UNIVERSITY OF SOUTHAMPTON

Tandem Reaction Sequences on a Zirconocene Template

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Abstract

FACULTY OF ENGINEERING, SCIENCE & MATHEMATICS
SCHOOL OF CHEMISTRY

Doctor of Philosophy

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The novel research work described in this thesis covers three areas of organozirconium chemistry.

The first area concerns the synthesis of rigid core structures containing the *cis*-bicyclo[3.3.0]oct-2-ene skeleton. Zirconocene mediated co-cyclisation of 1,6-enynes provides unsaturated 5-membered zirconacycles which are homologated to 6-membered zirconacycles by insertion of 1,1-dihalo-1-lithio species (dihalogenocarbenoids). Further rearrangement to a novel zirconium-alkenylidene complex driven by acetylides provided a powerful method for a rapid construction of novel bicyclic compounds with the potential for functionalization at multiple sites. Such obtained analogues provided an attractive template for structure-activity studies with respect to investigating the biological function of the human orphan nuclear receptors: LRH-1 and SF-1. Equivalent tandem insertion of 1,1-dihalo-1-lithio species and lithium acetylides into saturated zirconacycles resulted in the synthesis of novel bicyclo[3.3.0]octanes, though in many cases limited by a β-H elimination process.

In the second area is presented research work relating to acyclic organozirconocene systems. Insertion of allenyl and propargyl carbenoids into organochlorozirconocenes and bisalkyl/-alkynyl zirconocenes led to 1,2-zirconate rearrangement with expulsion of the corresponding leaving group. Lewis acid promoted insertion of aldehydes and ketones into the resulting allenyl/propargyl zirconocene intermediate gave after hydrolysis a series of propargylic alcohols. Insertion of carbenoids derived from chiral propargyl tosylates into organochlorozirconocenes and further 1,2-metallate rearrangement gave the final alcohols as enantiomerically enriched products.

The third area was an attempted total synthesis of the natural product mucosin, whose structure contains a bicyclo[4.3.0]nonane unit with four contiguous stereocentres. Zirconocene mediated co-cyclisation of the appropriate precursor provided four possible diastereoisomers. It was proved that thermodynamic equilibration of the zirconacycle gives the desired bicyclic product as a major isomer. Although the target molecule was not realised, thorough work on Zr-based total synthesis of mucosin has been achieved and a viable route for successful completion of the synthesis has also been proposed.

Declaration

This thesis is based solely on the work carried out by the author whilst registered for the degree of Doctor of Philosophy in the School of Chemistry at the University of Southampton, except where specific citations of literature examples are indicated.

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List of Abbreviations

Techniques

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

Reagents

BnBr	Benzyl bromide
$BnNH_2$	Benzylamine
BnOH	Benzyl alcohol
n-BuLi	*n*-Butyllithium
s-BuLi	*sec*-Butyllithium
t-BuLi	*tert*-Butyllithium
DCM	Dichloromethane
DHP	3,4-Dihydro-2*H*-pyran
DIBAL–H	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethyl sulfoxide

EtOH	Ethanol
HMPA	Hexamethylphosphoroamide
LDA	Lithium diisopropylamide
LiTMP	Lithium 2,2,6,6-tetramethylpiperidide
m-CPBA	*meta*-Chloroperoxybenzoic acid
MsCl	Methanesulfonyl chloride
N-TsIm	1-(*para*-Toluenesulfonyl)imidazole
PhLi	Phenyllithium
PhMe	Toluene
TBAF	Tetrabutylammonium fluoride
TBDMSOTf	*tert*-Butyldimethylsilyl trifluoromethanesulfonate
THF	Tetrahydrofuran
TMEDA	*N*, *N*, *N*, *N*-Tetramethylethylenediamine
TMP	2,2,6,6-Tetramethylpiperidine
TMSCl	Trimethylsilyl chloride
TsCl	*para*-Toluenesulfonyl chloride
TsOH	*para*-Toluenesulfonic acid

Chemical Groups

Ar	Aryl
n-Bu	*n*-Butyl
Bn	Benzyl
Cb	Carbamate
Cp	Cyclopentadienyl
Et	Ethyl
n-Hex	*n*-Hexyl
c-Hex	*c*-Cyclohexyl
LG	Leaving Group
Me	Methyl
Ms	Methanesulfonyl
Nu	Nucleophile
Oct	*n*-Octyl
n-Pent	*n*-Pentyl
Ph	Phenyl

Pr	*n*-Propyl
TBDMS	*tert*-Butyldimethylsilyl
TMS	Trimethylsilyl
Ts	*para*-Toluenesulfonyl

Biological abbreviations

APC	Allophycocyanin
DBD	DNA–Binding Domain
CNS	Central Nervous System
Dax-1	Dosage sensitive sex reversal-Adrenal hypoplasia congenita gene on the X chromosome, gene 1
Dox	Doxycycline
ES	Embryonic Stem Cell
FRET	Fluorescence Resonance Energy Transfer
hLRH-1	Human Liver Receptor Homolog-1
hSF-1	Human Steroidogenic Factor-1
LBD	Ligand-Binding Domain
LRH-1	Liver Receptor Homolog-1
NR(s)	Nuclear Receptor(s)
NR5A	Subclass A of the subfamily V Nuclear Receptors
ONR(s)	Orphan Nuclear Receptor(s)
PC	Phosphatidylcholine
PI	Phosphatidylinositol (3,4,5) triphosphate
SF-1	Steroidogenic Factor-1
SHP	Small Heterodimer Partner

Miscellaneous

aq	Aqueous
°C	Degrees Celsius
d	Day(s)
d.r.	Diastereoisomeric Ratio
eq	Equivalent(s)
h	Hour(s)
ia	Inactive

M	Moles per litre
mg	Milligram(s)
mL	Millilitre
min	Minute(s)
mmol	Millimole(s)
mol	Mole(s)
m.p.	Melting point
m/z	Mass Charge Ratio
lit.	Literature
R* or S*	Denotes relative stereochemistry
RE	Relative Efficacy
RT	Room Temperature
SAR	Structure-Activity Relationship
SD	Standard Deviation

Contents

Chapter 1. Introduction

1.1. Overview

At the outset, the aim of the PhD research project was to develop highly convergent, zirconocene-mediated, synthetic routes to rigid core structures for use in pharmaceutical discovery, which have the potential to be implemented in high throughput automated synthesis facilities. This involved optimisation of reaction conditions and substrate-scoping studies for the existing method for one-pot three-component coupling on a zirconocene template, originally discovered by previous members of the Whitby group. Application of this method with optimised conditions to a wide range of enynes resulted in synthesis of a series of novel compounds containing the rigid *cis*-bicyclo[3.3.0]oct-2-ene skeleton. Such analogues were used for structure-activity studies with respect to investigating the biological function of the human orphan nuclear receptors: Liver Receptor Homolog-1 (LRH-1) and Steroidogenic Factor-1 (SF-1).

The aim was also to explore novel methodology for synthetically attractive carbon-carbon bond forming reactions by using stoichiometric zirconium chemistry. Discussed in this thesis are examples of current methodology for further elaboration of cyclic and acyclic zirconocene systems *via* carbenoid insertion and a novel 1,3-Zr alkenylidene rearrangement.

Chapter 1 presents a brief description of biological background for a part of this project before the subject of zirconacycle formation and carbenoid insertion into organozirconium bonds is explained. The subsequent chapters then describe the results obtained. Firstly, the insertion of dihalogenocarbenoids into unsaturated and saturated zirconacycles and subsequent rearrangement to a novel zirconium-alkenylidene complex are discussed. Elaboration of acyclic zirconocene complexes through allenyl and propargyl carbenoids insertion with the potential for asymmetric synthesis is presented. Finally, attempted first total synthesis of the natural product mucosin based on zirconocene mediated co-cyclisation of the appropriate triene is described.

1.2. Orphan Nuclear Receptors (ONRs)

The nuclear hormone (NRs) superfamily in mammals comprises a highly conserved group of 49 receptors which act as transcription factors to regulate genetic networks involved in cell growth and differentiation and metabolism.[1] Most are ligand regulated responding to dietary or endocrine signals such as steroid hormones, retinoids, vitamin

D, fatty acids and thyroid hormone. NRs are attractive targets for drug discovery[2,3] and small molecules that regulate them comprise around 13% of current FDA-approved drugs.[4] Originally around half of the NRs had no known natural ligands and were termed Orphan Nuclear Receptors (ONRs).[5] Since most have a ligand binding pocket they provide great potential as novel targets for pharmaceuticals.[6] A key step is to find natural or synthetic regulatory ligands to probe their biology[7,8,9]-a process termed 'reverse endocrinology'.[10] Several have been 'adopted' (or deorphanized) recently, for example NR1H4 (FXR) by bile acids[11] and peroxisome proliferators-activated receptor family (PPAR's, NR1C's.),[12] leading to great advances in understanding and application. We have a particular interest in the Liver Receptor Homolog-1 (LRH-1, NR5A2)[13] and Steroidogenic Factor-1 (SF-1, NR5A1),[14] members of the subfamily V nuclear receptors (NR5A).

1.2.1. Structural features of NRs

NRs typically have a conserved domain structure (Figure 1.1) that includes the N-terminus A/B domain [often containing a ligand-independent activation function-1 (AF-1)]; also N-terminus, highly conserved DNA-binding domain (DBD or C domain), which is composed of two zinc fingers; the C-terminus ligand-binding domain (LBD or E domain), which contains an equally conserved ligand-dependent activation function-2 (AF-2) motif that mediates coactivator interaction; and the D domain, which serves as a flexible hinge between the DBD and LBD.[13,15]

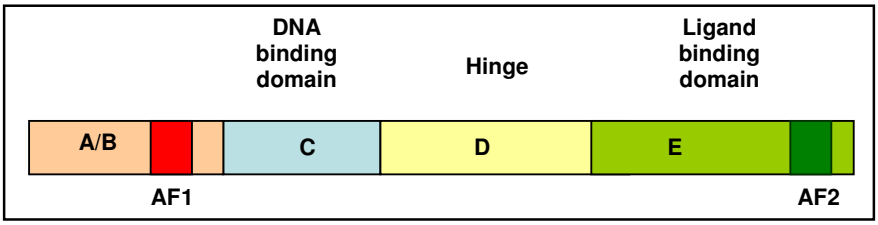


Figure 1.1 Canonical structure of generic nuclear receptor (NR).

The DBD is responsible for DNA response element recognition and dimerization, and the conserved LBD is involved in many overlapping functions including ligand binding, nuclear localization, dimerization, silencing and transactivation.[15] When bound by hormone (or other small lipophilic ligands, including metabolites and certain synthetic ligands), these receptors function as ligand-dependent transcription factors by binding to unique response elements in the promoter of specific target genes.[13,16]

1.2.2. Structural features of the NR5 subfamily in the NRs superfamily

Members of the NR5 family are orphan receptors that belong to one of the four subclasses of the Ftz-F1 subfamily (named for their homology with *Drosophila fushi tarazu* factor-1, the first cloned member of this group). Steroidogenic factor-1 (SF-1, NR5A1) and its closest homolog, liver receptor-homolog-1 (LRH-1, NR5A2) are the only human proteins that belong to this class.[17] These and other NR5A subfamily members are unique in the NR superfamily; however, because they contain a distinctive 26-amino acid motif, called the Fushi Tarazu-Factor1 domain (A box). The A box is located just C-terminal to the conserved zinc finger DNA-binding domain and contact the upstream motif in the binding site, thereby it is thought to be a key protein-protein interaction module (Figure 1.2).[18,19]

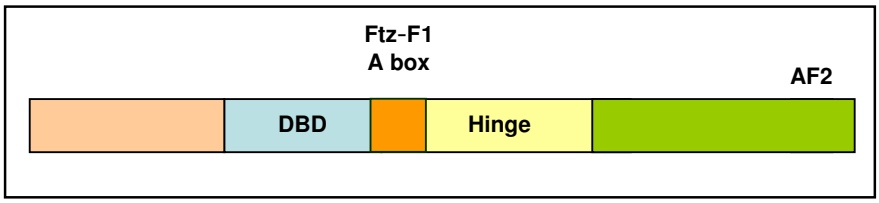


Figure 1.2 Specific structure of NR5A subfamily members.

Although SF-1 and LRH-1 are derived from two different genes, they share a highly conserved DBD (over 95% identity) and moderately conserved LBD (56%). Thus, both receptors can recognize the same DNA sequence and several reports demonstrate that genes expressed in the adrenal, in adipocytes, and in the ovary previously shown to be regulated by SF-1 can also be transactivated by LRH-1.[20-24] On the other hand, their different biological activities are contributed in part by distinct structural features in their LBDs, which recruit specific cofactors to regulate transcription.[25]

1.2.3. Biological functions of ONRs: Liver Receptor Homolog-1 (LRH-1) and Steroidogenic Factor-1 (SF-1)

LRH-1 plays a critical role in embryonic development of the endoderm.[26] In adults it is expressed in the intestine, liver, exocrine pancreas and ovary. It is extensively expressed in the mouse brain.[27] LRH-1 regulates the expression of genes involved in hepatic bile acid biosynthesis,[28] the bile salt export pump[29] and cholesterol homeostasis.[13] Thus, the receptor may be a target for the treatment of cardiovascular disease[30] and cholinostatic liver diease.[31] It is a key controller in the hepatic acute-phase response.[32]

Its regulation of aromatase expression[33] also suggests a possible utility in cancer therapy, particularly human breast carcinomas.[34, 35, 36-39] LRH-1 is expressed in human intestinal crypt cells where it controls cell proliferation and differentiation.[40] Its potential role in gastric cancer has been reviewed.[41] Expression of LRH-1 is found to be substantially raised in human gastric cancer cells,[42] and it influences tumor formation through effects on cell cycle and inflammation.[43] LRH-1 is a key regulator of Mouse Embryonic Stem cell pluripotency and differentiation.[44] It has been shown to be a key regulator of oct-4 expression,[26] and oct-4 is important in the maintenance of adult neural stem cell pluripotency,[45] so there may be applications in neurodegenerative disorders. LRH-1 probably has a key role in ovulation and female fertility, and is a possible target for contraception.[46]

Nuclear receptor SF-1 (NR5A1) plays multiple roles in endocrine development[47,48,49] including sex determination, for example SF-1 knock-out mice were phenotypically female independent of genetic sex,[50] and lack adrenals, gonads and the ventromedial hypothalamic nucleus.[51,50]

SF-1 is an important regulator of mouse ES pluripotence and differentiation.[44] In particular it promotes steroidogenesis demonstrating that is a dominant regulator of the steroidogenic cell phenotype. Forced expression of SF-1 transforms human bone marrow mesenchymal cells into steroidogenic cells.[52, 53, 54,55] Like LRH-1 SF-1 has been shown to regulate oct-4 expression with implications for control of stem cell pluripotence.[56]

SF-1 has an important role in steroid regulation throughout life, particularly *via* its control of the expression of the steroidogenic cytochrome P450 genes in endocrine tissues, such as the adrenal cortex, testes, and ovary.[57, 58] Mutation of the gene in humans correlates with disorders of testes development.[59] It is overexpressed in most cases of childhood adrenocortical tumors, and reverse agonists inhibit proliferation.[60]

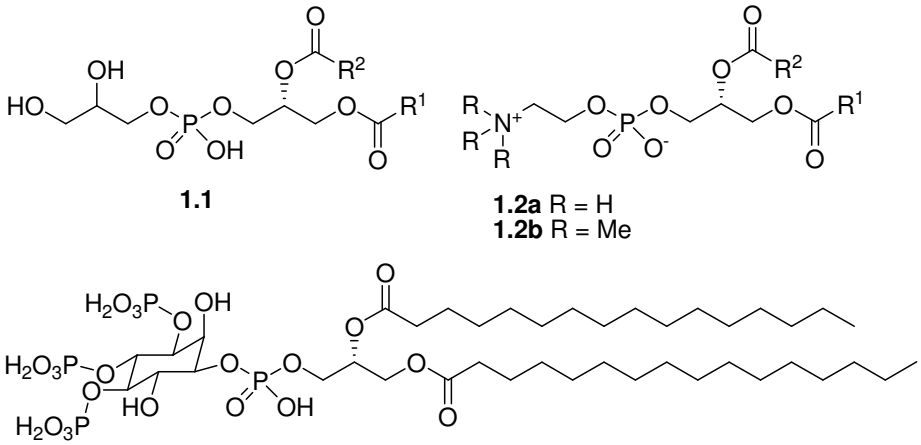
SF-1 is closely involved in the development of endometriosis and endometrial cancers.[61, 62, 63] It is also expressed in the hypothalamus and has been implicated in the regulation of feeding behaviour.[64, 65] A CNS selective knockout of SF-1 in mice has demonstrated strong effects on anxiety, energy homeostasis and appetite.[66, 67]

1.2.4. Mode of action of LRH-1 and SF-1 with suggested regulation of activity

Unlike most NRs, LRH-1 and SF-1 bind to DNA as monomers and show constitutive activation of transcription when expressed in cells.[13,14] Receptor activity can be regulated by phosphorylation,[68] sumoylation[69] or through interaction with the atypical orphan receptors SHP (NR0B1)[70,71] and DAX-1 (NR0B2)[72,73] that lack their own DNA-binding domains.

Although originally defined as ONRs X-ray crystallography coupled with mass spectroscopy (MS) has recently revealed the presence of *E. coli* derived phospholipids phosphatidylethanolamines **1.1** and phosphatidylglycerides **1.2a** in the ligand binding pockets of human LRH-1 and SF-1 (Figure 1.3).[74,75,76,77] The phospholipids identified in the crystals had C16 or 18 acyl groups, some of which were identified as having a *cis* alkene in the Δ9 position, but MS studies showed that a wide range of related phospholipids (C12-C18 acyl groups with various unsaturation) were also bound to the receptors. The binding of phospholipids in SF-1 was shown to strongly activate recruitment of co-activator peptide.[76] Mutation experiments on hLRH-1 showed a correlation between binding of phospholipid and LRH-1 induced activation of gene expression.[77] Exchange of bacterially derived phosphatidyl glyceride **1.1** (Figure 1.3) with inosityl phospholipids (particularly the triphosphate derivative **1.3**)[75] and phosphatidylcholine **1.2b**[78] has been demonstrated for SF-1. In the latter case the exchange had little effect on binding of coactivator peptides.[78] Recently Moore has reported that diundecanoyl (**1.2b**, $R^1 = R^2 = n\text{-}C_9H_{19}$) and dilauroyl (**1.2b**, $R^1 = R^2 = n\text{-}C_{11}H_{23}$) phosphatidylcholine (PC) act as agonists of the LRH-1 receptor and has shown that administration of these lipids to diabetic mice reduces blood glucose levels.[79]

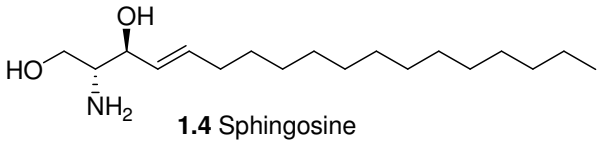
Indirect activation of SF-1 through increased levels of phosphatidylinositol (3,4,5) triphosphate **1.3** induced by a tamoxifen analogue has been suggested as relevant in endometrial cell proliferation.[63] Sphingosine **1.4** has also been reported to bind to SF-1 and suppresses expression of cytochrome P450 17 (CYP17) gene (which is regulated by SF-1) suggesting that it may be an antagonist of SF-1.[80,81,82] Derivatives of **1.4** such as sphingosylphosphorylcholine and *N*-Acyl-**1.4** (ceramides) may also be natural ligands.



1.1

1.2a R = H
1.2b R = Me

1.3 phosphatidylinositol (3,4,5) triphosphate (PI)



1.4 Sphingosine

Figure 1.3 Agonists and antagonists for LRH–1 and SF–1.

Recently, Whitby *et al*. reported the first synthetic small molecule, GSK8470 **1.5** (Figure 1.4), as a potent agonist for LRH-1 (EC_{50} = 430 nM) and SF-1 (EC_{50} = 54 nM). A SAR study on series **1.6** led to the more active analogue **1.7** with EC_{50} = 34 nM for LRH-1 and EC_{50} = 43 nM for SF-1.[83]

Subsequently the herbicide atrazine has also been reported[84-86] to bind to SF-1 and induce aromatase expression at relatively low concentrations (0.1 μM), but as mutations of the LBD of SF-1 have no effect the interaction must be other than with the ligand binding pocket.

Recently *p*-heptyoxyphenol **1.8** was reported as a potent (IC_{50} = 7.2 μM) inverse agonist for SF-1, but with no activity against LRH-1.[87] Expression of several reported SF-1 target genes was suppressed by **1.8** in cell based assays. Although **1.8** was reported to inhibit proliferation of adrenocortial carcinoma cell line H295R, it had the same effect with an SF-1 negative cell line (SW-13).[60]

Several isoquinoline based inverse agonists of SF-1 were discovered through high throughput screening and further SAR studies, of which **1.9** was the most active (IC_{50} = 200 nM).[88, 89] At high levels (10 μM) **1.9** modestly suppressed doxycycline (Dox) induced proliferation of H295R cell line with little effect on the SF-1 negative SW-13 cell line.

Closely related isoquinolines affected both cell lines in a similar way suggesting a non-SF-1 mechanism. The SAR for these series seems complex, for example replacing the methoxy group in **1.9** with ethoxy gave a compound highly active against a range of other receptors, and exhibiting strong cell toxicity suggesting transactivation assay artefacts (e.g. promiscuous inhibition of the reporter system).

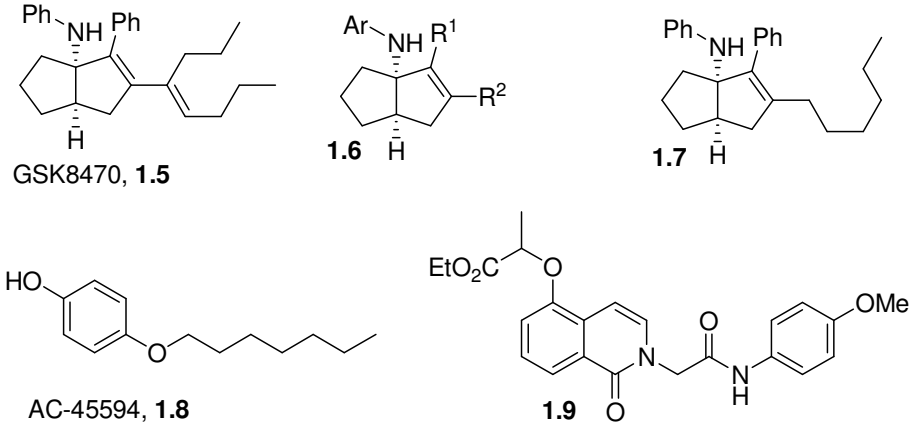


Figure 1.4 Discovery of small molecule agonist and inverse agonists for LRH-1 and SF-1.

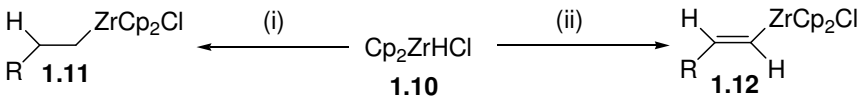
Although GSK8470 **1.5** and related compounds **1.6** have proven to be excellent biological probes for LRH-1 and SF-1 they have a number of drawbacks.

Most important is that they are very unstable to acid making handling difficult and raising doubts about stability during biological application. The series also shows little discrimination between LRH-1 and SF-1.

1.3. Organozirconium chemistry

1.3.1. Formation of carbon-zirconium bonds

The origin of organozirconium chemistry is dated by the preparation of the first organozirconium compounds, zirconocene dibromide ($ZrCp_2Br_2$) and soon after zirconocene dichloride ($ZrCp_2Cl_2$) by Wilkinson and Birmingham in 1954.[90] The use of organozirconium chemistry in organic chemistry originated in the early 1970's with the preparation of $HZrCp_2Cl$,[91] and the observation by Wailes *et al.* of its addition across carbon-carbon double bonds.[92] Extensive studies including synthetic utility of $HZrCp_2Cl$ were started by Schwartz in 1974,[93] whose name has been given to this reagent. Formation of acyclic organozirconium species **1.11** and **1.12** is achieved *via* hydrozirconation of alkanes or alkynes with the Schwartz reagent (Scheme 1.1).

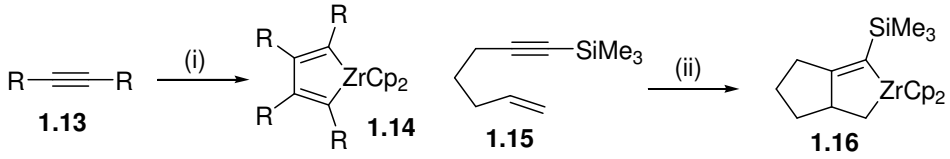


Reagents and Conditions: (i) 1.0 eq alkene, RT; (ii) 1.0 eq alkyne, RT.

Scheme 1.1 Hydrozirconation of alkenes and alkynes.

Products of hydrozirconation can be efficiently converted into organic compounds by reacting with electrophiles (halogens, acid chlorides) as well as with carbenoids (e.g. carbon monoxide).[93,94]

The original method for preparation of zirconacycles from alkenes and alkynes was based on formation of the 14-electron species zirconocene (Cp_2Zr), generated *in situ* by reducing zirconocene dichloride with Mg/Hg amalgams (Scheme 1.2).[95,96]

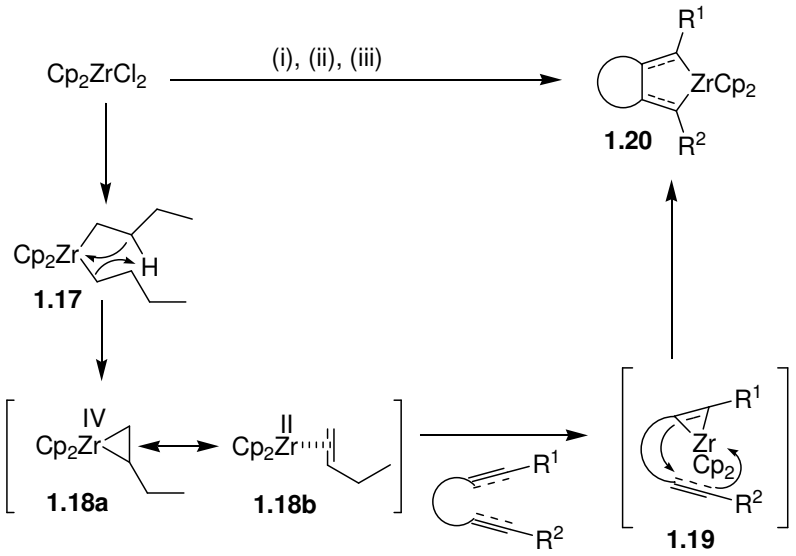


Reagents and Conditions: (i) 0.25 eq Cp_2ZrCl_2, 0.25 eq $HgCl_2$, 1.25 eq Mg, THF;
(ii) 1.0 eq Cp_2ZrCl_2, 1.0 eq $HgCl_2$, 10 eq Mg.

Scheme 1.2 Formation of zirconacycles.

Initially this method was satisfactory for performing co-cyclisations, however, a more experimentally convenient process avoiding the toxicity of mercury was developed,[97] which still remains the most versatile and commonly used today (Scheme 1.3).

Treatment of a cold solution of zirconocene dichloride in THF with 2 equivalents of *n*-BuLi gives dibutyl zirconocene **1.17** also known as the Negishi reagent. Warming to room temperature leads to loss of butane through β-hydrogen abstraction to form the active zirconocene(1-butene) **1.18**. Zirconocene(1-butene) **1.18** can either be considered as Cp_2Zr(IV) **1.18a** or a Cp_2Zr(II) **1.18b** species. The weakly bound butene ligand is readily displaced by alkene or alkyne from the co-cyclisation substrate, followed by carbometallation type reaction to expand the ring to a zirconacycle, such as **1.20** (Scheme 1.3).

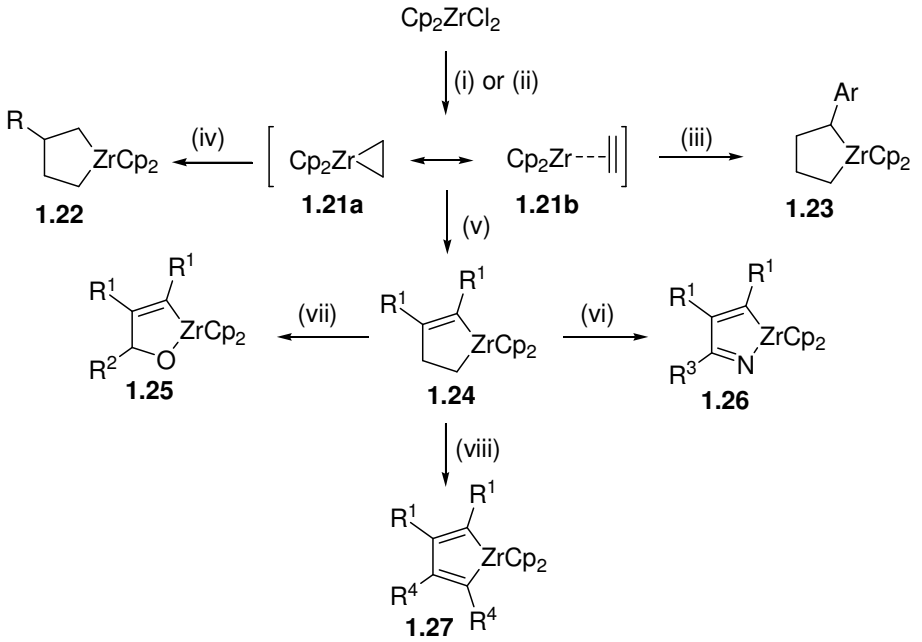


Reagents and Conditions: (i) *n*-BuLi (2.0 eq), THF, −78 ^{o}C, 15 min;
(ii) 1,*n*-diene,-diyne, -enyne; (iii) −78 ^{o}C to RT.

Scheme 1.3 Mechanism for co-cyclisation of unsaturated organic molecules with Negishi reagent.

The development of zirconocene(1-butene) and its wide applicability to reductive couplings of unsaturated organic molecules such as 1,*n*-dienes, -diynes and -enynes has led to rapid expansion of organozirconium chemistry. This method has also been successfully applied in the total synthesis of many natural products.[98-100]

The methodology for formation of monocyclic zirconacycles has also been developed (Scheme 1.4). Synthesis of zirconacyclopentanes **1.22**, **1.23**, zirconacyclopentenes **1.24** and zirconacyclopentadienes **1.27** is achieved by trapping zirconocene ethylene **1.21** with alkenes and alkynes.[101] The complex **1.21** is generated by either treating $ZrCp_2Cl_2$ with two equivalents of EtMgBr[102] or by synthesising zirconocene(1-butene) **1.18** under an atmosphere of ethylene gas.[103] One ethene molecule remains bound to the Zr atom when reaction with alkenes or alkynes occurs, thus leading to the observed selective cross-coupling reactions, so that specific monocycles **1.22**, **1.23** or **1.24** can be formed. Heating the resulting monocycle in the presence of aldehydes, nitriles or other alkynes results in the loss of ethane allowing the formation of unsymmetrical zirconamonocycles,[104] such as **1.25**, **1.26** and **1.27**.



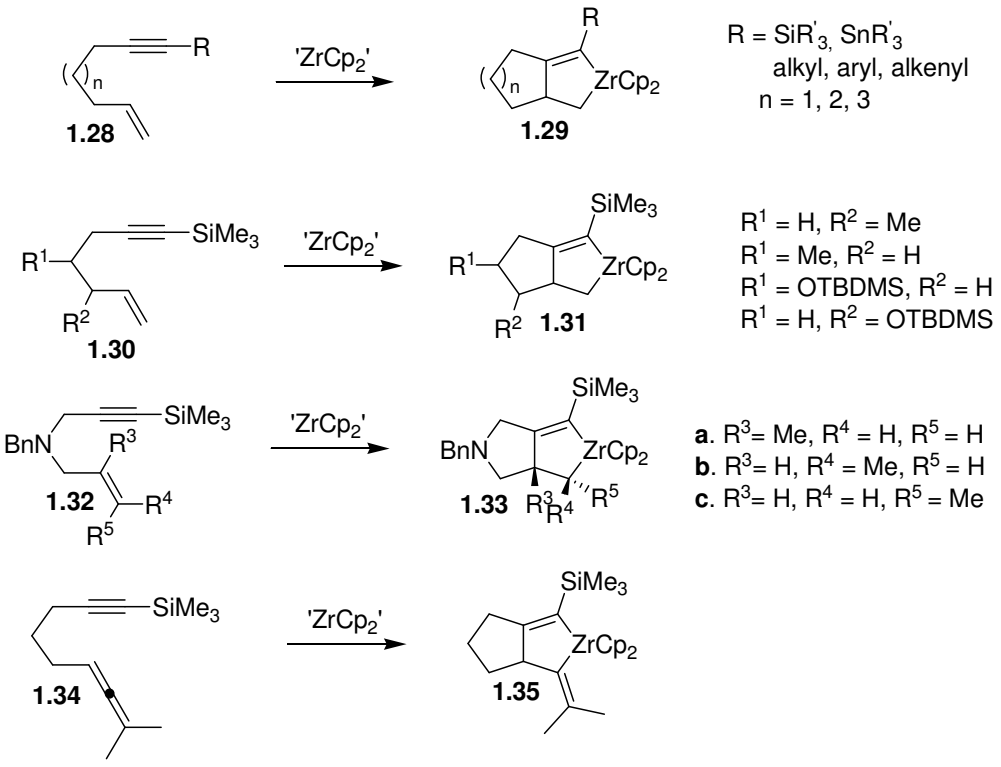
Reagents and Conditions: (i) 2.0 eq *n*-BuLi, −78 °C to RT, under an atmosphere of ethene; (ii) 2.0 eq EtMgBr, −78 °C to RT, 1 h; (iii) H_2CCHAr, 0 °C; (iv) H_2CCHR, 0 °C; (v) R^1CCR^1, 0 °C; (vi) R^3CN, 25 °C; (vii) R^2CHO, 50 °C; (viii) R^4CCR^4, 50 °C.

Scheme 1.4 Access to monocycles by trapping zirconocene ethylene complex.

1.3.2. Carbocycle formation by zirconocene mediated co-cyclisation of enynes

Both 1,6- and 1,7-enynes **1.28** are excellent substrates for zirconocene(1-butene) mediated co-cyclisation to afford the corresponding bicyclic zirconacycles usually in high yields.[105,106] Although preparation of bicyclic zirconacyclopentenes is limited by the ring size, a wide variety of substituents on both the ring and the alkyne are tolerated (Scheme 1.5).[105,107] Furthermore, substitution on the alkyne is required as terminal alkynes fail to cyclise under these conditions. Enynes with an α-substituent to the alkene show a high level of diastereoselectivity through control of the ring junction formed in the cyclisation step.[107-110]

Examples carrying ring substitutions such as alkyl, protected alcohol, amine and amide are also reported in the literature. Cyclisation of precursors possessing substitution on the double bond are known, including unusual examples such as allene **1.34**.[105]



Scheme 1.5 Variability of substituents on enynes.

1.4. Elaboration of unsaturated zirconacycles

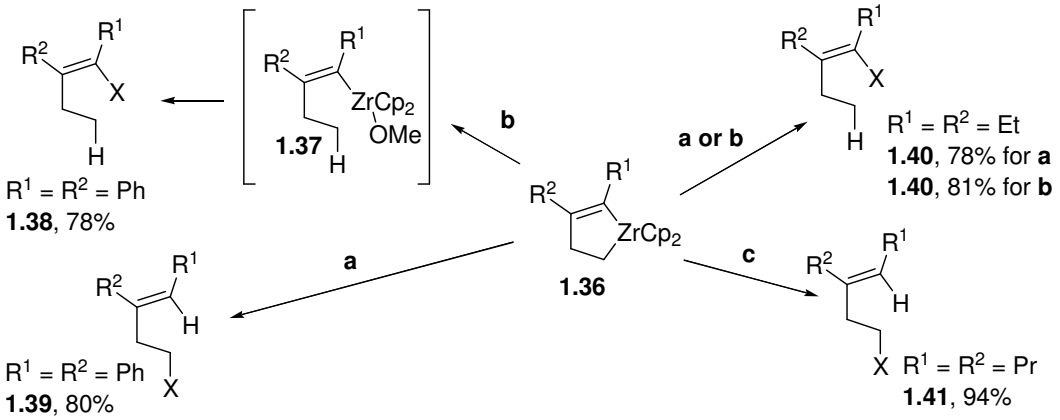
Although a broad spectrum of unsaturated organic molecules can be co-cyclised in intra- and/or inter-molecular fashion to give a variety of metallacycles, the potential of organozirconium chemistry is significantly increased by the ability to functionalise the C-Zr bond. Over the past two decades many sophisticated methods for elaboration of the C-Zr bond have been developed which allow access to a great deal of useful organic products. The selected methods will be concisely overviewed throughout the following section.

1.4.1. Protonation and halogenation

The simplest functionalisation of zirconacycles is protonation to give the corresponding hydrocarbon, which can be done under acidic or basic conditions. The widely used quenches are: MeOH, aqueous solution of $NaHCO_3$, aq HCl or aq H_2SO_4. Choice of the quenching conditions is dictated by the acid/base stability of the products.

The analogous reaction with MeOD, D_2O, DCl or D_2SO_4 can be used to perform deuterolysis. Incorporation of deuterium atom into products is very often a valuable tool for the determination of mechanisms.

Methodology for selective monohalogenation of zirconacyclopentenes has been explored by Takahashi (Scheme 1.6).[111] Depending on the reagent used and the substituents present on the double bond, halogenation can be regiospecific to give either vinyl halides **1.38**, **1.40** or the alkyl halides **1.39**, **1.41** in yields ranging from 78 to 94%.[112,113] With aryl substituents present on the double bond, vinyl halide is formed by method **b.** Selective methanolysis of the zirconium-alkyl bond was observed to form the alkoxy-zirconocene intermediate **1.37**, subsequent treatment of such obtained species with iodine resulted in alkenyl iodide **1.38** in excellent yield.[114] Direct halogenation of the zirconacyclopentene **1.36** with iodine, followed by acidic protonolysis gave the alkyl iodide with high selectivity. With alkyl substituents present on the double bond, the regioselectivity can be controlled by use of either I_2 or CBr_4.

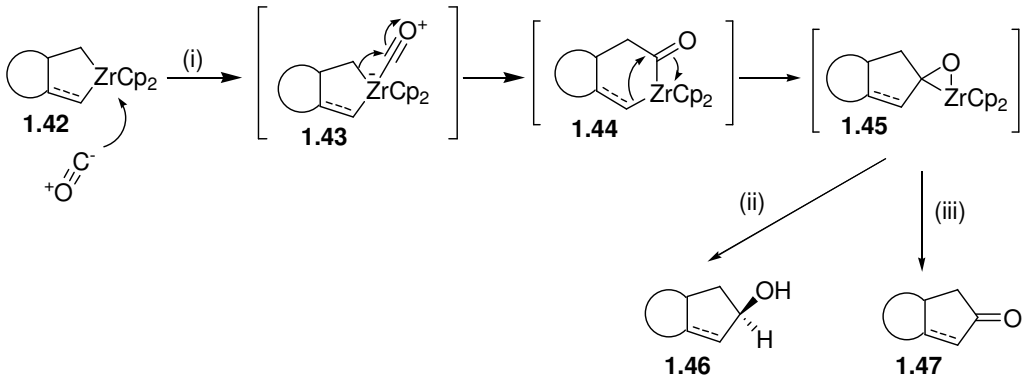


Reagents and Conditions: method **a**: 1.2 eq I_2, then HCl; method **b**: 1.5 eq MeOH, then 1.2 eq I_2; method **c**: CBr_4 or CCl_3Br.

Scheme 1.6 Selective halogenation of zirconacyclopentenes.

1.4.2. Carbonylation and isocyanide insertion

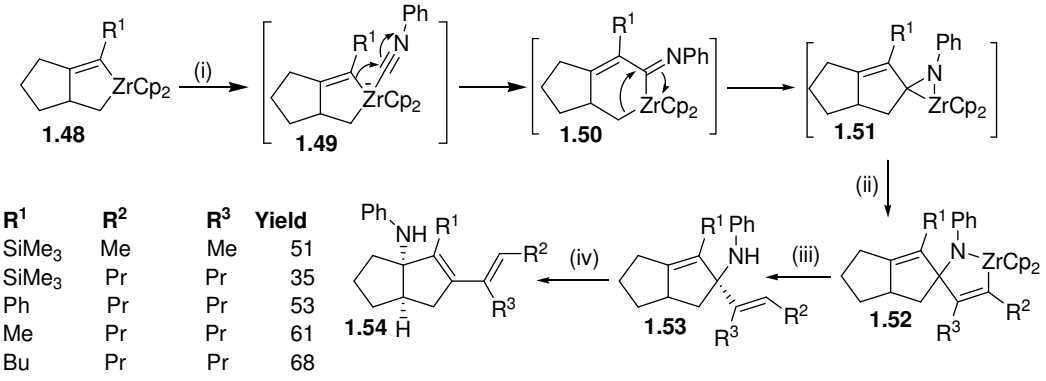
One of the earliest and most widely used methods for elaboration of zirconacycles is carbonylation.[96,115] The availability of the d-orbital on the zirconium atom and carbene-like nature of carbon monoxide are essential for the reaction to occur. Carbon monoxide donates a lone pair of electrons into the vacant d-orbital of the Zr atom to give the complex **1.43** (Scheme 1.7). Subsequent migration of the sp^3 carbon-zirconium bond gives the zirconocene acyl complex **1.44** and allows the zirconium atom to return to its favourable 16-electron state. Rearrangement to the zirconocene η^2-ketone complex **1.45** then follows, which can be converted to cyclopentanol **1.46** or cyclopentanone **1.47** on protonolysis, or oxidative work-up with iodine (prolonged exposure to CO is an alternative method), respectively.[116,117]



Reagents and Conditions: (i) CO, −78 ^{o}C; (ii) 3 M HCl; (iii) RT, I_2.

Scheme 1.7 Carbonylation of zirconacycles.

Insertion of isocyanides into zirconacycles is the analogous reaction to carbonylation, since isocyanides are isoelectronic with carbon monoxide (Scheme 1.8).



R^1	R^2	R^3	Yield
$SiMe_3$	Me	Me	51
$SiMe_3$	Pr	Pr	35
Ph	Pr	Pr	53
Me	Pr	Pr	61
Bu	Pr	Pr	68

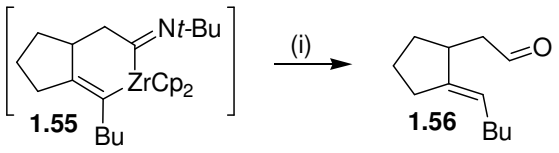
Reagents and Conditions: (i) PhNC, THF, −35 ^{o}C; (ii) Alkyne, reflux; (iii) MeOH; (iv) SiO_2 or spontaneous.

Scheme 1.8 Isocyanide insertion into zirconacyclopentenes.

Insertion of phenyl isocyanide into zirconacyclopentanes affords iminoacyl complex **1.50**, which slowly rearranges to give η^2-imine complex **1.51** (Scheme 1.8).[118]

Trapping the complex **1.51** with alkyne gives the expanded α,β-unsaturated η^2-imine complex **1.52**. Subsequent methanolysis provides diallylic amine **1.53**, which undergoes an unusual *anti*-1,3 allylic shift of amine[119] either on silica or spontaneously to give the tertiary amine product **1.54**.

Insertion of *t*-butyl isocyanide occurs specifically into the alkyl-zirconium bond to give the iminoacyl intermediate **1.55**, which does not rearrange to η^2-imine complex (Scheme 1.9). Protonolysis with HCl gave aldehyde **1.56**.



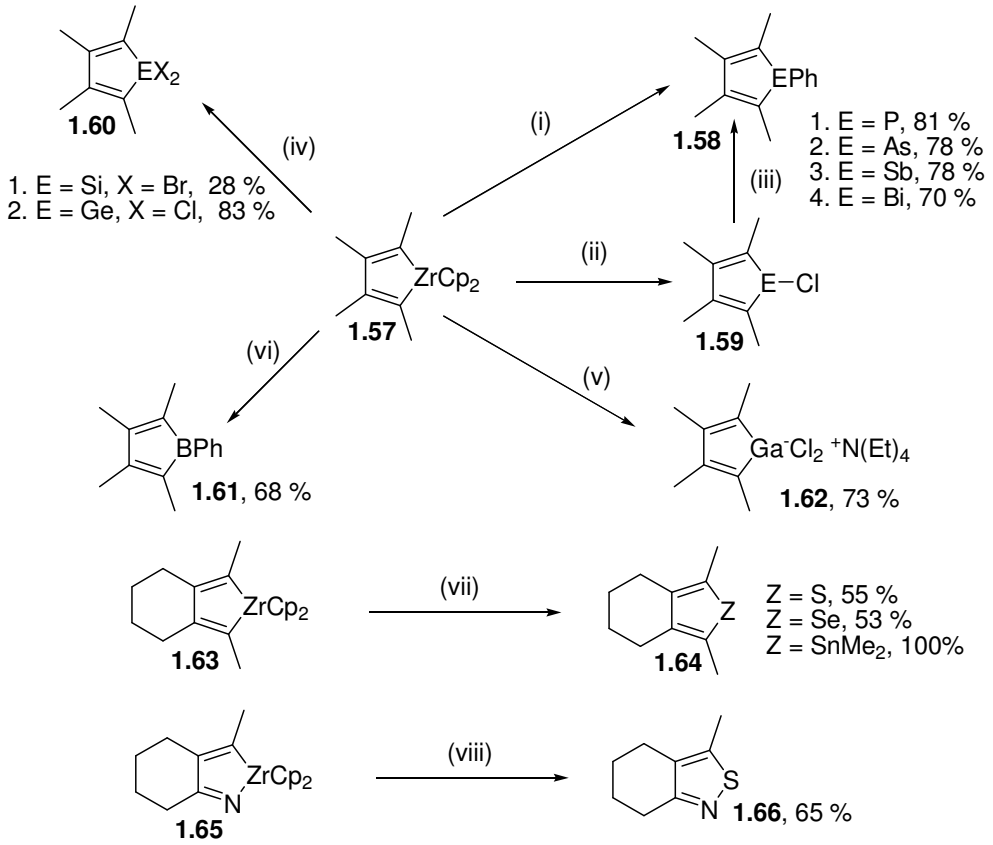
Reagents and Conditions: (i) 2 M HCl, RT.

Scheme 1.9 *t*-Butyl isocyanide insertion into zirconacyclopentaene complex.

More recently copper-mediated insertion of isocyanides into zirconacyclopentadienes has been reported.[120]

1.4.3. Metathesis to main group elements

Elaboration of both C-Zr bonds present in zirconacycles *via* exchange of the zirconium atom for a main group element provides a range of highly functionalized, often unusual, heterocycles (Scheme 1.10).



Reagents and Conditions: (i) for P, As: $PhECl_2$, 25 ^oC; (ii) for Sb, Bi: ECl_3, 25 ^oC; (iii) PhLi; (iv) a. for Si: $SiBr_4$ (neat), 150 ^oC, 2 d; b. for Ge: $GeCl_4$, 25 ^oC, 2 min; (v) $GaCl_3$, 25 ^oC, 5 min, then $(Et)_4N^+Cl$; (vi) $PhBCl_2$, 25 ^oC, 1 h; (vii) a. for S, Se: Z_2X_2, 25 ^oC, 1 h; b. Me_2SnBr_2, 25 ^oC, 2 d; (viii) S_2Cl_2, 25 ^oC, 1 h.

Scheme 1.10 Heterocycle synthesis *via* metathesis with main group elements.

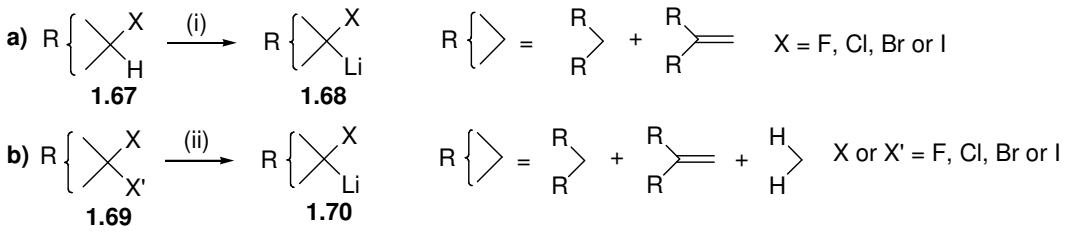
Nugent, who extensively developed this area, demonstrated the facile preparation of main group heterocycles **1.58**, **1.60 – 1.62**, **1.64**, **1.66** from zirconacyclopentanes, -enes and -dienes (Scheme 1.10).[108,121-123] The group 15 phenyl derivatives **1.58.1**-**4**, can be prepared by reaction of a zirconacycle with the element dichloride or trichloride. The latter case requires treatment of the cyclic monochloride **1.59** with PhLi. Group 14 and 16 compounds can also be prepared. For group 13 elements, borole **1.61** and gallole salt **1.62** can be synthesised, and the latter compounds are stable and do not undergo Diels-Alder reactions.

1.4.4. Carbenoid insertion

Organic species which exhibit reaction qualitatively similar to those of carbenes are referred to as carbenoids. Lithium carbenoids show the greatest utility in organic synthesis, although carbenoids with metals such as potassium, sodium and tin are known.[124] Insertion of lithium carbenoids into organozirconocenes has been extensively explored by Whitby[118] and a great deal of this thesis is related to this theme.

1.4.4.1. Synthesis and reactivity of lithium carbenoids

Lithium halocarbenoids are thermolabile molecules in which a single carbon atom is substituted with a halogen and lithium atom. These species are formed at temperatures usually below –78 °C by either deprotonation or halogen-lithium exchange.

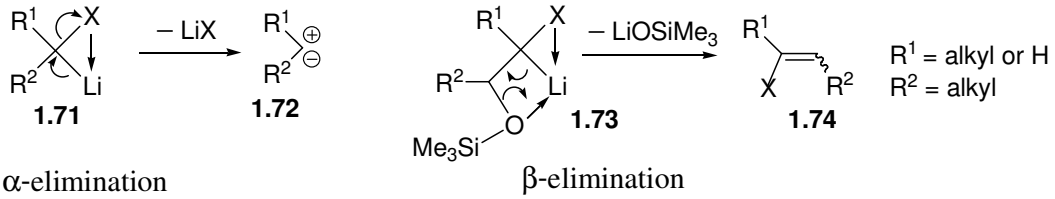


Reagents and Conditions: (i) 1.0 eq R_2NLi, < −70 ^oC; (ii) 1.0 eq RLi, ~ −100 ^oC.

Scheme 1.11 Formation of lithium carbenoids.

Deprotonation of an organohalide with an organolithium or lithium amide base generates the carbenoid molecule (equation **a**, Scheme 1.11)[125,126] A limitation of this method is the low acidity of the proton, which makes deprotonation at low temperatures difficult. Alternatively, halogen-lithium exchange of a *gem*-dihalo-compound leads to the same type of structure (equation **b**, Scheme 1.11)[127] however the main drawback related to this method is α-metallation.[128]

Carbenoids are usually unstable at temperatures higher than –70 °C and undergo decomposition through various reactions (Scheme 1.12). α-Elimination, which yields the highly reactive carbene species **1.72** is the main decomposition reaction.[129] For certain carbenoids β-elimination is an alternative route for decomposition and can result in formation of alkenes **1.74** (Scheme 1.12).[129]



Scheme 1.12 Decomposition routes for carbenoids.

Carbenoids show amphiphilic nature therefore they can react as both nucleophiles and as electrophiles.[124] Carbenoids generally undergo three main types of reaction:[126,130,131]

- **a.** Nucleophilic reactions such as alkylations and acylations with retention of the configuration at the carbenoid centre.
- **b.** Electrophilic behaviour includes reactions with strong nucleophiles with inversion of the configuration at the carbenoid centre.
- **c.** Combined nucleophilic and electrophilic properties allow carbenoids to insert into single and double bonds.

1.4.4.2. Allyl and alkyl carbenoid insertion into zirconacycles

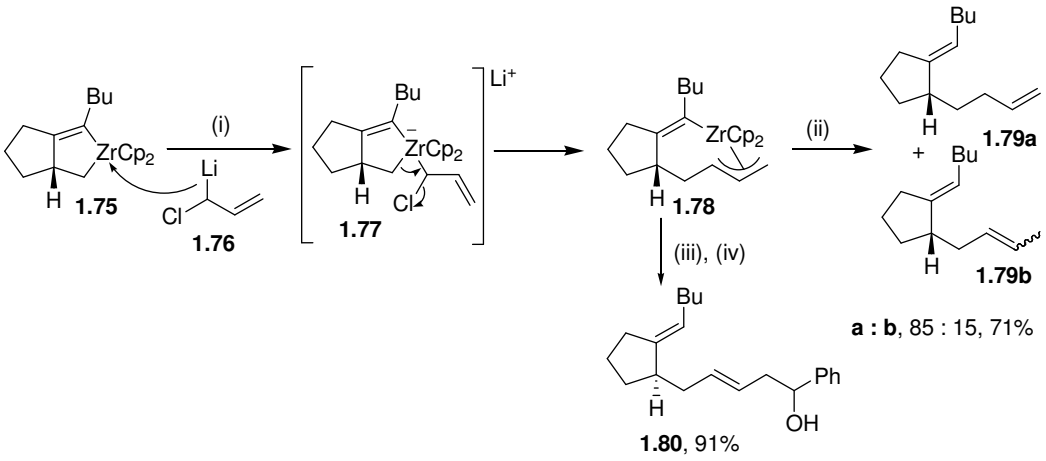
Selective means of elaborating carbon-zirconium bonds through regioselective insertion of alkyl and allyl carbenoids into unsymmetrical zirconacycles have been reported.[132,133] Distinct substitution patterns of zirconacycles and different electronic properties of the carbenoids account for complete selectivity observed in most of the investigated examples where a single product is isolated.

1.4.4.2.1. *Allyl carbenoid insertion into zirconacyclopentenes*

The first report on carbon-carbon bond forming reactions *via* insertion of carbenoids into organotransition metal complexes was by Negishi *et al.*[134] The authors describe the insertion of α- and γ-haloorganolithiums into acyclic organozirconocene derivates to give a good yield of alkenes and allenes on acid quench.

Whitby extended this methodology to the insertion of a wide range of carbenoids into zirconacycles. Initial nucleophilic attack of allyl carbenoid (lithium chloroallylide) **1.76** onto the Zr atom in zirconacyclopentene **1.75** generates an 18-electron 'ate' complex **1.77** (Scheme 1.13).[135] A 1,2-metallate rearrangement[136] with loss of the leaving group affords zirconocene η^3-complex **1.78**. Methanolysis of the allyl zirconium complex affords an 85 : 15 mixture of alkene products **1.79a** and **1.79b** in 71% yield. Further elaboration of the allyl zirconium complex by benzaldehyde insertion provides the alcohol **1.80** in excellent yield.

Extensive elaborations of this methodology include insertions of various allyl carbenoids into a wide range of saturated and unsaturated zirconacycles and trapping the resulting zirconocene η^3-complex with different electrophiles such as ketones, iminium and thienium ions and through the Lewis acid promoted addition of aldehydes, acetals and orthoesters.[137-139]



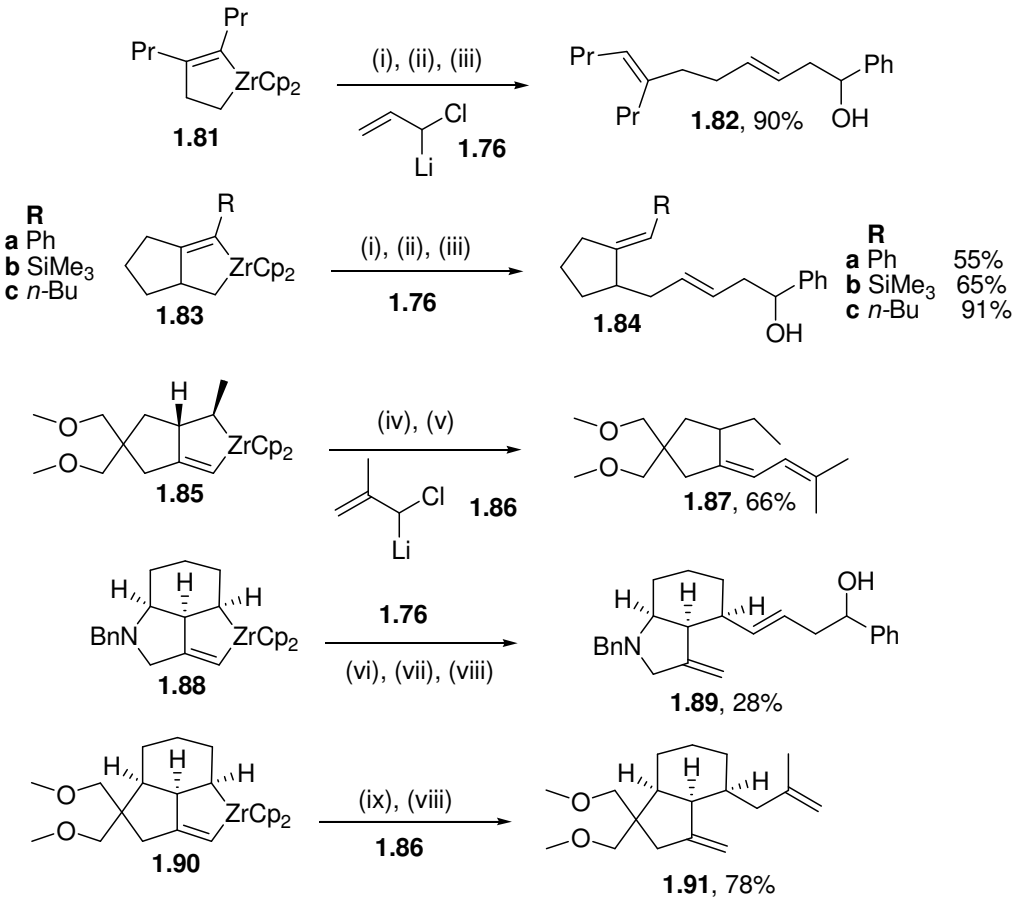
Reagents and Conditions: (i) 1.1 eq CH_2CHCH_2Cl, LiTMP, –78 to –60 ^oC, 1 h; (ii) MeOH, 48 h, RT; (iii) 1.5 eq PhCHO, 1.5 eq $BF_3{\cdot}Et_2O$, –60 ^oC to RT, 2 h; (iv) MeOH, aq $NaHCO_3$, RT, 16 h.

Scheme 1.13 Insertion of lithium chloroallylide into unsaturated zirconacycle.

1.4.4.2.2. *Allyl and alkyl carbenoid insertion into α-substituted zirconacyclopentenes*

A study of lithium chloroallylide and chloromethylallylide insertion into a wide range of unsymmetrical zirconacyclopentenes resulted in a very good regioselectivity. In all cases the final product was obtained as a single regioisomer (Scheme 1.14).[132,135] Complete selectivity for the alkyl zirconium bond was observed when the vinyl carbon α- to the zirconium centre was substituted (R' = Ph, $SiMe_3$, *n*-Bu) in both monocyclic **1.81** and bicyclic zirconacycles **1.83a**, **b**, **c** to provide the corresponding products **1.82** and **1.84a**,**b**, **c**. Zirconacyclopentene **1.85** with substitution at the alkyl carbon α- to

zirconium showed complete regioselectivity for the alkenyl zirconium bond. Further studies however, revealed that the nature of substitution at the alkyl carbon adjacent to Zr was also important, and exclusive insertions into the most hindered alkyl zirconium bond were observed (zirconacycles **1.88**, **1.90**).

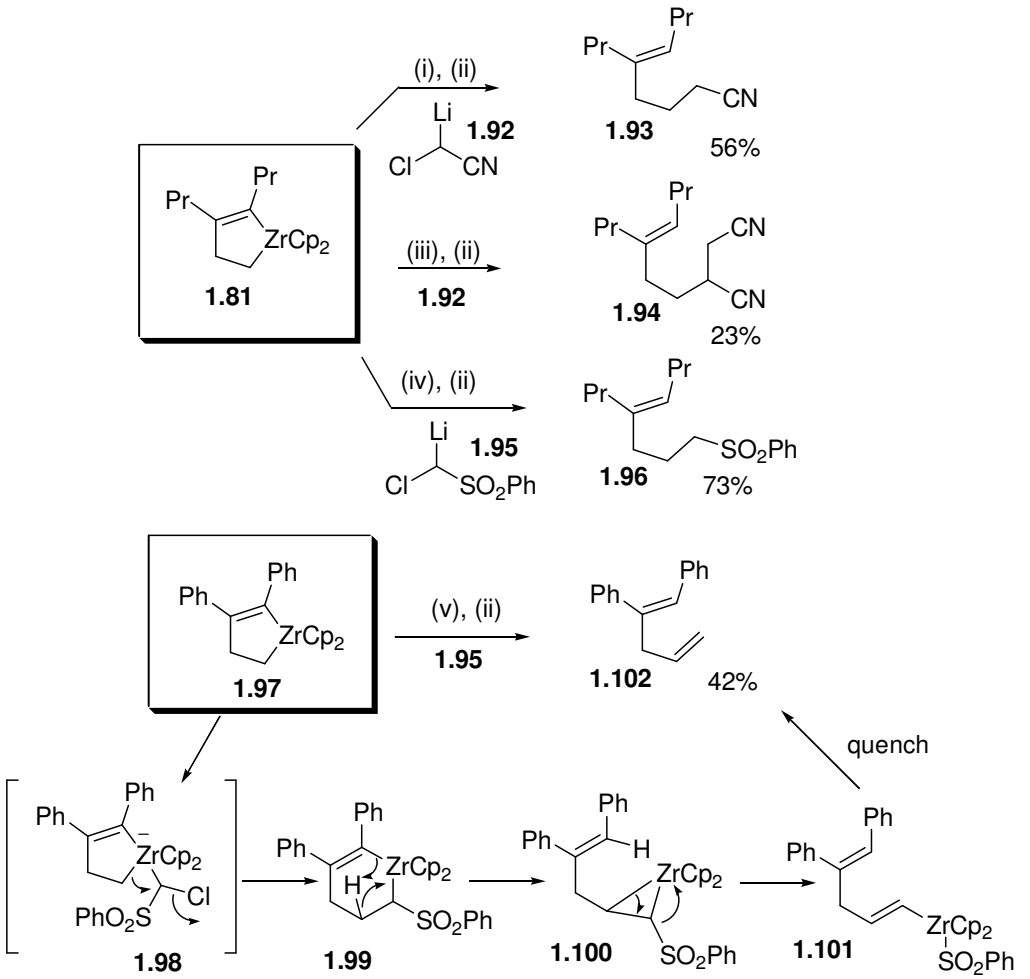


Reagents and Conditions: (i) 1.1 eq CH_2CHCH_2Cl, LiTMP, −78 to −60 ^oC, 1 h; (ii) 1.5 eq PhCHO, 1.5 eq $BF_3{\cdot}Et_2O$, −60 ^oC to RT, 2 h; (iii) MeOH, aq $NaHCO_3$, RT, 16 h; (iv) $CH_2C(CH_3)CH_2Cl$, LDA, −78 ^oC to RT, 2 h; (v) AcOH, RT, 24 h; (vi) 5 eq LiTMP, −78 to −30 ^oC, 2 h; (vii) 5 eq PhCHO, 5 eq $BF_3{\cdot}Et_2O$, −78 ^oC to RT, 5 h; (viii) MeOH, aq $NaHCO_3$, RT, 1 h; (ix) $CH_2C(CH_3)CH_2Cl$, LDA, −100 ^oC to −60 ^oC, 2 h.

Scheme 1.14 Regiochemistry of allyl carbenoid insertion into zirconacyclopentenes.

Insertion of alkyl carbenoids: lithiated chloroacetonitrile **1.92** and lithiated chloromethyl phenyl sulfone **1.95** into monocyclic zirconacyclopentene **1.81** afforded products **1.93** and **1.96** in good and very good yield, respectively (Scheme 1.15).[140] A double insertion was observed for lithiated chloroacetonitrile when used in excess to provide the double insertion product **1.94** in low yield.

Also elimination of the sulfone group from the zirconacycle **1.100** upon warming to RT is observed to give product **1.102** in moderate yield. This process can be explained by a novel endocyclic cyclometallation process[141] to afford the zirconocene η^2-alkene complex **1.100**, which allows the sulfone group to be eliminated **1.101**.

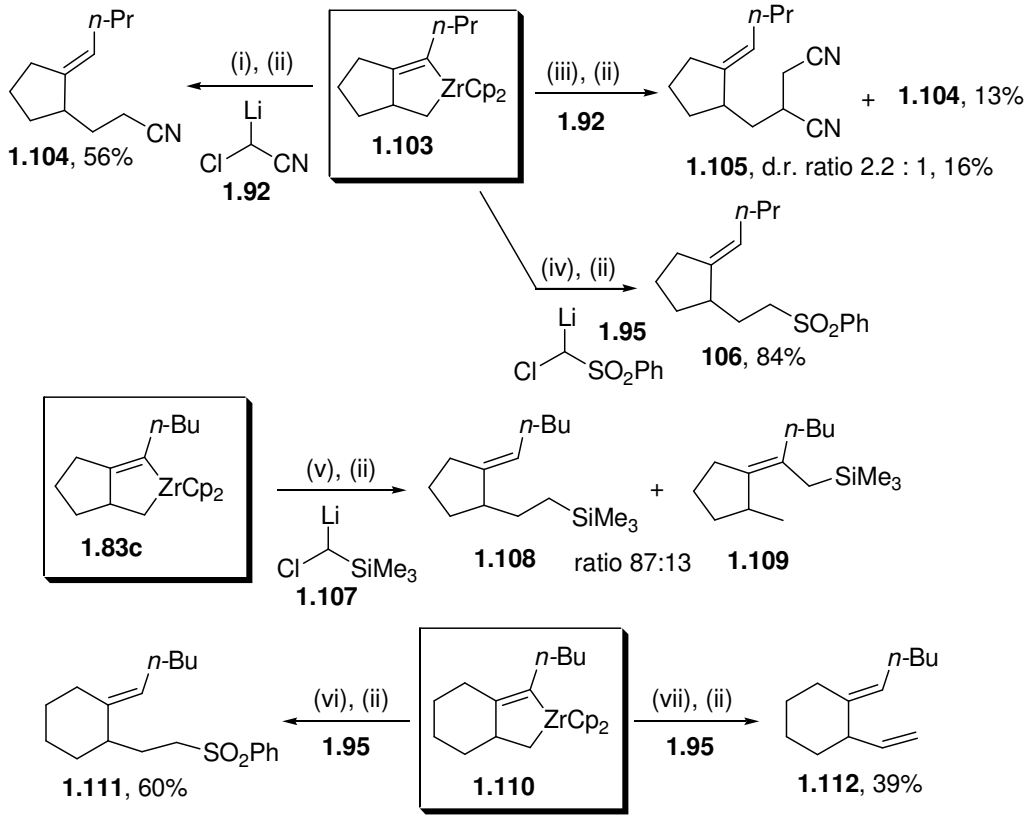


Reagents and Conditions: (i) 1.0 eq $ClCH_2CN$, LDA, −85 °C, 10 min; (ii) MeOH, aq $NaHCO_3$, RT, 16-24 h; (iii) 3.2 eq $ClCH_2CN$, LDA, −78 °C, 2 h, (iv) 2.2 eq $ClCH_2SO_2Ph$, LDA, −78 °C, 2.5 h; (v) 1.0 eq $ClCH_2SO_2Ph$, LDA, −78 °C to RT, 16 h.

Scheme 1.15 Regiochemistry of alkyl carbenoid insertion into monocyclic zirconacyclopentenes.

The insertion of electron rich and electron poor alkyl carbenoids into bicyclic zirconacycles **1.83c**, **1.103** and **1.110** has been examined (Scheme 1.16).[133,140] Insertion of lithiated chloroacetonitrile **1.92** and lithiated chloromethyl phenyl sulfone **1.95** (electron poor carbenoids), into zirconacyclopentenes **1.103** and **1.110** was successful and afforded products **1.104**, **1.106** and **1.111** in reasonable yields, and observed regioselectivity for the alkyl zirconium bond in all examples.

Treatment of zirconacycle **1.103** with five equivalents of lithiated chloroacetonitrile **1.92** resulted in double carbenoid insertion product **1.105**, isolated in low yield as a separable 2.2 : 1 mixture of diastereoisomers (Scheme 1.16).



Reagents and Conditions: (i) 1.0 eq $ClCH_2CN$, LDA, −78 ^oC, 30 min; (ii) MeOH, aq $NaHCO_3$, RT, 16-24 h; (iii) 5.0 eq $ClCH_2CN$, LDA, −78 ^oC, 45 min; (iv) 2.0 eq $ClCH_2SO_2Ph$, LDA, −78 ^oC to −20 ^oC over 1 h, −20 ^oC for 4 h, 0 ^oC for 2 h; (v) 1.1 eq $ClCH_2SiMe_3$, LDA, −78 ^oC for 30 min, then to RT; (vi) 1.3 eq $ClCH_2SO_2Ph$, LDA, −78 ^oC, 2 h; (vii) 1.5 eq $ClCH_2SO_2Ph$, LDA, −78 ^oC to RT over 16 h.

Scheme 1.16 Regiochemistry of alkyl carbenoid insertion into bicyclic zirconacyclopentenes.

Different conditions were required for efficient insertion of lithiated chloromethyl phenyl sulfone **1.95** into zirconacycles **1.103** and **1.110**. In the less constrained system **1.110** insertion occurred at –78 °C to afford sulfone **1.111**, however, for insertion into the more constrained system **1.103**, warming to 0 °C was required to afford sulfone **1.106**. Additionally when the reaction with zirconacyclopentene **1.110** was warmed to room temperature before quenching, the product of sulfone elimination, diene **1.112** was isolated (Scheme 1.16).

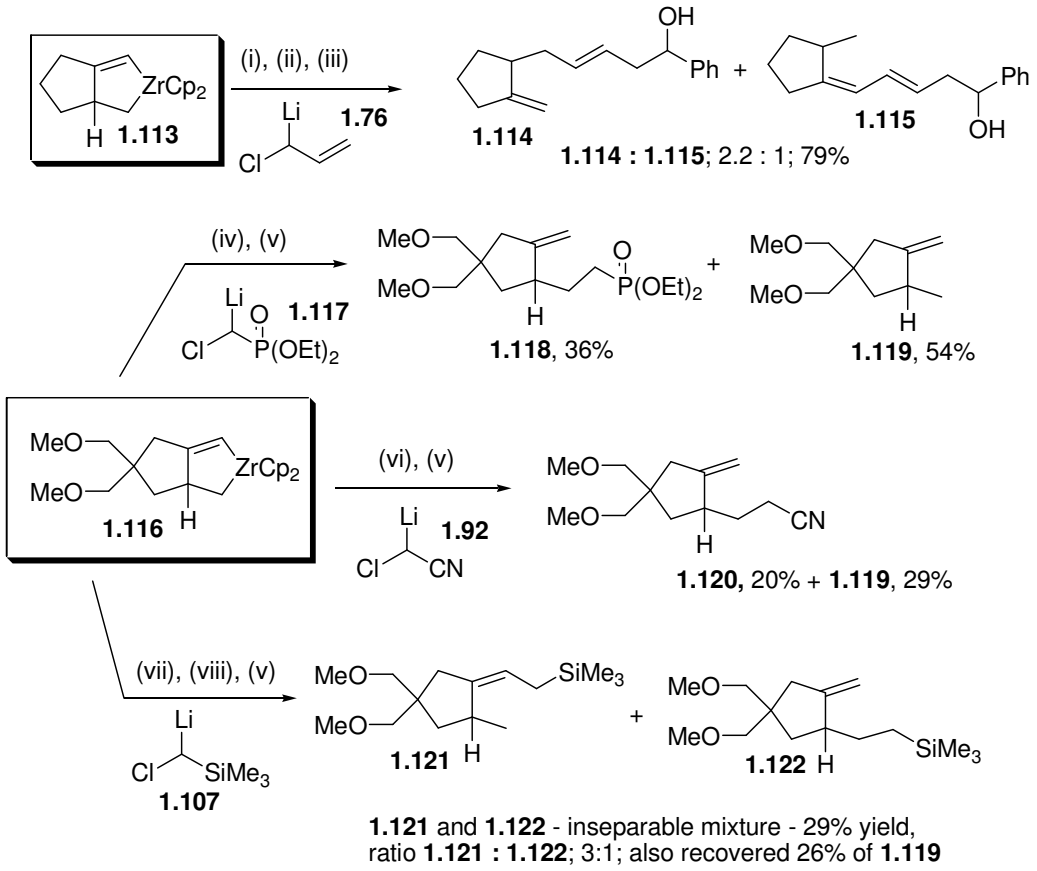
The electron rich silicon substituted carbenoid $Me_3SiCHLiCl$ **1.107** inserts efficiently into **1.83c** to give, on aqueous work-up, mostly the expected product **1.108**, but also a significant amount of the regioisomer **1.109** derived from insertion into the zirconium-alkenyl bond (Scheme 1.16).[133] Although other electron rich carbenoids such as lithiated chloromethyl methyl ether, 2-methoxyethoxymethyl chloride and chloromethyl phenyl sulfide insert into zirconacyclopentenes, the yields are low and the products too messy to properly characterise.

Different models can be used to explain the regiochemistry of carbenoid insertion into zirconacycles.[118,132] Favoured direction of lateral attack is used to explain the selectivity of carbenoid insertion for zirconacycles **1.81**, **1.83**, **1.103**, **1.110**. Considering a carbenoid as an electrophilic species provides an explanation for the selectivity of carbenoid insertion into the more hindered and electron rich C-Zr bond in zirconacycles **1.88** and **1.90**. In the third model, regioselectivity may be determined by the favoured 1,2-metallate rearrangement of a fluxional 'ate' complex created by initial nucleophilic attack of the carbenoid on Zr atom.

1.4.4.2.3. *Allyl and alkyl carbenoid insertion into α-unsubstituted zirconacyclopentenes*

Cyclisation of terminal alkynes with the zirconocene(1-butene) fails[105,142] but reaction of hept-1-en-6-yne with zirconocene(ethylene), followed by heating[104,143] gives the α-unsubstituted zirconacyclopentene **1.113** (Scheme 1.17).

Alternative conditions using a combination of activated magnesium and zirconocene dichloride also allowed co-cyclisation of the terminally unsubstituted enyne but was found to be unreliable and accounts for the poor yields often observed in the series based on zirconacycle **1.113**.[140] Insertion of one allyl and three alkyl carbenoids into zirconacyclopentenes **1.113** and **1.116** gave mixed results (Scheme 1.17). Insertion of lithium chloroallylide **1.76** followed by benzaldehyde gave a 2.2 : 1 mixture of regioisomeric insertion products **1.114** and **1.115**.[132] Insertion of lithiated chloromethylphosphonate **1.117** and lithiated chloroacetonitrile **1.92** (electron poor carbenoids) resulted in insertion with complete regioselectivity for the alkyl zirconium bond to give products **1.118** and **1.120**, respectively. Whereas, the electron rich lithiated chloromethyl trimethylsilane **1.107** displayed moderate 3 : 1 selectivity for the alkenyl zirconium bond, affording an inseparable mixture of compounds **1.121** and **1.122** (Scheme 1.17).[140]



Reagents and Conditions:(i) 1.5 eq CH_2CHCH_2Cl, LiTMP, −78 ^oC to −30 ^oC, 2 h; (ii) 2.0 eq PhCHO, 2.0 eq $BF_3{\cdot}Et_2O$, −78 ^oC to RT, 5 h; (iii) MeOH, aq $NaHCO_3$, RT, 1 h; (iv) 2.0 eq $ClCH_2PO(OEt)_2$, LiTMP, −78 ^oC to RT, 14 hr; (v) MeOH, aq $NaHCO_3$, RT, 16 h; (vi) 1.1 eq $ClCH_2CN$, LiTMP, −78 ^oC, 15 min; (vii) 1.39 eq $ClCH_2SiMe_3$, *s*-BuLi, TMEDA, −78 ^oC, 30 min; (viii) −78 ^oC to RT, 16 h.

Scheme 1.17 Allyl and alkyl carbenoid insertion into zirconacyclopentenes.

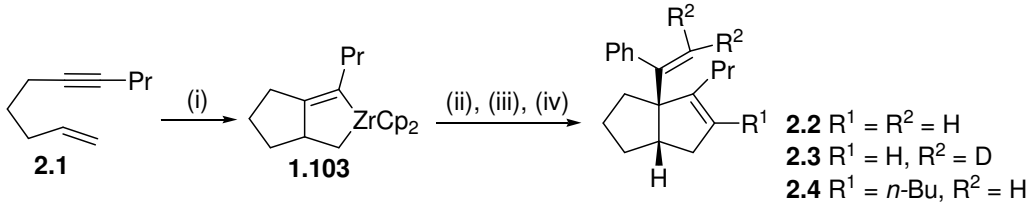
Results from the phosphonate and nitrile carbenoids appear to indicate initial carbenoid insertion occurs on the side of the alkyl zirconium bond. This could be explained by the alkenyl proton being positioned in the direction of lateral attack, preventing initial attack on the alkenyl side of the zirconacycle **1.113**. Thomas also gives the explanation for the results from lithiated chloromethyl trimethylsilane insertion. The β-silicon atom stabilises the 'ate' complex, formed from silyl carbenoid and zirconacycle **1.116**, slowing rearrangement and allowing the more electron rich carbon zirconium bond to migrate.[140]

Chapter 2. Three-component coupling of zirconacyclopentenes, dihalocarbenoids and acetylides *via* rearrangement to a novel zirconium-alkenylidene complex

This chapter presents a sophisticated method for elaboration of zirconacyclopentenes. Sequential addition of 1,1-dihalo-1-lithioalkanes and lithium acetylides to zirconacyclopentenes results in highly convergent, three-component coupling on a zirconocene template. This process is thought to proceed through the rearrangement to a novel zirconium-alkenylidene complex.

2.1. Introduction to research area

Addition of lithium 2,2,6,6-tetramethylpiperidide (LiTMP) to a mixture of zirconacycle **1.103**, formed by co-cyclisation of enyne **2.1**,[105] and dichloromethane (1.5 eq) at –78 °C followed by addition of lithium phenyl acetylide (1.1 eq) and quenching with MeOH and aq $NaHCO_3$ gave the bicyclic compound **2.2** in 52% yield (Scheme 2.1).[140,144] Work-up with MeOD/D_2O gave predominantly the bis-deuterated compound **2.3** (77% bis-deuterated, residue mono-deuterated) suggesting a zirconium-alkenylidene or 1-metallo(Zr or Li)-1-zircono-alkene intermediate. When $BuCHBr_2$ was used as the carbenoid precursor compound **2.4** was obtained in 42% yield. An important observation, with implications for the mechanism, was that the use of 2.2 equivalents of lithium phenyl acetylide substantially increased the yield of **2.4** to 86%. Examination of the reaction mixture after 1.1 equivalents of lithium phenyl acetylide had been added, showed around 50% conversion into **2.4**, with the residue being a product of carbenoid insertion (Scheme 2.1).

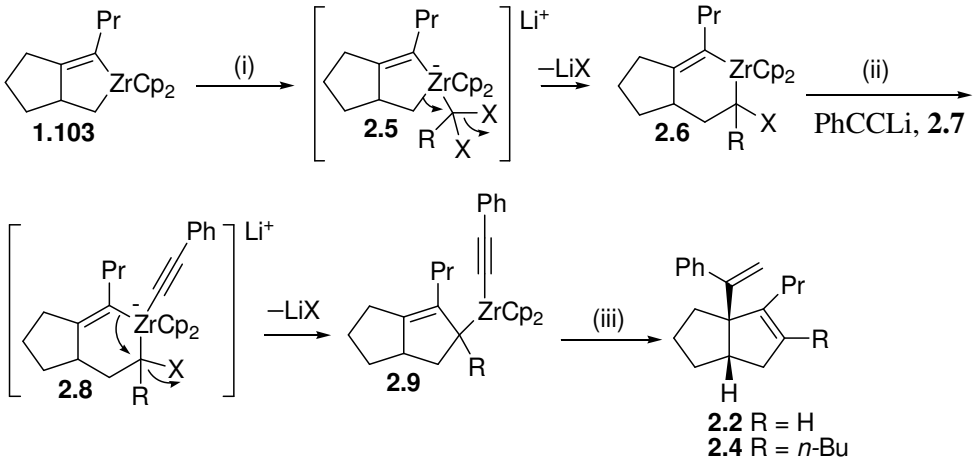


Reagents and Conditions:(i) Cp_2ZrCl_2, 2 eq *n*-BuLi, –78 °C to RT, 3 h; (ii) CHR^1X_2, LDA, –78 °C, 0.5 h; (iii) PhCCLi, –78 °C, 0.5 h; (iv) H_2O or D_2O, –78 °C to RT, 16 h.

Scheme 2.1 Insertion of alkyl lithium carbenoids in the presence of lithium phenyl acetylide.

2.2. Precedent and elucidation of the mechanism

The first proposed step is insertion of 1,1-dihalo-1-lithio species into **1.103** to form the expanded six-membered zirconacycle **2.6** *via* 1,2-metallate rearrangement (Scheme 2.2). After addition of lithiated phenyl acetylide **2.7** to afford the 'ate' complex **2.8** ring closure occurs *via* 1,2-bond migration to give intermediate **2.9**. It has been found from the previous work[145] that the 1,2-rearrangement of the neutral intermediate **2.6** to be slow at –78 °C hence the requirement for the formation of **2.8** before rearrangement (Scheme 2.2).



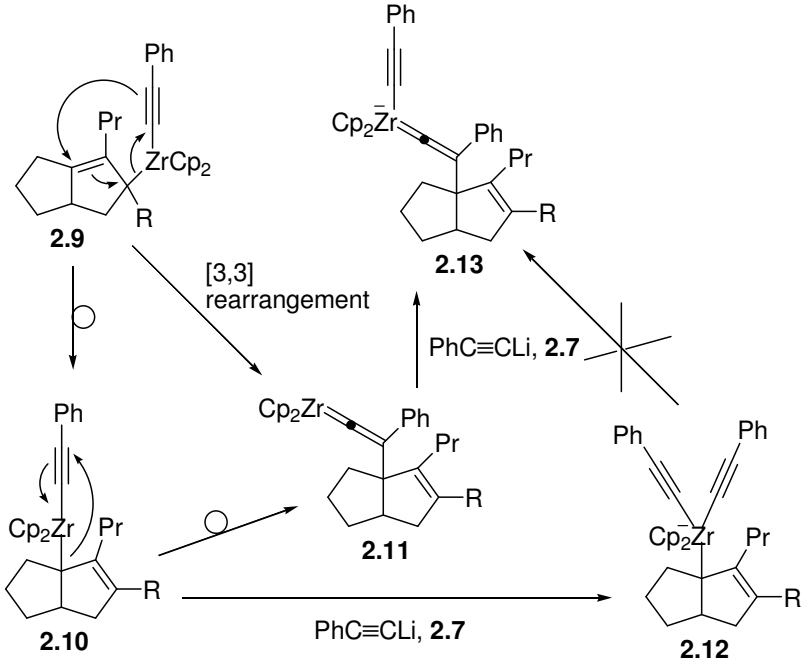
Reagents and Conditions:(i) $CHRX_2$, LDA (or LiTMP), –78 ^oC, 0.5 h;
(ii) PhCCLi, **2.7**, –78 ^oC, 0.5 h; (iii) H_2O, –78 ^oC to RT, 16 hr.

Scheme 2.2 Initial stages of the three-component coupling on zirconocene.

Initially a 3,3-sigmatropic Cope-type rearrangement of **2.9** to the Zr-alkenylidenate **2.13** was suspected (Scheme 2.3), but theoretical calculations indicated it to have a very high activation energy, inconsistent with the low temperature at which the reaction occurs.[140] Successive 1,3-migration of the zirconium to the ring junction to give **2.10** followed by a 1,3-alkyl shift from the metal to the beta-position of the alkyne **2.11** is an alternative (Scheme 2.3).

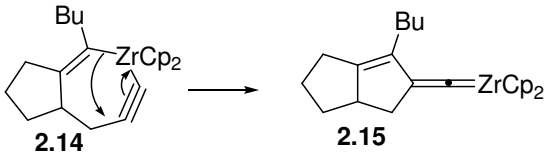
The failure to trap the supposed alkenylidene intermediate **2.11** with alkynes or carbonyl compounds[144] indicated that even if formed it must be rapidly trapped by lithiated alkyne as the ate complex **2.13**. Indeed calculations indicate this to be a very favourable process and could account for the need for two equivalents of the acetylide. It is not expected for complex **2.13** to show normal metal carbene reactivity as it lacks the empty orbital on the metal required for concerted [2+2] additions to be allowed.

Surprisingly, attempts to trap the intermediate **2.13** with electrophiles such as methyl iodide, NBS and benzaldehyde also failed.



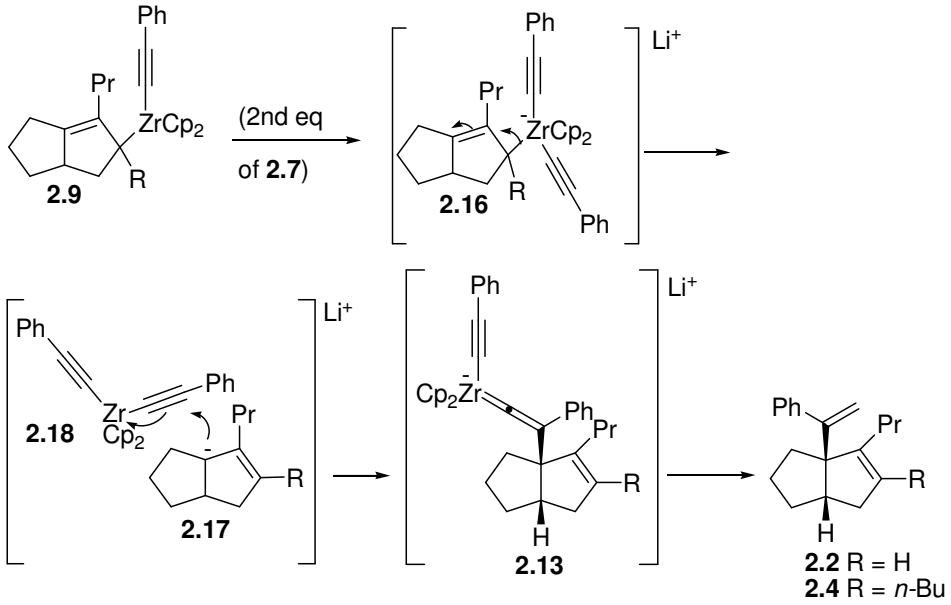
Scheme 2.3 Possible 3,3-sigmatropic rearrangement of 2.9 to give 2.13.

There is also precedent for the second migration in the ring contraction of zirconacycle **2.14** to afford a zirconium alkenylidene complex **2.15** (Scheme 2.4),[146] and similar transformations are known for mid-/late-transition-metal complexes.[147,148]



Scheme 2.4 Zirconocene-alkyne to -alkylidene rearrangement.

We would not expect the 'ate' complex **2.12** to make a 1,3-alkyl shift as it lacks the empty orbital on the metal which makes this a symmetry allowed process. Therefore it is believed that addition of the second equivalent of lithiated alkyne occurs before rearrangement to give the intermediate **2.16** (Scheme 2.5).

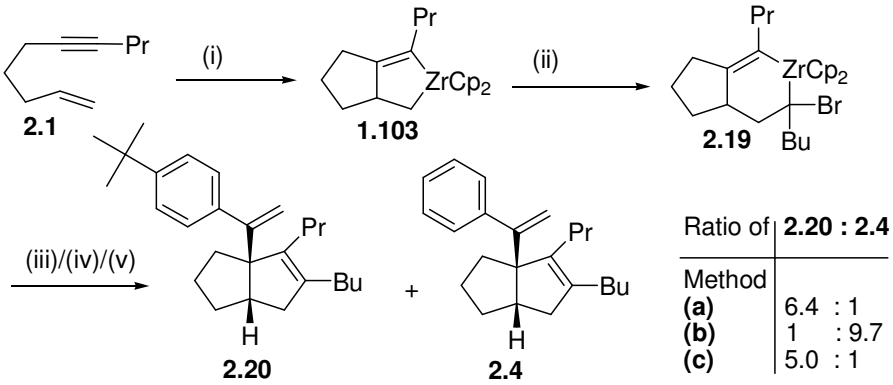


Scheme 2.5 Final stages of the three-component coupling on zirconocene.

A new mechanism (Scheme 2.5) was therefore proposed based on a fragmentation of the zirconate species **2.16** *via* elimination of the allylic carbanion **2.17** and its subsequent re-addition to the β-carbon of the bisphenylethynyl zirconium complex **2.18** to afford the novel zirconocene-alkenylidenate complex **2.13**. There is a driving force for the rearrangement in release of strain energy in going from a bicyclo[3.3.0]oct-1-ene to bicyclo[3.3.0]oct-2-ene system, as it was previously observed for a 1,3-amine rearrangement (Scheme 1.8).[119]

It is also possible that the fragments **2.17** and **2.18** are formed from **2.12** (Scheme 2.3). Rapid loss/re-addition of anions for zirconate complexes is known.[149-151] Although beta-addition to a metal alkyne is unknown for early transition metals, it is an established route for the formation of mid-/late-transition-metal alkenylidene complexes.[147,148]

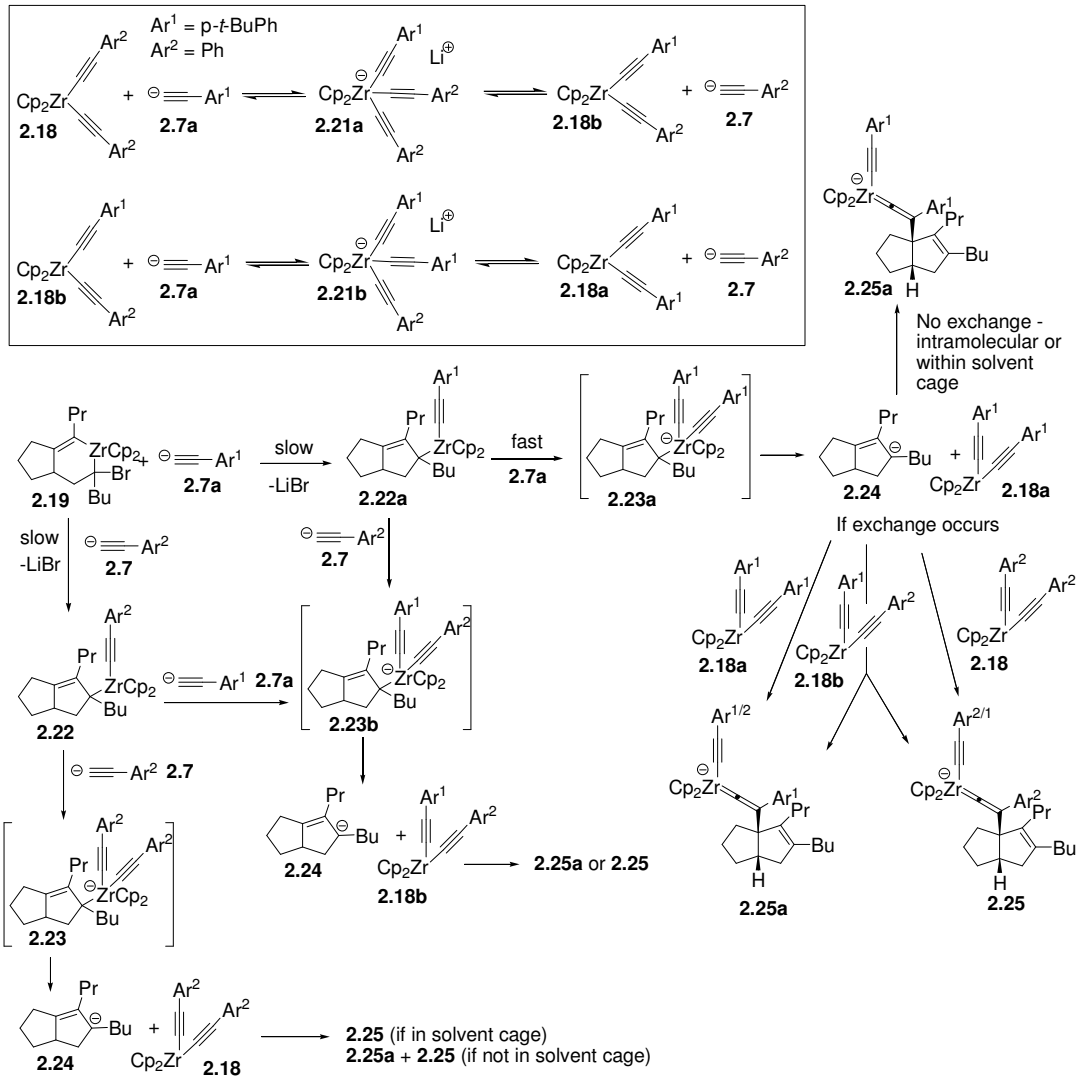
Further work to elucidate the mechanism of the multi-component coupling on zirconocene was done by the author. The normal test for a fragmentation/recombination mechanism would be a crossover experiment with a different bisalkynyl zirconocene added (Scheme 2.6).



Reagents and Conditions:(i) *n*-BuLi, THF, −78 ^{o}C to RT, 3 h; (ii) $BuCHBr_2$, LiTMP, −78 ^{o}C, 20 min; (iii) 1. $Cp_2Zr(CCPh)_2$ **2.18**, −78 ^{o}C, 5 min; 2. 3.0 eq *p-t*-BuPhCCLi **2.7a** (added sequentially), −78 ^{o}C to RT; 3. MeOH, aq $NaHCO_3$, RT, 16 h; (iv) 1. $Cp_2Zr(p\text{-}t\text{-}BuPhCC)_2$ **2.18a**, −78 ^{o}C, 5 min; 2. 3.0 eq PhCCLi **2.7**, (added sequentially), −78 ^{o}C to RT; 3. MeOH, aq $NaHCO_3$, RT, 16 h; (v) 1. $Cp_2Zr(CCPh)_2$ **2.18**, −78 ^{o}C, 5 min; 2. 3.0 eq *p-t*-BuPhCCLi **2.7a** (added rapidly), −78 ^{o}C, 30 min; 3. MeOH, aq $NaHCO_3$, RT, 16.

Scheme 2.6 Crossover experiment.

To the intermediate **2.19** (Scheme 2.7) was added at –78 °C previously prepared bisphenylethynyl zirconocene **2.18** followed by sequential addition of *p-t*-BuPhCCLi **2.7a**. The progress of the reaction was monitored by GC which showed no reaction after addition of the first equivalent of **2.7a**. A second equivalent of *p-t*-BuPhCCLi caused incorporation of both alkynes and the final compounds **2.20** and **2.4** were created, in an approximate ratio 1.9 : 1 respectively, with the residue being a product of carbenoid insertion. The third equivalent of the acetylide forced the remaining intermediate **2.19** to convert quickly into the final products in the ratio of 6.4 : 1. Addition to the reaction mixture of bis(*p-tert*-butylphenylethynyl) zirconocene **2.18a** in the first instance, followed by sequential addition of PhCCLi **2.7**, provided the final compounds **2.20** and **2.4** in the ratio of 1 : 9.7, respectively.



Scheme 2.7 Possible explanation of the results from crossover experiment.

Observation of no reaction during first addition of acetylide **2.7a** shows that it is all trapped by the bis-alkynyl zirconocene **2.18** to give the tris-alkynyl-zirconate **2.21a** which might further exchange to give **2.18a** and **2.7** species. We would expect trapping by bromide **2.19** to be slow as the zirconium is sterically hindered. If the formation of **2.21a** was fast and reversible it would lead to an equilbrium concentration of Ar^1CCLi and Ar^2CCLi in a ratio of 1 : 2. If this concentration was either significant, or the equilibrium fast, then we would expect the free acetylide to attack bromide **2.19** in an irreversible sequence leading to the cyclised product **2.22/2.22a** (and hence final rearranged products) – presumably as a 1 : 2 ratio of Ar^1 and Ar^2 substituted cases. This does not happen so the formation of **2.18/2.18a** + **2.7/2.7a** from **2.21a/2.21b** is either slow or very strongly in favour of **2.21a/2.21b**.

If formation of trisacetylide zirconate was a slow equilibrium, or effectively irreversible (i.e. minimal back reaction) then we would not expect any crossover product.

As soon as the second equivalent of acetylide **2.7a** starts to be added it can only react with bromide **2.19** leading to **2.22**, but this is much more reactive towards acetylide **2.7a** leading to the alkynate complex **2.23a** which does break down to bis-alkyne complex **2.18a** and allyl anion **2.24**.

2.22a would be expected to be more reactive towards addition of the acetylide **2.7a** than complex **2.19** as the zirconium is much less hindered.

There is now a competition between the allyl anion **2.24** and any acetylide present in solution for the bis-alkynyl complex **2.18a**. Since the reaction normally works well with 2 equivalents of acetylide the allyl anion **2.24** must react faster (indeed the reaction may take place through rapid recombination in the solvent cage). The prediction would be that the crossover products should not be seen and sole product **2.25a** should be obtained, but this is not in accord with the observations. The crossover product, however, could arise in two possible ways:

1. from the presence of **2.7** in solution competing with **2.7a** for **2.22a** (or **2.19**), or
2. from the presence of **2.18** (or **2.18b**) competing with **2.18a** for **2.24**.

If the equilibrium between **2.21a/2.21b** and **2.18/2.18a** + **2.7/2.7a** was strongly in favour of **2.21a/2.21b**, but fast, then the excess **2.7a** might exchange to give **2.7**.

The statistical ratio (i.e. would predict 2 : 1 **2.25 : 2.25a** initially moving to 2 : 3 at end of addition of third equivalent of **2.7a**) is not observed which may signify that this equilibriation is not occurring at a similar rate to the addition of **2.7a** and/or reaction of **2.7a** with **2.19** but a slow equilibriation could explain the results.

The observation of a great amount of the crossover product formed as the first part of the second equivalent of **2.7a** is added, but much less as the third equivalent is added could be a reflection of the greater amount of **2.7a** present, but the ratios are not statistical indicating that this is at best a partial answer.

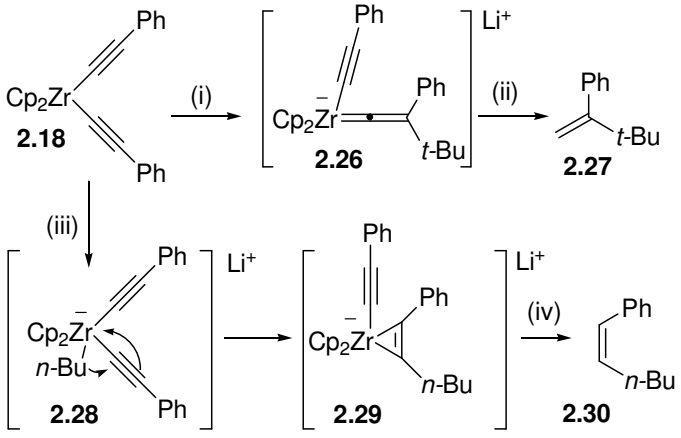
The two extreme cases can be considered: if formation of trisacetylide zirconates was a fast equilibrium, and gave a significant concentration of [acetylide + bisalkynylzirconium] we would expect substantial 'crossover' product (~2 : 1 in favour of crossover at start of addition of the second equivalent of acetylide moving to 3 : 2 in favour of non-crossover as last part of third equivalent of acetylide was added).

If the equilibrium of **2.18 + 2.7a** to **2.18a + 2.7** was slow, the prediction would be that if the three equivalents of acetylide **2.7a** were added rapidly no crossover products should

be observed. The experiment was carried out and the results showed that both products **2.20** and **2.4** were created in the ratio of 5 : 1, respectively. This result is inconsistent with the above assumption and may indicate that the fragmentation/recombination process occurs not entirely in an intramolecular fashion. Additionally, the crossover product may arise either from the attack of acetylide **2.7** onto bromide **2.19** or from trapping the bisalkynyl Zr complex **2.18a** (or **2.18b**) by the allylic anion **2.24**.

An indication that the proposed mechanism is reasonable is that addition of *t*-BuLi to bis(phenylethynyl)zirconocene **2.18** (Scheme 2.8) at –78 °C with immediate protic quench afforded the alkene **2.27** (88% isolated yield), probably *via* the alkenylidene-ate complex **2.26**. Addition of *n*-BuLi to bis(phenylethynyl)zirconocene gave (Z)-1-phenylhexene **2.30** (73%) only on warming to room temperature before protonolysis, presumably by initial addition to the metal to afford **2.28** followed by the type of 1,2-migration previously reported by Negishi,[152] to afford **2.29**. The result indicates that a bulky nucleophile is important for successful beta addition to the alkyne to inhibit direct attack on the metal.

Accordingly, attempts were made to add PhLi and *s*-BuLi to **2.18**; however, GC analysis of those reactions showed no conversion to such products even after warming the reaction mixture to RT.



Reagents and Conditions:(i) *t*-BuLi, –78 ^{o}C; (ii) H_2O, –78 ^{o}C, 0.5 h; (iii) *n*-BuLi, –78 ^{o}C to RT; (iv) H_2O, RT.

Scheme 2.8 Alternative route to alkenylidene zirconate complexes.

2.3. Substrate-scoping studies

The scope of the three-component coupling was investigated through variation of the co-cyclisation, carbenoid and acetylide precursors. It was essential to prepare a reasonable number of the bicyclic compounds with a wide range of various substituents for biological testing. It was hoped that high-throughput screening would lead to the identification of an active and selective agonist/antagonist for the human orphan nuclear receptors: LRH-1 and SF-1.

2.3.1. Synthesis of starting materials

2.3.1.1. Synthesis of substituted acetylenes

1-Ethynyl-3-methoxybenzene **2.31** (Figure 2.1) was prepared from commercially available starting materials using literature methods.[153,154] Other acetylenes used in the reactions were either purchased from suppliers or prepared by previous members of the Whitby group.

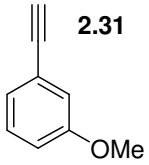
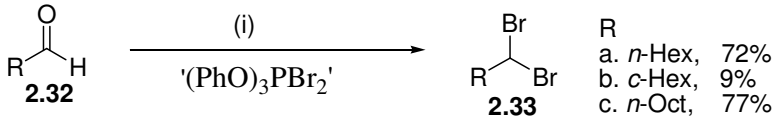


Figure 2.1 1-Ethynyl-3-methoxybenzene.

2.3.1.2. Synthesis of gem-dibromides

Dibromides **2.33a**,**b**,**c** (Scheme 2.9) were synthesised according to literature precedent[155] from the corresponding aldehydes **2.32**. Other 1,1-dihalides used in the reactions were either purchased from suppliers or prepared by previous members of the group.

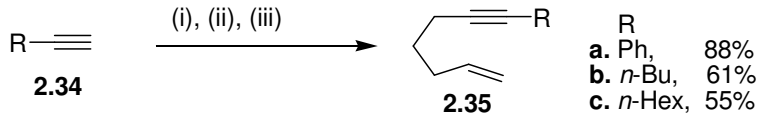


Reagents and Conditions:(i) $(PhO)_3P$, Br_2,CH_2Cl_2, –20 ^oC to 0 ^oC over 1 h.

Scheme 2.9 Conversion of aldehydes into 1,1–dibromoalkanes.

2.3.1.3. Synthesis of co-cyclisation precursors

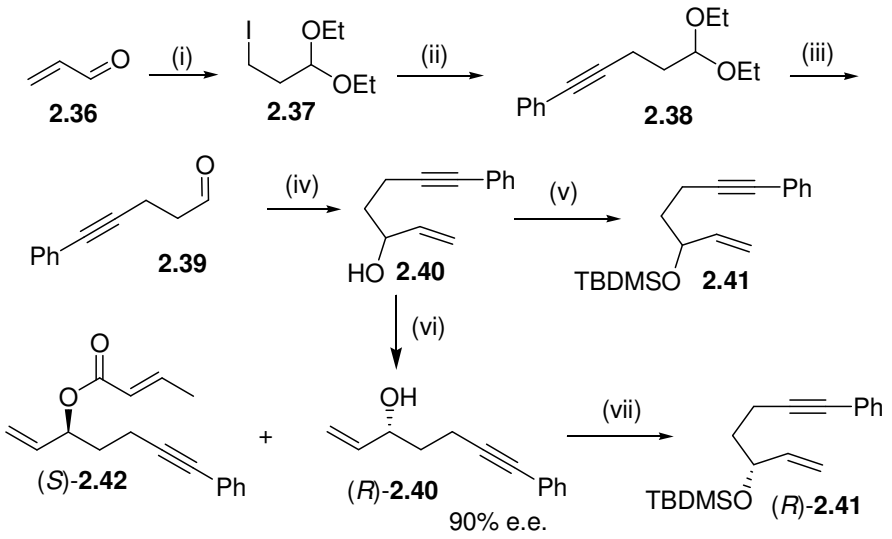
The following 1,6-enynes (Scheme 2.10) were prepared by alkylation of the corresponding lithiated alkynes with 5-bromo-1-pentene.



Reagents and Conditions:(i) *n*-BuLi, THF, −78 ^{o}C, 0.5 h; (ii) HMPA, −78 ^{o}C to −50 ^{o}C; (iii) 5-bromo-1-pentene, −50 ^{o}C to RT, 4-12 h, then aq NH_4Cl.

Scheme 2.10 Preparation of enynes.

Enynes carrying hydroxyl group have also been prepared. (7-Phenylhept-1-en-6-yn-3-yloxy)(*tert*-butyl)dimethylsilane **2.41** was synthesised as in Scheme 2.11. Ethanol and *in situ* generated Me_3SiI converted acrolein **2.36** into 1,1-diethoxy-3-iodopropane **2.37**,[156, 157] which after rapid purification by chromatography on basic alumina (grade III) was reacted with lithium phenyl acetylide to give (5,5-diethoxypent-1-yn-1-yl)benzene **2.38**. Hydrolysis of the acetal to give an aldehyde **2.39** was followed by reaction with vinyl magnesium bromide to afford the alcohol **2.40**. Protection of the hydroxyl group with *t*-BuMe_2SiOTf gave the desired cyclisation precursor **2.41**.



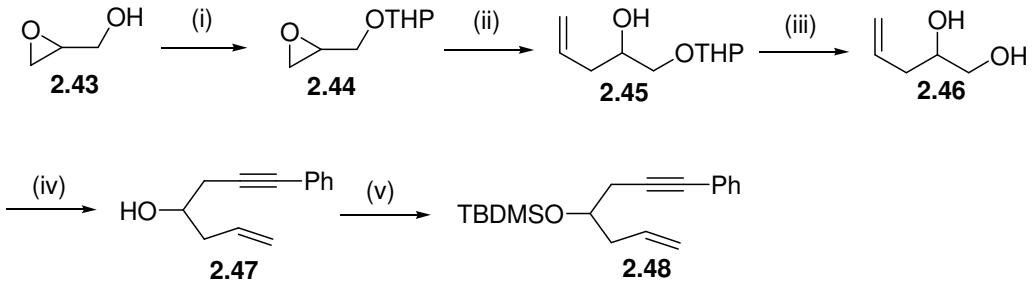
Reagents and conditions: (i) 1. NaI, Me_3SiCl, MeCN; 2. EtOH, 0 ^{o}C to RT, 2 h, 47%; (ii) 1.5 eq PhCCLi, 1.5 eq HMPA, THF, −78 ^{o}C, 1 h then RT, 14 h, 81%; (iii) THF : H_2O (4 :1), HCl (2M), RT, 3 h, 100%; (iv) 1. $CH_2CHMgBr$, −78^{o}C to −65 ^{o}C, 1 h; 2. aq NH_4Cl, 65%; (v) Me_2*t*-BuSiOTf, imidazole, DMAP, THF, RT, 18 h, 99%; (vi) (*E*)-vinyl crotonate, Novozyme 435, 42 ^{o}C, 72 h, 96%; (vii) Me_2*t*-BuSiOTf, Et_3N, DCM, 0 ^{o}C to RT, 0.5 h, 67%.

Scheme 2.11 Synthesis of (7-phenylhept-1-en-6-yn-3-yloxy)(*tert*-butyl)dimethylsilane.

The (*R*)-enantiomer of the alcohol **2.40** was obtained by crotylation reaction using Novozyme 435 as the catalyst, an immobilised *Candida antartica* lipase which is known to be selective for the (*S*)-enantiomer of alcohols with a similar structure.[158] Reaction was stopped at around 50% conversion and the recovered enantioenriched alcohol (*R*)-**2.40** (90% e.e.) converted through to (*R*)-**2.41** by the known procedure (Scheme 2.11).[159]

Synthesis of (1-phenylhept-6-en-1-yn-4-yloxy)(*tert*-butyl)dimethylsilane **2.48** was achieved in five steps (Scheme 2.12). Protection of the hydroxyl group in (±)-glycidol **2.43** as the tetrahydropyranyl ether **2.44**[160] followed by reaction of the crude product with vinylmagnesium bromide catalysed by CuBr gave the THP protected pent-4-ene-1,2-diol **2.45**.[161] Removal of the THP protecting group[162] gave pent-4-ene-1,2-diol **2.46**.[163] A one-pot ring closure/ring opening procedure was used to convert pent-4-ene-1,2-diol into 7-phenylhept-1-en-6-yn-4-ol **2.47**.[164,165] Thus selective tosylation of the primary alcohol was followed by *in situ* ring closure to an epoxide, and ring opening with lithium phenylacetylide to afford the alcohol **2.47**.

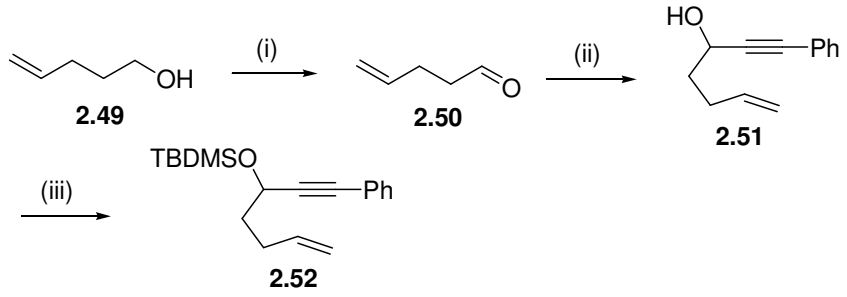
The overall yield was poor despite considerable optimization. TBDMS protection of alcohol **2.47** gave the desired compound **2.48**.



Reagents and conditions: (i) 1. DHP, CH_2Cl_2, TsOH, 0 ^oC, 15 min; 2. RT, 1 h, 100%; (ii) 1. $CH_2CHMgBr$, cat. CuBr, THF, −10 ^oC, 4 h; 2. aq NH_4Cl, 86%; (iii) MeOH, Amberlyst-15, 50 ^oC, 1 h, 60%; (iv) 1. NaH, THF, −10 ^oC; 2. N-Tosyl imidazole, −10 ^oC, 1 h; 3. 2.0 eq PhCCLi, THF, HMPA, −10 to 0 ^oC 1h. 4. RT, 40 h, then aq $NaHCO_3$, 28%; (v) Me_2*t*-BuSiOTf, imidazole, DMAP, THF, RT, 15 h, 82%.

Scheme 2.12 Synthesis of (1-phenylhept-6-en-1-yn-4-yloxy)(*tert*-butyl)dimethylsilane.

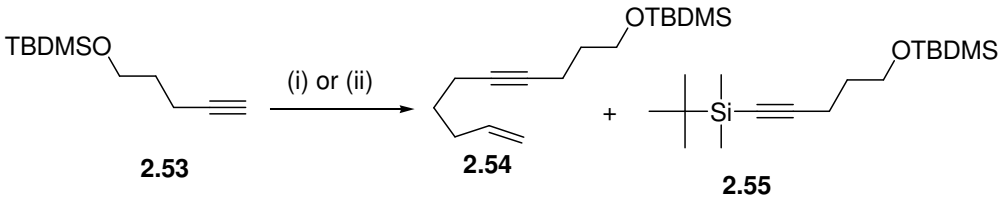
(1-Phenylhept-6-en-1-yn-3-yloxy)(*tert*-butyl)dimethylsilane **2.52** (Scheme 2.13) was synthesised from 4-penten-1-ol **2.49** through Swern oxidation to give the corresponding aldehyde **2.50**, and subsequent nucleophilic addition of phenyl acetylide to the carbonyl group to provide the alcohol **2.51**.[159] The poor yield over the two steps is explained by troublesome volatility of the aldehyde **2.50**. TBDMS protection of the hydroxyl group gave the co-cyclisation precursor **2.52**.



Reagents and conditions: (i) 1. DMSO, $(COCl)_2$, DCM, −78 ^oC, 1 h; 2. Et_3N, −78 ^oC to RT; 3. H_2O/brine; (ii) 1.5 eq PhCCLi, THF, HMPA, −78 ^oC to −55 ^oC, 1.5 h then aq NH_4Cl, 27% (over two steps); (iii) Me_2t-BuSiOTf, Et_3N, DCM, 0 ^oC to RT, 0.5 h, 74%.

Scheme 2.13 Preparation of (1-phenylhept-6-en-1-yn-3-yloxy)(*tert*-butyl)dimethylsilane.

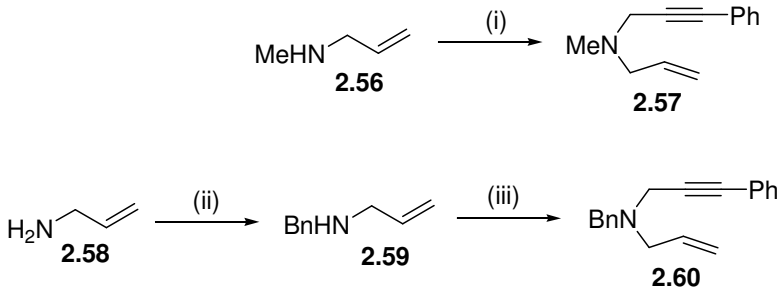
Reaction of lithiated *tert*-butyldimethyl(pent-4-ynyloxy)silane **2.53** with 5-bromo-1-pentene gave an inseparable mixture of two compounds **2.54** and **2.55** in the ratio of 2 : 1 respectively and 63% combined yield (Scheme 2.14). The undesired product **2.55** resulted from the nucleophilic attack of the lithiated alkyne onto silyl group. Use of 5-iodo-1-pentene instead provided the desired compound **2.54**[166] and the by-product **2.55** with improved ratio (5.7 : 1) and yield (75%). Subsequent zirconocene mediated co-cyclisation turned out to be selective for the enyne **2.54** and the by-product **2.55** present in the reaction mixture has been shown to have no effect on the reaction.



Reagents and Conditions: method (i) 1. *n*-BuLi, THF, −78 ^oC, 0.5 h; 2. HMPA, −78 ^oC to −50 ^oC; 3. 5-bromo-1-pentene, −50 ^oC to RT, 24 h, then aq NH_4Cl, 63%; method (ii) 1. *n*-BuLi, THF, −78 ^oC, 0.5 h; 2. HMPA, −78 ^oC to −50 ^oC; 3. 5-iodo-1-pentene, −50 ^oC to RT, 24 h, then aq NH_4Cl, 75%.

Scheme 2.14 Synthesis of 10-(*tert*-butyldimethylsiloxy)-l-decen-6-yn.

Enynes containing a nitrogen atom have been prepared (Scheme 2.15). *N*-methyl-*N*-(phenylprop-2-ynyl)prop-2-en-1-amine **2.57** and *N*-benzyl-*N*-(phenylprop-2-ynyl)prop-2-en-1-amine **2.60** (Scheme 2.15) were prepared from *N*-allyl-*N*-methylamine **2.56**, and *N*-allyl-*N*-benzylamine **2.59**, which was synthesised from allyl amine **2.58** in 78% yield,[167] respectively in copper-catalysed Mannich reaction.[168]

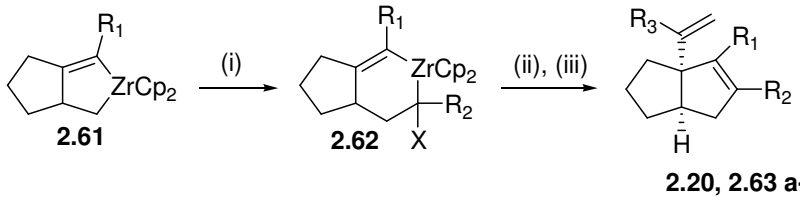


Reagents and Conditions: (i) PhCCH, CH_2O, DMSO, cat. CuI, 30 ^oC, 24 h, 41%; (ii) BnBr, 0 ^oC to RT, 16 h then aq $NaHCO_3$, 78%; (iii) PhCCH, CH_2O, DMSO, cat. CuI, 30 ^oC, 15 h, 89%.

Scheme 2.15 Synthesis of nitrogen containing substrates.

2.3.2. Synthesis of *cis*-bicyclo[3.3.0]oct-2-enes by using stoichiometric zirconium chemistry

Extension of the multi component reaction to the use of a wide range of starting enynes, dihalocarbenoids, and lithiated alkynes resulted in synthesis of a number of bicyclo[3.3.0]octanes (Scheme 2.16, Table 2.1).



Reagents and conditions: (i) R^2CHX_2 [X= Br for R^2 = *n*-Hex, *n*-Bu, *n*-Oct. X = Cl for R^2 = H, $SiMe_2Ph$], LDA or LiTMP, −78 ^oC, 15 min; (ii) 3 eq R^3CCLi, −78 ^oC to −60 ^oC over 0.5 h; (iii) MeOH, aq $NaHCO_3$, RT, 12-16 h.

Scheme 2.16 One-pot tandem reaction sequence on zirconocene.

The synthetic route introduced above (Scheme 2.16) provides an efficient method for construction and functionalisation at multiple sites rigid core structures containing *cis*-bicyclo[3.3.0]oct-2-ene skeleton. Yields range from good to very good (Table 2.1).

Use of a wide range of acetylides (**2.63a-l**) (Table 2.1) provided the final compounds in very good yields. Diminished yields were however observed for alkyl-substituted acetylides (**2.63i**,**k**,**l**) in comparison with acetylides carrying aromatic substituent. These results seem to imply that alkyl-substituted acetylides for some reasons are less reactive towards the zirconium-alkenylidene rearrangement than aryl-substituted acetylides.

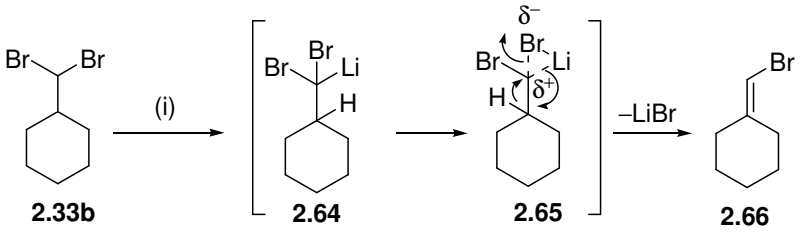
Compound	R^1	R^2	R^3	Yield / %[a]
2.20	*n*-Pr	*n*-Bu	4-*t*-BuPh	66
2.63a	Ph	*n*-Hex	Ph	86
2.63b	Ph	*n*-Hex	3-MeOPh	78
2.63c	Ph	*n*-Hex	4-MeOPh	72
2.63d	Ph	*n*-Hex	4-MePh	62
2.63e	Ph	*n*-Hex	4-EtPh	70
2.63f	Ph	*n*-Hex	4-*n*-BuPh	78
2.63g	Ph	*n*-Hex	4-*t*-BuPh	51
2.63h	Ph	*n*-Hex	4-PhPh	60
2.63i	Ph	*n*-Hex	*n*-Pr	54
2.63j	Ph	*n*-Hex	*n*-Bu	75
2.63k	Ph	*n*-Hex	*n*-Hex	65
2.63l	Ph	*n*-Hex	*n*-Oct	56
2.63m	3-MeOPh	*n*-Hex	Ph	75
2.63n	4-EtPh	*n*-Hex	Ph	70
2.63o	*n*-Pr	*n*-Hex	Ph	82
2.63p	*n*-Bu	*n*-Hex	Ph	88
2.63q	*n*-Hex	*n*-Hex	Ph	86
2.63r	*c*-Hex	*n*-Hex	Ph	80
2.63s	$(CH_2)_3OH$	*n*-Hex	Ph	61
2.63t	Ph	H	Ph	58
2.63u	Ph	*n*-Bu	Ph	71
2.63v	Ph	*n*-Oct	Ph	73
2.63w	Ph	$SiMe_2Ph$	Ph	45
2.63x	*n*-Bu	$SiMe_2Ph$	Ph	69
2.63y	*n*-Hex	*c*-Hex	Ph	10
2.63z	*n*-Hex	*n*-Hex	*n*-Bu	68
2.63aa	*n*-Pr	*n*-Hex	4-*t*-BuPh	86

Table 2.1 Variation of 1-(2-alkenyl)-bicyclo[3.3.0]oct-2-enes 2.63.

[a] isolated yield of >95% pure material.

The bicyclic compounds **2.63m-r** (Table 2.1) were obtained in very good yields for both R^1 = alkyl and R^1 = aryl. A slightly lower yield is observed for compound **2.63s**, but the yield was given for two steps: the reaction sequence on zirconocene and TBAF deprotection step.

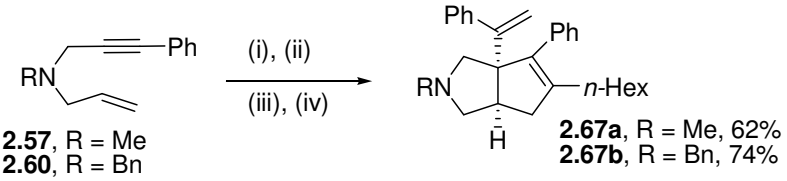
Insertion of lithiated dichloromethane followed by insertion of phenyl acetylide gave the product **2.63t** in 58% isolated yield. In this particular case the yield is lower due to multiple insertion of this carbenoid into the zirconacycle, therefore the purification was made difficult. Silyl substituted carbenoids were also examined, and the final compounds **2.63w**, **x** with incorporated $SiMe_2Ph$ group were obtained in 45% and 69% yield respectively. The final yield of product **2.63w** is significantly diminished by the undesired de-silylation which occurred under the reaction conditions. The same de-silylation process was observed by Thomas,[140] who has also noted that different quench conditions may have prevented this de-silylation process from occurring, however these were not tried. Incorporation of a carbenoid carrying an alpha-branch occurred very poorly and provided the desired compound **2.63y** only in 10% isolated yield. The poor yield is due to deprotonation of the α-branched 1,1-dihalo species **2.33b** being immediately followed by 1,2-H shift (even at –78 °C) with loss of LiBr, to give relatively unreactive alkenylhalide species **2.66** (Scheme 2.17). This process is thought to be occurring due to metal assisted ionisation as in **2.65**.[124,169-171]



Reagents and conditions: (i) LDA or LiTMP, THF, –78 °C.

Scheme 2.17 Decomposition of α-branched carbenoids.

The tandem reaction sequence also worked well for the formation of pyrrolidine fused systems **2.67a**, **b** (Scheme 2.18).



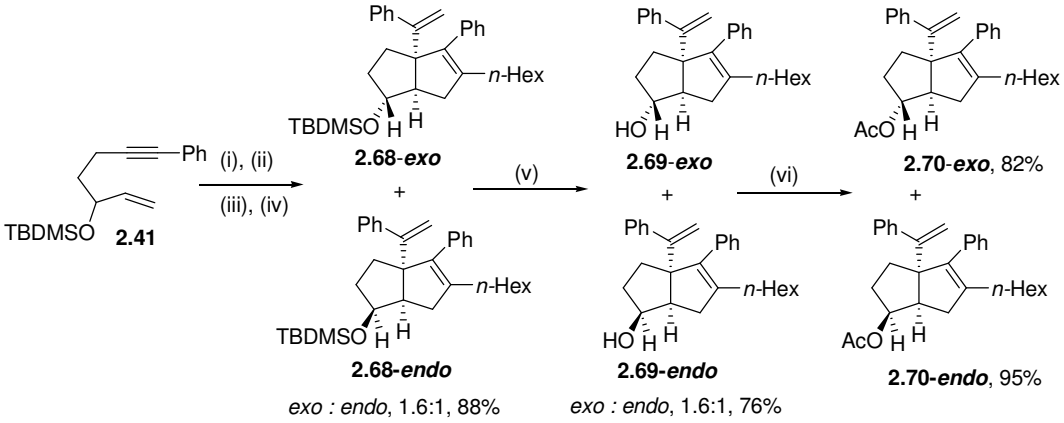
2.57, R = Me
2.60, R = Bn

2.67a, R = Me, 62%
2.67b, R = Bn, 74%

Reagents and conditions: (i) Cp_2ZrBu_2, THF, −78 °C to RT, 2 h; (ii) *n*-$HexCHBr_2$, LDA, −78 °C, 15 min; (iii) 3.0 eq PhCCLi, −78 °C to −60 °C over 0.5 h; (iv) MeOH, aq $NaHCO_3$, RT, 12-16 h.

Scheme 2.18 Formation of pyrrolidine fused systems.

Co-cyclisation of precursor **2.41**, and further carbenoid and acetylide insertion resulted in synthesis of compounds with oxygen-substitution on the saturated cyclopentane ring. The synthesis of the 6-oxygenated compounds is shown in Scheme 2.19.



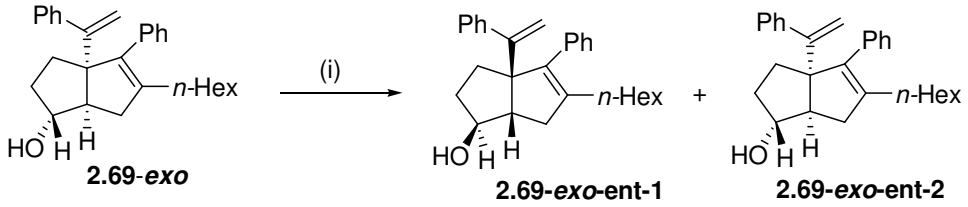
Reagents and conditions: (i) Cp_2ZrBu_2, THF −78 ^oC, 0.5 h, then 2 h at RT; (ii) *n*-$HexCHBr_2$, LDA, −78 ^oC, 15 min; (iii) 3.0 eq PhCCLi, −78 ^oC to −60 ^oC over 45 min; (iv) MeOH, aq $NaHCO_3$, RT, 5 h; (v) 5.0 eq TBAF, THF, RT, 20 h, then H_2O; (vi) Pyridine, 73 eq Ac_2O, 0.58 eq DMAP, RT, 13 h.

Scheme 2.19 Synthesis of 6-oxygenated series.

Precursor **2.41** underwent the zirconocene induced co-cyclisation, carbenoid insertion and phenyl acetylide addition to give a 1.6 : 1 mixture of the *exo*- and *endo*-isomers **2.68** after protonolysis. TBAF cleavage of the silyl group furnished the desired bicyclic alcohols **2.69**. The *exo*- and *endo*- isomers were partly separated by careful chromatography, the *endo*-isomer eluting first. The relative stereochemistries of the *exo*- and *endo*- isomers were clear from coupling patterns to the proton adjacent to the hydroxyl group. In the *endo*-isomer it appears as a ddd, J = 9.1, 8.5, 5.5 Hz, in the exo-isomer as a broad singlet, the patterns being in accord with expectations from molecular modelling and the Karplus relationship of couplings to dihedral angles.[172, 173]

The separated diastereoisomers of **2.69** were acylated to afford **2.70-*exo*** and **2.70-*endo***. A crystal structure of **2.70-*endo*** (attached in appendix) confirmed the stereochemical assignment.[174]

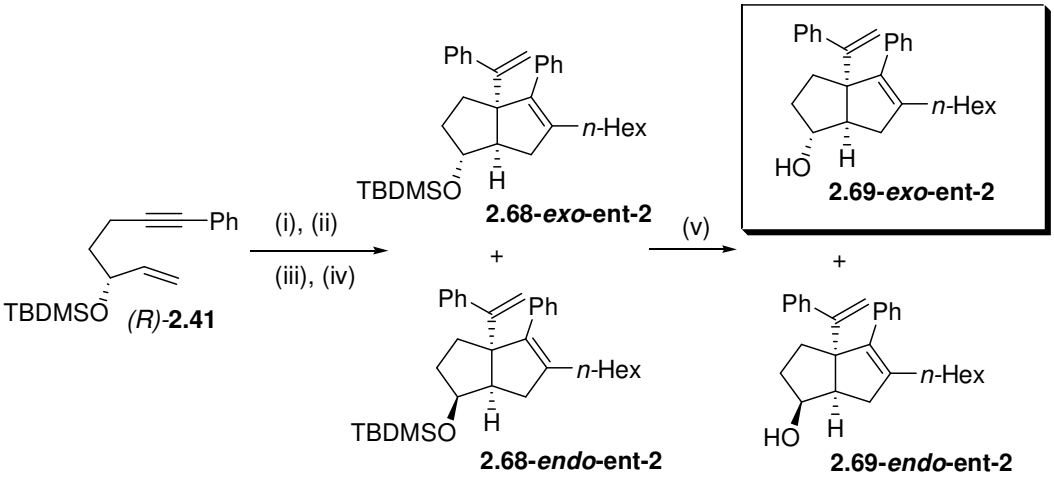
It was required to separate enantiomers of **2.69-*exo*** for biological testing (Scheme 2.20). The most convenient route to the enantiopure compounds proved to be separation by chiral HPLC on a Diacel OD-H column, the two enantiomers having remarkably different retention times (**2.69-*exo*-ent-1** at 11.7 min, **2.69-*exo*-ent-2** after 18.5 min – 1 mL/min 1% isopropanol in hexane on 4.6 x 250 mm column) allowing clean separation.



Reagents and conditions: (i) HPLC on Diacel OD-H chiral column.

Scheme 2.20 Chiral HPLC seperation of enantiomers of 2.69-*exo*.

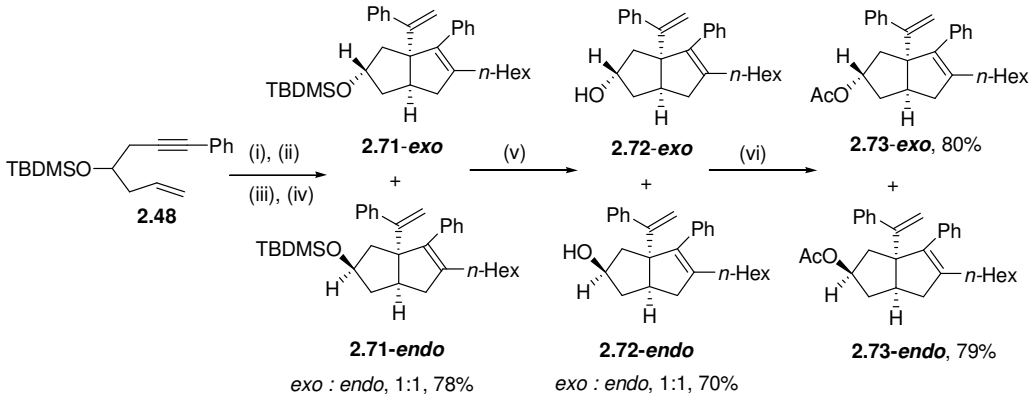
The identity of the enantiomers was proven by conversion of the enantioenriched TBDMS protected alcohol (*R*)-**2.41** (90% e.e.) through to **2.69-*exo*** (Scheme 2.21), which was found by chiral HPLC to be predominantly (20 : 1) the more slowly eluted enantiomer (**2.69-*exo*-ent-2**), thus identifying its absolute stereochemistry.



Reagents and conditions: (i) Cp_2ZrBu_2, THF −78 °C, 0.5 h then 2 h at RT; (ii) *n*-$HexCHBr_2$, LDA, −78 °C, 15 min; (iii) 3.0 eq PhCCLi, −78 °C to −60 °C over 45 min; (iv) MeOH, aq $NaHCO_3$, RT, 12 h, 90%; (v) 20 eq TBAF, THF, RT, 22 h, then H_2O, 65%.

Scheme 2.21 Asymmetric synthesis of alcohol 2.69-*exo*.

The 7-oxygenated series was synthesised as shown in Scheme 2.22. Enyne **2.48** was subjected to the zirconocene mediated co-cyclisation, dibromocarbenoid insertion and phenyl acetylide driven zirconate rearrangement to obtain a 1 : 1 mixture of the *exo*- and *endo*-isomers **2.71**. After TBAF cleavage of the silyl group, the *exo*- and *endo*- isomers of **2.72** were partly separated by careful chromatography, the *endo*-isomer eluting first. Acylation of the separated diastereoisomers gave **2.73-*exo*** and **2.73-*endo*** (Scheme 2.22).

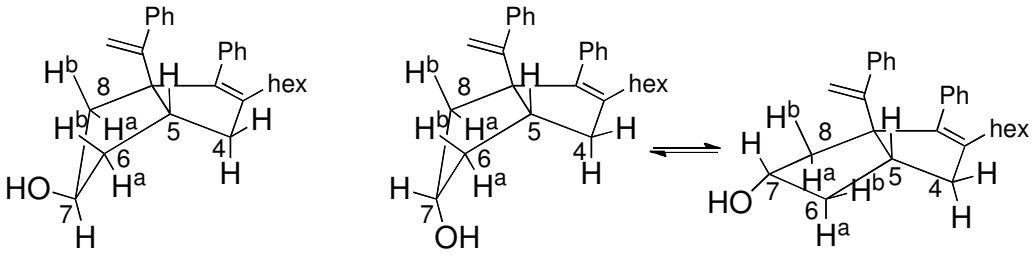


Reagents and conditions: (i) Cp_2ZrBu_2, THF −78 °C, 0.5 h, then 2 h at RT; (ii) *n*-$HexCHBr_2$, LDA, −78 °C, 15 min; (iii) 3.0 eq PhCCLi, −78 °C to −60 °C over 45 min; (iv) MeOH, aq $NaHCO_3$, RT, 5 h; (v) 2.0 eq TBAF, THF, RT, 20 h, then H_2O; (vi) Pyridine, 73 eq Ac_2O, 0.58 eq DMAP, RT, 17 h.

Scheme 2.22 Synthesis of 7-oxygenated series.

The relative stereochemistries of **2.72**-*exo* and **2.72**-*endo* (and hence **2.73**-*exo* and **2.73**-*endo*) were established by NMR studies combined with molecular modelling (Table 2.2) using the MMFF94 force field as implemented in Spartan 06 (Wavefunction Inc.).[175] The proton next to the hydroxyl group in one isomer appeared as a tt, J = 8.5, 5.9 Hz (due to couplings of 8.5, 8.3, 6.3 and 5.5 Hz), consistent with **2.72**-*exo* or the equatorial conformer of **2.72**-*endo* (**2.72**-*endo* eq. conf.), but as a quintet (J = 5.5 Hz) in the other diastereoisomer – not consistent with any minimum energy structure. Molecular modelling showed that **2.72**-*exo* had a well defined minimum energy conformer, but for **2.72**-*endo* the 'equatorial' and 'axial' hydroxy conformers (**2.72**-*endo* eq. and **2.72**-*endo* ax.) were <1 kJ/mol different in energy. The expected coupling patterns for each conformer of **2.72**-*endo* were calculated using the Altona modification[173] of the Karplus relationship[172] between dihedral angle and ^3J as implemented in the Mspin program[176] from Mestrec. The average showed a good

correlation to the observed coupling constants (Table 2.2). Final proof was hoped to come from low temperature ^{1}H NMR experiments, however, no splitting of all averaged signals for geminal protons into axial and equatorial signals was demonstrated even at the lowest temperature (–80 °C). NOE experiments of **2.72**-*endo* also turned out not to bring any relevant insights.



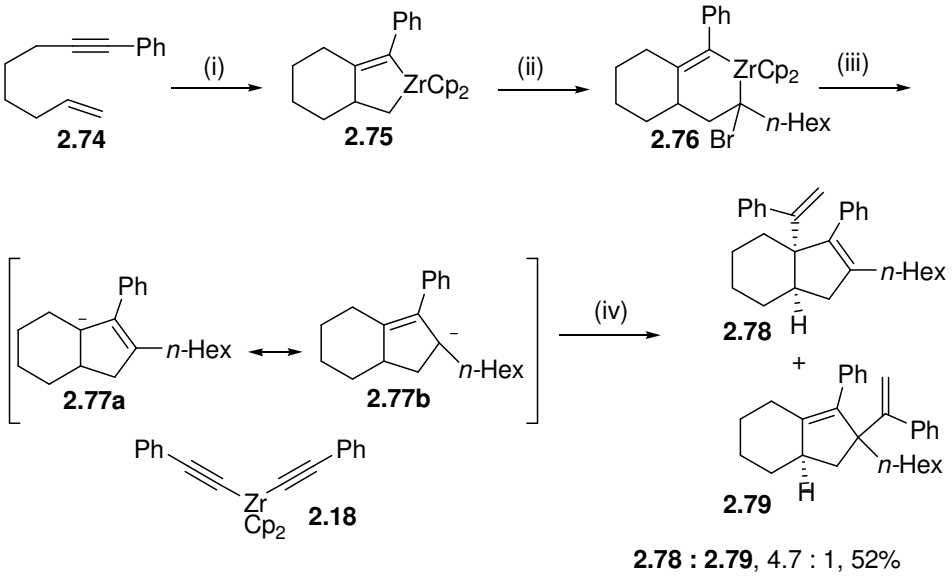
2.72-*exo* **2.72-*endo* ax. conf.** **2.72-*endo* eq. conf.**

	^{3}J coupling					
	H^7-H^{8b}	H^7-H^{8a}	H^7-H^{6b}	H^7-H^{6a}	H^{6b}-H^5	H^{6a}-H^5
2.72-*exo*						
Dihedral	164	47	154	37	14	104
Calculated ^{3}J	10.2	6.1	8.9	7.6	9.7	1.9
Observed ^{3}J	8.5	5.5	8.3	6.3	10	3.6
2.72-*endo* ax. conf.						
Dihedral	38	80	33	87	18	101
Calculated ^{3}J	5	1.3	5.9	1.3	9.4	1.6
2.72-*endo* eq. conf.						
Dihedral	44	159	46	165	35	155
Calculated ^{3}J	6.6	9.5	6.3	10.4	7.3	10.5
Average **2.72-*endo* eq.** and **-ax. conf.** ^{3}J	5.8	5.4	6.1	5.9	8.4	6.1
Observed ^{3}J	6.2	4.6	5.6	5	9.5	6

Table 2.2 Correlation between predicted and observed coupling constants for 2.72.

2.3.3. Insertion of alkyl carbenoid and phenyl acetylide into bicyclo[4.3.0]-zirconacyclopentene and sterically hindered zirconacyclopentenes

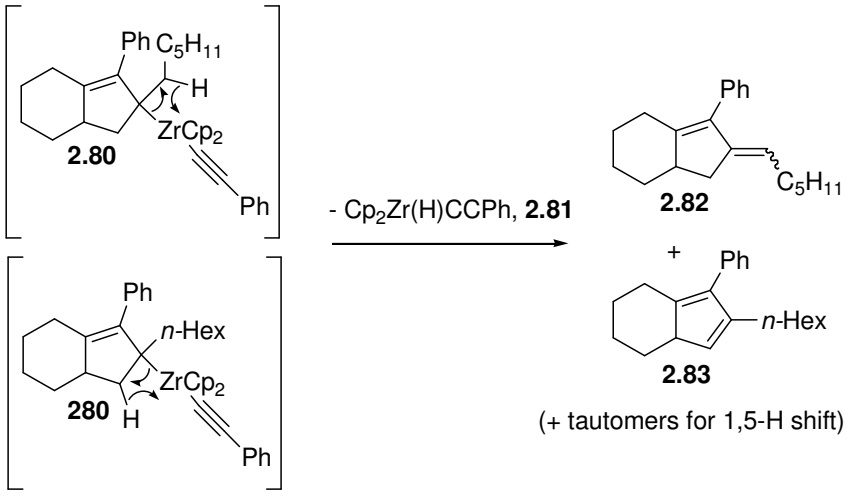
Variation in the ring size fused to the zirconacycles was sought in respect of the multi-component coupling sequence. Co-cyclisation with Negishi reagent of the homologous enyne, 1-(oct-7-en-1-ynyl)benzene **2.74** resulted in six-five fused zirconacycle **2.75** (Scheme 2.23). Subsequent insertion of lithiated dibromoheptane and lithium phenyl acetylide provided a mixture of compounds **2.78** and **2.79** in 52% combined yield and initial GC ratio of 4.7 : 1 respectively. Compounds **2.78** and **2.79** were partly separated by careful column chromatography to obtain the final products as single compounds in 26% and 4% yield, respectively.



Reagents and conditions: (i) Cp_2ZrBu_2, THF −78 °C, 0.5 h, then 2 h at RT; (ii) *n*-HexCHBr$_2$, LiTMP, −90 °C to −78 °C, 25 min; (iii) 3.0 eq PhCCLi, −78 °C to −55 °C over 45 min; (iv) MeOH, aq $NaHCO_3$, RT, 16 h.

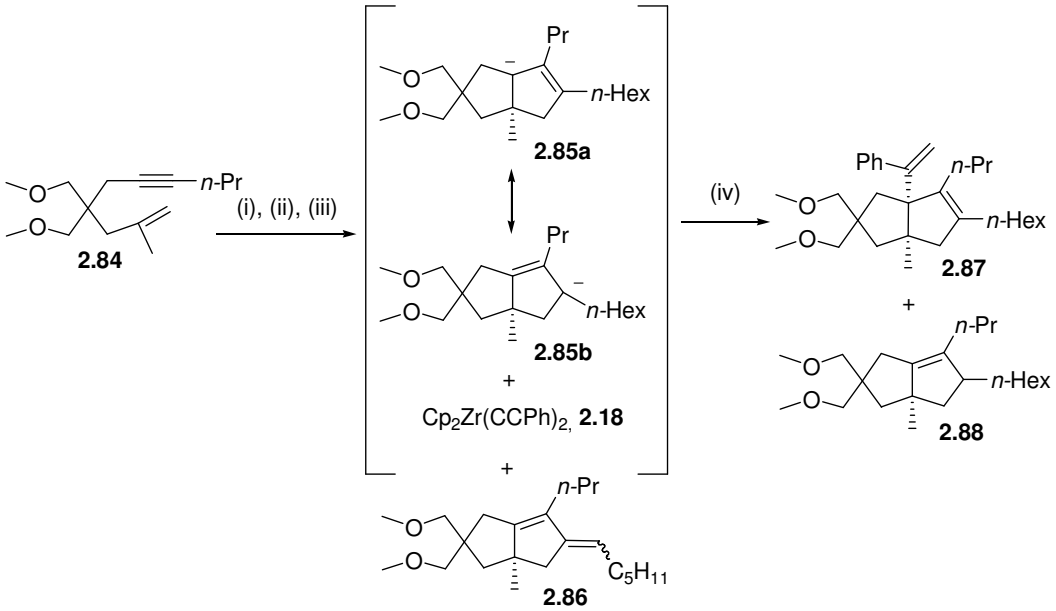
Scheme 2.23 Extension of the method to six-five fused zirconacyclopentene.

Other unexpected products emerged in the crude reaction mixture. GC and GCMS analysis revealed the molecular mass of these products corresponded to the β-H elimination products **2.82**, **2.83** (Scheme 2.24). The presence of a few compounds with the same molecular mass strongly suggests the products of both exo- and endocyclic β-H abstraction process, which occurs in the intermediate **2.80**.



Scheme 2.24 β-H Elimination process in six-five fused zirconacycles after alkyl carbenoid insertion.

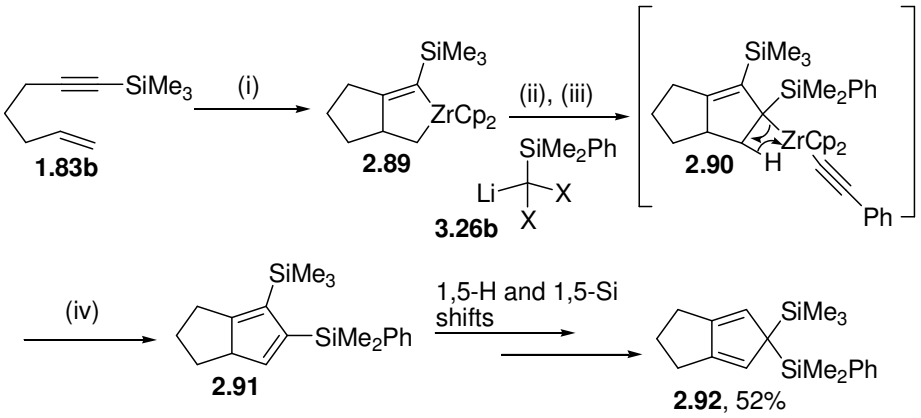
A conclusion can be drawn from these results, that release of strain energy *via* 1,3-Zr rearrangement in the intermediate **2.77** is impeded, thus making the undesired β-H elimination process more favourable at the stage of the intermediate **2.80** (Scheme 2.24). Additionally, trapping of the bisalkynyl Zr species **2.18** does not occur exclusively in the bridgehead position, which suggests that there is only a small difference in release of strain energy between these two resonance structures **2.77a** and **2.77b**. Similar results were obtained when enyne **2.84** was subjected to the reaction sequence (Scheme 2.25). In the examined reaction coordination of two molecules of phenyl acetylide **2.7** to Zr atom to give the corresponding allylic anion **2.85** and bis(phenylethynyl) zirconium complex **2.18** does seem to be more favourable process than β-H abstraction, however the latter process is still competitive and results in compounds **2.86** as minor products. Subsequent re-addition of the anion **2.85a** to the β carbon of the $Cp_2Zr(CCPh)_2$ complex occurs very slowly, even upon warming the reaction mixture to RT. As a result a mixture of compounds **2.87** (major product) and **2.88** (minor product) is obtained. The final compound **2.87** was isolated in only 25% yield since the purification was very difficult due to by-products **2.86** and **2.88**, all of which have similar polarity. It was assumed, but has not been proven, that the ring junction stereochemistry in the product **2.87** is *cis*.



Reagents and conditions: (i) Cp_2ZrBu_2, THF, −78 °C, 0.5 h then 2 h at RT; (ii) *n*-$HexCHBr_2$, LiTMP, −90 °C to −78 °C, 25 min; (iii) 3.0 eq PhCCLi, −78 °C to −55 °C over 45 min; (iv) −55 °C to RT, then MeOH, aq $NaHCO_3$, RT, 16 h.

Scheme 2.25 Tandem reaction sequence on enyne 2.84.

An endocyclic β-H elimination was observed in the case of insertion of lithiated (dichloromethyl)dimethyl(phenyl)silane into zirconacyclopentene **2.89** (Scheme 2.26).



Reagents and conditions: (i) Cp_2ZrBu_2, THF, −78 °C, 0.5 h then 3 h at RT; (ii) 1.3 eq $Cl_2CHSiMe_2Ph$, *n*-BuLi, −95 °C to −20 °C; (iii) 3.0 eq PhCCLi, −78 °C to −50 °C over 1 h; (iv) MeOH, aq $NaHCO_3$, RT, 12 h.

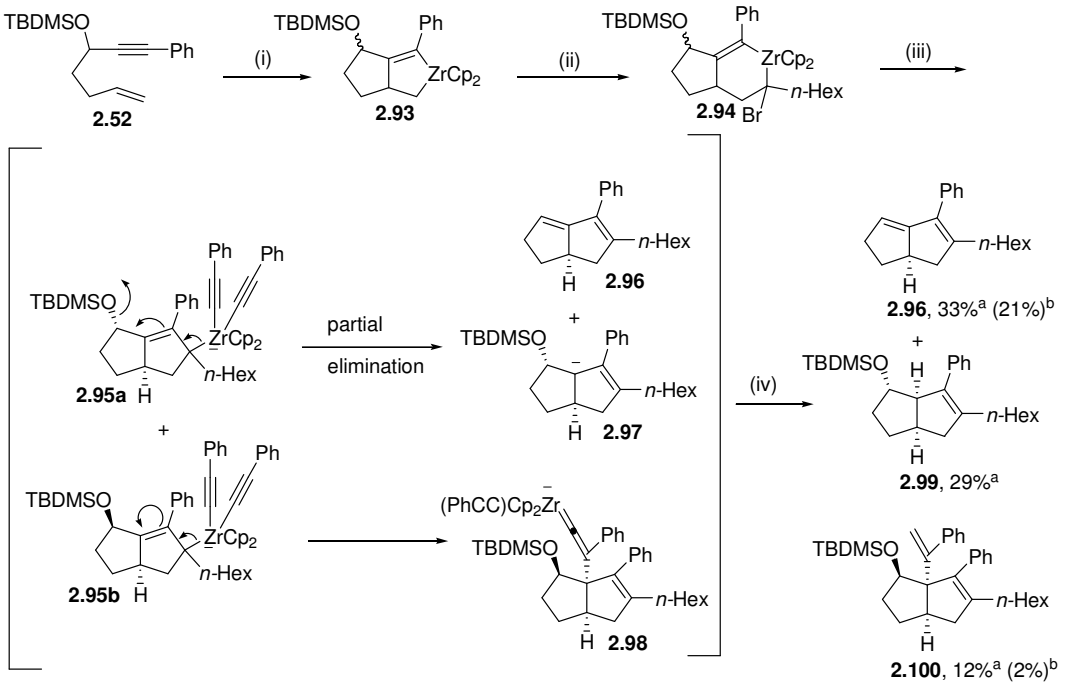
Scheme 2.26 Insertion of (dichloromethyl)dimethyl(phenyl)-silane into zirconacycle 2.89.

The steric encumbrance introduced by the silyl carbenoid favours the endocyclic β-H elimination process in intermediate **2.90**, to provide compound **2.91** which after 1,5-H and 1,5-Si shifts gives the final diene **2.92** in moderate yield.

2.3.4. Competition between TBDMSO group elimination and 1,3-zirconate rearrangement

Co-cyclisation of TBDMS protected 7-phenylhept-1-en-6-yn-5-ol **2.52** gave a mixture of *exo : endo* unsaturated zirconacycles **2.93** in the ratio of 5 : 1, respectively (ratio estimated by taking a sample of the reaction mixture and subsequent GC analysis), (**Scheme 2.27**). Insertion of lithiated 1,1-dibromoheptane and phenyl acetylide resulted in partial elimination of the TBDMS protected hydroxyl function in the *exo* position from intermediate **2.95a** to give the conjugated diene **2.96** as a major product. Also product **2.99**, which results from protonation of the remaining allylic anion **2.97**, was detected in the crude reaction mixture. The resulting allylic anion did not react with the bisphenylalkynyl complex **2.18** as the bulky TBDMSO group blocks the *exo* face. The compound **2.100** was obtained as a minor product from the Zr-alkenylidene rearrangement to give the alkenylidenate species **2.98**, as the TBDMSO group is *endo* directed, therefore prevents the elimination process from occurring in intermediate **2.95b**.

Products **2.96** and **2.100** were isolated as pure compounds in low yields (21% and 2%, respectively) as the purification on silica gel column was difficult; however, the yields of compounds **2.96**, **2.99** and **2.100** estimated by GC in the crude reaction mixture are much higher.



Reagents and conditions: (i) Cp_2ZrBu_2, THF −78 °C, 0.5 h then 2 h at RT; (ii) *n*-$HexCHBr_2$, LDA, −78 °C, 15 min; (iii) 3.0 eq PhCCLi, −78 °C to −55 °C over 45 min; (iv) MeOH, aq $NaHCO_3$, RT, 16 h.

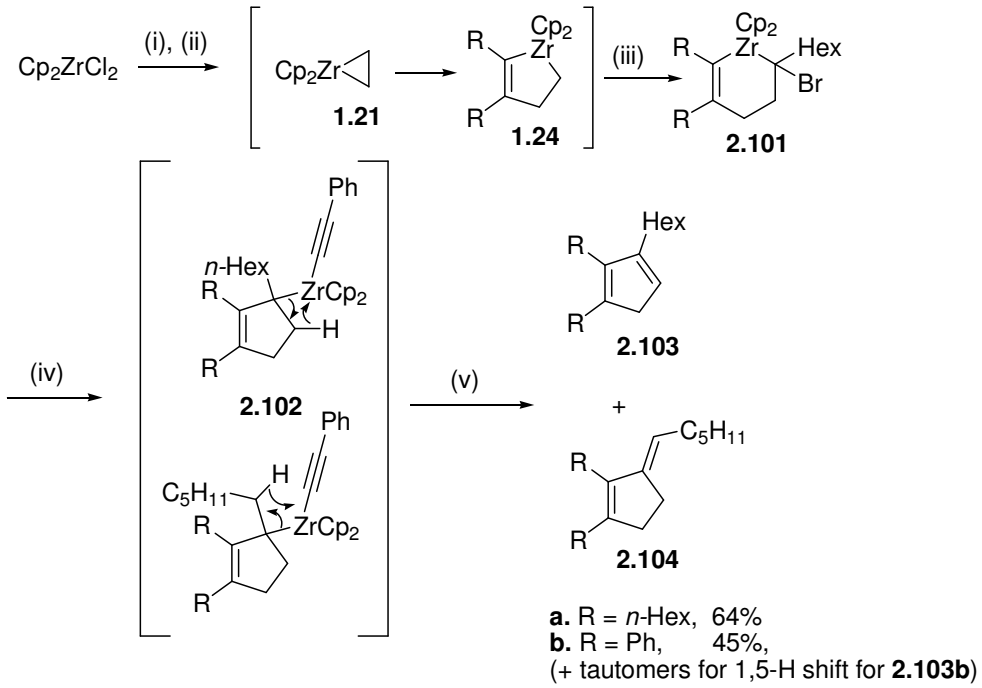
[a] yield estimated by GC in the crude reaction mixture,

[b] yield of isolated pure material,

Scheme 2.27 Competition between elimination of TBDMSO group and 1,3 Zr-alkenylidene rearrangement.

2.3.5. Application of the existing method to monocyclic zirconacyclopentenes

Insertion of lithium 1,1-dibromoheptane into zirconacyclopentene **1.24** (created *in situ* by insertion of the corresponding alkyne into Zr-ethene complex, **1.21**) gave the expanded six-membered zirconacyle **2.101** (Scheme 2.28). Further Zr-alkenylidene rearrangement driven by phenyl acetylide to give intermediate **2.102** followed by endo- and exocyclic β-H elimination to provide after protonolysis an inseparable mixture of products **2.103** and **2.104** in 64% and 45% combined yield for hexyl and phenyl substituent, respectively. Although the main limitation of the synthetic route presented below is the β-H abstraction, this method can be an alternative route for synthesis of substituted cyclopentadienes.

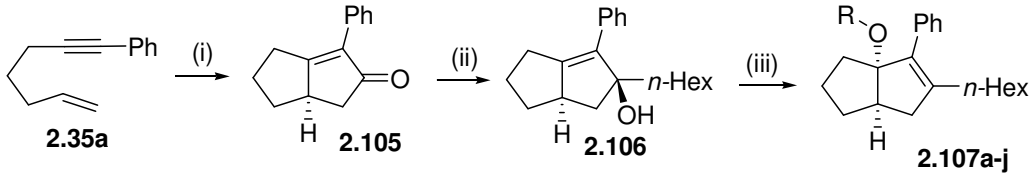


Reagents and conditions: (i) 2 eq EtMgBr, THF −78 °C, 45 min; (ii) RCCR, −78 °C to +5 °C, 3 h; (iii) 3.0 eq PhCCLi,−78 °C to 0 °C over 3 h; (iv) MeOH, aq $NaHCO_3$, RT, 12 h.

Scheme 2.28 Insertion of alkynes and carbenoids into Zr-ethene complex.

2.4. Synthesis of 1-alkoxy-*cis*-bicyclo[3.3.0]oct-2-enes

The results from testing for biological activity against LRH-1 and SF-1 of alkoxy analogues **2.107** of **1.7** were required to complete a series for publication (Scheme 2.29).



Reagents and conditions: (i) $Co_2(CO)_8$, 10 eq DMSO, THF, reflux, 5 h, 80%; (ii) *n*-HexMgBr, $CeCl_3$, −10 °C to RT, 1 h, 90%; (iii) 10 eq ROH, 0.1 eq camphorsulfonic acid, RT, 3.5 h, then aq $NaHCO_3$.

Scheme 2.29 Synthesis of alkoxy analogues of 1.7.

Tertiary alcohol **2.106** was synthesised as previously reported[83] from hept-6-en-1-yn-1-ylbenzene **2.35a** *via* Pauson-Khand cyclisation to give the cyclopentenone **2.105** and cerium trichloride assisted 1,2-addition of hexylmagnesium bromide (Scheme 2.29).

Exposure of **2.106** to various alcohols in the presence of catalytic amounts of camphorsulphonic acid gave a series of analogues **2.107** of **1.7** in which an alkoxy group replaced the aniline substituent. Yields for the last step were generally good (Table 2.3), the exception being when the alcohol carried an alpha-branch. The products **2.107** were unstable to silica, so were purified by column chromatography on basic grade III alumina.

Compound	R	Yield / %
2.107a	OMe	75
2.107b	OEt	69
2.107c	OPr	71
2.107d	O-*i*-Pr	7
2.107e	O-*n*-Bu	68
2.107f	$OCH_2CH(Me)(Et)$	64
2.107g	O-*n*-Pent	62
2.107h	O-*n*-Hex	65
2.107i	O-*c*-Hex	12
2.107j	OBn	63

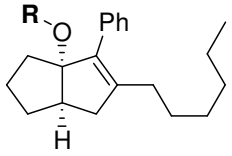
Table 2.3 Synthesis of 1-alkoxy-3-hexyl-2-phenyl-*cis*-bicyclo[3.3.0]oct-2-enes.

2.5. SAR for 1-alkoxy-*cis*-bicyclo[3.3.0]oct-2-enes and 'all carbon' analogues of GSK8470

The compounds **2.63a-w**, **2.67a-b**, **2.69**, **2.70**, **2.72**, **2.73**, **2.78** and **2.107a-j** were screened for activity against both hLRH-1 and hSF-1 using FRET-based peptide recruitment assay.[177] Purified bacterial expressed ligand binding domains[75] of human LRH-1 or human SF-1 were labelled with biotin and incubated with APC labelled streptavidin (Molecular Probes). Peptides derived from TIF2 amino acids 737-757 (B-QEPVSPKKKENALLRYLLDKDDTKD-CONH2) for LRH-1, or from DAX-1 amino acids 1-23 (B-MAGENHQWQGSILYNMLMSAKQT-CONH2) for SF-1 were labelled with biotin and incubated with europium labelled streptavidin (Wallac Inc.). The labelled receptor and peptide were incubated in the presence of various concentrations of test compound and the associated complexes quantified by time resolved fluorescence energy transfer (TR-FRET). The EC_{50}'s of the test compounds, which serve as a measure of the binding affinity for the receptor, was estimated from a plot using the ratio of fluorescence values collected at 671 nM to fluorescence values collected 618 nM versus concentration of test compound added.

Typically 11 points over certain concentration range were used to construct each dose-response curve and the EC_{50} was calculated using the appropriate software. For LRH-1 6 repeats were carried out, for SF-1 3. Standard deviation (SD) serves as a measure of uncertainty of the results. Test compounds that increased the affinity of the receptors for the peptide yielded an increase in fluorescent signal which is reported as the relative efficacy (RE) at peptide recruitment, which in the absence of a known standard was normalized to racemic **2.69-*exo*** for LRH-1 and **2.69-*exo*-ent-2** for SF-1.

The data is presented in several tables. Table 2.4 shows the alkoxy-substituted series **2.107a-j**, Table 2.5, Table 2.6 and Table 2.7 show the series **2.63** compounds with emphasis of variation at the 1, 2 and 3 positions of the bicyclo[3.3.0]oct-2-ene skeleton respectively. Table 2.8 contains the alternative core structures of **2.67** and **2.78**. Finally, Table 2.9 provides results from compounds **2.69**, **2.70**, **2.72** and **2.73** with oxygen substitution on the cyclopentane ring.[177]



2.107a-j

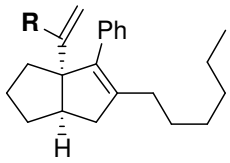
Compound	R	LRH-1		SF-1	
		pEC_{50} (±SD)	**RE (±SD)**	**pEC_{50} (±SD)**	**RE (±SD)**
1.5	–	6.2 (0.07)	0.89	6.8 (0.008)	0.35
1.7	–	7.5 (0.003)	0.38	7.4 (0.008)	0.70
2.107a	OMe	ia	ia	ia	ia
2.107b	OEt	5.6 (0.05)	0.17 (0.02)	6.3 (0.06)	0.50 (0.02)
2.107c	OPr	5.6 (0.10)	0.21 (0.04)	6.7 (0.04)	0.62 (0.02)
2.107d	O-*i*-Pr	5.5 (0.04)	0.19 (0.03)	6.4 (0.04)	0.46 (0.04)
2.107e	OBu	5.3 (0.05)	0.39 (0.03)	6.6 (0.07)	0.60 (0.03)
2.107f	$OCH_2CH(Me)(Et)$	5.6 (0.06)	0.18 (0.03)	6.7 (0.06)	0.52 (0.02)
2.107g	OPent	ia	ia	6.4 (0.08)	0.40 (0.02)
2.107h	O-*n*-Hex	ia	ia	ia	ia
2.107i	O-*c*-Hex	6.1 (0.03)	0.16 (0.02)	7.1 (0.05)	0.63 (0.006)
2.107j	OBn	ia	ia	ia	ia

Table 2.4 LRH-1 and SF-1 binding and activation of alkoxy substituted series 2.107.

Pleasingly, it was found that many of the alkoxy-substituted analogues were active against both LRH-1 and SF-1 showing that the nitrogen in the aniline series **1.6** (exemplified by **1.5** and **1.7**) was not necessary. All the compounds bound substantially less strongly to LRH-1 (pEC_{50} are ranging from 5.3 to 6.1), and induce less recruitment of peptide (RE from 0.16 to 0.39), than the aniline series (pEC_{50} = 7.5 and RE = 0.38 for **1.7**) suggesting that an aromatic group is preferred by LRH-1 in this region. Unfortunately it was not possible to make the OPh substituted system – it was too unstable, both because phenoxide is a much better leaving group than alkoxides, but also because phenol will act as an acid catalyst for decomposition. The compounds showed reasonable selectivity for SF-1, with binding approaching (pEC_{50} = 6.3 ÷ 7.1), and efficacy exceeding (RE = 0.40 ÷ 0.63) that of the currently most used biological tool **1.5** (pEC_{50} = 6.8 and RE = 0.35). For both LRH-1 and SF-1 was found a clear SAR relating to the size of the R group with both small groups (Me) and large groups giving compounds which bound weakly (pEC_{50} < 5.0). The cut-off for large chains is sharp indicating a defined pocket being filled. For LRH-1 this is above four carbons long (cyclohexyl, $CH_2CH(Me)(Et)$, and *n*-butyl all fit, *n*-pentyl does not. For SF-1 the pocket appears slightly larger with *n*-pentyl fitting, but *n*-hexyl not. Similar trend was observed with aniline series **1.6**, where compounds with *N*Ph bound strongly (pEC_{50} > 6.0) and were active (RE = 0.50 ÷ 1.0), whereas compounds with 3- or 4-substitution on the *N*Ar ring gave reduced binding (pEC_{50} < 5.0) or inactive compounds.[83]

Although the alkoxy-substituted series provided a candidate for one of the key-aims – the SF-1 selective compound **2.107g**, the compounds proved as acid sensitive as the aniline series. For example they decomposed on attempted chromatography on silica, or if stored in glassware which had not been base washed.

Due to acid instability of series **2.107**, compound **2.63a** was examined as it has similar *cis*-bicyclo[3.3.0]oct-2-ene structure but lacking the cause of acid instability – the bridgehead leaving group. Delightfully it was found to exhibit good binding and activation of both LRH-1 and SF-1 (Table 2.5).

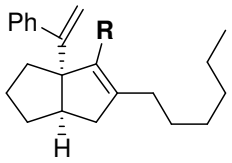


2.63a-l

Compound	R	LRH1 (RE)		SF1 (RE)	
		pEC_{50} (±SD)	RE (±SD)	pEC_{50} (±SD)	RE (±SD)
2.63a	Ph	6.6 (0.06)	0.24 (0.05)	7.2 (0.02)	0.82 (0.06)
2.63b	3-MeOPh	6.5 (0.05)	0.25 (0.04)	7.2 (0.1)	0.27 (0.008)
2.63c	4-MeOPh	ia	ia	ia	ia
2.63d	4-MePh	5.7 (0.12)	0.25 (0.02)	6.8 (0.05)	0.28 (0.004)
2.63e	4-EtPh	ia	ia	ia	ia
2.63f	4-*n*-BuPh	ia	ia	ia	ia
2.63g	4-*t*-BuPh	ia	ia	ia	ia
2.63h	4-PhPh	ia	ia	ia	ia
2.63i	*n*-Pr	5.5 (0.17)	0.23 (0.04)	6.8 (0.02)	0.63 (0.02)
2.63j	*n*-Bu	ia	ia	6.7 (0.07)	0.70 (0.03)
2.63k	*n*-Hex	ia	ia	ia	ia
2.63l	*n*-Oct	ia	ia	ia	ia

Table 2.5 Variation of bridgehead substituent in series 2.63 compounds.

Variation of the lithiated alkyne used in the multi-component synthesis of **2.63** allowed variation of the bridgehead substituent (Table 2.5). As with the series **2.107** compounds, a strict cut-off in the size of group R which can be accommodated is observed. Even addition of a para-methyl group to the preferred phenyl substituent decreased binding **2.63d**, and anything larger **2.63e-h** gave inactive compounds. Interestingly a 3-MeO group was well tolerated perhaps indicating some stabilisation *via* dipolar interactions or weak H-bonding, whereas a 4-OMe substitution gave an inactive compound (**2.63c**). When R is an alkyl group **2.63i-l** LRH-1 binds only the shortest tried **2.63i** (R = *n*-Pr), and then with low pEC_{50} and efficacy. Even compound **2.63j** with R = *n*-Bu is inactive, and since this is little longer that R = Ph indicates a strong preference for an aryl group. SF-1 bound the R= *n*-Bu compound **2.63j** strongly and with good efficacy confirming the larger pocket noted in the SAR of series **2.107**, and providing an excellent SF-1 selective analogue. Compounds with the longer chain R = *n*-Hex, *n*-Oct; **2.63k**,**l** respectively, were inactive.

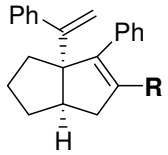


2.63a, m-s

Compound	R	LRH1 (RE)		SF1 (RE)	
		pEC_{50} (±SD)	**RE (±SD)**	**pEC_{50} (±SD)**	**RE (±SD)**
2.63a	Ph	6.6 (0.06)	0.24 (0.05)	7.2 (0.02)	0.82 (0.06)
2.63m	3-MeOPh	6.6 (0.02)	0.23	6.9 (0.02)	0.40
2.63n	4-EtPh	ia	ia	ia	ia
2.63o	*n*-Pr	ia	ia	6.4 (0.02)	0.52 (0.11)
2.63p	*n*-Bu	ia	ia	6.6 (0.08)	0.57 (0.03)
2.63q	*n*-Hex	ia	ia	ia	ia
2.63r	*c*-Hex	ia	ia	6.7 (0.05)	0.56 (0.04)
2.63s	$(CH_2)_3OH$	6.0 (0.04)	0.38 (0.05)	ia	ia

Table 2.6 Variation of 2-substituent in series 2.63 compounds.

Changing the 1,6-enyne starting material allowed the structure activity relationship due to variation of the substituent on position 2 of the bicyclo[3.3.0]oct-2-ene to be probed (Table 2.6). The tight constraints, and apparent preference for aryl groups of the LRH-1 binding site are again apparent. Although a 3-methoxy-phenyl group **2.63m** is tolerated, 4-ethylphenyl **2.63n** is not, and surprisingly none of R = *n*-Pr, *n*-Bu, or *c*-Hex **2.63o**,**p**,**r**, all similar sizes to a phenyl group, gave active compounds. SF-1 proved much more accommodating, consistent with the larger ligand binding pocket, although compounds with 4-ethyl-phenyl **2.63n** or *n*-Hex, **2.63q**, substituents were not active. *n*-Pr, *n*-Bu and *c*-Hex substituted compounds **2.63o**,**p**,**r** all gave similar binding and efficacy with SF-1, but distinctly poorer than compound **2.63a** (R = Ph). Remarkably, the 3-hydroxypropyl subsistent in **2.63s** gave good binding and activation of LRH-1, but is inactive against SF-1 providing the only example of a highly LRH-1 selective compound. It is believed that the hydroxyl group may be picking up binding to the polar area at the entrance to the ligand binding pocket where the phosphate portion of phospholipids is found in crystal structures of LRH-1. The inactivity of **2.63s** indicates this to be a very non-polar area in SF-1.



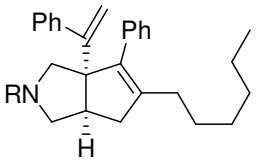
2.63a, t-w

Compound	R	LRH1 (RE)		SF1 (RE)	
		pEC_{50} (±SD)	**RE (±SD)**	**pEC_{50} (±SD)**	**RE (±SD)**
2.63a	Ph	6.6 (0.06)	0.24 (0.05)	7.2 (0.02)	0.82 (0.06)
2.63t	H	ia	ia	ia	ia
2.63u	*n*-Bu	6.7 (0.02)	0.54 (0.05)	7.4 (0.03)	0.85 (0.01)
2.63v	*n*-Oct	5.8 (0.16)	0.15 (0.02)	6.8 (0.07)	0.65 (0.04)
2.63w	$SiMe_2Ph$	6.8 (0.05)	0.54 (0.05)	7.2 (0.04)	0.33 (0.002)

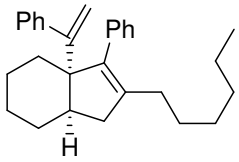
Table 2.7 Variation of 3-substituent in series 2.63 compounds.

Using alternative dihalocarbenoids in the formation of **2.63** allowed the biological effect of some variation in the 3-substituent (Table 2.7). Reducing it to a hydrogen, gave an inactive compound against both receptors indicating that the ligand binding pocket does need to be filled for binding/activity. Shortening the *n*-hexyl **2.63a** substituent to *n*-butyl **2.63u** gave a substantial increase in efficacy for LRH-1 without affecting SF-1.

The bulky $SiMe_2Ph$ substituent gave a substantial increase in efficacy for LRH-1, and a significant decrease in efficacy for SF-1. An *n*-octyl chain gave some reduction in binding and efficacy, particularly for LRH-1.



2.67a, R = Me
2.67b, R = Bn

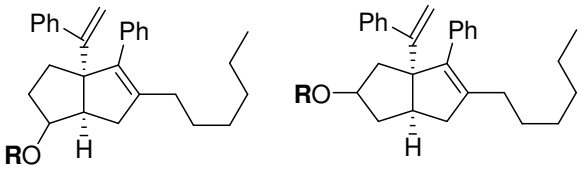


2.78

Compound	LRH1 (RE)		SF1 (RE)	
	pEC_{50} (±SD)	**RE (±SD)**	**pEC_{50} (±SD)**	**RE (±SD)**
2.63a	6.6 (0.06)	0.24 (0.05)	7.2 (0.02)	0.82 (0.06)
2.78	6.6 (0.05)	0.24 (0.04)	7.2 (0.05)	0.40 (0.004)
2.67a	5.9 (0.03)	0.20 (0.03)	6.5 (0.11)	0.49 (0.02)
2.67b	ia	ia	ia	ia

Table 2.8 Effect of variations in skeleton on biological activity.

Variation in the core skeleton was also considered (Table 2.8). The only effect of changing the fused saturated ring from cyclopentane (in **2.63a**) to cyclohexane (in **2.78**) was reduced efficacy against SF-1. The pyrrolidine fused systems **2.67a**,**b** offered the potential of improved solubility. The *N*-methyl compound **2.67a** was active against both receptors, although with reduced binding and efficacy, particularly against LRH-1. Given the improved solubility characteristic of **2.67a** c.f. the hydrocarbons **2.63** it is a useful SF-1 selective compound.



2.69, R = H
2.70, R = OAc

2.72, R = H
2.73, R = OAc

Compound	LRH1 (RE)		SF1 (RE)	
	pEC_{50} (±SD)	**RE (±SD)**	**pEC_{50} (±SD)**	**RE (±SD)**
2.63a	6.6 (0.06)	0.24 (0.05)	7.2 (0.02)	0.82 (0.06)
2.69-*exo* (racemic)	6.6 (0.05)	1.0 (0.05)	7.5 (0.10)	0.94 (0.05)
2.69-*exo*-ent-1	6.6 (0.02)	0.29 (0.04)	7.6 (0.04)	0.99 (0.03)
2.69-*exo*-ent-2	6.7 (0.19)	0.88 (0.06)	7.5 (0.21)	1.0 (0.10)
2.69-*endo*	6.4 (0.08)	0.68 (0.03)	7.2 (0.06)	0.74 (0.005)
2.70-*exo*	6.4 (0.09)	0.18 (0.03)	6.4 (0.01)	0.18 (0.007)
2.70-*endo*	6.6 (0.06)	0.18 (0.04)	7.0 (0.03)	0.25 (0.008)
2.72-*exo*	6.0 (0.07)	0.53 (0.06)	6.6 (0.07)	0.45 (0.02)
2.72-*endo*	5.8 (0.04)	0.32 (0.03)	6.5 (0.05)	0.87 (0.007)
2.73-*exo*	ia	ia	ia	ia
2.73-*endo*	6.3 (0.09)	0.13 (0.01)	6.7 (0.04)	0.32 (0.02)

Table 2.9 Effect of oxygen substitution on the cyclopentane ring.

Finally some analogues with oxygen substitution of the cyclopentane ring were examined (Table 2.9). The choice was driven by the crystal structure of LRH-1[75] which indicated a polar patch (Arg-393 and His-390) in the generally hydrophobic ligand binding site.

Pleasingly it was found that the compound with a 6-*exo*-hydroxy substituent (**2.69-*exo***) was the most active of all the compounds tested – both in binding and efficacy against both LRH-1 and SF-1.

The strong activity provided an incentive to separately test the two enantiomers of **2.69-*exo***, and surprisingly it turned out that both enantiomers have equal binding to both LRH-1 and SF-1. Indeed the only difference between them was the substantially greater efficacy of **ent-2** c.f. **ent-1** with LRH-1. It is usual for only one enantiomer of a compound to be active against a particular receptor, and particularly surprising in this case when such strong SAR effects against small changes in structure has been observed. The *endo*-epimer of **2.69** showed very similar binding and efficacy against both receptors as compound **2.63a** lacking the oxygen substitution. Acylation of the alcohol had little effect on binding (Table 2.9, entries 6 vs 2 and 7 vs 5), but substantially reduced efficacy, with the exception of **2.70-*exo*** where binding to SF-1 was reduced, incidentally providing one of the most 'LRH-1 selective' compounds produced.

The 7-hydroxyl substituted systems **2.72-*exo*** and **2.72-*endo*** showed reduced binding compared to the unsubstituted analogue **2.63a**, though efficacies were reasonable. Acylation of the *exo*-alcohol gave inactive compound **2.73-*exo*** against both LRH-1 and SF-1 (entry 10) indicating a size limitation of this part of the binding pocket. Acylation of the endo alcohol to give **2.73-*endo*** (entry 11) was well tolerated.

Agonist/antagonist crossover

For most compounds the biological results were clear – excellent agreement between the repeats, with nicely sigmoidal curves for active compounds (at least when EC_{50} >6) and inactive compounds showing no response. However, in a few cases variable results were obtained which might be attributed to agonist/antagonist crossover. For LRH-1 this is best illustrated by the curves for the *N*-benzyl pyrrolidine **2.67b** (Figure 2.2). In this case three runs showed agonist activity with a pEC_{50} of 6.5, but another three showed what may be interpreted as antagonist activity, with around the same binding constant. Similar behaviour, but with 4 agonist and 2 antagonist lines were observed for **2.63m** and **2.72-*endo*** (pEC_{50} 6.6 and 5.8 respectively). Since the protein used for assay is known to contain phospholipids, and some of these are known agonists for LRH-1 it is possible that **2.67b** has stronger binding, but lower efficacy than the natural ligand. If the amount or type of phospholipids varied between experiments it is possible to get the apparent agonist/antagonist crossover behaviour observed. Against SF-1 the agonist/antagonist behaviour was observed in two compounds – the *exo*-acetates **2.70-*exo*** and **2.73-*exo***. In the former case 2/3 curves showed agonist activity (as in Table

2.9), the other antagonist (~same pEC_{50} and RE of –0.2); in the later 1/3 curves was agonist (pEC_{50} 6.8, RE 0.2) and 2/3 antagonist (pEC_{50} 6.8, RE –0.2). In addition two compounds (**2.63n** and **2.63s**) showed quite convincing antagonist activity (sigmoidal curves showing negative response) with pEC_{50}'s of ~6.5.

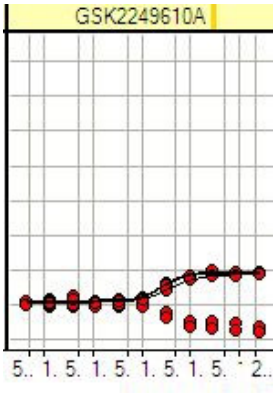


Figure 2.2 Agonist/antagonist crossover for 2.67b.

Comparison of efficacy and binding

It is notable that with both receptors examined the maximum activation (RE) varied widely. Ploting the RE against the pEC_{50} for all the 'all carbon' systems for LRH-1 and SF-1 (Figure 2.3) demonstrates the modest correlation between the two, particularly for LRH-1. In particular there are groups of compounds with strong binding, but poor efficacy, providing indications of how agonists can be developed.

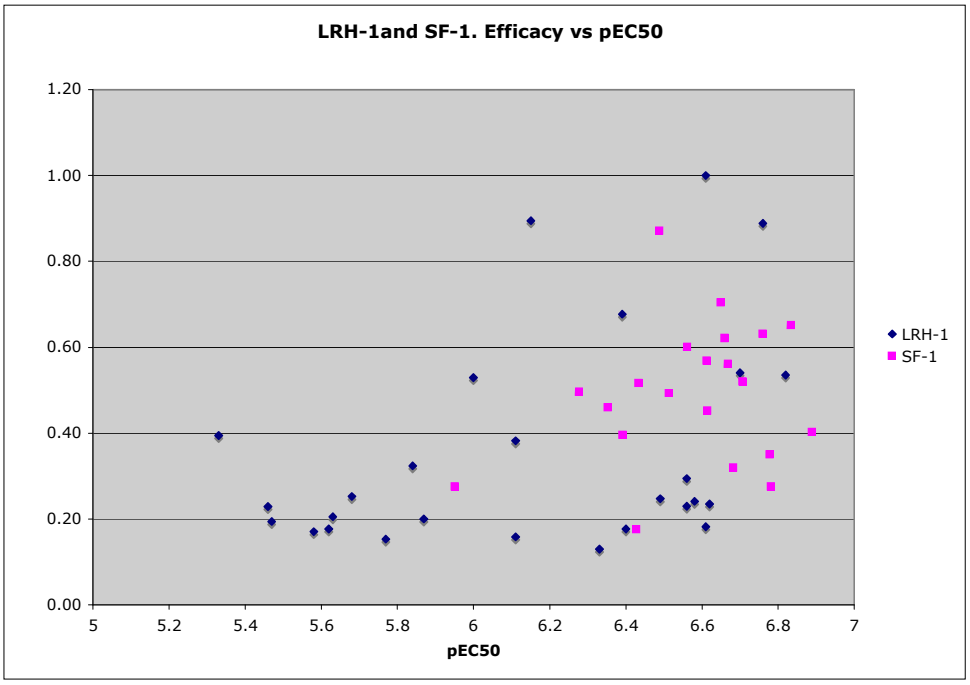


Figure 2.3 Comparison of efficacy and binding.

Choice of compounds recommend as biological probes

Compound **2.69-*exo*** provides an excellent replacement for compound **1.5** as a biological tool. It has excellent stability, reasonable solubility in polar solvents and improved binding and efficacy against both LRH-1 and SF-1. Little is lost by using the 1.6 : 1 mixture of **2.69-*exo*** and **2.69-*endo*** produced directly from the zirconium mediated reaction thus avoiding a tricky separation. Compound **2.63j** provides the best tool for selective activation of SF-1 (with **2.63o**,**p**,**r** also being good). Its main disadvantage is its non-polar nature which may cause solubility problems in polar solvents, in which case pyrrolidine **2.67a** provides reasonable selectivity and may be preferred.

2.6. Conclusions for chapter 2

Substrate scoping studies for the one-pot tandem reaction sequence on zirconocene template resulted in synthesis of a wide range of bicyclic compounds containing rigid *cis*-bicyclo[3.3.0]oct-2-ene skeleton. The final compounds were obtained in yields ranging from good to very good. For sterically encumbered zirconacycles (or carbenoids), the undesired β-hydride elimination process was observed. Nonetheless, the one-pot tandem reaction sequence provides an excellent method for construction of bicyclic compounds and potential for functionalisation at multiple sites. Such obtained compounds were tested for biological activity in search for active and selective agonists and antagonists for orphan nuclear receptors: hLRH-1 and hSF-1. Pleasantly, improvement in binding, efficacy, selectivity and acid stability in the case of certain compounds was observed in comparison with the previously reported 1-aryl amino *cis*-bicyclo[3.3.0]oct-2-enes.

Chapter 3. Dihalocarbenoid and acetylide insertion into saturated zirconacyclopentanes

3.1. Introduction to research area

3.1.1. Zirconocene mediated co-cyclisation of dienes

A wide range of 1,*n*-dienes can be cyclised with the Negishi reagent to afford saturated zirconacycles. Extensive research in this area is well described in literature[122,116,178,179] The great range of dienes containing heteroatoms, available for co-cyclisation has led to a number of heterocycles being synthesised by this method.[180] Also zirconocene mediated co-cyclisation of dienes has been applied to the total synthesis of natural products.[181]

3.1.2. Elaboration of zirconacyclopentanes

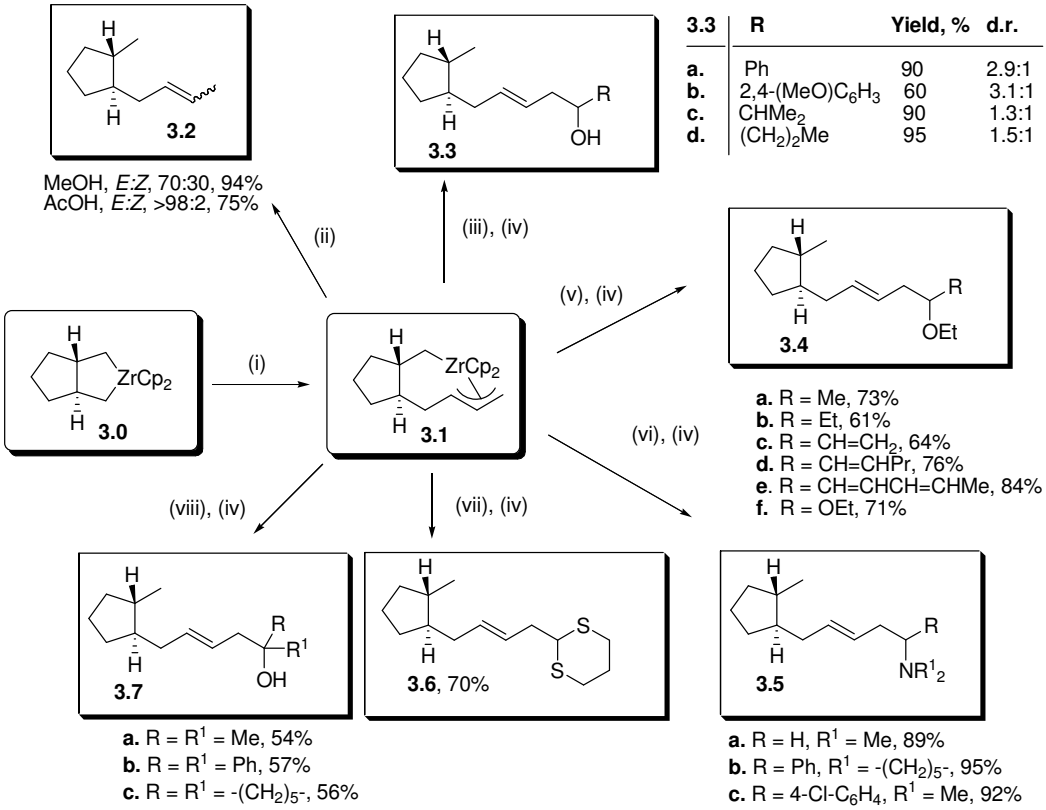
There are several well established methods in which zirconacyclopentanes can be further elaborated to give useful organic products. Similarly to unsaturated zirconacycles, zirconacyclopentanes can be protonated, halogenated,[111] transmetallated to Cu[182] and Mg.[102,183] They also undergo metathesis with main group elements,[121,123] carbon monoxide,[116,117] isonitrile[184] and carbenoid[118] insertion. The latter method is more relevant to research described in this section and therefore will be reviewed in more detail.

3.1.2.1. Allyl and methylallyl carbenoid insertion into saturated zirconacycles

Insertion of lithium chloroallylide and chloromethylallylide into zirconacyclopentanes has been extensively investigated by Whitby and co-workers. (Scheme 3.1).[138,185]

Insertion of lithiated allyl chloride **1.76** into saturated zirconacycle **3.0** affords the 18-electron allyl-zirconocene complex **3.1**. Protonolysis of this complex with acetic acid gives excellent control of the double bond geometry in product **3.2**.

The one-pot tandem reaction sequence on zirconocene allows a great deal of diversity in terms of diene, carbenoid and electrophile variability. The allyl-Zr complex **3.1** was found to react with a broad spectrum of electrophiles yielding the products shown in Scheme 3.1.[139] Lewis acid promoted insertion of aldehydes, acetals, and additional iminium ions provides the corresponding alcohols **3.3**, ethers **3.4** and amines **3.5**, though without significant diastereoselectivity. For insertion of ketones longer reaction times and higher temperatures were required to obtain tertiary alcohols **3.7**.



3.3	R	Yield, %	d.r.
a.	Ph	90	2.9:1
b.	2,4-(MeO)C_6H_3	60	3.1:1
c.	$CHMe_2$	90	1.3:1
d.	$(CH_2)_2Me$	95	1.5:1

Reagents and Conditions: (i) CH_2CHCH_2Cl, LDA or LiTMP, −78 ^oC, 0.5 h; (ii) MeOH or AcOH, 16 h; (iii) 1.1 eq RCHO, 1.1 eq $BF_3{\cdot}Et_2O$, −40 ^oC to RT, 3 h; (iv) MeOH, aq $NaHCO_3$, RT, 12 h; (v) $RCH(OEt)_2$, $BF_3{\cdot}Et_2O$, −78 ^oC to RT, 2 h; (vi) for a: 1.3 eq $(CH_2NR_2)I$, −78 ^oC to RT, 1.5 h; for b, c: 1.5 eq $RCH(NR^1{}_2)(OBu)$, 1.5 eq $BF_3{\cdot}Et_2O$, −78 ^oC to RT, 2 h; (vii) 2.0 eq 1,3-dithenium-tetrafluoroborate, −78 ^oC to RT, 1.5 h; (viii) for a: Me_2CO, benzene, 80 ^oC, 48 h; for b, c: Ph_2CO, cyclohexanone, toluene, 110 ^oC, 48 h.

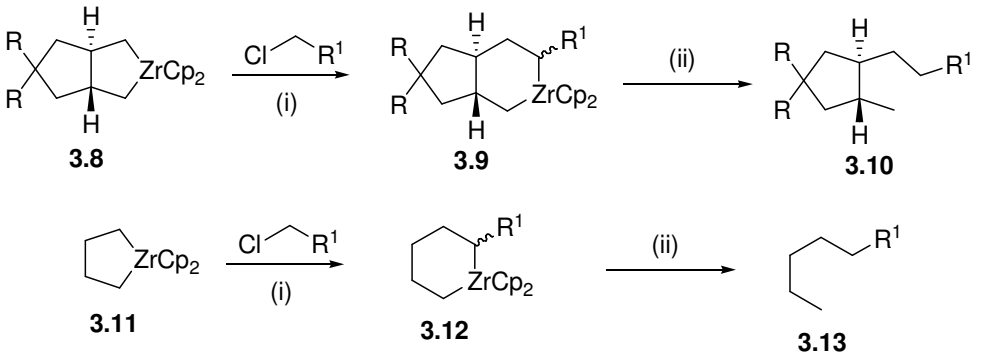
Scheme 3.1 Diversity of allyl zirconocene complexes elaboration.

Variations of allyl carbenoid in terms of leaving group and substitution have also been investigated.[137]

3.1.2.2. Insertion of 1-halo-1-lithioalkanes into zirconacyclopentanes

Alkyl carbenoid insertion into a wide range of zirconacyclopentanes has also been investigated.[133,186]

Carbenoids with electron-donating and electron-withdrawing groups were found to insert into bicyclic and monocyclic unsubstituted zirconacyclopentanes (Scheme 3.2).



Reagents and Conditions: (i) LiTMP or LDA, –78 ^{o}C;
(ii) MeOH, aq $NaHCO_3$, RT, 12 h.

Scheme 3.2 Insertion of alkyl carbenoids into zirconacyclopentanes.

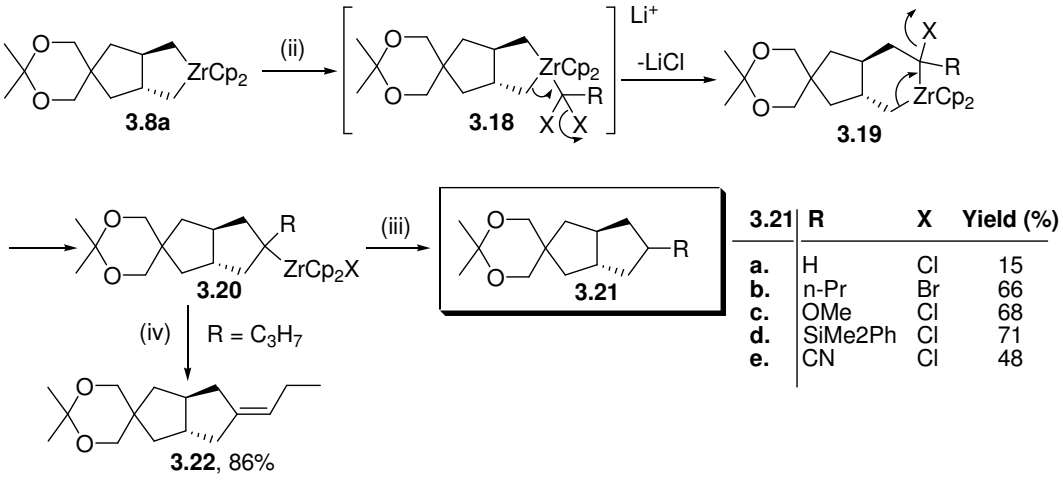
Entry	Zirconacycle/ R, R	Carbenoid/ R^1	Yields of 3.10, 3.13/ %
a	**3.8a/** -$CH_2OCMe_2OCH_2$-	**1.107/** $SiMe_3$,	78
b	**3.8a/** -$CH_2OCMe_2OCH_2$-	**3.14/** $SiMe_2Ph$	77
c	**3.8b/** -CH_2OMe, -CH_2OMe	**3.14/** $SiMe_2Ph$	70
d	**3.8b/** -CH_2OMe, -CH_2OMe	**3.15/** $SnBu_3$	11
e	**3.8a/** -$CH_2OCMe_2OCH_2$-	**3.16/** SPh	77
f	**3.8a/** -$CH_2OCMe_2OCH_2$-	**3.17/** OEt	45
g	**3.8b/** -CH_2OMe, -CH_2OMe	**1.117/** $P(O)(OEt)_2$	74
h	**3.8b/** -CH_2OMe, -CH_2OMe	**1.92/** CN	24
i	**3.8b/** -CH_2OMe, -CH_2OMe	**1.95/** SO_2Ph	67
j	**3.11**	**1.117/** $P(O)(OEt)_2$	56

Table 3.1 Yields of 3.10 and 3.13 from insertion o various carbenoids into zirconacycles 3.8a, b and 3.11.

Insertion of alkyl carbenoids into zirconacycles **3.8a**,**b** and **3.11** occurred successfully in many cases to provide the corresponding products, apart from a few cases, in very good yields (Table 3.1). In all but one case products of monoinsertion were obtained. The low yields of products **3.10d**,**f** and **h** are related to the peculiar reactivity of the carbenoids used in these reactions. The α-stannyl carbenoid **3.15** is suspected to undergo tin/lithium exchange very quickly, the α-ethoxy carbenoid **3.17** is thermally unstable and the complex **3.9f** decomposes above –20 ^{o}C, whereas insertion of lithiated chloroacetonitrile **1.92** resulted in bisinsertion product to be the major (45%) and monoinsertion product **3.10h** to be the minor (24%).[133]

3.1.2.3. Insertion of 1,1-dihalo-1-lithioalkanes into zirconacyclopentanes

A special case of insertion of a dihalocarbenoid into an organozirconium system **3.8a** was reported in 1999,[145] where the zirconacycle ring expansion was followed by a ring closure with loss of a second halide (Scheme 3.3). In this example, the 1,2-metallate rearrangement[134,136] to afford zirconacyclohexane **3.19** is followed by dyotropic rearrangement[187-189] to form the bicyclo-Zr complex **3.20**, which after protonolysis provides the bicyclo[3.3.0]octane system **3.21**. If the intermediate **3.20** with R = *n*-Pr was warmed to RT before quench, dehydrozirconation process occurred to give solely product **3.22** (Scheme 3.3).[145] Very poor yields were obtained for insertion of dichloromethane, but reasonable in other cases.



3.21	R	X	Yield (%)
a.	H	Cl	15
b.	n-Pr	Br	66
c.	OMe	Cl	68
d.	SiMe2Ph	Cl	71
e.	CN	Cl	48

Reagents and Conditions: (i) Cp_2ZrCl_2, n-BuLi, THF, −78 °C to RT, 2 h; (ii) 1.5 eq $RCHX_2$, 1.7 eq LDA, −78 °C to −55 °C over 2 h; (iii) MeOH, aq $NaHCO_3$, −78 °C to RT, 16 h; (iv) −78 °C to RT, then MeOH, aq $NaHCO_3$, 16 h.

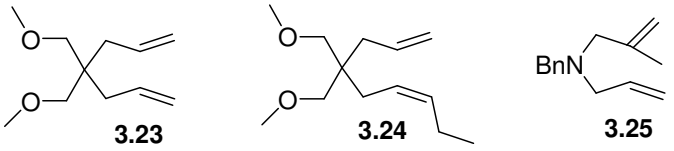
Scheme 3.3 Carbocycles synthesis *via* insertion of dihalocarbenoids into zirconacyclopentane.

3.2. Construction of bicyclo[3.3.0]octanes *via* insertion of 1,1-dihalo-1-lithio species and lithium acetylides into zirconacyclopentanes

The following section discusses further work in the area of dihalocarbenoid insertion into zirconacyclopentanes. Alkyl carbenoid and acetylide insertion into a range of zirconacyclopentanes has been investigated. The reaction sequence worked well in the case of unsubstituted dienes to provide the corresponding products of three-component coupling on a zirconocene template in reasonable yields. The main limitation of this method has arisen from the β-hydride elimination process observed in the case of sterically encumbered zirconacycles.

3.2.1. Preparation of cyclisation precursors

4,4-Bis(methoxymethyl)hepta-1,6-diene **3.23**, (*Z*)-4,4-bis(methoxymethyl)nona-1,6-diene **3.24** and *N*-allyl-*N*-benzyl-2-methylprop-2-en-1-amine **3.25** (Figure 3.1) were prepared from commercially available starting materials using literature methods and had spectral properties consistent with those included in the thesis of former group members or literature.[132]



3.23 **3.24** **3.25**

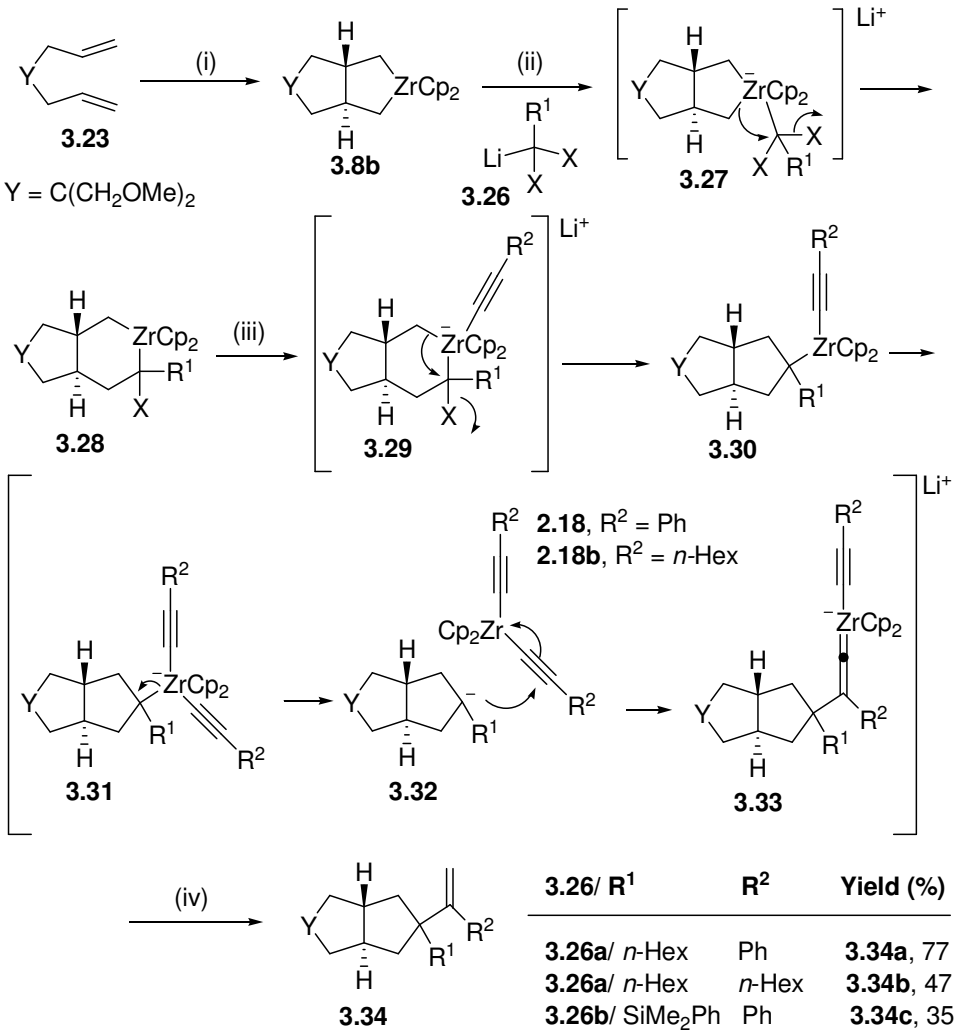
Figure 3.1 Dienes for Zr-mediated cyclisation and further elaboration.

3.2.2. Elaboration of zirconacyclopentanes *via* dihalocarbenoid and acetylide insertion

3.2.2.1 Insertion of alkyl carbenoids and acetylides into α-unsubstituted zirconacyclopentanes

Extension of the one-pot three-component coupling of saturated zirconacycles, dihalocarbenoids and acetylides resulted in synthesis of a series of novel compounds containing a bicyclo[3.3.0]octane core (Scheme 3.4).

Insertion of 1,1-dihalo-1-lithio species **3.26** into zirconacyclopentane **3.8b** affords the 'ate' complex **3.27** which undergoes 1,2-metallate rearrangement to provide the expanded zirconacyclohexane **3.28**. Nucleophilic attack of lithium acetylide onto the Zr atom forces the second C-Zr bond to migrate, thus to afford the carbobicyclo-Zr complex **3.30**. Insertion of a second equivalent of acetylide affords the bisalkynyl-zirconium species **2.18** (**2.18c**) through elimination of carbanion **3.32**. Subsequent re-addition of the anion to β-carbon of the bisalkynyl-zirconium intermediate **2.18** (**2.18c**) provides the novel zirconium-alkenylidenate complex **3.33** to give the carbobicyclic compounds **3.34a-c** after quenching (Scheme 3.4).



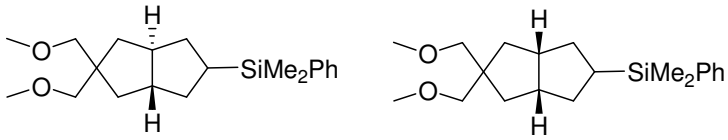
3.26/ R^1	R^2	Yield (%)
3.26a/ *n*-Hex	Ph	**3.34a**, 77
3.26a/ *n*-Hex	*n*-Hex	**3.34b**, 47
3.26b/ $SiMe_2Ph$	Ph	**3.34c**, 35

Reagents and Conditions: (i) Cp_2ZrCl_2, *n*-BuLi, THF, −78 °C to RT, 2 h; (ii) 1.3 eq R^1CHX_2, X = Br for R^1 = *n*-Hex, X = Cl for R^1 = $SiMe_2Ph$, 1.5 eq LDA or LiTMP, −78 °C, 15 min; (iii) 3.0 eq (4.0 for b) R^2CCLi, −78 °C to −55 °C (−25 °C for b and −15 °C for c); (iv) MeOH, aq $NaHCO_3$, RT, 12-16 h.

Scheme 3.4 Insertion of dihalocarbenoids and acetylides into zirconacyclopentanes.

Insertion of lithiated 1,1-dibromoheptane **3.26a** and acetylide **2.7** into zirconacycle **3.8b** provided the bicyclic compound **3.34a** in good yield. The much lower yield for **3.34b** is related to use of the acetylide with an aliphatic substituent **2.18b** (R^2 = *n*-Hex) which turned out to be less reactive than the acetylide with an aromatic substituent (observation consistent with insertion of acetylides in zirconacyclopentenes), therefore four equivalents of this reagent were required to obtain the desired product **3.34b** in an acceptable yield of 47%. Insertion of lithiated (dichloromethyl)dimethyl(phenyl)silane **3.26b** into zirconacycle **3.8b** occurred efficiently, however, the following phenyl

acetylide insertion turned out to be sluggish and gave the desired compound **3.34c** in only 35% yield, provided that the reaction mixture was warmed to –20 °C before quench. In this case a higher temperature was required to make the zirconium-alkenylidene rearrangement occur (**3.32c** → **3.33c**) since the resulting anion **3.32c** is stabilized by the adjacent silyl group, therefore the intermediate is less reactive towards the rearrangement. Additionally, the protonated compounds **3.35a**,**b** (96 : 4 respectively) were detected by GC in the crude reaction mixture in nearly equimolar amount.



3.35a **3.35b**

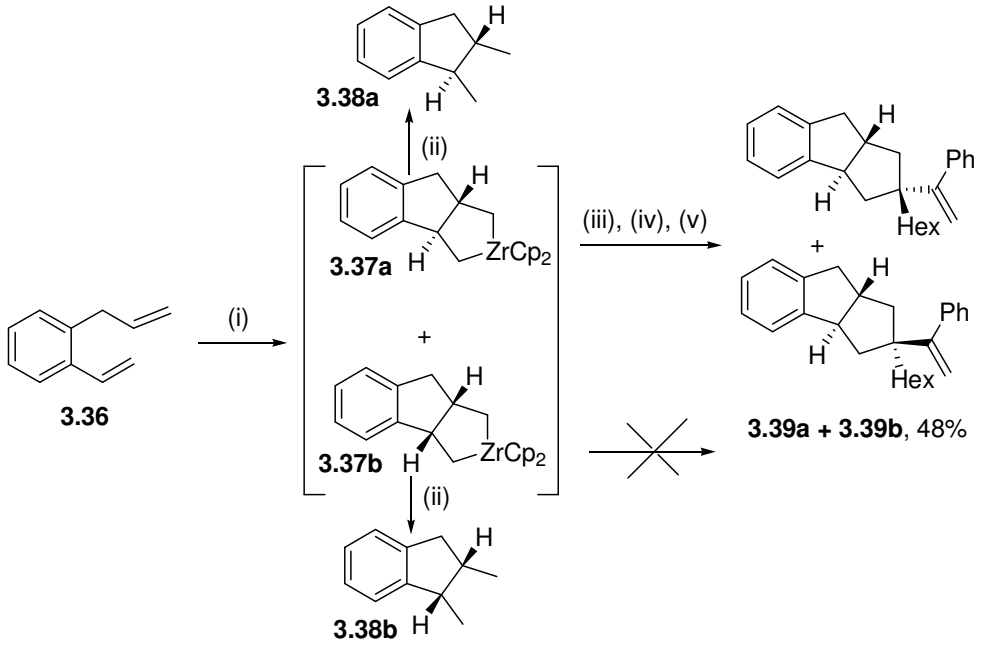
Figure 3.2 Product of protonation 3.32c.

When the procedure was modified by addition of phenylacetylide previously pre-mixed with HMPA to **3.28**, and the whole reaction mixture was allowed to warm to –15 °C before quenching, the major product obtained in the reaction was compound **3.35a**.

Zirconocene mediated co-cyclisation of 1-allyl-2-vinylbenzene **3.36** provided a mixture of *trans : cis* ring junction zirconacycles **3.37a**,**b** in GC ratio of protonated products 82 : 18, respectively (Scheme 3.5). The stereochemistries of the ring junction of these compounds were assigned by correlation of ^{1}H NMR shifts of the methyl groups in products **3.38a** and **b** with the reported spectra[190] of *trans*- and *cis*-1,2-dimethylindans. The proton NMR shifts of the methyl groups in *cis*-isomer were shifted upfield: 1.19 and 1.03 ppm (lit. 1.14, 0.98 ppm) in comparison with the shifts of the methyl groups being in *trans* relationship: 1.36 and 1.26 ppm (lit. 1.28, 1.19 ppm).

Further insertion of lithiated 1,1-dibromoheptane **3.26a** and phenyl acetylide **2.7**, however, occurred exclusively into the *trans* ring junction zirconacycle **3.37a** to give compounds **3.39a**,**b** as an inseparable mixture of two diastereoisomers in the ratio of 1.4 : 1. The stereochemistry at the quaternary carbon centre has not been assigned.

It is postulated that steric reasons of the *cis* ring junction zirconacycle **3.37b** inhibited the carbenoid and acetylide insertion, therefore the yield of the final products **3.39** is diminished (48%).



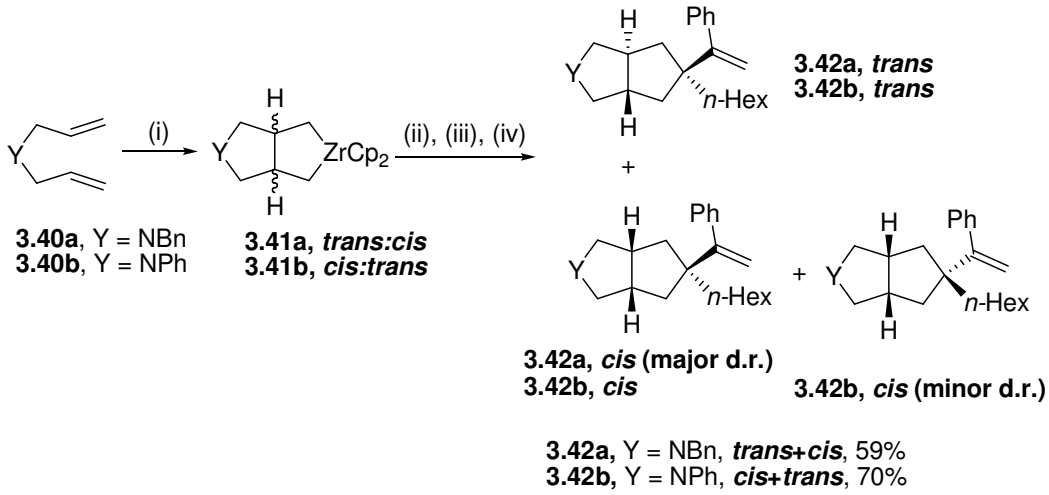
Reagents and Conditions: (i) Cp_2ZrCl_2, *n*-BuLi, THF, −78 ^oC to RT, 2 h; (ii) 2M HCl, RT, 20 h; (iii) 1.05 eq *n*-$HexCHBr_2$, 1.1 eq LDA, −78 ^oC, 15 min; (iv) 3.0 eq PhCCLi, −78 ^oC to −30 ^oC, 1.5 h; (v) MeOH, aq $NaHCO_3$, RT, 12 h.

Scheme 3.5 Insertion of lithiated 1,1-dibromoheptane and phenyl acetylide into zirconacycle 3.37a.

Dienes containing a nitrogen atom were examined next (Scheme 3.6). Co-cyclisation of *N*-allyl-*N*-benzylprop-2-en-1-amine **3.40a** provided a mixture of 3.2 : 1 *trans : cis* ring junction zirconacycles **3.41a** (ratio and stereochemistry determined by GC analysis of the quenched zirconacycles and comparison with the literature precedent). Literature precedent reports a zirconocene mediated co-cyclisation of this diene under similar conditions to give an 4 : 1 mixture of *trans : cis* ring junction zirconacycles.[116] Further insertion of lithiated 1,1-dibromoheptane followed by acetylide addition gave the final compound **3.42a** in 59% yield and the same ratio of 3.2 : 1, *trans : cis* ring junction diastereoisomers, which were separable by silica gel column chromatography.

In turn, zirconocene mediated co-cyclisation of *N,N*-diallylbenzenamine **3.40b** provided the final compounds **3.42b** as a mixture of *cis : trans* ring junction isomers in the ratio of 1.27 : 1 and 70% yield (Scheme 3.6). Nugent and Taber obtained the *cis : trans* ring junction zirconacycles **3.41b** in the ratio of 2 : 1.[122] Noteworthy is the fact that both *cis* diastereoisomers of the final product **3.42b** were created in GC ratio of 13.75 : 1 with respect to the newly formed quarternary carbon centre. The *cis, trans* stereochemistry of the final compounds was determined on the basis of ^{13}C NMR analysis.

For the *cis* isomer ^{13}C NMR symmetry was observed therefore the number of signals of the core carbons was twofold reduced whereas for the *trans* isomer all core carbon signals were observed.

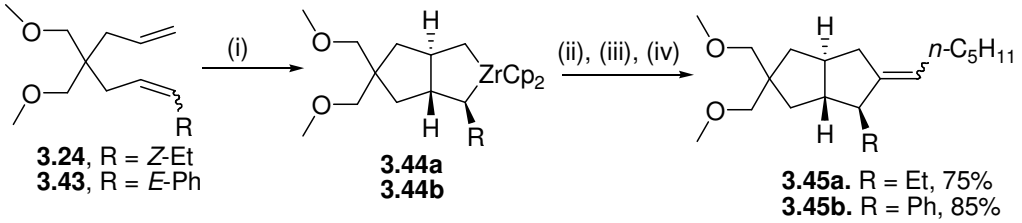


Reagents and Conditions: (i) Cp_2ZrCl_2, *n*-BuLi, THF, −78 ^oC to RT, 3 h; (ii) 1.05 eq *n*-HexCHBr$_2$, 1.5 eq LiTMP, −78 ^oC, 20 min; (iii) 3.0 eq PhCCLi, −78 ^oC to −45 ^oC, 1 h; (iv) MeOH, aq $NaHCO_3$, RT, 12 h.

Scheme 3.6 Construction of pyrrolidine-fused carbocycles 3.42.

3.2.2.2 Insertion of lithiated 1,1-dibromoheptane and phenyl acetylide into α-substituted zirconacyclopentanes

In the case of terminally substituted dienes **3.24** and **3.43** the sole products obtained in the one-pot tandem reaction sequence on a zirconocene template were compounds resulting from the β-hydride elimination (dehydrozirconation) process **3.45a** and **3.45b** (Scheme 3.7). Product **3.45a** was obtained as a single (*E*)-isomer from (*Z*)-Et substituted diene **3.24**, whereas product **3.45b** was obtained from (*E*)-Ph substituted diene **3.43** and consisted of two (*E*)- and (*Z*)-isomers in the ratio of 9 : 1, respectively (Figure 3.3).



Reagents and Conditions: (i) Cp_2ZrCl_2, *n*-BuLi, THF, −78 ^oC to RT, 14-15 h; (ii) 1.3 eq *n*-HexCHBr$_2$, 1.5 eq LiTMP, −78 ^oC, 0.5 h; (iii) 3.0 eq PhCCLi, −78 ^oC to −35 ^oC, (to −15 ^oC for b); (iv) MeOH, aq $NaHCO_3$, RT, 16 h.

Scheme 3.7 Insertion of carbenoid and acetylide into α-substituted zirconacyclopentanes 3.44a, b.

The (*E*)- and (*Z*)-isomers of **3.45b** were identified by means of ^{13}C NMR shifts of the crucial carbon 10 (Figure 3.3) which was shifted upfield in the (*E*)-isomer by steric compression ('*γ-gauche* effect'),[191] and this isomer appeared to be the major.

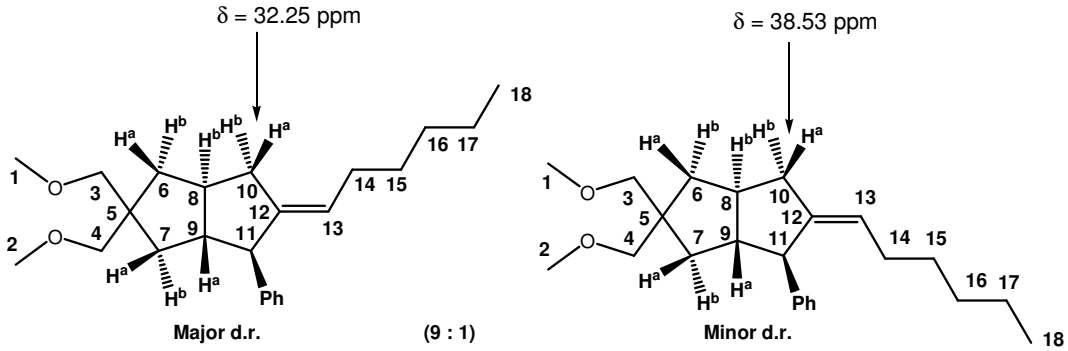
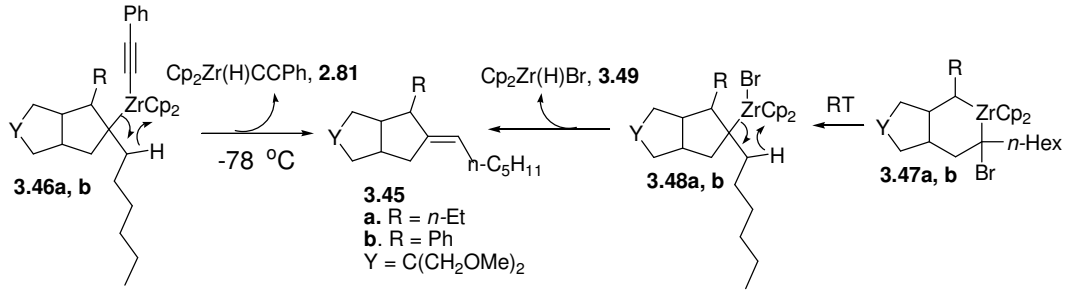


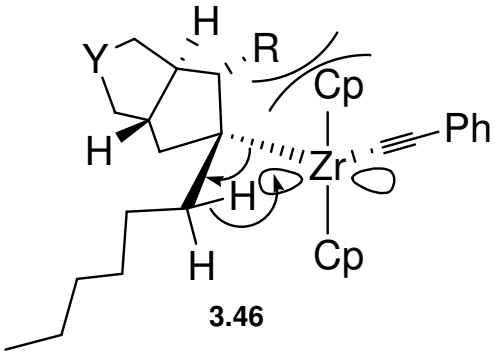
Figure 3.3 Difference in ^{13}C NMR shifts between *E* and *Z* isomers of 3.45b.

The β-hydride elimination was revealed to be a very fast process even at low temperature (–78 °C and lower) when carbenoid insertion was followed by phenyl acetylide addition to give the the intermediate **3.46** (Scheme 3.8).



Scheme 3.8 Dehydrozirconation process in complexes 3.46 and 3.48.

The availability of an empty orbital on Zr atom and the steric encumbrance in complex **3.46** (Figure 3.4) favour the undesired dehydrozirconation process before insertion of the second equivalent of phenyl acetylide and subsequent 1,3-Zr rearrangement. Therefore quick addition or increase in equivalents of the phenyl acetylide did not result in its incorporation into the final molecule.



3.46

Figure 3.4 Steric clash in complex 3.46 favours β-H elimination.

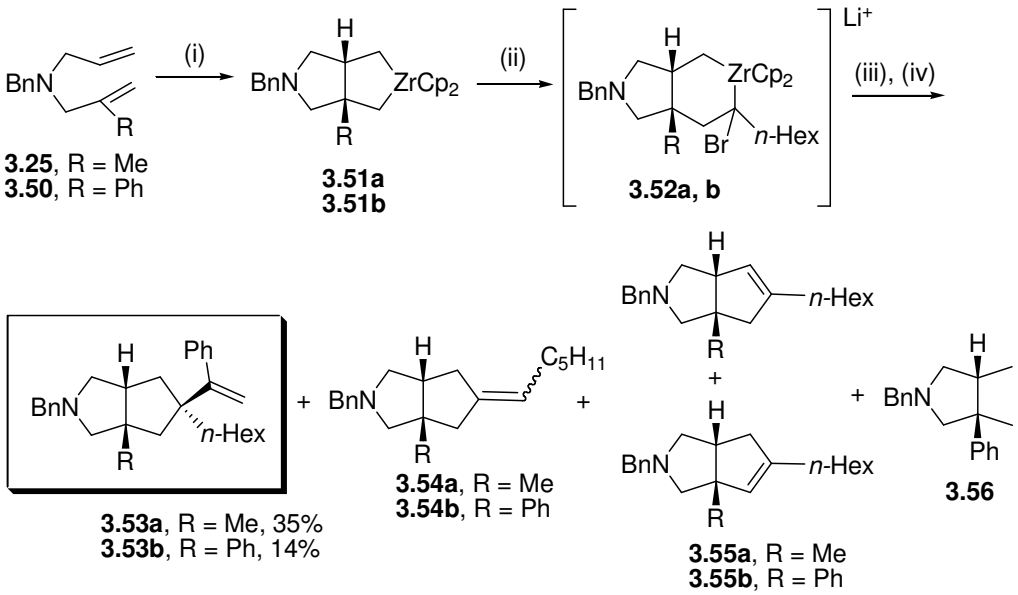
The same process, however, was observed when the zirconacyclohexane complex **3.47** was allowed to warm above 0 °C (Scheme 3.8). In this case the dyotropic rearrangement[187-189] to give carbocycle-Zr complex **3.48** is a temperature driven process and the resulting species **3.49** is postulated to be expelled from intermediate **3.48** through β-hydride elimination process.

3.2.2.3. Insertion of lithiated 1,1-dibromoheptane and phenyl acetylide into β-substituted zirconacyclopentanes

Zirconocene mediated co-cyclisation of dienes with internally substituted double bonds, **3.25** and **3.50** gave exclusively *cis*-fused zirconacycles **3.51a** and **3.51b** respectively (Scheme 3.9).[132] Subsequent addition of carbenoid **3.26a** and phenyl acetylide **2.7** resulted in obtaining a mixture of final compounds **3.53a**,**b** and both exo- and endocyclic β-H elimination products **3.54a**,**b** and **3.55a**,**b**. Product **3.53a** was obtained in 35% yield and contained 3% by ^{13}C NMR of the other isomer (at the carbenoid C centre). It was assumed, but has not been proven, that the major isomer is the shown *exo* addition product. Simultaneously in this reaction were obtained other products, which are deemed to be **3.54a** and **3.55a** in 44% combined yield, as an inseparable mixture of four compounds.

Product **3.53b** was obtained in only 14% overall yield and contained 6% (by ^{13}C NMR) of the other isomer (at the carbenoid C centre). Simultaneously in this reaction were obtained products **3.54b** and **3.55b** in 23% combined yield, as an inseparable mixture of four compounds. The residue consisted of product **3.56**, derived from protonation of zirconacycle **3.51b** (Scheme 3.9). These results suggest that the β-substituent in zirconacycles **3.51a** and **3.51b** clearly has an effect on the reaction by facilitating the β-H abstraction process as well as direction of the nucleophilic attack of the acetylide onto

Zr atom in intermediate **3.52**. It is believed that the acetylide attacks the zirconacyclohexane **3.52** from its *exo* face, however, the bulky bridgehead substituent introduces a steric clash therefore the nucleophilic attack also occurs in small amounts from the *endo* face, to provide an inseparable mixture of diastereoisomers of the final products **3.53a**,**b**. The size of the substituent is considered to play a role as for R = Me, there was found only 3% of the minor isomer, whereas for R = Ph, the amount was increased to 6%.



3.25, R = Me
3.50, R = Ph

3.51a
3.51b

3.52a, b

3.53a, R = Me, 35%
3.53b, R = Ph, 14%

3.54a, R = Me
3.54b, R = Ph

3.55a, R = Me
3.55b, R = Ph

3.56

Reagents and Conditions: (i) Cp_2ZrCl_2, *n*-BuLi, THF, −78 °C to RT, 3 h; (ii) 1.1 eq *n*-$HexCHBr_2$, 1.15 eq LiTMP, −90 °C to −78 °C, 0.5 h; (iii) 3.0 eq PhCCLi, −78 °C to −20 °C, 3 h; (iv) MeOH, aq $NaHCO_3$, RT, 12-16 h.

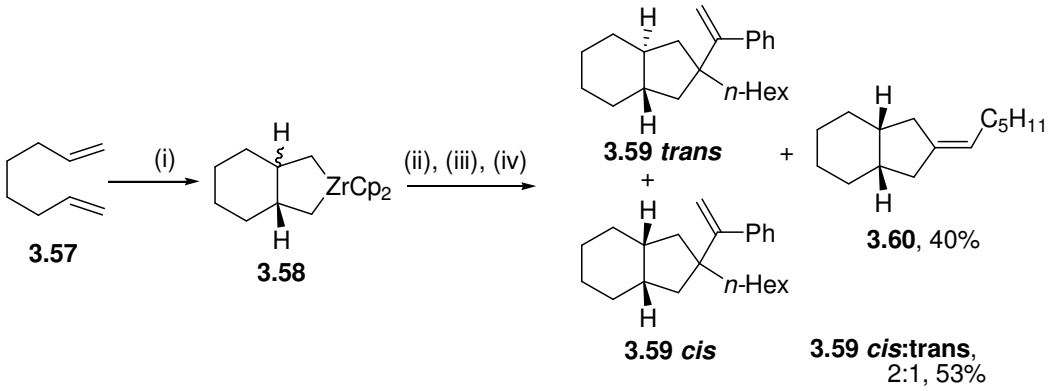
Scheme 3.9 Insertion of lithiated 1,1-dibromoheptane and phenyl acetylide into β-substituted zirconacyclopentanes 3.51a and b.

3.2.2.4 Insertion of lithiated 1,1-dibromoheptane and phenyl acetylide into zirconacyclopentanes fused to a six-membered ring

Variation in the ring size of zirconacycles was sought in respect of the multi-component coupling sequence. Zirconocene mediated co-cyclisation of 1,7-heptadiene **3.57** provided six-five fused zirconacycles as a mixture of *cis : trans* ring junction isomers, **3.58** in the ratio of 82 : 18 respectively. These zirconacycles were subjected to insertion of lithiated 1,1-dibromoheptane **3.26a** and further phenyl acetylide **2.7** to provide compounds **3.59** as an inseparable mixture of *cis : trans* ring junction isomers in the ratio of 2 : 1 and 53% combined yield (Scheme 3.10).

The *cis, trans* stereochemistry of the final compounds was determined on the basis of ^{13}C NMR analysis. For the *cis* isomer ^{13}C NMR symmetry was observed therefore the number of signals of the core carbons was twofold reduced whereas for the *trans* isomer splitting of the core carbon signals was observed. Also only one *cis* isomer was created in this reaction.

An exocyclic β-H elimination was observed for this system and alkene **3.60** was obtained as a single *cis* ring junction isomer in 40% yield.



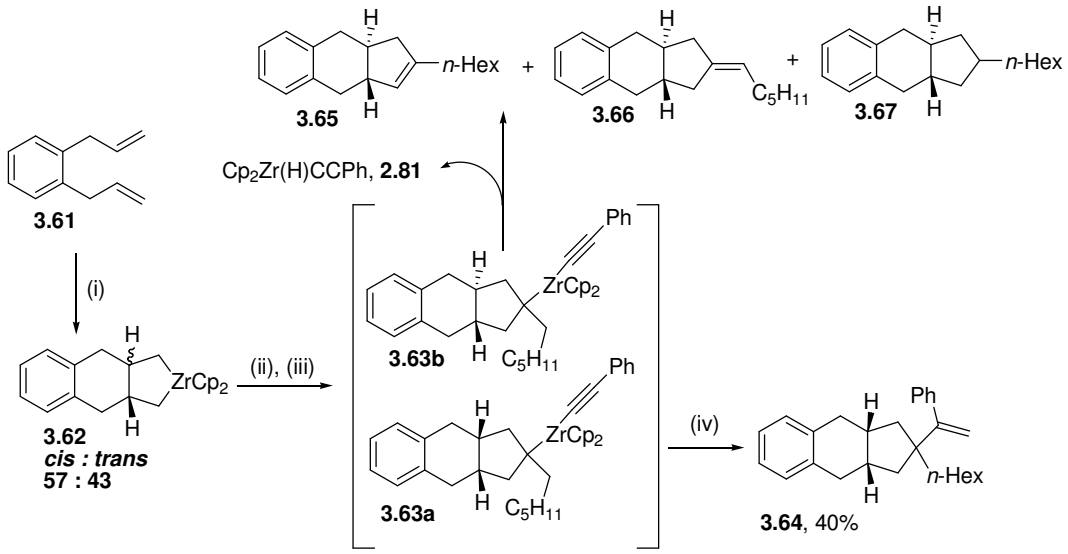
Reagents and Conditions: (i) Cp_2ZrCl_2, *n*-BuLi, THF, −78 °C to RT, 2 h; (ii) 1.3 eq *n*-HexCHBr$_2$, 1.5 eq LDA, −78 °C, 15 min; (iii) 3.0 eq PhCCLi, −78 °C to −50 °C, 0.5 h; (iv) MeOH, aq $NaHCO_3$, RT, 16 h.

Scheme 3.10 Coupling of zirconacycle 3.58, carbenoid and phenyl acetylide on zirconocene.

Three component coupling of zirconacycle **3.62**, derived from co-cyclisation of 1,2-diallylbenzene **3.61**, lithiated 1,1-dibromoheptane **3.26a** and phenyl acetylide **2.7** gave a single *cis* ring-fused product **3.64** in 40% yield (Scheme 3.11). The stereochemistry of the product **3.64** was assigned by ^{13}C NMR analysis which showed ^{13}C NMR symmetry for the core carbons. However, during the co-cyclisation step *cis : trans* zirconacycles **3.62** were formed in the ratio of 57 : 43 respectively. According to the literature precedent the zirconocene mediated co-cyclisation of **3.61** provided a mixture of *cis : trans* zirconacycles in the ratio of 92 : 8.[133]

An endocyclic and exocyclic β-hydride elimination as well as protonation of the intermediate **3.63b** occurred to provide the corresponding compounds **3.65**, **3.66** and **3.67** as an inseparable mixture in 33% combined yield and following GC ratio 65 : 31 : 4%, respectively. It is postulated that the *cis* ring junction intermediate **3.63a** favours the carbenoid and phenyl acetylide insertion to give the final products **3.64**, whereas the *trans* ring junction intermediate **3.63b** favours β-hydride elimination.

Results obtained from insertion of lithiated 1,1-dibromoheptane **3.26a** and phenyl acetylide **2.7** into zirconacycles **3.58** and **3.62** are consistent with those obtained from insertion of lithiated 1,1-dibromoheptane and phenyl acetylide into unsaturated zirconacycle **2.75**, and strongly indicate that the cyclohexane ring fused to zirconacycles introduces conformation constraints which somehow favours the β-hydride elimination process.

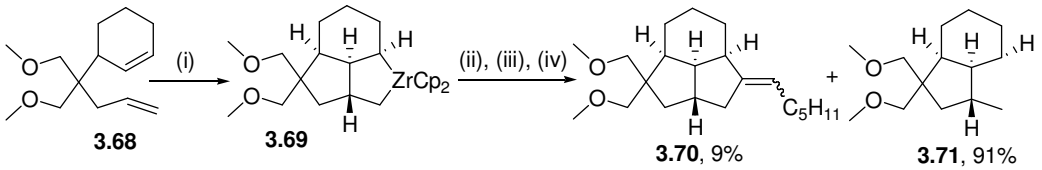


Reagents and Conditions: (i) Cp_2ZrCl_2, *n*-BuLi, THF, −78 °C to RT, 2.5 h; (ii) 1.3 eq *n*-HexCHBr$_2$, 1.5 eq LDA, −78 °C, 15 min; (iii) 3.0 eq PhCCLi, −78 °C to −55 °C, 1 h; (iv) MeOH, aq $NaHCO_3$, RT, 16 h.

Scheme 3.11 Cuopling of zirconacycle 3.62, alkyl carbenoid and phenyl acetylide on zirconocene.

3.2.2.5 Insertion of lithiated 1,1-dibromoheptane and phenyl acetylide into tricyclic zirconacycles

Insertion of alkyl carbenoid and phenyl acetylide into tricyclic zirconacycle **3.69** has also been probed (Scheme 3.12). The insertion of lithiated 1,1-dibromoheptane occurred very poorly and was followed by β-hydride elimination to provide an inseparable mixture of 3 : 1 (by ^{13}C NMR), *E : Z* isomers of **3.70** and 9% combined yield, the residue being the product of cyclisation **3.71**. It remains unclear why the insertion of the carbenoid did not work well; however, steric hindrance in the zirconacycle **3.69** is postulated to greatly inhibit the carbenoid insertion.

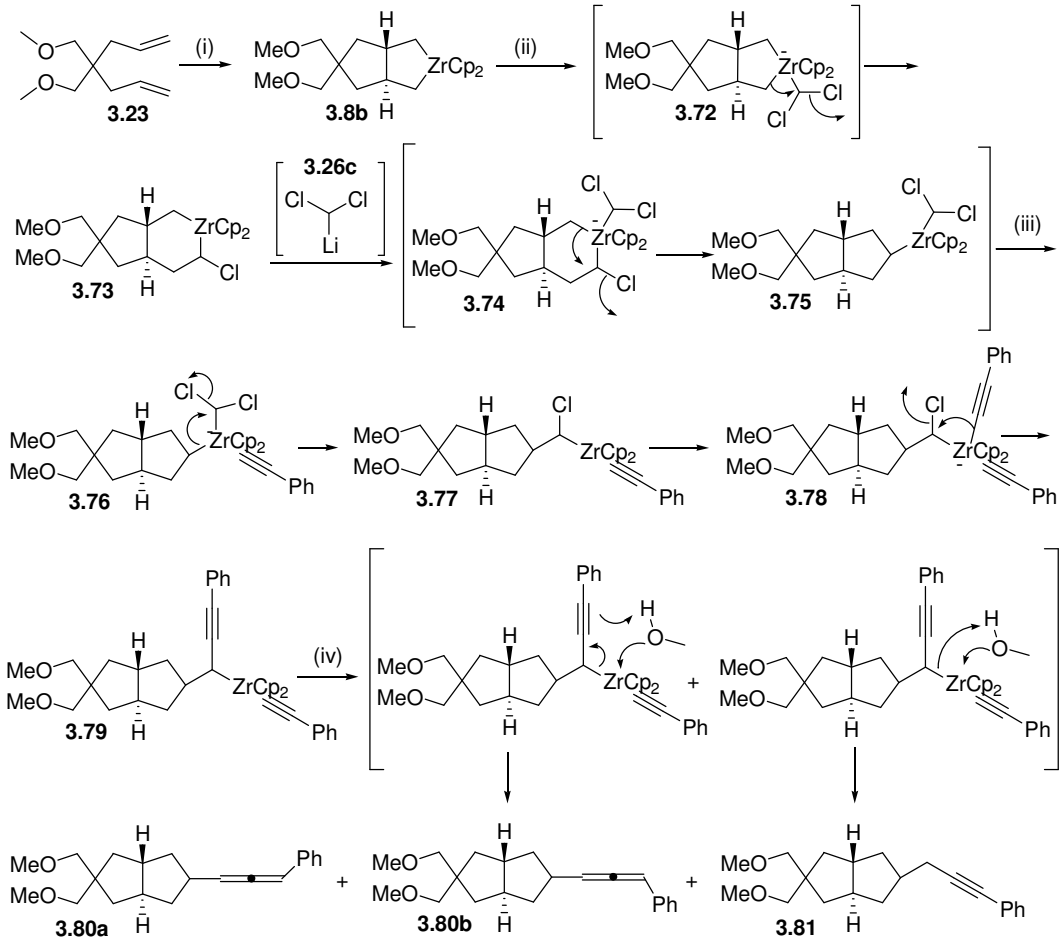


Reagents and Conditions: (i) Cp_2ZrCl_2, *n*-BuLi, THF, −78 ^oC to RT, 2 h; (ii) 1.1 eq *n*-$HexCHBr_2$, 1.15 eq LiTMP, −90 ^oC to −78 ^oC, 20 min; (iii) 3.0 eq PhCCLi, −78 ^oC to RT, 2 h; (iv) MeOH, aq $NaHCO_3$, RT, 16 h.

Scheme 3.12 Insertion of lithiated 1,1-dibromoheptane and acetylide 2.7 into tricyclic zirconacycle.

3.2.2.6 Insertion of lithiated 1,1-dichloromethane and phenyl acetylide into zirconacyclopentane

The unusual reactivity of lithiated dichloromethane **3.26c** towards insertion into zirconacycle **3.8b** was observed (Scheme 3.13).



Reagents and Conditions: (i) Cp_2ZrCl_2, *n*-BuLi, THF, −78 ^oC to RT, 12 h; (ii) 1.0 eq CH_2Cl_2, 1.2 eq LiTMP, −78 ^oC to −60 ^oC, 1 h; (iii) 3.0 eq PhCCLi, −78 ^oC to −35 ^oC, 3 h; (iv) MeOH, aq $NaHCO_3$, RT, 18 h.

Scheme 3.13 Insertion of lithiated dichloromethane and phenyl acetylide into zirconacycle 3.8b.

The initial 'ate' complex **3.72**, created by insertion of lithiated dichloromethane **3.26c** into saturated zirconacycle **3.8b**, and subsequent 1,2-metallate rearrangement provides the ring expanded zirconacyclohexane **3.73**, which undergoes second insertion of the lithium carbenoid and ring closure to provide the carbobicyclo-Zr complex **3.75**. Addition of phenyl acetylide causes a second 1,2-metallate rearrangement to occur, therefore the second molecule of the carbenoid is incorporated into the bicycle to give the intermediate **3.77**. Further acetylide insertion allows for incorporation of the alkynyl moiety into the molecule to provide intermediate **3.79**, which after protonolysis gives three products: **3.80a**,**b** and **3.81** as an inseparable mixture of compounds in 10% combined yield and following ratio: **3.80a/b : 3.80b/a**, 1.8 : 1 and **3.80 : 3.81**, 1 : 2 by NMR. Despite considerable optimization undertaken, the reaction proved to be low yielding and the purification of the final product difficult due to many unidentifiable products.

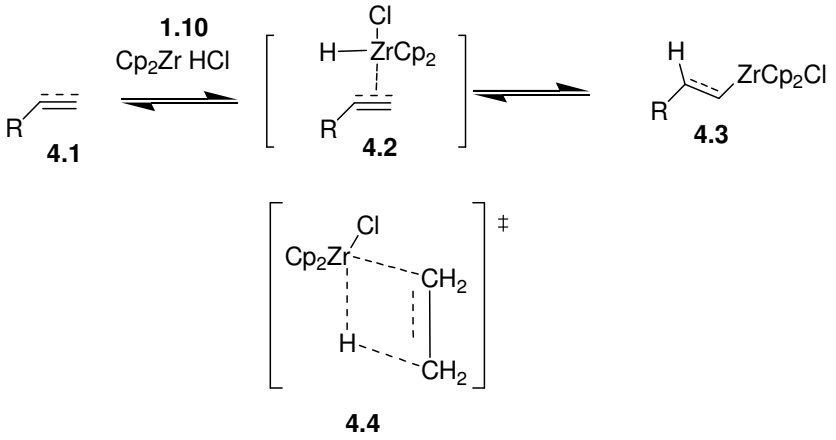
3.3. Conclusions for chapter 3

The one-pot three component coupling on zirconocene template was probed for construction of bicyclo[3.3.0]- and bicyclo[4.3.0]nonanes as well as tricyclic structures. Various saturated zirconacycles were examined for carbenoid insertion and subsequent 1,3-Zr rearrangement. The examined method was successful for unsubstituted zirconacycles and the expected carbobicycles were obtained in reasonable yields. However, β-H elimination was the main limitation of the method and occurred exclusively in the case of α-substituted zirconacycles to provide the corresponding alkenes. The undesired dehydrozirconation process was also competitive with the acetylide driven 1,3-Zr rearrangement in β-substituted zirconacycles. Insertion of dihalocarbenoid into tricyclic zirconacycle was very low yielding, and such obtained expanded zirconacycle was subjected to immediate β-H elimination process. Lithiated dichloromethane performed multiple insertion into saturated zirconacycle to provide interesting bicyclic compounds, albeit in low yield.

Chapter 4. Insertion of allenyl and propargyl carbenoids into acyclic organozirconium bonds

4.1. Introduction to research area

Acyclic organochlorozirconocenes can be prepared *via* hydrozirconation of alkenes and alkynes with the Schwartz reagent **1.10** and are very useful class of transition metal derivatives for use in organic synthesis.[192] Hydrozirconation of unsaturated organic molecules is very easy to perform with no need for any special glove-box techniques. The insertion of C,C-double and -triple bonds into Zr-H bond (hydrozirconation) occurs *via* a four-atom, concerted transition state **4.4** (Scheme 4.1) which is formally symmetry-allowed due to the vacant d-orbitals on Zr atom.[193,194] The final outcome of this process is a hydrometallation product **4.3** obtained by *cis*-addition of zirconium and hydrogen across the double or triple bond.

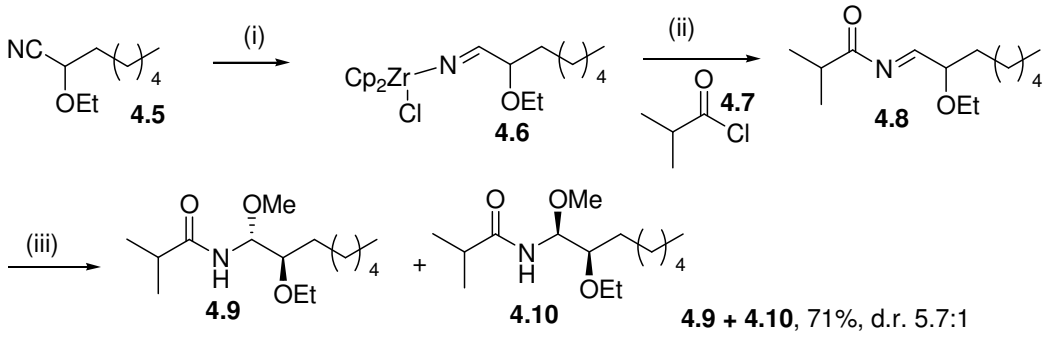


Scheme 4.1 Hydrozirconation of alkenes/alkynes.

Organochlorozirconocenes react with electrophiles such as halogens, acid chlorides and aldehydes to afford the corresponding organic halides, ketones and alcohols.[93,195] Insertion of carbon monoxide affords the acylzirconocene chlorides which can be converted into aldehydes, carboxylic acids, esters and acyl bromides by treatment with dilute HCl, $NaOH/H_2O_2$, Br_2/MeOH and NBS, respectively.[94] Insertion of isonitriles into alkyl- and alkenylzirconocene chlorides and subsequent treatment of the resulting iminoacyl complex with dilute acid provides a reliable route of aldehyde synthesis from corresponding alkenes and alkynes with one-carbon homologation.[196]

In spite of the substantial polarization of the zirconium-carbon bond, the organometallic chemistry of zirconocenes would be limited as a consequence of the steric shielding effect of the cyclopentadienyl ligands; therefore, much of the development of this chemistry has focused on indirect carbon-carbon bond forming reactions through transmetallation to other metals and further elaborations. This chemistry has been reviewed in depth by Wipf.[194]

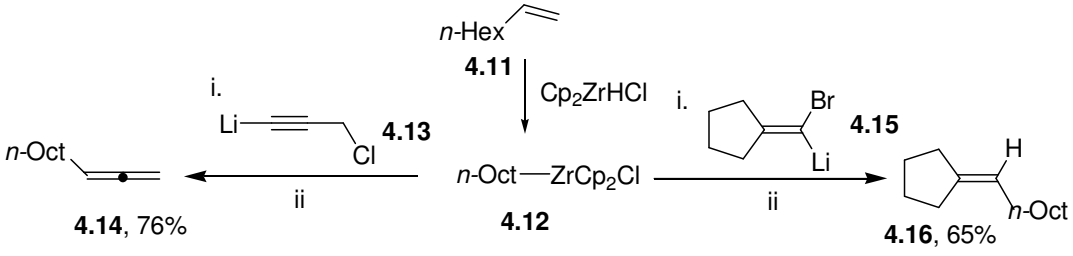
An emerging field in this chemistry is the use of zirconium complexes in asymmetric and diastereocontrolled transformations. Hydrozirconation can also be a fundamental step in multicomponent reactions allowing to access many useful organic products. Representative example from Floreancig's work[197] related to multicomponent synthesis of 'oxidized' amides through nitrile hydrozirconation is shown in Scheme 4.2.



Reagents and Conditions: (i) $Cp_2Zr(H)Cl$, CH_2Cl_2, RT, 10 min; (ii) 0 ^oC, 1.5 eq **4.7**, 10 min; (iii) 20 eq MeOH.

Scheme 4.2 Multicomponent approach to amide synthesis through nitrile hydrozirconation.

A particulary interesting method for elaboration of organochlorozirconocenes is the insertion of a wide range of carbenoids. The first insertion of carbenoids into an acyclic C-Zr bond was reported by Negishi,[134] and concerned the insertion of α- and γ-haloorganolithiums into acyclic organozirconocene derivates to give a good yield of the corresponding alkene **4.16** and allene **4.14** on acid quench (Scheme 4.3).



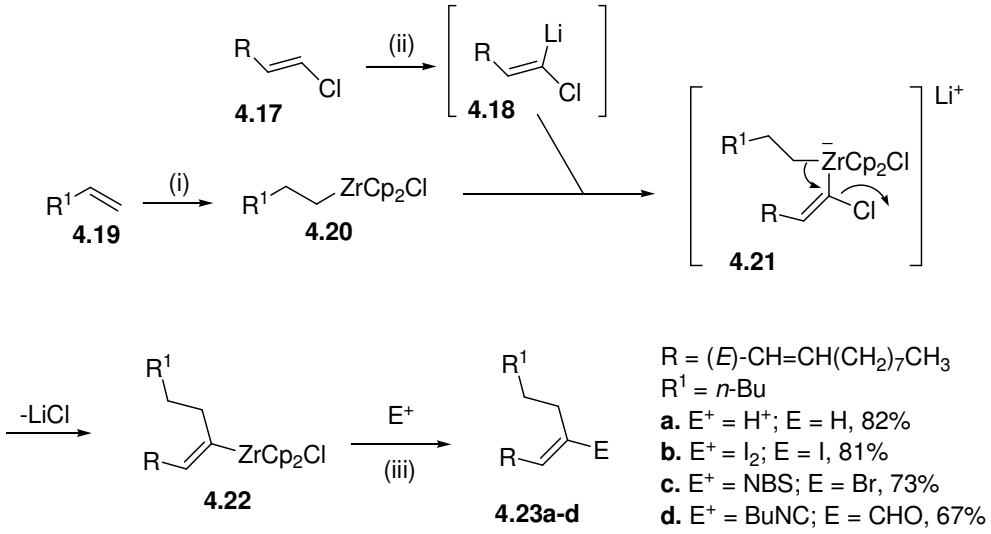
Reagents and Conditions: (i) THF, –78 ^oC; (ii) HCl.

Scheme 4.3 First insertion of lithium carbenoids into acyclic zirconocene systems.

Kasatkin and Whitby have extended the existing methodology by insertion of a wide range of carbenoids into acyclic organozirconium species to give substituted alkenes, dienes, trienes and dienynes.

4.1.1. Insertion of alkenyl carbenoids into organochlorozirconocenes

Alkenyl carbenoid **4.18**, created *in situ* by deprotonation of the corresponding vinyl halide **4.17**, has been inserted into acyclic zirconium species **4.20** to give the 'ate' complex **4.21**, which rearranges *via* 1,2-metallate rearrangement to afford the alkenyl zirconocene intermediate **4.22**. Trapping this intermediate with various electrophiles affords a range of useful organic products **4.23** (Scheme 4.4).[198,199]

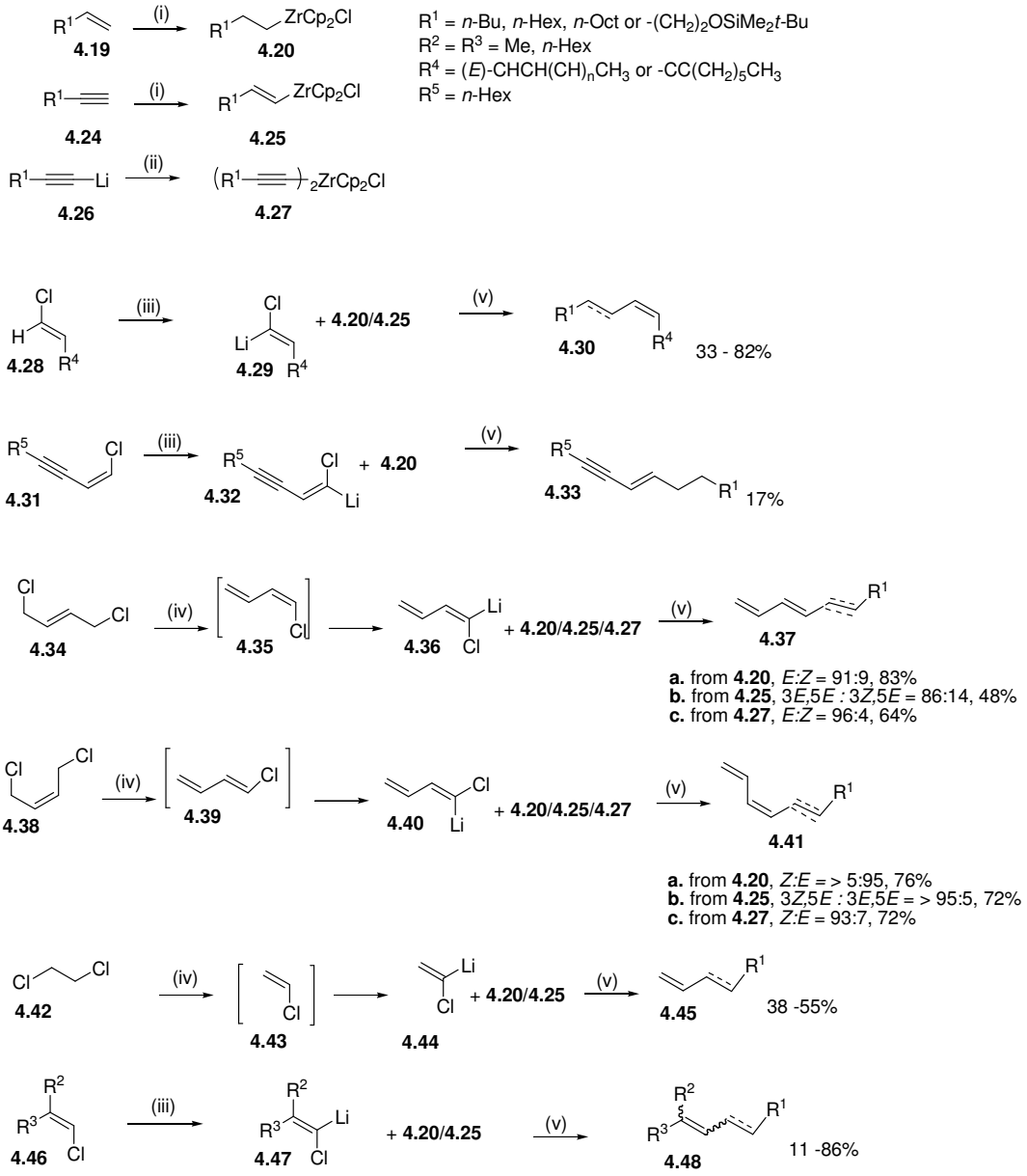


Reagents and Conditions: (i) 1.2 eq Cp_2ZrHCl, 20 ^oC, 1 h; (ii) carbenoids formed *in-situ*, 0.83 eq LiTMP, −90 ^oC to −80 ^oC, 15 min; (iii) a: 2M HCl, −78 ^oC to RT, 0.5 h; b: 1.5 eq I_2, −60 ^oC to −40 ^oC, 1 h; c: 1.5 eq NBS, −60 ^oC to −40 ^oC, 1 h; d: 1.3 eq BuNC, RT, 16 h, then 50% AcOH/H_2O, RT, 1 h.

Scheme 4.4 Elaboration of alkyl chlorozirconocenes *via* alkenyl carbenoid insertion.

A broad range of alkenyl carbenoids have been inserted into acyclic zirconium systems (Scheme 4.5). Insertion of 2-monosubstituted vinyl carbenoids **4.29**, **4.39** and butadiene derived carbenoids **4.36**, **4.40** provided the corresponding dienes **4.30**, enynes **4.33**, trienes and dienynes **4.37**, **4.41** with expected inversion of configuration on carbenoid carbon and good level of stereoselectivity. The unsubstituted carbenoid **4.44** generated from 1,2-dichloroethane inserted successfully into alkyl- and alkenyl-Zr bond to give prducts **4.45** in modest yields (Scheme 4.5).

Carbenoids carrying two different β-substituents **4.47** also inserted successfully; however, poor stereocontrol was observed due to rapid isomerisation of the carbenoid.[199]



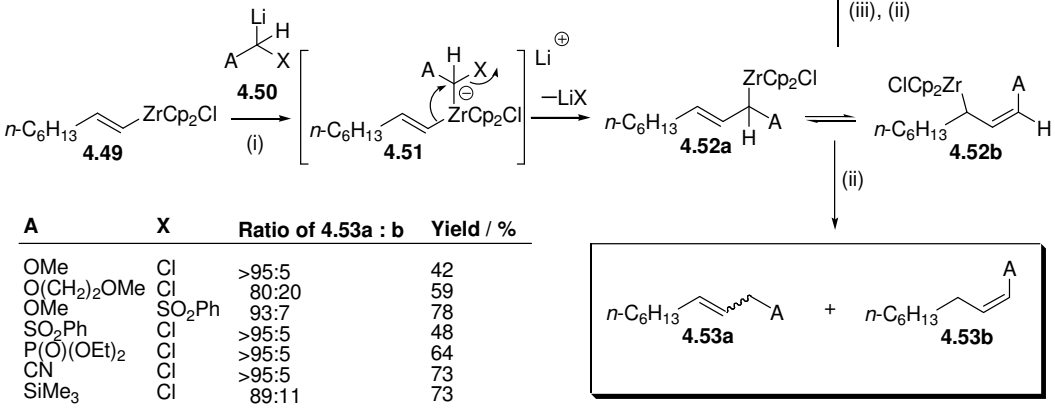
Reagents and Conditions: (i) 1.2 eq Cp_2ZrHCl, 20 °C, 1 h; (ii) 2.0 eq Cp_2ZrCl_2, −20 °C, then 0 °C, 2 h; (iii) carbenoids formed *in-situ*, 1.0 eq LiTMP, −90 °C to −80 °C, 15 min; (iv) carbenoids formed *in-situ*, 2.0 eq LiTMP, −90 °C to −80 °C, 15 min; (v) 2M HCl.

Scheme 4.5 Insertion of alkenyl carbenoids into acyclic organozirconium species.

4.1.2. Insertion of alkyl carbenoids into organochlorozirconocenes

Insertion of a range of lithium alkyl carbenoids was next examined (Scheme 4.6).[200,201]

	R^1	4.54	4.55	4.56	Yield / %
no $BF_3.Et_2O$	Ph	89	: 3	: 8	55
with $BF_3.Et_2O$	Ph	> 95	: < 5	: 0	57
no $BF_3.Et_2O$	Pr	64	: 7	: 29	65
with $BF_3.Et_2O$	Pr	83	: 4	: 13	55



A	X	Ratio of 4.53a : b	Yield / %
OMe	Cl	>95:5	42
$O(CH_2)_2OMe$	Cl	80:20	59
OMe	SO_2Ph	93:7	78
SO_2Ph	Cl	>95:5	48
$P(O)(OEt)_2$	Cl	>95:5	64
CN	Cl	>95:5	73
$SiMe_3$	Cl	89:11	73

Reagents and Conditions: (i) 1.3 eq ACH_2X, 1.3 eq LiTMP/LDA, −100 °C to −60/40 °C over 1 h; (ii) aq $NaHCO_3$; (iii) 1.3 eq PhCHO, $BF_3{\cdot}Et_2O$, −78 °C to RT, 18 h.

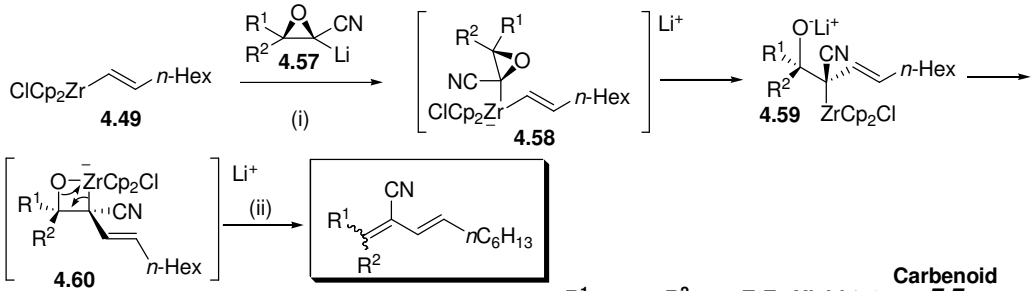
Scheme 4.6 Insertion of alkyl carbenoids into organochlorozirconocenes.

The insertion of alkyl carbenoids **4.50** into 1-octenylzirconocene **4.49** results in formation of functionalized allylmetallics **4.52**. Protonation of these species gives the two alkenes, generally with good selectivity (Scheme 4.6). The organometallic products **4.52** can be further elaborated by reacting with electrophiles such as aldehydes. Lewis acid promoted insertion of aldehydes into the resulting allylmetallics **4.52** gave higher selectivity for the β-hydroxysilane **4.54**.

4.1.3. Insertion of lithiated epoxynitriles into organochlorozirconocenes

Finally, lithiated epoxynitriles **4.57** were successfully inserted into alkenylchlorozirconocene **4.49** through 1,2-metallate rearrangement to give intermediate **4.59**. Elimination of zirconocene oxide in **4.60** followed by acid quench provides the corresponding 2-cyano-1,3-dienes **4.61** in good yield (Scheme 4.7).[202]

It is postulated that the lack of stereoselectivity of insertion of the carbenoids **4.57** is related to their configurational instabillity and rapid interconversion when formed under the reaction conditions.[202]



4.61	R^1	R^2	*Z:E*	Yield / %	Carbenoid *Z:E*
a.	Me	Me	-	64	-
b.	$-(CH_2)_4-$	-	-	42	-
c.	$(CH_2)_3OTBDMS$	H	90:10	57	100:0
			53:47	64	0:100
d.	Pr	H	88:12	55	100:0
			51:49	67	0:100
e.	Ph	H	95:5	70	100:0
			87:13	74	0:100

Reagents and Conditions: (i) 1.3 eq **4.57**, THF, –90 ^{o}C to –60 ^{o}C, over 1h; (ii) 2 M HCl.

Scheme 4.7 Insertion of metallated epoxynitriles into 1-octenylzirconocene.

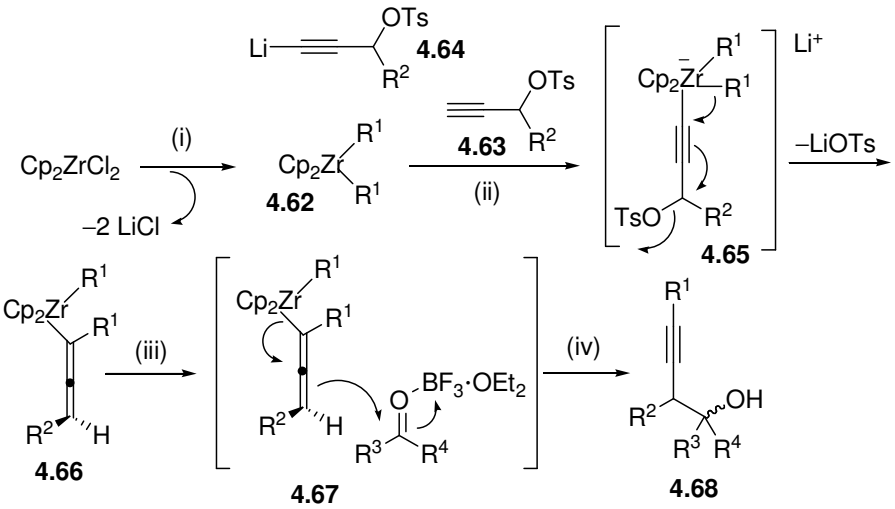
4.2. Insertion of allenyl carbenoids into acyclic zirconium species

Insertion of allenyl and propargyl carbenoids into bisalkyl/alkynyl biscyclopentadienyl zirconium complex led to a 1,2-zirconate rearrangement with expulsion of the corresponding leaving group. Trapping the resulting allenyl/propargyl Zr species with aldehydes gave, after hydrolysis, a series of propargylic alcohols.

Insertion of chiral carbenoids into alkyl/alkenyl organochlorozirconocenes and further asymmetric 1,2-metallate rearrangement provided the final alcohols as enantiomerically enriched products.

4.2.1. Insertion of allenyl carbenoid into acyclic bisalkyl-/alkynyl-zirconium species

Insertion of an allenyl carbenoid into an acyclic bisalkyl-/alkenyl-zirconium systems is shown in Scheme 4.8. Treatment of zirconocene dichloride with two equivalents of organolithium reagent gives the corresponding acyclic organozirconocene species **4.62** which inserts the γ-organolithium reagent **4.64** to provide the 'ate' complex **4.65**. Subsequent 1,2-metallate rearrangement gives the allenyl Zr intermediate **4.66** which can be trapped with electrophiles such as aldehydes and ketones to give secondary and tertiary alcohols **4.68**, respectively (Scheme 4.8).



Reagents and Conditions: (i) 2.0 eq R^1Li, THF, –78 ^oC, 0.5 h; (ii) 1.0 eq **4.63**, LDA or LiTMP, –78 ^oC to –50 ^oC, 1 h; (iii) a. for R^3 = Ph, R^4 = H, 1.5 eq PhCHO, $BF_3{\cdot}OEt_2$, –60 ^oC to RT over 1 h, then RT, 3 h; b. for R^3 = R^4 = Me, 3.0 eq Me_2CO, $BF_3{\cdot}OEt_2$, –60 ^oC to RT over 1 h, then RT, 2 h, then reflux 20 h; (iv) MeOH, aq $NaHCO_3$, RT, 12-16 h.

Scheme 4.8 Insertion of allenyl carbenoid into bisalkyl/alkynyl Zr species.

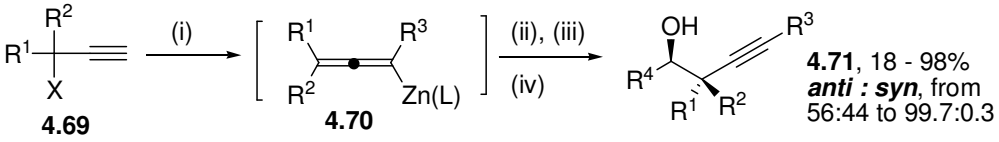
The secondary alcohols **4.68a-f** were obtained with modest diastereocontrol and in most cases poor yields (Table 4.1). The low yields for the final products can be somewhat related to the decreased reactivity of these carbenoids towards insertion into such sort of organozirconium complexes. Insertion of the allenyl carbenoid and benzaldehyde into the alkynyl Zr species **4.62** (R^1 = CCPh) provided compound **4.68d** in reasonable yield (62%), but worse diastereocontrol was observed in all the other examples. Insertion of acetone into the allenyl Zr intermediate **4.76** provided the corresponding tertiary alcohol **4.68g** only in 25% yield. This result is consistent to some extent with the observation regarding the low reactivity of allyl zirconocene species towards insertion of ketones.[138]

Entry	R^1	R^2	R^3	R^4	*anti : syn*	Yield of 4.68/ %
a	*n*-Bu	*n*-Hex	Ph	H	77 : 23	35
b	Me	*n*-Hex	Ph	H	79 : 21	40
c	Ph	*n*-Hex	Ph	H	79 : 21	35
d	PhCC	*n*-Hex	Ph	H	62 : 38	62
e	Ph	Me	Ph	H	81 : 19	39
f	Me	Me	Ph	H	73 : 27	37
g	Me	*n*-Hex	Me	Me	-	25

Table 4.1 Yields and *anti : syn* relationship of the secondary alcohols 4.68a-f.

Asymmetric synthesis of the secondary alcohols **4.68e**,**f** was attempted by insertion of the chiral carbenoid **4.64** (R^2 = Me, prepared by deprotonation with LDA of the corresponding tosylate **4.63** (R^2 = Me), derived from commercially available (*S*)-but-3-yn-2-ol) into acyclic organozirconium systems **4.62** (R^1 = Ph, Me). Such obtained compounds **4.68e**,**f** were analysed by chiral HPLC (on a Diacel OD-H column) which in both cases showed racemic products.

The *anti : syn* relationship of the products **4.68a-f** was assigned by correlation with literature precedent. In 1996 Harada *et al.* published a synthesis of a wide range of homopropargylic alcohols by trapping allenic zinc reagents with aldehydes (Scheme 4.9).[203]



Reagents and Conditions: (i) 1.0 eq $(R^3)_3ZnLi$, THF, –85 °C, 15 min; (ii) 3.0 eq $ZnCl_2$ over 15 min, –85 °C, 1 h; (iii) 1.5 eq R^4CHO, –85 °C to 0 °C over 2 h; (iv) HCl.

Scheme 4.9 Harada's synthesis of homopropargylic alcohols *via* allenic zinc complex.

There is a very close structural similarity between compound **4.68a** and compound **4.71a** synthesised in the Harada group (Table 4.2). The very good chemical correlation of compounds **4.68a** major and minor isomers with **4.71a** *anti* and *syn* isomers provided strong evidence for the assignment of stereochemistry of compound **4.68a**. The crucial proton adjacent to the hydroxyl group was shifted upfield in all *anti* isomers reported by Harada, and this trend is well retained for the major isomer of compounds **4.68a-f**; therefore, they were all assigned as the *anti* isomers and the minor isomers were identified as the *syn* isomers.

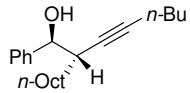
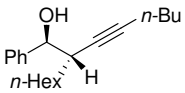
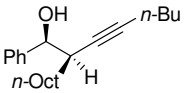
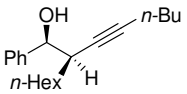
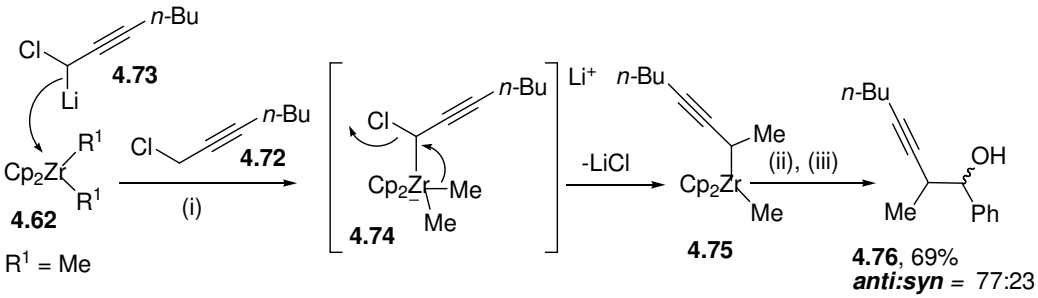
Compound	 **4.71a *anti***	 **4.68a major**	 **4.71a *syn***	 **4.68a minor**
$\delta_{H\ (CHOH)}$ (ppm)	4.47	4.49	4.69	4.71
Multiplet	dd	dd	dd	app. t
***J* (Hz)**	6.8, 3.9	6.8, 4.3	5.3, 3.6	4.8

Table 4.2 Correlation studies.

4.2.2. Insertion of propargyl carbenoid into acyclic bisalkylzirconium species

Insertion of propargyl carbenoid **4.73** (Scheme 4.10), created *in situ* by deprotonation of the propargyl chloride **4.72** with LDA, into bismethylzirconocene **4.62** (R^1 = Me) provided the 'ate' complex **4.74** which led to the propargylic Zr intermediate **4.75** *via* 1,2-metallate rearrangement. Trapping this species with benzaldehyde in the presence of $BF_3{\cdot}OEt_2$, gave after protonolysis the secondary alcohol in 69% yield as a 77 : 23 mixture of *anti : syn* diastereoisomers.



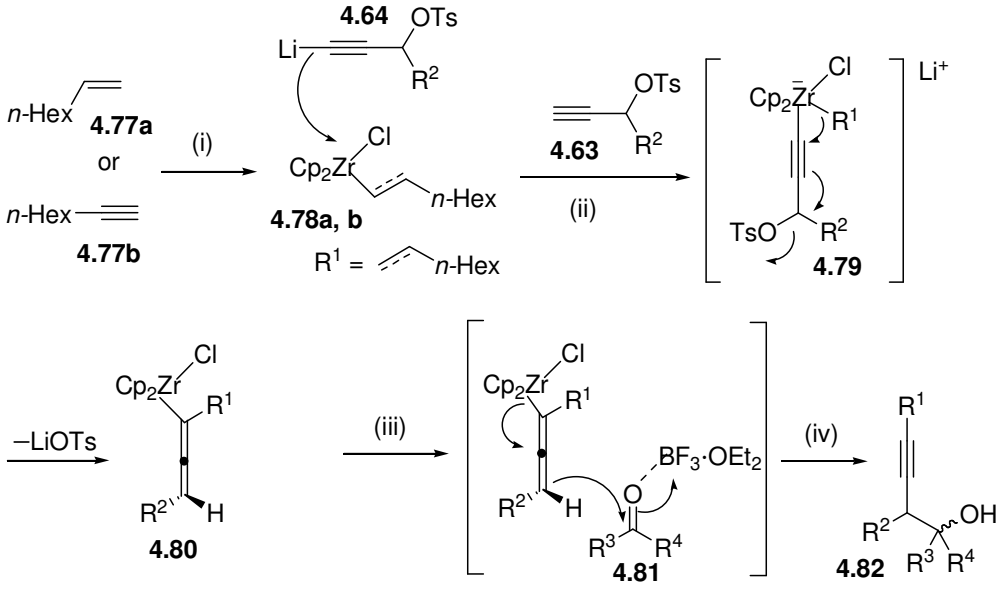
Reagents and Conditions: (i) 1.0 eq **4.72**, LDA, −78 °C to −65 °C, 1.5 h; (ii) 1.5 eq PhCHO, $BF_3{\cdot}OEt_2$, −60 °C to RT over 1 h, then RT, 3 h; (iii) MeOH, aq $NaHCO_3$, RT, 12-16 h.

Scheme 4.10 Insertion of propargyl carbenoid into acyclic Zr systems.

Although compound **4.76** structurally resembles the alcohols **4.68a-f** and has been obtained with comparable stereoselectivity, it has been synthesised by insertion of a different sort of carbenoid into an acyclic Zr system. The significantly better yield is thought to be related to the improved general reactivity of the propargyl carbenoid in comparison with the allenyl carbenoids **4.64**.

4.2.3. Insertion of allenyl carbenoid into organochlorozirconocenes with the potential for asymmetric synthesis

Hydrozirconation with Schwartz reagent of 1-octene **4.77a** or 1-octyne **4.77b** provides the organochlorozirconocene complex **4.78** which undergoes insertion of allenyl carbenoid **4.64** to provide the 'ate' complex **4.79** (Scheme 4.11). Subsequent 1,2-metallate rearrangement gives the allenic zirconium intermediate **4.80** which can be further elaborated through aldehyde and ketone insertion to provide secondary and tertiary alcohols respectively.



Reagents and Conditions: (i) 1.0 eq Cp_2ZrHCl, RT, 1 h; (ii) 1.0 eq **4.63**, LDA or LiTMP, −78 ^oC to RT, over 1 h; (iii) a. for R^3 = Ph, R^4 = H, 1.5 eq PhCHO, $BF_3{\cdot}OEt_2$, −78 ^oC to RT over 1 h, then RT, 2 h; b. for $R^3 = R^4$ = Me, 3.0 eq Me_2CO, −78 ^oC to RT over 1 h, then reflux 20 h; c. for R^3 = *n*-Hex, R^4 = H, 3.0 eq *n*-HexCHO, −78 ^oC to RT over 1 h, then RT, 3 h; (iv) MeOH, aq $NaHCO_3$, RT, 12-16 h.

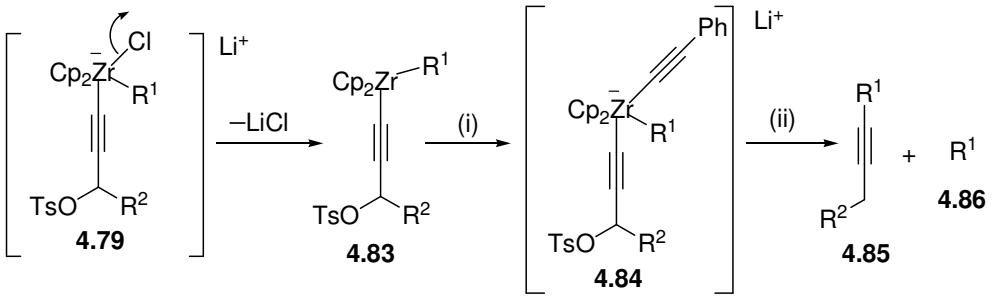
Scheme 4.11 Allenyl carbenoid insertion into organochlorozirconocenes.

Insertion of aromatic and aliphatic aldehydes **4.81** into the allenyl zirconocene complex **4.80** provides the corresponding secondary alcohols in modest yield and stereocontrol in favour of the *anti* isomer (Table 4.3). Insertion of heptanal into **4.80** occurred with the highest *anti* stereoselectivity compared with other examples to give the products **4.82c** as an inseparable mixture of *anti : syn* isomers. Surprisingly, insertion of acetone into the allenic Zr intermediate provided the tertiary alcohol **4.82d** in good 50% yield, which was contaminated with 10% of unidentified and inseparable products.

Entry	R^1	R^2	R^3	R^4	*anti : syn*	Yield of 4.82/ %
a	*n*-Oct	Me	Ph	H	74 : 26	60
b	(*E*)-1-Oct	Me	Ph	H	69 : 31	40
c	*n*-Oct	*n*-Hex	*n*-Hex	H	89 : 11	44
d	*n*-Oct	*n*-Hex	Me	Me	-	50

Table 4.3 Yields and *anti : syn* relationship of the alcohols 4.82a-d.

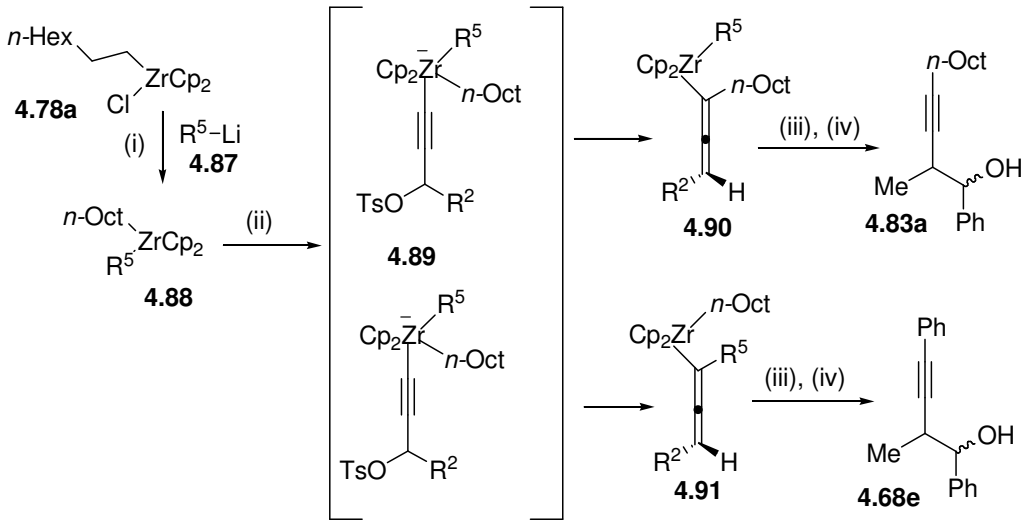
In this system the 1,2-zirconate rearrangement occurred in only 80 % yield (by GC) provided that the reaction mixture was warmed to RT. It is postulated that the 'ate' complex **4.79** loses the chloride anion to give the neutral Zr species **4.83** (Scheme 4.12). Reaction with an additional nucleophile (PhCCLi) at this stage was expected to provide the new 'ate' complex **4.84**; however, subsequent protonation gave two products: the rearranged product **4.85** and the product of initial hydrozirconation, **4.86** in approximate 1 : 1 ratio, showing that application of phenyl acetylide was not helpful.



Reagents and Conditions: (i) 1.0 eq PhCCLi, −78 ^{o}C to RT, over 1 h;
(iv) MeOH, aq $NaHCO_3$, RT.

Scheme 4.12 Possible explanation of incomplete 1,2-rearrangement in organochlorozirconocenes.

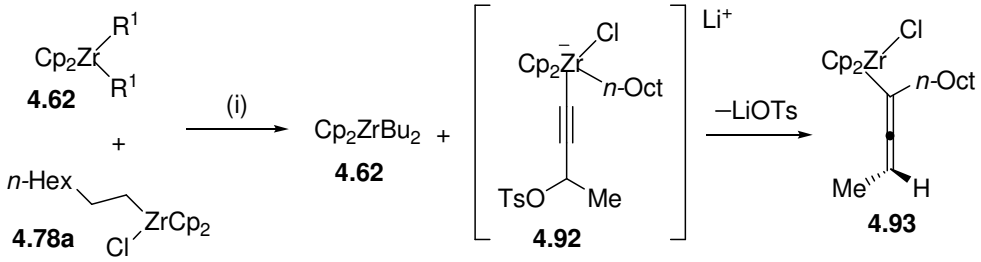
The concept of 'dummy ligands' has also been applied and the intermediate **4.78a** was treated with different nucleophiles **4.87** before insertion of allenyl carbenoid **4.63** (Scheme 4.13). The resultant intermediate **4.88** should be still reactive towards carbenoid insertion and further rearrangement. However, *s*-BuLi and Me_3SiLi completely inhibited the allenyl carbenoid insertion, PhCCLi afforded the desired intermediate **4.90** in approximately 25 % GC yield, though the reaction mixture was warmed to RT. Use of PhLi caused the R^5 group migration to give selectively the intermediate **4.91**, which after benzaldehyde insertion and protonolysis, provided product **4.68e** in low yield.



Reagents and Conditions: (i) 1.0 eq R^5Li, −78 °C, 15 min; (ii) 1.0 eq **4.63**, LDA or LiTMP, −78 °C to RT, over 1 h; (iii) 1.5 eq PhCHO, $BF_3{\cdot}OEt_2$, −78 °C to RT over 1 h, then RT, 2 h; (iv) MeOH, aq $NaHCO_3$, RT, 12-16 h.

Scheme 4.13 Application of dummy ligands to organochlorozirconocenes.

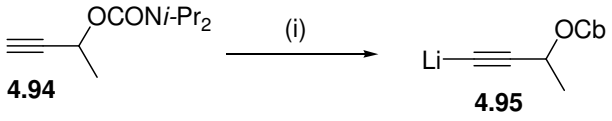
It remains unknown why the 1,2-metallate rearrangement is retarded for the organochlorozirconocene system. Competition studies of the carbenoid insertion **4.63** (R^2 = Me) into bisalkyl Zr species **4.62** (R^1 = Bu) and 1-octanylzirconocene **4.78a** species have shown that this carbenoid inserts selectively into **4.78a** in 80% GC yield (+ octane detected) (Scheme 4.14). This observation would be consistent with the electronic properties of **4.78a**, where the Zr atom is more electron poor (because of the chlorine atom present), than in **4.62**. This information, however, does not explain the incomplete 1,2-metallate rearrangement in these systems. Another concern is related to the stability of the allenyl carbenoids, which decompose even at –78 °C, immediately after deprotonation either with LDA or LiTMP to give unidentified products.



Reagents and Conditions: (i) 1.0 eq **4.63**, LDA, −78 °C to 0 °C, over 1 h.

Scheme 4.14 Competition studies for allenyl carbenoid insertion.

Insertion of carbamate carbenoid **4.95** (Scheme 4.15), prepared by deprotonation with LDA of the corresponding carbamate derivative **4.94** (prepared from commercially available but-3-yn-2-ol, according to the known procedure[204]), was unsuccessful. These results were unexpected as it is known that lithiated carbamates readily participate in 1,2-metallate rearrangement.[205]



Reagents and Conditions: (i) 1.0 eq LDA, THF, −78 ^{o}C, 15 min.

Scheme 4.15 Preparation of carbamate carbenoid.

Regardless of modest yields, asymmetric synthesis of the secondary alcohols **4.82a**, **b** was attempted by insertion of the chiral carbenoid **4.64** (R^2 = Me, prepared by deprotonation with LDA of the corresponding tosylate **4.63** (R^2 = Me), derived from commercially available (*S*)-but-3-yn-2-ol) into organochlorozirconocenes **4.7a**, **b**.

It could be assumed that the 1,2-metallate rearrangement in intermediate **4.79** will cause the elimination of the tosyl group completely in an *anti* fashion, therefore the chiral information from the carbenoid would not be lost and the allenic Zr complex **4.80** would be a chiral intermediate. Subsequent aldehyde insertion would provide the secondary alcohols as chiral products. Analysis by chiral HPLC (on a Diacel OD-H column) revealed that the compound **4.82a** was obtained in 71% e.e. It was suspected that the transfer of chiral information may be affected by the presence of the Lewis acid in the reaction mixture, thus the reaction for **4.82b** was carried out without using $BF_3{\cdot}OEt_2$ in the final step. Analysis by chiral HPLC showed that the compound **4.82b** was obtained with diminished, 62% e.e. These results imply, that the loss of chiral information occurs during the formation of the allenic Zr complex **4.80** (*syn* elimination of the tosyl group may occur partially); however, the loss of chiral information during aldehyde insertion into complex **4.80** cannot be ruled out. Nonetheless, insertion of allenyl carbenoids derived from chiral precursors **4.63** into organochlorozirconocenes **4.7a**, **b** showed potential for asymmetric synthesis.

4.3. Conclusion for chapter 4

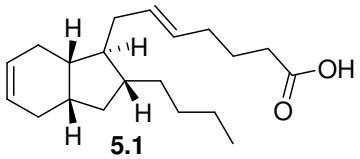
Allenyl and propargyl carbenoid have been inserted into acyclic zirconium systems. Trapping of the corresponding allenic and propargylic Zr intermediates with aldehydes and ketones gave after protonolysis secondary and tertiary alcohols respectively, mostly in modest yields and low level of diastereocontrol. The insertion of chiral allenyl carbenoid into organochlorozirconocenes showed promise for asymmetric synthesis of homopropargylic alcohols. More optimization studies in terms of yield and asymmetric course of the reaction are required to introduce the three component coupling of acyclic zirconocenes, carbenoid and aldehydes/ketones as a synthetically useful method.

Chapter 5. Towards the total synthesis of mucosin

5.1. Introduction to research area

5.1.1. Mucosin: a new bicyclic eicosanoid

Isolation of the natural product mucosin from the marine sponge *Reniera mucosa*, which is native to the Mediterranean has been reported in 1997 by Casapullo *et al.* (Figure 5.1).[206]



5.1

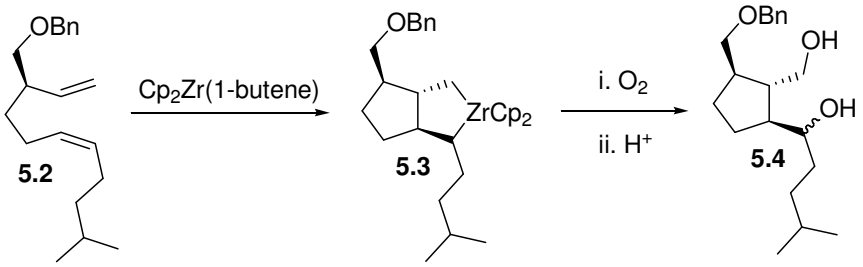
Figure 5.1 Reported structure of mucosin.

The natural product contains an unsaturated indene type skeleton with four contiguous stereocenters, a *cis*-6,5 ring junction and two side chains, one of which is carrying double bond and carboxyl functionality. The C-20, eicosanoid character of this molecule suggests its biosynthesis from arachidonic acid *via* an intramolecular cyclisation pathway. For characterisation purposes, the extracted carboxylic acid was converted to its methyl ester with diazomethane. The structure of the methyl ester was determined by its mass, infrared and high field NMR spectroscopy and the stereochemistry was assigned by means of various 2D NMR experiments. The compound was also optically active.

Although the biological activity of mucosin is unknown, the unusual bicyclo[4.3.0]nonene core and carboxylic acid side chain containing a *trans* double bond make the structure attractive to both total synthesis and testing for biological activity. The synthesis of mucosin has already been attempted by Owen[207] within the Whitby group.

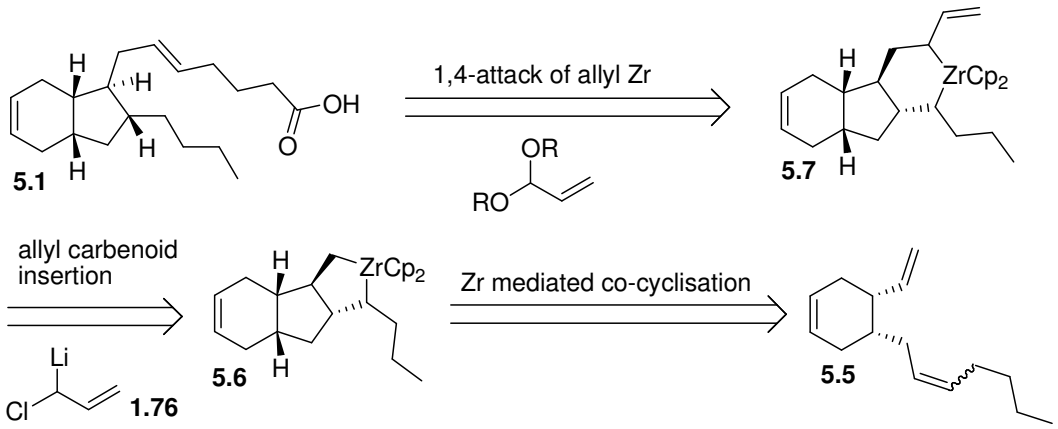
5.1.2. Literature precedent and Owen's approach to mucosin

Due to the four chiral centres present in the bicycle core of mucosin, stereocontrolled synthesis of the desired diastereoisomer would appear difficult, however, Taber and Louey[208] reported a reliable precedent for a zirconocene-mediated route to synthesise the natural product (Scheme 5.1).



Scheme 5.1 Stereocontrolled co-cyclisation of diene 5.2.

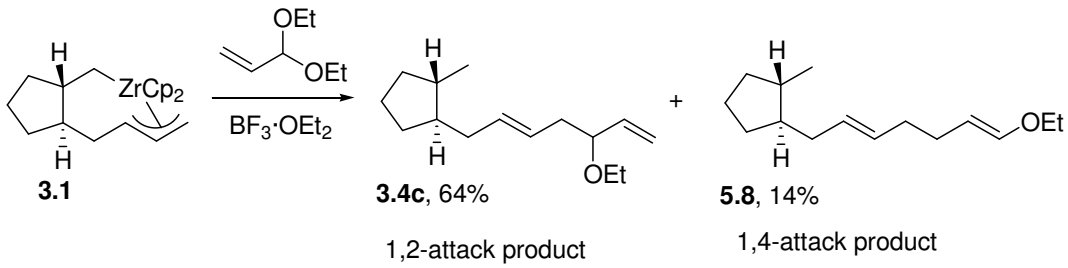
The zirconocene mediated co-cyclisation of diene **5.2** followed by oxygen quench[122,209] provided diol **5.4** as a 3 : 1 mixture of diastereoisomers, epimeric at the secondary alcohol centre. Thus, complete diastereoselectivity of the ring junction formed during cyclisation has been achieved through the presence of the methoxybenzyl substituent present in the cyclopentane ring. The *anti* relationship between the CH_2OBn group and the newly created hydroxymethyl group can be considered to be analogous to the *anti* relationship between the cyclohexene bridge and carboxylic acid bearing side chain in the natural product. The retrosynthetic strategy for the first total synthesis of mucosin proposed by Owen is shown in Scheme 5.2.



Scheme 5.2 Owen's retrosynthetic analysis of mucosin.

Zirconocene(1-butene) mediated co-cyclisation of triene **5.5** provides the zirconacycle **5.6** which undergoes allyl carbenoid insertion to give the corresponding allyl zirconocene complex **5.7**. 1,4-Attack of the resulting allyl zirconocene onto an acrolein acetal would provide the bicyclic molecule precursors with all carbon atoms in the bicycle and the desired stereochemistry and *trans* geometry of the double bond in carboxylic acid side chain. Further strightforward transformations would provide the desired product.

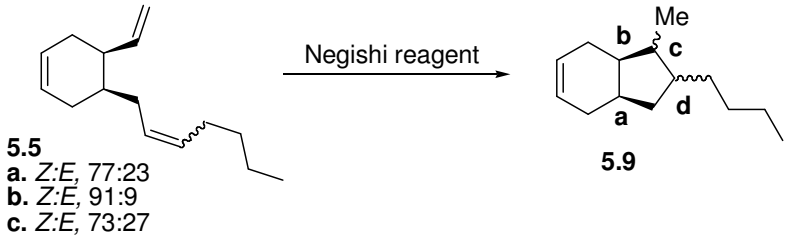
The precedent for selective insertion of an allyl carbenoid into less hindered C-Zr bond in saturated zirconacycles was reported by Gordon *et al.*[132] Therefore the desired allyl zirconocene **5.7** would be obtained selectively, and the remaining three carbons carrying carboxylic acid functionality would be incorporated into the molecule *via* a 1,4-attack of the resulting allyl zirconocene onto an appropriate Michael acceptor. This area of organozirconium chemistry was explored by Luker,[139] and the corresponding example is shown in Scheme 5.3.



Scheme 5.3 1,4-Attack by an allyl zirconocene onto acrolein acetal.

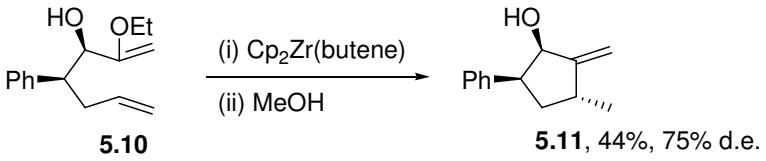
This strategy would provide an excellent method not only for bicyclic core construction but also for elaboration of the carboxylic acid side chain in a one-pot tandem reaction sequence on zirconocene, starting from the triene **5.5**. Further simple transformations would provide the desired target.

The crucial starting material, **5.5a** was initially prepared by Owen in a multistep reaction sequence as a 77 : 23 mixture of *Z : E* isomers.[207] Co-cyclisation of this precursor with Negishi reagent did not provide a single diastereomer but a mixture of three products, the major constituting 60%, as shown by ^{13}C NMR and GC analysis (Scheme 5.4).



Scheme 5.4 Owen's cyclisation of triene 5.5.

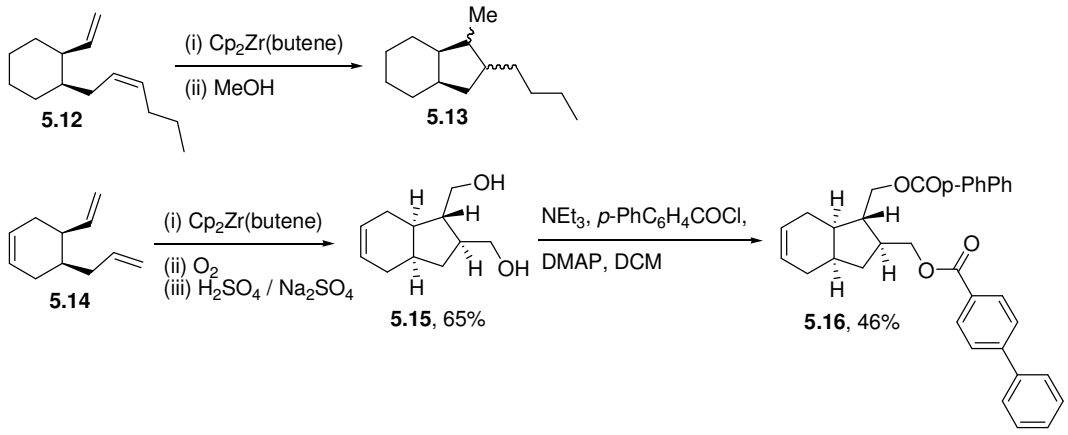
To investigate the stereoselectivity, each of the mixtures of the double bond isomers of precursor **5.5**, **b** and **c** were cyclised separately by Owen. As a result, the same product mixture was seen in each case, with three components dominating and roughly in the same GC ratio. Owen postulated that the probable reason for the mixture of products **5.9** is a lack of diastereoselectivity. The *anti* relationship between the newly created chiral centres 'c' and 'd' (Scheme 5.4) is very likely, as is the propensity for the chiral centre 'b' to induce complete control in 'c' in an *anti* fashion. The net result is a *syn* relationship between centres 'b' and 'd', and this would be in agreement with Taber's observations.[208] Co-cyclisation precursor **5.5**, however, contains an additional chiral centre 'a', and it is very likely that this centre will induce an *anti* relationship between itself and centre 'd', therefore contradicting the effects of centre 'b'. A reasonable proof for this hypothesis could be a 1,3-stereoinduction observed in his synthesis of cyclopentanol **5.11** *via* zirconocene-mediated co-cyclisation – β-elimination process (Scheme 5.5).[210]



5.10 **5.11**, 44%, 75% d.e.

Scheme 5.5 1,3-Stereoinduction observed by Owen.

The other factors which could affect the stereoselectivity in the co-cyclisation step and proposed by Owen are the additional double bond present in the cyclohexene ring and the propyl substituent on the double bond. To test this hypothesis Owen prepared the appropriate analogues **5.12** and **5.14** of triene **5.5**, which were next subjected to the zirconocene mediated co-cyclisation (Scheme 5.6).[207]



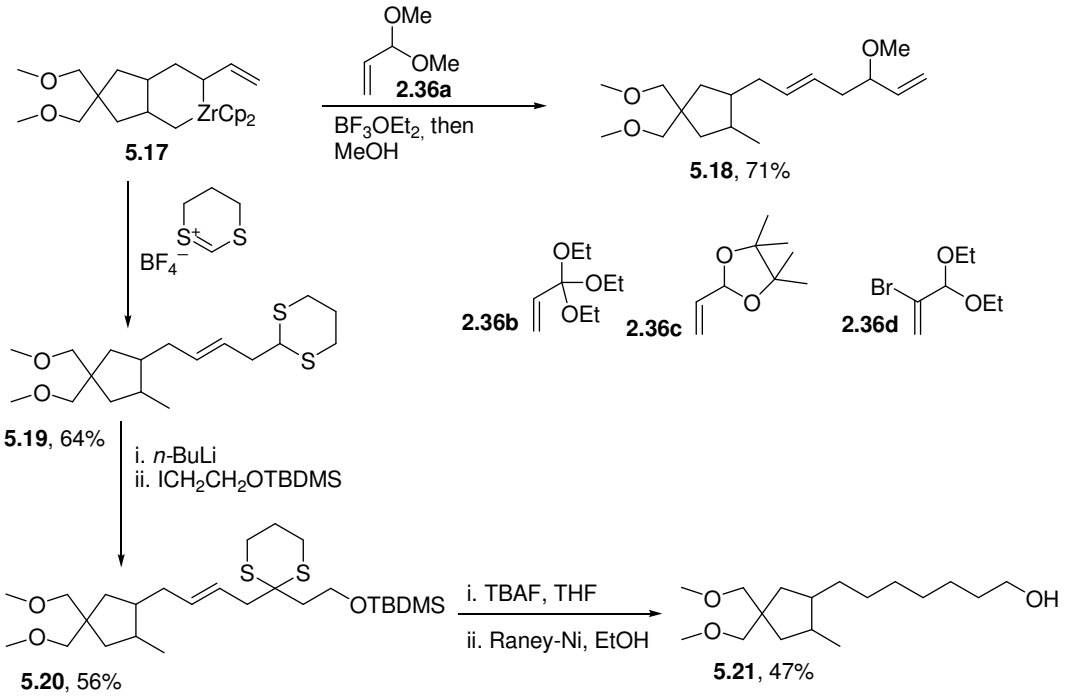
5.12 **5.13** **5.14** **5.15**, 65% **5.16**, 46%

Scheme 5.6 Zirconocene mediated co-cyclisation of precursors 5.12 and 5.14.

The co-cyclisation of diene **5.12** again provided a mixture of products **5.13** in combined yield 65%, whereas co-cylisation of **5.14** followed by oxygen quench of the C-Zr bonds provided the corresponding diol **5.15**, as a single diasteroisomer in 65% yield after column chromatography. However gas chromatography of the crude reaction mixture of **5.15** showed the major component making up 80% of the mixture and two minor products. The improved diastereoselectivity observed for the triene **5.14** suggests that the presence of a propyl chain on the doble bond is detrimental. The bis(*p*-phenylbenzoyl)ester of diol **5.15**, compound **5.16** proved the correct stereochemistry (Scheme 5.6).[207]

5.1.3. Studies towards the carboxylic acid side chain of mucosin

Owen also carried out thorough studies on elaboration of the carboxylic acid chain of the natural product (Scheme 5.7).[207]



Scheme 5.7 Owen's studies towards the carboxylic acid side chain of mucosin.

Relying on the discovery achieved within the Whitby group and relating to the selective insertion of allyl carbenoid into zirconacycles[132] and further elaboration of the resulting zirconocene η^3-complex *via* addition of different electrophiles,[139] Owen prepared the model π-allyl zirconocene system **5.17** and treated it with various Michael acceptors.

Owen repeated Luker's experiment, in which the allyl zirconocene attacks acrolein diethyl acetal, first using the dimethyl acetal **2.36a** (Scheme 5.7). However, the results indicated almost exclusively 1,2-attack product **5.18** and very small amount (<5%) of the desired 1,4-attack product. In order to induce the required 1,4-attack, three other acrolein acetals **2.36b**, **c** and **d** were prepared by Owen.[207] It was hoped that the additional steric encumbrance present in these Michael acceptors would induce the desired 1,4-attack of allyl Zr complex **5.17**. Unfortunately, the extra hindrance proved too great, and none of the three acetals reacted with the allyl zirconocene.

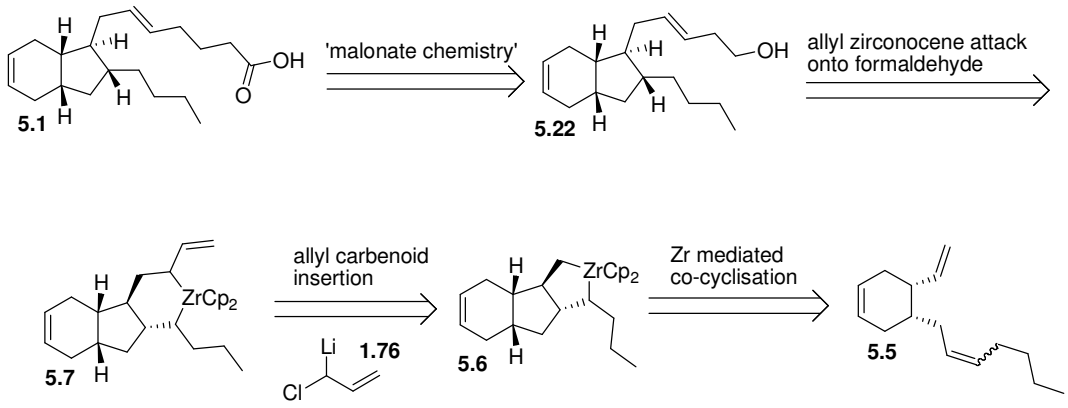
Owen, in his studies on the synthesis of the carboxylic acid side chain, used an alternative route, initially inspired by Luker's work. Trapping of the intermediate **5.17** with dithienium tetrafluoroborate provided the compound **5.19** in respectable yield and the chain was further elongated to obtain product **5.20**. De-silylation with TBAF was followed by removal of the dithiane with Raney-Ni, which also resulted in clean reduction of the double bond, providing alcohol **5.21** in moderate yield.

Although the synthesis was not completed, Owen had laid down groundwork for the second approach to the first total synthesis of mucosin.

5.2. Revised approach to the total synthesis of mucosin

5.2.1. Revised retrosynthetic analysis of mucosin

The revised retrosynthetic analysis of mucosin is shown in Scheme 5.8.



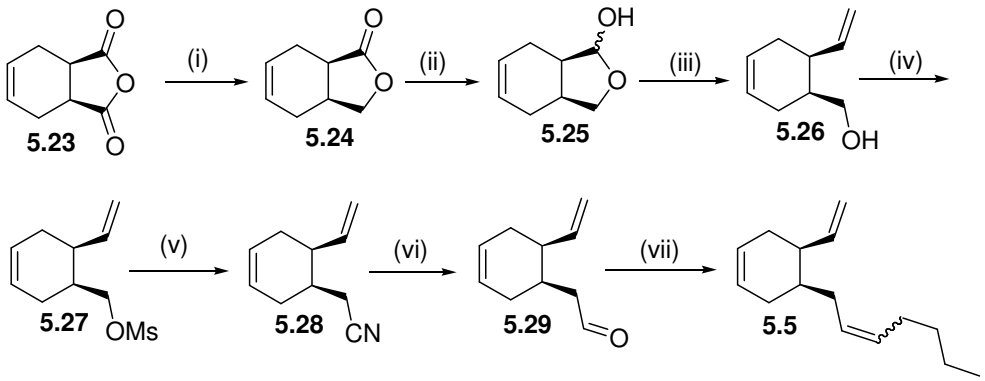
Scheme 5.8 Modified approach to the synthesis of mucosin.

This approach is very similar to that proposed by Owen; however, in this method the allyl zirconocene complex **5.7** is trapped with monomeric formaldehyde to give after protonolysis the desired homoallylic alcohol **5.22.** Subsequent homologation of the chain using malonate chemistry should provide the desired natural product.

5.2.2. Preparation of the crucial co–cyclisation precursor

The cheap and commercially available reagent, tetrahydrophthalic acid anhydride **5.23** was reduced with sodium borohydride in DMF to the lactone **5.24** in good yield (62% on 1.0 mol scale) in a convenient one-pot procedure[211] (**Scheme 5.9**). The lactone was converted into the alcohol **5.26** by following the two-step literature precedent.[212] Partial reduction of the lactone **5.24** with DIBAL-H provided the corresponding lactol **5.25**, which underwent a Wittig methylation to give the desired alcohol **5.26**. The yield of the alcohol over these two steps was 74% on 100 mmol scale (86% for each step). The one-pot procedure[213] was also followed in which DIBAL-H is added to the lactone **5.24** to form the aluminium salt of the lactol, and the resulting reaction mixture is added to a solution of methylene phosphorane. Refluxing the whole mixture for 16 h gave the desired alcohol **5.26** in modest 30% yield, on 30 mmol scale. Therefore the two-step procedure was applied on a scale-up process. The synthesis continues with one carbon homologation of alcohol **5.26**.

Quantitative conversion of the alcohol to its mesylate **5.27**, followed by cyanide displacement provided nitrile **5.28** in 86%. DIBAL-H reduction of the resultant nitrile followed by imine hydrolysis gave aldehyde **5.29** in 86% yield, which was further treated with the corresponding Wittig reagent to provide the co-cyclisation substrate **5.5** as a 4 : 1 mixture of *Z : E* isomers and 94% yield for the last step (**Scheme 5.9**). Such prepared triene **5.5** had already estabilished stereochemistry at two out of the four stereocentres present in the bicycle core of the natural product. Spectral data of all the intermediates and the triene **5.5** were consistent with those presented in the cited literature or reported by Owen.[207]



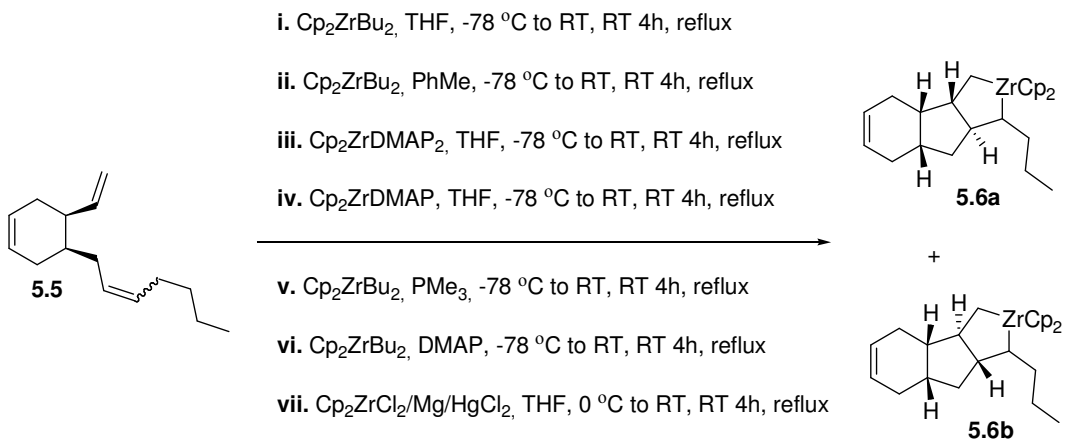
Reagents and Conditions: (i) $NaBH_4$, DMF, 0 °C to RT, then 1.0 M H_2SO_4, 62%; (ii) DIBAL-H (fast addition), PhMe, −78 °C, 1 h, then 3.0 M HCl, 86%; (iii) $MePh_3P^+Br^-$, *n*-BuLi, THF, 0 °C to RT, 2 h, then 1.0 M HCl, 86%; (iv) MsCl, Et_3N, DMAP, THF, 0 °C, 2 h, 100%; (v) KCN, NaI, 18-crown-6, 90 °C, 66 h, 86%; (vi) DIBAL-H (dropwise addition), THF, −78 °C to RT, 2 h, then MeOH, aq $NaHCO_3$, 86%; (vii) $BuPh_3P^+Br^-$, *n*-BuLi, THF, 0 °C to RT, 2 h, then 1.0 M HCl, 94%.

Scheme 5.9 Preparation of the co-cyclisation precursor 5.5.

5.2.3. Studies on zirconocene(1-butene) mediated co-cyclisation of triene 5.5

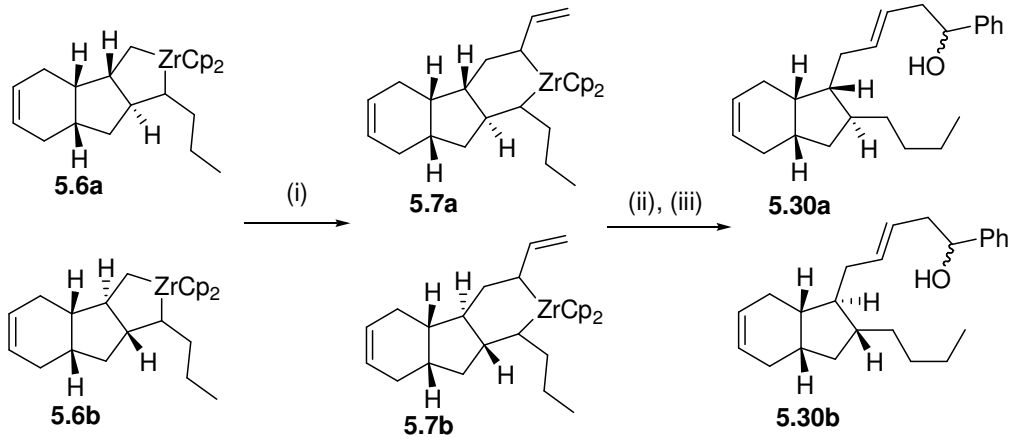
Screening of different Zr reagents for co-cyclisation of the triene **5.5** revealed that the best reagent for this purpose still remains Negishi reagent **i** and $Cp_2ZrDMAP_2$ **iii** (Scheme 5.10). Using the DMAP method[214,215] cyclisation of the starting material occurred faster in comparison with Cp_2ZrBu_2. In the latter case, the *Z* isomer of the precursor was co-cyclised in the first instance (after about 1 h upon stirring at RT) to give presumably the zirconacycle **5.6a**, which is a kinetic product of cyclisation.

The zirconacycle **5.6a** was then observed to be converting into another product, thought to be the needed **5.6b**, and the *E* isomer started to undergo the initial co-cyclisation. Subsequent heating of the reaction mixture at 60 °C for 0.5 h forced the co-cyclisation of the *E* isomer to completion and at that time gas chromatography showed four products to be created in the following ratio 58.5 : 22.5 : 14 : 5%. Also trace amounts of by-products were discernible by GC and further heating of the reaction mixture for several hours led to decomposition.



Scheme 5.10 Zirconocene mediated co-cyclisation of triene 5.5.

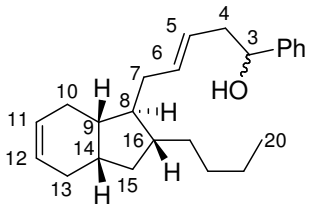
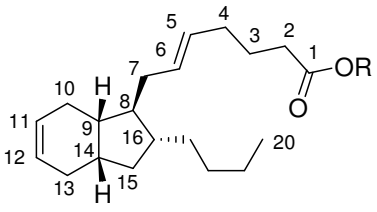
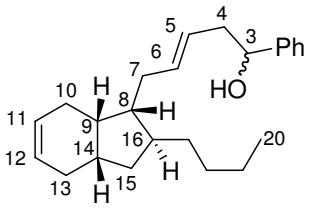
Both zirconacycles were prepared separately under kinetic and thermodynamic conditions and were further elaborated through allyl carbenoid and benzaldehyde insertion to obtain the corresponding alcohols **5.30a**, **b** (Scheme 5.11).



Reagents and Conditions: (i) 1.2 eq CH_2CHCl; LiTMP, −78 °C to −60 °C over 20 min; (ii) 3.0 eq PhCHO, $BF_3{\cdot}OEt_2$, −60 °C to −5 °C over 4 h; (iii) MeOH, aq $NaHCO_3$, RT, 12-16 h.

Scheme 5.11 Elaboration of zirconacycles 5.6a, b *via* allyl carbenoid and benzaldehyde insertion.

Alcohols **5.30** contained all the crucial carbons of the bicycle core and the double bond of one of the side chains, and therefore were appropriate for correlation with the reported spectral data of the natural product (Table 5.1).

 **5.30b** **Thermodynamic product**	 **Mucosin**	 **5.30a** **Kinetic product**

C	δ_C (ppm)				
	Experimental data major/minor d.r.	**Δδ**	**Literature data of mucosin**	**Δδ**	**Experimental data major/minor d.r.**
4	42.76	11.06	31.7	11.09	42.79
5	133.62	3.82	129.8	4.03/3.99	133.83/133.79
6	127.04	2.94	130.0	3.74/3.77	126.26/126.23
7	36.49/36.55	0.19/0.25	36.3	1.26	37.56
8	52.06/52.09	0.04/0.01	52.1	1.28/1.23	50.82/50.87
9	47.03/47.08	0.07/0.02	47.1	3.1/3.07	44.00/44.03
14	40.03	0.13	39.9	2.91/2.88	36.99 /37.02
16	42.21/42.25	0.11/0.15	42.1	1.88/1.93	40.22/40.17

Table 5.1 Comparison of ^{13}C signals of 5.30a, b with the reported spectral data of mucosin.

Comparison of the shifts of the crucial carbons in both products **5.30a**, **b** with the natural product led to the conclusion that the thermodynamic product **5.30b** had the same relative stereochemistry as the natural product. Strong evidence for this hypothesis is the excellent agreement of the carbon signals between the thermodynamic product **5.30b** and mucosin **5.1**, whereas product **5.30a** showed significant inconsistency with the natural product (Table 5.1). Additional support was provided by DFT relative energy calculations,[216] which indicated the zirconacycle **5.6a** to be less stable (≈ 4 kJ/mol) than zirconacycle **5.6b**. Therefore the thermal equilibration of the zirconacycles for mucosin synthesis gives the desired zirconacycle as the main product, though only in 60% yield.

5.2.4. Studies towards synthesis of the carboxylic acid side chain of mucosin

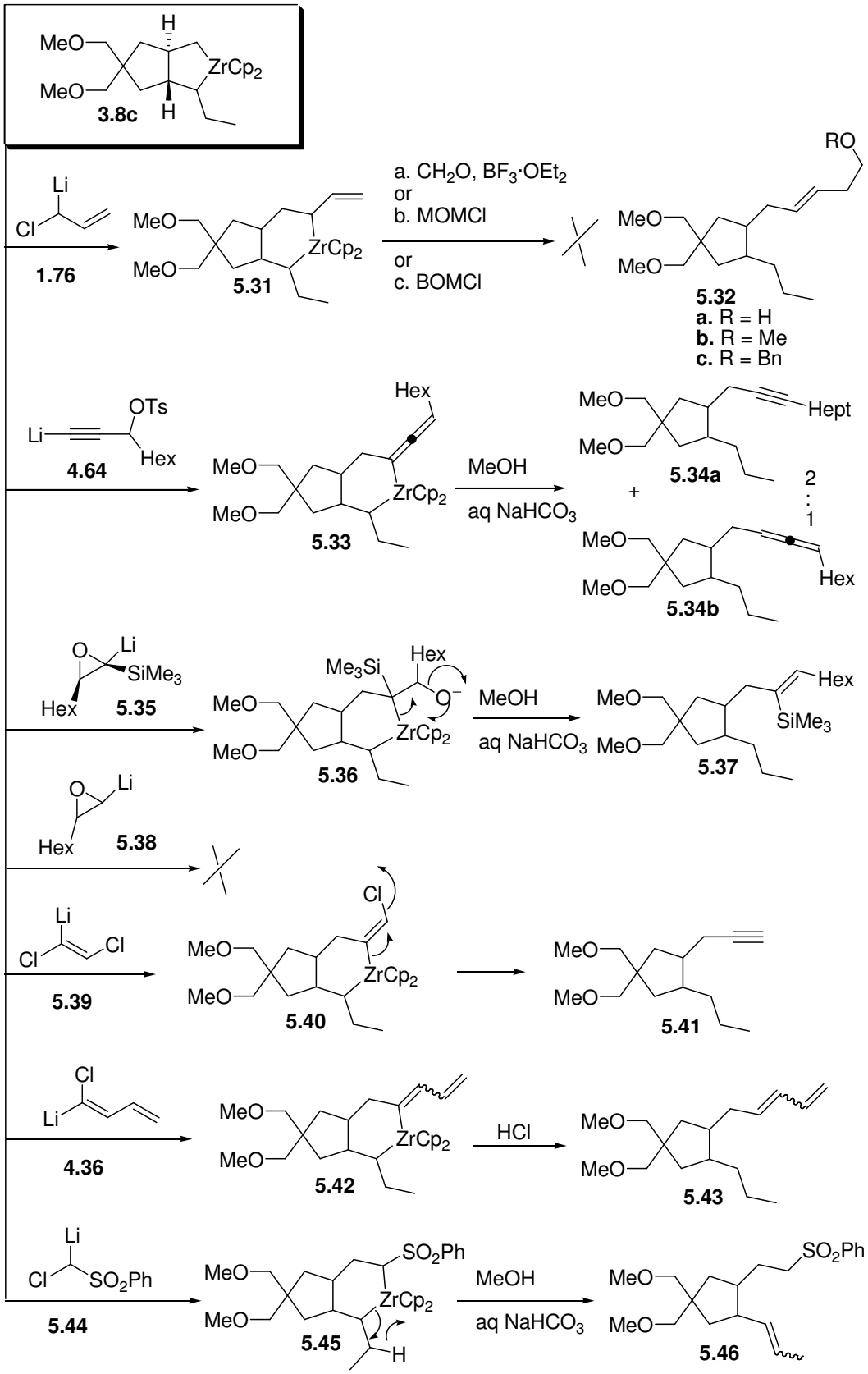
Following encouraging results from the zirconocene-mediated co-cyclisation of triene **5.5**, the synthesis of the carboxylic acid side chain was addressed.

Initial ideas for elaboration of the carboxylic acid side chain of mucosin through insertion of various carbenoids into zirconacycle were conceived (Scheme 5.12). All those experiments were carried out using the model zirconacycle **3.8c**.

Insertion of allyl carbenoid **1.76** into the model zirconacycle **3.8c** occurred quantitatively to give the η^3-Zr complex **5.31** (Scheme 5.12). Efforts were undertaken to trap the allyl zirconocene with monomeric formaldehyde (prepared according to the procedure reported by Schlosser *et al.*[217]), MOM or BOM chloride to obtain the alcohol or its Me or Bn ethers **5.32a**, **b**, **c**, respectively. Unfortunately, all three attempts failed. According to the known procedure,[218] allenyl carbenoids such as **4.64** insert into zirconacycles to give intermediate **5.33**, which after aldehyde quench, provides secondary alcohols. In the probed example, the insertion of the carbenoid occurred in only 75% yield by GC (although 2 equivalents of the carbenoid were used) and upon basic quench, a 2 : 1 mixture of compounds **5.34a**, **b** was obtained. The incomplete insertion of the carbenoid and difficulty to avoid the allene product makes this route less viable.

The insertion of metallated epoxides **5.35** into zirconacycles[202] was explored next and it appeared that the insertion of the carbenoid **5.35** occurs in only 30% by gas chromatography. Unfortunately, all the examples reported in the literature do not include α-substituted saturated zirconacycles as it is in the example below (Scheme 5.12). The results presented in chapter 3 relating to the carbenoid insertion in α-substituted saturated zirconacycles suggest, that substituents adjacent to the Zr atom may inhibit insertion of different types of carbenoids into such zirconacycles. Insertion of non-stabilized metallated epoxides **5.38** into zirconacyle **3.8c** failed.

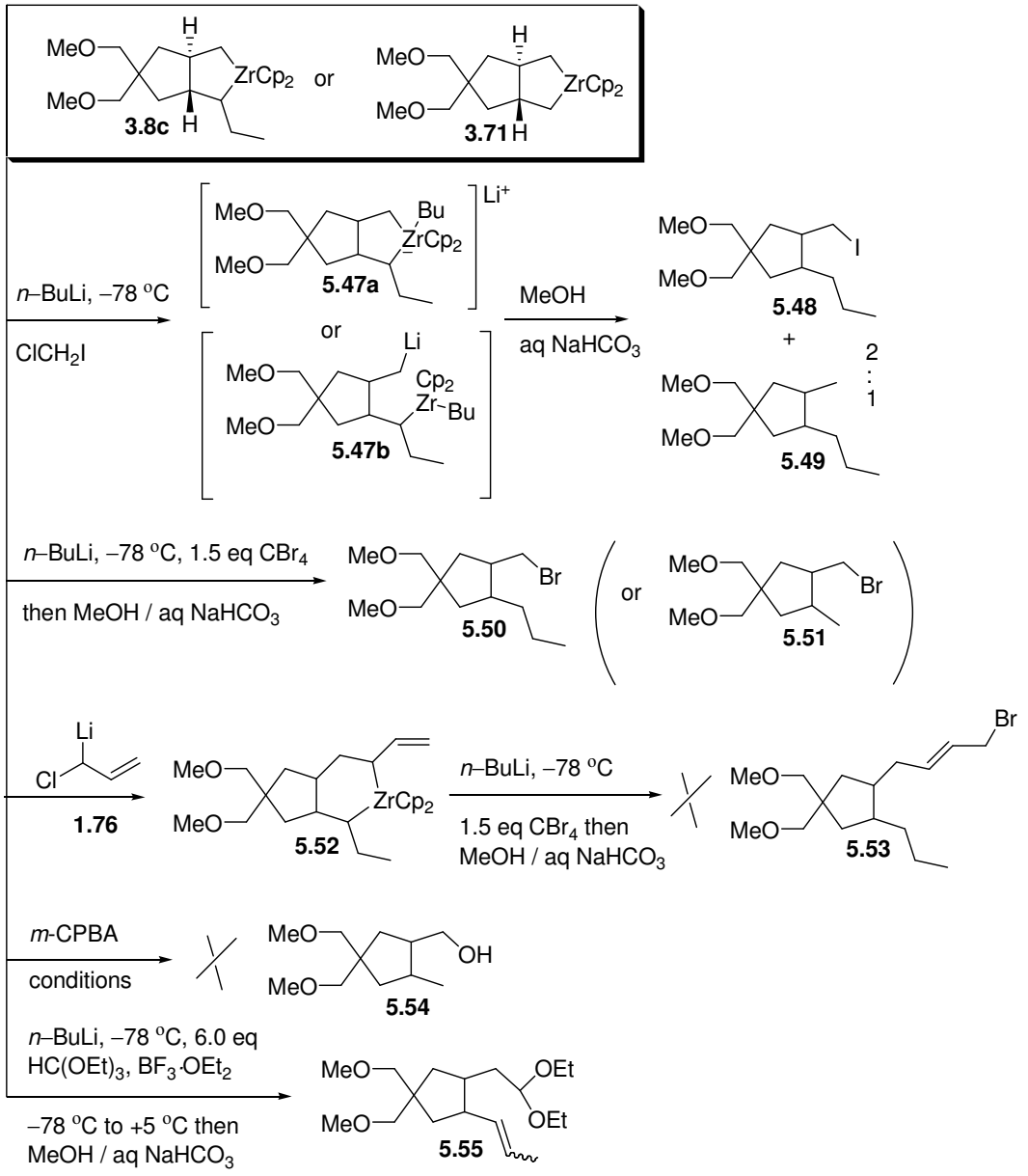
According to Norton's work,[146,219] insertion of lithiated *trans*-1,2-dichloroethylene **5.39** into saturated zirconacycle should proceed *via* expulsion of the terminal chlorine in the intermediate **5.40** to give the terminal alkyne **5.41** (Scheme 5.12). In this case, the insertion did not occur at all indicating, that the ethyl substituent indeed has a big effect on reactivity of the zirconacycle.



Scheme 5.12 Studies towards synthesis of the carboxylic acid side chain of mucosin.

Insertion of conjugated vinyl carbenoid **4.36** into zirconacycle[133] **3.8c** occurred in 75% (estimated by GC) to give upon acidic quench the compounds **5.43** as a mixture of *E* and *Z* isomers. Some loss of the stereo information must have happened during either deprotonation or the insertion step, as the 1,4-dichloro-*trans*-2-butene is contaminated with its *cis* isomer up to 10%, and the final compounds were obtained as a 3.7:1 mixture of *E* and *Z* isomers. If conjugated diene **5.43** had been formed cleanly and in high yield, it could have been elaborated *via* selective hydrometallation of the terminal double bond. A more elegant approach entails insertion of the sulfone carbenoid **5.44**. According to the work published by Dixon *et al.*,[133] the reaction should yield the desired one-carbon homologation product with incorporated sulfone group in good yield. The homologated product would be an ideal substrate for Julia-Kocieński[220,221] olefination as the crucial step in the construction of the *trans* double bond present in the side chain of mucosin. In this example insertion of the sulfone carbenoid occurs at temperatures above 0 °C and is immediately followed by β-H elimination from the ethyl substituent at the stage of the intermediate **5.45** to give the alkene products **5.46** in modest 45% yield, as a 3.8 : 1 mixture of *E* : *Z* isomers (Scheme 5.12).

Further attempts at selective functionalization of the unsubstituted C-Zr bond in zirconacycles **3.8c** or **3.71** are given in Scheme 5.13. Activation of the zirconacycle **3.8c** by addition of 1.1 eq of *n*-BuLi led to halogen-metal exchange with ICH_2Cl or CBr_4, either directly *via* the 18-electron Zr complex **5.47a**, or *via* the lithium species **5.47b**,[133] to give the corresponding iodide **5.48** or bromides **5.50** and **5.51**. Such method for ring opening of zirconacyclopentanes with alkyllithium reagents is known in the literature.[150] As the $ClCH_2^-$ anion is not the best leaving group, the desired iodide **5.48** was created in 66% GC yield only, and the protonated cyclised starting material **5.49** was also recovered (approximately 34% by GC). Choosing carbon tetrabromide as a source of halogen, the desired products **5.50** and **5.51** were obtained with 100% GC conversion and after column chromatography in 76% and 70% yield respectively. Following this idea, efforts were made to halogenate the allyl Zr species **5.52** to obtain the corresponding compound containing the allyl bromide motif **5.53**. The intermediate **5.52** which in practice is an η^3-Zr complex does seem to be very unreactive and even addition of *n*-BuLi does not force this species to perform nucleophilic attack on CBr_4. As a net result, the protonated zirconacycle **5.52** was obtained after quenching (Scheme 5.13).

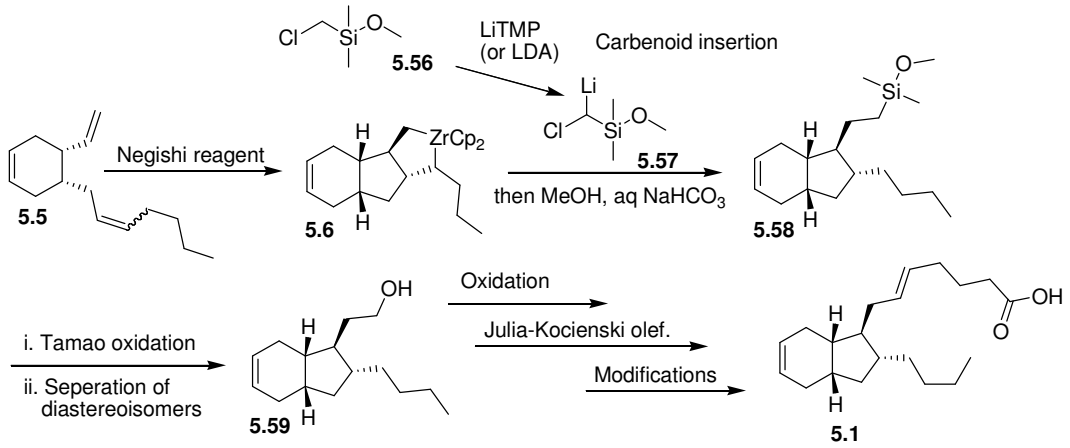


Scheme 5.13 Attempts to functionalise the unsubstituted C-Zr bond in saturated zirconacycles.

It was hoped that treatment of the zirconacycle **3.71** with *m*-CPBA under various conditions might result in oxidation of the C-Zr bond. Unfortunately, none of these reactions worked. Addition of orthoacetate to the activated Zr complex **5.47** resulted in incorporation of the electrophile into the molecule in good GC yield; however, the dq at 5.364 ppm (J = 13.0, 6.5 Hz) in the ^{1}H NMR spectra of the crude material strongly correlate to the vinylic proton in the β-H elimination product **5.55** (Scheme 5.13).

5.3. Future work towards mucosin

An idea for successful elaboration of the carboxylic acid side chain came at the end of the project and concerns the insertion of the carbenoid **5.57** (Scheme 5.14).



Scheme 5.14 Suggested elaboration of the carboxylic acid side chain of mucosin.

It is known from the previous work that α-alkoxy carbenoids are thermally unstable and insert into zirconacycles in poor yields but their silyl analogues insert usually selectively into C-Zr bond in good yields.[133] The use of the alkyl carbenoid **5.57** generated from the cheap and commercially available reagent, (chloromethyl)(methoxy) -dimethylsilane **5.56** could provide after quenching the product **5.58** which after Tamao oxidation[222] and further separation of the resulting diastereoisomers would give the desired alcohol **5.59**. Alcohols **5.59** could be oxidized to give the corresponding aldehyde, which in turn would be the substrate for a *trans* selective Julia-Kocieński olefination.[220,221] Subsequent modifications could provide the desired natural product. Unfortunately, due to time constraints, this idea was not pursued.

5.4. Conclusions for chapter 5

The synthesis of the natural product mucosin has been attempted. Extensive studies have been done on the zirconocene-mediated co-cyclisation of the appropriate triene as well as elaboration of the carboxylic acid side chain. This research revealed the Zr-based total synthesis of mucosin to be significantly limited. Nevertheless, the correct stereochemistry of the major product of zirconocene mediated co-cyclisation and the latest idea for elaboration of the carboxylic acid side chain seem to be viable and are encouraging for further work on the first synthesis of mucosin.

Chapter 6. Experimental

6.1. General experimental

All reactions involving air or moisture sensitive compounds were carried out under an argon atmosphere using standard Schlenk equipment and syringe techniques. All glassware was dried in a hot oven (>140 ºC, for at least 12 hours) and cooled in a sealed desiccator over silica gel or assembled while hot and cooled under vacuum.

Reactions were monitored by GC and/or TLC using Merck silica gel 60 F_{254} plates with detection by UV and/or polyphosphomolybdic acid and/or potassium permanganate stains. Silica gel 60A (particle size 35-70 microns) supplied by Fisher Scientific was used for flash chromatography columns and Merck silica gel 60 (0.040-0.063 mm) or basic alumina Brockman I deactivated with 6% of H_2O, were used for purification of final compounds or acid sensitive products respectively. Columns were packed and run under light pressure. Solvent compositions are described as ratios prior to mixing.

Unless otherwise stated, reagents were obtained from commercial suppliers and if necessary dried and distilled before use. Solvents for air or moisture sensitive reactions were prepared in the following ways. THF and diethyl ether were freshly distilled from sodium benzophenone ketal under argon. DCM and MeCN were freshly distilled over CaH_2 under argon. HMPA was distilled over CaH_2 and stored in stock bottles under argon. *n*-Butyllithium was used as a 2.5 M solution in hexanes (Aldrich), stored in stock bottles under argon. Lithium diisopropylamide was used as a 1.8 M solution in THF/heptane/ethylbenzene (Aldrich), stored in stock bottles under argon. DIBAL-H was used as a 1.0 M solution in toluene, stored in stock bottles under argon. Lithium 2,2,6,6-tetramethylpiperidide was prepared from 2,2,6,6-tetramethylpiperidine (freshly distilled, or distilled and stored over 4Å sieves under argon) in THF by addition of 1 equivalent of *n*-BuLi at 0 ºC and stirring for 20 minutes.

NMR spectra were recorded on Bruker AV300, AM300 or DPX400 spectrometers. The chemical shifts, δ, were recorded as values in ppm referenced to chloroform residual peaks at 7.27 ppm for ^1H spectra and 77.00 ppm (centre peak of triplet) for ^{13}C spectra and benzene 7.16 ppm for ^1H spectra and 128.39 ppm (centre peak of triplet) for ^{13}C spectra. The following abbreviations were used to denote multiplicity and may be compounded: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad,

fs = fine splitting. Coupling constants, *J*, are measured in Hertz (Hz). ^{13}C NMR spectra were proton decoupled and are reported as C, CH, CH_2, CH_3, depending on the number of directly attached protons. DEPT, COSY and ^{1}H-^{13}C correlation experiments were used to aid assignment of spectra. The lettered assignment for proton and carbon signal is for identification purposes only and does not represent the systematic IUPAC numbering. Proton chemical shifts, δ, are reported with three decimal places with the exception for compounds in experimental section for chapter 4 (whose chemical shifts, δ, are reported with two decimal places). Carbon-13 chemical shifts, δ, are reported with two decimal places in all cases.

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

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

Gas chromatography was performed on a Hewlett Packard HP 6890 series GC system, using a HP-5 (cross-linked 5% PH ME siloxane) 30 m column, with a film thickness of 0.25 μm and 0.32 mm internal diameter. The carrier gas was helium and the flow rate was 2.7 mL min^{-1}.

The X-ray structure of **2.70-*endo*** was determined by the EPSRC National Crystallography Service at the University of Southampton, Department of Chemistry.
Melting points were recorded on a Reichert 349 360 melting point apparatus and are uncorrected.

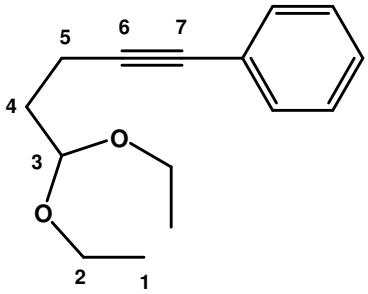
The following compounds were prepared by literature methods (or found in the laboratory chemicals collection) and had spectral properties consistent with those published or included in the thesis of former group members. These include:

- (hept-6-en-1-ynyl)trimethylsilane **1.83b**,[96]
- 1-ethynyl-3-methoxybenzene **2.31**,[153,154,223]
- 1,1-dibromoalkanes **2.33a, b, c**,[155,224]
- 1- (hept-6-en-1-ynyl)benzene **2.35a**,[225]
- undec-1-en-6-yne **2.35b**,[166]
- tridec-1-en-6-yne **2.35c**,[226]
- 1,1-diethoxy-3-iodopropane **2.37**,[156, 157]
- 7-phenylhept-1-en-6-yn-4-ol **2.47**,[227]
- 2-((oxiran-2-yl)methoxy)-tetrahydro-2*H*-pyran **2.44**,[160]
- 1-(tetrahydro-2*H*-pyran-2-yloxy)pent-4-en-2-ol **2.45**,[161]
- pent-4-ene-1,2-diol **2.46**,[163]
- 7-phenylhept-1-en-6-yn-4-ol **2.47**,[164,165,227]
- 1-phenylhept-6-en-1-yn-3-ol **2.51**,[228]
- (1-phenylhept-6-en-1-yn-3-yloxy)(*tert*-butyl)dimethylsilane **2.52**,[228]
- 10-(*tert*-butyldimethylsiloxy)-l-decen-6-yn **2.54**,[166]
- *N*-allyl-*N*-benzylamine **2.59**,[167]
- 1-(oct-7-en-1-ynyl)benzene **2.74**,[229]
- 4,4-bis(methoxymethyl)-2-methyldec-1-en-6-yne **2.84**,[141]
- (2*S*,3a*R*)-2-hexyl-2,3,3a,4,5,6-hexahydro-1-phenylpentalen-2-ol **2.106**,[83]
- 4,4-bis(methoxymethyl)hepta-1,6-diene **3.23**,[230]
- (*Z*)-4,4-bis(methoxymethyl)nona-1,6-diene **3.24**,[132]
- *N*-allyl-*N*-benzyl-2-methylprop-2-en-1-amine **3.25**,[132]
- 1-allyl-2-vinylbenzene **3.36**,[231]
- *N*-allyl-*N*-benzylprop-2-en-1-amine **3.40a**,[232]
- *N,N*-diallylbenzenamine **3.40b**,[233]
- 1-((*E*)-4,4-bis(methoxymethyl)hepta-1,6-dienyl)benzene **3.43**,[132]
- *N*-allyl-*N*-benzyl-2-phenylprop-2-en-1-amine **3.50**,[234]
- 1,2-diallylbenzene **3.61**,[235]
- 3-(1-methoxy-2- (methoxymethyl)pent-4-en-2-yl)cyclohex-1-ene **3.68**,[132]

6.2. Experimental from chapter 2

6.2.1. (7-Phenylhept-1-en-6-yn-3-yloxy)(*tert*-butyl)dimethylsilane (2.41)

Procedure: A 1 L Schlenk flask was charged with NaI (36.0 g, 0.24 mol) and dry MeCN (0.40 L) was added. After stirring for 0.5 h at RT the reaction mixture was cooled to –5 ^{o}C and addition of freshly distilled acrolein (12.6 mL, 0.20 mol), Me_3SiCl (30.5 mL, 0.24 mol) and dry EtOH (24.5 mL, 0.42 mol) followed. After stirring for 15 min at the same temperature, the reaction mixture was warmed to RT and the stirring was continued for 2 h before pouring the whole reaction mixture onto 5% aqueous $NaHCO_3$ solution (0.40 L). The products were extracted with pentane (3 × 0.20 L). The organic phases were washed with 5% aqueous $Na_2S_2O_3$ solution (0.30 L) and brine (3 × 0.20 L). Drying over K_2CO_3 and concentration *in vacuo* gave the crude material as a yellow oil which was immediately purified by flash column chromatography on Al_2O_3 (basic, grade III) with 10% Et_2O in pentane to provide the desired material (24.30 g, 47%). The pure iodide was immediately reacted in the next step. To a stirred solution of 1-ethynylbenzene (16.5 mL, 0.15 mol) in dry THF (0.30 L) at –78 ^{o}C was added dropwise *n*-BuLi (60.0 mL of a 2.5 M solution in hexanes, 0.15 mol). The reaction mixture was allowed to warm to –50 ^{o}C within 0.5 h. HMPA (26.0 mL, 0.15 mol) was added dropwise followed by dropwise addition of solution of the iodide (24.30 g, 0.094 mol) in dry THF (0.10 L). The reaction mixture was stirred under an Ar atmosphere for 13 h during which time it was allowed to warm to RT. The reaction was stopped by addition of saturated aqueous NH_4Cl solution (0.10 L) and the whole mixture was poured onto H_2O (0.30 L). The products were extracted with Et_2O (3 × 0.20 L) and the combined organic phases were washed with H_2O (3 × 0.20 L) and brine (2 × 0.20 L), dried over K_2CO_3, filtered and concentrated *in vacuo* to give the crude material as a yellow oil which was immediately purified by flash chromatography column on Al_2O_3 (basic, grade III) with 5% Et_2O in hexanes as the eluent to give the pure material as a colourless liquid (17.7 g, 81%).



^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.382 – 7.357 (2H, m, $H^{o\text{-}Ph}$), 7.260 – 7.242 (3H, m, $H^{m\text{-}Ph + p\text{-}Ph}$), 4.664 (1H, t, *J* = 5.7 Hz, H^3), 3.673 (2H, dq, *J* = 9.3, 7.0 Hz, H^2), 3.528 (2H, dq, *J* = 9.5, 7.0 Hz, H^2), 2.476 (2H, t, *J* = 7.3 Hz, H^5), 1.897 (2H, td, *J* = 7.2, 5.7 Hz, H^4), 1.212 (6H, t, *J* = 7.0 Hz, H^1).

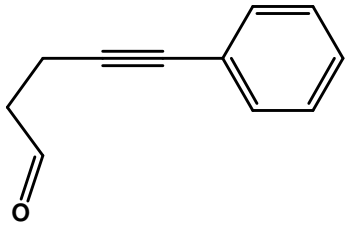
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 131.47 ($2CH^{o\text{-}Ph}$), 128.12 ($2CH^{m\text{-}Ph}$), 127.51 ($CH^{p\text{-}Ph}$), 123.88 ($C^{i\text{-}Ph}$), 101.81 (CH^3), 89.32 ($C^{6/7}$), 80.76 ($C^{6/7}$), 61.54 ($2CH_2{}^2$), 32.77 ($CH_2{}^4$), 15.30 ($2CH_3{}^1$), 15.01 ($CH_2{}^5$).

HRMS (EI): Found: $[M]^+$, 232.1465. $[C_{15}H_{20}O_2]^+$ requires: 232.1463.

LRMS (EI): *m/z*: 232 ($[M]^+$, 1%), 231 ($[M - H]^+$, 3%), 186 ($[M - EtOH]^+$, 67%), 157 ($[M - EtOH - Et]^+$, 100%), 127 (91%).

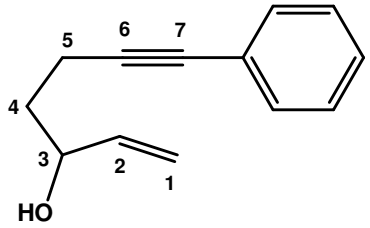
IR (thin film): $\tilde{\nu}$ **=** 2975 (m), 2926 (m), 2869 (m), 1599 (w), 1489 (m), 1448 (m), 1368 (m), 1123 (s), 1058 (s), 760 (s), 688 (s) cm^{-1}.

Such obtained acetal (17.67 g, 0.076 mol) was dissolved in THF : H_2O (4 : 1, 0.50 L) and after stirring at RT for 5 min, a 2 M solution of HCl (0.114 L, 0.228 mol) was slowly added and the stirring was continued for 3 h. The reaction mixture was poured onto saturated aqueous $NaHCO_3$ solution (0.20 L) and the products extracted with Et_2O (3 × 0.20 L), the combined organic phases were washed with H_2O (3 × 0.20 L) and brine (0.30 L), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude material (12.02 g, 100%) as a pale yellow oil which was immediately reacted in the next step without any purification.



^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.837 (1H, s), 7.379 – 7.241 (5H, m), 2.768 – 2.703 (4H, m).

To a stirred solution of the crude aldehyde (12.02 g, 0.076 mol) in dry THF (0.40 L) at –78 ^oC was added dropwise vinylmagnesium bromide (0.114 L of a 1.0 M solution in THF, 0.114 mol). The reaction mixture was stirred for a further 5 h during which time it was allowed to warm to RT before quenching with saturated aqueous NH_4Cl solution (0.10 L). The whole mixture was poured onto H_2O (0.20 L) and the products extracted with Et_2O (3 × 0.20 L) and the combined organic phases were washed with H_2O (3 × 0.15 L) and brine (0.20 L), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude material as a yellow oil. Purification by flash chromatography column on silica with EtOAc : hexane (1 : 3) as the eluent gave 7-phenylhept-1-en-6-yn-3-ol **2.40** as a pale yellow oil (9.21 g, 65%).



^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.431 – 7.381 (2H, m, $H^{o\text{-}Ph}$), 7.321 – 7.261 (3H, m, $H^{m\text{-}Ph + p\text{-}Ph}$), 5.925 (1H, ddd, *J* = 17.1, 10.3, 6.0 Hz, H^2), 5.315 (1H, dt, *J* = 17.3, 1.4 Hz, H^{1t}), 5.172 (1H, dt, *J* = 10.5, 1.3 Hz, H^{1c}), 4.353 (1H, m, H^3), 2.582 (1H, dt, *J* = 17.0, 7.5 Hz, H^5), 2.522 (1H, dt, *J* = 17.0, 6.8 Hz, H^5), 1.871 – 1.812 (3H, m, $2H^4$ + OH).

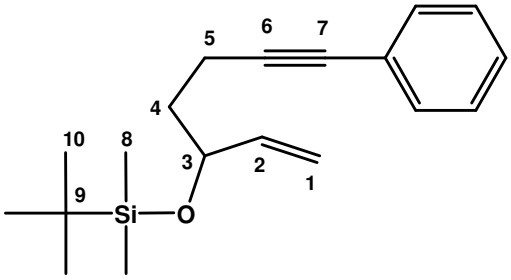
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 140.45 (CH^2), 131.52 ($2CH^{o\text{-}Ph}$), 128.19 ($2CH^{m\text{-}Ph}$), 127.65 ($CH^{p\text{-}Ph}$), 123.73 ($C^{i\text{-}Ph}$), 115.09 ($CH_2{}^1$), 89.37 ($C^{6/7}$), 81.16 ($C^{6/7}$), 72.01 (CH^3), 35.61 ($CH_2{}^4$), 15.64 ($CH_2{}^5$).

HRMS (EI): Found: $[M]^+$, 186.1044. $[C_{13}H_{14}O]^+$ requires: 186.1045.

LRMS (EI): *m/z*: 186 ($[M]^+$, 22%), 185 ($[M - H]^+$, 46%), 167 ($[M - H_2O + H]^+$, 77%), 152 (47%), 128 (69%), 115 (100%).

IR (thin film): $\tilde{\nu}$ **=** 3338 (m, br), 2941 (w), 2915 (w), 1599 (w), 1489 (m), 1433 (m), 1047 (m), 987 (m), 926 (m), 748 (s), 688 (s) cm^{-1}.

To a stirred solution of imidazole (1.904 g, 28.00 mmol) and DMAP (1.709 g, 14.00 mmol) in dry THF (60.0 mL) at RT was added dropwise TBDMSOTf (3.20 mL, 14.00 mmol). After stirring for 10 min, a solution of the allylic alcohol (1.303 g, 7.00 mmol) in dry THF (10 mL) was added and the stirring continued for 18 h at the same temperature before quenching with H_2O (20 mL). The whole mixture was poured onto H_2O (100 mL) and the products extracted with Et_2O (3 × 100 mL). The combined organic phases were washed with H_2O (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude material as a yellow oil. Purification by flash chromatography column on silica with 5% Et_2O in hexanes as the eluent provided the title compound as a yellow oil (2.079 g, 99%).



^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.423 – 7.399 (2H, m, $H^{o\text{-}Ph}$), 7.326 – 7.258 (3H, m, $H^{m\text{-}Ph + p\text{-}Ph}$), 5.850 (1H, ddd, *J* = 17.1, 10.5, 6.0 Hz, H^2), 5.228 (1H, dt, *J* = 17.1, 1.5 Hz, H^{1t}), 5.092 (1H, dt, *J* = 10.5, 1.7 Hz, H^{1c}), 4.330 (1H, apparent q, *J* = 6.0 Hz, H^3), 2.522 (1H, dt, *J* = 16.8, 7.5 Hz, H^5), 2.458 (1H, dt, *J* = 16.8, 6.5 Hz, H^5), 1.823 – 1.764 (2 H, m, H^4), 0.944 (9H, s, H^{10}), 0.129 (3H, s, H^8), 0.085 (3H, s, H^8).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 141.16 (CH^2), 131.50 ($2CH^{o\text{-}Ph}$), 128.18 ($2CH^{m\text{-}Ph}$), 127.50 ($CH^{p\text{-}Ph}$), 124.04 ($C^{i\text{-}Ph}$), 114.20 ($CH_2{}^1$), 89.98 ($C^{6/7}$), 80.83 ($C^{6/7}$), 72.39 (CH^3), 36.88 ($CH_2{}^4$), 25.89 ($3CH_3{}^{10}$), 18.24 (C^9), 15.36 ($CH_2{}^5$), –4.34 ($CH_3{}^8$), –4.86 ($CH_3{}^8$).

HRMS (EI): Found: $[M]^+$, 300.1908. $[C_{19}H_{28}OSi]^+$ requires: 300.1909.

LRMS (EI): *m/z*: 300 ($[M]^+$, 1%), 299 ($[M - H]^+$, 2%), 243 ($[M - C(CH_3)_3]^+$, 87%), 225 (15%), 189 (46%), 115 (71%), 75 (100%).

IR (thin film): $\tilde{\nu}$ = 2953 (m), 2911 (m), 2854 (m), 1467 (w), 1357 (w), 1247 (m), 1066 (m), 979 (m), 922 (m), 839 (s), 779 (s), 756 (s), 692 (s) cm^{-1}.

6.2.2. (*R*)-(7-Phenylhept-1-en-6-yn-3-yloxy)(*tert*-butyl)dimethylsilane ((*R*)-2.41)

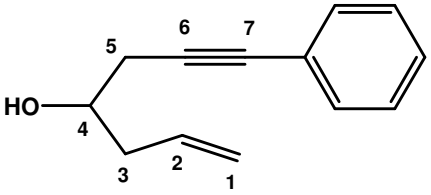
A solution of the racemic alcohol **2.40** (0.372 g, 2.00 mmol) in vinyl crotonate (0.91 mL) was placed in Schlenk tube and an immobilized *Candida antartica* lipase (Novozyme 435) was added (0.091 g). The reaction was incubated at 42 °C (without stirring) for 72 h. After this time the reaction mixture was filtered through sintered funnel and the resins were washed with dry Et_2O. The filtrate was concentrated *in vacuo* to give the crude products as a yellow oil. Purification by column chromatography on SiO_2 with hexane : ethyl acetate (4 : 1) as the eluent gave (*R*)-7-phenylhept-1-en-6-yn-3-ol **(*R*)-2.40** as a pale yellow oil (0.179 g, 96%, 90% e.e.) and (*E*)-(*S*)-7-phenylhept-1-en-6-yn-3-ylbut-2-enoate **2.42** as a yellow oil (0.229 g, 90%).

To a stirred solution of the alcohol **(*R*)-2.40** (0.179 g, 0.96 mmol) in dry DCM (12.0 mL) was added dropwise Et_3N (0.39 mL, 2.82 mmol) at 0 °C. The stirring was continued at the same temperature for 5 min before dropwise addition of TBDMSOTf (0.33 mL, 1.41 mmol). After stirring for 10 min at 0 °C the ice bath was removed and the stirring continued for 30 min at RT before quenching with H_2O (20 mL). The whole mixture was poured onto H_2O (100 mL) and the products extracted with DCM (2 × 75 mL). The combined organic phases were washed with H_2O (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude material as a yellow oil. Purification by flash chromatography column on Al_2O_3 (basic, grade III) with hexane as the eluent provided the title compound as a pale yellow oil (0.193 g, 67%) whose spectral data was consistent with those obtained for racemic product.

6.2.3. (1-Phenylhept-6-en-1-yn-4-yloxy)(*tert*-butyl)dimethylsilane (2.48)

To a stirred solution of pent-4-ene-1,2-diol **2.46** (2.05 g, 20.0 mmol) in dry THF (100 mL) at –10 °C was added sequentially NaH (2.40 g of a 60 % dispersion in mineral oil, 60.0 mmol). After 15 min N-tosyl imidazole (2.45 g, 20.0 mmol) (prepared in 62% yield by the known procedure)[236] was added and the reaction mixture continued to stir at –10 °C for 1 h. Freshly prepared lithium phenyl acetylide was added and the reaction mixture was allowed to warm to 0 °C. [Lithium phenyl acetylide was freshly prepared from phenylacetylene (4.40 mL, 40.0 mmol) in dry THF (50 mL) and *n*-BuLi (16.0 mL of a 2.5 M solution in hexanes, 40.0 mmol) at –10 °C for 30 min]. Subsequently, HMPA (14.0 mL, 40.0 mmol) was added dropwise to the reaction mixture and the stirring was continued at 0 °C for 1 h. After this time, the cooling bath was removed and the reaction

mixture was left at RT for 40 h. The reaction mixture was poured onto saturated aqueous $NaHCO_3$ solution (200 mL), and the products extracted with Et_2O (2 × 200 mL). The combined organic phases were washed with H_2O (2 × 200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product, 7-phenylhept-1-en-6-yn-4-ol **2.47** as a brown oil that was further purified by column chromatography on SiO_2 (for flash chromatography) with hexane : ethyl acetate (3 : 1) as the eluent to yield the title compound as a yellow oil (1.045 g, 28%). The spectral properties of **2.47** were consistent with those published.[227]



^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.316 – 7.257 (2H, m, $H^{o\text{-}Ph}$), 7.182 – 7.127 (3H, m, $H^{m\text{-}Ph\ +\ p\text{-}Ph}$), 5.744 (1H, ddt, *J* = 17.2, 10.2, 7.1 Hz, H^2), 5.068 (1H, ddt, *J* = 17.2, 2.0, 1.5 Hz, H^{1t}), 5.024 (1H, ddt, *J* = 10.2, 2.1, 1.1 Hz, H^{1c}), 3.778 (1H, tt, *J* = 7.1, 5.7 Hz, H^4), 2.538 (1H, dd, *J* = 16.8, 5.7 Hz, H^5), 2.462 (1H, dd, *J* = 16.8, 6.5 Hz, H-5), 2.383 – 2.171 (2H, m, H^3), 1.965 (1H, br s, OH).

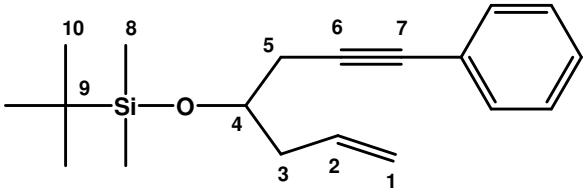
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 134.14 (CH^2), 131.66 ($2CH^{o\text{-}Ph}$), 128.26 ($2CH^{m\text{-}Ph}$), 127.94 ($CH^{p\text{-}Ph}$), 123.39 ($C^{i\text{-}Ph}$), 118.38 ($CH_2{}^1$), 85.92 ($C^{6/7}$), 83.13 ($C^{6/7}$), 69.38 (CH^4), 40.77 ($CH_2{}^3$), 27.63 ($CH_2{}^5$).

LRMS (EI): *m/z*: 186 ($[M]^{+\cdot}$, 3%), 168 ($[M - H_2O]^{+\cdot}$, 21%), 115 (100%), 91 (12%), 89 (33 %), 77 (13%).

IR (thin film): $\tilde{\nu}$ **=** 3380 (m, br), 2930 (w), 1637 (w), 1599 (w), 1486 (m), 1436 (w), 1349 (w), 1066 (m), 756 (s), 696 (s) cm^{-1}.

To a stirred solution of imidazole (2.250 g, 33.08 mmol) and DMAP (2.020 g, 16.54 mmol) in dry THF (100 mL) at RT was added dropwise TBDMSOTf (3.78 mL, 16.54 mmol). After stirring for 10 min, a solution of the alcohol **2.47** (1.54 g, 8.27 mmol) in dry THF (50 mL) was added and the stirring continued for 15 h at the same temperature before quenching with H_2O (20 mL). The mixture was poured onto H_2O (150 mL) and the products extracted with Et_2O (2 × 150 mL), the combined organic phases washed with H_2O (2 × 100 mL) and brine (2 × 100 mL), dried over $MgSO_4$, filtered and and concentrated *in vacuo* to give the crude material as a yellow oil.

Purification by flash chromatography column on silica with 3% Et_2O in hexanes provided pure title compound **2.48** as a pale yellow oil (2.034 g, 82%).



^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.447 – 7.388 (2H, m, $H^{o\text{-}Ph}$), 7.338 – 7.258 (3H, m, $H^{m\text{-}Ph + p\text{-}Ph}$), 5.887 (1H, ddt, *J* = 17.1, 10.3, 6.0 Hz, H^2), 5.174 – 5.086 (2H, m, H^1), 3.971 (1H, quintet, *J* = 5.9 Hz, H^4), 2.562 (2H, d, *J* = 6.2 Hz, H^5), 2.515 – 2.294 (2H, m, H^3), 0.931 (9H, s, H^{10}), 0.134 (3H, s, H^8), 0.115 (3H, s, H^8).

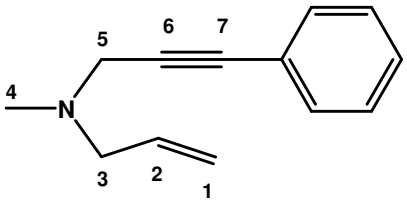
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 134.61 (CH^2), 131.53 ($2CH^{o\text{-}Ph}$), 128.17 ($2CH^{m\text{-}Ph}$), 127.59 ($CH^{p\text{-}Ph}$), 123.93 ($C^{i\text{-}Ph}$), 117.44 ($CH_2{}^1$), 87.48 ($C^{6/7}$), 82.09 ($C^{6/7}$), 71.03 (CH^4), 41.52 ($CH_2{}^3$), 27.89 ($CH_2{}^5$), 25.84 ($3CH_3{}^{10}$), 18.12 (C^9), –4.49 ($CH_3{}^8$), –4.58 ($CH_3{}^8$).

HRMS (EI): Found: $[M]^+$, 300.1898. $[C_{19}H_{28}OSi]^+$ requires: 300.1909.

LRMS (EI): *m/z*: 300 ($[M]^+$, 1%), 285 ($[M - CH_3]^+$, 3%), 259 (17%), 243 ($[M - (CH_3)_3]^+$, 83%), 225 (26%), 115 (67%), 75 (100%).

IR (thin film): $\tilde{\nu}$ = 2945 (m), 2922 (m), 2854 (m), 1489 (w), 1357 (w), 1247 (m), 1058 (s), 832 (s), 775(s), 756 (s), 684 (s) cm^{-1}.

6.2.4. *N*-Methyl-*N*-(phenylprop-2-ynyl)prop-2-en-1-amine (2.57)



1-Ethynylbenzene (0.33 mL, 3.0 mmol), *N*-allyl-*N*-methylamine (0.235 g, 3.3 mmol), formaldehyde (1.2 mL of a 35% aqueous solution) and CuI (0.012 g, 0.063 mmol) were dissolved in DMSO (6 mL). The reaction mixture was stirred at 30 ^oC for 15 h before quenching with saturated aqueous solution of NH_4Cl (50 mL). The products extracted with Et_2O (3 × 25 mL). The combined organic phases were washed with H_2O (3 × 50 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude material which was purified by flash chromatography on silica with 25% Et_2O in hexanes to give the title compound as a yellow oil (0.23 g, 41%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.463 – 7.430 (2H, m, $H^{o\text{-}Ph}$), 7.325 – 7.290 (3H, m, $H^{m\text{-}Ph + p\text{-}Ph}$), 5.896 (1H, ddt, *J* = 17.0, 10.3, 6.6 Hz, H^2), 5.266 (1H, dq, *J* = 17.1, 1.5 Hz, H^{1t}), 5.186 (1H, ddt, *J* = 10.1, 1.9, 1.0 Hz, H^{1c}), 3.554 (2H, s, H^5), 3.146 (2H, dt, *J* = 6.8, 1.1 Hz, H^3), 2.392 (3H, s, H^4).

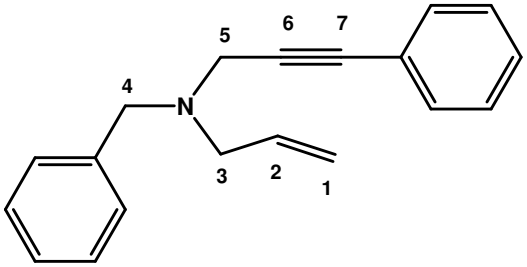
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 135.42 (CH^2), 131.69 ($2CH^{o\text{-}Ph}$), 128.22 ($2CH^{m\text{-}Ph}$), 127.97 ($CH^{p\text{-}Ph}$), 123.28 ($C^{i\text{-}Ph}$), 118.01 ($CH_2{}^1$), 85.34 ($C^{6/7}$), 84.47 ($C^{6/7}$), 59.18 ($CH_2{}^3$), 45.98 ($CH_2{}^5$), 41.71 ($CH_3{}^4$).

HRMS (ESI+): Found: $[M + H]^+$, 186.1276. $[C_{13}H_{16}N]^+$ requires: 186.1277.

LRMS (ESI+): *m/z*: 186 ($[M + H]^+$, 100%).

IR (thin film): $\tilde{\nu}$ **=** 3070 (w), 2933 (w), 2786 (w), 1641 (w), 1599 (w), 1493 (m), 1436 (m), 1331 (m), 1123 (m), 1002 (m), 926 (m), 748 (s), 692 (s) cm^{-1}.

6.2.5. *N*-Benzyl-*N*-(phenylprop-2-ynyl)prop-2-en-1-amine (2.60)



Benzyl bromide (19.99 g, 117 mmol) was added dropwise to neat allylamine (52.7 mL, 702 mmol) at 0 °C. After 16 h at room temperature, the reaction was quenched with aqueous $NaHCO_3$ solution (200 mL), extracted with Et_2O (3 × 100 mL), and dried over K_2CO_3. Purification by flash chromatography on silica with 30 → 50% Et_2O in hexanes gave *N*-allyl-*N*-benzylamine **2.59** (13.45 g, 78%) as a yellow oil whose spectral data was consistent with those published.[167] 1-Ethynylbenzene (1.10 mL, 10 mmol), *N*-allyl-*N*-benzylamine (1.77 g, 12.0 mmol), formaldehyde (4 mL of a 35% aqueous solution) and CuI (0.040 g, 0.21 mmol) were dissolved in DMSO (20 mL). The reaction mixture was stirred at 30 °C for 15 h before quenching with a saturated aqueous solution of NH_4Cl (200 mL). The products extracted with Et_2O (3 × 150 mL), the combined organic phases were washed with H_2O (3 × 150 mL) and brine (200 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude material which was purified by flash chromatography on silica with 25% Et_2O in hexanes to give the title compound as a yellow oil (2.34 g, 89%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.502 – 7.259 (10H, m, H^{Ar}), 5.948 (1H, ddt, *J* = 17.0, 10.3, 6.4 Hz, H^2), 5.328 (1H, dq, *J* = 17.2, 1.6 Hz, H^{1t}), 5.212 (1H, ddt, *J* = 10.1, 1.9, 1.0 Hz, H^{1c}), 3.738 (2H, s, $H^{4/5}$), 3.550 (2H, s, $H^{4/5}$), 3.276 (2H, dt, *J* = 6.4, 1.3 Hz, H^3).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 138.71 ($C^{i\text{-}Ph}$), 135.70 (CH^2), 131.74 ($2CH^{Ar}$), 129.19 ($2CH^{Ar}$), 128.28 ($2CH^{Ar}$), 128.26 ($2CH^{Ar}$), 127.97 ($CH^{p\text{-}Ph}$), 127.11 ($CH^{p\text{-}Ph}$), 123.41 ($C^{i\text{-}Ph}$), 117.94 ($CH_2{}^1$), 85.66 ($C^{6/7}$), 84.46 ($C^{6/7}$), 57.44 ($CH_2{}^{3/4}$), 56.84 ($CH_2{}^{3/4}$), 42.18 ($CH_2{}^5$).

HRMS (ESI+): Found: $[M + H]^+$, 262.1586. $[C_{19}H_{20}N]^+$ requires: 262.1590.

LRMS (ESI+): *m/z*: 262 ($[M + H]^+$, 100%).

IR (thin film): $\tilde{\nu}$ = 3024 (w), 2922 (w), 2816 (w), 1644 (w), 1599 (w), 1489 (m), 1315 (m), 1119 (m), 922 (m), 756 (s), 733 (s), 688 (s) cm^{-1}.

6.2.6. Preparation of compounds 2.20 and 2.63a-aa

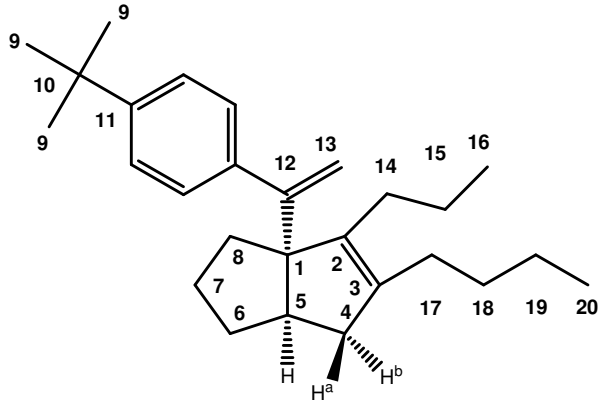
General procedure A: To a solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) dropwise (usually over 2 minutes). After 25 min, a solution of the appropriate enyne (1.0 mmol) in dry THF (3 mL) was added dropwise. After 30 min at –78 °C the reaction mixture was allowed to warm to room temperature and continued to stir for 2 – 3 h. After re-cooling the reaction mixture to –78 °C, a solution of the appropriate 1,1-dihalo alkane (1.1 mmol) in dry THF (1 mL) was added followed by dropwise addition of LDA (0.64 mL of a 1.8 M solution, 1.15 mmol) or freshly prepared LiTMP, [LiTMP prepared from freshly distilled 2,2,6,6-tetramethylpiperidine (0.187 mL, 1.1 mmol) in dry THF (2 mL) and *n*-BuLi (0.44 mL of a 2.5 M solution in hexanes, 1.1 mmol) at 0 °C over 20 min]. The reaction mixture was stirred at –78 °C for 15 min before dropwise addition of the corresponding lithium acetylide, [prepared from alkyne (3.0 mmol) in dry THF (3 mL) and *n*-BuLi (1.2 mL of a 2.5 M solution in hexanes, 3.0 mmol) at –5 °C over 15 min]. The stirring was continued for 0.5 – 1 h during which the reaction mixture was allowed to warm to –55 °C before addition of MeOH (10 mL) and saturated aqueous solution of $NaHCO_3$ (10 mL). The mixture was allowed to warm to room temperature and left stirring for 12 – 16 h. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 75 mL). The combined organic phases were

washed with H_2O (3 × 100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude products mostly as yellow oils.

Stability tests

The following compounds: **2.63a, 2.69-*exo*, 2.69-*endo*, 2.72-*exo*** and **2.72-*endo*** were stable after being kept in $CDCl_3$ (in NMR tube) at RT in the presence of daylight for 2 weeks. The compounds also turned out to be stable after being exposed to 1.0 equivalent of (+)-camphorsulfonic acid in $CDCl_3$ (in NMR tube) at RT in the presence of daylight for 1 week. **2.63a** was also resistant to 2.0 equivalents of (+)-camphorsulfonic acid in $CDCl_3$ for 2 weeks regardless of warming the NMR tube to 50 °C for the last two days.

6.2.6.1. *rac*-(1*R*,5*R*)-1-(4-*tert*-Butylphenyl)vinyl)-3-hexyl-2-propyl-bicyclo[3.3.0]oct-2-ene (2.20)



General procedure A was used with dec-1-en-6-yne, 1,1-dibromopentane and 1-*tert*-butyl-4-ethynylbenzene as components except that LiTMP was used instead of LDA. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a pale yellow oil in yield of 0.242 g (66%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.237 (2H, m, $H^{o\text{-}Ph}$), 7.129 (2H, m, $H^{m\text{-}Ph}$), 5.114 (1H, d, *J* = 1.8 Hz, H^{13}), 4.986 (1H, d, *J* = 1.8 Hz, H^{13}), 2.354 (1H, tt, *J* = 8.9, 2.1 Hz, H^5), 2.278 (1H, dd, *J* = 15.7, 8.9 Hz, H^{4b}), 2.082 (2H, t, *J* = 7.3 Hz, $H^{14/17}$), 1.966 (2H, t, *J* = 8.4 Hz, $H^{14/17}$), 1.835 – 1.700 (4H, m), 1.586 – 1.273 (9H, m), 1.324 (9H, s, H^9), 0.931 (3H, t, *J* = 7.2 Hz, $H^{16/20}$), 0.923 (3H, t, *J* = 7.3 Hz, $H^{16/20}$).

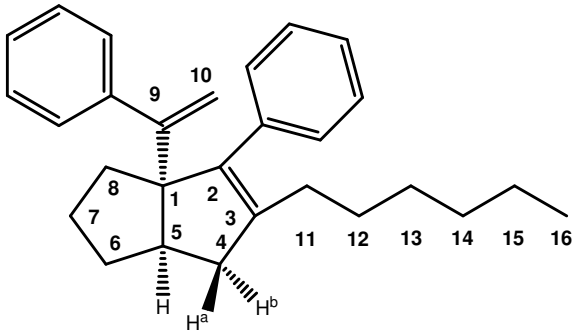
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 155.93 (C^{12}), 149.00 (C^{11}), 141.49 ($C^{i\text{-}Ph/2/3}$), 138.96 ($C^{i\text{-}Ph/2/3}$), 137.42 ($C^{i\text{-}Ph/2/3}$), 127.45 ($2CH^{o\text{-}Ph}$), 124.16 ($2CH^{m\text{-}Ph}$), 112.79 ($CH_2{}^{13}$), 70.37 (C^1), 43.96 (CH^5), 43.92 ($CH_2{}^4$), 36.60 (CH_2), 36.09 (CH_2), 34.33 (C^{10}), 31.39 ($3CH_3{}^9$), 30.05 (CH_2), 29.02 ($CH_2{}^{14/17}$), 28.92 ($CH_2{}^{14/17}$), 25.32 (CH_2), 23.73 (CH_2), 22.91 (CH_2), 15.09 ($CH_3{}^{16/20}$), 14.11 ($CH_3{}^{16/20}$).

HRMS (EI): Found: $[M]^+$, 364.3128. $C_{27}H_{40}$ requires: 364.3130.

LRMS (EI): *m/z*: 364 ($[M]^+$, 56 %), 335 ($[M - Et]^+$, 11 %), 307 ($[M - p\text{-}t\text{-}Bu]^+$, 55 %), 205 ($[M - p\text{-}t\text{-}Bu\text{-Styrene}]^+$, 100 %).

IR (thin film): $\tilde{\nu}$ = 2949 (s), 2862 (s), 1610 (w), 1504 (w), 1467 (m), 1365 (w), 1266 (w), 1119 (w), 1017 (w), 900 (s), 847 (s), 733 (s), 601 (w) cm^{-1}.

6.2.6.2. *rac*-(1*R*,5*R*)-3-Hexyl-2-phenyl-1-(1-phenylvinyl)-bicyclo[3.3.0]oct-2-ene (2.63a)



General procedure A was used with 1-(hept-6-en-1-ynyl)benzene, 1,1-dibromoheptane and 1-ethynylbenzene as components. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a pale yellow oil in yield of 0.318 g (86%).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.350 – 7.235 (10H, m, H^{Ar}), 5.038 (1H, d, *J* = 1.6 Hz, H^{10}), 5.022 (1H, d, *J* = 1.6 Hz, H^{10}), 2.433 (1H, tdd, *J* = 8.6, 3.2, 1.4 Hz, H^5), 2.342 (1H, ddd, *J* = 16.2, 8.4, 1.0 Hz, H^{4b}), 2.148 – 1.968 (3H, m), 1.854 (1H, dtd, *J* = 12.2, 9.7, 6.8 Hz), 1.706 – 1.661 (2H, m), 1.622 – 1.521 (3H, m), 1.429 – 1.206 (8H, m), 0.881 (3H, t, *J* = 6.8 Hz, H^{16}).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 155.39 (C^9), 144.40 ($C^{i\text{-}Ph}$), 142.48 ($C^{i\text{-}Ph}$), 138.95 ($C^{2\text{ or }3}$), 137.98 ($C^{2\text{ or }3}$), 129.69 ($2CH^{o\text{-}Ph\text{ or }m\text{-}Ph}$), 127.93 ($2CH^{o\text{-}Ph\text{ or }m\text{-}Ph}$), 127.55 ($2CH^{m\text{-}Ph\text{ or }o\text{-}Ph}$), 127.52 ($2CH^{m\text{-}Ph\text{ or }o\text{-}Ph}$), 126.47 ($CH^{p\text{-}Ph}$), 126.33 ($CH^{p\text{-}Ph}$), 114.45

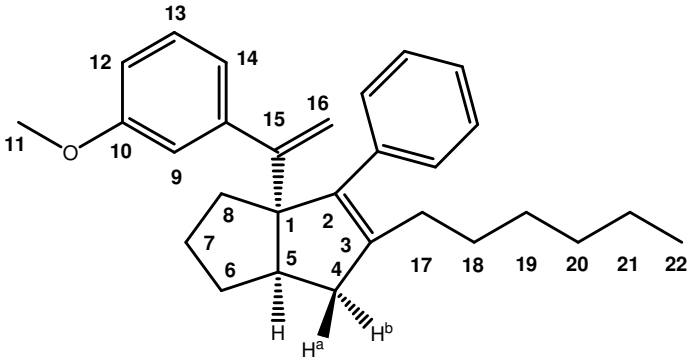
(CH_2^{10}), 70.16 (C^1), 45.71 (CH^5), 43.83 (CH_2), 36.33 (CH_2), 35.64 (CH_2), 31.70 (CH_2), 29.89 (CH_2), 29.41 (CH_2), 27.87 (CH_2), 25.60 (CH_2), 22.60 (CH_2), 14.06 (CH_3^{16}).

HRMS (EI): Found: $[M]^+$, 370.2655. $C_{26}H_{34}$ requires: 370.2661.

LRMS (EI): *m/z*: 370 ($[M]^{+\cdot}$, 100%), 299 ($[M - C_5H_{11}]^{+\cdot}$, 35%), 267 ($[M - Styrene]^{+\cdot}$, 85%).

IR (thin film): $\tilde{\nu}$ **=** 2926 (m), 2851 (m), 1632 (w), 1596 (w), 1491 (m), 1439 (w), 902 (m), 768 (m), 703 (s) cm^{-1}.

6.2.6.3. *rac*-(1*R*,5*R*)-3-Hexyl-1-(3-methoxyphenyl)vinyl)-2-phenyl-bicyclo[3.3.0]-oct-2-ene (2.63b)



General procedure A was used with 1-(hept-6-en-1-ynyl)benzene, 1,1-dibromoheptane and 1-ethynyl-3-methoxybenzene as components. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with 2.5 % Et_2O in hexane as the eluent gave the title compound as a pale yellow oil in yield of 0.312 g (78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.355 – 7.251 (5H, m, H^{Ar}), 7.199 (1H, t, *J* = 8.0 Hz, H^{13}), 6.957 (1H, ddd, *J* = 8.0, 1.5, 1.0 Hz, H^{14}), 6.916 (1H, dd, *J* = 2.5, 1.5 Hz, H^9), 6.833 (1H, ddd, *J* = 8.0, 2.5, 1.0 Hz, H^{12}), 5.081 (1H, d, *J* = 1.8 Hz, H^{16}), 5.017 (1H, d, *J* = 1.8 Hz, H^{16}), 3.793 (3H, s, H^{11}), 2.508 – 2.414 (2H, m, $H^{5 + 4b}$), 2.104 (1H, dt, *J* = 21.5, 8.0 Hz, H^{17}), 2.051 (1H, dt, *J* = 21.5, 8.0 Hz, H^{17}), 2.046 (1H, d, *J* = 15.3 Hz, H^{4a}), 1.870 (1H, tdd, *J* = 11.8, 10.0, 6.5 Hz, H^6), 1.716 – 1.501 (4H, m), 1.444 – 1.367 (3H, m), 1.332 – 1.240 (6H, m), 0.901 (3H, t, *J* = 7.0 Hz, H^{22}).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 158.90 (C^{10}), 155.23 (C^{15}), 145.88 ($C^{2 \text{ or } 3}$), 142.43 ($C^{2 \text{ or } 3}$), 139.14 ($C^{i\text{-}Ph}$), 137.94 ($C^{i\text{-}Ph}$), 129.72 ($2CH^{m\text{-}Ph}$), 128.45 (CH^{13}), 127.54 ($2CH^{o\text{-}Ph}$), 126.33 ($CH^{p\text{-}Ph}$), 120.48 (CH^{14}), 114.59 (CH_2^{16}), 113.68 (CH^9), 111.90 (CH^{12}), 70.13 (C^1), 55.10 (CH_3^{11}), 45.74 (CH^5), 43.96 (CH_2^4), 36.38 (CH_2^6), 35.82

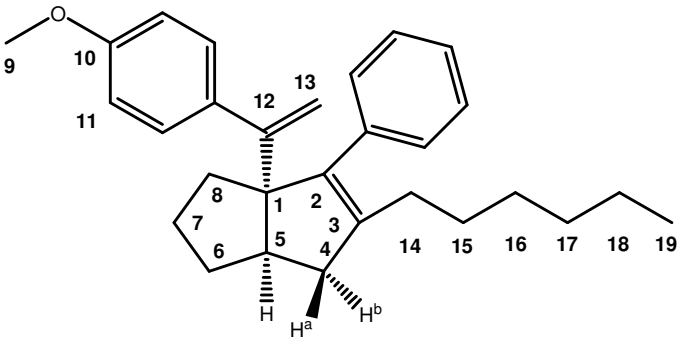
(CH_2^8), 31.71 (CH_2), 29.91 (CH_2^{17}), 29.41 (CH_2), 27.96 (CH_2), 25.55 (CH_2^7), 22.58 (CH_2), 14.07 (CH_3^{22}).

HRMS (EI): Found: $[M]^+$, 400.2763. $C_{29}H_{36}O$ requires: 400.2766.

LRMS (CI): *m/z*: 400 ($[M]^+$, 100%), 267 ([M – *m*-MeO – Styrene]$^+$, 24%).

IR (thin film): $\tilde{\nu}$ **=** 2934 (m), 2848 (m), 1574 (m), 1455 (m), 1283 (m), 1040 (m), 889 (m), 764 (m), 700 (s) cm^{-1}.

6.2.6.4. *rac*-(1*R*,5*R*)-3-Hexyl-1-(4-methoxyphenyl)vinyl)-2-phenyl-bicyclo[3.3.0]-oct-2-ene (2.63c)



General procedure A was used with 1-(hept-6-en-1-ynyl)benzene, 1,1-dibromoheptane and 1-ethynyl-4-methoxybenzene as components. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a yellow oil in yield of 0.290 g (72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.343 – 7.241 (7H, m, H^{Ar}), 6.838 – 6.801 (2H, m, H^{11}), 5.018 (1H, d, *J* = 1.8 Hz, H^{13}), 4.994 (1H, d, *J* = 1.8 Hz, H^{13}), 3.827 (3H, s, H^9), 2.430 (1H, td, *J* = 8.5, 2.4 Hz, H^5), 2.375 (1H, dd, *J* = 16.0, 8.5 Hz, H^{4b}), 2.077 (1H, dt, *J* = 21.3, 8.0 Hz, H^{14}), 2.058 (1H, dt, *J* = 21.3, 7.5 Hz, H^{14}), 2.012 (1H, d, *J* = 16.0 Hz, H^{4a}), 1.856 (1H, tdd, *J* = 12.0, 9.5, 7.0 Hz, H^6), 1.737 – 1.668 (2H, m, H^8), 1.623 – 1.484 (2H, m, H^7), 1.423 – 1.341 (3H, m), 1.323 – 1.204 (6H, m), 0.892 (3H, t, *J* = 7.0 Hz, H^{19}).

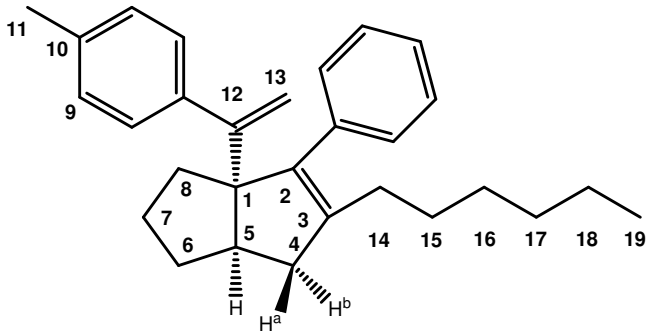
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 158.33 (C^{10}), 154.81 (C^{12}), 142.39 ($C^{2 \text{ or } 3}$), 138.98 ($C^{2 \text{ or } 3}$), 137.96 ($C^{i\text{-Ph}}$), 136.91 ($C^{i\text{-Ph}}$), 129.64 ($2CH^{o\text{- or m-Ph}}$), 128.91 ($2CH^{o\text{- or m-Ph}}$), 127.52 ($2CH^{o\text{- or m-Ph}}$), 126.29 ($CH^{p\text{-Ph}}$), 113.98 (CH_2^{13}), 112.89 ($2CH^{11}$), 70.23 (C^1), 55.16 (CH_3^9), 45.64 (CH^5), 43.90 (CH_2^4), 36.36 (CH_2^6), 35.62 (CH_2^8), 31.71 (CH_2), 29.88 (CH_2^{14}), 29.41 (CH_2), 27.87 (CH_2), 25.59 (CH_2^7), 22.60 (CH_2), 14.07 (CH_3^{19}).

HRMS (EI): Found: $[M]^+$, 400.2768. $C_{29}H_{36}O$ requires: 400.2766.

LRMS (CI): *m/z*: 401 ($[M + H]^+$, 100%), 267 ($[M – p\text{-MeO} – \text{Styrene}]^+$, 55%).

IR (thin film): $\tilde{\nu}$ **=** 2930 (m), 2854 (m), 1607 (m), 1508 (s), 1244 (s), 1176 (m), 1036 (m), 903 (w), 832 (s), 767 (m), 699 (s) cm^{-1}.

6.2.6.5. *rac*-(1*R*,5*R*)-3-Hexyl-1-(4-methylphenyl)vinyl)-2-phenyl-bicyclo[3.3.0]oct-2-ene (2.63d)



General procedure A was used with 1-(hept-6-en-1-ynyl)benzene, 1,1-dibromoheptane and 1-ethynyl-4-methylbenzene as components. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexane as the eluent gave the title compound as a pale yellow oil in yield of 0.237 g (62%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.344 – 7.234 (7H, m, H^{Ar}), 7.099 – 7.080 (2H, m, H^9), 5.035 (1H, d, *J* = 1.8 Hz, H^{13}), 4.998 (1H, d, *J* = 1.8 Hz, H^{13}), 2.470 – 2.346 (2H, m, $H^{5\ +\ 4b}$), 2.370 (3H, s, H^9), 2.096 (1H, dt, *J* = 21.5, 7.8 Hz, H^{14}), 2.061 (1H, dt, *J* = 21.5, 7.5 Hz, H^{14}), 2.016 (1H, d, *J* = 14.8 Hz, H^{4a}), 1.855 (1H, tdd, *J* = 12.0, 9.8, 6.8 Hz, H^6), 1.701 – 1.667 (2H, m), 1.601 – 1.535 (2H, m), 1.431 – 1.356 (3H, m), 1.325 – 1.229 (6H, m), 0.897 (3H, t, *J* = 7.0 Hz, H^{19}).

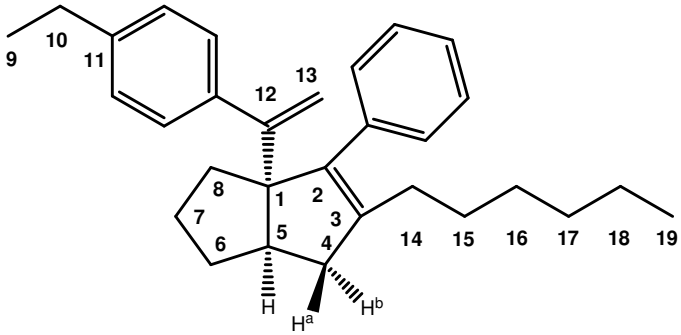
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 155.21 (C^{12}), 142.33 ($C^{2\ or\ 3}$), 141.53 ($C^{2\ or\ 3}$), 139.09 ($C^{i\text{-}Ph\ or\ 10}$), 137.99 ($C^{i\text{-}Ph\ or\ 10}$), 136.01 ($C^{i\text{-}Ph\ or\ 10}$), 129.71 ($2CH^{o\text{-}\ or\ m\text{-}Ph}$), 128.24 ($2CH^{o\text{-}\ or\ m\text{-}Ph}$), 127.76 ($2CH^{o\text{-}\ or\ m\text{-}Ph}$), 127.51 ($2CH^{o\text{-}\ or\ m\text{-}Ph}$), 126.28 ($CH^{p\text{-}Ph}$), 114.24 ($CH_2{}^{13}$), 70.19 ($C^1$), 45.67 ($CH^5$), 43.91 ($CH_2{}^4$), 36.36 ($CH_2{}^6$), 35.70 ($CH_2{}^8$), 31.72 ($CH_2$), 29.88 ($CH_2{}^{14}$), 29.40 ($CH_2$), 27.88 ($CH_2$), 25.58 ($CH_2{}^7$), 22.60 ($CH_2$), 21.08 ($CH_3{}^{11}$), 14.07 ($CH_3{}^{19}$).

HRMS (EI): Found: $[M]^+$, 384.2820. $C_{29}H_{36}$ requires: 384.2817.

LRMS (CI): *m/z*: 384 ($[M]^+$, 100%), 267 ($[M – p\text{-Me} – \text{Styrene}]^+$, 33%).

IR (thin film): $\tilde{\nu}$ **=** 2929 (m), 2848 (m), 1596 (w), 1493 (w), 1445 (w), 894 (m), 824 (m), 759 (m), 694 (s) cm^{-1}.

6.2.6.6. *rac*-(1*R*,5*R*)-1-(4-Ethylphenyl)vinyl)-3-hexyl-2-phenyl-bicyclo[3.3.0]oct-2-ene (2.63e)



General procedure A was used with 1-(hept-6-en-1-ynyl)benzene, 1,1-dibromoheptane and 1-ethyl-4-ethynylbenzene as components. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a pale yellow oil in yield of 0.280 g (70%).

^{1}H NMR (400 MHz, BENZENE-D$_6$): δ (ppm) = 7.440 – 7.047 (9H, m, H^{Ar}), 5.164 (1H, d, *J* = 1.8 Hz, H^{13}), 5.094 (1H, d, *J* = 1.8 Hz, H^{13}), 2.592 (1H, tdd, *J* = 8.3, 4.3, 1.5 Hz, H^5), 2.511 (1H, dd, *J* = 16.3, 8.3 Hz, H^{4b}), 2.500 (2H, q, *J* = 7.5 Hz, H^{10}), 2.154 – 2.115 (2H, m, H^{14}), 1.987 (1H, d, *J* = 16.3 Hz, H^{4a}), 1.881 – 1.730 (3H, m), 1.688 – 1.530 (2H, m), 1.426 – 1.348 (3H, m), 1.287 – 1.158 (6H, m), 1.131 (3H, t, *J* = 7.7 Hz, H^9), 0.863 (3H, t, *J* = 7.2 Hz, H^{19}).

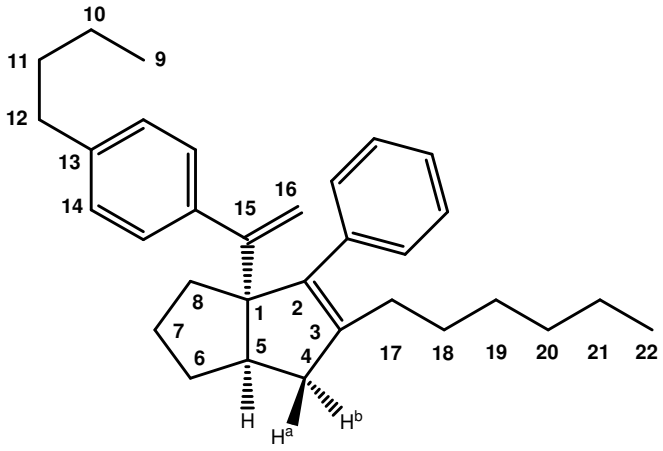
^{13}C NMR (100.5 MHz, BENZENE-D$_6$): δ (ppm) = 156.22 (C^{12}), 143.09 ($C^{2 \text{ or } 3}$), 142.81 (C^{11}), 142.64 ($C^{2 \text{ or } 3}$), 140.32 ($C^{i\text{-}Ph}$), 138.79 ($C^{i\text{-}Ph}$), 130.51 ($2CH^{o\text{- or } m\text{-}Ph}$), 128.71 ($2CH^{o\text{- or } m\text{-}Ph}$), 128.46 ($2CH^{o\text{- or } m\text{-}Ph}$), 127.87 ($2CH^{o\text{- or } m\text{-}Ph}$), 127.26 ($CH^{p\text{-}Ph}$), 114.96 ($CH_2{}^{10}$), 71.14 ($C^1$), 46.50 ($CH^5$), 44.68 ($CH_2{}^4$), 37.13 ($CH_2$), 36.54 ($CH_2$), 32.41 ($CH_2$), 30.64 ($CH_2$), 30.15 ($CH_2$), 29.24 ($CH_2$), 28.67 ($CH_2$), 26.39 ($CH_2$), 23.36 ($CH_2$), 16.22 ($CH_3{}^9$), 14.66 ($CH_3{}^{19}$).

HRMS (EI): Found: $[M]^+$, 398.2974. $C_{30}H_{38}$ requires: 398.2974.

LRMS (CI): *m/z*: 399 ($[M + H]^+$, 100%), 267 ($[M – p\text{-Et} – \text{Styrene}]^+$, 45%).

IR (thin film): $\tilde{\nu}$ **=** 2933 (s), 2850 (m), 1493 (w), 1452 (w), 902 (m), 835 (s), 760 (m), 695 (s) cm^{-1}.

6.2.6.7. *rac*-(1*R*,5*R*)-1-(4-Butylphenyl)vinyl)-3-hexyl-2-phenyl-bicyclo[3.3.0]oct-2-ene (2.63f)



General procedure A was used with 1-(hept-6-en-1-ynyl)benzene, 1,1-dibromoheptane and 1-butyl-4-ethynylbenzene as components. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a yellow oil in yield of 0.333 g (78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.370 – 7.265 (7H, m, H^{Ar}), 7.125 – 7.099 (2H, m, H^{14}), 5.066 (1H, d, *J* = 1.8 Hz, H^{16}), 5.025 (1H, d, *J* = 1.8 Hz, H^{16}), 2.650 (2H, t, *J* = 7.6 Hz, H^{12}), 2.466 (1H, td, *J* = 8.8, 2.8 Hz, H^5), 2.399 (1H, dd, *J* = 16.0, 8.8 Hz, H^{4b}), 2.118 (1H, dt, *J* = 21.0, 7.5 Hz, H^{17}), 2.087 (1H, dt, *J* = 21.0, 7.3 Hz, H^{17}), 2.027 (1H, d, *J* = 16.0 Hz, H^{4a}), 1.880 (1H, tdd, *J* = 12.3, 9.3, 6.8 Hz, H^6), 1.730 – 1.506 (6H, m), 1.469 – 1.368 (5H, m), 1.349 – 1.256 (6H, m), 0.991 (3H, t, *J* = 7.3 Hz, $H^{9 \text{ or } 22}$), 0.920 (3H, t, *J* = 7.0 Hz, $H^{9 \text{ or } 22}$).

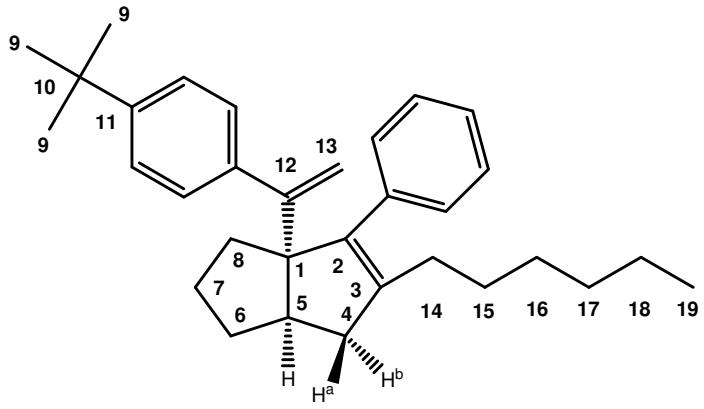
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 155.29 (C^{15}), 142.34 ($C^{2 \text{ or } 3}$), 141.64 (C^{13}), 141.05 ($C^{2 \text{ or } 3}$), 139.06 ($C^{i\text{-Ph}}$), 138.02 ($C^{i\text{-Ph}}$), 129.71 ($2CH^{o\text{- or m-Ph}}$), 127.74 ($2CH^{o\text{- or m-Ph}}$), 127.51 ($4CH^{o\text{- or m-Ph}}$), 126.27 ($CH^{p\text{-Ph}}$), 114.12 (CH_2^{10}), 70.19 (C^1), 45.69 (CH^5), 43.91 (CH_2^4), 36.35 (CH_2^6), 35.67 (CH_2), 35.29 (CH_2^{12}), 33.63 (CH_2), 31.73 (CH_2), 29.90 (CH_2^{17}), 29.43 (CH_2), 27.87 (CH_2), 25.60 (CH_2), 22.61 (CH_2), 22.42 (CH_2), 14.08 ($CH_3^{9 \text{ or } 22}$), 13.97 ($CH_3^{9 \text{ or } 22}$).

HRMS (EI): Found: $[M]^+$, 426.3293. $C_{32}H_{42}$ requires: 426.3286.

LRMS (CI): *m/z*: 427 ($[M + H]^+$, 100%), 267 ($[M – p\text{-Bu} – \text{Styrene}]^+$, 47%).

IR (thin film): $\tilde{\nu}$ = 2926 (s), 2854 (m), 1512 (w), 1459 (w), 900 (m), 835 (w), 752 (m), 699 (s) cm^{-1}.

6.2.6.8. *rac*-(1*R*,5*R*)-1-(4-*tert*-Butylphenyl)vinyl)-3-hexyl-2-phenyl-bicyclo[3.3.0]oct-2-ene (2.63g)



General procedure A was used with 1-(hept-6-en-1-ynyl)benzene, 1,1-dibromoheptane and 1-*tert*-butyl-4-ethynylbenzene as components. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a pale yellow oil in yield of 0.221 g (51%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.332 – 7.222 (9H, m, H^{Ar}), 5.040 (1H, d, *J* = 1.8 Hz, H^{13}), 4.976 (1H, d, *J* = 1.8 Hz, H^{13}), 2.440 (1H, td, *J* = 8.5, 2.2 Hz, H^5), 2.390 (1H, dd, *J* = 15.5, 8.3 Hz, H^{4b}), 2.085 – 2.040 (2H, m, H^{14}), 1.993 (1H, d, *J* = 15.5 Hz, H^{4a}), 1.835 (1H, tdd, *J* = 12.3, 10.0, 6.9 Hz, H^6), 1.692 – 1.658 (2H, m, H^8), 1.601 – 1.489 (2H, m, H^7), 1.409 – 1.208 (9H, m), 1.335 (9H, s, H^9), 0.877 (3H, t, *J* = 7.0 Hz, H^{19}).

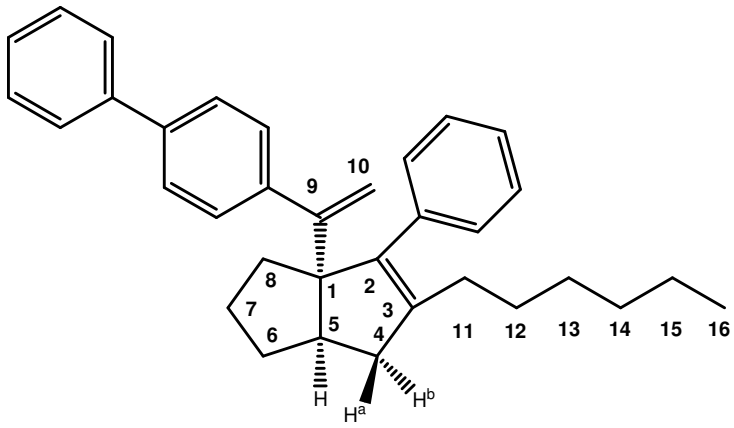
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 155.17 (C^{12}), 149.28 (C^{11}), 142.27 ($C^{2 \text{ or } 3}$), 141.37 ($C^{2 \text{ or } 3}$), 139.17 ($C^{i\text{-Ph}}$), 138.00 ($C^{i\text{-Ph}}$), 129.74 ($2CH^{o\text{- or m-Ph}}$), 127.47 ($4CH^{o\text{- or m-Ph}}$), 126.26 ($CH^{p\text{-Ph}}$), 124.37 ($2CH^{o\text{- or m-Ph}}$), 114.23 ($CH_2{}^{13}$), 70.17 (C^1), 45.66 (CH^5), 43.97 ($CH_2{}^4$), 36.38 ($CH_2{}^6$), 35.74 ($CH_2{}^8$), 34.38 (C^{10}), 31.73 (CH_2), 31.40 ($3CH_3{}^{11}$), 29.90 ($CH_2{}^{14}$), 29.42 (CH_2), 27.87 (CH_2), 25.56 ($CH_2{}^7$), 22.61 (CH_2), 14.08 ($CH_3{}^{19}$).

HRMS (EI): Found: $[M]^+$, 426.3283. $C_{32}H_{42}$ requires: 426.3286.

LRMS (CI): *m/z*: 427 ($[M + H]^+$, 100%), 267 ($[M – p\text{-}\ t\text{-Bu} – \text{Styrene}]^+$, 51%).

IR (thin film): $\tilde{\nu}$ = 2949 (s), 2930 (s), 2862 (m), 1508 (w), 1489 (w), 1467 (w), 1367 (w), 1270 (w), 903 (m), 843 (s), 763 (m), 699 (s) cm^{-1}.

6.2.6.9. *rac*-(1*R*,5*R*)-3-Hexyl-2-phenyl-1-(4-phenylphenyl)vinyl)-bicyclo[3.3.0]oct-2-ene (2.63h)



General procedure A was used with 1-(hept-6-en-1-ynyl)benzene, 1,1-dibromoheptane and 1-ethynyl-4-phenylbenzene as components. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a yellow oil in yield of 0.266 g (60%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.478 – 7.089 (14H, m, H^{Ar}), 4.943 (1H, d, *J* = 1.6 Hz, H^{10}), 4.885 (1H, d, *J* = 1.6 Hz, H^{10}), 2.324 (1H, td, *J* = 8.4, 2.3 Hz, H^5), 2.272 (1H, dd, *J* = 16.6, 8.4 Hz, H^{4b}), 1.937 (1H, dt, *J* = 21.6, 7.8 Hz, H^{11}), 1.906 (1H, dt, *J* = 21.6, 7.3 Hz, H^{11}), 1.868 (1H, d, *J* = 16.6 Hz, H^{4a}), 1.710 (1H, tdd, *J* = 12.0, 10.3, 7.0 Hz, H^6), 1.572 – 1.539 (2H, m, H^8), 1.477 – 1.382 (2H, m, H^7), 1.286 – 1.196 (3H, m), 1.168 – 1.022 (6H, m), 0.715 (3H, t, *J* = 6.9 Hz, H^{16}).

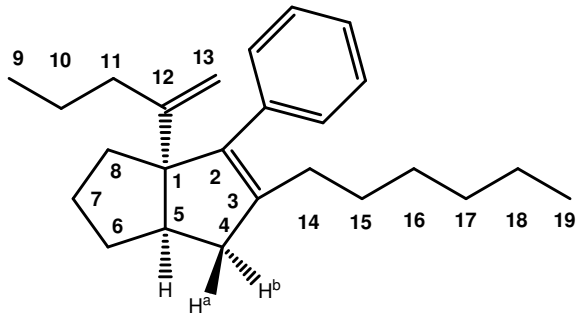
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 155.03 (C^9), 143.49 ($C^{2\text{ or }3}$), 142.52 ($C^{2\text{ or }3}$), 140.96 ($C^{i\text{-Ph}}$), 139.30 ($C^{i\text{-Ph}}$), 139.07 ($C^{i\text{-Ph}}$), 137.94 ($C^{i\text{-Ph}}$), 129.71 ($2CH^{o\text{- or }m\text{-Ph}}$), 128.71 ($2CH^{o\text{- or }m\text{-Ph}}$), 128.29 ($2CH^{o\text{- or }m\text{-Ph}}$), 127.57 ($2CH^{o\text{- or }m\text{-Ph}}$), 127.09 ($CH^{p\text{-Ph}}$), 126.95 ($2CH^{o\text{- or }m\text{-Ph}}$), 126.36 ($CH^{p\text{-Ph}}$), 126.23 ($2CH^{o\text{- or }m\text{-Ph}}$), 114.64 ($CH_2{}^{10}$), 70.20 ($C^1$), 45.69 ($CH^5$), 43.98 ($CH_2{}^4$), 36.41 ($CH_2$), 35.78 ($CH_2{}^8$), 31.71 ($CH_2$), 29.90 ($CH_2{}^{11}$), 29.42 ($CH_2$), 27.89 ($CH_2$), 25.56 ($CH_2{}^7$), 22.61 ($CH_2$), 14.07 ($CH_3{}^{16}$).

HRMS (EI): Found: $[M]^+$, 446.2972. $C_{34}H_{38}$ requires: 446.2974.

LRMS (CI): *m/z*: 446 ($[M]^+$, 100%), 267 ([M – *p*-Ph – Styrene]$^+$, 69%).

IR (thin film): $\tilde{\nu}$ **=** 2933 (m), 2858 (m), 1603 (w), 1482 (s), 1440 (w), 903 (m), 847 (m), 767 (s), 737 (s), 699 (s) cm^{-1}.

6.2.6.10. *rac*-(1*R*,5*R*)-3-Hexyl-1-(pent-1-en-2-yl)-2-phenyl-bicyclo[3.3.0]oct-2-ene (2.63i)



General procedure A was used with 1-(hept-6-en-1-ynyl)benzene, 1,1-dibromoheptane and 1-pentyne as components. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a colourless oil in yield of 0.183 g (54%).

^{1}H NMR (400 MHz, BENZENE-D$_6$): δ (ppm) = 7.248 – 7.187 (4H, m, $H^{o- + m-Ph}$), 7.116 – 7.072 (1H, m, H^{p-Ph}), 4.988 (1H, d, *J* = 1.0 Hz, H^{13}), 4.941 (1H, q, *J* = 1.5 Hz, H^{13}), 2.852 (1H, dd, *J* = 16.8, 8.3 Hz, H^{4b}), 2.440 (1H, tdd, *J* = 8.3, 3.3, 1.8 Hz, H^5), 2.287 – 2.070 (5H, m, H^{4a} + 4H), 1.918 – 1.741 (2H, m), 11.701 – 1.535 (5H, m), 1.459 – 1.355 (3H, m), 1.267 – 1.107 (6H, m), 0.981 (3H, t, *J* = 7.3 Hz, $H^{9 \text{ or } 19}$), 0.850 (3H, t, *J* = 7.1 Hz, $H^{9 \text{ or } 19}$).

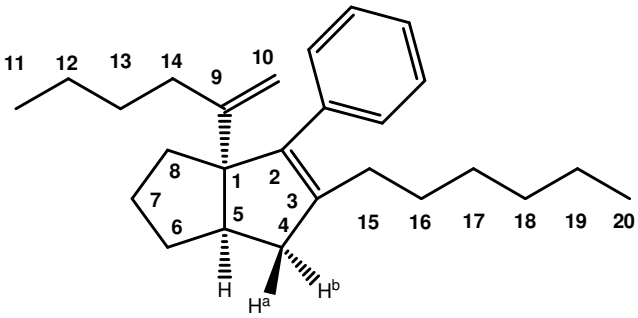
^{13}C NMR (100.5 MHz, BENZENE-D$_6$): δ (ppm) = 154.63 (C^{12}), 141.69 ($C^{2 \text{ or } 3}$), 140.80 ($C^{2 \text{ or } 3}$), 138.75 (C^{i-Ph}), 130.16 ($2CH^{o- \text{ or } m-Ph}$), 128.39 ($2CH^{o- \text{ or } m-Ph}$), 127.12 ($CH^{p-Ph}$), 108.43 ($CH_2{}^{13}$), 72.04 ($C^1$), 46.35 ($CH^5$), 44.97 ($CH_2{}^4$), 37.39 ($CH_2$), 35.50 ($CH_2$), 34.60 ($CH_2$), 32.36 ($CH_2$), 30.30 ($CH_2$), 29.84 ($CH_2$), 28.81 ($CH_2$), 26.52 ($CH_2$), 23.37 ($CH_2$), 22.39 ($CH_2$), 15.03 ($CH_3{}^{9 \text{ or } 19}$), 14.64 ($CH_3{}^{9 \text{ or } 19}$).

HRMS (EI): Found: $[M]^+$, 336.2818. $C_{25}H_{36}$ requires: 336.2817.

LRMS (CI): *m/z*: 337 ($[M + H]^+$, 100%), 293 ($[M – C_3H_7]^+$, 35%).

IR (thin film): $\tilde{\nu}$ **=** 2956 (s), 2926 (s), 2854 (m), 1633 (w), 1489 (w), 1455 (w), 892 (m), 877 (m), 760 (m), 699 (s) cm^{-1}.

6.2.6.11. *rac*-(1*R*,5*R*)-1-(Hex-1-en-2-yl)-3-hexyl-2-phenyl-bicyclo[3.3.0]oct-2-ene (2.63j)



General procedure A was used with 1-(hept-6-en-1-ynyl)benzene, 1,1-dibromoheptane and 1-hexyne as components. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a pale yellow oil in yield of 0.263 g (75%).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.292 – 7.172 (3H, m, $H^{m\text{-}Ph\ +\ p\text{-}Ph}$), 7.055 – 7.024 (2H, m, $H^{o\text{-}Ph}$), 4.806 (1H, q, *J* = 1.4 Hz, H^{10}), 4.792 (1H, q, *J* = 1.4 Hz, H^{10}), 2.841 (1H, dd, *J* = 16.8, 8.4 Hz, H^{4b}), 2.431 (1H, dddd, *J* = 9.7, 8.4, 3.2, 1.6 Hz, H^5), 2.207 – 2.006 (5H, m), 1.888 (1H, dtd, *J* = 12.0, 9.4, 7.0 Hz, H^6), 1.705 (1H, m), 1.595 – 1.478 (6H, m), 1.456 – 1.326 (4H, m), 1.297 – 1.211 (6H, m), 0.950 (3H, t, *J* = 7.2 Hz, $H^{11\ or\ 20}$), 0.860 (3H, t, *J* = 6.9 Hz, $H^{20\ or\ 11}$).

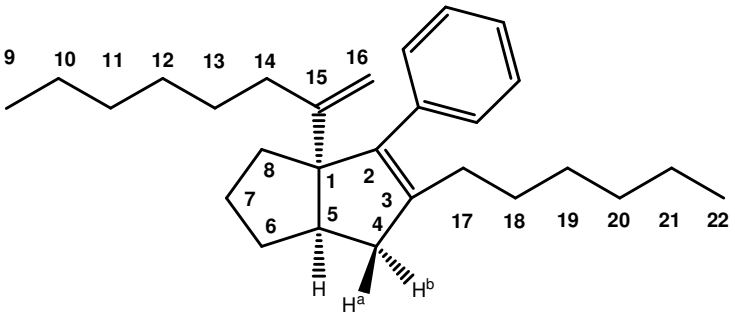
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 154.57 (C^9), 141.21 ($C^{i\text{-}Ph}$), 139.63 ($C^{2\ or\ 3}$), 138.04 ($C^{2\ or\ 3}$), 129.40 ($2CH^{o\text{-}\ or\ m\text{-}Ph}$), 127.42 ($2CH^{m\text{-}\ or\ o\text{-}Ph}$), 126.11 ($CH^{p\text{-}Ph}$), 107.27 ($CH_2{}^{10}$), 71.24 ($C^1$), 45.53 ($CH^5$), 44.33 ($CH_2$), 36.67 ($CH_2$), 33.84 ($CH_2$), 32.05 ($CH_2$), 31.68 ($CH_2$), 30.75 ($CH_2$), 29.59 ($CH_2$), 29.13 ($CH_2$), 28.06 ($CH_2$), 25.70 ($CH_2$), 23.05 ($CH_2$), 22.61 ($CH_2$), 14.15 ($CH_3{}^{11\ or\ 20}$), 14.04 ($CH_3{}^{20\ or\ 11}$).

HRMS (EI): Found: $[M]^+$, 350.2979. $C_{26}H_{38}$ requires: 350.2974.

LRMS (EI): *m/z*: 350 ($[M]^{+\cdot}$, 57%), 307 ($[M - C_3H_7]^{+\cdot}$, 26%), 293 ($[M - C_4H_9]^{+\cdot}$, 100%).

IR (thin film): $\tilde{\nu}$ **=** 2925 (m), 2852 (m), 1630 (w), 1487 (w), 1467 (m), 886 (m), 760 (m), 698 (s) cm^{-1}.

6.2.6.12. *rac*-(1*R*,5*R*)-3-Hexyl-1-(oct-1-en-2-yl)-2-phenyl-bicyclo[3.3.0]oct-2-ene (2.63k)



General procedure A was used with 1-(hept-6-en-1-ynyl)benzene, 1,1-dibromoheptane and 1-octyne as components. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a colourless oil in yield of 0.247 g (65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.286 – 7.186 (3H, m, $H^{o- + p-Ph}$), 7.053 – 7.023 (2H, m, H^{m-Ph}), 4.806 (1H, q, *J* = 1.5 Hz, H^{16}), 4.791 (1H, d, *J* = 1.0 Hz, H^{16}), 2.844 (1H, dd, *J* = 16.7, 8.3 Hz, H^{4b}), 2.430 (1H, tdd, *J* = 8.3, 3.3, 1.8 Hz, H^5), 2.193 – 2.018 (4H, m), 2.132 (1H, d, *J* = 16.7 Hz, H^{4a}), 1.888 (1H, tdd, *J* = 12.3, 9.5, 7.0 Hz, H^6), 1.736 – 1.667 (1H, m), 1.600 – 1.177 (20H, m), 0.916 (3H, t, *J* = 7.0 Hz, $H^{9 \text{ or } 22}$), 0.862 ppm (3H, t, *J* = 7.0 Hz, $H^{9 \text{ or } 22}$).

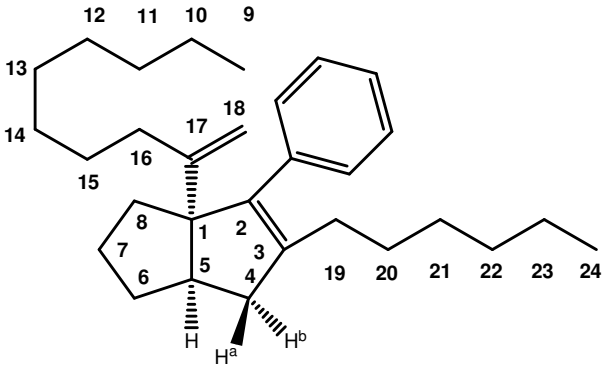
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 154.61 (C^{15}), 141.21 (C^{i-Ph}), 139.59 ($C^{2 \text{ or } 3}$), 138.01 ($C^{2 \text{ or } 3}$), 129.38 ($2CH^{o- \text{ or } m-Ph}$), 127.42 ($2CH^{o- \text{ or } m-Ph}$), 126.10 ($CH^{p-Ph}$), 107.23 ($CH_2{}^{16}$), 71.22 ($C^1$), 45.50 ($CH^5$), 44.33 ($CH_2{}^4$), 36.68 ($CH_2{}^6$), 33.82 ($CH_2$), 32.35 ($CH_2$), 31.95 ($CH_2$), 31.69 ($CH_2$), 29.70 ($CH_2$), 29.59 ($CH_2$), 29.14 ($CH_2$), 28.47 ($CH_2$), 28.05 ($CH_2$), 25.69 ($CH_2$), 22.71 ($CH_2$), 22.62 ($CH_2$), 14.11 ($CH_3{}^{9 \text{ or } 22}$), 14.06 ($CH_3{}^{9 \text{ or } 22}$).

HRMS (EI): Found: $[M]^+$, 378.3289. $C_{28}H_{42}$ requires: 378.3286.

LRMS (CI): *m/z*: 378 ($[M]^+$, 100%), 293 ($[M - C_6H_{13}]^+$, 63%).

IR (thin film): $\tilde{\nu}$ **=** 2926 (s), 2858 (m), 1633 (w), 1493 (w), 1467 (m), 884 (m), 763 (m), 699 (s) cm^{-1}.

6.2.6.13. *rac*-(1*R*,5*R*)-1-(Dec-1-en-2-yl)-3-hexyl-2-phenyl-bicyclo[3.3.0]oct-2-ene (2.63l)



General procedure A was used with 1-(hept-6-en-1-ynyl)benzene, 1,1-dibromoheptane and 1-decyne as components Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a pale yellow oil in yield of 0.229 g (56%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.291 – 7.192 (3H, m, $H^{o- + p-Ph}$), 7.060 – 7.030 (2H, m, H^{m-Ph}), 4.813 (1H, apparent q, *J* = 1.5 Hz, H^{18}), 4.798 (1H, d, *J* = 1.0 Hz, H^{18}), 2.852 (1H, dd, *J* = 16.6, 8.4 Hz, H^{4b}), 2.430 (1H, tdd, *J* = 8.4, 3.3, 1.5 Hz, H^5), 2.196 – 2.023 (4H, m), 2.138 (1H, d, *J* = 16.6 Hz, H^{4a}), 1.895 (1H, tdd, *J* = 12.3, 9.8, 7.0 Hz, H^6), 1.744 – 1.674 (1H, m), 1.621 – 1.480 (5H, m), 1.420 – 1.168 (19H, m), 0.914 (3H, t, *J* = 7.0 Hz, $H^{9 \text{ or } 24}$), 0.871 (3H, t, *J* = 7.0 Hz, $H^{9 \text{ or } 24}$).

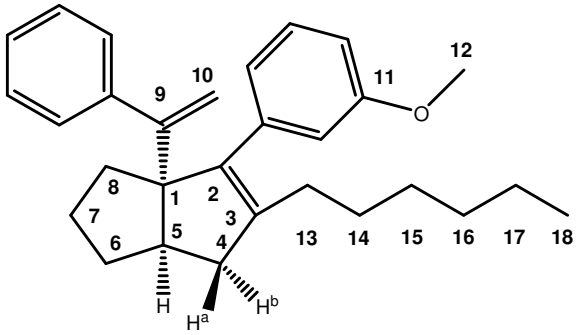
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 154.61 (C^{17}), 141.21 (C^{i-Ph}), 139.60 ($C^{2 \text{ or } 3}$), 138.01 ($C^{2 \text{ or } 3}$), 129.38 ($2CH^{o- \text{ or } m-Ph}$), 127.41 ($2CH^{o- \text{ or } m-Ph}$), 126.10 ($CH^{p-Ph}$), 107.28 ($CH_2{}^{18}$), 71.22 ($C^1$), 45.50 ($CH^5$), 44.34 ($CH_2{}^4$), 36.68 ($CH_2$), 33.82 ($CH_2$), 32.34 ($CH_2$), 31.92 ($CH_2$), 31.69 ($CH_2$), 30.03 ($CH_2$), 29.68 ($CH_2$), 29.59 ($CH_2$), 29.37 ($CH_2$), 29.14 ($CH_2$), 28.49 ($CH_2$), 28.05 ($CH_2$), 25.69 ($CH_2$), 22.70 ($CH_2$), 22.63 ($CH_2$), 14.12 ($CH_3{}^{9 \text{ or } 24}$),14.06 ($CH_3{}^{9 \text{ or } 24}$).

HRMS (EI): Found: $[M]^+$, 406.3598. $C_{30}H_{46}$ requires: 406.3600.

LRMS (CI): *m/z*: 406 ($[M]^+$, 100 %), 293 ($[M - C_8H_{17}]^+$, 47 %).

IR (thin film): $\tilde{\nu}$ **=** 2930 (s), 2858 (m), 1633 (w), 1493 (w), 1463 (m), 884 (m), 763 (m), 699 (s) cm^{-1}.

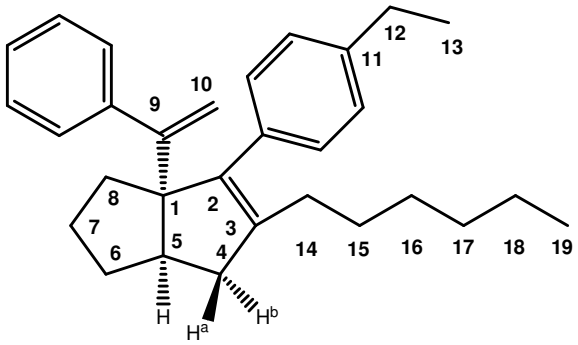
6.2.6.14. *rac*-(1*R*,5*R*)-3-Hexyl-2-(3-methoxyphenyl)-1-(phenylvinyl)-bicyclo[3.3.0]oct-2-ene (2.63m)



General procedure A was used with 1-(hept-6-en-1-ynyl)-3-methoxybenzene, 1,1-dibromoheptane and 1-ethynylbenzene as components. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a pale yellow oil in yield of 0.302 g (75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.346 – 7.219 (6H, m, H^{Ar}), 6.889 – 6.815 (3H, m, H^{Ar}), 5.082 (1H, d, *J* = 1.6 Hz, H^{10}), 5.051 (1H, d, *J* = 1.6 Hz, H^{10}), 3.793 (3H, s, H^{12}), 2.420 (1H, tdd, *J* = 8.3, 3.0, 1.3 Hz, H^5), 2.294 (1H, dd, *J* = 16.6, 8.3 Hz, H^{4b}), 2.116 (1H, dt, *J* = 25.5, 7.8 Hz, H^{13}), 2.082 (1H, dt, *J* = 25.5, 7.5 Hz, H^{13}), 1.985 (1H, d, *J* = 16.6 Hz, H^{4a}), 1.860 (1H, tdd, *J* = 12.3, 10.0, 6.8 Hz, H^6), 1.718 – 1.682 (2H, m, H^8), 1.612 – 1.466 (2H, m, H^7), 1.413 – 1.202 (9H, m), 0.888 (3H, t, *J* = 7.0 Hz, H^{18}).
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 158.92 (C^{11}), 155.54 (C^9), 144.28 ($C^{2 \text{ or } 3}$), 142.72 ($C^{2 \text{ or } 3}$), 139.41 ($C^{i\text{-Ph}}$), 138.55 ($C^{i\text{-Ph}}$), 128.44 ($CH^{o\text{- or m-Ph}}$), 127.97 ($2CH^{o\text{- or m-Ph}}$), 127.49 ($2CH^{o\text{- or m-Ph}}$), 126.46 ($CH^{p\text{-Ph}}$), 122.33 ($CH^{o\text{- or m-Ph}}$), 115.19 ($CH^{o\text{- or m-Ph}}$), 114.32 ($CH_2{}^{10}$), 111.74 ($CH^{o\text{- or m-Ph}}$), 70.09 (C^1), 55.07 ($CH_3{}^{12}$), 45.74 (CH^5), 43.75 ($CH_2{}^4$), 36.26 (CH^6), 35.47 ($CH_2{}^8$), 31.74 (CH_2), 29.96 ($CH_2{}^{13}$), 29.47 (CH_2), 27.89 (CH_2), 25.67 ($CH_2{}^7$), 22.61 (CH_2), 14.08 ($CH_3{}^{18}$).
HRMS (EI): Found: $[M]^+$, 400.2763. $C_{29}H_{36}O$ requires: 400.2766.
LRMS (CI): *m/z*: 401 ($[M + H]^+$, 100%), 297 ($[M – Styrene]^+$, 30%).
IR (thin film): $\tilde{\nu}$ = 2930 (m), 2858 (m), 1595 (m), 1572 (m), 1489 (m), 1455 (m), 1281 (m), 1051 (m), 903 (m), 779 (s), 703 (s) cm^{-1}.

6.2.6.15. *rac*-(1*R*,5*R*)-2-(4-Ethylphenyl)-3-hexyl-1-(phenylvinyl)-bicyclo[3.3.0]oct-2-ene (2.63n)



General procedure A was used with 1-ethyl-4-(hept-6-en-1-ynyl)benzene, 1,1-dibromoheptane and 1-ethynylbenzene as components. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a pale yellow oil in yield of 0.281 g (70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.380 – 7.163 (9H, m, H^{Ar}), 5.080 (1H, d, *J* = 1.8 Hz, H^{10}), 5.057 (1H, d, *J* = 1.8 Hz, H^{10}), 2.701 (2H, q, *J* = 7.5 Hz, H^{12}), 2.436 (1H, tdd, *J* = 8.3, 2.8, 1.0 Hz, H^5), 2.318 (1H, dd, *J* = 16.6, 8.3 Hz, H^{4b}), 2.133 (1H, dt, *J* = 21.3, 7.8 Hz, H^{14}), 2.080 (1H, dt, *J* = 21.3, 7.5 Hz, H^{14}), 2.002 (1H, d, *J* = 16,6 Hz, H^{4a}), 1.875 (1H, tdd, *J* = 12.3, 10.3, 7.0 Hz, H^6), 1.725 – 1.687 (2H, m, H^8), 1.601 – 1.509 (2H, m, H^7), 1.431 – 1.358 (3H, m), 1.339 – 1.211 (6H, m), 1.303 (3H, t, *J* = 7.5 Hz, H^{13}), 0.909 (3H, t, *J* = 7.0 Hz, H^{19}).

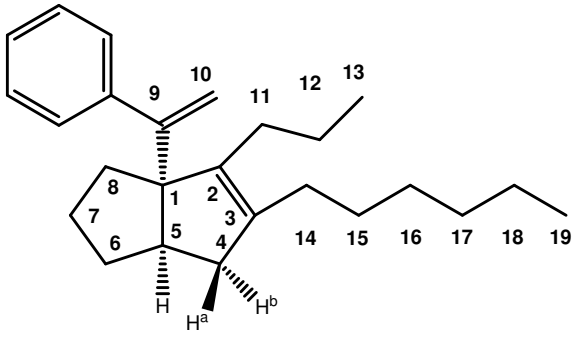
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 155.49 (C^9), 144.38 ($C^{2\text{ or }3}$), 142.17 (C^{11}), 142.06 ($C^{2\text{ or }3}$), 138.69 ($C^{i\text{-Ph}}$), 135.14 ($C^{i\text{-Ph}}$), 129.50 ($2CH^{o\text{- or m-Ph}}$), 128.00 ($2CH^{o\text{- or m-Ph}}$), 127.46 ($2CH^{o\text{- or m-Ph}}$), 127.03 ($2CH^{o\text{- or m-Ph}}$), 126.42 ($CH^{p\text{-Ph}}$), 114.25 ($CH_2{}^{10}$), 70.05 (C^1), 45.72 (CH^5), 43.71 ($CH_2{}^4$), 36.30 ($CH_2{}^6$), 35.49 ($CH_2{}^8$), 31.74 (CH_2), 29.96 ($CH_2{}^{14}$), 29.44 (CH_2), 28.52 ($CH_2{}^{12}$), 27.90 (CH_2), 25.64 ($CH_2{}^7$), 22.61 (CH_2), 15.33 ($CH_3{}^{13}$), 14.08 ($CH_3{}^{19}$).

HRMS (EI): Found: $[M]^+$, 398.2974. $C_{30}H_{38}$ requires: 398.2974.

LRMS (CI): *m/z*: 399 ($[M + H]^+$, 100%), 369 ($[M – Et]^+$, 39%).

IR (thin film): $\tilde{\nu}$ = 2933 (s), 2854 (m), 1508 (w), 1489 (w), 1452 (w), 903 (m), 824 (m), 771 (m), 703 (s) cm^{-1}.

6.2.6.16. *rac*-(1*R*,5*R*)-3-Hexyl-1-(phenylvinyl)-2-propyl-bicyclo[3.3.0]oct-2-ene (2.63o)



General procedure A was used with dec-1-en-6-yne, 1,1-dibromoheptane and 1-ethynylbenzene as components. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a pale yellow oil in yield of 0.277 g (82%).

^{1}H NMR (400 MHz, BENZENE-D$_6$): δ (ppm) = 7.306 – 7.270 (2H, m, $H^{o\text{-}Ph}$), 7.187 – 7.082 (3H, m, $H^{m\,+\,p\text{-}Ph}$), 5.189 (1H, t, *J* = 2.1 Hz, H^{10}), 5.071 (1H, t, *J* = 2.1 Hz, H^{10}), 2.484 (1H, tq, *J* = 8.8, 2.4 Hz, H^5), 2.333 (1H, dd, *J* = 16.0, 8.8 Hz, H^{4b}), 2.142 – 2.018 (4H, m), 1.875 – 1.716 (4H, m), 1.613 – 1.455 (4H, m), 1.384 – 1.242 (9H, m), 0.951 (3H, t, *J* = 7.3 Hz, $H^{13\text{ or }19}$), 0.913 (3H, t, *J* = 7.5 Hz, $H^{13\text{ or }19}$).

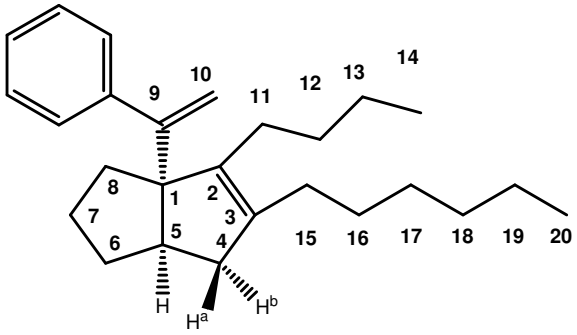
^{13}C NMR (100.5 MHz, BENZENE-D$_6$): δ (ppm) = 156.88 (C^9), 145.26 ($C^{i\text{-}Ph}$), 139.96 ($C^{2\text{ or }3}$), 138.03 ($C^{2\text{ or }3}$), 128.76 ($2CH^{m\text{-}Ph}$), 128.16 ($2CH^{o\text{-}Ph}$), 127.15 ($CH^{p\text{-}Ph}$), 113.77 ($CH_2{}^{10}$), 71.26 (C^1), 44.84 (CH^5), 44.51 ($CH_2{}^4$), 37.31 (CH_2), 36.70 (CH_2), 32.58 (CH_2), 30.29 (CH_2), 30.06 (CH_2), 29.78 (CH_2), 28.57 (CH_2), 26.17 (CH_2), 24.61 (CH_2), 23.43 (CH_2), 15.68 ($CH_3{}^{13\text{ or }19}$), 14.71 ($CH_3{}^{13\text{ or }19}$).

HRMS (EI): Found: $[M]^+$, 336.2820. $C_{25}H_{36}$ requires: 336.2817.

LRMS (CI): *m/z*: 336 ($[M]^+$, 100%), 233 ($[M - Styrene]^+$, 51%).

IR (thin film): $\tilde{\nu}$ **=** 2952 (s), 2926 (s), 2858 (m), 1486 (w), 1444 (m), 900 (m), 775 (m), 699 (s) cm^{-1}.

6.2.6.17. *rac*-(1*R*,5*R*)-2-Butyl-3-hexyl-1-(phenylvinyl)-bicyclo[3.3.0]oct-2-ene (2.63p)



General procedure A was used with undec-1-en-6-yne, 1,1-dibromoheptane and 1-ethynylbenzene as components. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a pale yellow oil in yield of 0.308 g (88%).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.238 – 7.151 (5H, m, H^{Ar}), 5.127 (1H, d, *J* = 1.8 Hz, H^{10}), 4.954 (1H, d, *J* = 1.8 Hz, H^{10}), 2.317 (1H, tt, *J* = 8.8, 2.3 Hz, H^5), 2.201 (1H, dd, *J* = 15.7, 8.8 Hz, H^{4b}), 2.081 – 1.962 (4H, m), 1.818 – 1.687 (4H, m), 1.564 – 1.503 (3H, m), 1.404 – 1.271 (12H, m), 0.916 (3H, t, *J* = 6.8 Hz, $H^{14 \text{ or } 20}$), 0.909 (3H, t, *J* = 6.8 Hz, $H^{14 \text{ or } 20}$).

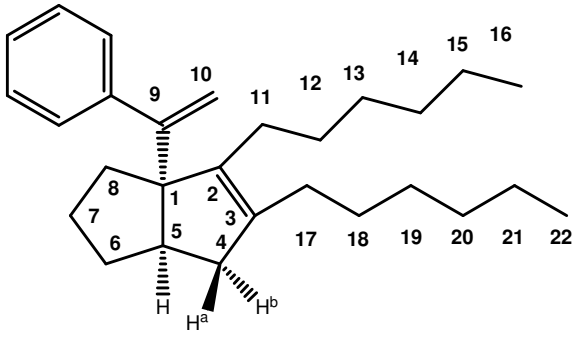
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 156.09 (C^9), 144.55 ($C^{i\text{-Ph}}$), 139.13 (C^2), 137.16 (C^3), 127.93 ($2CH^{o\text{- or }m\text{-Ph}}$), 127.30 ($2CH^{m\text{- or }o\text{-Ph}}$), 126.22 ($CH^{p\text{-Ph}}$), 113.05 ($CH_2{}^{10}$), 70.44 ($C^1$), 44.01 ($CH^5$), 43.79 ($CH_2$), 36.57 ($CH_2$), 35.93 ($CH_2$), 32.66 ($CH_2$), 31.83 ($CH_2$), 29.51 ($CH_2$), 29.26 ($CH_2$), 27.74 ($CH_2$), 26.24 ($CH_2$), 25.37 ($CH_2$), 23.68 ($CH_2$), 22.65 ($CH_2$), 14.10 ($CH_3{}^{14 \text{ or } 20}$), 13.91 ($CH_3{}^{20 \text{ or } 14}$).

HRMS (EI): Found: $[M]^+$, 350.2965. $C_{26}H_{38}$ requires: 350.2974.

LRMS (EI): *m/z*: 351 ($[M + H]^{+\cdot}$, 48%), 307 ($[M - C_3H_7]^{+\cdot}$, 25%), 247 ($[M - \text{Styrene}]^{+\cdot}$, 100%).

IR (thin film): $\tilde{\nu}$ **=** 2926 (s), 2856 (m), 1614 (w), 1497 (w), 1450 (w), 896 (m), 762 (m), 692 (s) cm^{-1}.

6.2.6.18. *rac*-(1*R*,5*R*)-2-Hexyl-3-hexyl-1-(phenylvinyl)-bicyclo[3.3.0]oct-2-ene (2.63q)



General procedure A was used with tridec-1-en-6-yne, 1,1-dibromoheptane and 1-ethynylbenzene as components. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a pale yellow oil in yield of 0.325 g (86%).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.224 – 7.148 (5H, m, H^{Ar}), 5.124 (1H, d, *J* = 1.8 Hz, H^{10}), 4.951 (1H, d, *J* = 1.8 Hz, H^{10}), 2.315 (1H, tt, *J* = 9.0, 2.0 Hz, H^5), 2.196 (1H, dd, *J* = 15.9, 9.0 Hz, H^{4b}), 2.056 – 1.953 (4H, m), 1.818 – 1.722 (4H, m), 1.579 – 1.500 (3H, m), 1.479 – 1.2700 (16H, m), 0.909 (3H, t, *J* = 6.7 Hz, $H^{16 \text{ or } 22}$), 0.897 (3H, t, *J* = 6.7 Hz, $H^{16 \text{ or } 22}$).

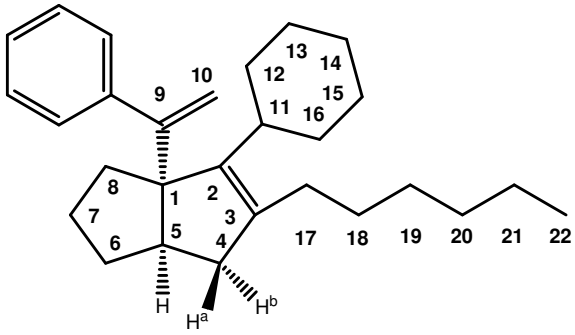
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 156.01 (C^9), 144.55 ($C^{i\text{-}Ph}$), 139.13 (C^2), 137.23 (C^3), 127.94 ($2CH^{o\text{-} \text{ or } m\text{-}Ph}$), 127.30 ($2CH^{m\text{-} \text{ or } o\text{-}Ph}$), 126.22 ($CH^{p\text{-}Ph}$), 113.03 ($CH_2{}^{10}$), 70.44 ($C^1$), 44.02 ($CH^5$), 43.80 ($CH_2$), 36.57 ($CH_2$), 35.94 ($CH_2$), 31.84 ($CH_2$), 31.63 ($CH_2$), 30.39 ($CH_2$), 30.33 ($CH_2$), 29.52 ($CH_2$), 29.28 ($CH_2$), 27.76 ($CH_2$), 26.56 ($CH_2$), 25.38 ($CH_2$), 22.70 ($CH_2$), 22.66 ($CH_2$), 14.09 ($2CH_3{}^{16 + 22}$).

HRMS (EI): Found: $[M]^+$, 378.3276. $C_{28}H_{42}$ requires: 378.3286.

LRMS (EI): *m/z*: 379 ($[M + H]^{+\cdot}$, 56%), 349 ($[M – CH_3]^{+\cdot}$, 13%), 293 ($[M – C_6H_{13}]^{+\cdot}$, 21%), 276 ($[M – \text{Styrene} + H]^{+\cdot}$, 100%).

IR (thin film): $\tilde{\nu}$ = 2926 (s), 1640 (w), 1491 (w), 1456 (w), 884 (w), 768 (w), 698 (m) cm^{-1}.

6.2.6.19. *rac*-(1*R*,5*R*)-2-Cyclohexyl-3-hexyl-1-(phenylvinyl)-bicyclo[3.3.0]oct-2-ene (2.63r)



General procedure A was used with (hept-1-en-6-yne)cyclohexane, 1,1-dibromoheptane and 1-ethynylbenzene as components. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a pale yellow oil in yield of 0.300 g (80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.311 – 7.202 (5H, m, H^{Ar}), 5.133 (1H, d, *J* = 1.8 Hz, H^{10}), 5.012 (1H, d, *J* = 1.8 Hz, H^{10}), 2.376 (1H, dd, *J* = 16.3, 9.0 Hz, H^{4b}), 2.272 – 2.234 (2H, m, H^{17}), 2.195 (1H, tt, *J* = 9.0, 2.2 Hz, H^5), 1.989 (1H, tt, *J* = 11.9, 3.9 Hz, H^{11}), 1.873 – 1.158 (25H, m), 0.926 (3H, t, *J* = 6.9 Hz, H^{22}).

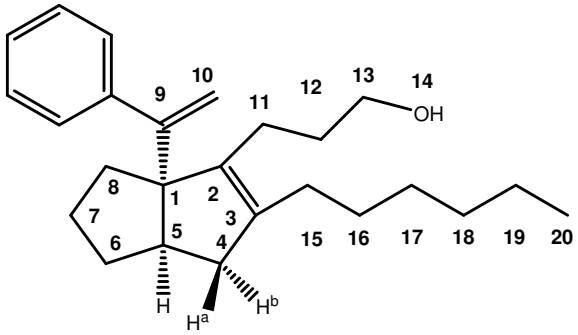
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 156.09 (C^9), 145.02 ($C^{2\text{ or }3}$), 140.67 ($C^{2\text{ or }3}$), 138.47 ($C^{i\text{-Ph}}$), 127.70 ($2CH^{o\text{- or }m\text{-Ph}}$), 127.46 ($2CH^{o\text{- or }m\text{-Ph}}$), 126.35 ($CH^{p\text{-Ph}}$), 113.48 ($CH_2{}^{10}$), 71.29 ($C^1$), 45.07 ($CH_2{}^4$), 43.70 ($CH^5$), 38.02 ($CH^{11}$), 37.00 ($CH_2$), 36.73 ($CH_2$), 33.12 ($CH_2$), 32.25 ($CH_2$), 31.90 ($CH_2$), 30.34 ($CH_2$), 29.75 ($CH_2{}^{17}$), 28.10 ($CH_2$), 27.55 ($CH_2$), 27.39 ($CH_2$), 26.50 ($CH_2$), 25.25 ($CH_2$), 22.70 ($CH_2$), 14.13 ($CH_3{}^{22}$).

HRMS (EI): Found: $[M]^+$, 376.3127. $C_{28}H_{40}$ requires: 376.3130.

LRMS (CI): *m/z*: 377 ($[M + H]^+$, 100 %), 271 (77%).

IR (thin film): $\tilde{\nu}$ **=** 2926 (s), 2850 (s), 1614 (w), 1486 (w), 1440 (m), 900 (m), 771 (m), 699 (s) cm^{-1}.

6.2.6.20. *rac*-(1*R*,5*R*)-3-Hexyl-1-(phenylvinyl)-2-(propan-3-ol)-bicyclo[3.3.0]oct-2-ene (2.63s)



General procedure A was used with TBDMS protected dec-9-en-4-yn-1-ol, 1,1-dibromoheptane and 1-ethynylbenzene as components with the exception that the reaction was carried out on 2.0 mmol scale. Crude product from the three component coupling was purified by flash column chromatography on silica to give the desired material which was put into TBDMS group cleavage with TBAF [2.0 mL of a 1.0 M solution in THF, (2.0 mmol) in dry THF (8.0) mL, at RT for 20 h]. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a yellow oil in yield of 0.430 g (61% over two steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.236 – 7.163 (5H, m, H^{Ar}), 5.146 (1H, d, *J* = 1.8 Hz, H^{10}), 4.983 (1H, d, *J* = 1.8 Hz, H^{10}), 3.649 (2H, q, *J* = 6.5 Hz, H^{13}), 2.343 (1H, tt, *J* = 9.0, 2.0 Hz, H^5), 2.244 (1H, dd, *J* = 16.0, 9.0 Hz, H^{4b}), 2.133 – 2.020 (4H, m, $H^{11 + 15}$), 1.870 – 1.611 (6H, m), 1.587 – 1.521 (1H, m), 1.485 – 1.385 (1H, m), 1.370 – 1.261 (10H, m), 0.909 (3H, t, *J* = 6.9 Hz, H^{20}).

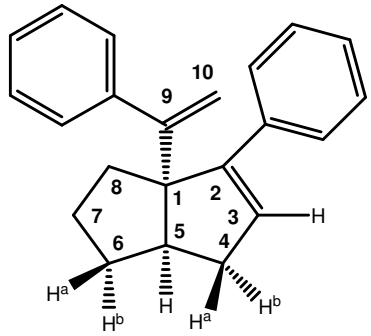
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 155.95 (C^9), 144.36 ($C^{i\text{-}Ph}$), 139.80 ($C^{2 \text{ or } 3}$), 136.21 ($C^{2 \text{ or } 3}$), 127.83 ($2CH^{o\text{- or } m\text{-}Ph}$), 127.37 ($2CH^{m\text{- or } o\text{-}Ph}$), 126.33 ($CH^{p\text{-}Ph}$), 113.26 ($CH_2{}^{10}$), 70.38 ($C^1$), 63.62 ($CH_2{}^{13}$), 43.99 ($CH^5$), 43.80 ($CH_2{}^4$), 36.55 ($CH_2$), 36.05 ($CH_2$), 33.45 ($CH_2$), 31.84 ($CH_2$), 29.52 ($CH_2$), 29.27 ($CH_2$), 27.73 ($CH_2$), 25.34 ($CH_2$), 22.65 ($CH_2$), 22.54 ($CH_2$), 14.10 ($CH_3{}^{20}$).

HRMS (EI): Found: $[M]^+$, 352.2767. $C_{25}H_{36}O$ requires: 352.2766.

LRMS (CI): *m/z*: 353 ($[M + H]^+$, 100%), 249 ($[M – Styrene]^+$, 37%).

IR (thin film): $\tilde{\nu}$ = 3312 (w, br), 2930 (s), 2854 (m), 1448 (m), 1062 (m), 900 (m), 771 (m), 699 (s) cm^{-1}.

6.2.6.21. *rac*-(1*R*,5*R*)-2-Phenyl-1-(phenylvinyl)-bicyclo[3.3.0]oct-2-ene (2.63t)



General procedure A was used with 1-(hept-6-en-1-ynyl)benzene, dichloromethane and 1-ethynylbenzene as components. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexane as the eluent gave the title compound as a pale yellow oil in yield of 0.332 g (58%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.609 – 7.579 (2H, m, $H^{o\text{-}Ph}$), 7.350 – 7.249 (8H, m, H^{Ar}), 6.149 (1H, t, *J* = 2.7 Hz, H^3), 5.296 (1H, d, *J* = 1.8 Hz, H^{10}), 5.032 (1H, d, *J* = 1.8 Hz, H^{16}), 2.693 (1H, *J* = 8.3, 6.0, 1.5 Hz, H^5), 2.396 (1H, ddd, *J* = 17.6, 8.0, 2.2 Hz, H^{4b}), 2.117 (1H, dt, *J* = 12.8, 7.3 Hz, $H^{8a\text{ or }8b}$), 2.084 (1H, ddd, *J* = 17.6, 3.0, 1.5 Hz, H^{4a}), 1.968 (1H, ddt, *J* = 12.3, 8.8, 6.8 Hz, H^{6b}), 1.792 (1H, dt, *J* = 12.8, 6.0 Hz, $H^{8a\text{ or }8b}$), 1.540 (2H, apparent quintet, *J* = 7.0 Hz, H^7) 1.366 (1H, dq, *J* = 12.3, 6.2 Hz, H^{6a}).

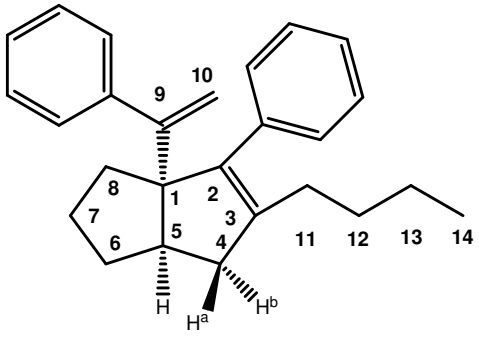
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 155.03 (C^9), 145.92 (C^2), 143.34 ($C^{i\text{-}Ph}$), 136.41 ($C^{i\text{-}Ph}$), 128.45 ($3CH^{p\text{- + o- or m-}Ph}$), 127.99 ($2CH^{o\text{- or m-}Ph}$), 127.40 ($2CH^{o\text{- or m-}Ph}$), 127.25 ($2CH^{o\text{ or m-}Ph}$), 126.68 ($CH^{3\text{ or p-}Ph}$), 126.53 ($CH^{3\text{ or p-}Ph}$), 113.51 ($CH_2{}^{10}$), 67.12 ($C^1$), 50.12 ($CH^5$), 38.84 ($CH_2{}^4$), 35.73 ($CH_2{}^6$), 35.04 ($CH_2{}^8$), 26.65 ($CH_2{}^7$).

HRMS (EI): Found: $[M]^+$, 286.1721. $C_{22}H_{22}$ requires: 286.1722.

LRMS (CI): *m/z*: 287 ($[M + H]^+$, 100%), 208 ($[M – Ph]^+$, 14%), 169 (20%).

IR (thin film): $\tilde{\nu}$ **=** 2949 (m), 2858 (w), 1493 (m), 1440 (m), 907 (m), 748 (s), 695 (s) cm^{-1}.

6.2.6.22. *rac*-(1*R*,5*R*)-3-Butyl-2-phenyl-1-(phenylvinyl)-bicyclo[3.3.0]oct-2-ene (2.63u)



General procedure A was used with 1-(hept-6-en-1-ynyl)benzene, 1,1-dibromopentane and 1-ethynylbenzene as components. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a pale yellow oil in yield of 0.244 g (71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.348 – 7.237 (10H, m, H^{Ar}), 5.037 (1H, d, *J* = 1.6 Hz, H^{10}), 5.024 (1H, d, *J* = 1.6 Hz, H^{10}), 2.430 (1H, tdd, *J* = 8.3, 3.0, 1.5 Hz, H^5), 2.338 (1H, dd, *J* = 16.3, 8.3 Hz, H^{4b}), 2.090 (1H, dt, *J* = 24.5, 7.8 Hz, H^{11}), 2.055 (1H, dt, *J* = 24.5, 7.3 Hz, H^{11}), 1.995 (1H, d, *J* = 16.3 Hz, H^{4a}), 1.851 (1H, tdd, *J* = 12.0, 10.0, 6.8 Hz, H^6), 1.697 – 1.663 (2H, m, H^8), 1.607 – 1.473 (2H, m, H^7), 1.419 – 1.214 (5H, m), 0.861 (3H, t, *J* = 7.2 Hz, H^{14}).

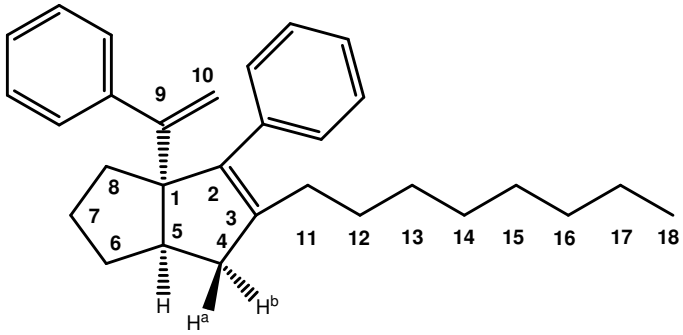
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 155.37 (C^9), 144.38 ($C^{2 \text{ or } 3}$), 142.46 ($C^{2 \text{ or } 3}$), 138.92 ($C^{i\text{-Ph}}$), 137.96 ($C^{i\text{-Ph}}$), 129.67 ($2CH^{o\text{- or m-Ph}}$), 127.92 ($2CH^{o\text{- or m-Ph}}$), 129.55 ($2CH^{o\text{- or m-Ph}}$), 127.51 ($2CH^{o\text{- or m-Ph}}$), 126.46 ($CH^{p\text{-Ph}}$), 126.33 ($CH^{p\text{-Ph}}$), 114.44 ($CH_2{}^{10}$), 70.14 (C^1), 45.69 (CH^5), 43.83 ($CH_2{}^4$), 36.33 (CH^6), 35.61 ($CH_2{}^8$), 30.17 (CH_2), 29.65 ($CH_2{}^{11}$), 25.60 ($CH_2{}^7$), 22.84 (CH_2), 14.13 ($CH_3{}^{14}$).

HRMS (EI): Found: $[M]^+$, 342.2351. $C_{26}H_{30}$ requires: 342.2348.

LRMS (CI): *m/z*: 343 ($[M + H]^+$, 100%) 239 ($[M – Styrene]^+$, 24%).

IR (thin film): $\tilde{\nu}$ = 2941 (m), 2850 (m), 2835 (w), 1595 (w), 1489 (m), 1436 (w), 907 (m), 763 (m), 695 (s) cm^{-1}.

6.2.6.23. *rac*-(1*R*,5*R*)-3-Octyl-2-phenyl-1-(phenylvinyl)-bicyclo[3.3.0]oct-2-ene (2.63v)



General procedure A was used with 1-(hept-6-en-1-ynyl)benzene, 1,1-dibromononane and 1-ethynylbenzene as components. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a pale yellow oil in yield of 0.291 g (73%).

^{1}H NMR (400 MHz, BENZENE-D$_6$): δ (ppm) = 7.457 – 7.393 (4H, m, $H^{m- + p-Ph}$), 7.257 – 7.111 (6H, m, $H^{o- + m- + p-Ph}$), 5.117 (1H, d, *J* = 1.8 Hz, H^{10}), 5.084 (1H, d, *J* = 1.8 Hz, H^{10}), 2.536 (1H, tdd, *J* = 8.5, 2.8, 1.3 Hz, H^{5}), 2.436 (1H, dd, *J* = 16.4, 8.5 Hz, H^{4b}), 2.147 – 2.108 (2H, m, H^{11}), 1.967 (1H, d, *J* = 16.4 Hz, H^{4a}), 1.856 – 1.513 (5H, m), 1.419 – 1.348 (3H, m), 1.302 – 1.192 (10H, m), 0.899 (3H, t, *J* = 6.9 Hz, H^{18}).

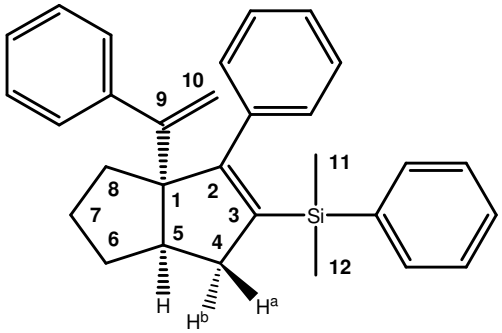
^{13}C NMR (100.5 MHz, BENZENE-D$_6$): δ (ppm) = 156.27 (C^{9}), 145.21 ($C^{2 \text{ or } 3}$), 142.99 ($C^{2 \text{ or } 3}$), 140.08 ($C^{i\text{-}Ph}$), 138.73 ($C^{i\text{-}Ph}$), 130.46 ($2CH^{o- \text{ or } m\text{-}Ph}$), 128.72 ($2CH^{o- \text{ or } m\text{-}Ph}$), 128.48 ($2CH^{o- \text{ or } m\text{-}Ph}$), 128.35 ($2CH^{o- \text{ or } m\text{-}Ph}$), 127.31 ($CH^{p\text{-}Ph}$), 127.29 ($CH^{p\text{-}Ph}$), 115.17 ($CH_2{}^{10}$), 71.05 ($C^{1}$), 46.48 ($CH^{5}$), 44.59 ($CH_2{}^{4}$), 37.10 ($CH_2$), 36.43 ($CH_2$), 32.63 ($CH_2$), 30.64 ($CH_2$), 30.49 ($CH_2$), 30.19 ($CH_2$), 30.04 ($CH_2$), 28.70 ($CH_2$), 26.38 ($CH_2$), 23.43 ($CH_2$), 14.70 ($CH_3{}^{18}$).

HRMS (EI): Found: $[M]^+$, 398.2978. $C_{30}H_{38}$ requires: 398.2974.

LRMS (CI): *m/z*: 399 ($[M + H]^+$, 100%), 295 ($[M – Styrene]^+$, 29%).

IR (thin film): $\tilde{\nu}$ **=** 2926 (s), 2858 (m), 1599 (w), 1493 (m), 1440 (w), 900 (m), 763 (m), 695 (s) cm^{-1}.

6.2.6.24. *rac*-(1*R*,5*R*)-3-Dimethyl(phenyl)silane-2-phenyl-1-(phenylvinyl)-bicyclo[3.3.0]oct-2-ene (2.63w)



General procedure B was used with 1-(hept-6-en-1-ynyl)benzene, (dichloromethyl)dimethyl(phenyl)silane and 1-ethynylbenzene as components. The carbenoid was generated *in situ* from (dichloromethyl)dimethyl(phenyl)silane (1.3 mmol) and LDA (0.83 mL of a 1.8 M solution, 1.50 mmol) at –85 °C for 15 min before dropwise addition of phenylacetylide. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a pale yellow oil in yield of 0.191 g (45%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.501 – 7.201 (15H, m, H^{Ar}), 5.097 (1H, d, *J* = 1.6 Hz, H^{10}), 4.970 (1H, d, *J* = 1.6 Hz, H^{10}), 2.533 – 2.448 (2H, m, $H^{5 + 4b}$), 2.186 (1H, d, *J* = 15.1 Hz, H^{4a}), 1.902 (1H, m, H^6), 1.818 (1H, m, H^7), 1.733 (1H, dd, *J* = 11.3, 5.5 Hz, H^8), 1.674 (1H, m, H^7), 1.614 (1H, dd, *J* = 11.3, 5.6 Hz, H^8), 1.474 (1H, m, H^6), 0.115 (3H, s, $H^{11 or 12}$), 0.096 (3H, s, $H^{11 or 12}$).

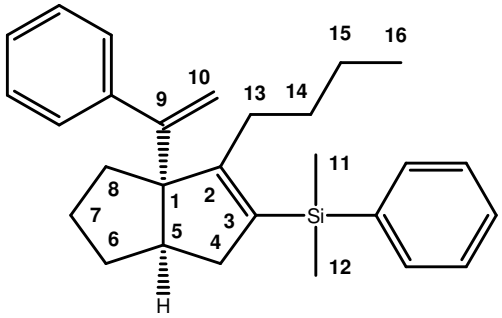
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 157.10 ($C^{2 or 9}$), 154.13 ($C^{2 or 9}$), 144.39 ($C^{i\text{-}Ph}$), 140.63 ($C^{i\text{-}Ph}$), 139.36 (C^3), 138.87 ($C^{Si\text{-}i\text{-}Ph}$), 133.62 ($2CH^{Si\text{-}o\text{-}Ph}$), 129.75 ($2CH^{Si\text{-}m\text{-}Ph}$), 128.62 ($CH^{Si\text{-}p\text{-}Ph}$), 127.72 ($2CH^{o\text{-} or m\text{-}Ph}$), 127.64 ($2CH^{o\text{-} or m\text{-}Ph}$), 127.56 ($2CH^{o\text{-} or m\text{-}Ph}$), 127.12 ($2CH^{o\text{-} or m\text{-}Ph}$), 126.88 ($CH^{p\text{-}Ph}$), 126.53 ($CH^{p\text{-}Ph}$), 115.04 ($CH_2{}^{10}$), 73.06 ($C^1$), 46.99 ($CH_2{}^4$), 46.65 ($CH^5$), 36.71 ($CH_2{}^6$), 36.02 ($CH_2{}^7$), 25.57 ($CH_2{}^8$), –2.36 ($CH_3{}^{11or\ 12}$), –2.72 ($CH_3{}^{11or\ 12}$).

HRMS (EI): Found: $[M]^+$, 420.2288. $C_{30}H_{32}Si$ requires: 420.2273.

LRMS (CI): *m/z*: 420 ($[M]^{+\cdot}$, 6%), 342 ($[M – Ph]^{+\cdot}$, 17%), 284 ($[M – HSiMe_2Ph]^{+\cdot}$, 18%), 135 ($[SiMe_2Ph]^{+\cdot}$, 100%).

IR (thin film): $\tilde{\nu}$ = 2964 (m), 2896 (w), 1610 (w), 1580 (m), 1486 (m), 1421 (m), 1251 (m), 1051 (m), 779 (s), 733 (s), 695 (s) cm^{-1}.

6.2.6.25. *rac*-(1*R*,5*R*)-2-Butyl-3-dimethyl(phenyl)silane-1-(phenylvinyl)-bicyclo[3.3.0]oct-2-ene (2.63x)



General procedure A was used with undec-1-en-6-yne, (dichloromethyl)dimethyl(phenyl)silane and 1-ethynylbenzene as components. The carbenoid was generated *in situ* from (dichloromethyl)dimethyl(phenyl)silane (1.3 mmol) and LDA (0.83 mL of a 1.8 M solution, 1.50 mmol) at –85 °C for 15 min before dropwise addition of phenylacetylide. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a pale yellow oil in yield of 0.275 g (69%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.428 – 7.074 (10H, m, H^{Ar}), 5.074 (1H, d, *J* = 1.8 Hz, H^{10}), 4.892 (1H, d, *J* = 1.8 Hz, H^{10}), 2.291 (1H, *J* = 8.8, 2.2 Hz, H^5), 2.186 (1H, dd, *J* = 15.2, 8.5 Hz, H^{4b}), 1.985 – 1.852 (2H, m, H^{13}), 1.886 (1H, d, *J* = 16.2, Hz, H^{4a}), 1.762 (1H, dd, *J* = 10.5, 5.9 Hz, H^8), 1.731 (1H, dd, *J* = 10.5, 5.5 Hz, H^8), 1.681 (1H, m, H^6), 1.484 (1H, quintet t, *J* = 6.0, 3.0 Hz, H^7), 1.361 (1H, m, H^7), 1.266 – 1.182 (3H, m, H^{6+14}), 1.104 – 0.969 (2H, m, H^{15}), 0.698 (3H, t, *J* = 7.3 Hz, H^{16}), 0.300 (3H, s, $H^{11/12}$), 0.278 (3H, s, $H^{11/12}$).

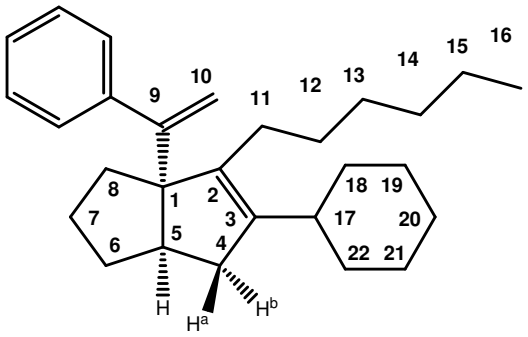
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 157.46 ($C^{2\text{ or }9}$), 155.29 ($C^{2\text{ or }9}$), 144.25 ($C^{i\text{-}Ph}$), 139.33 (C^3), 144.25 ($C^{Si\text{-}i\text{-}Ph}$), 133.79 ($2CH^{Si\text{-}o\text{-}Ph}$), 128.71 ($CH^{Si\text{-}p\text{-}Ph}$), 127.95 ($2CH^{Si\text{-}m\text{-}Ph}$), 127.66 ($2CH^{o\text{ or }m\text{-}Ph}$), 127.32 ($2CH^{o\text{ or }m\text{-}Ph}$), 126.36 ($CH^{p\text{-}Ph}$), 113.35 ($CH_2{}^{10}$), 73.31 ($C^1$), 46.58 ($CH_2{}^4$), 45.68 ($CH^5$), 36.62 ($CH_2{}^6$), 36.14 ($CH_2{}^8$), 34.05 ($CH_2{}^{14}$), 28.87 ($CH_2{}^{13}$), 25.53 ($CH_2{}^7$), 23.57 ($CH_2{}^{15}$), 13.80 ($CH_3{}^{16}$), –1.95 ($CH_3{}^{11/12}$), –2.03 ($CH_3{}^{11/12}$).

HRMS (EI): Found: $[M]^+$, 400.2587. $C_{28}H_{36}Si$ requires: 400.2586.

LRMS (CI): *m/z*: 400 ($[M]^{+\cdot}$, 11%), 297 ($[M - Styrene]^{+\cdot}$, 13%), 264 ($[M - HSiMe_2Ph]^{+\cdot}$, 15%), 135 (100%).

IR (thin film): $\tilde{\nu}$ = 2945 (m), 2854 (w), 1603 (w), 1251 (m), 1100 (m), 816 (m), 771 (s), 699 (s) cm^{-1}.

6.2.6.26. *rac*-(1*R*,5*R*)-2-Hexyl-3-cyclohexyl-1-(1-phenylvinyl)-bicyclo[3.3.0]oct-2-ene (2.63y)



General procedure A was used with tridec-1-en-6-yne, (dibromomethyl)cyclohexane (1.0 mmol) and 1-ethynylbenzene (2.2 mmol) as components. The carbenoid was generated *in situ* by using LiTMP [freshly prepared from distilled 2,2,6,6-tetramethylpiperidine (0.17 mL, 1.0 mmol) in dry THF (2 mL) and *n*-BuLi (0.40 mL of a 2.5 M solution in hexanes, 1.0 mmol) at 0 °C over 20 min] at –85 °C for 30 min before dropwise addition of phenylacetylide (2.2 mmol).

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a pale yellow oil in yield of 0.038 g (10%).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.232 – 7.161 (5H, m, H^{Ar}), 5.119 (1H, d, *J* = 1.8 Hz, H^{10}), 4.938 (1H, d, *J* = 1.8 Hz, H^{10}), 2.362 – 2.243 (2H, m, H^5 + H), 2.114 (1H, dd, *J* = 16.0, 8.7 Hz, H^{4b}), 1.989 – 1.937 (2H, m), 1.816 – 1.682 (5H, m), 1.592 – 1.392 (10H, m), 1.370 – 1.268 (10H, m), 0.904 (3H, t, *J* = 6.8 Hz, H^{16}).

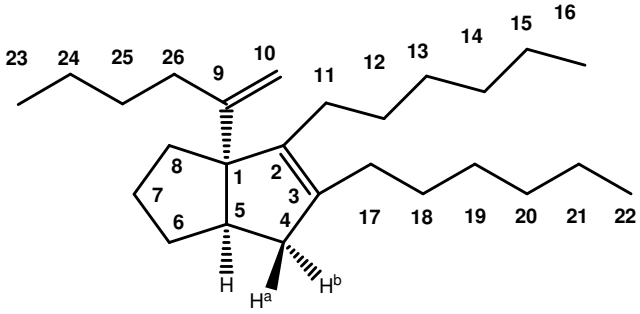
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 156.01 (C^9), 143.81 ($C^{i\text{-}Ph}$), 135.70 (C^2), 128.00 ($2CH^{o\text{-}\ or\ m\text{-}Ph}$), 127.21 ($2CH^{o\text{-}\ or\ m\text{-}Ph}$), 126.20 ($CH^{p\text{-}Ph}$), 124.44 ($C^3$), 112.86 ($CH_2{}^{10}$), 70.16 ($C^1$), 43.64 ($CH^5$), 40.11 ($CH_2$), 38.64 ($CH^{17}$), 36.64 ($CH_2$), 35.73 ($CH_2$), 31.91 ($CH_2$), 31.57 ($CH_2$), 30.63 ($CH_2$), 30.30 ($CH_2$), 29.70 ($CH_2$), 26.63 ($CH_2$), 26.41 ($CH_2$), 26.30 ($CH_2$), 25.28 ($CH_2$), 22.68 ($CH_2$), 14.09 ($CH_3{}^{16}$).

HRMS (EI): Found: $[M]^+$, 376.3125. $C_{28}H_{40}$ requires: 376.3130.

LRMS (EI): *m/z*: 376 ($[M]^{+\cdot}$, 54%), 293 ($[M - C_6H_{11}]^{+\cdot}$, 33%), 273 ($[M - Styrene]^{+\cdot}$, 100%).

IR (thin film): $\tilde{\nu}$ = 2909 (s), 2845 (s), 1573 (w), 1439 (m), 686 (m) cm^{-1}.

6.2.6.27. *rac*-(1*R*,5*R*)-2-Hexyl-3-hexyl-1-(hex-1-en-2-yl)bicyclo[3.3.0]oct-2-ene (2.63z)



General procedure A was used with tridec-1-en-6-yne, 1,1-dibromoheptane and 1-hexyne as components. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a pale yellow oil in yield of 0.243 g (68%).

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 4.851 (1H, d, *J* = 1.4 Hz, H^{10}), 4.731 (1H, q, *J* = 1.4 Hz, H^{10}), 2.643 (1H, dd, *J* = 16.2, 8.8 Hz, H^{4b}), 2.306 (1H, tt, *J* = 8.8, 2.1 Hz, H^{5}), 2.059 (2H, td, *J* = 7.3, 0.5 Hz, H^{26}), 1.949 – 1.843 (3H, m), 1.818 – 1.703 (4H, m), 1.667 – 1.518 (4H, m), 1.389 – 1.258 (20H, m), 0.925 – 0.867 (9H, m, $H^{16 + 22 + 23}$).

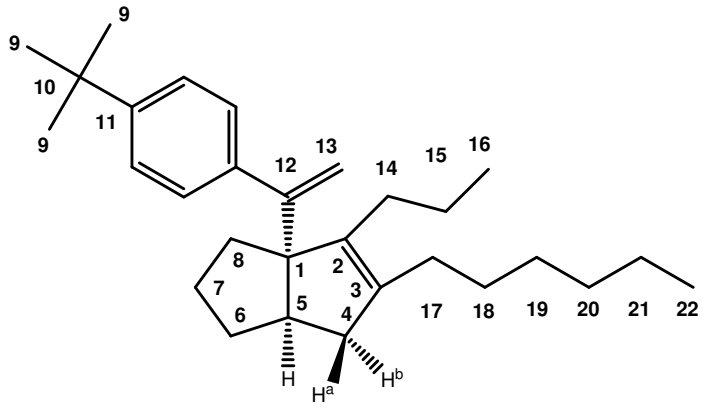
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 155.49 (C^{9}), 137. 99 ($C^{2 \text{ or } 3}$), 137.88 ($C^{2 \text{ or } 3}$), 106.24 ($CH_2{}^{10}$), 71.15 (C^{1}), 44.28 (CH_2), 43.95 (CH–5), 36.91 (CH_2), 34.16 (CH_2), 31.92 (CH_2), 31.86 (CH_2), 31.68 (CH_2), 30.97 (CH_2), 30.25 (CH_2), 30.19 (CH_2), 29.70 (CH_2), 29.36 (CH_2), 29.06 (CH_2), 28.03 (CH_2), 26.36 (CH_2), 25.40 (CH_2), 22.95 (CH_2), 22.66 (CH_2), 14.09 ($3CH_3{}^{16 + 22 + 23}$).

HRMS (EI): Found: $[M]^+$, 358.3601. $C_{26}H_{46}$ requires: 358.3600.

LRMS (EI): *m/z*: 358 ($[M]^{+\cdot}$, 52%), 315 ($[M - C_3H_7]^{+\cdot}$, 55%), 301 ($[M - C_4H_9]^{+\cdot}$, 74%), 287 ($[M - C_5H_{11}]^{+\cdot}$, 48%), 273 ($[M - C_6H_{13}]^{+\cdot}$, 100%).

IR (thin film): $\tilde{\nu}$ **=** 2921 (s), 2862 (s), 1637 (w), 1450 (w), 884 (m) cm^{-1}.

6.2.6.28. *rac*-(1*R*,5*R*)-1-(4-*tert*-Butylphenyl)vinyl)-3-hexyl-2-propyl-bicyclo[3.3.0]oct-2-ene (2.63aa)



General procedure A was used with dec-1-en-6-yne, 1,1-dibromoheptane and 1-*tert*-butyl-4-ethynylbenzene as components. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a pale yellow oil in yield of 0.341 g (86%).

^{1}H NMR (400 MHz, BENZENE-D$_6$): δ (ppm) = 7.348 – 7.273 (4H, m, $H^{o- + m-Ph}$), 5.222 (1H, d, *J* = 1.9 Hz, H^{13}), 5.154 (1H, d, *J* = 1.9 Hz, H^{13}), 2.560 (1H, tt, *J* = 8.9, 2.2 Hz, H^5), 2.438 (1H, dd, *J* = 16.2, 8.9 Hz, H^{4b}), 2.186 – 2.051 (4H, m), 1.906 – 1.849 (3H, m), 1.777 (1H, dddd, *J* = 12.0, 10.8, 8.9, 6.5 Hz, H^6), 1.654 – 1.475 (4H, m), 1.421 – 1.291 (9H, m), 1.257 (9H, s, H^9), 0.959 (3H, t, *J* = 7.3 Hz, $H^{16 \text{ or } 22}$), 0.919 (3H, t, *J* = 6.9 Hz, $H^{16 \text{ or } 22}$).

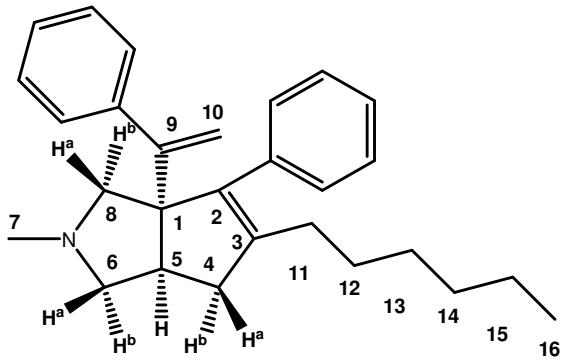
^{13}C NMR (100 MHz, BENZENE-D$_6$): δ (ppm) = 156.83 (C^{12}), 149.74 (C^{11}), 142.44 (C^{i-Ph}), 139.68 ($C^{2 \text{ or } 3}$), 138.41 ($C^{2 \text{ or } 3}$), 128.47 ($2CH^{o-Ph}$), 125.09 ($2CH^{m-Ph}$), 113.65 ($CH_2{}^{13}$), 71.26 (C^1), 44.94 (CH^5), 44.64 ($CH_2{}^4$), 37.31 (CH_2), 36.98 (CH_2), 34.80 (C^{10}), 32.60 (CH_2), 31.89 ($3CH_3{}^9$), 30.32 (CH_2), 30.11 (CH_2), 29.85 (CH_2), 28.61 (CH_2), 26.17 (CH_2), 24.60 (CH_2), 23.44 (CH_2), 15.69 ($CH_3{}^{16 \text{ or } 22}$), 14.71 ppm ($CH_3{}^{16 \text{ or } 22}$).

HRMS (EI): Found: $[M]^+$, 392.3448. $C_{29}H_{44}$ requires: 392.3443.

LRMS (CI): *m/z*: 392 ($[M]^+$, 100%), 335 ($[M - t\text{-Bu}]^+$, 24%), 233 ([M – *p*-*t*-Bu – Styrene]$^+$, 57%).

IR (thin film): $\tilde{\nu}$ **=** 2952 (s), 2926 (s), 2862 (m), 1614 (w), 1504 (w), 1463 (m), 1361 (w), 1270 (w), 1119 (w), 1017 (w), 896 (s), 835 (s), 601 (w) cm^{-1}.

6.2.6.29. *rac*-(1*S*,5*R*)-3-Hexyl-2-phenyl-1-(phenylvinyl)-7-methylaza-bicyclo[3.3.0]oct-2-ene (2.67a)



General procedure A was used with *N*-methyl-*N*-(phenylprop-2-ynyl)prop-2-en-1-amine, 1,1-dibromoheptane and 1-ethynylbenzene as components. Purification of the crude material by column chromatography on Al_2O_3 (basic, gr. III) with 2.5% of Et_2O in hexanes as the eluent gave the title compound as a pale yellow oil in yield of 0.240 g (62%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.385 – 7.251 (10H, m, H^{Ar}), 5.101 (1H, d, *J* = 1.1 Hz, H^{10}), 4.929 (1H, d, *J* = 1.1 Hz, H^{10}), 2.691 (1H, d, *J* = 9.4 Hz, $H^{8a\text{ or }8b}$), 2.679 (1H, dd, *J* = 8.4, 4.0 Hz, $H^{6a\text{ or }6b}$), 2.632 (1H, d, *J* = 9.4 Hz, $H^{8a\text{ or }8b}$), 2.626 (1H, tdd, *J* = 7.9, 4.0, 2.0 Hz, H^5), 2.496 (1H, fs ddd, *J* = 16.8, 8.8, Hz, H^{4b}), 2.446 (1H, dd, *J* = 8.4, 4.0 Hz, $H^{6a\text{ or }6b}$), 2.311 (3H, s, H^7), 2.152 (1H, dd, *J* = 16.8, 1.7 Hz, H^{4a}), 2.120 – 2.082 (2H, m, H^{11}), 1.454 – 1.345 (2H, m), 1.319 – 1.218 (6H, m), 0.892 (3H, t, *J* = 7.0 Hz, H^{16}).

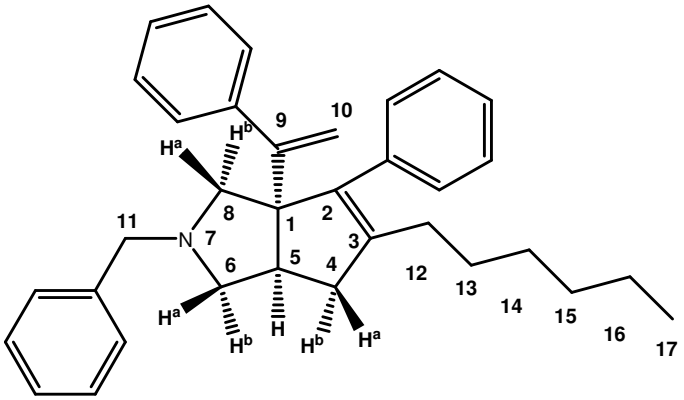
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 153.64 ($C^{2\text{ or }9}$), 143.66 ($C^{2\text{ or }9}$), 141.53 ($C^{i\text{-Ph}}$), 139.52 ($C^{i\text{-Ph}}$), 137.54 (C^3), 129.89 ($2CH^{o\text{- or m-Ph}}$), 127.73 ($2CH^{o\text{- or m-Ph}}$), 127.65 ($2CH^{o\text{- or m-Ph}}$), 127.57 ($2CH^{o\text{- or m-Ph}}$), 126.71 ($CH^{p\text{-Ph}}$), 126.46 ($CH^{p\text{-Ph}}$), 114.98 ($CH_2{}^{10}$), 70.11 (C^1), 65.77 ($2CH_2{}^{6\,+\,8}$), 46.35 (CH^5), 42.73 ($CH_3{}^7$), 41.98 ($CH_2{}^4$), 31.67 (CH_2), 29.81 (CH_2), 29.39 ($CH_2{}^{11}$), 27.72 (CH_2), 22.58 (CH_2), 14.06 ($CH_3{}^{16}$).

HRMS (ESI+): Found: $[M + H]^+$, 386.2832. $[C_{28}H_{36}N]^+$ requires: 386.2842.

LRMS (ESI+): *m/z*: 386 ($[M + H]^+$, 100%).

IR (thin film): $\tilde{\nu}$ = 2933 (m), 2858 (m), 2775 (m), 1595 (w), 1497 (m), 1436 (m), 1157 (m), 900 (m), 771 (m), 699 (s) cm^{-1}.

6.2.6.30. *rac*-(1*S*,5*R*)-3-Hexyl-2-phenyl-1-(phenylvinyl)-7-benzylaza-bicyclo[3.3.0]oct-2-ene (2.67b)



General procedure A was used with *N*-benzyl-*N*-(phenylprop-2-ynyl)prop-2-en-1-amine, 1,1-dibromoheptane and 1-ethynylbenzene as components. The carbenoid was generated *in situ* from 1,1-dibromoheptane (1.3 mmol) and LDA (0.83 mL of a 1.8 M solution, 1.50 mmol) at –85 °C for 15 min before dropwise addition of phenyl acetylide. Purification of the crude material by column chromatography on Al_2O_3 (basic, grade III) with 1% of Et_2O in hexanes as the eluent gave the title compound as a colourless oil in yield of 0.341 g (74%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.404 – 7.185 (15H, m, H^{Ar}), 5.071 (1H, d, *J* = 1.4 Hz, H^{10}), 4.856 (1H, d, *J* = 1.4 Hz, H^{10}), 3.583 (1H, d, *J* = 13.4 Hz, H^{11}), 3.538 (1H, d, *J* = 13.4 Hz, H^{11}), 2.725 (1H, dd, *J* = 8.5, 7.5 Hz, H^{6b}), 2.672 (1H, d, *J* = 9.4 Hz, H^{8}), 2.622 (1H, dddd, *J* = 8.6, 7.5, 3.8, 1.8 Hz, H^{5}), 2.542 (1H, d, *J* = 9.4 Hz, H^{8}), 2.512 (1H, dd, *J* = 16.8, 9.2 Hz, H^{4b}), 2.476 (1H, d, *J* = 8.5 Hz, H^{6a}), 2.184 (1H, dd, *J* = 16.8, 1.8 Hz, H^{4a}), 2.131 – 2.087 (2H, m, H^{12}), 2.106 (1H, dd, *J* = 6.6, 2.5 Hz), 1.465 – 1.392 (2H, m), 1.343 – 1.238 (6H, m), 0.906 (3H, t, *J* = 7.0 Hz, H^{17}).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 153.64 (C^{9}), 143.67 ($C^{2\text{ or }3}$), 141.50 ($C^{2\text{ or }3}$), 139.84 ($C^{i\text{-}Ph}$), 139.63 ($C^{i\text{-}Ph}$), 137.59 ($C^{i\text{-}Ph}$), 129.90 ($2CH^{o\text{- or }m\text{-}Ph}$), 128.30 ($2CH^{o\text{- or }m\text{-}Ph}$), 128.01 ($2CH^{o\text{- or }m\text{-}Ph}$), 127.73 ($2CH^{o\text{- or }m\text{-}Ph}$), 127.66 ($2CH^{o\text{- or }m\text{-}Ph}$), 127.48 ($2CH^{o\text{- or }m\text{-}Ph}$), 126.69 ($CH^{p\text{-}Ph}$), 126.59 ($CH^{p\text{-}Ph}$), 126.37 ($CH^{p\text{-}Ph}$), 115.02 ($CH_2{}^{10}$), 69.41 ($C^{1}$), 63.44 ($CH_2{}^{6}$), 62.77 ($CH_2{}^{8}$), 59.93 ($CH_2{}^{11}$), 45.98 ($CH^{1}$), 42.03 ($CH_2{}^{4}$), 31.75 ($CH_2$), 29.71 ($CH_2{}^{12}$), 29.26 ($CH_2$), 27.83 ($CH_2$), 22.62 ($CH_2$), 14.11 ($CH_3{}^{17}$).

HRMS (ESI+): Found: $[M + H]^+$, 462.3149. $[C_{34}H_{40}N]^+$ requires: 462.3155.

LRMS (ESI+): *m/z*: 462 ($[M + H]^+$, 100 %).

IR (thin film): $\tilde{\nu}$ = 2924 (m), 2848 (w), 2783 (w), 1498 (m), 1428 (w), 1142 (w), 1018 (w), 899 (m), 775 (m), 694 (s) cm^{-1}.

6.2.7. Preparation of compounds 2.69 and 2.70

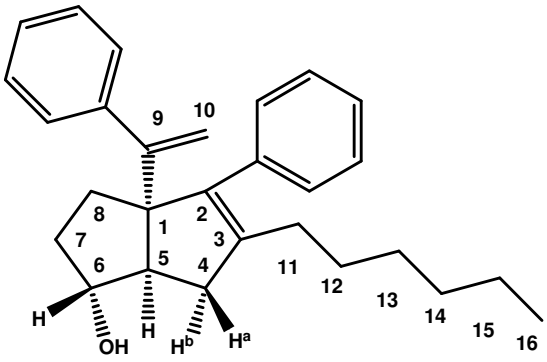
General procedure B: To a solution of Cp_2ZrCl_2 (1.465 g, 5.0 mmol) in dry THF (25 mL) cooled to –78 °C was added *n*-BuLi (4.0 mL of a 2.5 M solution in hexanes, 10.0 mmol) dropwise. After 20 min, a solution of TBDMS protected 7-phenylhept-1-en-6-yn-3-ol **2.41** (1.50 g, 5.0 mmol) in dry THF (15 mL) was added dropwise. After 30 min at –78 °C the reaction mixture was allowed to warm to room temperature and continued to stir for 3 h. After re-cooling the reaction mixture to –78 °C, a solution of 1,1-dibromoheptane (1.42 g, 5.5 mmol) in dry THF (5 mL) was added followed by dropwise addition of LDA (3.06 mL of a 1.8 M solution, 5.5 mmol). The reaction mixture was stirred at –78 °C for 15 min before dropwise addition of phenyl acetylide. [Lithium phenyl acetylide was freshly prepared from phenylacetylene (1.65 mL, 15.0 mmol) in dry THF (15 mL) and *n*-BuLi (6.0 mL of a 2.5 M solution in hexanes, 15.0 mmol) at –10 °C over 15 min].

The stirring was continued for 45 min during which the reaction mixture was allowed to warm to –55 °C before addition of MeOH (30 mL) and a saturated aqueous solution of $NaHCO_3$ (30 mL). The whole mixture was allowed to warm to room temperature and was left stirring for 5 h. The mixture was then poured onto H_2O (200 mL) and the products were extracted with Et_2O (3 × 200 mL). The combined organic phases were washed with H_2O (3 × 300 mL) and brine (300 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude products as yellow oils. Purification of the crude material by flash chromatography column with 2.5% of Et_2O in hexanes as the eluent provided the TBDMS protected alcohols **2.68** as a yellow oil (2.20 g, 88%).

The TBDMS protected alcohols **2.68** (2.20 g, 4.40 mmol) were dissolved in dry THF (44 and 38 mL respectively) followed by addition of TBAF (17.60 mL of 1.0 M solution in THF), and the reaction mixture was stirred at RT for 20 h. Then the mixture was poured onto H_2O (200 mL), the products extracted with Et_2O (2 × 150 mL). The organic phases were washed with H_2O (3 × 200 mL), brine (1 × 200 mL), and dried over $MgSO_4$. Concentration *in vacuo*, followed by separation by column chromatography on Al_2O_3 (basic, grade III) and 2.5% EtOAc in hexanes as the eluent

gave the partially separated isomers: 0.277 g of pure **2.69-*endo*** (14%), 0.650 g of mixed fractions (33%) and 0.556 of pure **2.69-*exo*** (29%), combined yield of 1.483 g (76%). Further chromatography of the mixed fractions allowed additional pure **2.69-*exo*** and **2.69-*endo*** to be isolated.

6.2.7.1. *rac*-(1*R*,5*R*,6*R*)-3-Hexyl-6-hydroxy-2-phenyl-1-(phenylvinyl)-bicyclo[3.3.0]oct-2-ene (2.69-*exo*)



Yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.372 – 7.192 (10H, m, H^{Ar}), 5.078 (1H, d, *J* = 1.5 Hz, H^{10}), 5.001 (1H, d, *J* = 1.5 Hz, H^{10}), 3.958 (1H, br s, H^{6}), 2.388 (1H, dd, *J* = 16.2, 9.6 Hz, H^{4b}), 2.303 (1H, fs dd, *J* = 9.6 Hz, H^{5}), 2.152 – 2.004 (4H, m), 1.792 – 1.670 (3H, m), 1.376 – 1.222 (9H, m, $8H^{aliphatic}$ + OH), 0.869 (3H, t, *J* = 6.8 Hz, H^{16}).

^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 154.69 (C^{9}), 144.21 ($C^{2\ or\ 3}$), 141.19 ($C^{2\ or\ 3}$), 139.17 ($C^{i\text{-}Ph}$), 137.43 ($C^{i\text{-}Ph}$), 129.73 ($2CH^{o\text{-}\ or\ m\text{-}Ph}$), 127.78 ($2CH^{o\text{-}\ or\ m\text{-}Ph}$), 127.72 ($2CH^{o\text{-}\ or\ m\text{-}Ph}$), 127.62 ($2CH^{o\text{-}\ or\ m\text{-}Ph}$), 126.66 ($CH^{p\text{-}Ph}$), 126.59 ($CH^{p\text{-}Ph}$), 114.99 ($CH_2{}^{10}$), 82.10 ($CH^{6}$), 69.40 ($C^{1}$), 55.92 ($CH^{5}$), 40.29 ($CH_2$), 34.04 ($CH_2$), 32.13 ($CH_2$), 31.66 ($CH_2$), 29.73 ($CH_2$), 29.37 ($CH_2$), 27.83 ($CH_2$), 22.58 ($CH_2$), 14.06 ($CH_3{}^{16}$).

HRMS (EI): Found: $[M]^+$, 386.2611. $C_{28}H_{34}O$ requires: 386.2610.

LRMS (EI): *m/z*: 386 ($[M]^{+\cdot}$, 36%), 283 ($[M - H_2O]^+$, 21%), 283 ($[M - Styrene]^{+\cdot}$, 100%).

IR (thin film): $\tilde{\nu}$ = 3327 (m, br), 2918 (m), 1599 (w), 1493 (m), 1338 (w), 771 (m), 699 (s) cm^{-1}.

6.2.7.2. (1*S*,5*S*,6*S*)-3-Hexyl-6-hydroxy-2-phenyl-1-(phenylvinyl)-bicyclo[3.3.0]oct-2-ene (2.69-*exo*-ent-1)

R_t 11.7 min on chiral HPLC on a Diacel OD-H, (1 mL/min 1% isopropanol in hexane on 4.6 x 250 mm column).

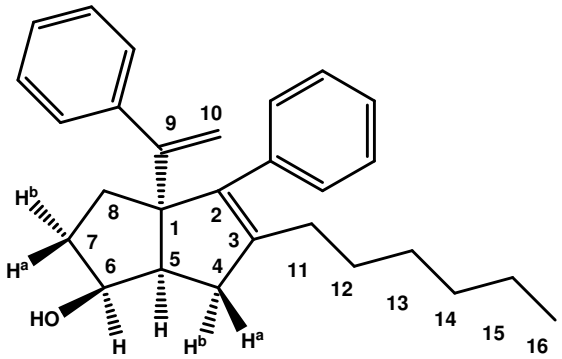
$[\alpha]_D^{25}$ –46.7 (c = 0.48, $CHCl_3$, 100% e.e.).

6.2.7.3. (1*R*,5*R*,6*R*)-3-Hexyl-6-hydroxy-2-phenyl-1-(phenylvinyl)-bicyclo[3.3.0]oct-2-ene (2.69-*exo*-ent-2)

R_t 18.5 min on chiral HPLC on a Diacel OD-H, (1 mL/min 1% isopropanol in hexane on 4.6 x 250 mm column).

$[\alpha]_D^{25}$ +45.1 (c = 0.49, $CHCl_3$, 100% e.e.).

6.2.7.4. *rac*-(1*R*,5*R*,6*S*)-3-Hexyl-6-hydroxy-2-phenyl-1-(phenylvinyl)-bicyclo[3.3.0]oct-2-ene (2.69-*endo*)



Yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 7.350 – 7.207 (10H, m, H^{Ar}), 5.074 (1H, d, *J* = 1.5 Hz, H^{10}), 4.955 (1H, d, *J* = 1.5 Hz, H^{10}), 4.178 (1H, ddd, *J* = 9.1, 8.5, 5.5 Hz, H^6), 2.633 (1H, dd, *J* = 17.2, 2.1 Hz, H^{4a}), 2.500 (1H, td, *J* = 8.5, 2.1 Hz, H^5), 2.166 – 2.006 (3H, m), 1.855 (1H, ddt, *J* = 10.4, 5.5, 4.4 Hz, H^{7b}), 1.742 – 1.699 (2H, m), 1.573 (1H, ddd, *J* = 10.4, 9.1, 8.1 Hz, H^{7a}), 1.496 – 1.346 (2H, m), 1.287 – 1.239 (7H, m, $6H^{aliphatic}$ + OH), 0.872 (3H, t, *J* = 6.8 Hz, H^{16}).

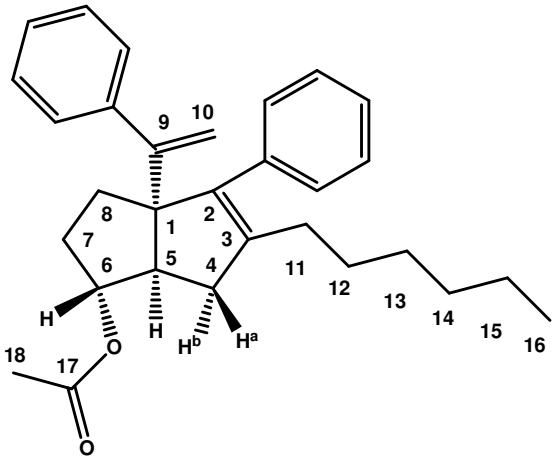
^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) = 154.86 (C^9), 144.00 ($C^{2\text{ or }3}$), 143.28 ($C^{2\text{ or }3}$), 139.37 ($C^{i\text{-Ph}}$), 137.06 ($C^{i\text{-Ph}}$), 129.82 ($2CH^{o\text{- or m-Ph}}$), 127.78 ($2CH^{o\text{- or m-Ph}}$), 127.70 ($2CH^{o\text{- or m-Ph}}$), 127.61 ($2CH^{o\text{- or m-Ph}}$), 126.70 ($CH^{p\text{-Ph}}$), 126.56 ($CH^{p\text{-Ph}}$), 114.88 (CH_2^{10}), 74.55 (CH^6), 68.83 (C^1), 49.19 (CH^5), 33.77 (CH_2), 33.49 (CH_2), 31.83 (CH_2), 31.66 (CH_2), 29.89 (CH_2), 29.47 (CH_2), 27.93 (CH_2), 22.60 (CH_2), 14.06 (CH_3^{16}).

HRMS (EI): Found: $[M]^+$, 386.2600. $C_{28}H_{34}O$ requires: 386.2610.

LRMS (EI): *m/z*: 386 ($[M]^{+\cdot}$, 12%), 368 ($[M - H_2O]^{+\cdot}$, 17%), 283 ($[M - Styrene]^{+\cdot}$, 69%).

IR (thin film): $\tilde{\nu}$ = 3323 (m, br), 2922 (m), 1595 (w), 1489 (m), 1289 (w), 1073 (m), 900 (m), 775 (m), 692 (s) cm^{-1}.

6.2.7.5. *rac*-(1*R*,5*R*,6*R*)-6-Acetoxy-3-hexyl-2-phenyl-1-(phenylvinyl)-bicyclo[3.3.0]oct-2-ene (2.70-*exo*)



Alcohol **2.69-*exo*** (0.028 g, 0.072 mmol) was dissolved in the mixture of anhydrous pyridine (0.15 mL, 1.85 mmol) and freshly distilled acetic anhydride (0.50 mL, 5.25 mmol). After stirring for 10 min at RT, DMAP (0.005 g, 0.041 mmol) was added and the stirring was continued at RT for 13 h. Then H_2O (5 mL) was added to the reaction mixture and the whole mixture was poured onto Et_2O (15 mL). The organic phase was separated and washed with HCl (15 mL of a 1.0 M solution), a saturated aqueous solution of $NaHCO_3$ (15 mL) and brine (2 × 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a yellow oil. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with 3% of EtOAc in hexanes as the eluent gave the title compound (*exo* diastereoisomer) as a colourless oil in yield of 0.0254 g (82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.350 – 7.220 (10H, m, H^{Ar}), 5.076 (1H, d, *J* = 1.5 Hz, H^{10}), 5.035 (1H, d, *J* = 1.5 Hz, H^{10}), 4.828 (1H, t, *J* = 2.9 Hz, H^6), 2.391 (1H, d, *J* = 9.4 Hz, H^5), 2.348 (1H, dd, *J* = 15.5, 9.4 Hz, H^{4b}), 2.182 (1H, d, *J* = 15.5 Hz, H^{4a}), 2.085 – 1.963 (3H, m), 2.010 (3H, s, H^{18}), 1.783 – 1.686 (3H, m), 1.365 – 1.193 (8H, m), 0.872 (3H, t, *J* = 7.0 Hz, H^{16}).

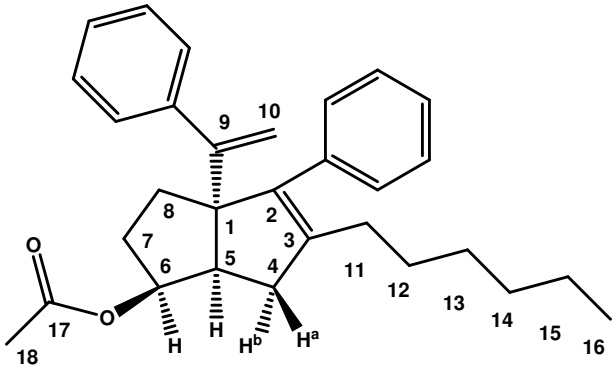
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 170.77 (C^{17}), 154.41 (C^{9}), 143.85 ($C^{2 \text{ or } 3}$), 141.87 ($C^{2 \text{ or } 3}$), 138.59 ($C^{\text{i-Ph}}$), 137.28 ($C^{\text{i-Ph}}$), 129.58 ($2CH^{\text{o- or m-Ph}}$), 127.76 ($2CH^{\text{o- or m-Ph}}$), 127.69 ($4CH^{\text{o- or m-Ph}}$), 126.71 ($CH^{\text{p-Ph}}$), 126.65 ($CH^{\text{p-Ph}}$), 115.03 ($CH_2{}^{10}$), 84.83 (CH^{6}), 69.35 (C^{1}), 53.23 (CH^{5}), 40.29 (CH_2), 32.38 (CH_2), 31.62 (CH_2), 31.44 (CH_2), 29.72 (CH_2), 29.37 (CH_2), 27.79 (CH_2), 22.57 (CH_2), 21.41 ($CH_3{}^{18}$), 14.06 ($CH_3{}^{16}$).

HRMS (ESI+): Found: $[M + Na]^+$, 451.2604. $[C_{30}H_{36}O_2Na]^+$ requires: 451.2608.

LRMS (EI): *m/z*: 428 ($[M]^{+\cdot}$, 6%), 368 ($[M – AcOH]^{+\cdot}$, 86%), 283 ($[M – AcOH – Hex]^{+\cdot}$, 43%), 265 ($[M – Ph – C_2H_5]^{+\cdot}$, 100%).

IR (thin film): $\tilde{\nu}$ **=** 2922 (m), 1731 (s), 1603 (w), 1493 (m), 1239 (s), 1021 (m), 907 (m), 767 (m), 703 (s) cm^{-1}.

6.2.7.6. *rac*-(1*R*,5*R*,6*S*)-6-Acetoxy-3-hexyl-2-phenyl-1-(phenylvinyl)-bicyclo[3.3.0]oct-2-ene (2.70-*endo*)



Alcohol **2.69-*endo*** (0.028 g, 0.072 mmol) was dissolved in the mixture of anhydrous pyridine (0.150 mL, 1.85 mmol) and freshly distilled acetic anhydride (0.50 mL, 5.25 mmol). After stirring for 10 min at RT, DMAP (0.005 g, 0.041 mmol) was added and the stirring was continued at RT for 13 h. Then H_2O (5 mL) was added to the reaction mixture and the whole mixture was poured onto Et_2O (15 mL). The organic phase was separated and washed with HCl (15 mL of a 1.0 M solution), saturated aqueous solution of $NaHCO_3$ (15 mL) and brine (2 × 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a pale yellow oil. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with 3% of EtOAc in hexanes as the eluent gave the title compound (*endo* diastereoisomer) as a colourless oil (0.021 g, 95%). Crystallization from hexanes gave white crystals.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.342 – 7.214 (10H, m, H^{Ar}), 5.078 (1H, d, *J* = 1.5 Hz, H^{10}), 5.012 (1H, td, *J* = 9.1, 7.0 Hz, H^6), 4.973 (1H, d, *J* = 1.5 Hz, H^{10}), 2.682 (1H, dd, *J* = 8.8, 1.8 Hz, H^5), 2.283 (1H, dd, *J* = 17.4, 1.8 Hz, H^{4a}), 2.120 – 2.024 (2H, m), 2.062 (3H, s, H^{18}), 1.998 (1H, dd, *J* = 17.4, 8.8 Hz, H^{4b}), 1.913 (1H, m), 1.754 – 1.626 (3H, m), 1.429 – 1.357 (2H, m), 1.310 – 1.205 (6H, m), 0.877 (3H, t, *J* = 6.9 Hz, H^{16}).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 170.64 (C^{17}), 154.35 (C^9), 143.67 ($C^{2 \text{ or } 3}$), 143.22 ($C^{2 \text{ or } 3}$), 138.58 ($C^{i\text{-Ph}}$), 136.95 ($C^{i\text{-Ph}}$), 129.72 ($2CH^{o\text{- or m-Ph}}$), 127.81 ($2CH^{o\text{- or m-Ph}}$), 127.71 ($2CH^{o\text{- or m-Ph}}$), 127.66 ($2CH^{o\text{- or m-Ph}}$), 126.75 ($CH^{p\text{-Ph}}$), 126.63 ($CH^{p\text{-Ph}}$), 115.16 ($CH_2{}^{10}$), 76.37 (CH^6), 68.59 (C^1), 46.94 (CH^5), 34.61 (CH_2), 31.73 (CH_2), 31.16 (CH_2), 30.12 (CH_2), 29.77 (CH_2), 29.39 (CH_2), 27.85 (CH_2), 22.61 (CH_2), 21.08 ($CH_3{}^{18}$), 14.08 ($CH_3{}^{16}$).

HRMS (EI): Found: $[M]^+$, 428.2721. $C_{30}H_{36}O_2$ requires: 428.2715.

LRMS (EI): *m/z*: 428 ($[M]^{+\cdot}$, 14%), 368 ($[M - AcOH]^{+\cdot}$, 94%), 325 ($[M - Styrene]^{+\cdot}$, 22%), 283 ($[M - AcOH - Hex]^{+\cdot}$, 42%), 265 ($[M - Ph - C_2H_5]^{+\cdot}$, 61%).

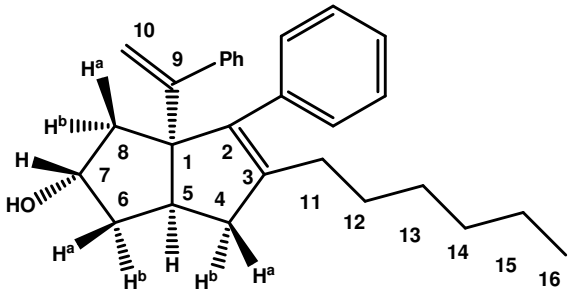
IR (thin film): $\tilde{\nu}$ **=** 2924 (m), 1741 (s), 1599 (w), 1493 (m), 1239 (s), 1055 (m), 907 (m), 770 (m), 703 (s) cm^{-1}.

m.p. 42 – 44 °C.

6.2.8. Preparation of compounds 2.72 and 2.73

Following general procedure B and using TBDMS protected 7-phenylhept-1-en-6-yn-4-ol **2.48**. Purification of the product by flash chromatography column with 2.5% of Et_2O in hexanes provided the TBDMS protected alcohols **2.71** as a yellow oil, in yield of 1.94 g (78%). The TBDMS protected alcohols (1.94 g, 3.88 mmol) were dissolved in dry THF (38 mL) followed by addition of TBAF (7.76 mL of 1.0 M), and the reaction mixture was stirred at RT for 20 h. Then the mixture was poured onto H_2O (200 mL), the products extracted with Et_2O (2 × 150 mL). The organic phases were washed with H_2O (3 × 200 mL), brine (1 × 200 mL), and dried over $MgSO_4$. Concentration *in vacuo*, followed by separation by column chromatography on Al_2O_3 (basic, grade III) and 2.5% EtOAc in hexanes as the eluent gave the partially separated isomers: 0.632 g of pure **2.72-*endo*** (33%), 0.349 g of mixed fractions (18%) and 0.361 of pure **2.72-*exo*** (19%), combined yield of 1.342 g (70%). Further chromatography of the mixed fractions allowed additional pure **2.72-*exo*** and **2.72-*endo*** to be isolated.

6.2.8.1. *rac*-(1*R*,5*R*,7*R*)-3-Hexyl-7-hydroxy-2-phenyl-1-(phenylvinyl)-bicyclo[3.3.0]oct-2-ene (2.72-*exo*)



Pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.291 – 7.191 (10H, m, H^{Ar}), 4.992 (1H, d, *J* = 1.5 Hz, H^{10}), 4.980 (1H, d, *J* = 1.5 Hz, H^{10}), 4.197 (1H, tt, *J* = 8.0, 5.9 Hz, H^7), 2.554 (1H, dddd, *J* = 10.0, 8.4, 3.6, 1.5 Hz, H^5), 2.186 (1H, dd, *J* = 16.8, 8.3 Hz, H^{4b}), 2.064 – 1.890 (3H, m, $2H^{11} + H^{4a}$), 1.927 (1H, ddd, *J* = 12.4, 5.5, 1.5 Hz, H^{8a}), 1.823 (1H, ddd, *J* = 12.7, 10.0, 8.3 Hz, H^{6b}), 1.718 (1H, dd, *J* = 12.4, 8.5 Hz, H^{8b}), 1.642 (1H, dddd, *J* = 12.7, 6.3, 3.6, 1.5 Hz, H^{6a}), 1.498 (1H, br s, OH) 1.301 – 1.152 (9H, m), 0.812 (3H, t, *J* = 7.0 Hz, H^{16}).

^{1}H NMR (400 MHz, BENZENE-D_6): δ (ppm) = 7.406 – 7.366 (4H, m, $H^{o\text{-}Ph}$), 7.252 – 7.095 (6H, m, $H^{m\,+\,p\text{-}Ph}$), 5.056 (2H, br s, H^{10}), 4.163 (1H, tt, *J* = 8.0, 5.9 Hz, H^7), 2.626 (1H, dddd, *J* = 10.0, 8.4, 3.6, 1.5 Hz, H^5), 2.225 (1H, dd, *J* = 16.6, 8.3 Hz, H^{4b}), 2.068 (2H, apparent t, *J* = 7.8 Hz, H^{11}), 2.035 (1H, ddd, *J* = 12.4, 5.5, 1.5 Hz, H^{8a}), 1.841 (1H, dd, *J* = 16.6, 1.5 Hz, H^{4a}), 1.804 (1H, ddd, *J* = 12.6, 10.0, 8.3 Hz, H^{6b}), 1.752 (1H, dd, *J* = 12.4, 8.8 Hz, H^{8b}), 1.582 (1H, dddd, *J* = 12.6, 6.3, 3.6, 1.5 Hz, H^{6a}), 1.321 – 1.098 (9H, m, $8H^{aliphatic}$ + OH), 0.863 (3H, t, *J* = 7.0 Hz, H^{16}).

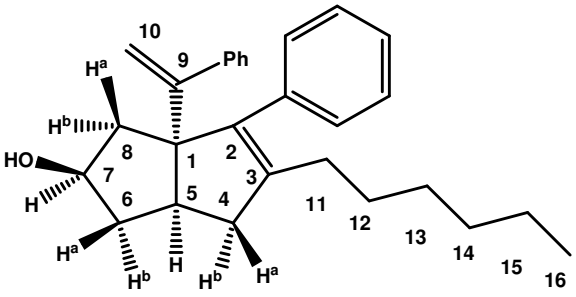
^{13}C NMR (100.5 MHz, BENZENE-D_6): δ (ppm) = 155.97 (C^9), 144.35 ($C^{2\text{ or }3}$), 142.36 ($C^{2\text{ or }3}$), 140.17 ($C^{i\text{-}Ph}$), 138.41 ($C^{i\text{-}Ph}$), 130.35 ($2CH^{o\text{- or }m\text{-}Ph}$), 128.91 ($2CH^{o\text{- or }m\text{-}Ph}$), 128.69 ($2CH^{o\text{- or }m\text{-}Ph}$), 128.59 ($2CH^{o\text{- or }m\text{-}Ph}$), 127.44 ($CH^{p\text{-}Ph}$), 127.41 ($CH^{p\text{-}Ph}$), 115.14 ($CH_2{}^{10}$), 73.34 ($CH^7$), 68.49 ($C^1$), 45.09 ($CH_2{}^6$), 44.77 ($CH^5$), 44.30 ($CH_2{}^{4\text{ or }8}$), 43.96 ($CH_2{}^{4\text{ or }8}$), 32.37 ($CH_2$), 30.59 ($CH_2$), 30.17 ($CH_2$), 28.55 ($CH_2$), 23.34 ($CH_2{}^{15}$), 14.66 ($CH_3{}^{16}$).

HRMS (EI): Found: $[M]^+$, 386.2597. $C_{28}H_{34}O$ requires: 386.2610.

LRMS (EI): *m/z*: 386 ($[M]^{+\cdot}$, 25%), 368 ($[M - H_2O]^{+\cdot}$, 22%), 283 ([M – Styrene]$^{+\cdot}$, 100%).

IR (thin film): $\tilde{\nu}$ **=** 3330 (m, br), 2930 (m), 1603 (w), 1504 (m), 1349 (w), 1073 (m), 907 (m), 775 (m), 692 (s) cm^{-1}.

6.2.8.2. *rac*-(1*R*,5*R*,7*S*)-3-Hexyl-7-hydroxy-2-phenyl-1-(phenylvinyl)-bicyclo[3.3.0]oct-2-ene (2.72-*endo*)



Yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.283 – 7.155 (10H, m, H^{Ar}), 4.990 (1H, d, *J* = 1.3 Hz, H^{10}), 4.939 (1H, d, *J* = 1.3 Hz, H^{10}), 4.107 (1H, quintet, *J* = 5.4 Hz, H^7), 2.472 (1H, tdd, *J* = 8.8, 6.2, 1.4 Hz, H^5), 2.311 (1H, dd, *J* = 16.8, 8.5 Hz, H^{4b}), 2.210 (1H, dddd, *J* = 13.3, 9.3, 5.6, 1.0 Hz, H^{6b}), 2.103 (1H, dd, *J* = 16.8, 1.4 Hz, H^{4a}), 2.070 – 1.966 (2H, m, H^{11}), 2.028 (1H, ddd, *J* = 13.5, 6.2, 1.1 Hz, H^{8b}), 1.791 (1H, ddd, *J* = 13.5, 4.6, 1.1 Hz, H^{8a}), 1.459 (1H, dddd, *J* = 13.3, 6.0, 5.0, 1.3 Hz, H^{6a}), 1.332 – 1.261 (2H, m), 1.221 – 1.135 (7H, m, $6H^{aliphatic}$ + OH), 0.792 (3H, t, *J* = 7.0 Hz, H^{16}).

^{1}H NMR (400 MHz, BENZENE-D_6): δ (ppm) = 7.498 (2H, dd, *J* = 8.1, 1.3 Hz, $H^{o\text{-}Ph}$), 7.322 (2H, dd, *J* = 8.1, 1.3 Hz, $H^{o\text{-}Ph}$), 7.257 – 7.109 (6H, m, $H^{m\,+\,p\text{-}Ph}$), 5.054 (1H, d, *J* = 1.5 Hz, H^{10}), 5.036 (1H, d, *J* = 1.5 Hz, H^{10}), 4.031 (1H, br s, H^7), 2.519 (1H, tdd, *J* = 8.8, 6.2, 1.4 Hz, H^5), 2.388 (1H, dd, *J* = 16.6, 8.5 Hz, H^{4b}), 2.115 – 2.011 (5H, m, $2H^{11}$ + 3H), 1.912 (1H, ddd, *J* = 13.6, 5.3, 1.3 Hz, H^{8a}), 1.485 (1H, dddd, *J* = 12.8, 6.5, 3.9, 1.3 Hz, H^{6a}), 1.382 – 1.307 (2H, m) 1.244 – 1.097 (7H, m, $6H^{aliphatic}$ + OH), 0.855 (3H, t, *J* = 7.0 Hz, H^{16}).

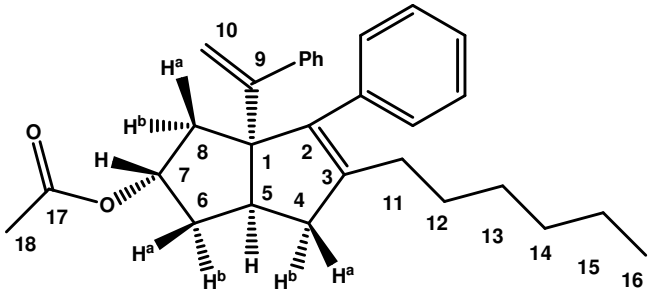
^{13}C NMR (100.5 MHz, BENZENE-D_6): δ (ppm) = 156.04 (C^9), 144.57 ($C^{2\text{ or }3}$), 142.39 ($C^{2\text{ or }3}$), 141.00 ($C^{i\text{-}Ph}$), 138.59 ($C^{i\text{-}Ph}$), 130.66 ($2CH^{o\text{- or }m\text{-}Ph}$), 128.84 ($2CH^{o\text{- or }m\text{-}Ph}$), 128.68 ($2CH^{o\text{- or }m\text{-}Ph}$), 128.58 ($2CH^{o\text{- or }m\text{-}Ph}$), 127.41 ($CH^{p\text{-}Ph}$), 127.38 ($CH^{p\text{-}Ph}$), 114.85 ($CH_2{}^{10}$), 74.60 ($CH^7$), 69.51 ($C^1$), 46.09 ($CH^5$), 45.05 ($CH_2{}^6$), 44.79 ($CH_2{}^8$), 43.39 ($CH_2{}^4$), 32.35 ($CH_2$), 30.65 ($CH_2$), 30.15 ($CH_2$), 28.53 ($CH_2$), 23.33 ($CH_2$), 14.66 ($CH_3{}^{16}$).

HRMS (EI): Found: $[M]^+$, 386.2597. $C_{28}H_{34}O$ requires: 386.2610.

LRMS (EI): *m/z*: 386 ($[M]^{+\cdot}$, 2%), 368 ($[M - H_2O]^{+\cdot}$, 16%), 283 ($[M - Styrene]^{+\cdot}$, 100%).

IR (thin film): $\tilde{\nu}$ **=** 3328 (m, br), 2932 (m), 1603 (w), 1504 (m), 1349 (w), 1070 (m), 907 (m), 775 (m), 692 (s) cm^{-1}.

6.2.8.3. *rac*-(1*R*,5*R*,7*R*)-7-Acetoxy-3-hexyl-2-phenyl-1-(phenylvinyl)-bicyclo[3.3.0]oct-2-ene (2.73-*exo*)



Alcohol **2.72-*exo*** (0.026 g, 0.067 mmol) was dissolved in the mixture of anhydrous pyridine (0.14 mL, 1.72 mmol) and freshly distilled acetic anhydride (0.48 mL, 5.06 mmol). After stirring for 10 min at RT, DMAP (0.0048 g, 0.038 mmol) was added and the stirring was continued at RT for 17 h. Then H_2O (5 mL) was added to the reaction mixture and the whole mixture was poured onto Et_2O (15 mL). The organic phase was separated and washed with HCl (15 mL of a 1.0 M solution), a saturated aqueous solution of $NaHCO_3$ (15 mL) and brine (2 × 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a yellow oil. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with 3% of EtOAc in hexanes as the eluent gave the title compound (*exo* diastereoisomer) as a colourless oil in yield of 0.023 g (80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.359 – 7.253 (10H, m, H^{Ar}), 5.056 (1H, tt, *J* = 8.0, 6.1 Hz, H^7), 5.027 (1H, d, *J* = 1.5 Hz, H^{10}), 5.019 (1H, d, *J* = 1.5 Hz, H^{10}), 2.622 (1H, dddd, *J* = 9.8, 7.8, 4.2, 1.0 Hz, H^5), 2.285 (1H, dd, *J* = 16.8, 8.0 Hz, H^{4b}), 2.121 – 1.907 (4H, m, $2H^{11}$ + H^{6b} + H^{8b}), 1.996 (1H, dd, *J* = 16.8, 1.0 Hz, H^{4a}), 1.961 (3H, s, H^{18}), 1.893 (1H, dd, *J* = 12.8, 8.3 Hz, H^{8a}), 1.807 (1H, dddd, *J* = 12.8, 6.6, 4.4, 1.5 Hz, H^{6a}), 1.378 – 1.180 (8H, m), 0.867 (3H, t, *J* = 7.0 Hz, H^{16}).

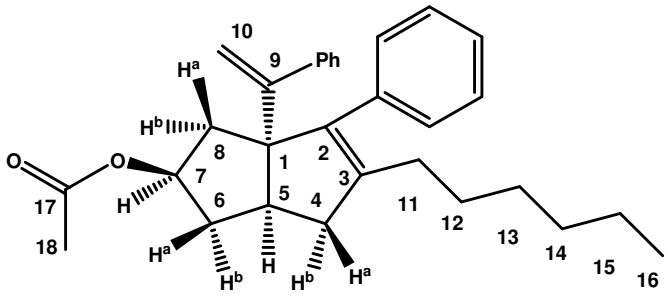
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 170.87 (C^{17}), 154.32 (C^9), 143.29 ($C^{2 \text{ or } 3}$), 142.04 ($C^{2 \text{ or } 3}$), 138.86 ($C^{i\text{-}Ph}$), 137.16 ($C^{i\text{-}Ph}$), 129.61 ($2CH^{o\text{- or } m\text{-}Ph}$), 128.14 ($2CH^{o\text{- or } m\text{-}Ph}$), 127.80 ($2CH^{o\text{- or } m\text{-}Ph}$), 127.57 ($2CH^{o\text{- or } m\text{-}Ph}$), 126.70 ($CH^{p\text{-}Ph}$), 126.65 ($CH^{p\text{-}Ph}$), 114.73 ($CH_2{}^{10}$), 75.56 ($CH^7$), 67.21 ($C^1$), 43.95 ($CH^5$), 42.80 ($CH_2$), 40.67 ($CH_2$), 39.79 ($CH_2$), 31.65 ($CH_2$), 29.88 ($CH_2$), 29.42 ($CH_2$), 27.75 ($CH_2$), 22.56 ($CH_2$), 21.21 ($CH_3{}^{18}$), 14.06 ($CH_3{}^{16}$).

HRMS (ESI+): Found: $[M + Na]^+$, 451.2605. $[_{30}H_{36}O_2Na]^+$ requires: 451.2608.

LRMS (EI): *m/z*: 428 ([M]$^{+\cdot}$, 9%), 368 ([M – AcOH]$^{+\cdot}$, 30%), 283 ([M – AcOH – Hex]$^{+\cdot}$, 16%), 265 ([M – Ph – C_2H_5]$^{+\cdot}$, 100%).

IR (thin film): $\tilde{\nu}$ = 2926 (m), 1741 (s), 1603 (w), 1493 (m), 1245 (s), 1051 (m), 907 (m), 767 (m), 703 (s) cm^{-1}.

6.2.8.4. *rac*-(1*R*,5*R*,7*S*)-7-Acetoxy-3-hexyl-2-phenyl-1-(phenylvinyl)-bicyclo[3.3.0]oct-2-ene (2.73-*endo*)



Alcohol **2.72-*endo*** (0.018 g, 0.046 mmol) was dissolved in the mixture of anhydrous pyridine (0.10 mL, 1.23 mmol) and freshly distilled acetic anhydride (0.33 mL, 3.46 mmol). After stirring for 10 min at RT, DMAP (0.0033 g, 0.027 mmol) was added and the stirring was continued at RT for 17 h. Then H_2O (5 mL) was added to the reaction mixture and the whole mixture was poured onto Et_2O (15 mL). The organic phase was separated and washed with HCl (15 mL of a 1.0 M solution), a saturated aqueous solution of $NaHCO_3$ (15 mL) and brine (2 × 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a pale yellow oil. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with 5% of EtOAc in hexanes as the eluent gave the title compound (*endo* diastereoisomer) as a colourless oil in yield of 0.016 g (79%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.340 – 7.248 (10H, m, H^{Ar}), 5.102 (1H, d, *J* = 1.4 Hz, H^{10}), 5.083 (1H, tt, *J* = 6.2, 5.1 Hz, H^7), 5.045 (1H, d, *J* = 1.4 Hz, H^{10}), 2.550 (1H, tdd, *J* = 8.5, 6.5, 1.9 Hz, H^5), 2.363 (1H, ddd, *J* = 13.5, 9.3, 6.2 Hz, H^{6b}), 2.314 (1H, dd, *J* = 16.8, 8.3 Hz, H^{4b}), 2.261 (1H, ddd, *J* = 13.9, 6.2, 0.5 Hz, H^{8b}), 2.171 – 2.048 (3H, m, $2H^{11}$ + H^{4a}), 1.998 (3H, s, H^{18}), 1.904 (1H, ddd, *J* = 13.9, 5.0, 1.1 Hz, H^{8a}), 1.568 (1H, dddd, *J* = 13.5, 6.5, 5.3, 1.2 Hz, H^{6a}), 1.423 – 1.339 (2H, m), 1.312 – 1.199 (6H, m), 0.883 (3H, t, *J* = 7.0 Hz, H^{16}).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 170.78 (C^{17}), 154.60 (C^{9}), 143.33 ($C^{2 \text{ or } 3}$), 140.49 ($C^{2 \text{ or } 3}$), 139.62 ($C^{i\text{-Ph}}$), 137.68 ($C^{i\text{-Ph}}$), 129.70 ($2CH^{o\text{- or } m\text{-Ph}}$), 128.10 ($2CH^{o\text{- or } m\text{-Ph}}$), 127.67 ($2CH^{o\text{- or } m\text{-Ph}}$), 127.60 ($2CH^{o\text{- or } m\text{-Ph}}$), 126.72 ($CH^{p\text{-Ph}}$), 126.47 ($CH^{p\text{-Ph}}$), 114.49 ($CH_2{}^{10}$), 76.37 ($CH^{7}$), 68.29 ($C^{1}$), 45.15 ($CH^{5}$), 42.42 ($CH_2$), 40.75 ($CH_2$), 40.65 ($CH_2$), 31.70 ($CH_2$), 30.02 ($CH_2$), 29.49 ($CH_2$), 27.84 ($CH_2$), 22.58 ($CH_2$), 21.36 ($CH_3{}^{18}$), 14.07 ($CH_3{}^{16}$).

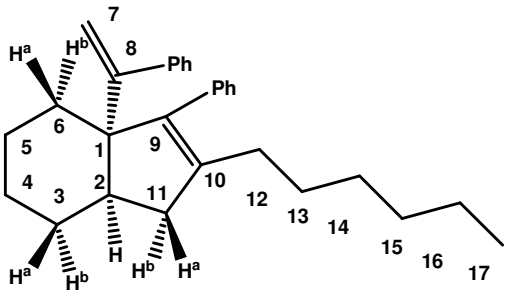
HRMS (ESI+): Found: $[M + Na]^+$, 451.2606. $[C_{30}H_{36}O_2Na]^+$ requires: 451.2608.

LRMS (EI): *m/z*: 428 ($[M]^{+\cdot}$, 8%), 368 ($[M – AcOH]^{+\cdot}$, 59%), 283 ($[M – AcOH – Hex]^{+\cdot}$, 30%), 265 ($[M – Ph – C_2H_5]^{+\cdot}$, 100%).

IR (thin film): $\tilde{\nu}$ **=** 2926 (m), 1735 (s), 1599 (w), 1501 (m), 1236 (s), 1017 (m), 907 (m), 775 (m), 703 (s) cm^{-1}.

6.2.9. Preparation of other bicyclic compounds

6.2.9.1. *rac*-(1*R*,5*R*)-3-Hexyl-2-phenyl-1-(phenylvinyl)-bicyclo[4.3.0]oct-2-ene (2.78)



General procedure A was used with 1-(oct-7-en-1-ynyl)benzene, 1,1-dibromoheptane and 1-ethynylbenzene as components, except that LiTMP [which was freshly prepared from 2,2,6,6-tetramethylpiperidine (0.19 mL, 1.1 mmol) in dry THF (1 mL) and *n*-BuLi (0.44 mL of a 2.5 M solution in hexanes, 1.1 mmol) at 0 °C over 15 min] was used instead of LDA. The carbenoid was generated *in situ* from 1,1-dibromoheptane (1.05 mmol) and LiTMP at –90 °C for 25 min (during which the reaction mixture was warmed to –80 °C), before dropwise addition of phenyl acetylide. Purification of the crude material by careful column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a pale yellow oil in yield of 0.101 g (26%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.352 – 7.224 (10H, m, H^{Ar}), 5.250 (1H, d, *J* = 1.6 Hz, H^7), 5.130 (1H, d, *J* = 1.6 Hz, H^7), 2.376 (1H, dt, *J* = 12.0, 6.3 Hz, H^2), 2.725 (1H, dd, *J* = 15.5, 7.0 Hz, $H^{11a \text{ or } b}$), 2.207 – 2.169 (2H, m, H^{12}), 2.129 (1H, dd, *J* = 15.5, 6.1 Hz, $H^{11a \text{ or } b}$), 2.010 (1H, ddd, *J* = 13.8, 7.8, 3.3 Hz, $H^{6a \text{ or } b}$), 1.610 (1H, ddd, *J* = 13.8, 8.5, 3.5 Hz, $H^{6a \text{ or } b}$), 1.525 – 1.236 (13H, m), 0.899 (3H, t, *J* = 7.0 Hz, H^{17}).

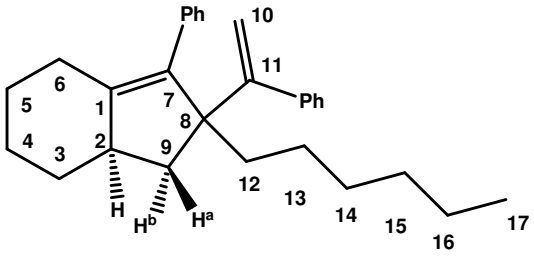
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 152.84 (C^8), 143.92 ($C^{9 \text{ or } 10 \text{ or i-Ph}}$), 142.08 ($C^{9 \text{ or } 10 \text{ or i-Ph}}$), 141.87 ($C^{9 \text{ or } 10 \text{ or i-Ph}}$), 137.84 ($C^{9 \text{ or } 10 \text{ or i-Ph}}$), 129.40 ($2CH^{o- \text{ or } m-Ph}$), 128.84 ($2CH^{o- \text{ or } m-Ph}$), 127.55 ($2CH^{o- \text{ or } m-Ph}$), 127.36 ($2CH^{o- \text{ or } m-Ph}$), 126.29 ($CH^{p-Ph}$), 126.13 ($CH^{p-Ph}$), 116.43 ($CH_2{}^7$), 58.89 ($C^1$), 40.84 ($CH^2$), 38.97 ($CH_2{}^{11}$), 31.70 ($CH_2$), 30.96 ($CH_2{}^6$), 29.96 ($CH_2{}^{12}$), 29.38 ($CH_2$), 28.11 ($CH_2$), 27.64 ($CH_2$), 22.63 ($CH_2$), 22.34 ($CH_2$), 21.43 ($CH_2$), 14.07 ($CH_3{}^{17}$).

HRMS (EI): Found: $[M]^+$, 384.2806. $C_{29}H_{36}$ requires: 384.2817.

LRMS (CI): *m/z*: 384 ($[M]^{+\cdot}$, 3%), 281 ([M – Styrene]$^{+\cdot}$, 100%), 197 ([M – Styrene – Hex]$^{+\cdot}$, 9%).

IR (thin film): $\tilde{\nu}$ **=** 2918 (s), 2853 (m), 1639 (m), 1527 (m), 1179 (w), 694 (s), 500 (s) cm^{-1}.

6.2.9.2. *rac*-(3a*R*)-2-Hexyl-2,3,3a,4,5,6,7-heptahydro-1-phenyl-2-(1-phenylvinyl)-2*H*-indene (2.79)



The product was obtained simultaneously with product **2.78**. Purification of the crude material by careful column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave a pure fraction of the title compound as a pale yellow oil in yield of 0.016 g (4%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.392 – 7.326 (4H, m, H^{Ar}), 7.294 – 7.246 (6H, m, H^{Ar}), 5.114 (1H, d, *J* = 1.6 Hz, H^{10}), 5.001 (1H, d, *J* = 1.6 Hz, H^{10}), 2.641 (1H, d, *J* = 14.3 Hz, H^{9a}), 2.074 (1H, dd, *J* = 13.1, 7.8 Hz, H^6), 1.881 – 1.783 (2H, m), 1.751 – 1.710 (1H, m), 1.661 – 1.571 (3H, m), 1.552 – 1.438 (2H, m), 1.365 – 1.083 (10H, m), 1.047 – 0.947 (1H, m), 0.845 (3H, t, *J* = 7.0 Hz, H^{17}).

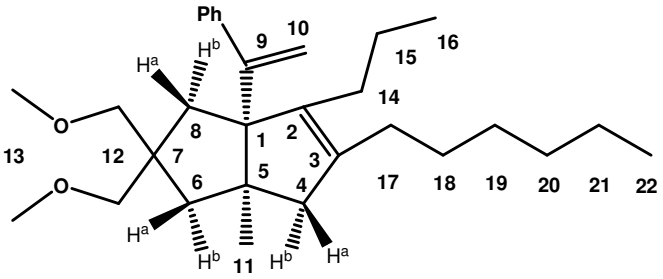
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 155.83 (C^{11}), 144.83 ($C^{1 \text{ or } 7}$), 143.90 ($C^{7 \text{ or } 1}$), 137.85 ($C^{i\text{-Ph}}$), 136.24 ($C^{i\text{-Ph}}$), 129.31 ($2CH^{o\text{- or } m\text{-Ph}}$), 128.82 ($2CH^{o\text{- or } m\text{-Ph}}$), 127.69 ($2CH^{o\text{- or } m\text{-Ph}}$), 127.14 ($2CH^{o\text{- or } m\text{-Ph}}$), 126.34 ($CH^{p\text{-Ph}}$), 126.21 ($CH^{p\text{-Ph}}$), 113.33 ($CH_2^{10}$), 59.11 ($C^8$), 44.77 ($CH^2$), 41.19 ($CH_2^6$), 36.27 ($CH_2$), 35.99 ($CH_2$), 31.73 ($CH_2$), 29.97 ($CH_2$), 27.32 ($CH_2^{12}$), 26.96 ($CH_2$), 25.99 ($CH_2$), 24.33 ($CH_2$), 22.56 ($CH_2$), 14.04 ($CH_3^{17}$).

HRMS (EI): Found: $[M]^+$, 384.2818. $C_{29}H_{36}$ requires: 384.2817.

LRMS (CI): *m/z*: 385 ($[M + H]^{+\cdot}$, 100 %), 281 ($[M – \text{Styrene}]^{+\cdot}$, 83 %).

IR (thin film): $\tilde{\nu}$ **=** 2930 (s), 2843 (m), 1482 (w), 1440 (w), 907 (w), 771 (w), 695 (s) cm^{-1}.

6.2.9.3. *rac*-(3a*R*,6a*R*)-5-Hexyl-1,2,3,3a,4,6a-hexahydro-2,2-bis(methoxymethyl)-3a-methyl-6a-(1-phenylvinyl)-6-propylpentalene (2.87)



General procedure A was used with 4,4-bis(methoxymethyl)-2-methyldec-1-en-6-yne, 1,1-dibromoheptane and 1-ethynylbenzene as components, except that LiTMP [freshly prepared from 2,2,6,6-tetramethylpiperidine (0.19 mL, 1.1 mmol) in dry THF (1 mL) and *n*-BuLi (0.44 mL of a 2.5 M solution in hexanes, 1.1 mmol) at 0 °C over 15 min] was used instead of LDA. The carbenoid was generated *in situ* from 1,1-dibromoheptane (1.05 mmol) and LiTMP at –90 °C for 25 min (during which the reaction mixture was warmed to –80 °C), before dropwise addition of phenyl acetylide. Subsequently the reaction mixture was allowed to warm to RT over 2 h before quench.

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with 5% of Et_2O in hexanes as the eluant gave the title compound as a pale yellow oil in yield of 0.110 g (25%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.343 – 7.320 (2H, m, $H^{o\text{-}Ph}$), 7.192 – 7.176 (2H, m, $H^{m\text{-}Ph}$), 7.112 (1H, tt, *J* = 7.3, 1.3 Hz, $H^{p\text{-}Ph}$), 5.252 (1H, d, *J* = 2.0 Hz, H^{10}), 5.124 (1H, d, *J* = 2.0 Hz, H^{10}), 3.353 (2H, s, H^{12}), 3.308 (1H, d, *J* = 8.3 Hz, H^{12}), 3.241 (3H, s, H^{13}), 3.163 (1H, d, *J* = 8.3 Hz, H^{12}), 3.120 (3H, s, H^{13}), 2.402 (1H, d, *J* = 14.3 Hz, H^{6}), 2.329 – 2.081 (6H, m), 1.978 (1H, d, *J* = 14.1 Hz, H^{8}), 1.956 (1H, d, *J* = 14.3 Hz, H^{6}), 1.859 – 1.688 (2H, m), 1.654 (1H, d, *J* = 14.1 Hz, H^{8}), 1.523 – 1.432 (2H, m), 1.413 – 1.339 (6H, m), 1.255 (3H, s, H^{11}), 1.020 (3H, t, *J* = 7.3 Hz, $H^{16 \text{ or } 22}$), 0.956 (3H, t, *J* = 6.8 Hz, $H^{16 \text{ or } 22}$).

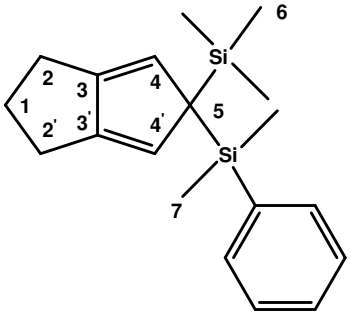
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 154.43 (C^{9}), 145.33 (C^{2}), 142.02 ($C^{i\text{-}Ph}$), 138.60 (C^{3}), 129.60 ($2CH^{o\text{-}Ph}$), 128.08 ($2CH^{m\text{-}Ph}$), 126.98 ($CH^{p\text{-}Ph}$), 118.14 ($CH_2{}^{10}$), 79.21 ($CH_2{}^{12}$), 77.02 ($CH_2{}^{12}$), 54.20 (C^{1}), 59.20 ($CH_3{}^{13}$), 59.09 ($CH_3{}^{13}$), 53.03 (C^{5}), 51.49 ($CH_2{}^{6}$), 50.58 ($CH_2{}^{4}$), 46.24 (C^{7}), 40.12 ($CH_2{}^{8}$), 32.56 (CH_2), 30.89 (CH_2), 30.48 (CH_2), 30.17 (CH_2), 28.40 (CH_2), 25.51 ($CH_3{}^{11}$), 24.27 (CH_2), 23.44 (CH_2), 15.90 ($CH_3{}^{16 \text{ or } 22}$), 14.71 ($CH_3{}^{16 \text{ or } 22}$).

HRMS (EI): Found: $[M]^+$, 438.3490. $C_{30}H_{46}O_2$ requires: 438.3498.

LRMS (CI): *m/z*: 438 ($[M]^+$, 15%), 406 ($[M - MeOH]^+$, 17%), 335 ($[M - Styrene]^+$, 77%), 303 ($[M - MeOH - Styrene]^+$, 100%).

IR (thin film): $\tilde{\nu}$ **=** 2949 (m), 2930 (s), 2862 (m), 1455 (m), 1376 (w), 1194 (m) 1104 (s), 964 (m), 911 (m), 771 (m), 703 (s) cm^{-1}.

6.2.9.4. *rac*-(1,2,3,5-Tetrahydro-5-(dimethyl(phenyl)silyl)-5-(trimethylsilyl)pentalene (2.92)



To a solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) dropwise over 3 minutes. After 25 min, a solution of (hept-6-en-1-ynyl)trimethylsilane (0.166 g, 1.0 mmol) in dry THF (3 mL) was added dropwise. After 30 min at –78 °C the reaction

mixture was allowed to warm to room temperature and stirred for 3 h. After this time, the reaction mixture (previously cooled to –94 °C) was transferred *via* cannula to freshly prepared carbenoid. The carbenoid was prepared from (dichloromethyl)dimethyl-(phenyl)silane (0.285 g, 1.3 mmol) in dry THF (2 mL) and *n*-BuLi (0.52 mL of a 2.5 M solution in hexanes, 2.0 mmol) for 5 min at –94 °C. The reaction mixture was stirred for further 7 h within which time was allowed to warm to -20 °C. After re-cooling to –78 °C, a dropwise addition of lithium phenylacetylide followed. [Lithium phenyl acetylide was freshly prepared from phenylacetylene (0.33 mL, 3.0 mmol) in dry THF (3 mL) and *n*-BuLi (1.2 mL of a 2.5 M solution in hexanes, 3.0 mmol) at –5 ^{o}C over 15 min]. The stirring was continued for 1 h during which the reaction mixture was allowed to warm to –50 °C before addition of MeOH (5 mL) and saturated aqueous solution of $NaHCO_3$ (6 mL). The whole mixture was allowed to warm to room temperature and was left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 75 mL). The combined organic phases were washed with H_2O (3 × 100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$, filtrated and concentrated *in vacuo* to give the crude product as a yellow oil. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as a colourless oil in yield of 0.165 g (53% of material in 91% GC purity).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.463 – 7.206 (5H, m, H^{Ar}), 5.947 (2H, s, $H^{4, 4'}$), 2.432 – 2.276 (4H, m, $H^{2, 2'}$), 2.173 – 2.009 (2H, m, H^{1}), 0.180 (6H, s, H^{7}), –0.281 (9H, s, H^{6}).

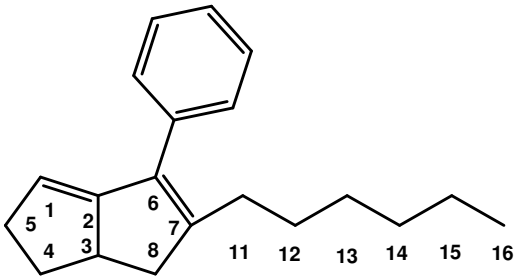
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 153.58 ($2C^{3, 3'}$), 138.76 ($C^{i\text{-}Ph}$), 134.10 ($2CH^{o\text{-}Ph}$), 128.69 ($CH^{p\text{-}Ph}$), 127.12 ($2CH^{m\text{-}Ph}$), 122.84 ($2CH^{4, 4'}$), 60.66 (C^{5}), 31.70 (CH_2^{1}), 25.71 ($2CH_2^{2, 2'}$), –0.97 ($3CH_3^{6}$), –2.62 ($2CH_3^{7}$).

HRMS (EI): Found: $[M]^+$, 312.1731. $C_{19}H_{28}Si_2$ requires: 312.1730.

LRMS (CI): *m/z*: 312 ($[M + H]^{+\cdot}$, 30%), 135 ($[SiMe_2Ph]^{+\cdot}$, 100%).

IR (thin film): $\tilde{\nu}$ **=** 2949 (w), 1429 (w), 1247 (s), 1111 (w), 968 (s), 869 (m), 828 (s), 775 (s), 733 (s), 699 (s) cm^{-1}.

6.2.9.5. *rac*-2-Hexyl-3,3a,4,5-tetrahydro-1-phenylpentalene (2.96)



General procedure A was used with TBDMS protected 7-phenylhept-1-en-6-yn-5-ol, 1,1-dibromoheptane and 1-ethynyl-4-methoxybenzene as components. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave a mixture of three compounds: **2.96**, and *rac*-((3a*R*,4*S*,6a*R*)-2-hexyl-1,3a,4,5,6,6a-hexahydro-3-phenylpentalen-4-yloxy)(*tert*-butyl)dimethylsilane **2.99** and *rac*-((3a*S*,4*S*,6a*R*)-2-hexyl-1,3a,4,5,6,6a-hexahydro-3-phenyl-3a-(1-phenylvinyl)-pentalen-4-yloxy)(*tert*-butyl)dimethylsilane **2.100** as a pale yellow oil, 0.264 g. Further careful purification of the material by column chromatography gave the title compound as a colourless oil in yield of 0.056 (21%); however, the yield of this compound estimated by GC in the crude reaction mixture was 33%.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.324 – 7.178 (5H, m, H^{Ar}), 5.183 (1H, q, *J* = 3.0 Hz, H^1), 3.094 (1H, tddd, *J* = 12.9, 6.6, 3.0, 1.5 Hz, H^3), 2.631 (1H, m, H^5), 2.518 (1H, m, H^5), 2.486 (1H, dd, *J* = 15.8, 8.0 Hz, H^8), 2.249 (2H, t, *J* = 8.0 Hz, H^{11}), 2.135 – 2.062 (2H, m, H^{4+8}), 1.499 – 1.382 (3H, m, H^{4+12}), 1.268 – 1.135 (6H, m), 0.812 (3H, t, *J* = 7.0 Hz, H^{16}).

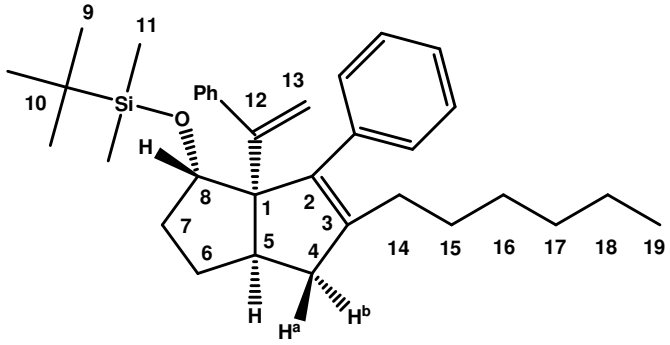
^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 158.99 (C^7), 152.74 (C^2), 136.40 ($C^{i\text{-}Ph}$), 133.73 (C^6), 128.52 ($2CH^{o\text{-}Ph}$), 128.08 ($2CH^{m\text{-}Ph}$), 126.60 ($CH^{p\text{-}Ph}$), 111.90 (CH^1), 49.73 (CH^3), 39.63 ($CH_2{}^8$), 37.56 ($CH_2{}^5$), 32.84 ($CH_2{}^4$), 31.67 (CH_2), 30.33 ($CH_2{}^{11}$), 29.35 (CH_2), 28.22 (CH_2), 22.59 (CH_2), 14.06 ($CH_3{}^{16}$).

HRMS (EI): Found: $[M]^+$, 266.2033. $C_{20}H_{26}$ requires: 266.2034.

LRMS (CI): *m/z*: 267 ($[M + H]^{+\cdot}$, 100%), 181 ($[M – Hex]^{+\cdot}$, 30%).

IR (thin film): $\tilde{\nu}$ **=** 2926 (s), 2854 (m), 2831 (m), 1603 (w), 1489 (m), 1463 (m), 1433 (m), 797 (m), 767 (m), 699 (s) cm^{-1}.

6.2.9.6. *rac*-((3a*S*,*4S*,*6aR*)-2-Hexyl-1,3a,4,5,6,6a-hexahydro-3-phenyl-3a-(1-phenylvinyl)pentalen-4-yloxy)(*tert*-butyl)dimethylsilane (2.100)



The title compound was obtained simultaneously with compounds **2.96** and **2.99**. Careful purification of the material by column chromatography allowed for partial separation to give a pure fraction of the title compound as a pale yellow oil in yield of 0.011 g (2%); however, the yield of this compound estimated by GC in the crude reaction mixture was 12%.

^{1}H NMR (400 MHz, BENZENE-D$_6$): δ (ppm) = 5.522 (2H, dd, *J* = 8.5, 1.5 Hz, $H^{o\text{-}Ph}$), 5.460 (2H, dd, *J* = 8.5, 2.0 Hz, $H^{o\text{-}Ph}$), 7.254 – 7.083 (10H, m, $H^{m\text{-} + p\text{-}Ph}$), 5.586 (1H, d, *J* = 1.9 Hz, H^{13}), 5.270 (1H, d, *J* = 1.9 Hz, H^{13}), 4.581 (1H, dd, *J* = 8.9, 5.4 Hz, H^{8}), 2.476 (1H, tt, *J* = 8.8, 2.8 Hz, H^{5}), 2.320 (1H, dd, *J* = 16.6, 8.5 Hz, H^{4b}), 2.192 (1H, dt, *J* = 22.0, 7.8 Hz, H^{14}), 2.138 (1H, dt, *J* = 22.0, 8.0 Hz, H^{14}), 1.974 (1H, dd, *J* = 16.6, 2.0 Hz, H^{4a}), 1.879 – 1.755 (2H, m, H^{7}), 1.696 (1H, tdd, *J* = 12.7, 10.3, 7.0 Hz, H^{6}), 1.434 – 1.360 (2H, m, H^{15}), 1.300 (1H, ddt, *J* = 12.7, 6.5, 3.0 Hz, H^{6}), 1.245 – 1.167 (6H, m), 0.866 (3H, t, *J* = 7.3 Hz, H^{19}), 0.772 (9H, s, H^{9}), –0.072 (3H, s, H^{11}), –0.076 (3H, s, H^{11})

^{13}C NMR (100.5 MHz, BENZENE-D$_6$): δ (ppm) = 155.43 (C^{12}), 145.95 (C^{2}), 145.00 ($C^{i\text{-}Ph}$), 140.72 ($C^{i\text{-}Ph}$), 137.48 (C^{3}), 130.56 ($2CH^{o\text{- or }m\text{-}Ph}$), 129.00 ($2CH^{o\text{- or }m\text{-}Ph}$), 128.68 ($CH^{o\text{- or }m\text{-}Ph}$), 128.36 ($2CH^{o\text{- or }m\text{-}Ph}$), 128.06 ($CH^{o\text{- or }m\text{-}Ph}$), 127.39 ($CH^{p\text{-}Ph}$), 126.44 ($CH^{p\text{-}Ph}$), 116.12 ($CH_2{}^{13}$), 80.65 ($CH^{8}$), 72.83 ($C^{1}$), 45.40 ($CH_2{}^{4}$), 45.05 ($CH^{5}$), 35.27 ($CH_2{}^{7}$), 32.42 ($CH_2$), 30.69 ($CH_2$), 30.60 ($CH_2$), 30.31 ($CH_2$), 28.84 ($CH_2$), 26.64 ($3CH_3{}^{9}$), 23.37 ($CH_2$), 18.61 ($C^{10}$), 14.67 ($CH_3{}^{19}$), –3.62 ($CH_3{}^{11}$), –4.21 ($CH_3{}^{11}$).

HRMS (EI): Found: $[M]^+$, 500.3465. $C_{34}H_{48}OSi$ requires: 500.3474.

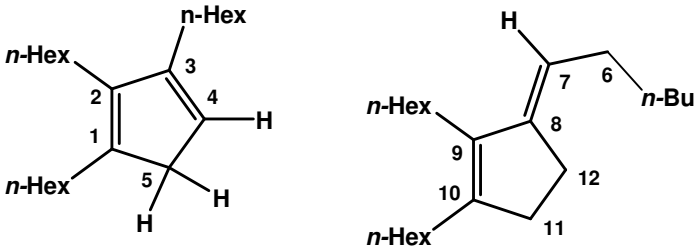
LRMS (CI): *m/z*: 369 ($[M - TBDMSO]^+$, 100%).

LRMS (ESI+): *m/z*: 539 ($[M + K]^+$, 2%), 168 (100%).

IR (thin film): $\tilde{\nu}$ **=** 2949 (m), 2930 (m), 2850 (m), 1599 (w), 1467 (w), 1255 (m), 1115 (m), 828 (s), 775 (s), 703 (s) cm^{-1}.

6.2.10. Preparation of monocyclic compounds

6.2.10.1. 1,2,3-Trihexylcyclopenta-1,3-diene (2.103a) and 1,2-dihexyl-3-hexylidene-cyclopent-1-ene (2.104a)



GC ratio, 64 : 36

To a solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added EtMgBr (2.0 mL of a 1.0 M solution in THF, 2.0 mmol) dropwise over 3 minutes. After 45 min, a solution of tetradec-7-yne (0.194 g, 1.0 mmol) in dry THF (3 mL) was added dropwise. After 30 min at –78 °C the reaction mixture was allowed to warm to +5 °C over a period of 3 h.

After cooling the reaction mixture to –78 °C, a solution of 1,1-dibromoheptane (0.271 g, 1.05 mmol) in dry THF (1 mL) was added, followed by dropwise addition of LDA (0.61 mL of a 1.8 M solution, 1.1 mmol). The reaction mixture was stirred at –78 °C for 15 min before dropwise addition of the lithium phenylacetylide, [prepared from phenylacetylene (0.33 ml, 3.0 mmol) in dry THF (3 mL) and *n*-BuLi (1.2 mL of a 2.5 M solution in hexanes, 3.0 mmol) at –5 °C over 15 min]. The stirring was continued for 2 h during which the reaction mixture was allowed to warm to 0 °C before addition of MeOH (10 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL). The whole mixture was allowed to warm to room temperature and left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 75 mL). The combined organic phases were washed with H_2O (3 × 100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude products as yellow oils.

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluant gave the title products as an inseparable mixture of two compounds **2.103a** and **2.104a** in GC ratio 64 : 36, respectively in combined yield of 0.204 g (64%, colourless oil).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.849 (1H, t, *J* = 1.5 Hz, H^4), 5.134 (1H, tt, *J* = 7.3, 2.3 Hz, H^7), 2.804 (2H, d, *J* = 1.5 Hz, H^5), 2.458 – 2.427 (2H, m, H^{12}), 2.380 – 2.360 (2H, m, H^{11}), 2.444 – 2.117 (10H, m), 2.380 – 2.360 (2H, q, *J* = 7.3 Hz, H^6),1.616 – 1.314 (46H, m), 0.913 – 0.899 (18H, m, $6CH_3$).

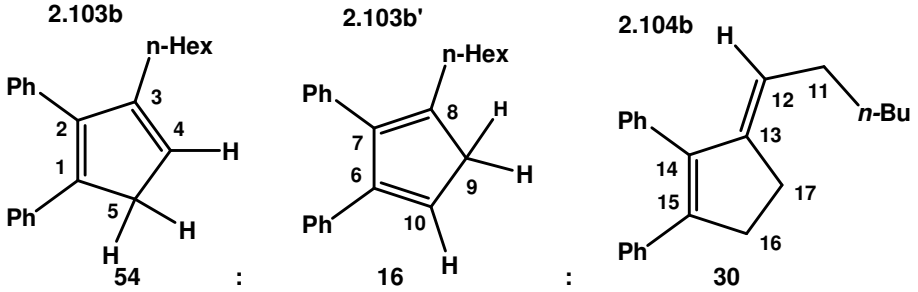
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 148.62 (C^3), 147.51 (C^{10}), 144.95 (C^8), 142.04 (C^1), 140.12 (C^2), 137.56 (C^9), 122.28 (CH^4), 114.84 (CH^7), 41.42 (CH_2^5), 32.83 (CH_2^{11}), 31.87 (CH_2^{major}), 31.84 ($2CH_2^{major + minor}$), 31.78 (CH_2^{major}), 31.72 (CH_2^{minor}), 30.59 (CH_2^{major}), 30.31 (CH_2^{major}), 29.74 (CH_2^{minor}), 29.66 (CH_2^{minor}), 29.63 (CH_2^{major}), 29.51 ($3CH_2^{major + minor}$), 29.45 (CH_2^6), 29.25 (CH_2^{minor}), 28.92 (CH_2^{minor}), 28.57 (CH_2^{major}), 28.47 ($3CH_2^{major + minor}$), 28.16 (CH_2^{minor}), 26.18 (CH_2^{12}), 25.64 (CH_2^{major}), 24.86 (CH_2^{minor}), 22.68 ($6CH_2^{major + minor}$), 14.10 ($6Me^{major + minor}$).

HRMS (EI): Found: $[M]^+$, 318.3286. $C_{23}H_{42}$ requires: 318.3286.

LRMS (CI): *m/z*: 322 ($[M + 4H]^+$, 100%), 289 ($[M – Et]^+$, 100%).

IR (thin film): $\tilde{\nu}$ = 2952 (m), 2926 (s), 2847 (s), 1463 (m), 1377 (m), 722 (m) cm^{-1}.

6.2.10.2. 1-(3-Hexyl-2-phenylcyclopenta-1,3-dienyl)benzene (2.103b), 1-(4-hexyl-5-phenylcyclopenta-1,4-dienyl)benzene (2.103b') and 1-((3*E*)-3-hexylidene-2-phenylcyclopent-1-enyl)benzene (2.104b)



To a solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added EtMgBr (2.0 mL of a 1.0 M solution in THF, 2.0 mmol) dropwise over 3 minutes. After 45 min, a solution of 1,2-diphenylethyne (0.178 g, 1.0 mmol) in dry THF (3 mL) was added dropwise. After 30 min at –78 °C the reaction mixture was allowed to warm to +6 °C over a period of 8 h. After cooling the reaction mixture to –78 °C, a solution of 1,1-dibromoheptane (0.271 g, 1.05 mmol) in dry THF (1 mL) was added, followed by dropwise addition of LDA (0.58 mL of a 1.8 M solution, 1.05 mmol). The reaction mixture was stirred at –78 °C for 15 min before dropwise addition of the lithium phenylacetylide, [prepared from phenylacetylene (0.33 ml, 3.0 mmol) in dry

THF (3 mL) and *n*-BuLi (1.2 mL of a 2.5 M solution in hexanes, 3.0 mmol) at –5 °C over 15 min]. The reaction mixture was allowed to warm to –15 °C before addition of MeOH (10 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL). The whole mixture was allowed to warm to room temperature and left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 75 mL). The combined organic phases were washed with H_2O (3 × 100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude products as yellow oils.

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluant gave the title products as an inseparable mixture of three compounds in GC ratio 54 : 30 : 16 in combined yield of 0.136 g (45%, pale yellow oil).

NMR characterysation does not contain complete data for compound 2.103b'.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.550 – 7.205 (30H, m, H^{Ar}), 6.534 (1H, t, *J* = 1.8 Hz, H^{10}), 6.298 (1H, quintet, *J* = 1.8 Hz, H^4), 5.233 (1H, tt, *J* = 7.4, 2.6 Hz, H^{12}), 3.608 (1H, d, *J* = 1.8 Hz, H^5), 3.598 (1H, d, *J* = 1.8 Hz, H^5), 3.241 (2H, d, *J* = 1.8 Hz, H^9), 3.164 – 3.131 (2H, m, H^{16}), 2.916 – 2.883 (2H, m, H^{17}), 2.860 – 2.783 (2H, m), 2.678 – 2.219 (10H, m), 2.013 – 1.938 (2H, m), 1.851 – 1.814 (1H, m), 1.724 – 1.336 (13H, m), 1.057 – 0.985 (9H, m, $6CH_3$).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 149.47 (C), 149.27 (C), 146.24 (C), 146.08 (C), 143.82 (C), 142.24 (C), 142.05 (C), 141.56 (C), 141.19 (C), 138.39 (C), 138.04 (C), 137.68 (C), 137.32 (C), 137.10 (C), 136.90 (C), 129.73 (CH), 129.62 (CH), 128.66 (CH), 128.47 (CH), 128.39 (CH), 128.32 (CH), 128.20 (CH), 127.98 (CH), 127.81 (CH), 127.74 (2CH), 127.61 (CH), 127.51 (CH), 127.36 (CH), 126.86 (CH), 126.79 (CH), 126.60 (CH), 126.48 (CH), 126.25 (CH), 125.94 (CH), 125.72 (CH), 125.63 (CH), 124.99 (CH), 121.17 (CH), 42.54 (CH_2), 42.29 (CH_2), 35.32 (CH_2), 34.02 (CH_2), 33.67 (CH_2), 31.72 (CH_2), 31.65 (CH_2), 30.62 (CH_2), 30.33 (CH_2), 29.57 (CH_2), 29.41 (CH_2), 29.34 (CH_2), 29.28 (CH_2), 29.13 (CH_2), 28.94 (CH_2), 28.78 (CH_2), 28.41 (CH_2), 28.28 (CH_2), 26.52 (CH_2), 22.65 (CH_2), 22.59 (CH_2), 22.54 (CH_2), 14.08 ($3CH_3$).

HRMS (EI): Found: $[M]^+$, 302.2040. $C_{23}H_{26}$ requires: 302.2035.

LRMS (CI): *m/z*: 304 ($[M + 2H]^+$, 68%), 289 ($[M – C_6H_{13} + 2H]^+$, 100%).

IR (thin film): $\tilde{\nu}$ **=** 2952 (m), 2922 (m), 2858 (m), 1486 (w), 1436 (w), 752 (s), 699 (s) cm^{-1}.

6.2.11. Procedure for crossover experiment

Method a: To a solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) dropwise. After 20 min, a solution of dec-1-en-6-yne (0.136 g, 1.0 mmol) in dry THF (3 mL) was added dropwise. After 30 min at –78 °C the reaction mixture was allowed to warm to RT and continued to stir for 2 h. After re-cooling the reaction mixture to –78 °C, a solution of the appropriate 1,1-dibromopentane (0.242 g, 1.05 mmol) in dry THF (1 mL) was added followed by dropwise addition of freshly prepared LiTMP [prepared from freshly distilled 2,2,6,6-tetramethylpiperidine (0.187 mL, 1.1 mmol) in dry THF (2 mL) and *n*-BuLi (0.44 mL of a 2.5 M solution in hexanes, 1.1 mmol) at 0 °C over 20 min]. The reaction mixture was stirred at –78 °C for 20 min before addition of previously prepared and cooled to –78 °C bis(phenylethynyl)zirconocene **2.18**.

Complex **2.18** was prepared by dropwise addition of lithium phenyl acetylide [generated from phenyl acetylene (0.22 mL, 2.0 mmol) and *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) at 0 °C over 15 min], to a stirred solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) at –78 °C, and the stirring was continued for 30 min at the same temperature before warming to RT and stirring for 5 h.

The whole reaction mixture was stirred at –78 °C for 5 min before first equivalent of lithium *p-tert*-butylphenyl acetylide **2.7a** [freshly prepared from *p-tert*-butylphenyl-ethynylbenzene (0.54 mL, 3.0 mmol) in dry THF (3 mL) and *n*-BuLi (1.2 mL of a 2.5 M solution in hexanes, 3.0 mmol) at –5 °C over 15 min] was added and the reaction mixture was stirred at the same temperature for 15 min. In the meantime, the reaction was sampled for GC analysis. After this time, the second equivalent of lithium *p-tert*-butylphenyl acetylide was added and the reaction mixture was stirred at –78 °C for 15 min. In the meantime, the reaction was sampled for GC analysis. The addition of the third equivalent of lithium *p-tert*-butylphenyl acetylide followed and the reaction mixture was stirred at the same temperature for 15 min. In the meantime, the reaction was sampled for GC analysis. The reaction mixture was then allowed to warm gradually to RT before addition of MeOH (10 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL). The whole mixture was allowed to warm to room temperature and left stirring for 16 h. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 75 mL). The combined organic phases were washed with H_2O (3 × 100 mL) and

brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a yellow oil.

Method b: Exactly as **method a** but bis(*p-tert*-butylphenylethynyl) zirconocene **2.18a** was used instead of **2.18** and PhCCLi **2.7** instead of *p-t*-BuPhCCLi **2.7a**.

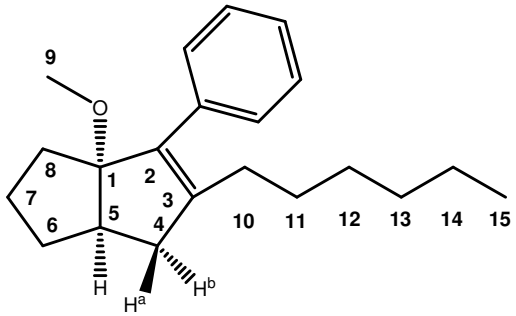
Method c: Exactly as **method a** but the *p-tert*-butylphenyl acetylide **2.7a** (3.0 eq) was added all at once at –78 °C to the reaction mixture. The stirring was continued for 30 min at the dame temperature before quenching.

6.2.12. Preparation of compounds 2.107a-j

General procedure C: To a stirred solution of (2*S*,3a*R*)-2-hexyl-2,3,3a,4,5,6-hexahydro-1-phenylpentalen-2-ol **2.106** (prepared as shown in Scheme 2.12) (142 mg, 0.50 mmol) in dry THF (4 ml) at RT was added ROH (5.0 mmol) followed by addition of a solution of (+)-camphorsulfonic acid (11.6 mg, 0.050 mmol) in dry THF (1 ml). The stirring was continued at the same temperature for 3.5 h after which the reaction mixture was poured onto a saturated aqueous solution of $NaHCO_3$ (100 mL), the products extracted with Et_2O (3 × 75 mL).

The combined organic phases were washed with H_2O (3 × 100 mL) and brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give the crude products as yellow oils.

6.2.12.1. *rac*-(1*S*,5*R*)-3-Hexyl-1-methoxy-2-phenyl-bicyclo[3.3.0]oct-2-ene (2.107a)



General procedure C was used with ROH = MeOH. Purification of the crude material by column chromatography on Al_2O_3 (basic, grade III) with 2.5% Et_2O in petroleum ether as the eluent gave the title compound as a yellow oil in yield of 0.112 g (75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.277 – 7.148 (5H, m, H^{Ar}), 3.160 (3H, s, H^9), 2.672 (1H, dd, *J* = 17.3, 8.5 Hz, H^{4b}), 2.416 (1H, tdd, *J* = 8.3, 6.0, 1.8 Hz, H^5), 2.186 – 2.070 (2H, m, H^{10}), 2.019 (1H, ddd, *J* = 12.3, 6.0, 2.5 Hz, H^6), 1.978 (1H, dd, *J* = 17.3, 1.8 Hz, H^{4a}), 1.644 – 1.504 (3H, m), 1.467 – 1.314 (3H, m), 1.243 – 1.097 (7H, m), 0.776 (3H, t, *J* = 6.9 Hz, H^{15}).

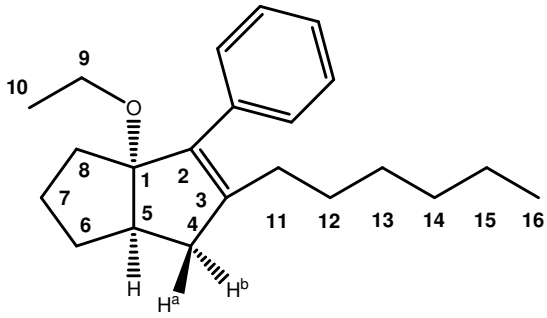
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 145.38 ($C^{i\text{-}Ph}$), 136.92 ($C^{2 \text{ or } 3}$), 135.15 ($C^{2 \text{ or } 3}$), 128.98 ($2CH^{o\text{- or } m\text{-}Ph}$), 127.93 ($2CH^{o\text{- or } m\text{-}Ph}$), 126.45 ($CH^{p\text{-}Ph}$), 103.77 ($C^1$), 50.82 ($CH_3{}^9$), 42.40 ($CH^5$), 41.80 ($CH_2{}^4$), 37.63 ($CH_2$), 35.63 ($CH_2$), 31.61 ($CH_2$), 29.69 ($CH_2$), 29.22 ($CH_2$), 28.06 ($CH_2$), 25.36 ($CH_2$), 22.58 ($CH_2$), 14.03 ($CH_3{}^{15}$).

HRMS (EI): Found: $[M]^+$, 298.2284. $C_{21}H_{30}O$ requires: 298.2297.

LRMS (CI): *m/z*: 266 ($[M - MeOH]^+$, 74%), 195 ($[M - MeOH - C_5H_{12}]^+$, 100%).

IR (thin film): $\tilde{\nu}$ **=** 2940 (s), 2864 (m), 1493 (w), 1461 (w), 1061 (s), 770 (s), 700 (s) cm^{-1}.

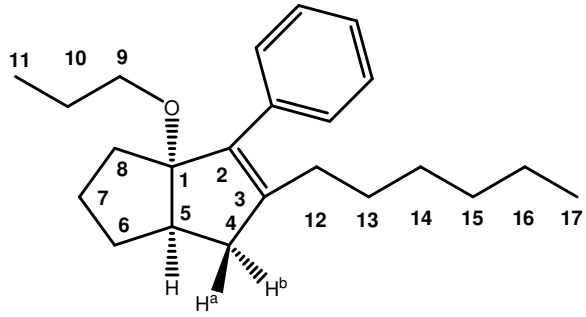
6.2.12.2. *rac*-(1*S*,5*R*)-1-Ethoxy-3-hexyl-2-phenyl-bicyclo[3.3.0]oct-2-ene (2.107b)



General procedure C was used with ROH = EtOH. Purification of the crude material by column chromatography on Al_2O_3 (basic, grade III) with 2.5% Et_2O in petroleum ether as the eluent gave the title compound as a yellow oil in yield of 0.108 g (69%).

Spectral data were consistent with those reported previously.[237]

6.2.12.3. *rac*-(1*S*,5*R*)-3-Hexyl-2-phenyl-1-propoxy-bicyclo[3.3.0]oct-2-ene (2.107c)



General procedure C was used with ROH = PrOH. Purification of the crude material by column chromatography on Al_2O_3 (basic, grade III) with 2% Et_2O in petroleum ether as the eluent gave the title compound as a yellow oil in yield of 0.115 g (71%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.356 – 7.225 (5H, m, H^{Ar}), 3.394 (1H, dt, *J* = 9.0, 7.0 Hz, H^9), 3.202 (1H, dt, *J* = 9.0, 7.0 Hz, H^9), 2.755 (1H, dd, *J* = 17.3, 8.3 Hz, H^{4b}), 2.490 (1H, tdd, *J* = 8.3, 5.8, 2.0 Hz, H^5), 2.239 – 2.199 (2H, m, H^{12}), 2.346 (1H, m, H^6), 2.060 (1H, dd, *J* = 17.3, 2.0 Hz, H^{4a}), 1.762 – 1.580 (5H, m), 1.532 – 1.405 (3H, m), 1.326 – 1.207 (7H, m), 0.944 (3H, t, *J* = 7.4 Hz, $H^{11 \text{ or } 17}$), 0.868 (3H, t, *J* = 7.0 Hz, $H^{11 \text{ or } 17}$).

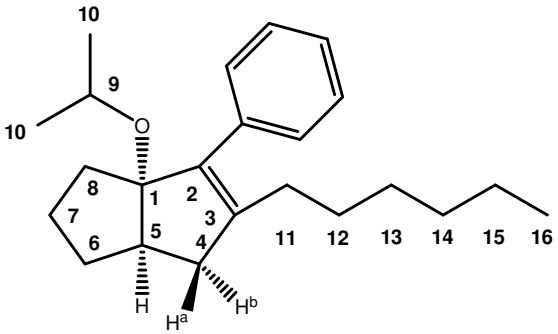
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 144.73 ($C^{i\text{-}Ph}$), 137.06 ($C^{2 \text{ or } 3}$), 135.92 ($C^{2 \text{ or } 3}$), 129.00 ($2CH^{o\text{- or } m\text{-}Ph}$), 127.86 ($2CH^{o\text{- or } m\text{-}Ph}$), 126.35 ($CH^{p\text{-}Ph}$), 103.08 ($C^1$), 64.84 ($CH_3{}^9$), 42.89 ($CH^5$), 41.93 ($CH_2{}^4$), 37.64 ($CH_2$), 35.60 ($CH_2$), 31.63 ($CH_2$), 29.72 ($CH_2$), 29.22 ($CH_2$), 28.02 ($CH_2$), 25.26 ($CH_2$), 23.54 ($CH_2$), 22.61 ($CH_2$), 14.04 ($CH_3{}^{11 \text{ or } 17}$), 10.87 ($CH_3{}^{11 \text{ or } 17}$).

HRMS (EI): Found: $[M]^+$, 326.2600. $C_{23}H_{34}O$ requires: 326.2610.

LRMS (CI): *m/z*: 267 ($[M - OPr]^+$, 100%), 195 ($[M - PrOH - C_5H_{12}]^+$, 81%).

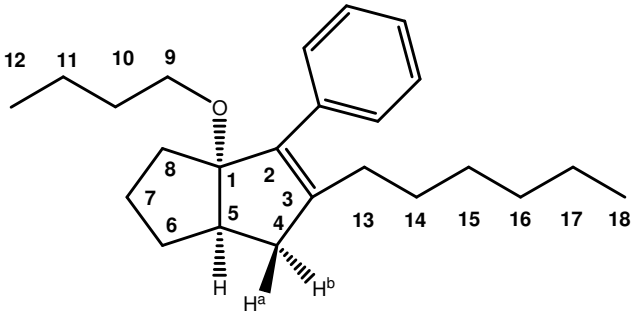
IR (thin film): $\tilde{\nu}$ **=** 2918 (s), 2859 (m), 1450 (w), 1083 (s), 770 (m), 694 (s) cm^{-1}.

6.2.12.4. *rac*-(1*S*,5*R*)-3-Hexyl-1-isopropoxy-2-phenyl-bicyclo[3.3.0]oct-2-ene (2.107d)



General procedure C was used with ROH = *i*-PrOH. Purification of the crude material by column chromatography on Al_2O_3 (basic, grade III) with 1% Et_2O in petroleum ether as the eluent gave the title compound as a yellow oil in yield of 0.011 g (7%).
Spectral data were consistent with those reported previously.[237]

6.2.12.5. *rac*-(1*S*,5*R*)-1-Butoxy-3-hexyl-2-phenyl-bicyclo[3.3.0]oct-2-ene (2.107e)



General procedure C was used with ROH = BuOH. Purification of the crude material by column chromatography on Al_2O_3 (basic, grade III) with 1% Et_2O in petroleum ether as the eluaent gave the title compound as a yellow oil in yield of 0.116 g (68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.327 – 7.195 (5H, m, H^{Ar}), 3.401 (1H, ddd, *J* = 9.0, 7.2, 6.2 Hz, H^9), 3.216 (1H, dt, *J* = 9.0, 7.0 Hz, H^9), 2.724 (1H, dd, *J* = 17.3, 8.3 Hz, H^{4b}), 2.454 (1H, tdd, *J* = 8.3, 5.8, 2.0 Hz, H^5), 2.211 – 2.168 (2H, m, H^{13}), 2.066 (1H, m, H^6), 2.028 (1H, dd, *J* = 17.3, 1.3 Hz, H^{4a}), 1.726 – 1.532 (5H, m), 1.479 – 1.317 (5H, m), 1.293 – 1.170 (7H, m), 0.907 (3H, t, *J* = 7.3 Hz, $H^{12 \text{ or } 18}$), 0.837 (3H, t, *J* = 6.9 Hz, $H^{12 \text{ or } 18}$).
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 144.70 ($C^{i\text{-}Ph}$), 137.07 ($C^{2 \text{ or } 3}$), 135.93 ($C^{2 \text{ or } 3}$), 128.99 ($2CH^{o\text{- or } m\text{-}Ph}$), 127.86 ($2CH^{o\text{- or } m\text{-}Ph}$), 126.34 ($CH^{p\text{-}Ph}$), 103.08 ($C^1$), 62.91

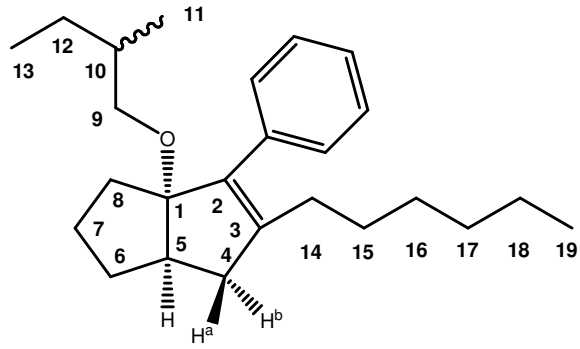
(CH_3^9), 42.91 (CH^5), 41.94 (CH_2^4), 37.64 (CH_2), 35.60 (CH_2), 32.53 (CH_2), 31.63 (CH_2), 29.72 (CH_2), 29.21 (CH_2), 28.02 (CH_2), 25.26 (CH_2), 22.60 (CH_2), 19.64 (CH_2), 14.08 ($CH_3^{12 \text{ or } 18}$), 14.04 ($CH_3^{12 \text{ or } 18}$).

HRMS (EI): Found: $[M]^+$, 340.2767. $C_{24}H_{36}O$ requires: 340.2766.

LRMS (CI): *m/z*: 266 ($[M - BuOH]^+$, 75%), 195 ($[M - BuOH - C_5H_{12}]^+$, 100%).

IR (thin film): $\tilde{\nu}$ = 2934 (s), 2853 (s), 1471 (m), 1083 (s), 764 (m), 710 (s) cm^{-1}.

6.2.12.6. *rac*-(1*S*,5*R*)-3-Hexyl-1-(2-methylbutoxy)-2-phenyl-bicyclo[3.3.0]oct-2-ene (2.107f)



General procedure C was used with ROH = 2-Me-BuOH. Purification of the crude material by column chromatography on Al_2O_3 (basic, grade III) with 0.5% Et_2O in petroleum ether as the eluent gave the title compound as a pale yellow oil in yield of 0.114 g (64%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.352 – 7.298 (4H, m, $H^{o- + m-Ph}$), 7.262 – 7.219 (1H, m, H^{p-Ph}), 3.327 (0.5H, dd, *J* = 8.9, 5.4 Hz, H^9), 3.215 (0.5H, dd, *J* = 8.8, 6.3 Hz, H^9), 3.058 (0.5H, dd, *J* = 9.0, 6.8 Hz, H^9), 2.958 (0.5H, dd, *J* = 8.9, 7.4 Hz, H^9), 2.748 (1H, dd, *J* = 17.2, 8.4 Hz, H^{4b}), 2.455 (1H, tdd, *J* = 8.6, 6.3, 1.8 Hz, H^5), 2.286 – 2.172 (2H, m, H^{14}), 2.086 (1H, m), 2.051 (1H, dd, *J* = 17.2, 1.3 Hz, H^{4a}), 1.734 (1H, m), 1.671 – 1.403 (7H, m), 1.312 – 1.205 (7H, m), 1.137 (1H, m), 0.945 (1.5H, d, *J* = 6.5 Hz, H^{11}), 0.906 (1.5H, t, *J* = 7.4 Hz, H^{13}), 0.904 (1.5H, d, *J* = 6.5 Hz, H^{11}), 0.900 (1.5H, 7, *J* = 7.4 Hz, H^{13}), 0.864 (3H, t, *J* = 7.0 Hz, H^{19}).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 144.46 (C^{i-Ph}), 137.12 ($C^{2 \text{ or } 3}$), 136.14 ($C^{2 \text{ or } 3}$), 129.03 ($2CH^{o- \text{ or } m-Ph}$), 127.82 ($2CH^{o- \text{ or } m-Ph}$), 126.30 ($CH^{p-Ph}$), 102.97 ($C^1$), 102.94 ($C^1$), 68.49 ($CH_3^9$), 68.47 ($CH_3^9$), 43.09 ($CH^5$), 43.06 ($CH^5$), 41.92 ($CH_2^4$), 37.61 ($CH_2$), 37.59 ($CH_2$), 35.57 ($CH^{10}$), 35.55 ($CH_2$), 35.37 ($CH^{10}$), 31.65 ($CH_2$), 29.73 ($CH_2$), 29.18

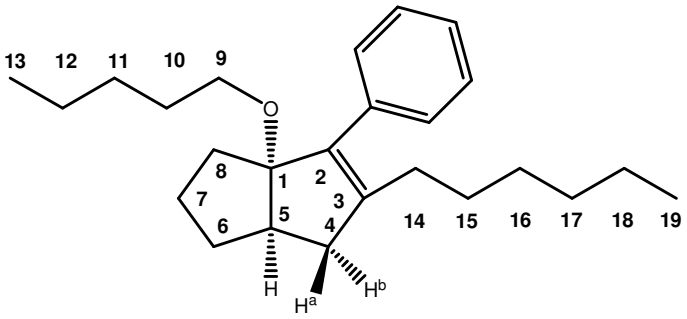
(CH_2), 27.98 (CH_2^{14}), 26.61 (CH_2), 26.57 (CH_2), 25.34 (CH_2), 22.61 (CH_2), 17.16 (CH_3^{11}), 16.74 (CH_3^{11}), 14.04 (CH_3^{19}), 11.55 (CH_3^{13}), 11.34 (CH_3^{13}).

HRMS (ESI+): Found: $[M + Na]^+$, 377.2808. $[C_{25}H_{38}NaO]^+$ requires: 377.2815.

LRMS (CI): *m/z*: 267 ($[M – 2\text{-Me-BuOH} + H]^+$, 75%), 195 ($[M – 2\text{-Me-BuOH} – C_5H_{12}]^+$, 100%).

IR (thin film): $\tilde{\nu}$ **=** 2961 (s), 2924 (s), 2853 (s), 1455 (w), 1077 (s), 764 (m), 700 (s) cm^{-1}.

6.2.12.7. *rac*-(1*S*,5*R*)-3-Hexyl-1-pentyloxy-2-phenyl-bicyclo[3.3.0]oct-2-ene (2.107g)



General procedure C was used with ROH = PentOH. Purification of the crude material by column chromatography on Al_2O_3 (basic, grade III) with 0.5% Et_2O in petroleum ether as the eluent gave the title compound as a yellow oil in yield of 0.110 g (62%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.328 – 7.196 (5H, m, H^{Ar}), 3.395 (1H, ddd, *J* = 8.9, 7.3, 6.3 Hz, H^9), 3.208 (1H, dt, *J* = 8.9, 7.1 Hz, H^9), 2.723 (1H, dd, *J* = 17.1, 8.3 Hz, H^{4b}), 2.455 (1H, tdd, *J* = 8.3, 5.8, 1.8 Hz, H^5), 2.212 – 2.169 (2H, m, H^{14}), 2.068 (1H, m, H^6), 2.027 (1H, dd, *J* = 17.1, 1.5 Hz, H^{4a}), 1.727 – 1.562 (5H, m), 1.492 – 1.373 (3H, m), 1.354 – 1.179 (11H, m), 0.887 (3H, t, *J* = 6.8 Hz, $H^{13 \text{ or } 19}$), 0.839 (3H, t, *J* = 6.8 Hz, $H^{13 \text{ or } 19}$).

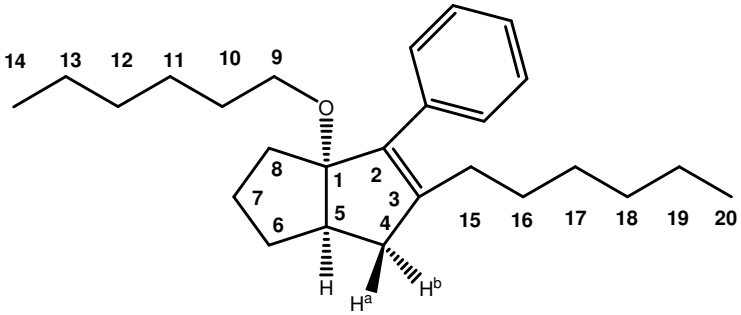
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 144.71 ($C^{i\text{-}Ph}$), 137.07 ($C^{2 \text{ or } 3}$), 135.93 ($C^{2 \text{ or } 3}$), 129.00 ($2CH^{o\text{- or } m\text{-}Ph}$), 127.86 ($2CH^{o\text{- or } m\text{-}Ph}$), 126.34 ($CH^{p\text{-}Ph}$), 103.09 ($C^1$), 63.21 ($CH_3^9$), 42.89 ($CH^5$), 41.94 ($CH_2^4$), 37.65 ($CH_2$), 35.60 ($CH_2$), 31.64 ($CH_2$), 30.10 ($CH_2$), 29.72 ($CH_2$), 29.21 ($CH_2$), 28.63 ($CH_2$), 28.02 ($CH_2$), 25.26 ($CH_2$), 22.67 ($CH_2$), 22.60 ($CH_2$), 14.07 ($CH_3^{13 \text{ or } 19}$), 14.04 ($CH_3^{13 \text{ or } 19}$).

HRMS (ESI+): Found: $[M + Na]^+$, 377.2809. $[C_{25}H_{38}NaO]^+$ requires: 377.2815.

LRMS (CI): *m/z*: 266 ($[M – PentOH]^+$, 75%), 195 ($[M – PentOH – C_5H_{12}]^+$, 100%).

IR (thin film): $\tilde{\nu}$ = 2930 (s), 2853 (s), 1466 (m), 1083 (s), 759 (m), 707 (s) cm^{-1}.

6.2.12.8. *rac*-(1*S*,5*R*)-3-Hexyl-1-hexyloxy-2-phenyl-bicyclo[3.3.0]oct-2-ene (2.107h)



General procedure C was used with ROH = HexOH. Purification of the crude material by column chromatography on Al_2O_3 (basic, grade III) with 0.5% Et_2O in petroleum ether as the eluent gave the title compound as a pale yellow oil in yield of 0.119 g (65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.353 – 7.223 (5H, m, H^{Ar}), 3.418 (1H, ddd, *J* = 8.9, 7.3, 6.5 Hz, H^9), 3.233 (1H, dt, *J* = 8.9, 7.3 Hz, H^9), 2.750 (1H, dd, *J* = 17.2, 8.5 Hz, H^{4b}), 2.482 (1H, tdd, *J* = 8.3, 5.8, 1.8 Hz, H^5), 2.237 – 2.193 (2H, m, H^{15}), 2.093 (1H, m, H^6), 2.052 (1H, dd, *J* = 17.2, 1.3 Hz, H^{4a}), 1.752 – 1.577 (5H, m), 1.513 – 1.399 (3H, m), 1.387 – 1.205 (13H, m), 0.899 (3H, t, *J* = 6.5 Hz, $H^{14 \text{ or } 20}$), 0.864 (3H, t, *J* = 6.8 Hz, $H^{14 \text{ or } 20}$).

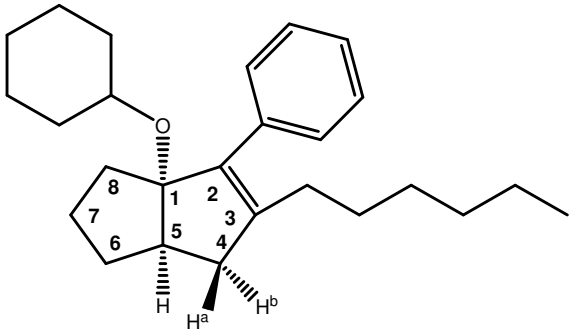
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 144.71 ($C^{i\text{-}Ph}$), 137.07 ($C^{2 \text{ or } 3}$), 135.93 ($C^{2 \text{ or } 3}$), 129.00 ($2CH^{o\text{- or } m\text{-}Ph}$), 127.86 ($2CH^{o\text{- or } m\text{-}Ph}$), 126.34 ($CH^{p\text{-}Ph}$), 103.09 ($C^1$), 63.24 ($CH_3{}^9$), 42.89 ($CH^5$), 41.94 ($CH_2{}^4$), 37.65 ($CH_2$), 35.59 ($CH_2$), 31.83 ($CH_2$), 31.63 ($CH_2$), 30.38 ($CH_2$), 29.72 ($CH_2$), 29.21 ($CH_2$), 28.02 ($CH_2$), 26.13 ($CH_2$), 25.26 ($CH_2$), 22.67 ($CH_2$), 22.60 ($CH_2$), 14.05 ($2CH_3{}^{14 + 20}$).

HRMS (EI): Found: $[M]^+$, 368.3064. $C_{26}H_{40}O$ requires: 368.3079.

LRMS (CI): *m/z*: 266 ($[M - HexOH]^+$, 60%), 195 ($[M - HexOH - C_5H_{12}]^+$, 100%).

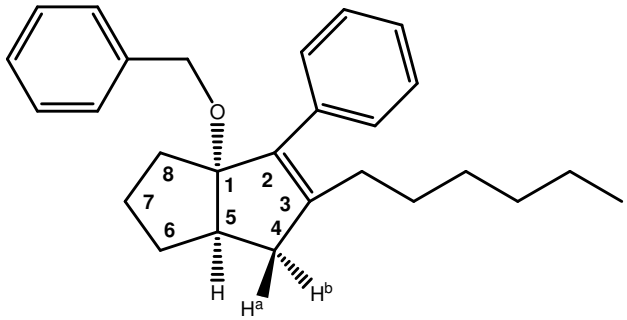
IR (thin film): $\tilde{\nu}$ = 2930 (s), 2854 (s), 1463 (w), 1092 (s), 767 (m), 699 (s) cm^{-1}.

6.2.12.9. *rac*-(1*S*,5*R*)-1-Cyclohexyloxy-3-hexyl-2-phenyl-bicyclo[3.3.0]oct-2-ene (2.107i)



General procedure C was used with ROH = *c*-HexOH. Purification of the crude material by column chromatography on Al_2O_3 (basic, grade III) with 1% Et_2O in petroleum ether as the eluent gave the title compound as a yellow oil in yield of 0.022 g (12%).
Spectral data were consistent with those reported previously.[237]

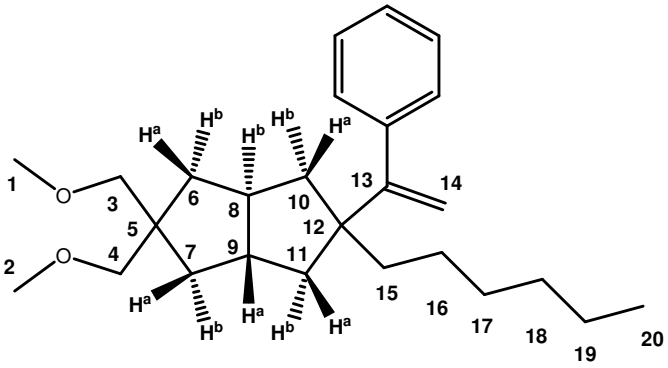
6.2.12.10. *rac*-(1*S*,5*R*)-1-Benzyloxy-3-hexyl-2-phenyl-bicyclo[3.3.0]oct-2-ene (2.107j)



General procedure C was used with ROH = *c*-HexOH. Purification of the crude material by column chromatography on Al_2O_3 (basic, grade III) with 1% Et_2O in petroleum ether as the eluent gave the title compound as a yellow oil in yield of 0.118 g (63%).
Spectral data were consistent with those reported previously.[237]

6.3. Experimental from chapter 3

6.3.1. *rac*-(3a*S*,6a*S*)-2-Hexyl-octahydro-5,5-bis(methoxymethyl)-2-(1-phenylvinyl)pentalene (3.34a)



To a solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same temperature, a solution of bis(methoxymethyl)hepta-1,6-diene (0.184 g, 1.0 mmol) in dry THF (3 mL) was added dropwise. After 30 min at –78 °C the reaction mixture was allowed to warm to room temperature and stirred for 3 h.

After cooling the reaction to –78 °C, a solution of 1,1-dibromoheptane (0.335 g, 1.3 mmol) in dry THF (1 mL) was added followed by dropwise addition of freshly prepared LiTMP [prepared from freshly distilled 2,2,6,6-tetramethylpiperidine (0.255 mL, 1.5 mmol) in dry THF (2 mL) and *n*-BuLi (0.6 mL of a 2.5 M solution in hexanes, 1.5 mmol) at –5 °C over 20 min]. The reaction mixture was stirred at –78 °C for 15 min before dropwise addition of lithium phenylacetylide [prepared from phenylacetylene (0.33 mL, 3.0 mmol) in dry THF (3 mL) and *n*-BuLi (1.2 mL of a 2.5 M solution in hexanes, 3.0 mmol) at –5 ^{o}C over 15 min]. The stirring was continued for 1 h during which the reaction mixture was allowed to warm to –55 °C before addition of MeOH (5 mL) and saturated aqueous solution of $NaHCO_3$ (6 mL). The whole mixture was allowed to warm to room temperature and left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with H_2O (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a yellow oil.

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with 2.5% of Et_2O in hexanes as the eluent gave the title compound as a pale yellow oil in yield of 0.295 g (77%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.330 – 7.240 (5H, m, H^{Ar}), 5.200 (1H, d, *J* = 1.2 Hz, H^{14}), 5.000 (1H, d, *J* = 1.2 Hz, H^{14}), 3.390 (3H, s, $H^{1 \text{ or } 2}$), 3.380 (3H, s, $H^{1 \text{ or } 2}$), 3.321 (1H, d, *J* = 8.8 Hz, $H^{3 \text{ or } 4}$), 3.303 (1H, d, *J* = 8.8 Hz, $H^{3 \text{ or } 4}$), 3.297 (1H, d, *J* = 8.8 Hz, $H^{3 \text{ or } 4}$), 3.276 (1H, d, *J* = 8.8 Hz, $H^{3 \text{ or } 4}$), 2.186 (1H, dd, *J* = 12.4, 5.9 Hz, $H^{10a \text{ or } 11b}$), 1.900 (1H, tt, *J* = 11.8, 5.9 Hz, $H^{8 \text{ or } 9}$), 1.808 (1H, tt, *J* = 11.8, 5.9 Hz, $H^{8 \text{ or } 9}$), 1.749 (1H, dd, *J* = 11.5, 5.8 Hz, $H^{10a \text{ or } 11b}$), 1.632 (1H, d, *J* = 12.0 Hz, $H^{6a \text{ or } 7b}$), 1.618 (1H, d, *J* = 12.2 Hz, $H^{6a \text{ or } 7b}$), 1.610 (1H, t, *J* = 6.0 Hz), 1.566 (1H, d, *J* = 11.5 Hz, $H^{10b \text{ or } 11a}$), 1.498 (1H, m), 1.357 – 1.172 (6H, m), 1.256 (1H, t, *J* = 6.9 Hz, H^{15}), 1.117 (1H, t, *J* = 12.0 Hz, $H^{10b \text{ or } 11a}$), 1.012 (2H, t, *J* = 11.6 Hz, $H^{6b + 7a}$), 0.936 (1H, t, *J* = 6.9 Hz, H^{15}), 0.891 (3H, t, *J* = 7.0 Hz, H^{20}).

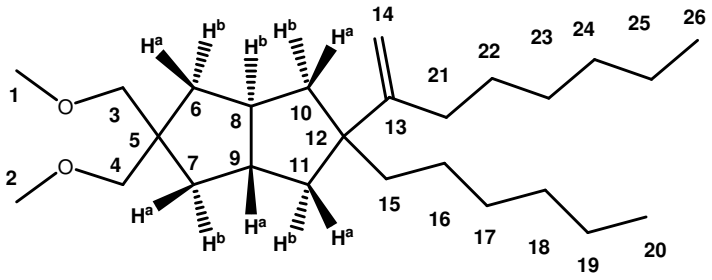
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 158.04 (C^{13}), 144.03 ($C^{i\text{-}Ph}$), 128.20 ($2CH^{o\text{-}Ph}$), 127.52 ($2CH^{m\text{-}Ph}$), 126.36 ($CH^{p\text{-}Ph}$), 113.05 ($CH_2{}^{14}$), 78.08 ($2CH_2{}^{3+4}$), 59.20 ($CH_3{}^{1 \text{ or } 2}$), 59.18 ($CH_3{}^{1 \text{ or } 2}$), 58.42 (C^{12}), 54.20 (C^5), 51.10 ($CH^{8 \text{ or } 9}$), 50.82 ($CH^{8 \text{ or } 9}$), 42.84 (CH_2), 42.67 ($CH_2{}^{10 \text{ or } 11}$), 39.70 ($CH_2{}^{10 \text{ or } 11}$), 34.74 ($CH_2{}^{6 \text{ or } 7}$), 34.70 ($CH_2{}^{6 \text{ or } 7}$), 31.75 ($CH_2$), 29.75 ($CH_2$), 24.86 ($CH_2$), 22.60 ($CH_2$), 14.04 ($CH_3{}^{20}$).

HRMS (EI): Found: $[M]^+$, 384.3021. $C_{26}H_{40}O_2$ requires: 384.3028.

LRMS (CI): *m/z*: 385 ($[M + H]^{+\cdot}$, 32%), 353 ($[M – MeOH + H]^{+\cdot}$, 32%), 339 ($[M – Et_2O + H]^{+\cdot}$, 13%), 321 ($[M – 2MeOH + H]^{+\cdot}$, 49%), 300 ($[M – Hex + H]^{+\cdot}$, 75%), 45 (100%).

IR (thin film): $\tilde{\nu}$ **=** 2929 (m), 2870 (m), 1461 (m), 1196 (m) 1104 (s), 894 (m), 775 (m), 700 (s) cm^{-1}.

6.3.2. *rac*-(3a*S*,6a*S*)-2-Hexyl-octahydro-5,5-bis(methoxymethyl)-2-(oct-1-en-2-yl)pentalene (3.34b)



To a solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same temperature, a solution of bis(methoxymethyl)hepta-1,6-diene (0.184 g, 1.0 mmol) in dry THF (3 mL) was added dropwise. After 30 min at –78 °C the reaction mixture was allowed to warm to room temperature and stirred for 12 h. After cooling the reaction to –78 °C, a solution of 1,1-dibromoheptane (0.335 g, 1.3 mmol) in dry THF (1 mL) was added followed by dropwise addition of freshly prepared LiTMP, [prepared from freshly distilled 2,2,6,6-tetramethylpiperidine (0.255 mL, 1.5 mmol) in THF (2 mL) and *n*-BuLi (0.6 mL of a 2.5 M solution in hexanes, 1.5 mmol) at –5 °C over 20 min]. The reaction mixture was stirred at –78 °C for 15 min before dropwise addition of lithium 1-octyne, [prepared from 1-octyne (0.59 mL, 4.0 mmol) in dry THF (4 mL) and *n*-BuLi (1.6 mL of a 2.5 M solution in hexanes, 4.0 mmol) at –5 ^{o}C over 15 min].

The stirring was continued for 2.5 h during which time the reaction mixture was allowed to warm to –25 °C before addition of MeOH (5 mL) and saturated aqueous solution of $NaHCO_3$ (6 mL). The whole mixture was allowed to warm to room temperature and left stirring overnight. The mixture then was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with H_2O (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a yellow oil.

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with 2.5% of Et_2O in hexanes as the eluent gave the title compound as a pale yellow oil in yield of 0.185 g (47%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 4.830 (1H, br s, H^{14}), 4.742 (1H, q, *J* = 1.3 Hz, H^{14}), 3.352 (3H, s, $H^{1 \text{ or } 2}$), 3.331 (3H, s, $H^{1 \text{ or } 2}$), 3.276 (1H, d, *J* = 8.8 Hz, $H^{3 \text{ or } 4}$), 3.250 (1H, d, *J* = 8.8 Hz, $H^{3 \text{ or } 4}$), 3.250 (1H, d, *J* = 8.8 Hz, $H^{3 \text{ or } 4}$), 3.220 (1H, d, *J* = 8.8 Hz, $H^{3 \text{ or } 4}$), 2.066 (1H, dd, *J* = 12.3, 5.8 Hz), 1.951 – 1.912 (2H, m, H^{21}), 1.783 (1H, qt, *J* = 11.7, 5.9 Hz, $H^{8 \text{ or } 9}$), 1.684 (1H, qt, *J* = 11.9, 6.1 Hz, $H^{8 \text{ or } 9}$), 1.601 – 1.519 (4H, m), 1.487 – 1.367 (3H, m), 1.349 – 1.217 (13H, m), 1.110 – 1.013 (2H, m), 0.987 – 0.907 (3H, m), 0.903 (3H, t, *J* = 7.0 Hz, $H^{20 \text{ or } 26}$), 0.879 ppm (3H, t, *J* = 7.0 Hz, $H^{20 \text{ or } 26}$).

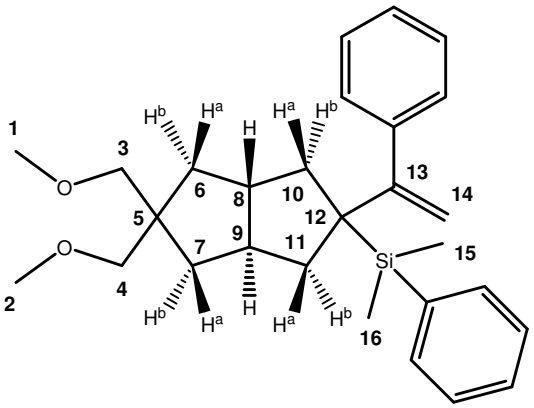
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 155.95 (C^{13}), 105.73 (CH_2^{14}), 78.10 ($CH_2^{3 \text{ or } 4}$), 78.08 ($CH_2^{3 \text{ or } 4}$), 59.23 ($CH_3^{1 \text{ or } 2}$), 59.19 ($CH_3^{1 \text{ or } 2}$), 59.14 (C^{12}), 54.10 (C^5), 50.77 ($CH^{8 \text{ or } 9}$), 50.24 ($CH^{8 \text{ or } 9}$), 42.40 (CH_2), 40.92 (CH_2), 38.34 (CH_2), 34.84 (CH_2), 34.73 (CH_2), 32.19 (CH_2), 31.92 (CH_2), 31.88 (CH_2), 29.97 (CH_2), 29.58 (CH_2), 28.92 (CH_2), 24.92 (CH_2), 22.70 (CH_2), 22.68 (CH_2), 14.08 ($2CH_3^{20 + 26}$).

HRMS (EI): Found: $[M]^+$, 392.9761. $C_{26}H_{48}O_2$ requires: 392.3654.

LRMS (CI): *m/z*: 393 ($[M + H]^{+\cdot}$, 13%), 361 ($[M – MeOH + H]^{+\cdot}$, 58%), 330 ($[M – 2MeOH + H]^{+\cdot}$, 28%), 243 ($[M – 2MeOH – Hex + H]^{+\cdot}$, 70%), 45 (100%).

IR (thin film): $\tilde{\nu}$ = 2929 (m), 2853 (m), 1461 (m), 1202 (m) 1110 (s), 883 (m) cm^{-1}.

6.3.3. *rac*-((3a*R*,6a*R*)-Octahydro-2,2-bis(methoxymethyl)-5-(1-phenylvinyl)-pentalen-5-yl)dimethyl(phenyl)silane (3.34c)



To a solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same temperature, a solution of bis(methoxymethyl)hepta-1,6-diene (0.184 g, 1.0 mmol) in dry THF (3 mL) was added dropwise. After 30 min at -78 °C the reaction mixture was allowed to warm to room temperature and stirred for 2 h. After cooling the reaction mixture to –78 °C, a solution of

(dichloromethyl)dimethyl(phenyl)silane (0.285 g, 1.3 mmol) in dry THF (1 mL) was added followed by dropwise addition of LDA (0.85 mL of a 1.8 M solution, 1.5 mmol). The reaction mixture was stirred for 0.5 h during which time was allowed to warm to –60 °C before re-cooling to –78 °C and dropwise addition of lithium phenyl acetylide, [prepared from phenylacetylene (0.33 mL, 3.0 mmol) in dry THF (3 mL) and *n*-BuLi (1.2 mL of a 2.5 M solution in hexanes, 3.0 mmol) at –5 ^{o}C over 15 min]. The stirring was continued for 3 h during which the reaction mixture was allowed to warm to –15 °C before addition of MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL). The whole mixture was allowed to warm to room temperature and left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 75 mL). The combined organic phases were washed with H_2O (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a red oil.

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with 2.5% of EtOAc in hexanes as the eluent gave the title compound as a yellow oil in yield of 0.152 g (35%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.600 – 7.565 (2H, m, H^{Ar}), 7.421 – 7.334 (3H, m, H^{Ar}), 7.177 – 7.125 (3H, m, H^{Ar}), 6.873 – 6.835 (2H, m, H^{Ar}), 4.976 (1H, d, *J* = 1.3 Hz, H^{14}), 4.850 (1H, d, *J* = 1.3 Hz, H^{14}), 3.327 (3H, s, $H^{1 \text{ or } 2}$), 3.321 (3H, s, $H^{1 \text{ or } 2}$), 3.228 (1H, d, *J* = 8.8 Hz, $H^{3 \text{ or } 4}$), 3.202 (1H, d, *J* = 8.8 Hz, $H^{3 \text{ or } 4}$), 3.129 (2H, s, $H^{3 \text{ or } 4}$), 2.166 (1H, dd, *J* = 11.5, 5.5 Hz, $H^{10b \text{ or } 11a}$), 2.004 (1H, dd, *J* = 12.0, 5.5 Hz, $H^{10b \text{ or } 11a}$), 1.712 (1H, qt, *J* = 11.5, 5.9 Hz, $H^{8 \text{ or } 9}$), 1.525 (1H, t, *J* = 12.0 Hz, $H^{10a \text{ or } 11b}$), 1.494 (1H, dd, *J* = 12.4, 6.2 Hz, $H^{6b \text{ or } 7a}$), 1.448 (1H, dd, *J* = 12.0, 6.0 Hz, $H^{6b \text{ or } 7a}$), 1.426 (1H, d, *J* = 11.5 Hz, $H^{10a \text{ or } 11b}$), 1.379 (1H, tt, *J* = 11.8, 5.5 Hz, $H^{8 \text{ or } 9}$), 0.862 (1H, t, *J* = 11.2 Hz, $H^{6a \text{ or } 7b}$), 0.810 (1H, t, *J* = 12.0 Hz, $H^{6a \text{ or } 7b}$), 0.397 (3H, s, $H^{15 \text{ or } 16}$), 0.392 (3H, s, $H^{15 \text{ or } 16}$).

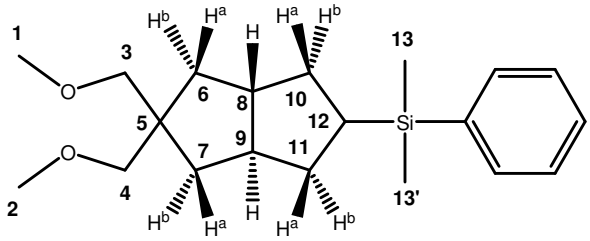
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 159.63 (C^{13}), 144.41 ($C^{Si\text{-}i\text{-}Ph}$), 138.21 ($C^{i\text{-}Ph}$), 134.79 ($2CH^{Si\text{-}o\text{-}Ph}$), 129.01 ($CH^{Si\text{-}p\text{-}Ph}$), 128.58 ($2CH^{Si\text{-}m\text{-}Ph}$), 127.53 ($2CH^{o\text{- or }m\text{-}Ph}$), 127.26 ($2CH^{o\text{- or }m\text{-}Ph}$), 126.10 ($CH^{p\text{-}Ph}$), 114.19 ($CH_2{}^{14}$), 77.84 ($2CH_2{}^{3+4}$), 59.15 ($2CH_3{}^{1+2}$), 54.63 ($C^{12}$), 52.10 ($CH^{8 \text{ or } 9}$), 51.13 ($CH^{8 \text{ or } 9}$), 47.74 ($C^{5}$), 39.22 ($CH_2{}^{10 \text{ or } 11}$), 37.73 ($CH_2{}^{10 \text{ or } 11}$), 34.58 ($CH_2{}^{6 \text{ or } 7}$), 34.06 ($CH_2{}^{6 \text{ or } 7}$), –4.09 ($CH_3{}^{15 \text{ or } 16}$), –4.18 ($CH_3{}^{15 \text{ or } 16}$).

HRMS (EI): Found: $[M]^+$, 434.2643. $C_{28}H_{38}O_2Si$ requires: 434.2641.

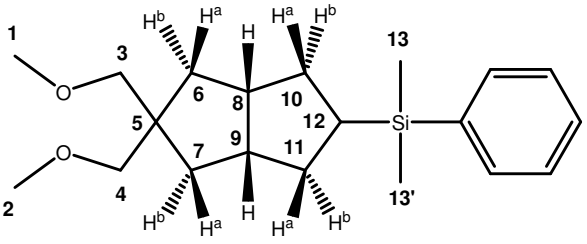
LRMS (CI): *m/z*: 434 ($[M]^{+\cdot}$, 10%), 300 ($[M - HSiMe_2Ph]^{+\cdot}$, 35%), 269 ($[M - MeOH - HSiMe_2Ph]^{+\cdot}$, 22%), 237 ($[M - 2MeOH - HSiMe_2Ph]^{+\cdot}$, 100%).

IR (thin film): $\tilde{\nu}$ = 2933 (m), 2873 (m), 1595 (w), 1448 (m), 1251 (m), 1202 (m), 1107 (s), 813 (s), 771 (s), 733 (s), 703 (s) cm^{-1}.

6.3.4. *rac*-((3a*S*,6a*S*)-Octahydro-2,2-bis(methoxymethyl)pentalen-5-yl)-dimethyl(phenyl)silane (major d.r.) (3.35a) and *rac*-((3a*S*,6a*R*)-octahydro-2,2-bis(methoxymethyl)pentalen-5-yl)-dimethyl(phenyl)silane (minor d.r.) (3.35b)



96 : 4



To a solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same temperature, a solution of bis(methoxymethyl)hepta-1,6-diene (0.184 g, 1.0 mmol) in dry THF (3 mL) was added dropwise. After 30 min at –78 °C the reaction mixture was allowed to warm to room temperature and stirred for 2 h. After cooling the reaction mixture to –78 °C, a solution of (dichloromethyl)dimethyl(phenyl)silane (0.285 g, 1.3 mmol) in dry THF (1 mL) was added followed by dropwise addition of LDA (0.85 mL of a 1.8 M solution, 1.5 mmol). The reaction mixture was stirred for 0.5 h during which was allowed to warm to –60 °C before dropwise addition of lithium phenyl acetylide pre-mixed with HMPA. [Lithium phenyl acetylide was freshly prepared from phenylacetylene (0.33 mL, 3.0 mmol) in dry THF (3 mL) and *n*-BuLi (1.2 mL of a 2.5 M solution in hexanes, 3.0 mmol) at 0 °C over 10 min, then HMPA (0.52 mL, 3.0 mmol) was added and the stirring was continued at the same temperature for further 15 min]. The stirring was continued for 3 h during

which time the reaction mixture was allowed to warm to –15 °C before addition of MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL). The whole mixture was allowed to warm to room temperature and left stirring overnight. The mixture then was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 75 mL). The combined organic phases were washed with H_2O (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a red oil.

Purification of the crude material by column chromatography on Al_2O_3 (basic, grade III) with 5% of Et_2O in hexanes as the eluent gave the title compounds as a yellow oil in yield of 0.072 g (22%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.547 – 7.496 (4H, m, $H^{o\text{-}Ph\ major\ +\ minor}$), 7.368 – 7.336 (6H, m, $H^{m\text{-}\ +\ p\text{-}Ph\ major\ +\ minor}$), 3.360 (3H, s, $H^{1/2\ minor}$), 3.357 (3H, s, $H^{1/2\ minor}$), 3.352 (3H, s, $H^{1/2\ major}$), 3.344 (3H, s, $H^{1/2\ major}$), 3.280 (1H, d, *J* = 8.8 Hz, $H^{3/4\ major}$), 3.276 (1H, d, *J* = 8.8 Hz, $H^{3/4\ major}$), 3.244 (1H, d, *J* = 8.8 Hz, $H^{3/4\ major}$), 3.218 (1H, d, *J* = 8.8 Hz, $H^{3/4\ major}$), 3.291 – 3.208 (4H, m, $H^{3\ +\ 4\ minor}$), 1.936 (1H, dddd, *J* = 12.0, 10.5, 8.3, 3.8 Hz, H^{major}), 1.790 (1H, m, H^{major}), 1.696 (1H, ddd, *J* = 11.3, 8.0, 5.5 Hz, H^{major}), 1.605 – 1.479 (12H, m, $H^{major\ +\ minor}$), 1.387 – 1.290 (2H, m, $H^{major\ +\ minor}$), 1.049 – 0.867 (5H, m, $H^{major\ +\ minor}$), 0.342 (3H, s, $H^{13/13'\ minor}$), 0.340 (3H, s, $H^{13/13'\ minor}$), 0.260 (3H, s, $H^{13/13'\ major}$), 0.250 (3H, s, $H^{13/13'\ major}$).

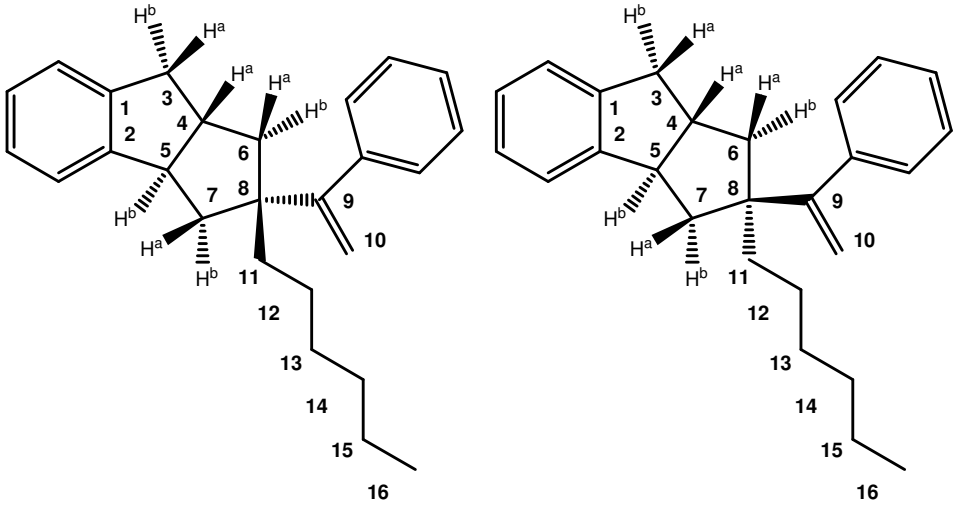
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 139.27 ($2C^{Si\text{-}i\text{-}Ph\ major\ +\ minor}$), 133.82 ($4CH^{Si\text{-}p\text{-}Ph\ major\ +\ minor}$), 128.69 ($2CH^{Si\text{-}p\text{-}Ph\ major\ +\ minor}$), 127.60 ($4CH^{Si\text{-}m\text{-}Ph\ major\ +\ minor}$), 78.02 ($CH_2^{3/4\ minor}$), 78.02 ($2CH_2^{3/4\ major\ +\ minor}$), 77.99 ($CH_2^{3/4\ major}$), 59.20 ($CH_3^{1/2\ major}$), 59.17 ($CH_3^{1/2\ major}$), 58.06 ($2CH_3^{1\ +\ 2\ minor}$), 54.95 ($C^{5\ major}$), 54.24 ($C^{5\ minor}$), 53.49 ($CH^{8/9\ major}$), 52.96 ($CH^{8/9\ major}$), 52.53 ($2CH^{8\ +\ 9\ minor}$), 34.28 ($CH_2^{6/7\ major}$), 33.97 ($CH_2^{6/7\ major}$), 31.57 ($2CH_2^{6\ +\ 7\ minor}$), 29.35 ($CH_2^{10/11\ major}$), 29.11 ($2CH_2^{12\ major\ +\ minor}$), 27.27 ($CH_2^{10/11\ major}$), 26.32 ($2CH_2^{10\ +\ 11\ minor}$), –3.12 ($CH_3^{13/13'\ minor}$), –3.20 ($CH_3^{13/13'\ minor}$), –4.56 ($CH_3^{13/13'\ major}$), –4.71 ($CH_3^{13/13'\ major}$).

HRMS (ESI+): Found: $[M + Na]^+$, 355.2604. $[C_{20}H_{32}NaO_2Si]^+$ requires: 355.2604.

LRMS (CI): *m/z*: 254 ($[M – Ph]^{+\cdot}$, 1%), 222 ($[M – MeOH]^{+\cdot}$, 2%), 190 ($[M – 2MeOH]^{+\cdot}$, 2%), 135 ($[M – 2MeOH – SiMe_2Ph]^{+\cdot}$, 100 %).

IR (thin film): $\tilde{\nu}$ **=** 2952 (m), 2922 (m), 2869 (m), 2820 (m), 1452 (w), 1421 (w), 1251 (m), 1202 (m), 1107 (s), 813 (s), 775 (s), 722 (s), 695 (s) cm^{-1}.

6.3.5. *rac*-(3a*S*,8a*R*)-2-Hexyl-1,2,3,3a,8,8a-hexahydro-2-(1-phenylvinyl)-cyclopenta[*a*]indene and *rac*-(3a*R*,8a*R*)-2-hexyl-1,2,3,3a,8,8a-hexahydro-2-(1-phenylvinyl)-cyclopenta[*a*]indene (3.39a, b)



To a solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same temperature, a solution of 1-allyl-2-vinyllbenzene (0.144 g, 1.0 mmol) in dry THF (3 mL) was added dropwise. After 30 min at –78 °C the reaction mixture was allowed to warm to room temperature and stirred for 2 h. After cooling the reaction to –78 °C, a solution of 1,1-dibromoheptane (0.271 g, 1.05 mmol) in dry THF (1 mL) was added followed by dropwise addition of LDA (0.61 mL of a 1.8 M solution, 1.1 mmol). After stirring the reaction mixture for 15 min at –78 °C, lithium phenylacetylide was added dropwise, [prepared from phenylacetylene (0.33 mL, 3.0 mmol) in dry THF (3 mL) and *n*-BuLi (1.2 mL of a 2.5 M solution in hexanes, 3.0 mmol) at –5 ^{o}C over 15 min]. The stirring was continued for 1.5 h during which the reaction mixture was allowed to warm to –30 °C before addition of MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL). The whole mixture was allowed to warm to room temperature and left stirring overnight. The mixture then was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with H_2O (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a yellow oil. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluent gave the title compound as an inseparable mixture of isomers in NMR ratio of 1.4 : 1 and combined yield of 0.165g (48%, pale yellow oil).

^{1}H NMR (400 MHz, BENZENE-D6): δ (ppm) = 7.311 – 7.249 (4H, m, $H^{o\text{-}Ph}$), 7.194 – 7.070 (14H, m, H^{Ar}), 5.211 (1H, d, *J* = 1.3 Hz, $H^{10\ major}$), 5.146 (1H, d, *J* = 1.3 Hz, $H^{10\ minor}$), 5.068 (1H, d, *J* = 1.3 Hz, $H^{10\ major}$), 5.029 (1H, d, *J* = 1.3 Hz, $H^{10\ minor}$), 2.952 (1H, td, *J* = 12.3, 5.8 Hz, $H^{5b\ major}$), 2.891 (1H, td, *J* = 11.8, 6.3 Hz, $H^{5b\ minor}$), 2.665 (1H, dd, *J* = 13.8, 5.8 Hz, $H^{3a\ major}$), 2.635 (1H, dd, *J* = 13.8, 5.8 Hz, $H^{3a\ minor}$), 2.550 (1H, dd, *J* = 12.3, 6.0 Hz, $H^{7a\ major}$), 2.329 (1H, ddt, *J* = 13.8, 11.5, 1.3 Hz, $H^{3b\ major}$), 2.316 (1H, t, *J* = 13.8 Hz, $H^{3b\ minor}$), 2.252 (1H, dd, *J* = 12.2, 5.7 Hz, $H^{7a\ minor}$), 2.157 – 1.940 (3H, m, $2H^{4}$ + $H^{6\ minor}$), 1.885 (1H, t, *J* = 11.3 Hz, $H^{6b\ major}$), 1.753 – 1.622 (2H, m, $H^{6\ minor}$ + H), 1.740 (1H, dd, *J* = 11.3, 5.8 Hz, $H^{6a\ major}$), 1.538 – 1.129 (19H, m), 1.412 (1H, t, *J* = 12.3 Hz, $H^{7b\ major}$), 1.324 (1H, t, *J* = 12.2 Hz, $H^{7b\ minor}$), 0.897 (3H, t, *J* = 7.0 Hz, $H^{16\ minor}$), 0.875 (3H, t, *J* = 7.0 Hz, $H^{16\ major}$).

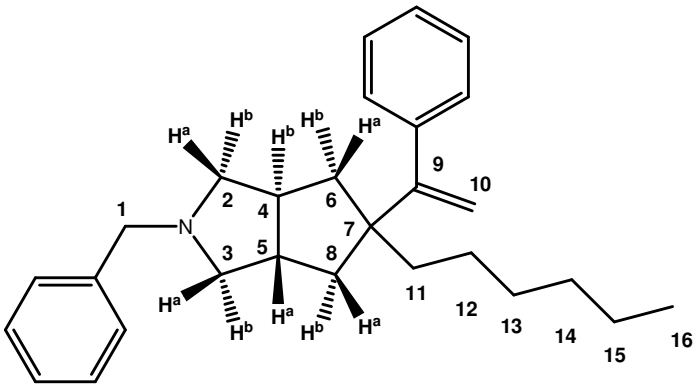
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 158.49 ($C^{9\ major}$), 158.40 ($C^{9\ minor}$), 149.66 ($C^{i\text{-}Ph\ major}$), 149.63 ($C^{i\text{-}Ph\ minor}$), 145.60 ($C^{1/2\ major}$), 145.56 ($C^{1/2\ minor}$), 144.68 ($C^{1/2\ minor}$), 144.63 ($C^{1/2\ major}$), 128.99 ($4CH^{Ar}$), 128.68 ($2CH^{Ar}$), 128.40 ($2CH^{Ar}$), 127.30 (CH^{Ar}), 127.27 (CH^{Ar}), 126.73 (CH^{Ar}), 126.70 (CH^{Ar}), 126.44 ($2CH^{Ar}$), 125.65 (CH^{Ar}), 125.61 (CH^{Ar}), 122.93 (CH^{Ar}), 122.88 (CH^{Ar}), 114.10 ($CH_2{}^{10\ minor}$), 113.99 ($CH_2{}^{10\ major}$), 58.10 ($C^{8\ major}$), 58.05 ($C^{8\ minor}$), 56.97 ($CH^{4/5\ major}$), 56.61 ($CH^{4/5\ minor}$), 55.40 ($CH^{4/5\ minor}$), 55.04 ($CH^{4/5\ major}$), 43.40 ($CH_2{}^{major}$), 43.28 ($CH_2{}^{minor}$), 42.67 ($CH_2{}^{major}$), 41.24 ($CH_2{}^{minor}$), 39.54 ($CH_2{}^{minor}$), 38.09 ($CH_2{}^{major}$), 35.00 ($2CH_2{}^{major\ +\ minor}$), 32.54 ($CH_2{}^{minor}$), 32.49 ($CH_2{}^{major}$), 30.58 ($CH_2{}^{minor}$), 30.53 ($CH_2{}^{major}$), 25.74 ($CH_2{}^{minor}$), 25.63 ($CH_2{}^{major}$), 23.40 ($2CH_2{}^{major\ +\ minor}$), 14.67 ($2CH_3{}^{16\ major\ +\ minor}$).

HRMS (EI): Found: $[M]^+$, 344.2505. $C_{26}H_{32}$ requires: 344.2504.

LRMS (CI): *m/z*: 345 ($[M + H]^{+\cdot}$, 61%), 260 ($[M – Hex + H]^{+\cdot}$, 14%), 130 (100%).

IR (thin film): $\tilde{\nu}$ **=** 2933 (m), 2858 (m), 1622 (w), 1489 (w), 1459 (m), 900 (m), 775 (m), 741 (s), 699 (s) cm^{-1}.

6.3.6. *rac*-(3a*R*,6a*R*)-2-Benzyl-5-hexyl-octahydro-5-(1-phenylvinyl)cyclopenta[*c*]-pyrrole (**3.42a** *trans*)



To a solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same temperature, a solution of *N*-allyl-*N*-benzylprop-2-en-1-amine (0.187 g, 1.0 mmol) in dry THF (3 mL) was added dropwise. After 30 min at –78 °C the reaction mixture was allowed to warm to room temperature and stirred for 3 h. After cooling the reaction to –78 °C, a solution of 1,1-dibromoheptane (0.271 g, 1.05 mmol) in dry THF (1 mL) was added followed by dropwise addition of freshly prepared LiTMP, [prepared from freshly distilled 2,2,6,6-tetramethylpiperidine (0.187 mL, 1.1 mmol) in dry THF (2 mL) and *n*-BuLi (0.44 mL of a 2.5 M solution in hexanes, 1.1 mmol) at 0 °C over 20 min]. The reaction mixture was stirred at –78 °C for 20 min before dropwise addition of lithium phenyl acetylide, [prepared from phenylacetylene (0.33 mL, 3.0 mmol) in dry THF (3 mL) and *n*-BuLi (1.2 mL of a 2.5 M solution in hexanes, 3.0 mmol) at 0 ^{o}C over 15 min]. The stirring was continued for 1 h during which time the reaction mixture was allowed to warm to –45 °C before addition of MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL). The whole mixture was allowed to warm to room temperature and left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with H_2O (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as an orange oil.

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with 10 → 50% of Et_2O in hexanes as the eluant gave the title compound as a yellow oil in yield of 0.175 g (45%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.295 – 7.148 (10H, m, H^{Ar}), 5.124 (1H, d, *J* = 1.2 Hz, H^{10}), 4.936 (1H, d, *J* = 1.2 Hz, H^{10}), 3.813 (1H, d, *J* = 13.3 Hz, H^1), 3.754 (1H, d, *J* = 13.3 Hz, H^1), 2.771 (1H, dd, *J* = 8.8, 6.3 Hz, $H^{2b \text{ or } 3a}$), 2.744 (1H, dd, *J* = 8.8, 6.3 Hz, $H^{2b \text{ or } 3a}$), 2.404 (1H, dd, *J* = 10.0, 8.8 Hz, $H^{2a \text{ or } 3b}$), 2.398 (1H, dd, *J* = 10.0, 8.8 Hz, $H^{2a \text{ or } 3b}$), 2.124 (1H, dd, *J* = 12.0, 6.0 Hz, $H^{6b \text{ or } 8a}$), 2.106 (1H, m, $H^{4 \text{ or } 5}$), 2.017 (1H, tt, *J* = 12.0, 6.0 Hz, $H^{4 \text{ or } 5}$), 1.696 (1H, dd, *J* = 11.8, 6.0 Hz, $H^{6b \text{ or } 8a}$), 1.614 (1H, t, *J* = 11.8 Hz, $H^{6a \text{ or } 8b}$), 1.572 (1H, m), 1.442 (1H, m), 1.272 – 1.104 (6H, m), 1.169 (1H, t, *J* = 7.0 Hz, H^{11}), 1.147 (1H, t, *J* = 12.0 Hz, $H^{6a \text{ or } 8b}$), 0.851 (1H, t, *J* = 7.0 Hz, H^{11}), 0.809 (3H, t, *J* = 7.0 Hz, H^{16}).

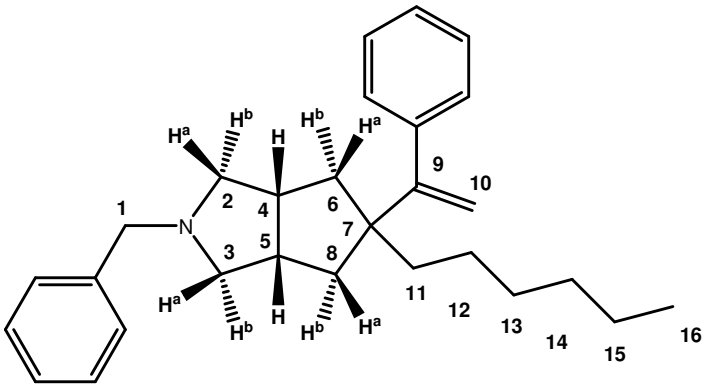
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 157.67 (C^9), 143.79 ($C^{i\text{-Ph}}$), 140.25 ($C^{i\text{-Ph}}$), 128.53 ($2CH^{o\text{- or m-Ph}}$), 128.18 ($2CH^{o\text{- or m-Ph}}$), 128.16 ($2CH^{o\text{- or m-Ph}}$), 127.58 ($2CH^{o\text{- or m-Ph}}$), 126.62 ($CH^{p\text{-Ph}}$), 126.45 ($CH^{p\text{-Ph}}$), 113.29 ($CH_2{}^{10}$), 61.80 ($CH_2{}^1$), 58.69 (C^7), 55.05 ($2CH_2{}^{2+3}$), 50.92 ($CH^{4 \text{ or } 5}$), 50.59 ($CH^{4 \text{ or } 5}$), 42.71 (CH_2), 40.94 ($CH_2{}^{6 \text{ or } 8}$), 38.09 ($CH_2{}^{6 \text{ or } 8}$), 31.71 (CH_2), 29.71 (CH_2), 24.86 ($CH_2{}^{11}$), 22.58 (CH_2), 14.04 ($CH_3{}^{16}$).

HRMS (ESI+): Found: $[M + H]^+$, 388.2994. $[C_{28}H_{38}N]^+$ requires: 388.2999.

LRMS (ESI+): *m/z*: 388 ($[M + H]^+$, 100%).

IR (thin film): $\tilde{\nu}$ **=** 2924 (m), 2853 (m), 2783 (m), 1498 (m), 1450 (m), 1029 (m) 894 (s), 770 (m), 737 (m), 700 (s) cm^{-1}.

6.3.7. *rac*-(3a*S*,6a*R*)-2-Benzyl-5-hexyl-octahydro-5-(1-phenylvinyl)cyclopenta[*c*]-pyrrole (3.42a *cis*)



This compound was obtained simultaneously with isomer **3.42a *trans***.

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with 10 → 50% of Et_2O in hexanes as the eluant gave the title compound as a pale yellow oil in yield of 0.055 g (14%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.357 – 7.212 (8H, m, H^{Ar}), 7.134 (2H, apparent dd, *J* = 7.7, 1.7 Hz, $H^{N\text{-}o\text{-}Ph}$), 5.170 (1H, d, *J* = 1.5 Hz, H^{10}), 5.009 (1H, d, *J* = 1.5 Hz, H^{10}), 3.584 (2H, br s, H^{1}), 2.627 – 2.560 (2H, m, $H^{4\,+\,5}$), 2.512 (2H, d, *J* = 9.0 Hz, $H^{2\,+\,3}$), 2.242 – 2.170 (4H, m, $H^{2\,+\,3\,+\,6\,+\,8}$), 1.556 – 1.516 (2H, m, H^{11}), 1.392 – 1.310 (8H, m), 1.269 – 1.216 (2H, m, $H^{6\,+\,8}$), 0.920 (3H, t, *J* = 6.8 Hz, H^{16}).

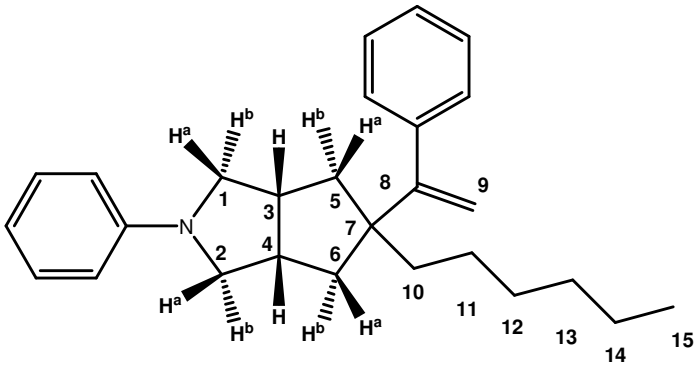
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 153.33 (C^{9}), 143.52 ($C^{i\text{-}Ph}$), 139.83 ($C^{i\text{-}Ph}$), 128.50 ($2CH^{o\text{-}\ or\ m\text{-}Ph}$), 128.42 ($2CH^{o\text{-}\ or\ m\text{-}Ph}$), 128.06 ($2CH^{o\text{-}\ or\ m\text{-}Ph}$), 127.45 ($2CH^{o\text{-}\ or\ m\text{-}Ph}$), 126.58 ($CH^{p\text{-}Ph}$), 126.37 ($CH^{p\text{-}Ph}$), 115.34 ($CH_2{}^{10}$), 60.43 ($2CH_2{}^{2\,+\,3}$), 59.76 ($CH_2{}^{1}$), 54.98 ($C^{7}$), 44.05 ($2CH_2{}^{6\,+\,8}$), 41.36 ($2CH^{4\,+\,5}$), 39.66 ($CH_2{}^{11}$), 31.94 ($CH_2$), 29.93 ($CH_2$), 25.93 ($CH_2$), 22.73 ($CH_2$), 14.12 ($CH_3{}^{16}$).

HRMS (ESI+): Found: $[M + H]^+$, 388.2997. $[C_{28}H_{38}N]^+$ requires: 388.2999.

LRMS (ESI+): *m/z*: 388 ($[M + H]^+$, 100%).

IR (thin film): $\tilde{\nu}$ **=** 2933 (m), 2850 (m), 2778 (m), 1489 (m), 1452 (m), 1334 (m) 896 (m), 775 (m), 737 (m), 699 (s) cm^{-1}.

6.3.8. *rac*-(3a*R*,6a*R*)-2-Benzyl-5-hexyl-octahydro-5-(1-phenylvinyl)cyclopenta[*c*]-pyrrole (3.42a, b *cis* + *trans*)



To a solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same temperature, a solution of *N,N*-diallylbenzenamine (0.173 g, 1.0 mmol) in dry THF (3 mL) was added dropwise. After 30 min at –78 °C the reaction mixture was allowed to warm to room temperature and stirred for 3 h. After cooling the reaction to –78 °C, a solution of 1,1-dibromoheptane (0.271 g, 1.05 mmol) in dry THF (1 mL) was added followed by dropwise addition of freshly prepared LiTMP, [prepared from freshly distilled 2,2,6,6-tetramethylpiperidine (0.187 mL, 1.1 mmol) in dry THF (2 mL) and *n*-BuLi (0.44 mL of a 2.5 M solution in hexanes, 1.1 mmol) at 0 °C over 20 min]. The reaction mixture was stirred at –78 °C for 20 min before dropwise addition of lithium phenyl acetylide, [prepared from phenylacetylene (0.33 mL, 3.0 mmol) in dry THF (3 mL) and *n*-BuLi i (1.2 mL of a 2.5 M solution in hexanes, 3.0 mmol) at 0 ^{o}C over 15 min]. The stirring was continued for 1 h during which time the reaction mixture was allowed to warm to –45 °C before addition of MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL). The whole mixture was allowed to warm to room temperature and left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with H_2O (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a yellow oil.

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with 5% of Et_2O in hexanes as the eluant gave the title compound as a pale yellow oil in yield of 0.263 g (70%) as inseparable mixture of 3.8 : 52.3 : 43.9 *cis : cis : trans* ring junction isomers. Re-crystallization from cold hexane provided the 2.2 : 1 *cis (major isomer) : trans* mixture of final compounds.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.356 – 7.178 (14H, m, H^{Ar}), 6.747 (1H, t, *J* = 7.3 Hz, $H^{N\text{-}p\text{-}Ph\ major}$), 6.699 (2H, dd, *J* = 7.8, 1.0 Hz, $H^{N\text{-}o\text{-}Ph\ major}$), 6.647 (1H, t, *J* = 7.3 Hz, $H^{N\text{-}p\text{-}Ph\ minor}$), 6.520 (2H, d, *J* = 7.8 Hz, $H^{N\text{-}o\text{-}Ph\ minor}$), 3.748 (1H, d, *J* = 1.3 Hz, $H^{9\ major}$), 5.236 (1H, br s, $H^{9\ minor}$), 5.086 (1H, d, *J* = 1.3 Hz, $H^{9\ major}$), 5.046 (1H, br s, $H^{9\ minor}$), 3.422 – 3.361 (2H, ddd, *J* = 9.5, 8.4, 6.5 Hz, $H^{(1+2)\ a/b\ minor}$), 3.290 – 3.266 (2H, d, *J* = 9.5 Hz, $H^{(1+2)\ a/b\ major}$), 3.159 – 3.118 (2H, apparent dd, *J* = 9.5, 7.3 Hz, $H^{(1+2)\ a/b\ major}$), 2.984 – 2.928 (2H, td, *J* = 8.4, 4.5 Hz, $H^{(1+2)\ a/b\ minor}$), 2.901 – 2.803 (2H, septet, *J*

= 8.4 Hz, $H^{(3 + 4)\ major}$), 2.412 – 2.361 (2H, dd, *J* = 12.8, 7.4 Hz, $H^{(5 + 6)\ a/b\ major}$), 2.351 – 2.306 (1H, dd, *J* = 12.5, 5.7 Hz, $H^{(5 + 6)\ a/b\ minor}$), 2.272 – 2.082 (2H, m, $H^{(3 + 4)\ minor}$), 1.904 (1H, dd, *J* = 11.8, 5.8 Hz, $H^{(5/6)\ a/b\ minor}$), 1.824 (1H, t, *J* = 11.8 Hz, $H^{(5/6)\ a/b\ minor}$), 1.742 – 1.670 (1H, m, H^{minor}), 1.609 – 1.52 (4H, m), 1.385 – 1.238 (18H, m), 0.911 (3H, t, *J* = 7.0 Hz, $H^{15\ major}$), 0.888 (3H, t, *J* = 7.0 Hz, $H^{15\ minor}$).

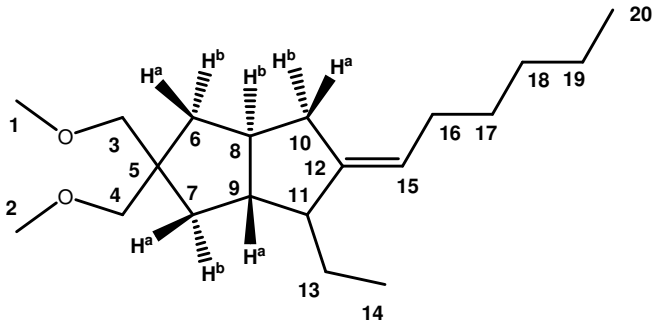
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 157.37 ($C^{8\ minor}$), 153.27 ($C^{8\ major}$), 149.46 ($C^{N\text{-}i\text{-}Ph\ major}$), 148.30 ($C^{N\text{-}i\text{-}Ph\ minor}$), 143.64 ($C^{i\text{-}Ph\ minor}$), 143.27 ($C^{i\text{-}Ph\ major}$), 129.13 ($2CH^{o\text{- or m-Ph minor}}$), 129.05 ($2CH^{o\text{- or m-Ph major}}$), 128.40 ($2CH^{o\text{- or m-Ph major}}$), 128.22 ($2CH^{o\text{- or m-Ph minor}}$), 127.68 ($2CH^{o\text{- or m-Ph minor}}$), 127.59 ($2CH^{o\text{- or m-Ph major}}$), 126.59 ($CH^{p\text{-}Ph\ minor}$), 126.55 ($CH^{p\text{-}Ph\ major}$), 116.91 ($CH^{N\text{-}p\text{-}Ph\ major}$), 115.47 ($CH_2{}^{9\ major}$), 114.94 ($CH^{N\text{-}p\text{-}Ph\ minor}$), 113.75 ($2CH^{N\text{-}o\text{-}Ph\ major}$), 113.54 ($CH_2{}^{9\ minor}$), 110.81 ($2CH^{N\text{-}o\text{-}Ph\ minor}$), 58.23 ($C^{7\ minor}$), 55.07 ($C^{7\ major}$), 55.00 ($2CH_2{}^{1 + 2\ major}$), 50.31 ($CH_2{}^{3/4\ minor}$), 50.01 ($CH_2{}^{4/3\ minor}$), 49.77 ($2CH_2{}^{1 + 2\ minor}$), 44.73 ($2CH_2{}^{5 + 6\ major}$), 42.76 ($CH_2{}^{minor}$), 41.08 ($2CH^{3 + 4\ major}$), 40.71 ($CH^{5/6\ minor}$), 39.84 ($CH_2{}^{major}$), 37.94 ($CH^{6/5\ minor}$), 31.84 ($CH_2{}^{major}$), 31.74 ($CH_2{}^{minor}$), 29.81 ($CH_2{}^{major}$), 29.71 ($CH_2{}^{minor}$), 25.84 ($CH_2{}^{major}$), 24.91 ($CH_2{}^{minor}$), 22.67 ($CH_2{}^{major}$), 22.61 ($CH_2{}^{minor}$), 14.09 ($CH_3{}^{16\ major}$), 14.07 ($CH_3{}^{16\ minor}$).

HRMS (ESI+): Found: $[M + H]^+$, 374.2838. $[C_{27}H_{36}N]^+$ requires: 374.2842.

LRMS (ESI+): *m/z*: 374 ($[M + H]^+$, 100%).

IR (thin film): $\tilde{\nu}$ **=** 2922 (m), 2922 (m), 2854 (m), 2812 (m), 1595 (s), 1504 (s), 1467 (s), 1357 (m), 1327 (m), 892 (m), 741 (s), 692 (s) cm^{-1}.

6.3.9. *rac*-(*E*,3a*R*,6a*R*)-1-Ethyl-2-hexylidene-octahydro-5,5-bis(methoxymethyl)-pentalene (3.45a)



To a solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same temperature, a solution of (*Z*)-4,4-bis(methoxymethyl)nona-1,6-diene (0.212 g, 1.0 mmol) in dry THF (3 mL) was added

dropwise. After 30 min at –78 °C the reaction mixture was allowed to warm to room temperature and stirred for 14 h.

After cooling the reaction to –78 °C, a solution of 1,1-dibromoheptane (0.335 g, 1.3 mmol) in dry THF (1 mL) was added followed by dropwise addition of freshly prepared LiTMP, [prepared from freshly distilled 2,2,6,6-tetramethylpiperidine (0.255 mL, 1.5 mmol) in dry THF (2 mL) and *n*-BuLi (0.6 mL of a 2.5 M solution in hexanes, 1.5 mmol) at –5 °C over 20 min]. The reaction mixture was stirred at –78 °C for 30 min before dropwise addition of lithium phenyl acetylide, [prepared from phenylacetylene (0.33 mL, 3.0 mmol) in dry THF (3 mL) and *n*-BuLi (1.2 mL of a 2.5 M solution in hexanes, 3.0 mmol) at –5 ^{o}C over 15 min]. The stirring was continued for 3 h during which the reaction mixture was allowed to warm to –35 °C before addition of MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL). The whole mixture was allowed to warm to room temperature and left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with H_2O (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a yellow oil.

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with 5% of Et_2O in hexanes as the eluant gave the title compound as colorless oil in yield of 0.231 g (75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.126 (1H, tq, *J* = 7.0, 2.3 Hz, H^{15}), 3.355 (3H, s, $H^{1\text{ or }2}$), 3.353 (3H, s, $H^{1\text{ or }2}$), 3.296 (1H, d, *J* = 8.8 Hz, $H^{3\text{ or }4}$), 3.288 (1H, d, *J* = 8.8 Hz, $H^{3\text{ or }4}$), 3.257 (1H, d, *J* = 8.8 Hz, $H^{3\text{ or }4}$), 3.253 (1H, d, *J* = 8.8 Hz, $H^{3\text{ or }4}$), 2.386 (1H, dd, *J* = 20.3, 12.3 Hz, H^{10}), 1.993 – 1.867 (3H, m, $2H^{16} + H^{9}$), 1.805 – 1.660 (2H, m, $H^{10} + H^{8}$), 1.684 (1H, dd, *J* = 12.0, 6.3 Hz, H^{7a}), 1.611 (1H, dd, *J* = 11.8, 5.9 Hz, H^{6b}), 1.394 – 1.229 (8H, m), 1.182 (1H, ddd, *J* = 13.8, 7.3, 2.0 Hz, H^{11}), 1.076 (1H, t, *J* = 12.0 Hz, H^{7b}), 0.958 (1H, t, *J* = 11.8 Hz, H^{6a}), 0.918 (3H, t, *J* = 7.4 Hz, H^{14}), 0.890 (3H, t, *J* = 7.0 Hz, H^{20}).

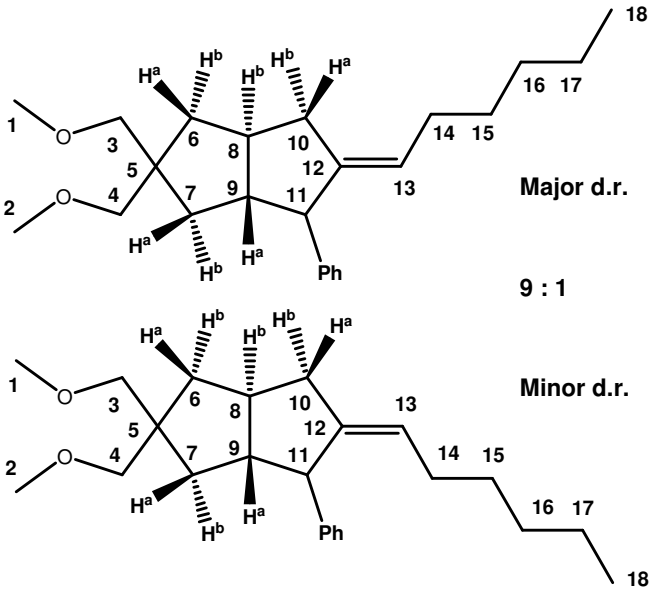
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 150.27 (C^{12}), 121.42 (CH^{15}), 78.50 ($CH_2^{3/4}$), 78.41 ($CH_2^{4/3}$), 59.24 ($2CH_3^{1+2}$), 56.84 (CH^{11}), 53.57 (C^{5}), 48.84 (CH^{8}), 48.32 (CH^{9}), 35.15 (CH_2^{7}), 34.31 (CH_2^{6}), 31.96 (CH_2^{10}), 31.57 (CH_2^{13}), 29.35 (CH_2), 29.12 (CH_2^{16}), 26.28 (CH_2), 22.62 (CH_2), 14.09 (CH_3^{20}), 12.18 (CH_3^{14}).

HRMS (EI): Found: $[M - MeOH]^+$, 276.2458. $[C_{19}H_{32}O]^+$ requires: 276.2453.

LRMS (CI): *m/z*: 309 ($[M + H]^{+\cdot}$, 100%), 277 ($[M – MeOH + H]^{+\cdot}$, 57%), 245 ($[M – 2MeOH + H]^{+\cdot}$, 43%).

IR (thin film): $\tilde{\nu}$ = 2952 (m), 2918 (m), 2858 (m), 1448 (w), 1198 (w), 1107 (s), 960 (w) cm^{-1}.

6.3.10. *rac*-(*E*,3a*R*,6a*R*)-2-Hexylidene-octahydro-5,5-bis(methoxymethyl)-1-phenylpentalene (major d.r.) and *rac*-(*Z*,3a*R*,6a*R*)-2-hexylidene-octahydro-5,5-bis(methoxymethyl)-1-phenylpentalene (minor d.r.) (3.45b)



To a solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same temperature, a solution of 1-((*E*)-4,4-bis(methoxymethyl)hepta-1,6-dienyl)benzene (0.260 g, 1.0 mmol) in dry THF (3 mL) was added dropwise. After 30 min at –78 °C the reaction mixture was allowed to warm to room temperature and stirred for 15 h. After cooling the reaction to –78 °C, a solution of 1,1-dibromoheptane (0.335 g, 1.3 mmol) in dry THF (1 mL) was added followed by dropwise addition of freshly prepared LiTMP, [prepared from freshly distilled 2,2,6,6-tetramethylpiperidine (0.255 mL, 1.5 mmol) in dry THF (2 mL) and *n*-BuLi (0.6 mL of a 2.5 M solution in hexanes, 1.5 mmol) at –5 °C over 20 min]. The reaction mixture was stirred at –78 °C for 30 min before dropwise addition of lithium phenyl acetylide, [prepared from phenylacetylene (0.33 mL, 3.0 mmol) in dry THF (3 mL) and *n*-BuLi

(1.2 mL of a 2.5 M solution in hexanes, 3.0 mmol) at –5 °C over 15 min]. The stirring was continued for 4.5 h during which time the reaction mixture was allowed to warm to –15 °C before addition of MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL). The whole mixture was allowed to warm to room temperature and left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with H_2O (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a yellow oil.

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with 5% of Et_2O in hexanes as the eluant gave the title compound as a pale yellow oil in yield of 0.303 g (85%) as an inseparable mixture of isomers (9 : 1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.304 – 7.155 (10H, m, $H^{Ar\ major + minor}$), 5.371 (1H, fs tq, *J* = 6.9 Hz, $H^{13\ minor}$), 4.869 (1H, tq, *J* = 6.7, 2.5Hz, $H^{13\ major}$), 3.366 – 3.125 (16H, m, H-1 + H-2 + H-3 + H-4 + H-11 (major + minor)), 3.331 (3H, s, $H^{1/2\ major}$), 3.303 (3H, s, $H^{2/1\ major}$), 2.564 (1H, fs dd, *J* = 11.0 Hz, $H^{10a\ major}$), 2.426 (1H, dd, *J* = 13.8, 5.0 Hz, $H^{10b\ minor}$), 2.288 – 2.113 (1H, m, $H^{10a\ minor}$), 1.959 – 1.770 (9H, m, $H\text{-}10^{b\ major}$ + 2H-8 + 2H-9 + 2H-14 (major + minor)), 1.725 (1H, dd, *J* = 12.3, 5.6 Hz, $H^{6/7\ major}$), 1.666 (1H, dd, *J* = 12.3, 6.0 Hz, $H^{6/7\ minor}$), 1.546 (1H, dd, *J* = 12.0, 6.0 Hz, $H^{7/6\ minor}$), 1.489 (1H, dd, *J* = 12.3, 6.0 Hz, $H^{7/6\ major}$), 1.323 – 1.181 (10H, m), 1.158 – 0.953 (6H, m), 0.876 (3H, t, *J* = 7.0 Hz, $H^{18\ major}$), 0.790 (3H, t, *J* = 7.0 Hz, $H^{18\ minor}$).

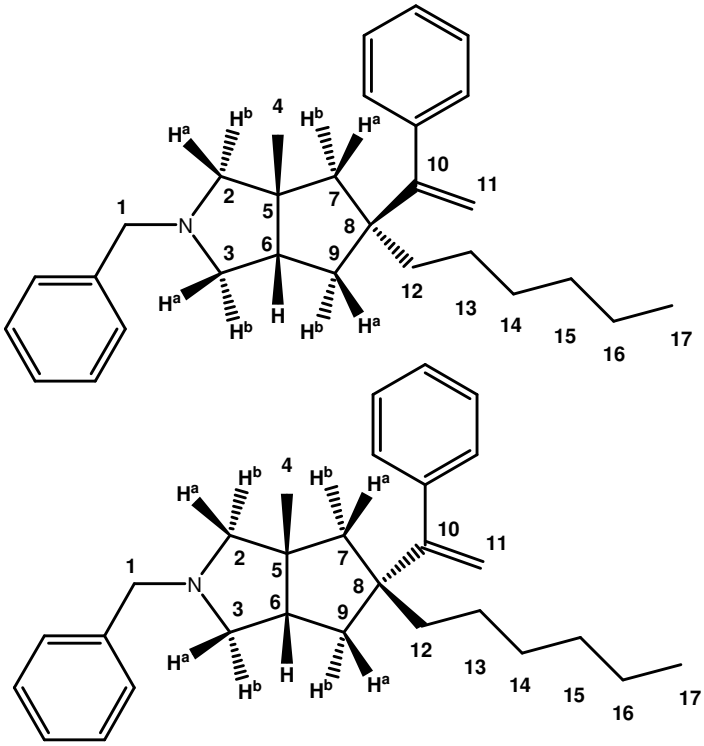
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 150.57 ($C^{12\ major}$), 148.97 ($C^{12\ minor}$), 146.01 ($C^{i\text{-}Ph\ minor}$), 144.68 ($C^{i\text{-}Ph\ major}$), 128.47 ($2CH^{o\text{-}\ or\ m\text{-}Ph\ major}$), 128.20 ($2CH^{o\text{-}\ or\ m\text{-}Ph\ minor}$), 128.09 ($2CH^{o\text{-}\ or\ m\text{-}Ph\ major}$), 127.45 ($2CH^{o\text{-}\ or\ m\text{-}Ph\ minor}$), 125.77 ($CH^{p\text{-}Ph\ major}$), 125.40 ($CH^{p\text{-}Ph\ minor}$), 125.22 ($CH^{13\ minor}$), 125.12 ($CH^{13\ major}$), 78.02 ($CH_2{}^{3/4\ major}$), 77.97 ($CH_2{}^{4/3\ major}$), 77.76 ($CH_2{}^{3/4\ minor}$), 77.21 ($CH_2{}^{4/3\ minor}$), 62.89 ($CH_3{}^{1/2\ minor}$), 59.48 ($CH_3/CH^{1/2/8/9\ major}$), 59.24 ($CH_3/CH^{1/2/8/9\ major}$), 59.15 ($CH_3/CH^{1/2/8/9\ major}$), 59.08 ($CH_3/CH^{1/2/8/9\ minor}$), 54.16 ($2CH^{11\ major + minor}$), 53.12 ($C^{5\ major}$), 52.96 ($C^{5\ minor}$), 50.90 ($CH^{8/9\ minor}$), 48.95 ($CH^{8/9\ major}$), 38.53 ($CH_2{}^{10\ minor}$), 34.60 ($CH_2{}^{6/7\ major}$), 34.29 ($CH_2{}^{minor}$), 33.40 ($CH_2{}^{minor}$), 33.20 ($CH_2{}^{7/6\ major}$), 32.25 ($CH_2{}^{10\ major}$), 31.54 ($CH_2{}^{major}$), 31.43 ($CH_2{}^{minor}$), 29.18 ($CH_2{}^{major}$), 29.04 ($CH_2{}^{major}$), 28.74 ($CH_2{}^{minor}$), 28.59 ($CH_2{}^{minor}$), 22.54 ($CH_2{}^{major}$), 22.41 ($CH_2{}^{minor}$), 14.07 ($CH_3{}^{18\ major}$), 13.99 ($CH_3{}^{18\ major}$).

HRMS (ESI+): Found: $[M + Na]^+$, 379.2607. $[C_{24}H_{36}NaO_2]^+$ requires: 379.2608.

LRMS (CI): *m/z*: 357 ($[M + H]^{+\cdot}$, 74%), 353 ($[M – MeOH]^{+\cdot}$, 65%), 293 ($[M – 2MeOH + H]^{+\cdot}$, 72%), 279 ($[M – Ph]^{+\cdot}$, 59%), 181 (72%), 91 (96%), 45 (100%).

IR (thin film): $\tilde{\nu}$ = 2929 (m), 2864 (m), 1450 (m), 1191 (m) 1099 (s), 964 (w), 700 (s) cm^{-1}.

6.3.11. *rac*-(2*S*,3a*R*,6a*S*)-5-Benzyl-2-hexyl-octahydro-3a-methyl-2-(1-phenylvinyl)-cyclopenta[*c*]pyrrole (major d.r.) and *rac*-(2*R*,3a*R*,6a*S*)-5-benzyl-2-hexyl-octahydro-3a-methyl-2-(1-phenylvinyl)cyclopenta[*c*]pyrrole (minor d.r.) (3.53a)



To a solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same temperature, a solution *N*-allyl-*N*-benzyl-2-methylprop-2-en-1-amine (0.201 g, 1.0 mmol) in in dry THF (3 mL) was added dropwise. After 30 min at –78 °C the reaction mixture was allowed to warm to room temperature and stirred for 3 h. After cooling the reaction mixture to –90 °C, a solution of 1,1-dibromoheptane (0.284 g, 1.1 mmol) in dry THF (1 mL) was added followed by dropwise addition of freshly prepared LiTMP, [prepared from freshly distilled 2,2,6,6-tetramethylpiperidine (0.196 mL, 1.15 mmol) in dry THF (2 mL) and *n*-BuLi (0.46 mL

of a 2.5 M solution in hexanes, 1.15 mmol) at 0 °C over 20 min]. The reaction mixture was stirred for 30 min during which was allowed to warm to –78 °C before dropwise addition of lithium phenyl acetylide, [prepared from phenylacetylene (0.33 mL, 3.0 mmol) in dry THF (3 mL) and *n*-BuLi (1.2 mL of a 2.5 M solution in hexanes, 3.0 mmol) at 0 ^{o}C over 15 min]. The stirring was continued for 3 h during which time the reaction mixture was allowed to warm to –20 °C before addition of MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL). The whole mixture was allowed to warm to room temperature and left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with H_2O (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a yellow oil.

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with 2.5% of Et_2O in hexanes as the eluant gave the title compounds as an inseparable mixture (97 : 3) of both diastereomers in yield of 0.142 g (35%, pale yellow oil).

NMR characterysation does not contain complete data for the minor isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.383 – 7.220 (10H, m, H^{Ar}), 5.270 (1H, d, *J* = 1.6 Hz, H^{11}), 5.110 (1H, d, *J* = 1.6 Hz, H^{11}), 5.071 (1H, d, *J* = 1.8 Hz, $H^{11\ minor}$), 4.958 (1H, d, *J* = 1.8 Hz, $H^{11\ minor}$), 3.587 (2H, br s, H^{1}), 2.701 (1H, d, *J* = 8.8 Hz, H^{2}), 2.568 (1H, d, *J* = 8.8 Hz, H^{3b}), 2.342 (1H, ddd, *J* = 13.0, 7.8, 2.5 Hz, H^{9b}), 2.295 (1H, dd, *J* = 8.8, 6.5 Hz, H^{3a}), 2.208 (1H, dd, *J* = 13.0, 2.3 Hz, H^{7b}), 2.112 (1H, dddd, *J* = 9.5, 7.8, 6.5, 1.3 Hz, H^{6}), 1.884 (1H, d, *J* = 8.8 Hz, H^{2}), 1.654 (1H, m), 1.610 (1H, d, *J* = 13.0 Hz, H^{7a}), 1.480 (1H, dd, *J* = 13.0, 9.5 Hz, H^{9a}), 1.470 (1H, m), 1.395 – 1.312 (7H, m), 1.241 (3H, s, H^{4}), 0.939 (3H, t, *J* = 6.9 Hz, H^{17}), 0.932 (1H, t, *J* = 6.9 Hz, H^{12}).

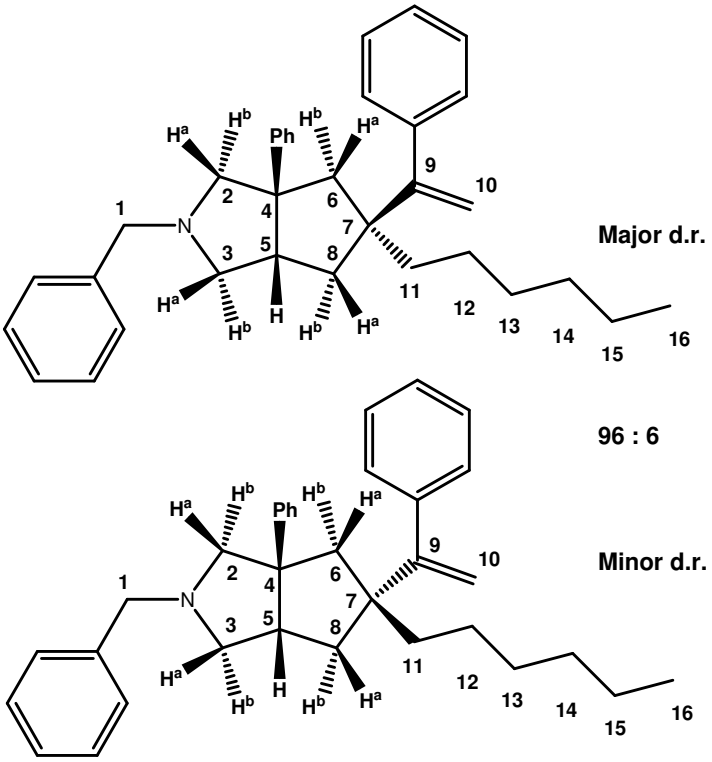
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 154.09 (C^{10}), 143.94 ($C^{i\text{-}Ph\ minor}$), 143.73 ($C^{i\text{-}Ph}$), 139.94 ($C^{i\text{-}Ph}$), 128.61 ($2CH^{o\text{-}\ or\ m\text{-}Ph}$), 128.38 ($2CH^{o\text{-}\ or\ m\text{-}Ph}$), 128.06 ($2CH^{o\text{-}\ or\ m\text{-}Ph}$), 127.48 ($2CH^{o\text{-}\ or\ m\text{-}Ph}$), 126.56 ($CH^{p\text{-}Ph}$), 126.38 ($CH^{p\text{-}Ph}$), 125.83 ($CH^{p\text{-}Ph\ minor}$), 115.97 ($CH_2^{11}$), 113.63 ($CH_2^{11\ minor}$), 70.67 ($CH_2^{2\ minor}$), 70.34 ($CH_2^{2}$), 60.51 ($CH_2^{3}$), 60.03 ($CH_2^{1/3\ minor}$), 59.81 ($CH_2^{3/1\ minor}$), 59.69 ($CH_2^{1}$), 53.98 ($C^{8}$), 53.26 ($C^{8}$), 51.67 ($CH_2^{7}$), 50.54 ($CH_2^{minor}$), 49.64 ($CH^{6}$), 49.31 ($C^{5}$), 49.24 ($C^{5\ minor}$), 48.10 ($CH_2^{minor}$), 45.15 ($CH_2^{minor}$), 45.04 ($CH_2^{9}$), 41.82 ($CH_2^{minor}$), 41.52 ($CH_2$), 31.96 ($CH_2$), 30.34 ($CH_2^{minor}$), 29.87 ($CH_2$), 29.69 ($CH_2^{minor}$), 28.82 ($CH_3^{4\ minor}$), 28.36 ($CH_3^{4}$), 27.39 ($CH_2^{minor}$), 25.72 ($CH_2$), 24.62 ($CH_2^{minor}$), 22.73 ($CH_2$), 14.13 ($CH_3^{17}$).

HRMS (ESI+): Found: $[M + H]^+$, 402.3148. $[C_{29}H_{40}N]^+$ requires: 402.3155.

LRMS (ESI+): *m/z*: 402 ($[M + H]^+$, 100%).

IR (thin film): $\tilde{\nu}$ **=** 2924 (m), 2843 (m), 2767 (m), 1488 (m), 1455 (m), 1029 (m) 905 (s), 775 (m), 737 (m), 700 (s) cm^{-1}.

6.3.12. *rac*-(3a*R*,5*S*,6a*S*)-2-Benzyl-5-hexyl-octahydro-3a-phenyl-5-(1-phenylvinyl)-cyclopenta[*c*]pyrrole (major d.r.) and *rac*-(3a*R*,5*R*,6a*S*)-2-benzyl-5-hexyl-octahydro-3a-phenyl-5-(1-phenylvinyl)-cyclopenta[*c*]pyrrole (minor d.r.) (3.53b)



To a solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same temperature, a solution *N*-benzyl-*N*-(2-phenylallyl)prop-2-en-1-amine (0.263 g, 1.0 mmol) in dry THF (3 mL) was added dropwise. After 30 min at –78 °C the reaction mixture was allowed to warm to room temperature and stirred for 3 h. After cooling the reaction mixture to –90 °C, a solution of 1,1-dibromoheptane (0.264 g, 1.1 mmol) in dry THF (1 mL) was added followed by dropwise addition of freshly prepared LiTMP, [prepared from freshly distilled 2,2,6,6-tetramethylpiperidine (0.196 mL, 1.15 mmol) in dry THF (2 mL) and *n*-BuLi (0.46 mL

of a 2.5 M solution in hexanes, 1.15 mmol) at 0 °C over 20 min]. The reaction mixture was stirred for 30 min during which was allowed to warm to –78 °C before dropwise addition of lithium phenyl acetylide, [prepared from phenylacetylene (0.33 mL, 3.0 mmol) in dry THF (3 mL) and *n*–BuLi (1.2 mL of a 2.5 M solution in hexanes, 3.0 mmol) at 0 ^{o}C over 15 min]. The stirring was continued for 3 h during which time the reaction mixture was allowed to warm to –20 °C before addition of MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL). The whole mixture was allowed to warm to room temperature and left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with H_2O (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a yellow oil.

Purification of the crude material by column chromatography on SiO_2 (230-400 mesh) with 5 → 10% of Et_2O in hexanes as the eluant gave the title compounds as an inseparable mixture (94 : 6) of both diastereomers in yield of 0.066 g (14%, pale yellow oil).

NMR characterysation does not contain complete data for the minor isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.331 – 6.938 (13H, m, H^{Ar}), 6.506 (2H, d, *J* = 6.8 Hz, $H^{C1\text{-}o\text{-}Ph}$), 5.054 (1H, d, *J* = 1.3 Hz, $H^{10\ minor}$), 4.916 (1H, d, *J* = 1.0 Hz, H^{10}), 4.002 (1H, d, *J* = 1.3 Hz, $H^{10\ minor}$), 4.710 (1H, d, *J* = 1.0 Hz, H^{10}), 3.604 (1H, d, *J* = 13.3 Hz, $H^{1\ minor}$), 3.542 (1H, d, *J* = 13.2 Hz, H^{1}), 3.464 (1H, d, *J* = 13.2 Hz, H^{1}), 3.071 (1H, q, *J* = 7.7 Hz, H^{5}), 3.011 (1H, d, *J* = 8.8 Hz, H^{2}), 2.711 (1H, d, *J* = 8.7 Hz, H^{3b}), 2.579 (1H, d, *J* = 13.0 Hz, H^{6}), 2.428 (1H, apparent t, *J* = 11.4 Hz, H^{8a}), 2.269 (1H, t, *J* = 7.7 Hz, H^{3a}), 1.943 (1H, d, *J* = 8.8 Hz, H^{2}), 1.862 (1H, d, *J* = 12.8 Hz, H^{6}), 1.642 (1H, m), 1.592 (1H, d, *J* = 11.4 Hz, H^{8b}), 1.432 (1H, m), 1.267 – 1.204 (8H, m), 0.864 (3H, t, *J* = 6.8 Hz, $H^{16\ major}$), 0.713 (1H, t, *J* = 7.3 Hz, $H^{16\ minor}$).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 156.05 ($C^{9\ major}$), 152.19 ($C^{9\ minor}$), 149.78 ($C^{i\text{-}Ph\ minor}$), 149.29 ($C^{i\text{-}Ph\ major}$), 143.79 ($C^{i\text{-}Ph\ minor}$), 143.16 ($C^{i\text{-}Ph\ major}$), 139.76 ($C^{i\text{-}Ph\ major}$), 139.71 ($C^{i\text{-}Ph\ minor}$), 128.49 ($2CH^{o\text{-}\ or\ m\text{-}Ph\ major}$), 128.44 ($2CH^{o\text{-}\ or\ m\text{-}Ph\ minor}$), 128.43 ($2CH^{o\text{-}\ or\ m\text{-}Ph\ minor}$), 128.37 ($2CH^{o\text{-}\ or\ m\text{-}Ph\ major}$), 128.19 ($2CH^{o\text{-}\ or\ m\text{-}Ph\ minor}$), 128.12 ($2CH^{o\text{-}\ or\ m\text{-}Ph\ major}$), 128.09 ($2CH^{o\text{-}\ or\ m\text{-}Ph\ minor}$), 128.01 ($2CH^{o\text{-}\ or\ m\text{-}Ph\ major}$), 127.49 ($2CH^{o\text{-}\ or\ m\text{-}Ph\ minor}$), 127.14 ($2CH^{o\text{-}\ or\ m\text{-}Ph\ major}$), 126.66 ($CH^{p\text{-}Ph\ major}$), 126.46 ($2CH^{o\text{-}\ or\ m\text{-}Ph\ major}$), 126.41 ($CH^{p\text{-}Ph\ minor}$), 126.26 ($2CH^{o\text{-}\ or\ m\text{-}Ph\ minor}$), 126.05 ($CH^{p\text{-}Ph\ major}$), 125.80 ($CH^{p\text{-}Ph\ minor}$), 125.42

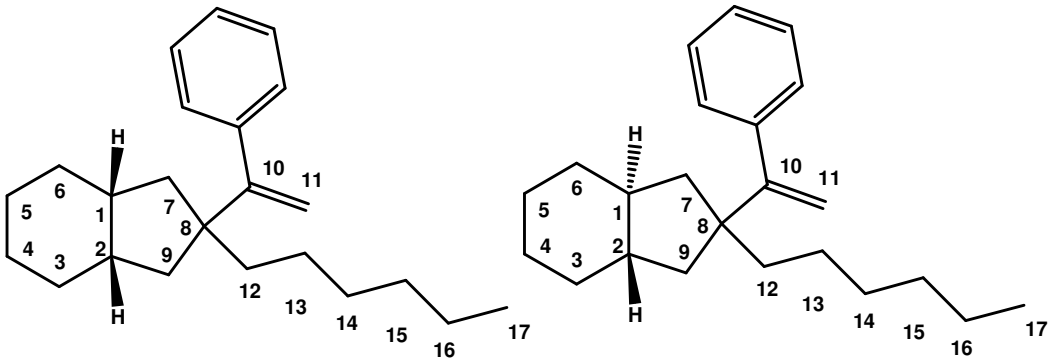
($CH^{p\text{-}Ph\ minor}$), 125.27 ($CH^{p\text{-}Ph\ major}$), 116.56 ($CH_2^{10\ major}$), 113.76 ($CH_2^{10\ minor}$), 71.38 ($CH_2^{2\ major}$), 68.09 ($CH_2^{2\ minor}$), 61.86 ($CH_2^{3\ minor}$), 60.93 ($CH_2^{3\ major}$), 59.65 ($CH_2^{1\ minor}$), 59.44 ($CH_2^{1\ major}$), 58.02 ($C^{7\ minor}$), 57.75 ($C^{7\ major}$), 53.55 ($C^{4\ major}$), 53.13 ($CH_2^{6\ major}$), 52.80 ($C^{4\ minor}$), 49.03 (CH_2^{minor}), 48.68 (CH_2^{minor}), 48.45 ($CH^{5\ minor}$), 44.67 ($CH^{5\ major}$), 44.54 ($CH_2^{8\ major}$), 40.68 (CH_2^{major}), 40.31 (CH_2^{minor}), 31.98 (CH_2^{major}), 31.88 (CH_2^{minor}), 29.88 (CH_2^{major}), 29.69 (CH_2^{minor}), 25.77 (CH_2^{major}), 24.23 (CH_2^{minor}), 22.74 (CH_2^{major}), 22.63 (CH_2^{minor}), 14.13 ($CH_3^{16\ major}$), 14.10 ($CH_3^{16\ minor}$).

HRMS (ESI+): Found: $[M + H]^+$, 464.3303. $[C_{34}H_{42}N]^+$ requires: 464.3312.

LRMS (ESI+): *m/z*: 464 ($[M + H]^+$, 100%).

IR (thin film): $\tilde{\nu}$ = 2956 (m), 2933 (m), 2847 (m), 2775 (m), 1607 (w), 1493 (m), 1452 (m), 1024 (m) 907 (s), 733 (s), 699 (s) cm^{-1}.

6.3.13. *rac*-(3a*R*,7a*S*)-2-Hexyl-octahydro-2-(1-phenylvinyl)-1-*H*-indene (major d.r.) and *rac*-(3a*R*,7a*R*)-2-hexyl-octahydro-2-(1-phenylvinyl)-1-*H*-indene (minor d.r.) (3.59)



Major d.r. **68 : 32** **Minor d.r.**

To a solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same temperature, a solution of 1,7-octadiene (0.110 g, 1.0 mmol) in dry THF (3 mL) was added dropwise. After 30 min at –78 °C the reaction mixture was allowed to warm to room temperature and stirred for 2 h. After cooling the reaction to –78 °C, a solution of 1,1-dibromoheptane (0.335 g, 1.30 mmol) in dry THF (1 mL) was added followed by dropwise addition of LDA (0.83 mL of a 1.8 M solution, 1.50 mmol). The reaction mixture was stirred at –78 °C for 15 min before dropwise addition of lithium phenyl acetylide, [prepared from phenylacetylene (0.33 mL, 3.0 mmol) in dry THF (3 mL) and *n*-BuLi (1.2 mL of a 2.5 M solution in hexanes, 3.0

mmol) at –5 °C over 15 min]. The stirring was continued for 30 min during which time the reaction mixture was allowed to warm to –50 °C before addition of MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL). The whole mixture was allowed to warm to room temperature and left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with H_2O (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as an orange oil.

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluant gave the title compounds as a pale yellow oil in combined yield of 0.165 g (53%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.315 – 7.214 (10H, m, $H^{Ar\ major\ +\ minor}$), 5.189 (1H, d, *J* = 1.4 Hz, $H^{11\ major}$), 5.172 (1H, d, *J* = 1.5 Hz, $H^{11\ minor}$), 5.008 (1H, d, *J* = 1.4 Hz, $H^{11\ major}$), 4.982 (1H, d, *J* = 1.5 Hz, $H^{11\ minor}$), 2.220 (1H, dd, *J* = 12.3, 5.5 Hz, H^{minor}), 2.158 – 2.041 (4H, m), 1.862 – 1.735 (3H, m), 1.612 – 1.394 (16H, m), 1.372 – 1.076 (22H, m), 1.024 – 0.916 (2H, m), 0.878 (3H, t, *J* = 7.0 Hz, $H^{17\ major}$), 0.870 (3H, t, *J* = 7.0 Hz, $H^{17\ minor}$).

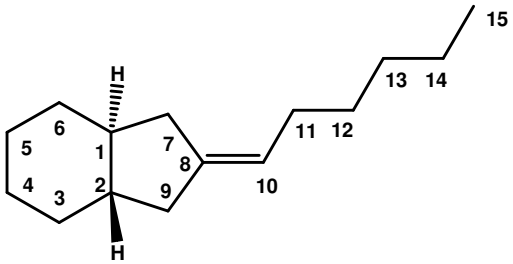
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 158.24 ($C^{10\ minor}$), 156.95 ($C^{10\ major}$), 144.14 ($C^{i\text{-}Ph\ minor}$), 143.90 ($C^{i\text{-}Ph\ major}$), 128.40 ($2CH^{o\text{-}\ or\ m\text{-}Ph\ major}$), 128.20 ($2CH^{o\text{-}\ or\ m\text{-}Ph\ minor}$), 127.50 ($2CH^{o\text{-}\ or\ m\text{-}Ph\ minor}$), 127.44 ($2CH^{o\text{-}\ or\ m\text{-}Ph\ major}$), 126.31 ($2CH^{p\text{-}Ph\ major\ +\ minor}$), 113.82 ($CH^{11\ major}$), 113.05 ($CH^{11\ minor}$), 50.71 ($C^{8\ major}$), 49.31 ($C^{8\ minor}$), 46.88 ($CH_2$ ^{minor}), 45.91 ($CH^{1/2\ minor}$), 45.64 ($CH^{2/1\ minor}$), 44.32 ($CH_2{}^{minor}$), 43.35 ($2CH_2$ ^{minor}), 43.07 ($2CH_2$ ^{major}), 42.78 (CH_2 ^{minor}), 37.84 ($2CH^{1\ +\ 2\ major}$), 31.87 ($CH_2{}^{minor}$), 31.77 ($2CH_2{}^{major}$), 29.80 ($2CH_2{}^{major\ +\ minor}$), 28.34 ($2CH_2{}^{major}$), 26.43 ($CH_2{}^{minor}$), 26.35 ($CH_2{}^{minor}$), 25.81 ($CH_2{}^{major}$), 25.03 ($CH_2{}^{minor}$), 23.17 ($2CH_2{}^{major}$), 22.63 ($2CH_2{}^{major\ +\ minor}$), 14.08 ($2CH_3{}^{17}$ $^{major\ +\ minor}$).

HRMS (EI): Found: $[M]^+$, 310.2661. $C_{23}H_{34}$ requires: 310.2661.

LRMS (CI): *m/z*: 311 ($[M + H]^{+\cdot}$, 4%), 310 ($[M]^{+\cdot}$, 3%), 226 ($[M – Hex + H]^{+\cdot}$, 100%).

IR (thin film): $\tilde{\nu}$ **=** 2922 (s), 2847 (s), 1444 (m), 896 (s), 771 (s), 695 (s) cm^{-1}.

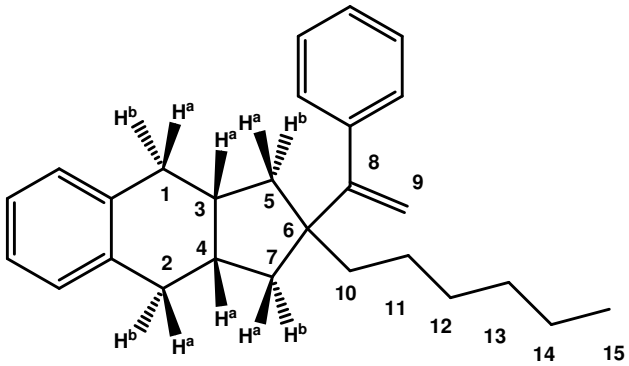
6.3.14. *rac*-(3a*S*,7a*R*)-2-Hexylidene-octahydro-1-*H*-indene (3.60)



The product was obtained simultaneously with products **3.59**. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluant gave the title compound as a pale yellow oil in yield of 0.084 g (40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.258 (1H, tdd, *J* = 9.3, 4.5, 2.3 Hz, H^{10}), 2.305 – 1.929 (8H, m), 1.538 – 1.279 (14H, m), 0.902 (3H, t, *J* = 7.0 Hz, H^{15}).
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 141.95 (C^8), 122.05 (CH^{10}), 38.21 ($CH^{1/2}$), 38.18 ($CH^{2/1}$), 37.91 (CH_2), 33.05 (CH_2), 31.62 (CH_2), 29.51 (CH_2), 29.40 (CH_2), 27.55 (CH_2), 27.19 (CH_2), 23.29 (CH_2), 22.76 (CH_2), 22.63 (CH_2), 14.10 (CH_3^{15}).
HRMS (EI): Found: $[M]^+$, 206.2036. $C_{15}H_{26}$ requires: 206.2034.
LRMS (CI): *m/z*: 207 ($[M + H]^{+\cdot}$, 10%), 206 ($[M]^{+\cdot}$, 18%), 121 ($[M – Hex]^{+\cdot}$, 100%).
IR (thin film): $\tilde{\nu}$ = 2922 (s), 2850 (m), 1448 (m) cm^{-1}.

6.3.15. *rac*-(3a*S*,9a*R*)-2-Hexyl-2,3,3a,4,9,9a-hexahydro-2-(1-phenylvinyl)-1*H*-cyclopenta[*b*]napthalene (3.64)



To a solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same temperature, a solution of 1,2-diallylbenzene (0.158 g, 1.0 mmol) in dry THF (3 mL) was added dropwise. After 30 min at –78 °C the

reaction mixture was allowed to warm to room temperature and stirred for 2.5 h. After cooling the reaction to –85 °C, a solution of 1,1-dibromoheptane (0.335 g, 1.3 mmol) in dry THF (1 mL) was added followed by dropwise addition of LDA (0.85 mL of a 1.8 M solution, 1.5 mmol). After 15 min a dropwise addition of lithium phenyl acetylide followed, [prepared from phenylacetylene (0.33 mL, 3.0 mmol) in dry THF (3 mL) and *n*-BuLi (1.2 mL of a 2.5 M solution in hexanes, 3.0 mmol) at –5 ^{o}C over 15 min]. The stirring was continued for 1 h during which time the reaction mixture was allowed to warm to –55 °C before addition of MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL). The whole mixture was allowed to warm to room temperature and left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with H_2O (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a yellow oil.

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluant gave the title compound as a pale yellow oil in yield of 0.142 g (40%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.447 – 7.373 (3H, m, H^{Ar}), 7.291 – 7.222 (6H, m, H^{Ar}), 5.357 (1H, d, *J* = 1.8 Hz, H^{9}), 5.158 (1H, d, *J* = 1.8 Hz, H^{9}), 2.888 (2H, dd, *J* = 13.9, 5.5 Hz, $H^{1b + 2b}$), 2.611 (2H, tdd, *J* = 16.2, 10.0, 5.7 Hz, $H^{3 + 4}$), 2.494 (2H, dd, *J* = 13.9, 6.2 Hz, $H^{1a + 2a}$), 2.305 (2H, ddd, *J* = 12.2, 5.0, 2.4 Hz, $H^{5b + 7b}$), 1.588 – 1.378 (10H, m), 1.074 (2H, dd, *J* = 12.2, 10.0 Hz, $H^{5a + 7a}$), 1.029 (3H, t, *J* = 6.9 Hz, H^{15}).

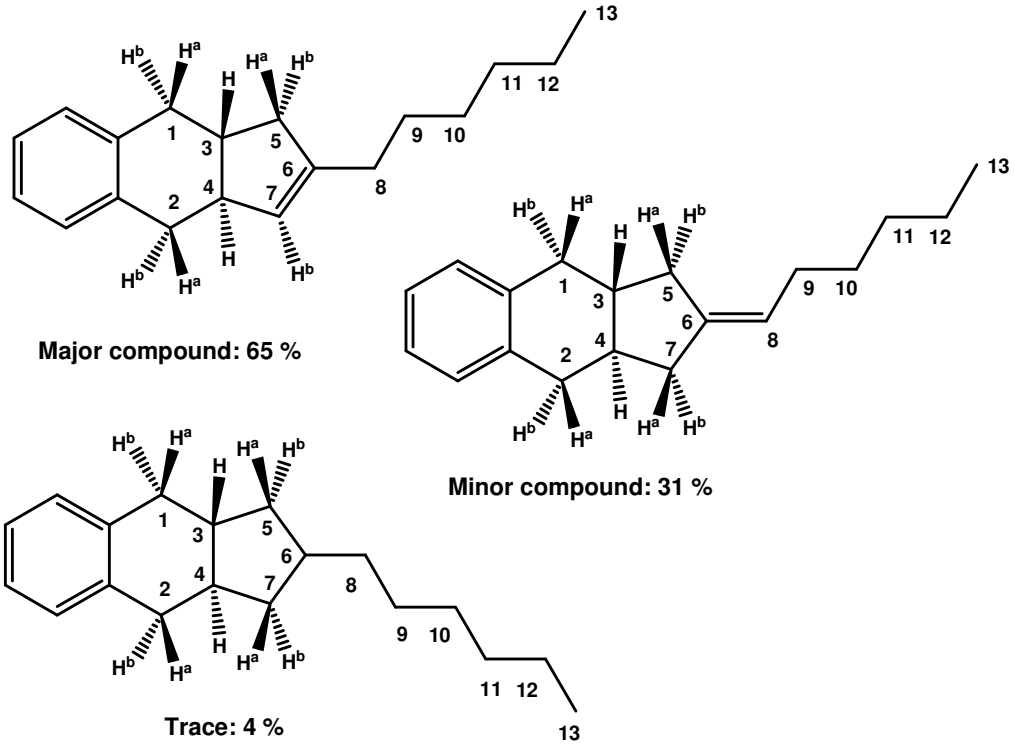
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 153.39 (C^{8}), 143.44 ($C^{i\text{-}Ph}$), 139.54 ($2C^{i\text{-}Ph}$), 128.40 ($2CH^{o\text{- or }m\text{-}Ph}$), 127.57 ($2CH^{o\text{- or }m\text{-}Ph}$), 127.49 ($2CH^{o\text{- or }m\text{-}Ph}$), 126.41 ($CH^{p\text{-}Ph}$), 125.81 ($2CH^{o\text{- or }m\text{-}Ph}$), 115.40 ($CH_2{}^{9}$), 51.99 ($C^{6}$), 44.03 ($2CH_2{}^{5 + 7}$), 40.07 ($CH_2$), 36.02 ($2CH^{3 + 4}$), 34.53 ($2CH_2{}^{1 + 2}$), 31.91 ($CH_2$), 29.86 ($CH_2$), 25.78 ($CH_2$), 22.71 ($CH_2$), 14.10 ($CH_3{}^{15}$).

HRMS (EI): Found: $[M]^{+}$, 358.2673. $C_{27}H_{34}$ requires: 358.2661.

LRMS (CI): *m/z*: 359 ($[M + H]^{+\cdot}$, 30%), 274 ($[M – Hex + H]^{+\cdot}$, 100%).

IR (thin film): $\tilde{\nu}$ **=** 2929 (s), 2853 (m), 2767 (m), 1488 (m), 1455 (m), 899 (m), 775 (m), 748 (s), 705 (s) cm^{-1}.

6.3.16. *rac*-(3a*R*,9a*S*)-1-Hexyl-3a,4,9,9a-tetrahydro-1*H*-cyclopenta[*b*]naphtalene (major compound, 3.65), *rac*-(3a*S*,9a*R*)-2-hexylidene-2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[*b*]naphtalene (minor compound, 3.66) and *rac*-(3a*S*,9a*R*)-2-hexyl-2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[*b*]naphtalene (trace, 3.67)



These products were obtained simultaneously with product **3.64**. Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexanes as the eluant gave the title compounds as colourless oil in yield of 0.083 g (33%) as an inseparable mixture of compounds with the ratio stated above.

NMR characterysation does not contain data for the compound 3.67.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.277 – 7.120 (8H, m, $H^{Ar\ major\ +\ minor}$), 5.264 (1H, m, $H^{8\ minor}$), 5.198 (1H, br s, $H^{7\ major}$), 3.084 (1H, m), 2.914 – 2.781 (4H, m), 2.741 – 2.660 (1H, m), 2.612 – 2.307 (9H, m), 2.098 (1H, dd, *J* = 15.0, 6.0 Hz, H^{minor}), 2.015 – 1.959 (6H, m), 1.415 – 1.184 (14H, m), 0.927 – 0.892 (6H, m, $H^{13\ major\ +\ minor}$).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 153.39 ($C^{6\ major}$), 141.12 ($C^{6\ minor}$), 139.77 ($C^{i\text{-}Ph\ major}$), 139.45 ($C^{i\text{-}Ph\ major}$), 137.74 ($C^{i\text{-}Ph\ minor}$), 137.52 ($C^{i\text{-}Ph\ minor}$), 128.17 ($CH^{Ar\ minor}$), 127.28 ($CH^{Ar\ major}$), 127.12 ($CH^{Ar\ major}$), 126.70 ($CH^{7\ major}$), 125.82 ($CH^{Ar\ minor}$), 125.69 ($2CH^{Ar\ major}$), 125.66 ($CH^{Ar\ minor}$), 125.64 ($CH^{Ar\ minor}$), 121.62 ($CH^{8\ minor}$), 45.41

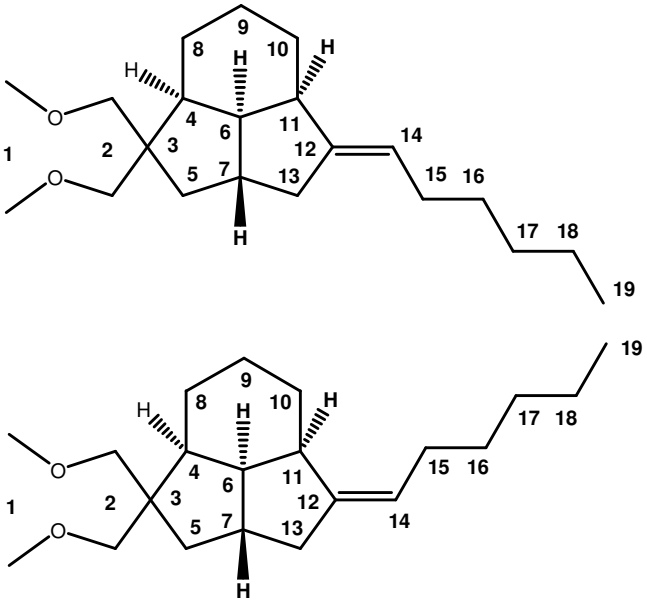
($CH^{4\ major}$), 42.22 (CH_2^{major}), 39.87 (CH_2^{minor}), 36.65 ($CH^{3/4\ minor}$), 36.09 ($CH^{4/3\ minor}$), 35.89 (CH_2^{major}), 35.79 ($CH^{3\ major}$), 34.68 (CH_2^{minor}), 34.39 (CH_2^{major}), 33.19 (CH_2^{minor}), 32.80 (CH_2^{minor}), 31.72 (CH_2^{major}), 31.55 (CH_2^{minor}), 30.92 (CH_2^{major}), 29.47 (CH_2^{minor}), 29.37 (CH_2^{minor}), 28.83 (CH_2^{major}), 27.49 (CH_2^{major}), 22.59 ($2CH_2^{major\ +\ minor}$), 14.10 ($2CH_3^{13\ major\ +\ minor}$).

HRMS (EI): Found: $[M]^+$, 254.2031. $C_{19}H_{26}$ requires: 254.2034.

LRMS (CI): *m/z*: 256 ($[M]^{+\cdot}$, 13%), 255 ($[M + H]^+$, 69%), 254 ($[M]^{+\cdot}$, 88%), 169 (67%), 128 (79%), 104 (100%).

IR (thin film): $\tilde{\nu}$ = 2922 (s), 2854 (m), 2824 (m), 1463 (m), 733 (s) cm^{-1}.

6.3.17. *rac*-(2a*R*,4*E*,4a*R*,7a*S*,7b*R*)-1,1-Bis(methoxymethyl)-4-hexylidenedecahydro-1*H*-cyclopenta[*cd*]indene (major d.r.) and *rac*-(2a*R*,4*Z*,4a*R*,7a*S*,7b*R*)-1,1-bis(methoxymethyl)-4-hexylidenedecahydro-1*H*-cyclopenta[*cd*]indene (minor d.r.) (3.70)



To a solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same temperature, a solution of 3-(1-methoxy-2-(methoxymethyl)pent-4-en-2-yl)cyclohex-1-ene (0.224 g, 1.0 mmol) in dry THF (3 mL) was added dropwise. After 30 min at –78 °C the reaction mixture was allowed to warm to room temperature and stirred for 2 h. After cooling the reaction mixture to –90 °C, a solution of 1,1-dibromoheptane (0.284 g, 1.1 mmol) in dry THF (1 mL) was added

followed by dropwise addition of freshly prepared LiTMP, [prepared from freshly distilled 2,2,6,6-tetramethylpiperidine (0.196 mL, 1.15 mmol) in dry THF (2 mL) and *n*-BuLi (0.46 mL of a 2.5 M solution in hexanes, 1.15 mmol) at 0 °C over 20 min]. The reaction mixture was stirred for 20 min during which was allowed to warm to –78 °C before dropwise addition of lithium phenyl acetylide. [prepared from phenylacetylene (0.33 mL, 3.0 mmol) in dry THF (3 mL) and *n*-BuLi (1.2 mL of a 2.5 M solution in hexanes, 3.0 mmol) at 0 ^{o}C over 15 min]. The stirring was continued for 2 h during which time the reaction mixture was allowed to warm to RT before addition of MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL). The whole mixture was allowed to warm to room temperature and left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with H_2O (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a yellow oil.

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with 5% of Et_2O in hexanes and Kugelrohr distillation (200 °C, 1.0 mmHg) gave the title compounds as an inseparable mixture 3 : 1 of *E : Z* isomers as a pale yellow oil in yield of 0.029 g (9%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 5.196 – 5.157 (2H, m, $H^{14\ major\ +\ minor}$), 3.383 (2H, d, *J* = 9.0 Hz, $H^{2\ major\ +\ minor}$), 3.345 (6H, s, $H^{1\ major\ +\ minor}$), 3.313 (6H, s, $H^{1\ major\ +\ minor}$), 3.345 – 3.313 (4H, m, $H^{2\ major\ +\ minor}$), 3.230 (1H, d, *J* = 8.8 Hz, $H^{2\ major}$), 3.225 (1H, d, *J* = 8.8 Hz, $H^{2\ minor}$), 2.538 (1H, dd, *J* = 17.3, 7.8 Hz, $H^{13\ minor}$), 2.421 (1H, dd, *J* = 15.0, 6.0 Hz, $H^{13\ major}$), 2.363 – 2.190 (4H, m, $H^{major\ +\ minor}$), 2.001 – 1.832 (6H, m, $H^{major\ +\ minor}$), 1.800 – 1.502 (14H, m, $H^{major\ +\ minor}$), 1.352 – 1.194 (14H, m, $H^{major\ +\ minor}$), 1.152 – 0.918 (4H, m, $H^{major\ +\ minor}$), 0.884 (6H, t, *J* = 6.8 Hz, $H^{19\ major\ +\ minor}$).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 152.16 ($C^{12\ major}$), 151.44 ($C^{12\ minor}$), 123.28 ($CH^{14\ minor}$), 122.41 ($CH^{14\ major}$), 78.50 ($2CH_2{}^{2\ major\ +\ minor}$), 74.53 ($2CH_2{}^{2\ major\ +\ minor}$), 59.18 ($2CH_3{}^{1\ major\ +\ minor}$), 58.91 ($2CH_3{}^{1\ major\ +\ minor}$), 55.73 ($C^{3\ major}$), 55.60 ($C^{3\ minor}$), 53.78 ($CH^{minor}$), 53.24 ($CH^{major}$), 41.70 ($CH^{major}$), 41.52 ($CH^{minor}$), 39.21 ($CH^{major}$), 38.83 ($CH^{minor}$), 38.67 ($CH^{major}$), 36.56 ($CH^{minor}$), 36.27 ($CH_2{}^{13\ minor}$), 35.06 ($CH_2{}^{major}$), 34.95 ($CH_2{}^{minor}$), 32.12 ($CH_2{}^{13\ major}$), 31.66 ($CH_2{}^{minor}$), 31.52 ($CH_2{}^{major}$), 29.91 ($CH_2{}^{minor}$), 29.51 ($CH_2{}^{major}$) 29.35 ($2CH_2{}^{major\ +\ minor}$), 29.13 ($CH_2{}^{major}$), 27.74 ($CH_2{}^{minor}$), 24.97

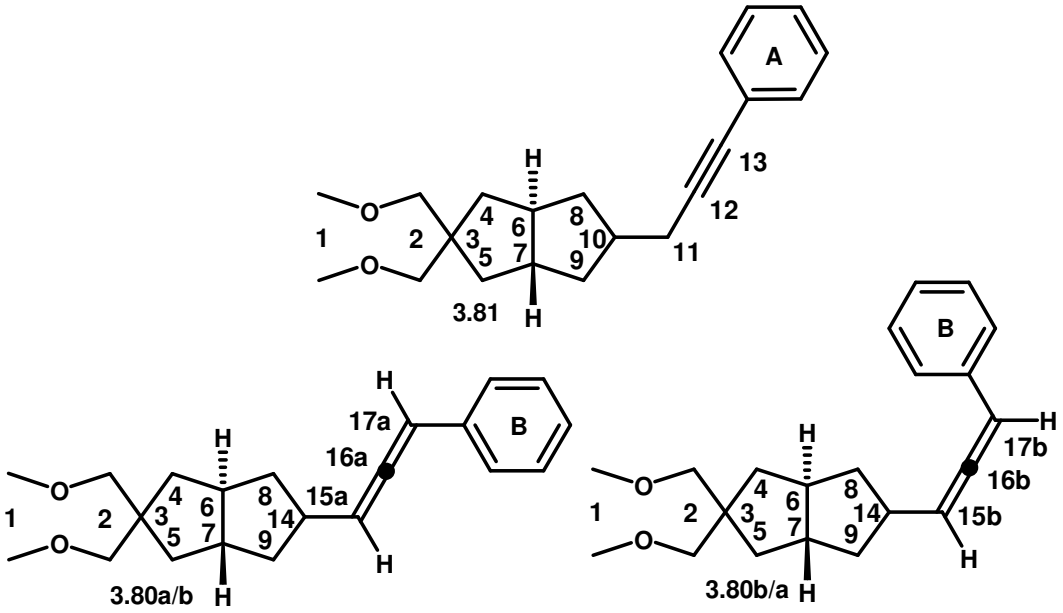
(CH_2^{minor}), 24.84 (CH_2^{major}), 23.22 (CH_2^{minor}), 23.19 (CH_2^{major}), 22.63 (CH_2^{minor}), 22.59 (CH_2^{major}), 14.08 ($2CH_3^{19\ major\ +\ minor}$).

HRMS (EI): Found: $[M]^+$, 320.2710. $C_{21}H_{36}O_2$ requires: 320.2715.

LRMS (EI): *m/z*: 322 ($[M + 2H]^{+\cdot}$, 5%), 321 ($[M + H]^{+\cdot}$, 23%), 320 ($[M]^{+\cdot}$, 28%), 289 ($[M – MeOH + H]^{+\cdot}$, 46%), 288 ($[M – MeOH]^{+\cdot}$, 56%), 243 (65%), 203 (100%).

IR (thin film): $\tilde{\nu}$ = 2926 (s), 2854 (s), 1452 (m), 1202 (m), 1111 (s), 956 (m) cm^{-1}.

6.3.18. *rac*-(3a*S*,6a*S*)-Octahydro-2,2-bis(methoxymethyl)-5-(3-phenylpropa1,2-dienyl)pentalene (3.80a, b) and *rac*-(3a*S*,6a*S*)-octahydro-2,2-bis(methoxymethyl)-5-(3-phenylprop-2-ynyl)pentalene (3.81)



To a solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same temperature, a solution of bis(methoxymethyl)hepta-1,6-diene (0.184 g, 1.0 mmol) in dry THF (3 mL) was added dropwise. After 30 min at –78 °C the reaction mixture was allowed to warm to room temperature and stirred for 12 h. After cooling the reaction to –78 °C, 1,1-dichloromethane (0.064 mL, 1.0 mmol) was added followed by dropwise addition of freshly prepared LiTMP, [prepared from freshly distilled 2,2,6,6-tetramethylpiperidine (0.20 mL, 1.2 mmol) in dry THF (2 mL) and *n*-BuLi (0.48 mL of a 2.5 M solution in hexanes, 1.15 mmol) at 0 °C over 20 min]. The reaction mixture was stirred for 1 h during which was allowed to warm to –65 °C

before re-cooling to –78 °C and dropwise addition of lithium phenyl acetylide, [prepared from phenylacetylene (0.33 mL, 3.0 mmol) in dry THF (3 mL) and *n*-BuLi (1.2 mL of a 2.5 M solution in hexanes, 3.0 mmol) at 0 ^{o}C over 15 min]. The stirring was continued for 3 h during which time the reaction mixture was allowed to warm to –35 °C before addition of MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL). The whole mixture was allowed to warm to room temperature and left stirring for 18 h. The mixture then was poured onto H_2O (100 mL), the products were extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with H_2O (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a brown oil.

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with 5% of Et_2O in hexanes gave the title compounds as an inseparable mixture of compounds in the following ratio: **3.80a/b : 3.80b/a**, 1 : 1.8 and **3.80 : 3.81**, 1 : 2, as a pale yellow oil in combined yield of 0.033 g (10%).

Spectral data contain NMR and LRMS analysis only.

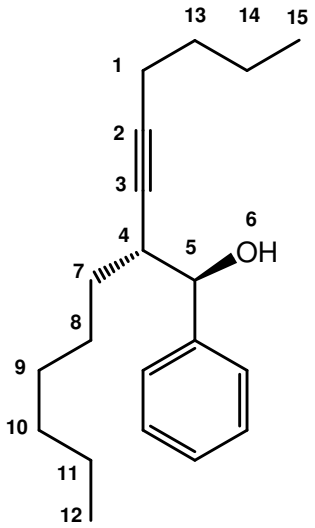
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.393 – 7.145 (15H, m, H^{Ar}), 6.162 (1H, dd, *J* = 6.3, 3.0 Hz, $H^{17a/b}$), 6.160 (1H, dd, *J* = 6.3, 2.9 Hz, $H^{17a/b}$), 5.685 (2H, td, *J* = 6.5, 3.5 Hz, H^{15}), 3.334 – 3.218 (30H, m), 2.723 – 2.650 (2H, m, H^{14}), 2.433 (2H, d, *J* = 7.0 Hz, H^{10}), 1.989 – 1.348 (27H, m), 1.319 – 0.841 (14H, m).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 203.46 ($C^{16a/b}$), 203.40 ($C^{16a/b}$), 135.18 ($2C^{i\text{-}Ph\ B}$), 131.54 ($2CH^{o\text{-}Ph\ A}$), 128.53 ($4CH^{m\text{-}Ph\ B}$), 128.14 ($2CH^{m\text{-}Ph\ A}$), 127.40 ($CH^{p\text{-}Ph\ A}$), 126.59 ($2CH^{o\text{-}Ph\ B}$), 126.54 ($2CH^{p\text{-}Ph\ B}$), 126.49 ($2CH^{o\text{-}Ph\ B}$), 124.15 ($C^{i\text{-}Ph\ A}$), 101.81 ($CH^{17a/b}$), 101.76 ($CH^{17a/b}$), 95.73 ($2CH^{15a+b}$), 89.90 (C^{12}), 80.45 (C^{13}), 78.17 ($2CH_2{}^{2}$), 78.10 ($4CH_2{}^{2}$), 59.20 ($6CH_3{}^{1}$), 54.42 ($2C^{3}$), 54.34 (C^{3}), 52.33 ($3CH^{6/7}$), 50.90 ($2CH^{6/7}$), 50.76 ($CH^{6/7}$), 43.33 (CH^{10}), 42.92 ($2CH^{14}$), 34.72 ($2CH_2$), 34.40 (CH_2), 34.33 ($2CH_2$), 34.25 ($2CH_2$), 34.20 ($2CH_2$), 33.61 ($2CH_2$), 32.51 (CH_2), 26.99 (CH_2).

LRMS (CI): *m/z*: 313 ($[M + H]^{+\cdot}$, 9%), 268 ($[M – MeOH + H]^{+\cdot}$, 6%), 267 ($[M – Et_2O + H]^{+\cdot}$, 4%), 249 ($[M – 2MeOH + H]^{+\cdot}$, 9%), 235 ($[M – Ph]^{+\cdot}$, 7%), 115 ($[C_9H_7]^{+\cdot}$, 34%).

6.4. Experimental from chapter 4

6.4.1. *rac*-(1*R*,2*R*)-2-Hexyl-1-phenyloct-3-yn-1-ol (4.68a)



To a stirred solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same tempereature, a solution of the non-1-yn-3-yl benzensulfonate (0.294 g, 1.0 mmol) in dry THF (1 mL) was added dropwise followed by dropwise addition of LDA (0.56 mL of a 1.8 M solution, 1.0 mmol). The stirring was continued for a further 1 h during which time the reaction mixture was allowed to warm to –50 °C. The reaction mixture was re-cooled to –78 °C and a solution of benzaldehyde (0.15 mL, 1.5 mmol) in dry THF (1 mL) was added followed by dropwise addition of $BF_3{\cdot}OEt_2$ (0.18 ml, 1.5 mmol). The reaction mixture was warmed gradually to RT and stirred at the same temperature for 3 h before quenching with MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL) and the mixture was left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 75 mL). The combined organic phases were washed with H_2O (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a yellow oil (*anti : syn* diastereoisomers in the ratio of 77 : 23).

Purification of the crude material by careful column chromatography on SiO_2 (230 – 400 mesh) with hexane : EtOAc (10 : 1) as the eluent to allow partial separation of the diasteroisomers to give a pure fraction of the title compound (*anti* isomer) as a pale yellow oil and a mixed fraction of both isomers in combined yield of 0.10 g (35%).

Spectral data of the *anti* diastereoisomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.36 – 7.29 (5H, m, H^{Ar}), 4.49 (1H, dd, *J* = 6.8, 4.3 Hz, H^5), 2.67 (1H, ddt, *J* = 6.8, 4.3, 2.3 Hz, H^4), 2.64 (1H, d, *J* = 4.3 Hz, OH^6), 2.23 (2H, td, *J* = 7.0, 2.3 Hz, H^1), 1.54 – 1.21 (14H, m), 0.92 (3H, t, *J* = 7.3 Hz, $H^{12/15}$), 0.87 (3H, t, *J* = 6.9 Hz, $H^{12/15}$).

^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 142.12 ($C^{i\text{-}Ph}$), 128.18 ($2CH^{m\text{-}Ph}$), 127.68 ($CH^{p\text{-}Ph}$), 126.61 ($2CH^{o\text{-}Ph}$), 85.29 (C^2), 79.35 (C^3), 76.37 (CH^5), 41.82 (CH^4), 31.71 ($2CH_2$), 31.07 (CH_2), 28.97 (CH_2), 27.36 (CH_2), 22.55 (CH_2), 21.92 (CH_2), 18.46 (CH_2^1), 14.04 ($CH_3^{12/15}$), 13.58 ($CH_3^{12/15}$).

HRMS (EI): Found: $[M - H_2O]^+$, 268.2186. $[C_{20}H_{28}]^+$ requires: 268.2191.

LRMS (CI): *m/z*: 287 ($[M + H]^+$, 38%), 286 ($[M]^+$, 42%), 269 ($[M - H_2O + H$, 100%).

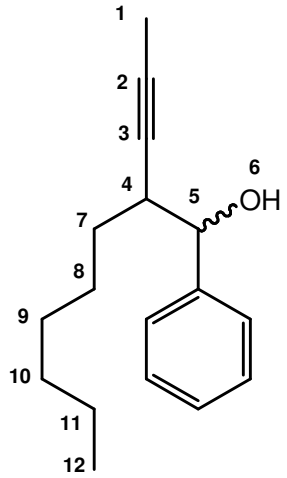
IR (thin film): $\tilde{\nu}$ **=** 3457 (m, br), 2958 (m), 2925 (s), 2848 (m), 1454 (m), 1185 (w), 1054 (w), 698 (s) cm^{-1}.

The following H and C signals of the *syn* isomer were identified in the spectra of the mixed fraction:

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 – 7.28 (5H, m, H^{Ar}), 4.71 (1H, apparent t, *J* = 4.8 Hz, H^5), 2.77 (1H, br s, H^4), 2.30 (1H, d, *J* = 4.3 Hz, OH^6), 2.16 (2H, td, *J* = 6.9, 2.3 Hz, H^1), 1.54 – 1.20 (14H, m), 0.90 (3H, t, *J* = 7.3 Hz, $H^{12/15}$), 0.87 ppm (3H, t, *J* = 6.9 Hz, $H^{12/15}$).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 141.86 ($C^{i\text{-}Ph}$), 127.94 ($2CH^{m\text{-}Ph}$), 127.47 ($CH^{p\text{-}Ph}$), 126.60 ($2CH^{o\text{-}Ph}$), 84.44 (C^2), 79.95 (C^3), 75.99 (CH^5), 40.39 (CH^4), 31.75 (CH_2), 31.01 (CH_2), 29.97 (CH_2), 29.06 (CH_2), 27.41 (CH_2), 22.58 (CH_2), 21.83 (CH_2), 18.41 (CH_2^1), 14.03 ($CH_3^{12/15}$), 13.57 ppm ($CH_3^{12/15}$).

6.4.2. *rac*-1-Phenyl-2-(prop-1-ynyl)octan-1-ol (4.68b)



To a stirred solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added MeLi (1.25 mL of a 1.6 M solution, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same tempereature, a solution of the non-1-yn-3-yl benzensulfonate (0.294 g, 1.0 mmol) in dry THF (1 mL) was added dropwise followed by dropwise addition of LDA (0.56 mL of a 1.8 M solution, 1.0 mmol). The stirring was continued for a further 1 h during which time the reaction mixture was allowed to warm to –50 °C. The reaction mixture was re-cooled to –78 °C and a solution of benzaldehyde (0.15 mL 1.5 mmol) in dry THF (1 mL) was added followed by dropwise addition of $BF_3{\cdot}OEt_2$ (0.18 mL, 1.5 mmol) and the reaction mixture warmed gradually to RT. The reaction mixture was stirred at the same temperature for 3 h before quenching with MeOH (5 mL) and saturated aqueous solution of $NaHCO_3$ (6 mL) and the mixture left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 75 mL). The combined organic phases were washed with H_2O (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as an orange oil (*anti : syn* diastereoisomers in the ratio of 79 : 21).

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexane : EtOAc (10 : 1) as the eluent to yield the title compounds as an inseparable mixture of *anti : syn* diastereoisomers in combined yield of 0.097 g (40%, pale yellow oil).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.31 – 7.18 (10H, m, H^{Ar}), 4.62 (1H, dd, *J* = 5.4, 3.7 Hz, $H^{5\ minor}$), 4.40 (1H, dd, *J* = 6.8, 3.9 Hz, $H^{5\ major}$), 2.65 (1H, m, $H^{4\ minor}$), 2.58 (1H, d, *J* = 3.9 Hz, $OH^{6\ major}$), 2.56 (1H, apparent ddq, *J* = 14.0, 7.0, 2.3 Hz, $H^{4\ major}$), 2.30 (1H, d, *J* = 3.7 Hz, $OH^{6\ minor}$), 1.77 (3H, d, *J* = 2.3 Hz, $H^{1\ major}$), 1.71 (3H, d, *J* = 2.5 Hz, $H^{1\ minor}$), 1.47 – 1.10 (20H, m), 0.96 (3H, overlap t, *J* = 7.1 Hz, $H^{12\ minor}$), 0.96 (3H, t, *J* = 7.0 Hz, $H^{12\ major}$).

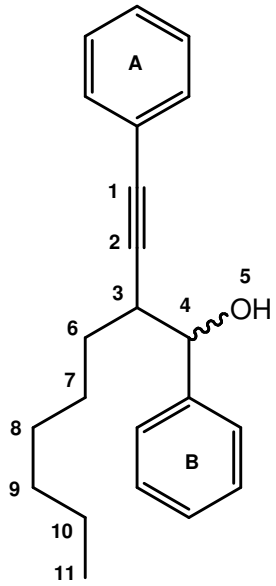
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 142.08 ($C^{i\text{-}Ph\ major}$), 141.80 ($C^{i\text{-}Ph\ minor}$), 128.16 ($2CH^{m\text{-}Ph\ major}$), 127.90 ($2CH^{m\text{-}Ph\ minor}$), 127.67 ($CH^{p\text{-}Ph\ major}$), 127.41 ($CH^{p\text{-}Ph\ minor}$), 126.57 ($2CH^{o\text{-}Ph\ major}$), 126.53 ($2CH^{o\text{-}Ph\ minor}$), 80.26 ($C^{2\ major}$), 79.47 ($C^{2\ or\ 3\ minor}$), 79.19 ($C^{3\ or\ 2\ minor}$), 78.61 ($C^{3\ major}$), 76.38 ($CH^{5\ major}$), 75.87 ($CH^{5\ minor}$), 41.67 ($CH^{4\ major}$), 40.34 ($CH^{4\ minor}$), 31.73 (CH_2^{minor}), 31.66 (CH_2^{major}), 31.60 ($2CH_2^{major\ +\ minor}$), 29.77 (CH_2^{minor}), 29.06 (CH_2^{minor}), 28.97 (CH_2^{major}), 27.43 (CH_2^{minor}), 27.34 (CH_2^{major}), 22.54 (CH_2^{major}), 14.00 ($2CH_3^{major\ +\ minor}$), 3.57 ($CH_3^{1\ major}$), 3.51 ($CH_3^{1\ minor}$).

HRMS (EI): Found: $[M - H_2O]^+$, 226.1720. $[C_{17}H_{22}]^+$ requires: 226.1722.

LRMS (CI): *m/z*: 245 ($[M + H]^+$, 70%), 227 ($[M - H_2O + H]^+$, 100%).

IR (thin film): $\tilde{\nu}$ **=** 3436 (m, br), 2917 (m), 2848 (m), 1454 (m), 1197 (w), 1042 (w), 706 (s) cm^{-1}.

6.4.3. *rac*-1-Phenyl-2-(2-phenylethynyl)octan-1-ol (4.68c)



To a stirred solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added PhLi (1.11 mL of a 1.8 M solution, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same tempereature, a solution of the non-1-yn-3-yl benzensulfonate (0.294 g, 1.0 mmol) in dry THF (1 mL) was added dropwise followed by dropwise addition of LDA (0.56 mL of a 1.8 M solution, 1.0 mmol). The stirring was continued for a further 1 h during which time the reaction mixture was allowed to warm to –65 °C. The reaction mixture was re-cooled to –78 °C and a solution of benzaldehyde (0.15 mL 1.5 mmol) in dry THF (1 mL) was added followed by dropwise addition of $BF_3{\cdot}OEt_2$ (0.18 mL, 1.5 mmol). The reaction mixture was warmed gradually to RT. The reaction mixture was stirred at the same temperature for 3 h before quenching with MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL) and the mixture left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 75 mL). The combined organic phases were washed with H_2O (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a yellow oil (*anti : syn* diastereoisomers in the ratio of 79 : 21).

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexane : EtOAc (10 : 1) as the eluent to yield the title compounds as an inseparable mixture of *anti : syn* diastereoisomers in combined yield of 0.106 g (35%, yellow oil).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.48 – 7.28 (20H, m, H^{Ar}), 4.82 (1H, dd, *J* = 6.0, 4.0 Hz, $H^{4\ minor}$), 4.68 (1H, dd, *J* = 6.5, 4.3 Hz, $H^{4\ major}$), 3.02 (1H, ddd, *J* = 9.8, 6.0, 3.9 Hz, $H^{3\ minor}$), 2.94 (1H, ddd, *J* = 9.6, 6.5, 4.3 Hz, $H^{3\ major}$), 2.60 (1H, dd, *J* = 4.3, 1.4 Hz, $OH^{6\ major}$), 2.30 (1H, dd, *J* = 3.9. 2.0 Hz, $OH^{6\ minor}$), 1.64 – 1.40 (8H, m), 1.35 – 1.23 (12H, m), 0.90 (3H, t, *J* = 7.2 Hz, $H^{11\ minor}$), 0.89 (3H, t, *J* = 6.8 Hz, $H^{11\ major}$).

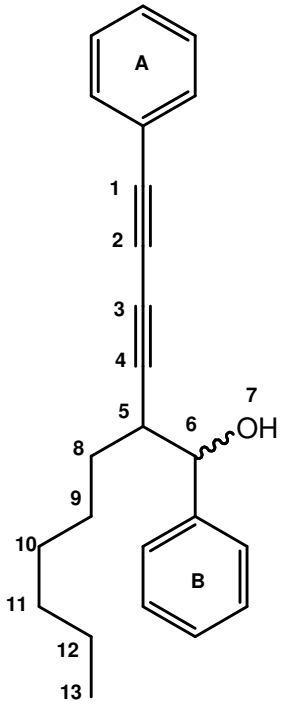
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 141.92 ($C^{i\text{-}Ph\ B\ major}$), 141.85 ($C^{i\text{-}Ph\ B\ minor}$), 131.69 ($2CH^{o\text{-}Ph\ A\ major}$), 131.55 ($2CH^{o\text{-}Ph\ A\ minor}$), 128.27 ($2CH^{m\text{-}Ph\ A\ major}$), 128.23 ($2CH^{m\text{-}Ph\ B\ major}$), 128.15 ($2CH^{m\text{-}Ph\ A/B\ minor}$), 128.05 ($2CH^{m\text{-}Ph\ B/A\ minor}$), 127.97 ($CH^{p\text{-}Ph\ A/B\ major}$), 127.86 ($CH^{p\text{-}Ph\ B/A\ major}$), 127.75 ($CH^{p\text{-}Ph\ A/B\ minor}$), 127.73 ($CH^{p\text{-}Ph\ B/A\ minor}$), 126.68 ($2CH^{o\text{-}Ph\ B\ minor}$), 126.60 ($2CH^{o\text{-}Ph\ B\ major}$), 123.53 ($C^{i\text{-}Ph\ A\ minor}$), 123.27 ($C^{i\text{-}Ph\ A\ major}$), 90.02 ($C^{1\ minor}$), 89.34 ($C^{1\ major}$), 84.86 ($C^{2\ major}$), 84.30 ($C^{2\ minor}$), 76.32 ($CH^{4\ major}$), 76.09 ($CH^{4\ minor}$), 42.20 ($CH^{3\ major}$), 41.09 ($CH^{3\ minor}$), 31.76 ($CH_2^{minor}$), 31.70 ($CH_2^{major}$), 31.46 ($CH_2^{major}$), 30.15 ($CH_2^{minor}$), 29.11 ($CH_2^{minor}$), 29.00 ($CH_2^{major}$), 27.44 ($2CH_2^{minor\ +\ minor}$), 22.58 ($2CH_2^{major\ +\ minor}$), 14.04 ($2CH_3^{11\ major\ +\ minor}$).

HRMS (EI): Found: $[M - H_2O]^+$, 288.1885. $[C_{22}H_{24}]^+$ requires: 288.1878.

LRMS (CI): *m/z*: 306 ($[M]^+$, 34%), 289 ($[M - H_2O + H]^+$, 66%).

IR (thin film): $\tilde{\nu}$ **=** 3363 (m, br), 2933 (m), 2864 (m), 1491 (m), 1446 (m), 1029 (m), 760 (s), 686 (s) cm^{-1}.

6.4.4. *rac*-1-Phenyl-2-(4-phenylbuta-1,3-diynyl)octan-1-ol (4.68d)



To a solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to -78 °C was added PhCCLi (freshly prepared from PhCCH (0.22 ml, 2.0 mmol) and *n*-BuLi (0.8 ml of a 2.5 M solution, 2.0 mmol) at 0 °C over 15 min) dropwise over 5 minutes. After 25 min the cooling bath was removed and the stirring was continued at RT for 4 h before re-cooling the reaction mixture to –78 °C. A solution of the non-1-yn-3-yl benzensulfonate (0.294 g, 1.0 mmol) in dry THF (1 mL) was added dropwise followed by dropwise addition of LDA (0.56 mL of a 1.8 M solution, 1.0 mmol). After stirring the reaction mixture for 30 min at the same temperature, a solution of benzaldehyde (0.15 mL, 1.5 mmol) in dry THF (1 mL) was added followed by dropwise addition of $BF_3{\cdot}OEt_2$ (0.18 mL, 1.5 mmol). The reaction mixture was warmed gradually to RT. The reaction mixture was stirred at RT for 1 h before quenching with MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL), the mixture left stirring overnight. The

mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 75 mL). The combined organic phases were washed with H_2O (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as yellow oil (*anti : syn* diastereoisomers in the ratio of 62 : 38).

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexane : EtOAc (10 : 1) as the eluent to yield the title compounds as an inseparable mixture of *anti : syn* diastereoisomers in combined yield of 0.208 g (62%, yellow oil).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.39 – 7.14 (20H, m, H^{Ar}), 4.66 (1H, dd, *J* = 5.9, 3.6 Hz, $H^{6\ minor}$), 4.53 (1H, dd, *J* = 6.5, 4.3 Hz, $H^{6\ major}$), 2.84 (1H, dddd, *J* = 10.0, 6.0, 3.7, 0.5 Hz, $H^{5\ minor}$), 2.76 (1H, dddd, *J* = 10.8, 6.5, 4.4, 0.8 Hz, $H^{5\ major}$), 2.35 (1H, dd, *J* = 4.4 Hz, $OH^{7\ major}$), 2.15 (1H, dd, *J* = 3.8 Hz, $OH^{7\ minor}$), 1.49 – 1.14 (20H, m), 0.77 (3H, t, *J* = 6.5 Hz, $H^{13\ minor}$), 0.76 (3H, t, *J* = 6.7 Hz, $H^{13\ major}$).

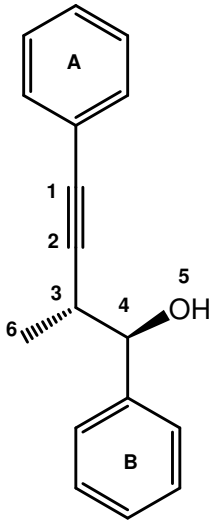
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 141.54 ($C^{i\text{-}Ph\ B\ major}$), 141.48 ($C^{i\text{-}Ph\ B\ minor}$), 132.50 ($2CH^{o\text{-}Ph\ A\ major}$), 132.48 ($CH^{p\text{-}Ph\ A\ major}$), 128.97 ($2CH^{o\text{-}Ph\ A\ minor}$), 128.89 ($CH^{p\text{-}Ph\ A\ minor}$), 128.39 ($2CH^{m\text{-}Ph\ A\ major}$), 128.34 ($2CH^{m\text{-}Ph\ B\ major}$), 128.30 ($2CH^{m\text{-}Ph\ A\ minor}$), 128.22 ($CH^{p\text{-}Ph\ B\ major}$), 128.05 ($2CH^{m\text{-}Ph\ B\ minor}$), 127.92 ($CH^{p\text{-}Ph\ B\ minor}$), 126.55 ($2CH^{o\text{-}Ph\ B\ minor}$), 126.48 ($2CH^{o\text{-}Ph\ B\ major}$), 121.88 ($C^{i\text{-}Ph\ A\ minor}$), 121.80 ($C^{i\text{-}Ph\ A\ major}$), 84.44 ($C^{1\ major}$), 84.08 ($C^{4\ major}$), 76.22 ($CH^{6\ major}$), 75.90 ($C^{4\ minor}$), 75.73 ($CH^{6\ minor}$), 75.65 ($C^{1\ minor}$), 74.16 ($C^{2\ or\ 3\ minor}$), 74.05 ($C^{3\ or\ 2\ minor}$), 68.84 ($C^{2\ or\ 3\ major}$), 68.49 ($C^{3\ or\ 2\ major}$), 42.22 ($CH^{5\ major}$), 41.30 ($CH^{5\ minor}$), 31.68 ($CH_2^{minor}$), 31.61 ($CH_2^{major}$), 31.26 ($CH_2^{major}$), 29.82 ($CH_2^{minor}$), 29.05 ($CH_2^{minor}$), 28.94 ($CH_2^{major}$), 27.36 ($CH_2^{minor}$), 27.34 ($CH_2^{major}$), 22.59 ($CH_2^{minor}$), 22.56 ($CH_2^{major}$), 14.02 ($2CH_3^{11\ major\ +\ minor}$).

HRMS (EI): Found: $[M]^+$, 330.1984. $C_{24}H_{26}O$ requires: 330.1984.

LRMS (CI): *m/z*: 331 ($[M + H]^+$, 34%), 313 ($[M – H_2O + H]^+$, 60%).

IR (thin film): $\tilde{\nu}$ **=** 3371 (m, br), 2925 (m), 2852 (m), 1487 (m), 1458 (m), 1025 (m), 764 (s), 690 (s) cm^{-1}.

6.4.5. *rac*-(1*R*,2*R*)-2-Methyl-1,4-diphenylbut-3-yn-1-ol (4.68e)



To a stirred solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added PhLi (1.11 mL of a 1.8 M solution, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same tempereature, a solution of the but-3-yn-2-yl benzensulfonate (0.224 g, 1.0 mmol) in dry THF (1 mL) was added dropwise followed by dropwise addition of LDA (0.56 mL of a 1.8 M solution, 1.0 mmol). The stirring was continued for a further 1 h during which the reaction mixture was allowed to warm to –65 °C.

The reaction mixture was re-cooled to –78 °C and a solution of benzaldehyde (0.15 mL 1.5 mmol) in dry THF (1 mL) was added followed by dropwise addition of $BF_3{\cdot}OEt_2$ (0.18 mL, 1.5 mmol). The reaction mixture was warmed gradually to RT. The reaction mixture was stirred at the same temperature for 2 h before quenching with MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL), the mixture left stirring overnight. The whole mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 75 mL). The combined organic phases were washed with H_2O (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a yellow oil (*anti : syn* diastereoisomers in the ratio of 81 : 19).

Purification of the crude material by careful column chromatography on SiO_2 (230 – 400 mesh) with hexane : EtOAc (10 : 1) as the eluent to allow partial separation of the diasteroisomers to give a pure fraction of the title compound (*anti* isomer) as a pale yellow oil and a mixed fraction (yellow oil) of both isomers in combined yield of 0.091 g (39%).

Spectral data of the *anti* diastereoisomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.44 – 7.30 (10H, m, H^{Ar}), 4.62 (1H, dd, *J* = 7.0, 3.8 Hz, H^4), 3.04 (1H, quintet, *J* = 7.0 Hz, H^3), 2.60 (1H, d, *J* = 3.8 Hz, OH^6), 1.20 (3H, d, *J* = 7.0 Hz, H^6).

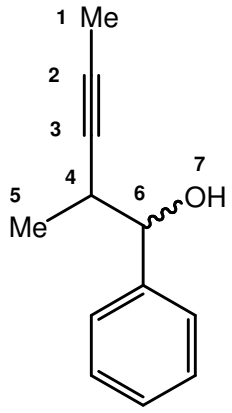
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 141.92 ($C^{i\text{-}Ph\ B}$), 131.68 ($2CH^{o\text{-}Ph\ A}$), 128.28 ($2CH^{m\text{-}Ph\ A/B}$), 128.24 ($2CH^{m\text{-}Ph\ B/A}$), 128.02 ($CH^{p\text{-}Ph\ A/B}$), 127.97 ($CH^{p\text{-}Ph\ B/A}$), 126.69 ($2CH^{o\text{-}Ph\ B}$), 123.15 ($C^{i\text{-}Ph\ A}$), 90.48 (C^1), 83.71 (C^2), 77.64 (CH^4), 36.08 (CH^3), 17.44 ($CH_3{}^6$).

HRMS (EI): Found: $[M - H_2O]^+$, 218.1094. $[C_{17}H_{14}]^+$ requires: 218.1096.

LRMS (CI): *m/z*: 237 ($[M + H]^+$, 41%), 221 ($[M - CH_3]^+$, 100%).

IR (thin film): $\tilde{\nu}$ = 3383 (m, br), 3032 (w), 2964 (w), 2877 (w), 1588 (w), 1493 (m), 1444 (m), 1032 (m), 752 (s), 692 (s) cm^{-1}.

6.4.6. *rac*-2-Methyl-1-phenylpent-3-yn-1-ol (4.68f)



To a stirred solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added MeLi (1.25 mL of a 1.6 M solution, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same tempereature, a solution of the but-3-yn-2-yl benzensulfonate (0.224 g, 1.0 mmol) in dry THF (1 mL) was added dropwise followed by dropwise addition of freshly prepared LiTMP, [prepared from freshly distilled 2,2,6,6-tetramethylpiperidine (0.17 mL, 1.0 mmol) in dry THF (2 mL) and *n*-BuLi (0.4 mL of a 2.5 M solution in hexanes, 1.0 mmol) at –5 °C over 15 min]. The stirring was continued for a further 1 h during which time the reaction mixture was allowed to warm to –50 °C. The reaction mixture was re-cooled to –60 °C and a solution of benzaldehyde (0.30 mL 3.0 mmol) in dry THF (1 mL). The reaction mixture was warmed gradually to RT. The

reaction mixture was stirred at the same temperature for 3 h before quenching with MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL), the mixture left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 75 mL). The combined organic phases were washed with H_2O (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a yellow oil (*anti : syn* diastereoisomers in the ratio of 73 : 27).

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexane : EtOAc (10 : 1) as the eluent to yield the title compounds as an inseparable mixture of *anti : syn* diastereoisomers in combined yield of 0.064 g (37%, yellow oil).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.30 – 7.18 (10H, m, H^{Ar}), 4.63 (1H, dd, *J* = 4.9, 3.4 Hz, $H^{6\ minor}$), 4.33 (1H, dd, *J* = 7.3, 3.5 Hz, $H^{6\ major}$), 2.74 (1H, m, $H^{4\ minor}$), 2.64 (1H, quintet q, *J* = 7.3, 2.4 Hz, $H^{4\ major}$), 2.58 (1H, dd, *J* = 3.5, 1.8 Hz, $OH^{7\ major}$), 2.25 (1H, t, *J* = 3.4 Hz, $OH^{7\ minor}$), 1.76 (3H, dd, *J* = 2.4, 0.5 Hz, $H^{1\ major}$), 1.71 (3H, dd, *J* = 2.5, 0.5 Hz, $H^{1\ minor}$), 0.96 (3H, overlap d, *J* = 7.0 Hz, $H^{5\ minor}$), 0.96 (3H, d, *J* = 7.0 Hz, $H^{5\ major}$).

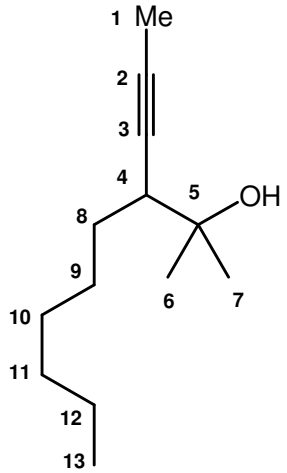
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 141.64 ($C^{i\text{-}Ph\ major}$), 141.48 ($C^{i\text{-}Ph\ minor}$), 128.19 ($2CH^{m\text{-}Ph\ major}$), 127.94 ($2CH^{m\text{-}Ph\ minor}$), 127.80 ($CH^{p\text{-}Ph\ major}$), 127.45 ($CH^{p\text{-}Ph\ minor}$), 126.66 ($2CH^{o\text{-}Ph\ major}$), 126.40 ($2CH^{o\text{-}Ph\ minor}$), 80.53 ($C^{2\ minor}$), 80.00 ($C^{2\ major}$), 79.20 ($C^{3\ major}$), 78.54 ($C^{3\ minor}$), 77.82 ($CH^{6\ major}$), 76.27 ($CH^{6\ minor}$), 35.55 ($CH^{4\ major}$), 34.25 ($CH^{4\ minor}$), 17.72 ($CH_3{}^{5\ major}$), 15.56 ($CH_3{}^{5\ minor}$), 3.55 ($CH_3{}^{1\ major}$), 3.50 ($2CH_3{}^{1\ minor}$).

HRMS (EI): Found: $[M]^+$, 174.1045. $C_{12}H_{14}O$ requires: 174.1045.

LRMS (CI): *m/z*: 174 ($[M]^+$, 2%), 156 ($[M - H_2O]^+$, 4%), 118 (27%), 107 (100%).

IR (thin film): $\tilde{\nu}$ **=** 3424 (br), 1454 (m), 1029 (m), 756 (s), 702 (s) cm^{-1}.

6.4.7. *rac*-2-Methyl-3-(prop-1-ynyl)nonan-2-ol (4.68g)



To a stirred solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added MeLi (1.25 mL of a 1.6 M solution, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same tempereature, a solution of the non-1-yn-3-yl benzensulfonate (0.294 g, 1.0 mmol) in dry THF (1 mL) was added dropwise followed by dropwise addition of LDA (0.56 mL of a 1.8 M solution, 1.0 mmol). The stirring was continued for a further 0.5 h during which time the reaction mixture was allowed to warm to –65 °C. At the same temperature a solution of acetone (0.22 mL 3.0 mmol) in dry THF (1 mL) was added to the reaction mixture followed by dropwise addition of $BF_3{\cdot}OEt_2$ (0.36 mL, 3.0 mmol). The reaction mixture was warmed gradually to RT. The reaction mixture was stirred at the same temperature for 2 h before refluxing for 20 h. After that time, the reaction mixture was cooled to RT and quenched with MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL), left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 75 mL). The combined organic phases were washed with H_2O (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a yellow oil.

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexane : EtOAc (10 : 1) as the eluent to yield the title compound as a pale yellow oil in yield of 0.048 g (25%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.31 (1H, m, H^4), 1.96 (1H, s, OH), 1.96 (3H, d, *J* = 2.3 Hz, H^1), 1.62 – 1.45 (2H, m), 1.39 – 1.28 (8H, m), 1.24 (3H, s, $H^{6/7}$), 1.23 (3H, s, $H^{6/7}$), 0.89 (3H, t, *J* = 6.9 Hz, H^{13}).

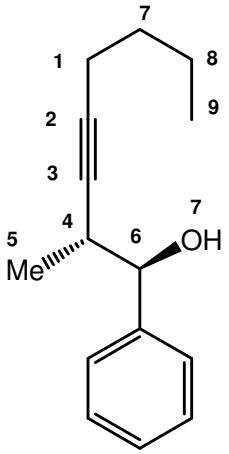
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 79.46 ($C^{2/3}$), 79.33 ($C^{2/3}$), 72.03 (C^5), 45.35 (CH^4), 31.80 (CH_2), 30.07 (CH_2), 29.17 (CH_2), 28.38 (CH_2), 27.07 ($CH_3{}^{6/7}$), 26.26 ($CH_3{}^{6/7}$), 22.65 (CH_2), 14.06 ($CH_3{}^{13}$), 3.52 ($CH_3{}^1$).

HRMS (ESI+): Found: $[M + Na]^+$, 219.1721. $[C_{13}H_{24}NaO]^+$ requires: 219.1719.

LRMS (CI): *m/z*: 196 ($[M]^+$, 42%), 179 ($[M – OH]^+$, 90%), 68 (100%).

IR (thin film): $\tilde{\nu}$ = 3375 (m, br), 2954 (s), 2933 (s), 2835 (s), 1438 (m), 1377 (s), 1148 (s), 760 (s), 894 (s) cm^{-1}.

6.4.8. *rac*-(1*R*,2*R*)-2-Methyl-1-phenyloct-3-yn-1-ol (4.76)



To a solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added MeLi (1.25 mL of a 1.8 M solution, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same tempereature, a solution of 1-chlorohept-2-yne (0.131 g, 1.0 mmol) in dry THF (1 mL) was added dropwise followed by dropwise addition of LDA (0.56 mL of a 1.8 M solution, 1.0 mmol). The stirring was continued for a further 1.5 h during which time the reaction mixture was allowed to warm to –65 °C. The reaction mixture was re-cooled to –78 °C and a solution of benzaldehyde (0.15 mL, 1.5 mmol) in dry THF (1 mL) was added followed by dropwise addition of $BF_3{\cdot}OEt_2$ (0.18 mL, 1.5 mmol). The reaction mixture warmed gradually to RT within. The reaction mixture was stirred at RT for 3-5 h before quenching with MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL), the mixture was left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 75 mL). The

combined organic phases were washed with H_2O (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as yellow oil (*anti : syn* diastereoisomers in the ratio of 77 : 23).

Purification of the crude material by careful column chromatography on SiO_2 (230 – 400 mesh) with hexane : EtOAc (10 : 1) as the eluent to allow partial separation of the diasteroisomers to give a pure fraction of the title compound (*anti* isomer) as a pale yellow oil and a mixed fraction (yellow oil) of both isomers in combined yield of 0.150 g (69%).

Spectral data of the *anti* diastereoisomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.29 – 7.18 (5H, m, H^{Ar}), 4.34 (1H, dd, *J* = 7.1, 3.7 Hz, H^6), 2.67 (1H, quintet t, *J* = 7.1, 2.3 Hz, H^4), 2.56 (1H, d, *J* = 3.7 Hz, OH^7), 2.12 (2H, td, *J* = 7.0, 2.3 Hz, H^1), 1.45 – 1.27 (4H, m, H^{7+8}), 0.97 (3H, d, *J* = 7.1 Hz, H^5), 0.83 (3H, t, *J* = 7.2 Hz, H^9).

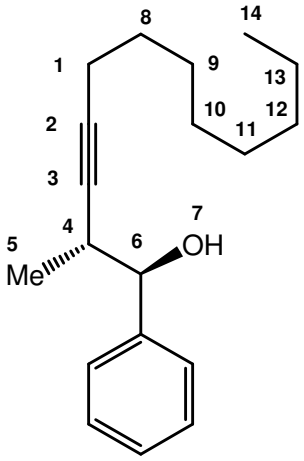
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 141.67 ($C^{i\text{-}Ph}$), 128.16 ($2CH^{m\text{-}Ph}$), 127.77 ($CH^{p\text{-}Ph}$), 126.67 ($2CH^{o\text{-}Ph}$), 84.10 (C^2), 80.71 (C^3), 77.76 (CH^6), 35.69 (CH^4), 31.03 ($CH_2{}^1$), 21.92 ($CH_2{}^{7\text{ or }8}$), 18.42 ($CH_2{}^{8\text{ or }7}$), 17.82 ($CH_3{}^5$), 13.58 ($CH_3{}^9$).

HRMS (EI): Found: $[M]^+$, 216.1521. $C_{15}H_{20}O$ requires: 216.1514.

LRMS (CI): *m/z*: 216 ($[M]^+$, 64%), 199 ($[M – OH]^+$, 100%).

IR (thin film): $\tilde{\nu}$ **=** 3375 (m, br), 2954 (s), 2933 (s), 2835 (s), 1438 (m), 1377 (s), 1148 (s), 760 (s), 894 (s) cm^{-1}.

6.4.9. *rac*-(1*R*,2*R*)-2-Methyl-1-phenyldodec-3-yn-1-ol (4.82a)



To a stirred suspension of Cp_2ZrHCl (0.258 g, 1.0 mmol) in dry THF (10 mL) at RT was added neat 1-octene (0.125 mL, 0.8 mmol) dropwise over 3 minutes. After stirring the yellow solution for 1 h at RT, the reaction mixture was cooled to –78 °C and a solution of the but-3-yn-2-yl benzensulfonate (0.224 g, 1.0 mmol) in dry THF (1 mL) was added dropwise followed by dropwise addition of freshly prepared LiTMP, [prepared from freshly distilled 2,2,6,6-tetramethylpiperidine (0.17 mL, 1.0 mmol) in dry THF (2 mL) and *n*-BuLi (0.4 mL of a 2.5 M solution in hexanes, 1.0 mmol) at –5 °C over 15 min]. The stirring was continued for a further 1 h during which time the reaction mixture was allowed to warm to RT. The reaction mixture was re-cooled to –60 °C and a solution of benzaldehyde (0.30 mL, 3.0 mmol) in dry THF (1 mL) was added. The reaction mixture was warmed gradually to RT. The stirring was continued at the same temperature for 3 h before quenching with MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL), the mixture left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 75 mL). The combined organic phases were washed with H_2O (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as yellow oil (*anti : syn* diastereoisomers in the ratio of of 74 : 26).

Purification of the crude material by careful column chromatography on SiO_2 (230-400 mesh) with hexane : EtOAc (10 : 1) as the eluent to allow partial separation of the diasteroisomers to give a pure fraction of the title compound (*anti* isomer) as a yellow oil and a mixed fraction (yellow oil) of both isomers in combined yield of 0.130 g (60%).

Spectral data of the *anti* diastereoisomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.29 – 7.17 (5H, m, H^{Ar}), 4.34 (1H, dd, *J* = 7.2, 3.6 Hz, H^6), 2.67 (1H, quintet t, *J* = 7.1, 2.1 Hz, H^4), 2.56 (1H, d, *J* = 3.5 Hz, OH^7), 2.11 (2H, td, *J* = 7.2, 2.3 Hz, H^1), 1.46 – 1.38 (2H, m), 1.32 – 1.14 (10H, m), 0.98 (3H, d, *J* = 6.8 Hz, H^5), 0.81 (3H, t, *J* = 6.9 Hz, H^{14}).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 141.68 ($C^{i\text{-}Ph}$), 128.17 ($2CH^{m\text{-}Ph}$), 127.78 ($CH^{p\text{-}Ph}$), 126.67 ($2CH^{o\text{-}Ph}$), 84.20 (C^2), 80.70 (C^3), 77.77 (CH^6), 35.70 (CH^4), 31.83 ($CH_2{}^1$), 29.18 (CH_2), 29.09 (CH_2), 28.95 (CH_2), 28.86 (CH_2), 22.64 (CH_2), 18.74 (CH_2), 17.83 ($CH_3{}^5$), 14.08 ($CH_3{}^{14}$).

HRMS (EI): Found: $[M - H_2O]^+$, 254.2040. $[C_{19}H_{26}]^+$ requires: 254.2034.

LRMS (CI): *m/z*: 273 ($[M + H]^+$, 54%), 255 ($[M – OH]^+$, 72%).

IR (thin film): $\tilde{\nu}$ **=** 3448 (m, br), 2925 (s), 2852 (m), 1454 (m), 1021 (m), 1760 (w), 706 (s) cm^{-1}.

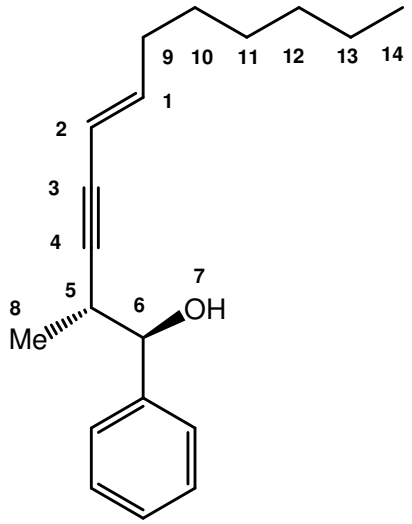
Preparation of the enantioenriched product: (1*R*,2*R/S*)-2-methyl-1-phenyldodec-3-yn-1-ol (4.82a)

To a stirred suspension of Cp_2ZrHCl (0.258 g, 1.0 mmol) in dry THF (10 mL) at RT was added neat 1-octene (0.125 mL, 0.8 mmol) dropwise over 3 minutes. After stirring the yellow solution for 1 h at RT, the reaction mixture was cooled to –78 °C and a solution of the (*S*)-but-3-yn-2-yl benzensulfonate (0.224 g, 1.0 mmol) in dry THF (1 mL) was added dropwise followed by dropwise addition of freshly prepared LiTMP, [prepared from freshly distilled 2,2,6,6-tetramethylpiperidine (0.17 mL, 1.0 mmol) in dry THF (2 mL) and *n*-BuLi (0.4 mL of a 2.5 M solution in hexanes, 1.0 mmol) at –5 °C over 15 min]. The stirring was continued for a further 1 h during which time the reaction mixture was allowed to warm to RT. The reaction mixture was re-cooled to –78 °C and a solution of benzaldehyde (0.30 mL, 3.0 mmol) in dry THF (1 mL) was added followed by dropwise addition of $BF_3{\cdot}OEt_2$ (0.36 mL, 3.0 mmol). The reaction mixture was warmed gradually to RT. The stirring was continued at the same temperature for 3 h before quenching with MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL), the mixture left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 75 mL). The combined organic phases were washed with H_2O (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as yellow oil (*anti : syn* diastereoisomers in the ratio of of 75 : 25).

Purification of the crude material by careful column chromatography on SiO_2 (230-400 mesh) with hexane : EtOAc (10 : 1) as the eluent to allow partial separation of the diasteroisomers to give a pure fraction of the title compound (*anti* isomer) as a yellow oil and a mixed fraction (yellow oil) of both isomers in combined yield of 0.134 g (61%).

R_t 11.0 min (minor enantiomer) and 12.9 min (major enantiomer) on chiral HPLC on a Diacel OD-H, (1 mL/min 2% isopropanol in hexane on 4.6 x 250 mm column).

6.4.10. *rac*-(*E*,1*R*,2*R*)-2-Methyl-1-phenyldodec-5-en-3-yn-1-ol (4.82b)



To a stirred suspension of Cp_2ZrHCl (0.258 g, 1.0 mmol) in dry THF (10 mL) at RT was added neat 1-octene (0.125 mL, 0.8 mmol) dropwise over 3 minutes. After stirring the yellow solution for 1.5 h at RT, the reaction mixture was cooled to –78 °C and a solution of the but-3-yn-2-yl benzensulfonate (0.202 g, 0.9 mmol) in dry THF (1 mL) was added dropwise followed by dropwise addition of LDA (0.50 mL of a 1.8 M solution, 0.9 mmol). The stirring was continued for a further 2 h during which the reaction mixture was allowed to warm to RT. After re-cooling the reaction mixture to –78 °C a solution of benzaldehyde (0.12 mL, 1.2 mmol) in dry THF (1 mL) was added followed by dropwise addition of $BF_3{\cdot}OEt_2$ (0.15 mL, 1.2 mmol). The reaction mixture was warmed gradually to RT and the stirring was continued at the same temperature for 2 h before quenching with MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL). The whole mixture was left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 75 mL). The combined organic phases were washed with H_2O (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as yellow oil (*anti : syn* diastereoisomers in the ratio of 69 : 31).

Purification of the crude material by careful column chromatography on SiO_2 (230 – 400 mesh) with hexane : EtOAc (10 : 1) as the eluent to allow partial separation of the diasteroisomers to give a pure fraction of the title compound (*anti* isomer) as a yellow oil and a mixed fraction (yellow oil) of both isomers in combined yield of 0.987 g (40%).

Spectral data of the *anti* diastereoisomer:

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.29 – 7.16 (5H, m, H^{Ar}), 6.03 (1H, dt, *J* = 15.8, 7.0 Hz, H^1), 5.39 (1H, dq, *J* = 15.8, 2.0 Hz, H^2), 4.38 (1H, dd, *J* = 7.2, 3.7 Hz, H^6), 2.79 (1H, quintet d, *J* = 7.2, 2.0 Hz, H^5), 2.47 (1H, dd, *J* = 3.7, 0.6 Hz, OH^7), 2. 2.00 (2H, qd *J* = 7.3, 1.5 Hz, H^9), 1.31 – 1.16 (8H, m), 0.99 (3H, d, *J* = 7.0 Hz, H^8), 0.80 (3H, t, *J* = 6.9 Hz, H^{14}).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 144.75 (CH^1), 141.51 ($C^{i\text{-}Ph}$), 128.25 ($2CH^{m\text{-}Ph}$), 127.92 ($CH^{p\text{-}Ph}$), 126.71 ($2CH^{o\text{-}Ph}$), 109.14 (CH^2), 88.68 (C^3), 82.52 (C^4), 77.78 (CH^6), 36.11 (CH^5), 33.01 ($CH_2{}^9$), 31.65 (CH_2), 28.78 (CH_2), 28.70 (CH_2), 22.58 (CH_2), 17.52 ($CH_3{}^8$), 14.07 ($CH_3{}^{14}$).

HRMS (EI): Found: $[M]^+$, 270.1982. $C_{19}H_{26}O$ requires: 270.1984.

LRMS (CI): *m/z*: 271 ($[M + H]^+$, 40%), 253 ($[M – H_2O]^+$, 28%).

IR (thin film): $\tilde{\nu}$ **=** 3379 (m, br), 2938 (m), 2864 (w), 1450 (m), 1029 (m), 935 (m), 756 (m), 706 (s) cm^{-1}.

Preparation of the enantioenriched product: (*E*,1*R*,2*R*)-2-methyl-1-phenyldodec-5-en-3-yn-1-ol (4.82b)

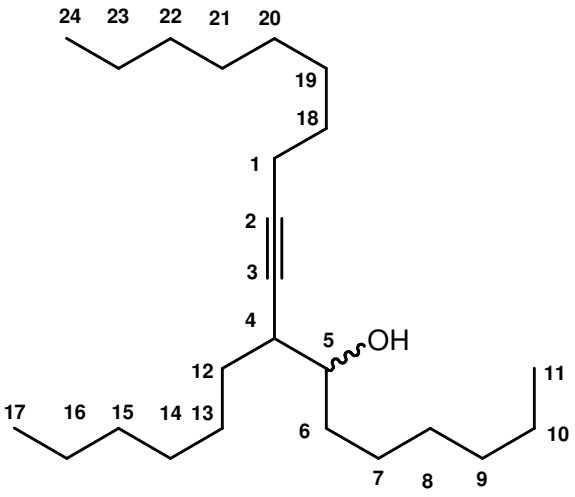
To a stirred suspension of Cp_2ZrHCl (0.258 g, 1.0 mmol) in dry THF (10 mL) at RT was added neat 1-octene (0.125 mL, 0.8 mmol) dropwise over 3 minutes. After stirring the yellow solution for 1 h at RT, the reaction mixture was cooled to –78 °C and a solution of the (*S*)-but-3-yn-2-yl benzensulfonate (0.224 g, 1.0 mmol) in dry THF (1 mL) was added dropwise followed by dropwise addition of freshly prepared LiTMP, [prepared from freshly distilled 2,2,6,6-tetramethylpiperidine (0.17 mL, 1.0 mmol) in dry THF (2 mL) and *n*-BuLi (0.4 mL of a 2.5 M solution in hexanes, 1.0 mmol) at –5 °C over 15 min]. The stirring was continued for a further 1 h during which time the reaction mixture was allowed to warm to RT. The reaction mixture was re-cooled to –60 °C and a solution of benzaldehyde (0.30 mL, 3.0 mmol) in dry THF (1 mL) was added. The reaction mixture was warmed gradually to RT. The stirring was continued at the same temperature for 3 h before quenching with MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL), the mixture left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 75 mL). The combined organic phases were washed with H_2O (2 × 100 mL) and brine (100 mL),

dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as yellow oil (*anti : syn* diastereoisomers in the ratio of of 70 : 30).

Purification of the crude material by careful column chromatography on SiO_2 (230-400 mesh) with hexane : EtOAc (10 : 1) as the eluent to allow partial separation of the diasteroisomers to give a pure fraction of the title compound (*anti* isomer) as a yellow oil and a mixed fraction (yellow oil) of both isomers in combined yield of 0.074 g (34%).

R_t 11.9 min (minor enantiomer) and 15.4 min (major enantiomer) on chiral HPLC on a Diacel OD-H, (1 mL/min 2% isopropanol in hexane on 4.6 x 250 mm column).

6.4.11. *rac*-8-Hexyloctadec-9-yn-7-ol (4.82c)



To a stirred suspension of Cp_2ZrHCl (0.258 g, 1.0 mmol) in dry THF (10 mL) at RT was added neat 1-octene (0.125 mL, 0.8 mmol) dropwise over 3 minutes. After stirring the yellow solution for 1 h at RT, the reaction mixture was cooled to –78 °C and a solution of the non-1-yn-3-yl benzensulfonate (0.294 g, 1.0 mmol) in dry THF (1 mL) was added dropwise followed by dropwise addition of freshly prepared LiTMP, [prepared from freshly distilled 2,2,6,6-tetramethylpiperidine (0.17 mL, 1.0 mmol) in dry THF (2 mL) and *n*-BuLi (0.4 mL of a 2.5 M solution in hexanes, 1.0 mmol) at –5 °C over 15 min]. The stirring was continued for a further 1.5 h during which time the reaction mixture was allowed to warm to RT. The reaction mixture was re-cooled to –78 °C and a solution of 1-heptanal (0.42 mL, 3.0 mmol) in dry THF (1 mL) was added. The

reaction mixture warmed gradually to RT. The reaction mixture was stirred at RT for 3 h before quenching with MeOH (5 mL) and $NaHCO_3$ (6 mL). The mixture left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 75 mL). The combined organic phases were washed with H_2O (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a yellow oil (*anti : syn* diastereoisomers in the ratio of 89 : 11).

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexane : EtOAc (10 : 1) as the eluent to yield the title compounds as an inseparable mixture of *anti : syn* diastereoisomers in combined yield of 0.123 g (44%, yellow oil).

NMR characterysation does not contain complete data of the minor (*syn*) isomer.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.42 (1H, m, $H^{5\ major}$), 3.33 (1H, m, $H^{5\ minor}$), 2.38 – 2.36 (2H, m, $H^{4\ major\ +\ minor}$), 2.19 (2H, overlap td, J = 6.9, 2.3 Hz, $H^{1\ major}$), 2.16 (2H, overlap td, J = 7.0, 2.0 Hz, $H^{1\ minor}$), 1.74 (1H, d, J = 7.8 Hz, OH^{major}), 1.70 (1H, d, J = 8.3 Hz, OH^{minor}), 1.67 – 1.63 (2H, m, H^{minor}), 1.56 – 1.24 (62H, m, $H^{major\ +\ minor}$), 0.91 – 0.87 (18H, m, $H^{11\ +\ 17\ +\ 24\ (major\ +\ minor)}$).

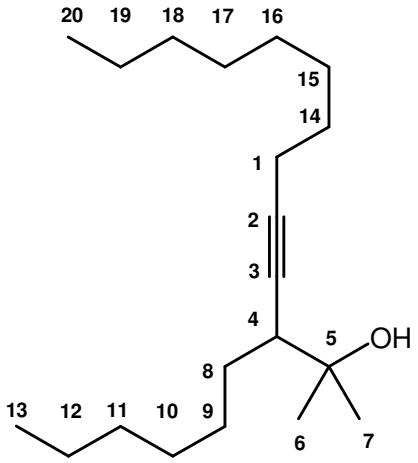
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 84.53 ($C^{2\ major}$), 83.72 ($C^{2\ minor}$), 79.29 ($C^{3\ major}$), 78.96 ($C^{3\ minor}$), 73.30 ($C^{5\ major}$), 73.23 ($C^{5\ minor}$), 39.91 ($CH^{4\ major}$), 39.22 ($CH^{4\ minor}$), 35.75 (CH_2^{major}), 35.71 (CH_2^{minor}), 32.22 (CH_2^{major}), 31.83 ($4CH_2^{major\ +\ minor}$), 31.79 ($2CH_2^{major\ +\ minor}$), 31.75 (CH_2^{minor}), 29.33 ($2CH_2^{major\ +\ minor}$), 29.23 (CH_2^{major}), 29.14 (CH_2^{major}), 29.10 ($2CH_2^{major\ +\ minor}$), 29.08 (CH_2^{major}), 28.85 ($2CH_2^{major\ +\ minor}$), 28.75 (CH_2^{minor}), 27.62 (CH_2^{major}), 27.57 (CH_2^{minor}), 25.82 ($2CH_2^{major\ +\ minor}$), 22.65 (CH_2^{major}), 22.62 ($4CH_2^{major\ +\ minor}$), 18.73 ($CH_2^{1\ major}$), 18.69 ($CH_2^{1\ minor}$), 14.06 ($6CH_3^{11\ +\ 17\ +\ 24\ (major\ +\ minor)}$).

HRMS (EI): Found: $[M - C_6H_{13}]^+$, 265.2536. $[C_{18}H_{33}O]^+$ requires: 265.2531.

LRMS (CI): *m/z*: 351 ($[M + H]^+$, 69%), 333 ($[M - H_2O + H]^+$, 55%).

IR (thin film): $\tilde{\nu}$ = 3387 (w, br), 2960 (m), 2933 (s), 2854 (s), 1467 (m), 1372 (w), 1043 (w, br), 718 (w) cm^{-1}.

6.4.12. *rac*-3-Hexyl-2-methyltridec-4-yn-2-ol (4.82d)



To a stirred suspension of Cp_2ZrHCl (0.258 g, 1.0 mmol) in dry THF (10 mL) at RT was added neat 1-octene (0.125 mL, 0.8 mmol) dropwise over 3 minutes. After stirring the yellow solution for 1 h at RT, the reaction mixture was cooled to –78 °C and a solution of the non-1-yn-3-yl benzensulfonate (0.294 g, 1.0 mmol) in dry THF (1 mL) was added dropwise followed by dropwise addition of freshly prepared LiTMP, [prepared from freshly distilled 2,2,6,6-tetramethylpiperidine (0.17 mL, 1.0 mmol) in dry THF (2 mL) and *n*-BuLi (0.4 mL of a 2.5 M solution in hexanes, 1.0 mmol) at –5 °C over 15 min]. The stirring was continued for a further 1.5 h during which time the reaction mixture was allowed to warm to RT. The reaction mixture was re-cooled to –78 °C and a solution of acetone (0.22 mL 3.0 mmol) in dry THF (1 mL) was added, the reaction mixture warmed gradually to RT. The reaction mixture was then refluxing for 20 h before cooling to RT and quenching with MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL), the mixture left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 75 mL). The combined organic phases were washed with H_2O (2 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a yellow oil.

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with hexane : EtOAc (10 : 1) as the eluent to yield the title compound as a yellow oil in yield of 0.118 g (50%, contained 10% of unidentified by-products).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 2.34 (1H, m, H^4), 2.20 (2H, td, *J* = 7.0, 2.0 Hz, H^1), 1.97 (1H, br s, OH), 1.61 (1H, m), 1.54 – 1.47 (3H, m), 1.41 – 1.26 (18H, m), 1.25 (3H, s, $H^{6/7}$), 1.24 (3H, s, $H^{6/7}$), 0.90 (3H, t, *J* = 6.8 Hz, $H^{13/20}$), 0.89 (3H, t, *J* = 6.8 Hz, $H^{13/20}$).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 84.33 (C^2), 80.35 (C^3), 71.98 (C^5), 45.34 (CH^4), 31.81 ($2CH_2$), 30.07 (CH_2), 29.21 (CH_2), 29.14 (CH_2), 29.07 ($2CH_2$), 28.84 (CH_2), 28.36 (CH_2), 27.01 ($CH_3^{6/7}$), 26.24 ($CH_3^{6/7}$), 22.63 ($2CH_2$), 18.70 (CH_2^1), 14.06 ($2CH_3^{13+20}$).

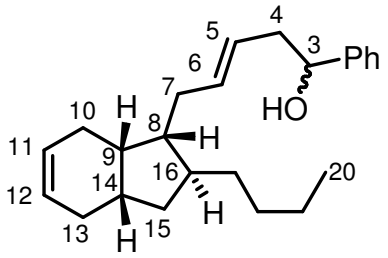
HRMS (EI): Found: $[M - CH_3]^+$, 279.2694. $[C_{19}H_{35}O]^+$ requires: 279.2688.

LRMS (CI): *m/z*: 294 ($[M]^+$, 26%), 277 ($[M - H_2O + H]^+$, 100 %).

IR (thin film): $\tilde{\nu}$ = 3410 (w, br), 2930 (s), 2854 (s), 1478 (m), 1372 (m), 1183 (m), 1142 (m), 903 (w), 722 (w) cm^{-1}.

6.5. Experimental from chapter 5

6.5.1. *rac*-(*R*,3*E*)-5-((2*S*,3*R*,3a*S*,7a*S*)-2-Butyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-3-yl)-1-phenylpent-3-en-1-ol and *rac*-(*S*,3*E*)-5-((2*S*,3*R*,3a*S*,7a*S*)-2-butyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-3-yl)-1-phenylpent-3-en-1-ol (5.30a)



5.30a

To a solution of Cp_2ZrCl_2 (0.307 g, 1.05 mmol) in dry THF (5 mL) cooled to –78 °C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same temperature, a solution of triene **5.5** (0.190 g, 1.0 mmol) in dry THF (3 mL) was added dropwise, the stirring continued for 20 min at –78 °C before the reaction mixture was allowed to warm to RT gradually and the stirring continued for 75 min. The reaction mixture was re-cooled to –78 °C, a solution of allyl chloride (0.098 mL, 1.2 mmol) in dry THF (1 mL) was added followed by dropwise addition of LiTMP, [prepared from freshly distilled 2,2,6,6-tetramethylpiperidine (0.20

mL, 1.2 mmol) in dry THF (2 mL) and *n*-BuLi (0.48 mL of a 2.5 M solution in hexanes, 1.2 mmol) at 0 °C over 20 min]. The reaction mixture was allowed to warm to –65 °C within 20 min before benzaldehyde (0.30 mL, 3.0 mmol) in dry THF (3 mL) and $BF_3{\cdot}OEt_2$ (0.36 ml, 3.0 mmol) were added dropwise. The reaction mixture was warmed gradually to –1 °C within 4 h before addition of MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL). The mixture left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with H_2O (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a pale yellow oil. Purification of the crude material by careful column chromatography on SiO_2 (230 – 400 mesh) with 10% of EtOAc in hexanes as the eluent gave a fraction of the title compounds as an inseparable mixture of diastereoisomers, epimeric at the secondary alcohol centre in the ^{13}C NMR ratio of 1.5 : 1 (0.20 g, pale yellow oil, 69% GC purity).

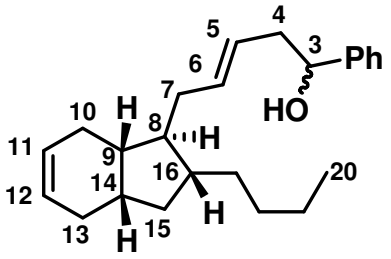
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.270 – 7.163 (10H, m, $H^{Ar\ major\ +\ minor}$), 5.615 – 5.440 (6H, m, $2H^{11}$ + $2H^{12}$ + $2H^{6}$), 5.345 – 5.264 (2H, m, $H^{5\ major\ +\ minor}$), 4.603 (2H, br dd, *J* = 7.3, 5.3 Hz, $H^{3\ major\ +\ minor}$), 2.444 – 2.316 (4H, m, $H^{4\ major\ +\ minor}$), 2.134 – 1.869 (12H, m, $H^{major\ +\ minor}$), 1.802 – 1.254 (13H, m, $H^{major\ +\ minor}$), 1.209 – 0.960 (13H, m, $H^{major\ +\ minor}$), 0.807 (6H, br t, *J* = 7.2 Hz, $H^{20\ major\ +\ minor}$).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 143.97 ($2C^{i\text{-}Ph\ major\ +\ minor}$), 133.83 ($CH^{5\ major}$), 133.79 ($CH^{5\ minor}$), 128.31 ($4CH^{m\text{-}Ph\ major\ +\ minor}$), 128.31 ($2CH^{11/12}$), 126.37 ($2CH^{11/12}$), 126.26 ($CH^{6\ major}$), 126.23 ($CH^{6\ minor}$), 125.99 ($2CH^{p\text{-}Ph\ major\ +\ minor}$), 125.82 ($2CH^{o\text{-}Ph\ minor}$), 125.79 ($2CH^{o\text{-}Ph\ major}$), 73.54 ($CH^{3\ minor}$), 73.50 ($CH^{3\ major}$), 50.87 ($CH^{8\ minor}$), 50.82 ($CH^{8\ major}$), 44.03 ($CH^{9\ minor}$), 44.00 ($CH^{9\ major}$), 42.79 ($2CH^{4\ major\ +\ minor}$), 40.22 ($CH^{16\ major}$), 40.17 ($CH^{16\ minor}$), 38.09 ($2CH_2^{major\ +\ minor}$), 38.09 ($2CH_2^{7\ major\ +\ minor}$), 37.02 ($CH^{14\ minor}$), 36.99 ($CH^{14\ major}$), 34.89 ($2CH_2^{major\ +\ minor}$), 30.97 ($2CH_2^{major\ +\ minor}$), 27.77 ($2CH_2^{major\ +\ minor}$), 27.63 ($2CH_2^{major\ +\ minor}$), 22.91 ($2CH_2^{major\ +\ minor}$), 14.12 ($2CH_3^{20\ major\ +\ minor}$).

LRMS (EI): *m/z*: 321 ($[M - H_2O]^+$, 11%), 232 ($[M - BnOH + H]^+$, 5%), 175 (29%), 130 (32%), 107 (100%).

IR (thin film): $\tilde{\nu}$ **=** 3353 (w, br), 3028 (w), 2922 (m, br), 1452 (m), 1024 (m), 975 (m), 745 (m), 688 (s) cm^{-1}.

6.5.2. *rac*-(*R*,3*E*)-5-((2*R*,3*S*,3a*S*,7a*S*)-2-Butyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-3-yl)-1-phenylpent-3-en-1-ol and *rac*-(*S*,3*E*)-5-((2*R*,3*S*,3a*S*,7a*S*)-2-butyl-2,3,3a,4,7,7a-hexahydro-1*H*-inden-3-yl)-1-phenylpent-3-en-1-ol (5.30b)



5.30b

To a solution of Cp_2ZrCl_2 (0.307 g, 1.05 mmol) in dry THF (5 mL) cooled to –78 °C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same temperature, a solution of triene **5.5** (0.190 g, 1.0 mmol) in dry THF (3 mL) was added dropwise, the stirring continued for 15 min at –78 °C before the reaction mixture was allowed to warm to RT gradually and heated at 65 °C for 30 min. The reaction mixture was re-cooled to –78 °C, a solution of allyl chloride (0.098 mL, 1.2 mmol) in dry THF (1 mL) was added followed by dropwise addition of LiTMP, [prepared from freshly distilled 2,2,6,6-tetramethylpiperidine (0.20 mL, 1.2 mmol) in dry THF (2 mL) and *n*-BuLi (0.48 mL of a 2.5 M solution in hexanes, 1.2 mmol) at 0 °C over 20 min]. The reaction mixture was allowed to warm to –65 °C within 20 min before benzaldehyde (0.30 mL, 3.0 mmol) in dry THF (3 mL) and $BF_3{\cdot}OEt_2$ (0.36 ml, 3.0 mmol) were added dropwise. The reaction mixture was warmed gradually to –5 °C within 4 h before addition of MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL). The mixture left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with H_2O (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a pale yellow oil.

Purification of the crude material by careful column chromatography on SiO_2 (230 – 400 mesh) with 2.5 → 10% of EtOAc in hexanes as the eluent gave a fraction of the title compounds as an inseparable mixture of diastereoisomers, epimeric at the secondary alcohol centre in the ^{13}C NMR ratio of 3.1 : 1 (0.026 g, pale yellow oil, fraction pure in 89% by GC).

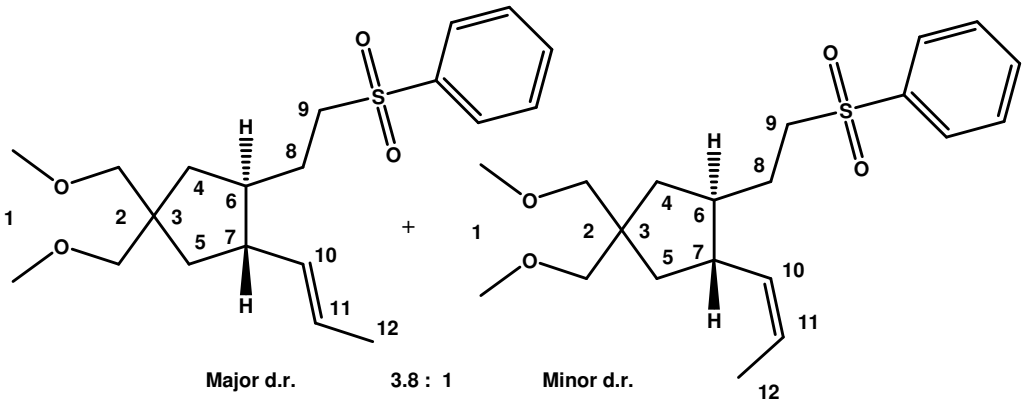
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.270 – 7.162 (10H, m, $H^{Ar\ major\ +\ minor}$), 5.613 – 5.476 (6H, m, $2H^{11} + 2H^{12} + 2H^{6}$), 5.356 – 5.283 (2H, m, $H^{5\ major\ +\ minor}$), 4.624 – 4.584 (2H, m, $H^{3\ major\ +\ minor}$), 2.443 – 2.319 (4H, m, $H^{4\ major\ +\ minor}$), 2.197 – 1.960 (10H, m, $H^{major\ +\ minor}$), 1.695 – 1.587 (4H, m, $H^{major\ +\ minor}$), 1.528 – 1.389 (6H, m, $H^{major\ +\ minor}$), 1.359 – 0.964 (18H, m, $H^{major\ +\ minor}$), 0.813 (6H, br t, J = 7.0 Hz, $H^{20\ major\ +\ minor}$).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 143.99 ($2C^{i\text{-}Ph\ major\ +\ minor}$), 133.62 ($2CH^{5\ major\ +\ minor}$), 128.33 ($4CH^{m\text{-}Ph\ major\ +\ minor}$), 127.38 ($2CH^{11/12}$), 127.28 ($2CH^{11/12}$), 126.37 ($2CH^{p\text{-}Ph\ major\ +\ minor}$), 127.04 ($2CH^{6\ major\ +\ minor}$), 125.83 ($2CH^{o\text{-}Ph\ minor}$), 125.79 ($2CH^{o\text{-}Ph\ major}$), 73.58 ($CH^{3\ minor}$), 73.54 ($CH^{3\ major}$), 52.09 ($CH^{8\ minor}$), 52.06 ($CH^{8\ major}$), 47.08 ($CH^{9\ minor}$), 47.03 ($CH^{9\ major}$), 42.76 ($2CH^{4\ major\ +\ minor}$), 42.25 ($CH^{16\ minor}$), 42.21 ($CH^{16\ major}$), 40.03 ($2CH^{14\ major\ +\ minor}$), 36.92 ($2CH_2^{major\ +\ minor}$), 36.67 ($2CH_2^{major\ +\ minor}$), 36.55 ($CH_2^{7\ minor}$), 36.49 ($CH_2^{7\ major}$), 32.37 ($2CH_2^{major\ +\ minor}$), 31.50 ($2CH_2^{major\ +\ minor}$), 30.69 ($2CH_2^{major\ +\ minor}$), 22.91 ($2CH_2^{major\ +\ minor}$), 14.15 ($2CH_3^{20\ major\ +\ minor}$).

LRMS (EI): *m/z*: 321 ($[M - H_2O + H]^+$, 6%), 320 ($[M - H_2O]^+$, 27%), 192 (5%), 130 (100%).

IR (thin film): $\tilde{\nu}$ **=** 3380 (w, br), 3024 (w), 2956 (m), 2911 (m, br), 1459 (m), 1433 (m), 1021 (m), 971 (m), 756 (m), 692 (s), 669 (s) cm^{-1}.

6.5.3. *rac*-1-(2-((1*S*,2*R*)-4,4-Bis(methoxymethyl)-2-((E)-prop-1-enyl)cyclopentyl)ethylsulfonyl)benzene (major d.r.) and *rac*-1-(2-((1*S*,2*R*)-4,4-bis(methoxymethyl)-2-((E)-prop-1-enyl)cyclopentyl)ethylsulfonyl)-benzene (minor d.r.) (5.46)



To a solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same temperature, a solution of (*Z*)-4,4-bis(methoxymethyl)nona-1,6-diene (0.212 g, 1.0 mmol) in dry THF (3 mL) was added dropwise, the stirring continued for 30 min at –78 °C before the reaction mixture was allowed to warm to RT and stirred for a further 4 h. After cooling the reaction to –78 °C, a solution of 1-(chloromethylsulfonyl)benzene (0.76 g, 4.0 mmol) in dry THF (3 mL) was added dropwise followed by dropwise addition of LDA (2.22 mL of a 1.8 M solution, 4.0 mmol). The reaction mixture was allowed to warm to RT within 5 h and stirred at this temperature for a further 4 h, before addition of MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL). The mixture left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with H_2O (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a dark brown oil.

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with 20 → 50% of Et_2O in hexanes as the eluent gave the title compounds as an inseparable mixture of *E : Z* isomers in the ratio of 3.8 : 1 (0.232 g, 45%, pale yellow oil).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.990 – 7.915 (2H, m, $H^{o\text{-}Ph\ minor}$), 7.896 – 7.866 (2H, m, $H^{o\text{-}Ph\ major}$), 7.670 – 7.634 (1H, m, $H^{p\text{-}Ph\ minor}$), 7.651 (1H, t, *J* = 7.5 Hz, $H^{p\text{-}Ph\ minor}$), 7.597 – 7.543 (2H, m, $H^{m\text{-}Ph\ minor}$), 7.562 (2H, t, *J* = 7.5 Hz, $H^{m\text{-}Ph\ minor}$), 5.471 – 5.326 (1H, m, $H^{11\ minor}$), 5.368 (1H, dq, *J* = 15.1, 6.5 Hz, $H^{11\ major}$), 5.180 – 5.075 (1H, m, $H^{11\ minor}$), 5.150 (1H, fs ddq, *J* = 15.1, 8.0, 1.0 Hz, $H^{10\ major}$), 3.319 (6H, s, $H^{1\ minor}$), 3.289 (6H, s, H^{1major}), 3.214 – 3.035 (10H, m, $H^{2\ major\ +\ minor}$ + $H^{9\ minor}$), 3.072 (2H, dd, *J* = 9.0, 7.5 Hz, $H^{9\ major}$), 2.400 (1H, m, $H^{7\ minor}$), 2.033 – 1.816 (2H, m, $H^{7\ major}$ + H), 1.781 – 1.655 (4H, m), 1.609 (3H, dd, *J* = 6.5, 1.5 Hz, $H^{12\ major}$), 1.558 (3H, dd, *J* = 7.0, 1.7 Hz, $H^{12\ minor}$), 1.534 – 1.382 (3H, m), 1.318 – 1.117 (4H, m), 1.033 (1H, dd, *J* = 13.1, 11.0 Hz, H^{minor}), 0.974 (1H, dd, *J* = 13.1, 11.0 Hz, H^{major}).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 139.27 ($C^{i\text{-}Ph\ major}$), 139.21 ($C^{i\text{-}Ph\ minor}$), 133.54 ($CH^{p\text{-}Ph/10\ major}$), 133.54 ($CH^{p\text{-}Ph/10\ minor}$), 133.52 ($CH^{p\text{-}Ph/10\ major}$), 133.34 ($CH^{p\text{-}Ph/10\ minor}$), 129.16 ($4CH^{m\text{-}Ph\ major\ +\ minor}$), 127.99 ($4CH^{o\text{-}Ph\ major\ +\ minor}$), 125.81 ($CH^{11\ major}$),

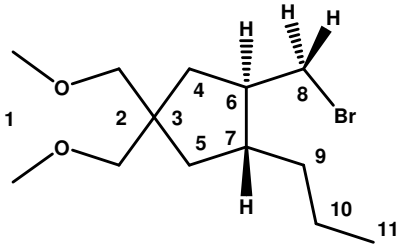
124.87 ($CH^{11\ minor}$), 77.75 ($CH_2^{2\ minor}$), 77.71 ($CH_2^{2\ major}$), 77.67 ($2CH_2^{2\ major + minor}$), 59.18 ($4CH_3^{1\ major + minor}$), 55.32 ($CH_2^{9\ minor}$), 55.24 ($CH_2^{9\ major}$), 49.31 ($CH^{7\ major}$), 45.73 ($C^{3\ minor}$), 45.39 ($C^{3\ major}$), 44.61 ($CH^{7\ minor}$), 43.74 ($CH^{6\ major}$), 43.42 ($CH^{6\ minor}$), 39.84 ($CH_2^{4/5\ major}$), 39.75 ($CH_2^{4/5\ minor}$), 38.59 ($CH_2^{4/5\ minor}$), 38.43 ($CH_2^{4/5\ major}$), 26.60 ($CH_2^{8\ minor}$), 26.25 ($CH_2^{8\ major}$), 17.88 ($CH_3^{12\ major}$), 13.24 ($CH_3^{12\ minor}$).

HRMS (EI): Found: $[M - MeOH]^+$, 334.1597. $[C_{19}H_{26}O_3S]^+$ requires: 334.1603.

LRMS (EI): *m/z*: 334 ($[M - MeOH]^+$, 3%), 289 ($[M - Ph]^+$, 20%), 192 (29%), 160 (100%).

IR (thin film): $\tilde{\nu}$ **=** 2922 (m), 2865 (m), 2824 (m), 1448 (s), 1308 (s), 1138 (s), 1107 (s), 1085 (s), 968 (s), 729 (s), 684 (s), 533 (s) cm^{-1}.

6.5.4. *rac*-(3*R*,4*R*)-3-(Bromomethyl)-1,1-bis(methoxymethyl)-4-propylcyclopentane (5.50)



To a solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same temperature, a solution of (*Z*)-4,4-bis(methoxymethyl)nona-1,6-diene (0.212 g, 1.0 mmol) in dry THF (3 mL) was added dropwise, the stirring continued for 30 min at –78 °C before the reaction mixture was allowed to warm to RT and stirred for a further 2 h. After cooling the reaction to –78 °C, dropwise addition of *n*-BuLi (0.44 mL of a 2.5 M solution in hexanes, 1.1 mmol) followed. After stirring the reaction mixture at the same temperature for 5 min, a solution of CBr_4 (0.497 g, 1.5 mmol) in dry THF (1 mL) was added dropwise and the stirring was continued for 15 min at –78 °C, before addition of MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL). The whole mixture was allowed to warm to RT, left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 50 mL). The combined organic phases were washed

with H_2O (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a dark brown oil.

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with 10% of Et_2O in hexanes as the eluent gave the title compound as a yellow oil in yield of 0.223 g (76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.584 (1H, dd, *J* = 9.8, 3.3 Hz, H^8), 3.344 (3H, s, H^1), 3.341 (3H, s, H^1), 3.318 (1H, dd, *J* = 10.0, 7.5 Hz, H^8), 3.225 (2H, br d, *J* = 9.0 Hz, H^2), 3.195 (1H, d, *J* = 9.0 Hz, H^2), 3.191 (1H, d, *J* = 9.0 Hz, H^2), 1.881 – 1.823 (3H, m), 1.642 (1H, m), 1.501 (1H, m), 1.417 – 1.179 (3H, m), 1.131 (1H, dd, *J* = 13.0, 11.0 Hz), 1.072 (1H, m), 0.892 (3H, t, *J* = 7.3 Hz, H^{11}).

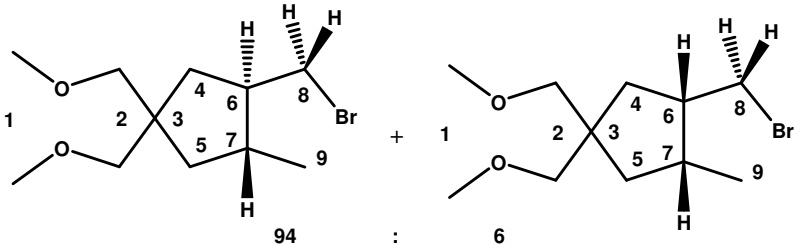
^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 77.76 (CH_2^2), 77.56 (CH_2^2), 59.25 ($2CH_3^1$), 47.05 (CH^6), 44.95 (C^3), 42.98 (CH^7), 39.25 (CH_2), 38.46 (CH_2), 37.84 (CH_2), 36.17 (CH_2^8), 21.21 (CH_2), 14.35 (CH_3^{11}).

HRMS (EI): Found: $[M + Na]^+$, 315.0932. $[C_{13}H_{25}NaBrO_2]^+$ requires: 315.0930.

LRMS (EI): *m/z*: 262 ($[M - C_2H_6]^+$, 11%), 260 ($[M - MeOH]^+$, 7%), 230 (58%), 228 (54 %), 148 (90%), 45 (100%).

IR (thin film): $\tilde{\nu}$ **=** 2949 (m), 2922 (m), 2869 (m), 1452 (m), 1198 (m), 1104 (s), 960 (m), 729 (w), 642 (w) cm^{-1}.

6.5.5. *rac*-(3*R*,4*R*)-3-(Bromomethyl)-1,1-bis(methoxymethyl)-4-methylcyclopentane (major d.r.) and *rac*-(3*S*,4*R*)-3-(bromomethyl)-1,1-bis(methoxymethyl)-4-methylcyclopentane (minor d.r.) (5.51)



To a solution of Cp_2ZrCl_2 (0.293 g, 1.0 mmol) in dry THF (5 mL) cooled to –78 °C was added *n*-BuLi (0.80 mL of a 2.5 M solution in hexanes, 2.0 mmol) dropwise over 3 minutes. After 25 min at the same temperature, a solution of bis(methoxymethyl)hepta-1,6-diene (0.184 g, 1.0 mmol) in dry THF (3 mL) was added dropwise, the stirring continued for 30 min at –78 °C before the reaction mixture was allowed to warm to RT

and stirred for a further 2 h. After cooling the reaction to –78 °C, dropwise addition of *n*-BuLi (0.44 mL of a 2.5 M solution in hexanes, 1.1 mmol) followed. After stirring the reaction mixture at the same temperature for 5 min, a solution of CBr_4 (0.497 g, 1.5 mmol) in dry THF (1 mL) was added dropwise and the stirring was continued for 15 min at –78 °C, before addition of MeOH (5 mL) and a saturated aqueous solution of $NaHCO_3$ (6 mL). The whole mixture was allowed to warm to RT, left stirring overnight. The mixture was poured onto H_2O (100 mL), the products extracted with Et_2O (3 × 50 mL). The combined organic phases were washed with H_2O (3 × 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the crude product as a dark brown oil.

Purification of the crude material by column chromatography on SiO_2 (230 – 400 mesh) with 10% of Et_2O in hexanes as the eluent gave the title compounds as an inseparable mixture of *trans : cis* ring junction isomers in the ratio of 94 : 6 (0.186 g, 70%, yellow oil).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 3.562 (1H, dd, *J* = 9.8, 3.3 Hz, $H^{8\ major}$), 3.365 (1H, dd, *J* = 7.9, 2.1 Hz, $H^{8\ minor}$), 3.332 (6H, s, H^{1major}), 3.326 (6H, s, $H^{1\ minor}$), 3.304 (1H, dd, *J* = 9.8, 7.0 Hz, $H^{8\ major}$), 3.241 – 3.155 (4H, m, $H^{2\ minor}$), 3.215 (2H, d, *J* = 8.8 Hz, $H^{2\ major}$), 3.186 (2H, d, *J* = 8.8 Hz, $H^{2\ major}$), 1.855 (1H, dd, *J* = 12.8, 7.3 Hz, $H^{4\ major}$), 1.819 (1H, dd, *J* = 12.8, 7.0 Hz, $H^{5\ major}$), 1.819 – 1.646 (2H, m, $H^{6\ +\ 7\ major}$), 1.306 (1H, dd, *J* = 12.8, 9.8 Hz, $H^{4\ major}$), 1.146 (1H, dd, *J* = 12.8, 10.5 Hz, $H^{5\ major}$), 0.970 (3H, d, *J* = 6.3 Hz, $H^{9\ major}$), 0.906 (3H, d, *J* = 7.3 Hz, $H^{9\ minor}$).

^{13}C NMR (100.5 MHz, $CDCl_3$): δ (ppm) = 78.30 ($CH_2^{2\ minor}$), 77.86 ($CH_2^{2\ major}$), 77.55 ($CH_2^{2\ major}$), 77.35 ($CH_2^{2\ minor}$), 59.21 ($4CH_3^{1\ major\ +\ minor}$), 48.43 ($CH^{6\ major}$), 46.60 ($C^{3\ minor}$), 45.16 ($CH^{6\ minor}$), 44.88 ($C^{3\ major}$), 41.74 ($CH^{5\ major}$), 39.68 ($CH^{5\ minor}$), 38.57 ($CH_2^{8\ major}$), 38.05 ($CH_2^{7\ major}$), 37.41 ($CH_2^{4\ major}$), 36.40 ($CH_2^{8\ minor}$), 35.57 ($CH^{7\ minor}$), 35.19 ($CH_2^{4\ minor}$), 17.87 ($CH_3^{9\ major}$), 15.19 ($CH_3^{9\ minor}$).

HRMS (EI): Found: $[M - MeOH]^+$, 232.0462. $[C_{10}H_{17}OBr(79)]^+$ requires: 232.0463.

LRMS (EI): *m/z*: 265 ($[M + H]^+$, 2%), 234 ($[M - 2CH_3]^+$, 15%), 232 ($[M - MeOH]^+$, 13%), 202 (71%), 200 (59%), 107 (97%), 45 (100%).

IR (thin film): $\tilde{\nu}$ **=** 2949 (m), 2915 (m), 2865 (m), 2824 (m), 1444 (m), 1194 (m), 1100 (s), 960 (m), 642 (w) cm^{-1}.

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Chapter 8. Appendix – X-ray data of 2.70-*endo*

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Table 1. Crystal data and structure refinement.

Identification code	**2007sot0730**	
Empirical formula	$C_{30}H_{36}O_2$	
Formula weight	428.59	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	*P*–1	
Unit cell dimensions	a = **9.5488(6) Å**	α = 10**6.772(4)**°
	b = **11.0306(6) Å**	β = **110.048(3)**°
	c = **13.4198(9) Å**	γ = **95.736(4)**°
Volume	1239.89(13) Å^3	
Z	2	
Density (calculated)	1.148 Mg / m^3	
Absorption coefficient	0.070 mm^{-1}	
F(000)	464	
Crystal	Block; Colourless	
Crystal size	0.14 × 0.12 × 0.10 mm^3	
θ range for data collection	2.98 – 27.48°	
Index ranges	$-12 \le h \le 12$, $-14 \le k \le 14$, $-17 \le l \le 17$	
Reflections collected	20095	
Independent reflections	5646 [R_{int} = 0.0537]	
Completeness to θ = 27.48°	99.0 %	
Absorption correction	Semi–empirical from equivalents	
Max. and min. transmission	0.9931 and 0.9903	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5646 / 0 / 292	
Goodness-of-fit on F^2	1.071	
Final *R* indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0570, *wR2* = 0.1296	
R indices (all data)	*R1* = 0.0752, *wR2* = 0.1437	
Extinction coefficient	0.020(4)	
Largest diff. peak and hole	0.345 and –0.235 e Å^{-3}	

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

Special details:

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

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	4935(2)	4604(2)	1560(1)	24(1)	1
C2	3793(2)	3981(2)	1921(2)	26(1)	1
C3	2601(2)	4797(2)	1742(2)	26(1)	1
C4	3559(2)	6211(2)	2246(1)	22(1)	1
C5	4125(2)	6672(2)	3547(1)	22(1)	1
C6	5646(2)	6934(2)	4057(1)	23(1)	1
C7	6401(2)	6779(2)	3221(1)	25(1)	1
C8	5084(2)	6091(2)	2054(1)	23(1)	1
C9	3023(2)	6728(2)	4106(1)	22(1)	1
C10	3052(2)	6028(2)	4826(1)	26(1)	1
C11	2020(2)	6070(2)	5353(2)	30(1)	1
C12	935(2)	6815(2)	5166(2)	31(1)	1
C13	894(2)	7519(2)	4456(2)	30(1)	1
C14	1924(2)	7481(2)	3936(2)	26(1)	1
C15	2715(2)	7133(2)	1735(1)	24(1)	1
C16	1210(2)	6827(2)	1145(2)	30(1)	1
C17	3607(2)	8421(2)	1900(1)	24(1)	1
C18	4638(2)	9276(2)	2955(2)	27(1)	1
C19	5414(2)	10481(2)	3071(2)	31(1)	1
C20	5163(2)	10860(2)	2141(2)	35(1)	1
C21	4148(2)	10025(2)	1091(2)	38(1)	1
C22	3379(2)	8822(2)	972(2)	32(1)	1
C23	6604(2)	7400(2)	5306(1)	26(1)	1
C24	7800(2)	8660(2)	5729(2)	27(1)	1
C25	8869(2)	9026(2)	6964(2)	29(1)	1
C26	10212(2)	10153(2)	7335(2)	29(1)	1
C27	11366(2)	10496(2)	8537(2)	31(1)	1
C28	12644(2)	11652(2)	8856(2)	35(1)	1
C29	7389(2)	4428(2)	1533(1)	26(1)	1
C30	8790(2)	3942(2)	2015(2)	35(1)	1
O1	6342(1)	4169(1)	1952(1)	26(1)	1
O2	7215(2)	4996(1)	873(1)	36(1)	1

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

Symmetry transformations used to generate equivalent atoms:

Table 4. Bond lengths [Å] and angles [°].

C1–O1	1.4507(19)
C1–C2	1.516(2)
C1–C8	1.553(2)
C1–H1	1.0000
C2–C3	1.519(2)
C2–H2A	0.9900
C2–H2B	0.9900
C3–C4	1.551(2)
C3–H3A	0.9900
C3–H3B	0.9900
C4–C15	1.530(2)
C4–C5	1.545(2)
C4–C8	1.575(2)
C5–C6	1.335(2)
C5–C9	1.483(2)
C6–C23	1.506(2)
C6–C7	1.510(2)
C7–C8	1.543(2)
C7–H7A	0.9900
C7–H7B	0.9900
C8–H8	1.0000
C9–C10	1.395(2)
C9–C14	1.401(2)
C10–C11	1.393(2)
C10–H10	0.9500
C11–C12	1.387(3)
C11–H11	0.9500
C12–C13	1.385(3)
C12–H12	0.9500
C13–C14	1.384(2)
C13–H13	0.9500
C14–H14	0.9500
C15–C16	1.332(2)
C15–C17	1.497(2)
C16–H16A	0.9500
C16–H16B	0.9500

C17–C22	1.396(2)
C17–C18	1.397(2)
C18–C19	1.394(2)
C18–H18	0.9500
C19–C20	1.380(3)
C19–H19	0.9500
C20–C21	1.382(3)
C20–H20	0.9500
C21–C22	1.388(3)
C21–H21	0.9500
C22–H22	0.9500
C23–C24	1.530(2)
C23–H23A	0.9900
C23–H23B	0.9900
C24–C25	1.524(2)
C24–H24A	0.9900
C24–H24B	0.9900
C25–C26	1.525(2)
C25–H25A	0.9900
C25–H25B	0.9900
C26–C27	1.518(2)
C26–H26A	0.9900
C26–H26B	0.9900
C27–C28	1.521(2)
C27–H27A	0.9900
C27–H27B	0.9900
C28–H28A	0.9800
C28–H28B	0.9800
C28–H28C	0.9800
C29–O2	1.202(2)
C29–O1	1.348(2)
C29–C30	1.498(3)
C30–H30A	0.9800
C30–H30B	0.9800
C30–H30C	0.9800

O1–C1–C2	108.43(13)
O1–C1–C8	114.91(13)
C2–C1–C8	105.96(13)
O1–C1–H1	109.1
C2–C1–H1	109.1
C8–C1–H1	109.1

C1–C2–C3	101.32(13)
C1–C2–H2A	111.5
C3–C2–H2A	111.5
C1–C2–H2B	111.5
C3–C2–H2B	111.5
H2A–C2–H2B	109.3
C2–C3–C4	103.89(13)
C2–C3–H3A	111.0
C4–C3–H3A	111.0
C2–C3–H3B	111.0
C4–C3–H3B	111.0
H3A–C3–H3B	109.0
C15–C4–C5	113.22(13)
C15–C4–C3	113.02(13)
C5–C4–C3	109.01(13)
C15–C4–C8	113.70(13)
C5–C4–C8	102.27(13)
C3–C4–C8	104.77(12)
C6–C5–C9	126.46(15)
C6–C5–C4	112.69(14)
C9–C5–C4	120.79(14)
C5–C6–C23	127.87(15)
C5–C6–C7	111.89(15)
C23–C6–C7	120.17(14)
C6–C7–C8	104.75(13)
C6–C7–H7A	110.8
C8–C7–H7A	110.8
C6–C7–H7B	110.8
C8–C7–H7B	110.8
H7A–C7–H7B	108.9
C7–C8–C1	114.57(13)
C7–C8–C4	106.25(13)
C1–C8–C4	103.88(12)
C7–C8–H8	110.6
C1–C8–H8	110.6
C4–C8–H8	110.6
C10–C9–C14	117.65(15)
C10–C9–C5	120.73(15)
C14–C9–C5	121.62(15)
C11–C10–C9	121.23(16)
C11–C10–H10	119.4
C9–C10–H10	119.4

C12–C11–C10	120.14(16)
C12–C11–H11	119.9
C10–C11–H11	119.9
C13–C12–C11	119.34(17)
C13–C12–H12	120.3
C11–C12–H12	120.3
C14–C13–C12	120.51(16)
C14–C13–H13	119.7
C12–C13–H13	119.7
C13–C14–C9	121.12(16)
C13–C14–H14	119.4
C9–C14–H14	119.4
C16–C15–C17	118.79(15)
C16–C15–C4	122.17(15)
C17–C15–C4	119.04(14)
C15–C16–H16A	120.0
C15–C16–H16B	120.0
H16A–C16–H16B	120.0
C22–C17–C18	117.44(16)
C22–C17–C15	119.33(15)
C18–C17–C15	123.19(15)
C19–C18–C17	121.10(17)
C19–C18–H18	119.4
C17–C18–H18	119.4
C20–C19–C18	120.40(17)
C20–C19–H19	119.8
C18–C19–H19	119.8
C19–C20–C21	119.30(17)
C19–C20–H20	120.4
C21–C20–H20	120.4
C20–C21–C22	120.44(18)
C20–C21–H21	119.8
C22–C21–H21	119.8
C21–C22–C17	121.31(17)
C21–C22–H22	119.3
C17–C22–H22	119.3
C6–C23–C24	113.93(14)
C6–C23–H23A	108.8
C24–C23–H23A	108.8
C6–C23–H23B	108.8
C24–C23–H23B	108.8
H23A–C23–H23B	107.7

C25–C24–C23	112.77(14)
C25–C24–H24A	109.0
C23–C24–H24A	109.0
C25–C24–H24B	109.0
C23–C24–H24B	109.0
H24A–C24–H24B	107.8
C24–C25–C26	112.84(15)
C24–C25–H25A	109.0
C26–C25–H25A	109.0
C24–C25–H25B	109.0
C26–C25–H25B	109.0
H25A–C25–H25B	107.8
C27–C26–C25	114.78(15)
C27–C26–H26A	108.6
C25–C26–H26A	108.6
C27–C26–H26B	108.6
C25–C26–H26B	108.6
H26A–C26–H26B	107.5
C26–C27–C28	111.70(15)
C26–C27–H27A	109.3
C28–C27–H27A	109.3
C26–C27–H27B	109.3
C28–C27–H27B	109.3
H27A–C27–H27B	107.9
C27–C28–H28A	109.5
C27–C28–H28B	109.5
H28A–C28–H28B	109.5
C27–C28–H28C	109.5
H28A–C28–H28C	109.5
H28B–C28–H28C	109.5
O2–C29–O1	123.74(16)
O2–C29–C30	125.01(17)
O1–C29–C30	111.24(15)
C29–C30–H30A	109.5
C29–C30–H30B	109.5
H30A–C30–H30B	109.5
C29–C30–H30C	109.5
H30A–C30–H30C	109.5
H30B–C30–H30C	109.5
C29–O1–C1	116.66(13)

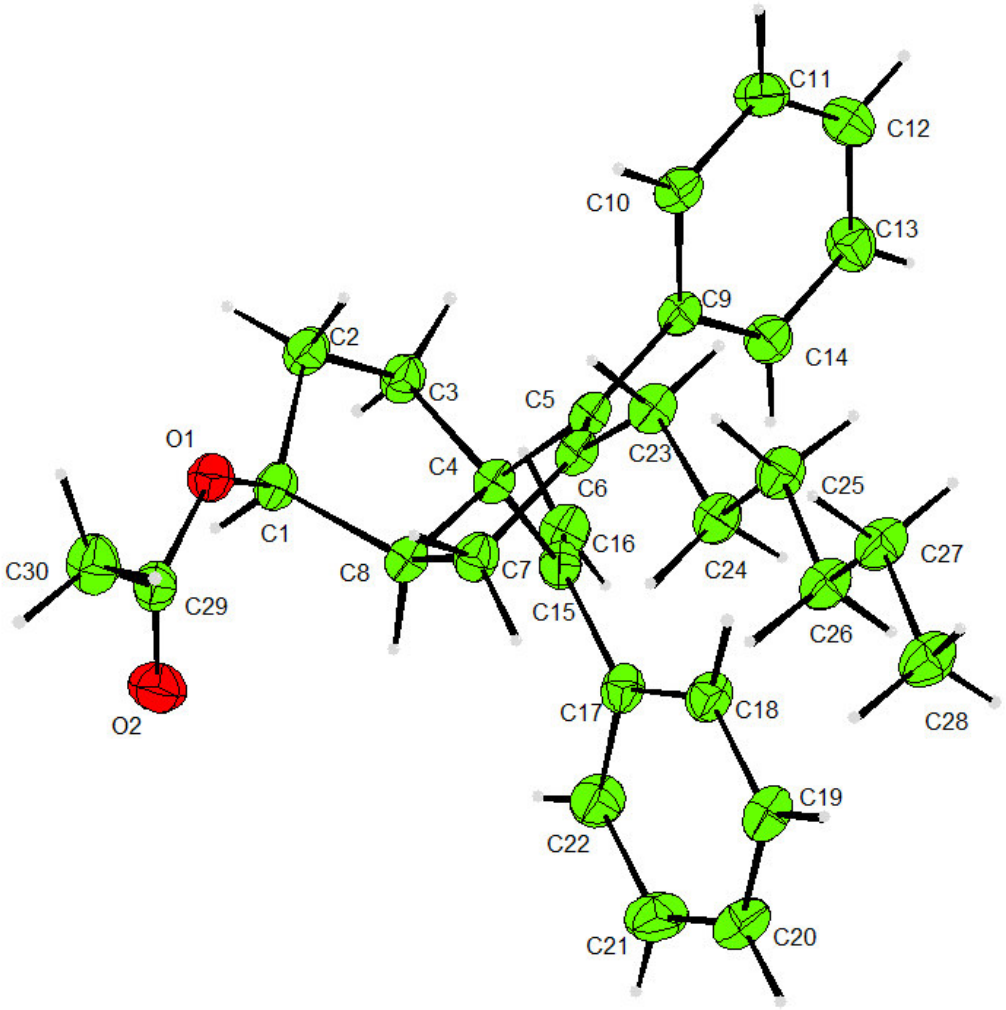
Symmetry transformations used to generate equivalent atoms:

Table 5. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\,h\,k\,a^*\,b^*\,U^{12}]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C1	24(1)	21(1)	26(1)	9(1)	10(1)	9(1)
C2	26(1)	20(1)	32(1)	7(1)	11(1)	4(1)
C3	24(1)	21(1)	29(1)	5(1)	10(1)	3(1)
C4	23(1)	18(1)	23(1)	6(1)	8(1)	4(1)
C5	24(1)	16(1)	24(1)	7(1)	9(1)	5(1)
C6	24(1)	17(1)	25(1)	7(1)	8(1)	5(1)
C7	22(1)	22(1)	27(1)	6(1)	8(1)	4(1)
C8	24(1)	19(1)	24(1)	7(1)	8(1)	5(1)
C9	23(1)	19(1)	23(1)	6(1)	7(1)	3(1)
C10	26(1)	22(1)	29(1)	11(1)	10(1)	7(1)
C11	34(1)	29(1)	32(1)	15(1)	15(1)	5(1)
C12	30(1)	35(1)	34(1)	13(1)	18(1)	7(1)
C13	29(1)	33(1)	30(1)	12(1)	12(1)	12(1)
C14	27(1)	26(1)	27(1)	11(1)	11(1)	9(1)
C15	26(1)	22(1)	21(1)	6(1)	9(1)	7(1)
C16	27(1)	28(1)	31(1)	9(1)	7(1)	7(1)
C17	26(1)	23(1)	26(1)	9(1)	10(1)	10(1)
C18	31(1)	23(1)	27(1)	9(1)	10(1)	8(1)
C19	33(1)	22(1)	32(1)	7(1)	8(1)	6(1)
C20	38(1)	25(1)	43(1)	16(1)	14(1)	7(1)
C21	46(1)	37(1)	37(1)	23(1)	15(1)	11(1)
C22	37(1)	31(1)	26(1)	12(1)	8(1)	8(1)
C23	24(1)	24(1)	26(1)	8(1)	6(1)	5(1)
C24	25(1)	23(1)	28(1)	7(1)	7(1)	5(1)
C25	29(1)	26(1)	27(1)	7(1)	7(1)	5(1)
C26	29(1)	24(1)	29(1)	9(1)	6(1)	4(1)
C27	32(1)	24(1)	30(1)	9(1)	6(1)	3(1)
C28	35(1)	26(1)	33(1)	9(1)	5(1)	1(1)
C29	28(1)	23(1)	26(1)	5(1)	11(1)	6(1)
C30	28(1)	36(1)	39(1)	10(1)	13(1)	10(1)
O1	25(1)	25(1)	30(1)	12(1)	12(1)	10(1)
O2	40(1)	40(1)	39(1)	21(1)	21(1)	14(1)

Table 6. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1	4516	4321	716	28	1
H2A	4263	4048	2722	32	1
H2B	3353	3057	1440	32	1
H3A	1928	4680	2143	31	1
H3B	1965	4566	928	31	1
H7A	7173	6246	3362	30	1
H7B	6907	7635	3270	30	1
H8	5164	6515	1504	27	1
H10	3788	5512	4959	31	1
H11	2060	5588	5841	36	1
H12	227	6843	5521	38	1
H13	154	8031	4325	36	1
H14	1885	7975	3456	31	1
H16A	722	7422	839	36	1
H16B	624	6014	1032	36	1
H18	4813	9033	3604	33	1
H19	6119	11045	3795	37	1
H20	5683	11685	2222	42	1
H21	3976	10276	446	45	1
H22	2683	8262	244	38	1
H23A	7132	6714	5482	31	1
H23B	5922	7534	5722	31	1
H24A	8413	8561	5259	32	1
H24B	7272	9372	5638	32	1
H25A	9266	8261	7081	34	1
H25B	8282	9265	7445	34	1
H26A	10747	9934	6814	35	1
H26B	9809	10929	7260	35	1
H27A	11810	9737	8612	37	1
H27B	10840	10700	9064	37	1
H28A	13170	11451	8336	52	1
H28B	13373	11837	9630	52	1
H28C	12211	12412	8805	52	1
H30A	9273	3729	1468	52	1
H30B	8503	3164	2176	52	1
H30C	9510	4617	2715	52	1


C11
C12
C10
C13
C9
C14
C2
C3
C5
O1
C4
C23
C6
C25
C1
C16
C27
C30
C8
C7
C24
C29
C15
C26
O2
C17
C18
C28
C19
C22
C21
C20