UNIVERSITY OF SOUTHAMPTON

FACULTY OF NATURAL AND ENVIRONMENTAL SCIENCES

School of Chemistry

Organozirconium Approaches to Small Molecule Synthesis

by

Alan Robert Henderson

Thesis for the degree of Doctor of Philosophy

January 2012

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

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A review of zirconocene mediated intramolecular cocyclisations and the elaboration of the resultant zirconacycles is presented as a background to the work presented in this thesis. The first area of novel work is the attempted intramolecular trapping of zirconocene η^2-alkene complexes, generated by an unprecedented endocyclic cyclometallation, with a pendant alkyne. A series of inter- and intramolecular transformations other than the desired transformation were observed.

The second area of work presented is the synthesis and biological testing of two ligands for receptors from the NR4A subfamily of orphan nuclear receptors. Our interest in this area stemmed from previous work in our group on the zirconocene mediated synthesis of ligands for receptors in the NR5 subfamily.

The third area of research presented is the zirconocene mediated cocyclisation of a series of novel ynamides and elaboration of the resulting zirconacyclopentadienes. Also presented in this chapter is the use of the exocyclic dienes formed through protonolysis of the zirconacyclopentadienes in a series of Diels-Alder reactions in excellent regio- and stereoselectivity.

The penultimate area of research is the first total synthesis of (+)-mucosin utilising a zirconocene mediated cocyclisation of a diene followed by the insertion of an α-silyl alkyl carbenoid to gain the major diastereoisomer with the correct stereochemistry of the four contiguous stereocentres. The route taken to (+)-mucosin can be easily adapted in order for the synthesis of the natural product (−)-mucosin to be realised.

Finally the well established chemistries of carbenoid insertion and isonitrile insertion into zirconacyclopentanes are combined in order to furnish a series of novel cyclohexanones.

CONTENTS

DECLARATION OF AUTHORSHIP

I, Alan Robert Henderson

declare that the thesis entitled

Organozirconium Approaches to Small Molecule Synthesis

and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

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ACKNOWLEDGEMENTS

Firstly I would like to thank my supervisor Prof. Richard Whitby for his tireless help and encouragement throughout my time at Southampton. His endless enthusiasm for chemistry was a constant inspiration. I would also like to thank my advisor Prof. Richard Brown for providing useful ideas and excellent feedback from quarterly reports. I am grateful to Dr Surinder Sahota for allowing me to carry out the biological work in his laboratory. I am also grateful to Dr Nicola Weston-Bell and Mr Gavin Babbage for their help with the biological work.

I wish to thank Dr John Langley and Ms Julie Herniman in MS, Dr Neil Wells in NMR and the glassblowing staff. A special mention is due to Clive, Graham, Karl and Keith in stores who as well as providing an excellent service have also been the source of much entertainment over the years.

I owe a great deal of gratitude to past and present members of the Whitby group, particularly Joe, Fra, Louise, Cyril, David, Jason, Bogdan and Lloyd who have not only been a source of ideas but also great people to work with. Beyond the Whitby group there are a great number of people within Chemistry who have become good friends over the years and I am grateful for that friendship. I am grateful to Dave, Roger, Sarah and Scott for the speedy and eagle eyed proof reading. I am grateful to my family and friends for providing welcome distractions from chemistry.

Most of all I wish to thank Sarah for her love, patience and support without which none of this would have been possible.

ABBREVIATIONS

°C	Degrees Celsius
µL	Microlitre(s)
AF-2	Activated function-2
aq.	Aqueous
Ar	Aryl
Bn	Benzyl
BOM	Benzyloxymethyl group
Bu	Butyl
CI	Chemical Ionisation
COSY	Correlation Spectroscopy
Cp	Cyclopentadienyl
d	Day(s)
DCM	Dichloromethane
de	Diastereomeric excess
DEPT	Distortionless Enhancement by Polarisation Transfer
DFT	Density functional theory
DIBAL-H	Diisobutylaluminium hydride
DMAD	Dimethyl acetylenedicarboxylate
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
dmfu	Dimethyl fumarate
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DBD	DNA binding domain
dr	Diastereoisomeric ratio
EA	Ethyl acetate
ee	Enantiomeric excess
EI	Electron Impact
eq.	Equivalent(s)
ES	Electrospray
Et	Ethyl

EWG	Electron withdrawing group
FITC	Fluorescein isothiocyanate
FSC	Forward scatter channel
g	Gram(s)
GC	Gas chromatography
h	Hour(s)
HMPA	Hexamethylphosphoramide
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry
i	Iso
IR	Infrared
LBD	Ligand binding domain
LDA	Lithium diisopropylamide
lit.	Literature
LRH-1	Liver Receptor Homolog-1
LRMS	Low resolution mass spectrometry
M	Molarity in moles per litre
mBq	Millibecquerel(s)
mCi	Millicurie(s)
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
mg	Milligram(s)
min	Minute(s)
mL	Millilitre(s)
MM	Molecular modelling
mM	Molarity in millimoles per litre
mmol	Millimole(s)
mol	Mole(s)
MOM	Methoxymethyl group
m.p.	Melting point
Ms	Methanesulfonyl group
m/z	Mass Charge Ratio
n	Normal

NBS	*N*-Bromosuccinimide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NR	Nuclear receptor(s)
NR4A	Subclass A of the subfamily 4 Nuclear Receptors
NR5A	Subclass A of the subfamily 5 Nuclear Receptors
ONR	Orphan nuclear receptor(s)
PDC	Pyridinium dichromate
Ph	Phenyl
PhMe	Toluene
PI	Propidium iodide
Pr	Propyl
rpm	Revolutions per minute
RPMI	Roswell Park Memorial Institute
rt	Room temperature
sat.	Saturated
SF-1	Steroidogenic Factor-1
SSC	Side scatter channel
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
Tf	Trifluoromethanesulfonate
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	*N*,*N*,*N*,*N*-Tetramethylethylenediamine
TMP	2,2,6,6-Tetramethylpiperidine
TMS	Trimethylsilyl
Ts	*para*-Toluenesulfonyl

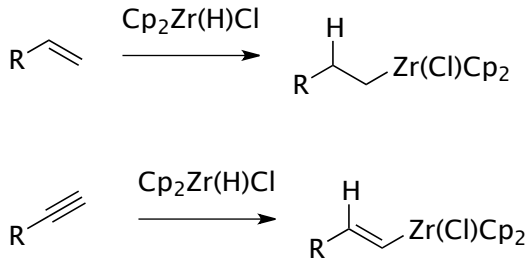
Chapter 1 Review of zirconocene mediated cocyclisations

1.1 Introduction

Zirconium is found in the Group 4 transition metal series between titanium and hafnium. Zirconium has several favourable properties making it ideal for use in synthesis. It is found in the lithosphere to the extent of 0.022%, making it as abundant as carbon, it is one of the least expensive transition metals and does not show any signs of acute or severe toxicity.[1]

At least 70–80% of the currently known organozirconium compounds are derivatives of zirconocene, whereby the zirconium has two η^5–cyclopentadienyl ligands. Given the importance of zirconocene derivatives the birth of organozirconium chemistry can be viewed as the synthesis by Wilkinson and Birmingham of zirconocene dibromide (Cp_2ZrBr_2) in 1952 and their subsequent synthesis of zirconocene dichloride (Cp_2ZrCl_2) in 1954.[2]

The use of organozirconium chemistry in organic synthesis began in 1970 with the synthesis of $Cp_2Zr(H)Cl$ by Wailes and the use of it for the hydrozirconation of alkenes and alkynes (**Scheme 1**).[3, 4] Starting in 1974 Schwartz, after whom the reagent is now named, developed a systematic study of hydrozirconation.[5-8] The exclusive *cis* addition of Zr-H to alkynes allows for the formation of stereodefined alkenes through transmetallation of the alkenylzirconocenes.[9-11]



Scheme 1: Hydrozirconation of alkenes and alkynes using Schwartz reagent.

$Cp_2Zr(H)Cl$ is a Zr(IV) complex containing one empty valence shell orbital. The lack of a lone pair in Zr(IV) complexes prevents the formation of stable complexes

with π-ligands. Reduction of Zr(IV) complexes to d^2 Zr(II) complexes gives the theoretical 14 electron '$ZrCp_2$' species containing two empty and one full non bonding orbitals. The empty orbitals allow acceptance of π-electrons while the lone pair can donate back into the π* orbital of the unsaturated substrate forming the zirconacyclopropane or zirconacyclopropene **1**. Carbometallation of a second unsaturated substrate utilising the remaining empty orbital on the zirconium and one of the two pairs of bonding electrons allows for ring expansion to the five membered zirconacycle **2** (**Figure 1**). This zirconocene mediated reductive coupling of two unsaturated substrates is particularly valuable when the two π-components are contained within the same molecule. This intramolecular zirconocene mediated cocyclisation along with the further elaboration of the resultant zirconacycle forms the basis for the rest of this review chapter.

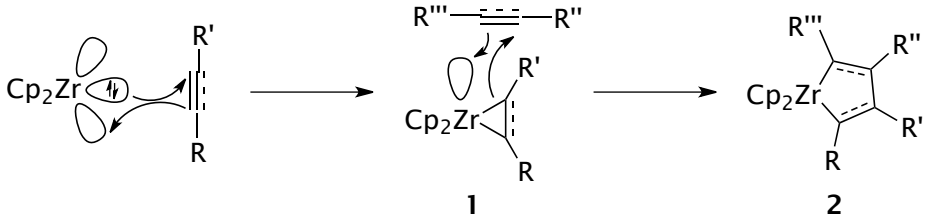


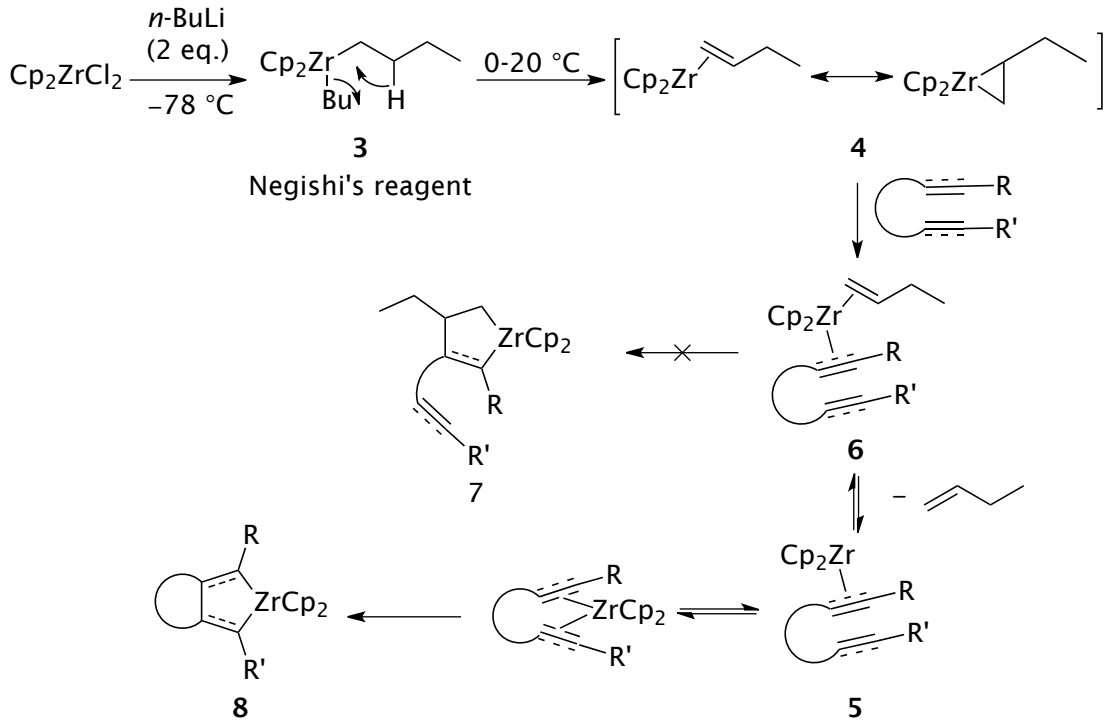
Figure 1: Zirconocene mediated cocyclisation of two unsaturated substrates.

1.2 Zirconocene mediated cocyclisations

Initial attempts at the cocyclisation of dienes, enynes and diynes utilised the *in-situ* reduction of Cp_2ZrCl_2 using Na/naphthalene, $Mg/HgCl_2$ or Na/Hg to produce the reactive '$ZrCp_2$' species.[12-14] Negishi developed a simpler method that did not require the use of toxic reagents for zirconocene mediated cocyclisations.[15, 16] Negishi's method involved the treatment of Cp_2ZrCl_2 with two equivalents of *n*-BuLi at −78 °C to produce Cp_2ZrBu_2 **3**. Upon warming this complex to room temperature a non-dissociative β−hydrogen abstraction occurs leading to the formation of Cp_2Zr(1-butene) **4** and the loss of butane. Initially Negishi had erroneously identified free Cp_2Zr as the 'Cp_2Zr' source arising through reductive elimination of *n*-butane from $Cp_2Zr(H)n$-Bu. It was Buchwald who proposed the correct structure of the 'Cp_2Zr' source and Negishi later confirmed this.[17, 18]

Cp_2ZrBu_2 **3** rather than Cp_2Zr(1-butene) **4** is generally referred to as the Negishi reagent as a result of this initial mistake.

Cp_2Zr(1-butene) **4** is regarded as a Zr (II) species. The weakly bound 1-butene ligand is readily displaced by either an alkene or an alkyne leading to complex **5**, most probably occurring through a complex such as complex **6**, which avoids the formation of the unstable free zirconocene. The carbometallation of complex **6** to form zirconacycle **7** is much slower than dissociation of 1-butene to give complex **5**. Complexation and carbometallation of a second alkene or alkyne, particularly if it is intramolecular rapidly leads to the ring expanded zirconacycle **8** (**Scheme 2**).[19]

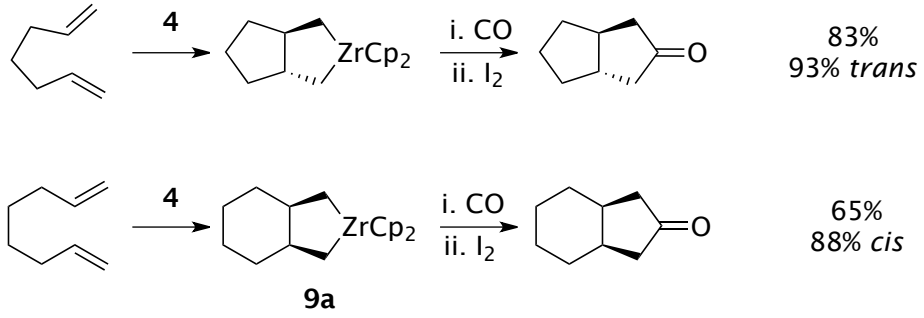


Scheme 2: Formation of Negishi's reagent **3** and its use in the cocyclisation of dienes, enynes or diynes.

1.2.1 Zirconocene mediated cocyclisation of dienes

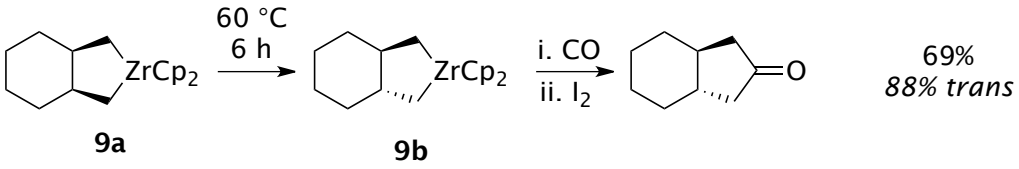
Much of the early work utilising Negishi's reagent was focussed on the intramolecular cocyclisation of dienes. Independent work by both Nugent and Negishi showed that the zirconocene mediated cocyclisation of 1,6-dienes and 1,7-dienes was successful in furnishing 5 and 6 membered carbocycles respectively.[20, 21] Neither Nugent nor Negishi could obtain 4 or 8 membered carbocycles through cocyclisation with Negishi's reagent. This appears to be a limitation with zirconocene mediated cocyclisations rather than Negishi's reagent as the cocyclisation of 1,8-nonadiene using other methods of generating zirconocene has thus far only resulted in intermolecular cocyclisation.[22, 23]

Both Nugent and Negishi also found that the zirconocene mediated cocyclisation of dienes proceeded with high stereocontrol. The cocyclisation of 1,6-dienes is found to give 90–97% *trans* selectivity while the cocyclisation of 1,7-dienes is found to initially give predominantly the *cis* product (**Scheme 3**).



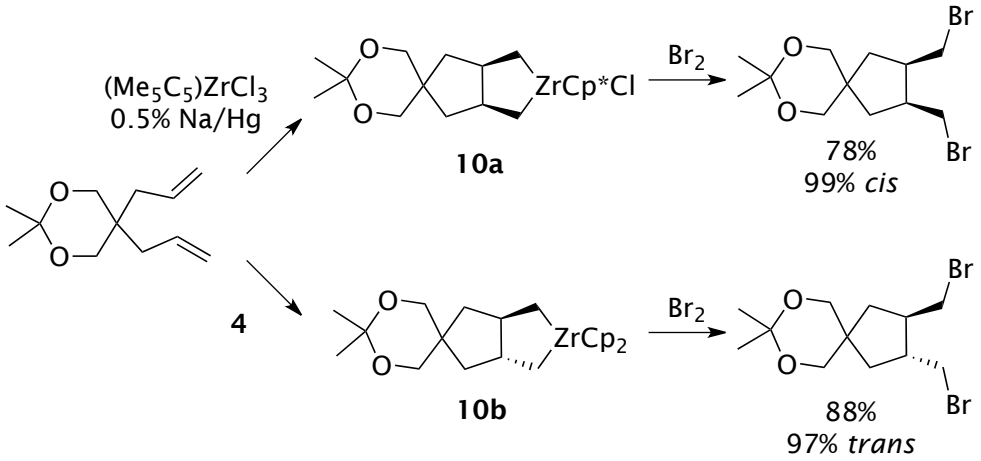
Scheme 3: Zirconocene mediated cocyclisation of 1,6-heptadiene and 1,7-octadiene.

Zirconacycle formation is a reversible process and Nakamura has shown that heating of the *cis* fused zirconacycle **9a** for 6 h at 60 °C results in thermal equilibration to the *trans* fused zirconacycle **9b** (**Scheme 4**).[22]



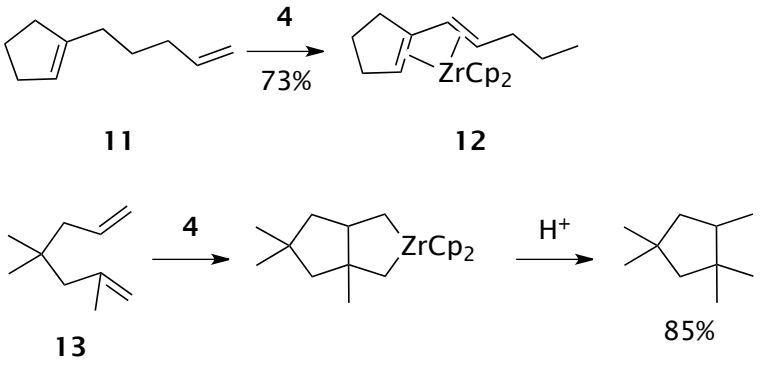
Scheme 4: Thermal equilibration of zirconacycle **9**.

Nugent showed that by using a different Zr(II) source in the zirconocene mediated cocyclisation of 1,6-dienes the *cis* isomer **10a** could be exclusively obtained instead of the *trans* isomer **10b** obtained with Negishi's reagent (**Scheme 5**).[20]



Scheme 5: Variation of the Cp_2Zr source allows access to either the *cis* or *trans* isomers of zirconacycle **10**.

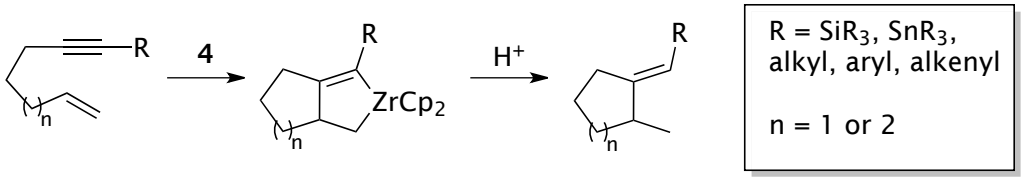
Heavily substituted dienes do not usually undergo cocyclisation. This is generally true of dienes where both alkenes are disubstituted or in dienes where one or both of the alkenes are tri- or tetrasubstituted. Some exceptions to this are known such as in the total synthesis of dendrobine where a diene with a trisubstituted alkene undergoes cocyclisation.[24] Where one of the alkenes is mono- or disubstituted and the other alkene is more heavily substituted, such as diene **11**, the least hindered alkene will undergo regioisomerisation to give the conjugated zirconocene-diene complex **12** (**Scheme 6**).[25] The incorporation of a quaternary carbon or a heteroatom into the tether prevents this regioisomerisation such as in the cocyclisation of diene **13**.[21, 25] Substitution on the tether is tolerated and is often desirable as a high degree of 1,2-stereoinduction and 1,3-stereoinduction with the ring junction has been observed.[20, 26, 27]



Scheme 6: Zirconocene mediated cocyclisation of dienes where one or more alkenes are highly substituted.

1.2.2 Zirconocene mediated cocyclisation of enynes

As with dienes, zirconocene mediated cocyclisation of enynes is successful in furnishing 5 and 6 membered carbocyclic structures but not smaller or larger ring sizes. Unlike alkenes, alkynes with a wide range of substituents are tolerated (**Scheme 7**).[16, 28] Terminal alkynes are not tolerated in cocyclisations using Negishi's reagent.



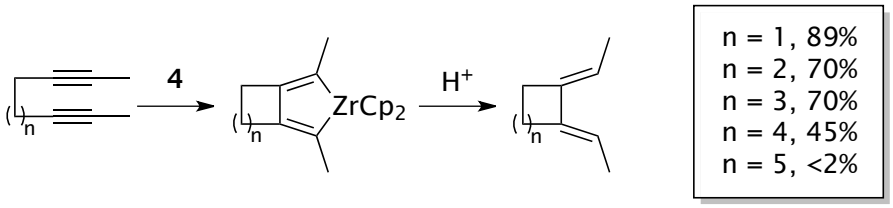
Scheme 7: Zirconocene mediated cocyclisation of enynes tolerates a wide variety of substituents on the alkyne.

As with dienes, enyne cocyclisation is unsuccessful when tri- or tetra-substituted alkenes are used, generally intermolecular cocyclisation between the two alkynes dominates in these instances. As with the cocyclisation of dienes, enynes with a substituent on the tether can exert high degrees of 1,2-stereoinduction or 1,3-stereoinduction.[29]

1.2.3 Zirconocene mediated cocyclisation of diynes

Unlike dienes and enynes the zirconocene mediated cocyclisation of diynes can be used to form 4 membered rings as well as those with 7 or more members in

addition to 5 and 6 membered rings (**Scheme 8**).[16] As in the case of enynes a wide variety of substituents is tolerated on both alkynes although terminal alkynes do not undergo cocyclisation when using Negishi's reagent. The *E*,*E*-exocyclic dienes formed by the zirconocene mediated cocyclisation of diynes have been used successfully in Diels-Alder reactions.[30, 31]



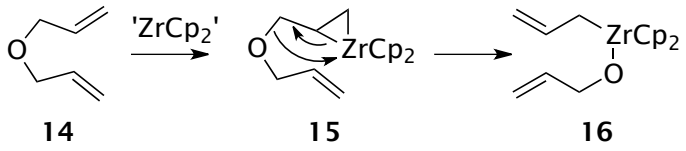
Scheme 8: Zirconocene mediated cocyclisation of diynes successfully leads to a variety of ring sizes.

1.2.4 Heterocycle synthesis via zirconocene mediated cocyclisations

The incorporation of a heteroatom into dienes, enynes and diynes has been used in order to synthesise a number of different heterocycles, expanding the scope of zirconocene mediated cocyclisations significantly.

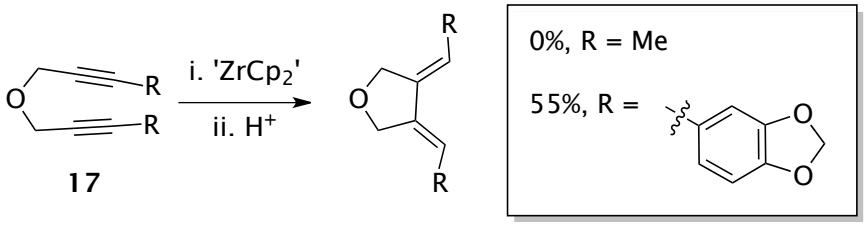
1.2.4.1 Synthesis of oxygen containing heterocycles

The synthesis of oxygen containing heterocycles through zirconocene mediated cocyclisation is rather limited. The cocyclisation of diallyl ether **14** has been attempted with a zirconocene equivalent but elimination of the β-oxygen occurs in the intermediate zirconacycle **15** to give allyl zirconocene **16** (**Scheme 9**).[21, 30]



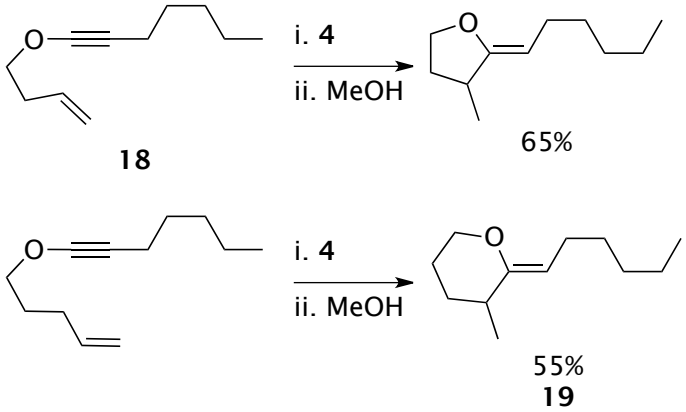
Scheme 9: Attempted zirconocene mediated cocyclisation of diallyl ether **14**.

The zirconocene mediated cocyclisation of the corresponding dipropargylic ether **17** is only successful when the alkynes possess bulky substituents and the reaction mixture is heated at 40 °C for 72 hours (**Scheme 10**).[30]



Scheme 10: Zirconocene mediated cocyclisation of dipropargylic ethers **17**.

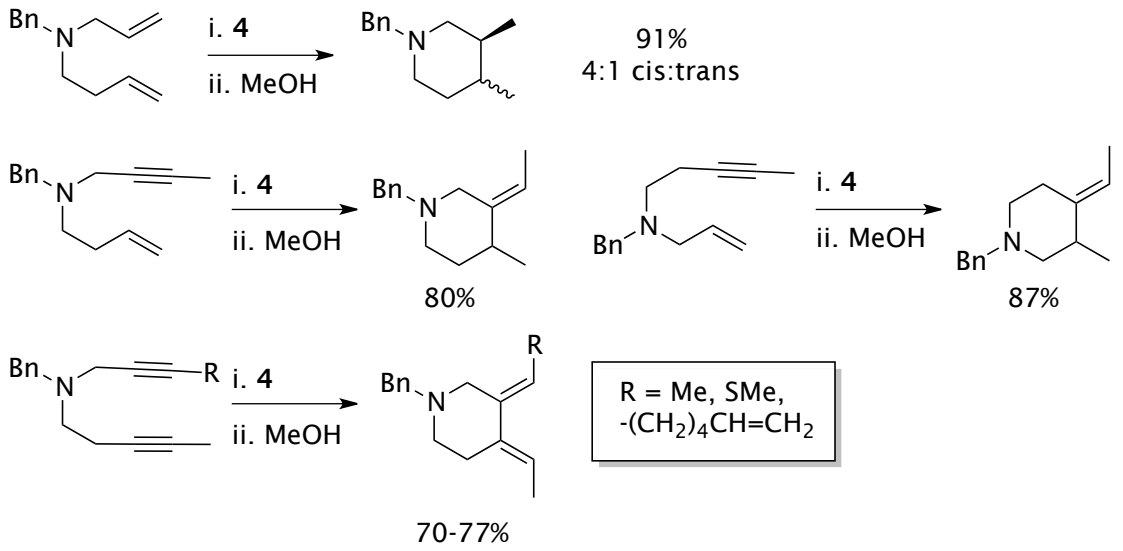
More success is obtained where the oxygen is situated adjacent to the acetylene in an enyne. Kemp has demonstrated the synthesis of tetrahydrofurans using zirconocene mediated cocyclisation of enynes **18** (**Scheme 11**).[32] Owen has extended this work to the synthesis of tetrahydropyrans **19**.[33]



Scheme 11: Zirconocene mediated cocyclisation of alkoxyalkynes.

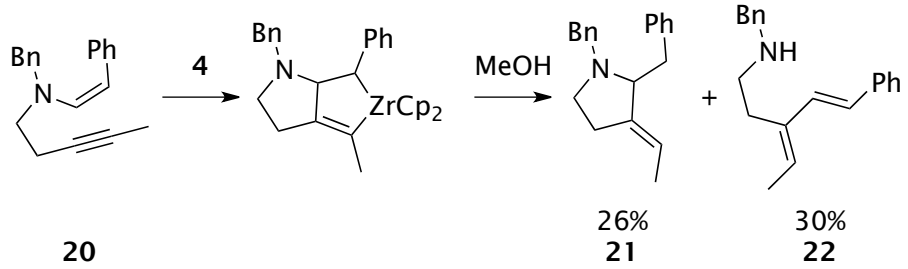
1.2.4.2 Synthesis of nitrogen containing heterocycles

Unlike their oxygen containing analogues 1,6-dienes, enynes and diynes containing a β-nitrogen all successfully undergo zirconocene mediated cocyclisation.[21, 28, 34] Kemp successfully extended this work to 1,7-dienes, enynes and diynes containing a β-nitrogen (**Scheme 12**) while Macfarlane was successful in synthesising azepanes through zirconocene mediated cocyclisations.[31, 35, 36] Unlike their all carbon analogues dienes and enynes with a disubstituted alkene successfully undergo cocyclisation.[24, 28]



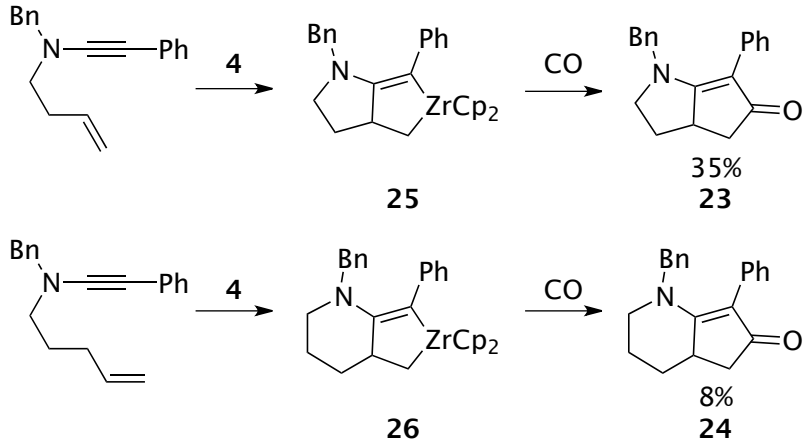
Scheme 12: Zirconocene mediated cocyclisation of nitrogen containing dienes, enynes and diynes.

Kemp also attempted the zirconocene mediated cocyclisations of a series of substrates where the nitrogen was adjacent to either an alkene or alkyne with some limited success.[32] Kemp found that enamine **20** could be successfully cyclised to give pyrrolidine **21** in 26% yield (**Scheme 13**), however, the conjugated diene **22** was also obtained as a side product, postulated by Kemp to form through β-elimination of the nitrogen.



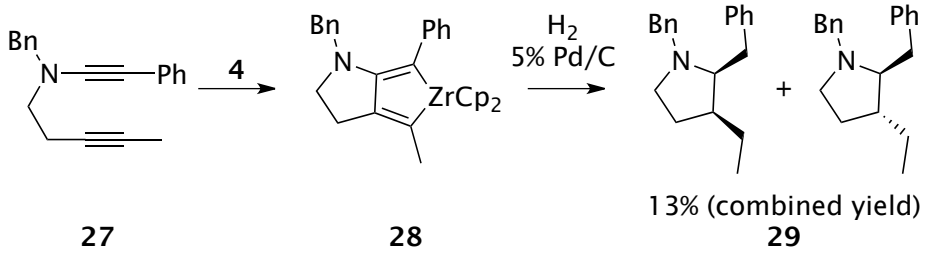
Scheme 13: Zirconocene mediated cocyclisation of enamine **20**.

Cocyclisation of ynamines, where the nitrogen is adjacent to an alkyne, was also found to be successful by Kemp. The synthesis of bicyclic enones **23** and **24**, albeit in low yields, was achieved through the carbonylation of zirconacyclopentenes **25** and **26** (**Scheme 14**).



Scheme 14: Synthesis of bicyclic enones through zirconocene mediated cocyclisation.

The final example that Kemp utilised to investigate the cocyclisation of ynamines was the cocyclisation of ynamine **27**, which possesses two alkynes (**Scheme 15**). Kemp found that simple protonolysis of zirconacyclopentadiene **28** yielded a complicated mixture of products. Protonolysis of zirconacyclopentadiene **28** in the presence of 5% Pd/C under a H_2 atmosphere yielded a mixture of the *cis* and *trans* isomers of pyrrolidine **29** in 13% combined yield.



Scheme 15: Zirconocene mediated cocyclisation of ynamine **27**.

1.3 Elaboration of zirconacycles

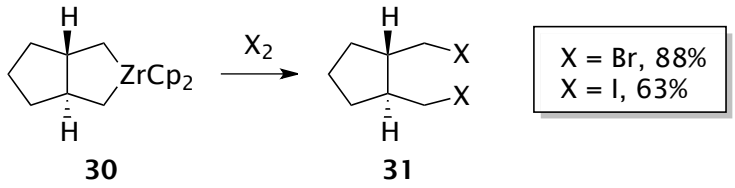
The range of substrates that undergo zirconocene mediated cocyclisation leads to a large array of organic compounds. Elaboration of the resultant zirconacycle before removal of the zirconium can extend the range even further. The following section summarises some of the elaborations that have been developed for use with zirconacycles and is applicable to both bicyclic zirconacycles as well as monocyclic zirconacycles.

1.3.1 Protonolysis and deuterolysis

The simplest elaboration of a zirconacycle is protonolysis. The conditions for protonolysis can be varied to accommodate acid or base sensitive compounds. Methanol, methanol / sat. aq. $NaHCO_3$ and dilute HCl or H_2SO_4 are all efficient for protic quench of C-Zr bonds. Equally the corresponding deuterated compounds; MeOD, DCl or D_2SO_4 can be used for deuterolysis. Deuterolysis is particularly useful for establishing the mechanism of a reaction as it reliably confirms the presence of C-Zr bonds.[37]

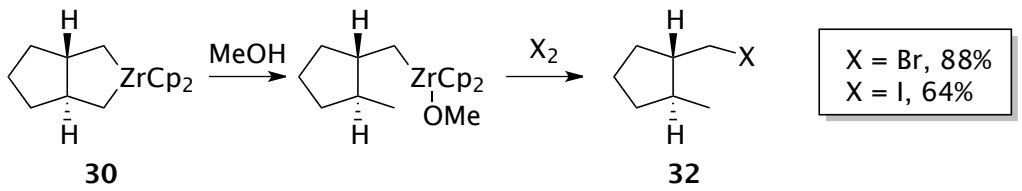
1.3.2 Halogenolysis

Treatment of zirconacyclopentanes **30** with bromine, NBS or iodine leads to the dihalides **31** in good yield (**Scheme 16**).[20, 21] The same method can be used for the bishalogenation of zirconacyclopentenes.[19]



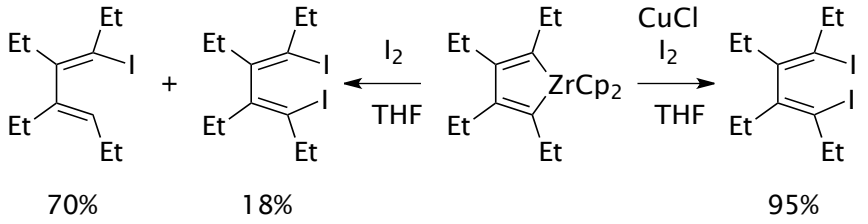
Scheme 16: Bishalogenation of zirconacylopentanes **30**.

Monohalogenation of zirconacyclopentanes **30** is achieved through protonolysis of one of the C-Zr bonds with methanol followed by halogenolysis of the remaining C-Zr bond to furnish the monohalide **32** (**Scheme 17**).[38] Monohalogenation is also possible with zirconacyclopentenes and the halogenolysis can be of the alkyl-zirconium or vinyl-zirconium bond depending on the reagent used.[39]



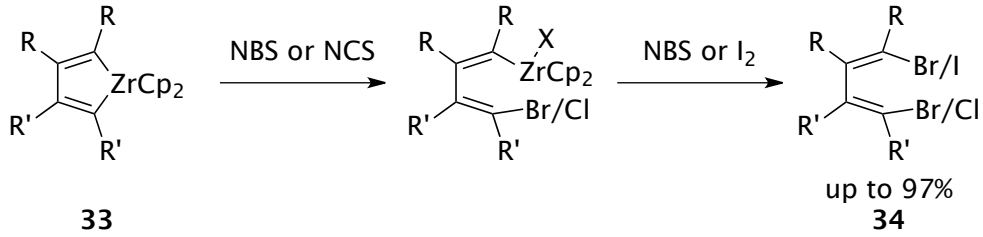
Scheme 17: Monohalogenation of zirconacylopentanes **30**.

The halogenolysis of zirconacyclopentadienes is also possible but is solvent dependent. Bisiodination dominates when the reaction is carried out in DCM, while in THF monoiodination dominates.[40, 41] Takahashi overcame this drawback by transmetallating zirconacyclopentadienes to copper before treatment with iodine resulting in exclusively the bisiodide (**Scheme 18**).[42]



Scheme 18: Dramatic effect of CuCl on the yield of bisiodination of zirconacyclopentadienes.

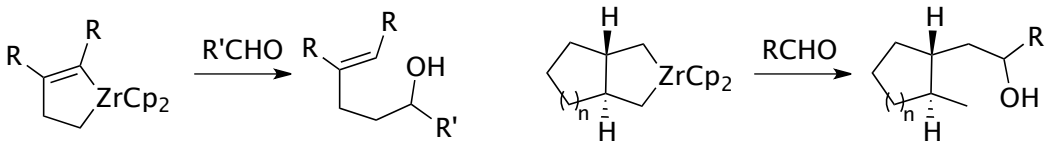
Takahashi has also developed the synthetically useful selective mixed halogenation of zirconacyclopentadienes. Treatment of zirconacyclopentadienes **33** with NCS followed by iodine or NBS or alternatively treatment with NBS followed by iodine is successful in furnishing the mixed halides **34** in excellent yields (**Scheme 19**).[43]



Scheme 19: Synthesis of mixed halides **34**.

1.3.3 Aldehyde insertion

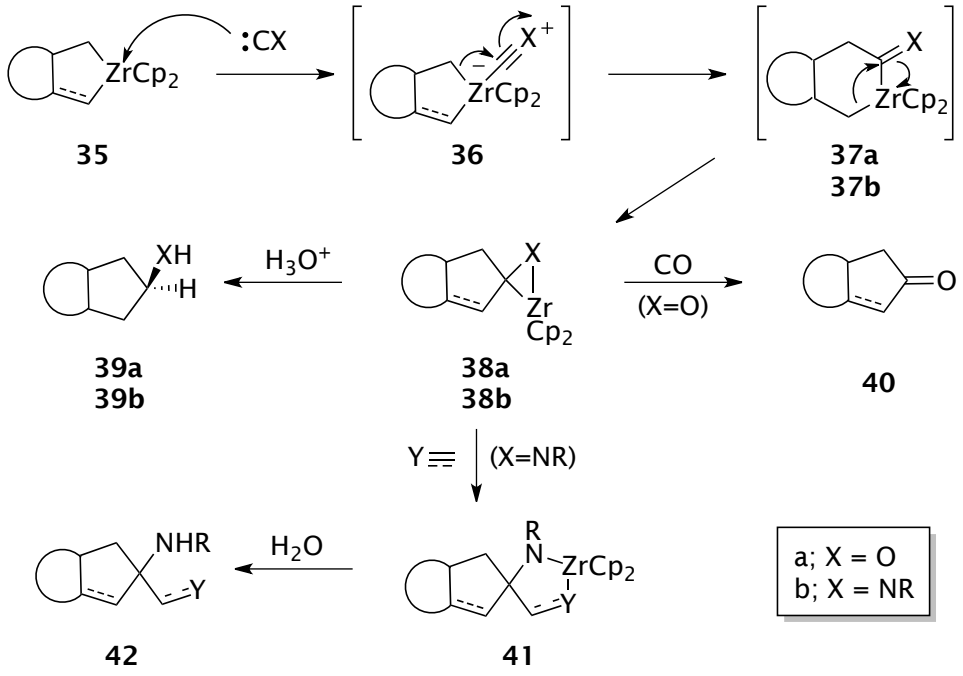
Similar to the use of halogens as electrophiles, zirconacyclopentanes and zirconacyclopentenes react efficiently with aldehydes to form various alcohols (**Scheme 20**).[44] The stereocontrol at the newly formed alcohol centre is poor, however, regiocontrol in the unsymmetrical zirconacyclopentenes is excellent as insertion occurs exclusively into the alkyl-zirconium bond.



Scheme 20: Insertion of aldehydes into zirconacyclopentanes and zirconacyclopentenes.

1.3.4 Carbonylation and isonitrile insertion

A key characteristic of zirconacycles **35** is that the zirconium has a 16 electron configuration. The unsaturated zirconium accepts an electron pair into its empty orbital to form the 18 electron 'zirconate' species **36**, which readily undergoes a 1,2-rearrangement to form a new carbon-carbon bond (**Scheme 21**). Carbenes such as carbon monoxide and isonitriles are both excellent donors for this insertion.



Scheme 21: Elaboration of zirconacycles **35** with carbon monoxide and isonitriles.

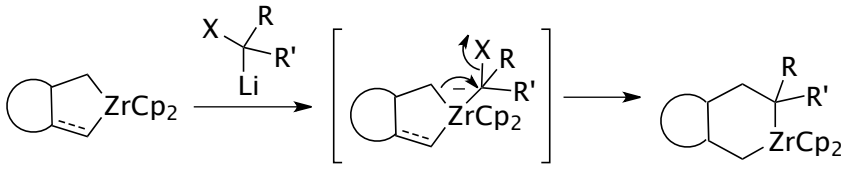
Carbonylation of zirconacycles **35** results in the formation of the η^2-acyl complex **37a** which rapidly rearranges to the η^2-ketone complex **38a**. Carbonylation of saturated zirconacycles tends to lead to the formation of alcohols **39a** upon protonation. Prolonged exposure to carbon monoxide, however, leads to the formation of ketone **40**, postulated to be a result of the replacement of the η^2-ketone ligand with a carbon monoxide.[45] Increased yields of ketone **40** can be

obtained when the reaction is worked-up with iodine.[46] Zirconacyclopentenes generally furnish ketones **40** in good yield without the need for iodine.[47, 48]

The isonitrile group is isoelectronic with carbon monoxide and so insertion of isonitriles into zirconacycles **35** follows the same path as the insertion of carbon monoxide; first the formation of the 'zirconate' species **36** followed by 1,2-rearrangment to the η^2-iminoacyl complex **37b**. Unlike carbon monoxide insertion where rearrangement to the η^2-ketone complex **38a** is rapid, rearrangement to the η^2-imine complex **38b** is slow. Protonation of the η^2-imine complex **38b** gives the amine **39b**. Insertion of a π-component into the η^2-imine complex **38b** gives zirconacycle **41**, which on protonolysis yields amine **42**. Variation of both the isonitrile and the π-component are possible and lead to a variety of different organic compounds.[49-52]

1.3.5 Carbenoid insertion

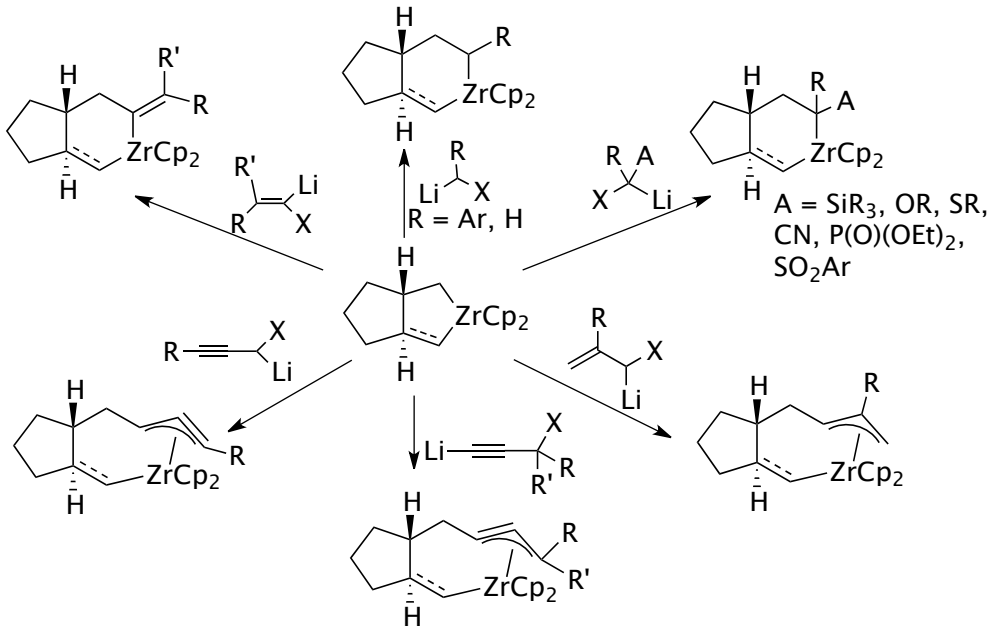
Carbenoids, which can be defined as a species with both a metal and a leaving group on the same carbon, have the same carbenic nature as both carbon monoxide and isonitriles.[53-57] The insertion of carbenoids into zirconacycles proceeds in the same fashion as with carbon monoxide and isonitriles. The 'zirconate' species **43** is initially formed followed by a 1,2-rearrangement and elimination of the leaving group to give the new zirconacyclohexane **44** (**Scheme 22**).[45]



35 **43** **44**

Scheme 22: Insertion of carbenoids into zirconacycles.

Many different classes of carbenoids, such as 1-halo-1-lithioalkenes, allenyl carbenoids, allyl carbenoids, propargyl carbenoids, alkyl carbenoids and benzyl carbenoids have all been shown to insert into zirconacycles as summarised in **Scheme 23**.[58-71]

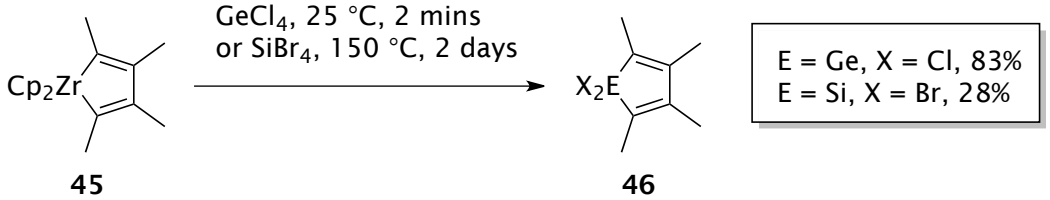


Scheme 23: A wide range of carbenoids can be inserted into zirconacycles.

1.3.6 Heteroatom transfer

Detailed earlier in this review (Section 1.2.4) were routes to heterocycles through zirconocene mediated cocyclisations of substrates containing a heteroatom. It is also possible to synthesise a range of heterocycles by transfer of a main group element with a zirconacyclopentadiene.[72, 73] The driving force behind these transfers is the recovery of Cp_2ZrX_2.[41]

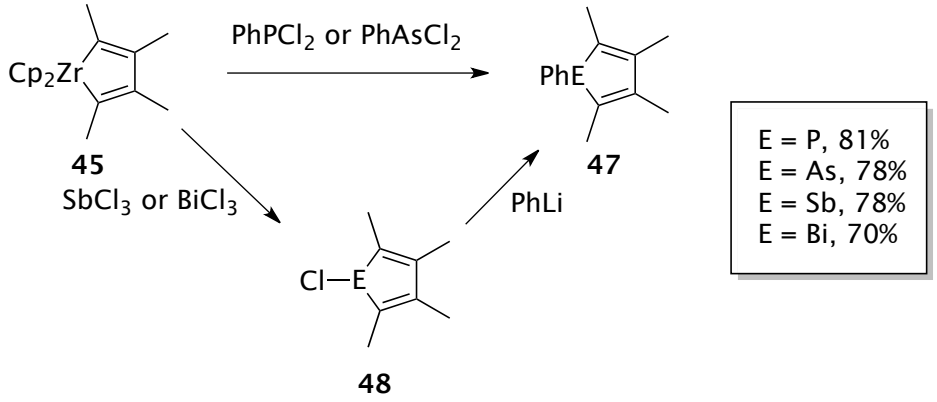
The Group 14 compounds $GeCl_4$ and $SiBr_4$ both readily react with zirconacyclopentadiene **45** to furnish the corresponding heterocycles **46** (**Scheme 24**). The yield of the silol **46** formed using $SiBr_4$ is relatively low at 28% but interestingly reaction with $MeHSiCl_2$ is successful in 88% yield and with H_2SiCl_2 the yield is 92% suggesting that steric effects play a large role in the overall yield.[74]



45 **46**

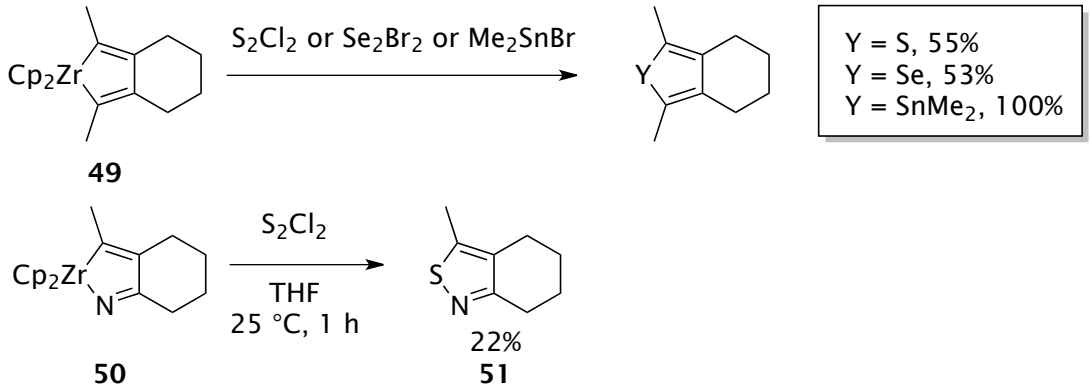
Scheme 24: Heteroatom transfer of Group 14 compounds.

Reaction of zirconacyclopentadiene **45** with Group 15 compounds gives the Group 15 phenyl derivatives **47** in good yield (**Scheme 25**). This either occurs through a one step process with the corresponding Group 15 phenyl dichloride or through a two step process involving the Group 15 trichloride to form the monochloride **48** and subsequent displacement of the chlorine with phenyl lithium.



Scheme 25: Heteroatom transfer of Group 15 compounds.

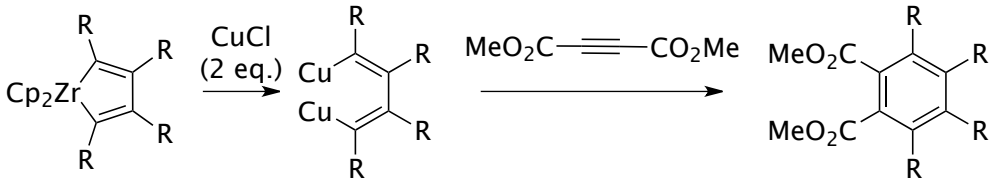
Group 16 compounds S_2Cl_2, Se_2Br_2 and Me_2SnBr_2 readily undergo heteroatom transfer with zirconacyclopentadiene **49** in moderate to excellent yields (**Scheme 26**). This has also been undertaken with the azazirconacycle **50** as a concise, although low yielding, route for the synthesis of isothiazoles **51**.[73]



Scheme 26: Heteroatom transfer of Group 16 compounds.

1.3.7 Transmetallation

Although zirconacycles are capable of a large number of direct elaborations, they have a relatively poor nucleophilicity compared with other metallocycles. Fortunately transmetallation to a number of other metals is possible. Of particular note is the work by Takahashi on the transmetallation of zirconacyclopentadienes to copper which, amongst other elaborations, allows the incorporation of a further π-component for the formation of benzene derivatives (**Scheme 27**).[41] One limitation of the organocopper derivatives is that an electron withdrawing group is required on the new π-component, this limitation is overcome by transmetallation to nickel instead.[41]



Scheme 27: Formation of benzene derivatives through transmetallation of zirconacycles with copper.

1.4 Summary

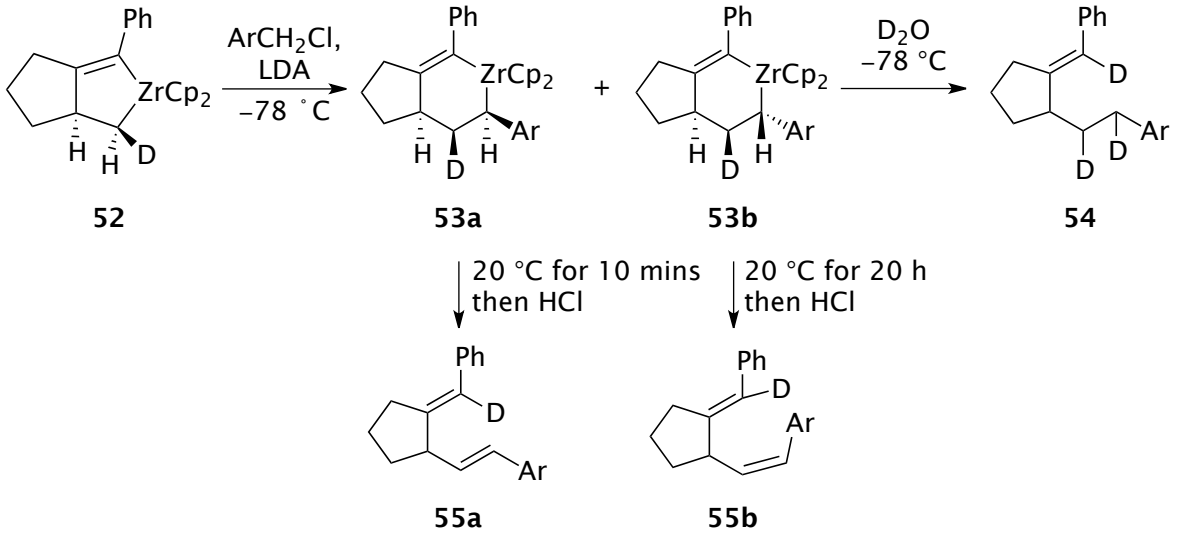
Zirconocene mediated cocyclisation of dienes, enynes and diynes offers a concise route to a variety of carbocyclic and heterocyclic structures. Zirconocene mediated cocyclisations are notable for their generality. Variation of the substituents on the π-component, the substituents on the tether and the length of the tether are all tolerated. Once formed further elaboration of the zirconacycle is possible through protonolysis, halogenolysis, heteroatom transfer, insertion of carbenic species such as carbon monoxide, isonitriles or carbenoids and transmetallation. The variety of organic structures that can be synthesised in this manner have meant that organozirconium chemistry has been used in a number of natural product syntheses.[24, 31, 75-81] The remainder of this thesis will detail novel work that has been undertaken to extend the scope of zirconocene mediated cocyclisations as well as to apply known organozirconium chemistry to natural product synthesis.

Chapter 2 Zirconocene mediated tandem tricyclisations

2.1 Background to the research area

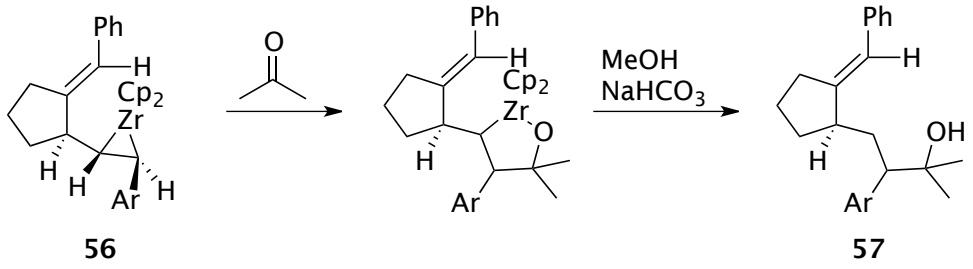
2.1.1 Novel endocyclic cyclometallation

As part of her studies into benzyl carbenoid insertions into zirconacycles Norman observed that altering the temperature at which the reaction mixture was quenched gave different products.[69] As expected insertion of a benzyl carbenoid into zirconacyclopentene **52** gives zirconacyclohexenes **53a** and **53b**. Quenching of these zirconacyclohexenes at −78 ºC with D_2O produced the expected product **54**. Allowing the reaction mixture to warm to room temperature before quenching with DCl instead produced a 1:1 mixture of the (*E*) and (*Z*)-alkenes **55a** and **55b** (**Scheme 28**).



Scheme 28: The different products obtained by Norman depending on the temperature of the quench.

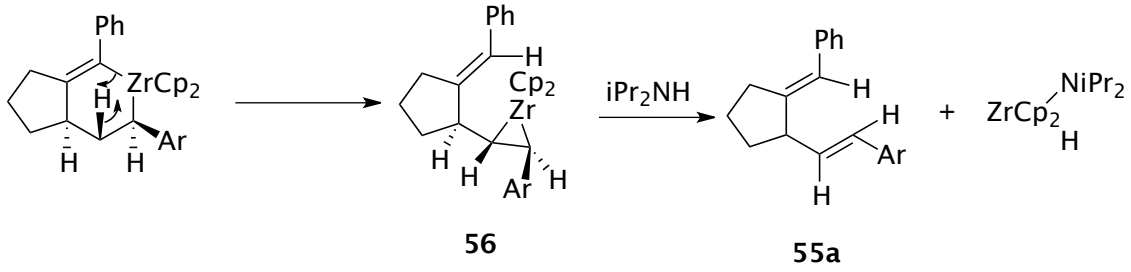
Norman postulated that a novel endocyclic cyclometallation process to afford a zirconocene η^2-alkene complex **56** was responsible for the formation of alkenes **55a** and **55b**. The successful trapping of the zirconocene η^2-alkene complex with acetone to yield alcohol **57** provided evidence for **56** as an intermediate (**Scheme 29**).



56 **57**

Scheme 29: Trapping of zirconacycle **56** with acetone.

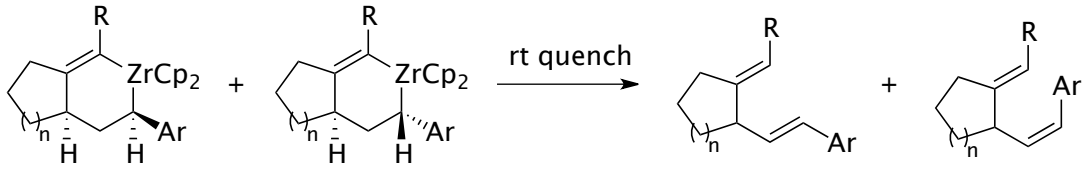
The formation of the zirconocene η^2-alkene complex **56** was followed by decomplexation of the zirconocene. Diisopropylamine, formed during the *in-situ* generation of the benzyl carbenoid was found to aid the decomplexation of the zirconocene (**Scheme 30**).



56 **55a**

Scheme 30: Decomplexation of zirconocene from zirconocene η^2-alkene complex **56** aided by diisopropylamine.

Norman investigated the scope of the novel endocyclic cyclometallation by variation of the benzyl carbenoid inserted, the alkyne substituent and the size of the ring fused to the zirconacycle (**Scheme 31**). Significant differences in the selectivity and rate of cyclometallation were observed by changing the size of the fused ring or the alkyne substituent (**Table 1**).



53a **53b**

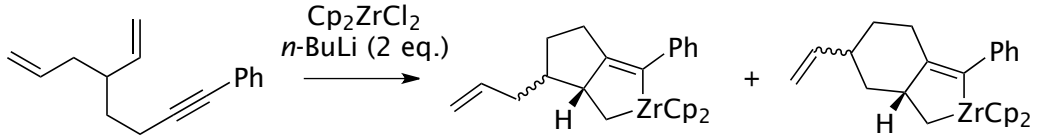
Scheme 31: Variation of the alkyne substituent, benzyl carbenoid and fused ring size allowed investigation of the scope of the endocyclic cyclometallation.

n	R	E/Z ratio	Half life of zirconacycle **53a** at 20 °C (mins)	Half life of zirconacycle **53b** at 20 °C (mins)
1	Ph	1:1	16.5	578
1	Bu	3:1	<4	28
2	Ph	1:0	<10	12.8
2	Bu	1:0	<10	<10

Table 1: Variation of the fused ring size and alkyl substituent affected both the rate and selectivity of the endocyclic cyclometallation.

2.1.2 Intramolecular trapping of zirconocene η^2-alkene complexes

The successful trapping of the η^2-alkene complexes with acetone led to the concept of intramolecular trapping with pendant alkenes. Norman attempted the intramolecular trapping of the zirconocene η^2-alkene complex with a number of substrates. Enyne **58**, which possessed a β-branched alkene was the first to be investigated. Zirconocene mediated cocyclisation of enyne **58** yielded a mixture of zirconacycles **59** and **60** arising from cyclisation between the alkyne and either of the alkenes (**Scheme 32**). DFT calculations later confirmed that the undesired cyclisation to give zirconacycle **60** was more favourable and so this system was taken no further.

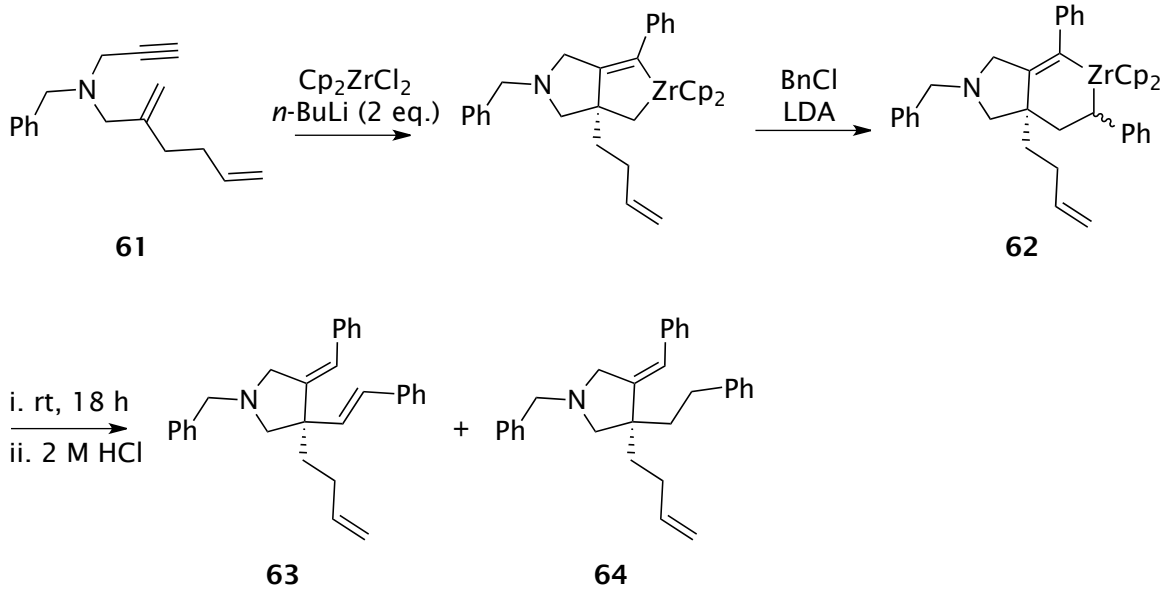


58 **59** **60**

Scheme 32: Zirconocene mediated cocyclisation of enyne **58**.

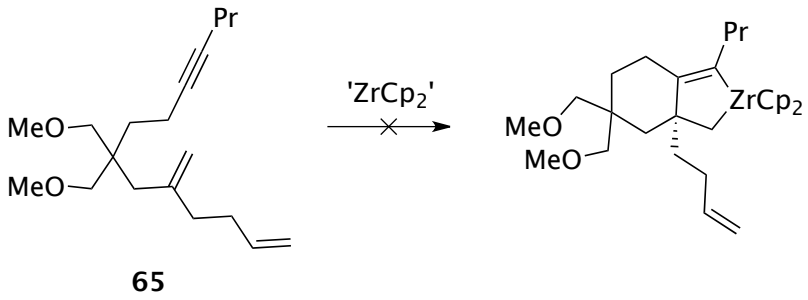
In order to prevent competitive cocyclisation between the different alkenes Norman next attempted the cocyclisation of enyne **61**. Cocyclisation of enyne **61** will either form a five membered or an eight membered ring, with the formation of a five membered ring more energetically favourable. Cocyclisation and carbenoid insertion occurred as expected to yield zirconacycle **62**. Unfortunately

when the reaction mixture was warmed to room temperature and quenched with HCl a 1:1 mixture of alkenes **63** and **64** was formed (**Scheme 33**). Norman proposed that only one of the diastereoisomers of zirconacycle **62** was undergoing the endocyclic cyclometallation and that the diisopropylamine aided decomplexation of the zirconocene was more favourable than intramolecular trapping of the zirconocene η^2-alkene. Attempting to cocyclise alkene **63** with Negishi's reagent was also unsuccessful suggesting that something other than the diisopropylamine-aided decomplexation of the zirconocene is preventing intramolecular trapping of the zirconocene η^2-alkene.



Scheme 33: Zirconocene mediated cocyclisation of enyne **61**.

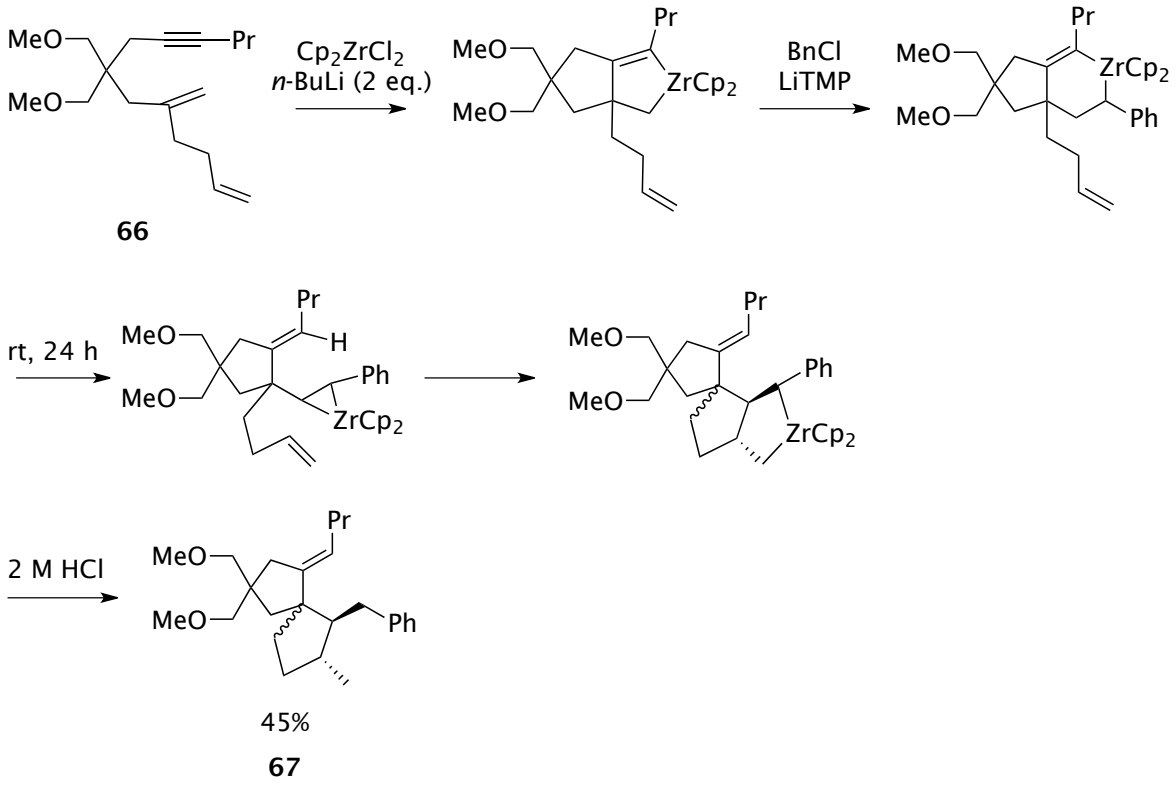
Norman then attempted the intramolecular trapping with zirconacycles containing a fused six membered ring as she had shown these to undergo the endocyclic cyclometallation faster than those with a fused five membered ring (**Table 1**). Attempted zirconocene mediated cocyclisation of enyne **65** was unsuccessful under a series of different conditions (**Scheme 34**). The only products obtained were those from intermolecular dimerisation of the enyne.



65

Scheme 34: Attempted zirconocene mediated cocyclisation of enyne **65**.

Finally Norman attempted the intramolecular trapping of the zirconocene η^2-alkene using enyne **66** (**Scheme 35**). This proved to be successful in furnishing spirocyclic compound **67** as a 1:1 mixture of diastereoisomers in 45% yield.



66

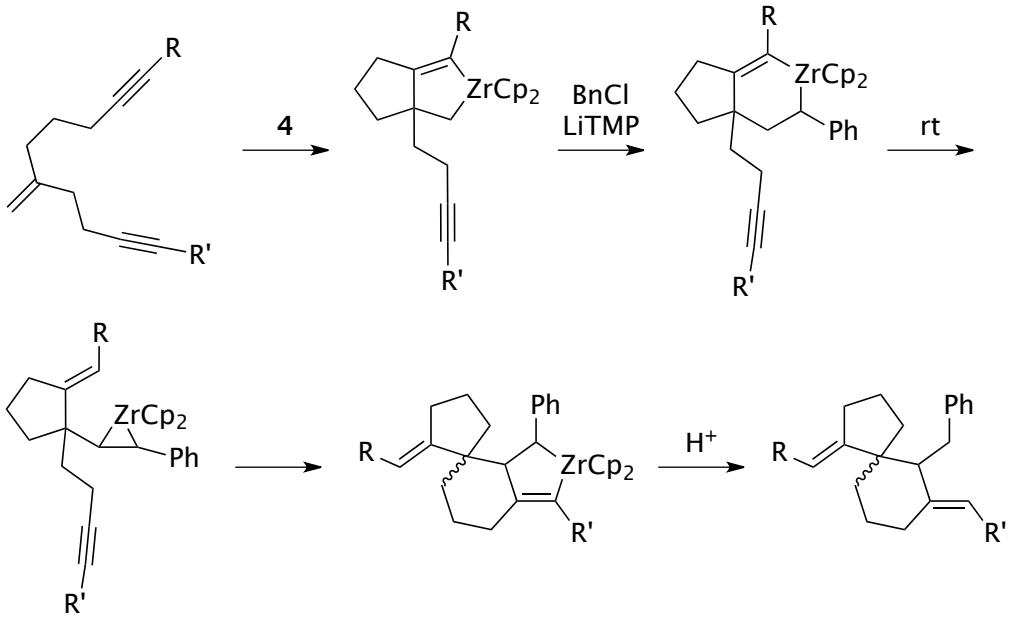
45%

67

Scheme 35: Zirconocene mediated cocyclisation of enyne **66**.

2.2 Intramolecular trapping with pendant alkynes

Norman had established the principle of intramolecular trapping of zirconocene η^2-alkene complexes with a pendant alkene. It was envisaged that this work could be extended to the trapping of zirconocene η^2-alkene complexes with pendant alkynes as well. This would allow access to a series of spirocyclic structures with two exocyclic alkenes bearing substituents that could be easily altered (**Scheme 36**).



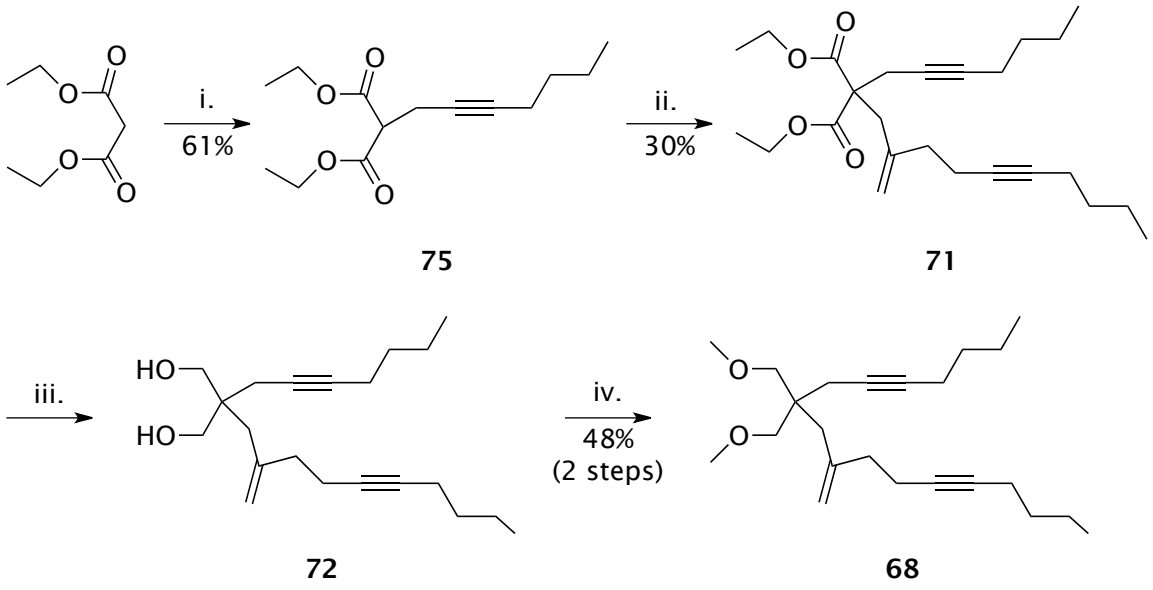
Scheme 36: Synthesis of spirocycles via the intramolecular trapping of a zirconocene η^2-alkene complex.

2.2.1 Synthesis of the α-branched substrate

Careful design of the enediyne to be cocyclised was needed to ensure that the pendant alkyne did not itself interfere with the initial cocyclisation. Enediyne **68** was chosen as the first target because cocyclisation between the two alkynes was highly unlikely as this would involve formation of an eight membered ring. Equally cocyclisation between the pendant alkyne and the alkene would have involved the formation of a four membered ring fused to a zirconacyclopentene which has never been observed before.

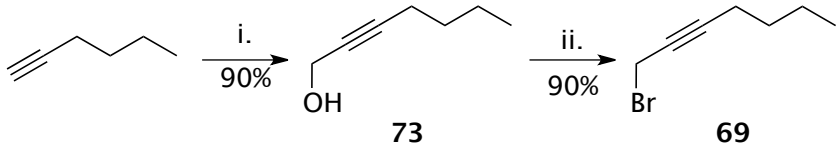
The route chosen to synthesise the α-branched substrate **68** involved the synthesis and coupling of two different alkynyl bromides **69** and **70** to diethyl

malonate followed by reduction of the resulting diester **71** to the diol **72**. Alkylation with MeI would furnish enediyne **68** (**Scheme 37**).



Scheme 37: Synthesis of enediyne **68**. *Reagents and conditions:* i. NaH, THF, rt, 1 h, bromide **69**, rt, 15 h; ii. NaH, THF, rt, 1 h, bromide **70**, rt, 15 h; iii. $LiAlH_4$, THF, 0 °C → RT, 2 h; iv. NaH, THF, 0 °C → rt, 1 h, MeI, 0 °C → rt, 3.5 h.

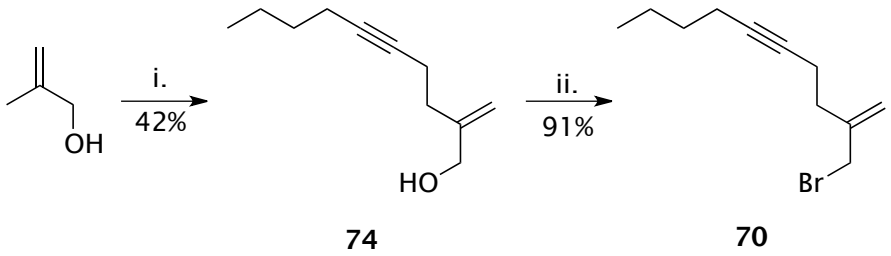
The first of the alkynyl bromides, 1-bromohept-2-yne (**69**), was synthesised by simple reaction of paraformaldehyde with hex-1-yne deprotonated by *n*-BuLi.[82] The resulting alcohol **73** was then converted to the bromide **69** with PBr_3 and catalytic pyridine in 90% yield (**Scheme 38**).[83] The conversion to the bromide **69** was briefly attempted with CBr_4 and PPh_3 but this lowered the yield. Separation of the product from any remaining CBr_4 and PPh_3 was also troublesome.



Scheme 38: Synthesis of bromide **69**. *Reagents and conditions:* i. paraformaldehyde, THF, −78 °C, 3 h, rt, 3.5 days; ii. PBr_3, Et_2O, reflux, 55 mins.

The second alkynyl bromide **70** was synthesised by reaction of alkynyl bromide **69** with the dianion derived from β-methallyl alcohol and subsequent conversion of the resulting alcohol **74** to the bromide **70**, again using PBr_3 (**Scheme 39**).[83, 84] The

reaction with the dianion derived from β-methallyl alcohol proved troublesome producing several unwanted by-products, reducing the yield to 42%.



74 **70**

Scheme 39: Synthesis of bromide **70.** *Reagents and conditions:* i. TMEDA, *n*-BuLi, Et_2O, −78 °C → rt, 15 h, bromide **69**, −78 °C, 2 h, rt, 6 h; ii. PBr_3, Et_2O, reflux, 105 mins.

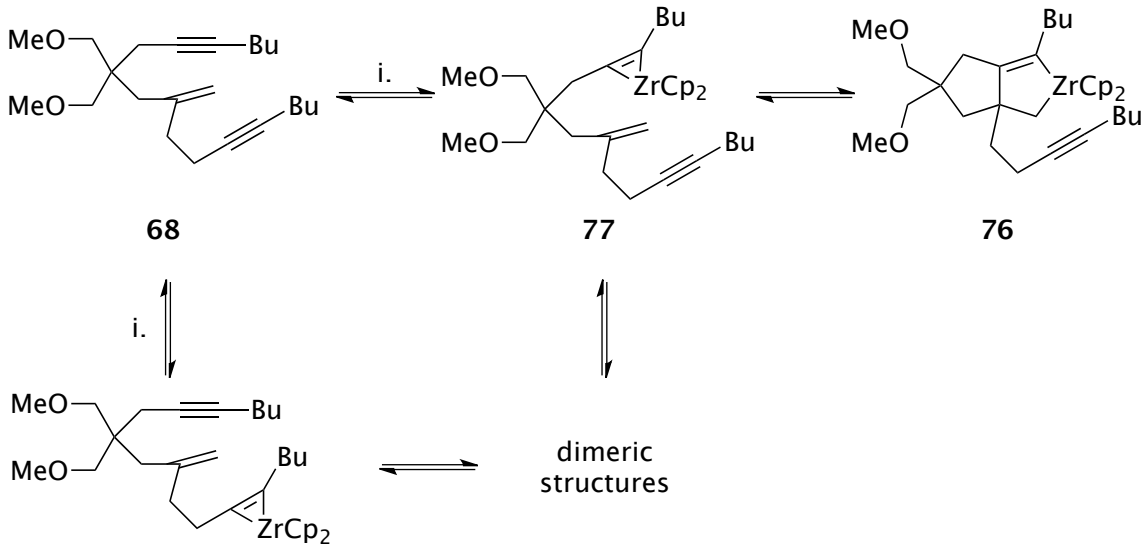
Alkylation of diethyl malonate with bromide **69** was achieved in yields of 18% to 61%. The major obstacle to good conversion was the formation of the undesired bis alkylated malonate. The yield of the desired malonate **75** was increased by using a large excess of malonate to NaH and the alkynyl bromide as had been done with a similar alkyl bromide in the literature.[85] The insertion of the second alkynyl bromide **70** had a yield of only 30%. This yield could have been explained by the second insertion being less favourable than the first, however, the difficulty in preventing bis insertion of alkynyl bromide **69** would tend to contradict this.

The final step in the synthesis of the enediyne substrate **68** was the reduction of the bis alkylated malonate **71** to the diol **72** achieved using $LiAlH_4$ followed by the alkylation of the alcohols to methyl ethers using methyl iodide which was achieved in 48% yield across the two steps.

2.2.2 Tricyclisation of the α-branched substrate

Tricyclisation of the α-branched enediyne substrate **68** was unsuccessful. GC monitoring of the initial cyclisation showed the formation of a new peak. The new peak had a retention time similar to that of enediyne **68** indicating that it was the result of protonolysis of zirconacycle **76**. As time progressed the new peak was seen to disappear. It is postulated that intermolecular dimerisation was occurring (**Scheme 40**). ^{1}H NMR spectroscopy showed that the doublets at 4.95 ppm and 4.87 ppm corresponding to the alkene in the starting enediyne **68** were still

present. If cocyclisation had occurred between the two alkynes the ^{1}H spectrum would have shown two new triplets in the alkene region, however, the ^{1}H NMR spectrum had several new peaks in the region of 4.60 ppm to 5.80 ppm indicating that instead dimerisation may have occurred. In addition to this GCMS of the product mixture obtained showed a peak at 349.2 m/z which is higher than the molecular weight of the starting enediyne **68** and would correspond with a dimer of enediyne **68** which had fragmented to lose parts of the long alkyl chains. There are a variety of different dimers that are possible as either or both alkynes can be complexed by the zirconium. Further to this the dimer can form between the same alkyne on each enediyne or between different alkynes on each enediyne. The number of possible dimers is even greater if regioisomers exist.



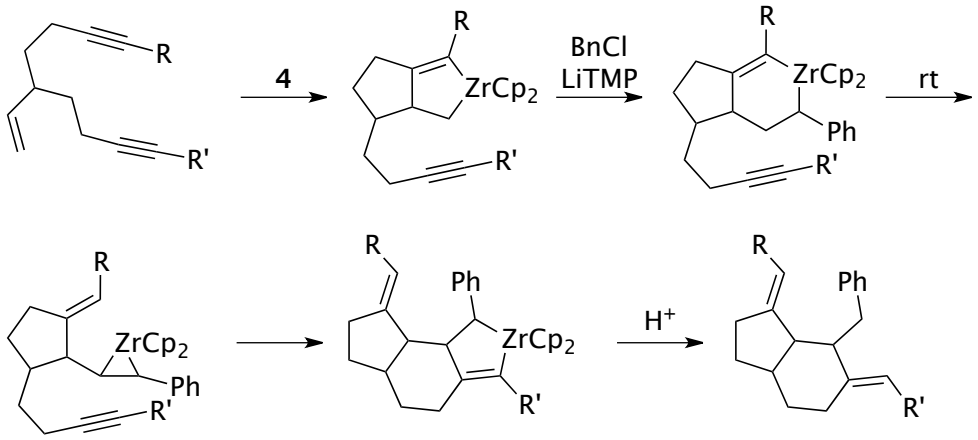
Scheme 40: Attempted synthesis of zirconacycle **76**. *Reagents and conditions:* i. $ZrCp_2Cl_2$, *n*-BuLi (2 eq.), THF, −78 °C → rt, 2 h.

Three conclusions can be drawn from the results obtained with the α-branched system. The first is that formation of the zirconacycle **76** from zirconocene η^2-alkyne complex **77** is reversible, as shown by its disappearance from the gas chromatogram, presumably going on to form dimers. Secondly intramolecular complexation of both alkynes by the zirconium is less favourable than intermolecular complexation of two alkynes, suggesting that the displacement of one alkyne ligand by another is a very slow process. Finally the α-branched alkene is too sterically hindered to be complexed by the zirconium as this was less favoured than intermolecular cyclisation between two alkynes. Norman had

also observed in her work that zirconocene(1-butene) fails to complex such hindered alkenes.[69] In order to overcome the last observation it was decided to instead attempt the tricyclisation with β-branched enediynes.

2.3 β-Branched enediynes

Unlike α-branched substrates which would have formed spirocyclic structures (**Scheme 36**) β-branched substrates should form fused bicyclic structures (**Scheme 41**).



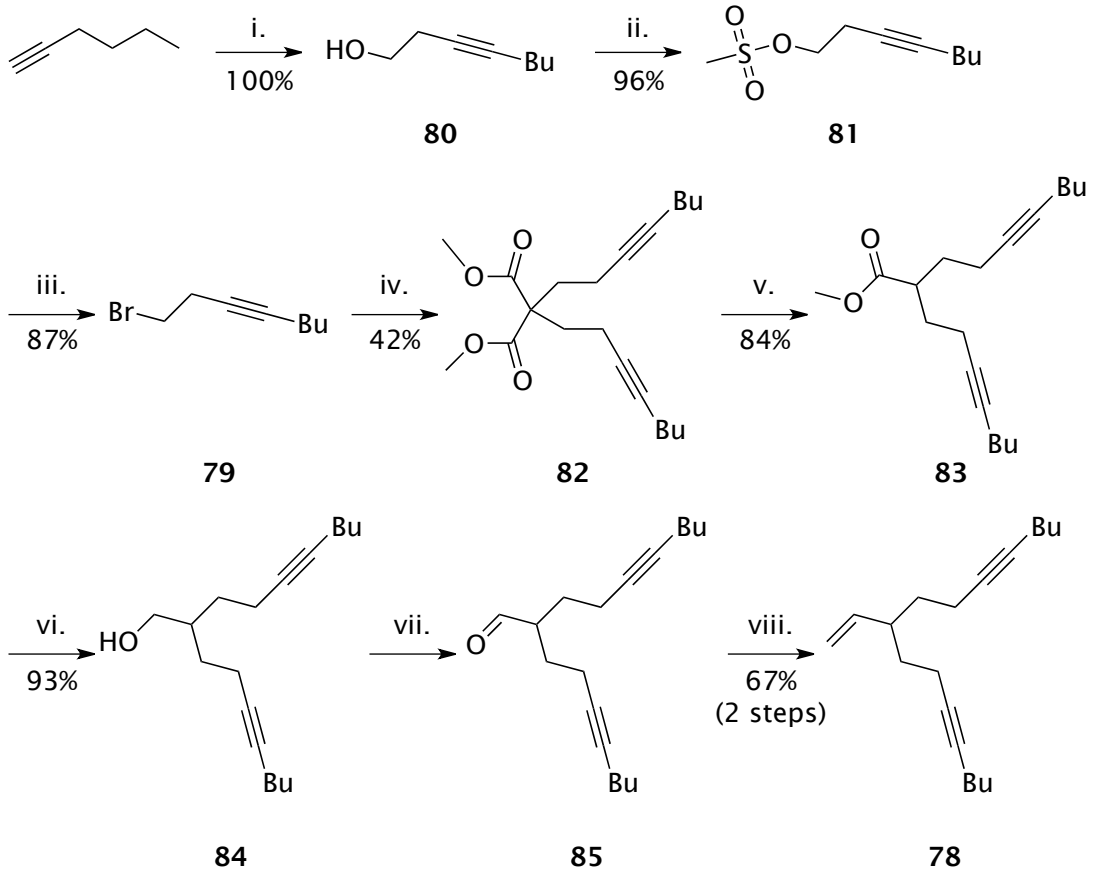
Scheme 41: Synthesis of fused bicyclic structures via the intramolecular trapping of a zirconocene η^2-alkene complex.

One of the problems encountered with cocyclisation of the α-branched enediyne **68** was that no selectivity was observed between the two alkynes. In order to overcome this selectivity problem the first β-branched substrate to be investigated was a symmetrical β-branched enediyne **78**.

2.3.1 Synthesis of the symmetrical β-branched substrate

The eight step synthesis of enediyne **78** (**Scheme 42**) was achieved in an 18% overall yield starting from hex-1-yne. Hex-1-yne was converted to bromide **79** via alcohol **80** and mesylate **81** in almost quantitative yield.[86, 87] Double addition of the bromide **79** to dimethyl malonate was achieved in 42% yield. Elimination of HBr from the bromide **79** to give the corresponding enyne was the main reason for the low yield of this step. Some mono alkylated product was also recovered which

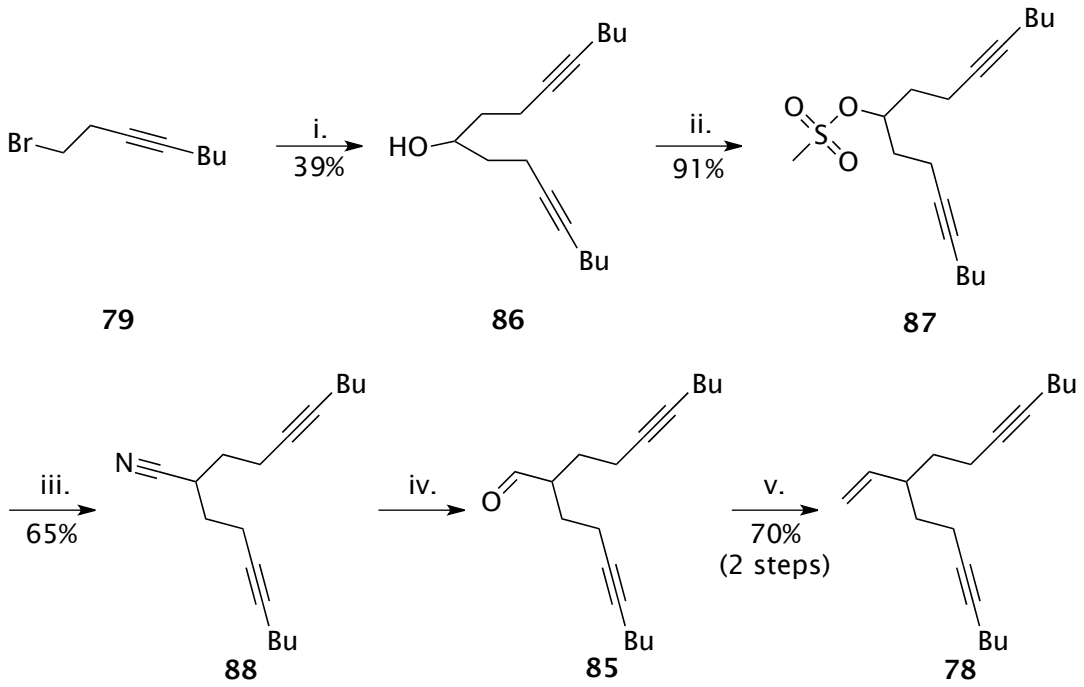
could be further alkylated to increase the yield. Krapcho decarboxylation of the malonate ester **82** was used to give the mono-ester **83**. Reduction of the ester **83** to the alcohol **84**, Swern oxidation to the aldehyde **85** and a simple Wittig reaction gave the desired enediyne substrate **78**.



Scheme 42: Synthesis of enediyne **78**. *Reagents and conditions:* i. *n*-BuLi, THF, ethylene oxide, HMPA, −10 °C, 3 h, rt, overnight; ii Et_3N, MsCl, DCM, −10 °C, 45 mins, rt, 45 mins; iii. LiBr, THF, reflux, 3 h; iv. dimethyl malonate, NaH, DMF, rt, 1 h, bromide **79**, rt, 30 mins, NaH, rt, 1 h, bromide **79**, 80 °C, 3 h, rt, overnight, NaH, rt, 1 h, bromide **79**, 80 °C, 3 h; v. DMSO, water, LiCl, 160 °C, 5 h; vi. $LiAlH_4$, THF, 0 °C, 30 mins, rt, 2 h; vii. DMSO, DCM, $(COCl)_2$, alcohol **84**, Et_3N, −60 °C, 15 mins, rt, 1 h; viii. *n*-BuLi, $MePPh_3Br$, THF, −20 °C, 30 mins, aldehyde **85**, −78 °C, 30 mins, rt, 45 mins.

Other routes were investigated to avoid the low yielding double addition to dimethyl malonate. The use of malononitrile and ethylcyanoacetate rather than dimethyl malonate was attempted as the steric hindrance around the anion was reduced making addition more favourable than elimination. No significant increase in yield was seen with either nitrile. A route involving the use of the corresponding Grignard of bromide **79** was investigated (**Scheme 43**). Double addition of the Grignard to ethyl formate afforded alcohol **86** in 39% yield which

was easily converted to the mesylate **87** in 91% yield. Cyanide displacement of the mesylate to give nitrile **88** was achieved in 65% yield. DIBAL-H reduction gave aldehyde **85** in 93% yield. The Grignard step was comparable in yield to the double addition to dimethyl malonate; however, the Grignard step was far more reliable as yields were consistently above 30% while the double addition to dimethyl malonate had been as low as 11%. The drawback of the Grignard route was the relatively poor yield of the cyanide displacement. This second low yielding step resulted in an overall yield from the homopropargylic bromide **79** to aldehyde **85** of 22% while the malonate route achieved this conversion in 29% yield.

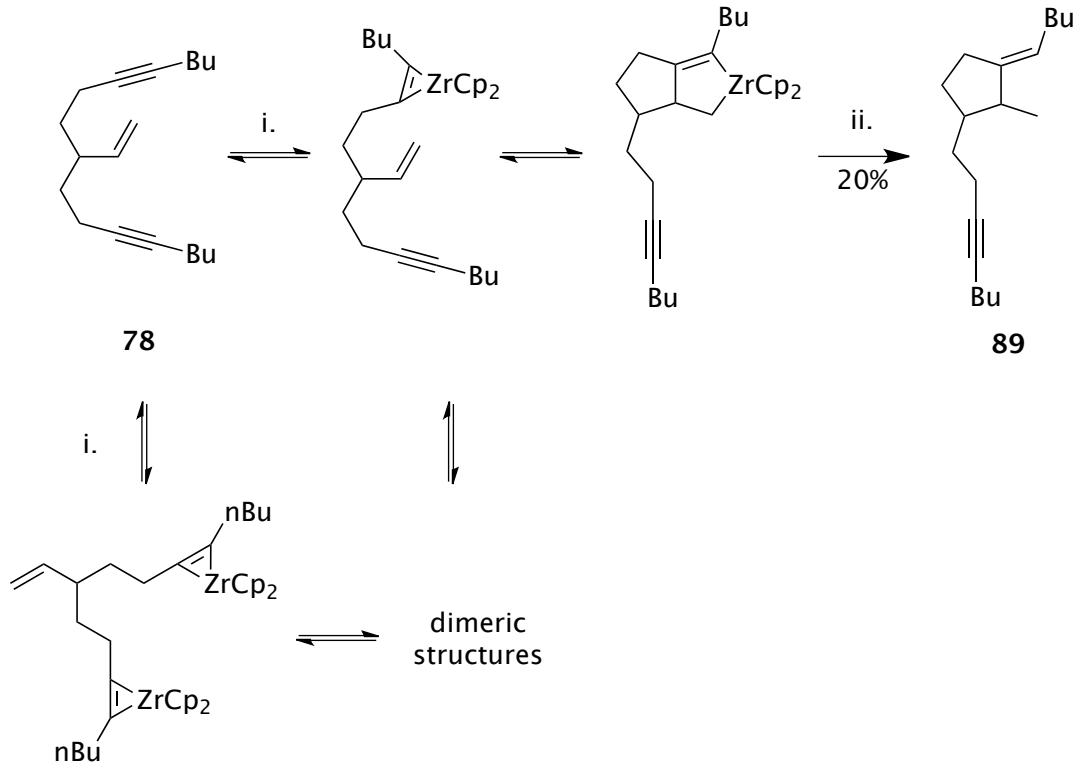


Scheme 43: Alternative synthesis of enediyne **78**. *Reagents and conditions:* i. Mg turnings, rt, overnight, I_2, THF, 1,2-dibromoethane, bromide **79**, reflux, 2 h, ethyl formate, rt, 3 h; ii. Et_3N, MsCl, DCM, −20 °C, 45 mins, rt, 2 h; iii. KCN, DMF, 65 °C, 24 h; iv. DIBAL-H, THF, −78 °C, rt, 2 h; v. *n*-BuLi, $MePPh_3Br$, THF, −20 °C, 30 mins, aldehyde **85**, −78 °C, 30 mins, rt, 45 mins.

2.3.2 Tricyclisation of the symmetric β-branched substrate

The initial zirconocene mediated cocyclisation to form cyclopentane **89** was achieved in 20% yield (**Scheme 44**). In addition to this the ^1H spectrum of the product mixture also contained several new peaks in the region between 4.90 ppm and 5.70 ppm. Given the large number of multiplets in this region it

can be postulated that dimerisation of the starting enediyne **78** was occurring. Starting enediyne **78** was also recovered from the reaction mixture giving evidence of two molecules of zirconocene(1-butene) being complexed by a single molecule of enediyne **78**.



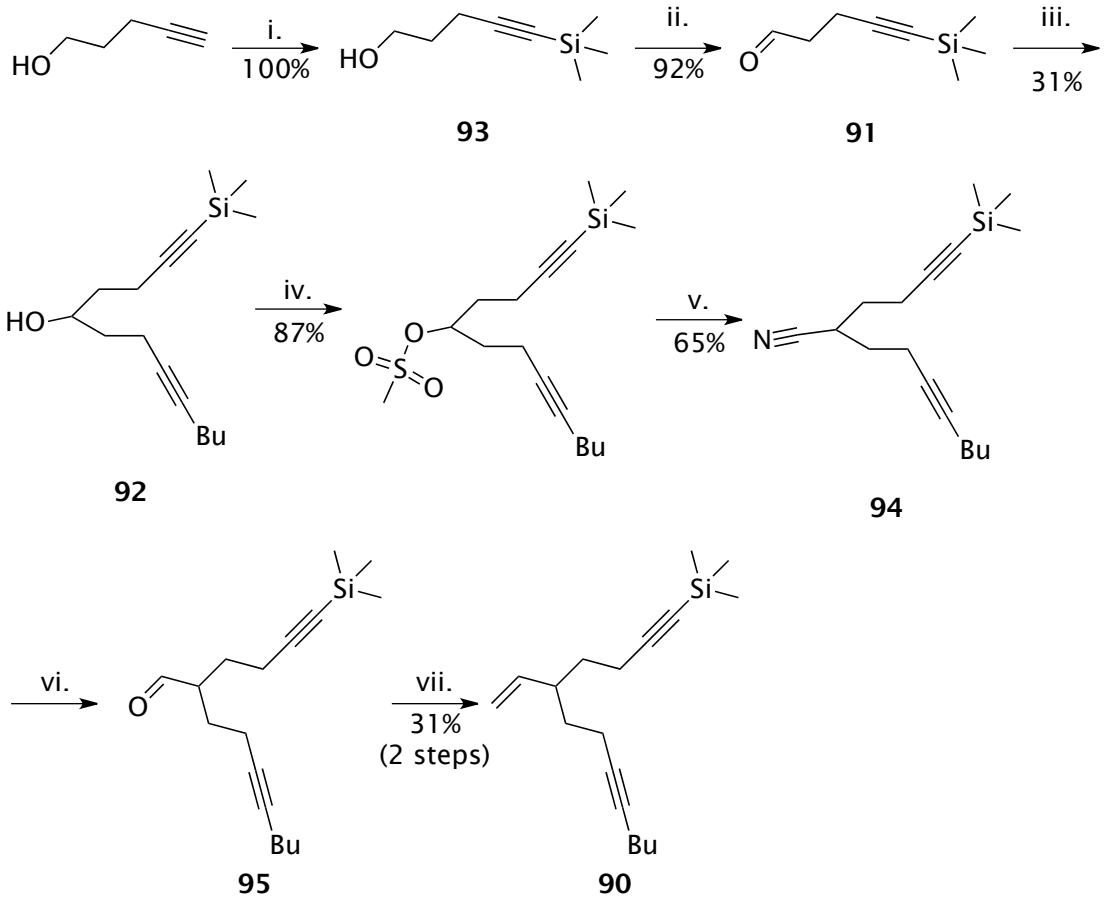
Scheme 44: Zirconocene mediated cocyclisation of enediyne **78**. *Reagents and conditions:* i. $ZrCp_2Cl_2$, *n*-BuLi (2 eq.), THF, −78 °C → rt, 2 h; ii. MeOH, sat. aq. $NaHCO_3$, rt, 8 h.

2.3.3 Asymmetric β-branched system

In order to overcome the problem of both alkynes within a single enediyne being complexed by two molecules of zirconocene(1-butene) some differentiation between the alkynes was needed. Trimethylsilyl substituted alkynes have been observed to be complexed much slower by zirconocene(1-butene) than alkyl substituted alkynes.[88] It was envisaged that asymmetric enediyne **90**, which has one alkyl substituted alkyne and one trimethylsilyl substituted alkyne would show enough differentiation between the alkynes.

2.3.3.1 Synthesis of the asymmetric β-branched substrate

Although the Grignard route to enediyne **78** had a lower yield than the malonate route it did provide an easier route for the synthesis of asymmetric enediyne substrates such as enediyne **90**. This route involved the conversion of bromide **79** to the corresponding Grignard before reaction with aldehyde **91** to give alcohol **92** in 31% yield. Aldehyde **91** was synthesised in 92% yield by Swern oxidation of alcohol **93** which had been prepared quantitatively by the reaction of deprotonated 4-pentyn-1-ol with trimethylsilyl chloride (**Scheme 45**).



Scheme 45: Synthesis of enediyne **90**. *Reagents and conditions:* i. *n*-BuLi (2 eq.), TMSCl, −78 °C, rt, 18 h; ii. DMSO, DCM, $(COCl)_2$, Et_3N, −60 °C, 15 mins, rt, 1 h; iii. Mg turnings, rt, overnight, I_2, THF, 1,2-dibromoethane, bromide **79**, reflux, 2 h, bromide **79**, rt, 3 h; iv. Et_3N, MsCl, DCM, −20 °C, 45 mins, rt, 2 h; v. KCN, DMF, 65 °C, 24 h; vi. DIBAL-H, THF, −78 °C, rt, 2 h; vii. *n*-BuLi, $MePPh_3Br$, THF, −20 °C, 30 mins, aldehyde **95**, −78 °C, 30 mins, rt, 45 mins.

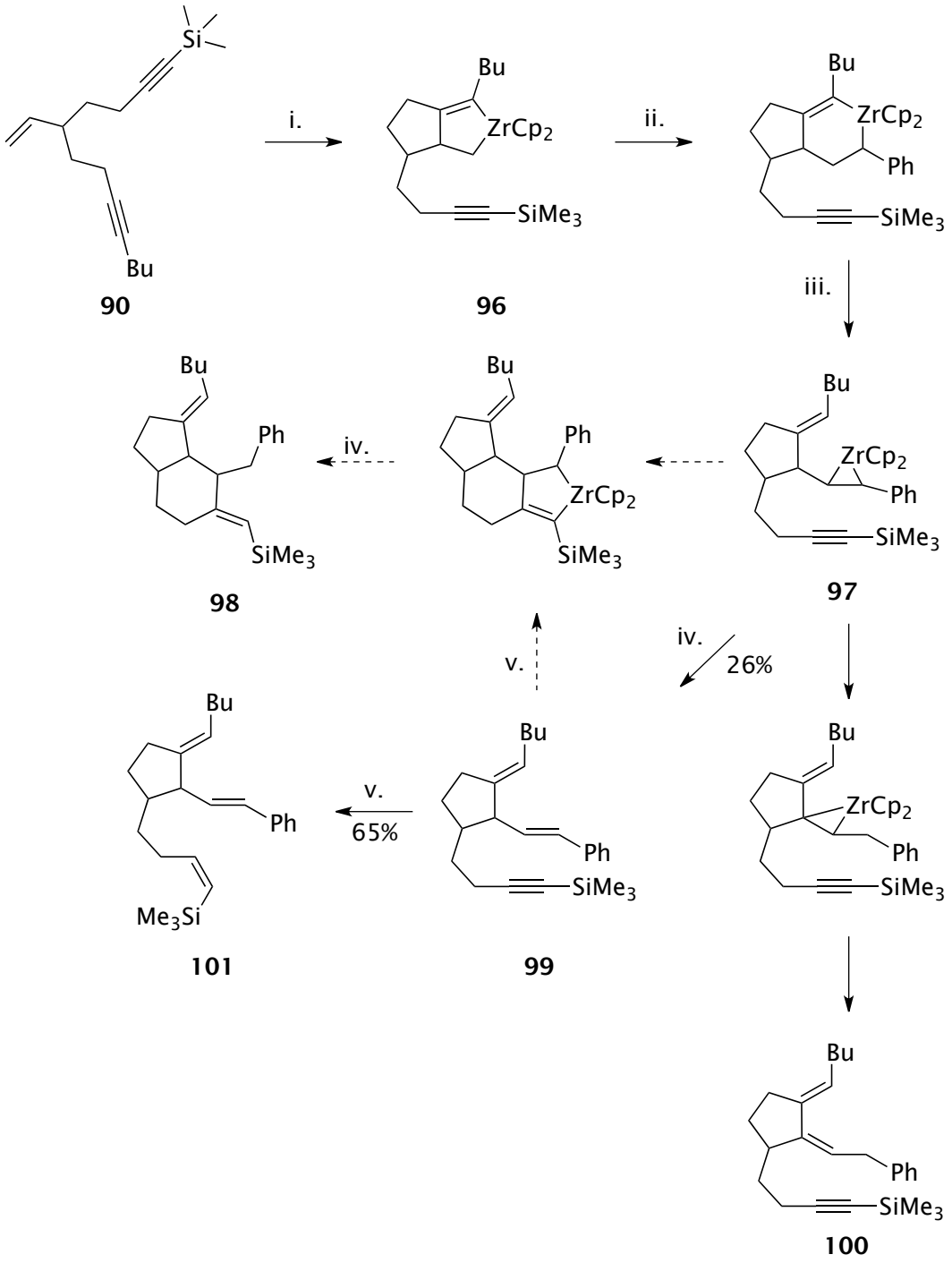
Alcohol **92** was converted to enediyne **90** in exactly the same manner as before with an overall yield of 17% from alcohol **92**. The two step reduction of nitrile **94** and a Wittig reaction of the resulting aldehyde **95** with

methyltriphenylphosphonium bromide was achieved in 31% yield. Given the previously high yields of similar Wittig reactions this was unexpected. The poor yield is thought to be attributable to the incomplete hydrolysis of the imine intermediate to aldehyde **95** in the DIBLAL-H reduction of the nitrile **94**. The ^{1}H NMR spectrum showed the ratio of imine to aldehyde **95** present to be 1:0.59, this ratio is calculated based on the imine doublet at 7.48 ppm and the aldehyde doublet at 9.72 ppm.

2.3.3.2 Tricyclisation of the asymmetric β-branched substrate

The cyclisation of enediyne **90** was achieved with some success (**Scheme 46**). Initial cocyclisation to form zirconacycle **96**, benzyl carbenoid insertion and endocyclic cyclometallation to give zirconocene η^2-alkene complex **97** were successful. Unfortunately, zirconocene η^2-alkene complex **97** did not undergo the desired intramolecular trapping with the pendant alkyne to give bicyclic compound **98**. After quenching the reaction mixture a mixture of cyclopentanes **99** and **100** were recovered. HPLC separation of the two cyclopentanes gave cyclopentane **99** in 26% yield. Cyclopentane **100** could not be isolated as a pure compound but the triplet at 5.05 ppm in the ^{1}H NMR spectrum gave strong evidence that migration of the double bond had occurred with the triplet occurring due to coupling to the new methylene group adjacent to the phenyl group.

It was envisaged that treatment of cyclopentane **99** with zirconocene(1-butene) would give the desired cyclised product **98**. Unfortunately triene **101** was obtained in 65% yield. Unfortunately the trimethylsilyl group that was used to give alkyne selectivity in the first cyclisation has made the second cyclisation far less favourable as well and so the cyclisation did not occur.



Scheme 46: Attempted synthesis of bicyclic compound **98**. *Reagents and conditions:* i. $ZrCp_2Cl_2$, *n*-BuLi (2 eq.), THF, −78 °C → rt, 2 h; ii. BnCl, LiTMP, THF, −78 °C; iii. rt, 18 h; iv. MeOH, sat. aq. $NaHCO_3$, rt, 8 h; v. $ZrCp_2Cl_2$, *n*-BuLi (2 eq.), THF, −78 °C → rt, 2h, MeOH, sat. aq. $NaHCO_3$, rt, 14 h.

2.4 Conclusions

The synthesis of three novel enediynes has been achieved. Two of the enediynes underwent a series of undesired intermolecular dimerisations when treated with Negishi's reagent. The final enediyne bearing a trimethylsilyl substituted pendant alkyne successfully underwent the desired zirconocene mediated cocyclisation, benzyl carbenoid insertion and rearrangement to the zirconocene η^2-alkene complex. Unfortunately the trapping of the resultant η^2-alkene complex with the pendant alkyne was unsuccessful. This is postulated to be due to the reduced reactivity of the trimethylsilyl substituted alkyne that is needed in the system to give selectivity in the initial cocyclisation.

Chapter 3 Synthesis of ligands for orphan nuclear receptors

3.1 Background to the research area

Nuclear receptors are one of the largest families of ligand dependent transcription factors and are divided into seven subfamilies (NR0–NR6).[89] Nuclear receptors contain four distinct structural domains; the ligand independent activation domain or A/B domain at the amino terminus, the conserved zinc finger DNA binding domain (DBD), a flexible hinge linker and the ligand binding domain (LBD) which is associated with the second activation domain (AF2) at the carboxy terminus (**Figure 2**).[90] The LBD serves as a molecular switch that recruits coactivator proteins and activates the transcription of target genes when flipped into the active conformation by hormone binding. The integration of the different domains within the receptor results in the specificity of the hormonal response.[91]

Figure 2: Structural domain of the NR superfamily.

Nuclear receptors play an important role in many processes including cell proliferation, differentiation and cellular homeostasis.[92] Due to their importance in human biology both nuclear receptors and their ligands have become important targets for drug discovery.[93] Compounds such as vitamin D, thyroid hormones and retinoic acid are known to be natural ligands for nuclear receptors.[94] Half of the nuclear receptor family were originally termed orphan nuclear receptors (ONR's) as no natural ligand was known for them. Since then ligands for several ONR's have been discovered and these receptors have been referred to as adopted orphans.[95] Examples of adopted orphans include NR1H4 and the NR1C series.[96, 97] An entirely new approach termed reverse endocrinology was used to describe the search for either synthetic or natural ligands for these receptors.[91] As well as large scale screening of available compounds to find ligands, more

selective design based approaches using the crystal structures of the ligand binding domain have been successful.[98]

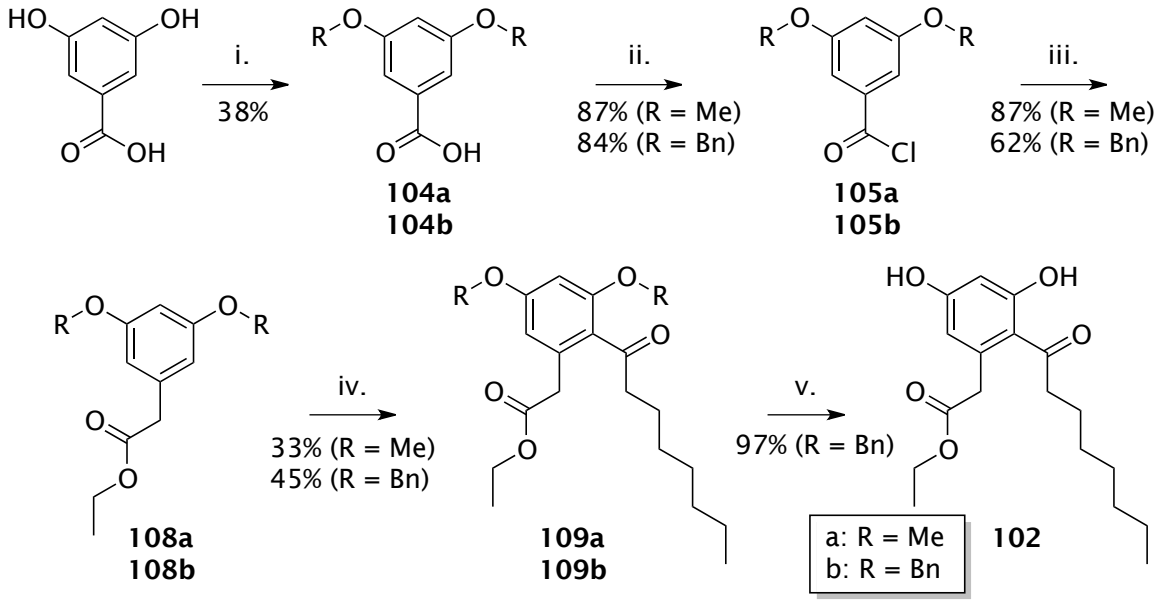
Our interest in ONR's stems from the discovery in a high throughput screen that substituted cis-bicyclo[3.3.0]-oct-2-enes, synthesised by means of an organozirconium intermediate, were identified as ligands for ONR's LRH-1 and SF-1, both of which are members of the NR5A subfamily of NR's.[99] Further work in the area developed compounds that were selective for either LRH-1 or SF-1 as well as overcoming the acid sensitivity of the original compounds.[100] Work in this area of research was intended to be continued in collaboration with Prof. Neil Hanley within the School of Medicine at the University of Southampton, however, his relocation resulted in a change of collaborator to Dr Surinder Sahota whose research was more interested in the NR4A subfamily of NR's.

The three members of the NR4A subfamily are Nur77, Nurr1 and NOR1. Nur77 has been shown to be required for T-cell receptor mediated apoptosis,[101, 102] Nurr1 is essential for dopaminergic cell development[103] and both Nurr77 and NOR1 have a critical role in glucose homeostasis.[95] Expression of members of the NR4A subfamily of NR's has also been observed in renal cell cancer which Dr Surinder Sahota has an interest in.[104] As a result the aim of this part of the project was to synthesise compounds that had been shown to act as ligands for members of the NR4A subfamily and test their ability to stimulate a response from the NR4A receptors which subsequently either promote or inhibit cell proliferation of the renal cell cancer line 769-P.[105] Two ligands were initially chosen based on their reported role as ligands for members of the NR4A subfamily as well as their straightforward syntheses. Cytosporone B (**102**) has been identified as an agonist for Nur77 while the benzimidazole based ligand **103** has been identified as an agonist for Nurr1.[106, 107]

3.2 Synthesis of the NR4A ligands

3.2.1 Cytosporone B synthesis

Initially a four step synthesis of cytosporone B (**102**) was devised starting from 3,5-dimethoxybenzoic acid (**104a**) (**Scheme 47**). The initial conversion of 3,5-dimethoxybenzoic acid (**104a**) to the acid chloride **105a** was achieved in quantitative yield using thionyl chloride.[108]



Scheme 47: Synthesis of cytosporone B (**102**). Reagents and conditions: i. BnBr, K_2CO_3, acetone, reflux, 24 h, KOH, EtOH, water, reflux, 25 h; ii. $SOCl_2$, pyridine, benzene, reflux, 1 h; iii. CH_2N_2, Et_2O, rt, 3 h, Ag_2O, EtOH, reflux, 2 h; iv. octanoic anhydride, $HClO_4$, rt, 4 h; v. 5% Pd/C, H_2, EtOH, rt, 1 h.

The second step in the synthesis was the use of diazomethane to form a diazoketone **106a** which underwent a silver catalysed Wolff-Rearrangement using ethanol to trap the ketene intermediate **107a** forming arene **108a** in 87% yield (**Figure 3**).[109]

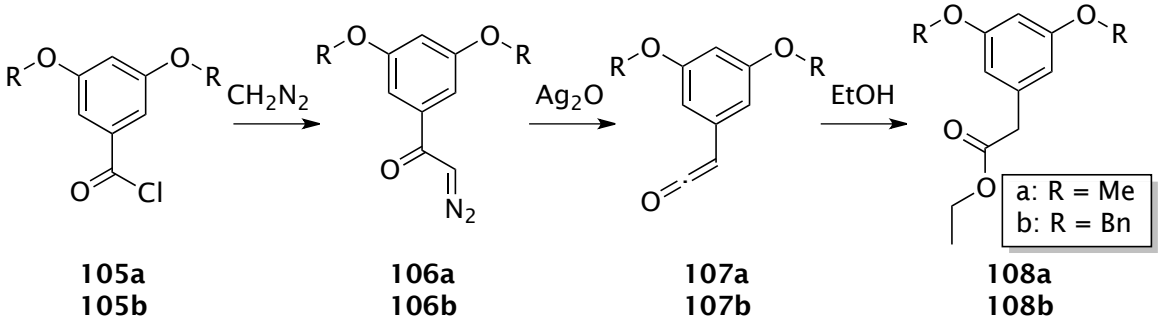


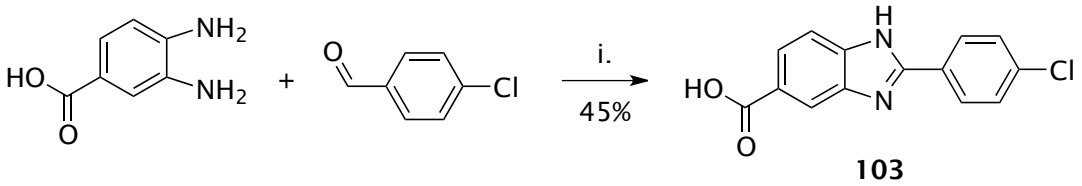
Figure 3: Intermediates formed in the Arndt-Eistert synthesis of heteroarene **108**.

Friedel-Crafts acylation of arene **108a** was achieved with octanoic anhydride and acid catalysis in 33% yield. Friedel-Crafts acylation using octanyl chloride was unsuccessful with both aluminium chloride and perchloric acid catalysis. Interestingly Friedel-Crafts acylation using octanoic anhydride was unsuccessful in toluene, despite literature precedence, although it was successful when carried out neat.[110] The final step in the synthesis of cytosporone B (**102**) required the deprotection of the methyl ethers of 3,5-dimethoxycytosporone B (**109a**). Unfortunately the deprotection was unsuccessful as the use of acidic reagents, such as BBr_3, resulted in an undesired intramolecular aldol reaction. As a result benzyl protecting groups were used instead as they could be easily removed under neutral conditions. This new route (**Scheme 47**) added an extra step as the benzyl ether protected 3,5-dihydroxybenzoic acid **104b** was unavailable commercially unlike the methyl ether **104a**.

The protection of the hydroxyl groups of 3,5-dihydroxybenzoic acid as benzyl ethers was achieved in 38% yield.[111] The next three steps in the synthesis; conversion to the acid chloride,[112] Wolff rearrangement and Friedel-Crafts acylation were completed in 23% for three steps compared with the methyl ether route which completed these steps in 29%. The hydrogenation of 3,5-dibenzyloxycytosporone B (**109b**) successfully yielded cytosporone B (**102**) in 97% yield.

3.2.2 Synthesis of a benzimidazole based ligand

The second NR4A ligand to be synthesised was the benzimidazole based ligand **103**. This was successfully synthesised in a one step reaction (**Scheme 48**) based on a procedure by Bahrami.[113] Other literature methods that included heating the two components in nitrobenzene, DMF or in the presence of ammonium acetate were attempted in order to increase the yield but in each case the product could not be obtained pure.[107, 114, 115]



103

Scheme 48: Synthesis of the benzimidazole based ligand **103**. *Reagents and conditions:* i. 30% aq. H_2O_2, 36% aq. HCl, MeCN, rt, 2 h.

3.3 Biological testing of NR4A ligands

3.3.1 Cell proliferation assays

If either cytosporone B (Cyt B) or the benzimidazole based compound (Nurr1) do act as ligands for NR4A receptors and these receptors are expressed in renal cell cancer then you would expect the level of proliferation of the 769-P cells to be different from that of unstimulated cells. In order to test this a series of cell proliferation assays were undertaken.

In order to accurately measure the level of cell proliferation the cells were treated with tritiated thymidine so that new cells forming would incorporate the tritiated thymidine into their DNA. The number of cells present can then be estimated relative to each other using a scintillation counter which measures the fluorescence given off by the cells when treated with scintillation fluid as when tritium decays it fluoresces. This technique was used with three different concentrations of cells and two different concentrations of ligands. Neither of the two compounds were water soluble and so had to be added as solutions in DMSO. In order to negate the effects of the DMSO extra wells were treated with two different volumes of neat DMSO. The volume of DMSO added was equivalent to the volume of DMSO used for each concentration of the ligands.

The first assay was conducted with a cell concentration of 2×10^4 cells per well (**Figure 4**). As can be seen both ligands can be seen to increase cell proliferation against the unstimulated cells, however, the effect over that of neat DMSO is low. There is very little difference in this assay between the two concentrations of ligands.

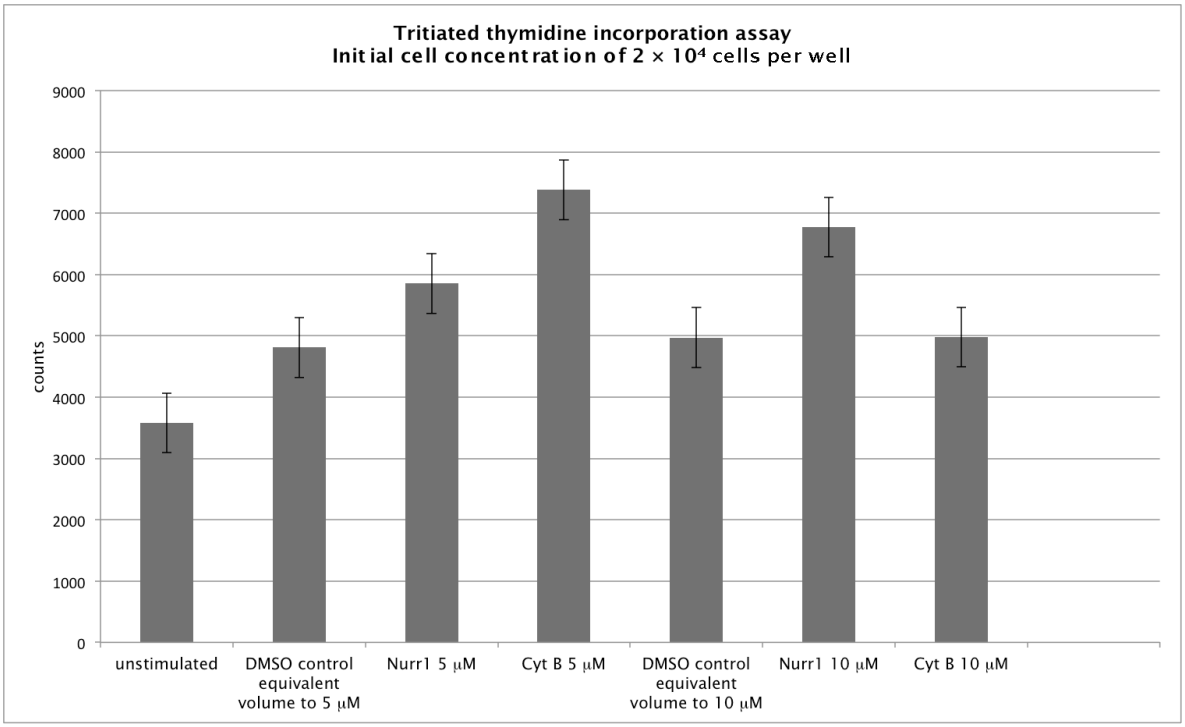


Figure 4: Relative cell numbers observed for 769-P cell line treated with cytosporone B (Cyt B) and the benzimidazole based ligand (Nurr1) at a cell concentration of 2 x 10^4 cells per well.

The second assay was conducted with a cell concentration of 4 × 10^4 cells per well (**Figure 5**). A very modest reduction in cell proliferation was observed with both cytosporone B and the benzimidazole based ligand over the effect of DMSO at a cell concentration of 4 x 10^4 cells per well. Once again the concentration of the ligand did not show any difference. The third assay was carried out with a cell concentration of 8 × 10^4 cells per well (**Figure 6**). No significant difference in cell proliferation between the unstimulated and stimulated cells was observed. It is possible that more of an effect is observed at a cell concentration of 2 × 10^4 cells per well as the low concentration of cells may magnify the effect of the inherent error in the assay leading to distorted results.

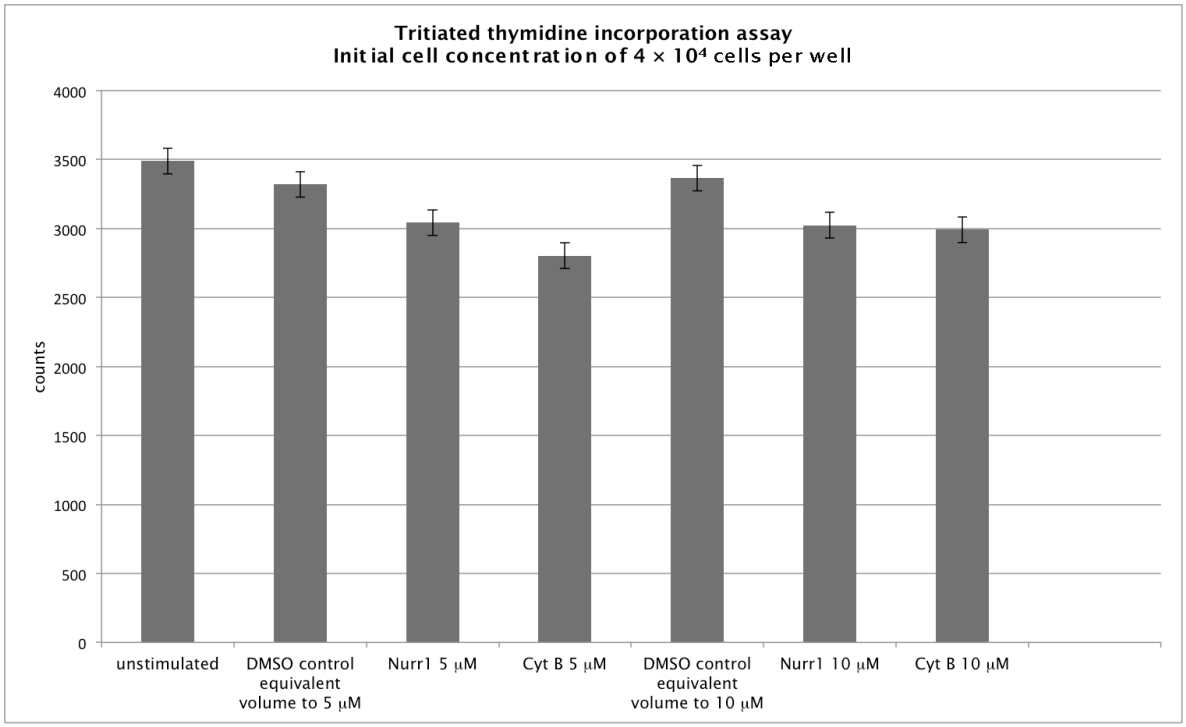


Figure 5: Relative cell numbers observed for 769-P cell line treated with cytosporone B (Cyt B) and the benzimidazole based ligand (Nurr1) at a cell concentration of 4 x 10^4 cells per well.

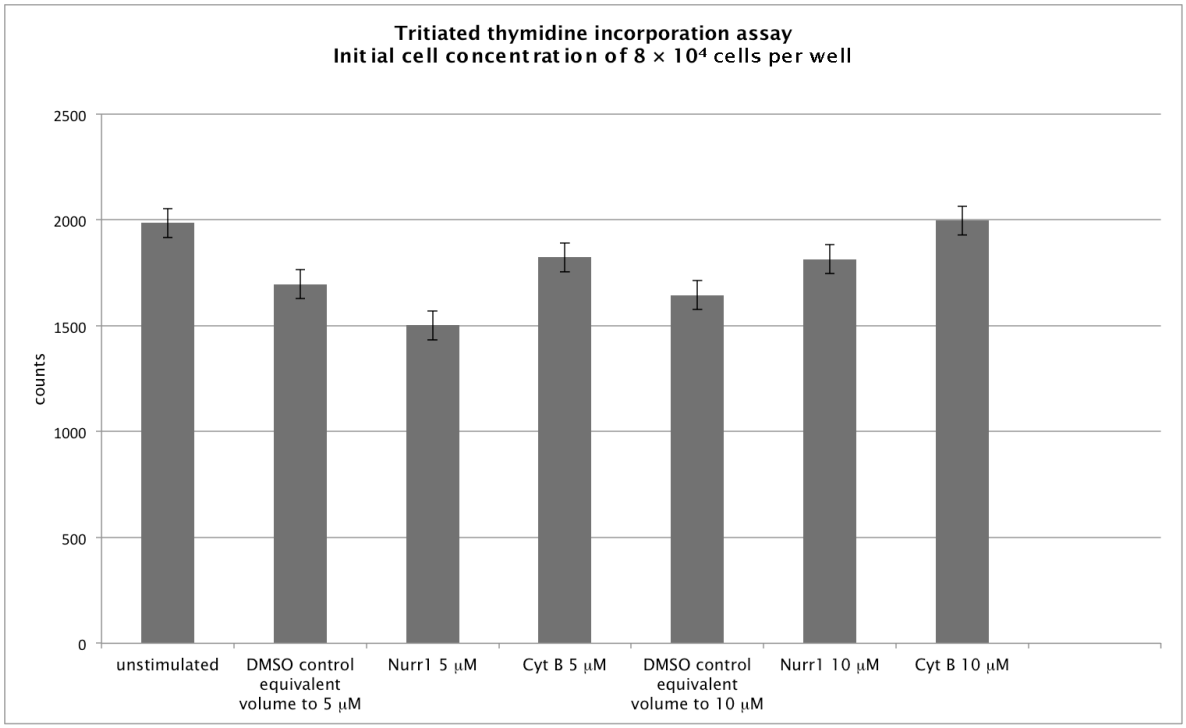


Figure 6: Relative cell numbers observed for 769-P cell line treated with cytosporone B (Cyt B) and the benzimidazole based ligand (Nurr1) at a cell concentration of 8 x 10^4 cells per well.

3.3.2 Flow cytometry assays

The tritium incorporation assay has the limitation that it relies on averaging to produce a meaningful result. Flow cytometry has the advantage that it allows you to measure the physical and chemical characteristics of each individual cell.[116] Two assays were conducted using flow cytometry, the first looked at the granularity and size of the cells while the second studied apoptosis.

The first assay plotted cells dependent on their side scatter channel (SSC) and forward scatter channel (FSC). In order to remove results caused by debris, cells were gated into regions according to their size and granularity, this allowed the percentage of cells found to be either living or dead to quantified (**Figure 7** and **Figure 8**).

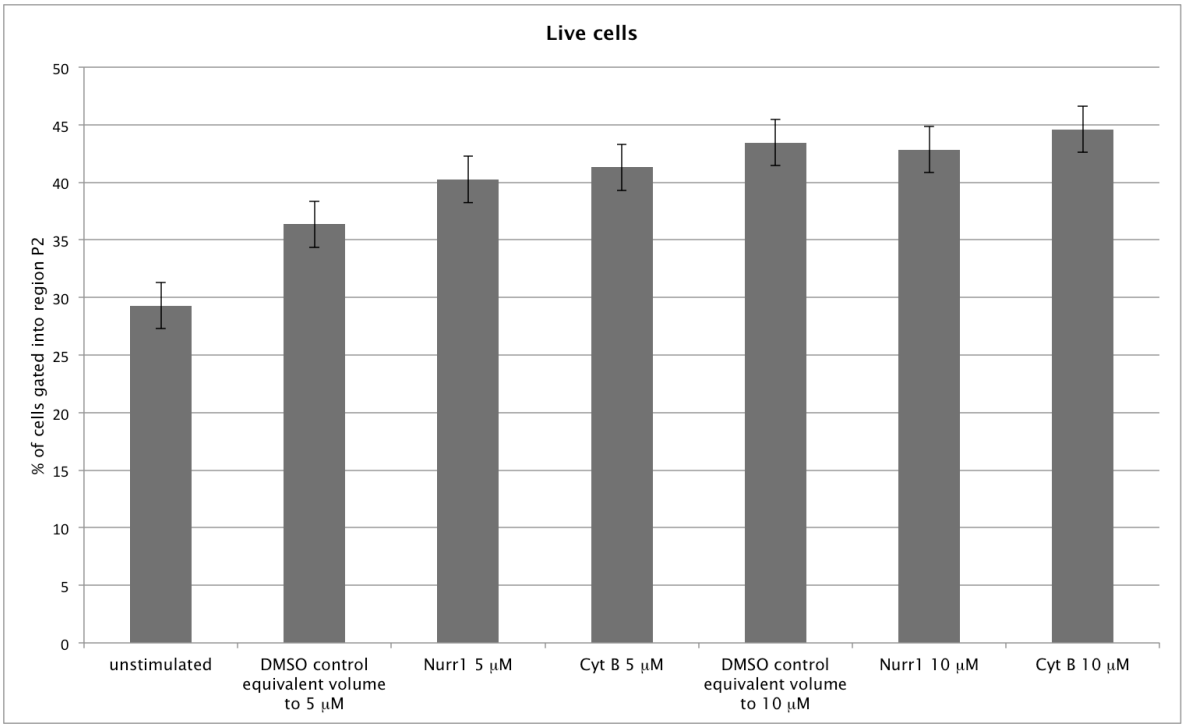


Figure 7: Percentage of cells gated into region P2 showing characteristic granularity and size of live cells.

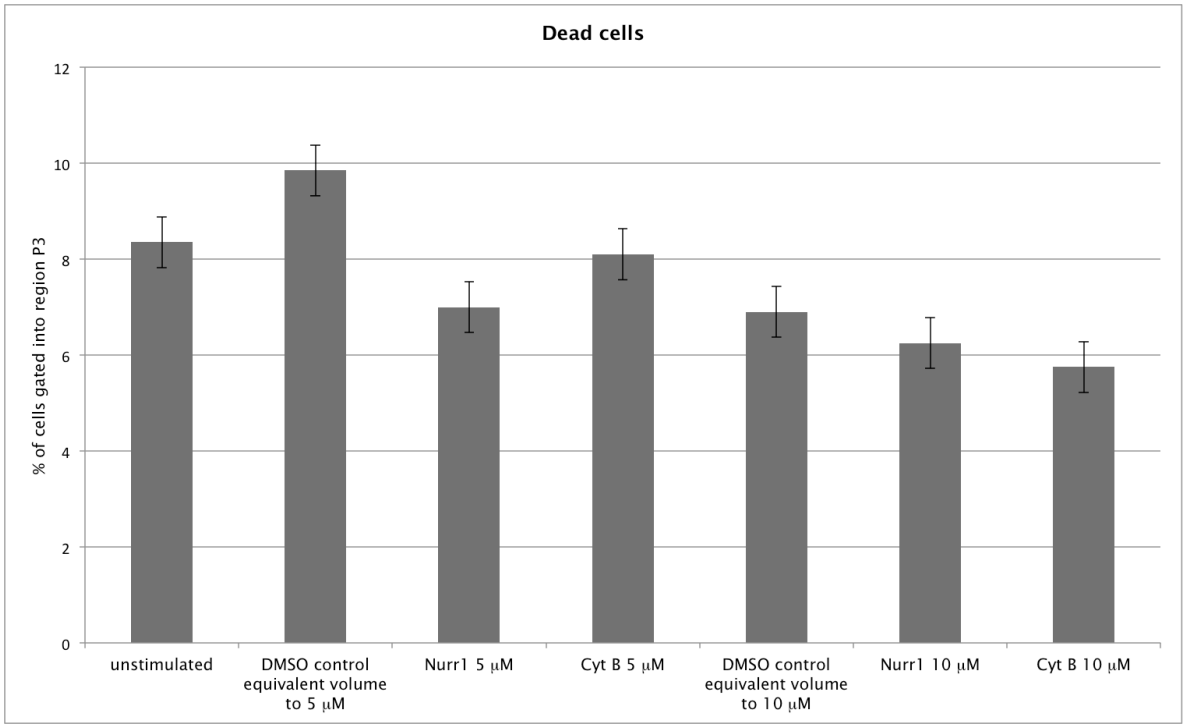


Figure 8: Percentage of cells gated into region P3 showing characteristic granularity and size of dead cells.

When the cells were treated with both cytosporone B (Cyt B) and the benzimidazole based ligand (Nurr1) the number of living cells was seen to increase (**Figure 7**) with a corresponding drop in the number of dead cells (**Figure 8**). As with the previous assays, however, the difference is also observed when the cells are treated with DMSO alone.

The second assay using flow cytometry was used to look for apoptosis. During apoptosis phosphatidylserine moves from within the membrane to the surface of the cell.[117] Annexin V preferentially binds to negatively charged phospholipids such as phosphatidylserine and so this binding can be used as a marker for apoptosis.[118] Fluorescein isothiocyanate (FITC)-labelled annexin V allows for quantification of apoptotic cells.[119] Combining this with a propidium iodide (PI) stain which is an indicator of cell membrane integrity allows distinction between late and early apoptosis.[120] The positive and negative responses to both of these stains allow the sorting of cells into one of four quadrants. When a cell is negative to both annexin V and PI it is a viable cell (**Figure 9**). There was an

increase in the number of viable cells against the number of viable unstimulated cells but the effect was also seen when the cells were treated with DMSO alone. Once again the concentration of the ligand did not show any difference.

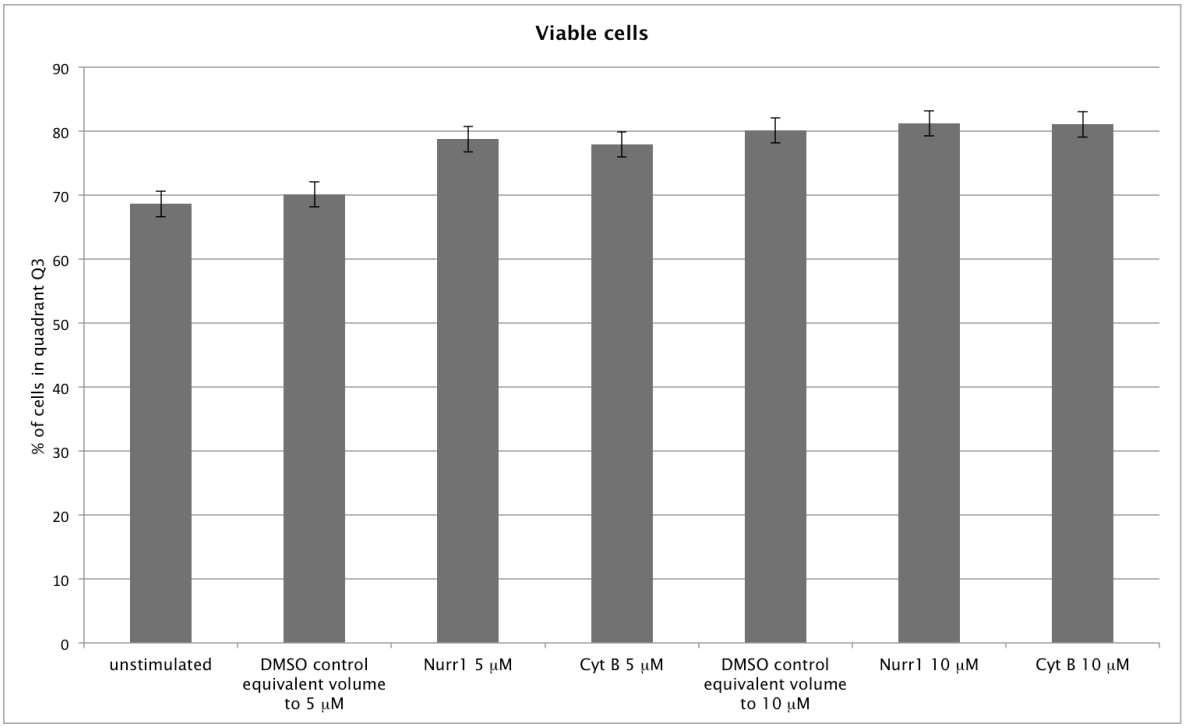


Figure 9: Percentage of cells within quadrant Q3 that are negative to both annexin V and PI, characteristic of viable cells.

Cells which are negative to annexin V but positive to PI are necrotic dead cells (**Figure 10**). The number of necrotic dead cells did drop against those that were unstimulated but once again this can be observed with DMSO alone.

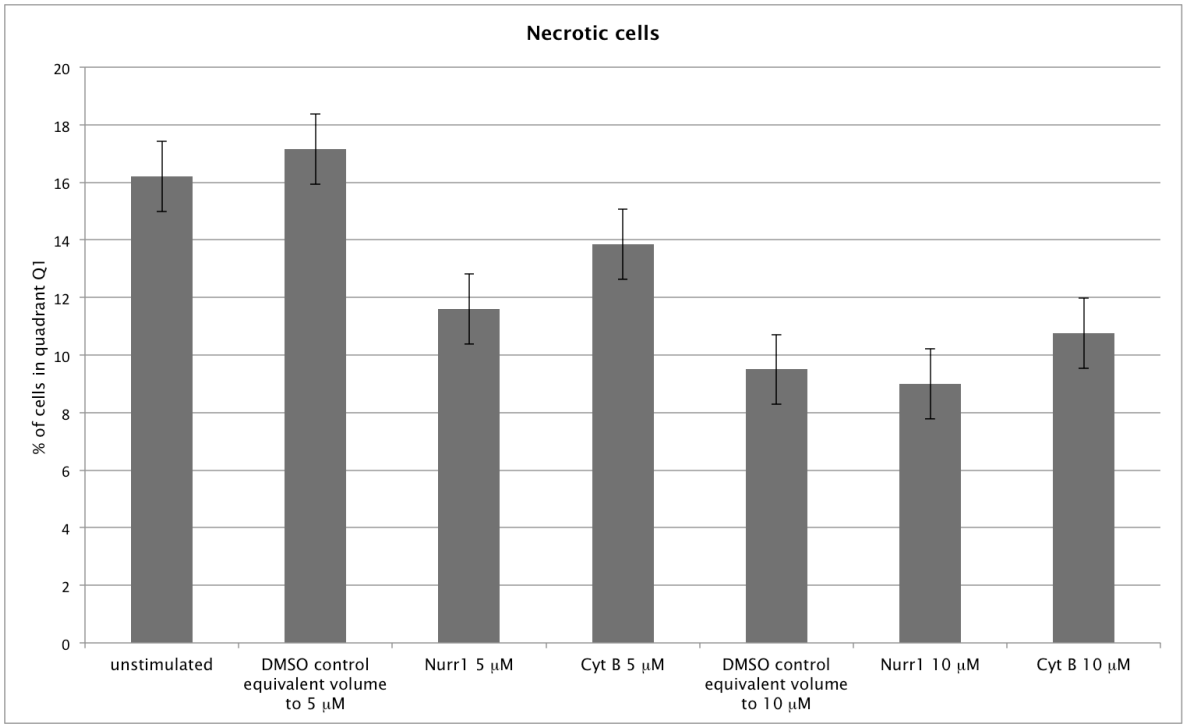


Figure 10: Percentage of cells within quadrant Q1 that are negative to annexin V and positive to PI, characteristic of necrotic dead cells.

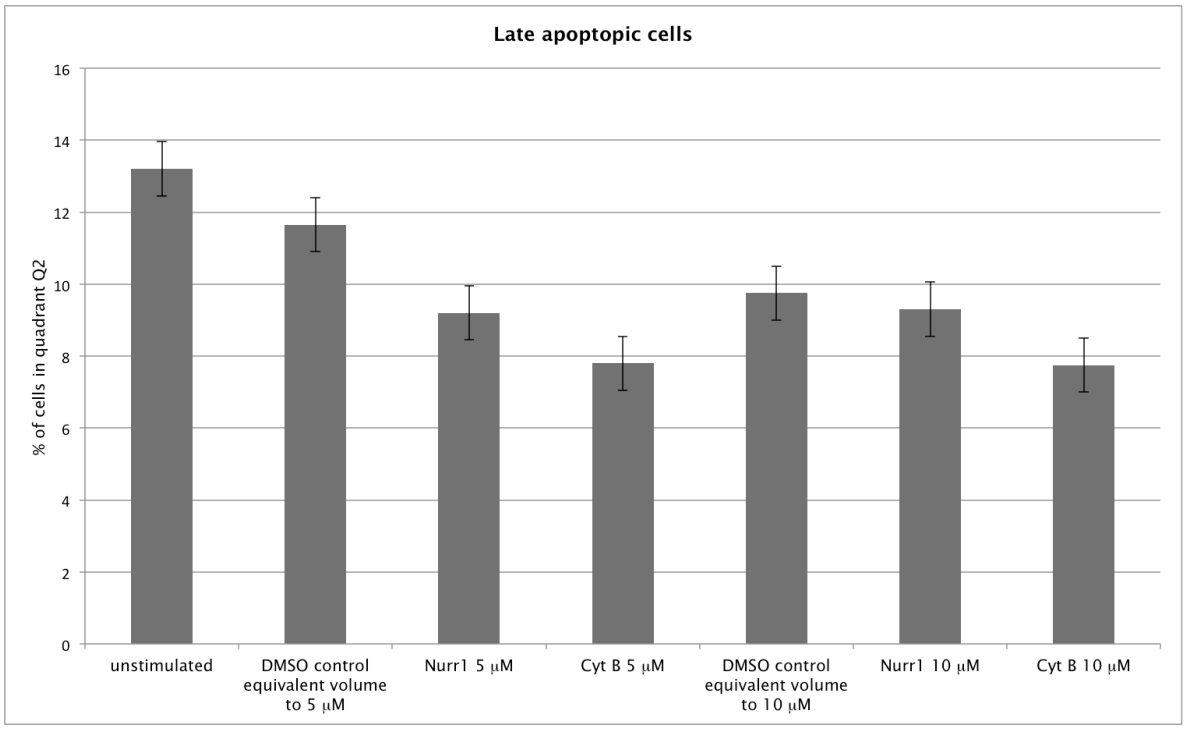


Figure 11: Percentage of cells within quadrant Q2 that are positive to both annexin V and PI, characteristic of late apoptotic cells.

Cells which are positive to both annexin V and PI are late apoptotic dead cells (**Figure 11**). There was a drop in the number of late apoptotic cells when treated with both of the ligands; however, once again the effect is largely mirrored by the effect of the DMSO.

Finally cells which are positive to annexin V but negative to PI are early apoptotic cells (**Figure 12**). There was a dramatic drop in the number of early apoptotic cells over the unstimulated cells at both concentrations of ligands. Unfortunately DMSO appears to account for the bulk of this effect.

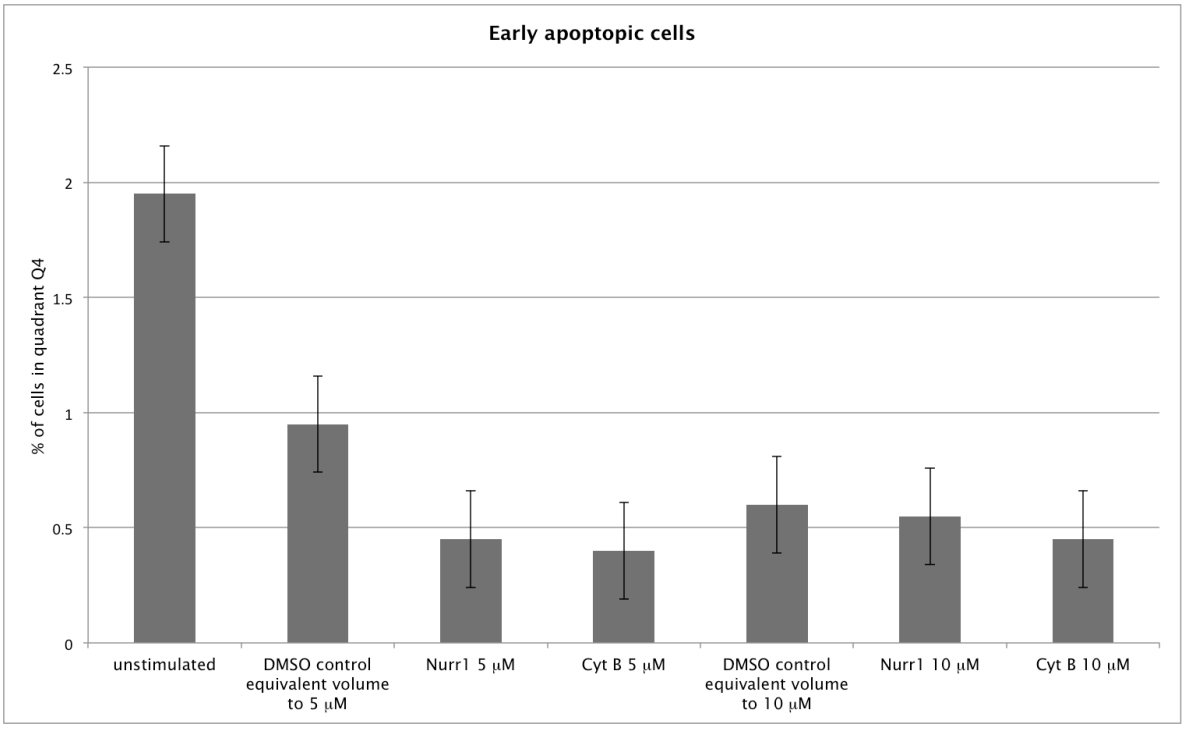


Figure 12: Percentage of cells within quadrant Q4 that are positive to annexin V and negative to PI, characteristic of early apoptotic cells.

The second assay conducted using flow cytometry confirmed the result from the other assays; cell death was reduced by both cytosporone B (Cyt B) and the benzimidazole based ligand (Nurr1) although not to a significantly greater extent than those treated with DMSO alone. The reduced cell death appears evenly spread amongst necrotic cells as well as early and late apoptotic cells.

3.4 Further work

The initial results obtained were encouraging, however, the effect of DMSO appears to account for much of the responses in the assays. In order to confirm this it would be useful to extend this work by either finding ligands which are water soluble or altering the structure of the current ligands to increase their hydrophilicity.

3.5 Conclusions

Two ligands of NR's within the NR4A subfamily have been successfully synthesised. The biological testing of these in a series of assays has also been achieved. The cell proliferation assays showed a moderate reduction in cell proliferation at higher cell concentrations and increased cell proliferation at low cell concentrations. The effect of DMSO accounts for most of these responses. The flow cytometry assays showed a reduction in cell proliferation, although again not significantly greater than with DMSO alone. The difference between the results with different cell concentrations may well be a result of the averaging that is used in the tritium incorporation assay.

Chapter 4 Zirconocene mediated cocyclisations of ynamides

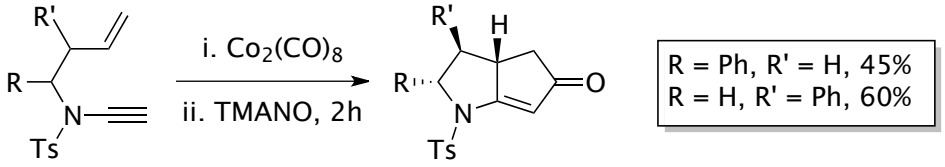
4.1 Background to the research area

As covered in the review chapter (Section 1.2.4) we have previously reported the successful cocyclisation of substrates bearing heteroatoms including those where the heteroatom is adjacent to the alkyne.[31, 121] The cocyclisation of ynamines, however, has shown limited success due to the instability of the cyclised products.[32] This chapter explores the use of ynamides as a solution to the difficulties encountered with ynamines. The reliable cocyclisation of ynamides would offer an easy route to the synthesis of a wide range of nitrogen containing heterocycles where the nitrogen was adjacent to an exocyclic diene.

The first ynamide was synthesised in 1972 by Viehe and the last decade has seen a rapid increase in their utilisation in synthesis, particularly in transition metal mediated reactions.[122, 123] This renewed interest may in part be due to the expanding number of synthetic routes to ynamides.[124-135]

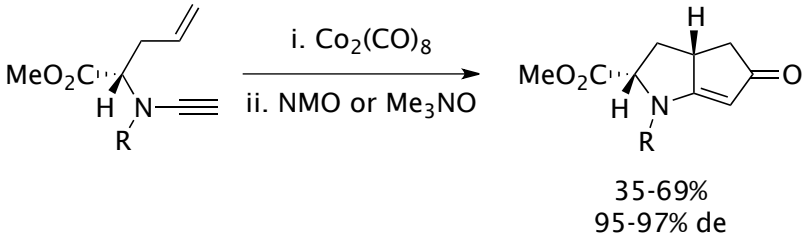
4.1.1 Transition metal mediated reactions of ynamides

Witulski was one of the first to apply established transition metal cyclisations to ynamides. He first utilised ynamides for a series of intramolecular [2+2+1] cycloadditions mediated by dicobalt octacarbonyl (**Scheme 49**).[124] The cycloaddition was achieved in yields of 40-60% and with complete diastereoselectivity.



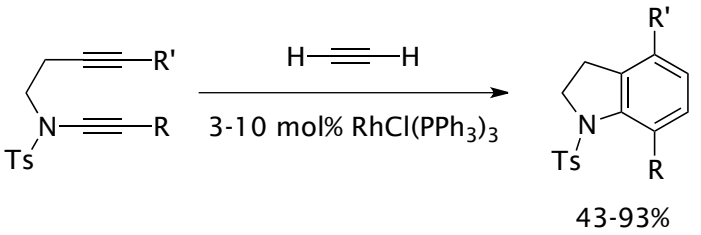
Scheme 49: Witulski's intramolecular [2+2+1] cycloadditions.

Witulski successfully extended this work to an optically enriched ynamide and different electron withdrawing groups on the nitrogen (**Scheme 50**).[136]



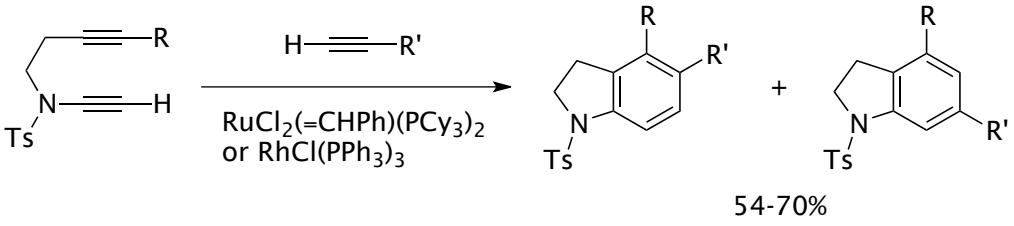
Scheme 50: Witulski's chiral intramolecular [2+2+1] cycloadditions.

Following this work Witulski also utilised ynamides in a series of different metal mediated reactions for the synthesis of indolines. Firstly he successfully achieved intramolecular [2+2+2] cycloadditions mediated by rhodium with ynamides and ethylene (**Scheme 51**).[137] In addition to the use of ethylene Witulski also used substituted acetylenes and achieved regioselectivities of up to 20:1.



Scheme 51: Witulski's intramolecular [2+2+2] cycloadditions.

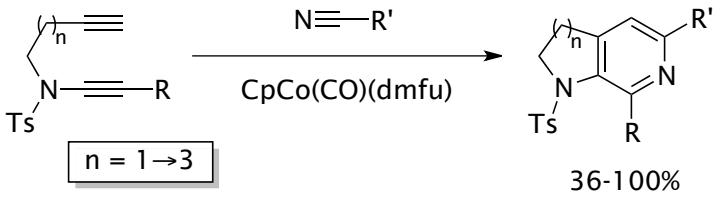
Witulski then developed a route using either Grubbs' catalyst or Wilkinson's catalyst to give substituted indolines (**Scheme 52**).[138] Grubbs' catalyst gave predominantly the *meta* regioisomer with a dr of up to 9.5:1 while Wilkinson's catalyst gave predominantly the *ortho* regioisomer with a dr of up to 20:1.



Scheme 52: Witulski's intramolecular [2+2+2] cycloadditions for the formation of substituted indolines.

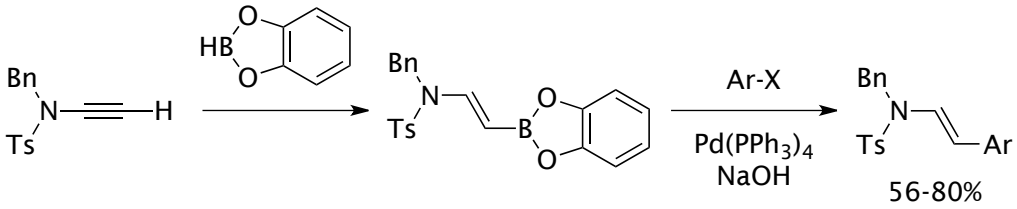
Gandon has since shown that the intramolecular [2+2+2] cycloadditions of ynamides is not limited to the formation of indolines. He has successfully used

nitriles as the third π-component to form pyridines with complete regioselectivity.[139]



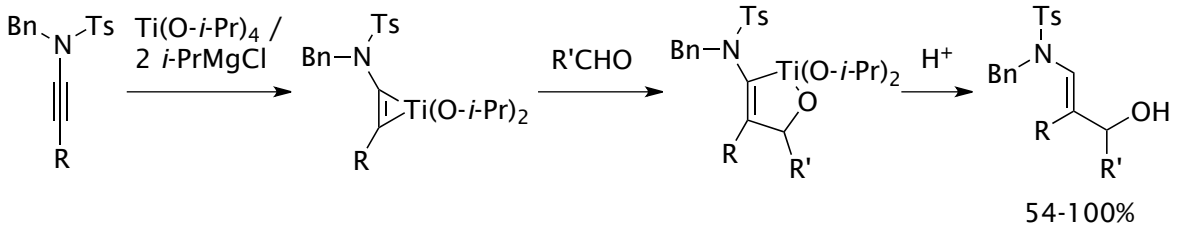
Scheme 53: Synthesis of pyridines through intramolecular [2+2+2] cycloadditions of ynamides and nitriles.

In addition to transition metal mediated cyclisations Witulski has also utilised an ynamide in a Suzuki-Miyaura coupling with aryl halides (**Scheme 54**).[140] The hydroboration gave exclusively the (*E*)-alkene.



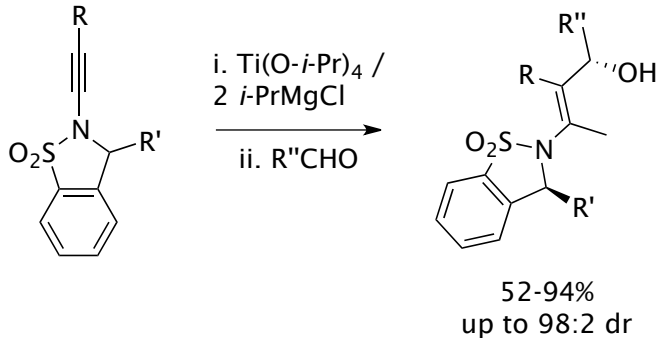
Scheme 54: Suzuki-Miyaura coupling of an ynamide with aryl halides.

Of most relevance to the novel work in this chapter on the zirconocene mediated cocyclisation of ynamides is the work carried out by Sato on ynamides using titanium. Sato demonstrated that ynamides could form titanium alkoxide complexes in 2003 through addition to a series of aldehydes (**Scheme 55**).[141]



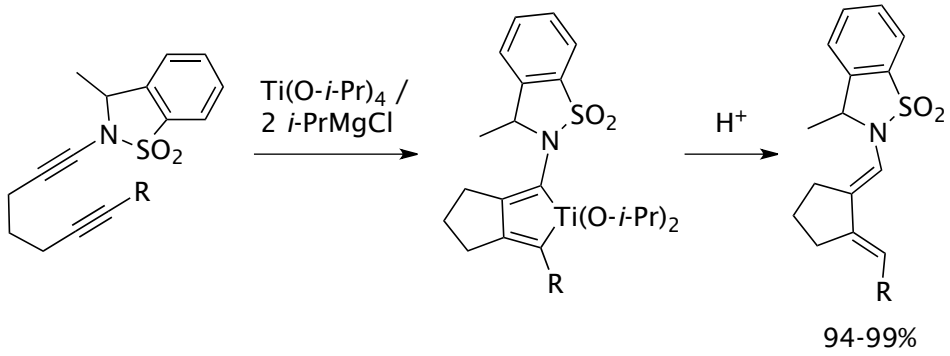
Scheme 55: Addition of ynamide-titanium alkoxide complexes to aldehydes.

In 2004 Sato extended the scope of this reaction and also demonstrated excellent diastereocontrol of the new alcohol centre (**Scheme 56**).[127]



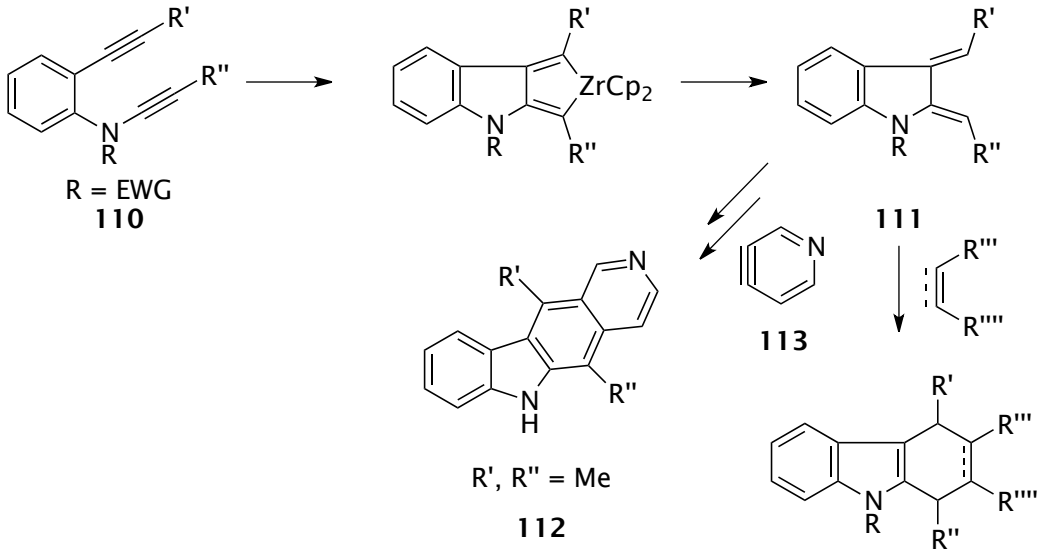
Scheme 56: Sato observed excellent 1,5-diastereocontrol of the new alcohol centre.

Sato has also demonstrated the intermolecular and intramolecular titanium alkoxide mediated cocyclisation of ynamides albeit with the nitrogen outside of the newly formed ring (**Scheme 57**).[132, 141]



Scheme 57: Intramolecular cocyclisation of ynamides by a titanium alkoxide complex.

To build on this work it was envisaged that zirconium mediated cocyclisation of ynamides **110** could be followed by Diels-Alder trapping of the resultant exocyclic dienes **111** with dienophiles (**Scheme 58**). This would give a concise route to interesting products such as the natural product ellipticine (**112**) by using pyridyne **113** as a dienophile



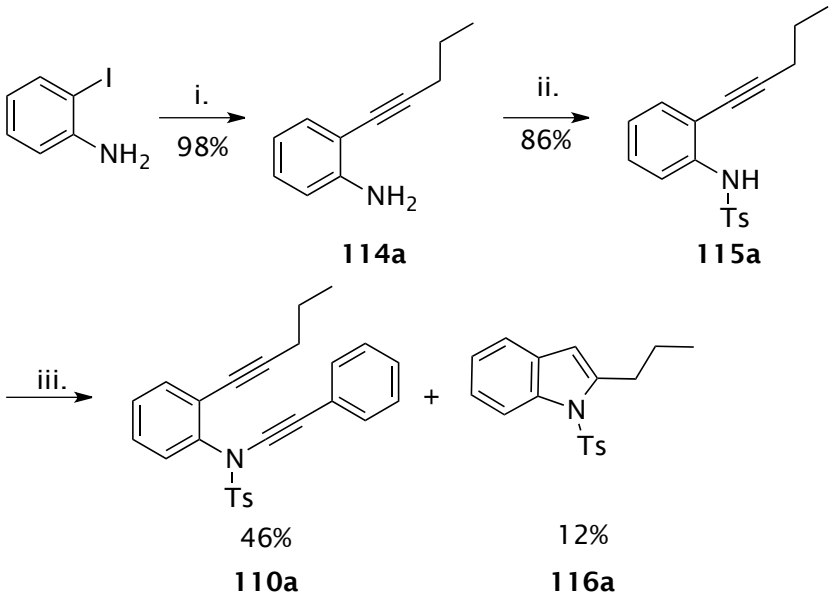
Scheme 58: Zirconium mediated cocyclisation of ynamides **110** and the Diels-Alder trapping of the exocyclic dienes **111** formed.

4.2 Ynamides bearing a fused aromatic ring

4.2.1 Synthesis of an ynamide bearing a fused aromatic

Initially the focus was to utilise ynamides bearing a fused aromatic in zirconocene mediated cocyclisations so that the total synthesis of ellipticine (**112**) could be achieved. In order to determine whether or not the zirconocene mediated cocyclisation of ynamides bearing a fused aromatic ring was possible the synthesis of ynamide **110a** was undertaken. Synthesis of ynamide **110a** was achieved in three steps (**Scheme 59**). The first step was the Sonogoshira coupling of iodoaniline and pent-1-yne to give amine **114a** in 98% yield. The second step was the tosylation of amine **114a**, which was achieved in 86%. The final step in the synthesis of ynamide **110a**; *N*-alkynylation of amide **115a** was achieved in 46% yield using $CuSO_4.5H_2O$ as a catalyst with 1,10-phenanthroline.[128] The low yield is accounted for by the competing formation of known indole **116a**.[142] In an attempt to minimise the formation of indole **116a** various modifications taken from the literature were explored including using copper (I) iodide as the catalyst, changing the base from K_2CO_3 to Cs_2CO_3, using 1,4-dioxane rather than DMF as the solvent and attempting the *N*-alkynylation step before the Sonogoshira

coupling.[127, 132-134] None of these modifications gave any significant improvement in the yield and many led to the complete failure of the *N*-alkynylation.



114a **115a** **110a** **116a**

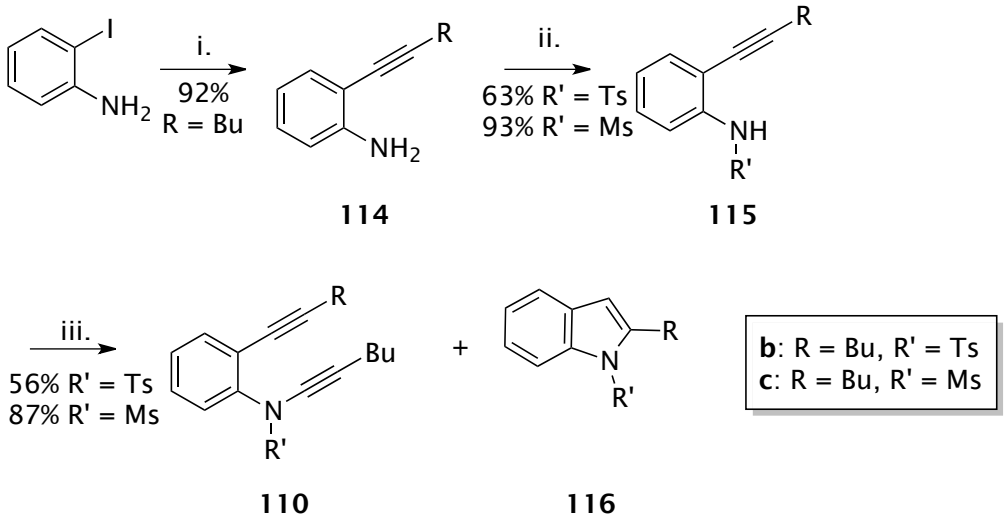
Scheme 59: Synthesis of ynamide **110a**. *Reagents and conditions:* i. pent-1-yne, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, rt, 5 h; ii. pyridine, TsCl, 0 °C, 30 mins, rt, overnight; iii. (bromoethynyl)benzene, DMF, K_2CO_3, $CuSO_4.5H_2O$, 1,10-phenanthroline, 65 °C, 13 h.

4.2.2 Attempted zirconocene mediated cocyclisation

Zirconocene mediated cocyclisation of ynamide **110a** using Negishi's reagent proved to be unsuccessful as only starting material was recovered. In an attempt to overcome this two different methods of generating the active '$ZrCp_2$' species were investigated. Firstly reduction of zirconocene dichloride with $Mg/HgCl_2$ and secondly by using DMAP as the labile ligand as opposed to 1-butene, unfortunately neither method was successful in cocyclising ynamide **110a**.

The possibility of a steric clash between the phenyl substituent on the alkyne and the phenyl ring of the tosyl group was also identified as a potential reason for the failure of the zirconocene mediated cocyclisation. In order to test this hypothesis the synthesis of two ynamides with less steric hindrance was undertaken. Ynamide **110b** had an alkyl substituent in place of the phenyl substituent on the alkyne. Ynamide **110c** was even less sterically hindered as not only was the phenyl substituent on the alkyne replaced the tosyl group was also replaced with

the smaller mesyl group. Both ynamides **110b** and **110c** were synthesised in the same three step procedure as for ynamide **110a** (**Scheme 60**). The indole **116** that had been formed previously in the synthesis of ynamide **110a** was again formed with both ynamides **110b** and **110c**, however, as both of these ynamides lacked the polarity of the phenyl substituent on the alkyne the indole could not be separated from the ynamide in either case. It was decided to attempt the zirconocene mediated cocyclisation with the indole present as it was not thought that this would interfere.



114 **115**

110 **116**

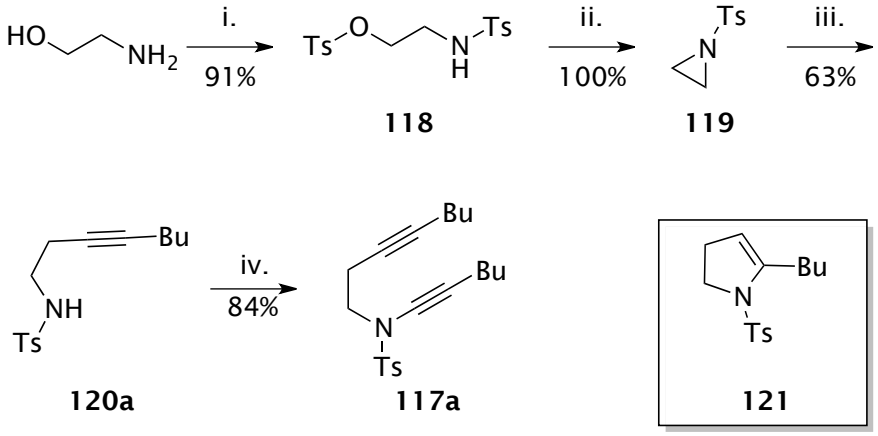
Scheme 60: Synthesis of ynamides **110b,c**. *Reagents and conditions:* i. hex-1-yne, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N, rt, 5 h; ii. pyridine, $R'SO_2Cl$, 0 °C, 30 mins, rt, overnight; iii. K_3PO_4, CuI, 1-bromohex-1-yne, $(CH_3)_2NCH_2CH_2NH_2$, PhMe, reflux, 16 h.

Zirconocene mediated cocyclisation of ynamides **110b** and **110c** was again unsuccessful. This result suggests that steric hindrance was not preventing the cocyclisation of ynamide **110a**. Indole **116** was recovered in quantitative yield from the reaction confirming that it had not interfered with the cocyclisation. The ^{1}H NMR spectrum of the product obtained from the attempted cocyclisation of ynamide **110b** had a singlet at 5.42 ppm. The ^{1}H NMR spectrum of the product obtained from the attempted cocyclisation of ynamide **110c** had a singlet at 5.82 ppm. These singlets give evidence of intermolecular dimerisation between two of the alkynes with the zirconium placed nearest the phenyl ring. This observation demonstrates how unreactive ynamides are towards zirconium, either in the initial complexation or the subsequent carbometallation. The rigidity that

the fused aromatic imposes on the system may well be hindering the cocyclisation even further. This led to a change in focus to that of ynamides that did not have a fused aromatic ring.

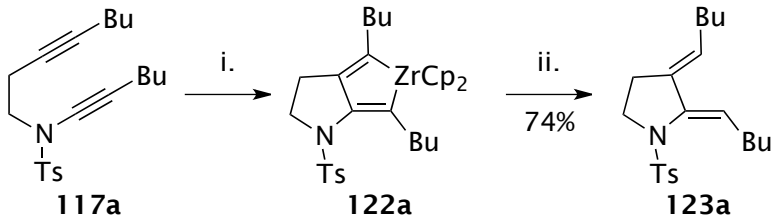
4.3 Ynamides without a fused aromatic ring

In order to determine whether the fused aromatic ring was making the ynamide too rigid for cocyclisation ynamide **117a** was synthesised in four steps (**Scheme 61**). Double tosylation of ethanolamine to give sulfonamide **118** was achieved in 91% yield followed by quantitative conversion to 1-tosylaziridine (**119**) using KOH.[143, 144] Ring opening of the aziridine **119** using hex-1-yne, which had been deprotonated with *n*-BuLi, was achieved in 63% yield. *N*-Alkynylation of amide **120** was achieved in 84% yield using $CuSO_4.5H_2O$ as a catalyst with 1,10-phenanthroline. Thankfully pyrroline **121** was not formed during the final step in an analogous fashion to the formation of indole **116** in the *N*-alkynylation of amides **115**.



Scheme 61: Synthesis of ynamide **117a**. *Reagents and conditions:* i. pyridine, TsCl, −78 °C, 30 mins, rt, overnight; ii. KOH, benzene, rt, 45 mins; iii. LiCCBu, THF, rt, 5 h; iv. BrCCBu, DMF, K_2CO_3, $CuSO_4.5H_2O$, 1,10-phenanthroline, 65 °C, 13 h.

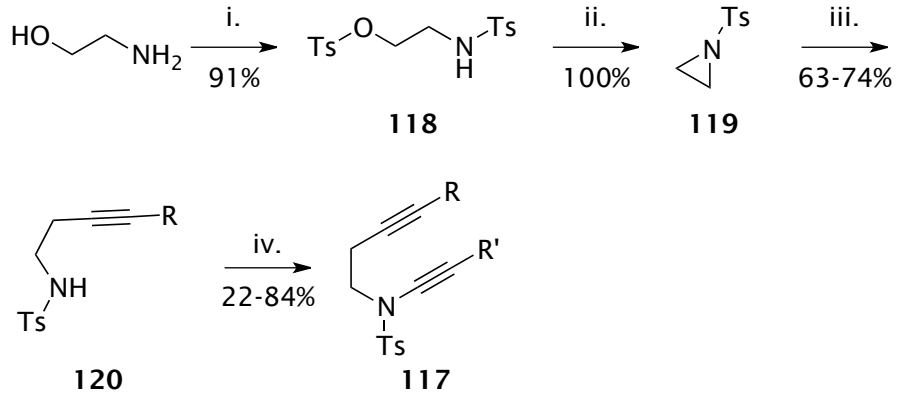
Zirconocene mediated cocyclisation of ynamide **117a** using Negishi's reagent was successful in furnishing zirconacycle **122a**. Protonolysis of zirconacycle **122a** with methanol yielded pyrrolidine **123a** in 74% yield (**Scheme 62**).



Scheme 62: Cocyclisation of ynamide **117a**. *Reagents and conditions:* i. *n*-BuLi, $ZrCp_2Cl_2$, THF, −78 °C → rt, 3 h; ii. MeOH, −78 °C, 1 h, rt, overnight.

4.3.1 Synthesis of a series of ynamides without a fused aromatic

In order to determine the scope of the zirconocene mediated cocyclisation of ynamides more effectively a series of analogues of ynamide **117a** were prepared. Firstly ynamides with different substituents on both alkynes were prepared in the same four step synthesis as ynamide **117a** (**Scheme 63**). The *N*-alkynylation of amides **120** using $CuSO_4.5H_2O$ was not successful when amide **120** possessed a trimethylsilyl group or when (bromoethynyl)trimethylsilane was used. In these circumstances a procedure using CuI, K_3PO_4 and *N*,*N*-dimethylethylenediamine was found to be successful in tolerable yields (**Table 2**).[132]

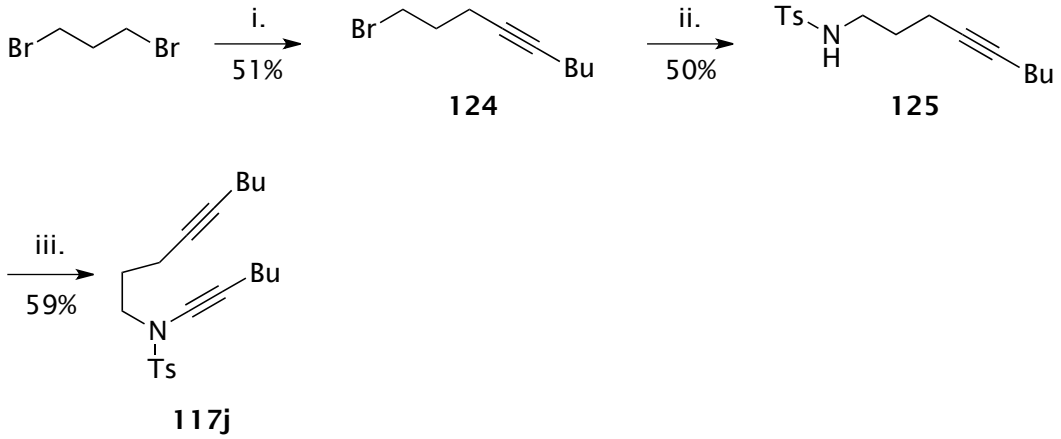


Scheme 63: Synthesis of ynamides **117a-i**. *Reagents and conditions:* i. pyridine, TsCl, −78 °C, 30 mins, rt, overnight; ii. KOH, benzene, rt, 45 mins; iii. LiCCR, THF, rt, 5 h; iv. Method A: BrCCR', DMF, K_2CO_3, $CuSO_4.5H_2O$, 1,10-phenanthroline, 65 °C, 13 h or Method B: BrCCR', *N*,*N*-dimethylethylenediamine, K_3PO_4, CuI, PhMe, reflux,16 h.

Entry	Method	R	R'	Isolated yield
a	A	Bu	Bu	84%
b	A	Ph	Bu	51%
c	B	$SiMe_3$	Bu	32%
d	A	Bu	Ph	22%
e	A	Ph	Ph	60%
f	B	$SiMe_3$	Ph	42%
g	B	Bu	$SiMe_3$	30%
h	B	Ph	$SiMe_3$	47%
i	B	$SiMe_3$	$SiMe_3$	36%

Table 2: Isolated yields from the *N*-alkynylation of amides **120**.

As well as varying the substituents on both alkynes variation of the ring size formed by the zirconocene mediated cocyclisation was also investigated. Synthesis of ynamide **117j** was achieved in three steps (**Scheme 64**).

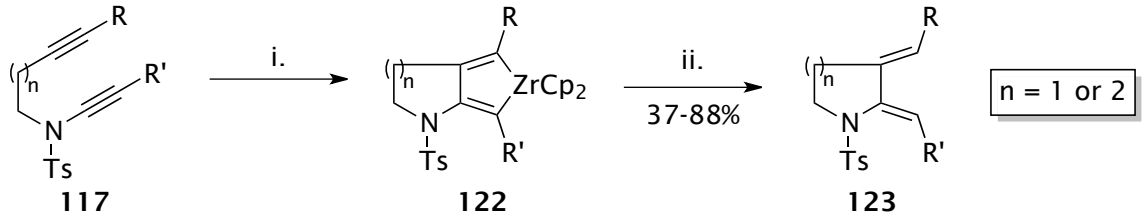


Scheme 64: Synthesis of ynamide **117j**. *Reagents and conditions:* i. LiCCBu, HMPA, THF, −78 °C → rt, 1 h, rt, 16 h; ii. $TsNH_2$, NaOH, DMSO 50 °C, 30 mins, bromide **124**, 50 °C, 2 h; iv. BrCCBu, DMF, K_2CO_3, $CuSO_4.5H_2O$, 1,10-phenanthroline, 65 °C, 13 h.

Nucleophilic substitution of one of the bromines on 1,3-dibromopropane using hex-1-yne, which had been deprotonated with *n*-BuLi, was achieved in 51% yield. Conversion of the resulting bromide **124** to the tosylate **125** was achieved using tosylamide and sodium hydroxide in DMSO in 50% yield. *N*-Alkynylation of amide **125** was achieved as before using $CuSO_4.5H_2O$ and 1,10-phenanthroline in 59% yield.

4.3.2 Zirconocene mediated cocyclisation of ynamides

Zirconocene mediated cocyclisation of ynamides **117a-j** using Negishi's reagent was successful in up to 88% yield (**Scheme 65**). The results shown in **Table 3** show that the zirconocene mediated cocyclisation of ynamides is successful with a range of substituents on either alkyne as well as with different ring sizes.



117 **122** **123**

Scheme 65: Cocyclisation of ynamides **117a-j**. *Reagents and conditions:* i. *n*-BuLi, $ZrCp_2Cl_2$, THF, −78 °C → rt, 3 h; ii. MeOH, −78 °C, 1 h, rt, overnight.

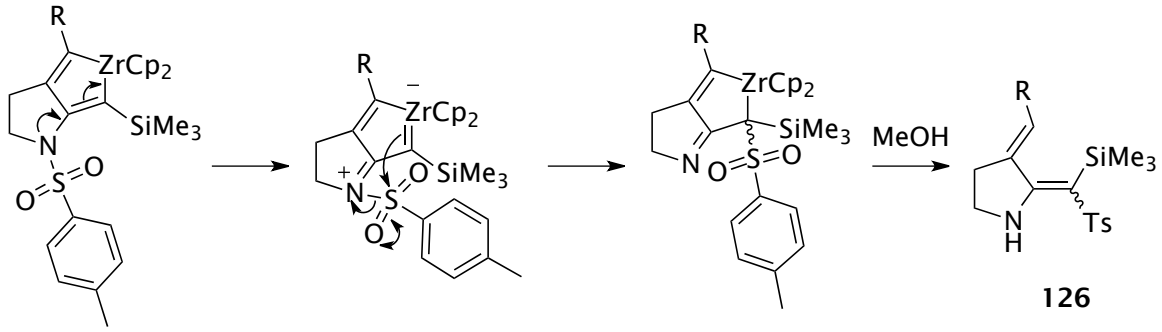
The yields for the zirconocene mediated cocyclisation were generally good to excellent with only one product being formed with the exception of the zirconocene mediated cocyclisation of ynamides **117h** and **117i** (**Table 3**).

Entry	n	R	R'	Isolated yield
a	1	Bu	Bu	74%
b	1	Ph	Bu	61%
c	1	$SiMe_3$	Bu	64%
d	1	Bu	Ph	88%
e	1	Ph	Ph	49%
f	1	$SiMe_3$	Ph	74%
g	1	Bu	$SiMe_3$	73%
h	1	Ph	$SiMe_3$	45% (38%)[a]
i	1	$SiMe_3$	$SiMe_3$	37% (18%)[a]
j	2	Bu	Bu	74%

Table 3: Isolated yields from the zirconocene mediated cocyclisation of ynamides **117**. [a]Yield in parenthesis is the isolated yield of diene **126** obtained as a side product.

The zirconocene mediated cocyclisation of ynamides **117h** and **117i** produced a second product **126**, a possible mechanism for the formation of diene **126** is shown below (**Scheme 66**). The ^{1}H NMR spectrum of the reaction mixture prior to

quenching with methanol shows the presence of two distinct products and so rearrangement of the product on quenching can be ruled out. Attempts to establish the stereochemistry of the double bond containing the $SiMe_3$ and tosyl groups using NOE experiments was unsuccessful, however it does appear as a single isomer.

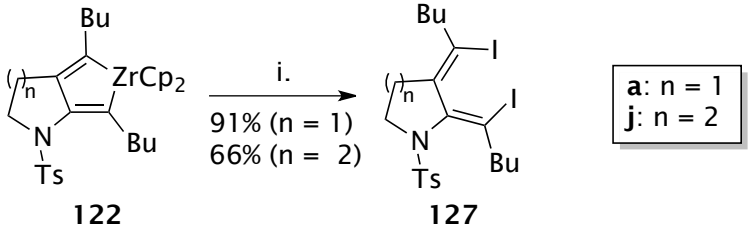


Scheme 66: Possible mechanism for the formation of dienes **126**.

4.3.3 Elaboration of the zirconacyclopentadiene

Takahashi has previously reported several elaborations of zirconacyclopentadienes beyond simple protonolysis.[41] In order to increase the scope of the zirconocene mediated cocyclisations of ynamides **117** various elaborations of zirconacyclopentadienes **122** were attempted.

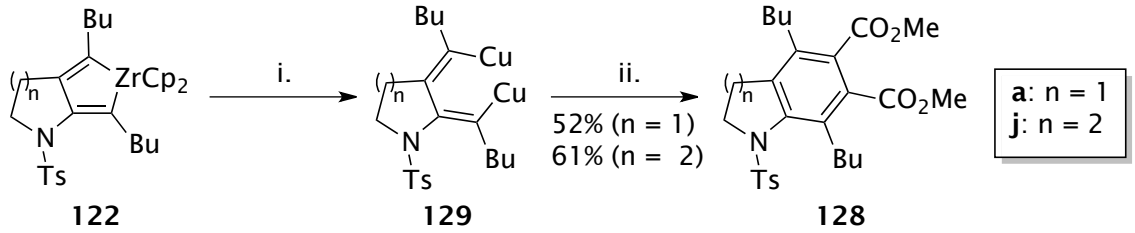
The first such elaboration was the treatment of zirconacyclopentadienes **122a** and **122j** with CuCl and iodine to give the bis iodides **127** in good yields (**Scheme 67**).[42]



Scheme 67: Bis-iodination of zirconacyclopentadienes 9. *Reagents and conditions:* i. I_2, CuCl, THF 0 °C, rt, overnight.

The next elaboration to be attempted again involved initial transmetallation of zirconacyclopentadiene to copper followed by insertion of DMAD to give benzene

derivatives **128**. This was achieved with zirconacyclopentadienes **122a** and **122j** in good yield.



122 **129** **128**

Scheme 68: Synthesis of tetrahydroquinolines **128**. *Reagents and conditions:* i. CuCl, THF, rt; ii. DMAD, rt, 3 h.

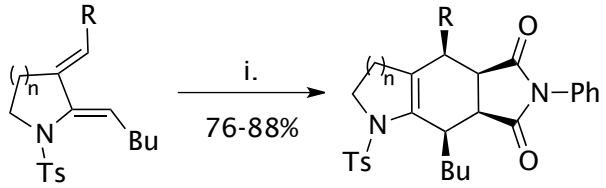
The formation of benzene derivatives via transmetallation to copper has the limitation that at least one of the substituents on the alkyne to be inserted must be electron withdrawing.[145] Formation of the benzene derivatives occurs via addition of the alkenyl copper moiety **129** to the carbon-carbon triple bond hence electron donating groups cannot be present on the alkyne. Takahashi has shown that this limitation can be overcome using transmetallation to nickel instead, whereby alkynes with either electron withdrawing or electron donating substituents can be used.[146] Attempted transmetallation of zirconacycles **122a** and **122j** using $NiCl_2(PPh_3)_2$ or $NiBr_2(PPh_3)_2$ and treatment with oct-4-yne yielded only the protonated dienes **123a** and **123j** in comparable yields to the simple zirconocene mediated cocyclisation reactions.

Fagan and Nugent have demonstrated an easy route to five membered heterocycles via heteroatom transfer of zirconacyclopentadienes.[72] This was attempted with zirconacyclopentadiene **122a**. Unfortunately heteroatom transfers from sulfur monochloride and phenyl phosphine dichloride did not show any sign of success and good recovery of protonated diene **123a** was achieved.

It appears from these results that while ynamides have proven good substrates for zirconocene mediated cocyclisation the presence of the nitrogen adjacent to one of the double bonds in the resultant zirconacyclopentadiene **122** reduces the reactivity of the zirconacyclopentadiene significantly.

4.3.4 Elaboration of the exocyclic diene

The exocyclic diene **123** that is formed upon protonolysis of zirconacycle **122** leads itself to further elaboration. The most logical elaboration is its use in a Diels-Alder reaction. Diels-Alder reactions were carried out by combining an exocyclic diene **123** with *N*-phenylmaleimide in refluxing benzene for 16 hours (**Scheme 69**).



123 **130**

Scheme 69: Diels-Alder reactions involving dienes **123**. *Reagents and conditions:* i. *N*-phenylmaleimide, benzene, reflux, 16 h.

The Diels-Alder reactions were successfully extended to include a series of dienophiles (**Table 4**). The Diels-Alder adducts were all formed as single stereoisomers with the exception of the reaction using acrylonitrile as the dienophile (**Table 4, entry f**) which formed a 2.8:1 mixture of stereoisomers. The Diels-Alder adducts formed using acyclic dienophiles (**Table 4, entries d-f**) were all formed with complete regioselectivity.

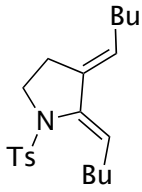
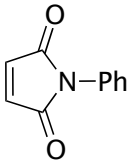
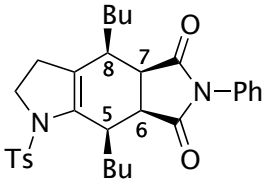
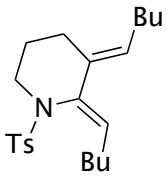
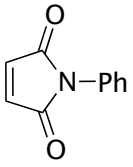
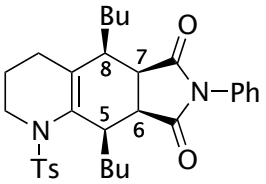
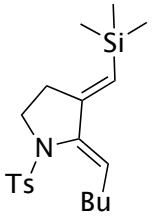
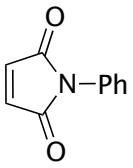
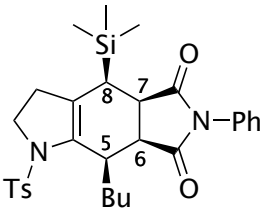
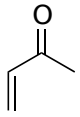
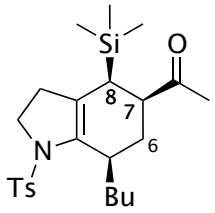
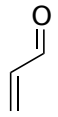
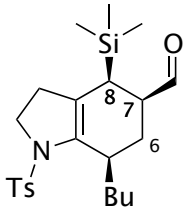
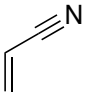
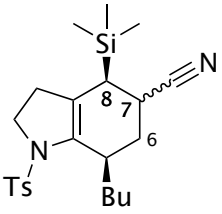
Entry	Diene	Dienophile	Diels-Alder adduct	Yield
a				76%
b				88%
c				79%
d				72%
e				80%
f				13% (*exo*) 36% (*endo*)

Table 4: Diels-Alder adducts formed using exocyclic dienes **123**.

The stereochemistry of the Diels-Alder adducts **130** was assigned by comparison of the observed coupling constants of the protons on the newly formed adjacent chiral centres with those obtained through computer modelling. An extensive search of conformations of each species was made using Molecular Mechanics

(MMFF force field). A number of the lowest energy conformations, manually selected to cover a reasonable conformational space, were minimised using DFT (B3LYP model using 6-31G* basis set). Poor correlation between the lowest energy structure predicted by MM and that from the DFT calculations was observed. The Spartan 10 program was used for all calculations.[147] The coupling constants were calculated using the Altona modification of the Karplus equation.[148]

The observed coupling constants (**Table 5**) in the adducts formed using *N*-phenylmaleimide as the dienophile (**Table 4, entries a-c**) while not in excellent agreement with the calculated values for the *endo* isomers were much closer than to the calculated values for the *exo* isomer and so each of these adducts was assigned as the *endo* stereoisomer.

Diels-Alder adduct	Calculated coupling constants for *endo* isomer (Hz)		Observed coupling constants $J_{H5\text{-}H6}$ and $J_{H7\text{-}H8}$ (Hz)	Calculated coupling constants for *exo* isomer (Hz)	
	$J_{H5\text{-}H6}$	$J_{H7\text{-}H8}$		$J_{H5\text{-}H6}$	$J_{H7\text{-}H8}$
130a	5.9	9.9	9.3, 9.3	1.0	1.2
130b	7.4	6.6	9.5, 10.0	2.5	3.1
130c	5.4	7.6	9.3, 9.6	1.9	4.6

Table 5: Calculated and observed coupling constants for Diels-Alder adducts formed using *N*-phenylmaleimide as the dienophile.

The observed coupling constants (**Table 6**) in the adducts formed using methyl vinyl ketone and acrolein as the dienophiles (**Table 4, entries d and e**) were in excellent agreement with those calculated for the *endo* isomers. As mentioned before the use of acrylonitrile as the dienophile resulted in a mixture of stereoisomers (**Table 4, entry f**). The first obtained isomer was judged to be the *exo* isomer based on the observation that despite the key multiplets in the ^{1}H NMR spectrum being indefinable the couplings present in the multiplet all appeared to be below 5 Hz which is consistent with the *exo* isomer. In addition to this the

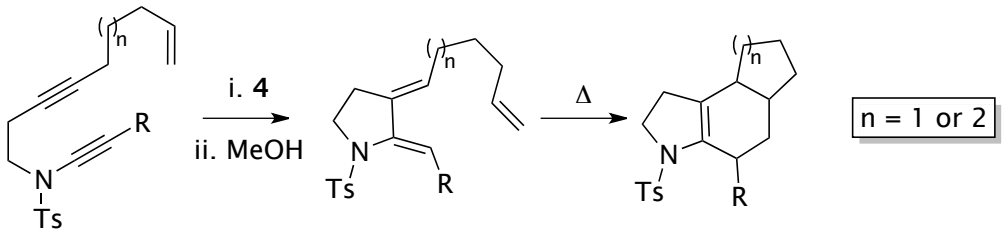
second obtained isomer had coupling constants in excellent agreement with those calculated for the *endo* isomer.

Diels-Alder adduct	Calculated coupling constants for *endo* isomer (Hz)		Observed coupling constants J_{H6-H7} and J_{H7-H8} (Hz)	Calculated coupling constants for *exo* isomer (Hz)	
	J_{H6-H7}	J_{H7-H8}		J_{H6-H7}	J_{H7-H8}
130d	12.7, 1.9	4.5	11.6, 4.0, 3.6	3.9, 3.3	1.0
130e	13.0, 3.2	4.3	12.5, 3.6, 3.6	4.0, 3.5	1.4
130f-*exo*	13.1, 1.9	4.5	Indistinguishable*	4.2, 3.4	1.3
130f-*endo*			12.5, 4.3, 3.4		

Table 6: Calculated and observed coupling constants for Diels-Alder adducts formed using acyclic dienophiles. *Although the coupling constants for this isomer were indistinguishable they were all judged to be less than 5 Hz.

4.3.5 Intramolecular Diels-Alder reactions

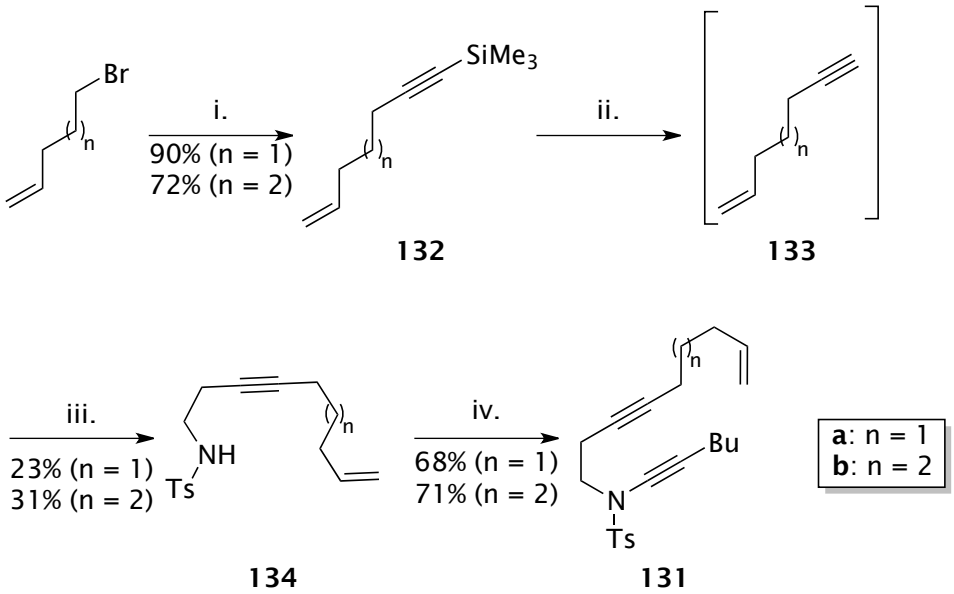
Given the success of the Diels-Alder reactions it seemed sensible to attempt to synthesise and cyclise an ynamide bearing a pendant alkene so that intramolecular Diels-Alder reactions could be attempted (**Scheme 70**).



Scheme 70: Proposed zirconocene mediated cocyclisation of an ynamide bearing a pendant alkene and subsequent Diels-Alder cyclisation of the resulting exocyclic diene and pendent alkene.

4.3.5.1 Synthesis of ynamides bearing a pendant alkene

Synthesis of ynamides **131a,b** was achieved in four steps (**Scheme 71**).

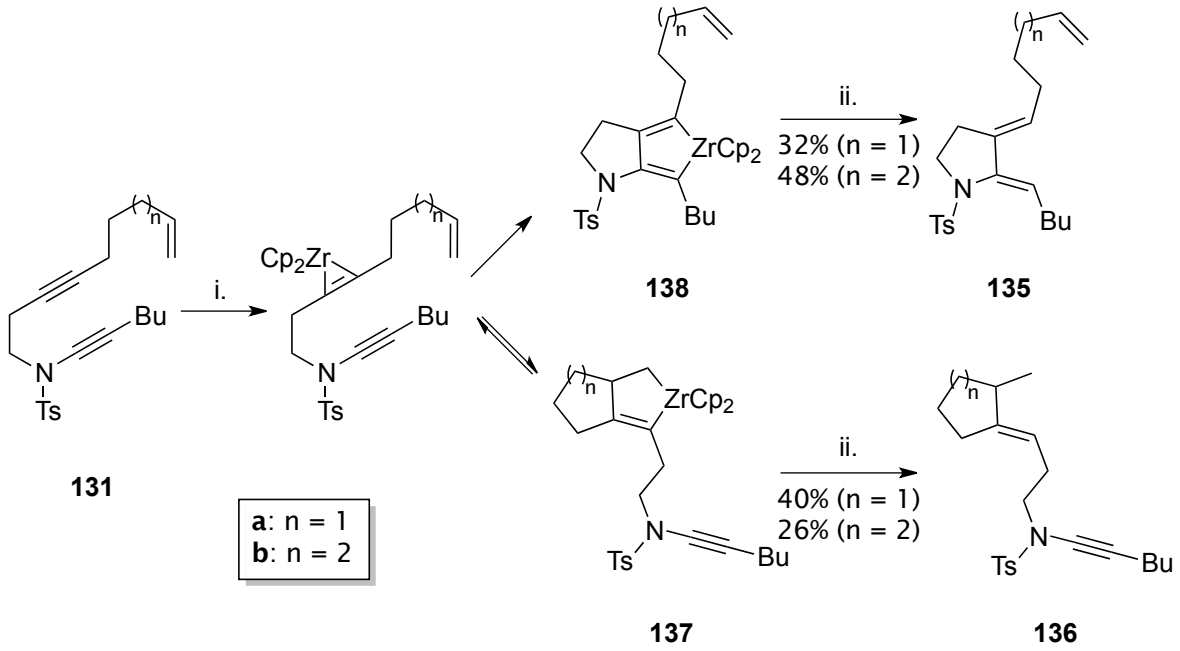


Scheme 71: Synthesis of ynamides **131a,b**. *Reagents and conditions:* i. $LiCCSiMe_3$, HMPA, THF, −78 °C, 1 h, rt, 16 h; ii. TBAF, THF, rt, 16 h; iii. *n*-BuLi, −78 °C → rt , 30 min, 1-tosylaziridine, THF, rt, 16 h; iv. BrCCBu, DMF, K_2CO_3, $CuSO_4.5H_2O$, 1,10-phenanthroline, 65 °C, 16 h.

The first step was the nucleophilic substitution of the bromine on 5-bromopent-1-ene or 6-bromohex-1-ene using trimethylsilylacetylene which had been deprotonated using *n*-BuLi to give enynes **132** achieved in 72–90% yield. TBAF desilylation of enynes **132** gave volatile enynes **133**. Due to their volatility enynes **133** were never isolated but were instead immediately deprotonated with *n*-BuLi and used to ring open 1-tosylaziridine. These two steps to amides **134** were achieved in 23–31% yield. *N*-Alkynylation of amides **134** was achieved in 68–71% yield using $CuSO_4.5H_2O$ and 1,10-phenanthroline.

4.3.5.2 Zirconocene mediated cocyclisation

Zirconocene mediated cocyclisation of ynamides **131a,b** yielded two products in each case (**Scheme 72**). The first product was the expected pyrrolidines **135a** and **135b** but also formed were ynamides **136a** and **136b**. The unexpected products were a result of cyclisation between the alkyne and the alkene rather than between the two alkynes.



Scheme 72: Cocyclisation of ynamides **131**. *Reagents and conditions:* i. *n*-BuLi, $ZrCp_2Cl_2$, THF, −78 °C → rt, 3–16 h; ii. MeOH, −78 °C, 1 h, rt, overnight.

It is known that complexation of an alkene by zirconium is reversible. Heating of the reaction mixture can force the formation of the thermodynamically more favourable product. In this instance the desired product **135** is expected to be the thermodynamic product. Heating of the reaction mixture to 50 °C did appear to convert the undesired zirconacycle **137a** to the desired zirconacycle **138a**; however, at this temperature the desired zirconacycle was observed to decompose.

Diels-Alder reaction of pyrrolidines **135a** and **135b** was unsuccessful; ^{1}H NMR spectroscopy showed a gradual degradation of the alkene peaks while ^{13}C NMR spectroscopy showed no appearance of any aliphatic CH peaks. This is surprising given the success of the intermolecular Diels-Alder reactions but is perhaps further evidence of the reduced reactivity of ynamides.

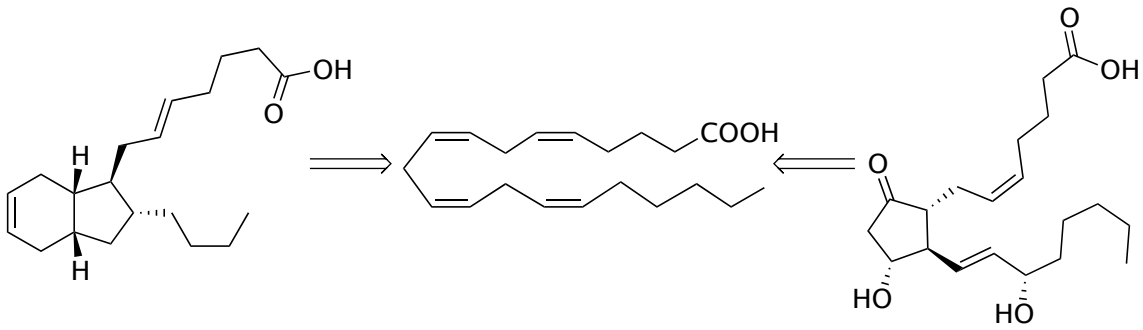
4.4 Conclusions

A series of novel ynamides have been synthesised in good yield using copper mediated coupling methods. The zirconocene mediated cocyclisation of these ynamides has also been successful in good to excellent yields. Elaboration of the intermediate zirconacycles has expanded the scope of the products formed. Diels-Alder reactions of the exocyclic dienes with a series of dienophiles have been achieved with complete regioselectivity and excellent stereoselectivity.

Chapter 5 The total synthesis of mucosin

5.1 Background to the research area

The natural product mucosin (**139**) was first isolated in 1997 by Cimino *et al.* from the Mediterranean marine sponge *Reniera mucosa*.[149] Although no biological activity is reported for mucosin, its close structural relationship with the prostaglandins subclass of eicosanoids, many of which do have potent biological activity in a number of physiological areas makes it an interesting target. It is a bicyclic C-20 structure whose eicosanoid character suggests a biosynthesis from arachidonic acid through a series of enzyme catalysed intramolecular cyclisations and isomerisations, as is the case with prostaglandin E2 (**Figure 13**).



mucosin (**139**) arachidonic acid prostaglandin E2

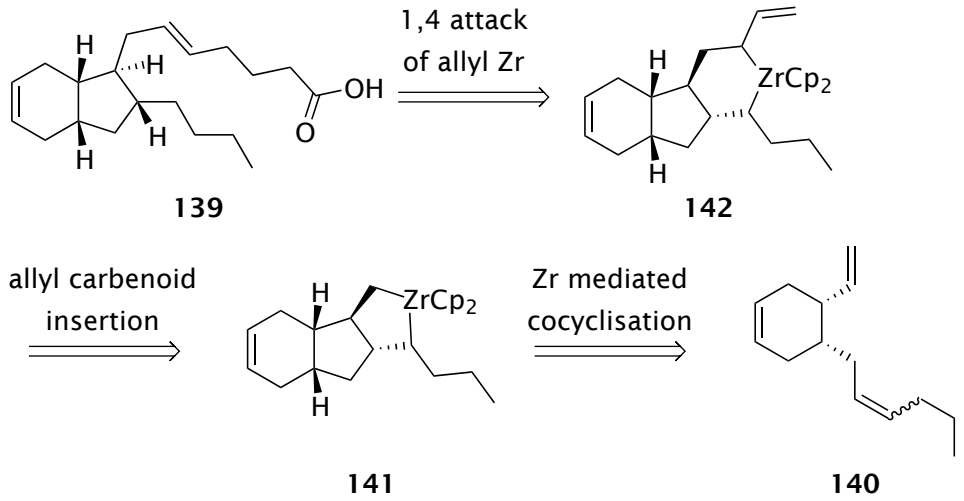
Figure 13: The natural product mucosin (**139**) is most likely derived from arachidonic acid.

The structure of mucosin was established through analysis of the NMR, IR and mass spectra of its methyl ester. These revealed an interesting bicyclo[4.3.0]nonene core and carboxylic acid side chain containing a *trans* double bond. This coupled with the four contiguous stereocentres, with known relative stereochemistry but unknown absolute stereochemistry, provides an interesting synthetic challenge.

5.1.1 Owen's approach to mucosin

Owen proposed a retrosynthetic route that would not only create the bicyclic core structure with the correct relative stereochemistry but would also install the *trans* double bond in one step as well.[33] Zirconocene mediated cocyclisation of triene **140** would provide zirconacycle **141** which would undergo allyl carbenoid

insertion giving zirconacycle **142**. 1,4-Attack of zirconacycle **142** onto an acrolein based acetal would furnish the bicyclic core with the desired stereochemistry and *trans* geometry of the double bond. Further simple transformations to the carboxylic acid containing side chain would furnish the desired product **139** (**Figure 14**).

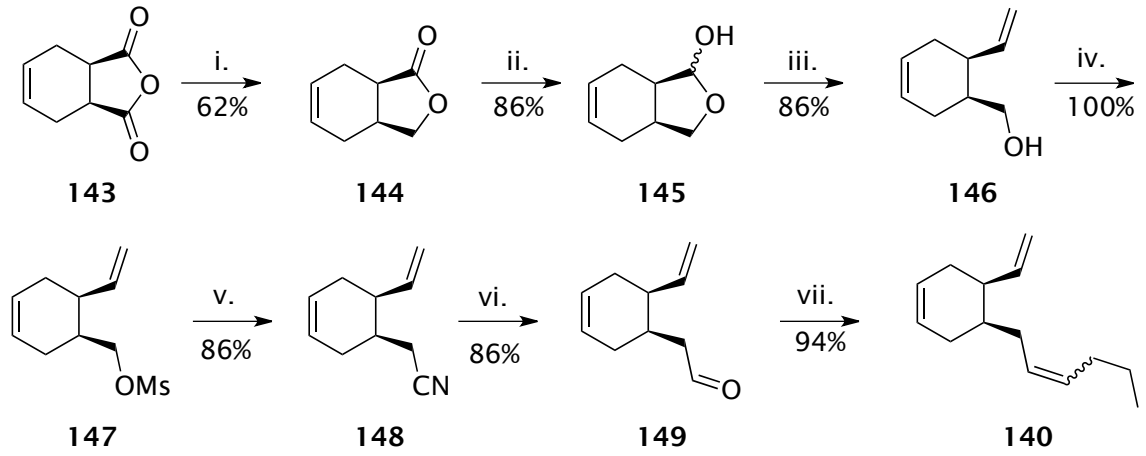


139 **142** **141** **140**

Figure 14: Owen's retrosynthetic approach to mucosin.

5.1.1.1 Synthesis of the cocyclisation precursor

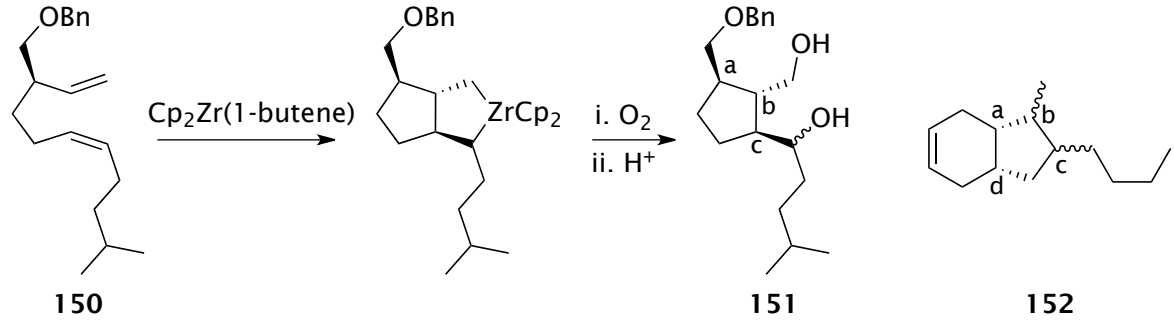
Owen synthesised the cocyclisation precursor in seven steps from commercially available anhydride **143** (**Scheme 73**). Reduction of the anhydride **143** to give lactone **144** with $NaBH_4$ was achieved in 62% yield.[150] Partial reduction of the lactone **144** using DIBAL-H was achieved in 86% yield to furnish lactol **145** which underwent a Wittig methylation to yield alcohol **146** in 86% yield.[151] The second alkene branch was installed by quantitative conversion of alcohol **146** to its mesylate **147** followed by cyanide displacement to give nitrile **148** in 86% yield. DIBAL-H reduction and treatment of the resultant aldehyde **149** with the corresponding Wittig reagent gave triene **140** in 81% yield (2 steps).



Scheme 73: Synthesis of the cocyclisation precursor. *Reagents and Conditions:* i. $NaBH_4$, DMF, 0 °C → rt; ii. DIBAL-H (fast addition), PhMe, −78 °C, 1 h; iii. $MePh_3P^+Br^-$, *n*-BuLi, THF, 0 °C → rt, 2 h; iv. MsCl, Et_3N, DMAP, THF, 0 °C, 2 h; v. KCN, NaI, 18-crown-6, 90 °C, 66 h; vi. DIBAL-H (dropwise addition), THF, −78 °C → rt, 2 h; vii. $BuPh_3P^+Br^-$, *n*-BuLi, THF, 0 °C → rt, 2 h.

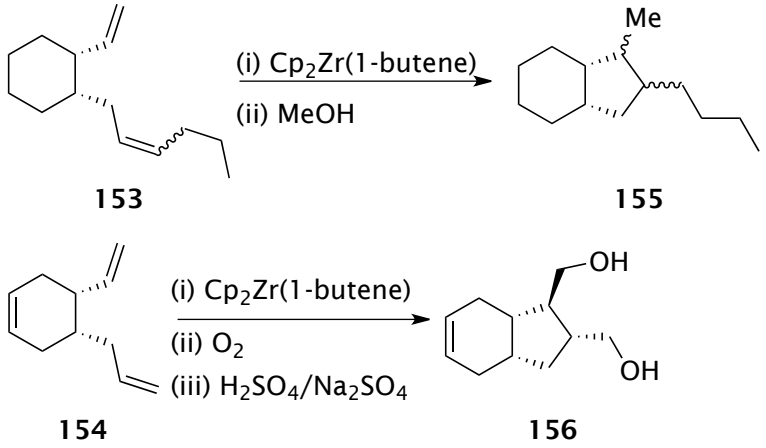
5.1.1.2 Control of the relative stereochemistry

Although the four contiguous stereocentres appear at first challenging Owen had good reason to believe that his route would furnish the correct stereochemistry. Work by Taber and Louey had shown that zirconocene mediated cocyclisation of diene **150** with an oxygen quench yielded diol **151** as a 3:1 mixture of diastereoisomers.[26] Complete diastereoselectivity was obtained at the ring junction between centres 'b' and 'c' as well as the desired *anti* relationship between centres 'a' and 'b'. These two relationships when combined and applied to the cyclised triene **152** would give the correct relative stereochemistry for the natural product (**Scheme 74**).



Scheme 74: Work by Taber and Louey and the analogous centres on cyclisation product **152**.

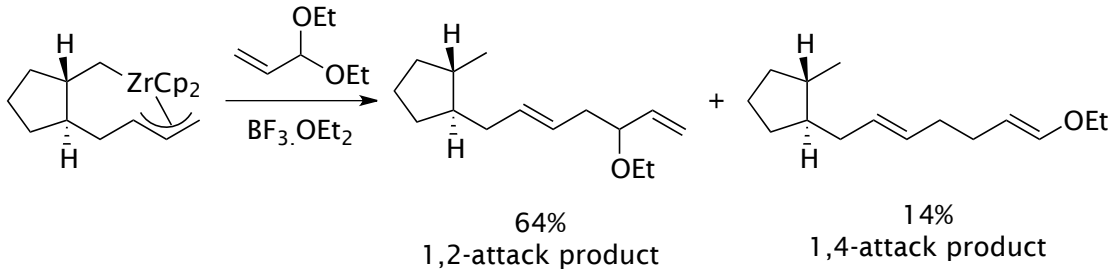
Unfortunately cyclised triene **152** also contains a fourth chiral centre 'd' which due to previously reported 1,3-stereoinduction will give an anti relationship with centre 'c'.[121] Indeed Owen found that zirconocene mediated cocyclisation of triene **140** did yield a mixture of diastereoisomers of cyclised triene **152**. Owen postulated that two other factors may influence the stereoselectivity of the cocyclisation; firstly the double bond in the cyclohexene ring and secondly the propyl substituent. To test this Owen subjected analogues **153** and **154** to zirconocene mediated cocyclisation. Owen found that the cocyclisation of diene **153** again produced a mixture of diastereoisomers of bicycle **155** while the cocyclisation and oxygen quench of triene **154** produced a single diastereoisomer of diol **156** suggesting that the presence of the propyl substituent has a detrimental effect on the stereoselectivity of the zirconocene mediated cocyclisation (**Scheme 75**).



Scheme 75: Cocyclisation of analogues **153** and **154**.

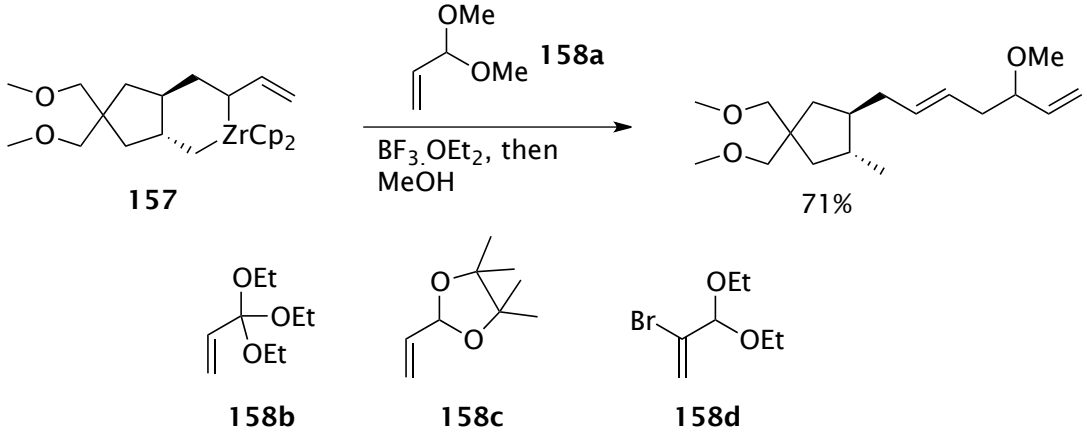
5.1.1.3 Insertion of allyl carbenoids

Work by Luker gave Owen good precedence for the 1,4-attack of allyl zirconocene complexes onto acrolein based acetals (**Scheme 76**).[61]



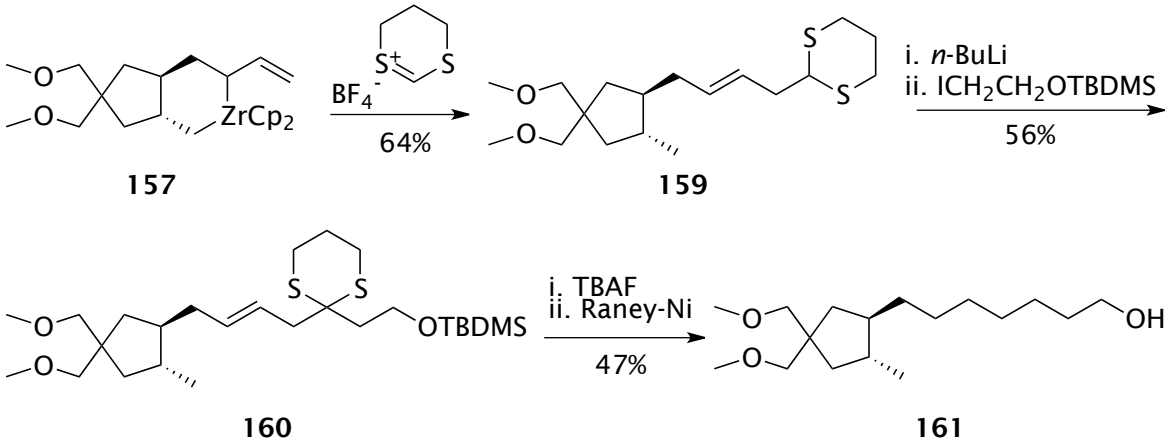
Scheme 76: 1,4-attack of allyl zirconocene onto an acrolein based acetal.

When Owen attempted the 1,4-attack of the model allyl zirconocene system **157** onto acetal **158a** he observed almost exclusively 1,2-attack with less than 5% of the product resulting from 1,4-attack being observed. In an attempt to promote 1,4-attack Owen used three electrophiles **158b-d** with greater steric bulk, unfortunately the increased steric bulk prevented the allyl zirconocene complex **157** from attacking the electrophiles altogether (**Scheme 77**).



Scheme 77: Attempted 1,4-attack of allyl zirconocene complex **157**.

Owen's focus then moved to trapping of the allyl zirconocene complex **157** with dithienium tetrafluoroborate yielding dithiane **159** in 64% yield. The chain was elongated with TBDMS protected 2-iodoethanol to obtain the protected alcohol **160**. TBAF deprotection of the alcohol **160** was followed by removal of the dithiane and reduction of the double bond with Raney-Ni to give alcohol **161** (**Scheme 78**).



Scheme 78: Owen's revised approach to the carboxylic acid side chain.

While Owen did not complete the synthesis of mucosin he had confirmed the formation of at least two diastereoisomers due to the conflicting stereoinduction effects around the bicyclic core. He had also introduced the basis for Stec's attempt towards the synthesis of mucosin.

5.1.2 Stec's approach to mucosin

Stec proposed a route that still utilised allyl carbenoid insertion into zirconacycle **141** in order to install the *trans* double bond. Stec's route differed by trapping the allyl zirconocene complex **142** with monomeric formaldehyde to yield alcohol **162**. Two carbon homologation of the side chain using malonate chemistry would furnish the natural product (**Figure 15**).

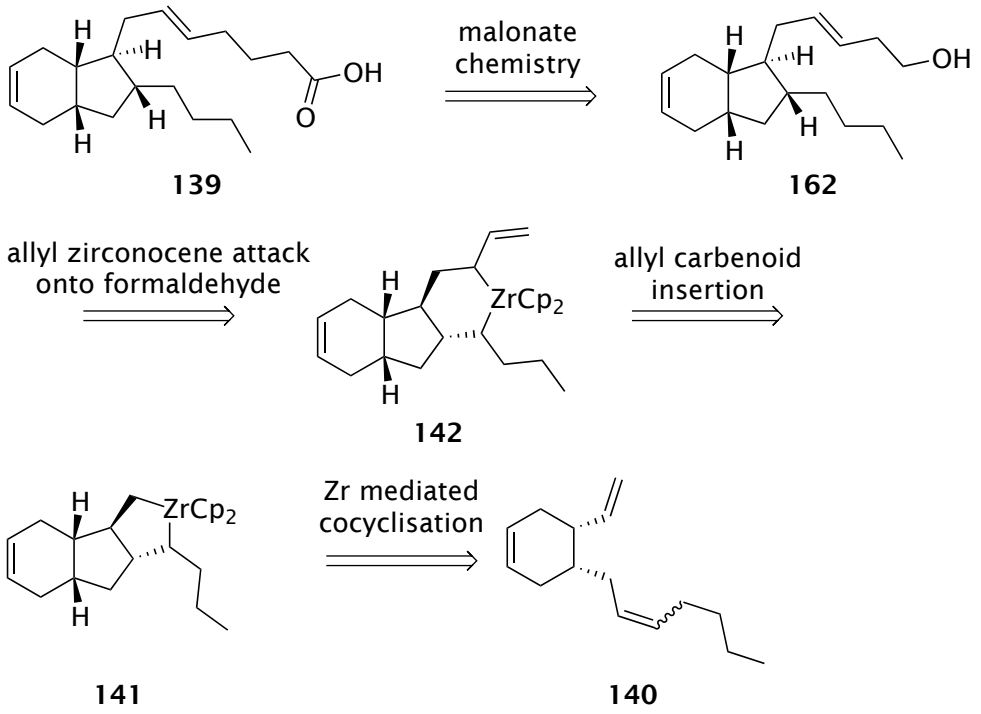
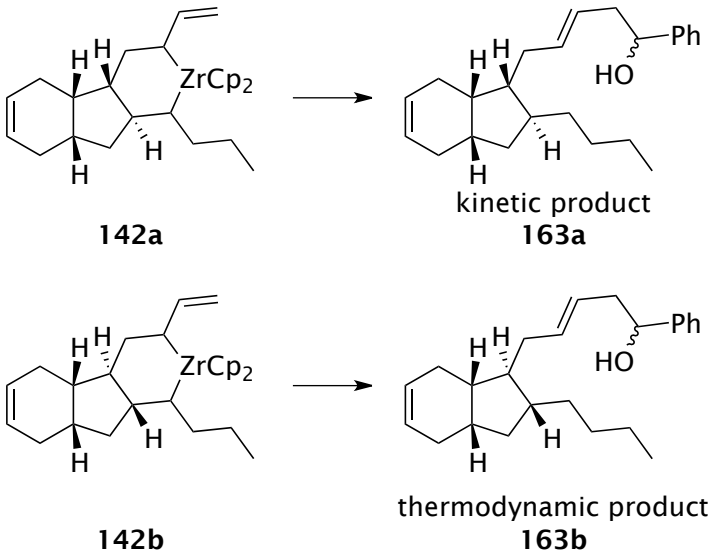


Figure 15: Stec's proposed route to mucosin **139**.

5.1.2.1 Further work to control the relative stereochemistry

Following on from the work of Owen, Stec observed that when zirconacycle **141** was heated to 65 °C for 30 minutes thermal equilibration of the diastereoisomers occurred. In order to determine which diastereoisomer was the thermal product and which was the kinetic product, Stec prepared both zirconacycles separately under thermodynamic and kinetic conditions. Elaboration of the zirconacycles with allyl carbenoid insertion and benzaldehyde trapping gave alcohols **163** (**Scheme 79**).

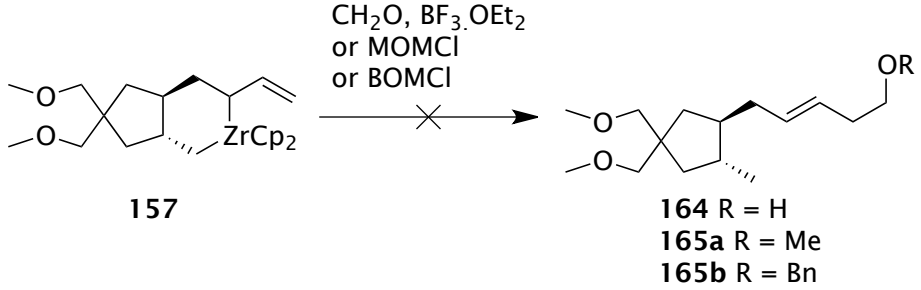
By comparison of the spectral data of the obtained alcohols **163** with those of the methyl ester of mucosin, Stec was able to establish that the major product obtained under thermodynamic conditions had the desired stereochemistry. Thermal equilibration of zirconacycle **141** gave the desired zirconacycle as the main product in 65% yield.



Scheme 79: Synthesis of the kinetic and thermodynamic products of alcohol **163**.

5.1.2.2 Construction of the carboxylic acid side chain

Stec attempted to trap model allyl zirconocene complex **157** with monomeric formaldehyde, MOMCl and BOMCl in order to form alcohol **164** or its ether derivative **165**. All three attempts failed to furnish the desired product.



Scheme 80: Attempts to trap allyl zirconocene complex **157** with formaldehyde, MOMCl and BOMCl.

5.2 Revised synthetic route to mucosin

The routes investigated by both Owen and Stec had the advantage that they both installed the correct relative stereochemistry around the bicyclic core of mucosin as well as the *trans* double bond in the carboxylic acid side chain. The revised route to mucosin does not install the *trans* double bond but does install the

correct relative stereochemistry around the bicyclic core (**Figure 16**). The *trans* double bond can, however, be installed later using a Takai olefination.

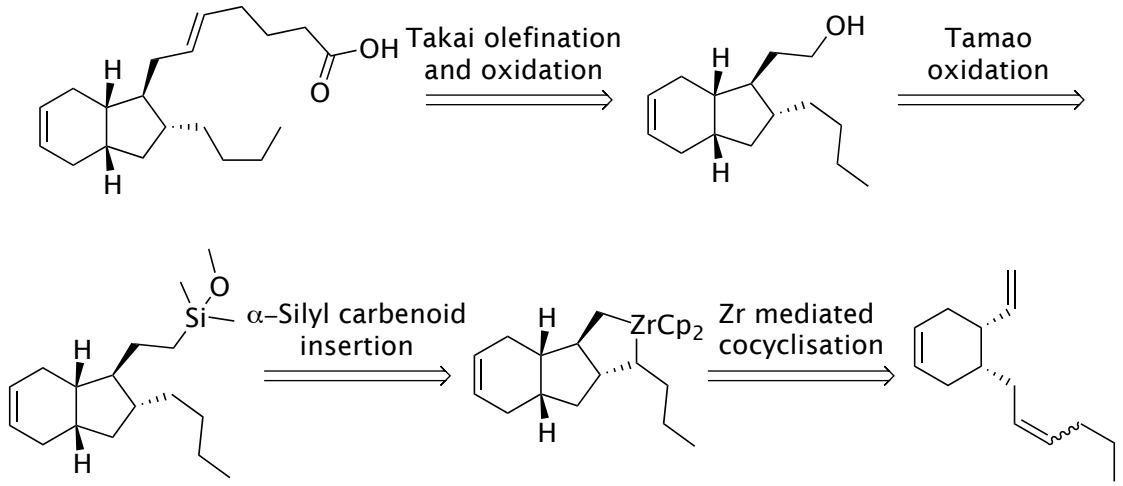
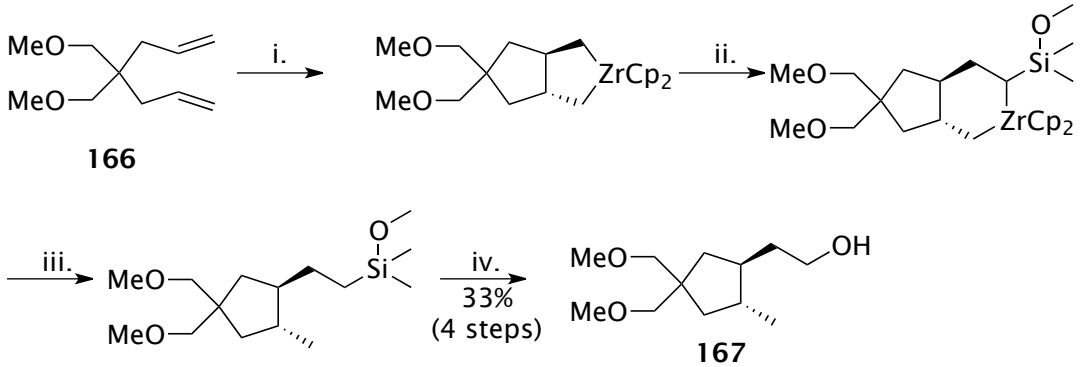


Figure 16: Revised synthetic route to mucosin.

5.2.1 Chloromethyl(dimethyl)methoxysilane derived carbenoid

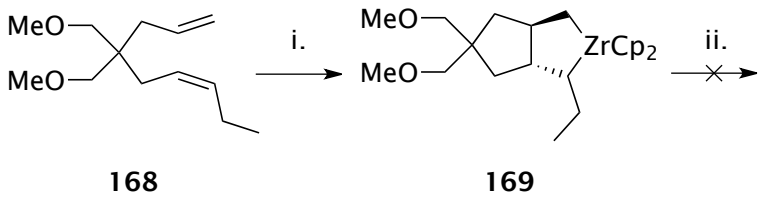
Initially the zirconocene mediated cocyclisation and α-silyl carbenoid insertion was attempted on a simple model diene **166**. The first α-silyl carbenoid to be used was one derived from chloromethyl(dimethyl)methoxysilane. Cocyclisation, carbenoid insertion and Tamao oxidation all proceeded as expected and alcohol **167** was obtained in 33% yield over the three steps (**Scheme 81**).



Scheme 81: Synthesis of alcohol **167**. *Reagents and conditions: n*-BuLi, $ZrCp_2Cl_2$, THF, −78 °C → rt, 2 h; ii. $ClCH_2SiMe_2(OMe)$, LiTMP, THF, −78 °C, 45 mins; iii. $NaHCO_3$, MeOH, −78 °C → rt, overnight; iv. KF, $KHCO_3$, H_2O_2, MeOH/THF (1:1), rt, 18 h.

The cocyclisation and carbenoid insertion was repeated with a second model diene **168**. This diene shares the disubstituted alkene that triene **140** has and so

was thought a good model. Unfortunately while cocyclisation to zirconacycle **169** proceeded cleanly no evidence of carbenoid insertion was seen by GC or ^{1}H NMR (**Scheme 82**).



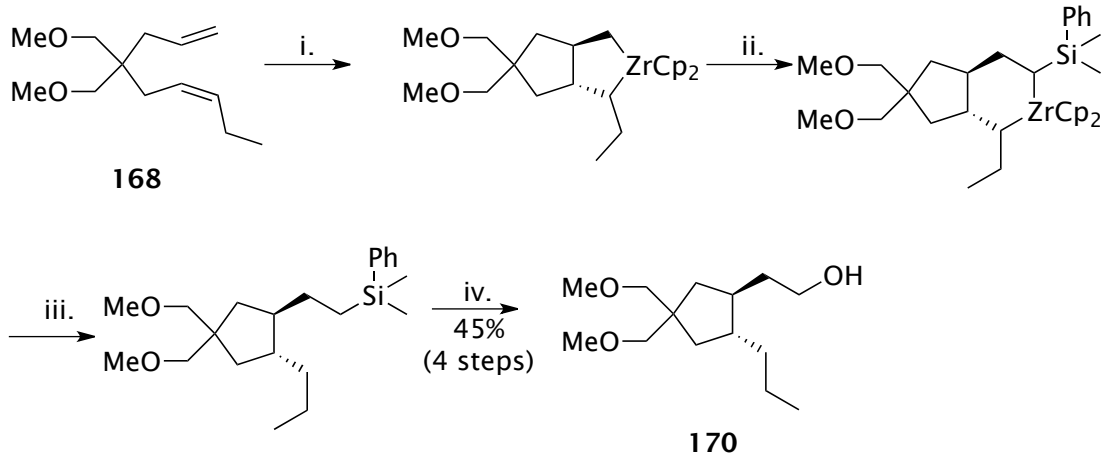
168 **169**

Scheme 82: Attempted α-silyl carbenoid insertion into zirconacycle **169**. *Reagents and conditions:* i. *n*-BuLi, $ZrCp_2Cl_2$, THF, −78 °C → rt, 2 h; ii. $ClCH_2SiMe_2(OMe)$, LiTMP, THF, −78 °C → rt, 18 h.

Prolonging the reaction time and increasing the temperature from −78 °C to room temperature did not show any improvement. Clearly the α-alkyl group is preventing insertion of the carbenoid and so it was thought unlikely that carbenoid insertion would occur with the cocyclisation product of triene **140**.

5.2.2 Chloromethyl(dimethyl)phenylsilane derived carbenoid

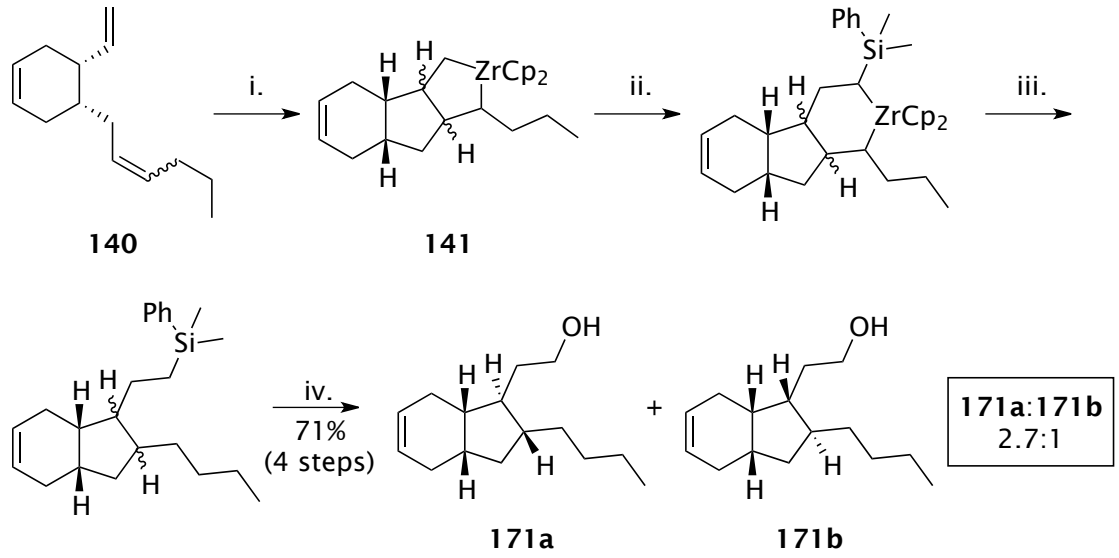
Fortunately the second carbenoid chosen, derived from chloromethyl(dimethyl)phenylsilane did cleanly insert into the model diene **168**. The Tamao oxidation using conditions developed by Woerpel proceeded smoothly to give the alcohol **170** in 45% yield over the three steps (**Scheme 83**).[152]



168 **170**

Scheme 83: Synthesis of alcohol **170**. *Reagents and conditions:* i. *n*-BuLi, $ZrCp_2Cl_2$, THF, −78 °C → rt, 2 h; ii. $ClCH_2SiMe_2(Ph)$, LiTMP, THF, −78 °C, 45 mins; iii. $NaHCO_3$, MeOH, −78 °C → rt, overnight; iv. KH, NMP, *t*-BuOOH, 0 °C → rt, 10 mins, TBAF, 70 °C, 14 h.

The cocyclisation, carbenoid insertion and Tamao oxidation were repeated with triene **140** (**Scheme 84**). Stec in his attempted synthesis of mucosin demonstrated that the cocyclisation of triene **140** gives two diastereoisomers. Further to this he demonstrated that the thermodynamic product is the desired diastereoisomer. Heating the zirconacycle **141** to 65 °C increases the yield of the thermodynamic diastereoisomer. With this in mind alcohol **171** was obtained in 71% yield as a 2.7:1 mixture of diastereoisomers.



Scheme 84: Synthesis of alcohol **171**. *Reagents and conditions:* i. *n*-BuLi, $ZrCp_2Cl_2$, THF, −78 °C → rt, 2 h; ii. $ClCH_2SiMe_2(Ph)$, LiTMP, THF, −78 °C, 45 mins; iii. $NaHCO_3$, MeOH, −78 °C → rt, overnight; iv. KH, NMP, *t*-BuOOH, 0 °C → rt, 10 mins, TBAF, 70 °C, 14 h.

5.2.3 Separation of the diastereoisomers

It was initially envisaged that diastereoisomers **171a** and **171b** would be separable by column chromatography, but unfortunately, no separation of the diastereoisomers was achieved by this method. Alcohol **171** is not UV active but HPLC separation of the diastereoisomers was achieved on a HPLC equipped with a refractive index detector.

In an attempt to separate large quantities of the diastereoisomers a chemical separation was attempted by the iodoetherification of the minor diastereoisomer **171b**. The major diastereoisomer **171a** will not undergo iodoetherification

because the alcohol side chain is on the same face of the molecule as the bridgehead proton preventing cyclisation with the iodonium ion (**Figure 17**).

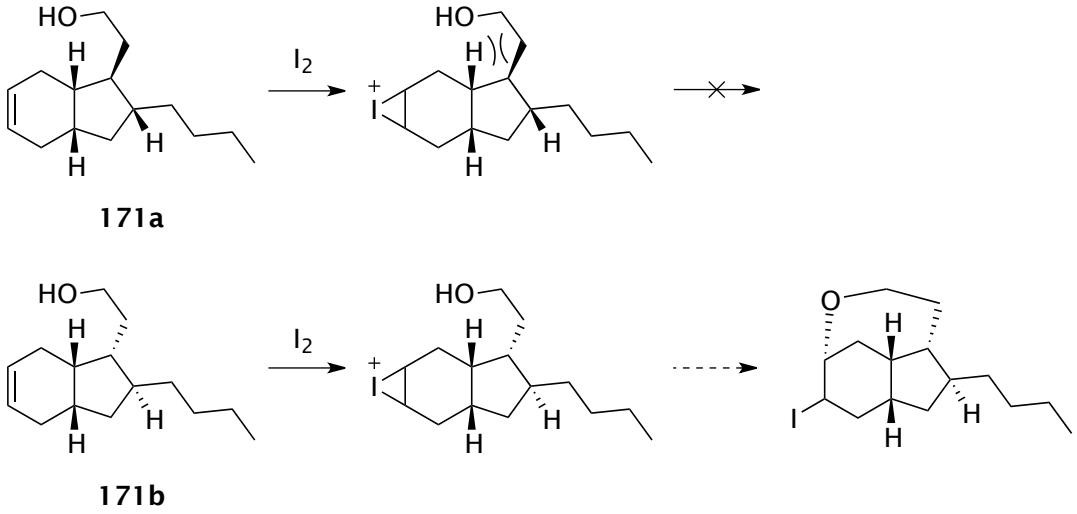
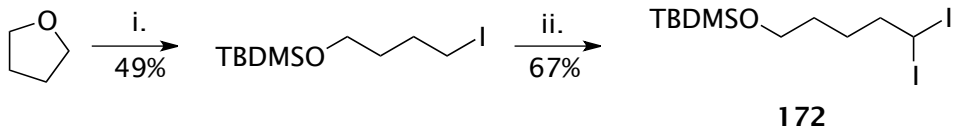


Figure 17: Iodoetherification is impossible with diastereoisomer **171a**.

Iodoetherification was attempted using iodine in refluxing benzene under acidic, basic and neutral conditions as well as at room temperature in THF. In addition the iodoetherification was also attempted with *N*-iodosuccinimide in THF at room temperature and in benzene at reflux. Of these conditions refluxing with iodine in benzene gave the best conversion of the minor diastereoisomer **171b**. The expected recovery of the major diastereoisomer **171a** as a single isomer was 73% based on the 2.7:1 major:minor ratio, however, the actual recovery was only 39% indicating that large amounts of the major diastereoisomer **171a** had been lost in a competing process.

5.2.4 Construction of the carboxylic acid side chain

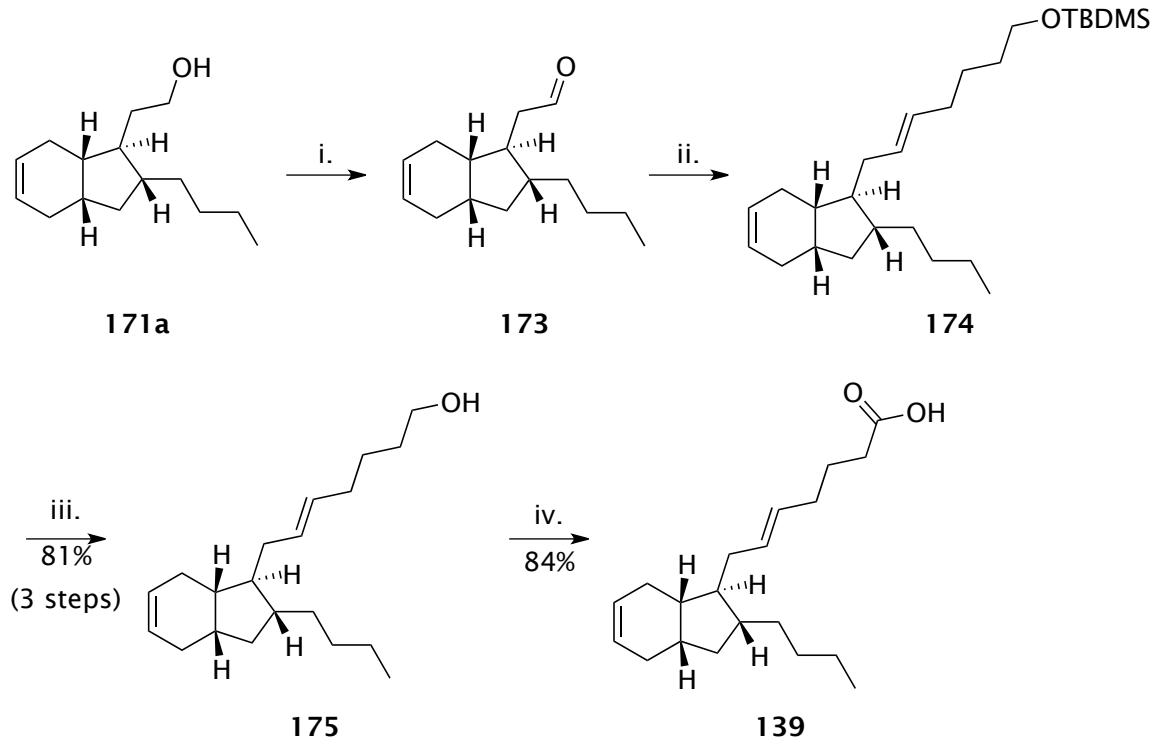
The next task was to install the *trans* alkene. This was achieved using a Takai olefination using diiodide **172**.[153] Diiodide **172** was synthesised in two steps according to literature procedures (**Scheme 85**).[154, 155]



172

Scheme 85: Synthesis of diiodide **172**. *Reagents and conditions:* i. THF, TBDMSCl, NaI, MeCN, rt, 36 h; ii. NaHMDS, CH_2I_2, THF, Et_2O, −78 °C → rt, 16 h.

The Takai olefination of aldehyde **173**, obtained by a Swern oxidation of alcohol **171a**, with diiodide **172** was followed by TBAF deprotection of silane **174** which gave alcohol **175** in 81% yield (3 steps). Finally alcohol **175** was successfully oxidised to the acid **139** using PDC in DMF in 84% yield (**Scheme 86**)



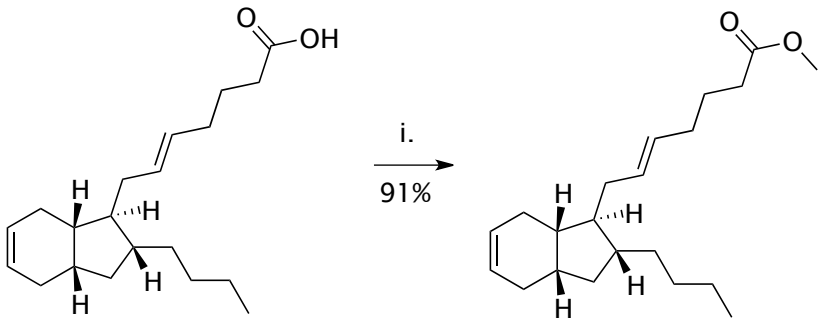
171a **173** **174**

175 **139**

Scheme 86: Construction of the carboxylic acid side chain of mucosin (**139**). *Reagents and conditions:* i. DMSO, DCM, oxalyl chloride, −60 °C, 15 min, Et_3N, −60 °C → rt, 1 h; ii. $CrCl_2$, DMF, THF, diiodide **172**, rt, 2.5 h; iii. TBAF, THF, rt, 3 h; iv. PDC, DMF, 0 °C → rt, 15 h.

5.2.5 Comparison of the spectral data

The spectral data reported when mucosin was first isolated was of its methyl ester rather than the acid. As such the synthetic sample of mucosin (**139**) was converted to its methyl ester **176** using diazomethane in 91% yield (**Scheme 87**).



139 **176**

Scheme 87: Conversion of mucosin (**139**) to its methyl ester **176**. *Reagents and conditions:* i. CH_2N_2, Et_2O, rt, 1 h.

Both the ^{1}H NMR (**Table 7**) and ^{13}C NMR (**Table 8**) are in excellent agreement with those reported by Cimino.[149]

^{1}H NMR ($CDCl_3$)	
Methyl ester of natural sample of mucosin (500 MHz)	Methyl ester of synthetic sample of mucosin (400 MHz)
5.67 (2H, m)	5.73–5.60 (2H, m)
5.45 (1H, dt, *J* 15.6, 7.2 Hz)	5.46 (1H, m)
5.39 (1H, dt, *J* 15.6, 6.9 Hz)	5.38 (1H, m)
3.66 (3H, s)	3.67 (3H, s)
2.31 (2H, t, *J* 7.5 Hz)	2.31 (2H, t, *J* 7.5 Hz)
2.25 (1H, m)	2.23 (1H, m)
2.19 (1H, m)	2.17 (1H, m)
2.12 (2H, m)	2.15–2.08 (2H, m)
2.02 (2H, q, J 7.0 Hz)	2.03 (2H, q, J 7.0 Hz)
1.72 (1H, m)	1.80–1.65 (4H, m)
1.70 (1H, m)	
1.69 (2H, m)	
1.59 (1H ,m)	1.64–1.48 (3H, m)
1.55 (1H ,m)	
1.50 (1H ,m)	
1.40 (2H ,m)	1.46–1.33 (2H, m)
1.33 (1H ,m)	1.33–1.23 (3H, m)
1.28 (2H ,m)	
1.15 (2H ,m)	1.19–1.13 (2H, m)
1.12 (1H ,m)	1.13–1.08 (2H, m)
1.11 (1H ,m)	
0.88 (3H, t, *J* 6.7 Hz)	0.89 (3H, t, *J* 6.9 Hz)

Table 7: Comparison of the ^{1}H NMR of the natural and synthetic samples of the methyl ester of mucosin **176**.

^{13}C NMR ($CDCl_3$)	
Methyl ester of natural sample of mucosin (125 MHz)	Methyl ester of synthetic sample of mucosin (100 MHz)
174.2	174.2
130.0	130.3
129.8	129.8
127.0	127.3
127.0	127.2
52.1	52.2
51.4	51.4
47.1	47.2
42.1	42.3
39.9	40.1
36.7	37.0
36.5	36.7
36.4	36.7
33.2	33.4
32.0	32.4
31.7	31.9
31.5	31.6
30.7*	30.7
24.5	24.7
22.6	22.9
13.8	14.1

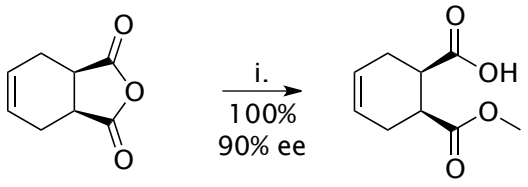
Table 8: Comparison of the ^{13}C NMR of the natural and synthetic samples of the methyl ester of mucosin **176**. * was erroneously reported at 36.3 ppm in the original publication. I am grateful to Prof. Casapullo for re-running the spectra of natural Mucosin to allow correction.

5.3 Chiral synthesis of mucosin

5.3.1 Asymmetric anhydride opening

The route chosen for the chiral synthesis of mucosin was very similar to that of the racemic sample. The chirality was introduced in the first step utilising an asymmetric opening of anhydride **143**. There are a number of asymmetric

openings of anhydrides in the literature with varying yields and ee's.[156] The alkaloid method established by Bolm was used in the synthesis of mucosin because it was not only relatively inexpensive and straightforward but more importantly gave access to both enantiomers by varying the alkaloid.[157] As the absolute stereochemistry of mucosin was unknown there was no way to know which alkaloid to use. Quinidine was chosen and the (1*R*,6*S*) enantiomer of acid ester **177** was obtained in 100% yield and 90% ee (**Scheme 88**).



143 **177**

Scheme 88: Synthesis of acid ester **177**. *Reagents and Conditions:* i. MeOH, quinidine, PhMe, −55 °C, 8 h, then −18 °C, 3 days then 2.0 M HCl.

The exclusively used method in the literature for calculating the ee of acid ester **177** has been chiral GC. Unfortunately the chiral column needed for this was not available. Instead the ee of acid ester **177** was determined using ^{1}H NMR of the adduct formed by addition of quinidine to a solution of acid ester **177** in $CDCl_3$. The integrals of the methyl ester singlets in the 3.6 ppm region gave an ee of 90% (**Figure 18**).

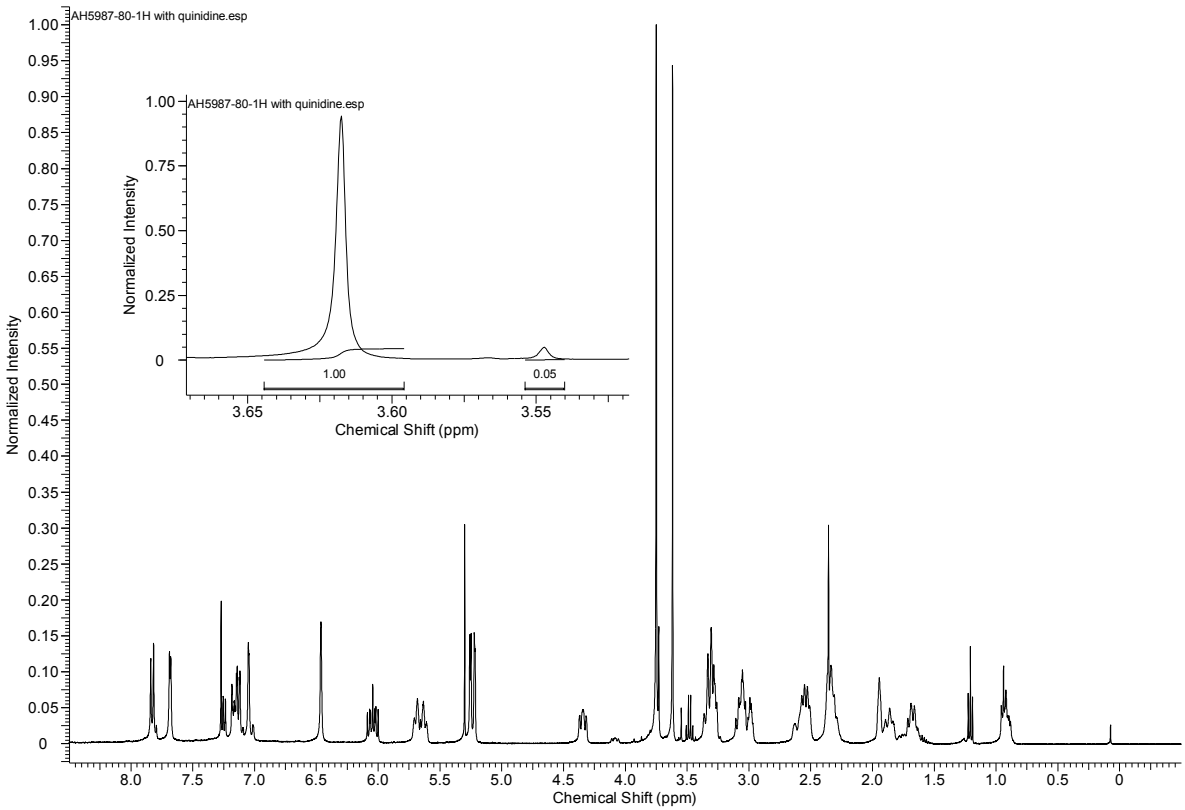
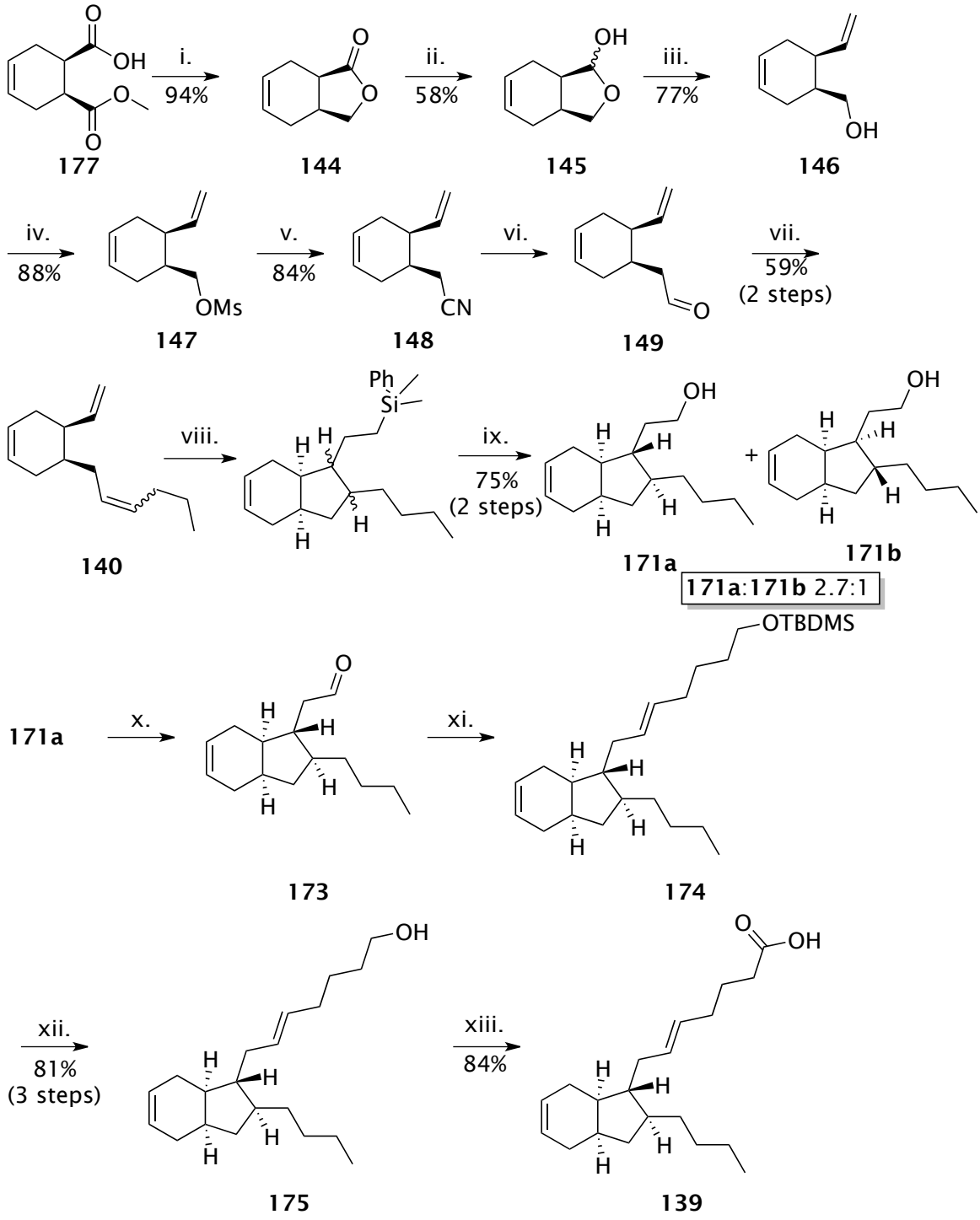


Figure 18: ^{1}H NMR spectrum of quinidine adduct of acid ester **177**.

5.3.2 Completion of the chiral synthesis

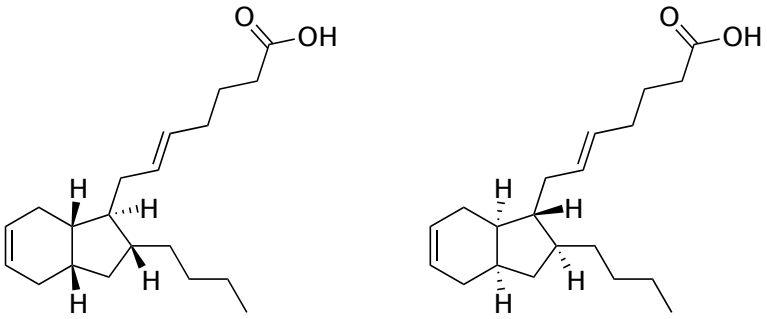
The selective reduction of acid ester **177** using Super-Hydride® gave lactone **144** in 94% yield. At this point the chiral and racemic synthesis converge. None of the subsequent steps in the racemic synthesis were likely to cause epimerisation of any chiral centres and so the chiral lactone **144** was successfully taken through the rest of the synthesis (**Scheme 89**).



Scheme 89: Completion of the chiral synthesis of mucosin (**139**). *Reagents and Conditions:* i. $Li(Et)_3BH$, THF, 0 °C, 1 h then rt, 15 h; ii. DIBAL-H (fast addition), PhMe, –78 °C, 1 h; iii. $MePh_3P^+Br^-$, *n*-BuLi, THF, 0 °C → rt, 2 h; iv. MsCl, Et_3N, DMAP, THF, 0 °C, 2 h; v. KCN, NaI, 18-crown-6, 90 °C, 66 h; vi. DIBAL-H (dropwise addition), THF, –78 °C → rt, 2 h; vii. $BuPh_3P^+Br^-$, *n*-BuLi, THF, 0 °C → rt, 2 h; viii. *n*-BuLi, $ZrCp_2Cl_2$, THF, −78 °C → rt, 2 h then $ClCH_2SiMe_2(Ph)$, LiTMP, THF, −78 °C, 45 mins then $NaHCO_3$, MeOH, −78 °C → rt, overnight; ix. KH, NMP_2, *t*-BuOOH, 0 °C → rt, 10 mins, TBAF, 70 °C, 14 h; x. DMSO, DCM, $(COCl)_2$, −60 °C, 15 min, Et_3N, −60 °C → rt, 1 h; xi. $CrCl_2$, DMF, THF, diiodide **172**, rt, 2.5 h; xii. TBAF, THF, rt, 3 h; xiii. PDC, DMF, 0 °C → rt, 15 h.

5.3.3 Determination of the absolute stereochemistry of mucosin

As was stated earlier (Section 5.3.1) the absolute stereochemistry of mucosin (**139**) was unknown. The optical rotation for the synthetic sample of the methyl ester **176** was +38.2° while the optical rotation of the methyl ester of the natural product is reported as −35.5°. This allows for the first time the absolute configuration of the natural product (−)-mucosin to be established (**Figure 19**).



(−)-mucosin
(natural product)

(+)-mucosin
(synthetic product)

Figure 19: Absolute stereochemistries of the natural product (−)-mucosin and the synthetic sample of (+)-mucosin.

5.4 Conclusions

The first total synthesis of a racemic sample of the natural product mucosin has been completed. The key step in the synthesis was the zirconocene mediated cocyclisation of a triene precursor followed by an α-silyl carbenoid insertion. This step provided the major diastereoisomer with the correct absolute stereochemistry of the four contiguous stereocentres around the bicyclic core. The synthetic route was adapted to give a sample of (+)-mucosin. This allowed the first ever determination of the absolute stereochemistry of the natural product (−)-mucosin. The route to the correct enantiomer of the natural product would only require the use of a different alkaloid in the first step of this total synthesis.

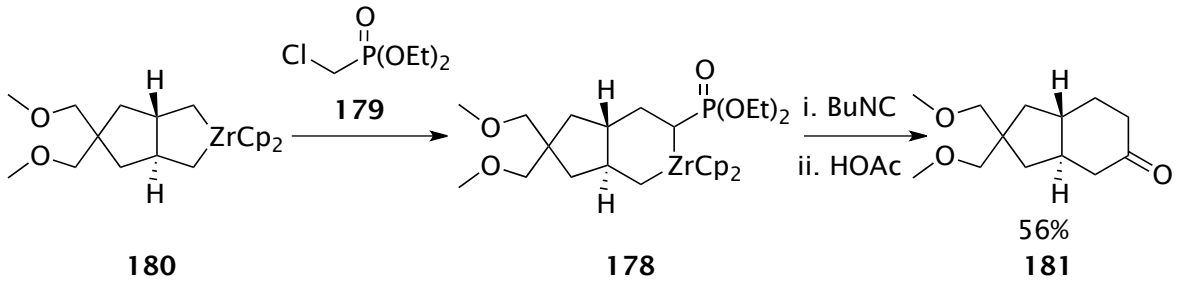
Chapter 6 Further elaborations of zirconacyclohexanes

6.1 Background to the research area

As discussed in the review chapter of this thesis (Section 1.3) both the insertion of carbenoids and isonitriles into zirconacyclopentanes leads to the formation of zirconacyclohexanes. After insertion the zirconium is once again 16-electron and hence should be capable of further elaboration. Indeed the propensity for bis-insertion of benzyl carbenoids into zirconacyclopentanes gives evidence for this continued reactivity.[69] With this in mind it could be envisaged that the insertion of a carbenoid could be followed by the insertion of an isonitrile leading to an increased number of interesting structures.

6.1.1 Previous work in the area

Previously unpublished work by Kasatkin demonstrated the potential for this chemistry.[158] Insertion of butyl isonitrile into zirconacyclohexane **178** which had been formed by insertion of a carbenoid derived from phosphonate **179** into zirconacyclopentene **180** gave cyclohexanone **181** after quenching with acetic acid.



180 **178** **181**

Scheme 90: Formation of cyclohexanone **181** by sequential insertion of carbenoid **179** and butylisonitrile.

It is expected that the insertion of butyl isonitrile into zirconacyclohexanes should proceed in the same manner as insertion into zirconacyclopentanes. The first step in this insertion is formation of the 18-electron 'zirconate' species **182**. Rapid rearrangement to iminoacyl complex **183** is followed by the slow rearrangement to η^2-imine complex **184**.[45] At this point it is postulated that

migration of the phosphonate group onto the zirconium occurs to form enamine **185**. Hydrolysis of enamine **185** with acetic acid yields cyclohexanones **181** (**Figure 20**).

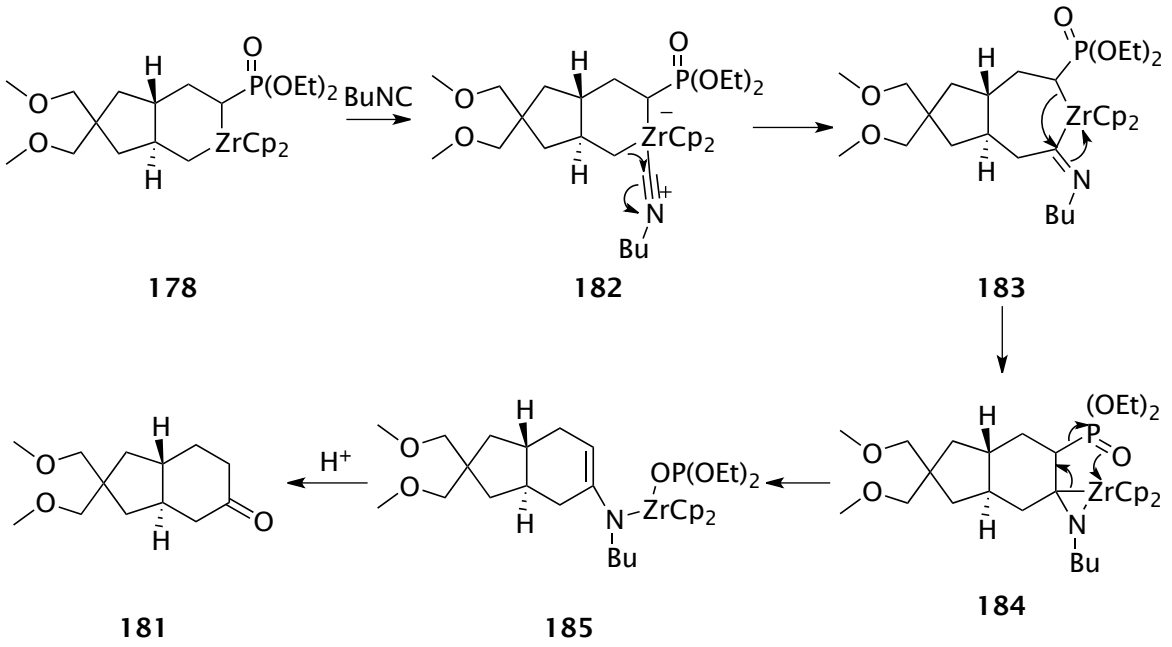
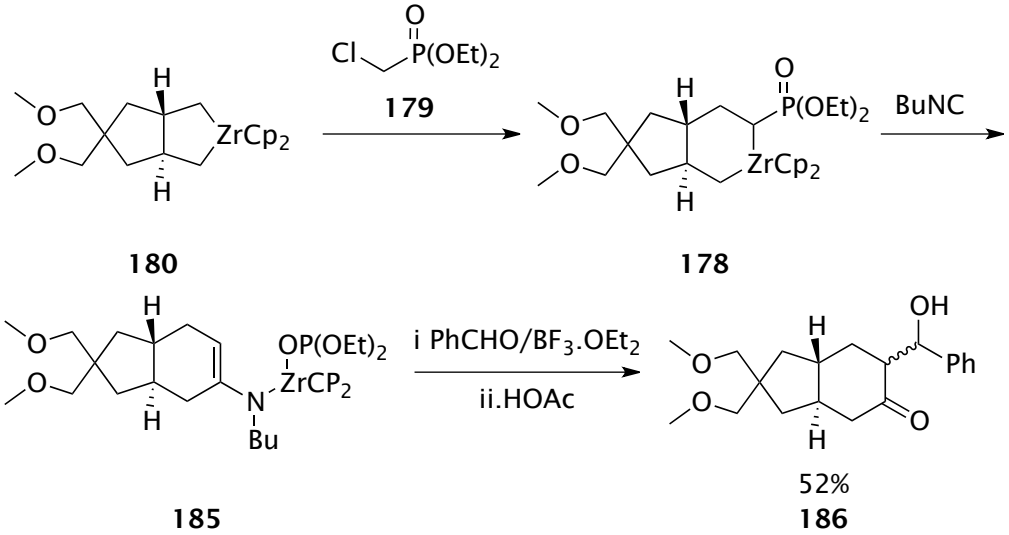


Figure 20: Proposed route to cyclohexanones **181** from zirconacycle **178**.

Treatment of the reaction mixture with benzaldehyde and $BF_3.OEt_2$ prior to quenching gave alcohol **186** as a mixture of diastereoisomers in 52% yield (**Scheme 91**) providing good evidence for the formation of enamine **185**.



Scheme 91: Trapping of enamine intermediate **185** with benzaldehyde.

Kasatkin successfully synthesised a range of cyclohexanones **181** in moderate yields from a variety of dienes using this methodology (**Table 9**).

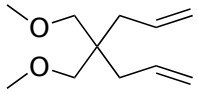
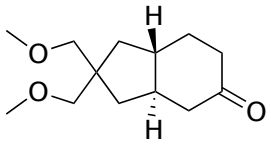
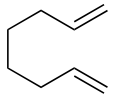
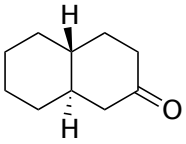
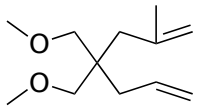
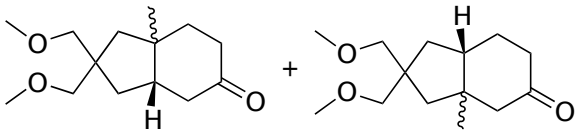
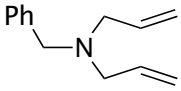
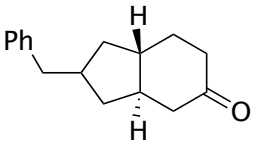
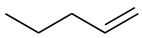
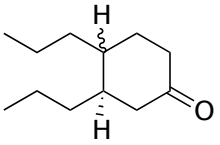
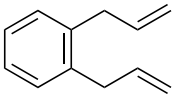
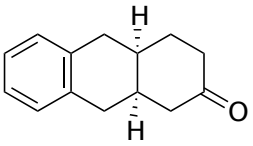
Diene	Cyclohexanone **181**	Yield
		56%
		44%
		28%
		52%
		42%
		50%

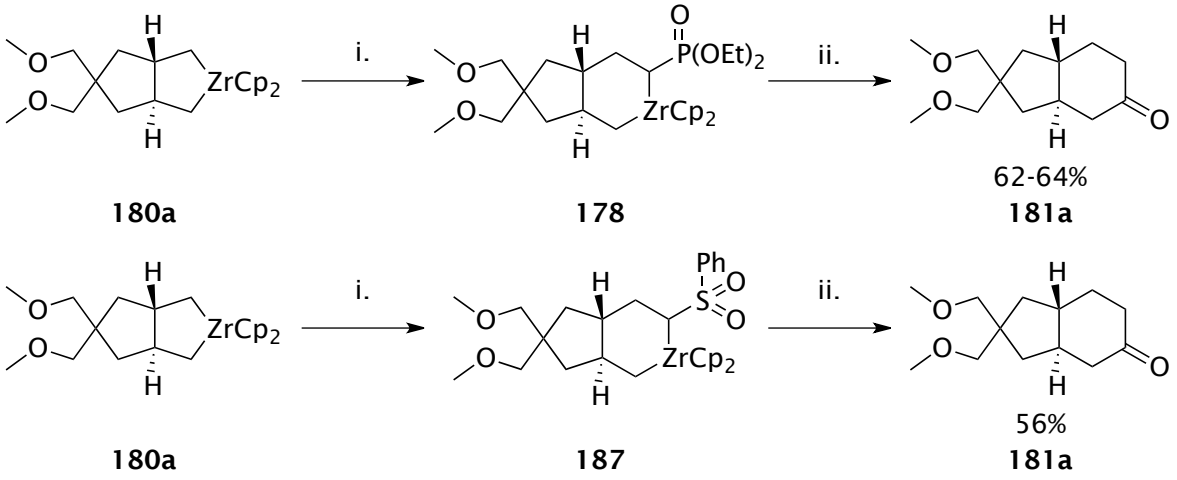
Table 9: Range of cyclohexanones **181** formed from different dienes.

6.2 Extension of phosphonate work

Kasatkin had shown the scope of this work with regards to the starting diene. It was envisaged that exploring different ways of trapping enamine **185** as well as using different carbenoids and isonitriles could extend this work further.

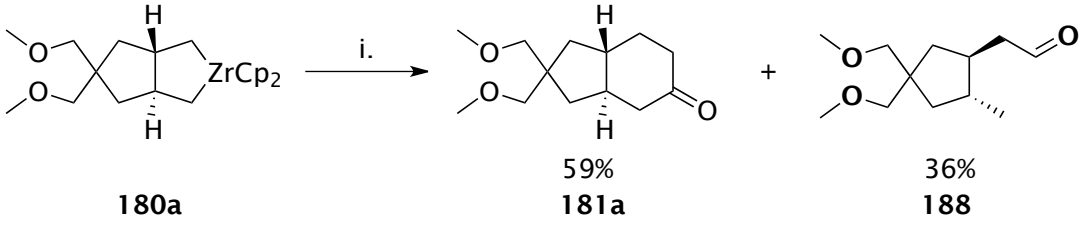
The synthesis of cyclohexanone **181a** was successfully achieved using both butyl isonitrile and phenyl isonitrile in 64% and 62% yield respectively. The synthesis of

cyclohexanone **181a** was also achieved using the carbenoid derived from ((chloromethyl)sulfonyl)benzene through zirconacycle **187** in 56% yield (**Scheme 92**).



Scheme 92: Synthesis of cyclohexanone **181a**. *Reagents and conditions:* i. $ClCH_2PO(OEt)_2$ or $ClCH_2SO_2Ph$, LDA, THF, −90 °C → −40 °C, 2 h; ii. BuNC or PhNC, −40 °C → rt, overnight, then 50% HOAc, rt, 1 h.

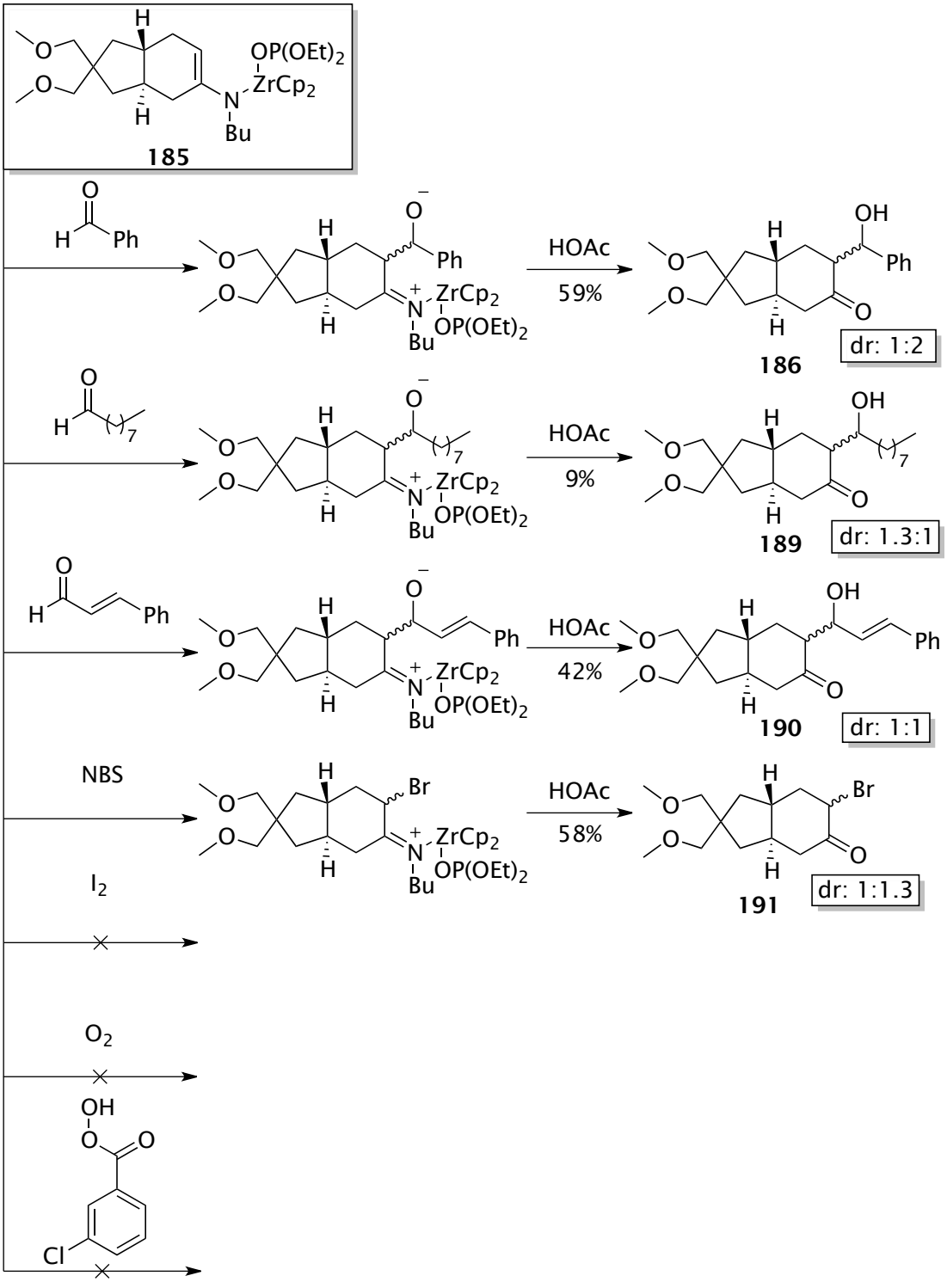
Changing the isonitrile does not significantly alter the yield of cyclohexanone **181** obtained. This is consistent with the experimental observation that aldehyde **188** was obtained in addition to cyclohexanone **181a** when butyl isonitrile was used in excess. Aldehyde **181a** is formed from isonitrile insertion into zirconacycle **180a** (**Scheme 93**). This suggests that the yield is limited by the extent of carbenoid insertion achieved. The reported isolated yields for insertion of the phosphonate and sulfonate carbenoids used is 74% and 67% respectively so there is minimal loss of yield from the isonitrile insertion.[68]



Scheme 93: Synthesis of cyclohexanone **181a**. *Reagents and conditions:* i. $ClCH_2PO(OEt)_2$, LDA, THF, −90 °C → −40 °C, 2 h, then BuNC or PhNC, −40 °C → rt, overnight, then 50% HOAc, rt, 1 h.

6.2.1 Trapping of the enamine intermediate

A variety of methods for trapping enamine **185** were attempted (**Scheme 94**).



Scheme 94: Trapping of enamine **185.** *Reagents and conditions:* trapping reagent, −40 °C → rt, overnight, then 50% HOAc, rt, 1 h.

As Kasatkin had shown aldehydes were effective traps for enamine **185**. Trapping of enamine **185** with benzaldehyde, nonanal and cinnamaldehyde successfully yielded alcohols **186**, **189** and **190** respectively. NBS also proved to be a good quench resulting in the formation of bromides **191**. There appears to be little diastereocontrol with any of these systems with the exception of benzaldehyde, which yields a 2:1 ratio of diastereoisomers presumably due to the increased steric bulk in comparison with the other trapping reagents. Trapping with iodine, oxygen and *m*-CPBA was unsuccessful as only cyclohexanone **181a** was recovered in each case.

6.3 Insertion of benzyl carbenoid and isonitriles

The insertion of benzyl carbenoids into zirconacyclopentanes has been explored previously.[69] Given their thermal stability and propensity for bis insertion it was envisaged that benzyl carbenoids would be ideal for extending this work further. Benzyl carbenoid was inserted into zirconacycle **180** to give zirconacyclohexane **192**. The insertion of a series of isonitriles into zirconacyclohexane **192** was attempted. Interestingly as well as the expected cyclohexanone **193** being obtained, aldehydes **194** and **195** were also obtained under certain conditions (**Table 10**).

Isonitrile	Isolated yield of cyclohexanone **193**	Isolated yield of aldehyde **194**	Isolated yield of aldehyde **195**
BuNC	0%	61%	0%
PhNC	61%	0%	0%
TMSCN	32%	0%	23%
TBDMSCN	24%	0%	25%

Table 10: Products obtained from insertion of different isonitriles into zirconacyclohexane **193**

Several observations can be made from the results obtained. Firstly the extent of rearrangement of iminoacyl complexes **196** and **197** to η^2-imine complex **198** is dependent on the isonitrile used. Use of PhNC achieves full conversion; use of BuNC does not achieve any rearrangement while TMSCN and TBDMSCN both

achieve moderate rearrangement. Secondly the isonitrile can insert into either C-Zr bond not just the least hindered bond as was expected. Thirdly rearrangement to the η^2-imine complex **198** is not dependent on which C-Zr bond the isonitrile inserts into.

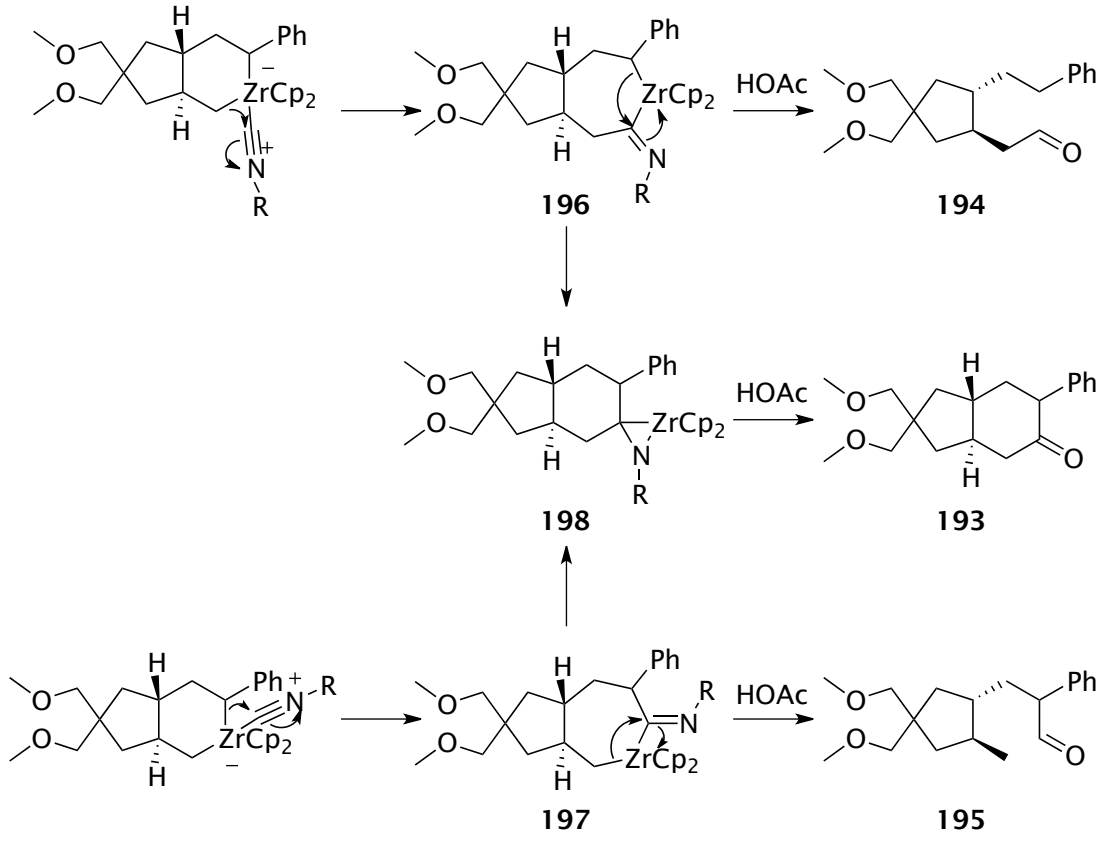


Figure 21: Mechanism for the formation of cyclohexanone **193** and aldehydes **194** and **195**

6.4 Further Work

There is scope for further work within this area of research. The obvious extension to this work would be to vary the benzyl carbenoid used. This would not only lead to the synthesis of further interesting structures but may also help in the understanding of why varying the isonitrile has such a dramatic effect on the rearrangement to the η^2-imine complex. Finally trapping of the η^2-imine complex could expand the potential for this reaction further than simple hydrolysis.

6.5 Conclusions

A series of zirconacyclohexanes formed by insertion of phosphonate, sulfonate and benzyl carbenoids have been further elaborated to a series of cyclohexanones by insertion of a series of isonitriles. The trapping of the intermediate enamine with a series of aldehydes as well as NBS has also been achieved.

Chapter 7 Experimental

7.1 General experimental information

All reactions were carried out under an argon atmosphere using standard Schlenk equipment and syringe techniques. All glassware was dried in a hot oven (160 ºC, for at least 12 h) and cooled in a sealed desiccator over silica gel or assembled while hot and cooled under vacuum.

DCM, DMSO and MeCN were freshly distilled from CaH_2. DMF was freshly distilled from $MgSO_4$. Et_2O, THF and toluene were freshly distilled from sodium/benzophenone. *n*-BuLi was used as a 2.5 M solution in hexanes and was stored at 4 °C. DIBAL-H was used as a 1.0 M solution in THF or as a 1.0 M solution in toluene; both were stored at 4 °C. LDA was used as a 1.8 M solution in THF and was stored at 4 °C. The RPMI complete medium used in the cell proliferation assays was RPMI 1640 (PAA laboratories), 20% fetal calf serum (PAA laboratories), 1 mM sodium pyruvate MEM (Lonza, Cambridge, UK), 0.1 mM MEM non-essential amino acids (Lonza, Cambridge, UK), 2 mM L-glutamine (Lonza, Cambridge, UK). All other solvents and commercially obtained reagents were used as received or purified using standard procedures.

Reactions were monitored by GC and/or TLC. GC was performed on a Hewlett Packard HP 6890 series GC system, using a HP-5 (cross-linked 5% Ph Me siloxane) 30 m column, with a film thickness of 0.25 μm and 0.32 mm internal diameter. The carrier gas was helium and the flow rate was 2.7 mL min^{-1}. TLC was performed using Merck silica gel 60 F_{254} plates with detection by UV and/or polyphosphomolybdic acid dip.

Fisher Scientific silica gel 60A (particle size 35–70 microns) or Merck silica gel 60 (0.040–0.063 mm) was used for flash chromatography columns. Basic alumina Brockman I deactivated with 6% of H_2O was used for purification of acid sensitive products. Columns were packed and run under light pressure. Solvent compositions are described as ratios prior to mixing.

NMR spectra were recorded on Bruker AV300, AM300 or DPX400 spectrometers. Chemical shifts for proton and carbon NMR spectra are reported on the δ scale in ppm and were referenced to residual chloroform peaks at 7.27 ppm for ^{1}H spectra and 77.00 ppm (centre peak of triplet) for ^{13}C spectra. The coupling constants (*J*) are measured in Hz (Hertz) and rounded to 0.1 Hz. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), sextet (sxt), multiplet (m), broad (br), or a combination of these. ^{13}C NMR spectra were proton decoupled. DEPT, COSY and ^{1}H-^{13}C correlation experiments were used to aid assignment of spectra. The numbered assignment for proton and carbon signals is for identification purposes only and does not represent the systematic IUPAC numbering.

Electron impact ionisation (EI) and chemical ionisation (CI) mass spectra were recorded on a ThermoQuest TraceMS GCMS. Electrospray mass spectra (ESI) were recorded using a VG platform quadrupole spectrometer. Accurate mass spectra were recorded on a VG analytical 70-250-SE double focusing mass spectrometer using EI at 70 eV or a Bruker Apex III using ESI.

Infra-red spectra were run as neat films on a Thermo Nicolet 380 FT-IR spectrometer with a Smart Orbit Goldengate attachment. Absorptions are given in wavenumbers (cm^{-1}). Peaks are recorded as s (strong), m (medium), w (weak), sh (shoulder) or br (broad).

Melting points were recorded on a Reichert 349 360 melting point apparatus and are uncorrected.

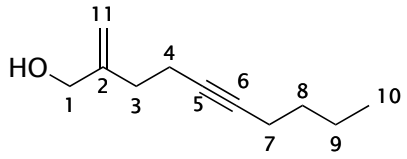
The following compounds were prepared by literature methods and had spectral properties consistent with those published:

- Hept-2-yn-1-ol (**73**)[82, 159]
- 1-Bromohept-2-yne (**69**)[83, 160]
- Diethyl 2-(hept-2-yn-1-yl)malonate (**75**)[85]
- Oct-3-yn-1-ol (**80**)[86, 161]
- 1-Bromooct-3-yne (**79**)[87, 162]

- 5-(Trimethylsilyl)pent-4-yn-1-ol (**93**)[163, 164]
- 5-(Trimethylsilyl)pent-4-ynal (**91**)[164, 165]
- 3,5-Dimethoxybenzoyl chloride (**105a**)[108, 109]
- 3,5-Bisbenzyloxybenzoic acid (**104a**)[111]
- 3,5-(Bisbenzyloxy)benzoyl chloride (**105b**)[109, 112]
- 2-(4-Chlorophenyl)-1*H*-benzo[*d*]imidazole-5-carboxylic acid (**103**)[107, 113]
- 2-(Pent-1-yn-1-yl)aniline (**114a**)[166, 167]
- 2-(Hex-1-yn-1-yl)aniline (**114b**)[166, 168]
- *N*-(2-(Hex-1-yn-1-yl)phenyl)methanesulfonamide (**115c**)[168, 169]
- *N*-(2-(Hex-1-yn-1-yl)phenyl)-4-methylbenzenesulfonamide (**115b**)[169]
- 2-(4-Methylphenylsulfonamido)ethyl 4-methylbenzenesulfonate (**118**)[143, 144]
- 1-Tosylaziridine (**119**)[144]
- 4-Methyl-*N*-(oct-3-yn-1-yl)benzenesulfonamide (**120a**)[170, 171]
- 4-Methyl-*N*-(4-phenylbut-3-yn-1-yl)benzenesulfonamide (**120b**)[169, 170]
- 4-Methyl-*N*-(4-(trimethylsilyl)but-3-yn-1-yl)benzenesulfonamide (**120c**)[170, 172]
- 1-Bromonon-4-yne (**124**)[173]
- 1-Bromohex-1-yne (**199a**)[174, 175]
- (Bromoethynyl)benzene (**199b**)[174, 176]
- (Bromoethynyl)trimethylsilane (**199c**)[174, 177]
- Hept-6-en-1-yn-1-yltrimethylsilane (**132a**)[16, 173]
- Trimethyl(oct-7-en-1-yn-1-yl)silane (**132b**)[16, 173]
- (1*R*,6*S*)-6-(Methoxycarbonyl)cyclohex-3-enecarboxylic acid (**177**)[157]
- (3a*S*,7a*R*)-3a,4,7,7a-Tetrahydroisobenzofuran-1(3*H*)-one (**144**)[151]
- ((1*S*,6*S*)-6-Vinylcyclohex-3-en-1-yl)methanol (**146**)[151]
- *tert*-Butyl(4-iodobutoxy)dimethylsilane[154]
- *tert*-Butyl((5,5-diiodopentyl)oxy)dimethylsilane (**172**)[155]

7.2 Experimental for chapter 2

2-Methylenedec-5-ynol (74)



TMEDA (5.1 mL, 34.0 mmol) and 2-methyl-2-propen-1-ol (1.43 g, 17.0 mmol) were added dropwise sequentially to *n*-BuLi (13.5 mL of a 2.5 M solution in hexanes, 34.0 mmol) in ether (10.0 mL) at −78 °C. The reaction mixture was left stirring at room temperature for 15 h. Bromide **69** (2.24 g, 12.8 mmol) was added dropwise to the reaction mixture at −78 °C. The reaction mixture was left stirring at −78 °C for 2 h and at room temperature for 6 h. The reaction mixture was poured into a sat. aq. NH_4Cl solution (100 mL) and extracted with ether (2 × 50 mL). The organic extracts were combined, washed sequentially with sat. aq. $CuSO_4$ solution (3 × 25 mL) and brine (3 × 25 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as a colourless oil (1.10 g). Purification by column chromatography (SiO_2, hexane/Et_2O 1:1) gave the title compound as a pale yellow oil (898 mg, 42%).

IR: ν_{max} (neat)/cm^{-1} 3333 (br), 2957 (sh), 2930 (m), 2872 (w)

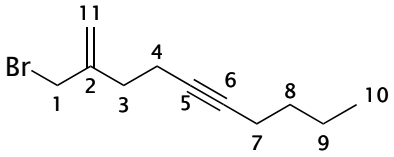
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 5.07 (1H, d, *J* 1.3 Hz, H-11a), 4.92 (1H, d, *J* 1.1 Hz, H-11b), 4.10 (2H, s, H-1), 2.37–2.21 (4H, m, H-3,4), 2.13 (2H, tt, *J* 6.8, 2.3 Hz, H-7), 1.53–1.29 (4H, m, H-8,9), 0.90 (3H, t, *J* 7.0 Hz, H-10)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 147.58 (C, C-2), 110.47 (CH2, C-11), 80.91 (C), 79.38 (C), 65.77 (CH_2, C-1), 32.49 (CH_2), 31.11 (CH_2), 21.87 (CH_2), 18.35 (CH_2), 17.79 (CH_2), 13.57 (CH_3, C-10)

LRMS: (ES+) m/z 189.1 ([M+Na]$^+$)

HRMS: (EI) Calculated for $C_{11}H_{18}O$: 166.13577 Da, found: 166.13633 Da

1-Bromo-2-methylenedec-5-yne (70)



Dry pyridine (0.03 mL, 0.30 mmol) and PBr_3 (0.56 mL, 6.0 mmol) were added dropwise sequentially to a stirred solution of alcohol **74** (2.76 g, 16.6 mmol) in dry ether (40 mL). The reaction mixture was heated to reflux for 1.75 h. The reaction mixture was poured into cold water (200 mL) and extracted with ether (3 × 50 mL). The organic extracts were combined, washed sequentially with sat. aq. $NaHCO_3$ solution (75 mL) and brine (75 mL), dried ($MgSO_4$), filtered and the solvent distilled off under atmospheric pressure to give the crude product as an orange oil (3.48 g, 91%).

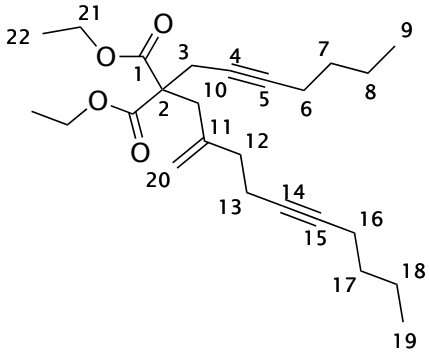
IR: ν_{max} (neat)/cm^{-1} 2956 (sh), 2930 (w), 2860 (w)

^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 5.22 (1H, br. s, H-11a), 5.02 (1H, d, *J* 1.1 Hz, H-11b), 4.00 (2H, s, H-1), 2.46–2.29 (4H, m, H-3,4), 2.13 (2H, tt, *J* 6.9, 2.4 Hz, H-7), 1.55–1.33 (4H, m, H-8,9), 0.90 (3H, t, *J* 7.0 Hz, H-10)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 144.10 (C, C-2), 115.82 (CH_2, C-11), 81.12 (C), 78.77 (C), 36.47 (CH_2), 32.76 (CH_2), 31.09 (CH_2), 21.86 (CH_2), 18.35 (CH_2), 17.40 (CH_2), 13.57 (CH_3, C-10)

LRMS: (EI) m/z 229.9 ($[M]^{+\bullet}$, ^{81}Br, 1%), 228.0 ($[M]^{+\bullet}$, ^{79}Br, 1%), 186.8 ($[M-C_3H_7]^+$, ^{81}Br, 3%), 184.6 ($[M-C_3H_7]^+$, ^{79}Br, 3%), 172.9 ($[M-C_4H_9]^+$, ^{81}Br, 2%), 171.0 ($[M-C_4H_9]^+$, ^{79}Br, 2%), 149.2 ($[M-Br]^+$, 20%), 135.0 ($[M-CH_2Br]^+$, 11%), 92.9 (100%)

Diethyl 2-(hept-2-yn-1-yl)-2-(2-methylenedec-5-yn-1-yl)malonate (71)



Malonate ester **75** (390 mg, 1.5 mmol) was added dropwise to a stirred suspension of NaH (88.0 mg of a 60% dispersion in mineral oil, 2.2 mmol) in dry THF (14.0 mL). The reaction mixture was left stirring at room temperature for 1 h. Bromide **70** (438 mg, 1.9 mmol) was added dropwise to the reaction mixture at room temperature. The reaction mixture was left stirring at room

temperature for 15 h. The reaction mixture was poured into a sat. aq. NH_4Cl solution (50 mL) and extracted with ether (3 × 30 mL). The organic extracts were combined, washed with brine (3 × 50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as an orange oil (642 mg). Purification by column chromatography (SiO_2, hexane/Et_2O 5:1) gave the title compound as a colourless oil (186 mg, 30%).

IR: ν_{max} (neat)/cm^{-1} 2957 (sh), 2932 (w), 2872 (w), 1734 (m)

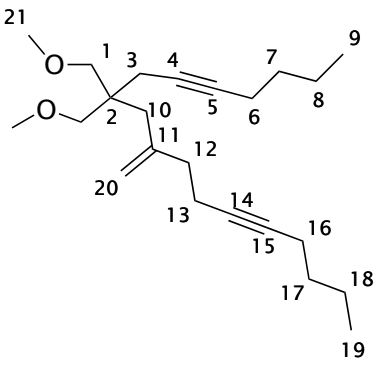
^{1}**H NMR:** δ_H (300 MHz, $CDCl_3$) 4.93 (1H, d, *J* 1.5 Hz, H-20a), 4.90 (1H, br. s, H-20b), 4.26–4.07 (4H, m, H-21), 2.80 (2H, s, H-10), 2.76 (2H, t, *J* 2.4 Hz, H-3), 2.30–2.19 (2H, m, H-6), 2.17–2.03 (6H, m, H-12,13,16), 1.51–1.30 (8H, m, H-7,8,17,18), 1.24 (6H, t, *J* 7.1 Hz, H-22), 0.88 (6H, t, *J* 7.2 Hz, H-9,19)

^{13}**C NMR:** δ_C (75 MHz, $CDCl_3$) 170.27 (C, C-1), 142.79 (C, C-11), 115.43 (CH_2, C-20), 83.86 (C), 80.62 (C), 79.18 (C), 74.58 (C), 61.42 (CH_2, C-21), 56.92 (C, C-2), 36.92 (CH_2), 36.17 (CH_2), 31.11 (CH_2), 30.91 (CH_2), 22.83 (CH_2), 21.81 (CH_2), 21.78 (CH_2), 18.33 (CH_2), 18.26 (CH_2), 17.81 (CH_2), 13.94 (CH_3, C-22), 13.55 (CH_3), 13.49 (CH_3)

LRMS: (ES+) m/z 425.3 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{25}H_{39}O_4$: 403.2843 Da, found: 403.2833 Da

8,8-Bis(methoxymethyl)-10-methyleneoctadeca-5,13-diyne (68)



Malonate ester **71** (1.69 g, 4.2 mmol) was added dropwise to a stirred suspension of $LiAlH_4$ (512 mg, 13.5 mmol) in dry THF (30 mL) at 0 °C. The reaction mixture was left stirring at 0 °C for 30 mins and at room temperature for 2 h. 2 M aq. NaOH solution was added cautiously until all of the $LiAlH_4$ had been destroyed. The reaction mixture was extracted with ether (3 × 75 mL). The organic extracts were combined, washed with water (2 × 200 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude intermediate diol **72** as a colourless oil (1.15 g). Purification by column chromatography (SiO_2, hexane/ethyl acetate 2:1) removed the major impurities to

give intermediate diol **72** as a colourless oil (766 mg). Intermediate diol **72** (741 mg, 2.3 mmol) was added dropwise to a stirred suspension of NaH (448 mg of a 60% dispersion in mineral oil, 11.2 mmol) in dry THF (10.0 mL) at 0 °C. The reaction mixture was left stirring at room temperature for 1 h. MeI (0.70 mL, 11.2 mmol) was added dropwise to the reaction mixture and left stirring for 3.5 h. MeOH (5.0 mL) was added dropwise and the reaction mixture extracted with ether (3 × 50 mL). The organic extracts were combined, washed with brine (2 × 50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as a colourless oil (909 mg). Purification by column chromatography (SiO_2, hexane/ethyl acetate 10:1) gave the title compound as a colourless oil (675 mg, 48% over 2 steps).

IR: ν_{max} (neat)/cm^{-1} 2956 (sh), 2928 (m), 2873 (sh), 2808 (sh)

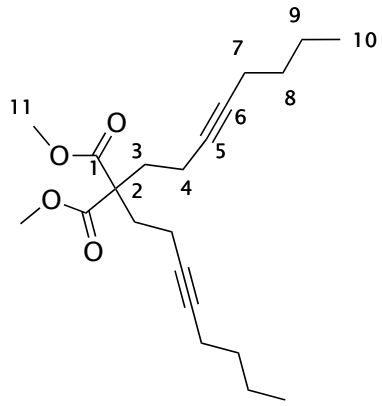
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 4.95 (1H, d, *J* 1.7 Hz, H-20a), 4.87 (1H, d, *J* 1.7 Hz, H-20b), 3.31 (6H, s, H-21), 3.23 (2H, d, *J* 9.0 Hz, H-1a), 3.19 (2H, d, *J* 9.0 Hz, H-1b), 2.33–2.07 (12H, m, H-3,6,10,12,13,16), 1.58–1.34 (8H, m, H-7,8,17,18), 0.97–0.84 (6H, m, H-9,19)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 144.47 (C, C-11), 114.32 (CH_2, C-20), 82.56 (C), 80.37 (C), 79.81 (C), 76.63 (C), 74.18 (CH_2, C-1), 58.99 (CH_3, C-21), 42.59 (C, C-2), 37.21 (CH_2), 36.21 (CH_2), 31.23 (CH_2), 31.21 (CH_2), 22.49 (CH_2), 21.95 (CH_2), 21.87 (CH_2), 18.46 (CH_2), 18.41 (CH_2), 18.03 (CH_2), 13.60 (CH_3), 13.58 (CH_3)

LRMS: (EI) m/z 346.3 ($[M]^{+\bullet}$, 7%), 315.4 ($[M-CH_3O]^+$, 2%), 303.4 ($[M-C_3H_7]^+$, 1%), 301.2 ($[M-C_2H_5O]^+$, 13%), 289.2 ($[M-C_4H_9]^+$, 2%), 149.2 ($[M-C_{12}H_{21}O_2]^+$, 11%), 45.0 ($[M-C_{21}H_{33}O]^+$, 100%)

HRMS: (ES+) Calculated for $C_{23}H_{38}NaO_2$: 369.2764 Da, found: 369.2761 Da

Dimethyl-2,2-di(oct-3-ynyl)malonate (82)



Dimethyl malonate (1.15 mL, 10.0 mmol) was added dropwise to a stirred suspension of NaH (404 mg of a 60% dispersion in mineral oil, 10.1 mmol) in dry DMF (10.0 mL). The reaction mixture was stirred at room temperature for 1 h. Bromide **79** (2.17 g, 10.1 mmol) was added dropwise to the reaction mixture at room temperature. The reaction mixture was stirred at room temperature for 30 mins. NaH (404 mg of a 60% dispersion in mineral oil, 10.1 mmol) was added and the reaction mixture stirred at room temperature for 55 mins. Bromide **79** (2.17 g, 10.1 mmol) was added dropwise to the reaction mixture at room temperature. The reaction mixture was stirred at 80 °C for 3 h and room temperature for 15 h. NaH (400 mg of a 60% dispersion in mineral oil, 10.0 mmol) was added to the reaction mixture at room temperature. The reaction mixture was stirred at room temperature for 1 h. Bromide **79** (2.13 g, 10.0 mmol) was added dropwise to the reaction mixture at room temperature. The reaction mixture was stirred at 80 °C for 3 h. Once cool the reaction mixture was poured into water (100 mL) and extracted with ether (3 × 50 mL). The organic extracts were combined, washed with brine (2 × 100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as a pale yellow oil (4.89 g). Purification by column chromatography (SiO_2, hexane/Et_2O 5:1) gave the title compound as a colourless oil (1.40 g, 42%).

IR: ν_{max} (neat)/cm^{-1} 2955 (w), 2932 (w), 2872 (sh), 1732 (s)

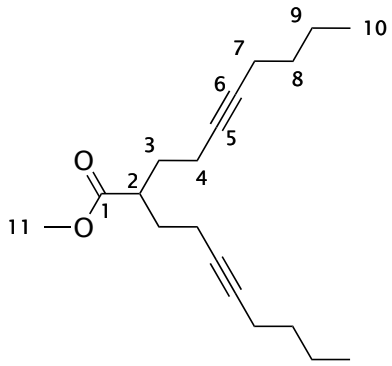
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 3.71 (6H, s, H-11), 2.25–2.01 (12H, m, H-3,4,7), 1.53–1.30 (8H, m, H-8,9), 0.89 (6H, t, *J* 7.1 Hz, H-10)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 171.19 (C, C-1), 80.90 (C), 78.39 (C), 56.71 (C, C-2), 52.44 (CH_3, C-11), 31.97 (CH_2), 31.01 (CH_2), 21.92 (CH_2), 18.39 (CH_2), 14.25 (CH_2), 13.57 (CH_3, C-10)

LRMS: (ES+) m/z 371.2 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{21}H_{33}O_4$: 349.2373 Da, found: 349.2366 Da

Methyl-2-(oct-3-ynyl)dec-5-ynoate (83)



Malonate ester **82** (1.52 g, 4.6 mmol), DMSO (12.0 mL), water (0.09 mL, 5.0 mmol) and LiCl (579 mg, 13.7 mmol) were stirred at 160 °C for 5 h followed by stirring at room temperature for 15 h. The reaction mixture was diluted with water (75 mL) and extracted with ether (3 × 30 mL). The organic extracts were combined, washed sequentially with water (2 × 50 mL) and brine (2 × 50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as an orange oil (1.26 g). Purification by column chromatography (SiO_2, hexane/Et_2O 10:1) gave the title compound as a colourless oil (1.10 g, 84%).

IR: ν_{max} (neat)/cm^{-1} 2955 (sh), 2931 (m), 2861 (w), 1735 (m)

^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 3.68 (3H, s, H-11), 2.65 (1H, tt, *J* 8.6, 5.4 Hz, H-2), 2.31–2.02 (8H, m, H-4,7), 1.93–1.73 (2H, m, H-3a), 1.73–1.56 (2H, m, H-3b), 1.54–1.31 (8H, m, H-8,9), 0.90 (6H, t, *J* 7.3 Hz, H-10)

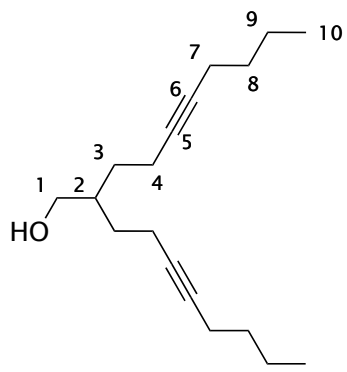
^{13}C NMR: δ_C (75 MHz, $CDCl_3$)

175.79 (C, C-1), 80.94 (C), 78.78 (C), 51.52 (CH_3, C-11), 43.49 (CH, C-2), 31.29 (CH_2), 31.14 (CH_2), 21.91 (CH_2), 18.40 (CH_2), 16.83 (CH_2), 13.59 (CH_3, C-10)

LRMS: (ES+) m/z 313.3 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{19}H_{30}NaO_2$: 313.2138 Da, found: 313.2134 Da

2-(Oct-3-ynyl)dec-5-yn-1-ol (84)



Ester **83** (701 mg, 2.4 mmol) was added dropwise to $LiAlH_4$ (137 mg, 3.6 mmol) in dry THF (20 mL). The reaction mixture was stirred at 0 °C for 30 mins and at room temperature for 2 h. 2 M aq. NaOH solution (2 mL) was added to the reaction mixture. The reaction mixture was extracted with ether (3 × 50 mL). The organic extracts were combined, washed with water (2 × 100 mL), dried ($MgSO_4$), filtered and the solvent

distilled off under atmospheric pressure to give the crude product as a colourless oil (980 mg). Purification by column chromatography (SiO_2, hexane/Et_2O 2:1) gave the title compound as a colourless oil (588 mg, 93%).

IR: ν_{max} (neat)/cm^{-1} 3346 (br), 2956 (sh), 2929 (s), 2861 (m)

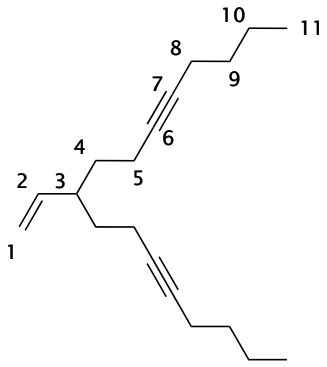
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 3.62 (2H, dd, *J* 5.8, 5.3 Hz, H-1), 2.27–2.18 (4H, m, H-4 or H-7), 2.14 (4H, tt, *J* 6.9, 2.5 Hz, H-4 or H-7), 1.76 (1H, ttt, *J* 7.1, 5.8, 4.9 Hz, H-2), 1.66–1.29 (13H, m, OH and H-3,8,9), 0.91 (6H, t, *J* 7.1 Hz, H-10)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 80.61 (C), 79,88 (C), 64.47 (CH_2, C-1), 39.01 (CH, C-2), 31.18 (CH_2), 30.25 (CH_2), 21.95 (CH_2), 18.40 (CH_2), 16.38 (CH_2), 13.60 (CH_3, C-10)

LRMS: (EI) m/z 262.1 ($[M]^{+\bullet}$, 2%), 244.1 ($[(M-H_2O]^{+\bullet}$, 9%), 219.2 ($[M-C_3H_7^+$, 8%), 201.0 ($[M-H_2O,C_3H_7]^{+\bullet}$, 11%), 187.0 ($[M-H_2O,C_4H_9]^{+\bullet}$, 15%), 41.2 (100%)

HRMS: (EI) Calculated for $C_{18}H_{30}O$: 262.22967 Da, found: 262.22931 Da

9-Vinylheptadeca-5,12-diyne (78)



DMSO (0.32 mL, 4.5 mmol) in dry DCM (1.00 mL) was added dropwise to oxalyl chloride (0.19 mL, 2.2 mmol) in dry DCM (5.0 mL) at −60 °C. The reaction mixture was stirred at −60 °C for 2 mins. Alcohol **84** (531 mg, 2.0 mmol) in dry DCM (2.0 mL) was added dropwise to the reaction mixture at −60 °C. The reaction mixture was stirred at −60 °C for 15 mins. Et_3N (1.40 mL, 10.1 mmol) was added dropwise to the reaction mixture. The reaction mixture was stirred at −60 °C for 15 mins followed by stirring at room temperature for 1 h. The reaction mixture was poured into water (50 mL) and extracted with DCM (2 × 25 mL). The organic extracts were combined, washed sequentially with brine (50 mL), 1% aq. HCl solution (2 × 25 mL), water (50 mL) and 5% aq. Na_2CO_3 solution (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude intermediate aldehyde **85** as a pale yellow oil (470 mg). *n*-BuLi (1.12 mL of a 2.5 M solution in hexanes, 2.8 mmol) was added dropwise to methyltriphenylphosphonium

bromide (1.00 g, 2.8 mmol) in dry THF (10.0 mL) at −20 °C and left stirring at this temperature for 30 mins. The reaction mixture was cooled to −78 °C. Intermediate aldehyde **85** (370 mg, 1.4 mmol) was added dropwise to the reaction mixture at −78 °C and the reaction mixture stirred at this temperature for 30 mins. The reaction mixture was then stirred at room temperature for 45 mins, poured into a cold sat. aq. NH_4Cl solution (50 mL) and extracted with ether (3 × 30 mL). The organic extracts were combined, washed with brine (2 × 40 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo*, filtered through a plug of silica and the solvent removed *in vacuo* to give the crude product as a colourless oil (381 mg). Purification by column chromatography (SiO_2, hexane/Et_2O 20:1) gave the title compound as a colourless oil (274 mg, 67% over 2 steps).

IR: ν_{max} (neat)/cm^{-1} 2957 (sh), 2930 (m), 2860 (w)

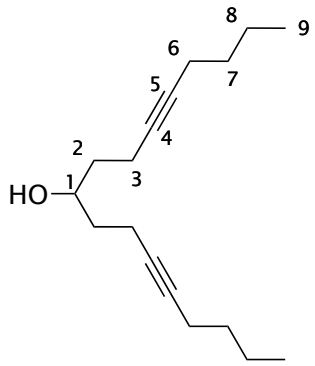
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 5.45 (1H, ddd, *J* 18.0, 9.3, 9.0 Hz, H-2), 5.03 (1H, dd, *J* 18.0, 2.1 Hz, H-1a), 5.03 (1H, dd, *J* 9.3, 2.1 Hz, H-1b), 2.31–1.97 (9H, m, H-3,5,8), 1.53–1.32 (12H, m, H-4,9,10), 0.91 (6H, t, *J* 7.1 Hz, H-11)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 141.18 (CH, C-2), 115.83 (CH, C-1), 80.26 (C), 79.86 (C), 42.51 (CH, C-3), 34.12 (CH_2), 31.24 (CH_2), 21.92 (CH_2), 18.42 (CH_2), 16.59 (CH_2), 13.60 (CH_3, C-11)

LRMS: (CI) m/z 276.4 ($[M+NH_4]^+$, 27%), 259.3 ($[M+H]^+$, 100%), 243.3 ($[M-CH_3]^+$, 5%), 229.3 ($[M-C_2H_5^+$, 16%), 215.3 ($[M-C_3H_7]^+$, 26%), 201.3 ($[M-C_4H_9]^+$, 56%), 173.2 ($[M-C_6H_{13}]^+$, 63%), 131.1 ($[M-C_9H_{19}]^+$, 63%)

HRMS: (EI) Calculated for $C_{19}H_{30}$ ($[M-C_2H_5]^+$): 229.19563 Da, found: 229.19557 Da

Heptadeca-5,12-diyn-9-ol (86)



Magnesium turnings (2.43 g, 0.10 mol) were ground in a mortar and pestle followed by vigorous stirring under argon overnight. The stirring was stopped, dry THF (4.0 mL) and iodine (1 crystal) were added. Bromide **79** (3.78 g, 20.0 mmol), 1,2-dibromoethane (1.70 mL, 20.0 mmol) and dry THF (8.0 mL) were combined. Approximately 10% of the 1-bromooct-3-yne containing mixture was added to the magnesium turnings. Once bubbling had started the remainder of the mixture containing bromide **79** was added slowly to maintain a gentle reflux. The reaction mixture was heated to reflux for 2 h. The reaction mixture was cooled to 0 °C and ethyl formate (0.81 mL, 10.0 mmol) in dry THF (8.0 mL) added. After stirring at room temperature for a further 3 h ethyl formate (0.81 mL, 10.0 mmol) in dry THF (8.0 mL) was added. The reaction mixture was poured into a sat. aq. NH_4Cl solution (80 mL) and extracted with ether (3 × 50 mL). The organic extracts were combined washed sequentially with sat. aq. $NaHCO_3$ solution (100 mL) and water (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give an orange oil. The product was dissolved in THF (20 mL) and stirred with a solution of K_2CO_3 in methanol/water for 3 h. The reaction mixture was extracted with ether (3 × 50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as an orange oil (1.91 g). Purification by column chromatography (SiO_2, hexane/Et_2O 5:1) gave the title compound as an orange oil (963 mg, 39%).

IR: ν_{max} (neat)/cm^{-1} 3346 (br), 2955 (sh), 2929 (m), 2861 (w)

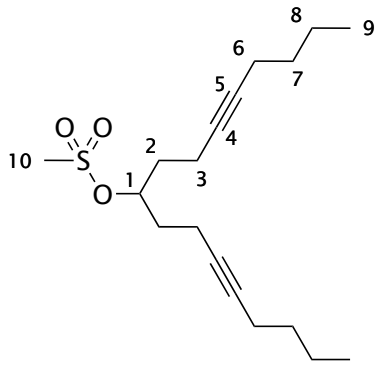
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 3.87 (1H, ttd, *J* 7.8, 4.2, 4.2 Hz, H-1), 2.42–2.21 (4H, m, OH and H-3 or H-6), 2.20–1.99 (4H, m, H-3 or H-6), 1.72–1.54 (4H, m, H-2), 1.52–1.31 (8H, m, H-7,8), 0.89 (6H, t, *J* 7.0 Hz, H-9)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 81.03 (C), 79.45 (C), 70.51 (CH, C-1), 36.08 (CH_2), 31.11 (CH_2), 21.91 (CH_2), 18.37 (CH_2), 15.33 (CH_2), 13.54 (CH_3, C-9)

LRMS: (ES+) m/z 271.2 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{17}H_{29}O$: 249.2213 Da, found: 249.2214 Da

Heptadeca-5,12-diyn-9-yl mesylate (87)



Et_3N (0.46 mL, 3.3 mmol) and methane sulfonyl chloride (0.16 mL, 2.4 mmol) were added dropwise to alcohol **86** (540 mg, 2.2 mmol) in dry DCM (2.0 mL) at −20 °C. The reaction mixture was stirred at −20 °C for 45 mins and at room temperature for 2 h. The reaction mixture was poured into 2 M aq. HCl solution (30 mL). The aqueous layer was further extracted with DCM (30 mL). The organic extracts were combined, washed with water (2 × 30 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as an orange oil (652 mg, 91%).

IR: ν_{max} (neat)/cm^{-1} 2957 (sh), 2931 (w), 2872 (w), 2361 (w), 1172 (s), 900 (s)

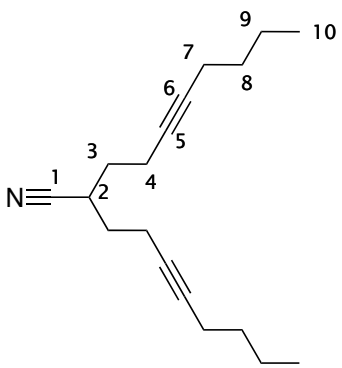
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 4.91 (1H, tt, *J* 6.0, 6.0 Hz, H-1), 3.06 (3H, s, H-10), 2.41–2.21 (4H, m, H-3 or H-6), 2.14 (4H, tt, *J* 6.8, 2.4 Hz, H-3 or H-6), 2.02–1.82 (4H, m, H-2), 1.53–1.30 (8H, m, H-7,8), 0.91 (6H, t, *J* 7.0 Hz, H-9)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 81.67 (CH, C-1), 78.09 (C, C-4,5), 38.28 (CH_3, C-10), 33.78 (CH_2), 31.04 (CH_2), 21.93 (CH_2), 18.35 (CH_2), 14.80 (CH_2), 13.56 (CH_3, C-9)

LRMS: (ES+) m/z 349.2 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{18}H_{30}NaO_3S$: 349.1808 Da, found: 349.1808 Da

2-(Oct-3-ynyl-dec-5-yne nitrile (88)



Mesylate **87** (904 mg, 2.8 mmol) in dry DMF (8.5 mL) was added to KCN (365 mg, 5.6 mmol). The reaction mixture was heated to 65 °C for 24 h. The reaction mixture was poured into water (20 mL) and extracted with ether (3 × 25 mL). The organic extracts were combined, washed with water (3 × 20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as an orange oil (858 mg).

Purification by column chromatography (SiO_2, hexane/Et_2O 10:1) gave the title compound as an orange oil (468 mg, 65%).

IR: ν_{max} (neat)/cm^{-1} 2956 (sh), 2931 (w), 2861 (w), 2361 (w)

^{1}H NMR: δ_H (300 MHz, $CDCl_3$)

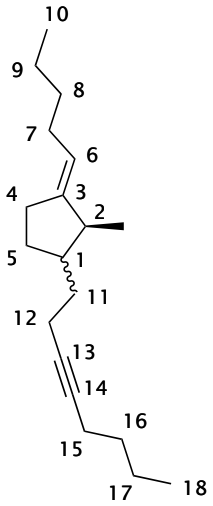
2.98 (1H, tt, *J* 8.9, 5.9 Hz, H-2), 2.52–2.27 (4H, m, H-4 or H-7), 2.15 (4H, tt, *J* 6.9, 2.5 Hz, H-4 or H-7), 1.92–1.65 (4H, m, H-3), 1.54–1.32 (7H, m, H-8,9), 0.92 (6H, t, *J* 7.0 Hz, H-10)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 121.32 (C, C-1), 82.07 (C, C-5,6), 31.35 (CH_2), 31.04 (CH_2), 29.56 (CH, C-2), 21.94 (CH_2), 18.35 (CH_2), 16.78 (CH_2), 13.57 (CH_3, C-10)

LRMS: (EI) m/z 257.4 ($[M]^{+\bullet}$, 1%), 242.2 ($[M-CH_3]^+$, 6%), 228.2 ($[M-C_2H_5]^+$, 22%), 214.1 ($[M-C_3H_7]^+$, 33%), 200.0 ($[M-C_4H_9]^+$, 29%), 186.0 ($[M-C_5H_{12}]^+$, 44%), 172.0 ($[M-C_6H_{14}]^+$, 50%), 158.2 ($[M-C_7H_{16}]^+$, 29%), 78.9 ($[M-C_{12}H_{19}N]^+$, 100%)

HRMS: (EI) Calculated for $C_{18}H_{26}N$ ($[M-H]^+$): 256.20652 Da, found: 256.20653 Da

2-Methyl-1-(oct-3-ynyl)-3-pentylidenecyclopentane (89)



n-BuLi (0.60 mL of a 2.5 M solution in hexanes, 1.5 mmol) was added dropwise to a solution of Cp_2ZrCl_2 (219 mg, 0.80 mmol) in dry THF (5.0 mL) at −78 °C. Enediyne **78** (194 mg, 0.80 mmol) in dry THF (3.0 mL) was added dropwise to the reaction mixture at −78 °C. The reaction mixture was warmed to room temperature over 1 h and left stirring at room temperature for 4 h. HCl (2.0 mL of a 2 M solution in Et_2O) was added dropwise to the reaction mixture and left stirring overnight. The reaction mixture was poured into water (100 mL) and extracted with ether (2 × 75 mL). The organic extracts were combined, washed sequentially with water (75 mL) and sat. aq. $NaHCO_3$ solution (75 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as an orange oil (199 mg). Purification by column chromatography (SiO_2, hexane) gave the title compound as an orange oil (39.0 mg, 20%).

IR: ν_{max} (neat)/cm^{-1} 2955 (sh), 2926 (m), 2858 (m)

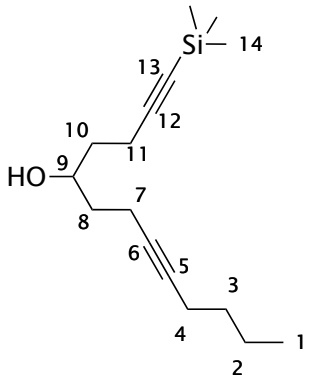
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 5.11 (1H, tq, *J* 7.0, 2.4 Hz, H-6), 2.39–2.05 (7H, m, H-1,2,4,7), 2.04–1.74 (6H, m, H-11,12,15), 1.53–1.19 (10H, m, H-5,8,9,16,17), 1.04 (3H, d, *J* 6.6 Hz, H-19), 0.96–0.81 (6H, m, H-10,18)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 147.36 (C, C-3), 119.64 (CH, C-6), 80.25 (C), 80.12 (C), 47.07 (CH), 44.47 (CH), 33.65 (CH_2), 31.96 (CH_2), 31.25 (CH_2), 30.21 (CH_2), 28.81 (CH_2), 27.90 (CH_2), 22.41 (CH_2), 21.92 (CH_2), 18.43 (CH_2), 17.49 (CH_2), 17.22 (CH_3), 14.06 (CH_3), 13.62 (CH_3)

LRMS: (CI): m/z 278.4 ($[M+NH_4]^+$, 7%), 261.4 ($[M+H]^+$, 100%), 245.4 ($[M-CH_3]^+$, 15%), 231.4 ($[M-C_2H_5]^+$, 3%), 217.3 ($[M-C_3H_7]^+$, 9%), 203.3 ($[M-C_4H_9]^+$, 29%), 163.3 ($[M-C_7H_{13}]^+$, 29%), 107.2 ($[M-C_{11}H_{21}]^+$, 36%)

HRMS: (EI) Calculated for $C_{18}H_{29}$ ($[M-CH_3]^+$): 245.22693 Da, found: 245.22700 Da

1-(Trimethylsilyl)trideca-1,8-diyn-5-ol (92)



Magnesium turnings (608 mg, 25.0 mmol) were ground in a mortar and pestle followed by vigorous stirring under argon overnight. The stirring was stopped, dry THF (1.0 mL) and iodine (1 crystal) were added. Bromide **79** (759 mg, 4.0 mmol), 1,2-dibromoethane (0.43 mL, 5.0 mmol) and dry THF (4.0 mL) were combined. Approximately 10% of the 1-bromooct-3-yne containing mixture was added to the magnesium turnings. Once bubbling had started the remainder of the mixture containing bromide **79** was added slowly to maintain a gentle reflux. The reaction mixture was heated to reflux for 2 h. The Grignard formed was added dropwise to a solution of 5-(trimethylsilyl)pent-4-ynal (694 mg, 5.0 mmol) in dry THF (20 mL) at 0 °C. After stirring at room temperature for 3 h the reaction mixture was poured into a sat. aq. NH_4Cl solution (20 mL) and extracted with ether (3 × 10 mL). The organic extracts were combined washed with water (2 × 20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as an orange oil (1.49 g). Purification by column chromatography (SiO_2, hexane/Et_2O 3:1) gave the title compound as an orange oil (330 mg, 31%).

IR: ν_{max} (neat)/cm^{-1} 3339 (br), 2956 (w), 2930 (w), 2174 (w), 838 (s)

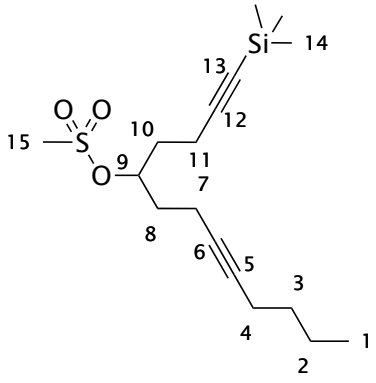
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 3.88 (1H, tdt, *J* 8.1, 4.4, 4.2 Hz, H-9), 2.37 (2H, t, *J* 7.0 Hz, H-11), 2.34–2.26 (2H, m, H-4 or H-7), 2.22 (1H, d, *J* 4.4 Hz, OH), 2.14 (2H, tt, *J* 6.9, 2.3 Hz, H-4 or H-7), 1.72–1.56 (4H, m, H-8,10), 1.52–1.31 (4H, m, H-2,3), 0.90 (3H, t, *J* 7.0 Hz, H-1), 0.15 (9H, s, H-14)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 106.96 (C, C-12), 85.22 (C), 81.17 (C), 79.34 (C), 70.45 (CH, C-9), 36.02 (CH_2), 35.65 (CH_2), 31.11 (CH_2), 21.94 (CH_2), 18.39 (CH_2), 16.44 (CH_2), 15.33 (CH_2), 13.59 (CH_3, C-1), 0.06 (CH_3, C-14)

LRMS: (ES+): m/z 287.2 ([M+Na]$^+$)

HRMS: (ES+) Calculated for $C_{16}H_{28}OSi$: 265.1982 Da, found: 265.1987 Da

1-(Trimethylsilyl)trideca-1,8-diyn-5-yl mesylate (200)



Et_3N (0.23 mL, 1.7 mmol) and methane sulfonyl chloride (0.08 mL, 1.2 mmol) were added dropwise to alcohol **92** (287 mg, 1.1 mmol) in dry DCM (2.0 mL) at −20 °C. The reaction mixture was stirred at −20 °C for 45 mins and at room temperature for 2 h. The reaction mixture was poured into 2 M aq. HCl solution (30 mL). The aqueous layer was further extracted with DCM (30 mL). The organic extracts were combined, washed with water (2 × 30 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as an orange oil (327 mg, 87%).

IR: ν_{max} (neat)/cm^{-1} 2958 (w), 2933 (w), 2175 (w), 839 (s)

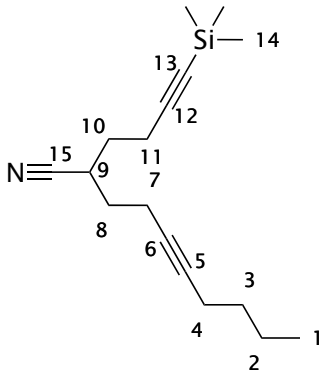
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 4.89 (1H, ttd, *J* 6.0, 6.0, 2.6 Hz, H-9), 3.06 (3H, s, H-15), 2.37 (2H, td, *J* 7.1, 2.6 Hz, H-11), 2.33–2.25 (2H, m, H-4 or H-7), 2.14 (2H, tt, *J* 6.6, 2.2 Hz, H-4 or H-7), 2.03–1.84 (4H, m, H-8,10), 1.53–1.31 (4H, m, H-2,3), 0.90 (3H, t, *J* 7.0 Hz, H-1), 0.15 (9H, s, H-14)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 105.30 (C, C-12), 85.93 (C), 81.73 (C), 81.35 (CH, C-9), 77.96 (C), 38.27 (CH_3, C-15), 33.70 (CH_2), 33.28 (CH_2), 30.99 (CH_2), 21.91 (CH_2), 18.32 (CH_2), 15.78 (CH_2), 14.80 (CH_2), 13.56 (CH_3, C-1), −0.04 (CH_3, C-14)

LRMS: (ES+): m/z 365.1 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{17}H_{30}NaO_3SSi$: 365.1577 Da, found: 365.1580 Da

2-(4-(Trimethylsilyl)but-3-ynyl)dec-5-yne nitrile (94)



Mesylate **200** (281 mg, 0.80 mmol) in dry DMF (10.0 mL) was added to KCN (146 mg, 2.2 mmol) in dry DMF (5.0 mL). The reaction mixture was heated to 65 °C for 24 h. The reaction mixture was poured into water (20 mL) and extracted with ether (3 × 25 mL). The organic extracts were combined, washed with water (3 × 20 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as an orange oil (241 mg). Purification by column chromatography (SiO_2, hexane/Et_2O 10:1) gave the title compound as an orange oil (146 mg, 65%).

IR: ν_{max} (neat)/cm^{-1} 2957 (w), 2933 (w), 2176 (w), 840 (s)

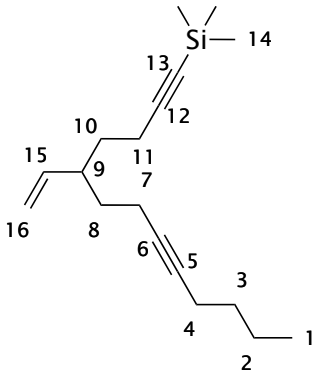
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 2.95 (1H, tt, *J* 8.7, 6.1 Hz, H-9), 2.56–2.31 (4H, m, H-7,11), 2.13 (3H, tt, *J* 7.0, 2.2 Hz, H-4), 1.92–1.69 (4H, m, H-8,10), 1.56–1.31 (4H, m, H-2,3), 0.90 (3H, t, *J* 7.1 Hz, H-1), 0.15 (9H, s, H-14)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 121.04 (C, C-15), 104.32 (C, C-11), 86.30 (C), 82.05 (C), 77.22 (C), 31.27 (CH_2), 30.97 (CH_2), 30.80 (CH_2), 29.53 (CH, C-9), 21.88 (CH_2), 18.31 (CH_2), 17.75 (CH_2), 16.69 (CH_2), 13.53 (CH_3, C-1), −0.05 (CH_3, C-14)

LRMS: (ES+): m/z 291.3 ($[M+NH_4]^+$)

HRMS: (ES+) Calculated for $C_{17}H_{28}NSi$: 274.1986 Da, found: 274.1984 Da

Trimethyl(5-vinyltrideca-1,8-diynyl)silane (90)



DIBAL-H (2.6 mL of a 1.0 M solution in THF, 2.6 mmol) was added dropwise to a solution of nitrile **94** (349 mg, 1.3 mmol) in dry THF (4.0 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 15 mins and at room temperature for 2 h. Ethyl acetate (5.0 mL) was added followed by a sat. aq. solution of Rochelle salt (15.0 mL) and stirring was continued for 30 mins. The reaction mixture was extracted with ether (3 × 20 mL). The organic extracts were combined, washed with brine (2 × 25 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude intermediate aldehyde **95** as a colourless oil (345 mg). *n*-BuLi (0.96 mL of a 2.5 M solution in hexanes, 2.4 mmol) was added dropwise to methyltriphenylphosphonium bromide (874 mg, 2.4 mmol) in dry THF (5.0 mL) at −20 °C and left stirring at this temperature for 30 mins. Intermediate aldehyde **95** (338 mg, 1.2 mmol) was added dropwise to the reaction mixture at −78 °C and the reaction mixture stirred at this temperature for 30 mins. The reaction mixture was then stirred at room temperature for 90 mins, poured into a cold sat. aq. NH_4Cl solution (50 mL) and extracted with ether (3 × 30 mL). The organic extracts were combined, washed with brine (2 × 40 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo* filtered through a plug of silica and the solvent removed *in vacuo* to give the crude product as a pale yellow oil (302 mg). Purification by column chromatography (SiO_2, hexane/Et_2O 30:1) gave the title compound as a colourless oil (106 mg, 31% over 2 steps).

IR: ν_{max} (neat)/cm^{-1} 2958 (sh), 2932 (w), 2175 (w), 839 (s)

^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 5.45 (1H, ddd, *J* 18.6, 9.2, 8.8 Hz, H-15), 5.05 (1H, dd, *J* 9.2, 2.0 Hz, H-16a), 5.04 (1H, dd, *J* 18.6, 2.0 Hz, H-16b), 2.36–1.98 (7H, m, H-4,7,9,11), 1.77–1.52 (2H, m, H-8a,10a), 1.52–1.30 (6H, m, H-2,3,8b,10b), 0.91 (3H, t, *J* 7.1 Hz, H-1), 0.15 (9H, s, H-14)

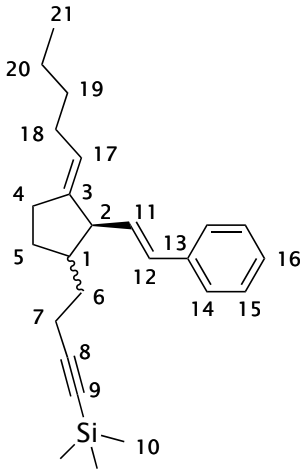
^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 140.92 (CH, C-15), 116.12 (CH_2, C-16), 107.46 (C, C-12), 84.41 (C), 80.34 (C), 79.78 (C), 42.57 (CH, C-9), 34.09 (CH_2), 33.56 (CH_2),

31.24 (CH_2), 21.93 (CH_2), 18.42 (CH_2), 17.75 (CH_2), 16.59 (CH_2), 13.62 (CH_3, C-1), 0.15 (CH_3, C-14)

LRMS: (EI): m/z 274.1 ($[M]^{+\bullet}$, 2%), 259.2 ($[M-CH_3]^+$, 3%), 245.2 ($[M-C_2H_5]^+$, 2%), 231.1 ($[M-C_3H_7]^+$, 3%), 217.1 ($[M-C_4H_9]^+$, 4%), 201.3 ($[M-C_3H_9Si]^+$, 11%), 125.1 ($[M-C_{11}H_{17}]^+$, 2%), 73.1 ($[M-C_{15}H_{21}]^+$, 100%)

HRMS: (EI) Calculated for $C_{17}H_{27}Si$ ($[M-CH_3]^+$): 259.18820 Da, found: 259.18870 Da

Trimethyl(4-(3-pentylidene-2-styrylcyclopentyl)but-1-ynyl)silane (99)



n-BuLi (0.25 mL of a 2.5 M solution in hexanes, 0.62 mmol) was added dropwise to Cp_2ZrCl_2 (91 mg, 0.31 mmol) in dry THF (2.0 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 mins. Enediyne **90** (85 mg, 0.31 mmol) in dry THF (1.0 mL) was added dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 30 mins followed by stirring at room temperature for 2 h. Benzyl chloride (0.04 mL, 0.33 mmol) and LiTMP [prepared by dropwise addition of *n*-BuLi (0.12 mL of a 2.5 M solution in hexanes, 0.31 mmol) to TMP (0.06 mL, 0.33 mmol) in dry THF (1.00 mL) at 0 °C and stirring at 0 °C for 30 mins] were added dropwise sequentially at −78 °C. After stirring at −78 °C for 30 mins the reaction mixture was stirred at room temperature for 18 h. MeOH (5.0 mL) and sat. aq. $NaHCO_3$ solution (5.0 mL) were added and the reaction mixture stirred at room temperature for 8 h. The reaction mixture was poured into water (50 mL) and extracted with ether (3 × 25 mL). The organic extracts were combined, washed sequentially with water (3 × 50 mL) and brine (50 mL) dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as a yellow oil (213 mg). Purification by column chromatography (SiO_2, hexane) and HPLC (hexane) gave the title compound as a colourless oil (29.3 mg, 26%).

IR: ν_{max} (neat)/cm^{-1} 3026 (w), 2955 (w), 2925 (w), 2857 (sh), 2173 (w), 838 (s)

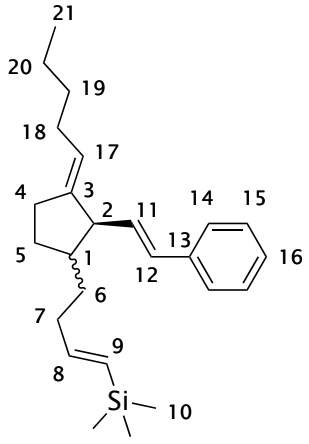
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.46–7.16 (5H, m, H-14,15,16), 6.38 (1H, d, *J* 15.7 Hz, H-12), 5.97 (1H, dd, *J* 15.7, 8.8 Hz, H-11), 5.13 (1H, tq, *J* 7.1, 2.4 Hz, H-17), 2.67 (1H, ddd, *J* 9.5, 8.8, 2.4 Hz, H-2), 2.41 (1H, m), 2.34–2.14 (3H, m), 2.10–1.92 (3H, m), 1.86 (1H, m), 1.72 (1H, m), 1.45 (1H, m), 1.38–1.17 (5H, m), 0.89 (3H, t, *J* 6.6 Hz, H-21), 0.15 (9H, s, H-10)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 144.67 (C), 137.69 (C), 132.73 (CH), 131.44 (CH), 128.47 (2 × CH), 126.90 (CH), 126.08 (2 × CH), 122.92 (CH), 107.67 (C, C-8), 84.25 (C, C-9), 55.65 (CH), 46.16 (CH), 32.97 (CH_2), 31.73 (CH_2), 30.83 (CH_2), 28.99 (CH_2), 28.21 (CH_2), 22.42 (CH_2), 18.72 (CH_2), 14.01 (CH_3, C-21), 0.14 (CH_3, C-10)

LRMS: (EI): m/z 364.0 ($[M]^{+\bullet}$, 2%), 321.0 ($[M-C_3H_7]^+$, 3%), 307.0 ($[M-C_4H_9]^+$, 14%), 291.1 ($[M-C_3H_9Si]^+$, 19%), 261.1 ($[M-C_8H_7]^+$, 1%), 253.0 ($[M-C_6H_{11}Si]^+$, 2%), 239.0 ($[M-C_7H_{13}Si]^+$, 1%), 73.0 ($[M-C_{22}H_{27}]^+$, 100%)

HRMS: (EI) Calculated for $C_{25}H_{36}Si$: 364.25863 Da, found: 364.25848 Da

Trimethyl(4-((*Z*)-3-pentylidene-2-styrylcyclopentyl)but-1-enyl)silane (101)



n-BuLi (0.04 mL of a 2.5 M solution in hexanes, 0.10 mmol) was added dropwise to Cp_2ZrCl_2 (15.1 mg, 0.05 mmol) in dry THF (2.0 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 mins. Enyne **99** (18.8 mg, 0.05 mmol) in dry THF (1.0 mL) was added dropwise at −78 °C. The reaction mixture was stirred at −78 °C for 20 mins followed by stirring at room temperature for 2 h. MeOH (5.0 mL) and sat. aq. $NaHCO_3$ solution (5.0 mL) were added and the reaction mixture stirred at room temperature for 16 h. The reaction mixture was poured into water (50 mL) and extracted with ether (3 × 25 mL). The organic extracts were combined, washed sequentially with water (3 × 50 mL) and brine (50 mL) dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as an orange oil (51.6 mg). Purification by column chromatography (SiO_2, hexane) and HPLC (hexane) gave the title compound as a colourless oil (11.9 mg, 65%).

IR: ν_{max} (neat)/cm^{-1} 2954 (w), 2924 (w), 2855 (w), 1604 (w)

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 7.48–7.12 (5H, m, H-14,15,16), 6.36 (1H, d, *J* 15.8 Hz, H-12), 6.29 (1H, dt, *J* 14.0, 7.3 Hz, H-8), 5.96 (1H, dd, *J* 15.8, 9.0 Hz, H-11), 5.45 (1H, d, *J* 14.0 Hz, H-9), 5.13 (1H, tq, *J* 7.1, 2.4 Hz, H-17), 2.66 (1H, ddd, *J* 9.3, 9.0, 2.4 Hz, H-2), 2.49–1.89 (7H, m, H-1,4,7,18), 1.79–1.58 (2H, m), 1.41–1.15 (6H, m), 0.89 (3H, t, *J* 7.0 Hz, H-21), 0.10 (9H, s, H-10)

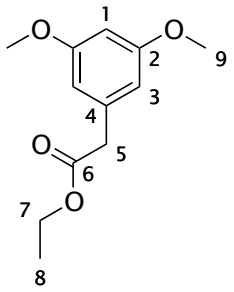
^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 149.15 (CH), 144.93 (C), 137.77 (C), 132.93 (CH), 131.38 (CH), 128.76 (CH), 128.46 (2 × CH), 126.84 (CH), 126.08 (2 × CH), 122.78 (CH), 55.86 (CH), 46.78 (CH), 33.99 (CH_2), 32.20 (CH_2), 31.75 (CH_2), 31.11 (CH_2), 28.98 (CH_2), 28.25 (CH_2), 22.42 (CH_2), 14.02 (CH_3, C-21), 0.20 (CH_3, C-10)

LRMS: (EI): m/z 366.1 ($[M]^{+\bullet}$, 15%), 323.1 ($[M-C_3H_7]^+$, 5%), 309.0 ($[M-C_4H_9]^+$, 2%), 293.1 ($[M-C_3H_9Si]^+$, 2%), 253.1 ($[M-C_6H_{13}Si]^+$, 1%), 239.1 ($[M-C_7H_{15}Si]^+$, 5%), 126.9 ($[M-C_{18}H_{23}]^+$, 4%), 72.9 ($[M-C_{22}H_{29}]^+$, 100%)

HRMS: (EI) Calculated for $C_{25}H_{38}Si$: 366.27428 Da, found: 366.27414 Da

7.3 Experimental for chapter 3

Ethyl(3,5-dimethoxyphenyl)acetate (108a)



Diazomethane in dry ether [produced by addition of KOH (4.00 g, 71.0 mmol) in 96% ethanol (50 mL) to Diazald® (4.00 g, 19.0 mmol) in dry ether (100 mL)] was distilled into a flask containing a solution of acid chloride **105a** (1.00 g, 5.0 mmol) in dry ether (10.0 mL) at −78 °C. The reaction mixture was stirred at room temperature with a dry ice condenser attached for 2 h and for a further 1 h without dry ice in the condenser to remove excess diazomethane. The solvent was removed *in vacuo* to give a pale yellow solid, which was refluxed in ethanol (16.0 mL) with Ag_2O (200 mg) for 1 h. Further Ag_2O (200 mg) was added and refluxing continued for 1 h. The reaction mixture was filtered through celite and the solvent removed *in vacuo* to give the crude product as an orange oil (1.14 g). Purification by column chromatography (SiO_2, hexane/Et_2O 4:1) gave the title compound as a colourless oil (98 mg, 87%).

IR: ν_{max} (neat)/cm^{-1} 2939 (w), 2839 (w), 1731 (s), 1594 (s), 1204 (s), 1146 (s), 1064 (s), 1029 (s)

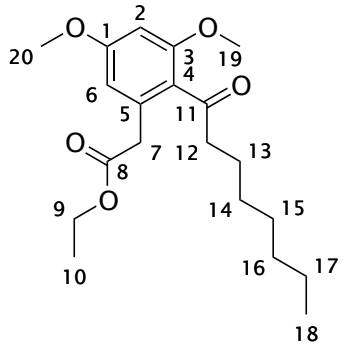
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 6.45 (2H, d, *J* 2.3 Hz, H-3), 6.38 (1H, t, *J* 2.3 Hz, H-1), 4.16 (2H, q, *J* 7.1 Hz, H-7), 3.79 (6H, s, H-9), 3.55 (2H, s, H-5), 1.27 (3H, t, *J* 7.1 Hz, H-8)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 171.29 (C, C-6), 160.78 (C, C-2), 136.17 (C, C-4), 107.26 (CH, C-3), 99.15 (CH, C-1), 60.83 (CH_2, C-7), 55.26 (CH_3, C-9), 41.65 (CH_2, C-5), 14.15 (CH_3, C-8)

LRMS: (EI) m/z 224.3 ($[M]^{+\bullet}$, 95%), 195.8 ($[M-C_2H_5]^+$, 19%), 151.4 ($[M-C_3H_5O_2]^+$, 100%), 137.1 ($[M-C_4H_7O_2]^+$, 9%)

HRMS: (ES+) Calculated for $C_{12}H_{16}NaO_4$: 247.0941 Da, found: 247.0942 Da

3,5-Dimethoxycytosoporone B (109a)



Perchloric acid (0.10 mL of a 70% solution in water, 1.2 mmol) was added dropwise to acetate **108a** (224 mg, 1.0 mmol) in octanoic anhydride (1.80 mL, 6.0 mmol). The reaction mixture was stirred at room temperature for 4 h, extracted with ether (35 mL), washed with sat. aq. $NaHCO_3$ solution (5 × 50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as a green oil (630 mg). Purification by column chromatography (SiO_2, hexane/Et_2O 1:1) gave the title compound as an orange oil (116 mg, 33%).

IR: ν_{max}(neat)/cm^{-1} 2927 (w), 2854 (w), 1734 (m), 1682 (w), 1601 (m), 1581 (m), 1152 (s)

^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 6.40 (1H, d, *J* 2.3 Hz, H-2 or H-6), 6.38 (1H, d, *J* 2.3 Hz, H-2 or H-6), 4.14 (2H, q, *J* 7.1 Hz, H-9), 3.82 (3H, s, OMe), 3.81 (3H, s, OMe), 3.62 (2H, s, H-7), 2.82 (2H, t, *J* 7.5 Hz, H-12), 1.65 (2H, quin, *J* 7.5 Hz, H-13), 1.38–1.28 (8H, m, H-14,15,16,17), 1.26 (3H, t, *J* 7.1 Hz, H-10), 0.88 (3H, t, *J* 6.8 Hz, H-18)

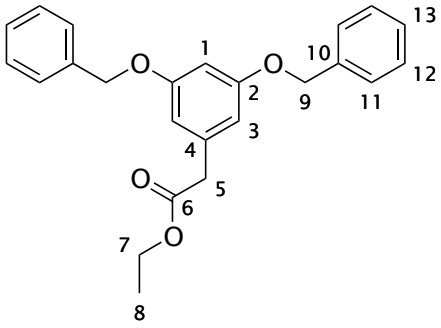
^{13}C NMR: δ_C (75 MHz, $CDCl_3$)

207.04 (C, C-11), 171.29 (C, C-8), 161.23 (C, C-1 or C-3), 158.74 (C, C-1 or C-3), 134.40 (C), 124.25 (C), 107.74 (CH, C-6), 97.51 (CH, C-2), 60.84 (CH_2, C-9), 55.54 (CH_3, OMe), 55.35 (CH_3, OMe), 44.52 (CH_2), 38.88 (CH_2), 31.73 (CH_2), 29.30 (CH_2), 29.15 (CH_2), 24.07 (CH_2), 22.62 (CH_2), 14.15 (CH_3), 14.06 (CH_3)

LRMS: (ES+) m/z 373.2 ([M+Na]$^+$)

HRMS: (ES+) Calculated for $C_{20}H_{30}NaO_5$: 373.1985 Da, found: 373.1986 Da

Ethyl-3,5-(bisbenzyloxy)benzene (108b)



Diazomethane in dry ether [produced by addition of KOH (2.97 g, 53.0 mmol) in 96% ethanol (35 mL) to Diazald® (2.91 g, 13.6 mmol) in dry ether (50 mL)] was distilled into a flask containing a solution of acid chloride **105b** (1.19 g, 3.4 mmol) in dry ether (15.0 mL) at −78 °C. The reaction mixture was stirred at room temperature with a dry ice condenser attached for 2 h and for a further 1 h without dry ice in the condenser to remove excess diazomethane. The solvent was removed *in vacuo* to give a pale yellow solid which was refluxed in ethanol (20 mL) with Ag_2O (200 mg) for 1 h. Further Ag_2O (200 mg) was added and refluxing continued for a further 2 h. The reaction mixture was filtered through celite and the solvent removed *in vacuo* to give the crude product as an orange oil (1.204 g). Purification by column chromatography (SiO_2, hexane/Et_2O 4:1) gave the title compound as a colourless oil (796 mg, 62%).

IR: ν_{max} (neat)/cm^{-1} 3032 (w), 2978 (w), 1731 (m), 1592 (s), 1147 (s), 696 (s)

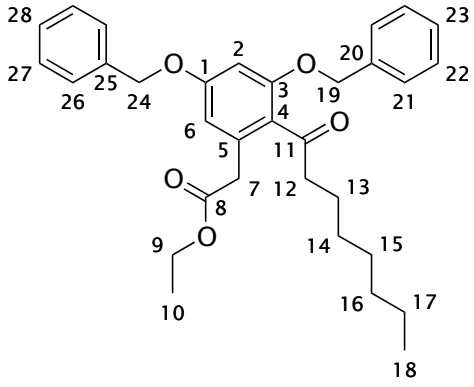
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.53–7.31 (10H, m, H-11,12,13), 6.64–6.52 (3H, m, H-1,3), 5.05 (4H, s, H-9), 4.18 (2H, q, *J* 7.0 Hz, H-7), 3.57 (2H, s, H-5), 1.28 (3H, t, *J* 7.0 Hz, H-8)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 171.27 (C, C-6), 159.94 (C, C-2), 136.78 (C), 136.21 (C), 128.51 (2 × CH), 127.93 (CH), 127.49 (2 × CH), 108.41 (CH, C-3), 100.76 (CH, C-1), 69.98 (CH_2, C-9), 60.84 (CH_2, C-7), 41.60 (CH_2, C-5), 14.13 (CH_3, C-8)

LRMS: (ES+) m/z 399.2 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{24}H_{24}NaO_4$: 399.1567 Da, found: 399.1571 Da

3,5-(Bisbenzyloxy)cytosporone B (109b)



Perchloric acid (0.10 mL of a 70% aq. solution, 1.2 mmol) was added dropwise to acetate **108b** (224 mg, 1.0 mmol) in octanoic anhydride (1.80 mL, 6.0 mmol). The reaction mixture was stirred at room temperature for 4 h, extracted with ether (35 mL), washed with sat. aq. $NaHCO_3$ solution (5 × 50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as a green oil (2.38 g). Purification by column chromatography (SiO_2, hexane/Et_2O 3:1) gave an orange oil which was dissolved in ether (50 mL) and washed with 2 M aq. NaOH solution (50 mL) to remove excess octanoic acid. The organic extract was dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the title compound as an orange oil (675 mg, 45%).

IR: ν_{max} (neat)/cm^{-1} 2925 (w), 2854 (w), 1728 (m), 1678 (w), 1598 (m), 1156 (s)

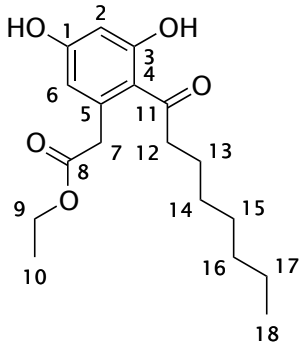
^{1}H NMR: δ_H (300 MHz, d_6-DMSO) 7.51–7.27 (10H, m, H-21,22,23,26,27,28), 6.82 (1H, d, *J* 2.2 Hz, H-2 or H-6), 6.61 (1H, d, *J* 2.2 Hz, H-2 or H-6), 5.14 (2H, s, H-19 or H-24), 5.13 (2H, s, H-19 or H-24), 4.02 (2H, q, *J* 7.0 Hz, H-9), 3.57 (2H, s, H-7), 2.69 (2H, t, *J* 7.3 Hz, H-12), 1.41 (2H, quin, *J* 7.3 Hz, H-13), 1.27–1.04 (8H, m, H-14,15,16,17), 1.15 (3H, t, *J* 7.0 Hz, H-10), 0.83 (3H, t, *J* 7.0 Hz, H-18)

^{13}C NMR: δ_C (75 MHz, d_6-DMSO) 205.63 (C, C-11), 170.54 (C, C-8), 159.89 (C, C-1 or C-3), 157.38 (C, C-1 or C-3), 136.60 (C), 136.30 (C), 134.23 (C), 128.46 (2 × CH), 128.43 (2 × CH), 128.08 (CH), 128.02 (3 × CH), 127.87 (2 × CH), 123.81 (C), 109.84 (CH, C-6), 99.14 (CH, C-2), 70.20 (CH_2), 69.50 (CH_2), 60.21 (CH_2, C-9), 43.69 (CH_2), 38.09 (CH_2), 31.11 (CH_2), 28.54 (CH_2), 28.49 (CH_2), 23.53 (CH_2), 22.00 (CH_2), 14.03 (CH_3), 13.91 (CH_3)

LRMS: (ES+) m/z 525.3 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{32}H_{38}NaO_5$: 525.2611 Da, found: 525.2619 Da

Cytosporone B (102)



A solution of 3,5-dibenzyloxycytosoporone B (206 mg, 0.40 mmol) in ethanol (5.0 mL) was added dropwise to 5% Pd/C (85 mg, 0.04 mmol) and stirred at room temperature under hydrogen for 1 h. The reaction mixture was filtered through celite and the solvent removed *in vacuo* to give the crude product as a white solid (124 mg). Purification by column chromatography (SiO_2, hexane/Et_2O 1:2) gave the title compound as a white solid (119 mg, 97%).

IR: ν_{max} (neat)/cm^{-1} 3244 (br), 2925 (w), 2855 (w), 1708 (m), 1613 (sh), 1574 (m)

m.p.: 79–81 °C

^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 6.25 (1H, d, *J* 2.6 Hz, H-2 or H-6), 6.23 (1H, d, *J* 2.6 Hz, H-2 or H-6), 4.21 (2H, q, *J* 7.0 Hz, H-9), 3.78 (2H, s, H-7), 2.83 (2H, t, *J* 7.3 Hz, H-12), 1.68 (2H, quin, *J* 7.3 Hz, H-13), 1.38–1.18 (11H, m, H-10,14,15,16,17), 0.87 (3H, t, *J* 7.0 Hz, H-18)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 207.00 (C, C-11), 172.26 (C, C-8), 163.27 (C), 160.38 (C), 136.26 (C), 116.95 (C), 112.79 (CH), 103.24 (CH), 61.75 (CH_2, C-9), 43.55 (CH_2), 41.54 (CH_2), 31.64 (CH_2), 29.21 (CH_2), 29.05 (CH_2), 24.91 (CH_2), 22.56 (CH_2), 14.06 (CH_3), 14.03 (CH_3)

LRMS: (ES+) m/z 345.2 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{18}H_{26}NaO_5$: 345.1672 Da, found: 345.1675 Da

Spectra were consistent with published data.[106]

Procedure for tritiated thymidine incorporation assays

All cell proliferation assays were conducted in 96 well plates. Cells were counted, pelleted by centrifugation (1500 rpm, 5 minutes). The supernatant was removed. Cells were resuspended in complete RPMI medium to the desired concentration. To each well was added an aliquot (100 µL) of the cells. The compounds of interest were diluted to the desired concentration and the appropriate amount of each compound added to the appropriate wells. The cells were incubated for 54–

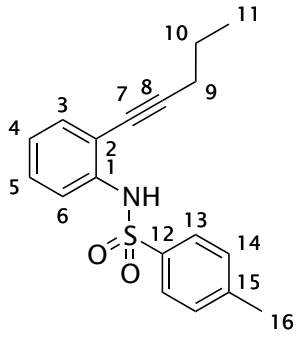
60 hours. Diluted thymidine [methyl-^{3}H]-, 1mCi (37 MBq) / mL, (10 µL) was added to each well and the incubation continued for a further 12–18 hours. After the final period of incubation the cells were harvested with a Packard Bioscience Filtermate microplate harvester. Microscint 0 scintillation fluid (37 µL) was added to each well and the fluorescence measured using a Packard Bioscience Microplate Scintillation & Luminescence Counter.

Procedure for flow cytometry assays

All flow cytometry assays were conducted in 96 well plates. Cells were counted, pelleted by centrifugation (1500 rpm, 5 minutes). The supernatant was removed. Cells were resuspended in complete RPMI medium to the desired concentration. To each well was added an aliquot (100 µL) of the cells. The compounds of interest were diluted to the desired concentration and the appropriate amount of each compound added to the appropriate wells. The cells were incubated for 72 hours. Cells were washed in complete RPMI medium and pelleted by centrifugation (1500 rpm for 5 minutes). The supernatant was removed. Cells were resuspended in complete RPMI medium containing [8 µg/mL] annexin V-FITC (BD Biosciences, conjugated to FITC by Patrick Duriez, Cancer Sciences Division, University of Southampton) and [2.5 µg/mL] propidium iodide (BD Pharmingen) and incubated for 10 minutes at room temperature. Cells were washed in complete RPMI medium to remove excess annexin V / propidium iodide and pelleted by centrifugation (1500 rpm, 5 minutes). The supernatant was removed and cells resuspended in 100 µL complete RPMI medium. Data was acquired on a BD Biosciences FACS Canto II using FACS Diva software.

7.4 Experimental for chapter 4

4-Methyl-*N*-(2-(pent-1-yn-1-yl)phenyl)benzenesulfonamide (115a)



Dry pyridine (2.1 mL, 26.0 mmol) was added dropwise to 2-(Pent-1-yn-1-yl)aniline (2.08 g, 13.0 mmol) in dry DCM (100 mL) at 0 °C. Tosyl chloride (3.05 g, 16 mmol) was added at 0 °C. The reaction mixture was stirred for 30 mins at 0 °C and at room temperature overnight. The reaction mixture was poured into water (100 mL) and extracted with ether (3 × 50 mL). The organic extracts were combined, washed sequentially with water (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as an orange solid (4.95 g). Purification by column chromatography (SiO_2, hexane/Et_2O 9:1) gave the title compound as a pale yellow solid (3.52 g, 86%).

IR: ν_{max}(neat)/cm^{-1} 3249 (w), 2961 (w), 2928 (w), 2870 (w), 1598 (w), 1573 (w), 1165 (s), 1156 (s), 531 (s)

m.p.: 84–86 °C

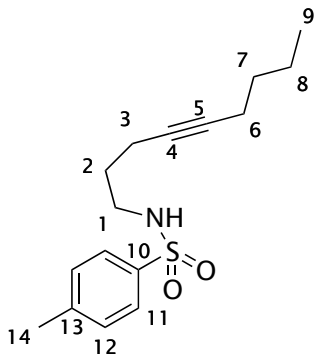
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.67 (2 H, d, *J* 8.2 Hz), 7.56 (1 H, d, *J* 8.2 Hz), 7.27–7.15 (4 H, m), 6.98 (1 H, td, *J* 7.6, 1.1 Hz), 2.39 (2 H, t, *J* 7.1 Hz, H-9), 2.36 (3 H, s, H-16), 1.63 (2 H, sxt, *J* 7.1 Hz, H-10), 1.05 (3 H, t, *J* 7.1 Hz, H-11)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 143.83 (C), 137.64 (C), 136.13 (C), 131.87 (CH), 129.50 (2 × CH), 128.72 (CH), 127.18 (2 × CH), 124.05 (CH), 119.27 (CH), 114.86 (C), 97.61 (C, C-8), 75.51 (C, C-7), 22.04 (CH_2), 21.47 (CH_3, C-16), 21.43 (CH_2), 13.54 (CH_3, C-11)

LRMS: (ES+) m/z 336.1 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{18}H_{19}NNaO_2S$: 336.1029 Da, found: 336.1029 Da

4-Methyl-*N*-(non-4-yn-1-yl)benzenesulfonamide (125)



4-Methylbenzenesulfonamide (5.19 g, 30.0 mmol) and NaOH (2.42 g, 2.4 mmol) in DMSO (50 mL) were heated at 50 °C for 30 mins. 1-bromonon-4-yne (5.13 g, 25.0 mmol) was added and the reaction mixture stirred at 50 °C for a further 2 h. The reaction mixture was poured into water (100 mL) and extracted with ether (3 × 50 mL). The organic extracts were combined, washed with water (2 × 100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as a colourless oil (5.85 g). Purification by column chromatography (SiO_2, hexane) gave the title compound as a colourless oil (3.74 g, 50%).

IR: ν_{max} (neat)/cm^{-1} 3256 (w), 2930 (w), 2871 (w), 1598 (w), 1155 (w), 549 (s)

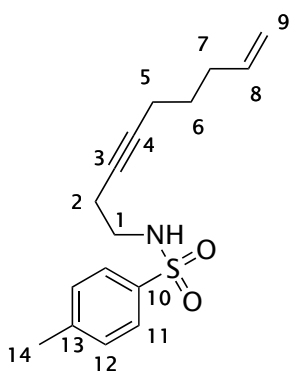
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.76 (2H, d, *J* 8.1 Hz, H-11), 7.32 (2H, d, *J* 8.1 Hz, H-12), 4.67 (1H, t, *J* 6.0 Hz, NH), 3.08 (2H, td, *J* 6.7, 6.0 Hz, H-1), 2.44 (3H, s, H-14), 2.23–2.14 (2H, m, H-3 or H-6), 2.13–2.07 (2H, m, H-3 or H-6), 1.68–1.58 (2H, m, H-2), 1.48–1.31 (4H, m, H-7,8), 0.90 (3H, t, *J* 7.1 Hz, H-9)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 143.33 (C), 137.03 (C), 129.67 (2 × CH), 127.11 (2 × CH), 81.78 (C), 78.31 (C), 42.49 (CH_2, C-1), 31.01 (CH_2), 28.46 (CH_2), 21.93 (CH_2), 21.49 (CH_3, C-14), 18.32 (CH_2), 16.17 (CH_2), 13.57 (CH_3, C-9)

LRMS: (ES+) m/z 316.3, ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{16}H_{23}NNaO_2S$: 316.1342 Da, found: 316.1339 Da

4-Methyl-*N*-(non-8-en-3-yn-1-yl)benzenesulfonamide (134a)



TBAF (40 mL of a 1.0 M solution in THF, 40.0 mmol) was added dropwise to a solution of enyne **132a** (3.33 g, 10.0 mmol) in THF (40 mL). The reaction mixture was left stirring at room temperature for 16 h. The reaction mixture was poured into water (100 mL) and extracted with pentane (2 × 10 mL). The organic extracts were combined, washed with water (4 × 200 mL), dried ($MgSO_4$) and filtered to give an orange solution. The solution was diluted in dry THF (10.0 mL). *n*-BuLi (7.8 mL of a 2.5 M solution in hexanes, 19.5 mmol) was added dropwise to the reaction mixture at −78 °C. The reaction mixture was left at room temperature for 30 mins. 1-Tosylaziridine (2.56 g, 13.0 mmol) in dry THF (10.0 mL) was added dropwise to the reaction mixture at room temperature. The reaction mixture was left stirring at room temperature for 16 h. The reaction mixture was poured into a sat. aq. $NaHCO_3$ solution (100 mL) and extracted with ether (3 × 50 mL). The organic extracts were combined, washed sequentially with water (2 × 100 mL) and brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as a yellow oil (2.40 g). Purification by column chromatography (SiO_2, hexane/Et_2O 4.5:5.5) gave the title compound as a yellow oil (859 mg, 23%).

IR: ν_{max}(neat)/cm^{-1} 3283 (br), 2932 (w), 2860 (w), 1640 (w), 1598 (w), 1157 (s), 549 (s)

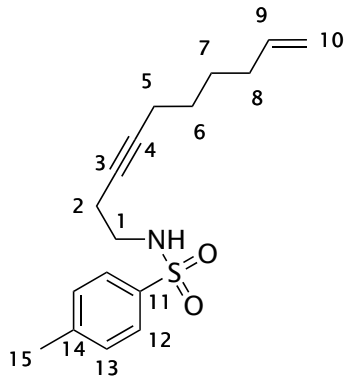
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.76 (2H, d, *J* 8.1 Hz, H-11), 7.31 (2H, d, *J* 8.1 Hz, H-12), 5.77 (1H, ddt, *J* 17.0, 10.2, 6.7 Hz, H-8), 5.13–4.93 (2H, m, H-9), 4.88 (1H, t, *J* 6.4 Hz, NH), 3.05 (2H, dt, *J* 6.4, 6.4 Hz, H-1), 2.43 (3H, s, H-14), 2.35–2.22 (2H, m), 2.18–2.02 (4H, m), 1.54 (2H, quin, *J* 7.3 Hz, H-6)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 143.43 (C), 137.73 (CH, C-8), 136.94 (C), 129.68 (2 × CH), 127.02 (2 × CH), 115.12 (CH_2, C-9), 82.67 (C), 75.98 (C), 42.09 (CH_2, C-1), 32.72 (CH_2), 27.90 (CH_2), 21.46 (CH_3, C-14), 19.86 (CH_2), 17.98 (CH_2)

LRMS: (ES+) m/z 314.3 ([M+Na]$^+$)

HRMS: (ES+) Calculated for $C_{16}H_{21}NNaO_2S$: 314.1185 Da, found: 314.1189 Da

N-(Dec-9-en-3-yn-1-yl)-4-methylbenzenesulfonamide (134b)



TBAF (30 mL of a 1.0 M solution in THF, 30.0 mmol) was added dropwise to a solution of enyne **132b** (1.80 g, 10.0 mmol) in THF (20 mL). The reaction mixture was left stirring at room temperature for 16 h. The reaction mixture was poured into water (100 mL) and extracted with pentane (2 × 10 mL). The organic extracts were combined, washed with water (4 × 200 mL), dried ($MgSO_4$) and filtered to give an orange solution. The solution was diluted in dry THF (10.0 mL). *n*-BuLi (3.6 mL of a 2.5 M solution in hexanes, 9.0 mmol) was added dropwise to the reaction mixture at −78 °C. The reaction mixture was left at room temperature for 30 mins. 1-Tosylaziridine (1.58 g, 8.0 mmol) in dry THF (5 mL) was added dropwise to the reaction mixture at room temperature. The reaction mixture was left stirring at room temperature for 16 h. The reaction mixture was poured into a sat. aq. $NaHCO_3$ solution (100 mL) and extracted with ether (3 × 50 mL). The organic extracts were combined, washed sequentially with water (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as an orange oil (2.37 g). Purification by column chromatography (SiO_2, hexane/Et_2O 4.5:5.5) gave the title compound as an orange oil (762 mg, 31%).

IR: ν_{max}(neat)/cm^{-1} 3282 (br), 2931 (w), 2861 (w), 1640 (w), 1598 (w), 1156 (s), 549 (s)

^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.75 (2H, d, *J* 8.1 Hz, H-12), 7.30 (2H, d, *J* 8.1 Hz, H-11), 5.79 (1H, ddt, *J* 17.0, 10.3, 6.7 Hz, H-9), 5.05–4.87 (3H, m, NH and H-10), 3.04 (2H, dt, *J* 6.5, 6.5 Hz, H-1), 2.42 (3H, s, H-15), 2.29 (2H, tt, *J* 6.5, 2.3 Hz, H-2), 2.17–1.94 (4H, m, H-5,8), 1.54–1.35 (4H, m, H-6,7)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 143.39 (C), 138.47 (CH, C-9), 136.95 (C), 129.65 (2 × CH), 127.01 (2 × CH), 114.53 (CH_2, C-10), 82.82 (C), 75.79 (C), 42.08 (CH_2, C-1), 33.12 (CH_2), 28.16 (CH_2), 27.95 (CH_2), 21.44 (CH_3, C-15), 19.85 (CH_2), 18.41 (CH_2)

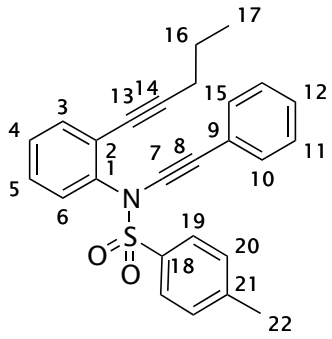
LRMS: (ES+) m/z 328.2 ([M+Na]$^+$)

HRMS: (ES+) Calculated for $C_{17}H_{23}NNaO_2S$: 328.1342 Da, found: 328.1338 Da

General procedure A: synthesis of ynamides

A solution of the appropriate sulfonamide **115a**, **120a,b**, **125** or **134a,b** (1 eq.) and the appropriate bromide **199a-c** (1.1 eq.) in DMF (35 mL) was added to K_2CO_3 (2 eq.), $CuSO_4.5H_2O$ (0.1 eq.) and 1,10-phenanthroline (0.2 eq.). The reaction mixture was stirred at 65 °C for 16 h. The reaction mixture was poured into water (200 mL) and extracted with ether (3 × 50 mL). The organic extracts were combined, washed with water (2 × 100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product, which was purified as described.

4-Methyl-*N*-(2-(pent-1-yn-1-yl)phenyl)-*N*-(phenylethynyl)benzenesulfonamide (110a)



General procedure A with sulfonamide **115a** (1.13 g, 3.6 mmol) and bromide **199b** (752 mg, 4.0 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 9:1) gave the title compound as a pale red oil (691 mg, 46%).

IR: ν_{max}(neat)/cm^{-1} 2962 (w), 2871 (w), 1597 (w), 1569 (w), 1152 (s), 1119 (s), 656 (s)

^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 8.18 (1H, d, *J* 8.4 Hz), 7.73–7.59 (3H, m), 7.59–7.48 (2H, m), 7.45–7.29 (5H, m), 7.20 (2H, d, *J* 8.1 Hz), 3.23 (2H, t, *J* 7.3 Hz, H-15), 2.34 (3H, s, H-22), 1.89 (2H, sxt, *J* 7.3 Hz, H-16), 1.06 (3H, t, *J* 7.3 Hz, H-17)

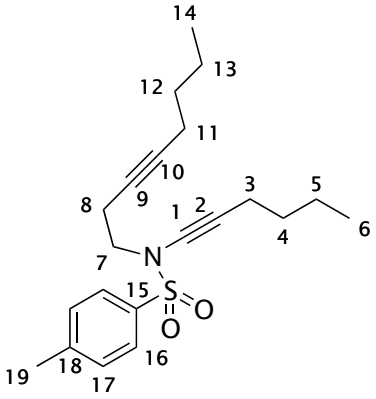
^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 145.52 (C), 144.95 (C), 136.10 (C), 135.83 (C), 131.42 (2 × CH), 129.88 (2 × CH), 128.40 (2 × CH), 128.22 (CH), 126.33 (2 × CH), 124.85 (CH), 124.00 (CH), 123.39 (C), 119.59 (CH), 115.02 (CH), 95.58 (C), 81.07 (C), 30.12 (CH_2), 23.89 (CH_2), 21.54 (CH_3, C-22), 13.95 (CH_3, C-17)

Note: two expected quaternary carbons were not observed in the ^{13}C NMR spectrum.

LRMS: (ES+) m/z 436.2 ([M+Na]$^+$)

HRMS: (ES+) Calculated for $C_{26}H_{23}NNaO_2S$: 436.1342 Da, found: 436.1347 Da

N-(Hex-1-yn-1-yl)-4-methyl-*N*-(oct-3-yn-1-yl)benzenesulfonamide (117a)



General procedure A with sulfonamide **120a** (9.12 g, 33.0 mmol) and bromide **199a** (6.58 g, 36.0 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 9:1) gave the title compound as an orange oil (9.82 g, 84%).

IR: ν_{max} (neat)/cm^{-1} 2956 (w), 2931 (w), 2871 (w), 1597 (w), 1167 (s), 544 (s)

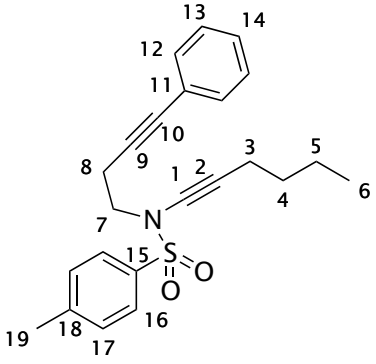
^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, *J* 8.2 Hz, H-16), 7.33 (2H, d, *J* 8.2 Hz, H-17), 3.41 (2H, t, *J* 7.8 Hz, H-7), 2.50–2.40 (2H, m, H-8), 2.46 (3H, s, H-19), 2.25 (2H, t, *J* 6.9 Hz, H-3), 2.10 (2H, tt, *J* 6.8, 2.1 Hz, H-11), 1.51–1.30 (8H, m, H-4,5,12,13), 0.94–0.85 (6H, t, *J* 7.1 Hz, H-6,14)

^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 144.29 (C, C-18), 134.74 (C, C-15), 129.57 (2 × CH), 127.57 (2 × CH), 82.43 (C), 75.39 (C), 72.52 (C), 70.55 (C), 50.62 (CH_2, C-7), 30.92 (CH_2), 30.88 (CH_2), 21.85 (CH_2), 21.79 (CH_2), 21.56 (CH_3, C-19), 18.53 (CH_2), 18.32 (CH_2), 18.09 (CH_2), 13.54 (CH_3), 13.52 (CH_3)

LRMS: (ES+) m/z 382.3 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{21}H_{29}NNaO_2S$: 382.1811 Da, found: 382.1803 Da

N-(Hex-1-yn-1-yl)-4-methyl-*N*-(4-phenylbut-3-yn-1-yl)benzenesulfonamide (117b)



General procedure A with sulfonamide **120b** (1.50 g, 5.0 mmol) and bromide **199a** (886 mg, 5.5 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 4:1) gave the title compound as an orange oil (975 mg, 51%).

IR: ν_{max} (neat)/cm^{-1} 2956 (w), 2930 (w), 2872 (w), 2254 (w), 1597 (w), 1166 (s), 582 (s), 544 (s)

^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.81 (2H, d, *J* 8.1 Hz, H-16), 7.43–7.22 (7H, m, H-12,13,14,17), 3.56 (2H, t, *J* 7.6 Hz, H-7), 2.74 (2H, t, *J* 7.6 Hz, H-8), 2.43 (3H, s,

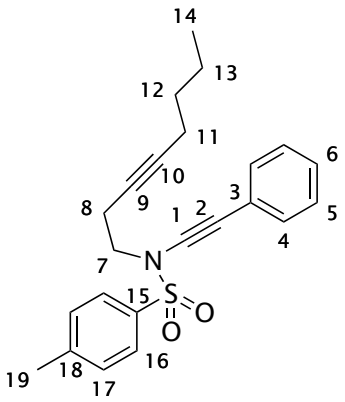
H-19), 2.28 (2H, t, *J* 6.9 Hz, H-3), 1.54–1.29 (4H, m, H-4,5), 0.90 (3H, t, *J* 7.3 Hz, H-6)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 144.40 (C, C-18), 134.74 (C, C-15), 131.62 (2 × CH), 129.64 (2 × CH), 128.19 (2 × CH), 127.93 (CH, C-14), 127.64 (2 × CH), 123.24 (C, C-11), 85.45 (C), 82.41 (C), 72.50 (C), 70.84 (C), 50.27 (CH_2, C-7), 30.95 (CH_2), 21.85 (CH_2), 21.60 (CH_3, C-19), 19.27 (CH_2), 18.16 (CH_2), 13.56 (CH_3, C-6)

LRMS: (ES+) m/z 402.3 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{23}H_{25}NNaO_2S$: 402.1498 Da, found: 402.1493 Da

4-Methyl-*N*-(oct-3-yn-1-yl)-*N*-(phenylethynyl)benzenesulfonamide (117d)



General procedure A with sulfonamide **120a** (1.33 g, 4.8 mmol) and bromide **199b** (996 mg, 5.5 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 9:1) gave the title compound as an orange oil (424 mg, 22%).

IR: ν_{max}(neat)/cm^{-1} 2956 (w), 2930 (w), 2871 (w), 2234 (m), 1597 (w), 1167 (s), 581 (s), 544 (s)

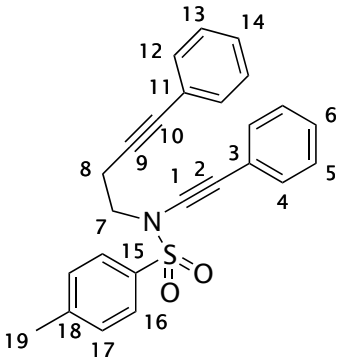
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.77 (2H, d, *J* 8.2 Hz, H-16), 7.34–7.25 (4H, m), 7.24–7.19 (3H, m), 3.48 (2H, t, *J* 7.6 Hz, H-7), 2.48 (2H, tt, *J* 7.6, 2.3 Hz, H-8), 2.38 (3H, s, H-19), 2.03 (2H, tt, *J* 6.8, 2.3 Hz, H-11), 1.41–1.23 (4H, m, H-12,13), 0.81 (3H, t, *J* 7.2 Hz, H-14)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 144.68 (C, C-18), 134.70 (C, C15), 131.36 (2 × CH), 129.78 (2 × CH), 128.23 (2 × CH), 127.82 (CH), 127.66 (2 × CH), 122.72 (C, C-3), 82.75 (C), 81.88 (C), 75.21 (C), 70.93 (C), 50.81 (CH_2, C-7), 30.87 (CH_2), 21.88 (CH_2), 21.63 (CH_3, C-19), 18.80 (CH_2), 18.35 (CH_2), 13.55 (CH_3, C-14)

LRMS: (ES+) m/z 402.2 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{23}H_{26}NO_2S$: 380.1679 Da, found: 380.1673 Da

4-Methyl-*N*-(4-phenylbut-3-yn-1-yl)-*N*-(phenylethynyl)benzenesulfonamide (117e)



General procedure A with sulfonamide **120b** (1.50 g, 5.0 mmol) and bromide **199b** (996 mg, 5.5 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 4:1) gave the title compound as an orange oil (1.20 g, 60%).

IR: ν_{max}(neat)/cm^{-1} 3054 (w), 2234 (m), 1597 (w), 1166 (s), 753 (s), 689 (s), 674 (s), 584 (s), 544 (s)

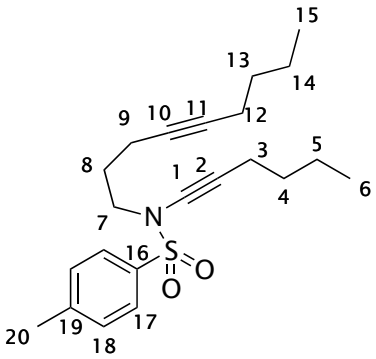
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.87 (2H, d, *J* 8.1 Hz, H-16), 7.44–7.19 (12H, m, H-4,5,6,12,13,14,17), 3.70 (2H, t, *J* 7.5 Hz, H-7), 2.83 (2H, t, *J* 7.5 Hz, H-8), 2.43 (3H, s, H-19)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 144.77 (C, C-18), 134.65 (C, C-15), 131.64 (2 × CH), 131.45 (2 × CH), 129.82 (2 × CH), 128.25 (2 × CH), 128.17 (2 × CH), 127.97 (CH), 127.90 (CH), 127.69 (2 × CH), 123.15 (C), 122.65 (C), 85.22 (C), 82.65 (C), 81.82 (C), 71.12 (C), 50.45 (CH_2, C-7), 21.63 (CH_3, C-19), 19.51 (CH_2, C-8)

LRMS: (ES+) m/z 422.2 ([M+Na]$^+$)

HRMS: (ES+) Calculated for $C_{25}H_{21}NNaO_2S$: 422.1185 Da, found: 422.1173 Da

N-(Hex-1-yn-1-yl)-4-methyl-*N*-(non-4-yn-1-yl)benzenesulfonamide (117i)



General procedure A with sulfonamide **125** (1.47 g, 5.0 mmol) and bromide **199a** (886 mg, 5.5 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 4:1) gave the title compound as an orange oil (1.09 g, 59%).

IR: ν_{max} (neat)/cm^{-1} 2956 (w), 2930 (w), 2871 (w), 1597 (w), 1166 (s), 544 (s)

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 7.79 (2H, d, *J* 8.5 Hz, H-17), 7.33 (2H, d, *J* 8.5 Hz, H-18), 3.37 (2H, t, *J* 7.0 Hz, H-7), 2.45 (3H, s, H-20), 2.26 (2H, t, *J* 7.0 Hz, H-9), 2.22–2.09 (4H, m, H-3,12), 1.80 (2H, quin, *J* 7.0 Hz, H-8), 1.54–1.31 (8H, m,

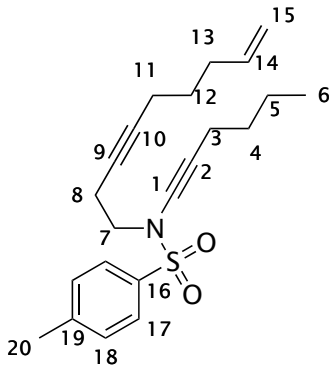
H-4,5,13,14), 0.91 (3H, t, *J* 7.3 Hz, H-6 or H-15), 0.90 (3H, t, *J* 7.5 Hz, H-6 or H-15)

^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 144.18 (C, C-19), 134.64 (C, C-16), 129.53 (2 × CH), 127.64 (2 × CH), 81.21 (C), 78.33 (C), 72.89 (C), 70.22 (C), 50.50 (CH_2, C-7), 31.10 (CH_2), 30.98 (CH_2), 27.43 (CH_2), 21.89 (CH_2), 21.81 (CH_2), 21.59 (CH_3, C-20), 18.37 (CH_2), 18.11 (CH_2), 15.90 (CH_2), 13.58 (CH_3), 13.55 (CH_3)

LRMS: (ES+) m/z 396.3 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{22}H_{31}NNaO_2S$: 396.1968 Da, found: 396.1974 Da

N-(Hex-1-yn-1-yl)-4-methyl-*N*-(non-8-en-3-yn-1-yl)benzenesulfonamide (131a)



General procedure A with sulfonamide **134a** (807 mg, 2.8 mmol) and bromide **199a** (499 mg, 3.1 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 9:1) gave the title compound as a yellow oil (710 mg, 68%).

IR: ν_{max} (neat)/cm^{-1} 2931 (w), 2862 (w), 2255 (w), 1641 (w), 1597 (w), 906 (s), 727 (s)

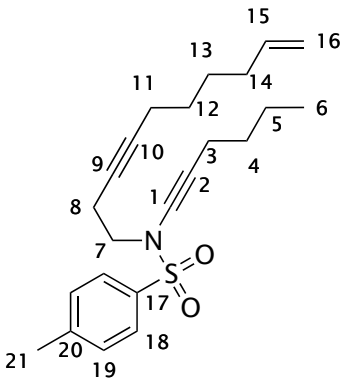
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.78 (2H, d, *J* 8.2 Hz, H-17), 7.33 (2H, d, *J* 8.2 Hz, H-18), 5.78 (1H, ddt, *J* 17.0, 10.3, 6.7 Hz, H-14), 5.10–4.89 (2H, m, H-15), 3.41 (2H, t, *J* 7.9 Hz, H-7), 2.54–2.38 (2H, m, H-8), 2.44 (3H, s, H-20), 2.25 (2H, t, *J* 6.7 Hz, H-3), 2.18–2.04 (4H, m, H-11,13), 1.67–1.26 (6H, m, H-4,5,12), 0.89 (3H, t, *J* 7.0 Hz, H-6)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 144.30 (C, C-19), 137.86 (CH, C-14), 134.67 (C, C-16), 129.57 (2 × CH), 127.55 (2 × CH), 115.01 (CH_2, C-15), 82.02 (C), 75.75 (C), 72.49 (C), 70.55 (C), 50.58 (CH_2, C-7), 32.69 (CH_2), 30.90 (CH_2), 27.92 (CH_2), 21.78 (CH_2), 21.56 (CH_3, C-20), 18.52 (CH_2), 18.08 (CH_2), 18.02 (CH_2), 13.52 (CH_3, C-6)

LRMS: (ES+) m/z 394.3 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{22}H_{29}NNaO_2S$: 394.1811 Da, found: 394.1815 Da

N-(Dec-9-en-3-yn-1-yl)-*N*-(hex-1-yn-1-yl)-4-methylbenzenesulfonamide (131b)



General procedure A with sulfonamide **134b** (706 mg, 2.3 mmol) and bromide **199a** (403 mg, 2.5 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 9:1) gave the title compound as a yellow oil (628 mg, 71%).

IR: ν_{max}(neat)/cm^{-1} 2931 (w), 2861 (w), 2253 (w), 1640 (w), 1597 (w), 1167 (s), 544 (s)

^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.71 (2H, d, *J* 8.1 Hz, H-18), 7.25 (2H, d, *J* 8.1 Hz, H-19), 5.72 (1H, ddt, *J* 17.0, 10.3, 6.6 Hz, H-15), 5.03–4.74 (2H, m, H-16), 3.33 (2H, t, *J* 8.1 Hz, H-7), 2.46–2.29 (2H, m, H-8), 2.37 (3H, s, H-21), 2.17 (2H, t, *J* 7.0 Hz, H-3), 2.09–1.88 (4H, m, H-11,14), 1.49–1.17 (8H, m, H-4,5,12,13), 0.82 (3H, t, *J* 7.2 Hz, H-6)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 144.28 (C), 138.55 (CH, C-15), 134.64 (C), 129.54 (2 × CH), 127.52 (2 × CH), 114.44 (CH_2), 82.19 (C), 75.52 (C), 72.47 (C), 70.51 (C), 50.55 (CH_2, C-7), 33.16 (CH_2), 30.87 (CH_2), 28.16 (CH_2), 27.93 (CH_2), 21.75 (CH_2), 21.53 (CH_3, C-21), 18.49 (CH_2), 18.46 (CH_2), 18.05 (CH_2), 13.50 (CH_3, C-6)

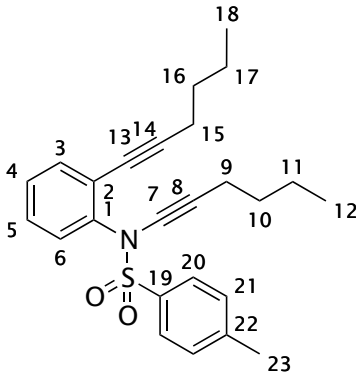
LRMS: (ES+) m/z 408.3 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{23}H_{31}NNaO_2S$: Da, 408.1968 found: 408.1971 Da

General procedure B: synthesis of ynamides

A solution of the appropriate bromide **199a-c** (1 eq.) and *N,N*-dimethylethylenediamine (0.2 eq.) in dry toluene (20 mL) was added to the appropriate sulfonamide **115b,c** or **120a-c** (1 eq.), K_3PO_4 (2 eq.) and CuI (0.05 eq.) in toluene (10.0 mL). The reaction mixture was heated to reflux for 16 h. The reaction mixture was filtered through a plug of silica using ether to elute and the solvent removed *in vacuo* to give the crude product, which was purified as described.

N-(Hex-1-yn-1-yl)-*N*-(2-(hex-1-yn-1-yl)phenyl)-4-methylbenzenesulfonamide (110b)



General procedure B with sulfonamide **115b** (1.64 g, 5.0 mmol) and bromide **199a** (805 mg, 5.0 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 9:1) gave an inseparable 3.3:1 mixture of the title compound and 2-butyl-1-tosyl-1*H*-indole (**116b**) as a yellow oil (1.69 g, 87%).

IR: ν_{max} (neat)/cm^{-1} 2959 (sh), 2938 (w), 2872 (w), 2862 (sh), 1595 (w), 572 (s), 539 (s)

^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.58 (2H, d, *J* 8.1 Hz, H-20), 7.50 (1H, dd, *J* 5.9, 3.0 Hz), 7.31–7.23 (2H, m), 7.22–7.08 (3H, m), 3.12 (2H, t, *J* 7.5 Hz, H-9 or H-15), 2.48 (2H, t, *J* 6.8 Hz, H-9 or H-15), 2.30 (3H, s, H-23), 1.86–1.33 (8H, m, H-10,11,16,17), 1.01–0.90 (6H, m, H-12,18)

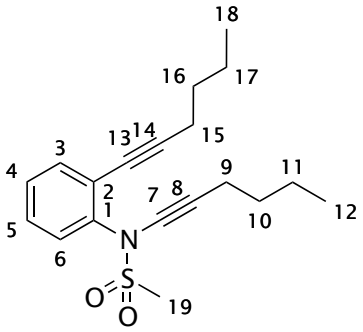
^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 144.98 (C), 144.74 (C), 130.36 (C), 129.76 (2 × CH), 126.28 (2 × CH), 124.55 (CH), 123.79 (CH), 119.45 (CH), 114.92 (CH), 114.80 (C), 96.67 (C), 71.78 (C), 32.49 (CH_2), 30.92 (CH_2), 27.74 (CH_2), 22.47 (CH_2), 21.92 (CH_2), 21.50 (CH_3, C-23), 19.35 (CH_2), 13.81 (CH_3), 13.59 (CH_3)

Note: two expected quaternary carbons were not observed in the ^{13}C NMR spectrum. Both the ^{1}H and ^{13}C NMR spectra contained peaks not reported above that were consistent with the published spectra data for 2-butyl-1-tosyl-1*H*-indole (**116b**).[178]

LRMS: (ES+) m/z 430.4 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{25}H_{29}NNaO_2S$: 430.1811 Da, found: 430.1812 Da

N-(Hex-1-yn-1-yl)-*N*-(2-(hex-1-yn-1-yl)phenyl)methanesulfonamide (110c)



General procedure B with sulfonamide **115c** (525 mg, 2.1 mmol) and bromide **199a** (385 mg, 2.1 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 9:1) gave an inseparable 3.3:1 mixture of the title compound and 2-butyl-1-(methylsulfonyl)-1*H*-indole (**116c**) as a yellow oil (438 mg, 56%).

IR: ν_{max} 3019 (w), 2956 (w), 2929 (w), 2868 (w), 1168 (s), 543 (s)

^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.60 (1H, dd, *J* 6.4, 2.7 Hz), 7.38–7.19 (3H, m), 3.15–3.05 (2H, m, H-9 or H-15), 2.97 (3H, s, H-19), 2.53 (2H, t, *J* 6.8 Hz, H-9 or H-15), 1.81–1.31 (8H, m, H-10,11,16,17), 1.04–0.90 (6H, m, H-12,18)

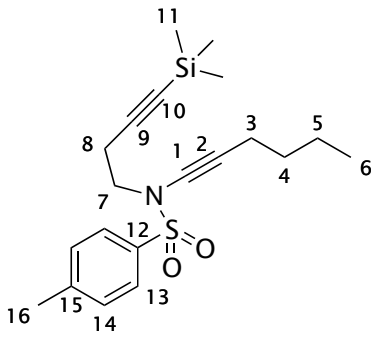
^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 142.45 (C, C-1), 124.80 (CH), 124.03 (CH), 119.74 (CH), 114.23 (CH), 106.16 (C, C-2), 96.78 (C), 71.54 (C), 40.36 (CH_3, C-19), 32.32 (CH_2), 30.93 (CH_2), 27.33 (CH_2), 22.40 (CH_2), 21.93 (CH_2), 19.35 (CH_2), 13.78 (CH_3), 13.60 (CH_3)

Note: two expected quaternary carbons were not observed in the ^{13}C NMR spectrum. Both the ^{1}H and ^{13}C NMR spectra contained peaks not reported above that were consistent with the published spectral data for 2-butyl-1-(methylsulfonyl)-1*H*-indole (**116c**).[179]

LRMS: (ES+) m/z 332.3 ($[M+H]^+$)

HRMS: (ES+) Calculated for $C_{19}H_{25}NNaO_2S$: 354.1498 Da, found: 354.1495 Da

N-(Hex-1-yn-1-yl)-4-methyl-*N*-(4-(trimethylsilyl)but-3-yn-1-yl)benzenesulfonamide (117c)



General procedure B with sulfonamide **120c** (1.48 g, 5.0 mmol) and bromide **199a** (805 mg, 5.0 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 9:1) gave the title compound as a yellow oil (617 mg, 32%).

IR: ν_{max}(neat)/cm^{-1} 2958 (w), 2931 (w), 2872 (w), 2179

(s), 1597 (w), 1167 (s), 839 (s), 586 (s), 544 (s)

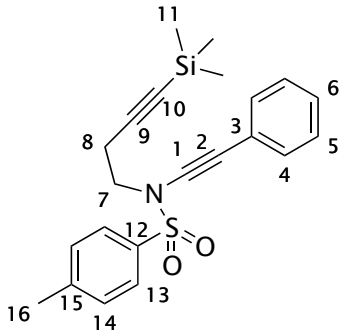
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.79 (2H, d, *J* 8.2 Hz, H-13), 7.34 (2H, d, *J* 8.2 Hz, H-14), 3.45 (2H, t, *J* 7.8 Hz, H-7), 2.54 (2H, t, *J* 7.8 Hz, H-8), 2.45 (3H, s, H-16), 2.25 (2H, t, *J* 7.0 Hz, H-3), 1.55–1.26 (4H, m, H-4,5), 0.90 (3H, t, *J* 7.0 Hz, H-6), 0.14 (9H, s, H-11)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 144.41 (C, C-15), 134.65 (C, C-12), 129.64 (2 × CH), 127.58 (2 × CH), 102.16 (C, C-9), 86.86 (C), 72.44 (C), 70.70 (C), 50.14 (CH_2, C-7), 30.91 (CH_2), 21.82 (CH_3, C-16), 21.60 (CH_2), 19.64 (CH_2), 18.09 (CH_2), 13.54 (CH_3, C-6), −0.07 (CH_3, C-11)

LRMS: (ES+) m/z 398.3 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{20}H_{30}NO_2SSi$: 376.1761 Da, found: 376.1753 Da

4-Methyl-*N*-(phenylethynyl)-*N*-(4-(trimethylsilyl)but-3-yn-1-yl)benzenesulfonamide (117f)



General procedure B with sulfonamide **120c** (1.48 g, 5.0 mmol) and bromide **199b** (905 mg, 5.0 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 9:1) gave the title compound as an orange oil (832 mg, 42%).

IR: ν_{max} (neat)/cm^{-1} 2920 (w), 2845 (w), 2235 (w), 2178 (w), 1597 (w), 589 (s), 544 (s)

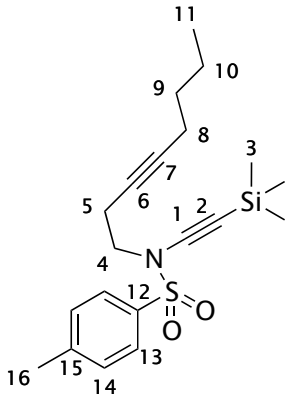
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.82 (2H, d, *J* 8.3 Hz, H-13), 7.36–7.29 (4H, m), 7.28–7.22 (3H, m), 3.56 (2H, t, *J* 7.9 Hz, H-7), 2.60 (2H, t, *J* 7.9 Hz, H-8), 2.42 (3H, s, H-16), 0.10 (9H, s, H-11)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 144.79 (C, C-15), 134.62 (C, C-12), 131.40 (2 × CH), 129.84 (2 × CH), 128.25 (2 × CH), 127.91 (CH), 127.66 (2 × CH), 122.60 (C, C-3), 101.88 (C, C-9), 87.21 (C), 81.74 (C), 71.02 (C), 50.33 (CH_2, C-7), 21.64 (CH_3, C-16), 19.88 (CH_2, C-8), −0.09 (CH_3, C-11)

LRMS: (ES+) m/z 418.2 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{22}H_{25}NNaO_2SSi$: 418.1267 Da, found: 418.1271 Da

4-Methyl-*N*-(oct-3-yn-1-yl)-*N*-((trimethylsilyl)ethynyl)benzenesulfonamide (117g)



General procedure B with sulfonamide **120a** (1.40 g, 5.0 mmol) and bromide **199c** (886 mg, 5.0 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 4:1) gave the title compound as an orange oil (445 mg, 30%).

IR: ν_{max}(neat)/cm^{-1} 2957 (w), 2932 (w), 2156 (m), 1597 (w), 1169 (s), 839 (s)

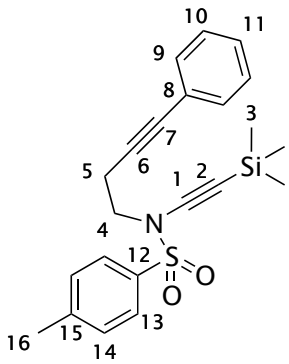
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.79 (2H, d, *J* 8.1 Hz, H-13), 7.34 (2H, d, *J* 8.1 Hz, H-14), 3.44 (2H, t, *J* 7.7 Hz, H-4), 2.54–2.39 (2H, m, H-5), 2.46 (3H, s, H-16), 2.10 (2H, tt, *J* 7.0, 2.6 Hz, H-8), 1.51–1.24 (4H, m, H-9,10), 0.90 (3H, t, *J* 7.0 Hz, H-11), 0.15 (9H, s, H-3)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 144.65 (C, C-15), 134.52 (C, C-12), 129.60 (2 × CH), 127.72 (2 × CH), 94.44 (C, C-1), 82.60 (C), 75.18 (C), 73.48 (C), 50.44 (CH_2, C-4), 30.86 (CH_2), 21.87 (CH_2), 21.62 (CH_3, C-16), 18.57 (CH_2), 18.32 (CH_2), 13.56 (CH_3, C-11), 0.04 (CH_3, C-3)

LRMS: (ES+) m/z 398.2 ([M+Na]$^+$)

HRMS: (ES+) Calculated for $C_{20}H_{30}NO_2SSi$: 376.1761 Da, found: 376.1759 Da

4-Methyl-*N*-(4-phenylbut-3-yn-1-yl)-*N*-((trimethylsilyl)ethynyl)benzenesulfonamide (117h)



General procedure B with sulfonamide **120b** (1.50 g, 5.0 mmol) and bromide **199c** (886 mg, 5.0 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 4:1) gave the title compound as a yellow solid (930 mg, 47%).

IR: ν_{max}(neat)/cm^{-1} 2958 (w), 2156 (m), 1597 (w), 1168 (s), 838 (s), 659 (s), 542 (s)

m.p.: 87–89 °C

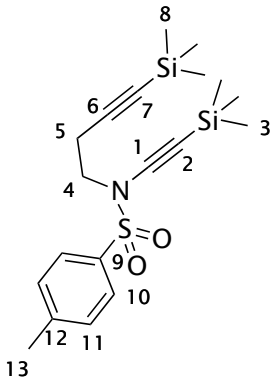
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.81 (2H, d, *J* 8.1 Hz, H-13), 7.42–7.21 (7H, m, H-9,10,11,14), 3.58 (2H, t, *J* 7.6 Hz, H-4), 2.74 (2H, t, *J* 7.6 Hz, H-5), 2.43 (3H, s, H-16), 0.16 (9H, s, H-3)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 144.73 (C, C-15), 134.51 (C, C-12), 131.61 (2 × CH), 129.65 (2 × CH), 128.18 (2 × CH), 127.97 (CH, C-11), 127.77 (2 × CH), 123.17 (C, C-8), 94.41 (C, C-1), 85.19 (C), 82.55 (C), 73.75 (C), 50.11 (CH_2, C-4), 21.62 (CH_3, C-16), 19.30 (CH_2, C-5), 0.05 (CH_3, C-3)

LRMS: (ES+) m/z 418.2 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{22}H_{26}NNaO_2SSi$: 396.1448 Da, found: 396.1446 Da

4-Methyl-*N*-(4-(trimethylsilyl)but-3-yn-1-yl)-*N*-((trimethylsilyl)ethynyl)benzenesulfonamide (117i)



General procedure B with sulfonamide **120c** (1.48 g, 5.0 mmol) and bromide **199c** (886 mg, 5.0 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 9:1) gave the title compound as a yellow oil (707 mg, 36%).

IR: ν_{max} (neat)/cm^{-1} 2959 (w), 2989 (w), 2177 (w), 2157 (w), 1597 (w), 837 (s)

^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.80 (2H, d, *J* 8.2 Hz, H-10), 7.35 (2H, d, *J* 8.2 Hz, H-11), 3.49 (2H, t, *J* 8.1 Hz, H-4), 2.56 (2H, t, *J* 8.1 Hz, H-5), 2.47 (3H, s, H-13), 0.16 (9H, s, H-3 or H-8), 0.15 (9H, s, H-3 or H-8)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 144.76 (C, C-12), 134.50 (C, C-9), 129.67 (2 × CH), 127.75 (2 × CH), 101.89 (C), 94.32 (C), 87.09 (C), 73.70 (C), 49.95 (CH_2, C-4), 21.64 (CH_3, C-13), 19.67 (CH_2, C-5), 0.05 (CH_3), −0.07 (CH_3)

LRMS: (ES+) m/z 414.2 ($[M+Na]^+$)

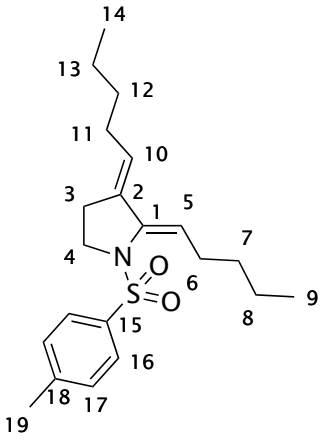
HRMS: (ES+) Calculated for $C_{19}H_{29}NNaO_2SSi_2$: 414.1350 Da, found: 414.1350 Da

General procedure C: zirconocene mediated cocyclisation of ynamides

n-BuLi (0.88 mL of a 2.5 M solution in hexanes, 2.2 mmol) was added dropwise to a solution of Cp_2ZrCl_2 (322 mg, 1.1 mmol) in dry THF (5.0 mL) at −78 °C. A

solution of the appropriate ynamide **117a-j** or **131a,b** (1.0 mmol) in dry THF (3.0 mL) was added dropwise at −78 °C. The reaction mixture was warmed to room temperature and stirred for 5 h. The reaction mixture was cooled to −78 °C and MeOH (10.0 mL) added. After stirring at −78 °C for 1 h the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was poured into water (100 mL) and extracted with ether (3 × 50 mL). The organic extracts were combined, washed sequentially with water (2 × 100 mL) and brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product, which was purified as described.

(2*Z*,3*E*)-2,3-Dipentylidene-1-tosylpyrrolidine (123a)



General procedure C with ynamide **117a** (360 mg, 1.0 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 9:1) gave the title compound as a pale yellow oil (268 mg, 74%).

IR: ν_{max} (neat)/cm^{-1} 2956 (w), 2926 (w), 2857 (w), 1598 (w), 1163 (s), 730 (s)

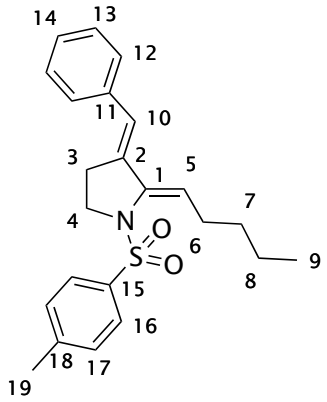
^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 7.67 (2H, d, *J* 8.0 Hz, H-16), 7.20 (2H, d, *J* 8.0 Hz, H-17), 5.72 (1H, t, *J* 7.3 Hz, H-5), 5.61 (1H, tt, *J* 7.0, 2.5 Hz, H-10), 3.55 (2H, t, *J* 7.3 Hz, H-4), 2.52 (2H, dt, *J* 7.3, 7.3 Hz, H-6), 2.39 (3H, s, H-19), 1.81–1.65 (4H, m), 1.51–1.32 (4H, m), 1.20–1.08 (4H, m), 0.92 (3H, t, *J* 7.3 Hz, H-9 or H-14), 0.84 (3H, t, *J* 6.8 Hz, H-9 or H-14)

^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 143.50 (C), 137.04 (C), 135.87 (C), 134.70 (C), 129.28 (2 × CH), 127.83 (2 × CH), 120.39 (CH), 120.23 (CH), 48.45 (CH_2, C-4), 31.80 (CH_2), 31.01 (CH_2), 29.29 (CH_2), 29.17 (CH_2), 25.73 (CH_2), 22.45 (CH_2), 22.21 (CH_2), 21.49 (CH_3, C-19), 13.98 (CH_3), 13.91 (CH_3)

LRMS: (ES+) m/z 362.3 ($[M+H]^+$)

HRMS: (ES+) Calculated for $C_{21}H_{32}NO_2S$: 362.2148 Da, found: 362.2145 Da

(2*Z*,3*E*)-3-Benzylidene-2-pentylidene-1-tosylpyrrolidine (123b)



General procedure C with ynamide **117b** (380 mg, 1.0 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 4:1) gave the title compound as a yellow solid (224 mg, 61%).

IR: ν_{max} (neat)/cm^{-1} 2961 (w), 2930 (w), 2872 (w), 2856 (w), 1594 (w)

m.p.: 114–116 °C

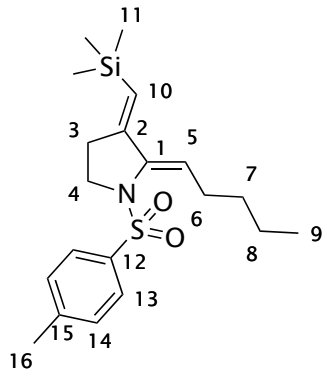
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.70 (2H, d, *J* 8.0 Hz, H-16), 7.33–7.01 (7H, m, H-12,13,14,17), 6.62 (1H, t, *J* 2.4 Hz, H-10), 5.99 (1H, t, *J* 7.3 Hz, H-5), 3.62 (2H, t, *J* 7.3 Hz, H-4), 2.61 (2H, dt, *J* 7.2, 7.2 Hz, H-6), 2.31 (3H, s, H-19), 2.07 (2H, td, *J* 7.1, 2.6 Hz, H-3), 1.56–1.33 (4H, m, H-7,8), 0.95 (3H, t, *J* 7.0 Hz, H-9)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 143.87 (C), 138.27 (C), 137.16 (C), 136.10 (C), 135.50 (C), 129.36 (2 × CH), 128.28 (2 × CH), 128.16 (2 × CH), 127.78 (2 × CH), 126.68 (CH), 121.91 (CH), 119.64 (CH), 48.74 (CH_2, C-4), 31.76 (CH_2), 29.50 (CH_2), 28.03 (CH_2), 22.48 (CH_2), 21.41 (CH_3, C-19), 14.00 (CH_3, C-9)

LRMS: (ES+) m/z 382.2 ($[M+H]^+$)

HRMS: (ES+) Calculated for $C_{23}H_{28}NO_2S$: 382.1835 Da, found: 382.1831 Da

(2*Z*,3*E*)-2-Pentylidene-1-tosyl-3-((trimethylsilyl)methylene)pyrrolidine (123c)



General procedure C with ynamide **117c** (376 mg, 1.0 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 4:1) gave the title compound as a white solid (242 mg, 64%).

IR: ν_{max} (neat)/cm^{-1} 2959 (w), 2932 (w), 2856 (w), 1609 (w), 1597 (w), 849 (s), 541 (s)

m.p.: 89–91 °C

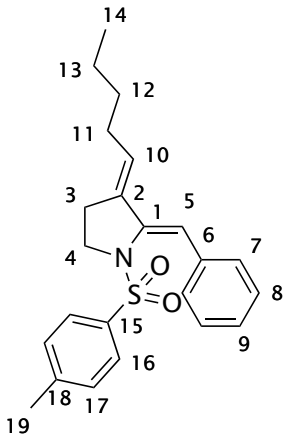
^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 7.66 (2H, d, *J* 8.0 Hz, H-13), 7.21 (2H, d, *J* 8.0 Hz, H-14), 5.91 (1H, t, *J* 7.2 Hz, H-5), 5.74 (1H, t, *J* 2.3 Hz, H-10), 3.56 (2H, t, *J* 7.5 Hz, H-4), 2.56 (2H, q, *J* 7.2 Hz, H-6), 2.40 (3H, s, H-16), 1.76 (2H, td, *J* 7.2, 2.3 Hz, H-3), 1.51–1.32 (4H, m, H-7,8), 0.94 (3H, t, *J* 7.0 Hz, H-9), −0.07 (9H, s, H-11)

^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 150.46 (C), 143.74 (C), 138.28 (C), 135.70 (C), 129.39 (2 × CH), 127.83 (2 × CH), 122.60 (CH), 117.04 (CH), 48.44 (CH_2, C-4), 31.65 (CH_2), 29.34 (CH_2), 28.37 (CH_2), 22.49 (CH_2), 21.46 (CH_3, C-16), 13.99 (CH_3, C-9), −0.96 (CH_3, C-11)

LRMS: (ES+) m/z 378.3 ($[M+H]^+$)

HRMS: (ES+) Calculated for $C_{20}H_{32}NO_2SSi$: 378.1918 Da, found: 378.1917 Da

(2*Z*,3*E*)-2-Benzylidene-3-pentylidene-1-tosylpyrrolidine (123d)



General procedure C with ynamide **117d** (380 mg, 1.0 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 4:1) gave the title compound as a yellow oil (337 mg, 88%).

IR: ν_{max}(neat)/cm^{-1} 3024 (w), 2955 (w), 2926 (w), 2855 (w), 1596 (m), 1350 (s), 1163 (s), 586 (s)

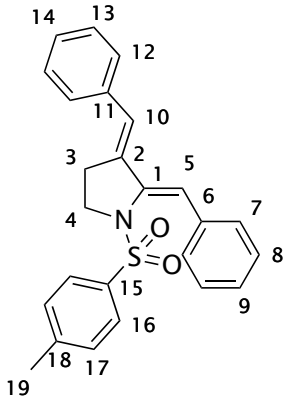
^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 7.81 (2H, d, *J* 7.5 Hz, H-7), 7.69 (2H, d, *J* 8.0 Hz, H-16), 7.33 (2H, t, *J* 7.5 Hz, H-8), 7.25–7.18 (3H, m, H-9,17), 6.60 (1H, s, H-5), 5.88 (1H, tt, *J* 7.2, 2.5 Hz, H-10), 3.69 (2H, t, *J* 7.3 Hz, H-4), 2.41 (3H, s, H-19), 1.87 (2H, dt, *J* 7.2, 7.2 Hz, H-11), 1.77 (2H, td, *J* 7.3, 2.5 Hz, H-3), 1.37–1.14 (4H, m, H-12,13), 0.90 (3H, t, *J* 6.5 Hz, H-14)

^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 143.79 (C), 136.74 (C), 135.94 (C), 135.79 (C), 135.51 (C), 129.33 (4 × CH), 128.00 (2 × CH), 127.91 (2 × CH), 127.19 (CH), 122.04 (CH), 116.40 (CH), 48.55 (CH_2, C-4), 31.01 (CH_2), 29.58 (CH_2), 25.49 (CH_2), 22.28 (CH_2), 21.52 (CH_3, C-19), 13.93 (CH_3, C-14)

LRMS: (ES+) m/z 404.2 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{23}H_{28}NO_2S$: 382.1835 Da, found: 382.1832 Da

(2*Z*,3*E*)-2,3-Dibenzylidene-1-tosylpyrrolidine (123e)



General procedure C with ynamide **117e** (400 mg, 1.0 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 4:1) gave the title compound as a yellow solid (189 mg, 49%).

IR: ν_{max}(neat)/cm^{-1} 3055 (w), 3022 (w), 2962 (w), 2899 (w), 1597 (m), 1573 (w), 1162 (s), 1155 (s), 691 (s), 585 (s)

m.p.: 138–140 °C

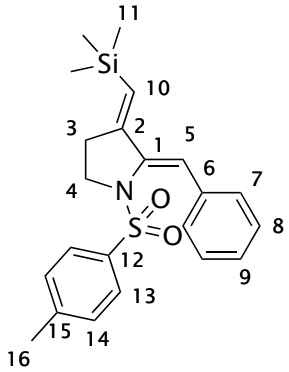
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.87 (2H, d, *J* 7.3 Hz, H-7), 7.71 (2H, d, *J* 8.4 Hz, H-16), 7.44–7.06 (10H, m, H-8,9,12,13,14,17), 6.91–6.79 (2H, m, H-5,10), 3.74 (2H, t, *J* 7.1 Hz, H-4), 2.33 (3H, s, H-19), 2.09 (2H, td, *J* 7.1, 2.6 Hz, H-3)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 144.13 (C), 137.86 (C), 137.04 (C), 136.92 (C), 135.78 (C), 135.15 (C), 129.58 (2 × CH), 129.42 (2 × CH), 128.46 (2 × CH), 128.40 (2 × CH), 128.00 (2 × CH), 127.97 (2 × CH), 127.56 (CH), 127.06 (CH), 120.95 (CH), 117.48 (CH), 48.93 (CH_2, C-4), 27.90 (CH_2, C-3), 21.46 (CH_3, C-19)

LRMS: (ES+) m/z 424.2 ([M+Na]$^+$)

HRMS: (ES+) Calculated for $C_{25}H_{23}NO_2S$: 402.1522 Da, found: 402.1515 Da

(2*Z*,3*E*)-2-Benzylidene-1-tosyl-3-((trimethylsilyl)methylene)pyrrolidine (123f)



General procedure C with ynamide **117f** (396 mg, 1.0 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 4:1) gave the title compound as an off white solid (292 mg, 74%).

IR: ν_{max}(neat)/cm^{-1} 3024 (w), 2962 (w), 2925 (w), 1596 (w)

m.p.: 128–130 °C

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 7.86 (2 H, d, *J* 7.5 Hz, H-7),

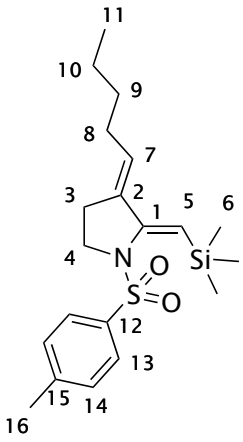
7.69 (2 H, d, *J* 8.0 Hz, H-13), 7.35 (2 H, t, *J* 7.5 Hz, H-8), 7.29–7.15 (3 H, m, H-9,14), 6.75 (1 H, s, H-5), 6.00 (1 H, t, *J* 2.5 Hz, H-10), 3.70 (2 H, t, *J* 7.3 Hz, H-4), 2.41 (3 H, s, H-16), 1.80 (2 H, td, *J* 7.3, 2.5 Hz, H-3), −0.01 (9 H, s, H-11)

^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 151.25 (C), 144.02 (C), 137.40 (C), 135.51 (C), 135.35 (C), 129.68 (2 × CH), 129.44 (2 × CH), 128.00 (2 × CH), 127.97 (2 × CH), 127.71 (CH, C-9), 118.64 (CH), 118.48 (CH), 48.43 (CH_2, C-4), 28.02 (CH_2, C-3), 21.49 (CH_3, C-16), −0.94 (CH_3, C-11)

LRMS: (ES+) m/z 420.2 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{22}H_{28}NO_2SSi$: 398.1605 Da, found: 398.1594 Da

(2*Z*,3*E*)-3-Pentylidene-1-tosyl-2-((trimethylsilyl)methylene)pyrrolidine (123g)



General procedure C with ynamide **117g** (342 mg, 1.0 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 4:1) gave the title compound as a pale yellow oil (276 mg, 73%).

IR: ν_{max} (neat)/cm^{-1} 2954 (w), 2928 (w), 2857 (w), 1599 (m), 1163 (s), 839 (s)

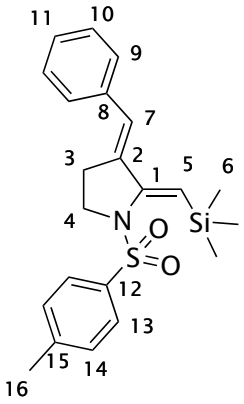
^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 7.64 (2H, d, *J* 8.2 Hz, H-13), 7.20 (2H, d, *J* 8.2 Hz, H-14), 5.79 (1H, tt, *J* 7.2, 2.5 Hz, H-7), 5.66 (1H, s, H-5), 3.57 (2H, t, *J* 7.3 Hz, H-4), 2.40 (3H, s, H-16), 1.82 (2H, dt, *J* 7.2, 7.2 Hz, H-8), 1.69 (2H, td, *J* 7.3, 2.5 Hz, H-3), 1.33–1.06 (4H, m, H-9,10), 0.84 (3H, t, *J* 7.0 Hz, H-11), 0.27 (9H, s, H-6)

^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 148.71 (C), 143.48 (C), 136.08 (C), 135.66 (C), 129.31 (2 × CH), 127.70 (2 × CH), 123.54 (CH), 113.44 (CH), 47.84 (CH_2, C-4), 30.90 (CH_2), 29.40 (CH_2), 25.21 (CH_2), 22.19 (CH_2), 21.50 (CH_3, C-16), 13.89 (CH_3, C-11), 0.06 (CH_3, C-6)

LRMS: (ES+) m/z 378.3 ($[M+H]^+$)

HRMS: (ES+) Calculated for $C_{20}H_{32}NO_2SSi$: 378.1918 Da, found: 378.1912 Da

(2*Z*,3*E*)-3-Benzylidene-1-tosyl-2-((trimethylsilyl)methylene)pyrrolidine (123h)



General procedure C with ynamide **117h** (396 mg, 1.0 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 4:1) gave the title compound as the major product as a yellow oil (181 mg, 45%).

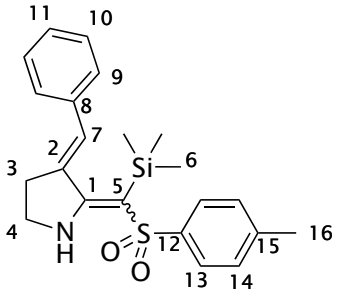
IR: ν_{max} (neat)/cm^{-1} 2952 (w), 2898 (w), 1597 (m), 1162 (s), 839 (s), 590 (s)

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 7.70 (2H, d, *J* 8.3 Hz, H-13), 7.37–7.25 (2H, m), 7.24–7.16 (3H, m), 7.13 (2H, d, *J* 7.3 Hz), 6.79 (1H, t, *J* 2.5 Hz, H-7), 5.96 (1H, s, H-5), 3.65 (2H, t, *J* 7.2 Hz, H-4), 2.35 (3H, s, H-16), 2.04 (2H, td, *J* 7.2, 2.5 Hz, H-3), 0.36 (9H, s, H-6)

^{13}C NMR: δ_C (100 MHz, $CDCl_3$) 149.58 (C), 143.78 (C), 136.77 (C), 136.61 (C), 135.70 (C), 129.37 (2 × CH), 128.45 (2 × CH), 128.30 (2 × CH), 127.60 (2 × CH), 127.07 (CH), 122.29 (CH), 115.01 (CH), 48.10 (CH_2, C-4), 27.48 (CH_2, C-3), 21.40 (CH_3, C-16), 0.09 (CH_3, C-6)

LRMS: (ES+) m/z 398.2 ($[M+H]^+$)

HRMS: (ES+) Calculated for $C_{22}H_{28}NO_2SSi$: 398.1605 Da, found: 398.1597 Da.



The minor product was (3*E*)-3-benzylidene-2-(tosyl(trimethylsilyl)methylene)pyrrolidine (**126h**) obtained as a pale yellow oil (149 mg, 38%).

IR: ν_{max} (neat)/cm^{-1} 3285 (br), 3063 (w), 3026 (w), 2959 (w), 2908 (w), 2139 (w), 1160 (s), 871 (s), 661 (s)

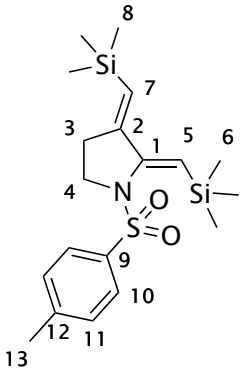
^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 7.70 (2H, d, *J* 8.1 Hz, H-13), 7.40–7.11 (7H, m, H-9,10,11,14), 6.97 (1H, s, H-7), 4.73 (1H, t, *J* 6.6 Hz, NH), 3.27 (2H, dt, *J* 6.6, 6.6 Hz, H-4), 2.53 (2H, t, *J* 6.6 Hz, H-3), 2.39 (3H, s, H-16), 0.19 (9H, s, H-6)

^{13}C NMR: δ_C (101 MHz, $CDCl_3$) 143.25 (C), 139.47 (CH, C-7), 137.01 (C), 135.57 (C), 129.63 (2 × CH), 128.78 (2 × CH), 128.40 (2 × CH), 127.77 (CH, C-11), 126.99 (2 × CH), 120.49 (C), 105.94 (C), 95.86 (C), 41.70 (CH_2, C-4), 30.86 (CH_2, C-3), 21.46 (CH_3, C-16), −0.16 (CH_3, C-6)

LRMS: (ES+) m/z 420.2 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{22}H_{27}NNaO_2SSi$: 420.1424 Da, found: 420.1425 Da

(2*Z*,3*E*)-1-Tosyl-2,3-bis((trimethylsilyl)methylene)pyrrolidine (123i)



General procedure C with ynamide **117i** (392 mg, 1.0 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 4:1) gave the title compound as the major product as a pale yellow oil (147 mg, 37%).

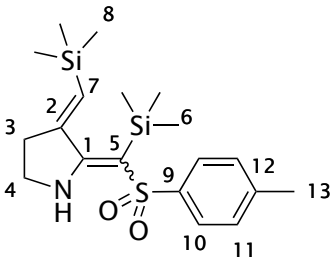
IR: ν_{max} (neat)/cm^{-1} 2953 (w), 2896 (w), 1615 (w), 1597 (w), 1162 (s), 834 (s), 812 (s)

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 7.62 (2H, d, *J* 8.1 Hz, H-10), 7.20 (2H, d, *J* 8.1 Hz, H-11), 5.93 (1H, t, *J* 2.6 Hz, H-7), 5.86 (1H, s, H-5), 3.56 (2H, t, *J* 7.4 Hz, H-4), 2.39 (3H, s, H-13), 1.72 (2H, td, *J* 7.4, 2.6 Hz, H-3), 0.28 (9H, s, H-6 or H-8), −0.06 (9H, s, H-6 or H-8)

^{13}C NMR: δ_C (101 MHz, $CDCl_3$) 150.86 (C), 149.36 (C), 143.69 (C), 135.86 (C), 129.35 (2 × CH), 127.67 (2 × CH), 120.27 (CH), 116.14 (CH), 47.57 (CH_2, C-4), 27.63 (CH_2, C-3), 21.43 (CH_3, C-13), −0.11 (CH_3), −1.10 (CH_3)

LRMS: (ES+) m/z 394.2 ($[M+H]^+$)

HRMS: (ES+) Calculated for $C_{19}H_{31}NNaO_2SSi_2$: 416.1506 Da, found: 416.1499 Da



The minor product was (3*E*)-2-(tosyl(trimethylsilyl)methyl ene)-3-((trimethylsilyl)methylene)pyrrolidine **(126i)** obtained as a pale yellow oil (70.6 mg, 18%).

IR: ν_{max} (neat)/cm^{-1} 3253 (br), 2958 (w), 2898 (w), 2139 (w), 1573 (w), 836 (s)

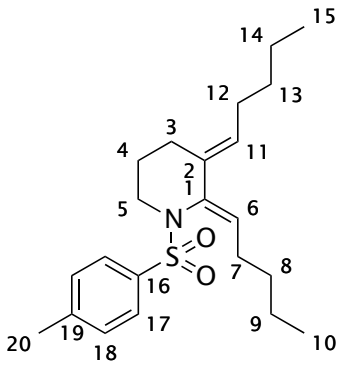
^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 7.76 (2H, d, *J* 8.1 Hz, H-10), 7.31 (2H, d, *J* 8.1 Hz, H-11), 6.16 (1H, s, H-7), 4.70 (1H, t, *J* 6.6 Hz, NH), 3.17 (2H, dt, *J* 6.6, 6.6 Hz, H-4), 2.42 (3H, s, H-13), 2.40 (2H, t, *J* 6.6 Hz, H-3), 0.14 (9H, s, H-6 or H-8), 0.11 (9H, s, H-6 or H-8)

^{13}C NMR: δ_C (101 MHz, $CDCl_3$) 143.32 (C), 142.86 (CH, C-7), 136.90 (C), 134.55 (C), 129.67 (2 × CH), 127.11 (2 × CH), 106.32 (C), 94.24 (C), 41.94 (CH_2, C-4), 35.60 (CH_2, C-3), 21.45 (CH_3, C-13), −0.23 (CH_3, C-6,8)

LRMS: (ES+) m/z 416.2 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{19}H_{31}NNaO_2SSi_2$: 416.1506 Da, found: 416.1504 Da

(2*Z*,3*E*)-2,3-Dipentylidene-1-tosylpiperidine (123j)



General procedure C with ynamide **117j** (374 mg, 1.0 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 9:1) gave the title compound as a colourless oil (277 mg, 74%).

IR: ν_{max} (neat)/cm^{-1} 2955 (w), 2925 (w), 2858 (w), 1159 (s)

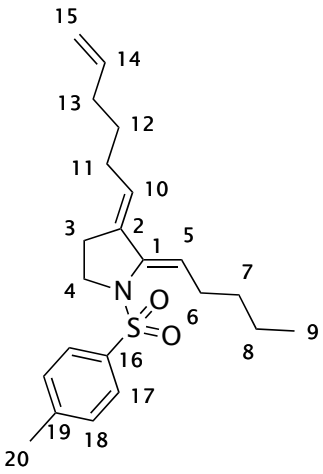
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.69 (2H, d, *J* 8.2 Hz, H-17), 7.21 (2H, d, *J* 8.2 Hz, H-18), 5.74 (1H, t, *J* 7.3 Hz, H-6), 5.48 (1H, t, *J* 7.5 Hz, H-11), 3.53 (2H, t, *J* 5.7 Hz, H-5), 2.40 (3H, s, H-20), 2.36 (2H, m), 1.90 (2H, t, *J* 5.7 Hz), 1.82 (2H, q, *J* 6.8 Hz), 1.48–1.17 (10H, m), 0.99–0.84 (6H, m, H-10,15)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 142.92 (C), 137.29 (C), 136.68 (C), 134.71 (C), 131.68 (CH), 129.13 (2 × CH), 128.15 (2 × CH), 125.80 (CH), 48.12 (CH_2, C-5), 31.58 (CH_2), 31.36 (CH_2), 28.31 (CH_2), 26.91 (CH_2), 25.75 (CH_2), 22.61 (CH_2), 22.44 (CH_2), 22.38 (CH_2), 21.94 (CH_2), 21.49 (CH_3, C-20), 14.01 (CH_3), 13.97 (CH_3)

LRMS: (ES+) m/z 398.3 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{22}H_{33}NNaO_2S$: 398.2124 Da, found: 398.2117 Da

(2*Z*,3*E*)-3-(Hex-5-en-1-ylidene)-2-pentylidene-1-tosylpyrrolidine (135a)



General procedure C with ynamide **131a** (372 mg, 1.0 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 9:1) gave the title compound as the minor product as a pale yellow oil (119 mg, 32%).

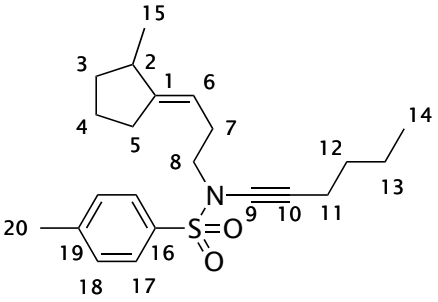
IR: ν_{max} (neat)/cm^{-1} 2955 (w), 2925 (w), 2855 (w), 1640 (w), 1597 (w), 1162 (s), 540 (s)

^{1}H NMR: δ_H (300 MHz, C_6D_6) 7.71 (2H, d, *J* 8.2 Hz, H-17), 6.72 (2H, d, *J* 8.2 Hz, H-18), 5.77 (1H, t, *J* 7.4 Hz, H-5), 5.66 (1H, ddt, *J* 17.0, 10.4, 6.8 Hz, H-14), 5.47 (1H, tt, *J* 7.5, 2.7 Hz, H-10), 5.01–4.85 (2H, m, H-15), 3.40 (2H, t, *J* 7.4 Hz, H-4), 2.89 (2H, dt, *J* 7.5 Hz, H-11), 1.90 (3H, s, H-20), 1.73 (2H, td, *J* 7.4, 6.8 Hz, H-13), 1.50 (8H, m, H-3,6,7,8), 1.14 (2H, quin, *J* 7.4 Hz, H-12), 0.93 (3H, t, *J* 7.2 Hz, H-9)

^{13}C NMR: δ_C (75 MHz, C_6D_6) 143.53 (C), 139.07 (CH, C-14), 138.16 (C), 137.50 (C), 136.40 (C), 129.77 (2 × CH), 128.63 (2 × CH), 120.77 (CH), 119.96 (CH), 115.16 (CH_2, C-15), 49.08 (CH_2, C-4), 33.82 (CH_2), 32.68 (CH_2), 30.32 (CH_2), 29.66 (CH_2), 28.82 (CH_2), 26.38 (CH_2), 23.31 (CH_2), 21.55 (CH_3, C-20), 14.62 (CH_3, C-9)

LRMS: (ES+) m/z 412.3 ($[M+K]^+$)

HRMS: (ES+) Calculated for $C_{22}H_{31}NNaO_2S$: 396.1968 Da, found: 396.1964 Da



The major product was (*E*)-*N*-(hex-1-yn-1-yl)-4-methyl-*N*-(3-(2-methylcyclopentylidene)propyl)benzenesulfonamide (**136a**) obtained as a pale yellow oil (150 mg, 40%).

IR: ν_{max} (neat)/cm^{-1} 2954 (w), 2930 (w), 2868 (w), 2254 (w), 1597 (w), 1166 (s), 544 (s)

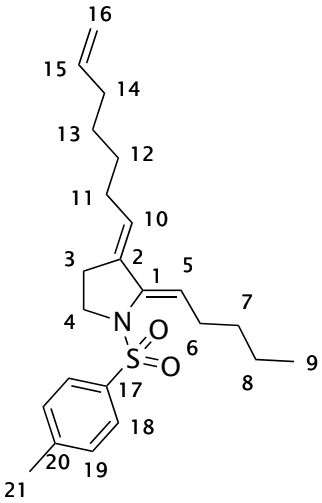
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.78 (2H, d, *J* 8.1 Hz, H-17), 7.32 (2H, d, *J* 8.1 Hz, H-18), 5.02 (1H, m, H-6), 3.27 (2H, t, *J* 7.7 Hz, H-8), 2.44 (3H, s, H-20), 2.36–2.00 (7H, m), 1.93–1.65 (2H, m), 1.59–1.28 (6H, m), 1.00 (3H, d, *J* 6.7 Hz, H-15), 0.90 (3H, t, *J* 7.1 Hz, H-14)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 151.16 (C), 144.07 (C), 134.84 (C), 129.48 (2 × CH), 127.54 (2 × CH), 114.02 (CH, C-6), 73.01 (C), 70.14 (C), 51.09 (CH_2, C-8), 38.98 (CH, C-2), 35.32 (CH_2), 30.97 (CH_2), 28.98 (CH_2), 28.09 (CH_2), 23.83 (CH_2), 21.78 (CH_2), 21.54 (CH_3, C-20), 18.81 (CH_3, C-15), 18.11 (CH_2), 13.53 (CH_3, C-14)

LRMS: (ES+) m/z 412.3 ($[M+K]^+$)

HRMS: (ES+) Calculated for $C_{22}H_{31}NNaO_2S$: 396.1968 Da, found: 396.1973 Da

(2*Z*,3*E*)-3-(Hept-6-en-1-ylidene)-2-pentylidene-1-tosylpyrrolidine (135b)



General procedure C with ynamide **131b** (386 mg, 1.0 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 9:1) gave the title compound as the major product as a pale yellow oil (187 mg, 48%).

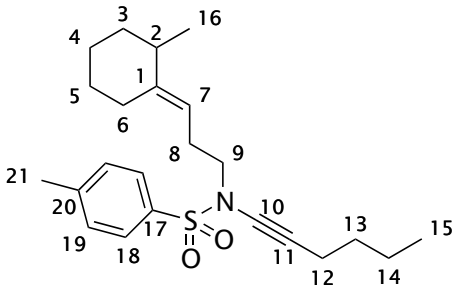
IR: ν_{max} (neat)/cm^{-1} 2954 (w), 2925 (w), 2855 (w), 1640 (w), 1597 (w), 1163 (s), 540 (s)

^{1}H NMR: δ_H (300 MHz, C_6D_6) 7.71 (2H, d, *J* 8.1 Hz, H-18), 6.74 (2H, d, *J* 8.1 Hz, H-19), 5.77 (1H, t, *J* 7.2 Hz, H-5), 5.73 (1H, m, H-15), 5.51 (1H, tt, *J* 7.6, 2.6 Hz, H-10), 5.08–4.90 (2H, m, H-16), 3.40 (2H, t, *J* 7.4 Hz, H-4), 2.88 (2H, dt, *J* 7.6, 7.4 Hz), 1.96–1.84 (2H, m, H-3), 1.91 (3H, s, H-21), 1.65–1.32 (8H, m), 1.18–1.01 (4H, m), 0.93 (3H, t, *J* 7.2 Hz, H-9)

^{13}C NMR: δ_C (75 MHz, C_6D_6) 143.47 (C), 139.20 (CH, C-15), 138.21 (C), 137.50 (C), 136.13 (C), 129.75 (2 × CH), 128.64 (2 × CH), 120.64 (CH), 120.26 (CH), 115.17 (CH_2, C-16), 49.09 (CH_2, C-4), 34.34 (CH_2), 32.67 (CH_2), 30.31 (CH_2), 30.11 (CH_2), 29.12 (CH_2), 28.98 (CH_2), 26.36 (CH_2), 23.31 (CH_2), 21.55 (CH_3, C-21), 14.62 (CH_3, C-9)

LRMS: (ES+) m/z 410.3 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{23}H_{33}NNaO_2S$: 410.2124 Da, found: 410.2128 Da



The minor product was (*E*)-*N*-(hex-1-yn-1-yl)-4-methyl-*N*-(3-(2-methylcyclohexylidene)propyl)benzenesulfonamide (**136b**) obtained as a pale yellow oil (102 mg, 26%).

IR: ν_{max} (neat)/cm^{-1} 2956 (w), 2926 (w), 2854 (w), 2255(w), 1597 (w), 1167 (s), 544 (s)

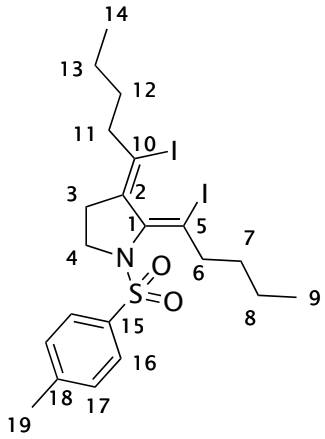
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.78 (2H, d, *J* 8.2 Hz, H-18), 7.33 (2H, d, *J* 8.2 Hz, H-19), 4.96 (1H, t, *J* 7.1 Hz, H-7), 3.24 (2H, t, *J* 7.8 Hz, H-9), 2.53–2.39 (2H, m), 2.44 (3H, s, H-21), 2.38–2.21 (4H, m), 1.88–1.56 (4H, m), 1.54–1.24 (6H, m), 1.09 (1H, m), 0.98 (3H, d, *J* 6.7 Hz, H-16), 0.90 (3H, t, *J* 7.0 Hz, H-15)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 147.02 (C), 144.13 (C), 134.93 (C), 129.56 (2 × CH), 127.60 (2 × CH), 113.35 (CH, C-7), 73.11 (C), 70.17 (C), 51.65 (CH_2, C-9), 38.49 (CH, C-2), 36.66 (CH_2), 31.03 (CH_2), 28.32 (CH_2), 28.16 (CH_2), 25.97 (CH_2), 25.47 (CH_2), 21.85 (CH_2), 21.61 (CH_3, C-21), 18.57 (CH_3, C-16), 18.18 (CH_2), 13.59 (CH_3, C-15)

LRMS: (ES+) m/z 410.3 ([M+Na]$^+$)

HRMS: (ES+) Calculated for $C_{23}H_{33}NNaO_2S$: 410.2124 Da, found: 410.2123 Da

(2*E*,3*Z*)-2,3-Bis(1-iodopentylidene)-1-tosylpyrrolidine (127a)



n-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) was added dropwise to a solution of Cp_2ZrCl_2 (293 mg, 1.0 mmol) in dry THF (5.0 mL) at −78 °C. A solution of ynamide **117a** (360 mg, 1.0 mmol) in dry THF (3.0 mL) was added dropwise at −78 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was cooled to 0 °C and iodine (508 mg, 2.0 mmol) and CuCl (99.0 mg, 1.0 mmol) added. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was poured into sat. aq. ammonium chloride solution (100 mL) and extracted with ether (3 × 50 mL). The organic extracts were combined, washed sequentially with

sat. aq. $Na_2S_2O_3$ solution (100 mL), and sat. aq. $NaHCO_3$ solution (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as an orange oil (758 mg). Purification by column chromatography (SiO_2, hexane/Et_2O 4:1) gave the title compound as an orange oil (573 mg, 91%).

IR: ν_{max} (neat)/cm^{-1} 2956 (w), 2928 (w), 2859 (w), 1597 (w), 1161 (s), 727 (s)

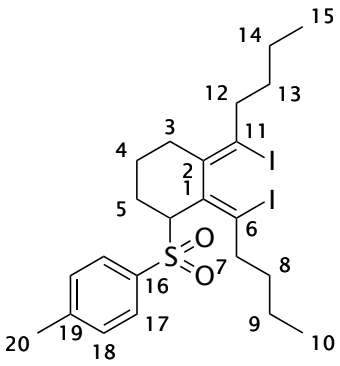
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.79 (2H, d, *J* 8.1 Hz, H-16), 7.29 (2H, d, *J* 8.1 Hz, H-17), 3.72–3.34 (2H, m, H-4), 3.05–2.89 (2H, m), 2.42 (3H, s, H-19), 2.30–2.05 (4H, m), 1.70–1.53 (2H, m), 1.51–1.34 (2H, m), 1.33–1.02 (4H, m), 0.97 (3H, t, *J* 7.3 Hz, H-9 or H-14), 0.83 (3H, t, *J* 7.3 Hz, H-9 or H-14)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 143.77 (C), 139.49 (C), 139.06 (C), 134.52 (C), 129.64 (2 × CH), 128.82 (2 × CH), 111.01 (C), 104.18 (C), 46.19 (CH_2), 43.05 (CH_2), 41.72 (CH_2), 32.08 (CH_2), 30.80 (CH_2), 27.11 (CH_2), 21.85 (CH_2), 21.57 (CH_2), 21.52 (CH_3, C-19), 14.04 (CH_3), 14.00 (CH_3)

LRMS: (ES+) m/z 636.2 ([M+Na]$^+$)

HRMS: (ES+) Calculated for $C_{21}H_{29}I_2NNaO_2S$: 635.9901 Da, found: 635.9899 Da

(2*E*,3*Z*)-2,3-Bis(1-iodopentylidene)-1-tosylpiperidine (127j)



n-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) was added dropwise to a solution of Cp_2ZrCl_2 (293 mg, 1.0 mmol) in dry THF (5.0 mL) at −78 °C. A solution of ynamide **117j** (374 mg, 1.0 mmol) in dry THF (3.0 mL) was added dropwise at −78 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was cooled to 0 °C and iodine (508 mg, 2.0 mmol) and CuCl (99.0 mg, 1.0 mmol) added. The reaction mixture was warmed to room temperature and stirred overnight. The reaction mixture was poured into sat. aq. ammonium chloride solution (100 mL) and extracted with ether (3 × 50 mL). The organic extracts were combined, washed sequentially with sat. aq. $Na_2S_2O_3$ solution (100 mL), and sat. aq. $NaHCO_3$ solution (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the

crude product as a brown oil (670 mg). Purification by column chromatography (SiO_2, hexane/Et_2O 4:1) gave the title compound as an orange oil (416 mg, 66%).

IR: ν_{max}(neat)/cm^{-1} 2955 (w), 2926 (w), 2870 (w), 1597 (w)

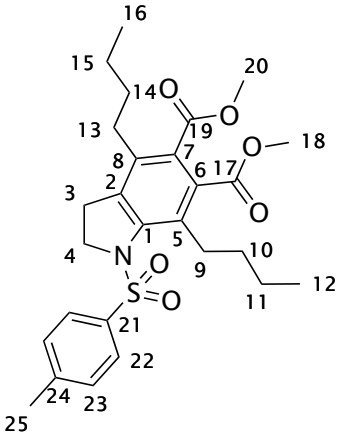
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.94 (2H, d, *J* 8.2 Hz, H-17), 7.28 (2H, d, *J* 8.2 Hz, H-18), 3.81 (1H, ddd, *J* 13.8, 3.6, 3.6 Hz, H-5a), 3.28 (1H, ddd, *J* 13.8, 11.7, 3.3 Hz, H-5b), 2.89–2.66 (2H, m), 2.58 (1H, dt, *J* 13.5, 4.0 Hz), 2.53–2.44 (2H, m), 2.43 (3H, s, H-20), 2.05 (1H, td, *J* 12.8, 4.8 Hz), 1.73–1.49 (3H, m), 1.48–1.32 (3H, m), 1.32–1.12 (4H, m), 0.96 (3H, t, *J* 7.1 Hz, H-10 or H-15), 0.89 (3H, t, *J* 7.0 Hz, H-10 or H-15)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 143.28 (C), 140.94 (C), 139.75 (C), 137.36 (C), 129.38 (2 × CH), 128.47 (2 × CH), 117.48 (C), 107.11 (C), 50.07 (CH_2, C-5), 41.15 (CH_2), 39.64 (CH_2), 31.62 (CH_2), 31.08 (CH_2), 30.47 (CH_2), 24.77 (CH_2), 22.10 (CH_2), 21.79 (CH_2), 21.53 (CH_3, C-20), 14.03 (CH_3), 14.00 (CH_3)

LRMS: (ES+) m/z 650.2 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{22}H_{31}I_2NNaO_2S$: 650.0057 Da, found: 650.0062 Da

Dimethyl-4,7-dibutyl-1-tosylindoline-5,6-dicarboxylate (128a)



n-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) was added dropwise to a solution of Cp_2ZrCl_2 (293 mg, 1.0 mmol) in dry THF (5.0 mL) at −78 °C. A solution of ynamide **117a** (360 mg, 1.0 mmol) in dry THF (3.0 mL) was added dropwise at −78 °C. The reaction mixture was warmed to room temperature and stirred for 1.5 h. The reaction mixture was cooled to 0 °C. CuCl (297 mg, 3.0 mmol) and DMAD (0.25 mL, 2.0 mmol) were added. The reaction mixture was warmed to room temperature and stirred for 6.5 h. Water (10.0 mL) was added and the reaction mixture stirred at room temperature for 16 h. The reaction mixture was poured into water (200 mL) and extracted with ether (3 × 50 mL). The organic extracts were combined, washed with brine (2 × 200 mL), dried ($MgSO_4$), filtered and the

solvent removed *in vacuo* to give the crude product as an orange oil (602 mg). Purification by column chromatography (SiO_2, hexane/Et_2O 4:1 → 1:1) gave the title compound as an orange oil (259 mg, 52%).

IR: ν_{max} (neat)/cm^{-1} 2955 (w), 2872 (w), 1731 (m), 1597 (w), 728 (s)

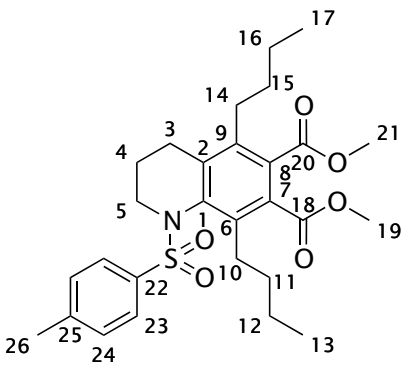
^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 7.32 (2H, d, *J* 8.3 Hz, H-22), 7.13 (2H, d, *J* 8.3 Hz, H-23), 3.92 (2H, t, *J* 7.3 Hz, H-4), 3.84 (3H, s, H-18 or H-20), 3.80 (3H, s, H-18 or H-20), 3.17 (2H, t, *J* 7.3 Hz, H-3), 2.36 (2H, t, *J* 7.5 Hz, H-9 or H-13), 2.34 (3H, s, H-25), 2.01 (2H, t, *J* 7.3 Hz, H-9 or H-13), 1.47–1.35 (2H, m), 1.32–1.18 (2H, m), 1.16–1.00 (4H, m), 0.84 (3H, t, *J* 7.3 Hz, H-12 or H-16), 0.78 (3H, t, *J* 6.5 Hz, H-12 or H-16)

^{13}C NMR: δ_C (101 MHz, $CDCl_3$) 168.54 (C, C-17 or C-19), 168.33 (C, C-17 or C-19), 144.15 (C), 143.41 (C), 139.46 (C), 135.19 (C), 134.01 (C), 133.90 (C), 133.16 (C), 130.95 (C), 129.44 (2 × CH), 127.63 (2 × CH), 52.28 (CH_2, C-4), 52.22 (CH_3, C-18 or C-20), 52.19 (CH_3, C-18 or C-20), 32.30 (CH_2), 31.83 (CH_2), 30.28 (CH_2), 29.38 (CH_2), 27.74 (CH_2), 22.58 (CH_2), 22.42 (CH_2), 21.33 (CH_3, C-25), 13.68 (CH_3, C-12,16)

LRMS: (ES+) m/z 524.3 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{27}H_{35}NNaO_6S$: 524.2077 Da, found: 524.2064 Da

Dimethyl-5,8-dibutyl-1-tosyl-1,2,3,4-tetrahydroquinoline-6,7-dicarboxylate (128j)



n-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) was added dropwise to a solution of Cp_2ZrCl_2 (293 mg, 1.0 mmol) in dry THF (5.0 mL) at −78 °C. A solution of ynamide **117j** (374 mg, 1.0 mmol) in dry THF (3.0 mL) was added dropwise at −78 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction mixture was cooled to 0 °C. CuCl (297 mg, 3.0 mmol) and DMAD (0.25 mL, 2.0 mmol) were added. The reaction mixture was warmed to room temperature and stirred for 6.5 h. Water

(10.0 mL) was added and the reaction mixture stirred at room temperature for 16 h. The reaction mixture was poured into water (200 mL) and extracted with ether (3 × 50 mL). The organic extracts were combined, washed with brine (2 × 200 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as an orange oil (633 mg). Purification by column chromatography (SiO_2, hexane/Et_2O 1:1) gave the title compound as an orange oil (316 mg, 61%).

IR: ν_{max} (neat)/cm^{-1} 2954 (w), 2872 (w), 1731 (m), 1160 (s)

^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.50 (2H, d, *J* 8.1 Hz, H-23), 7.23 (2H, d, *J* 8.1 Hz, H-24), 4.10 (1H, m), 3.87 (6H, s, H-19,21), 3.83 (1H, m), 3.44–3.26 (2H, m), 2.80 (1H, m), 2.62–2.36 (4H, m), 2.43 (3H, s, H-26), 2.07 (1H, m), 1.54–1.09 (8H, m, H-11,12,15,16), 0.99–0.81 (6H, m, H-13,17)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 169.17 (C, 18 or C-20), 168.67 (C, C-18 or C-20), 143.77 (C), 140.63 (C), 140.15 (C), 138.14 (C), 136.70 (C), 135.84 (C), 131.64 (C), 131.18 (C), 129.63 (2 × CH), 127.61 (2 × CH), 52.40 (CH_3, C-19 or C-21), 52.36 (CH_3, C-19 or C-21), 45.54 (CH_2, C-5), 33.19 (CH_2), 32.88 (CH_2), 29.76 (CH_2), 29.46 (CH_2), 23.92 (CH_2), 22.78 (CH_2), 22.63 (CH_2), 22.22 (CH_2), 21.54 (CH_3, C-26), 13.90 (CH_3), 13.88 (CH_3)

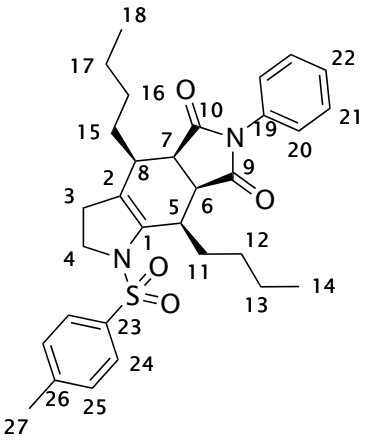
LRMS: (ES+) m/z 538.3 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{28}H_{37}NNaO_6S$: 538.2234 Da, found: 538.2243 Da

General procedure D: Diels-Alder reactions

The appropriate dienophile (1.1 eq.) was added to diene **123a,c** or **j** (1 eq.) in benzene (1.00 mL). The reaction mixture was heated at reflux for 16 h. The solvent was removed *in vacuo* to give the crude product, which was purified as described.

endo-4,8-Dibutyl-6-phenyl-1-tosyl-2,3,4,4a,7a,8-hexahydropyrrolo[3,4-f]indole-5,7(1*H*,6*H*)-dione (130a)



General procedure D with diene **123a** (287 mg, 0.79 mmol) and *N*-phenylmaleimide (151 mg, 0.87 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 1:1) gave the title compound as a white solid (320 mg, 76%).

IR: ν_{max}(neat)/cm^{-1} 2954(w), 2930 (w), 2861 (w), 1707 (m), 1597 (w)

m.p.: 69–71 °C

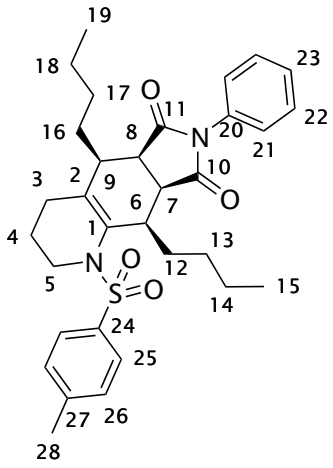
^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 7.68 (2H, d, *J* 7.9 Hz, H-24), 7.53–7.45 (2H, m), 7.41 (1H, m), 7.31 (2H, d, *J* 7.9 Hz), 7.29–7.22 (2H, m), 3.99–3.72 (3H, m), 3.38 (1H, dd, *J* 9.3, 9.3 Hz), 3.15 (1H, dd, *J* 9.3, 9.3 Hz), 2.69 (1H, m), 2.45 (3H, s, H-27), 2.21 (1H, m), 2.12–1.93 (2H, m), 1.86 (1H, m), 1.63 (1H, m), 1.48–1.17 (9H, m), 0.92–0.79 (6H, m, H-14,18)

^{13}C NMR: δ_C (101 MHz, $CDCl_3$) 176.45 (C, C-9 or C-10), 176.02 (C, C-9 or C-10), 143.97 (C), 141.20 (C), 134.54 (C), 131.78 (C), 129.71 (2 × CH), 129.28 (C), 129.22 (2 × CH), 128.69 (CH, C-22), 127.39 (2 × CH), 126.45 (2 × CH), 50.25 (CH_2, C-4), 44.43 (CH), 44.10 (CH), 34.90 (CH), 33.36 (CH_2) 32.55 (CH), 32.08 (CH_2), 31.33 (CH_2), 30.97 (CH_2), 30.05 (CH_2), 22.93 (CH_2), 22.70 (CH_2), 21.59 (CH_3, C-27), 13.91 (CH_3, C-14 or C-18), 13.85 (CH_3, C-14 or C-18)

LRMS: (ES+) 557.4 ([M+Na]$^+$)

HRMS: (ES+) Calculated for $C_{31}H_{38}N_2NaO_4S$: 557.2444 Da, found: 557.2439 Da

endo-5,9-Dibutyl-7-phenyl-1-tosyl-3,4,5,5a,8a,9-hexahydro-1*H*-cyclopenta[*g*]quinoline-6,8(2*H*,7*H*)-dione (130b)



General procedure D with diene **123j** (247 mg, 0.66 mmol) and *N*-phenylmaleimide (125 mg, 0.72 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 1:1) gave the title compound as an orange oil (319 mg, 88%).

IR: ν_{max} (neat)/cm^{-1} 2956 (w), 2872 (w), 1707 (s), 1598 (w), 906 (s), 724 (s)

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 7.73 (2H, d, *J* 8.2 Hz, H-25), 7.52–7.33 (4H, m), 7.33–7.22 (3H, m), 3.56 (1H, dd, *J* 9.5, 7.6 Hz), 3.38 (2H, dd, *J* 10.0, 7.6 Hz), 2.59 (1H, m), 2.43 (3H, s, H-28), 2.14 (1H, m), 2.02–1.75 (5H, m), 1.67 (1H, m), 1.58–1.41 (3H, m), 1.41–1.08 (8H, m), 0.90 (3H, t, *J* 7.0 Hz, H-15 or H-19), 0.82 (3H, t, *J* 7.1 Hz, H-15 or H-19)

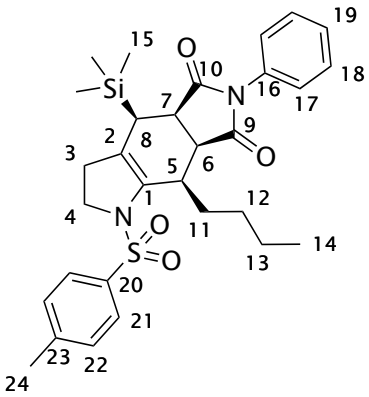
^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 177.13 (C, C-10 or C-11), 176.72 (C, C-10 or C-11), 143.62 (C), 137.70 (C), 134.18 (C), 131.95 (C), 129.59 (2 × CH), 129.09 (2 × CH), 128.47 (C), 127.28 (2 × CH), 126.42 (2 × CH), 126.04 (CH. C-23), 46.48 (CH_2, C-5), 43.73 (CH), 43.66 (CH), 39.76 (CH), 32.20 (CH), 30.52 (CH_2), 22.91 (CH_2), 22.87 (CH_2), 21.73 (CH_2), 21.51 (CH_3, C-28), 13.94 (CH_3, C-15 or C-19), 13.92 (CH_3, C-15 or C-19)

Note: four expected methylene carbons were not observed in the ^{13}C NMR spectrum.

LRMS: (ES+) m/z 571.4 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{32}H_{40}N_2NaO_4S$: 571.2601 Da, found: 571.2602 Da

endo-8-Butyl-6-phenyl-1-tosyl-4-(trimethylsilyl)-2,3,4,4a,7a,8-hexahydropyrrolo[3,4-f]indole-5,7(1*H*,6*H*)-dione (130c)



General procedure D with diene **123c** (100 mg, 0.27 mmol) and *N*-phenylmaleimide (69.2 mg, 0.29 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 9:1) gave the title compound as a white solid (117 mg, 79%).

IR: ν_{max}(neat)/cm^{-1} 2939 (w), 1707 (s), 1596 (w), 582 (s)

m.p.: 130–132 °C

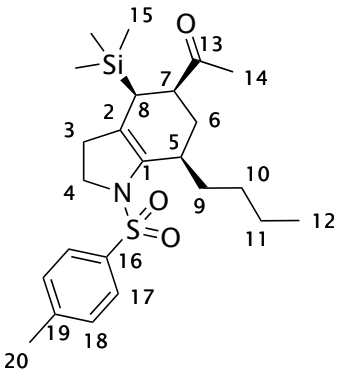
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.68 (2H, d, *J* 8.1 Hz, H-21), 7.54–7.23 (7H, m), 3.98–3.66 (3H, m), 3.44 (1H, dd, *J* 9.6, 7.5 Hz), 3.26 (1H, dd, *J* 9.3, 7.5 Hz), 2.43 (3H, s, H-24), 2.22–2.03 (2H, m), 1.99–1.64 (2H, m), 1.61–1.15 (5H, m), 0.87 (3H, t, *J* 7.2 Hz, H-14), 0.14 (9H, s, H-15)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 177.64 (C, C-9 or C-10), 176.23 (C, C-9 or C-10), 143.82 (C), 137.22 (C), 134.55 (C), 131.69 (C), 129.64 (2 × CH), 129.13 (2 × CH), 128.45 (CH, C-19), 127.82 (C), 127.37 (2 × CH), 126.13 (2 × CH), 49.91 (CH_2, C-4), 45.24 (CH), 41.69 (CH), 33.46 (CH), 32.01 (CH_2), 31.92 (CH_2), 29.68 (CH_2), 25.71 (CH), 22.90 (CH_2), 21.53 (CH_3, C-24), 13.91 (CH_3, C-14), 0.88 (CH_3, C-15)

LRMS: (ES+) m/z 573.4 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{30}H_{38}N_2NaO_4SSi$: 573.2214 Da, found: 573.2214 Da

endo-1-(7-Butyl-1-tosyl-4-(trimethylsilyl)-2,3,4,5,6,7-hexahydro-1*H*-indol-5-yl)ethanone (130d)



General procedure D with diene **123c** (100 mg, 0.27 mmol) and methyl vinyl ketone (0.04 mL, 0.29 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 9:1) gave the title compound as a colourless oil (87.0 mg, 72%).

IR: ν_{max}(neat)/cm^{-1} 2949 (w), 2867 (w), 2817 (w), 1704 (m), 1598 (w), 1123 (s), 836 (s), 547 (s)

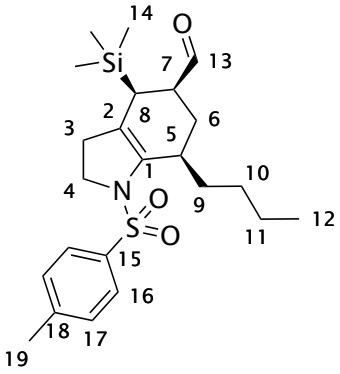
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.66 (2H, d, *J* 8.3 Hz, H-17), 7.29 (2H, d, *J* 8.3 Hz, H-18), 3.87 (1H, ddd, *J* 12.4, 9.1, 3.2 Hz, H-4a), 3.72–3.54 (2H, m, H-4b,5), 2.53 (1H, ddd, *J* 11.6, 4.0, 3.6 Hz, H-7), 2.43 (3H, s, H-20), 2.26 (3H, s, H-14), 1.97 (1H, m), 1.86–1.59 (3H, m), 1.49–1.14 (7H, m), 0.84 (3H, t, *J* 7.3 Hz, H-12), −0.03 (9H, s, H-15)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 210.24 (C, C-13), 143.59 (C), 137.96 (C), 134.91 (C), 129.54 (2 × CH), 127.21 (2 × CH), 126.81 (C), 52.74 (CH, C-7), 50.00 (CH_2, C-4), 34.77 (CH), 31.62 (CH_2), 31.09 (CH_2), 30.14 (CH_2), 28.99 (CH_3, C-14), 24.08 (CH), 23.16 (CH_2), 21.51 (CH_3, C-20), 20.29 (CH_2), 13.85 (CH_3, C-12), −2.47 (CH_3, C-15)

LRMS: (ES+) m/z 470.3 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{24}H_{37}NNaO_3SSi$: 470.2156 Da, found: 470.2156 Da

endo-7-Butyl-1-tosyl-4-(trimethylsilyl)-2,3,4,5,6,7-hexahydro-1*H*-indole-5-carbaldehyde (130e)



General procedure D with diene **123c** (100 mg, 0.27 mmol) and acrolein (0.03 mL, 0.29 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 9:1) gave the title compound as a yellow oil (93.7 mg, 80%).

IR: ν_{max}(neat)/cm^{-1} 2954 (w), 2858 (w), 1719 (m), 1597 (w), 1162 (s), 837 (s), 547 (s)

^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 9.92 (1H, s, H-13), 7.66 (2H, d, *J* 8.4 Hz, H-16), 7.31 (2H, d, *J* 8.4 Hz, H-17), 3.85 (1H, ddd, *J* 12.5, 9.2, 3.6 Hz, H-4a), 3.78–3.61 (2H, m, H-4b,5), 2.50 (1H, ddd, *J* 12.5, 3.6, 3.6 Hz, H-7), 2.45 (3H, s, H-19), 2.09–1.71 (3H, m), 1.66–1.17 (8H, m), 0.88 (3H, t, *J* 7.0 Hz, H-12), 0.01 (9H, s, H-14)

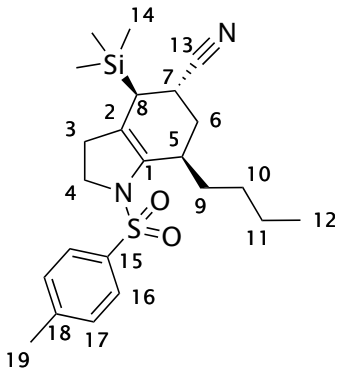
^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 203.59 (C, C-13), 143.61 (C), 137.79 (C), 134.66 (C), 129.59 (2 × CH), 127.25 (2 × CH), 126.83 (C), 52.71 (CH, C-7), 49.83 (CH_2, C-4), 33.55 (CH), 31.92 (CH_2), 31.13 (CH_2), 30.52 (CH_2), 23.96 (CH), 23.12 (CH_2), 21.53 (CH_3, C-19), 18.93 (CH_2), 13.85 (CH_3, C-12), −2.45 (CH_3, C-14)

LRMS: (ES+) m/z 456.3 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{23}H_{35}NNaO_3SSi$: 456.1999 Da, found: 456.1992 Da

7-Butyl-1-tosyl-4-(trimethylsilyl)-2,3,4,5,6,7-hexahydro-1*H*-indole-5-carbonitrile (130f)

General procedure D with diene **123c** (100 mg, 0.27 mmol) and acrylonitrile (0.03 mL, 0.29 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 9:1) gave both the *exo* and *endo* isomers of the title compound:



The *exo* isomer (5-*exo*) was a colourless oil (16.2 mg, 13%).

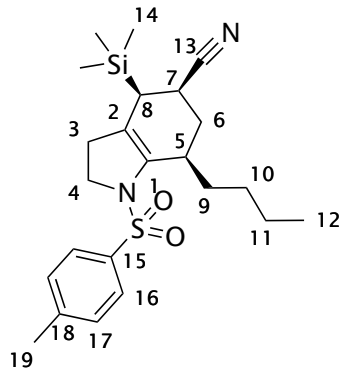
IR: ν_{max} (neat)/cm^{-1} 2954 (w), 2858 (w), 1598 (w)

^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.73 (2H, d, *J* 8.3 Hz, H-16), 7.32 (2H, d, *J* 8.3 Hz, H-17), 3.72–3.60 (2H, m, H-4), 3.37 (1H, m), 3.02 (1H, m), 2.42 (3H, s, H-19), 2.16–1.80 (4H, m), 1.77–1.60 (2H, m), 1.50–1.13 (5H, m), 0.93 (3H, t, *J* 7.0 Hz, H-12), 0.02 (9H, s, H-14)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 143.76 (C), 135.63 (C), 133.74 (C), 129.83 (2 × CH), 127.59 (2 × CH), 124.78 (C), 121.94 (C), 49.02 (CH_2, C-4), 36.98 (CH), 32.18 (CH_2), 31.36 (CH_2), 29.24 (CH_2), 27.98 (CH), 22.71 (CH_2), 22.58 (CH_2), 22.00 (CH), 21.56 (CH_3, C-19), 14.00 (CH_3, C-12), −2.30 (CH_3, C-14)

LRMS: (ES+) m/z 453.3 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{23}H_{34}NNaO_2SSi$: 453.2002 Da, found: 453.2006 Da



The *endo* isomer (5-*endo*) was a colourless oil (40.9 mg, 36%).

IR: ν_{max} (neat)/cm^{-1} 2954 (w), 2860 (w), 1597 (w), 1161 (s), 546 (s)

^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.60 (2H, d, *J* 8.2 Hz, H-16), 7.29 (2H, d, *J* 8.2 Hz, H-17), 3.86 (1H, ddd, *J* 12.5, 9.2, 3.3 Hz, H-4a), 3.65 (1H, m, H-4b), 3.42 (1H, m), 2.69 (1H, ddd, *J* 12.5, 4.3, 3.4 Hz, H-7), 2.44 (3H, s, H-19), 2.08–1.91 (2H, m), 1.89–1.16 (9H, m), 0.92 (3H, t, *J* 7.3 Hz, H-12), 0.00 (9H, s, H-14)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 143.82 (C), 136.30 (C), 134.62 (C), 129.69 (2 × CH), 127.20 (2 × CH), 126.02 (C), 121.41 (C), 49.69 (CH_2, C-4), 34.15 (CH), 32.26 (CH_2),

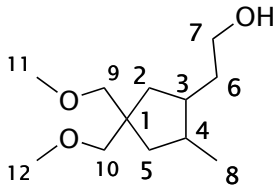
31.17 (CH_2), 31.06 (CH), 29.89 (CH_2), 24.52 (CH), 24.25 (CH_2), 23.10 (CH_2), 21.56 (CH_3, C-19), 13.89 (CH_3, C-12), −2.48 (CH_3, C-14)

LRMS: (ES+) m/z 453.3 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{23}H_{34}NNaO_2SSi$: 453.2002 Da, found: 453.2007 Da

7.5 Experimental for chapter 5

2-(4,4-Bis(methoxymethyl)-2-methylcyclopentyl)ethanol (167)



n-BuLi (0.80 mL of a 2.5 M solution in hexanes, 1.0 mmol) was added dropwise to a solution of Cp_2ZrCl_2 (293 mg, 1.0 mmol) in dry THF (5.0 mL) at −78 °C. Diene **166** (170 mg, 0.92 mmol) in dry THF (3.0 mL) was added dropwise to the reaction mixture at −78 °C. After stirring at −78 °C for 20 mins the reaction mixture was warmed to room temperature. After stirring at room temperature for 2 h the reaction mixture was cooled to −78 °C. Chloromethyl(dimethyl)methoxysilane (0.15 mL, 1.1 mmol) was added dropwise. LiTMP [prepared by adding *n*-BuLi (0.42 mL of a 2.5 M solution in hexanes, 1.1 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.18 mL, 1.1 mmol) in THF (3.0 mL) at 0 °C and stirring at 0 °C for 30 mins] was added dropwise at −78 °C. After stirring at −78 °C for 45 mins the reaction mixture was stirred at room temperature for 30 mins. MeOH (5.0 mL) and sat. aq. $NaHCO_3$ solution (5.0 mL) were added and the reaction mixture stirred at room temperature for 16 h. The reaction mixture was poured into water (100 mL) and extracted with ether (3 × 50 mL). The organic extracts were combined, washed sequentially with water (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the intermediate silane as a yellow oil (313 mg). KF (334 mg, 5.7 mmol), $KHCO_3$ (360 mg, 3.6 mmol) and H_2O_2 (2 ml of a 30% solution in water, 20 mmol) were added to the intermediate silane (313 mg, 0.92 mmol) in MeOH (2.0 mL) and water (2.0 mL). The reaction mixture was stirred at room temperature for 18 h. 5% Pd/C (200 mg, 94.0 mmol) was added to the reaction mixture. The reaction mixture was filtered through celite and extracted with ether (2 × 20 mL). The organic extracts were combined, washed with water (3 × 100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as a yellow oil (136 mg). Purification by column chromatography (SiO_2, hexane/Et_2O 1:1) gave the title compound as a colourless oil (70.4 mg, 33% over 2 steps).

IR: ν_{max} (neat)/cm^{-1} 3374 (br), 2948 (sh), 2923 (w), 2824 (sh), 2868 (m), 1104 (s)

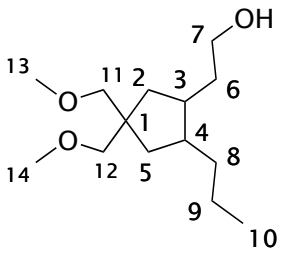
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 3.80–3.49 (2H, m, H-7), 3.32 (6H, s, H-11,12), 3.23–3.12 (4H, m, H-9,10), 2.01–1.59 (5H, m), 1.57–1.14 (3H, m), 0.94 (3H, d, *J* 6.2 Hz, H-8)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 77.88 (CH_2), 77.81 (CH_2), 62.09 (CH_2, C-7), 59.18 (CH_3, C-11,12), 45.34 (C, C-1), 43.22 (CH), 41.56 (CH_2), 39.99 (CH), 39.33 (CH_2), 36.90 (CH_2), 17.97 (CH_3, C-8)

LRMS: (CI) m/z 217.1 ($[M+H]^+$, 100%), 185.1 ($[M-CH_3O]^+$, 10%), 153.0 ($[M-C_2H_70_2]^+$, 94%), 151.9 ($[M-C_2H_8O_2]^+$, 83%), 139.0 ($[M- C_3H_9O_2]^+$, 57%), 125.0 ($[M-C_4H_{11}O_2]^+$, 78%), 120.9 ($[M-C_7H_{11}]^+$, 80%), 109.0 ($[M-C_4H_{11}O_3]^+$, 48%)

HRMS: (ES+) Calculated for $C_{12}H_{24}NaO_3$: 239.1618 Da, found: 239.1615 Da

2-(4,4-Bis(methoxymethyl)-2-propylcyclopentyl)ethanol (170)



n-BuLi (0.80 mL of a 2.5 M solution in hexanes, 1.0 mmol) was added dropwise to a solution of Cp_2ZrCl_2 (293 mg, 1.0 mmol) in dry THF (5.0 mL) at −78 °C. Diene **168** (190 mg, 0.90 mmol) in dry THF (3.0 mL) was added dropwise to the reaction mixture at −78 °C. After stirring at −78 °C for 20 mins the reaction mixture was warmed to room temperature. After stirring at room temperature for 3 h the reaction mixture was cooled to −78 °C. Chloromethyl(dimethyl)phenylsilane (0.18 mL, 1 mmol) was added dropwise. LiTMP [prepared by adding *n*-BuLi (0.40 mL of a 2.5 M solution in hexanes, 1.0 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.17 mL, 1.0 mmol) in THF (1.0 mL) at 0 °C and stirring at 0 °C for 30 mins] was added dropwise at −78 °C. After stirring at −78 °C for 45 mins the reaction mixture was stirred at room temperature for 30 mins. MeOH (5.0 mL) and sat. aq. $NaHCO_3$ solution (5.0 mL) were added and the reaction mixture stirred at room temperature for 16 h. The reaction mixture was poured into water (100 mL) and extracted with ether (3 × 50 mL). The organic extracts were combined, washed sequentially with water (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the intermediate silane as a yellow oil (381 mg). NMP (2.0 mL) was added to KH (642 mg of a 25–35% suspension in

mineral oil, washed with hexane (3 × 5 mL), 4.0 mmol). The reaction mixture was cooled to 0 °C. *t*-Butylhydroperoxide (1.10 mL, 4.0 mmol) was added and the reaction mixture warmed to room temperature. The intermediate silane (240 mg, 0.66 mmol) in NMP (3.0 mL) was added and the reaction mixture stirred at room temperature for 10 mins. TBAF (1.50 mL of a 1.0 M solution in THF, 1.5 mmol) was added and the reaction mixture heated to 70 °C for 15 h. $Na_2S_2O_3$ (150 mg) and water (5 mL) were added and the reaction mixture stirred for 5 mins. The reaction mixture was extracted with ether (3 × 10 mL). The organic extracts were combined, washed sequentially with water (2 × 25 mL), 2 M aq. NaOH solution (25 mL) and brine (25 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as a yellow oil (273 mg). Purification by column chromatography (SiO_2, hexane/ether 1:2) gave the title compound as a colourless oil (72.7 mg, 45% over 2 steps).

IR: ν_{max}(neat)/cm^{-1} 3387 (br), 2953 (sh), 2922 (w), 2869 (m), 2825 (sh), 1106 (s)

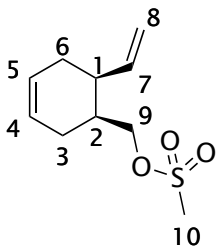
^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 3.77–3.50 (2H, m, H-7), 3.33 (3H, s, H-13 or H-14), 3.33 (3H, s, H-13 or H-14), 3.24–3.09 (4H, m, H-11,12), 1.96–1.60 (4H, m), 1.57–1.15 (8H, m), 0.91 (3H, t, *J* 7.2 Hz, H-10)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 77.83 (CH_2), 77.78 (CH_2), 62.04 (CH_2, C-7), 59.20 (CH_3, C-13,14), 45.45 (C, C-1), 45.10 (CH), 41.79 (CH), 39.21 (CH_2), 39.07 (CH_2), 37.28 (CH_2), 36.31 (CH_2), 21.35 (CH_2), 14.42 (CH_3, C-10)

LRMS: (CI) m/z 245.1 ([M+H]$^+$, 100%), 227.1 ([M−OH]$^+$, 2%), 213.1 ([M−CH_3O]$^+$, 15%), 199.2 ([M−C_2H_5O]$^+$, 1%), 181.1 ([M−$C_2H_7O_2$]$^+$, 99%), 163.1 ([M−$C_2H_9O_3$]$^+$, 93%), 153.1 ([M−$C_4H_{11}O_2$]$^+$, 14%), 135.0 ([M−$C_4H_{13}O_3$]$^+$, 65%)

HRMS: (ES+) Calculated for $C_{14}H_{28}NaO_3$: 267.1931 Da, found: 267.1930 Da

((1*S*,6*S*)-6-Vinylcyclohex-3-enyl)methyl methanesulfonate (147)



Et_3N (4.3 mL, 31.1 mmol), DMAP (257 mg, 2.1 mmol) and methane sulfonyl chloride (1.90 mL, 25.0 mmol) were added dropwise sequentially to alcohol **146** (2.87 g, 20.8 mmol) in dry THF (100 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, poured into a sat. aq. NH_4Cl solution (200 mL) and extracted with ether (3 × 50 mL). The organic extracts were combined, washed sequentially with 2 M aq. HCl solution (150 mL), sat. aq. $NaHCO_3$ solution (150 mL) and brine (150 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as a yellow oil (4.14 g). Purification by column chromatography (SiO_2, hexane/Et_2O 2:1) gave the title compound as a colourless oil (3.95 g, 88%).

IR: ν_{max} (neat)/cm^{-1} 3026 (w), 2904 (w), 2839 (w), 1170 (s), 941 (s)

Optical rotation: $[\alpha]_D^{28} = -7°$ (c = 0.5, $CHCl_3$)

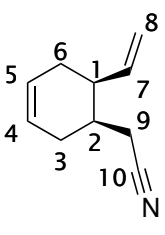
^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 5.83 (1H, ddd, *J* 17.8, 9.7, 8.3 Hz), 5.69 (2H, br. s), 5.14 (1H, m), 5.10 (1H, m), 4.17–4.03 (2H, m, H-9), 3.00 (3H, s, H-10), 2.61 (1H, sxt, *J* 4.4 Hz, H-1), 2.42–2.08 (3H, m), 2.05–1.81 (2H, m)

^{13}C NMR: δ_C (101 MHz, $CDCl_3$) 137.65 (CH, C-7), 125.50 (CH), 124.65 (CH), 116.50 (CH_2, C-8), 71.52 (CH_2, C-9), 37.60 (CH), 37.22 (CH_3, C-10), 36.15 (CH), 29.60 (CH_2), 25.13 (CH_2)

LRMS: (CI) m/z 234.1 ([M+NH_4]$^+$, 100%), 121.1 ([M−CH_3O_3S]$^+$, 14%), 108.1 ([M−C_8H_{11}]$^+$, 1%)

HRMS: (ES+) Calculated for $C_{10}H_{16}NaO_3S$: 239.0712 Da, found: 239.0709 Da

2-((1*R*,6*S*)-6-Vinylcyclohex-3-enyl)acetonitrile (148)



A solution of mesylate **147** (3.91 g, 18.1 mmol) and 18-crown-6 (2.59 g, 9.8 mmol) in dry MeCN (65 mL) was added to KCN (2.36 g, 36.2 mmol) and NaI (195 mg, 1.3 mmol). The reaction mixture was heated to reflux for 60 h. After cooling to room temperature the reaction mixture was poured into water (200 mL) and extracted with ether (3 × 50 mL). The organic extracts were combined,

washed with brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as an orange oil (2.80 g). Purification by column chromatography (SiO_2, hexane/Et_2O 5:1) gave the title compound as a colourless oil (2.25 g, 84%).

IR: ν_{max} (neat)/cm^{-1} 3028 (w), 2907 (w), 2840 (w), 729 (s)

Optical rotation: $[\alpha]_D^{28} = -17°$ (c = 1.0, $CHCl_3$)

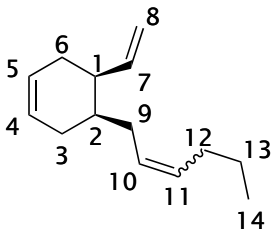
^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 5.76 (1H, ddd, *J* 17.7, 9.8, 8.2 Hz), 5.70–5.61 (2H, m), 5.15 (1H, m), 5.12 (1H, m), 2.55 (1H, m), 2.36–2.13 (5H, m), 2.02–1.87 (2H, m)

^{13}C NMR: δ_C (101 MHz, $CDCl_3$) 137.27 (CH, C-7), 125.22 (CH), 124.48 (CH), 119.22 (C, C-10), 116.84 (CH_2, C-8), 39.55 (CH), 33.90 (CH), 29.02 (CH_2), 28.22 (CH_2), 19.73 (CH_2, C-9)

LRMS: (EI) m/z 147.0, ($[M]^{+\bullet}$, 35%), 133.0 ($[M-N]^+$, 7%), 121.0 ($[M-CN]^+$, 4%), 119.9 ($[M-C_2H_3]^+$, 20%), 107.0 ($[M-C_2H_2N]^+$, 29%), 67.0 ($[M-C_6H_8]^+$, 44%), 53.5 ($[M-C_7H_{10}]^+$, 100%), 40.1 ($[M-C_8H_{11}]^+$, 21%)

HRMS: (EI) Calculated for $C_{10}H_{13}N$: 147.10480 Da, found: 147.10488 Da

(4*S*,5*S*)-4-(Hept-2-enyl)-5-vinylcyclohex-1-ene (140)



DIBAL-H (31 mL of a 1.0 m solution in toluene, 31.0 mmol) was added dropwise to a stirred solution of nitrile **148** (2.17 g, 14.7 mmol) in dry THF (45 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 mins followed by stirring at room temperature for 2 h. Saturated aq. $NaHCO_3$ solution (100 mL) was added and the reaction mixture stirred at room temperature for 2 h. The reaction mixture was extracted with ether (3 × 50 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the intermediate aldehyde **149** as a colourless oil (2.13 g). *n*-BuLi (8.4 mL of a 2.5 M solution in hexanes, 21.0 mmol) was added dropwise to butyltriphenylphosphonium bromide (8.39 g, 21.0 mmol) in dry THF (60 mL) at 0 °C and left stirring at room temperature for 45 mins. The reaction mixture was cooled to 0 °C. Intermediate

aldehyde **149** (2.11 g, 14.0 mmol) was added dropwise to the reaction mixture at 0 °C and the reaction mixture stirred at room temperature for 45 mins. The reaction mixture was poured into a sat. aq. NH_4Cl solution (300 mL) and extracted with ether (3 × 50 mL). The organic extracts were combined, washed sequentially with water (200 mL) and brine (200 mL), dried ($MgSO_4$), filtered, concentrated *in vacuo*, filtered through a plug of silica and the solvent removed *in vacuo* to give the crude product as a pale yellow oil (4.67 g). Purification by column chromatography (SiO_2, pentane) gave the title compound as a colourless oil (1.64 g, 59% over 2 steps).

IR: ν_{max} (neat)/cm^{-1} 3022 (w), 2958 (w), 2908 (w), 2837 (w)

Optical rotation: $[\alpha]_D^{28}$ = +4° (c = 0.5, $CHCl_3$)

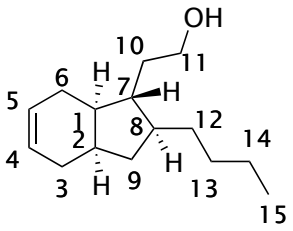
^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 5.87 (1H, m), 5.65 (2H, br. s), 5.48–5.30 (2H, m), 5.11–4.97 (2H, m), 2.45 (1H, m), 2.25 (1H, m), 2.14–1.92 (5H, m), 1.91–1.68 (2H, m), 1.46–1.20 (3H, m), 0.91 (3H, t, *J* 7.3 Hz, H-14)

^{13}C NMR: δ_C (101 MHz, $CDCl_3$) major isomer: 139.62 (CH, C-7), 130.71 (CH), 128.61 (CH), 126.18 (CH), 125.35 (CH), 114.83 (CH_2, C-8), 40.36 (CH), 37.20 (CH), 30.07 (CH_2), 29.44 (CH_2), 29.33 (CH_2), 28.68 (CH_2), 22.88 (CH_2), 13.81 (CH_3, C-14); minor isomer: 139.44 (CH, C-7), 131.59 (CH), 129.01 (CH), 126.27 (CH), 125.31 (CH), 114.85 (CH_2, C-8), 40.14 (CH), 36.87 (CH), 35.13 (CH_2), 34.76 (CH_2), 30.25 (CH_2), 28.57 (CH_2), 22.75 (CH_2), 13.65 (CH_3, C-14)

LRMS: (EI) m/z 190.0 ($[M]^{+\bullet}$, 7%), 175.0 ($[M-CH_3]^+$, 2%), 161.0 ($[M-C_2H_5]^+$, 9%), 147.0 ($[M-C_3H_7]^+$, 17%), 121.0 ($[M-C_5H_9]^+$, 6%), 106.9 ($[M-C_8H_{11}]^+$, 28%), 78.9 ($[M-C_8H_{14}]^+$, 100%), 43.0 ($[M-C_{11}H_{15}]^+$, 8%)

HRMS: (EI) Calculated for $C_{14}H_{22}$: 190.17215 Da, found: 190.17245 Da

2-((1*R*,2*S*,3a*R*,7a*R*)-2-Butyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-yl)ethanol (171a)



n-BuLi (6.8 mL of a 2.5 M solution in hexanes, 17.0 mmol) was added dropwise to a solution of Cp_2ZrCl_2 (2.49 g, 8.5 mmol) in dry THF (40 mL) at −78 °C. Triene **140** (1.62 g, 8.5 mmol) in dry THF (25 mL) was added dropwise to the reaction mixture at −78 °C. After stirring at −78 °C for 20 mins the reaction mixture was warmed to room temperature. After stirring at room temperature for 2 h the reaction mixture was heated to 65 °C for 30 mins. The reaction mixture was cooled to −78 °C. Chloromethyl(dimethyl)phenylsilane (1.50 mL, 8.5 mmol) was added dropwise. LiTMP [prepared by adding *n*-BuLi (3.4 mL of a 2.5 M solution in hexanes, 8.5 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (1.40 mL, 8.5 mmol) in THF (25 mL) at 0 °C and stirring at 0 °C for 30 mins] was added dropwise at −78 °C. After stirring at −78 °C for 1 h the reaction mixture was stirred at room temperature for 2 h. MeOH (40 mL) and sat. aq. $NaHCO_3$ solution (40 mL) were added and the reaction mixture stirred at room temperature for 16 h. The reaction mixture was poured into water (300 mL) and extracted with ether (3 × 50 mL). The organic extracts were combined, washed sequentially with water (300 mL) and brine (300 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the intermediate silane as a yellow oil (3.08 g). NMP (26 mL) was added to KH (8.18 g of a 25–35% suspension in mineral oil, washed with hexane (3 × 20 mL), 8.5 mmol). The reaction mixture was cooled to 0 °C. *t*-Butylhydroperoxide (9.3 mL, 51.0 mmol) was added and the reaction mixture warmed to room temperature. The intermediate silane (2.72 g, 7.5 mmol) in NMP (50 mL) was added and the reaction mixture stirred at room temperature for 10 mins. TBAF (26 mL of a 1.0 M solution in THF, 26.0 mmol) was added and the reaction mixture heated to 70 °C for 15 h. $Na_2S_2O_3$ (17.0 g) and water (50 mL) were added and the reaction mixture stirred for 5 mins. The reaction mixture was extracted with ether (3 × 50 mL). The organic extracts were combined, washed sequentially with water (2 × 100 mL), 2 M aq. NaOH solution (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as a colourless

oil (7.96 g). Purification by column chromatography (SiO_2, DCM) gave a 2.7:1 mixture of diastereoisomers of alcohol **171** as a colourless oil (1.42 g, 75%). Purification by HPLC (hexane/EA 10:1) allowed isolation of the pure required diastereoisomer.

IR: ν_{max}(neat)/cm^{-1} 3323 (br), 3020 (w), 2955 (sh), 2920 (m), 2875 (sh), 2858 (sh)

Optical rotation: $[\alpha]_D^{28}$ = +56° (c = 0.5, $CHCl_3$)

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 5.72–5.62 (2H, m, H-4,5), 3.72 (2H, t, *J* 7.2 Hz, H-11), 2.35–2.15 (2H, m), 1.89–1.01 (16H, m), 0.90 (3H, t, *J* 6.9 Hz, H-15)

^{13}C NMR: δ_C (101 MHz, $CDCl_3$) 127.31 (CH), 126.93 (CH), 62.02 (CH_2, C-11), 48.89 (CH), 48.16 (CH), 43.67 (CH), 40.15 (CH), 37.99 (CH_2), 37.10 (CH_2), 37.04 (CH_2), 32.32 (CH_2), 31.72 (CH_2), 30.80 (CH_2), 22.93 (CH_2), 14.15 (CH_3, C-15)

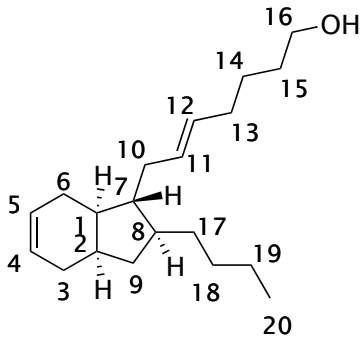
LRMS: (CI) m/z 240.2 ($[M+NH_4]^+$, 29%), 223.2 ($[M+H]^+$, 29%), 222.2 ($[M]^{+\bullet}$, 37%), 221.1 ($[M-H]^+$, 100%), 207.1 ($[M-CH_3]^+$, 4%), 205.2 ($[M-OH]^+$, 3%), 193.1 ($[M-C_2H_5]^+$, 4%), 191.1 ($[M-CH_3O]^+$, 49%)

HRMS: (ES+) Calculated for $C_{15}H_{26}NaO$: 245.1876 Da, found: 245.1877 Da

Purification of 2-((1*R*,2*S*,3a*R*,7a*R*)-2-butyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-yl)ethanol (171a) by iodoetherification of other diastereoisomers.

Alcohol **171** (1.36 g, 6.1 mmol) and iodine (609 mg, 2.4 mmol) were refluxed in benzene (12 mL) for 5 h. The reaction mixture was poured into a saturated solution of $Na_2S_2O_3$ (300 mL) and extracted with ether (3 × 50 mL). The organic extracts were combined, dried ($MgSO_4$), filtered and the solvent removed in vacuo to give the crude product as a black liquid (1.81 g). Purification by column chromatography (SiO_2, DCM) gave the title compound as a colourless liquid and single diastereoisomer (533 mg, 39% recovery).

(*E*)-7-((1*R*,2*S*,3a*R*,7a*R*)-2-Butyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-yl)hept-5-en-1-ol (175)



DMSO (0.36 mL, 5.1 mmol) in dry DCM (0.60 mL) was added dropwise to oxalyl chloride (0.21 mL, 2.5 mmol) in dry DCM (5.3 mL) at −60 °C. The reaction mixture was stirred at −60 °C for 2 mins. Alcohol **171a** (512 mg, 2.3 mmol) in dry DCM (2.3 mL) was added dropwise to the reaction mixture at −60 °C. The reaction mixture was stirred at −60 °C for 15 mins. Et_3N (1.60 mL, 11.5 mmol) was added dropwise to the reaction mixture at −60 °C. The reaction mixture was stirred at −60 °C for 15 mins and then left stirring at room temperature for 1 h. The reaction mixture was poured into water (25 mL). The aqueous phase was extracted with DCM (3 × 30 mL). The organic extracts were combined, washed sequentially with brine (50 mL), 1% aq. HCl solution (50 mL) and 5% aq. Na_2CO_3 solution (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give intermediate aldehyde **173** as an orange oil (501 mg). Dry DMF (0.48 mL, 6.2 mmol) was added dropwise to $CrCl_2$ (762 mg, 6.2 mmol) in THF (15 mL) at room temperature. After stirring at room temperature for 45 mins a solution of intermediate aldehyde **173** (171 mg, 0.77 mmol) and diiodide **172** (727 mg, 1.6 mmol) in THF (2.5 mL) was added to the reaction mixture. Stirring was continued at room temperature for 3 h. The reaction mixture was diluted with pentane (15.0 mL) and poured into water (50 mL). The aqueous phase was further extracted with pentane (3 × 20 mL). The organic extracts were combined, washed with brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude intermediate silane **174** as a brown oil (976 mg). Purification by column chromatography (SiO_2, hexane→hexane/Et_2O 19:1) removed the major impurities to give intermediate silane **174** as a colourless oil (583 mg). To a solution of intermediate silane **174** (519 mg, 0.69 mmol) in THF (3.0 mL) TBAF (4.8 mL of a 1.0 M solution in THF, 4.8 mmol) was added dropwise. The reaction mixture was left stirring at room temperature for a further 3 h. The reaction mixture was poured into water (30 mL) and extracted with ether (3 × 15 mL). The organic extracts were combined, washed with brine (2 × 30 mL), dried ($MgSO_4$), filtered

and the solvent removed *in vacuo* to give the crude product as a yellow oil (776 mg). Purification by column chromatography (SiO_2, hexane/Et_2O 4:1) gave the title compound as a colourless oil (162 mg, 81% over 3 steps).

IR: ν_{max}(neat)/cm^{-1} 3326 (br), 3019 (w), 2917 (m), 2878 (sh), 2857 (sh), 2833 (sh)

Optical rotation: $[\alpha]_D^{29}$ = +45° (c = 0.5, $CHCl_3$)

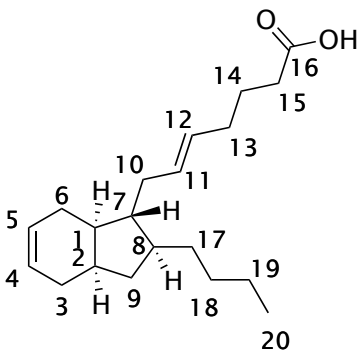
^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 5.72–5.62 (2H, m), 5.52–5.33 (2H, m), 3.65 (2H, t, *J* 6.5 Hz, H-16), 2.35–1.95 (8H, m), 1.81–1.05 (16H, m), 0.89 (3H, t, *J* 6.9 Hz, H-20)

^{13}C NMR: δ_C (101 MHz, $CDCl_3$) 130.74 (CH), 129.48 (CH), 127.28 (CH), 127.17 (CH), 62.90 (CH_2, C-16), 52.25 (CH), 47.18 (CH), 42.31 (CH), 40.07 (CH), 36.97 (CH_2), 36.73 (CH_2), 36.66 (CH_2), 32.42 (CH_2), 32.28 (CH_2), 32.27 (CH_2), 31.60 (CH_2), 30.72 (CH_2), 25.64 (CH_2), 22.93 (CH_2), 14.15 (CH_3, C-20)

LRMS: (CI) m/z 308.2 ($[M+NH_4]^+$, 100%), 291.2 ($[M+H]^+$, 42%), 290.2 ($[M]^{+\bullet}$, 20%), 273.2 ($[M-OH]^+$, 17%), 259.1 ($[M-CH_3O]^+$, 2%), 233.1 ($[M-C_4H_9]^+$, 6%), 231.2 ($[M-C_3H_7O]^+$, 2%), 177.1 ($[M-C_7H_{13}O]^+$, 42%

HRMS: (EI) Calculated for $C_{20}H_{34}O$: 290.26097 Da, found: 290.26139 Da

(+)-Mucosin (139)



PDC (271 mg, 0.72 mmol) was added to alcohol **175** (32.0 mg, 0.11 mmol) in DMF (1.0 mL) at 0 °C. After stirring at room temperature overnight the reaction mixture was poured into water (30 mL) and extracted with ether (3 × 20 mL). The organic extracts were combined, washed with brine (50 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product as a colourless oil (92.3 mg). Purification by column chromatography (SiO_2, hexane/Et_2O 1:1) gave the title compound as a colourless oil (28.1 mg, 84%).

IR: ν_{max}(neat)/cm^{-1} 3019 (w), 2954 (sh), 2917 (m), 2857 (sh), 1706 (m)

Optical rotation: $[\alpha]_D^{26}$ = +37.1° (c = 0.8, *n*-hexane)

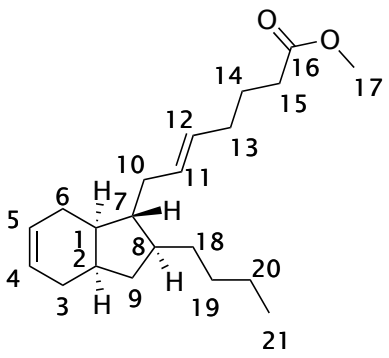
^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 7.91 (1H, br. s., COOH), 5.85–5.56 (2H, m), 5.53–5.29 (2H, m), 2.35 (2H, t, J 7.5 Hz, H-15), 2.31–2.16 (2H, m), 2.15–2.09 (2H, m), 2.06 (2H, q, J 6.9 Hz), 1.81–1.65 (4H, m), 1.65–1.46 (3H, m), 1.46–1.36 (2H, m), 1.36–1.25 (3H, m), 1.24–1.16 (2H, m), 1.15–1.07 (2H, m), 0.89 (3H, t, J 6.8 Hz, H-20)

^{13}C NMR: δ_C (101 MHz, $CDCl_3$) 179.70 (C, C-16), 130.47 (CH), 129.64 (CH), 127.27 (CH), 127.13 (CH), 52.22 (CH), 47.21 (CH), 42.33 (CH), 40.08 (CH), 36.96 (CH_2), 36.74 (CH_2), 36.67 (CH_2), 33.34 (CH_2), 32.40 (CH_2), 31.82 (CH_2), 31.60 (CH_2), 30.72 (CH_2), 24.45 (CH_2), 22.92 (CH_2), 14.14 (CH_3, C-21)

LRMS: (ES−) m/z 303.4 ($[M-H]^-$)

HRMS: (ES^+) Calculated for $C_{20}H_{32}NaO_2$: 327.2295 Da, found: 327.2300 Da

(*E*)-Methyl 7-((1*R*,2*S*,3a*R*,7a*R*)-2-butyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-1-yl)hept-5-enoate (176)



Diazomethane in dry ether [produced by addition of KOH (99.0 mg, 1.9 mmol) in 96% ethanol (4.0 mL) to Diazald® (107 mg, 0.50 mmol) in dry ether (14.0 mL)] was distilled into a flask containing acid **139** (40.0 mg, 0.13 mmol) in ether (1.00 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 20 mins followed by stirring at room temperature for 1 h to remove excess diazomethane. The solvent was removed *in vacuo* to give a pale yellow oil (112 mg). Purification by column chromatography (SiO_2, hexane/Et_2O 20:1) gave the title compound as a colourless oil (37.5 mg, 91%).

IR: ν_{max}(neat)/cm^{-1} 3019 (w), 2951 (sh), 2919 (w), 2857 (sh), 1740 (m)

Optical rotation: $[\alpha]_D^{26}$ = +38.2° (c = 0.8, *n*-hexane)

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 5.73–5.60 (2H, m), 5.46 (1H, m), 5.38 (1H, m), 3.67 (3H, s, H-17), 2.31 (2H, t, *J* 7.5 Hz, H-15), 2.23 (1H, m), 2.17 (1H, m), 2.15–2.08 (2H, m), 2.03 (2H, q, J 7.0 Hz), 1.80–1.65 (4H, m), 1.64–1.48 (3H, m), 1.46–1.33 (2H, m), 1.33–1.23 (3H, m), 1.19–1.13 (2H, m), 1.13–1.08 (2H, m), 0.89 (3H, t, *J* 6.9 Hz, H-21)

^{13}C NMR: δ_C (101 MHz, $CDCl_3$) 174.17 (C, C-16), 130.30 (CH), 129.81 (CH), 127.27 (CH), 127.15 (CH), 52.24 (CH), 51.43 (CH_3, C-17), 47.20 (CH), 42.33 (CH), 40.08 (CH), 36.96 (CH_2), 36.73 (CH_2), 36.67 (CH_2), 33.43 (CH_2), 32.41 (CH_2), 31.92 (CH_2), 31.61 (CH_2), 30.72 (CH_2), 24.73 (CH_2), 22.93 (CH_2), 14.14 (CH_3, C-21)

LRMS: (CI) m/z 336.3 ($[M+NH_4]^+$, 100%), 319.3 ($[M+H]^+$, 75%), 318.2 ($[M]^{+\bullet}$, 3%), 303.2 ($[M-CH_3]^+$, 5%), 287.2 ($[M-CH_3O]^+$, 1%), 261.2 ($[M-C_4H_9]^+$, 2%)

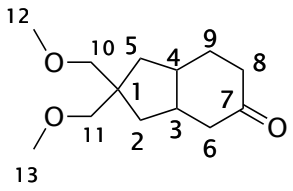
HRMS: (EI) Calculated for $C_{21}H_{34}O_2$: 318.25588 Da, found: 318.25597 Da

7.6 Experimental for chapter 6

General procedure E: zirconocene mediated synthesis of cyclohexanones

n-BuLi (2 eq.) was added dropwise to a solution of Cp_2ZrCl_2 (1 eq.) in dry THF (5.0 mL per 1.0 mmol of Cp_2ZrCl_2) at −78 °C. A solution of diene **166** (1 eq.) in dry THF (3.0 mL per 1.0 mmol of diene **166**) was added dropwise at −78 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was cooled to −78 °C and the appropriate carbenoid precursor (1–1.3 eq.) and LDA (1–1.3 eq.) added sequentially. After stirring at −78 °C for 1 h the reaction mixture was warmed to −40 °C and the appropriate isonitrile (1–1.3 eq.) added. The reaction mixture was allowed to warm slowly to room temperature and stirred at this temperature for 16 h. 50% aq. HOAc solution (3 mL) was added to the reaction mixture followed by stirring at room temperature for 1 h. The reaction mixture was saturated with K_2CO_3, poured into water (100 mL) and extracted with ether (3 × 50 mL). The organic extracts were combined, washed sequentially with sat. aq. $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product, which was purified as described.

2,2-Bis(methoxymethyl)hexahydro-1*H*-inden-5(6*H*)-one (181a)



General procedure E with diene **166** (92.0 mg, 0.50 mmol), diethyl (chloromethyl)phosphonate (0.10 mL, 0.65 mmol) and butyl isonitrile (0.07 mL, 0.65 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 3:1) gave the title compound as a pale yellow oil (72.3 mg, 64%).

IR: ν_{max}(neat)/cm^{-1} 2924 (w), 2868 (w), 2824 (w), 1710 (m), 1103 (s)

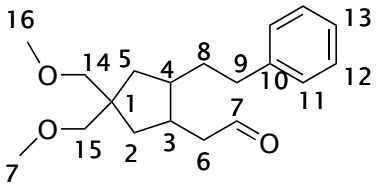
^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 3.33 (3H, s, OMe), 3.30 (3H, s, OMe), 3.23 (2H, d, *J* 1.1 Hz, H-10a,11a), 3.18 (2H, d, *J* 1.1 Hz, H-10b,11b), 2.50 (1H, m), 2.36 (1H, m), 2.25 (1H, m), 2.14–2.02 (2H, m), 1.81–1.58 (4H, m), 1.38 (1H, m), 1.15 (1H, m), 1.05 (1H, m)

^{13}C NMR: δ_C (101 MHz, $CDCl_3$) 211.59 (C, C-7), 77.99 (CH_2), 77.93 (CH_2), 59.16 (CH_3), 59.12 (CH_3), 47.26 (C, C-1), 47.12 (CH_2), 45.56 (CH), 43.76 (CH), 40.73 (CH_2), 38.86 (CH_2), 37.48 (CH_2), 29.47 (CH_2)

LRMS: (ES+) m/z 249.3 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{13}H_{22}NaO_3$: 249.1461 Da, found: 249.1463 Da

2-(4,4-Bis(methoxymethyl)-2-phenethylcyclopentyl)acetaldehyde (194)



General procedure E with diene **166** (184 mg, 1.0 mmol), benzyl chloride (0.12 mL, 0.65 mmol) and butyl isonitrile (0.10 mL, 1.0 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 3:1) gave the title compound as a pale yellow oil (186 mg, 61%).

IR: ν_{max} (neat)/cm^{-1} 2922 (w), 2872 (w), 2823 (w), 1722 (m)

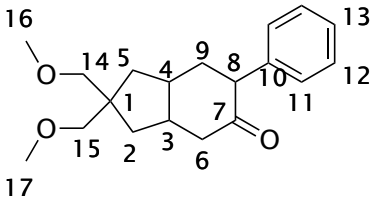
^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 9.74 (1H, s, H-7), 7.33–7.25 (2H, m), 7.22–7.13 (3H, m), 3.36 (3H, s, OMe), 3.35 (3H, s, OMe), 3.28–3.16 (4H, m, H-14,15), 2.72 (1H, m), 2.64–2.45 (2H, m), 2.22 (1H, ddd, *J* 16.2, 9.0, 2.1 Hz), 2.04–1.77 (4H, m), 1.55 (1H, dtd, *J* 17.8, 10.4, 3.0 Hz), 1.39 (1H, m), 1.22–1.05 (2H, m)

^{13}C NMR: δ_C (101 MHz, $CDCl_3$) 202.41 (C, C-7), 142.42 (C, C-10), 128.31 (2 × CH), 128.18 (2 × CH), 125.72 (CH, C-13), 77.76 (CH_2, C-14,15), 59.23 (CH_3), 59.22 (CH_3), 48.16 (CH_2), 45.65 (C, C-1), 44.84 (CH), 39.51 (CH), 39.25 (CH_2), 38.60 (CH_2), 35.67 (CH_2), 34.48 (CH_2)

LRMS: (CI) m/z 305.1 ($[M+H]^+$, 7%), 226.9 ($[M-C_6H_5]^+$, 2%), 156.0 ($[M-C_{10}H_{12}O]^+$, 2%) 90.9 (100%)

HRMS: (ES+) Calculated for $C_{19}H_{28}NaO_3$: 327.1931 Da, found: 327.1938 Da

2,2-Bis(methoxymethyl)-6-phenylhexahydro-1*H*-inden-5(6*H*)-one (193)



General procedure E with diene **166** (92.0 mg, 0.50 mmol), benzyl chloride (0.06 mL, 0.50 mmol) and trimethylsilyl cyanide (0.06 mL, 0.50 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 3:1) gave the title compound as the major product as a pale yellow oil (48.0 mg, 32%).

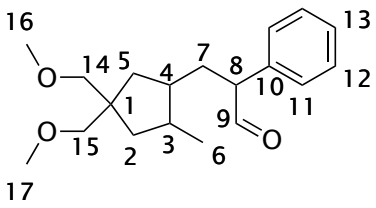
IR: ν_{max} (neat)/cm^{-1} 2984 (sh), 2959 (sh), 2918 (sh), 2869 (w), 2806 (w), 1710 (m), 1103 (s)

^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 7.36–7.30 (2H, m), 7.26 (1H, m), 7.14–7.06 (2H, m), 3.56 (1H, dd, *J* 12.9, 5.7 Hz, H-8), 3.38 (3H, s, OMe), 3.36 (3H, s, OMe), 3.30 (2H, d, *J* 1.9 Hz, H-14a,15a), 3.25 (2H, d, *J* 1.9 Hz, H-14b,15b), 2.68 (1H, dd, *J* 13.5, 3.7 Hz), 2.42–2.26 (2H, m), 1.98 (1H, m), 1.91–1.68 (4H, m), 1.35–1.08 (2H, m)

^{13}C NMR: δ_C (101 MHz, $CDCl_3$) 209.65 (C, C-7), 139.14 (C, C-10), 128.81 (2 × CH), 128.26 (2 × CH), 126.81 (CH, C-13), 78.09 (CH_2), 78.03 (CH_2), 59.26 (CH_3), 59.23 (CH_3), 56.67 (CH, C-8), 47.40 (CH_2), 47.38 (C, C-1), 46.51 (CH), 44.42 (CH), 38.89 (CH_2), 38.39 (CH_2), 37.48 (CH_2)

LRMS: (ES+) m/z 303.2 ($[M+H]^+$)

HRMS: (ES+) Calculated for $C_{19}H_{26}NaO_3$: 325.1774 Da, found: 325.1777 Da



The minor product was 3-(4,4-bis(methoxymethyl)-2-methylcyclopentyl)-2-phenylpropanal **(195)** obtained as a pale yellow oil (34.9 mg, 23%).

IR: ν_{max} (neat)/cm^{-1} 2923 (w), 2870 (w), 2822 (w), 1722 (s), 1104 (s)

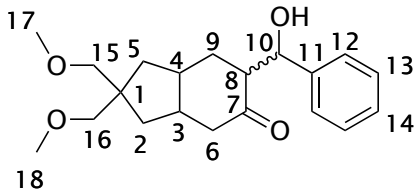
^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 9.68 (1H, d, *J* 1.6 Hz, H-9), 7.42–7.35 (2H, m), 7.31 (1H, m), 7.23–7.17 (2H, m), 3.54 (1H, m, H-8), 3.34 (3H, s, OMe), 3.28 (3H, s, OMe), 3.22 (1H, d, *J* 8.6 Hz), 3.17 (1H, d, *J* 8.6 Hz), 3.10 (1H, d, *J* 8.6 Hz), 3.06 (1H, d, *J* 8.6 Hz), 2.07 (1H, ddd, *J* 13.7, 10.8, 2.9 Hz), 1.79–1.65 (3H, m), 1.55 (1H, m), 1.15–0.99 (2H, m), 0.92 (1H, m), 0.87 (3H, d, *J* 6.4 Hz, H-6)

^{13}C NMR: δ_C (101 MHz, $CDCl_3$) 201.05 (C, C-9), 136.07 (C, C-10), 129.03 (2 × CH), 128.82 (2 × CH), 127.54 (CH, C-13), 77.76 (CH_2), 77.69 (CH_2), 59.23 (CH_3), 59.18 (CH_3), 58.26 (CH, C-8), 45.31 (C, C-1), 43.33 (CH), 41.65 (CH_2), 39.88 (CH), 38.97 (CH_2), 33.51 (CH_2), 17.67 (CH_3, C-6)
LRMS: (ES+) m/z 327.3 ($[M+Na]^+$)
HRMS: (ES+) Calculated for $C_{19}H_{28}NaO_3$: 327.1931 Da, found: 327.1934 Da

General procedure F: elaboration of enamine 185

n-BuLi (2 eq.) was added dropwise to a solution of Cp_2ZrCl_2 (1 eq.) in dry THF (5.0 mL per 1.0 mmol of Cp_2ZrCl_2) at −78 °C. A solution of diene **166** (1 eq.) in dry THF (3.0 mL per 1.0 mmol of diene **166**) was added dropwise at −78 °C. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was cooled to −78 °C and the appropriate carbenoid precursor (1–1.3 eq.) and LDA (1–1.3 eq.) added sequentially. After stirring at −78 °C for 1 h the reaction mixture was warmed to −40 °C and the appropriate isonitrile (1 eq.) added. The reaction mixture was allowed to warm slowly to room temperature and stirred at this temperature for 16 h. The reaction mixture was cooled to −40 °C and the trapping reagent (1.5–2 eq.) was added. The reaction mixture was allowed to warm slowly to room temperature and stirred at this temperature for 16 h. 50% aq. HOAc solution (3 mL) was added to the reaction mixture followed by stirring at room temperature for 1 h. The reaction mixture was saturated with K_2CO_3, poured into water (100 mL) and extracted with ether (3 × 50 mL). The organic extracts were combined, washed sequentially with sat. aq. $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo* to give the crude product, which was purified as described.

6-(Hydroxy(phenyl)methyl)-2,2-bis(methoxymethyl)hexahydro-1*H*-inden-5(6*H*)-one (186)



General procedure F with diene **166** (92.0 mg, 0.50 mmol), diethyl (chloromethyl)phosphonate (0.10 mL, 0.65 mmol), butyl isonitrile (0.07 mL, 0.65 mmol), benzaldehyde (0.10 mL, 1.0 mmol) and $BF_3.OEt_2$ (0.12 mL, 1.0 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 3:1) gave two diastereoisomers (dr 1:2) of the title compound. The first diastereoisomer was obtained as a pale yellow oil (64.0 mg, 39%).

IR: ν_{max}(neat)/cm^{-1} 3524 (br), 2924 (w), 2870 (w), 2825 (w), 1695 (m)

^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.50–7.15 (5H, m, H-12,13,14), 5.42 (1H, br. s., OH), 3.31 (6H, s, H-17,18), 3.22 (2H, s, H-15 or H-16), 3.17 (2H, s, H-15 or H-16), 2.58 (1H, m, H-10), 2.22 (1H, m), 1.89–1.59 (4H, m), 1.52 (1H, m), 1.38–0.72 (4H, m)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 214.13 (C, C-7), 141.51 (C, C-11), 128.13 (2 × CH), 126.90 (CH, C-14), 125.65 (2 × CH), 78.04 (CH_2), 77.97 (CH_2), 70.39 (CH, C-10), 59.20 (CH_3, C-17,18), 56.17 (CH, C-8), 47.56 (CH_2), 47.31 (C, C-1), 46.38 (CH), 43.78 (CH), 38.67 (CH_2), 37.49 (CH_2), 28.23 (CH_2)

LRMS: (ES+) m/z 355.3 ([M+Na]$^+$)

HRMS: (ES+) Calculated for $C_{20}H_{28}NaO_4$: 355.1880 Da, found: 355.1887 Da

The second diastereoisomer was obtained as a pale yellow oil (33.6 mg, 20%).

IR: ν_{max}(neat)/cm^{-1} 3434 (br), 2952 (w), 2927 (sh), 2870 (w), 2828 (w), 2809 (sh), 1697 (m), 1128 (s)

^{1}H NMR: δ_H (300 MHz, $CDCl_3$) 7.42–7.25 (5H, m, H-12,13,14), 4.80 (1H, dd, *J* 8.8, 2.4 Hz, H-10), 4.10 (1H, d, *J* 2.4 Hz, OH), 3.31 (3H, s, OMe), 3.31 (3H, s, OMe), 3.25–3.15 (4H, m, H-15,16), 2.68–2.52 (2H, m), 2.22 (1H, m), 1.80–1.50 (4H, m), 1.36–0.92 (3H, m), 0.82 (1H, m)

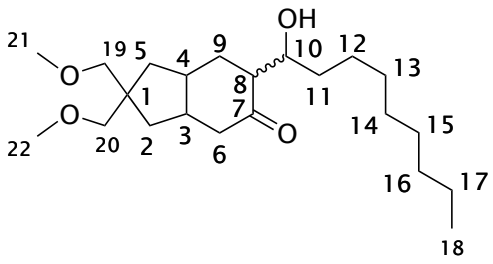
^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 215.37 (C, C-7), 140.94 (C, C-11), 128.36 (2 × CH), 127.87 (CH, C-14), 127.00 (2 × CH), 78.03 (CH_2), 77.99 (CH_2), 74.86 (CH, C-10),

59.20 (CH_3, C-17,18), 56.17 (CH, C-8), 47.85 (CH_2), 47.33 (C, C-1), 46.52 (CH), 43.78 (CH), 38.62 (CH_2), 37.22 (CH_2), 33.38 (CH_2)

LRMS: (ES+) m/z 355.3 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{20}H_{28}NaO_4$: 355.1880 Da, found: 355.1887 Da

6-(1-Hydroxynonyl)-2,2-bis(methoxymethyl)hexahydro-1*H*-inden-5(6*H*)-one (189)



General procedure F with diene **166** (184 mg, 1.0 mmol), diethyl (chloromethyl)phosphonate (0.20 mL, 1.0 mmol), butyl isonitrile (0.1 mL, 1.0 mmol), nonanal (0.34 mL, 2.0 mmol) and $BF_3.OEt_2$ 0.25 mL, 2.0 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 2:1) gave the title compound as an inseparable mixture of diastereoisomers (dr 1.3:1) as a pale yellow oil (33.9 mg, 9%).

IR: ν_{max} (neat)/cm^{-1} 3463 (br), 2923 (m), 2855 (m), 1739 (sh), 1701 (m)

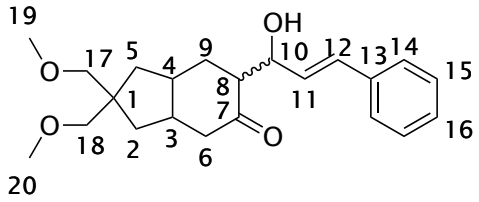
^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 4.03 (1H, br. s., H-10^{dr1}), 3.68 (1H, br. s., H-10^{dr2}), 3.29 (3H, s, OMe), 3.25 (3H, s, OMe), 3.21–3.09 (4H, m, H-19,20), 2.47 (1H, m), 2.24 (1H, m), 2.15–1.96 (2H, m), 1.81–1.51 (4H, m), 1.48–1.30 (3H, m), 1.28–1.08 (14H, m), 0.81 (3H, t, *J* 6.4 Hz, H-18)

^{13}C NMR: δ_C (101 MHz, $CDCl_3$) 215.53 (C, C-7^{dr2}), 214.45 (C, C-7^{dr1}), 78.07 (CH_2^{dr2}), 78.05 (CH_2^{dr2}), 77.99 (CH_2^{dr1}), 71.47 (CH, C-10^{dr2}), 69.02 (CH, C-10^{dr1}), 59.24 (CH_3^{both}), 59.20 (CH_3^{both}), 54.61 (CH, C-8^{dr2}), 53.69 (CH, C-8^{dr1}), 47.97 (CH_2^{dr2}), 47.61 (CH_2^{dr1}), 47.40 (C, C-1^{dr2}), 47.34 (C, C-1^{dr1}), 46.37 (CH^{dr2}), 46.04 (CH^{dr1}), 43.91 (CH^{dr2}), 43.80 (CH^{dr1}), 38.75 (CH_2^{dr1}), 38.71 (CH_2^{dr2}), 37.69 (CH_2^{dr1}), 37.43 (CH_2^{dr2}), 33.51 (CH_2^{dr2}), 33.11 (CH_2^{dr2}), 32.84 (CH_2^{dr1}), 31.86 (CH_2^{dr1}), 31.85 (CH_2^{dr1}), 29.69 (CH_2^{dr2}), 29.61 (CH_2^{dr1}), 29.58 (CH_2^{dr2}), 29.53 (CH_2^{dr1}), 29.28 (CH_2^{dr2}), 29.25 (CH_2^{dr1}), 28.71 (CH_2^{dr2}), 26.16 (CH_2^{dr1}), 25.09 (CH_2^{dr2}), 22.64 (CH_2^{both}), 14.07 (CH_3, C-18^{both})

LRMS: (ES+) m/z 391.4 ($[M+Na]^+$)

HRMS: (ES+) Calculated for $C_{22}H_{40}NaO_4$: 391.2819 Da, found: 391.2820 Da

(*E*)-6-(1-Hydroxy-3-phenylallyl)-2,2-bis(methoxymethyl)hexahydro-1*H*-inden-5(6*H*)-one (190)



General procedure F with diene **166** (184 mg, 1.0 mmol), diethyl (chloromethyl)phosphonate (0.20 mL, 1.0 mmol), butyl isonitrile (0.1 mL, 1.0 mmol), cinnamaldehyde (0.25 mL, 2.0 mmol) and $BF_3.OEt_2$ (0.25 mL, 2.0 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 2:1) gave two diastereoisomers (dr 1:1.3) of the title compound. The first diastereoisomer was obtained as a pale yellow oil (65.8 mg, 18%).

IR: ν_{max} (neat)/cm^{-1} 3294 (br), 2924 (w), 2871 (w), 2824 (w), 1708 (m), 1678 (sh)

^{1}**H NMR:** δ_H (300 MHz, $CDCl_3$) 7.43–7.15 (5H, m, H-14,15,16), 6.63 (1H, d, *J* 15.7 Hz, H12), 6.21 (1H, dd, *J* 15.7, 5.9 Hz, H-11), 4.78 (1H, br. s., H-10), 3.35 (3H, s, OMe), 3.35 (1H, t, *J* 4.2 Hz, OH), 3.32 (3H, s, OMe), 3.26–3.17 (4H, m, H-17,18), 2.57 (1H, m, H-8), 2.26–2.06 (2H, m), 1.87–1.58 (4H, m), 1.47 (1H, m), 1.32–0.98 (3H, m)

^{13}**C NMR:** δ_C (75 MHz, $CDCl_3$) 213.70 (C, C-7), 136.73 (C, C-13), 130.80 (CH), 129.06 (CH), 128.50 (2 × CH), 127.50 (CH), 126.37 (2 × CH), 78.03 (CH_2), 77.93 (CH_2), 70.60 (CH, C-10), 59.22 (CH_3), 59.17 (CH_3), 54.48 (CH, C-8), 47.54 (CH_2), 47.32 (C, C-1), 46.05 (CH), 43.73 (CH), 38.69 (CH_2), 37.51 (CH_2), 29.83 (CH_2)

LRMS: (ES+) m/z 357.3 ([M−H]$^-$)

HRMS: (ES+) Calculated for $C_{22}H_{30}NaO_4$: 381.2036 Da, found: 381.2033 Da

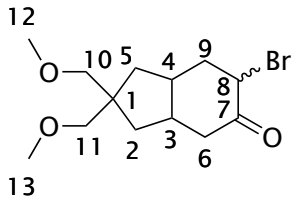
The second diastereoisomer was obtained as a pale yellow oil (85.5 mg, 24%).

IR: ν_{max} (neat)/cm^{-1} 3446 (br), 2924 (w), 2870 (w), 2825 (w), 1700 (m)

^{1}**H NMR:** δ_H (300 MHz, $CDCl_3$) 7.57–7.00 (5H, m, H-14,15,16), 6.53 (1H, d, *J* 15.9 Hz, H-12), 6.11 (1H, dd, *J* 15.9, 7.3 Hz, H-11), 4.38 (1H, dd, *J* 7.3, 7.3 Hz, H-10), 3.27 (1H, m, OH), 3.27 (3H, s, OMe), 3.24 (3H, s, OMe), 3.20–3.10 (4H, m, H-17,18), 2.48 (1H, m, H-8), 2.09 (1H, m), 1.90–1.47 (4H, m), 1.31–1.07 (3H, m), 1.05–0.71 (2H, m)

^{13}C NMR: δ_C (75 MHz, $CDCl_3$) 214.77 (C, C-7), 136.57 (C, C-13), 132.01 (CH), 128.83 (CH), 128.51 (2 × CH), 127.68 (CH), 126.50 (2 × CH), 78.04 (CH_2), 77.96 (CH_2), 73.09 (CH, C-10), 59.23 (CH_3), 59.19 (CH_3), 54.99 (CH, C-8), 47.85 (CH_2), 47.38 (C, C-1), 46.40 (CH), 43.80 (CH), 38.67 (CH_2), 37.31 (CH_2), 33.19 (CH_2)
HRMS: (ES+) Calculated for $C_{22}H_{30}NaO_4$: 381.2036 Da, found: 381.2041 Da

6-Bromo-2,2-bis(methoxymethyl)hexahydro-1*H*-inden-5(6*H*)-one (191)



General procedure F with diene **166** (184 mg, 1.0 mmol), diethyl (chloromethyl)phosphonate (0.20 mL, 1.0 mmol), butyl isonitrile (0.1 mL, 1.0 mmol) and NBS (267 mg, 1.5 mmol). Purification by column chromatography (SiO_2, hexane/Et_2O 3:1) gave two diastereoisomers (dr 1:1.3) of the title compound. The first diastereoisomer was obtained as an orange oil (77.4 mg, 25%).

IR: ν_{max} (neat)/cm^{-1} 2925 (w), 2874 (w), 2825 (w), 1715 (m), 1102 (s)
^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 4.30 (1H, m, H-8), 3.35 (3H, s, OMe), 3.31 (3H, s, OMe), 3.27–3.17 (4H, m, H-10,11), 2.88 (1H, m), 2.48–2.29 (2H, m), 2.20 (1H, m), 1.90 (1H, ddd, *J* 15.1, 11.6, 3.9 Hz), 1.82–1.69 (2H, m), 1.64 (1H, m), 1.22 (1H, t, *J* 11.9 Hz), 1.10 (1H, t, *J* 12.3 Hz)
^{13}C NMR: δ_C (101 MHz, $CDCl_3$) 203.63 (C, C-7), 77.79 (CH_2), 77.77 (CH_2), 59.18 (CH_3), 59.15 (CH_3), 50.58 (CH), 47.18 (C, C-1), 45.60 (CH), 41.60 (CH_2), 38.71 (CH_2), 38.07 (CH_2), 37.99 (CH), 36.62 (CH_2)
LRMS: (ES+) m/z 327.3 ([M+Na]$^+$)
HRMS: (ES+) Calculated for $C_{13}H_{21}BrNaO_3$: 327.0566 Da, found: 327.0567 Da

The second diastereoisomer was obtained as a pale yellow oil (101.3 mg, 33%).

IR: ν_{max} (neat)/cm^{-1} 2924 (w), 2870 (w), 2824 (w), 1713 (m), 1103 (s)
^{1}H NMR: δ_H (400 MHz, $CDCl_3$) 4.63 (1H, m, H-8), 3.33 (3H, s, OMe), 3.30 (3H, s, OMe), 3.25–3.14 (4H, m, H-10,11), 2.73 (1H, m), 2.49 (1H, m), 2.30 (1H, m), 2.09 (1H, m), 1.94–1.64 (4H, m), 1.29–0.99 (2H, m)

^{13}C NMR: δ_C (101 MHz, $CDCl_3$) 200.94 (C, C-7), 77.99 (CH_2), 77.93 (CH_2), 59.25 (CH_3), 59.21 (CH_3), 55.90 (CH, C-8), 47.33 (C, C-1), 45.97 (CH), 45.39 (CH), 40.81 (CH_2), 38.93 (CH_2), 37.55 (CH_2), 36.94 (CH_2)

LRMS: (CI) m/z 306.9 ($[M+H]^+$, ^{81}Br, 1%), 305.0 ($[M+H]^+$, ^{79}Br, 1%), 225.0 ($[M-Br]^+$, 2%), 45.0 (100%)

HRMS: (ES+) Calculated for $C_{13}H_{21}{}^{79}BrNaO_3$: 327.0566 Da, found: 327.0562 Da

References

1. E. Negishi, *Dalton Transactions*, 2005, 827-848.
2. G. Wilkinson and J. M. Birmingham, *J. Am. Chem. Soc.*, 1954, **76**, 4281-4284.
3. P. C. Wailes and H. Weigold, *J. Organomet. Chem.*, 1970, **24**, 405-411.
4. P. C. Wailes, H. Weigold and A. P. Bell, *J. Organomet. Chem.*, 1971, **27**, 373-378.
5. D. W. Hart and J. Schwartz, *J. Am. Chem. Soc.*, 1974, **96**, 8115-8116.
6. D. W. Hart, T. F. Blackburn and J. Schwartz, *J. Am. Chem. Soc.*, 1975, **97**, 679-680.
7. C. A. Bertelo and J. Schwartz, *J. Am. Chem. Soc.*, 1976, **98**, 262-264.
8. J. Schwartz and J. A. Labinger, *Angew. Chem. Int. Ed.*, 1976, **15**, 333-340.
9. M. J. Loots and J. Schwartz, *J. Am. Chem. Soc.*, 1977, **99**, 8045-8046.
10. M. J. Loots and J. Schwartz, *Tetrahedron Lett.*, 1978, 4381-4382.
11. N. Okukado, D. E. Vanhorn, W. L. Klima and E. I. Negishi, *Tetrahedron Lett.*, 1978, 1027-1030.
12. G. W. Watt and F. O. Drummond, *J. Am. Chem. Soc.*, 1966, **88**, 5926-5927.
13. D. J. Sikora, K. J. Moriarty and M. D. Rausch, *Inorg. Synth.*, 1990, **28**, 248-257.
14. M. D. Fryzuk, T. S. Haddad and D. J. Berg, *Coord. Chem. Rev.*, 1990, **99**, 137-212.
15. E. Negishi, F. E. Cederbaum and T. Takahashi, *Tetrahedron Lett.*, 1986, **27**, 2829-2832.
16. E. Negishi, S. J. Holmes, J. M. Tour, J. A. Miller, F. E. Cederbaum, D. R. Swanson and T. Takahashi, *J. Am. Chem. Soc.*, 1989, **111**, 3336-3346.
17. S. L. Buchwald, B. T. Watson and J. C. Huffman, *J. Am. Chem. Soc.*, 1987, **109**, 2544-2546.
18. E. Negishi, D. R. Swanson and T. Takahashi, *J. Chem. Soc., Chem. Commun.*, 1990, 1254-1255.
19. R. J. Whitby, in *Transition Metals in Organic Synthesis: A Practical Approach*, ed. S. E. Gibson, Oxford University Press, Oxford, 1997.
20. W. A. Nugent and D. F. Taber, *J. Am. Chem. Soc.*, 1989, **111**, 6435-6437.
21. C. J. Rousset, D. R. Swanson, F. Lamaty and E. Negishi, *Tetrahedron Lett.*, 1989, **30**, 5105-5108.
22. M. Akita, H. Yasuda, H. Yamamoto and A. Nakamura, *Polyhedron*, 1991, **10**, 1-9.
23. H. Yasuda, K. Nagasuna, M. Akita, K. Lee and A. Nakamura, *Organometallics*, 1984, **3**, 1470-1478.
24. M. Mori, N. Uesaka and M. Shibasaki, *J. Org. Chem.*, 1992, **57**, 3519-3521.
25. J. P. Maye and E. Negishi, *Tetrahedron Lett.*, 1993, **34**, 3359-3362.
26. D. F. Taber and J. P. Louey, *Tetrahedron*, 1995, **51**, 4495-4506.
27. D. F. Taber and Y. N. Wang, *Tetrahedron Lett.*, 1995, **36**, 6639-6642.
28. E. Negishi, D. R. Swanson, F. E. Cederbaum and T. Takahashi, *Tetrahedron Lett.*, 1987, **28**, 917-920.
29. E. C. Lund and T. Livinghouse, *J. Org. Chem.*, 1989, **54**, 4487-4488.

30. W. A. Nugent, D. L. Thorn and R. L. Harlow, *J. Am. Chem. Soc.*, 1987, **109**, 2788-2796.
31. M. I. Kemp, R. J. Whitby and S. J. Coote, *Synthesis*, 1998, 557-568.
32. M. I. Kemp, University of Southampton, 1996.
33. D. R. Owen, University of Southampton, 2000.
34. F. Mohamadi and M. M. Spees, *Organometallics*, 1992, **11**, 1398-1400.
35. M. I. Kemp, R. J. Whitby and S. J. Coote, *Synlett*, 1994, 451-453.
36. D. P. S. Macfarlane, D. Norton, R. J. Whitby and D. Tupper, *Synlett*, 2006, 3439-3442.
37. E. Negishi and S. Huo, in *Titanium and Zirconium in Organic Synthesis*, ed. I. Marek, Wiley-VCH, Weinheim, 1st edn., 2002.
38. T. Takahashi, K. Aoyagi, R. Hara and N. Suzuki, *Chem. Lett.*, 1992, 1693-1696.
39. T. Takahashi, K. Aoyagi and D. Y. Kondakov, *J. Chem. Soc., Chem. Commun.*, 1994, 747-748.
40. S. L. Buchwald and R. B. Nielsen, *J. Am. Chem. Soc.*, 1989, **111**, 2870-2874.
41. T. Takahashi and Y. Li, in *Titanium and Zirconium in Organic Synthesis*, ed. I. Marek, Wiley-VCH, Weinheim, 1st edn., 2002.
42. C. J. Xi, S. Q. Huo, T. H. Afifi, R. Hara and T. Takahashi, *Tetrahedron Lett.*, 1997, **38**, 4099-4102.
43. H. Ubayama, Z. F. Xi and T. Takahashi, *Chem. Lett.*, 1998, 517-518.
44. C. Copéret, E.-i. Negishi, Z. Xi and T. Takahashi, *Tetrahedron Lett.*, 1994, **35**, 695-698.
45. S. Dixon and R. J. Whitby, in *Titanium and Zirconium in Organic Synthesis*, ed. I. Marek, Wiley-VCH, Weinheim, 1st edn., 2002.
46. D. R. Swanson, C. J. Rousset, E. Negishi, T. Takahashi, T. Seki, M. Saburi and Y. Uchida, *J. Org. Chem.*, 1989, **54**, 3521-3523.
47. E. Negishi, in *Comprehensive Organic Synthesis*, eds. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 5, p. 1163.
48. R. D. Broene, in *Comprehensive Organometallic Chemistry II: A Review of the Literature 1982-1994*, eds. E. W. Abel, F. G. A. Stone and G. Wilkinson, Pergamon, Oxford, 1995, vol. 12, p. 323.
49. J. M. Davis, R. J. Whitby and A. Jaxachamiec, *Tetrahedron Lett.*, 1992, **33**, 5655-5658.
50. J. M. Davis, R. J. Whitby and A. Jaxachamiec, *Synlett*, 1994, 110-112.
51. J. M. Davis, R. J. Whitby and A. Jaxachamiec, *Tetrahedron Lett.*, 1994, **35**, 1445-1448.
52. G. D. Probert, R. J. Whitby and S. J. Coote, *Tetrahedron Lett.*, 1995, **36**, 4113-4116.
53. G. Köbrich, *Angew. Chem. Int. Ed.*, 1967, **6**, 41-52.
54. G. Kobrich, *Angew. Chem. Int. Ed.*, 1972, **11**, 473-485.
55. H. Siegel, *Top. Curr. Chem.*, 1982, **106**, 55-78.
56. M. Braun, *Angew. Chem. Int. Ed.*, 1998, **37**, 430-451.
57. G. Boche and J. C. W. Lohrenz, *Chem. Rev.*, 2001, **101**, 697-756.
58. T. Luker and R. J. Whitby, *Tetrahedron Lett.*, 1994, **35**, 9465-9468.
59. T. Luker and R. J. Whitby, *Tetrahedron Lett.*, 1994, **35**, 785-788.
60. G. J. Gordon and R. J. Whitby, *Synlett*, 1995, 77-78.
61. T. Luker and R. J. Whitby, *Tetrahedron Lett.*, 1995, **36**, 4109-4112.
62. T. Luker and R. J. Whitby, *Tetrahedron Lett.*, 1996, **37**, 7661-7664.

63. S. M. Fillery, G. J. Gordon, T. Luker and R. J. Whitby, *Pure Appl. Chem.*, 1997, **69**, 633-638.
64. G. J. Gordon and R. J. Whitby, *Chem. Commun.*, 1997, 1321-1322.
65. S. M. Fillery, University of Southampton, 1998.
66. M. W. Tuckett, W. J. Watkins and R. J. Whitby, *Tetrahedron Lett.*, 1998, **39**, 123-126.
67. G. J. Gordon, T. Luker, M. W. Tuckett and R. J. Whitby, *Tetrahedron*, 2000, **56**, 2113-2129.
68. S. Dixon, S. M. Fillery, A. Kasatkin, D. Norton, E. Thomas and R. J. Whitby, *Tetrahedron*, 2004, **60**, 1401-1416.
69. L. D. Norman, University of Southampton, 2009.
70. C. Burford, F. Cooke, G. Roy and P. Magnus, *Tetrahedron*, 1983, **39**, 867-876.
71. Z. F. Xi, S. Q. Huo, Y. Noguchi and T. Takahashi, *Chem. Lett.*, 2000, 218-219.
72. P. J. Fagan and W. A. Nugent, *J. Am. Chem. Soc.*, 1988, **110**, 2310-2312.
73. P. J. Fagan, W. A. Nugent and J. C. Calabrese, *J. Am. Chem. Soc.*, 1994, **116**, 1880-1889.
74. K. Kanno and M. Kira, *Chem. Lett.*, 1999, 1127-1128.
75. P. A. Wender and F. E. Mcdonald, *Tetrahedron Lett.*, 1990, **31**, 3691-3694.
76. G. Agnel and E. Negishi, *J. Am. Chem. Soc.*, 1991, **113**, 7424-7426.
77. G. Agnel, Z. Owczarczyk and E. Negishi, *Tetrahedron Lett.*, 1992, **33**, 1543-1546.
78. M. Mori, F. Saitoh, N. Uesaka and M. Shibasaki, *Chem. Lett.*, 1993, 213-216.
79. E. Negishi, S. M. Ma, T. Sugihara and Y. Noda, *J. Org. Chem.*, 1997, **62**, 1922-1923.
80. P. A. Wender, K. D. Rice and M. E. Schnute, *J. Am. Chem. Soc.*, 1997, **119**, 7897-7898.
81. M. I. Kemp, R. J. Whitby and S. J. Coote, *Synthesis*, 1998, 552-556.
82. S. Nowotny, C. E. Tucker, C. Jubert and P. Knochel, *J. Org. Chem.*, 1995, **60**, 2762-2772.
83. M. S. Newman and J. H. Wotiz, *J. Am. Chem. Soc.*, 1949, **71**, 1292-1297.
84. B. M. Trost, D. M. T. Chan and T. N. Nanninga, *Org. Synth.*, 1984, **62**, 58-63.
85. Q. Zhang, W. Xu and X. Lu, *J. Org. Chem.*, 2005, **70**, 1505-1507.
86. B. M. Trost and Z. T. Ball, *J. Am. Chem. Soc.*, 2005, **127**, 17644-17655.
87. M. S. F. Lie Ken Jie, O. Bakare and M. M. L. Lau, *Arkivoc*, 2002, 188-197.
88. S. Bourne and R. J. Whitby, University of Southampton, Southampton, 2009.
89. E. Fayard, J. Auwerx and K. Schoonjans, *Trends in Cell Biology*, 2004, **14**, 250-260.
90. S. Mukherjee and S. Mani, *Pharm. Res.*, 2010, **27**, 1439-1468.
91. S. A. Kliewer, J. M. Lehmann and T. M. Willson, *Science*, 1999, **284**, 757-760.
92. R. M. Evans, *Molecular Endocrinology*, 2005, **19**, 1429-1438.
93. J. T. Moore, J. L. Collins and K. H. Pearce, *Chemmedchem*, 2006, **1**, 504-523.
94. I. G. Schulman and R. A. Heyman, *Chem Biol*, 2004, **11**, 639-646.
95. P. Germain, B. Staels, C. Dacquet, M. Spedding and V. Laudet, *Pharmacological Reviews*, 2006, **58**, 685-704.

96. D. J. Parks, S. G. Blanchard, R. K. Bledsoe, G. Chandra, T. G. Consler, S. A. Kliewer, J. B. Stimmel, T. M. Willson, A. M. Zavacki, D. D. Moore and J. M. Lehmann, *Science*, 1999, **284**, 1365-1368.
97. C. H. Lee, P. Olson and R. M. Evans, *Endocrinology*, 2003, **144**, 2201-2207.
98. H. A. Ingraham and M. R. Redinbo, *Current Opinion in Structural Biology*, 2005, **15**, 708-715.
99. R. J. Whitby, S. Dixon, P. R. Maloney, P. Delerive, B. J. Goodwin, D. J. Parks and T. M. Willson, *J. Med. Chem.*, 2006, **49**, 6652-6655.
100. R. J. Whitby, J. Stec, R. D. Blind, S. Dixon, L. M. Leesnitzer, L. A. Orband-Miller, S. P. Williams, T. M. Willson, R. Xu, W. J. Zuercher, F. Cai and H. A. Ingraham, *J. Med. Chem.*, 2011, **54**, 2266-2281.
101. Z. G. Liu, S. W. Smith, K. A. Mclaughlin, L. M. Schwartz and B. A. Osborne, *Nature*, 1994, **367**, 281-284.
102. J. D. Woronicz, B. Calnan, V. Ngo and A. Winoto, *Nature*, 1994, **367**, 277-281.
103. R. H. Zetterstrom, L. Solomin, L. Jansson, B. J. Hoffer, L. Olson and T. Perlmann, *Science*, 1997, **276**, 248-250.
104. S. Holbeck, J. Chang, A. M. Best, A. L. Bookout, D. J. Mangelsdorf and E. D. Martinez, *Molecular Endocrinology*, 2010, **24**, 1287-1296.
105. R. Williams, A. Elliott, N. Stein and E. Fraley, *In Vitro Cellular & Developmental Biology - Plant*, 1978, **14**, 779-786.
106. Y. Zhan, X. Du, H. Chen, J. Liu, B. Zhao, D. Huang, G. Li, Q. Xu, M. Zhang, B. C. Weimer, D. Cheng, L. Zhang, Q. Li, S. Li, Z. Zheng, S. Song, Y. Huang, Z. Ye, W. Su, S.-C. Lin, Y. Shen and Q. Wu, *Nature Chemical Biology*, 2008, **4**, 548-556.
107. C. Dubois, B. Hengerer and H. Mattes, *Chemmedchem*, 2006, **1**, 955-958.
108. G. Pickaert, M. Cesario and R. Ziessel, *J. Org. Chem.*, 2004, **69**, 5335-5341.
109. Y. P. Pang and A. P. Kozikowski, *J. Org. Chem.*, 1991, **56**, 4499-4508.
110. M. W. B. McCulloch and R. A. Barrow, *Molecules*, 2005, **10**, 1272-1278.
111. C. J. Hawker, R. Lee and J. M. J. Fréchet, *J. Am. Chem. Soc.*, 1991, **113**, 4583-4588.
112. D. M. Haddleton, H. S. Sahota, P. C. Taylor and S. G. Yeates, *J. Chem. Soc., Perkin Trans. 1*, 1996, 649-656.
113. K. Bahrami, M. M. Khodaei and I. Kavianinia, *Synthesis*, 2007, 547-550.
114. M. L. Richards, S. C. Lio, A. Sinha, H. Banie, R. J. Thomas, M. Major, M. Tanji and J. C. Sircar, *European Journal of Medicinal Chemistry*, 2006, **41**, 950-969.
115. K. L. Arienti, A. Brunmark, F. U. Axe, K. McClure, A. Lee, J. Blevitt, D. K. Neff, L. M. Huang, S. Crawford, C. R. Pandit, L. Karlsson and J. G. Breitenbucher, *J. Med. Chem.*, 2005, **48**, 1873-1885.
116. H. M. Shapiro, *Practical Flow Cytometry*, 4th edn., John Wiley and Sons, Hoboken, 2003.
117. V. A. Fadok, D. R. Voelker, P. A. Campbell, J. J. Cohen, D. L. Bratton and P. M. Henson, *J. Immunol.*, 1992, **148**, 2207-2216.
118. H. A. M. Andree, C. P. M. Reutelingsperger, R. Hauptmann, H. C. Hemker, W. T. Hermens and G. M. Willems, *J. Biol. Chem.*, 1990, **265**, 4923-4928.
119. G. Koopman, C. P. M. Reutelingsperger, G. A. M. Kuijten, R. M. J. Keehnen, S. T. Pals and M. H. J. Vanoers, *Blood*, 1994, **84**, 1415-1420.

120. A. Moore, C. J. Donahue, K. D. Bauer and J. P. Mather, in *Methods in Cell Biology*, eds. P. M. Jennie and B. David, Academic Press, London, 1998, vol. 57, pp. 265-278.
121. D. R. Owen and R. J. Whitby, *Synthesis*, 2005, 2061-2074.
122. Z. Janousek, H. G. Viehe and J. Collard, *Angew. Chem. Int. Ed.*, 1972, **11**, 917-918.
123. G. Evano, A. Coste and K. Jouvin, *Angew. Chem. Int. Ed.*, 2010, **49**, 2840-2859.
124. B. Witulski and T. Stengel, *Angew. Chem. Int. Ed.*, 1998, **37**, 489-492.
125. M. O. Frederick, J. A. Mulder, M. R. Tracey, R. P. Hsung, J. Huang, K. C. M. Kurtz, L. C. Shen and C. J. Douglas, *J. Am. Chem. Soc.*, 2003, **125**, 2368-2369.
126. J. R. Dunetz and R. L. Danheiser, *Org. Lett.*, 2003, **5**, 4011-4014.
127. S. Hirano, R. Tanaka, H. Urabe and F. Sato, *Org. Lett.*, 2004, **6**, 727-729.
128. Y. S. Zhang, R. P. Hsung, M. R. Tracey, K. C. M. Kurtz and E. L. Vera, *Org. Lett.*, 2004, **6**, 1151-1154.
129. A. L. Kohnen, X. Y. Mak, T. Y. Lam, J. R. Dunetz and R. L. Danheiser, *Tetrahedron*, 2006, **62**, 3815-3822.
130. X. J. Zhang, Y. S. Zhang, J. Huang, R. P. Hsung, K. C. M. Kurtz, J. Oppenheimer, M. E. Petersen, I. K. Sagamanova, L. C. Shen and M. R. Tracey, *J. Org. Chem.*, 2006, **71**, 4170-4177.
131. D. Bruckner, *Tetrahedron*, 2006, **62**, 3809-3814.
132. S. Hirano, Y. Fukudome, R. Tanaka, F. Sato and H. Urabe, *Tetrahedron*, 2006, **62**, 3896-3916.
133. T. Hamada, X. Ye and S. S. Stahl, *J. Am. Chem. Soc.*, 2008, **130**, 833-835.
134. A. Coste, G. Karthikeyan, F. Couty and G. Evano, *Angew. Chem. Int. Ed.*, 2009, **48**, 4381-4385.
135. B. B. Yao, Z. J. Liang, T. M. Niu and Y. H. Zhang, *J. Org. Chem.*, 2009, **74**, 4630-4633.
136. B. Witulski and M. Gossmann, *Chem. Commun.*, 1999, 1879-1880.
137. B. Witulski and T. Stengel, *Angew. Chem. Int. Ed.*, 1999, **38**, 2426-2430.
138. B. Witulski, T. Stengel and J. M. Fernandez-Hernandez, *Chem. Commun.*, 2000, 1965-1966.
139. P. Garcia, Y. Evanno, P. George, M. Sevrin, G. Ricci, M. Malacria, C. Aubert and V. Gandon, *Org. Lett.*, 2011, **13**, 2030-2033.
140. B. Witulski, N. Buschmann and U. Bergstrasser, *Tetrahedron*, 2000, **56**, 8473-8480.
141. T. Tanaka, S. Hirano, H. Urabe and F. Sato, *Org. Lett.*, 2003, **5**, 67-70.
142. K. Okuma, J.-i. Seto, K.-i. Sakaguchi, S. Ozaki, N. Nagahora and K. Shioji, *Tetrahedron Lett.*, 2009, **50**, 2943-2945.
143. D. B. Hope and K. C. Horncastle, *J. Chem. Soc. C.*, 1966, 1098-1101.
144. A. E. Martin, T. M. Ford and J. E. Bulkowski, *J. Org. Chem.*, 1982, **47**, 412-415.
145. T. Takahashi, Z. F. Xi, A. Yamazaki, Y. H. Liu, K. Nakajima and M. Kotora, *J. Am. Chem. Soc.*, 1998, **120**, 1672-1680.
146. T. Takahashi, F. Y. Tsai, Y. Z. Li, K. Nakajima and M. Kotora, *J. Am. Chem. Soc.*, 1999, **121**, 11093-11100.
147. J. Kong, C. A. White, A. I. Krylov, D. Sherrill, R. D. Adamson, T. R. Furlani, M. S. Lee, A. M. Lee, S. R. Gwaltney, T. R. Adams, C. Ochsenfeld, A. T. B. Gilbert, G. S. Kedziora, V. A. Rassolov, D. R. Maurice, N. Nair, Y. Shao, N. A.

Besley, P. E. Maslen, J. P. Dombroski, H. Daschel, W. Zhang, P. P. Korambath, J. Baker, E. F. C. Byrd, T. Van Voorhis, M. Oumi, S. Hirata, C.-P. Hsu, N. Ishikawa, J. Florian, A. Warshel, B. G. Johnson, P. M. W. Gill, M. Head–Gordon and J. A. Pople, *J. Comput. Chem.*, 2000, **21**, 1532-1548.
148. A. Navarro-Vázquez, J. C. Cobas, F. J. Sardina, J. Casanueva and E. Díez, *J. Chem. Inf. Comput. Sci.*, 2004, **44**, 1680-1685.
149. A. Casapullo, G. Scognamiglio and G. Cimino, *Tetrahedron Lett.*, 1997, **38**, 3643-3646.
150. R. M. Boden, *Synthesis*, 1975, 784-784.
151. A. T. Stevens, J. R. Bull and K. Chibale, *Org. Biomol. Chem.*, 2008, **6**, 586-595.
152. J. H. Smitrovich and K. A. Woerpel, *J. Org. Chem.*, 1996, **61**, 6044-6046.
153. T. Okazoe, K. Takai and K. Utimoto, *J. Am. Chem. Soc.*, 1987, **109**, 951-953.
154. G. E. Keck and S. A. Heumann, *Org. Lett.*, 2008, **10**, 4783-4786.
155. J. A. Bull and A. B. Charette, *J. Org. Chem.*, 2008, **73**, 8097-8100.
156. I. Atodiresei, I. Schiffers and C. Bolm, *Chem. Rev.*, 2007, **107**, 5683-5712.
157. C. Bolm, I. Schiffers, C. L. Dinter and A. Gerlach, *J. Org. Chem.*, 2000, **65**, 6984-6991.
158. A. Kasatkin and R. J. Whitby, University of Southampton, Southampton, 1999.
159. G. D. K. Kumar and S. Baskaran, *J. Org. Chem.*, 2005, **70**, 4520-4523.
160. Y. I. M. Nilsson, R. G. P. Gatti, P. G. Andersson and J. Bäckvall, *Tetrahedron*, 1996, **52**, 7511-7523.
161. M. Schlosser, B. Schaub, B. Spahic and G. Sleiter, *Helv. Chim. Acta*, 1973, **56**, 2166-2170.
162. J. Flahaut and P. Miginiac, *Helv. Chim. Acta*, 1978, **61**, 2275-2285.
163. C. Mukai, I. Nomura and S. Kitagaki, *J. Org. Chem.*, 2003, **68**, 1376-1385.
164. P. Cruciani, R. Stammler, C. Aubert and M. Malacria, *J. Org. Chem.*, 1996, **61**, 2699-2708.
165. A. J. Mancuso, S.-L. Huang and D. Swern, *J. Org. Chem.*, 1978, **43**, 2480-2482.
166. T. Saito, H. Nihei, T. Otani, T. Suyama, N. Furukawa and M. Saito, *Chem. Commun.*, 2008, 172-174.
167. R. C. Larock and L. W. Harrison, *J. Am. Chem. Soc.*, 1984, **106**, 4218-4227.
168. K. Hiroya, S. Itoh and T. Sakamoto, *J. Org. Chem.*, 2004, **69**, 1126-1136.
169. Y. Yin, W. Y. Ma, Z. Chai and G. Zhao, *J. Org. Chem.*, 2007, **72**, 5731-5736.
170. D. M. Pinkerton, M. G. Banwell and A. C. Willis, *Org. Lett.*, 2007, **9**, 5127-5130.
171. F. Bertolini, S. Woodward, S. Crotti and M. Pineschi, *Tetrahedron Lett.*, 2009, **50**, 4515-4518.
172. B. M. Trost, M. Machacek and M. J. Schnaderbeck, *Org. Lett.*, 2000, **2**, 1761-1764.
173. N. Asao, K. Sato, Menggenbateer and Y. Yamamoto, *J. Org. Chem.*, 2005, **70**, 3682-3685.
174. L. Brandsma, *Preparative Acetylenic Chemistry*, 2nd edn., Elsevier Science Publishers B.V., Amsterdam, 1988.
175. A. Trofimov, N. Chernyak and V. Gevorgyan, *J. Am. Chem. Soc.*, 2008, **130**, 13538-13539.
176. M. Okutani and Y. Mori, *J. Org. Chem.*, 2009, **74**, 442-444.

177. F. Suzenet, J.-L. Parrain and J.-P. Quintard, *Eur. J. Org. Chem.*, 1999, 2957-2963.
178. Y. Monguchi, S. Mori, S. Aoyagi, A. Tsutsui, T. Maegawa and H. Sajiki, *Org. Biomol. Chem.*, 2010, **8**, 3338-3342.
179. N. Isono and M. Lautens, *Org. Lett.*, 2009, **11**, 1329-1331.