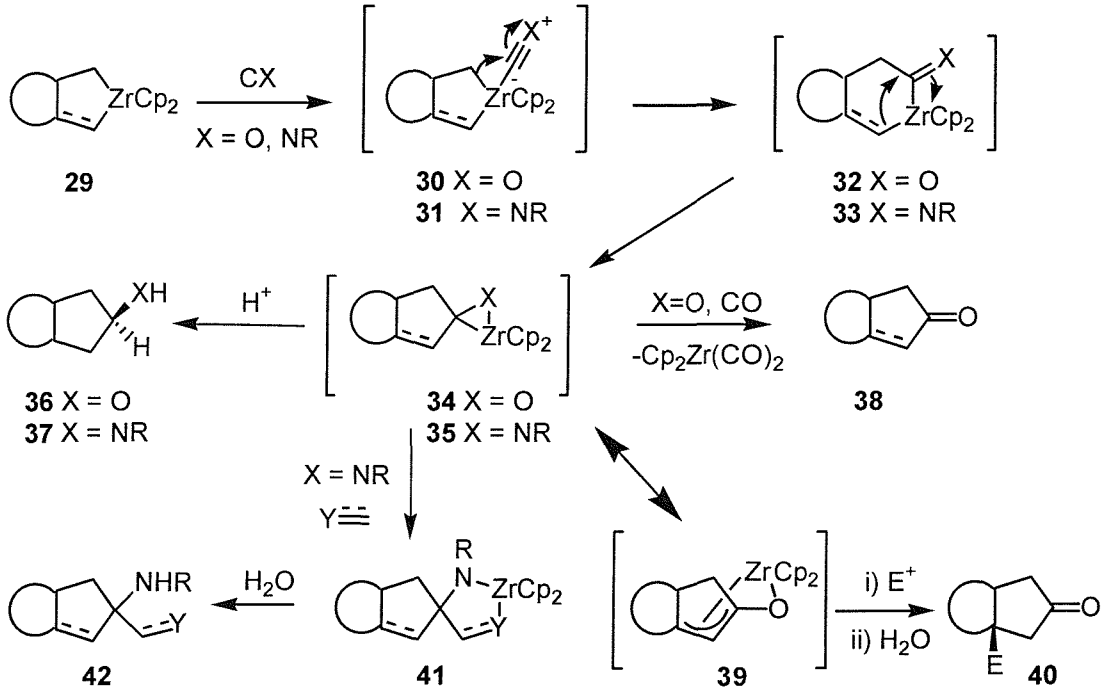
Scheme 1.8 Isonitrile insertion into organozirconocene chlorides.



1.2.2 Insertion into Zirconacycles.

In the carbonylation of zirconacycles **29**[30] the initially formed acyl complex **32** rapidly rearranges to the η^2-ketone complex **34**, presumably because **32** is locked in the acyl-out form (c.f. **23**) (Scheme 1.9). In the case of carbonylation of saturated zirconacycles the η^2-ketone complex **34** is rather stable and protonation after a short time gives the alcohol **36**. Prolonged exposure to CO affords the saturated ketone **38**, probably *via* displacement of the η^2-ketone ligand by CO. Higher yields of the ketone **38** are generally obtained by work-up of **34** with iodine[31]. Carbonylation of zirconacyclopentenes **29** (1 atm CO, 20 °C, 16 h) generally gives cyclopentenones **38** in high yield[3,4]. It has been observed with certain zirconacyclopentene substrates that carbonylation for a short time followed by work-up with electrophiles affords the saturated ketones **40** implying the intermediate formation of the allyl-zirconocene tautomer **39** of **34**[32,33]. It is not yet clear how general this process will be.

Scheme 1.9 Carbonylation and isonitrile insertion into zirconacycles.



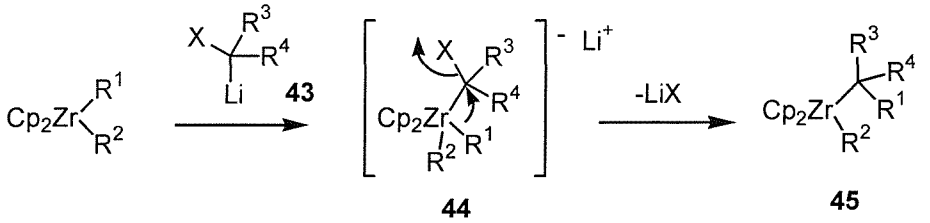
Isonitrile insertion into zirconacycles to afford iminoacyl complexes **33** is fast, but rearrangement to η^2-imine complexes **35** is slow. In the case of ^{t}BuNC the rearrangement does not occur. Amines **37** are formed on protonolysis of the η^2-imine complex. The η^2-imine complexes **35** readily insert π-components (alkenes, alkynes, ketones, aldehydes, imines, isocyanates) to provide a wide variety of products **42** *via* zirconacycles **41**. The overall sequence is an elegant demonstration of how a number of components may be assembled sequentially on a zirconocene template. A variety of isonitriles (R = Ph, Bu, Cy, Me_3Si) may be used, the most useful of which is the insertion of trimethylsilyl cyanide (*via* its isocyanide isomer) to give primary amines[34-37].

1.3 Insertion Of 1-Halo-1-Lithio Species Into Organozirconocenes.

The success of the described carbonylation and isonitrile insertion reactions for exploitation of organozirconium species in carbon-carbon bond formation is attributed to the carbenic character of carbon monoxide and isonitriles which facilitates initial donation of an electron pair to the 16 electron zirconium atom. Compounds containing a lithium atom and a nucleofugal group on the same carbon (R^3R^4CLiX, **43**), for which we use the term 'carbenoid' introduced by Köbrich, show similar reactivity[38-42]. As introduced in

section 1.0, initial attack on the 16 electron zirconium atom to form an 18 electron metallate complex **44** may be followed by a 1,2-rearrangement[43] with loss of halogen to give a new organozirconocene **45** (Scheme 1.10). The mechanism predicts clean inversion of configuration at the carbenoid carbon.

Scheme 1.10 Carbenoid insertion into the carbon-zirconium bond.

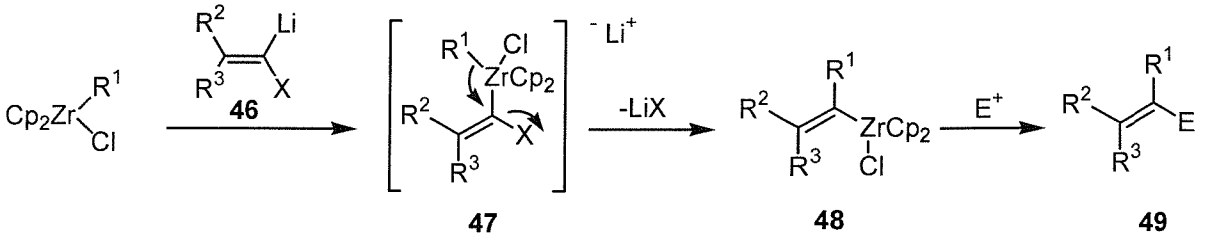


In an important communication of 1989 Negishi reported[44] the first insertions of α- and γ-haloorganolithium reagents into acyclic zirconocene chlorides. Recently this work has been extended to a wide variety of carbenoids and organozirconium species, including zirconacycles, to provide a variety of new synthetic methods described below.

1.3.1 Insertion of 1-Halo-1-Lithioalkenes into Acyclic Organozirconocene Chlorides.

Scheme 1.11 illustrates the potential for synthesis of highly functionalised, stereodefined, alkenes **49** from insertion of 1-halo-1-lithioalkenes **46** into organozirconocene chlorides. Alkenyl carbenoids (**46**) may be generated by halogen/lithium exchange at low temperature or by deprotonation of alkenyl halides. The latter process may be carried out with *in situ* trapping by the organozirconocene, reducing the need for very low temperatures.

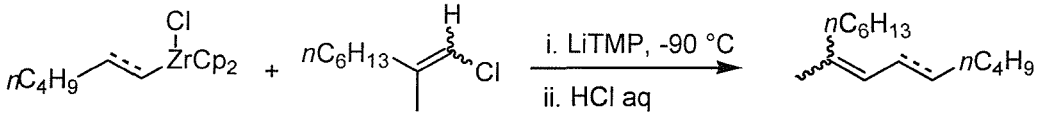
Scheme 1.11 Alkenyl carbenoid insertion into organozirconocene chlorides.



1.3.1.1 Insertion of 1-Chloro-1-Lithio-2,2-Disubstituted Alkenes.

Insertion of 2,2-disubstituted alkenyl carbenoids into alkyl- or alkenyl-zirconocene chlorides occurs in high yield[44,45]. Insertion of the carbenoids derived by *in situ* deprotonation of the stereodefined (*E*)- or (*Z*)-1-chloro-2-methyl-1-octenes **50** into alkyl- or alkenyl-zirconocene chlorides gives mixtures of isomeric products **51** showing between 86% inversion and 26% retention of configuration at the alkenyl carbenoid centre however (Scheme 1.12)[45]. This poor stereocontrol appears to contradict the clean inversion of configuration at the carbenoid-carbon required by concerted 1,2-rearrangement of the intermediate **47** (Scheme 1.11). However, mechanistic studies have established that interconversion of the (*E*)- and (*Z*)-alkenyl carbenoids occurs at a rate comparable with insertion into the organozirconocene chloride and is responsible for the loss of stereochemistry.

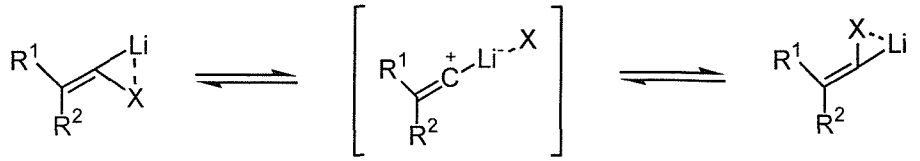
Scheme 1.12 Insertion of 2,2-disubstituted alkenyl carbenoids into organozirconocene chlorides.



50 (*E*) or (*Z*) **51**

Similar loss of stereochemical integrity of 2,2-disubstituted-1-halo-1-lithioalkenes generated by deprotonation of the corresponding alkenyl halides has been described and attributed to 'metal-assisted ionisation' (Scheme 1.13)[46-48]. Theoretical calculations show that the ground state structure of alkenyl carbenoids is best represented as **52**, and isomerisation to **54** *via* the intermediate **53** has a relatively low activation energy. β-Alkyl substituents should favour formation of the intermediate **53** both by inductive electron donation, and by relief of steric strain. As described below β-monosubstituted alkenyl carbenoids do not isomerise at a significant rate relative to trapping by organozirconocenes.

Scheme 1.13 Metal assisted ionisation.

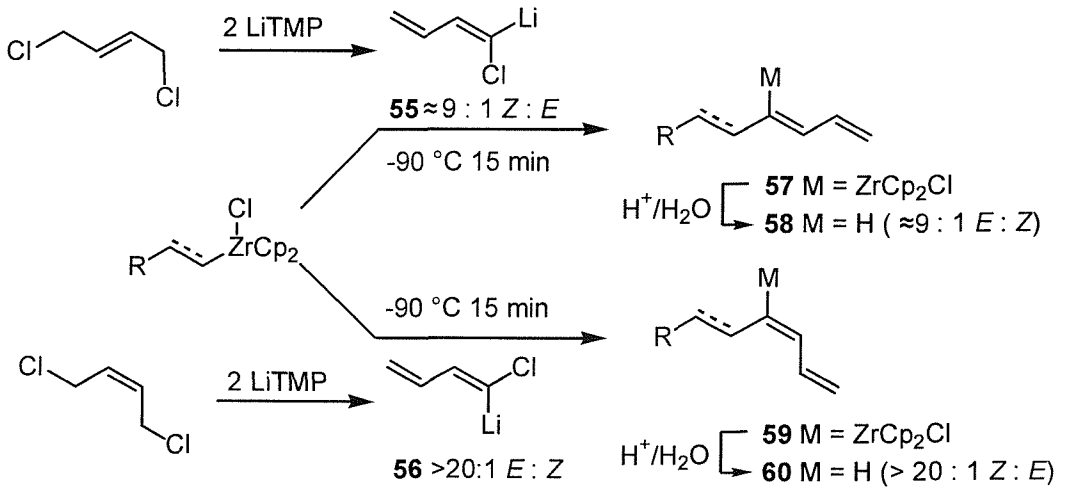


52 **53** **54**

1.3.1.2 Insertion of 1-Chloro-1-Lithio-2-Monosubstituted Alkenes.

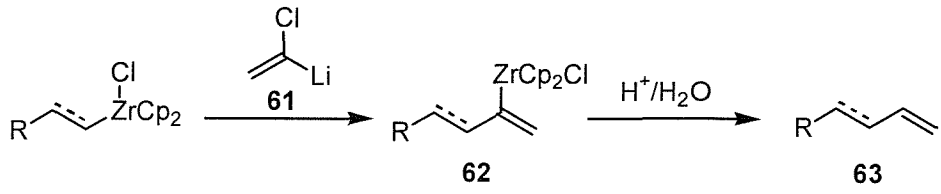
Unlike the insertion of 2,2-disubstituted alkenyl carbenoids, the insertion of 2-monosubstituted alkenyl carbenoids is found to be stereospecific in accordance with Scheme 1.11 (R^2 or R^3 = H)[45]. The carbenoids (*Z*)- or (*E*)-1-chloro-1-lithio-1,3-butadiene (**55** and **56**) may be generated *in situ* from (*E*)- or (*Z*)-1,4-dichloro-2-butene respectively, by elimination of hydrogen chloride followed by α-deprotonation of the alkenyl halide so formed using two equivalents of lithium 2,2,6,6-tetramethylpiperidide (LiTMP) (Scheme 1.14). Inversion of configuration at the carbenoid carbon during 1,2-metallate rearrangement stereospecifically yields the organozirconocenes **57** and **59**[49]. Protonation affords terminal conjugated (*E*)- or (*Z*)- dienes, or (*E*,*E*) and (*E*,*Z*)-trienes **58** and **60** in a single pot from terminal alkenes or alkynes respectively. The carbenoid derived double bond is formed as ≈ 9:1 *E*:*Z* and >20:1 *Z*:*E* isomers respectively, this being determined by the initial elimination of hydrogen chloride from the starting (*E*)- or (*Z*)-1,4-dichloro-2-butenes.

Scheme 1.14 Stereospecific insertion of 1,3-butadienyl carbenoids.



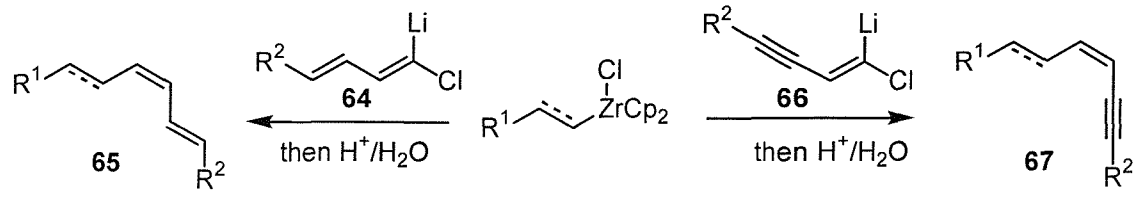
The only other alkenyl carbenoid with a proton *trans* to the halide which may be generated well by deprotonation is the parent 1-lithio-1-chloroethene **61** (Scheme 1.15)[50]. Insertion into organozirconocenes derived by hydrozirconation of alkenes and alkynes affords terminal alkenes and (*E*)-dienes **63** respectively following protonation[45]. The latter provides a useful complement to the synthesis of **58** in Scheme 1.14 since stereocontrol is >99%.

Scheme 1.15 Vinyl carbenoid insertion.



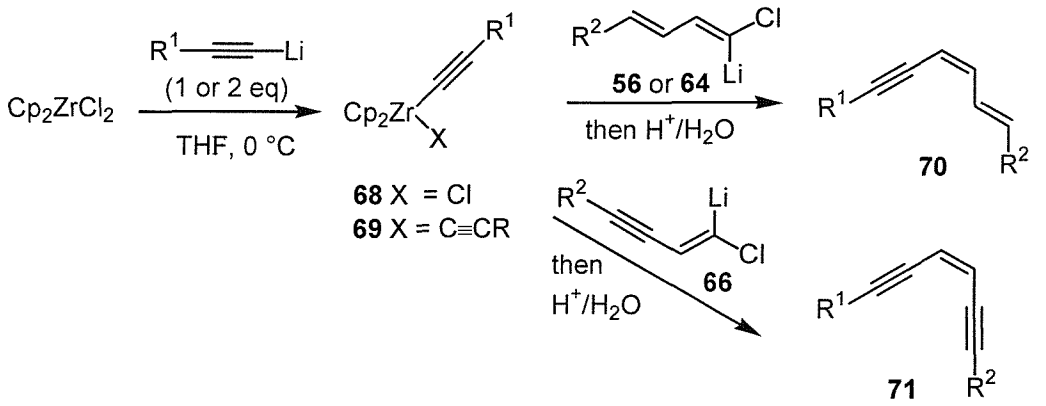
Access to non-terminal (*E*,*Z*)-dienes and (*E*,*Z*,*E*)-trienes **65** is provided analogously through deprotonation of (*E*,*E*)-4-alkyl-1-chloro-1,3-butadienes followed by insertion of the resultant carbenoid **64** into alkyl- and alkenyl-zirconocene chlorides (Scheme 1.16)[45]. The corresponding internal (*Z*,*Z*)-dienes and (*Z*,*Z*,*E*)-trienes are also readily obtained *via* insertion of β-alkynyl carbenoids **66**[51] into alkyl- and alkenyl-zirconocene chlorides respectively (Scheme 1.16). Reduction of the triple bond moiety in the products **67** to afford the *cis*-alkenes is well known[52-54].

Scheme 1.16 Insertion of 1,3-dienyl- and 1-en-3-ynyl-carbenoids.



To complete the range of geometric isomers of terminal and non-terminal dienes and trienes available, systems nominally derived from inaccessible (*Z*)-alkenylzirconocenes are desirable. Fortunately insertion of the various carbenoids discussed above into mono- or bis-alkynyl zirconocenes **68** and **69** affords dienyne products **70**[45] which are readily reduced to the desired (*E*,*Z*,*Z*)-trienes (Scheme 1.17)[52-54]. Insertion of the β-alkynyl carbenoid **66** allows a convenient access to (*Z*)-enediynes **71**.

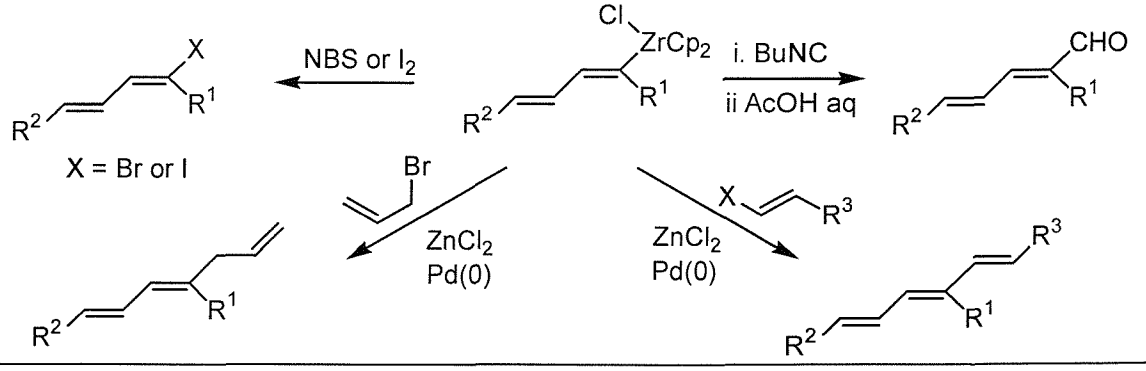
Scheme 1.17 Insertions into alkynylzirconocenes.



1.3.1.3 Further Elaboration of Carbenoid Insertion Products.

A key feature of the elaboration of organozirconocenes by insertion of a carbenoid is that the product retains the carbon-zirconium bond functionality of the substrate. Several useful elaborations are shown in Scheme 1.18, introduced here to illustrate the case of the organozirconium product of insertion of alkenyl carbenoids **56** or **64**[45].

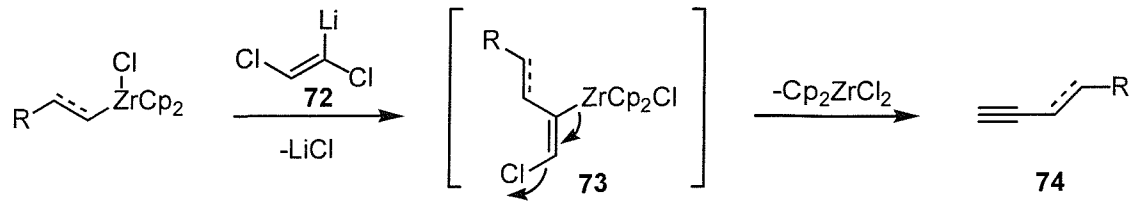
Scheme 1.18 Further elaboration of alkenylzirconocene chlorides.



1.3.1.4 Insertion of 1-Lithio-1,2-Dihaloalkenes into Acyclic Organozirconocene Chlorides.

A useful synthesis of alkynes and particularly terminal (*E*)-enynes results from the insertion of readily formed (*E*)-1,2-dichloro-1-lithioethene (**72**) into organozirconocene chlorides (Scheme 1.19). An intermediate (*E*)-2-chloroalkenyl zirconium species **73** undergoes *anti*-elimination of zirconocene dichloride to yield terminal alkynes **74**[45].

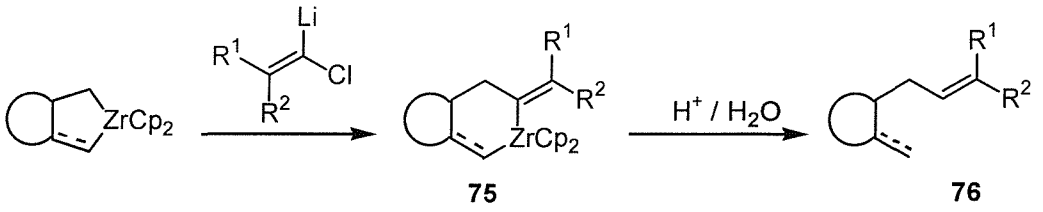
Scheme 1.19 Insertion / elimination of (E)-1,2-dichloro-1-lithioethene.



1.3.2 Insertion of 1-Halo-1-Lithioalkenes into Zirconacycles.

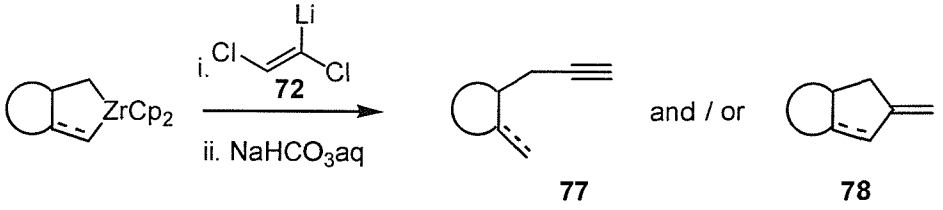
Symmetrical 2,2-disubstituted-1-lithio-1-chloroalkenes mono-insert cleanly and in high yield into zirconacycles to give trisubstituted olefin products following protic work-up of the ring-expanded 6-member zirconacycle (Scheme 1.20, $R^1 = R^2 =$ alkyl)[55]. The insertion of non-symmetrical 2,2-disubstituted alkenyl carbenoids has not yet been reported. A wide range of 2-monosubstituted alkenyl carbenoids (**55**, **56**, **64**,) derived by *in situ* deprotonation of alkenyl chlorides insert successfully into zirconacyclopent-anes and -enes with the expected inversion of the carbenoid carbon[56].

Scheme 1.20 Insertion of alkenyl carbenoids into zirconacycles.



Insertion of (*E*)-1-lithio-1,2-dichloroethene (**72**) into zirconacycles is followed by elimination of Cp_2ZrCl to afford a terminal alkyne **77** and / or the product **78** of further cyclisation (Scheme 1.21)[57]. The alkyne **77** is the sole product with saturated zirconacycles whereas unsaturated zirconacycles give predominantly **78**.

Scheme 1.21 Insertion of (E)-1,2-dichloro-1-lithioethene into zirconacycles.

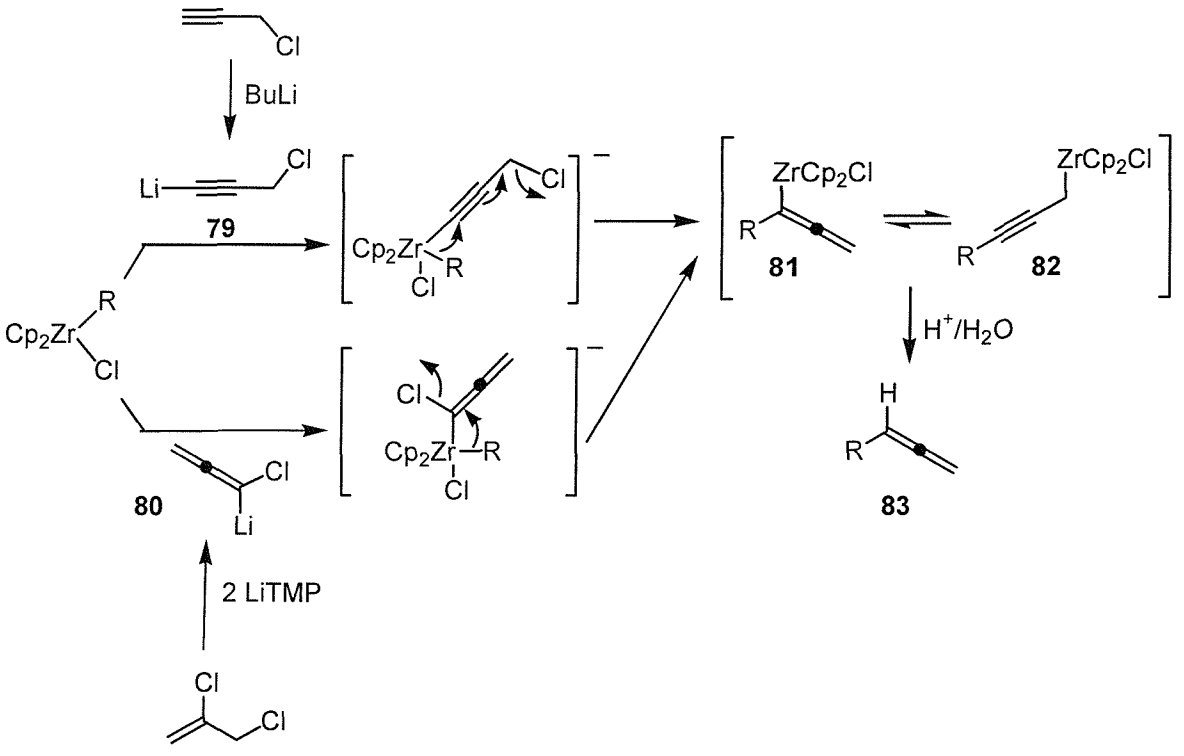


1.3.3 Insertion of Allenyl Carbenoids into Organozirconium Species.

1.3.3.1 Insertions of Allenyl Carbenoids into Acyclic Organozirconocene Chlorides.

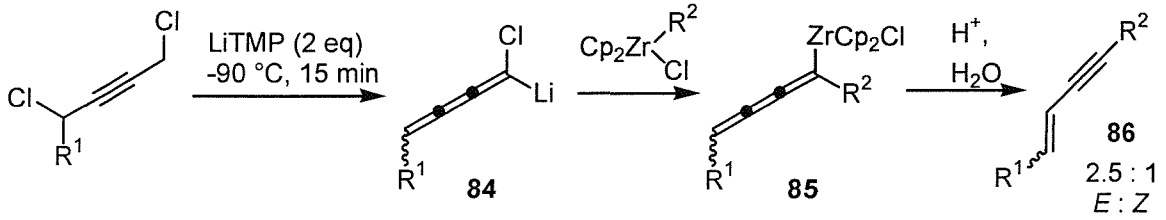
Negishi first observed the insertion of the γ-halo-lithium species **79** obtained by deprotonation of propargyl chloride into octylzirconocene chloride, protonation of the product affording an allene **83** (Scheme 1.22)[44]. The overall effect is insertion of an allenyl carbenoid. The α-halolithium equivalent **80** is conveniently generated by addition of two equivalents of base to 2-chloroallyl chloride[58] and affords the same products. The organometallic product **81** of allenyl carbenoid insertion is either in equilibrium with the propargyl form **82**, or exists as an η^3-allenyl / propargyl species of which **81** and **82** are extreme representations. We would expect **81** / **82** to be reactive towards carbonyl compounds however this has not yet been reported.

Scheme 1.22 Insertion of allenyl carbenoids into organozirconocene chlorides.



A more complex cumulenyl carbenoid **84** may be generated *in situ* from 1,4-dihalo-but-2-ynes and two equivalents of base (Scheme 1.23). Insertion into organozirconocene chlorides gives allenyl zirconium species **85** which protonate regioselectively to afford enyne products **86**[45]. The stereochemistry of the alkene in **86** stems from initial elimination of hydrogen chloride to form **84**.

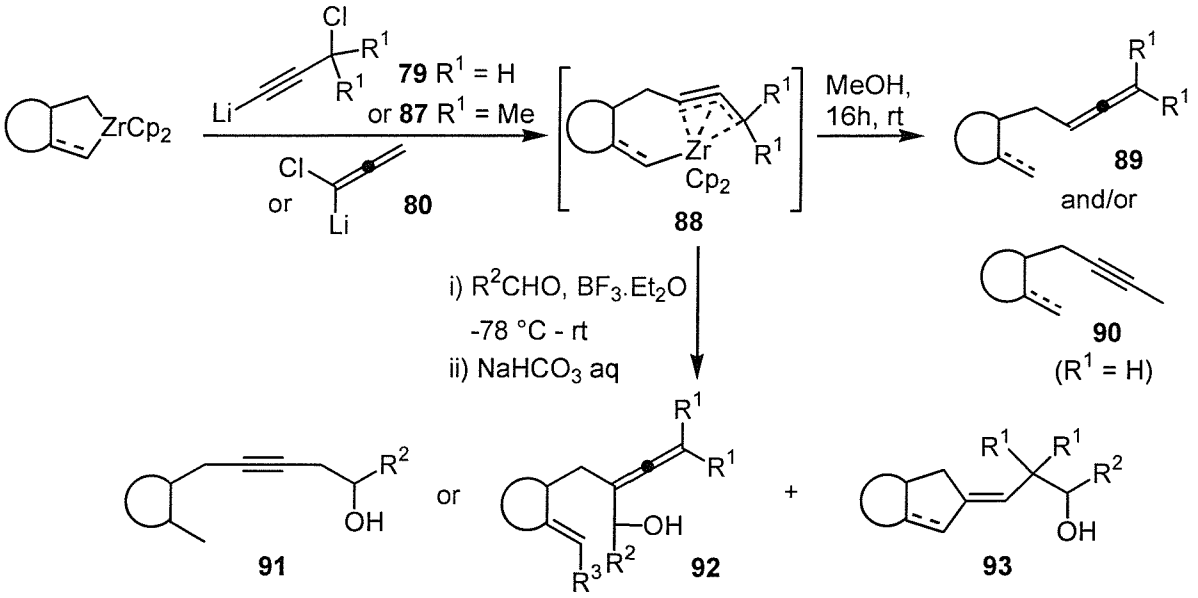
Scheme 1.23 Insertion of 1,2,3-butatrienyl carbenoids into organozirconocene chlorides.



1.3.3.2 Insertions of Allenyl Carbenoids into Zirconacycles.

1-Lithio-3-chloro-1-propyne (**79**), 1-lithio-1-chloroallene (**80**), and 1-lithio-3-methyl-3-chloro-but-1-yne (**87**) insert efficiently into zirconacycles to afford η^3-propargyl/allenyl complexes **88** (Scheme 1.24)[59,60]. Protonation affords the allenes **89** and/or alkynes **90**, the former being exclusive for saturated zirconacycles, or when R^1 = Me. Lewis acid induced addition of aldehydes occurs to give either **91**, from saturated zirconacycles, or **92** from unsaturated. In many cases however, the cyclised compound **93** is formed as the major or exclusive product[60].

Scheme 1.24 Tandem insertion of allenyl carbenoids and electrophiles into zirconacycles.

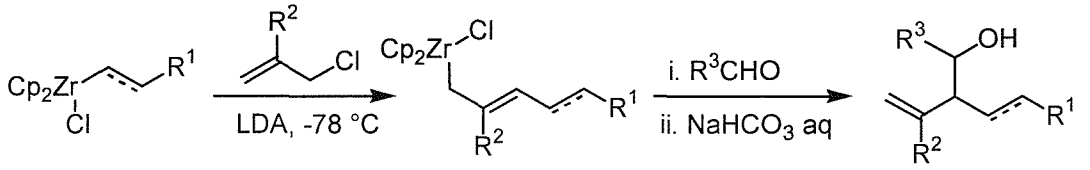


1.3.4 Insertion of Allyl Carbenoids into Organozirconium Species.

1.3.4.1 Insertion of Allyl Carbenoids into Acyclic Organozirconocene Chlorides.

Allyl chlorides are readily deprotonated α to the halide by strong base to give allyl carbenoids which insert into organozirconocene chlorides to afford allyl- or pentadienyl-zirconocene chlorides (Scheme 1.25). These allylmetallic species are reactive towards carbonyl compounds so an efficient three component coupling results[56].

Scheme 1.25 Tandem insertion of allyl carbenoids and aldehydes into organozirconocene chlorides.

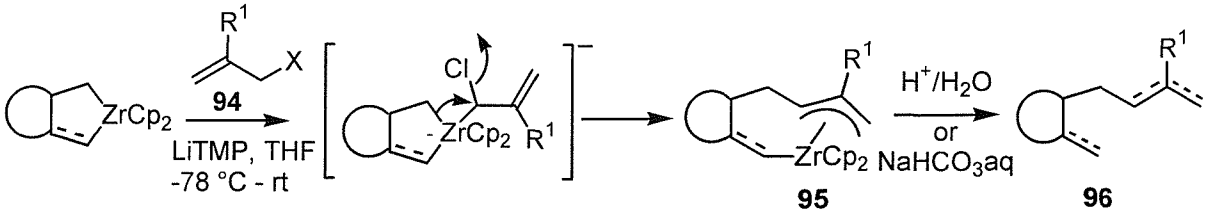


1.3.4.2 Insertion of Allyl Carbenoids into Zirconacycles.

The most extensively studied application of carbenoid insertion into organozirconocene species' is the insertion of allyl carbenoids into zirconacycles and subsequent elaboration of the so formed allylzirconocenes with electrophiles (Schemes 1.26-1.29[55] [59,61-66].

Deprotonation of a variety of allylic systems **94** in the presence of zirconacyclo-pentanes and -pentenes affords η^3-allyl zirconacycles **95** in quantitative yield (Scheme 1.26)[59]. The leaving group (X) on the allyl fragment may be halide, tosylate, or carbamate. Phenoxide or alkoxide give low yields (<25%). When the group X substantially stabilises the carbanion (X = SPh, SO_2Ph, P^+Ph_3) insertion does not occur. The allyl fragment tolerates a variety of substitution at the 2-position (R^1 = Me, CH_2SiMe_3, CH_2Cl, OCH_2OMe)[61]. Protonation affords products **96** as the terminal, internal, or a mixture of both alkene regioisomers depending upon substrate and conditions.

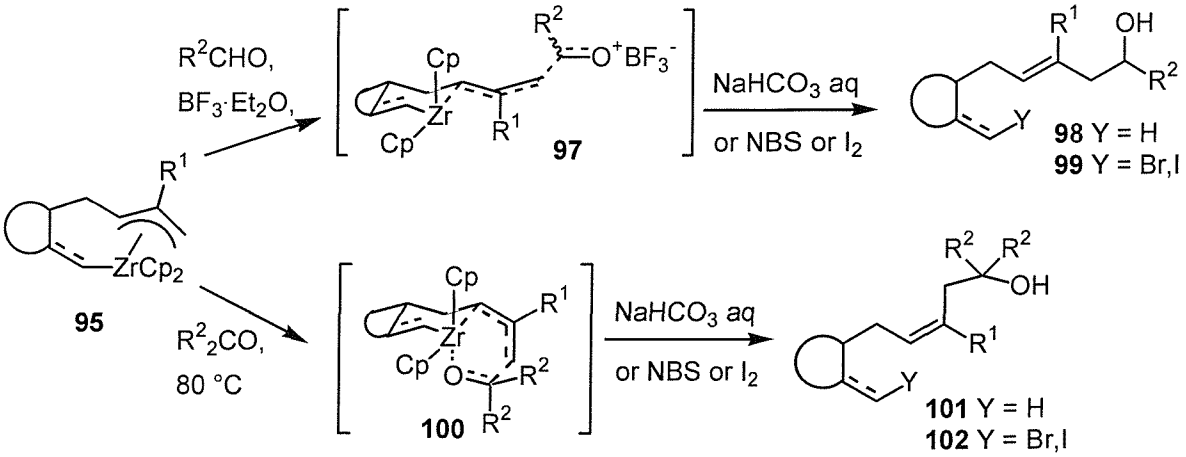
Scheme 1.26 Allyl carbenoid insertion into zirconacycles.



X = Cl, Br, OTs, $OCON^iPr_2$ R^1 = H, CH_3, $CH_2Si(CH_3)_3$, CH_2Cl, OCH_2OMe

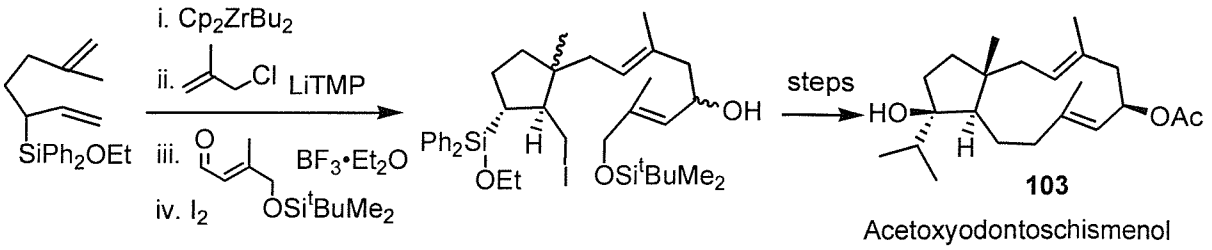
Allyl zirconium species **95** are reactive towards carbonyl compounds to give homoallylic-alcohol products **98** and **101** respectively from aldehydes and ketones in very high overall yield over the four component coupling (Scheme 1.27). The remaining carbon-zirconium bond after addition of the carbonyl component may be halogenated to give **99** or **102**. The addition of aldehydes requires a Lewis acid (BF_3•Et_2O normally works best, but $TiCl_4$ and $SnCl_4$ are also effective). Addition of ketones fails in the presence of BF_3•Et_2O. The remarkable switch in stereochemistry of the formed alkene between addition of aldehyde/BF_3•Et_2O and ketone/Δ may be understood in terms of the transition states **97** and **100**. The Lewis acid mediated addition of aldehydes takes place through an open transition state **97** in which the stereochemistry of the η^3-allyl moiety in **95** is retained in the product alkene. The observed lack of remote diastereocontrol (<3 : 1) between the ring junction stereocentres and the introduced hydroxy group is also accounted for. Geometry about the double bond in **101** results from allylzirconocene reaction with ketones *via* a postulated *cis*-decalin type transition state **100**. It is significant that *cis*-decalins become more stable than *trans*-decalins when the bonds to a bridgehead atom become long[67].

Scheme 1.27 Tandem insertion of allyl carbenoids and electrophiles into zirconacycles.



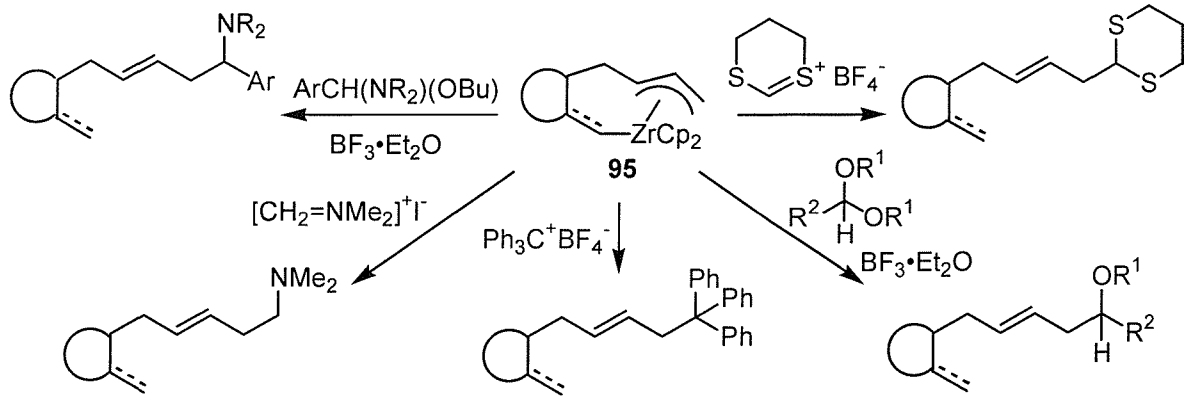
The tandem zirconocene induced co-cyclisation of dienes or enynes / insertion of allyl carbenoid / addition of electrophile is a powerful method for assembling organic structures. An elegant illustration of its application is synthesis of the dollabelane natural product acetoxyodontoschismenol **103** (Scheme 1.28)[63,68,69].

Scheme 1.28 Application of tandem insertion to synthesis of acetoxyodontoschismenol.



A variety of other powerful electrophiles add to the allylzirconium species **95** as shown in Scheme 1.29. These include the Lewis acid catalysed addition of aryl, alkyl or allyl acetals, derived from aldehydes, but not from ketones, and iminium species which lack β-hydrogens[62,64].

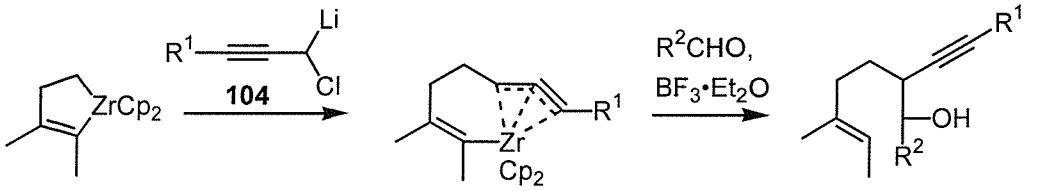
Scheme 1.29 Insertion of electrophiles into cyclic allylzirconocenes.



1.3.5 Insertion of Propargyl Carbenoids into Zirconacycles.

Closely related to both allyl carbenoids, and allenyl carbenoids discussed above, propargyl carbenoids **104** are readily generated *in situ* and insert into zirconacycles to afford species **105** (Scheme 1.30) closely related to **88** derived from allenyl carbenoids (Scheme 1.24)[70]. Protonation affords a mixture of allene and alkyne products, but the Lewis acid assisted addition of aldehydes is regioselective to afford the homopropargylic alcohol products **106** in high yield. Bicyclic zirconacyclopentenes react similarly, there is little diastereocontrol from the ring junction to newly formed stereocentres however. The η^3-propargyl complexes derived from saturated zirconacycles are inert towards aldehyde addition.

Scheme 1.30 Insertion of propargyl carbenoids into zirconacycles.

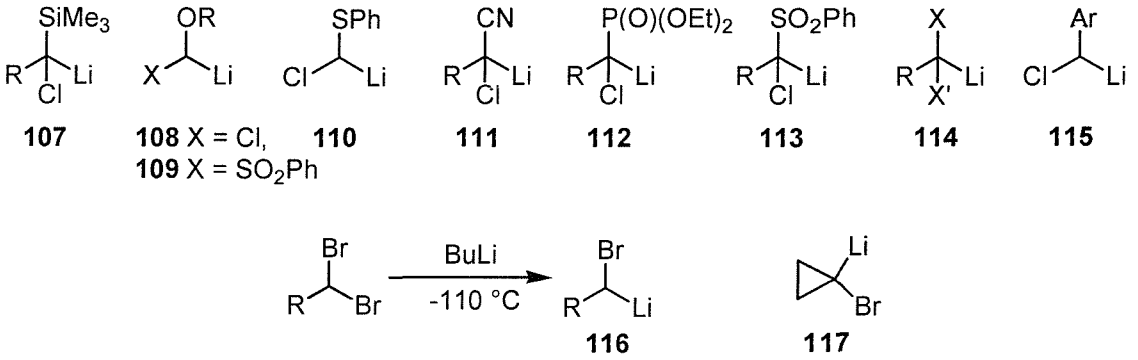


105 106

1.3.6 Insertion of α-Substituted Alkyl Carbenoids into Organozirconium Species.

A wide variety of alkyl carbenoids, for example **107 - 115** (Figure 1.1) may be generated by deprotonation using a strong base. In the absence of an activating / stabilising group, bromine lithium exchange at low temperatures provides access to **116**, for example, or the more stable special case **117**. Most of these carbenoids insert into both organozirconocene chlorides and zirconacycles. The chemistry has been only sparingly investigated and the account below focuses on the most synthetically useful transformations so far developed.

Figure 1.1 Alkyl carbenoids.



107 **108** X = Cl, **109** X = SO_2Ph **110** **111** **112** **113** **114** **115**

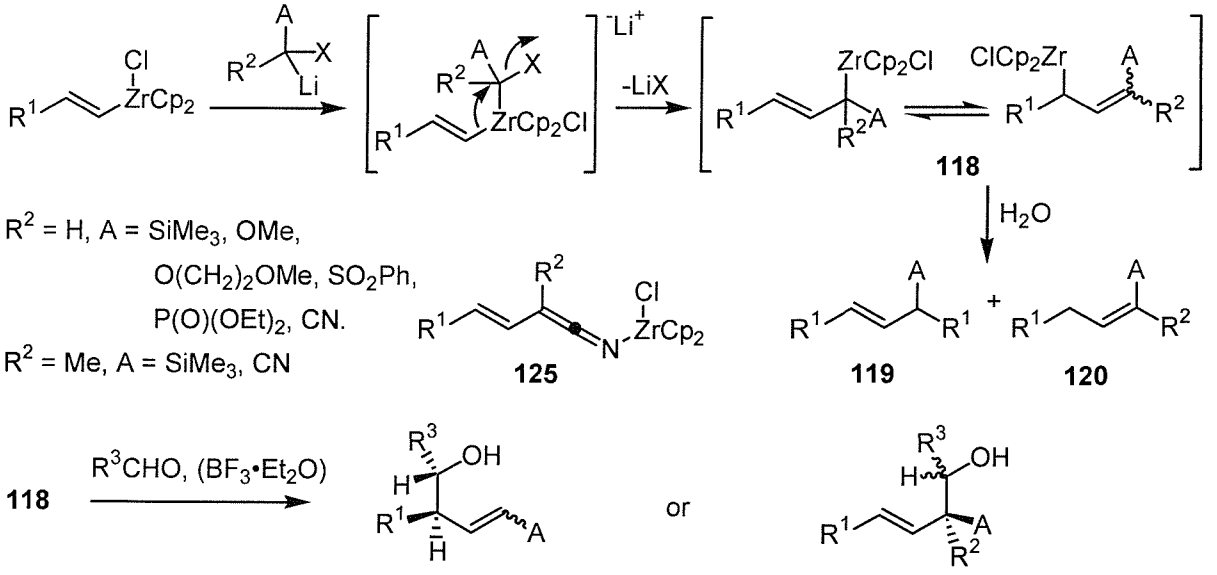
116 **117**

1.3.6.1 Insertions of Alkyl Carbenoids into Acyclic Alkenylzirconocene Chlorides. A Convergent Route to Functionalised Allylzirconocenes.

The high reactivity of allylzirconium species towards electrophiles has been described for cyclic complexes (Section 1.3.3.2). A versatile convergent route to allyl zirconocene reagents **118** has been demonstrated by the insertion of alkyl carbenoids **107-109** and **111-113** into alkenylzirconocenes (Scheme 1.31)[56,71,72]. The allylzirconocene **118** bears some η^3 character, or at least the two η^1-forms are expected to rapidly interconvert, so the ends of the allyl moiety (R^1 c.f. R^2 and A) need to be sufficiently different that good

regioselectivity of electrophile addition may be realised. Hydrolysis yields >95% **119** (c.f. **120**) as the (*E*)-alkene, the only exception being the case A = $SiMe_3$ and R^2 = H which gives around a 1 : 1 *E* : *Z* mixture and also gives 11% of the alkenyl silane product **120**. Addition of aldehydes to allylzirconocenes **118** derived from OR, $SiMe_3$, and CN substituted carbenoids (**107-109** & **111**) gives the adducts **121-124**. In the case A = $SiMe_3$ and R^2 = H the γ-regioisomer **121** is formed with excellent (*E*)-*anti*-selectivity, particularly with the addition of BF_3•Et_2O. When A = $SiMe_3$ and R^2 = Me or Pr the α-adduct **122** is formed, again with excellent (*E*)-*anti*-stereocontrol. When A = OR the *anti*-γ-adduct **123** is formed, but with only around 2 : 1 *E* : *Z* control of the alkene geometry. Surprisingly the addition of BF_3•Et_2O switches the stereochemistry to the (*E*)-*syn* form. With A = CN, R^1 = H or Me the (*E*)-α-adduct **124** is formed, but with no *anti* : *syn* control. The lack of *anti* : *syn* control, and the exclusive formation of α-adducts may be due to the nitrile-substituted allylzirconocene existing in the nitrogen-bound form **125**. The sulphonate and phosphonate substituted allyl zirconocenes **118** (A = SO_2Ph, $P(O)(OEt)_2$) do not react cleanly with aldehydes.

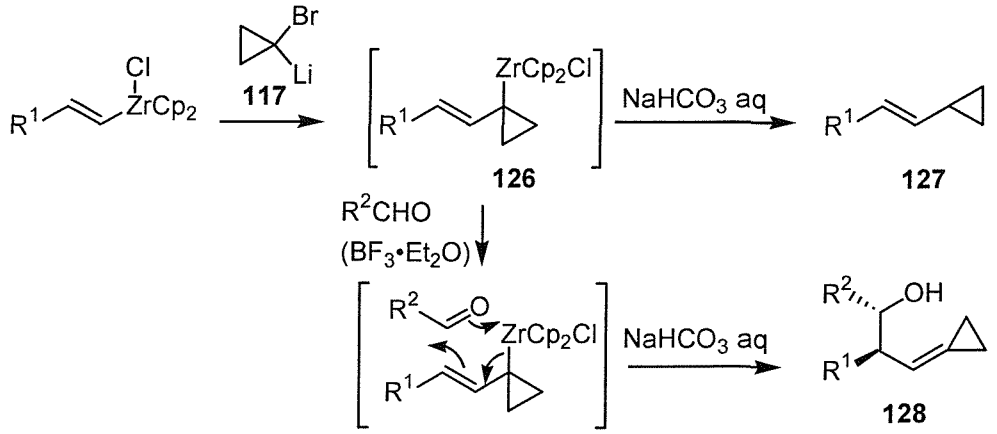
Scheme 1.31 Convergent synthesis and elaboration of functionalised allylzirconocenes.



Insertion of alkyl carbenoids into alkenylzirconocenes is not a generally useful route to allylzirconocenes because the two ends of the allyl fragment are not sufficiently differentiated to give good regiocontrol on reaction with electrophiles. An exception is the insertion of the cyclopropyl carbenoids **117** where zirconium is localised on the cyclopropyl carbon in the so formed allylzirconocene **126** (Scheme 1.32). Protonation

provides a useful route to alkenylcyclopropanes **127**, and reaction with aldehydes affords alkylidenecyclopropanes **128**[56]. Alkenylcyclopropanes and alkylidenecyclopropanes are valuable intermediates in organic synthesis.

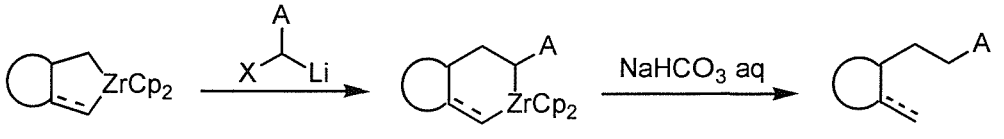
Scheme 1.32 Synthesis of alkenyl- and alkylidene-cyclopropanes.



1.3.6.2 Insertions of Alkyl Carbenoids into Zirconacycles.

Many alkyl carbenoids insert into saturated and unsaturated zirconacycles to afford zirconacyclohex-anes and -enes **129** which give the expected products **130** on hydrolysis (Scheme 1.33)[55 56,73]. There should be comparable scope for further elaboration of the 6-member zirconacycles as has already been established for the 5-member analogues. Yields are generally high in the insertion, one exception being the insertion of lithiated chloroacetonitrile into saturated zirconacycles where double insertion predominates[56].

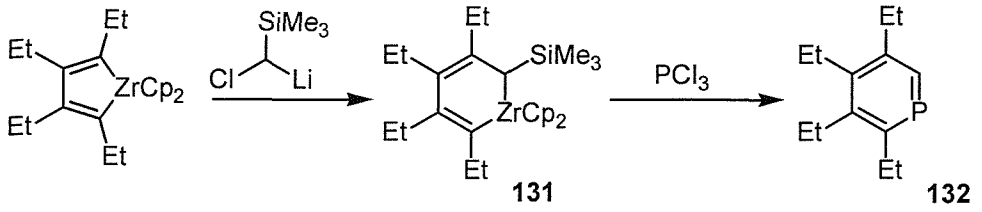
Scheme 1.33 Ring expansion of zirconacycles with alkyl carbenoids.



Lithiated chloromethyltrimethylsilane is a remarkably stable carbenoid[74] and shows exceptional reactivity for insertions into the alkenyl-zirconium bond of unsaturated zirconacycles. Of the carbenoids tried, only it will insert into zirconacyclopentadienes which are substituted α to zirconium (Scheme 1.34)[75,76]. The so formed

zirconacyclohexadienes **131** are valuable precursors of heteroaromatic compounds such as phosphinines (phosphabenzenes) **132**[76].

Scheme 1.34 Synthesis of phosphines.

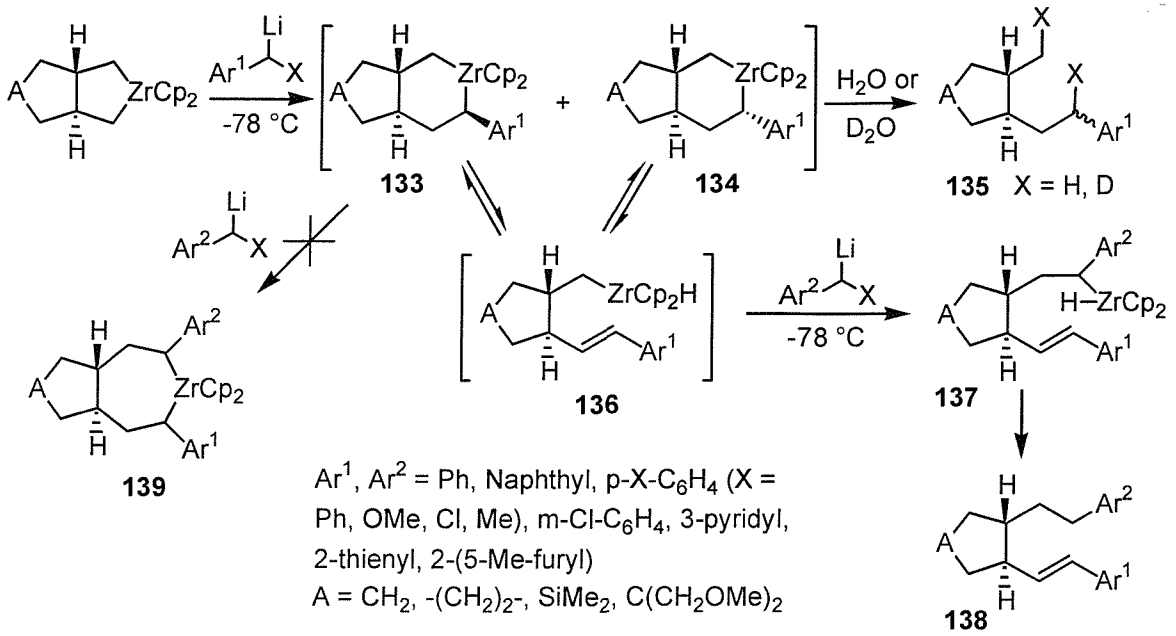


131 **132**

1.3.6.3 Insertion of Benzyl Carbenoids into Zirconacycles.

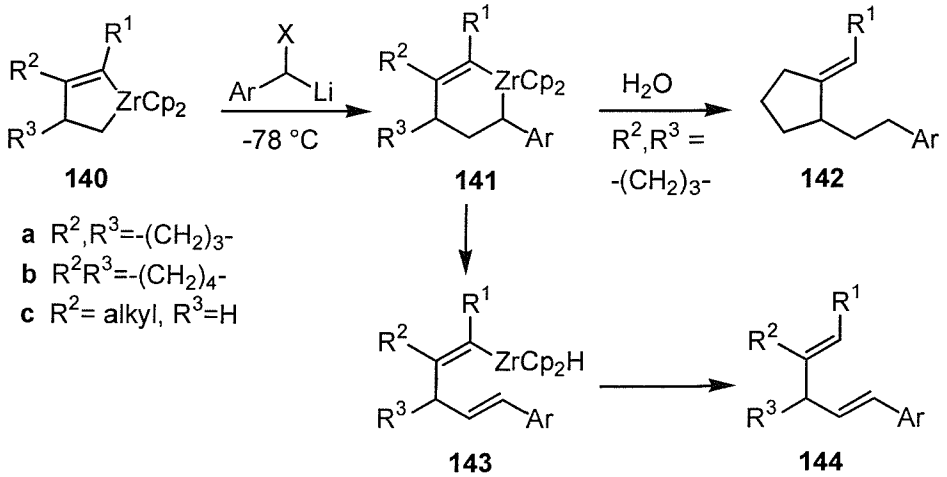
A wide range of benzyl chlorides are readily metalated using lithium diisopropylamide (LDA)[77-80] and insertion of the so formed carbenoids into zirconacycles is mechanistically interesting[73]. Insertion into saturated bicyclic zirconacycles gives initially a 1:1 mixture of the diastereoisomeric zirconacyclohexanes **133** and **134** as would be expected for the stereospecific insertion of a racemic carbenoid into a racemic zirconacycle (Scheme 1.35). However, after several hours at room temperature or a few minutes at 60°C, complete isomerisation into the more stable diastereoisomer **133** is observed. Quenching with water or D_2O gives the expected products **135**. Yields are high and a wide range of aromatic- and heteroaromatic groups are tolerated, an exception being electron poor systems such as *p*-nitrobenzyl chloride. A possible mechanism for the isomerisation of **134** into **133** is *via* the zirconium hydride **136** formed by a reversible β-hydrogen transfer to the metal. Strong evidence for the intermediacy of **136** comes from the insertion of a second benzyl carbenoid to afford **138** where the regiochemistry of the alkene is defined. If the second insertion occurred *via* the zirconacycloheptane **139** a mixture of regioisomeric alkenes would be expected. Presumably the zirconium centre in **136** is sufficiently less sterically hindered than in **133/134** such that it is selectively trapped by the carbenoid despite its low concentration (below detection limits of NMR). It is notable that aqueous work-up is unnecessary in the formation of **138**; and indeed work-up with deuterium oxide gives no deuterium incorporation.

Scheme 1.35 *Mono-* and *bis*-insertion of benzyl carbenoids into zirconacycles.



Insertion of benzyl carbenoids into zirconacyclopentenes follows a different, but mechanistically related path (Scheme 1.36). When the zirconacyclopentene is fused to a five-membered ring (**140a**) zirconacyclohexenes **141** are formed as a 1:1 mixture of diastereoisomers. The ratio of diastereoisomers does not change on prolonged storage or heating, implying that there is no equilibrium with the zirconocene hydride species **143**. Hydrolysis gives the expected product **142** in high yield. In comparison, monocyclic zirconacyclopentenes **140c** and those fused to a six-membered ring (**140b**) directly form the products **144** of β-hydride transfer in high yield, presumably *via* **143**. Possibly the constraint of the fused five-membered ring in **141a** prevents the β-hydride transfer.

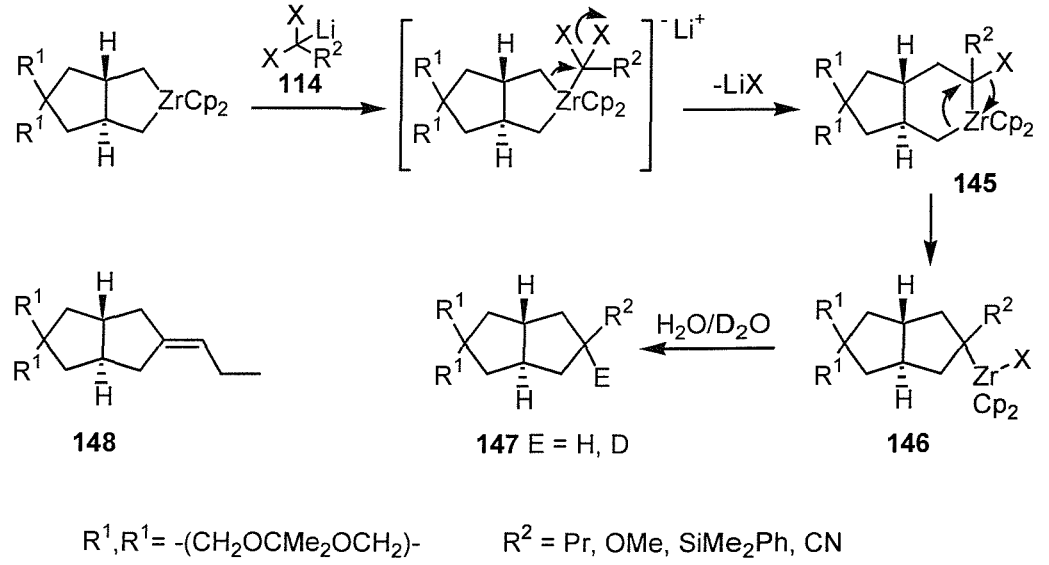
Scheme 1.36 Insertion of benzyl carbenoids into unsaturated zirconacycles.



1.3.6.4 Insertion of 1-Halo-Substituted Carbenoids into Zirconacycles.

α,α-Dihalolithium species **114** are readily formed by *in situ* deprotonation of 1,1-dihalides with LDA and insert efficiently into zirconacycles. The initially formed zirconacyclohexanes **145** further rearrange to form cyclopentanes **146** (Scheme 1.37). The rearrangement of **145** to **146** is analogous to the rearrangement of **32** to **34** during carbonylation (Scheme 1.9). Quench of **146** with water or deuterium oxide affords the expected products **147**[81]. When the carbenoid substituent R^2 bears protons β to zirconium in **146** warming to room temperature before quenching affords an alkylidenecyclopentane (for example **148**) in high yield. Insertion of α,α-dihalolithium species **114** into zirconacyclopentenes occurs similarly, but the analogous intermediate to **146** is an allylzirconium and quenches with little regioselectivity.

Scheme 1.37 Insertion/cyclisation of halocarbenoids into zirconacycles.

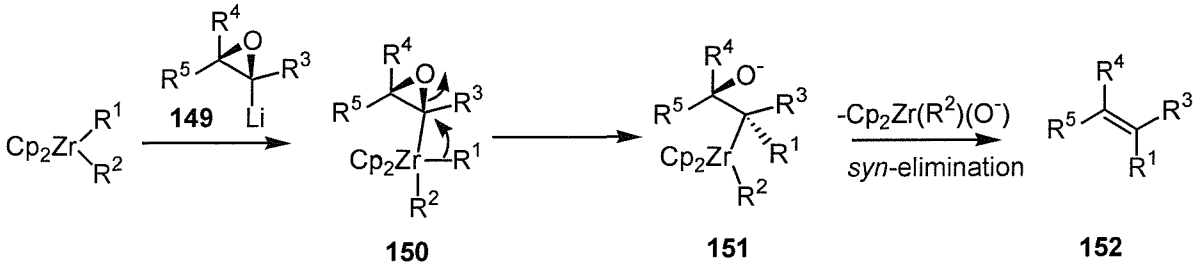


1.3.7 Insertion of Metalated Epoxides into Organozirconium Species.

Metalated epoxides **149**[82,83] have been used as nucleophiles but more commonly are implied intermediates in the formation of carbenes. A stabilising aryl, alkenyl, alkynyl, nitrile or silyl group R^3 (Scheme 1.38) is required for formation by deprotonation[84-88], although unstabilised systems may be generated by tin/lithium exchange[89]. Insertion of metalated epoxides into organozirconocenes *via* 1,2-rearrangement of an 'ate' complex **150** is expected to give the β-alkoxyzirconocene species **151** which may undergo stereospecific *syn*-elimination to afford an alkene **152**. The overall process is

complementary to the insertion of alkenyl carbenoids described in Sections 1.3.1 and 1.3.2.

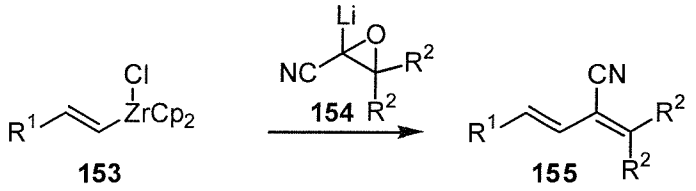
Scheme 1.38 Insertion of metalated epoxides into organozirconocenes.



1.3.7.1 Insertion of 1-Cyano-1-Lithio Epoxides into Acyclic Organozirconocene Chlorides.

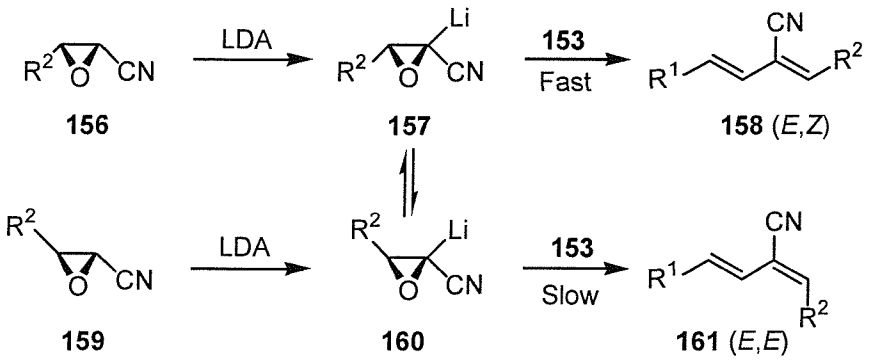
Although a range of metalated epoxides insert efficiently into acyclic organozirconocenes, only the insertion of lithiated epoxynitriles into alkenylzirconocenes has been properly investigated[90]. A single product **155** is formed from symmetrically β,β-disubstituted lithiated epoxynitriles **154** (Scheme 1.39).

Scheme 1.39 Insertion of β,β-disubstituted lithiated epoxynitriles.



Insertion of the lithiated epoxides formed by deprotonation of stereodefined (*E*)- and (*Z*)-mono-β-substituted epoxynitriles **156** and **159** is not stereospecific however. The (*Z*)-epoxides **156** give around a 9:1 mixture of **158**:**161** whereas the (*E*)-epoxides **159** give 1:1 mixtures. The case **159** (R^2 = Ph) gives an 8:1 mixture of **158**:**161** however. The lack of stereospecificity is due to configurational instability of the lithiated epoxynitriles, combined with preferential trapping of the (*Z*)-lithioepoxide **157** (Scheme 1.40)[90].

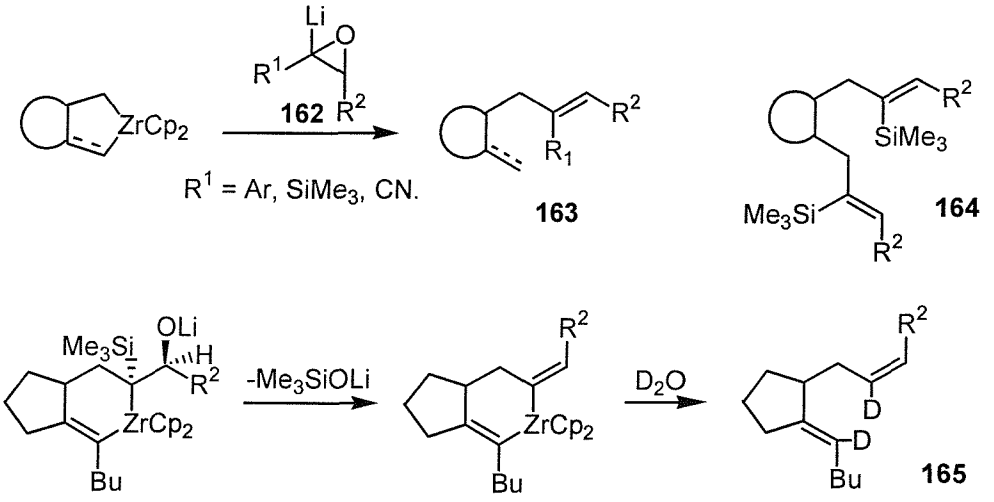
Scheme 1.40 Insertion and isomerisation of β-monosubstituted lithiated epoxynitriles.



1.3.7.2 Insertion of 1-Silyl-, 1-Cyano and 1-Aryl-1-Lithio Epoxides into Zirconacycles.

Insertion of phenyl, trimethylsilyl, and nitrile-stabilised metalated epoxides into zirconacycles gives the product **163**, generally in good yields (Scheme 1.41). With trimethylsilyl-substituted epoxides the insertion/elimination has been shown to be stereospecific whereas with nitrile-substituted epoxides it is not, presumably due to isomerisation of the lithiated epoxide prior to insertion[91]. With lithiated trimethylsilyl-substituted epoxides, up to 25% of a double insertion product **164** is formed in the reaction with zirconacyclopentanes. Surprisingly the ratio of mono- : bis-inserted products is little affected by the quantity of the carbenoid used. In the case of insertion of trimethylsilyl substituted epoxides into zirconacyclopentenes, no double insertion product is formed but up to 26% of products **165**, derived from elimination of Me_3SiO^-, result.

Scheme 1.41 Insertion of metalated epoxides into zirconacycles.



1.3 Conclusion.

In summary, insertion of carbenoids into metal-carbon bonds to form new organometallics is an as yet little explored but potentially highly valuable transformation. Complementary to well established methods for synthesis of organozirconocenes, the application of carbenoid insertion to the area of zirconium chemistry has been described herein.

The field is young and progress in those areas omitted from the literature to date is addressed in forthcoming Chapters Two-Four.

Chapter Three represents logical progression in development of the field, covering application of methods for known alkyl/alkenyl carbenoid insertion into acyclic organozirconocenes to zirconacycles, elaboration of six-membered zirconacycles, novel carbenoids for introduction of functionality and carbenoids of increased thermal stability. The area of regiochemistry of insertion into non-symmetrical zirconacycles is introduced in Chapter Four.

Application of powerful tandem reaction sequences for iterative carbon-carbon bond formation to organic synthesis is perhaps salient. To this end, Chapter Two now describes the chemistry of novel monocyclic zirconium species, adjunct to their use in natural product targeted synthesis.

Chapter Two : α-Substituted Monocyclic Zirconacyclopentenes; Behaviour in the Tandem Carbenoid / Electophile Addition Protocol and Application to Synthesis.

2.0 Introduction.

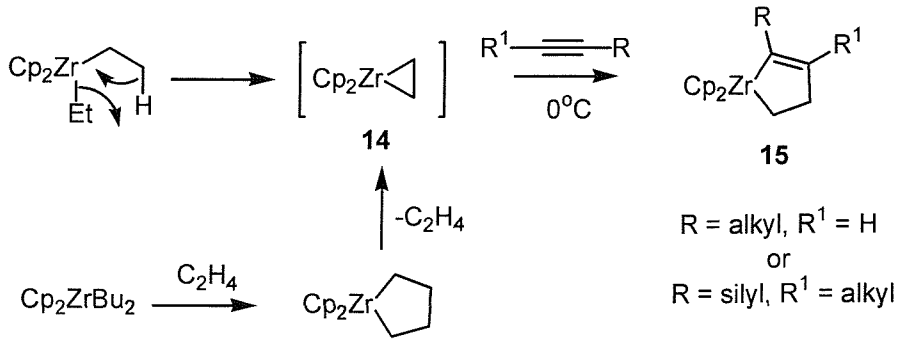
To date, tandem zirconocene–mediated bond formation has not been fully exploited. Total synthesis of the bicyclo[9.3.0]tetradecane (dolabellane) skeleton of Acetoxyodontoschismenol[1-3] exemplifies the potential of this methodology[4,5] (Section 1.3.4.2) and further elegant demonstrations of synthesis based comprehensively upon zirconocene–mediated bond formation remain desirable. To this end the following chapter describes novel work towards such concise synthesis, preceded by a brief overview of necessary zirconacyclopentene chemistry (Section 2.0.1) and an introduction to targeted linear terpenoids (Section 2.0.2).

2.0.1 Scope of Zirconacyclopentene Synthesis and Functionalisation.

Formation of monocyclic zirconacyclopentenes *via* intermolecular cross–coupling between alkynes and a zirconocene-alkene complex[6-9] is now well documented[10,11] and a body of research examining the regioselectivity of zirconacyclopentene functionalisation has arisen[5,12-17].

Substitution of the zirconacycle α to zirconium upon the alkenyl side is reliant upon controlled regioselectivity of coupling for a non-symmetrical alkyne with Cp_2ZrEt_2. Buchwald has carried out regiochemical studies upon zirconacyclopentadiene systems[18], the results of which apply also to the closely related zirconacyclopentenes, and found selectivity only in coupling of terminal alkynes or silyl-substituted alkynes. In the former case then cyclisation occurs such that hydrogen is in the β-position of the zirconacyclopentene **15** (R^1 = H) whilst in the latter, the silyl substituent is α to zirconium (R = $SiMe_3$, Scheme 2.1). It is notable that yield in the coupling of silyl-substituted alkynes with zirconocene-ethene (**14**) is significantly improved when **14** is derived from Cp_2ZrBu_2 and ethene gas rather than Cp_2ZrEt_2[11].

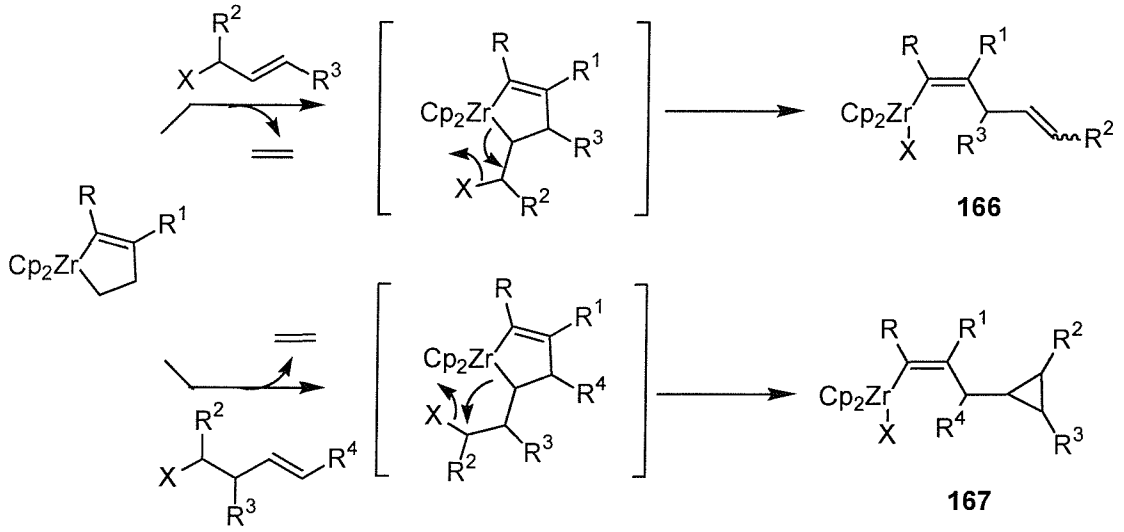
Scheme 2.1 Zirconacyclopentene synthesis.



Explanation of the observed regiocontrol may involve an electronic factor, as trialkylsilyl groups stabilise an α carbanion[19], and could also depend upon the relative rate of cyclisation leading to each of the two possible regioisomers. A steric constraint upon more bulky substituents in the β position, possibly more hindered than the α position in intramolecular co-cyclisation, probably does not influence this intermolecular system. Cyclisation of other asymmetrical internal alkynes ($R \neq R^1 \neq H$) results in regioisomeric mixtures.

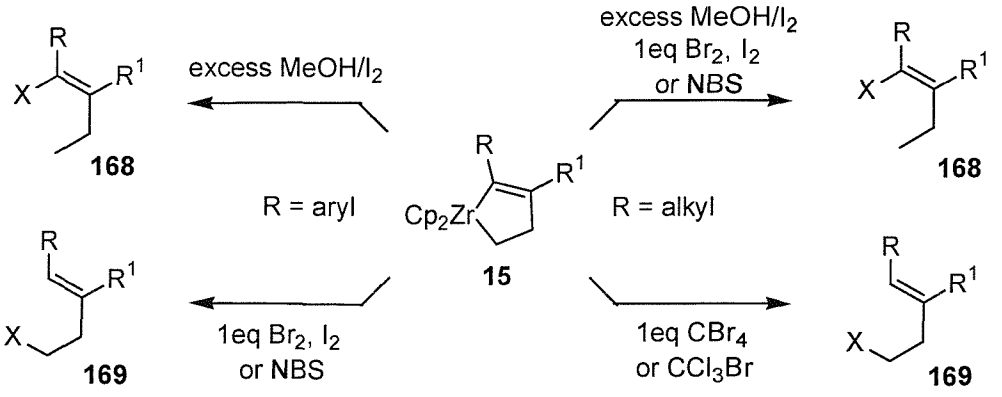
Funtionalisation of zirconacyclopentenes may be carried out in one of two ways; firstly, as introduced in section 1.1.3, thermal displacement of ethene from **15** to yield a Cp_2Zr-alkyne complex then allows coupling with π-donor compounds[20] (Scheme 1.5). Well developed as a means for accessing allyl zirconation products **166** and **167**, and falling into this first category, is the replacement of ethene with allylic/homoallylic halides as π-donors[13,14,21] (Scheme 2.2).

Scheme 2.2 Ethene displacement in zirconacyclopentenes with allylic/homoallylic halides.



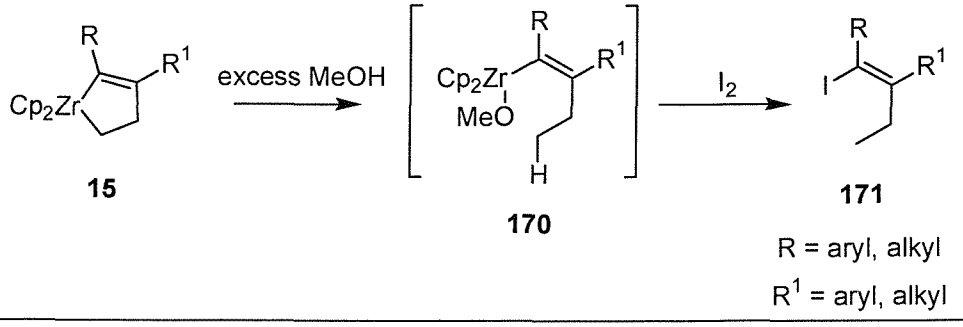
Importantly, the second means for elaboration of zirconacyclopentenes preserves existing carbon-carbon bonds and exploits the different reactivities of the two carbon-zirconium bonds. In this way convergent use of the metal can be maximised and selectivity achieved by functionalisation of either the Zr-sp^{3}carbon or Zr-sp^{2}carbon bond. Monohalogenation provides an excellent illustration of this control[12] (Scheme 2.3).

Scheme 2.3 Zirconacyclopentene monohalogenation.



Iodination with I_2 is substituent dependent for zirconacyclopentenes α-substituted upon the alkenyl side. α-Aryl substituents direct iodination to the sp^{3}carbon-Zr bond yielding **169** whilst the α-alkyl substituted case gives selective iodination of the sp^{2}carbon-Zr bond to give **168**. Substituent independent monoiodination may be achieved by treatment with an excess of methanol followed by I_2, selective monoprotonation of the more basic sp^{3}carbon yields only the alkenyl iodide **171** *via* **170** (Scheme 2.4).

Scheme 2.4 sp^{2}C-Zr bond iodination of zirconacyclopentenes.



Scheme 2.3 also depicts reagent dependent control. Treatment of **15** with CBr_4 or CCl_3Br gives selective bromination of the sp^{3}C-Zr bond whilst use of *N*-bromosuccinimide or Br_2 results in the alkenyl bromide following hydrolysis. Mixed dihalogenation therefore becomes possible .

Fused zirconacyclopentenes (both bicyclic and tricyclic systems) have displayed conflicting reactivity for both the alkyl carbon-Zr bond[22] and the alkenyl carbon-Zr side[23] in isonitrile insertion. Isonitrile insertion into the monocycle **15** is, however, highly chemoselective. Both ^{t}BuNC and ^{n}BuNC insert into the sp^{3}C-Zr bond[12] and regioselective addition of trimethyltin chloride occurs similarly[12].

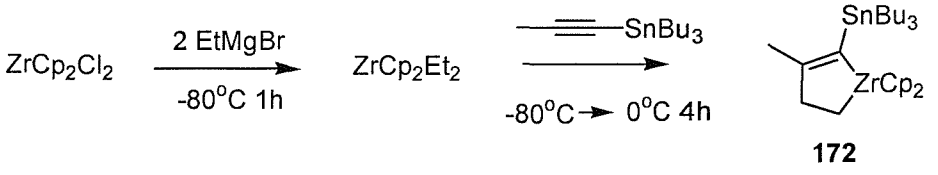
Concluding the known scope for zirconacyclopentene functionalisation are recent examples of carbenoid insertion from the Whitby group, insertion of both allenyl and allyl carbenoids into the alkyl (sp^{3}C-Zr) side of zirconacyclopentenes has been demonstrated[5,16].

Alkenyl substitution, α to zirconium, with groups which may later be subjected to functional group interconversion is problematic with respect to regioselectivity of coupling but will prove crucial in the synthetic work presented in section 2.1.2. It is therefore pertinent to here include known examples for such α-alkenyl substitution.

Livinghouse first demonstrated complexation between a stable zirconocene-DMAP complex and 1-methylthioalkynes to yield sulphide substituted zirconacyclopropenes which were then coupled with carbonyl compounds to yield α-sulphur substituted heterozirconacyclopentenes[24]. Single examples of both zirconocene- and titanocene-mediated cyclisation of sulphur substituted enynes have since been reported[25,26], yielding bicyclic zirconacyclopentenes with α-sulphur groups. The simple monocyclic example **15** (R = thioether) has not yet been communicated.

Finally, synthesis of a tributylstannyl substituted zirconacyclopentene **172** has been previously carried out in the Whitby group[27] (Scheme 2.5).

Scheme 2.5 Synthesis of a tributylstannyl substituted zirconacyclopentene.



172

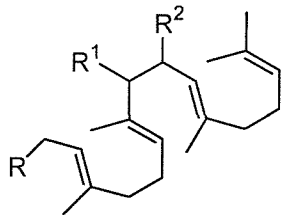
Regioselectivity in the coupling occurs, the β-stannyl regioisomer is not observed, and is predicted based upon the similarity in electronegativity between Sn(IV) and Si(IV) compounds.

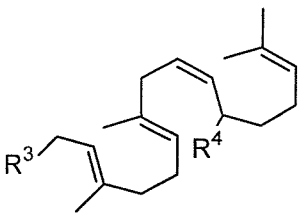
2.0.2 Naturally Occurring Terpenoids of the Families *Sargassaceae, Cystoseiraceae* and *Plexauridae.*

Terpenoids and steroids, under the collective title of isoprenoids derived due to biosynthetic origin of all members of this natural product class from biological equivalents[a] of 2-methylbutadiene or 'isoprene', constitute a family of compounds vast in both number and structural diversity. Many terpenoids are of great interest with the class possessing an array of functions in both the natural world (hormones, pigments, anti-feedants, fragrances, anti-fungals) and by human application (medicines, fragrances, narcotics)[28].

In 1979, Kakisawa *et al* reported isolation of seven diterpenoid (geranylgeranyl) substituted benzoquinones and hydroquinones from the brown marine algae *Sargassum tortile*[29]. Sargatetraol (**173**) alongside two hydroquinone isomers (**174** and **175**), two methylether substituted quinones (**176** and **177**) and two further quinones (**178** and **179**) were characterised by exhaustive NMR analysis. This work precipitated further scrutiny of diterpenoids extracted from *S.tortile* such that compound **180**, analogously acyclic to structures **173-179** but bearing an allylic alcohol moiety in contrast to the quinone group, was subsequently isolated and subjected to resolution of absolute configuration (9-*R*)[30] (Figure 2.1).

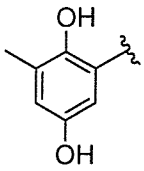
Figure 2.1 Linear diterpenoid products of the marine algae *Sargassum tortile.*



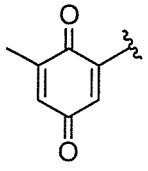


173 R=**Q** R^1=OH R^2=H
174 R=**Q** R^1=H R^2=H
176 R=**Q**^{1} R^1=H R^2=OMe
178 R=**Q**^{1} R^1=OH R^2=OH
179 R=**Q**^{1} R^1=H R^2=H
180 R=OH R^1=H R^2OH
181 R=**Q**^{1} R^1=H R^2=OH

175 R^3=**Q** R^4=OH
177 R^3=**Q**^{1} R^4=OMe



Q



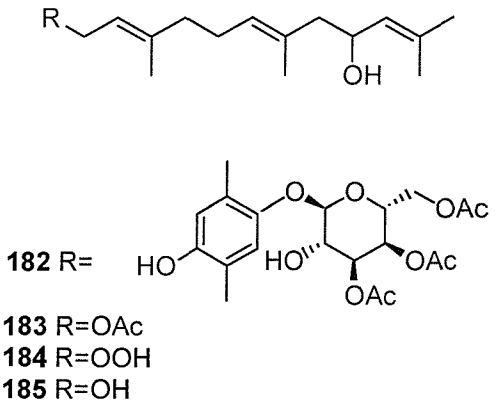
Q^1

[a] Isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP).

Crinitol (**180**) is an insect growth inhibitor which also exhibits antimicrobial activity against gram-negative bacteria, demonstrated by inhibition of growth of *E.coli* at 50μg/mL[30]. Crinitol is so named due to its previous isolation[31], without full deduction of configuration, from the marine algae *Cystoseira crinita*. Correlation of the newly assigned structure with the older isolated product was made by comparison of that spectral data which was known. Subsequently, the 9-hydroxy substituted quinone **181** has been shown to be a further product of *S.tortile*, displaying significant cytotoxicity in the cultured P-388 lymphocytic leukaemia cell assay[32].

Such mixed biogenetic (part polyketide) diterpenes from *Sargassaceae* and *Cystoseiraceae* execute a role in chemical defence against predation which is exemplified however by a sesquiterpene structure, moritoside **182**. Isolated and characterised from the gorgonian[b] *Euplexaura sp.*[33,34], moritoside inhibits cell division in the fertilised star fish egg assay[33]. **182**, together with other euplexides and the plant products 9-hydroxyfarnesyl acetate[35,36] (**183**), 9-hydroxyfarnesoic acid[35] (**184**) and 9-hydroxyfarnesol[35,37] (**185**), constitutes a group of sesquiterpenes of analogous structure to the diterpenes **173** – **181** (Figure 2.2).

Figure 2.2 Linear sesquiterpenes.



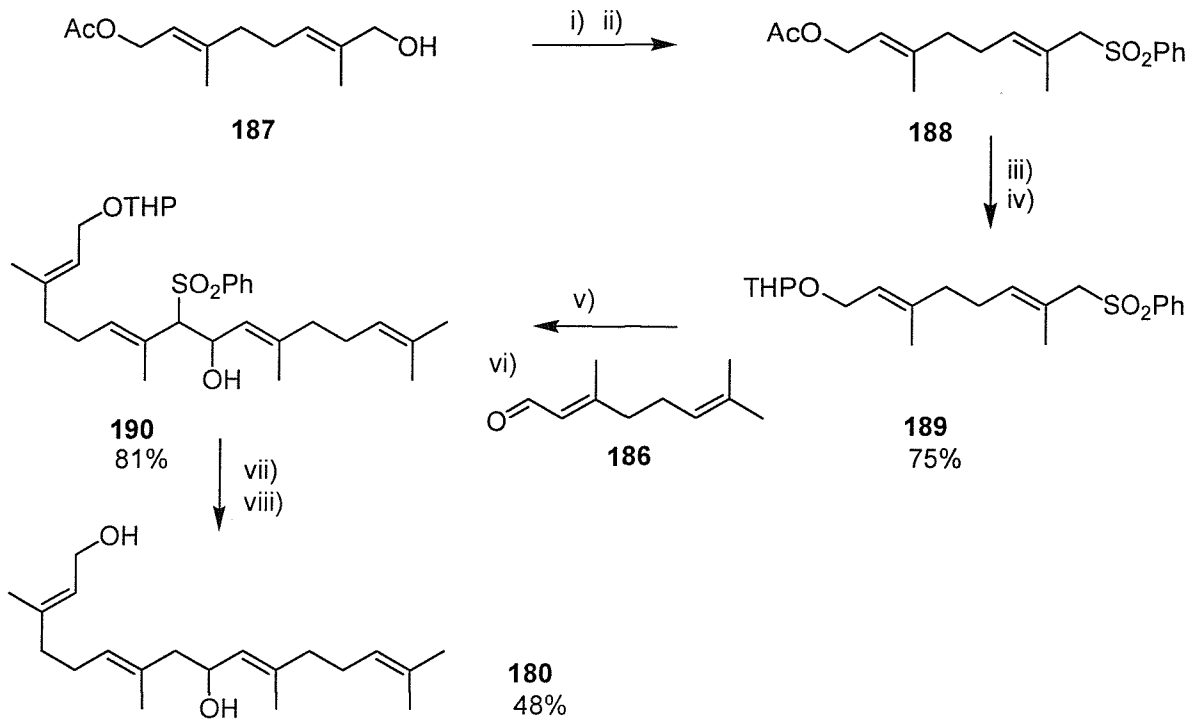
2.1 Synthetic Approaches to Crinitol and Other Natural Terpenoids.

Promptly following first isolation of crinitol but preceding determination of the 9-R configuration, synthesis of the molecule non-stereodefined at C9 was completed by Kato *et al*[38] (Scheme 2.6).

[b] Gorgonians are sea whips and sea fans of Phylum *Cnidaria* and order *Gorgonacea*.

Regioselective α-alkylation of geranial (**186**) with a lithiated benzenesulphonyl derivative precedes hydrolysis of the THP protecting group and subsequent reduction to yield Crinitol, **180**, in an overall yield of 29.2% over eight steps.

Scheme 2.6 Literature reported synthesis of Crinitol.



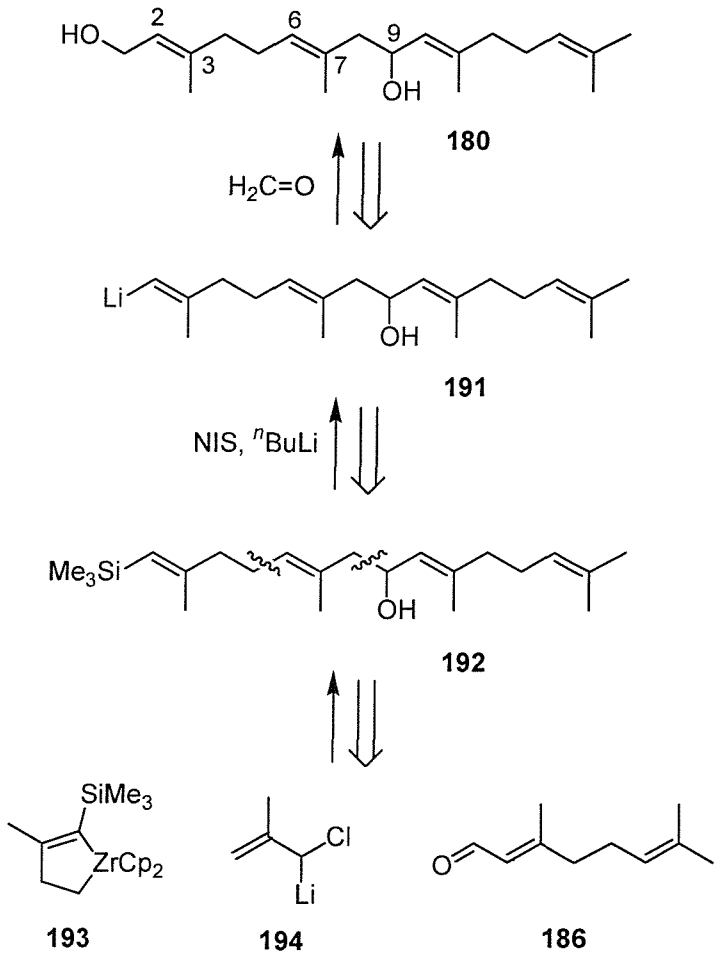
Reagents and Conditions: i) PPh_3, CCl_3, Δ. ii) $PhSO_2Na$, DMF. iii) KOH/MeOH, -20°C. iv) dihydropyran, H^+. v) LDA, THF, -76°C. vi) **186**, -76°C. vii) *p*-TsOH/MeOH. viii) ethylamine, Li, -76°C.

Employing Crinitol also as representative of the targeted group of terpenoids therefore, Scheme 2.7 demonstrates intended application of zirconocene-mediated methodology to its efficient synthesis.

Methallyl carbenoid insertion into the alkyl C-Zr bond of an α-$SiMe_3$ zirconacyclopentene **193** yields an allyl zirconium species precursor to geranial addition which in turn gives rise to the full diterpene core **192** in a single pot. *Trans* geometry about the C2-C3 double bond results from the cocyclisation step and $BF_3{\cdot}Et_2O$ mediated aldehyde addition is also expected to result in *trans* geometry for the C6-C7 double bond (*via* an open transition state **97**, Scheme 1.27, Section 1.3.4.2). C9 remains non-stereodefined at this stage however it is envisaged that this (R)-stereocentre can be set using a chiral Lewis acid to give enantioenduction in the aldehyde addition (Section 2.1.2).

Scheme 2.7 is also relevant for sesquiterpene synthesis by replacement of geranial with 3-methyl-2-butenal.

Scheme 2.7 Retrosynthetic analysis of Crinitol.



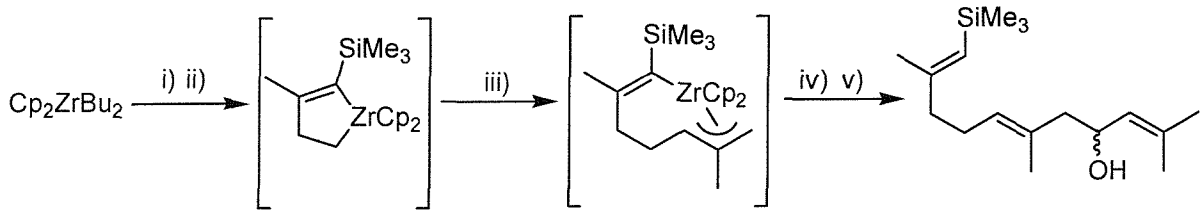
Reason for trialkylsilyl substitution at the α-alkenyl position is two-fold. This group possesses potential for elaboration principally *via* the alkenyl iodide which, specifically in the case of crinitol synthesis, precedes iodine/lithium exchange and then treatment with formaldehyde. The iodide may also be precursor to Pd(0) catalysed couplings with benzylic zinc halides[39] or Pd(0) catalysed carbonylation[40] to access other terpenoids introduced in section 2.0.2.

Secondly and importantly, predictable regioselectivity in the coupling of trialkylsilyl substituted alkynes with Cp_2ZrEt_2 to yield only α-SiR_3 substituted zirconacyclopentenes (Section 2.0.1) removes the potential for isomeric by-products and enhances the expected yield.

2.1.0 Application of α-$SiMe_3$ Substituted Zirconacyclopentenes in Tandem Carbenoid / Aldehyde Addition.

Quantitative, regioselective monocyclisation to form **193** from 1-trimethylsilyl-1-propyne and Cp_2Zr-ethene, derived from Cp_2ZrBu_2 and ethene gas, is known in the work of Takahashi *et al*[11,14,41]. With this precedent **196**, the sesquiterpene analogue of **192**, was targeted according to scheme 2.8.

Scheme 2.8 Synthesis of an alkenylsilane terpenoid precursor.



193 **195** **196**

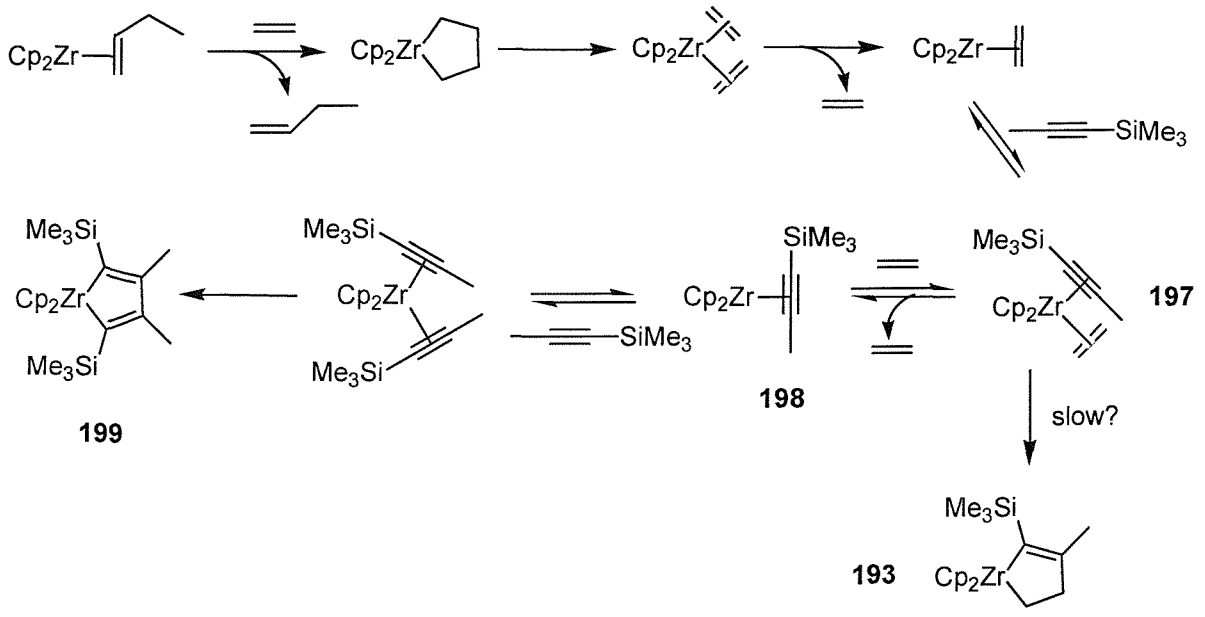
39.3%

Reagents and Conditions: i) ethene gas (excess), -78 °C to rt, 1 h. ii) 1-trimethylsilyl-1-propyne (0.85 eq), rt, 1h. iii) 3-chloro-2-methylpropene, LiTMP, -80 °C to –70 °C, 40 min. iv) 3-methyl-2-butenal (1.7 eq), $BF_3{\cdot}Et_2O$ (1.7 eq), -70 °C to rt, 3 h. v) MeOH, $NaHCO_3$(aq), rt, 16 h.

Ethene cross-coupling with 1-trimethylsilyl-1-propyne was not quantitative as expected but a maximal conversion of 70% observed for this step, up to 30% alkyne dimerisation taking place.

In attempting to optimise this step to a quantitative conversion, it was assumed that cyclisation to both the zirconacyclopentene **193** and zirconacyclopentadiene **199** was irreversible (scheme 2.9). Suppression of the formation of **199** requires that reversible loss of ethene from **197** to give **198** be controlled. Increased pressure of ethene and slow addition of 1-trimethylsilyl-1-propyne to maintain low alkyne concentration, at both room temperature and 35 °C, each failed to suppress formation of **199** however. Takahashi *et al* have reported stability of **197** to loss of ethene even at 50°C for six hours[11,42]. It is consequently surprising to observe the dimer resulting from hydrolysis of **199** here.

Scheme 2.9 α-$SiMe_3$-β-methylzirconacyclopentene synthesis.



GC monitoring of the product ratio (hydrolysis products of **193**:**199**) displayed fluctuation in the yields of the alkene and diene of between 65% and a maximal 75% in the former case and 35-25% for the diene. It is apparent that cross-coupling *via* formation of **197** and cyclisation to **193** is neither rapid upon alkyne addition nor irreversible. Similarly, cyclisation to the zirconacyclopentadiene **199** is also reversible, an equilibrium becoming established between **193** and **199**, *via* intermediate complexes, in which **193** is the major product. Maximal yield of the desired zirconacyclopentene is attained one hour following alkyne addition (as per Takahashi[11]) and, although not quantitative, was accepted in order that the methallyl carbenoid insertion and aldehyde addition be completed.

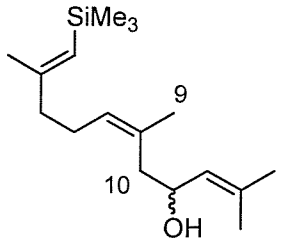
It should be noted that co-cyclisation to give **193** from 1-trimethylsilyl-1-propyne and Cp_2ZrEt_2 (from Cp_2ZrCl_2 and EtMgCl) is high yielding but insertion of the carbenoid fails, presumably due to Mg/Li exchange in the presence of residual MgCl.

Insertion of 1-chloro-1-lithio-2-methylpropene into only the sp^3C-Zr bond of **193** takes place however to yield the allylzirconium species **195** quantitatively in the ethene gas derived system. This is the first example of allyl carbenoid insertion into a monocycle formed from ethene and Cp_2ZrBu_2 rather than Cp_2ZrEt_2.

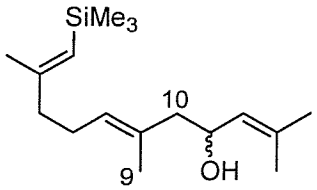
Addition of 3-methyl-2-butenal to **195** in the presence of $BF_3{\cdot}Et_2O$ completes the one-pot sequence in 39.3% overall yield from 1-trimethylsilyl-1-propyne. Surprisingly, two isomers of **196** were obtained and ascertained to be the two geometric isomers about the double bond of the homoallylic moiety. Furthermore, with a ratio of 5:2, the major isomer

is that with *cis* geometry. ^{13}C shifts of alkenyl methyl and methylene carbon atoms C9 and C10 are diagnostic in assigning geometry of the double bond (Table 2.1).

Table 2.1 Comparison of diagnostic ^{13}C NMR data for *cis*(major) and *trans*(minor) isomers of **196.**



cis-**196**



trans-**196**

	δ_C(ppm) major isomer	δ_C(ppm) minor isomer
C9	21.52	16.08
C10	40.37	48.47

^{13}C NMR spectra of the alkenyl silane **196** were recorded in C_6D_6 at 100.5 MHz.

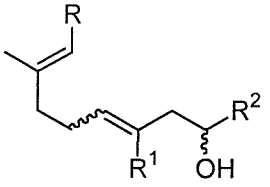
The alkenyl methyl group C9 of *cis*-**196** has a ^{13}C shift characteristically 5.44 ppm downfield of that for C9 of the *trans* isomer whilst the C10 methylene atom in *cis*-**196** shows a ^{13}C shift 8.10 ppm upfield of that for the corresponding C10 atom of *trans*-**196.** The upfield shift of the ^{13}C resonances of atoms *cis* to another alkyl substituent is a manifestation of the γ-gauche effect, more often observed in saturated systems.

No precedent for the formation of a *cis* alkene from aldehyde insertion into allyl zirconium species in the presence of $BF_3{\cdot}Et_2O$ is found in the previous work of Whitby *et al*[5,16,43] and verification of this unexpected result was made by repetition. It is recalled that the usual *trans* geometry resultant from aldehyde/$BF_3{\cdot}Et_2O$ treatment of allyl zirconacycles arises from an open transition state facilitated by co-ordination of BF_3 to the carbonyl group (Scheme 1.27, Section 1.3.4.2). The formation of *cis*-**196** *via* a cyclic *cis*-decalin transition state involving O-Zr co-ordination is difficult to rationalise in the presence of $BF{\cdot}Et_2O$. Use of BCl_3 or Et_2AlCl as the Lewis acid did not affect the *cis*:*trans* ratio and omission of Lewis acid altogether from this step also results in the same E : Z mixture, although in a lower yielding and messy reaction which implicates the Lewis acid in the transition state. This consistency, although limited in scope, is indicative that a structural element is responsible for the unexpected geometry.

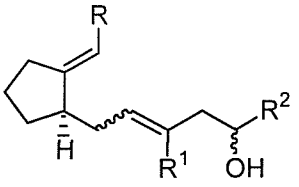
The effect upon the system of alteration to a bicyclic zirconacyclopentene is to favour the *trans* isomer, in a 1:4 ratio where methallyl carbenoid is inserted (**201a**) whilst the simple allyl case yields only the *trans* products (**201b, 201c**) originally anticipated, without trace of the *cis* form (Table 2.2).

It might be generalised that where $R^1 = CH_3$ the *cis* form becomes more favoured but an overriding preference for the *trans* product is observed in the bicyclic system such that now the only manifestation of the presence of the CH_3 group is the observation of *cis*-**201a** as a minor isomer. The presence of the α-trimethylsilyl moiety must effect this as carbenoid insertion (R^1 = H or Me) and subsequent aldehyde addition (R^2 = CH=CHPh, $CH=CH(CH_3)_2$, ^{i}Pr, Ph) into bicyclic zirconacyclopentenes where R = ^{n}butyl is known to yield only *trans* geometry about the double bond[44].

Table 2.2 Alkene geometry arising from aldehyde addition to trimethylsilyl-substituted allyl zirconacycles.



200



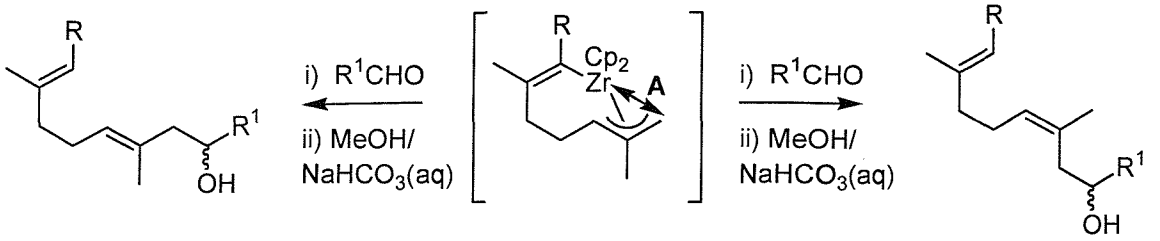
201

	R	R^1	R^2	*cis*:*trans*	d.r [a]
200 / 196	$SiMe_3$	CH_3	$CH=CH(CH_3)_2$	5 : 2	-
201a	$SiMe_3$	CH_3	$CH=CH(CH_3)_2$	1 : 4	1 : 1
201b	$SiMe_3$	H	$CH=CH(CH_3)_2$	*trans* only	1 : 1
201c	$SiMe_3$	H	Ph	*trans* only	1 : 1

[a] Diastereoisomeric ratio.

Hence the methyl group R^1 is implicated, however better understanding of the cause of contrasting double bond geometry in aldehyde addition to a methallyl zirconacycle **202** bearing alkyl versus trimethylsilyl substitution α to zirconium (Scheme 2.10) results from PM3 modelling of the species.

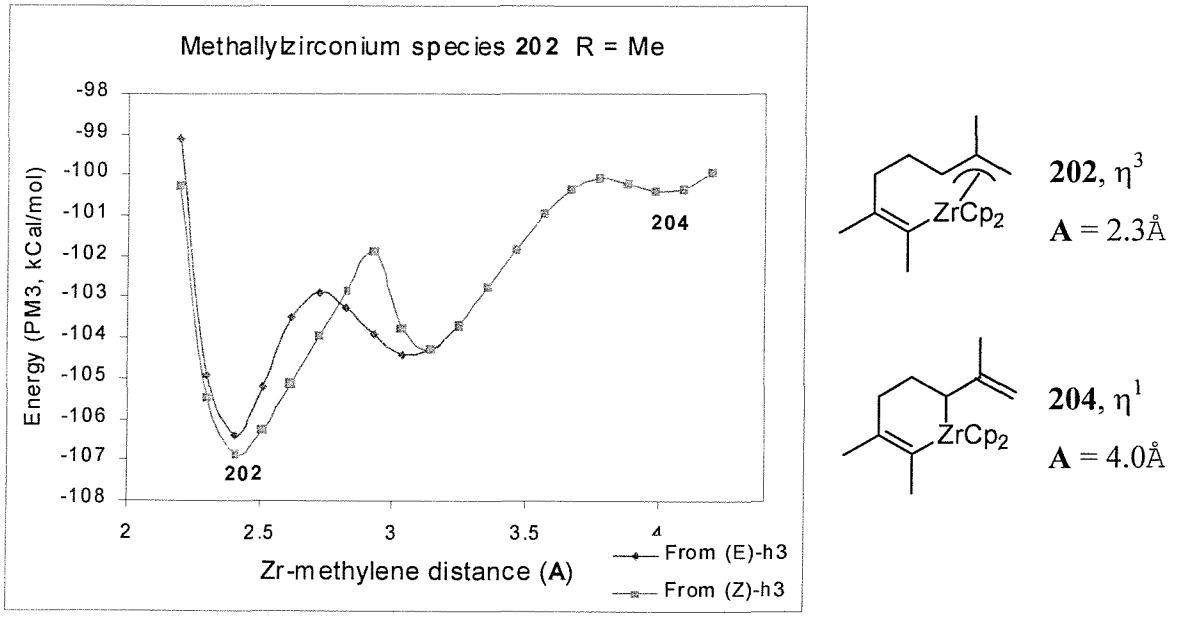
Scheme 2.10 Aldehyde addition to differentially α substituted allyl zirconacycles.

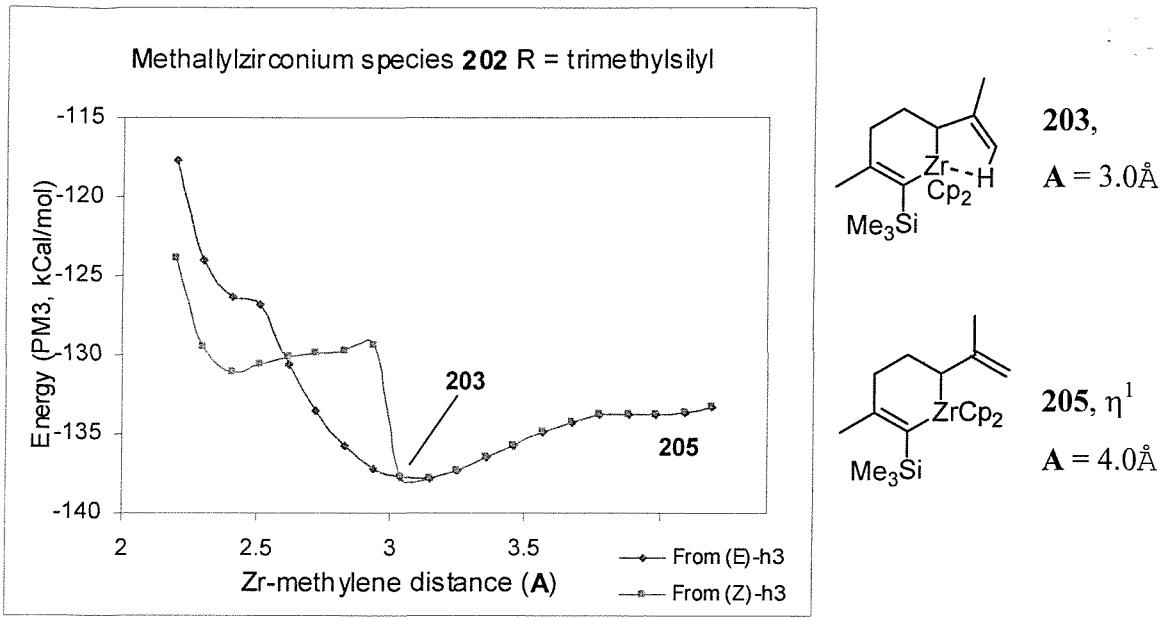


$R = CH_3$ **202** $R = SiMe_3$

The $Zr\text{-}CH_2$ bond length **A** is 2.3 Å in the η^3-allyl zirconium species represented in scheme 2.10 and thought to be stable for all such structures. Stretching of this bond reveals that whilst **202** $R = CH_3$ behaves as expected with a relative stability observed for the η^3 structure (**A** = 2.3 Å, figure 2.3), when $R = SiMe_3$ an alternative form is found to stable where **A** = 3.0 Å. An agostic bond between zirconium and a terminal methylene-H corresponds to this length and such an 'agostic form' **203** can be envisaged to arise if zirconium attempts to achieve 18e configuration simply by donation of electron density from the C-H bond towards Zr··H-C 2e-3c bond formation[45].

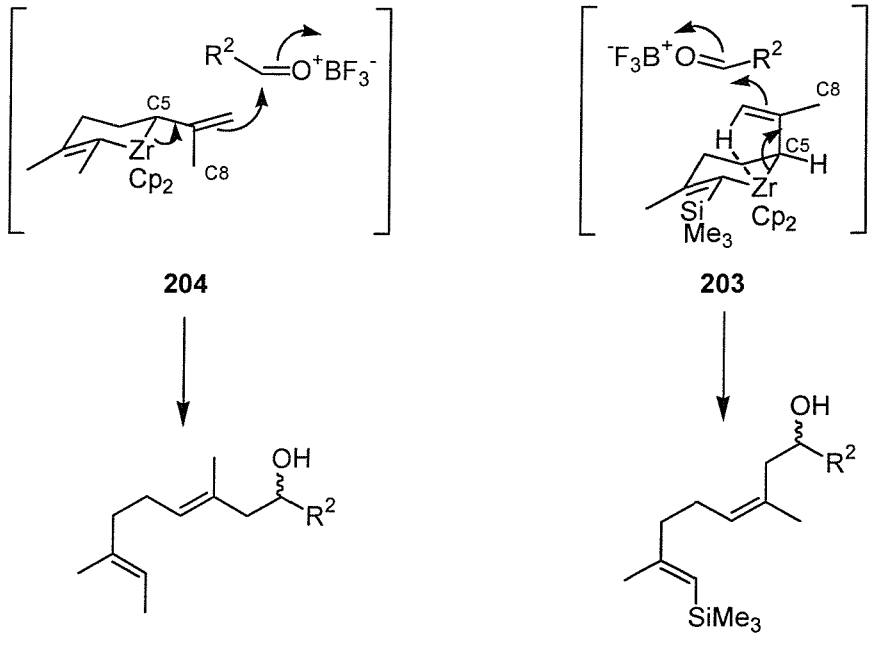
Figure 2.3 α-Substituent effects on methallyl zirconium species.





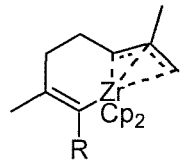
Occupation of zirconium's 'empty' valence shell orbital in this way does not preclude addition of BF_3 – activated aldehyde to the species. It is therefore reasonable to rationalise formation of the *cis* alkene *via* this agostic form **203**, in which the C8 methyl group eclipses the ring junction proton and gives rise to *cis* geometry about the new double bond. This is not observed in the usual transition state, for structures with alkyl substitution α to zirconium (**204**, represented η^1 for clarity) where no agostic bond exists (Figure 2.4). Poor alignment of the C5-Zr bond with the allyl π system for aldehyde addition to **203** prevents conclusive implication of the agostic structure as a reactive intermediate however.

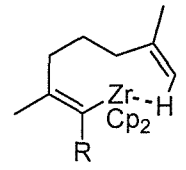
Figure 2.4 Postulated transition states for aldehyde addition to α-substituted methallyl zirconacycles.

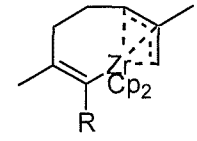


Use of DFT to calculate accurate absolute minima also allows comparison of the (E) and (Z) isomers of η^3 methallyl zirconium species', for both the trimethylsilyl and methyl substituted cases. Intriguingly, the (E)η^3 form is more stable when the zirconacycle is α-methyl substituted however the (Z)η^3 form has greater stability for the α-$SiMe_3$ substituted case (Table 2.3). Hence, reaction with Lewis acid – activated aldehyde of these monocyclic η^3 structures might be expected to yield *trans* alkenes (R = Me) or *cis* alkenes (R = $SiMe_3$) as is indeed observed.

Table 2.3 DFT calculated stability of α-substituted methallyl zirconacycles.







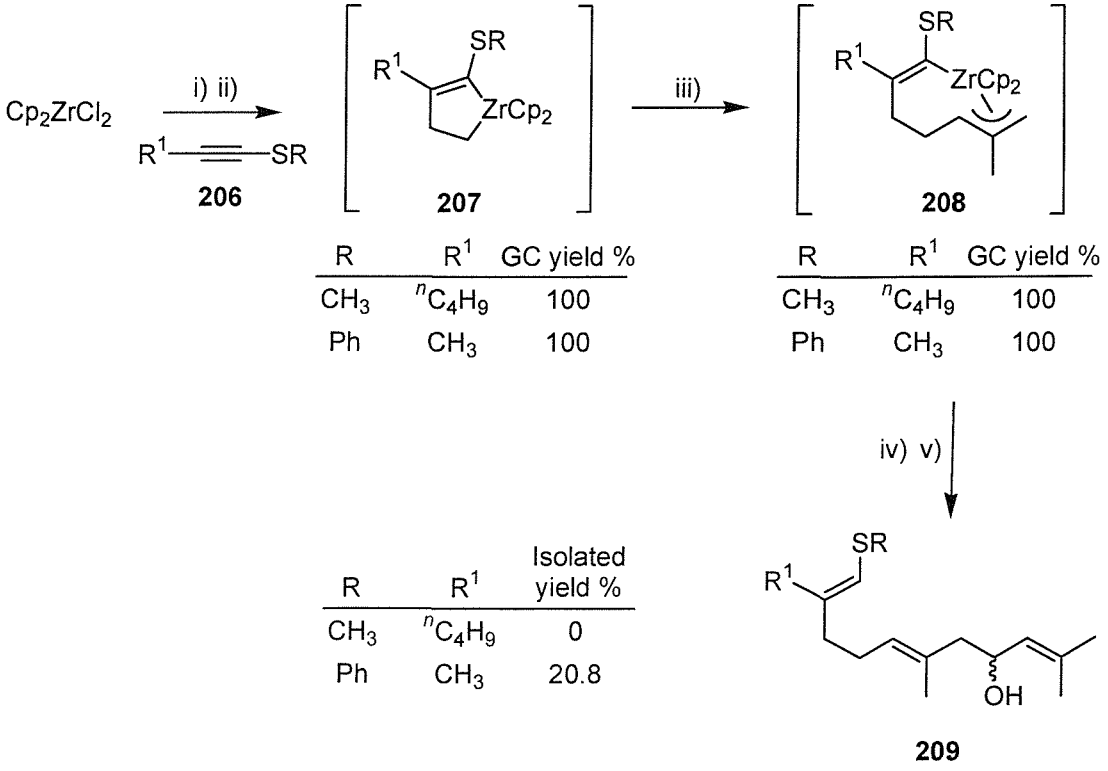
R	(E)η^3-methallyl KCal/Mol	Agostic KCal/Mol	(Z)η^3-methallyl KCal/Mol
Me	0.0	....	4.0
$SiMe_3$	No minima	-7.0	0.0

Factors influencing the observed 5:2 *cis*:*trans* ratio for **196** are not conclusive then. A contribution both by the transition state for the agostic structure **203** (figure 2.4) and the calculated greater stability of the (Z)η^3 allyl zirconacycle over the (E) form may be postulated. It is unclear if a steric constraint in the case of the bicyclic allyl zirconacycle prevents the agostic intermediate, in accounting for the dominance of *trans* geometry in alkenes **201a-c**. Modelling of this system has not been carried out due to time constraints. Lastly, the clear preference for the agostic-bonded methallyl zirconium species is dictated by trimethylsilyl substitution α to the metal and reason for this remains unknown. Alteration of this moiety is therefore now described (sections 2.1.1 and 2.1.2). This is both in order to better understand the behaviour of the novel monocyclic methallyl species in the Lewis acid mediated aldehyde addition and also to gain access to precursor compounds of the linear terpenoids earlier described (section 2.0.2) for which *cis*-**196** is not useful.

2.1.1 Application of α-SR Substituted Zirconacyclopentenes in Tandem Carbenoid / Electrophile Addition.

Alkenyl sulphides react with Grignard reagents in the presence of palladium or nickel catalysts[46]. Direct sulphur / lithium exchange is also known[47,48] and grounds for targeting **209** as a sesquiterpenoid precursor are established in this way (Scheme 2.11).

Scheme 2.11 Synthesis of an alkenyl sulphide terpenoid precursor.



R	R^1	GC yield %
CH_3	$^nC_4H_9$	100
Ph	CH_3	100

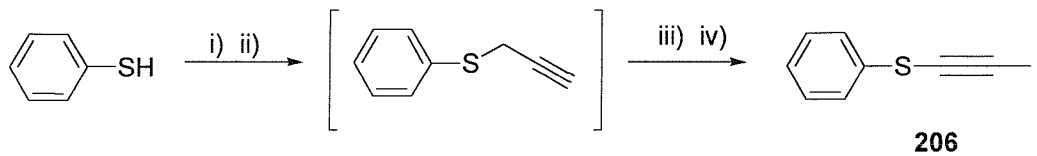
R	R^1	GC yield %
CH_3	$^nC_4H_9$	100
Ph	CH_3	100

R	R^1	Isolated yield %
CH_3	$^nC_4H_9$	0
Ph	CH_3	20.8

Reagents and Conditions: i) ethene gas (excess), -78 °C to rt, 1h (R = CH_3), or i) EtMgCl (2 eq), -78°C, 1 h (R = Ph). ii) **206** (1 eq), -78 °C to rt, 4 h. iii) 3-chloro-2-methylpropene, LiTMP, -80 °C to –70 °C, 40 min. iv) 3-methyl-2-butenal (1.7 eq), $BF_3{\cdot}Et_2O$ (1.7 eq), -70 °C to rt, 3 h. v) MeOH, $NaHCO_3$(aq), rt, 12 h.

Precursor alkynes for cyclisation (**206**) were synthesised *via* terminal alkyne lithiation and treatment with methyl disulphide (R = CH_3, R^1 = $^nC_4H_9$, 99.6%) or from thiophenol where R = Ph[49] (Scheme 2.12).

Scheme 2.12 Synthesis of 1-thiobenzene-1-propyne.



206
90.0%

Reagents and conditions: i) Na, EtOH, 0 °C, 10 min. ii) propargyl bromide, 0 °C to rt. iii) Δ, 2.5 h. iv) 1M HCl.

Co-cyclisation to yield an α-SCH_3 substituted zirconacyclopentene **207** was first carried out, followed by similarly quantitative insertion of 1-lithio-1-chloro-methallyl carbenoid into the sp^3C-Zr bond only. Regioselectivity in the co-cyclisation is confirmed by the alkenic singlet peak in the ^{1}H NMR (δ_H = 5.9 ppm, 300 MHz, $CDCl_3$). The product of opposite regioselectivity, with a thiomethyl group β to zirconium, would of course display an alkenic quartet. Addition of BF_3-activated 3-methyl-2-butenal to the allyl zirconium species **208** (R = CH_3) was not successful and treatment of **208** with the aldehyde in the absence of Lewis acid also failed to yield the elaborated product **209**. It is thought that electron donation from a sulphur lone pair into the zirconium p-orbital results in unavailability for co-ordination such that **208** (R = CH_3) is σ-allylic in character rather than π-allylic and therefore less activated towards complexation with the aldehyde. Where sulphur is aryl substituted, some delocalisation of sulphur's lone pairs into the aromatic ring may inhibit their donation towards zirconium. Indeed, following co-cyclisation of 1-thiobenzene-1-propyne with Cp_2Zr-ethene (the unwanted zirconacyclopentadiene potentially resulting from alkyne self-cyclisation is not observed) and subsequent carbenoid insertion, 3-methyl-2-butenal addition is successful in yielding **209** (R = Ph) although in disappointing yield, only 20.8%.

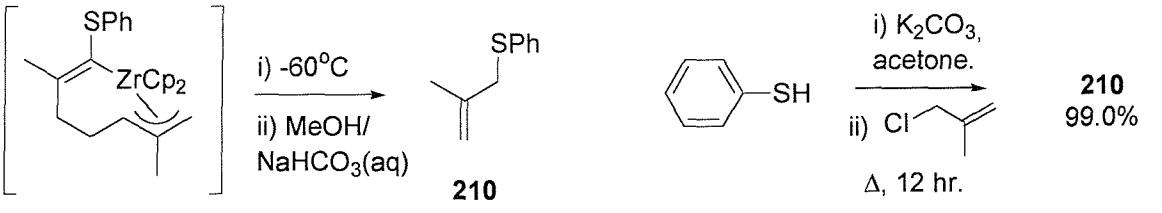
Once again, a mixture of geometric isomers about the double bond of the homoallylic alcohol moiety of **209** was apparent. Purification problems at this stage allowed conclusion only that the *trans* isomer was the major one, as required, and optimisation of the one-pot sequence became priority.

Attempted characterisation of the interesting methallyl zirconium species **208** (R = Ph, R^1 = CH_3) provided insight into this problem, the methallyl zirconacycle proved highly unstable. It was not possible to obtain NMR characterisation as the species was not stable to THF removal nor to washing with toluene and subsequent solvent removal. A general

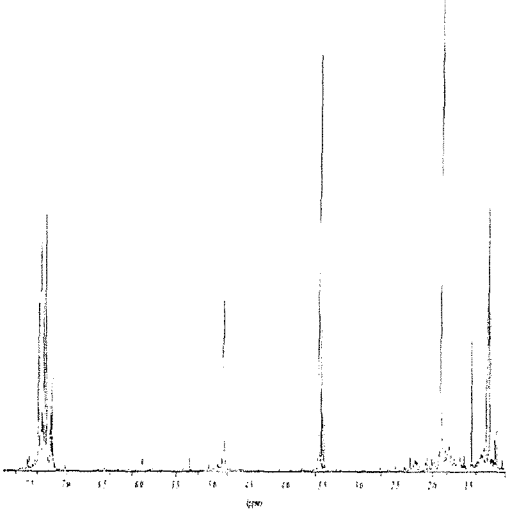
degradation was observed upon warming from –70 °C, occurring progressively with stirring in THF at room temperature or upon aqueous work-up.

The fragmentation product **210** was isolated and its structure confirmed by independent synthesis of this compound and comparison of ^{1}H NMR data (Figure 2.5).

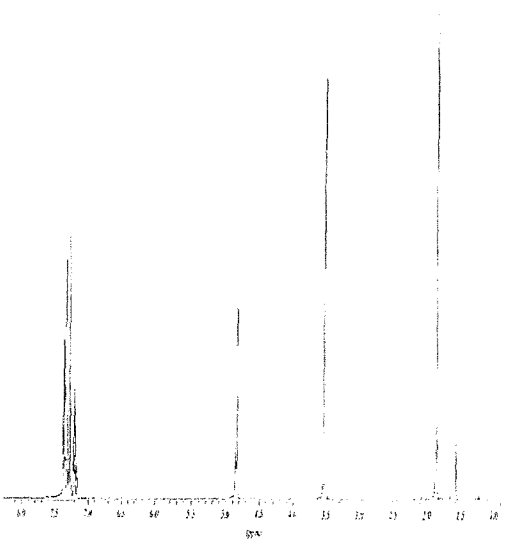
Figure 2.5 Characterisation of a fragmentation product of α-SPh substituted methallyl zirconacycle.



^{1}H NMR (300 MHz, $CDCl_3$)
Fragmentation product **210**.



^{1}H NMR (300 MHz, $CDCl_3$)
Synthetic product **210**.



Allyl zirconium species are usually stable at room temperature[44] however the α-sulphide structures are previously unknown and we describe the fragmentation mechanistically *via* electron pair donation from sulphur to zirconium and consequent ring-opening of the η^1 form (figure 2.6). Clearly delocalistion of electron density into the aromatic ring does not surpress this however the fragmentation of **208** (R = CH_3) was not earlier observed.

Figure 2.6 Ring-opening of an α-sulphide substituted methallyl zirconacycle.

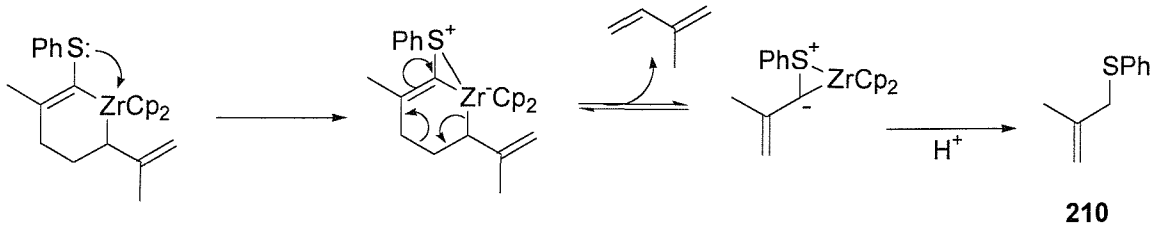
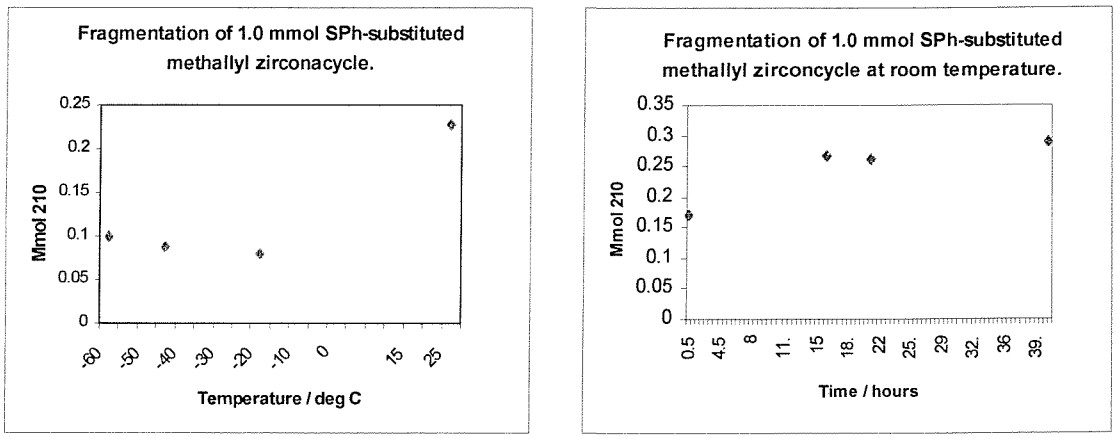


Figure 2.7 indicates that the level of fragmentation of the allyl zirconacycle becomes significant when the reaction mixture reaches room temperature, increased fragmentation then takes place at room temperature up to 29%.

Figure 2.7 Fragmentation of an α-SPh substituted methallyl zirconacycle.



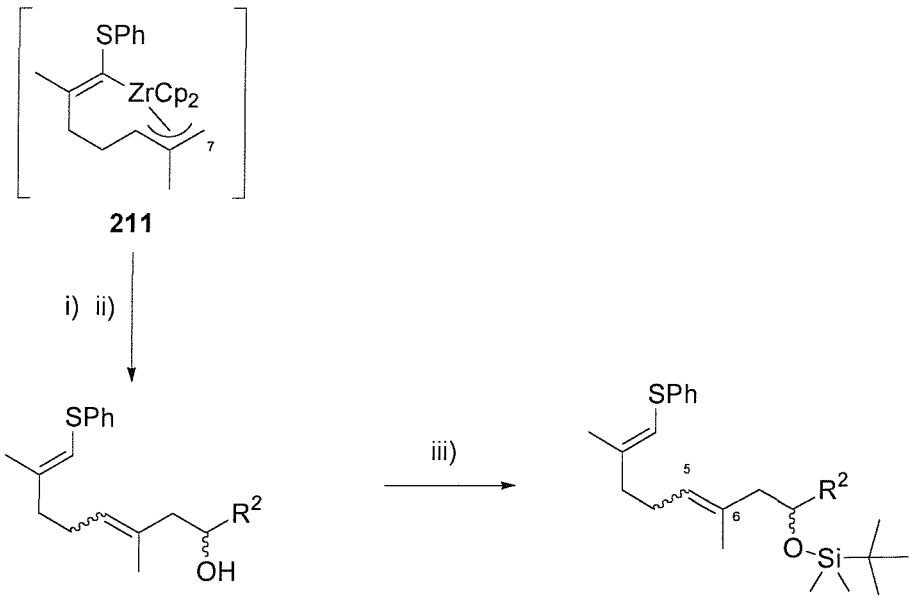
Addition of $R^2CHO/BF_3{\cdot}Et_2O$ complex (1.7 eq) to the α-SPh substituted allyl zirconacycle **208** at –70 °C and then holding of the reaction mixture below –65 °C for one hour improves the yield of the final product somewhat, 33% isolated (R^2 $CH{=}C(CH_3)_2$) and 44% isolated (R^2 = Ph), following $MeOH/NaHCO_3$(aq) quench at –65 °C due to the uncertain stability of the pre-hydrolysis compound also to warming. Quench at –20 °C gives the fragment **210** as the major product whilst quench onto an ice/$MeOH/NaHCO_3$(aq) slurry under argon also gives mainly **210**. **210** is not observed upon quench at –65 °C.

It is apparent that aldehyde addition is incomplete at –65 °C, to support this we had previously observed highest yields for aldehyde addition to other, stable, allyl zirconacycles following warming and stirring at room temperature for several hours[16,43,44,50,51].

No improvement in yield could be achieved under these low temperature conditions, with use of 1 – 3eq R^2CHO [R^2 = $CH=C(CH_3)_2$ or $CH=C(CH_3)-(CH_2)_2-CH=C(CH_3)_2$] or 1 – 3eq $BF_3{\cdot}Et_2O$, Et_2AlCl, or $Ti(O^iPr)_4$ as Lewis acid. Pre-complexation of aldehyde and Lewis acid also effected no change.

High yielding silylation of the hydroxyl group with ^{tert}butyldimethylsilyl triflate was necessary for clean isolation of the product (Scheme 2.13). The overall yield from the tandem carbenoid / aldehyde addition is unsatisfactory for natural product synthesis, once again as grounds for further modification of the α-alkenyl substituent (section 2.1.2 describes the α-$SnBu_3$ system), however a surprising reversal in the introduced alkene geometry could now be identified in the structure. Benzaldehyde addition to the methallyl zirconacycle results in *cis* geometry about this double bond whilst 3-methyl-2-butenal addition yields a 2.45 : 1 *trans*:*cis* mixture of geometric isomers.

Scheme 2.13 Optimal synthesis of alkenyl-sulphide substituted linear terpenoid precursors.



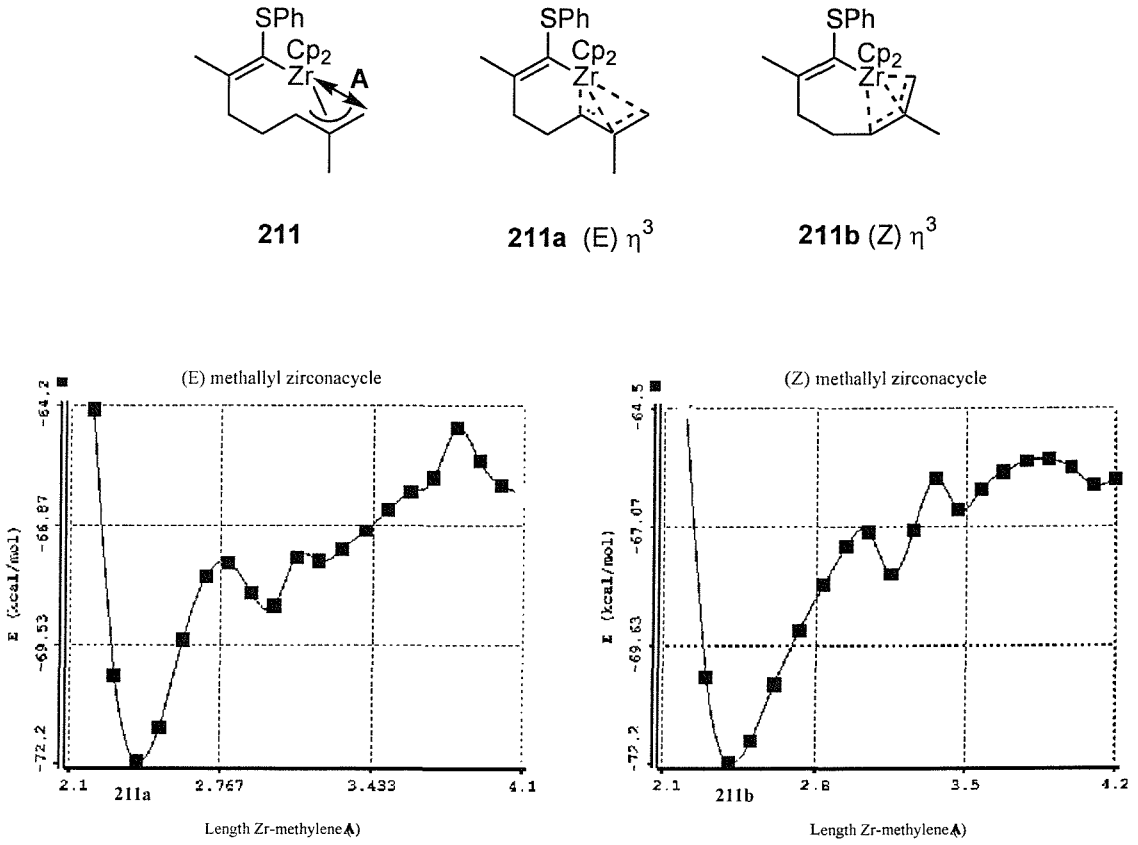
	R^2	Isolated yield %		R^2	Isolated yield %	C5-C6 *cis*:*trans*
212	$CH=C(CH_3)_2$	33.2%	**214**	$CH=C(CH_3)_2$	91.8	1 : 2.45
213	Ph	44.3%	**215**	Ph	93.4	*cis* only

Reagents and conditions: i) R^2CHO (1.7 eq), $BF_3{\cdot}Et_2O$ (1.7 eq), -70 °C to –65 °C, 1 h. ii) $MeOH/NaHCO_3$(aq) –65 °C to rt, 12 h. iii) TBDMSTf, DMAP, imidazole, rt, 24 h.

Although dominant *cis* geometry was observed in the $SiMe_3$-substituted system, formation of **215** is unexpected and the mixture **214** also displays rather small bias towards the *trans*

isomer. PM3 profiling of the Zr-C7 bond distance in **211** indicates stability of the η^3 form (Zr-CH_2 = 2.3Å, Figure 2.8). There is no evidence of the agostic form (Zr-CH_2 = 3.0Å) observed for the α-$SiMe_3$ zirconacycle and implicated in formation of a (Z)-alkene (section 2.1.0). Moreover, the (E)η^3 form of **211** is found to be more stable than the (Z)η^3 structure using DFT and no explanation for alkene geometry arising from η^3-methallyl zirconacycle geometry can be postulated.

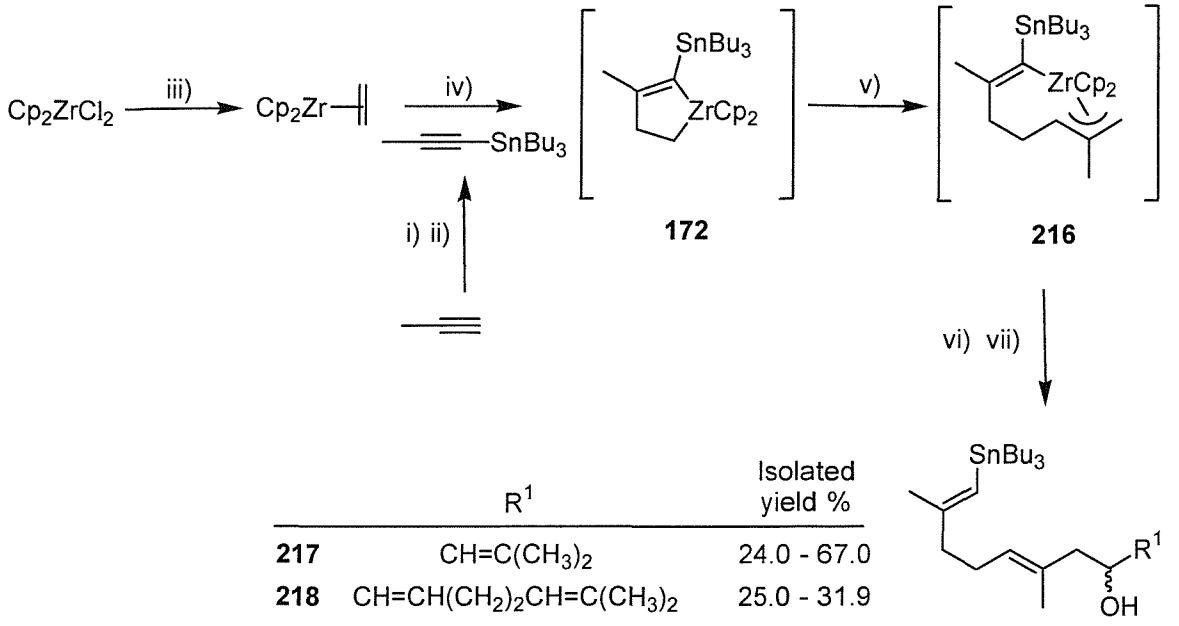
Figure 2.8 α-SPh effect upon methallyl zirconium species'.



2.1.2 Application of α-$SnBu_3$ Substituted Zirconacyclopentenes in Tandem Carbenoid / Electrophile Addition.

Encouraging precedent for the regioselective synthesis of a monocyclic α-tributylstannyl substituted zirconacyclopentene **172** is found in the work of Gordon[27] (scheme 2.5, section 2.0.1) and was repeated according to Scheme 2.14, steps i) – iv), in quantitative yield.

Scheme 2.14 Synthesis of an alkenyl stannyl terpenoid precursor.



	R^1	Isolated yield %
217	$CH=C(CH_3)_2$	24.0 - 67.0
218	$CH=CH(CH_2)_2CH=C(CH_3)_2$	25.0 - 31.9

Reagents and conditions: i) ^{n}BuLi, -78 °C to 0 °C, 1 h. ii) Bu_3SnCl (1.3 eq) 0 °C to rt, 8 h. iii) EtMgCl (2.0 eq) –78 °C , 20 min. iv) 1-tributylstannyl-1-propyne, -78 °C to 0 °C, 1 h then 0 °C to rt, 2 h. v) 3-chloro-2-methylpropene, LiTMP, -78 °C to –70 °C, 40 min. vi) R^1CHO (2.0 eq) –70 °C to rt, 3 h. vii) MeOH, $NaHCO_3$ (aq), rt 12 h.

Cyclisation to yield **172** using the dibutylzirconocene / ethene gas method is also quantitative. Following 1-lithio-1-chloro-2-methylpropene insertion, subsequent aldehyde addition is then unsuccessful however. This may be attributed to the absence of any Lewis acid for aldehyde co-ordination, $BF_3{\cdot}Et_2O$ is omitted due to known destannylation of alkenyl tin compounds in its presence[27]. When zirconocene-ethene is derived from β-H elimination of Cp_2ZrEt_2 as in scheme 2.14, residual $MgCl_2$ is thought to act as a weak Lewis Acid for the aldehyde addition step. Elaborated alkenyl stannanes **217** and **218** were obtained, as sesquiterpenoid and diterpenoid precursors respectively, from 3-methyl-2-butenal or geranial addition to **216** without added Lewis acid.

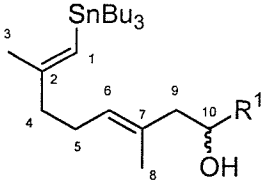
Maximal yields of 67% (**217**) and 32% (**218**) are somewhat disappointing and represent the best examples of an erratic sequence. Failed carbenoid insertion into an α-$SiMe_3$ zirconacyclopentene in the presence of $MgCl_2$ (section 2.0.1) suggested that optimisation of the α-$SnBu_3$ system could be achieved by zirconocene-mediated coupling of 1-tributylstannane with ethene gas followed by carbenoid insertion and subsequent aldehyde

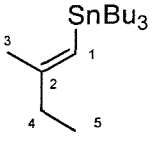
addition with $MgBr_2$ added at this stage. Unfortunately this strategy proved unsuccessful and a thorough optimisation programme is described later in this section.

Double bond geometry about C6-C7 in **217** and **218** was a concern with two factors for consideration; failure of added $MgBr_2$ to influence the yield of aldehyde addition suggests that zirconium may co-ordinate the aldehyde oxygen in a cyclic transition state[51] from which (Z) geometry might result. Secondly, undesired (Z)-alkenes have resulted from 3-methyl-2-butenal addition to the analogous α-$SiMe_3$ substituted allyl zirconacycle (section 2.1.0) and also from benzaldehyde addition to the α-SPh allyl zirconacycle (section 2.1.1). ^{13}C NMR shifts of alkenyl methyl and methylene carbon atoms C8 and C9 are again diagnostic in assignment of alkene geometry (table 2.4). Alkenyl methyl C8 ^{13}C shifts at δ_C = 16.77 and 16.78 ppm for **217** and **218** respectively are observed, alkenyl methylene C9 ^{13}C shifts are δ_C = 47.42 and 49.17 ppm. **217** and **218** both possess the desired *trans* geometry around the C6-C7 double bond therefore. Table 2.4 also includes the product **219** of benzaldehyde insertion into allyl zirconacycle **216**. Geometry is also *trans* about C6-C7 in this case (C8 δ_C = 16.51 ppm, C9 δ_C = 51.52 ppm).

Correlation of ^{13}C shifts for C1-C5 with the known zirconacyclopentene protonation product[27] **220** is also made, 1(E) configuration is assured from inclusion in the zirconacyclopentene ring.

Table 2.4 Correlation of ^{13}C NMR data for 1(E) 6(E) configuration of alkenyl stannane compounds.





220

	R^1
217	$CH=C(CH_3)_2$
218	$CH=C(CH_3)(CH_2)_2CH=C(CH_3)_2$
219	Ph

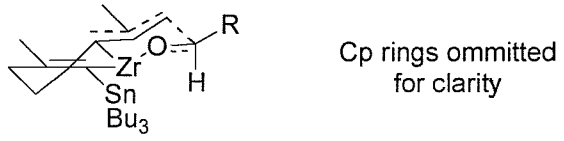
	δ_C (ppm) **217**	δ_C (ppm) **218**	δ_C (ppm) **219**	δ_C (ppm) **220**
C1	121.02	122.81	122.99	119.57
C2	153.55	155.31	155.24	156.57
C3	24.36	25.01	25.01	24.57
C4	40.87	42.66	42.56	34.47

C5	25.72	27.32	27.39	13.70
C6	127.94	125.02	127.68	-
C7	131.98	132.68	132.63	-
C8	16.77	16.78	16.51	-
C9	47.42	49.17	51.52	-
C10	64.86	66.67	71.65	-

^{13}C NMR spectra of the alkenyl stannanes **217-219** were recorded in C_6D_6 at 100.5 MHz, **220** was recorded in $CDCl_3$ at 75 MHz, and are referenced to solvent peak.

Selective (E) geometry from aldehyde addition to the α-stannyl methallyl zirconium species **216** is consistently observed. Formation of (E) alkenes *via* an open transition state involving aldehyde-Lewis acid co-ordination has been described for *trans*-fused bicyclic zirconacyclopentanes, this is discredited for the monocyclic system however as no yield improvement can be effected with added Lewis acid. It is instead conceivable that the conformationally flexible allyl zirconacycle **216** may attain a closed *trans* decalin transition state, with O - co-ordination to zirconium, which also leads to (E) geometry in the alkene formed[27].

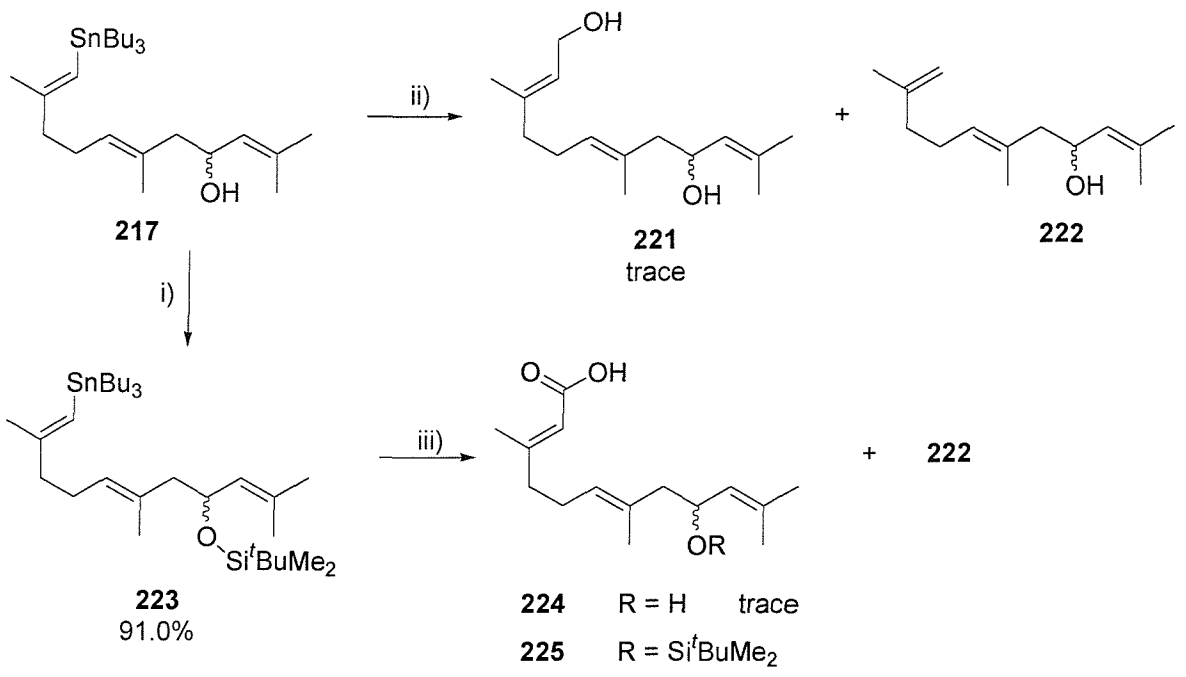
Figure 2.9 Postulated transition state for RCHO addition.



Transmetalation of the alkenyl tin compound **217** with butyl lithium should lead directly to the terminal alkenyl lithium, trapping of which *in situ* with either formaldehyde or CO_2 was considered a possibility for accessing 9-hydroxyfarnesol **221** and 9-hydroxyfarnesoic acid **224** respectively. To this end, small scale experiments were carried out, summarised in scheme 2.15. Treatment of **217** with ^{n}BuLi or ^{sec}BuLi leads to a trace finding of 9-hydroxfarnesol by GC following addition of excess paraformaldehyde. The major product is terminal olefin **222** resulting from either incomplete trapping of the intermediate alkenyl lithium or protonation from the free C9-OH proton. Intentional deprotonation of the hydroxyl group, with up to thee equivalents of butyl lithium added, does not suppress the terminal alkene formation and protection of the alcohol with a ^{tert}butyldimethylsilyl ether was made. Tin / lithium exchange of this protected compound **223** was attempted with

subsequent CO_2 trapping of the alkenyl lithium. The crude NMR spectra indicated some deprotection with 1.1 eq ^{n}BuLi so deliberate deprotection was sought with 3.0 eq ^{n}BuLi and a trace of **224** was now obtained. Incomplete deprotection persisted with **225** a major contaminant and, despite use of excess base, incomplete Sn/Li exchange was also indicated by the presence of **222** once more; thought to result from destannylation of the starting alkenyl stannane during acidic work-up. The starting materials **217** or **223** remain because tin / lithium exchange is limited by the transmetalation equilibrium[52], circumvention of this problem was anticipated *via* I/Li exchange however conversion of **217** to the alkenyl iodide (using N-iodosuccinimide) failed. Finally, all crude product mixtures were heavily contaminated by tetrabutyltin and isolation of the trace natural product compounds **221** and **224** became problematic therefore.

Scheme 2.15 Small scale investigation of Sn / Li exchange and alkenyl lithium trapping.

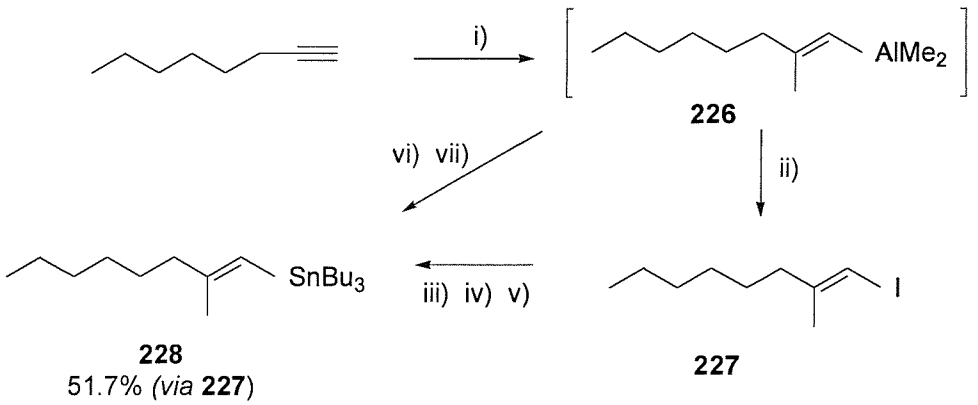


Reagents and conditions: i) ^{tert}Butyldimethylsilyl triflate, DMAP, imidazole, THF, rt, 24 h. ii) ^{n}BuLi, (2 – 3 eq) or ^{sec}BuLi (3 eq), -20 °C, 2 h then $(H_2C{=}O)_n$ (excess), -78 °C 1 h. iii) ^{n}BuLi (1.1 eq or 3.0 eq), -20 °C 1 h then CO_2, -20 °C to rt, 1 h.

A model compound **228** upon which synthetic manipulation of the α-$SnBu_3$ functional group could be tested was conceived in order to mimic the tin – substituted double bond of the alkenyl stannane moiety whilst omitting all of the remaining structure from **217**. H_2O elimination, driven by formation of the conjugated triene, occurs readily from **217** such that the compound is costly to obtain in terms of both time and yield. Conversely,

synthesis of **228** is rapid and straightforward in a reasonable unoptimised yield (scheme 2.16).

Scheme 2.16 Model system synthesis.



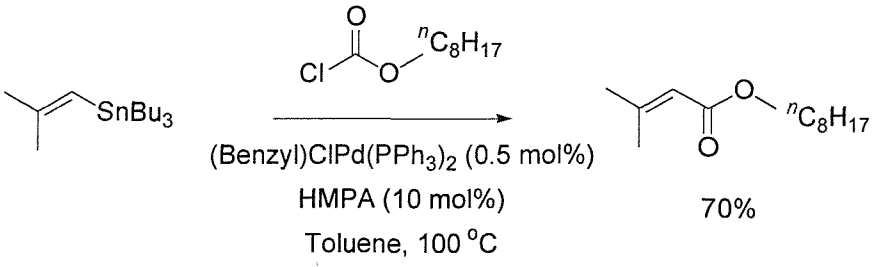
Reagents and conditions: i) Cp_2ZrCl_2 (10 mol%), Me_3Al, 0 °C to rt, 1,2-dichloroethane. ii) I_2, THF, 0 °C. iii) ^{t}BuLi (2.0 eq), -78 °C to rt. iv) Bu_3SnCl (1.0 eq), -78 °C to rt. v) KF (10%, aq), 48 h. vi) MeLi (1.1 eq). vii) Bu_3SnCl (2.5 eq), -78 °C to rt.

Zirconium – catalysed methyl alumination of 1-octyne[53] gives the intermediate alkenyl dimethylalane **226** and two routes to **228** were carried out from **226**. Conversion to the methyl alanate with MeLi, followed by treatment with Bu_3SnCl, gives the desired alkenyl stannane **228** in the same pot[54] however Bu_3SnMe is then a difficult contaminant to remove. Clean procurement of **228** was instead achieved following iodine quench of the alkenyl alane and isolation of the resultant alkenyl iodide **227**. Conversion of **227** to a stable alkenyl lithium with two equivalents of ^{t}BuLi[55] precedes treatment with excess Bu_3SnCl. Residual tributyltin halides are simply removed from **228** upon stirring in aqueous KF solution.

Tin / lithium exchange in which the presence of either the free or protected C9-hydroxyl group of **217** / **223** was problematic is indicative that best use of the model system would be made in development of palladium – catalysed 'Stille'[56] coupling conditions for the alkenyl stannane with appropriate organohalides.

Alkoxycarbonylation of β,β-dimethyl-substituted vinyltributylstannane was reported in 1991[57] (scheme 2.17). This isolated precedent has potential for application to our alkenyl stannane **217** and hence synthesis of 9-hydroxyfarnesoic acid *via* reduction of the resultant ester in an overall carboxylation step.

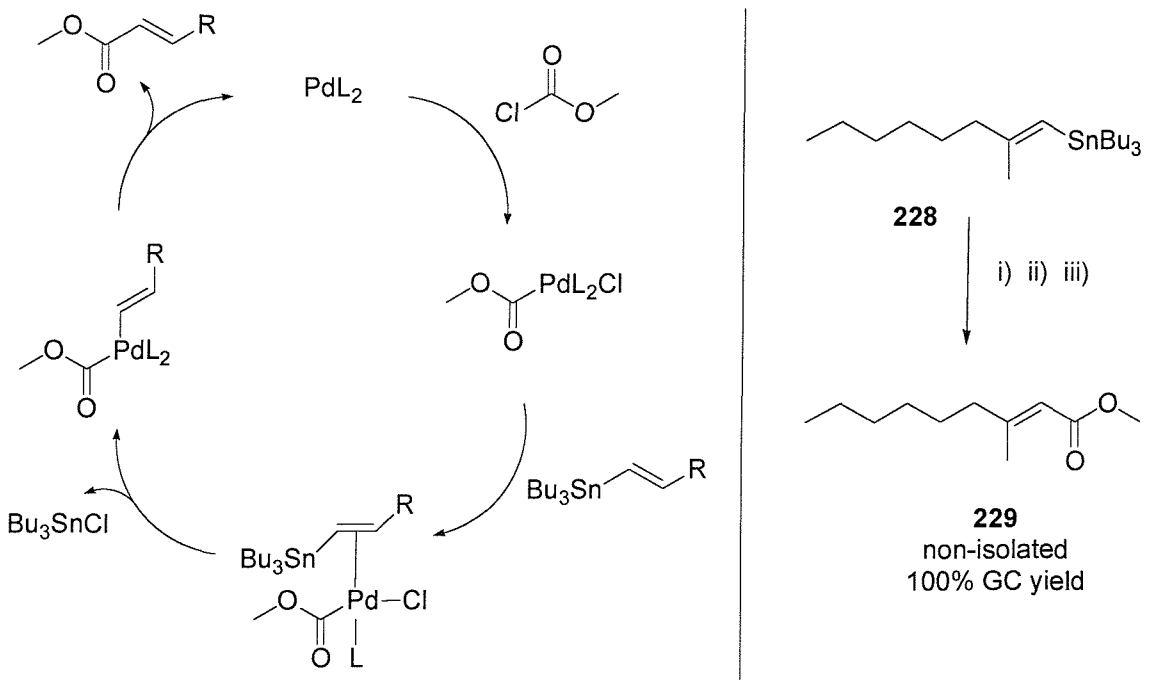
Scheme 2.17 Literature palladium – catalysed coupling of octylchloroformate with an alkenyl stannane.



Rate acceleration of the palladium – catalysed coupling between vinylic stannanes and various electrophiles has since been reported by Farina[58] with the use of triphenyl arsine and tri-2-furylphosphine ligands. Improved Stille coupling conditions to those of scheme 2.17 were therefore designed and tested upon the coupling of model alkenyl stannane **228** with methyl chloroformate (scheme 2.18). Triphenylarsine is employed as a ligand for the $Pd_2(dba)_3$ catalyst in order that ready dissociation from Pd(II) allows formation of a π complex between palladium and the alkenyl stannane, thought to be intermediate in the rate – determining transmetalation step. $AsPh_3$ is more labile than the traditional PPh_3 ligand[59,60].

Potential decomposition of methyl chloroformate to phosgene was of concern with the symmetrical ketone from successive alkenyl stannane couplings with phosgene a possible product. To avoid this, following warming of a solution of the stannane, HMPA[61] and premixed $Pd_2(dba)_3 \cdot CHCl_3$ (0.4 mol%) / $AsPh_3$ (3.2 mol%) to reflux, 1.5 equivalents of methyl chloroformate were added slowly (0.025 mmol min^{-1}). More usually, stoichiometric equivalents of stannane and organohalide are added to the catalyst before heating in the Stille coupling, the modified conditions successfully yielded the desired α,β-unsaturated methyl ester **229** without trace of unwanted ketone however. Retention of geometry at the sp^2 methine carbon occurs in the coupling of alkenyl tins[61].

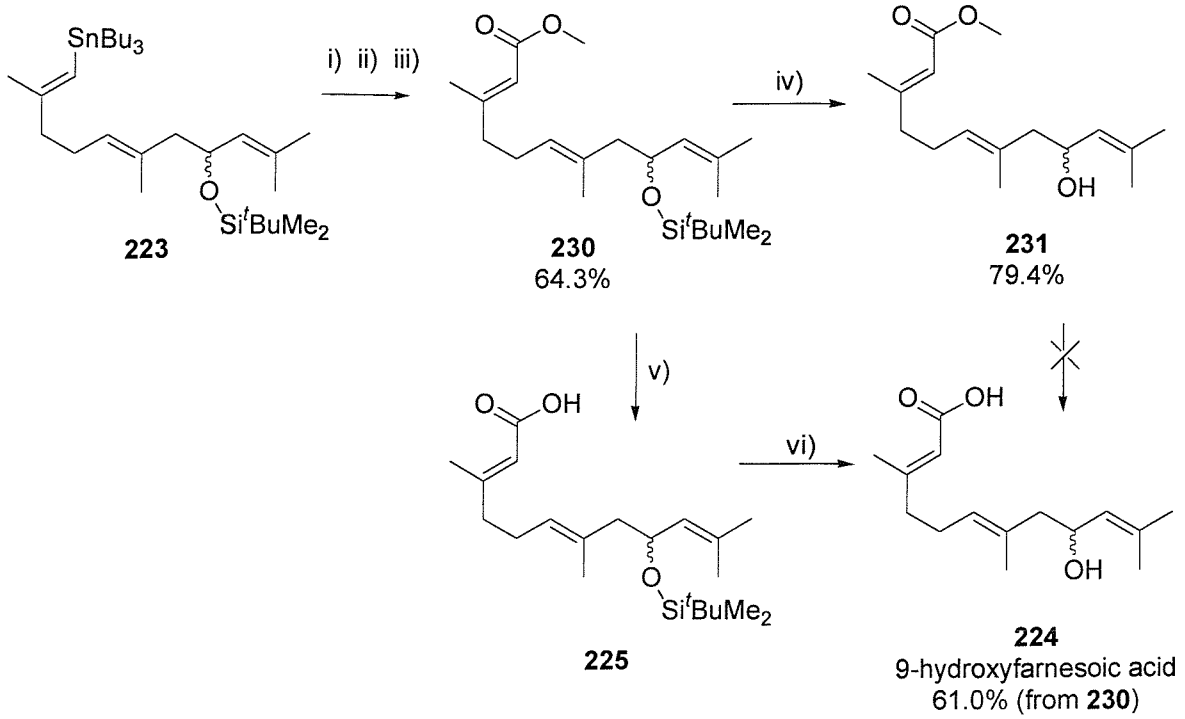
Scheme 2.18 Catalytic cycle and application of 'Farina' conditions to Stille coupling , synthesis of an α,β-unsaturated methyl ester.



Reagents and conditions: i) $Pd_2(dba)_3{\cdot}CHCl_3$ (0.4 mol%), $AsPh_3$ (3.2 mol%), THF, 15 min then HMPA (10 mol%) + **228**, rt to Δ. ii) methylchloroformate (1.5 eq) added over 1 h at Δ then rt, 12 h. iii) KF (10%, aq), 4 days.

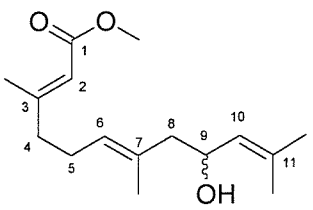
Pleasingly, application of these modified Stille coupling conditions to the alkenyl stannane **223** proceeds well, yielding **230** in an isolated yield of 64.3% (scheme 2.19). ^{t}Butyldimethylsilyl protection of the C9 hydroxyl group simply allows much cleaner procurement of the starting material than is the case with the precursor alcohol. Cleavage of the silyl ether, with tetra^{n}butyl ammonium fluoride, yields **231** and choice of ***methyl*** chloroformate for the Stille coupling step is now clear. Sesquiterpenoid 9-hydroxyfarnesoic acid was isolated by Naya *et al* from the root tissue of fungi – infected sweet potato in the form of its methyl ester[35] and represents the only reported data allowing correlation with the natural product. 9-Hydroxyfarnesoic acid itself is obtained *via* ester hydrolysis before the silyl ether is cleaved from crude **225**, direct saponification of methyl ester **231** cannot be effected as acidification of the carboxylate salt results in H_2O elimination across C8-C9 to yield a conjugated triene.

Scheme 2.19 Synthesis of 9-hydroxyfarnesoic acid and correlation of methyl ester **231** with literature data.



Reagents and conditions: : i) $Pd_2(dba)_3{\cdot}CHCl_3$ (0.4 mol%), $AsPh_3$ (3.2 mol%), THF, 15 min then HMPA (10 mol%) + **223**, rt to Δ. ii) methyl chloroformate (1.5 eq) added over 1 h at Δ then rt, 12 h. iii) KF (10%, aq), 2 days. iv) TBAF-THF, rt, 4 h. v) ^{t}BuOH / H_2O (1 : 1), 1M NaOH, 48 h . vi) TBAF-THF, rt, 24 h.

Table 2.5 Correlation of diagnostic ^{1}H NMR shifts, IR and MS data.



	Synthetic **231**	Naya *et al* isolated methyl ester
δ_H (ppm)		
O-CH_3	3.31 (s)	3.68 (s)
H2	5.68 (s)	5.62 (s)
C3-CH_3	2.03 (s)	2.16 (d, J = 1.5 Hz)
H4	1.71 (t, J = 6.8 Hz)	2.19 (m)
H5	1.81 (apparent q, J = 6.9 Hz)	2.19 (m)
H6	4.94 (t, J = 6.9 Hz)	5.20 (t, J = 6.0 Hz)
H8	1.99 (dd, J = 13.3, 5.0 Hz)	2.19 (m)
	2.09 (dd, J = 13.3, 8.8 Hz)	
H9	4.29 (q, J = 5.5 Hz)	4.43 (t, J = 7.6 Hz)
H10	5.13 (d, J = 8.3 Hz)	5.15 (t, J = 7.1 Hz)
IR cm^{-1}	1721.72, 1650.76	1720, 1650

MS, m/z	248 $(M - H_2O)^+$	248 $(M - H_2O)^+$

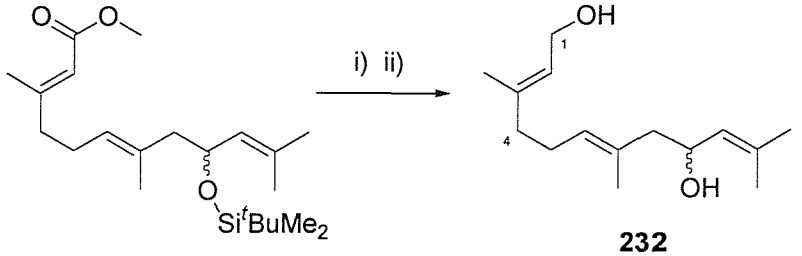
^1H NMR spectra for **231** were recorded in C_6D_6 at 400 MHz. Field and solvent are unreported for the literature compound. MS spectra for **231** is low resolution EI, unreported for the literature compound.

The ^1H spectrum obtained for our synthetic methyl ester **231** has better resolution than that for the literature reported compound (unfortunately Naya *et al* do not state the field at which their spectra were recorded) and Comparison of methylene proton shifts H4, H5 and H8 in particular is not possible. Downfield signals for H2, O-CH_3 and C3-CH_3 protons of the introduced α,β-unsaturated ester moiety are diagnostic however and our spectra (including IR and MS data), match the synthetic product **231** to the targeted compound (table 2.5, insert scheme 2.19). We attribute differences with the reported literature data to poor assignment in the reporting of the isolated compound by Naya, splitting of signals from H9 and H10, for example, we do not believe to be correctly assigned for the methyl ester.

Diisobutylaluminium hydride reduction of the (C9-^{t}butyldimethylsilyl protected) methyl ester **230**, obtained earlier from Stille coupling, installs a terminal allylic alcohol. Cleavage of the silyl ether gave 9-hydroxyfarnesol **232**, a second stress metabolite of the sweet potato[35,37] (scheme 2.20). comparison of vinylic methylene ^{13}C NMR shifts in **232** with those of literature reported 9-hydroxyfarnesol[37] – synthesised from geraniol without manipulation of the (E)-alkene – allows confirmation that retention of alkene geometry is observed in the Stille coupling.

The two-step yield of 9-hydroxyfarnesol is rather poor however no remaining starting material or side product was indicated in either the reduction or deprotection step. The cause of low recovery is unknown.

Scheme 2.20 9-Hydroxyfarnesol synthesis.



230

232
9-hydroxyfarnesol
19.4%

232	(E) C3-C4 9-hydroxyfarnesol

δ_C (ppm) C1	59.62	59.2
δ_C (ppm) C4	39.80	39.2

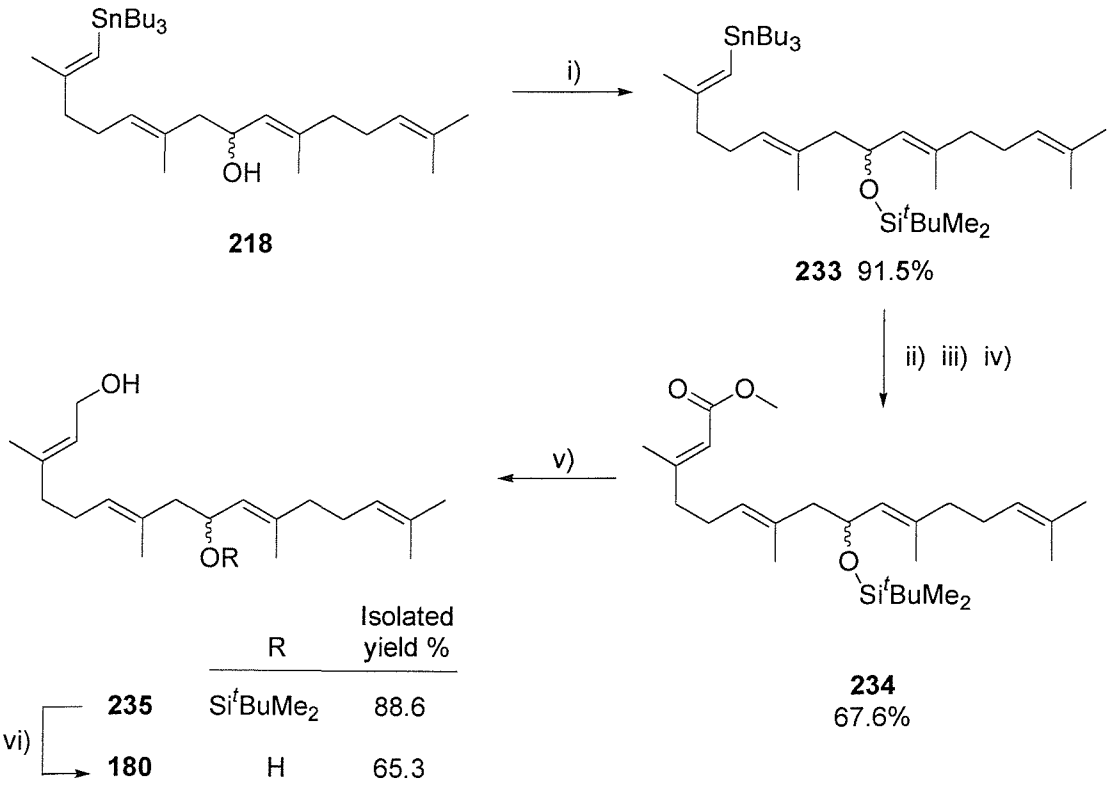
^{13}C spectrum of **232** was recorded in C_6D_6 at 400 MHz, literature compound in $CDCl_3$ at unknown field.

Reagents and conditions: i) DIBAL-H, CH_2Cl_2, -78 °C, 2 h. ii) TBAF-THF, rt, 12 h.

9-Hydroxyfarnesol is the sesquiterpene analogue of crinitol, the diterpene target whose retrosynthesis introduced our synthetic work towards linear terpenoids (scheme 2.7, section 2.1). Together with synthesis of 9-hydoxyfarnesoic acid **224**, procurement of 9-hydroxfarnesol represents successful application to natural product synthesis of tandem methallyl carbenoid insertion / 3-methyl-2-butenal addition to an α-tributylstannyl – substituted zirconacyclopentene. By way of interposition, these sesquiterpenes are phytoalexins which inhibit spore germination and growth of the fungus *Ceratocystis fimbriata*[36,37] and are significant compounds for biosynthetic studies[35].

Scheme 2.21 describes application of the developed conditions for palladium–catalysed coupling to efficient synthesis of the longer chain (diterpenoid) α,β-unsaturated terminal methyl ester **234** from alkenyl stannane **218** (scheme 2.14) *via* its $^tBuMe_2Si$- protected ether as before. As with 9-hydroxyfarnesol, DIBAL-H ester reduction and silyl ether cleavage furnish the desired diol **180**, crinitol[30,31].

Scheme 2.21 Synthesis of crinitol.

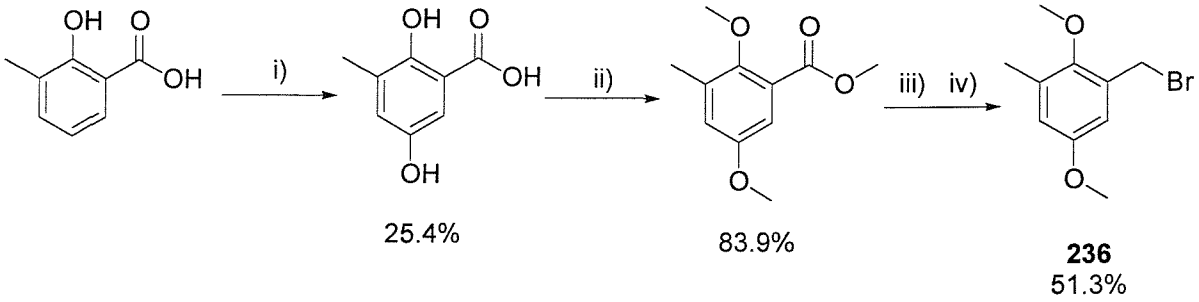


Reagents and conditions: i) ^{t}butyldimethylsilyl triflate, DMAP, imidazole, THF, rt, 24 h. ii) $Pd_2(dba)_3{\cdot}CHCl_3$ (0.4 mol%), $AsPh_3$ (3.2 mol%), THF, 15 min then HMPA (10 mol%) + **233**, rt to Δ. iii) methylchloroformate (1.5 eq) added over 1 h at Δ then rt, 12 h. iv) KF (10%, aq), 3 days. v) DIBAL-H, CH_2Cl_2, -78 °C, 2.5 h. vi) TBAF-THF, rt, 12 h.

Crinitol was obtained in an overall yield of 11.4% over the entire five steps. The yield is limited by a 31.9% yield in the tandem zirconium-mediated sequence and optimisation of this sequence will be described. C9-hydroxyl 'protection' and subsequent cleavage also accounts for some loss of material and detracts from an otherwise elegant sequence. Higher-yielding (hence cleaner) synthesis of the initial alkenyl stannane **218** might also remove the need for formation of the silyl ether (which allows clean separation of **233** cf **218**). Execution of the palladium–catalysed coupling step between methyl chloroformate and crude **218** has not been attempted but this strategy is now described for targeting 9-hydroxysargaquinone **181**, a cytotoxic product of marine algae *Sargassum tortile*[32] introduced in section 2.0.2.

Stille coupling of **218** directly with a stable 2,5-bismethoxy-3-methyl substituted benzylic bromide **236** was anticipated followed by oxidative demethylation of the coupling product[62,63] to yield 9-hydroxysargaquinone. Synthesis of the required benzylic bromide was made in four steps from 2-hydroxy-3-methyl benzoic acid using known chemistry (scheme 2.22). Elbs oxidation[64] to yield 2,5-dihydroxy-3-methyl benzoic acid was carried out in only 25.4% yield consistently with the literature[65]. Exhaustive methylation, methyl ester reduction and conversion to the bromide were then trivial.

Scheme 2.22 2,5-Bismethoxy-3-methyl benzylic bromide synthesis.

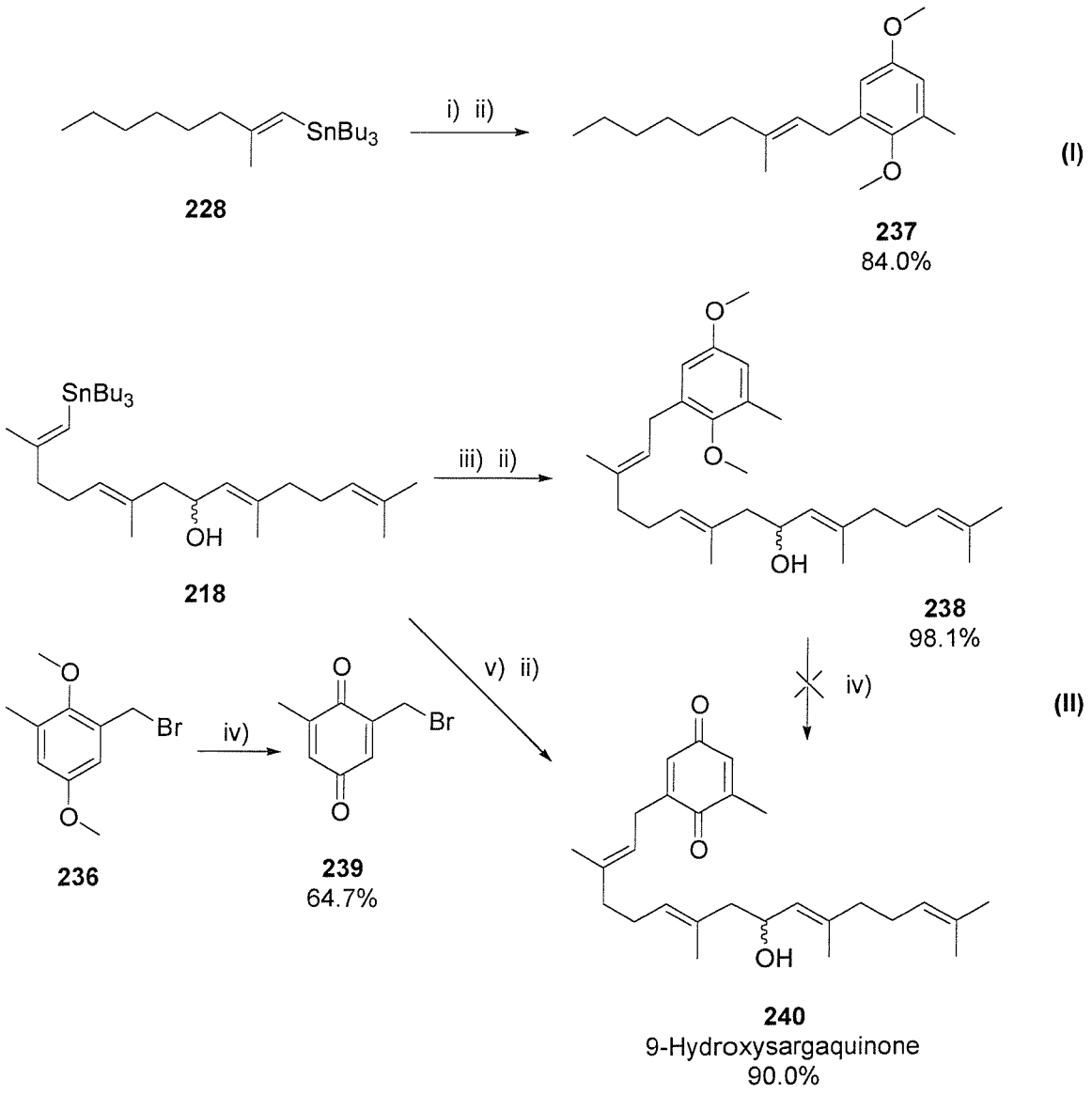


Reagents and conditions: i) $K_2S_2O_8$, NaOH (10%, aq), H_2O, -5 °C to –15 °C, 7 h then rt, 12 h. ii) $(CH_3)_2SO_4$, K_2CO_3, acetone, Δ, 24 h. iii) $LiAlH_4$, Et_2O, Δ, 3 h. iv) PBr_3, C_6H_6, rt, 20 h.

The expected coupling product **237** was obtained in high yield from palladium – catalysed coupling of stoichiometric equivalents of **236** and our model alkenyl stannane **228**

(scheme 2.23, **I**). Application of the same conditions to the longer chain alkenyl stannane **218** successfully yields an elaborated diterpenoid **238** in a near-quantitative isolated yield of 98.1%. Demethylation of this bismethoxy compound was anticipated using mild conditions[63], simple addition of ceric ammmonium nitrate (CAN) in water, but proved messy and yielded multiple products. Fortunately, oxidation of the benzylic bromide fragment **236** was clean using CAN and direct coupling of the resultant *p*-quinone (**239**) with **218** led to the desired compound, 9-hydroxysargaquinone[32,66], in excellent yield (scheme 2.23, **II**). This is the first known synthesis of 9-hydroxysargaquinone and the natural product has been obtained in only a single further step following tandem zirconium-mediated co-cyclisation, carbenoid insertion and geranial addition.

Scheme 2.23 9-hydroxysargaquinone synthesis.

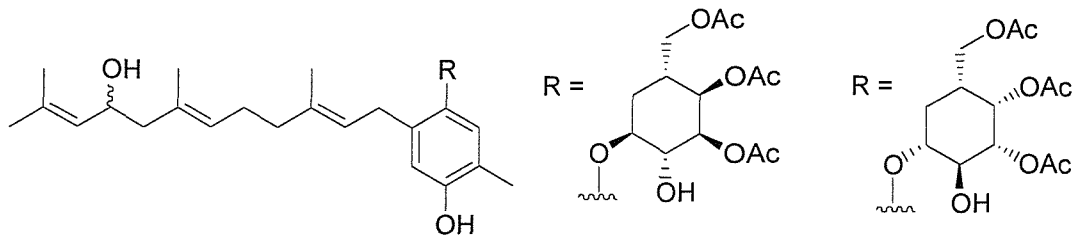


Reagents and conditions: i) $Pd_2(dba)_3{\cdot}CHCl_3$ (0.4 mol%), $AsPh_3$ (3.2 mol%), THF, 15 min, rt then **228** (1.0 eq), **236** (1.0 eq), Δ, 12 h. ii) KF (10%, aq), rt, 4 days. iii) $Pd_2(dba)_3{\cdot}CHCl_3$ (0.4 mol%), $AsPh_3$ (3.2 mol%), THF, 15 min, rt, then **218** (1.0 eq), **236** (1.0 eq), Δ, 1.5 h. iv) ceric ammonium nitrate, H_2O/MeCN, rt 20 min. v) $Pd_2(dba)_3{\cdot}CHCl_3$ (0.4 mol%), $AsPh_3$ (3.2 mol%), THF, 15 min, rt then **218** (1.0 eq), **239** (1.0 eq), Δ, 1.0 h.

Characteristic in the ^1H NMR spectrum of 9-hydroxysargaquinone are ring proton signals at δ_H = 6.47 ppm (dt, J = 2.5, 1.5 Hz) and δ_H = 6.40 ppm (dq, J = 2.5, 1.5 Hz), as well as a doublet arising from the allylic methylene protons α to the quinone ring, δ_H = 3.06 ppm (d, J = 7.3 Hz). Spectra were recorded in $CDCl_3$ at 400 MHz and are consistent with the reported data of Numata[32] and Rivera[66], as is all other structural data reported in chapter five of this thesis.

We hoped to exploit the (1E)-retentive coupling of our alkenyl stannanes with benzylic bromides in a synthesis returning to the shorter chain sesquiterpenoid structure. Moritoside[33] **182** is an interesting hydroquinone glycoside, introduced in section 2.0.2 and recalled below (figure 2.10) alongside euplexide A[34] (**241**) structurally analogous to moritoside but possessing a β-D-galactose linked monosaccharide in contrast to the β-D-altrose of moritoside. Both molecules possess cytotoxic and antioxidant properties[34] and the structure(s) have features unusual in natural products; the occurrence of D-altrose, triple acetylation of the sugar and an uncommon substitution pattern around the hydroquinone ring.

Figure 2.10 Gorgonian natural products moritoside and euplexide A.



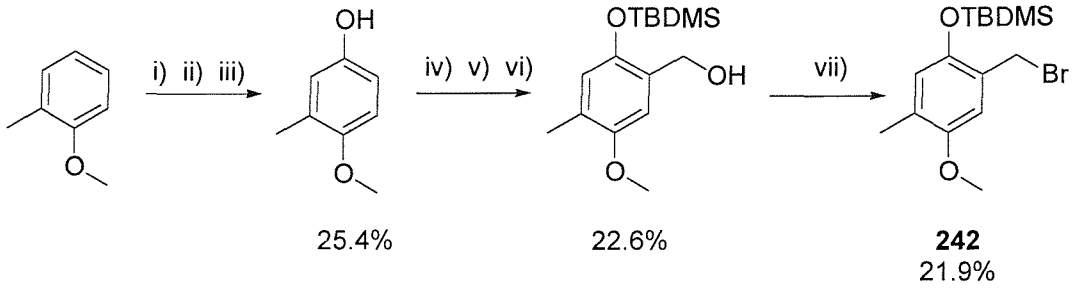
Moritoside **182** Euplexide A **241**

A sesquiterpene hydroquinone fragment with free hydroxyl group for construction of an ether linkage to the monosaccharide in the presence of a protected *para*-hydroxyl group would be a common precursor to both moritoside and euplexide A.

The pattern of substitution around the hydroquinone is such that functionalised structural precursors to a differentially protected hydroquinone with ethyl bromide substitution for the Stille coupling step were found to be somewhat expensive. A seven step synthesis

from 2-methyl anisole was thus devised (scheme 2.24). Friedel-Crafts acylation followed by Baeyer-Villiger oxidation installs ester functionality *para* to the methoxy substituent. Hydrolysis then yields the phenol and *ortho*-selective monohydroxymethylation is effected with formaldehyde[67]. Selective silyl ether protection of the phenolic hydroxyl group[68] was not attempted, rather exhaustive ^{t}butyldimethylsilyl ether formation followed by deprotection of the 1° alcohol only[69,70], with pyridinium *p*-toluene sulphonate under mild conditions, was effective. Simple bromination[71] then gave a functionalised benzylic bromide **242**.

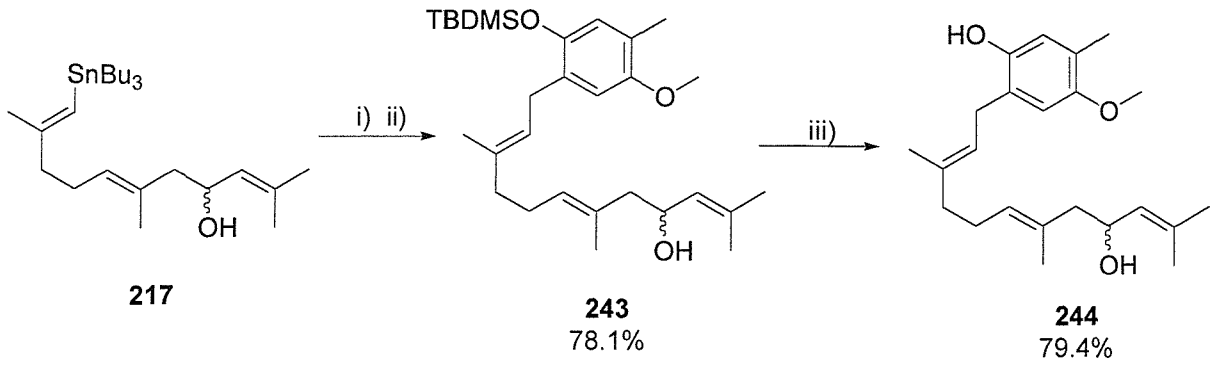
Scheme 2.24 Synthesis of a functionalised benzylic bromide.



Reagents and conditions: i) acetyl chloride, $AlCl_3$, CH_2Cl_2, Δ, 2 h. ii) *m*CPBA, CH_2Cl_2, Δ, 16 h. iii) 2M HCl, THF, Δ, 12 h. iv) NaOH (aq), $(H_2C{=}O)_n$, rt, 24 h. v) ^{t}butyldimethylsilyl triflate, DMAP, imidazole, THF, 12 h. vi) PPTS, EtOH, 50 °C, 3 h. vii) CBr_4, PPh_3, MeCN, 0 °C to rt, 20 h.

Palladium – catalysed coupling of **242** with the sesquiterpenoid alkenyl stannane **217** proceeded cleanly under the stoichiometric conditions employed for synthesis of 9-hydroxysargaquinone previously, to yield **243** in good yield. Silyl ether cleavage was then straightforward, phenol **244** was obtained in this way – also in good yield (scheme 2.25). Detailed strategy for coupling of **224** with the sugar is considered beyond the scope of this thesis. However, displacement of an anomeric acetoxy group, from either acetylated D-altrose or D-galactose, by bromide could precede Williamson ether synthesis with **244**, with overall retention of configuration at the anomeric carbon. C9-hydroxyl protection would, of course, be required. Cleavage of the aryl methyl ether is then the final step for prospective synthesis of moritoside and euplexide A, it is hoped that our successful synthesis of **244** *via* tandem zirconium – mediated methodology will allow completion of these steps in the future.

Scheme 2.25 Synthesis of a functionalised precursor to moritoside and euplexide A.



217

243
78.1%

244
79.4%

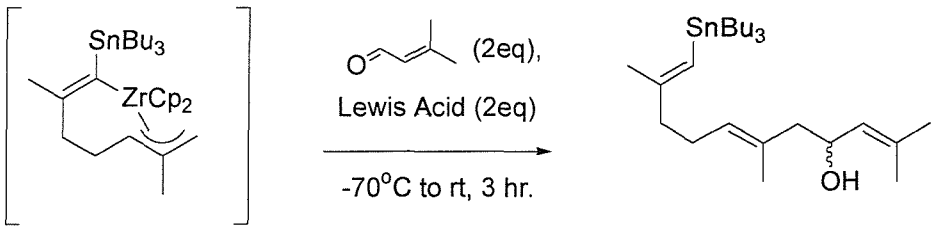
Reagents and conditions: i) $Pd_2(dba)_3{\cdot}CHCl_3$ (0.4 mol%), $AsPh_3$ (3.2 mol%), THF, 15 min, rt then **242** (1.0 eq), **217** (1.0 eq), Δ, 1 h. ii) KF (10%, aq), rt, 4 days. iii) TBAF-THF, rt, 12 h.

The key constraint upon efficient synthesis of all the natural product terpenoids discussed has been the erratic and generally low–yielding nature of the zirconium–mediated tandem insertion sequence. Both co-cyclisation and 1-lithio-1-chloro-2-methyl propene insertion are quantitative steps and it is thought that incomplete aldehyde addition to the so-formed intermediate methallyl zirconium species (**216**, scheme 2.14) is responsible for reduced yield. Monitoring of the aldehyde addition step is difficult as the product alkenyl stannane cannot be observed by gas chomatography. For successful optimisation, it was hoped that intentional, quantitative destannylation would allow reaction monitoring *via* yield of the resulting terminal alkene.

Methods for clean destannylation were explored using the model alkenyl tin fragment **228**, earlier synthesised (scheme 2.16), however without success. HCl/MeOH or HF-pyridine were found optimal for clean destannylation of **228** however acidic conditions resulted in partial H_2O elimination from the 'real' system whilst HF-pyridine did not then cleave the tributyltin group cleanly but gave several products.

Balance between increased yield in the aldehyde addition and product destannylation is clearly Lewis acid dependent and a survey of Lewis acid effect therefore pertinent. Initial examination of the crude NMR established those cases where full or significant loss of the tin moiety had occurred, isolation of product alkenyl stannane **217** from reaction mixtures not displaying destannylation then gave quantitative yields (table 2.6).

Table 2.6 Effect of added Lewis acid upon 3-methyl-2-butenal addition to an α-$SnBu_3$ substituted allyl zirconacycle.



216 **217**

Entry	Added Lewis Acid	Yield (%) **217**
1	None	24.0 – 67.0
2	$BF_3{\cdot}Et_2O$	0.0
3	BCl_3	< 10.0
4	Scandium triflate	18.9
5	$Ti(O^iPr)_4$	24.1
6	$AlCl_3$	< 10.0
7	$MgBr_2$	22.1
8	Et_2AlCl	< 10.0
9	Magnesium triflate	23.7
10	$ZnCl_2$	0.0
11	$TiCl_4$	0.0

Entries 1,4,5,7 and 9 : isolated yield. Entries 2,3,6,8,10 and 11 : determined from crude ^1H NMR (300 MHz, $CDCl_3$) by comparison of alkenic singlet δ_H = 5.81 ppm integration (1H) with singlet δ_H = 7.19 ppm (3H) for 1eq added 1,3,5-trichlorobenzene. Approximate value is given where alkenic signals from destannylated compound overlap.

Scandium triflate, magnesium triflate, $MgBr_2$ and $Ti(O^iPr)_4$ each result in a yield only comparable to that obtained without added Lewis acid, $Ti(O^iPr)_4$ is marginally the best of these and all stronger Lewis acids give extensive destannylation. Whilst, disappointingly, no enhanced yield of **217** is observed, addition of the weaker Lewis acids may activate 3-methyl-2-butenal towards self-condensation. Self-aldol reaction of 3-methyl-2-butenal was carried out to obtain the condensation product and the mass spectrum found to have an identical fragmentation pattern to the major by-product of above optimisation attempts. A difference in GC retention time of the two is thought to be attributable to α- versus γ-nucleophilic attack in the dimerisation.

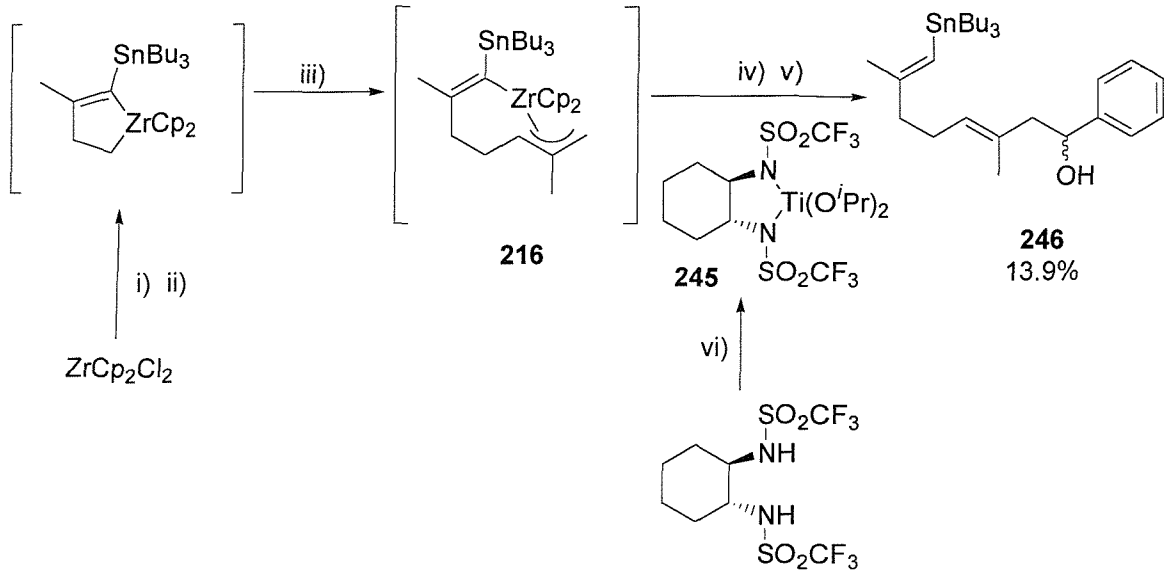
Aldehyde dimerisation was found to be incidental to the low yielding addition to methallyl zirconacycle **216** however. Treatment of **216** with $Ti(O^iPr)_4$ – activated benzaldehyde (no possible aldol) gave the expected benzylic alcohol product in an isolated yield of only 16.7%. Conclusively therefore, those weaker Lewis acids which do not induce destannylation of the tributyltin group also do not sufficiently activate 3-methyl-2-butenal for high-yielding addition to **216**. This is expected to be applicable also to geranial addition although no work upon optimisation of the diterpenoid system was carried out.

The synthesis of chiral secondary homoallylic alcohols from the enantioselective allylation of aldehydes using a chiral allyl borane reagent is known in the work of Corey[72,73]. In achieving catalytic enantioenduction we hoped to exploit the mildness of $Ti(O^iPr)_4$ as an added Lewis acid. The disulphonamide-$Ti(O^iPr)_4$-dialkylzinc catalysed enantioselective alkylation of aldehydes is well documented[74-78] and utilises electron-withdrawing chiral ligands which increase the Lewis acidity of the complex ideally for our application to enantioselective allylation of aldehydes with an allylzirconacycle.

Stronger Lewis acidity may result in aldehyde activation and an open, chiral transition state for addition in preference to the closed *trans* decalin transition state postulated earlier (figure 2.9).

Kobayashi has reported a chiral titanium complex[79] **245**, simply generated from $Ti(O^iPr)_4$ and the disulphonamide and potentially useful as a chiral Lewis acid. Hence the chiral disulphonamide was cleanly obtained from (R,R)-(-)-*trans*-diaminocyclohexane following resolution of Rac(+/-)-*trans*-diaminocyclohexane with D-tartaric acid according to known procedure[80]. A first attempt at enantioenduction in 3-methyl-2-butenal addition to the α-$SnBu_3$ substituted methallyl zirconacycle was then made (scheme 2.26). Addition of benzaldehyde to the allyl species **216** was followed by addition of a solution of the preformed titanium complex at –70 °C. The mixture was maintained at –60 °C before warming to room temperature, quench and isolation of an enantiomeric mixture of benzylic alcohols **246** in low yield.

Scheme 2.26 Potential chiral Lewis Acid – catalysed enantioenduction in PhCHO addition to **216**.



Reagents and conditions: i) EtMgCl (2 eq), -78 °C, 20 min ii) 1-tributylstannyl-1-propyne, -78 °C to 0 °C, 1 h then 0 °C to rt, 2 h. iii) 3-chloro-2-methylpropene, LiTMP, -78 °C to –70 °C, 40 min. iv) benzaldehyde (1.0 eq), **245** (1.7 mol%), -60 °C, 3h then –60 °C to rt. v) MeOH, $NaHCO_3$ (aq), rt, 6 h. vi) 1R,2R-sulphonamide, $Ti(O^iPr)_4$, 40 °C, 20 min, PhMe.

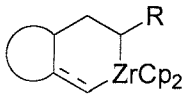
Esterification of **246** to the (R)-(+)-α-methoxy-α-trifluoromethylphenylacetate (MTPA) esters[81,82] was carried out in order to establish whether enantioenduction had been achieved. Unfortunately, crude NMR indicated loss of the tributyltin group and although diastereomeric alkenic protons could not be confidently assigned, the integrals of these peaks suggested a 1.4 : 1.0 ratio of isomers. Disappointingly, a purified sample could not be obtained due to time constraints and absolute stereochemistry of the major diastereoisomer was not determined, nevertheless it is promising that potential for enantioselective chiral Lewis Acid catalysed aldehyde addition has been demonstrated. As well as the general synthetic potential, development of this chemistry and incorporation into the described synthetic route for terpenoid synthesis may allow a future stereodefined synthesis of (9R)-Crinitol.

Chapter Thee : Elaboration of Five Membered Zirconacycles By insertion Of Alkyl and Alkenyl Carbenoids.

3.0 Introduction.

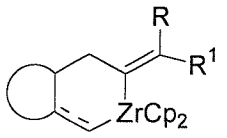
Ring expansion of zirconacyclopent –anes / -enes to zirconacyclohex –anes / -enes by carbenoid insertion is a well documented route to six – membered zirconacycles **300** and **301** (figure 3.1, see Chapter One for a comprehensive review)[4,5,15,16,43,44,50,51,83-87].

Figure 3.1 Zirconacyclohex –anes / -enes resulting from homologation of five-membered zirconacycles.



300

R = $SiMe_3$, $SiMe_2Ph$, OR, SO_2Ph, CN, SPh, $P(O)(OEt)_2$,Br, Ar, allyl, allenyl, propargyl.



301

$R = R^1 = Me$

$R = H, R^1 = HC{=}CH_2$

$R = HC{=}CH_2, R^1 = H$

Insertion of simple, unfunctionalised alkyl and alkenyl carbenoids into zirconacycles is a poorly developed area of organozirconium chemistry and limits the scope of available six-membered zirconacycles. Figure 3.1 cites the only examples, insertion of symmetrical 1-chloro-1-lithio-2-methyl prop-1-ene is the only reported instance of insertion of a 2,2-disubstituted alkenyl carbenoid, stereospecific insertion of 1,3-butadienyl carbenoids into both saturated and unsaturated five – membered zirconacycles has also been demonstrated by Kasatkin[87]. Synthesis of stereodefined tri- and di-substituted alkenes, respectively, in this way is complemented by early investigation into the insertion of stabilised lithiated epoxides into zirconacycles. This process yields *cis* alkenes following syn-elimination of a zirconocene alkoxide (section 1.3.7.2, earlier).

Better developed is the insertion of alkenyl carbenoids into acyclic zirconocene chlorides, obtained from hydrozirconation of alkenes and alkynes with $Cp_2Zr(H)Cl$, as a route to synthesis of stereodefined acyclic alkenes[88-90] (section 1.3.1).

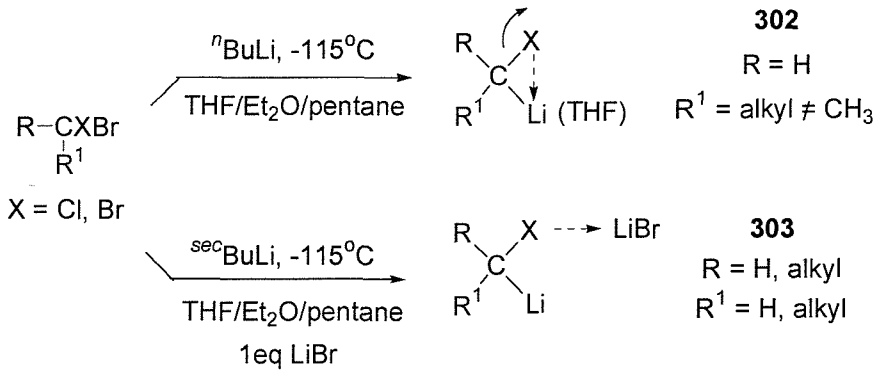
Insertion of a cyclopropyl carbenoid represents the only good example of simple alkyl carbenoid insertion[87], many other alkyl carbenoids show poor regiocontrol in the insertion into acyclic zirconocene chlorides and insertion into zirconacycles remains to be explored.

Herein we present novel work extending the scope of carbenoid insertion into five – membered zirconacycles, preceded by brief introduction to the preparation and use of unstable α-halo-α-lithio alkyl species.

3.0.1 α-Halo-α-Lithio Alkyl Species.

Preparation of α-haloalkyl lithium carbenoids and their trapping with organozirconocenes presents several problems, caused by the high instability of such species'[91-94]. Decomposition of α-halo alkyl/alkenyl lithiums *via* α-elimination is promoted by inductive electron donation to the α carbon which also reduces the ease with which such carbenoids may be formed by α-deprotonation. Metalation in this way cannot be achieved at the low temperatures (<-100 °C) required for alkyl carbenoid stability, however this difficulty may be overcome by halogen / metal exchange of 1,1-dihalo alkanes which proceeds to afford alkyl carbenoids effectively. Scheme 3.1 describes formation of unstable α-haloalkyl lithiums in this way[92-95].

Figure 3.1 Zirconacyclohex –anes / -enes resulting from homologation of five-membered zirconacycles.

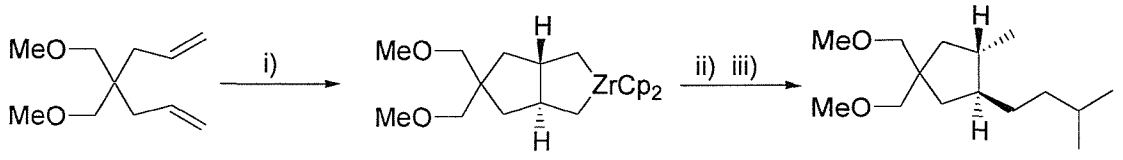


Stabilisation of the carbenoid is achieved with one equivalent added lithium bromide and 1,1-dialkyl species **303** shown to be stable at –115 °C under these conditions by Villieras *et al*[94]. Yields of between 70% and 90% for carbenoids **302** and **303** are reported and Villieras has demonstrated the synthesis of α-haloaldehydes and α-haloketones though acylation of RCHXLi with alkyl formates or esters respectively, *via* the lithium salt of the halohydrin[92,93]. This is reported to take place at low temperatures between –110 °C and –115 °C and is promising for nucleophilic insertion into zirconacycles.

3.1 Insertion of α-Halo Alkyl Lithium Carbenoids into Zirconacycles.

Deprotonation of 1-chloro-2-methyl propane with ^{n}butyl lithium at –100 °C or ^{sec}butyl lithium in the presence of TMEDA at –130 °C was attempted, followed by addition of a cooled solution of saturated zirconacyclopentane **304**. No trace of the desired product **305**, resulting from 1-chloro-1-lithio-2-methyl propane insertion and subsequent hydrolysis, was observed however (scheme 3.2).

Scheme 3.2 Attempted 1-chloro-1-lithio-2-methyl propane insertion.

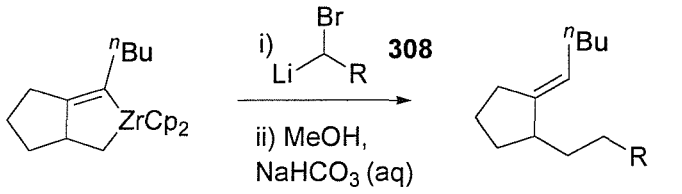


304 **305** 0%

Reagents and Conditions: i) Cp_2ZrCl_2, ^{n}BuLi, THF, -78 °C to room temp, 2 h. ii) 1-chloro-2-methyl propane, THF/Et_2O/pentane, either ^{n}BuLi, -100 °C or ^{sec}BuLi, TMEDA, -130 °C. iii) MeOH, $NaHCO_3$ (aq), room temp, 6 h.

We attribute lack of insertion to failed α-deprotonation of the chloride and quickly decided to explore the alternative bromine / lithium exchange route to low temperature alkyl carbenoid formation. Hence 1,1-dibromo alkanes (1,1 dibromobutane and 1,1 dibromohexane) were readily obtained from alkylation of lithiated dibromomethane with 1-bromopropane or 1-iodopentane respectively. Bromine / lithium exchange and insertion of 1-bromo-1-lithio alkanes into α-alkenyl substituted zirconacyclopentene **306** was now examined (table 3.1).

Table 3.1 1-bromo-1-lithio alkene insertion into a zirconacyclopentene.



306

307a R = $^{n}C_3H_7$

307b R = $^{n}C_5H_{11}$

Entry	R	Base	Temperature °C	Other conditions[a]	Outcome
1	$^{n}C_5H_{11}$	^{n}BuLi	<-100	A	No insertion
2	$^{n}C_3H_7$	^{n}BuLi	<-110	A	20% GC conversion to **307a**
3	$^{n}C_5H_{11}$	^{n}BuLi	<-112	A	20% GC conversion to **307b**
4	$^{n}C_5H_{11}$	^{tert}BuLi	<-90	B	No insertion
5	$^{n}C_5H_{11}$	^{tert}BuLi	<-100	B	No insertion
6	$^{n}C_5H_{11}$	^{n}BuLi	<-90	B	No insertion
7	$^{n}C_5H_{11}$	^{n}BuLi	<-100	B	No insertion
8	$^{n}C_5H_{11}$	^{n}BuLi	<-110	B	No insertion

[a] A: **306** added to pre-formed carbenoid. B: carbenoid prepared *in situ*.

Entries 1-8 are presented chonologically and success in this insertion reaction was very limited. Addition of a cooled solution of the zirconacyclopentene **306** to a pre-formed solution of the carbenoid (one equivalent, entries 1,2 and 3) firstly resulted in no insertion with the temperature held below –100 °C. No remaining *gem*-dibromide was observed however, indicating complete bromine/lithium exchange. Under the assumption that 1-bromo-1-lithio hexane is not stable at –100 °C and decomposition is faster than insertion therefore, the insertion was attempted at –110 °C and a little cooler at –112 °C. In both cases a 20% conversion to **307** following low temperature hydrolysis was observed by gas chomatography. Substantial remaining *gem*-dibromide in these latter examples was indicative of incomplete Br/Li exchange at the lower temperature, and may partially account for low yield of insertion. Upon warming above –60 °C the homologated zirconacyclohexene was found to be unstable.

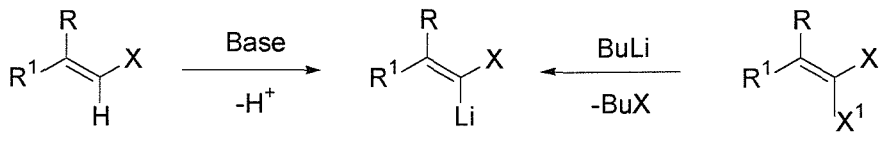
Difficulty in maintaining reaction temperature below −110 °C was experienced, particularly during addition of the zirconacycle – the solution temperature and addition rate of which are difficult to jointly control. Therefore, *in situ* formation of the carbenoid was sought according to the method of Villieras[93] (table 3.1, entry 8). No insertion was observed however we assumed complete Br/Li exchange both from the known precedent and also from absence of starting dibromide. Entries 8 and 3 are in contrast then, failed insertion at <-110 °C following *in situ* carbenoid insertion is unexpected and we can only attribute the result to our observation of poor dissolution of the zirconacycle in Trapp's solvent at the low temperature of *in situ* carbenoid formation. Addition of the zirconacycle in a minimal volume of THF to a Trapp's solution of the carbenoid was effected for entries 1-3 without this solubility problem.

Use of ^{tert}BuLi rather than ^{n}BuLi for Br/Li exchange effected no change upon the system. Attack upon the zirconium centre by the base, with loss of cyclopentadienyl anion, is a further complicating factor, the behaviour of $R_2ZrCpBu$ species is an unexplored area of organozirconium chemistry.

3.2 Insertion of α-Halo Alkenyl Lithium Carbenoids into Zirconacycles.

Choice of alkenyl carbenoid for insertion into zirconacycles is made based on the following structural factors. Firstly, 2,2-dialkyl substituted alkenyl carbenoids are thermolytically unstable[91,96,97] and 2-*mono* substituted alkenyl species will therefore be the starting choice for exploring the insertion reaction into zirconacycles. Furthermore, the nature of the β-substituent influences the method of formation of the carbenoid (scheme 3.3). Deprotonation of 2-monosubstituted alkenyl halides is known to be effective only in the case where R^1 is an alkenyl, alkynyl or aryl substituent (**308** R = H, R^1 = unsaturated)[90]. For β-alkyl substituted alkenyl bromides (**308** R = H, R^1 = alkyl, X = Br) bromo/lithium exchange is a likely although little explored route to the carbenoid. Stereoselective Br/Li exchange of 1,1-dibromides (**310** X = X^1 = Br, R = H, R^1 = alkyl) is known and takes place predominantly *trans* to the β-hydrogen[98], yielding **309**, R = H, R^1 = alkyl.

Scheme 3.3 Alkenyl carbenoid preparation.



308 R = H, R^1 = aryl, alkenyl alkynyl

309

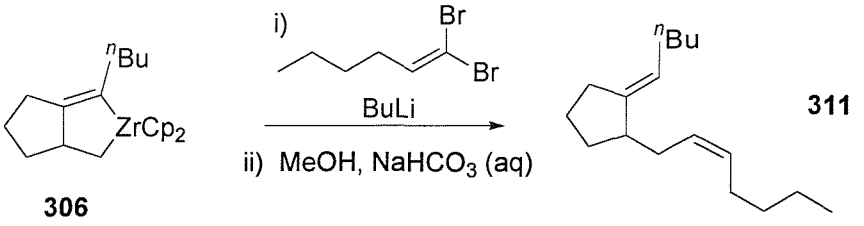
310 R = H, R^1 = alkyl

Bromine/lithium exchange of a 1,1-dibromo alkene with a 2-alkyl group, to give an unfunctionalised carbenoid **309** (R = H, R^1 = alkyl), is the strategy described below (section 3.2.1). This is then complemented by extending the known scope for insertion of a stabilised alkenyl lithium **309** (R = H, R^1 = alkynyl) into acyclic organozirconocenes to insertion into zirconacycles (section 3.2.2).

3.2.1 1-Lithio-1-Bromo-1-Hexene Insertion.

1,1-Dibromo-1-hexene was readily obtained from valeraldehyde and CBr_4/PPh_3 by Wittig synthesis[99]. Bromine/lithium exchange and insertion of 1-lithio-1-bromo-1-hexene into a zirconacyclopentene **306**, α-substituted on the alkenyl side, was now explored (table 3.2). Regioselective insertion into the alkyl C-Zr bond of **306** is expected and (Z) geometry about the introduced double bond is predicted from stereoselective Br/Li exchange[98]. Isomerisation of a 2-monosubstituted alkenyl carbenoid has not been reported although partial isomerisation of 2,2-dialkyl substituted alkenyl carbenoids has been previously observed by our group and would result of course in mixed geometry.

Table 3.2 1-Lithio-1-bromo-1-hexene insertion into a zirconacyclopentene.



Entry	Base (eq)	Temperature °C	Eq added dibromide	Other conditions[a]	Outcome
1	^{tert}BuLi (1.0)	-78	1.0	B	No Br/Li exchange
2	^{tert}BuLi (2.0)	-78	1.0	B	No Br/Li exchange
3	^{tert}BuLi (1.0)	-110	1.0	B	No Br/Li exchange
4	^{n}BuLi (2.0)	-78	2.0	B	No Br/Li exchange
5	^{n}BuLi (1.0)	-110	1.0	A	Trace conversion

6	^{n}BuLi (2.0)	-78	2.0	A	No Br/Li exchange
7	^{n}BuLi (2.0)	-110	2.0	A	50% GC conversion to **311**
8	^{n}BuLi (4.0)	-110	4.0	A	50% GC conversion to **311**
9	^{n}BuLi (1.0)	-110	1.0	C	Trace conversion

[a] A: **306** added to pre-formed carbenoid solution then temperature maintained for 20 min. B: Carbenoid prepared *in situ*. C: **306** added to pre-formed carbenoid solution then temperature maintained for 1 hour.

All attempts to form the carbenoid *in situ* (entries 1-4) failed. We hoped to see rapid trapping of the carbenoid at –78 °C but no Br/Li exchange took place at this temperature. *In situ* ^{tert}butyl lithium addition at –110 °C also failed, high-yielding Br/Li exchange under the conditions of entry 4 (^{tert}BuLi, -105 °C) has been reported by Grandjean[98] and we therefore surmise preferential attack of the base upon zirconium here.

Addition of the cooled zirconacycle **306** to a pre-formed solution of the carbenoid (entries 5-9) met with more success although attempted Br/Li exchange at –78 °C remained unsuccessful (entry 6) and clearly the lower temperature of –110 °C is required.

One equivalent ^{n}BuLi, added to 1,1-dibromo-1-hexene at –110 °C, gave partial Br/Li exchange after 10 minutes and all of the so-formed carbenoid inserted into the added zirconacycle. Use of two equivalents ^{n}BuLi and two equivalents dibromide under the same conditions gave the same percentage Br/Li exchange as expected but of course the yield of insertion was now higher (entry 7). 50% conversion was observed by gas chomatography and the hydrolysis product identified as a 1:1 pair of isomers, each with m/z = 235.4 ($M+H^+$, monoinserted product **311**, $C_{17}H_{30}$ = 234.5) by low resolution CIMS. Carbenoid insertion into the alkyl C-Zr bond of zirconacyclopentenes α-substituted on the alkenyl side is entirely regioselective (with the lone special exception of $Me_3SiCHClLi$ insertion, see section 4.2.2) and discounts the possibility of monoinserted regioisomers here. It is thought that the isomer pair obtained are geometric alkene isomers about the double bond introduced from the alkenyl carbenoid, resulting from non-stereoselective Br/Li exchange. Near identical gas chomatographic retention times were observed, unfortunately **311** proved troublesome to separate from the hydrolysis product of uninserted zirconacyclopentene **306** and time constraints precluded a thorough optimisation program to obtain quantitative insertion. However, use of up to four

equivalents of carbenoid (entry 8) again resulted in only 50% insertion into **306** as a result of incomplete Br/Li exchange (none of the protonated carbenoid product was recovered). Partial metal/halogen exchange may be attributable to the increased difficulty associated with maintaining –110 °C in the larger scale reaction.

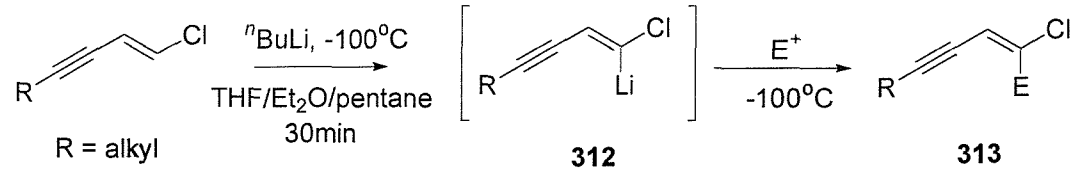
This preliminary observation of insertion of a non-functionalised alkenyl carbenoid into a zirconacycle for the first time is promising and marks a starting point for a thorough investigation of the stereoselectivity of Br/Li exchange of 1,1-dibromoalkanes, stability and isomerisation of 1-lithio-1-bromo alkenes, and optimal conditions for the insertion in future.

3.2.2 1-Chloro-1-Lithio Enyne Insertion.

As introduced in section 3.2, α-deprotonation of haloalkenes 2-monosubstituted with a stabilising alkynyl group is an effective means for preparation of the corresponding 1-halo-1-lithio alkenyl carbenoid.

Metalation of (E)-1-chloro-1-alken-3-ynes has been demonstrated at low temperature by Alami[100] and product carbenoid **312** reacted with various electrophiles to give α-substituted chloroenynes **313** (scheme 3.4). Stereoselective reaction with the electrophile indicates stability of this alkenyl carbenoid to isomerisation.

Scheme 3.4 Literature preparation of stabilised alkenyl carbenoids.

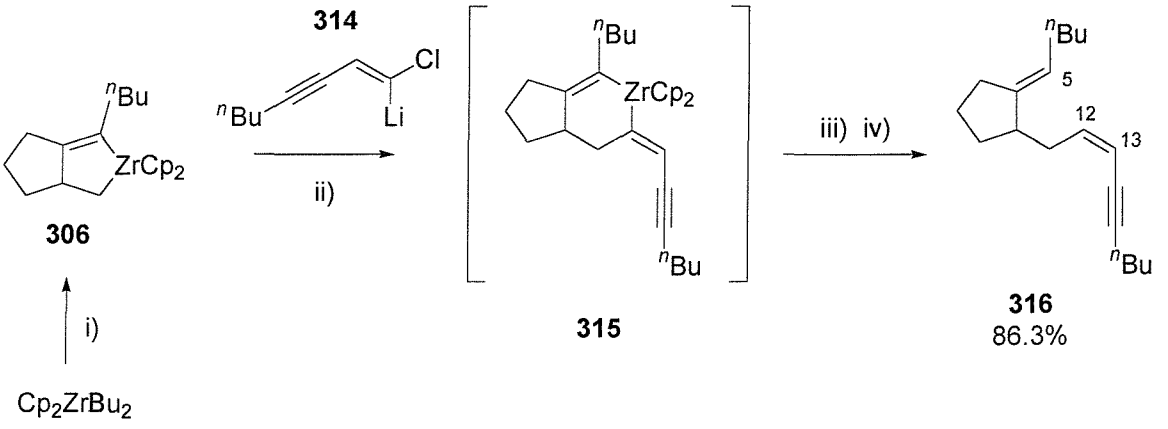


Alami's conditions are not suitable for *in situ* carbenoid preparation and insertion into organozirconocenes following earlier discussed evidence of direct butyl lithium attack upon zirconium and poor solubility of organozirconocenes in Trapp's solvent.

Preparation of 1-chloro-1-lithio-2-methyl prop-1-ene with lithium tetramethylpiperidine in the presence of a zirconacyclopentene at –90 °C (in THF) has been previously demonstrated in our group however and results in 30% insertion into the zirconacycle[5]. Replication of this insertion with variation in the amount of carbenoid and temperature was now found to give an optimal insertion of 1-chloro-1-lithio-2-methyl prop-1-ene into a saturated zirconacycle to give the known product in a GC conversion of 60% at –78 °C with two equivalents of carbenoid. Hence application of these conditions to novel

insertion of the alkenyl carbenoid **314** into zirconacyclopentene **306** was made (scheme 3.5). The carbenoid precursor 1-chloro-1-octen-3-yne was synthesised in 84.4% isolated yield by Pd-catalysed coupling between 1-hexyne and 1,2-dichloroethene.

Scheme 3.5 1-Lithio-1-chloro enyne insertion into a zirconacyclopentene .



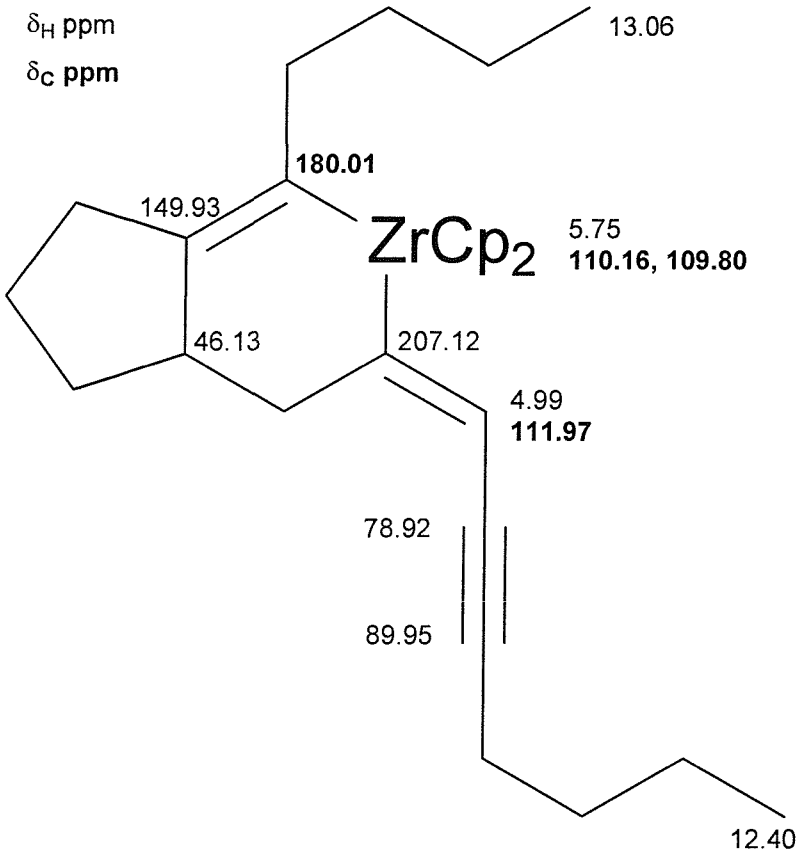
	δ_H ppm	splitting	Coupling J / Hz
H5	6.80	t	6.8
H12	5.77	dt	10.6, 7.4
H13	5.40	t	10.6

^{1}H NMR spectrum of **316** was recorded in $CDCl_3$ at 400 MHz.

Reagents and Conditions: i) 1-undec-6-yne, THF, -78 °C to room temp', 2 h. ii) 1-chloro-1-octen-3-yne (2 eq), LiTMP (2 eq, freshly prepared from 2,2,6,6 TMP and ^{n}BuLi, THF, 0 °C, 30 min), -78 °C, 20 min. iii) – 78 °C to room temp', 16 h. iv) MeOH, $NaHCO_3$ (aq), room temp', 2 h.

A single, monoinserted product **316** was isolated in good yield following hydrolysis of zirconacyclohexene **315**. **315** was formed quantitatively and found to be a stable species, permitting NMR characterisation at room temperature (figure 3.2). Regioselectivity of insertion is assigned from the ^{1}H NMR spectrum of the protonated product **316**. Alkenic signals arise from protonation at C5 (δ_H = 6.80 ppm, 1H, triplet, J = 6.8 Hz) and C12 (δ_H = 5.77 ppm, 1H double triplet, J = 10.5, 7.4 Hz) and are characteristic of the regioisomer **316** shown in scheme 3.5.

Figure 3.2 NMR of a novel zirconacyclohexene resulting from alkenyl carbenoid insertion into **306** .

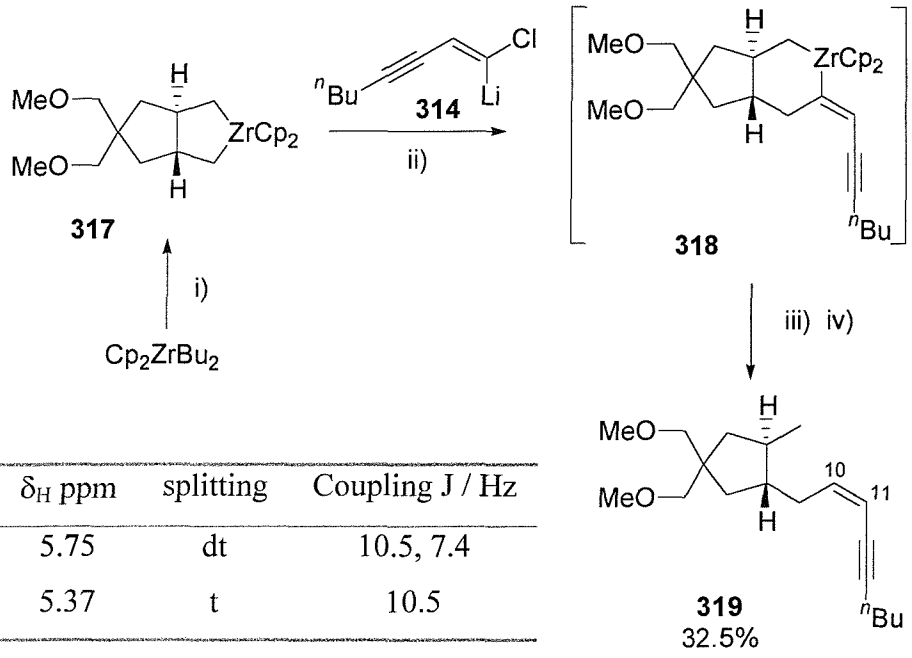


NMR spectra were recorded in C_6D_6 at 400 MHz (proton) and 100.5 MHz (carbon). δ_H ppm in plain text and δ_C **ppm** in **bold**. Overlapping methine and methylene proton shifts and unassigned triplet carbon shifts are omitted.

Coupling between protons H12 and H13 of **316** is $^3J_{HH}$ = 10.6 Hz across the (Z) alkene and confirms clean inversion of configuration at the carbenoid carbon during 1,2 metallate rearrangement to form **315**. As introduced in section 1.3.1.1, the isomerisation of 2,2-disubstituted alkenyl carbenoids[90] is associated with stabilisation of the cationic carbenoid component arising from metal assisted ionisation by β alkyl substituents. Hence the isomerisation had not been observed for alkenyl carbenoids with *mono* substitution at the β position and isolation of the (Z) alkene **316** is consistent with this.

Insertion of **314** into simple zirconacyclopentane **317** under the same conditions was also successful (scheme 3.6). Hydrolysis of the intermediate zirconacyclohexane **318** yielded the expected product **319**, again as a result of monoinsertion and without isomerisation of the introduced (Z) double bond. The ^{1}H NMR spectrum of **319** displayed alkenic signals at δ_H = 5.37 ppm (doublet, J = 10.5 Hz, H11) and δ_H = 5.75 ppm (double triplet, J = 10.5, 7.4 Hz, H10).

Scheme 3.6 1-Lithio-1-chloro enyne insertion into a zirconacyclopentane .



	δ_H ppm	splitting	Coupling J / Hz
H10	5.75	dt	10.5, 7.4
H11	5.37	t	10.5

^{1}H NMR spectrum of **319** was recorded in $CDCl_3$ at 400 MHz.

Reagents and Conditions: I) 4,4-dimethoxymethyl-1,6-diene, THF, -78 °C to room temp', 2 h. ii) 1-chloro-1-octen-3-yne (2 eq), LiTMP (2 eq, freshly prepared from 2,2,6,6 TMP and ^{n}BuLi, THF, 0 °C, 30 min), -90 °C, 20 min. iii) –90 °C to room temp', 16 h. iv) MeOH, $NaHCO_3$ (aq), room temp', 2 h.

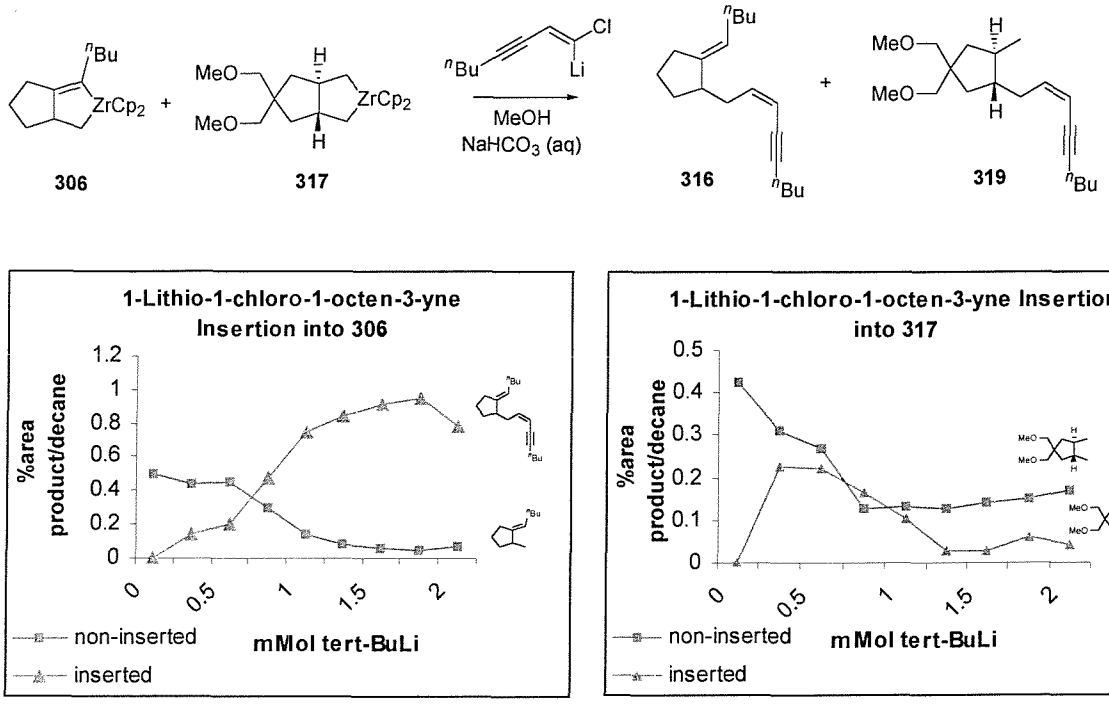
Enyne **319** was isolated in a yield of only 32.5%, remaining starting material (i.e. hydrolysis product of **317**) accounts for the lower recovery and insertion of 1-chloro-1-lithio enyne **314** into zirconacyclopentane **317** is therefore not quantitative as was seen for insertion into zirconacyclopentene **306**.

In order to make comparison between the two systems, a combined 1:1 solution of zirconacycles **306** and **317** (0.5 mMol of each) and two equivalents (2 mMol) 1-chloro-1-octen-3-yne was prepared. To the cooled mixture was then added 0.25 mMol aliquots of ^{tert}BuLi up to a total of 2 mMol base. For convenience, ^{tert}BuLi replaces the amide base of schemes 3.5 and 3.6 following repetition of the separate insertion reactions in which 50% and 100% insertion of **314**, formed by α-deprotonation with ^{tert}BuLi, into **306** and **317** was seen respectively – mirroring that observed when the carbenoid was prepared with LiTMP.

Figure 3.3 depicts the outcome, by gas chomatographic monitoring, of competitive insertion of the alkenyl carbenoid into the two zirconacycles. The two plots are not overlaid for the sake of clarity, however the 'time scale' of decreasing concentration of non-inserted products is measured as increasing addition of aliquots of base and is closely

comparable for the two zirconacycles. This indicates that there is no 'preference' or faster insertion into the zirconacyclopentene **306** to account for higher yield of insertion into **306** compared with into **317** during the limited time scale imposed by the conditions of schemes 3.5 and 3.6.

Figure 3.3 Alkenyl carbenoid insertion into a zirconacyclopent –ane and –ene in mixed solution.



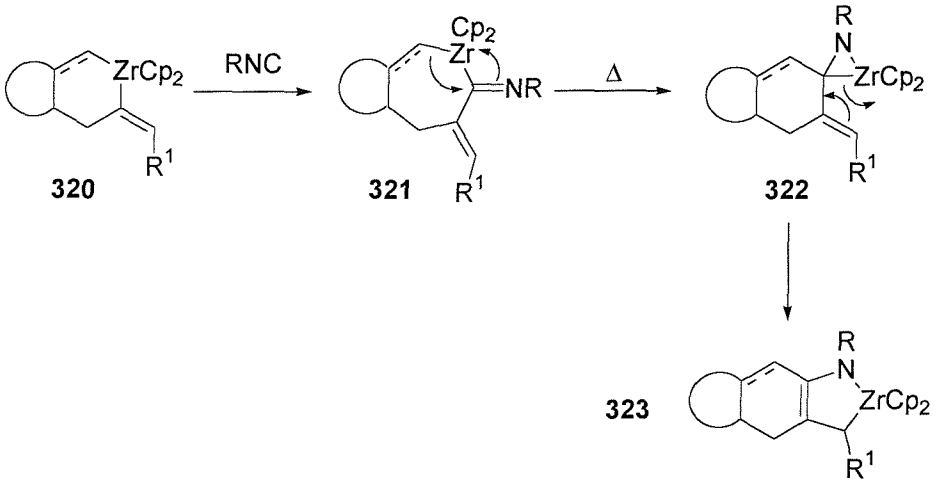
Insertion into **306** yields **316** in increasing yield and is straightforward. In the case of insertion into **317** however, disappearance of the ring-expanded zirconacyclohexane **318** is indicated by decreasing GC yield of the hydrolysis product **319** over time and accounts for the reduced yield seen in the insertion (scheme 3.6). Stability of **318** up to room temperature was established and hence we must attribute the effect to a further reaction of the zirconacyclohexane **318**. The most likely explanation is a second insertion of the alkenyl carbenoid into **318** and in support of this proposal is the observation that no re-protonated 1-chloro-1-octen-3-yne was recovered, post work-up, following formation of the full two equivalents carbenoid. No direct evidence of an unexpected double insertion product was sought here, this phenomenon has since become established in the work of our group however[101].

3.2.3 Further Elaboration of Six–Membered Zirconacycles.

Six–membered zirconacycles have potential for elaboration *via* a wide range of reactions with known application to five–membered zirconacycle elaboration, for example carbonylation and isonitrile insertion (Chapter One), further carbenoid insertions and metal-catalysed selective functionalisation of one or both C-Zr bonds[102-109].

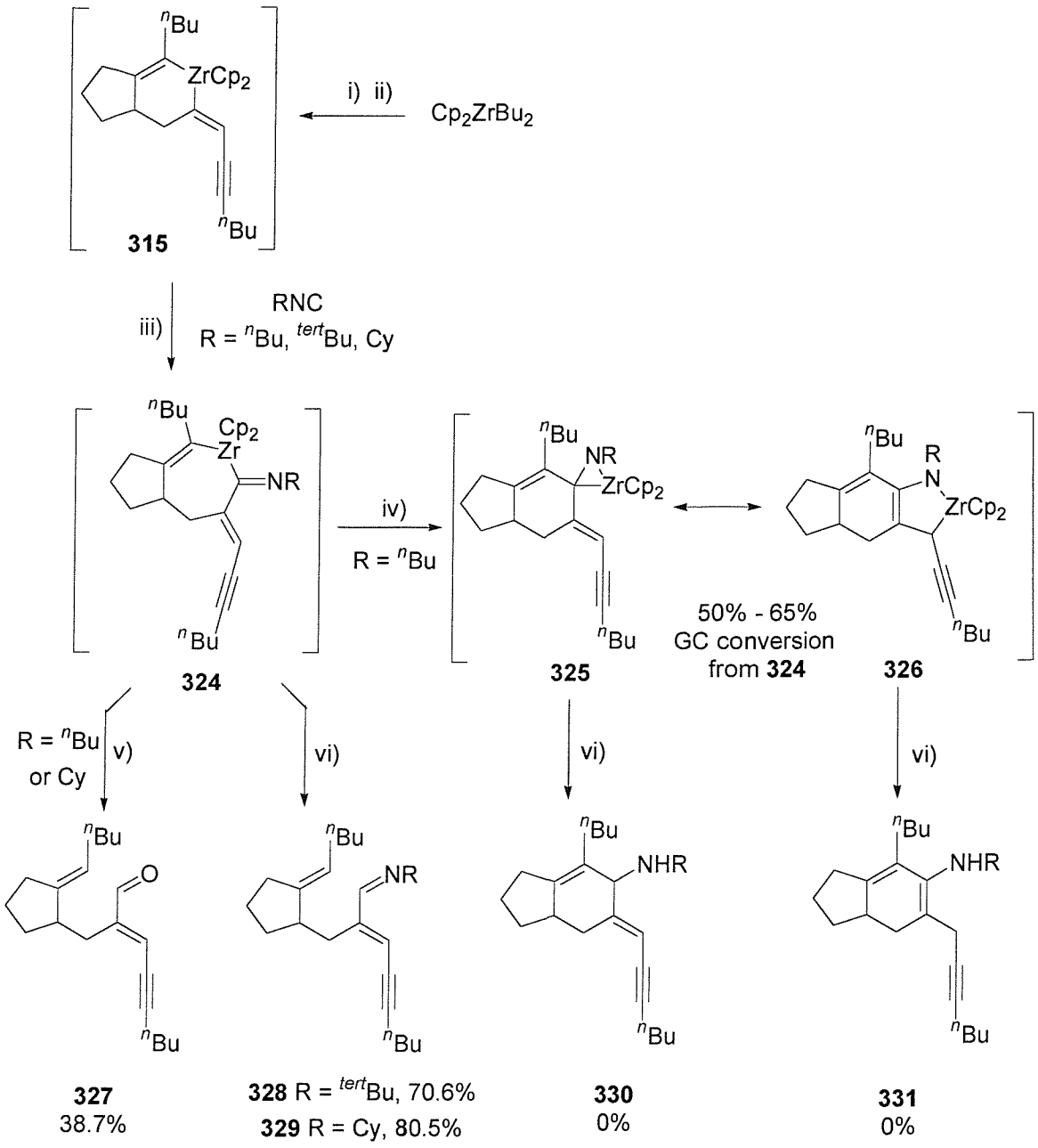
Insertion of isonitriles, RNC, into α-alkenyl substituted zirconacycles **320** should give thermodynamically favourable azadiene complexes **323** from the η^2 imine **322** (scheme 3.7) and will yield amine products following protic quench. Rearrangement of the initially formed iminoacyl complex **321** should be slow however and imine or aldehyde products are potentially obtained from protonation or hydrolysis of **321** respectively.

Scheme 3.7 Potential for isocyanide insertion into six-membered zirconacycles.



Controlled access to amine, imine or aldehyde products from six-membered zirconacycles would beautifully complement the tandem co-cyclisation/carbenoid insertion methodology developed for obtaining them. Insertion of isonitriles into zirconacyclohexene **315**, which we are able to synthesise quantitatively (section 3.2.2), is therefore described in scheme 3.8.

Scheme 3.8 Isonitrile insertion into a zirconacyclohexene with α-alkenyl substitution.

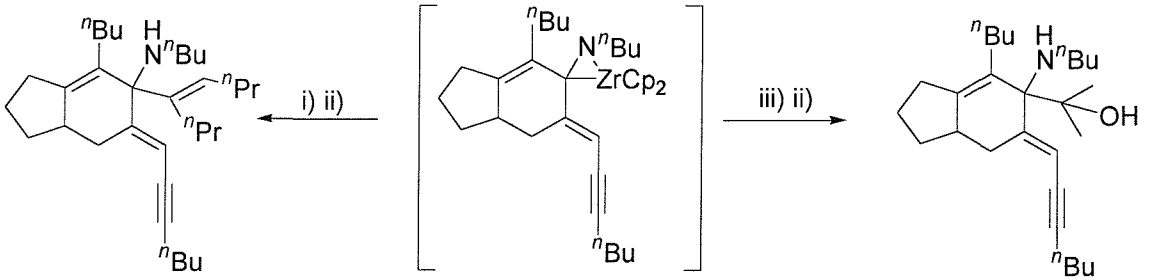


Reagents and Conditions: i) 1-undec-6-yne, THF, -78 °C to room temp', 2 h. ii) 1-chloro-1-octen-3-yne, ^{tert}BuLi, -78 °C, 20 min. iii) RNC, room temp', 30 min. iv) room temp', 12 h OR Δ, 1 h. v) 1M AcOH, room temp', 12 h. vi) MeOH, $NaHCO_3$ (aq), room temp', 2 h.

Regioselective insertion of ^{n}butyl, ^{tert}butyl and cyclohexyl isocyanides into **315** took place rapidly and quantitatively to produce a novel, homologated zirconacycloheptene iminoacyl complex **324**, acid hydrolysis of which gave the α,β-unsaturated aldehyde **327** when R = ^{n}Bu or Cy. Hydrolysis of the ^{tert}butyl imine was not successful but is of course of no consequence for synthesis as the same aldehyde results regardless of which imine is used.

Mild aqueous quench of **324** preserves the imine functionality and imines **328** and **329** were obtained in high yield in this way, as additional evidence of the intermediacy of the iminoacyl **324**. Thermal rearrangement of **324** was now considered for the case resulting from ^{n}butyl isonitrile insertion. Stability of the azazirconacyclopentene **326** might be expected to assist the equilibrium of rearrangement of **324** to **325** and it was found that rearrangement of the iminoacyl took place in a maximal GC conversion of 65% following either 12 hours at room temperature or one hour reflux. The product of rearrangement appeared a single peak by gas chomatography following rapid, small-scale protic work-up, with m/z = 342 by LRCIMS ($M+H^+$, $C_{24}H_{39}N$, **330** or **331**), although may be either **330**, **331** or a mixture of the two. Isolation of the amine(s) repeatedly proved unsuccessful, aqueous work-up or acid extraction of the amine salt each resulted in a plethora of breakdown products. Identification of the rearrangement product was also attempted *via* π-trapping of the η^2 imine **325** (scheme 3.9), expected to yield **332** and **333** from exposure to 4-octyne and acetone respectively[110,111].

Scheme 3.9 Attempted trapping of an η^2 imine with π-component.



332 0%

325

333 0%

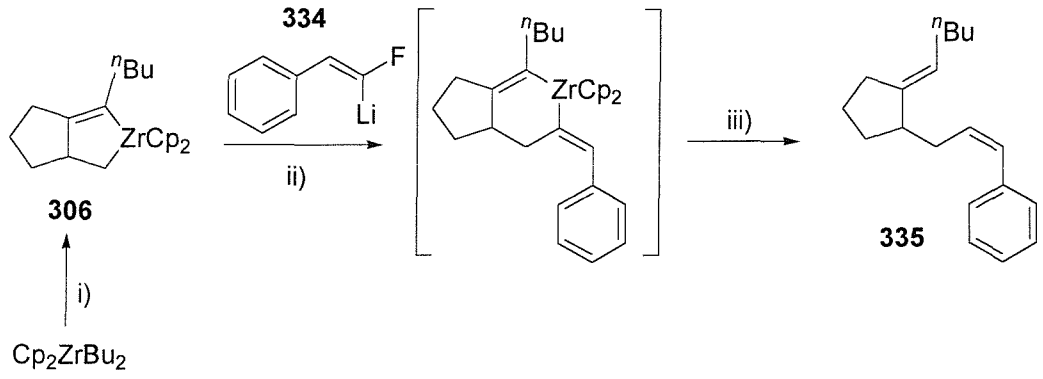
Reagents and Conditions: i) 4-octyne, Δ, 20 h. ii) MeOH, $NaHCO_3$ (aq), room temp', iii) acetone, Δ, 1 h.

No addition products were observed, the product of iminoacyl (**324**) rearrangement remained unchanged under the conditions of scheme 3.9. From this we tentatively assume the azazirconacyclopentene **326** to be the stable form over the η^2 imine **325** as it is unlikely that **326** will react with added alkyne or acetone to give a highly strained azazirconacycloheptadiene. This is the first, indirect, evidence for the existence of synthetically valuable azadiene complexes of type **326** resulting from multi-component coupling.

3.2.4 Insertion *via* Alkynate Complex Rearrangement.

In order to improve the yield and known scope of alkenyl carbenoid insertion, examination of the insertion of potentially stable 1-lithio-1-fluoro alkenes into zirconacycles was made. β-Fluorostyrene was synthesised from benzaldehyde *via* a Wittig reaction, in which (E)-geometry is preferred in a (87:13) (E:Z) ratio from a stabilised ylid intermediate[112], and *in situ* deprotonation to yield the carbenoid **334** in the presence of zirconacyclopentene **306** was expected to yield **335** (scheme 3.10).

Scheme 3.10 Attempted insertion of alkenyl fluoride into a zirconacyclopentene.

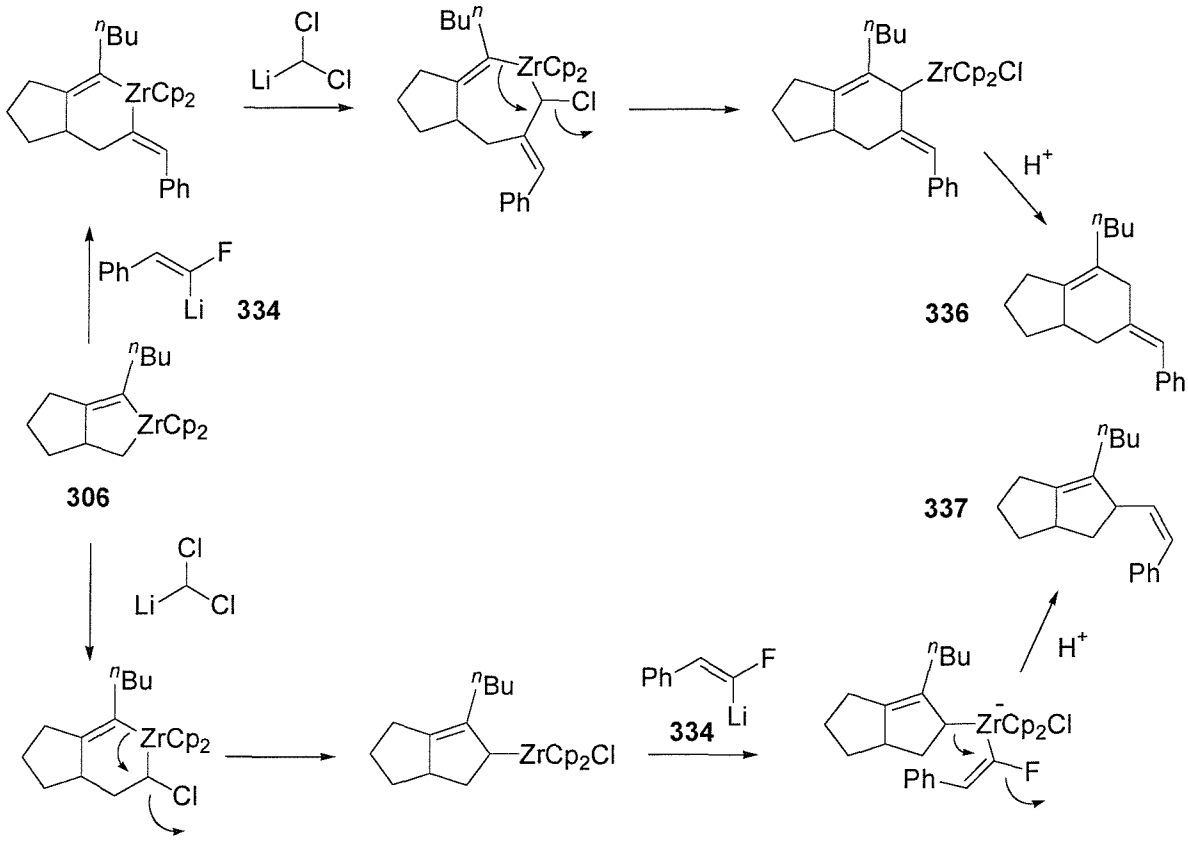


Reagents and Conditions: i) 1-undec-6-yne, THF, -78 °C to room temp', 2 h. ii) β-fluorostyrene (1 eq), LiTMP (1.5 eq, freshly prepared from 2,2,6,6 TMP and ^{n}BuLi, THF, 0 °C, 30 min), -78 °C to –60 °C, 45 min. iii) MeOH, $NaHCO_3$ (aq), room temp', 2 h.

A single insertion product was cleanly obtained in an isolated yield of 35% based upon molecular weight $C_{19}H_{26}$ (**335**) = 254.5. Mass spectroscopy was clearly indicative of incorporation of an extra carbon atom however with m/z = 266 (M^+, $C_{20}H_{26}$, EI) or 267 ($M+H^+$, $C_{20}H_{26}$, CI). β-Fluorostyrene is a highly volatile compound from which it is difficult to efficiently strip the solvents used for its extraction following synthesis. It was found that the supply of β-fluorostyrene obtained from Wittig synthesis, and subsequently used, retained dichloromethane – thought to be the source of C-incorporation therefore. Deprotonation of dichloromethane and insertion of the resulting 1,1-dichloro-1-lithio species into zirconacycles is known[85] and insertion of $CHLiCl_2$ either before or after insertion of PhCH=CFLi would account for the observed carbon incorporation. Low recovery is also accounted for in this way as the solution of β-fluorostyrene:CH_2Cl_2 used in attempted insertion was a 2.63:1.0 ratio and hence contained 1.22 mMol (E)-β-fluorostyrene (0.067 mMol (Z)-β-fluorostyrene) and 0.49 mMol CH_2Cl_2. Insufficient base for deprotonation of species present was included.

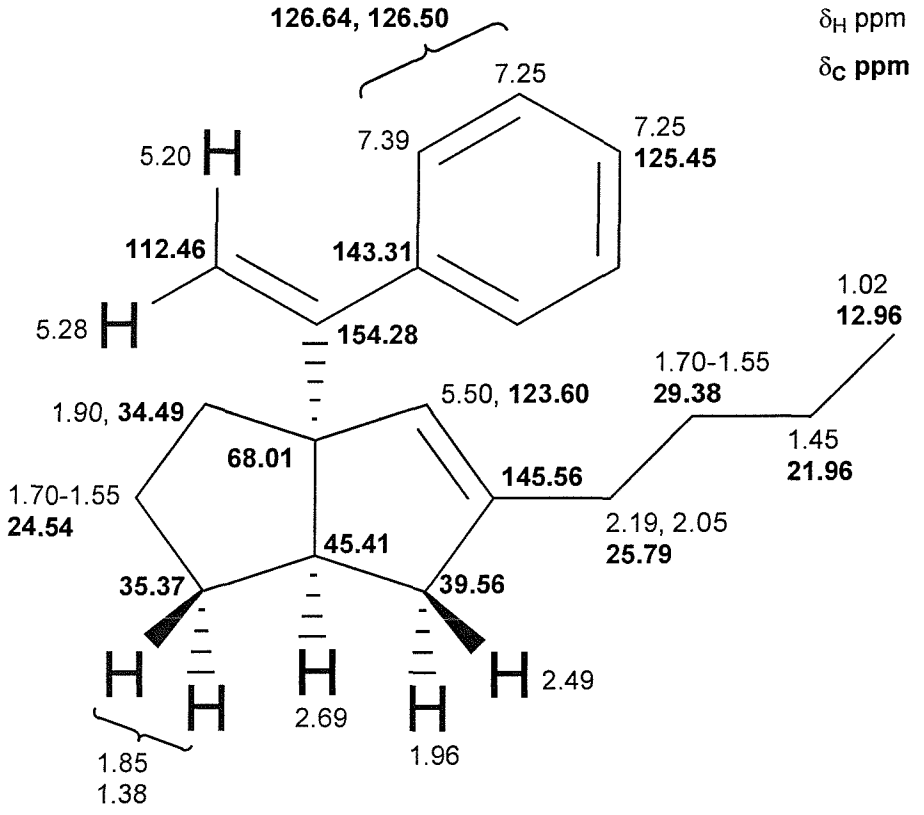
Sequential insertion of PhCH=CFLi (**334**) and $CHLiCl_2$ is shown below (scheme 3.11) *via* the known mechanism for carbocycle synthesis from insertion of 1,1-dihalo-1-lithio species.

Scheme 3.11 Theoretical sequential insertion to obtain a homologated product.

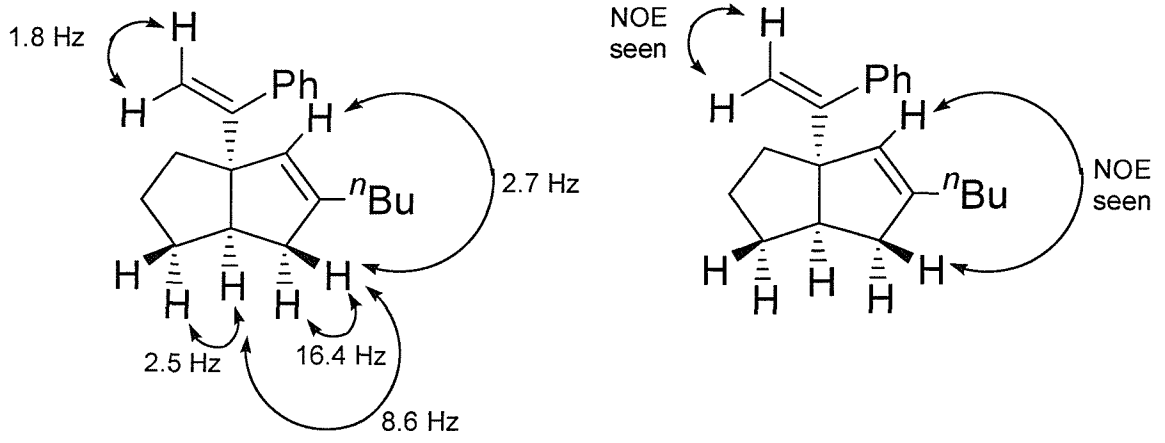


We expected to elucidate the structure of the 'double-insertion' product in accordance with either **336** or **337** therefore. Unexpectedly however, NMR analysis of the compound showed the structure to be a rearranged styrene **338** (figure 3.4). The double bond introduced is terminal (δ_H = 5.28 ppm, 1H doublet $^2J_{HH}$ = 1.8 Hz and δ_H = 5.20 ppm, 1H doublet $^2J_{HH}$ = 1.8 Hz) and the internal double bond of the carbocycle has migrated with its ^{n}butyl substituent – now β to the ring junction. This alkenic proton appears at δ_H = 5.50 ppm (1H pentet, J = 2.0 Hz). Ring junction stereochemistry is assigned *cis* based upon the vicinal coupling of the ring junction proton with α methylene protons. Vicinal coupling $^3J_{HH}$ = 8.6 Hz is observed, appropriate for the 120° dihedral angle. A dihedral angle close to 180° in the rather strained *trans* ring junction isomer would manifest as a large coupling constant. 2D C-H and long range C-H coupling allowed full assignment of the molecule as in figure 3.4.

Figure 3.4 Structural elucidation of a double insertion product **338** by NMR analysis.



NMR spectra were recorded in C_6D_6 at 400 MHz (proton) and 100.5 MHz (carbon). δ_H ppm in plain text and δ_C **ppm** in **bold**. Diagnostic J_{HH} couplings and NOEs are shown below.

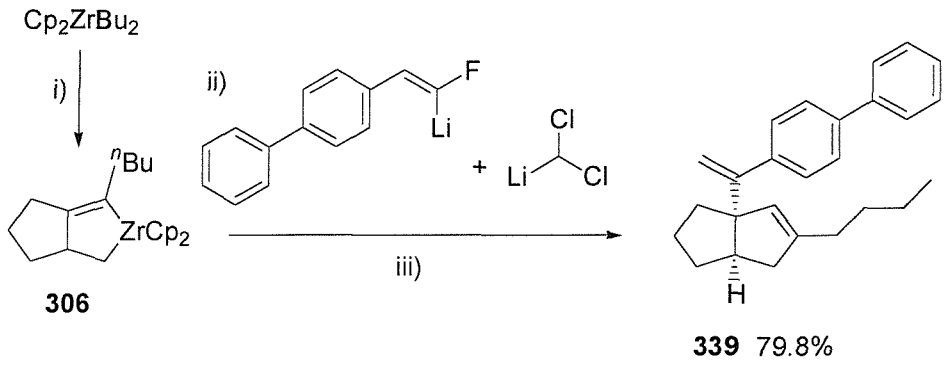


It was surprising to observe the shown NOE between alkenic proton of the internal olefin and a methylene proton across the ring, apparent in both directions but as the only signal from irradiation of the alkenic proton. Further confirmation of the structure was sought by introduction of a group likely to result in a crystalline product and required replication of the 'accidental' synthesis of **338**. This was successful, i.e. 1.29 eq CH_2Cl_2-free β-

fluorostyrene and 0.49 eq added CH_2Cl_2 in the presence of 1.0 eq zirconacyclopentene **306**. Improved yield (84.8% based upon CH_2Cl_2 vs. 71.4% previously) was resultant when 2.0 eq LiTMP base were used. Interestingly, during attempted optimisation to give high yield based upon the zirconacycle, it was observed that with addition of >0.5 eq CH_2Cl_2 the insertion products of lithiated dichloromethane only were consistently obtained.

Our ability to replicate the reaction using β-fluorostyrene permitted variation in substitution and it was hoped that introduction of a biphenyl moiety would result in a crystalline product **339** (scheme 3.12). 4-Biphenyl-β-fluorostyrene was obtained in 69.9% yield, from 4-phenyl carboxaldehyde. This alkenyl fluoride is a solid, non-volatile product.

Scheme 3.12 Novel double insertion of fluoroalkenyl and 1,1-dihalo carbenoids into a zirconacyclopentene.



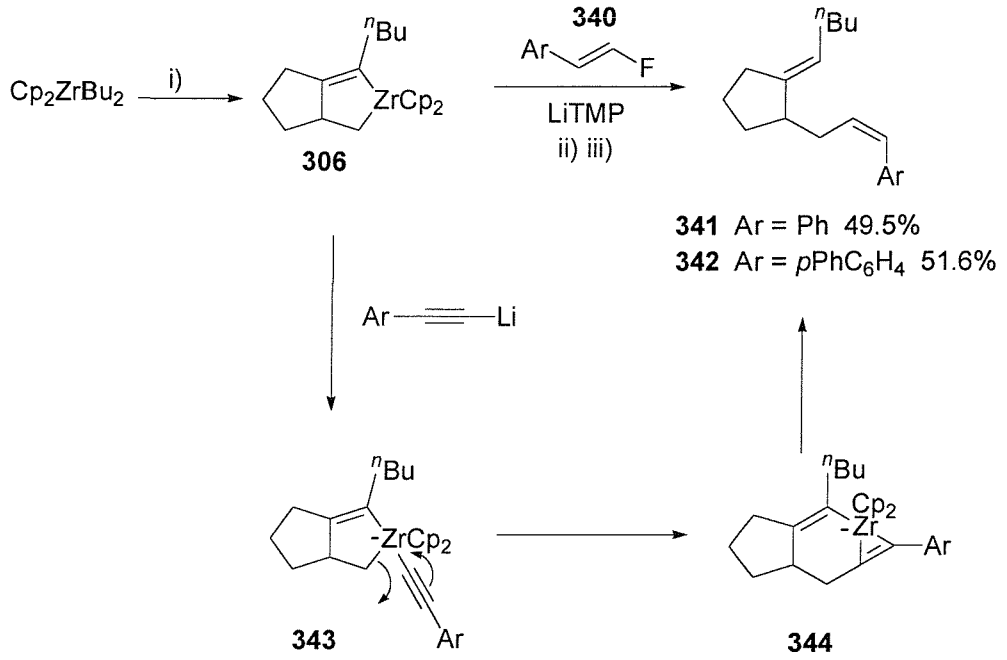
Reagents and Conditions: i) 1-undec-6-yne, THF, -78 °C to room temp', 2 h. ii) 4-biphenyl-β-fluorostyrene (1.48 eq, (87:13, E:Z), CH_2Cl_2 (0.49 eq), LiTMP (2.0 eq, freshly prepared from 2,2,6,6 TMP and ^{n}BuLi, THF, 0 °C, 30 min), -78 °C to –60 °C, 45 min. iii) MeOH, $NaHCO_3$ (aq), room temp', 12 h.

The expected product **339** was obtained in good yield, unfortunately as an oil. Derivatisation of the structure for X-ray crystallographic studies has so far proved messy and is likely to constitute an extensive area of future work from which the mechanism of this intriguing reaction may be understood as well as its scope for application to other zirconacycles.

Double insertion of simple PhCH=CFLi **334** and $CHLiCl_2$ was found to be fluorine specific following repetition of the procedure with replacement of β-fluorostyrene by (E)-β-chlorostyrene. The crucial difference between behaviour of chloro- and fluoro-styrene following low temperature lithiation was discovered upon returning to the originally intended insertion of the 1-lithio-1-fluoro alkenyl carbenoid without CH_2Cl_2

contamination. The desired products, **341** and **342**, of regioselective monoinsertion into the alkyl carbon-zirconium bond of **306** were obtained in reasonable yield (scheme 3.13). Only trace insertion could be detected in the reaction mixture below -60°C however, not consistent with all previous trapping of carbenoids by organozirconocenes described thoughout this thesis. The apparent insertion products **341** and **342** arose only after the mixture had been warmed to room temperature and this is an observation consistent with rapid elimination of fluoride from the precursor **340** to afford aryl alkynes which are subsequently lithiated and add to the zirconacycle[113] to give the zirconate **343**. Slow rearrangement of **343** to **344** has been reported to occur at room temperature in monocyclic systems by Negishi[114].

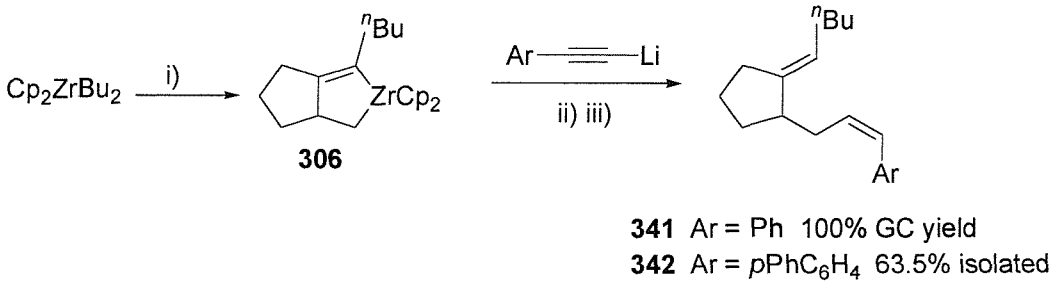
Scheme 3.13 Insertion of alkenyl fluorides – actually *via* alkynate rearrangement.



Reagents and Conditions: : i) 1-undec-6-yne, THF, -78 °C to room temp', 2 h. ii) **340** (1.0 eq), LiTMP (1.0 eq, freshly prepared from 2,2,6,6 TMP and ^{n}BuLi, THF, 0 °C, 30 min), -78 °C to room temp', 12 h. iii) MeOH, $NaHCO_3$ (aq), room temp', 2 h.

(E)-aryl substituted products **341**and **342** could each be obtained in good yield therefore from direct lithiation and insertion of the appropriate aryl alkyne itself (scheme 3.14), proving applicability of Negishi's 'ate' complex formation and rearrangement to this system.

Scheme 3.14 Replication of aryl alkyne lithiation and insertion .



Reagents and Conditions: : i) 1-undec-6-yne, THF, -78 °C to room temp', 2 h. ii) Aryl alkyne (1.0 eq), LiTMP (1.0 eq, freshly prepared from 2,2,6,6 TMP and ^{n}BuLi, THF, 0 °C, 30 min), -78 °C to room temp', 12 h. iii) MeOH, $NaHCO_3$ (aq), room temp', 2 h.

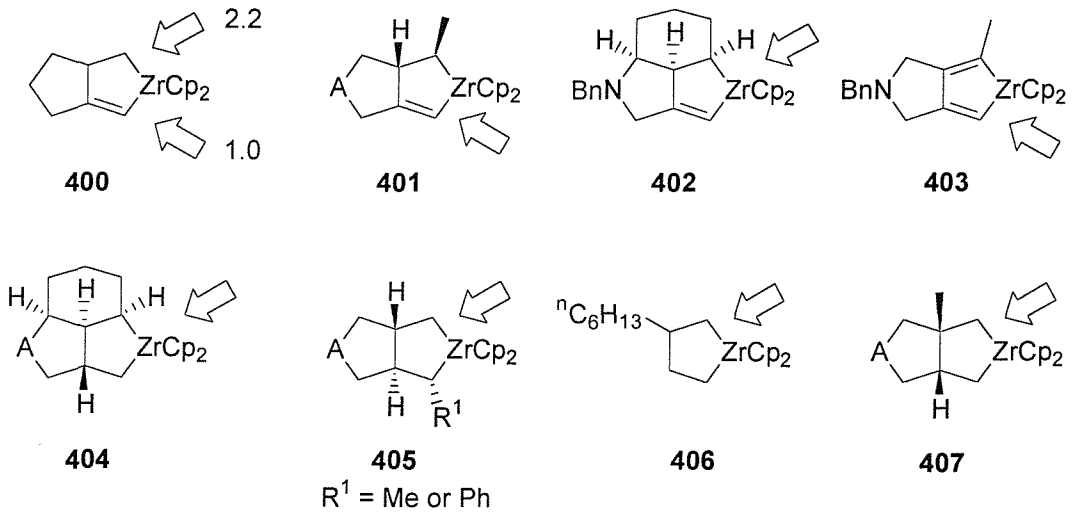
Whilst it is disappointing that direct insertion of 1-fluoro-1-lithio species has not been demonstrated, the known insertion of lithiated (E)-β-chlorostyrene at –78 °C[101] combined with the failure of this species to yield a 'double insertion' product with CH_2Cl_2 as earlier described implicates a lithiated aryl alkyne, generated only from the alkenyl fluorides, in the formation of novel products **338** and **339** (scheme 3.12, earlier). Specifically, the double insertion takes place below –60 °C at which temperature 'ate' complex **343** is present according to scheme 3.13. Preparation of **343** *via* insertion of lithiated phenyl acetylene was not found to lead to the double insertion product **338** following subsequent addition of dichloromethane however, rather **341** is obtained quantitatively. Insertion of $CHLiCl_2$ into **306**, rearrangement to the cyclopentene at –78 °C and subsequent addition of lithiated phenyl acetylene is found to give the double insertion product in good yield (~60% GC conversion) however. Very little postulation can be made regarding the formation of **338** and **339**, deuterium quench gives single incorporation into the terminal alkenic position *trans* to the aryl substituent however the mechanism remains to be understood.

In brief conclusion, several forays into previously unexplored aspects of carbenoid insertion chemistry have been made in this chapter. Chiefly, limits for alkyl and alkenyl carbenoid formation and insertion into zirconacycles have been defined although successful first elaborations of six-membered zirconacycles resulting from insertion of stabilised alkenyl carbenoids into a zirconacyclopentene represents excellent demonstration of multi-component synthesis.

4.0 Introduction.

For application in organic synthesis the regiochemistry of insertion of carbenoids into unsymmetrical zirconacycles must be predictable. In the case of insertion into bicyclic zirconacyclopentenes where there is an α-substituent on the alkenyl but not alkyl side, selective insertion of alkenyl, allenyl, allyl, propargyl, alkyl and benzyl carbenoids into the alkyl carbon-zirconium bond is well established[5,17,44], as was described in chapter one and built upon in chapter thee. Similarly, chapter two described regioselective allyl carbenoid insertion into monocyclic zirconacyclopentenes with $SnBu_3$, $SiMe_3$, SCH_3 or SPh substitution α- to the metal. For zirconacycles more complex than α-alkenyl substituted zirconacyclopentenes, regiocontrol has only been previously studied for the insertion of lithium chloroallylides (as in section 1.3.4.2)[15]. Representative literature examples of regiocontrol for lithium chloroallylide insertion are shown in figure 4.1.

Figure 4.1 Regiochemistry of allyl carbenoid insertion.



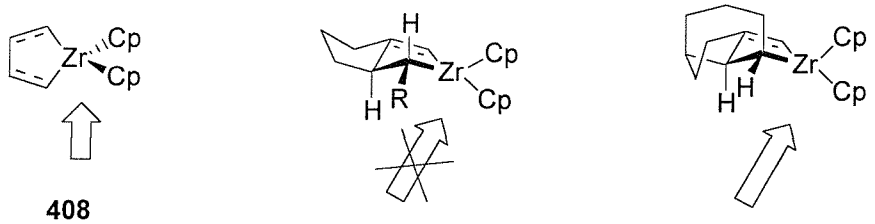
A = $C(CH_2OCH_3)_2$ and/or $C(CH_2OC(CH_3)_2OCH_2)$ and/or NR

It is observed that insertion into a zirconacyclopentene **400**, which is not α-substituted on either the alkyl or alkenyl sides of the metal, shows only a 2.2 : 1.0 selectivity in favour of insertion into the alkyl side. Steric hindrance of approach to the alkenyl side by use of a terminally substituted *trans*-alkene in the co-cyclisation to form **401** gives complete selectivity for insertion into the alkenyl side. However, insertion into the zirconacycle **402**, derived from a cyclic alkene, surprisingly gives complete selectivity for insertion into

the alkyl side. In the proposed 1,2-metallate rearrangement mechanism for insertion (scheme 1.10, earlier) nucleophilic attack of a carbenoid on zirconium to form the 'ate' complex must be lateral, occurring upon the empty Zr-orbital in the σ ligand plane (figure 4.2, **408**)[115,116]. Hence the observed difference in regiochemistry of attack upon **401** and **402** may have a steric basis, the methyl substituent in **401** occupies the plane of lateral attack (figure 4.2, **409** illustrates) whereas in **402** the alkyl substituent lies well out of the plane (**410** illustrates). However, the difference between **400** and **402** cannot be justified on steric grounds – **402** is more hindered on the alkyl side.

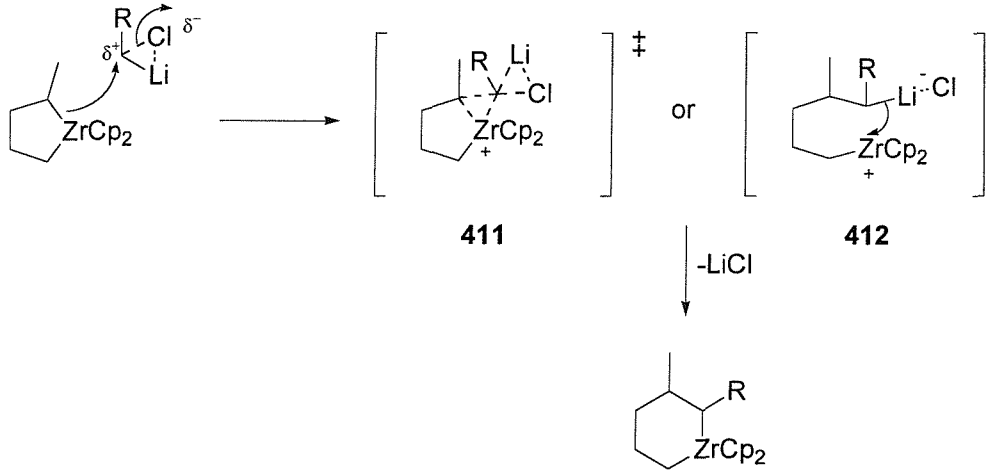
A similar pattern is observed for insertion into zirconacyclopentanes **404** and **405** where insertion into the more hindered, cyclohexyl substituted, side is observed for the former. Zirconacyclopentanes **406** and **407** are alkyl substituted β to zirconium and show remarkable selectivity for insertion into this, somewhat more hindered, side.

Figure 4.2 Direction of carbenoid attack upon zirconacycles.



For those regiochemical results which cannot be explained using steric arguments (**402**, **404**, **406**, **407**) the observed selectivity correlates with the largest coefficient of the Highest Occupied Molecular Orbital (HOMO) of the zirconacycle, rather than of the Lowest Unoccupied Molecular Orbital (LUMO), suggesting that the carbenoid may be attacking as an electrophile[15]. α-Lithio-α-halo species' behave as powerful electrophiles[117] and reaction pathways which occur *via* concerted insertion into the carbon-zirconium bonds and transition state **411**, or electrophilic attack on the carbon-zirconium bond and intermediate **412**, are reasonable (scheme 4.1).

Scheme 4.1 Alternative mechanisms for carbenoid insertion into organozirconocenes.

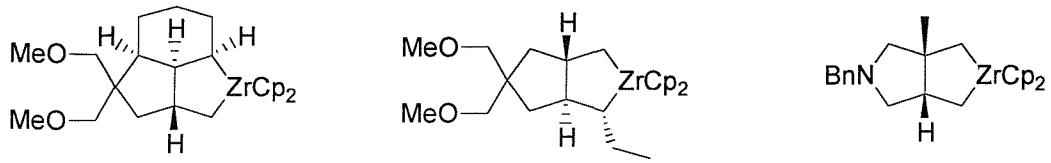


Substantiation of this proposed electrophilic carbenoid attack upon organozirconocenes could be made by carrying out the insertion of carbenoids in which the electrophilicity of the carbenoid carbon is influenced by substitution with groups possessing electron withdrawing or donating effects. It might be expected that, according to the concerted mechanism of scheme 4.1, enhancement of the δ^+ve charge in the former case would correlate with the dominant frontier molecular orbital interaction between the LUMO of the carbenoid and the HOMO of the zirconacycle. It is unknown how this effect will manifest upon insertion into a zirconacycle in which the steric argument for regioselective insertion is made (for example α-alkyl substituted zirconacycle **405**). The forthcoming chapter describes novel work investigating the insertion of differentially substituted 1-lithio-1-chloro species' into α- and β-substituted non-symmetrical zirconacyclopentanes.

4.1 Synthesis and Stereochemistry of Non-symmetrical Zirconacyclopentanes.

Two zirconacyclopentanes of type **404** and **405**, bearing an alkyl substituent α to zirconium but displaying opposite regioselectivity for allyl carbenoid insertion (figure 4.1), were deemed crucial for investigation of the carbenoid insertion mechanism. Additionally, the regiocontrol apparently resulting from β-substitution of **406** and similarly at the ring junction of **407**, is striking. Choice of zirconacycles **413**, **414** and **415** for investigation of regiochemistry of carbenoid insertion was therefore made, providing consistency with earlier work from our group examining insertion of allyl carbenoids (figure 4.3).

Figure 4.3 Non-symmetrical zirconacyclopentanes chosen for regiochemical studies.



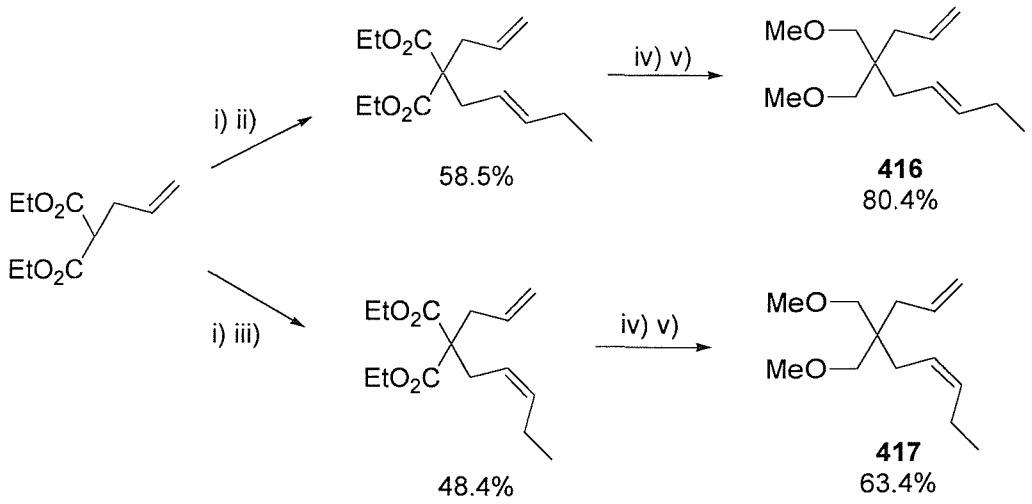
413 **414** **415**

Some clarification of this choice, and specifically the relative stereochemistries depicted in figure 4.3, is required.

Tricycle **413** is formed by intramolecular cocyclisation between a terminal alkene and cyclohexene group, a previously reported zirconacycle in which *trans* ring junction stereochemistry across the C-C bond newly formed during co-cyclisation is known[15].

The α-ethyl substituted zirconacyclopentane **414** results from cocyclisation of, importantly, either a *cis* **or** *trans* disubstituted alkene intramolecularly with the terminal olefin. (E)- and (Z)-diethyl-3-allyl-3-(2-pentenyl)pentanedioate (**416** and **417** respectively) were synthesised simply from diethylallylmalonate and the (E)- or (Z)-2-pentenyl methanesulphonate, followed by reduction and methylation (scheme 4.2). Yields are reasonable as without optimisation and sufficed to provide enough material for cyclisation.

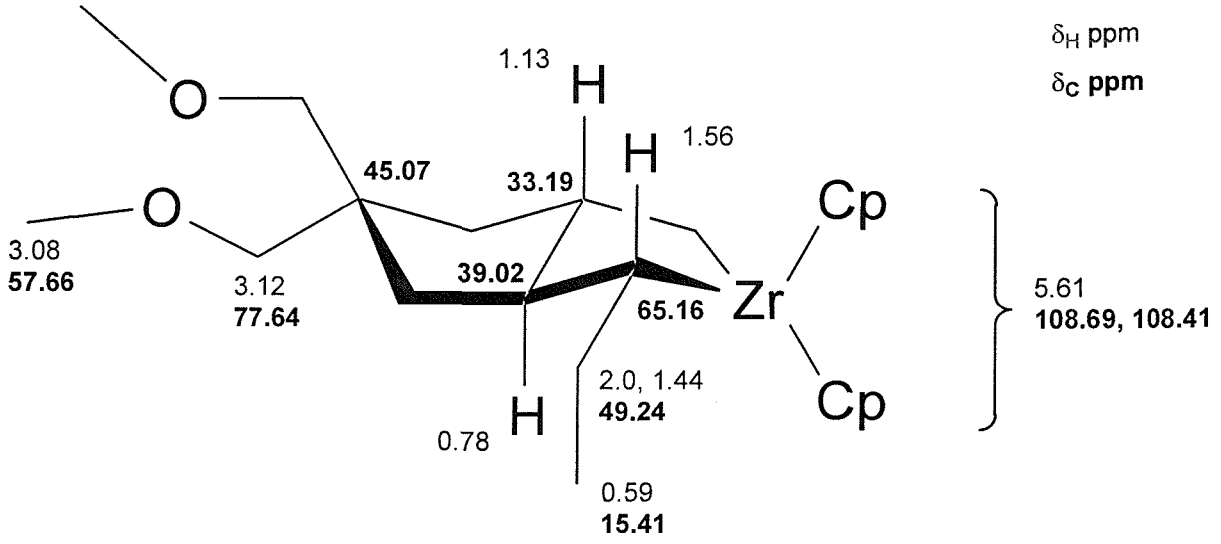
Scheme 4.2 Dimethyl-3-allyl-3-(2-pentenyl)pentanedioate synthesis.



Reagents and conditions: i) Na, EtOH, 0 °C, 20 min. ii) (E)-2-pentenyl methanesulphonate, room temp', 16 h. iii) (Z)-2-pentenyl methanesulphonate, room temp', 16 h. iv) $LiAlH_4$, Et_2O, 0 °C to room temp', 16 h. v) NaH, THF, MeI, room temp'.

NMR analysis of the zirconacycles resulting from cocyclisation of **416** and **417** shows them to be the same (figure 4.4). In both cases the ZrCH methine proton resonance is identified at δ_H = 1.56 ppm as a ddd (J = 11.5, 11.5, 4.5 Hz) and therefore *trans* to the ring junction proton. Cocyclisation of **417** has been previously reported and the relative stereochemistry between the ring junction proton and ethyl substituent incorrectly assumed to be *trans* in the zirconacycle (wrongly predicted from the (Z)-alkene precursor)[15]. Presumably β-H elimination and readdition to the (E)-alkene **420** (scheme 4.3) is responsible for isomerisation and our observation of a common zirconacycle from both **416** and **417**.

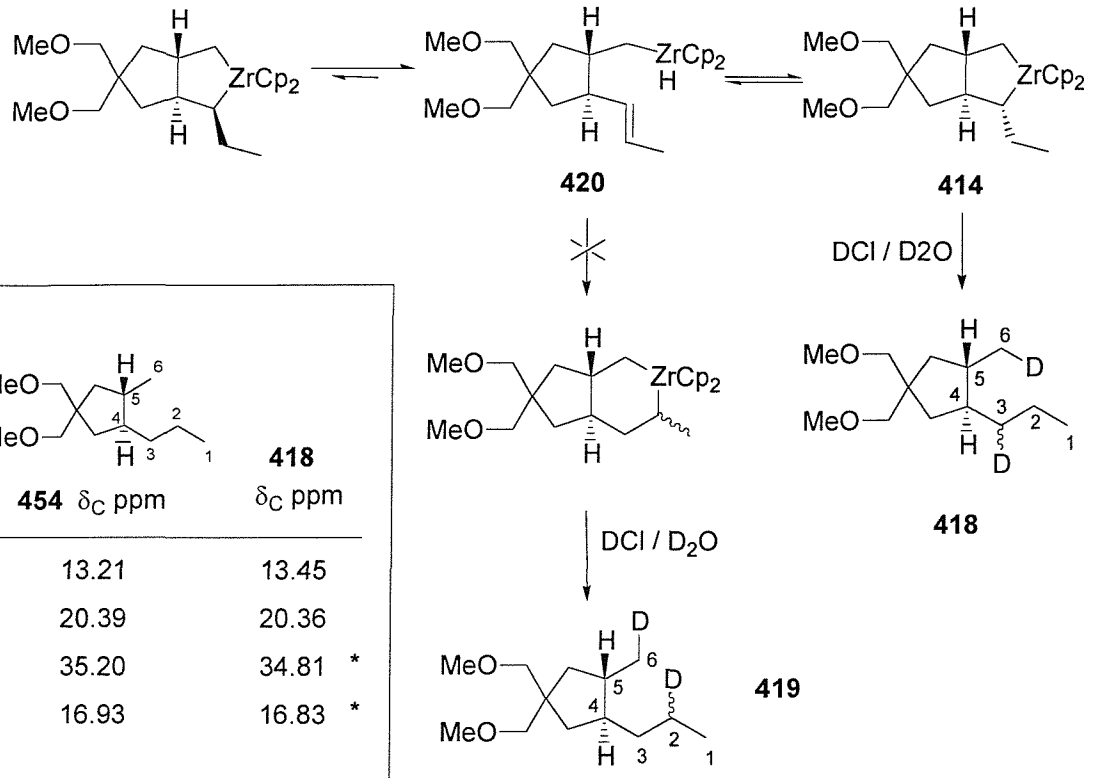
Figure 4.4 Structural elucidation of zirconacyclopentane **414**.



NMR spectra were recorded in C_6D_6 at 400 MHz (proton) and 100.5 MHz (carbon). δ_H ppm in plain text and δ_C **ppm** in **bold**. Non-diagnostic methylene proton shifts / triplet carbon shifts are omitted for clarity.

Readdition to give a six- rather than five-membered zirconacycle is feasible however the terminal CH_3 resonance at δ_H = 0.59 ppm is a triplet (J = 7.3 Hz) and indicative of the five-membered zirconacycle. Furthermore, deuterium quench also conclusively indicates the five-membered zirconacycle (scheme 4.3), firstly as the C1 shift (δ_C = 13.45 ppm) is a triplet in the DEPT135 and must therefore arise from **418** as C1 of the deuterated compound **419**, from a six-membered zirconacycle, would appear a doublet. Also, the ^{13}C shift of the deuterated carbon atom is δ_C = 34.81 ppm and the structure is **418** therefore. A theoretical deuterated methylene carbon atom C2 in **419** would have a shift around δ_C = 20.4 ppm.

Scheme 4.3 Proof of 5-membered zirconacyclopentane **414** *via* deuteration and (insert) ^{13}C shifts of product cf. ^{13}C of protonated compound **454**.



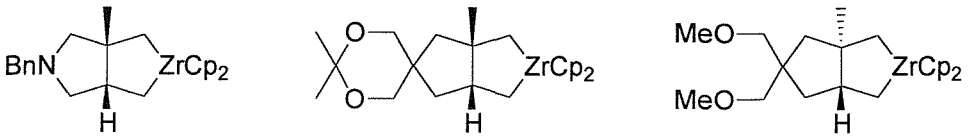
	454 δ_C ppm	**418** δ_C ppm
C1	13.21	13.45
C2	20.39	20.36
C3	35.20	34.81 *
C6	16.93	16.83 *

^{13}C NMR spectra of **454** recorded in C_6D_6 at 100.5 MHz, **418** in $CDCl_3$ at 100.5 MHz. Asterisk denotes deuterated carbon observed following DCl / D_2O quench of **414**.

A zirconacyclopentane, methyl substituted β to zirconium, **421**, has been previously reported with *cis*-fused stereochemistry predominant in a 4:1 ratio over the *trans*-fused zirconacycle[15]. *Cis* ring junction stereochemistry in the zirconacycle is exclusively observed following cocyclisation of *N*-allyl-*N*-benzyl-*N*-(2-methylallyl)amine to form **415** however. For this reason, choice of **415** for investigation of regiochemistry of carbenoid insertion into a β-substituted zirconacyclopentane was made, in preference to the mixture of ring-junction enantiomers, and will be described (section 4.2).

Interestingly, the zirconacycle **422** was synthesised and found to have a *trans*-fused ring junction, as is usually observed in simple bismethylmethoxy- substituted zirconacyclopentane but is here in contrast to the acetonide system **421** (figure 4.5).

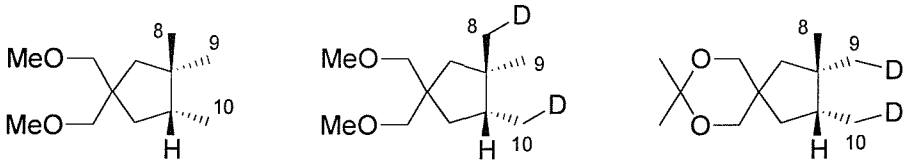
Figure 4.5 β-Methyl substituted zirconacyclopentanes.



415 **421** **422**

The stereochemistry of **422** was determined (and that of **421** also confirmed) by deuterium quench to give **424** and **425** respectively (figure 4.6). In the former *trans*-fused case the ^{13}C NMR shift of the deuterated methyl group at the quaternary centre (C8) occurs at δ_C = 28.67 ppm. The deuterated carbon C9 is shifted upfield in **425** (δ_C = 22.50 ppm) by steric compression and indicates the *cis*-fused ring junction.

Figure 4.6 NMR determination of ring-junction stereochemistry in β-methyl substituted zirconacyclopentanes.



423 **424** **425**

	δ_C ppm **423**	δ_C ppm **424**	δ_C ppm **425**
C8	28.99	28.67 *	29.64
C9	22.98	22.96	22.50 *
C10	13.46	13.17 *	13.24 *

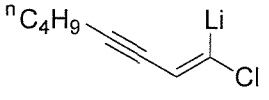
^{13}C NMR spectra were recorded in $CDCl_3$ at 100.5 MHz. Asterisk denotes deuterated carbon atom CH_2-D.

A steric interaction between the ring-junction methyl substituent and methylene protons of the constrained acetonide ring accounts for the difference in ring-junction stereochemistry observed between **421** and **422**.

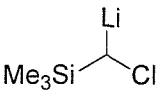
4.2 Regiochemistry of Carbenoid Insertion into Non-symmetrical, Saturated Zirconacycles.

Alkynyl substituted alkenyl carbenoid **426** is known[100] and predictably shows insertion into the alkyl C-Zr bond of a zirconacyclopentene, α-substituted on the alkenyl side, and also monoinsertion into a symmetrical zirconacyclopentane at –78 °C (chapter thee, section 3.2.2). Bulky β substitution upon the alkenyl carbenoid is likely to promote metal-assisted ionisation of **426** and an electrophilic carbenoid character (section 1.3.1.1). Conversely, stabilisation of -ve charge upon carbon in an α-$SiMe_3$ substituted carbenoid **427** is expected. α-Halo-α-lithio species bearing electron donating methoxymethyl (MOM) or 2-methoxyethoxymethyl (MEM) groups (**428** and **429** respectively) are predicted to act as strongly nucleophilic carbenoids (figure 4.7).

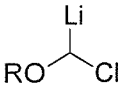
Figure 4.7 Carbenoids for regiochemical studies.



426



427



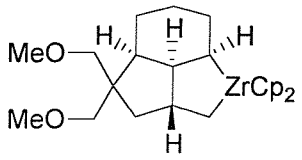
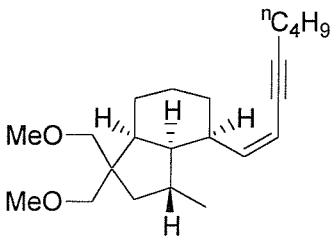
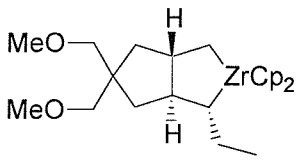
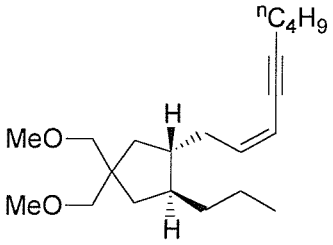
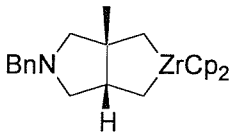
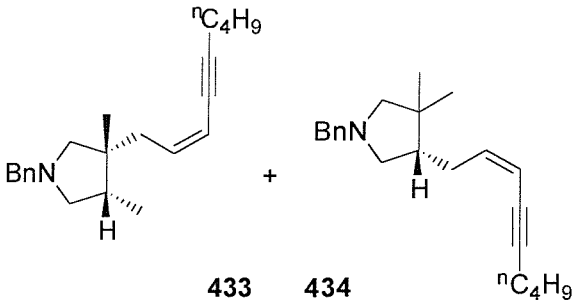
428 R = CH_3

429 R = $(CH_2)_2OCH_3$

4.2.1 Insertion of a 1-Chloro-1-lithio Alkene.

Insertion of alkenyl carbenoid **426** into non-symmetrical zirconacyclopentanes **413**, **414** and **415** was examined (table 4.1).

Table 4.1 Regiochemistry of 1-chloro-1-lithio alkene insertion.

Zirconacycle	Product	Isolated yield %
 **413**	 **431**	62.0
 **414**	 **432**	80.8
 **415**	 **433** : **434** 5 : 1	82.4

Insertion method: i) *in situ* addition of (1E)-1-chloro-1-octen-3-yne (1.0 eq) and LiTMP (1.0 eq) to the zirconacycle, THF, -78 °C to –65 °C, 40 min. ii) room temp', 12 h. iii) MeOH, $NaHCO_3$ (aq).

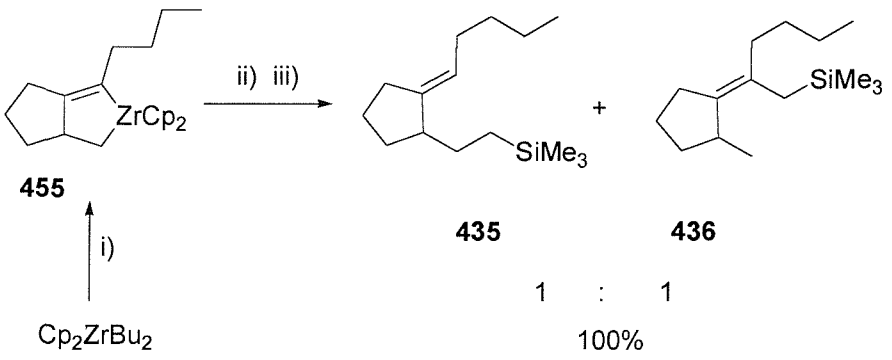
Regioselectivity of insertion of our alkenyl carbenoid **426** into the unsubstituted C-Zr bond of α-ethyl zirconacyclopentane **414** is observed to yield **432** following hydrolysis, in accordance with steric hindrance to carbenoid approach (figure 4.2). Exclusive insertion into the ring-substituted C-Zr side of **413** selectively yields **431**, also as earlier described for allyl carbenoid insertion. Preference for insertion into the C-Zr bond of **415** nearest the β-methyl substituent is observed, with a 5:1 ratio of product regioisomers **433**:**434**

recovered in good yield. Favoured electrophilic attack upon this side is expected due to the inductive electron donating effect of the methyl group.

4.2.2 Insertion of 1-Chloro-1-lithio-1-trimethylsilane and 1-Chloro-1-lithio-1 alkoxy Carbenoids.

We next examined the insertion of $LiCH(Cl)SiMe_3$, **427**, a stable carbenoid whose insertion into alkenyl zirconocene chlorides is an excellent route for preparation of versatile silylated allylzirconocene reagents[118]. Lithiated chloromethyl trimethylsilane has been shown to insert into the *alkenyl* C-Zr bond of unsaturated zirconacyclopentadienes (section 1.3.6.2) and, previously demonstrated in our group[87], treatment of α-^{n}butyl-substituted zirconacyclopentene **455** with chloromethyl trimethylsilane and 1.0 eq LiTMP at -78°C leads to a 1:1 mixture of monoinserted regioisomers following hydrolysis (scheme 4.4).

Scheme 4.4 Known insertion of $LiCH(Cl)SiMe_3$ into both C-Zr bonds of a zirconacyclopentene.



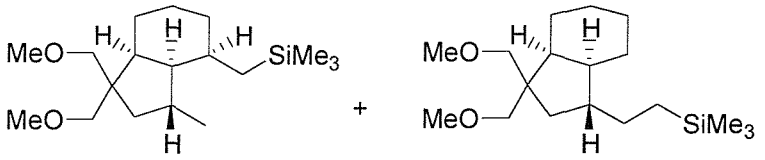
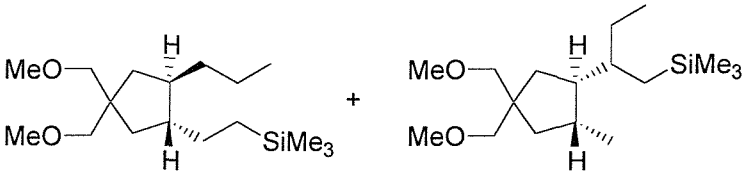
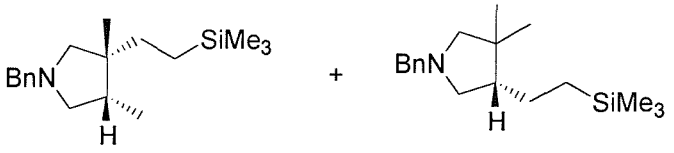
Reagents and conditions: i) 1-undec-6-yne, THF, -78 °C to room temp', 2 h. ii) Me_3SiCH_2Cl, LiTMP, -78 °C to room temp', 12 h. iii) MeOH, $NaHCO_3$ (aq), room temp', 6 h.

The mechanism for insertion of **427** into sp^2carbon-zirconium bonds when other carbenoids do not is not understood, stabilisation of an η^3 allyl zirconocene by the silyl group is unlikely due to large ring strain in such a species.

Unfortunately, no insight is gained from the results of insertion of $LiCH(Cl)SiMe_3$ into zirconacyclopentanes **413**, **414** and **415** (table 4.2). As with known insertion of allyl (section 4.0) and alkenyl (section 4.2.1) carbenoids, selectivity for insertion into the substituted side of **413** and the unsubstituted side of **414** is observed, giving **437** and **439** in good yield. Minor regioisomers **438** and **440** were also observed.

Preference for the electron rich carbon-zirconium bond nearest to the ring junction methyl group of **415** is once again seen, although with much lower selectivity than has been shown for allyl carbenoid insertion where insertion is exclusively into this side. Hydrolysis products **441** and **442** were recovered as an inseparable mixture.

Table 4.2 Regiochemistry of 1-chloro-1-lithio-1-trimethylsilane insertion.

Zirconacycle	Products	Isolated yield % [a]
413	 **437** 8 : 1 **438**	64.0
414	 **439** 39 : 1 **440**	83.2
415	 **441** 1.7 : 1 **442**	43.7

[a]Isolated yields of major isomers **437** and **439**, and mixture **441**+**442**.

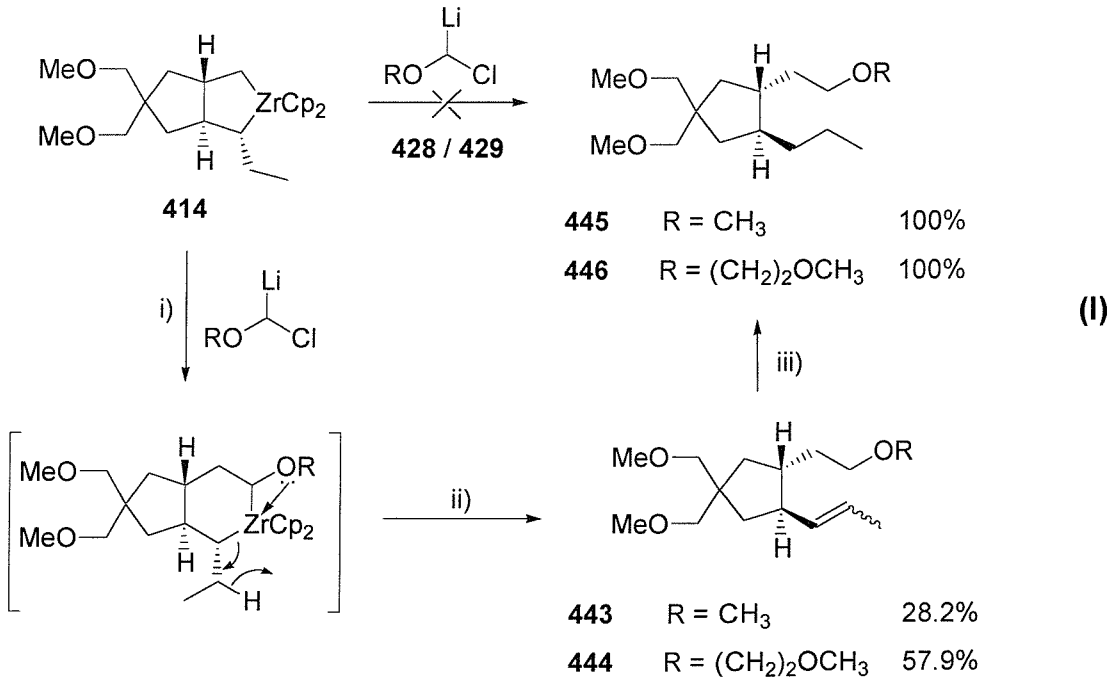
Insertion method: I) zirconacycle added to pre-formed carbenoid solution from chloromethyl trimethylsilane (1.25 eq), ^{sec}BuLi (1.25 eq), TMEDA (1.25 eq), THF, -78 °C, 30 min. Then i) –78 °C to –40 °C, 1 h. ii) room temp', 12 h. iii) MeOH, $NaHCO_3$ (aq).

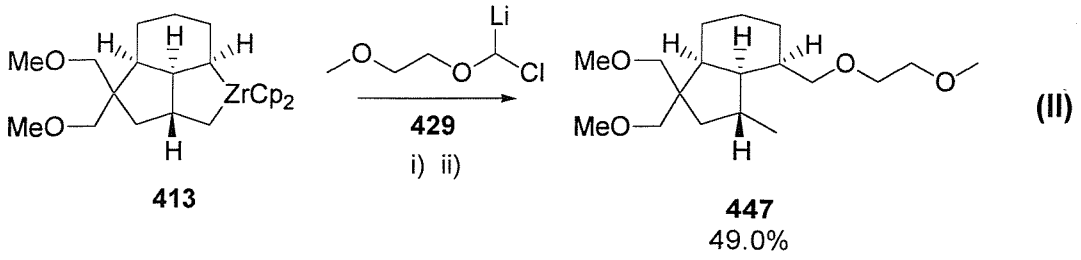
1-Alkoxy substituted 1-chloro-1-lithio species' **428** and **429** are found also to insert into α-substituted zirconacyclopentanes **413** and **414** with an identical pattern of regiocontrol. These MOM and MEM substituted carbenoids are somewhat unstable and insertion is

carried out following *in situ* deprotonation of the MOM / MEM- substituted methylene chloride at –100 °C, followed by warming to –65 °C over 1.5 hours. Following quench at -65°C, isomeric E / Z alkene pairs **443** and **444** are obtained from insertion of lithiated MOM-chloride and lithiated MEM-chloride, respectively, into **414**. Presumably *via* electron pair donation from oxygen and facile β-H elimination from the six-membered zirconacycle. Yields for this insertion were low, 28.2% and 57.9% from respective MOM- and MEM-substituted carbenoid insertion, and took place again into the non-substituted C-Zr bond (scheme 4.5, **I**). Quantitative hydrogenation of the olefinic products was effected simply to allow straightforward isolation of the single, intended products **445** and **446**.

No β-H elimination resulted following insertion of the higher yielding MEM-carbenoid only into **413**, the anticipated product **447** of insertion solely into the α-substituted C-Zr bond was isolated in a reasonable yield of 49.0% (scheme 4.5, **II**). No improvement in yield was sought in any of these cases (for example with extra equivalents of added carbenoid) but deemed unnecessary for this regiochemical work.

Scheme 4.5 Regiochemistry of 1-chloro-1-lithio-1-alkoxy insertion.





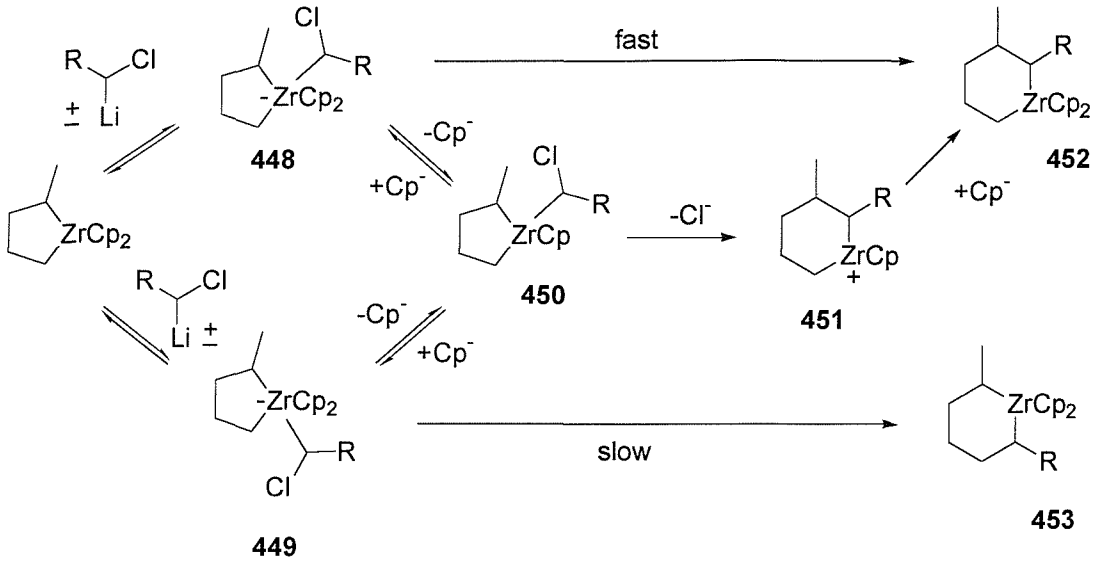
Reagents and conditions: i) MOM- or MEM-chloride (1.0 eq), LiTMP (1.0 eq), -100 °C to –65 °C, 1.5 h. ii) MeOH, $NaHCO_3$ (aq), -65 °C to room temp', 12 h. iii) H_2, Pd/C, room temp', 20 h.

Hence with strongly electron donating alkoxy substituents and a clearly nucleophilic nature to the carbenoid, attack upon the α-substituted side of the cyclohexyl-fused zirconacyclopentane prevails. Overall, work presented in this chapter suggests the nature of the carbenoid to be inconsequent upon regioselectivity of insertion. On this basis, a final postulation returns to the original view of the mechanism involving nucleophilic attack upon zirconium.

Regioselectivity of insertion into zirconacyclopentanes (**452** versus **453**) may be determined by the rate of 1,2-metallate rearrangement of regioisomeric 'ate' complexes **448** and **449**, their formation being fast and reversible (scheme 4.6). Interconversion of **448** and **449** could take place by loss / readdition of the carbenoid but more likely is reversible loss of cyclopentadienide anion to afford a common tetrahedral intermediate **450**. It is also possible that **450** rearranges directly to afford **451** which adds cyclopentadienide to yield **452**.

Direct interconversion of **448** and **449** by 'Berry' pseudorotation is a further possibility.

Scheme 4.6 Alternative mechanism for regioselectivity in carbenoid insertion.



Chapter Five : Experimental Section.

5.0 General Notes.

5.0.1 General procedures.

All reactions involving organometallic intermediates or other air or moisture sensitive compounds were carried out under an argon atmosphere using standard Schlenk and syringe techniques. Argon was pre-dried by passage over 4Å molecular sieves. All apparatus was dried in a hot oven (>140 °C, 12 hours) before either cooling in a sealed dessicator over silica gel or assembly while hot and cooling under vacuum (0.1 mm Hg).

5.0.2 Spectroscopy and Analysis.

NMR spectra were recorded on Bruker AM300 (300 MHz proton, 75 MHz carbon) or DPX400 (400MHz proton, 100.5MHz carbon) spectrometers. The NMR spectra of organozirconium compounds were recorded in deuterobenzene (stored over 4Å molecular sieves) and are referenced to the residual benzene peak at 7.18 ppm (^{1}H NMR) and 128.70 ppm (centre peak of triplet, ^{13}C NMR). Unless otherwise stated all other spectra were recorded in deuterochloroform (stored over K_2CO_3) and are referenced to the residual chloroform peak at 7.27 ppm (^{1}H NMR) and 77.20 ppm (centre peak of triplet, ^{13}C NMR). Chemical shifts are reported in parts per million downfield of TMS on the δ scale and coupling constants (J) in Hertz (Hz). For ^{1}H NMR spectra the following abbreviations have been used to denote coupling patterns: s (singlet), d (doublet), t (triplet), q (quartet), br (broad), fs (fine splitting). ^{13}C NMR spectra were proton decoupled and are reported as s, d, t or q depending on the number of directly attached protons (0, 1, 2 or 3 respectively), this being determined by DEPT experiments. COSY (H-H and C-H) experiments were used to conclusively assign spectra and these experiments have not been specifically documented.

Infra-red spectra were recorded on a Perkin-Elmer 1600 series FTIR instrument as neat films (for oils) or as solutions in the given solvent (for solids). Absorptions are given in wavenumbers (cm^{-1}) and the following abbreviations used to denote intensity and peak shape: s (strong), m (medium), w (weak), br (broad).

Mass spectra, including accurate mass, were recorded on a VG Analytical 70-250-SE double focusing mass spectrometer using Chemical Ionisation (CI) (with ammonia as the

reagent gas) or Electron Impact Ionisation (EI) (at 70eV). LRMS (EI and CI) were also recorded on a ThermoQuest TraceMS GCMS. Values of m/z are reported in atomic mass units (a. m. u.) followed in parentheses by the peak intensity (relative to the base peak of 100%).

5.0.3 Materials.

Unless given below all materials were obtained from commercial sources and if necessary dried and distilled before use. The following compounds were prepared by literature methods and had spectral properties consistent with those published: 2-methy -3-(phenylthio)propene[121,122] (**210**), (1E)-1-chloro-1-octen-3-yne[123], 1-undec-6-yne[124], 1-(methylthio)-1-hexyne[119] (**206** R = Me, R^1 = ^{n}Bu), 1-(trimethylsilyl)-6-hepten-1-yne[112], 1-[(E)-2-fluoro-1-ethenyl]benzene[125], (Z)-diethyl-3-allyl-3-(2-pentenyl)pentanedioate[27] (**417**), *N*-allyl-*N*-benzyl-*N*-(2-methylallyl)amine[27], 1-tributylstannyl-1-propyne[128], 5-allyl-2,2-di methyl-5-(2-methylallyl)-1,3-dioxane[27], 3-(1,1-di(methoxymethyl)-3-butenyl)-1-cyclo-hexene[27], 1,1-dibromo-1-hexene[120], 1,1-dibromohexane[127], 1,1-dibromobutane[127], 4-hydroxy-3-methylanisole[126], geranial[122].

Zirconium- mediated co-cyclisation of 1-undec-6-yne, 1-(trimethylsilyl)-6-hepten-1-yne, (E)-diethyl-3-allyl-3-(2-pentenyl)pentanedioate (**416**), *N*-allyl-*N*-benzyl-*N*-(2-methylallyl) amine, 5-allyl-2,2-di methyl-5-(2-methylallyl)-1,3-dioxane and 3-(1,1-di(methoxymethyl)-3-butenyl)-1-cyclohexene has been previously reported and therefore individual experimental details and spectral data have not been given.

Petroleum ether refers to the fraction which boils between 40 °C and 60 °C and was distilled before use. THF and Et_2O used in reactions were freshly distilled from sodium/benzophenone. Pentane and CH_2Cl_2 were dried over CaH_2 and degassed before use. *n*-Butyllithium was used as a 2.5M solution in hexanes (Aldrich). Lithium 2,2,6,6-tetramethylpiperidine was prepared freshly from 2,2,6,6-tetramethylpiperidine in THF and *n*-BuLi in hexanes at a concentration of ≈ 0.5M by stirring at 0 °C for 30 minutes.

5.0.4 Chromatography.

Thin layer chromatography was carried out on 0.25 mm Kieselgel 60 G UV_{254} aluminium foil backed sheets pre-coated with SiO_2 or on 0.20 mm Polygram N UV_{254} plastic backed sheets pre-coated with Al_2O_3 and were visualised with 254 nm UV lamp followed by phosphomolybdic acid (12 g in 150 mL EtOH), sulphuric acid (5% v/v in MeOH) or iodine (dispersed in silica).

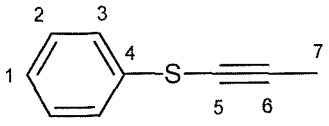
Column chromatography on silica used Kieselgel 60 230-400 mesh (Merck 9385) silica, columns being packed and run under light pressure. Alumina columns used Brockman grade III alumina (commercial grade I, deactivated with 6% w/w distilled water) and were packed and run by gravity.

5.0.5 Assignment of Data.

All novel compounds are illustrated in full structural form with progressive numbering of each individual carbon atom. The ^{1}H and ^{13}C NMR data are assigned using these numbers. In cases where there is some ambiguity in assigning two or more very similar consecutive resonances, which have not been satisfactorily determined by 1D and 2D NMR, the signals are characterised by quoting the appropriate signals separated by a slash within the bracket of the furthest upfield resonance of the set, e.g. 14.37 (q), 14.07 (q), (C11/C14). It should be noted that the numbering of compounds is done primarily for ease of assignment and does not necessarily follow the nomenclature given.

5.1 Experimental Details for Synthesis of Compounds in Chapter Two.

Prop-1-ynyl sulphanyl benzene (206).



Sodium (1.5 g, 65 mmol) was added portion-wise to EtOH (45 mL) at 0 °C following washing with hexane. After dissolution, thiophenol (5.3 mL, 50 mmol) was added dropwise over 3 min and the solution was stirred at 0 °C for 10 min before addition of propargyl bromide (4.4 mL, 50 mmol) dropwise over 5 min at 0 °C. Following addition, the milky brown mixture was brought to room temperature and then heated at reflux for 2.5 h before cooling to room temperature and pouring onto 1M HCl (200 mL). The product was extracted with Et_2O (200 mL) and washed with $NaHCO_3$ (aq) (100 mL) and brine (100 mL) before drying over $MgSO_4$ and removal of solvents *in vacuo*. Purification by Kugelrohr distillation (75°C, 10mm Hg) gave a pale yellow oil (6. 7 g, 90 %).

^{1}H NMR (300MHz, $CDCl_3$): δ = 7.46 (2H, d, J = 7.4 Hz, H3), 7.36 (2H, t, J = 7.7 Hz, H2), 7.23 (1H, t, J = 7.4 Hz, H1), 2.15 (3H, s, H7).

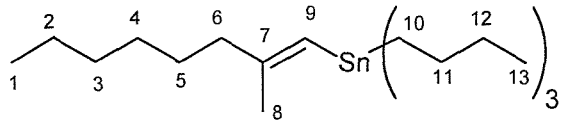
^{13}C NMR (75MHz, $CDCl_3$): δ = 133.77 (s, C4), 129.25 (d), 126.36 (d), 126.05 (d), 95.54 (s, C6), 64.03 (s, C5), 5.42 (q, C7).

IR(thin film): ν = 2359.8 (m), 1584.0 (m), 1478.4 (s), 736.3 (s) cm^{-1}.

LRMS (CI): m/z = 149 ($M+H^+$, 100%), 166 ($M+NH_4^+$, 15%).

HRMS (EI): C_9H_8S requires m/z = 148.0347. Found 148.0345.

Butyl-(2-methyl-oct-1-enyl)-stannane (228).

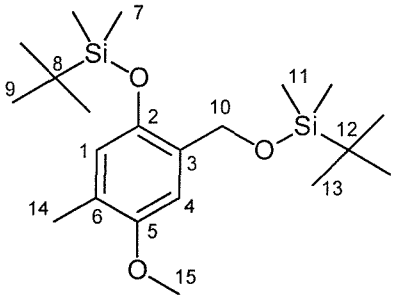


To a stirred solution of Cp_2ZrCl_2 (585 mg, 2.0 mmol) and 1-octyne (2.9 mL, 20 mmol) in 1,2-dichloroethane (80 mL) at 0 °C was added Me_3Al (30 mL of a 2.0M solution in hexanes, 60 mmol) *via* cannula. The mixture was warmed to room temperature and stirred for 12 h before cooling to 0 °C and addition of a solution of iodine (25.4 g, 200 mmol) in THF (100 mL), dropwise over 30 min. The mixture was stirred at 0 °C for 30 min before warming to room temperature and stirring for 1.5 h. The solution was then extracted with Et_2O (100 mL), washed with $Na_2S_2O_3$ (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. To a solution of so-formed 1-iodo-2-methyl oct-1-ene (2.5 g, 10 mmol) in Et_2O (40 mL) at –78 °C was added ^{tert}BuLi (11.8 mL of a 1.7M solution, 20 mmol) dropwise over 10 min. The

solution was stirred at –78 °C for 1 h before warming to room temperature and stirring for 1 h. The solution was then recooled to –78 °C and Bu_3SnCl (2.7 mL, 10 mmol) added dropwise over 10 min. The mixture was then stirred for 12 h, warming to room temperature during this time, before pouring onto H_2O (200 mL), extraction with Et_2O (200 mL), washing with $NaHCO_3$ (150 mL) and brine (150 mL), drying over $MgSO_4$ and concentration *in vacuo*. Purification by column chromatography (Al_2O_3, eluted with 10:1 petrol:Et_2O) gave the title compound as a colourless oil (2.1 g, 52 %).

^{1}H NMR (400MHz, $CDCl_3$): δ = 5.35 (1H, s, H9), 2.06 (2H, t, J = 7.5 Hz, H6), 1.67 (3H, s(fs), H8), 1.47-1.32 (8H, m), 1.28-1.18 (11H, m), 0.84-0.78 (19H, m).
^{13}C NMR (100.5MHz, $CDCl_3$): δ = 154.35 (s, C7), 120.21 (d, C9), 41.15 (t, C6), 30.79 (t), 28.33 (t, C11/C12), 27.91 (t), 26.30 (t), 26.03 (t, C11/C12), 23.43 (q, C8), 21.64 (t), 13.07 (q, C1), 12.69 (q, C13), 9.05 (t, C10).
IR(thin film): ν = 1606.3 (m), 1260.4 (m), 1019.8 (m, br), 804.2 (m) cm^{-1}.
LRMS (EI): m/z = 359 ([M-Bu]$^+$, 95%).
HRMS (EI): $C_{21}H_{44}{}^{120}Sn$ requires m/z = 416.2465. Found 416.2468.

1-(*tert*-Butyl-dimethylsilanyloxy)-2-(*tert*-butyl-dimethyl-silanyloxymethyl)-4-methoxy -5-methylbenzene.



To a stirred solution of 4-methoxy-3-methyl phenol (7.0 g, 50.7 mmol) and NaOH (2.5 g, 63.4 mmol) in H_2O (50 mL) at room temperature, was added formaldehyde (4.11 mL of a 37% solution in H_2O, 50.7 mmol) dropwise over 5 min. The solution continued to stir at room temperature for 24 h before addition of AcOH (100 mL of a 10% aqueous solution), extraction with Et_2O (200 mL), washing with H_2O (2 × 150 mL), drying over $MgSO_4$ and concentration *in vacuo* to yield 2-hydroxymethyl-4-methoxy-5-methyl phenol as a white crystalline solid (2.3 g, 27 %). To a stirred solution of DMAP (880 mg, 7.2 mmol), imidazole (980 mg, 14.4 mmol) and *tert*butyldimethylsilyl triflate (1.7 mL, 7.2 mmol) in THF (50 mL) at room temperature was added a solution of 2-hydroxymethyl-4-methoxy-5-methyl phenol (302 mg, 1.8 mmol) in THF (10 mL) dropwise over 10 min. The solution was stirred at room temperature for 12 h before addition of H_2O (40 mL) and stirring for 20 min. The mixture was then poured onto H_2O (200 mL) and extracted with Et_2O (200 mL) before washing with brine (200 mL), drying

over $MgSO_4$ and concentration *in vacuo*. Purification by column chromatography (SiO_2 eluted with 10:1 petrol:Et_2O) gave the title compound as a white solid (710 mg, 99 %).

^{1}H NMR (300MHz, $CDCl_3$): δ = 6.79 (1H, s, H1/H4), 6.36 (1H, s, H1/H4), 4.55 (2H, s, H10), 3.60 (3H, s, H15), 1.98 (3H, s, H14), 0.82 (9H, s, H9), 0.78 (9H, s, H13), 0.02 (6H, s, H7), 0.00 (6H, s, H11).

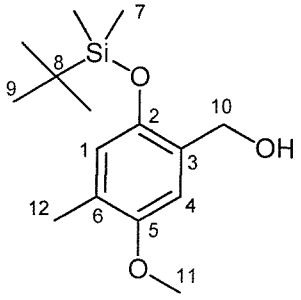
^{13}C NMR (75MHz, $CDCl_3$): δ = 152.13 (s), 144.83 (s), 129.68 (s), 124.87 (s), 120.72 (d), 109.18 (d), 60.61 (t, C10), 55.85 (q, C15), 26.11 (3 × q, C13), 25.91 (3 × q, C9), 18.36 (2 × s, C8 + C12), 16.14 (q, C14), -4.06 (4 × q, C7 + C11).

IR(thin film): ν = 2855.6 (s, br), 1502.7 (s), 912.6 (s, br), 834.9 (s, br) cm^{-1}.

LRMS (EI): m/z = 396 (M^+, 20%), 265 (100%).

HRMS (ES^+): $C_{21}H_{40}O_3Si_2Na^+$ requires m/z = 419.2408. Found 419.2407.

[2-(*tert*-Butyl-dimethyl-silanyloxy)-5-methoxy-4-methyl-phenyl]-methanol.



To a stirred solution of the bis-silylether (above) (700 mg, 1.76 mmol) in EtOH (5 mL) at room temperature was added pyridinium *p*-toluene sulphonate (44.3 mg, 0.176 mmol). The mixture was then heated at 50°C for 3 h before cooling to room temperature and concentration *in vacuo*. The mixture was the extracted with Et_2O (150 mL), washed with H_2O (2 × 150 mL), dried over $MgSO_4$ and solvents removed *in vacuo* once more to yield the title compound as a white solid without further purification (413 mg, 83 %).

^{1}H NMR (300MHz, $CDCl_3$): δ = 6.80 (1H, s), 6.63 (1H, s), 4.65 (2H, s, H10), 3.81 (3H, s, H11), 2.19 (3H, s, H12), 1.04 (9H, s, H9), 0.25 (6H, s, H7).

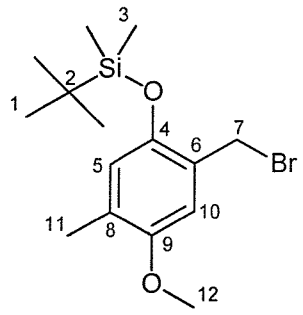
^{13}C NMR (75MHz, $CDCl_3$): δ = 152.25 (s), 146.62 (s), 128.98 (s), 126.73 (s), 121.26 (d), 110.87 (d), 62.06 (t, C10), 55.96 (q, C11), 25.92 (3 × q, C9), 18.29 (s, C8), 16.30 (q, C12), -4.03 (2 × q, C7).

IR(thin film): ν = 3354.9 (w, br), 1503.6 (m), 1206.6 (s), 1026.1 (m), 832.5 (s) cm^{-1}.

LRMS (EI): m/z = 282 (M^+, 40%), 209 (100%).

HRMS (ES^+): $C_{15}H_{26}O_3SiNa^+$ requires m/z = 305.1543. Found 305.1543.

(2-Bromomethyl-4-methoxy-5-methyl-phenoxy)-*tert*-butyl-dimethylsilane.



To a stirred solution of [2-(*tert*-Butyl-dimethyl-silanyloxy)-5-methoxy-4-methyl-phenyl]-methanol (350 mg, 1.24 mmol) in acetonitrile (6 mL) at 0°C was added CBr_4 (431 mg, 1.3 mmol) followed by triphenylphosphine (341 mg, 1.3 mmol). The solution was warmed to room temperature and stirred for 20 h before extraction with Et_2O (100 mL), washing with H_2O (2 × 100 mL), drying over $MgSO_4$ and concentration *in vacuo*. Purification by column chromatography (SiO_2 eluted with petrol) gave the title compound as a white solid (94 mg, 22 %).

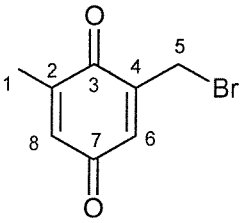
^{1}H NMR (300MHz, $CDCl_3$): δ = 6.77 (1H, s, H5/H10), 6.61 (1H, s, H5/H10), 4.54 (2H, s, H7), 3.80 (3H, s, H12), 2.17 (3H, s, H11), 1.05 (9H, s, H1), 0.35 (6H, s, H3).

^{13}C NMR (75MHz, $CDCl_3$): δ = 152.12 (s), 147.23 (s), 128.84 (s), 125.60 (s), 121.37 (d), 112.31 (d), 55.90 (q, C12), 30.18 (t, C7), 25.98 (3 × q, C1), 18.42 (s, C2), 18.32 (q, C11), -3.94 (q, C3).

LRMS (EI): m/z = 265 ($M-Br^+$, 84%), 209 (100%).

HRMS (EI): $C_{15}H_{25}O_2{}^{79}BrSi$ requires m/z = 344.0807. Found 344.0807.

2-Bromomethyl-6-methyl-[1,4]benzoquinone (239).



To a stirred solution of 1-bromomethyl-2,5-dimethoxy-3-methyl benzene (245mg, 1.0 mmol) in acetonitrile (6 mL) was added a solution of ceric ammonium nitrate (1.5 g, 2.7 mmol) in H_2O (3 mL) dropwise over 10 min. The solution was stirred for 20 min before addition of H_2O (10 mL), extraction with Et_2O (100 mL), washing with H_2O (100 mL), drying over $MgSO_4$ and concentration *in vacuo*. Purification by column chromatography (Al_2O_3 eluted with 10:1 petrol:EtOAc) gave the title compound as a white solid (139 mg, 65 %).

^{1}H NMR (300MHz, $CDCl_3$): δ = 6.83 (1H, dt, J = 2.6, 0.9 Hz, H6), 6.64 (1H, dq, J = 2.6, 1.5 Hz, H8), 4.26 (2H, d, J = 0.9 Hz, H5), 2.10 (3H, d, J = 1.5 Hz, H1).

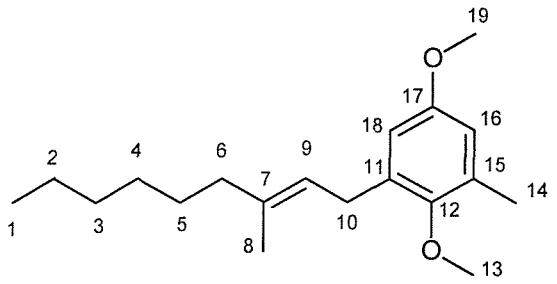
^{13}C NMR (75MHz, $CDCl_3$): δ = 187.22 (s,), 185.85 (s, C3/C7), 146.19 (s,), 144.20 (s, C2/C4), 134.54 (d), 133.84 (d, C6/C8), 25.16 (t, C5), 16.13 (q, C1).

IR(thin film): ν = 1649.3 (s), 1614.6 (m), 681.7 (m) cm^{-1}.

LRMS (EI): m/z = 215 (M^+,6%), 39 (100%).

HRMS (ES): $C_8H_7O_2{}^{79}Br$ requires m/z = 213.9629. Found 213.9637.

2,5-Dimethoxy-1-methyl-3-(3-methyl-non-[2E]-enyl)-benzene (237).



A solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (42 mg, 0.04 mmol) and $AsPh_3$ (98 mg, 0.32 mmol) in THF (5 mL) was stirred at room temperature for 15 min, becoming yellow, before addition of a solution of butyl-(2-methyl-oct-1-enyl)-stannane (415 mg, 1.0 mmol) and 1-bromomethyl-2,5-dimethoxy-3-methyl benzene (245 mg, 1.0 mmol) in THF (2 mL). The solution was heated to reflux for 12 h, cooled and then filtered before stirring in KF (25 mL of a 10% w/v aqueous solution) at room temperature for 4 days. The solution was then extracted with Et_2O (150 mL), washed with H_2O (100 mL), $NaHCO_3$ (100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (Al_2O_3 eluted with petrol) gave the title compound as a pale yellow oil (244 mg, 84 %).

^1H NMR (400MHz, $CDCl_3$): δ = 6.49 (1H, s), 6.48 (1H, s, H16/H18), 5.21 (1H, tsextet, J = 7.3, 1.0 Hz, H9), 3.67 (3H, s), 3.62 (3H, s, H13/H19), 3.28 (2H, d, J = 7.0 Hz, H10), 2.20 (3H, s, H14), 1.94 (2H, t, J = 7.8 Hz, H6), 1.64 (3H, s(br), H8), 1.34 (2H, m), 1.19 (6H, m), 0.80 (3H, t, J = 6.8 Hz, H1).

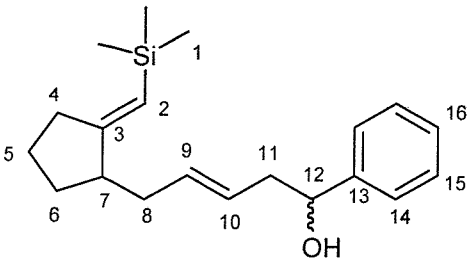
^{13}C NMR (100.5MHz, $CDCl_3$): δ = 155.92 (s), 150.84 (s), 137.12 (s), 135.93 (s), 132.10 (s), 122.91 (d, C9), 114.04 (d), 113.05 (d, C18/C16), 60.88 (q), 55.78 (q, C13/C19), 40.15 (t), 32.21 (t), 29.45 (t), 28.65 (t),28.37 (t), 23.05 (t), 16.71 (q), 16.48 (q, C8/C14), 14.49 (q, C1).

IR(thin film): ν = 2856.1 (m), 1584.9 (w), 1162.0 (m,br) cm^{-1}.

LRMS (EI): m/z = 290 (M^+, 100%), 259 (M-OMe^+, 25%).

HRMS (EI): $C_{19}H_{30}O_2$ requires m/z = 290.2246. Found 290.2251.

1-Phenyl-5-(2-trimethylsilanylmethylene-cyclopentyl)-pent-[3E]-en-1-ol (201c).



1:1 ds

To a stirred solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C was added ^{n}BuLi (0.8 mL of a 2.5 M solution in hexanes, 1.0 mmol) dropwise over 15 sec. The mixture was stirred at –78°C for 1 h before addition of a solution of hept-6-en-1-ynyl trimethylsilane (166 mg, 1.0 mmol) in THF (2 mL) dropwise over 1 min. After stirring at –78 °C for 20 min, the mixture was warmed to room temperature and stirred for 2 h before recooling to –78 °C. Addition of allyl chloride (0.082 mL, 1.0 mmol) followed by LiTMP (1.0 mmol freshly prepared from 2,2,6,6-tetramethypiperidine (0.17 mL, 1.0 mmol) and ^{n}BuLi (0.4 mL of a 2.5M solution, 1.0 mmol) in THF (4 mL) at 0 °C for 30 min) was made and the mixture continued to stir for 40 min, warming to –70 °C, before addition of benzaldehyde (0.17 mL, 1.7 mmol) followed by $BF_3{\cdot}Et_2O$ (0.22 mL, 1.7 mmol). The mixture was then warmed to room temperature over 3 h before addition of MeOH (5 mL) and $NaHCO_3$ (aq) (5 mL) and stirring for 12 h. The solution was poured onto H_2O (200 mL), extracted with Et_2O (200 mL), washed with $NaHCO_3$ (aq) (2 × 150 mL) and brine (150 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (Al_2O_3 eluted with 10:1 petrol:Et_2O) gave the title compound as a colourless oil (172 mg, 55 %).

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.26 (4H, m), 7.18 (1H, m), 5.48 (1H, m), 5.34 (1H, m, H9/H10), 5.20 (1H, s(fs), H2), 4.61 (1H, dd, J = 13.3, 6.5 Hz, H12), 2.48 (1H, heptet, J = 7.8 Hz), 2.38 (1H, m), 2.30-2.08 (4H, m), 1.88 (1H, m), 1.65 (2H, m), 1.44 (1H, m), 0.00 (9H, d, J = 2.0 Hz, H1).

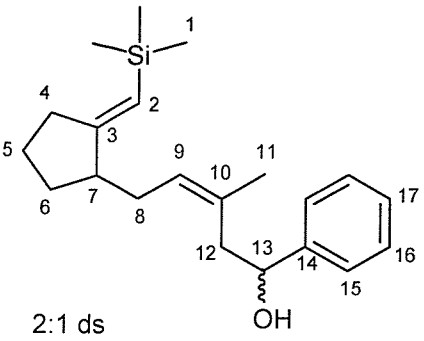
^{13}C NMR (100.5MHz, $CDCl_3$): δ = 165.65 (s), 144.37 (s), 144.27 (s, extra peak), 133.91 (d, extra peak), 132.48 (d), 128.60 (d, C14/C15), 127.76 (d), 126.88 (d), 126.74 (d, extra peak), 126.37 (d), 117.61 (d), 74.20 (d, C12), 73.71 (d, C12, extra peak), 47.19 (d, C7), 43.15 (t), 37.70 (t), 33.15 (t), 32.00 (t), 24.70 (t), 0.00 (q, C1).

IR(thin film): ν = 3384.4 (m, br), 1618.7 (s), 1245.9 (s), 838.4 (s, br), 754.9 (s) cm^{-1}.

LRMS (EI): m/z = 296 (M-H_2O^+, 12%), 143 (96%).

HRMS (EI): $C_{20}H_{28}Si$ (M-H_2O^+) requires m/z = 296.1960. Found 296.1957.

3-Methyl-1-phenyl-5-(2-trimethylsilanylmethylene-cyclopentyl)-pent-[3Z]-en-1-ol.



To a stirred solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C was added ^{n}BuLi (0.8ml of a 2.5M solution in hexanes, 1.0 mmol) dropwise over 15 sec. The mixture was stirred at –78 °C for 1 h before addition of a solution of hept-6-en-1-ynyl trimethylsilane (166 mg, 1.0 mmol) in THF (2 mL) dropwise over 1 min. After stirring at –78 °C for 20 min, the mixture was warmed to room temperature and stirred for 2 h before recooling to –78 °C. Addition of 3-chloro-2-methyl-1-propene (0.12 mL, 1.0 mmol) followed by LiTMP (1.0 mmol freshly prepared from 2,2,6,6-tetramethypiperidine (0.17 mL, 1.0 mmol) and ^{n}BuLi (0.4 mL of a 2.5M solution, 1.0 mmol) in THF (4 mL) at 0 °C for 30 min) was made and the mixture continued to stir for 40 min, warming to –70 °C, before addition of benzaldehyde (0.17 mL, 1.7 mmol) followed by $BF_3{\cdot}Et_2O$ (0.22 mL, 1.7 mmol). The mixture was then warmed to room temperature over 3 h before addition of MeOH (5 mL) and $NaHCO_3$ (aq) (5 mL) and stirring for 12 h. The solution was poured onto H_2O (200 mL), extracted with Et_2O (200 mL), washed with $NaHCO_3$ (aq) (2 × 150 mL) and brine (150 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (Al_2O_3 eluted with 10:1 petrol:Et_2O) gave the title compound as a colourless oil (215 mg, 65 %).

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.30 (2H, m) 7.26 (2H, m), 7.18 (1H, tt, J = 7.0, 1.5 Hz, H17), 5.30 (1H, t, J = 6.8 Hz, H9), 5.20 (0.64H, q, J = 2.0 Hz, H2), 5.16 (0.36H, q, J = 2.3 Hz, H2), 4.72 (0.64H, m, H13), 0.36H, m, H13), 2.56 (1H, ddd, J =13.3, 11.3, 9.0 Hz), 2.37-2.10 (4H, m), 1.91 (1H, m), 1.82 (1H, m), 1.67 (3H, s, H11), 1.46 (1H, m), 1.20–1.04 (2H, m), 0.77 (1H, m), 0.00 (9H, s).

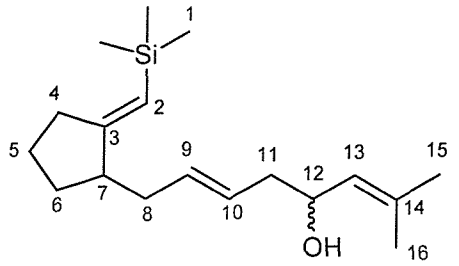
^{13}C NMR (100.5MHz, $CDCl_3$): δ = 165.82 (s, extra peak, minor isomer), 165.72 (s), 144.62 (s), 144.45 (s, extra peak, minor isomer), 131.92 (s), 128.82 (d), 128.61 (d), 127.70 (d), 126.03 (d), 117.76 (d, extra peak, minor isomer), 117.52 (d), 72.54 (d, C13), 72.36 (d, C13, extra peak, minor isomer), 47.64 (d, C7, extra peak, minor isomer), 47.47 (d, C7), 42.83 (t, C12, extra peak, minor isomer), 42.70 (t, C12), 33.13 (t), 32.94 (t, extra peak, minor isomer), 32.68 (t), 32.09 (t), 24.71 (t), 24.11 (q, C11), 0.00 (q, C1).

IR(thin film): ν = 3359.9 (w), 1617.9 (w), 1245.7 (m), 825.0 (m) cm^{-1}

LRMS (EI): m/z = 310 ($M\text{-}H_2O^+$, 22%), 219 (30%), 157 (98%).

HRMS (EI): $C_{21}H_{30}Si$ ($M\text{-}H_2O^+$) requires m/z = 310.2117. Found 310.2120.

2-Methyl-8-(2-trimethylsilanylmethylene-cyclopentyl)-octa-2,[6E]-dien-4-ol (201b).



1:1 ds

To a stirred solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C was added ^{n}BuLi (0.8ml of a 2.5M solution in hexanes, 1.0 mmol) dropwise over 15 sec. The mixture was stirred at –78 °C for 1 h before addition of a solution of hept-6-en-1-ynyl trimethylsilane (166 mg, 1.0 mmol) in THF (2 mL) dropwise over 1 min. After stirring at –78 °C for 20 min, the mixture was warmed to room temperature and stirred for 2 h before recooling to –78 °C. Addition of allyl chloride (0.082 mL, 1.0 mmol) followed by LiTMP (1.0 mmol freshly prepared from 2,2,6,6-tetramethypiperidine (0.17 mL, 1.0 mmol) and ^{n}BuLi (0.4 mL of a 2.5M solution, 1.0 mmol) in THF (4 mL) at 0 °C for 30 min) was made and the mixture continued to stir for 40 min, warming to –70 °C, before addition of 3-methyl-2-butenal (0.16 mL, 1.7 mmol) followed by $BF_3{\cdot}Et_2O$ (0.22 mL, 1.7 mmol). The mixture was then warmed to room temperature over 3 h before addition of MeOH (5 mL) and $NaHCO_3$ (aq) (5 mL) and stirring for 12 h. The solution was poured onto H_2O (200 mL), extracted with Et_2O (200 mL), washed with $NaHCO_3$ (aq) (2 × 150 mL) and brine (150 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (Al_2O_3 eluted with 10:1 petrol:Et_2O) gave the title compound as a colourless oil (219 mg, 75 %).

^{1}H NMR (400MHz, $CDCl_3$): δ = 5.45 (1H, m), 5.32 (1H, dt, J = 15.1, 7.0 Hz, H9/H10), 5.22 (2 × 0.5H q, J = 2.0 Hz, H2), 5.10 (2 × 0.5H, d(fs), J = 8.5 Hz, H13), 4.26 (1H, m, H12), 2.35-2.17 (3H, m), 2.12 (2H, t, J = 6.8 Hz), 1.89 (1H, m), 1.73 (1H, m), 1.64 (3H, s), 1.60 (3H, s(fs), H15/H16), 1.46 (1H, m), 1.23-1.11 (2H, m), 0.78 (1H, m), 0.00 (9H, s, H1).

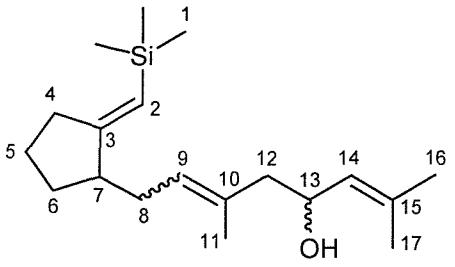
^{13}C NMR (100.5MHz, $CDCl_3$): δ = 165.69 (s) 135.56 (s, extra peak), 135.40 (s), 133.23 (d, extra peak), 131.89 (d, extra peak), 127.83 (d, extra peak), 127.69 (d), 127.02 (d), 125.76 (d), 125.73 (d, extra peak), 117.61 (d), 68.28 (d, C12, extra peak), 68.23 (d, C12), 47.13 (d, extra peak), 47.06 (d), 41.38 (t), 37.85 (t), 36.02 (t, extra peak), 33.35 (t), 32.35 (t, extra peak), 32.28 (t, extra peak), 31.84 (t), 26.03 (q, C15/C16), 24.71 (t), 18.53 (q, C15/C16), 0.00 (q, C1).

IR(thin film): ν = 2966.5 (m), 1615.3 (w), 1203.4 (m), 960.0 (m) cm^{-1}

LRMS (EI): m/z = 274 ($M-H_2O^+$, 8%), 121 (64%).

HRMS (EI): $C_{18}H_{30}Si$ ($M-H_2O^+$) requires m/z = 274.2117. Found 274.2118.

2,6-Dimethyl-8-(2-trimethylsilanylmethylene-cyclopentyl)-octa-2,[6E]-dien-4-ol (201a).



To a stirred solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C was added ^{n}BuLi (0.8ml of a 2.5M solution in hexanes, 1.0 mmol) dropwise over 15 sec. The mixture was stirred at –78 °C for 1 h before addition of a solution of hept-6-en-1-ynyl trimethylsilane (166 mg, 1.0 mmol) in THF (2 mL) dropwise over 1 min. After stirring at –78 °C for 20 min, the mixture was warmed to room temperature and stirred for 2 h before recooling to –78 °C. Addition of 3-chloro-2-methyl-1-propene (0.12 mL, 1.0 mmol) followed by LiTMP (1.0 mmol freshly prepared from 2,2,6,6-tetramethypiperidine (0.17 mL, 1.0 mmol) and ^{n}BuLi (0.4 mL of a 2.5M solution, 1.0 mmol) in THF (4 mL) at 0 °C for 30 min) was made and the mixture continued to stir for 40 min, warming to –70 °C, before addition of 3-methyl-2-butenal (0.16 mL, 1.7 mmol) followed by $BF_3{\cdot}Et_2O$ (0.22 mL, 1.7 mmol). The mixture was then warmed to room temperature over 3 h before addition of MeOH (5 mL) and $NaHCO_3$ (aq) (5 mL) and stirring for 12 h. The solution was poured onto H_2O (200 mL), extracted with Et_2O (200 mL), washed with $NaHCO_3$ (aq) (2 × 150 mL) and brine (150 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (Al_2O_3 eluted with 10:1 petrol:Et_2O) gave the title compound as a colourless oil (176 mg, 57 %).

^{1}H NMR (400MHz, $CDCl_3$): δ = 5.26 (1H, t, J = 6.8 Hz, H9), 5.21 (1H, s(fs), H2), 5.10 (2 × 0.5H, dheptet, J = 7.0, 1.3 Hz, H14), 4.41 (0.5H, m, H13), 4.33 (0.5H, m, H13), 2.26 (5H, m), 2.08 (2H, m), 2.04-1.81 (3H, m), 1.67 (1.5H, s), 1.63 (6H, s), 1.60 (1.5H, s).

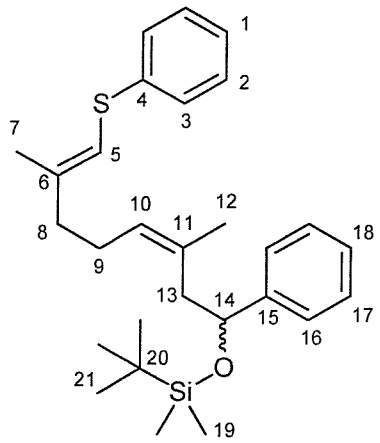
^{13}C NMR (100.5MHz, $CDCl_3$): δ = 165.86 (s), 135.24 (s), 132.32 (s), 127.85 (d) 127.69 (d), 117.46 (d), 67.11 (d), 48.60 (t, C12 *trans* isomer), 47.60 (d), 40.60 (t, C12 *cis* isomer), 33.17 (t), 33.00 (t), 32.84 (t), 32.69 (t), 26.03 (q, C16/C17), 24.73 (q, C11 *cis* isomer), 18.45 (q, C16/C17), 16.65 (q, C11 *trans* isomer), 0.00 (q, C1).

IR(thin film): ν = 3370.1 (w), 1615.3 (w), 1245.9 (w), 836.1 (s) cm^{-1}

LRMS (EI): m/z = 288 ($M-H_2O^+$, 18%), 134 (98%).

HRMS (EI): $C_{19}H_{32}Si$ ($M-H_2O^+$) requires m/z = 288.2273. Found 288.2267.

***tert*-Butyl-(3,7-dimethyl-1-phenyl-8-phenylsulphanyl-octa-[3Z,7E]-dienyloxy)-dimethyl-silane (215).**



To a stirred solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C was added EtMgCl (1.0 mL of a 2M solution, 2.0 mmol) dropwise over 5 min. The solution was stirred at –78 °C for 20 min before dropwise addition of a solution of prop-1-ynyl sulphanyl benzene (148 mg, 1.0 mmol) in THF (2 mL). The mixture was now warmed to 0 °C over 1 h before warming to room temperature and stirring for 1 h. The mixture was cooled to –78 °C before . addition of 3-chloro-2-methyl-1-propene (0.12 mL, 1.0 mmol) followed by LiTMP (1.0 mmol freshly prepared from 2,2,6,6-tetramethypiperidine (0.17 mL, 1.0 mmol) and ^{n}BuLi (0.4 mL of a 2.5M solution, 1.0 mmol) in THF (4 mL) at 0 °C for 30 min). The mixture continued to stir for 40 min, warming to –70 °C, before addition of benzaldehyde (0.2 mL, 2.0 mmol) followed by $BF_3{\cdot}Et_2O$ (0.25 mL, 2.0 mmol). The mixture was then warmed to -60°C over 30 min before addition of MeOH (5 mL) and $NaHCO_3$ (aq) (5 mL), warming to room temperature and stirring for 12 h. The solution was poured onto H_2O (200 mL), extracted with Et_2O (200 mL), washed with $NaHCO_3$ (aq) (2 × 150 mL) and brine (150 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Partial purification by column chromatography (Al_2O_3 eluted with 10:1 petrol:Et_2O) gave the free alcohol as an impure yellow oil (150 mg, 44 %).

To a stirred solution of DMAP (122 mg, 1.0 mmol), imidazole (136 mg, 2.0 mmol) and ^{tert}butyldimethylsilyl triflate (0.23 mL, 1.0 mmol) in THF (10 mL) was added a solution of 3,7-dimethyl-1-phenyl-8-phenylsulphanyl-octa-3,7-dien-1-ol (169 mg, 0.5 mmol) in THF (5 mL). The solution was stirred at room temperature for 24 h before addition of H_2O (10 mL) and stirring for 10 min. The mixture was extracted with Et_2O (100 mL), washed with H_2O (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$ and solvents removed *in vacuo*. Purification by column chromatography (Al_2O_3 eluted with petrol) gave the title compound as a pale yellow oil (201 mg, 93 %).

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.28-7.25 (8H, m, H2+H3+H16+H17), 7.21-7.13 (2H, m, H1+H18), 5.83 (3H, s(fs), H5), 5.16 (1H, t, J = 6.5 Hz, H10), 4.74 (1H, t, J = 6.5 Hz, H14), 2.49 (1H, dd J = 13.3, 7.0 Hz, H13), 2.29 (1H, dd, J = 13.1, 6.3 Hz, H13), 2.06-1.92

(4H, m, H8+H9), 1.79 (3H, s(fs), H7), 1.70 (3H, s, H12), 0.85 (9H, s, H21), 0.00 (3H, s, H19), -0.15 (3H, s, H19).

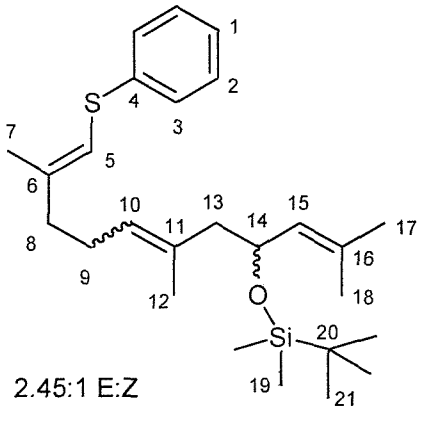
^{13}C NMR (100.5MHz, $CDCl_3$): δ = 145.63 (s, C15), 143.26 (s, C4), 137.67 (s), 132.51 (s), 129.03 (d), 128.13 (d), 128.03 (d), 127.14 (d), 127.09 (d), 126.10 (d), 125.71 (d), 115.58 (d), 74.27 (d, C14), 44.17 (t, C13), 39.42 (t, C8/C9), 26.37 (t, C8/C9), 25.05 (q, C21), 24.71 (q, C12), 18.40 (s, C20), 18.27 (q, C7), -4.54 (q, C19), -4.77 (q, C19).

IR(thin film): ν = 1582.4 (w), 1242.4 (m, br), 1047.0 (m), 738.0 (s) cm^{-1}

LRMS (CI): m/z = 322 ([M-OSi^{t}BuMe$_2$]+H^+, 78%), 221 (100%).

HRMS (EI): $C_{28}H_{40}OSiS$ requires m/z = 452.2569. Found 452.2561.

***tert*-Butyl-[3,7-dimethyl-1-(2-methyl-propenyl)-8-phenylsulphanyl-octa-[3E,7E]-dienyloxy]-dimethylsilane (214).**



2.45:1 E:Z

To a stirred solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C was added EtMgCl (1.0 mL of a 2M solution, 2.0 mmol) dropwise over 5 min. The solution was stirred at –78 °C for 20 min before dropwise addition of a solution of prop-1-ynyl sulphanyl benzene (148 mg, 1.0 mmol) in THF (2 mL). The mixture was now warmed to 0 °C over 1 h before warming to room temperature and stirring for 1 h. The mixture was cooled to –78 °C before addition of 3-chloro-2-methyl-1-propene (0.12 mL, 1.0 mmol) followed by LiTMP (1.0 mmol freshly prepared from 2,2,6,6-tetramethypiperidine (0.17 mL, 1.0 mmol) and ^{n}BuLi (0.4 mL of a 2.5M solution, 1.0 mmol) in THF (4 mL) at 0 °C for 30 min). The mixture continued to stir for 40 min, warming to –70 °C, before addition of 3-methyl-2-butenal (0.19 mL, 2.0 mmol) followed by $BF_3{\cdot}Et_2O$ (0.25 mL, 2.0 mmol). The mixture was then warmed to –60 °C over 30 min before addition of MeOH (5 mL) and $NaHCO_3$ (aq) (5 mL), warming to room temperature and stirring for 12 h. The solution was poured onto H_2O (200 mL), extracted with Et_2O (200 mL), washed with $NaHCO_3$ (aq) (2 × 150 mL) and brine (150 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Partial purification by column chromatography (Al_2O_3 eluted with 10:1 petrol:Et_2O) gave the free alcohol as an impure yellow oil (105 mg, 33 %).

To a stirred solution of DMAP (122.2 mg, 1.0 mmol), imidazole (136 mg, 2.0 mmol) and ^{tert}butyldimethylsilyl triflate (0.23 mL, 1.0 mmol) in THF (10 mL) was added a solution of

2,6,10-trimethyl-11-phenylsulphanyl-undeca-2,6,10-trien-4-ol (158 mg, 0.5 mmol) in THF (5 mL). The solution was stirred at room temperature for 24 h before addition of H_2O (10 mL) and stirring for 10 min. The mixture was extracted with Et_2O (100 mL), washed with H_2O (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$ and solvents removed *in vacuo*. Purification by column chromatography (Al_2O_3 eluted with petrol) gave the title compound as a pale yellow oil (208 mg, 92 %).

^{1}H NMR (400MHz, $CDCl_3$): δ = 7.30-7.26 (4H, m, H2+H3), 7.16 (1H, t(fs), J = 6.5 Hz, H1), 5.94 (0.71H, s(fs), H5 *trans* isomer), 5.93 (0.29H, s(fs), H5 *cis* isomer), 5.15 (1H, m, H10), 5.11 (1H, dseptet, J = 8.5, 1.5 Hz, H15), 4.48 (0.29H, apparent dt J = 8.5, 6.8 Hz, H14 *cis* isomer), 4.42 (0.71H, ddd, J = 8.5 7.3, 5.8 Hz, H14 *trans* isomer), 2.28 (0.29H, dd, J = 12.8, 6.8 Hz, H13 *cis* isomer), 2.24-2.16 (4.71H, m, H8+H9+[H13 *trans* isomer]), 2.12 (0.29 H, dd, J = 13.0, 6.0 Hz, H13 *cis* isomer), 2.04 (0.71H, dd, J = 13.0, 5.5 Hz, H13 *trans* isomer), 1.87 (3H, s), 1.68 (3H, s), 1.64 (3H, s), 1.60 (3H, s), 0.86 (9H, s, H21), 0.01 (3H, s, H19), 0.00 (3H, s, H19).

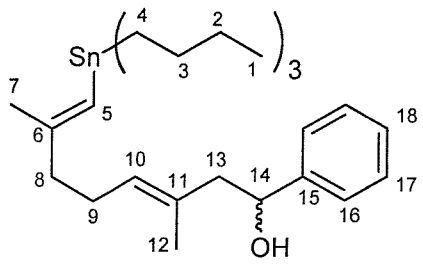
^{13}C NMR (100.5MHz, $CDCl_3$): δ = 143.41 (s, *cis* isomer), 143.23 (s), 137.64 (s), 133.05 (s, *cis* isomer), 132.83 (s), 131.05 (s, *cis* isomer), 131.00 (s), 129.81 (d, *cis* isomer), 129.74 (d), 129.07 (d,), 129.04 (d, *cis* isomer), 128.15 (d), 128.05 (d, *cis* isomer), 126.50 (d), 126.36 (d, *cis* isomer), 125.77 (d), 125.72 (d, *cis* isomer), 115.76 (d), 115.66 (d, *cis* isomer) 69.21 (d, C14), 69.05 (d, C14, *cis* isomer), 49.00 (t, C13), 41.31 (t, C13, *cis* isomer), 39.71 (t, C8/C9, *cis* isomer), 39.54 (t, C8/C9), 26.74 (t, C8/C9), 26.65 (t, C8/C9, *cis* isomer), 26.09 (q, C21), 25.83 (q, C17/C18), 22.83 (q, C12, *cis* isomer), 18.42 (q, C7, *cis* isomer), 18.41 (q, C7), 18.32 (q, C12), 17.10 (q, C17/C18), -4.06 (q, C19), -4.61 (q, C19).

IR(thin film): ν = 1583.2 (w), 1478.9 (m), 1025.5 (m, br), 690.1 (s).cm^{-1}

LRMS (CI): m/z = 299 ([M-OSi^{t}BuMe$_2$]+H^+, 70%), 163 (100%).

HRMS (EI): $C_{26}H_{42}OSiS$ requires m/z = 430.2726. Found 430.2722.

8-(Tributylstannyl)-3,7-dimethyl-1-phenyl-octa-[3E,7E]-dien-1-ol (219).



To a stirred solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C was added EtMgCl (1.0 mL of a 2M solution, 2.0 mmol) dropwise over 5 min. The solution was stirred at –78 °C for 20 min before dropwise addition of a solution of 1-tributylstannyl-1-propyne (329 mg, 1.0 mmol) in THF (2 mL). The mixture was now warmed to 0°C over 1 h before warming to room temperature and stirring for 1 h. The mixture was cooled to –78 °C before addition of 3-chloro-2-methyl-1-propene (0.12 mL, 1.0 mmol) followed by LiTMP (1.0 mmol freshly prepared from 2,2,6,6-tetramethypiperidine (0.17 mL, 1.0 mmol) and ^{n}BuLi (0.4 mL of a 2.5M solution, 1.0 mmol) in THF (4 mL) at 0 °C for 30 min). The mixture continued to stir for 40 min, warming to –70 °C, before addition of benzaldehyde (0.2 mL, 2.0 mmol) followed by $Ti(O^iPr)_4$ (0.61 mL, 2.0 mmol). The mixture was then warmed to room temperature over 3 h before addition of MeOH (5 mL) and $NaHCO_3$ (aq) (5 mL) and stirring for 12 h. The solution was extracted with Et_2O (200 mL), washed with H_2O (150 mL), $NaHCO_3$ (aq) (150 mL) and brine (150 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (Al_2O_3 eluted with 10:1 petrol:Et_2O) yielded the title compound as a colourless oil (97 mg, 19%).

^{1}H NMR (400MHz, C_6D_6): δ = 7.48 (2H, d, J = 7.8 Hz, H16), 7.32 (1H, t, J = 7.3 Hz, H18), 7.22 (2H, m, H17), 5.71 (1H, s, H5), 5.31 (1H, m, H10), 4.76 (1H, m, H14), 2.43 (2H, m), 2.26 (4H, m), 1.97 (3H, s), 1.81-1.66 (6H, m), 1.64 (3H, s), 1.52 (6H, sextet, J = 7.3 Hz, H2), 1.22-1.12 (6H, m), 1.06 (9H, t, J = 7.3 Hz, H1).

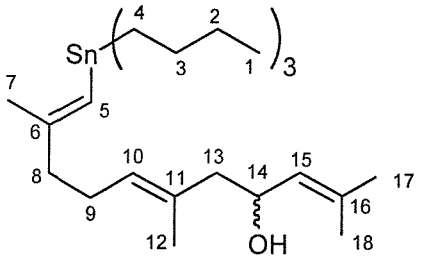
^{13}C NMR (100.5MHz, C_6D_6): δ = 155.24 (s), 145.62 (s), 132.63 (s), 129.29 (d), 128.82 (d), 127.68 (d), 126.42 (d), 122.99 (d), 71.65 (d, C14), 51.52 (t, C13), 42.56 (t), 30.11 (t), 28.16 (t), 27.39 (t), 25.01 (q, C7), 16.51 (q, C12), 14.33 (q, C1), 10.87 (t, C4).

IR(thin film): ν = 3028.2 (w), 1604.5 (m), 799.6 (m, br), 698.7 (s) cm^{-1}.

LRMS (EI): m/z = 445 (M-H_2O-Bu$^+$, 94%), 335 (25%), 251 (58%).

HRMS (EI): $C_{24}H_{39}O^{120}Sn$ (M-Bu) requires m/z = 463.2025. Found 463.2023.

2,6,10-Trimethyl-11-tributylstannyl-undea-[2,6E,10E]-trien-4-ol (217).



To a stirred solution of Cp_2ZrCl_2 (584 mg, 2.0 mmol) in THF (10 mL) at –78 °C was added EtMgCl (2.0 mL of a 2M solution, 4.0 mmol) dropwise over 1 min. The solution was stirred at –78 °C for 1 h before dropwise addition of a solution of 1-tributylstannyl-1-propyne (658 mg, 2.0 mmol) in THF (4 mL) dropwise over 2 min. The mixture was now warmed to 0°C over 1 h before warming to room temperature and stirring for 1 h. The mixture was cooled to –78 °C before addition of 3-chloro-2-methyl-1-propene (0.24 mL, 2.0 mmol) followed by LiTMP (2.0 mmol freshly prepared from 2,2,6,6-tetramethypiperidine (0.34 mL, 2.0 mmol) and ^{n}BuLi (0.8 mL of a 2.5M solution, 2.0 mmol) in THF (8 mL) at 0 °C for 30 min). The mixture continued to stir for 40 min, warming to –70 °C, before addition of 3-methyl-2-butenal (0.44 mL, 4.0 mmol). The mixture was then warmed to room temperature over 3 h before addition of MeOH (5 mL) and $NaHCO_3$ (aq) (5 mL) and stirring for 12 h. The solution was extracted with Et_2O (200 mL), washed with H_2O (200 mL), $NaHCO_3$ (aq) (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (Al_2O_3 eluted with 10:1 petrol:Et_2O) yielded the title compound as a colourless oil (666.2 mg, 67 %). NMR data obtained is consistent with G. J. Gordon (PhD thesis, University of Southampton, 1997).

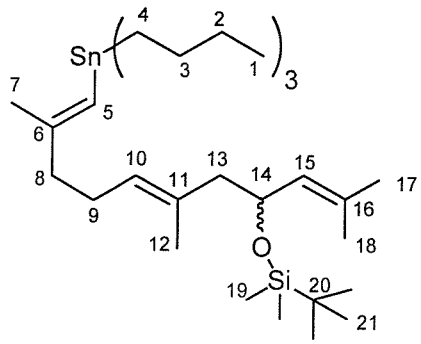
^{1}H NMR (400MHz, C_6D_6): δ = 5.81 (1H, s, H5), 5.38 (2H, m, H10+H15), 4.55 (1H, m, H14), 2.35-2.25 (6H, m), 1.90 (3H, s(br), H12), 1.76 (6H, t, J = 10.0 Hz, H4), 1.71 (3H, s), 1.69 (3H, s), 1.66 (3H, s), 1.50 (6H, tq, J = 7.3, 7.5 Hz, H2), 1.15 (6H, m, H3), 1.08 (9H, t, J = 7.3 Hz, H1).

^{13}C NMR (100.5MHz, C_6D_6): δ = 154.65 (s, C6), 133.08 (s), 131.84 (s, C11/C18), 129.04 (d), 127.99 (d), 122.12 (d), 65.96 (d, C14), 48.52 (t, C13), 41.97 (t, C8), 29.46 (t, C3/C2), 27.52 (t, C3/C2), 26.82 (t, C9), 25.46 (q), 24.42 (q), 17.87 (q, C12), 16.07 (q), 13.70 (q, C1), 10.17 (t, C4).

IR(thin film): ν = 3246.5 (w), 1681.0 (m), 1603.4 (w), 1443.4 (m, br), 1375.5 m), 1018.1 (w) cm^{-1}

LRMS (EI, CI, ES, FAB): all failed to find a molecular ion.

***tert*-Butyl-[3,7-dimethyl-1-(2-methylpropenyl)-8-tributylstannyl-octa-[3E,7E]-dienyloxy]-dimethylsilane (223).**



To a stirred solution of DMAP (555 mg, 4.54 mmol), imidazole (619 mg, 9.1 mmol) and ^{tert}butyldimethylsilyl triflate (1.04 mL, 4.54 mmol) in THF (30 mL) was added a solution of 2,6,10-trimethyl-11-tributylstannyl-undea-2,6,10-trien-4-ol (1.13 g, 2.27 mmol) in THF (20 mL). The solution was stirred at room temperature for 12 h before addition of H_2O (50 mL) and stirring for 30 min. The mixture was extracted with Et_2O (200 mL), washed with H_2O (2 × 200 mL) and brine (200 mL), dried over $MgSO_4$ and solvents removed *in vacuo*. Purification by column chromatography (Al_2O_3 eluted with 10:1 petrol:EtOAc) gave the title compound as a colourless oil (1.206 g, 87 %).

^{1}H NMR (400MHz, C_6D_6): δ = 5.64 (1H, s, H5), 5.23 (1H, m, H10), 5.17 (1H, d(fs), J = 8.2 Hz, H15), 4.44 (1H, ddd, J = 7.8, 8.2, 6.0 Hz, H14), 2.28 (1H, dd, J = 13.1, 7.3 Hz, H13), 2.15 (4H, s(br), H8+H9), 2.09 (1H, dd, J = 13.3, 5.5 Hz, H13), 1.72 (3H, s), 1.56 (3H, s), 1.54-1.47 (6H, m, H3), 1.45 (3H, s), 1.40 (3H, s), 1.28 (6H, sextet, J = 7.3 Hz, H2), 0.94-0.91 (6H, m, H4), 0.90 (9H, s, H21), 0.86-0.80 (9H, m, H1), 0.00 (2 × 3H, s, H19).

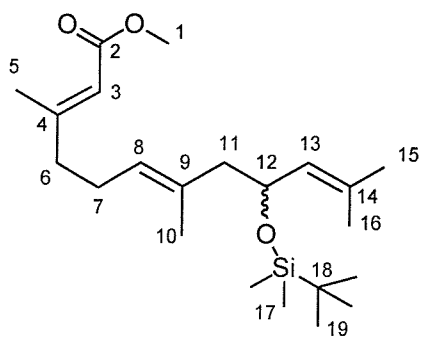
^{13}C NMR (100.5MHz, C_6D_6): δ = 155.57 (s, C6), 132.57 (s), 131.15 (s, C11/C16), 130.70 (d), 127.83 (d), 122.32 (d), 69.86 (d, C14), 49.74 (t, C13), 42.79 (t, C8), 30.22 (3 × t), 38.15 (3 × t, C2/C3), 27.88 (t, C9), 26.55 (3 × q, C21), 26.02 (q), 25.20 (q), 18.83 (s, C20), 18.57 (q), 17.44 (q), 14.35 (3 × q, C1), 10.86 (3 × t, C4), -3.55 (q, C19), -4.18 (q, C19).

IR(thin film): ν = 1253.1 (m), 1071.4 (m, br), 834.7 (s) cm^{-1}.

LRMS (EI): m/z = 423 (90%), 309 (32%), 199 (92%).

HRMS (EI): $C_{28}H_{55}O^{120}SnSi$ (M-Bu) requires m/z = 555.3044. Found 555.3043.

9-(*tert*-Butyl-dimethylsilanyloxy)-3,7,11-trimethyl-dodeca-[2E,6E],10-trienoic acid methyl ester (230).



A solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (28 mg, 0.027 mmol) and $AsPh_3$ (66 mg, 0.21 mmol) in THF (5 mL) was stirred at room temperature for 15 min, becoming yellow, before addition of a solution of *tert*-Butyl-[3,7-dimethyl-1-(2-methylpropenyl)-8-tributylstannyl-octa-3,7-dienyloxy]-dimethylsilane (411 mg, 0.67 mmol) and HMPA (0.012 mL, 0.068 mmol) in THF (2 mL). The mixture was warmed to 65°C before addition of a solution of methyl chloroformate (0.08 mL, 1.01 mmol) in THF (2 mL) dropwise over 1 h. The solution darkened during this time and was stirred at 65°C (reflux) for 30 min before cooling to room temperature and stirring for 12 h. The mixture was then filtered before stirring in KF (25 mL of a 10% w/v aqueous solution) at room temperature for 2 days. The solution was then extracted with Et_2O (200 mL), washed with H_2O (100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (Al_2O_3 eluted with 20:1 petrol:Et_2O) gave the title compound as a colourless oil (164 mg, 64 %).

^{1}H NMR (400MHz, C_6D_6): δ = 6.05 (1H, sextet, J = 1.3 Hz, H3), 5.50 (1H, dspetet, J = 8.5, 1.5 Hz, H13), 5.37 (1H, tsextet, J = 6.8, 1.1 Hz, H8), 4.77 (1H, ddd, J = 8.5, 5.8, 7.3 Hz, H12), 3.68 (3H, s, H1), 2.58 (1H, dd, J = 13.1, 7.5 Hz, H11), 2.43 (3H, d, J = 1.3 Hz, H5), 2.40 (1H, dd, J = 13.1, 5.8 Hz, H11), 2.26 (2H, t, J = 7.2 Hz, H6), 2.18 (2H, td, J = 7.3, 1.1 Hz, H7), 1.84 (3H, d, J = 0.8 Hz, H15), 1.82 (3H, d, J = 1.3 Hz, H16), 1.76 (3H, d, J = 1.1 Hz, H10), 1.26 (9H, s, H19), 0.35 (2 × 3H, s, H17).

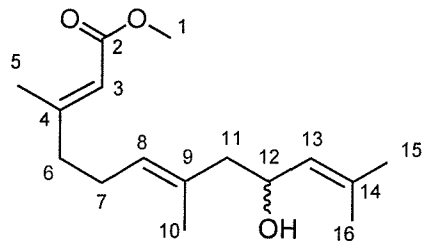
^{13}C NMR (100.5MHz, C_6D_6): δ = 167.46 (s, C2), 160.26 (s, C4), 133.76 (s), 131.57 (s, C9/C14), 130.85 (d, C13), 126.95 (d, C8), 116.57 (d, C3), 70.06 (d, C12), 51.06 (t, C1), 49.89 (t, C11), 41.46 (t, C7), 27.16 (t, C6), 26.82 (3 × q, C19), 26.30 (q, C15/C16), 19.43 (q, C5), 19.11 (s, C18), 18.83 (q, C10), 17.63 (q, C15/C16), -3.26 (q, C17), -3.94 (q, C17).

IR(thin film): ν = 1723.4 (s), 1223.7 (s), 834.6 (s) cm^{-1}.

LRMS (EI): m/z = 323 ($M\text{-}Bu^+$, 12%), 199 (96%), 135 (94%).

HRMS (ES^+): $C_{22}H_{40}O_3SiNa^+$ requires m/z = 403.2639. Found 403.2641.

9-hydroxy-3,7,11-trimethyl-dodeca-[2E,6E],10-trienoic acid methyl ester (231).



To a stirred solution of 9-(*tert*-butyl dimethyl silanyl oxy)-(3,7,11-trimethyl-dodeca-2,6,10-trienoic acid methyl ester (100 mg, 0.26 mmol) in THF (2 mL) at room temperature was added $Bu_4N^+F^-$ (0.52 mL of a 1M solution in THF, 0.52 mmol). The solution was then stirred for 4 h before addition of H_2O (5 mL), extraction with Et_2O (100 mL), drying with $MgSO_4$ and concentration *in vacuo*. Purification by column chromatography (Al_2O_3 eluted with 20:1 petrol:Et_2O) gave the title compound as a colourless oil (55 mg, 79 %). Correlation of the data reported below with the literature reported compound is discussed in section 2.1.2.

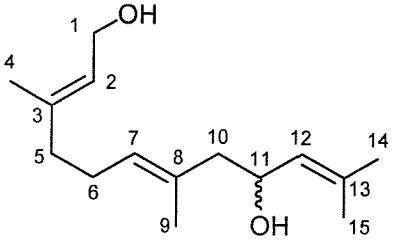
^{1}H NMR (400MHz, C_6D_6): δ = 5.68 (1H, s, H3), 5.13 (1H, d(fs), J = 8.3 Hz, H13), 4.94 (1H, t, J = 6.9 Hz, H8), 4.29 (1H, apparent q, J = 5.5 Hz, H12), 3.31 (3H, s, H1), 2.09 1H, dd, J = 13.3, 8.0 Hz, H11), 2.03 (3H, s), 1.99 (1H, dd, J = 13.3, 5.0 Hz, H11), 1.81 (2H, apparent q, J = 6.9 Hz, H7), 1.71 (2H, t, J = 6.8 Hz, H6), 1.47 (3H, s), 1.40 (3H, s), 1.37 (3H, s).

^{13}C NMR (100.5MHz, C_6D_6): δ = 167.16 (s, C2), 159.80 (s, C4), 133.88 (s), 133.56 (s, C9/C14), 129.59 (d), 127.08 (d, C8/C13), 116.36 (d, C3), 67.00 (d, C12), 50.81 (q, C1), 48.93 (t), 41.06 (t), 26.51 (t), 26.07 (q), 19.07 (q), 18.47 (q), 16.73 (q).

IR(thin film): ν = 3434.2 (m, br), 1721.7 (s), 1650.7 (m), 1223.7 (s), 1152.8 (s) cm^{-1}.

LRMS (EI): m/z = 248 ($M-H_2O^+$, 8%), 135 (62%), 107 (100%).

3,7,11-Trimethyl-dodeca-[2E,6E],10-triene-1,9-diol (232).

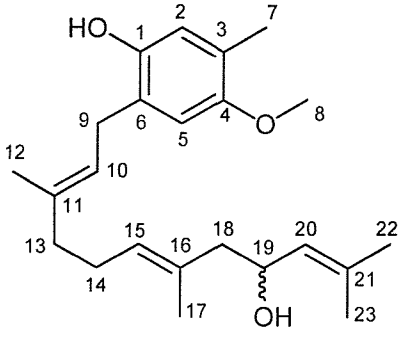


To a stirred solution of 9-(*tert*-Butyl-dimethylsilanyloxy)-3,7,11-trimethyl-dodeca-2,6,10-trienoic acid methyl ester (150mg, 0.39 mmol) in CH_2Cl_2 (5 mL) at –78 °C was added diisobutyl aluminium hydride (0.78 mL of a 1.5M solution in toluene, 1.17 mmol) dropwise over 3 min. the mixture was stirred at –78 °C for 12 h before pouring onto H_2O (100 mL), extraction with CH_2Cl_2 (100 mL), washing with $NaHCO_3$ (aq) (100 mL), drying over $MgSO_4$ and concentration *in vacuo*. To a stirred solution of the so-formed 9-(*tert*butyl dimethyl silanyloxyl)-3,7,11-trimethyl-dodeca-2,6,10-trien-1-ol in THF (5 mL) at room temperature, was added $Bu_4N^+F^-$ (0.78 mL of a 1M solution in THF, 0.78 mmol) and the

mixture stirred for 12 h before addition of H_2O (10 mL), extraction with Et_2O (100 mL), washing with H_2O (100 mL), drying over $MgSO_4$ and concentration *in vacuo*. Purification by column chromatography (Al_2O_3 eluted with 5:1 petrol:EtOAc) gave the title compound as a colourless oil (18 mg, 19 %). Reported data are consistent with literature values for 9-hydroxyfarnesol.

^{1}H NMR (400MHz, C_6D_6): δ = 5.27 (1H, t, J = 6.5 Hz, H2), 5.17 (1H, d(fs), J = 7.8 Hz, H12), 5.00 (1H, t, J = 7.3 Hz, H7), 4.29 (1H, dt, J = 5.5, 7.8 Hz, H11), 3.92 (2 × 1H, dd, J = 12.4, 6.6 Hz, H1), 2.02 (2H, m), 1.96 (1H, dd, J = 14.3, 7.5 Hz, H10), 1.90-1.76 (3H, m), 1.46 (3H, s), 1.40 (6H, s), 1.30 (3H, s).
^{13}C NMR (100.5MHz, C_6D_6): δ = 137.83 (s), 134.01 (s), 132.96 (s), 129.27 (d), 128.57 9d), 126.67 (d), 66.41 (d, C11), 59.62 (t, C1), 49.02 (t, C10), 39.80 (t, C5), 26.47 (t, C6), 26.07 (q, C14), 18.46 (q, C15), 16.59 (q), 16.06 (q).
HRMS (ES^+): $C_{15}H_{26}O_2Na^+$ requires m/z = 261.1825. Found 261.1824.

2-(9-hydroxy-3,7,11-trimethyl-dodeca-[2E,6E],10-trienyl)-4-methoxy-5-methyl phenol (244).



A solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (10.8 mg, 0.01 mmol) and $AsPh_3$ (25.6 mg, 0.083 mmol) in THF (5 mL) was stirred at room temperature for 15 min, becoming yellow, before addition of a solution of 2,6,10-trimethyl -11-tributylstannyl-undea-2,6,10-trien-4-ol (129.6 mg, 0.26 mmol) and (2-bromomethyl-4-methoxy-5-methyl-phenoxy)-*tert*-butyl-dimethylsilane (90 mg, 0.26 mmol) in THF (2 mL). The solution was heated to reflux for 1 h, cooled and then filtered before stirring in KF (100 mL of a 10% w/v aqueous solution) at room temperature for 4 days. The solution was then extracted with Et_2O (200 mL), washed with H_2O (2 × 150 mL), and dried over $MgSO_4$ before concentration *in vacuo*. Purification by column chromatography (Al_2O_3 eluted with 10:1 petrol:EtOAc) gave the ^{tert}butyldimethylsilyl-phenol as colourless oil (96 mg, 78 %).
To a stirred solution of the silyl ether prepared above (50 mg, 0.106 mmol) in THF (2 mL) at room temperature was added $Bu_4N^+F^-$ (0.211 mL of a 1M solution in THF, 0.211 mmol). The solution was then stirred for 12 h before addition of H_2O (4 mL), extraction

with Et_2O (30 mL), washing with H_2O (30 mL), drying over $MgSO_4$ and concentration *in vacuo*. Purification by column chromatography (Al_2O_3 eluted with 5:1 petrol:EtOAc) gave the title compound as a colourless oil (30 mg, 79 %).

^{1}H NMR (400MHz, C_6D_6): δ = 6.64 (1H, s), 6.68 (1H, s, H2/H5),5.39 (1H, m, H10/H5), 5.30 (1H, d(fs), J = 8.3 Hz, H20), 5.14 (1H, m, H10/H5), 4.42 (1H, ddd, J = 8.0, 8.0, 5.5 Hz, H19), 3.44 (3H, s, H8), 3.38 (2H, d, J = 6.5 Hz, H9), 2.25 (3H, s, H7), 2.16-1.93 (6H, m), 1.59 (2 × 3H, s), 1.55 (3H, s), 1.49 (3H, s).

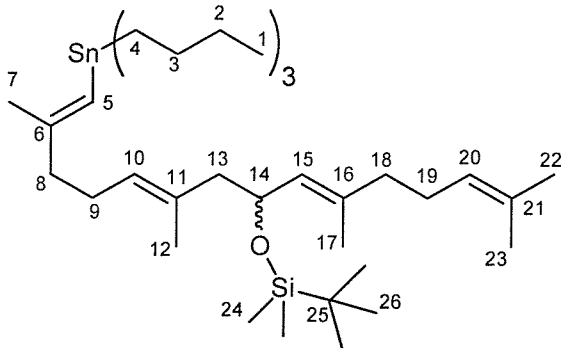
^{13}C NMR (100.5MHz, C_6D_6): δ = 150.91 (s), 147.11 (s, C1/C4), 134.78 (s), 132.48 (s), 130.97 (s), 127.26 (d), 127.07 (d), 124.23 (s), 123.87 (s), 123.49 (d), 118.16 (d), 111.14 (d), 64.67 (d, C19), 54.14 (q, C8), 47.21 (t, C18), 38.15 (t, C13), 28.67 (t), 24.90 (t, C9/C14), 24.34 (q, C22), 16.74 (q), 14.76 (q), 14.71 (q), 14.47 (q).

IR(thin film): ν = 3361.3 (m, br), 1670.9 (w, br), 1515.8 (m), 1200.9 (s) cm^{-1}.

LRMS (EI): m/z = 340 ($M-H_2O^+$, 20%), 189 (96%).

HRMS (ES^+): $C_{23}H_{34}O_3Na^+$ requires m/z = 381.2400. Found 381.2415.

tert-Butyl-[1-(2,6-dimethyl-7-tributylstannyl-hepta-[2E,6E]-dienyl)-3,7-dimethyl-octa-2,6-dienyloxy]-dimethylsilane (233).



To a stirred solution of Cp_2ZrCl_2 (1.17 g, 4.0 mmol) in THF (20 mL) at –78 °C was added EtMgCl (4.0 mL of a 2M solution, 8.0 mmol) dropwise over 1 min. The solution was stirred at –78 °C for 1 h before dropwise addition of a solution of 1-tributylstannyl-1-propyne (1.32 g, 4.0 mmol) in THF (8 mL) dropwise over 2 min. The mixture was now warmed to 0°C over 1 h before warming to room temperature and stirring for 1 h. The mixture was cooled to –78 °C before addition of 3-chloro-2-methyl-1-propene (0.48 mL, 4.0 mmol) followed by LiTMP (4.0 mmol freshly prepared from 2,2,6,6-tetramethypiperidine (0.68 mL, 4.0 mmol) and ^{n}BuLi (1.6 mL of a 2.5M solution, 4.0 mmol) in THF (16 mL) at 0 °C for 30 min). The mixture continued to stir for 40 min, warming to –70 °C, before addition of geranial (1.37 mL, 8.0 mmol). The mixture was then warmed to room temperature over 3 h before addition of MeOH (10 mL) and $NaHCO_3$ (aq) (10 mL) and stirring for 12 h. The solution was

extracted with Et_2O (200 mL), washed with H_2O (200 mL), $NaHCO_3$ (aq) (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Partial purification by column chromatography (Al_2O_3 eluted with 10:1 petrol:Et_2O) yielded the free alcohol as a yellow oil (722 mg, 32 %).

To a stirred solution of DMAP (122.2 mg, 1.0 mmol), imidazole (136.2 mg, 2.0 mmol) and ^{tert}butyldimethylsilyl triflate (0.23 mL, 1.0 mmol) in THF (10 mL) was added a solution of 2,6,10,14-tetramethyl-1-tributylstannanyl-pentadeca-1,5,9,13-tetraen-8-ol, prepared above, (282.8 mg, 0.5 mmol) in THF (5 mL). The solution was stirred at room temperature for 24 h before addition of H_2O (10 mL) and stirring for 20 min. The mixture was extracted with Et_2O (100 mL), washed with H_2O (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$ and solvents removed *in vacuo*. Purification by column chromatography (Al_2O_3 eluted with 10:1 petrol:Et_2O) gave the title compound as a colourless oil (311 mg, 92 %).

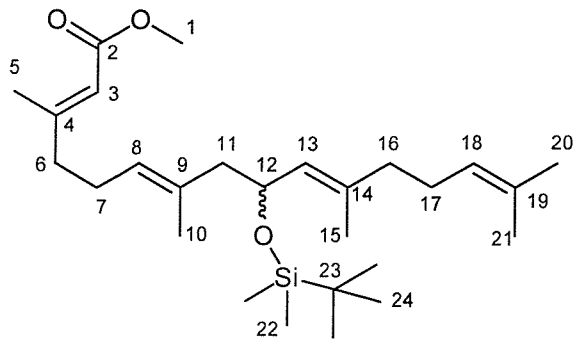
^{1}H NMR (400MHz, C_6D_6): δ = 5.89 (1H, s), 5.51-5.41 (2H, m), 5.29 (1H, t, J = 6.8 Hz), 4.71 (1H, ddd, J = 7.5, 7.5, 5.8 Hz, H14), 2.53 (1H, dd, J = 13.3, 7.5 Hz, H13), 2.40 (4H, m), 2.34 (1H, dd, J = 13.3, 5.3 Hz, H13), 2.25 (4H, m), 2.12 (2H, t, J = 7.5 Hz, H18/H8), 1.96 (3H, s(fs)), 1.82 (3H, s), 1.79 (3H, s), 1.78-1.71 (6H, m), 1.68 (3H, s), 1.66 (3H, s), 1.51 (6H, sextet, J = 7.3 Hz, H2), 1.15 (13H, m), 1.07 (9H, m, H1), 0.25 (2 × 3H, s).

^{13}C NMR (100.5MHz, C_6D_6): δ = 153.80 (s, C6), 132.92 (s), 130.81 (s), 129.90 (s), 128.86 (d), 126.08 9d), 123.30 (d), 120.54 (d), 68.07 (d, c14), 47.93 (t, C13), 41.04 (t0, 38.49 (t), 28.36 (t), 26.39 (t), 26.14 (t), 25.41 (t), 24.79 (q, C26), 24.54 (q), 23.44 (q), 17.07 (s, C2), 16.34 (q), 15.72 (q), 15.15 (q), 12.59 (q), 9.08 (t), 0.00 (q, C24), -4.14 (q, C24).

IR(thin film): ν = 2955.6 (s), 1606.0 (w), 1251.2 (m), 1068.7 (s, br), 828.7 (s) cm^{-1}.

LRMS (EI, CI, ES, FAB): failed to find a molecular ion.

9-(*tert*-Butyl-dimethyl-silanyloxy)-3,7,11,15-tetramethyl-hexadeca-[2E,6E,10E],14-tetraenoic acid methyl ester (234).



A solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (22.8 mg, 0.022 mmol) and $AsPh_3$ (55.2 mg, 0.18 mmol) in THF (5 mL) was stirred at room temperature for 15 min, becoming yellow, before addition of a solution of *tert*-butyl-[1-(2,6-dimethyl-7-tributylstannyl-hepta-2,6-dienyl)-3,7-dimethyl-octa-2,6-dienyloxy] -dimethylsilane (375 mg, 0.55 mmol) and HMPA (0.01 mL, 0.055 mmol) in THF (2 mL). The mixture was warmed to 65°C before addition of a solution of methyl chloroformate (0.064 mL, 0.83 mmol) in THF (1 mL) dropwise over 30 min. The solution darkened during this time and was stirred at 65 °C (reflux) for 1 h before cooling to room temperature. The mixture was then filtered before stirring in KF (25 mL of a 10% w/v aqueous solution) at room temperature for 3 days. The solution was then extracted with Et_2O (100 mL), washed with $NaHCO_3$ (aq) (100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (Al_2O_3 eluted with petrol) gave the title compound as a colourless oil (167 mg, 68 %).

^{1}H NMR (400MHz, C_6D_6): δ = 5.69 (1H, s, H3), 5.19 (1H, d, J = 8.5 Hz, H13), 5.05 (1H, t(fs), J = 6.5 Hz), 4.42 (1H, ddd, J = 7.8, 7.8, 5.8 Hz, H12), 3.30 (3H, s, H1), 2.22 (1H, dd, J = 13.3, 7.5 Hz, H11), 2.06 (3H, s, H5), 2.04-1.97 (3H, m), 1.94-1.80 (8H, m), 1.54 (3H, s), 1.48 (3H, s), 1.42 (6H, s, H20+H21), 0.89 (9H, s, H24), 0.00 (3H, s, H22), -0.02 (3H, s, H22).

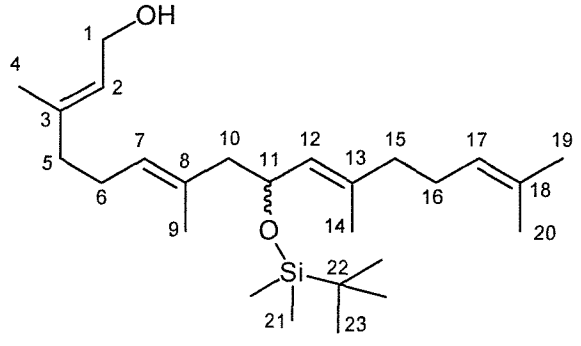
^{13}C NMR (100.5MHz, C_6D_6): δ = 167.47 (s, C2), 160.28 (s), 135.07 (s), 133.78 (s), 132.02 (s), 130 80 (d), 125.31 (d), 122.60 (d), 117.01 (d), 69.89 (d, C12), 51.06 (q, C1), 49.84 (t, C11), 41.58 (t), 40.51 (t), 27.45 (t), 27.05 (t), 26.51 (q), 25.50 (q), 19.44 (q), 19.11 (s, C23), 17.81 (q), 17.16 (q), 16.23 (q), -3.21 (q, C22), -3.96 (q, C22).

IR(thin film): ν = 1714.7 (m), 1264.8 (s), 740.7 (s) cm^{-1}.

LRMS (EI): m/z = 391 ($M-Bu^+$, 2%), 267 (24%), 135 (88%).

HRMS (ES^+): $C_{27}H_{48}O_3SiNa^+$ requires m/z = 471.3265. Found 471.3260

9-(*tert*-Butyl-dimethyl-silanyloxy)-3,7,11,15-tetramethyl-hexadeca-[2E,6E,10E],14-tetraen-1-ol (235).



To a stirred solution of 9-(*tert*-butyl-dimethyl-silanyloxy) -3,7,11,15-tetramethyl-hexadeca-2,6,10,14-tetraenoic acid methyl ester (167 mg, 0.37 mmol) in CH_2Cl_2 (5 mL) at –78 °C was added diisobutyl aluminium hydride (1.67 mL of a 1.5M solution in toluene, 1.11 mmol) dropwise over 5 min. the mixture was stirred at –78 °C for 2.5 h before pouring onto H_2O (100 mL), extraction with CH_2Cl_2 (100 mL), washing with $NaHCO_3$ (aq) (100 mL), drying over $MgSO_4$ and concentration *in vacuo*. Purification by column chromatography (Al_2O_3 eluted with 10:1 petrol:EtOAc) gave the title compound as a colourless oil (138 mg, 89 %).

^{1}H NMR (400MHz, C_6D_6): δ = 5.52 (1H, tq, J = 6.5, 1.3 Hz), 5.46 (1H, d(fs), J = 8.5 Hz, H12), 5.40 (1H, t, J = 6.8 Hz), 5.30 (1H, t, (fs), J = 6.8 Hz), 4.71 (1H, ddd, J = 7.8, 7.8, 5.5 Hz, H11), 4.09 (2H, m, H1), 2.52 (1H, dd, J = 13.3, 7.5 Hz, H10), 2.32 (1H, dd, J = 13.3, 5.5 Hz, H10), 2.29-2.21 (4H, m), 2.16-2.10 (4H, m), 1.80 (3H, s), 1.79 (3H, s), 1.68 (3H, s), 1.66 (3H, s), 1.60 (3H, s), 1.14 (9H, s, H23), 0.26 (3H, s, H21), 0.25 (3H, s, H21).

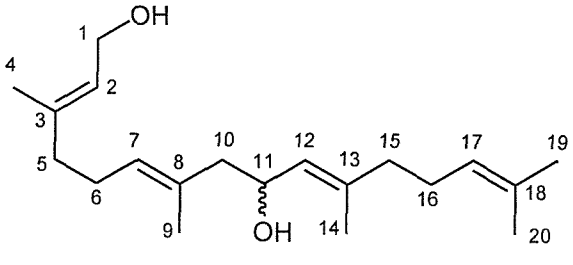
^{13}C NMR (100.5MHz, C_6D_6): δ = 138.52 (s), 134.71 (s), 132.73 (s), 131.70 (s), 130.58 (d), 127.64 (d), 125.29 (d), 125.04 (d), 69.83 (d, C11), 59.72 (t, C1), 49.62 (t, C10), 40.23 (t), 40.20 (t), 27.34 (t), 27.16 (t), 26.54 (q, C23), 26.20 (q, C19), 18.08 (q), 17.43 (q), 16.89 (q), 16.56 (q), -3.50 (q, C21), -4.23 (q, C21).

IR(thin film): ν = 3451.3 (w), 1738.9 (m, br), 1375.8 (m), 1063.7 (m, br), 834.8 (s) cm^{-1}.

LRMS (ES^+): m/z = 364 ($M\text{-}Bu^+$, 8%), 323 (28%), 187 (100%).

HRMS (ES^+): $C_{26}H_{48}O_2SiNa^+$ requires m/z = 443.3316. Found 443.3316.

3,7,11,15-Tetramethyl-hexadeca-[2E,6E,10E],14-tetraene-1,9-diol (180).



To a stirred solution of 9-(*tert*-butyl-dimethyl-silanyloxy) -3,7,11,15-tetramethyl-hexadeca-2,6,10,14-tetraen-1-ol, prepared above, (60 mg, 0.14 mmol) in THF (2 mL) at room temperature was added $Bu_4N^+F^-$ (0.28 mL of a 1M solution in THF, 0.28 mmol). The solution was then stirred for 12 h

before addition of H_2O (4 mL), extraction with Et_2O (50 mL), washing with H_2O (50 mL), drying over $MgSO_4$ and concentration *in vacuo*. Purification by column chromatography (Al_2O_3 eluted with 5:1 petrol:EtOAc) gave the title compound as a colourless oil (28 mg, 65 %). ^1H and ^{13}C data below match those reported in the literature for crinitol.

^1H NMR (400MHz, $CDCl_3$): δ = 5.33 (1H, t, J = 7.0 Hz, H2), 5.12 (1H, t, J = 6.8 Hz), 5.08 (1H, d, J = 8.0 Hz, H12), 5.02 (1H, t, J = 6.8 Hz), 4.33 (1H, ddd, J = 8.8, 8.8, 4.3 Hz, H11), 4.05 (2 × 1H, dd, J = 12.3, 7.3 Hz, H1), 2.18 (1H, m, H10), 2.12-1.97 (7H, m), 1.96-1.90 (2H, m), 1.61 (6H, s), 1.58 (6H, s), 1.52 (3H, s).

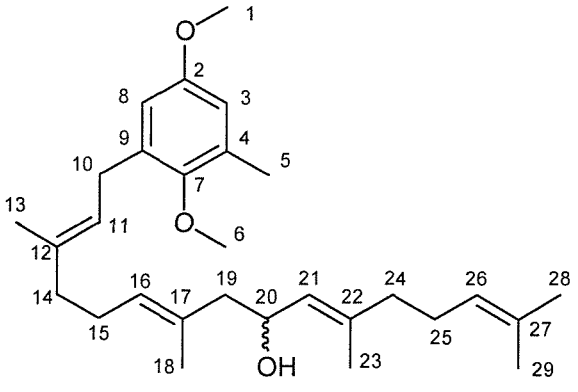
^{13}C NMR (100.5MHz, $CDCl_3$): δ = 139.10 (s), 138.39 (s), 132.40 (s), 131.75 (s), 128.36 (d), 127.19 (d), 124.76 (d), 124.12 (d), 65.57 (d), 59.36 (t), 48.26 (t), 39.66 (t), 39.34 (t), 26.56 (t), 26.01 (t), 25.79 (q), 17.81 (q), 16.73 (q), 16.30 (q), 16.03 (q).

IR(thin film): ν = 3377.9 (w, br), 1736.8 (m,br), 1668.7 (w), 1012.6 (m, br), 736.4 (s) cm^{-1}.

LRMS (EI): m/z = 270 (12%), 159 (22%), 145 (32%), 41 (100%), no molecular ion found.

HRMS (EI): $C_{20}H_{32}O$ requires m/z = 288.2453. Found 288.2438.

16-(2,5-Dimethoxy-3-methyl-phenyl)-[2E,6E,10E],14-tetramethyl-hexadeca-2,6,10,14-tetraen-8-ol (238).



A solution of $Pd_2(dba)_3{\cdot}CHCl_3$ (14 mg, 0.014 mmol) and $AsPh_3$ (33.4 mg, 0.11 mmol) in THF (5 mL) was stirred at room temperature for 15 min, becoming yellow, before addition of a solution of 2,6,10,14-tetramethyl-1-tributylstannyl-pentadeca-1,5,9,13-tetraen-8-ol (190 mg, 0.34 mmol) and 1-bromomethyl-2,5-dimethoxy-3-methyl benzene (83 mg, 0.34 mmol) in THF (2 mL). The solution was heated to reflux for 2 h, cooled and then filtered before stirring in KF (100 mL of a 10% w/v aqueous solution) at room temperature for 2 days. The solution was then extracted with Et_2O (200 mL), washed with H_2O (2 × 150 mL), and dried over $MgSO_4$ before concentration *in vacuo*. Purification by column chromatography (Al_2O_3 eluted with 20:1 petrol:Et_2O) gave the title compound as a colourless oil (147 mg, 98 %).

^{1}H NMR (400MHz, C_6D_6): δ = 6.93 (1H, d, J = 3.0 Hz), 6.70 (1H, d, J = 3.0 Hz, H3/H8), 5.58 (1H, t(br), J = 7.2 Hz, H11), 5.48 (1H, d(br), J = 8.0 Hz, H21), 5.36 (1H, t, J = 6.3 Hz, H16), 5.30 (1H, tseptet, J = 7.0, 1.3 Hz, H26), 4.60 (1H, dddd, J = 8.1, 8.2, 3.2, 4.8 Hz, H20), 3.60 (2H, d, J = 7.2 Hz, H10), 3.58 (3H, s), 3.52 (3H, s, H1/H6), 2.37 (1H, dd, J = 13.3, 8.2 Hz, H19), 2.32 (3H, s), 2.30-2.18 (5H, m), 2.16-2.11 (4H, m), 1.78 (3H, s), 1.76 (3H, s), 1.70 (3H, s), 1.67 (3H, s), 1.65 (3H, s).

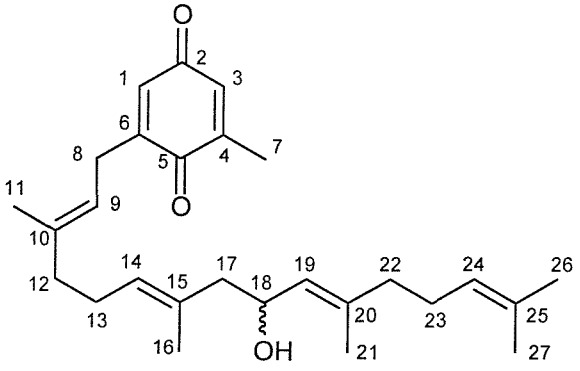
^{13}C NMR (100.5MHz, C_6D_6): δ = 156.71 (s), 151.55 (s), 137.23 (s), 136.09 (s), 132.63 (s), 132.22 (s), 131.75 (s), 129.52 (d, C16), 128.55 (d, C21), 125.02 (d, C26), 124.56 (d, C11), 114.48 (d), 113.90 (d, C3/C8), 66.77 (d, C20), 60.51 (q, C1/C6)), 55.40 (q, C1/C6), 49.12 (t, C19), 40.33 (t), 40.24 (t), 29.34 (t, C10), 27.33 (t), 27.17 (t), 26.20 (q, C5), 18.11 (q), 16.96 (q), 16.93 (q), 16.76 (q), 16.49 (q).

IR(thin film): ν = 1604.5 (m, br), 1090.8 (m), 865.0 (w) cm^{-1}.

LRMS (CI): m/z = 420 (M-H_2O^+, 8%), 165 (100%).

HRMS (EI): $C_{29}H_{44}O_3$ requires m/z = 440.3291. Found 440.3293.

2-(9-Hydroxy-3,7,11,15-tetramethyl-hexadeca-[2E,6E,10E],14-tetraenyl)-6-methyl-[1,4]benzoquinone (240).



A solution of $Pd_2(dba)_3$·$CHCl_3$ (17.6 mg, 0.017 mmol) and $AsPh_3$ (41.4 mg, 0.134 mmol) in THF (5 mL) was stirred at room temperature for 15 min, becoming yellow, before addition of a solution of 2,6,10,14-tetramethyl-1-tributylstannyl-pentadeca-1,5,9,13-tetraen-8-ol (237.6 mg, 0.42 mmol) and 2-Bromomethyl-6-methyl-[1,4]benzoquinone (90 mg, 0.42 mmol) in THF (2 mL). The solution was heated to reflux for 1 h, cooled and then filtered onto H_2O (50 mL) before extraction with Et_2O (100 mL), washing with H_2O (50 mL), $NaHCO_3$ (aq) (50 mL) and brine (50 mL), drying over $MgSO_4$ and concentration *in vacuo*. Purification by rapid column chromatography (SiO_2 eluted with 5:1 petrol:EtOAc) gave the title compound as a yellow oil (155 mg, 90 %). ^{1}H and ^{13}C NMR data below match the literature values for 9-hydroxysargaquinone.

^{1}H NMR (400MHz, $CDCl_3$): δ = 6.47 (1H, dt, J = 2.5, 1.5 Hz, H1), 6.40 (1H, dq, J = 2.5, 1.5 Hz, H3), 5.19 (1H, t, J = 7.0 Hz, H14), 5.14 (1H, t(fs), J = 7.3 Hz), 5.10 (1H, d(br), J = 8.3 Hz, H19), 5.02 (1H, t(fs), J = 6.8 Hz), 4.36 (1H, dt, J = 8.3, 6.5 Hz, H18), 3.06 (2H, d,

J = 7.3 Hz, H8), 2.14-2.01 (8H, m), 1.99 (2H, m), 1.94 (2H, m), 1.67 (3H, s), 1.61 (3H, s), 1.60 (3H, s), 1.56 (3H, s), 1.53 (3H, s).

^{13}C NMR (100.5MHz, $CDCl_3$): δ = 187.99 (s), 187.93 (s), 148.36 (s), 145.93 (s), 139.55 (s), 138.07 (s), 136.11 (s), 131.56 (s), 128.27 (d), 127.87 (d), 127.27 (d), 123.99 (d), 120.98 (d), 118.39 (d), 65.83 (d, C18), 48.11 (t, C17), 4014 (t), 39.51 (t, C12), 27.56 (t, C8), 26.69 (t), 26.41 (t), 25.64 (q, C26/C27), 17.65 (q), 16.57 (q), 16.40 (q), 16.23 (q), 16.00 (q)

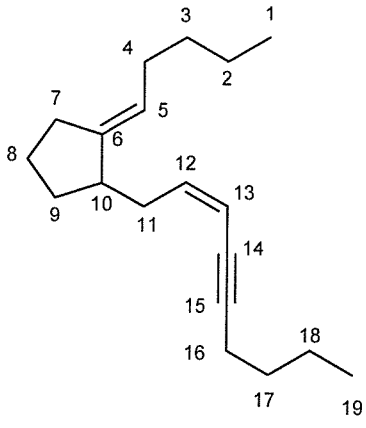
IR(thin film): ν = 3442.6 (m, br), 1654.8 (s), 979.8 (m, br) cm^{-1}.

LRMS (EI, CI, ES): m/z = no molecular ion found.

HRMS (EI): $C_{27}H_{38}O_3$ requires m/z = 410.2821. Found 410.2829.

5.2 Experimental Details for Synthesis of Compounds in Chapter Three.

(2E)-1-[(2Z)-2-nonen-4-ynyl]-2-pentylidenecyclopentane (316).



To a stirred solution of Cp_2ZrCl_2 (292mg, 1.0 mmol) in THF (5.0 mL) at –78 °C was added ^{n}BuLi (0.8 mL of a 2.5M solution, 2.0 mmol) dropwise over 30 sec. The solution continued to stir at –78 °C for 1 h before addition of a solution of 1-decen-6-yne (150 mg, 1.0 mmol) in THF (2.0 mL). The mixture was then warmed to room temperature and stirred for 2 h before recooling to –78 °C and addition of (1E)-1-chloro-1-octen-3-yne (0.2 mL, 2.0 mmol) followed by LiTMP (2.0 mmol formed from 2,2,6,6-tetramethylpiperidine (0.34 mL, 2.0 mmol) and ^{n}BuLi (0.8 mL of a 2.5M solution, 2.0 mmol) in THF (4.0 mL) at 0 °C). The mixture continued to stir at –78 °C for 20 min for quantitative conversion and was then stirred at room temperature overnight before addition of MeOH (5.0 mL) and $NaHCO_3$ (aq) (6.0 mL) and stirring for a further 2 h. The mixture was extracted with Et_2O (200 mL) and washed with $NaHCO_3$ (aq) (150 mL) and brine (150 mL) before drying over $MgSO_4$ and removal of solvents *in vacuo*. Purification by Kugelrohr distillation (110 °C, 15mm Hg) gave a pale yellow oil (223 mg, 86 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.77 (1H, dt, J = 10.5, 7.4 Hz, H12), 5.40 (1H d(br), J = 10.8 Hz, H13), 5.13 (1H t, J = 6.8 Hz, H5), 2.44 (1H, dt, J = 13.3, 6.8 Hz), 2.33 (1H, m, H10), 2.27 (1H, t, J = 7.0 Hz), 2.30-2.15 (4H, m), 1.91 (2H, m), 1.75-1.16 (2H, m), 1.44 (2H, sextet, J = 6.8 Hz, H2/H18), 1.36 (3H, m), 1.25 (5H, m), 0.85 (6H, m, H1+H19).

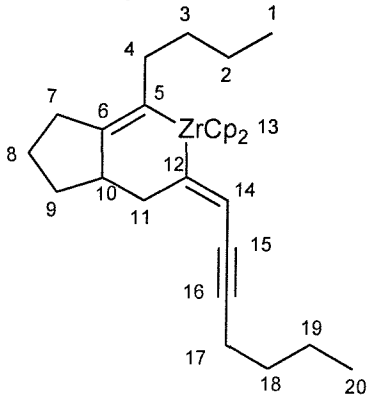
^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.66 (s, C6), 141.38 (d), 120.65 (d), 110.09 (d), 94.49 (s), 77.72 (s), 43.90 (d, C10), 34.95 (t), 32.47 (t), 32.07 (t), 31.11 (t), 29.33 (t), 29.27 (t), 24.19 (t), 22.54 (t), 22.09 (t), 19.37 (t), 14.21 (q, C1), 13.75 (q, C19).

IR(thin film): ν = 2360.0 (m), 1739.2 (m, br), 1465.3 (m, br) cm^{-1}.

LRMS (CI): m/z = 259 (M + H$^+$, 90%), 137 (100%).

HRMS (EI): $C_{19}H_{30}$ requires m/z = 258.2348. Found = 258.2338.

2-Butyl-3,3-*bis*-(η^2-cyclopentadienyl)-zirconabicyclo[4.3.0]-pent-(2E)-ene-(4Z)-nonen-6-yne (315).

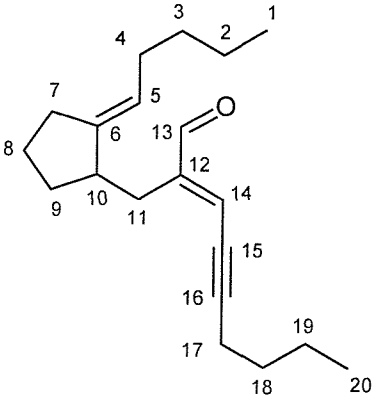


To a stirred solution of Cp_2ZrCl_2 (292mg, 1.0 mmol) in THF (5.0 mL) at –78 °C was added ^{n}BuLi (0.8 mL of a 2.5M solution, 2.0 mmol) dropwise over 30 sec. The solution was stirred at –78 °C for 1 h before addition of a solution of 1-decen-6-yne (150 mg, 1.0 mmol) in THF (2.0 mL). The mixture was then warmed to room temperature and stirred for 2 h before recooling to –78 °C and addition of (1E)-1-chloro-1-octen-3-yne (0.11 mL, 1.1 mmol) followed by ^{tert}BuLi (0.65 mL of a 1.7M solution in hexanes, 1.1 mmol). The mixture continued to stir at –78 °C for 20 min before removal of solvents and redissolution in the NMR solvent.

^{1}H NMR (400 MHz, C_6D_6): δ = 5.75 (2 × 5H, S, H13), 4.99 (1H, s, H14), 2.32-2.19 (3H, m), 2.08 (1H, m), 1.95 (1H, m), 1.69 (1H, m), 1.53-1.31 (10H, m), 1.30-1.12 (5H, m), 0.90 (3H, t, J = 7.0 Hz), 0.76 (3H, t, J = 7.0 Hz).

^{13}C NMR (100 MHz, C_6D_6): δ = 207.12 (s, C12), 180.01 (s, C5), 149.93 (s, C6), 111.97 (d, C14), 110.16 (5 × d, C13), 109.80 (5 × d, C13), 89.95 (s, C16), 78.92 (s, C15), 46.13 (d, C10), 44.67 (t), 35.67 (t), 33.82 (t), 31.94 (t), 30.43 (t), 30.10 (t), 24.79 (t), 22.96 (t), 20.94 (t), 18.50 (t), 13.06 (q, C1), 12.40 (q, C19).

2-(2-Pentylidene-cyclopentylmethyl)-non-(2Z)-en-4-ynal (327).

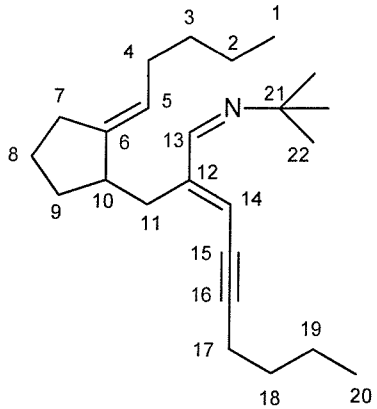


To a stirred solution of Cp_2ZrCl_2 (292mg, 1.0 mmol) in THF (5.0 mL) at –78 °C was added ^{n}BuLi (0.8 mL of a 2.5M solution, 2.0 mmol) dropwise over 30 sec. The solution was stirred at –78 °C for 30 min before addition of a solution of 1-decen-6-yne (150 mg, 1.0 mmol) in THF (2.0 mL). The mixture was then warmed to room temperature and stirred for 2 h before recooling to –78 °C and addition of (1E)-1-chloro-1-octen-3-yne (0.11 mL, 1.1 mmol) followed by ^{tert}BuLi (0.65 mL of a 1.7M solution in hexanes, 1.1 mmol). The mixture continued to stir at –78 °C for 20 min and was then warmed to room temperature and stirred for 1 h. ^{n}BuNC (0.11 mL, 1.0 mmol) was added dropwise and the mixture stirred for 30 min. 1M AcOH (10

mL) was added and the mixture stirred for 12 h before extraction with Et_2O (200 mL), washing with $NaHCO_3$ (aq) (150 mL) and brine (150 mL), drying over $MgSO_4$ and removal of solvent *in vacuo*. Purification by column chromatography (SiO_2 eluted with 10:1 petrol:Et_2O) gave the title compound as a colourless oil (111.0 mg, 39 %).

^1H NMR (300 MHz, $CDCl_3$): δ = 9.35 (1H, s, H13), 6.37 (1H, t, J = 2.0 Hz, H14), 5.21 (1H, tq (br), J = 8.0, 1.5 Hz, H5), 2.59 (2H, dt, J = 8.0, 5.2 Hz, H4), 2.48 (2H, dt, J = 2.2, 7.0 Hz, H17),2.35 (1H, dd, J = 13.6, 11.6 Hz, H11), 2.24 (2H, apparent t (br), J = 6.6 Hz), 1.97 (2H, m), 1.75 (1H, ddt, J = 11.8, 5.9, 5.9 Hz, H10), 1.64-1.52 (4H, m), 1.50-1.41 (3H, m), 1.35-1.28 (4H, m), 0.94 (3H, t, J = 7.0 Hz), 0.90 (3H, t, J = 5.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.63 (d, C13), 150.89 (s, C12), 145.70 (s, C6), 131.22 (d, C14), 121.09 (d, C5), 109.42 (s, C16), 77.65 (s, C15), 43.24 (d, C10), 32.41 (t), 32.02 (t), 31.32 (t), 30.58 (t), 29.33 (t), 28.90 (t), 23.92 (t), 22.56 (t), 22.13 (t), 20.04 (t), 14.21 (q, C1), 13.69 (q, C20).
IR (thin film): ν = 2957.5 (s), 1681.4 (s) (br), 1595.1 (m), 1456.0 (m), 1378.2 (w) cm^{-1}.
LRMS (EI, CI, ES): no molecular ion found.
HRMS (EI): $C_{20}H_{30}O$ requires m/z = 286.2297. Found 286.2286.

tert-Butyl-[2-(2-pentylidene-cyclopentylmethyl)-non-(2Z)-en-4-ynylidene]-amine (328).



To a stirred solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C was added ^nBuLi (0.8 mL of a 2.5M solution, 2.0 mmol) dropwise over 30 sec. The mixture continued to stir at –78 °C for 30 min before addition of a solution of 1-decen-6-yne (150 mg, 1.0 mmol) in THF (2 mL). The mixture was warmed to room temperature and stirred for 2 h before cooling to –78 °C and addition of (1E)-1-chloro-1-octen-3-yne (0.11 mL, 1.1 mmol) followed by ^tBuLi (0.65 mL of a 1.7M solution, 1.1 mmol). The mixture was stirred at –78 °C for 20 min and then warmed to room temperature and stirred for 1 h. ^tBuNC (0.11 mL, 1.0 mmol) was then added dropwise and the mixture stirred for 30 min before addition of MeOH (5 mL) and $NaHCO_3$ (aq) (6 mL). The mixture was stirred for 2 h before pouring onto H_2O (200 mL), extraction with Et_2O (200 mL), washing with $NaHCO_3$ (aq) (150 mL) and brine (150 mL),

drying over $MgSO_4$ and removal of solvents *in vacuo*. Column chromatography (Al_2O_3 (basic, activated) eluted with 10:1 petrol:Et_2O) gave the title compound as a pale yellow oil (241 mg, 71 %).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.68 (1H, s, H13), 5.69 (1H, t (br), J = 2.0 Hz, H14), 5.18 (1H, tq, J = 8.1, 1.4 Hz, H5), 2.61 (2H, dt, J = 8.1, 4.8 Hz, H4), 2.47 (1H, dd, J = 13.1, 11.5 Hz), 2.33 (2H, dt, J = 2.0, 7.0 Hz, H17), 2.21 (4H, m), 1.90 (2H, m), 1.68 (1H, m, H10), 1.50-1.39 (4H, m), 1.39-1.30 (3H, m), 1.29-1.23 (4H, m), 1.10 (9H, s, H21), 0.85 (3H, t, J = 7.0 Hz), 0.84 (3H, t, J = 7.3 Hz).

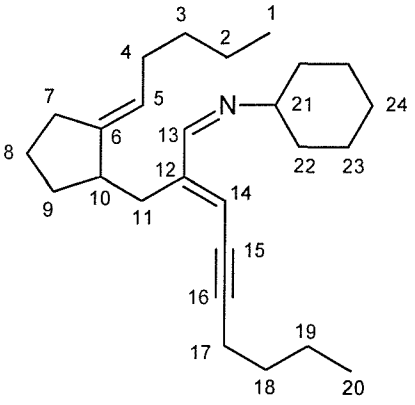
^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 157.17 (d, C13), 151.51 (s, C12), 146.97 (s, C6), 120.66 (d, C5), 117.93 (d, C14), 101.08 (s, C16), 78.81 (s, C15), 57.36 (s, C22), 43.99 (d, C10), 32.41 (t), 31.26 (t), 30.95 (t), 30.22 (t), 30.03 (q C21), 29.63 (t), 29.48 (t), 24.27 (t), 22.85 (*t*), 22.39 (*t*), 20.02 (*t*), 14.46 (*q*), 13.94 (*q*).

IR(thin film): ν = 2358.5 (m), 1624.3 (w), 909.8 (s), 847.9 (m) cm^{-1}.

LRMS (CI): m/z = 343 ($M+H^+$, 100%), 286 ([M – C_4H_9] + H^+,21%), 262 (11%), 204 (60%).

HRMS (EI): $C_{24}H_{39}N$ requires m/z = 341.3083. Found = 341.3084.

Cyclohexyl-[2-(2-pentylidene-cyclopentylmethyl)-non-(2Z)-en-4-ynylidene]-amine (329).

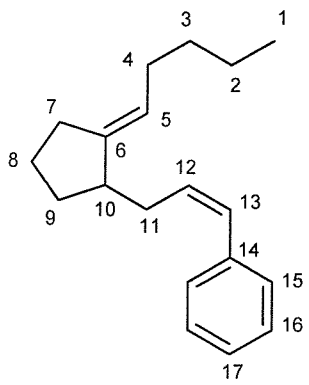


To a stirred solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C was added ^{n}BuLi (0.8 mL of a 2.5M solution, 2.0 mmol) dropwise over 30 sec. The mixture continued to stir at –78 °C for 30 min before addition of a solution of 1-decen-6-yne (150 mg, 1.0 mmol) in THF (2 mL). The mixture was warmed to room temperature and stirred for 2 h before cooling to –78 °C and addition of (1E)-1-chloro-1-octen-3-yne (0.11 mL, 1.1 mmol) followed by ^{t}BuLi (0.65 mL of a 1.7M solution, 1.1 mmol). The mixture was stirred at –78 °C for 20 min and then warmed to room temperature and stirred for 1 h. CyNC (0.12 mL, 1.0 mmol) was added dropwise and the mixture stirred for 30 min before addition of MeOH (5 mL) and $NaHCO_3$ (aq) (6 mL). The mixture was stirred for 2 h before pouring onto H_2O (200 mL), extraction with Et_2O (200 mL), washing with $NaHCO_3$ (aq) (150 mL) and brine (150 mL), drying over $MgSO_4$ and removal of solvents *in vacuo*. Column

chromatography (Al_2O_3 (basic, activated) eluted with 10:1 petrol:Et_2O) gave the title compound as a pale yellow oil (296 mg, 81 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (1H, s, H13), 5.69 (1H, t (br), J = 2.0 Hz, H14), 5.16 (1H, tq, J = 8.5, 1.7 Hz, H5), 2.96 (1H, tt, J = 10.0, 4.0 Hz, H21), 2.61 (2H, dt, J = 8.3, 5.3 Hz, H4), 2.33 (2H, dt, J = 2.0, 7.0 Hz, H17), 2.16 (2H, apparent t, J = 6.8 Hz), 1.57-1.37 (20H, m), 1.30-1.19 (5H, m), 0.85 (3H, t, J = 7.3 Hz), 0.84 (3H, t, J = 7.3 Hz).
^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 160.80 (d, C13), 150.94 (s, C12), 146.74 (s, C6), 120.74 (d, C5), 118.27 (d, C14), 101.43 (s), 78.75 (s), 69.91 (d, C21), 43.87 (d, C10), 34.75 (t), 33.65 (t), 32.57 (t), 32.39 (t), 31.22 (t), 29.61 (t), 29.46 (t), 29.28 (t), 25.00 (t), 24.27 (t), 22.84 (t), 22.37 (t), 20.03 (t), 14.46 (q), 13.96 (q).
IR(thin film): ν = 2363.0 (m), 1625.2 (m), 847.9 (s) cm^{-1}.
LRMS (CI): m/z = 287 ([M-Cy] + H^+, 100%), 273 ([M-NCy] + H^+, 30%), 150 (16%).
HRMS (EI): $C_{26}H_{41}N$ requires m/z = 367.3239. Found = 367.3222.

[3-(2-Pentylidene-cyclopentyl)-propenyl]-benzene (341).



To a stirred solution of Cp_2ZrCl_2 (146 mg, 0.5 mmol) in THF (5 mL) at –78 °C was added ^{n}BuLi (0.4 mL of a 2.5M solution, 1.0 mmol) dropwise over 20 sec. The mixture was stirred at –78 °C for 20 min before dropwise addition of a solution of 1-undec-6-yne (75 mg, 0.5 mmol) in THF (2 mL). The mixture was then warmed to room temperature and stirred for 2 h before recooling to –78 °C and addition of 1-[(E)-2-fluoro-1-ethenyl]benzene (0.06 mL, 0.5 mmol) followed by LiTMP (0.5 mmol freshly prepared from 2,2,6,6-tetramethypiperidine (0.085 mL, 0.5 mmol) and ^{n}BuLi (0.2 mL of a 2.5M solution, 0.5 mmol) in THF (2 mL) at 0°C for 30 min). The mixture was stirred for 12 h, warming to room temperature during this time, before addition of MeOH (5 mL) and $NaHCO_3$ (aq) (5 mL) and stirring for 2 h. The solution was then poured onto H_2O (200 mL), extracted with Et_2O (200 mL), washed with $NaHCO_3$ (aq) (2 × 150 mL) and brine (150 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2 eluted with petrol) yielded the title compound as a colourless oil (63 mg, 50 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.30 (5H, m, H15+H16+H17), 6.46 (1H, d(br), J = 11.8 Hz, H13), 5.73 (1H, dt, J = 11.8, 7.0 Hz, H12), 5.21 (1H, ddq, J = 7.0, 7.0, 2.0 Hz, H5), 2.60 (1H, dddd, J = 14.7, 10.3, 4.5, 1.5 Hz, H7), 2.45 (1H, m), 2.35-2.15 (3H, m), 1.98 (2H, apparent q, J = 5.9 Hz), 1.86 (1H, m), 1.70 (1H, m), 1.50-1.41 (2H, m), 1.35-1.21

(4H, m), 0.90 (3H, t, J = 6.8 Hz, H1).

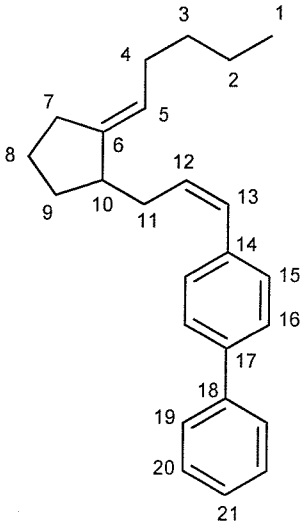
^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.65 (s, C6), 138.03 (s, C14), 132.07 (d), 129.36 (d, C17), 128.93 (d), 128.25 (d, C15/C16), 126.53 (d), 120.76 (d), 44.60 (d, C10), 33.33 (t), 32.75 (t), 32.05 (t), 29.34 (t), 29.32 (t), 24.17 (t), 22.57 (t), 14.23 (q, C1).

IR(thin film): ν = 3010.3 (w), 2954.0 (s), 1599.8 (w), 1493.7 (m), 764.9 (w) cm^{-1}.

LRMS (EI): m/z = 254 (M^+, 42%), 197 (M^+-C_4H_9, 11%), 137 (100%), 115 (100%).

HRMS (EI): $C_{19}H_{26}$ requires m/z = 254.2035. Found 254.2047.

4-[3-(2-Pentylidene-cyclopentyl)-propenyl]-biphenyl (342).



To a stirred solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C was added ^{n}BuLi (0.8 mL of a 2.5M solution, 2.0 mmol) dropwise over 20 sec. The solution was stirred at –78 °C for 30 min before addition of a solution of 1-decen-6-yne (150 mg, 1.0 mmol) in 2 mL THF. The mixture was then warmed to room temperature and stirred for 2 h before recooling to –78 °C and addition of 4-ethynyl biphenyl (178 mg, 1.0 mmol) followed by LiTMP (1.0 mmol formed from 2,2,6,6-tetramethylpiperidine (0.17 mL, 1.0 mmol) and ^{n}BuLi (0.4 mL of a 2.5M solution, 1.0 mmol) in THF (2.0 mL) at 0 °C). The solution was then warmed to room temperature and stirred for 12 h before addition of MeOH (5 mL) and $NaHCO_3$ (aq) (6 mL) and stirring for a further 5 h. The mixture was extracted with Et_2O (200 mL) and washed with $NaHCO_3$ (aq) (150 mL) and brine (150 mL) before drying over $MgSO_4$ and removal of solvents *in vacuo*. Purification by column chromatography (SiO_2 eluted with petrol) gave the title compound as a colourless oil (210 mg, 64 %).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.65-7.57 (4H, m), 7.50-7.31 (5H, m), 6.50 (1H, d, J = 11.8 Hz, H13), 5.77 (1H, dt, J = 11.8, 7.0 Hz, H12), 5.25 (1H, tq, J = 7.4, 2.0 Hz, H5), 2.68 (1H, dddd, J = 14.3, 7.0, 4.8, 1.8 Hz), 2.49 (1H, m), 2.42-2.20 (3H, m), 2.00 (2H, d(br), J = 7.0 Hz), 1.90 (1H, ddt, J = 11.8, 4.8, 6.6 Hz), 1.74 (1H, m), 1.56 (1H, m), 1.40-1.26 (5H, m), 0.91 (3H, t, J = 7.0 Hz).

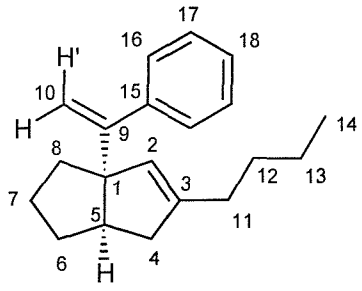
^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.66 (s), 141.03 (s), 139.27 (s), 137.10 (s), 132.72 (d), 137.37 (d), 129.39 (d), 129.04 (d), 127.90 (d), 127.35 (d), 127.14 (d), 126.97 (d), 120.82 (d), 44.63 (d, C10), 33.52 (t), 32.80 (t), 32.07 (t), 30.18 (t), 29.38 (t), 24.22 (t), 22.60 (t), 14.26 (q).

IR(thin film): ν = 3029.0 (m), 2926.6 (s), 1600.2 (w), 1485.9 (s), 769.5 (s) cm^{-1}.

LRMS (EI): m/z = 330 (M^+, 32%), 193 (100%), 178 (88%).

HRMS (EI): $C_{25}H_{30}$ requires m/z = 330.2348. Found = 330.2352.

5-Butyl-6a-(1-phenyl-vinyl)-1,2,3,3a,4,6a-hexahydro-pentalene (338).



To a stirred solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C was added ^{n}BuLi (0.8 mL of a 2.5M solution, 2.0 mmol) dropwise over 20 sec. The solution was stirred at –78 °C for 20 min before addition of a solution of 1-decen-6-yne (150 mg, 1.0 mmol) in 2 mL THF. The mixture was then warmed to room temperature and stirred for 2 h before recooling to –78 °C and addition of 2-(fluorovinyl)-benzene/CH_2Cl_2 solution (0.2 mL, (1.22 mmol (E)-2-(fluorovinyl)-benzene, 0.067 mmol (Z)-2-(fluorovinyl)-benzene and 0.49 mmol CH_2Cl_2) followed by LiTMP (1.5 mmol formed from 2,2,6,6-tetramethylpiperidine (0.26 mL, 1.5 mmol) and ^{n}BuLi (0.6 mL of a 2.5M solution, 1.5 mmol) in THF (2.0 mL) at 0 °C). The solution was stirred for 45 min, warming to –65 °C, and then warmed to room temperature and stirred for 3 h before addition of MeOH (5 mL) and $NaHCO_3$ (aq) (6 mL) and stirring for a further 12 h. The mixture was poured onto H_2O (150 mL), extracted with Et_2O (200 mL) and washed with $NaHCO_3$ (aq) (150 mL) and brine (150 mL) before drying over $MgSO_4$ and removal of solvents *in vacuo*. Purification by column chromatography (SiO_2 eluted with petrol) gave the title compound as a colourless oil (88 mg, 33 %).

^{1}H NMR (400 MHz, C_6D_6): δ = 7.39 (2H, m, H16), 7.25 (3H, m, H17+H18), 5.50 (1H, pentet, J = 2.0 Hz, H2), 5.28 (1H, d, J = 1.8 Hz, H10), 5.20 (1H, d, J = 1.8 Hz, H10'), 2.69 (1H, tt, J = 8.8, 2.5 Hz, H5), 2.49 (1H, ddq, J = 16.4, 8.5, 2.7 Hz, H4), 2.19 (1H, m, H11), 2.05 (1H, m, H11), 1.96 (1H, m, H4), 1.90 (2H, m, H8), 1.85 (1H, m, H6), 1.70-1.55 (4H, m, H7+H12), 1.45 (2H, m, H13), 1.38 (1H, m, H6), 1.02 (3H, m, H14).

^{13}C NMR (100 MHz, C_6D_6): δ = 154.28 (s, C9), 145.56 (s, C3), 143.31 (s, C15), 126.64 (2 × d), 126.50 (2 × d), 125.45 (d, C18), 123.60 (d, C2), 112.46 (t, C10), 68.01 (s, C1), 45.41 (d, C5), 39.56 (t, C4), 35.37 (t, C6), 34.49 (t, C8), 29.38 (t, C12), 25.79 (t, C11), 24.54 (t, C7), 21.96 (t, C13), 12.96 (q, C14).

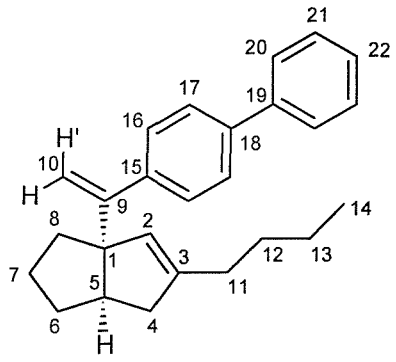
IR(thin film): ν = 3079. 9 (m), 3050.3 (m), 1620.1 (m), 1598.2 (w), 772.8 (s) cm^{-1}.

LRMS (EI): m/z = 266 (M^+, 88%), 251 (20%), 223 (80%), 181 (100%).

LRMS (CI): m/z = 267 ($M + H^+$, 100%), 251 (6%), 223 (18%), 163 (20%).

HRMS (EI): $C_{20}H_{26}$ requires m/z = 266.2035. Found = 266.2035.

4-[1-(5-Butyl-2,3,6,6a-tetrahydro-1*H*-pentalen-3a-yl)-vinyl]-biphenyl (339).



To a stirred solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C was added ^{n}BuLi (0.8 mL of a 2.5M solution, 2.0 mmol) dropwise over 20 sec. The solution was stirred at –78 °C for 30 min before addition of a solution of 1-decen-6-yne (150 mg, 1.0 mmol) in 2 mL THF. The mixture was then warmed to room temperature and stirred for 2 h before recooling to –78 °C and addition of 4-(2-fluorovinyl)-biphenyl (294 mg, (87:13 E:Z) mixture, 1.48 mmol 4-([2E]-fluorovinyl)-biphenyl) followed by CH_2Cl_2 (0.03 mL, 0.49 mmol) and LiTMP (2.3 mmol formed from 2,2,6,6-tetramethylpiperidine (0.39 mL, 2.3 mmol) and ^{n}BuLi (0.92 mL of a 2.5M solution, 2.3 mmol) in THF (5.0 mL) at 0°C). The solution was stirred for 45 min, warming to –60 °C, and then warmed to room temperature and stirred for 3 h before addition of MeOH (5 mL) and $NaHCO_3$ (aq) (6 mL) and stirring for a further 12 h. The mixture was poured onto H_2O (200 mL), extracted with Et_2O (200 mL) and washed with $NaHCO_3$ (aq) (150 mL) and brine (150 mL) before drying over $MgSO_4$ and removal of solvents *in vacuo*. Purification by column chromatography (SiO_2 eluted with petrol) gave the title compound as a colourless oil (134 mg, 80 %).

^{1}H NMR (400 MHz, C_6D_6): δ = 7.51 (2H, d, J = 7.8 Hz, H20), 7.44 (2H, d, J = 8.3 Hz), 7.35 (2H, d, J = 8.3 Hz, H16/H17), 7.22 (2H, t, J = 7.8 Hz, H21), 7.14 (1H, tt, J = 7.8, 1.0 Hz, H22), 5.44 (1H, pentet, J = 1.8 Hz, H2), 5.20 (1H, d, J = 1.8 Hz, H10), 5.16 (1H, d, J = 1.5 Hz, H10'), 2.64 (1H, tt, J = 8.8, 2.3 Hz, H5), 2.46 (1H, ddq, J = 16.6, 8.5, 2.5 Hz, H4), 2.12 (1H, m), 1.97-1.77 (5H, m), 1.60-1.44 (4H, m), 1.41-1.29 (3H, m), 0.92 (3H, t, J = 7.3 Hz, H14).

^{13}C NMR (100 MHz, C_6D_6): δ = 155.93 (s), 147.66 (s), 144.31 (s), 142.01 (s), 140.50 (s), 129.61 (d), 129.25 (d), 128.90 (d, C22), 127.91 (d), 127.28 (d), 125.62 (d, C2), 114.58 (t, C10), 70.01 (s, C1), 47.44 (d, C5), 41.63 (t), 37.38 (t), 36.60 (t), 31.39 (t), 27.81 (t), 26.50 (t), 23.93 (t), 14.93 (q, C14).

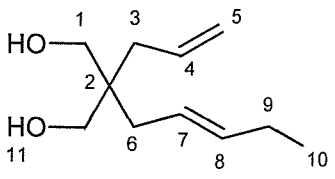
IR(thin film): ν = 2949.2 (s), 1589.7 (w), 1485.7 (m), 1448.1 (m), 768.5 (s) cm^{-1}.

LRMS (EI): m/z = 342 (M^+, 100%), 327 (26%), 299 (62%), 285 (M-Bu^+, 70%).

HRMS (EI): $C_{26}H_{30}$ requires m/z = 342.2348. Found = 342.2356.

5.3 Experimental Details for Synthesis of Compounds in Chapter Four.

2-Allyl-2-pent-2-enyl-propane-1,3-diol.



To a stirred solution of *trans*-2-penten-1-ol (2.0 g, 23.22 mmol) and Et_3N (10 mL) in CH_2Cl_2 (50 mL) at –30 °C was added mesylchloride (2.93 g, 25.54 mmol) dropwise over 2 min. The mixture was stirred at –30 °C for 15 min before filtration. Sodium (635 mg, 27.61 mmol) was washed with hexane and then added portion-wise to EtOH (40 mL) at 0 °C. Following dissolution, diethyl allyl malonate (3.64 mL, 18.41) mmol) was added dropwise and the solution was stirred at 0 °C for 20 min before addition of the solution of methane sulphonic acid pent-2-enyl ester formed above. The mixture was warmed to room temperature and stirred for 16 h before extraction with Et_2O (200 mL), washing with H_2O (150 mL) and brine (150 mL), drying over $MgSO_4$ and concentration *in vacuo*. Purification by column chromatography (SiO_2 eluted with 10:1 petrol:Et_2O) gave the diester as a colourless oil (2.9 g, 59 %).

To a stirred suspension of $LiAlH_4$ (1.14 g, 30.0 mmol) in Et_2O (100 mL) at 0 °C was added a solution of the diester (2.5 g, 9.3 mmol), in Et_2O (50 mL) dropwise over 15 min. The mixture was then warmed to room temperature and stirred for16 h before dropwise addition of HCl (40 mL of a 2M aqueous solution) at 0 °C, extraction with Et_2O (200 mL), washing with HCl (150 mL of a 2M aqueous solution) and brine (150 mL), drying over $MgSO_4$ and removal of solvents *in vacuo*. Purification by Kugelrohr distillation (130 °C, 5 mm Hg) gave the title compound as a colourless oil (1.4 g, 80 %).

^{1}H NMR (300MHz, $CDCl_3$): δ = 5.83 (1H, ddt, J = 18.4, 8.8, 7.4 Hz, H4), 5.54 (1H, dt, J = 15.4, 5.9 Hz), 5.39 (1H, dt, J = 15.1, 7.4 Hz), 5.10 (2H, m, H5), 3.55 (4H, s, H1), 2.99 (2H, s, H11), 2.08-1.95 (6H, m, H3+H6+H9), 0.97 (3H, t, J = 7.4 Hz, H10).

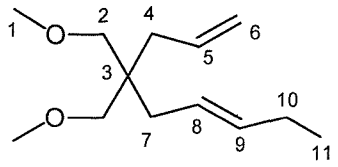
^{13}C NMR (75MHz, $CDCl_3$): δ = 136.05 (d), 134.22, (d), 123.86 (d), 118.10 (t, C5), 68.25 (2 × t, C1), 42.25 (s, C2), 36.06 (t, C3), 34.69 (t, C6), 25.87 (t, C9), 14.06 (q, C10).

IR(thin film): ν = 3354.3 (m, br), 1638.7 (w), 1439.3 (w), 1024.0 (s) cm^{-1}.

LRMS (CI): m/z = 185 ($M+H^+$, 6%), 135 (15%), 67, (36%).

HRMS (EI): $C_{11}H_{18}O$ ($M-H_2O^+$) requires m/z = 166.1358. Found 166.1349.

4,4-Bis-methoxymethyl-nona-1,6-diene (416).



To a suspension of sodium hydride (632 mg of a 60% dispersion in mineral oil, 15.8 mmol) in THF (20 mL) was added a solution of 2-allyl-2-pent-2-enyl-propane-1,3-diol (1.0 g, 5.4 mmol) in THF (10 mL) dropwise over 15 min. The solution was stirred for 30 min before addition of methyl iodide (0.5 mL, 7.9 mmol) in THF (5 mL). The mixture was stirred for a further 40 min before addition of methyl iodide (0.5 mL, 7.9 mmol) in THF (5 mL) once more. The mixture was then stirred at room temperature for 16 h before pouring onto H_2O (200 mL), extraction with Et_2O (200 mL), washing with H_2O (2 × 100 mL) and brine (2 × 100 mL), drying over $MgSO_4$ and concentration *in vacuo*. Purification by Kugelrohr distillation (145 °C, 15 mm Hg) gave the title compound as a colourless oil (1.1 g, 100 %).

^{1}H NMR (300MHz, $CDCl_3$): δ = 5.81 (1H, ddt, J = 18.0, 9.2, 7.4 Hz, H5), 5.48 (1H, dt, J = 15.4, 5.9 Hz, H8), 5.37 (1H, dt, J = 15.1, 7.2 Hz, H9), 5.05 (2H, m, H6), 3.31 (6H, s, H1), 3.15 (4H, s, H2), 2.08-1.95 (6H, m, H10+H7+H4), 0.98 (3H, t, J = 7.4 Hz, H11).

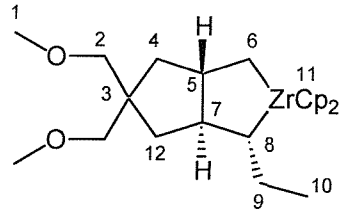
^{13}C NMR (75MHz, $CDCl_3$): δ = 135.42 (d), 134.51 (d), 124.07 (d), 117.39 (t, C6), 75.08 (2 × t, C2), 59.11 (2 × q, C1), 41.81 (s, C3), 36.44 (t, C4), 34.91 (t, C7), 25.80 (t, C10), 14.04 (q, C11).

IR(thin film): ν = 1638.4 (w), 1109.7 (s), 970.8 (m), 913.2 (m) cm^{-1}.

LRMS (CI): m/z = 213 ($M+H^+$, 8%), 139 (17%), 98, (42%).

HRMS (EI): $C_{13}H_{24}O_2$ requires m/z = 212.1776. Not found.

1-Ethyl-5,5-bis-methoxymethyl-octahydro-9,9-bis(η^2-cyclopentadienyl)-zirconabi-cyclo[3.3.0]-pentalene (414).

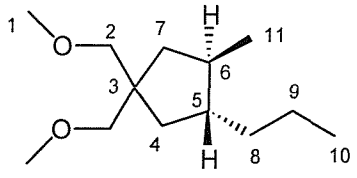


To a stirred solution of Cp_2ZrCl_2 (146 mg, 0.5 mmol) in THF (5.0 mL) at –78 °C was added ^{n}BuLi (0.4 mL of a 2.5M solution, 1.0 mmol) dropwise over 30 sec. The solution continued to stir at –78 °C for 1 h before addition of a solution of 4,4-bis-methoxymethyl-nona-1,6-diene (106 mg, 0.5 mmol) in THF (2.0 mL). The mixture was then warmed to room temperature and stirred for 2 h before removal of solvents *in vacuo* and redissolution in the NMR solvent.

^{1}H NMR (400 MHz, C_6D_6): δ = 5.61 (10H, s, H11), 3.12 (2 × 2H, s(br), H2), 3.08 (6H, s, H1), 2.17-2.05 (2H, m), 2.04-1.96 (1H, m, H9), 1.56 (1H, ddd, J = 11.5, 11.5, 4.5 Hz, H8), 1.49-1.38 (1H, m, H9), 1.13 (1H, m, H5), 1.12-1.00 (2H, m), 0.94-0.83 (2H, m), 0.78 (1H, m, H7), 0.59 (3H, t, J =7.3 Hz, H10).

^{13}C NMR (100.5 MHz, C_6D_6): δ = 108.69 (5 × s), 108.41 (5 × s, C11), 77.64 (2 × t, C2), 65.16 (d, C8), 57.66 (2 × q, C1), 49.24 (t, C9), 45.78 (t), 45.07 (s, C3), 41.44 (t), 39.02 (d, C7), 33.19 (d, C5), 31.24 (t), 15.41 (q, C10).

1,1-Bis-methoxymethyl-3-methyl-4-propyl-cyclopentane.



To a stirred solution of Cp_2ZrCl_2 (146 mg, 0.5 mmol) in THF (5 mL) at –78 °C was added ^{n}BuLi (0.4 mL of a 2.5M solution, 1.0 mmol) dropwise over 10 sec. The solution continued to stir at –78 °C for 20 min before addition of a solution of dimethyl-3-allyl-3-[(E)-2-pentenyl]pentanedioate (106 mg, 0.5 mmol) in THF (2 mL). The mixture was then warmed to room temperature and stirred for 2 h before addition of HCl (aq) (8.0 mL of a 2M solution) and stirring for a further 12 h. The mixture was extracted with Et_2O (100 mL) and washed with $NaHCO_3$ (aq) (100 mL) and brine (100 mL) before drying over $MgSO_4$ and removal of solvents *in vacuo*. Purification by Kugelrohr distillation (85 °C, 15 mm Hg) gave the title compound as a colourless oil (200 mg, 93 %).

^{1}H NMR (400MHz, $CDCl_3$): δ = 3.26 (2 × 3H, s, H1), 3.11 (4H, m, H2), 1.66 (2 × 1H, dd, J = 13.3, 7.5 Hz), 1.48-1.38 (2H, m), 1.38-1.10 (3H, m), 0.94-0.87 (3H, m), 0.86 (3H, d, J = 6.3 Hz, H11), 0.81 (3H, t, J = 7.1 Hz, H10).

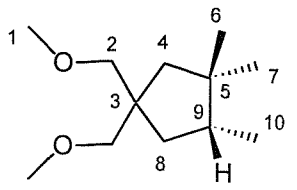
^{13}C NMR (100MHz, $CDCl_3$): δ = 78.45 (t, C2), 78.30 (t, C2), 59.63 (q, C1), 59.53 (q, C1), 46.86 (d, C5), 45.59 (s, C3), 42.31 (t, C7), 40.27 (d, C6), 39.92 (t, C4), 36.63 (t, C8), 21.86 (t, C9), 18.55 (q, C11), 14.89 (q, C10).

IR(thin film): ν = 1458.0 (m, br), 1198.3 (m), 1110.1 (s) cm^{-1}.

LRMS (CI): m/z = 215 (M + H$^+$, 100%), 182 ([M-OCH_3] + H$^+$, 44%), 151 ([M-$(OCH_3)_2$] + H$^+$, 97%).

HRMS (EI): $C_{13}H_{26}O_2$ requires m/z = 214.1933. Found = 214.1932.

4,4-Bis-methoxymethyl-1,1,2-trimethyl-cyclopentane (423).



To a stirred solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C was added ^{n}BuLi (0.8 mL of a 2.5M solution, 2.0 mmol) dropwise over 30 sec. The solution continued to stir at –78 °C for 20 min before addition of a solution of 4,4-bis-methoxymethyl-2-methyl-hepta-1,6-diene (198 mg, 1.0 mmol) in THF (2 mL). The mixture was then warmed to room temperature and stirred for 2 h before addition of MeOH (5.0 mL) and $NaHCO_3$ (aq) (6.0 mL) and stirring for a further 2 h. The mixture was extracted with Et_2O (150 mL) and washed with $NaHCO_3$ (aq) (150 mL) and brine (150 mL) before drying over $MgSO_4$ and removal of solvents *in vacuo*. Purification by Kugelrohr distillation (110 °C, 5mm Hg) gave a colourless oil (140 mg, 70 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.26 (6H, s(br), H1), 3.17-3.05 (4H, m, H2), 1.56 (2H, m),1.34 (1H, d, J = 13.8 Hz, H4), 1.22 (1H, d, J = 13.8 Hz, H4), 1.15 (1H, m), 0.87 (3H, s, H6/H7), 0.74 (3H, d, J = 6.5 Hz, H10), 0.71 (3H, s, H6/H7).

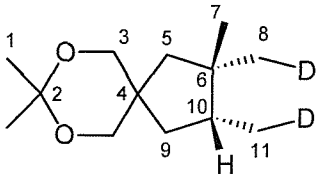
^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 77.22 (t), 76.23 (t), 58.17 (2 × q, C1), 47.24 (t, C4), 43.53 (s), 41.89 (d, C9), 39.60 (s), 39.15 (t, C8), 27.79 (q, C6), 21.79 (q, C7), 12.27 (q, C10).

IR(thin film): ν = 2874.7 (m, br), 1454.1 (m), 1110.9 (s) cm^{-1}.

LRMS (CI): m/z = 201 ($M+H^+$, 100%), 168 (52%), 136 (94%), 123 (100%).

HRMS (EI): $C_{11}H_{20}O$ ($M-OCH_3^+$) requires m/z = 168.1514. Found 168.1523.

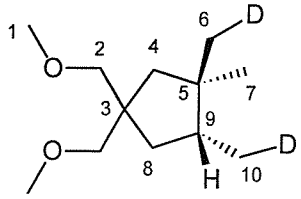
2,2,3(bis-deutero),8,8-Pentamethyl-7,9-dioxa-spiro[4.5]decane (425).



To a stirred solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C was added ^{n}BuLi (0.8 mL of a 2.5M solution, 2.0 mmol) dropwise over 30 sec. The solution continued to stir at –78 °C for 20 min before addition of a solution of 5-allyl-2,2-dimethyl-5-(2-methylallyl)-[1,3]-dioxane (210 mg, 1.0 mmol) in THF (2 mL). The mixture was then warmed to room temperature and stirred for 2 h before addition of MeOD (1.0 mL) followed by D_2O (2.0 mL) and stirring for a further 16 h. The mixture was extracted with Et_2O (150 mL) and washed with $NaHCO_3$ (aq) (150 mL) and brine (150 mL) before drying over $MgSO_4$ and removal of solvents *in vacuo*. Purification by Kugelrohr distillation (120°C, 10 mm Hg) gave the title compound as a colourless oil (201.6 mg, 94 %).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 97.83 (s, C2), 71.46 (t, C3), 70.70 (t, C3), 49.43 (t, C5), 43.14 (d, C10), 41.45 (t, C9), 40.74 (s, C4/C6), 39.28 (s, C4/C6), 28.94 (q, C7), 25.54 (q, C1), 23.00 (CH_2-D, C8), 13.74 (CH_2-D, C11).

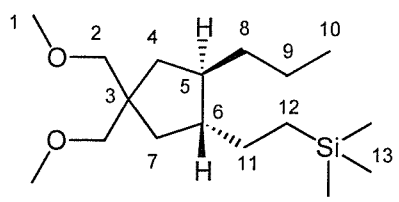
4,4-Bis-methoxymethyl-1,1,2(bis-deutero)-trimethyl-cyclopentane (424).



To a stirred solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C was added ^{n}BuLi (0.8 mL of a 2.5M solution, 2.0 mmol) dropwise over 30 sec. The solution continued to stir at –78 °C for 20 min before addition of a solution of 4,4-bis-methoxymethyl-2-methyl-hepta-1,6-diene (198 mg, 1.0 mmol) in THF (2 mL). The mixture was then warmed to room temperature and stirred for 2 h before addition of DCl (5.0 mL of a 20% w/v solution in D_2O) and stirring for a further 12 h. The mixture was extracted with Et_2O (200 mL) and washed with HCl (2M) (150 mL) and dried over $MgSO_4$ before removal of solvents *in vacuo*. Purification by Kugelrohr distillation (110°C, 5mm Hg) gave the title compound as a colourless oil (176 mg, 87 %).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 78.41 (t, C2), 77.92 (t, C2), 59.03 (2 × q, C1), 48.40 (t, C4), 44.74 (s), 42.98 (d, C9), 40.72 (s), 40.31 (t, C8), 28.67 (CH_2-D, C6), 22.96 (q, C7), 13.17 (CH_2-D, C10).

{2-[4,4-di(methoxymethyl)-2-propylcyclopentyl]ethyl}trimethylsilane (439).

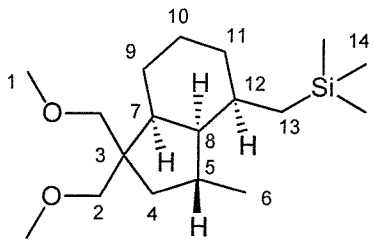


To a stirred solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C was added ^{n}BuLi (0.8 mL of a 2.5M solution, 2.0 mmol) dropwise over 20 sec. The solution was stirred at –78 °C for 20 min before dropwise addition of a solution of (E)-4,4-bis(methoxymethyl)-1,6-nonadiene (212 mg, 1.0 mmol) in THF (2 mL). The mixture was warmed to room temperature and then stirred for 2 h before recooling to –78 °C. To a separately stirred solution of chloromethyltrimethylsilane (0.14 mL, 1.0 mmol) in THF (9 mL) at –78 °C was added ^{sec}BuLi (0.79 mL of a 1.4M solution, 1.1 mmol) followed by TMEDA (0.17 mL, 1.1 mmol). The mixture was stirred for 30 min, warming to -65°C during this time, before cooling to –78 °C and slow addition of the zirconacycle solution (6.2 mL, 0.8 mmol). The mixture continued to stir for 1h, warming to –50 °C before addition of MeOH (5 mL) and

$NaHCO_3$ (aq) (6 mL). The solution was then stirred for 12 h, warming to room temperature before pouring onto H_2O (150 ML) and extraction with Et_2O (200 mL), washing with $NaHCO_3$ (aq) (150 mL) and brine (150 mL), drying over $MgSO_4$ and concentration *in vacuo*. Purification by column chromatography (SiO_2, eluted with 10:1 petrol;EtOAc) yielded the title compound as a colourless oil (200 mg, 83 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.38 (4H, s(br), H2), 3.22 (6H, m, H1), 2.07 (1H, m), 1.80 (2H, dt, J = 12.8, 6.3 Hz, H8), 1.59 (2H, m, H11), 1.39 (2H, m, H5+H6), 1.24 (1H, m), 1.01 (4H, m), 0.91 (3H, t, J = 7.3 Hz, H10), 0.57 (1H, ddd, J = 12.8, 12.5, 4.3 Hz, H12), 0.41 (1H, ddd, J = 12.3, 12.6, 5.3 Hz, H12), 0.00 (9H, s, H13).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 79.62 (t, C2), 79.49 (t, C2), 60.94 (q, C1), 60.82 (q, C1), 49.80 (d, C5), 46.15 (d, C6), 46.06 (s, C3), 40.75 (t), 40.09 (C8), 37.22 (t), 29.46 (t, C11), 23.16 (t), 16.49 (t, C12), 16.20 (q, C10), 0.00 (q, C13).
IR(thin film): ν = 2823.9 (s), 2359.7 (w), 1247.6 (s), 837.0 (s) cm^{-1}.
LRMS (CI): m/z = 301 (M + H$^+$, 72%), 268 (8%), 223 (21%).
HRMS (EI): $C_{16}H_{32}OSi$ (M – OCH_3^+) requires m/z = 268.2222. Found 268.2219.

{[1,1-di(methoxymethyl)-3-methylperhydro-4-indenyl]methyl}(trimethyl)silane (437).



To a stirred solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C was added ^{n}BuLi (0.8 mL of a 2.5M solution, 2.0 mmol) dropwise over 20 sec. The solution was stirred at –78 °C for 20 min before dropwise addition of a solution of 3-(1,1-di(methoxymethyl)-3-butenyl)-1-cyclohexene (224 mg, 1.0 mmol) in THF (2 mL). The mixture was warmed to room temperature and then stirred for 2 h before recooling to –78 °C. To a separately stirred solution of chloromethyltrimethylsilane (0.14 mL, 1.0 mmol) in THF (9 mL) at –78 °C was added ^{sec}BuLi (0.79 mL of a 1.4M solution, 1.1 mmol) followed by TMEDA (0.17 mL, 1.1 mmol). The mixture was stirred for 30 min, warming to –65 °C during this time, before cooling to –78 °C and slow addition of the zirconacycle solution (6.2 mL, 0.8 mmol). The mixture was then stirred for 1 h, warming to –50 °C and was then warmed to room temperature and MeOH (5 mL) and $NaHCO_3$ (aq) (6 mL) added before stirring for a further 2 h. The mixture was extracted with Et_2O (200 mL) and washed with $NaHCO_3$ (150 mL) and brine (150 mL) before drying over $MgSO_4$ and concentration *in vacuo*.

Purification by column chromatography (SiO_2, eluted with 10:1 petrol:EtOAc) yielded the title compound as a colourless oil (160 mg, 64 %)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.36 (4H, m, H2), 3.27 (2 ×3H, s, H1), 2.09 (1H, m, H5), 1.73 (5H, m). 1.47 (2×1H, d(br), J = 12.8 Hz, H13), 1.26-1.12 (2H, m), 1.09 (3H, d, J = 6.5 Hz, H6), 1.04 (2H, dt, J = 12.6, 3.5 Hz), 0.66-0.48 (2H, m, H13), 0.00 (9H, s(fs), H14).

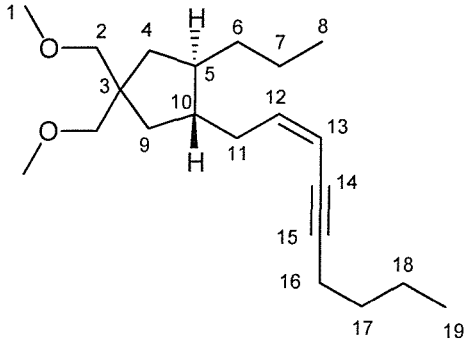
^{13}C NMR (100 MHz, $CDCl_3$): δ = 76.24 (t, C2), 74.77 (t, C2), 59.77 (q, C1), 59.57 (q, C1), 52.80 (d), 49.03 (s, C3), 46.37 (d), 40.64 (t), 36.12 (d), 30.34 (d), 30.22 (t), 26.90 (t), 25.19 (q, C6), 24.51 (t), 24.42 (t), 0.00 (q, C14).

IR (thin film): ν = 1247.6 (m), 1106.5 (s), 1115.6 (s), 836.0 (s) cm^{-1}.

LRMS (CI): 313 (M + H^+, 60%), 281 ([M – OCH_3] + H^+, 10%), 235 (22%).

HRMS (EI): $C_{17}H_{32}OSi$ (M – OCH_3^+) requires m/z = 280.2222. Found 280.2222.

(Z)-1-[4,4-di(methoxymethyl)-2-propylcyclopentyl]-2-nonen-4-yne (432).



To a stirred solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C was added ^{n}BuLi (0.8 mL of a 2.5M solution, 2.0 mmol) dropwise over 20 sec. The solution was stirred at –78 °C for 20 min before dropwise addition of a solution of (E)-4,4-bis(methoxymethyl)-1,6-nonadiene (212 mg, 1.0 mmol) in THF (2 mL). The mixture was warmed to room temperature and then stirred for 2 h before recooling to –78 °C and addition of (1E)-1-chloro-1-octen-3-yne (0.1 mL, 1.0 mmol) followed by LiTMP (1.0 mmol freshly prepared from 2,2,6,6-tetramethypiperidine (0.17 mL, 1.0 mmol) and ^{n}BuLi (0.4 mL of a 2.5M solution, 1.0 mmol) in THF (2 mL) at 0 °C for 30 min). The mixture continued to stir for 40 min, warming to –65 °C before addition of MeOH (5 mL) and $NaHCO_3$ (aq) (6 mL) and stirring for 12 h, warming to room temperature during this period. The mixture was poured onto H_2O (150 mL) and extracted with Et_2O (200 mL) before washing with $NaHCO_3$ (aq) (150 mL) and brine (150 mL), drying over $MgSO_4$ and concentration *in vacuo*. Purification by column chromatography (SiO_2, eluted with 10:1 petrol:Et_2O) yielded the title compound as a pale yellow oil (259 mg, 81 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75 (1H, dt, J = 10.6, 7.5 Hz, H12), 5.36 (1H, d(br), J = 10.6 Hz, H13), 3.26 (2 ×3H, s, H1), 3.11 (4H, m, H2), 2.48 (1H, m), 2.27 (2H, dt, J = 1.7, 6.8 Hz, H16), 2.04-1.96 (3H, m), 1.74-1.62 (4H, m), 1.48-1.24 (5H, m), 1.22-1.13 (3H, m), 0.88-0.78 (6H, m).

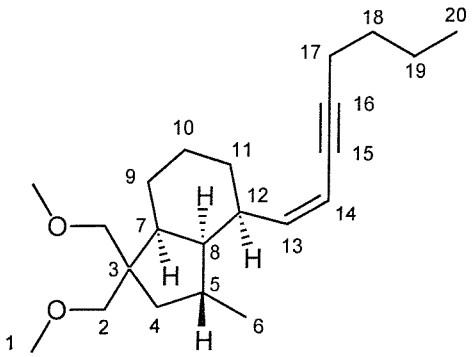
^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 140.07 (d, C12), 108.82 (d, C13), 93.48 (s, C15), 77.04 (s, C14), 76.77 (t, C2), 58.21 (q, C1), 44.26 (s, C3), 43.91 (d), 43.49 (d, C5/C10), 38.09 (t), 37.90 (t), 35.38 (t), 32.96 (t), 29.97 (t), 20.97 (t), 20.36 (t,), 18.21 (t, C16/C17/C18), 13.46 (q), 12.59 (q).

IR(thin film): ν = 2916.9 (s, br), 2060.8 (w), 1450.6 (m), 1105.4 (s), 750.8 (m) cm^{-1}.

LRMS (CI): m/z = 321 ($M + H^+$, 23%), 288 ([$M - OCH_3$] + H^+, 35%), 257 (22%).

HRMS (EI): $C_{20}H_{32}O$ ($M - OCH_3$) requires m/z = 288.2448. Found 288.2453.

1,1-di(methoxymethyl)-3-methyl-4-[(Z)-1-octen-3-ynyl]perhydroindene (431).



To a stirred solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C was added ^{n}BuLi (0.8 mL of a 2.5M solution, 2.0 mmol) dropwise over 20 sec. The solution was stirred at –78 °C for 20 min before dropwise addition of a solution of 3 (1,1-di(methoxymethyl)-3-butenyl)-1-cyclohexene (224 mg, 1.0 mmol) in THF (2 mL). The mixture was warmed to room temperature and then stirred for 2h before recooling to –78 °C and addition of (1E)-1-chloro-1-octen-3-yne (0.1 mL, 1.0 mmol) followed by LiTMP (1.0 mmol freshly prepared from 2,2,6,6-tetramethypiperidine (0.17 mL, 1.0 mmol) and ^{n}BuLi (0.4 mL of a 2.5M solution, 1.0 mmol) in THF (2 mL) at 0 °C for 30 min). The mixture continued to stir for 40 min, warming to –65 °C before addition of MeOH (5 mL) and $NaHCO_3$ (aq) (6 mL) and stirring for 12 h, warming to room temperature during this period. The mixture was poured onto H_2O (150 mL) and extracted with Et_2O (200 mL) before washing with $NaHCO_3$ (aq) (150 mL) and brine (150 mL), drying over $MgSO_4$ and concentration *in vacuo*. Purification by column chromatography (SiO_2, eluted with 10:1 petrol:EtOAc) yielded the title compound as a colourless oil (206 mg, 62 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.70 (1H, t, J = 10.5 Hz, H13), 5.28 (1H, d(br), J = 10.5 Hz, H14), 3.23 (10H, m, H1+H2), 2.88 (1H, tt, J = 10.8, 4.3 Hz, H12), 2.28 (2H, dt, J = 1.8, 7.0 Hz, H17), 2.07 (1H, m), 1.95 (2H, m), 1.66 (3H, m), 1.42 (4H, m), 1.10 (4H, m),

0.92 (3H, d, J = 6.5 Hz, H6), 0.87 (3H, t, J = 7.1 Hz, H20).

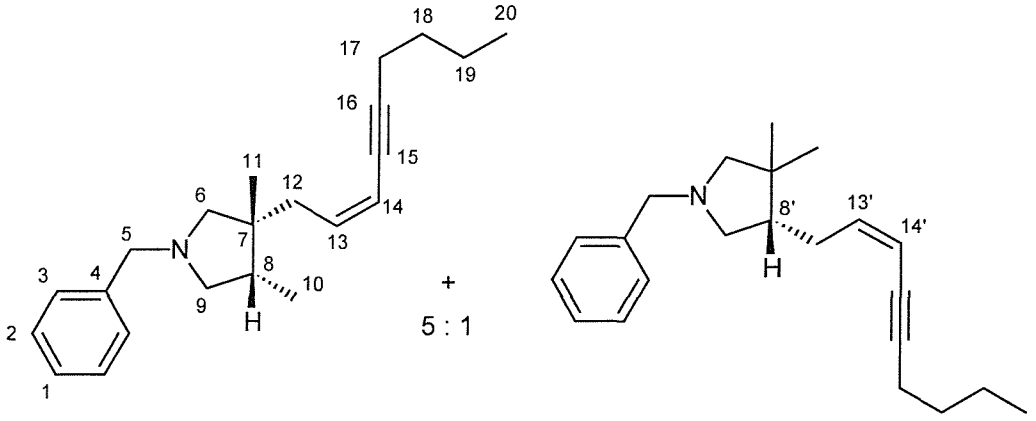
^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 146.21 (d, C13), 106.54 (d, C14), 93.43 (s, C16), 75.84 (s, C15), 73.19 (t, C2), 72.96 (t, C2), 58.04 (q, C1), 57.99 (q, C1), 47.92 (d), 47.75 (s, C3), 44.29 (d), 38.96 (d), 38.57 (t), 29.91 (t), 28.93 (d), 26.27 (t), 24.97 (t), 22.79 (q, C6), 22.59 (t), 20.88 (t), 18.21 (t, C17), 12.60 (q, C20).

IR(thin film): ν = 3016.7 (w), 2806.2 (m), 2359.8 (w, br), 2206.4 (w, br), 750.8 (m) cm^{-1}.

LRMS (CI): m/z = 333 ($M + H^+$, 35%), 255 (17%), 192 (64%), 147 (100%).

HRMS (EI): $C_{22}H_{36}O_2$ requires m/z = 332.2715. Found 332.2723.

1-Benzyl-3,4-dimethyl-3-[(Z)-non-2-en-4-ynyl]-pyrrolidine + 1-benzyl-3,3-dimethyl-4-[(Z)-non-2-en-4-ynyl]-pyrrolidine (433 + 434).



To a stirred solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C was added ^nBuLi (0.8 mL of a 2.5M solution, 2.0 mmol) dropwise over 20 sec. The solution was stirred at –78 °C for 20 min before addition of a solution of *N*-allyl-*N*-benzyl-*N*-(2-methallyl)amine (202 mg, 1.0 mmol) in THF (2 mL). The mixture was then warmed to room temperature and stirred for 2 h before recooling to –78 °C and addition of (1E)-1-chloro-1-octen-3-yne (0.1 mL, 1.0 mmol) followed by LiTMP (1.0 mmol formed from 2,2,6,6-tetramethylpiperidine (0.17 mL, 1.0 mmol) and ^nBuLi (0.4 mL of a 2.5M solution, 1.0 mmol) in THF (2.0 mL) at 0 °C). The mixture was warmed to –65 °C over 40 min before addition of MeOH (5.0 mL) and $NaHCO_3$ (aq) (6.0 mL) and stirring for a further 12 h. The mixture warmed to room temperature during this time and was then poured onto H_2O (150 mL), extracted with Et_2O (200 mL) and washed with $NaHCO_3$ (aq) (150 mL) and brine (150 mL) before drying over $MgSO_4$ and removal of solvents *in vacuo*.

Purification by column chromatography (SiO_2, eluted with 10:1 petrol:Et_3N) yielded the title compound as a pale yellow oil (255 mg, 82 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27-7.17 (5H, m), 5.76 (1H, dt, J = 10.8, 7.5 Hz, H13), 5.69 (0.2H, dt, J = 10.5, 7.3 Hz, H13'), 5.45 (1H, d, J = 10.8 Hz, H14), 5.36 (0.2H, d, J = 10.5 Hz, H14'), 3.59 (1H, d, J = 13.0 Hz), 3.55 (1H, d, J = 13.8 Hz), 3.51 (1H, d, J = 13.3 Hz), 2.81 (0.2H, m), 2.42-2.36 (3H, m), 2.33-2.23 (4H, m), 2.20-2.11 (2H, m), 1.89 (1H, sextet, J = 7.3 Hz, H8), 1.51-1.34 (5H, m), 0.96 (3H, s, H11), 0.86 (3H, d, J = 6.8 Hz, H10), 0.84 (3H, m).

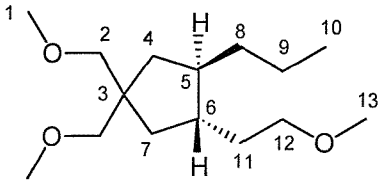
^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 146.61 (s, C4), 140.09 (d, C13'/C14', minor isomer), 139.87 (d, C13/C14), 128.77 (d), 128.30 (d), 126.84 (d), 111.54 (d, C13'/C14', minor isomer), 111.36 (d, C13/C14), 94.83 (s), 77.91 (s), 65.73 (t), 61.65 (t), 61.02 (t), 59.58 (t, minor isomer), 49.27 (d, C8', minor isomer), 43.74 (d, C8), 43.14 (s, C7), 36.34 (t, minor isomer), 36.19 (t), 31.16 (t), 29.72 (t, minor isomer), 25.88 (q, C11), 22.14 (t), 19.42 (t), 13.79 (q), 13.29 (q).

IR(thin film): ν = 2783.7 (m), 2209.9 (w), 1705.4 (m), 1119.7 (s) cm^{-1}.

LRMS (CI): m/z = 310 ($M + H^+$, 44%), 252 (22%), 186 (44%), 91 (100%).

HRMS (EI): $C_{22}H_{32}N$ requires m/z = 310.2529. Found = 310.2533.

3-(2-Methoxyethyl)-1,1-bis-methoxymethyl-4-propyl-cyclopentane (445).

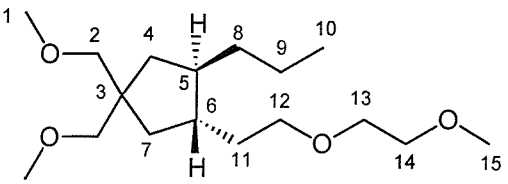


To a stirred solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) THF (5 mL) at –78 °C was added ^{n}BuLi (0.8 mL of a 2.5M solution, 2.0 mmol) dropwise over 20 sec. The solution was stirred at –78 °C for 20 min before addition of a solution of dimethyl-3-allyl-3-[(E)-2-pentenyl]pentanedioate (212 mg, 1.0 mmol) in 2 mL THF. The mixture was then warmed to room temperature and stirred for 2 h before cooling to –100 °C and addition of MOM-Cl (0.075 mL, 1.0 mmol) followed by LiTMP (1.0 mmol formed from 2,2,6,6-tetramethylpiperidine (0.17 mL, 1.0 mmol) and ^{n}BuLi (0.4 mL of a 2.5M solution, 1.0 mmol) in THF (2.0 mL) at 0 °C). The solution warmed to –65 °C over 1.5 h before addition of MeOH (5.0 mL) and $NaHCO_3$ (aq) (6.0 mL) and stirring for a further 12 h. The mixture warmed to room temperature during this time and was then extracted with Et_2O (200 mL) and washed with $NaHCO_3$ (aq) (150 mL) and brine (150 mL) before drying over $MgSO_4$ and removal of solvents *in vacuo*. Purification by

column chromatography (SiO_2, eluted with 10:1 petrol:EtOAc) yielded a mixture of geometrically isomeric C8-C9 alkenes resulting from β-elimination.To the alkene mixture (73 mg, 0.28 mmol) in MeOH (3 mL) under H_2 gas at room temperature was added Pd/C (excess). The solution was stirred at room temperature for 20 h before filtration through celite. Removal of solvents *in vacuo* gave the title compund as a colourless oil (60 mg, 23 % over both steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.27 (2H, m), 3.265 (3H, s), 3.263 (3H, s), 3.24 (3H, s), 3.12 (4H, m), 1.84 (1H, dtd, J = 12.8, 4.8, 3.0 Hz), 1.68 (2 × 1H, dd, J = 7.0, 13.0 Hz), 1.57 (1H, m), 1.45 (1H, m), 1.18 (4H, m), 0.93 (3H, m), 0.80 (3H, t, J = 7.3 Hz).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 76.88 (t, C2), 71.05 (t, C12), 64.83 (s, C3), 58.22 (2 × q, C1), 57.51 (q, C13), 44.10 (d), 40.99 (d), 38.25 (t), 35.33 (t), 32.99 (t), 25.62 (t), 20.36 (t), 13.43 (q).
IR(thin film): ν = 2871.5 (s, br), 1457.4 (m, br), 1110.1 (s, br), 804.1 (s, br) cm^{-1}.
LRMS (CI): m/z = 259 ($M + H^+$, 100%), 210 (23%), 193 (52%).
HRMS (CI): $C_{15}H_{31}O_3$ requires m/z = 259.2273. Found = 259.2269.

3-[2-(2-Methoxyethoxy)-ethyl]-1,1-bis-methoxymethyl-4-propyl-cyclopentane (446).



To a stirred solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C was added ^{n}BuLi (0.8 mL of a 2.5M solution, 2.0 mmol) dropwise over 20 sec. The solution was stirred at –78 °C for 20 min before addition of a solution of dimethyl-3-allyl-3-[(E)-2-pentenyl]pentanedioate (212 mg, 1.0 mmol) in THF (2mL). The mixture was then warmed to room temperature and stirred for 2 h before cooling to –100 °C and addition of MEM-Cl (0.11 mL, 1.0 mmol) followed by LiTMP (1.0 mmol formed from 2,2,6,6-tetramethylpiperidine (0.17 mL, 1.0 mmol) and ^{n}BuLi (0.4 mL of a 2.5M solution, 1.0 mmol) in THF (2.0 mL) at 0 °C). The solution warmed to –65 °C over 1.5 h before addition of MeOH (5.0 mL) and $NaHCO_3$ (aq) (6.0 mL) and stirring for a further 12 h. The mixture warmed to room temperature during this time and was then extracted with Et_2O (200 mL) and washed with $NaHCO_3$ (aq) (150 mL) and brine (150 mL) before drying over $MgSO_4$ and removal of solvents *in vacuo*. Purification by column

chromatography (SiO_2, eluted with 5:1 petrol:EtOAc) yielded a mixture of geometrically isomeric C8-C9 alkenes resulting from β-elimination. To the alkene mixture (175 mg, 0.58 mmol) in MeOH (5 mL) under H_2 gas at room temperature was added Pd/C (excess). The solution was stirred at room temperature for 20 h before filtration through celite. Removal of solvents *in vacuo* gave the title compund as a colourless oil (172 mg, 57 % over both steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.47 (3H, m), 3.44-3.33 (3H, m), 3.31 (3H, s, H15), 3.26 (2 × 3H, s, H1), 3.16-3.08 (4H, m), 1.87 (1H, dddd, J = 12.3, 9.5, 7.0, 3.0 Hz), 1.67 (2 × 1H, ddd, J = 13.1, 6.5, 5.3 Hz), 1.45 (1H, m), 1.38-1.20 (3H, m), 1.14 (1H, m), 0.93 (3H, m), 0.80 (3H, t, J = 7.0 Hz, H10).

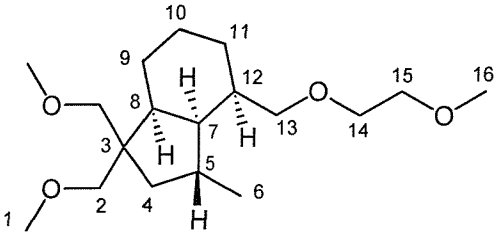
^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 76.88 (t), 70.99 (t), 69.73 (t), 68.99 (t), 58.22 (q, C1), 58.05 (q, C15), 44.48 (s, C3), 44.09 (d, C5/C6), 40.98 (d, C5/C6), 38.23 (t), 38.09 (t), 35.30 (t), 32.97 (t), 20.33 (t), 13.42 (q, C10).

IR(thin film): ν = 2957.7 (s), 2871.3 (s, br), 1110.1 (s, br), 1027.1 (m, br) cm^{-1}.

LRMS (CI): m/z = 303 ($M + H^+$, 34%), 239 (23%), 163 (100%).

HRMS (EI): $C_{17}H_{34}O_4$ requires m/z = 302.2457. Found = 302.2459.

4-[(2-methoxyethoxy)methyl]-1,1-di(methoxymethyl)-3-methylperhydroindene (447).



To a stirred solution of Cp_2ZrCl_2 (292 mg, 1.0 mmol) in THF (5 mL) at –78 °C was added ^{n}BuLi (0.8 mL of a 2.5M solution, 2.0 mmol) dropwise over 20 sec. The solution was stirred at –78 °C for 20 min before dropwise addition of a solution of 3-(1,1-di(methoxymethyl)-3-butenyl)-1-cyclohexene (224 mg, 1.0 mmol) in THF (2 mL). The mixture was warmed to room temperature and then stirred for 2 h before cooling to –100 °C and addition of MEM-chloride (0.11 mL, 1.0 mmol) followed by LiTMP (1.0 mmol freshly prepared from 2,2,6,6-tetramethypiperidine (0.17 mL, 1.0 mmol) and ^{n}BuLi (0.4 mL of a 2.5M solution, 1.0 mmol) in THF (2 mL) at 0 °C for 30 min). The mixture continued to stir for 40 min, warming to –65 °C before addition of MeOH (5 mL) and $NaHCO_3$ (aq) (6 mL) and stirring for 12 h, warming to room temperature during this period. The mixture was poured onto H_2O (150 mL) and extracted with Et_2O (200 mL)

before washing with $NaHCO_3$ (aq) (150 mL) and brine (150 mL), drying over $MgSO_4$ and concentration *in vacuo*. Purification by column chromatography (SiO_2, eluted with 5:1 petrol:EtOAc) yielded the title compound as a colourless oil (154 mg, 49 %).

^1H NMR (400 MHz, $CDCl_3$): δ = 3.47 (3H, s(br), H16), 3.32-3.15 (16H, m, (H1+H2+H13+H14+H15), 2.04-1.87 (3H, m), 1.69-1.62 (3H, m), 1.52 (1H, d(br), J = 12.8 Hz), 1.44 (1H, m), 1.16-0.95 (4H, m), 0.91 (2H, d, J = 6.3 Hz), 0.85 (1H, m).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 76.18 (t, C2), 76.08 (t, C2), 74.43 (t), 72.36(t), 70.44(t, C13/C14/C15), 59.60 (q, C16) 59.45 (q, C1), 59.42 (q,C1), 49.18 (s, C3), 47.18 (d, C7/C8), 45.88 (d, C7/C8), 40.27 (t, C4), 39.64 (d), 29.92 (d), 25.95 (t), 25.28(t), 24.72 (t, C9/C10/C11), 23.63 (q, C6).

IR(thin film): ν = 2923.4 (s, br), 2359.5 (w), 100.7 (s, br), 963.6 (m) cm^{-1}.

LRMS (CI): m/z = 315 ($M + H^+$, 100%), 251 (9%), 207 (47%), 175 (100%).

HRMS (EI): $C_{18}H_{35}O_4$ requires m/z = 315.2535. Found 315.2518.

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