UNIVERSITY OF SOUTHAMPTON

SYNTHESIS OF POTENTIALLY NEUROACTIVE HETEROCYCLES USING EARLY TRANSITION METAL CHEMISTRY

by Donald Peter Scott Macfarlane

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

FACULTY OF SCIENCE

DEPARTMENT OF CHEMISTRY

This thesis was submitted for examination in August 2001

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

FACULTY OF SCIENCE

CHEMISTRY

Doctor of Philosophy

SYNTHESIS OF POTENTIALLY NEUROACTIVE HETEROCYCLES USING EARLY TRANSITION METAL CHEMISTRY

by Donald Peter Scott Macfarlane

The work presented in this thesis illustrates the synthetic utility of organozirconium chemistry through the synthesis of three distinct pharmacophores. A number of 3,4- and 4,5-disubstituted azepines have been synthesised from 3- or 4-aza-1,8-dienes, enynes and diynes through zirconium induced cocyclisation reactions. The exocyclic dienes formed from the 1,8-diynes could be elaborated by Diels-Alder reactions, including examples where subsequent aromatisation afforded benzazepines. The zirconacyclopentadienes derived from 3- or 4-aza-1,8-diynes could also be elaborated directly to benzo[c]- or benzo[d]-azepines by copper induced addition to an alkyne. Some of the azepines and benzazepines have undergone biological testing at Eli Lilly (UK).

A novel synthesis of the 4-phenylpiperidine pharmacophore by zirconocene induced co-cyclisation of 3-arylbutenylallylamines have been developed. The aryl ring could be incorporated by a modified Suzuki coupling of an aryl boronate with 3-bromobutenylamines. The synthesis of a variety of other aryl substituted piperidines was attempted, but the yields were general poor. An exception was co-cyclisation of diynes to give piperidines incorporating exocyclic dienes.

The cyclisation of 3-phenyl, 3-benzyl, and 3-benzylidiene pyrrolidines by zirconium induced co-cyclisation of 4-aza-1,6-dienes –enynes and –diynes was generally high yielding.

ACKNOWLEDGEMENTS

Firstly I would like to thank Prof. Richard Whitby for allowing me to work on this project and for his valuable help, interest, enthusiasm and friendship over the past three years. I would also like to extend my thanks to Dr. David Harrowven for all the help he has given me during my time in Southampton. I am also indebted to Joan Street, John Langley and Julie Herniman for running such effective analytical services. Additional thanks must also go to Eli Lilly (UK) for generous support particularly Dr. David Tupper.

A big thank you to past, present and surrogate members of the Whitby group for all your help and friendship throughout my PhD. Speecial thanks must go to **Sally Dixon**, Rupert Hunter, Dr. A. Kasatkin, Gustaf Saluste, Steven Harrison, David Dossett, Matt Lucas, David Norton and Manoj Pabari for making it possible for me to submit my thesis on schedule. I owe a debt of gratitude to ThuHai Macfarlane for her patience over the past three years and for getting me through. Sonia, Angela, Matt and Salvo Camiolo thanks for being great housemates. Thanks to all members of the chemistry department for making my life enjoyable.

Finally, I would like to thank my family, in particular Mum and Dad. Your love and unquestioning support has not, and will not, ever be taken for granted so for all the years of encouragement, patience and consideration I would like to dedicate this thesis to you.

For Mum and Dad

ABBREVIATIONS

Techniques

APCI	atmospheric pressure chemical ionisation
COSY	correlation spectroscopy
CI-MS	chemical ionisation mass spectroscopy
DEPT	distortionless enhancement by polarisation transfer
EI-MS	electron impact mass spectroscopy
GC	gas chromatography
HMQC	heteronuclear multiple quantum coherance spectroscopy
HRMS	high resolution mass spectroscopy
IR	infrared spectroscopy
MS	mass spectroscopy
NMR	nuclear magnetic resonance
NOe	nuclear overhauser effect
t.l.c	thin layer chromatography
UV	ultraviolet

REAGENTS AND SOLVENTS

3BP	3-benzylpyrrolidine
3BzP	3-benzylidinepyrrolidine
3PP	3-phenylpyrroldine
4PP	4-phenylpiperidine
Ar	aryl
^{n}BuLi	*n*-butyllithium
^{t}BuLi	*tert*-butyllithium
Bn	benzyl
C_6D_6	deuterated benzene

Cp	cyclopentadienyl
DMAD	Dimethyl acetylenedicarboxylate
DMF	dimethylformamide
Et	ethyl
HMPA	hexamethylphosphoramide
Me	methyl
$MgSO_4$	magnesium sulfate
Ms	mesyl (methanesulfonyl)
Np	napthyl
NBS	*N*-bromosuccinimide
PPTS	pyridinium *p*-toluenesulfonate
TBAF	tetrabutylammonium fluoride
THF	tetrahydrofuran
THP	tetrahydropyran
$Ti(^iOPr)_4$	titanium tetraisopropoxide
TMS	trimethylsilyl
Ts	tosyl (*p*-toluenesulfonyl)

MISCELLANEOUS

b.p.	boiling point
ca.	approximately
conc.	concentrated
eq.	equivalents
h	hour(s)
min	minute(s)
mp	melting point
r.t.p	room temperature and pressure
sat.	saturated

Chapter 1: Pharmacology behind the project Page

Chapter 2: Background to organozirconium chemistry

Chapter 6: Experimental section

1.1 Introduction to neuropharmacology

There are a large number of molecules which are known to be biologically active in a number of neuropharmacological disease states[1]. Many of these compounds are nitrogen heterocycles with a phenyl group β or γ to the nitrogen, a feature necessary for activity. Noting this important feature we have set out to utilise organozirconium mediated chemistry in the synthesis of a number of novel compounds based around the active pharmacophore found in three main classes of compound. These are benzazepines, morphine analgesics and 3-phenylpyrrolidines. In order to demonstrate the importance of the three areas a short background to each will be presented in the following section.

1.2 Background to Parkinson's disease

Parkinson's disease is a progressive neurodegenerative disorder of the basal ganglia[2][3] which is characterised by tremor, muscular rigidity, difficulty in initiating motor activity and loss of postural reflexes. At present 1 % of the western world population over 55 suffer from this debilitating disease[2]. Parkinson's disease can be defined in purely biochemical terms as primarily a dopamine deficiency state resulting from degeneration or injury to dopaminergic neurons[4].

The main strategy used in the treatment of Parkinson's disease has been to enhance existing dopamine function in the brain using pharmacological agents acting as agonists at the dopamine receptor and more recently by neural grafting of dopamine containing cells. Pharmacological strategies include i) direct substrate supplementation e.g. administering L-dihydroxyphenylalanine (L-DOPA), ii) indirect dopamine agonist, iii) inhibition of metabolic inhibition and iv) uptake inhibitors. Direct agonists are used where patients are unresponsive to L-DOPA e.g. bromocriptine. There are two broad classes of dopamine receptor. These are the D_1 and D_2 receptors subtypes and recent behavioural and elecrophysiological studies have shown D_1 activation is necessary for the effects of D_2 receptor stimulation to be expressed maximally[5]. The interaction between subtypes will be key in future treatment of Parkinson's disease. Thus it seems probable

that knowledge of the optimal ratio of relative drug activity at D_1 and D_2 receptors, to elicit effective stimulation of dopamine mediated function, will lead to the development of drugs[2].

1.3 Background to Schizophrenia

As in the case of Parkinson's disease the etiology of Schizophrenia has been linked to an inappropriate level of dopamine, and it is widely believed that Schizophrenia is related to a relative excess of dopaminergic activity. In contrast to Parkinson's disease, Schizophrenia is commonly recognised in young adults, particularly when confronted with severely stressful life events. Schizophrenia is a chronic disorganisation of mental function that effects

i) thinking – paranoid thoughts, inability to maintain a focused thought, easily distracted, loose associations between thoughts, inappropriate responses to situations (so called blunted effect).

ii) movement – states ranging from hyperactivity and excitement to persistent inactivity, to the point of maintaining posture for long periods of time.

It is known that one subtype of dopamine receptor (D_2) shows increased expression in Schizophrenia patients. Recently the D_4 receptor subtype has been shown to play a prominent role in the treatment of Schizophrenia because it binds the antipsychotic drug Clozapine with a higher affinity than D_2. It appears that future treatments for Schizophrenia will require a greater understanding of the complex interaction between receptor subtypes. There are 3 specific drug classes used to treat Schizophrenia, antipsychotic drugs (major tranquillisers), anxiolytics (minor tranquillisers) and antidepressants[2],[6].

1.4 Introduction to dopamine and its role in the body

Dopamine is a prominent monoamine neurotransmitter known to act in the brain. In 1960 Sibley and Mansma[7] observed regional differences in distribution between

dopamine and noradrenaline in the CNS. This key observation led to the postulation that dopamine acted as a neurotransmitter, independent of its function as a precursor for norepinephrine biosynthesis.

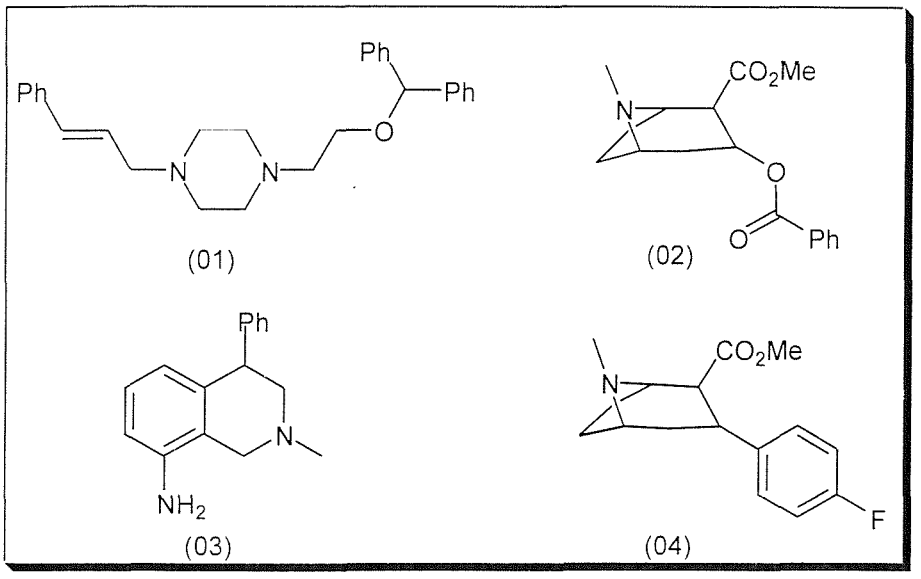
The biosynthesis of dopamine takes place within the dopaminergic neuron. The rate-limiting step in dopamine biosynthesis lies in the conversion of L-tyrosine to L-DOPA, catalysed by the enzyme tyrosine hydroxylase. The activity of the enzyme is subject to a number of regulatory influences including cofactors, autoreceptor stimulation and feedback from associated neurological pathways. Once synthesised, L-DOPA is subsequently converted to dopamine by an aromatic amino acid decarboxylase, which turns over so rapidly that the concentration of L-DOPA in the brain is negligible under normal physiological conditions. Numerous observations have shown that abnormal concentration of L-DOPA in the brain results in a number of disease states including Parkinson's disease and Schizophrenia.

1.5 Dopamine uptake and the dopamine transporter

Many pharmacological agents are known to modify dopaminergic activity, however few are selective as most interact with other catecholamine systems (noradrenaline and adrenaline). Dopamine uptake is carried out by a specific membrane carrier which can transport in either direction. Such regulation is vital in maintaining transmitter homeostasis and in terminating transmitter action. Chemical agents such as amphetamine, cocaine, benzotropine and nomifensine interact with the presynaptic reuptake transporter on the nerve terminal from which dopamine is released. This increases synaptic concentration of dopamine such that there is potential for treatment of Parkinson's disease. One important advance in investigation of these molecules was the development of selective dopamine uptake inhibitors; a class of compounds known as the GBR series[8].

Following the development of the GBR series, structural equivalents (01-04) were developed which were highly selective, potent ligands for the dopamine uptake

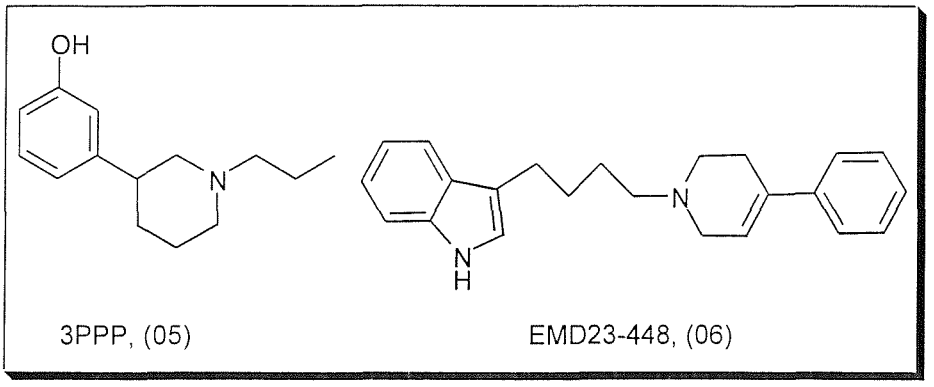
transporter. This lead to the development of a number of subtype selective agonists and antagonists e.g. benzazepine pharmaceuticals[9],[10].



Scheme 1.1 Dopamine active compounds.

1.6 Drug interactions at dopamine D_1 and D_2 receptors.

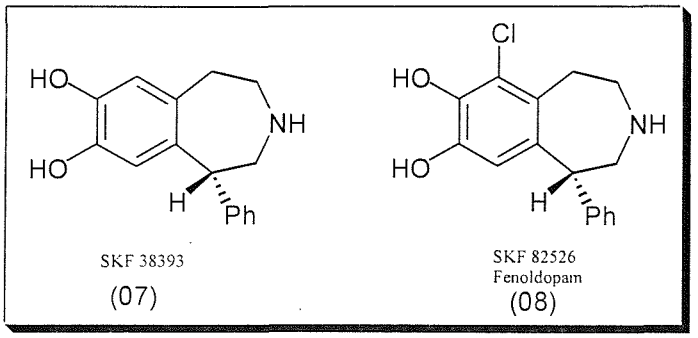
Dopamine receptors can be classified as either the D_1-type or D_2-type. Both the D_1 and D_2 receptors have received a large amount of interest in the 1980's. The distinction is based upon the fact that (D_1) is a G-coupled protein receptor whereas (D_2) acts through a different pathway. Biochemically the D_2 receptor is also characterised by a picomolar affinity for antagonists such as 3PPP (05) and EMD23-448 (06) whereas the D_1 is characterised by a millimolar affinity[11].



Scheme 1.2 Selective dopamine presynaptic receptor (D_2) agonists.

Recent research has shown that activation of the D_1 receptor is required for full postsynaptic expression of D_2 effects, illustrating that D_1 and D_2 receptors act co-operatively reinforcing the action of each other. The D_2 receptor is a presynaptic autoreceptor which inhibits dopamine release when an agonist binds, thus the two pathways are linked.

The concentration of dopamine receptors have been observed to change in disease states. In Schizophrenia the density of the dopamine transporter and the D_1 receptor remains normal however the D_2 receptor density is elevated in the brain. In Parkinson's disease less dopamine in the brain results in a reduction in the concentration of D_1 and D_2 receptors. Two benzazepine compounds have been found to be particularly important pharmaceuticals, SKF 38393 (07) and SKF 82526 (08)[2],[12].

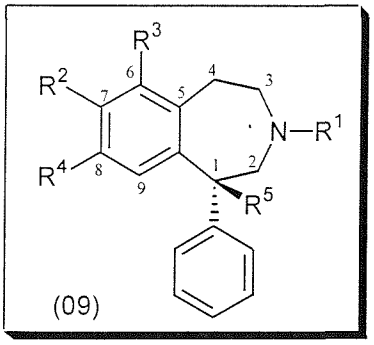


Scheme 1.3 Benzazepine pharmaceuticals.

Fenoldopam is a selective D_1 agonist, which due to its hydrophilicity is unable to cross the blood brain barrier. Consequently Fenoldopam (08) is metabolised in the periphery, with only a minimal amount of drug reaching the target D1 receptor. The resultant metabolites in the periphery possess vasodilation properties and therefore cause hypotension as an acute side effect. SAR data has provided information concerning the features necessary for increased capacity to cross the blood brain barrier[13]. The SAR described in section 1.7 was carried out in an attempt to develop second generation drugs with fewer side effects[2], [14].

1.7 Benzazepine pharmaceuticals

One pharmacologically important class of dopamine agonists are the benzazepines. Benzazepine derivatives have received particular attention in the treatment of Parkinson's i.e. benzazepines as D_1 selective agonists.



Scheme 1.4 General benzazepine structure.

Benzazepine Name (09)	R^1	R^2	R^3	R^4	R^5
SCH 23390	CH_3	Cl	H	H	H
SCH 23982	CH_3	I	H	H	H
SCH 38548	CH_3	Cl	H	I	NH_2
SKF 38393	H	OH	H	H	H
SKF 82526	H	OH	Cl	H	OH
FISCH	CH_3	Cl	H	I	H
TISCH	CH_3	Cl	H	H	I

A large number of benzazepines (9) have been synthesised and subsequent structure activity relationship data has led to a number of key deductions of necessary structural features for activity. Adapted from Niznik[14]:

1. Dopaminergic activity is not enhanced by β-phenyl substitution.
2. Substitution around C7 and C8 is essential for activity as a D_1 agonist.
3. Introduction of a halogen at C7 or C8 increase activity, further substitution at C6 and C9 abolishes activity.

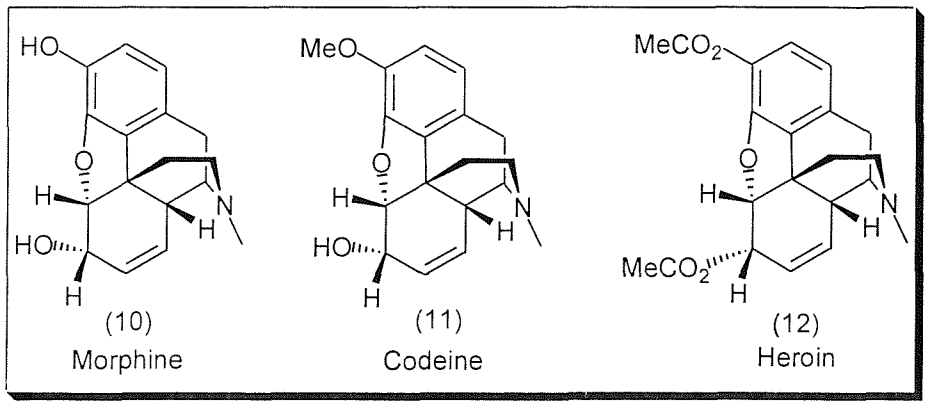
4. Substitution on the nitrogen atom with allyl or methyl increases activity.
5. Introduction of small groups to the fused-benzene ring (opposite to the halogen) decreases efficacy of the agonist whereas introduction of larger groups results in the production of a D_1 antagonist.
6. Substitution of the β-phenyl group produces variable effects.

1.8 Conclusion

Benzazepines and benzazepine derivatives are important pharmaceutical tools in the search to improve treatments for Parkinson's disease. Organozirconium chemistry is ideally suited to the synthesis of highly elaborated novel skeletons from simple precursors and since these compounds have never been investigated they have the potential to be biologically active.

1.9 Background to morphine alkaloids

Morphine (10) [from the Greek Morpheus, god of dreams], is an alkaloid isolated from the opium poppy which has found widespread use as an analgesic. The medicinal use of morphine has been known since the seventeenth century when crude extracts from the gum and seeds of the opium poppy (*Papaver somniferum*) were utilised in the treatment of pain. A number of close relatives are known to occur naturally, such as codeine (11). Heroin (12) is the diacyl derivative[15] of morphine.



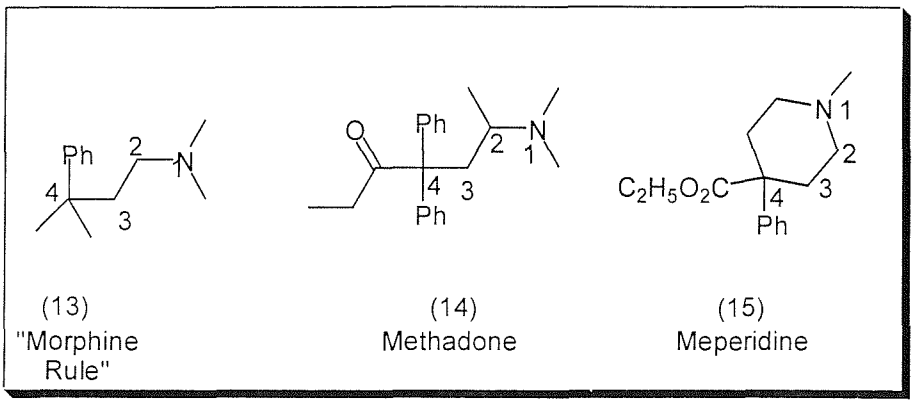
Scheme 1.5 Morphine analogues.

1.10 Morphine analgesics and the opioid receptor

The opioid receptors (μ, δ_1, δ_2 and κ) and their subtypes are involved in control of various aspects of the perception of pain, pleasure and mood. The development of selective opioid receptor ligands offers the potential for treatment of a number of disease states[16]. It is believed that morphine and its analogues bind to the opiate receptors in the brain. Once bound these compounds are able alleviate pain, by interfering with the brains perception of pain. Morphine analgesics probably accomplish pain relief by stopping signal transduction at the molecular receptor level, although at present their exact mode of action is unconfirmed. It has been postulated that they are able to mimic the shape and properties of small peptide called enkephalins (these are the body's own painkillers) [1],[3].

1.11 Morphine to analgesics

Research into the opioid receptor has demonstrated that biological activity of morphine is not wholly dependent upon the complex tetracyclic skeleton found in the parent compound. As a simple guide the "morphine rule" states that biological activity requires a) an aromatic ring attached to b) a quaternary centre and c) a β tertiary amine (13). Two examples of this are Methadone (14) and Meperidine (15) both of which were shown to act as analgesics.



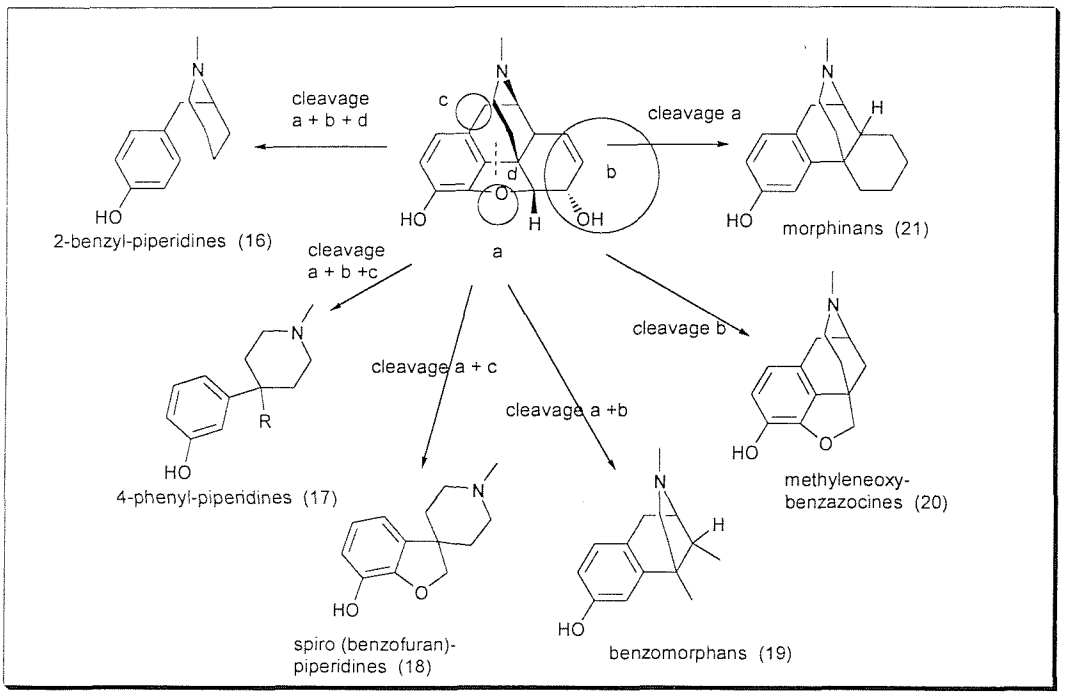
(13) "Morphine Rule"

(14) Methadone

(15) Meperidine

Scheme 1.6 Morphine rule and related compounds.

Although morphine and its analogues are extremely useful pharmaceutical reagents they also have abuse potential due to their addictive properties, as characterised by heroin. As a result a large amount of research has been devoted to the development of analogues which retain the desired analgesic activity but do not exhibit addiction potential. In the 1940's a Hoffman/LaRoche group recognised structures such as 4-phenylpiperidines and 2-benzylpiperidines as substructures of morphine[4]. All clinically significant analgesics used in the treatment of severe pain derive from the morphine disconnection model. These classes of compounds have received renewed interest in the past twenty years thanks to the discovery of the opiate receptor[8].



Scheme 1.7 Disconnection of morphine into various substructures.

One particularly important class of pharmaceuticals are the 4-phenylpiperidines (17) which are known to act at the opioid receptor. The skeleton is derived from morphine by deletion of three rings.

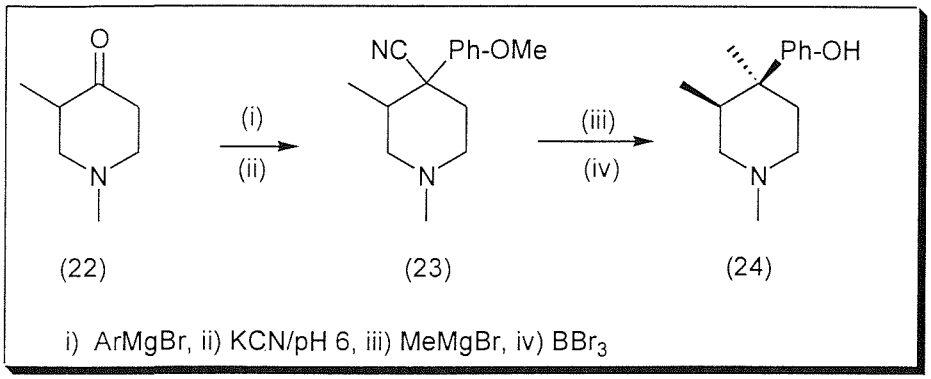
1.12 The 4-phenylpiperidine pharmacophore

The development of potent highly selective drugs has been the target of medicinal chemists over the past thirty years. In 1978 Zimmerman[17] discovered a structurally unique series of true opioid antagonists based upon *N*-substituted analogues of (+/-)-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine. These compounds proved to be novel opioid antagonists because their intrinsic antagonist activity was not mediated solely by the *N*-substituent but rather by the 3,4-dimethyl substituents[18].

In a recent binding study 4-phenylpiperidines were examined [19] and it was found that 4PP's can bind to the μ-opioid receptor in either the phenyl-axial or the phenyl-equatorial conformer, depending on the nature of the second substituent in the C4 position. Where R is an alkyl group, phenyl-axial conformers are favoured whereas when an ester is used phenyl-equatorial conformers are favoured. Loew[20] have calculated conformational energy profiles for a series of 4-phenylpiperidines and shown that the calculated energy profiles match these observations. In another paper Zimmerman[17] has synthesised a number of opioid agonists and antagonists displaying activity at both the μ and κ receptors. Several highly potent antagonists were discovered however no agonists were found. Interestingly when two derivatives were resolved and the activities of the enantiomers compared, only a limited stereochemical effect was observed. The existence of a lipophilic binding site distal to the nitrogen for both μ and κ was postulated. *N*-Methyl-4-phenylpiperidine has been shown to exhibit antagonism at the μ and κ receptors however they also show significant affinity for the δ receptor. Thus modification of the group attached to nitrogen may allow better selectivity between receptor subtypes. However when testing was carried out only limited selectivities were achieved.

1.13 Traditional syntheses of 4-phenylpiperidines

At present there is great interest in producing a large number of 4-phenylpiperidines quickly and in an efficient manner.



Scheme 1.8 Traditional synthesis of 4PP's.

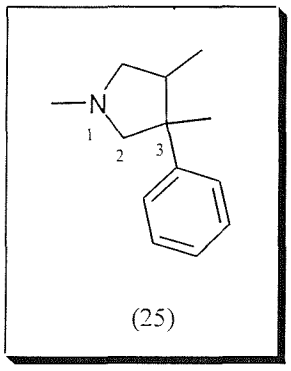
Initially scheme 1.8 appears to be an attractive synthesis however there are a number of problems:

1) The starting material (22) is not trivial although it may be synthesised from 4-piperidone monohydrate.
2) The Grignard reaction to introduce the phenyl ring (23) is inappropriate as it must be introduced early and many substitutions of the aromatic are not tolerated e.g. ester functionality.
3) Substitution of the cyano group with a methyl is not facile when the stereochemistry of the product (24) is considered.
4) Stereoselective methylation is not a sensible final step as activity is wholly dependent upon the product being the biologically active *trans* isomer.

Overall the routes to these compounds, including classical syntheses of piperidines are fraught with problems and have a number of key limitations which reduces scope and applicability. We decided to seek an alternative route through to the 4PP's based around an entirely new disconnection (see chapter 4).

1.14 Introduction to the 3-phenylpyrrolidines

The β-phenyl substituted pyrrolidines have received only minimal investigation over the past 30 years[21], somewhat unusual in light of the fact that these compounds bear a quaternary carbon with an aromatic ring β a nitrogen essential for potency as previously discussed. The 3-phenylpyrrolidine (25) bears a strong resemblance to the 4PP's (which are known to be active) and thus should be of interest to the pharmaceutical industry.



(25)

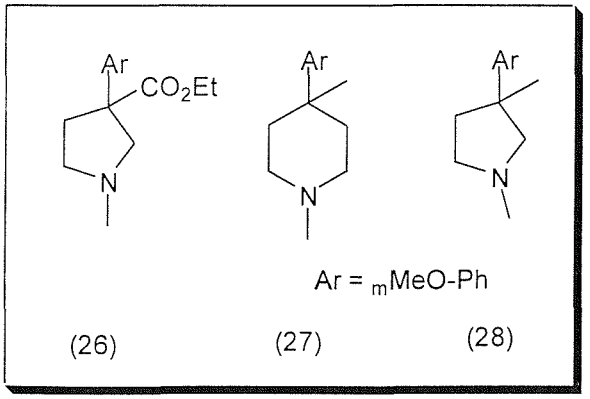
Scheme 1.9 Generalised 3PP.

Following an extensive search of the literature it was discovered that analysis of 3-phenylpyrrolidine derivatives has not been reported since 1965[21] when they were investigated for their analgesic properties. According to the literature these compounds have not been subjected to analysis using high throughput screening for potential biological activity. The combination of a modern organometallic synthesis (organozirconium based) and modern techniques of analysis may make these compounds of pharmaceutical interest once more.

1.15 Background and synthesis of 3-phenylpyrrolidines

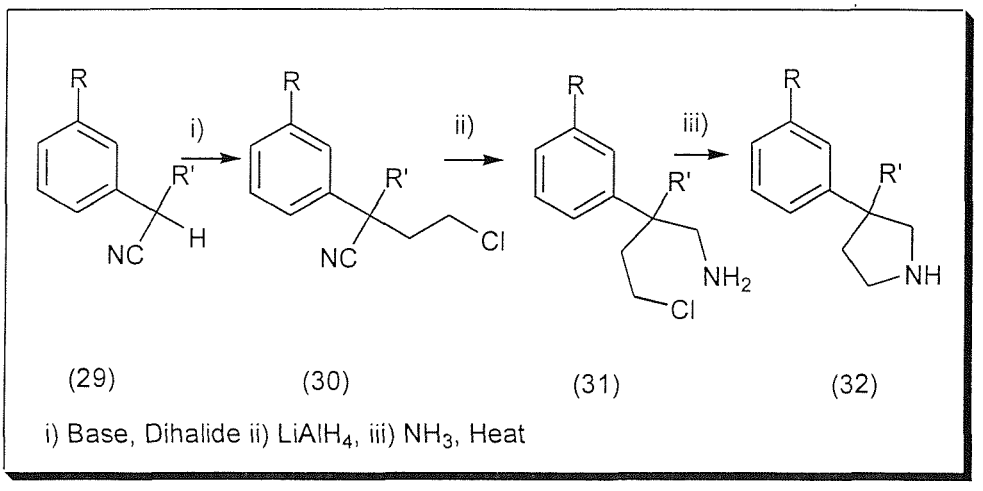
During the 1960's a large amount of work concerning pyrrolidine analgesics was carried out by Parke Davis and Company[21]. These compounds did not possess the desired level of analgesic activity. Initial biological activity studies indicated that these compounds possessed a level of analgesic activity equivalent to meperidine (27), thus a large number of compounds were synthesised and screened. The results of screening indicated that

subtle changes in the nature and number of substituents (scheme 1.10) could convert an inactive compound (26) to one possessing clear analgesic activity (28). Note the similarity between (28) and Zimmerman's 4-phenylpiperidine molecule (27) with only an extra carbon difference.



Scheme 1.10 3PP's and related molecules.

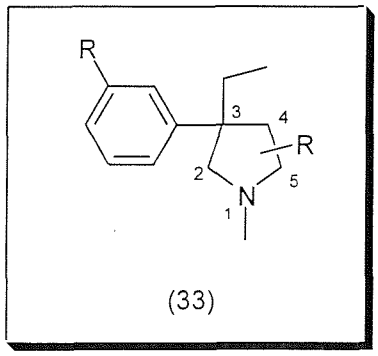
Most compounds in the series were synthesised using the methodology indicated in scheme 1.11. It involved alkylation of an appropriate benzyl cyanide (29) to afford (30) which, following reduction with lithium aluminium hydride and subsequent cyclisation, afforded the desired pyrrolidine (32).



Scheme 1.11 Cavalla's synthesis of 3PP's.

1.16 The 3-phenylpyrrolidines as pharmaceuticals

Cavalla investigated the pharmacology of 3PP's (33) extensively during the 1950's and 1960's, however these compounds failed to meet their selection criteria as analgesics. At this time 3PP's were not tested for a wide range of biological activity as receptor assays were not available. Modern biological assays may show that these novel 3PP's possess desirable pharmaceutical properties.



(33)

Scheme 1.12 Cavalla's lead compound.

Structure activity relationship analysis was carried out using antinociceptive rats (analgesic) and the following observations recorded:

Mono substitution of the β-phenyl generally increases analgesic activity with the *meta* position being the best.

Alkylation at C3 is necessary for activity; propyl>butyl>ethyl>>methyl.

Alkylation at C2 has intermediate effects.

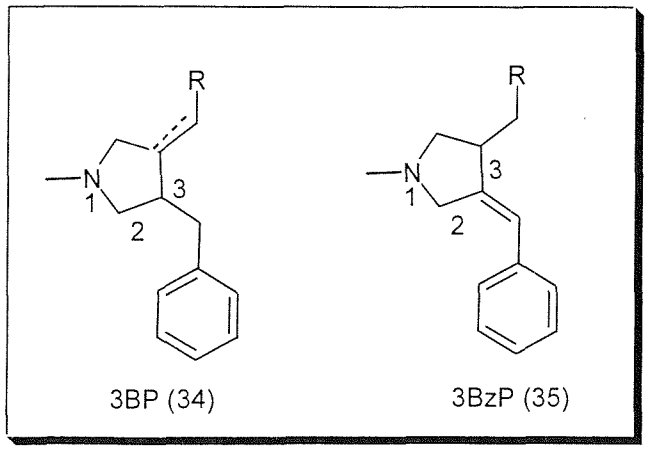
Alkylation at C4 destroyed analgesic activity (effect of alternative groups is unknown).

Methylation at *N*1 proved optimal compared to other aromatics/aliphatics.

1.17 The 3-benzylpyrrolidines and 3-benzylidinepyrrolidines.

Thus far we have confined ourselves to discussing the 3-phenylpiperidines but another class (regioisomer) of compound is also available using organozirconium chemistry; these are the 3-benzylpyrrolidines [3BP's] (34). They fit the morphine rule, although the

biological activity of 3BP's is unreported in the literature. Furthermore organozirconium chemistry allows the synthesis of 3-benzylidinepyrrolidines [3BzP's] (35) which are another interesting class of compounds which have not been investigated for their potential biological activity.



Scheme 1.13 Basic pharmacophores.

CHAPTER 2

BACKGROUND TO ORGANOZIRCONIUM CHEMISTRY

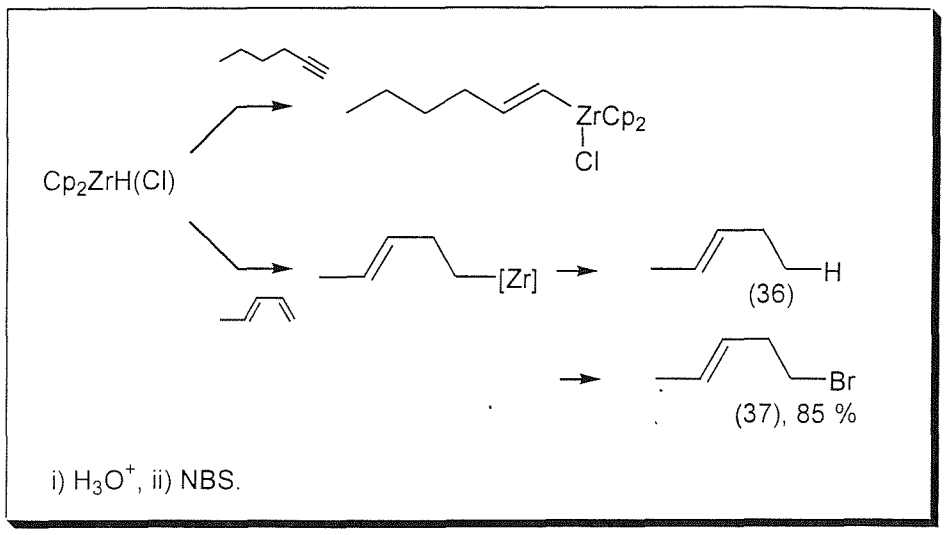
2.1 Background to zirconium chemistry

Over the past twenty years there has been a rapidly increasing level of interest in the chemistry of the early transition metals. A large body of research has focused on zirconium and titanium organometallics[22]. Many researchers have utilised these metals in their search for solutions to important synthetic problems. Organometallic reagents generally find use as reagents in organic synthesis or act as catalysts in chemical reactions. Frequently these organometallic methods offer considerable advantages over classical synthetic routes such as better functional group compatibility or transformations not accessible by conventional routes. In organic synthesis, zirconium and titanium reagents are frequently used as complexes containing two cyclopentadienyl (Cp) ligands. *bis*-Zirconocene dichloride ($ZrCp_2Cl_2$) are available at relatively low cost. Both metals form stable complexes in which the oxidation state of the metal is +2 or +4, (Ti is also stable in a +3 state).

Prior to 1970, formation of carbon-carbon bonds by organometallic species was achieved utilising reagents containing highly electropositive metals such as lithium, magnesium and zinc and by reaction with polar electrophiles such as carbonyl compounds, epoxides and alkyl halides. In contrast many organotransition metal mediated proceed well with poor electrophiles and with good functional group compatibility.

2.2 Organozirconium reagents in organic chemistry

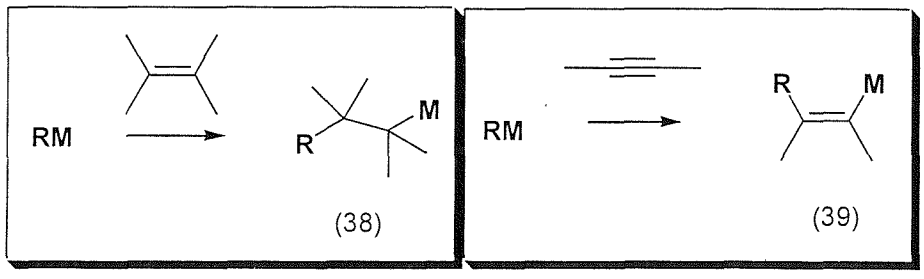
Although zirconium was discovered in 1824 by J.J. Berzelius[23], it was not until the mid 1970's that organozirconium compounds were first used in organic synthesis. Zirconocene hydrochloride, first reported in 1969, was shown to add to alkenes and alkynes to afford the corresponding zirconocene(IV) chloro-alkanes and alkenes(36 and 37)[24,25]. The stereochemistry pure (E)-alkenyl zirconocene chloride is formed and could be alkylated to afford organic compounds in a variety of ways.



Scheme 2.1 - Hydrozirconation.

2.3.1 Metal mediated carbometallation reactions

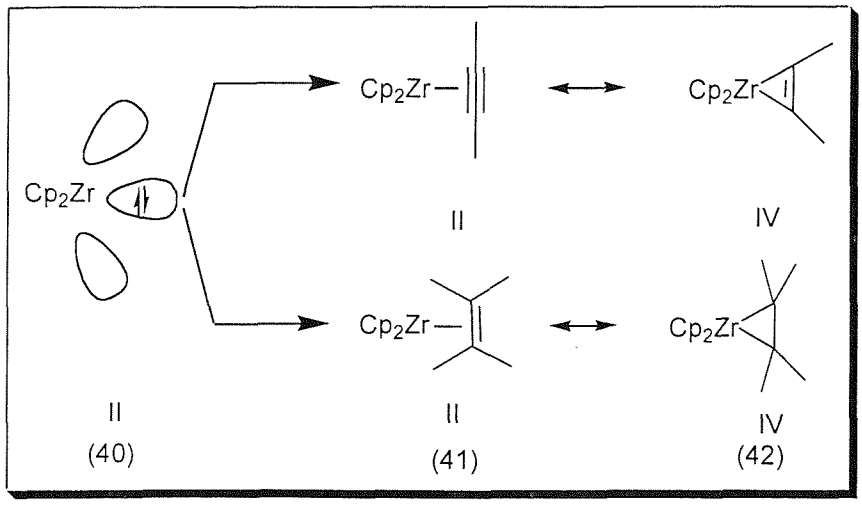
Carbometallation[28] is a powerful carbon-carbon bond forming reaction mediated by organometallics (Ziegler-Natta polymerisation). Zirconocene dichloride in the presence of excess methylalumoxane (MAO) was found to catalyse the polymerisation of ethene and propene[29]. Variation of the cyclopentadienyl ligands has led to catalysis for both isotactic and syndiotactic polymerisations of propylene (38 and 39). A large body of evidence exists for the active species being monomeric cationic zirconocene alkyls e.g. $[ZrCp_2R]^+$ [30]. The role of MAO in this case is to generate and stabilise the d^0 fourteen electron cationic species.



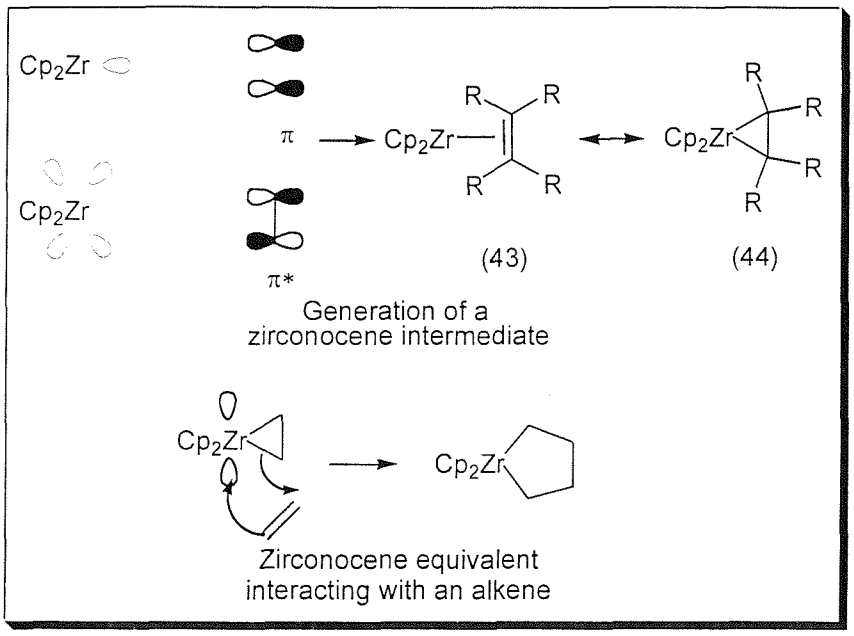
Scheme 2.2 - Illustration of carbometallation.

2.3.2 Zirconocene "Cp_2Zr"

Although uncharacterised, 'Cp_2Zr' would be a 14 electron Zr^{II} species (40) able to interact strongly with unsaturated compounds. Reaction with alkynes and alkenes should produce π-complexes such as (41), which may also be viewed in their resonance hybrid form (42).



Scheme 2.3 – Reaction of zirconocenes with unsaturated molecules.

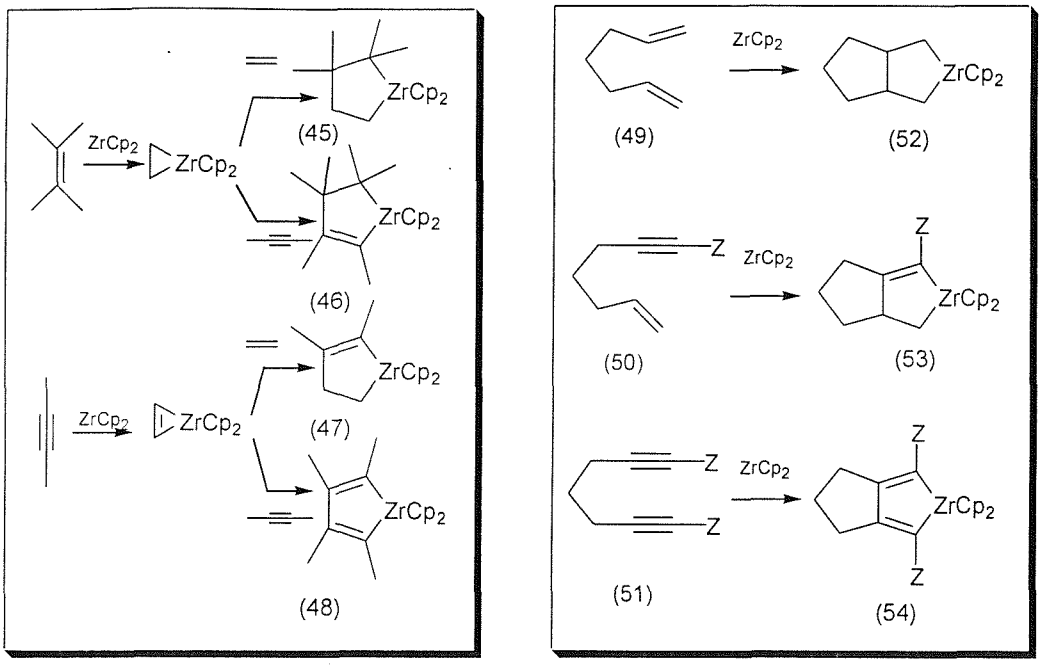


Scheme 2.4 – Interaction between a zirconocene equivalent and unsaturated molecules.

Zirconocene contains both a vacant low energy σ_g orbital and a filled non-bonding π_H orbital. This allows a strong interaction with unsaturated molecules (σ donor, π acceptor) to form an η^2-alkene complex (scheme 2.5). X-ray and NMR studies suggest that the intermediate zirconocyclopropane (44) is a more realistic view than the η^2 alkene complex (43).

2.4 Inter/Intra organozirconium mediated cocyclisation

Cp_2Zr^{II} is extremely reactive and as such, would be extremely difficult to utilise chemically. Therefore, synthetic equivalents have been developed[29], which are described in section 2.4.1. Zirconacycles are formed by reductively coupling unsaturated molecules, a process is mediated formally by zirconocene $Cp_2Zr(II)$ as a $Cp_2Zr(II)$ equivalent[31].



Scheme 2.5 – Zirconocene mediated cyclisations.

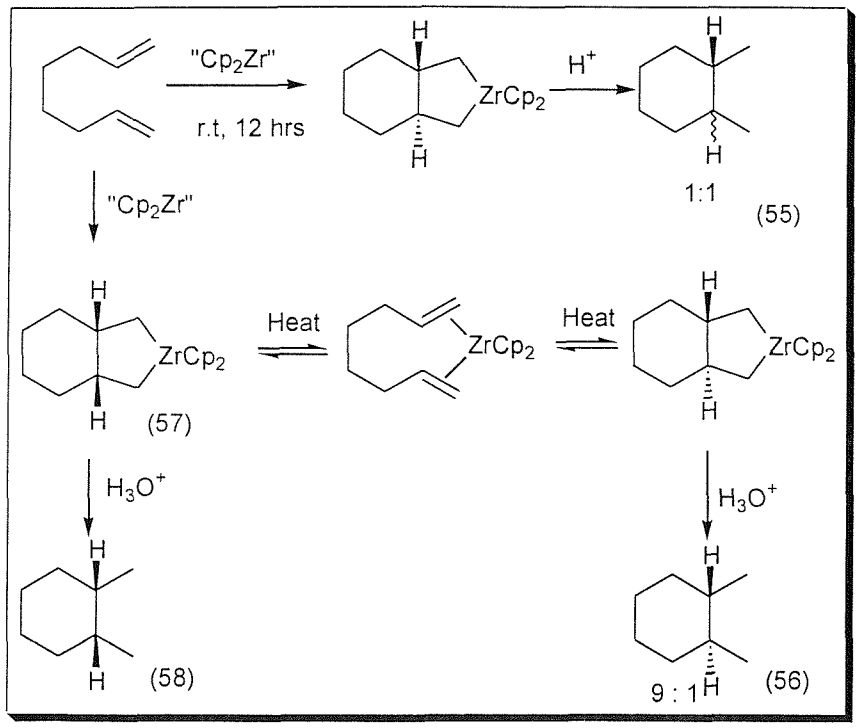
The intermolecular co-cyclisation reaction can be complicated by poor regiocontrol with non-symmetrical alkenes and alkynes (45-48). Such difficulties are overcome by linking the two unsaturated units. Cyclisation of 1,6-dienes affords zirconacycles (such as 52).

Additionally enyne (50) and diyne (51) can be cyclised to afford the corresponding metallobicycles (53 and 54).

2.4.1 Generation of zirconocene equivalents

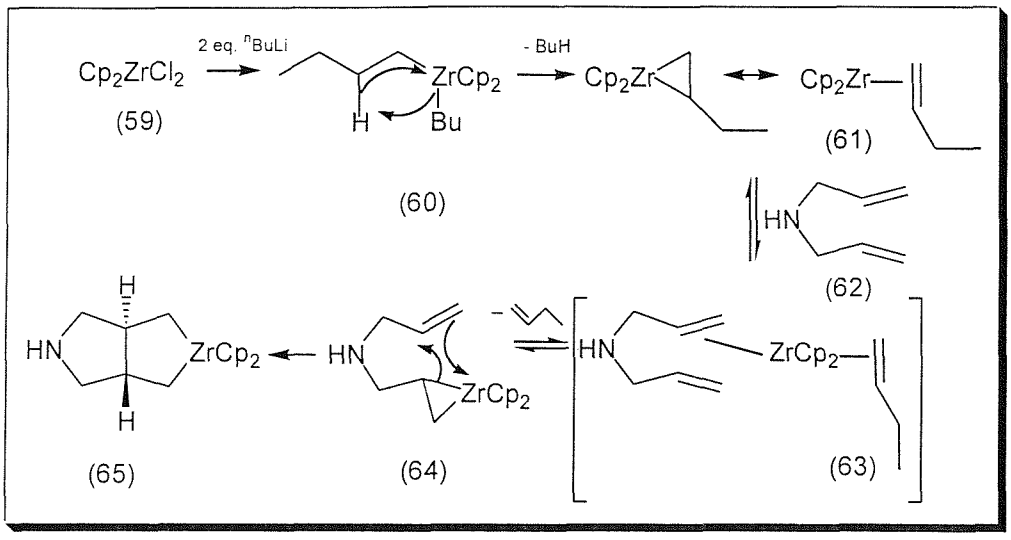
Historically a number of methods have been developed to generate zirconocene intermediates, these include metal reduction of $ZrCp_2Cl_2$[32], metal hydride reduction of Cp_2ZrCl_2[33], thermolysis or photolysis[34]. However, zirconocene is generally utilised in the form of a stabilised zirconocene equivalent generated *in situ* by addition of an organolithium to zirconocene dichloride.

The first intramolecular coupling of a non-conjugated diene by Schwartz[27] utilised a zirconocene *bis*-phosphine complex. This afforded a 1:1 mixture of isomers (55). However a later publication reported selectivities as high as 9:1 (*trans* : *cis*) (56). Nakamura later explained this inconsistency by demonstrating that under normal conditions zirconocene(1-butene) mediated co-cyclisation afforded the *cis* product (58) in 99 % yield ; the kinetic product. Nakamura demonstrated that heating the reaction allows equilibration to favour the thermodynamic product (*trans* isomer, 56).



Scheme 2.6 - Equilibria in zirconacycle formation.

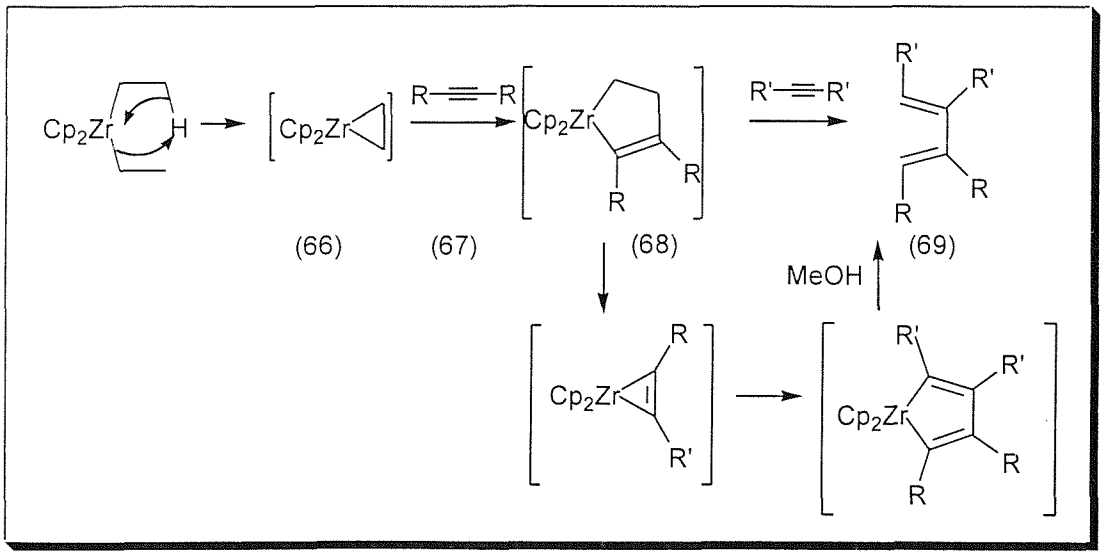
Negishi described bicyclisation of enynes [35], whereby $ZrCp_2Cl_2$ at 0 °C under nitrogen, was reduced using an amalgam generated from $HgCl_2$ and Mg. Although operationally simple, in view of the toxicity of the $HgCl_2$, alternatives were sought. A widely used zirconocene equivalent, termed the 'Negishi reagent' is generated from $ZrCp_2Cl_2$ (59) and 2 equivalents of ^nBuLi, to initially generate dibutyl zirconium (60) which undergoes a concerted cyclometallation to afford zirconocene(1-butene) (61). Initially Negishi proposed that the active species was free '$ZrCp_2$'[36],[37]. However Buchwald postulated that this hypothesis was incorrect[38] and proposed the stabilised zirconocene, $ZrCp_2$-(1-butene), which has subsequently been proved[39]. The loosely bound ligand (1-butene) is easily exchanged with the unsaturated substrate via initial co-ordination to form an 18 electron species (63), followed by elimination of butene. Zirconium has a vacant orbital and a concerted insertion of the second unsaturated moiety occurs (64) to form the zirconabicycle (65). The key to this method lies in its simplicity and reproducibility[40].



Scheme 2.7 – Intramolecular co-cyclisation.

It should be pointed out that Negishi's reagent is extremely versatile but possesses a number of limitations, one being it's incompatibility with substrates containing terminal alkynes[41].

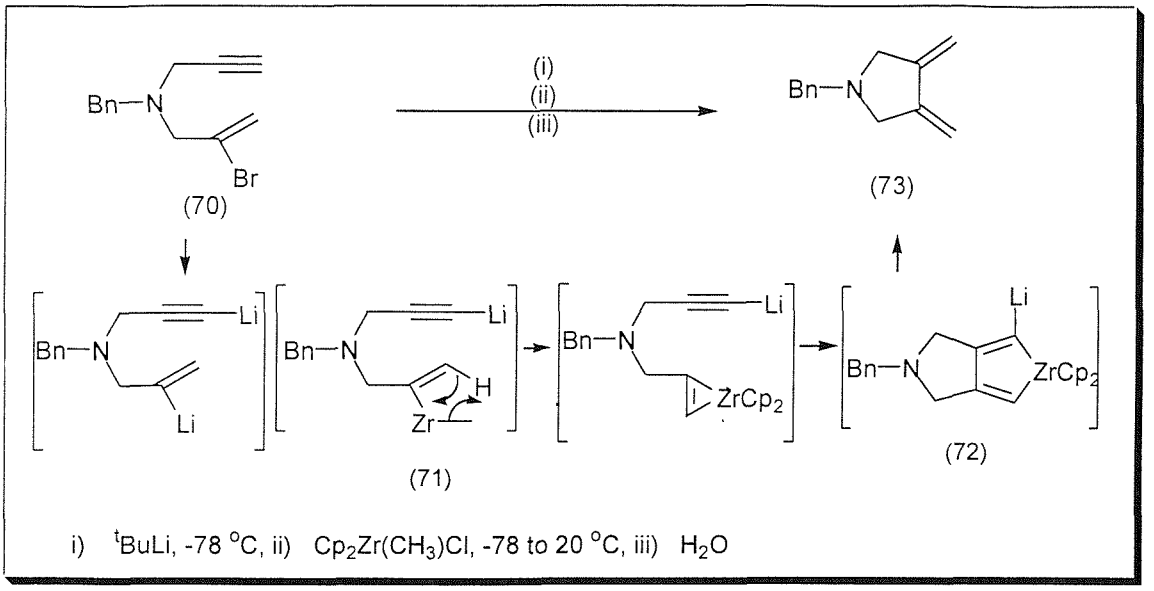
Zirconocene-ethylene can be synthesised by reacting EtLi or EtMgBr with $ZrCp_2Cl_2$ at -78 °C, then warmed to room temperature, forming zirconacyclopropane (66). Addition of an unsaturated molecule such as alkyne (67) results in formation of zirconacycle (68). Addition of another alkyne and heating forms a zirconocyclopentadiene which may be protonated to form diene (69)[42].



Scheme 2.8 – Generation of zirconocene-ethylene.

Zirconocene-ethylene tolerates substrates containing a terminal alkyne. Zirconium-alkenes are appreciably oxophilic and Buchwald found that changing the metal from zirconium to titanium facilitated cyclisation of substrates containing an ester functionality[43],[42].

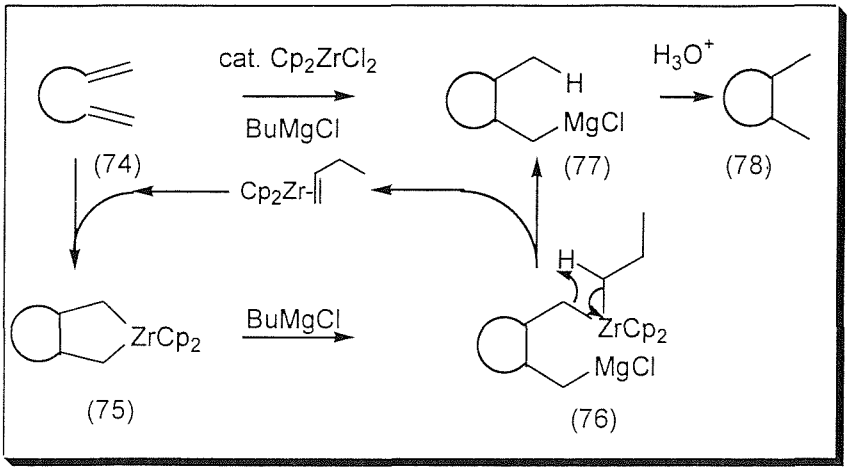
Barluenga[44] has shown (following work by Buchwald) that zirconocne complexes of terminal alkynes may be prepared indirectly from vinyl lithium. Demonstrating that a lithiated alkyne may act as a terminal alkyne equivalent in a trapping reaction (scheme 2.9).



Scheme 2.9 – An alternative cyclisation strategy.

Unsaturated substrates such as 2-bromo-6-alkynes (70) when treated with two equivalents of ^{t}BuLi in Et_2O, generate the corresponding dianion (71). Reaction with bis(cyclopentadienyl)zirconium methyl chloride and heating to eliminate methaneaffords zirconacyclopentadiene (72) which upon hydrolysis generates the exocyclic diene (73) in 71 % yield[44].

It is possible to carry out zirconium promoted reductive coupling on a diene (74) using BuMgX in the presence of a catalytic amount of $ZrCp_2Cl_2$. Cyclisation is accomplished by forming zirconocene (1-butene) *in situ* which then carries out intramolecular cocyclisation to form the zirconabicycle (75). Excess Grignard then transmetallates to give complex (76) which undergoes β-hydride elimination reforming zirconocene (1-butene). Protonation of the Grignard (77) affords the desired cyclised product (78).



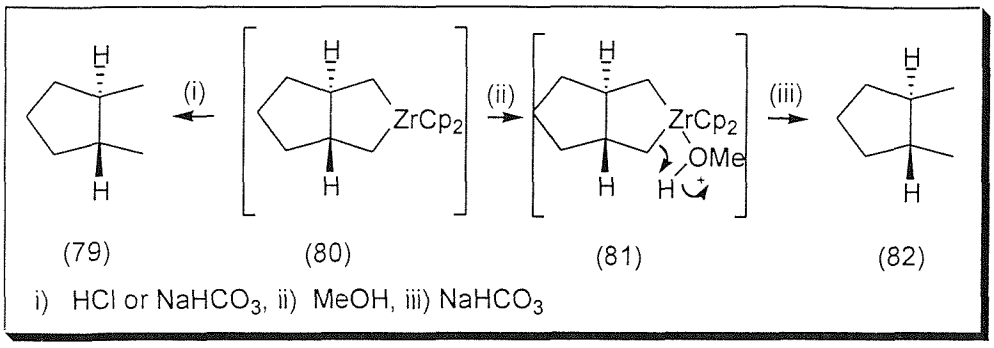
2.10 - Catalytic cyclisation.

2.5 Elaboration of zirconacycles

The previous section provides an overview of the range of zirconacycles available from simple organic precursors via efficient, convergent routes. Elaboration of zirconacycles extends the scope of transformations available.

2.5.1 Zirconacycle elaboration by protonation

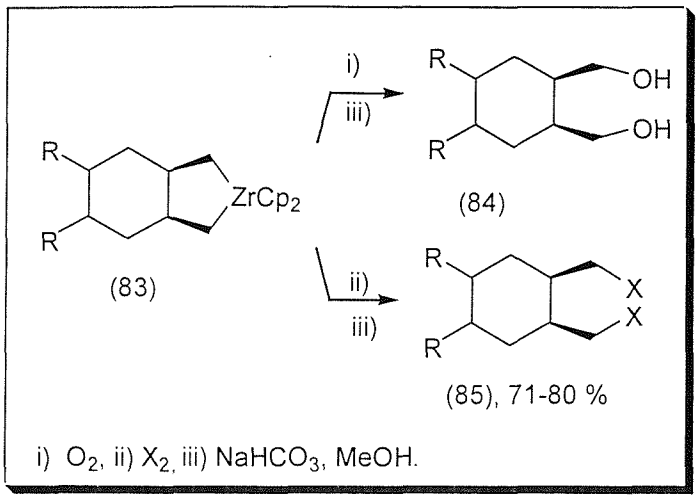
The simplest elaboration of a zirconacycle (80) is protonation, which can be carried out under acidic conditions (typically 2M HCl) or basic conditions (aqueous $NaHCO_3$). The choice of protonation conditions is dependent upon the sensitivity of the substrate. Methanol has also found use as a protonation agent, as this rapidly hydrolyses the first C-Zr bond potentially allowing functionalisation of the second. The mechanism of protonation has been suggested following a number of observations. Firstly, the stereochemistry of the zirconacycle at the ring junction [45] is retained and vinyl-Zr bonds are also known to retain their alkene geometry after hydrolysis[37]. Both of these facts indicate a concerted reaction mechanism via a four centre transition state (81).



Scheme 2.11 – Mechanism of protonation.

2.5.2 Zirconacycle elaboration by halogenation and monohalogenation

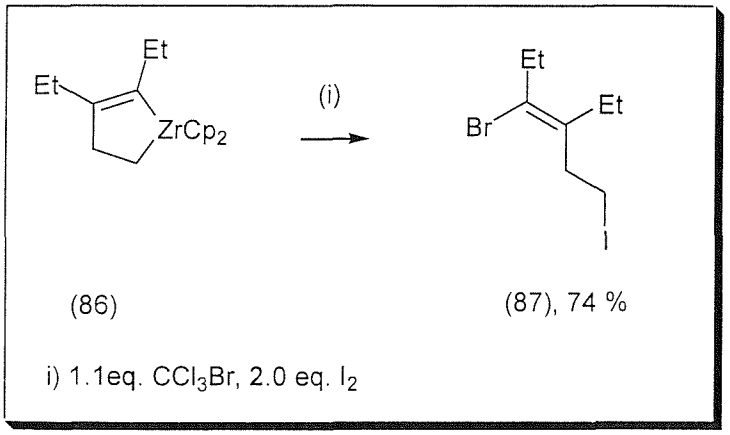
Work by Nugent[46] and Negishi[45] demonstrated that zirconacyclopentane (83) bonds could be elaborated with halogens and molecular oxygen to afford dihalides (85) and diols (84) respectively. Further elaboration via halogenation was further extended by development of monohalogenation and mixed dihalogenation reactions by Takahashi[47].



Scheme 2.12 – Dihalogenation of zirconacycles.

Takahashi also demonstrated[48] monobromination reactions of 2,3-dialkylzirconocyclopentenes which are chemoselective and highly reagent dependent (scheme 2.13). Monohalogenation allows synthesis of a large number of synthetically

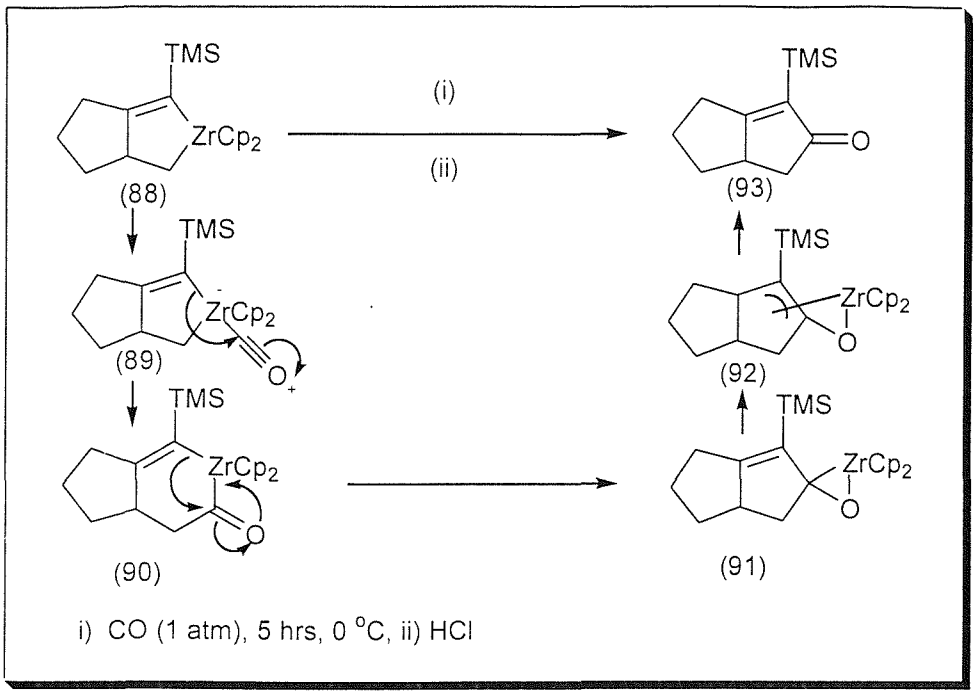
useful compounds (such as 87) from zirconacycles (such as 86), regioselectively and in high yield .



Scheme 2.13 Stereoselectivity of halogenation.

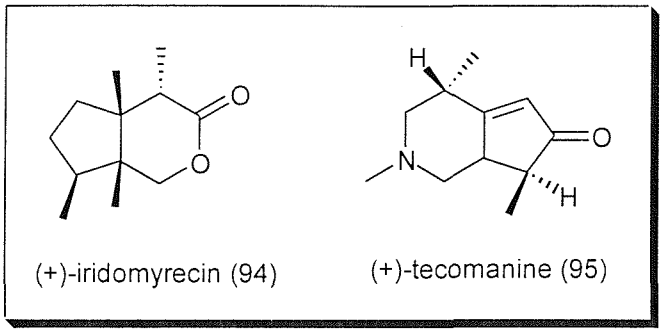
2.5.3 Carbonylation and Isocyanide insertion

Initial work on carbonylation on zirconacycles was carried out by Erker[49] and was further extended by Negishi[41],[50]. Both demonstrated that carbon monoxide was absorbed rapidly by a solution of zirconacycle (88) at 0 °C to afford the carbocyclic compound (93). The reaction proceeds via donation of a lone pair of electrons from CO into an empty d-orbital (LUMO) in Zr, followed by a 1,2 migration (illustrated in 89) which yields an η^2-ketone zirconium complex (91).



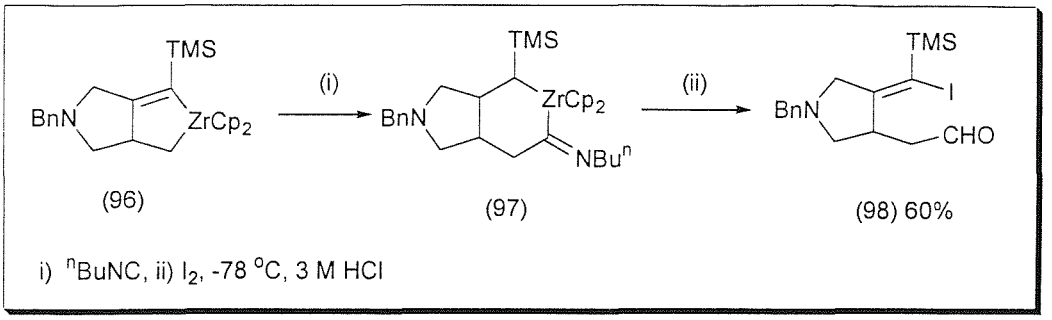
Scheme 2.14 -.Mechanism of zirconacycle carbonylation.

Further rearrangement to the π-allyl complex (92) occurs before the final ketone is generated (93) [45],[51]. There are at least three known examples of carbonylation as the central step in a total synthesis, (+)-iridomyrmecin (94)[52], (+)-tecomanine (95)[53] and pentalenic acid[54].



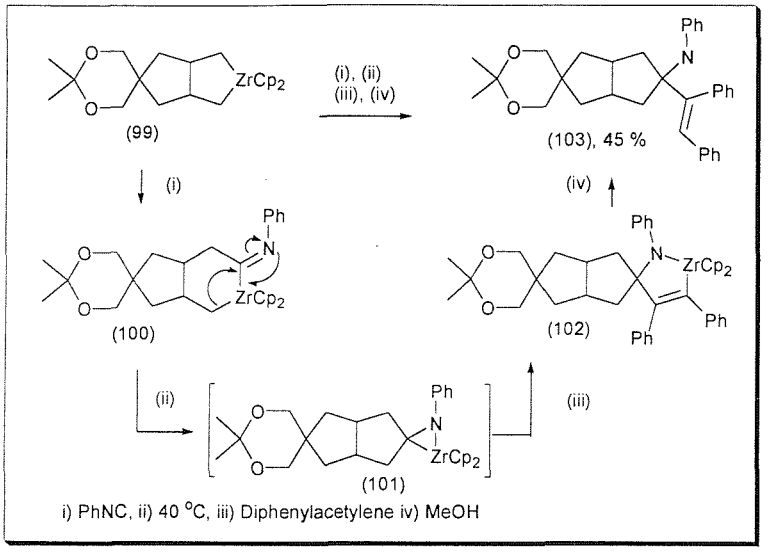
2.15 - Natural product synthesised using carbonylation.

Negishi[55] reported that it was possible to insert butyl isocyanide into a zirconocyclopentane (96), which upon hydrolysis yielded an aldehyde (98).



Scheme 2.16 – Isocyanide insertion.

Isocyanides are isoelectronic with CO, and as both are carbenes, it was reasoned that both mechanisms of insertion are similar to that of carbonylation. Whitby[56] proved the mechanism by demonstrating that insertion of the isocyanide quantitatively affords the iminoacyl complex (100) which upon warming rearranges to the η^2-imine complex (101).

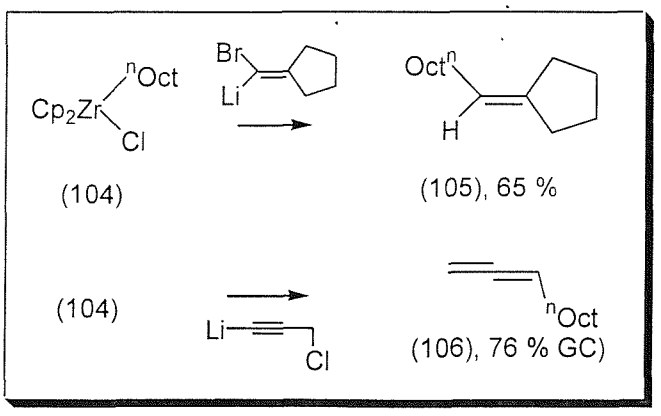


Scheme 2.17 – Mechanism of isocyanide insertion.

These imine complexes are known to be extremely potent carbometallating agents. Whitby[57],[58] extended this methodology by further elaborating to the zirconabicycle intermediate (101) using an alkyne to afford (102), which following protonation afforded the highly elaborated vinyl amine (103)[56].

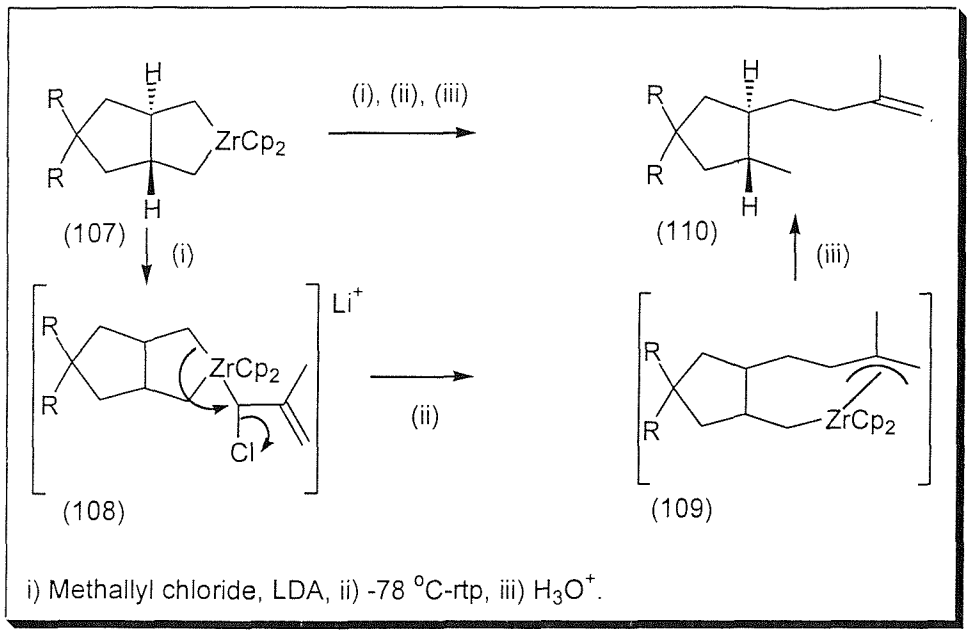
2.5.4 Zirconacycle elaboration via carbenoid insertion

Migratory insertion is a type of organometallic transformation allowing carbon-carbon and carbon heteroatom bond formation. In 1989 Negishi[37] examined carbon-carbon bond forming processes that proceed with migratory insertion and found that both organozirconium and organohafnium compounds mediated bond formation with α- or γ-haloorganolithiums e.g. to form (105) or (106) from (104).



Scheme 2.18 – Initial carbenoid insertion.

The initial work on carbenoid chemistry was extended by Whitby[59],[60],[61] see scheme 2.19. The successful insertion of these compounds is due to their carbenic character i.e. donation of an electron pair into the 16 electron metal centre to form an unstable 18 electron complex (108). This is then followed by migratory insertion of the reagent into the carbon zirconium bond.

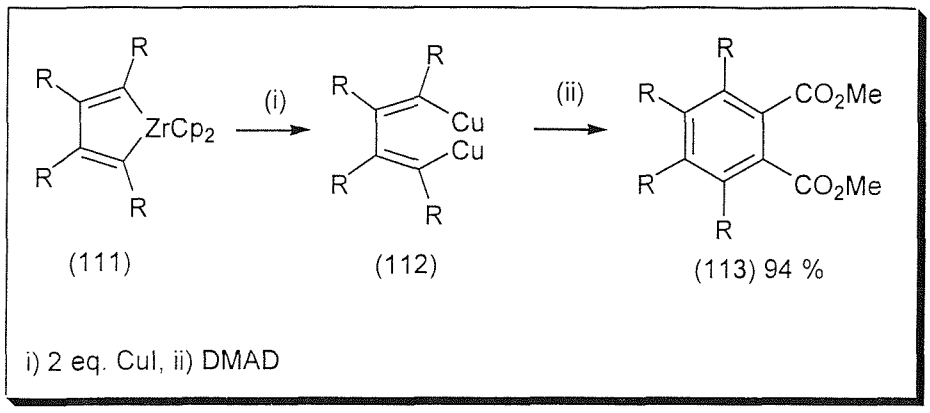


Scheme 2.19 – Mechanism of insertion of a metal carbenoid.

Whitby investigated the insertion of carbenoids into bicyclic zirconium complexes and found that *in situ* reaction with lithium chloroallylide at –78 ° C led to the generation of a novel allyl zirconocene complex (109), with complete reaction within 5 minutes. The η^3-allyl zirconium complex (109) has been fully characterised by NMR[60],[61].

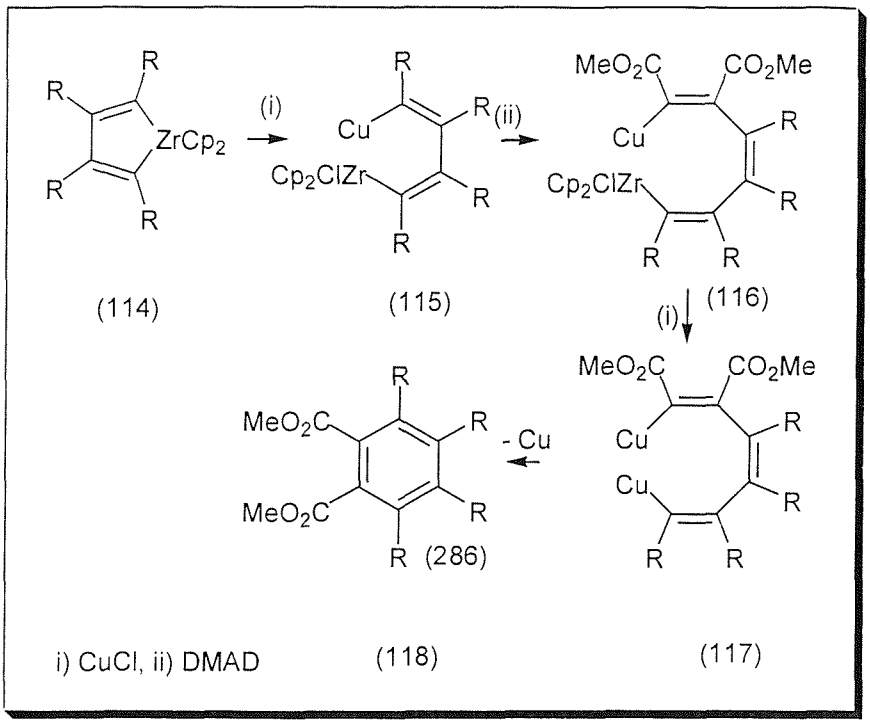
2.5.5 Zirconacycle elaboration via transmetallation

Negishi investigated transmetallation reactions with palladium, carrying out arylation, alkenylation and alkynation elaborations[62], [63]. Schwartz showed that alkylzirconocenes, after transmetallation using $AlCl_3$, could be acylated leading to the production of ketones[64]. Zirconocyclopentadienes (111) do not, by themselves, react with a third alkyne such as dimethyl acetylenedicarboxylate. Following transmetallation to copper, a cycloaromatisation reaction becomes feasible. Zirconocylopentadienes (111) have been transformed *in situ* by transmetallation with two equivalents of copper to form the dicuprate (112) and subsequent reaction with DMAD affords fully functionalised benzenediesters (113) in high yield[65].



Scheme 2.20 – Formation of functionalised benzenes.

The mechanism of the transmetallation reaction has been studied extensively by a number of research groups[66]. Two possible reaction mechanisms have been proposed to explain the conversion of metallacyclopentadienes to benzene derivatives. One being a pericyclic pathway (analogous to a Diels-Alder reaction), the other is a stepwise insertion path postulated (akin to a Michael addition). It appears likely that following formation of the zirconacycle, addition of copper chloride initially generates the active species (115) which then reacts with DMAD to yield the intermediate (116). A reductive coupling then provides the desired benzene derivative (118).



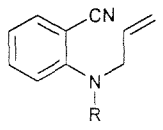
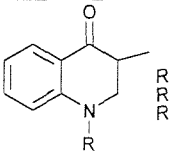
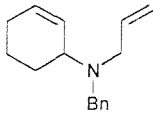
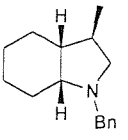
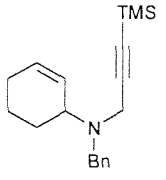
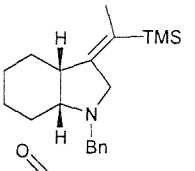
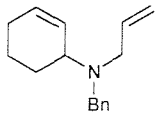
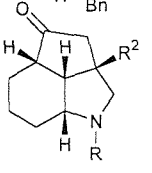
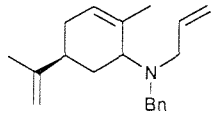
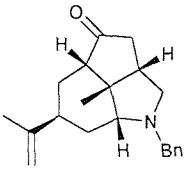
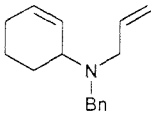
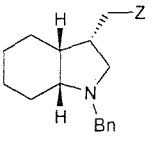
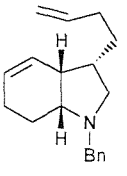
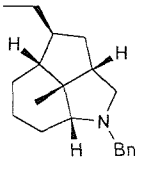
Scheme 2.21 - Copper mediated cycloaromatisation.

Scheme 2.22 illustrates the likely course of the reaction. The third alkyne is inserted into the carbon-metal bond. Transmetallation of one or two sp^2 carbons must occur to form (115) by reaction with CuCl. It is then reasonable to propose that the sp^2 carbon attached to the copper metal centre via Michael addition to afford the dimetallotriene (116). Reductive elimination of copper then affords the fully functionalised benzene (118).

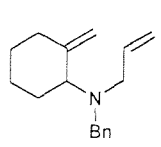
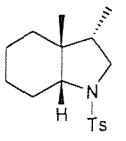
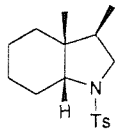
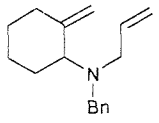
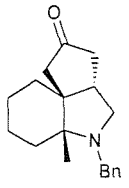
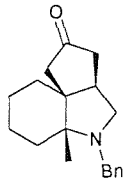
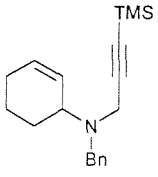
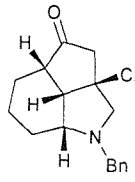
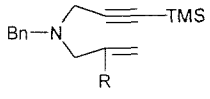
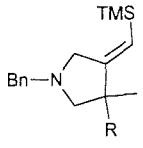
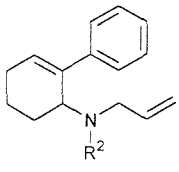
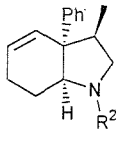
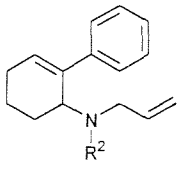
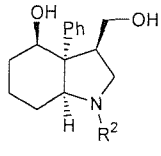
2.6 Review of zirconocene mediated cyclisation reactions containing nitrogen in the literature

This project is directed at the formation of particular nitrogen heterocycles by zirconium induced co-cyclisation/elaboration method. The following table summarises the other co-cyclisation reactions to generate nitrogen heterocycles known.

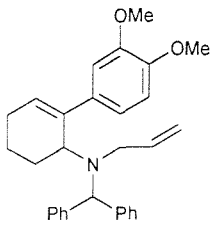
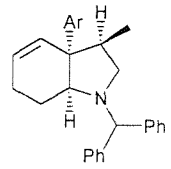
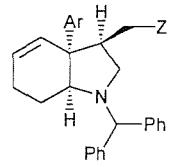
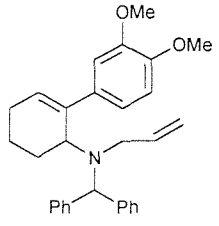
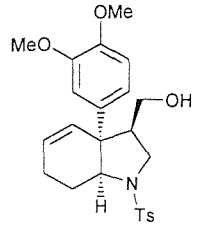
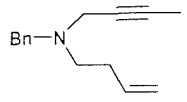
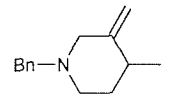
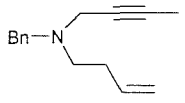
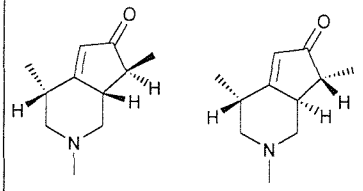
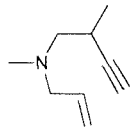
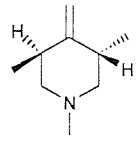
2.6.1 Table of cyclisation/elaboration reactions

No.	PRECURSOR	CYCLISED PRODUCT		REF
1			R = Ts 60 % R = Bn 54 % R = H 21 %	[78]
2			89 %	[79]
3			75 %	
4			R=CHO R^2= CHO 30 %	
5			47 %	
6			Z = I = 43 % Z = OH = 41 % Z = allyl = 25 %	[88]
7			74 %	

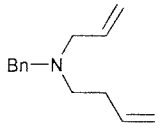
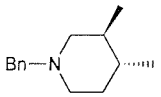
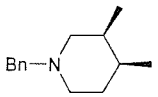
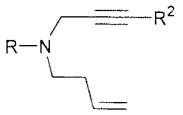
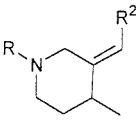
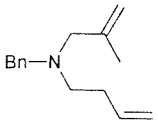
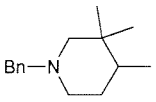
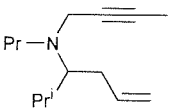
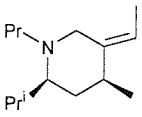
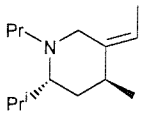
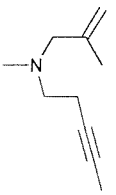
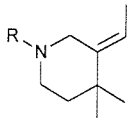
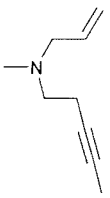
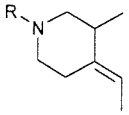
2.6.1 Table of cyclisation/elaboration reactions

No.	PRECURSOR	CYCLISED PRODUCT	REF
8		 59 %  (29 %)	[88]
9		 36 %  18 %	
10		 30 %	
11		 R = H 66 % R = Me 75 %	[89]
12		 R = Bn 26 % R = Ph_2CH 58 %	
13		 R = Ph_2CH	

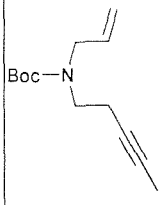
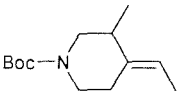
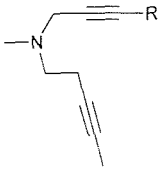
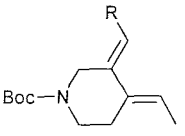
2.6.1 Table of cyclisation/elaboration reactions

No.	PRECURSOR	CYCLISED PRODUCT		REF
14			61 %	[90]
			Z = OH 14 % Z = D 73 %	
15			43 %	
16			50 %	[47]
17			31 % 4 :1	
18			46 %	

2.6.1 Table of cyclisation/elaboration reactions

No.	PRECURSOR	CYCLISED PRODUCT	REF
19		  91 % 4:1	[71]
20		 R=Bn, R^2=Me 80 % R=Bn, R^2=TMS 64 % R=Pr, R^2=Ph 88 %	
21		 70 %	
22		  91 % 4:6	
23		 30 %	
24		 87 %	

2.6.1 Table of cyclisation/elaboration reactions

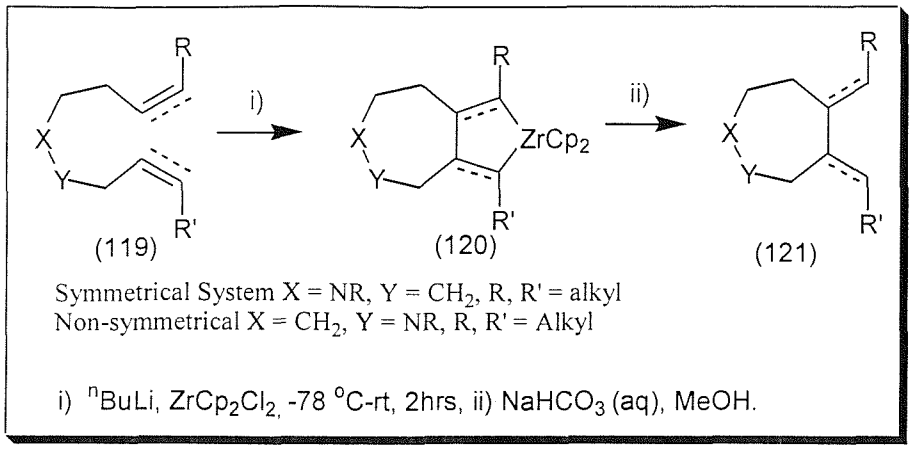
No.	PRECURSOR	CYCLISED PRODUCT		REF
25			60 %	[71]
26		 R=Me 72 % R=SMe 77 % R= $(CH_2)_4CH=CH_2$ 70 %		

CHAPTER 3

ZIRCONIUM MEDIATED SYNTHESIS OF AZEPINES AND BENZAZEPINES

3.1 Zirconium mediated synthesis of azepines

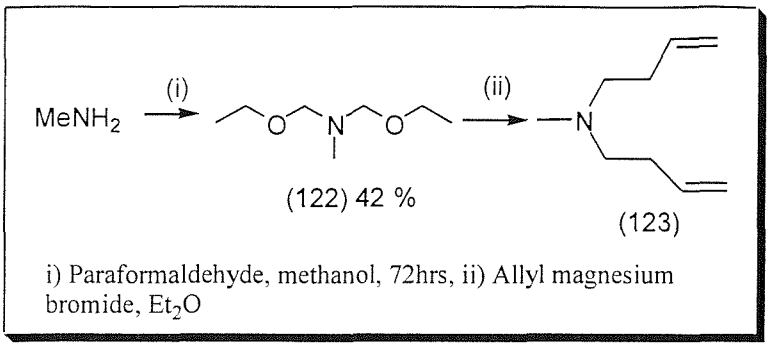
Organozirconium mediated co-cyclisation provides potential routes for the synthesis of 4,5-disubstituted azepines (termed the symmetrical system) and 3,4-disubstituted compounds (non-symmetrical system) and in each case diene, enyne and diyne co-cyclisations can be envisioned. There are 7 types allowing for symmetry (scheme 3.1). Additionally the synthesis of azepines and azepines containing an exocyclic diene (121) moiety from zirconabicycles (120) derived form diyne co-cyclisations (119) and protonation allows further elaboration through Diels-Alder chemistry to provide a variety of bicyclic azepines. Other important elaborations of zirconocyclopentadienes include copper catalysed addition to alkynes to afford functionalised benzazepines.



Scheme 3.1 - The symmetrical and non-symmetrical systems.

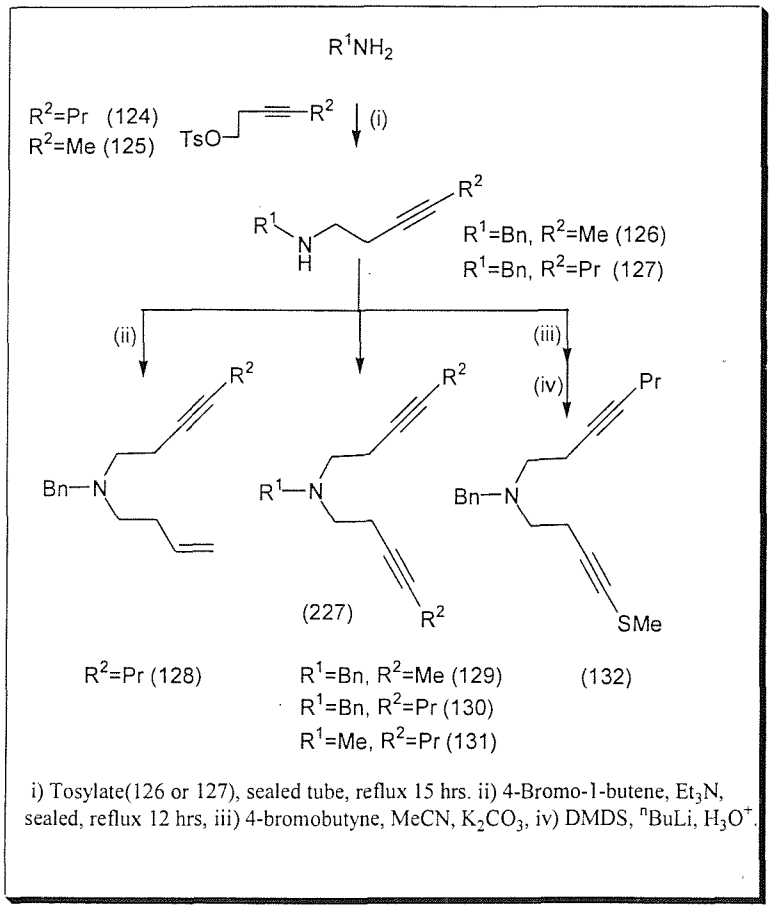
3.2 Synthesis of precursors for 4,5-disubstituted azepines

The diene (123) was synthesised from the tertiary amine (122). Compound (122) was synthesised according to a procedure developed by Heaney[67], reacted with two equivalents of allylmagnesium bromide to afford the diene (123) in 58 % yield. Direct alkylation of methylamine using two equivalents of 4-bromobutene gave a poor yield of (123).



Scheme 3.2 - Synthesis of diene precursor.

In order to synthesise a number of enynes and diynes, 3-heptyn-1-ol was synthesised on a large scale from ethylene oxide, 4-pentyn-1-ol and lithium amide in excellent yield (92 %). 3-Pentyn-1-ol was purchased and following conversion to the tosylates (124 and 125), alkylation with a primary amine afforded the desired secondary amines (126 and 127).

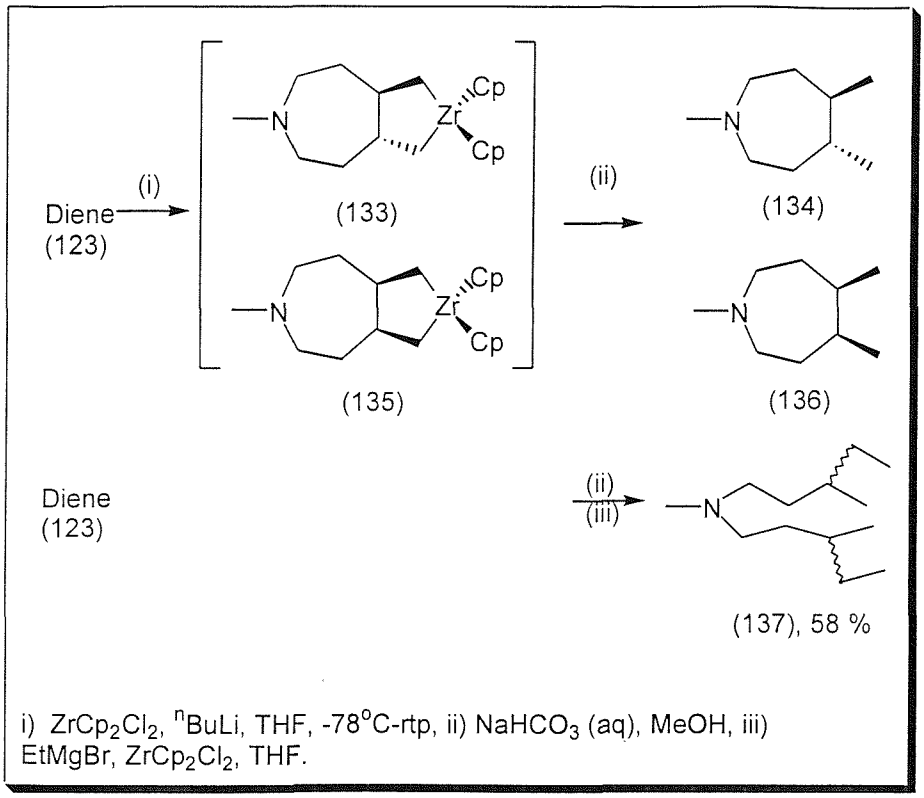


Scheme 3.3 - Synthesis of starting materials.

A large excess of primary amine was used to minimise formation of the *bis*-alkylated product and to act as solvent and base. Despite this the *bis*-alkylated diyne (130) was isolated as a by-product in the synthesis of the secondary amine (127) in moderate yield (31 %). The *bis*-alkylated amine was also produced by alkylation of the secondary amine (127) and the tosylate (124) in two high yielding steps (89 %). The secondary amine (127) proved a valuable starting material in the synthesis of enyne (128) and as a precursor to compounds (129-132). Enyne (128) was synthesised from the secondary amine (127) in 76 % yield. The thiomethylated compound (132) was isolated from secondary amine (127) in two high yielding steps, alkylation and subsequent thiomethylation afforded the desired compound (132) in good yield (76 %).

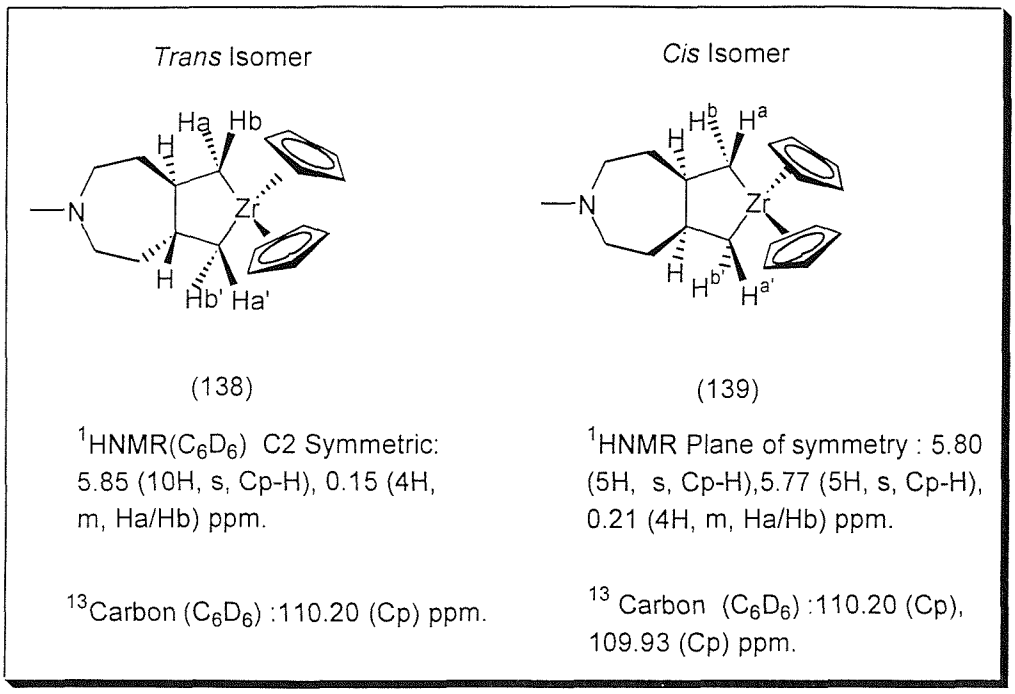
3.3 Saturated 4,5-disubstituted azepines from dienes

Intramolecular co-cyclisation of (123) was carried out using ethylmagnesium bromide to reduce zirconocene dichloride (rather than ^{n}BuLi) however this only afforded the addition product (137, 58 %) which was isolated as a mixture of diastereoisomers. Intramolecular co-cyclisation of diene (123) using standard Negishi conditions and protonation afforded the 1,4,5-trimethylazepine (134 or 136) in 83 % yield as a single isomer.



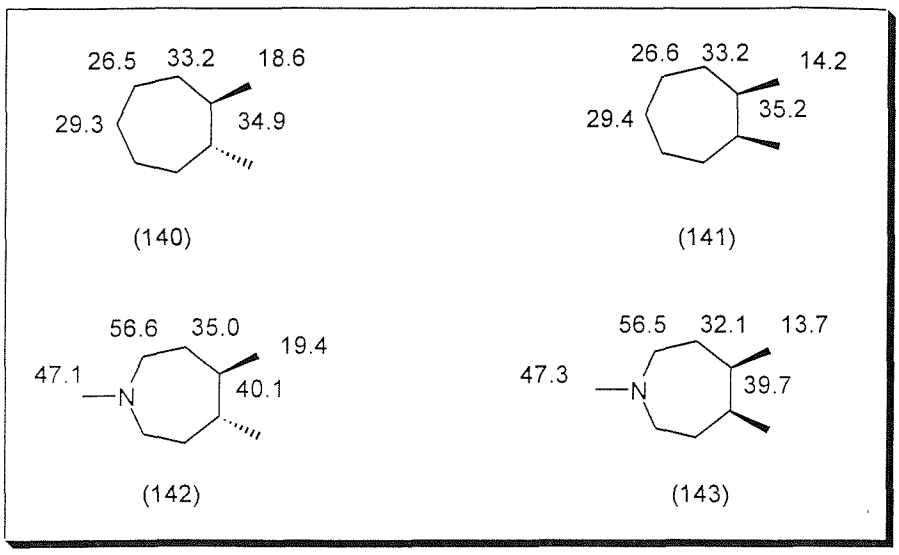
Scheme 3.4 - Stereochemistry of the azepines.

To establish the relative stereochemistry of the product the intermediate zirconabicycles (133 and 135) were analysed. In the *trans* isomer (134) the Cp rings are equivalent, in the *cis* isomer (136) they are not. We observed one Cp peak in both the proton and carbon NMR suggesting that the intermediate compound is zirconacycle (135) [see scheme 3.5].



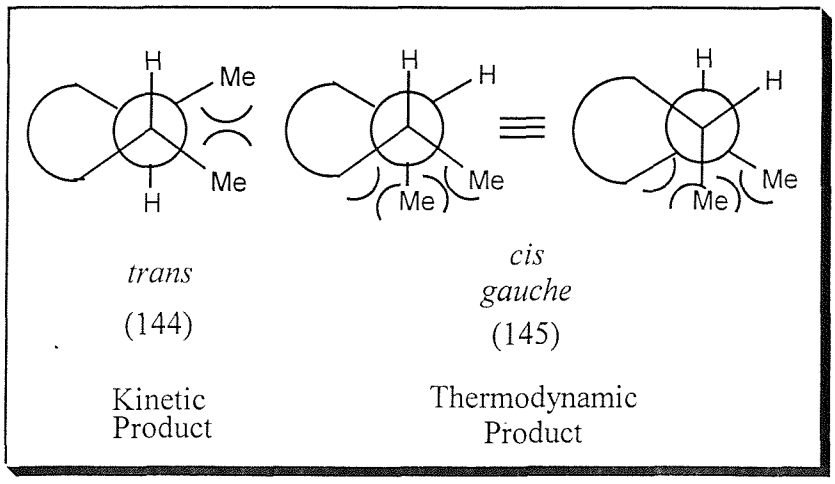
Scheme 3.5 - Data from zirconacycle NMR analysis.

Thus the *trans* methyl azepine (138) was formed on protonation. The complex (138) was stored under argon in the NMR tube for 72 hrs and re-analysed by NMR. This showed that the *trans* isomer was epimerising on standing to the *cis* zirconacycle (139) as the two Cp groups become non-equivalent with 2 Cp signals being observed in the proton and carbon NMR. Quenching of the mixture after 72 hours afforded a 4:1 mixture of the *trans* and *cis*-1,4,5-trimethylazepines. Unfortunately an isomerically pure sample (139) could not be obtained but both isomers could be clearly distinguished in the carbon NMR, with the cis isomer gradually increasing upto a maximum of 25 % after 72 hours.



Scheme 3.6 - Data from carbon NMR analysis of the product.

The γ-gauche effect provided further evidence for the relative stereochemistry of the azepine being *trans*. Essentially the γ-gauche effect is due to the shielding observed for a carbon atom if it is sterically compressed typically when substituents are introduced in the γ-position. Frequently upfield shifts are observed in cases where the stereochemistry leads to van der Waals interactions. Carbon atoms three bonds away from a substituent exhibit upfield shifts due to sterically induced polarisation of C-H bonds (see 3.7). The 13C shift of the methyl groups in (142, 19.4) shows much better correlation with the *trans*-1,2-dimethylcyclopentane (140, 18.6 ppm)[68] than the cis (143, 14.2 ppm) [scheme 3.6].

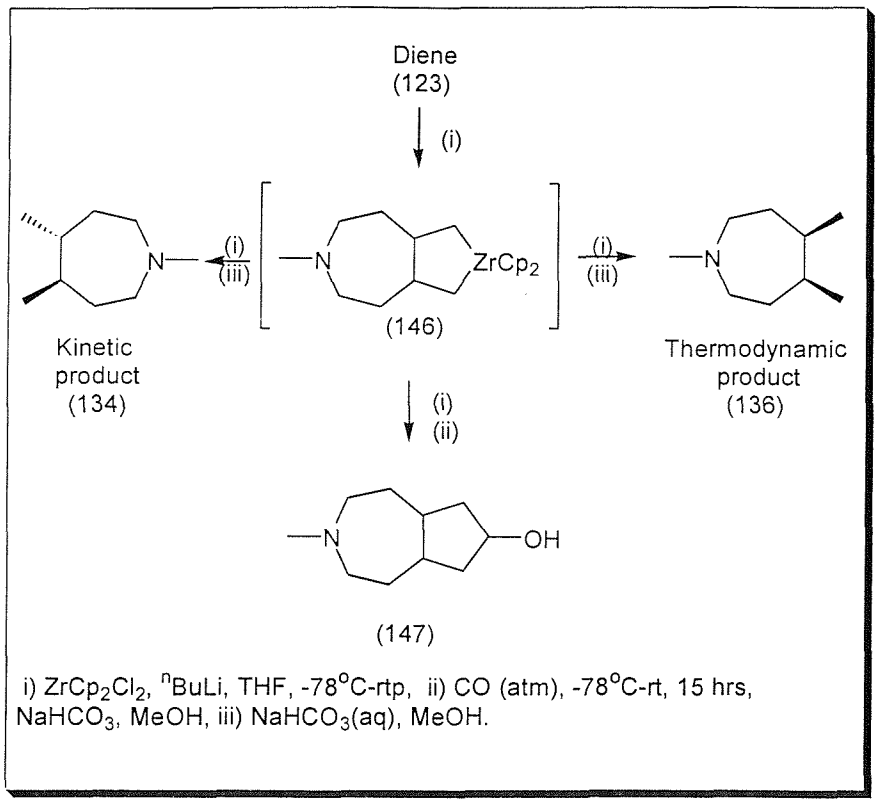


Scheme 3.7 - gamma-gauche effect.

As can be seen in scheme 3.7 the *cis* isomer (145) possesses an additional bad interaction thus helping to illustrate why the *trans* isomer is the favoured product initially in the reaction (kinetic product, 144).

3.3.1 Elaboration reactions

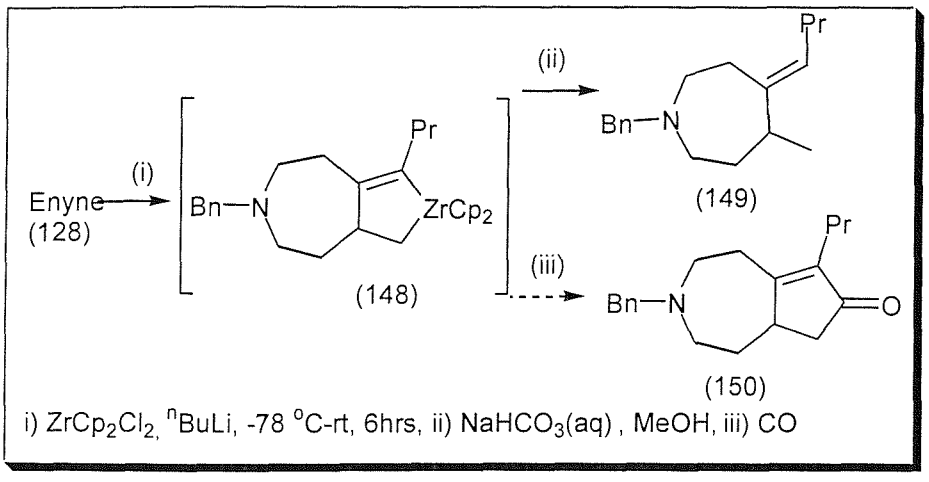
Cyclisation of diene (123) to afford *trans*-1,4,5-trimethylazepine (134) has been reported in section 2.7.5. Following this a carbonylation reaction was carried out. It was hoped that the bicyclic alcohol (147) would be isolated. Unfortunately this reaction failed to yield the desired compound and gave rise to a number of unidentifiable compounds. A sample of protonated zirconacycle taken prior to addition of carbon monoxide, showed the presence of the azepine (134), thus demonstrating that the reaction fails at the addition/insertion of carbon monoxide stage. As the problem step appeared to be the insertion of CO and not formation of the zirconacycle two other elaboration reactions were attempted.



Scheme 3.8 - Attempted elaborations of a diene.

3.4 Synthesis of 4,5-disubstituted azepines from enynes

Intramolecular co-cyclisation of enyne (128) using Negishi's reagent afforded the desired 4,5-disubstituted azepine (149) in 54 % yield. Attempted carbonylation of the intermediate zirconabicycle (148) to afford (150) failed, the majority of the material isolated being the protonated compound (149).

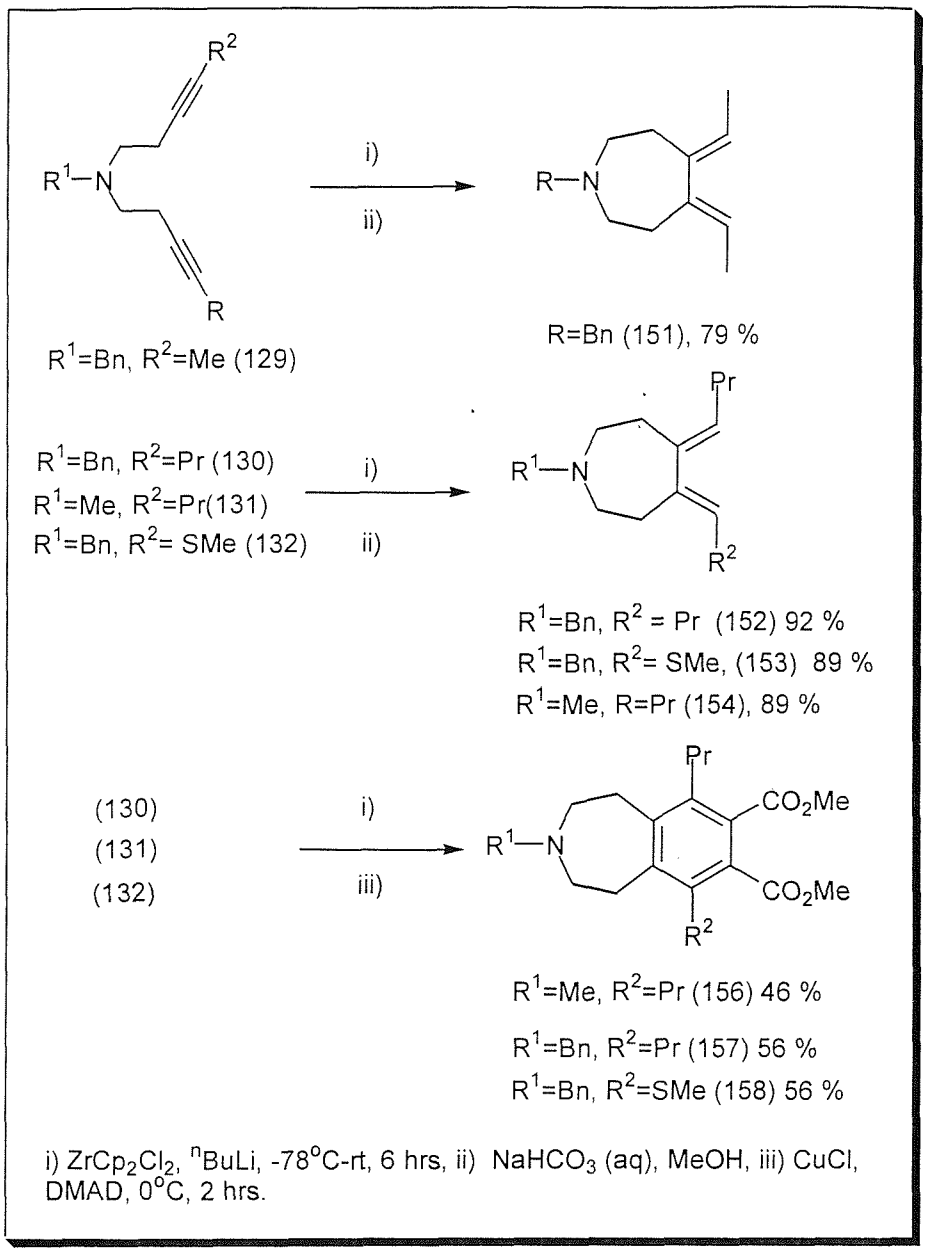


Scheme 3.9 - Enyne cyclisation and elaboration.

3.5 Synthesis of 4,5-disubstituted azepines from diynes

The synthesis of a number of diynes has been described previously (see section 3.3). Diynes (129 and 130) were cyclised using Negishi reagent to afford the expected exocyclic dienes (151 and 152) in good yield (79 % and 92 %). Diyne (131) was successfully cyclised, using Negishi reagent, which following protonation afforded the exocyclic diene (154) in good yield (89 %). The thiomethylated diyne (132) was cyclised to afford exocyclic diene (153) possessing a thiomethylated group in good yield (89 %).

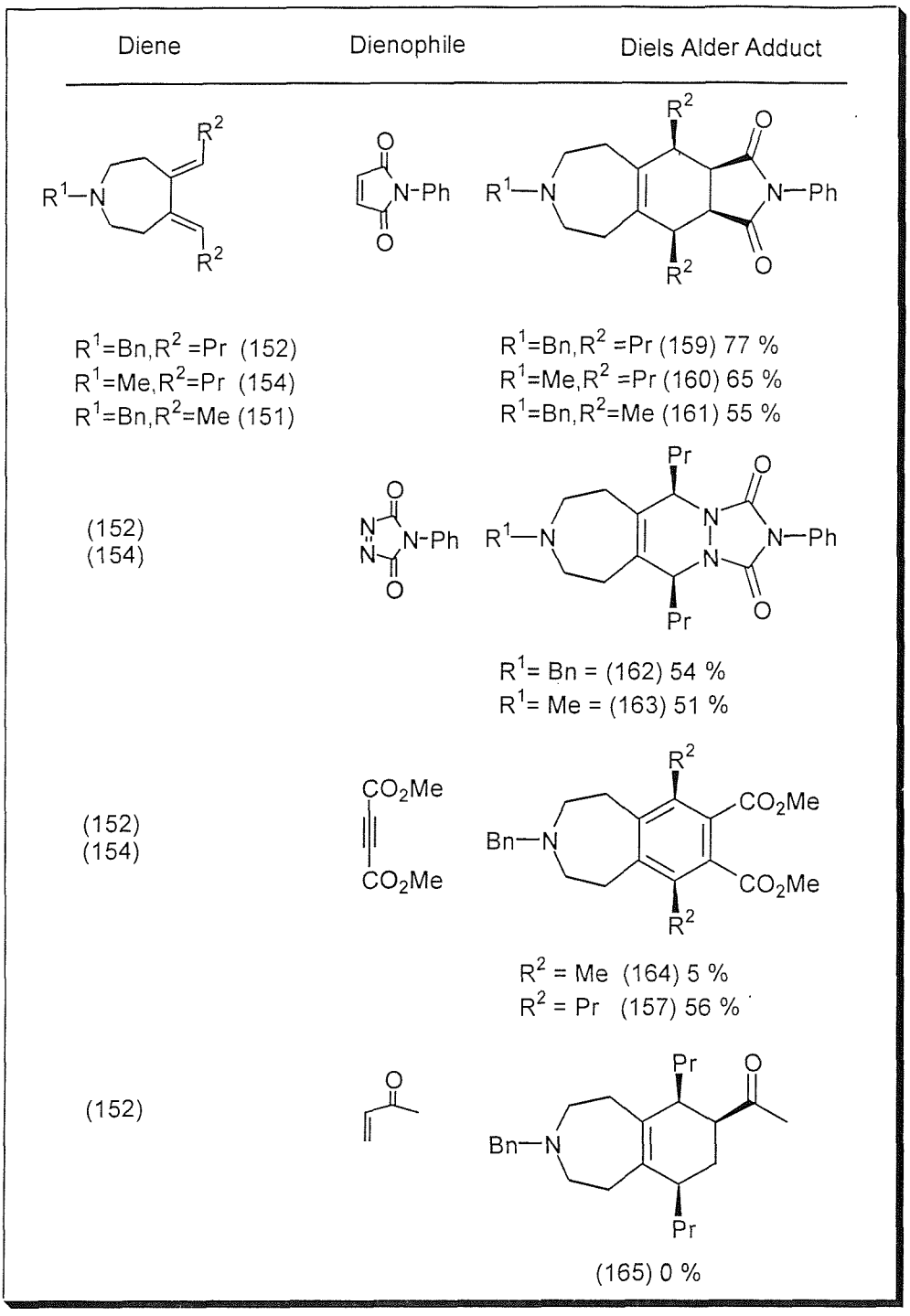
Compounds (156-158) were synthesised in a single step by treatment of a zirconocyclopentadiene with DMAD in the presence of copper chloride (see section 2.5.4). The fully aromatised heterobicycles were isolated in one step from the simple diynes (130-132).



Scheme 3.10 - Synthesis of an exocyclic diene.

3.6 Diels-Alder elaboration of 4,5-disubstituted azepines

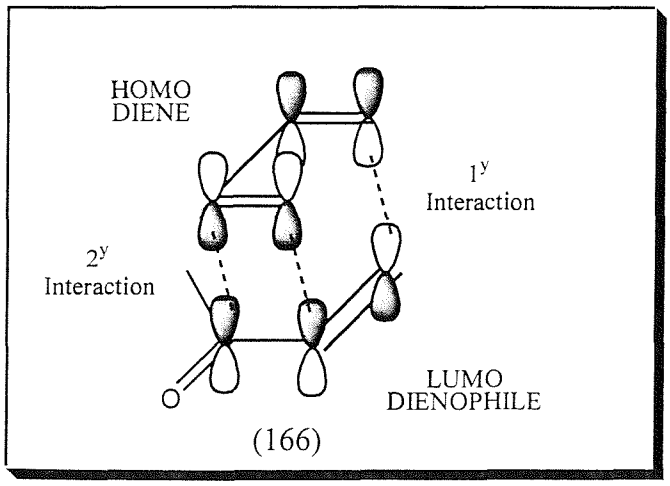
Having synthesised a number of *cis* exocyclic dienes (151, 152 and 154), we examined their further elaboration by Diels-Alder reaction. Initial analysis using NMR to follow the reaction demonstrated that the dialkyl dienes were poor reactants in Diels-Alder reactions as powerful dienophiles were needed (scheme 3.11).



Scheme 3.11 - Diels Alder elaboration reactions.

The *cis* exocyclic diene (152) was reacted in THF with *N*-phenylmaleimide and Et_2AlCl as catalyst, at room temperature with vigorous stirring for 2 hours. This afforded the

expected Diels Alder adduct (159) in good yield (77 %) FMO analysis and comparison of NMR data showed that the expected *endo* compound was isolated.



(166)

Scheme 3.12 - Formation of the endo adduct by FMO.

Dienes (151 and 154) were also reacted with *N*-phenylmaleimide (using Lewis acid catalysis) to afford the desired adducts (160) in 65 % and (161) in 55 % yield. The benzyl and methyl dienes (152 and 154) were also reacted with 4-phenyl-4,5-dihydro-3*H*-3,5-pyrazoledione. Prior NMR analysis demonstrated that the uncatalysed reaction was extremely fast thus the reaction was carried out at –78 °C in THF, warmed to room temperature, quenched using $NaHCO_3$ and purified to afford the desired adducts (162, 54 %) and (163, 51 %).

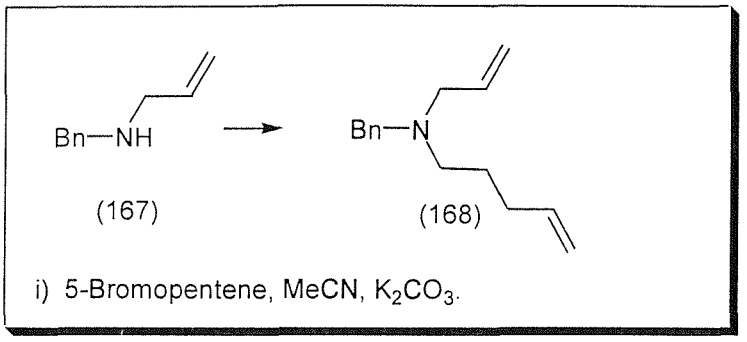
Another aim of this project was to synthesise novel benzazepines. It was thought that Diels-Alder elaboration of dienes (152 and 154) using DMAD followed by aromatisation would afford the corresponding benzazepine. However the reaction failed, probably as a result of a debenzylation reaction following addition of the nitrogen lone pair to the DMAD in a Michael reaction. There is formation of a quaternary amine, which then breaks the bond to the nitrogen group releasing the benzyl group. In an attempt to reduce this effect the reaction was repeated using a methyl protected nitrogen. Although the Diels-Alder elaboration of (152) using DMAD afforded the desired benzazepine (164)

following self aromatisation the yield was only 5 %. This compares to an isolated yield of 56 % from the diyne (152) using a copper catalysed cycloaromatisation reaction.

The cycloaddition reaction between diene (152) and methyl vinyl ketone did not afford the expected adduct (165). Even addition of a Lewis acid was not enough to bring about formation of the desired adduct. In this case the failure was attributed to the fact that methyl vinyl ketone is not sufficiently electron poor enough to react and the bulky propyl groups on the diene hinder the approach of the dienophile. Furthermore, because the diene is fused to a seven member ring it is slightly twisted so the Diels-Alder reaction is unfavourable (the overlap is not good in the transition state).

3.7 Synthesis of starting materials for 3,4-disubstituted azepines

The secondary amine (167) was synthesised in good yield from benzylamine and allyl bromide (86 %). Further alkylation using 5-bromopentene afforded the desired tertiary amine (168) in 85 % yield.

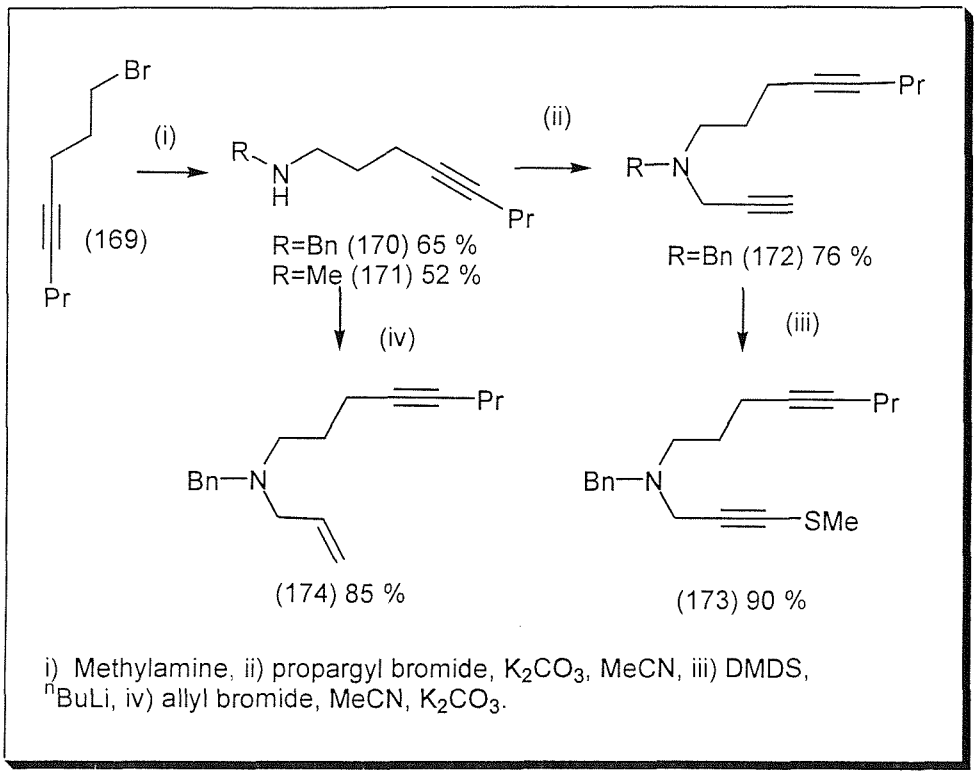


Scheme 3.13 - Synthesis of non-symmetrical diene.

Bromide (169) was synthesised on a molar scale from pentyn-1-ol and 1,3-dibromopropane. The crude product was then used to alkylate benzyamine and methylamine to give (170) and (171) in 65 % and 52 % yield respectively. The excess benzylamine was removed by distillation (219 mm, 87 °C), and the remaining impurities of 4,9-tridecadiyne (non-polar) and 1,3-diaminopropane (polar) were removed by column chromatography to afford pure (170) . The large scale synthesis of the methylamine

derived secondary amine (171) was more difficult due to its volatility. All attempts to purify the *N*-methyl compound (171) by chromatography were unsuccessful. Purification by Kugelrohr distillation afforded the desired compound in 52 % yield.

The enyne (174) was synthesised from the secondary amine (170) in good yield (85 %). Further alkylation of secondary amine (170) with propargyl bromide afforded the tertiary amine (172) in 76 % overall yield. Thiomethylation of the tertiary amine (172) afforded the expected compound (173) in good 90 % yield.

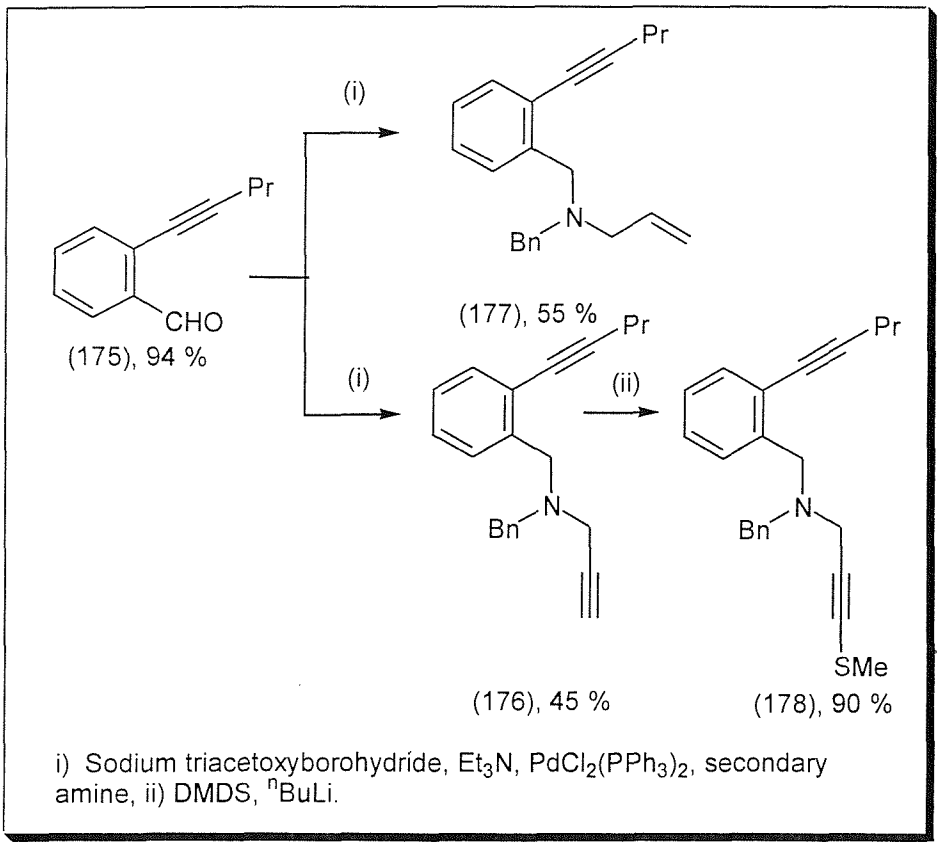


Scheme 3.14 - Synthesis of diynes and enynes.

3.8 Synthesis of starting materials for 3,4-disubstituted benzazepines

The aldehyde (175, scheme 3.15) was synthesised from commercially available 2-bromobenzaldehyde using a palladium catalysed cross coupling reaction incorporating modified Castro-Stevens conditions[69] in 94 % yield. Reductive amination of (175) with benzylallylamine, gave the cyclisation precursor (177) in 55 % yield. Reductive

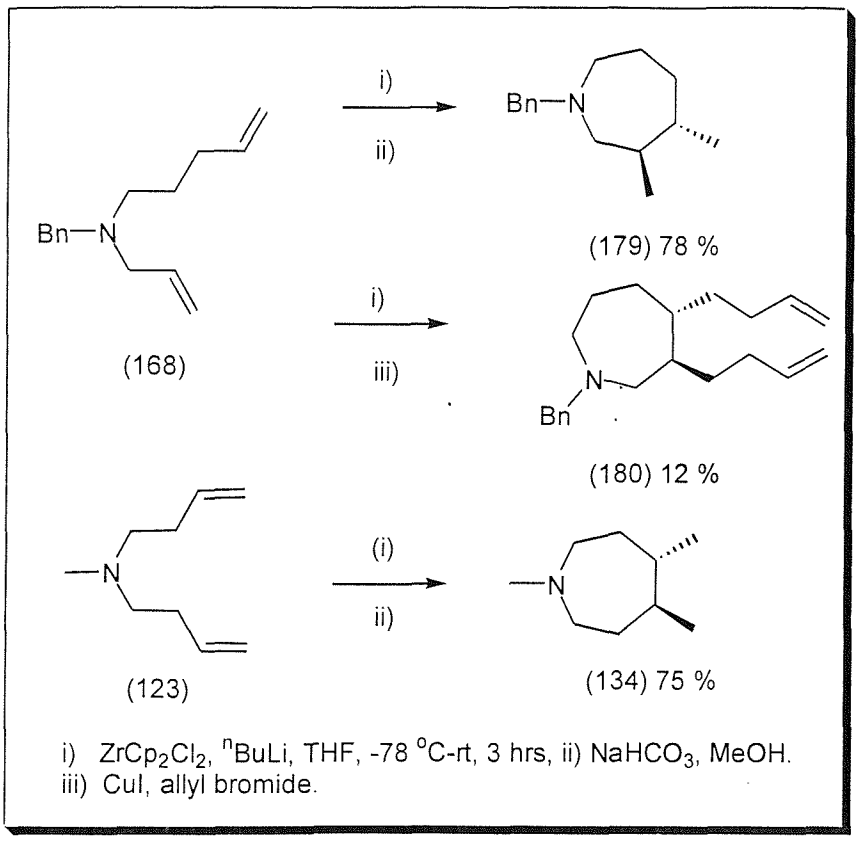
amination was also used to prepare diyne (176), using propargylbenzylamine, in modest yield (45 %). Propargyl diyne (176) was converted to the thiomethyl derivative (178) in high yield (90 %), thus allowing Negishi's reagent to be used for subsequent cyclisation [70].



Scheme 3.15 - Synthesis of starting materials.

3.9 3,4-disubstituted azepines from diene cyclisations

The non-symmetrical diene (167) underwent intramolecular co-cyclisation to afford the expected dimethyl tertiary amine (179) as a single isomer and in good yield (78 %). Additionally the zirconabicycle derived from (167) was synthesised *in situ* but rather than protonating, to give (179), the dicuprate was formed by addition of CuI and then quenched with allyl bromide to afford diene (180) in poor yield.

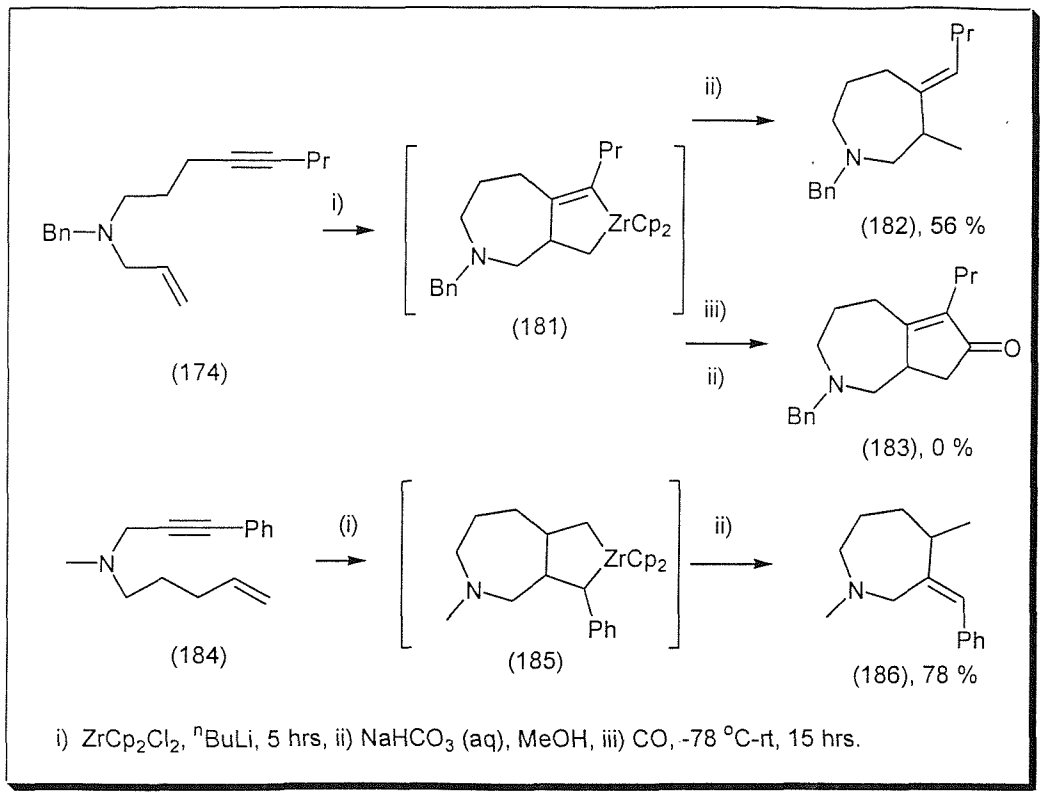


Scheme 3.16 - NS diene cyclisation and elaboration.

NMR of compound (179) showed good correlation to the *trans*-1,4,5methyl azepine (134), with the carbon NMR chemical shift values (19.9 and 22.2 ppm) similar to those observed in the azepine [134, (19.4 ppm)]. We would expect the groups in the cis isomer to have a much lower ^{13}C shift due to the γ-gauche effect.

3.10 3,4-disubstituted azepines from enyne cyclisations

Intramolecular co-cyclisation of (174) afforded the desired 3,4-disubstituted azepine (182) in 56 % yield. Carbonylation was attempted on the corresponding zirconabicycle (181) but only the protonated compound and a small amount of unreacted enyne (174) was isolated inferring that carbon monoxide actually encouraged the retro-reaction, by forcing the equilibrium backwards.



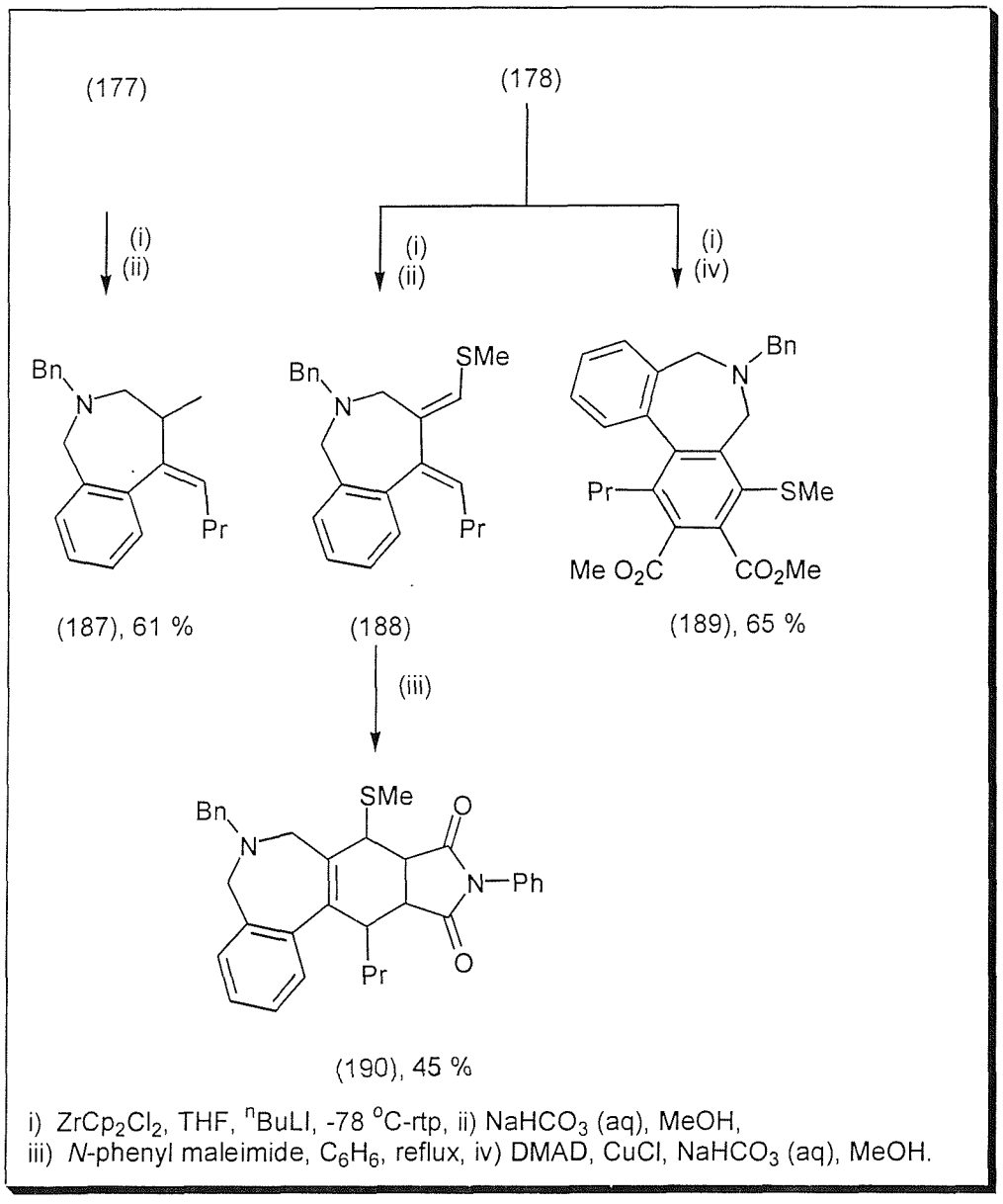
Scheme 3.17 - Enyne cyclisation.

Additionally enyne (184) was synthesised from 5-bromopentene and the appropriate phenyl substituted secondary amine in 73 % yield. Reductive coupling of enyne (184) using Negishi's reagent afforded the desired exocyclic alkene (186) in good yield (78 %). Further information concerning the synthesis of phenyl substituted alkynes can be found in section 5.13.

3.11 Synthesis of 3,4-disubstituted benzazepines

Cyclisation of the enyne (177), using Negishi's reagent, afforded the expected exocyclic alkene (187) in good yield (61 %). Cyclisation and protonation of precursor (178) afforded the exocyclic diene (188) in poor yield. The *cis* exocyclic diene (188) was ideally suited to further elaboration using Diels-Alder chemistry. Following a [4+2] cycloaddition with *N*-phenylmaleimide the Diels-Alder adduct (190) was isolated in 45 % overall yield. Attempts to improve the yield using Lewis acid catalysis failed.

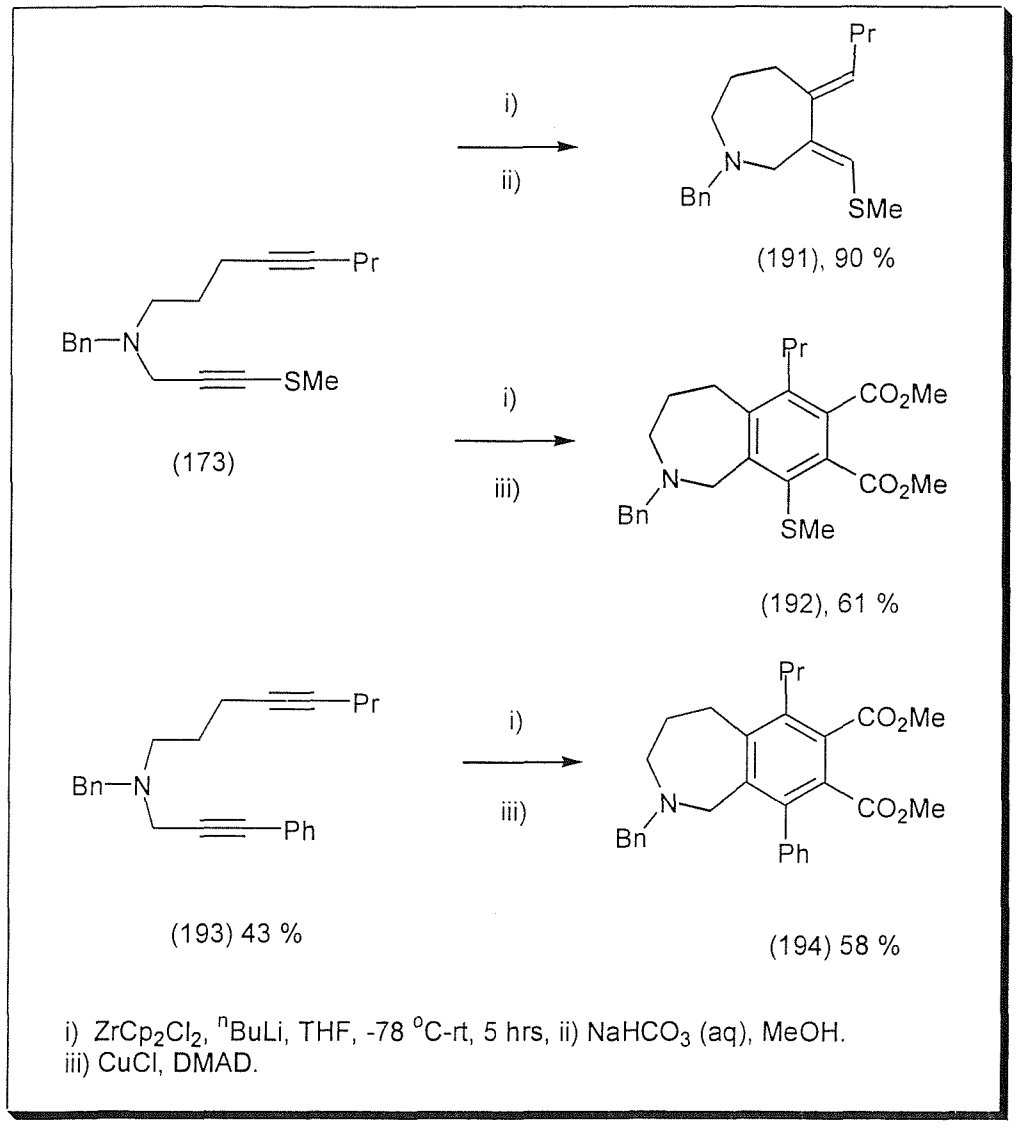
The thiomethylated diyne (178) was cyclised using Negishi's reagent, the corresponding zirconacycle transmetallated to the dicuprate, and subsequent cycloaromatisation with DMAD (described in section 2.5.3) afforded the fully aromatised compound (189) in good yield (65 %). Elaboration via the copper mediated reaction has been shown to have a number of advantages, in that the adduct is isolated in higher overall yield.



Scheme 3.18 - Synthesis of benzazepines.

3.12 3,4-disubstituted azepines from diyne cyclisations

Reductive coupling of (173) with Negishi's reagent, gave the desired thiomethylated diene (191) in 90 % yield. Copper mediated cycloaromatisation reaction on the intermediate zirconacyclapentadiene was carried out with DMAD to give benzazepine (192) in good yield (61 %). The presence of the thiomethyl group appeared to help the reaction as the yield was higher than for the all carbon case.



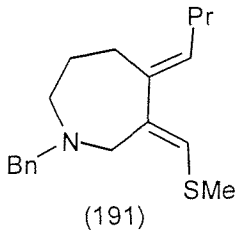
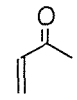
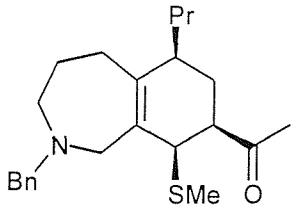
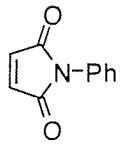
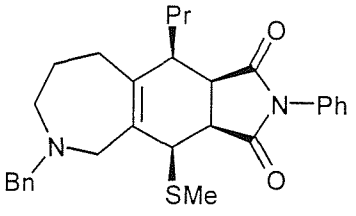
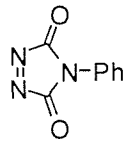
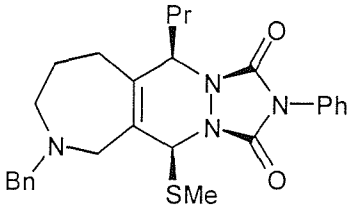
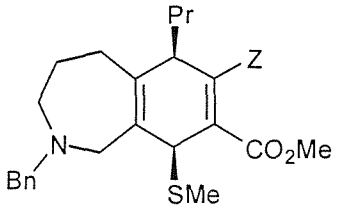
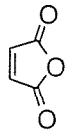
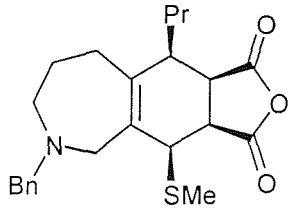
Scheme 3.19 - Synthesis of exocyclic diene.

Diyne (193) was synthesised from the secondary amine (170) and 3-chloro-1-propynylbenzene in 43 % yield. Diyne (193) was then cyclised using Negishi's reagent and further elaborated using the copper mediated cycloaromatisation reaction to afford the benzazepine (194) in 58 % yield.

3.13 Diels-Alder elaborations of 3,4-dialkylidene azapines

The *cis* exocyclic diene (191) possesses a thiomethylated *cis* exocyclic diene moiety, which is ideally suited to further elaboration via Diels-Alder reactions. A series of small scale NMR tube experiments were carried out to assess the viability of a number of dienophiles. After dissolving the dienophile in D_6-benzene under argon, the diene (191) was added to the tube and analysed over a 72 hour period. The results of these experiments showed that the reaction of diene (191) with *N*-phenylmaleimide was complete in 2 hrs at room temperature giving adduct (196). In contrast the Diels-Alder reaction using methyl vinyl ketone required reaction to be heated at 80 °C for 16 hrs. Maleic anhydride did not afford adduct (200). The cycloaddition reaction involving DMAD failed to yield the desired adduct (198). The NMR data suggested that DMAD was acting as a Michael acceptor (being attacked by nitrogen lone pair) rather than acting as a dienophile.

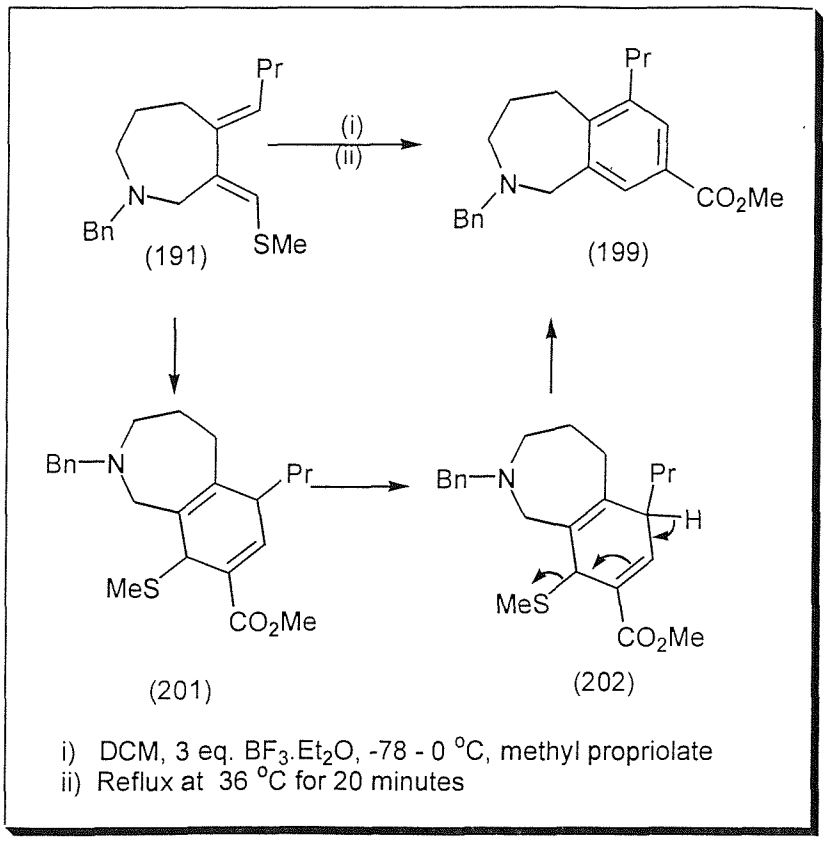
Following NMR analysis the reaction was carried out on a larger scale. An excess of methyl vinyl ketone (3 equivalents) was refluxed in toluene with the exocyclic diene (191) for 16 hours. Following work-up and purification by radial chromatography, the Diels-Alder adduct (195) was isolated. Analysis of compound (195) showed that a single regio and stereo isomer had been isolated. Comparison with literature compounds[71] showed that the expected endo adduct had been isolated (discussed in section 3.6). Diels-Alder elaboration of diene (191) with *N*-phenylmaleimide afforded the desired adduct (196) in 55 % yield. The Diels-Alder adduct (197) derived from the reaction between diene (191) and the powerful dienophile 4-phenyl-4,5-dihydro-3*H*-1,2,4-triazole-3,5-dione was isolated in low yield (15 %).

Diene	Dienophile	Diels-Alder Adcuct
 (191)		 (195), 56 %
(191)		 (196), 55 %
(191)		 (197), 15 %
(191)	$MeO_2C{-}{\equiv}{-}Z$	 (198), Z = CO_2Me, 0 % (199), Z = H, 46 % (aromatised and without the SMe group)
(191)		 (200), 0 %

Scheme 3.20 - NMR Diels Alder elaborations.

After carrying out a number of thermal Diels-Alder reactions, a number of Lewis acid catalysed Diels-Alder reactions were carried out. Different Lewis acids were screened for their ability to catalyse the reaction, however most were inappropriate or unsuitable. Overall it was discovered that the reaction proceeded effectively when either Et_2AlCl or $BF_3.OEt_2$ were used as the Lewis acid.

Although the main reason for carrying out thiomethylation of diyne (172) to the non-terminal diyne (173) was to allow cyclisation with Negishi's reagent, another possibility was to use this thiomethyl group to synthesise a fused benzazepine (illustrated in scheme 3.21). The main problem initially was that methyl propriolate proved to be a poor dienophile in the thermal Diels-Alder reaction. However this problem was solved by using a Lewis acid to catalyse the Diels-Alder reaction with methyl propriolate. Experimentally the diene and dienophile were mixed under argon at –78 °C, then three equivalents of $BF_3.OEt_2$ added, warmed to room temperature and left to stir for 1 hour. Following heating at 40 °C for 1 hour the reaction was quenched with sodium bicarbonate. The intermediate (201) can be observed by mass spectrometry (M+H = 386.2) prior to heating, but only (199) is observed after heating. Benzazepine (199) was obtained as a single regioisomer.



Scheme 3.21- LA catalysed route to benzazepines.

3.14 Conclusion

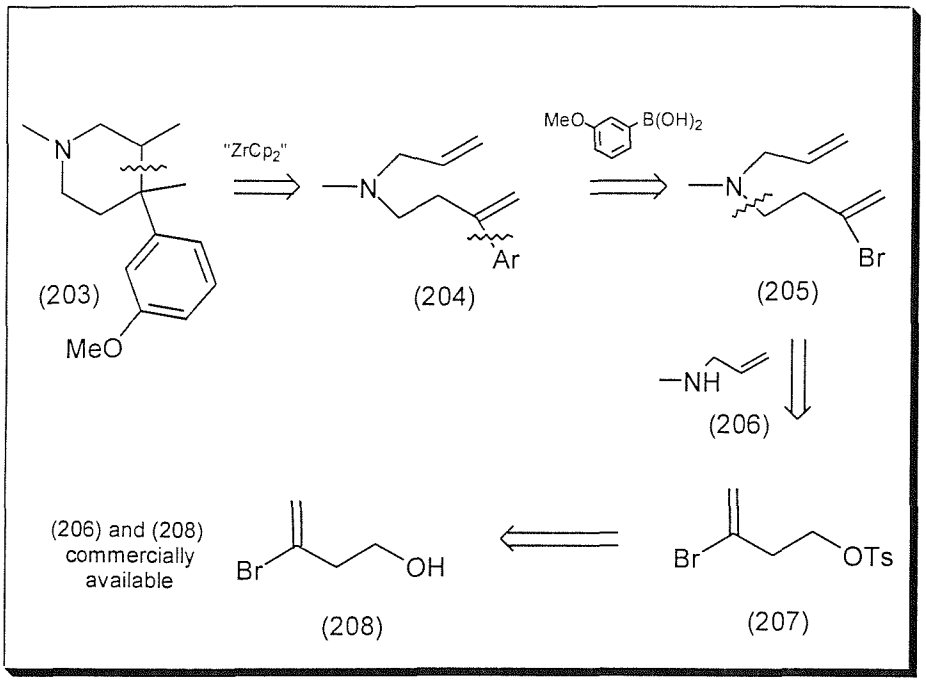
The preceding chapter has discussed the synthesis of a number of 3,4- and 4,5-disubstituted azepines and benzazepines. The stereochemistry of the azepine products derived from cyclisation of simple dienes, has been discussed. Elaboration of exocyclic dienes synthesised using organozirconium chemistry, has been successfully carried out using Diels-Alder and copper mediated cycloaromatisation reactions. The azepines and benzazepines resulting from these further elaboration reactions have undergone biological testing at Eli Lilly (see appendix for data) and were found to be active at relatively high concentrations.

CHAPTER 4

ZIRCONIUM MEDIATED SYNTHESIS OF 4-PHENYLPIPERIDINES

4.1 Retrosynthesis of 4-phenylpiperidines (4PP's)

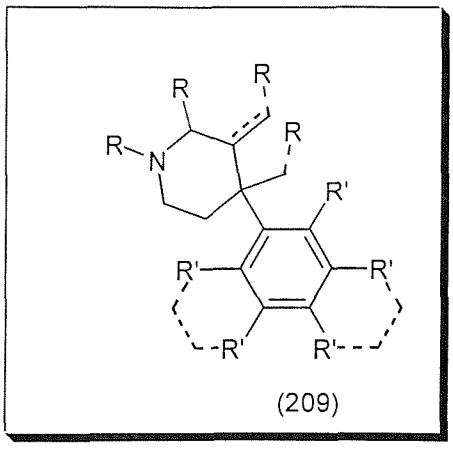
As described in section 1.12 the 4PP pharmacophore is extremely important in the pharmaceutical industry. Examination of the 4PP pharmacophore (203) suggests a synthesis using transition metal cyclisation reactions.



Scheme 4.1 - Novel disconnection of 4-phenyl piperidine.

One potential disconnection, between the two methyl groups (203), leads to diene (204). The forward cyclisation reaction should be feasible using a zirconocene equivalent. Synthesis of diene (204) looked attractive assuming conditions for coupling an aromatic moiety onto a vinylic halide could be developed. The aromatic coupling step represents one of the main advantages of the route described in scheme 4.1, as insertion of the aromatic group at the penultimate step in the synthesis allows a number of variations to be synthesised. Further disconnection affords a vinylic halide (204) which should be available using well precedented alkylation chemistry. Another advantage of our route is that a large number of secondary amines (such as 206) can be brought in, allowing a large number of unique 4PP's to be synthesised. Alkylation of (207) with *N*-

methylpropargylamine rather than *N*-methylallylamine (206) would result in a 4-phenyl piperidine containing an alkene functionality at the C4 position. Further functionalisation of the exocyclic alkene could be achieved in a number of different ways such as epoxidation or ozonolysis. Tosylate (207) can be prepared trivially from commercially available 3-bromo-3-buten-1-ol (209) in high yield. Commercially available (209) is expensive (£96/5g) and thus does not represent a viable starting material. Fortunately compound (209) can be prepared by hydrobromination of 3-butyn-1-ol (£85/50g).



(209)

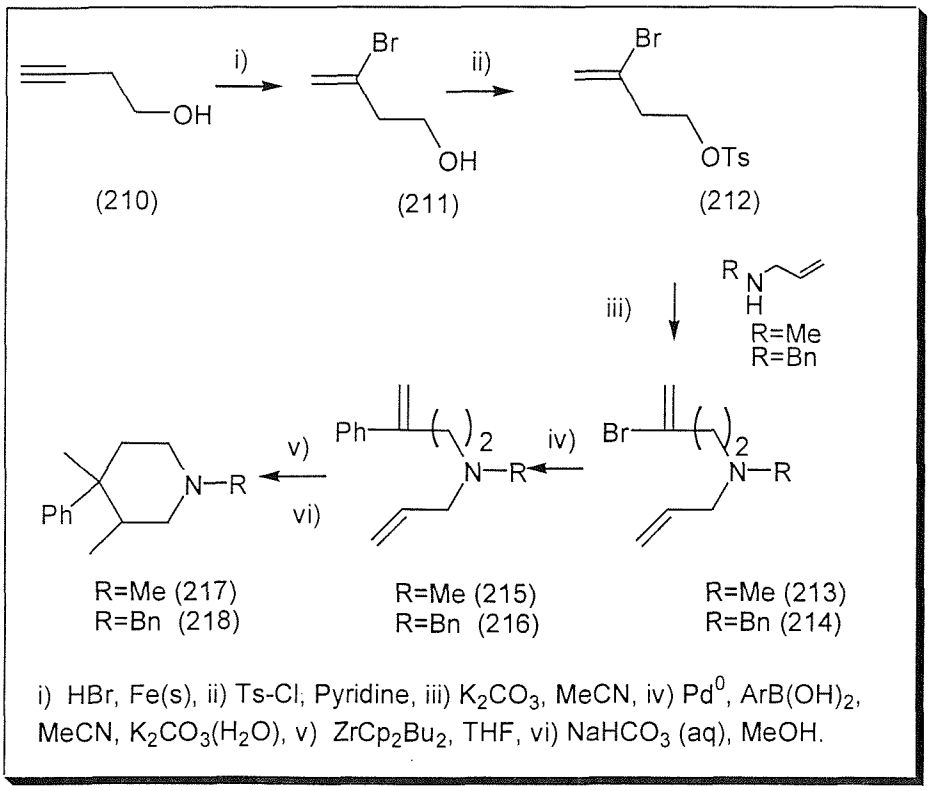
Scheme 4.2 - Available analogues.

The retrosynthesis (described in section 4.1) has a high degree of variation and uses cheap starting materials. Scheme 4.2 illustrates the large number of compounds potentially available using our methodology.

4.2 Synthesis of 4-phenylpiperidines

Treatment of 3-butyn-1-ol (210) with 40 % w/v HBr in the presence of iron filings (see scheme 4.3) affords the vinylic bromide (211) in acceptable yield (43 %)[72]. The yield was actually higher but the major impurity (10-20 %) in the reaction was the dibromide compound. The dibromide was a useful compound in the sequence, since it already possesses a good leaving group in place of the alcohol. Following separation of the alcohol and the dibromide by column chromatography, the alcohol (217) was isolated in 49 % yield. The tosylate (212) could be reacted with a secondary amine to afford diene

(213) in 73 % yield. However it seemed more advantageous to convert alcohol (211) through to the dibromide, as opposed to separation of the two compounds. Although numerous conditions were investigated none of these proved suitable, as generally the isolated yield of the dibromide was poor (28 %).



Scheme 4.3 - Synthesis of 4-phenyl-piperidine.

The primary alcohol (211) was stirred with *para*-tolulenesulfonyl chloride in pyridine for 12 hours to afford the desired tosylate (212) in high yield (92 %). Alkylation of the secondary amine using the tosylate (212) afforded diene (213) in 73 % yield. Thus the key intermediate diene (213) is available in 3 steps from a cheap starting alcohol via a series of high yielding transformations. Diene (213) contains a vinylic bromide, which we felt would be amenable to palladium mediated coupling reactions, such as Suzuki or Stille, to afford the terminal alkene (215). We were surprised to discover that the coupling reaction with alkenyl halides incorporating nearby amine groups was not

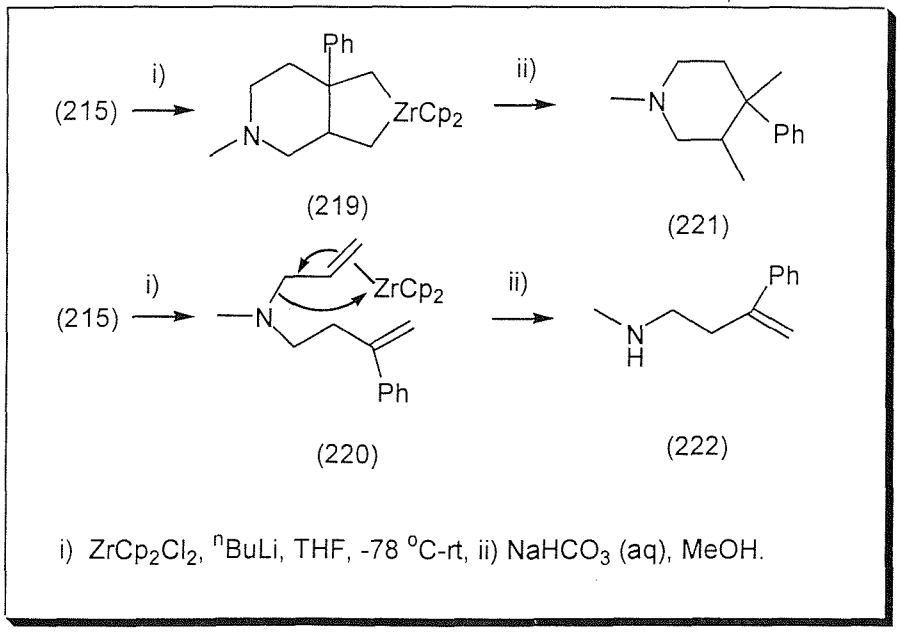
documented in the literature. We initially investigated Pd catalysed reactions between (213) and Phenylmagnesium bromide without success.

The Suzuki cross coupling reaction was investigated, it possesses has a number of advantages including the ease of purification and good functional group compatibility. Additionally a large number of boronic acids are available commercially thus allowing many analogues to be synthesised. Examination of the literature showed that no information was available on the coupling of vinyl bromides with nearby amine groups and boronic acids. We successfully developed conditions, utilising Na_2CO_3(aq) and heating to 70 °C, to accomplish the coupling reaction, which allowed us to synthesis compound (215) where R is a phenyl group (65 %). We were also able to synthesise the compound where the aryl group was a naphthyl group (68 %). Some work was carried out in an attempt to widen the scope of this reaction. As a result coupling was attempted using secondary amines, but although successful, the results proved to be unreproducible. It is believed that temperature is a key factor in this reaction as the product contains a large amount of palladium residues. All attempts to use a substituted aromatic boronic acid, such as *meta*-methoxyphenyl boronic acid failed. One reason for this may be that the boronate is soluble in the aqueous phase or is readily converted to a phenol which is water soluble. Some additional work using a variety of solvents should circumvent the problem.

4.3 Cyclisation to afford 4-phenyl piperidines

Cyclisation of the tertiary amine (215) to afford the 4-phenyl piperidine (217) is not trivial. Upon examination of the literature it is apparent that cyclisation of hindered terminal double bonds is technically challenging as only a few examples are reported (3 in total). Analysing the progress of the cyclisation reaction throughout using GC, GC-MS and NMR afforded many valuable insights into the reaction mechanism. For example GC-MS analysis of '$ZrCp_2Bu_2$' mediated cyclisation of (215) demonstrated that the major product of Zr cyclisation was the deallylated product (222) and that the desired

4PP (221) was not formed. The problem was that when the zirconocene-alkene complex (220) forms it reductively eliminates to afford the secondary amine (222).

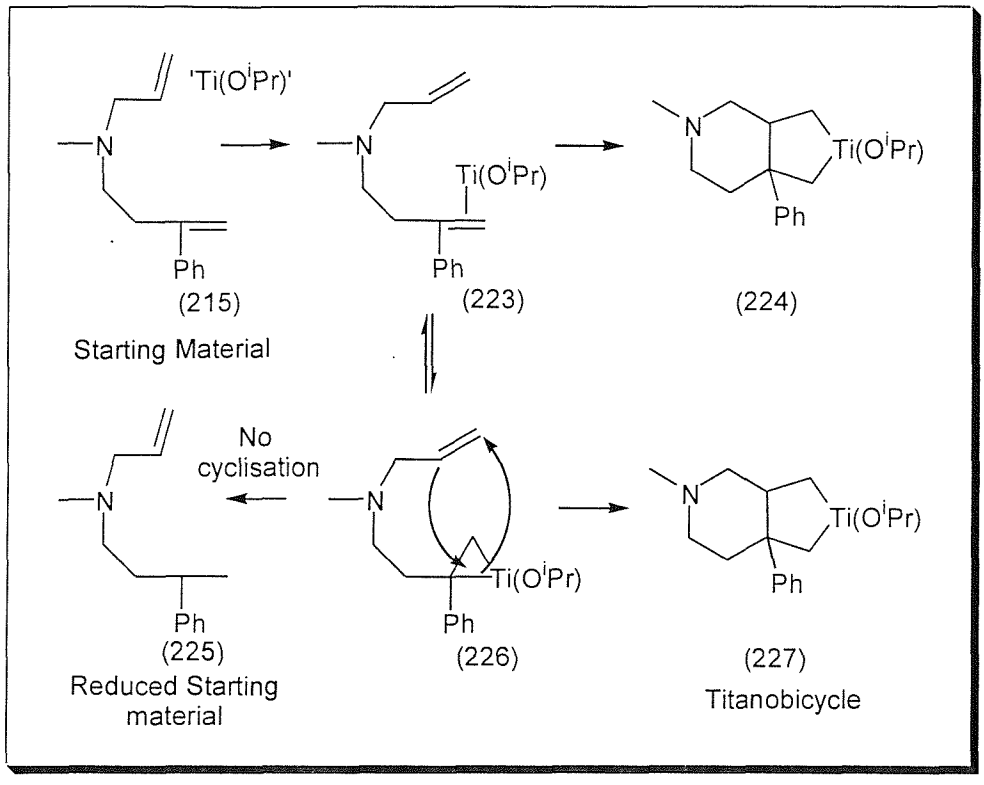


Scheme 4.4 - Problems associated with cyclisation.

Having demonstrated that $ZrCp_2$(1-butene) mediated cyclisation was incompatible with diene (215) alternative zirconium based strategies were sought. Examination of the literature suggested that the Livinghouse reagent may furnish the desired 4-phenylpiperidine (221). The Livinghouse reagent is zirconocene-(4-dimethylaminopyridine)$_2$ which is generated *in situ* by treating $ZrCp_2Cl_2$ with ^nBuLi at – 78 °C in the presence of 4-dimethylaminopyridine (DMAP). Upon warming an extremely reactive complex is formed *in situ* which would be expected to form the desired zirconabicycle (219). Unfortunately analysis of the reaction by GC showed that cyclisation did not proceed and a large number of by-products were formed including the deallylated compound (222). Optimisation failed to afford the 4-phenylpiperidine.

We next tried a titanium mediated cyclisation strategy using the Sato reagent[42]. The Sato reagent is generated at – 78 °C *in situ*, by stirring a solution of $Ti(^iOPr)_4$ with ^iPrMgCl in Et_2O for 1 hour. Following addition of the diene (215), the solution was

warmed to – 40 °C, generating diisopropoxy(η^2-propene)titanium. The Sato reagent is highly reactive and was kept between –40 °C and –30 °C for two hours. If the solution is too cold the reagent never forms and if the solution is too warm the cyclisation reaction does not proceed well as side reactions become favoured. Following the protocol described above and quenching the solution with MeOH/Na_2CO_3(aq)/Et_2O overnight, afforded the desired product (221) in 7 %. The organotitanium reagent did not cause deallylation of the starting material. Presumably the titanobicycle (226) forms extremely quickly and since it is relatively stable stays in solution until it is quenched. It is believed that modification of the conditions should allow the product to be isolated in higher yield.



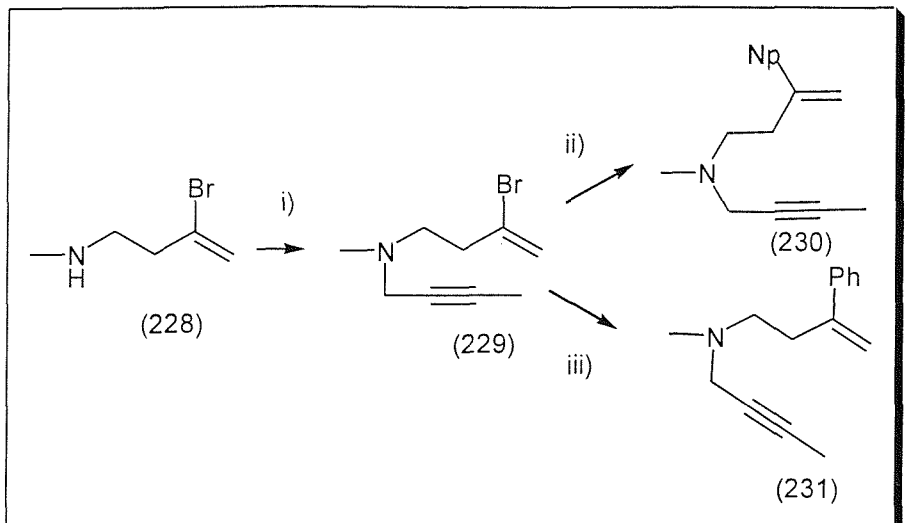
Scheme 4.5 - Titanium mediated cyclisation.

A zirconium catalysed cyclisation was also attempted using conditions developed by Mori[76]. The cyclisation was successfully applied to the synthesis of 3PP (287) [section 5.5], but failed to bring about cyclisation of diene (215). Only starting material was isolated after heating at 80 °C for 168 hours. Whilst researching this strategy it was noticed that Mori refers to a deallylation side reaction as stopping cyclisation.

Interestingly all successful 6 member ring cyclisations (reported in the literature) did not possess a methylated nitrogen and thus we decided to try a substrate with a benzyl nitrogen (216). We hoped that the carbon nitrogen bond in the benzyl system would not migrate as quickly as the corresponding bond in the *N*-methylated substrate. To our relief cyclisation proceeded with Negishi's reagent to afford the desired benzylated 4PP (218) [see scheme 4.3] but still in poor yield. More work is required to develop this cyclisation further but our methodology has been shown to afford the desired 4PP in reasonable yield using organozirconium chemistry.

4.4 Cyclisation of 4-phenyl piperidine from enynes

Although the organotitanium reagent cyclised diene (215) it was felt that the Sato reagent would be better suited to cyclisation of enynes as most Sato methodologies described in the literature are of enyne substrates. Thus enyne (230) was synthesised.

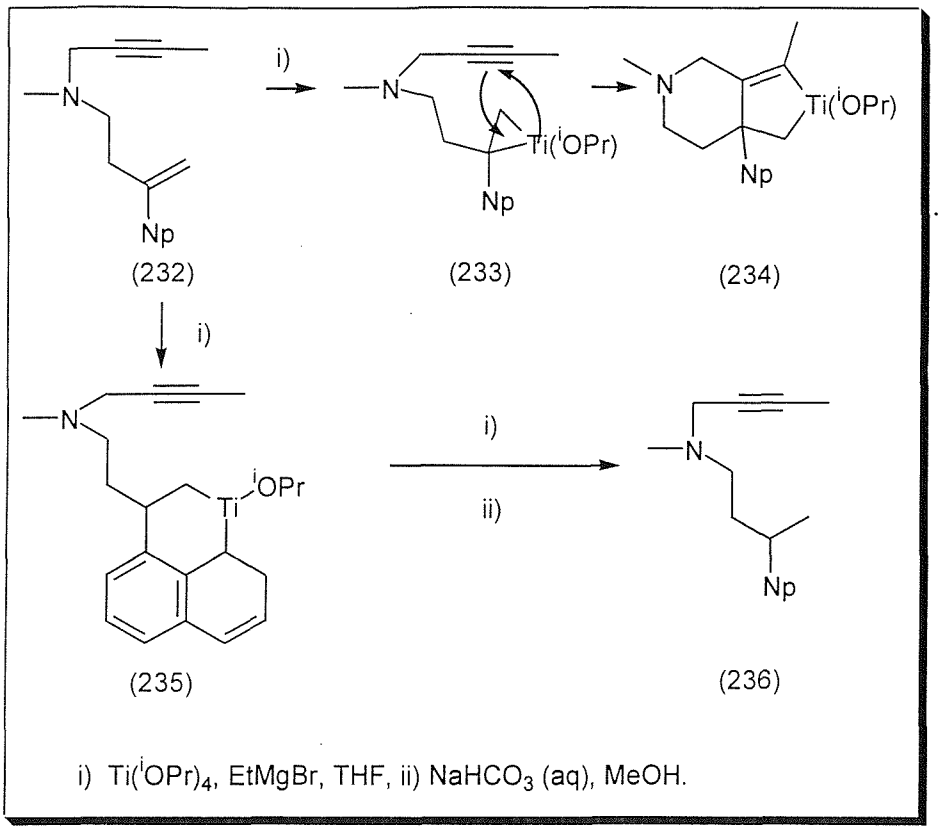


i) 2-butyn-1-mesylate, K_2CO_3, MeCN, ii) Naphthalene boronic acid, Pd^0, THF, Na_2CO_3, iii) Phenyl boronic acid, Pd^0, THF, Na_2CO_3.

Scheme 4.6 - Synthesis of a aryl enynes.

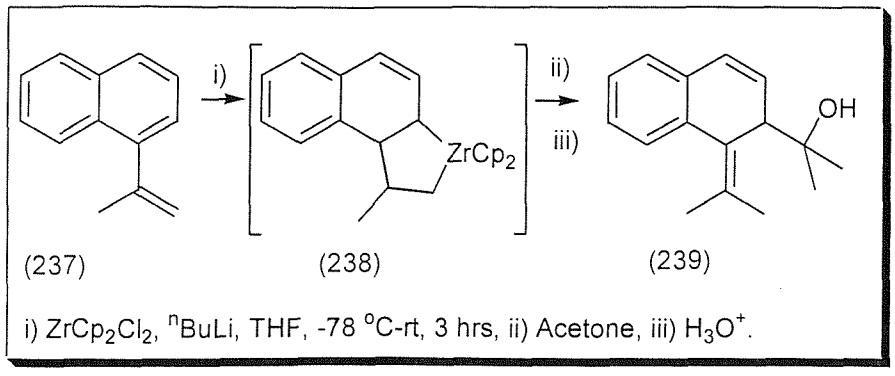
The synthesis of the secondary amine (228) was by alkylation of methylamine with tosylate (212) but isolation of the pure secondary amine could only be achieved in low yield. The enyne (229) was synthesised by forming the mesylate of 2-butyn-1-ol and reacting it directly with the crude secondary amine (228). Once synthesised the vinylic bromide (229) was substituted for an aromatic moiety (230 and 231). Cyclisation of both compounds (230 and 231) was attempted using the Sato reagent (see scheme 4.8) but poor yields from the Suzuki coupling reaction made detailed analysis difficult.

Unfortunately the major product of cyclisation only afforded reduced starting material (236), possibly due to the stability of the titanobicycle (235). It is also plausible that the desired titanobicycle (233) was not formed. It is believed that titanobicycle (235) is too stable and reductive elimination does not occur.



Scheme 4.7 - Titanium mediated cyclisation of enynes.

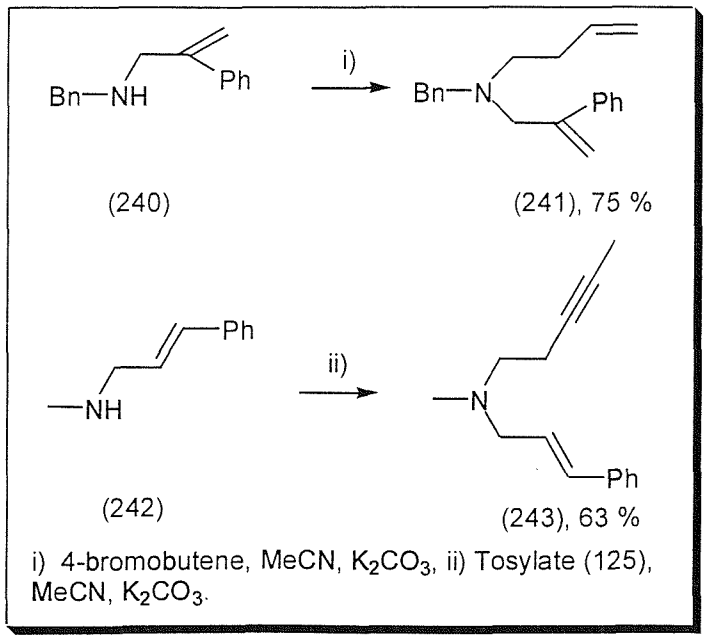
In an attempt to illustrate the stability of the metalobicycle (235), naphthalene derivative (237, 93 %) was synthesised by carrying out a Wittig reaction on the commercially available 2-acetonaphthalene. Cyclisation was attempted using Negishi's reagent in an attempt to form the desired compound (239). Analysis of the zirconabicycle proved inconclusive in both C_6D_6 and $CDCl_3$. In an attempt to prove the existence of zirconacycle (238) the intermediate was quenched with acetone. Unfortunately the acetone quench did not afford the desired alcohol and only the reduced starting material was isolated.



Scheme 4.8 - A naphthalene zirconabicycle.

4.5 Synthesis of 3-phenylpiperidine and 3-benzylpiperidine precursors

The secondary amine (240) was synthesised from benzylamine in 54 % yield. A second alkylation using 4-bromobutene afforded the desired diene (241) in 75 % yield.



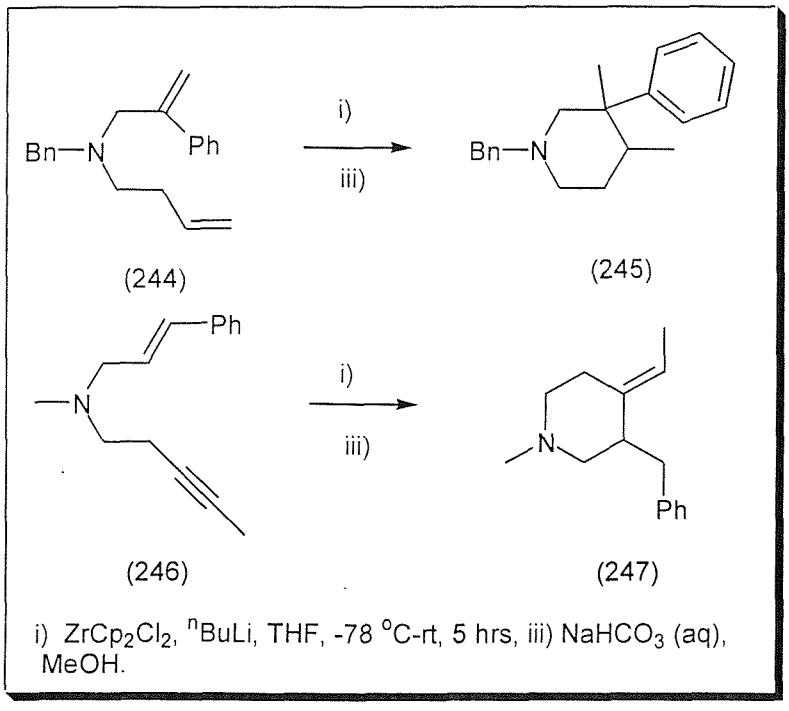
Scheme 4.9 - Synthesis of a diene and an enyne.

Secondary amine (242) was synthesised by the alkylation of methylamine with cinnamyl bromide which proceeded in good yield (75 %). Alkylation of (242) using the tosylate derived from 3-pentyn-1-ol afforded the desired enyne (243) in 63 % yield.

4.6 Cyclisation to afford 3-phenylpiperidines and 3-benzylpiperidines

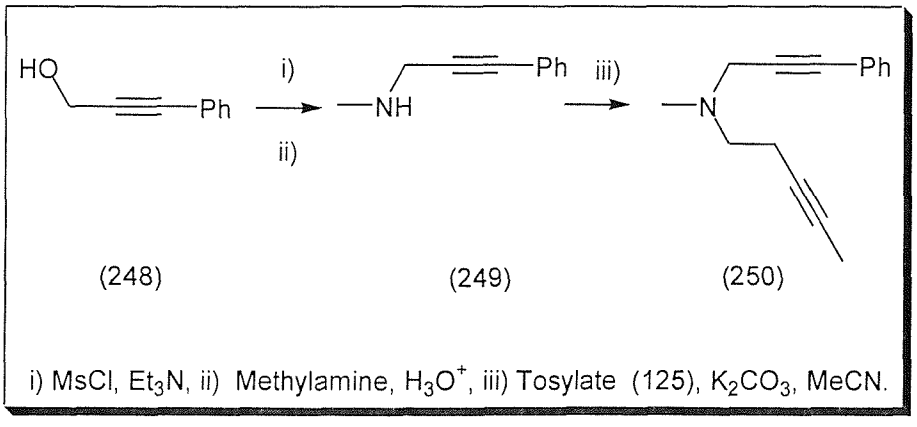
The synthesis of the 3-phenylpiperidine (245) proved challenging due to the low yield encountered at the co-cyclisation step. It was expected that enyne cyclisation would proceed in higher yield because the organozirconium would co-ordinate preferentially with the alkyne rather than the terminal alkene.

Diene (244) underwent intramolecular co-cyclisation using the Negishi reagent to afford the desired 3-phenylpiperidine (245) in poor yield (33 %). It was expected that cyclisation of enyne (246) to afford the 2-benzyl piperidine (247) would occur in higher yield. Unfortunately cyclisation did not proceed well with only 25 % conversion and the desired compound could not be separated from the other amine products.



Scheme 4.10 - Diene and diyne cyclisation.

4.6.1 Synthesis of 3-benzylidinepiperidine precursors

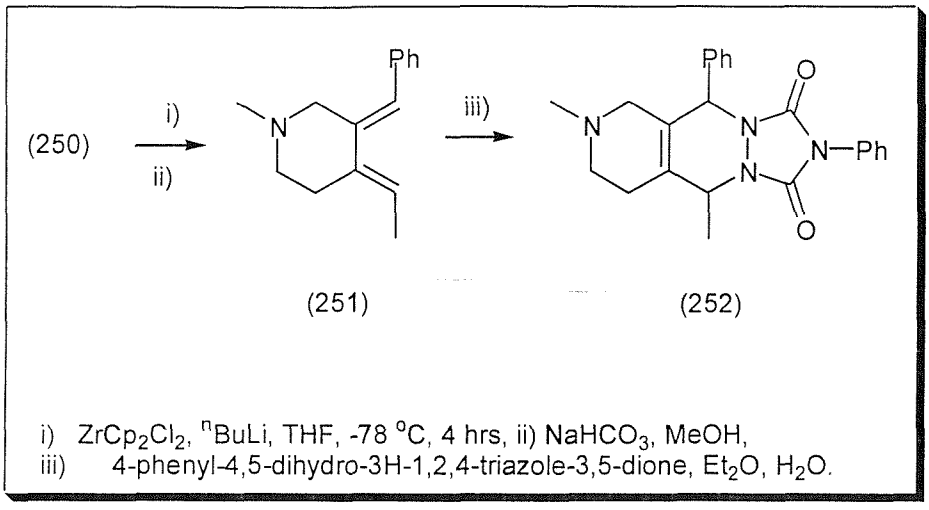


Scheme 4.11 - Synthesis of the benzylidine precursors.

Phenylacetylene was treated with ^{n}BuLi then quenched with paraformaldehyde to afford the desired alcohol (248) in good yield as a white solid. Conversion to the mesylate and alkylation using methylamine afforded the secondary amine (249) [scheme 4.11]. Tertiary amine (250) was synthesised from (249) using standard alkylation procedure in 75 % yield.

4.6.2 Cyclisation to afford 3-benzylidinepiperidine

Having only enjoyed limited success in the cyclisation of dienes and enynes to afford piperidines, it was hoped the comparatively electron rich diynes of the benzylidine series would prove to be superior cyclisation substrates.



Scheme 4.12 Cyclisation then DA elaboration.

The diyne (250) was cyclised using Negishi's reagent to afford the exocyclic diene (251) in 64 % yield. A further Diels-Alder elaboration afforded the adduct (252) in poor yield following chromatography. Analysis of the maleate salt confirmed the presence of the Diels Alder adduct (252). No further time was spent on this series.

4.7 Conclusion

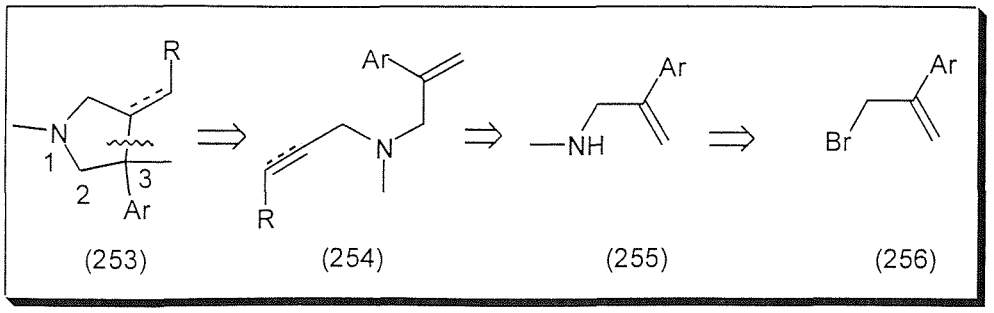
The preceding chapter has discussed the synthesis of the 4PP pharmacophore. Suzuki reaction conditions have been successfully developed allowing coupling of an aromatic boronic acid vinylic bromide with a nearby amine. Cyclisation to afford 4PP's was shown to be optimal when the amine was protected with a benzyl group, but in poor yield. An exeption was diyne cyclisation. Our work has demonstrated that the Suzuki coupling route offers numerous advantages in that it allows a variety of 4PP's can be synthesised from a common vinylic bromide intermediate.

CHAPTER 5

ZIRCONIUM MEDIATED SYNTHESIS OF SUBSTITUTED PYRROLIDINES

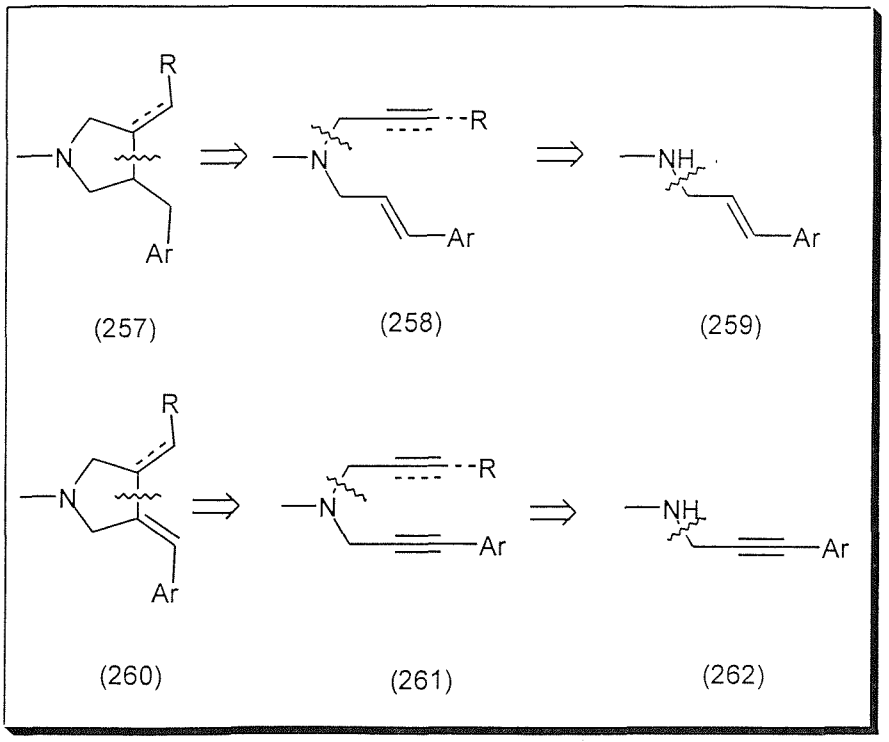
5.1 Retrosynthesis of the pyrrolidines

As described previously (section 1.15) the 3-phenylpyrrolidines have generally been prepared from benzyl cyanides in 4 or 5 steps. Overall synthesis from benzyl cyanides is not ideal as it uses a number of reagents that are undesirable in modern syntheses. The retrosynthetic route (scheme 5.1) takes advantage of the ability of organozirconium reagents to cyclise amino dienes/enynes to afford pyrrolidines.



Scheme 5.1 - Disconnection to afford 3PP's.

The 3PP (253) can be synthesised by two routes from the readily available tertiary amine (254) using organozirconium chemistry. 3PP synthesis from the tertiary amine has the additional advantage that the aryl group can be varied, thus allowing a number of analogues to be synthesised. The ability to vary the aromatic moiety is advantageous since previous SAR data implies that the substitution of the β-phenyl is crucial in obtaining biological activity. The primary amine (255) can be synthesised from the vinylic aromatic compound (256).

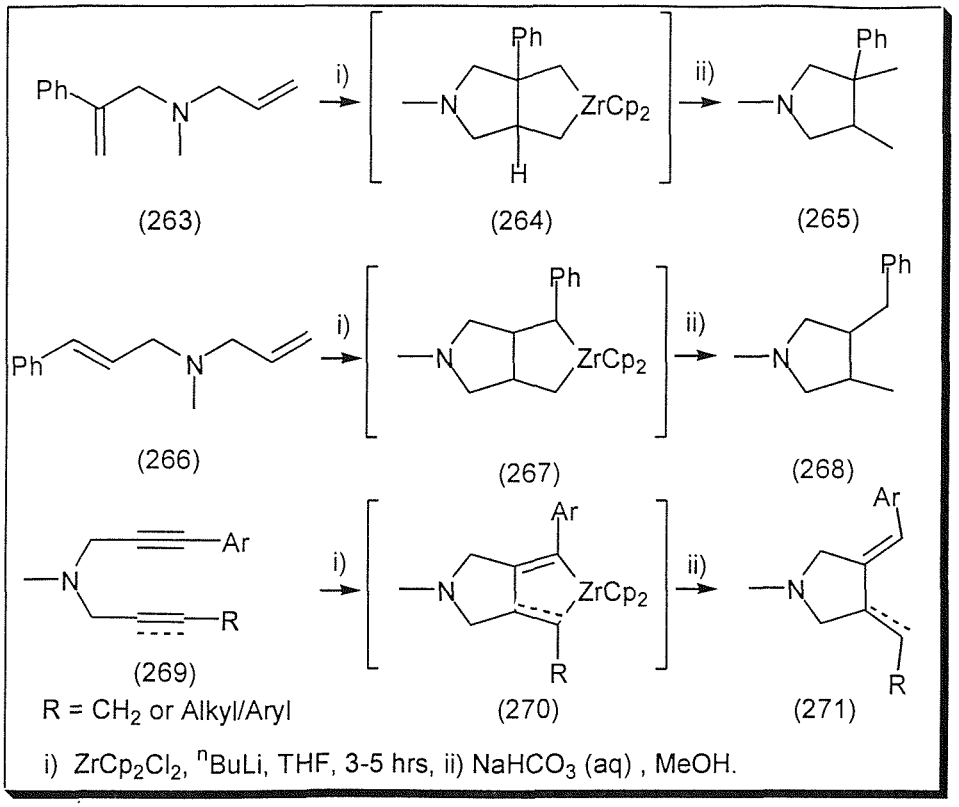


Scheme 5.2 - Disconnection to afford 3BP's and 3BzP's.

The 3BP (257) was prepared in an analogous manner to the 3PP (253). The cyclisation precursor (258) was prepared by alkylation of the secondary amine (259). An alternative structure available using organozirconium chemistry are the 3-benzylidinepyrrolidine (3BzP). Synthesis of the secondary amine (262) can be envisioned using Sonagashira chemistry to form a propargylic alcohol, followed by alkylation then displacement with an amine. Subsequent alkylation of amine (262) should afford the tertiary amine (261).

5.2 Synthesis using organozirconium

Scheme 5.3 illustrates the forward synthesis of three types of pyrrolidine molecule using organozirconium reagents. The zirconabicycle (264) can be formed from diene (263) by zirconocene co-cyclisation. Following protonation the 3PP (271) is given. Similarly, zirconabicycle (267) can be protonated to afford the 3BP (268). The diene or enyne (269) underwent cyclisation using Negishi's reagent to afford the zirconabicycle (270), which upon protonation affords the 3BzP (271) [see section 5.3].



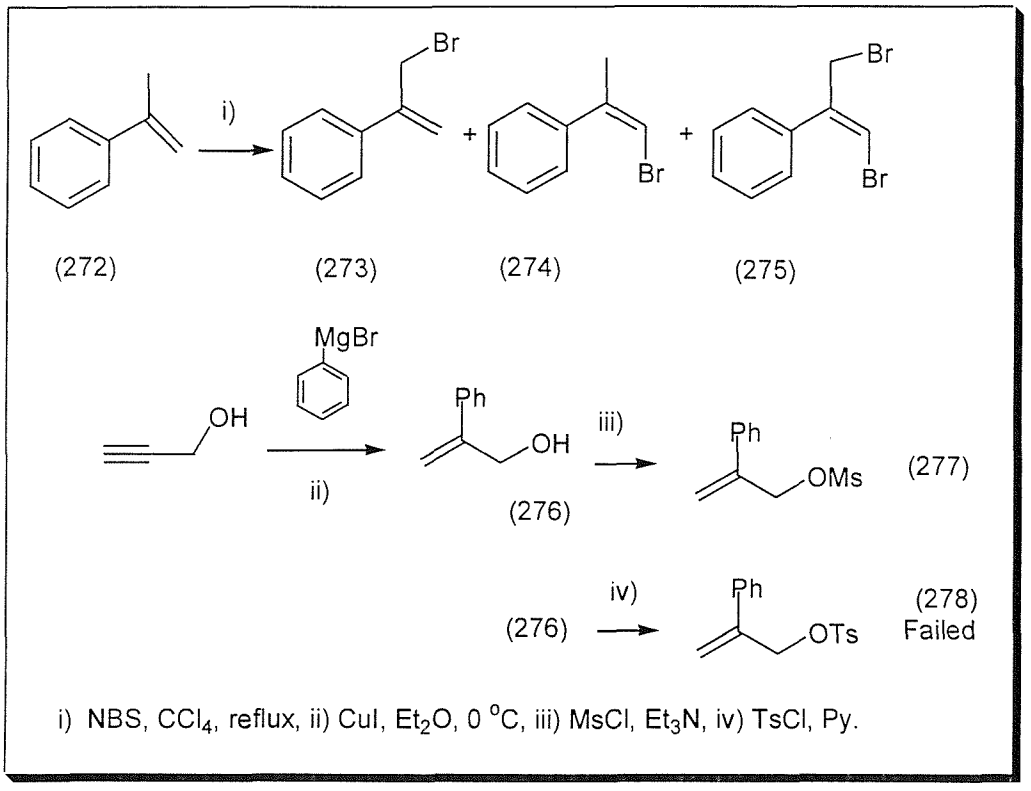
Scheme 5.3 - Organozirconium based synthesis.

The 3BzP's such as (271) have the advantage that Diels-Alder elaboration is possible on the exocyclic diene. Additionally copper mediated cycloaromatisation can also be envisioned from zirconocycle (270). The results and discussion section will be split into 3 sub-sections based upon the three substructures, the 3-phenyl pyrrolidines, 3-benzyl pyrrolidines and 3-benzylidine pyrrolidines.

5.3 Synthesis of 3-phenylpyrrolidine precursors

In order to synthesise 3PP's it was necessary to prepare intermediate bromide (273) on a large scale. One simple method of preparing (273) involves radical bromination of α-methylstyrene (272). The reagents were refluxed overnight within strict ratios of styrene (2 eq.) and *N*-bromosuccinimide (NBS, 1 eq.). Failure to observe these restrictions resulted in the formation of approximately 40 % undesired by products (274) and (275). Somewhat unfortunately bromides (273) and (274) are inseparable by column

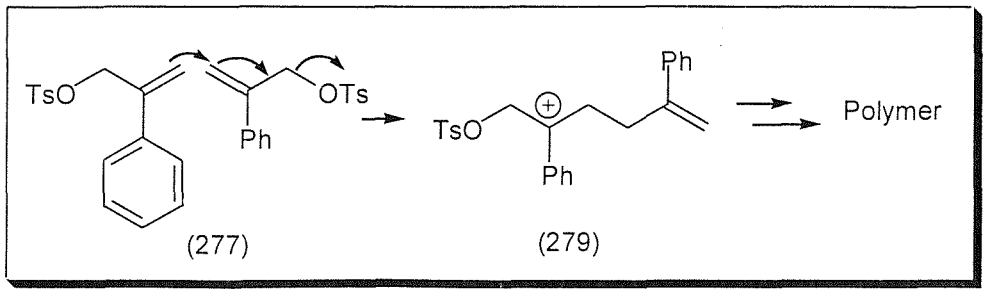
chromatography and Kugelrohr distillation. For this reason the crude bromides were further reacted with methylamine, and the resulting secondary amine (280) purified. Using literature procedure and NMR data as a guide to the composition of the crude mixture, the reaction mixture contained at least 70 % of the desired bromide (273). The dibromide (275) was observed but could be separated from the desired bromide using column chromatography.



Scheme 5.4 - Attempted synthesis of allylic alkylating agents.

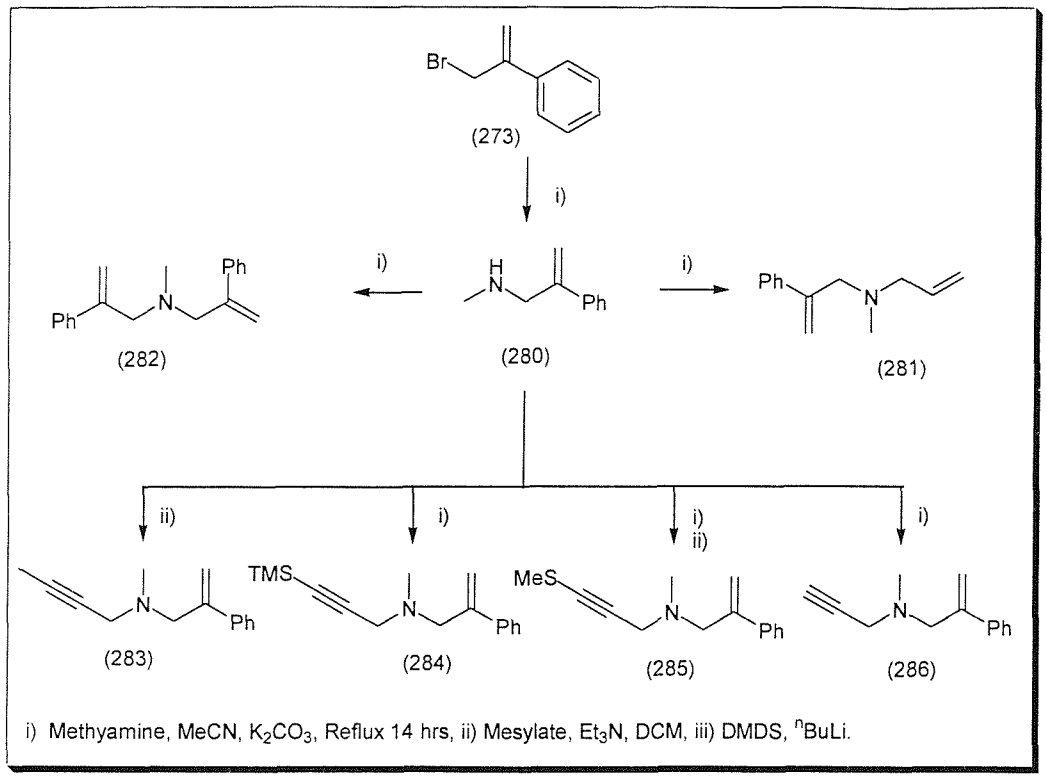
Another method of synthesising the desired terminal alkene (276) involved the addition of an organocuprate to 2-propyn-1-ol. Conversion of the alcohol to a tosyl/mesyl group (277 and 278) and subsequent alkylation would result in the secondary amine (280). This route avoids the purification problems associated with bromination of α-methyl styrene. One advantage of this method, other than ease of purification relative to bromination of α-methylstyrene, is that substituted phenyl groups can be introduced easily, whereas substituted α-methylstyrenes are not readily available. Unfortunately conversion of the

alcohol to a leaving group proved problematic. All attempts to utilise the tosylate or mesylate (277 or 278) were unsuccessful. The reason for this may be that tosylate and mesylate are displaced to form a quaternary ammonium salt (pyridine or triethylamine) however it is more likely that (277) polymerises spontaneously under the reaction conditions (scheme 5.5).



Scheme 5.5 - Possible polymerisation of tosylate.

Cross-coupling reactions using using phenylboronic acid and vinylic bromides with a proximal nitrogen but failed when attempted with substituted boronic acids (containing methoxy groups). Overall it proved easier to synthesise alkene (280) using the bromide (273) derived from the radical bromination of α-methylstyrene.



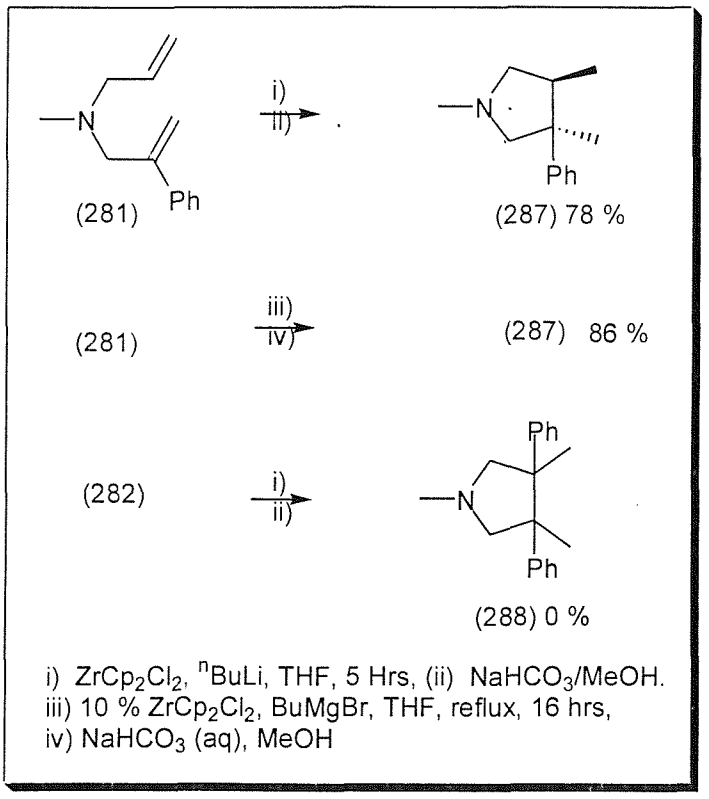
Scheme 5.6 - Synthesis of precursors.

The secondary amine (280) was synthesised from the crude bromide (273) in 50 % overall yield. The secondary amine was then alkylated with allyl bromide to afford diene (281) in 73 % yield. Bis-alkylated diene (282) was isolated as a by-product in the synthesis of secondary amine (280). Enyne (283) was synthesised by alkylation using 1 equivalents of amine (acting as reactant and base) with 1 equivalent of TMS propargyl bromide. When no secondary amine was visible the reaction was worked up using basic conditions then another equivalent of bromide was added. This afforded the desired tertiary amine (284). The terminal alkyne (286) was synthesised by alkylation of (280) with propargyl bromide and proceeded in 73 % yield. The mesylate of 2-butyn-1-ol was used to alkylate amine (280) to afford the desired enyne (283) in 71 % yield.

5.4 Cyclisation to afford 3-phenylpyrrolidine's

Diene (281) was cyclised using Negishi's reagent to afford the desired 3PP (287) in 78 % yield. Interestingly, if cyclisation is carried out for 14 hours, only one isomer is isolated

after protonation. However, if it is quenched after 6 hours, a 3:1 mixture of isomers is isolated. The 3PP (287) was also synthesised using a catalytic cyclisation reaction developed by Mori using 10 mol % $ZrCp_2Cl_2$ and 10 equivalents of butylmagnesium bromide and afforded the *trans* 3PP (287) in 86 % yield (see section 2.4.2 for discussion).

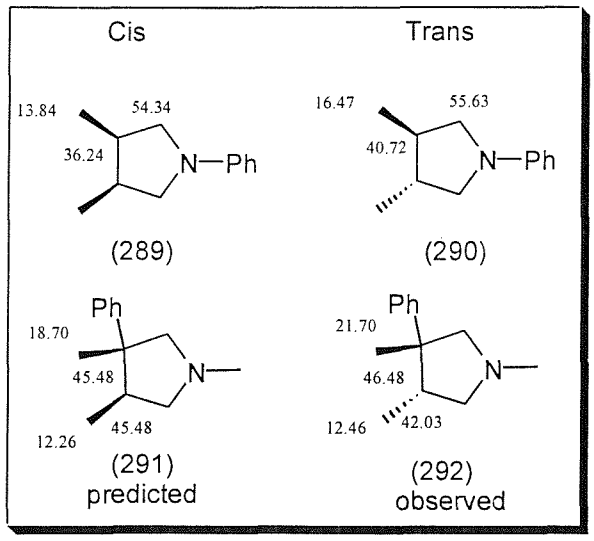


Scheme 5.7 - Diene synthesis and cyclisation.

The bis-alkylated tertiary amine (282) was isolated as a byproduct in the synthesis of (280). Unfortunately intramolecular co-cyclisation with Negishi's reagent did not afford the desired pyrrolidine (288). This was presumably due to unfavourable steric encumbrance caused by the two phenyl groups interacting, probably stopping formation of the intermediate zirconabicycle.

5.5 Stereochemistry of the 3-phenylpyrrolidine's

The stereochemistry of the cyclised compounds can be determined using previously cyclised compounds and the gamma-gauche effect. The cyclised compound (289) and (290) were prepared by Whitby[56]. Using the data outlined above, in conjunction with NMR data, and utilising a number of physical effects particularly the gamma-gauche effect the stereochemistry of the product was determined experimentally. Analysis by carbon NMR yielded the following data (scheme 5.8).

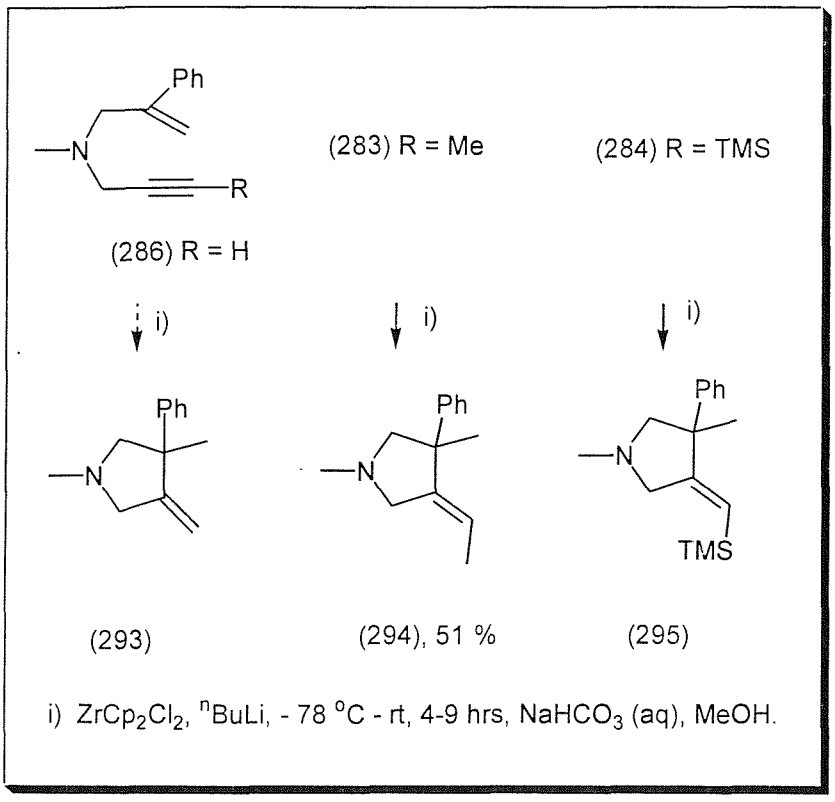


Scheme 5.8 - *Cis* and *trans* 3BP's and 3PP's.

Clearly the methyl groups in the two isomers (289 and 290) are in very different environments, as evidenced by the carbon NMR spectrum due to the gamma gauche effect. Using carbon NMR it can be seen that the methyl groups in the unsymmetrical *cis* 3PP (291) lie in a different environment to the methyl groups in the *trans* 3PP isomer (292). Clearly the isolated compound (292) is the *trans* isomer. The chemical shifts show excellent agreement with those published[56]. Furthermore the data presented for the azepine in section 3.3 concurs with these observations.

5.6 Cyclisation of enynes to 3PP's

Following the successful cyclisation of diene (286) to afford the desired 3-phenylpyrrolidine (292) a number of exocyclic alkenes were synthesised from enynes. Cyclisation of enyne (283) afforded the desired exocyclic alkene (294) in 51 % yield. Cyclisation of enyne (286) was expected to proceed well, however following protonation of the zirconacycle and subsequent purification, the desired TMS alkene (293) was not isolated.

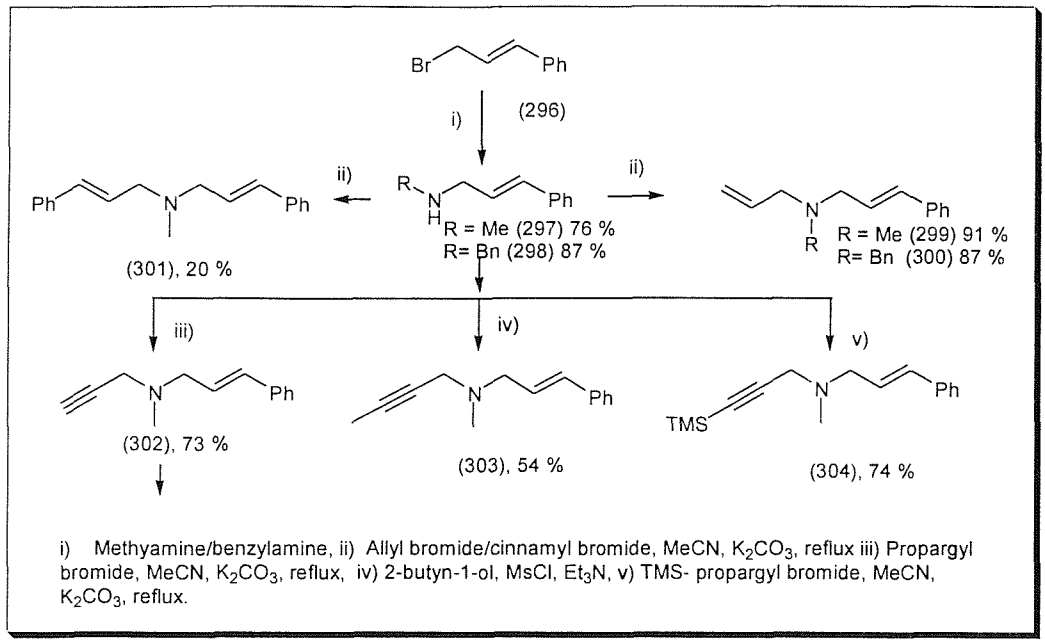


Scheme 5.9 - Enyne synthesis and cyclisation.

Although no starting material remained (284) the product of the reaction appeared to be the terminal alkene (293) in low yield. This result was surprising in light of the 3BP (304) case where the exocyclic TMS alkene (322) was isolated in 61 % yield (see scheme 5.16).

5.7 Synthesis of precursors for 3-benzyl pyrrolidines synthesis

Following exhaustive searches it was noticed that 3-benzylpyrrolidines (3BP's) have received no attention as potential drug candidates, in the published literature. Cyclisation of cinnamyl containing dienes (such as 299), derived by alkylation of amines (297 and 298) with a cinnamyl halide (296) and utilising organozirconium chemistry is a convenient route to 3BP's. The methodology described in section 5.11 also has the advantage that a large number of cinnamyl fragments are available cheaply. The secondary amine (297) was synthesised from methylamine and cinnamyl bromide (296) in good yield (76%). The benzyl alkene (298) was synthesised in 87 % in the same way as the *N*-methyl amine (297). The *bis* amine (301, 20 %) was isolated as a byproduct in the synthesis of (297).



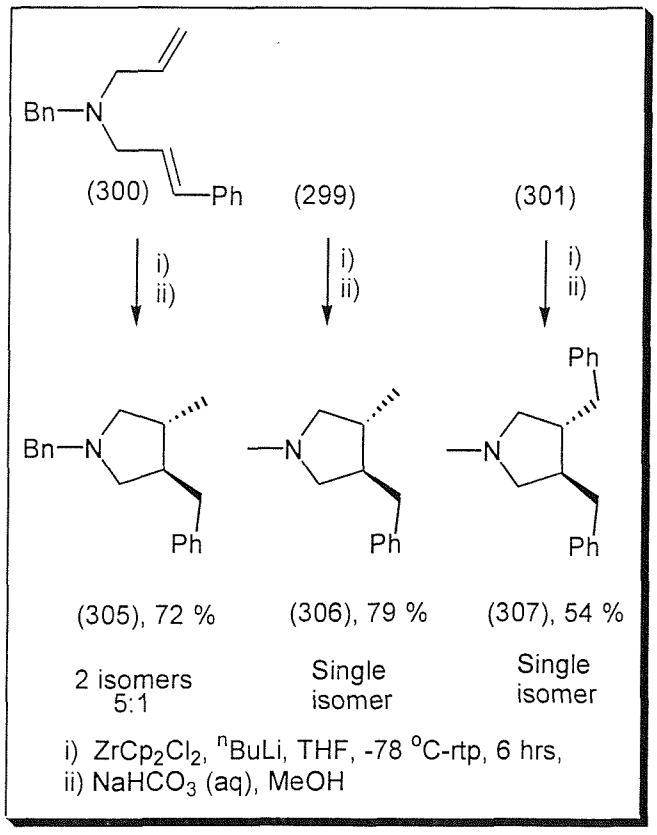
Scheme 5.10 - Diene and enyne synthesis.

Secondary amine (297) was converted to the tertiary amine (299) by reaction with allyl bromide at 0 °C, using two equivalents of amine (acting as base and reactant), warming to room temperature and working up using basic conditions. The crude mixture was then reacted again with another equivalent of allyl bromide to afford the desired diene (299,

91 %). This unusual method was found to be the most efficient method for conversion of (297) to the desired tertiary amine (299). This recycling approach saved a large amount of time as continual recovery of the starting material, subsequent purification and further reaction was unnecessary. Diene (300) was synthesised in a similar manner. Enyne (302) was synthesised from the alkylation of secondary amine (297) with propargyl bromide in 73 % yield. Enyne (303) was prepared by alkylation of (297) using the mesylate of 2-butyn-ol to afford the desired enyne in 54 % yield. Enyne (304) was isolated in 68 % following alkylation with TMS-bromide.

5.8 Cyclisation of dienes to afford 3BP's

Cyclisation of tertiary amine (300) through to the desired benzyl pyrrolidine was carried out successfully, using Negishi conditions, to afford the final compound (305, 72 %). The 3BP (305) was shown to be a mixture of isomers, which upon examination was found to be 5:1 *trans*:*cis* (described in next section). Diene (299) was cyclised using Negishi's reagent to afford the 3BP (306) as a single isomer. The *bis* tertiary amine (301) was cyclised using standard Negishi conditions, to afford the 1,3,4-trisubstituted pyrrolidine (307) in 54 % yield. This was an unexpected result since cyclisation of the bis-alkylated diene (282) failed to give the desired 3PP (288).

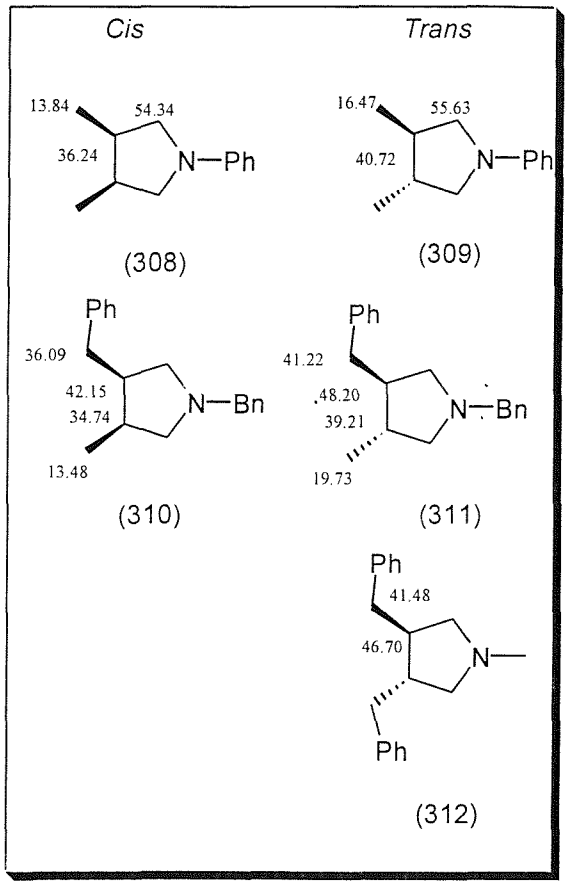


Scheme 5.11 - Cyclisation of dienes.

The successful cyclisation of (299) was unexpected as few examples have been reported of hindered dienes undergoing cyclisation using organozirconium reagents have been achieved. It seems likely that the extra activation of the alkene, due to the presence of the phenyl groups, more than compensates for the steric constraint associated with the bulky groups.

5.9 Stereochemistry of 3-benzylpyrrolidine's

Cyclisation of the diene (300) afforded a 5:1 mixture of diastereomers, using the gamma gauche effect this was shown to be in favour of the *trans* isomer (305). As stated in scheme 5.12 both diene (299) and (301) afforded a single isomer products (306) and (307) which were assigned as the *trans* isomers using carbon NMR. See scheme 5.12 for an overview of the data.

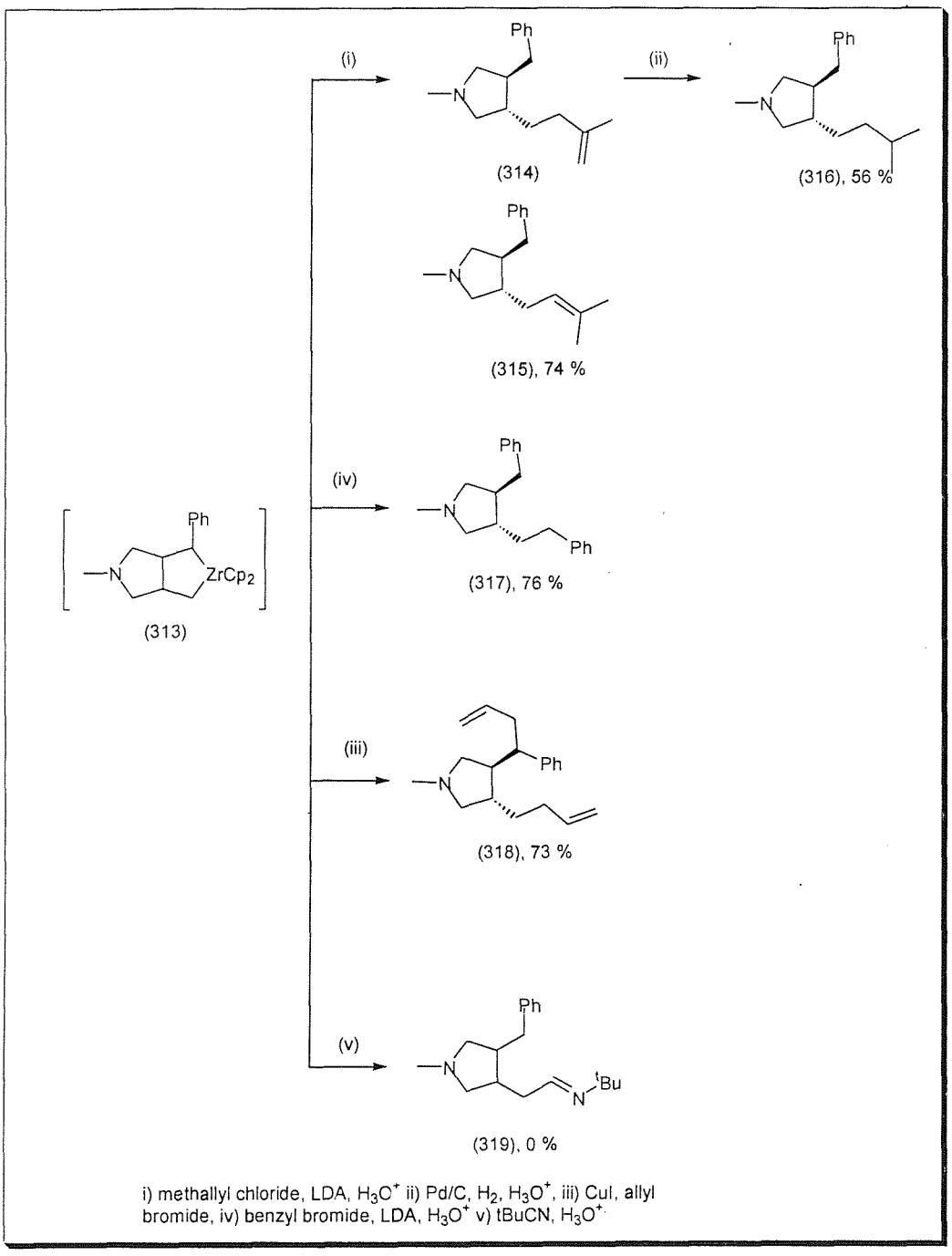


Scheme 5.12 - Stereochemical data.

5.10 3-Benzylpyrrolidine's zirconacycle elaboration

A number of zirconabicycle elaborations were attempted using the zirconacycle (313) derived from diene (299). The carbenoid insertion illustrated in scheme 4.16 using methallyl chloride was carried out successfully to afford the desired product. This elaboration could only be carried out using LDA as the base, as Li-TMP failed. The carbenoid insertion afforded two regioisomers (314) and (316) in a 1:1 ratio in 74 % yield. This mixture of products arises due to differential protonation of the allyl zirconacycle intermediate. The mixture of products was converted to a single compound using hydrogenation to afford (315). Carbenoid insertion of benzyl chloride was also successful and afforded the desired compound (317) in 76 % yield. Using 2 equivalents of Li-benzyl bromide afforded only the mono-inserted product (317). Insertion only

occurs in the least hindered bond suggesting that steric factors dominate which side the carbenoid inserts.



Scheme 5.13 - Elaboration's of 3BP's.

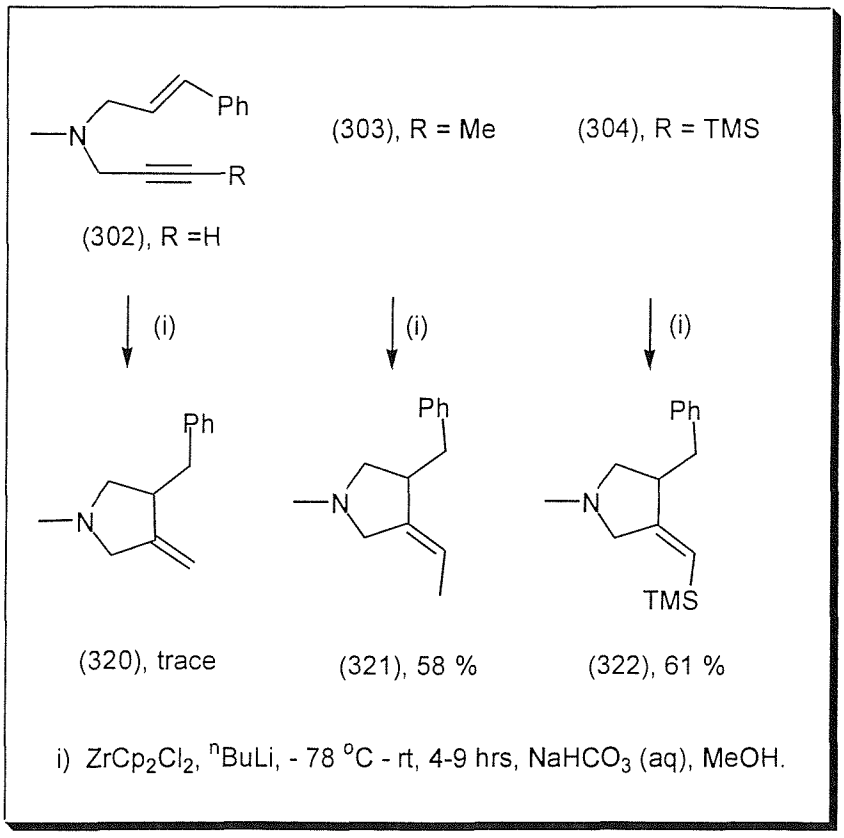
Treatment of the zirconacycle (313) with ^{t}BuCN did not afford the expected imine (319), with only the protonated compound (306) being isolated. The zirconabicycle (313) was

formed *in situ* using standard Negishi conditions, transmetallated to the dicuprate then quenched using allyl bromide to afford the diene (318) in 73 % yield.

5.11 Cyclisation of enynes to afford 3BP's

Having successfully cyclised a number of dienes to afford 3BP's, and performed a series of zirconabicycle elaborations, a number of enyne precursors were now cyclised. It was expected that these enynes would cyclise successfully to afford novel exocyclic alkenes. Once again these were synthesised from the key secondary amine (297) using standard alkylation techniques (see scheme 5.10).

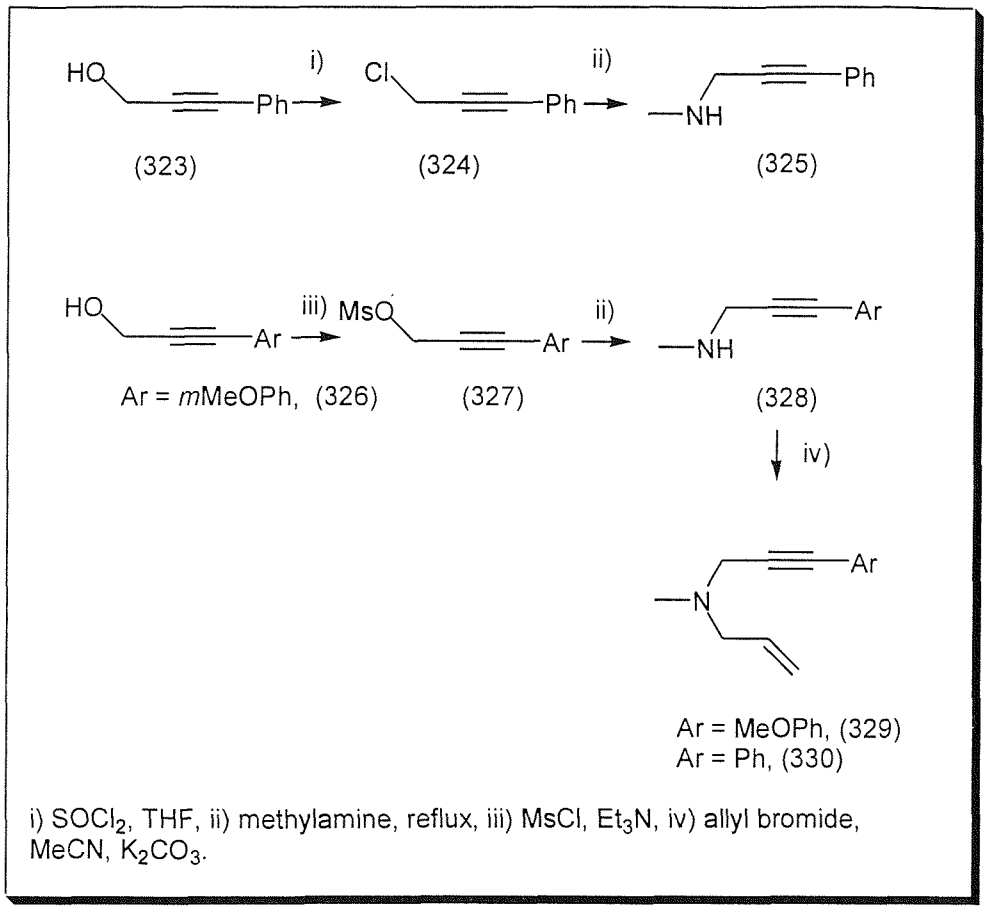
Terminal alkyne (302) did not cyclise using Negishi cyclisation conditions, to yield the desired exocyclic alkene (320). The reason for failure was that the terminal proton on the alkyne was too acidic and to combat this the trimethylsilyl derivative (304) was synthesised. Enyne (304) underwent intermolecular co-cyclisation to afford the desired exocyclic alkene (322) in 61 % yield. This result is in contrast to the 3PP equivalent where the alkene (295) proved too unstable to isolate. Enyne (303) was cyclised to afford the desired exocyclic alkene (321) in 58 % yield.



Scheme 5.14 - Cyclisation of enynes.

5.12 Synthesis of precursors for 3-benzylidinpyrrolidine's

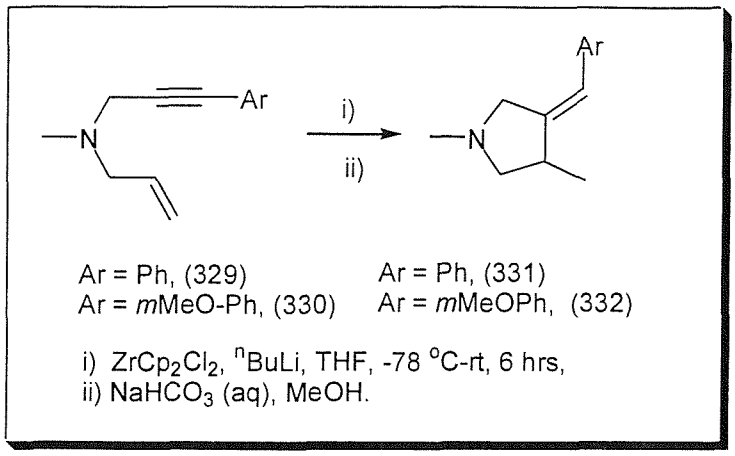
However it was our intention to develop a synthesis that allowed a number of substituted aromatics to be produced. Towards this aim a Sonagashira coupling was used to synthesise alcohol (326), from *meta*-methoxy aromatic iodide and coupled to propargyl alcohol in 65 % yield. The reaction using Ar-Br failed to afford the desired compound. Conversion of the alcohol to the mesylate *in situ*, and alkylation with methylamine afforded the secondary amine (328) in 75 % yield. Enynes (329) and (330) were synthesised by alkylation of the appropriate secondary amine with allyl bromide. It is worth pointing out that all attempts to carry out the Sonagashira coupling using a tertiary propargyl amine failed presumably due to the basicity of the nitrogen disrupting the reaction sequence.



Scheme 5.15 - Benzylidine precursor synthesis.

5.13 Cyclisation of enynes to afford 3-benzylidinpyrrolidine's

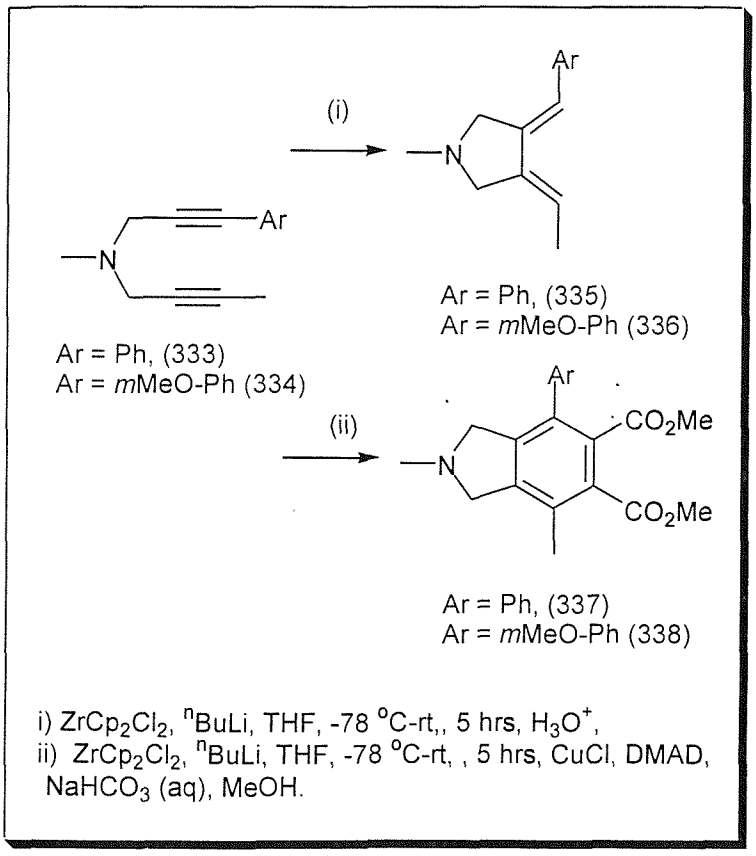
Enyne (329) was cyclised to afford the desired 3BzP (331) in 64 % yield. Enyne (330) which contains a *meta*-methoxy arene was shown to undergo cyclisation to afford the desired *meta*-methoxy 3BzP (332) in 78 %. This methodology has demonstrated the suitability of this synthetic route in the synthesis of a number of potentially neuroactive compounds. It is ideally suited to the synthesis of a number of analogues, where the aromatic group and/or the group attached to nitrogen is varied e.g. in an SAR study.



Scheme 5.16 - Synthesis of benzylidines.

5.14 Cyclisation of diynes to afford 3-benzylidin-4-alkylidine

Diyne (333) successfully underwent intramolecular co-cyclisation with Negishi's reagent to afford the expected *cis* exocyclic diene (335) in 78 % yield. Furthermore diyne (334) underwent co-cyclisation to afford the exocyclic diene (349). Diyne (333) was cyclised using standard Negishi conditions to afford the zirconabicycle which then underwent copper mediated cycloaromatisation to afford the substituted benzene (337). Unfortunately the final compound co-eluted with a polyamine adduct which could not be separated by chromatography. The adduct (337) was converted to the maleate salt and its presence was confirmed by mass spectroscopy.



Scheme 5.17 - Elaboration of benzylidines.

5.15 Conclusion

In the preceding chapter the synthesis of a number of 3PP and 3BP has been described using organozirconium chemistry. A number of zirconabicycle elaborations have been successfully carried out to afford novel 3BP's. A Sonagashira coupling procedure has been utilised to furnish a meta methoxy substituted pyrrolidine. Overall aromatic substituted alkynes have been shown to undergo co-cyclisation and afford benzylidines in good yield.

Chapter 6

6 Experimental section: General notes

6.1.1 Air and moisture sensitive compounds

All reactions carried out in this PhD involving organometallic intermediates or other air/moisture sensitive compounds were carried out under an argon atmosphere using standard Schlenk and syringe techniques. The argon was pre-dried by passage over 4 Angstrom molecular sieves. All apparatus was dried in a hot oven (150 °C, >12 Hrs) before either cooling in a sealed dessicator over silica gel, or assembling while hot and cooling under vacuum (0.1 mm Hg).

6.1.2 Spectroscopic Instrumentation

NMR spectra (both ^{1}HNMR and ^{13}CNMR) were recorded on either Bruker AM300 (300 MHz proton, 75 MHz carbon) or Bruker DPX400 (400 MHz proton, 100 MHz carbon) Fourier Transform spectrometers. Unless otherwise specified all spectra were recorded in deuterochloroform (stored over K_2CO_3) and referenced to the residual chloroform peak at 7.27 ppm (^{1}HNMR) and 77.27 (^{13}CNMR). Chemical shifts are given in units of ppm on the δ scale and coupling constants (J) are given in Hertz (Hz). When quoting proton NMR the following abbreviations are used to denote multiplicity and signal morphology: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; fs, fine splitting; m, multiplet. Carbon NMR, unless otherwise stated, were run proton decoupled and are quoted as: C, quaternary; CH, tertiary carbon; CH_2, secondary carbon; CH_3, primary carbon. The number of attached protons being determined using DEPT (Distortionless Enhancement by Polarisation Transfer) NMR experiments. Additionally 2D correlation experiments, were recorded on either the Bruker AM300 or Bruker DPX400, and were used to conclusively assign complex spectra, these have not been recorded individually in this section. Each signal in the proton NMR is assigned in the following manner: chemical shift (number of protons, coupling constant, proton assignment). The numbers quoted for

the molecule's proton assignment are for NMR identification purposes only and do not necessarily correspond to the molecules IUPAC name. Each signal in the carbon NMR is assigned in the following manner: chemical shift (multiplicity, carbon assignment). When diastereoisomers are quoted and each are distinguishable by carbon NMR these are quoted as major and minor isomers, unless otherwise stated these were not isolated as distinct compounds.

Infrared spectra were recorded on a Perkin-Elmer 1600 series FTIR instrument, carried out as neat films (for oils) or as solutions in dichloromethane. Absorptions are given in wavenumber (cm^{-1}) and are reported as follows: s, strong; m, medium; br broad; w, weak.

Low Resolution Mass Spectrometry (LRMS) was recorded on a Micromass platform quadrupole mass analyser using an electrospray ion source. The instrument was calibrated with a mixture of sodium and caesium carbonate. Atmospheric Pressure Chemical Ionisation (APCI) was carried out where indicated. High Resolution Mass Spectrometry (HRMS) was recorded on a VG Analytical 70-250-SE double focusing mass spectrometer. Perfluoroketone was used to calibrate the mass spectrometer before high resolution electron ionisation analysis. Data acquired by mass spectrometry (m/z) are reported in atomic mass units followed by the observed peak and assignments where obvious.

X- Ray analysis was carried out at Southampton University by the EPSRC National Crystallography Service using Enraf Nonius KappaCCD area detector and SHELXS86 to solve the structure.

Melting points were recorded using Griffin melting point apparatus and the figures are uncorrected. Microanalysis was carried out by the Microanalytical Department, University College London. All compounds named in this thesis were named using ACD labs software using standard IUPAC nomenclature

6.1.3 Reagent purification

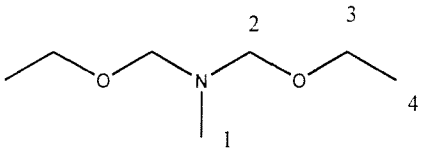
Unless otherwise stated materials were obtained from commercial suppliers, the purity being checked by NMR prior to use, then used without further purification. THF was distilled from sodium/benzophenone and petroleum ether (b.p 40-60 ° C) was distilled through a Vigreaux column prior to use. HMPA and chlorinated solvents were distilled from calcium hydride and stored under argon. When Grignard reactions were carried out, magnesium was activated by washing sequentially with 0.1 M HCl, water, ethanol and diethyl ether then dried for 2 hours at 100 °C. Prior to use the magnesium was stirred, under argon, vigorously for 12 hours.

6.1.4 Chromatography

Thin layer chromatography (t.l.c.) was carried out on 0.25 mm Kieselgel 60 G UV_{254} precoated aluminium foil or plastic plates and visualised with a 254 nm UV lamp followed by Iodine dip (55 g iodine in 50 g silica), phosphomolybdic acid (12 g, in 150 mL EtOH) or sulphuric acid (5 %, v/v in MeOH). Column chromatography on silica used Kieselgel 60 (230-400 mesh) silica gel, columns were packed and run under light pressure. Alumina columns, were run where indicated, using Brockman grade III alumina (commercial grade I, deactivated using 6 % w/w distilled water) and packed and run without light pressure. In the text, chromatography eluants are described as % volumes.

GC analysis was carried out using the following programme conditions: 1 μL was injected at 80 °C increasing by 25 °C per minute until 250 °C using an HP-5 silicon column operating on an HP Gas chromatography machine.

***N*, *N*-Diethoxymethyl-*N*-methylamine (122)**



Into ice bath at 0°C, paraformaldehyde (30.0 g, 2.0 equivalents,) was added to a stirred mixture of methylamine (66 % solution in IMS, 15.0 g, 0.5 M), ethanol (250.0 mL) and potassium carbonate (69.0 g, 0.50 M). The mixture was stirred vigorously for 3 days at room temperature, then filtered and distilled using a Dufton column (52 °C at 13mm Hg) to afford the title compound as a colourless oil (20.5 g, 140 mmol, 42 %).

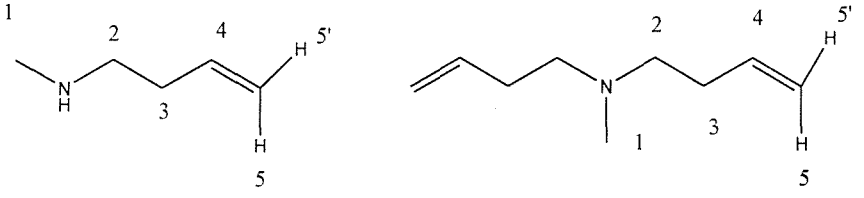
^{1}H (300 MHz, $CDCl_3$) δ = 4.15 (4H, s, H2), 3.41 (4H, q, *J* = 7.0 Hz, H3), 2.41 (3H, s, H1), 1.16 (6H, t, *J* = 7.0 Hz, H4) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 86.04 (CH_2, C2), 63.10 (CH_2, C3), 37.11 (CH_3, C1), 15.31 (CH_3, C4) ppm.

IR (neat oil) = 2973 (brs), 1472 (m), 1377, 1253 (m), 1101 (brm) cm^{-1}.

Boiling point (52 °C at 13mm) in good agreement with the literature[67]

***N*-(3-Butenyl)-*N*-methylamine and *N*,*N*-di(3-butenyl)-*N*-methylamine (123)[78]**



To a pre-dried sealed tube, with a screw down Young tap, methylamine (66 % solution in ethanol, 27.2 mL, 544 mmol) was added followed by 4-bromo-1-butene (20.0 g, 136.0 mmol). The tube was sealed, heated to 80 °C in an oil bath for 48 hours, the reaction mixture cooled to 0 °C, then quenched with a saturated solution of $NaHCO_3$ (50.0 mL). The product was extracted into diethyl ether (3 x 50 mL), washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure at 0 °C. The product was purified by distillation through a Dufton column at atmospheric pressure (b.p. 80-82 °C) to afford *N*-(3-butenyl)-*N*-methylamine (2.50 g, 29 mmol, 21 %) as a colourless oil. *N*,*N*-di(3-butenyl)-*N*-methylamine was isolated by

distillation at atmospheric pressure (b.p. 120-122°C) as a colourless oil (4.8 g, 34 mmol, 51 %).

Method 2: *N*,*N*-di(3-butenyl)-*N*-methylamine was also prepared using the following methodology.

To a stirring solution of ether (10 mL) and ***N*, *N***-diethoxymethyl-*N*-methylamine (**122**, 2.0 g, 13.6 mmol), at 0 °C, allylmagnesium bromide (10 mL, 1.0 mmol solution) was added dropwise. The reaction was left to stir for 16 hours at room temperature then quenched with a saturated solution of $NaHCO_3$ (50.0 mL). The product was extracted into diethyl ether (3 x 100 mL), washed with water (3 x 50 mL), brine (100.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure at 0 °C. *N*,*N*-Di(3-butenyl)-*N*-methylamine was isolated by distillation at atmospheric pressure (b.p. 120-122°C) as a colourless oil (1.2 g, 8.5 mmol, 63 %).

***N*-(3-Butenyl)-*N*-methylamine**

^{1}H (300 MHz, $CDCl_3$) δ = 5.78 (1H, ddt, *J* = 16.9, 10.0, 6.6 Hz, H4), 5.12.(1H, d, *J* = 16.9 Hz, H5), 5.10 (1H, d, *J* = 10.0 Hz, H5'), 2.57 (2H, t, *J* = 6.6 Hz, H2), 2.35 (3H, s, H1), 2.19 (2H, dt, *J* = 6.6 and 6.6 Hz, H3) 1.60 (1H, s (broad), N*H*) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 136.35 (CH, C4), 116.50 (CH_2, C5), 57.62 (CH_2, C2), 50.85 (CH_3, C1), 34.03 (CH_2, C3) ppm.

IR (neat oil) = 3341 (m), 2791 (m), 1640 (m), 1483 (m), 1280 (s), 911 (s) cm^{-1}.

LRMS (ES^+, m/z) 86.4 (M+H).

^{1}HNMR in agreement with the literature[78]

***N*,*N*-Di(3-butenyl)-*N*-methylamine (122)**

^{1}H (300 MHz, $CDCl_3$) δ = 5.78 (2H, ddt, *J* = 17.5, 10.5, 7.0 Hz, H4), 5.12 (2H, d, *J* = 17.5 Hz, H5), 5.01 (2H, d, *J* = 10.5 Hz, H5'), 2.61 (4H, t, *J* = 7.0 Hz, H2), 2.39 (3H, s, H1), 2.24 (4H, dt, *J* = 7.0 and 6.0 Hz, H3) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 136.88 (CH, C4), 115.70 (CH_2, C5), 57.06 (CH_2, C2), 50.23 (CH_3, C1), 33.82 (CH_2, C3) ppm.

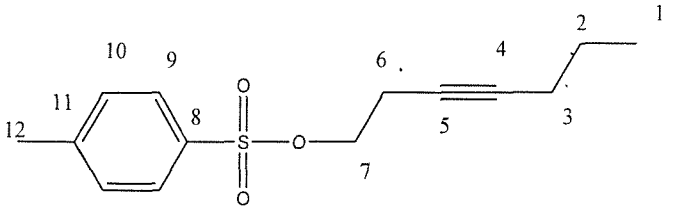
IR (neat oil) = 3344 (brs), 2789 (m), 1639 (s), 1080 (brs), 911 (m) cm^{-1}.

LRMS (APCI, m/z) 140.2 (M+H).

CI-HRMS = $C_9H_{18}N$ requires 140.1439 found 140.1435.

Boiling point and 1H NMR in agreement with the literature[78].

3-Heptynyl 4-methyl-1-benzenesulfonate (124)



3-Heptyn-1-ol (10.0 g, 89.3 mmol) was added to p-toluene sulphonyl chloride (16.9 g, 89.0 mmol) in anhydrous pyridine (39.5 g, 500 mmol) at 0-5 °C. After stirring overnight at room temperature, the reaction mixture was cooled to 0 °C and 6M HCl (30.0 mL) was added. The product was extracted into diethyl ether (3 x 100 mL) and the combined organic extracts washed with water (4 x 100 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title product as a pale oil (17.32 g, 65 mmol, 73 %).

^{1}H (300MHz, $CDCl_3$) δ = 7.81 (2H, d, *J* = 8.0 Hz, H9), 7.39 (2H, d, *J* = 8.0 Hz, H10), 4.05 (2H, t, *J* = 8.0 Hz, H7), 2.53 (2H, tt, *J* = 8.0 and 2.0 Hz, H6), 2.46 (3H, s, H12), 2.05 (2H, tt, *J* = 7.0, 2.0 Hz, H3), 1.45 (2H, tq, *J* = 7.0 and 7.0 Hz, H2), 0.95 (3H, t, *J* = 7.0 Hz, H1) ppm.

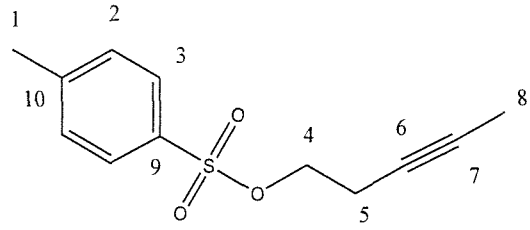
^{13}C (75 MHz, $CDCl_3$) δ = 145.00 (C, C8), 131.05 (C, C11), 130.00 (CH, C9), 128.11 (CH, C10), 82.15, 74.15 (C, C5 and C4), 68.46 (CH_2, C7), 22.29 (CH_3, C12), 21.80 (CH_2, C6), 20.75 (CH_2, C3 or C2), 19.87 (CH_2, C2 or C3), 13.58 (CH_3, C1) ppm.

IR (solution in DCM) = 3032 (m), 2961 (brm), 1597 (s), 1462 (m) cm^{-1}.

LRMS (ES^+, m/z) 267.6 (M+H).

EI-HRMS = $C_{14}H_{19}SO_3$ requires 267.1055 found 267.1057 (M+H).

3-Pentynyl 4-methyl-1-benzenesulfonate (125)[85]



3-Pentyn-1-ol (2.0 g, 23.81 mmol) was added to p-toluene sulphonyl chloride (4.60 g, 23.81 mmol) in anhydrous pyridine (18.8 g, 238 mmol), at 0-5 °C. After stirring overnight at room temperature, HCl (6M, 6.0 mL) was added at 0 °C. The product extracted into diethyl ether (3 x 100 mL), the combined organic extracts washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100% Et_2O:petroleum including 5 % Et_3N) afforded the title product as a pale oil (4.5 g, 19 mmol, 83 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.80 (2H, d, *J* = 8.0 Hz, H3), 7.40 (2H, d, *J* = 8.0 Hz H-2), 4.01 (2H, t, *J* = 7.0 Hz, H4), 2.47 (2H, tq, *J* = 7.0 and 2.0 Hz, H5), 2.45 (3H, s, H1), 1.71 (3H, t, *J* = 2.0 Hz, H8) ppm.

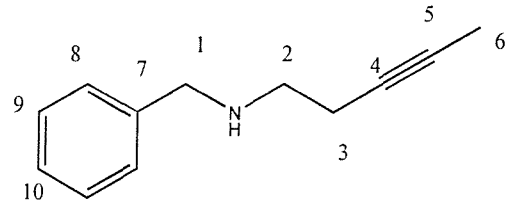
^{13}C (75 MHz, $CDCL_3$) δ = 145.01 (C, C9), 136 (C, C10), 129.94 (CH, C3), 128.03 (CH, C2), 78.63, 73.27 (C, C6 and C7), 68.38 (CH_2, C4), 21.72 (CH_2, C5), 19.81 (CH_3, C1), 13.43 (CH_3, C8) ppm.

IR (neat oil) = 3036 (brm), 2155 (m), 1594 (brm), 1360 (brm), 962 (m) cm^{-1}.

LRMS (APCI, m/z) 238.5 (M+H).

Data in agreement with literature[85]

***N*-Benzyl-*N*-(3-pentynyl)amine (126)**



Toluene sulfonate (**125**, 1.0 g, 4.2 mmol) was added to stirring benzylamine (5.0 g, 46.0 mmol) and the reactants refluxed for 16 hours, at room temperature, before quenching with saturated $NaHCO_3$ solution (50.0 mL). The product was extracted into diethyl ether

(3 x 100 mL), the combined organic extracts washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Distillation under reduced pressure (121°C, 19 torr) followed by column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title product as a clear oil (350 mg, 1.7 mmol, 46 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.50-7.35 (5H, m, Ph-H), 3.77 (2H, s, H1), 2.78 (2H, t, *J* = 6.0 Hz, H2), 2.37 (2H, tq, *J* = 6.0 and 2.5 Hz, H3), 1.80 (3H, t, *J* = 2.5 Hz, H6), 1.70 (1H, broad s, N*H*) ppm.

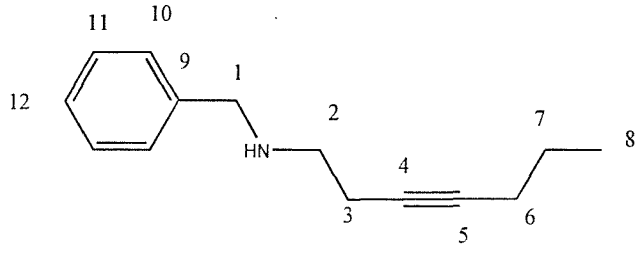
^{13}C (75 MHz, $CDCl_3$) δ = 140.35 (C, C7), 128.44, 128.16, 126.95 (CH, C8, C9 and C10), 77.09, 76.93 (C, C4 and C5), 53.49 (CH_2, C1), 47.94 (CH_2, C2), 19.87 (CH_2, C3), 3.58 (CH_3, C6) ppm.

IR (neat oil) = 3314 (brm), 2919 (brm), 2253 (w), 1454 (m), 1360 (m) cm^{-1}.

LRMS (APCI, m/z) 174.1 (M+H).

Data in agreement with the literature[71]

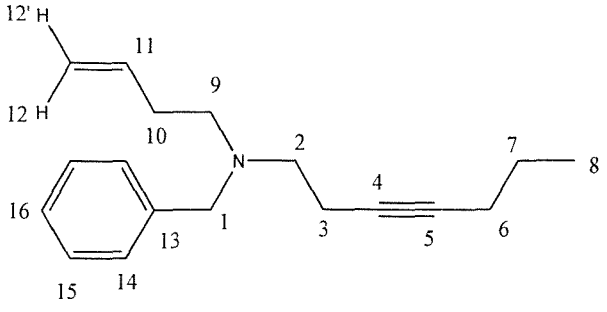
***N*-Benzyl-*N*-(3-heptynyl)amine (127)**



Toluene sulfonate (**124**, 7.4 g, 27.8 mmol) was added to vigorously stirring benzylamine (50.0 mL, 0.46 mol). Catalytic iodine (200 mg, 0.27 mmol) was added and the reactants brought to reflux for 18 hrs. Excess benzylamine was removed by distillation (15 mm, 89 °C), and the reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (30.0 mL). The product was extracted into diethyl ether (3 x 100 mL), the combined organic layers washed with water (3 x 100 mL), brine (50.0 mL) and dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Kugelrohr distillation (110 °C, 1.0 mm) afforded the title product as a clear oil (5.13 g, 25.5 mmol, 91 %).

^{1}H (300MHz, $CDCl_3$) δ = 7.35-7.15 (5H, m, Ph-H), 3.78 (2H, s, H1), 2.75 (2H, t, *J* = 7.0 Hz, H2), 2.41 (2H, tt, *J* = 7.0, 2.1 Hz, H3), 2.15 (2H, tt, *J* = 7.1, 2.1 Hz, H6), 1.60 (1H, s (broad), N*H*), 1.45 (2H, tq, *J* = 7.1 and 7.1 Hz, H7), 0.95 (3H, t, *J* = 7.1 Hz, H8) ppm.
^{13}C (75 MHz, $CDCl_3$) δ = 140.47 (C, C9), 128.55, 128.25, 127.06 (CH, C10, C11 and C12), 81.76, 78.09 (C, C5 and C4), 53.57 (CH_2, C1), 48.12 (CH_2, C2), 22.60 (CH_2, C6), 20.91 (CH_2, C7), 19.93 (CH_2, C3), 13.66 (CH_3, C8) ppm.
IR (neat oil) = 3307 (m), 2897 (brm), 1452 (m), 1118 (m), 734 (brs) cm^{-1}.
LRMS (ES^+, m/z) 202.2 (M+H).

***N*-Benzyl-*N*-(3-butenyl)-*N*-(3-heptynyl)amine (128)**



4-Bromo-1-butene (0.608 g, 4.5 mmol) was added dropwise to a stirring solution of *N*-benzyl-*N*-(3-heptynyl)amine (**127**, 1.0 g, 4.3 mmol) in MeCN (10.0 mL) and K_2CO_3 (1.0 g, 12 mmol) at 0 °C. The solution was refluxed for 4 hours then quenched with saturated $NaHCO_3$ solution (50.0 mL). The product was extracted into diethyl ether (3 x 50 mL) washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Chromatography (SiO_2, 0-50 % Et_2O:petroleum including 5 % Et_3N) afforded the title product as a viscous orange oil (0.99 g, 3.7 mmol, 76 %).

^{1}H (300MHz, $CDCl_3$) δ = 7.40-7.27 (5H, m, Ph-H), 5.78 (1H, ddt, *J* = 16.1, 10.0, 6.2 Hz, H11), 5.22 (1H, d, *J* = 16.1 Hz, H12), 5.21 (1H, d, *J* = 10.0 Hz, H12'), 3.67 (2H, s, H1), 2.62 (2H, t, *J* = 7.0 Hz, H2), 2.43 (2H, t, J = 7.0 Hz, H9), 2.18 (4H, m, H3 and H10), 2.05 (2H, tt, *J* = 7.0 and 2.0 Hz, H6), 1.49 (2H, tq, *J* = 7.0 and 7.0 Hz, H7), 0.94 (3H, t, *J* = 7.0 Hz, H8) ppm.

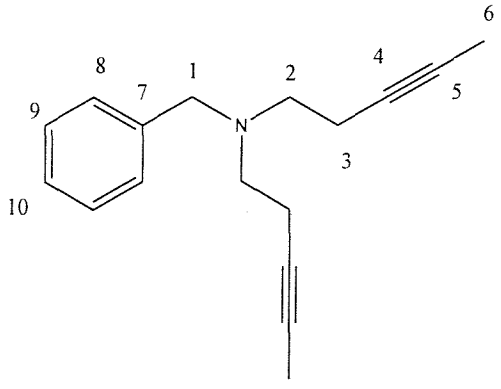
^{13}C (75 MHz, $CDCl_3$) δ = 140.39 (C, C13), 137.07, 128.84, 128.30 (CH, C14, C15 and C16), 126.95 (CH, C11), 115.56 (CH_2, C12), 80.35, 79.25 (C, C5 and C4), 58.47 (CH_2, C1), 53. 27 (CH_2, C9), 31.86 (CH_2, C2), 22.59 (CH_2, C6), 20.94 (CH_2, C3), 17.37 (CH_2, C7), 13.66 (CH_3, C8) ppm.

IR (neat oil) = 2958 (brm), 2270 (w), 1635 (w), 1358 (m) 707 (w)cm^{-1}.

LRMS (ES^+, m/z) 256.4 (M+H).

CI-HRMS = $C_{18}H_{25}N$ requires 254.1944 found 254.1936.

***N*-Benzyl-*N*,*N*-di(3-pentynyl)amine (129)**



A stirred solution of *N*-benzyl-*N*-(3-pentynyl)amine (**126**, 173 mg, 1.0 mmol), K_2CO_3 (1.0 g, 10.0 mmol) toluene sulfonate (**125**, 238 mg, 1.0 mmol) in MeCN (10 mL) was boiled under reflux for 24 hrs. After quenching with a saturated solution of $NaHCO_3$ (20.0 mL), the product was extracted into diethyl ether (3 x 25 mL). The combined organic layer was washed with water (3 x 25 mL), brine (25.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-50 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a pale oil (100 mg, 0.4 mmol, 40 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.40-7.20 (5H, m, Ph-H), 3.55 (2H, s, H1), 2.70 (4H, t, *J* = 7.0 Hz, H2), 2.30 (4H, tq, *J* = 7.0 and 2.0 Hz, H3), 1.79 (6H, t, *J* = 2.0 Hz, H6) ppm.

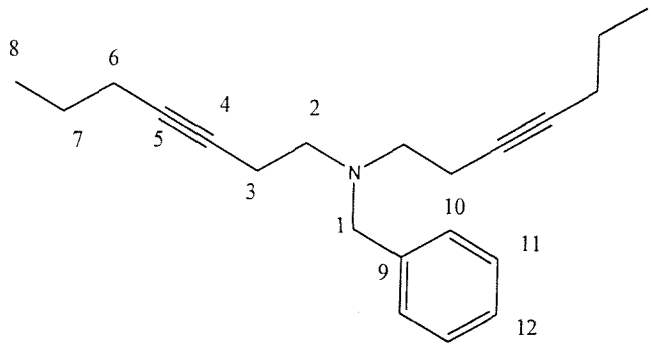
^{13}C (75 MHz, $CDCl_3$) δ = 140.35 (C, C7), 128.44, 128.16, 126.95 (CH, C8, C9 and C10), 77.09, 76.93 (C, C4 and C5), 53.49 (CH_2, C1), 47.94 (CH_2, C2), 19.87 (CH_2, C3), 13.58 (CH_3, C6) ppm.

IR (solution DCM) = 3259 (brm), 2148 (w), 1654 (w), 733 (m), 697 (m) cm^{-1}.

LRMS (ES^+, m/z) 240.1 (M+H).

EI-HRMS $C_{17}H_{22}N$ requires 240.1747 found 240.1755 (M+H).

***N*-Benzyl-*N*,*N*-di(3-heptynyl)amine (130)**



To a stirring solution of *N*-benzyl-*N*-(3-heptynyl)amine (**127**, 1.0 g, 4.8 mmol), K_2CO_3 (1.2 g, 12.0 mmol) and MeCN (10.0 mL), tolulene sulfonate (**124**, 1.33 g, 5.0 mmol) was added dropwise. The reactants were boiled under reflux for 24 hrs then quenched using NaOH (6M, 30.0 mL). The product was extracted into diethyl ether (3 x 100 mL) and the combined organic layers washed with water (3 x 100 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a viscous clear oil (1.3 g, 4.4 mmol, 88 %).

^{1}H (300MHz, $CDCl_3$) δ = 7.40-7.20 (5H, m, Ph-H), 3.65 (2H, s, H1), 2.75 (4H, t, *J* = 7.0 Hz, H2), 2.31 (4H, tt, *J* = 6.5, 2.0 Hz, H6), 2.12 (4H, tt, *J* = 7.0, 2.0 Hz, H3), 1.51 (4H, tq, *J* = 6.5 and 6.5 Hz, H7), 0.95 (6H, t, *J* = 6.5 Hz, H8) ppm.

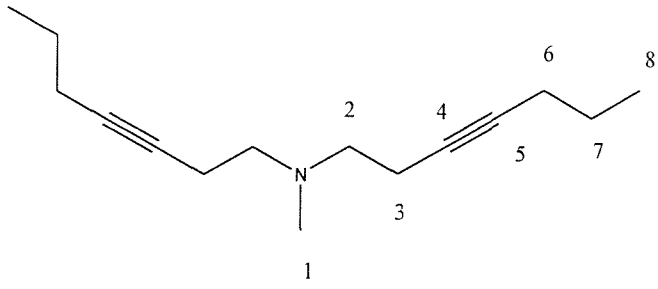
^{13}C (75 MHz, $CDCl_3$) δ = 139.86 (C, C9), 128.75, 128.32, 126.99 (CH, C10, C11 and C12), 81.07, 78.66 (C, C4 and C5), 58. 46 (CH_2, C1), 53.17 (CH_2, C2), 22.58 (CH_2, C6), 20. 93 (CH_2, C7), 17.68 (CH_2, C3), 13. 64 (CH_3, C8) ppm.

IR (neat oil) = 3077 (brm), 3015 (s), 2269 (w), 834 (brs) cm^{-1}.

LRMS (ES^+, m/z) 296.4 (M+H).

EI-HRMS = $C_{21}H_{28}N$ required 294.2222 found 294.2233 (M-H).

***N*,*N*-Di(3-heptynyl)-*N*-methylamine (131)**



To a stirred solution of *N*-(3-heptynyl)-*N*-methylamine (0.63 g, 5.0 mmol), K_2CO_3 (1.2 g, 12.0 mmol) and MeCN (5 mL), tolulenesulfonate (**124**, 1.33 g, 5.0 mmol) was added dropwise. The solution was refluxed for 15 hrs then quenched with NaOH (6 M, 20.0 mL). The product extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 100 mL), brine (50.0 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N), afforded the title compound as a pale oil (0.94 g, 4.3 mmol, 86 %).

^{1}H (300MHz, $CDCl_3$) δ = 2.50 (4H, t, *J* = 8.0 Hz, H2), 2.33 (4H, tt, *J* = 8.0, 2.0 Hz, H3), 2.22 (3H, s, H1), 2.11 (4H, tt, *J* = 7.0, 2.0 Hz, H6), 1.48 (4H, tt, *J* = 7.0 Hz, H7), 0.94 (6H, t, *J* = 7.0 Hz, H8) ppm.

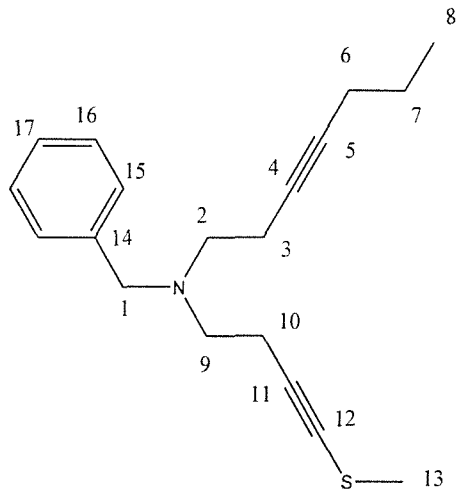
^{13}C (75 MHz, $CDCl_3$) δ = 81.87 (C, C4), 78.31 (C, C5), 56.61 (CH_2, C2), 41.88 (CH_3, C1), 22.41 (CH_2, C6), 20.76 (CH_2, C7), 17.38 (CH_2, C3), 13.42 (CH_3, C8) ppm.

IR (neat oil) 2919 (w), 2215 (w), 1095 (m), 907 (brs) cm^{-1}.

LRMS (ES^+, m/z) 220.1 (M+H).

EI-HRMS = $C_{15}H_{25}N$ requires 220.2059 found 220.2055 (M+H).

Benzyl-hept-3-ynyl-(4-methylsulfanyl-but-3-ynyl)-amine (132)



To a stirred solution of triethylamine (1.0 mL, 10.0 mmol), methanesulphonyl chloride (354 mg, 3.5 mmol) in DCM (10.0 mL) at 0 °C, 3-butyn-1-ol (3.0 mmol, 211 mg) was added dropwise. The solution stirred for 20 minutes at 0 °C, warmed to room temperature and stirred for 20 minutes before quenching with Et_2O (30.0 mL), filtered and the solvent removed under reduced pressure. The product was dissolved in MeCN (10.0 mL) and then added dropwise to a stirring solution of *N*-benzyl-*N*-(3-heptynyl)amine (**127** , 0.402 mg, 2.0 mmol). After 4 hours at room temperature the reaction was quenched with a saturated solution of $NaHCO_3$ (150.0 mL) and the product extracted into diethyl ether (3 x 30 mL). The combined organic layer was washed with water (3 x 30 mL), brine (150.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure.

The resulting crude material was dissolved in THF (5.0 mL) under argon at –78 °C, ^{n}BuLi (0.96 mL, 2.5 M solution in hexanes, 2.41 mmol) was added dropwise. After 10 minutes, pre-dried dimethyldisulphide (0.26 mL, 2.82 mmol) was added and the reaction warmed to room temperature. After 12 hours the reaction was quenched with a saturated solution of $NaHCO_3$ (50.0 mL) and the product extracted into diethyl ether (3 x 50 mL). The combined organic layer was washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a pungent yellow oil (0.463 g, 1.53 mmol, 52 %).

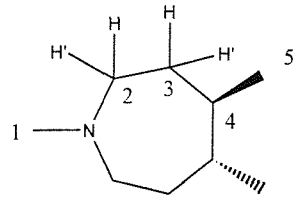
^{1}H (300MHz, $CDCl_3$) δ = 7.40-7.20 (5H, m, Ph-H), 3.64 (2H, s, H1), 2.73 (2H, t, *J* = 7.5, H2 or H9), 2.71 (2H, t, *J* = 7.5 Hz, H2 or H9), 2.44 (2H, t, *J* = 7.5 Hz, H10), 2.31 (3H, s, H13), 2.29 (2H, tt, *J* = 7.5 and 2.0 Hz, H3), 2.10 (2H, tt, *J* = 7.5 and 2.0 Hz, H6), 1.49 (2H, tq, *J* = 7.5 and 7.5 Hz, H7), 0.95 (3H, t, *J* = 7.5 Hz, H8) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 139.70 (C, C14), 128.74, 128.35, 127.06 (CH, C15, C16, and C17), 91.68, 81.02, 78.58, 70.20 (C, C4, C5, C11 and C12), 58.47 (CH_2, C1), 53.18 (CH_2, C9), 52.66 (CH_2, C2), 22.59 (CH_2, C6), 20.94 (CH_2, C7), 19.32 (CH_3, C13), 19.03 (CH_2, C10), 17.77 (CH_2, C3), 13.69 (CH_3, C8) ppm.

IR (neat oil) = 2958 (m), 1453 (brm), 1027 (m), 735 (s) cm^{-1}.

LRMS ($APCI^+$, m/z) 300.2 (M+H).

1,4,5-Trimethyl-azepine (134)



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in THF (5.0 mL) under argon at –80 °C, ^{n}BuLi (0.8 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise and the reaction stirred for 30 minutes. *N*,*N*-Di(3-butenyl)-*N*-methylamine (**123**, 0.141, 1.0 mmol) in THF (3.0 mL) was added dropwise and the reaction warmed to room temperature. The reaction was stirred for 6 hours, before quenching with methanol (5.0 mL) and a saturated solution of $NaHCO_3$ (8.0 mL). The product was extracted into diethyl ether (3 x 50 mL), and the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure at 0 °C. Kugelrohr distillation (130 °C and 120 torr) afforded the title compound (107 mg, 0.75 mmol, 75 %).

^{1}H (300 MHz, $CDCl_3$) δ = 2.64 (2H, dddd, *J* = 12.7, 7.2, 2.2 and 0.7 Hz, H2), 2.42 (2H, dddd, *J* = 12.5, 9.7, 2.4 and 0.9 Hz, H2'), 2.29 (3H, s, H1), 1.67 (2H, dddd, *J* = 14.9, 7.2, 3.7 and 2.2 Hz, H3), 1.55 (2H, dddd, *J* = 14.9, 9.5, 5.0 and 2.4 Hz, H3'), 1.25 (2H, m, H4), 0.95 (6H, d, *J* = 6.5 Hz, H5) ppm.

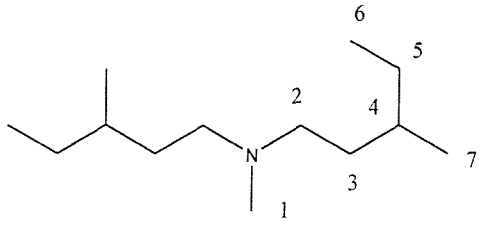
^{13}C (75 MHz, $CDCl_3$) δ = 64.63 (CH_2, C2), 53.07 (CH_3, C1), 40.13 (CH, C4), 27.97 (CH_2, C3), 19.41 (CH_3, C5) ppm.

IR (neat oil) = 3075 (brm), 2870 (brs), 1020 (brm), 801 (m) cm^{-1}.

LRMS (ES^+, m/z) 142.2 (M+H).

EI-HRMS = $C_9H_{19}N$ requires 141.1517 found 141.1520 (M+).

***N*-Methyl-*N*-*N*-di(3-methylpentyl)amine (137)**



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in THF (5.0 mL) under argon at –80 °C, ethyl magnesium bromide (1.0 mL of a 3.0 M solution in diethyl ether, 3 mmol) was added dropwise. *N*,*N*-Di(3-butenyl)-*N*-methylamine (**123** , 0.140 g, 1.0 mmol) in THF (5.0 mL), was added to the solution. The reaction was allowed to warm to room temperature, stirred for 4 hours, after which the solution was refluxed for 2 hours. The reaction was quenched with methanol (5.0 mL) and a saturated solution of $NaHCO_3$ (8.0 mL), then stirred overnight. The product was extracted into diethyl ether (3 x 50 mL), the combined organic extracts washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure at 0°C. Kugelrohr distillation (130°C, 120 torr) afforded the title compound (116 mg, 0.58 mmol, 58 %).

^{1}H (300 MHz, $CDCl_3$) δ = 2.35 (4H, t, *J* = 7.0 Hz, H2), 2.20 (3H, s, H1), 1.25 (10H, m, H3/4/5), 0.86 (6H, d, *J* = 6.0 Hz, H7), 0.85 (6H, t, *J* = 7.0 Hz, H6) ppm.

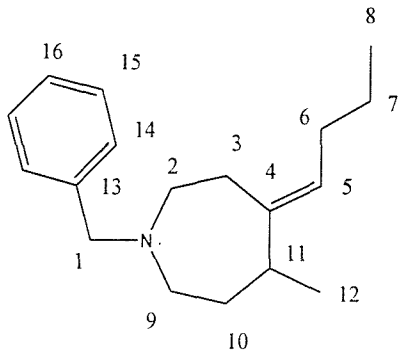
^{13}C (75 MHz, $CDCl_3$) δ = 46.05 (CH_2, C2), 42.42 (CH_3, C1), 33.92 (CH_2, C3), 33.14 (CH, C4), 29.76 (CH_3, C7), 19.46 (CH_2, C5), 11.44 (CH_3, C6) ppm.

IR (neat oil) = 2859 (brm), 1461 (brm), 1259 (brs) cm^{-1}.

LRMS (ES^+, m/z) 200.2 (M+H).

EI-HRMS = $C_{13}H_{29}N$ requires 199.2300 found 199.2296 (M+).

1-Benzyl-4-butylidene-5-ethylidene-azepane (149)



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in dry THF (5.0 mL) under argon at $^{-}$80 °C, ^{n}BuLi (0.8 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise and then stirred for 20 minutes. *N*-Benzyl-*N*-(3-butenyl)-*N*-(3-heptynyl)amine (**128**, 0.221 g, 1 mmol) in THF (2.0 mL) was added dropwise to the solution warmed to room temperature, and stirred for 7 hrs. The reaction was quenched with methanol (5.0 mL) and a saturated solution of $NaHCO_3$ (8.0 mL). The product extracted into diethyl ether (3 x 100 mL), the combined organic layer washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title product as a pale viscous oil (138 mg, 0.54 mmol, 54 %).

^{1}H (300MHz, $CDCl_3$) δ = 7.45-7.30 (5H, m, Ph-H), 5.36 (1H, t, *J* = 7.0 Hz, H5), 3.61 (1H, d, *J* = 13.5 Hz, H1), 3.56 (1H, d, *J* = 13.5 Hz, H1'), 2.93 (1H, dd, *J* = 6.5 and 6.5 Hz, H2), 2.75 (1H, dd, *J* = 12.0 and 7.5 Hz, H2'), 2.4-2.2 (4H, m, H3 and H9), 1.98 (2H, dt, *J* = 7.0 and 7.0 Hz, H6), 1.85 (2H, m, H10), 1.5-1.3 (3H, m, H7 and H11), 0.97 (3H, d, *J* = 7.0 Hz, H12), 0.84 (3H, t, *J* = 7.0 Hz, H8) ppm.

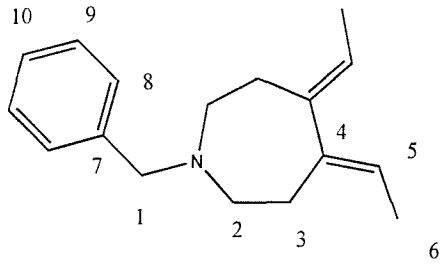
^{13}C (75 MHz, $CDCl_3$) δ = 144.55 (C, C4), 139.78 (C, C13), 129.12, 128.31, 126.97 (CH, C14, C15 and C16), 124.56 (CH, C5), 62.76 (CH_2, C1), 56.99 (CH_2, C9), 53.90 (CH_2, C2), 40.68 (CH, C11), 34.67 (CH_2, C3), 29.71 (CH_2, C6), 26.88 (CH_2, C10), 23.28 (CH_2, C7), 17.35 (CH_3, C12), 13.79 (CH_3, C8) ppm.

IR (neat oil) = 2956 (brm), 1623 (s), 1454 (m), 1215 (m) cm^{-1}.

LRMS (ES^{+}, m/z) 258.3 (M+H).

EI-HRMS = $C_{18}H_{27}N$ requires 257.2144 found 257.2149

1-Benzyl-4,5-di[(E)ethylidene]azepane (151)



To a stirring solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in pre-dried THF (5.0 mL) under argon at –80 °C, ^nBuLi (0.8 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise and stirred at –78 ° C for 10 minutes. *N*-Benzyl-*N*,*N*-di(3-pentynyl)amine (**129** , 240 mg, 1.0 mmol) as a solution in THF (3.0 mL) was added, warmed to room temperature and stirred for 5 hours. The reaction was quenched with methanol (3.0 mL) and a saturated solution of $NaHCO_3$ (6.0 mL). The product was extracted into diethyl ether (3 x 100 mL), the combined organic layer washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a viscous yellow oil (0.191 g, 0.79 mmol, 79 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.45-7.25 (5H, m, Ph-H), 5.40 (2H, q, *J* = 6.0 Hz, H5), 3.65 (2H, s, H1), 2.61 (4H, m, H2), 2.42 (4H, m, H3), 1.64 (6H, d, *J* = 6.0 Hz, H6) ppm.

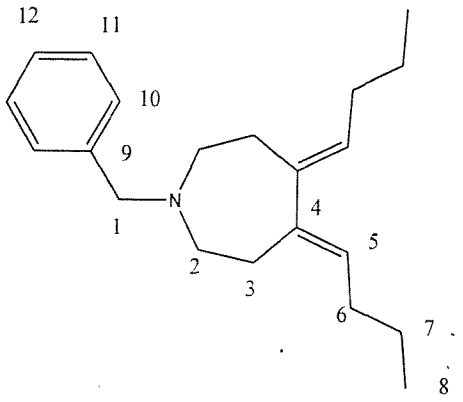
^{13}C (75 MHz, $CDCl_3$) δ = 144.43 (C, C4), 139.59 (C, C7), 129.02, 128.36, 126.95 (CH, C8, C9 and C10), 117.90 (CH, C5), 62.35 (CH_2, H1), 54.82 (CH_2, H2), 29.95 (CH_2, H3), 13.24 (CH_3, C6) ppm.

IR (neat oil) = 3305 (brm), 1656 (w), 1452 (s), 1358 (brm), 697 (brs) cm^{-1}.

LRMS (APCI, m/z) 242.4 (M+H).

EI-HRMS = $C_{17}H_{23}N$ requires 241.1831 found 241.1830.

1-Benzyl-4,5-di[(E)butylidene]azepane (152)



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in pre-dried THF (5.0 mL) under argon at - 80 °C, ^nBuLi (0.8 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise and stirred for 10 minutes. *N*-Benzyl-*N*,*N*-di(3-heptynyl)amine (**130** , 0.295 g, 1.0 mmol) in THF (3.0 mL) was added to the reaction, which was warmed to room temperature, and stirred for 8 hours. The reaction was quenched with methanol (3.0 mL) and a saturated solution of $NaHCO_3$ (6.0 mL). The product was extracted into diethyl ether (3 x 100 mL), the combined organic layer washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title diene as a viscous oil (0.273 g, 0.92 mmol, 92 %).

^{1}H (300MHz, $CDCl_3$) δ = 7.45-7.30 (5H, m, Ph-H), 5.45 (2H, t, *J* = 7.5 Hz, H5), 3.65 (2H, s, H1), 2.58-2.45 (4H, m, H2), 2.42-2.30 (4H, m, H3), 2.00 (4H, q, *J* = 7.5 Hz, H6), 1.39 (4H, sextet, *J* = 7.5 Hz, H7), 0.92 (6H, t, *J* = 7.5 Hz, H8) ppm.

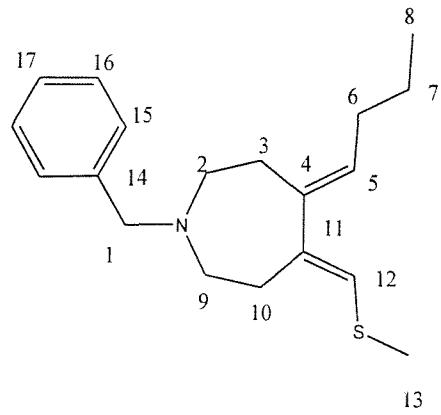
^{13}C (75 MHz, $CDCl_3$) δ = 143.60 (C, C4), (C, C9) not observed, 129.10, 128.35, 127.02 (CH, C10, C11 and C12), 122.55 (CH, C5), 62.50 (CH_2, C1), 55.32 (CH_2, C2), 30.00 (CH_2, C3 or C6), 29.45 (CH_2, C6 or C3), 23.06 (CH_2, C7), 14.15 (CH_3, C8) ppm.

IR (solution in DCM) = 3048 (brs), 1601 (weak), 1413 (m), 1260 (brw), 737 (brs) cm^{-1}.

LRMS (ES^+, m/z) 298.4 (M+H).

EI-HRMS = $C_{21}H_{31}N$ requires 297.2456 found 297.2456 (M+).

1-Benzyl-4-butylidene-5-methylsulfanylmethylene-azepane (153)



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in pre-dried THF (5.0 mL) under argon at - 80 °C, ^nBuLi (0.8 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise. Benzyl-hept-3-ynyl-(4-methylsulfanyl-but-3-ynyl)-amine (**132**, 0.221 g, 1.0 mmol) as a solution in THF (2.0 mL) was added, the reaction warmed to room temperature, and then stirred for 5 hrs. The reaction was quenched with methanol (5.0 mL) and a saturated solution of $NaHCO_3$ (8.0 mL). The product was extracted into diethyl ether (3 x 100 mL), the organic layer washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including Et_3N) afforded the title compound as a viscous oil (268 mg, 0.89 mmol, 89 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.30-7.10 (5H, m, Ph-H), 5.75 (1H, s, H12), 5.29 (1H, t, *J* = 7.0 Hz, H5), 3.50 (2H, s, H1), 2.58-2.42 (4H, m, H2 and H9), 2.29 (3H, s, H13), 1.93 (2H, q, *J* = 7.0 Hz, H6), 1.85-1.65 (4H, m, H3 and H10), 1.41 (2H, tq, *J* = 7.0 and 7.0 Hz, H7), 0.90 (3H, t, *J* = 7.0 Hz, H8) ppm.

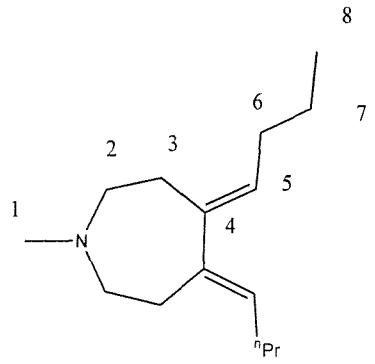
^{13}C (75 MHz, $CDCl_3$) δ = 142.70, 142.17 (C, C4 and C11), 139.01 (C, C14), 129.06, 128.35, 127.02 (CH, C15, C16 and C17), 125.35 (CH, C12), 120.29 (CH, C5), 62. 36 (CH_2, C1), 55.38, 54.36 (CH_2, C9 and C2), 31.35, 30.05 (CH_2, C3 and C10), 29.50 (CH_2, C6), 23.02 (CH_2, C7), 17.35 (CH_3, C13), 14.13 (CH_3, C8) ppm.

IR (neat oil) = 3106 (m), 1652 (m), 1603 (m), 1094 (brs), 732 (brm) cm^{-1}.

LRMS (ES^+, m/z) 302.2 (M+H).

EI-HRMS = $C_{19}H_{27}NS$ requires 301.1864 found 301.1854 (M+).

4,5-Di[(E)butylidene]-1-methylazepane (154)



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in dry THF (5.0 mL) under argon at - 80 °C was added dropwise, ^nBuLi (0.8 mL, 2.5 M solution in hexanes, 2.0 mmol) and stirred for 20 minutes. *N*,*N*-Di(3-heptynyl)-*N*-methylamine (**131**, 0.221 g, 1.0 mmol) in THF (2.0 mL) was added dropwise and the reaction was warmed to room temperature, and then stirred for 7 hrs. The reaction was quenched with methanol (5.0 mL) and a saturated solution of $NaHCO_3$ (8.0 mL). The product was extracted into diethyl ether (3 x 100 mL), the combined organic layer washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a pale oil (0.198 g, 0.89 mmol, 89 %).

^{1}H (300 MHz, $CDCl_3$) δ = 5.35 (2H, t, *J* = 7.0 Hz, H5), 2.46-240 (4H, m, H2), 2.35-2.30 (4H, m, H3), 2.25 (3H, s, H1), 1.89 (4H, dt, *J* = 7.0 and 7.0 Hz, H6), 1.35 (4H, tq, *J* = 7.0 and 7.0 Hz, H7), 0.98 (6H, t, *J* = 7.0 Hz, H8) ppm.

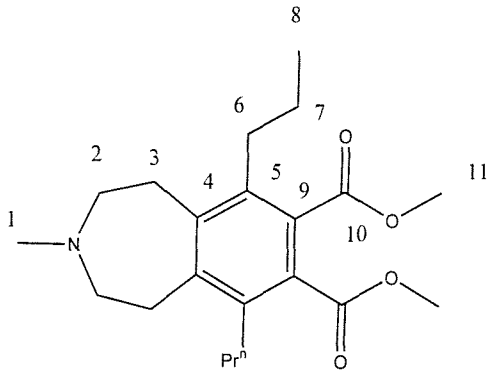
^{13}C (75 MHz, $CDCl_3$) δ = 143.30 (C, C4), 124.39 (CH, C5), 57.87 (CH_2, C2), 46.98 (CH_3, C1), 29.99 (CH_2, C3 or C6), 29.52 (CH_2, C6 or C3), 23.06 (CH_2, C7), 14.14 (CH_3, C8) ppm.

IR (solution in DCM) = 3098 (brm), 3005 (brs), 1605 (brm), 908 (brm), cm^{-1}.

LRMS (ES^+, m/z, %) 222.2 (M+H).

EI-HRMS = $C_{15}H_{27}N$ requires 222.2143 found 222.2128 (M+).

Dimethyl 3-methyl-6,9-dipropyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7,8-dicarboxylate (156)



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in pre-dried THF (5.0 mL) under argon at -80 °C, ^{n}BuLi (0.8 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise and stirred for 20 minutes. *N*,*N*-Di(3-heptynyl)-*N*-methylamine (**131**, 222 mg, 1.0 mmol) in THF (3.0 mL) was added, warmed to room temperature and the reaction stirred. After 4 hours, at 0 °C, CuCl (198 mg, 2.0 mmol), pre-sonicated and dried under vacuum (0.1 mm Hg), and DMAD (284 mg, 2.0 mmol) were added. The resulting solution was stirred vigorously for 4 hours, quenched with methanol (5.0 mL) and a saturated solution of $NaHCO_3$ (6.0 mL). The product was extracted into diethyl ether (3 x 100 mL), the combined organic layer washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a viscous oil (166 mg, 0.46 mmol, 46 %).

^{1}H (400 MHz, $CDCl_3$) δ = 3.78 (6H, s, H11), 2.95 (4H, dd, *J* = 6.5 and 5.0, H2), 2.52 (4H, m, H3), 2.41 (4H, m, H6), 2.23 (3H, s, H1), 1.45 (4H, tq, *J* = 7.0 and 8.0 Hz, H7), 0.98 (6H, t, *J* = 8.0 Hz, H8) ppm.

^{13}C NMR (100 MHz, $CDCl_3$) δ = 168.68 (C, C10), 142.83, 134.70, 129.62 (C, C4, C5 and C9), 55.72 (CH_2, C2), 51.20 (CH_3, C11), 46.00 (CH_3, C1), 32.18 (CH_2, C3), 29.10 (CH_2, C6), 23.60 (CH_2, C7), 13.41 (CH_3, C8) ppm.

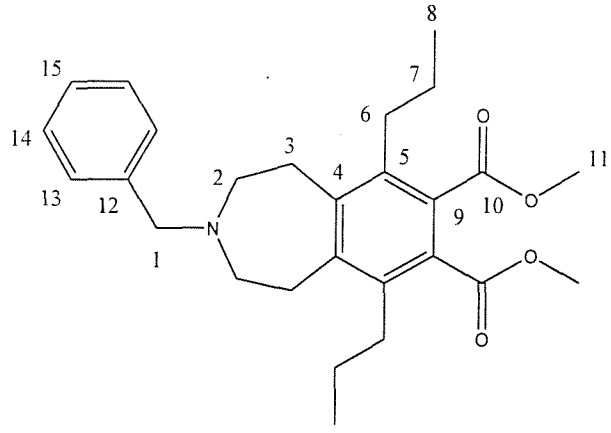
IR (neat oil) = 2923 (brm), 2804 (m), 1730 (s), 1553 (m) cm^{-1}.

LRMS (ES^+, m/z, %) 362.6 (M+H).

EI-HRMS = $C_{21}H_{32}O_4N$ requires 362.2331 found 362.2317 (M+H).

EA = $C_{21}H_{31}NO_4$ requires C 69.78, H 8.64, N 3.87 found C 69.77, H 8.65, N 3.80.

3-Benzyl-6,9-dipropyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine-7,8-dicarboxylic acid dimethyl ester (157)



To a stirred solution of $ZrCp_2Cl_2$ (321 mg, 1.1 mmol) in dry THF (5.0 mL) under argon at - 80 °C, ^nBuLi (0.8 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise. *N*-Benzyl-*N*,*N*-di(3-heptynyl)amine (**130**, 222 mg, 1.0 mmol) dissolved in THF (3.0 mL) was added and the solution allowed to warm to room temperature. After 4 hours, at 0 °C, the resulting solution was added to CuCl (198 mg, 2.0 mmol), sonicated previously and dried under vacuum (0.1 mm Hg), and DMAD (284 mg, 2.0 mmol). The resulting solution was stirred vigorously for 3 hours, then quenched with methanol (5 mL) and a saturated solution of $NaHCO_3$ (6.0 mL). The product was extracted into diethyl ether (3 x 100 mL), the combined organic layer washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum) afforded the title compound as a viscous oil (244 mg, 0.56 mmol, 56 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.45-7.25 (5H, m, Ph-H), 3.86 (6H, s, H11), 3.50 (2H, s, H1), 2.91 (4H, m, H2), 2.79 (4H, m, H3), 2.29 (4H, m, H6), 1.65 (4H, tq, *J* = 7.0 and 8.0 Hz, H7), 0.98 (6H, t, *J* = 8.0 Hz, H8) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 168.68 (C, C10), 143.82 (C, C4), 138.56 (C, C12), 134.69 (C, C5), 129.62 (C, C9), 128.26, 128.44, 127.24 (CH, C13, C14 and C15), 62.55 (CH_2, C1),

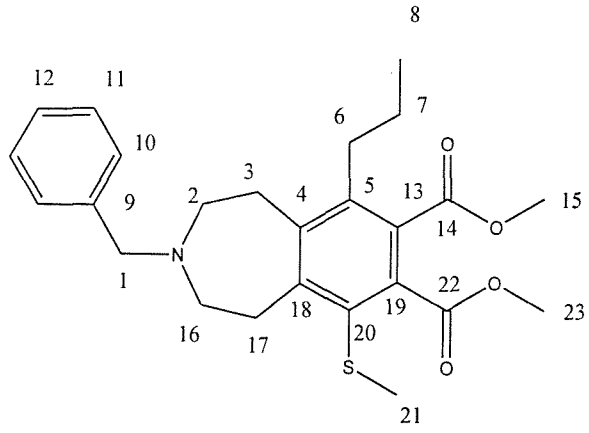
54.82 (CH_2, C2), 53.20 (CH_3, C11), 32.57 (CH_2, C3), 28.99 (CH_2, C6), 23.60 (CH_2, C7), 13.14 (CH_3, C8) ppm.

IR (neat oil) = 3042 (m), 2986 (m), 1547 (w), 1272 (s) cm^{-1}.

LRMS (ES^+, m/z, %) 438.6 (M+H).

EI-HRMS = $C_{27}H_{35}NO_4$ requires 437.2536 found 437.2546 (M+).

Dimethyl 3-benzyl-6-(methylsulfanyl)-9-propyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7,8-dicarboxylate (158)



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in pre-dried THF (5.0 mL) under argon at - 80 °C, ^nBuLi (0.8 mL of 2.5 M solution in hexanes, 2.0 mmol) was added dropwise. Benzyl-hept-3-ynyl-(4-methylsulfanyl-but-3-ynyl)-amine (**132**, 299 mg, 1.0 mmol) in THF (3.0 mL) was added, warmed to room temperature, and stirred for 3 hours. After this, at 0 °C, CuCl (198 mg, 2.0 mmol), pre-sonicated and dried under vacuum (0.1 mm Hg), and DMAD (284 mg, 2.0 mmol) were added to the solution. The reaction was stirred vigorously for 3 hours, then quenched with methanol and a saturated solution of $NaHCO_3$ (10.0 mL). The product was extracted into diethyl ether (3 x 100 mL), the combined organic layer washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a viscous oil (202 mg, 0.56 mmol, 56 %).

^1H (300 MHz, $CDCl_3$) δ = 7.40-7.25 (5H, m, Ph-H), 3.90 (3H, s, H15 or H23), 3.85 (3H, s, H23 or H15), 3.57 (2H, s, H1), 3.49 (2H, m, H2 or H16), 3.00 (2H, m, H16 or H2),

2.65-2.55 (6H, m, H3, H17 and H6), 2.23 (3H, s, H21), 1.55 (4H, tq, J = 7.0 and 7.0 Hz, H7), 0.98 (6H, t, J = 7.0 Hz, H8) ppm.

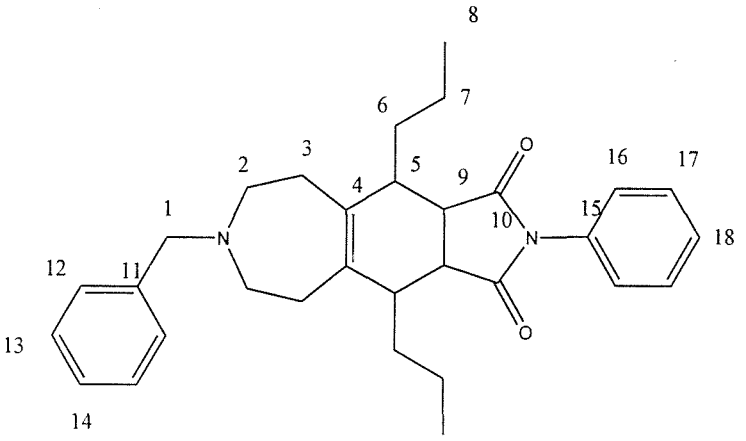
^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.02, 168.80 (C14 and C22), 150.07, 144.42, 139.40, 138.62, 138.20, 130.08, 129.70 (C, C4, C5, C9, C13, C18, C19 and C20), 129.16, 128.44, 127.24 (CH, C10, C11 and C12), 63.44 (CH_2, C1), 54.83, 54.58 (CH_2, C2 and C16), 52.61, 52.18 (CH_3, C15 and C23), 33.50 (CH_2, C3 or C17), 32.59 (CH_2, C17 or C3), 30.88 (CH_2, C6), 24.60 (CH_2, C7), 21.10 (CH_3, C21), 24.60 (CH_3, C8) ppm.

IR (neat oil) = 3051 (m), 2968 (brm), 1730 (s), 1343 (m), 1264 (m) cm^{-1}.

LRMS (ES^+, m/z) 442.1 (M+H).

CI-HRMS = $C_{25}H_{31}NO_4S$ requires 441.1974 found 441.1998 (M+).

7-Benzyl-2-phenyl-4,10-dipropyl-1,2,3,3a,4,5,6,7,8,9,10,10a-dodecahydroazepino[4,5-f]isoindole-1,3-dione (159)



To a stirring solution of 1-benzyl-4,5-di[(E)butylidene]azepane (**152**, 0.297 g, 1.0 mmol) in benzene (1.0 mL), under argon, N-phenylmaleimide (0.190 g, 1.1 mmol) was added dropwise. The reaction was refluxed for 15 hrs and then quenched with a saturated solution of $NaHCO_3$ (20.0 mL). The product was extracted with diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Radial chromatography (SiO_2, 0-100 % Et_2O:petroleum then 50% ethyl acetate:petroleum including 5 % Et_3N) afforded the title compound as a viscous yellow oil (365 mg, 0.77 mmol, 77 %).

^{1}H (400MHz, C_6D_6) δ = 7.55-7.25 (10H, m, Ph-H), 3.31 (2H, s, H1), 2.71 (4H, m, H2), 2.55 (4H, m, H3), 2.4-2.2 (6H, m, H3 and H5), 2.10-1.85 (4H, m, H6), 1.65 (2H, m, H9), 1.35 (4H, m, H7), 0.98 (6H, t, *J* = 8.0 Hz, H8) ppm.

^{13}C (75 MHz, C6D6) δ = 176.70 (C, C10), 139.89 (C, C15), 139.47 (C, C4), 133.22 (C, C11), 129.31, 128.94, 128.13, 127.82, 127.27, 126.79 (CH, C12, C13, C14, C16, C17 and C18), 63.91 (CH_2, C1), 54.53 (CH_2, C2), 44.08 (CH, C9 or C5), 40.44 (CH, C5 or C9), 32.01 (CH_2, C3), 29.06 (CH_2, C6), 22.27 (CH_2, C7), 14.70 (CH_3, C8) ppm.

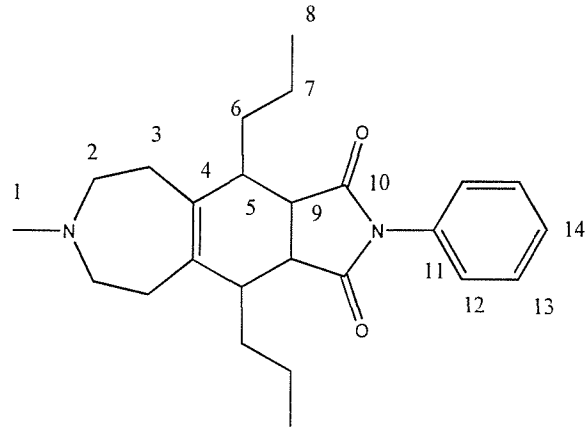
IR (solution DCM) = 3033 (brm), 3001 (m), 1755 (m), 1601 (m), 890 (s) cm^{-1}.

LRMS (ES^+, m/z) 471.8 (M+H).

EI-HRMS = $C_{31}H_{38}N_2O_2$ requires 470.2933 found 470.2946 (M+).

EA = $C_{31}H_{38}N_2O_2$ requires C 79.13, H 8.24, N, 5.92 found C 79.14, H 8.29, N 5.94.

7-Methyl-2-phenyl-4,10-dipropyl-1,2,3,3a,4,5,6,7,8,9,10,10a-dodecahydroazepino[4,5-f]isoindole-1,3-dione (160)



To a stirred solution of 4,5-di[(E)butylidene]-1-methylazepane (**154**, 0.111 g, 0.50 mmol) in benzene (1.0 mL), under argon, *N*-phenylmaleimide (0.087 g, 0.50 mmol) was added. The reaction refluxed for 16 hrs and then quenched with methanol (5 mL) and a saturated solution of $NaHCO_3$ (30.0 mL). The product was extracted into diethyl ether (3 x 30 mL), the combined organic layer washed with water (3 x 40 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Radial chromatography (SiO_2, 0-100 % Et_2O:petroleum followed by 9:1 ethyl acetate:diethyl ether) afforded the title compound as a viscous yellow oil (256 mg, 0.65 mmol, 65 %).

^{1}H (300MHz, $CDCl_3$) δ = 7.45-7.27 (5H, m, Ph-H), 3.25 (2H, brs, H2), 2.50 (4H, m, H3), 2.25 (3H, s, H1), 2.10 (4H, m, H5 or H9), 1.87 (4H, m, H9 or H5), 1.55 (4H, m, H6), 1.37 (4H, tq, J = 8.0 Hz, H7), 0.98 (6H, t, J = 8.0 Hz, H8) ppm.

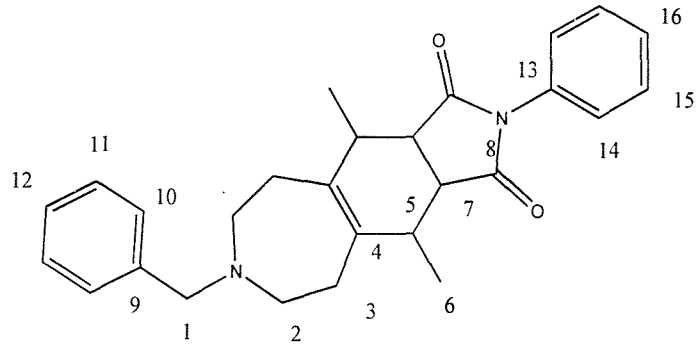
^{13}C (75 MHz, $CDCl_3$) δ = 177.40 (C, C10), 139.42 (C, C11), 132.12 (C, C4), 129.09, 128.48, 126.54 (CH, C12, C13 and C14), 56.21 (CH_2, C2), 47.71 (CH_3, C1), 44.40 (CH, C5 or C9), 40.53 (CH, C9 or C5), 31.97 (CH_2, C3), 28.83 (CH_2, C6 or C7), 22.28 (CH_2, C7 or C6), 14.78 (CH_3, C8) ppm.

IR (solution DCM) = 3048 (brm), 1705 (m), 1413 (m), 702 (brs) cm^{-1}.

LRMS (ES^+, m/z) 395.3 (M+H).

CI-HRMS = $C_{25}H_{34}N_2O_2$ requires 394.1430 found 394.1444 (M+).

7-Benzyl-4,10-dimethyl-2-phenyl-1,2,3,3a,4,5,6,7,8,9,10,10a-dodecahydroazepino[4,5-f]isoindole-1,3-dione (161)



To a stirred solution of 1-benzyl-4,5-di[(E)ethylidene]azepane (**151**, 0.100 g, 0.41 mmol) in diethyl ether (1.0 mL), under argon, *N*-phenylmaleimide (0.87 g, 0.50 mmol) was added, and the reaction refluxed for 12 hrs. The reaction was quenched with methanol (5 mL) and a saturated solution of $NaHCO_3$ (30.0 mL). The product was extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Radial chromatography (SiO_2, 0-100 % Et_2O:petroleum followed by 2:1 ethyl acetate:diethyl ether including 5 % Et_3N) afforded the title compound as a pale yellow oil (135 mg, 0.3 mmol, 55 %).

^{1}H (300MHz, $CDCl_3$) δ = 7.45-7.25 (10H, m, Ph-H), 3.59 (2H, s, H1), 3.17 (2H, m, H7) 2.68 (4H, m, H2), 2.45-2.30 (6H, m, H3 and H6), 1.39 (6H, d, *J* = 9.0 Hz, H6) ppm.

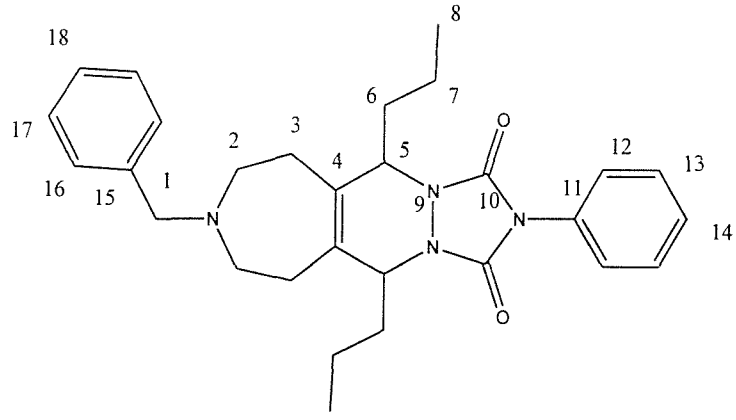
^{13}C (75 MHz, C_6D_6) δ = 169.68 (C, C8), 138.39 (C, C10 or C13), 134.36 (C, C4), (C, C9) not observed, 129.31, 128.37, 128.14, 126.66, 126.24, 126.10 (CH, C10, C11, C12, C14, C15 and C16), 63.01 (CH_2, C1), 54.35 (CH_2, C2), 35.22 (CH, C7), 30.74 (CH_2, C3), 30.48 (CH, C5), 16.14 (CH_3, C6) ppm. Reprocess these.

IR (neat) = 3044 (brm), 1772 (m), 1655 (w), 1056 (m), 702 (m) cm^{-1}.

LRMS (ES^+, m/z) 415.4 (M+H).

EI-HRMS = $C_{27}H_{30}O_2N_2$ requires 414.2307 found 414.2309 (M+).

7-Benzyl-2-phenyl-4,10-dipropyl-4,5,6,7,8,9,10,10a-octahydro-3aH-2,7-diaza-cyclohepta[f]indene-1,3-dione (162)



To a stirred solution of 1-benzyl-4,5-di[(E)butylidene]azepane (**152**, 0.150 g, 0.5 mmol) in diethyl ether (1.0 mL), under argon, 4-phenyl-4,5-dihydro-3H-1,2,4-triazole-3,5-dione (100 mg, 0.59 mmol) was added, and the reaction refluxed for 12 hrs. The reaction was quenched with methanol (5 mL) and a saturated solution of $NaHCO_3$ (30.0 mL). The product was extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Radial chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a pale yellow oil (135 mg, 0.3 mmol, 54 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.54-7.30 (10H, m, Ph-H), 4.22 (2H, t, *J* = 7.0 Hz, H5), 2.55-2.48 (4H, m, H2), 2.15-2.07 (4H, m, H3), 1.90 (4H, dt, *J* = 7.0 and 7.0 Hz, H6), 1.50 (4H, tq, *J* = 7.0 and 7.0 Hz, H7), 0.89 (6H, t, *J* = 7.0 Hz, H8) ppm.

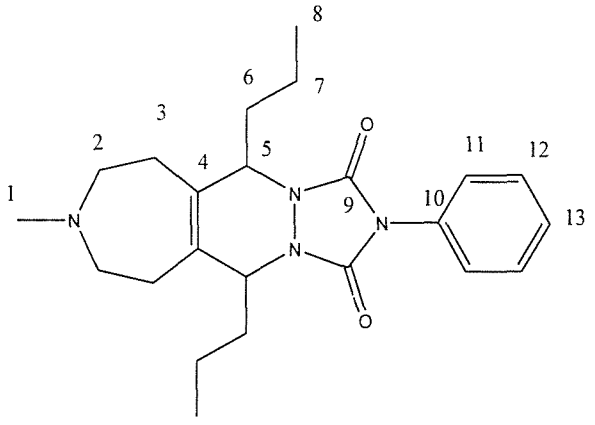
^{13}C (75 MHz, $CDCl_3$) δ = 175.67 (C, C10), 137.86 (C, C11), 135.45 (C, C15), 132.21 (C, C4), 129.30, 128.93, 128.58, 128.11, 127.26, 127.11 (CH, C12, C13, C14, C16, C17 and C18), 62.89 (CH, C5), 54.81 (CH_2, C1), 34.79 (CH_2, C3), 29.12 (CH_2, C6), 17.96 (CH_2, C7), 13.45 (CH_3, C8) ppm.

IR (neat oil) = 3008 (brm), 2271 (w), 1705 (s), 1465 (m), 807 (brm) cm^{-1}.

LRMS (ES^+, m/z, %) 473.6 (M+H).

EI-HRMS = $C_{29}H_{36}N_4O_2$ requires 472.2834 found 472.2839 (M+).

8-Methyl-2-phenyl-5,11-dipropyl-2,3,6,7,8,9,10,11-octahydro-1H,5H-[1,2,4]triazolo[1',2':1,2]pyridazino[4,5-d]azepine-1,3-dione (163)



To a stirred solution of 4,5-di[(E)butylidene]-1-methylazepane (**154,** 0.111 g, 0.50 mmol) and boron trifluoride diethyl etherate complex (0.30 mL, 2.0 mmol) in dichloromethane (1.0 mL), 4-phenyl-4,5-dihydro-3H-1,2,4-triazole-3,5-dione (100 mg, 0.59 mmol) in THF (3.0 mL) at – 78 °C was added. The mixture was warmed to room temperature, stirred for 2 hours and quenched with a saturated solution of $NaHCO_3$ (20.0 mL). The product was extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Radial chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a viscous yellow oil (240 mg, 0.54 mmol, 51 %).

^{1}H (300MHz, $CDCl_3$) δ = 7.50-7.20 (5H, m, Ph-H), 4.19 (2H, m, H5), 2.48 (4H, m, H2), 2.27 (3H, s, H1), 2.25 (4H, m, H3), 1.90 (4H, dt, *J* = 6.5 and 7.0 Hz, H6), 1.35 (4H, m, H7), 0.89 (6H, t, *J* = 7.0 Hz, H8) ppm.

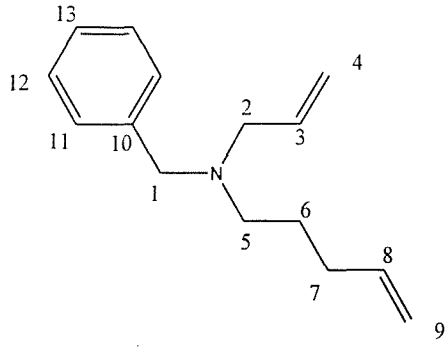
^{13}C (100 MHz, $CDCl_3$) δ = 149.86 (C, C9), 132.08 (C, C10), 130.62 (C, C4), 128.00, 126.84, 124.82 (CH, C11, 12 and C13), 65.55 (CH, C5), 54.45 (CH_2, C2), 44.60 (CH_3, C1), 34.18 (CH_2, C3), 29.88 (CH_2, C6), 17.95 (CH_2, C7), 13.49 (CH_3, C8) ppm.

IR (neat oil) = 2998 (brm), 2107 (w), 1704 (s), 1465 (m), 807 (brm) cm^{-1}.

LRMS (ES^+, m/z) 397.7 (M+H).

CI-HRMS = $C_{23}H_{32}N_4O_2$ requires 396.2525 found 396.2529 (M+).

Allyl-benzyl-pent-4-enyl-amine (168)



5-bromopentyne (745 mg, 5.0 mmol) was added dropwise to a stirring solution of *N*-benzyl-*N*-allylamine (662 mg, 4.5 mmol), MeCN (10.0 mL) and K_2CO_3 (3.0 g, 28.0 mmol). The solution was then refluxed for 10 hours before quenching with a saturated solution of $NaHCO_3$ (10.0 mL). The product was extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-50 % Et_2O:petroleum including 5 % Et_3N) afforded the title product as a viscous orange oil (1.02 g, 3.9 mmol, 86 %).

^{1}H (400 MHz, $CDCl_3$) δ = 7.35-7.10 (5H, m, Ph-H), 5.75-5.57 (2H, m, H8 and H3), 5.15 (1H, d, *J* = 17.0 Hz, H4), 5.05 (1H, d, *J* = 10.5 Hz, H4'), 4.95 (1H, d, *J* = 16.5 Hz, H9), 4.83 (1H, d, *J* = 11.0 Hz, H9'), 3.45 (2H, s, H1), 2.98 (2H, d, *J* = 8.0 Hz, H2), 2.35 (2H,

t, J = 7.0 Hz, H5), 2.00 (2H, dt, J = 7.0 and 7.0 Hz, H7), 1.45 (2H, tt, J = 7.0 and 7.0 Hz, H6) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 139.96 (CH, C8 or C3), 138.88 (C, C10), 136.25 (CH, C3 or C8), 129.94, 128.23, 126.83 (CH, C11, C12 and C13), 117.13 (CH_2, C4 or C9), 114.48 (CH_2, C9 or C4), 58.27 (CH_2, C1), 56.92 (CH_2, C2), 53.06 (CH_2, C5), 31.64 (CH_2, C7), 26.54 (CH_2, C6) ppm.

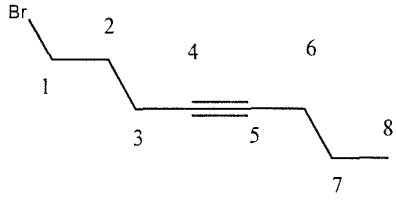
IR (neat oil) = 2932 (brm), 2789 (brm), 1640 (m), 1494 (m), 911 (s) cm^{-1}.

GC = 4.655 min.

LRMS (ES^+, m/z) 216.1 (M+H).

EI-HRMS = $C_{15}H_{22}N$ requires 216.1747 found 216.1742 (M+H).

1-Bromooct-4-yne (169)[79]

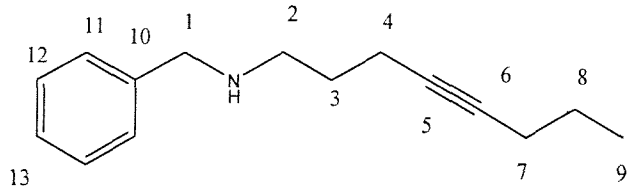


To a stirred solution, at –10 °C under argon, of 1-pentyne (9.86 mL, 0.10 mol) in THF (90 mL) ^{n}BuLi (44 mL, 2.5 M solution in hexanes, 0.11 mol) was added slowly. After 10 minutes the resulting solution was cooled to –20 °C before addition of 1,3-dibromopropane (10.15 mL, 0.10 mol) followed by HMPA (17.4 mL, 0.10 mol). The reaction was warmed to room temperature, stirred for 16 hours then quenched with a saturated solution of $NaHCO_3$ (20.0 mL). The product was extracted with diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to afford the crude product (estimated yield of title compound 45 % by NMR). The crude product was used directly in subsequent reactions.

^{1}H (300 MHz, $CDCl_3$) δ = 3.52 (2H, t, J = 7.0 Hz, H1), 2.35 (2H, tt, J = 7.0, 2.2 Hz, H3 or H6), 2.13 (2H, tt, J = 7.0, 2.2 Hz, H6 or H3), 2.02 (2H, tt, J = 6.5 and 6.5 Hz, H2), 1.51 (2H, tq, J = 7.0 and 7.0 Hz, H7), 0.98 (3H, t, J = 7.0 Hz, H8) ppm.

^{1}HNMR data in agreement with the literature[79].

N-Benzyl-*N*-(4-octynyl)amine (170)[80]



A solution of 1-bromooct-4-yne (**169**, 10.0 g, 53.5 mmol) in benzylamine (86.7 mL, 0.79 mol) was refluxed for 16 hours then quenched with a saturated solution of $NaHCO_3$ (50.0 mL). The product was extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude reaction mixture was purified by reduced pressure distillation (121 °C and 19 torr) to afford the title compound as a colourless oil [7.56 g, 34.8 mmol, 65 %].

^{1}H (400 MHz, $CDCl_3$) δ = 7.40-7.27 (5H, m, Ph-H), 3.80 (2H, s, H1), 2.75 (2H, t, *J* = 7.1 Hz, H2), 2.26 (2H, tt, *J* = 7.1, 2.6 Hz, H4), 2.12 (2H, tt, *J* = 7.4, 2.6 Hz, H7), 1.71 (2H, tt, *J* = 7.1 and 7.1 Hz, H3), 1.49 (2H, tq, *J* = 7.5 and 7.5 Hz, H8), 0.98 (3H, t, *J* = 7.5 Hz, H9) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 140.56 (C, C10), 129.21, 128.88, 127.06 (CH, C11, C12 and C13), 80.74, 79.80 (C, C5 and C6), 54.37 (CH_2, C1), 48.60 (CH_2, C2), 29.69 (CH_2, C4), 22.89 (CH_2, C7), 21.17 (CH_2, C8), 17.80 (CH_2, C3), 13.80 (CH_3, C9) ppm.

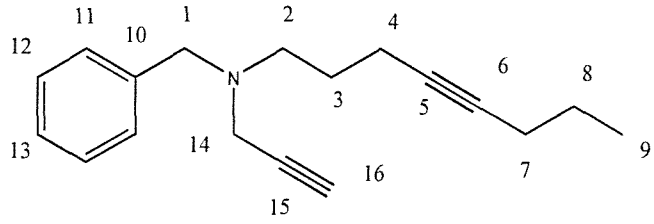
IR (neat oil) = 3327 (brm), 2931 (brm), 1644 (brs),1452 (s), 1119 (brs) cm^{-1}.

LRMS (ES^+, m/z) 216.3 (M+H)

CI-HRMS = $C_{15}H_{20}N$ requires 214.1596 found 214.1595 (M-H).

^{1}HNMR data in agreement with the literature [80].

***N*-Benzyl-*N*-(2-propynyl)-*N*-(4-octynyl)amine (172)**[80]



Propargyl bromide (80 % wt. in toluene, 2.67 mL, 30.0 mmol) was added dropwise to a stirred solution of *N*-benzyl-*N*-(4-octynyl)amine (**170**, 6.52 g, 30 mmol), K_2CO_3 (2.0 g, 20 mmol) and MeCN (20 mL), refluxed for 8 hours, quenched with a saturated solution of $NaHCO_3$ (20.0 mL). The product was extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-50 % Et_2O:petrol including 5 % Et_3N) afforded the title product as a viscous yellow oil (5.1 g, 23 mmol, 76 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.45-7.27 (5H, m, Ph-H), 3.65 (2H, s, H1), 3.32 (2H, d, J = 2.0 Hz, H14), 2.70 (2H, t, J = 7.0 Hz, H2), 2.39 (1H, tt, J = 6.5, 3.0 Hz, H4), 2.26 (1H, t, J = 2.2 Hz, H16), 2.12 (2H, tt, J = 7.0, 2.6 Hz, H7), 1.72 (2H, tt, J = 7.0 and 7.0 Hz, H3), 1.48 (2H, tq, J = 7.5 and 7.5 Hz, H8), 0.98 (3H, t, J = 7.5 Hz, H9) ppm.

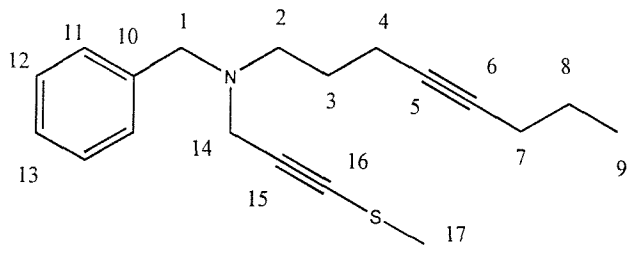
^{13}C (75 MHz, $CDCl_3$) δ = 138.98 (C, C10), 129.19, 128.41, 127.21 (CH, C11, C12 and C13), 80.26 (C, C5), 80.00 (C, C6), 78.75 (CH, C16), 73.14 (C, C15), 57.89 (CH_2, C1), 52.43 (CH_2, C2), 41.52 (CH_2, C14), 27.31 (CH_2, C4), 22.66 (CH_2, C7), 20.11 (CH_2, C8), 16.73 (CH_2, C3), 13.67 (CH_3, C9) ppm.

IR (neat oil) = 3299 (m), 2331 (brs), 1810 (m), 1705 (m), 1602 (m) cm^{-1}.

LRMS (ES^+, m/z); 254.3 (M+H)

CI-HRMS = $C_{18}H_{24}N$ requires 254.1903 found 254.1910 (M+H).

_N_-Benzyl-_N_-[3-(methylsulfanyl)-2-propynyl]-_N_-(4-octynyl)amine (173)



To a stirred solution of _N_-benzyl-_N_-(2-propynyl)-_N_-(4-octynyl)amine (**172**, 0.516 g, 2.0 mmol) in THF (5.0 mL) under argon at –78 °C, ^{n}BuLi (0.96 mL of 2.5 M solution in hexanes, 2.41 mmol) was added dropwise. Pre-dried dimethyldisulphide (0.26 mL, 2.82 mmol) was added and the solution warmed to room temperature, stirred for 2 hours before quenching with a saturated solution of $NaHCO_3$ (50.0 mL). The product was extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a pungent yellow oil (540 mg, 1.80 mmol, 90 %).

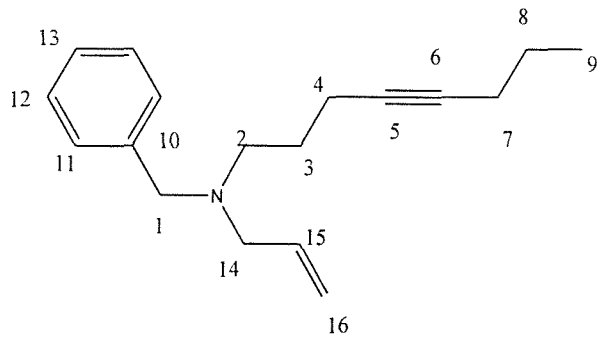
^{1}H (300 MHz, $CDCl_3$) δ = 7.45-7.27 (5H, m, H-Ph), 3.55 (2H, s, H1), 3.35 (2H, s, H14), 2.55 (2H, t, _J_ = 7.0 Hz, H2), 2.35 (3H, s, H17), 2.11 (2H, tt, _J_ = 7.0 and 2.6 Hz, H4), 2.00 (2H, tt, _J_ = 7.0 and 2.6 Hz, H7), 1.60 (2H, tt, _J_ = 7.0 and 7.0 Hz, H3), 1.39 (2H, tq, _J_ = 7.0 Hz, H8), 0.97 (3H, t, _J_ = 7.0 Hz, H9) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 139.01 (C, C10), 129.21, 128.38, 127.15 (CH, C11, C12 and C13), 88.31 (C, C15), 80.62 (C, C5), 80.05 (C, C6), 76.74 (C, C16), 58.01 (CH_2, C1), 53.25 (CH_2, C14), 52.55 (CH_2, C2), 29.43 (CH_2, C4), 27.30 (CH_2, C7), 20.91 (CH_2, C8), 19.62 (CH_3, C17), 16.82 (CH_2, C3), 13.75 (CH_3, C9) ppm.

IR (neat oil) = 3027 (brm), 2695 (m), 1678 (s), 1378 (m), 1074 (m) cm^{-1}.

LRMS (ES^{+}, m/z) 300.1 (M+H)

***N*-Allyl-*N*-benzyl-*N*-(4-octynyl)amine (174)**



Allyl bromide (1.20 g, 10.0 mmol) was added dropwise to a stirring solution of *N*-benzyl-*N*-(4-octynyl)amine (**170**, 1.0 g, 4.6 mmol), K_2CO_3 (2.0 g, 20.0 mmol) and MeCN (20.0 mL). The solution refluxed for 4 hours before quenching with a saturated solution of $NaHCO_3$ (40.0 mL). The product was extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 mL), brine (40.0 mL), dried over $MgSO_4$ and the solvent removed under reduced pressure. Chromatography (SiO_2, 0-50 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as an orange oil (1.02 g, 3.9 mmol, 85 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.40-7.23 (5H, m, Ph-H), 5.85 (1H, ddt, J = 14.5, 9.8, 6.1 Hz, H15), 5.19 (1H, d, J = 14.5 Hz, H16), 5.10 (1H, d, J = 9.8 Hz, H16'), 3.59 (2H, s, H1), 3.10 (2H,d, J = 6.2 Hz, H14), 2.55 (2H, t, J = 6.9 Hz, H2), 2.19 (2H, tt, J = 7.0 and 2.6 Hz, H4 or H7), 2.09 (2H, tt, J = 7.0 and 2.6 Hz, H7 or H4), 1.72 (2H, tt, J = 7.5 and 7.5 Hz, H3), 1.48 (2H, tq, J = 7.0 and 7.0 Hz, H8), 0.98 (3H, t, J = 7.0 Hz, H9) ppm.

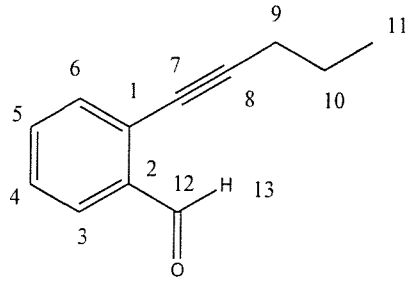
^{13}C (75 MHz, $CDCl_3$) δ = 136.20 (C, C10), 129.06, 128.98, 128.28 (CH, C11, C12 and C13), 126.88 (CH, C15), 117.55 (CH_2, C16), 80.16 (C, C6 or C5), 78.50 (CH, C5 or C6), 58.26 (CH_2, C14), 57.67 (CH_2, C1), 56.93 (CH_2, C2), 26.91 (CH_2, C3), 22.65 (CH_2, C4 or C7), 20.90 (CH_2, C7 or C4), 16.75 (CH_2, C8), 13.66 (CH_3, C9) ppm.

IR (neat oil) = 2934 (s), 1737 (brm), 1489 (s), 1358 (brm) cm^{-1}.

LRMS (ES^+, m/z) 256.4 (M+H).

CI-HRMS = $C_{18}H_{25}N$ requires 255.1987 found 255.1973 (M+).

2-(1-Pentynyl)benzaldehyde (175)[70]



To a stirring solution of 2-bromobenzaldehyde (1.85 g, 1.17 mL, 10.0 mmol), 1-pentyne (750 mg, 1.1 mL), CuI (100 mg, 0.50 mmol), triphenylphosphine (100 mg, 0.40 mmol) and Et_3N (20 mL), bis-triphenylphosphinepalladium(II) chloride (100 mg, 0.14 mmol) was added dropwise. The reaction was refluxed for 17 hours before quenching with a saturated solution of $NaHCO_3$ (20.0 mL). The product was extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum) afforded the title compound as a red oil (9.00 g, 9.0 mmol, 94 %).

^{1}H (300 MHz, $CDCl_3$) δ = 10.40 (1H, s, H13), 7.72 (1H, d, J = 8.0 Hz, H3), 7.45-7.10 (3H, m, Ph-H), 2.45 (2H, t, J = 8.0, H9), 1.50 (2H, tq, J = 8.0 and 8.0, H10), 0.89 (3H, t, J = 8.0 Hz, H11) ppm.

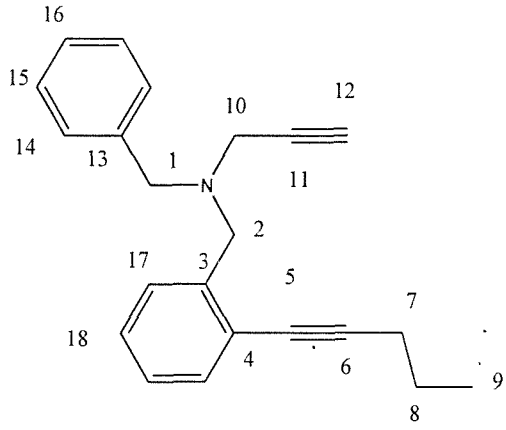
^{13}C (75 MHz, $CDCl_3$) δ = 192.12 (CH, C12), 136.04 (C, C2), 134.69 (C, C1), 133.69, 133.30, 127.84, 126.90 (CH, C3, C4, C5 and C6), 129.80 (C, C7), 98.00 (C, C8), 22.00 (CH_2, C9), 21.57 (CH_2, C10), 11.37 (CH_3, C11) ppm.

GC = 7.15 min.

IR (neat oil) = 3061 (w), 2963 (m), 2232 (m), 1687 (s), 1594 (m) cm^{-1}.

LRMS ($APCI^+$, m/z,) 173.0 (M+H).

Benzyl-(2-pent-1-ynyl-benzyl)-prop-2-ynyl-amine (176)[70]



A solution of propargylbenzylamine (8.7 g, 8.9 mL, 60.0 mmol) in methanol (25.0 mL) was acidified with HCl (6M, 4.0 mL) before adding 2-(1-pentynyl)benzaldehyde (**175**, 1.96 g, 10.0 mmol). After 15 minutes, sodium triacetoxyborohydride (6.4 g, 30.0 mmol) was added and stirred for 72 hours before quenching with a saturated solution of $NaHCO_3$ (100.0 mL). The product was extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a yellow oil (758 mg, 2.5 mmol, 25 %).

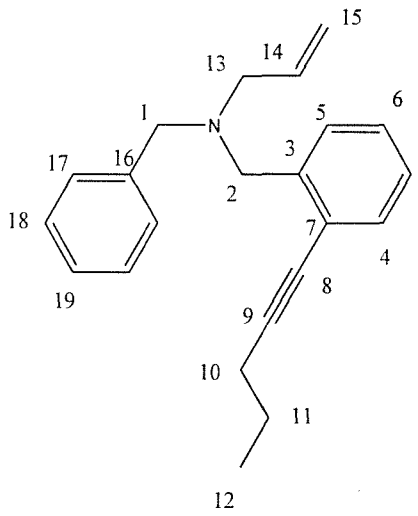
^{1}H (300 MHz, $CDCl_3$) δ = 7.55-7.10 (9H, m, Ph-H), 3.95 (2H, s, H2), 3.73 (2H, s, H1), 3.29 (2H, s, H10), 2.45 (2H, t, J = 7.0 Hz, H7), 2.29 (1H, s, H12), 1.65 (2H, tq, J = 7.0 and 7.0 Hz, H8), 1.11 (3H, t, J = 7.0 Hz, H9) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 140.10 (C, C3 or C4), 139.84 (C, C4 or C3), 132.41, 129.17, 128.17, 127.67, 127.21, 126.87 (CH, C14, C15, C16, C17 and C18), 88.61, 78.70, 73. 27 (C, C5, C6 and C11), 71.05 (CH, C12), 57.41 (CH_2, C1), 55.88 (CH_2, C2), 41.31 (CH_2, C10), 22.43 (CH_2, C7), 21.80 (CH_2, C8), 13.86 (CH_3, C9) ppm.

IR (neat oil) = 2923 (brm), 1631 (m), 1463 (m), 1016 (brs) cm^{-1}.

LRMS ($APCI^+$, m/z) 302.2 (M+H).

Allyl-benzyl-(2-pent-1-ynyl-benzyl)-amine (177)[70]



A solution of *N*-allylbenzylamine (4.42 g, 4.5 mL, 30.0 mmol) in methanol (25.0 mL) was acidified with HCl (6.0 M, 4.0 mL) before adding 2-(1-pentynyl)benzaldehyde (**175**, 1.05 g, 5 mmol). After 15 minutes, sodium triacetoxyborohydride (6.30 g, 30 mmol) was added and stirred for 72 hours before quenching with a saturated solution of $NaHCO_3$ (100.0 mL). The product was extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a yellow oil (456 mg, 1.5 mmol, 55 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.50-7.10 (9H, m, Ph-H), 5.95 (1H, ddt, *J* = 15.0, 10.5 and 6.6 Hz, H14), 5.20 (1H, d, *J* = 15.0 Hz, H15), 5.10 (1H, d, *J* = 10.5 Hz, H15'), 3.85 (2H, s, H2), 3.60 (2H, s, H1), 3.10 (2H, d, *J* = 6.2 Hz, H13), 2.40 (2H, t, *J* = 7.0 Hz, H10), 1.65 (2H, tq, *J* = 7.5 and 7.5 Hz, H11), 0.89 (3H, t, *J* = 7.5 Hz, H12) ppm.

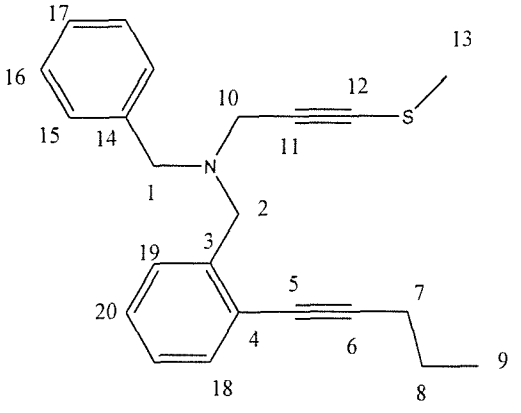
^{13}C (75 MHz, $CDCl_3$) δ = 141.90 (C, C7), 139.14 (C, C16), 136.23 (C, C3), 132.18 (CH, C14), 128.88, 128.70, 128.30, 127.70, 126.90, 126.45 (CH, C4, C5, C6, C17, C18, C19), 117.35 (CH_2, C15), 93.40, 79.54 (C, C8 and C9), 58.06, 56.68 (CH_2, C1 and C2), 55.70 (CH_2, C13), 22.45 (CH_2, C10), 21.75 (CH_2, C11), 13.80 (CH_3, C12) ppm.

IR (neat oil) = 3026 (m), 1631 (m), 1950 (w), 1600 (m), 1451 (s) cm^{-1}.

LRMS (ES^+, m/z) 304.1 (M+H)

ES-HRMS $C_{22}H_{26}N$ requires 304.2059 found 304.2048 (M+H).

Benzyl-(3-methylsulfanyl-prop-2-ynyl)-(2-pent-1-ynyl-benzyl)-amine (178)[70]



To a stirred solution of benzyl-(2-pent-1-ynyl-benzyl)-prop-2-ynyl-amine (**176**, 740 mg, 2.46 mmol) in THF (5.0 mL) under argon at –78 °C, ^{n}BuLi (0.96 mL, 2.5 M solution in hexanes, 2.41 mmol) was added dropwise. Pre-dried dimethyldisulphide (0.26 mL, 2.82 mmol) was added, the solution warmed to room temperature, stirred for 2 hours before quenching with a saturated solution of $NaHCO_3$ (50.0 mL). The product was extracted with diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a pungent yellow oil (810 mg, 2.10 mmol, 90 %).

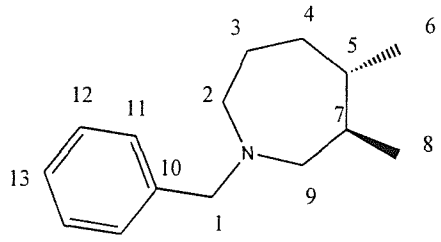
^{1}H (300 MHz, $CDCl_3$) δ = 7.53-7.15 (9H, m, Ph-H), 3.88 (2H, s, H10), 3.66 (2H, s, H1), 3.29 (2H, s, H2), 2.45 (3H, s, H13), 1.75 (2H, t, *J* = 7.5 Hz, H7), 1.65 (2H, tq, *J* = 7.5 and 7.5 Hz, H8), 1.05 (3H, t, *J* = 7.5 Hz, H9) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 140.62 (C, C3), 139.17 (C, C14), 132. 41 (C, C4), 129.21, 129.13, 128.40, 127.68, 127.20, 126.84 (CH, C15, C16, C17, C18, C19 and C20), 93.40, 88.61, 79.80, 76.10 (C, C11, C12, C5 and C6), 57.61 (CH_2, C2), 55.98 (CH_2, C1), 42.79 (CH_2, C10), 22.53 (CH_2, C7), 21.83 (CH_2, C8), 19.70 (CH_3, C13), 13.85 (CH_3, C9) ppm.

IR (neat oil) = 3061 (brm), 2972 (w), 1641 (m), 1483 (m), 1324 (m) cm^{-1}.

LRMS (ES^+, m/z) 348.2 (M+H)

1-Benzyl-3,4-dimethyl-azepane (179)



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in dry THF (5.0 mL) under argon at - 80 °C, ^nBuLi (0.8 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise and left for 20 minutes. *N*-Allyl-*N*-benzyl-*N*-(4-octynyl)amine (**168,** 0.221 g, 1.0 mmol) in THF (2.0 mL) was added dropwise and the mixture warmed to room temperature, and stirred for 7 hrs. The reaction was quenched with methanol (5.0 mL) and a saturated solution of $NaHCO_3$ (8.0 mL). The product was extracted with diethyl ether (3 x 100 mL), the combined organic layer washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title diene as a pale, viscous oil (170 mg, 0.78 mmol, 78 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.35-7.10 (5H, m, Ph-H), 3.60 (2H, s, H1), 2.50-2.38 (4H, m, H2 and H9), 1.75-1.65 (2H, m, H4), 1.56 (2H, m, H3), 1.46 (1H, m, H7 or H5), 1.20 (1H, m, H5 or H7), 0.95 (3H, d, *J* = 7.0 Hz, H6), 0.85 (3H, d, *J* = 7.0 Hz, H8) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 140.21 (C, C10), 128.83, 128.37, 126.64 (CH, C11, C12 and C13), 63.82 (CH_2, C1), 61.14 (CH_2, C9 or C2), 56.86 (CH_2, C2 or C9), 40.86 (CH, C7 or C5), 40.59 (CH, C5 or C7), 34.09 (CH_2, C3), 27.21 (CH_2, C4), 22.24 (CH_3, C8 or C6), 19.96 (CH_3, C6 or C8) ppm.

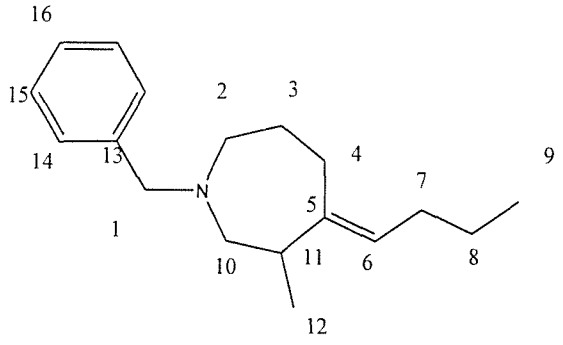
GC = 5.088 mins.

IR (neat oil) = 2956 (m), 1640 (w), 1259 (brm), 801 (m) cm^{-1}.

LRMS (ES^+, m/z) 218.3 (M+H).

EA = $C_{15}H_{23}N$ requires C 82.89, H 10.67, N 6.44 found C 82.85, H 10.68, N 6.70.

1-Benzyl-4-[(E)butylidene]-3-methylazepane (182)



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in dry THF (5.0 mL) under argon at – 80 °C, ^{n}BuLi (0.8 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise and stirred for 20 minutes. *N*-Allyl-*N*-benzyl-*N*-(4-octynyl)amine (**174**, 257 mg, 1.0 mmol) dissolved in THF (2.0 mL) was added dropwise warmed to room temperature, then stirred for 7 hrs before quenching with a saturated solution of $NaHCO_3$ (8.0 mL) and methanol (5.0 mL). The product was then extracted with diethyl ether (3 x 100 mL), the combined organic layer washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title diene as a pale, oil (143 mg, 0.56 mmol, 56 %).

^{1}H (300MHz, $CDCl_3$) δ = 7.45-7.25 (5H, m, Ph-H), 5.36 (1H, t, *J* = 7.0Hz, H6), 3.58 (2H, s, H1), 3.35 (2H, m, H10), 2.46-2.28 (2H, m, H2), 2.15-1.98 (5H, m, H4, H7 and H11), 1.62 (2H, tq, *J* = 7.0 and 7.0 Hz, H8), 1.61-1.51 (2H, m, H3), 0.92 (3H, d, *J* = 8.0 Hz, H12), 0.85 (3H, t, *J* = 7.0 Hz, H9) ppm.

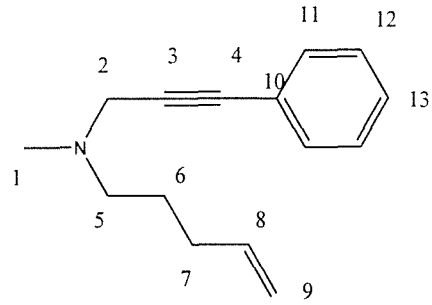
^{13}C (75 MHz, $CDCl_3$) δ = 141.90 (C, C5), 136.45 (C, C13), 129.31, 128.46, 127.77 (CH, C14, C15 and C16), 121.39 (CH, C6), 60.39 (CH_2, C1), 57.85 (CH_2, C2), 52.01 (CH_2, C10), 40.14 (CH, C11), 31.41 (CH_2, C4), 29.79 (CH_2, C7), 26.98 (CH_2, C3), 23.30 (CH_2, C8), 18.10 (CH_3, C17), 17.33 (CH_3, C12), 13.70 (CH_3, C9) ppm.

IR (neat oil) = 3301 (brm), 1621 (m), 1459 (m), 1156 (m), 899 (m) cm^{-1}.

LRMS (ES^+, m/z) 258.3 (M+H)

EI-HRMS = $C_{18}H_{27}N$ requires 257.2144 found 257.2139 (M+).

Benzyl-but-2-ynyl-pent-4-enyl-amine (184)



5-Bromopentene (745 mg, 5.0 mmol) was added dropwise to a stirring solution of methyl-(3-phenyl-prop-2-ynyl)-amine (667 mg, 4.6 mmol), K_2CO_3 (2.0 g, 20.0 mmol) and MeCN (20.0 mL). The solution was refluxed for 12 hours before quenching with a saturated solution of $NaHCO_3$ (40.0 mL). The product was extracted with diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Chromatography (SiO_2, 0-50 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as an orange oil (715 mg, 3.4 mmol, 73 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.45-7.15 (5H, m, Ph-H), 5.75 (1H, ddt, J = 16.5, 10.5 and 6.6 Hz, H8), 4.98 (1H, d, J = 16.5 Hz, H9), 4.85 (1H, d, J = 10.9 Hz, H9'), 3.45 (2H, s, H2), 2.40 (2H, t, J = 6.5 Hz, H5), 2.27 (3H, s, H1), 2.08 (2H, dt, J = 6.6 and 6.6 Hz, H7), 1.50 (2H, tt, J = 6.6 and 6.6 Hz, H6) ppm.

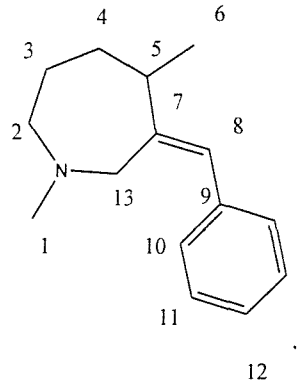
^{13}C (75 MHz, $CDCl_3$) δ = 138.64 (C, C10), 131.85 (CH, C8), 128.39, 128.12, 127.89 (CH, C11, C12 and C13), 114.81 (CH_2, C9), 86.22, 86.11 (C, C3 and C4), 55.61 (CH_2, C2), 46.62 (CH_2, C5), 42.16 (CH_3, C1), 31.72 (CH_2, C7), 27.04 (CH_2, C6) ppm.

GC = 5.414 mins.

IR (neat oil) = 2934 (brm), 1620 (m), 1489 (w), 1046 (m) cm^{-1}.

LRMS (ES^+, m/z) 214.3 (M+H).

1-Benzyl-3-benzylidene-4-methyl-azepane (186)



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in dry THF (5 mL) under argon at -80 °C, ^nBuLi (0.8 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise and left for 10 minutes. Benzyl-but-2-ynyl-pent-4-enyl-amine (**184**, 213 mg, 1.0 mmol) dissolved in THF (2.0 mL) was added dropwise. The solution was warmed to room temperature, stirred for 7 hrs before quenching with a saturated solution of $NaHCO_3$ (8.0 mL) and methanol (5.0 mL). The product was extracted with diethyl ether (3 x 100 mL), the combined organic layer washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a pale oil (168 mg, 0.78 mmol, 78 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.43-7.15 (5H, m, Ph-H), 6.41 (1H, s, H8), 3.31 (1H, d, *J* = 12.0 Hz, H13), 3.01 (1H, d, *J* = 12.0 Hz, H13'), 2.91 (1H, m, H2), 2.74-2.70 (1H, m, H2'), 2.32 (3H, s, H1), 2.00-1.65 (5H, m, H3, H4 and H5), 1.15 (3H, d, *J* = 8.0 Hz, H6) ppm.

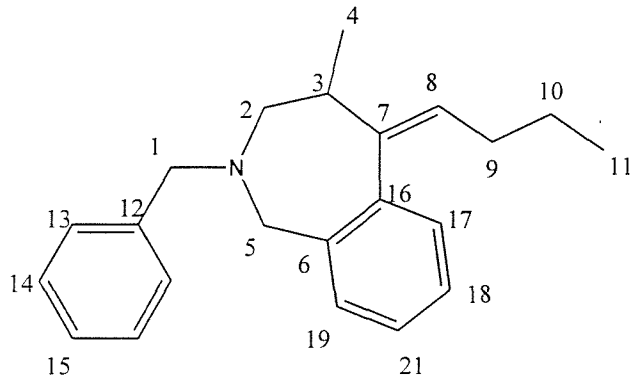
^{13}C (75 MHz, $CDCl_3$) δ = 141.12 (C, C7), 135.42 (C, C9), 128.75, 128.03, 127.77, (CH, C10, C11 and C12), 119.27 (CH, C8), 61.16 (CH_2, C1), 57.12 (CH_2, C2), 52.33 (CH_2, C13), 38.36 (CH, C5), 26.35 (CH_2, C4), 18.10 (CH_2, C3), 17.69 (CH_3, C6) ppm.

IR (neat oil) = 3011 (brm), 1602 (w), 1459 (m), 906 (m) cm^{-1}

LRMS (ES^+, m/z) 216.3 (M+H).

EI-HRMS = $C_{15}H_{21}N$ requires 215.1674 found 215.1669.

2-Benzyl-5-butylidene-4-methyl-2,3,4,5-tetrahydro-1H-benzo[c]azepine (187)[70]



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in dry THF (5.0 mL) under argon at –80 °C was added dropwise, nBuLi (0.8 mL of 2.5 M solution in hexanes, 2.0 mmol) and left for 10 minutes. Allyl-benzyl-(2-pent-1-ynyl-benzyl)-amine (**177**, 304 mg, 1.0 mmol) in THF (2.0 mL) was added dropwise and the mixture warmed to room temperature before stirring for 7 hrs. The reaction was quenched with methanol (5 mL) and a saturated solution of $NaHCO_3$ (8.0 mL). The product was extracted into diethyl ether (3 x 100 mL), the organic layer washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a viscous oil (185 g, 0.61 mmol, 61 %).

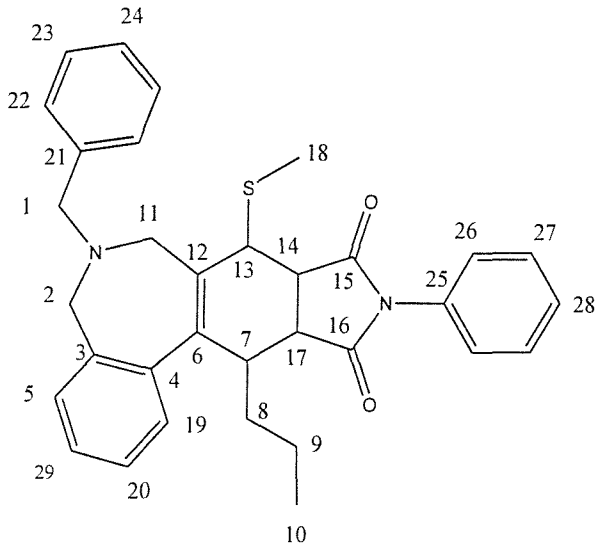
^{1}H (300 MHz, $CDCl_3$) δ = 7.45-7.05 (9H, m, Ph-H), 5.53 (1H, t, *J* = 7.5 Hz, H8), 3.62 (2H, s, H1), 3.58 (2H, s, H5), 2.70 (2H, m, H2), 1.61-1.51 (1H, m, H3), 1.39 (2H, dt, *J* = 6.0 and 6.0 Hz, H9), 1.05 (2H, tq, *J* = 6.0 and 6.0, H10), 0.91 (3H, t, *J* = 6.0 Hz, H11), 0.85 (3H, d, *J* = 7.0 Hz, H4) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 145.50 (C, C7), 139.84 (C, C16), 138.56 (C, C12), 136.71 (C, C6), 128.38, 128.30, 127.06, 127.05, 126.80, 126.51, 124.39 (CH, C13, C14, C15, C17, C18, C19 and C20), 123.45 (CH, C8), 67.36 (CH_2, C5), 58.28 (CH_2, C1), 46.39 (CH_2, C2), 30.53 (CH_2, C8), 30.52 (CH, C3), 23.42 (CH_2, C9), 14.00 (CH_3, C11), 11.65 (CH_3, C4) ppm.

IR (neat oil) = 3028 (m), 2960 (m), 2872 (w), 1601 (w), 1175 (m), cm^{-1}.

LRMS (ES^+, m/z) 306.2 (M+H).

6-Benzyl-8-methylsulfanyl-10-phenyl-12-propyl-6,7,8,8a,11a,12-hexahydro-5H-6,10-diaza-benzo[3,4]cyclohepta[1,2-f]indene-9,11-dione (190)[70]



To a stirred solution of 2-benzyl-5-butylidene-4-methylsulfanylmethylene-2,3,4,5-tetrahydro-1H-benzo[c]azepine (350 mg, 1.0 mmol) in diethyl ether (1.0 mL), *N*-phenylmaleimide (173 mg, 1.0 mmol) was added, refluxed for 12 hrs then quenched with a saturated solution of $NaHCO_3$ (30.0 mL). The product was extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Radial chromatography (SiO_2, 0-100 % Et_2O:petroleum followed by 2:1 ethyl acetate:diethyl ether including 5 % Et_3N) afforded the title compound as a pale yellow oil (238 mg, 0.5 mmol, 45 %).

^{1}H (400 MHz, $CDCl_3$) δ = 7.50-7.30 (18H, m, Ph-H), 3.85-3.35 (6H, m, H1, H2, H14 and H17), 2.97 (1H, d, J = 12.0 Hz, H11), 2.81 (1H, d, J = 12.0 Hz, H11'), 2.42 (3H, s H18), 2.00-1.77 (4H, m, H7, H8 and H13), 1.75 (2H, tq, J = 7.5 and 7.5 Hz, H9), 0.83 (3H, t, J = 7.5 Hz, H10) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 177.52, 176.23 (C, C15 and C16), 142.71, 141.66 (C, C3 and C4), 139.78, 135.08 (C, C12 and C6), 132.45 (C, C25), 130.62 (C, C21), 129.65, 129.31, 129.15, 128.80, 127.99, 127.86, 127.49, 127.15, 126.83 (CH, C5, C19, C20, C22, C23, C24, C26, C27, C28 and C29), 60.82 (CH_2, C11), 56.88, 56.53 (CH_2, C2 and C1), 49.18,

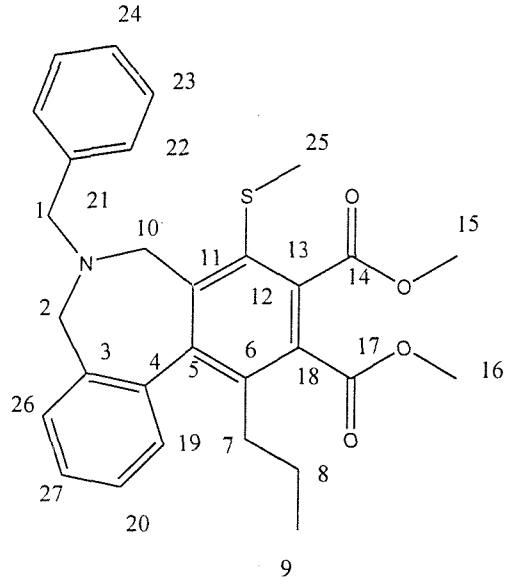
46.60, 44.95 (CH, C7, C14 and C17), 38.89 (CH_3, C18), 37.01 (CH, C13), 22.47 (CH_2, C8), 20.98 (CH_2, C9), 14.61 (CH_3, C10) ppm.

IR (neat oil) = 3049 (w), 2961 (w), 1712 (m), 1598 (w), 1189 (m) cm^{-1}.

LRMS (ES^+, m/z) 523.0 (M+H)

EI-HRMS = $C_{33}H_{33}N_2O_2S$ requires 522.2255 found 522.2263 (M+).

6-Benzyl-4-methylsulfanyl-1-propyl-6,7-dihydro-5H-dibenzo[c,e]azepine-2,3-dicarboxylic acid dimethyl ester (189)



To a stirred solution of $ZrCp_2Cl_2$ (321 mg, 1.1 mmol) in dry THF (5.0 mL) under argon at – 80 °C, ^nBuLi (0.8 mL of 2.5 M solution in hexanes, 2.0 mmol) was added dropwise. Benzyl-(3-methylsulfanyl-prop-2-ynyl)-(2-pent-1-ynyl-benzyl)-amine (**178**, 347 mg, 1.0 mmol) in THF (3.0 mL) was added and the solution was allowed to warm to room temperature. After 4 hours, at 0 °C, the resulting solution was added by cannula addition to CuCl (198 mg, 2.0 mmol), sonicated previously and dried under vacuum (0.1 mm Hg), and DMAD (284 mg, 2.0 mmol). The resulting solution was then stirred vigorously for 12 hours, $NaHCO_3$ (6.0 mL, 6M) was added to the resulting dark brown solution. The product was extracted into diethyl ether (3 x 100 mL), the combined organic layer washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 %

Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a viscous oil (319 mg, 0.65 mmol, 65 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.50-7.20 (9H, m, Ph-H), 4.61 (1H, d, *J* = 12.0 Hz, H10'), 3.91 (3H, s, H16), 3.85 (3H, s, H15), 3.75 (1H, d, *J* = 12.0 Hz, H10), 3.44 (1H, d, *J* = 12.5 Hz, H1), 3.10 (1H, d, *J* = 12.5 Hz, H1'), 3.05 (1H, d, *J* = 8.5 Hz, H2), 2.78 (1H, d, *J* = 8.5 Hz, H2'), 2.64 (2H, t, *J* = 7.5 Hz, H7), 2.45 (3H, s, H25), 1.20 (2H, tq, *J* = 7.5 and 7.5 Hz, H8), 0.79 (3H, t, *J* = 7.5 Hz, H9) ppm.

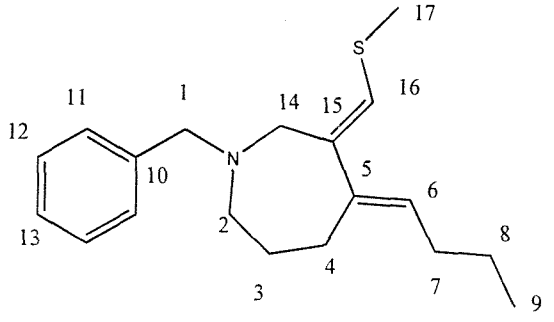
^{13}C (75 MHz, $CDCl_3$) δ = 170.05, 169.20 (C, C14 and C17), 145.30, 143.20 (C, C5 and C11), 142.50, 139.70 (C, C3 and C4), 139.22, 138.41 (C, C6 and C12), 135.76, 134.21 (C, C13 and C18), 129.49 (C, C21), 129.16, 128.84, 128.64, 128.47, 128.37, 127.24, 127.08 (CH, C19, C20, C22, C23, C24, C26 and C27), 59.42 (CH_3, C16), 57.66 (CH_3, C15), 53.28 (CH_2, C10), 53.05 (CH_2, C2), 52.73 (CH_2, C1), 32.56 (CH_2, C7), 24.43 (CH_2, C8), 21.56 (CH_3, C25), 14.30 (CH_3, C9) ppm.

IR (neat oil) = 3042 (m), 2986 (m), 1737 (w), 1547 (w), 1421 (s), 1272 (s) cm^{-1}.

LRMS (ES^+, m/z) 490.4 (M+H).

ES-HRMS $C_{29}H_{32}NO_4S_2$ requires 490.2047 found 490.2045 (M+H).

4-[(E)Butylidene]-3-[(Z)-1-(methylthio)methylidene]-1-(phenylmethyl)perhydroazepine (191)

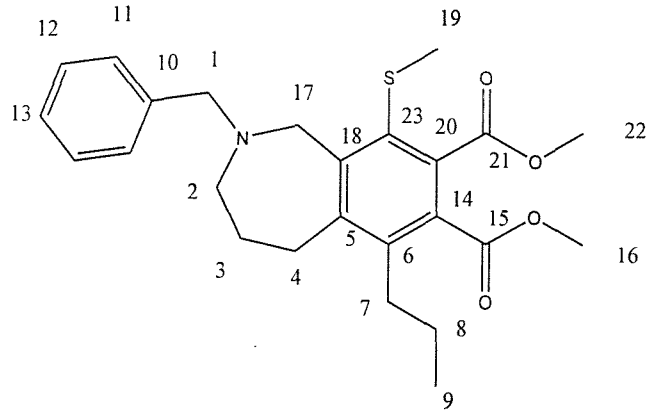


A solution of ^{n}BuLi (0.80 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise to a stirred solution of zirconocene dichloride (0.295 g, 1.0 mmol) in THF (2.0 mL) at –78 °C. *N*-Benzyl-*N*-(3-methylthio-(2-propynyl)-*N*-(4-octynyl)amine (**173**, 0.300 g, 1.0 mmol) was added to the solution. The solution was warmed to room temperature and stirred for 7 hours. The resulting black solution was quenched with methanol (5.0 mL)

and a saturated solution of $NaHCO_3$ (5.0 mL). The product was extracted into diethyl ether (3 x 50 mL), and the combined organic layer washed with water (3 x 50 ml), brine (50.0 mL) dried over $MgSO_4$, filtered and solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title product as a viscous pale yellow oil (0.287 g, 0.9 mmol, 90 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.45-7.27 (5H, m, Ph-H), 5.80 (1H, s, H16), 5.35 (1H, t, *J* = 7.0 Hz, H6), 3.59 (2H, s, H1), 3.45 (2H, s, H14), 2.73 (2H, m, H2), 2.35 (2H, m, H3), 2.18 (3H, s, H17), 2.05 (2H, dd, *J* = 7.0 and 7.0 Hz, H4), 1.65 (2H, m, H7), 1.47 (2H, tq, *J* = 7.5 and 7.5 Hz, H8), 0.97 (3H, t, *J* = 7.5 Hz, H9) ppm.
^{13}C (75 MHz, $CDCl_3$) δ = 143.05 (C, C15), 141.90 (C, C5), 139.45 (C, C10), 129.84, 129.51, 128.38 (CH, C11, C12 and C13), 125.10 (CH, C16), 121.39 (CH, C6), 60.39 (CH_2, C1), 57.85 (CH_2, C14), 56.01 (CH_2, C2), 30.41 (CH_2, C7), 29.29 (CH_2, C4), 26.98 (CH_2, C3), 23.30 (CH_2, C8), 18.10 (CH_3, C17), 13.70 (CH_3, C9) ppm.
IR (neat oil) = 3106 (m), 2613 (s), 1603 (m), 1379 (s), 732 (brm) cm^{-1}.
LRMS (ES^+, m/z, %) 302.5 (M+H).
CI-HRMS = $C_{19}H_{27}NS$ requires 301.1864 found 301.1862 (M+).

Dimethyl 2-benzyl-9-(methylsulfanyl)-6-propyl-2,3,4,5-tetrahydro-1H-2-benzazepine-7,8-dicarboxylate (192)



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in dry THF (5 mL) under argon at $^-$80 °C, ^{n}BuLi (0.8 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise and stirred for 10 minutes. *N*-Benzyl-*N*-(3-methylthio-(2-propynyl)-*N*-(4-octynyl)amine

(**173**, 299 mg, 1.0 mmol) as a solution in THF (3 mL) was added dropwise and the solution was allowed to warm to room temperature. After stirring for 4 hours CuCl (198 mg, 2.0 mmol), sonicated previously and dried under vacuum (0.1 mm Hg), and DMAD (284 mg, 2.0 mmol) were added. The resulting solution was stirred for 12 hours, HCl (6M, 6 mL) was added to the resulting black solution. The product was extracted into diethyl ether (3 x 100 mL), the combined organic layer washed with water (4 x 50 mL) and brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification by column chromatography (SiO_2, 0-100 % Et_2O:petroleum) afforded the title compound as a viscous oil (269 mg, 0.56 mmol, 61 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.50-7.15 (10H, m, Ph-H), 4.05 (2H, s, H17), 3.75 (3H, s, H16 or H22), 3.70 (3H, s, H22 or H16), 3.59 (2H, s, H1), 2.90 (2H, m, H2), 2.75 (2H, m, H4), 2.65-2.45 (2H, m, H7), 2.10 (3H, s, H19), 1.60 (2H, m, H3), 1.40 (2H, tq, J = 8.0 and 8.0 Hz, H8), 0.89 (3H, t, J = 8.0 Hz, H9) ppm.

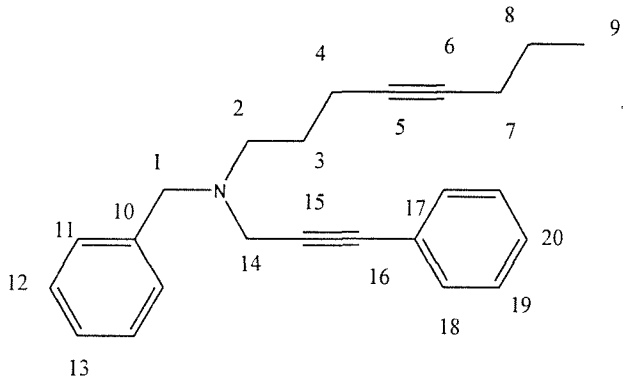
^{13}C NMR (75 MHz, $CDCl_3$) δ = 168.04, 168.83 (C, C15 and C21), 147.74 (C, C5), 147.27 (C, C18), 145.34 (C, C6), 139.21 (C, C23), 138.55 (C, C10), 137.82, 136.94 (C, C14 and C20), 129.15, 128.74, 127.17 (CH, C11, C12 and C13), 61.38, 59.72 (CH_3, C16 and C22), 57.75 (CH_2, C1), 52.88 (CH_2, C17), 52.64 (CH_2, C2), 33.61 (CH_2, C4), 29.57 (CH_2, C7), 26.19 (CH_2, C3), 24.52 (CH_2, C8), 21.39 (CH_3, C19), 14.62 (CH_3, C9) ppm.

IR (neat oil) = 3001 (brs), 2905 (m), 1730 (s), 1434 (m), 1260 (s) cm^{-1}.

LRMS (ES^+, m/z) 443.4 (M+H)

CI-HRMS = $C_{25}H_{32}NO_4S$ requires 442.2052 found 442.2043 (M+H).

***N*-Benzyl-*N*-(4-octynyl)-*N*-(3-phenyl-2-propynyl)amine (193)**



To a stirred solution of *N*-benzyl-*N*-(4-octynyl)amine (**170**, 0.215 g, 1.0 mmol), MeCN (4.0 mL) and K_2CO_3 (1.2 g, 12.0 mmol), 1-(3-chloro-1-propynyl)benzene (150 mg, 1.0 mmol) was added. The reaction mixture was refluxed for 24 hrs extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 100 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:peteroleum including 5 % Et_3N) afforded the title compound as a pale oil (0.279 g, 0.85 mmol, 43 %).

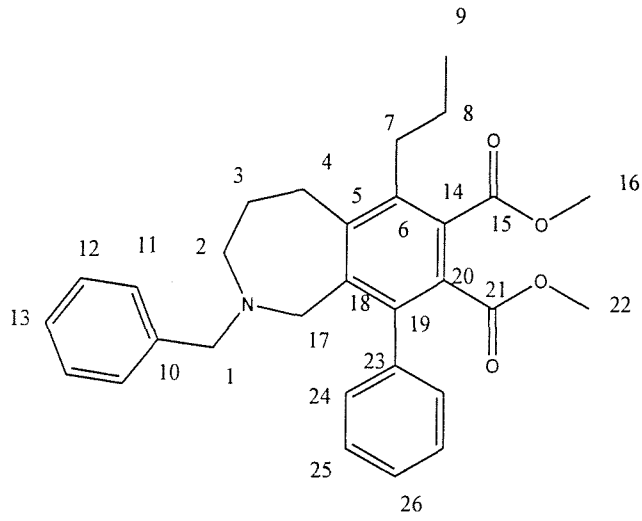
^{1}H (300 MHz, $CDCl_3$) δ = 7.45-7.30 (10H, m, Ph-H), 3.70 (2H, s, H1), 3.52 (2H, s, H14), 2.60 (2H, t, *J* = 7.0 Hz, H2), 2.11 (2H, tt, *J* = 7.0, 2.6 Hz, H4), 2.01 (2H, tt, *J* = 7.0, 2.6 Hz, H7), 1.60 (2H, tt, *J* = 8.0 and 8.0 Hz, H3), 1.39 (2H, tq, *J* = 8.0 Hz, H8), 0.97 (3H, t, *J* = 7.0 Hz, H9) ppm.

^{13}C NMR (75 MHz, $CDCl_3$) δ = 137.10 (C, C10), (C, C17) not observed, 131.90, 129.28, 128.41 (2 siganls), 128.10, 127.19 (CH, C11, C12, C13, C18, C19, and C20) 86.13 (C, C16), 84.45 (C, C15), 80.10 (C, C5 or C6), 79.98 (C, C6 or C5), 58.16 (CH_2, C1), 52.70 (CH_2, C2), 42.41 (CH_2, C14), 27.36 (CH_2, C3), 22.67 (CH_2, C4), 20.91 (CH_2, C7), 16.807 (CH_2, C8), 13.66 (CH_3, C9) ppm.

IR (neat oil) = 2928 (brm), 1452 (m), 1029 (m), 699 (m) cm^{-1}.

LRMS (ES^+, m/z) 330.7 (M+H).

Dimethyl 2-benzyl-9-phenyl-6-propyl-2,3,4,5-tetrahydro-1H-2-benzazepine-7,8-dicarboxylate (194)



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in dry THF (5.0 mL) under argon at $^{-}$80 °C, ^{n}BuLi (0.8 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise and stirred for 20 minutes. *N*-Benzyl-*N*-(4-octynyl)-*N*-(3-phenyl-2-propynyl)amine (**193**, 329 mg, 1.0 mmol) in THF (3.0 mL) was added dropwise and the solution warmed to room temperature, stirred for 3 hours. CuCl (198 mg, 2.0 mmol), sonicated previously and dried under vacuum (0.1 mm Hg), and DMAD (284 mg, 2 mmol) were added to the solution at 0 °C. The resulting solution was stirred vigorously for 12 hours, HCl (6M, 6 mL) was added and stirred for 2 hours. The product extracted into diethyl ether (3 x 100 mL), the combined organic layer washed with water (4 x 50 mL) and brine (50.0 mL) and dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % diethyl ether:petroleum) yielded the title compound as a viscous oil (273 mg, 0.58 mmol, 58 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.50-7.30 (10H, m, Ph-H), 3.87 (3H, s, H17), 3.69 (2H, s, H1), 3.41 (3H, s, H16), 3.35 (2H, s, H22), 3.05 (2H, m, H2), 2.80-2.65 (4H, m, H4 and H7), 1.80 (2H, m, H3), 1.62 (2H, tq, *J* = 7.0 and 7.0 Hz, H8), 0.97 (3H, t, *J* = 8.0 Hz, H9) ppm

^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.70 (C, C21), 169.21 (C, C15), 145.15 (C, C19), 141.41 (C, C5), 139.31 (C, C18), 138.42 (2xC, C23 and C10), 137.05 (C, C6), 131.39 (C,

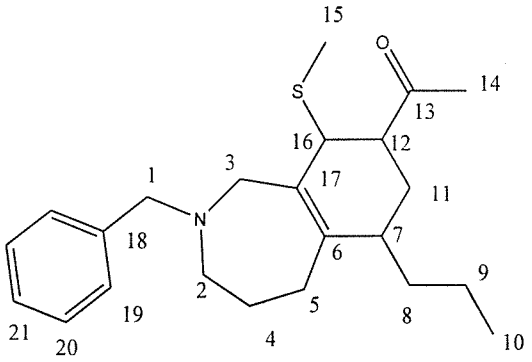
C20), 130.64 (C, C14), 129.69 (CH, C11 or C24), 128.89 (CH, C11 or C24), 128.34 (CH, C12 or C25), 127.93 (CH, C25 or C12), 127.40 (CH, C26 or C13), 127.05 (CH, C13 or C26), 61.30 (CH_2, C1), 57.56 (CH_2, C2), 56.76 (CH_2, C17), 52.57 (CH_3, C22), 52.09 (CH_3, C16), 33.48 (CH_2, C4), 29.28 (CH_2, C3), 26.59 (CH_2, C7), 24.72 (CH_2, C8), 14.68 (CH_3, C9) ppm.

IR (neat oil) = 3023 (brm), 2456 (w), 1730 (m), 1235 (m) cm^{-1}.

LRMS (ES^+, m/z) 472.4 (M+H).

CI-HRMS = $C_{30}H_{34}NO_4$ requires 472.2488 found 472.2457 (M+).

1-[2-Benzyl-9-(methylsulfanyl)-6-propylperhydro-2-benzazepin-8-yl]-1-ethanone (195)



To a stirred solution of methyl vinyl ketone (77.0 mg, 1.1 mmol), dissolved in benzene (1 mL), 4-[(E)Butylidene]-3-[(Z)-1-(methylthio)methylidene]-1-(phenylmethyl) perhydro-azepine (**191**, 304 mg, 1.0 mmol) was added dropwise. The solution was refluxed for 12 hours, quenched with methanol (5 mL) and a saturated solution of $NaHCO_3$ (40.0 mL). The product was extracted into diethyl ether (3 x 30 mL), the combined organic layer washed with water (3 x 30 ml), brine (30.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Radial chromatography (SiO_2, 5% Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a pale oil (0.156 g, 0.42 mmol, 56 %).

^{1}H (300MHz, $CDCl_3$) δ = 7.47-7.21 (5H, m, H-Ph), 3.63 (1H, d, J = 13 Hz, H1), 3.45 (1H, d, J = 13.0 Hz, H1'), 3.15 (2H, s, H3), 3.05 (2H, brs, H3), 2.85 (2H, m, H2), 2.70-2.59 (3H, m, H5 and H7), 2.36-2.25 (2H, m, H16 and H12), 2.10 (3H, s, H15), 2.05-1.85

(3H, m, H11 and H12), 1.70 (3H, s, H14), 1.59-1.1 (6H, m, H4, H8 and H9), 0.97 (3H, t, J = 7.0 Hz, H10) ppm.

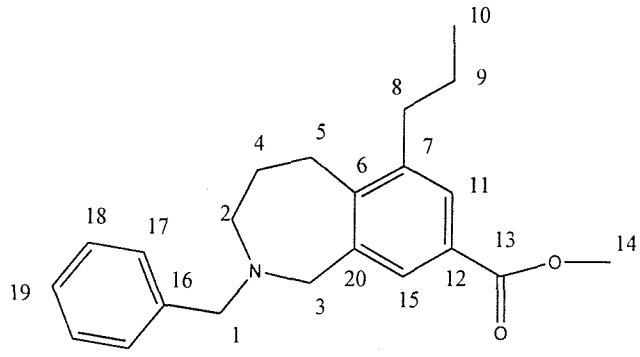
^{13}C (75 MHz, $CDCl_3$) δ = 209.15 (C, C13), 143.67 (C, C6), 139.45 (C, C17), 131.84 (C, C18), 129.26, 128.19, 127.20 (CH, C19, C20 and C21), 62.23 (CH_2, C1), 59.97 (CH_2, C3), 57.41 (CH_2, C2), 52.62 (CH, C12), 49.46 (CH, C7), 39.56 (CH, C16), 35.76 (CH_2, C5), 30.02 (CH_2, C11), 28.73 (CH_3, C15), 26.73 (CH_2, C4), 26.05 (CH_2, C8), 19.59 (CH_2, C9), 16.68 (CH_3, C14), 14.35 (CH_3, C10) ppm.

IR (neat oil) = 3007 (brs), 2720 (brw), 1711 (s), 1683 (s), 1651 (m), 1492 (s), 1420 (m), 1264 (brs), 1104 (m) cm^{-1}.

LRMS (ES^+, m/z) 372.7 (M+H).

CI-HRMS = $C_{23}H_{32}NOS$ requires 370.2205 found 370.2217 (M-H)

Methyl 2-benzyl-6-propyl-2,3,4,5-tetrahydro-1H-2-benzazepine-7-carboxylate (199).



To a stirred solution of methyl propriolate (84.0 mg, 1.0 mmol) and boron trifluoride diethyl ether complex (0.40 mL, 3.0 mmol) dissolved in dichloromethane (1.0 mL) at –78 °C, 4-[(E)butylidene]-3-[(Z)-1-(methylthio)methylidene]-1-(phenylmethyl)perhydro-azepine (**191**, 0.304 g, 1.0 mmol) was added dropwise, warmed to room temperature and refluxed for 1 hrs. The product was extracted into diethyl ether (3 x 30 mL), the combined organic layer washed with water (3 x 30 mL), brine (30.0 mL), dried over $MgSO_4$, filtered and solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % diethyl ether:petroleum) yielded the title compound as a pale oil (162 mg, 0.48 mmol, 46 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.60 (1H, s, H11 or H15), 7.41 (1H, s, H15 or H11), 7.40-7.25 (5H, m, Ph-H), 3.79 (2H, s, H3), 3.77 (3H, s, H14), 3.41 (2H, s, H1), 3.00-2.90 (4H, m, H2 and H5) 2.55 (2H, t, *J* = 7.0 Hz, H8), 1.75-1.60 (2H, m, H4) 1.47 (2H, tq, *J* = 7.0 and 7.0 Hz, H9), 0.97 (3H, t, *J* = 7.0 Hz, H10) ppm.

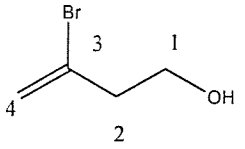
^{13}C (75 MHz, $CDCl_3$) δ = 168.15 (C, C13), 146.22, 141.85 (C, C6 and C20), 140.22 (C, C7), 139.13 (CH, C12), 138.93 (C, C16), 130.30 (CH, C11), 129.12 (CH, C15), 128.49, 128.38, 127.15 (CH, C17, C18 and C19), 59.74 (CH_2, C1), 58.61 (CH_2, C3), 58.36 (CH_2, C2), 52.07 (CH_3, C14), 36.47 (CH_2, C4), 29.62 (CH_2, C8), 24.90 (CH_2, C5), 24.73 (CH_2, C9), 14.21 (CH_3, C10) ppm.

IR (neat oil) = 2996 (brm), 1702 (m), 1643 (m), 1203 (brm) cm^{-1}.

LRMS (ES^+, m/z) 338.7 (M+H).

CI-HRMS = $C_{22}H_{27}NO_2$ requires 337.2042 found 337.2038 (M+).

3-Bromo-3-buten-1-ol (211)[83].



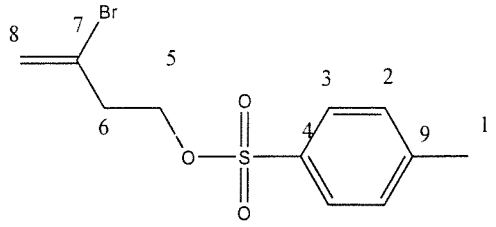
To a stirred mixture of 3-butyn-1-ol (26.0 g, 400.0 mmol) and iron powder (0.45 g) was added to hydrobromic acid (48 % in water, 97.0 g, 1.20 mol). The mixture was stirred at room temperature overnight and then at 70 °C for 3 hours. The product was extracted with Et_2O (250.0 mL), the combined organic layer washed with water (3 x 50 mL), brine (100.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a pale yellow oil (29.27 g, 197.1 mmol, 49 %).

^{1}H (300 MHz, $CDCl_3$) δ = 5.71 (1H, s, H4), 5.43 (1H, s, H4'), 3.83 (2H, t, *J* = 7.0 Hz, H1), 2.65 (2H, t, *J* = 7.0 Hz, H2), 1.80 (1H, brs, OH) ppm.

IR (oil) = 3421 (brs), 2920 (m), 1711 (m), 1430 (m), 1116 (s), 890 (brs) cm^{-1}.

^{1}HNMR and IR data in excellent agreement with commercial sample[83].

3-Bromo-3-butenyl 4-methyl-1-benzenesulphonate (212)[82].



3-Bromo-3-buten-1-ol (**211**, 10.0 g, 66.2 mmol) was added to *para*-tolulenesulphonyl chloride (13.3 g, 70 mmol) in anhydrous pyridine (18.8 g, 238 mmol) at 0-5 °C. After stirring for 12 hours, the reaction mixture was cooled to 0 °C and HCl (6M, 6.0 mL) was added. The product was extracted into diethyl ether (3 x 100 mL), the combined organic layer washed with water (4 x 50 mL), brine (50.0 mL), filtered, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-50 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a yellow oil (15.18 g, 50.0 mmol, 75 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.85 (2H, d, *J* = 8.0 Hz, H3), 7.42 (2H, d, *J* = 8.0 Hz, H2), 5.23 (1H, s, H8), 5.10 (1H, s, H8'), 4.15 (2H, t, *J* = 6.0 Hz, H5), 2.70 (2H, t, *J* = 6.0 Hz, H6), 2.39 (3H, s, H1) ppm.

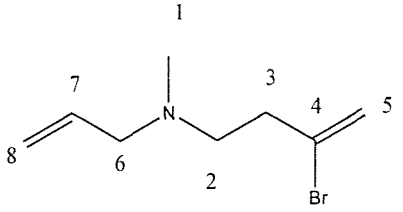
^{13}C (75 MHz, $CDCl_3$) δ = 145.13 (C, C4), 132.91 (C, C9), 132.51 (C, C7), 130.05 (CH, C3 or C2), 128.14 (CH, C2 or C3), 120.39 (CH_2, C8), 67.36 (CH_2, C5), 40.91 (CH_2, C6), 21.83 (CH_3, C1) ppm.

IR (neat oil) = 3056 (brm), 1711 (m), 1592 (w), 1162 (m), 695 (brs) cm^{-1}.

LRMS (ES+, m/z) 304.7 (M+H).

^{1}HNMR data in agreement with the literature[82]

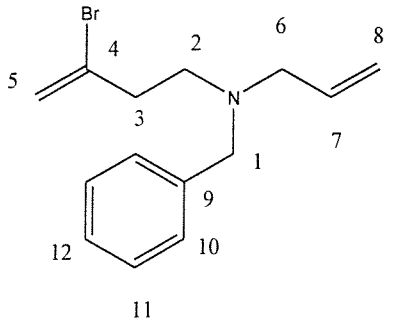
***N*-Allyl-*N*-(3-bromo-3-butenyl)-*N*-methylamine (213)**



N-Methyl-allyl-amine (2.28 g, 30.0 mmol) was added dropwise to a stirred solution of 3-bromo-3-butenyl 4-methyl-1-benzenesulphonate (**212**, 5.58 g, 17.3 mmol) in MeCN (20.0 mL) and K_2CO_3 (2.3 g, 18.0 mmol). The solution was heated at 70 °C for 14 hours. The product of the reaction was extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered, and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-50 % Et_2O:petroleum including 5 % Et_3N) afforded the title product as a pale yellow oil (2.74 g, 13.50 mmol, 78 %).

^{1}H (300 MHz, $CDCl_3$) δ = 5.88 (1H, ddt, *J* = 16.1, 10.5 and 8.0 Hz, H7), 5.61 (1H, s, H5), 5.45 (1H, s, H5'), 5.19 (1H, d, *J* = 16.1 Hz, H8), 5.12 (1H, d, *J* = 10.5 Hz, H8'), 3.05 (2H, d, *J* = 8.0 Hz, H6), 2.65 (4H, m, H2 and H3), 2.21 (3H, s, H1) ppm.
^{13}C (75 MHz, $CDCl_3$) δ = 135.62 (CH, C7), 132.53 (C, C4), 117.88, 117.65 (CH_2, C8 and C5), 61.04 (CH_2, C6), 53.22 (CH_2, C2), 39.43 (CH_3, C1), 34.36 (CH_2, C3) ppm.
IR (neat oil) = 1723 (w), 1653 (m), 1591 (m), 1439 (brw), 1123 (brm) cm^{-1}.
LRMS (APCI+, m/z) 204.1 (M+H).
CI-HRMS = $C_8H_{14}{}^{79}BrN$ requires 203.0316 found 203.0329 (isotope).

Allyl-benzyl-(3-bromo-but-3-enyl)-amine (214)



N-Benzyl-allyl-amine (588 mg, 4.0 mmol) was added dropwise to a stirred solution of benzenesulphonate (**212**, 1.37 g, 4.5 mmol) in MeCN (20.0 mL) and K_2CO_3 (2.3 g, 18 mmol), and heated at 70 °C for 14 hours. The product extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-50 % Et_2O:petroleum including 5 % Et_3N) afforded the title product as a pale yellow oil (753 mg, 2.72 mmol, 67 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.35-7.10 (5H, m, Ph-H), 5.75 (1H, ddt, *J* = 15.5, 10.5 and 6.0 Hz, H7), 5.40 (1H, s, H5), 5.30 (1H, s, H5'), 5.05 (1H, d, *J* = 15.5 Hz, H8), 5.00 (1H, d, *J* = 10.0 Hz, H8' Hz), 3.52 (2H, s, H1), 3.05 (2H, d, *J* = 6.0 Hz, H6), 2.60-2.47 (2H, t, *J* = 7.5 Hz, H3), 2.46 (2H, t, *J* = 7.5 Hz, H2) ppm.

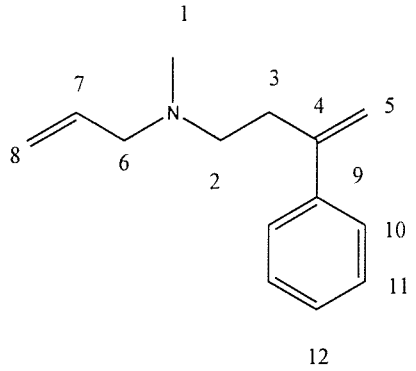
^{13}C (75 MHz, $CDCl_3$) δ = 146.05 (C, C4), 141.58 (C, C9), 139.65 (CH, C7), 128.98, 128.35, 127.05 (CH, C10, C11, C12), 124.68 (CH_2, C8), 117.59 (CH_2, C5), 58.21 (CH_2, C1), 56.96 (CH_2, C6), 51.86 (CH_2, C2), 39.37 (CH_2, C3) ppm.

IR (neat oil) 2795 (m), 1641 (m), 1453 (w), 912 (s), 697 (s) cm^{-1}.

GC = 5.494 mins.

LRMS (APCI+, m/z) 279.1 (M+H).

_N_-Allyl-_N_-methyl-_N_-(3-phenyl-3-butenyl)amine (215)



_N_-Allyl-_N_-(3-bromo-3-butenyl)-N-methylamine (**213**, 1.0 mmol, 203 mg) was added to a 25 mL flask. The flask was fitted with a reflux condenser, septum and flushed with argon. Dry THF (10.0 mL) was added under argon, followed by benzeneboronic acid (244 mg, 2.0 mmol) and $PdCl_2(PPh_3)_2$ (0.10 mol eq., 70.0 mg). To this yellow solution was added a saturated solution of Na_2CO_3 (30.0 mL), the mixture was then heated for 12 hours at 70 °C. When the reaction was deemed to be complete (absence of vinyl bromide by t.l.c) the crude reaction mixture was extracted into Et_2O (50.0 mL). The combined organic layer was washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and solvent removed. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum ether including 5 % Et_3N) afforded the title compound as a yellow oil (131 mg, 0.65 mmol, 65 %). Carried out based on a procedure developed by Johnson and Johns[75].

^{1}H (300 MHz, $CDCl_3$) δ = 7.50-7.35 (5H, m, Ph-H), 5.84 (1H, ddt, _J_ = 17.0, 9.5 and 8.0 Hz, H7), 5.32 (1H, s, H5), 5.14 (1H, d, _J_ = 17.0 Hz, H8), 5.12 (1H, d, _J_ = 10.0 Hz, H8'), 5.09 (1H, s, H5'), 2.94 (2H, d, _J_ = 8.0 Hz, H6), 2.55 (2H, t, _J_ = 6.0 Hz, H2), 2.40 (2H, t, _J_ = 6.0 Hz, H3), 2.21 (3H, s, H1) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 146.80 (C, C4), 141.13 (C, C9), 135.81 (CH, C7), 128.50 (CH, C12), 127.57 (CH, C11), 126.17 (CH, C10), 117.67 (CH_2, C8), 113.27 (CH_2, C5), 61.07 (CH_2, C6), 56.50 (CH_2, C2), 42.22 (CH_3, C1), 33.45 (CH_2, C3) ppm.

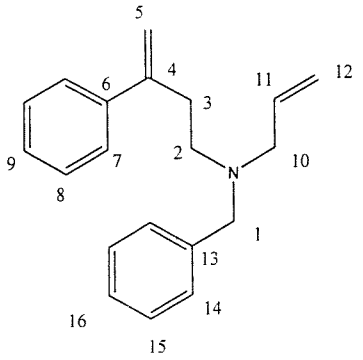
GC = 4.497 mins.

IR (neat oil) = 3024 (m), 2781 (m), 1642 (m), 1450 (m), 966 (m) cm^{-1}.

LRMS (ES+, m/z) 202.2 (M+H).

CI-HRMS = $C_{14}H_{19}N$ requires 201.1517 found 201.1528.

Allyl-benzyl-(3-phenyl-but-3-enyl)-amine (216)



Allyl-benzyl-(3-bromo-but-3-enyl)-amine (**214**, 2.0 mmol, 560 mg) was added to a 25 mL flask, fitted with a reflux condenser, septum and flushed with argon. Dry THF (10.0 mL) was added under argon, followed by benzeneboronic acid (244 mg, 2.0 mmol) and $PdCl_2(PPH_3)$ (0.10 mmol., 70.0 mg). To this yellow solution was added a saturated solution of Na_2CO_3 (40.0 mL.), the mixture heated at 70 °C for 12 hours. When the reaction was complete (absence of vinyl bromide by t.l.c) the product was extracted into Et_2O (3 x 50.0 mL). The combined organic layer were washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound (376 mg, 1.36 mmol, 68 %). Carried out based on a procedure developed by Johnson and Johns[75].

^{1}H (300 MHz, $CDCl_3$) δ = 7.45-7.10 (10H, m, Ph-H), 5.75 (1H, ddt, *J* = 15.5, 9.5 and 6.0 Hz, H11), 5.19 (1H, s, H5), 5.11 (1H, d, *J* = 15.5 Hz, H12), 5.05 (1H, d, *J* = 9.5 Hz, H12'), 4.97 (1H, s, H5'), 3.50 (2H, s, H1), 2.99 (2H, d, *J* = 9.5 Hz, H10), 2.59 (2H, t, *J* = 5.5 Hz, H3), 2.45 (2H, t, *J* = 5.5 Hz, H2) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 146.34 141.23 (C, C6 and C4), 139.46 (C, C13), 137.99 (CH, C11), 128.39, 128.31, 127.47, 127.32, 126.94, 126.17 (CH, C7, C8, C9, C14, C15, C16), 117.36 (CH_2, C12), 113.24 (CH_2, C5), 58.22 (CH_2, C10), 56.98 (CH_2, C1), 52.74 (CH_2, C2), 33.16 (CH_2, C3) ppm.

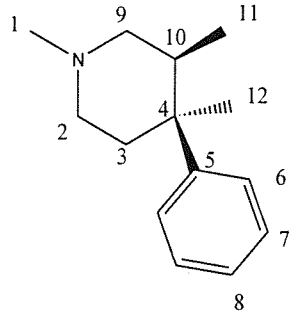
IR (neat oil) 3024 (w), 2781 (m), 2457 (w), 1450 (s), 966 (s), 671 (s) cm^{-1}.

GC = 6.887 mins.

LRMS (ES+, m/z) 278.2 (M+H).

ES-HRMS $C_{20}H_{23}N$ requires 278.1903 found 278.1908 (M+H).

1,3,4-Trimethyl-4-phenylpiperidine (217)[81]



To a stirring solution of titanium isopropoxide (2.5 mmol, 0.74 mL), Et_2O (10.0 mL), and ^{i}PrMgCl (2.75 mL, 5.5 mmol) at – 78 °C, *N*-allyl-*N*-methyl-*N*-(3-phenyl-3-butenyl)amine (**215**, 201.0 mg, 1.0 mmol) was added dropwise. The mixture was stirred at –50 °C for 1 hour, then warmed to between –40 °C and –30 °C for 5 hours. When no starting material remained (GC analysis) the reaction was quenched by the addition of methanol (6.0 mL) and a saturated solution of $NaHCO_3$ (8.0 mL). The product was extracted into diethyl ether (3 x 100 mL), the combined organic layer washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound (24 mg, 0.12 mmol, 12 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.45-7.25 (5H, m Ph-H), 2.60-2.55 (2H, m, H9), 2.35 (3H, s, H1), 1.98-1.90 (2H, m, H2), 1.65 (3H, m, H3 and H10), 1.15 (3H, s, H12), 0.65 (3H, d, *J* = 5.0 Hz, H11) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 149.95, 128.54, 127.06, 126.25 (Ar-C), 59.76, 52.65 (CH_2, C2 and C9), 46.77 (CH_3, C1), 39.50 (CH_2, C3), 32.39 (CH, C10), 24.48 (CH_3, C12), 14.14 (CH_3, C11) ppm.

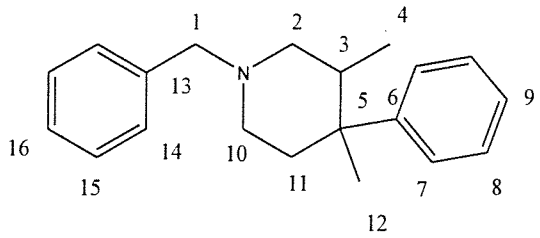
GC = 4.979 min.

IR (neat oil) = 3057 (brm), 1592 (m), 1455 (m), 1337 (br), 1150 (m) cm^{-1}.

LRMS (ES+, m/z) 204.1 (M+H).

Proton and Carbon signals in agreement with the patent.

1-Benzyl-3,4-dimethyl-4-phenyl-piperidine (218) [81]



To a solution of zirconocene dichloride (0.292 g, 1.0 mmol) in THF (2.0 mL) at –78 °C, ^{n}BuLi (0.80 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise over 5 minutes. After stirring for 5 minutes, allyl-benzyl-(3-phenyl-but-3-enyl)-amine (**216**, 277 mg, 1.0 mmol) as a solution in THF (2.0 mL) was added dropwise, warmed to room temperature and stirred for 10 hours. The resulting black solution was quenched with methanol (5.0 mL) and a saturated solution of $NaHCO_3$ (5.0 mL). The product was extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 ml), brine (50.0 mL), dried over $MgSO_4$, filtered and solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title product as a viscous oil (42 mg, 0.15 mmol, 15 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.45-7.25 (10H, m, Ph-H), 3.60 (2H, s, H1), 2.60-2.50 (2H, m, H2 and H10), 1.65-1.53 (3H, m, H3 and H11), 1.40 (3H, d, *J* = 8.0 Hz, H4), 1.15 (3H, s, H12) ppm.

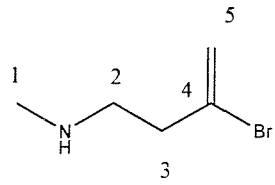
^{13}C (75 MHz, $CDCl_3$) δ = 140.95, 139.36, 128.54, 128.25, 127.79, 127.06, 126.88, 126.25 (Ar-C), 59.76 (CH_2, C2 or C10), 52.65 (CH_2, C1), 46.77 (CH_2, C10 or C2), 39.50 (CH, C3), 32.39 (C, C5), 31.66 (CH_2, C11), 24.48 (CH_3, C4 or C12), 14.14 (CH_3, C12 or C4) ppm.

IR (oil) 3057 (brm), 2929 (m), 1455 (m), 1337 (br), 1150 (m) cm^{-1}.

LRMS (ES+, m/z) 280.2 (M+H).

Proton and carbon signals in agreement with the patent.

***N*-(3-Bromo-3-butenyl)-*N*-methylamine (228)**[84]



N-Methyl-allyl-amine (2.28 g, 30.0 mmol) was added dropwise to a stirred solution of benzenesulphonate (**212**, 5.58 g, 17.3 mmol) in MeCN (20.0 mL) and K_2CO_3 (2.3 g, 18.0 mmol), heated at 70 °C for 14 hours, the reaction quenched with a saturated solution of $NaHCO_3$ (50.0 mL). The product extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL) dried over $MgSO_4$, the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-50 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a pale yellow oil (2.74 g, 13.5 mmol, 78 %).

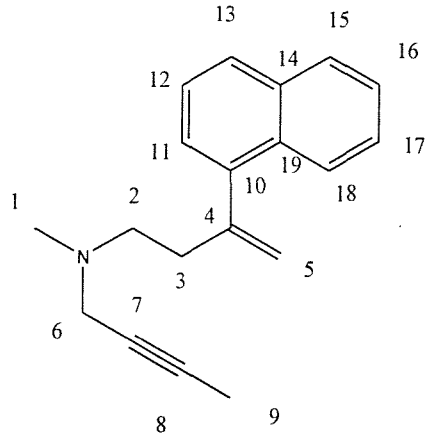
^{1}H (300 MHz, $CDCl_3$) δ = 5.63 (1H, s, H5), 5.45 (1H, s, H5'), 2.78 (2H, t, J = 8.0 Hz, H2), 2.60 (2H, t (fs), J = 8.0 Hz, H3), 2.40 (3H, s, H1) ppm.

LRMS (ES+, m/z) 163.9 (M+H).

EI-HRMS = $C_5H_{11}N^{79}Br$ requires 164.0075 found 164.0071.

^{1}H data in excellent agreement with the literature [84].

***N*-(2-Butynyl)-*N*-methyl-*N*-[3-(1-naphthyl)-3-butenyl]amine (230)**



3-Bromo-but-3-enyl)-but-2-ynyl-methyl-amine (1.0 mmol, 203 mg) was added to a 25 mL flask, fitted with a reflux condenser, septum and flushed with argon. Dry THF (10.0

mL) was added, followed by naphthaleneboronic acid (344.0 mg, 2.0 mmol) and $PdCl_2(PPh_3)_2$ (0.1 mol eq., 70.0 mg). To this yellow solution was added a saturated solution of Na_2CO_3 (50.0 mL) and the heterogeneous solution heated at 70 °C for 12 hours. When the reaction was complete (absence of vinyl bromide by t.l.c) the product was extracted into Et_2O (3 x 50.0 mL). The combined organic layer washed with water (3 x 40 mL), brine (50.0 mL) and dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the desired compound as an orange oil (133 mg, 0.51 mmol, 51 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.75-6.90 (7H, m, Np-H), 5.39 (1H, s, H5), 5.10 (1H, s, H5'), 3.23 (2H, t, *J* = 7.5 Hz, H2), 2.89 (2H, q, *J* = 1.0 Hz, H6), 2.75 (3H, s, H1), 2.58 (2H, t, *J* = 7.5 Hz, H3) 1.71 (3H, t, *J* = 1.0 Hz, H9) ppm.

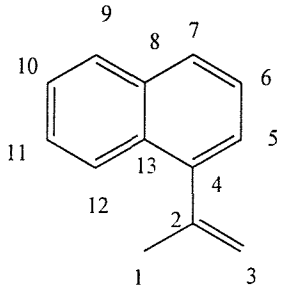
^{13}C (75 MHz, $CDCl_3$) δ = 146.18 (C, C4), 134.95 (C, C10), 128.08, 127.64 (C, C19 and C14), 127.36, 126.85, 126.26, 125.96, 125.18, 124.79, 124.68 (CH, C11, C12, C13, C15, C16, C17 and C18), 117.25 (CH_2, C5), 80.65, 79.68 (C, C7 and C8), 56.58 (CH_2, C2), 44.23 (CH_2, C6), 43.32 (CH_3, C1), 33.27 (CH_2, C3), 12.55 (CH_3, C9) ppm.

GC = 6.434 mins.

IR (neat oil) = 2930 (brm), 2204 (m), 1365 (m), 1216 (brm), 911 (m) cm^{-1}.

LRMS (ES+, m/z) 264.2 (M+H).

1-Isopropenyl-naphthalene (237)



To a stirring solution of $Ph_3P^+CH_3Br^-$ (7.86 g, 22.0 mmol) in THF (40.0 mL) at 0 °C, ^{n}BuLi (8.8 mL, 2.5 M solution in hexanes, 22.0 mmol) stirred for 15 minutes, 1-naphthalen-1-yl-ethanone (10.0 mmol, 1.70 g) was added then stirred for 15 hrs. The

product was extracted into diethyl ether (3 x 50 mL), the combined organic layers washed with water (3 x 50 ml), brine (50.0 mL), dried over $MgSO_4$, filtered and solvent removed under reduced pressure. The product was recrystallised from diethyl ether and pentane to afford the title product as a white crystalline solid (8.2 g, 8.2 mmol, 82 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.70-7.30 (7H, m, Np-H), 5.50 (1H, s, H3), 5.05 (1H, s, H3'), 2.20 (3H, s, H1) ppm.

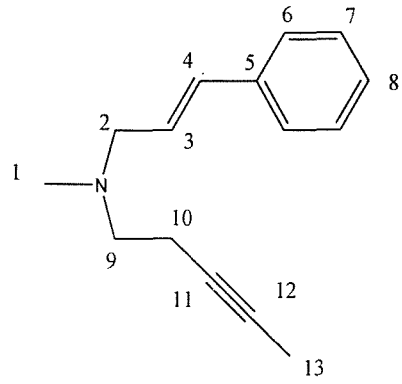
^{13}C (75 MHz, $CDCl_3$) δ = 143.55 139.30, 133.54, 133.10 (C, C2, C4, C13 and C8), 130.38, 129.72, 128.62, 128.61, 128.00, 126.96, 124.08 (CH, C5, C6, C7, C9, C10, C11 and C12), 113.41 (CH_2, C3), 22.28 (CH_3, C1) ppm.

IR (neat oil) 2915 (brm), 2360 (w), 1452 (w), 699 (s) cm^{-1}.

LRMS (ES+, m/z) unsuitable for analysis.

IR consistant with commercial sample

Methyl-pent-3-ynyl-(3-phenyl-allyl)-amine (243)



N-Methyl-*N*-[(E)-3-phenyl-2-propenyl]amine (**297**, 396 mg, 2.0 mmol) was added dropwise to a stirred solution of tolulenesulphonate (**125**, 608 mg, 2.0 mmol) in MeCN (20.0 mL) and K_2CO_3 (23 g, 18 mmol), and heated at 70 °C for 14 hours. The product was extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-50 % Et_2O:petroleum including 5 % Et_3N) afforded the title product as a pale yellow oil (362 mg, 1.7 mmol, 63 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.40-7.10 (5H, m, Ph-H), 6.40 (1H, d, *J* = 16.5 Hz, H4), 6.20 (1H, dt, *J* = 16.5 and 7.0 Hz, H3), 3.15 (2H, d, *J* = 7.0 Hz, H2), 2.45 (2H, t, *J* = 6.0 Hz, H9), 2.15 (3H, s, H1), 1.76 (2H, dt, *J* = 6.0 and 1.5 Hz), 1.50 (3H, t, *J* = 1.5 Hz, H13) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 136.75 (C, C5), 135.98 (CH, C4), 127.52, 126.40, 126.30 (CH, C6, C7 and C8), 125.26 (CH, C3), 85.55 (C, C12), 75.31 (C, C11), 59.20 (CH_2, C2), 55.26 (CH_2, C9), 41.05 (CH_3, C1), 16.46 (CH_2, C10), 2.55 (CH_3, C13) ppm.

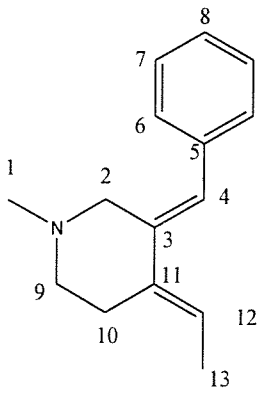
IR (neat oil) 2937 (brm), 2357 (w), 1489 (w), 1046 (m), 755 (s) cm^{-1}.

GC = 5.846 mins.

LRMS (ES+, m/z) 214.2 (M+H).

EI-HRMS = $C_{15}H_{19}N$ requires 147.1080 found 147.1044 (- pentyl group)

3-Benzylidene-4-ethylidene-1-methyl-piperidine (257)



To a solution of zirconocene dichloride (0.321 g, 1.1 mmol) in THF (2.0 mL) at –78 °C ^{n}BuLi (0.80 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise over 5 minutes. After stirring for 5 minutes, methyl-pent-3-ynyl-(3-phenyl-prop-2-ynyl)-amine (**246**, 211 mg, 1.0 mmol) as a solution in THF (2.0 mL) was added dropwise to the yellow solution, warmed to room temperature, and stirred for 7 hours. The resulting black solution quenched with methanol (5.0 mL) and $NaHCO_3$ (5.0 mL). The product was extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 ml), brine (50.0 mL), dried over $MgSO_4$, filtered and solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title product as a viscous pale yellow oil (145 mg, 0.68 mmol, 68 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.35-7.05 (5H, m, Ph-H), 6.45 (1H, s, H4), 5.75 (1H, q, *J* = 6.0 Hz, H12), 3.15 (2H, s, H2), 2.45-2.34 (4H, m, H9 and H10), 2.20 (3H, s, H1), 1.53 (3H, d, *J* = 6.0 Hz, H13) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 138.57, 136.78, 136.47 (C, C3, C11 and C5), 128.35, 127.01, 125.44 (CH, C6, C7 and C8), 122.29 (CH, C4), 118.62 (CH, C12), 56.21 (CH_2, C2), 53.99 (CH_2, C9), 45.16 (CH_3, C1), 26.43 (CH_2, C10), 13.27 (CH_3, C13) ppm.

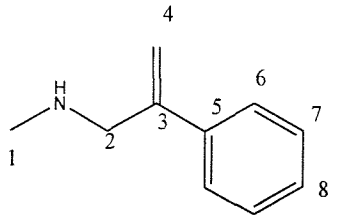
IR (neat oil) 2915 (brm), 1621 (m), 1452 (m), 699 (m) cm^{-1}.

GC = 5.790 mins.

LRMS (ES+, m/z) 214.3 (M+H).

CI-HRMS = $C_{15}H_{15}N$ requires 213.1517 found 213.1523 (M+).

***N*-Methyl-*N*-(2-phenylallyl)amine (280)**[85]



To a stirred solution of methylamine (66 % solution in IMS, 30.0 mL, 787 mmol), 1-[1-(bromomethyl)vinyl]benzene (**273**, 5.00 g, 26.0 mmol) was added dropwise, and heated at 44 °C for 18 hours before quenching with a saturated solution of $NaHCO_3$ (30.0 mL). The product was extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) and Kugelrohr distillation (7.0 mm Hg, 135 °C) afforded the title compound (381 mg, 2.5 mmol, 50 %).

^{1}H (400 MHz, $CDCl_3$) δ = 7.47-7.27 (5H, m, Ph-H), 5.41 (1H, s, H4), 5.24 (1H, s, H4'), 3.64 (2H, s, H2), 2.43 (3H, s, H1), 1.50 (1H, brs, NH) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 146.43 (C, C5), 140.02 (C, C3), 128.61, 127.81, 126.32 (CH, C6, C7 and C8), 113.56 (CH_2, C4), 55.71 (CH_2, C2), 35.96 (CH_3, C1) ppm.

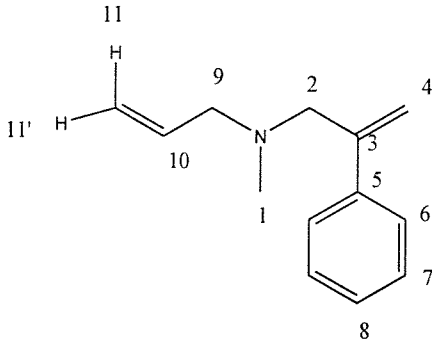
IR (neat oil) = 3025 (m), 2789 (w), 1620 (m), 1493 (w), 891 (s) cm^{-1}.

GC = 3.308 min.

LRMS (ES^+, m/z) 148.1 (M+H).

^{1}HNMR Data in agreement with the literature[85].

***N*-Allyl-*N*-methyl-*N*-(2-phenylallyl)amine (281)[86]**



To a stirred solution of *N*-methyl-*N*-(2-phenylallyl)amine (**280**, 1.01 g, 14.08 mmol), MeCN (10 mL) and K_2CO_3 (2.40 g, 24 mmol), allyl bromide (1.79 g, 15.0 mmol) was added dropwise. The solution refluxed for 12 hours before quenching with a saturated solution of $NaHCO_3$ (30.0 mL). The product was extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a yellow oil (1.99 g, 10.6 mmol, 73 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.49-7.27 (5H, m, Ph-H), 5.91 (1H, ddt, *J* = 15.5, 9.6 and 6.6 Hz, H10), 5.48 (1H, s, H4), 5.29 (1H, s, H4'), 5.19 (1H, d, *J* = 15.5 Hz, H11), 5.12 (1H, d, *J* = 9.6 Hz, H11'), 3.39 (2H, s, H2), 3.00 (2H, d, *J* = 6.6 Hz, H9), 2.25 (3H, s, H1) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 145.53 (C, C5), 140.41 (C, C3), 136.08 (CH, C10), 128.49, 128.23, 126.50 (CH, C8, C7 and C6), 117.62 (CH_2, C4), 115.41 (CH_2, C11), 61.74, 60.96 (CH_2, C9 and C2), 42.31 (CH_3, C1) ppm.

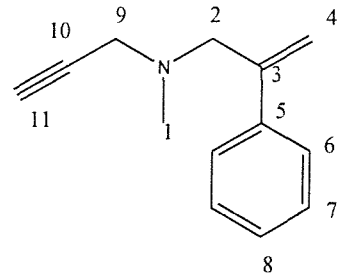
IR (neat oil) = 2977 (brm), 2784 (brw), 1617 (m), 1028 (m), 906 (s) cm^{-1}.

GC = 3.975 min.

LRMS (ES^+, m/z) 188.1 (M+H).

^{1}HNMR in agreement with literature[86].

***N*-Methyl-*N*-(2-phenylallyl)-*N*-(2-propynyl)amine (286)**



To a stirred solution of *N*-methyl-*N*-(2-phenylallyl)amine (**280**, 296 mg, 2.0 mmol), K_2CO_3 (1.0 g, 7.5 mmol), MeCN (10.0 mL), propargyl bromide (354 mg, 3.0 mmol) was added dropwise. The solution was refluxed for 12 hrs then quenched with a saturated solution of $NaHCO_3$ (30 mL). The product extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as an orange oil (271 mg, 1.5 mmol, 73 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.40-7.27 (5H, m, Ph-H), 5.50 (1H, s, H4), 5.20 (1H, s, H4'), 3.45 (2H, s, H2), 3.35 (2H, d, *J* = 1.5 Hz, H9), 2.25 (1H, d, *J* = 1.5 Hz, H11), 2.15 (3H, s, H1) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 144.10 (C, C5), 139.45 (C, C3), 128.67, 127.97, 126.39 (CH, C6, C7 and C8), 115.98 (CH_2, C4), 77.40 (C, C10), 73.46 (CH, C11), 60.05 (CH_2, C2), 44.93 (CH_2, C9), 41.74 (CH_3, C1) ppm.

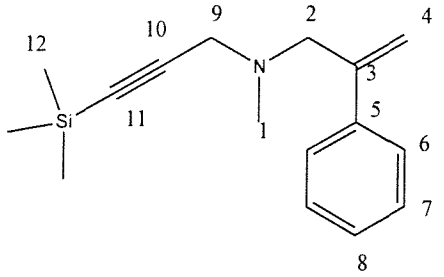
IR (neat oil) = 3292 (brw), 3025 (brm), 2791 (m), 966 (s) cm^{-1}.

GC = 4.170 min.

LRMS (ES^+, m/z) 186.6 (M+H).

ES-HRMS compound gave incorrect readings by mass spectrometry.

***N*-Methyl-*N*-(2-phenylallyl)-*N*-[3-(1,1,1-trimethylsilyl)-2-propynyl]amine (284)**



To a stirred solution of *N*-methyl-*N*-(2-phenylallyl)amine (**280**, 512 mg, 2.0 mmol), (3-bromo-prop-1-ynyl)-trimethyl-silane (382 mg, 2.0 mmol) was added dropwise, heated at 80 °C for 12 hours, before quenching with a saturated solution of $NaHCO_3$ (20.0 mL). The product was extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a viscous oil (363 mg, 1.4 mmol, 71 %).

^{1}H (400 MHz, $CDCl_3$) δ = 7.45-7.30 (5H, m, Ph-H), 5.49 (1H, s, H4), 5.28 (1H, s, H4'), 3.46 (2H, s, H2), 3.36 (2H, s, H9), 2.30 (3H, s, H1), 0.21 (9H, s, H12) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 144.54 (C, C5), 139.78 (C, C3), 128.12, 127.48, 126.13 (CH, C6, C7 and C8), 115.63 (CH_2, C4), 100.96 (C, C11), 90.02 (C, C10), 59.84 (CH_2, C2), 45.81 (CH_2, C9), 41.55 (CH_3, C1), 0.26 (CH_3, C12) ppm.

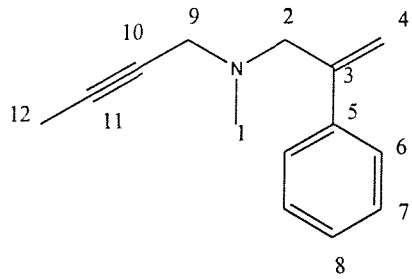
IR (neat oil) = 2954 (brm), 2792 (brw), 2163 (m), 1599 (w), 760 (s) cm^{-1}.

GC = 5.442 min.

LRMS (ES^+, m/z) 258.2 (M+H).

CI-HRMS = $C_{13}H_{15}N$ requires 184.1126 found 184.1125 (M+H without TMS group).

***N*-(2-Butynyl)-*N*-methyl-*N*-(2-phenylallyl)amine (283)**



To a stirred solution of triethylamine (1.0 mL, 10.0 mmol), methanesulphonyl chloride (354 mg, 3.5 mmol) in DCM (10.0 mL) at 0 °C, 2-butyn-1-ol (3.0 mmol, 211 mg) was added dropwise. The solution stirred for 20 minutes at 0 °C, warmed to room temperature and stirred for 20 minutes before quenching with Et_2O (30.0 mL), filtered and the solvent removed under reduced pressure. The product was dissolved in MeCN (10.0 mL), then *N*-Methyl-*N*-(2-phenylallyl)amine (**280**, 296 mg, 2.0 mmol) was added to the solution and stirred for 10 minutes. After this K_2CO_3 (1.0 g, 9.0 mmol) was added and the solution refluxed for 30 minutes, the reaction was quenched with a saturated solution of $NaHCO_3$ (30.0 mL). The product was extracted into diethyl ether (2 x 50 mL), the combined organic layer washed with brine (30.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as an orange oil (248 mg, 1.2 mmol, 62 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.45-7.25 (5H, m, Ph-H), 5.40 (1H, s, H4), 5.20 (1H, s, H4'), 3.39 (2H, s, H2), 3.21 (2H, q, *J* = 1.5 Hz, H9), 2.20 (3H, s, H1), 1.75 (3H, t, *J* = 1.5 Hz, H12) ppm.

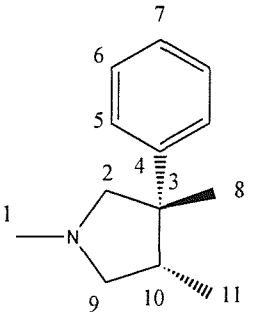
^{13}C (75 MHz, $CDCl_3$) δ = 144.96 (C, C5), 140.15 (C, C3), 128.41, 127.71, 126.40 (CH, C6, C7 and C8), 115.71 (CH_2, C4), 80.98 (C, C11), 74.11 (C, C10), 60.98 (CH_2, C2), 45.67 (CH_2, C9), 41.82 (CH_3, C1), 3.67 (CH_3, C12) ppm.

IR (neat oil) = 2917 (m), 2788 (m), 1 (w), 1027 (m), 905 (s) cm^{-1}.

GC = 4.879 min.

LRMS (ES^+, m/z) 200.1 (M+H).

1,3,4-Trimethyl-3-phenylpyrrolidine (287)



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in dry THF (5.0 mL) under argon at –80 °C, ^nBuLi (0.8 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise and stirred for 10 minutes. *N*-Allyl-*N*-methyl-*N*-(2-phenylallyl)amine (**281**, 188 mg, 1.0 mmol) as a solution in THF (2.0 mL) was added dropwise and the resulting solution was allowed to warm to room temperature, then stirred for 7 hrs. The reaction was quenched with methanol (5.0 mL) and a saturated solution of $NaHCO_3$ (8.0 mL). The product was extracted into diethyl ether (3 x 100 mL), the combined organic extracts washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a pale oil (154 mg, 0.78 mmol, 78 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.40-7.27 (5H, m, Ph-H), 3.05 (1H, d, *J* = 9.5 Hz, H2), 2.80 (1H, dd, *J* = 9.5 and 2.5 Hz, H9), 2.48-2.37 (3H, m, H2', H9' and H10), 2.25 (3H, s, H1), 1.25 (3H, s, H8), 0.95 (3H, d, *J* = 7.0 Hz, H11) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 150.08 (C, C4), 128.31, 125.93, 125.77 (CH, C5, C6 and C7), 72.24 (CH_2, C2), 63.98 (CH_2, C9), 47.63 (C, C3), 44.21 (CH_3, C1), 43.22 (CH, C10), 22.86 (CH_3, C8), 13.67 (CH_3, C11) ppm.

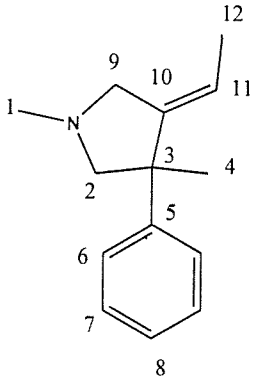
IR (neat oil) = 3013 (brm), 2929 (brw), 1601 (m), 1452 (m), 965 (s) cm^{-1}.

GC = 4.203 min.

LRMS (ES^+, m/z) 190.2 (M+H).

EI-HRMS = $C13H_{19}N$ requires 189.1517 found 189.1525 (M+H).

4-[(Z)Ethylidene]-1,3-dimethyl-3-phenylpyrrolidine (294)



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in dry THF (5.0 mL) under argon at – 80 °C, ^nBuLi (0.8 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise and stirred for 10 minutes. *N*-(2-Butynyl)-*N*-methyl-*N*-(2-phenylallyl)amine (**283**, 200 mg, 1.0 mmol) as a solution in THF (2.0 mL) was added dropwise and the solution allowed to warm to room temperature, then left to stir for 5 hrs before quenching with methanol (5.0 mL) and a saturated solution of $NaHCO_3$ (8.0. mL). The product was extracted into diethyl ether (3 x 100 mL), the combined organic layer washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a pale, viscous oil (103 mg, 0.51 mmol, 51 %).

^{1}H (400 MHz, $CDCl_3$) δ = 7.40-7.25 (5H, m, Ph-H), 5.27 (1H, q, *J* = 6.5 Hz, H11), 3.41 (1H, d, *J* = 13.5 Hz, H9), 3.35 (1H, d, *J* = 13.5 Hz, H9'), 3.07 (1H, d, *J* = 9.9 Hz, H2), 2.72 (1H, d, *J* = 9.9 Hz, H2'), 2.47 (3H, s, H1), 1.85 (3H, d, *J* = 6.5 Hz, H12), 1.60 (3H, s, H4) ppm.

^{13}C (100 MHz, $CDCl_3$) δ = 147.62 (C, C10), 147.37 (C, C5), 127.23, 126.86, 125.23 (CH, C6, C7 and C8), 115.55 (CH, C11), 71.55 (CH_2, C2), 58.55 (CH_2, C9), 49.66 (C, C3), 42.07 (CH_3, C1), 22.95 (CH_3, C4), 13.64 (CH_3, C12) ppm.

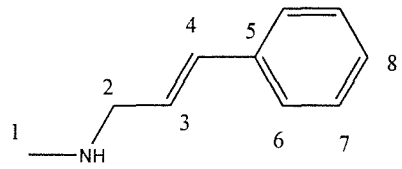
IR (neat oil) = 2922 (brm), 2767 (m), 1374 (brm), 1216 (m), 884 (brm) cm^{-1}.

GC = 4.521 min.

LRMS (ES^+, m/z) 202.1 (M+H).

CI-HRMS = $C_{14}H_{19}N$ required 201.1517 found 201.1518 (M+).

_N_-Methyl-_N_-[(E)-3-phenyl-2-propenyl]amine (297) and _N_-methyl-_N,N_-di[(E)-3-phenyl-2-propenyl]amine (301)[85].



To a stirred solution of methylamine (66 % solution in IMS, 30.0 mL, 787 mmol), cinnamyl bromide (30.0 g, 197.0 mmol) was added at 0 °C, warmed to room temperature and refluxed for 2 hours. The reaction was quenched with a saturated solution of $NaHCO_3$ (30.0 mL). The products extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL), dried with $MgSO_4$, filtered an the solvent removed under reduced pressure. Kugelrohr distillation afforded the desired secondary amine (, 135 °C, 9 mm Hg, 21.55 g, 145 mmol, 76 %) as a colourless oil and the *bis* tertiary amine (, 165 °C, 5 mm Hg, 9.75 g, 40.0 mmol, 20 %) as a viscous oil.

_N_-Methyl-_N_-[(E)-3-phenyl-2-propenyl]amine (297)

^{1}H (300 MHz, $CDCl_3$) δ = 7.45-7.30 (5H, m, Ph-H), 6.50 (1H, d, J = 16.5 Hz, H4), 6.20 (1H, dt, J = 16.5 and 7.0 Hz, H3), 3.35 (2H, d, J = 7.0 Hz, H2) 2.42 (3H, s, H1), 1.60 (CH_3, NH) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 137.27 (C, C5), 132.97 (C, C4), 131.51 (CH, C3), 128.71, 127.51, 127.39 (CH, C6, C7 and C8), 53.99 (CH_2, C2), 36.11 (CH_3, C1) ppm.

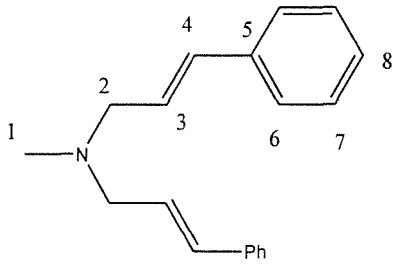
IR (neat oil) = 3021 (brm), 2789 (m), 1598 (m), 1448, 966 (s) cm^{-1}.

GC = 3.737 min.

LRMS (ES^+, m/z) 148.2 (M+H)

EI-HRMS = $C_{10}H_{13}N$ requires 147.1048 found 147.1044 (M+).

***N*-methyl-*N*,*N*-di[(E)-3-phenyl-2-propenyl]amine (301)**



^{1}H (300 MHz, $CDCl_3$) δ = 7.40-7.27 (10H, m, Ph-H), 6.45 (2H, d, *J* = 16.2 Hz, H4), 6.19 (2H, dt, *J* = 16.2 and 7.5 Hz, H3), 3:09 (4H, d, *J* = 7.5 Hz, H2), 2.42 (3H, s, H1) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 137.20 (C, C5), 132.92 (CH, C4), 128.74 (CH, C3), 127.60, 127.50, 126.48 (CH, C6, C7 and C8), 60.04 (CH_2, C2), 42.37 (CH_3, C1) ppm.

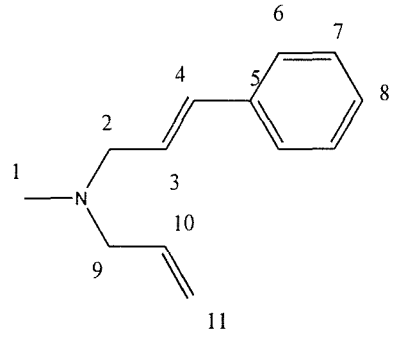
IR (neat oil) = 3024 (m), 2783 (m), 1598 (m), 1448 (m), 964 (s) cm^{-1}.

GC = 7.781 min.

LRMS (ES^+, m/z) 264.3 (M+H).

CI-HRMS =$C_{19}H_{21}N$ requires 263.1674 found 263.1678 (M+).

***N*-Allyl-*N*-methyl-*N*-[(Z)-3-phenyl-2-propenyl]amine (299)**



To a stirred solution of *N*-methylallylamine (710 mg, 10.0 mmol), K_2CO_3 (2.00 g, 20.0 mmol) and MeCN (20 mL), cinnamyl bromide (1.97 g, 10.0 mmol) was added dropwise at 0 °C. The solution was allowed to warm to room temperature, refluxed for 1 hour, before quenching with a saturated solution of $NaHCO_3$ (50.0 mL). The product was extracted into diethyl ether (3 x 40 mL), the combined organic layer washed with water (3 x 30 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as an orange oil (1.71 g, 9.1 mmol, 91 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.50-7.30 (5H, m, Ph-H), 6.45 (1H, d, *J* = 16.2 Hz, H4), 6.19 (1H, dt, *J* = 16.2 and 6.8 Hz, H3), 5.82 (1H, ddt, *J* = 16.4, 10.7 and 6.6 Hz, H10), 5.25 (1H, d, *J* = 16.4 Hz, H11), 5.08 (1H, d, *J* = 10.7 Hz, H11'), 3.15 (2H, d, *J* = 6.8 Hz, H2), 3.05 (2H, d, *J* = 6.6 Hz, H9), 2.10 (3H, s, H1) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 137.53 (C, C5), 136.16 (CH, C4), 133.03 (CH, C3), 131.96 (CH, C10), 128.96, 127.82, 126.92 (CH, C6, C7 and C8), 118.03 (CH_2, C11), 60.96, 60.16 (CH_2, C2 or C9), 42.46 (CH_3, C1) ppm.

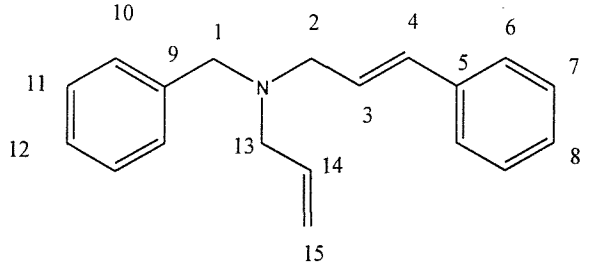
IR (neat oil) = 3025 (m), 2795 (m), 1599 (w), 1494 (s) cm^{-1}.

GC = 4.540 min.

LRMS (ES^+, m/z) 188.2 (M+H).

HRMS did not give coherent data.

***N*-Allyl-*N*-benzyl-*N*-[(Z)-3-phenyl-2-propenyl]amine (300)**[87]



To a stirred solution of *N*-benzylallylamine (1.46g, 10.0 mmol), K_2CO_3 (2.0 g, 20.0 mmol) in MeCN (30.0 mL) at 0 °C, cinnamyl bromide (1.97 g, 10.0 mmol) was added dropwise. The solution was warmed to room temperature, stirred for 1 hour then refluxed for 1 hour, quenched with a saturated solution of $NaHCO_3$ (50.0 mL). The product was extracted into diethyl ether (3 x 40 mL), the combined organic layer washed with water (3 x 30 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as an orange oil (2.31 g, 8.7 mmol, 87 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.45-7.30 (10H, m, Ph-H), 6.45 (1H, d, *J* = 16.2 Hz, H4), 6.21 (1H, dt, *J* = 16.2 and 6.6 Hz, H3), 5.82 (1H, ddt, *J* = 16.5, 10.8 and 6.6 Hz, H14), 5.20 (1H, d, *J* = 16.5 Hz, H15), 5.08 (2H, d, *J* = 10.8 Hz, H15'), 3.55 (2H, s, H1), 3.15 (2H, d, *J* = 6.6 Hz, H2), 3.05 (2H, d, *J* = 6.6 Hz, H13) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 141.23, 139.45 (C, C5 or C9), 137.16 (CH, C4), 133.03 (CH, C3), 132.96 (CH, C14), 129.05, 128.86, 128.75, 128.47, 128.19, 127.16 (CH, C6, C7, C8, C10, C11 and C12), 116.10 (CH_2, C15), 58.25 (CH_2, C1), 56.55 (CH_2, C2), 53.27 (CH_2, C13) ppm.

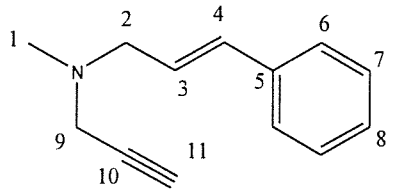
IR (neat oil) = 3025 (m), 2795 (m), 1599 (w), 1494 (s) cm^{-1}.

GC = 7.339 min.

LRMS (ES^+, m/z) 264.1 (M+H).

ES-HRMS $C_{19}H_{22}N$ requires 264.1746 found 264.1751 (M+H).

***N*-Methyl-*N*-[(E)-3-phenyl-2-propenyl]-*N*-(2-propynyl)amine (302)**



To a stirred solution of *N*-methyl-*N*-[(E)-3-phenyl-2-propenyl]amine (**297**, 372 mg, 2.0 mmol), propargyl bromide (260 mg, 2.2 mmol) was added dropwise at 0 °C. The mixture was then heated to 34 °C for 5 minutes before quenching with a saturated solution of $NaHCO_3$ (15.0 mL). The product was extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL), filtered and the solvent removed under reduced pressure. Additional propargyl bromide (260 mg, 2.2 mmol) was added to the crude product and the procedure repeated before quenching the reaction with a saturated solution of $NaHCO_3$ (15.0 mL). The product was extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 30 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a pale oil (264 g, 1.4 mmol, 73 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.45-7.25 (5H, m, Ph-H), 6.50 (1H, d, *J* = 16.2 Hz, H4), 6.27 (1H, dt, *J* = 16.1 and 6.2 Hz, H3), 3.40 (2H, d, *J* = 2.2 Hz, H9), 3.23 (2H, d, *J* = 6.7 Hz, H2), 2.38 (3H, s, H1), 2.28 (1H, t, *J* = 2.2 Hz, H11) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 137.06 (C, C5), 133.23 (CH, C4), 128.73 (CH, C3), 127.59, 126.96, 126.51 (CH, C6, C7 and C8), 78.75 (C, C10), 73.39 (CH, C11), 58.32 (CH_2, C2), 46.41 (CH_2, C9), 42.35 (CH_3, C1) ppm.

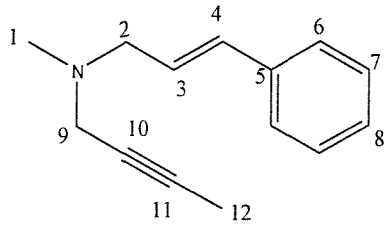
IR (neat oil) = 3292 (brm), 3025 (brw), 2791 (m), 1740 (m), 966 (s) cm^{-1}.

GC = 4.691 min.

LRMS (ES^+, m/z) 186.1 (M+H).

CI-HRMS = $C_{13}H_{15}N$ required 185.1204 found 185.1188 (M+).

***N*-(2-Butynyl)-*N*-methyl-*N*-[(E)-3-phenyl-2-propenyl]amine (303).**



To a stirring solution of triethylamine (1 mL, 10.0 mmol) and methanesulphonyl chloride (354 mg, 3.5 mmol) in DCM (10.0 mL), 2-butyn-1-ol (3.0 mmol, 211 mg) was added under argon at 0 °C. The solution was stirred for 20 minutes at 0 °C, warmed to room temperature and stirred for 20 minutes before quenching with a solution of Et_2O (30.0 mL). The mixture was filtered, and the solvent removed under reduced pressure. The product was dissolved in MeCN (10.0 mL), *N*-methyl-*N*-[(E)-3-phenyl-2-propenyl]amine (**297**, 2.0 mmol, 294 mg) added at 0 °C, stirred with K_2CO_3 (1.0 g, 7.5 mmol), triethylamine (3.0 mL) and the solution refluxed for 30 minutes. The reaction was quenched with a solution of $NaHCO_3$ (15.0 mL), the product extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (30.0 mL), brine (30.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a yellow oil (218 mg, 1.1 mmol, 54 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.48-7.27 (5H, m, Ph-H), 6.45 (1H, d, *J* = 16.3 Hz, H4), 6.35 (1H, dt, *J* = 16.2 and 6.2 Hz, H3), 3.20 (2H, q, *J* = 1.5 Hz, H9), 3.10 (2H, d, *J* = 6.7 Hz, H2), 2.30 (3H, s, H1), 1.71 (3H, t, *J* = 1.5 Hz, H12) ppm.

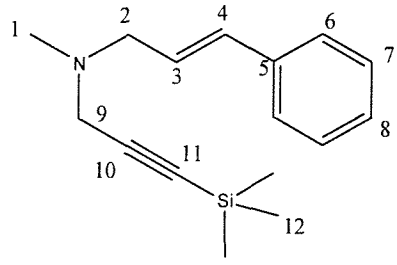
^{13}C (75 MHz, $CDCl_3$) δ = 137.04 (C, C5), 132.97 (CH, C4), 128.68 (CH, C3), 127.60, 127.30, 126.48 (CH, C6, C7 and C8), 80.10 (C, C11), 72.15 (C, C10), 58.63 (CH_2, C2), 45.95 (CH_2, C9), 41.88 (CH_3, C1), 3.68 (CH_3, C12) ppm.

IR (neat oil) = 3111 (brw), 2950 (brm), 1726 (m), 1249 (m), 843 (s) cm^{-1}.

GC = 5.414 min.

LRMS (ES^+, m/z) 200.1(M+H).

***N*-Methyl-*N*-[(E)-3-phenyl-2-propenyl]-*N*-[3-(1,1,1-trimethylsilyl)-2-propynyl]amine (304).**



To a stirred solution of *N*-methyl-*N*-[(E)-3-phenyl-2-propenyl]amine (**297**, 298 mg, 2.0 mmol), (3-bromo-prop-1-ynyl)-trimethyl-silane (403 mg, 2.1 mmol) was added dropwise at 0 °C, then heated at 34 °C for 5 minutes. The solution quenched with a saturated solution of $NaHCO_3$ (30.0 mL), filtered, and the solvent removed under reduced pressure. The product dissolved in MeCN (10.0 mL), (3-bromo-prop-1-ynyl)-trimethyl-silane (2.0 mmol, 296 mg) added at 0 °C, stirred with K_2CO_3 (1.0 g, 7.5 mmol), triethylamine (3.0 mL) and refluxed for 30 minutes. The reaction was quenched with a solution of $NaHCO_3$ (15.0 mL), the product extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 30.0 mL), brine (30.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a clear oil (355 mg, 1.5 mmol, 75 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.50-7.35 (5H, m, Ph-H), 6.51 (1H, d, *J* = 16.2 Hz, H4), 6.30 (1H, dt, *J* = 16.2 and 6.4 Hz, H3), 3.45 (2H, s, H9), 3.20 (2H, d, *J* = 6.4 Hz, H2), 2.37 (3H, s, H1), 0.15 (9H, s, H12) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 137.10 (C, C5), 133.19 (CH, C4), 128.71 (CH, C3), 127.65, 127.02, 126.49 (CH, C6, C7 and C8), 101.05 (C, C11), 89.89 (C, C10), 58.51 (CH_2, C2), 46.40 (CH_2, C9), 41.91 (CH_3, C1), 0.255 (CH_3, C12) ppm.

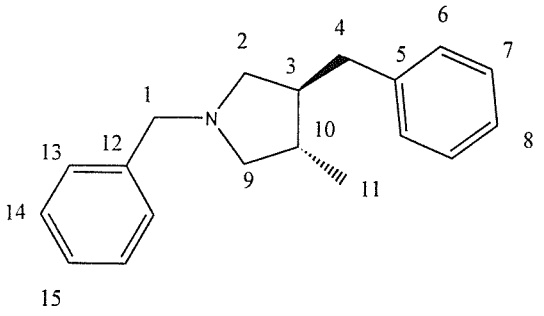
IR (neat oil) = 3111 (brw), 2959 (brm), 1249 (m), 843 (s) cm^{-1}.

GC = 5.923 min.

LRMS (ES^+, m/z) 258.2 (M+H).

EI-HRMS = $C_{16}H_{24}NSi$ requires 258.1678 found 258.1679 (M+H).

1,3-Dibenzyl-4-methylpyrrolidine (305)[87]



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in dry THF (5.0 mL) under argon at -80 °C, ^{n}BuLi (0.8 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise and stirred for 10 minutes. *N*-Allyl-*N*-benzyl-*N*-[(Z)-3-phenyl-2-propenyl]amine (**300**, 526 mg, 2.0 mmol) as a solution in THF (2.0 mL) was added dropwise and the solution and allowed to warm to room temperature, then left to stir for 5 hrs before quenching with methanol (5.0 mL) and a saturated solution of $NaHCO_3$ (8.0 mL). The product was extracted into diethyl ether (3 x 100 mL), the combined organic layer washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a pale viscous oil (389 mg, 1.46 mmol, 72 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.45-7.25 (10H, m, Ph-H), 3.55 (1H, d, *J* = 13.0 Hz, H1), 3.45 (1H, d, *J* = 13.0 Hz, H1'), 2.63-2.57 (2H, m, H2), 2.58-2.45 (2H, m, H9), 2.22 (2H, d, *J* = 6.9 Hz, H4), 2.08-2.00 (1H, m, H3), 1.86 (1H, m, H10), 0.81 (3H, d, *J* = 7.0 Hz, H11) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 142.01 (C, C12), 139.89 (C, C5), 129.30, 129.06, 128.06, 127.56, 127.05, 126.23, (CH, C6, C7, C8, C13, C14 and C14), 62.61 (CH_2, C1), 61.15 (CH_2, C9), 60.57 (CH_2, C2), 48.20 (CH, C3), 41.22 (CH_2, C4), 39.21 (CH, C10), 19.73 (CH_3, C11) ppm. Major isomer (*trans*).

^{13}C (75 MHz, $CDCl_3$) δ = 141.78 (C, C12), 139.90 (C, C5), 129.16, 128.60, 128.20, 127.21, 126.86, 126.15 (CH, C6, C7, C8, C13, C14 and C15), 62.89 (CH_2, C1), 61.40 (CH_2, C9), 60.11 (CH_2, C2), 42.15 (CH, C3), 36.09 (CH_2, C4), 34.74 (CH, C10), 13.48 (CH_3, C11) ppm. Minor isomer (*cis*).

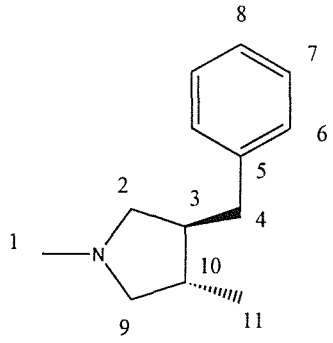
IR (neat oil) = 3025 (m), 2795 (m), 1599 (w), 1494 (s) cm^{-1}.

GC = 7.069 min.

LRMS (ES^+, m/z) 266.2 (M+H).

EI-HRMS = $C_{19}H_{23}N$ requires 265.1830 found 265.1837 (M+).

3-Benzyl-1,4-dimethyl-pyrrolidine (306)



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in dry THF (5.0 mL) under argon at –80 °C, ^{n}BuLi (0.8 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise and left for 10 minutes. *N*-Allyl-*N*-methyl-*N*-[(Z)-3-phenyl-2-propenyl]amine (, 188 mg, 1.0 mmol) as a solution in THF (2.0 mL) was added dropwise, warmed to room temperature, stirred for 7 hours before quenching with methanol (5.0 mL) and a saturated solution of $NaHCO_3$ (8.0 mL). The product was extracted into diethyl ether (3 x 100 mL), the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a pale oil (150 mg, 0.79 mmol, 79 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.50-7.30 (5H, m, Ph-H), 2.63-2.27 (2H, m, H2), 2.58-2.45 (2H, m, H9), 2.22-2.11 (1H, m, H10), 2.21 (3H, s, H1), 2.08-2.00 (1H, m, H3), 1.90 (2H, m, H4), 0.81 (3H, d, J = 7.0 Hz, H11) ppm.

^{13}C (75 MHz, $CDCl_3$) δ =141.71 (C, C5), 129.19, 128.67, 126.22 (CH, C6, C7 and C8), 65.05, 62.78 (CH_2, C2 and C9), 48.82 (CH, C3), 42.97 (CH_3, C1), 41.37 (CH_2, C4), 39.90 (CH, C10), 19.78 (CH_3, C11) ppm.

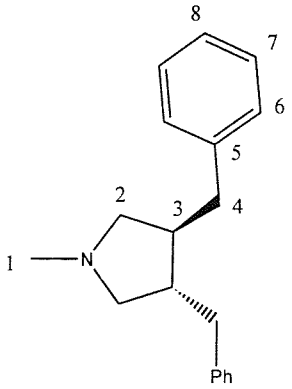
IR (neat oil) = 2968 (brm), 1592 (w), 1330 (brm), 961 (m) cm^{-1}.

GC = 4.225 min.

LRMS (ES^+, m/z) 190.1 (M+H)

EI-HRMS = $C_{13}H_{19}N$ requires 189.1817 found 189.1824 (M+H).

3,4-Dibenzyl-1-methylpyrrolidine (307)



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in dry THF (5.0 mL) under argon at -80 °C, ^{n}BuLi (0.8 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise and stirred for 10 minutes. *N*-methyl-*N*,*N*-di[(E)-3-phenyl-2-propenyl]amine (**301**, 264 mg, 1.0 mmol) as a solution in THF (2.0 mL) was added dropwise warmed to room temperature, stirred for 7 hrs, before quenching with methanol (5.0 mL) and a saturated solution of $NaHCO_3$ (8.0 mL). The product was extracted into diethyl ether (3 x 100 mL), the combined organic layer washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) to afford the title compound as an orange oil (140 mg, 0.54 mmol, 54 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.45-7.20 (10H, m, Ph-H), 2.95-2.75 (4H, m, H2), 2.60 (4H, d, *J* = 7.7 Hz, H4), 2.11 (3H, s, H1), 2.05-1.95 (2H, m, H3) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 141.26 (C, C5), 128.97, 128.46, 126.07 (CH, C6, C7 and C8), 62.60 (CH_2, C2), 46.70 (CH, C3), 42.26 (CH_3, C1), 41.48 (CH_2, C4) ppm.

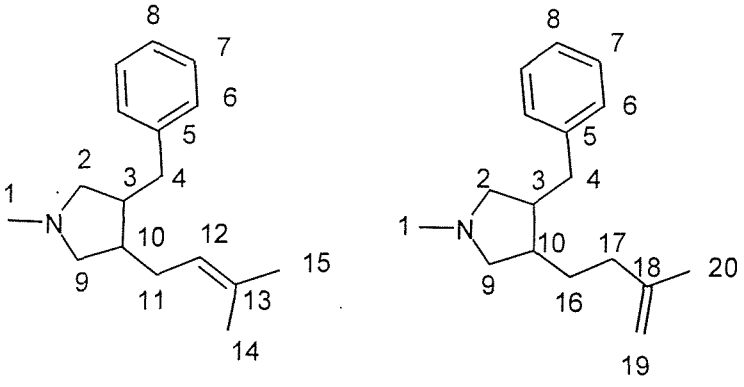
GC = 7.001 min.

IR (neat oil) = 3005 (brm), 2975 (m), 2698 (m), 1601 (m), 1205 (m) cm^{-1}.

LRMS (ES^+, m/z) 266.2 (M+H).

EI-HRMS = $C_{19}H_{23}N$ requires 265.1830 found 265.1839 (M+).

3-Benzyl-1-methyl-4-(3-methyl-but-2-enyl)-pyrrolidine (314) and 3-benzyl-1-methyl-4-(3-methyl-but-3-enyl)-pyrrolidine (315).



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in dry THF (5.0 mL) under argon at -80 °C, ^{n}BuLi (0.8 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise and stirred for 10 minutes. *N*-Allyl-*N*-methyl-*N*-[(Z)-3-phenyl-2-propenyl]amine (**299**, 188 mg, 1.0 mmol) as a solution in THF (2.0 mL) was added dropwise, and the resulting solution stirred for 5 hrs. After cooling the reaction mixture to -78 °C methallyl chloride (0.20 mL, 2 mmol) followed by LDA (1.0 mL, 2.0 mmol) was added dropwise over 5 minutes. The reaction was kept below –50 °C for 1 hour before warming to room temperature, then quenched with methanol (5.0 mL) and a saturated solution of $NaHCO_3$ (8.0 mL). The product was extracted into diethyl ether (3 x 100 mL), the combined organic layer washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compounds (1:1) as a viscous colourless oil (198 mg, 0.74 mmol, 74 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.40-7.10 (5H, m, Ph-H), 5.090 (1H, t, *J* = 8.5 Hz, H12), 4.67 (1H, s, H19), 4.63 (1H, s, H19'). 2.78-2.50 (6H, m, H2 and H9), 2.30 (6H, s, H1), 2.29-1.95 (12H, m, H17, H11, H3, H4 and H10), 1.70-1.60 (9H, m, H14, H15 and H20) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = (C, C5) not observed, 128.98, 128.81, 128.44 (CH, C6, C7 and C8), 123.02 (C, C18), 109.95 (CH_2, C19), 62.97, 62.27 (CH_2, C2 and C9), 47.04 (CH, C3), 44.71 (CH, C10), 42.71 (CH_3, C1), 41.66 (CH_2, C4), 36.66 (CH_2, C17), 33.40 (CH_2, C16), 25.97 (CH_3, C20) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 141.56 (C, C13), (C, C5) not observed, 128.97, 128.44, 126.45 (CH, C6, C7 and C8), 123.17 (CH, C12), 62.70, 62.52 (CH_2, C2 and C9), 46.51, 45.35 (CH, C3 and C10), 42.17 (CH_3, C1), 41.64 (CH_2, C4), 33.38 (CH_2, C11), 25.97, 18.00 (CH_3, C15 and C14) ppm.

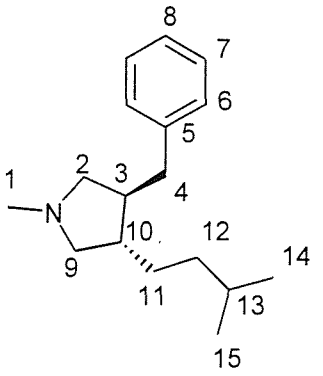
IR (neat oil) = 2952 (brm), 2345 (w), 1516 (w), 1365 (m), 1019 (m) cm^{-1}.

GC = 5.714 and 6.058 min.

LRMS (ES^+, m/z) 244.2 (M+H).

EI-HRMS $C_{17}H_{25}N$ requires 243.1987 found 243.1990 (M+).

3-Benzyl-1-methyl-4-(3-methyl-butyl)-pyrrolidine (316)



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in dry THF (5.0 mL) under argon at -80 °C, ^nBuLi (0.8 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise and stirred for 10 minutes. *N*-Allyl-*N*-methyl-*N*-[(Z)-3-phenyl-2-propenyl]amine (**299**, 188.0 mg, 1.0 mmol) as a solution in THF (2.0 mL) was added dropwise, warmed to room temperature stirred for 5 hrs. Methallyl chloride (0.20 mL, 2.0 mmol) followed by LDA (1.0 mL, 2.0 mmol) was added dropwise over 5 minutes then cooled to –78 °C. The reaction was kept below –50 °C for 1 hour before warming to room temperature before quenching with methanol (5.0 mL) and a saturated solution of $NaHCO_3$ (8.0 mL). The product was extracted into diethyl ether (3 x 100 mL), the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. The crude products were then dissolved in DCM (10 mL), Pd/C (250 mg, 0.1 mmol) was added then hydrogenated (1 atmosphere hydrogen) for 12 hours, before quenching with a saturated solution of $NaHCO_3$ (8.0 mL). The product was extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (3 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a viscous colourless oil (138 mg, 0.56 mmol, 56 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.40-7.10 (5H, m, Ph-H), 2.75-2.53 (2H, m, H2), 2.50-2.35 (2H, m, H9), 2.29 (3H, s, H1), 2.08-1.70 (4H, m, H3, H4 and H10), 1.48-1.15 (5H, m, H11, H12 and H13), 0.84 (3H, d, J = 6.5 Hz, H15 or H14), 0.81 (3H, d, J = 6.5 Hz, H14 or H15) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 141.86 (C, C5), 128.97, 128.41, 125.98 (CH, H6, H7 and H8), 63.20, 62.26 (CH_2, C2 and C9), 47.07, 45.38 (CH, C3 and C10), 42.72 (CH_3, C1), 41.69 (CH_2, C4), 37.76 (CH_2, C11), 33.15 (CH_2, C12), 28.26 (CH, C13), 22.87, 22.65 (CH_3, C14 or C15) ppm.

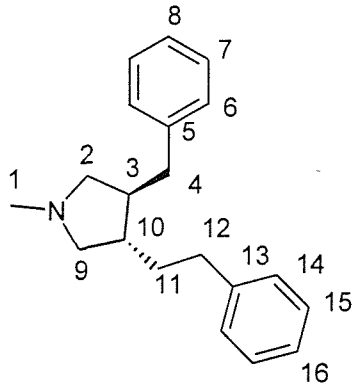
IR (neat oil) = 2956 (brm), 2393 (m), 1577 (w), 1078 (brm), 872 (brs) cm^{-1}.

GC = 5.668 min.

LRMS (ES^+, m/z) 246.6 (M+H).

CI-HRMS $C_{17}H_{27}N$ requires 245.2143 found 245.2143 (M+).

3-Benzyl-1-methyl-4-phenethyl-pyrrolidine (317).



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in dry THF (5.0 mL) under argon at -80 °C, ^{n}BuLi (0.8 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise and stirred for 10 minutes. *N*-Allyl-*N*-methyl-*N*-[(Z)-3-phenyl-2-propenyl]amine (**299**, 188 mg, 1.0 mmol) as a solution in THF (2.0 mL) was added dropwise, warmed to room temperature stirred for 5 hrs. After cooling the reaction mixture to –78 °C, benzyl chloride (129 mg, 1.1 mmol) was added followed by LDA (2.0 mmol, 1.0 mL). The mixture was stirred for 1 hrs before quenching with methanol (5.0 mL) and a saturated solution of $NaHCO_3$ (8.0 mL). The product was extracted into diethyl ether (3 x 100 mL), the combined organic layer washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a viscous colourless oil (198 mg, 0.76 mmol, 76 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.35-7.15 (10H, m, Ph-H), 2.74-2.63 (4H, m, H2 and H9), 2.27 (3H, s, H1), 2.18-2.00 (4H, m, H4 and H12), 1.99-1.83 (4H, m, H3, H10 and H11) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 142.78, 141.86 (C, C5 and C13), 127.07, 129.01, 128.77, 128.71, 126.56, 126.28 (CH, C6, C7, C8, C14, C15, C16), 63.21, 62.58 (CH_2, C2 and C9), 47.53, 45.27 (CH, C3 and C10), 42.95 (CH_3, C1), 41.84 (CH_2, C4), 37.39 (CH_2, C12), 35.06 (CH_2, C11) ppm.

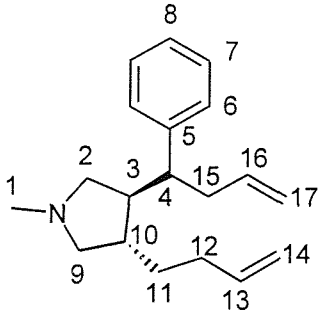
IR (neat oil) = 3013 (brm), 1555 (w), 1437 (m), 1119 (brs), 961 (brm) cm^{-1}.

GC = 7.365 min.

LRMS (ES^+, m/z) 280.4 (M+H).

EI-HRMS $C_{20}H_{25}N$ requires 279.1987 found 279.1985 (M+).

3-But-3-enyl-1-methyl-4-(1-phenyl-but-3-enyl)-pyrrolidine (318).



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in dry THF (5.0 mL) under argon at $^-$80 °C, ^{n}BuLi (0.8 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise and stirred for 10 minutes. *N*-Allyl-*N*-methyl-*N*-[(Z)-3-phenyl-2-propenyl]amine (**299**, 188 mg, 1.0 mmol) as a solution in THF (2.0 mL) was added dropwise, warmed to room temperature stirred for 5 hrs. After cooling to –78 °C the solution was added to a stirring solution of CuI (2.0 mmol, 380.0 mg) and allyl bromide (2.0 mmol, 240 mg). The resulting mixture was stirred for 12 hours before quenching with methanol (8.0 mL) and a saturated solution of $NaHCO_3$ (8.0 mL). The product was extracted into diethyl ether (3 x 100 mL), the combined organic layer washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a viscous colourless oil (193 mg, 0.73 mmol, 73 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.40-7.10 (5H, m, Ph-H), 5.85 (1H, ddt, *J* = 17.5, 10.5 and 6.5 Hz, H16 or H13), 5.58 (1H, ddt, *J* = 17.5, 10.5 and 6.5 Hz, H13 or H16), 5.05 (1H, d, *J* = 17.5 Hz, H17 or H14), 5.00 (1H, d, *J* = 17.5 Hz, H14 or H17), 4.86 (1H, d, *J* = 10.5 Hz, H17' or H14'), 4.84 (1H, d, *J* = 10.5 Hz, H17' or H14'), 2.59-2.35 (4H, m, H2 and H9), 2.29 (3H, s, H1), 2.28-1.96 (4H, m, H15 and H12), 1.90-1.50 (5H, m, H4, H3, H10 and H11) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 142.78 (C, C5), 138.54, 136.84 (CH, C13 and C16), 128.31, 128.15, 126.13 (CH, C6, C7 and C8), 115.95, 114.87 (CH_2, C14 and C17), 62.58, 61.59 (CH_2, C2 and C9), 51.17, 50.64 (CH, C3 and C10), 42.81 (CH_3, C1), 42.40 (CH, C4), 39.08, 35.91 (CH_2, C12 or C15), 32.79 (CH_2, C11) ppm.

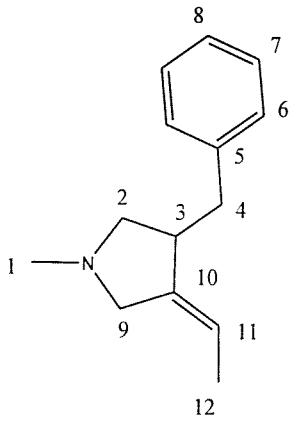
IR (neat oil) = 2958 (brm), 1577 (w), 1350 (brm), 872 (m) cm^{-1}.

GC = 6.120 min.

LRMS (ES^+, m/z) 270.4 (M+H).

CI-HRMS = $C_{19}H_{27}N$ requires 269.2143 found 269.2137 (M+).

3-Benzyl-4-[(Z)ethylidene]-1-methylpyrrolidine (321).



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in dry THF (5.0 mL) under argon at -80 °C, ^{n}BuLi (0.8 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise and stirred for 10 minutes. *N*-(2-Butynyl)-*N*-methyl-*N*-[(E)-3-phenyl-2-propenyl]amine (**303**, 258 mg, 1.0 mmol) as a solution in THF (2.0 mL) was added dropwise. The mixture warmed to room temperature, stirred for 4 hrs, before quenching with methanol (5.0 mL) and a saturated solution of $NaHCO_3$ (8.0 mL). The product was extracted into diethyl ether (3 x 100 mL), the combined organic layer washed with water (4 x 50 mL), brine

(50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a viscous oil (112 mg, 0.58 mmol, 58 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.40-7.27 (5H, m, Ph-H), 5.18 (1H, q, J = 7.0 Hz, H11), 3.24 (1H, d, J = 13.6 Hz, H9), 3.15 (1H, d, J = 13.5 Hz, H9'), 2.84-2.63 (2H, m, H2), 2.49 (1H, m, H3), 2.26 (3H, s, H1), 2.15-2.13 (2H, m, H4), 1.55 (3H, d, J = 7.0 Hz, H12) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 142.46 (C, C5), 139.96 (C, C10), 127.32, 127.24, 124.85 (CH, C6, C7 and C8), 113.69 (CH, C11), 61.17 (CH_2, C9), 57.89 (CH_2, C2), 43.98 (CH_3, C1), 41.62 (CH, C3), 39.16 (CH_2, C4), 13.58 (CH_3, C12) ppm.

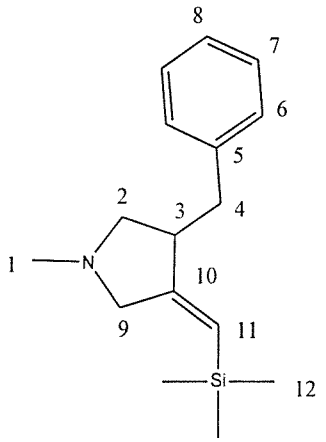
IR (neat oil) = 2953 (m), 1640 (m), 1259 (m), 799 (s) cm^{-1}.

GC = 4.85 min.

LRMS (ES^+, m/z) 202.1 (M+H).

ES-HRMS $C_{14}H_{20}N$ requires 202.1590 found 202.1593 (M+H).

3-Benzyl-1-methyl-4-[(Z)-1-(1,1,1-trimethylsilyl)methylidene]pyrrolidine (322).



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in dry THF (5.0 mL) under argon at -80 °C, ^{n}BuLi (0.8 mL, 2.5 M solution in hexanes, 2.0 mmol) was added dropwise and stirred for 10 minutes. *N*-Methyl-*N*-[(E)-3-phenyl-2-propenyl]-*N*-[3-(1,1,1-trimethylsilyl)-2-propynyl]amine (**304**, 258 mg, 1.0 mmol) as a solution in THF (2.0 mL) was added dropwise, the mixture warmed to room temperature, stirred for 5 hrs, before quenching with methanol (5.0 mL) and a saturated solution of $NaHCO_3$ (8.0 mL). The

product extracted into diethyl ether (3 x 100 mL), the combined organic extracts washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a viscous colourless oil (161 mg, 0.61 mmol, 61 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.40-7.25 (5H, m, Ph-H), 5.38 (1H, s, H11), 3.37 (1H, d, J = 14.0 Hz, H9), 3.11 (1H, d, J = 14.0 Hz, H9'), 2.97 (2H, m, H2), 2.62 (1H, m, H3), 2.33 (3H, s, H1), 2.15 (2H, m, H4) 0.24 (9H, s (br), H12) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 161.13 (C, C10), 141.06 (C, C5), 129.01, 128.45, 126.09 (CH, C6, C7 and C8), 118.25 (CH, C11), 61.70 (CH_2, C9), 61.48 (CH_2, C2), 48.19 (CH_3, C1), 42.77 (CH, C3), 40.17 (CH_2, C4), 0.26 (CH_3, C12) ppm.

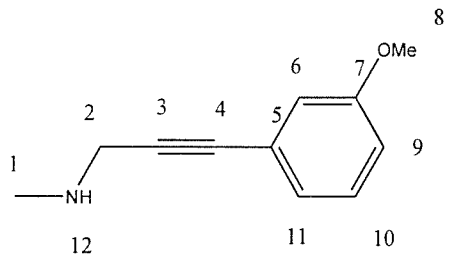
IR (neat oil) = 3059 (brm), 1593 (w), 1233 (m), 754 (brm) cm^{-1}.

GC = 5.647 min.

LRMS (ES^+, m/z) 260.1 (M+H).

HRMS analysis did not give desired peak.

[3-(3-Methoxy-phenyl)-prop-2-ynyl]-methyl-amine (328)



To a stirred solution of triethylamine (1.0 mL, 10.0 mmol) and methanesulphonyl chloride (354 mg, 3.5 mmol) in DCM (10.0 mL), 3-(3-methoxy-phenyl)-prop-2-yn-1-ol (486 mg, 3.0 mmol) was added under argon at 0 °C. The solution was stirred for 20 minutes at -20 °C, before quenching with a solution of ether (30.0 mL), cold filtered, and the solvent removed under reduced pressure. The product was dissolved in EtOH (10.0 mL), and methylamine (66 % solution in IMS, 3.0 mL, 10.0 mmol) was added at 0 °C. The resulting solution was refluxed for 30 minutes, before quenching with a saturated solution of $NaHCO_3$ (15.0 mL). The product was extracted into diethyl ether (3 x 50

mL), the combined organic layer washed with water (3 x 30.0 mL), brine (30.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the desired compound as a yellow oil (361 mg, 2.1 mmol, 59 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.25 (1H, d, J = 8.0 Hz, H9), 7.04 (1H, d, J = 8.0 Hz, H11), 6.97 (1H, s, H6), 6.88 (1H, dd, J = 8.0 and 8.0 Hz, H10), 4.50 (3H, s, H8), 3.75 (2H, s, H2), 2.24 (3H, s, H1) ppm.

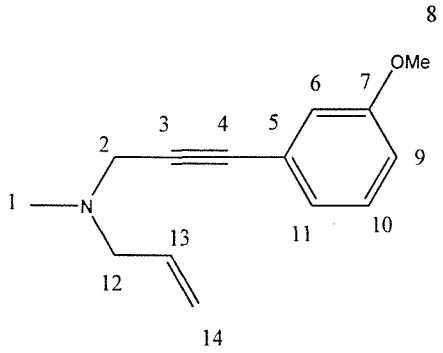
^{13}C (75 MHz, $CDCl_3$) δ = 159.55 (C, C7), (C, C5) not observed, 129.55, 124.34, 116.68, 115.21 (CH, C6, C9, C10 and C11), 87.27, 85.68 (C, C3 and C4), 55.42 (CH_2, C2), 51.72 (CH_3, C8), 46.20 (CH_3, C1) ppm.

IR (neat oil) = 2937 (m), 1489 (w), 1046 (m), 755 (s) cm^{-1}.

GC = 4.801 min

LRMS (ES^+, m/z) 176.2 (M+H).

Allyl-[3-(3-methoxy-phenyl)-prop-2-ynyl]-methyl-amine (330)



To a stirred solution of [3-(3-methoxy-phenyl)-prop-2-ynyl]-methyl-amine (**328**, 350 mg, 2.0 mmol), K_2CO_3 (2.0 g, 14.7 mmol) in MeCN (30.0 mL) at 0 °C, allyl bromide (240 mg, 2.0 mmol) was added dropwise. The solution was warmed to room temperature, stirred for 1 hour then refluxed for 1 hour, before quenching with a saturated solution of $NaHCO_3$ (50.0 mL). The product was extracted into diethyl ether (3 x 40 mL), the combined organic layer washed with water (3 x 30 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column

chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as an orange oil (134 mg, 1.3 mmol, 64 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.30-6.75 (4H, m, Ph-H), 5.89 (1H, ddt, *J* = 16.0, 10.0 and 6.0 Hz, H13), 5.15 (1H, d, *J* = 16.0 Hz, H14), 5.05 (1H, d, *J* = 10.0 Hz, H14'), 3.67 (3H, s, H8), 3.45 (2H, s, H2), 3.15 (2H, d, *J* = 6.0 Hz, H12), 2.39 (3H, s, H1) ppm.

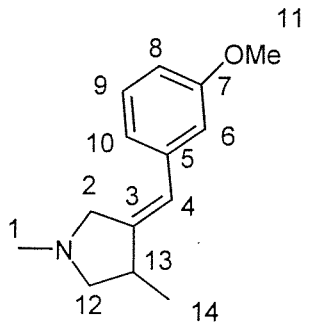
^{13}C (75 MHz, $CDCl_3$) δ = 159.43 (C, C7), 135.55 (CH, C13), 129.46 (C, C5), 124.41, 118.28, 116.78, 114.68 (CH, C6, C9, C10 and C11), 113.93 (CH_2, C14), 85.41 (C, C4), 84.50 (C, C3), 59.38 (CH_2, C12), 55.52 (CH_3, C8), 46.13 (CH_2, C2), 41.92 (CH_3, C1) ppm.

IR (neat oil) = 3001 (br,), 2360 (m), 1489 (w), 1046 (s) cm^{-1}.

GC = 5.651 min.

LRMS (ES^+, m/z) 216.2 (M+H).

3-(3-Methoxy-benzylidene)-1,4-dimethyl-pyrrolidine (332).



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in dry THF (5.0 mL) under argon at $^-$80 °C, ^{n}BuLi (0.8 mL of 2.5 M solution in hexanes, 2.0 mmol) was added dropwise and stirred for 10 minutes. Allyl-[3-(3-methoxy-phenyl)-prop-2-ynyl]-methyl-amine (**330**, 216 mg, 1.0 mmol) as a solution in THF (2.0 mL) was added dropwise, warmed to room temperature stirred for 5 hrs, before quenching with methanol (5.0 mL) and a saturated solution of $NaHCO_3$ (8.0 mL). The product was extracted into diethyl ether (3 x 100 mL), the combined organic layer washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a viscous colourless oil (149 mg, 0.64 mmol, 64 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.25-6.70 (4H, m, Ph-H), 6.10 (1H, s, H4), 3.70 (3H, s, H11), 3.20-2.85 (4H, m, H2 and H12), 2.35 (3H, s, H1), 2.00 (1H, m, H13), 1.10 (3H, d, J = 7.0 Hz, H14) ppm.

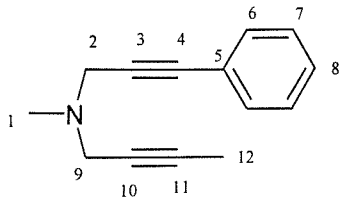
^{13}C (75 MHz, $CDCl_3$) δ = 159.43 (C, C7), 148.70 (C, C3), 139.66 (C, C5), 129.40, 120.71, 120.37, 113.80 (CH, C6, C8, C9 and C10), 111.62 (CH, C4), 63.70 (CH_2, C2), 60.62 (CH_2, C12), 55.36 (CH_3, C11), 42.78 (CH_3, C1), 39.94 (CH, C13), 18.10 (CH_3, C14) ppm.

IR (neat oil) = 2869 (brw), 1680 (m), 1554 (m), 1475 (m), 1259 (s) cm^{-1}.

GC = 5.823 mins

LRMS (ES^+, m/z) 218.2 (M+H).

But-2-ynyl-methyl-(3-phenyl-prop-2-ynyl)-amine (333)



To a stirring solution of triethylamine (1.0 mL, 10.0 mmol) and methanesulphonyl chloride (3.5 mmol, 354 mg) in DCM (10.0 mL) at 0 °C, 2-butyn-1-ol (3.0 mmol, 211 mg) was added under argon. The solution was left to stir for 20 minutes at 0 °C, warmed to room temperature and stirred for 20 minutes before quenching with a solution of diethyl ether (30.0 mL), filtered, and the solvent removed under reduced pressure. The product dissolved in MeCN (10.0 mL), secondary amine (**325**, 290 mg, 2.0 mmol) added at 0 °C, stirred with K_2CO_3 (1.0 g, 7.5 mmol), triethylamine (3.0 mL) and the solution refluxed for 30 minutes. The reaction was quenched with a solution of $NaHCO_3$ (15.0 mL), the product extracted into diethyl ether (3 x 50 mL), the combined organic layer washed with water (30.0 mL), brine (30.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the desired compound as a pale oil (242 mg, 1.2 mmol, 61 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.40-7.15 (5H, m, Ph-H), 3.45 (2H, s, H2), 3.25 (2H, q, *J* = 1.5 Hz, H9), 2.35 (3H, s, H1), 1.75 (3H, t, *J* = 1.5 Hz, H12) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 134.87 (C, C5), 128.38, 128.20, 127.05 (CH, C6, C7 and C8), 86.67, 85.23, 79.50, 74.76 (C, C3, C4, C10 and C11), 45.55, 45.30 (CH_2, C2 and C9), 41.55 (CH_3, C1), 3.70 (CH_3, C12) ppm.

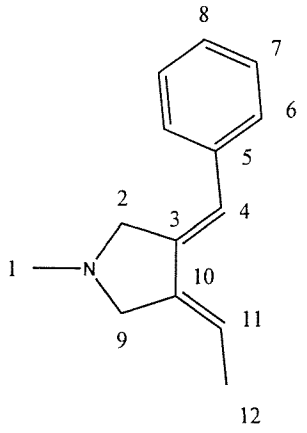
IR (neat oil) = 2923 (m), 1463 (m), 910 (m) cm^{-1}.

GC = 5.477 mins

LRMS (ES^+, m/z) 198.2 (M+H).

EI-HRMS $C_{14}H_{16}N$ requires 198.1204 found 198.1269.

3-Benzylidene-4-ethylidene-1-methyl-pyrrolidine (335)



To a stirred solution of $ZrCp_2Cl_2$ (0.292 g, 1.0 mmol) in dry THF (5.0 mL) under argon at -80 °C, ^{n}BuLi (0.8 mL of 2.5 M solution in hexanes, 2.0 mmol) was added dropwise and stirred for 10 minutes. But-2-ynyl-methyl-(3-phenyl-prop-2-ynyl)-amine (**333**, 197 mg, 1.0 mmol) as a solution in THF (2.0 mL) was added dropwise, warmed to room temperature stirred for 5 hrs, quenched with a saturated solution of $NaHCO_3$ (8.0 mL) and methanol (5.0 mL). The product was extracted into diethyl ether (3 x 100 mL), the combined organic layer washed with water (4 x 50 mL), brine (50.0 mL), dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Column chromatography (SiO_2, 0-100 % Et_2O:petroleum including 5 % Et_3N) afforded the title compound as a viscous colourless oil (156 mg, 0.78 mmol, 78 %).

^{1}H (300 MHz, $CDCl_3$) δ = 7.40-7.10 (5H, m, Ph-H), 6.60 (1H, s, H4), 5.95 (1H, q, *J* = 6.0 Hz, H11), 3.50 (2H, s, H2), 3.40 (2H, s, H9), 2.45 (3H, s, H1), 1.65 (3H, d, *J* = 6.0 Hz, H12) ppm.

^{13}C (75 MHz, $CDCl_3$) δ = 139.48, 139.21, 137.93 (C, C3, C5 and C10), 128.58, 128.47, 126.57 (CH, C6, C7 and C8), 117.10 (CH, C4), 113.93 (CH, C11), 60.92 (CH_2, C2), 58.25 (CH_2, C9), 42.76 (CH_3, C1), 15.16 (CH_3, C12) ppm.

IR (neat oil) = 3044 (brw), 2869 (brm), 1403 (m), 1015 (w), 905 (m) cm^{-1}.

GC = 5.36 mins

LRMS (ES^+, m/z) 200.1 (M+H).

REFERENCES

1. Alberts, B. *Molecular Cell Biology,* **1994**, New York, Garland publishing *inc.*
2. Cooper, J. C.; Bloom, F. E.; Roth, R. H. *Molecular Neuropharmacology*, **1996,** Oxford University Press.
3. Zubay, G. *Biochemistry,* **1993**, New York, Wm. C. Brown Publishers.
4. Baltimore, D. *Molecular Cell Biology*, **1995**, New York: Scientific American Books.
5. Civelli, O.; Bunzow, J. R.; Grandy, D. R. *Annual Review of Pharmacology and Toxicology*, **1993**. 32: p. 281-307.
6. Bores, G.; Kosley, W. *Drugs of the Future*, **1996,** 21(6), p. 621-635.
7. Sibley, D. R.; Monsma, F. J. *Trends in Pharmaceutical Science*, **1992**. 13(2), p. 61-69.
8. Amara, S. G. *Neuroscience*, **1995**, 1, p. 259-268.
9. Cossey, J.; Poitevin, J. C.; Pardo, P. *Journal of Organic Chemistry*, **1998**. 63, p. 4554-4557.
10. Kawase, M. *Heterocycles*, **1998**. 48: p. 555-561.
11. Andersen, P. H. *Trends in Pharmacological Sciences II*, **1990**, p. 231-236.
12. Jensen, E.; Nielson, H. *Heterocycles*, **1995**. 41, p. 2441-2457.
13. Wolf, M. E., Roth, R. H. *Pharmaceuticals*, **1987**, Amsterdam: Elsevier.
14. Niznik, H. ed. Hall. *Receptors*, **1988**, Amsterdam: Elsevier.
15. Szmuszkovicz, J. *Drug Research*, **1999**. 52, p. 169-195.
16. Iwasaki, N.; Ohashi, T.; Nishino, H.; Smith, S. *Journal of Medicinal Chemistry*, **1995**, 38, p. 496-507.
17. Leander, D. J.; Cantrell, B. E.; Reel, J. K.; Snoddy, J.; Laurane, M. G.; Johnson, B. G.; Mitch, C. H.; Zimmerman, D. M. *Journal of Medicinal Chemistry*, **1993**, 36, p. 2833-2850.
18. Leander, D. J.; Cantrell, B. E.; Reel, J. K.; Snoddy, J.; Laurane, M. G.; Johnson, B. G.; Mitch, C. H.; Zimmerman, D. M. *Journal of Medicinal Chemistry*, **1993**, 36, p. 2283-2298.
19. Mitch, H. *Journal of Medicinal Chemistry*, **1993**, 36, p. 2842-2846.

20. Loew, G. H.; Polgar, W.; Toll, T. *European Journal of Medicinal Chemistry*, **1991**, 26, p. 775-778.
21. Bishop, D. C.; Selway, R. A.; Webb, N. E.; Winder, C. V.; Welford, M.; Cavalla, J. F. *Journal of Medicinal Chemistry*, **1965**, 1, p. 316-326.
22. Negishi, E. *Organometallics in Organic synthesis*, **1980**, 1, p. 532, Oxford University Press.
23. Berzelius, J. *J. Ann. Chim. Phys.*, **1824**, 26, p. 43.
24. Wailes, P.C.; Weigold, H. J. *Organometallic Chemistry*, **1970**, 24, p. 405-415.
25. Bell, A.P.; Wailes, P. C.; Weigold, H. J. *Journal of Organometallic Chemistry*, **1970**, 27, p. 373-379.
26. Schwartz, J. *Angew. Chem. Int. Ed. Engl.*, **1976**, 15(6), p. 333-340.
27. Schwartz, S.; Hart, D.W. *Journal of the American Chemical Society*, **1974**, 96, p. 8115-8124.
28. Normant, J.F. *Synthesis*, **1981**, p. 841.
29. Anderson, A. *Angew. Chem. Eng*, **1976**, 25, p. 507.
30. Cossee, P.; Arlman, E. J. *Catalysis*, **1964**, 3, p. 99-108.
31. Negishi, E., *Journal of the American Chemical Society,* **1989**, 111, p. 3089-3091.
32. Thanedar, S.; Garana, F., *Journal of Organometallic Chemistry*, **1982**, 235, p. 65-68.
33. Erker, G.; Oietron, W.; Rosenfeldt, F.; Wicher, K. *Journal of the American Chemical Society*, **1981**, 103, p. 2687-2695.
34. Schwartz J.; Gell K. I. *Journal of the American Chemical Society*, **1980**, 102, p. 6344-6346.
35. Negishi, E.; Tour, J. M.; *Journal of the American Chemical Society*, **1985**, 107, p. 8289-8291.
36. Cedarbaum, F.E.; Negishi, E.; Takahashi, T. *Tetrahedron Letters*, **1986**, 27, p. 2829-2832.
37. Negishi, E. *Journal of the American Chemical Society*, **1989**, 111, p. 3336-3346.
38. Buchwald, S. L.; Huffman, J.C.; Watson, B. T. *Journal of the American Chemical Society*, **1987**, 109, p. 2568-2569.

39. Negishi, E.; Swanson, D. R.; Takahashi, T. *Journal of the Chemical Society Chemical Communications*, **1990**, p. 1254-1256.
40. Holmes, S. J.; Miller, J. A.; Negishi, E.; Tour, S. J. *Tetrahedron Letters*, **1986**, 27, p. 775-778.
41. Negishi, E.; Sawada, H.; Stoll, T.; Webb, M. *Journal of the American Chemical Society*, **1985**, 107, p. 2568-2569.
42. Sato, F.; Hata, T.; Urabe, H. *Tetrahedron Letters*, **1995**, 36, p. 4261.
43. Nugent, W. A.; Calabrese, J. C. *Journal of the American Chemical Society*, **1984**, 106, p. 6422-6424.
44. Barluenga, J.; Sanz, R.; Fananas, F. *Journal of the Chemical Society Euopean Journal*, **1997**, 8(3): p. 1324-1336.
45. Negishi, E. *Tetrahedron Letters*, **1989**, 30, p. 5105-5108.
46. Nugent, W. A.; Taber, D. F. *Journal of the American Chemical Society*, **1989**, 111, p. 6435-6437.
47. Takahashi, T. *Journal of the Chemical Society Chemical Communications*, **1993**, p. 1042-1044.
48. Takahashi, T.; Aoyagi, K.; Kondakov, D. Y. *Journal of the Chemical Society Chemical Communications*, **1994**, p. 747-748.
49. Erker, G. *Journal of the American Chemical Society*, **1980**, 102, p. 6344-6346.
50. Negishi, E. *Tetrahedron Letters*, **1987**, 28, p. 917-920.
51. Negishi, E.; Swanson, D. R.; Rousset, C. J. *Journal of Organic Chemistry*, **1989**, 54, p. 3521-3523.
52. Negishi, E.; Agnel, G.; Owczarczyk, Z. *Tetrahedron Letters*, **1992**, 33(12), p. 1543-1546.
53. Coote, S.J.; Kemp, M. I.; Whitby, R. J. *Synthesis*, **1998**, p. 552-536.
54. Negishi, E. and Agnel, G. *Journal of the American Chemical Society*, **1991**, 113, p. 7424-7426.
55. Negishi, E.; Swanson, D. R.; Miller, S. R. *Tetrahedron Letters*, **1988**, 29, p. 1631-1634.
56. Whitby, R. J.; and Davis, J. M. *Tetrahedron Letters*, **1992**, 33(38), p. 5655-5658.
57. Davis, J. M.; Jaxa-Chamiec, A.; Whitby, R. J. *Synlett*, **1994**, p. 110-116.

58. Davis, J. M.; Jaxa-Chamiec, A.; Whitby, R. J. *Tetrahedron Letters*, **1994**, 35, p. 1445.
59. Luker, T.; Whitby, R. J. *Tetrahedron Letters*, **1994**, 35(5), p. 785-788.
60. Luker, T.; Whitby, R. J. *Tetrahedron Letters.*, **1995**, 36(23), p. 4109-4112.
61. Coote, S. J.; Probert, G.D.; Whitby, R. J. *Tetrahedron Letters*, **1995**, 36(23), p. 4113-4116.
62. Negishi, E.; Van Horn D. E. *Journal of the American Chemical Society*, **1977**, 99, p. 3168-3170.
63. Okukadao, N.; Negishi, E.; Van Horn D. E. *Tetrahedron letters*, **1978**. 19, p. 1027-1031.
64. Schwartz, J.; Carr, D. B. *Journal of the American Chemical Society*, **1979**, 101, p. 3521.
65. Takahashi, T. *Journal of the American Chemical Society*, **1998**, 120, p. 1672-1680.
66. Wakatsuki, Y.; Kuramitsu, T.; Yamazaki, H. *Tetrahedron Letters*, **1974**, p. 4549-4555.
67. Heaney, H.; Papageorgiou, G. *Tetrahedron*, **1996**, 52, p. 3473-3486.
68. Christl, M.; Roberts, J. D. *Journal of Organic Chemistry*, **1972**, 37, p. 3443-3452.
69. Tsuji, J. *Organopalladium reagents in organic synthesis*, **1995**, Chichester: Wiley and sons.
70. Norton, D. *Zirconium based routes to neuroactive compounds(MChem)*, **1999**, University of Southampton.
71. Coote, S. J.; Kemp, M. I.; Whitby, R. J. *Synthesis*, **1998**, p. 557-568.
72. Heck, J. *Journal of Organic Chemistry*, **1983**, 48, p. 22.
73. Suzuki. T. *Chemical Communications*, **1979**, p. 866-868.
74. Martin I.; Yang Z. *Acta Chemica Scandinavia*, **1993**, 47, p. 221-230.
75. Johnson, C.; Johns, B. *Tetrahedron Letters*, **1997**, 38, p. 7977-7980.
76. Mori, M.; Uesaka, N.; Shibasaki, M. *Journal of Organic Chemistry*, **1992**, 57, p. 3519-3521.
77. Luker, T. *Organozirconium chemistry (PhD)*, **1995**, University of Southampton.
78. Allinger, N. L. *Journal of Organic Chemistry*, **1973**, 38, p. 316-317.

79. Brandsma, L. *Preparative Acetylenic Chemistry*, **1988**, Amsterdam: Elsevier.
80. Extrance, A. *Synthesis of potentially active hetrerocycles(MChem)*, **1998**, University of Southampton.
81. Belfield, E.; Tommasini, I. *Treatment of Pruritus* (patent), **1999**: USA.
82. Robertson, J. *Tetrahedron Letters*, **1996**, 32, p. 5825.
83. Lancaster, *Lancaster Chemicals.* **1999**.
84. White, W. L. *Journal of Chemical Society*, **1971**, p. 2062-2068.
85. Sindelar, K. Collect. *Journal of Czech Chemical Society Chemical Communications*, **1981**. 46, p. 597-606.
86. Beckwith, E., *Australian Journal.of Chemistry*, **1976**. 29, p. 995-1000.
87. Bain, S. *Synthesis of potentially neuroactive heterocycles (MChem)*, **2000**, University of Southampton.
88. Mori, M.; Uesaka, N.; Shibasaki, M. *Journal of Chemical Society Chem. Commun.*, **1990**, p. 1222-1224.
89. Mori, M.; Uesaka, N.; Okamura, T.; Date, T. *Journal of Organic Chemistry*, **1994**, 59, p. 4542-4547.
90. Mori, M.; Sato, Y. *Journal of Organic Chemistry*, **1997**, 62, p 3262-3270.

APPENDIX

Get Physicochemical Properties v1.6

Enter the LY number (no prefix) here:

Or enter the Smiles here:

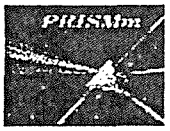
Or select an SDF file here:

Click here to compute ☐ Verbose Output (turned on automatically if there are errors)

Melting point for solubility estimate 500

Learn how to SMILE

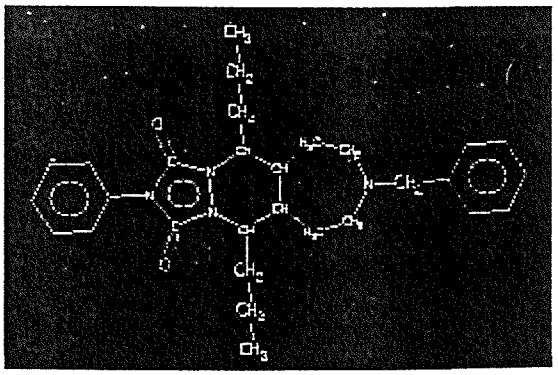
Learn how to create SDF files on the PC

Click on the icon for industrial strength Prismm! 

Calculated Parameters for Your Molecule

SMILES: C1C2C(CCC)N3N(C(CCC)C2CCN(CC2=CC=CC=C2)C1)C(=O)N(C1=CC=CC=C1)C3=O

Molecular Weight: 474.65



ClogP

Ghose/Crippen:

ClogP = 7.96

Ghose/Crippen version: April99

Daylight:

ClogP = 9.73

Version: 4.51

Toxic groups

No problems found

Chromophoric groups

The presence of groups that absorb at wavelengths of 300nm or above is not desirable, and may affect the error rates in HTRF screens

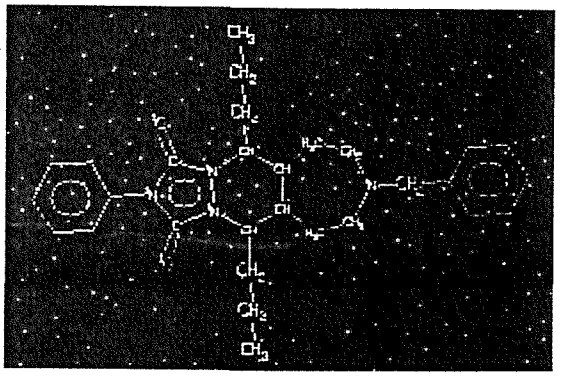
No problems found

Oral absorption/permeability:

Lipinski Rule-of-5 check

Status of compound:

H-bond acceptors by Lipinski definition:	6	
Number of atoms:	35	
H-bond donors by Lipinski definition:	0	
ClogP:	9.731	
Molecular weight:	474.652	



Your molecule **passed** the Lipinski rule-of-5.

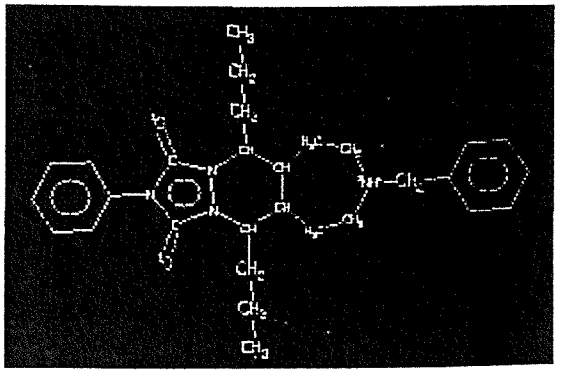
Diagnostic information:

ClogP too high: 9.731 found, limit is 5.

Doug Johnson's Bodacious BBB Model

Status of compound:

Number of atoms:	35	
ClogP:	9.731	
H-bond donors by Bruns definition:	1	
H-bond acceptors by Bruns definition:	2	
Solvation DG:	1.10884	



Your molecule is predicted to have **good** penetration by the Johnson BBB rules.

Polar Surface Area Estimates (using the Palm vdw parameters):

The PSA is 51 A**2, which indicates good intestinal absorption.

BBB permeability Estimate: logBB = 0.86

As a rough guide, logBB values > -1 indicate that the compound can get into the CNS

This estimate is approximate, and is based on the equation from Clark et al.

Biopharmaceutics Classification System:

Your compound thought to be in class 2: High Permeability, Low Solubility

BCS: van de Waterbeemd: The fundamental variables of the biopharmaceutics classification system (BCS): a commentary. *Eur. J. Pharm. Sci.*, 1998, 7, 1-3.

Solubility Estimate:

Estimated aqueous solubility: 2.2e-13 mg/ml

As a rough guide, values > 10 mg/ml indicate reasonable solubility

This estimate is highly approximate, and is based on the Yalkowsky equation. No correction has been made for pH effects. Contact Greg Durst for something better.

Credits:

Doug Johnson for the BBB model

Bob Coner for the LY database

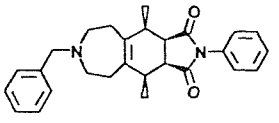
Ian Watson for lots of code

Complaints to Richard Lewis for the hacked code

Uptake Summary Report (By Lilly No List)

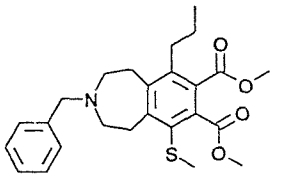
480142

18048

			%Change_avg	%Change_n	%Change_sterr
	EW 5HT Binding Nisoxetine	1000 nM	-30.0	2.0	1.0
	EW 5HT Binding WIN 35 428	1000 nM	-50.0	2.0	2.0

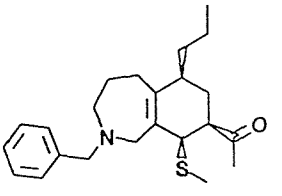
480143

18049

			%Change_avg	%Change_n	%Change_sterr
	EW 5HT Binding Nisoxetine	1000 nM	-39.0	2.0	2.0
	[illegible]		-26.0	1.0	0.0

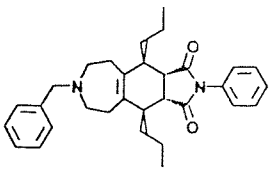
480144

18050

			%Change_avg	%Change_n	%Change_sterr
	EW 5HT Binding Nisoxetine	1000 nM	-35.5	2.0	5.5
	EW 5HT Binding WIN 35 428	1000 nM	-1.5	2.0	9.5

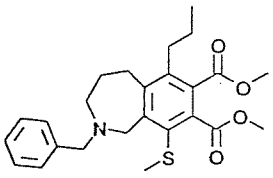
480145

18051

			%Change_avg	%Change_n	%Change_sterr
	EW 5HT Binding WIN 35 428	[illegible]	-50.0	2.0	1.0

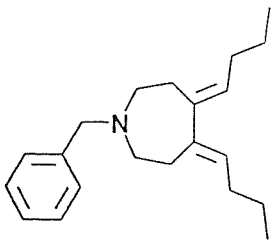
480156

18052

			%Change_avg	%Change_n	%Change_sterr
	EW 5HT Binding Nisoxetine	1000 nM	-42.0	2.0	1.0
	EW 5HT Binding WIN 35 428	1000 nM	-53.0	2.0	8.0

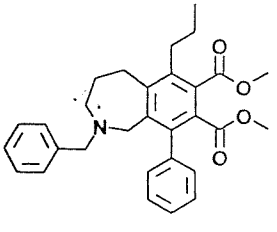
480158

18054

			%Change_avg	%Change_n	%Change_sterr
	EW 5HT Binding Nisoxetine	[illegible]	-41.0	2.0	2.0
	EW 5HT Binding WIN 35 428	1000 nM	-13.5	2.0	16.5

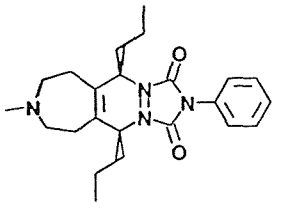
480353

18055

			%Change_avg	%Change_n	%Change_sterr
	EW 5HT Binding Nisoxetine	[illegible]	-43.5	2.0	3.5
	EW 5HT Binding WIN 35 428	[illegible]	21.0	2.0	3.0

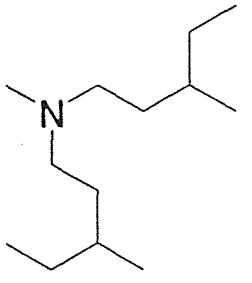
480354

18056

			%Change_avg	%Change_n	%Change_sterr
	EW 5HT Binding Nisoxetine	1000 nM	-43.0	2.0	0.0
	EW 5HT Binding WIN 35 428	1000 nM	-8.0	2.0	8.0

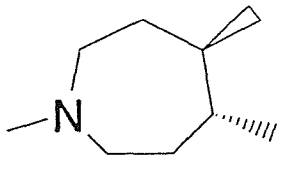
480355

18057

			%Change_avg	%Change_n	%Change_sterr
	EW 5HT Binding Nisoxetine	1000 nM	-46.0	2.0	2.0
	EW 5HT Binding WIN 35 428	1000 nM	17.0	2.0	4.0

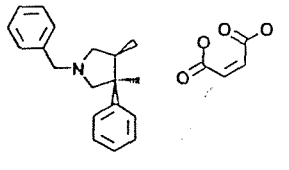
480356

18058

			%Change_avg	%Change_n	%Change_sterr
	EW 5HT Binding Nisoxetine	1000 nM	-45.0	2.0	2.0
	EW 5HT Binding WIN 35 428	1000 nM	-2.0	2.0	20.0

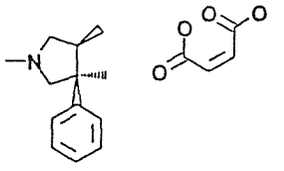
480360

18060

			%Change_avg	%Change_n	%Change_sterr
	EW 5HT Binding WIN 35 428	1000 nM	-26.0	2.0	1.0

480361

18061

			%Change_avg	%Change_n	%Change_sterr
	EW 5HT Binding Nisoxetine	1000 nM	-45.0	2.0	2.0
	EW 5HT Binding WIN 35 428	1000 nM	-19.5	2.0	8.5

Data Entry Sheet

Method ID : EW 5HT Binding 5HT Upt [Cit]
Technique : Binding
Target : 5HT Upt
Method Type : In vitro
Research Grp : 5HT
Run Site : Erl Wood
Lab Book Ref : R3727/110.1
Researcher : YE05504
Run Date : 30/07/1999
Comments :

Lot Note Book Ref	DROID Lot Id	Lilly No.	%Change Conc 10 nM	%Change Conc 50 nM	%Change Conc 100 nM	%Change Conc 1000 nM	Ki	Comments
39B-2944-185K	18057	480355				-102		
39B-2944-185K	18057	480355				-109		
39B-2944-185J	18058	480356				-87		
39B-2944-185J	18058	480356				-94		
39B-2944-185L	18060	480360				-74		
39B-2944-185L	18060	480360				-64		
39B-2944-185M	18061	480361				-69		
39B-2944-185M	18061	480361				-66		

Method ID : EW 5HT Binding 5HT Upt [Cit]
Technique : Binding
Target : 5HT Upt
Method Type : In vitro
Research Grp : 5HT
Run Site : Erl Wood
Lab Book Ref : R3727/109.2
Researcher : YE05504
Run Date : 30/07/1999
Comments :

Lot Note Book Ref	DROID Lot Id	Lilly No.	%Change Conc 10 nM	%Change Conc 50 nM	%Change Conc 100 nM	%Change Conc 1000 nM	Ki	Comments
39B-2944-185G	18052	[redacted]				-91		
39B-2944-185G	18052	[redacted]				-96		
39B-2944-185E	18054	[redacted]				-102		
39B-2944-185E	18054	[redacted]				-103		
39B-2944-185H	18055	[redacted]				-96		
39B-2944-185H	18055	[redacted]				-98		
39B-2944-185I	18056	[redacted]				-98		
39B-2944-185I	18056	[redacted]				-96		
		[redacted]						
		[redacted]						
		[redacted]						
		[redacted]						
		[redacted]						
		[redacted]						
		[redacted]						
		[redacted]						
		[redacted]						
		[redacted]						
		[redacted]						
		[redacted]						
		[redacted]						
		[redacted]						
		[redacted]						
		[redacted]						
		[redacted]						
		[redacted]						
		[redacted]						
		[redacted]						
		[redacted]						

Table 1. Crystal data and structure refinement for Nme TAKA.

Identification code	99DPM001
Empirical formula	$C_{21}H_{33}NO_5$
Formula weight	379.48
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C2/c
Unit cell dimensions	a = 40.2701(13) Å
	b = 10.7494(4) Å β = 91.649(19)°.
	c = 9.5907(2) Å
Volume	4149.9(2) $Å^3$
Z	8
Density (calculated)	1.215 Mg/m^3
Absorption coefficient	0.086 mm^{-1}
F(000)	1648
Crystal size	0.30 x 0.20 x 0.20 mm^3
Theta range for data collection	3.04 to 25.03°.
Index ranges	-47<=h<=47, -12<=k<=12, -10<=l<=11
Reflections collected	11909
Independent reflections	3647 [R(int) = 0.0732]
Completeness to theta = 25.03°	94.0 %
Max. and min. transmission	0.9831 and 0.9748
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3647 / 0 / 376
Goodness-of-fit on F^2	1.022
Final R indices [I>2sigma(I)]	R1 = 0.0461, wR2 = 0.1119
R indices (all data)	R1 = 0.0759, wR2 = 0.1260
Largest diff. peak and hole	0.284 and -0.205 $e.Å^{-3}$

Table 1. Crystal data and structure refinement.

Identification code	**s92**	
Empirical formula	$C_{23}H_{32}N_4O_2$	
Formula weight	396.53	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	?	
Unit cell dimensions	a = 19.353(4) Å	α = 90°
	b = 11.375(2) Å	β = 102.48(3)°
	c = 19.697(4) Å	γ = 90°
Volume	4233.6(14) Å^3	
Z	8	
Density (calculated)	1.244 Mg / m^3	
Absorption coefficient	0.081 mm^{-1}	
F(000)	1712	
Crystal	?; ?	
Crystal size	0.20 × 0.20 × 0.05 mm^3	
θ range for data collection	3.14 – 23.05°	
Index ranges	$-21 \le h \le 21$, $-12 \le k \le 12$, $-20 \le l \le 21$	
Reflections collected	15580	
Independent reflections	2957 [R_{int} = 0.2455]	
Completeness to θ = 23.05°	47.0 %	
Max. and min. transmission	0.9960 and 0.9840	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2957 / 0 / 266	
Goodness-of-fit on F^2	0.897	
Final R indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0545, *wR2* = 0.0880	
R indices (all data)	*R1* = 0.1785, *wR2* = 0.1187	
Extinction coefficient	0.00052(13)	
Largest diff. peak and hole	0.164 and –0.161 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: *SORTAV* (R. H. Blessing, Acta Cryst. A**51** (1995) 33–37; R. H. Blessing, J. Appl. Cryst. **30** (1997) 421–426). **Program used to solve structure**: *SHELXS86* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). **Program used to refine structure**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Further information: http://www.soton.ac.uk/~xservice/strat.htm

Special details:

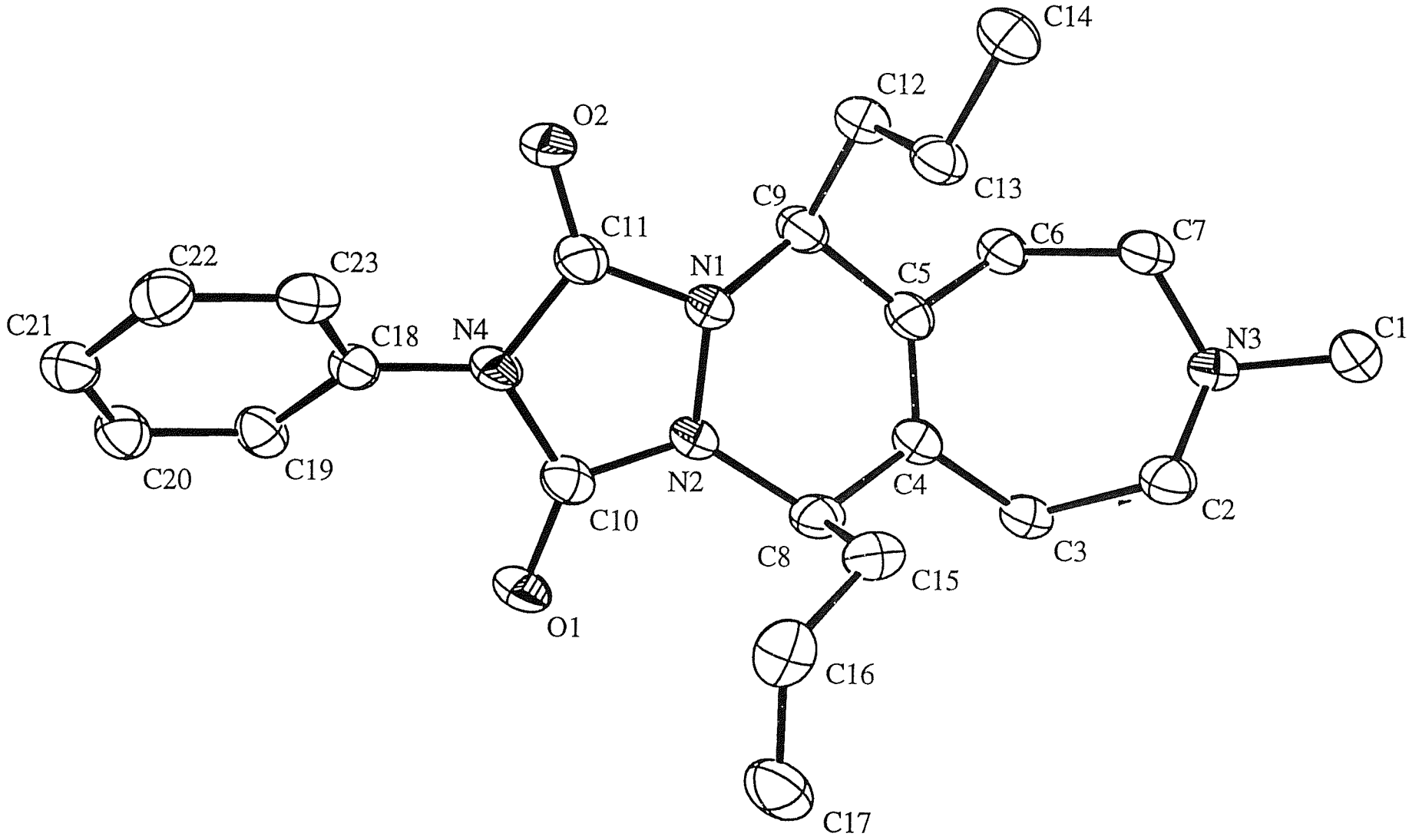

C14
C12
O2
C13
C9
C11
C6
C7
C22
C23
N1
C5
C21
C18
N4
N3
C1
C20
C19
N2
C4
C2
C10
C8
C3
C15
O1
C16
C17

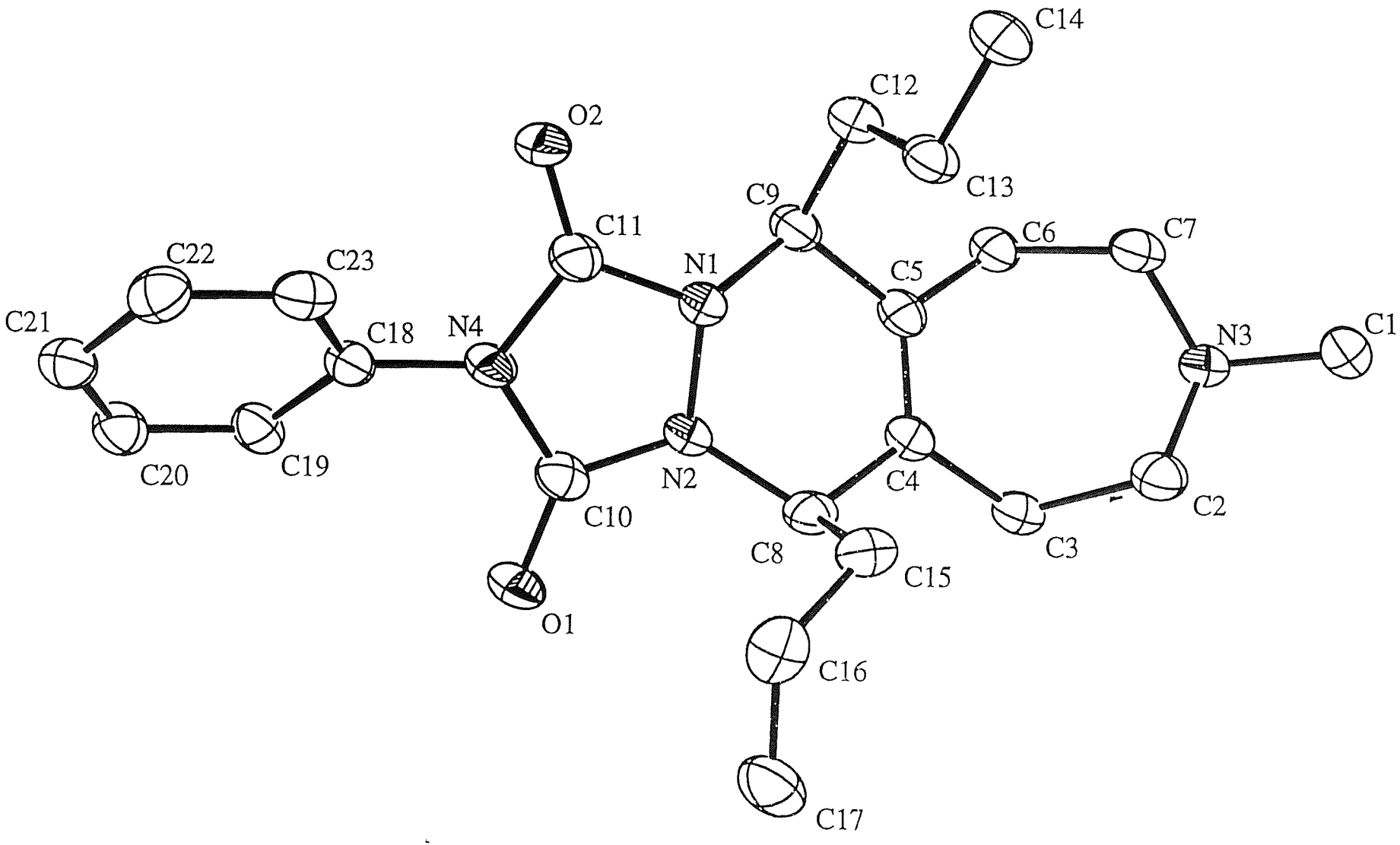
Table 1. Crystal data and structure refinement.

Identification code	s92	
Empirical formula	$C_{23}H_{32}N_4O_2$	
Formula weight	396.53	
Temperature	150(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	?	
Unit cell dimensions	a = 19.353(4) Å	α = 90°
	b = 11.375(2) Å	β = 102.48(3)°
	c = 19.697(4) Å	γ = 90°
Volume	4233.6(14) Å^3	
Z	8	
Density (calculated)	1.244 Mg / m^3	
Absorption coefficient	0.081 mm^{-1}	
F(000)	1712	
Crystal	?; ?	
Crystal size	0.20 × 0.20 × 0.05 mm^3	
θ range for data collection	3.14 – 23.05°	
Index ranges	$-21 \le h \le 21$, $-12 \le k \le 12$, $-20 \le l \le 21$	
Reflections collected	15580	
Independent reflections	2957 [R_{int} = 0.2455]	
Completeness to θ = 23.05°	47.0 %	
Max. and min. transmission	0.9960 and 0.9840	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2957 / 0 / 266	
Goodness-of-fit on F^2	0.897	
Final R indices [$F^2 > 2\sigma(F^2)$]	*R1* = 0.0545, *wR2* = 0.0880	
R indices (all data)	*R1* = 0.1785, *wR2* = 0.1187	
Extinction coefficient	0.00052(13)	
Largest diff. peak and hole	0.164 and –0.161 e Å^{-3}	

Diffractometer: *Enraf Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *Ewald* sphere). **Data collection and cell refinement:** *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. 276: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction:** *SORTAV* (R. H. Blessing, Acta Cryst. A51 (1995) 33–37; R. H. Blessing, J. Appl. Cryst. 30 (1997) 421–426). **Program used to solve structure:** *SHELXS86* (G. M. Sheldrick, Acta Cryst. (1990) A46 467–473). **Program used to refine structure:** *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany).

Further information: http://www.soton.ac.uk/~xservice/strat.htm

Special details:


C14
C12
O2
C13
C9
C11
C6
C7
C22
C23
N1
C5
C21
C18
N4
N3
C1
C20
C19
N2
C4
C2
C10
C8
C3
C15
O1
C16
C17