UNIVERSITY OF SOUTHAMPTON

FACULTY OF SCIENCE

DEPARTMENT OF CHEMISTRY

ZIRCONOCENE MEDIATED CO-CYCLISATION REACTIONS

by David Rodney Owen BSc

A thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

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ABSTRACT

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The novel work in this thesis covers three quite different areas of organozirconium chemistry.

The first is the synthesis of oxacycles by zirconocene mediated co-cyclisation, of which the literature contains few examples. 1,7-Enyne substrates based on alkoxyalkynes cyclise in good yield to provide tetrahydropyrans. The presence of an exocyclic, tethered alcohol functionality in the cyclised product allows a second, acid catalysed cyclisation to occur, providing a novel route to spiroketals.

In the second area, the feature peculiar to the zirconacycles prepared is a leaving group β to zirconium. In all cases, elimination of Zr-leaving group occurs to provide an alkene. Where the cyclisation substrates are 1,6-dienes or enynes prepared from dihydrofuran, cyclisation occurs despite the hindered nature of the enol ether double bond. Where the substrates are prepared from ethyl vinyl ether, the enol ether double bond is disubstituted, and a wider variety of 1,6-dienes and -enynes can be cyclised in yields of up to 89%. Chiral centres in the substrate often induce excellent diastereocontrol of the newly generated methyl group. The important feature of the cyclisation products is an exocyclic methylene group. As these methylene cyclopentanes are difficult to prepare from terminal alkyne substrates, our methodology provides an excellent route to these compounds. The cyclisation products are also monoalkyl zirconocenes, which we wished to functionalise further using carbenoid insertion chemistry. We have shown that ethoxy groups on zirconium inhibit carbenoid insertion, whereas chloride groups allow vinyl carbenoid insertions to occur in yields of up to 75%.

The third area of research was an attempted total synthesis of the natural product mucosin, whose structure contains a bicyclo [4.3.0] nonane unit with four contiguous stereocentres. We prepared a co-cyclisation substrate which precedent suggested would provide only the desired diastereomer of the bicycle, and a handle for introduction of the remainder of the natural product skeleton. Unfortunately, the co-cyclisation provided a mixture of products. Investigation was made into dihydro and despropyl analogues, which we hoped would provide single products on co-cyclisation. Although the synthesis was not completed, we have laid down groundwork which we hope will lead to a successful completion at a later stage.

Contents

Acknowledgements

Thanks first and foremost to Prof. Richard Whitby for his supervision, for the endless stream of ideas and for being round when needed. Thanks next to the people with the machines: to Mrs Joan Street for a top class NMR service which most take for granted; to Dr John Langley and Ms Julie Herniman for an excellent open access LRMS facility and for putting up with my apparently endless supply of HRMS samples; to Prof. Mike Hursthouse and Dr Mark Light for sorting out my x-ray crystallographic needs and to Jim and Dave for help with IR.

Thanks to the members of the Whitby group past and present for making the worst parts bearable and the best bits even enjoyable. For advice, ideas and useful discussions I'd particularly like to thank Cliff Veighey, Ian Baldwin, Mark Tuckett and Stifun Mittoo. Thanks to those mentioned and also Don, Sally, Jon and Matt for proof reading.

For providing a distraction, priceless escapism and keeping me sane, thanks to the members of SMCC and SUCC. In true tradition, thanks likewise to all of those who have partaken in "The Beautiful Game" with me.

Thanks finally to Mum and Dad for their love and support, without which none of this could have happened.

List of Abbreviations

Techniques

APCI	Atmospheric Pressure Chemical Ionisation
CI	Chemical Ionisation
^{13}C NMR	Carbon Magnetic Resonance
COSY	Correlation Spectroscopy
DEPT	Distortionless Enhancement by Polarisation Transfer
EI	Electron Impact
ES	Electrospray
GC	Gas Chromatography
GOESY	Gradient Overhauser Enhancement Spectroscopy
^{1}H NMR	Proton Magnetic Resonance
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectroscopy
IR	Infra Red
LRMS	Low Resolution Mass Spectroscopy
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
TLC	Thin Layer Chromatography

Reagents and Solvents

Ac	Acetyl
AIBN	2,2'-Azobisisobutyronitrile
BiPh	Biphenyl
Bn	Benzyl
Cp	Cyclopentadienyl
Cp*	Pentamethylcyclopentadienyl
CSA	Camphorsulphonic acid
DCM	Dichloromethane
DIBAL-H	Diisobutylaluminium hydride

DMAD	Dimethylacetylenedicarboxylate
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMPU	Di-*N*-methylpropylene urea
DMSO	Dimethyl sulphoxide
EVL	Ethoxy vinyl lithium
HMPA	Hexamethylphosphoramide
IPA	Isopropyl alcohol
LDA	Lithium diisopropylamide
LiTMP	Lithium 2,2,6,6-tetramethylpiperidide
Ms	Methanesulphonyl (mesyl)
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
PPTS	Pyridine *para*-toluenesulphonate
TBAF	Tetrabutyl ammonium fluoride
TBS or TBDMS	*tert*-Butyldimethylsilyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMP	Tetramethylpiperidine
TMS	Trimethylsilyl
Ts	*para*-Toluenesulphonyl (tosyl)

Miscellaneous

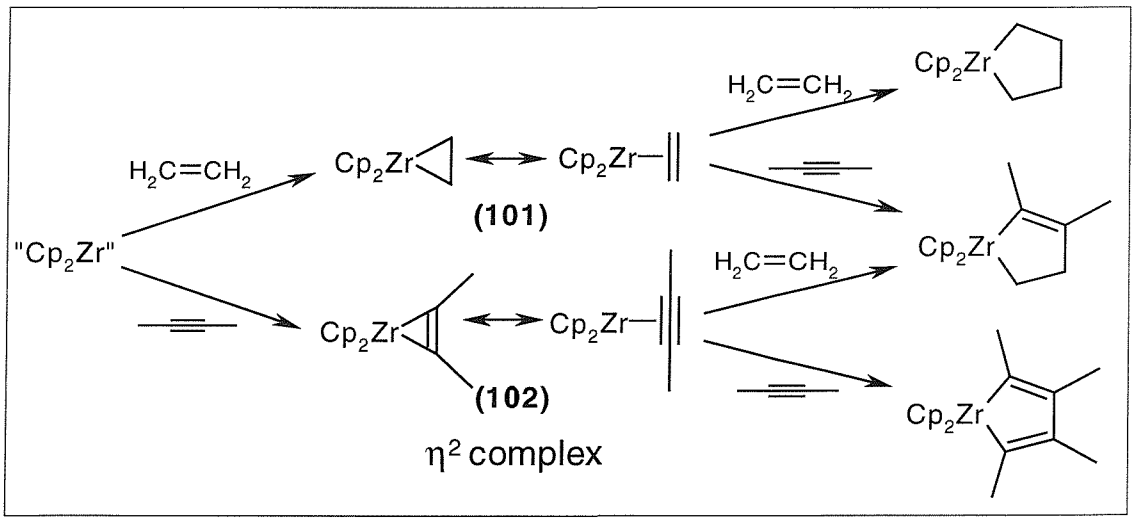
d	Days
h	Hours
lit.	Literature
min	Minutes
R* or S*	Denotes relative stereochemistry
RT	Room temperature

Chapter 1: Review of Zirconocene Mediated Synthetic Methods.

1.1: Introduction – Scope of Zirconocene Mediated Co-Cyclisation.

Investigations into the use of organozirconium species in organic chemistry began in 1970 with the preparation of $HZrCp_2Cl$,[1] and the observations by Wailes *et al.* of its addition to alkenes and alkynes.[2] A more systematic study was started in 1974 by Schwartz,[3,4] whose name has now been given to this reagent. Exclusive *cis* addition of H-Zr to alkynes allows the synthesis of stereodefined alkenes, in particular by further elaboration of the (*E*)-vinyl zirconocene formed, *via* nickel[5,6] and palladium[7] catalysed reactions. The analogous carboalumination of alkynes can be performed with a catalytic amount of zirconium.[8] The hydrozirconation of alkenes provides alkyl zirconium reagents which can be transmetallated to copper and elaborated further. This chemistry has recently been reviewed by Wipf.[9]

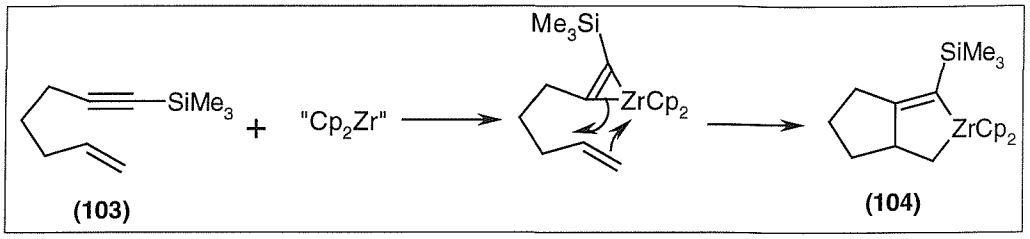
The chemistry mentioned above involves the +4 oxidation state of zirconium, for example in $HZrCp_2Cl$. The +2 oxidation state, represented by the theoretical 14 electron species "$ZrCp_2$" (zirconocene) should provide a reagent which is more reactive towards π-bonded systems, and is capable of forming η^2 complexes with alkenes and alkynes. This is by virtue of the one full and two empty orbitals of zirconocene in the +2 oxidation state. Such η^2 complexes can be represented as zirconacyclo-propanes **(101)** and –propenes **(102)** (Scheme 1.1). Ring expansion by insertion of alkenes or alkynes provides the zirconacycles shown.[10]



Scheme 1.1 – Zirconacycle formation *via* alkene and alkyne insertion.

Scheme 1.1 shows the stepwise addition of two unsaturated systems to zirconocene to provide a zirconacycle. If the two systems are tethered, a bicycle is produced. This forms the basis of the co-cyclisation reaction, whereby a carbocycle and a

zirconacycle are formed. The novel work presented in Chapters 2 to 4 of this thesis is concerned with the co-cyclisation reaction, to provide carbocycles, and also oxygen and nitrogen containing rings. The example shown in Scheme 1.2 represents one of the early examples by the Negishi group.[11]



Scheme 1.2 – Mechanism for zirconacycle formation.

The bicyclic zirconacyclopentene **(104)** was formed by treatment of the 1,6-enyne **(103)** with an equivalent of zirconocene. The analogous cyclisation of dienes and diynes provides zirconacyclo-pentanes and –pentadienes respectively. As zirconocene itself would be unstable, a synthetic equivalent must be generated *in situ*. The original method of achieving this was reduction of zirconocene dichloride (Cp_2ZrCl_2) with excess magnesium metal, activated by mercuric chloride.[11,12] Initially, this method of zirconocene preparation was satisfactory for performing co-cyclisations, but to make this chemistry less toxic and more reproducible, an alternative method was sought. The publication in 1986 of the treatment of zirconocene dichloride with two equivalents of an alkyl metal to form a zirconocene equivalent was a major breakthrough.[13] Most applicable was the displacement of both chlorides with two equivalents of n-butyllithium at –78°C to provide dibutyl zirconocene, which decomposes to butane and the active reagent, zirconocene (1-butene), on warming to around 10 to 20 °C. This active reagent is now known as Negishi's reagent.

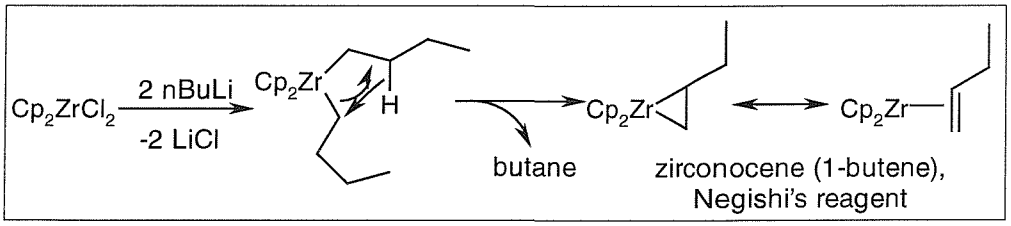


Figure 1.1 – Mechanism for formation of Negishi's reagent.

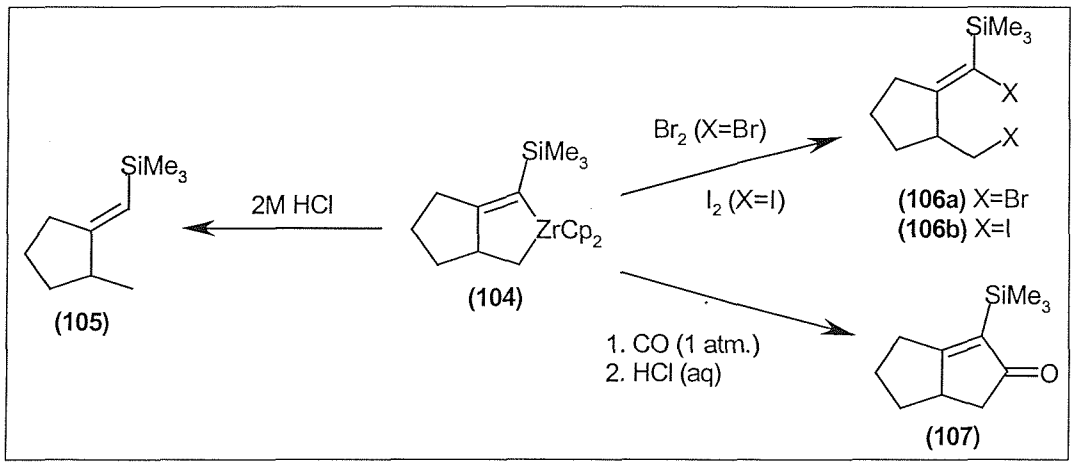
The reaction of zirconocene (1-butene) with an enyne involves the exchange of the labile butene ligand for the acetylene moiety, followed by ring expansion to a zirconacyclopentene such as **(104)**. Since this initial research, the scope of

zirconocene chemistry has expanded rapidly, with Negishi's reagent being shown to cyclise a wide variety of dienes, enynes and diynes. Ring sizes varying from 4 to 8 membered, and containing heteroatoms have been prepared by this method.

1.2: Carbocycle Formation by Zirconocene Mediated Methods.

The more covalent nature of the C-Zr bond, compared with carbon-metal bonds in other organometallics, such as organolithium or organomagnesium reagents has several consequences. Due to their higher stability towards water, zirconacycles can be isolated if handled under an inert atmosphere, and can be subjected to NMR analysis. More importantly, a large number of elaborations of the C-Zr bond are available to the chemist. These elaborations will be described in some detail in the second half of this review. The first half will concentrate on the range of compounds that can be produced by zirconium mediated bicyclisation chemistry, and the elaborations pertinent to this half will be described briefly first.

The simplest reaction of a zirconacycle is protonolysis of the C-Zr bonds. This can be achieved under acidic (dilute HCl) or basic ($MeOH/NaHCO_{3\,(aq)}$) conditions. In an analogous manner, bromination[14] or iodination[11] of the C-Zr bonds in **(104)**, for example, provides **(106a)** and **(106b)** respectively (Scheme 1.3).

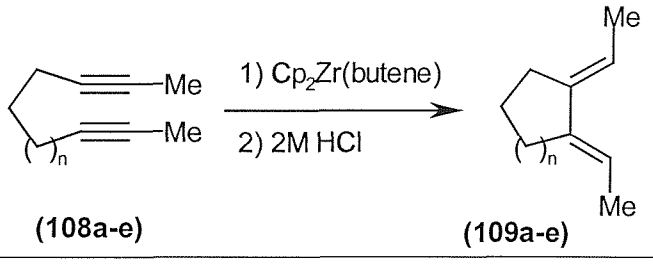


Scheme 1.3 – Elaborations of zirconacycle (104).

Exposure of **(104)** to an atmosphere of carbon monoxide provides an insertion product **(107)** after hydrolysis.[15] The mechanism of this reaction will be described later in Section 1.4.4, and should be accepted as an elaboration method for zirconacyclo-pentanes and –pentenes for now.

1.2.1: Co-Cyclisation of Diynes.

The scope of diyne co-cyclisation has been described concisely in publications by Negishi *et al.*[13] and Nugent *et al.*[16] The failure of zirconocene induced co-cyclisation reactions involving terminal alkynes is believed to be due to an oxidative addition into the terminal C-H bond due to the acidity of the alkyne proton. Thus the diynes to be investigated must be terminally substituted for cyclisation with Negishi's reagent, zirconocene (1-butene) to be successful. The former of the two research groups used simple alkyl substituents to investigate the ring sizes available. It was found that 4 to 7 membered rings could be obtained[13] (Table 1.1).



n	ring size	yield/%
0	4	89
1	5	70
2	6	70
3	7	45
4	8	<2

Table 1.1 – Ring sizes available by co-cyclisation of diynes.

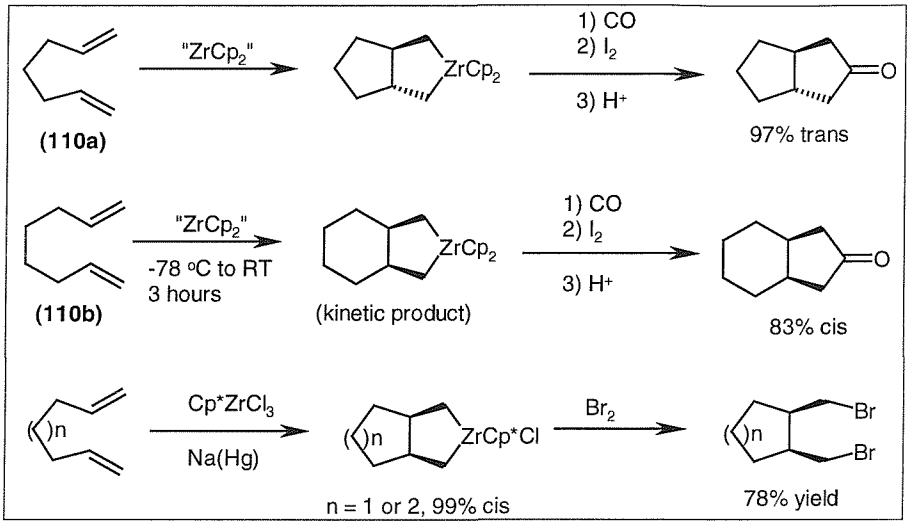
Substituents other than methyl groups, such as Et, iPr, nBu, tBu, $SiMe_3$, $(CH_2)_2NH_2$ and $(CH_2)_2OH$ are also tolerated, as is the presence of sterically demanding terminal substituents on both acetylenes.[16] Although carbonylation is not available as an elaboration of the intermediate zirconacyclopentadiene, the dienes obtained after protonolysis are excellent Diels Alder substrates.[16,17]

1.2.2: Formation of Carbocycles by Co-Cyclisation of Dienes.

The synthesis of carbocycles by the co-cyclisation of dienes has been investigated in great detail, and constituted some of the early work on the applicability of the Cp_2ZrCl_2 / nBuLi method for zirconacycle preparation. Preparation of 4, 5, 6 and 7 membered rings from the appropriate dienes was attempted by the groups of Nugent[14] and Negishi.[18] Both groups found that four and seven membered rings could not be obtained, though in a later report Akita *et al.* obtained a seven membered ring compound as a "minor product" in the co-cyclisation / carbonylation of 1,8-

nonadiene.[19] It is known from recent work within our group that seven membered rings containing nitrogen atoms can be cyclised successfully and in good yield from simple dienes.[20]

Scheme 1.4 shows the ring junction stereochemistries observed in diene co-cyclisation.

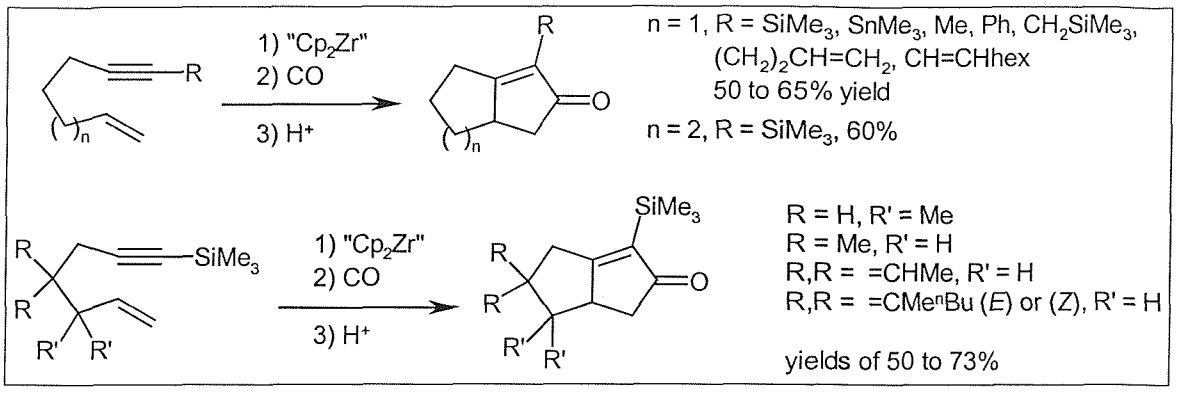


Scheme 1.4 – Ring junction stereochemistry in cyclisation of dienes.

Contrasting ring junction stereochemistry was observed in preparation of 5 and 6 membered rings. Five membered carbocycles provide exclusively *trans* ring junctions, whereas six membered rings provide mostly *cis* under the same conditions. However, this *cis* relationship is known to be a kinetic phenomenon, and heating of the zirconacycle for 6 h at 60 °C has been shown to give quantitative conversion to the *trans* isomer.[19] This bias for *trans* ring junctions of zirconacycles compared with 5,5-fused hydrocarbon bicycles prepared by other ring closure methods is a consequence of the length of the C-Zr bond (2.2 Å for C-Zr, 1.5 Å for C-C). In both five and six membered cases, exclusive *cis* stereochemistry can be obtained by the use of Cp^*ZrCl_3 / Na(Hg) as the zirconocene source.[14] The *trans* stereochemistry seen with 1,6-heptadiene **(110a)** is in contrast to the cyclisation of diallylbenzylamine with zirconocene (1-butene), where the presence of a nitrogen atom in the ring provides predominantly the *cis* stereochemistry.[14,21]

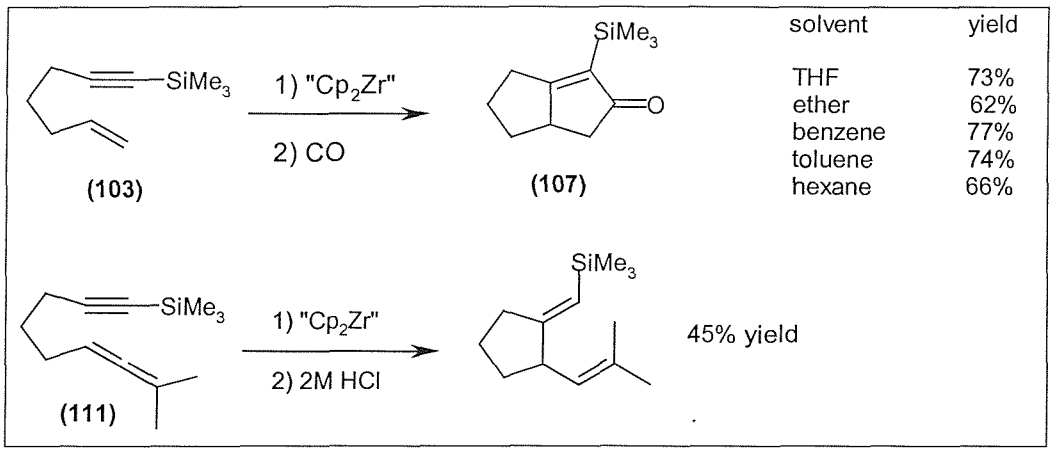
1.2.3: Formation of Carbocycles by Co-Cyclisation of Enynes.

The formation of carbocycles from enynes is again limited to five and six membered rings. However, a wide variety of substituents on both the ring and the alkyne are tolerated.[15, 22] Some representative examples are shown in Scheme 1.5.



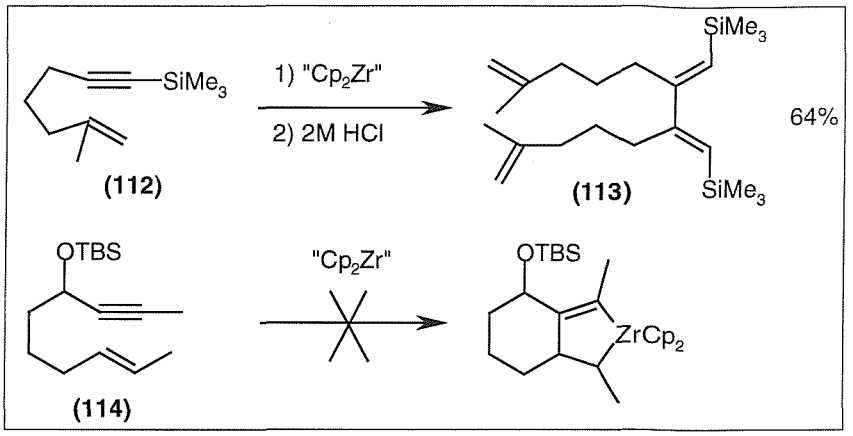
Scheme 1.5 – Variability of substituents on enynes.

The co-cyclisation of enyne **(103)** and subsequent carbonylation has been performed successfully in a variety of solvents. The same report presented the zirconocene mediated cyclisation of allene **(111)**[15] (Scheme 1.6).



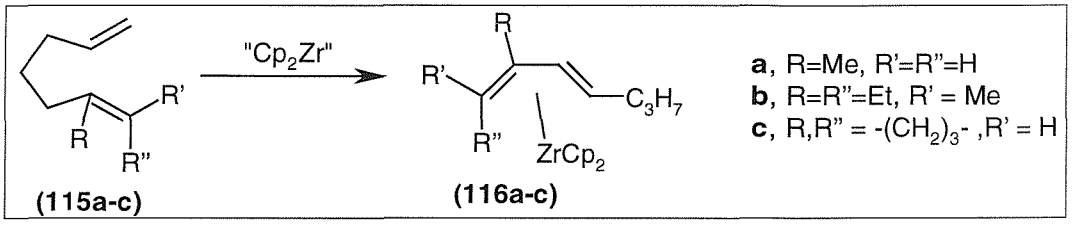
Scheme 1.6 – Variability of solvent; co-cyclisation of an allene.

Although the substitution of the tether part of the enynes has not provided any hindrance to co-cyclisation, substituents on the double bond can have a great effect on reactivity. The first example investigated was the enyne **(112)**. The methyl group blocked co-cyclisation, and a dimeric product **(113)** was obtained[22] (Scheme 1.7). Cyclisation of the terminally substituted 1,7-enyne[23] **(114)** also failed.



Scheme 1.7 – Limitations of sterically hindered enynes.

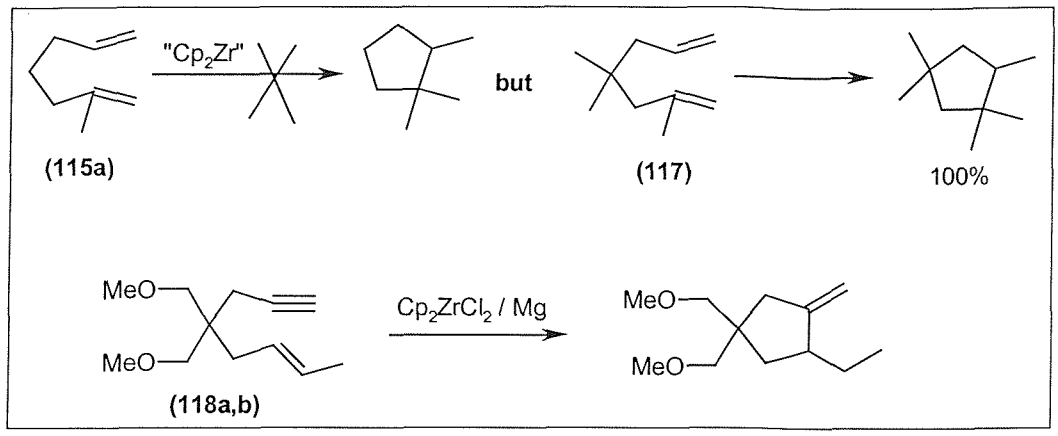
The limitations are also known for dienes, where a high degree of substitution on one of the double bonds disfavours cyclisation[24] (Scheme 1.8).



Scheme 1.8 – Double bond migration in hindered dienes.

In these cases, migration of the terminal double bond occurs as far as the more substituted double bond, to form zirconocene – diene complexes (**116a-c**). On protic quench, the more substituted double bond is protonated.

These alternative reaction pathways of dienes and enynes can be suppressed, however. The first method is the presence of a quaternary carbon in the tether, which blocks intermolecular reaction of enynes and double bond migration of dienes.[18,24] Thus where (**115a**) fails to cyclise, diene (**117**) gives a quantitative yield of 1,1,3,3,5-pentamethylcyclopentane (Scheme 1.9). The successful cyclisation of enyne (**118**) may be attributable to the *gem*-dimethoxymethyl functionality.[25,26]

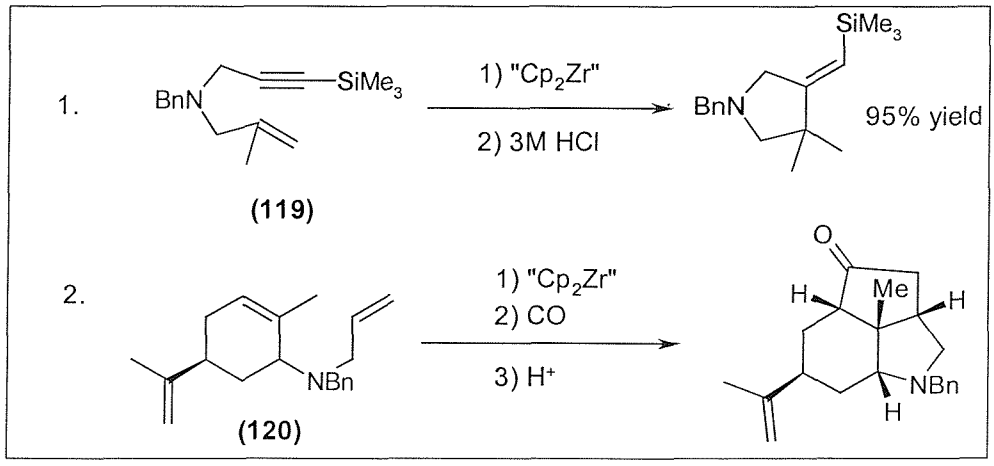


Scheme 1.9 – Effect of quaternary carbons on co-cyclisation.

The second factor which is known to promote bicyclisation is the presence of a nitrogen atom in the tether. The general success of amine substrates, and the greater range of substrates available for co-cyclisation, has led to a number of heterocycles being synthesised by this method.

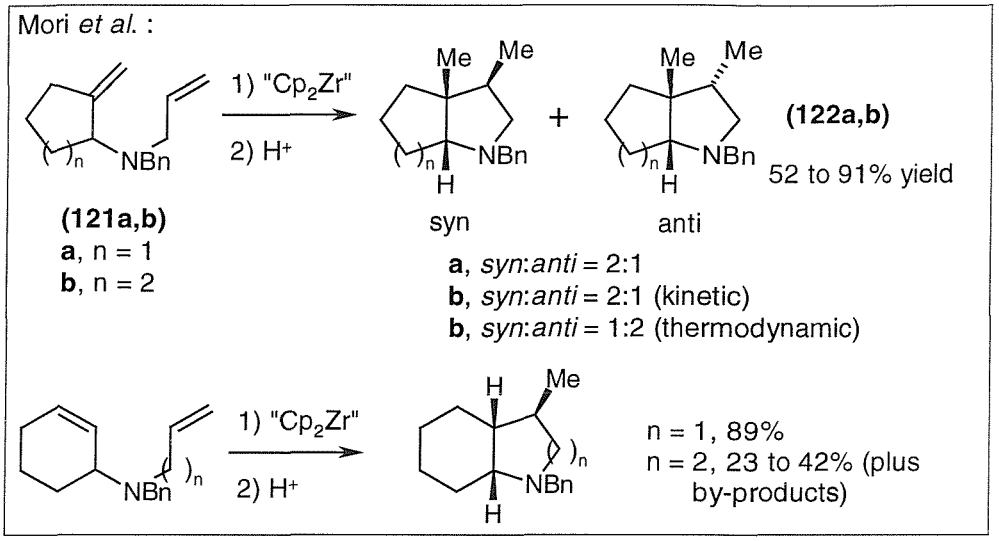
1.2.4: Co-Cyclisation of Nitrogen Containing Substrates.

Two examples of the superiority of amines as co-cyclisation substrates are shown in Scheme 1.10. The first, enyne **(119)**, is the nitrogen containing analogue of enyne **(112)**, seen in Scheme 1.7. Instead of dimeric products **(113)** being formed, the cyclisation occurs cleanly.[22] The second example is the cyclisation of a highly substituted diene **(120)**, used by Mori in a total synthesis of the natural product dendrobine.[27]



Scheme 1.10 – Cyclisation of hindered amine substrates.

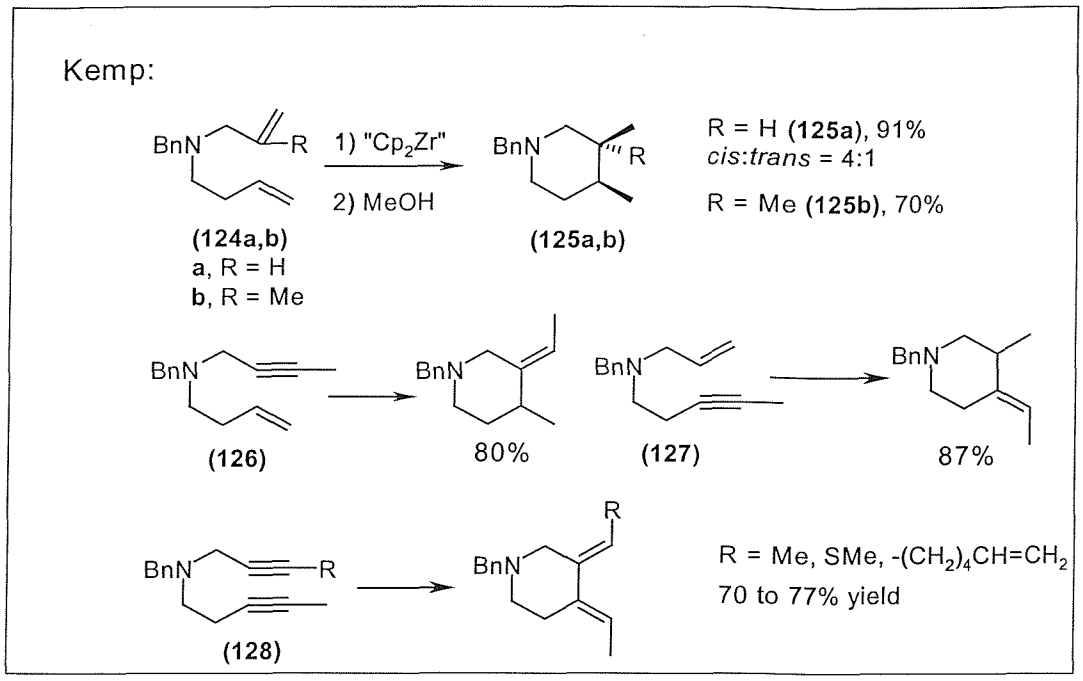
The co-cyclisation of nitrogen containing dienes has been investigated in some depth by Mori and co-workers, often towards natural product systems such as that in Scheme 1.10. These substrates often contain fused cyclohexane and cyclopentanes.[28,29] Representative examples of Mori's work are shown in Scheme 1.11.



Scheme 1.11 – Co-cyclisation of nitrogen containing dienes by Mori *et al.*

The cyclisations of the exocyclic methylene compounds **(121a,b)** provided excellent yields of the desired pyrrolidines, although the *syn*:*anti* selectivity was poor and was influenced by kinetic and thermodynamic factors. Where the double bond was inside the ring, the selectivity was excellent, due the absence of a bridgehead methyl group. Unfortunately, for the six membered rings the yields were poorer, due to the formation of by-products. These arose mostly from migration of the terminal double bond one carbon towards the nitrogen, and co-cyclisation of the resulting 1,6-diene.

A systematic study of 1,7-dienes, enynes and diynes has been performed within our group by Kemp[17,30] and is shown in Scheme 1.12.

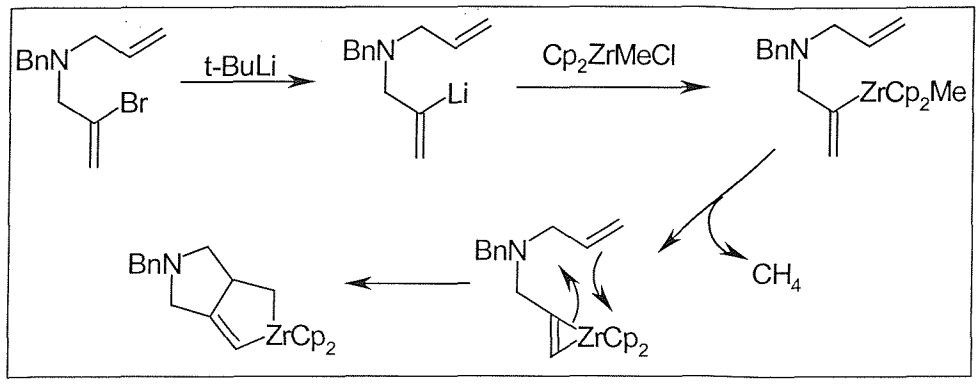


Scheme 1.12 – Synthesis of piperidines by Kemp.

The diene **(124a)** cyclises in excellent yield to give the piperidine **(125a)**, with a *cis*:*trans* ratio identical to that of the hydrocarbon analogue, 1,7-octadiene, under kinetic control. The enynes **(126)** and **(127)**, with the nitrogen atom at different positions in the tether, both cyclise cleanly to give the 3,4-disubstituted piperidines shown. Finally, the terminally substituted diynes **(128)** give good yields of the respective dienes. These have been shown to be excellent Diels Alder substrates for reaction with several dienophiles.

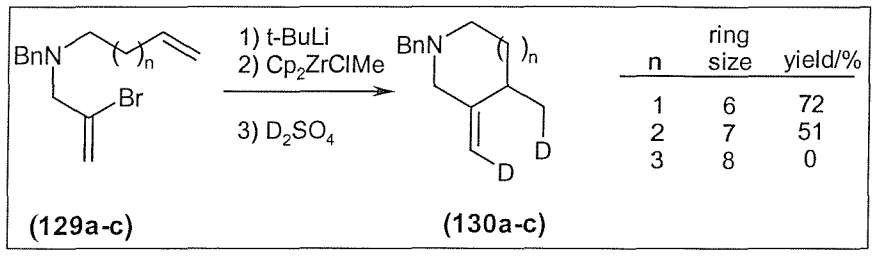
1.2.5: Synthesis of Seven and Eight Membered Rings by Zirconocene Mediated Cyclisation.

Barluenga *et al.*[31] have reported the preparation of amine heterocycles varying in size from 5 to 8 membered, the larger sizes being the more noteworthy. The method for formation of the initial zirconacyclopropenes is rather different from the standard Negishi method (Cp_2ZrCl_2 / nBuLi), but the ring expansion to the five membered zirconacycle is the same. Lithiation of a vinyl bromide followed by zirconation with $Cp_2ZrClMe$ provides a methyl alkenyl zirconocene, which loses methane to provide a zirconacyclopropene, as shown for the synthesis of a pyrrolidine in Scheme 1.13.



Scheme 1.13 – Barluenga's preparation of zirconacyclopropenes.

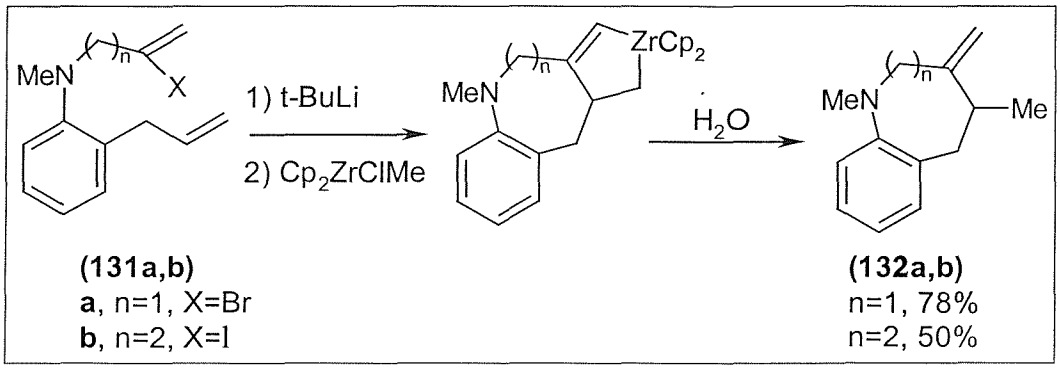
This method was used in an attempt to produce 6, 7 and 8 membered rings **(130a-c)** from straight chained nitrogen containing dienes **(129a-c)**. The yields of product diminished with increasing ring size, indeed the eight membered ring was not obtained (Scheme 1.14).



n	ring size	yield/%
1	6	72
2	7	51
3	8	0

Scheme 1.14 – Synthesis of 6 and 7 membered heterocycles.

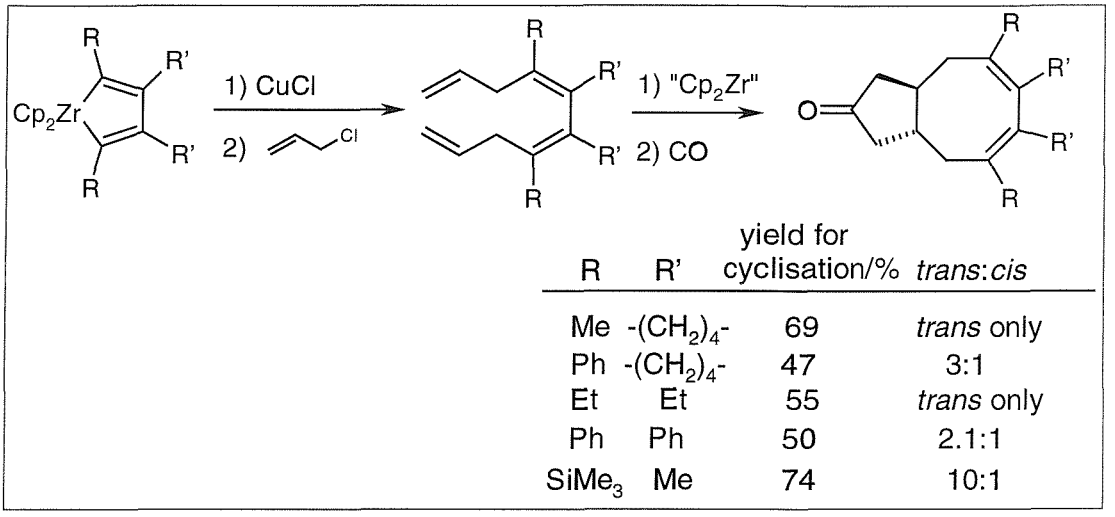
In order to access seven and eight membered rings in increased yields, an aromatic backbone was used to confer rigidity to the systems, bringing the double bonds closer together. In this way, formation of cyclic products would be more favourable and the larger rings could be produced (Scheme 1.15).



Scheme 1.15 – Barluenga's synthesis of 7 and 8 membered rings.

The formation of an eight membered ring in good yield shows the strength of Barluenga's cyclisation procedure, the effect of a nitrogen atom in the ring, and a

fused aromatic ring templating the cyclisation by bringing the ends of the chain together. The larger ring compounds prepared by this method may have potential biological activity. The method of templating the formation of eight membered rings, here with a benzene ring, has also been used by Takahashi *et al.*[32] In this publication, stereodefined alkenes were used to template the cyclisation. A zirconocene mediated method for formation of the co-cyclisation precursors was also used, whereby a zirconacyclopentadiene is transmetallated to copper and diallylated. The sequential zirconium mediated route to eight membered rings is shown in Scheme 1.16.



R	R'	yield for cyclisation/%	*trans*:*cis*
Me	$-(CH_2)_4-$	69	*trans* only
Ph	$-(CH_2)_4-$	47	3:1
Et	Et	55	*trans* only
Ph	Ph	50	2.1:1
$SiMe_3$	Me	74	10:1

Scheme 1.16 – Takahashi's synthesis of eight membered rings.

The cyclisations proceed in good yield in all cases, and some degree of selectivity is obtained with respect to the ring junction stereochemistry, with the *trans* isomer predominating.

1.3: Conclusions for Scope and Limitations.

In summary, a wealth of five and six membered rings are readily available by the zirconocene mediated co-cyclisation of dienes, enynes and diynes. These rings can be carbocyclic or heterocyclic. Cyclisation products with nitrogen atoms in the ring have been described, and oxygen and silicon containing substrates have also been cyclised.[33] The work in Chapter 2 of this thesis provides precedent for further oxacycle formation, complementing the chemistry reviewed herein. The Negishi reagent, zirconocene (1-butene)[13] has proven successful in the cyclisation of most of the substrates which have been investigated, though large ring sizes and hindered

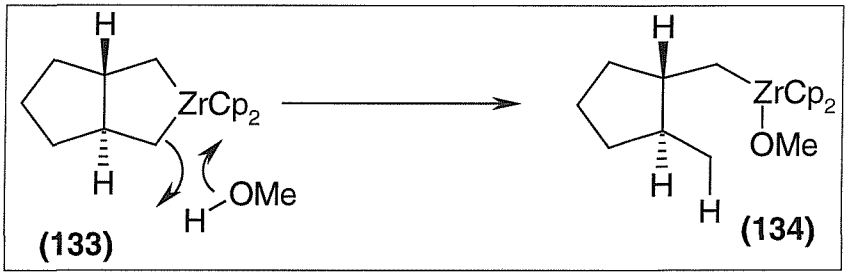
substrates can fail. Apart from the superiority of Barluenga's method for preparation of the larger rings[31], the major failing of Negishi's reagent is in the cyclisation of terminal alkynes to give methylene cycloalkanes. Recently, however, even this limitation has been surpassed. Although the original method of zirconocene preparation (Cp_2ZrCl_2 / Mg / $HgCl_2$)[12] is successful in this respect, the use of zirconocene (ethylene) prepared from Cp_2ZrCl_2 and ethyl magnesium halide,[34,35] or Cp_2ZrCl_2 reduced by magnesium metal activated by 1,2-dibromoethane, rather than mercury prove cleaner practically.[25] A titanium mediated cyclisation of terminal alkynes has also been reported.[36] In Chapter 3 of this thesis we present another route for the preparation of exocyclic methylene groups which complements these methods. Another strength of the zirconocene chemistry described herein is the scope for elaboration of the C-Zr bond, and is reviewed next.

1.4: Elaborations of Zirconacycles.

Although a diverse range of organic compounds can be synthesised by varying the substitution on the co-cyclisation substrates, the potential of this chemistry is increased further by the ability to functionalise the C-Zr bond. The covalent nature of these bonds, and the electronic nature of zirconium allows a great deal of elaboration, of which the popular methods are described in the next section. The examples described are relevant to zirconabicycles, though many are applicable to monocyclic zirconium compounds also.

1.4.1: Protonolysis.

Treatment of a zirconacycle, or indeed any C-Zr bond with methanol allows protic quench at the carbon atom, possibly *via* a 2+2 mechanism (Scheme 1.17).

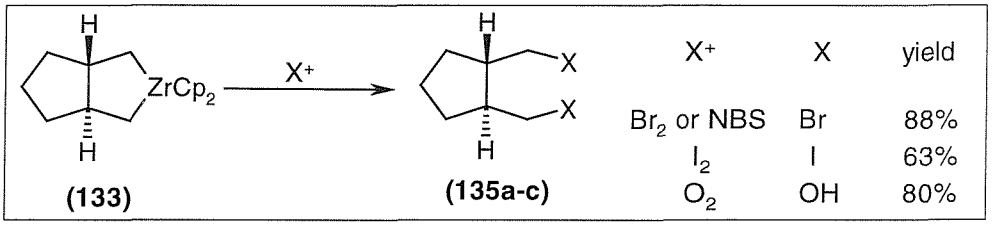


Scheme 1.17 – Methanolic quench of a zirconacycle.

The analogous reaction with MeOD provides deuterated products, and is a valuable tool for the determination of mechanisms, by identification of the site of the zirconium atom prior to quench. Complete quench with excess methanol provides the organic product free of the metal, this representing the usual hydrolysis of a zirconacycle. However, the rate of methanolysis of a zirconacycle[37] is faster than the subsequent quench of the organozirconium such as **(134)**, so treatment of a zirconacycle with 1.5 equivalents of methanol provides the mono-quenched product initially. The resultant organozirconium **(134)** can be reacted again with a halogen, allowing selective substitution of a symmetrical zirconacycle. Where basic quench of a zirconacycle with methanol / $NaHCO_{3\ (aq)}$ can be used to quench acid sensitive zirconacycles, dilute HCl or H_2SO_4 can also be used if no sensitive functionality is present. Correspondingly, DCl or D_2SO_4 can be used to perform deuterolysis.

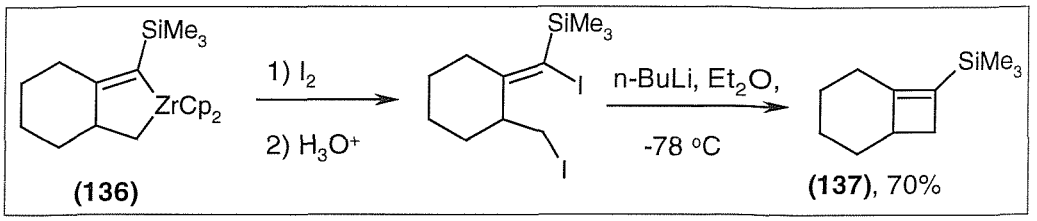
1.4.2: Halogenolysis and Oxygen Quench.

Treatment of an organozirconium or zirconacycle with bromine,[14] iodine[18] or oxygen[14,38] allows functionalisation of the carbon atoms, and opens the organic product to a range of subsequent reactions (Scheme 1.18).



Scheme 1.18 – Bromine, iodine and oxygen quench.

Incorporation of halogen into the cyclisation product provides compounds of higher molecular weight than those which would be obtained by simple protic quench. Decreased volatility of the products facilitates their isolation, which aided the investigation into the methodology of ring junction stereochemistry.[14] Iodinolysis of the zirconacycle **(136)** provides an interesting route to cyclobutene **(137)**[15] (Scheme 1.19).

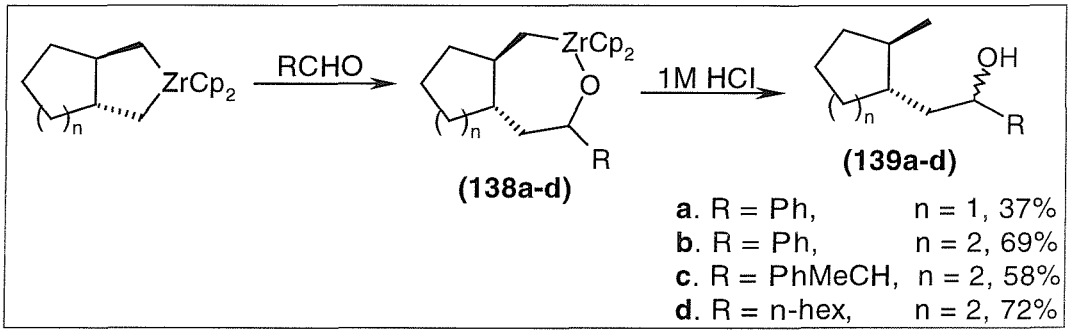


Scheme 1.19 – Cyclobutene formation *via* iodinolysis.

The iodination of vinyl zirconium reagents derived from the hydrozirconation of alkynes provides stereodefined vinyl iodides amenable to Pd or Ni catalysed reactions.[39]

1.4.3: Aldehyde Quench.

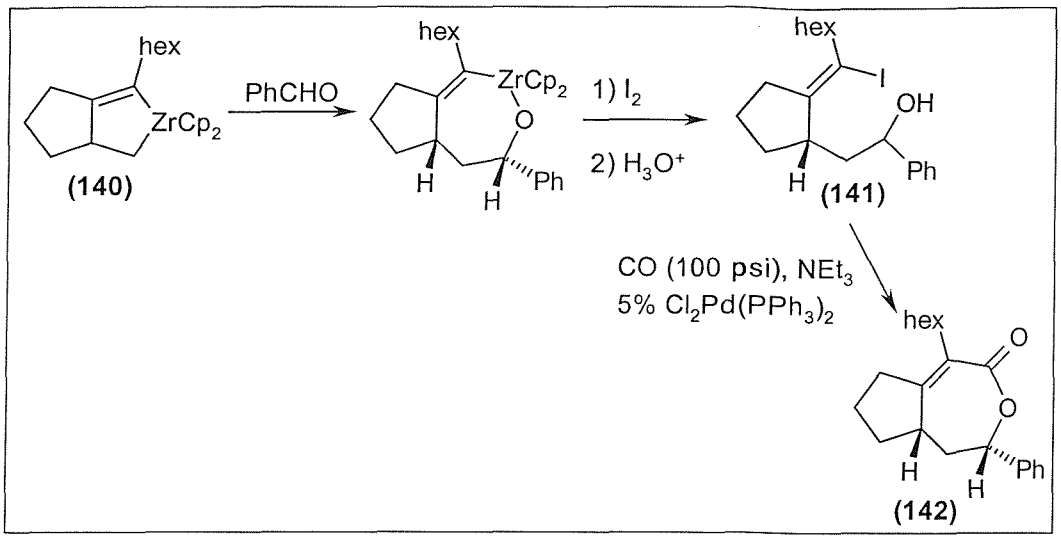
Where iodine or bromine can be used as electrophiles for attack by organozirconium reagents such as zirconacycles, aldehydes are also captured efficiently.[40] Zirconacyclo-pentanes and –pentenes fused to cyclopentanes and cyclohexanes attack aldehydes to give the corresponding expanded zirconacycles (**138a-d**) (Scheme 1.20). Work up with dilute acid provides alcohols (**139a-d**).



Scheme 1.20 – Aldehyde quench of zirconacycles.

Although the yields are good in most cases, the control over the newly generated chiral centre (at the alcohol) is poor, giving a 2:1 ratio at best.

The zirconacyclopentene (**140**) provides a vinyl iodide (**141**) after aldehyde insertion and quench with iodine. Treatment of (**141**) with carbon monoxide in the presence of a catalytic amount of a palladium catalyst provides a seven membered lactone[41] (**142**) in 85% diastereomeric purity (Scheme 1.21).

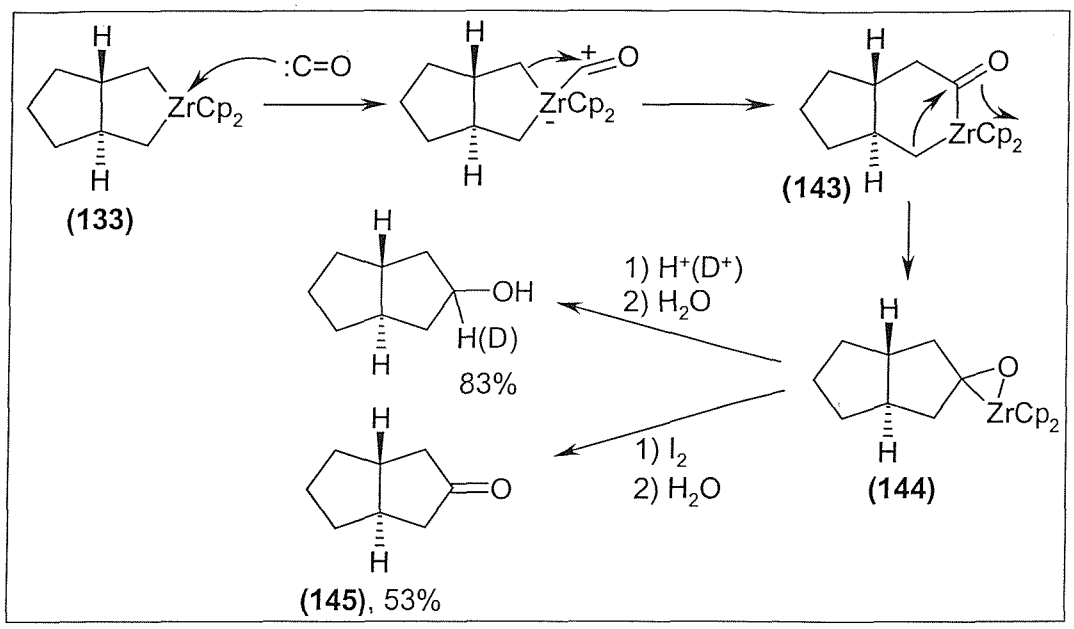


Scheme 1.21 – Lactone formation *via* aldehyde quench and iodinolysis.

As well as being an interesting application of palladium chemistry, the lactonisation allowed identification of the major diastereomer by NOE experiments, by locking the conformation of the two chiral centres.

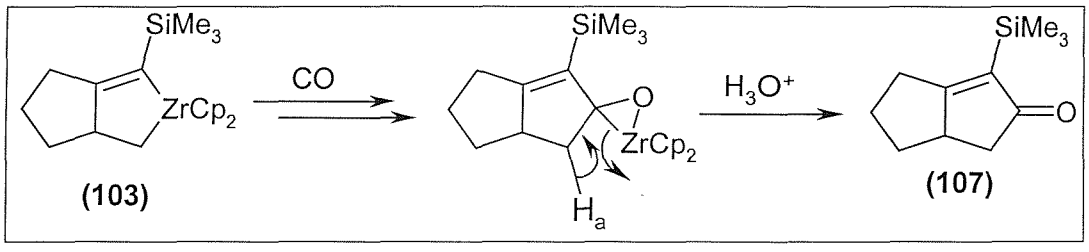
1.4.4: Carbonylation.

The carbene-like nature of carbon monoxide, and an empty orbital on the zirconium atom in a zirconacycle allows nucleophilic attack by CO, on exposure of a zirconacycle to an atmosphere of the gas. Migration of a carbon atom in the zirconacycle onto the carbon of CO provides electroneutrality to the organometallic, and an expanded zirconacycle **(143)** (Scheme 1.22). A second bond migration provides an η^2-ketone complex **(144)** which can be converted to a cyclopentanol or cyclopentanone **(145)** on protonolysis, or oxidative work up with iodine respectively.[18, 42]



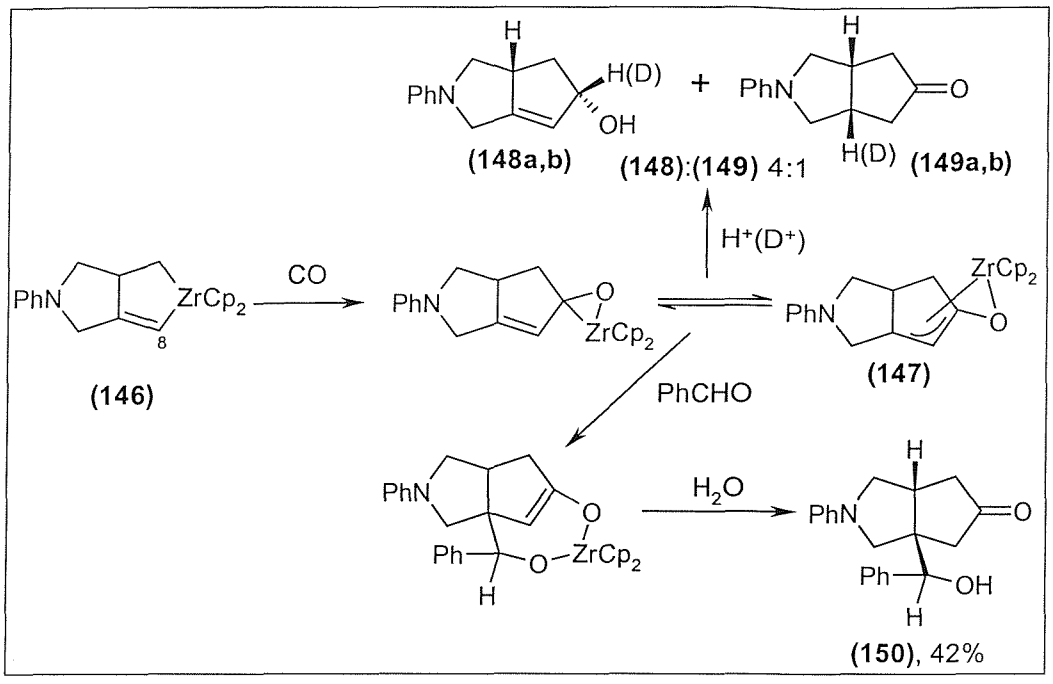
Scheme 1.22 – Carbonylation to provide a cyclopentanol or cyclopentanone.

Support for this mechanism, with the complex **(144)** as an intermediate, is provided by deuterolysis.[42] Overall, a metathesis from $ZrCp_2$ to C=O has been achieved. The formation of *trans* fused cyclopentanones by this method is noteworthy. The corresponding carbonylation of zirconacyclopentenes is shown in Scheme 1.23.



Scheme 1.23 – Speculated route for cyclopentenone formation *via* carbonylation.

It should be noted that the oxidative iodine work up required to give the cyclopentanone **(145)** is not required here, and simple protic work up gives the cyclopentenone **(107)**. Although abstraction of 'H_a' shown in Scheme 1.23, to give a final enol zirconate with hydride on zirconium has been ruled out,[15] it seems likely that a related pathway to the ketone is taken. Barluenga[31,43] has investigated this phenomenon by comparison of this example with the 8-unsubstituted bicycle **(146)** (Scheme 1.24).



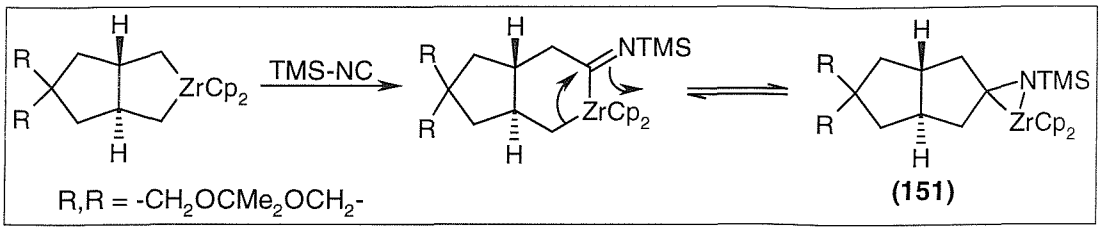
Scheme 1.24 – Barluenga's carbonylation reactions.

Treatment of **(146)** with CO again provides an η^2-ketone complex, shown here as the tautomeric π-allyl zirconocene **(147)**. It is suggested that formation of an allyl complex **(147)** is preferred to the β-hydride extraction accounting for **(107)** (Scheme 1.23) in which the 8-position is substituted. This explains the formation of the hydrolysis and deuterolysis products **(148a,b)** and **(149a,b)**, and the product of benzaldehyde quench, **(150)**.

In summary, the co-cyclisation / CO insertion reaction has proved popular in the synthesis of bicyclic ketones, and of various natural products such as dendrobine[27] and iridomymecin.[44]

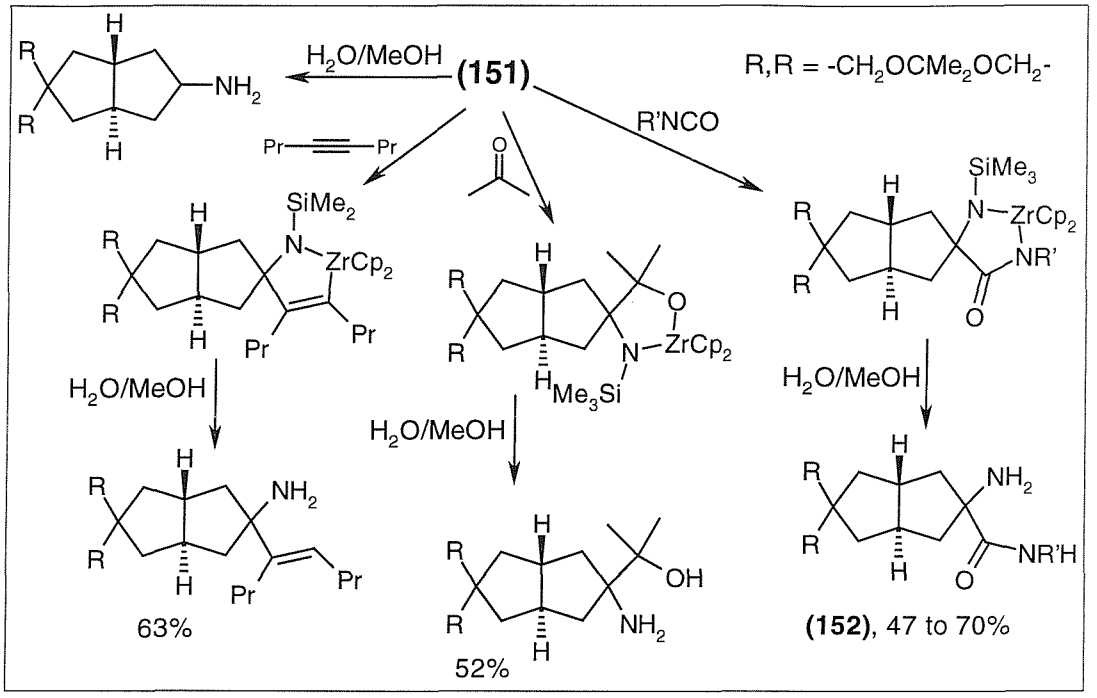
1.4.5: Isocyanide Insertion.

Analogous to carbonylation is the insertion of isocyanides, which are isoelectronic to carbon monoxide, into zirconacycles. The route to the η^2-imine complex **(151)**[45,46] for trimethylsilyl isocyanide[47] is shown in Scheme 1.25.



Scheme 1.25 – Isocyanide insertion to give η^2- imine complex (151).

A number of elaborations are available for (**151**), such as protic quench, alkyne or alkene insertion,[48] reaction with a carbonyl compound, and isocyanate[47] insertion (Scheme 1.26).

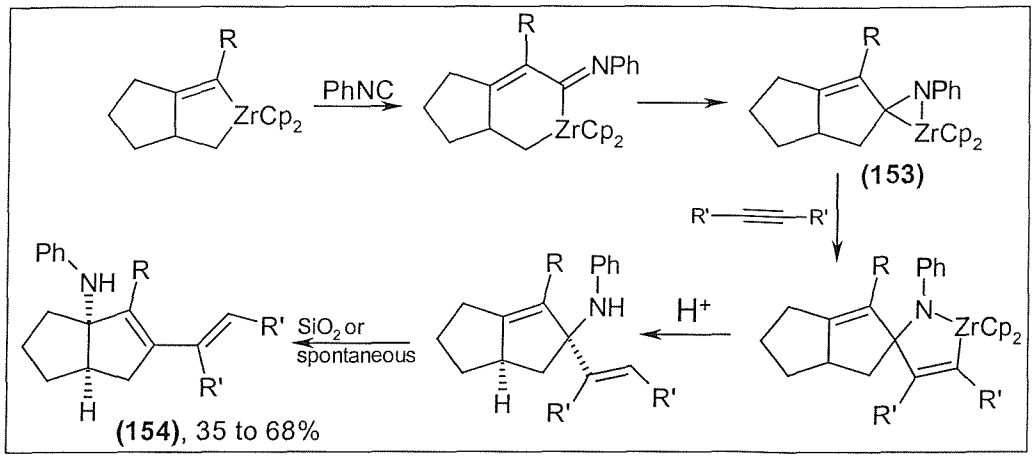


Scheme 1.26 – Elaborations of imine complex (151).

This methodology allows production of a range of cyclopentylamines, with isocyanate (R'CHO) insertion into (**151**) allowing production of unusual α-amino amides (**152**). The use of TMS-NC provides free amines after hydrolysis of the final organozirconium, where the TMS group is cleaved from the amine under the hydrolysis conditions. Phenyl and benzyl isocyanides also can also be inserted into zirconacycles, and provide anilines and benzylamines[49] respectively.

The analogous insertions into zirconacyclopentenes also provide η^2-imine complexes, such as (**153**) (Scheme 1.27). Subsequent alkyne insertion followed by methanolysis

provides diallylic amines, which undergo an unusual 1,3-amine shift[50] spontaneously or on silica gel to give a bridgehead amine product **(154)**.

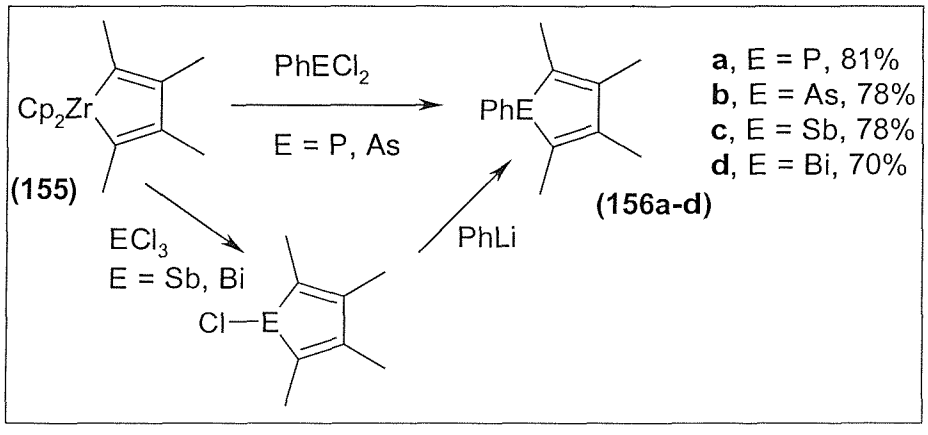


Scheme 1.27 – Isocyanide insertion into zirconacyclopentenes.

The ability to generate and further elaborate the η^2-imine complex allows the formation of four new carbon-carbon bonds in one pot, and thus complex molecules can be developed rapidly with this chemistry.

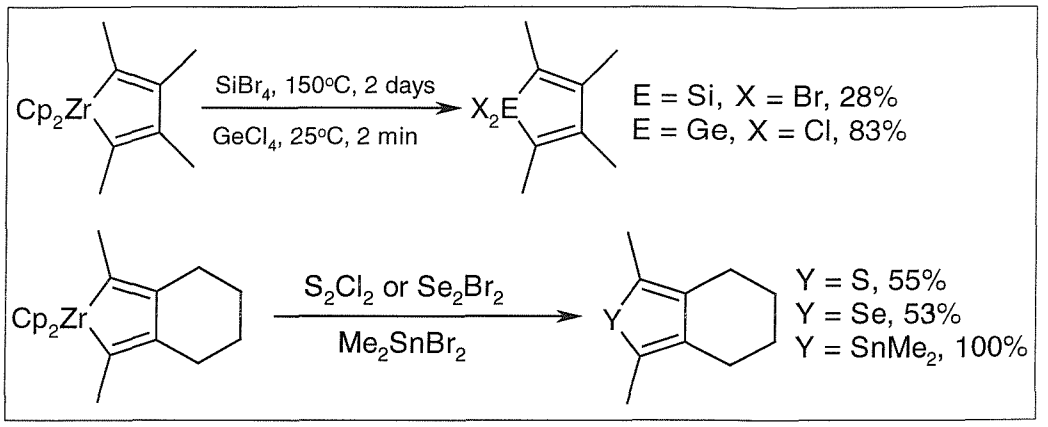
1.4.6: Metathesis With Main Group Elements.

The exchange of the zirconium atom in a zirconacycle for a main group element provides a range of unusual heterocycles.[21,51] For example, the group 15 phenyl derivatives **(156a-d)** can be prepared in good yield by reaction of a zirconacycle such as **(155)** with the element phenyl dichloride, or *via* the unstable cyclic monochloride by treatment with the appropriate trichloride, then phenyl lithium displacement of chloride (Scheme 1.28).



Scheme 1.28 – Metathesis with group 15 elements.

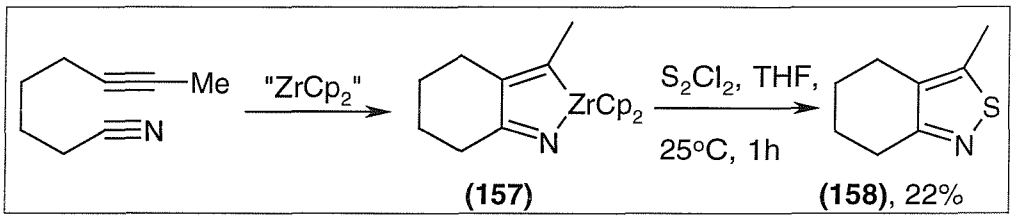
The heterocycles (**156a-d**) can be purified by chromatography or distillation, and are stable at room temperature. Group 14 and 16 compounds can also be prepared (Scheme 1.29).



Scheme 1.29 – Metathesis with group 14 (Si, Ge, Sn) and 16 (S, Se) elements.

Dihydro- and tetrahydro- heterocycles can be prepared by the same methods, starting from zirconacyclo-pentenes and –pentanes respectively.

An interesting isothiazole synthesis is possible by metathesis of an azazirconacycle[52] (**157**) (Scheme 1.30).



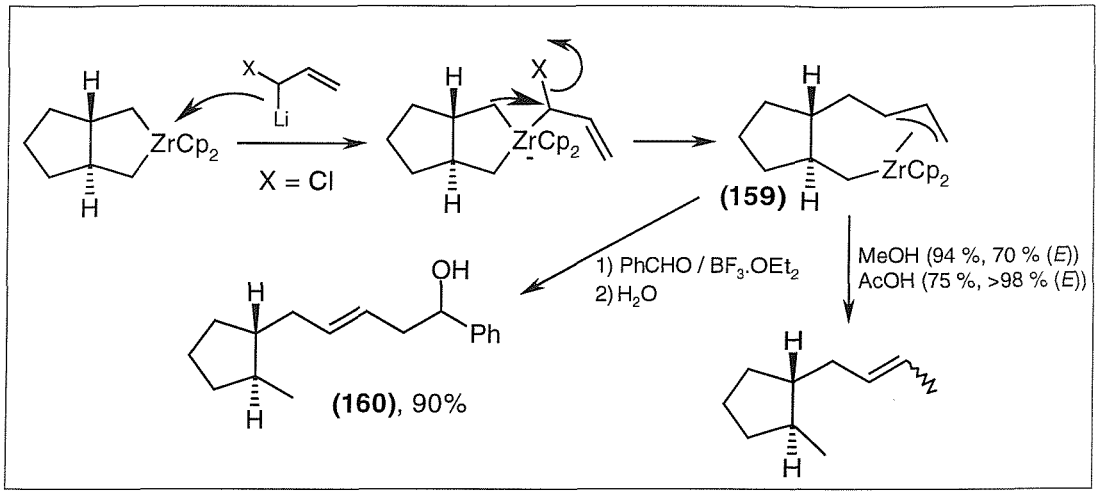
Scheme 1.30 – Isothiazole formation *via* metathesis with sulphur.

Isothiazole (**158**) was prepared in a poor 22% yield overall. However, 62% of the starting nitrile was recovered (suggesting incomplete formation of (**157**)), giving a 65% yield of the heterocycle based on recovered starting material.

1.4.7: Carbenoid Insertion.

The success of carbonylation and isocyanide insertion as elaboration methods is due to their carbenoid nature, whereby nucleophilic attack on zirconium is followed by electrophilic attack to form an expanded zirconacycle. Metal carbenoids such as

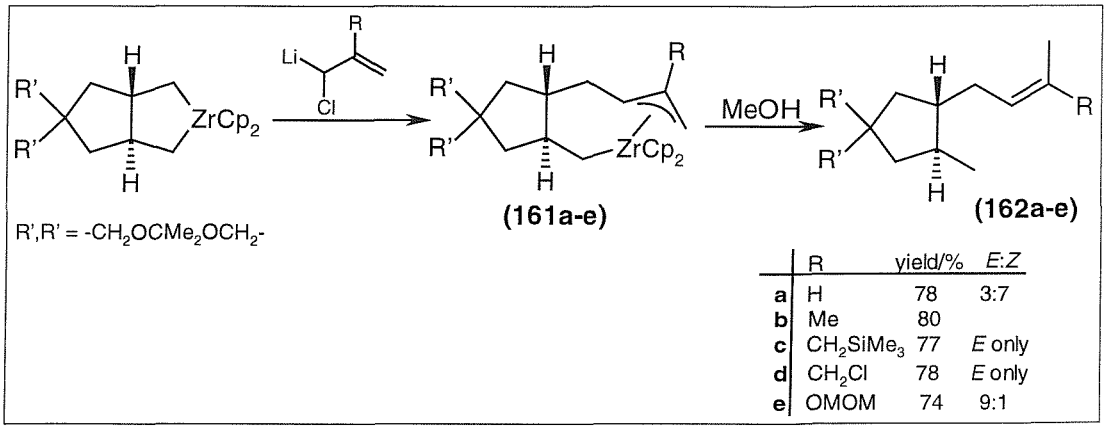
lithiated allyl and propargyl chlorides[53,54] act in a similar manner, with the allyl carbenoids giving π-allyl complexes such as **(159)** (Scheme 1.31).



Scheme 1.31 – Allyl carbenoid insertion and protic or benzaldehyde quench.

Protonolysis of **(159)** with acetic acid gives excellent control of the double bond geometry of the protic quenched product, and is superior to methanol in this aspect.[37] Reaction with benzaldehyde activated with $BF_3{\cdot}OEt_2$, then hydrolysis provides alcohol **(160)** in 90% yield and as a 2.9:1 mixture of diastereomers. This tandem, one pot synthesis allows a great deal of diversity in terms of diene, carbenoid and aldehyde variability.[37]

Firstly, the carbenoid leaving group ('X', given as Cl in Scheme 1.31) can also be Br, OTs or $OCON^iPr_2$.[55] Alkoxy or sulphur leaving groups give diminished (<10%) yields. A range of 2-substituents on the carbenoid are tolerated, thus allyl complexes **(161a-e)** can be generated (Scheme 1.32).

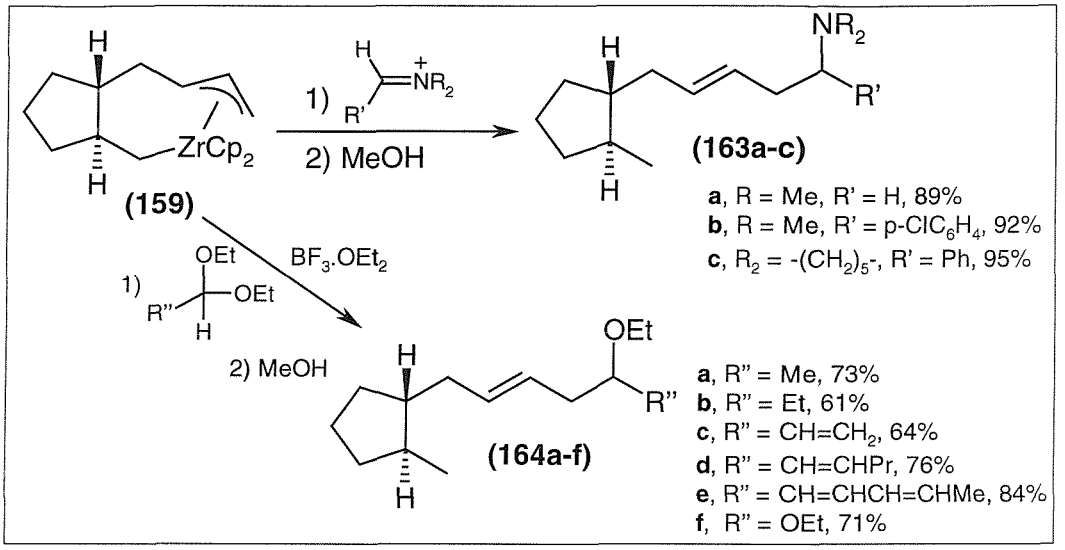


	R	yield/%	E:Z
a	H	78	3:7
b	Me	80	
c	CH_2SiMe_3	77	E only
d	CH_2Cl	78	E only
e	OMOM	74	9:1

Scheme 1.32 – Variability of allyl carbenoid substituents.

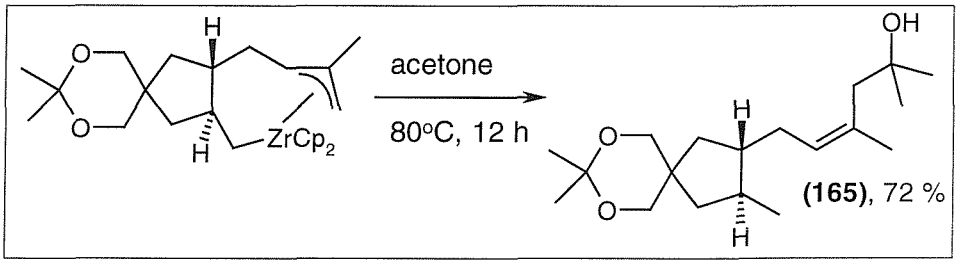
Interestingly, if R = Ph, the subsequent reaction with benzaldehyde provides a single diastereomer of the alcohol (analogous to **(160)** in Scheme 1.31) by NMR. This is an interesting example of total 1,6-stereocontrol.[26]

So far, only H^+ and benzaldehyde / $BF_3{\cdot}OEt_2$ have been shown as electrophiles for the allyl complexes. Iminium ions and acetals are also efficient in this role,[56] providing amines **(163a-c)** and ethers **(164a-f)** respectively, in excellent yields (Scheme 1.33).



Scheme 1.33 – Iminium and acetal quenches of allyl zirconocenes.

Reaction of allyl complexes with imines gave none of the desired secondary amines, however quench with acetone gave the alcohol **(165)**.[55] The reaction proceeded under thermal conditions and no Lewis acid was used (Scheme 1.34).

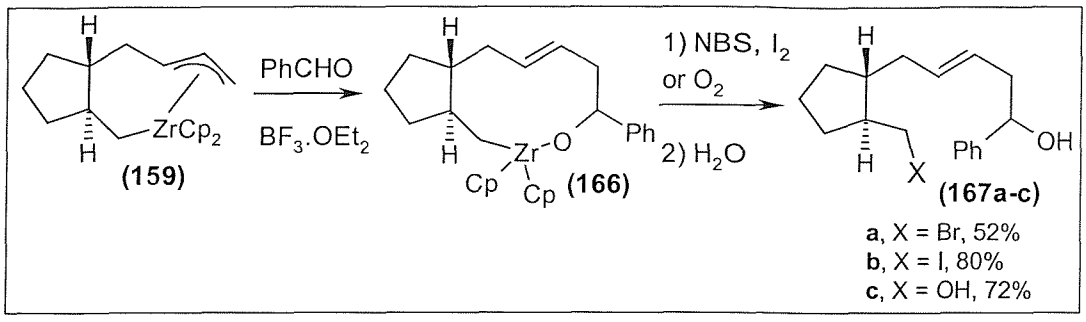


Scheme 1.34 – Acetone quench of an allyl zirconocene.

Surprisingly, the double bond geometry was opposite to that obtained with PhCHO / $BF_3{\cdot}OEt_2$. This could be due to the absence of Lewis acid in the acetone quench, or the reaction being carried out under thermodynamic conditions.

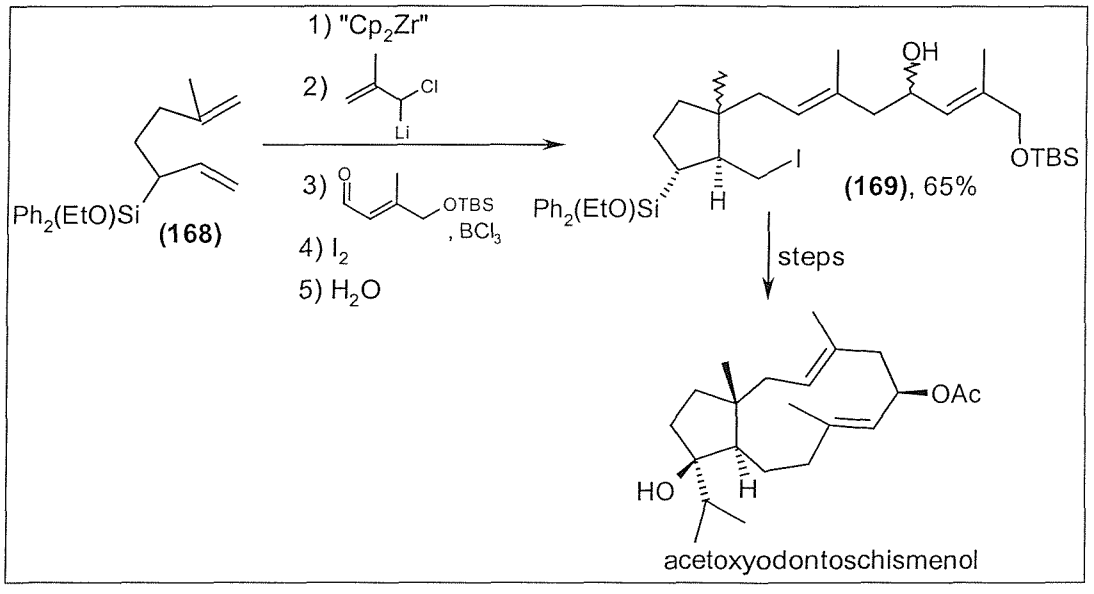
After reaction of an allyl complex with an aldehyde, one C-Zr bond still remains, and can also be elaborated. Reaction of **(159)** with PhCHO / $BF_3{\cdot}OEt_2$ provides

intermediate **(166)**, which can be converted to **(167a-c)** with bromine, iodine or oxygen, respectively (Scheme 1.35).



Scheme 1.35 – Functionalisation of the final C-Zr bond.

In this remarkable reaction, carried out in one pot starting from the co-cyclisation substrate, 1,6-heptadiene, three C-C bonds are formed, along with one C-heteroatom bond, allowing further functionalisation. An excellent example of this chemistry applied to the synthesis of a natural product[57,58] is shown in Scheme 1.36.

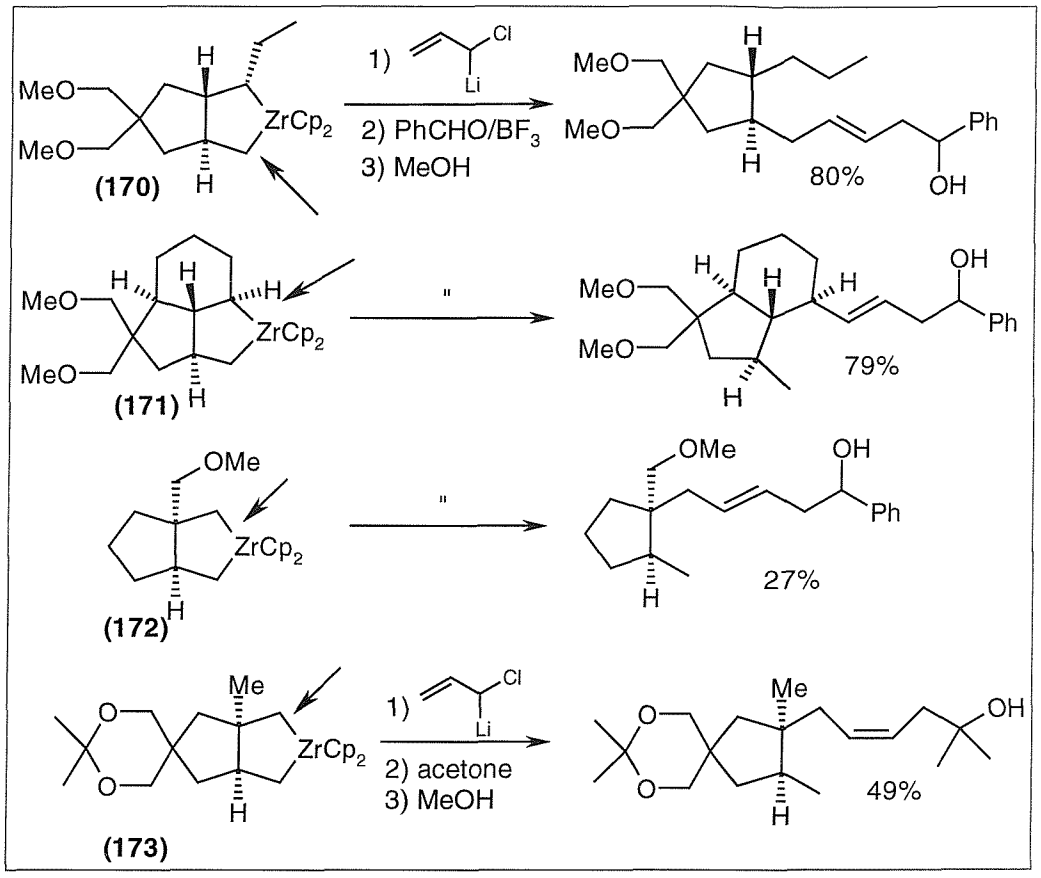


Scheme 1.36 – Zirconium mediated route to acetoxyodontoschismenol.

Co-cyclisation, carbenoid insertion, aldehyde quench, iodide quench and hydrolysis provide **(169)** in 65% yield. All of the carbons in the natural product, except for an isopropyl group are assembled in one reaction. A series of functional group interconversions and a macrocyclisation provide the natural product target.

In the example above, the diene is asymmetrical, and the zirconacycle formed after treatment of the diene with zirconocene thus has two different C-Zr bonds. The insertion of the carbenoid is selective for the side with the bridgehead methyl group.

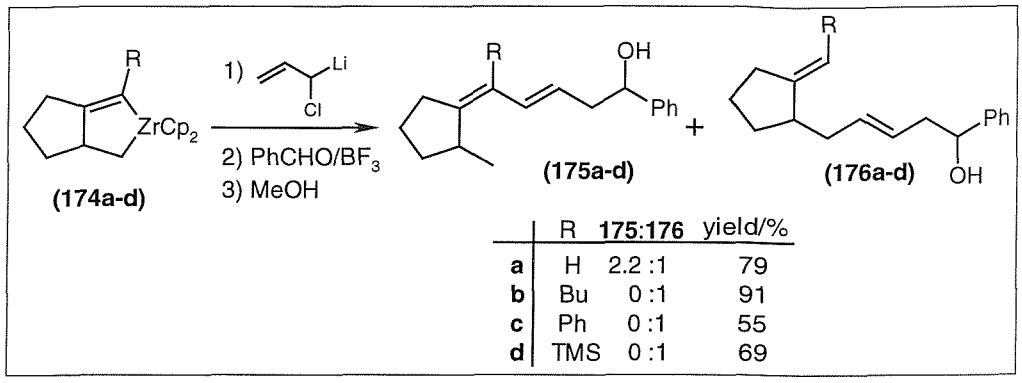
The regiochemistry of carbenoid insertion has been thoroughly investigated recently.[25] Where zirconacyclopentanes are involved, prediction of the regiochemistry is relatively straightforward. Co-cyclisation of a terminally substituted diene provides a zirconacycle such as **(170)** with secondary and tertiary carbons α to zirconium (Scheme 1.37). Insertion is into the least hindered side. This is reversed where there is a fused cyclohexane, where insertion into the zirconacycle **(171)** is into the more hindered side.



Scheme 1.37 – Regiochemistry of carbenoid insertion into zirconacyclopentanes.

Where substitution is present at the bridgehead position, in **(172)** and **(173)** (Scheme 1.37) and **(168)** (Scheme 1.36), insertion is into the same side as the substituent. In all of the examples in Scheme 1.37, the regioisomer shown was the only one isolated.

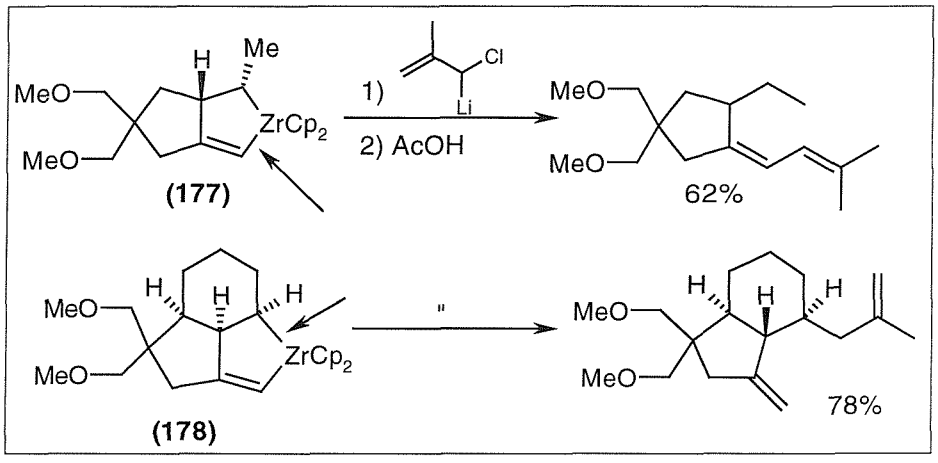
Selectivity of insertion into zirconacyclopentenes is affected by the same factors as above, and also depends on whether the alkyne moiety of the enyne co-cyclisation substrate is substituted. This effect is seen in the reactions of zirconacycles **(174a-d)** (Scheme 1.38).



	R	175:176	yield/%
a	H	2.2 :1	79
b	Bu	0 :1	91
c	Ph	0 :1	55
d	TMS	0 :1	69

Scheme 1.38 – Effect of alkene substituent on regiochemistry of insertion.

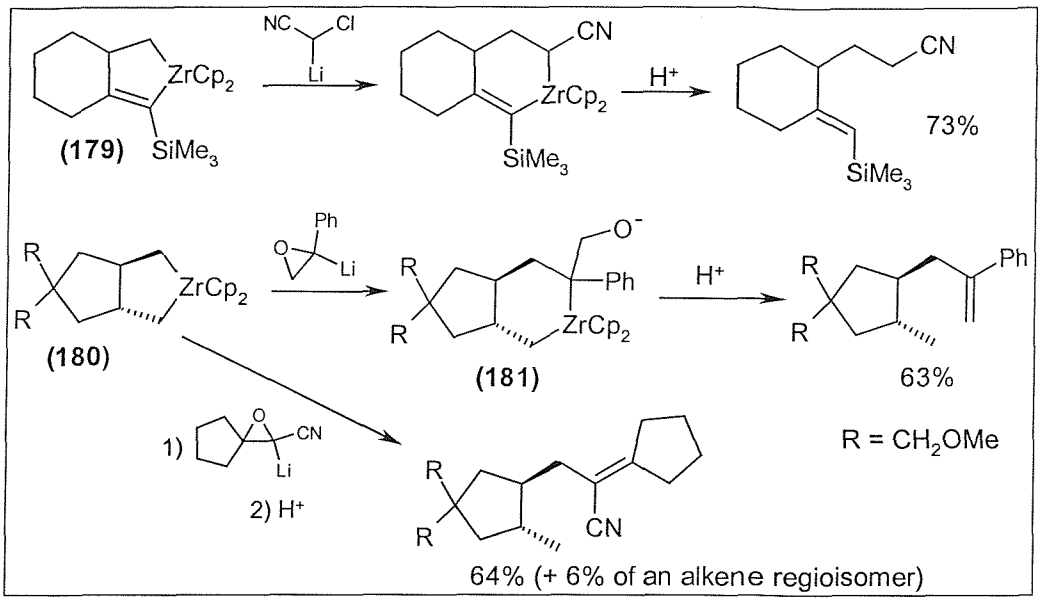
In these examples, insertion is predominantly into the alkenyl side, unless it is substituted. Where the alkene is unsubstituted (Scheme 1.39), substitution α to zirconium has the same effect as for zirconacyclopentanes, where insertion is into the least hindered side unless a fused cyclohexane is present. The difference between methyl substituted (**177**) and cyclohexane fused (**178**) is shown in Scheme 1.39.



Scheme 1.39 – Regiochemistry of insertion into unsubstituted zirconacyclopentenes.

Explanations for the differences in reactivity can be attributed to both steric and electronic effects, and have implications for the mechanism of carbenoid insertion. The literature[25] should be consulted for a full explanation.

Recently, a range of novel lithium carbenoids have been shown to insert into alkyl and alkenyl zirconocenes, and also zirconamono- and bi-cycles. These carbenoids include 1-halo-1-lithio-1-alkenes[59,60] (vinyl carbenoids), and carbenoids stabilised by adjacent sulfur, silicon, ether and nitrile groups.[61] The insertions into zirconabicycles (**179**) and (**180**) are shown in Scheme 1.40.

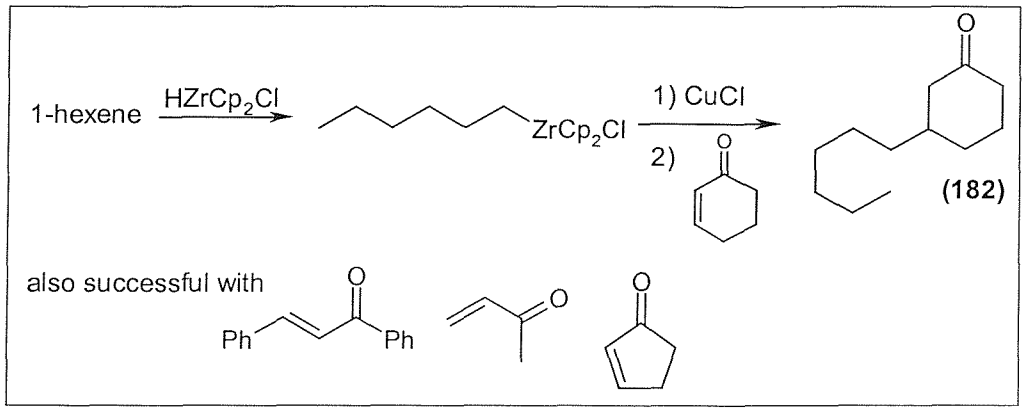


Scheme 1.40 – Insertions of lithiated nitriles and epoxides into zirconacycles.

The insertion of an epoxide forms an intermediate such as **(181)**, which subsequently undergoes elimination to afford an alkene. Good yields were obtained in all of these reactions, providing rapid access to further substituted products.

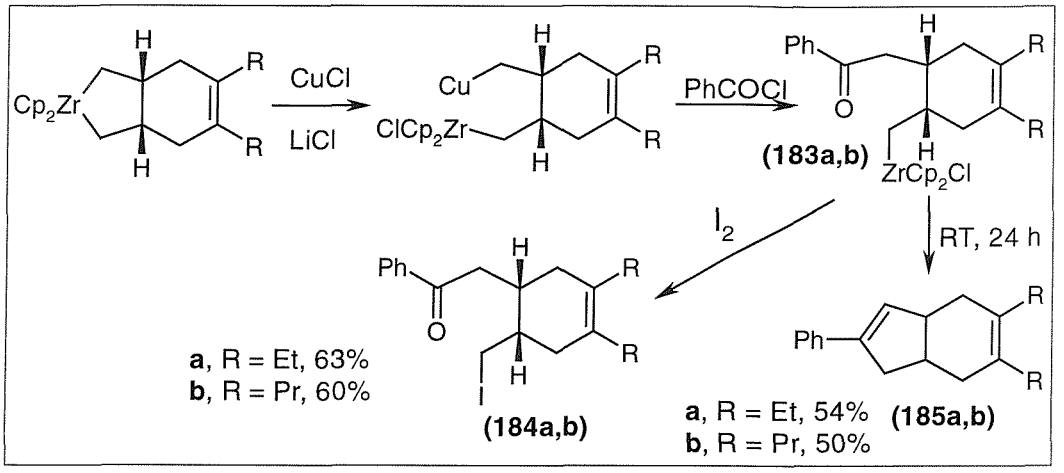
1.4.8: Copper Catalysed Reactions.

The hydrozirconation chemistry described in Section 1.1 provides a wide variety of organometallic reagents. The availability of these reagents can be combined with the attractive features of organocopper chemistry, by transmetallation of zirconium to copper and subsequent reaction.[62] An example from alkyl zirconocene chemistry, of transmetallation to copper and conjugate addition to an enone[63] is shown in Scheme 1.41.



Scheme 1.41 – Conjugate addition of an organocopper to enones.

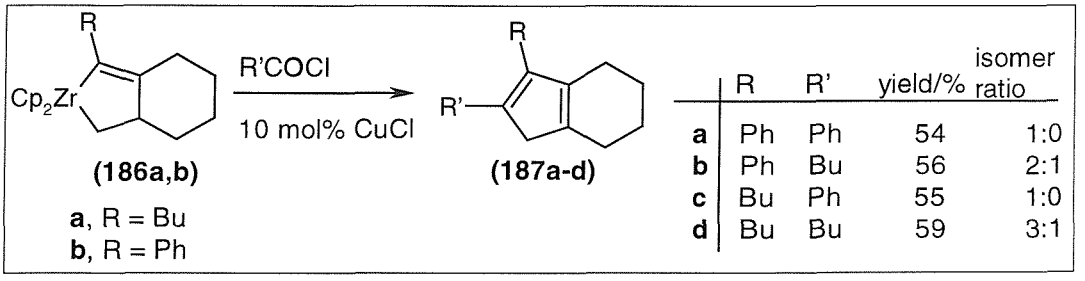
A variety of copper (I) salts and enones can be used in this reaction. This chemistry has been reviewed by Wipf,[9] and zirconabicycle chemistry is detailed further here. Treatment of a zirconacyclopentane with an acid chloride in the presence of catalytic CuCl/LiCl provides an insertion product (**183a,b**) by the mechanism shown[64] (Scheme 1.42). Treatment with iodine provides an iodide (**184a,b**), whereas stirring at room temperature for 24 h provides a bicyclic product (**185a,b**).



Scheme 1.42 – Copper catalysed reaction of an acid chloride with a zirconacycle.

Zirconacycles fused to cyclohexanes rather than cyclohexenes, and other acid chlorides such as ^{i}PrCOCl and EtCOCl can also be used, and yields of up to 85% obtained. For the synthesis of (**185**), from the co-cyclisation precursor, three C-C bonds and 2 rings are formed in one pot.

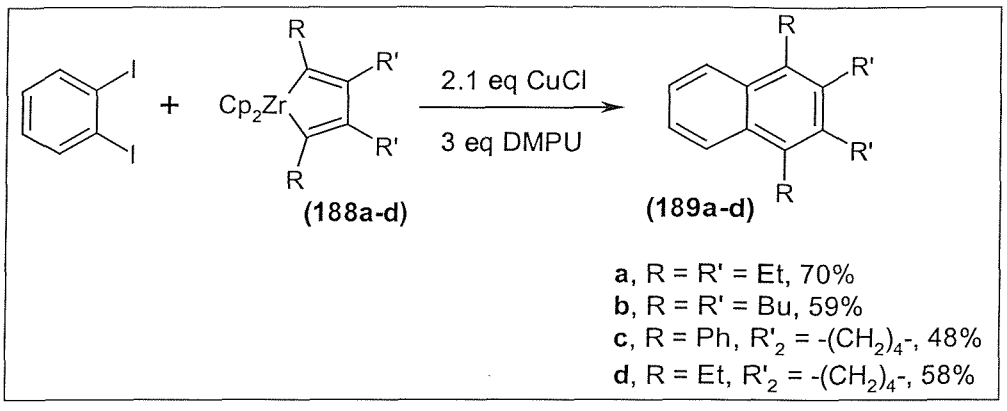
Application of the same copper chemistry to the reaction of zirconacyclopentenes with acid chlorides provides cyclopentadienes[65] (Scheme 1.43). Although mixtures of up to four positional double bond isomers are produced from zirconamonocycles, zirconabicycles such as (**186a,b**) give better selectivity, especially where large substituents are present. The position of the double bonds in the major product, where more than one is produced, is as shown by (**187**).



	R	R'	yield/%	isomer ratio
a	Ph	Ph	54	1:0
b	Ph	Bu	56	2:1
c	Bu	Ph	55	1:0
d	Bu	Bu	59	3:1

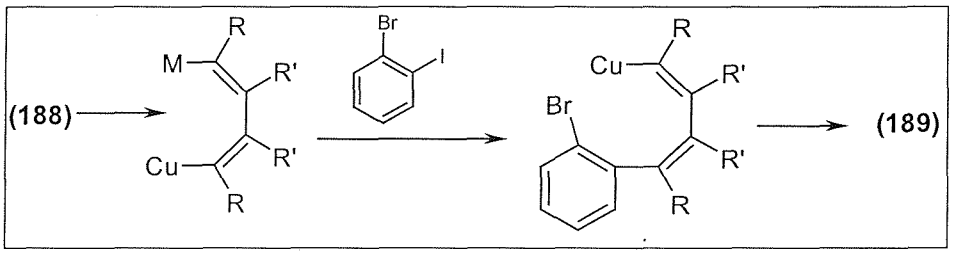
Scheme 1.43 – Cyclopentadiene formation by copper catalysed chemistry.

The reaction of zirconacyclopentadienes with copper (I) salts and subsequent allylation was represented in Scheme 1.16 for the preparation of co-cyclisation precursors for the synthesis of 8-membered rings. A similar reaction with aryl halides has also been reported,[66] and examples of naphthalene formation by this method are shown in Scheme 1.44.



Scheme 1.44 – Naphthalene formation *via* transmetallation to copper.

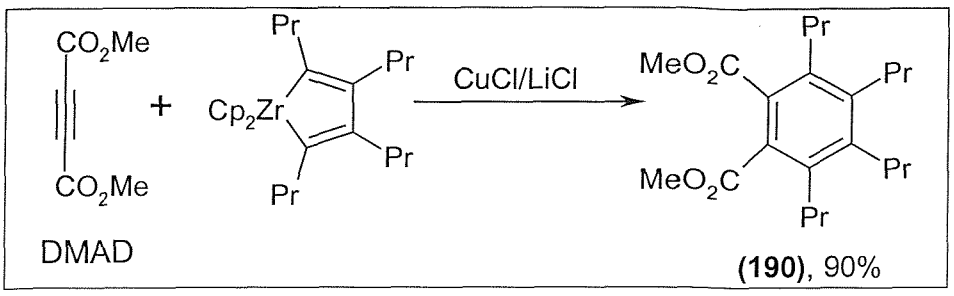
In this reaction a stoichiometric amount of a copper (I) salt and excess DMPU are required to give good yields. Investigation into the mechanism of the reaction showed that dibromobenzene instead of diiodobenzene failed to give an appreciable amount of **(189)**. However, 1-bromo-2-iodobenzene worked well. This suggests a stepwise reaction (Scheme 1.45).



Scheme 1.45 - Stepwise mechanism of naphthalene formation.

The high reactivity of iodide is required for the first, intermolecular step to take place. However, bromide is reactive enough for the second, intramolecular step.

A related route to hexasubstituted benzenes **(190)** has been investigated,[67] a generic example of which is shown in Scheme 1.46.



Scheme 1.46 – Formation of benzenes by zirconium / copper chemistry.

Again, stoichiometric amounts of copper are required, and the reaction probably proceeds stepwise, though the exact order of transmetallation and nucleophilic attack is uncertain. The highly activated alkyne, DMAD is required for reaction to occur. This copper mediated reaction of zirconacyclopentadienes has recently been shown to be successful for zirconabicycles, produced by co-cyclisation of 1,7-diynes.[68]

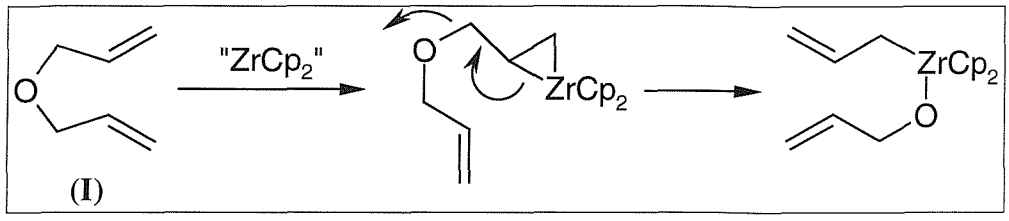
1.5: Conclusions for Elaboration Methods.

In summary, the methods shown for elaboration of zirconacycles complement the variety of co-cyclisation substrates available, opening up the area of zirconium chemistry to the production of a vast amount of highly functionalised compounds. The potential application of this chemistry to further methodology of academic interest, and to the synthesis of biologically active compounds is clear. Much of the work can be performed as one pot, multi-step sequences, starting from simple molecules. The extension of organozirconium chemistry to organocopper chemistry *via* transmetallation combines the advantages of both areas.

Chapter 2: Co-Cyclisation of Alkoxyalkynes – A Novel Synthesis of Spiroketals.

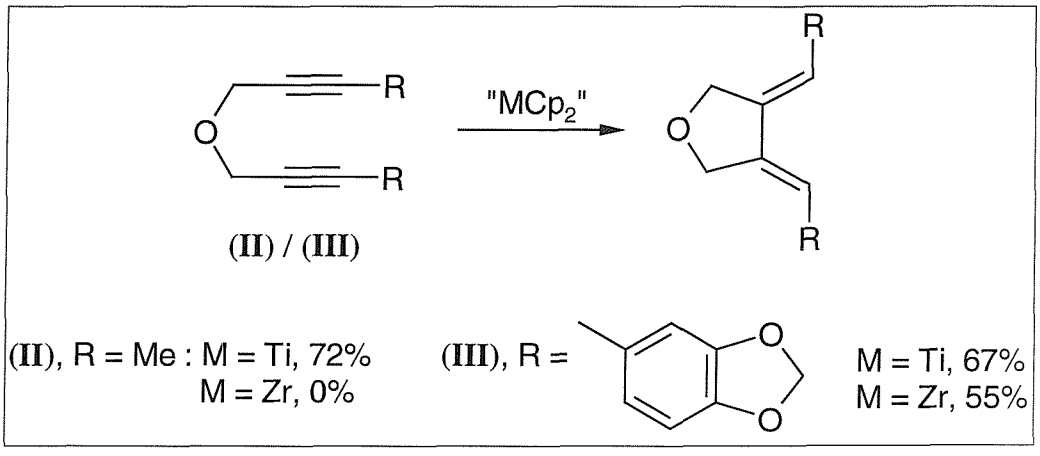
2.1: Introduction.

The synthesis of oxacycles by zirconocene mediated co-cyclisations is rather limited in scope. The simplest oxygen containing diene, diallyl ether (**I**), has been treated with a zirconocene equivalent[1,2] but after initial formation of a zirconacyclopropane, elimination of the β-oxygen occurs leaving an allyl zirconocene (Scheme 2.1).



Scheme 2.1 – Reaction of diallyl ether with zirconocene.

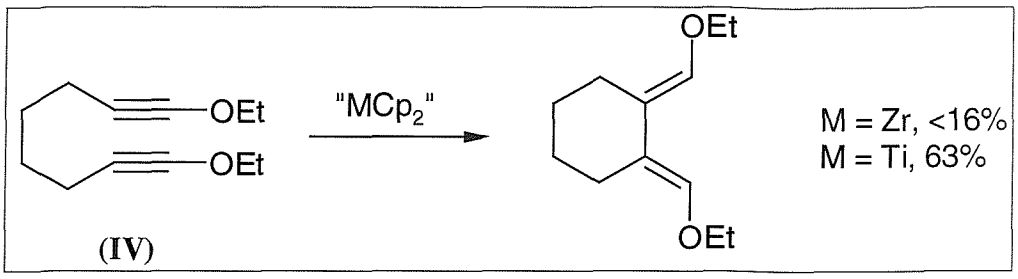
The analogous dipropargylic ether (**II**) likewise fails to cyclise using zirconium, although a titanium reagent is more successful due to its less oxophilic nature.[1] A bulkier propargyl ether (**III**) can be cyclised by zirconocene, though rather forcing conditions (72 h at 40 °C, compared with 2 h at RT for most diynes) are required (Scheme 2.2).



Scheme 2.2 – Cyclisations of dipropargylic ethers.

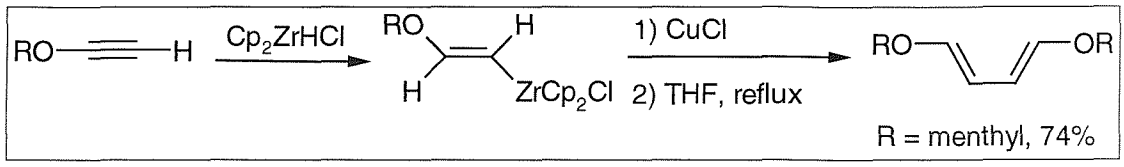
An alternative method of oxacycle formation is the co-cyclisation of substrates where the oxygen atom is adjacent to the acetylene in an enyne or diyne. The substrates are now alkoxyalkynes, and their reaction with zirconocene is known, as shown in the following examples.

The di-alkoxyalkyne (**IV**) has been co-cyclised with Cp_2ZrCl_2 / Mg / $HgCl_2$, providing a cyclohexane with the oxygen atoms outside the ring[1] (Scheme 2.3). However, the equivalent titanocenes again provide better yields.



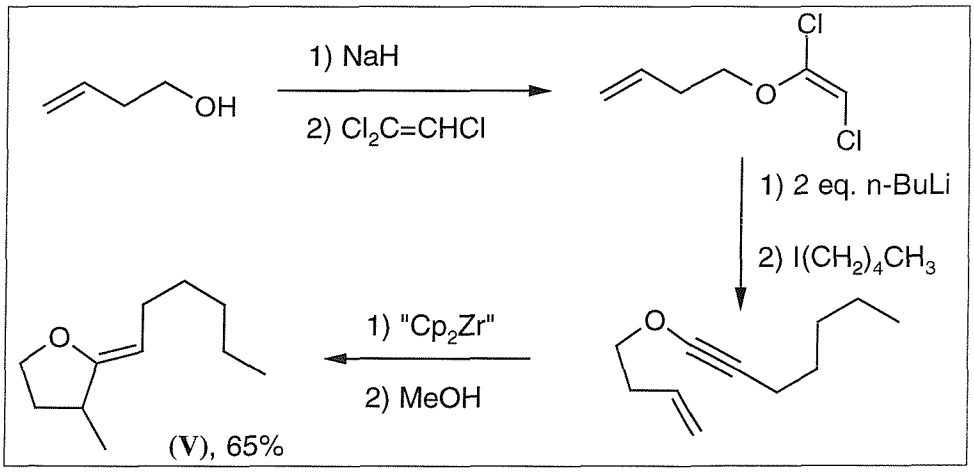
Scheme 2.3 – Co-cyclisation of a di-alkoxyalkyne.

Hydrozirconation of alkoxyalkynes has been used as a route to 1,4-dialkoxy 1,3-dienes, *via* transmetallation of zirconium to copper and subsequent dimerisation[3] (Scheme 2.4).



Scheme 2.4 – Application of hydrozirconation of alkoxyalkynes.

A more recent co-cyclisation of an alkoxyalkyne has been reported within our group by Kemp,[4] who prepared the tetrahydrofuran (**V**) in 65% yield from the corresponding enyne substrate (Scheme 2.5).

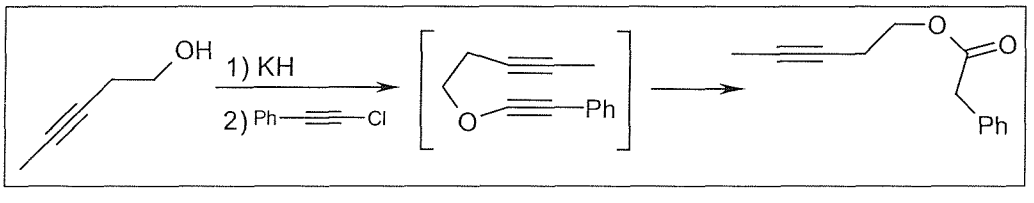


Scheme 2.5 – Kemp's alkoxyalkyne co-cyclisation.

The novel work in this thesis expands on this initial investigation.

2.2: Synthesis of Alkoxyalkyne Substrates.

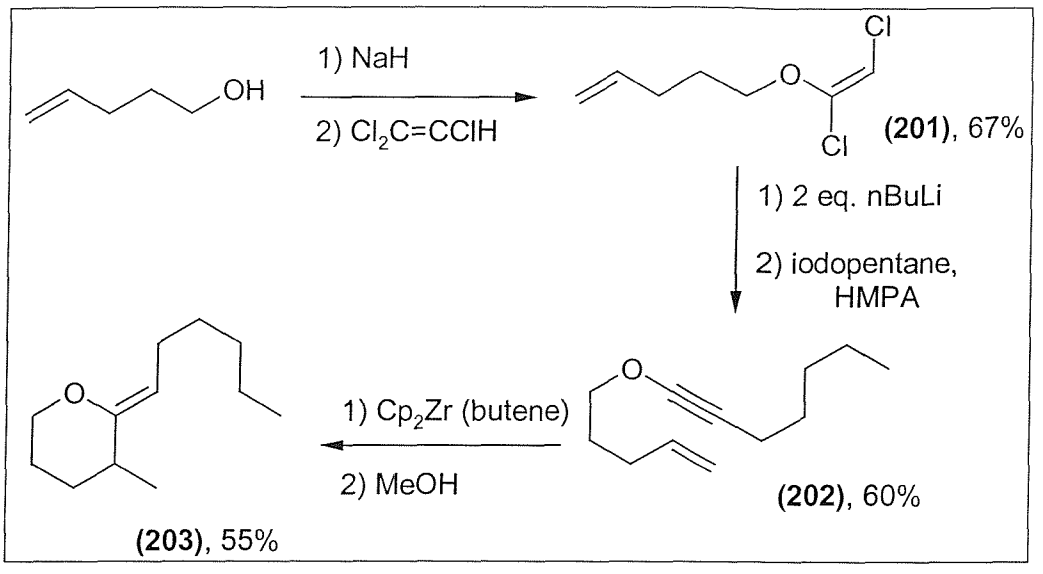
The alkoxyalkynes were prepared by a modified version (Scheme 2.5) of the procedure published by Kann *et al.*[5] in which an alcohol is deprotonated with potassium hydride and reacted with trichloroethylene. In the same pot, the resultant dichlorovinyl ether is converted to the lithium acetylide and this alkylated with an electrophile. For our synthesis, sodium hydride was preferred for the deprotonation, and the dichlorovinyl ethers were isolated. These vinyl ethers proved rather stable, and after up to two years storage at – 20 °C, little or no decomposition was observed. A single distillation sufficed as purification, if required. Conversion to the lithium acetylide and alkylation was performed exactly as reported, and an internal thermometer used to monitor the temperature during butyllithium addition, as decomposition occurs above about –70 °C. Although the reported procedure used three equivalents of iodoethane as the electrophile, the excess of which could be removed later *in vacuo*, we found that with our heavier and more precious iodides, one equivalent was sufficient, with some sacrifice of yield. The product alkoxyalkynes could be purified by column chromatography on neutral alumina, and were generally reacted on within two days. Unfortunately, this procedure for elimination of dichlorovinyl ethers using n-butyllithium only worked for the synthesis of enynes and not diynes. The presence of an alkyne in the starting material resulted in decomposition of the product during butyllithium addition, even when the temperature was strictly controlled. An alternative synthesis of alkoxyalkynes was thus attempted,[6] in which an alkoxide is reacted with 2-chloro-phenylacetylene. This also failed, as the product obtained (Scheme 2.6), was the result of hydrolysis of the alkoxyalkyne. Performing the reaction strictly under argon and with a thoroughly non-aqueous work-up did not overcome the problem.



Scheme 2.6 – Attempt to synthesis yne-alkoxyalkyne.

Our investigations continued with ene-alkoxyalkynes targeted. Having repeated the synthesis of **(V)** (Scheme 2.5) reported by Kemp,[4] the analogous enyne from 4-

penten-1-ol was prepared, which would provide a six membered ring after co-cyclisation. This reaction sequence was successful, providing the tetrahydropyran **(203)** in moderate yield (Scheme 2.7).

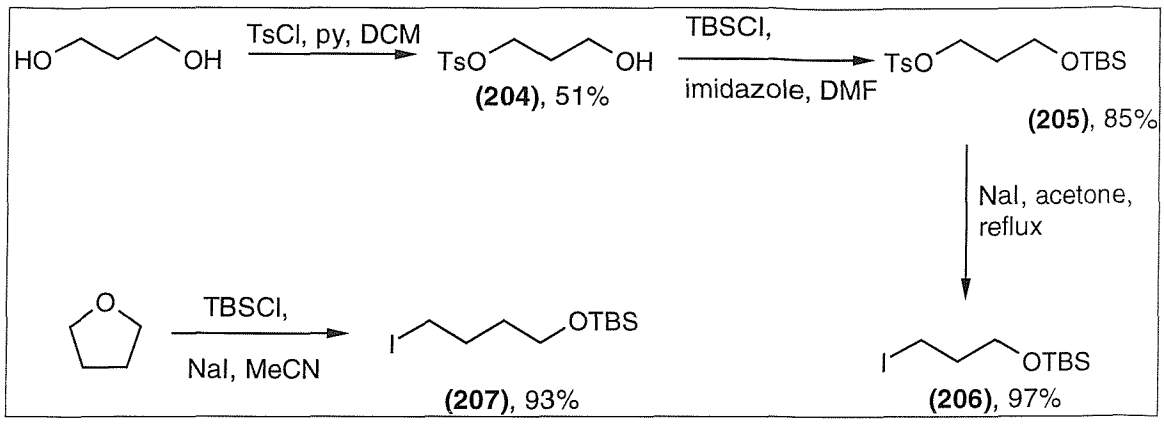


Scheme 2.7 – Synthesis of tetrahydropyran (203) *via* an alkoxyalkyne substrate.

We were pleased to observe good yields at each stage of the sequence, and proceeded to exploit this chemistry.

2.3: Application to Spiroketal Synthesis.

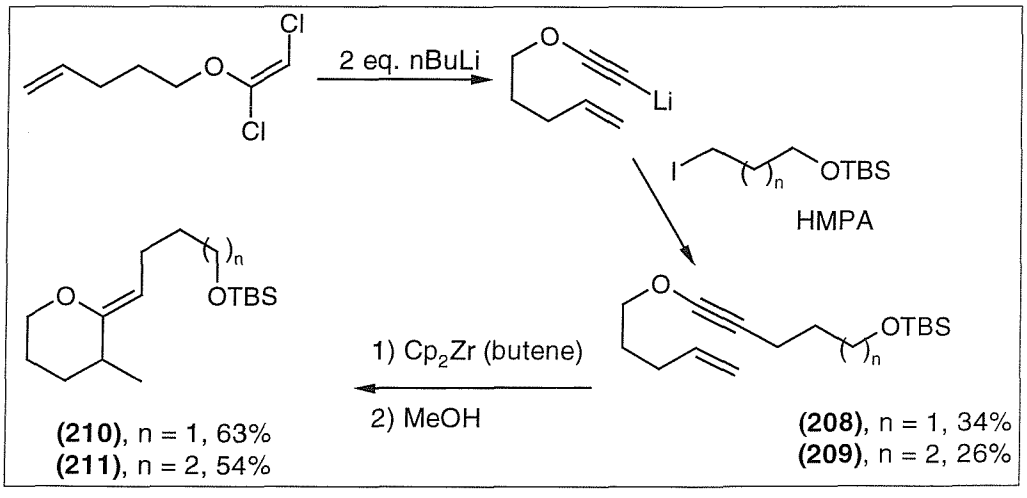
It was decided to extend this chemistry to more interesting systems by employing electrophiles containing some functionality for the alkylation of the alkoxy acetylides. Simple spiroketals are known to be pheromones for insects such as wasps,[7] bees[8] and flies,[9,10] and thus their synthesis is of academic interest. Application of the alkoxyalkyne chemistry to their synthesis is now described. The syntheses require alkyl iodide electrophiles bearing pendant, protected alcohols. Two examples were synthesised in excellent yield, as shown in Scheme 2.8.



Scheme 2.8 – Synthesis of electrophiles (206) and (207).

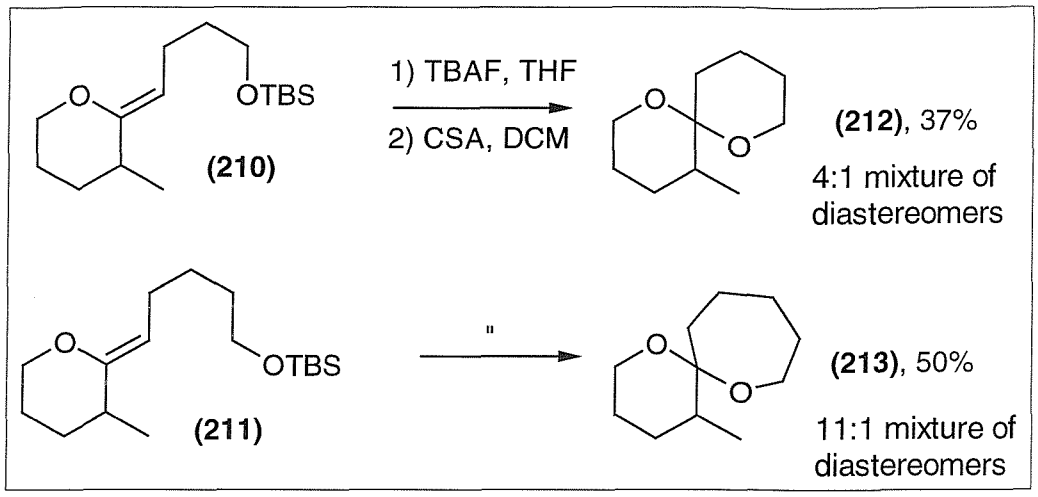
The iodide (**206**) was synthesised in high yield *via* monotosylation of propane 1,3-diol, silyl protection of the alcohol and Finkelstein exchange[11] of the tosylate to afford iodide (**206**). The longer chain iodide (**207**) was prepared by ring opening of tetrahydrofuran and *in situ tert*-butyl dimethylsilyl protection.[12]

The incorporation of these electrophiles into the required alkoxyalkyne substrates proceeded successfully, but in rather low yield. This can probably be explained by the hindered nature of the iodides, by virtue of the large pendant silyl ether group. However, the yields for the cyclisations were encouraging (Scheme 2.9).



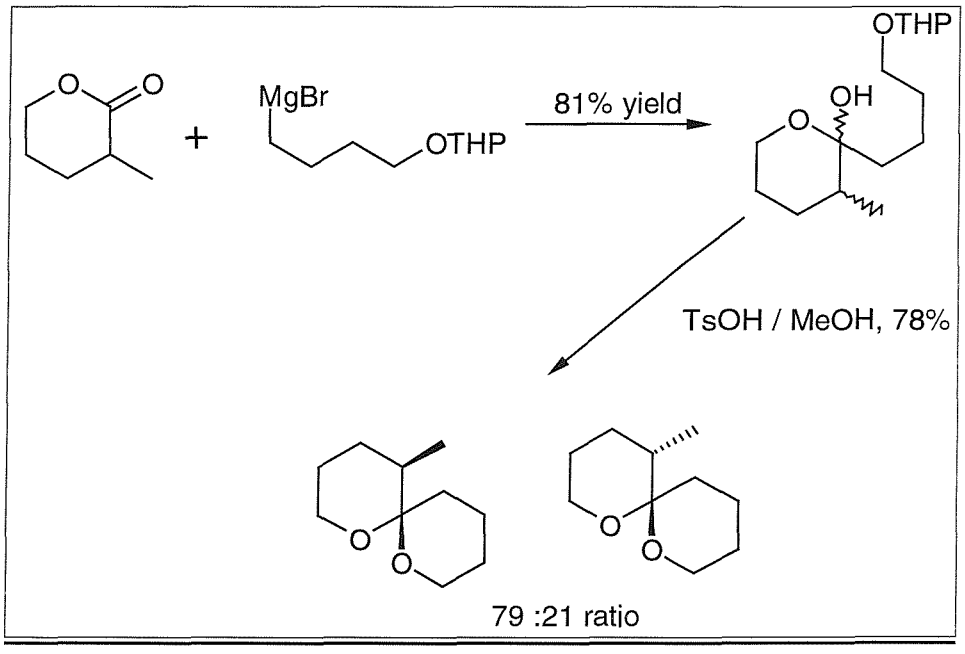
Scheme 2.9 – Synthesis and co-cyclisation of enynes (208) and (209).

The final conversion to the spiroketals requires deprotection of the silyl ether, and acid catalysed ring closure. In practise, TBAF was used to remove the TBS group and treatment of the crude alcohol with CSA in DCM successfully catalysed formation of the second ring within 1 hour at room temperature (Scheme 2.10).



Scheme 2.10 – Conversion of co-cyclisation products to spiroketals (212) and (213).

The spiroketal **(212)** was obtained in moderate yield, and as a 4:1 mixture of diastereoisomers, as determined by GC. An alternative synthesis of **(212)** has been reported previously by Oikawa *et al.*[13,14] with the same diastereomer ratio being observed (Scheme 2.11).



Scheme 2.11 – Synthesis of spiroketal (212) by Oikawa *et al.*

However, the spiro [5.6] dodecane **(213)** is novel, and we were pleased to observe a good diastereomeric ratio of 11:1. Although the identity of each diastereomer has not been determined, this provides good precedent for the synthesis of medium size rings by this method.

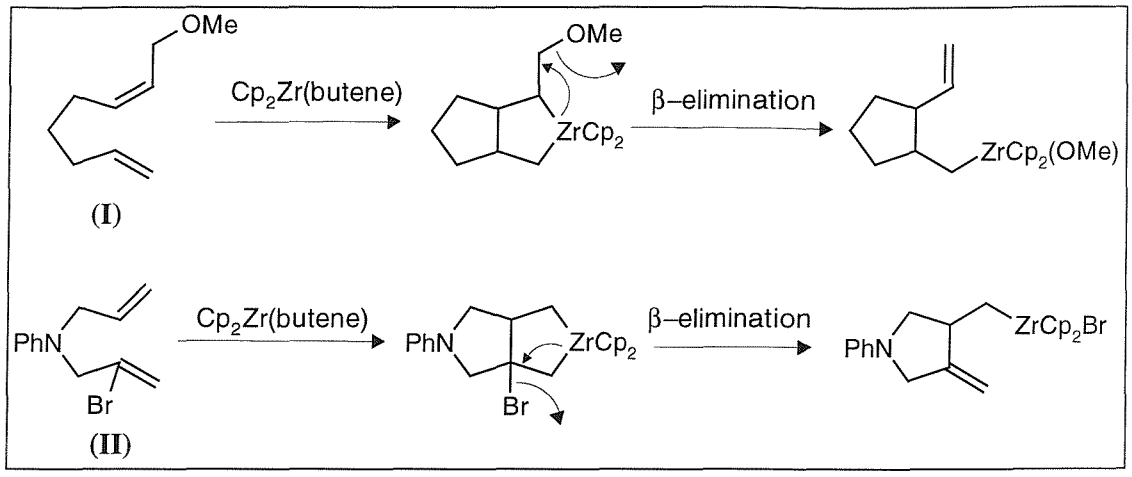
2.4: Conclusions.

We have shown an extension to the range of substrates that can be co-cyclised by zirconium and as a result a viable route to five and six membered oxacycles has been developed. Kemp's work on five membered ring formation has been supplemented by the synthesis of tetrahydropyrans. An interesting and novel approach to the synthesis of spiroketals has also been demonstrated. These results are pleasing, and although the yields are generally low, they offer an alternative to the standard syntheses of spiroketals.[15,16]

Chapter 3: 2-Hetero-Substituted 1,6- and 1,7- Dienes and Enynes – Synthesis of Zirconacycles Bearing β-Leaving Groups.

3.1: Introduction.

In a recent publication, Millward and Waymouth[17] reported the zirconocene mediated co-cyclisation of the dienes **(I)** and **(II)**. The mechanisms are shown in Scheme 3.1.



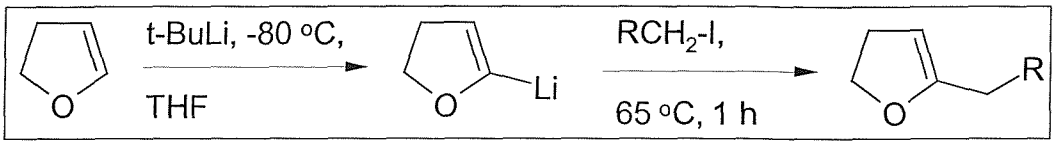
Scheme 3.1 – Waymouth's examples of β-leaving groups.

In both examples, the initially formed zirconacycle has a leaving group at the carbon atom β to zirconium. Elimination of the metal and leaving group from the C-C bond occurs immediately to provide a mono-substituted organozirconium species containing a five membered ring with, in the second example, an exocyclic methylene group. The studies reported were primarily concerned with the mechanistics of the cyclisation and β - elimination reactions of the vinyl bromide, and involved detailed deuteration studies. The analogous reaction of monocyclic zirconocenes is also well known.[18,19]

Herein, we wish to report a substantially greater number and variety of dienes and enynes bearing potential leaving groups at the 2 – position, corresponding to the β - position in the derived zirconacycles. In each case where co-cyclisation is successful, elimination of Zr and the leaving group occurs, leaving an exocyclic methylene group and a single C – Zr bond. The remainder of the chapter is concerned with the synthesis of a wide range of 2-hetero-substituted dienes and enynes, and their co-cyclisations mediated by zirconocene (1-butene).

3.2: Dienes and Enynes Based on Dihydrofurans and Dihydropyrans.

The acidity of the α - vinyl proton in 2,3-dihydrofuran and 3,4-dihydro-2*H*-pyran and the strong nucleophilicity of the corresponding lithiated species was exploited in the synthesis of substrates for zirconocene mediated co-cyclisation. Lithiation of these cyclic enol ethers can be conveniently achieved by treatment with *tert*-butyllithium in THF at –80 °C, and alkylation with alkyl iodides requires no chelating co-solvents[20] (Scheme 3.2).

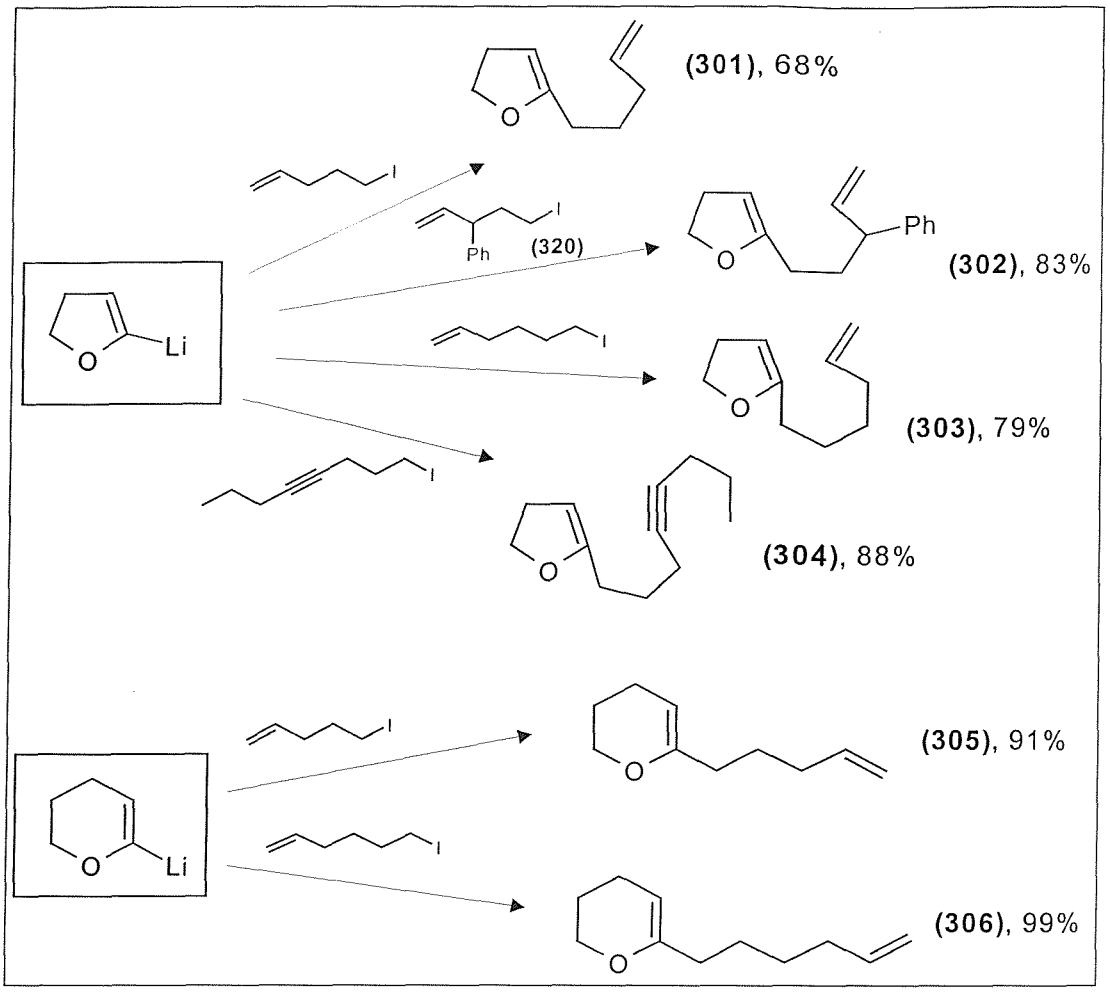


Scheme 3.2 – Lithiation and alkylation of 2,3-dihydrofuran.

The alkylation products often require no purification, though flash chromatography on alumina or Kugelrohr distillation are both convenient. Where the R group contains an unsaturated moiety, the product is a diene or enyne. The oxygen atom in the dihydrofuran ring now takes the role of the heteroatom substituent at the β-position in the resultant zirconacycles.

3.2.1: Synthesis of Substrates.

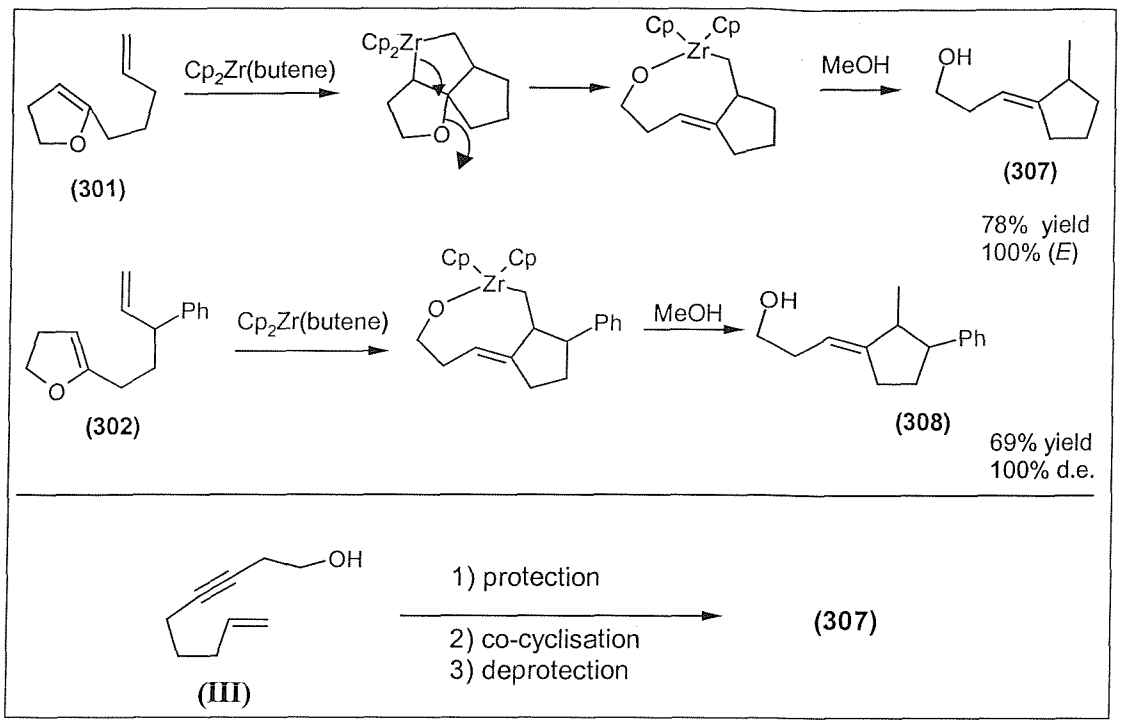
As described above, lithiation of 2,3-dihydrofuran with *tert*-butyllithium and subsequent alkylation with 1-iodo-4-pentene (R = $CH_2CH_2CH{=}CH_2$) provides diene **(301)**. In a similar manner, substrates **(302)** to **(306)** were prepared (Scheme 3.3). Altogether, a range of substrates, covering dihydrofurans, dihydropyrans, 1,6- and 1,7- dienes, and an enyne can be applied to zirconocene mediated cyclisation. Synthesis of iodide **(320)**, used in the preparation of **(302)** is described in Section 3.3.1.



Scheme 3.3 – Synthesis of substrates based on dihydrofuran and dihydropyran.

3.2.2: Co-Cyclisations of Dihydrofurans and Dihydropyrans.

As shown in Scheme 3.4 below, dienes **(301)** and **(302)** cyclise cleanly, and in good yield when treated with 1.1 equivalents of zirconocene (1-butene) to give **(307)** and **(308)** respectively. Diene **(301)** can be seen as an alternative substrate to the enyne **(III)**, which requires protection before the cyclisation step. The dihydrofuran unit possesses, in effect, a protected alcohol and a masked acetylene.



Scheme 3.4 – Cyclisation of dienes (301) and (302); alternative enyne to (301).

It was pleasing to observe complete control of the double bond geometry in these products, and the new chiral centre in **(308)** formed in >98% diastereomeric excess. No minor diastereomer could be seen by NMR or GC. Figure 3.1 shows the investigation of the stereochemistries.

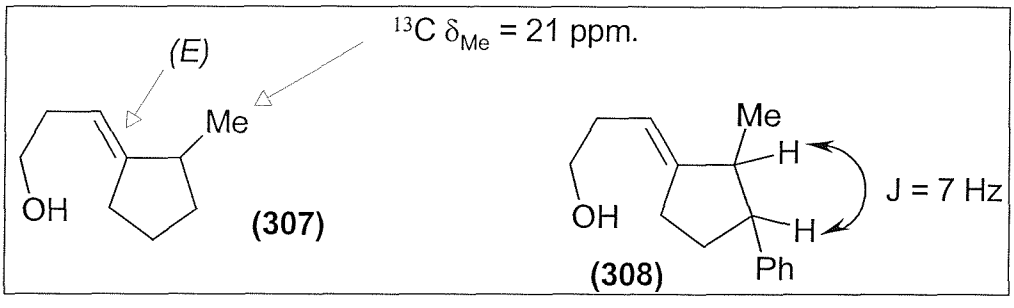
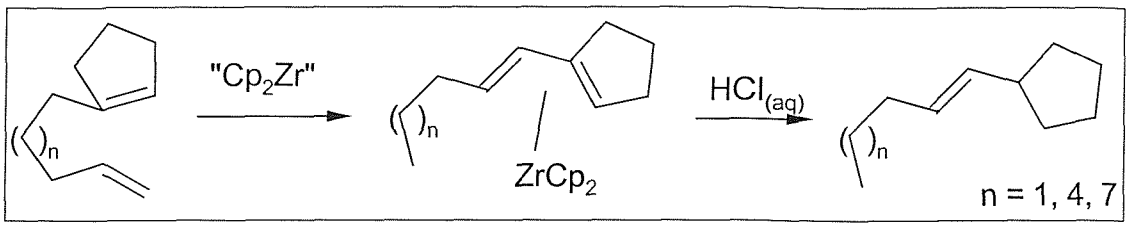


Figure 3.1 – Stereochemistry of (307) and (308).

The double bond geometry is unambiguous, with the ^{13}C NMR chemical shift of the methyl group, of 21 ppm indicative of (*E*) stereochemistry,[21] consistent with *anti* elimination of the zirconacycle. A chemical shift of around 13 ppm would be expected for the (*Z*) isomer, the large difference being accounted for by the proximity of the methyl group to the alcohol side chain in the (*Z*) case. Unfortunately, the relationship between the Me and Ph groups in **(308)** is in doubt, as the coupling constant of 7 Hz is ambiguous. The stereochemistry can be tentatively assigned as *anti*, by comparison with compound **(338)**, discussed later.

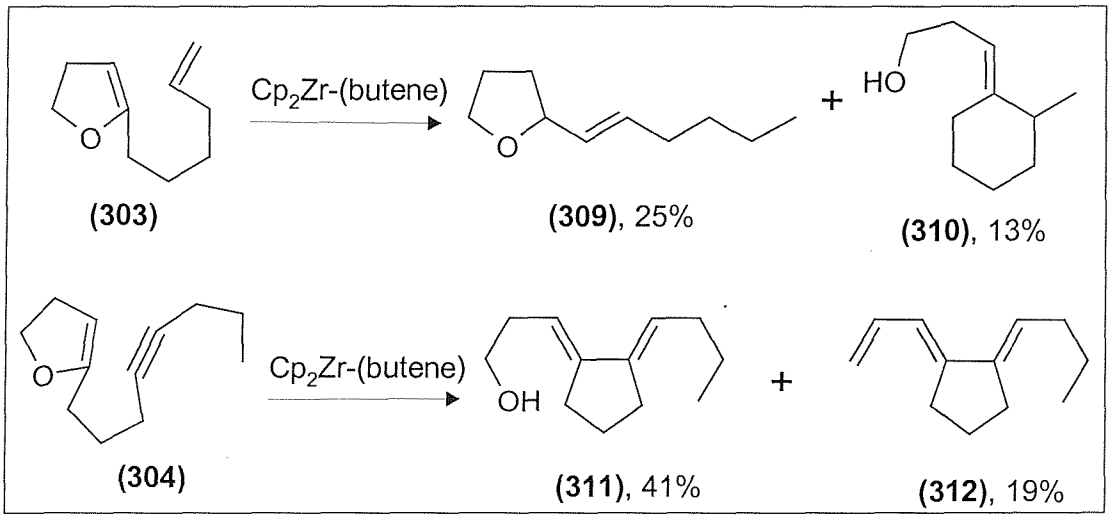
The success in cyclisation of **(301)** is in marked contrast to the failure of the hydrocarbon analogue investigated by Maye and Negishi,[22] which is shown in Scheme 3.5.



Scheme 3.5 – Maye and Negishi's regioisomeration.

We attribute the difference in reactivity to the more electron rich nature of the enol ether double bond in **(301)**, which will favour cyclisation, compared with the cyclopentene. The migration of the double bond seen in Scheme 3.5 is observed with three of our dienes.

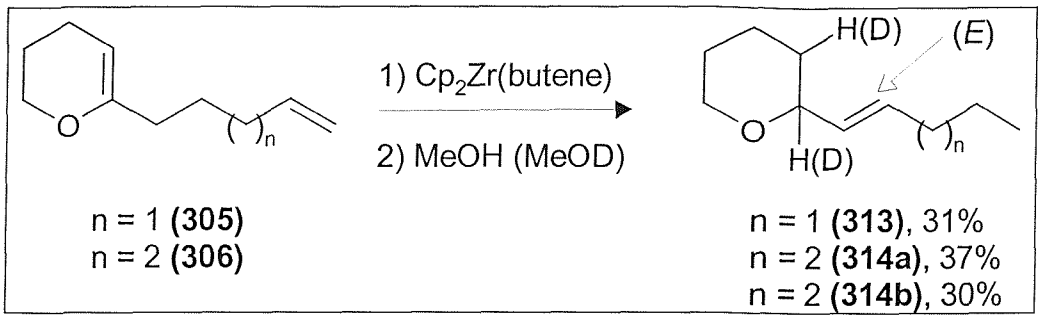
Treatment of 1,7-diene **(303)** with zirconocene (1-butene) provided a small amount (13%) of the desired cyclohexane **(310)**, along with 25% of the by-product **(309)**[23] explained later, whereas enyne **(304)** cyclised to give 41% of the desired dienol **(311)** and 19% of an elimination product **(312)**. NMR analysis of the crude reaction, in the latter case, showed the elimination to have taken place during the reaction, and not during silica gel chromatography (Scheme 3.6).



Scheme 3.6 – Cyclisation of 1,7-diene (303) and enyne (304).

The regioisomerisation mechanism accounting for the formation of **(309)** also accounts for the products obtained when **(305)** and **(306)** are treated with zirconocene (1-butene) and the organozirconium product subjected to protic quench (Scheme 3.7).

The double bonds produced in each of these products are exclusively *trans*, with a coupling constant between the vinyl protons of 15.5 Hz.



Scheme 3.7 – Reactions of dihydropyran based dienes with zirconocene (1-butene).

Interestingly, the observed product **(314a)** was the target of a recent publication by Balzano *et al.*[24] due to its homology to the natural product roseoxide.[25]

Analysis of the 1-D and correlation NMR spectra of these undesired products, and the deuterium quenched product **(314b)** from the organozirconium resulting from **(306)**, allowed confirmation of the mechanism taking place, and is consistent with the results of Maye.[22] After initial bonding of zirconium to the terminal C=C double bond, if cyclisation is to occur, a ring expansion of the zirconacyclopropane onto the endocyclic, enol double bond must take place. However, the competing pathway of β-hydride elimination of the allylic hydrogen takes place. This β-hydride elimination is accompanied by migration of zirconium along the chain until it comes into conjugation with the internal double bond, producing an η^4 complex (Scheme 3.5), and providing exclusively the *trans* double bond. The more substituted double bond is protonated on quench, again as seen by Maye. Our explanations for the β-hydride pathway dominating over co-cyclisation in these cases are as follows. Firstly, the slower formation of a 6-membered ring compared with 5-membered accounts for the difference between the zirconium mediated reactions of 1,6-dienes **(301)** and **(302)** (cyclisation) and 1,7-dienes **(303)** and **(306)** (regioisomerisation). Secondly, the C=C double in the dihydrofuran ring of **(301)** is sufficiently more strained, and therefore more reactive, than the less strained therefore less reactive dihydropyran ring in **(305)**, and allows co-cyclisation of **(301)** to take place.

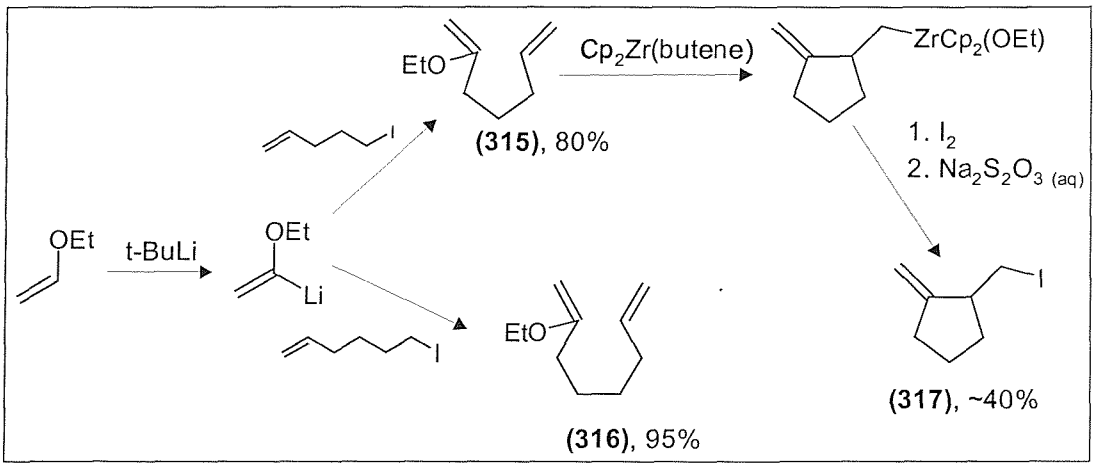
The success with the first two of these substrates, **(301)** and **(302)**, and an explanation for an alternative reaction pathway in the other substrates, showed that this chemistry is promising, and should be pursued. A move from cyclic enol ethers to acyclic enol ethers is described in the next section.

3.3: Co-Cyclisation Substrates Based on Ethyl Vinyl Ether.

The failures of the previous cyclisations were put down in part to the lack of reactivity of the double bond in the dihydrofuran or dihydropyran ring. In fact, it is known that trisubstituted double bonds provide poor substrates due to their hindered nature.[2] A disubstituted analogue can be prepared using ethyl vinyl ether instead of dihydrofuran. The α-vinyl proton of ethyl vinyl ether can likewise be removed using *tert*-butyllithium, resulting in another excellent nucleophile, 1-ethoxy vinyl lithium[26] (EVL) (Scheme 3.8). Reaction of this species with aldehydes or alkyl iodides provides a variety of viable substrates for zirconium mediated cyclisation. The synthesis of these substrates is now discussed.

3.3.1: Synthesis of Dienes Based On Ethyl Vinyl Ether.

The simple dienes 2-ethoxy-1,6-heptadiene **(315)** and 2-ethoxy-1,7-octadiene **(316)** were first investigated. Both were synthesised in excellent yield. The expected co-cyclisation products would be C-7 and C-8 hydrocarbons respectively, which would be volatile and thus difficult to isolate. To introduce some mass into the products, iodine quench of the organozirconium products was attempted (Scheme 3.8).

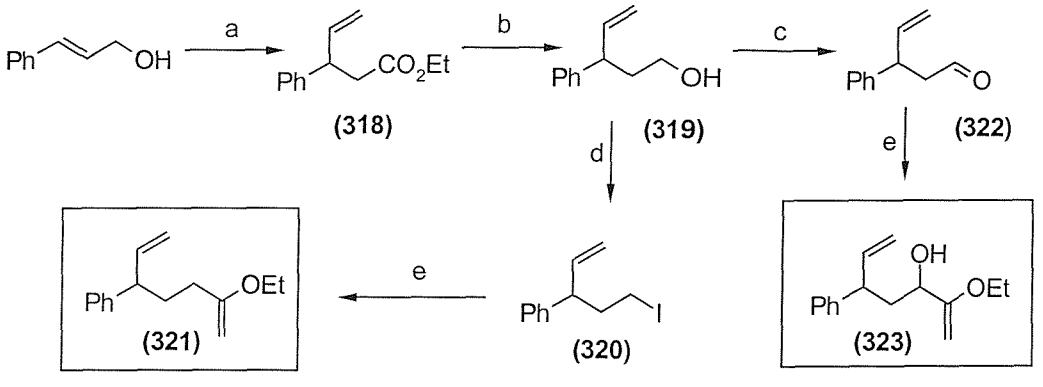


Scheme 3.8 – Synthesis of dienes (315) and (316); cyclisation of (315).

The iodide **(317)** could be isolated in ~40% yield, but proved rather unstable, and decomposed on distillation, or chromatography on alumina or silica. This result did however provide sufficient proof of the cyclisation being successful. No identifiable

product could be obtained from co-cyclisation followed by protic or iodine quench of **(316)**.

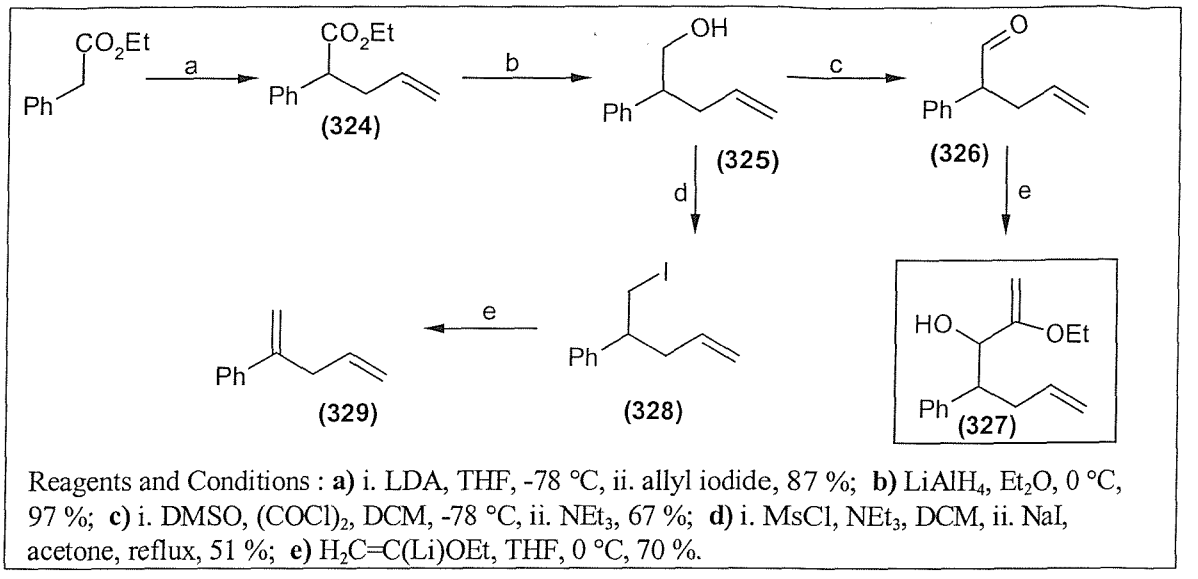
To introduce some molecular weight into the potential cyclisation products, a variety of substituted substrates were synthesised, as shown in Schemes 3.9 to 3.12. Cinnamyl alcohol provided the starting material for the first two dienes **(321)** and **(323)** (Scheme 3.9). The Johnson ortho ester variant[27] of the Claisen rearrangement[28] provides ester **(318)**, with subsequent reduction to the alcohol, mesylation and conversion to the iodide producing 1-iodo-3-phenyl-4-pentene **(320)**. This is a suitable electrophile for reaction with ethoxy vinyl lithium (EVL), and provides diene **(321)**. Alcohol **(319)** can also be oxidised to the aldehyde **(322)** by treatment with pyridinium chlorochromate, or under Swern conditions.[29, 30] The latter proved cleaner and higher yielding. Diene **(323)** is the product of attack of EVL on **(322)**, and is obtained as a 1:1 mixture of diastereomers.



Reagents and Conditions : **a)** $EtCO_2H$ (cat.), $MeC(OEt)_3$, 130 °C, 81 %; **b)** $LiAlH_4$, Et_2O, 0 °C, 81 %; **c)** i. DMSO, $(COCl)_2$, DCM, - 78°C, ii. NEt_3, 83 %; **d)** i. MsCl, NEt_3, DCM, -40 °C, ii. NaI, acetone, reflux, 61 %; **e)** $H_2C{=}C(Li)OEt$, THF, 0 °C, 72 – 81 %.

Scheme 3.9 – Synthesis of dienes (321) and (323).

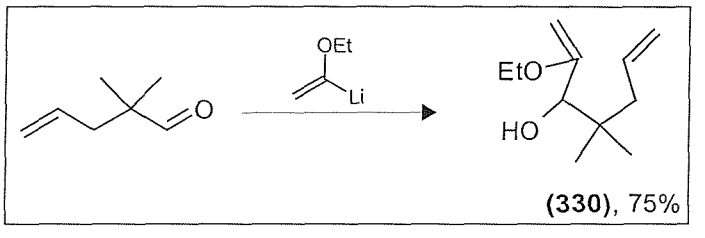
An analogous alcohol **(327)** can be synthesised as shown in Scheme 3.10. LDA deprotonation of ethyl phenyl acetate, followed by alkylation with allyl iodide[31] provides ester **(324)** which is converted to diene **(327)** by an identical route to that of **(318)** to **(323)**. In this case, the product is a single diastereomer.



Reagents and Conditions : **a)** i. LDA, THF, -78 °C, ii. allyl iodide, 87 %; **b)** $LiAlH_4$, Et_2O, 0 °C, 97 %; **c)** i. DMSO, $(COCl)_2$, DCM, -78 °C, ii. NEt_3, 67 %; **d)** i. MsCl, NEt_3, DCM, ii. NaI, acetone, reflux, 51 %; **e)** H_2C=C(Li)OEt, THF, 0 °C, 70 %.

Scheme 3.10 – Synthesis of diene (327); failure of displacement of iodide from (328).

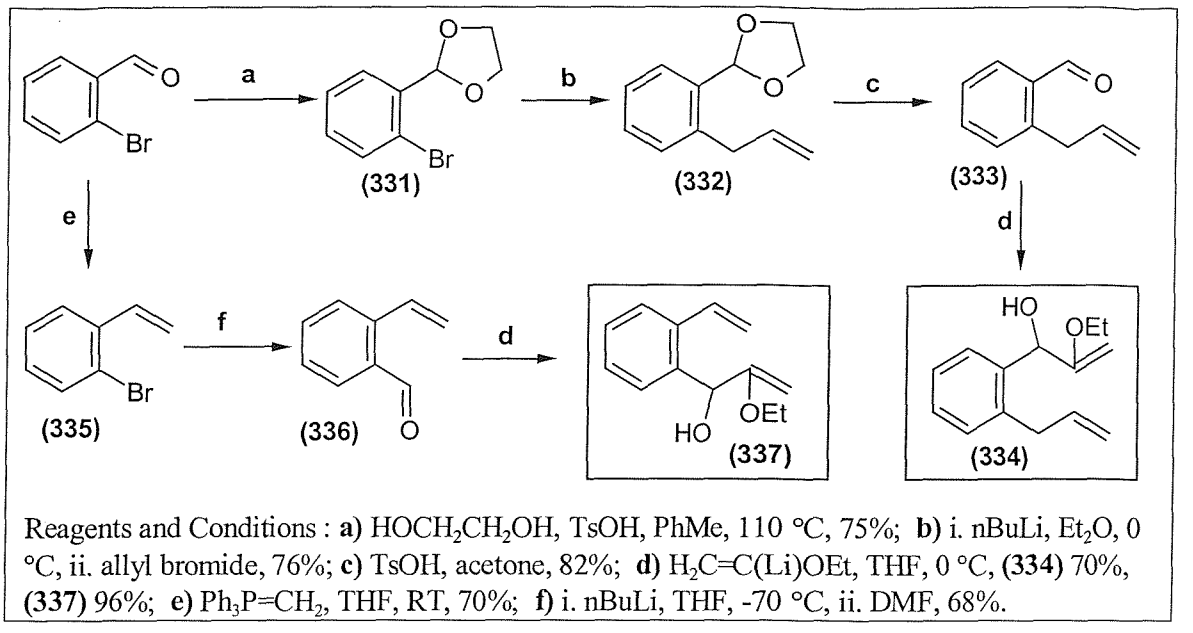
Reaction of EVL with **(328)** to afford a novel diene failed, due to elimination of HI revealing a double bond conjugated to the phenyl group in **(329)**. However, conversion of a commercially available aldehyde to the novel *gem*-dimethyl substituted diene **(330)** proceeded successfully and in good yield (Scheme 3.11).



Scheme 3.11 – Synthesis of diene (330).

To introduce some variety into the range of substrates to be co-cyclised, two aromatic back-boned dienes **(334)** and **(337)** were prepared, as shown in Scheme 3.12.

Starting from commercially available 2-bromobenzaldehyde, sequential acetal formation, halogen – metal exchange from bromide to lithium, alkylation with allyl bromide, and acetal deprotection provided 2-allyl benzaldehyde[32] **(333)**. Finding conditions for the lithiation of bromide **(331)** took some experimentation, with the combination of n-butyllithium in ether at 0 °C proving optimal. Reaction of aldehyde **(333)** with ethoxy vinyl lithium gives the novel 1,7-diene **(334)**.



Reagents and Conditions : **a)** $HOCH_2CH_2OH$, TsOH, PhMe, 110 °C, 75%; **b)** i. nBuLi, Et_2O, 0 °C, ii. allyl bromide, 76%; **c)** TsOH, acetone, 82%; **d)** $H_2C{=}C(Li)OEt$, THF, 0 °C, **(334)** 70%, **(337)** 96%; **e)** $Ph_3P{=}CH_2$, THF, RT, 70%; **f)** i. nBuLi, THF, -70 °C, ii. DMF, 68%.

Scheme 3.12 – Synthesis of aromatic back-boned dienes (334) and (337).

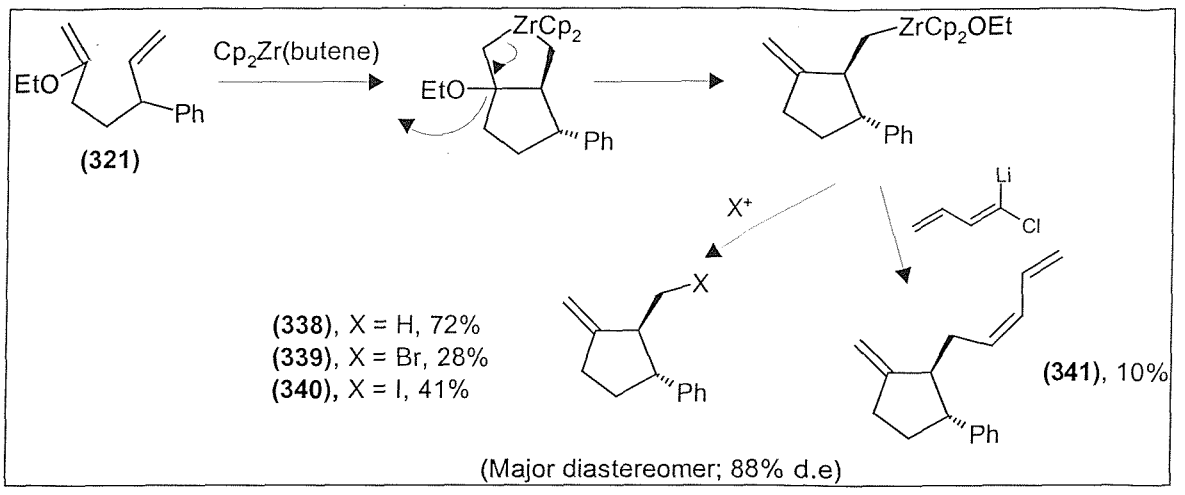
An analogous 1,6-diene **(337)** can also be synthesised from 2-bromobenzaldehyde, by successive Wittig methylenation, metal – halogen exchange, alkylation with *N,N*-dimethyl formamide[33] and reaction of the resultant 2-vinyl benzaldehyde **(336)** with 1-ethoxy vinyl lithium.

The co-cyclisation of each of the dienes described is discussed in the next section.

3.3.2: Co-Cyclisation of Dienes Based on Ethyl Vinyl Ether.

Having in hand several diene substrates with sufficient molecular mass to allow isolation of the protic quenched organozirconium products, their zirconocene mediated co-cyclisations were investigated. As a result of the substituents present in the dienes, the issue of diastereoselectivity in the cyclisations was raised.

Cyclisation of **(321)** using 1.1 equivalents of zirconocene (1-butene) and subsequent *in situ* elimination of the ethoxy group provides a monosubstituted organozirconium reagent, which has been quenched in a variety of ways (Scheme 3.13).



Scheme 3.13 – Cyclisation and variety of elaborations of diene (321).

Co-cyclisation / elimination and protic quench proceeded in good yield to provide cyclopentane **(338)**. The phenyl group induces the *anti* relative stereochemistry of the newly generated stereocentre to the extent of an 88% diastereomeric excess, corresponding to a 17:1 mixture, as determined by gas chromatography analysis on the crude reaction product. Elaboration with NBS or iodine provided the corresponding halides **(339)** and **(340)** in poor yield. Insertion of the carbenoid 1-chloro-1-lithio-1,3-butadiene[34] into the intermediate C – Zr bond provided a triene **(341)** in a meagre 10% isolated (12% GC) yield. This result is discussed in detail in Section 3.4.3. Oxygen quench[35] to give an alcohol failed, with only the protic quenched material obtained after aqueous work-up. An attempt at elaboration of the organozirconium by the method of Wipf,[36] whereby transmetallation from Zr to Cu is followed by conjugative Michael addition to an enone also failed. The hindered nature of the organometallic may account for this, as the original examples were performed on straight chain reagents. The relative stereochemistry of the major isomer of **(338)** was determined by high field NMR (Figure 3.2).

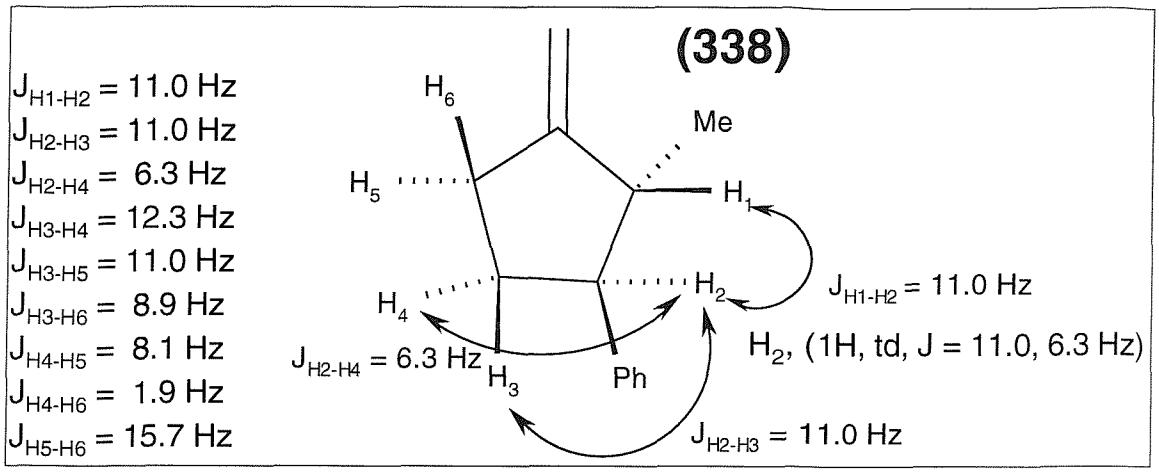
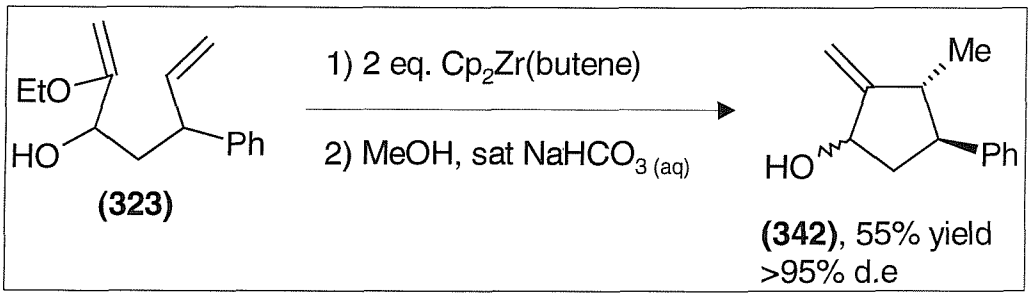


Figure 3.2 – Determination of the relative stereochemistry of (338), major isomer.

All of the coupling constants shown could be determined after assignment of the signals by correlation experiments, then by the splitting patterns in the resolution enhanced proton NMR spectrum obtained at 400 MHz. The H_1-H_2 coupling constant of 11 Hz is unambiguous, as all of the other couplings can be accounted for.

The hydroxyl bearing diene (**323**) is a 1:1 mixture of diastereoisomers, as expected, but we were pleased to observe complete stereocontrol during the cyclisation to give cyclopentanol (**342**) in 55% yield (Scheme 3.14). No sign of a minor diastereomer could be detected by either NMR or GC. The presence of the free hydroxyl group in the diene made it necessary to use two equivalents of zirconocene (1-butene) in the cyclisation, as the first equivalent reacts with the alcohol. This is equivalent to an *in situ* protection.

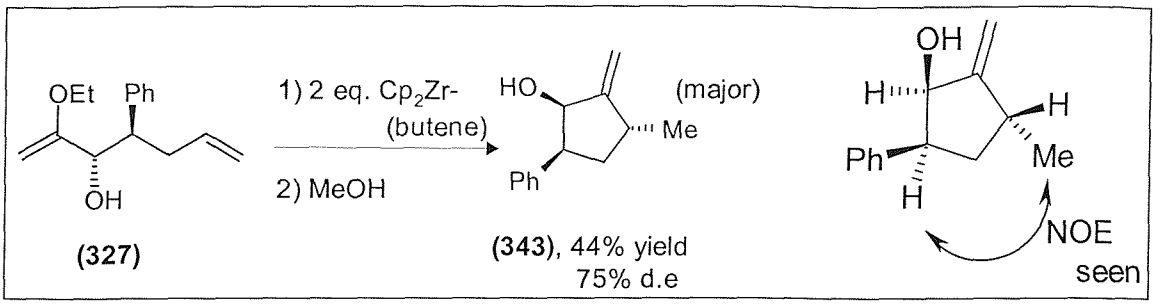


Scheme 3.14 – Cyclisation of diene (323) to give cyclopentanol (342).

The coupling constant between the protons α to the Ph and Me groups was again 11 Hz, confirming the expected *trans* relationship.

Where the phenyl group in (**323**) is adjacent to the newly formed stereocentre, giving a >95% d.e. of the product, in diene (**327**) the phenyl group is one carbon atom further removed, and the diastereocontrol of the cyclisation suffers accordingly (Scheme

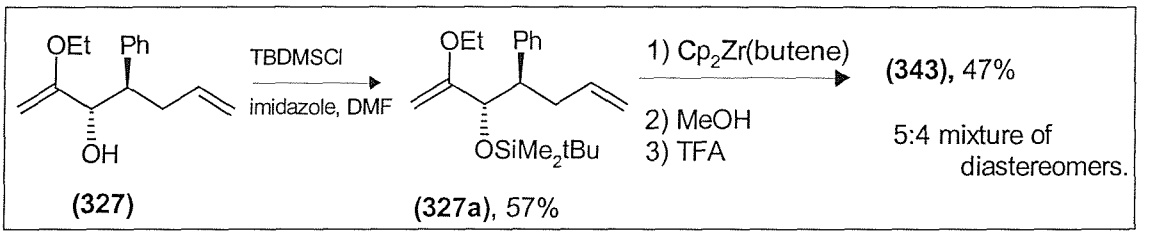
3.15). Cyclopentanol **(343)** was obtained in a modest 44% yield, and as a 7:1 mixture of diastereomers, epimeric at the methyl group.



Scheme 3.15 – Cyclisation of diene (327), determination of stereochemistry.

The relationship shown between the Ph and OH groups is based on the expected *anti* configuration in the diene **(327)**. GOESY NMR analysis showed an NOE in the major isomer, seen in the methyl group when the CHPh proton is irradiated, suggesting that this hydrogen atom is on the same face of the ring as the methyl group.

An interesting difference in the stereospecificity of the cyclisation reaction is seen when the hydroxyl group in **(327)** is protected as its *tert*-butyldimethylsilyl ether **(327a)**. The protection can be performed under the standard conditions (Scheme 3.16).



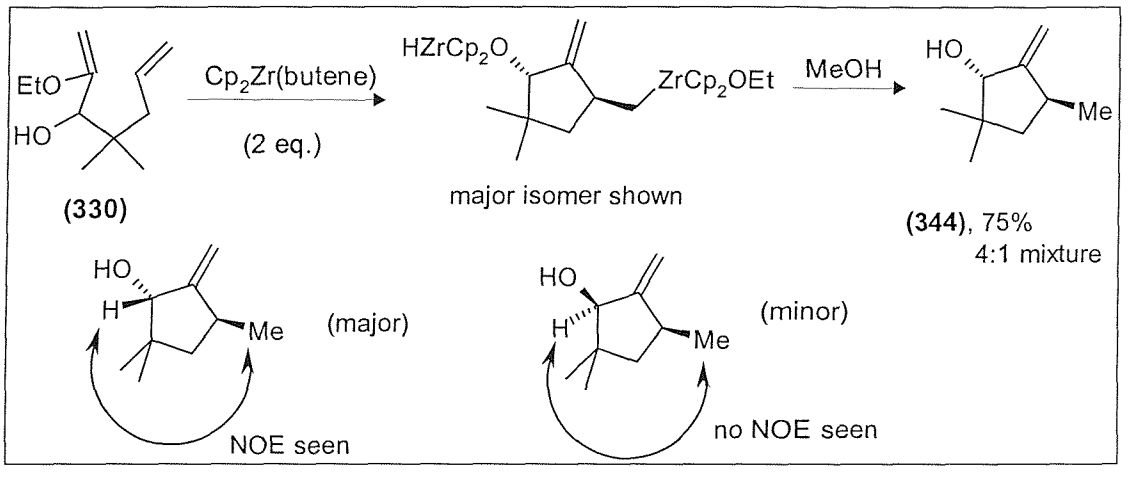
Scheme 3.16 – Cyclisation of TBS protected alcohol (327a).

Co-cyclisation of **(327a)**, using one equivalent of zirconocene, followed by removal of the silicon protecting group with trifluoroacetic acid, provides the same cyclopentanol **(343)**, but as a 5:4 mixture of diastereomers. The difference may be solely due to the larger size of $ZrCp_2H$ compared with TBS, or some interaction between the zirconium acting as a protecting group and that mediating the cyclisation.

The final straight chained diene **(330)** was successfully converted into cyclopentanol **(344)**, when treated with two equivalents of zirconocene (1-butene), and the resultant organozirconium compound subjected to methanolysis (Scheme 3.17). The diastereomer ratio (4:1) of the product was again determined by GC, and the relative stereochemistry by GOESY analysis on the mixture of diastereomers, which were

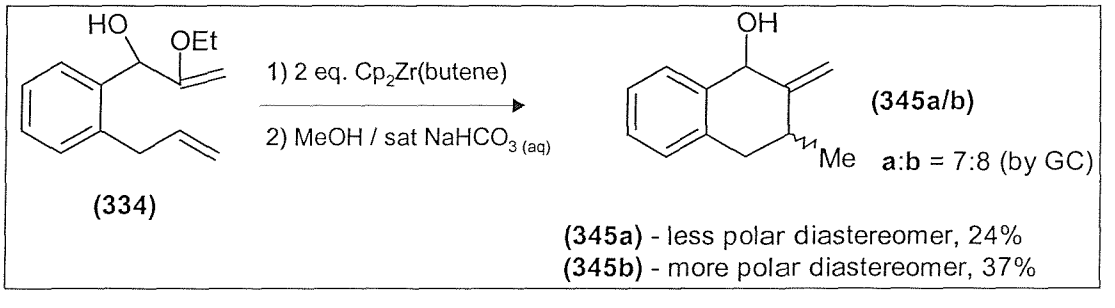
inseparable by chromatography. The signals for the C**H**-OH proton of each diastereomer were distinct from each other in the NMR spectrum, and irradiation of each in turn provided the stereochemical information. When this methylidine proton in the major isomer was irradiated, an effect was seen in the methyl group. This was not the case for the minor isomer, suggesting that the major diastereomer bears the C**H**-OH hydrogen on the same face of the ring as the methyl group.

It should be noted that in this case, the hydroxyl group alone is controlling the stereochemistry of the new stereogenic centre, whereas in the previous examples a bulkier phenyl group has been present. The *gem*-dimethyl group may be having an effect by locking the conformation of the ring. The favourable effect of *gem*-dimethyl groups in co-cyclisations has previously been seen by Rousset *et al.*[2] The same report also detailed co-cyclisation of a diene analogous to **(330)** where the ethoxy group is missing. A diastereomer ratio of 3:1 was obtained in that case.



Scheme 3.17 – Cyclisation of diene (330); determination of relative stereochemistry.

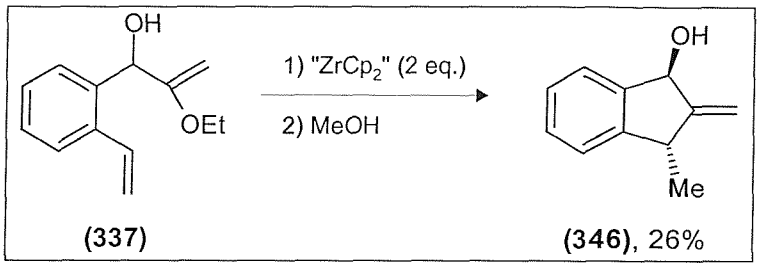
The aromatic back-boned 1,7-diene **(334)** was also successfully co-cyclised using 2 equivalents of zirconocene (1-butene), producing a mixture of diastereomeric solid tetrahydronaphthalenols **(345a/b)** in 61% total yield (Scheme 3.18).



Scheme 3.18 – Co-cyclisation of diene (334) to bicycles (345a/b).

Unfortunately, the diastereocontrol was poor, with an 8:7 mixture being obtained, as determined by GC analysis of the crude product. However, the diastereomers were separable from each other by careful chromatography, though presence of a small quantity of an almost co-polar impurity necessitated some sacrifice of yield in order to obtain pure material. Due to the lack of stereoselectivity no attempt was made to determine the stereochemical identity of each isomer.

Co-cyclisation of the analogous aromatic 1,6-diene **(337)** to provide the solid indanol **(346)** was achieved in a somewhat poorer yield of 26%. However, this product was found to be a single diastereomer (Scheme 3.19). Unfortunately, the relative stereochemistry could not determined conclusively by GOESY experiments. The stereochemistry shown is that assumed.



Scheme 3.19 – Co-cyclisation of aromatic 1,6-diene (337).

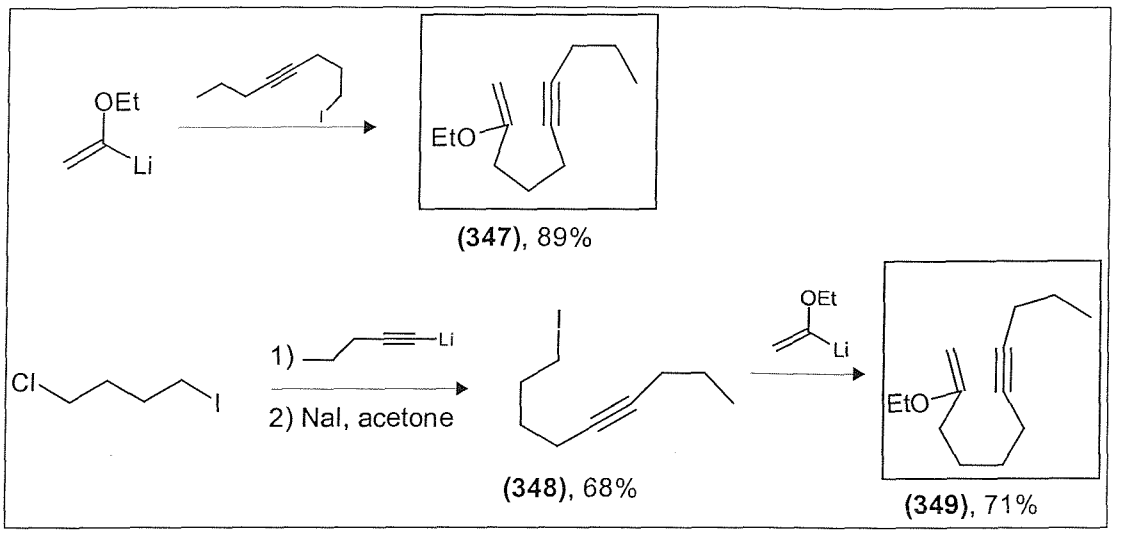
The differences in the cyclisations of **(334)** and **(337)** are noteworthy. Whereas the non-backboned 1,6-diene **(315)** and other straight chained 2-ethoxy-1,6-dienes cyclise successfully, but 1,7-diene **(316)** failed, the aromatic backbone causes a reverse in the reactivity. The backbone in **(334)** templates the cyclisation, by placing the double bonds in close proximity making cyclisation more favourable. The 6,6-fused ring system is also rather unstrained. The ring strain in **(346)** resulting from a benzene ring fused to a cyclopentane may prefer side reactions, accounting for the poor yield, whereas the lack of freedom results in the hydroxyl group inducing complete 1,3-stereoinduction of the newly formed stereogenic centre.

3.3.3: Synthesis of Enynes From Ethyl Vinyl Ether.

The simple unsubstituted enynes **(347)** and **(349)** were synthesised by the standard method, as shown in Scheme 3.20.

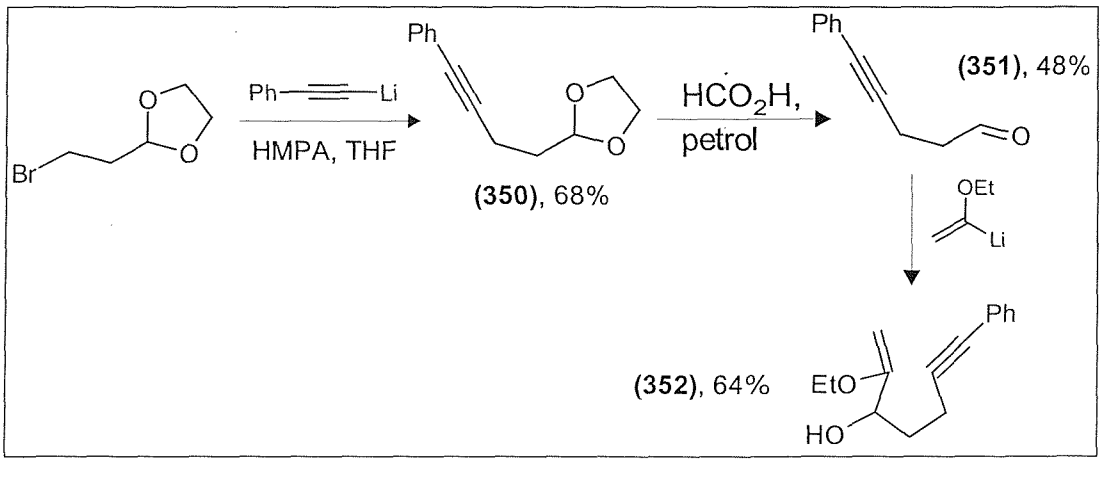
Enyne **(347)** is prepared using the known iodide, 1-iodo-4-octyne.[37] Synthesis of enyne **(349)** starts with the lithium acetylide prepared from 1-pentyne selectively

displacing the iodide in 1-chloro-4-iodobutane. 1-Iodo-5-nonyne was produced *via* a Finkelstein exchange,[11] and **(349)** is obtained by displacement of iodide by ethoxy vinyl lithium.



Scheme 3.20 – Synthesis of enynes (347) and (349).

The hydroxyl bearing enyne **(352)** was prepared in three steps starting from phenylacetylene, according to Scheme 3.21. The ketal **(350)** was produced from 1-lithio-1-phenylacetylene and 2-(2-bromoethyl)-1,3-dioxolane.[38] Hydrolysis of the acetal unit to give the aldehyde **(351)** proved troublesome, and was attempted under a variety of conditions. No reaction was observed with acetic acid / water at reflux,[39] with TFA / water or with PPTS in refluxing acetone. The action of 2 M HCl in THF[40] hydrolysed the acetal slowly, but using wet formic acid in petrol[41] at room temperature induced complete conversion after 3 hours. Conversion to enyne **(352)** with ethoxy vinyl lithium proceeded in good yield.

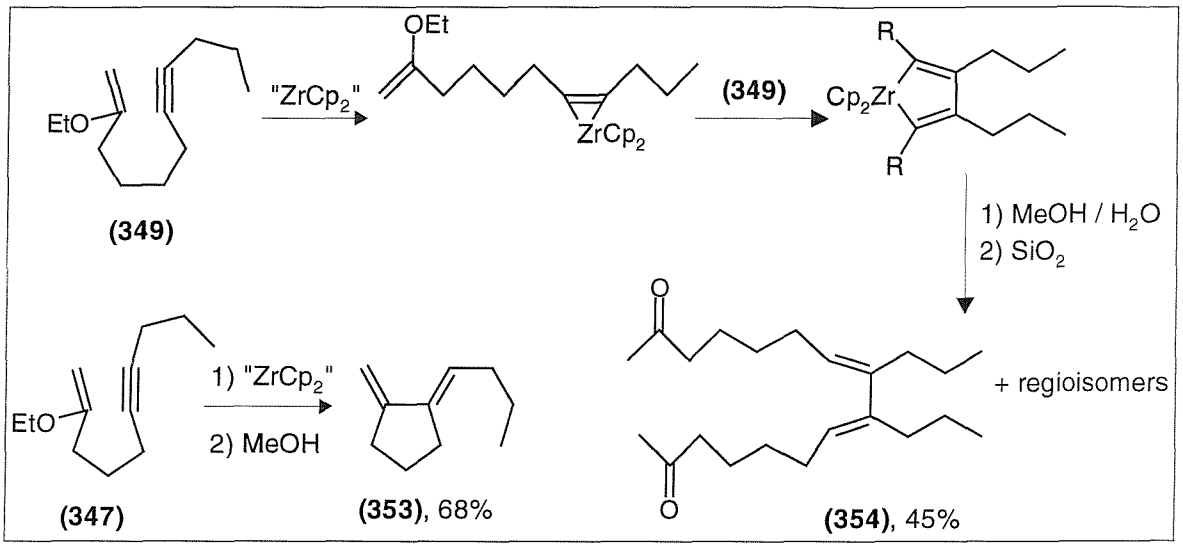


Scheme 3.21 – Synthesis of enyne (352).

The zirconocene mediated cyclisations of enynes (**347**), (**349**) and (**352**) are now discussed.

3.3.4: Co-Cyclisation of Enynes Derived From Ethyl Vinyl Ether.

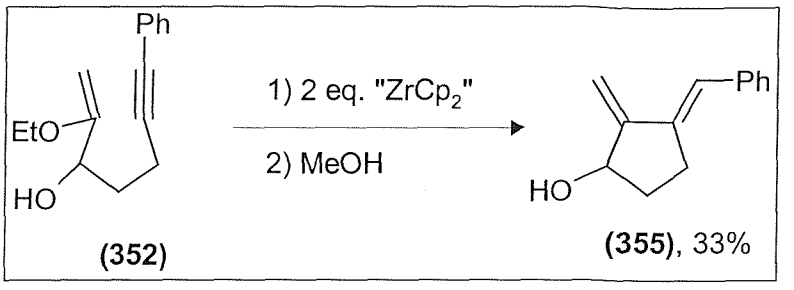
Treatment of enyne (**347**) with zirconocene (1–butene) and subsequent hydrolysis of the resultant C - Zr bond provided the desired cyclopentane (**353**) in 68% yield (Scheme 3.22).



Scheme 3.22 – Cyclisation of (347); dimerisation of (349).

However, the corresponding cyclohexane was not produced from (**349**). As seen with the dihydrofuran and dihydropyran substrates earlier, 6-membered ring formation is less favoured than 5-membered. β-Elimination did not take place with this enyne, as a high energy allene would be formed. Instead, the organozirconium species resulting from addition of Cp_2Zr to the carbon – carbon triple bond carbometallated another molecule of (**349**) forming a zirconacyclopentadiene.[42,43] A diene was produced on hydrolytic quench, and on chromatography the enol ether functionalities were hydrolysed, giving a mixture of regioisomers of diene (**354**) (Scheme 3.22).

Zirconocene mediated cyclisation of the third enyne substrate, (**352**) furnished the expected cyclopentanol (**355**), though in a poor 33% yield (Scheme 3.23).



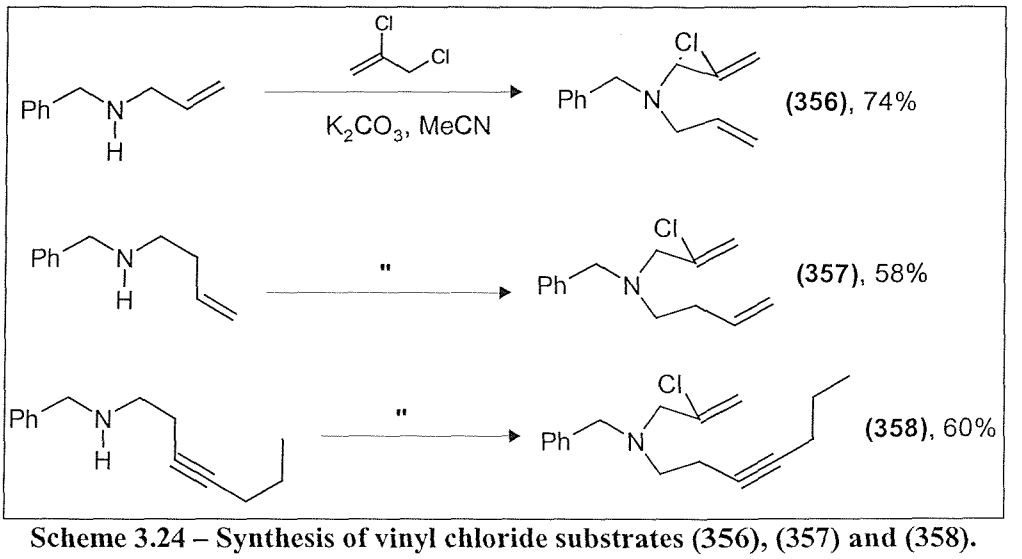
Scheme 3.23 – Co-cyclisation of enyne (352).

3.4: Substrates Based On Vinyl Chlorides.

The publication by Waymouth[17] precedenting the β-elimination in zirconacycles includes an example of a vinyl bromide (**II**) (Scheme 3.1). For our work, a family of vinyl chloride substrates was prepared. This allowed extension of Waymouth's work to 6-membered ring formation and cyclisation of enynes to be explored. Furthermore, investigations into carbenoid insertions into our novel organozirconium reagents (see **(321)** to **(341)**, Scheme 3.13) could be undertaken. These investigations are described in Section 3.4.3. Firstly, the synthesis of five vinyl chloride substrates are described.

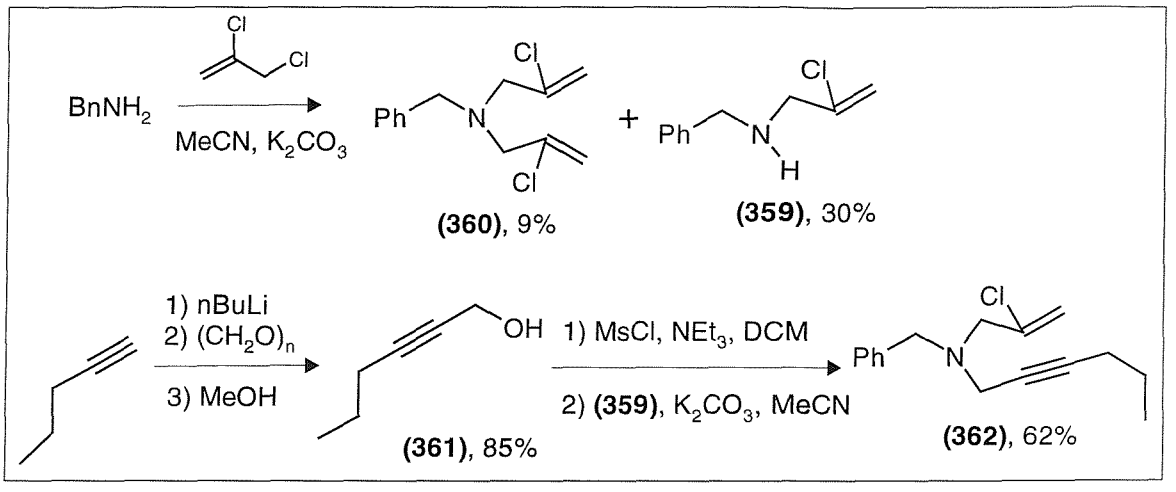
3.4.1: Synthesis of Vinyl Chloride Based Dienes and Enynes.

For ease of synthesis the dienes and enynes herein were prepared from an appropriately substituted benzylamine and 2,3-dichloro-1-propene (2-chloroallyl chloride). Dienes **(356)** and **(357)** and enyne **(358)** were prepared by this method, as shown in Scheme 3.24.



Scheme 3.24 – Synthesis of vinyl chloride substrates (356), (357) and (358).

The yields were moderate for these syntheses, but all were without optimisation, and provided sufficient material for the co-cyclisations. Although (**356**) is essentially identical to Waymouth's vinyl bromide, it allows direct comparison with the enol ethers, and the other, novel vinyl chlorides, and was used later for carbenoid insertions (see Section 3.4.3). Enyne (**362**) and by-product diene (**360**) were prepared by a slightly different route (Scheme 3.25).



Scheme 3.25 – Synthesis of enyne (362).

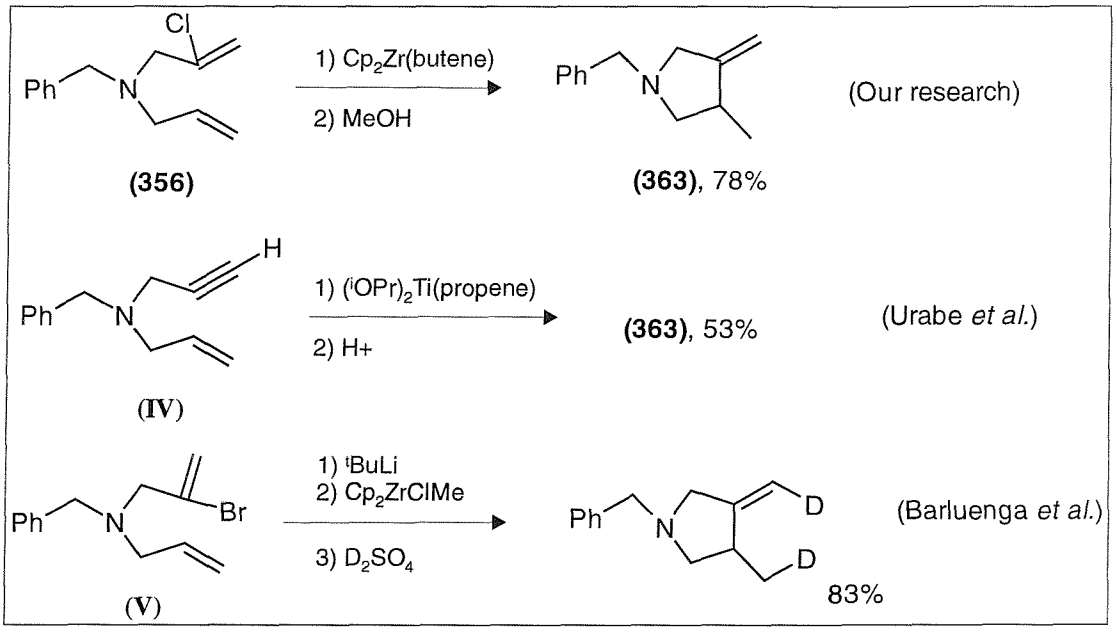
The mono chloroallylated benzylamine (**359**) could be prepared in sufficient quantity as required, and isolation of the *bis*-chloroallylated amine (**360**) provided another novel substrate, cyclisation of which could be attempted. The appropriate propargyl mesylate for coupling with (**359**) to provide enyne (**362**) was synthesised in excellent yield from 1-pentyne *via* alcohol (**361**).

3.4.2: Co-Cyclisations of Vinyl Chloride Based Dienes and Enynes.

The 1,6-diene (**356**) cyclised cleanly and in good yield, to give pyrrolidine (**363**) (Scheme 3.26). The same compound has been prepared previously by Urabe *et al.*[44] from enyne (**IV**), using a titanium reagent, diisopropoxy titanium propene, developed by Sato's group, which is produced by the action of two equivalents of isopropyl magnesium halide on titanium tetraisopropoxide (Scheme 3.26). The mode of action of the active reagent is analogous to that of zirconocene (1–butene). In the cyclisation of (**IV**) with zirconium the acidity of the acetylene proton necessitates an alternative organometallic to zirconocene (1–butene). The use of activated magnesium as a

reductant of zirconocene dichloride, providing an active 'bare' zirconocene, has been demonstrated to allow cyclisation of terminal acetylenes in excellent yield.[45,46] However, the cyclisation / elimination protocol provides **(363)** in 78% yield, compared with only 53% for Sato's titanium reagent.

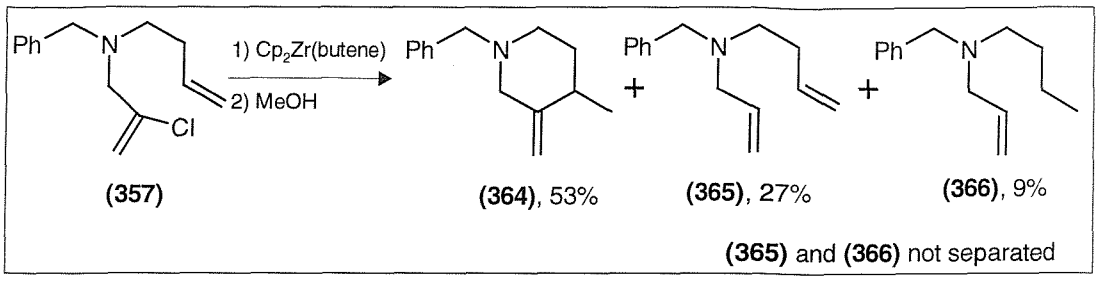
Barluenga *et al.*[47] have prepared a deuterated analogue of **(363)** by a zirconium-mediated method. Lithiation of vinyl bromide **(V)** with *tert*-butyllithium followed by displacement of chloride from $Cp_2ZrMeCl$ (see Section 1.2.5) generated an organozirconium intermediate which cyclised onto the other allylic double bond (Scheme 3.26). Deuterolytic quench gave the product shown in 83%. No protic quench was reported in this paper. This route is rather less convenient than our cyclisation under the simpler Negishi conditions.



Scheme 3.26 – Various routes to pyrrolidine (363).

Another route to **(363)** has been reported in which $Ni(COD)_2$ is used as the metal template, with the metal ultimately removed by borohydride reduction, providing **(363)** in 45% yield.[48]

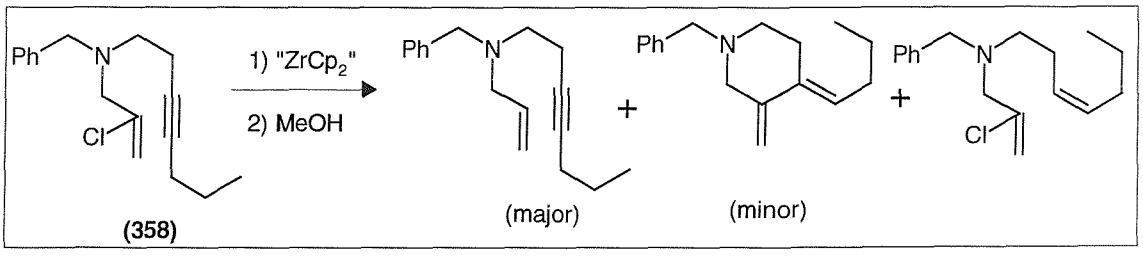
Cyclisation of 1,7-diene **(357)** provided a mixture of three products, the major (53%) being the desired piperidine **(364)**[49] (Scheme 3.27).



Scheme 3.27 – Cyclisation of diene (357).

The success of the reaction is something of a contrast to the enol ether 1,7-diene seen earlier. However, it is known that formation of nitrogen containing rings using zirconium is generally more facile than that of hydrocarbon rings.[4,22] The piperidine **(364)** could be chromatographically separated from lesser amounts of two by-products, **(365)** and **(366)**. Diene **(365)** is the result of oxidative addition of zirconium into the carbon – chlorine bond,[50] followed by hydrolysis of the resultant C-Zr bond. It is interesting to see a competition between addition to the monosubstituted double bond followed by co-cyclisation, and oxidative addition to the vinyl chloride. We can assume that the cyclisation to form the five membered ring of **(363)** is faster than six membered ring formation to form **(364)** as no oxidative addition into **(356)** is observed. The small amount of a doubly reduced product **(366)** is consistent with the 1.1 equivalents of zirconium used, whereby oxidative addition, as seen in formation of **(365)**, is followed by addition of the excess zirconocene to the butenyl double bond, and hydrolysis of all three C-Zr bonds on quench.

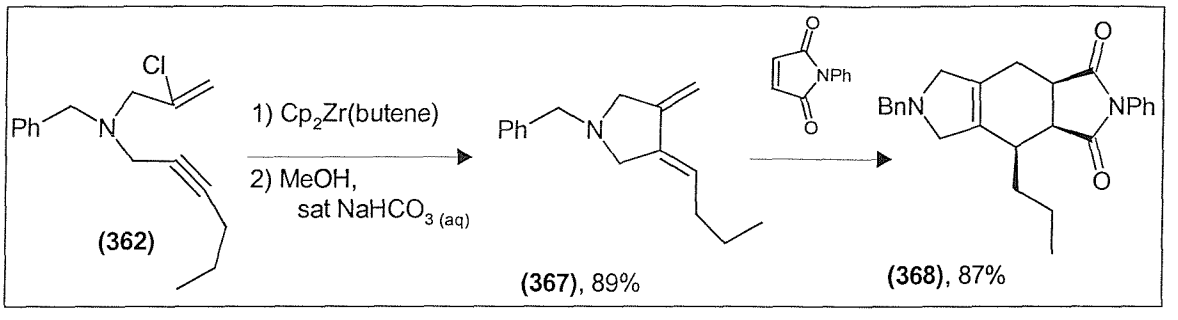
Treatment of 1,7-enyne **(358)** with zirconocene (1-butene) provided little success. Unfortunately the products obtained were inseparable by chromatography. From analysis of the double bond region in the proton NMR spectrum, the products obtained are believed to be as shown in Scheme 3.28, with similar mechanisms as above taking place.



Scheme 3.28 – Attempted cyclisation of 1,7-enyne (358).

Subjection of the by-product bis (chloroallyl) diene **(360)** (Scheme 3.25) to the standard co-cyclisation conditions resulted only in production of the diene **(356)** by oxidative addition to the vinyl chloride. A roughly equal amount of the starting material was also recovered.

The co-cyclisation / elimination of 1,6-enyne **(362)** produced an excellent 89% of the desired pyrrolidine **(367)**, bearing an exocyclic diene. This product presented an ideal substrate for a Diels Alder reaction. Indeed, treatment of diene **(367)** with the dienophile *N*-phenylmaleimide in diethyl ether for 7 hours at room temperature resulted in a facile [4+2] cycloaddition producing the tricycle **(368)** in excellent yield (Scheme 3.28).

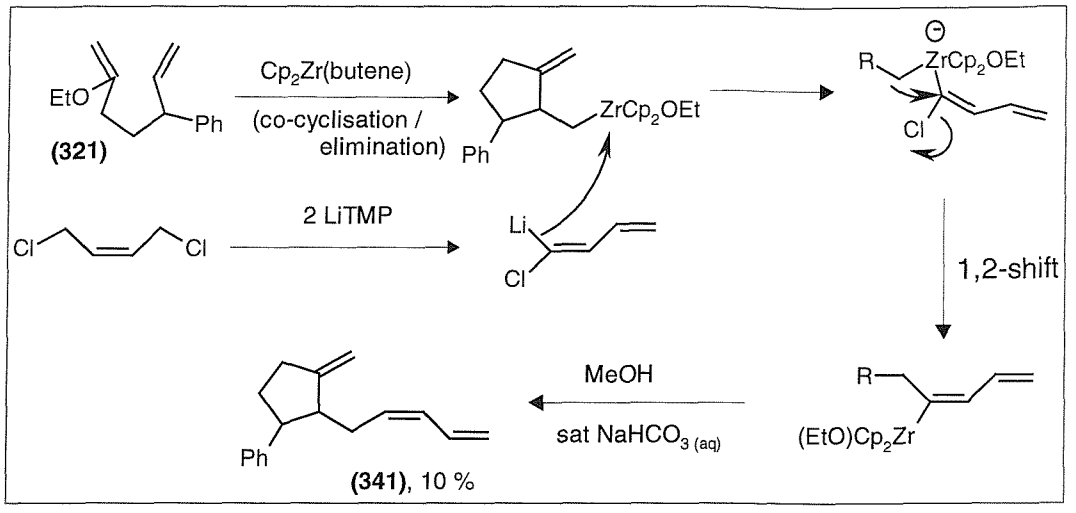


Scheme 3.29 – Cyclisation of enyne (362) and Diels Alder reaction of the product, (367).

NMR analysis of the protons on the adjacent chiral centres of the cyclohexene ring in **(368)** shows a 6.5 Hz coupling between the protons. This figure is ambiguous with respect to determining the relative stereochemistry, and the stereochemistry shown is based on a similar Diels Alder adduct produced by Kemp.[43]

3.4.3: Carbenoid Insertions Into an Organozirconium Derived From a Cyclisation / Elimination Reaction.

An attempt at insertion of a vinyl carbenoid into the organozirconium produced from diene **(321)** was shown earlier (Scheme 3.13) and provided only 10% of the desired insertion product. The mechanism of this carbenoid insertion is shown below (Scheme 3.30).[46]



Scheme 3.30 – Mechanism of carbenoid insertion, shown for the organozirconium generated from diene (321).

In the original paper presenting the insertion of this carbenoid into a C-Zr bond, the yields are generally >70%.[34] The explanation for the poor yield in this example is as follows. The first step of insertion is nucleophilic attack of the carbenoid onto the metal centre to give a zirconocene 'ate' complex. However, the ethoxy group on zirconium pushes electron density into the metal centre, deactivating it to nucleophilic attack, and disfavouring formation of the 'ate' complex. Indeed, the initial work on this insertion was performed on a zirconium centre bearing a chloride rather than an alkoxide. We therefore wished to produce a co-cyclisation / elimination substrate which would give a mono-substituted zirconocene bearing a chloride, the vinyl chlorides described previously being ideal. The ability to insert carbenoids into our organozirconium reagents in good yield would allow a greater applicability of this chemistry, due to an increased potential for elaboration of the cyclised products. In Section 3.4 only hydrolysis of these organozirconium reagents was shown.

Treatment of diene (**356**) with zirconocene (1-butene) produced the desired organo-zirconium, as shown by the production of (**363**) after its protic quench. On cooling to –90 °C and exposure to *cis*-1,4-dichloro-2-butene then two equivalents of lithium tetramethyl piperidide, the organozirconium reacted with the *in situ* generated carbenoid to give, after protic quench of the final C-Zr bond, the desired insertion product (**369**), in 75% yield (Table 3.1). Our hypothesis was thus proved correct, and the chloride rather than ethoxide group on the zirconium atom was allowing good yields for the carbenoid insertion and the route to the alkyl zirconium was inconsequential. Vinyl chloride substrates thus allow more varied elaboration methods

than the enol ether substrates. A further three known carbenoids[51] were reacted with the same organozirconium, each inserting successfully to give the products shown in Table 3.1.

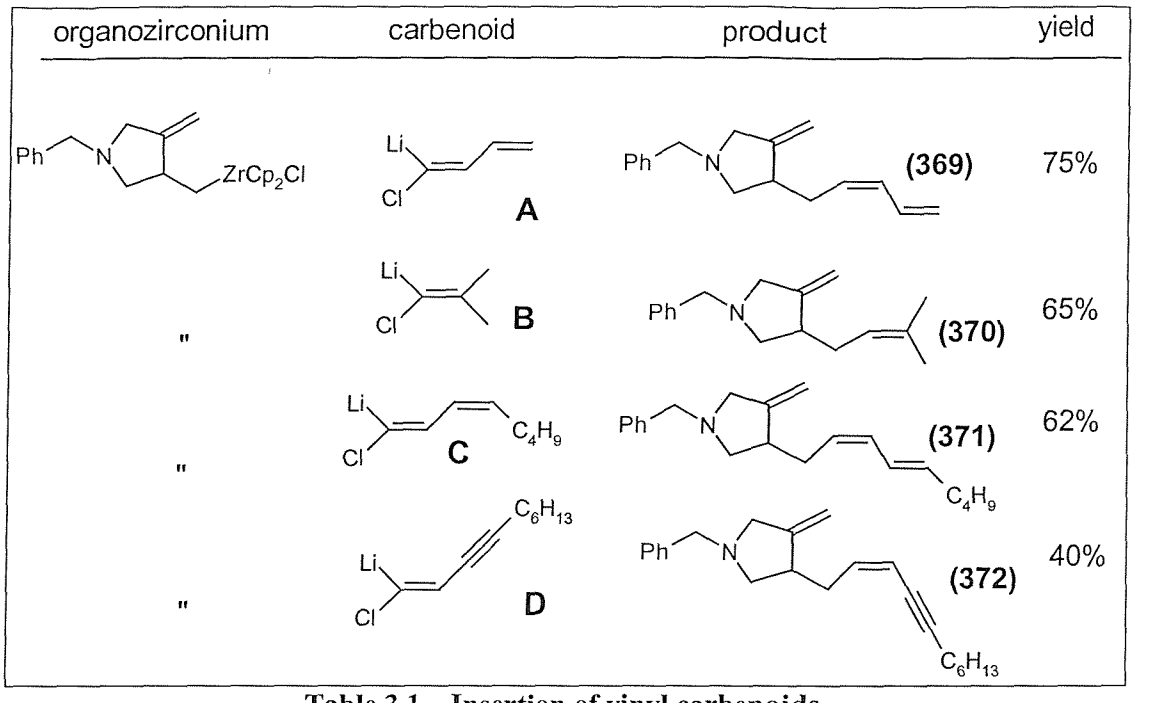


Table 3.1 – Insertion of vinyl carbenoids.

Carbenoid '**A**' was prepared by treatment of *cis*-1,4-dichloro-2-butene (1.3 equivalents with respect to zirconium) with 2.6 equivalents of lithium tetramethyl piperidide (LiTMP). The carbenoids '**B**', '**C**' and '**D**' were each prepared from the corresponding vinyl chloride (1.3 eq.) and 1.3 equivalents of LiTMP. The yields for these reactions are unoptimised, and longer reaction times at between –90 °C and –80 °C for the insertion / 1,2-shift may improve this. Nevertheless, these results show the strength of this vinyl carbenoid chemistry.

3.5: Conclusions For Chapter 3.

The co-cyclisation / elimination methodology has been shown to be successful. A variety of dienes and enynes based on cyclic and acyclic enol ethers, and vinyl chlorides have been prepared and the syntheses shown to be straightforward. In all of the cases where cyclisation has taken place, elimination of the β-leaving group has occurred. The substrates studied initially, such as **(301)** and **(302)**, containing dihydrofuran units reveal a pendant hydroxyl group on elimination of the

zirconacycle, and opening of the tetrahydrofuran ring, thus in effect, the hydroxyl has been protected in the form of a cyclic enol ether. Unfortunately, the dihydrofurans and dihydropyrans are not widely applicable due to the lack of reactivity of the enol ether double bond. The limitation of trisubstituted double bonds has been demonstrated, and only 1,6-dienes generated from dihydrofurans can be used reliably. However, the interesting mechanism of double bond migration to form η^4 zirconocenes as reported by Maye and Negishi[22] has also been seen with our substrates.

The non-cyclic enol ethers generated from ethyl vinyl ether, which contain disubstituted double bonds, provide much more successful dienes and enynes, allowing facile synthesis of methylene cyclopentanes. Unfortunately, six-membered rings appear to be unavailable unless a rigid backbone is present to template the diene around the metal. Our method for the introduction of exocyclic methylene groups provides a strong and viable alternative to the use of terminal enynes for co-cyclisations. The alternative Cp_2ZrCl_2/Mg[45] or $(^iPrO)_2Ti$ (propene)[44] reagents for cyclising terminal enynes are practically less convenient, and poorer yielding respectively.

On cyclisation / elimination of a 2-heteroatomic substituted diene then protic quench, a chiral centre bearing a methyl group is produced, and where there are other chiral centres already present, we often observed good to excellent diastereoselectivities, induced by phenyl or hydroxyl groups. The diastereomeric excesses can be readily determined by gas chromatography, and elucidation of the relative stereochemistry can be determined by NMR, using the coupling constants of the protons in question (through bond interactions), or GOESY experiments (through space interactions). The *in situ* protection of hydroxyl groups during co-cyclisations using a second equivalent of zirconocene has been shown as effective for the cyclisation of our substrates. Indeed, use of a silicon protecting group in one example (dienes (**327**) and (**327a**)) saw a significant decrease in diastereoselectivity from 7:1 to 5:4.

The major failing of the enol ether substrates was in the resultant ethoxy group on zirconium, which disfavoured carbenoid insertion into the C-Zr bond. However, the poor yield for this carbenoid insertion has implications for the mechanism of the insertion reaction. Unfortunately, halogenolysis was the only successful elaboration as a result. The change from enol ethers to vinyl chlorides overcame this reactivity problem, as these substrates also co-cyclised successfully, and provided

organozirconium reagents amenable to carbenoid insertions. These insertions proceeded in moderate to good yield. The presence of a nitrogen atom in the substrates allowed a 1,7-diene to be cyclised in moderate yield. These vinyl chlorides contain a monosubstituted double bond, and a disubstituted double bond bearing an alkyl and chloride group, and it was interesting to see zirconium being non-specific for bonding first to the less substituted double bond. This was shown for example in product **(365)** (Scheme 3.27), in which the more substituted, vinyl chloride, double bond underwent oxidative insertion by zirconocene and was reduced to a monosubstituted double bond. Finally, the 1,6-enyne **(367)** was shown to cyclise in excellent yield, producing a diene on cyclisation / elimination / hydrolysis which was ideal for Diels Alder chemistry.

Chapter 4: Towards the Total Synthesis of Mucosin.

4.1: Introduction.

In 1997, Casapullo *et al.* reported the isolation of the natural product mucosin[52] (Figure 4.1) from the marine sponge *Reniera mucosa*, which is native to the Mediterranean.

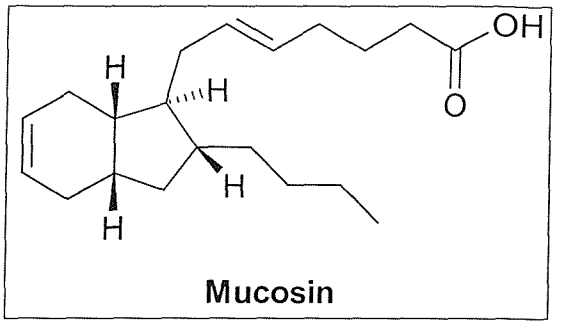


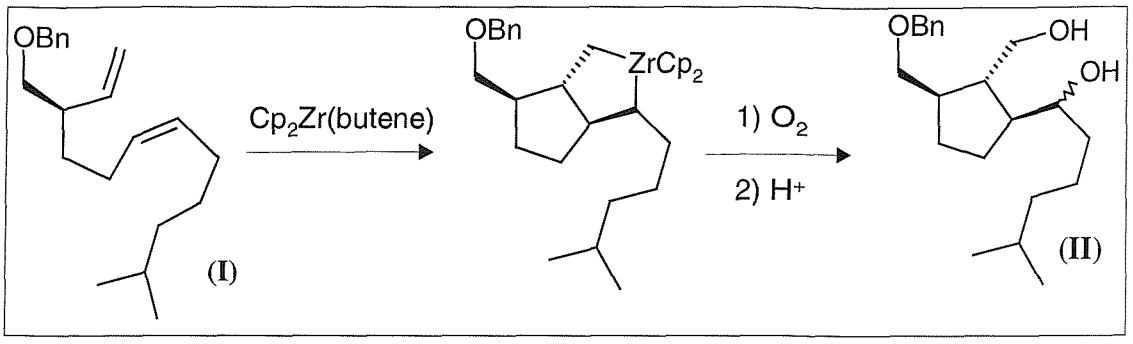
Figure 4.1 – Reported structure of mucosin.

The C-20, eicosanoid character of mucosin suggests its biosynthesis from arachidonic acid *via* intramolecular cyclisation reactions. For purposes of characterisation, the isolated mucosin was converted to its methyl ester using diazomethane. The gross structure of the methyl ester was determined by its mass, infrared and high field NMR spectra, and the precise stereochemistry by various 2-D NMR experiments, while the α_D showed the isolated compound to be enantiomerically enriched. Although the biological activity of mucosin is unknown, the unusual bicyclo [4.3.0] nonane skeleton and carboxylic acid side chain make the structure interesting and attractive to total synthesis. We undertook the synthesis particularly in the light of a publication by Taber and Louey[53] on co-cyclisation of 1,6-dienes bearing chiral centres, providing diastereomerically pure cyclopentanes, as described below.

4.2: Retrosynthesis and Precedent.

The bicyclic nucleus of mucosin contains four contiguous stereocentres, a *cis*-6,5 ring junction and a cyclohexene ring. Synthesis of the desired diastereomer of this bicycle would appear to be difficult, however the publication by Taber and Louey[53] provides good precedent for a zirconocene mediated route to the natural product. They showed that cyclisation of diene **(I)** followed by oxygen quench (Scheme 4.1) provided a 3:1 mixture of diastereomeric diols **(II)**, epimeric at the secondary alcohol centre. Thus

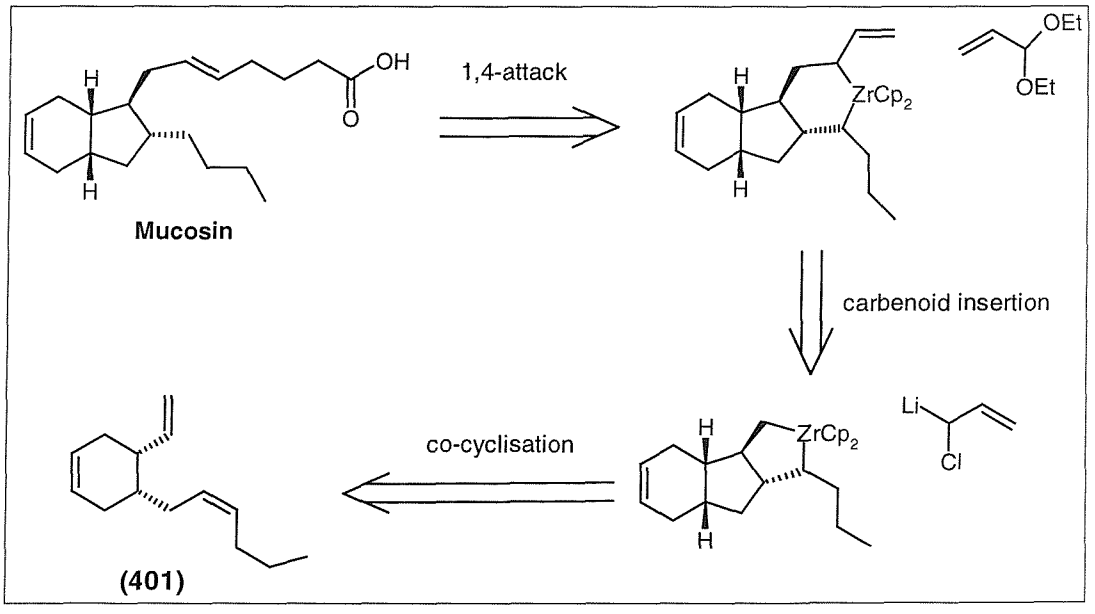
there was complete control over the stereochemistry of the chiral centres on the cyclopentane ring.



Scheme 4.1 – Co-cyclisation of diene (I), stereocontrol induced by existing chiral centre.

The *anti* relationship between the existing CH_2OBn group and newly generated hydroxymethyl group is analogous to the *anti* relationship between the cyclohexene bridge and carboxylic acid bearing side chain in mucosin. The required *anti* relationship was also observed between the two new chiral centres on the cyclopentane ring.

Precedent for the introduction of the acid bearing side chain *via* a carbenoid insertion reaction (see Section 1.4.7) suggests the disconnection shown in Scheme 4.2.



Scheme 4.2 – Retrosynthetic strategy.

Starting from triene (**401**), tandem co-cyclisation, allyl carbenoid insertion and 1,4-attack of the resultant allyl zirconocene onto an acrolein acetal would provide the desired bicycle and all of the carbon atoms in the side chain, including the *trans* double bond. Simple transformations would provide the carboxylic acid moiety.

Gordon *et al.*[46] have provided precedent for the carbenoid insertion shown, where the allylic carbenoid attacks the less hindered C-Zr bond when the more substituted double bond is not part of a ring (Figure 4.2). (See also section 1.4.7).

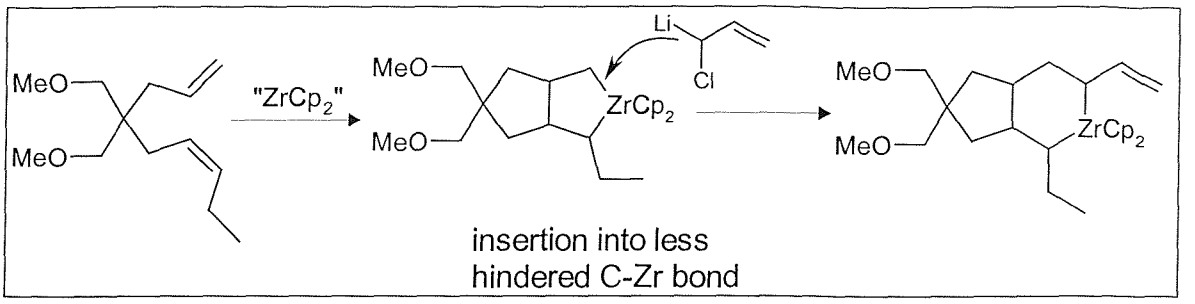


Figure 4.2 – Precedent for regioselectivity of carbenoid insertion.

This would allow elaboration of the side chain, which would ultimately terminate in a carboxylic acid moiety. One method of introducing the remaining three carbons of the side chain would be *via* a 1,4-attack of the allyl zirconocene onto an appropriate Michael acceptor. Luker has shown that such allyl zirconocenes can engage acrolein acetals in a 1,4-fashion,[54] albeit in low yield (Figure 4.3).

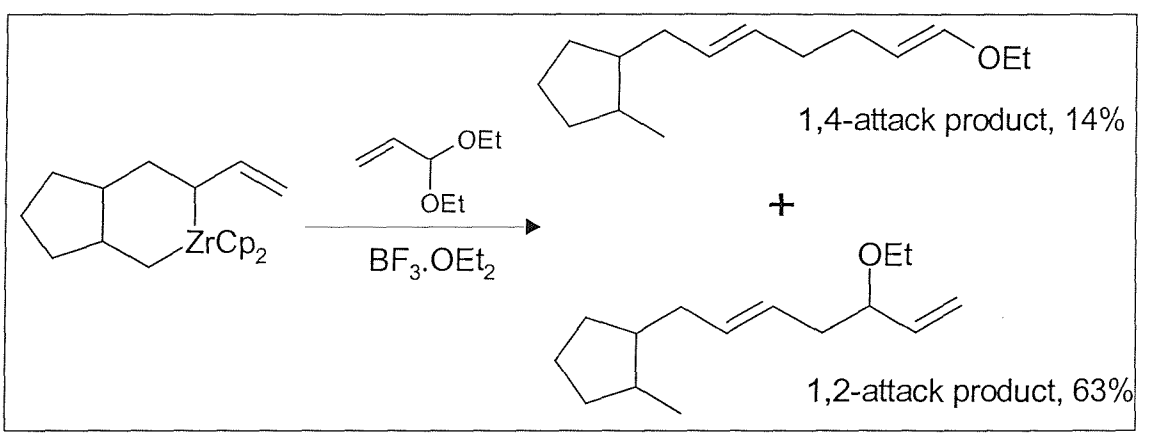


Figure 4.3 – Precedent for 1,4-attack by an allyl zirconocene.

Hydrolysis of the enol ether moiety in the 1,4-attack product, followed by oxidation of the resultant aldehyde to the acid using pyridinium dichromate in DMF,[55] for example, would complete the synthesis of the side chain. Although the selectivity for 1,4-attack is poor, we hoped that larger alkyl groups on the acetal, or use of α,β - unsaturated orthoesters would provide a greater degree of 1,4-attack.

With precedent for obtaining the desired ring junction stereochemistry, and for introduction of the functionalised side chain, the total synthesis can now be addressed. The first target is the co-cyclisation substrate, triene **(401)**.

4.3: Synthesis of the Co-Cyclisation Substrate, Triene (401).

As the triene **(401)** has a *cis* relationship between the vinyl and hexenyl groups, it is logical to begin the synthesis with a starting material already having this relationship.

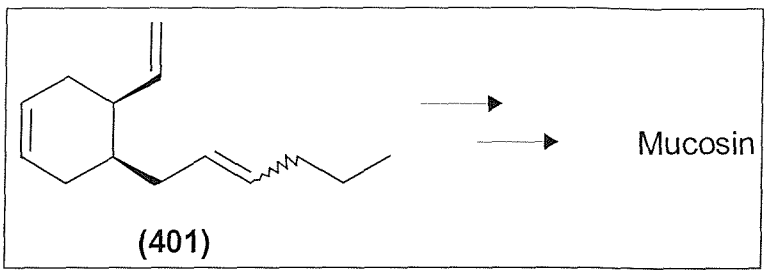
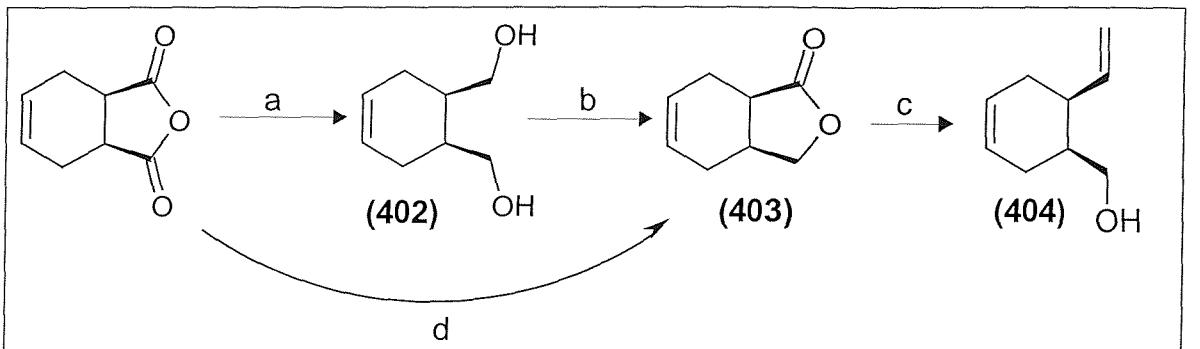


Figure 4.4 – Required co-cyclisation substrate (401).

The cheap, commercially available tetrahydrophthalic anhydride fulfils this requirement. The first steps of the synthesis are shown in Scheme 4.3.

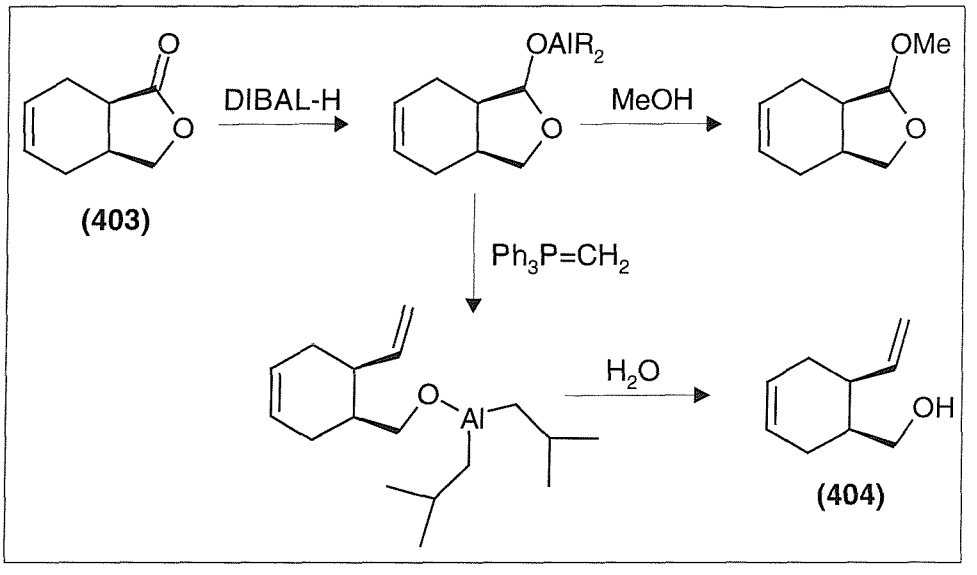


Reagents and Conditions: **a)** $LiAlH_4$, Et_2O, 0 °C, 84 %; **b)** PCC, SiO_2, DCM, 42 %; **c)** i. DIBAL-H, PhMe, ii. $Ph_3P{=}CH_2$, THF, 45 %; **d)** $NaBH_4$, DMF, 63 %.

Scheme 4.3 – Synthesis of alcohol (404).

Lithium aluminium hydride reduction of the anhydride to the diol **(402)**, followed by PCC oxidation[56] provided lactone **(403)** in moderate yield. On scale up of the reaction sequence, the use of large amounts of lithium aluminium hydride was undesirable. Even more so was the use of large amounts of the carcinogenic PCC, and the corresponding work up. The quality of the crude lactone product also suffered. A simpler and more scaleable alternative was partial reduction of the anhydride directly to the lactone.[57] This could be achieved with sodium borohydride in either DMF or IPA. Introduction of the required vinyl group in triene **(401)** could be achieved by Wittig methylenation of the lactol produced by partial DIBAL-H reduction of lactone **(403)**. Precedent for a one-pot procedure was followed,[58,59] in which DIBAL-H is added to the lactone to form the aluminium salt of the lactol, and the resulting O-Al

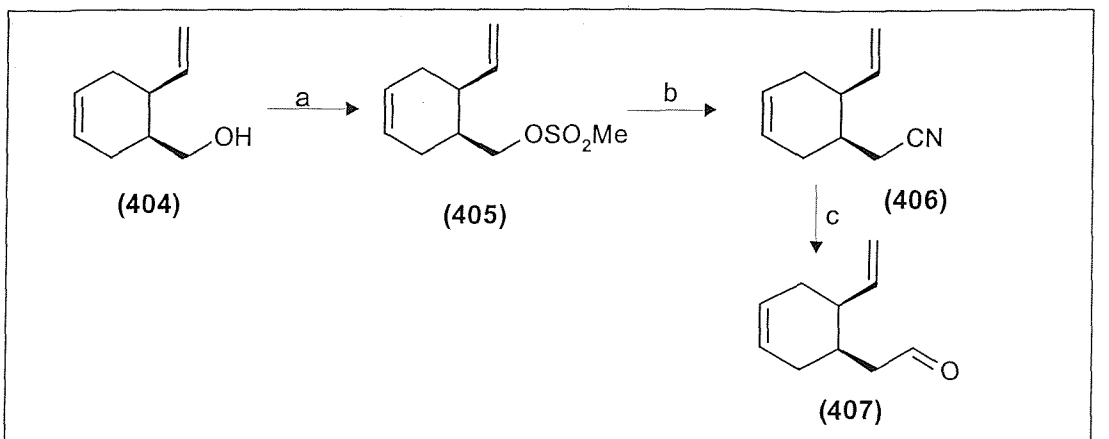
bond and excess aluminium reagent quenched with methanol. This reaction mixture would then be added to a solution of methylene phosphorane to provide (**404**). On carrying out this procedure, addition of methanol to the reduction mixture provided an unwanted ketal (Scheme 4.4). To overcome this problem, the aluminium bearing intermediate from the reduction was added to the Wittig reagent and a shift of the aluminium group induced by heating over night (Scheme 4.4).



Scheme 4.4 – One pot conversion of lactone (403) to alcohol (404).

Moderate yields of up to 45% for the 2 step, one-pot formation of (**404**) could be obtained, and the reaction performed on a 100 mM scale. The synthesis continues with one carbon homologation of alcohol (**404**) (Scheme 4.5).

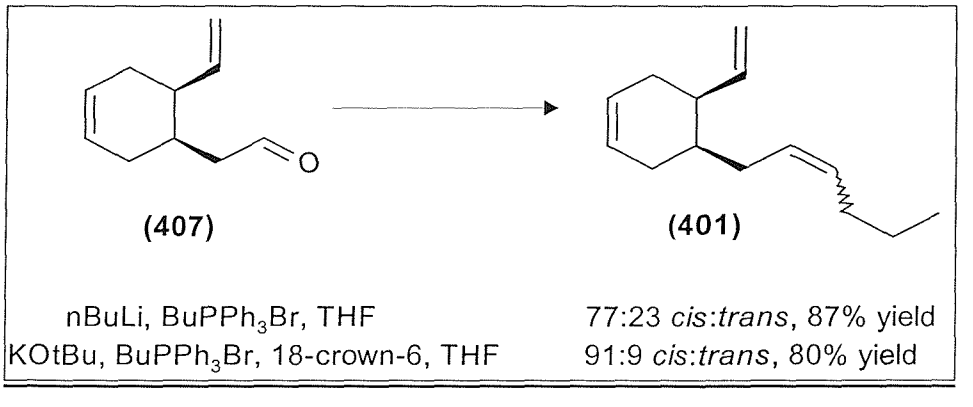
Quantitative conversion of the alcohol to its mesylate (**405**) provided a good leaving group for cyanide displacement. However, despite the ability of the leaving group, the displacement required rather forcing conditions. After some experimentation, it was found that heating the mesylate with 2 equivalents of KCN, 0.5 equivalents of 18-crown-6 and a catalytic amount of sodium iodide in refluxing acetonitrile for up to 7 days forced the reaction to completion. DIBAL-H reduction of the resultant nitrile (**406**) followed by imine hydrolysis provided aldehyde (**407**) in good yield.



Reagents and Conditions: **a)** MsCl, NEt_3, DCM, 100 %; **b)** KCN, 18-crown-6, NaI, MeCN, reflux, 3 days, 68 %; **c)** ii. DIBAL-H, PhMe, -70 °C, ii. $NaHCO_{3\,(aq)}$, 70 %.

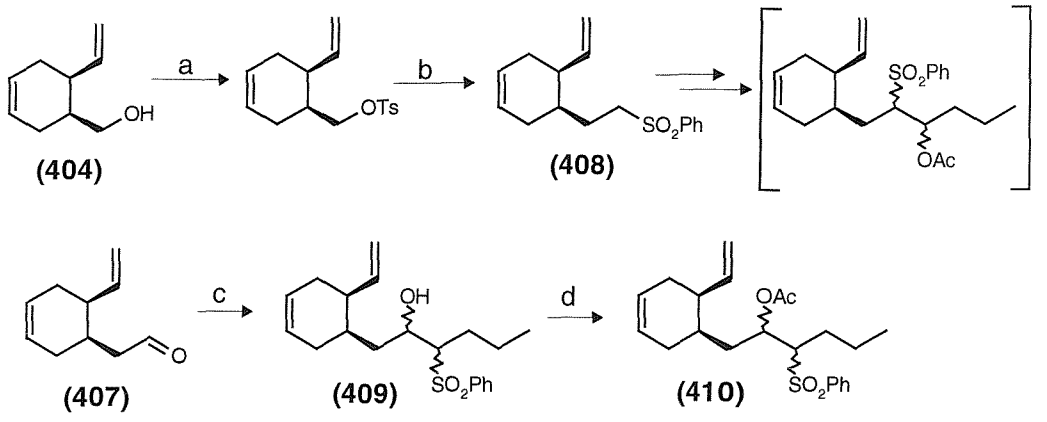
Scheme 4.5 – Synthesis of intermediate aldehyde (407).

The next step of the synthesis was the conversion of aldehyde **(407)** to the co-cyclisation substrate **(401)**. The geometry of the hexenyl double bond in **(401)** should be of no importance, as one of the double bond carbons will become an sp^3 hybridised, non-symmetry bearing CH_2 group on co-cyclisation and protic quench. However, it is possible that the geometry of the double bond could affect the ring junction stereochemistry, and also the regiochemistry of the carbenoid insertion. As a result, both the *cis* and *trans* isomers were sought. A classical Wittig reaction should provide the *cis* isomer. Treatment of aldehyde **(407)** with the corresponding Wittig reagent generated by addition of n-butyllithium to butyl triphenyl phosphonium bromide in THF[60] provided the desired triene **(401)** in excellent yield, but as a 77:23 *cis*:*trans* mixture, as determined by gas chromatography. This ratio could be improved to 91:9 using a crown ether catalysed reaction, the Wittig reagent being generated by deprotonation of butyl triphenyl phosphonium bromide with potassium *tert*-butoxide, in the presence of a catalytic amount of 18-crown-6[61] (Scheme 4.6).



Scheme 4.6 – Wittig reaction of aldehyde (407) to give (401).

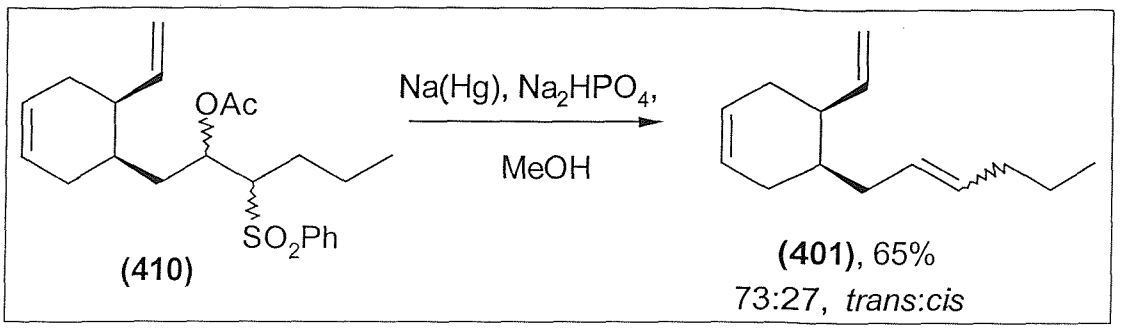
One route to *trans* double bonds from aldehydes is the Julia olefination.[62] The aldehyde is first converted to the corresponding β-acetoxysulfone, which is reductively eliminated using sodium amalgam. A choice of acetoxysulfones is available, each of which could be synthesised from intermediates already prepared (Scheme 4.7).



Reagents and Conditions: **a)** TsCl, pyridine, 86%; **b)** $MeSO_2Ph$, n-BuLi, THF, 38%; **c)** $BuSO_2Ph$, n-BuLi, 93%; **d)** Ac_2O, pyridine, 92%.

Scheme 4.7 – Alternative routes to acetoxysulfones for reductive elimination.

Sulfone (**408**) was synthesised *via* tosylation of alcohol (**404**), but due to the poor yield, the alternative route *via* alcohol (**409**) to β-acetoxysulfone (**410**) was preferred. The elimination of (**410**) to give triene (**401**) was first attempted under the standard conditions of 5.6% Na(Hg) in THF/MeOH.[63] This method proved to be unsuccessful, as indicated by the absence of the desired triene in the product mixture. We postulated that the reaction of sodium from the amalgam with the methanolic solvent produced sodium methoxide *in situ*, which eliminated AcOH with no loss of the sulfone group, thus forming a vinyl sulfone. Following a literature procedure[64] a base scavenger, Na_2HPO_4 was used to consume any methoxide formed, and thus attenuate the side reaction. The revised conditions of Na(Hg) and Na_2HPO_4 in methanol performed the desired radical removal of the sulfone group, with subsequent elimination of the acetate, to provide triene (**401**) in respectable yield (Scheme 4.8).



Scheme 4.8 – Completion of the Julia coupling by reduction using Na(Hg).

Unfortunately, the selectivity of the elimination was poor, only 73% of the mixture having the desired *trans* geometry. This may be accountable for by the lack of steric bulk presented by the n-propyl group. Nevertheless, the co-cyclisation of the isomerically enriched trienes **(401)** can now be addressed.

4.4: Co-Cyclisation of Triene (401).

It was hoped that the zirconocene mediated co-cyclisation of our first substrate, the 77% *cis* triene **(401)**, would provide a single diastereomer of the four possible, in accordance with the observations of Taber *et al.*[53] However, a mixture of three significant products was formed, the major constituting 60%, as shown clearly by ^{13}C NMR and GC analysis. No starting material was present in the gas chromatograph of the product mixture.

To investigate the stereoselectivity, each of the mixtures of double bond isomers of **(401)** (91, 77 and 27% *cis*) was cyclised separately. The reactions were followed by GC, and were shown to go to completion within 4 hours of addition of the triene to zirconocene (1-butene) in each case. The same product mixture was seen in each case, with three components dominating, and in roughly the same ratio. The major component contributed to between 45 and 55% of the mixture depending on the starting material.

The probable reason for the mixture of products is a lack of diastereoselectivity. The *anti* relationship between the newly generated chiral centres 'c' and 'd' (Figure 4.5) is very likely, as is the propensity for the chiral centre 'b' to induce complete control in 'c', in an *anti* fashion. The net result is a *syn* relationship between 'b' and 'd'. This is in agreement with Taber's observations.[53]

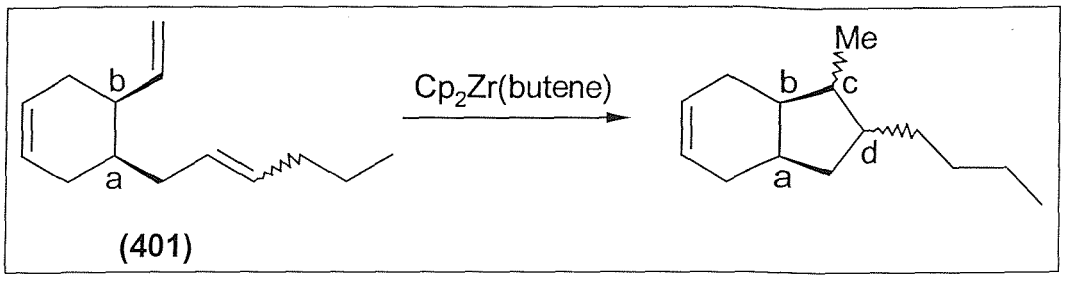


Figure 4.5 – Cyclisation of triene (401).

However, present in our co-cyclisation substrate, but not in that of Taber, is the chiral centre 'a'. It is probable that 'a' will induce an *anti* relationship between itself and 'd', which contradicts the effects of centre 'b'. Indeed in Section 3.3.2 we saw a 1,3-stereoinduction by the phenyl group (or possibly the hydroxyl group, or both) to the extent of a 7:1 mixture of *anti*:*syn* products (Figure 4.6).

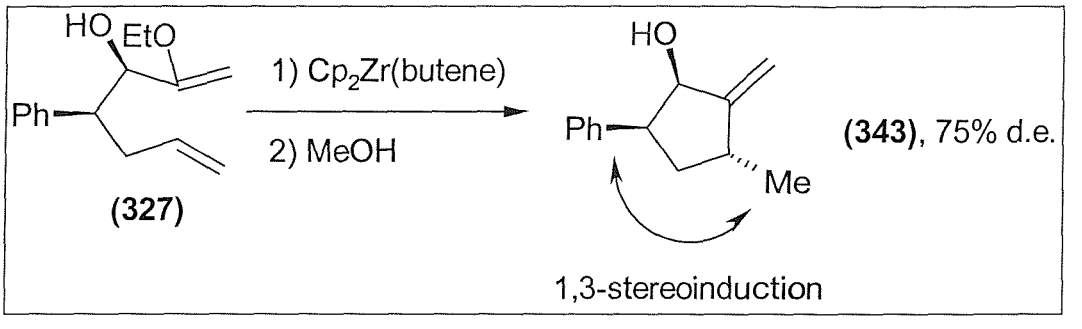


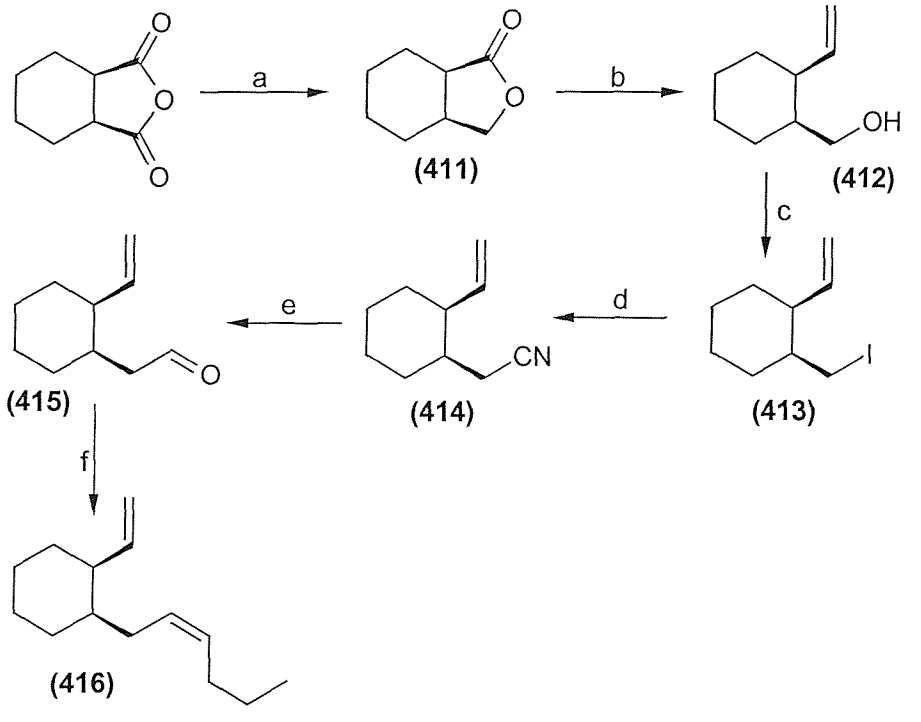
Figure 4.6 - 1,3 - Stereoinduction in zirconocene mediated cyclisation.

Therefore, the opposite action of each of the cyclohexene stereocentres ('a' and 'b', Figure 4.5) results in a net lack of stereocontrol.

An alternative explanation for the mixture of products on cyclisation is the presence of the cyclohexene double bond. It is possible that this double bond is reacting with zirconocene, or with an intermediate organozirconium formed during the reaction, particularly as one of the other double bonds is disubstituted. If zirconocene adds first to the less substituted vinyl double bond the resultant zirconacyclopropane has a choice of which disubstituted double bond to attack, as each would provide a five membered ring. Although the exocyclic, hexenyl, double bond is ideally oriented to react preferentially, it is conceivable that the cyclohexene could react to some degree.

To test this hypothesis, the analogue of triene **(401)** containing a cyclohexane rather than cyclohexene was synthesised. The synthesis of this diene **(416)**, starting from 1,2-cyclohexane dicarboxylic acid anhydride, is described in Scheme 4.9. This pathway is analogous to that of the synthesis of triene **(401)**. The synthesis was on the

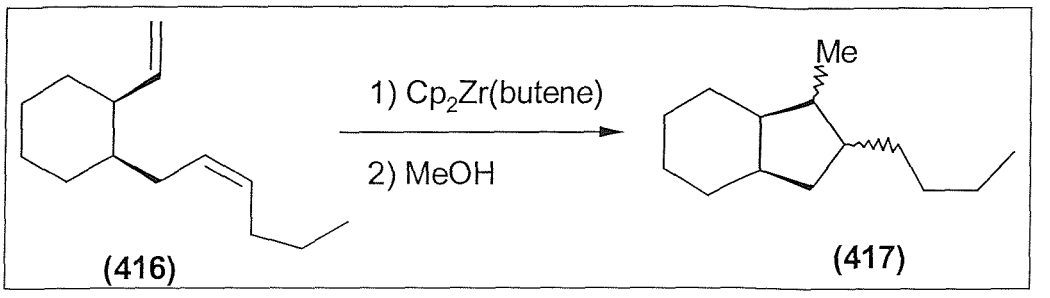
whole straightforward, though the cyanide displacement again proved difficult. After 5 days at 80 °C, a mixture of iodide **(413)**, potassium cyanide and 18-crown-6 in acetonitrile provided a 40% yield of the desired nitrile **(414)** along with about 20% of recovered iodide and an elimination product. The crown ether catalysed Wittig reaction of aldehyde **(415)** provided >95% selectivity in favour of the *cis* double bond geometry.



Reagents and Conditions : **a)** $NaBH_4$, DMF, 16 h, 63%; **b)** i. DIBAL-H, toluene, ii. $Ph_3P{=}CH_2$, THF, 33%; **c)** i. MsCl, NEt_3, DCM, ii. NaI, acetone, reflux, 42 h, 82%; **d)** KCN, 18-crown-6, MeCN, 80 °C, 5 days, 40 %; **e)** i. DIBAL-H, toluene, ii. $NaHCO_{3\,(aq)}$, 63%; **f)** $BuPh_3PBr$, 18-crown-6, KO^tBu, THF, 73%.

Scheme 4.9 – Synthesis of diene (416).

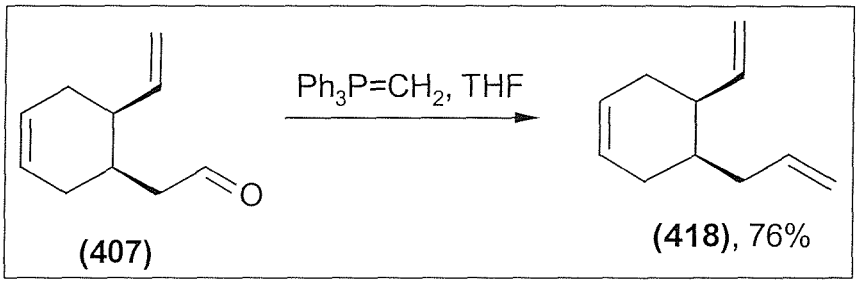
The zirconocene mediated co-cyclisation of diene **(416)** provided a mixture of products **(417)**, again likely to be diastereomers (Scheme 4.10). However, this cyclisation was somewhat cleaner than that of **(401)**; GC analysis showed the major component of the crude reaction mixture, and of the distilled product to be present as 65% of the total. This product was shown unambiguously by ^{13}C and DEPT NMR to be consistent with the structure given for **(417)**.



Scheme 4.10 – Co-cyclisation of diene (416).

The cleaner reaction of **(416)** suggests that the cyclohexene double bond of our original substrate **(401)** was interfering with the cyclisation to some degree. However, saturation of this double bond would not alleviate the contrary stereoinducive effects of the two chiral centres present in the starting material. This disappointing result suggests that the desired bicyclic nucleus of mucosin can not be obtained diastereomerically pure, unless a separation could be performed at a later stage.

Another investigation into the synthesis of the mucosin bicyclic unit was performed on triene **(418)** (Scheme 4.11). This substrate allowed investigation into the effect of the exocyclic disubstituted double of **(401)** and **(416)**, as it is replaced by a terminal double bond in **(418)**.

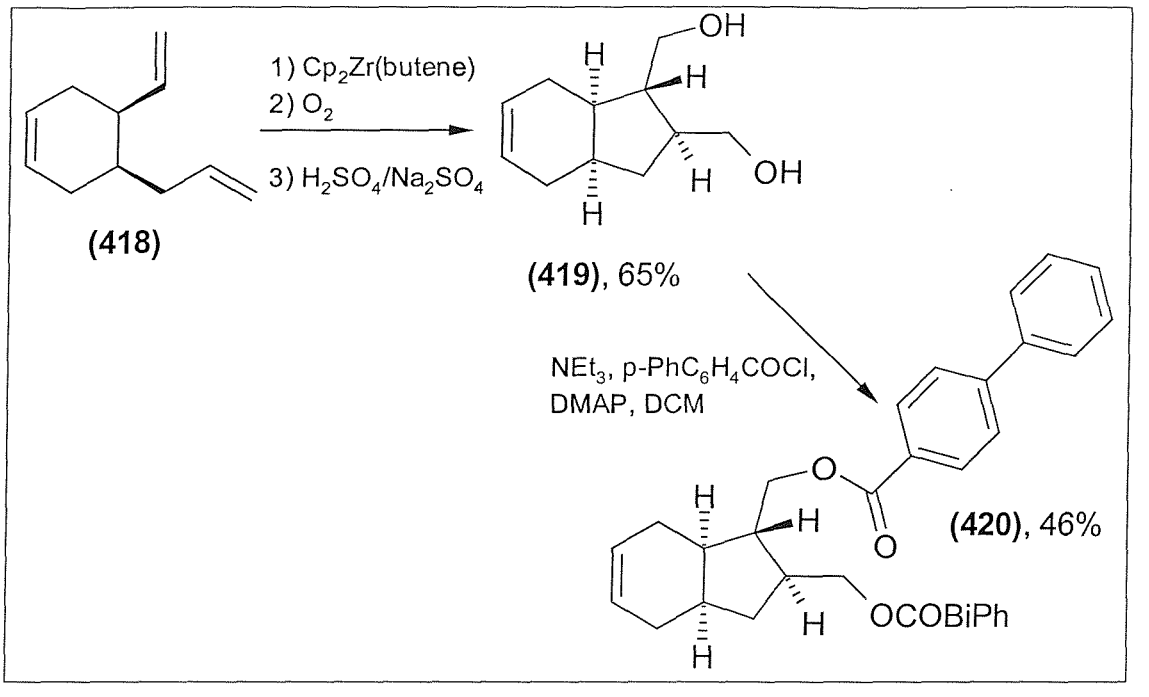


Scheme 4.11 – Synthesis of diene (418).

Co-cyclisation of **(418)** followed by oxygen quench[35,65] of the C-Zr bonds provided diol **(419)** (Scheme 4.12), which was obtained as a single diastereomer after column chromatography. Gas chromatography analysis of the protic quenched product from cyclisation of **(418)** showed a major product making up 80% of the mixture, plus two minor components. If these minor components of the protic quenched products were diastereomers, it is conceivable that minor diastereomers of diol **(419)** were lost on chromatography, as complete control in cyclisation of **(418)** is inconsistent with the cyclisations of **(401)** and **(416)**. The undesired 1,3-stereocontrol should be independent of the terminal substituents on the allyl double bond of each of these three substrates. Nevertheless, the 80% of one component in the above mentioned GC

trace, compared with 65% of the major product of cyclisation of **(416)**, shows that the presence of a propyl chain on the end of the allyl double bond (thus a hexenyl chain) is detrimental.

The bis (biphenoyl) ester of diol **(419)**, compound **(420)** (Scheme 4.12), was prepared, and after much experimentation, small crystals of sufficient quality for x-ray analysis were obtained and examined.



Scheme 4.12 – Cyclisation of diene (418), synthesis of a crystalline derivative.

The x-ray crystal structure of the diester **(420)** proved that the desired stereochemistry of the mucosin bicycle had been obtained in the cyclisation reaction. This was encouraging, and suggests that the studies towards the synthesis of mucosin should not be abandoned yet. The bicyclic unit of the x-ray structure of the diester is shown in Figure 4.7. For clarity, the biphenoyl units have been omitted, and only the hydrogen atoms on the chiral centres are shown. The full x-ray structure and data can be found in the appendix to this thesis.

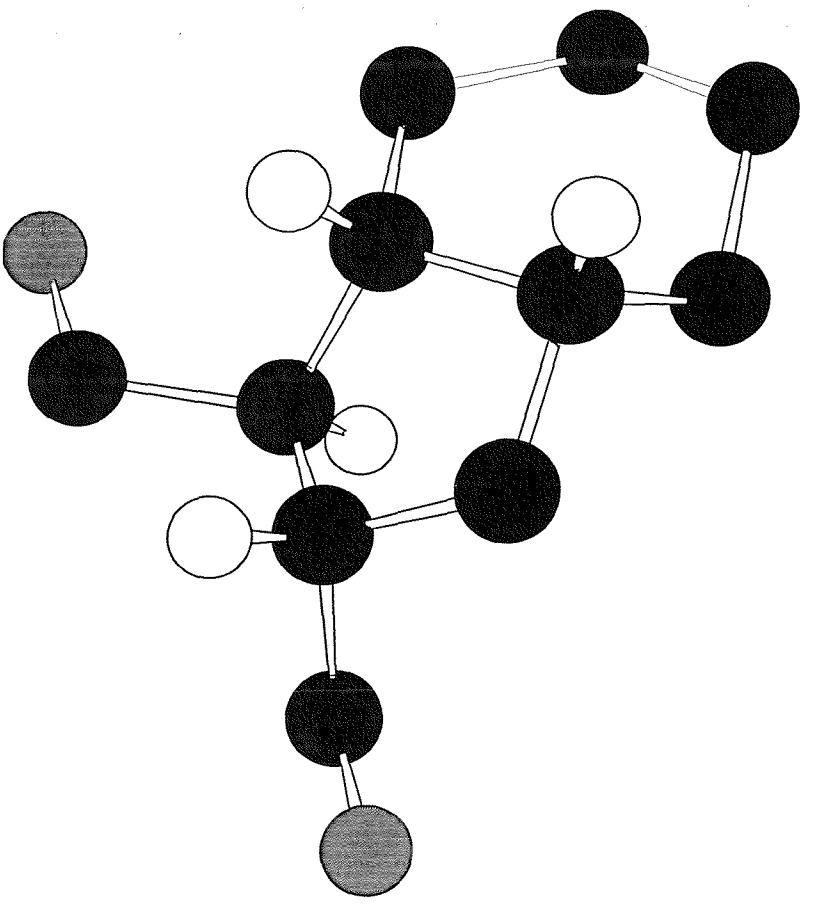
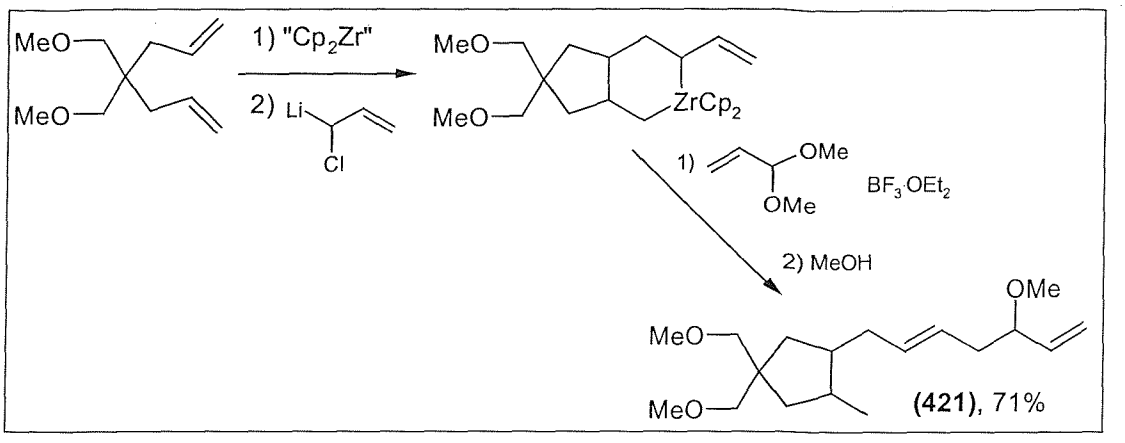


Figure 4.7 – Bicyclic unit of the crystal structure of diester (420).

Key: black - carbon; grey - oxygen; white - hydrogen

4.5: Studies Towards The Carboxylic Acid Side Chain Of Mucosin

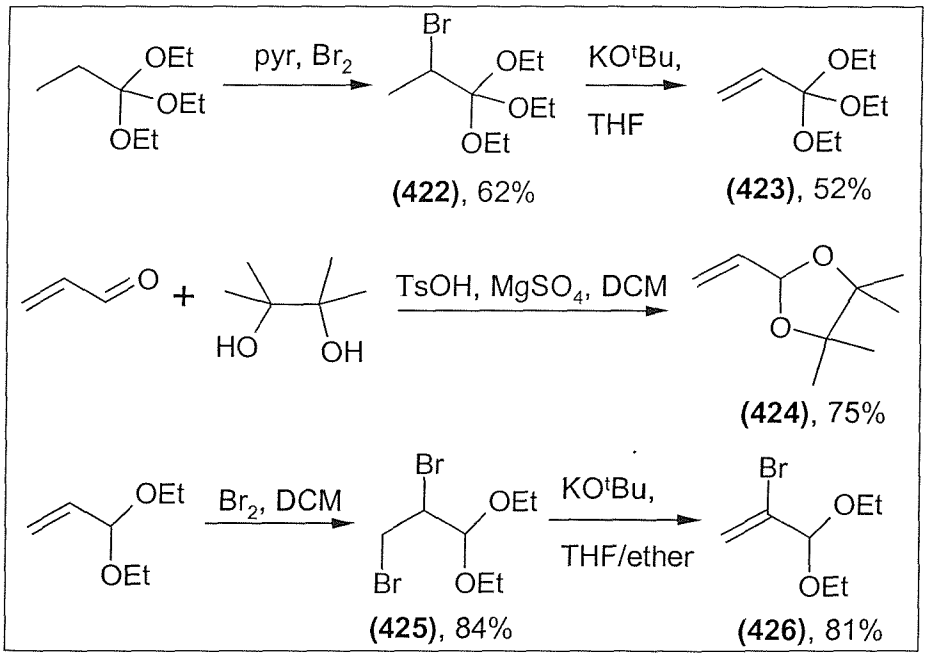
While the synthesis of the co-cyclisation substrate, triene **(401)**, was underway the synthesis and incorporation of the side chain was being addressed on a model system. As described earlier (Section 4.2), the ideal way to introduce the side chain would be *via* allyl carbenoid insertion into the less substituted C-Zr bond,[46] followed by 1,4-attack on an acrylate. This route provides the double bond at the desired position in the chain, and as the required *trans* isomer (see Figures 4.2 and 4.3). Luker's experiment[54] in which the π - allyl zirconocene attacks acrolein diethyl acetal was repeated, again on a model system, first using the dimethyl acetal (Scheme 4.13).



Scheme 4.13 - 1,2-attack of a model allyl zirconocene on acrolein dimethyl acetal.

NMR analysis of the crude product showed a very small amount (<5%) of the 1,4-addition product, which could not be isolated. The vinyl ether protons are characteristic of this product. The remainder of the product mixture was the 1,2-addition product, isolated in 71% yield after column chromatography. 1,2-Attack was again seen as the major pathway when the diethyl acetal was used.

In order to induce 1,4-attack, three other acrolein acetals were synthesised (Scheme 4.14).

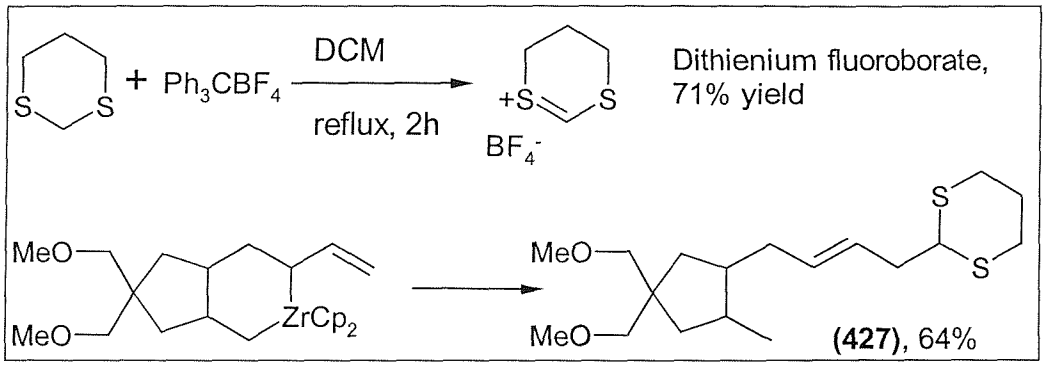


Scheme 4.14 – Synthesis of acrylates (423), (424) and (426).

We hoped that orthoacetate **(423)**[66] and the bulky acetal **(424)**[67] would induce 1,4-attack by virtue of extra hindrance inhibiting 1,2-attack. The vinyl bromide acetal **(426)**[68] has been shown to induce Michael attack by Grignard reagents.[69] Unfortunately, the extra hindrance proved too great, and none of the three acetals

reacted with the allyl zirconocene. For example, the reaction with bromide **(426)** showed no sign of incorporation after 5 days.

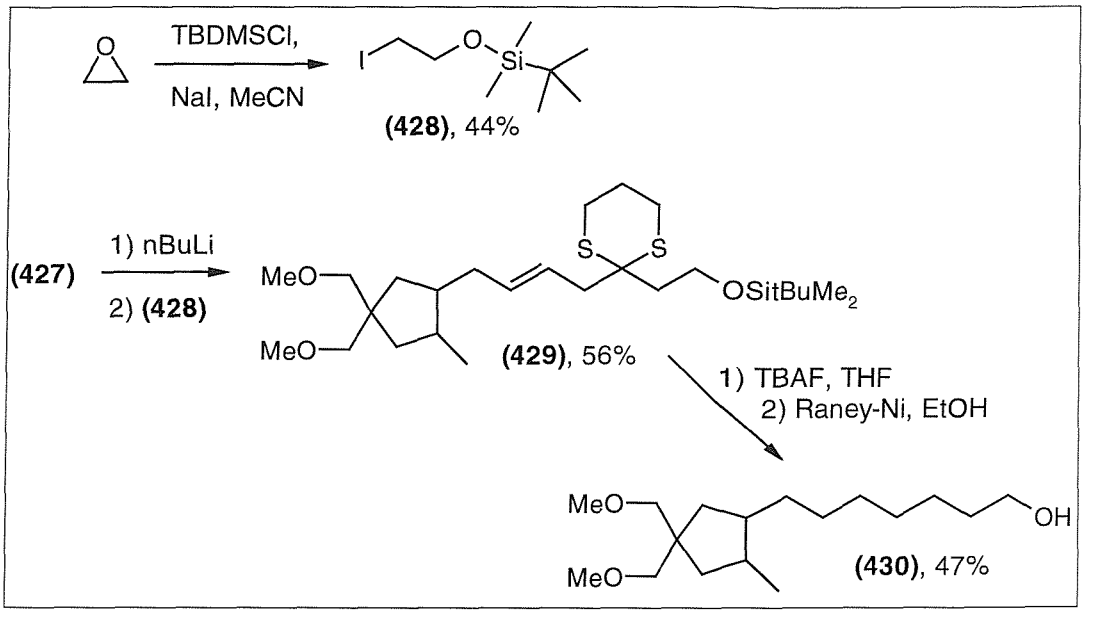
An alternative, albeit less elegant route to the side chain was again inspired by the work of Luker, who has shown that dithienium tetrafluoroborate provides an efficient electrophile for capture by allyl zirconocenes[54] (Scheme 4.15). This reaction was repeated on a model diene. The dithienium reagent was synthesised by hydride extraction from 1,3-dithiane using triphenylmethyl (trityl) fluoroborate. In practice, heating 1,3-dithiane with 1.4 equivalents of trityl fluoroborate in freshly distilled DCM at reflux for 2 hours provided a yellow solid under a yellow solution. After decantation of the supernatant, the residue was washed with freshly distilled ether, then dry DCM. The solid was dried under vacuum and could be kept for some weeks. It was found essential to use thoroughly dry solvents in the synthesis of this reagent. The characteristic bright yellow colour of the dithienium salt is attenuated by the use of slightly wet solvents and the material is obtained in poorer quality.



Scheme 4.15 – Synthesis and incorporation of dithienium fluoroborate.

We planned to remove the dithiane group with Raney nickel, after chain extension. Introduction of the remaining two carbon atoms and the terminal functionality can thus now be addressed. Having used the dithienium cation to introduce the dithiane group, the anion can now be generated, using butyllithium, and alkylation performed. The first electrophile attempted was methyl bromoacetate, as this would incorporate a methyl ester. This would appear attractive, as mucosin was characterised as its methyl ester. Unfortunately, only starting material was recovered from this reaction. We found that a successful alkylating agent was a silicon protected iodoethanol **(428)**, which was generated by ring opening of ethylene oxide with TBDMSCl and sodium iodide in acetonitrile. This protected iodide was incorporated in 56% yield to provide the dithiane **(429)** (Scheme 4.16).

The final desilylation using TBAF was successful, but removal of the dithiane with Raney-Ni also resulted in a clean reduction of the double bond, providing alcohol (**430**) in moderate yield. The initial reaction conditions of 2 hours in refluxing ethanol were suspected to be too forcing, but repeating the reaction at room temperature for 20 minutes gave the same result. Given more material, other reagents for dithiane reduction, such as $LiAlH_4$ / $TiCl_4$[70] or Bu_3SnH / AIBN[71] could be attempted.



Scheme 4.16 – Alkylation of dithiane (427) to give (429), and subsequent over reduction.

4.6: Conclusions and Further Work Towards Mucosin.

The methodology presented herein towards the total synthesis of mucosin still appears attractive despite the problems encountered. The main area of uncertainty is the stereoinductive effects in co-cyclisations. Further studies into the co-cyclisation of dienes bearing chiral centres first need to be undertaken. The competition between 1,2 and 1,3-stereoinduction, which is proposed as an explanation for the mixtures of diastereomers obtained on co-cyclisation of triene (**401**) and diene (**416**), should be studied. This may also provide some interesting novel methodology. One might postulate that 1,2-stereoinduction would overwhelm 1,3-control, but we cannot be certain without more results.

One worthwhile investigation might be the synthesis and cyclisation of triene (**III**) (Figure 4.8).

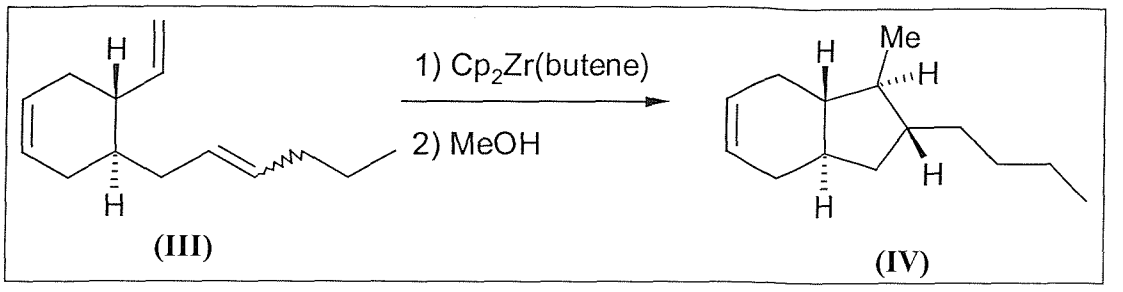
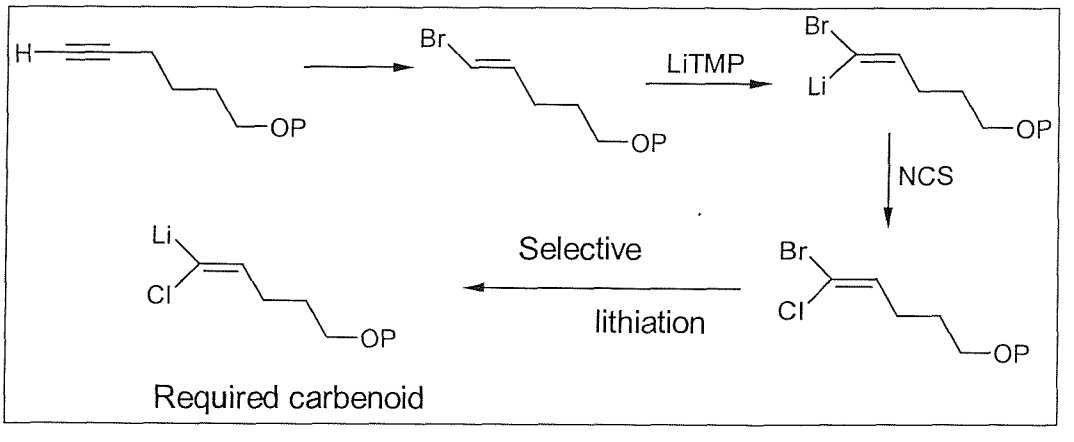


Figure 4.8 – Potential stereocontrol in cyclisation of *trans* substituted diene (III).

The *trans* relationship between the ring substituents would result in each of these two chiral centres inducing the same relative stereochemistry at the new chiral centres around the cyclopentane ring in **(IV)**. If a single diastereomer was obtained in this reaction any worries about the cyclohexene or exocyclic disubstituted double bonds interfering with the co-cyclisation could be dispelled.

The route to potential co-cyclisation substrates (eg. **(401)**, **(416)**) for the later stages of the natural product synthesis is somewhat cumbersome and contains low yielding steps. However, this route is now well practised and sufficient amounts of material with which to finish off the total synthesis could easily be procured, if convenient methods for the introduction of the carboxylic acid chain can be developed on a model system. The problems encountered in the elaboration of the side chain could be overcome in the light of the recent work on vinyl carbenoid insertions.[34,51] A rather different approach might prove more rapid and more successful. A possible synthesis for an appropriate carbenoid is shown in Scheme 4.17.



Scheme 4.17 – Possible route to a carbenoid appropriate for mucosin synthesis.

Although vinyl carbenoids can be prepared easily from *trans* vinyl chlorides, producing *cis* carbenoids, the *trans* stereochemistry in the natural product would necessitate a slightly longer route to the carbenoid. This would rely on a selective

lithiation of bromide over chloride, to form the carbenoid from the 1-bromo-1-chloro-1-alkene, and would again produce novel methodology. All of the carbon atoms in the side chain are already present in the carbenoid, and only manipulation of the protected alcohol to the acid would be required to complete the total synthesis of the natural product.

Chapter 5: Experimental Section.

5.1: General Experimental Details.

Air and Moisture Sensitive Compounds.

All reactions and procedures involving air or moisture compounds, for example organometallics, were carried out under an atmosphere of argon, using standard Schlenk techniques. Argon was dried by passage through a column of 4 □ molecular sieves and indicating silica gel. All apparatus was dried at >160 °C for 12 h before cooling in a sealed desiccator over silica gel, or assembled while hot and cooled under vacuum.

Spectroscopic and Analytical Instrumentation.

Proton and carbon NMR spectra were recorded on Bruker AM300, AC300 (300 MHz proton, 75 MHz carbon) and DPX400 (400 MHz proton, 100 MHz carbon) Fourier Transform spectrometers. Spectra were recorded in deuterochloroform, $CDCl_3$ (stored over K_2CO_3) or deuterobenzene, C_6D_6 (stored over molecular sieves), and referenced to residual chloroform (δ 7.27 ppm proton, δ 77.15 ppm carbon) or benzene (δ 7.4 proton, δ 128.70 carbon). Chemical shifts are given as δ values in ppm and coupling constants (J) in Hertz (Hz). The abbreviations for peak shape and multiplicity in the ^1H NMR spectra are as follows, and may be compounded: s (singlet), d (doublet), t (triplet), br (broad), fs (fine splitting). ^{13}C NMR spectra were proton decoupled and are reported with the number of attached protons (0, 1, 2 or 3), usually determined by DEPT experiments. 2D spectra were recorded on either the AC300 or DPX400 machines, and GOESY experiments on the DPX400 machine, in order to conclusively assign spectral data and relative stereochemistries. The lettered assignment for each proton or carbon signal is for identification purposes only and does not represent the systematic IUPAC numbering. ^1H NMR signals are assigned as follows: chemical shift (integration, multiplicity, coupling constant, assignment); eg. 2.10 (2H, t, J = 7.0 Hz, e). ^{13}C NMR signals are assigned similarly.

Infrared spectra were recorded on Perkin-Elmer 1600 series FTIR, Nicolet Impact 400, or Bio-Rad FT-IR Spectrometer (fitted with a Graseby Specac Golden Gate

Platform) machines as neat films (for oils), solutions in the given solvent, or solid films (using the Golden Gate facility) for solids. Absorptions are given in wavenumbers (cm^{-1}) and the following abbreviations used to denote peak intensity and shape: s (strong), m (medium), w (weak), br (broad).

Mass spectra were recorded on a Micromass Platform quadrupole mass analyser (Micromass, Tudor Road, Altrincham, UK) with an electrospray ion source. The instrument was calibrated with a mixture of sodium and caesium iodide, the operating conditions were capillary 3.50 kV, HV lens 0.5 kV, cone voltage 20 V, source temperature 100 °C, ES (Electrospray) eluent: 100% acetonitrile at 100 μL min^{-1}, nitrogen drying gas 300 L h^{-1} and nebulising gas 20 L h^{-1}. 10 μL injections of ~1-10 μg mL^{-1} solutions were made using a Hewlett Packard (Palo Alto, CA. USA) HP 1050 autosampler.

APCI (Atmospheric Pressure Chemical Ionisation) spectra operating conditions were capillary 3.5 kV, HV lens 0 kV, cone voltage 20 V, source temperature 150 °C, probe temperature 450 °C, ES eluent: 100 % acetonitrile at 200 μL min^{-1}, nitrogen drying gas 250 L h^{-1} and APCI sheath gas 50 L h^{-1}.
Negative ion data were recorded under identical conditions except for different polarity voltages, and capillary voltages of -3.0 kV for ES and APCI.

EI spectra were recorded at 70 eV electron energy, 200 °C source temperature, 100 μA trap current. Data were acquired at 6 kV accelerating voltage, at a scan rate of 3 s per decade over a mass range of 1000 amu to 20 amu, with an inter-scan delay of 1 second.

HRMS measurements were carried out at 10,000 resolution using mixtures of polyethylene glycols (PEGs) and/or polyethylene glycolmethyl ethers (Me-PEGs) as mass calibrants for CI. Perfluorokerosene (PFK) was used as mass calibrant for HREI analyses.

Gas chromatography was performed on a Hewlett Packard HP 6890 Series machine, using HP-5 or HP-wax columns.

Microanalytical determinations were performed by the Microanalytical Department, University College London, and assigned as the percentage composition by mass of the indicated element.

The x-ray structure of **(420)** was determined by the EPSRC National Crystallography Service at the University of Southampton, Department of Chemistry. The crystal structure was determined by a literature method.[72]

Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected.

Reagent Purification.

Unless otherwise stated, reagents were obtained from commercial suppliers and used without further purification. Specific purifications were carried out according to standard methods.[73]

Where anhydrous or oxygen free conditions were required, the following procedures were used. THF and diethylether were freshly distilled from purple solutions of sodium benzophenone ketal under argon. HMPA, chlorinated solvents and amines were distilled from calcium hydride and stored under argon. Methanol was distilled from magnesium / iodine and acetone dried over calcium sulphate. Petrol refers to the 40 – 60 °C boiling fraction, and was distilled before use. HPLC grade hexane was used. Ethyl vinyl ether was distilled from sodium metal to remove stabilisers present in the commercially obtained reagent. DMSO and DMF were dried over activated molecular sieves (dried in a microwave oven). Magnesium and sodium sulphates used for drying solutions of crude products were oven dried (100 °C, 12 h) before use. Organolithium reagents were titrated against a solid alcohol, using fluorene as the indicator.

Chromatography.

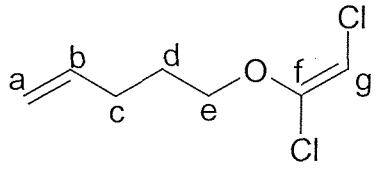
Thin layer chromatography (TLC) was carried out on 0.25 mm Kieselgel 60 G UV_{254} precoated aluminium foil or plastic backed plates and were visualised by UV (254 nm UV lamp), iodine (10% on silica), phosphomolybdic acid (solution in ethanol) or sulphuric acid (5% w/w in methanol) as appropriate.

Column chromatography on silica was performed on Kieselgel 60 230-400 mesh (Merck 9385) silica gel. Alumina refers to Brockman grade III alumina, prepared by deactivation of commercial grade I material with 6% w/w distilled water. Columns were packed and run under light pressure. The solvents compositions given are described as % volumes before mixing.

Experimental Details for Chapter 2

5-(1, 2-Dichloro-1-ethenyl)oxy)-1-pentene (201)

A solution of 4-pentene-1-ol (4.306 g, 50 mmol) in THF (20 mL) was added to a solution of pentane washed sodium hydride (1.92 g, 48 mmol) in THF (35 mL) and the mixture stirred until effervescence ceased (3 h). Trichloroethene (4.13 mL, 6.04 g, 46 mmol) was added and the solution heated to reflux overnight. After cooling, MeOH (10 mL), H_2O (25 mL) and Et_2O (50 mL) were added. The layers were separated and the aqueous layer extracted with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to give an orange oil. The crude product was purified by column chromatography (SiO_2, petrol) to give the title compound as a clear, colourless oil (5.614 g, 67%).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.83 (1H, ddt, J = 17, 10, 7 Hz, b), 5.52 (1H, s, g), 5.09 (1H, ddt, J = 17, 1.5, 1.5 Hz, a), 5.03 (1H, ddt, J = 10, 1.5, 1 Hz, a), 4.04 (2H, t, J = 6.5 Hz, e), 2.24 (2H, tddd, J = 7, 7, 1.5, 1 Hz, c), 1.82 (2H, tt, J = 7, 6.5 Hz, d) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 143.87 (0, f), 137.41 (1, b), 115.73 (2, a), 97.85 (1, g), 71.32 (2, e), 29.93 (2), 28.17 (2) ppm

IR (thin film) ν = 3107m, 3090w, 2952s, 2848w, 1627s, 1447m, 1386w, 1272s, 1094s, 993m, 916s, 828s cm^{-1}

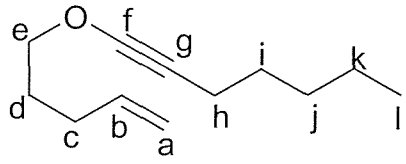
HRMS: $C_7H_{10}OCl$ $(M - Cl)^+$ requires m/z = 145.0420, found 145.0416

The following is a general procedure for alkoxyalkyne synthesis[5] from a dichlorovinyl ether such as **(201)**.

n-Butyllithium (4.2 mL of a 2.5 M solution in hexanes, 10.5 mmol) is added dropwise to a solution of **(201)** (835 mg, 5 mmol) in THF (8 mL) at –78 °C (internal thermometer) under Ar. After 30 minutes at below –70 °C, the solution is allowed to warm to –40 °C over 30 minutes. The appropriate iodide (5 mmol) in HMPA (2 mL) is added, and the resultant orange solution stirred to room temperature for 4 h. MeOH (3 mL) is added to the dark red solution, and the mixture poured into cold saturated NH_4Cl solution (20 mL) and pentane (20 mL). The aqueous layer is separated, and extracted into pentane (3 x 20 mL). The combined organic phases are washed with water then brine, dried over Na_2SO_4, filtered and concentrated, to give a brown oil. The crude product is purified by column chromatography (neutral alumina, petrol) to give the product alkoxyalkyne.

1-(4-Pentenyloxy)-1-heptyne (202)

The title compound was prepared by the general procedure above, and was obtained as a clear, pale yellow oil (534 mg, 60%).



^1H NMR (300 MHz, $CDCl_3$) δ = 5.81 (1H, ddt, J = 17, 10, 7 Hz, b), 5.06 (1H, dq, J = 17, 2 Hz, a), 5.01(1H, ddt, J = 7, 2, 1 Hz, a), 3.98 (2H, t, J = 7 Hz, e), 2.15 (2H, q, J = 6.5 Hz, c), 2.11 (2H, t, J = 6 Hz, h), 1.82 (2H, tt, J = 6.5, 6.5 Hz, d), 1.5 - 1.2 (6H, m, i, j and k), 0.90 (3H, t, J = 6.5 Hz, l) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.39 (1, b), 115.64 (2, a), 89.68 (0, f), 77.51 (2, e), 37.32 (0, g), 34.25 (2, c), 31.19 (2), 29.58 (2), 28.07 (2), 22.41 (2), 17.32 (2), 14.19 (3, l) ppm

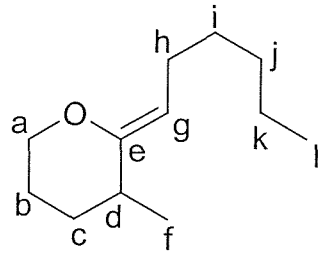
IR (thin film) ν = 3076w, 2929s, 2858s, 2270s, 1642m, 1466m, 1379w, 1240s, 994m, 910s cm^{-1}

LRMS (APCI) m/z = 181 $(M + H)^+$

HRMS: $C_{12}H_{21}O$ (M + H) requires m/z = 181.1592, found 181.1589

2-[(*Z*)-Hexylidene]-3-methyltetrahydro-2*H*-pyran (203)

To a solution of Cp_2ZrCl_2 (867 mg, 2.97 mmol) in THF (10 mL) under Ar at –80 °C was added dropwise n-butyllithium (2.4 mL of a 2.5 M solution in hexanes, 5.94 mmol). After 15 minutes a solution of 1-(4-pentenyloxy)-1-heptyne **(202)** (510 mg, 2.83 mmol) in THF (3 mL) was added. The pale yellow solution was allowed to warm to room temperature and stirred for 4 h. MeOH (2 mL) and saturated $NaHCO_3$ solution (2 mL) were added to the dark red reaction mixture, providing a pale yellow suspension. After 4 h, the mixture was poured into saturated $NaHCO_3$ solution (10 mL) and pentane (20 mL). The layers were separated, and the aqueous extracted with pentane. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (neutral alumina, petrol) to provide the desired product as a pale yellow oil (287 mg, 55%).



^1H NMR (300 MHz, $CDCl_3$) δ = 4.52 (1H, td, J = 7, 1 Hz, g), 4.00 (1H, dtd, J = 10.5, 4, 1.5 Hz, a), 3.60 (1H, td, J = 10.5, 4 Hz, a), 2.21 (1H, m, d), 2.05 (2H, q, J = 7 Hz, h), 1.75 (4H, m, b and c), 1.29 (6H, m, i, j and k), 1.04 (3H, d, J = 6.5 Hz, f), 0.88 (3H, t, J = 6 Hz, l) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 157.21 (0, e), 106.90 (1, g), 70.07 (2, a), 33.81(1, d), 32.61 (2, j), 31.76 (2, h), 30.00 (2, i), 25.45 (2, b), 24.37 (2, c), 22.75 (2, k), 18.47 (3, f), 14.22 (3, l) ppm.

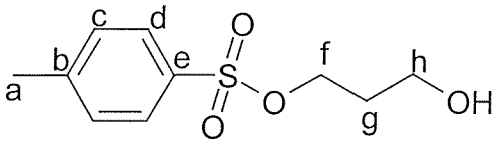
IR (thin film) ν = 2927s, 2857s, 1677w, 1654w, 1465m, 1377w, 1276w, 1160m, 1086m, 908s cm^{-1}

LRMS m/z = 183 $(M + H)^+$, 100%, 182 (M^+), 55%

HRMS: $C_{12}H_{22}O$ requires m/z = 182.1671, found 182.1649

3-Hydroxy-propane-1-(paratoluenesulfonate) (204)

To a solution of propane-1,3-diol (100 mmol, 7.61 g) and pyridine (95 mmol, 7.52 g) in chloroform (100 mL) at 0 °C was added *para*-toluene sulfonyl chloride (79 mmol, 15.06 g). The reaction was stirred for 3 h, when H_20 (10 mL) and Et_2O (30 mL) were added. The layers were separated and the aqueous extracted with ether. The combined organic phases were washed with 2 M HCl (20 mL), $NaHCO_3$ solution (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (SiO_2, 70% ether in petrol) providing the title compound as a viscous, colourless oil (9.524 g, 51%).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.76 (2H, d, J = 8.5 Hz, d), 7.33 (2H, d, J = 8 Hz, c), 4.14 (2H, t, J = 6 Hz, f), 3.65 (2H, q, J = 6 Hz, h), 2.42 (3H, s, a), 2.34 (1H, t, J = 6 Hz, -OH), 1.85 (2H, quintet, J = 6 Hz, g) ppm

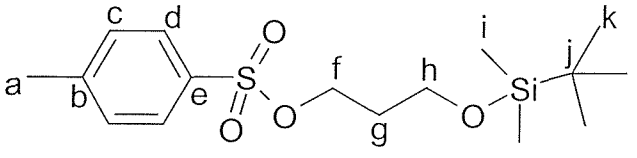
^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.96 (0, e), 132.78 (0, b), 129.92 (1, d), 127.82 (1, c), 67.68 (2, f), 58.13 (2, h), 31.61 (2, g), 21.31 (3, a) ppm

IR (thin film) ν = 3412br m, 2961s, 2892s, 1598m, 1359s, 1177s, 1098s cm^{-1}

NMR data is consistent with literature values.[74]

3-(Dimethyl-*tert*-butylsilyloxy)-propane-1-(*para*-toluene sulfonate) (205)

tert-Butyl dimethyl silyl chloride (7.75 g, 51.5 mmol) and imidazole (3.18 g, 46.8 mmol) were added to a stirred solution of 3-hydroxy-propane-1-(paratoluenesulfonate) **(204)** (10.76 g, 46.8 mmol) in DMF (20 mL). After 2.5 h, the reaction mixture was diluted with water (10 mL) and ether (25 mL) and the phases separated. The aqueous was extracted with ether, and the combined organic phases washed with brine, dried over Na_2SO_4, filtered and concentrated to give the title compound as a clear, colourless oil (13.64 g, 39.4 mmol, 85%).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.78 (2H, d, J = 8 Hz, d), 7.33 (2H, d, J = 8 Hz, c), 4.13 (2H, t, J = 6 Hz, f), 3.62 (2H, t, J = 6 Hz, h), 2.44 (3H, s, a), 1.82 (2H, quintet, J = 6 Hz, g), 0.82 (9H, s, k), -0.02 (6H, s, i) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.80 (0, e), 133.22 (0, b), 129.95 (1, d), 128.04 (1, c), 67.68 (2, f), 58.53 (2, h), 32.11 (2, g), 21.74 (3, a), 18.29 (0, j), 15.40 (3, k), -3.44 (3, i) ppm

IR (thin film) ν = 2927s, 2855s, 1598m, 1471m, 1364s, 1255s, 1177s, 1099s, 1006m, 945s cm^{-1}

NMR data is consistent with literature values.[75]

(3-Iodopropoxy)(*tert*-butyl)dimethylsilane (206)

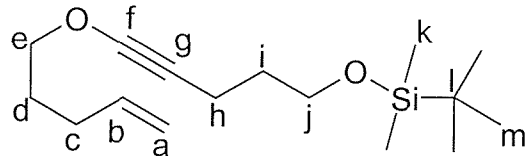
The title compound was prepared by the method of Yotsu-Yamashita *et al.*[76]

(4-Iodobutoxy)(*tert*-butyl)dimethylsilane (207)

The title compound was prepared by the method of Sodeoka *et al.*[12]

((5-(4-Pentenyloxy)-4-pentynyl)oxy)-(*tert*-butyl)dimethylsilane (208)

The title compound was prepared by the general procedure for alkoxyalkynes, described earlier for **(202)**, using (3-iodopropoxy)(*tert*-butyl)dimethyl silane as the electrophile and in 34% yield.



^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.80 (1H, ddt, J = 17, 10, 7 Hz, b), 5.06 (1H, ddt, J = 17, 1.5, 1.5 Hz, a), 5.02 (1H, ddt, J = 10, 1.5, 1 Hz, a), 3.98 (2H, t, J = 6.5 Hz, e), 3.69 (2H, t, J = 6 Hz, j), 2.20 (2H, t, J = 7 Hz, h), 2.16 (2H, m, c), 1.82 (2H, tt, J = 7.5, 6.5 Hz, d), 1.66 (2H, app. quintet, J = 6.5 Hz, i), 0.91 (9H, s, m), 0.07 (6H, s, k) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.34 (1, b), 115.68 (2, a), 89.72 (0, f), 77.52 (2, e), 61.94 (2, j), 36.76 (0, g), 32.85 (2, h), 29.56 (2, c), 28.05 (2, d), 26.10 (3, m), 18.51 (0, l), 13.73 (2, i), -4.79 (3, k), ppm

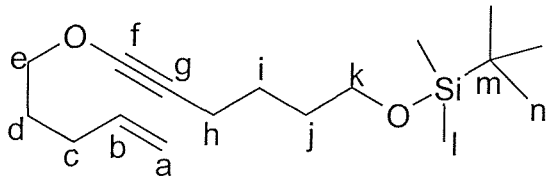
IR (thin film) ν = 2959s, 2856s, 2268m, 1641w, 1471m, 1387w, 1256s, 1104s, 910s, 837s cm^{-1}

LRMS (APCI) m/z = 300 $(M + NH_4)^+$, 25%, 156 $(M - TBDMS - H)^+$, 90%, 116 (TBDMS + H), 100%

HRMS: $C_{16}H_{31}O_2Si$ (M + H) requires m/z = 283.2093, found 283.2082

((6-(4-Pentenyloxy)-5-hexynyl)oxy)-(*tert*-butyl)dimethylsilane (209)

The title compound was prepared by the general procedure for alkoxyalkynes, described previously for **(202)**, using (4-iodobutoxy)(*tert*-butyl)dimethyl silane as the electrophile and in 26% yield.



^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.80 (1H, ddt, J = 17, 10, 7 Hz, b), 5.06 (1H, ddt, J = 17, 1.5, 1.5 Hz, a), 5.01 (1H, ddt, J = 9, 1.5, 1 Hz, a), 3.98 (2H, t, J = 6.5 Hz, e), 3.63 (2H, t, J = 6 Hz, k), 2.14 (4H, m, h and c), 1.81 (2H, app. quintet, J = 7 Hz, d), 1.56 (4H, m, i and j), 0.90 (9H, s, n), 0.06 (6H, s, l) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.36 (1, b), 115.66 (2, a), 89.83 (0, f), 77.52 (2, e), 62.97 (2, k), 37.08 (0, g), 32.12 (2), 29.57 (2), 28.07 (2), 26.23 (2), 26.12 (3, n), 18.50 (0, m), 17.19 (2, i), -3.66 (3, l) ppm

IR (thin film) ν = 1930s, 2858s, 2270s, 1641w, 1471m, 1387w, 1360w, 1254s, 1105s, 912s, 836s cm^{-1}

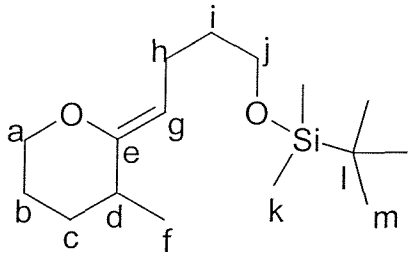
LRMS (APCI) m/z = 314 $(M + NH_4)^+$, 15%, 156 (TBDMS + H), 100%

HRMS: $C_{17}H_{33}O_2Si$ (M + H) requires 297.2250, found 297.2229

***tert*-Butyldimethyl((4-(3-methyltetrahydro-2*H*-2-pyranyliden)butyl)oxy) silane (210)**

To a solution of $ZrCp_2Cl_2$ (514 mg, 1.76 mmol) in THF (7 mL) under Ar at –80 °C was added dropwise n-butyllithium (1.40 mL of a 2.5 M solution in hexanes, 3.52 mmol). After 10 minutes, ((5-(4-pentenyloxy)-4-pentynyl)oxy)-(*tert*-butyl) dimethylsilane **(208)** (280 mg, 1 mmol) was added. The solution was allowed to warm for 2 h, before addition of MeOH (1 mL) and $NaHCO_3$ solution (2 mL). After stirring over night, the reaction mixture was poured into saturated $NaHCO_3$ solution (10 mL) and pentane (15 mL). The aqueous layer was separated and extracted with pentane.

The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated to provide the title compound as a pale yellow oil (286 mg, 1.00 mmol, 63%)



^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.54 (1H, td, J = 7, 1.5 Hz, g), 4.00 (1H, dtd, J = 10.5, 4.5, 1.5 Hz, a), 3.62 (2H, t, J = 7 Hz, j), 3.60 (1H obscured multiplet, a), 2.25 – 2.15 (1H, m, d), 2.09 (2H, q, J = 7 Hz, h), 1.85 – 1.7 (4H, m, b and c), 1.56 (2H, ttd, J = 6.5, 6.5, 1 Hz, i), 1.04 (3H, d, J = 6.5 Hz, f), 0.90 (9H, s, m), 0.06 (6H, s, k) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 157.55 (0, e), 106.15 (1, g), 69.98 (2, a), 63.22 (2, j), 33.76 (1, d), 33.49 (2), 32.51 (2), 26.12 (3, m), 25.44 (2, b), 20.71 (2, c), 18.50 (0, l), 18.43 (3, f), -3.84 (3, k) ppm

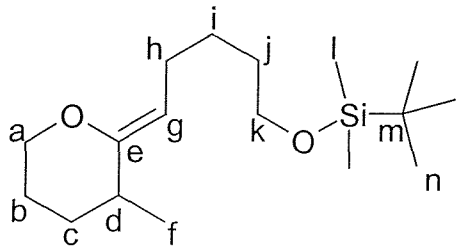
IR (thin film) ν = 2919s, 2853s, 1462s, 1387m, 1360m, 1253s, 1100s, 836s, 775s cm^{-1}

LRMS (APCI) m/z = 285 $(M + H)^+$, 30%, 156 (TBDMS + H), 100%

HRMS: $C_{16}H_{33}O_2Si$ (M + H) requires m/z = 285.2250, found 285.2226

<u>*tert*-Butyldimethyl((5-(3-methyltetrahydro-2*H*-2-pyranyliden)pentyl)oxy) silane (211)</u>

To a solution of $ZrCp_2Cl_2$ (375 mg, 1.29 mmol) in THF (5 mL) at –80 °C under Ar was added n-butyllithium (1.03 mL of a 2.5 M solution in hexanes, 2.58 mmol). After 10 minutes, ((6-(4-pentenyloxy)-5-hexynyl)oxy)-(*tert*-butyl)dimethylsilane **(209)** (347 mg, 1.17 mmol) in THF (2 mL) was added. The solution was allowed to warm to room temperature and after 4 h MeOH (2 mL) and saturated $NaHCO_3$ solution (4 mL) were added. After stirring over night the mixture was poured into water and ether, and the layers separated. The aqueous phase was extracted with ether, and the combined organic extracts washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (neutral alumina, 10% ether in petrol) to provide the desired compound as a colourless oil (189 mg, 0.63 mmol, 54%).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.52 (1H, td, J = 7, 1.5 Hz, g), 4.00 (1H, dtd, J = 10.5, 4, 1.5 Hz, a), 3.62 (2H, t, J = 7 Hz, k), 3.60 (1H, obscured m, a), 2.25 – 2.15 (1H, m, d), 2.07 (2H, q, J = 7 Hz, h), 1.85 – 1.65 (4H, m, b and c), 1.54 (2H, app. q, J = 7 Hz, j), 1.35 (2H, m, i), 1.04 (3H, d, J = 6.5 Hz, f), 0.90 (9H, s, n), 0.06 (6H, s, l) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 157.43 (0, e), 106.58 (1, g), 70.03 (2, a), 63.41 (2, k), 33.78 (1, d), 32.69 (2), 32.55 (2), 26.40 (2), 25.47 (2), 24.10 (2), 26.14 (3, n), 18.53 (0, m), 18.45 (3, f), -3.84 (3, l) ppm

IR (thin film) ν = 2930s, 2858s, 1676m, 1462m, 1255s, 1098s, 1005m, 836s, 775s, 735m cm^{-1}

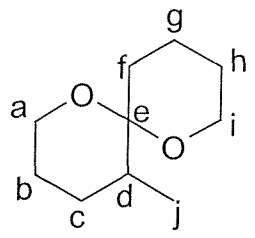
LRMS (APCI) m/z = 299 $(M + H)^+$, 60%, 156 (TBDMS + H), 100%

HRMS: $C_{17}H_{35}O_2Si$ (M + H) requires m/z = 299.2406, found 299.2399

5-Methyl-1,7-dioxaspiro[5.5]undecane (212)

To a solution of *tert*-butyldimethyl((4-(3-methyltetrahydro-2*H*-2-pyranyliden) butyl)oxy)silane **(210)** (227 mg, 0.8 mmol) in THF (5 mL) was added dropwise tetrabutyl ammonium fluoride (1.2 mL of a 1 M solution in THF, 1.2 mmol) and the solution stirred for 1 h, whereupon H_2O (10 mL) and ether (10 mL) were added. The phases were separated, and the aqueous extracted with ether. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated. To this crude product was added DCM (10 mL) and camphor sulfonic acid (20 mg, 0.08 mmol). After stirring for 1h, TLC analysis showed absence of the starting alcohol, and water (10 mL) was added to the reaction mixture. The phases were separated and the organic layer dried over Na_2SO_4, filtered and concentrated to a volume of about 5 mL. This crude solution was subjected to column chromatography (SiO_2, 10% ether in pentane) to provide the title compound as a colourless oil (50 mg, 0.29 mmol, 37%). GC analysis showed the product to be a 4:1 mixture of diastereomers (HP-5 column,

conditions: 60 °C for 4 min, then increase at 15 °C / min to 250 °C. Retention times: 9.30 min (major), 9.60 min (minor)).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.74 - 3.56 (4H, m, a and i), 1.85 - 1.25 (11H, m, b, c, d, f, g and h), 0.91 (3H, d, J = 6 Hz, j) ppm. Minor diastereomer shows protons 'j' at 1.00 ppm (d, J = 6 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) δ = 97.63 (0, e), 60.30 (2, a or i), 60.02(2, a or i), 39.00 (1, d), 32.00 (2, f), 27.49 (2), 26.34 (2), 25.48 (2), 18.64 (2), 16.92 (3, j) ppm. Minor diastereomer (where seen) δ = 60.72 (2), 60.58 (2), 36.02 (1), 32.42 (2), 25.83 (2), 25.32 (2), 20.13 (2), 18.75 (2), 14.56 (3) ppm.

IR (thin film) ν = 2940s, 2877m, 1464w, 1377w, 1088m, 1067m, 976m, 907s cm^{-1}

LRMS (APCI) m/z = 170 (M^+), 85%, 171 $(M + H)^+$, 100%

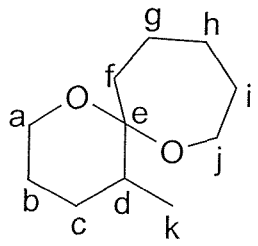
HRMS: $C_{10}H_{18}O_2$ requires m/z = 170.1307, found 170.1298

NMR data is consistent with literature values.[13,14]

5-Methyl-1,7-dioxaspiro[5.6]dodecane (213)

To a solution of *tert*-butyldimethyl((5-(3-methyltetrahydro-2*H*-2-pyranyliden) pentyl)oxy)silane **(211)** (169 mg, 0.5 mmol) in THF (3 mL) was added dropwise TBAF (0.75 mL of a 1 M solution in THF, 0.75 mmol). After stirring for 1 h, water (8 mL) was added, the phases separated, and the aqueous extracted with ether. The combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated. DCM (8 mL) was added to the concentrate, followed by camphor sulfonic acid (20 mg). After 1 h, TLC analysis showed complete conversion, and water (10 mL) was added. The organic phase was separated, dried over Na_2SO_4, filtered and concentrated to a volume of about 3 mL. This solution was subjected to column chromatography (SiO_2, 10% ether in pentane) to provide the desired product as a colourless oil (46 mg, 0.25 mmol, 50%). GC analysis showed the product to be an 11:1 mixture of diastereomers (HP-5 column, conditions: 60 °C for 4 min, then

increase at 15 °C / min to 250 °C. Retention times: 11.35 min (major), 11.64 min (minor)).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 3.81 - 3.52 (4H, m, a and j), 2.06 (1H, qt, J = 7, 7 Hz, d), 1.85 - 1.20 (12H, m, b, c, f, g, h and i), 0.95 (3H, d, J = 7 Hz, k) ppm.

Methyl signal 'k' of minor diastereomer seen at 1.02 ppm (3H, d, J = 7 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) major diastereomer δ = 101.71 (0, e), 61.83 (2, a or j), 60.66 (2, a or j), 42.13 (2, f), 40.05 (1, d), 30.81 (2), 30.46 (2), 28.25 (2), 26.32 (2), 24.64 (2), 16.86 (3, k) ppm. Minor diastereomer (where seen) δ = 61.48 (2), 61.40 (2), 35.73 (2), 34.09 (1), 30.72 (2), 29.74 (2), 21.64 (2), 20.45 (2), 16.25 (3) ppm.

IR (thin film) ν = 2935s, 2877s, 1462m, 1373m, 1282m, 1063s, 944s, 841m, 735s cm^{-1}

LRMS (APCI) m/z = 185 $(M + H)^+$, 100%

HRMS: $C_{11}H_{20}O_2$ requires m/z = 184.1463, found 184.1456

Experimental Details for Chapter 3

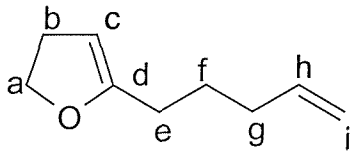
The following is the general method **(Method A)** for lithiation of 2,3-dihydrofuran or 3,4-dihydro-2*H*-pyran, and subsequent alkylation with an alkyl iodide, according to the procedure of Kocienski.[20]

To a solution of dihydrofuran (1.06 mL, 981 mg, 14 mmol) in THF (8 mL) at –40 °C under Ar, is added dropwise *tert*-butyllithium (6.1 mL of a 1.3 M solution in pentanes, 8 mmol). The solution is allowed to warm to 0 °C and stirred for 30 minutes before cooling to –20 °C and treatment with a solution of the alkyl iodide (6 mmol) in THF (2 mL). The yellow reaction mixture is allowed to warm to RT and heated at reflux for 1 h. The solution is allowed to cool and poured into saturated $NaHCO_3$ solution (10 mL) and pentane (20 mL). The aqueous layer is separated and extracted with pentane (3 x 50 mL), and the combined organic phases dried over Na_2SO_4,

filtered and concentrated. The crude product is purified by column chromatography or Kugelrohr distillation as indicated.

2-(4-Pentenyl)-4,5-dihydrofuran (301)

The title compound was prepared according to **Method A**, using 2,3-dihydrofuran (981 mg, 14 mmol) and 1-iodo-4-pentene (1.176 g, 6 mmol). Column chromatography (alumina, petrol) afforded the desired compound as a clear, colourless oil (559 mg, 4.05 mmol, 68%).



^{1}H NMR (300 MHz, C_6D_6) δ = 5.70 (1H, ddt, J = 17, 10, 6.6 Hz, h), 4.98 (1H, dd, J = 17, 1.1 Hz, i), 4.94 (1H, dd, J = 10, 1.1 Hz, i), 4.47 (1H, t, J = 2.2 Hz, c), 4.07 (2H, t, J = 9.4 Hz, a), 2.31 (2H, td, J = 9.4, 1.8 Hz, b), 2.10 (2H, t, J = 7.0 Hz, e), 1.96 (2H, br q, J = 7.1 Hz, g), 1.58 (2H, quintet, J = 7.4 Hz, f) ppm

^{13}C NMR (C_6D_6, 75 MHz) δ = 159.37 (0, d), 138.73 (1, h), 115.05 (2, i), 93.82 (1, c), 69.84 (2, a), 33.69 (2), 30.44 (2), 27.81 (2), 26.45 (2) ppm

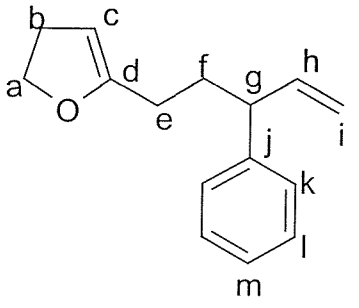
IR (thin film) ν = 3074w, 2948s, 2861s, 1666s, 1640m, 1455m, 1362m, 1244m, 1175s, 1004s, 930s, 910s, 719m cm^{-1}

LRMS (APCI) m/z = 139 $(M + H)^+$

HRMS: $C_9H_{14}O$ requires m/z = 138.1045, found 138.1034

5-(3-Phenyl-4-pentenyl)-2,3-dihydrofuran (302)

The title compound was prepared according to **Method A**, using 2,3-dihydrofuran (560 mg, 8 mmol) and 1-iodo-3-phenyl-4-pentene **(320)** (816 mg, 3 mmol). The crude product was purified by Kugelrohr distillation (100 °C, 0.8 mbar) to give the desired compound as a viscous, clear, colourless oil (532 mg, 2.5 mmol, 83%).



^{1}H NMR (300 MHz, C_6D_6) δ = 7.3 – 7.0 (5H, m, Ar), 5.899 (1H, ddd, J = 17.3, 10.2, 7.4 Hz, h), 5.036 (1H, d, J = 17.2 Hz, i), 5.005 (1H, d, J = 10.0 Hz, i), 4.517 (1H, tt, J = 2.2, 1.3 Hz, c), 4.129 (2H, t, J = 9.3 Hz, a), 3.256 (1H, q, J = 7.4 Hz, g), 2.362 (2H, tq, J = 9.4, 2.0 Hz, b), 2.17 (2H, m, e), 2.03 (2H, m, f) ppm

^{13}C NMR (75 MHz, C_6D_6) δ = 159.20 (0, d), 144.28 (0, j), 142.34 (1, h), 128.78 (1, k or l), 127.94 (1), 126.53 (1, m), 114.30 (2, i), 93.80 (1, c), 69.76 (2, a), 49.63 (1, g), 32.74 (2), 30.36 (2), 26.42 (2) ppm

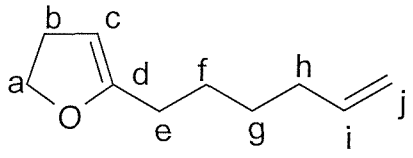
IR (thin film) ν = 2926s, 2870s, 1666s, 1636m, 1600m, 1492m, 1452s, 1175m, 1004s, 915s cm^{-1}

LRMS (APCI) m/z = 215 $(M + H)^+$, 100%, 214 (M^+), 50%

HRMS: $C_{15}H_{18}O$ requires m/z = 214.1358, found 214.1362

2-(5-Hexenyl)-4,5-dihydrofuran (303)

The title compound was prepared according to **Method A**, using dihydrofuran (1.06 mL, 981 mg, 14 mmol) and 1-iodo-5-hexene (1.26 g, 6 mmol). Column chromatography (alumina, petrol) afforded the desired compound as a clear, colourless oil (735 mg, 4.84 mmol, 80%).



^{1}H NMR (300 MHz, C_6D_6) δ = 5.72 (1H, ddt, J = 16.9, 9.9, 6.6 Hz, i), 4.98 (1H, dd, J = 16.9, 1.8 Hz, j), 4.94 (1H, m, obscured by other 'j' proton, j), 4.48 (1H, app. quintet, J = 2.1 Hz, c), 4.08 (2H, t, J = 9.4 Hz, a), 2.32 (2H, td, J = 9.2, 1.8 Hz, b), 2.09 (2H, td, J = 7.4, 0.8 Hz, e), 1.92 (2H, q, J = 6.6 Hz, h), 1.50 (2H, quintet, J = 7.5 Hz, g), 1.32 (2H, m, f) ppm

^{13}C NMR (75 MHz, C_6D_6) δ = 159.58 (0, d), 139.05 (1, i), 114.74 (2, j), 93.64 (1, c), 69.83 (2, a), 34.01 (2), 30.45 (2), 28.95 (2). 28.30 (2), 26.69 (2) ppm

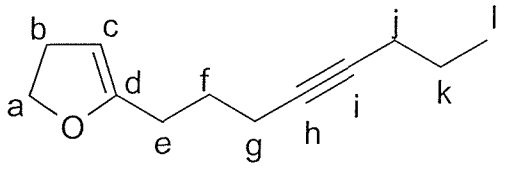
IR (thin film) ν = 3074w, 2930s, 2859s, 1666s, 1640m, 1462m, 1363m, 1235m, 1175s, 1004s, 933s, 910s cm^{-1}

LRMS (APCI) m/z = 152 (M^+)

NMR data is consistent with literature values.[20]

2-(4-Octynyl)-4,5-dihydrofuran (304)

The title compound was synthesised according to **Method A**, using 2,3-dihydrofuran (0.76 mL, 10 mmol) and 1-iodo-4-octyne (944 mg, 4 mmol). The crude product was purified by Kugelrohr distillation (120 °C, 0.7 mbar) to yield the desired product (624 mg, 88%).



^{1}H NMR (300 MHz, C_6D_6) δ = 4.590 (1H, m, c), 4.152 (2H, t, J = 9.2 Hz, a), 2.42 – 2.32 (4H, m), 2.252 (2H, tt, J = 7.2, 2.4 Hz, g), 2.133 (2H, tt, J = 7.0, 2.4 Hz, j), 1.842 (2H, quintet, J = 7.3 Hz, f), 1.505 (2H, app. sextet, J = 7.2 Hz, k), 0.998 (3H, t, J = 7.4 Hz, l) ppm

^{13}C NMR (75 MHz, C_6D_6) δ = 158.91 (0, d), 94.08 (1, e), 80.85 (0), 80.20 (0), 69.83 (2, a), 30.42 (2), 27.52 (2), 26.90 (2), 22.98 (2), 21.22 (2), 18.83 (2), 13.71 (3, l) ppm

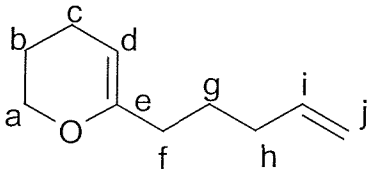
IR (thin film) ν = 2933s, 2869s, 1667s, 1456m, 1433m, 1245m, 1175m, 1005s, 931s, 722m cm^{-1}

LRMS (APCI) m/z = 178 (M^+), 179 $(M + H)^+$

HRMS: $C_{12}H_{18}O$ requires m/z = 178.1358, found 178.1353

2-(4-Pentenyl)-5,6-dihydro-4*H*-pyran (305)

The title compound was prepared according to **Method A**, using 3,4-dihydro-2*H*-pyran (631 mg, 7.5 mmol) and 1-iodo-4-pentene (980 mg, 5 mmol). The crude product was purified by Kugelrohr distillation (75 °C, .0.4 mbar) to give the desired product as a clear, colourless oil (693 mg, 4.56 mmol, 91%).



^{1}H NMR (300 MHz, C_6D_6) δ = 5.83 (1H, ddt, J = 16.9, 9.9, 6.6 Hz, i), 5.09 (1H, dd, J = 16.9, 1.5 Hz, j), 5.03 (1H, m, obscured by other 'j' proton, j), 4.52 (1H, t, J =

3.7 Hz, d), 3.82 (2H, t, J = 5.1 Hz, a), 2.1 (4H, m, f and c), 1.88 (2H, m, h), 1.71 (2H, quintet, J = 7.4 Hz, g), 1.54 (2H, app. quintet, J = 5.8 Hz, b) ppm

^{13}C NMR (75 MHz, C_6D_6) δ = 154.59 (0, e), 138.83 (1, i), 114.66 (2, j), 95.20 (1, d), 65.87 (2, a), 34.14 (2), 33.42 (2), 26.60 (2), 22.67 (2), 20.51 (2) ppm

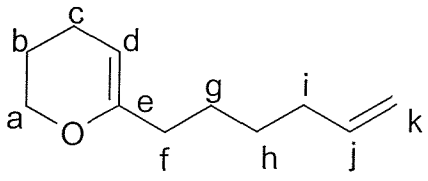
IR (thin film) ν = 3073w, 2948s, 2865s, 1674s, 1640m, 1464m, 1436m, 1362m, 1234s, 1064s, 911s cm^{-1}

LRMS (APCI) m/z = 175 $(M + Na)^+$

HRMS: $C_{10}H_{16}O$ requires m/z = 152.1201, found 152.1201

2-(5-Hexenyl)-5,6-dihydro-4*H*-pyran (306)

The title compound was prepared according to **Method A**, using 3,4-dihydro-2*H*-pyran (631 mg, 7.5 mmol) and 1-iodo-5-hexene (1.05 g, 5 mmol). The crude product was purified by Kugelrohr distillation (100 °C, 0.8 mbar) to give the desired product as a clear, colourless oil (692 mg, 4.17 mmol, 83%).



^{1}H NMR (300 MHz, C_6D_6) δ = 5.75 (1H, ddt, J = 16.9, 10.3, 6.6 Hz, j), 5.00 (1H, d + fs, J = 16.9 Hz, k), 4.96 (1H, d, J = 10.3 Hz, k), 4.45 (1H, t, J = 3.5 Hz, d), 3.77 (2H, t, J = 5.1 Hz, a), 2.06 (2H, t, J = 7.4 Hz, f), 1.97 (2H, m, c), 1.82 (2H, q, J = 5.4 Hz, i), 1.55 (2H, quintet, J = 7.5 Hz, g or h), 1.48 (2H, app. quintet, J = 6.1 Hz, g or h), 1.35 (2H, m, b) ppm

^{13}C NMR (75 MHz, C_6D_6) δ = 155.21 (0, e), 139.40 (1, j), 114.82 (2, k), 95.37 (1, d), 66.28 (2, a), 35.02 (2), 34.32 (2), 29.09 (2), 27.24 (2), 23.10 (2), 20.94 (2) ppm

IR (thin film) ν = 3073w, 2926s, 2881s, 1674s, 1640m, 1464m, 1362m, 1234s, 1164m, 1065s, 991m, 910s cm^{-1}

LRMS (APCI) m/z = 166 (M^+)

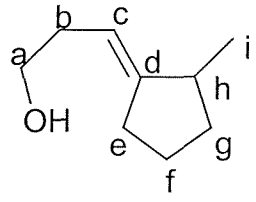
HRMS: $C_{11}H_{18}O$ requires m/z = 166.1358, found 166.1350

The following is a general method **(Method B)** for co-cyclisation of dienes and enynes mediated by zirconocene (1-butene), in accordance with the procedure of Negishi.[77]

To a solution of $ZrCp_2Cl_2$ (321 mg, 1.1 mmol) in THF (5 mL) at –80 °C under Ar is added dropwise n-butyllithium (0.88 mL of a 2.5 M solution in hexanes, 2.2 mmol). In the case of substrates containing a free hydroxyl group, 2.2 equivalents of $ZrCp_2Cl_2$ (642 mg) and 4.4 equivalents of n-butyllithium (1.76 mL) are used. After the addition of butyllithium, a solution of the diene or enyne (1 mmol) in THF (2 mL) is added dropwise and the solution allowed to warm to RT. After between 3 h and 16 h at RT, MeOH (3 mL) and saturated $NaHCO_3$ solution (7 mL) are added and the cloudy white or pale yellow reaction mixture stirred for between 2 h and 16 h. After dilution of the reaction mixture with ether (20 mL) and water (20 mL), the aqueous phase is separated and extracted with ether (3 x 50 mL). The combined organic phases are combined and washed with brine, dried over $MgSO_4$, filtered and concentrated. Purification is by column chromatography and on occasion subsequent Kugelrohr distillation, as indicated.

3-(2-(*E*)-Methylcyclopentyliden)-1-propanol (307)

The title compound was prepared according to **Method B**, using 2-(4-pentenyl)-4,5-dihydrofuran **(301)** (331 mg, 2.4 mmol). The crude oil was purified by column chromatography (SiO_2, 25% ether in petrol) to give the desired product as a clear, colourless oil (263 mg, 78%).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.18 (1H, tq, J = 7.4, 1.8 Hz, c), 3.64 (2H, br s, a), 2.71 (1H, m, h), 2.32 (4H, m, b, e and g), 1.84 (1H, dq, J = 12.5, 7.7 Hz, g), 1.69 (1H, m, e), 1.6 (1H, m, OH), 1.5 (1H, m (obscured), f), 1.40 (1H, m, f), 1.02 (3H, d, J = 7.4 Hz, i) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.02 (0, d), 115.79 (1, c), 62.84 (2, a), 35.07 (2), 34.88 (1, h), 33.51 (2), 32.81 (2), 24.14 (2, f), 20.92 (3, i) ppm

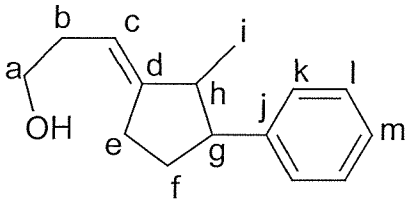
IR (thin film) ν = 3330br s, 2950s, 2866s, 1650w, 1453m, 1372m, 1050s, 872w cm^{-1}

LRMS (EI) m/z = 140 (M^+)

HRMS: $C_9H_{16}O$ requires m/z = 140.1201, found 140.1201

(2S*,3R*)-3-(2-Methyl-3-phenylcyclopentyliden)-1-propanol (308)

The title compound was prepared according to **Method B**, using 5-(3-phenyl-4-pentenyl)-2,3-dihydrofuran **(302)** (214 mg, 1 mmol). The crude product was purified by column chromatography (SiO_2, 20% ether in hexane) to provide the desired product as a viscous, clear colourless oil (150 mg, 69% yield). This product was obtained as a single diastereomer.



^{1}H NMR (400 MHz, $CDCl_3$), δ = 7.25 – 7.1 (5H, m, Ar), 5.213 (1H, tq, J = 7.4, 1.9 Hz, c), 3.585 (2H, td, J = 6.5, 1.5 Hz, a), 2.656 (1H, dt, J = 9.6, 6.6 Hz, g), 2.580 (1H, quintet, J = 7.0 Hz, h), 2.45 – 2.35 (1H, m, e), 2.325 (1H, dddd, J = 15.0, 7.0, 3.0, 1.0 Hz, e), 2.262 (1H, ddt, J = 6.2, 1.8, 0.9 Hz, b), 2.228 (1H, ddt, J = 6.5, 2.0, 0.8 Hz, b), 2.014 (1H, dtd, J = 12.3, 7.0, 3.3 Hz, f), 1.623 (1H, dddd, J = 12.0, 10.5, 9.5, 7.0 Hz, f), 1.436 (1H, s, -OH), 1.076 (3H, d, J = 6.8 Hz, i) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 150.62 (0, d), 145.62 (0, i), 128.50 (1), 127.48 (1), 126.23 (1, m), 116.68 (1, c), 62.82 (2, a), 54.99 (1, g), 43.61 (1, h), 34.28 (2), 34.06 (2), 32.43 (2), 20.38 (3, i) ppm

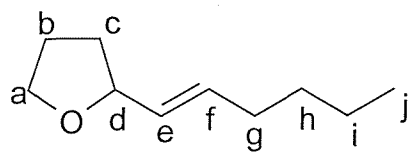
IR (thin film) ν = 3344 br s, 2952s, 2868s, 1675w, 1600m, 1580w, 1493m, 1453m, 1044s, 700s cm^{-1}

LRMS (ES) m/z = 198 $(M - H_2O)^+$

HRMS: $C_{15}H_{20}O$ requires m/z = 216.1514, found 216.1522.

2-(1-(*E*)-Hexenyl)tetrahydrofuran (309) and 3-(2-(*E*)-Methylcyclohexyliden)-1-propanol (310)

The title compounds were prepared according to **Method B**, using 2-(5-hexenyl)-4,5-dihydrofuran **(303)** (152 mg, 1 mmol). Column chromatography of the crude material (SiO_2, 10% ether in petrol – 30% ether in petrol) yielded **(309)** and **(310)** in 25% and 13% yields respectively.



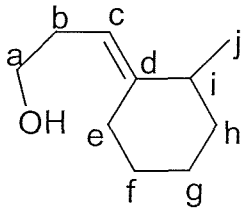
^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.67 (1H, dtd, J = 15.4, 6.6, 0.75 Hz, f), 5.44 (1H, ddt, J = 15.1, 7.0, 1.5 Hz, e), 4.21 (1H, q, J = 7.0 Hz, a), 3.89 (1H, dt, J = 8.5, 7.0 Hz, d), 3.75 (1H, td, J = 7.9, 6.2 Hz, a), 2.02 (2H, q, J = 6.4 Hz, g), 1.90 (2H, m), 1.57 (1H, dq, J = 11.8, 8.1 Hz), 1.34 (5H, m), 0.88 (3H, t, J = 7.2 Hz, j) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 133.01 (1, e or f), 130.71 (1, e or f), 80.15 (1, d), 67.98 (2, a), 32.38 (2), 32.04 (2), 31.40 (2), 26.09 (2), 22.35 (2)i, 14.06 (3, j) ppm

IR (thin film) ν = 2957s, 2922s, 2870s, 1459w, 1377w, 1050s, 968s, 909s, 734s cm^{-1}

LRMS (APCI) m/z = 154 (M^+)

HRMS: $C_{10}H_{18}O$ requires m/z = 154.1358, found 154.1371



^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.200 (1H, tq, J = 6.6, 1.8 Hz, c), 3.648 (2H, m, a), 2.505 (1H, m, -OH), 2.315 (4H, m), 1.8 – 1.74 (1H, m), 1.73 – 1.65 (1H, m), 1.63 – 1.44 (4H, m), 1.25 (1H, m), 0.897 (3H, t, J = 7.4, j) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 151.10 (0, d), 116.07 (2, c), 62.88 (2, a), 42.12 (1, i), 33.71 (2), 32.93 (2), 31.48 (2), 27.89 (2), 24.11 (2), 12.34 (3, j) ppm

IR (thin film) ν = 3343brs, 2953s, 2868s, 1456m, 1373m, 1120m, 1048s, 872w cm^{-1}

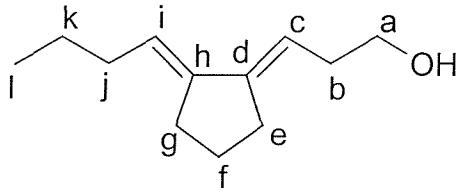
LRMS (APCI) m/z = 196 (M + MeCN)$^+$

HRMS: $C_{10}H_{18}O$ requires m/z = 154.1358, found 154.1359

3-{2-[(*E*)-Butylidene]cyclopentyliden}-1-propanol (311) and 3-{2-[(*E*)-butylidene] cyclopentyliden}-2-propene (312)

The title compounds were prepared according to **Method B**, starting from 2-(4-octynyl)-4,5-dihydrofuran **(304)** (178 mg, 1 mmol). The crude material was purified by column chromatography (SiO_2, petrol – 20% ether – 40% ether gradient) to give

the title compounds. The alcohol **(311)** was obtained as a clear, colourless oil (73 mg, 41%). The triene **(312)** was also obtained as a clear, colourless oil (45 mg, 28%), contaminated with a small amount of material derived from a slight impurity in the starting enyne.



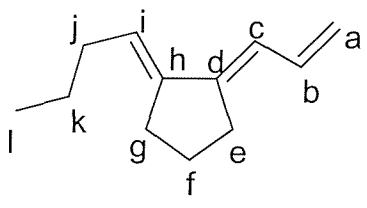
^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.729 (1H, t, J = 7.3 Hz, c), 5.363 (1H, t, J = 7.1 Hz, i), 3.319 (2H, m, a), 2.563 (2H, q, J = 7.0 Hz, b), 2.42 – 2.33 (4H, m), 2.077 (2H, q, J = 7.4 Hz, j), 1.648 (2H, quintet, J = 7.3 Hz, f), 1.5 (1H, br, s, -OH), 1.447 (2H, app. sextet, J = 7.2 Hz, k), 0.938 (3H, t, J = 7.4 Hz, l) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 143.16 (0), 140.00 (0), 126.75 (1), 117.89 (1), 63.08 (2, a), 36.65 (2), 32.87 (2), 32.43 (2), 31.24 (2), 23.89 (2), 22.89 (2), 14.14 (3, l) ppm

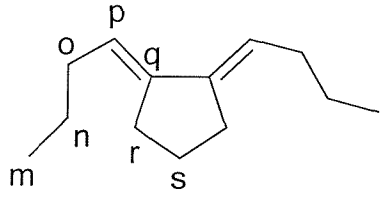
IR (thin film) ν = 3330 br m, 2956s, 2870s, 1463w, 1432w, 1041m, 884w cm^{-1}

LRMS (APCI) m/z = 181 $(M + H)^+$

HRMS: $C_{12}H_{20}O$ requires m/z = 180.1514, found 180 1510



and

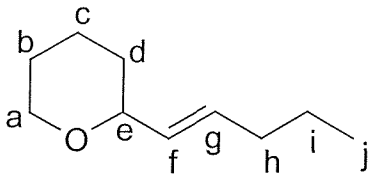


^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.465 (1H, ddd, J = 16.9, 11.0. 10.1 Hz, b), 6.294 (1H, dt, J = 11.2, 2.4 Hz, c), 5.802 (1H, tt, J = 7.5 Hz, 2.6 Hz, i), 5.650 (1H, tt, J = 7.4, 2.5 Hz, p), 5.100 (1H, dd, J = 16.7, 1.5 Hz, a), 4.956 (1H, dd, J = 10.2, 1.0 Hz, a), 2.434 (2H, td, J = 7.3, 2.4 Hz, e), 2.32 – 2.25 (4H, m, g and r), 2.15 – 1.95 (4H, m, j and o), 1.7 – 1.6 (3H, m, f and s), 1.4 – 1.3 (4H, m, k and n), 0.9 – 0.8 (6H, m, l and m) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.20 (0, d), 141.09 (0, q or h), 141.04 (0, q or h), 134.99 (1, c), 120.53 (1, b), 117.73 (1, i or p), 117.65 (1, i or p), 115.35 (2, a), 32.08 (2), 31.90 (2), 31.00 (2), 30.47 (2), 30.37 (2), 24.04 (2), 23.98 (2), 23.01 (2), 22.89 (2), 14.17 (3, l or m), 14.11 (3, l or m) ppm.

2-[(*E*)-1-Pentenyl]tetrahydro-2*H*-pyran (313)

The title compound was prepared according to **Method B**, using 2-(4-pentenyl)-5,6-dihydro-4*H*-pyran **(305)** (308 mg, 2 mmol). Column chromatography allowed separation of the title compound (95 mg, 31%) from a mixture of other, inseparable components.



^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.67 (1H, dtd, J = 15.5, 6.6, 0.75 Hz, g), 5.47 (1H, ddt, J = 15.5, 6.3, 1.3 Hz, f), 4.01 (1H, d + fs, J = 11 Hz, a), 3.75 (1H, br dd, J = 10, 7 Hz, e), 3.48 (1H, t, J = 11 Hz, a), 2.00 (2H, q, J = 7.1 Hz, h), 1.85 (1H, m, b), 1.65 – 1.45 (5H, m), 1.39 (2H, app. sextet, J = 7.4 Hz, i), 0.89 (3H, t, J = 7.4 Hz, j) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 131.83 (1, f or g), 131.50 (1, f or g), 78.45 (1, e), 68.49 (2, a), 34.58 (2, h), 32.37 (2, b), 26.03 (2), 23.58 (2), 22.39 (2, i), 13.86 (3, j) ppm

IR (thin film) ν = 2929s, 2840s, 1462m, 1438m, 1375m, 1260m, 1202s, 1086s, 1034s, 968s, 898m cm^{-1}

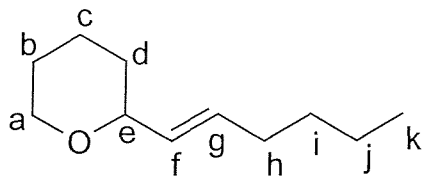
LRMS (APCI) m/z = 154 (M^+)

HRMS: $C_{10}H_{17}O$ (M – H) requires m/z = 153.1279, found 153.1274

2-[(*E*)-1-Hexenyl]-tetrahydro-2*H*-pyran (314a) and 2-[(*E*)-1-Hexenyl]-2,3-dideutero-tetrahydro-2*H*-pyran (314b).

To a solution of Cp_2ZrCl_2 (964 mg, 3.3 mmol) in THF (15 mL) at –80 °C under Ar was added dropwise n-butyllithium (2.64 mL of a 2.5 M solution in hexanes, 6.6 mmol). After 10 min 2-(5-hexenyl)-5,6-dihydro-4*H*-pyran **(306)** (498 mg, 3 mmol) in THF (3 mL) was added. The solution was allowed to warm to room temperature and stirred for 3 h. 7 mL (one third) of the reaction mixture was removed and added to a stirred mixture of MeOD (1 mL) and D_2O (2 mL) and quenched for 1 h. The remainder of the reaction mixture was quenched with MeOH (3 mL) and saturated $NaHCO_3$ solution (6 mL) for 1 h. The products of both quenches were worked up and purified identically: The white suspension was diluted with water and ether, and the aqueous phase separated and extracted with ether. The combined organic phases were

washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude oils were purified by column chromatography (SiO_2, 5% ether in petrol). The protic quenched product **(314a)** was obtained in 35% yield (116 mg) and the deuterium quenched product **(314b)** in 30% yield (51 mg). Both were clear, colourless oils.



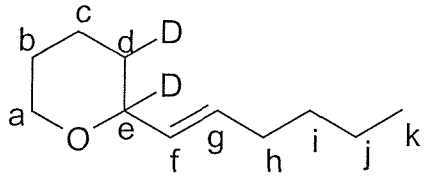
^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.67 (1H, dtd, J = 15.5, 6.6, 1.1 Hz, g), 5.46 (1H, ddt, J = 15.5, 6.2, 1.3 Hz, f), 4.00 (1H, ddt, J = 11.4, 4.4, 1.8 Hz, a), 3.74 (1H, m, e), 3.47 (1H, m, a), 2.02 (2H, q, J = 6.6 Hz, h), 1.84 (1H, m), 1.60 (2H, m), 1.53 (2H, m), 1.25 – 1.4 (5H, m), 0.88 (3H, t, J = 7.0 Hz, k) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 132.07 (1, g), 131.31 (1, f), 78.45 (1, e), 68.49 (2, a), 32.36 (2, d), 32.16 (2), 31.40 (2), 26.03 (2), 23.58 (2), 22.37 (2), 14.08 (3, k) ppm

IR (thin film) ν = 2933s, 2852s, 1439w, 1379w, 1111s, 1081s, 1033m, 970m, 910s, 732s cm^{-1}

LRMS (APCI) m/z = 168 (M^+)

NMR data is consistent with literature values.[24]



^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.66 (1H, dt, J = 15.5, 6.6 Hz, g), 5.45 (1H, d, J = 15.4 Hz, f), 4.00 (1H, ddt, J = 11.0, 4.1, 1.8 Hz, a), 3.47 (1H, td, J = 11.4, 2.9 Hz, a), 2.02 (2H, q, J = 6.6 Hz, h), 1.83 (1H, m), 1.52 (3H, m), 1.34 (5H, m), 0.88 (3H, t, J = 7.2 Hz, k) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 132.08 (1, g), 131.24 (1, f), [78.29 (0, e) triplet, J = 15.3 Hz], 68.44 (2, a), 32.16 (2), [31.73 (1, d) triplet, J = 19.4 Hz], 31.40 (2), 25.98 (2), 23.45 (2), 22.37 (2), 14.07 (3, k) ppm

IR (thin film) ν = 2930s, 2854s, 1462m, 1436m, 1375w, 1289w, 1081s, 971s, 909s cm^{-1}

LRMS (APCI) m/z = 171 $(M + H)^+$

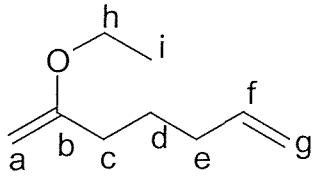
HRMS: $C_{11}H_{18}OD_2$ requires m/z = 170.1640, found 170.1650

The following is the general method **(Method C)** for lithiation of ethyl vinyl ether and subsequent alkylation with an alkyl iodide or aldehyde, according to the procedure of Baldwin *et al.*[26]

To a solution of ethyl vinyl ether (0.95 mL, 721 mg, 10 mmol) in THF (8 mL) at –70 °C under Ar is added dropwise *tert*-butyllithium (4.7 mL of a 1.7 M solution in pentanes, 8 mmol), resulting in a bright yellow suspension. The reaction is allowed to warm, resulting in dissolution of the yellow precipitate, and disappearance of the yellow colour at around 0 °C. The solution is re-cooled to –70 °C and a solution of the electrophile (5 mmol) in THF (2 mL) is added. After warming to 0 °C and stirring for between 1 h and 5 h, saturated NH_4Cl solution (10 mL) is added. After dilution with ether (20 mL), the aqueous phase is separated and extracted with ether (3 x 50 mL), and the combined organic phases washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product is purified by Kugelrohr distillation.

2-Ethoxy-1,5-heptadiene (315)

The title compound was prepared according to **Method C**, using 1-iodo-4-pentene (392 mg, 2 mmol), yielding a clear, colourless oil (224 mg, 80%).



^{1}H NMR (300 MHz, C_6D_6) δ = 5.851 (1H, ddt, J = 16.9, 10.3, 6.6 Hz, f), 5.132 (1H, ddt, J = 17.2, 1.8, 1.8 Hz, g), 5.061 (1H, ddt, J = 10.3, 2.2, 1.1 Hz, g), 4.044 (1H, d, J = 1.5 Hz, a), 3.971 (1H, d, J = 1.5 Hz, a), 3.581 (2H, q, J = 7.0 Hz, h), 2.252 (2H, t, J = 7.7 Hz, c), 2.106 (2H, q, J = 7.2 Hz, e), 1.760 (2H, quintet, J = 7.7 Hz, d), 1.183 (3H, t, J = 7.0 Hz, i) ppm

^{13}C NMR (75 MHz, C_6D_6) δ = 163.18 (0, b), 138.54 (1, f), 114.54 (2, g), 80.67 (2, a), 62.37 (2, h), 34.74 (2), 33.24 (2), 26.85 (2, d), 14.25 (3, i), ppm

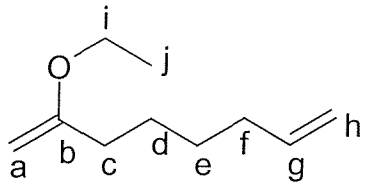
IR (thin film) ν = 3077m, 2978s, 1651s, 1595m, 1443m, 1261s, 1074s, 975m, 911s, 795s cm^{-1}

LRMS (APCI) m/z = 140 (M^+), 141 $(M + H)^+$

HRMS: $C_9H_{16}O$ requires m/z = 140.1201, found 140.1189

2-Ethoxy-1,7-octadiene (316)

The title compound was prepared according to **Method C**, using 1-iodo-5-hexene (2.10 g, 10 mmol), yielding a clear, colourless oil (1.457 g, 95%).



^{1}H NMR (300 MHz, C_6D_6) δ = 5.850 (1H, ddt, J = 17.3, 10.3, 6.8 Hz, g), 5.107 (1H, ddt, J = 17.3, 1.7, 1.7 Hz, h), 5.060 (1H, ddt, J = 10.3, 2.2, 1.1 Hz, h), 4.047 (1H, d, J = 1.5 Hz, a), 3.970 (1H, d, J = 1.5 Hz, a), 3.593 (2H, q, J = 7.0 Hz, i), 2.244 (2H, t, J = 7.5 Hz, c), 2.065 (2H, qt, J = 7.2, 1.5 Hz, f), 1.673 (2H, quintet, J = 7.6 Hz), 1.444 (2H, quintet, J = 7.3 Hz), 1.196 (3H, t, J = 7.0 Hz, j) ppm

^{13}C NMR (75 MHz, C_6D_6) δ = 163.74 (0, b), 139.14 (1, g), 114.62 (2, h), 80.85 (2, a), 62.72 (2, i), 35.56 (2, c or f), 34.04 (2, c or f), 28.86 (2, d or e), 27.42 (2, d or e), 14.64 (3, j) ppm

IR (thin film) ν = 3076w, 2930s, 2861s, 1652s, 1593m, 1444m, 1278s, 1075s, 975m, 911s, 785s cm^{-1}

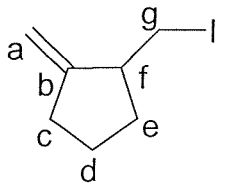
LRMS (APCI) m/z = 154 (M^+), 155 $(M + H)^+$

HRMS: $C_{10}H_{19}0$ (M + H) requires m/z = 155.1436, found 155.1437

2-Methylene-1-(iodomethyl)cyclopentane (317)

To a solution of Cp_2ZrCl_2 (321 mg, 1.1 mmol) in THF (5 mL) at –80 °C under Ar was added dropwise n-butyllithium (0.88 mL of a 2.5 M solution in hexanes, 2.2 mmol), followed by a solution of 2-ethoxy-1,6-heptadiene **(315)** (140 mg, 1 mmol) in THF (2 mL). The solution was allowed to warm to room temperature and stirred for 3 h. The orange solution was re-cooled to –80 °C and iodine (254 mg, 1 mmol) in THF (2 mL) was added. The solution was allowed to warm to 0 °C and quenched with 2 M HCl (6 mL). The mixture was extracted with pentane and the organic phases washed with saturated $Na_2S_2O_3$ solution and brine, dried over $MgSO_4$, filtered and concentrated to give a brown oil. Purification by column chromatography (SiO_2, pentane) removed much of the coloured and inorganic material, but resulted in some

decomposition of the product. The iodide was obtained in 45% yield, and about 80% purity.



^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.020 (1H, q, J = 2.2 Hz, a), 4.882 (1H, q, J = 2.2 Hz, a), 3.414 (1H, dd, J = 9.5, 4.0 Hz, g), 3.110 (1H, t, J = 9.5 Hz, g), 2.68 (1H, m, f), 2.45 – 2.38 (2H, m), 2.10 – 2.00 (1H, m), 1.79 – 1.70 (1H, m), 1.65 – 1.45 (2H, m) ppm

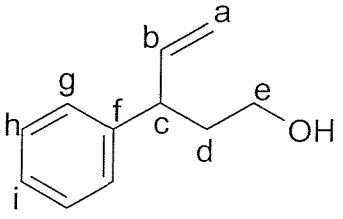
^{13}C NMR (75 MHz, $CDCl_3$) δ = 154.16 (0, b), 107.02 (2, a), 46.28 (1, f), 34.64 (2, c or e), 33.97 (2,c or e), 23.87 (2, d), 12.66 (2, g) ppm

Ethyl-(3-phenyl-pent-4-enoate) (318)

The title compound was prepared by the method of Arnold *et al.*[78] NMR data is consistent with literature values.[79]

3-Phenyl-pent-4-en-1-ol (319)

To a suspension of $LiAlH_4$ (5.7 g, 150 mmol) in ether (100 mL) was added dropwise a solution of ethyl(3-phenyl-pent-4-enoate) (20.4 g, 100 mmol) in ether (50 mL) at 0 °C. The suspension was stirred for 15 h before quenching with ethyl acetate (10 mL) then 2 M HCl until the solution became clear. The organic layer was separated and the aqueous extracted with ether. The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated. The crude product was purified by Kugelrohr distillation (120 °C, 1 mbar) to provide pure material (13.10 g, 81% yield).

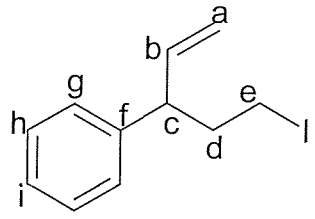


^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.4 – 7.2 (5H, m, Ar), 6.008 (1H, ddd, J = 17.6, 10.2, 7.4 Hz, b), 5.15 – 5.10 (2H, m, a), 3.602 (2H, td, J = 6.6, 1.5 Hz, e), 3.497 (1H, q, J = 7.6 Hz, c), 2.838 (1H, s, -OH), 2.003 (2H, m, d) ppm

NMR data is consistent with literature values.[79]

1-Iodo-3-phenyl-4-pentene (320)

Methanesulphonylchloride (1.89 g, 16.5 mmol) was added slowly to a solution of 3-phenyl-4-penten-1-ol **(319)** (2.43 g, 15 mmol) and triethylamine (1.82 g, 18 mmol) in dry DCM (30 mL) at –40 °C, under Ar. After 2 h, the reaction mixture was filtered and the filtrate washed with brine, dried over $MgSO_4$, filtered and concentrated. A solution of the crude mesylate in dry acetone (10 mL) was added to a refluxing solution of sodium iodide (7.5 g, 50 mmol) in dry acetone (50 mL). After 1.5 h, TLC analysis showed complete consumption of starting material and the reaction mixture was allowed to cool. After pouring into saturated $Na_2S_2O_3$ solution (30 mL), and pentane (30 mL), the aqueous phase was extracted with pentane, and the combined organic phases washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (SiO_2, 10% ether in petrol) to give the desired iodide as a clear, colourless oil (2.509 g, 61%).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.4 – 7.2 (5H, m, Ar), 5.948 (1H, ddd, J = 17.6, 9.9, 7.7 Hz, b), 5.2 – 5.1 (2H, m, a), 3.471 (1H, q, J = 7.4 Hz, c), 3.12 (2H, m, e), 2.23 (2H, m, d) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 142.67 (0, f), 140.55 (1, b), 128.85 (1, g or h), 127.79 (1, g or h), 126.83 (1, i), 115.38 (2, a), 50.16 (1, c), 38.88 (2, d), 4.97 (2, e) ppm

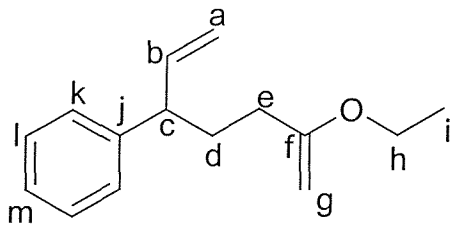
IR (thin film) ν = 3060m, 3026s, 2929m, 1636m, 1600m, 1492s, 1452s, 1422m, 1228s, 1171m, 993m, 918s cm^{-1}

LRMS (APCI) m/z = 145 $(M - I)^+$

NMR data is consistent with literature values.[79]

2-Ethoxy-5-phenyl-1,6-heptadiene (321)

The title compound was prepared according to **Method C**, using 1-iodo-3-phenyl-4-pentene (952 mg, 3.5 mmol). The crude product was purified by Kugelrohr distillation (100 °C, 0.6 mbar) to provide a clear, colourless oil (614 mg, 81% yield). The desired product was contaminated with roughly 10% of the elimination product.



^{1}H NMR (300 MHz, C_6D_6) δ = 7.3 – 7.0 (5H, m, Ar), 5.923 (1H, ddd, J = 17.4, 9.9, 7.7 Hz, b), 5.1 – 4.9 (2H, m, a), 3.977 (1H, s, g), 3.915 (1H, s, g), 3.523 (2H, q, J = 7.0 Hz, h), 3.278 (1H, q, J = 7.3 Hz, c), 2.21 (2H, m, d or e), 2.09 (2H, m, d or e), 1.122 (3H, t, J = 6.9 Hz, i) ppm

^{13}C NMR (75 MHz, C_6D_6) δ = 163.36 (0, f), 144.45 (0, j), 142.50 (1, b), 128.73 (1, k or l), 128.09 (1), 126.46 (1, m), 114.20 (2, a), 81.04 (2, g), 62.67 (2, h), 49.63 (1, c), 33.63 (2, d or e), 33.51 (2, d or e), 14.52 (3, i) ppm

IR (thin film) ν = 3026m, 2977s, 2928s, 1652s, 1630m, 1600m, 1492m, 1452m, 1276s, 1070s, 914m cm^{-1}

LRMS (APCI) m/z = 217 $(M + H)^+$, 30%, 215 $(M - H)^+$, 20%, 187 $(M - OEt)^+$, 100%, 171 $(M - OEt)^+$, 55%

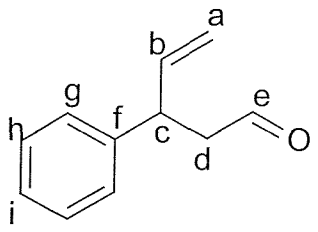
HRMS: $C_{15}H_{20}O$ requires m/z = 216.1514, found 216.1530.

3-Phenyl-pent-4-enal (322)

The title compound was prepared by standard Swern oxidation conditions.[29]

To a solution of oxalyl chloride (1.752 g, 13.8 mmol) in DCM (70 mL) at –80 °C under Ar was added dimethylsulfoxide (1.900 g, 24.3 mmol). After 30 min, a –78 °C solution of 3-phenyl-pent-4-en-1-ol **(319)** (1.312 g, 8.1 mmol) in DCM (20 mL) was added, resulting in a white suspension. After 40 min at –80 °C triethylamine (3.28 g, 32.4 mmol) was added and the solution allowed to warm to RT. The reaction mixture was diluted with saturated $NaHSO_4$ solution and extracted into DCM. The extracts were washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, filtered

and concentrated. The crude compound was purified by column chromatography (Al_2O_3, 10% ether in petrol) to give the desired product (1.070 g, 83%).

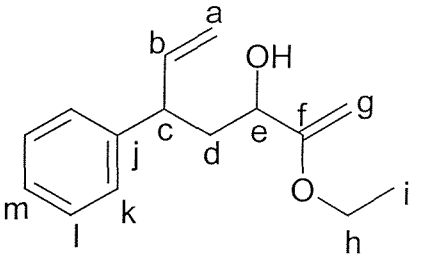


^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.738 (1H, s, e), 7.4 – 7.2 (5H, m, Ar), 6.007 (1H, ddd, J = 17.1, 10.4, 6.9 Hz, b), 5.132 (1H, d, J = 9.9 Hz, a), 5.088 (1H, d, J = 16.9 Hz, a), 3.975 (1H, q, J = 7.2 Hz, c), 2.857 (2H, m, d) ppm

NMR data is consistent with literature values.[80]

2-Ethoxy-3-hydroxy-5-phenyl-1,6-heptadiene (323)

The title compound was prepared according to **Method C**, using 3-phenyl-4-pentenal **(322)** (800 mg, 5 mmol). The crude product was purified by Kugelrohr distillation (130 °C, 0.8 mbar) to provide a clear, colourless oil (838 mg, 72%). The product was a 1:1 mixture of diastereomers.



^{1}H NMR (300 MHz, C_6D_6) δ = 7.4 – 7.1 (5H, m, Ar), 6.046 (1H, m, b), 5.3 – 5.0 (2H, m, a), 4.3 – 3.7 (4H, m), 3.495 (2H, m, h), 2.4 – 2.2 (2H, m, d), 1.846 (1H, t, J = 5.5 Hz, -OH), (1.123 (td, J = 7.2, 1.0 Hz) and 1.083 (td, J = 7.2, 1.0 Hz,) total 3H, i) ppm

^{13}C NMR (75 MHz, C_6D_6) δ = 164.77 and 164.68 (0, f), 144.84 and 143.78 (0, j), 142.97 and 141.90 (1, b), 128.80 (1), 128.47 (1), 126.59 and 126.46 (1, m), 80.86 and 80.72 (2, g), 70.92 and 70.75 (1, e), 62.90 and 62.83 (2, h), 46.49 and 46.35 (1, c), 41.85 and 41.44 (2, d), 14.35 and 14.29 (3, i) ppm

IR (thin film) ν = 3383 br m, 2977s, 2928m, 1660m, 1646m, 1630m, 1452m, 1295s, 1247s, 1072s, 915m, 810m cm^{-1}

LRMS (APCI) m/z = 232 (M^+), 10%, 215 $(M - OH)^+$, 100%, 187 $(M - OEt)^+$, 60%, 169 $(M - OEt - H_2O)^+$, 70%

HRMS: $C_{15}H_{20}O_2$ requires m/z = 232.1463, found 232.1457

Ethyl-(2-phenyl-pent-4-enoate) (324)

The title compound was prepared by the method of Padwa *et al.*[31] NMR data is consistent with literature values.[81]

2-Phenyl-pent-4-en-1-ol (325)

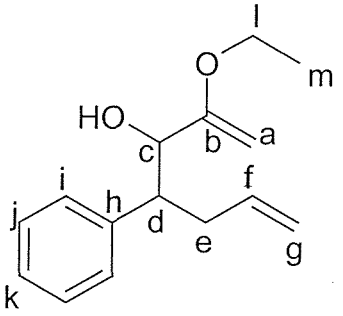
The title compound was prepared by an analogous procedure to **(319)**, by $LiAlH_4$ reduction of **(324)**. NMR data is consistent with literature values.[82]

2-Phenyl-4-pentenal (326)

The title compound was prepared by standard Swern oxidation conditions,[29] from the alcohol **(325)**, in an analogous manner to **(322)**. NMR data is consistent with literature values.[82]

(3R*,4S*)-2-Ethoxy-3-hydroxy-4-phenyl-1,6-heptadiene (327)

The title compound was prepared according to **Method C**, using 2-phenyl-4-pentenal **(326)** (800 mg, 5 mmol). The crude product was purified by Kugelrohr distillation (100 °C, 1 mbar) to provide pure material as a clear colourless oil (808 mg, 70%). The product was a single diastereomer.



^1H NMR (300 MHz, C_6D_6) δ = 7.3 – 7.1 (5H, m, Ar), 5.844 (1H, ddt, J = 17.1, 10.2, 6.9 Hz, f), 5.154 (1H, ddt, J = 17.1, 2.2, 1.5 Hz, g), 5.014 (1H, ddt, J = 10.2, 2.2, 1.3 Hz, g), 4.214 (1H, br t, J = 6.2 Hz, c), 4.154 (1H, d, J = 2.0 Hz, a), 3.863 (1H, d, J = 2.0 Hz, a), 3.376 (2H, m, l), 3.228 (1H, ddd, J = 10.9, 6.7, 4.0 Hz, d), 2.956 (1H,

dddt, J = 10.9, 7.0, 1.5 Hz, e), 2.611 (1H, dddt, J = 14.4, 10.9, 7.0, 1.5 Hz, e), 1.974 (1H, d, J = 6.2 Hz, -OH), 1.068 (3H, t, J = 6.9 Hz, m) ppm

^{13}C NMR (75 MHz, C_6D_6) δ = 162.26 (0, b), 142.31 (0, h), 137.59 (1, f), 129.12 (1), 128.31 (1), 126.60 (1, k), 115.99 (2, g), 82.83 (2, a), 77.17 (1, c), 62.69 (2, l), 50.66 (1, d), 35.21 (2, e), 14.28 (3, m) ppm

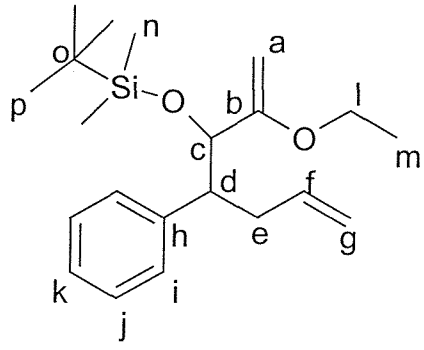
IR (thin film) ν = 3440 br m, 2977s, 2928m, 1650m, 1639m, 1630m, 1510m, 1453m, 1294s, 1242s, 1072s, 912m, 811m cm^{-1}

LRMS (APCI) m/z = 232 (M^+), 30%, 215 $(M - OH)^+$, 100%, 187 $(M - OEt)^+$, 60%, 169 $(M - OEt, - H_2O)^+$, 65%

HRMS: $C_{15}H_{20}O_2$ requires m/z = 232.1463, found 232.1468.

(1R*,2S*)-*tert*-Butyl{[1-(1-ethoxyvinyl)-2-phenyl-4-pentenyl]oxy}dimethyl silane (327a)

tert-Butyldimethylsilylchloride (155 mg, 1.03 mmol) and imidazole (64 mg, 0.94 mmol) were added to a solution of 2-ethoxy-3-hydroxy-4-phenyl-1,6-heptadiene **(327)** (203 mg, 0.94 mmol) in DMF (1.5 mL). The reaction mixture was stirred 16 h, and poured into saturated NH_4Cl solution and ether. The layers were separated and the aqueous extracted with ether. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (neutral alumina, petrol) to give the desired silyl ether (186 mg, 57%).



^1H NMR (300 MHz, $CDCl_3$) δ = 7.3 – 7.1 (5H, m, Ar), 5.817 (1H, ddt, J = 17.1, 10.1, 6.8 Hz, f), 5.116 (1H, d, J = 17.4 Hz, g), 4.955 (1H, d, J = 10.1 Hz, g), 4.298 (1H, d, J = 1.7 Hz, a), 4.270 (1H, d, J = 5.5 Hz, c), 3.932 (1H, d, J = 1.7 Hz, a), 3.390 (2H, m, d), 3.317 (1H, m, d), 3.05 – 2.9 (1H, m, e), 2.8 – 2.7 (1H, m, e), 1.077 (9H, s, p), 1.072 (3H, t, J = 7.1 Hz, m), 0.078 (3H, s, n), -0.147 (3H, s, n) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 163.37 (0, b), 142.26 (0, h), 137.78 (1, f), 129.56 (1), 128.19 (1), 126.54 (1), 115.88 (2, g), 82.88 (2, a), 78.30 (1, c), 62.72 (2, l), 50.73 (1, d), 33.75 (2, e), 26.22 (3, p), 18.48 (0, o), 14.40 (3, m), -4.56 (3, n), -5.41 (3, n) ppm.

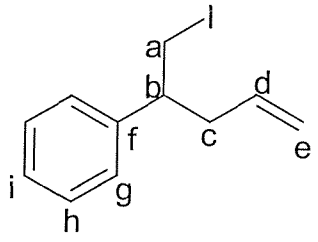
IR (thin film) ν = 3028w, 2928s, 2856m, 1660w, 1640w, 1620w, 1472m, 1253s, 1106s, 836s, 777s, 699s cm^{-1}

LRMS (APCI) m/z = 301 $(M - OEt)^+$, 10%, 215 $(M - OSi^tBuMe_2)^+$, 25%

HRMS: $C_{21}H_{34}O_2Si$ requires m/z = 346.2328, found 346.2328

1-Iodo-2-phenyl-4-pentene (328)

The title compound was prepared from alcohol **(325)** by an analogous procedure to the preparation of **(320)**.



^1H NMR (300 MHz, $CDCl_3$) δ = 7.4 – 7.1 (5H, m, Ar), 5.669 (1H, ddt, J = 16.9, 9.9, 7.0 Hz, d), 5.2 – 5.0 (2H, m, e), 3.474 (1H, dd, J = 9.7, 6.7, a), 3.410 (1H, dd, J = 9.9, 6.9 Hz, a), 2.973 (1H, quintet, J = 6.9 Hz, b), 2.7 – 2.4 (2H, m, c) ppm

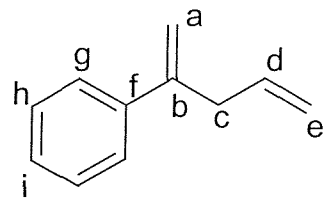
^{13}C NMR (75 MHz, $CDCl_3$) δ = 142.72 (0, f), 135.61 (1, d), 128.67 (1, g or h), 127.61 (1, g or h), 127.20 (1, i), 117.35 (2, e), 47.78 (1, b), 40.09 (2, c), 13.17 (2, a) ppm

IR (thin film) ν = 3061m, 3026s, 2911m, 1639m, 1601w, 1493s, 1452s, 1175s, 995m, 919s cm^{-1}

LRMS (APCI) m/z = 145 $(M - I)^+$

2-Phenyl-1,4-pentadiene (329)

The title compound was prepared according to **Method C**, using 1-iodo-2-phenyl-4-pentene **(328)** (952 mg, 3.5 mmol). The crude material was purified by Kugelrohr distillation (110 °C, 0.5 mbar). The product (186 mg, 37%) was found to be the result of elimination of HI from the iodide starting material.



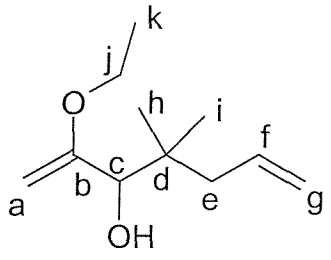
^{1}H NMR (300 MHz, C_6D_6) δ = 7.4 – 7.1 (5H, m, Ar), 5.877 (1H, ddt, J = 16.6, 9.9, 6.5 Hz, d), 5.415 (1H, d, J = 0.75 Hz, a), 5.2 – 5.0 (3H, m, a and e), 3.144 (2H, dd, J = 6.5, 1.4 Hz, c) ppm

^{13}C NMR (75 MHz, C_6D_6) δ = 146.81 (0, b), 141.37 (0, f), 136.43 (1, d), 128.55 (1, g or h), 127.73 (1, g or h), 126.40 (1, i), 116.53 (2, a), 113.20 (2, e), 39.81 (2, c) ppm

NMR data is consistent with literature values.[83]

4,4-Dimethyl-2-ethoxy-3-hydroxy-1,6-heptadiene (330)

The title compound was synthesised by Method C, using 2,2-dimethyl-4-penten-1-al (336 mg, 3 mmol). The crude product was purified by Kugelrohr distillation (110 °C, 1.0 mbar), yielding a clear, colourless oil (414 mg, 75%).



^{1}H NMR (300 MHz, C_6D_6) δ = 6.031 (1H, ddt, J = 17.9, 10.4, 7.7 Hz, f), 5.20 – 5.10 (2H, m, g), 4.163 (1H, d, J = 1.0 Hz, a), 3.990 (1H, d, J = 1.0 Hz, a), 3.908 (1H, d, J = 6.2 Hz, c), 3.428 (2H, m, j), 2.432 (1H, dd, J = 13.4, 7.7 Hz, e), 2.233 (1H, dd, J = 13.4, 7.2 Hz, e), 1.133 (3H, s), 1.089 (3H, s), 1.068 (3H, t, J = 7.0 Hz, k) ppm

^{13}C NMR (75 MHz, C_6D_6) δ = 163.21 (0, b), 136.56 (1, f), 117.72 (2, g), 83.81 (2, a), 79.82 (1, c), 63.09 (2, j), 44.58 (2, e), 38.58 (0, d), 24.04 (3), 23.72 (3), 14.79 (3, k) ppm

IR (thin film) ν = 3466 br m, 3073w, 2978s, 1657m, 1637m, 1625m, 1292m, 1069s, 912m, 813m cm^{-1}

LRMS (APCI) m/z = 167 $(M - OH)^+$, 100%, 184 (M^+), 20%, 183 $(M - H)^+$, 15%

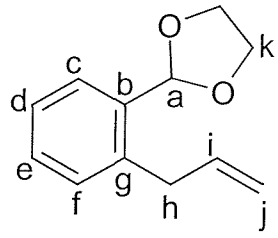
HRMS: $C_{11}H_{20}O_2$ requires m/z = 184.1463, found 184.1457.

2-(2-Bromophenyl)-dioxolane (331)

The title compound was prepared by the method of Whitnall *et al.*[84] NMR data is consistent with literature values.[84]

2-(2-Allylphenyl)-dioxolane (332)

To a solution of 2-(2-bromophenyl)-dioxolane (331) (2.29 g, 10 mmol) in ether (15 mL) at 0 °C was added *n*-butyllithium (4.4 mL of a 2.5 M solution in hexane, 11 mmol). After 2.5 h, GC analysis showed lithiation to be complete. Allyl bromide (1.4 mL, 16 mmol) was added and the solution allowed to warm to RT. GC analysis showed incorporation to be complete after 20 h, whereupon saturated NH_4Cl solution (8 mL) was added. The aqueous layer was separated and extracted with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (SiO_2, 10% ether in petrol) to provide pure material, a clear, colourless oil (1.441 g, 76%).

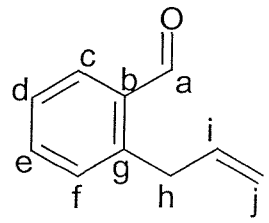


^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.6 – 7.2 (4H, m, Ar), 6.034 (1H, ddtd, J = 16.6, 10.2, 6.5, 0.75 Hz, i), 6.023 (1H, s, a), 5.1 – 5.0 (2H, m, j), 4.2 – 4.0 (4H, m, k), 3.573 (2H, d, J = 6.5 Hz, h) ppm

NMR data is consistent with literature values.[85]

2-Allyl benzaldehyde (333)

p-Toluenesulfonic acid (135 mg, 0.71 mmol) was added to a stirred solution of 2-(2-allylphenyl)-dioxolane **(332)** (1.35 g, 7.1 mmol) in acetone (20 mL). After 16 h, the reaction mixture was diluted with ether and washed with saturated $NaHCO_3$ solution and brine, then dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (SiO_2, 8% ether in petrol) to yield the desired product (846 mg, 82%).

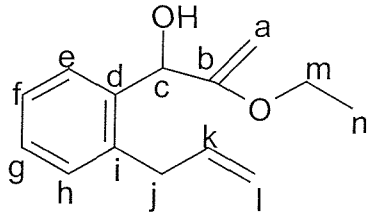


^{1}H NMR (300 MHz, $CDCl_3$) δ = 10.264 (1H, s, a), 7.859 (1H, d, J = 7.4 Hz, c), 7.543 (1H, t, J = 7.4 Hz), 7.408 (1H, t, J = 7.4 Hz), 7.295 (1H, t, J = 7.0 Hz), 6.048 (1H, ddt, J = 16.9, 10.3, 6.2 Hz, i), 5.099 (1H, d, J = 10.3, j), 4.991 (1H, d, J = 16.9 Hz, j), 3.842 (2H, d, J = 5.9 Hz, h) ppm

NMR data is consistent with literature values.[32]

1-(2-Allylphenyl)-2-ethoxy-2-propen-1-ol (334)

The title compound was prepared according to **Method C**, using 2-allylbenzaldehyde **(333)** (730 mg, 5 mmol). The crude product was purified by Kugelrohr distillation (110 °C, 1 mbar) to furnish the desired product as a clear, colourless oil (763 mg, 70%).



^{1}H NMR (300 MHz, C_6D_6) δ = 7.636 (1H, d, J = 6.9 Hz, e), 7.1 – 7.0 (3H, m, f, g and h), 5.875 (1H, ddt, J = 15.9, 9.4, 6.3 Hz, k), 5.325 (1H, s, c), 5.0 – 4.9 (2H, m, l), 4.298 (1H, dd, J = 2.2, 1.0 Hz, a), 3.918 (1H, d, J = 2.3 Hz, a), 3.429 (1H, ddt, J = 15.9, 6.5, 3 Hz, j), 3.342 (1H, ddt, J = 15.9, 6.2, 3.5 Hz, j), 3.324 (1H, td, J = 6.9, 2.5 Hz, m), 3.277 (1H, td, J = 7.1, 2.7 Hz, m), 2.065 (1H, s, -OH), 0.853 (3H, t, J = 7.1 Hz, n) ppm

^{13}C NMR (75 MHz, C_6D_6) 164.13 (0, b), 140.24 (0), 138.23 (0), 137.86 (1, k), 129.94 (1), 128.04 (1), 127.50 (1), 126.73 (1), 115.81 (2, l), 82.08 (2, a), 71.25 (1, c), 63.09 (2, m), 37.11 (2, j), 14.26 (3, n) ppm

IR (thin film) ν = 3422 br m, 2978m, 2929m, 1636m, 1451m, 1246s, 1071s, 915m, 811s, 758s cm^{-1}

LRMS (APCI) m/z = 218 (M^+), 10%, 201 $(M - OH)^+$, 100%, 189 $(M - Et)^+$, 15%, 173 $(M - OEt)^+$, 50%

HRMS: $C_{14}H_{18}O_2$ requires m/z = 218.1307, found 218.1306

2-Bromostyrene (335)

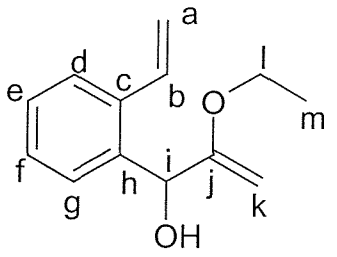
The title compound was prepared by the Wittig coupling procedure reported by Guanti *et al.*[60] NMR data is consistent with literature values.[86]

2-Vinylbenzaldehyde (336)

The title compound was prepared by the method of Clark *et al.*[33] NMR data is consistent with literature values.[87]

1-(2-Vinylphenyl)-2-ethoxy-2-propen-1-ol (337)

The title compound was prepared by **Method C**, using 2-vinylbenzaldehyde **(336)** (444 mg, 3.4 mmol). The crude product was purified by Kugelrohr distillation (110 °C, 0.8 mbar), furnishing the desired product as a clear, colourless oil (590 mg, 86%).



^{1}H NMR (300 MHz, C_6D_6) δ = 7.732 (1H, dd, J = 7.7, 1.7 Hz), 7.456 (1H, dd, J = 7.7, 1.5 Hz), 7.249 (1H, dd, J = 17.4, 10.9 Hz, b), 7.203 (1H, td, J = 7.7, 1.5 Hz), 7.126 (1H, td, J = 7.7, 1.5 Hz), 5.587 (1H, dd, J = 17.4, 1.5 Hz, a), 5.472 (1H, br s, i), 5.214 (1H, dd, J = 10.9, 1.5 Hz, a), 4.361 (1H, dd, J = 2.3, 0.7 Hz, k), 4.016 (1H, d, J = 2.2 Hz, k), 3.398 (2H, m, l), 2.187 (1H, br s, -OH), 0.961 (3H, t, J = 7.1 Hz, m) ppm

^{13}C NMR (75 MHz, C_6D_6) δ = 163.75 (0, j), 139.29 (0), 137.34 (0), 135.27 (1, b), 128.33 (1), 128.00 (1), 127.35 (1), 126.25 (1), 116.02 (2, a), 82.47 (2, k), 71.49 (1, i), 63.11 (2, l), 14.24 (3, m) ppm

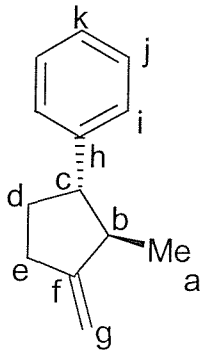
IR (thin film) ν = 3412br s, 2979s, 1660m, 1626s, 1580w, 1247s, 1074s, 916m, 813m, 771s cm^{-1}

LRMS (APCI) m/z = 187 $(M - OH)^+$, 100%, 175 $(M - Et)^+$, 20%, 159 $(M - OEt)^+$, 85%

HRMS: $C_{13}H_{16}O_2$ requires m/z = 204.1150, found 204.1145

(1R*,2S*)-1-(2-Methyl-3-methylenecyclopentyl)benzene (338)

The title compound was prepared by **Method B**, using 2-ethoxy-5-phenyl-1,6-heptadiene **(321)** (216 mg, 1 mmol). The crude product was purified by column chromatography (SiO_2, hexane) to give the desired product as a clear, colourless oil (123 mg, 72% yield). The product was a 17:1 mixture of diastereomers, as determined by gas chromatography (HP-5 column, conditions: 60 °C for 5 min then increase at 15 °C / min to 250 °C, retention times: 13.85 min (major peak), 14.06 min (minor peak). The major isomer is the (1R*,2S*) (*anti*) diastereomer, determined by the 11 Hz coupling between protons 'b' and 'c'.



^{1}H NMR (400 MHz, $CDCl_3$), major diastereomer: δ = 7.3 – 7.1 (5H, m, Ar), 4.844 (1H, q, J = 2.3 Hz, g), 4.759 (1H, q, J = 2.5 Hz, g), 2.525 (1H, ddq, J = 15.7, 8.9, 2.0 Hz, e), 2.411 (1H, td, J = 11.1, 6.3 Hz, c), 2.4 – 2.3 (2H, m, e and b), 1.983 (1H, dddd, J = 12.3, 8.1, 6.3, 1.9 Hz, d), 1.689 (1H, dtd, J = 12.4, 10.9, 8.9 Hz, d), 0.929 (3H, d, J = 6.2 Hz, a) ppm. Methyl group of minor diastereomer δ = 0.629 (3H, d, J = 7.0 Hz)

^{13}C NMR (100 MHz, $CDCl_3$) major diastereomer: δ = 157.35 (0, f), 144.29 (0, h), 128.82 (1), 127.92 (1), 126.68 (1, k), 104.86 (2, g), 54.80 (1, c), 46.94 (1, b), 33.60 (2, d), 32.21 (2, e), 16.63 (3, a) ppm. Minor diastereomer (quaternaries not seen) δ = 128.66 (1), 128.42 (1), 126.28 (1, k), 105.43 (2, g), 49.66 (1, c), 43.76 (1, b), 31.84 (2), 28.85 (2), 16.22 (3, a) ppm

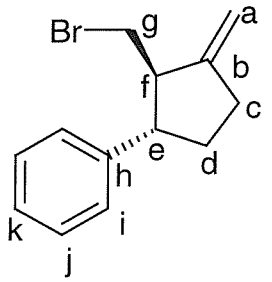
IR (thin film) ν = 3070m, 3027m, 2857s, 2870m, 1654m, 1602m, 1492m, 1452m, 1372w, 979s cm^{-1}

LRMS (APCI) m/z = 172 (M^+), 10%, 157 $(M - Me)^+$, 100%

HRMS: $C_{13}H_{16}$ requires m/z = 172.1252, found 172.1251

(1R*,2S*)-1-[2-(Bromomethyl)-3-methylenecyclopentyl]benzene (339)

To a solution of $ZrCp_2Cl_2$ (321 mg, 1.1 mmol) in THF (5 mL) at –80 °C under Ar was added dropwise *n*-butyllithium (0.88 mL of a 2.5 M solution in hexanes, 2.2 mmol). A solution of 2-ethoxy-5-phenyl-1,6-heptadiene **(321)** (216 mg, 1 mmol) in THF (2 mL) was added and the solution allowed to warm to RT. After 14 h, the red solution was cooled to –80 °C and treated with a solution of *N*-bromo succinimide (196 mg, 1.1 mmol) in THF (4 mL). The solution was allowed to warm to RT and stirred 1 h before addition of saturated $Na_2S_2O_3$ solution (1 mL) and saturated $NaHCO_3$ solution (20 mL). The reaction mixture was diluted with ether and the layers separated. The aqueous was extracted with ether, and the combined organic phases washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (SiO_2, hexane) to give the desired bromide as a clear, colourless oil (71 mg, 28%).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.4 – 7.15 (5H, m, Ar), 5.145 (1H, q, J = 2.3 Hz, a), 5.015 (1H, q, J = 2.3 Hz, a), 3.626 (1H, dd, J = 10.4, 4.2 Hz, g), 3.464 (1H, dd, J = 10.4, 4.0 Hz, g), 3.129 (1H, ddd, J = 10.9, 9.9, 6.5 Hz, e), 2.78 (1H, m, f), 2.610 (1H, ddq, J = 16.4, 8.2, 2.0 Hz, c), 2.55 – 2.40 (1H, m, c), 2.133 (1H, m, d), 1.877 (1H, dtd, J = 12.7, 11.2, 8.4 Hz, d) ppm

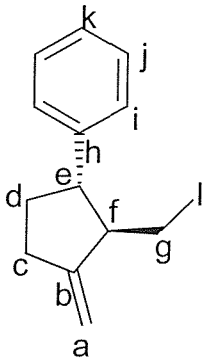
^{13}C NMR (75 MHz, $CDCl_3$) δ = 151.77 (0, b), 143.35 (0, h), 128.81 (1), 127.66 (1), 126.81 (1, k), 107.15 (2, a), 52.80 (1, e or f), 49.79 (1, e or f), 35.52 (2, g), 32.98 (2, c or d), 32.86 (2, c or d) ppm

IR (thin film) ν = 3026m, 2954s, 1656m, 1601m, 1492s, 1432s, 1244s, 894m, 754s cm^{-1}

LRMS (APCI) m/z = 171 $(M - Br)^+$

(1R*,2S*)-1-[2-(Iodomethyl)-3-methylenecyclopentyl]benzene (340)

To a solution of $ZrCp_2Cl_2$ (321 mg, 1.1 mmol) in THF (5 mL) at –80 °C under Ar was added dropwise *n*-butyllithium (0.88 mL of a 2.5 M solution in hexanes, 2.2 mmol). A solution of 2-ethoxy-5-phenyl-1,6-heptadiene **(321)** (216 mg, 1 mmol) in THF (2 mL) was added and the solution allowed to warm to RT. After 3.5 h, the red solution was cooled to –70 °C and a solution of iodine (279 mg, 1.1 mmol) in THF (2 mL) was added. The reaction was allowed to warm to 0 °C and quenched with saturated $Na_2S_2O_3$ solution (1 mL) and saturated $NaHCO_3$ solution (20 mL). The reaction mixture was extracted into pentane and the combined organic extracts washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (SiO_2, hexane) to give the desired iodide as a pale pink oil (122 mg, 41%).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.4 – 7.2 (5H, m, Ar), 5.178 (1H, q, J = 2.3 Hz, a), 4.952 (1H, q, J = 2.3 Hz, a), 3.432 (1H, dd, J = 10.2, 4.0 Hz, g), 3.260 (1H, dd, J = 10.2, 3.7 Hz, g), 2.976 (1H, ddd, J = 11.2, 9.9, 6.5 Hz, e), 2.611 (1H, ddq, J = 16.4, 8.2, 2.0 Hz, c), 2.55 – 2.4 (1H, m, f), 2.29 (1H, m, c), 2.14 (1H, m, d), 1.932 (1H, dtd, J = 12.4, 11.3, 8.3 Hz, d) ppm

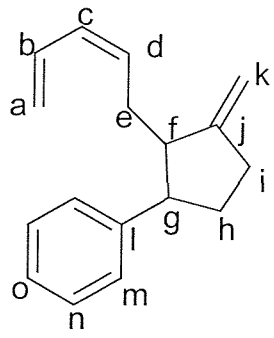
^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.57 (0, b), 143.09 (0, h), 128.81 (1), 127.66 (1), 126.86 (1, k), 107.10 (2, a), 51.97 (1, e or f), 51.68 (1, e or f), 32.70 (2, c or d), 32.59 (2, c or d), 11.77 (2, g) ppm

IR (thin film) ν = 3063w, 3026m, 2953s, 1655m, 1602w, 1492m, 1212m, 909s, 760s, 733s, 700s cm^{-1}

LRMS (APCI) m/z = 171 $(M - I)^+$

(1R*,2S*)-1-{3-Methylene-2-[(2*Z*)-2,4-pentadienyl]cyclopentyl}benzene (341)

To a solution of $ZrCp_2Cl_2$ (321 mg, 1.1 mmol) in THF (5 mL) at –80 °C under Ar was added dropwise *n*-butyllithium (0.88 mL of a 2.5 M solution in hexanes, 2.2 mmol). A solution of 2-ethoxy-5-phenyl-1,6-heptadiene **(321)** (216 mg, 1 mmol) in THF (2 mL) was added and the solution allowed to warm to RT. After 16 h, the solution was cooled to –90 °C and *cis*-1,4-dichlorobutene (0.14 mL, 163 mg, 1.3 mmol) added, followed by a solution of LiTMP (2.6 mmol), prepared by addition of *n*-butyllithium (1.04 mL, 2.6 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (367 mg, 2.6 mmol) in THF (4 mL) at 0 °C and stirred 1 h. After 30 min at –90 °C to –80 °C the reaction was quenched with 2 M HCl (5 mL). The layers were separated, and the aqueous extracted with pentane. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product consisted mainly of protic quenched material, but contained 12% of the desired carbenoid insertion product by GC. The insertion product was isolated by column chromatography (SiO_2, petrol) as a clear, colourless oil (22 mg, 10% yield).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.4 – 7.1 (5H, m, Ar), 6.527 (1H, dddd, J = 16.9, 10.9, 9.9, 1.0 Hz, b), 6.018 (1H, t, J = 11.0 Hz, c), 5.441 (1H, q, J = 8.5 Hz, d), 5.177 (1H, dd, J = 16.9, 1.7 Hz, a), 5.070 (1H, d, J = 9.9 Hz, a), 5.006 (1H, m, k), 4.928 (1H, br q, J = 2.2 Hz, k), 2.786 (1H, td, J = 10.5, 6.5 Hz, f), 2.69 – 2.52 (2H, m), 2.50 – 2.33 (3H, m), 2.081 (1H, dtd, J = 8.4, 6.7, 2.3 Hz, h), 1.769 (1H, dtd, J = 12.4, 10.9, 8.4 Hz, h) ppm

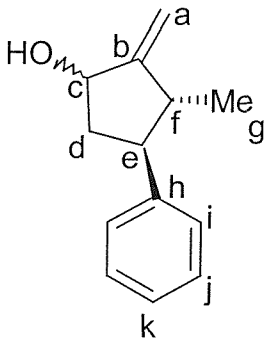
^{13}C NMR (75 MHz, $CDCl_3$) δ = 154.79 (0, j), 144.54 (0, l), 132.68 (1), 130.40 (1), 130.37 (1), 128.54 (1), 127.82 (1), 126.40 (1), 117.14 (2, a), 105.77 (2, k), 51.35 (1), 51.15 (1), 33.92 (2), 33.11 (2), 29.71 (2) ppm

IR (thin film) ν = 3081w, 3026m, 2950s, 1652w, 1602w, 1595w, 1492m, 1433m, 999m, 903s, 882s, 752s, 699s cm^{-1}

HRMS: $C_{17}H_{20}$ requires m/z = 224.1565, found 224.1552

(1S*,3S*,4R*)- and (1R*,3S*,4R*)-3-Methyl-2-methylene-4-phenyl-1-cyclo pentanol (342)

The title compound was prepared by **Method B**, using 2-ethoxy-3-hydroxy-5-phenyl-1,6-heptadiene **(323)** (232 mg, 1 mmol). The crude product was purified by column chromatography (10% ether in hexanes) to give the desired product as a viscous oil (103 mg, 55%). The product was a 1:1 mixture of diastereomers, as determined by gas chromatography (HP-wax column, conditions: 60 °C for 5 min, then increase at 15 °C / min to 250 °C, then 2 min at 250 °C. Retention times 16.95 min and 19.05 min).



^{1}H (300 MHz, $CDCl_3$) δ = 7.4 – 7.2 (5H, m, Ar), [5.320 (dd, J = 2.9, 1.5 Hz), 5.248 (dd, J = 2.9, 2.2 Hz), 5.090 (dd, J = 2.2, 1.5 Hz), 5.051 (t, J = 2.6 Hz), total 2H, protons 'a')], 4.690 (0.5H, m, c), 4.628 (0.5H, tt, J = 6.8, 2.2 Hz, c), 2.914 (0.5H, td, J = 11.4, 7.0 Hz, e), 2.669 (0.5H, m, e), 2.489 (1H, m, f), 2.135 (0.5H, ddd, J = 13.6, 6.6, 1.8 Hz, d), 2.006 (0.5H, ddd, J = 13.6, 11.8, 5.9 Hz, d), 1.796 (1H, m, d), 1.449 (0.5H, s, -OH), 1.292 (0.5H, s, -OH), 1.105 (1.5H, d, J = 6.6 Hz, g), 1.054 (1.5H, d, J = 6.6 Hz, g) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 160.68 (0) and 159.43 (0, b), 143.45 (0) and 143.04 (0, h), 128.65 (1) and 128.63 (1, i or j), 127.65 (1) and 127.62 (1, i or j), 126.67 (1) and 126.58 (1, k), 108.55 (2) and 107.41 (2, a), 74.42 (1) and 73.83 (1, c), 50.93 (1) and 50.10 (1, e), 45.73 (1) and 45.00 (1, f), 43.13 (2) and 42.89 (2, d), 17.11 (3) and 16.79 (3, g) ppm

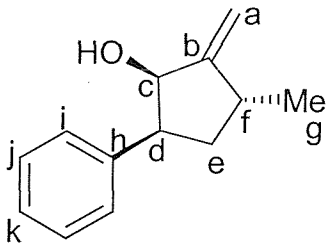
IR (thin film) ν = 3352br s, 3027w, 2959s, 2870m, 1648 w, 1601w, 1494m, 1454s, 1023m, 899m, 754s, 700s cm^{-1}

LRMS (APCI) m/z = 171 $(M - OH)^+$

HRMS: $C_{13}H_{16}O$ requires m/z = 188.1201, found 188.1208.

(1S*,3S*,5R*)-3-Methyl-2-methylene-5-phenyl-1-cyclopentanol (343)

The title compound was prepared according to **Method B**, using 2-ethoxy-3-hydroxy-4-phenyl-1,6-heptadiene **(327)** (232 mg, 1 mmol). The crude product was purified by column chromatography (5% ether in hexanes) to give the desired product as a viscous oil (82 mg, 44%). The product was a 7:1 mixture of diastereomers, as determined by gas chromatography (HP-wax column, conditions: 60 °C for 5 min, then increase at 15 °C / min to 250 °C, then 2 min at 250 °C. Retention times: 14.51 min (major peak), 14.20 min (minor peak). The major diastereomer has the relative stereochemistry (1S*,3S*,5R*), as determined by GOESY experiments (correlation between proton 'd' and methyl group).



NMR data provided is for the major diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.4 – 7.2 (5H, m, Ar), 5.249 (1H, ddd, J = 2.4, 1.3, 0.6 Hz, a), 5.094 (1H, ddd, J = 2.2, 1.5, 0.7, a), 4.603 (1H, d, J = 5.0 Hz, c), 3.364 (1H, td, J = 7.8, 5.5 Hz, d), 3.0 – 2.9 (1H, m, f), 2.461 (1H, dtd, J = 12.9, 8.8, 0.3 Hz, e), 1.710 (1H, dddt, J = 12.3, 7.2, 4.5, 0.5 Hz, e), 1.564 (1H, br s, -OH), 1.200 (3H, d, J = 7.1 Hz, g) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.37 (0, b), 139.61 (0, h), 128.86 (1), 128.66 (1), 126.90 (1, k), 109.45 (2, a), 77.63 (1, c), 48.58 (1, d), 35.89 (2, e), 34.93 (1, f), 22.34 (3, g) ppm.

IR (thin film) ν = 3415br m, 2958s, 2869m, 1660w, 1600m, 1496m, 1453m, 1077m, 899m cm^{-1}

LRMS (APCI) m/z = 171 $(M - OH)^+$

HRMS: $C_{13}H_{16}O$ requires m/z = 188.1201, found 188.1196

The title compound was also prepared from *tert*-butyl{[1-(1-ethoxyvinyl)-3-phenyl-4-pentenyl]oxy}dimethyl silane **(327a)** (300 mg, 0.87 mmol) *via* co-cyclisation (**Method B**). A portion of the crude cyclisation product (112 mg, 0.37

mmol) was treated with trifluoroacetic acid (3 mL) in 1:1 H_2O / methanol (6 mL) over 20 h, resulting in clean removal of the TBDMS protecting group. After addition of saturated $NaHCO_3$ solution (10 mL) and ether (20 mL), the aqueous phase was extracted with ether (3 x 50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated. Column chromatography (SiO_2, 20% ether in hexanes) provided **(343)** (33 mg, 47%) as a 5:4 mixture of diastereomers. The major isomer in this case was the same as for cyclisation of the free alcohol.

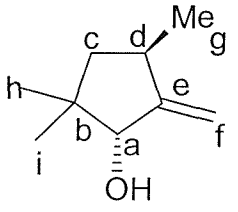
Full NMR data for the minor diastereomer (1S*, 3R*, 5R*) is provided:

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.4 – 7.2 (5H, m, Ar), 5.319 (1H, d, J = 2.0 Hz, a), 5.121 (1H, s, a), 4.556 (1H, d, J = 5.2 Hz, c), 3.168 (1H, dt, J = 11.9, 5.7 Hz, d), 2.7 – 2.55 (1H, m, f), 2.189 (1H, dt, J = 11.9, 6.7 Hz, e), 1.912 (1H, q, J = 11.8 Hz, e), 1.290 (3H, d, J = 6.7 Hz, g) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 158.95 (0, b), 139.31 (0, h), 128.66 (1), 128.51 (1), 126.75 (1), 109.33 (2, a), 76.74 (1, c), 49.57 (1, d), 36.81 (2, e), 36.47 (1, f), 19.35 (3, g) ppm

(1S*,4S*)-2,2,4-Trimethyl-5-methylene-1-cyclopentanol (344)

The title compound was prepared according to **Method B**, using 4,4-dimethyl-2-ethoxy-3-hydroxy-1,6-heptadiene **(330)** (184 mg, 1 mmol). The crude product was purified by column chromatography (SiO_2, 20% ether in petrol) to give the desired product as a viscous, colourless oil (103 mg, 74% yield) This product was a 4:1 mixture of diastereomers as determined by gas chromatography (HP-wax column, conditions: 60 °C for 5 min, then increase at 15 °C / min to 250 °C, then 2 min at 250 °C. Retention times: 8.64 min (minor peak), 8.77 min (major peak). The major diastereomer has the relative configuration (1S*,4S*) as determined by GOESY experiments (correlation between proton 'a' and methyl group).



(Major diastereomer)

^{1}H NMR (400 MHz, $CDCl_3$) major diastereomer δ = 5.113 (1H, t, J = 2.6 Hz, f), 4.989 (1H, td, J = 2.5, 0.6 Hz, f), 4.001 (1H, q, J = 2.5 Hz, a), 2.65 – 2.50 (1H, m, d), 1.743 (1H, dd, J = 12.7, 8.2 Hz, c), 1.582 (1H, br s, -OH), 1.098 (3H, d, J = 6.9 Hz, g), 1.081 (3H, s, h or i), 1.050 (1H, ddq, J = 12.7, 10.2, 0.7 Hz, c), 0.791 (3H, s, h or i) ppm; minor diastereomer (where seen): δ = 5.157 (1H, m, f), 4.966 (1H, td, J = 2.2, 0.6 Hz, f), 3.923 (1H, t, J = 1.6 Hz, a), 1.145 (3H, d, J = 7.0 Hz, g), 0.988 (3H, s, h or i), 0.906 (3H, s, h or i) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) major diastereomer: δ = 159.98 (0, e), 106.52 (2, f), 82.46 (1, a), 45.15 (1, d), 41.06 (0, b), 33.52 (2, c), 26.64 (3), 21.45 (3), 19.61 (3) ppm; minor diastereomer (where seen): δ = 106.74 (2), 83.00 (1), 33.08 (2), 26.79 (3), 22.19 (3), 20.88 (3) ppm

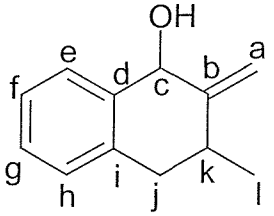
IR (thin film) ν = 3386br m, 2956s, 2887m, 1650m, 1459m, 1366m, 1082s, 892s cm^{-1}

LRMS (APCI) m/z = 123 $(M - OH)^+$

HRMS: $C_9H_{16}O$ requires m/z = 140.1201, found 140.1205

3-Methyl-2-methylene-1,2,3,4-tetrahydro-1-naphthalenol (345a/b)

The title compound was synthesised by **Method B**, using 1-(2-allylphenyl)-2-ethoxy-2-propen-1-ol **(334)** (436 mg, 2 mmol). The product was obtained as a mixture of two diastereomers in a ratio of 8:7, as determined by gas chromatography, the more polar being the major. The diastereomers were separated and purified by column chromatography (SiO_2, 5% ether in hexanes). The less polar diastereomer was isolated as a white wax (85 mg, 24%), and the more polar as a powdery white solid (130 mg, 37%). The less polar could be precipitated from methanol / pentane to provide material for microanalysis.



Higher running (less polar) diastereomer:

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.604 (1H, d, J = 7.0 Hz), 7.271 (1H, td, J = 7.2, 1.2 Hz), 7.222 (1H, td, J = 7.2, 1.7 Hz), 7.097 (1H, dd, J = 7.0, 1.7 Hz), 5.283 (1H, d

+ fs, J = 1 Hz, a), 5.228 (1H, br d, J = 3.7 Hz, c), 5.029 (1H, quintet, J = 1.1 Hz, a), 2.959 (1H, q, J = 10.3 Hz, k), 2.4 (2H, m, j), 2.162 (1H, br d, J = 7.4 Hz, -OH), 1.278 (3H, d, J = 6.2 Hz, l) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 153.34 (0, b), 139.48 (0), 136.69 (0), 128.16 (1), 127.54 (1), 127.23 (1), 126.67 (1), 105.02 (2, a), 72.35 (1, c), 39.89 (2, j), 33.97 (1, k), 18.91 (3, l) ppm

IR (solid film) ν = 3271w, 2958w, 2873w, 1657m, 1487m, 1452m, 1400m, 1032s, 898s cm^{-1}

LRMS (APCI) m/z = 157 $(M - OH)^+$

HRMS: $C_{12}H_{14}O$ requires m/z = 174.1045, found 174.1040

Microanalysis: $C_{12}H_{14}O$ requires C 82.72%, H 8.10%, found C 82.42%, H 8.09%.

Melting point: 39 – 41 °C

Lower running (more polar) diastereomer:

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.5 – 7.1 (4H, m, Ar), 5.207 (1H, d, J = 1.0 Hz, a), 5.121 (1H, br s, c), 5.016 (1H, t, J = 1.2 Hz, a), 3.023 (1H, dd, J = 15.6, 5.3 Hz, j), 2.95 – 2.8 (1H, m, k), 2.482 (1H, dd, J = 15.6, 10.5 Hz, j), 1.992 (1H, br s, -OH), 1.253 (3H, d, J = 6.7 Hz, l) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.62 (0, b), 138.06 (0), 137.05 (0), 128.85 (1), 128.49 (1), 127.95 (1), 126.66 (1), 109.31 (2, a), 72.89 (1, c), 39.67 (2, j), 30.99 (1, k), 18.22 (3, l) ppm

IR (solid film) ν = 3226br m, 2965w, 2893w, 1655w, 1492w, 1456w, 991s, 956s, 908s, 885s cm^{-1}

LRMS (APCI) m/z = 173 $(M - H)^+$, 15%, 157 $(M - OH)^+$, 100%

HRMS: $C_{12}H_{14}O$ requires m/z = 174.1405, found 174.1405

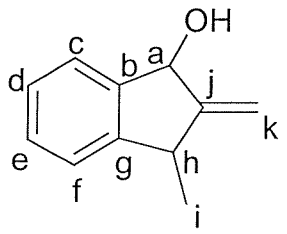
Microanalysis: $C_{12}H_{14}O$ requires C 82.72%, H 8.10%, found C 81.37%, H 7.75%.

Melting point: 74 – 75 °C

3-Methyl-2-methylene-1-indanol (346)

The title compound was synthesised according to **Method B**, using 1-(2-vinylphenyl)-2-ethoxy-2-propen-1-ol **(337)** (204 mg, 1 mmol). The crude material was purified by column chromatography (SiO_2, 10% ether in petrol), then again by

column chromatography (SiO_2, 10% ether in hexane) to provide pure material as a waxy white solid (41 mg, 26%).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.50 – 7.45 (1H, m, Ar), 7.4 – 7.2 (3H, m, Ar), 5.5 (2H, m, k and a), 5.284 (1H, d, J = 1.5 Hz, k), 3.884 (1H, q, J = 7.1 Hz, h), 2.003 (1H, br s, -OH), 1.390 (3H, d, J = 7.4 Hz, i) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 158.80 (0, j), 146.73 (0, b), 142.83 (0, g), 129.14 (1), 127.51 (1), 125.13 (1), 124.05 (1), 110.71 (2, k), 76.22 (1, a), 41.84 (1, h), 21.34 (3, i) ppm

IR (DCM solution) ν = 3350br s, 2963s, 2926s, 2868s, 1664w, 1609w, 1478s, 1461s, 1383m, 1020s, 760s, 685s cm^{-1}

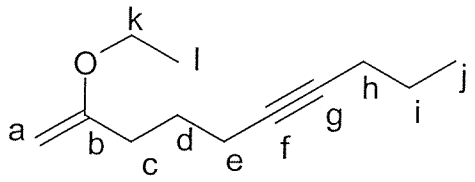
LRMS (APCI) m/z = 160 (M^+), 8%, 143 $(M - OH)^+$, 100%

HRMS: $C_{11}H_{12}O$ requires 160.0888, found 160.0887.

Melting point: 50 – 52 °C

2-Ethoxy-dec-1-ene-6-yne (347)

The title compound was prepared by **Method C**, using 1-iodo-4-octyne (1.18 g, 5 mmol), giving the desired product as a clear, colourless oil (803 mg, 4.46 mmol, 89%).



^{1}H NMR (300 MHz, C_6D_6) δ = 4.046 (1H, d, J = 1.5 Hz, a), 3.939 1H, d, J = 1.5 Hz, a), 3.546 (2H, q, J = 7.0 Hz, k), 2.375 (2H, t, J = 7.4 Hz, c), 2.261 (2H, tt, J = 7.2, 2.4 Hz, e), 2.133 (2H, tt, J = 7.0, 2.4 Hz, h), 1.877 (2H, quintet, J = 7.2 Hz, d), 1.506 (2H, sextet, J = 7.1 Hz, i), 1.156 (3H, t, J = 7.0 Hz, l), 0.998 (3H, t, J = 7.4 Hz, j) ppm

^{13}C NMR (75 MHz, C_6D_6) δ = 163.06 (0, b), 81.25 (2, a), 80.65 (0, f or g), 80.35 (0, f or g), 62.72 (2, k), 34.80 (2), 27.59 (2), 22.98 (2), 21.21 (2), 18.70 (2), 14.57 (3, l), 13.65 (3, j) ppm

IR (thin film) ν = 2960s, 2872s, 1653s, 1598m, 1456s, 1253s, 1158m, 1080s, 975m, 797s cm^{-1}

LRMS (APCI) m/z = 180 (M^+) 181 $(M + H)^+$

HRMS $C_{12}H_{20}O$ requires m/z = 180.1514, found 180.1521

1-Iodo-5-nonyne (348)

To a solution of 1-pentyne (3.4 g, 4.9 mL, 50 mmol) in THF (55 mL) at below –30 °C under Ar was added slowly n-butyllithium (22 mL of a 2.5 M solution in hexanes, 55 mmol). After 30 min 1-chloro-4-iodobutane (8.74 g, 40 mmol) in THF (5 mL) was added followed by HMPA (8.7 mL, 50 mmol). The solution was allowed to warm to room temperature and stirred for 40 h. The resulting white suspension was diluted with pentane and water and the aqueous phase separated and extracted with pentane. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was added to a refluxing solution of sodium iodide (18 g, 120 mmol) in acetone (150 mL). After a further 15 h at reflux, the reaction mixture was allowed to cool and poured into water and pentane. The aqueous layer was separated and washed with pentane. The combined organic phases were washed with $Na_2S_2O_3$ solution and brine, dried over $MgSO_4$, filtered and concentrated to give the desired compound (6.760 g, 27.0 mmol, 68%).

^1H NMR (300 MHz, $CDCl_3$) δ = 3.218 (2H, t, J = 7.0 Hz), 2.199 (2H, tt, J = 7.0, 2.4 Hz), 2.123 (2H, tt, J = 7.2, 2.4 Hz), 1.943 (2H, m), 1.593 (2H, m), 1.503 (2H, app. sextet, J = 7.4 Hz), 0.970 (3H, t, J = 7.4 Hz) ppm

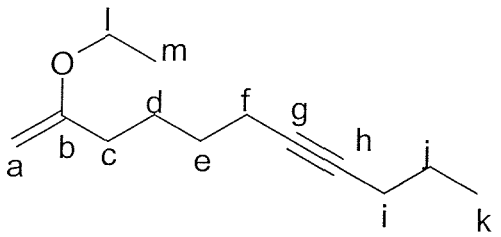
^{13}C NMR (75 MHz, $CDCl_3$) δ = 81.00 (0), 79.41 (0), 32.62 (2), 29.89 (2), 22.63 (2), 20.88 (2), 17.88 (2), 13.66 (3)a, 6.62 (2) ppm

IR (thin film) ν = 2964s, 2930s, 2861m, 1459m, 1436m, 1339m, 1213s cm^{-1}

HRMS: $C_9H_{15}I$ requires m/z = 250.0212, found 250.0219

2-Ethoxy-undec-1-ene-7-yne (349)

The title compound was prepared by **Method C**, using freshly distilled 1-iodo-5-nonyne **(348)** (1.195 g, 4.78 mmol). Purification by Kugelrohr distillation (130 °C, 0.8 mbar) gave the desired product as a clear, colourless oil (655 mg, 71% yield).



^{1}H NMR (300 MHz, C_6D_6) δ = 3.976 (1H, d, J = 1.5 Hz, a), 3.898 (1H, d, J = 1.5 Hz, a), 3.524 (2H, q, J = 7.0 Hz, l), 2.20 – 2.14 (4H, m), 2.100 (2H, tt, J = 7.0, 2.4 Hz, f or i), 1.744 (2H, m, d), 1.63 – 1.41 (4H, m, j and e), 1.136 (3H, t, J = 7.2 Hz, m), 0.962 (3H, t, J = 7.4 Hz, k) ppm

^{13}C NMR (75 MHz, C_6D_6) δ = 163.31 (0, b), 80.72 (2, a), 80.31 (0), 80.22 (0), 62.48 (2, l), 34.98 (2), 28.86 (2), 26.86 (2), 22.77 (2), 21.01 (2), 18.87 (2), 14.42 (3, m), 13.47 (3, k) ppm

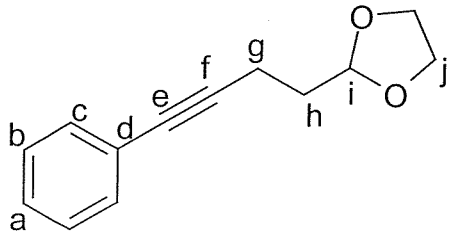
IR (thin film) ν = 2932s, 2870s, 1652s, 1594m, 1458s, 1276s, 1086s, 975m, 795s cm^{-1}

LRMS (APCI) m/z = 194 (M^+), 30%, 195 $(M + H)^+$, 50%, 224 (100%)

HRMS: $C_{13}H_{22}O$ requires m/z = 194.1670, found 194.1650

2-(4-Phenyl-but-2-ynyl)-1,3-dioxolane (350)

To a solution of phenyl acetylene (1.02 g, 10 mmol) in THF (8 mL) at –40 °C under Ar was added dropwise *n*-butyllithium (4.4 mL of a 2.5 M solution in hexanes, 11 mmol). After 30 min, a solution of 2-(2-bromoethyl)-1,3-dioxolane (1.81 g, 10 mmol) in THF (2 mL) was added, followed by HMPA (1.75 mL, 10 mmol). The reaction was allowed to warm to RT and stirred 15 h. The reaction mixture was diluted with brine, and the aqueous layer separated and extracted into ether. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified by column chromatography (SiO_2, 10% ether in petrol), followed by Kugelrohr distillation (120 °C, 1 mbar) to provide the desired compound as a clear, colourless oil (1.377 g, 68%).



^{1}H NMR (400 MHz, $CDCl_3$) 7.5 – 7.3 (5H, m, Ar), 5.100 (1H, t, J = 4.6 Hz, i), 4.1 – 3.9 (4H, m, j), 2.610 (2H, t, J = 7.5 Hz, g), 2.028 (2H, td, J = 7.4, 4.5 Hz, h) ppm

^{13}C NMR (100 MHz, $CDCl_3$) δ = 130.63 (1, b or c), 126.78 (1, b or c), 125.57 (1, a), 122.62 (0, d), 102.03 (1, i), 87.88 (0, f), 79.54 (0, e), 63.77 (2, j), 31.83 (2, h), 13.10 (2, g) ppm

IR (thin film) ν = 2961m, 2884s, 2249w, 1598w, 1490s, 1442m, 1410m, 1140s, 1041s, 910s cm^{-1}

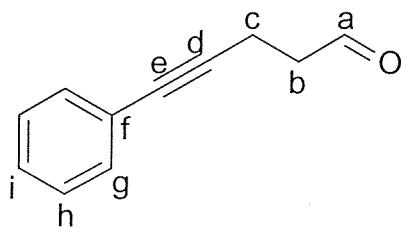
LRMS (APCI) m/z = 201 $(M - H)^+$, 30%, 202 (M^+), 15%, 203 $(M + H)^+$, 20%

HRMS: $C_{13}H_{14}O_2$ requires m/z = 202.0994, found 202.0995

5-Phenyl-pent-4-yn-1-al (351)

The title compound was prepared by the acetal hydrolysis method of Lecker *et al.*[41]

To a solution of 2-(4-phenyl-but-2-ynyl)-1,3-dioxolane **(350)** (1.01 g, 5 mmol) in hexane (25 mL) was added formic acid (10 mL) and the solution stirred at RT. After 2 h TLC analysis showed complete consumption of starting material. The mixture was extracted into ether, and the combined extracts washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified by column chromatography (Al_2O_3, 20% ether in petrol) to give the desired aldehyde as a cloudy colourless oil (383 mg, 48%). Further purification could be performed by Kugelrohr distillation (95 °C, 0.5 mbar).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.855 (1H, s, a), 7.4 – 7.25 (5H, m, Ar), 2.758 (4H, m, b and c) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 200.59 (1, a), 131.76 (1, g), 128.39 (1, h), 128.04 (1, i), 123.54 (0, f), 87.88 (0, e), 81.62 (0, d), 42.79 (2, b), 12.85 (2, c) ppm

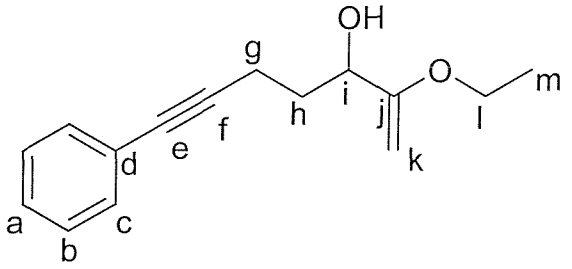
IR (thin film) ν = 2912m, 2830m, 2728m, 2234w, 1727s, 1490s, 1442m, 1409m, 1070m, 915w cm^{-1}

LRMS (APCI) m/z = 159 $(M + H)^+$, 75%, 158 (M^+), 100%

NMR data is consistent with literature values.[88]

2-Ethoxy-3-hydroxy-7-phenylhepta-1-ene-6-yne (352)

The title compound was prepared according to **Method C**, using 5-phenyl-4-pentynal (272 mg, 1.7 mmol). Purification by Kugelrohr distillation (150 °C, 0.8 mbar) gave the desired product as a clear, colourless oil (249 mg, 1.08 mmol, 64%).



^1H NMR (300 MHz, C_6D_6) δ = 7.506 (2H, m, Ar), 7.038 (3H, m, Ar), 4.258 (1H, d, J = 2.3 Hz, k), 4.232 (1H, m, i), 3.895 (1H, d, J = 2.0 Hz, k), 3.420 (2H, q, J = 7.0 Hz, l), 2.569 (1H, dd, J = 7.7, 3.2 Hz, g), 2.546 (1H, dd, J = 7.7, 1.7 Hz, g), 2.15 – 1.85 (2H, m, h), 1.780 (1H, d, J = 5.0 Hz, -OH), 1.035 (3H, t, J = 7.1 Hz, m) ppm

^{13}C NMR (75 MHz, C_6D_6) δ = 164.03 (0, j), 131.98 (1, c), 128.51 (1, b), 127.73 (1, a), 124.79 (0, d), 90.39 (0, e), 81.64 (0, f), 80.95 (2, k), 71.83 (1, i), 62.92 (2, l), 34.97 (2, h), 16.11 (2, g), 14.31 (3, m) ppm

IR (thin film) ν = 3417br m, 2977m, 2929m, 2240w, 1659m, 1626m, 1606w, 1585w, 1490s, 1245m, 1070s, 813m, 756s, 692s cm^{-1}

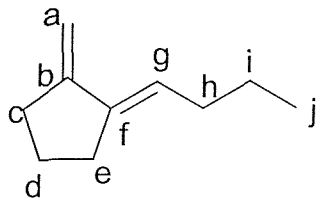
LRMS (APCI) m/z = 231 $(M + H)^+$, 30%, 185 $(M - OEt)^+$, 50%

HRMS: $C_{15}H_{18}O_2$ requires m/z = 230.1307, found 230.1314.

2-Methylene-(*Z*)-butylidenecyclopentane (353)

The title compound was prepared by **Method B**, using 2-ethoxy-dec-1-ene-6-yne **(347)** (180 mg, 1 mmol). Purification by column chromatography provided the desired compound, and roughly 15% of an inseparable co-polar contaminant, in total

92 mg (68% yield). After Kugelrohr distillation (120 °C, 10 mbar), the contaminant was still present.



^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.873 (1H, tt, J = 7.4, 2.6 Hz, g), 5.228 (1H, t, J = 2.4 Hz, a), 4.777 (1H, t, J = 2.2 Hz, a), 2.419 (2H, tt, J = 7.4, 2.2 Hz, c), 2.370 (2H, m, e), 2.074 (2H, qt, J = 7.4, 1.5 Hz, h), 1.685 (2H, quintet, J = 7.3 Hz, d), 1.445 (2H, app. sextet, J = 7.4 Hz, i), 0.940 (3H, t, J = 7.4 Hz, j) ppm

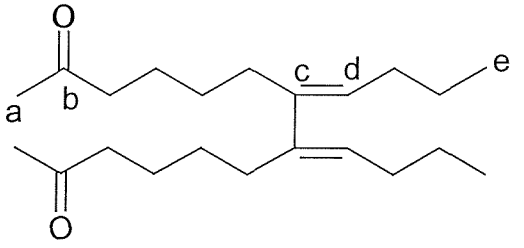
^{13}C NMR (75 MHz, $CDCl_3$) δ = 149.77 (0, f), 140.02 (0, b), 120.46 (1, g), 100.55 (2, a), 34.60 (2), 31.85 (2), 30.10 (2), 24.05 (2), 22.66 (2), 14.01 (3, j) ppm

IR (thin film) ν = 3076w, 2956s, 2871s, 1463m, 1438m, 1377w, 871s cm^{-1}

NMR data is consistent with literature values.[89]

Undec-7-ene-2-one dimers (354)

The title compounds were prepared by **Method B**, using 2-ethoxy-undec-1-en-7-yne **(349)** (194 mg, 1 mmol). The crude product was subjected to column chromatography (SiO_2, pentane then ether flush) to provide the title compound as a clear, colourless oil (87 mg, 45%). The product was a mixture or regioisomers.



and isomers

Selected signals from the NMR spectra are listed:

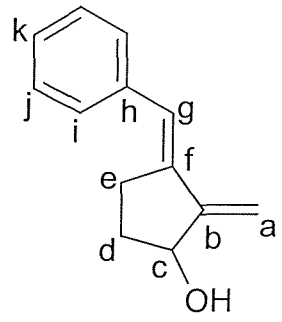
^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.324 (2H, qd, J = 7.4, 2.5 Hz, d), 2.135 (3H, s) and 2.125 (3H, s, a), 0.905 (3H, t, J = 7.4 Hz, e), 0.863 (3H, t, J = 7.4 Hz, e) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 209.33 (0, b), 141.54 and 140.82 (0, c), 126.53 and 125.74 (1, d), 29.99 (3, a), 14.25 and 14.08 (3, e) ppm.

LRMS (APCI) m/z = 335 $(M + H)^+$

2-Methylene-3-[(*E*)-1-phenylmethylidene]-1-cyclopentanol (355)

The title compound was synthesised by **Method B**, using 2-ethoxy-3-hydroxy-7-phenylhepta-1-ene-6-yne **(352)** (229 mg, 1 mmol). The crude product was purified by column chromatography (SiO_2, 20% - 35% ether in petrol) to give the desired product as a clear, colourless oil (62 mg, 33% yield).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.5 – 7.2 (5H, m, Ar), 6.915 (1H, t, J = 2.6 Hz, g), 5.603 (1H, d, J = 1.7 Hz, a), 5.205 (1H, d, J = 1.5 Hz, a), 4.618 (1H, t, J = 6.2 Hz, c), 2.899 (1H, dddd, J = 16.6, 8.2, 5.7, 2.5 Hz, e), 2.659 (1H, dtd, J = 16.8, 7.7, 2.7 Hz, e), 2.101 (1H, ddt, J = 13.3, 7.9, 5.7 Hz, d), 2.05 (1H, br s, -OH), 1.721 (1H, m, d) ppm

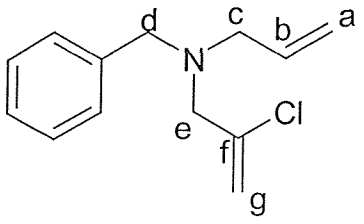
^{13}C NMR (75 MHz, $CDCl_3$) δ = 153.71 (0, f), 139.13 (0, b or h), 137.73 (0, b or h), 128.97 (1, i or j), 128.49 (1, i or j), 126.91 (1, k), 121.58 (1, g), 104.85 (2, a), 75.21 (1, c), 33.88 (2, e), 28.80 (2, d) ppm

IR (thin film) ν = 3372 br s, 2932s, 1598w, 1493m, 1450m, 1049m, 737m, 698s cm^{-1}

HRMS: $C_{13}H_{14}O$ requires m/z = 186.1046, found 186.1045

***N*-Allyl-*N*-benzyl-*N*-(2-chloroallyl)amine (356)**

A solution of 2,3-dichloro-1-propene (3.33 g, 30 mmol) in MeCN (10 mL) was added to a suspension of potassium carbonate (6.9 g, 50 mmol) and *N*-allyl benzylamine (2.94 g, 20 mmol) in MeCN (60 mL). The reaction mixture was subsequently heated at reflux for 19 h, before cooling and dilution with water and ether. The aqueous phase was extracted with ether, and the combined organic phases washed with water then brine, dried over $MgSO_4$, filtered and concentrated. The crude material was purified by column chromatography (SiO_2, petrol), then Kugelrohr distillation (120 °C, 0.7 mbar) to yield the desired product as a clear, colourless oil (3.282 g, 14.8 mmol, 74%).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.4 – 7.2 (5H, m, Ar), 5.904 (1H, ddt, J = 16.9, 10.3, 6.2 Hz, b), 5.512 (1H, s, g), 5.368 (1H, s, g), 5.3 – 5.15 (2H, m, a), 3.684 (2H, s, d), 3.259 (2H, s, e), 3.164 (2H, d, J = 5.9 Hz, c) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 140.35 (0), 139.16 (0), 135.48 (1), 128.85 (1), 128.43 (1), 127.16 (1), 117.90 (2), 113.99 (2), 59.69 (2), 57.57 (2), 56.29 (2) ppm.

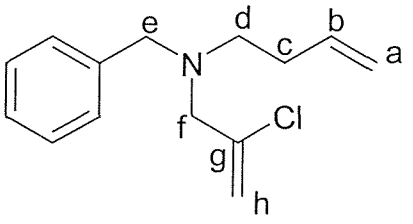
IR (thin film) ν = 3027m, 2924m, 2805s, 1634s, 1454s, 1370m, 1254m, 1122s cm^{-1}

LRMS (ES+) m/z = 224 (^{37}Cl M + H)$^{+}$, 55%, 222 (^{35}Cl M + H)$^{+}$, 100%

HRMS: $C_{13}H_{16}NCl$ requires m/z = 224.1565, found 224.1552

<u>*N*-Benzyl-*N*-(3-butenyl)-*N*-(2-chloroallyl)amine (357)</u>

A solution of 2,3-dichloro-1-propene (888 mg, 8 mmol) in MeCN (5 mL) was added to a suspension of K_2CO_3 (2.07 g, 15 mmol) and 3-butenylbenzylamine (805 mg, 5 mmol) in MeCN (15 mL). The reaction mixture was heated at reflux for 16 h, before being allowed to cool and diluted with ether and water. The layers were separated and the aqueous washed with ether. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated to provide a crude product. Purification by column chromatography (SiO_2, 10% ether in petrol) followed by Kugelrohr distillation (115 °C, 0.7 mbar) yielded the desired product as a clear, colourless oil (681 mg, 58%).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.35 – 7.15 (5H, m, Ar), 5.719 (1H, ddt, J = 16.9, 9.9, 7.0 Hz, b), 5.400 (1H, s, h), 5.246 (1H, s, h), 5.0 – 4.9 (2H, m, a), 3.591 (2H, s, e), 3.158 (2H, s, f), 2.520 (2H, t, J = 7.4 Hz, d), 2.187 (2H, q, J = 7.1 Hz, c) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 140.45 (0), 139.33 (0), 136.81 (1), 128.83 (1), 128.40 (1), 127.13 (1), 115.79 (2), 113.88 (2), 60.28 (2), 57.99 (2), 53.06 (2), 31.81 (2) ppm.

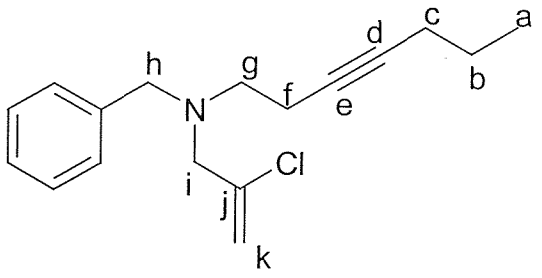
IR (thin film) ν = 3067w, 2930m, 2810s, 1636s, 1498m, 1453s, 1379m, 1133m, 898s, 698s cm^{-1}

LRMS (ES+) m/z = 238 (^{37}Cl M + H)$^+$, 35%, 236 (^{35}Cl M + H)$^+$, 100%

HRMS: $C_{14}H_{18}N^{35}Cl$ requires m/z = 194.0737, found 194.0735. $C_{14}H_{18}N^{37}Cl$ requires m/z = 196.0707, found 196.0709

<u>*N*-Benzyl-*N*-(2-chloroallyl)-*N*-(3-heptynyl)amine (358)</u>

A solution of 2,3-dichloro-1-propene (888 mg, 8 mmol) in MeCN (5 mL) was added to a suspension of K_2CO_3 (2.07 g, 15 mmol) and 3-heptynylbenzylamine (1.00 g, 5 mmol) in MeCN (15 mL). The reaction mixture was heated at reflux for 16 h, before being allowed to cool and diluted with ether and water. The layers were separated and the aqueous washed with ether. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated to provide a crude product. Purification by column chromatography (SiO_2, 10% ether in petrol) followed by Kugelrohr distillation (125 °C, 0.6 mbar) yielded the desired product as a clear, colourless oil (829 mg, 60%).



^1H NMR (300 MHz, $CDCl_3$) δ = 7.4 – 7.2 (5H, m, Ar), 5.530 (1H, s, k), 5.338 (1H, s, k), 3.713 (2H, s, h), 3.295 (2H, s, i), 2.743 (2H, t, J = 7.4 Hz, g), 2.349 (2H, m, f), 2.123 (2H, tt, J = 7.1, 2.4 Hz, c), 1.505 (2H, app. sextet, J = 7.2 Hz, b), 0.971 (3H, t, J = 7.3 Hz, a) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 140.29 (0), 139.22 (0), 128.76 (1), 128.42 (1), 127.18 (1), 113.87 (2), 81.30 (0), 78.45 (0), 60.23 (2), 57.87 (2), 52.87 (2), 22.56 (2), 20.94 (2), 17.67 (2), 13.69 (3) ppm.

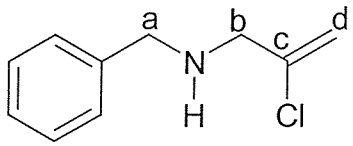
IR (thin film) ν = 2964s, 2930s, 2815m, 1636m, 1465s, 1384m, 1133m, 1133s, 892s, 734s, 709s cm^{-1}

LRMS (ES+) m/z = 278 (^{37}Cl M + H)$^+$, 35%, 276 (^{35}Cl M + H)$^+$, 100%

HRMS: $C_{17}H_{22}N^{35}Cl$ requires m/z = 275.1441, found 275.1440. $C_{17}H_{22}N^{37}Cl$ requires m/z = 277.1411, found 277.1437

<u>*N*-(2-Chloroallyl)benzylamine (359) and *N,N*-Di(2-chloroallyl)benzyl amine (360)</u>

A suspension of benzylamine (10.7 g, 100 mmol), 2,3-dichloro-1-propene (11.1 g, 100 mmol) and K_2CO_3 (27.6 g, 200 mmol) in MeCN (200 mL) was heated at reflux for 18 h, giving a black solution. After cooling, the mixture was diluted with water. After extraction with ether, the combined organic phases were washed water, dried over $MgSO_4$, filtered and concentrated. The crude product mixture was purified by column chromatography to provide **(359)** (5.422 g, 30 mmol, 30%) after Kugelrohr distillation (100 °C, 0.6 mbar) and **(360)** (1.097 g, 4.3 mmol, 9%) after Kugelrohr distillation (105 °C, 0.6 mbar).



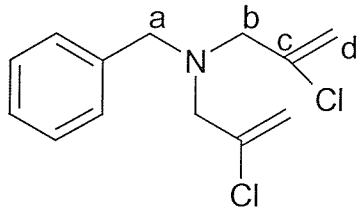
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.4 – 7.2 (5H, m, Ar), 5.382 (2H, s, d), 3.782 (2H, s, a), 3.446 (2H, s, b), 1.854 (1H, s, N-H) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 141.02 (0, c), 139.85 (0), 128.63 (1), 128.44 (1), 127.29 (1), 113.75 (2, d), 54.91 (2, b), 51.88 (2, a) ppm.

IR (thin film) ν = 3033m, 2838m, 1734w, 1642s, 1465s, 1453s, 1110s, 904s, 743s, 703s cm^{-1}

LRMS (ES+) m/z = 184 (^{37}Cl M + H)$^+$, 35%, 182 (^{35}Cl M + H)$^+$, 100%

HRMS: $C_{10}H_{12}N^{35}Cl$ requires m/z = 181.0658, found 181.0651



^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.5 – 7.2 (5H, m, Ar), 5.556 (2H, t, J = 1.5 Hz, d), 5.391 (2H, s, d), 3.757 (2H, s, a), 3.343 (4H, s, b) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.68 (0), 138.57 (0), 128.77 (1), 128.53 (1), 127.38 (1), 114.45 (2, d), 59.58 (2, b), 57.25 (2, a) ppm.

IR (thin film) ν = 3039w, 2930w, 2815s, 1636s, 1505m, 1442s, 1390s, 1110s, 898s, 749s, 698s cm^{-1}

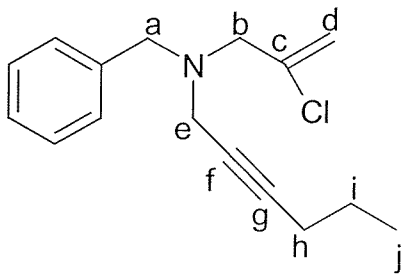
LRMS (ES+) m/z = 260 $(M + H)^+$, 10 %, 258 $(M + H)^+$, 65 %, 256 $(M + H)^+$, 100 %

2-Hexyn-1-ol (361)

The title compound was prepared by the method of Brandsma.[90] NMR data is consistent with literature values.[91]

***N*-Benzyl-*N*-(2-hexynyl)-*N*-(2-chloroallyl)amine (362)**

To a solution of 2-hexyn-1-ol **(361)** (2.0 g, 20.4 mmol) and triethylamine (2.48 g, 24.5 mmol) in dry DCM (40 mL) at –50 °C under Ar was added dropwise methane sulphonyl chloride (1.73 mL, 2.57 g, 22.4 mmol). After 2 h, the suspension was filtered and the residue washed with DCM. The combined organic phases were washed with water, dried over $MgSO_4$, filtered and concentrated. The crude mesylate was combined with *N*-(2-chloroallyl) benzylamine (3.63 g, 20 mmol) and K_2CO_3 (5.53 g, 40 mmol) in MeCN (40 mL) and the suspension heated at reflux for 16 h. After cooling, the reaction mixture was diluted with ether and water. After separation of the aqueous layer and extraction with ether, the combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (SiO_2, 5% ether in petrol) then Kugelrohr distillation (110 °C, 0.4 mbar) to yield the desired enyne as a clear, colourless oil (3.236 g, 12.4 mmol, 62%).



^1H NMR (300 MHz, $CDCl_3$) δ = 7.5 – 7.2 (5H, m, Ar), 5.526 (1H, s, d), 5.384 (1H, s, d), 3.708 (2H, s, a), 3.370 (2H, t, J = 2.2 Hz, e), 3.346 (2H, s, b), 2.253 (2H, tt,

J = 7.0, 2.2 Hz, h), 1.604 (2H, app. sextet, J = 7.2 Hz, i), 1.062 (3H, t, J = 7.4 Hz, j) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.95 (0), 138.65 (0), 129.17 (1), 128.47 (1), 127.33 (1), 114.69 (2, d), 86.09 (0), 74.21 (0), 59.85 (2, b), 57.07 (2, a), 41.86 (2, e), 22.66 (2), 20.90 (2), 13.74 (3, j) ppm.

IR (thin film) ν = 3027w, 2970s, 2838s, 2260w, 1642s, 1459s, 1322s, 1138s, 887s, 761s, 698s cm^{-1}

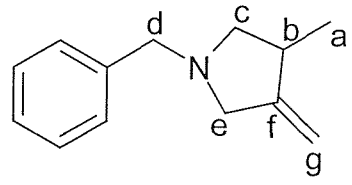
LRMS (ES+) m/z = 264 (^{37}Cl M + H)$^+$, 35 %, 262 (^{35}Cl M + H)$^+$, 100 %.

HRMS: $C_{16}H_{20}N_{35}Cl$ requires m/z = 261.1284, found 261.1284

Microanalysis: $C_{16}H_{20}NCl$ requires C 73.41%, H 7.70%, N 5.35%, found C 73.35%, H 7.89%, N 5.37%

1-Benzyl-3-methyl-4-methylenepyrrolidine (363)

The title compound was prepared according to **Method B**, using *N*-allyl-*N*-benzyl-*N*-(2-chloroallyl)amine **(356)** (221 mg, 1 mmol). The crude product was purified by column chromatography (SiO_2, 20% ether in petrol) to provide the desired product as a clear, colourless oil (132 mg, 0.71 mmol, 71%). This compound has been synthesised previously by different methods,[44, 48] however, no data was provided, so that obtained from our sample is provided here.



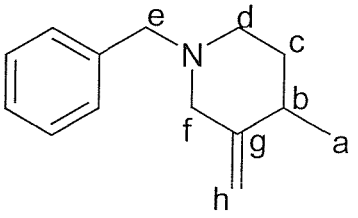
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.4 – 7.2 (5H, m, Ar), 4.905 (1H, q, J = 2.2 Hz, g), 4.842 (1H, q, J = 2.5 Hz, g), 3.676 (1H, d, J = 13.2 Hz, d), 3.597 (1H, d, J = 12.9 Hz, e), 3.466 (1H, d, J = 13.2 Hz, d), 3.1 – 3.0 (2H, m, e and c), 2.8 – 2.7 (1H, m, b), 2.111 (1H, t, J = 8.8 Hz, c), 1.132 (3H, d, J = 6.6 Hz, a) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 154.08 (0, f), 138.96 (0), 129.01 (1), 128.42 (1), 127.17 (1), 104.06 (2, g), 62.44 (2), 60.83 (2), 59.63 (2), 37.67 (1, b), 17.82 (3, a) ppm.

LRMS (ES+) m/z = 188 (M + H)$^+$

1-Benzyl-4-methyl-3-methylenepiperidine (364), *N*-Benzyl-*N*-allyl-*N*-(3-butenyl)amine (365) and *N*-allyl-*N*-butylbenzylamine (366)

The title compounds were prepared according to **Method B**, using *N*-benzyl-*N*-butenyl-*N*-(2-chloroallyl)amine **(357)** (236 mg, 1 mmol). Purification and separation was by column chromatography (SiO_2, 10% ether in petrol) to provide the cyclised product **(364)** as a clear, colourless oil (107 mg, 53%). Further purification by Kugelrohr distillation provided 80 mg (40%) of material. The non-cyclised (reduced) product **(365)** was obtained as a clear, colourless oil (72 mg, 36%), contaminated with roughly 20% of the further reduced product, *N*-allyl-*N*-butylbenzylamine **(366)**.

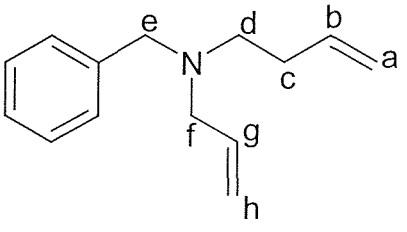


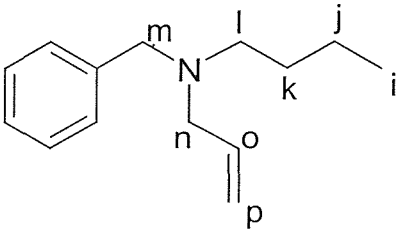
^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.25 – 7.1 (5H, m, Ar), 4.660 (1H, d, J = 1.5 Hz, h), 4.610 (1H, t, J = 1.5 Hz, h), 3.419 (1H, s, e), 3.414 (1H, s, e), 3.147 (1H, dd, J = 11.9, 1.5 Hz, f), 2.758 (1H, dtd, J = 11.4, 3.7, 1.5 Hz, d), 2.526 (1H, d, J = 11.9 Hz, f), 2.082 (1H, td, J = 11.4, 3.0 Hz, d), 2.0 – 1.9 (1H, m, b), 1.596 (1H, ddt, J = 12.9, 4.5, 3.5 Hz, c), 1.228 (1H, dtd, J = 12.9, 11.4, 4.0 Hz, c), 0.970 (3H, d, J = 6.5 Hz, a) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 149.19 (0, g), 138.42 (0), 129.42 (1), 128.32 (1), 127.13 (1), 107.21 (2, h), 62.96 (2), 60.96 (2), 53.48 (2, d), 35.74 (1), 34.74 (2), 17.88 (3, a) ppm.

LRMS (ES+) m/z = 202 $(M + H)^+$

NMR data is consistent with literature values.[49]





(365) 4 : 1 **(366)**

^{1}H NMR (300 MHz, $CDCl_3$) **(365)** δ = 7.4 – 7.2 (5H, m, Ar), 6.0 – 5.7 (2H, m, b and g), 5.3 – 4.9 (4H, m, a and h), 3.617(2H, s, e), 3.119 (2H, d, J = 6.5 Hz, f), 2.558 (2H, t, J = 7.4 Hz, d), 2.278 (2H, q, J = 7.1 Hz, c) ppm.

NMR data is consistent with literature values.[43]

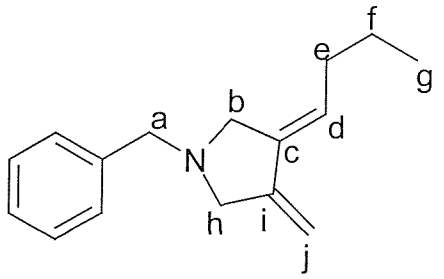
^{1}H NMR (300 MHz, $CDCl_3$) **(366)** selected peaks: δ = 3.591 (2H, s, m), 2.453 (2H, t, J = 7.2 Hz, l), 1.498 (2H, app. quintet, J = 7.3 Hz, k), 1.324 (2H, app.sextet, J = 7.3 Hz, j), 0.903 (3H, t, J = 7.4 Hz, i) ppm

NMR data is consistent with literature values.[92]

LRMS (ES+) m/z for mixture: 202 ((**369**) M + H)$^+$, 100%, 204 ((**370**) M + H)$^+$, 55%

1-Benzyl-3-[(*Z*)-butylidene]-4-methylenepyrrolidine (367)

The title compound was prepared according to **Method B**, using of *N*-benzyl-*N*-(2-hexynyl)-*N*-(2-chloroallyl)amine **(362)** (786 mg, 3 mmol). The crude product was purified by column chromatography (SiO_2, 10% ether in petrol) to provide the desired product as a clear, colourless oil (605 mg, 2.67 mmol, 89%).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.4 – 7.2 (5H, m, Ar), 5.867 (1H, tt, J = 7.4, 2.2 Hz, d), 5.264 (1H, t, J = 2.2 Hz, j), 4.796 (1H, s, j), 3.694 (2H, s, a), 3.337 (2H, d, J = 2.2 Hz, b and h), 3.316 (2H, t, J = 2.2 Hz, b and h), 2.015 (2H, q, J = 7.6 Hz, e), 1.434 (2H, app. sextet, J = 7.4 Hz, f), 0.925 (3H, t, J = 7.4 Hz, g) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 145.27 (0), 138.80 (0), 136.44 (0), 129.03 (1), 128.46 (1), 127.24 (1), 120.70 (1), 100.70 (2), 60.91 (2), 60.28 (2), 57.10 (2), 31.84 (2), 22.64 (2), 14.07 (3) ppm.

IR (thin film) ν = 3033m, 2970s, 2941s, 2787s, 1676w, 1648m, 1505m, 1453s, 1379s, 1138s, 881s, 749s, 703s cm^{-1}

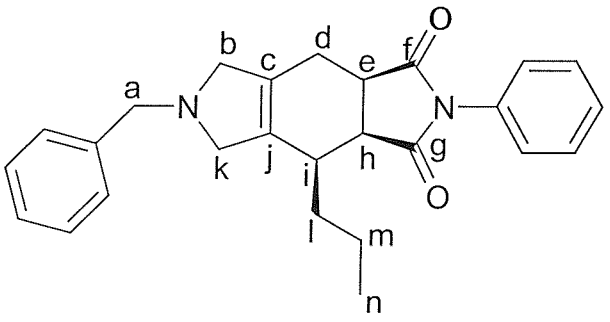
LRMS (ES+) m/z = 228 (M + H)$^+$

HRMS: $C_{16}H_{21}N$ requires m/z = 227.1674, found 227.1675

Microanalysis: $C_{16}H_{21}N$ requires C 84.53%, H 9.31%, N 6.16%, found C 83.04%, H 9.29%, N 5.98%.

(3aS*,4R*,8aR*)-6-Benzyl-2-phenyl-4-propyl-1,2,3,3a,4,5,6,7,8,8a-decahydro pyrrolo[3,4-f]isoindole-1,3-dione (368)

A solution of 1-benzyl-3-[(*Z*)-butylidene]-4-methylenepyrrolidine **(367)** (125 mg, 0.55 mmol) in dry ether (1 mL) was added dropwise to a solution of *N*-phenyl maleimide (87 mg, 0.5 mmol) in dry diethyl ether (3 mL), and the resultant yellow solution stirred at RT for 7 h. The solvent was removed *in vacuo* and the residue purified by column chromatography (SiO_2, ether) to yield the desired Diels Alder adduct as a sticky, colourless gum (173 mg, 87%).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.6 – 7.2 (10H, m, Ar), 3.826 (2H, s, a), 3.7 – 3.4 (4H, m, b and k), 3.333 (1H, td, J = 9.2, 4.4 Hz, e), 3.292 (1H, dd, J = 8.8, 2.9 Hz, h), 2.764 (1H, q, J = 6.5 Hz, i), 2.662 (1H, d, J = 17.6 Hz, d), 2.475 (1H, d, J = 16.9, 8.1 Hz, d), 1.8 – 1.3 (4H, m, l and m), 0.920 (3H, t, J = 7.4 Hz, n) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 179.30 (0), 177.33 (0), 139.40 (0), 136.80 (0), 132.27 (0), 132.08 (0), 129.36 (1), 128.80 (1), 128.59 (1), 127.26 (1), 126.60 (1), 62.34 (2), 61.85 (2), 60.58 (2), 44.08 (1), 39.87 (1), 35.42 (1), 31.95 (2), 21.98 (2), 21.50 (2), 14.32 (3) ppm.

IR (thin film) ν = 2958w, 2873w, 2260w, 1716s, 1510m, 1459m, 1390s, 1184m, 909s, 732s cm^{-1}

LRMS (ES+) m/z = 401 $(M + H)^+$

HRMS: $C_{26}H_{28}N_2O_2$ requires m/z = 400.2151, found 400.2146

Carbenoid insertions

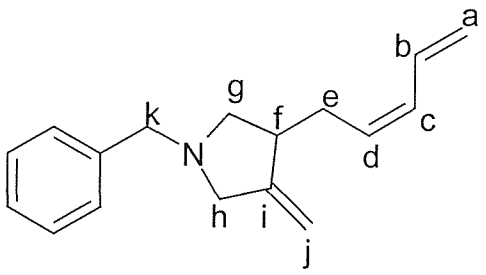
The following represents a generalised procedure **(Method D)** for insertion of vinyl carbenoids[34] into the organozirconium reagent derived from *N*-allyl-*N*-(2-chloro allyl)benzylamine **(356)**, on roughly a 1 mM scale:

To a solution of Cp_2ZrCl_2 (1.1 equivalents) in THF (4 mL) at –80 °C under Ar is added dropwise n-butyllithium (2.2 eq, 2.5 M solution in hexanes). A solution of *N*-

allyl-*N*-(2-chloroallyl)benzylamine (1 eq) in THF (2 mL) is added and the solution allowed to warm to RT and stirred for 3 h. The solution is re-cooled to –90 °C and a solution of the vinyl chloride (1.3 eq) (2.6 eq in the case of *cis*-1,4-dichloro-2-butene) in THF (1 mL) is added, followed by a solution of LiTMP (1.3 eq, prepared by addition of n-butyllithium to a solution of 2,2,6,6-tetramethylpiperidine (1.3 eq) in THF (4 mL) under Ar at 0 °C and stirred 30 min.). In the case of *cis*-1,4-dichloro-2-butene, 2.6 equivalents of LiTMP are used. After 30 min at – 90 °C to – 80 °C, MeOH (3 mL) and saturated $NaHCO_3$ solution (6 mL) are added and the reaction allowed to warm to RT and stirred 16 h. The reaction mixture is subsequently diluted with water and ether. The aqueous phase is extracted with ether and the combined organic phases washed with brine, dried over $MgSO_4$, filtered and concentrated. Purification is by column chromatography (SiO_2, 10% ether in hexanes).

1-Benzyl-3-methylene-4-[(2*Z*)-2,4-pentadienyl)pyrrolidine (369)

The title compound was prepared according to **Method D**, performed on a 1.5 mM scale, using the carbenoid generated by reaction of *cis*-1,4-dichloro-2-butene with 2 equivalents of LiTMP. The desired product was obtained as a clear, colourless oil (270 mg, 1.13 mmol, 75%)



^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.4 – 7.2 (5H, m, Ar), 6.657 (1H, dddd, J = 16.6, 11.2, 9.9, 1.0 Hz, b), 6.059 (1H, t, J = 11.0 Hz, c), 5.470 (1H, dt, J = 10.4, 7.7 Hz, d), 5.209 (1H, d, J = 16.8 Hz, a), 5.120 (1H, d, J = 10.1 Hz, a), 4.946 (1H, q, J = 2.2 Hz, j), 4.910 (1H, q, J = 2.2 Hz, j), 3.682 (1H, d, J = 12.9 Hz, k), 3.583 (1H, d, J = 12.9 Hz, k), 3.369 (1H, d, J = 13.4 Hz, h), 3.117 (1H, d, J = 13.4 Hz, h), 2.925 (1H, t, J = 7.9 Hz, g), 2.754 (1H, m, f), 2.55 – 2.3 (2H, m, e), 2.276 (1H, t, J = 8.1 Hz, g) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.01 (0), 138.96 (0), 132.34 (1), 130.52 (2C, 1), 128.86 (1), 128.38 (1), 127.11 (1), 117.46 (2, a), 104.94 (2, j), 60.65 (2), 59.81 (2C, 2), 42.93 (1, f), 31.80 (2, e) ppm.

IR (thin film) ν = 2909s, 2784s, 1663m, 1592w, 1453s, 1140s, 997s, 740s cm^{-1}

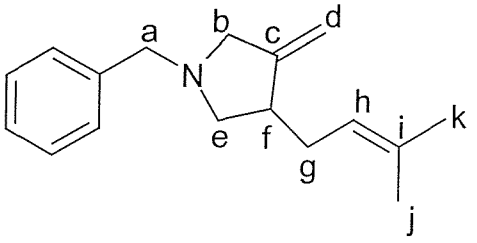
LRMS (ES+) m/z = 240 $(M + H)^+$

HRMS: $C_{17}H_{21}N$ requires m/z = 239.1674, found 239.1667

Microanalysis: $C_{17}H_{21}N$ requires C 85.30%, H 8.84%, N 5.85%, found C 84.94%, H 8.94%, N 5.90%.

1-Benzyl-3-methylene-4-(3,3-dimethyl-2-propenyl)pyrrolidine (370)

The title compound was prepared according to **Method D**, performed on a 1 mM scale, using the carbenoid derived from 1-chloro-2-methyl-1-propene. The desired product was obtained as a clear, colourless oil (156 mg, 0.65 mmol, 65%).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.4 – 7.2 (5H, m, Ar), 5.144 (1H, t + fs, J = 7.2 Hz, h), 4.920 (1H, q, J = 2.2 Hz, d), 4.890 (1H, q, J = 2.2 Hz, d), 3.673 (1H, d, J = 13.2 Hz, a), 3.575 (1H, d, J = 13.2 Hz, a), 3.361 (1H, d + fs, J = 13.6 Hz, b), 3.090 (1H, dq, J = 13.6, 2.3 Hz, b), 2.922 (1H, dd, J = 8.8, 7.0 Hz, e), 2.75 – 2.65 (1H, m, f or g), 2.35 – 2.25 (1H, m, f or g), 2.223 (1H, dd, J = 8.8, 7.4 Hz, e), 2.2 – 2.1 (1H, m, g), 1.707 (3H, d, J = 1.1 Hz, j or k), 1.624 (3H, s, j or k) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.66 (0), 139.18 (0), 132.71 (0), 128.92 (1), 128.38 (1), 127.08 (1), 122.81 (1), 104.51 (2), 60.82 (2), 60.15 (2), 60.01 (2), 43.34 (1), 32.32 (2), 25.95 (3), 18.05 (3) ppm.

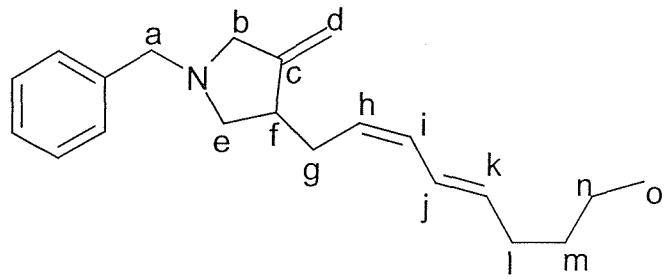
IR (thin film) ν = 3039w, 2924s, 2781s, 1665m, 1510m, 1459s, 1384m, 1144m, 881s, 755m cm^{-1}

LRMS (ES+) m/z = 242 $(M + H)^+$

HRMS: $C_{17}H_{23}N$ requires m/z = 241.1831, found 241.1827

1-Benzyl-3-methylene-4-[(2*Z*,4*E*)-2,4-nonadienyl)pyrrolidine (371)

The title compound was prepared according to **Method D**, on a 0.8 mM scale, using the carbenoid derived from 1-chloro-1,3-octadiene. The desired product was obtained as a clear, colourless oil (145 mg, 62%).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.4 – 7.2 (5H, m, Ar), 6.331 (1H, dd, J = 15.1, 11.0 Hz, j), 6.011 (1H, t, J = 11.0 Hz, i), 5.698 (1H, dt, J = 14.7, 7.4 Hz, k), 5.318 (1H, dt, J = 11.0, 7.4 Hz, h), 4.940 (1H, q, J = 2.2 Hz, d), 4.912 (1H, q, J = 2.2 Hz, d), 3.662 (1H, d, J = 12.9 Hz, a), 3.584 (1H, d, J = 12.9 Hz, a), 3.361 (1H, d, J = 13.6 Hz, b), 3.094 (1H, dq, J = 13.2, 2.2 Hz, b), 2.932 (1H, dd, J = 8.8, 7.4 Hz, e), 2.8 – 2.7 (1H, m, f), 2.5 – 2.4 (1H, m, g), 2.4 – 2.3 (1H, m, g), 2.264 (1H, t, J = 6.6 Hz, e), 2.129 (2H, q, J = 6.6 Hz, l), 1.5 – 1.3 (4H, m, m and n), 0.926 (3H, t, J = 7.0 Hz, o) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 152.12 (0), 138.94 (0), 135.33 (1), 129.89 (1), 128.74 (1), 128.23 (1), 127.39 (1), 126.94 (1), 125.53 (1), 104.65 (2, d), 60.61 (2), 59.84 (2), 59.74 (2), 42.92 (1, f), 32.60 (2), 31.60 (2), 31.54 (2), 22.30 (2), 13.98 (3, o) ppm.

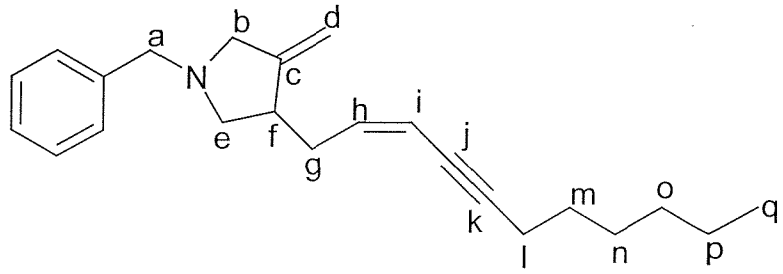
IR (thin film) ν = 3027w, 2958s, 2930s, 2792m, 1671w, 1499m, 1459s, 1379w, 1144w, 892s, 732s, 698s cm^{-1}

LRMS (ES+) m/z = 296 $(M + H)^+$

HRMS: $C_{21}H_{29}N$ requires m/z = 295.2300, found 295.2287

1-Benzyl-3-methylene-4-[(2*Z*)-undeca-2-en-4-ynyl)pyrrolidine (372)

The title compound was prepared according to **Method D**, on a 0.8 mM scale, using the carbenoid prepared from 1-chloro-dec-1-en-3-yne. The desired product was obtained as a clear, colourless oil (102 mg, 40%).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.4 – 7.2 (5H, m, Ar), 5.850 (1H, dt, J = 10.3, 7.4 Hz, h), 5.510 (1H, d + fs, J = 11.0 Hz, i), 4.949 (1H, q, J = 2.2 Hz, d), 4.917 (1H, q, J = 2.2 Hz, d), 3.668 (1H, d, J = 12.5 Hz, a), 3.587 (1H, d, J = 12.5 Hz, a), 3.395 (1H, d, J = 13.2 Hz, b), 3.053 (1H, dq, J = 13.2, 2.2 Hz, b), 2.976 (1H, dd, J = 8.8, 7.4 Hz, e), 2.85 – 2.4 (3H, m, f and g), 2.362 (2H, td, J = 7.0, 2.2 Hz, l), 2.272 (1H, t, J = 8.5 Hz, e), 1.6 – 1.25 (8H, m, m, n, o and p), 0.915 (3H, t, J = 7.0 Hz, q) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 151.96 (0, c), 140.05 (1, h), 139.11 (0), 128.89 (1), 128.40 (1), 127.11 (1), 110.87 (1, i), 104.87 (2, d), 95.22 (0, j), 77.46 (0, k), 60.77 (2), 60.02 (2), 59.83 (2), 42.53 (1, f), 33.74 (2), 31.54 (2), 29.00 (2), 28.75 (2), 22.76 (2), 19.71 (2), 14.26 (3, q) ppm.

IR (thin film) ν = 3016w, 1941s, 2855s, 2798s, 2210w, 1665w, 1499m, 1459s, 1447m, 1150m, 887s, 749s, 709s cm^{-1}

LRMS (ES+) m/z = 322 $(M + H)^+$

HRMS: $C_{23}H_{31}N$ requires m/z = 321.2457, found 321.2449

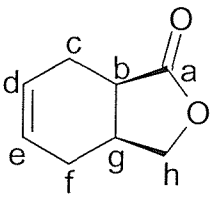
Experimental Details for Chapter 4

[6-(Hydroxymethyl)-3-cyclohexenyl]methanol (402)

The title compound was prepared by the method of Mundy *et al.*[93]

1,3,3a,4,7,7a-Hexahydro-1-isobenzofuranone (403)

To a stirred mixture of pyridinium chlorochromate (54.28 g, 252 mmol) and SiO_2 (54 g) was added a solution of [6-(hydroxymethyl)-3-cyclohexenyl] methanol **(402)** (11.92 g, 84 mmol) in DCM (200 mL), resulting in an exotherm. The reaction mixture was stirred for 2 h, then poured onto a column of silica. The product was eluted with 3 bed volumes of ether, and the eluant concentrated to give a pale yellow oil which was purified by Kugelrohr distillation (110 °C / 0.7 mbar) to provide a clear, colourless oil (4.918 g, 35.6 mmol, 42%).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.66 (2H, m, d and e), 4.28 (1H, dd, J = 9, 5 Hz, h), 3.98 (1H, dd, J = 9, 2 Hz, h), 2.75 (1H, td, J = 8, 2.5 Hz, b), 2.59 (1H, m, g), 2.50-2.34 (1H, m, c), 2.32-2.10 (2H, m, c and f), 1.86 (1H, m, f) ppm

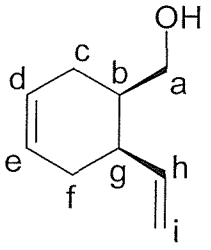
^{13}C NMR (75 MHz, $CDCl_3$) δ = 179.26 (0, a), 125.24 (1) 124.97 (1), 72.90 (2, h), 37.38 (1, b), 32.07 (1, g), 24.80 (2, c), 22.12 (2, f) ppm

IR (thin film) ν = 3028m, 2904m, 2842m, 1774s, 1437m, 1372m, 1135s, 1042s, 1011m, 946m, 730w, 666m cm^{-1}

NMR data is consistent with literature values.[94]

(6-Vinyl-3-cyclohexenyl) methanol (404)

To a solution of 1,3,3a,4,7,7a-hexahydro-1-isobenzofuranone **(403)** (13.8 g, 100 mmol) in toluene (150 mL) at –80 °C was added slowly diisobutyl aluminium hydride (67 mL of a 1.5 M solution in toluene, 100 mmol. After 1 h, the cold solution was poured into a solution of methylene triphenyl phosphorane (150 mmol, generated by addition of n-butyllithium (60 mL of a 2.5 M solution in hexanes, 150 mmol) to methyl triphenyl phosphonium bromide (53.6 g, 150 mmol) in THF (150 mL) at 0 °C and stirred for 1 h). The reaction mixture was heated at 70 °C over night, and after cooling, poured into ether. The ethereal solution was washed with ice, 2 M HCl and brine, dried over $MgSO_4$, filtered and concentrated to a volume of about 100 mL. Pentane (100 mL) was added, and the mixture kept at –20 °C for 4 h. The precipitated phosphine oxide was filtered off and washed with pentane. The combined washings were concentrated to give a crude product, which was purified by column chromatography (SiO_2, 20% ether in petrol) to provide the desired alcohol as a clear, colourless oil (6.219 g, 45 mmol, 45%).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.90 (1H, ddd, J = 17.5, 10.5, 8.5 Hz, h), 5.68 (2H, m, d,e), 5.10 (1H, ddd, J = 17.5, 2.0, 1 Hz, i), 5.06 (1H, ddd, J = 10.5, 2, 1 Hz,

i), 3.55 (2H, m, a), 2.61 (1H, m, g), 2.31 (1H, m, b), 2.14-1.85 (4H, m, c and f), 1.6 (1H, s, -OH) ppm.

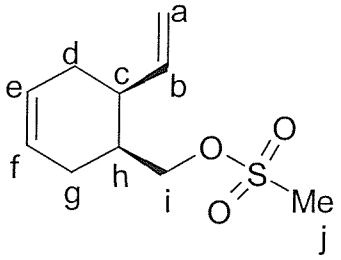
^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.42 (1, h), 125.81 (1), 125.53 (1), 115.39 (2, i), 64.96 (2, a), 39.31 (1), 38.30 (1), 30.22 (2, c), 25.70 (2, f) ppm.

IR (thin film) ν = 3346 br s, 3023s, 2906s, 2837s, 1637m, 1436s, 1090m, 1029s, 998m, 912s cm^{-1}

NMR data is consistent with literature values.[59]

(6-Vinyl-3-cyclohexenyl)methyl methanesulfonate (405)

Methanesulfonyl chloride (0.37 mL, 552 mg, 4.84 mmol) was added dropwise to a solution of (6-vinyl-3-cyclohexenyl) methanol **(404)** (607 mg, 4.4 mmol) and triethylamine (533 mg, 5.28 mmol) in DCM (10 mL) at –40 °C. After 2 h, ether (50 mL) and water (20 mL) were added. The product was extracted into ether, and the combined extracts dried over $MgSO_4$ and concentrated to give the product as a colourless oil (950 mg, 4.4 mmol, 100%), which was reacted immediately without purification.



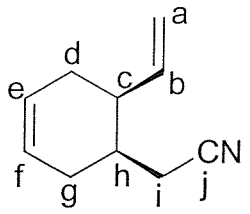
^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.81 (1H, ddd, J = 18, 9.5, 8.5 Hz, b), 5.67 (2H, m, e and f), 5.11 (2H, m, a), 4.13 (1H, dd, J = 9.5, 7.5 Hz, i), 4.05 (1H, dd, J = 9.5, 7.5 Hz, i), 2.90 (3H, s, j), 2.59 (1H, m, c), 2.36 - 1.80 (5H, m, d, g and h) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.79 (1, b), 125.64 (1), 124.81 (1), 116.67 (2, a), 71.73 (2, i), 37.71 (1), 36.27 (1), 37.31 (3, j), 29.74 (2, g), 25.24 (2, d) ppm.

(6-Vinyl-3-cyclohexenyl)ethanenitrile (406)

A solution of (6-vinyl-3-cyclohexenyl) methyl methanesulfonate **(405)** (2.94 g, 13.6 mmol), potassium cyanide (1.82 g, 28 mmol), sodium iodide (150 mg, 1 mmol) and 18-crown-6 (2.0 g, 7.6 mmol) in dry acetonitrile (50 mL) was heated to reflux at 90 °C. The progress of the reaction was followed by TLC, and after 68 h the starting material had been consumed. The red reaction mixture was poured into water and

ether. The aqueous phase was extracted with ether, and the combined organic phases washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (SiO_2, 20% ether in petrol) to give the desired nitrile as a clear, colourless oil (1.398 g, 9.5 mmol, 68%).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.77 (1H, ddd, J = 18, 10, 8 Hz, b), 5.67 (2H, m, e and f), 5.14 (2H, m, a), 2.56 (1H, m, c), 2.36-2.21 (5H, m, i, d and g), 2.01-1.88 (2H, m, g and h) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.50 (1, b), 125.46 (1, e or f), 124.72 (1, e or f), 119.50 (0, j), 117.10 (2, a), 39.78 (1, c), 34.12 (1, h), 29.25 (2), 28.45 (2), 19.97 (2, i), ppm.

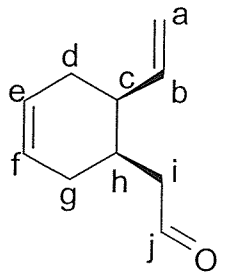
IR (thin film) ν = 3029m, 2910s, 2840s, 2251m, 1638w, 1438m, 1422m, 1000m, 912s, 735s, 651m cm^{-1}

LRMS (APCI) m/z = 148 $(M + H)^+$

HRMS: $C_{10}H_{13}N$ requires m/z = 147.1048, found 147.1030

(6-Vinyl-3-cyclohexenyl)ethanal (407)

Diisobutyl aluminium hydride (10 mL of a 1.5 M solution in toluene, 15 mmol) was added dropwise to a solution of (6-vinyl-3-cyclohexenyl) ethane nitrile **(406)** (1.104 g, 7.5 mmol) in THF (20 mL) at below –70 °C under Ar. The reaction was allowed to warm for 3 h, and methanol (2 mL) was added followed by saturated $NaHCO_3$ solution (10 mL). After 4 h, the mixture was extracted with ether and the combined extracts dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (SiO_2, 10% ether in petrol) to provide the desired aldehyde as a clear, colourless oil (788 mg, 5.25 mmol, 70%) which was reacted immediately.



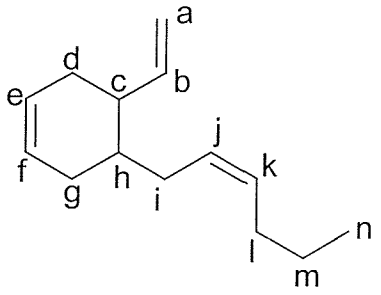
^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.78 (1H, s, j), 5.80 (1H, ddd, J = 17.5, 10.5, 7.5 Hz, b), 5.64 (2H, m, e and f), 5.07 (2H, m, a), 2.45 - 2.15 (6H, m, c, d, g, h and i), 1.99 - 1.74 (2H, m, d and g) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 202.79 (1, j), 139.15 (1, b), 125.59 (1), 125.40 (1), 115.85 (2, a), 45.81 (2, i), 40.17 (1, c), 30.90 (1, h), 29.24 (2, d), 29.08 (2, g) ppm.

1-(6-Vinyl-3-cyclohexenyl)-(2*Z*)-hexene (*cis*-401)

The title compound was prepared by a method developed by Boden.[61]

To an orange suspension of butyl triphenyl phosphonium bromide (639 mg, 1.6 mmol), potassium *tert*-butoxide (180 mg, 1.6 mmol) and 18-crown-6 (4 mg) in THF (2 mL) under Ar was added a solution of (6-vinyl-3-cyclohexenyl)ethanal **(407)** (200 mg, 1.33 mmol) in THF (2.5 mL), producing a white suspension. After stirring at RT for 16 h water and pentane were added. The aqueous layer was separated and extracted with pentane. The combined organic phases were washed with 2 M HCl then brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (SiO_2, pentane) to provide the title product as a clear, colourless oil (202 mg, 1.06 mmol, 80%). GC analysis showed the product to contain 9% of the *trans* isomer.



^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.88 (1H, ddd, J = 17, 12, 7 Hz, b), 5.65 (2H, m, e and f), 5.39 (2H, m, j and k), 5.06 (1H, d, J = 12 Hz, a), 5.05 (1H, d, J = 17 Hz, a), 2.46 (1H, m, c), 2.26 (1H, m, h), 2.1-1.7 (8H, m, d, g, i and l), 1.37 (2H, qt, J = 7.5, 7 Hz, m), 0.91 (3H, t, J = 7.5 Hz, n) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) Major isomer (*cis*) δ = 139.75 (1, b), 130.86 (1, j or k), 128.76 (1, j or k), 126.33 (1, e or f), 125.49 (1, e or f), 115.00 (2, a), 40.50 (1, c), 37.34 (1, h), 30.21 (2, d or g), 28.82 (2, d or g), 29.59 (2, i or l), 29.49 (2, i or l), 23.04 (2, m), 13.99 (3, n) ppm.

IR (thin film) ν = 3073w, 3022m, 2908s, 2836s, 1638m, 1456m, 1435m, 998m, 912s, 736m, 655m cm^{-1}

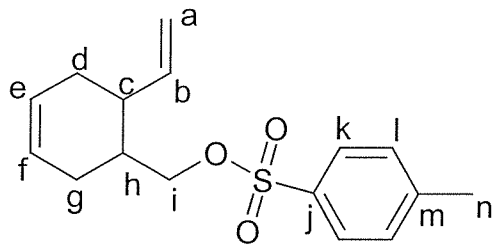
LRMS (APCI) m/z = 190 (M^+)

HRMS: $C_{14}H_{22}$ requires m/z = 190.1722, found 190.1708

4-[2-(Phenylsulfonyl)ethyl]-5-vinyl-1-cyclohexene (408)

The title compound was prepared *via* the tosylate of 6-vinyl-3-cyclohexenylmethanol **(404)**, as follows:

A solution of 6-vinyl-3-cyclohexenylmethanol **(404)** (690 mg, 5 mmol) and toluene sulfonyl chloride (1.05 g, 5.5 mmol) in pyridine (10 mL) was stirred overnight at room temperature. The resultant mixture was poured into 2 M HCl (40 mL) and ether (50 mL) and the aqueous phase extracted into ether. The combined organic phases were washed with 2 M HCl and brine, then dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (SiO_2, 20% ether in petrol) to give the intermediate tosylate (1.250 g, 4.3 mmol, 86%).

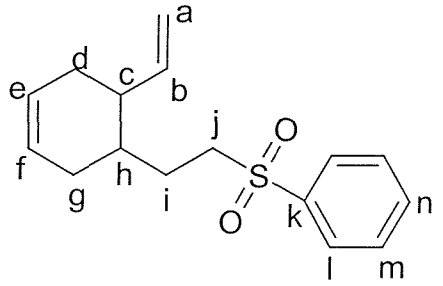


^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.79 (2H, d, J = 8 Hz, k), 7.35 (2H, d, J = 8 Hz, l), 5.70 (1H, ddd, J = 17.5, 10.5, 8.5 Hz, b), 5.62 (2H, m, e and f), 4.99 (1H, d, J = 10.5 Hz, a), 4.94 (1H, d, J = 17.5 Hz, a), 3.93 (1H, dd, J = 9.5, 7.5 Hz, i), 3.87 (1H, dd, J = 9.5, 7.5 Hz, i), 2.53 (1H, m, c), 2.46 (3H, s, n), 2.3-1.7 (5H, m, d, g and h) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 144.84 (0, j), 137.54 (1, b), 133.19 (0, m), 129.95 (1, k or l), 128.06 (1, k or l), 125.57 (1, e or f), 124.87 (1, e or f), 116.55 (2, a), 72.09 (2, i), 37.55 (1, c or h), 36.11 (1, c or h), 29.78 (2, d or g), 25.13 (2, d or g), 21.81 (3, n) ppm.

This tosylate was converted to the title sulfone as follows:

n-Butyllithium (2.36 mL of a 2.5 M solution in hexanes, 5.9 mmol) was added dropwise to a solution of methyl phenyl sulfone (921 mg, 5.9 mmol) in THF (11 mL) at 0 °C under Ar. The yellow suspension was stirred for 30 minutes before being cooled to –80 °C, whereupon a solution of the tosylate (1.148 g, 3.93 mmol) in THF (4 mL) was added dropwise. The solution was allowed to warm to room temperature and stirred overnight, whereupon the reaction mixture was poured into a cold, saturated solution of ammonium chloride. The layers were separated, and the aqueous phase extracted with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (25% ether in petrol), furnishing the desired sulfone as a clear, colourless oil (412 mg, 1.49 mmol, 38%).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.89 (2H, d, J = 7 Hz, l), 7.65 (1H, t, J = 7.5 Hz, n), 7.55 (2H, t, J = 7.5 Hz, m), 5.71 (1H, ddd, J = 17.5, 10.5, 8.5 Hz, b), 5.58 (2H, m, e and f), 4.97 (1H, d, J = 8.5 Hz, a), 4.93 (1H, d, J = 17 Hz, a), 3.10 (2H, dd, J = 9, 7 Hz, j), 2.4-1.6 (6H, m, c, d, g, h and i) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.28 (0, k), 138.22 (1, b), 133.80 (1, n), 129.40 (1, l or m), 128.16 (1, l or m), 125.49 (1, e or f), 125.39 (1, e or f), 115.94 (2, a), 54.67 (2, j), 40.28 (1, c), 35.51 (1, h), 30.17 (2), 28.54 (2), 25.13 (2) ppm.

IR (thin film) ν = 2975m, 2892s, 2838m, 1447s, 1306s, 1151s, 1087s, 999m, 910s, 735s cm^{-1}

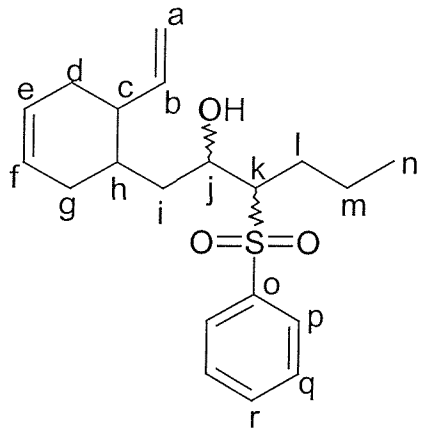
LRMS (APCI) m/z = 277 $(M + H)^+$

HRMS: $C_{16}H_{20}O_2S$ requires m/z = 276.1150, found 276.1169

3-(Phenylsulfonyl)-1-(6-vinyl-3-cyclohexenyl)-2-hexanol (409)

To a solution of butyl phenyl sulfone (1.62 g, 8.2 mmol) in THF (25 mL) at –80 °C under Ar was added dropwise n-butyllithium (3.28 mL of a 2.5 M solution in

hexanes, 8.2 mmol), producing a bright yellow solution. After 30 min, a solution of (6-vinyl-3-cyclohexenyl)ethanal **(407)** (1.23 g, 8.2 mmol) in THF (7 mL) was added. The orange solution was allowed to warm to room temperature and stirred over night. The reaction mixture was poured into water and ether, and the aqueous layer extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to give a yellow oil. The crude product was purified by column chromatography (SiO_2, 40% to 60% ether in petrol, gradient) to give the title compound as a mixture of diastereomers which were not separated (2.66 g, 7.6 mmol, 93%).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.91 (2H, dd, J = 7.3, 1.8 Hz, p), 7.68 (1H, dd, J = 7.3, 1.5 Hz, r), 7.60 (2H, td, J = 7.5, 2.5 Hz, q), 5.83-5.66 (1H, m, b), 5.58 (2H, m, e and f), 4.87 (1H, dd, J = 10.3, 1.8 Hz, a), 4.62 (1H, dd, J = 17.3, 1.5 Hz, a), 4.22 (1H, ddd, J = 13.6, 8.1, 3.7 Hz, j), 3.06 (1H, m, k), 2.87 (1H, m, c), 2.30 (1H, m, h), 2.24 (1H, s, -OH), 2.0-1.8 (4H, m, d and g), 1.8-1.3 (6H, m, i, l and m), 0.89 (3H, t, J = 7.3 Hz, n) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = [139.06 (1), 138.80 (1) b], 138.25 (0, o), 134.12 (1, r), [129.52 (1), 128.70 (1) p and q], [126.08 (1), 125.68 (1), 125.25 (1) e and f], 115.51 (2, a), [68.75 (1), 68.37 (1), j], 66.39 (1, k), [40.86 (1), 39.60 (1), c], [36.71 (2), 36.59 (2), i], [32.75 (1), 32.52 (1), h], [30.61 (2), 30.12 (2), 29.22 (2), 28.26 (2) d and g], [24.85 (2), 24.49 (2), l], [22.54 (2), 22.33 (2), m], [14.15 (3), 14.09 (3), n] ppm.

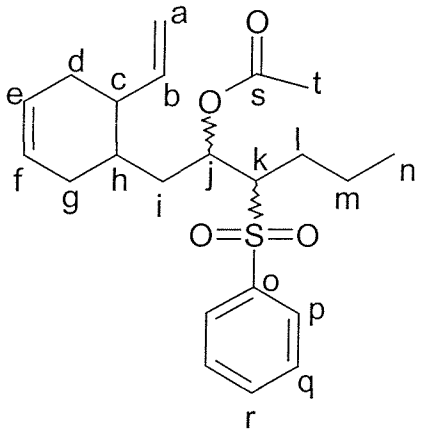
IR (thin film) ν = 3508m, 3020w, 2960m, 2907m, 1456m, 1288s, 1143s, 1082m, 912s cm^{-1}

LRMS (APCI) m/z = 349 $(M + H)^+$

HRMS: $C_{20}H_{28}O_3S$ requires m/z = 348.1759, found 348.1764

2-(Phenylsulfonyl)-1-[(6-vinyl-3-cyclohexyl)methyl]pentyl acetate (410)

A solution of 3-(phenylsulfonyl)-1-(6-vinyl-3-cyclohexenyl)-2-hexanol **(409)** (2.630 g, 7.56 mmol) and acetic anhydride (10.2 g, 100 mmol) in pyridine (50 mL) was stirred at room temperature over night. The reaction mixture was diluted with 2 M HCl and ether, and the aqueous layer extracted with ether. The combined organic extracts were washed with 2 M HCl and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (SiO_2, 30% ether in petrol) to give the required acetate as a clear, colourless oil as a mixture of diastereomers (2.710 g, 6.9 mmol, 91%).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.89 (2H, d, J = 7.3 Hz, p), 7.66 (1H, t, J = 7.3 Hz, r), 7.57 (2H, t, J = 7.3 Hz, q), 5.70 (1H, ddd, J = 18.4, 10.3, 7.7 Hz, b), 5.57 (2H, m, e and f), 5.39 (1H, m, j), 5.05-4.67 (2H, m, a), 3.06 (1H, m, k), 2.3-1.3 (12H, m); 1.83 (3H, s, t), 0.96 (3H, m, n) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.22 (0) s, [138.82 (0), 138.58 (0), o], [138.65 (1), 138.50 (1), b], 133.81 (1, r), [129.27 (1), 129.21 (1) p and q], [125.78 (1), 125.62 (1), 125.52 (1), 125.36 (1) e and f], [115.96 (2), 115.91 (2), a], [68.29 (1), 68.23 (1), j], [66.88 (1), 66.76 (1), k], [40.11 (1), 39.62 (1), c], [35.22 (2), 34.74 (2)], [32.83 (1), 32.80 (1), h], [30.35 (2), 29.93 (2)], [28.72 (2), 28.43 (2)], [26.07 (2), 25.89 (2)], [22.34 (2), 22.09 (2)], [20.97 (3), 20.92 (3), t], [14.26 (3), 14.19 (3), n] ppm.

IR (thin film) ν = 3021m, 2962s, 2908s, 1740s, 1446m, 1372s, 1308s, 1238s, 1149s, 1084s, 1025s cm^{-1}

LRMS (APCI) m/z = 391 $(M + H)^+$

HRMS: $C_{22}H_{30}O_4S$ requires m/z = 390.1865, found 390.1867

1-(6-Vinyl-3-cyclohexenyl)-(2*E*)-hexene (*trans*-401)

Sodium amalgam (5.6%) was prepared by the method of Vogel.[95]

Mercury (34 g, 170 mmol) was added to sodium flakes (2 g, 87 mmol) under Ar. The resultant solid product was crushed to a powder under a flush of argon before use.

The reductive elimination was performed by the method of Trost *et al.*[64]

Freshly prepared 5.6% sodium amalgam (3.4 g) was added to a solution of 2-(phenylsulfonyl)-1-[(6-vinyl-3-cyclohexyl)methyl]pentyl acetate **(410)** (780 mg, 2 mmol) and Na_2HPO_4 (1.136 g, 8 mmol) in dry methanol (20 mL) at –20 °C. After 1 h the reaction mixture was carefully diluted with water, and ether was added. The aqueous phase was extracted with ether, and the combined organic phases washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product purified by column chromatography (SiO_2, pentane) to give the desired product as a clear, colourless oil (248 mg, 1.3 mmol, 65%). The product was obtained as an inseparable mixture of double bond isomers, 73% of which was of *trans* geometry.

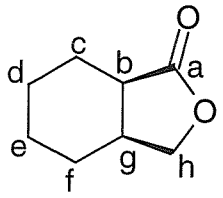
The proton NMR was essentially identical to that of the *cis* isomer. The carbon NMR of the *trans* isomer is given below.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.57 (1, b), 131.75 (1, j or k), 129.17 (1, j or k), 126.42 (1, e or f), 125.50 (1, e or f), 115.00 (2, a), 40.29 (1, c), 37.00 (1, h), 35.31 (2, i or l), 34.93 (2, i or l), 30.40 (2, d or g), 28.71 (2, d or g), 22.91 (2, m), 13.82 (3, n) ppm

Perhydro-1-isobenzofuranone (411)

The title compound was prepared by the method of Belleau *et al.*[57]

To a solution of sodium borohydride (11.4 g, 300 mmol) in DMF (150 mL) was added a solution of *cis*-1,2-cyclohexane dicarboxylic acid anhydride (30.8 g, 200 mmol) in DMF (150 mL) at between 0 °C and 10 °C. After stirring for 16 h, 2 M H_2SO_4 and ether (200 mL) were added. The aqueous phase was separated and extracted with ether (3 x 200 mL). The combined organic phases were washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by distillation to provide the desired lactone as a clear, colourless oil (17.7 g, 126 mmol, 63%).



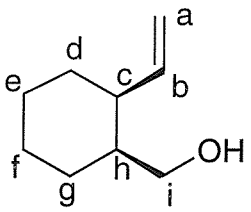
^{1}H NMR (300 MHz, $CDCl_3$) δ = 4.089 (1H, dd, J = 8.8, 5.2 Hz, h), 3.826 (1H, d, J = 8.8 Hz, h), 2.542 (1H, td, J = 6.4, 2.9 Hz, b), 2.371 (1H, app. sextet, J = 5.5 Hz, g), 2.2 – 1.9 (1H, m), 1.8 – 1.65 (1H, m), 1.6 – 1.4 (3H, m), 1.2 – 1.0 (3H, m) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 178.66 (0, a), 71.87 (2, h), 39.48 (1, b), 35.41 (1, g), 27.26 (2), 23.49 (2), 22.95 (2), 22.60 (2) ppm.

NMR data is consistent with literature values.[96]

(2-Vinylcyclohexyl)methanol (412)

The title compound was prepared by an analogous procedure to **(404)**, in 33% yield from the lactone **(411)**. This compound has been previously prepared by a different method.[97] No data was provided, so that obtained from our sample is presented here.



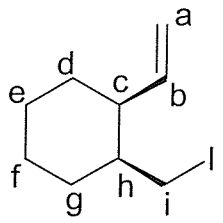
^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.048 (1H, ddd, J = 17.4, 9.9, 8.4 Hz, b), 5.1 – 5.0 (2H, m, a), 3.512 (1H, dd, J = 10.9, 7.9 Hz, i), 3.434 (1H, dd, J = 9.9, 7.4 Hz, i), 2.486 (1H, app. sextet J = 4.5 Hz, c), 1.8 – 1.3 (10 H, m) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.42 (1), 115.29 (2), 65.54 (2), 42.61 (1), 41.11 (1), 31.07 (2), 25.36 (2), 25.10 (2), 22.51 (2) ppm

1-(Iodomethyl)-2-vinylcyclohexane (413)

Methanesulfonyl chloride (4.10 g, 2.77 mL, 35.8 mmol) was added dropwise to a solution of (2-vinylcyclohexyl)methanol **(412)** (4.55 g, 32.5 mmol) and triethylamine (3.95 g, 39 mmol) in DCM (60 mL) at –50 °C under Ar. After 4 h, the suspension was filtered and the residue washed with DCM. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated. A solution of the crude mesylate in dry acetone (20 mL) was added dropwise to a refluxing solution of

sodium iodide (16.5 g, 110 mmol) in acetone (110 mL). After 42 h, saturated $Na_2S_2O_3$ solution (50 mL) was added. The aqueous phase was extracted with petrol, and the combined organic phases washed with saturated $Na_2S_2O_3$ solution and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (SiO_2, 10% ether in petrol) to provide the desired iodide as a clear, colourless oil (6.67 g, 82%).

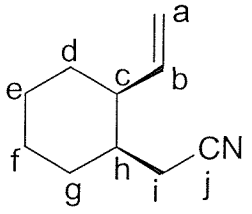


^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.891 (1H, ddd, J = 17.3, 10.4, 8.9 Hz, b), 5.172 (1H, d, J = 17.4 Hz, a), 5.108 (1H, dd, J = 10.4, 1.7 Hz, a), 3.082 (1H, dd, J = 9.4, 7.4 Hz, i), 3.031 (1H, dd, J = 9.4, 7.0 Hz, i), 2.58 (1H, m, c), 1.9 – 1.75 (1H, m, h), 1.75 – 1.2 (8H, m) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.29 (1, b), 116.70 (2, a), 43.06 (1), 43.00 (1), 31.07 (2), 29.01 (2), 25.30 (2), 22.06 (2), 12.69 (2, i) ppm

(2-Vinylcyclohexyl)methylcyanide (414)

A solution of 1-(iodomethyl)-2-vinylcyclohexane (6.6 g, 26.5 mmol) in acetonitrile (20 mL) was added dropwise to a refluxing solution of potassium cyanide (3.45 g, 53 mmol) and 18-crown-6 (1.75 g, 6.63 mmol) in acetonitrile (80 mL). After 5 days, conversion had ceased, and the reaction mixture was worked up. Column chromatography (SiO_2, 10% - 20% ether in petrol, gradient) allowed isolation of iodide **(413)** containing an elimination product (1.68 g total, 25% recovery) and the desired nitrile (1.60 g, 40%), which was further purified by Kugelrohr distillation (110 °C, 0.5 mbar) to provide a clear, colourless oil (1.54 g, 39%). This compound has been previously prepared by Suh *et al.*[97] from the alcohol **(412)**. No data was provided, so that obtained from our sample is presented here.



^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.916 (1H, ddd, J = 16.2, 11.9, 8.8 Hz, b), 5.2 – 5.1 (2H, m, a), 2.478 (1H, app. sextet, J = 4.4 Hz, c), 2.211 (1H, s, i), 2.187 (1H, s, i), 1.97 (1H, m, h), 1.75 – 1.35 (8H, m) ppm

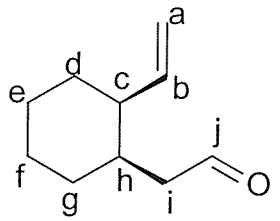
^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.15 (1, b), 119.58 (0, j), 117.30 (2, a), 42.58 (1, c), 37.21 (1, h), 30.12 (2), 28.07 (2), 24.58 (2), 21.89 (2), 20.94 (2) ppm

IR (thin film) ν = 3079w, 2936s, 2855s, 2243m, 1642w, 1459m, 1425m, 1007m, 915s cm^{-1}

HRMS: $C_{10}H_{15}N$ requires m/z = 149.1205, found 149.1210

2-(2-Vinylcyclohexyl)acetaldehyde (415)

To a solution of 2-(vinylcyclohexyl)methylcyanide (1.45 g, 9.54 mmol) in THF (25 mL) at below –70 °C under Ar was added dropwise diisobutyl aluminium hydride (12.7 mL of a 1.5 M solution in toluene, 19.1 mmol). After warming to RT and stirring for 16 h, methanol (5 mL) and saturated sodium hydrogen carbonate solution (40 mL) were added. After 4 h, the cloudy white reaction mixture was poured into ether. The aqueous layer was extracted with ether, and the combined organic extracts washed with brine, dried over $MgSO_4$, filtered and concentrated. The desired aldehyde was obtained as a clear, colourless oil (917 mg, 63%). The product was used immediately in the subsequent Wittig reaction. This compound has been previously synthesised by Suh *et al.*[97] by an identical procedure, but using DCM as solvent. No data was provided, so that obtained from our sample is presented here.

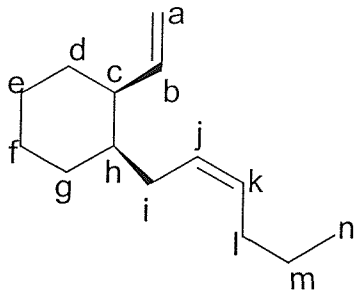


^{1}H NMR (300 MHz, $CDCl_3$) δ = 9.731 (1H, t, J = 1.7 Hz, j), 5.911 (1H, ddd, J = 17.4, 10.4, 8.4 Hz, b), 5.1 – 4.9 (2H, m, a), 2.5 – 2.2 (4H, m), 1.7 – 1.3 (8H, m) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 202.98 (1, j), 139.41 (1, b), 115.81 (2, a), 46.45 (1, c), 43.26 (2), 34.28 (2), 29.83 (1, h), 29.11 (2), 24.23 (2), 22.83 (2) ppm

1-(2-Vinylcyclohexyl)-2-(*Z*)-hexene (416)

The title compound was prepared by the method of Boden.[61] The product was a clear, colourless oil (780 mg, 73%), and the double bond geometry >95% *cis*, as determined by GC and NMR analysis.



^{1}H NMR (300 MHz, $CDCl_3$) δ = 6.003 (1H, ddd, J = 16.6, 11.2, 8.4 Hz, b), 5.45 – 5.3 (2H, m, j and k), 5.1 – 4.9 (2H, m, a), 2.4 – 2.3 (1H, m, c), 2.1 – 1.8 (4H, m), 1.8 – 1.2 (11H, m), 0.908 (3H, t, J = 7.3 Hz, n) ppm.

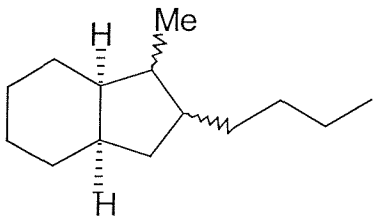
^{13}C NMR (75 MHz, $CDCl_3$) δ = 140.17 (1, b), 130.48 (1, j or k), 129.12 (1, j or k), 114.84 (2, a), 43.55 (1), 40.72 (1), 30.85 (2), 30.01 (2), 29.71 (2), 28.42 (2), 25.01 (2), 23.10 (2), 22.97 (2), 14.02 (3, n) ppm.

IR (thin film) ν = 3016w, 2936s, 2861m, 1642w, 1453m, 1007m, 920s, 909s cm^{-1}

HRMS: $C_{14}H_{24}$ requires m/z = 192.1863, found 192.1878

2-Butyl-1-methyl-perhydroindene (417)

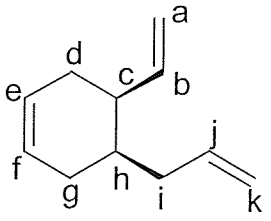
To a solution of Cp_2ZrCl_2 (257 mg, 0.88 mmol) in THF (4 mL) at –80 °C under Ar was added dropwise n-butyllithium (0.70 mL of a 2.5 M solution in hexanes, 1.76 mmol). After 10 minutes, a solution of 1-(2-vinylcyclohexyl)-2-(*Z*)-hexene **(416)** (154 mg, 0.8 mmol) in THF (2 mL) was added dropwise. The solution was allowed to warm to RT and stirred for 4 h. Methanol (3 mL) and saturated $NaHCO_3$ solution (6 mL) were added and the reaction stirred for 16 h. After dilution with water and pentane, the aqueous layer was separated and extracted with pentane. The combined organic phases were washed with 2 M HCl and brine, dried over $MgSO_4$, filtered and concentrated. The crude product was subjected to Kugelrohr distillation (120 °C, 20 mmHg) to provide a clear, colourless oil (147 mg, 76%). The product was a mixture of components, probably diastereomers, the major product constituting 64% of the total. The proton NMR was unassignable, however the carbon NMR spectrum was consistent with the desired product.



^{13}C NMR (75 MHz, $CDCl_3$) δ = 47.071 (2C, (1)), 41.71 (1), 38.04 (1), 37.11 (2), 36.87 (2), 31.17 (2), 30.45 (2), 26.75 (2), 24.94 (2), 23.22 (2), 22.93 (2), 19.17 (3), 14.34 (3) ppm.

4-Allyl-5-vinylcyclohexene (418)

n-Butyllithium (5.9 mL of a 2.5 M solution in hexanes (14.8 mmol) was added to a solution of methyl triphenyl phosphonium bromide (5.28 g, 14.8 mmol) in THF (20 mL) at 0 °C under Ar. After 30 minutes, this red solution was added to a solution of (6-vinyl-3-cyclohexenyl)ethanal **(407)** (1.115 g, 7.4 mmol) in THF (20 mL) at –80 °C under Ar until a permanent yellow colour was observed (20 mL, 11.4 mmol of phosphorane solution added). The reaction was allowed to warm to room temperature and stirred over night. The reaction mixture was poured into pentane and 2 M HCl. The aqueous layer was separated and extracted with pentane. The combined organic phases were washed with 2 M HCl and brine, dried over $MgSO_4$, filtered and concentrated. The crude compound was purified by column chromatography (SiO_2, pentane) to give the desired product as a clear, colourless oil (827 mg, 5.6 mmol, 76%).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.83 (2H, m, b and j), 5.66 (2H, m, e and f), 5.03 (4H, m, a and k), 2.48 (1H, m, c), 2.28 (1H, m, h), 2.1-1.7 (6H, m, d, g, and i) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 139.45 (1, b), 137.93 (1, j), 126.27 (1, e or f), 125.48 (1, e or f), 115.74 (2, a or k), 115.19 (2, a or k), 40.30 (1, c), 36.53 (2, i), 36.53 (1, h), 30.30 (2, d or g), 28.66 (2, d or g) ppm.

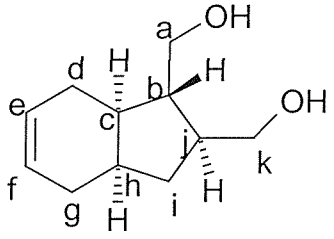
IR (thin film) ν = 3074m, 3023m, 2908s, 2836m, 1639m, 1436m, 994m, 911s, 658m cm^{-1}

LRMS (APCI) m/z = 148 (M^+)

HRMS: $C_{11}H_{16}$ requires m/z = 148.1252, found 148.1259

(2S*,3S*,3aR*,7aS*)-[2-(Hydroxymethyl)-2,3,3a,4,7,7a-hexahydro-1*H*-1-indenyl] methanol (419)

To a solution of $ZrCp_2Cl_2$ (234 mg, 0.8 mmol) in THF (5 mL) at –80 °C under Ar was added dropwise n-butyllithium (0.64 mL of a 2.5 M solution in hexanes, 1.6 mmol). After 10 minutes, a solution of 4-allyl-5-vinylcyclohexene **(418)** (104 mg, 0.7 mmol) in THF (3 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for 5 h resulting in a brown solution. Oxygen gas was bubbled through the solution for 10 min, resulting in a slight exotherm and a change of colour to pale yellow. The reaction was quenched by pouring into a 1:1 mixture of 5% H_2SO_4 / saturated sodium sulphate solution (20 mL) and ether (25 mL). The aqueous layer was separated and extracted with ether (6 x 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. The crude product was subjected to column chromatography (SiO_2, 70% ether in petrol) providing the title compound as a viscous pale yellow oil (83 mg, 65%).



^{1}H NMR ($CDCl_3$, 300 MHz) δ = 5.67 (2H, m, e and f), 4.30 (2H, br s, -OH), 3.76 (2H, ddd, J = 13.2, 10.3, 3.7 Hz, a), 3.36 (2H, dt, J = 18.0, 9.9 Hz, k), 1.7 – 2.3 (10H, m) ppm.

^{13}C NMR ($CDCl_3$, 75 MHz) δ = 126.16 (1, e or f), 125.78 (1, e or f), 67.80 (2, a or k), 66.44 (2, a or k), 52.15 (1, b), 47.40 (1, j), 39.48 (1, c), 35.15 (2, i), 34.66 (1, h), 28.20 (2, d or g), 26.87 (2, d or g) ppm.

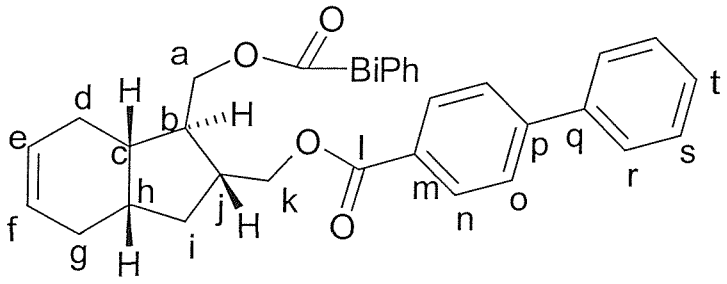
IR (thin film) ν = 3281 br s, 3022w, 2907s, 1467m, 1433m, 1037s, 911s cm^{-1}

LRMS (APCI) m/z = 183 $(M + H)^+$

HRMS: $C_{11}H_{16}O$ (M – H_20) requires m/z = 164.1201, found 164.1204

(2S*,3S*,3aR*,7aS*)-[2-(Hydroxymethyl)-2,3,3a,4,7,7a-hexahydro-1*H*-1-indenyl] methanol dibiphenoyl ester (420)

A solution of biphenyl carbonyl chloride (238 mg, 1.1 mmol) in DCM (1 mL) was added dropwise to a solution of [2-(hydroxymethyl)-2,3,3a,4,7,7a-hexahydro-1*H*-1-indenyl]methanol **(419)** (50 mg, 0.27 mmol), triethylamine (81 mg, 0.8 mmol) and DMAP (5 mg) in DCM (2 mL). After 1 h the reaction mixture was diluted with water and ether. The aqueous layer was extracted with ether and the combined organic phases washed with brine, dried over $MgSO_4$, filtered and concentrated. Column chromatography of the crude product (SiO_2, 40% ether in petrol) provided the desired product contaminated with biphenyl carbonyl chloride. Further chromatography (SiO_2, 30% - 40% DCM in petrol gradient) provided the desired compound in pure form as a white solid (67 mg, 46%). Crystallization from methanol provided a crystal suitable for x-ray analysis.



^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.13 (4H, d, J = 8.1 Hz, n), 7.7 – 7.6 (8H, m, Ar), 7.5 – 7.35 (6H, m, Ar), 5.75 (2H, m, e and f), 4.5 – 4.4 (2H, m, a and k), 2.5 – 2.2 (4H, m), 2.2 – 1.9 (5H, m), 1.50 (1H, dt, J = 12.5, 8.1 Hz, i) ppm.

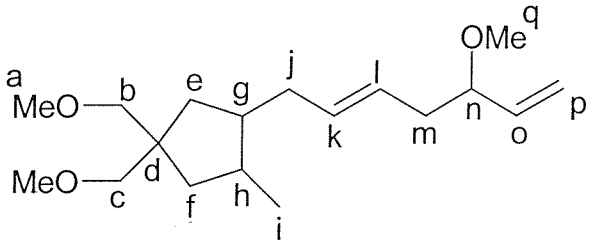
^{13}C NMR (75 MHz, $CDCl_3$) δ = 166.73 (0, l), 145.82 (0, p or q), 145.77 (0, p or q), 140.13 (0, m), 130.27 (1, n or s), 129.09 (1, n or s), 128.31 (1, t), 127.44 (1, o or r), 127.26 (1, o or r), 126.12 (1, e or f), 125.52 (1, e or f), 69.16 (2, a), 67.39 (2, k), 47.04 (1, b), 41.09 (1, j), 38.87 (1, c), 35.19 (2, i), 35.10 (1, h), 27.48 (2, d or g), 27.06 (2, d or g) ppm.

Melting Point: 63 – 65 °C.

(5*E*)-7-[4,4-Di(methoxymethyl)-2-methylcyclopentyl]-3-methoxy-1,5-heptadiene (421)

To a solution of $ZrCp_2Cl_2$ (642 mg, 2.2 mmol) in THF (8 mL) at –80 °C under Ar was added dropwise n-butyllithium (1.76 mL of a 2.5 M solution in hexanes, 4.4

mmol). A solution of 4,4-di(methoxymethyl)-1,6-heptadiene (368 mg, 2 mmol) in THF (3 mL) was added, and the solution allowed to warm for 2.5 h. After cooling to –90 °C, allyl chloride (0.18 mL, 168 mg, 2.2 mmol) then LiTMP (2.2 mmol, generated by addition of n-butyllithium (0.88 mL of a 2.5 M solution in hexanes, 2.2 mmol) to 2,2,6,6-tetramethylpiperidine (311 mg, 2.2 mmol) in THF (4 mL) at 0 °C and stirred for 1 h) were added. After 15 min the solution was allowed to warm for 30 min, then divided in two halves. One half was cooled to –80 °C and acrolein dimethyl acetal (0.18 mL, 153 mg, 1.5 mmol) then boron trifluoride diethyletherate (0.19 mL, 1.5 mmol) were added. The bright yellow suspension was allowed to warm to RT over 1.5 h, then quenched with methanol (3 mL) and saturated $NaHCO_3$ solution (6 mL) to give a white suspension. After stirring over night the reaction mixture was poured into water (150 mL) and extracted into ether. The extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (SiO_2, 10% ether in petrol) to give the title compound as a clear, colourless oil (209 mg, 0.71 mmol, 71%).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.64 (1H, ddd, J = 16.5, 11, 7.5 Hz, o), 5.44 (1H, dt, J= 15, 6.5 Hz, k or l), 5.35 (1H, dt, J = 15.5, 6.5 Hz, k or l), 5.17 (2H, m, p), 3.51 (1H, dt, J = 7, 7 Hz, n), 3.32 (6H, s, a), 3.26 (3H, s, q), 3.17 (4H, m, b and c), 2.22 (4H, m, j and m), 1.7 (4H, m, e, f, g and h), 1.01 (2H, m, e and f), 0.92 (3H, d, J = 6Hz, i) ppm.

^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.53 (1, o), 131.83 (1, l), 126.42 (1, k), 117.28 (2, p), 83.03 (1, n), 78.06 (2, b), 77.92 (2, c), 59.33 (3, a), 56.28 (3, q), 46.71 (1, g), 45.14 (0, d), 41.87 (2), 39.29 (1, h), 39.24 (2), 39.00 (2), 36.60 (2), 18.19 (3, i) ppm.

IR (thin film) ν = 2981s, 2925s, 1642w, 1449m, 1199m, 1105s, 967m, 909s, 734s, 648s cm^{-1}

LRMS (APCI) m/z = 297 $(M + H)^+$, 25%, 314 $(M + NH_4)^+$, 100%

HRMS: $C_{18}H_{32}O_3$ requires m/z = 296.2351, found 296.2326

2-Bromo-1,1,1-triethoxypropane (422)

The title compound was prepared by the method of Beverstedt *et al.*[98] The NMR data was consistent with literature values.[99]

Triethyl orthoacrylate (423)

The title compound was prepared by the method of Stetter *et al.*[66]

4,4,5,5-Tetramethyl-2-vinyl-1,3-dioxolane (424)

The title compound was prepared by the method of Hopkins *et al.*[100]

Additional data: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.83 (1H, ddd, J = 17, 10, 6.5 Hz), 5.41 (1H, d, J = 17 Hz), 5.32 (1H, d, J = 6.5 Hz), 5.29 (1H, d, J = 10 Hz), 1.22 (12 H, s) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.05 (1), 119.48 (2), 100.84 (1), 82.37 (0), 24.04 (3), 22.09 (3) ppm.

IR (thin film) ν = 3084w, 2979s, 2871m, 1433s, 1388s, 1160s, 1101s, 979s, 932s, 868m, 742w cm^{-1}

1,1-Diethoxy-2,3-dibromopropane (425)

The title compound was prepared by the method of Sheehan *et al.*[101]

1,1-Diethoxy-2-bromo-2-propene (426)

The title compound was prepared by the method of Ley *et al.*[68] The NMR data was consistent with literature values.[102]

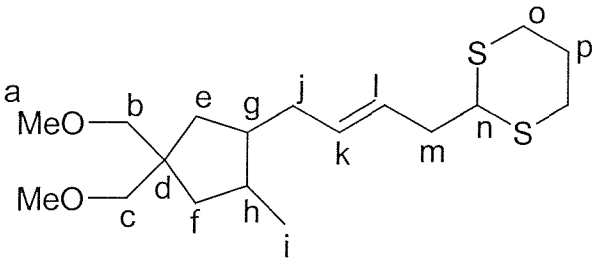
Dithienium tetrafluoroborate

A solution of 1,3-dithiane (871mg, 7.24 mmol) and trityl fluoroborate (3.30 g, 10 mmol) in DCM (15 mL) was heated at reflux under Ar for 2 h. After cooling, the supernatant liquid was decanted off, and the resultant yellow solid washed with dry ether (2 x 20 mL) and dry DCM (1 x 20 mL). It was essential to use thoroughly dried solvents. The desired yellow solid product was dried under vacuum to provide pure material (1.063 g, 5.16 mmol, 71% yield).

Melting point: 187 - 191 °C (dec.) (literature[103]: 188 - 190 °C (dec.))

2-{(*E*)-4-[4,4-Di(methoxymethyl)-2-methylcyclopentyl]-2-butenyl}-1,3-dithiane (427)

To a solution of $ZrCp_2Cl_2$ (1.095 g, 3.75 mmol) in THF (15 mL) under Ar at -80 °C was added dropwise n-butyllithium (3.0 mL of a 2.5 M solution in hexanes, 7.5 mmol). After 10 min 4,4-di(methoxymethyl)-1,6-heptadiene (626 mg, 3.4 mmol) in THF (5 mL) was added dropwise. The solution was allowed to warm for 2h, then re-cooled to -90 °C. Allyl chloride (287 mg, 0.3 mL, 3.75 mmol), then LiTMP (3.75 mmol, produced from TMP (530 mg, 3.75 mmol) and n-butyllithium (1.5 mL of a 2.5 M solution in hexanes, 3.75 mmol) in THF (6 mL)) were added. After stirring for 1 h to room temperature and re-cooling to -80 °C the reaction mixture was transferred by syringe to a suspension of dithienium fluoroborate (1.05 g, 5.1 mmol) in THF (10 mL). The bright yellow reaction mixture was allowed to warm for 2 h before addition of methanol (5 mL) and saturated $NaHCO_3$ solution (6 mL). After stirring for 18 h, the mixture was poured into water and ether. The aqueous phase was extracted with ether and the combined extracts washed with brine, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (SiO_2, DCM) and a second chromatography (SiO_2, 20% ether in petrol) to give a colourless, viscous oil (745 mg, 2.2 mmol, 64%).



^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.52 (1H, dt, J = 15, 6 Hz, k or l), 5.43 (1H, dt, J = 15.5, 6 Hz, k or l), 4.04 (1H, t, J = 7 Hz, n), 3.32 (6H, s, a), 3.17 (4H, m, b and c), 2.84 (4H, m, o), 2.43 (2H, t, J = 6.5 Hz, m), 2.26 (1H, m, j), 2.11 (1H, m, j), 1.83 (2H, m, p), 1.71 (4H, m, e, f, g and h), 1.02 (2H, m, e and f), 0.93 (3H, d, J = 6Hz) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 132.96 (1, k or l), 125.84 (1, k or l), 78.06 (2, b or c), 77.92 (2, b or c), 59.38 (3, a), 47.80 (1, n or g), 46.66 (1, n or g), 45.17 (0, d), 41.86 (2, m), 39.30 (1, h), 39.23 (2, e or f), 38.85 (2, e or f), 30.60 (2, o), 26.00 (2, p), 18.21 (3, i) ppm.

IR (thin film) ν = 2948s, 2888s, 1448w, 1422w, 1276w, 1198m, 1108s, 965m, 908w cm^{-1}

LRMS (APCI) m/z = 345 $(M + H)^+$

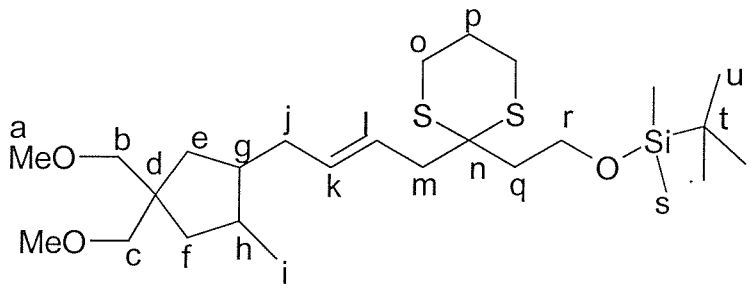
HRMS: $C_{18}H_{32}O_2S_2$ requires m/z = 344.1844, found 344.1849

(2-Iodoethoxy)-*tert*-butyldimethylsilane (428)

The title compound was prepared by the method of Poleschner *et al.*[104]

***tert*-Butyl[2-(2-{(*E*)-4-[4,4-di(methoxymethyl)-2-methylcyclopentyl]-2-butenyl}-1,3-dithian-2-yl)ethoxy]dimethylsilane (429)**

n-Butyllithium (0.21 mL of a 2.5 M solution in hexanes, 0.525 mmol) was added dropwise to a solution of 2-{(*E*)-4-[4,4-di(methoxymethyl)-2-methylcyclopentyl]-2-butenyl}-1,3-dithiane **(427)** in THF (3 mL) under Ar at –40 °C. The reaction was stirred for 2 h and allowed to warm to –20 °C. After cooling to –78 °C, HMPA (0.2 mL) was added, resulting in a bright yellow suspension, which was decolourised on addition of a solution of (2-iodoethoxy)-*tert*-butyl dimethyl silane (143 mg, 0.5 mmol) in THF (1 mL). After 30 min, the solution was allowed to warm to room temperature and stirred over night. The reaction mixture was poured into water and ether, and the aqueous layer extracted with ether. The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated. Column chromatography (SiO_2, 10% ether in petrol) furnished the desired compound as a viscous, colourless oil (141 mg, 0.28 mmol, 56%) contaminated with a small amount of an inseparable impurity.



^{1}H NMR (300 MHz, $CDCl_3$) δ = 5.51 (2H, m, k and l), 3.81 (2H, t, J = 7.3 Hz, r), 3.33 (6H, s, a), 3.18 (4H, m, b and c), 2.82 (4H, m, o), 2.60 (2H, m, m), 2.29 (1H, m, j), 2.15 (2H, t, J = 7.3 Hz, q), 1.95 (2H, m, j and g), 1.83 (2H, m, p), 1.73 (2H, m, e and f), 1.67 (1H, m, h), 1.05 (2H, m, e and f), 0.94 (3H, d, J = 6.2 Hz, i), 0.90 (9H, s, u), 0.07 (6H, s, s) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 133.54 (1, l), 124.88 (1, k), 78.09 (2, b or c), 77.94 (2, b or c), 59.80 (2, r), 59.38 (3, a), 51.32 (0, n), 46.57 (1, g), 45.03 (0, d),

42.41 (2), 41.71 (2), 40.37 (2), 39.15 (1, h), 39.12 (2), 36.39 (2), 26.09 (3, u), 25.23 (2, q), 18.31 (0, t), 18.06 (3, i), -5.23 (3, s) ppm.

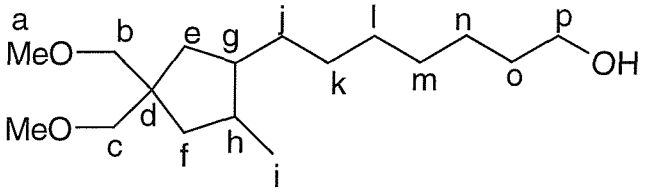
IR (thin film) ν = 2958s, 2930s, 1461m, 1389w, 1257m, 1199w, 1098s, 907s, 733s cm^{-1}

LRMS (APCI) m/z = 503 $(M + H)^+$

HRMS: $C_{26}H_{50}O_3S_2Si$ requires m/z = 502.2971, found 502.2980

7-[4,4-Di(methoxymethyl)-2-methylcyclopentyl]-1-heptanol (430)

To a solution of *tert*-butyl[2-(2-{(*E*)-4-[4,4-di(methoxymethyl)-2-methylcyclo pentyl]-2-butenyl}-1,3-dithian-2-yl)ethoxy]dimethylsilane **(429)** (117 mg, 0.23 mmol) in THF (3 mL) was added dropwise tetrabutyl ammonium fluoride (0.35 mL of a 1 M solution in THF, 0.35 mmol). The mixture was stirred for 1 h, before being quenched with water (5 mL). The solution was diluted with ether, and the aqueous phase extracted with ether. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated. To the crude product was added ethanol (5 mL) and Raney nickel (10 g of a 1:1 slurry in water). The mixture was heated at reflux for 2 h, then filtered through a sinter, with ether and water washing. The phases of the filtrate were separated and the aqueous extracted with ether. The combined extracts were washed with brine, dried over $MgSO_4$ and concentrated. Purification of the crude product by column chromatography (SiO_2, 20% ether in petrol) yielded the title compound (31 mg, 0.11 mmol, 47%).



^1H NMR (300 MHz, $CDCl_3$) δ = 3.62 (2H, t, 6.6 Hz, p), 3.33 (6H, s, a), 3.18 (4H, m, b and c), 1.72 (2H, td, J = 13.6, 7.3 Hz, j), 1.55 (4H, m, e, f, g, and h), 1.43 (1H, s, -OH), 1.38-1.23 (10H, m, k, l, m, n and o), 0.97 (2H, m, e and f), 0.92 (3H, d, J = 6.2 Hz, i) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 77.97 (2, b or c), 77.82 (2, b or c), 62.99 (2, p), 59.22 (3, a), 46.65 (1, g), 45.09 (0, d), 41.86 (2, e), 39.83 (1, h), 39.54 (2, f), 33.83 (2), 32.77 (2), 29.97 (2), 29.41 (2), 28.29 (2), 25.70 (2), 18.12 (3, i) ppm.

IR (thin film) ν = 3464br s, 3154w, 2927s, 2856s, 1460m, 1384m, 1199m, 1100s cm^{-1}

LRMS (APCI) m/z = 285 $(M - H)^+$

HRMS: $C_{17}H_{35}O_3$ $(M + H)^+$ requires m/z = 287.2586, found 287.2610

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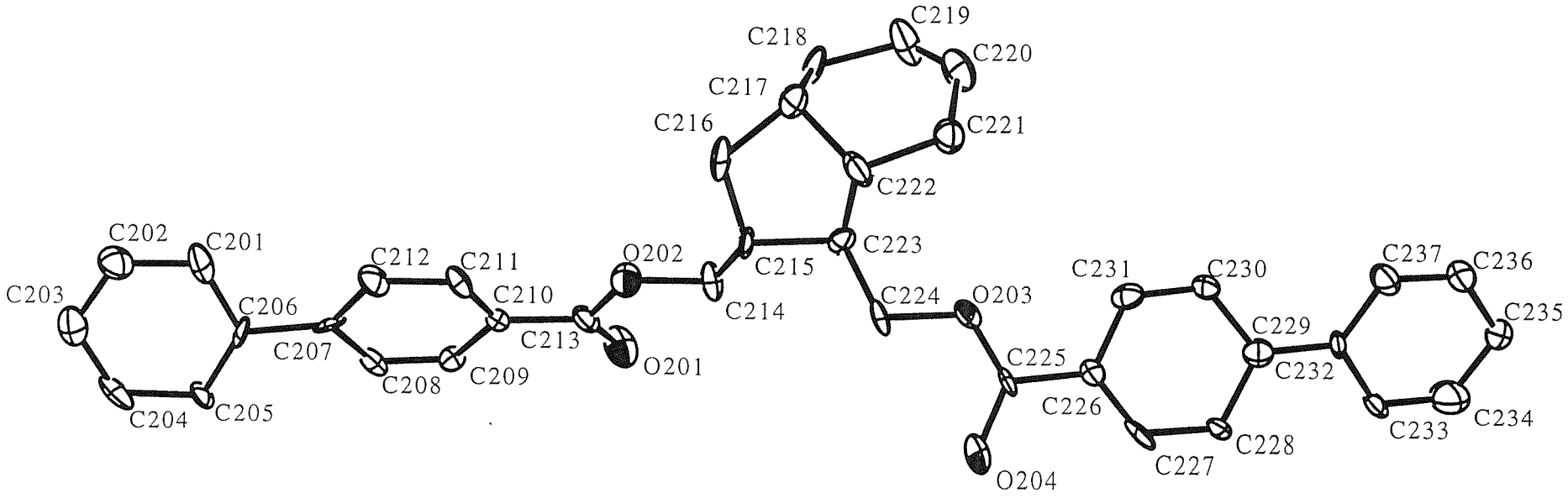
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C213
C229
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C208
C209
C226
C234
C233
C204
C205
C228
C227
O204

Table 1. Crystal data and structure refinement.

Identification code	**99SOT026**	
Empirical formula	$C_{37}H_{34}O_4$	
Formula weight	542.64	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P*1	
Unit cell dimensions	$a = 9.3378(10)$ Å	$\alpha = 80.548(6)°$
	$b = 10.0810(13)$ Å	$\beta = 89.178(7)°$
	$c = 15.368(2)$ Å	$\gamma = 79.890(7)°$
Volume	1404.7(3) Å3	
Z	2	
Density (calculated)	1.283 Mg / m3	
Absorption coefficient	0.082 mm-1	
F(000)	576	
Crystal	Colourless; block	
Crystal size	0.10 × 0.10 × 0.10 mm3	
θ range for data collection	2.93 – 20.81°	
Index ranges	$-9 \le h \le 9, -10 \le k \le 10, -15 \le l \le 15$	
Reflections collected	11956	
Independent reflections	5710 [$R_{int} = 0.1214$]	
Completeness to $\theta = 20.81°$	99.7 %	
Absorption correction	Empirical, SORTAV	
Max. and min. transmission	0.9918 and 0.9918	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5710 / 447 / 740	
Goodness-of-fit on F^2	0.914	
Final *R* indices [$F2 > 2\sigma(F^2)$]	$R1 = 0.0604$, $wR2 = 0.1117$	
R indices (all data)	$R1 = 0.1759$, $wR2 = 0.1535$	
Extinction coefficient	0.0033(7)	
Largest diff. peak and hole	0.182 and –0.183 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Further information: http://www.soton.ac.uk/~xservice/strat.htm

Special details: Structure is pseudo-centrosymmetric (can't refine as P-1).

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

O201–C213	1.24(2)	C111–C110	1.42(3)
O102–C113	1.35(2)	C105–C104	1.36(3)
O102–C114	1.467(19)	C105–C106	1.43(3)
O202–C213	1.35(2)	C229–C230	1.42(3)
O202–C214	1.44(2)	C229–C232	1.43(3)
O203–C225	1.30(2)	C229–C228	1.44(3)
O203–C224	1.48(2)	C133–C134	1.41(2)
C107–C108	1.35(3)	C131–C130	1.43(2)
C107–C112	1.40(3)	O101–C113	1.17(2)
C107–C106	1.50(3)	C101–C102	1.37(3)
O103–C125	1.38(2)	C101–C106	1.39(3)
O103–C124	1.440(19)	C118–C119	1.43(3)
O104–C125	1.15(2)	C118–C117	1.63(3)
C225–O204	1.27(2)	C221–C220	1.56(3)
C225–C226	1.48(2)	C220–C219	1.21(3)
C137–C132	1.38(3)	C211–C212	1.41(3)
C137–C136	1.42(3)	C136–C135	1.37(3)
C224–C223	1.44(3)	C203–C202	1.37(3)
C132–C133	1.38(3)	C203–C204	1.38(3)
C132–C129	1.52(3)	C128–C127	1.41(3)
C108–C109	1.40(3)	C115–C114	1.51(3)
C206–C205	1.34(3)	C115–C123	1.53(2)
C206–C201	1.38(3)	C115–C116	1.61(2)
C206–C207	1.48(2)	C219–C218	1.57(2)
C129–C128	1.35(3)	C207–C212	1.39(3)
C129–C130	1.37(3)	C207–C208	1.42(2)
C112–C111	1.38(3)	C202–C201	1.41(3)
C210–C209	1.35(3)	C113–C110	1.49(3)
C210–C211	1.37(3)	C230–C231	1.35(2)
C210–C213	1.49(3)	C235–C236	1.39(3)
C222–C223	1.49(3)	C235–C234	1.40(3)
C222–C217	1.56(3)	C110–C109	1.40(3)
C222–C221	1.58(3)	C228–C227	1.35(2)
C226–C227	1.31(3)	C237–C236	1.33(3)
C226–C231	1.41(2)	C237–C232	1.39(3)
C215–C216	1.48(3)	C116–C117	1.57(2)
C215–C214	1.51(3)	C123–C124	1.57(3)
C215–C223	1.55(2)	C123–C122	1.61(3)
C126–C131	1.39(3)	C103–C102	1.37(3)
C126–C127	1.44(2)	C103–C104	1.37(3)
C126–C125	1.47(3)	C134–C135	1.36(3)
C217–C218	1.43(3)	C204–C205	1.43(3)
C217–C216	1.52(3)	C234–C233	1.33(3)
C209–C208	1.34(3)	C122–C121	1.48(3)

C122–C117	1.53(3)	C119–C120	1.43(3)
C233–C232	1.39(3)	C121–C120	1.43(3)
C113–O102–C114	114.5(14)	C216–C217–C222	95.4(15)
C213–O202–C214	115.6(15)	C208–C209–C210	123.4(19)
C225–O203–C224	118.8(14)	C224–C223–C222	119.1(18)
C108–C107–C112	119.3(18)	C224–C223–C215	113.4(15)
C108–C107–C106	123.4(18)	C222–C223–C215	100.3(14)
C112–C107–C106	117.3(18)	O202–C214–C215	106.2(14)
C125–O103–C124	115.1(16)	C112–C111–C110	116.4(19)
O204–C225–O203	125.8(16)	C104–C105–C106	125(2)
O204–C225–C226	118.5(17)	C230–C229–C232	123.8(18)
O203–C225–C226	115.3(16)	C230–C229–C228	112.6(18)
C132–C137–C136	124.5(18)	C232–C229–C228	123.4(17)
C223–C224–O203	110.2(14)	C132–C133–C134	121(2)
C133–C132–C137	116.0(19)	C126–C131–C130	119.4(19)
C133–C132–C129	120.8(19)	C102–C101–C106	122.8(18)
C137–C132–C129	122.6(18)	C119–C118–C117	111.0(18)
C107–C108–C109	120.5(19)	C220–C221–C222	108.3(18)
C205–C206–C201	122.5(18)	C219–C220–C221	127(2)
C205–C206–C207	123.7(17)	C210–C211–C212	122.3(18)
C201–C206–C207	113.4(18)	C135–C136–C137	116(2)
C128–C129–C130	121.3(18)	C202–C203–C204	117(2)
C128–C129–C132	117.6(17)	C129–C128–C127	121.2(19)
C130–C129–C132	120.8(17)	C114–C115–C123	110.3(15)
C111–C112–C107	123.3(18)	C114–C115–C116	108.6(16)
C209–C210–C211	117.2(18)	C123–C115–C116	107.2(14)
C209–C210–C213	121.8(19)	C220–C219–C218	124(2)
C211–C210–C213	121.0(19)	C212–C207–C208	116.5(17)
C223–C222–C217	106.8(17)	C212–C207–C206	124.3(16)
C223–C222–C221	117.7(17)	C208–C207–C206	119.2(18)
C217–C222–C221	113.1(16)	C203–C202–C201	122(2)
O201–C213–O202	121.0(19)	O101–C113–O102	124(2)
O201–C213–C210	123(2)	O101–C113–C110	126(2)
O202–C213–C210	115.5(19)	O102–C113–C110	109.8(18)
C227–C226–C231	116.1(18)	C231–C230–C229	122.7(19)
C227–C226–C225	123.0(17)	C236–C235–C234	114(2)
C231–C226–C225	120.9(18)	C230–C231–C226	122.1(19)
C216–C215–C214	119.7(17)	C111–C110–C109	120.5(18)
C216–C215–C223	104.5(15)	C111–C110–C113	124.2(19)
C214–C215–C223	112.7(15)	C109–C110–C113	115.3(18)
C131–C126–C127	119.6(18)	C227–C228–C229	121.5(18)
C131–C126–C125	125.2(18)	C236–C237–C232	120(2)
C127–C126–C125	115.2(18)	C129–C130–C131	120.1(19)
C218–C217–C216	113.4(19)	C101–C106–C105	113.9(17)
C218–C217–C222	111.7(16)	C101–C106–C107	128.2(17)

C105–C106–C107	117.8(18)	C121–C122–C123	118.3(17)
C215–C216–C217	112.1(15)	C117–C122–C123	97.5(14)
C108–C109–C110	119.8(18)	C234–C233–C232	122(2)
C226–C227–C228	125.0(17)	O103–C124–C123	105.9(14)
C237–C236–C235	125(2)	C118–C119–C120	127(2)
C117–C116–C115	100.2(13)	C209–C208–C207	121.4(19)
C207–C212–C211	119.1(18)	C105–C104–C103	116(2)
C206–C201–C202	118.3(19)	C206–C205–C204	117.2(19)
C115–C123–C124	109.0(14)	C120–C121–C122	119(2)
C115–C123–C122	102.4(15)	C122–C117–C116	110.3(13)
C124–C123–C122	111.2(17)	C122–C117–C118	113.8(15)
C102–C103–C104	123(2)	C116–C117–C118	106.8(14)
C103–C102–C101	118.6(19)	O104–C125–O103	120(2)
C128–C127–C126	118.4(18)	O104–C125–C126	130(2)
C135–C134–C133	119.0(19)	O103–C125–C126	109.6(18)
C203–C204–C205	122(2)	C121–C120–C119	119(2)
O102–C114–C115	107.4(14)	C237–C232–C233	116.3(18)
C233–C234–C235	122(2)	C237–C232–C229	121.2(18)
C134–C135–C136	123(2)	C233–C232–C229	122.0(18)
C121–C122–C117	113.5(16)	C217–C218–C219	111.5(16)

Symmetry transformations used to generate equivalent atoms: