STUDIES TOWARDS THE SYNTHESIS OF HIMBACINE

A thesis submitted to the board of the Faculty of Physical Sciences in partial fulfilment of the requirements for the degree of Doctor of Philosophy of the University of Oxford

by

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August 1997

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THESIS

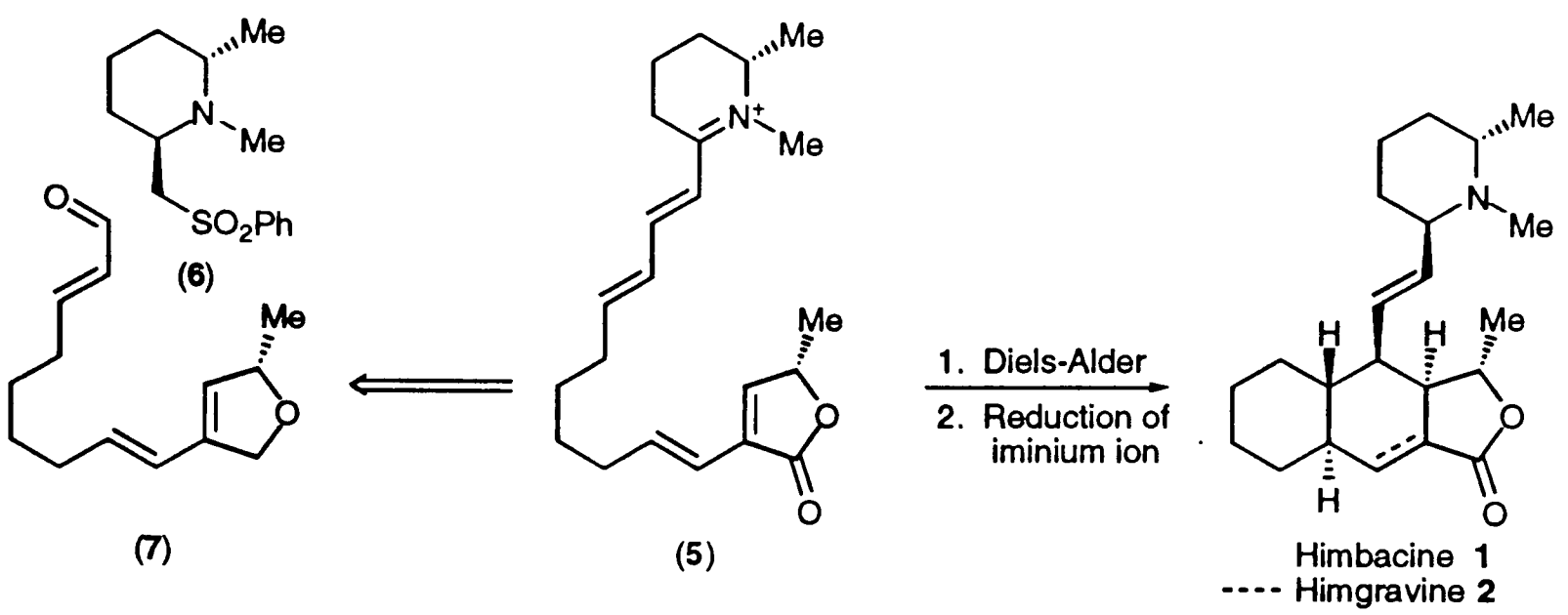
ABSTRACT

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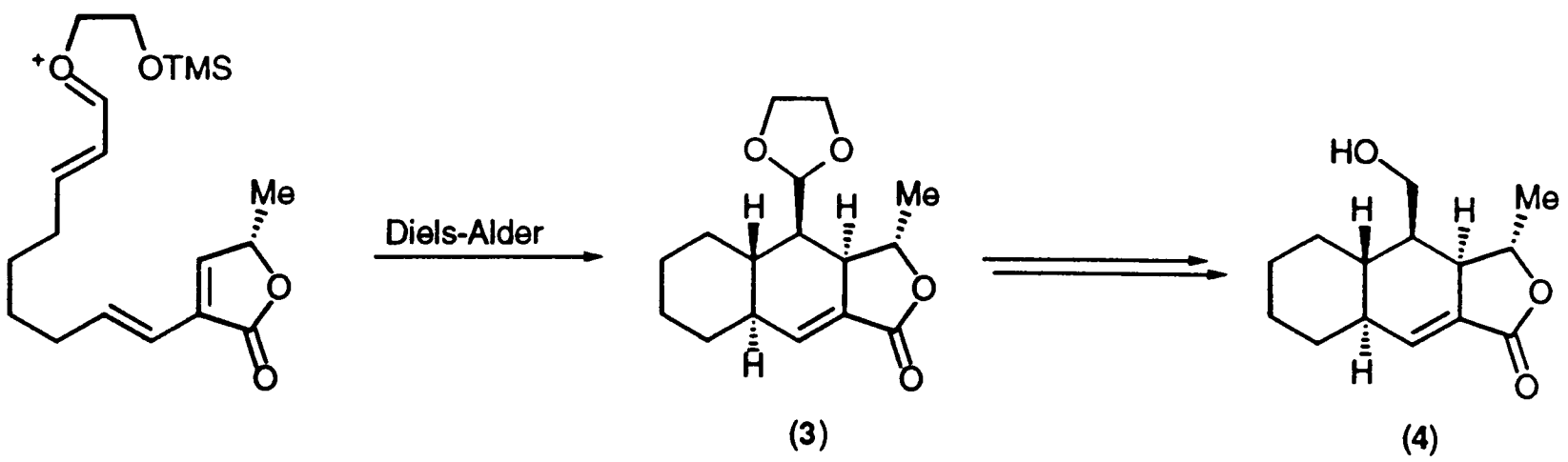
Studies Towards the Synthesis of Himbacine

The natural alkaloid himbacine **1**, first isolated in 1955 from *Galbulimina baccata* Bail, has attracted attention as a potential therapetic agent for Alzheimer's disease. It is proposed that a late stage in the biosynthesis of this compound may proceed *via* an iminium ion mediated Diels-Alder reaction (Scheme 1), which would yield the related alkaloid himgravine **2**, which can be reduced to himbacine **1**.



Scheme 1

Precident for the iminium ion mediated Diels-Alder reaction has been provided by a related oxonium ion mediated cycloaddition reaction (Scheme 2). Confirmation of the stereochemistry of the product of this reaction (**3**) has been obtained by X-ray crystallography of the tricyclic alcohol (**4**).



Scheme 2

Studies towards the synthesis of the iminium ion (**5**) have been undertaken. Piperidine sulfone (**6**) has been synthesised in a 17% yield over 16 linear steps, and a synthesis of dihydrofuran (**7**) has been investigated involving an enyne metathesis reaction. Additionally, methodology has been developed for a Julia coupling to join piperidine sulfone (**6**) to dihydrofuran (**7**), and a Polonovski reaction for generation of the required iminium ion (**5**).

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Spem Alit

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ABBREVIATIONS

Å	angstrom
Ac	acetyl
AIBN	2,2'-azobis(isobutyroisonitrile)
APCI	atmospheric pressure chemical ionisation
aq	aqueous
BOC	*tert*-butoxycarbonyl
b.p.	boiling point
Bu	butyl
Bz	benzoyl
Cardice®	solid carbon dioxide pellets
cat	catalytic
Celite®	high grade diatomaceous earth
CI	chemical ionisation
COD	cyclooctadiene
Cy	cyclohexyl
Δ	heat
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEPT	distortionless enhancement by polarisation transfer
DIBAL	diisobutyl aluminium hydride
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMSO	dimethyl sulfoxide
eda	ethylene diamine
eg	for example
EI	electron impact

eq	equivalents
Et	ethyl
etc	*et cetera* (Latin: and so on)
g	gram
GCMS	gas chromatography/mass spectrometry
GB	*Galbulimima begraveana*
h	hours
HMPA	hexamethylphosphoramide
imid	imidazole
i	iso
ie	*id est* (Latin: that is)
IR	infrared (spectroscopy)
J	coupling constant
LDA	lithium diisopropylamide
M1	M1 muscarinic receptor
M2	M2 muscarinic receptor
*m*CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MEM	(methoxyethoxy)methyl
mg	milligram
min	minutes
mmHg	millimetres of mercury
m.p.	melting point
Ms/mesyl	methanesulfonyl
m/z	mass/charge ratio
n	normal
NMO	*N*-methyl morpholine *N*-oxide
NMR	nuclear magnetic resonance
Oxone®	potassium peroxymonosulfate, sulfate and hydrogen sulfate

PCC	pyridinium chlorochromate
Ph	phenyl
Piv	pivaloyl
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
py	pyridine
rds	rate determining step
Red-Al®	sodium bis(2-methoxyethoxy) aluminium hydride
rt	room temperature
s	secondary
SEM	2-(trimethylsilyl)ethoxymethyl
t	tertiary
TBAF	tetrabutyl ammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy, free radical
Tf/triflyl	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
TRIS	tris(hydroxymethyl)aminomethane
Ts/tosyl	*para*-toluenesulfonyl
Z	benzyloxycarbonyl

Chapter 1

INTRODUCTION

1.1. The *Galbulimima* Alkaloids

The discovery by Webb in 1948 that the bark of *Himantandra baccata* FM Bail gave a strong, positive alkaloid test led to a programme of isolation and structural elucidation chemistry that extended for over a decade[1,2].

The trees, which belong to the order Magnoliales, are a small relic family consisting of only one genus. They grow up to 130 feet in height and are found in North Queensland, Australia (NQ) and New Guinea (NG). The naming, genus and number of species in it were the subject of some discussion. Originally four species were accepted:

- *Galbulimima baccata* FM Bail, (NQ)
- *Galbulimima belgraveana* (F. Muell) Spargue, (NG)
- *Galbulimima nitida* (Bak. f. and Norman) Spargue, (NG)
- *Galbulimima parvifolia* (Bak. f. and Norman) Spargue, (NG)

In a revision of the genus in 1942 Smith suggested that the name *Himantandra* was more consistent, and that only the first two species were valid, the other two being reduced to synonyms of *Himantandra belgraveana* (F. Muell) Diels. His conclusions were criticised by Smith in 1960 on the grounds that by the rules of the International Code of Botanic Nomenclature (1956), the correct name of the genus was *Galbulimima* FM Bail, and that an insufficient number of plant specimens had been examined to enable a conclusion concerning the number of species involved to be reached. Finally, van Royan, re-examining the question in 1962, confirmed *Galbulimima* as the correct name of the genus. He also concluded that because of the extreme morphological variation throughout the habitat of the genus, which extends

through all parts of New Guinea, the Molucca, and the rain forest areas of North Queensland, only one species, *Galbulimima belgraveana* (F. Muell) Sprague, should be recognised. The groups working on the isolation of the alkaloids chose to avoid the issue of naming by identifying the plant material by source (NQ or NG)[1].

1.2. Isolation of the *Galbulimima* alkaloids

The first isolations were reported by Ritchie in 1956, who identified 10 new alkaloids from the bark[3,4]. Further work, published in 1964, identified a further 19 alkaloids[5], which, with some corrections to the previous work, brought the total to 28.

The alkaloids fall into four classes based on their structure[1] (Table 1):

- Tetracyclic lactones (eg himbacine **1**, himbeline **2**)
- Highly oxygenated hexacyclic ester (eg himbosine **3**, himandridine **4**)
- One hexacyclic and two pentacyclic bases of low oxygen content (eg himgaline **5**, himbadine **6**)
- Miscellaneous (eg himgrine **7**)

The total amount and constitution of the alkaloids isolated varied significantly between each sample of bark; even samples collected in the same area and at approximately the same time were shown to be quite dissimilar. The total yield of alkaloid varied from trace to 0.5% of the mass of the bark. The major and commonest alkaloids in the bark from both sources were himbacine **1** and himandridine **4**. Himbadine **6** and himgaline **5**, which are structurally related, were also major alkaloids in bark from North Queensland but were not found in material from New Guinea, except in one case when a trace of himgaline **5** was isolated. Himbosine **3** was usually present in small amounts in all samples but all the other alkaloids occurred irregularly and should be regarded as minor: some of them were only isolated once.

	Alkaloid	Source
Class 1		
	Himbacine **1**	NQ, NG
	Himbeline **2**	NG
	Himandravine **8**	NG
	Himgravine **9**	NQ, NG
Class 2		
	Himbosine **3**	NQ, NG
	Himandridine **4**	NQ, NG
	Himandrine **10**	NQ, NG
	GB 1 **11**	NQ, NG
	GB 2 **12**	NQ, NG
	GB 3 **13**	NG
	GB 4 **14**	NQ, NG
	GB 5 **15**	NQ, NG
	GB 6 **16**	NQ
	GB 7 **17**	NQ
	GB 8 **18**	NG
	GB 9 **19**	NG
	GB 10 **20**	NG
	GB 11 **21**	NG
	GB 12 **22**	NG
Class 3		
	Himgaline **5**	NQ, NG
	Himbadine **6**	NQ
	GB 13 **23**	NQ
Class 4		
	Himgrine **7**	NG
	GB 14 **24**	NG
	GB 15 **25**	NG
	GB 16 **26**	NG
	GB 17 **27**	NQ
	GB 18 **28**	NQ

Table 1

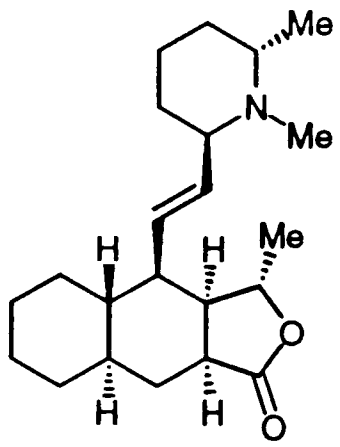
Due to the variability in yield and constitution it was not possible to devise a general method for isolation. The separation of the main bulk of the alkaloids into two major

fractions was accomplished by taking advantage of the fact that one fraction formed chloroform-soluble hydrochlorides while the other did not. Each major fraction was then separated by a combination of column chromatography on alumina and counter-current distribution between ethyl acetate and phosphate-citrate buffers (pH 4-7).

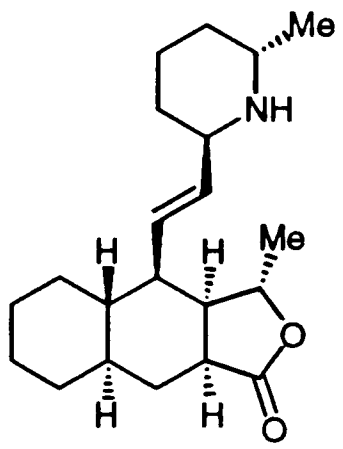
1.3. Structural Elucidation of the *Galbulimima* alkaloids

The structure of the alkaloids (figures 1, 2 and 3) was determined by a wide range of techniques[1,2,6], including elemental analysis, spectroscopic analysis and degradation experiments.

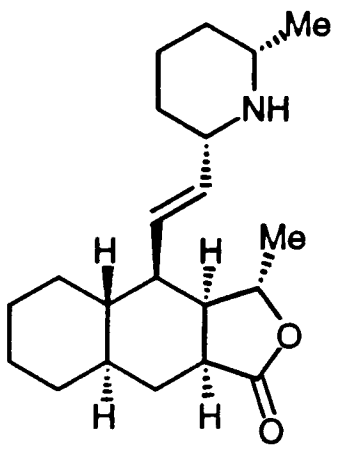
Class 1



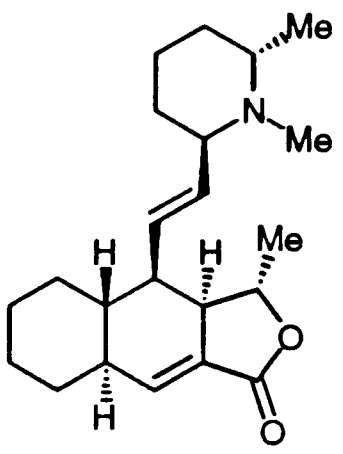
Himbacine **1**



Himbeline **2**



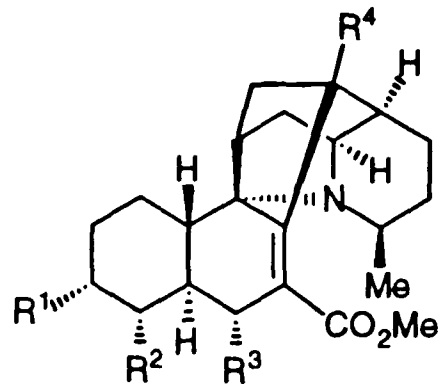
Himandravine **8**



Himgravine **9**

Figure 1

Class 2

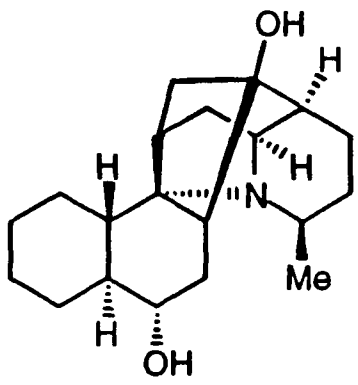


3, 4, 10, 11-22

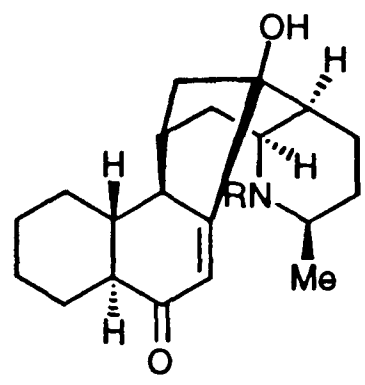
	Alkaloid	R^1	R^2	R^3	R^4
3	Himbosine	OAc	OBz	OAc	OAc
11	GB1	OAc	OBz	OAc	OH
12	GB 2	OAc	OAc	OAc	OAc
13	GB 3	OAc	OH	OH	OAc
14	GB 4	OBz	OH	OH	OAc
15	GB 5	OH	OH	OH	OAc
4	Himandridine	OH	OMe	OBz	OH
16	GB 6	OAc	OMe	OBz	OH
17	GB 7	OH	OMe	OBz	OAc
10	Himandrine	H	OMe	OBz	OH
18	GB 8	H	OMe	OH	OH
19	GB 9	H	OMe	OAc	OH
20	GB 10	H	OMe	OAc	OAc
21	GB 11	H	OH	OH	OAc
22	GB 12	H	OAc	OAc	OAc

Figure 2

Class 3



Himgaline **5**

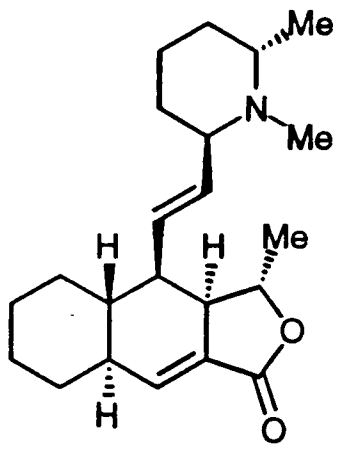


R=Me Himbadine **6**
R=H GB13 **23**

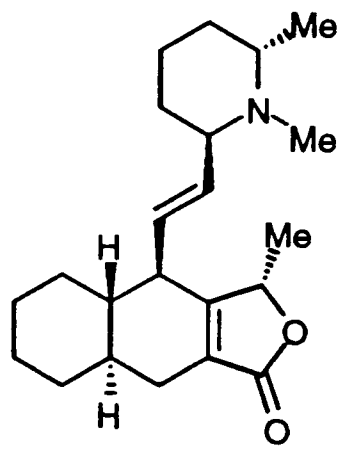
Figure 3

Himbacine **1** was the first member of the *Galbulimima* alkaloids to have its structure determined. Analytical methods revealed the presence of one *N*-methyl and two terminal methyl groups and the formation of a methiodide established the presence of a tertiary nitrogen. The infrared spectrum indicated the presence of a γ-lactone and a *trans*-disubstituted double bond. Structural degradation established the presence of the γ-lactone, a 1,2-dimethylpiperidine and a decalin ring system, and confirmed the connectivity of these portions. The absolute stereochemistry of the molecule was confirmed by X-ray crystallography of the hydrobromide salt[7].

Analysis of himgravine **9** showed that the molecule contained two atoms of hydrogen less than himbacine **1**. Catalytic hydrogenation of himgravine **9** under mild conditions (Adam's Catalyst, ethanol, 1 atmosphere hydrogen, 1 hour) afforded himbacine **1** in good yield, suggesting that the structures of two alkaloids were closely related. The ultraviolet and infrared spectra of himgravine **9** suggested the presence of an αβ-unsaturated γ-lactone ring which led to two possible structures, **9** and (**29**) (Figure 4).



9



(29)

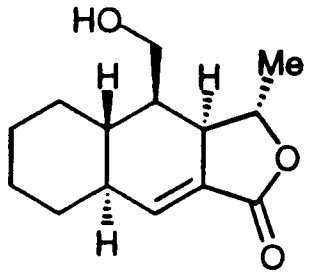
Figure 4

^{1}H NMR analysis was used to confirm the structure of himgravine as **9**, with an alkenic proton observed at 6.80ppm[8]. The conversion of himgravine **9** to himbacine **1** represents a unusual reaction in the fact that a seemingly less reactive trisubstituted alkene is reduced in the presence of a disubstituted alkene (hydrogenation of the

disubstituted alkene requires Adam's Catalyst, acetic acid, 3-4 atmospheres hydrogen, 16 hours). Two possible explanations for this observation are:

- Shielding of the disubstituted alkene. Studies using molecular models, and considering the 1,3-allylic strain[9], suggests that both π-faces of the disubstituted alkene are shielded, one by the *N*-methyl group and the other by the lactone methyl group. Experimental evidence to support this explanation comes from the hydrogenation of himbeline **2**, structurally identical to himbacine **1**, except for the absence of the *N*-methyl group, which proceeds under mild conditions (Adam's Catalyst, acetic acid, 1 atmosphere hydrogen, 1 hour).

- Reactivity of the trisubstituted alkene. Consideration of the strain of the alkene suggest the double bond is highly reactive due to a torsion angle of 42° (measured on the crystal structure of alcohol (**30**) (Figure 5), which is an analogue of the tricyclic portion of himgravine **9**). Hydrogenation of the alkene would thus allow relief of this strain.



(30)

Figure 5

1.4. Pharmacology of Himbacine

Initially, himbacine was of interest because it exhibited anti-spasmodic activity, with low toxicity and few side effects[10]. More recently testing has shown it to be a potent and selective muscarinic antagonist, properties that have lead to discussion of its use in the treatment of Alzheimer's disease[11].

1.5. Alzheimer's Disease

1.5.1. Introduction

Alzheimer's disease is the most common dementia in the elderly. It is a relentless, degenerative brain disease, characterised by a progressively impaired cognitive capacity. The most prominent symptom is memory loss, normally accompanied by impairment of speech, paranoia and general disorientation[12].

Alzheimer's disease affects 10.3% of the world's population over the age of 65, and is present in 47% of those over the age of 85. By the year 2000, the number of persons in the world aged 65 and over is expected to be about 423 million[13], and the elderly population is currently growing 2.5 times as fast as the population at large. With this recent, unprecedented expansion in the elderly population, Alzheimer's disease is becoming one of the world's most notable diseases, now the fourth largest cause of death among adults, behind heart disease, cancer and stroke. The costs of treatment and management of the disease are currently estimated to be US$20 billion each year, a price that is expected to increase significantly with the rise in the elderly population[12].

These statistics have lead to Alzheimer's disease being labelled 'the disease of the century'. The disease may have always existed, but it has only been recognised and studied for a relatively short period of time. In 1907, psychologist Alois Alzheimer (1864-1915) described the dementia that would eventually bear his name. He observed a case of what he labelled 'presenile dementia' and a 'unique illness involving the cerebral cortex' in a 51 year old woman[14].

The current impact of Alzheimer's disease has led to a critical need for a definitive therapy for the condition. However, none presently exists or is on the immediate

horizon. Studies on the disease have made significant advances in recent years, both in the area of diagnosis and treatment, and there is optimism in the scientific community that this research will be of significance in the future.

1.5.2. Symptoms and Diagnosis of Alzheimer's Disease

The two key neuropathological features of Alzheimer's disease are plaques and tangles[15].

Senile plaques are abnormal deposits of β-amyloid protein, commonly found in Alzheimer's diseased brains, although the significance it may play in the disease itself is still unclear. As more information on the condition accumulates there is growing evidence that amyloid metabolism is crucial to the neurodegeneration process of the disease. Recent *in vitro* studies have demonstrated that in familial Alzheimer's disease a mutation occurs in the gene encoding β-amyloid, resulting in overproduction of the protein[16,17]. However, many unanswered questions remain about the ways in which β-amyloid may contribute to Alzheimer's disease. There is discussion that β-amyloid plays an active role in causing the neurodegeneration in Alzheimer's disease. Alternatively, the existence of the β-amyloid in plaques may merely be a consequence of the disease process. A thorough understanding of the function of this protein could ultimately help researchers create approaches for blocking or retarding the pathological process.

Neurofibrillary tangles are a more direct marker of the disease process as they correlate well with cognitive decline. Furthermore, tangles occur within neurones and hence are likely to participate in the disruption of neuronal function. Tangles are composed of paired helical filaments - entwined polymers, the principle component of which has been shown to be *tau* protein. *Tau* protein is an integral part of the neuronal cytoskeleton, and both maintains cell integrity and is essential to neuronal

transport. In healthy neurones, *tau* binds to tubulin and in doing so stabilises microtubules. In Alzheimer's diseased brain *tau* is hyperphosphorylated and in this state, does not bind so readily to microtubules. Thus, the contribution of this marker to Alzheimer's disease is cytoskeletal disruption, with hyperphosphorylated *tau* failing to bind effectively to microtubules and instead aggregating into paired helical filaments.

Until recently a definitive diagnosis was only possible on autopsy (or more rarely biopsy), when the levels of senile plaques and neurofibrillary tangles could be evaluated. However diagnosis is now possible using NMR imaging techniques[18].

1.5.3. Causes of Alzheimer's Disease

Identification of a definite cause or causes of Alzheimer's disease have yet to be achieved[12,15]. The only clear risk factors continue to be increased age and family history, neither of which can be influenced by drug therapy. Early theories about the causes involved linking the disease with strokes or arterioscerosis, however these were discounted long ago. Other more recent theories, including those attributing Alzheimer's disease to a slow viral infection, have also been abandoned due to a lack of evidence.

Research is currently being pursued in a large number of directions, from investigation into defects in β-amyloid protein metabolism to environmental influences, with the hope of discovering clues that could improve understanding of the disease and aid drug development. The possible role of aluminium, for example, in the causation of Alzheimer's disease has been studied for decades. Some of the earliest research found increased concentrations of aluminium in Alzheimer's disease neocortical tissue[19]. Other evidence, however, has raised doubts about aluminium as a cause of Alzheimer's disease, including a recent study using nuclear microscopy to examine neuritic plaque cores in postmortem brain tissue[20]. Using this sensitive technique

researchers did not find aluminium concentrations that exceeded the trace levels detected in healthy brains. However, research is on-going in this area, with a recent trial of deferoxamine, an aluminium chelator, showing that the agent administered intramuscularly to Alzheimer's disease patients decreased the rate of disease progression[21]. Thus studies examining the association between aluminium and Alzheimer's disease have been, at best, inconclusive.

1.5.4. Molecular Biology of Alzheimer's Disease

At the cellular level the effect of Alzheimer's disease is cholinergic degeneration of the basal forebrain, cerebral cortex and hippocampul. In simple terms this process involves the breakdown of message transmission in the brain, caused by a reduction in the level of the chemical neurotransmitter acetylcholine **31** (Figure 6). Acetylcholine **31** is the chemical signal that allows transmission of a message across the synaptic gap from one neuron to another, and reduced levels have been shown to cause symptoms associated with in Alzheimer's disease.[22]. The reduction in the levels of acetylcholine **31** has been found to be due to reduced levels of acetyl cholinesterase, the final enzyme responsible for the biosynthesis of acetylcholine **31**, and a reduction in concentration of choline acetyltransferase, another important enzyme on the biological pathway[23]. The current thrust of treatment for Alzheimer's disease has been based on identifying and utilising strategies that raise the levels of acetylcholine, an approach known as cholinomimetic therapy[24].

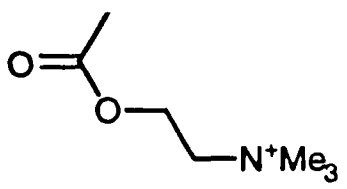
These strategies can be divided into four categories:

- Acetylcholine precursor loading
- Acetylcholine esterase inhibition
- Cholinergic Agonists
- Acetylcholine release enhancers

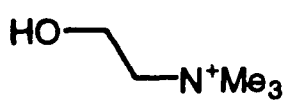
1.6. Cholinomimetic Therapy

1.6.1. Acetylcholine Precursor Loading

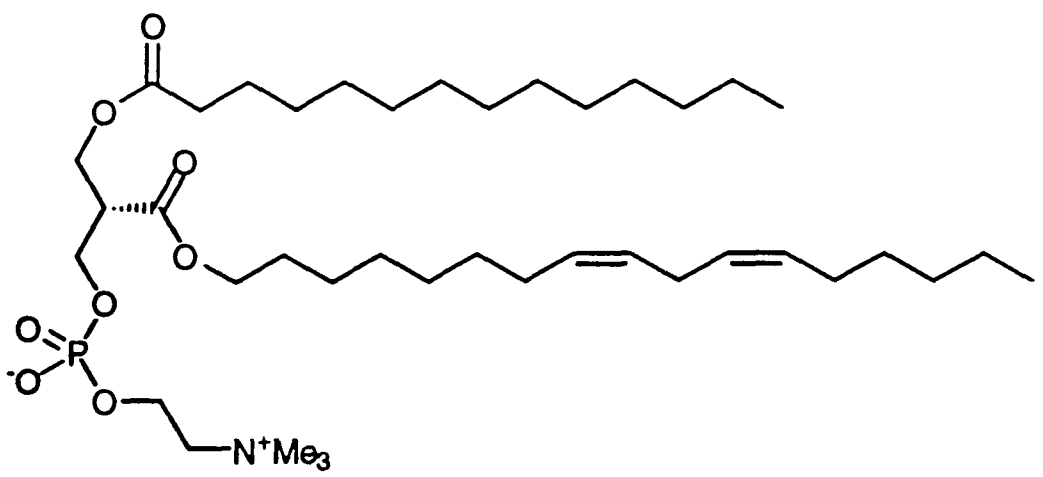
Choline **32** (Figure 6) is acetylated rapidly by the enzyme choline acetyltransferase to give acetylcholine **31**. An early strategy for increasing available acetylcholine in the central nervous system was direct administration of choline **32** to patients. Unfortunately, intestinal bacteria break down this compound to triethylamine. Phosphatidylcholine **33** (lecithin, Figure 6) has been shown to be a more successful choline source, but the results of feeding experiments have been variable, some groups claiming moderate improvements in verbal learning and memory, others finding no benefit. In general, this compound has been regarded as relatively unsuccessful in the improvement of cognitive function in Alzheimer's disease. One possible reason is that it has been calculated that extracellular choline levels would have to be increased more than 50-fold to enable an Alzheimer's diseased brain to synthesise acetylcholine **31** at a normal rate.



Acetylcholine **31**



Choline **32**

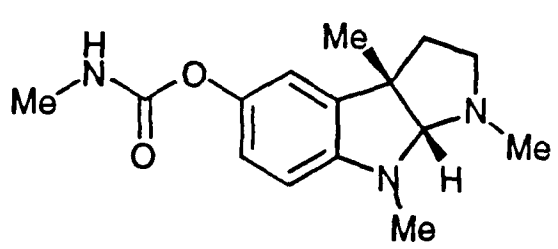


Phosphatidylchloine **33**

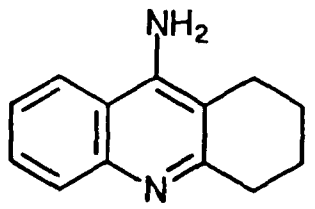
Figure 6

1.6.2. Acetylcholine Esterase Inhibition

The development of acetylcholine esterase inhibition constitutes the most widely used strategy in experimental Alzheimer's disease therapy. Acetylcholine esterase inhibitors prevent the hydrolysis of synaptically released acetylcholine **31**, thereby increasing the efficiency of cholinergic transmission. The most extensively used acetylcholine esterase inhibitor in Alzheimer's disease has been physostigmine **34**[25]. Physostigmine **34** (Figure 7) has been shown to give modest and short term improvement of cognitive function in Alzheimer's disease patients, its therapeutic efficacy being limited by a short duration of action, a poor access to the central nervous system and toxic side effects. A more recent drug with a considerably longer duration of action is tacrine **35** (tetrahydroaminoacridine). Tacrine **35** (Figure 7) has been reported to give a significant improvement in Alzheimer's disease patients. However, like physostigmine **34**, the therapeutic value of tacrine **35** may be limited by its side effects[26].



Physostigmine **34**



Tacrine **35**

Figure 7

1.6.3. Cholinergic Agonists

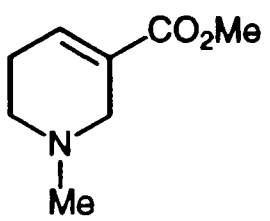
Cholinergic agonists increase the effect of acetylcholine **31** itself, either directly or by sensitising the receptor site. Acetylcholine **31** activates two types of receptor:

- Nicotinic receptors, which are ligand gates for ion channels. The nicotinic receptors are found at the junction between motor neurons and skeletal tissue.

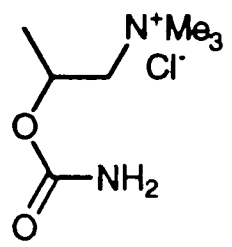
- Muscarinic receptors, which are part of the secondary messenger system. The muscarinic receptors are found on smooth muscle, cardiac muscle and in the brain. There are five distinct subtypes of muscarinic receptor: M1, M2, M3, M4 and M5. Of particular interest in the treatment of Alzheimer's disease are the M1 and M2 subtypes. The M1 receptor is mainly located within the central nervous system, particularly in the cortical and hippocampal areas. At a cellular level the M1 receptor is located on the post-synaptic face of the synaptic gap. The M2 receptor is located throughout the body, with substantial populations in gastro-intestinal and cardiac tissue. In the central nervous system the M2 receptor is believed to be a pre-synaptic inhibitory autoreceptor found on cholinergic nerve endings[27].

It has been shown that postsynaptic M1 muscarinic receptors are unaffected in Alzheimer's disease[28], thus activation of these receptors by selective agonists is a method for direct cholinomimetic treatment. Additionally, recent research has suggested that the use of muscarinic agonists could be a method of preventing the deposition of amyloid fragments in the brain, retarding the progress of the disease[29].

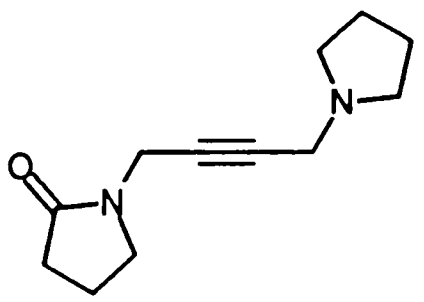
Several muscarinic agonists were evaluated in Alzheimer's disease patients following the observation of cholinergic degeneration (Figure 8). These first generation muscarinic agonists were not specifically designed for use in Alzheimer's disease. They were generally products of natural origin (arecoline **36**, pilocarpine **37**) or older pharmacological agents that had been designed for other uses (bethanechol **38**, RS-86 **39**, oxotremorine **40**). The results of these early clinical trials were consistently disappointing. Administration of these compounds was associated with a high incidence of parasympathetic side effects as well as poor oral bioavailability, short duration of action and other pharmacokinetic limitations[30].



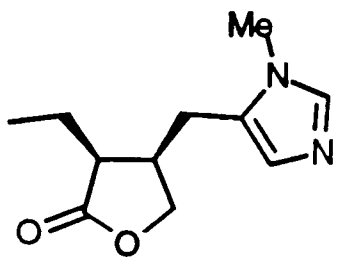
Arecoline **36**



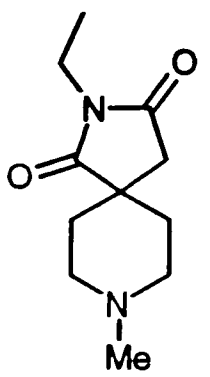
Bethanecol **38**



Oxotremorine **40**



Pipocarpine **37**

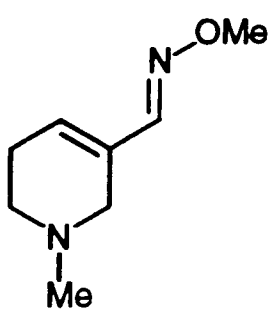


RS-86 **39**

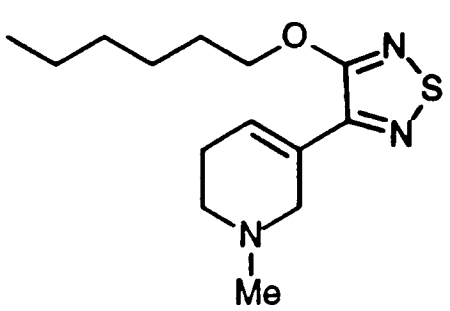
Figure 8

In order to overcome these limitations, it was suggested in the late 1980s that muscarinic agonists with good central nervous system permeability and a high degree of selectivity for M1 receptors would be ideal candidates for Alzheimer's disease therapy.

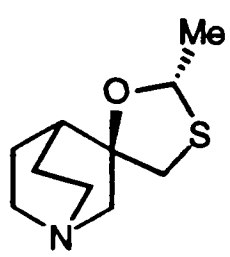
The development of second generation muscarinic agonists has focused on these requirements, and several are in advanced stages of clinical or late pre-clinical evaluation such as milameline **41**, xanomeline **42**, AF-102B **43**, WAL-2014 **44** and PD 151852 **45** (Figure 9)[31].



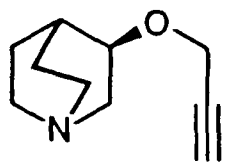
Milameline **41**



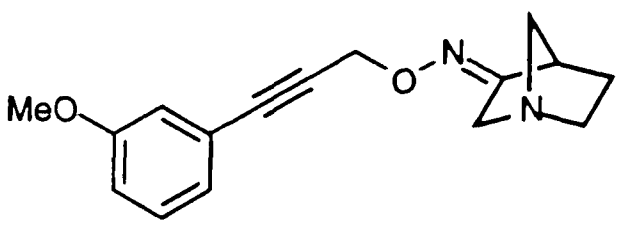
Xanomeline **42**



AF-102B **43**



WAL 2014 **44**



PD 151832 **45**

Figure 9

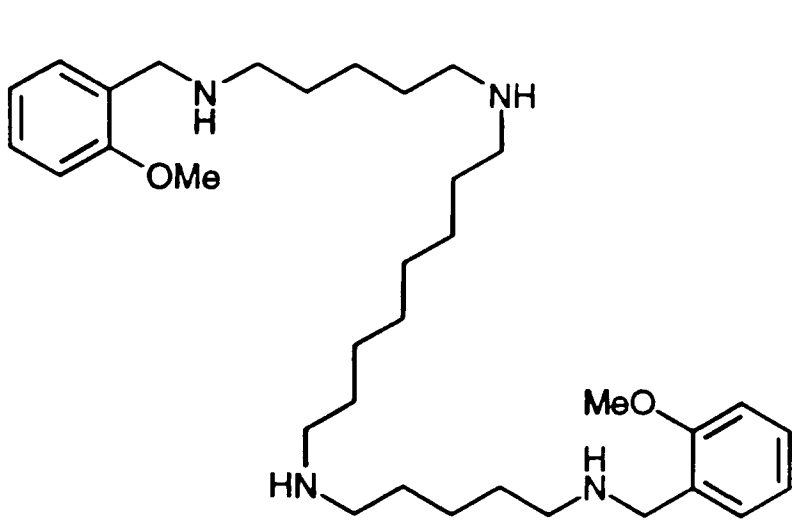
1.6.4. Acetylcholine Release Enhancers

Several distinct pharmacological mechanisms result in the enhancement of acetylcholine release in the central nervous system[27]:

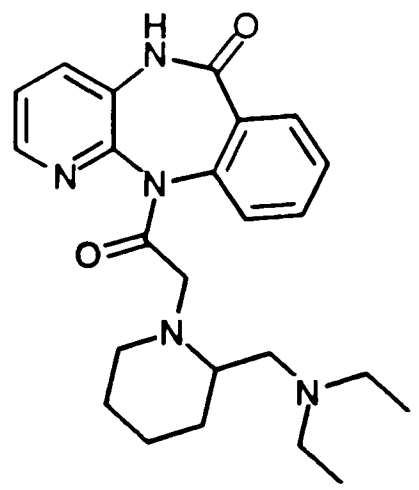
- M2 Antagonists
- Nicotinic Agonists

1.6.4.1. M2 Antagonists

Blockade of the M2 muscarinic receptors on cholinergic terminals stimulates a release of acetylcholine from cholinergic neurons[32]. Thus, selective M2 antagonists such as methoctramine **46**, AF-DX 116 **47** (Figure 10) and himbacine **1**[33,34] offer the potential to act as acetylcholine releasing agents. However, since M2 receptors are located in high concentration in gastro-intestinal and cardiac tissues, the potential for side effects is high.



Methoctramine **46**

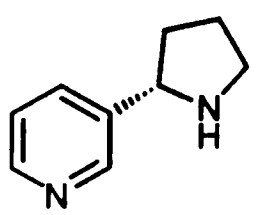


AF-DX 116 **47**

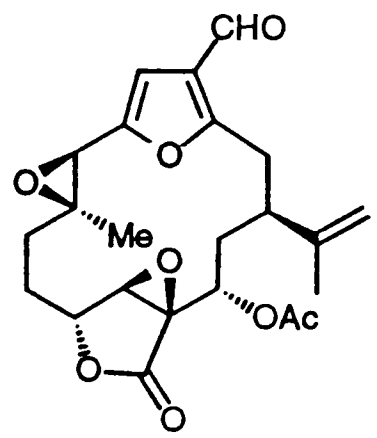
Figure 10

1.6.4.2. Nicotinic Agonists

Activation of presynaptic receptors by nicotinic agonists, such as nicotine **48** and lophotoxin **49**[35] (Figure 11), increases release of acetylcholine from cholinergic nerve terminals[36]. Again the wide distribution of nicotinic receptors in and outside the central nervous system raises the question of selectivity for potential drug candidates. Interestingly there have been a number of reports showing that smokers appear to have less chance of getting Alzheimer's disease than do non-smokers. However, the exact reason for the connection between the two statistics remains unknown[22].



Nicotine **48**



Lophotoxin **49**

Figure 11

Thus, there are a wide variety of strategies available for the task of finding a treatment for Alzheimer's disease. With the vast amount of research currently being undertaken,

hopefully some or all of these pathways will be successful.

1.7. Muscarinic Receptors

Muscarinic receptors are proteins which are acted on by acetylcholine **31**, the first neurotransmitter to be discovered. The five subtypes of muscarinic receptor are part of a 'superfamily' of evolutionarily related proteins. Other members of this family include β-adrenergic, substance K and rhodopsin receptors[37,38].

1.7.1. M1 Muscarinic Acetylcholine Receptor

The M1 receptor is a protein comprising 460 amino-acid residues with a molecular weight of 51.4kDa. The receptor has a tertiary structure consisting of seven membrane-spanning α-helices (Figure 12). The *N*-terminus of the receptor lies on the extracelluar face of the membrane and the *C*-terminus lies in the cytoplasmic space, where it has a number of serine and threonine residues which could be involved in cytoplasmic phosphorylation[37].

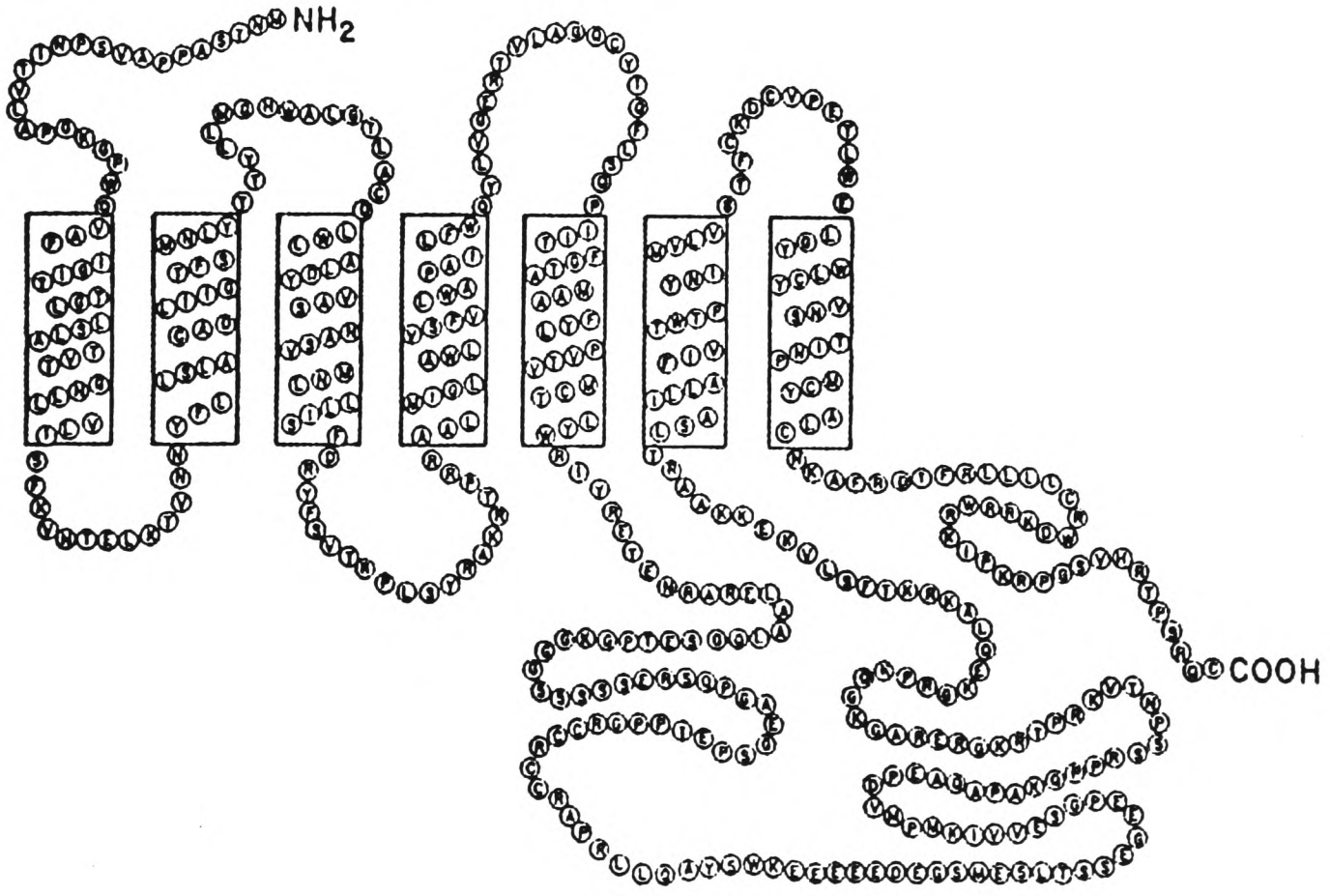


Figure 12

1.7.2. M2 Muscarinic Acetylcholine Receptor

The M2 receptor is a protein comprising 466 amino-acids residues with a molecular weight of 51.7kDa, making it slightly large than the M1 receptor. The M2, similarly to the M1 receptor, consists of 7 transmembrane α-helical bundles (Figure 13)[37].

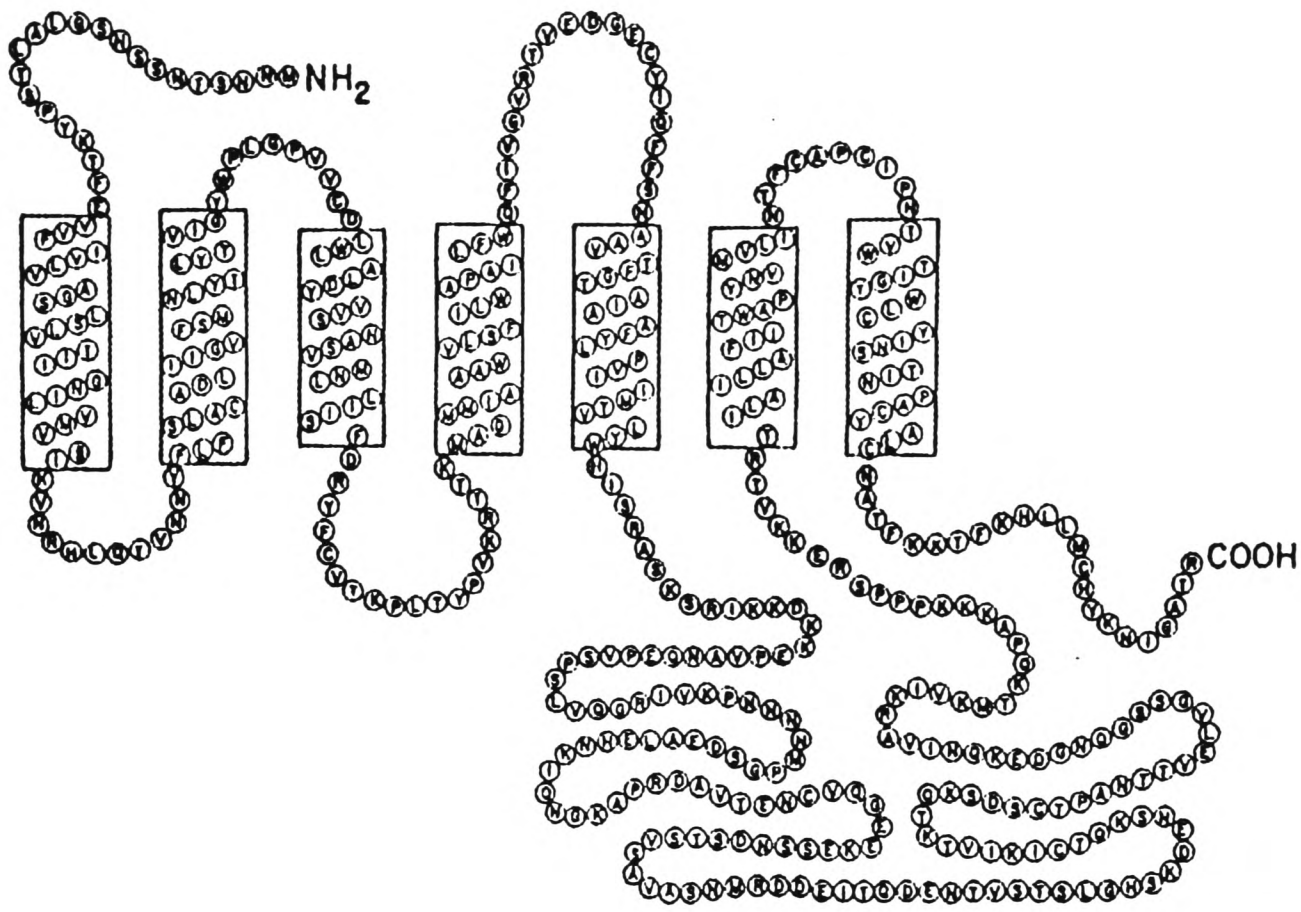


Figure 13

1.7.3. Selective Targeting of Muscarinic Receptors

Achieving selectivity between the different muscarinic receptor subtypes is an essential task for cholinomimetic therapy. The two strategies involving muscarinic receptors require the use of an M1 agonist or an M2 antagonist. The use of an M1 agonist is the preferred method of cholinomimetic therapy as the M1 receptors are located mainly in the central nervous system, whereas the M2 receptors have a low population in the brain[39]. For successful treatment the agonist needs to be completely selective for the M1 over the M2 muscarinic receptor. However, achieving selectivity between the two receptors is a difficult task as the two display many similarities:

- The two receptors have very similar secondary structures consisting of 7 transmembrane α-helical bundles (Figures 12 and 13).

- The two receptors have similar tertiary structures.

- There is an 82% homology of conservative (replacement of an amino-acid residue by another which resembles the physico-chemical properties of the original) and identical amino acids between the two receptors.

- Acetylcholine is believed to bind primarily to the third transmembrane α-helical bundle in both receptors[40,41]. Comparison of the amino acid sequences for the two receptors shows that the third α-helical bundles only differ by two residues, and that the differences (Figure 14) are conservative substitutions (alanine for valine and leucine for isoleucine).

M1 DLWLALDYV<u>A</u>SNASVMNLL<u>L</u>IS

M2 DLWLALDYV<u>V</u>SNASVMNLL<u>I</u> IS

Figure 14

With the remarkable similarities between the two receptors, developing selective drugs has been a difficult task. Most compounds tested to date have displayed little or no selectivity. However recent work has offered considerable advancement in the development of M1 muscarinic agonists, and a large number of companies have compounds in clinical trials (Table 2)[31].

Compound	Phase	Company
AF-102B	Phase III	Snow Brand
CI-979	Phase II	Warner Lambert
L-689,660	Preclinical	Merck and Co.
Lu25-109	Preclinical	Lundbeck
S-9977-2	Phase II	Servier
SB 202,026	Phase II	SmithKline Beecham
SR 46559	Phase II	Sanofi
Thiopilocarpine	Phase I	Sandoz
WAL 2014	Phase II	Boehringer Ingelheim
Xanomeline	Phase II	Lilly
YM 786	Phase II	Yamamouchi

Table 2

The selectivity of these drugs has yet to be reported.

Developing selective M2 antagonists has also progressed in recent years, with AF-DX 116 displaying a 5-fold selectivity for M2 over the M1 receptor. Himbacine **1** has been shown to be a potent M2 ligand[33], however the discovery that the alkaloid has a 20 to 1 selectivity as an antagonist for M2 over M1 muscarinic receptors[11] has promoted significant interest in the molecule. This demonstration of selectivity (K_d (M1) 175nM, K_d (M2) 4.6nM) has led to himbacine **1** being studied by a large number of groups[42-52].

The reason for himbacine **1** acting as an M2 muscarinic antagonist is possibly that the alkaloid acts as a conformationally restricted acetylcholine analogue (Figure 15). Examination of molecular models of himbacine **1** and acetylcholine **31** show considerable structural overlap. It should be noted that whilst neither molecule is adopting the lowest energy conformation, this is not necessary for energetically profitable binding to muscarinic receptors.



Himbacine 1 **Acetylcholine 31**

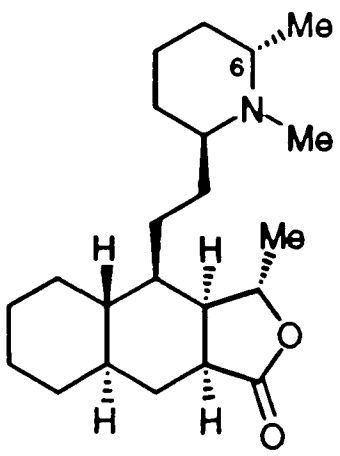
Figure 15

Structure-activity relationship studies on himbacine **1** offer a method of identifying the structural features that afford M2 selectivity, aiding the design of a selective M1 agonist.

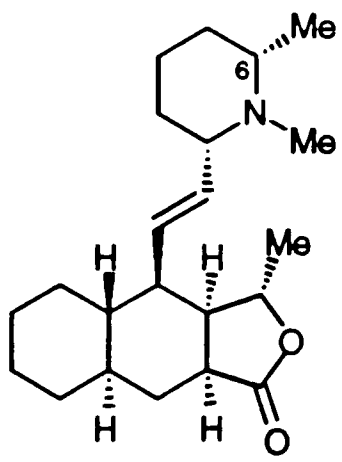
1.8. Pharmacology of Himbacine Analogs

Himbacine's **1** unprecedented selectivity for M2 over M1 muscarinic receptors has led to considerable structure-activity relationship studies on the alkaloid. By identifying the structural features that allow differentiation between the M1 and M2 muscarinic receptors, it may be possible to design a ligand that is a selective M1 agonist.

The first studies in this area had been carried out by Darroch on the class 1 alkaloids, and simple structural modifications of these, including himbeline **2**, *N*-methylhimandravine **50** and himandravine **8**[33]. The work showed that himbacine **1** was the most potent compound, and with a 15-fold selectivity for the M2 muscarinic receptor compared to the M3 receptor, it was an order of magnitude better than any of the other compounds tested. Reduction of the alkene linking the decalin ring to the piperidine ring to afford dihydrohimbacine **51** (Figure 16) almost abolished the selectivity. Removal of the *N*-methyl group of himbacine **1** to form himbeline **2** was also associated with reduced selectivity. However the corresponding change in converting *N*-methylhimandravine **50** (Figure 16) to himandravine **8** was not associated with any change in selectivity, suggesting that the orientation of the 6-methyl group on the piperidine ring is important for selectivity.



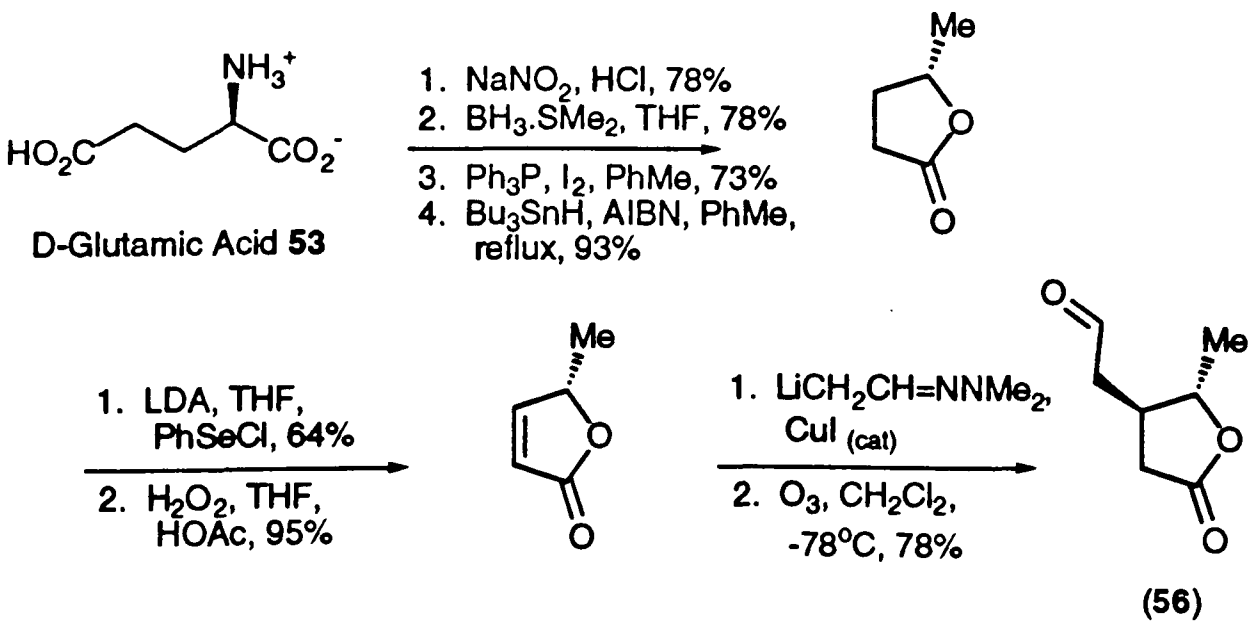
Dihydrohimbacine **51**



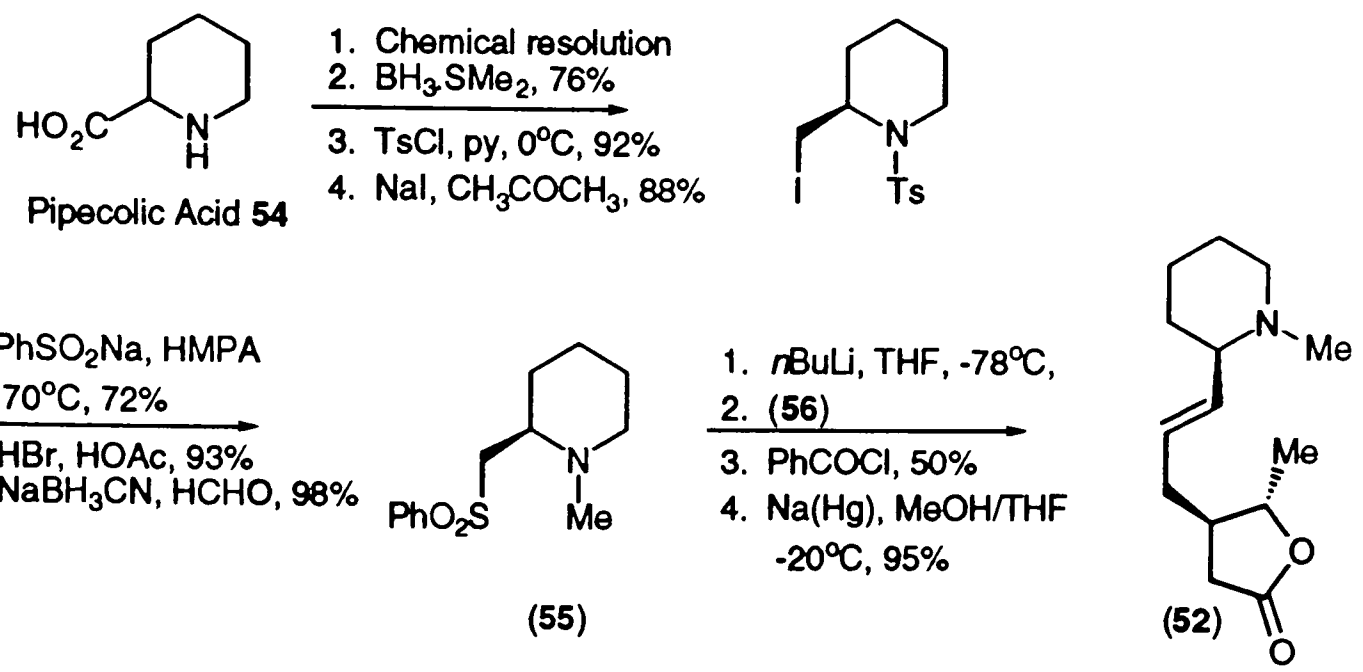
N-Methylhimandravine **50**

Figure 16

The important discovery of himbacine's **1** selectivity for M2 over M1 muscarinic receptor by Kozikowski, and the potential application that this activity would have to Alzheimer's therapy, focused research on the specific features of the alkaloid that differentiated between these two receptors. Work by Kozikowski was based on a simplified substrate (**52**), which maintained the hydrophobic elements of himbacine **1**, namely the γ-lactone ring connected *via* a *trans*-alkene to the piperidine ring[11]. Not only was this for ease of synthesis, but also to study the contribution of the hydrophobic decalin ring system to the selectivity and potency of the alkaloid. The synthesis started from D-glutamic acid **53** and racemic pipecolic acid **54** (schemes 1 and 2), the key step in the synthesis involved a Julia coupling of piperidine (**55**) to γ-lactone (**56**).



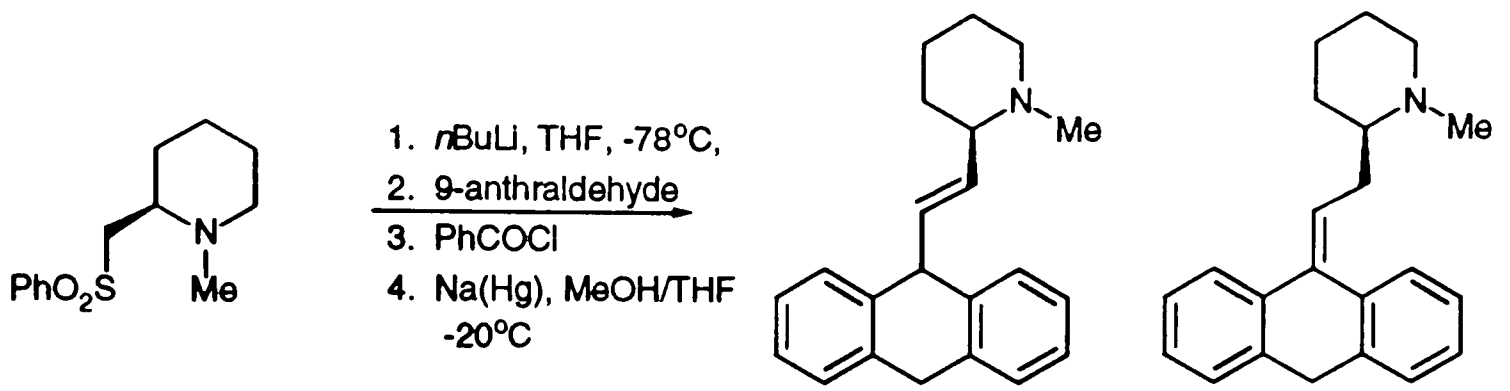
Scheme 1



Scheme 2

Rat brainstems were used as a source of M2 receptors, while CHO-K1 cells (chinese hamster ovaries) transfected with the hm1 receptor sequence were used as a source of M1 receptor protein. The analogue (**52**) was found to bind to M1 receptors with a K_d value of 9.70μm and to the M2 receptor with a K_d value of 1.21μm. These results represent a 260-fold loss of potency, and reduction of selectivity from 20:1 to 8:1 for M2 over M1 receptors. These results suggest that the hydrophobic decalin ring of himbacine **1** plays an important role in binding to the muscarinic receptors. An additional reason why the potency might be lost was identified by molecular modelling studies. These showed that (**52**) would have to adopt a high energy orientation in order to bind to the muscarinic receptors. The loss of selectivity suggests that the decalin ring is important for the alkaloid differentiating between the two receptors.

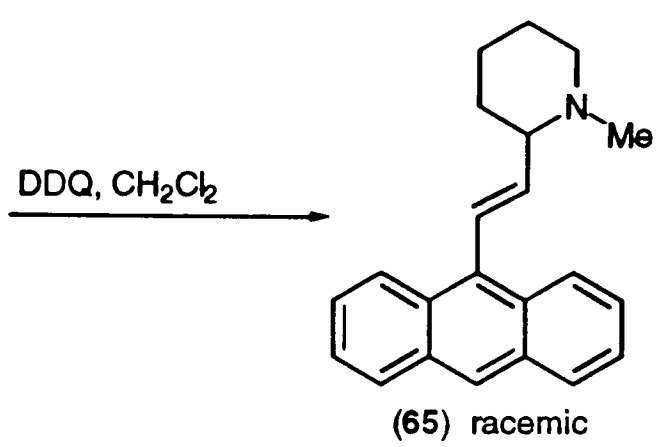
The importance of the hydrophobic interactions between the substrate and receptors was clearly demonstrated by synthesis of a new group of structural analogs[53]. The substrate analogs (**59-65**), with a hydrophobic dihydroanthracene replacing the γ-lactone, were synthesised using, as before, a Julia coupling to connect the piperidine (**55**, **57**, **58**) to the lower portion of the molecule (Scheme 3).



(55) *R*
(57) *S*
(58) racemic

(59) *R*
(60) *S*
(61) racemic

(62) *R*
(63) *S*
(64) racemic



(65) racemic

Scheme 3

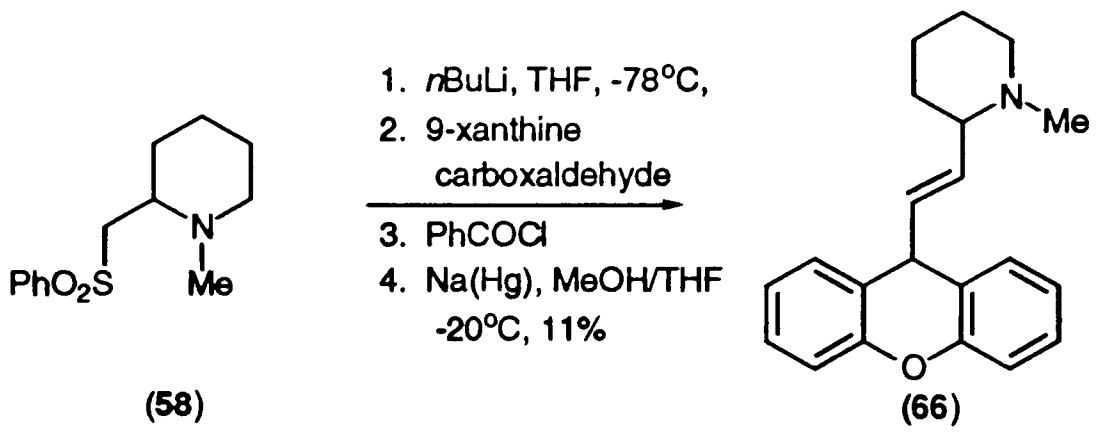
The Julia coupling produced a variety of products (**59-64**), all involving reduction of the central aromatic ring, and some involving migration of the alkene. Rearomatisation was achieved using DDQ, but the reaction was extremely low yielding. The binding affinity of new substrates for the muscarinic M1 and M2 receptors was tested using the previously developed assay (Table 3).

Compound	K_d (M1)/ nM	K_d (M2)/ nM
(**59**) (*R*)	1.53 ± 0.234	3.17 ± 0.694
(**60**) (*S*)	4.92 ± 1.4	21.9 ± 2.67
(**61**) (racemic)	1.75 ± 1.0	20.5 ± 0.758
(**62**) (*R*)	11.6 ± 1.25	14.5 ± 0.478
(**63**) (*S*)	24.2 ± 6.6	35.0 ± 2.62
(**64**) (racemic)	2.7	3.0
(**65**)	679 ± 189	635 ± 3

Table 3

The results clearly demonstrated that the presence of a highly hydrophobic tricyclic section significantly increases the potency of the substrates. However the selectivity was further reduced with a reversal of binding preference, the new substrates having a 2:1 or greater selectivity for M1 over M2 receptors. The one analogous result involved the rearomatised tricyclic (**65**), which, due to geometry, electronics or both, caused a significant loss in potency.

Introduction of a oxygen atom into the tricyclic section was achieved using the 9-xanthine group. This substrate (**66**) represented a distinct variation from the previous tricyclic portions studied which all had a hydrophobic group in this position, the most extreme example being the aromatic tricycle (**65**). Synthesis was completed by coupling piperidine (**58**) to 9-xanthine carboxaldehyde (Scheme 4).



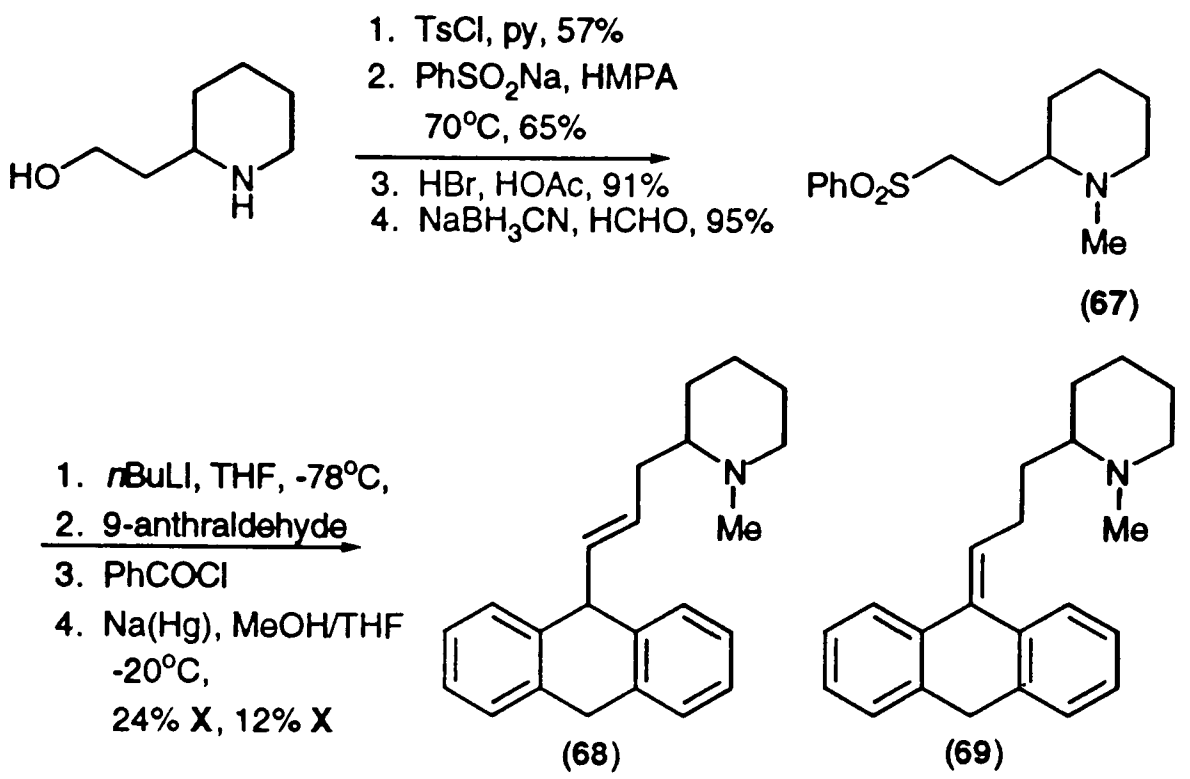
(**58**) (**66**)

Scheme 4

The binding of (**66**) was measured at a K_d value of 3.35 $\pm$ 0.405nM for M1 receptors and a K_d value of 25.4 $\pm$ 7.21nM for M2 receptors. Thus, the potency of (**66**) was fairly similar to that found in the substrates with dihydroanthrcene; however the selectivity for M1 over M2 receptors had increased to 7:1.

Another section of work in this study involved changing the length of the linker between the two ring systems. It had been postulated that the orientation of the nitrogen head group in relation to the tricycle is of major importance for achieving selectivity between the M1 and M2 receptors. Adjustment of the chain length would

allow more conformational mobility between the ring systems. Piperidine sulfone (**67**), differing from (**58**) (by the inclusion of an extra methylene group between the sulfone and the piperidine ring), was coupled to 9-anthraldehyde to give substrates (**68** and **69**) (Scheme 5).



Scheme 5

The binding affinities for the compounds were measured as follows (Table 4):

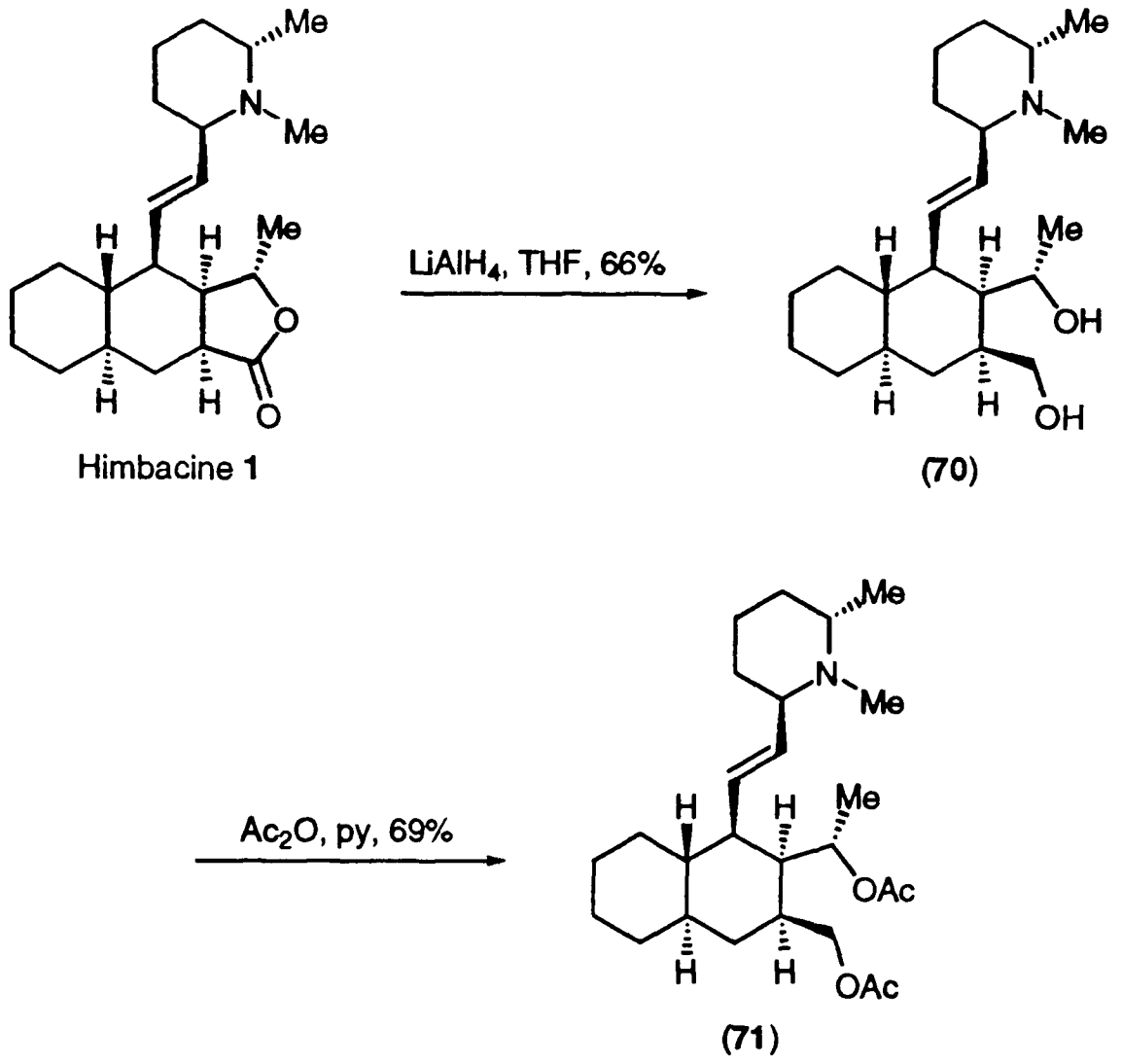
Compound	K_d (M1)/ nM	K_d (M2)/ nM
(**68**)	5.23 ± 1.6	22.6 ± 1.4
(**69**)	4.99 ± 1.0	7.64 ± 1.5

Table 4

As can be seen from the figures, lengthening the tether had little effect on the binding of the substrates compared to (**61**) and (**64**). Additionally the selectivity was not significantly changed, with a similar binding affinity for M1 and M2 receptors as for (**66**).

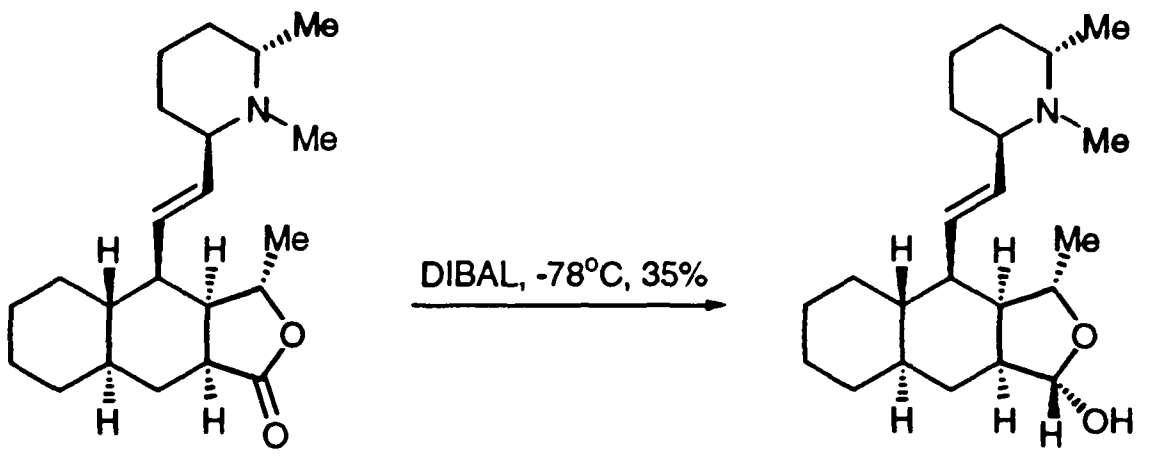
The final piece of work completed in this area by Kozikowski involved removal of the carbonyl oxygen of himbacine **1** by structural degradation[54]. Starting from a sample

of himbacine **1**, the γ-lactone ring was opened to afford diol (**70**), which was then bisacylated to give (**71**) (Scheme 6). An alternative reduction afforded the lactol (**72**). This was then acylated to give acetate (**73**), and pivalate (**74**) (Scheme 7). Finally (**70**) was cyclised with tosyl chloride and potassium hydroxide to afford tetrahydrofuran (**75**) (Scheme 8).

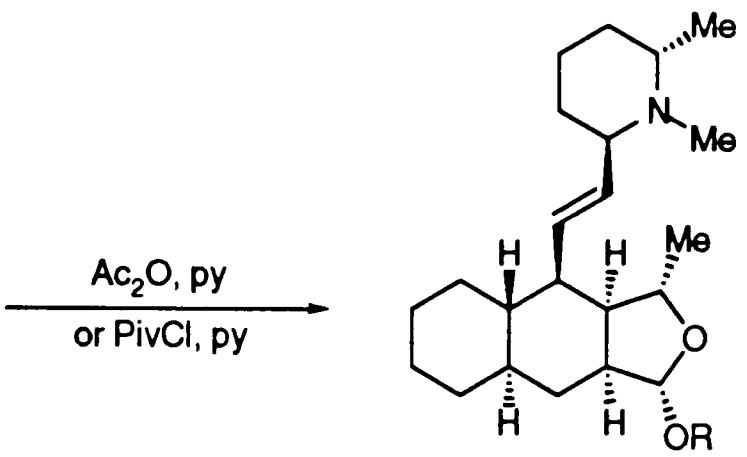


Himbacine **1** (70) (71)

Scheme 6

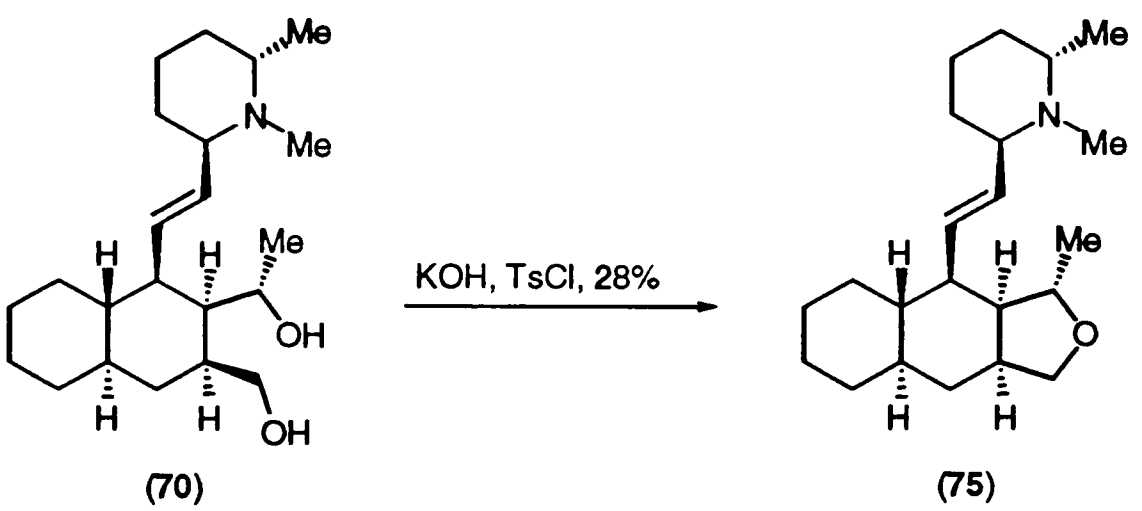


Himbacine **1** (72)



(73) (R = $COCH_3$)
(74) (R = $COC(CH_3)_3$

Scheme 7



(70) **(75)**

Scheme 8

The binding affinities of all the compounds prepared were measured (Table 5):

Compound	K_d (M1)/ nM	K_d (M2)/ nM
(70)	494 ± 8	293 ± 0.3
(71)	604.7 ± 12.5	248.5 ± 6
(72)	423 ± 13	96 ± 4
(73)	866	89
(74)	2520	464
(75)	167 ± 69	353 ± 55

Table 5

The ring opened diol (**70**) bound to the M1 and M2 receptors with 3- and 29-fold lower affinity respectively, than himbacine **1**, a near complete loss of M2 selectivity. While removal of the γ-lactone ring could be an important factor in the loss of binding activity,

it is possible that the receptor pocket is not sterically capable of accommodating two hydrophilic alcohol groups. The binding of (**71**), in which the two hydroxyl groups are 'capped off' as acetate esters, however, reveals no improvement in binding at either receptor.

Four of the compounds examined contained an intact tricyclic portion (**72-75**). These compounds showed decreased affinity at both M1 and M2 receptors compared to himbacine **1**. However, when compared to diol (**70**), the lactol (**72**) has approximately the same binding affinity at the M1 receptor, while it binds slightly (2.5 fold) better at the M2 receptor. Thus it would appear that an intact five membered ring alone is not sufficient to ensure M2 selectivity and potency. Compounds (**73**) and (**74**) have derivatized hydroxyl groups, but interestingly the added bulk of (**73**) does not decrease M2 potency relative to (**72**) and the compound retains an M2:M1 selectivity of 10:1. Analogue (**74**), with the additional pivaloyl group appears to be too bulky for effective binding and only modest M2 selectivity remains. All these results point strongly towards the need for a γ-lactone ring for potency at the M2 receptor. Thus, a carbonyl oxygen in or around the heterocyclic ring of himbacine **1** appears to be necessary for M2 selectivity.

This conclusion is supported by the most important result in this group, the binding of tetrahydrofuran (**75**). This compound differs from himbacine **1** only in that the carbonyl oxygen is removed, thus the tricyclic portion of (**75**) resembles himbacine **1** sterically but differs in its electrostatic field. The binding data shows a 40-fold decrease in potency for the M2 receptor, while the binding to the M1 receptor remains unchanged. Thus, removal of the carbonyl oxygen affects only the binding to the M2 receptor.

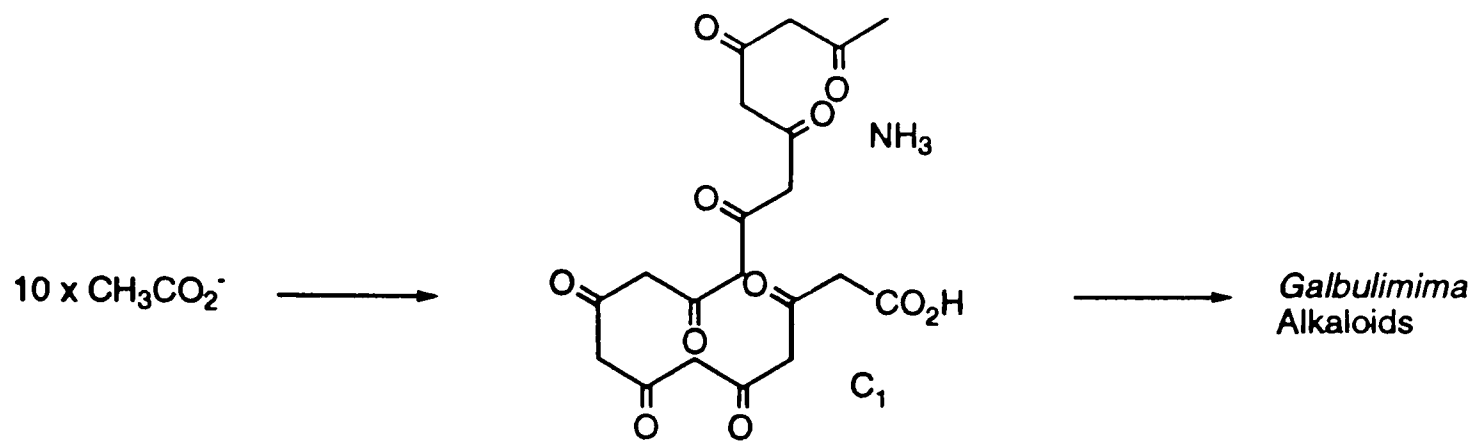
The most recent piece work in this area was reported by a group at Schering-Plough[55], following on from the total synthesis of himbacine **1** that they had reported

earlier that year[56]. In the brief abstract of the work, it was noted that the *trans*-methyl group in the piperidine ring is critical for potency and selectivity at the M1 and M2 muscarinic receptors. They also reported that studies on the importance of the double bond, substituents in the bridge area and on the γ-lactone ring, as well as the nature of the basic group, although the effect of these variations were not included. Considering the efficiency of the total synthesis developed by Schering-Plough, the facile synthesis of many more advanced substrate analogues of himbacine **1** should now be possible, which should yield more details about the key pharmacological features of this molecule.

The information obtained so far is that the features imparting potency to the alkaloid are the decalin ring, the *trans*-piperidine ring and the alkene bridge. The selectivity of the alkaloid for the M2 receptor over the M1 receptor comes, most notably, from the presence of the γ-lactone, particularly the carbonyl oxygen and the *trans*-piperidine ring.

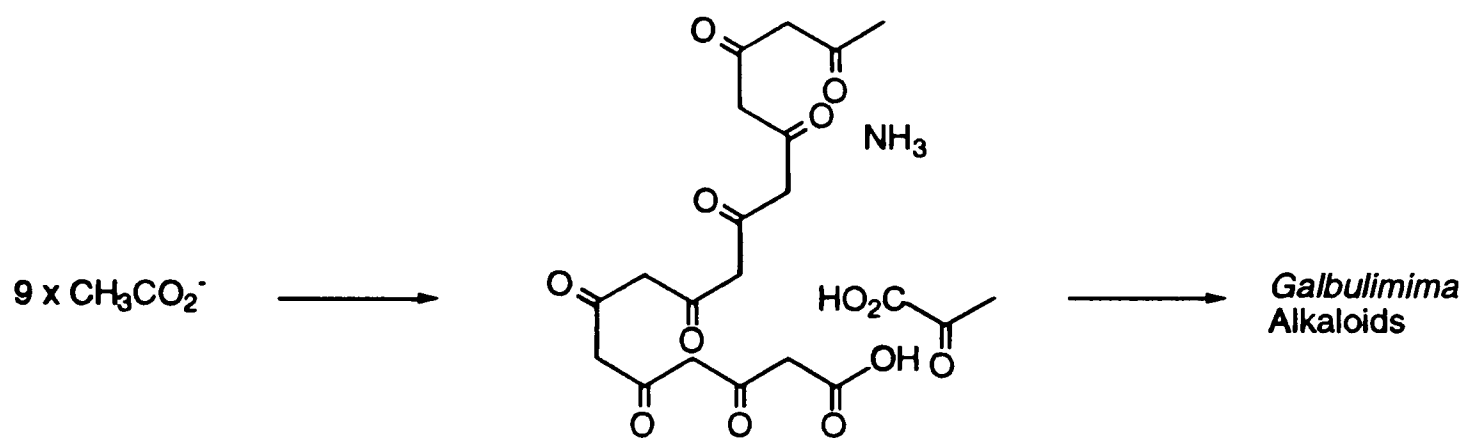
1.9. Biogenesis of Himbacine and the *Galbulimima* Alkaloids

Although there has been no biosynthetic study on the origins of the *Galbulimima* alkaloids, two biosynthetic theories have been proposed, the first by Leete and the second by Ritchie and Taylor[2,6]. Both schemes are based on a derivation from C_2 acetate units, a proposal based on the biosynthetic origins of piperidines. Leete speculated that the alkaloids originate from ten acetate units and one C_1 unit (two if decarboxylation occurs) (Scheme 9).



Scheme 9

Ritchie and Taylor made the alternative suggestion that nine acetate units and a C3 fragment such as pyruvate (or oxalacetate or succinate) could be involved (Scheme 10).

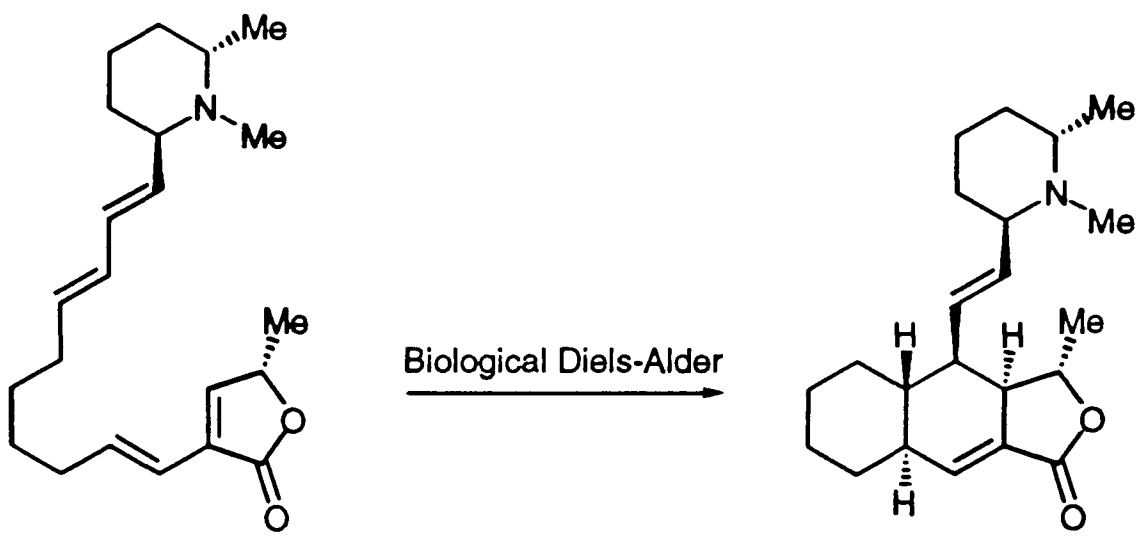


Scheme 10

Consideration of steps further down the biosynthetic pathway, focused on the possibility that himgravine **9** could preceed himbacine **1**. This proposal is supported by two facts:

- Himgravine **9** can be converted to himbacine **1** by a simple reduction.
- Himbacine **1** is found in much greater quantities than himgravine **9**.

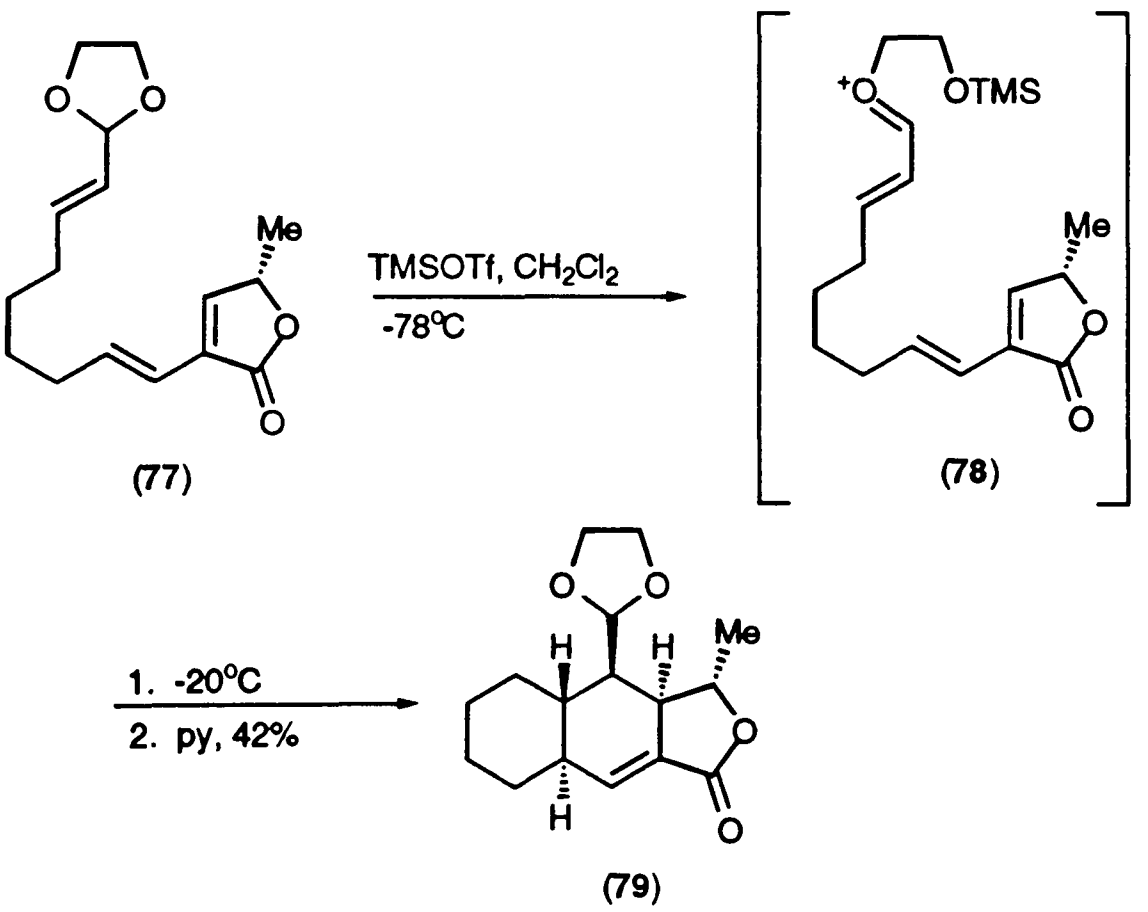
Himgravine **9** is of particular interest as its stereochemistry is consistent with an intramolecular Diels-Alder reaction, proceeding *via* an *endo* transition state[57]. This transformation would involve a species containing a lactone diene and piperidine diene (**76**) as the precursor for the reaction (Scheme 11).



(76) **Himgravine 9**

Scheme 11

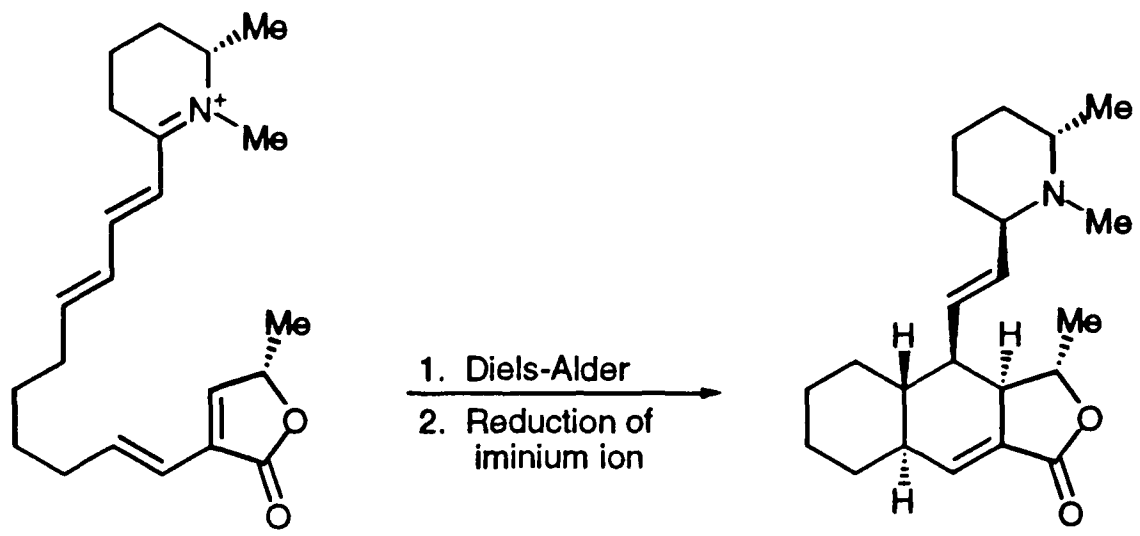
Synthetic studies in this area suggest that the construction of tricyclic systems of this type is possible *via* a Diels-Alder reaction, the reaction proceeds with the highest selectivity and in the mildest conditions when the dienophile is an electron-deficient allylic cation[58]. Specifically the reaction of acetal butenolide (**77**) with a Lewis acid to generate allylic oxonium cation (**78**) as the dienophile[59], allowed the Diels-Alder reaction to proceed at -20°C to yield tricyclic acetal (**79**), demonstrating the effectiveness of this methodology (Scheme 12).



(77) **(78)** **(79)**

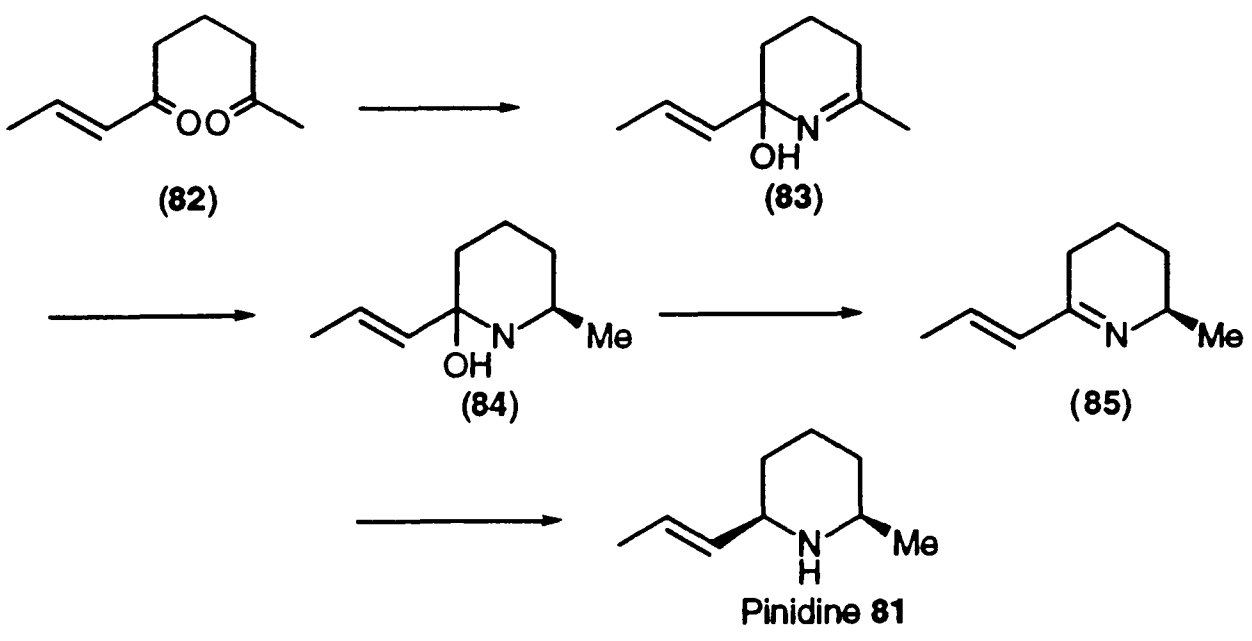
Scheme 12

The success of this chemistry led to the proposal that the potential Diels-Alder reaction on the biosynthetic pathway to himgravine **9** could be mediated by a conjugated iminium ion (Scheme 13)[60].



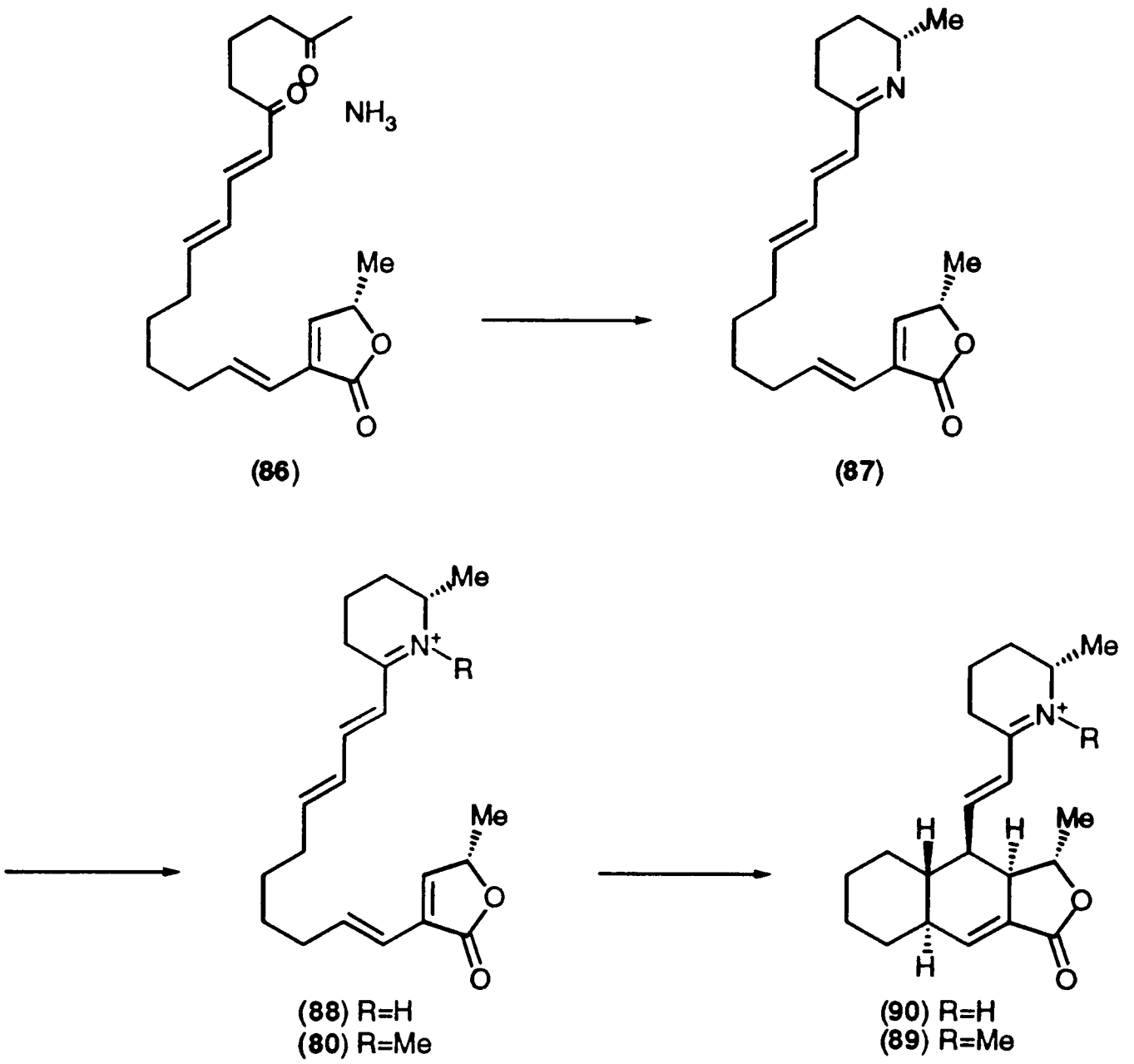
Scheme 13

This iminium ion intermediate (**80**) could be prepared by a reductive amination, a reaction that has been observed widely on the biosynthetic pathway to piperidines[61,62]. The biosynthesis of pinidine **81**, has been shown to proceed from polyketide derived diketone (**82**) *via* this mechanism. Initial amination forms hydroxy-imine (**83**), which can be reduced by a hydride source to afford hemi-aminal (**84**). This then dehydrates to give imine (**85**) which is again reduced to give pinidine **81** (Scheme 14)[61].



Scheme 14

For the biosynthesis of himgravine **9**, possible conversion of a polyketide to diketone (**86**), followed by a similar reductive amination, would afford imine (**87**). This could be *N*-methylated or protonated to afford iminuim ion (**80** or **88**), which could undergo the required biological Diels-Alder reaction to give tricycle (**89** or **90**) (Scheme 15).



(86) (87)

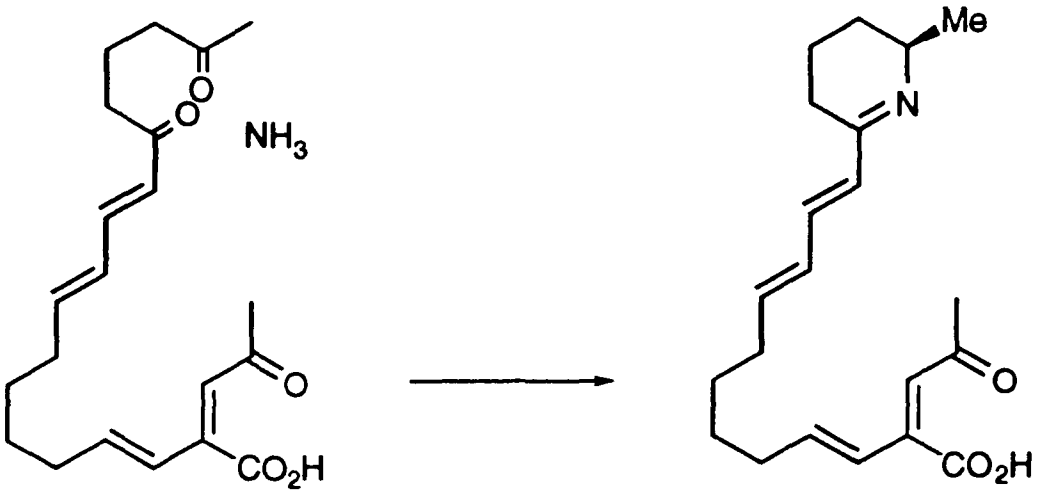
(88) R=H
(80) R=Me

(90) R=H
(89) R=Me

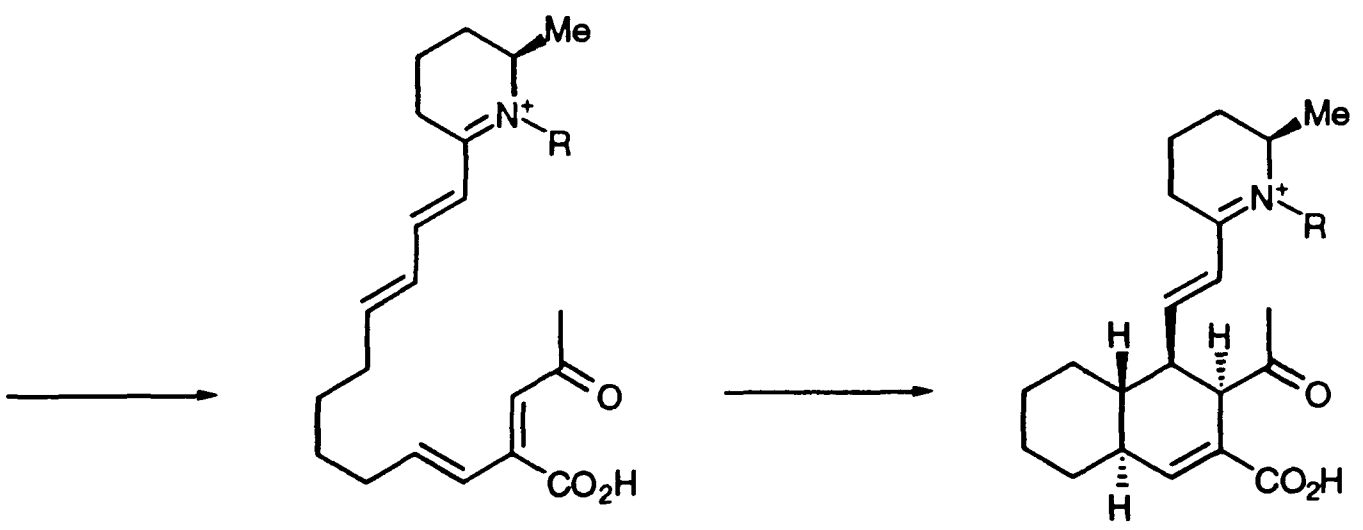
Scheme 15

The reduction of tricycle (**89**), by delivery of the hydride from either the α or β face, gives rise to the possibility of either a *cis*- and *trans*-piperidine ring. Reduction to give the *trans*-piperidine would afford himgravine **9**, whereas the *cis*-isomer would afford himandravine **8**. The presence of both alkaloids suggests that non-stereoselective reduction of a common iminium ion precursor is a possibility on the biosynthetic pathway.

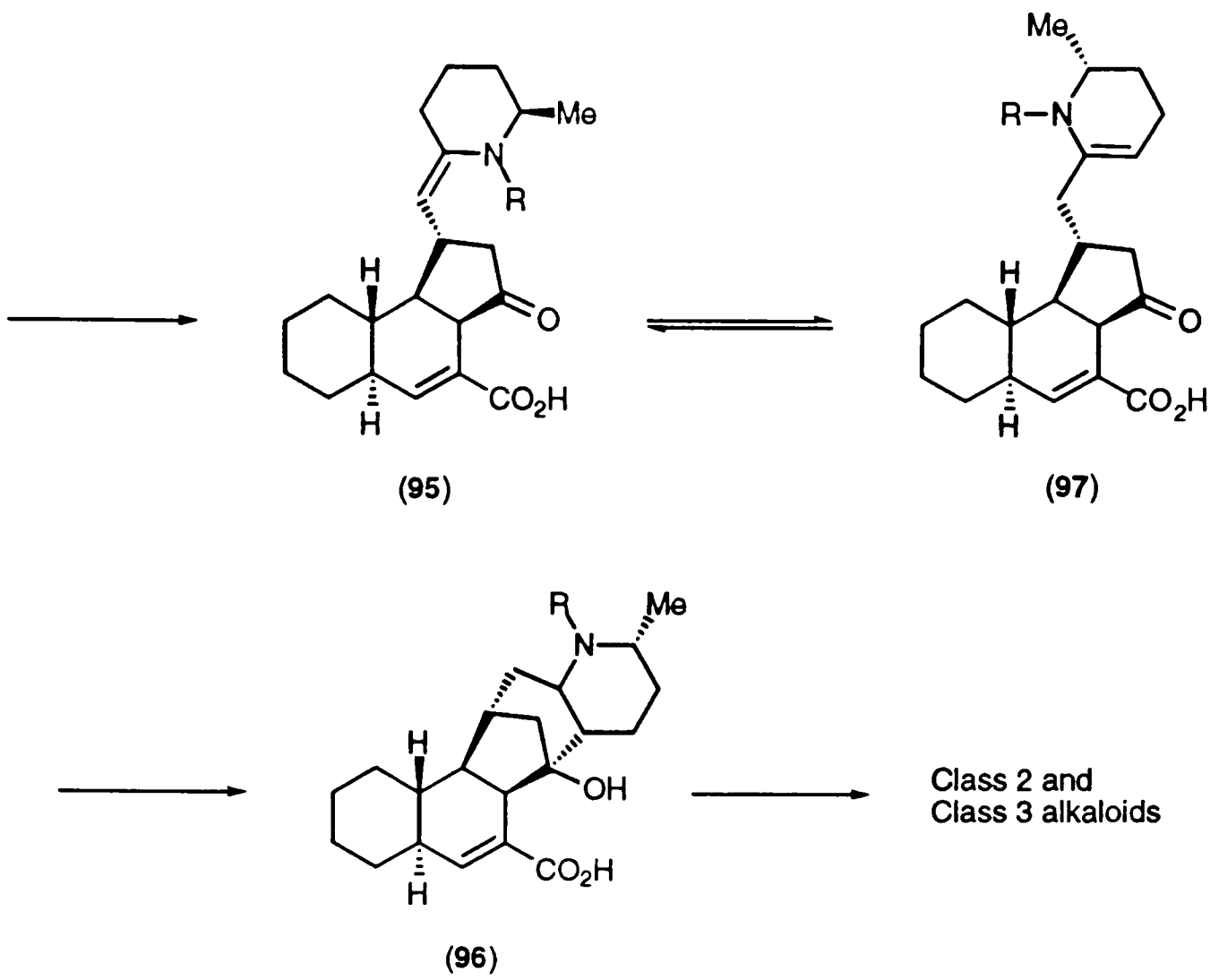
The possible intermediacy of an iminium ion species in the biosynthesis of the *Galbulimima* alkaloids also offers a plausible route to the Class 2 and Class 3 alkaloids. Starting from common intermediate (**91**), synthesis of the Class 1 alkaloids would proceed *via* reductive lactonisation to afford (**86**) followed by reductive amination would yield imine (**87**). Iminium ion formation followed by the required Diels-Alder reaction would afford (**89** or **90**), reduction of which would give one of the Class 1 alkaloids (Scheme 15). Alternatively, reductive amination of (**91**) to imine (**92**), followed by iminium ion formation to give (**93**), would allow the Diels-Alder reaction to proceed before closure of the γ-lactone to afford (**94**). Enolisation followed by a Michael addition closes the fourth ring to give (**95**), after which enamine equilibration allows the system to complete a further ring closure to afford (**96**) *via* an enamine addition to the ketone (**97**). Oxidation of this species (**96**) would lead to the range of different Class 2 and Class 3 alkaloids (Scheme 16).



(**91**) (**92**)



(**93**) (**94**)



Scheme 16

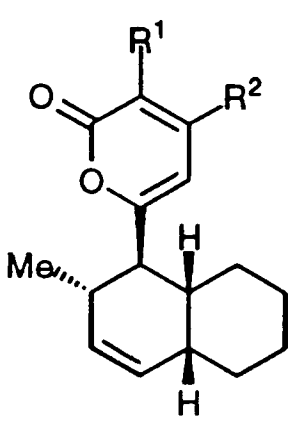
1.10. Biological Diels-Alder Reactions

The presence of Diels-Alder reactions on biological pathways is a fairly recent concept, but the evidence accumulating is compelling[63,64]. The variety of molecules which now have a Diels-Alder reaction proposed as part of their biosynthesis is extremely large. Among the most famous examples is the proposed biosynthesis of endiandric acid, originally postulated by Black[65] and synthetically demonstrated by Nicolaou[66-69]. Another proposed biosynthesis involving a Diels-Alder reaction is Heathcock's elegant synthesis of the Daphniphyllum alkaloids[70].

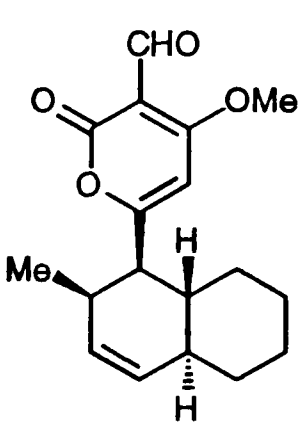
Of particularly of interest to this project is the construction of decalin ring systems *via* Diels-Alder reactions. Such reactions in the biosynthetic pathways of natural products offers further supporting evidence that the biosynthesis of the *Galbulimima* alkaloids may include such a reaction. Investigations into the construction of such frameworks

has produced some of the most important evidence for the occurrence of biological Diels-Alder reactions.

The most significant work to date has been completed on the biosynthesis of the solanapyrones. These molecules are phyotoxins isolated with other metabolites from the culture broth of *Alternaria solani*, a causal fungus of early blight disease of potatoes and tomatoes (Figure 17). Solanapyrones A-C **98-100** were found to be the major components of the mixture, with solanapyrone D **101** isolated only in trace amounts[71].



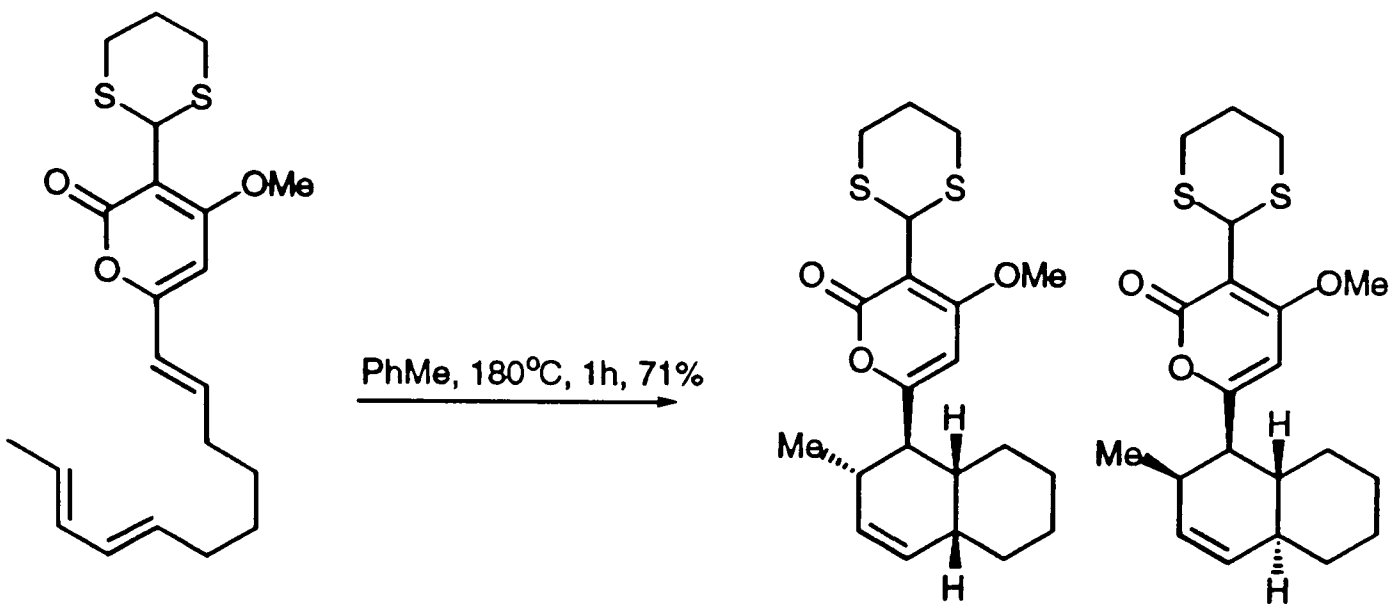
Solanapyrone A **98**, R^1=CHO, R^2=OMe
Solanapyrone B **99**, R^1=CH_2OH, R^2=OMe
Solanapyrone C **100**, R^1=CHO, R^2=$NHCH_2CH_2OH$



Solanapyrone D **101**

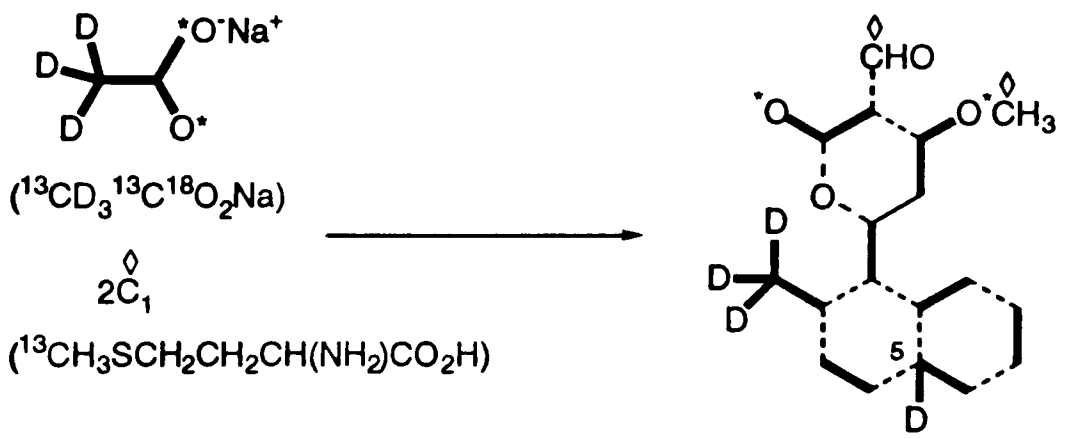
Figure 17

The use of a Diels-Alder reaction for construction of the solanapyrones was demonstrated by the thermal cyclisation of triene (**102**) (Scheme 17)[72]. However, the reaction produced a mixture of diastereomers in a ratio of 3:2 in preference for *trans*-fused decalin (**103**) which would occur *via* an *endo* transition state. The smaller component of the product mixture was *cis*-fused decalin (**104**), the structural analogue of solanapyrone A **98**, which would occur *via* an *exo* transition state.



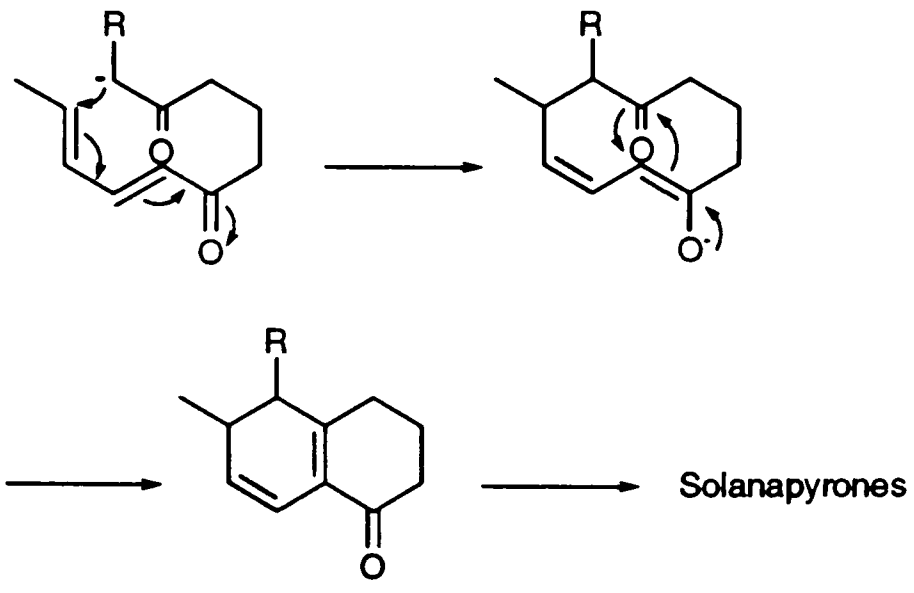
Scheme 17

The variation in the ratio of products from isolation and from the thermal Diels-Alder reaction strongly suggested that in the biological system there were significant factors influencing the and stereochemical course of the reaction, biasing the production towards the *exo* adduct. Studies on the biosynthesis of the solanapyrones was undertaken, and the biological origins of the compounds from polyketides was demonstrated by feeding experiments using labelled sodium acetate and methionine (Scheme 18)[73].



Scheme 18

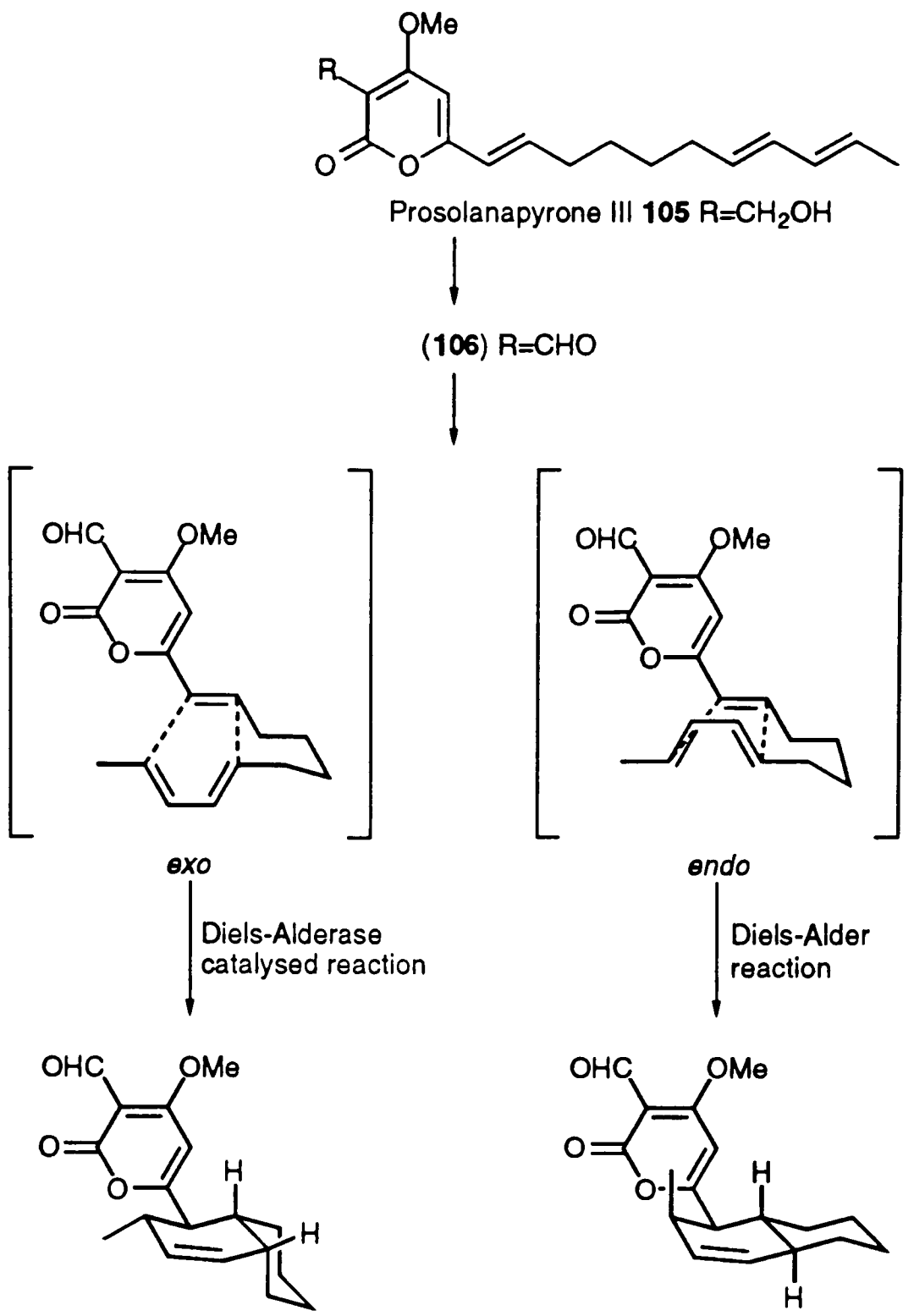
The incorporation pattern was consistent with either a Diels-Alder cycloaddition or a series of carbonyl condensations (Scheme 19) forming the bicyclic ring system.



Scheme 19

The carbonyl condensation pathway was ruled out however, as the feeding experiments with the deuterium labelled acetate had shown retention of the deuterium label at C5, an observation incompatible with the proposed mechanism. Thus a Diels-Alder reaction in the biological pathway to these molecules was more consistent. Therefore it seems possible that the biosynthesis involves an enzyme catalysed Diels-Alder reaction *via* an *exo* transition state to yield solanapyrones A-C **98-100** and the trace amount of solanapyrone D **101** isolated being produced by the non-enzyme catalyzed cycloaddition reaction.

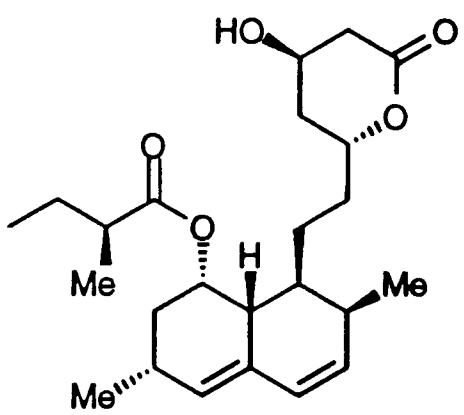
Further evidence towards this conclusion has been the subject of the most recent work published in this area[74-76]. Treatment of prosolanapyrone III **105** with a cell-free extract of *Alternaria solani* at 30°C for 10 minutes yielded a mixture of **98** and **101** (25% conversion) with an *exo:endo* ratio of 53:47. In the absence of the cell-free extract under the same conditions the aldehyde (**106**) undergoes an uncatalysed Diels-Alder reaction to **98** and **101** (15% conversion) with an *exo:endo* ratio of 3:97, which is comparable to the *endo* ratio of other Diels-Alder reactions in aqueous media. Treatment of (**106**) with denatured cell-free extract also yielded an *exo:endo* ratio of 3:97. Thus, the enzyme related conversion is about 15% and the *exo:endo* ratio 87:13 (>92% ee for **98**) (Scheme 20).



Scheme 20

The amount of product biosynthesised *via* the *exo* transition state is remarkable, as it cannot be achieved by chemical means, strongly suggesting the presence of a enzymatic catalyst. However, isolation of such an enzyme has yet to be achieved, all the current published work being based on the use of cell-free extract. Isolation and characterisation of an enzyme complex would provide the final, crucial piece of evidence to confirm the existence of a biosynthetic pathway containing a Diels-Alder reaction.

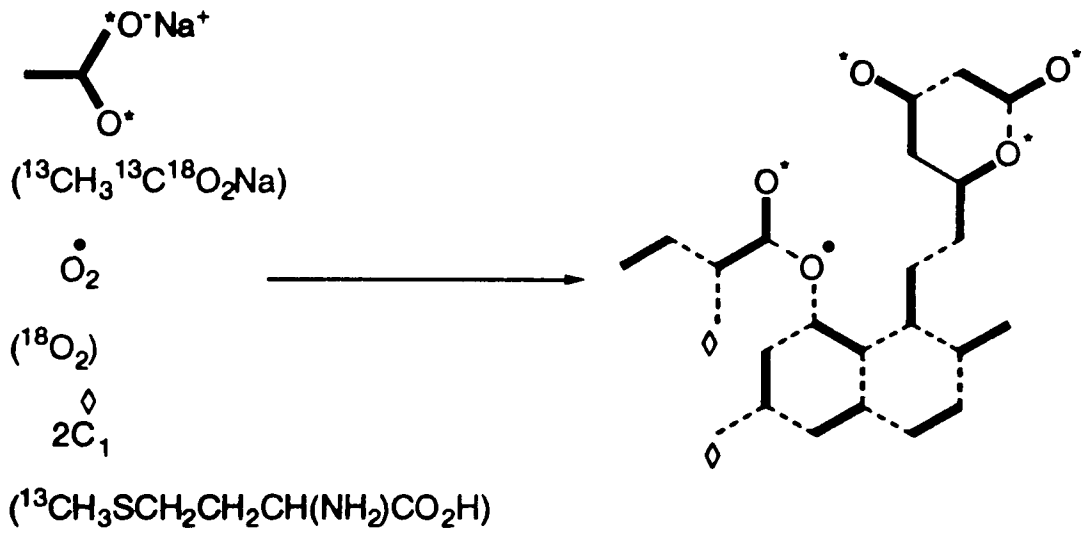
Another compound of interest, due to a structure that might be constructed by a biological Diels-Alder reaction is mevinolin **107** (also known as lovastatin), a widely prescribed drug for reduction of plasma cholesterol levels in humans, produced by fermentation of fungi such as *Aspergillus terrus* (Figure 18).



Mevinolin **18**

Figure 18

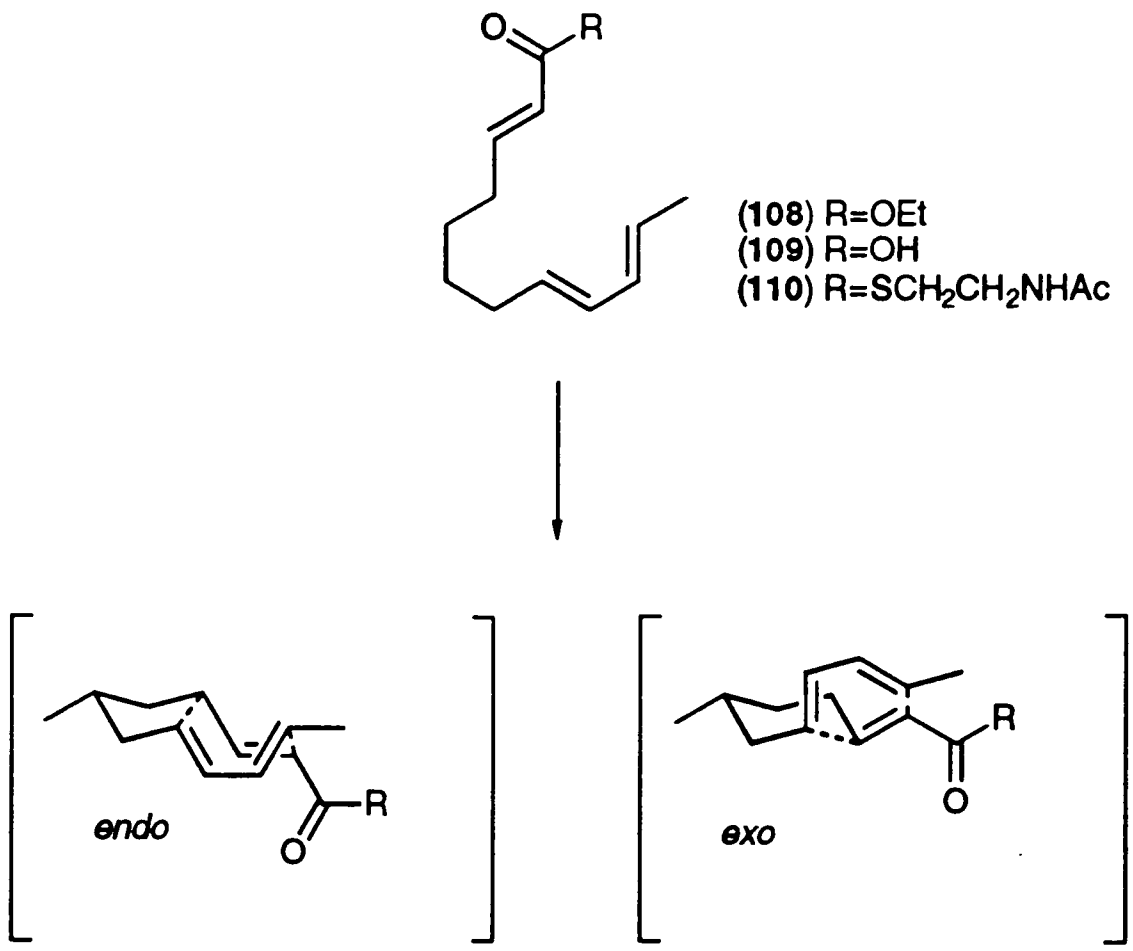
The biosynthesis of the molecule was examined by feeding experiments using labelled sodium acetate, methionine[77] and molecular oxygen[78,79] (Scheme 21).



Scheme 21

The studies showed that the carbon framework consists of two polyketide chains, one C_{18} and the other C_4. This observation leads to a number of possible biosynthetic pathways to mevinolin **107**. A series of carbonyl condensations offers a route to the decalin portion. However, precedent for such schemes involves retention of the acetate oxygen near the starter end of the polyketide, and the feeding studies suggest that this end is highly reduced.

Alternative pathways involve Diels-Alder reactions, which additionally would explain the observed stereochemistry. Studies of the Diels-Alder reaction with simplified analogues yielded a number of interesting results (Scheme 22).



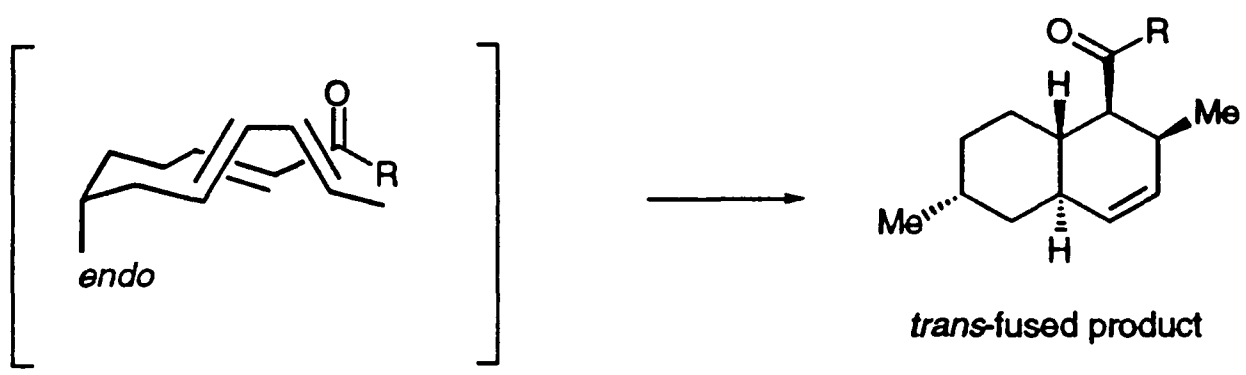
Scheme 22

All the Diels-Alder reactions were carried out under standard reaction conditions (Table 6) to yield a mixture of *trans*- and *cis*-cycloadducts.

Starting Material	Reaction Conditions	Yield %	*trans:cis* ratio
(**108**)	PhMe, 160°C, 4 days	72	1:1 (**111**:**114**)
(**109**)	PhMe, 160°C, 4 days	83	1:1 (**112**:**115**)
(**110**)	PhMe, 160°C, 4 days	81	1:1 (**113**:**116**)
(**108**)	PhMe, $EtAlCl_2$, 25°C, 3h	58	19:1 (**111**:**114**)
(**110**)	PhMe, $EtAlCl_2$, 25°C, 3h	80	19:1 (**113**:**116**)

Table 6

The results show that equal amounts of *cis*- and *trans*- cycloadduct are produced by all the substrates under standard thermal conditions. The use of Lewis acids allows the reaction to proceed under milder conditions affording a greater yield of the *trans*-cycloadduct, which passes through the *endo* transition state. The most significant result however, is that the stereochemistry of the obtained product does not match with that of the natural product. The two cycloadducts obtained from the synthetic Diels-Alder reactions involve the substrates passing though a transition state with the methyl substituent pseudoequatorial (Scheme 22). For the stereochemistry of the biological product to be achieved, the substrate is required to adopt an *endo* conformation with the methyl substituent pseudoaxial (Scheme 23).



Scheme 23

These results suggest that if mevinolin **107** is produced by a Diels-Alder cyclisation, the reaction is enzyme controlled, ensuring the substrate adopts the required *endo* transition state with the methyl substituent pseudoaxial. The validity of these observations were confirmed by incubation of the triene (**110**) with cell-free extract of

Aspergillus terreus to afford mevinolin **107**, confirming the presence of (**110**) in the biosynthetic pathway. As before, the isolation and characterisation of a mediating enzyme would be the final piece of evidence required to confirm this pathway.

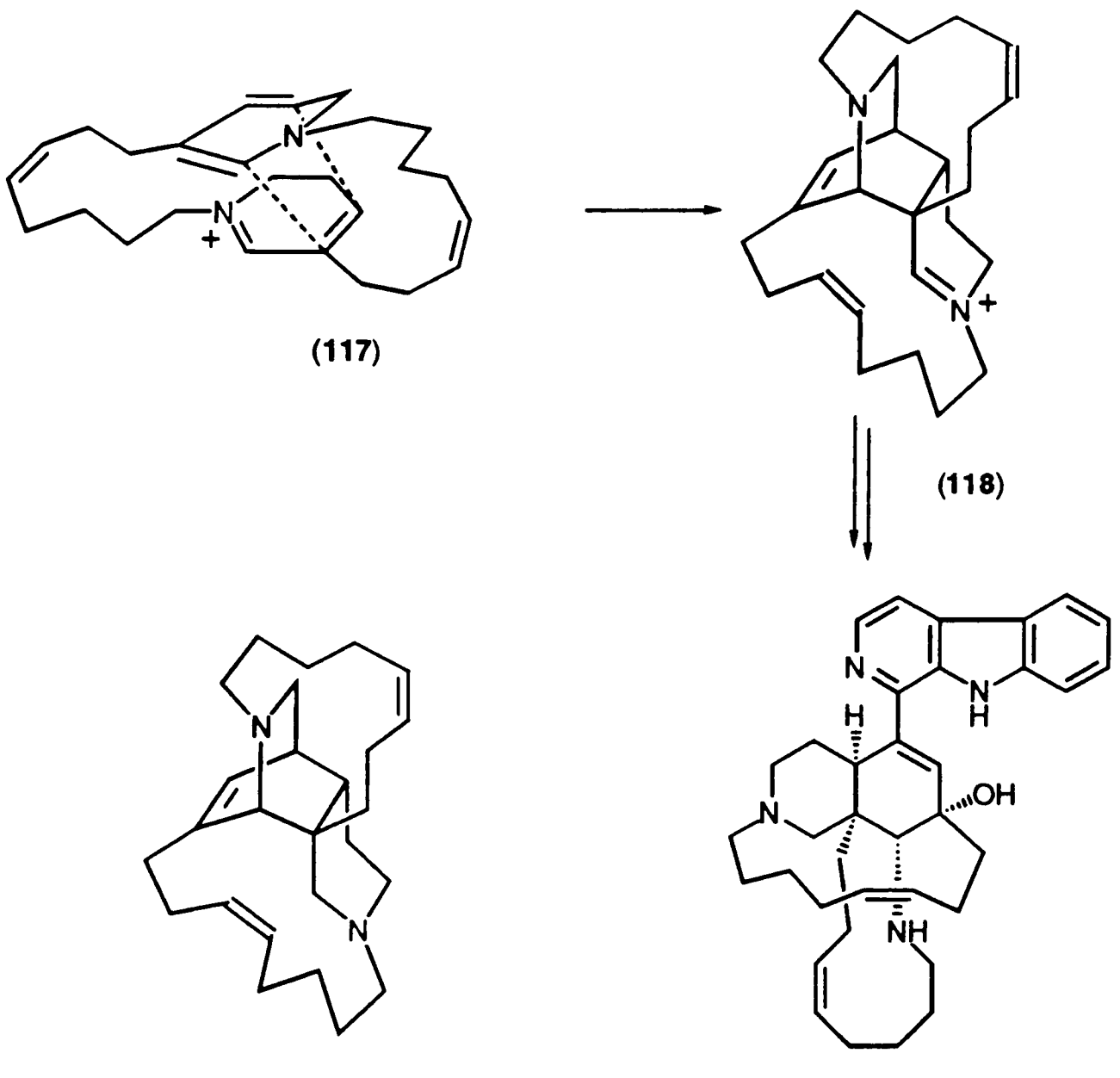
A number of other natural compounds contain decalin frameworks and stereochemistry consistent with a Diels-Alder reaction. These include the antibiotic nagenicin[80-83] and structurally related compound coloradocin[84]; the phytotoxin betaenone B[85] and the antibiotic aldecalmycin[86-89]. All these compounds have been shown, by feeding studies, to have polyketide origins with an incorporation pattern consistent with a Diels-Alder reaction. However, further evidence for a Diels-Alder reaction in the biological pathways of these molecules has yet to be reported.

The work completed on all the above compounds lends plausibility to the proposed occurrence of Diels-Alder reactions in biosynthetic pathways. However, until the isolation and characterisation of a Diels-Alderase enzyme is completed, these transformations will remain hypothetical.

1.10.1. Iminium Ion Mediated Diels-Alder Reactions

Another group of compounds proposed to occur with a Diels-Alder reaction in their biosynthetic pathway are the manzamine alkaloids. These are a group of β-carboline alkaloids which have been isolated from three different genera of marine sponges. A proposed biosynthesis of these compounds involves the use of a conjugated iminium ion (**117**) as the dienophile in a Diels-Alder reaction to afford (**118**), following which further elaboration would yield structures such as manzamine A **119**[90] (Scheme 24). This biosynthetic proposal is of particular interest as it involves a conjugated iminium ion as the dienophile, a similar proposal to that suggested for the biosynthesis of himbacine **1**. A recent piece of evidence for the biosynthesis of the manzamines was

the isolation of keramaphidin B **120**, the reduced cycloadduct in the proposed pathway.

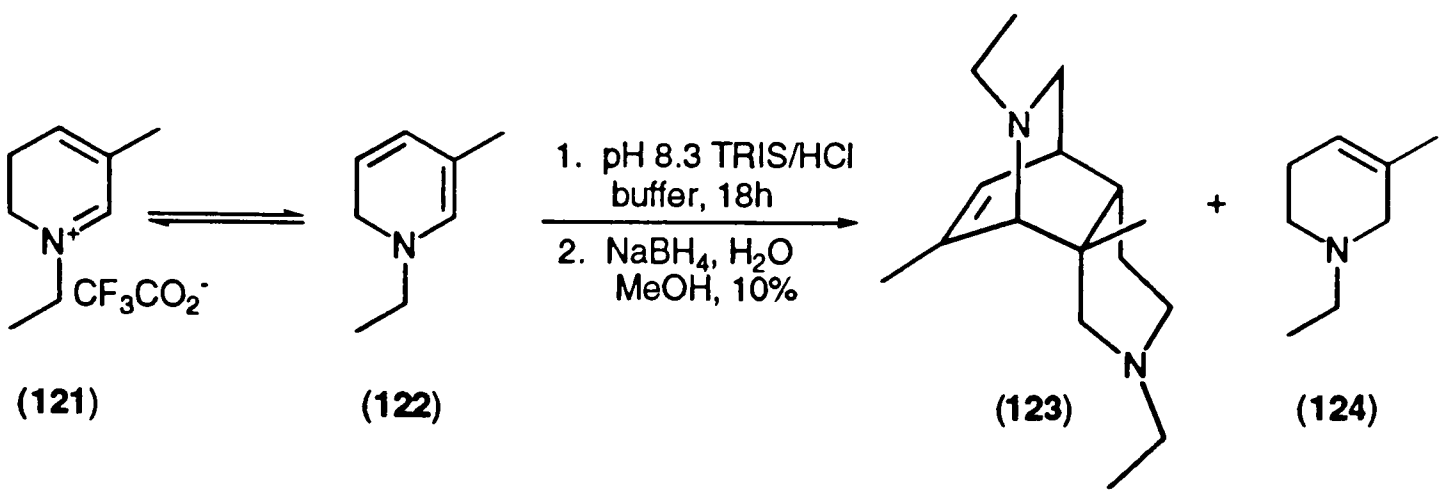


(117) **(118)**

Keramaphidin B **120** Manzamine A **119**

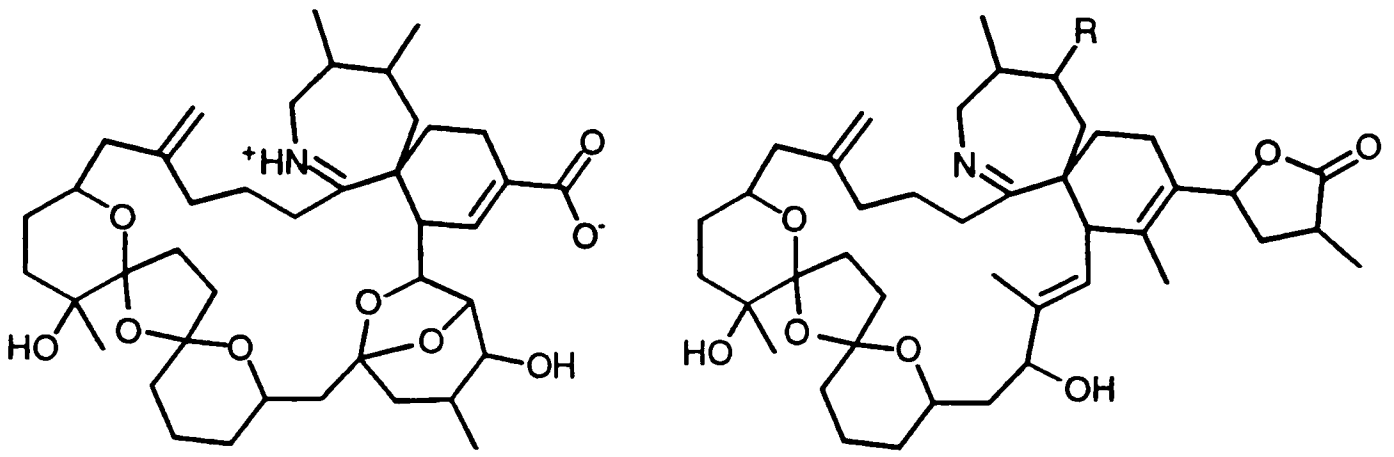
Scheme 24

Studies on simple model systems have shown that iminium ion mediated Diels-Alder reactions are possible in such molecules; however application to the total synthesis of the manzamines has yet to be completed. The studies involved use of a 3-alkyl-5,6-dihydropyridinium ion (**121**), which in pH 8.3 aqueous buffer exists in equilibra with the 1,6-dihydropyridine (**122**). A Diels-Alder reaction *via* an *endo* transition state between these two components afforded cycloadduct (**123**) as the minor product, with tetrahydropyridine (**124**) as the major product (Scheme 25)[91-93].



Scheme 25

There have been a number of other compounds recently isolated that could be constructed by an iminium ion mediated Diels-Alder reaction[94]. However there have been no investigations into whether such reactions occur in the biosynthetic pathway to these molecules. The most interesting has been the isolation of pinnatoxin A **125**[95], and the structurally related macrocycles, spirolides B and D[96], **126** and **127** respectively (Figure 19).

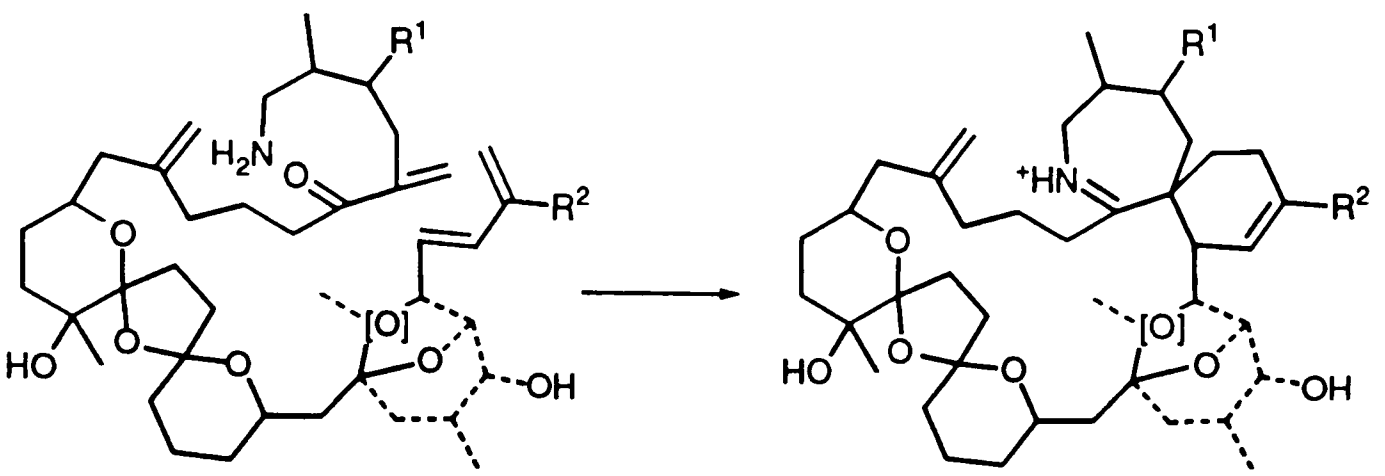


Pinnatoxin A **125**

Spirolide B **126** R=H
Spirolide D **127** R=Me

Figure 19

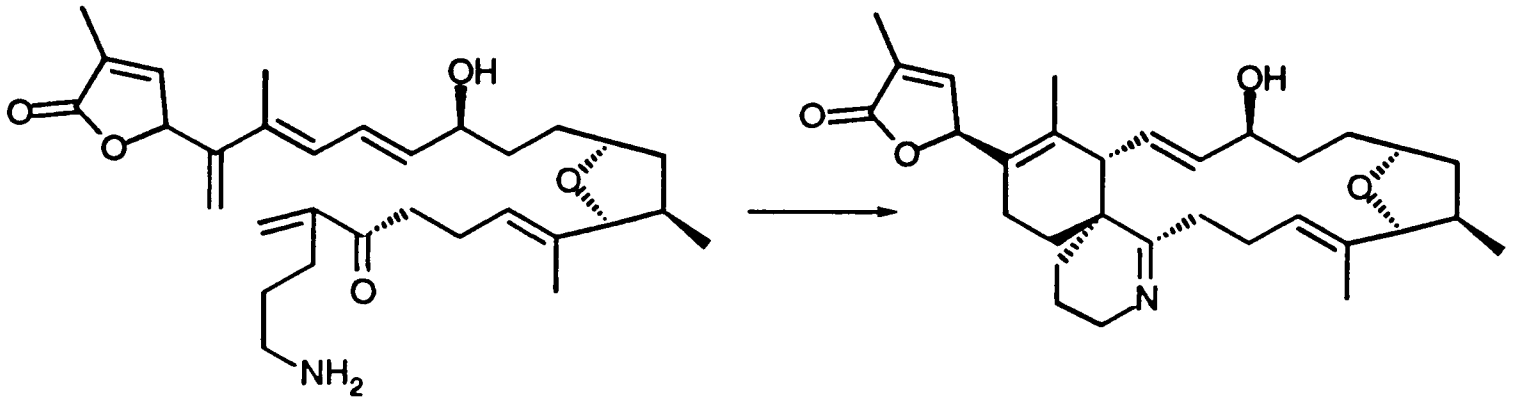
The construction of these two molecules by amination of αβ-unsaturated ketone (**128**) to form an iminium ion (**129**) (or imine) and a Diels-Alder reaction can be visualised (Scheme 26). However, at this time it is not known whether the amination to form the iminium ion occurs first, promoting the Diels-Alder reaction, or if the reactions occur in a different order.



(128) **(129)**

Scheme 26

The final example of a potential iminium ion mediated Diels-Alder reaction is in the biosynthetic pathway to the shellfish toxin gymnodamine **130**[97,98]. As with the previous examples, the presence of an imine α to a cyclohexene ring suggests the possible intermediacy of an iminum ion formed from αβ-unsaturated ketone (**131**), mediating a Diels-Alder reaction (Scheme 27).



(131) Gymnodimine **130**

Scheme 27

These results strongly suggest the presence of iminium ion mediated Diels-Alder reactions in a variety of biosynthetic pathways, offering support for the proposed biosynthesis of the *Galbulimima* alkaloids.

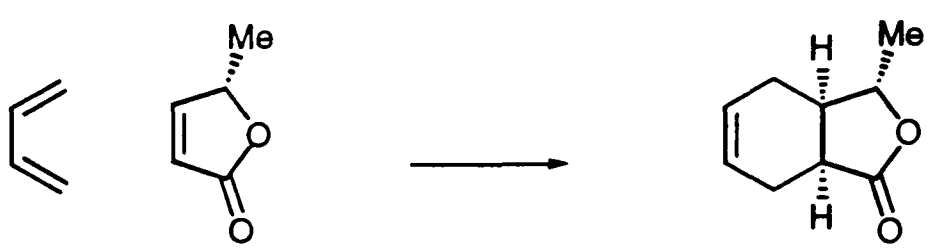
1.11. The Diels-Alder Reaction Applied to the Synthesis of Himbacine

1.11.1. Regiochemical Factors

Considering in detail the proposed Diels-Alder reaction, two principle factors will influence the stereochemical course of the reaction:

- The steric influence of the methyl group on the butenolide.
- The *endo*:*exo* selectivity.

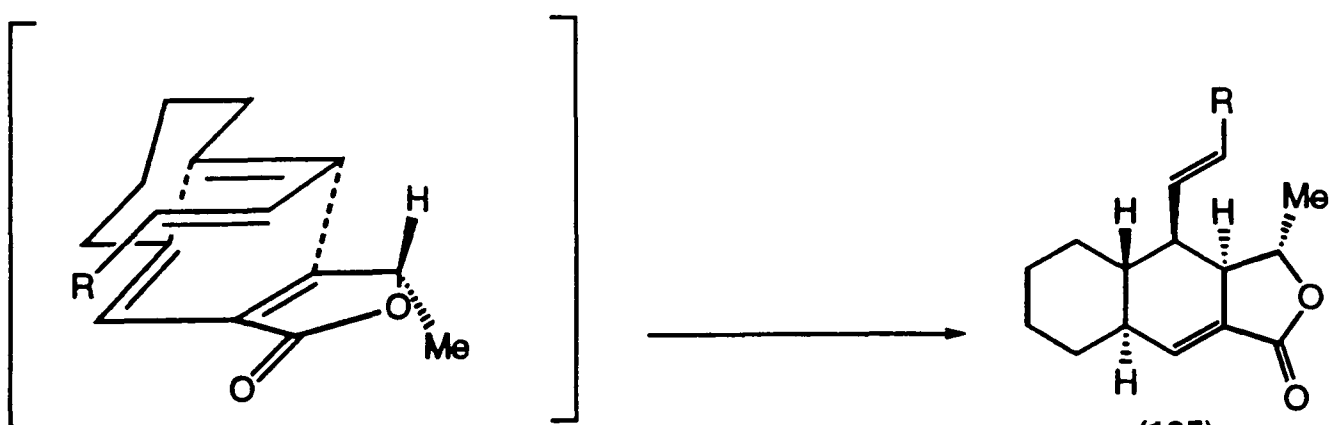
The methyl group should direct the dienophile to the π-face *anti* to the methyl group. This proposal is supported by the Diels-Alder reaction of the butenolide (**132**) and butadiene **133** to afford cycloadduct (**134**) (Scheme 28)[99].



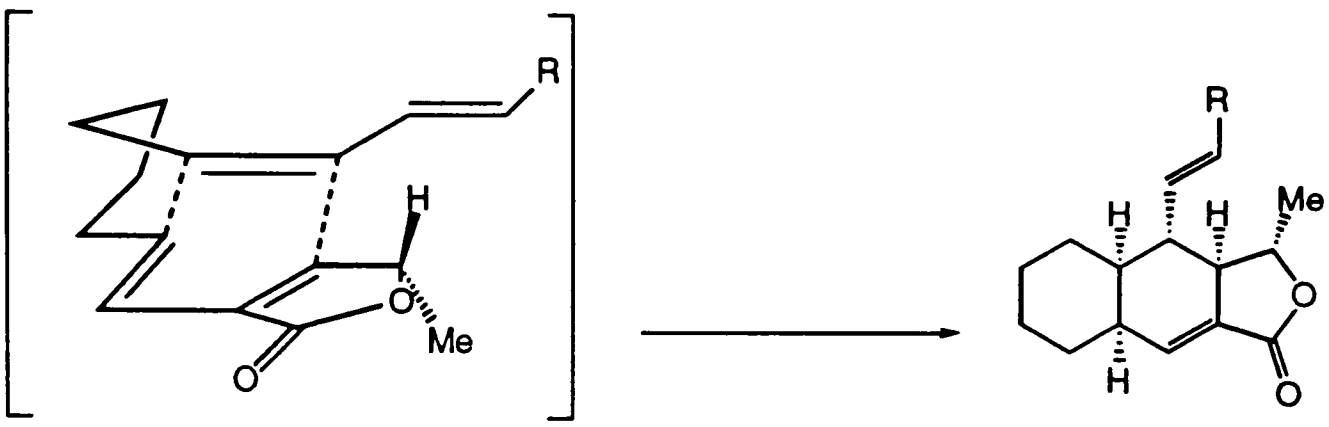
Butadiene **133** (**132**) (**134**)

Scheme 28

The transition state geometry must be *endo* to achieve the correct stereochemistry in the product (**135**). As the reaction is assumed to be exothermic, using the Hammond postulate which states that the transition state should represent the reactant more than the product, molecular models of both the *endo* and *exo* transition states were examined (Diagram 1).



Desired *endo*-transition state (**135**)

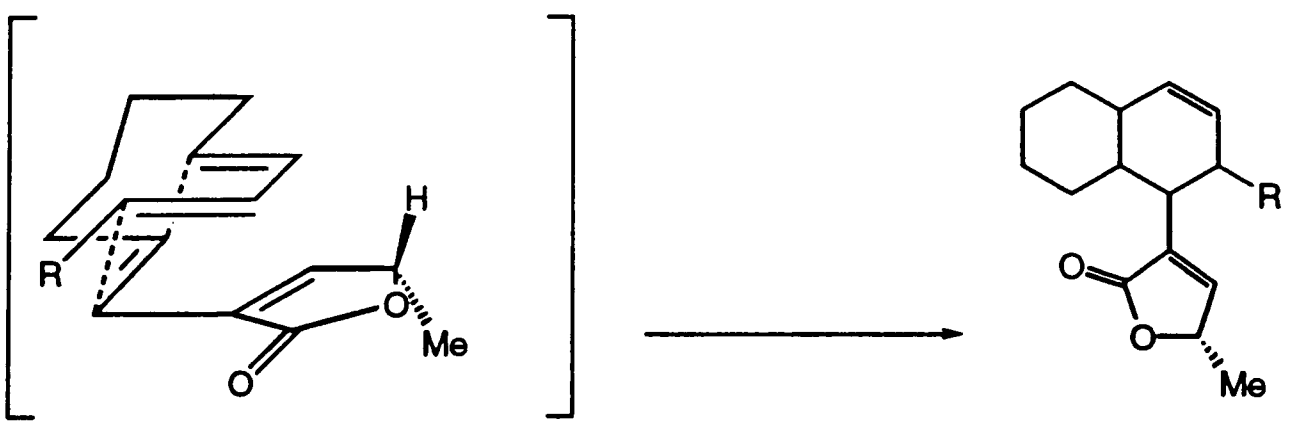


Undesired *exo*-transition state

Diagram 1

Examination of the *exo* transition state shows it to adopt a high energy pseudo boat-boat conformation with no secondary orbital interactions to stabilise the transition state. The *endo* transition state adopts a lower energy pseudo chair-boat conformation with secondary orbital overlap with the alkene conjugated to the dienophile. These observations suggest that the required *endo* transition state would be preferred, leading to the desired stereochemistry.

Further modelling studies of the *endo* transition state show the possibility of an alternative Diels-Alder reaction occurring (Diagram 2). This would involve the exocyclic alkene of the vinyl-butenolide acting as the dienophile and reacting with the diene in the carbon chain.



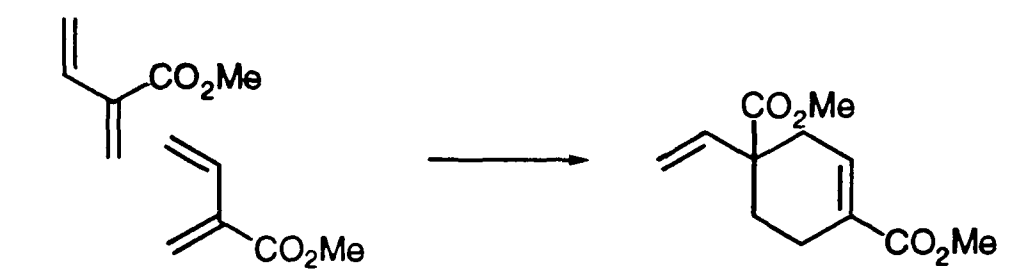
endo-transition state

Diagram 2

Thus, careful control of the electronics of the reaction is required, to bias the reaction towards the desired tricyclic product (**135**).

1.11.2. Electronic Factors

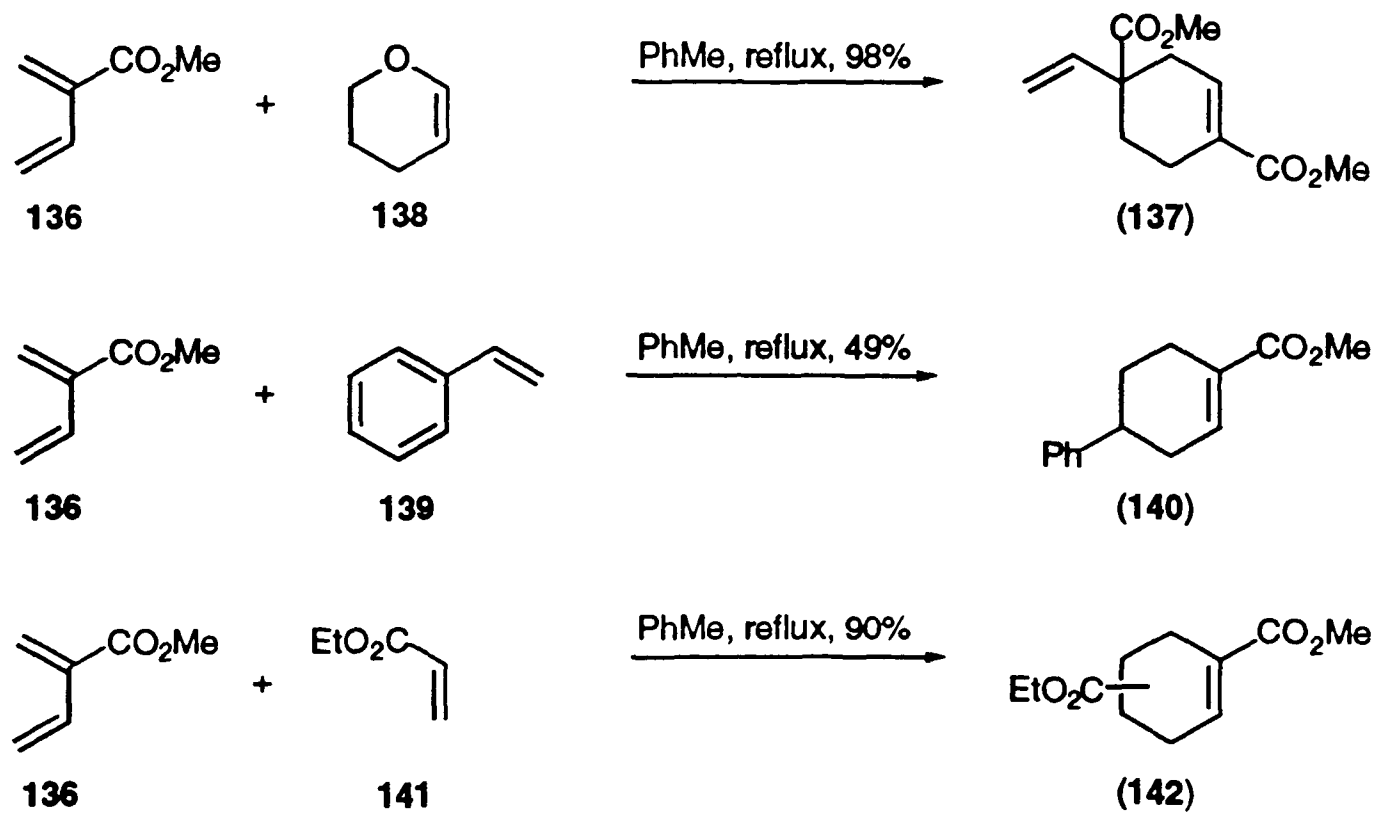
The proposed Diels-Alder reaction involves the use of a 2-carboxydiene, which is an unusual class of diene. The simplest member of this class, 2-carbomethoxydiene **136**, is extremely reactive, and undergoes spontaneous dimerisation forming the cyclohexene (**137**) (Scheme 29)[100,101].



2-Carbomethoxydiene **136** (**137**)

Scheme 29

The reaction is unusual in that what would appear to be an electron deficient diene reacts with the most electron deficient dienophile. This result has been confirmed by the reaction of 2-carbomethoxydiene **136** with a variety of dienophiles (Scheme 30). In all the reactions the source of 2-carbomethoxydiene **136** was *via* the cheleotropic extrusion of sulfur dioxide from the appropriate sulfolene[100,101].

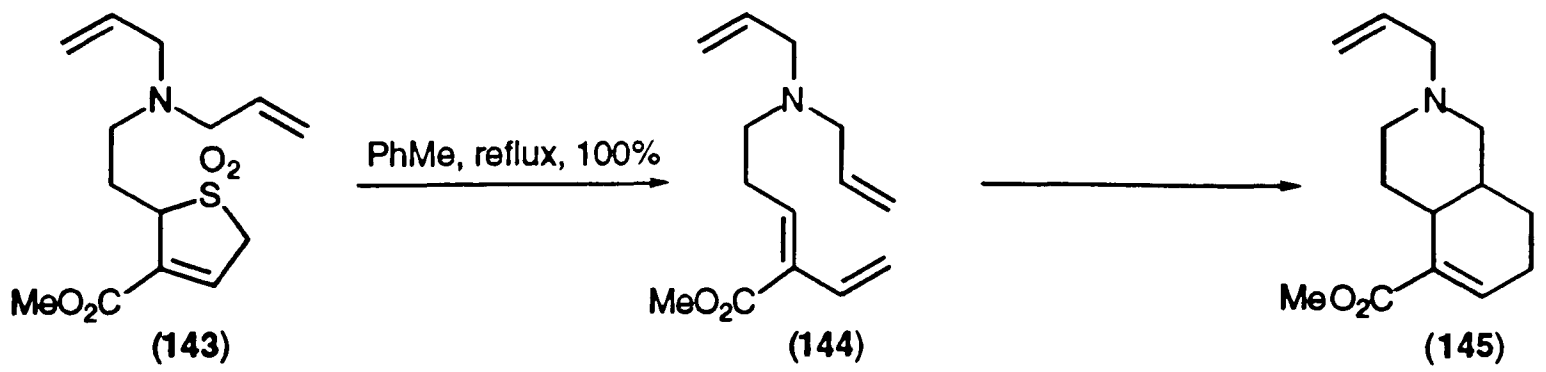


Scheme 30

The use of an electron rich dienophile, 3,4-dihydropyran **138**, afforded only the 2-carbomethoxydiene dimer (**137**). A conjugated dienophile, styrene **139**, gave a 48% yield of cycloadduct (**140**), and the dimer (**137**) in an unspecified yield. Finally electron deficient dienophile, ethyl acrylate **141**, afforded only the cycloadduct (**142**). These results illustrate the preference of 2-carboxydienes to react with electron deficient dienophiles, an unusual result considering that electron deficient dienes normally react preferentially with electron rich dienophiles.

Thus use of the proposed Diels-Alder reaction should involve careful control of the electronics of the dienophile, the reaction being more likely to proceed with an electron deficient dienophile, such as the proposed conjugated iminium ion (**80**). Additionally the reactivity of the 2-carboxydienes towards dimerisation would need to be addressed. The use of a Diels-Alder reaction for the synthesis of himgravine **9** would not be possible if the required 2-carboxydiene (**76**) dimerised.

The second of these problems was investigated in work published simultaneously by Marko[102] and Leonard[103]. Additionally these studies demonstrated that the Diels-Alder reactions of 2-carboxydienes can occur intramolecularly. The work completed by Leonard involved thermal conversion of the sulfolene (**143**) to the 2-carboxydiene (**144**) which cyclised under the reaction conditions to give hydroisoquinoline (**145**) (Scheme 31).



Scheme 31

The work by Marko mirrored the work by Leonard, except that the 2-carboxydiene (**144**) was isolated before the Diels-Alder reaction was attempted. The Diels-Alder reaction proceed as before, to yield only a 41% yield of the hydroisoquinoline (**145**).

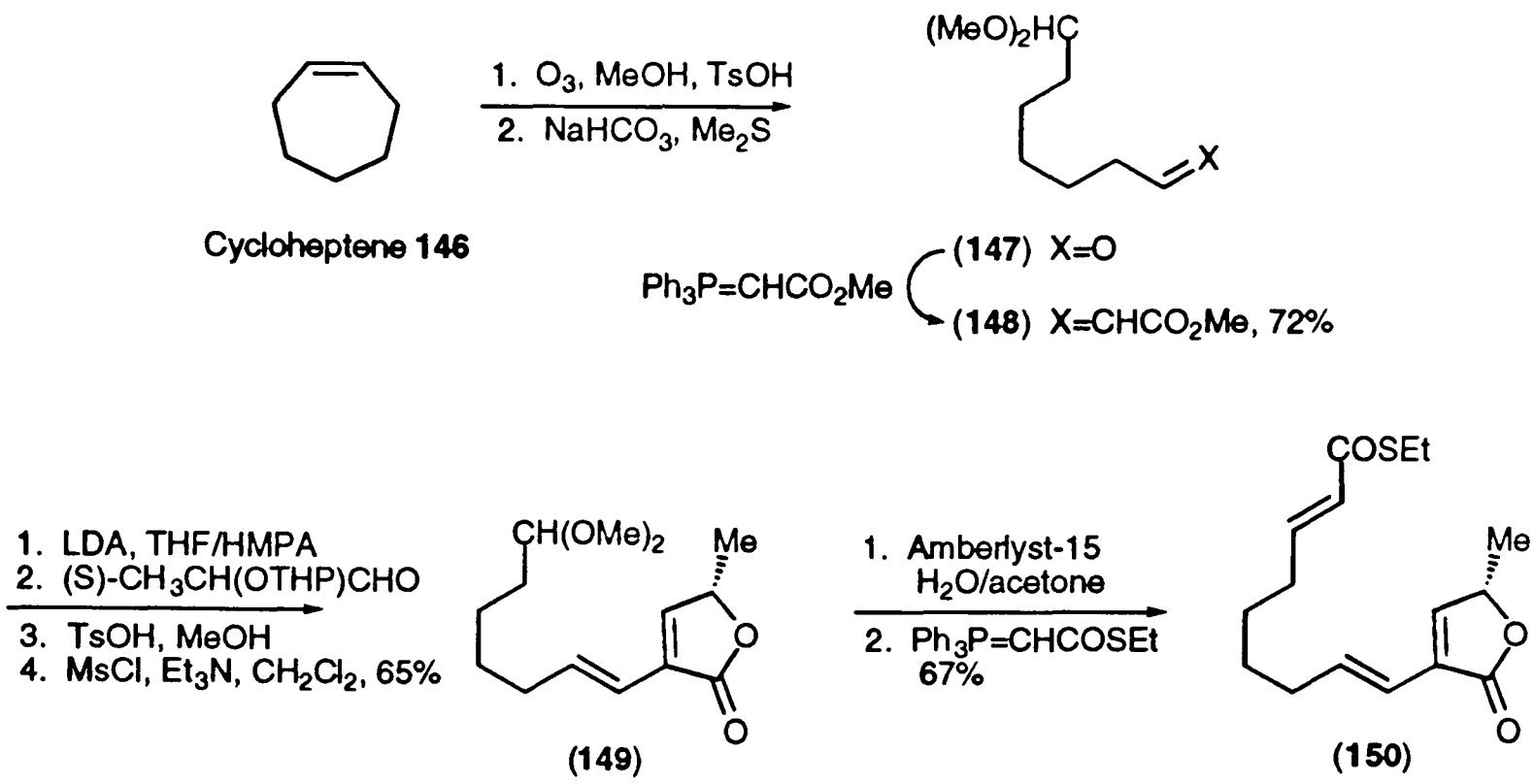
The isolation of the 2-carboxydiene (**144**) suggests that increasing the substitution on the diene reduces the reactivity. This observation means that the 2-carboxydienes required for the proposed synthesis of himbacine **1** should be more stable than **136**. Additionally, for the Diels-Alder reaction to proceed an elevated temperature may be required.

In summary, the Diels-Alder reaction required for synthesis of the tricyclic portion of himbacine **1** will be governed by steric and electron factors which favour the reaction passing through an *endo* transition state to give the correct stereochemistry.

1.12. Synthetic Approaches to Himbacine

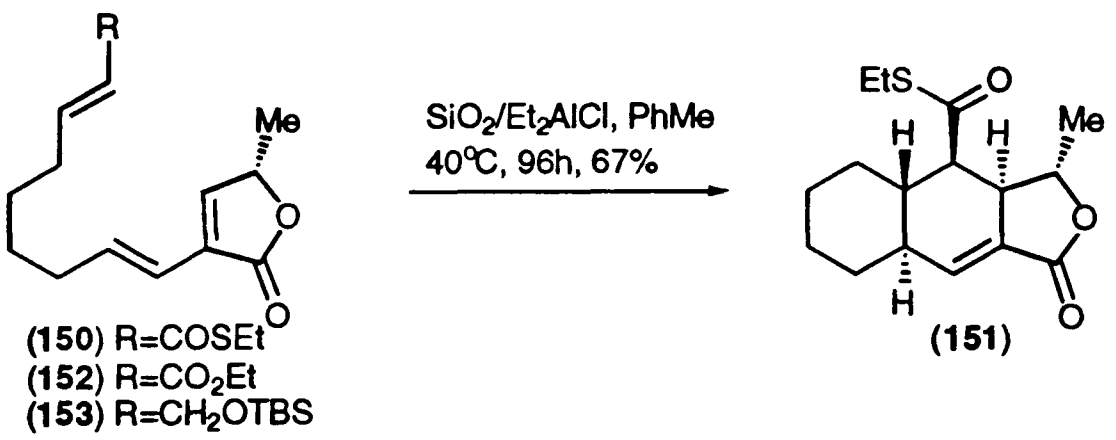
The recent interest generated by the pharmacology of himbacine **1** has prompted a number of groups to develop synthetic routes to the alkaloid. The key step in all these approaches has involved the use of the suggested Diels-Alder reaction[57].

The first reported total synthesis was completed in 1995 by Hart[104,105]. Starting from cycloheptene **146**, ozonolysis to give aldehyde (**147**), following which a Wittig reaction afforded (**148**) as a 2:1 mixture of geometrical isomers. Addition of the dienolate of (**148**) to the tetrahydropyranyl ether of (*S*)-2-hydroxypropanal, followed by acetal hydrolysis, lactonisation and dehydration afforded diene (**149**) as an 8:1 mixture of geometrical isomers. The ratio was improved to 32:1 by allowing the mixture to stand in sunlight in the presence of iodine. Acetal hydrolysis, followed by a Wittig reaction, afforded unsaturated thioester (**150**) (Scheme 32).



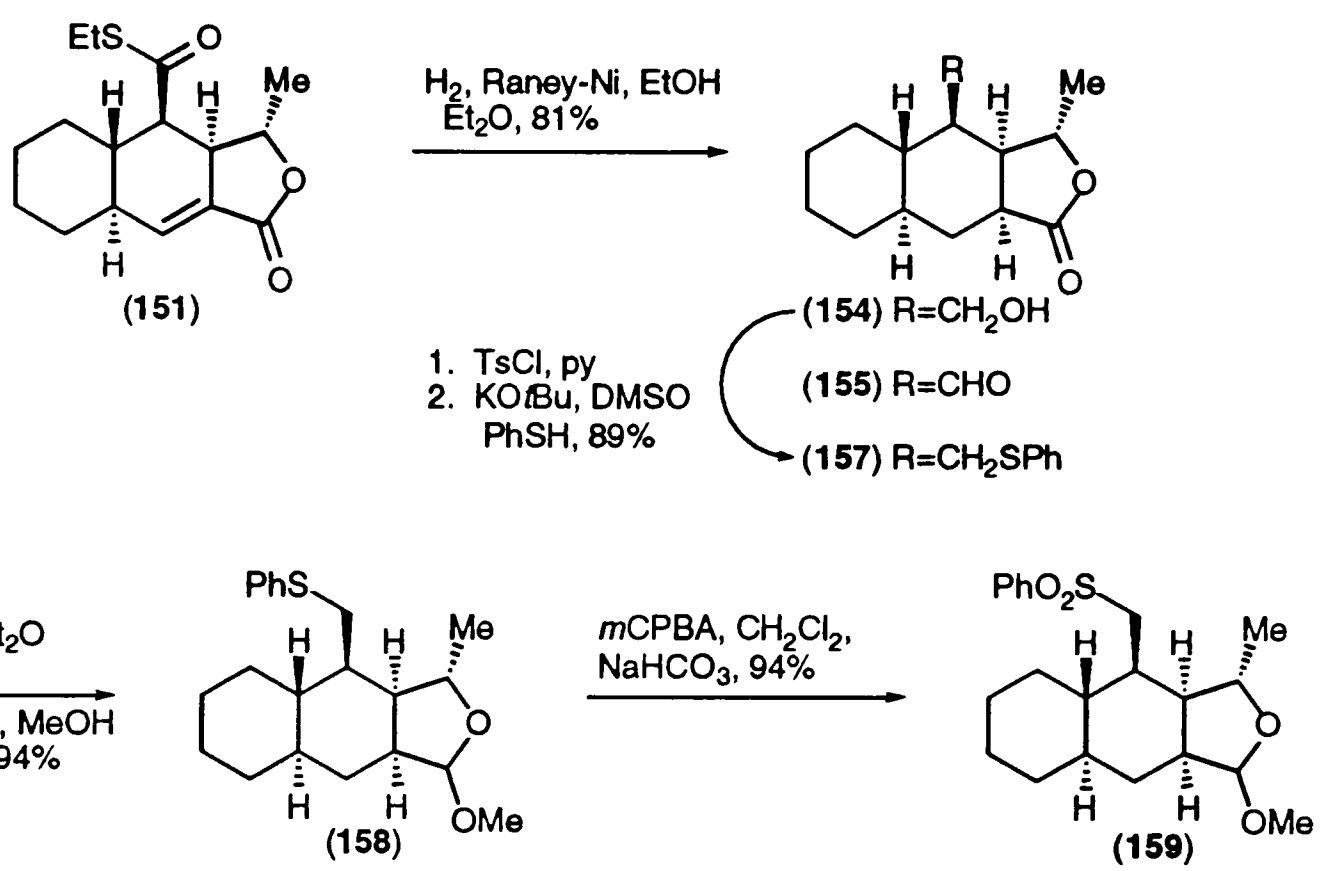
Scheme 32

Using thermal conditions to promote the Diels-Alder reaction (110°C, 16h) afforded (**151**) and the *exo* cycloadduct in a 3:2 ratio. The best *endo*:*exo* selectively of 20:1 was obtained when a promoter prepared from diethylaluminium chloride and silica gel (a Lewis acid on a solid support[106]) was used and the reaction was conducted at 40°C for 96 hours. Using this methodology the Diels-Alder adduct (**151**) was isolated in a 67% yield. Interestingly, ester (**152**) and silyl alcohol (**153**) failed to provide the stereoselectivity required for an efficient total synthesis under the same conditions (Scheme 33).



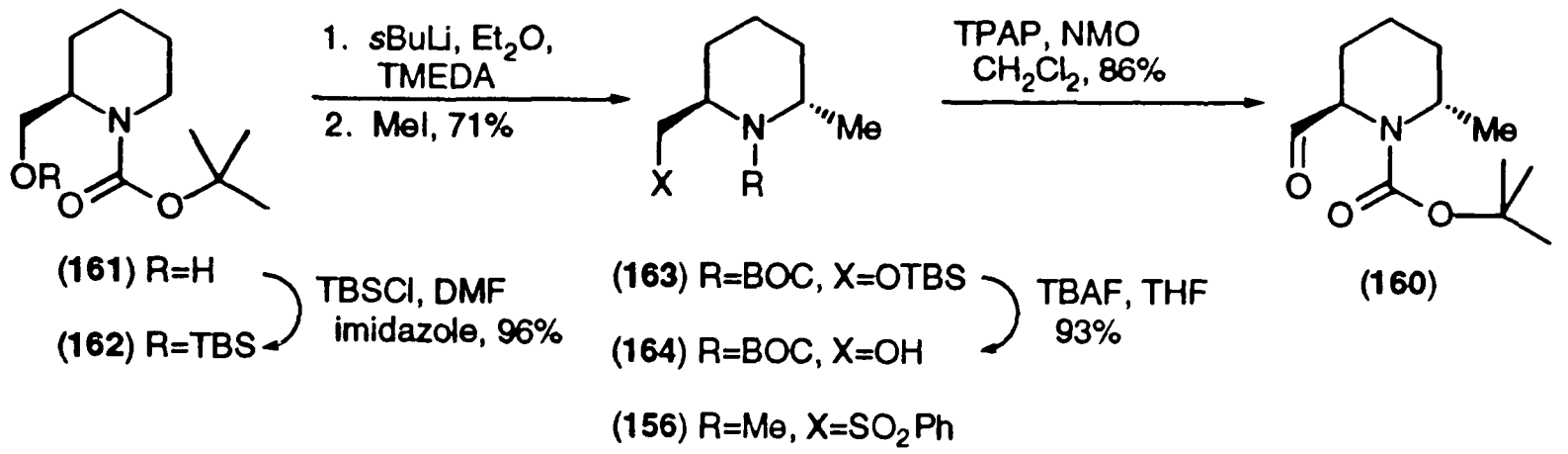
Scheme 33

Treatment of (**151**) with Raney nickel gave alcohol (**154**), following which oxidation afforded aldehyde (**155**). The attempted Julia Coupling of this with piperidine sulfone (**156**) (Figure in Scheme 35) failed, probably due to steric hindrance. Thus reversal of the coupling partners was identified as a new strategy for completing the synthesis. Thus alcohol (**154**) was tosylated, followed by displacement of the tosyl group with thiophenoxide to afford (**157**). The γ-lactone was then converted to acetal (**158**) by reduction and methylation. Finally the sulfide was oxidised to sulfone (**159**) (Scheme 34).



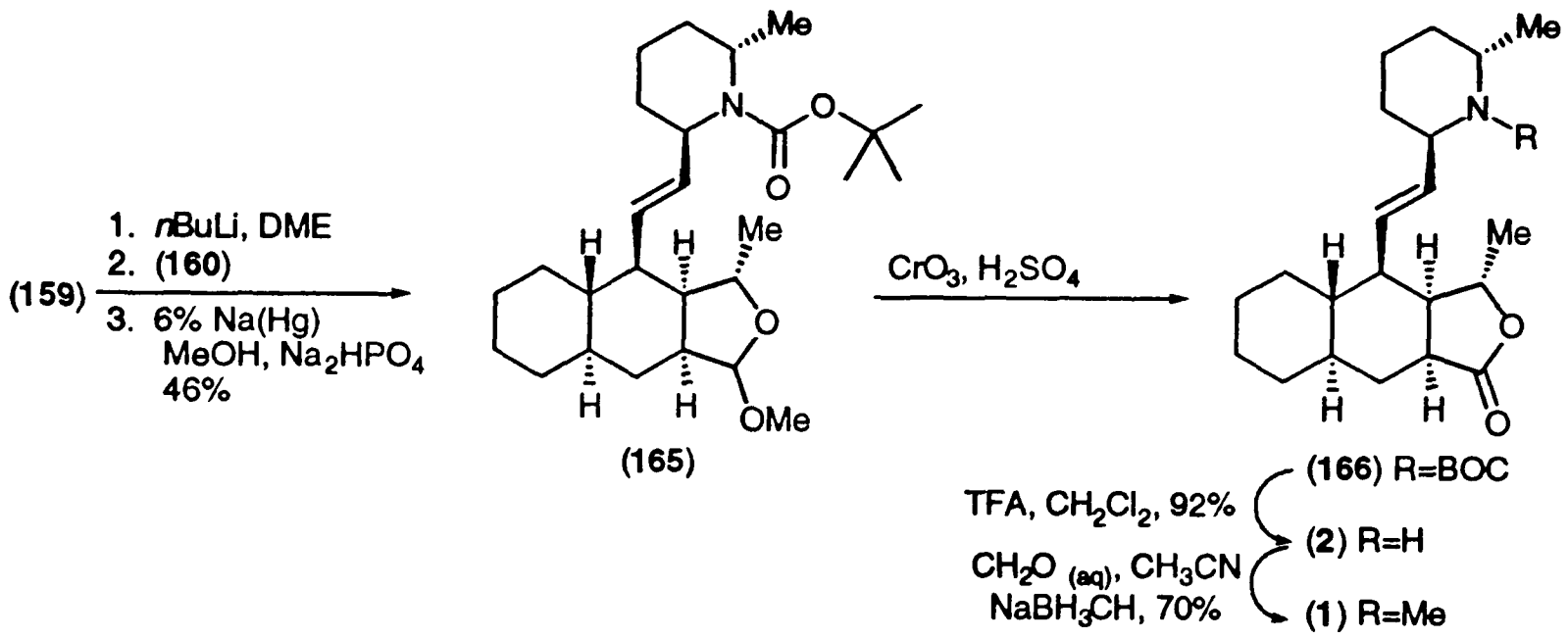
Scheme 34

Synthesis of the required piperidine (**160**) was completed using the Beak methylation as the key step. Thus starting from (*R*)-piperidine-2-carboxylic acid, reduction followed by *N*-BOC protection afforded (**161**). Protection of the primary alcohol to afford (**162**), followed by application of the Beak methylation gave *trans*-piperidine (**163**). Deprotection to give alcohol (**164**), followed by oxidation then afforded piperidine aldehyde (**160**) (Scheme 35).



Scheme 35

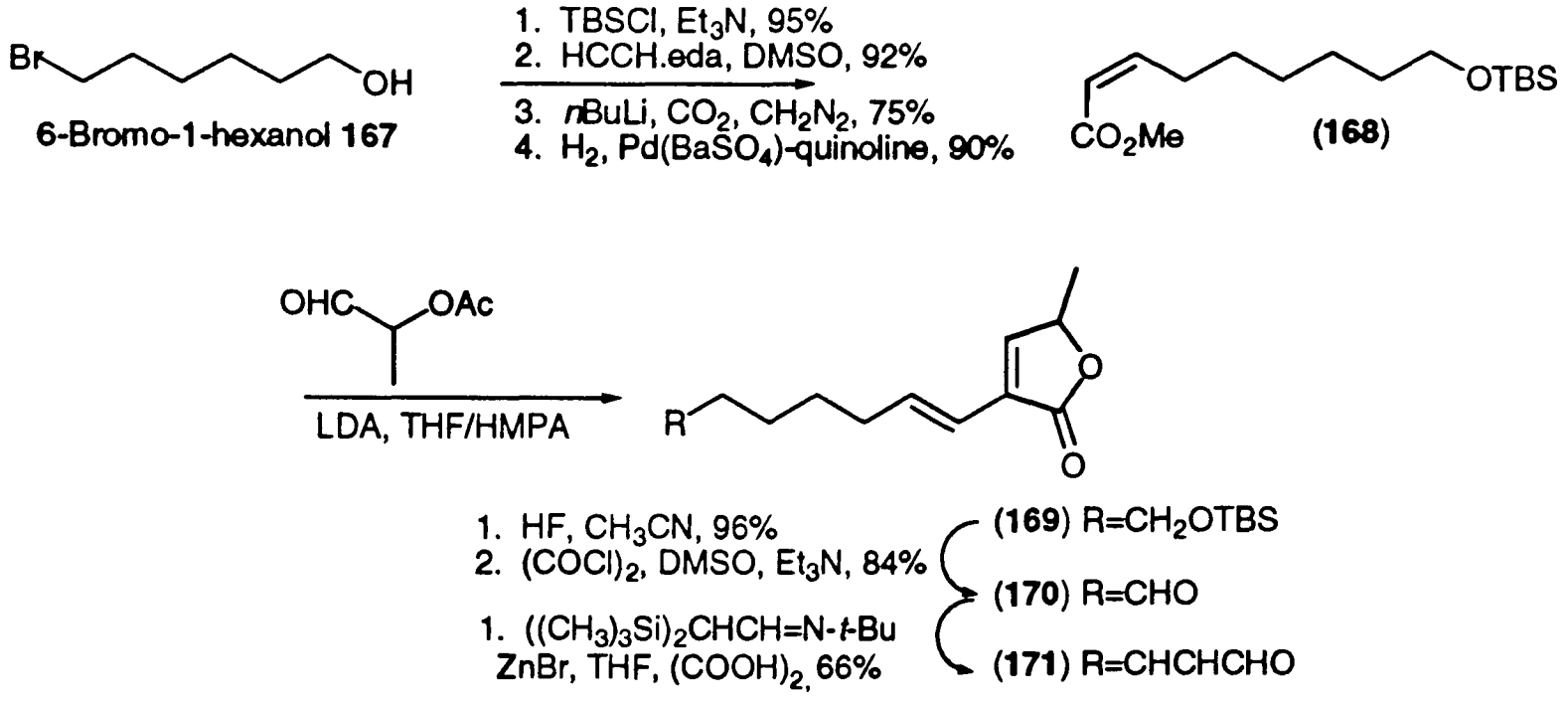
The synthesis was completed by the successful use of a Julia coupling to join piperidine (**160**) and tricyclic sulfone (**159**) to give (**165**), following which oxidation of the acetal afforded (**166**). Removal of the *N*-BOC group gave himbeline **2** and a reductive methylation completed the synthesis of himbacine **1** (Scheme 36).



Scheme 36

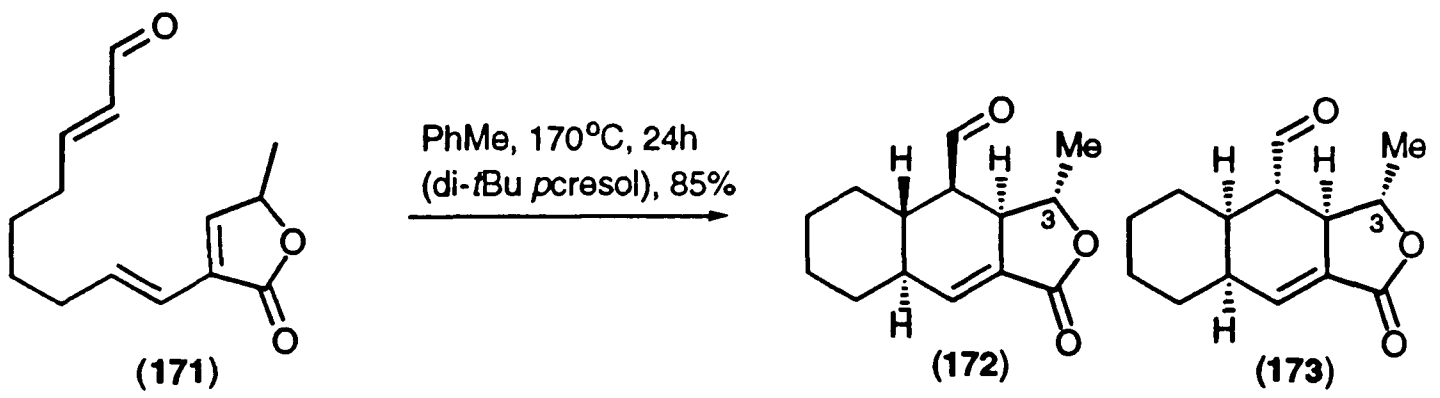
Shortly after the report by Hart, De Clercq published studies undertaken towards the total synthesis of himbacine **1**[107]. The use of a Diels-Alder reaction was again identified as the key step in the synthesis. The synthesis of the Diels-Alder precursor was achieved starting from 6-bromo-1-hexanol **167**, which was converted to (*Z*)-enolate (**168**) by a fairly straightforward procedure. The butenolide was then closed by conjugative deprotonation followed by alkylation with 2-acetoxypropanal, then two consecutive transesterifications to generate a γ-lactone, finally elimination of acetic

acid afforded the butenolide (**169**). Desilylation, followed by oxidation to give aldehyde (**170**), then elongation of the carbon-chain using Gaudemar's modification of Corey's aldimine approach afforded Diels-Alder precursor (**171**) (Scheme 37).



Scheme 37

The Diels-Alder reaction proceeded under thermal conditions, requiring 24 hours at 170°C, affording a mixture of 4 diastereomers (**172**), (**173**), 3-epi-(**172**) and 3-epi-(**173**) in a ratio of 8:5:6:1 respectively (Scheme 38).



Scheme 38

The results show that, as before, the observed stereochemistry is in favour of the *trans*-fused decalins, with the reaction proceeding *via* an *endo* transition state, to give desired diastereomer (**172**) as the major isomer. Also, the ratio of products suggest that the most important factor in determining diastereoselectivity is the formation of the

trans-decalin ring, the facial directing effect of the methyl group being a less important factor. However, the resultant mixture underlines the lack of selectivity achieved by the vigorous reaction conditions needed to allow the reaction of the enal of (**171**) with the 2-carboxydiene to proceed under standard thermal conditions.

The most recent report of a total synthesis of himbacine **1** was the publication by the group at Schering-Plough[56]. The approach, as before, was based around a Diels-Alder reaction. However, unlike the previous work, this reaction involved construction of the γ-lactone and central cyclohexene rings, rather than the decalin portion. Consideration of the possible transition states suggested that the vinylcyclohexenyl portion would act as the diene portion, as it is more likely to adopt the required cisoid conformation. Also the methyl group α to the ester would confer the *s-cis* orientation to the ester linkage, further promoting the cyclisation. The facial selectivity of the reaction would be similarly controlled by the methyl group. In this case 1,3-axial interactions between the alkenyl proton and the methyl group would bias the reaction towards the desired confirmation (Diagram 3).

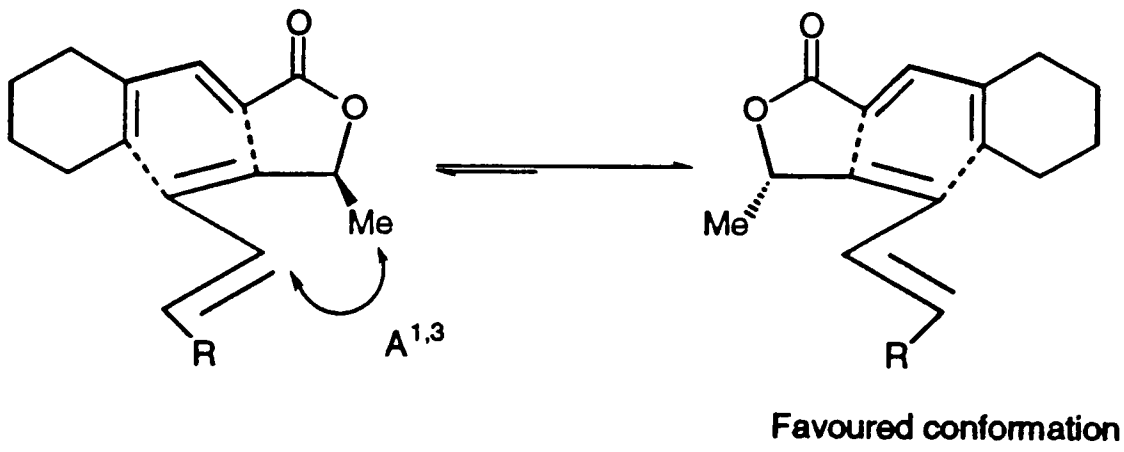
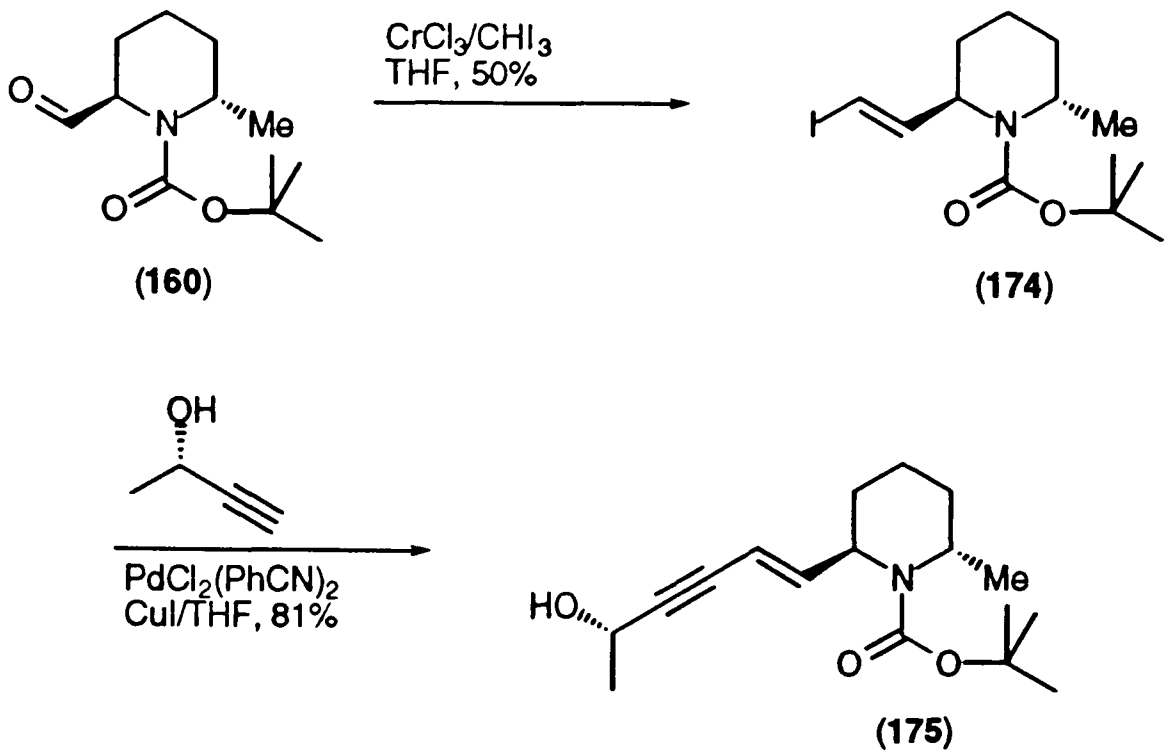


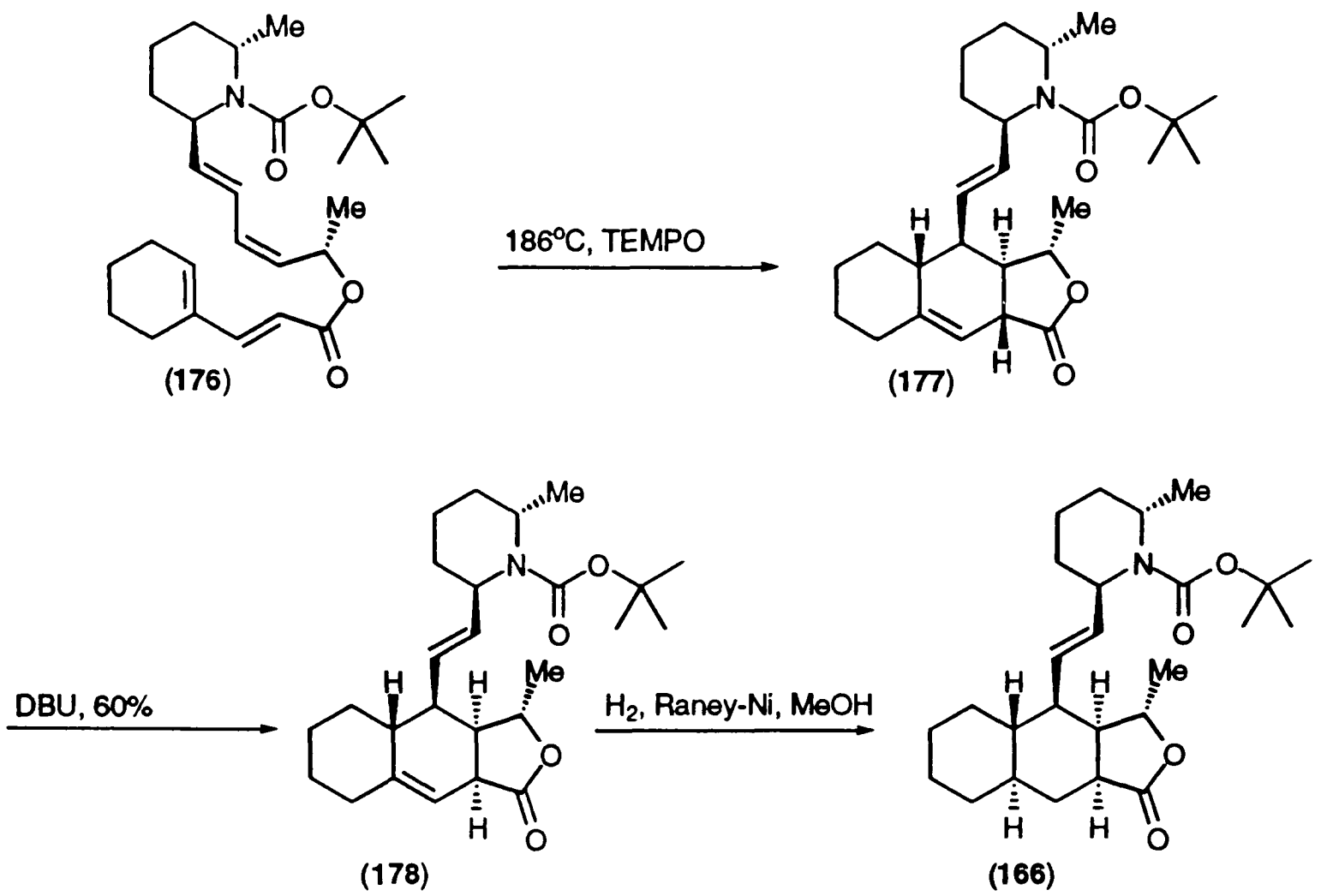
Diagram 3

The *trans*-piperidine was synthesised using the Beak methylation to afford piperidine aldehyde (**160**). This was converted to vinyl iodide (**174**) using the Takai protocol, then (*S*)-3-butyn-2-ol was introduced using a palladium-mediated coupling to afford (**175**). The alkyne (**175**) was then reduced to a *cis*-alkene and the vinylcyclohexenyl portion introduced by esterification to afford Diels-Alder precursor (**176**) (Scheme 39).



Scheme 39

The Diels-Alder reaction proceeded under thermal conditions (8 hours at 186°C) to afford exclusively the predicted *exo* adduct (**177**), which under the reaction conditions underwent partial isomerisaton to the *cis*-lactone (**178**). The isomerisation was completed using 1,8-diazabicyclo[5.4.0]undec-7-ene, following which regioselective reduction of the internal double bond occurred stereoselectively from the less hindered α-face to afford *N*-BOC himbeline (**166**) (Scheme 40). This was converted to himbacine **1** by the same procedure used by Hart.



Scheme 40

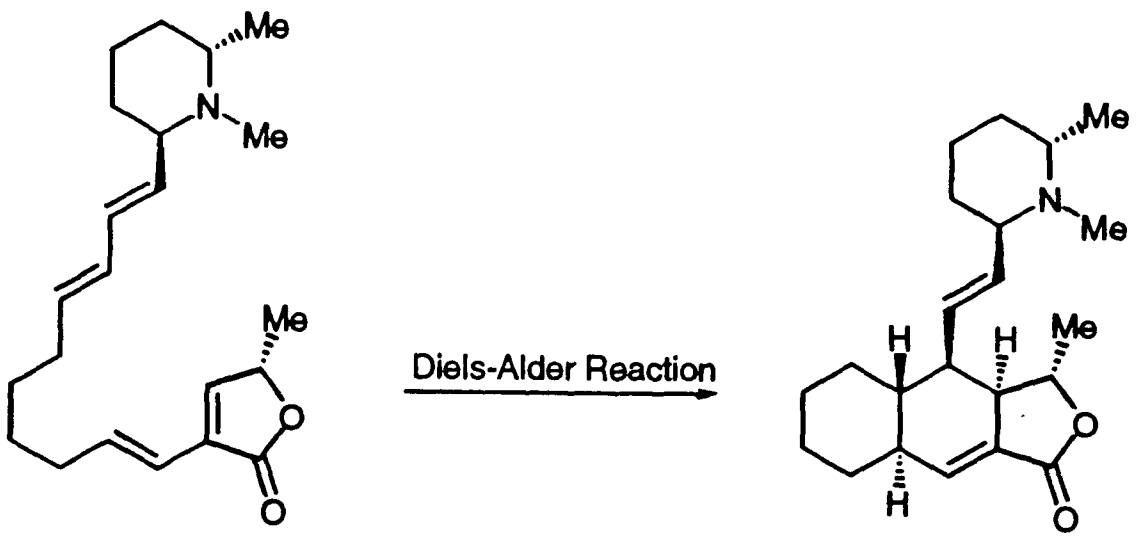
To date, all approaches to himbacine **1** have been based around the use of a Diels-Alder reaction, an obvious strategy considering the remarkable stereocontrol that can be achieved. The work completed has confirmed the predicted preference for the reaction to pass through an *exo* transition state, for facial selectivity to be directed by the butenolide methyl group and for the reaction and selectivity to be promoted by a reduction in the electron density of the dienophile. Additionally the recent work by Chackalamannil has demonstrated that, with careful consideration of the steric and electronic features it is not necessary to use the most obvious Diels-Alder reaction.

Chapter 2

RESULTS AND DISCUSSION

2.1. Synthetic Strategy

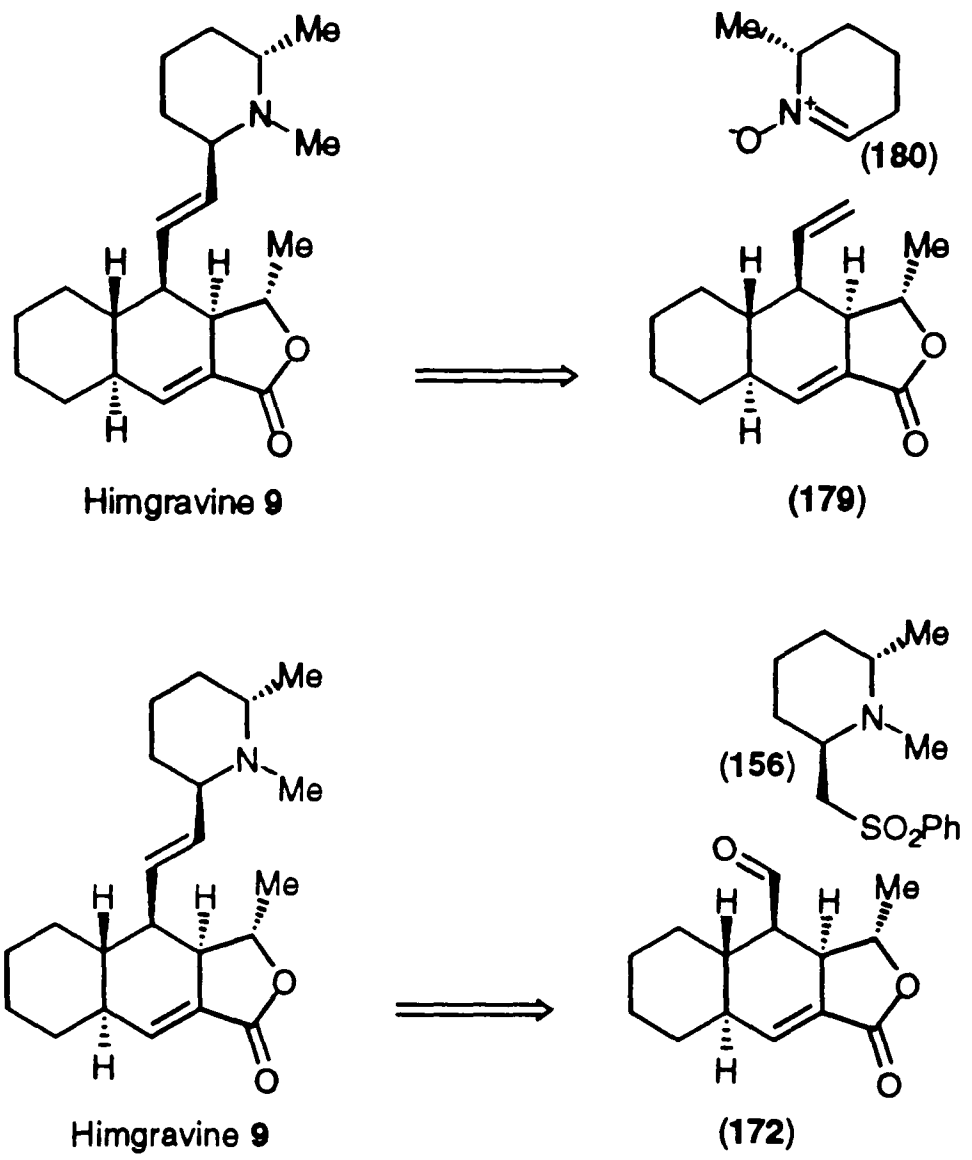
The use of a Diels-Alder reaction for the synthesis of himgravine **9**, and hence himbacine **1** lies at the centre of this project (Scheme 41).



(76) Himgravine **9**

Scheme 41

Initial studies focused on using such a reaction for a total synthesis of the alkaloid. It was decided to detach the *trans*-piperidine ring for ease of synthesis, which could be reconnected either *via* a nitrone cycloaddition involving tricyclic alkene (**179**) and nitrone (**180**) or *via* a Julia coupling involving tricyclic aldehyde (**172**) and piperidine sulfone (**156**) (Scheme 42).



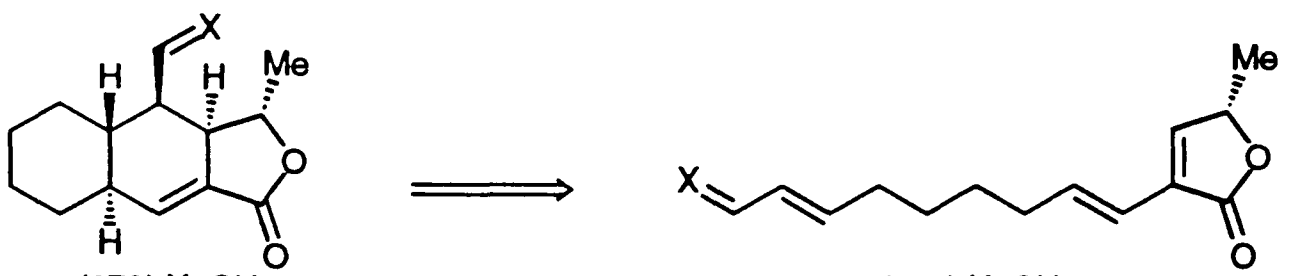
Scheme 42

The nitrone cycloaddition should proceed with the correct regiochemistry (the oxygen adding to the most hindered end of the alkene), and control of the stereochemistry by the piperidine methyl group, which would direct the cycloaddition onto the face *anti* to the methyl group, should afford the required *trans*-piperidine[108-110]. Reduction of the N-O bond using aluminium amalgam, followed by *N*-methylation, and functionalisation of the alcohol then elimination, would afford himgravine **9**.

The Julia coupling should be possible *via* a four step procedure; deprotonation of the sulfone (**156**), coupling to the aldehyde (**172**), acylation of the resulting alkoxide and elimination to afford exclusively the *trans*-alkene[111].

Disconnection of the tricyclic portions (**179** and **172**) proceeds *via* the required Diels-Alder reaction passing through an *endo* transition state (Scheme 43). As noted

before, the transition state geometry should be controlled by the methyl group on the butenolide, and by the molecule adopting the preferred *endo* transition state (Section 1.11). The electronic requirements of the reaction is a factor that needs careful control, and the diene (**181**) and enal (**182**) offer significant variation in the electron density of the dienophile. This variation should give some indication of the importance of using an electron-deficient dienophile in Diels-Alder reactions with 2-carboxydienes such as (**181**) and (**182**).

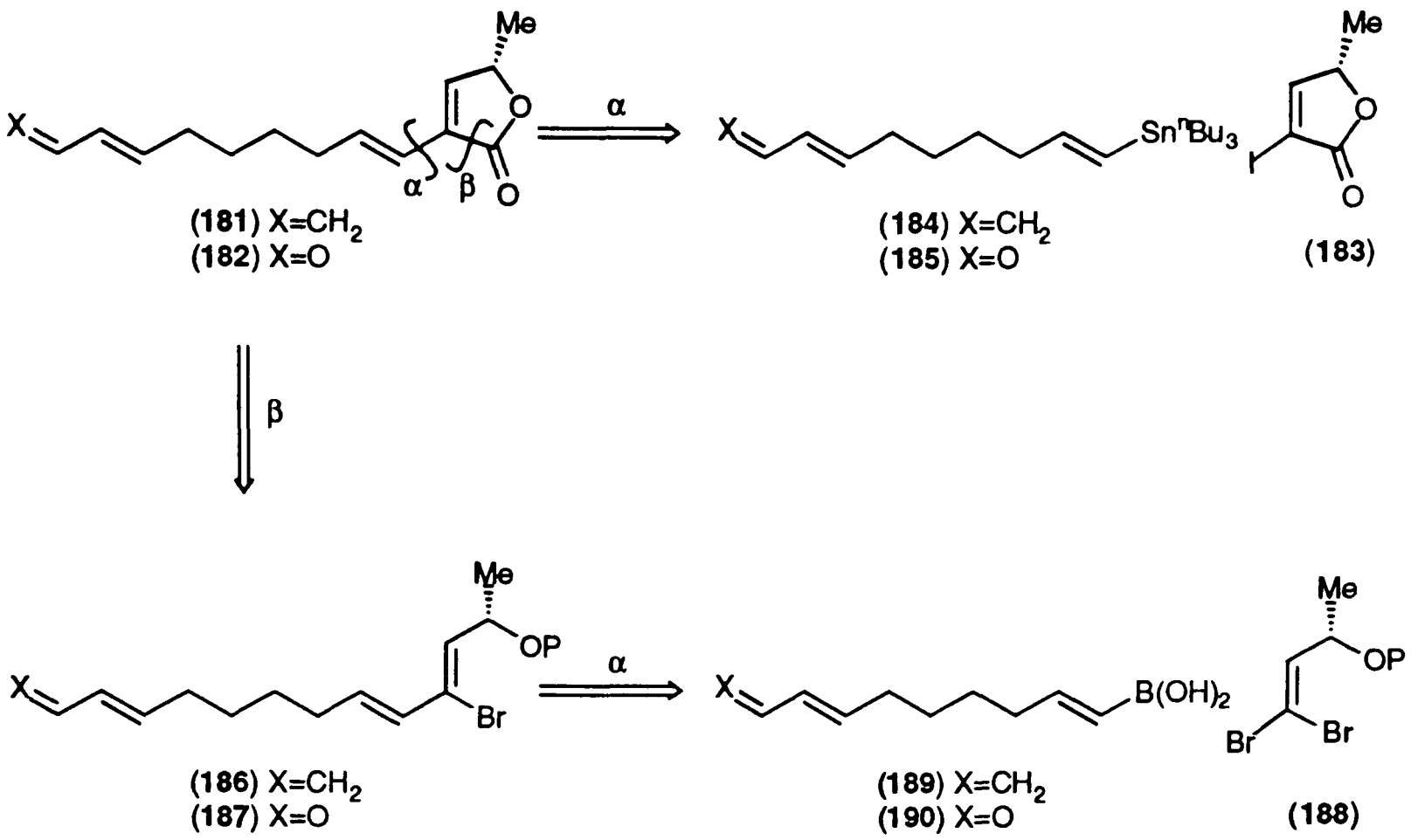


(179) X=CH_2
(172) X=O

(181) X=CH_2
(182) X=O

Scheme 43

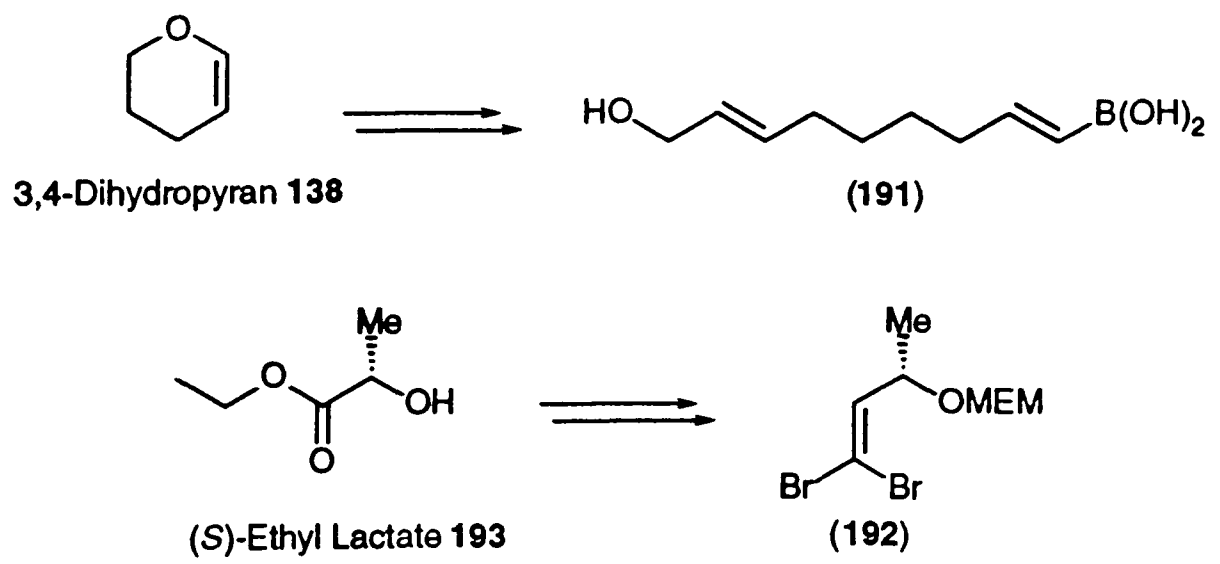
Consideration of the synthesis of the 2-carboxydienes (**181**) and (**182**) identified two key disconnections, attachment of the sidechain to the butenolide (disconnection α), and closure of the butenolide (disconnection β) (Scheme 44). Initial, unsuccessful studies[58] had attempted to connect the side chain (**184** or **185**) to the closed butenolide (**183**) (β then α) *via* a Stille coupling. Subsequent work reversed the two key steps, coupling the side-chain (**189** or **190**) to a butenolide precursor (**188**) *via* a Suzuki coupling to afford (**186** or **187**) which was then closed (α then β).



Scheme 44

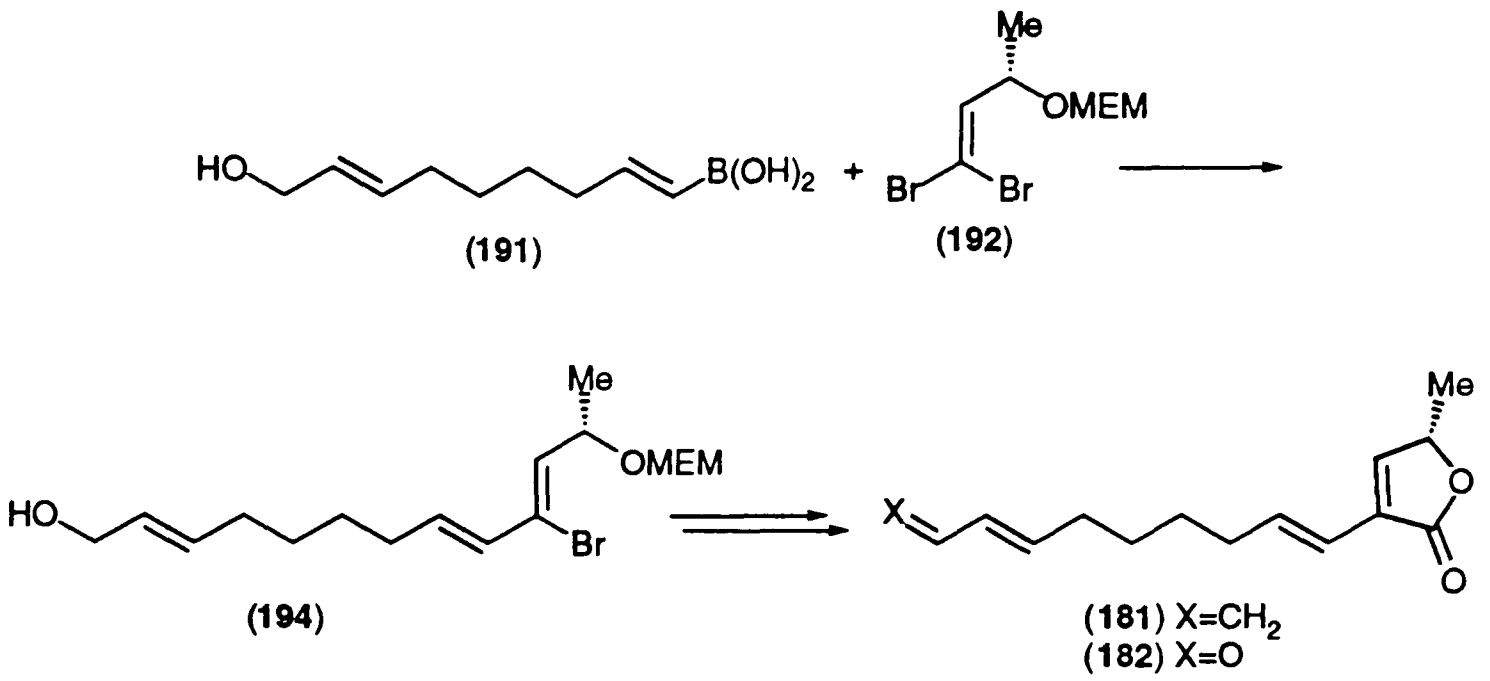
2.2. Previous Synthetic Work

Previous work on this project was completed by Chesworth[58], using the synthetic strategy outlined above (α then β). Thus the two components for the Suzuki coupling (**191**) and (**192**) were prepared from 3,4-dihydropyran **138** and (*S*)-ethyl lactate **193** respectively (Scheme 45).



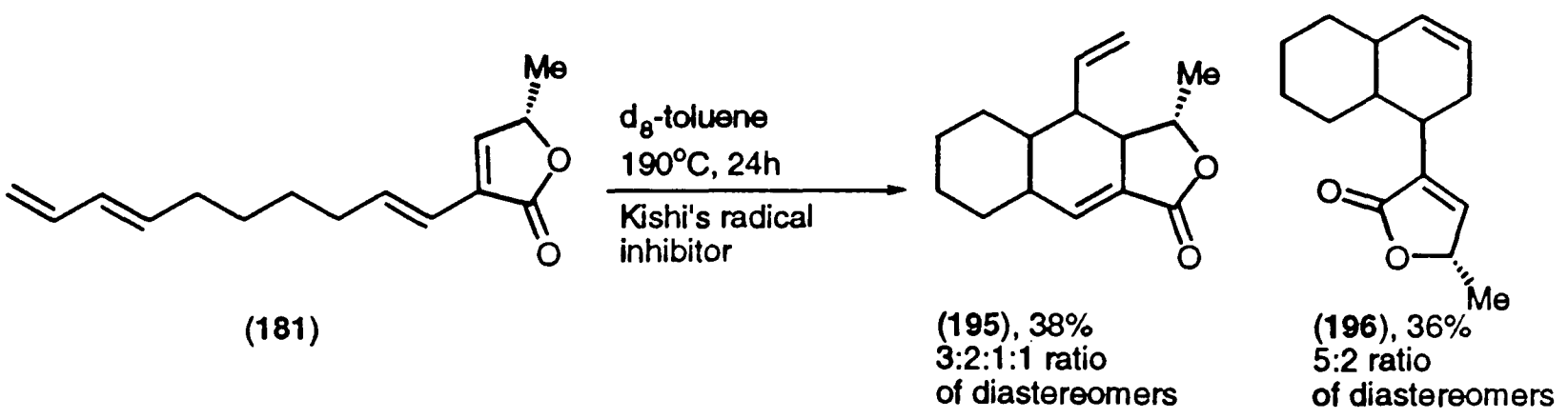
Scheme 45

The two molecules were then connected *via* a Sukuzi coupling affording (**194**), the butenolide closed and the terminus functionalised to afford diene (**181**) and enal (**182**) (Scheme 46).



Scheme 46

The Diels-Alder reaction was initially investigated using diene (**181**). The reaction was found to reach completion in 24 hours at 190°C, affording 38% of the required tricycle (**195**) as a mixture of four diastereomers (3:2:1:1), and 36% of a Diels-Alder product (**196**), which involves the exocyclic alkene of the butenolide as the dienophile (**181**), as a mixture of two diastereomers (5:2) (Scheme 47).

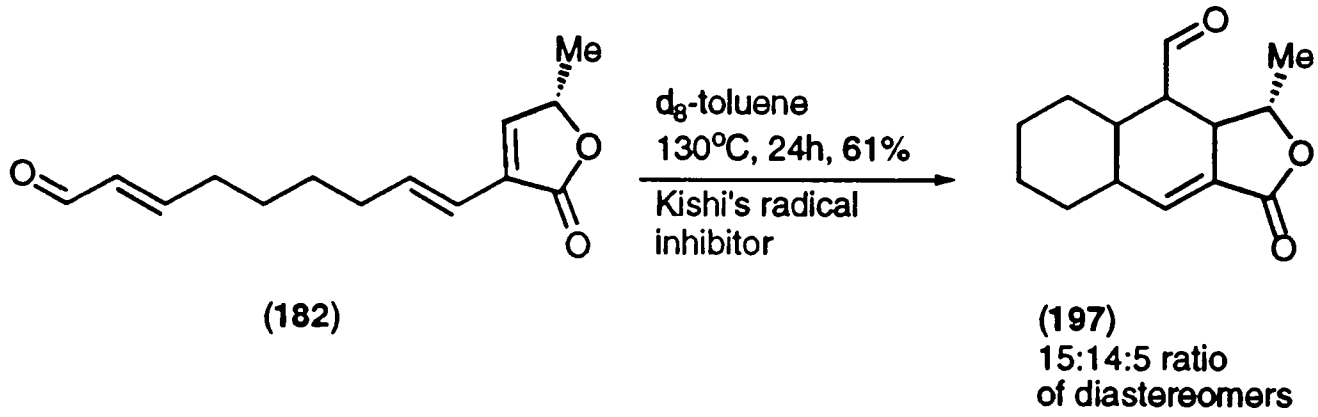


Scheme 47

This result was disappointing due to the fact that two different Diels-Alder reactions were occurring in similar yields to afford different products, especially as theoretical

consideration of the reaction suggested that formation of the second product (**196**) would be disfavoured. Additionally the lack of diastereoselectivity seen in the formation of the required tricycle (**195**) suggested the reaction was not an effective method of synthesising the tricycle (**179**) with the correct stereochemistry.

The results obtained suggested that the required reaction conditions were too vigorous, and methods of allowing the reaction to proceed under milder conditions were considered. The studies on 2-carboxydienes had shown that the Diels-Alder reaction would proceed under milder conditions if a more electron-deficient dienophile was used. The first reaction using this strategy was the Diels-Alder reaction of enal (**182**), which was shown to reach completion in 24 hours at 130°C, affording the required tricycle (**197**) in a 61% yield as a mixture of 3 diastereomers (15:14:5) (Scheme 48).



(182)

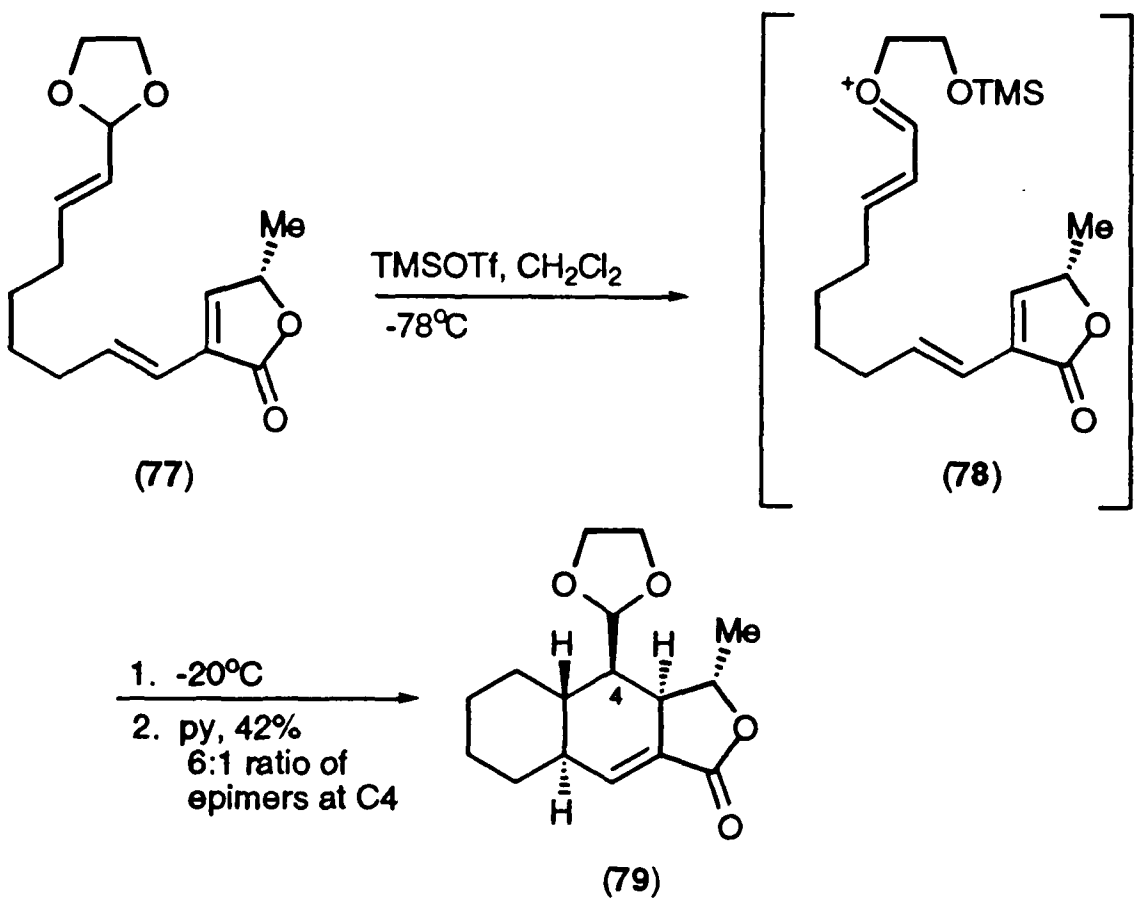
(197)
15:14:5 ratio
of diastereomers

Scheme 48

This result confirmed that the reaction would proceed to completion under milder conditions with a more electron deficient dienophile, and that better chemoselectivity could be achieved under such conditions, with none of the alternative Diels-Alder adduct being observed. However, further reduction of the electron-density of the dienophile was necessary to allow the reaction to proceed under conditions mild enough to increase diastereoselectivity.

Work followed using Lewis acids such as dimethylaluminium chloride and tin tetrachloride[112-118] to coordinate to the aldehyde and further reduce the electron density of the dienophile. The results were disappointing with reduced yields and no improvement in diastereoselectivity. The failure of this approach may be due to the Lewis acids preferentially coordinating to the more basic butenolide carbonyl group and deactivating the diene[58].

The most successful and important result was the use of an allylic oxonium ion, a method originally described by Gassman[59], to generate a dienophile with an electron density low enough to allow the Diels-Alder reaction to proceed below room temperature (Scheme 49).

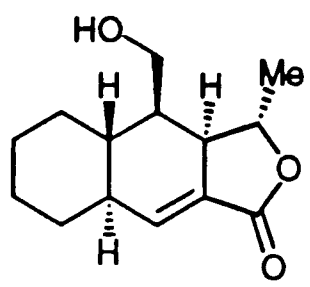


Scheme 49

The success of this procedure offers support to the proposed iminium ion mediated Diels-Alder reaction for the biosynthesis of himgravine **9**, and additionally affords an extremely effective method for preparing the tricyclic portion of the alkaloid. Deprotection of the acetal (**79**), the stereochemistry of which had been tentatively

assigned by NMR studies, afforded a small sample (10mg) of the crystalline alcohol (**30**)[58]. Thus the immediate aim of the project became confirmation of the developed synthetic route and verification of the stereochemistry of the Diels-Alder reaction by X-ray crystallography of the alcohol (**30**) (Figure 20).

2.3. Synthesis of Tricyclic Alcohol (30)

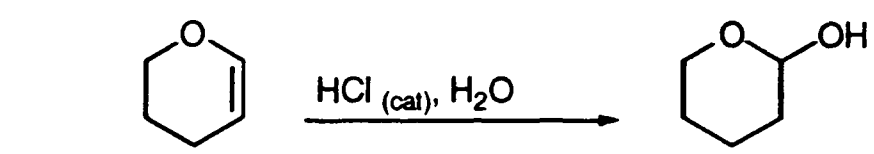


(30)

Figure 20

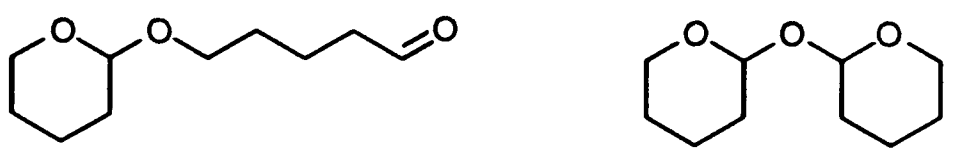
2.3.1. Synthesis of Vinyl Boronic Acid (191)

Synthesis of vinyl boronic acid (**191**) was completed starting from 3,4-dihydropyran **138**. Conversion to 2-hydroxypyran (**198**) was achieved by slow addition of the pyran to a vigorously stirred solution of 0.002M hydrochloric acid[119], which was then stirred overnight (Scheme 50). The reaction concentration and acid molarity were kept extremely low to avoid the formation of byproducts, such as dimers (**199**) and (**200**) (Figure 21). This method afforded a reproducible yield of 35-40%, which could be used without further purification.



3,4-Dihydrofuran 138 **(198)**

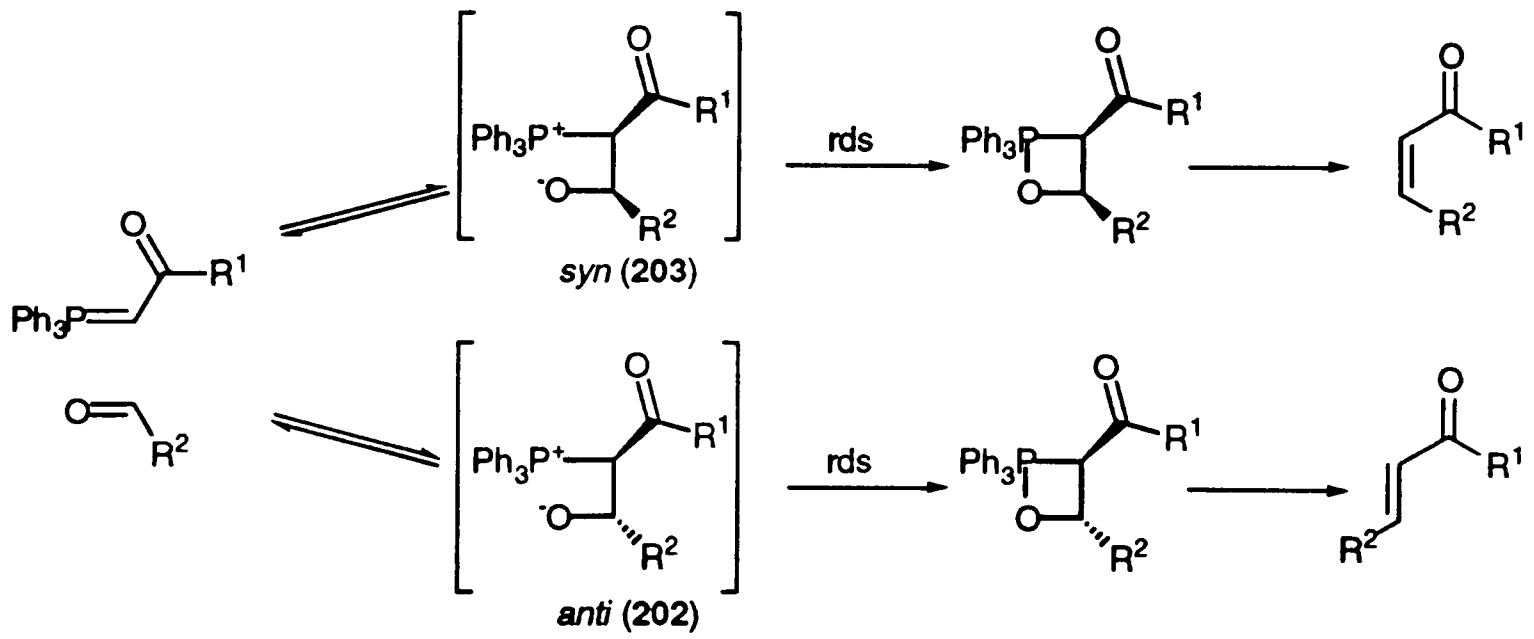
Scheme 50



(199) **(200)**

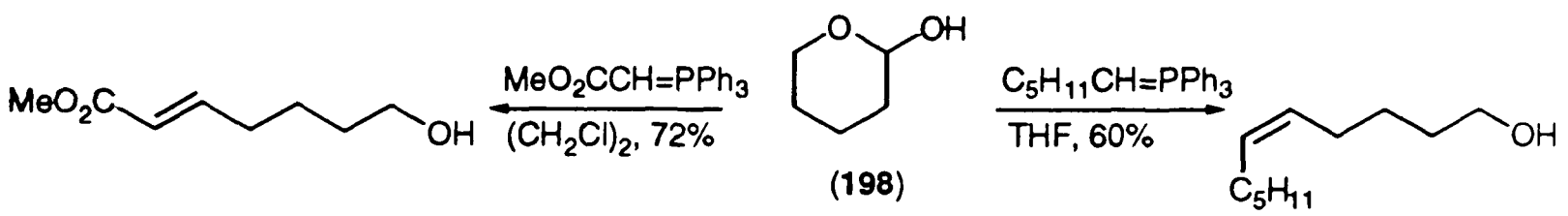
Figure 21

Formation of the *E*-alkene (**201**) was completed using a Wittig reaction. To obtain the required *E*-geometry it was necessary to use a stabilised Wittig reagent, carboethoxymethylenetriphenylphosphorane. The requirement for a stabilised Wittig reagent[120] arises from such species reacting under thermodynamic control[121]. Thus, as the formation of the intermediate is reversible, it is mainly the *anti*-isomer (**202**) which forms the oxaphosphatane *via* a more favourable transition state, which undergoes *syn* elimination to afford the *E*-alkene (Scheme 51). Simple alkyl phosphoranes, which are not resonance stabilised, are believed to react under kinetic control to afford *Z*-alkenes. Recent work however, has suggested that there are additional factors influencing the reaction and investigations are continuing[122,123].



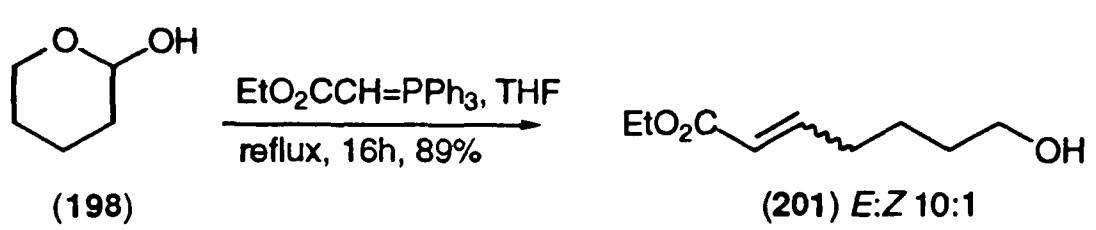
Scheme 51

The above observations have been confirmed in Wittig reactions using 2-hydroxypyran (**198**), where stabilised phosphoranes afford *E*-isomers[124] and unstabilised afford *Z*-isomers[125] (Scheme 52).



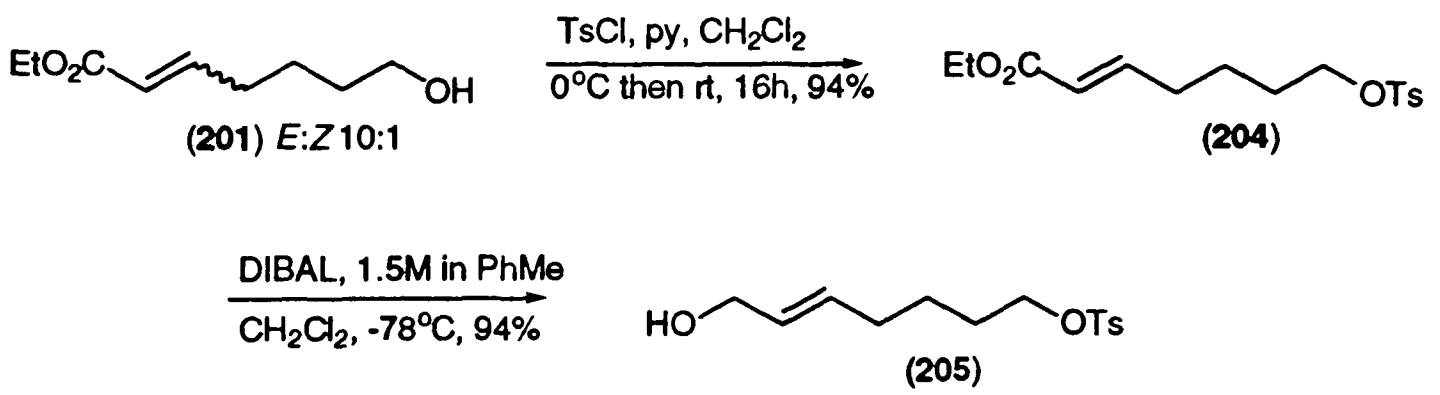
Scheme 52

The Wittig reaction of 2-hydroxypyran (**198**) with carboethoxymethylenephosphorane afforded ester (**201**) in an *E*:*Z* ratio of 10:1 (Scheme 53). Previous work had shown that use of the less bulky carbomethoxymethylenephosphorane gave a lower *E*:*Z* ratio of 6:1, but that the more bulky and more expensive carbo-*tert*-butoxymethylene phosphorane did not improve the previously obtained *E*:*Z* ratio of 10:1.



Scheme 53

Ester (**201**) was converted to tosylate (**204**), at which stage the *E* and *Z* isomers could be separated by careful flash chromatography. Reduction of the ester functionality using DIBAL (2.2eq) afforded allylic alcohol (**205**) (Scheme 54).



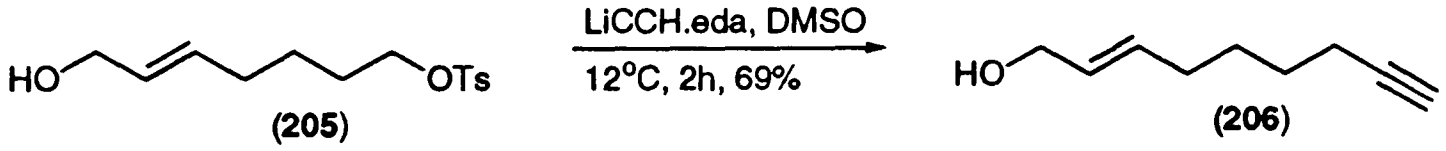
Scheme 54

Introduction of an alkyne portion by displacement of the tosyl group was achieved using lithium acetylide ethylene diamine complex (Scheme 55). This procedure has

been widely demonstrated[126,127] and the optimised conditions for these reactions have been identified:

- Dimethyl sulfoxide as the solvent.
- Concentration of the lithium acetylide slurry should be 2 molar.
- Reaction temperature 8-20°C.
- Slow addition of the substrate over a 20 minute period.

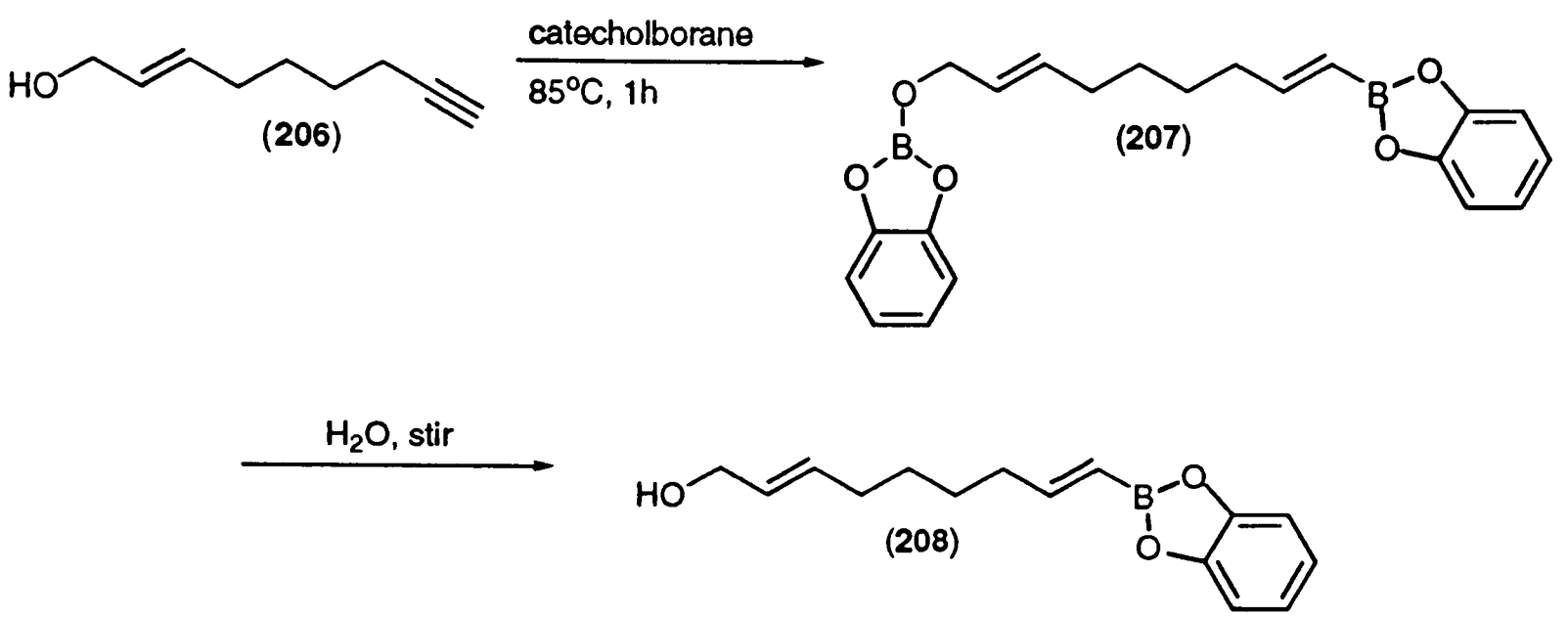
Thus, to a cooled 2M slurry of lithium acetylide ethylene diamine complex in DMSO was added tosylate (**205**) over a 20 minute period. The reaction mixture was maintained at 12°C for 2 hours at which time the reaction was quenched. With longer reaction times base catalysed isomerisation of the terminal alkyne into the alkyl chain had been observed[128]. Isolation of the product (**206**) was problematic due to volatility and solubility in aqueous media; however, once these problems had been overcome a reproducible yield of 60-65% could be achieved (Scheme 55).



Scheme 55

The final step in this sequence involved conversion of the alkyne (**206**) to boronic acid (**191**). This was achieved *via* a two step procedure; initial hydroboration with a mono-hydroborane followed by hydrolysis. The hydroboration is limited to phenoxyboranes, as alkoxyboranes are too unreactive due to significant overlap of the oxygen atom lone pairs with the empty p-orbital on the boron[129,130]. The empty p-orbital is essential to the hydroboration mechanism as it is used to coordinate to a π-bond of the alkyne prior to delivery of the hydrogen and boron atoms, forming a 'π-complex'. Phenoxyboranes are more reactive due to delocalisation of the oxygen atom lone pairs into the aromatic π-system. The reagent of choice for such reactions is catecholborane which gives excellent yields, high stereo- and regioselectivity, and being less reactive than borane or other dialkylboranes, no over-reduction is

observed. Reaction of alkyne (**206**) with neat catecholborane (2.2eq) afforded hydroxy borate ester (**207**). Complete hydrolysis of (**207**) was then achieved by shaking the crude product in water for 1 hour, followed by stirring for 16 hours[131,132]. It was found that such a procedure was necessary for complete hydrolysis, as stirring removed only the hydroxy borate ester to afford (**208**). Studies using co-solvents, elevated temperatures and sonication to complete hydrolysis had failed, thus it seems that the shaking is essential to yield boronic acid (**191**) (Scheme 56).



Scheme 56

Rapid flash chromatography of boronic acid (**191**) was required to avoid decomposition[131], affording the product as a colourless foam in a 65-70% yield.

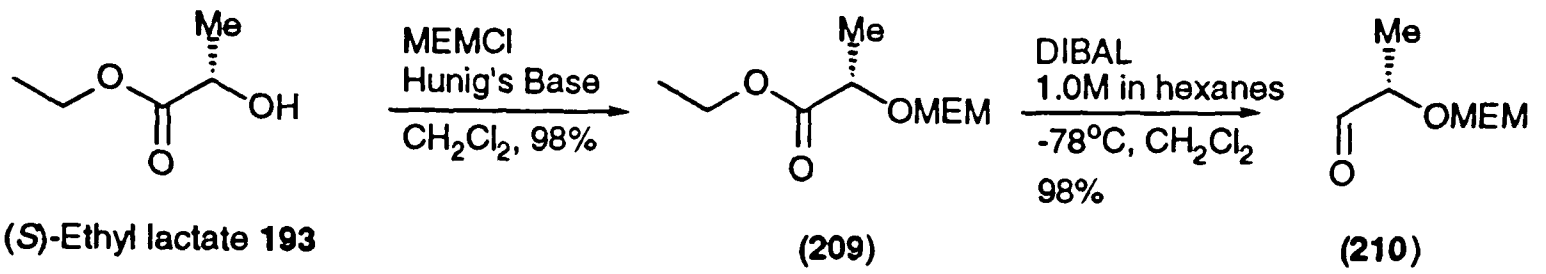
2.3.2. Synthesis of Dibromoalkene (192)

Synthesis of dibromoalkene (**192**) was completed using chemistry described by Braun[133]. This chemistry involved conversion of the readily available chiral starting material, (*S*)-ethyl lactate **193**, to dibromoalkene (**192**) *via* a three step procedure:

- MEM protection of the alcohol.

- Reduction of the ester to the aldehyde.
- Dibromoalkenation using a Corey-Fuchs reaction.

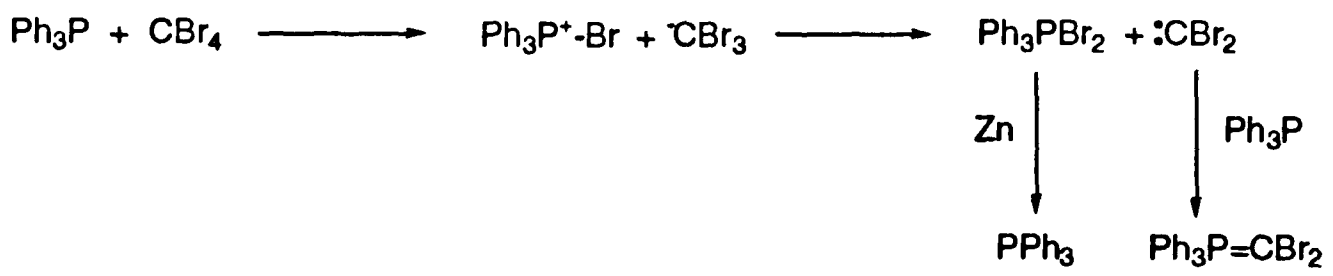
MEM protection was achieved using MEMCl and Hunig's base to afford ester (**209**)[134]. The crude product was then carefully reduced using DIBAL, with the temperature maintained below -75°C to avoid side-reactions, to afford aldehyde (**210**)[135] (Scheme 57).



(*S*)-Ethyl lactate **193** (**209**) (**210**)

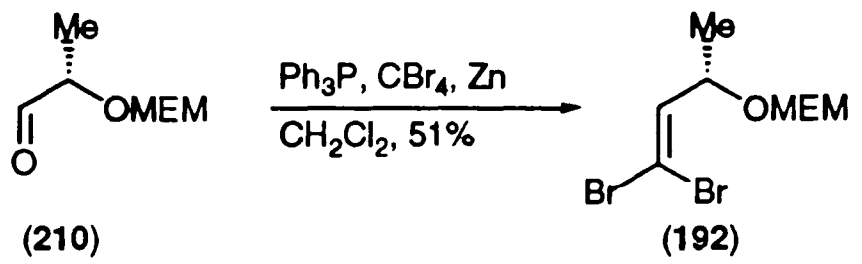
Scheme 57

The dibromoalkenation was completed using a Corey-Fuchs reaction. This reaction can be envisaged as a one-carbon Wittig reaction, the required reagent being prepared *in situ* followed by addition of the aldehyde substrate[136,137]. The reagent can either be prepared using a 2:1 ratio of Ph_3P to CBr_4, or a ratio of 1:1:1 Ph_3P to CBr_4 to zinc dust (Scheme 58). The purpose of the zinc is to reduce the produced Ph_3PBr_2 back to Ph_3P.



Scheme 58

The methodology using zinc dust was utilised as less phosphine is needed and the isolation procedure is simpler[136]. Preparation of the reagent by careful addition of a solution of CBr_4 to a cooled suspension of Ph_3P and zinc dust, followed by addition of the aldehyde (**210**) at room temperature afforded dibromoalkene (**192**) in reasonable yield (Scheme 59).

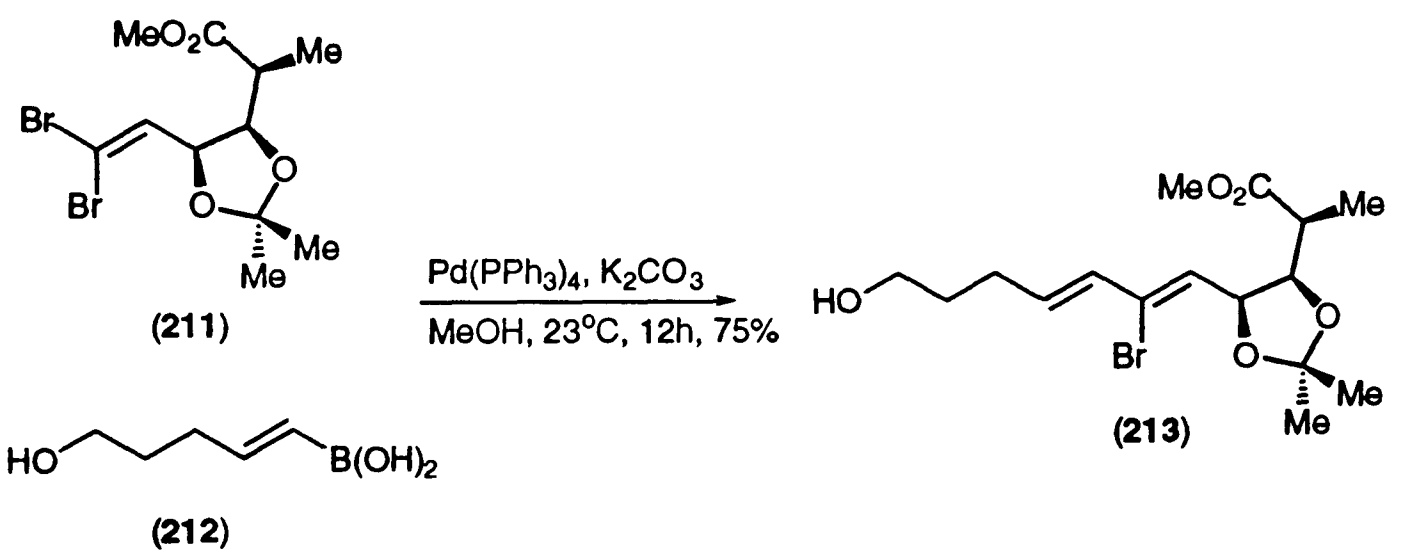


(210) **(192)**

Scheme 59

2.3.3. Synthesis of Enal Butenolide (182)

The Suzuki coupling of boronic acid (**191**) to dibromoalkene (**192**) was originally completed using chemistry developed by Roush, who had coupled dibromoalkene (**211**) to vinyl boronic acid (**212**) affording (**213**)[138] (Scheme 60).

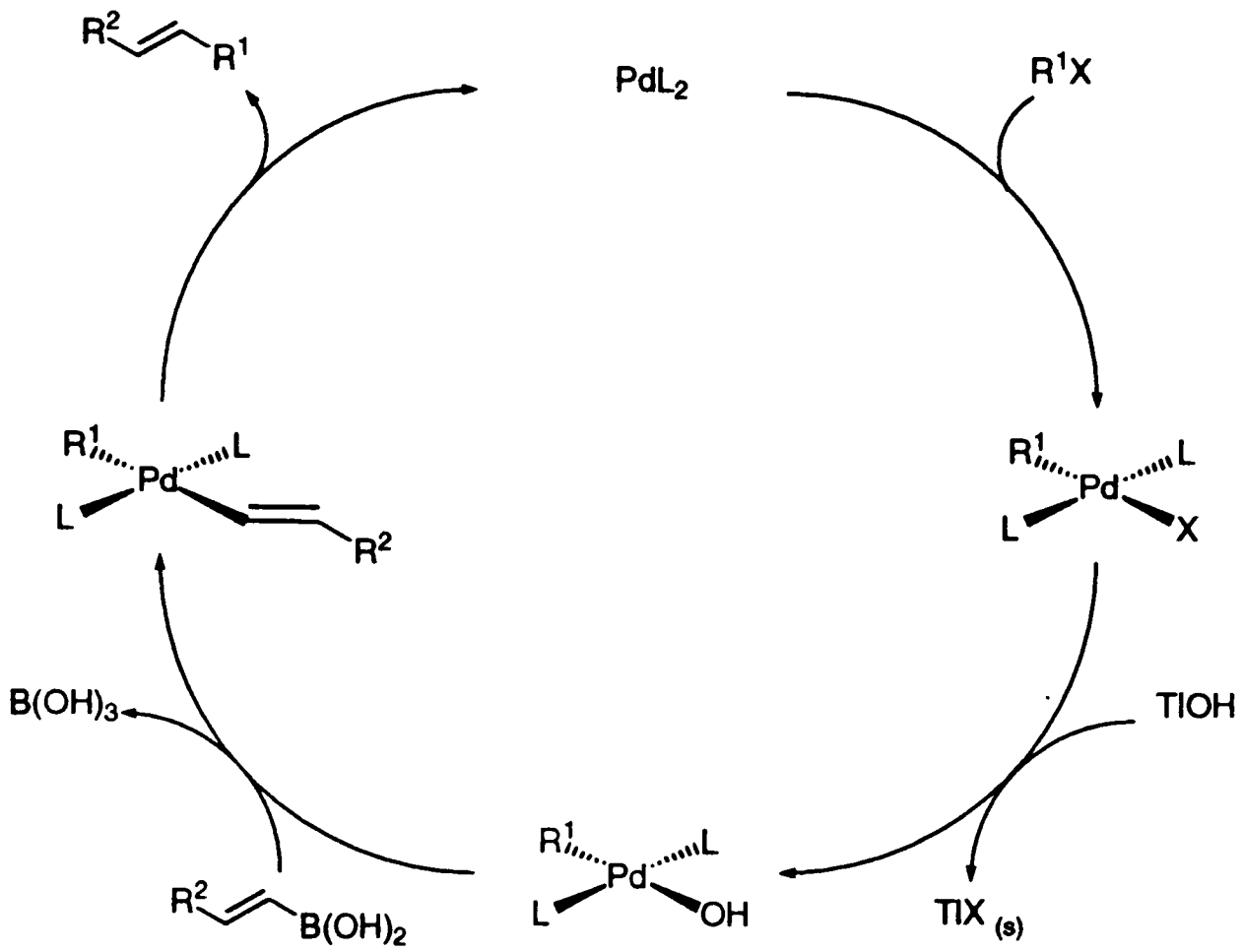


(211) **(212)** **(213)**

Scheme 60

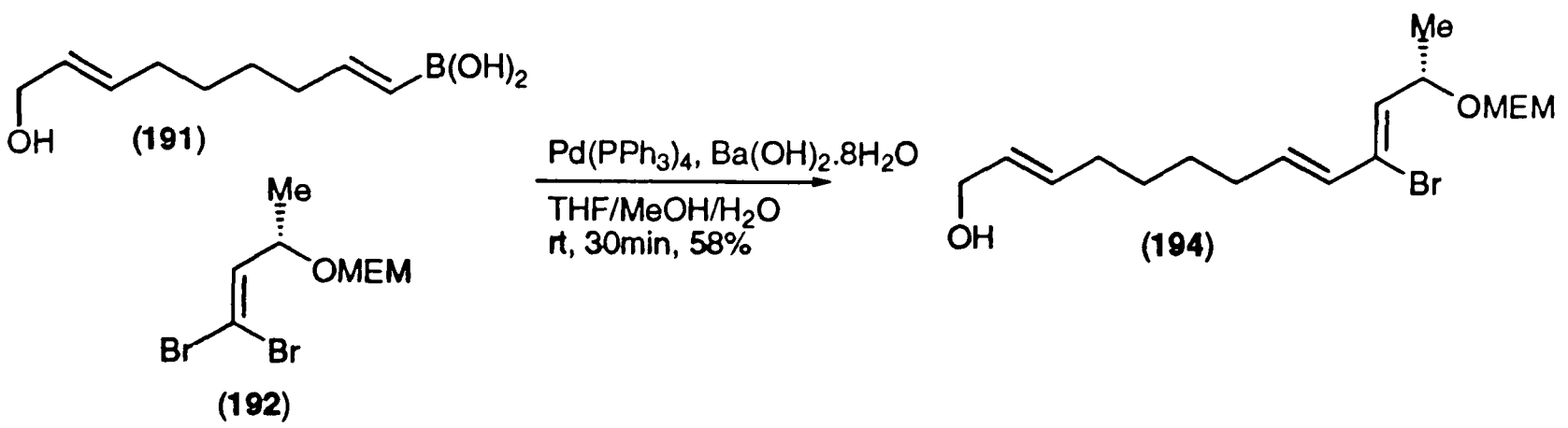
However for the reaction to reach competition it was necessary to heat to reflux for 16 hours, and the yield varied between 30% and 50%. Thus, it was decided that changing the reaction conditions in an attempt to improve the yield was necessary. Work by Kishi on the total synthesis of palytoxin had shown that the use of species such as thallium hydroxide can accelerate the Suzuki coupling by up to 1000 times[139]. Suzuki had found that a base was required as it exchanged with the halide on the oxidative addition complex, then was eliminated from the palladium-boron complex allowing transmetallation of the vinyl group on the palladium[140]. Species such as thallium hydroxide are thought to increase the rate by coordination to the halide atom

of the oxidative addition complex followed by precipitation of the insoluble thallium halide (Scheme 61). As replacement of the halide ion is the rate determining step in the coupling reaction, this modification gives the dramatic rate accelerations observed.



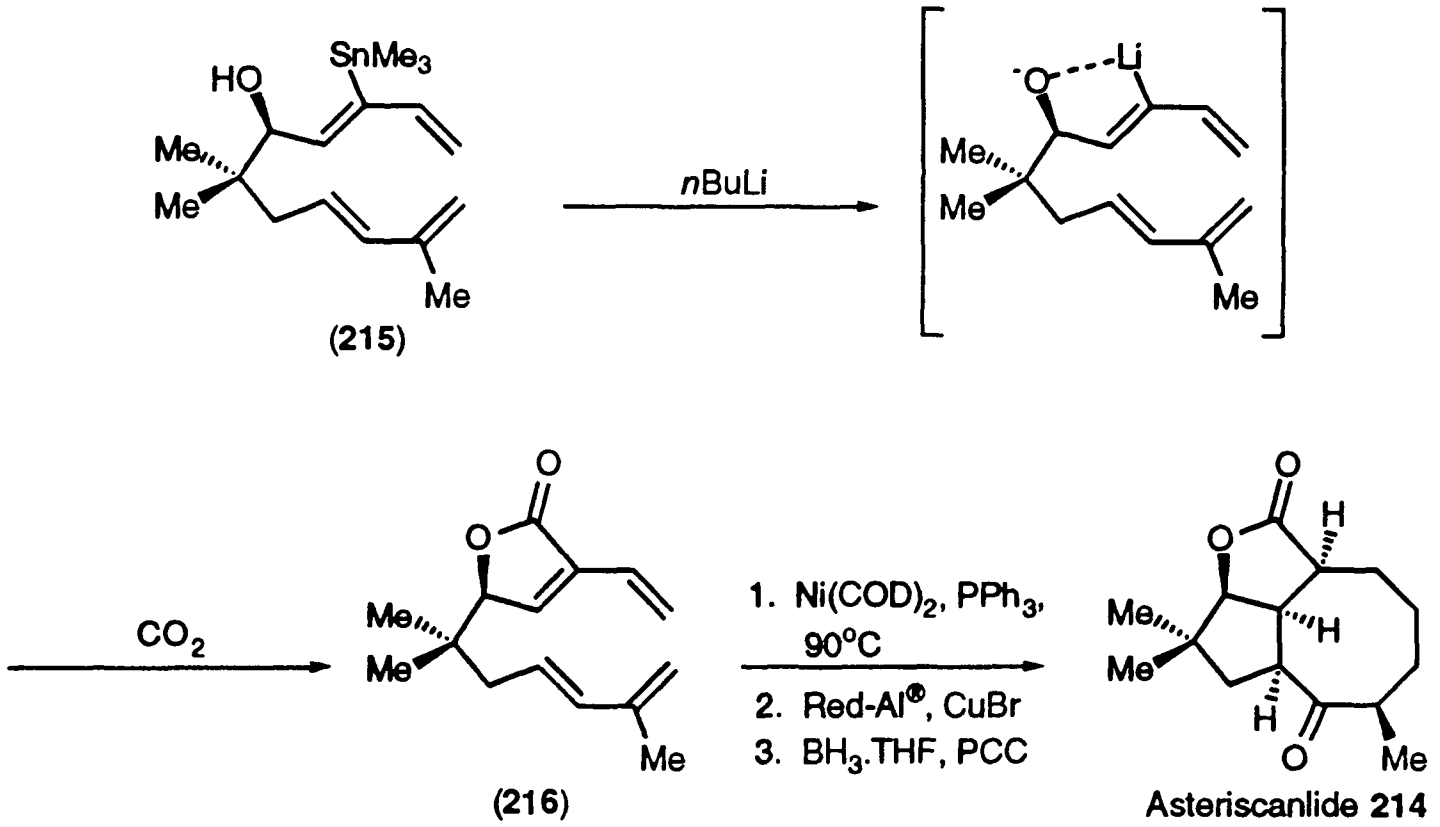
Scheme 61

As thallium hydroxide is highly toxic this procedure is problematic, but subsequent reports have shown that barium hydroxide can be used as a less harmful alternative[141,142]. Thus, to boronic acid (**191**) in THF/MeOH was added barium hydroxide (4.0eq) in water, following which dibromoalkene (**192**) and tetrakistriphenylphosphine palladium (0) in THF were added producing a pale green precipitate. The reaction was shown to be complete after 30 minutes at ambient temperature, and on isolation of the coupling product (**194**) the yield had improved to 58% (Scheme 62).



Scheme 62

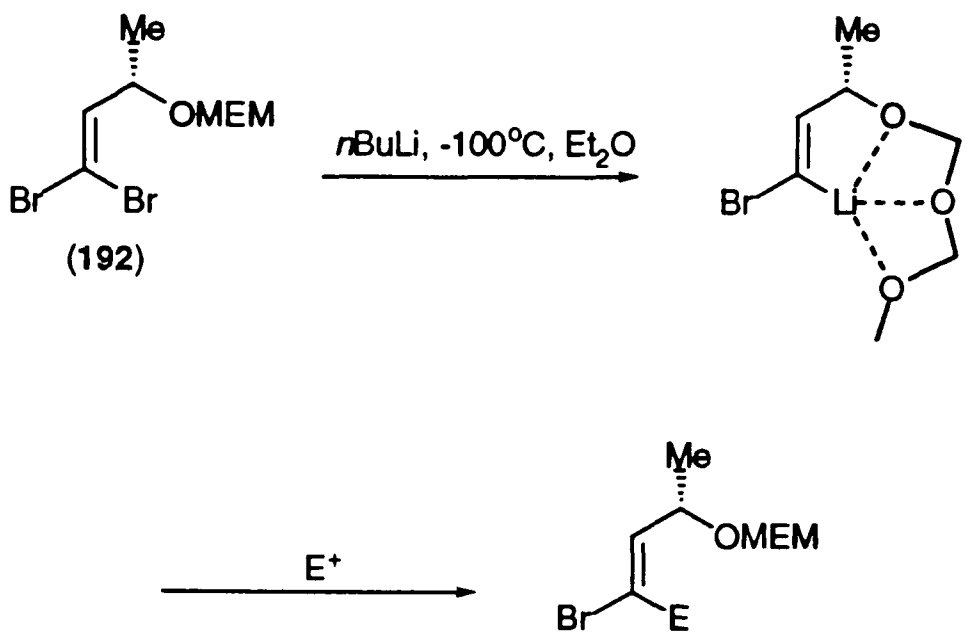
The final steps to enal butenolide (**182**) involve closure to the butenolide, the second key step identified in the disconnection, and oxidation of the allylic alcohol to the enal. Closure of the butenolide was completed using chemistry developed by Wender[143] who had shown, as part of a synthesis of asteriscanolide **214**, that transmetallation[144] and carboxylation of stannane (**215**) followed by lactonisation afforded butenolide (**216**) (Scheme 63).



Scheme 63

The importance of the chelating hydroxyl group to stop reaction of the anion *via* the allylic alkene was noted, and use of the MEM group in the synthesis of enal butenolide (**182**) had been deliberate, as such groups are known to be effective

lithium-coordinators, ensuring the correct regiochemistry for the carboxylation (Scheme 64)[133].



Scheme 64

Protection of the allylic alcohol as a silyl ether[145] to afford bromide (**217**) was necessary as the transmetallation reaction failed to proceed with alcohol (**194**). Using TBSCl with imidazole in THF/CH_2Cl_2 afforded bromide (**217**), following which the transmetallation reaction was attempted. The reaction turned out to be capricious and careful control of the reaction conditions was necessary:

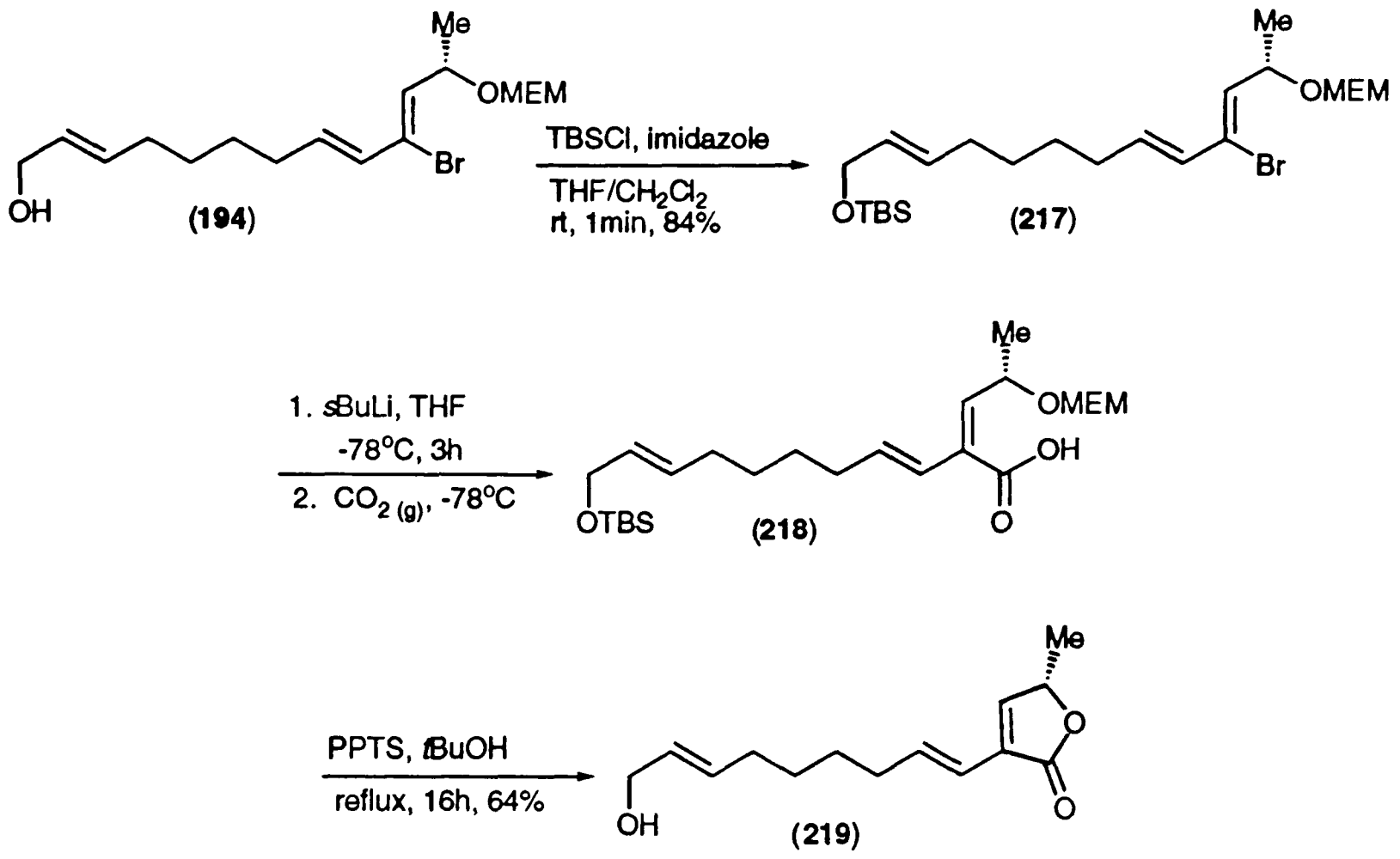
- *s*BuLi was used in preference to *n*BuLi, as this stronger base afforded higher yields (an increase of 10-20%).

- A maximum internal reaction temperature of -75°C.

- The bromide (**217**) was dried immediately prior to use.

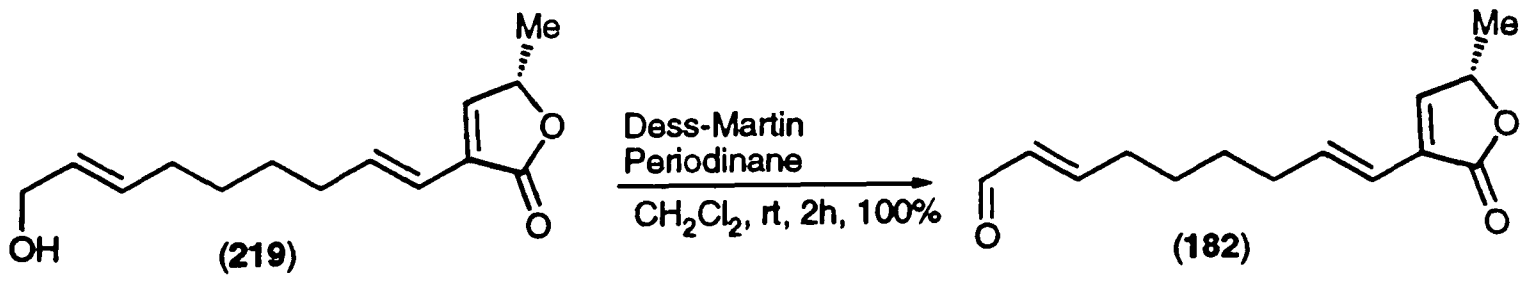
- CO_2 from a lecture bottle was passed through a drying column before use. CO_2 from Cardice® was found to be too wet for use.

The obtained crude acid (**218**) was deprotected using PPTS in *t*BuOH[146], which removed the MEM group allowing lactonisation, and the use of extended reaction times additionally removed the TBS group to afford allylic alcohol (**219**) (Scheme 65).



Scheme 65

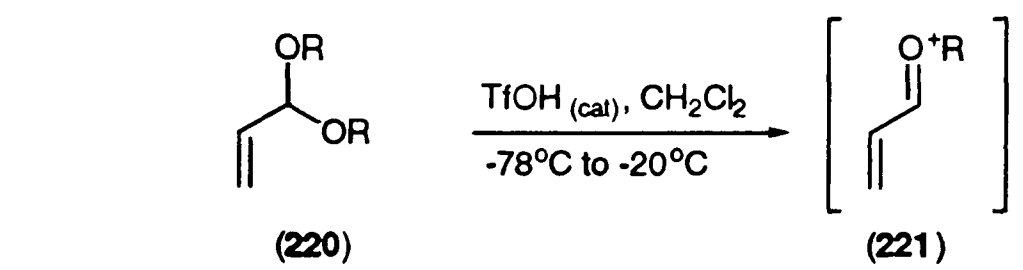
The final step in preparation of enal butenolide (**182**) was oxidation of the allylic alcohol (**219**). Originally TPAP/NMO[147,148] had been used affording the enal (**182**) in a 70-80% yield. However, oxidations using the Dess-Martin periodinane[149] have been shown to regularly give quantitative yields[150], and additionally the procedure is simpler than the use of TPAP which requires anhydrous conditions. Simply stirring alcohol (**219**) with the Dess-Martin periodinane in CH_2Cl_2 at ambient temperature for 2 hours afforded enal (**182**) in quantitative yield, requiring no further purification (Scheme 66).



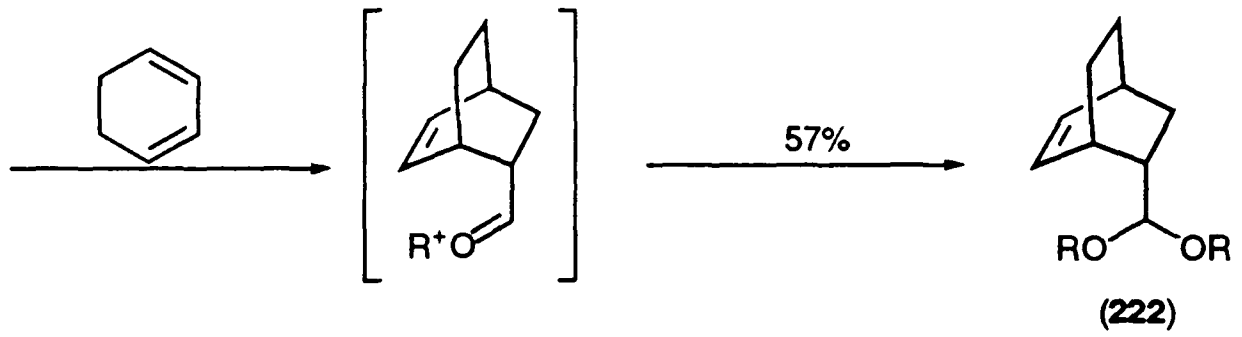
Scheme 66

2.3.4. Diels-Alder Reaction of Enal Butenolide (182)

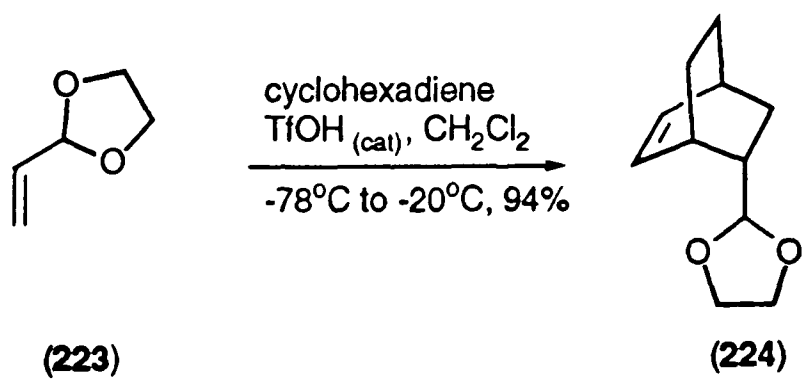
The chemistry developed by Gassman[59,151,152] involved the use of acrolein acetals (**220**), which in the presence of Lewis or protic acids, form oxonium ions (**221**) containing an allylic cation resonance structure. These cations (**221**) are highly reactive dienophiles and undergo cycloadditions with dienes at temperatures as low as -78°C to afford (**222**). Cyclic acetals (**223**) afford better yields than acyclic acetals (**220**); this observation is attributed to diffusion of the alcohol away from the oxonium ion (**221**). The reaction favours the *endo* product (**224**), an additional reason for use of this methodology (Scheme 67).



(**220**) (**221**)



(**222**)

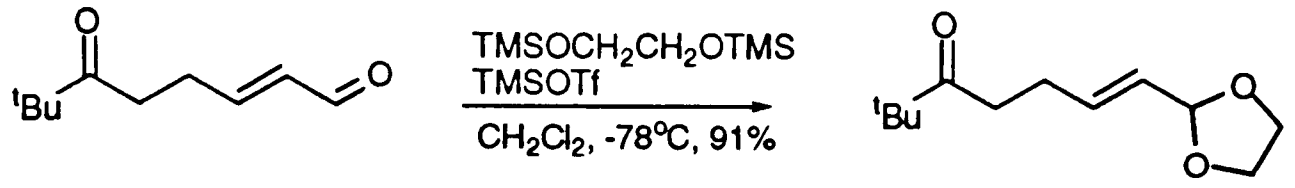


(**223**) (**224**)

Scheme 67

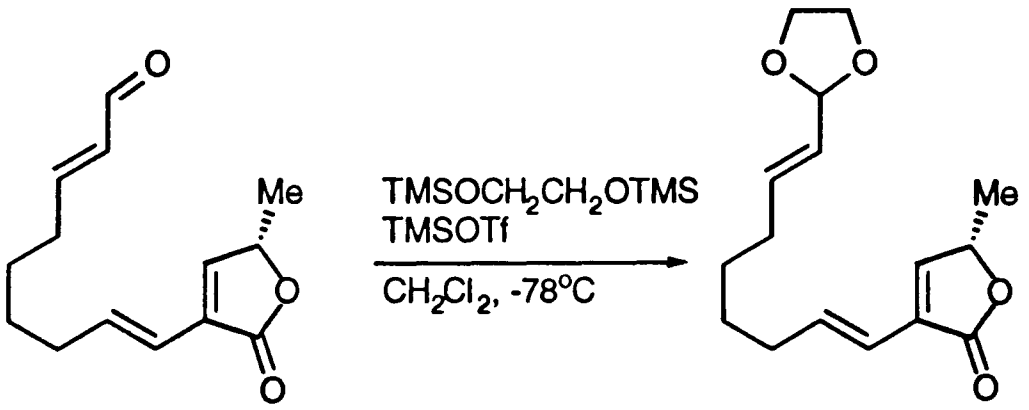
Conversion of enal butenolide (**182**) to acetal (**77**) was achieved using conditions developed by Noyori, as normal acetalisation of α,β enals using Dean-Stark conditions usually results in migration of the alkene to the β,γ position. The Noyori

procedure involves the use of low temperature conditions, using 1,2-bis(trimethylsilyloxy)ethane as the acetal source and TMSOTf as the catalyst[153,154] (Scheme 68).

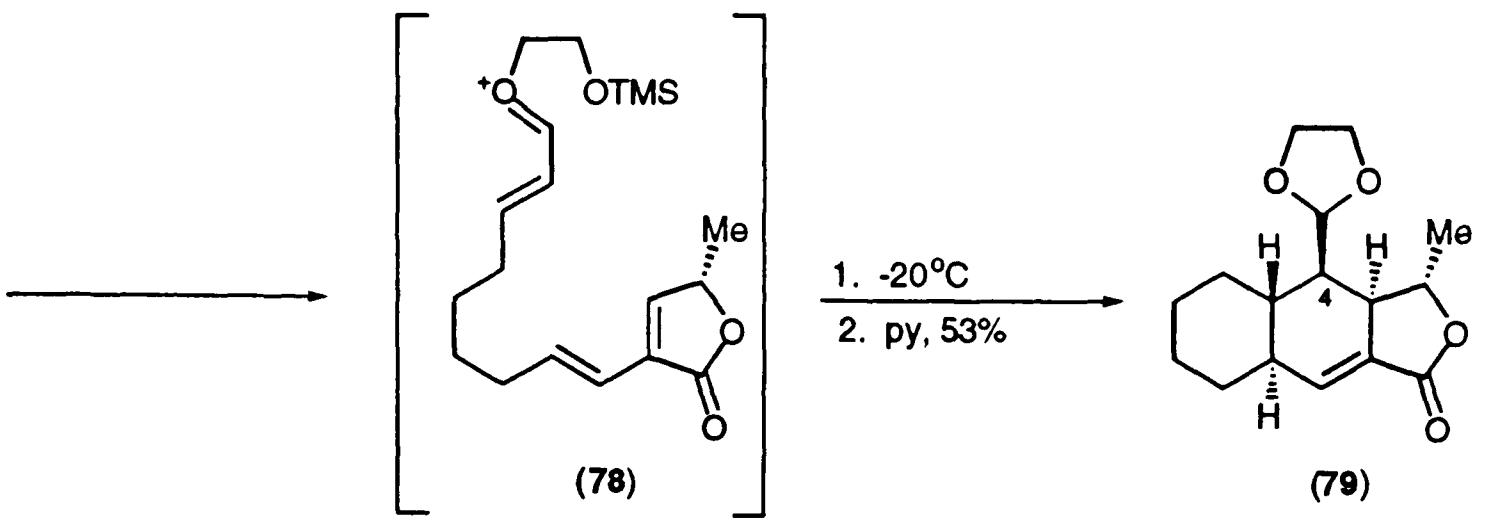


Scheme 68

Thus using optimised conditions of 1,2-bis(trimethylsilyloxy)ethane (3.0eq) and TMSOTf (1.0eq), introduced to a solution of enal butenolide (**182**) at -78°C, afforded acetal (**77**), which could be isolated if the reaction was quenched by addition of pyridine. However, if the acetalisation reaction was allowed to warm to -20°C, the presence of TMSOTf, acting as a Lewis acid, promoted a Gassman Diels-Alder reaction *via* the formation of an oxonium ion intermediate (**78**). Tricyclic acetal (**79**) was isolated in a 40-50% yield (53% best yield) with a 40:1 ratio of diastereomers at C4 (Scheme 69), a marked improvement on the previously observed best diastereomeric ratio of 6:1.



(182) **(77)**



Scheme 69

If the reaction is performed in the absence of the 1,2-bis(trimethylsilyloxy)ethane only a 20% yield of the tricyclic acetal (**79**) was obtained as a mixture of 3 diastereomers, indicating that it is indeed an oxonium ion derived from the acetal (**77**) which is responsible for the improved cycloaddition reaction, rather than a TMSOTf catalysed Diels-Alder reaction of the enal (**182**) followed by acetalisation[58]. As noted before, this is an important result as it offers precedent for the proposed iminium ion mediated Diels-Alder reaction for the construction of the Class 1 *Galbulimima* alkaloids, and allows an extremely efficient method for construction of the tricyclic portion of himgravine **9**, forming 2 new σ-bonds, one new π-bond and 4 stereocentres in one step.

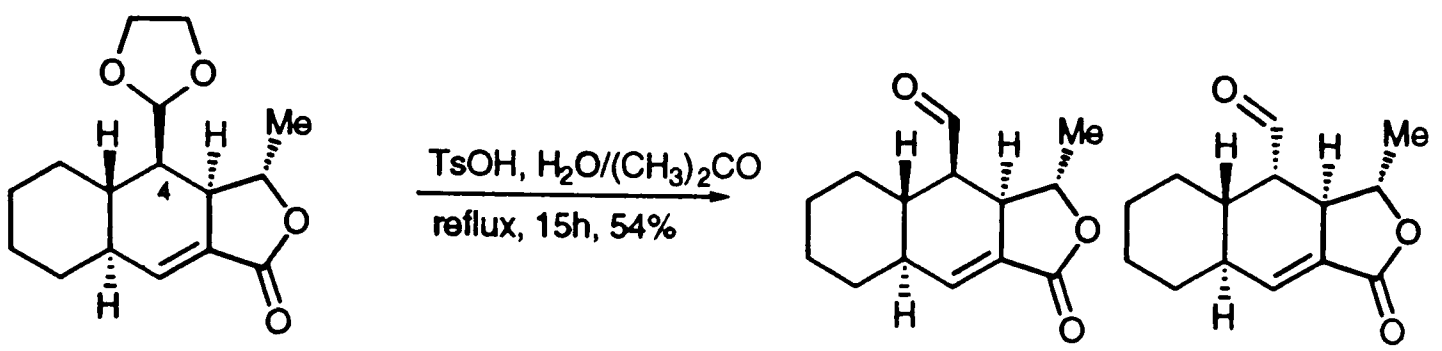
2.3.5. Conversion of Acetal (79) to Alcohol (30)

Deprotection of acetal (**79**) to aldehyde (**172**) proved to be problematic due to the following problems:

- The aldehyde (**172**) and acetal (**79**) have identical chromatographical R_f values, thus it is not possible to separate them by standard methods.

- Removal of the acetal functionality required vigorous acid-catalysed conditions (3.0eq TsOH, water:acetone, reflux) for full deprotection. However, use of these conditions caused epimerisation at C4 to yield diastereomeric aldehydes (**172**

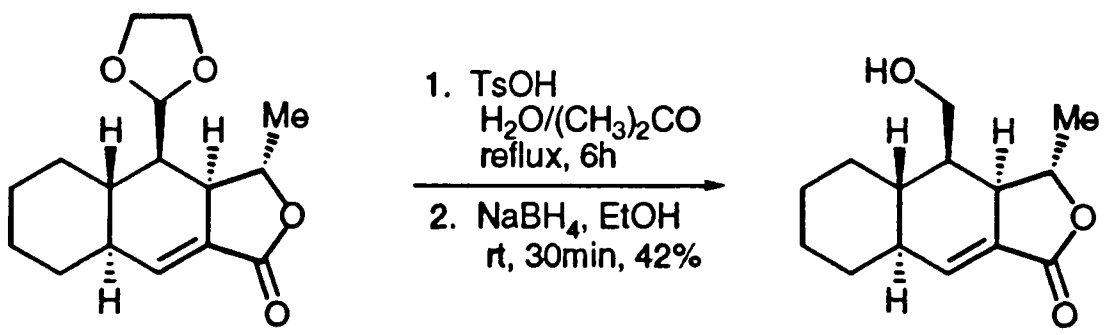
and **173**). Use of reagents such as DDQ[155] were also found to give epimerisation (Scheme 70).



(79) **(172)** Ratio 3:1 **(173)**

Scheme 70

Shorter reaction times using the same conditions had been shown to give only a 70% conversion to the aldehyde; however, no epimerisation was seen. This result suggests that epimerisation of the aldehyde (**172**) occurs as a result of the long reaction times required for full deprotection. Using the shorter reaction times afforded a 7:3 ratio of aldehyde (**172**):acetal (**79**), which could not be separated by chromatography. Thus it was necessary to reduce the aldehyde (**172**) to alcohol (**30**) *in situ* using sodium borohydride, at which stage the alcohol (**30**) and acetal (**79**) could be separated (Scheme 71).



(79) **(30)**

Scheme 71

This two step procedure is an inefficient method of deprotection, particularly as it is aldehyde (**172**) that is required for the proposed Julia coupling to piperidine (**156**). Alternative methods of acetal cleavage involve the use of $Pd(MeCN)_2Cl_2$[156] or transketalisation to the *bis*-methoxy acetal followed by aqueous hydrolysis[157]. Work to

investigate these methods of deprotection on a model system, and to determine whether any epimerisation occurred during use, was started (Section 2.4). However, the synthesis of alcohol (**30**) remained the immediate aim of the project as, unlike the acetal (**79**) and aldehyde (**172**), the alcohol (**30**) was crystalline.

2.3.6. Crystallisation of Alcohol (30)

Initial attempts to grow crystals suitable for X-ray diffraction analysis involved crystallisation from diethyl ether with petroleum ether 30-40°C, then ethyl acetate with petroleum ether 40-60°C. Both solvent systems were shown to cause problems (presumably due to their components volatility), with extremely rapid crystallisation, producing large amounts of poor quality crystals. On changing the solvent system to ethyl acetate with benzene, crystals of sufficient quality were obtained (Figure 22).

The crystal structure was determined by James Bartleet at the Department of Chemical Crystallography (Appendix 1). The structure proved the absolute stereochemistry of the alcohol (**30**), confirming the transition state of the Diels-Alder reaction as having afforded the *endo* cycloadduct, and most importantly, offering the most compelling piece of evidence so far for the construction of the Class 1 *Galbulimima* alkaloids *via* an intramolecular Diels-Alder reaction.

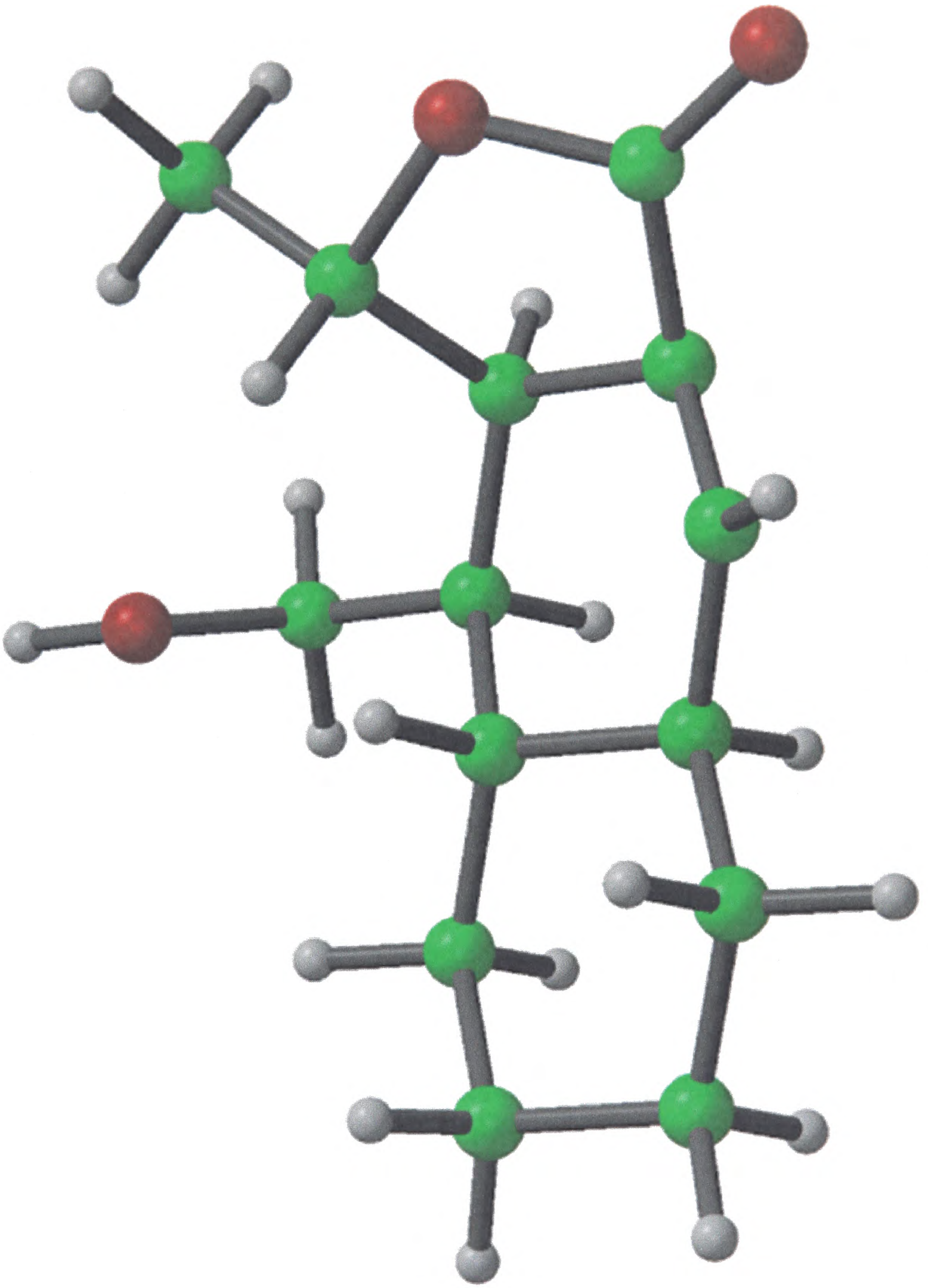
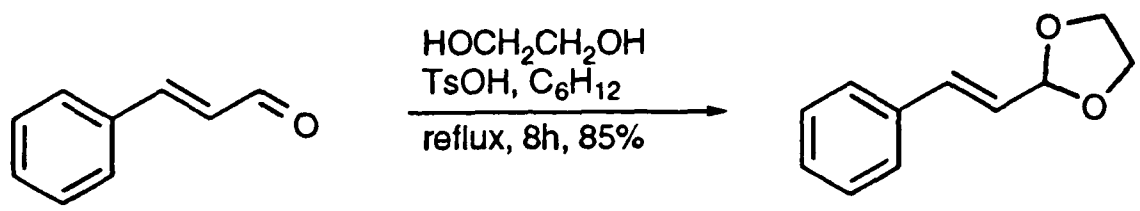


Figure 22

2.4. Synthesis of an Acetal Deprotection Model

Developing conditions for complete cleavage of the acetal functionality of tricycle (**79**), without causing epimerisation represented an important piece of methodology that would be required for the total synthesis of himgravine **9** and himbacine **1**. Studies on such a reaction require a model that would undergo epimerisation under the previously used conditions (TsOH, acetone/water), and would thus demonstrate whether other deprotection conditions cause epimerisation[158,159]. It was decided to synthesise a number of model systems using the previously demonstrated Gassman methodology. This would allow construction of cyclic systems *via* a Diels-Alder reaction, containing an acetal functionality, which would then allow deprotection studies.

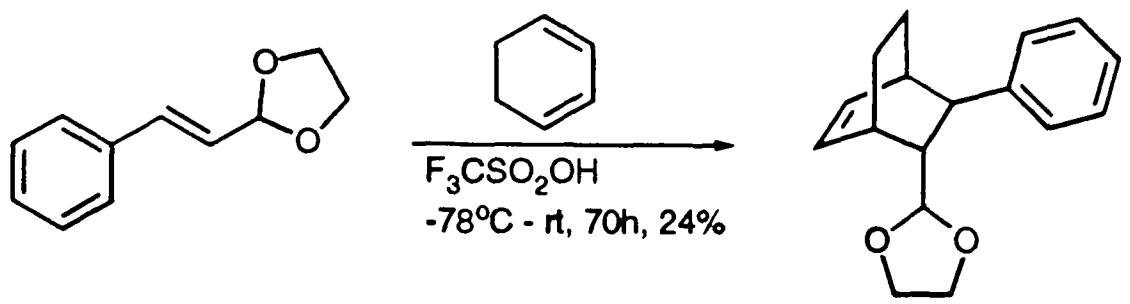
The first system synthesised involved the use of acetal-protected cinnamaldehyde (**226**) as the dienophile and cyclohexadiene as the diene in the Diels-Alder reaction. Acetal (**226**) was prepared by acid-catalysed protection of cinnamaldehyde **225**[160] (Scheme 72).



Cinnamaldehyde **225** (226)

Scheme 72

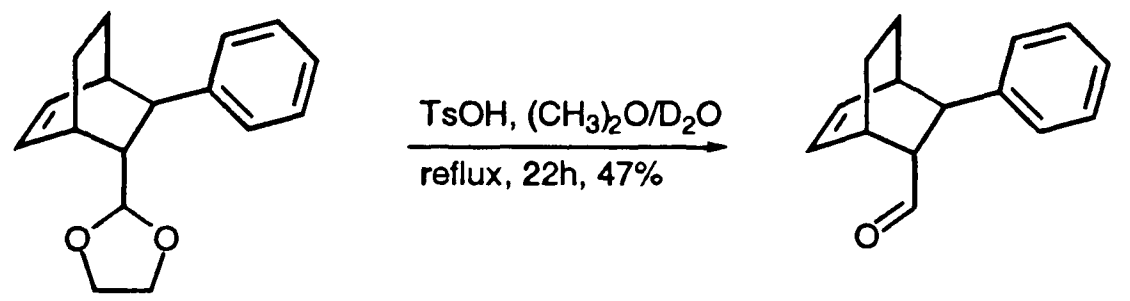
This acetal (**226**) was then used in a Gassman Diels-Alder reaction with cyclohexadiene to form bicyclic product (**227**). Thus, to a solution of the two components in CH_2Cl_2 cooled to -78°C, was added trifluoromethylsulfonic acid which turned the colourless solution dark blue. The reaction was then allowed to warm slowly to ambient temperature, and on quenching afforded the product (**227**) (Scheme 73).



(226) **(227)**

Scheme 73

Deprotection of this bicyclic system was then achieved using the standard conditions (TsOH, acetone/water). Deuterium oxide was used as the 'proton' source to detect any epimerisation at the centre α to the aldehyde, which would result in a product deuterated at this position. The deprotection was extremely rapid (*ca* 1 hour), however no deuterium incorporation was detected after this period, and only after extended reaction times was a trace of deuterium incorporated into the molecule (**228**) (Scheme 74).



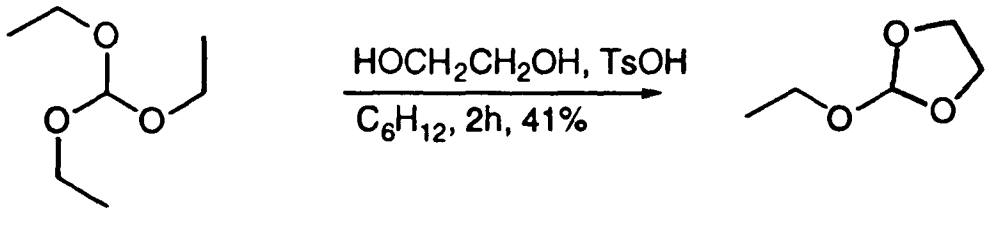
(227) **(228)**

Scheme 74

A likely reason for the lack of epimerisation during deprotection is the fact that the acetal is located on the unhindered *endo* face of the bicyclic molecule. For epimerisation to occur, it would be necessary for the acetal to be on the more hindered *exo* face of the molecule, providing an energetic impetus for the reaction. Thus it was decided to attempt synthesis of a model system with the acetal and alkyl/aryl functionality on the same face of the molecule. This should cause epimerisation to occur as such a reaction would allow relief of the steric crowding of the face where both functional group are located. It was proposed that such

deprotection models could be prepared by the use of a *cis*-alkene in the Gassman Diels-Alder reaction rather than a *trans*-alkene, locating both the alkene substituents on the same face of the bicyclic product.

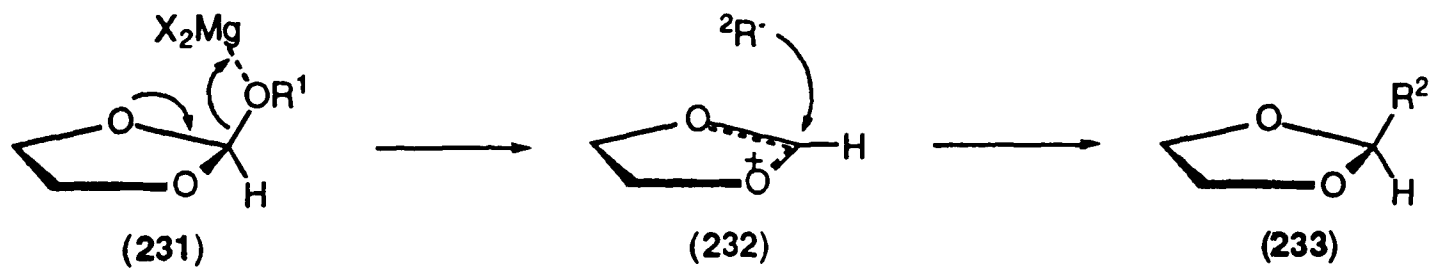
Thus, synthesis of a *cis*-alkene acetal was undertaken. It was decided to synthesise such systems by reaction of a Grignard reagent with an orthoester, a well developed method of connecting alkenyl substituents to orthoesters, which are aldehyde surrogates. Conversion of triethylorthoformate **229** to the cyclic orthoester (**230**) was achieved by acid catalysed transacetalisation with ethylene glycol, the reaction being driven to completion by azeotropic removal of the produced ethanol[161] (Scheme 75).



Triethylorthoformate **229** (230)

Scheme 75

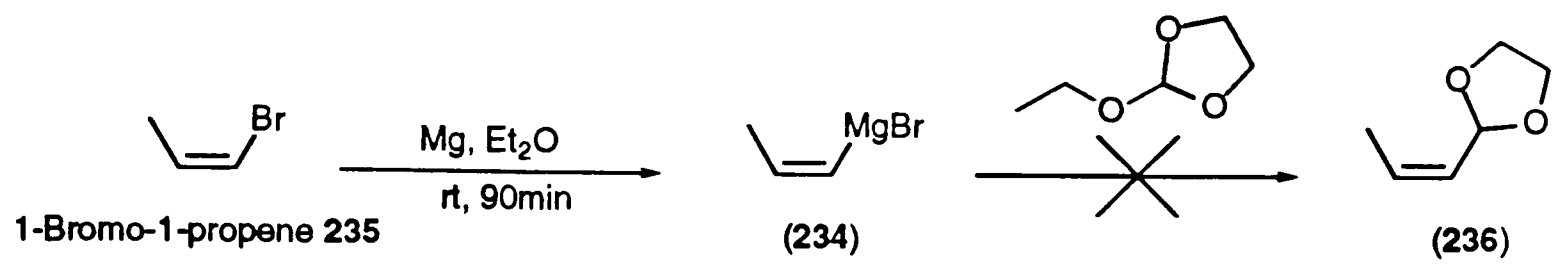
Reaction of cyclic orthoesters (**231**) with Grignard reagents has been proposed to proceed *via* a bisoxocarbonium ion (**232**), which is then attacked by the alkyl group to afford (**233**)[162,163] (Scheme 76).



Scheme 76

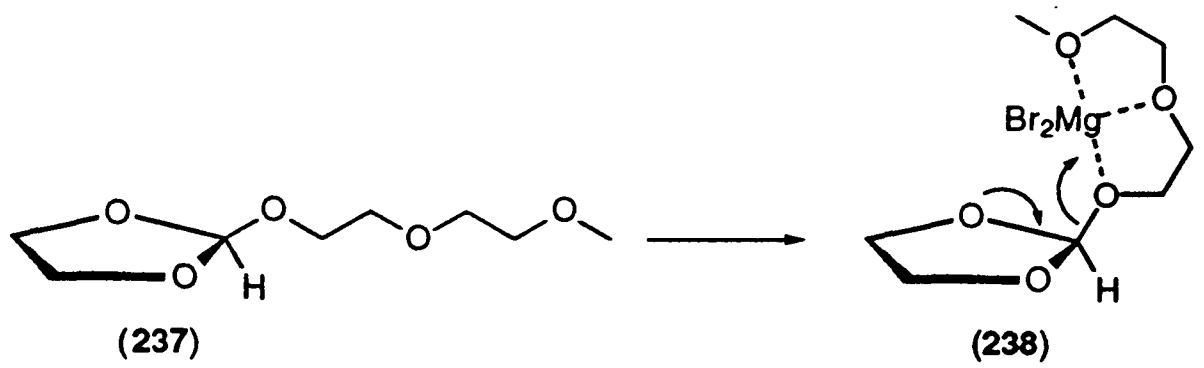
Preparation of a *cis*-alkenyl Grignard (**234**) was completed from 1-bromo-1-propene **235** using the method of Brown[164] (activation of the magnesium by magnetic stirring overnight under an atmosphere of argon). However, reaction of this reagent with

cyclic orthoester (**230**) was unsuccessful, with none of the required product (**236**) detected (Scheme 77).



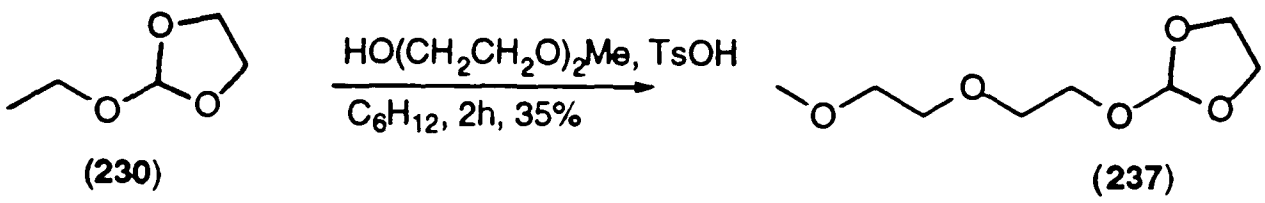
Scheme 77

Work on such reactions had been studied by Houghton[165], who had demonstrated that the use of linear poly(ethoxy) orthoformates (**237**) promoted the reaction of such compounds with Grignard reagents. This effect is attributed to more effective coordination of the poly(ethoxy) substituent to the Grignard reagent prior to elimination (**238**) (Scheme 78).



Scheme 78

Conversion of cyclic orthoformate (**230**) to poly(ethoxy) orthoformate (**237**) was achieved by acid-catalysed transesterification, the reaction being driven to completion by azeotropic removal of the produced ethanol (Scheme 79). Subsequent reactions showed that it was possible to convert triethylorthoformate **229** directly to poly(ethoxy) orthoformate (**237**) *via* a single pot procedure, firstly by transacetalisation with ethylene glycol, then tranesterification with 2-(2-methoxyethoxy)ethanol.

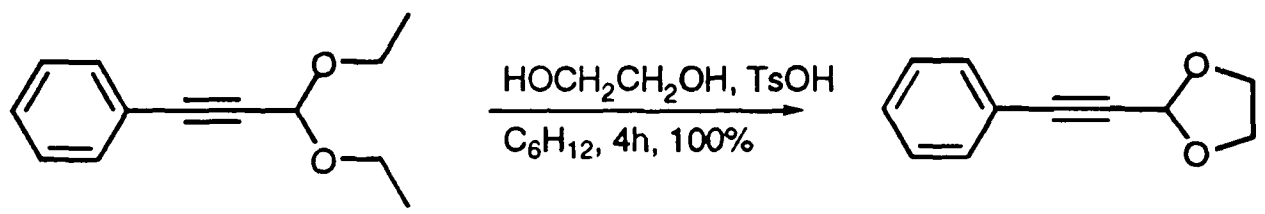


(230) **(237)**

Scheme 79

Reaction of this species (**237**) with the alkenyl Grignard reagent (**234**) was also unsuccessful, so attention was focused on the formation and reactivity of the Grignard reagent (**234**). However, changing the solvent from Et_2O to THF failed to improve the yield of the reaction of the Grignard (**234**) with orthoformate (**237**). The failure of this approach to produce even a trace of the required *cis*-alkenyl acetal (**236**) led to consideration of an alternative approach to the synthesis of such species.

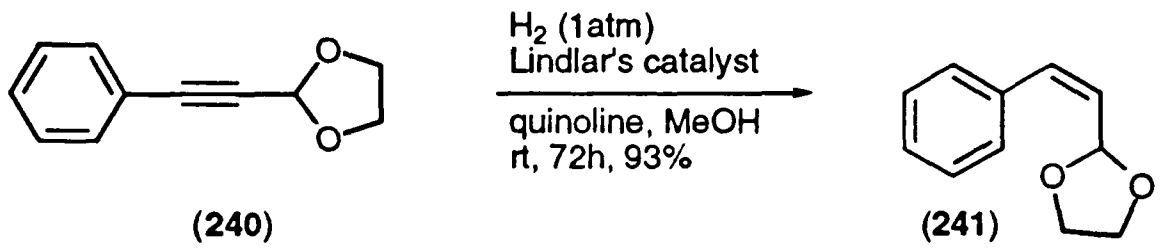
The synthesis of *cis*-alkenes is often achieved by catalytic hydrogenation of alkynes mediated by Lindlar's catalyst. Thus, synthesis of an alkynyl acetal, followed by hydrogenation offers an alternative method of synthesising *cis*-alkenyl acetals. Starting from phenylpropargyl aldehyde diethyl acetate **239**, acid catalysed transacetalisation with ethylene glycol afford alkynyl acetal (**240**) (Scheme 80).



Phenylpropargyl Aldehyde Diethyl Acetate **239** **(240)**

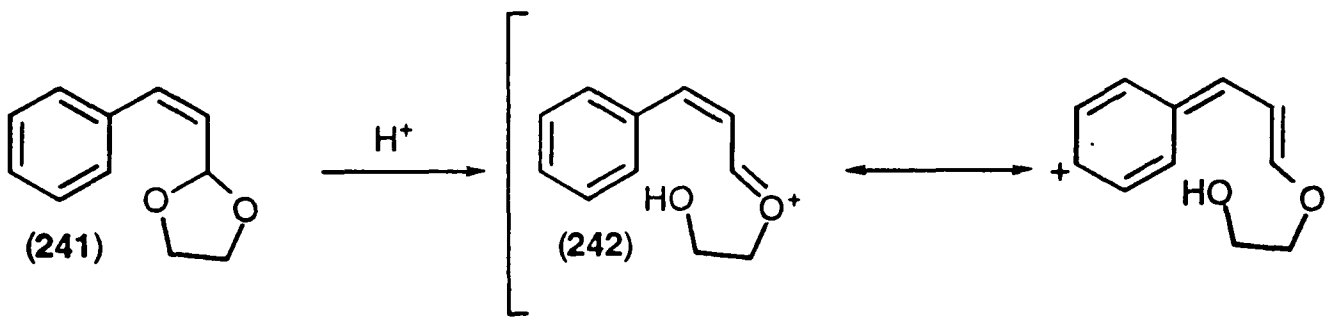
Scheme 80

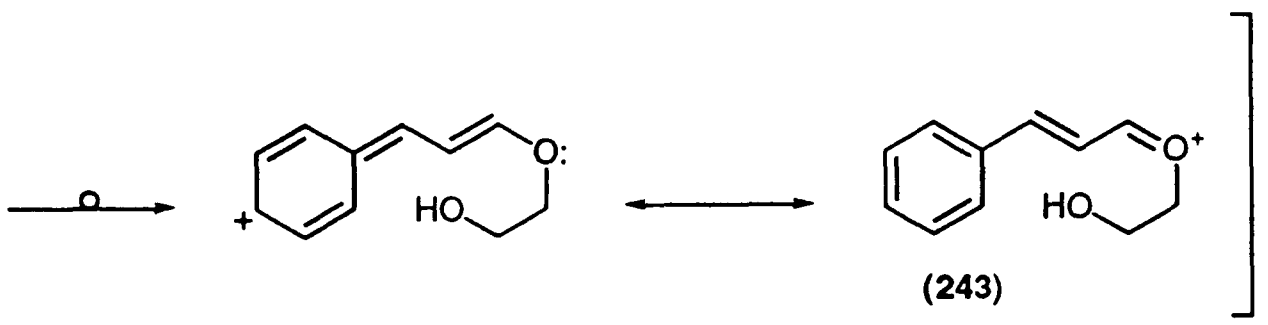
Hydrogenation of alkynyl acetal (**240**) in the presence of Lindlar's catalyst and quinoline proceeded at atmospheric pressure, taking 72 hours to reach completion affording *cis*-alkenyl acetal (**241**) (Scheme 81).



Scheme 81

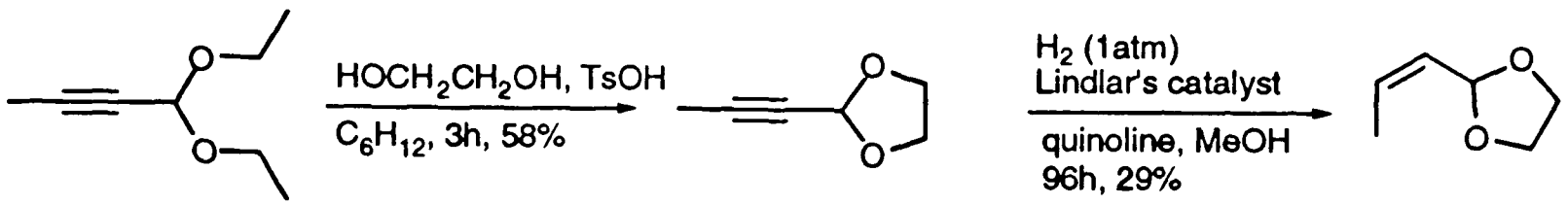
The Gassman Diels-Alder reaction was then attempted using identical conditions as for the *trans*-alkenyl acetal (**226**); however, the only product obtained was the previously obtained *trans*-bicyclic acetal (**227**). Under the reaction conditions isomerisation of the *cis*-alkene to the *trans*-alkene must be occurring *via* resonance stabilisation of the oxonium cation intermediates (**242** and **243**) (Scheme 82).





Scheme 82

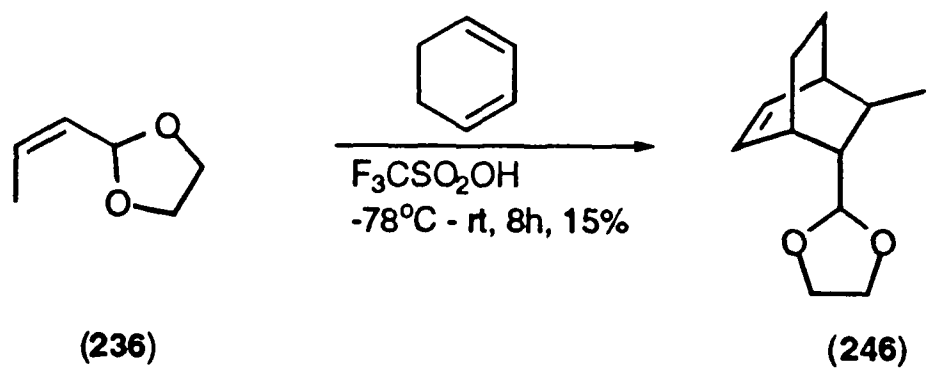
In an attempt to avoid this problem it was decided to synthesise a *cis*-alkenyl acetal with an alkyl rather than an aryl substituent, which should be less susceptible to such rearrangements. Starting from 2-butyn-1-al diethyl acetal **244**, transacetalisation to afford alkynyl acetal (**245**), followed by hydrogenation afforded *cis*-alkenyl acetal (**236**) (Scheme 83).



2-Butyn-1-al Diethyl Acetal **244** **(245)** **(236)**

Scheme 83

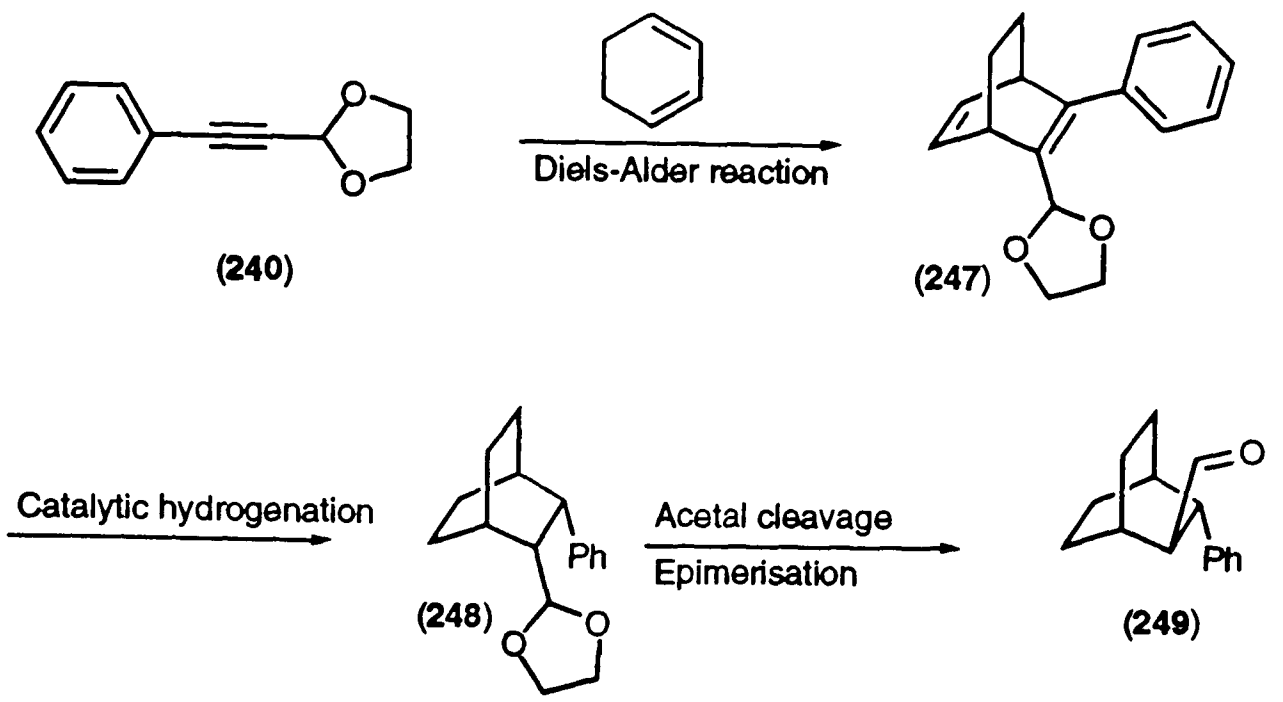
The Gassman Diels-Alder reaction of *cis*-alkenyl acetal (**236**) using the previous conditions afforded only the *trans*-bicyclic product (**246**), the structure of which was confirmed by NOE studies (Scheme 84). Presumably, as before, isomerisation of the *cis*-alkene to the *trans*-alkene was occurring under the reaction conditions prior to the Diels-Alder reaction.



(236) **(246)**

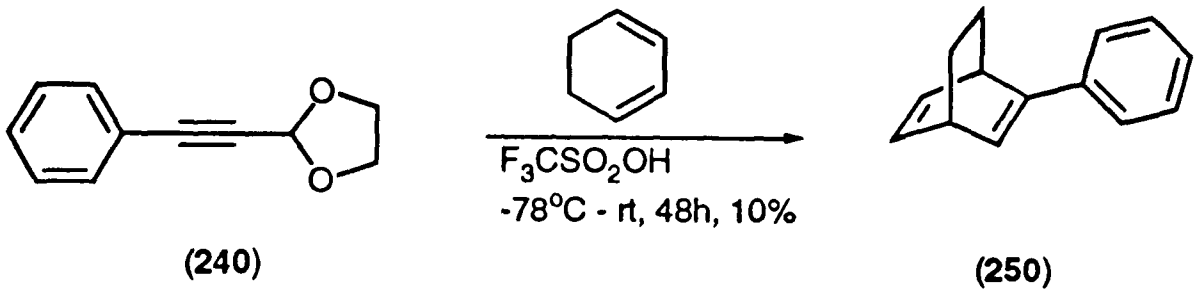
Scheme 84

In a final attempt to synthesise a deprotection model it was decided to investigate a Diels-Alder reaction between alkynyl acetal (**240**) and cyclohexadiene. Reactions of alkynes as dienophiles are known, but are not as widely used[166]. The Diels-Alder reaction of alkynyl acetal (**240**) should yield bicyclic diene (**247**), which on catalytic hydrogenation of the two double bonds, should yield a bicyclic acetal (**248**). This molecule, with the phenyl and acetal substituents of the same face, should be prone to epimerisation on acetal cleavage, yielding aldehyde (**249**) (Scheme 85).



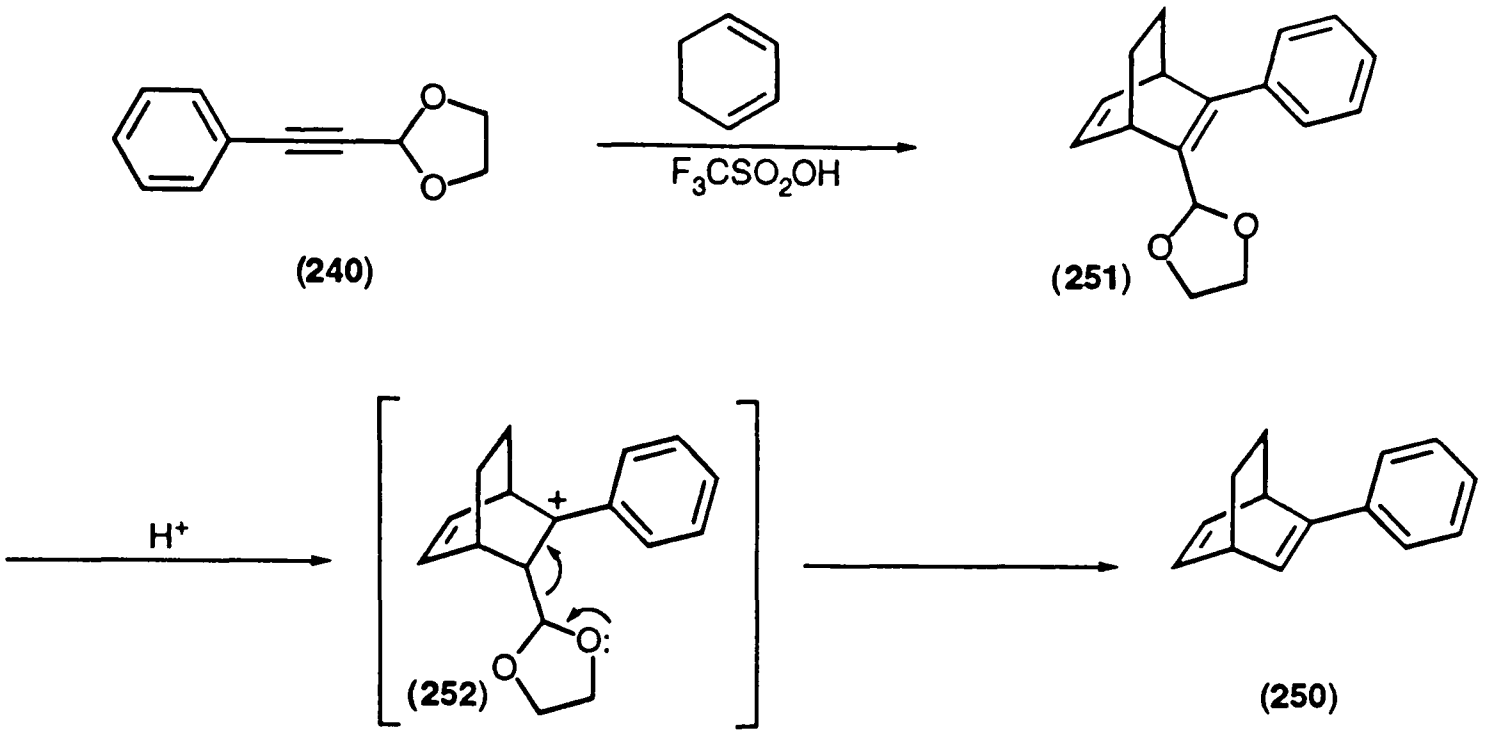
Scheme 85

However, the Diels-Alder reaction of alkynyl acetal (**240**) under the conditions previously used, afforded only a trace amount of diene (**250**), with some recovery of starting material (**240**) but no sign of desired bicyclic acetal (**247**) (Scheme 86).



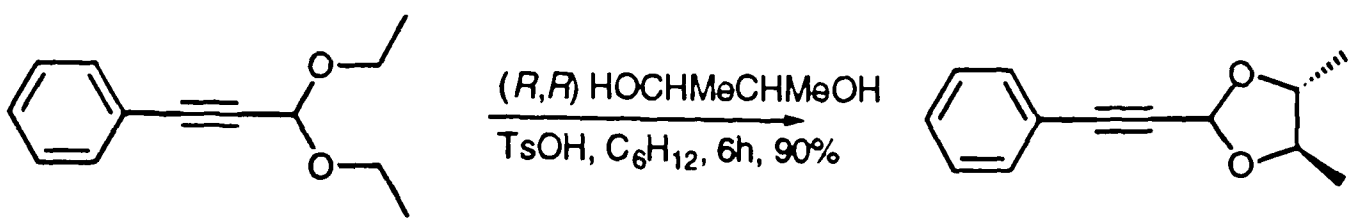
Scheme 86

Formation of diene (**250**) presumably occurs *via* a Diels-Alder reaction to afford bicyclic acetal (**251**), followed by protonation of the alkene to afford a resonance stabilised carbocation intermediate (**252**). Elimination of the acetal functionality would then afford the product diene (**250**) (Scheme 87).



Scheme 87

This reaction, although disappointing as it failed to afford the bicyclic acetal (**247**) required for deprotection studies, is interesting as it represents a new method of synthesising bicyclic dienes. These molecules are of interest as they exist as a pair of enantiomers. Such molecules when isolated as single enantiomers have found widespread application in enantioselective synthesis, particularly in chiral reductions as ligands for organometallic reagents or boranes. Thus, after the failure of the Gassman methodology to afford a useful model to study acetal deprotection, it was decided that a final piece of work using this chemistry would be an investigation into inducing chirality into this new synthesis of bicyclic dienes. It was hoped that use of a chiral acetal would induce some enantioselectivity during the course of the reaction. Synthesis of such an acetal was completed by transacetalisation of phenylpropargyl aldehyde diethyl acetal **239** with (2*R*,3*R*)-(-)-2,3-butanediol to afford alkynyl acetal (**253**) (Scheme 88).



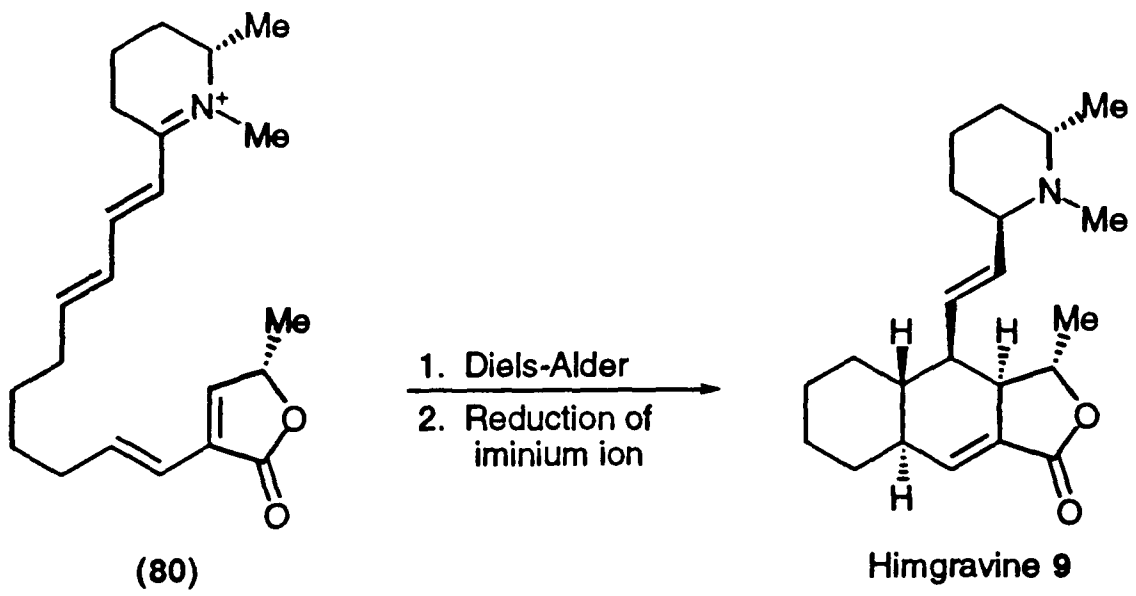
Phenylpropargyl Aldehyde Diethyl Acetate 239 **(253)**

Scheme 88

Diels-Alder reactions attempted using this acetal (**253**) however, failed to give any of the desired bicyclic diene (**250**), suggesting the formation of the product is dependent on achieving exactly the correct reaction conditions, which have yet to be conclusively identified.

2.5. Synthetic Strategy for Iminium Ion Mediated Diels-Alder Reaction

Following the success of the oxonium ion mediated Diels-Alder reaction (Scheme 69) it was decided to change the aim of the project from the total synthesis of himbacine **1** *via* connection of tricyclic aldehyde (**172**) to piperidine sulfone (**156**) to a biomimetic synthesis involving an iminium ion mediated Diels-Alder reaction (Scheme 89).

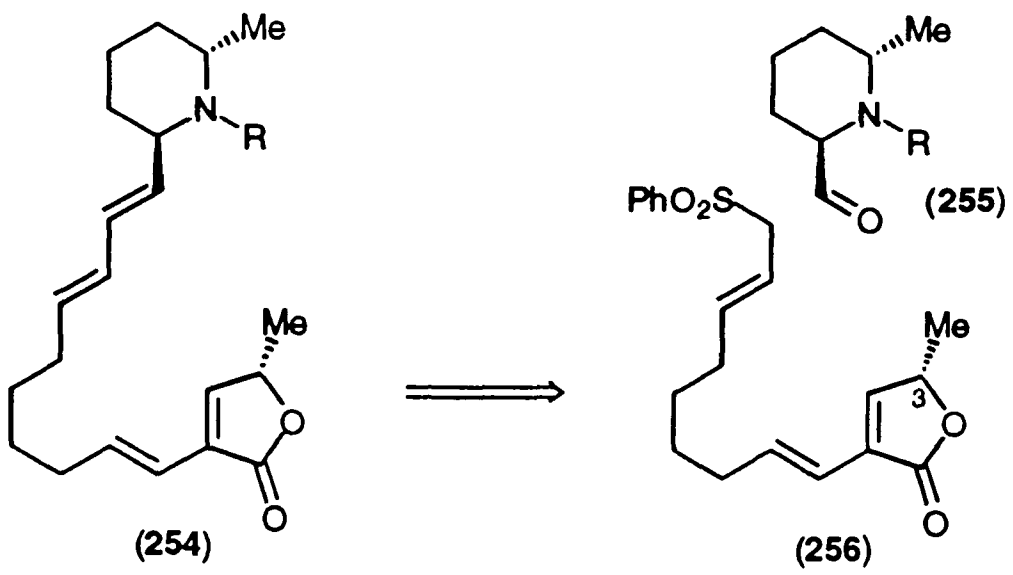


(80) **Himgravine 9**

Scheme 89

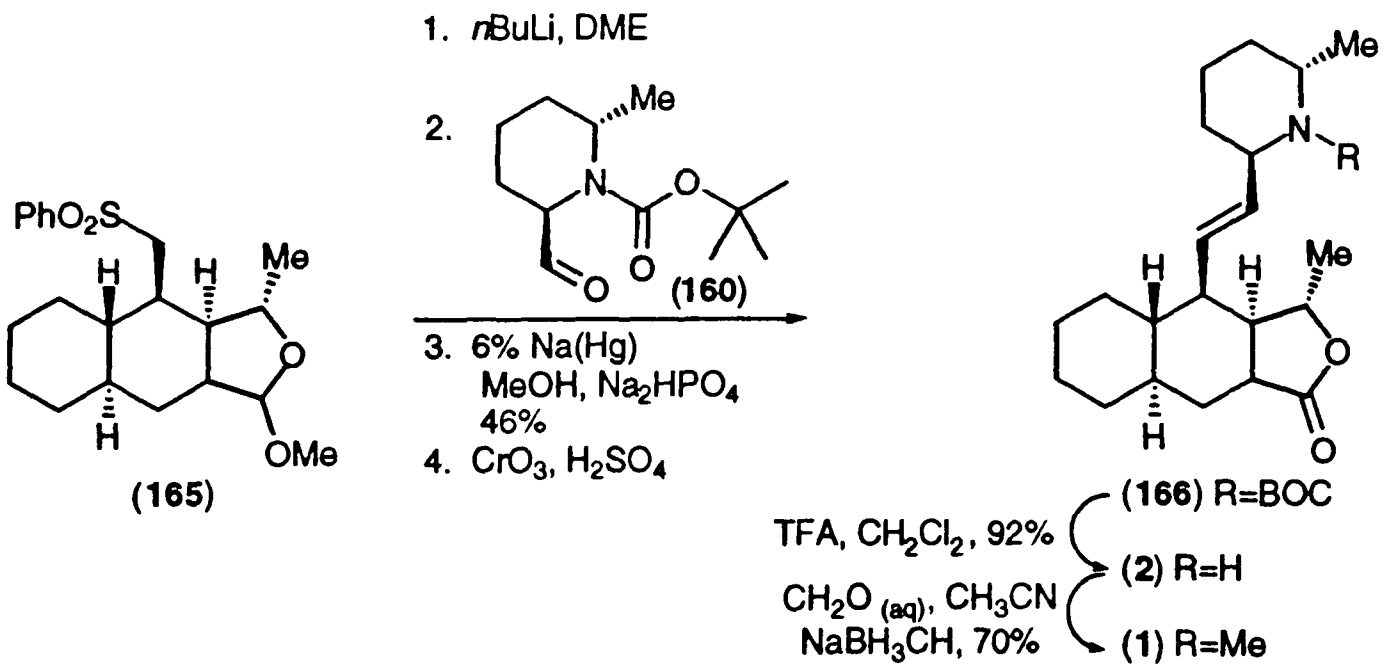
Considering the disconnections required for the synthesis of the iminium ion (**80**), the final few steps would involve a Polonovski reaction to convert the tertiary nitrogen of

the piperidine (**76**) to an iminium ion. For construction of the required carbon framework it was decided to disconnect the molecule (**254**) into two portions, which would be reconnected, as before, *via* a Julia coupling (Scheme 90).



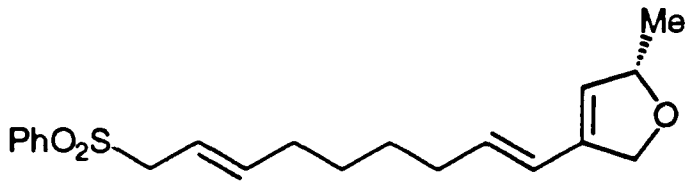
Scheme 90

Thus, synthesis of a piperidine aldehyde (**255**) and an allylic sulfone (**256**) was required. For piperidine aldehyde (**255**) it was decided to synthesise *N*-BOC piperidine aldehyde (**160**), which had previously been used in a Julia coupling by Hart in his total synthesis of himbacine **1**[104]. Following the coupling the *N*-BOC group was converted to an *N*-methyl group by acid catalysed deprotection followed by a reductive methylation to afford himbacine **1** (Scheme 91).



Scheme 91

For synthesis of the allylic sulfone (**256**), synthesis of dihydrofuran (**257**) was required (Figure 23), as the presence of the carbonyl group on butenolide (**256**) increases the acidity of hydrogen at C3 to such an extent that during the deprotonation step of the Julia coupling it is likely that epimerisation would occur at this centre. It should be possible to introduce the carbonyl group into the dihydrofuran (**257**) by direct oxidation after the Julia coupling, either before or after the iminium ion mediated Diels-Alder reaction.



(257)

Figure 23

Following the synthesis of these two molecules two key steps remain to complete the biomimetic synthesis of himgravine **9** and then himbacine **1**:

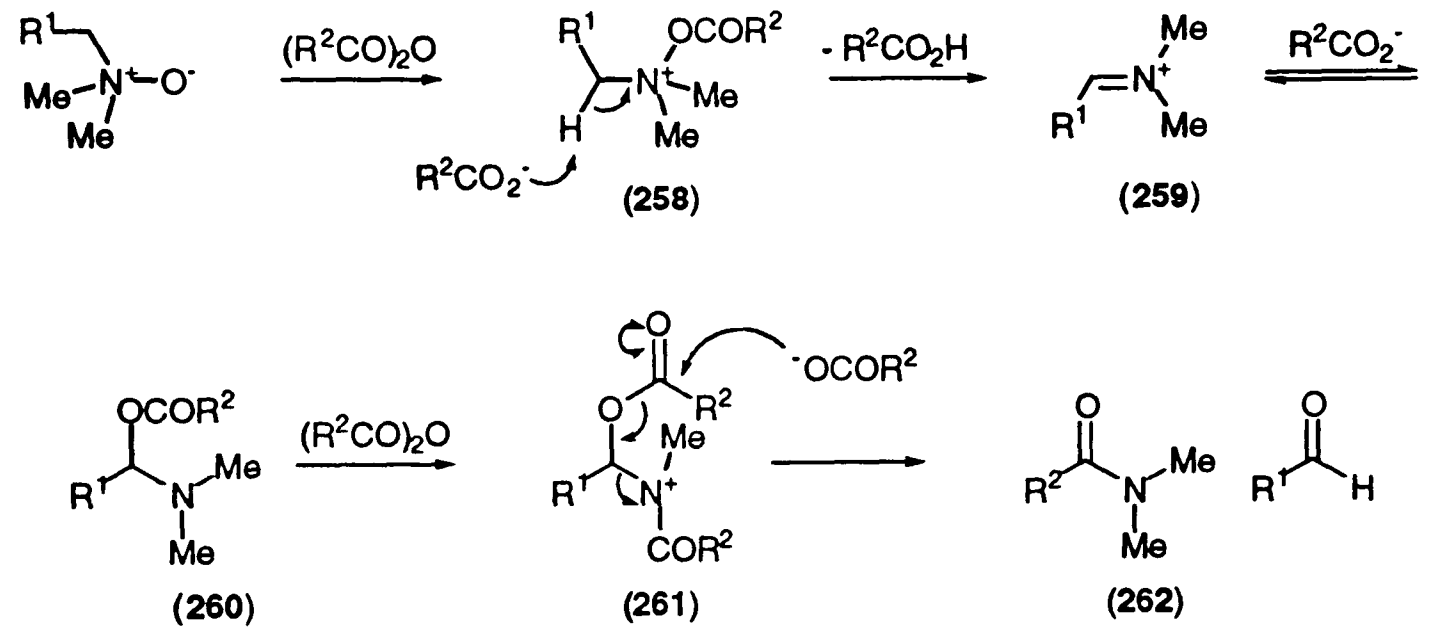
- Julia coupling of piperidine aldehyde (**160**) and allylic sulfone (**257**).
- Polonovski reaction of *N*-methyl piperidine (**76**).

As a first study on this proposed biosynthetic scheme, it was decided to investigate the chemistry of these two key steps.

2.6. Studies on the Polonovski Reaction

The Polonovski reaction (reaction of a tertiary amine *N*-oxide with acid anhydride, acyl chloride or chloroformate ester) was originally used as a mild method for *N*-demethylation of tertiary amines; however, it is now recognised that the reaction provides ready access to iminium ions, enamines, tertiary amides and/or secondary amines and aldehydes[167].

The first step in the reaction is the formation of an *O*-acylimonium salt (**258**). Such species are highly unstable and rapidly convert to iminium ion (**259**) by an ionic *E2*-type elimination mechanism (Scheme 92). Evidence for this mechanism is that the reaction is accelerated by the addition of acetate ions or amine bases, and decelerated when carried out in acidic media. These observations point to the involvement of the counterion $R^2CO_2^-$ in the removal of the proton from the α-carbon. Further support comes from studies which demonstrate that there is a marked preference for the loss of the hydrogen which is antiperiplanar to the N-O bond.

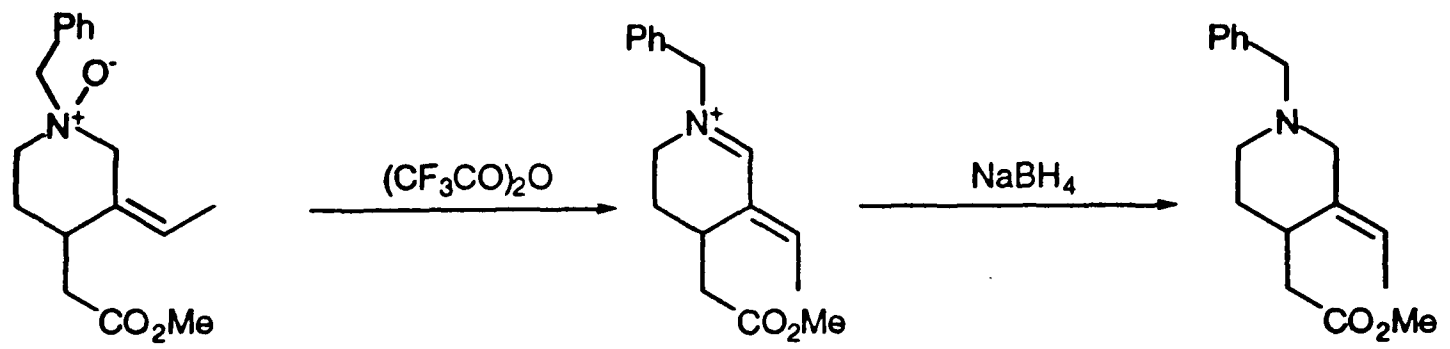


Scheme 92

The equilibrium between the iminium ion (**259**) and addition product (**260**) is a function of the nucleophilicity of the counterion $R^2CO_2^-$ and the acidity of the reaction medium. When $R^2CO_2^-$ is an acetate anion, this equilibrium is displaced entirely towards intermediate (**260**). In the presence of trifluoroacetic acid, intermediate (**260**) reverts back to the iminium ion (**259**). This reversibility and the low nucleophilicity of the trifluoroacetate anion explain why the Polonovski reaction using trifluoroacetic anhydride does not proceed beyond the iminium ion stage. Thus, this modified Polonovski reaction offers an effective method of generating the iminium ion required for the proposed Diels-Alder reaction (Scheme 89).

The other important consideration is the regiochemistry of the reaction. For unsymmetrical *N*-oxides the regiochemistry of the Polonovski reaction is determined by a preference for loss of a proton from any of the carbon centres α to the nitrogen in the step that forms the iminium ion (**259**). The anhydride plays a fundamental role in the orientation of this *E2* elimination reaction, since both the base and the leaving group on the nitrogen are derived from it. As a rule it is found that the thermodynamically more stable iminium ion is produced when trifluoroacetic anhydride is used, while with acetic anhydride the product generally obtained depends on the kinetic acidity of the α-hydrogens. These results can be explained by the fact that with trifluoroacetic anhydride an excellent leaving group is generated along with a weak base, whereas with acetic anhydride a comparatively poor leaving group and a much stronger base are produced.

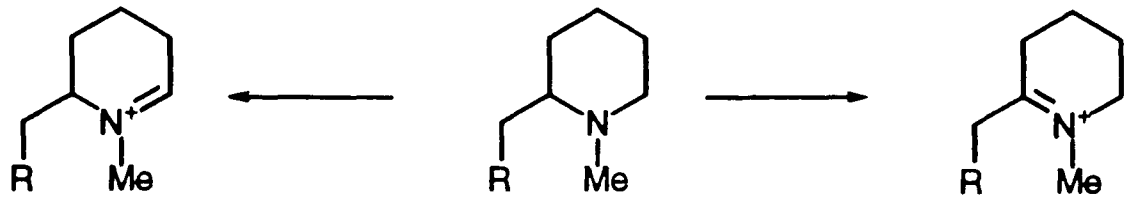
These results additionally support the use of the modified Polonovski reaction for generation of iminium ion (**80**), as the reaction with *N*-methylpiperidine (**76**) should afford the iminium ion by elimination of the allylic proton, which is the most acid proton, to afford the conjugated iminium ion (**80**), which will be the thermodynamic product. This proposal is supported by the Polonovski reaction of *N*-oxide (**263**) with trifluoroacetic anhydride, to form conjugated iminium ion (**264**), which was then reduced to (E)-ethylidene product (**265**)[168] (Scheme 93).



(263) **(264)** **(265)**

Scheme 93

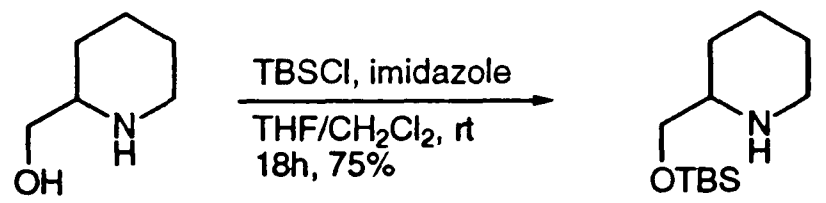
As an initial investigation into the chemistry of the Polonovski reaction, it was decided to investigate the chemoselectivity of the reaction with piperidines. For the synthesis of a model for the *N*-methylpiperidine (**266**), it was decided to start from the readily available 2-piperidinemethanol **267**. A first investigation to determine the extent that the iminium ion forms by elimination of methine rather than methylene protons to form the most thermodynamically stable product (**268**), rather than (**269**), was undertaken (Scheme 94).



(269) **(266)** **(268)**

Scheme 94

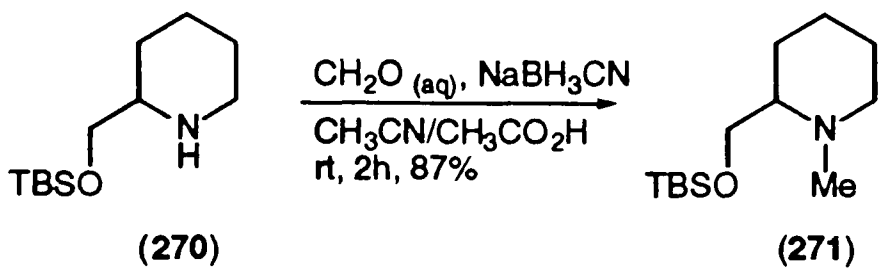
Thus as a first step in the synthesis of a model system of the type (**266**), 2-piperidinemethanol **267** was *O*-protected using TBSCl to afford piperidine (**270**) (Scheme 95).



2-Piperidinemethanol 267 **(270)**

Scheme 95

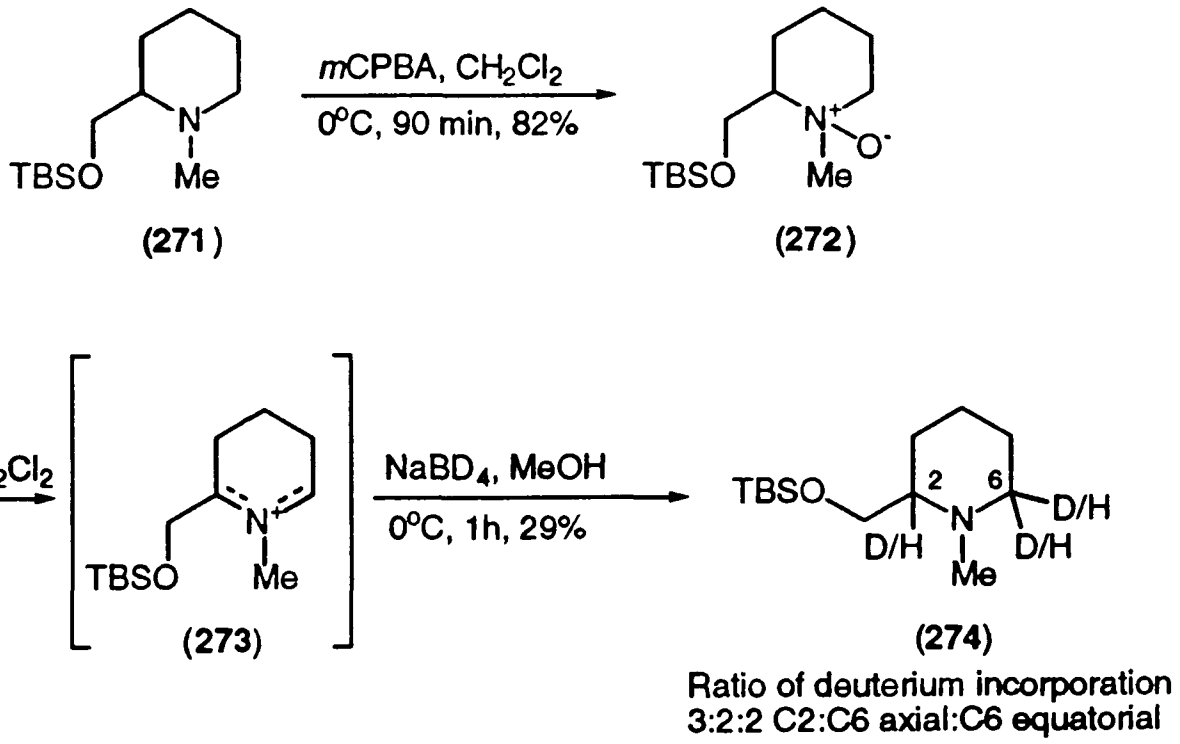
The *N*-methyl group was then introduced by a reductive methylation. This chemistry was developed as a milder alternative to the Eschweiler-Clark reaction using the cyanoborohydride ion, which is relatively stable under mild acid conditions, as the hydride source[169]. To a solution of piperidine (**270**) and aqueous formaldehyde in acetonitrile was added sodium cyanoborohydride, affording *N*-methylpiperidine (**271**) in excellent yield (Scheme 96).



(270) **(271)**

Scheme 96

The Polonovski reaction was then investigated using conditions developed by Potier for the synthesis of vinblastine-type alkaloids[170]. *N*-methylpiperidine (**271**) was oxidised using *m*CPBA, to tertiary *N*-oxide (**272**) which was isolated before the second step of the reaction. The *N*-oxide (**272**) was then dissolved in CH_2Cl_2 and treated with trifluoroacetic anhydride to afford iminium ion (**273**). The solvent was then removed and the crude iminium ion (**273**) dissolved in methanol and reduced with sodium borodeuteride affording deuterium labelled *N*-methylpiperidine (**274**) (Scheme 97).



(271) **(272)** **(273)** **(274)**

Ratio of deuterium incorporation
3:2:2 C2:C6 axial:C6 equatorial

Scheme 97

The ratio of deuterium inclusion demonstrates that this Polonovski reaction only slightly favours the more thermodynamically stable product (a ratio of 1:1:1 deuterium incorporation would suggest no bias). A possible explanation for this result is that elimination of the methine proton affords an iminium ion with significant 1,3-allylic

interactions between the *N*-methyl group and the methylene group α to the oxygen atom (Diagram 4), which will reduce the thermodynamic stability of this product.

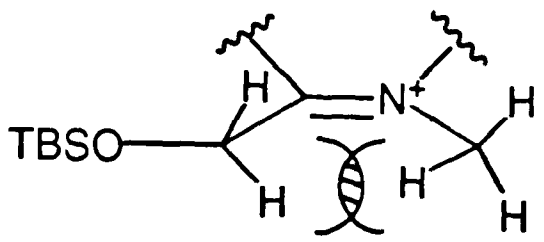


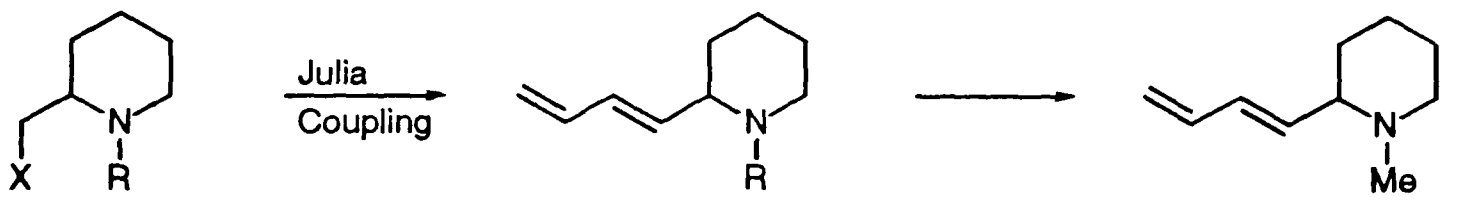
Diagram 4

Thus, further investigations of the Polonovski reaction were required to determine the effect that the following structural features of the *N*-methylpiperidine (**76**) would have on the ratio of iminium ions formed:

- The diene side chain, which will increase the acidity of the proton at C2, as it will now be allylic.

- The methyl group at C6, which will also have 1,3-allylic interactions with the *N*-methyl group if the iminium ion forms by elimination of the proton at C6.

To investigate the effect of the diene side chain on the chemoselectivity of the Polonovski reaction, it was decided to synthesise piperidinediene (**275**) *via* a Julia coupling, allowing investigation of both reactions (Scheme 98).



(275)

Scheme 98

2.7. Studies on the Julia Coupling

The coupling reaction of phenyl alkyl sulfones and carbonyls was originally reported by Julia in 1973[171]. The Julia reaction consists of four distinct stages[111] (Scheme 99):

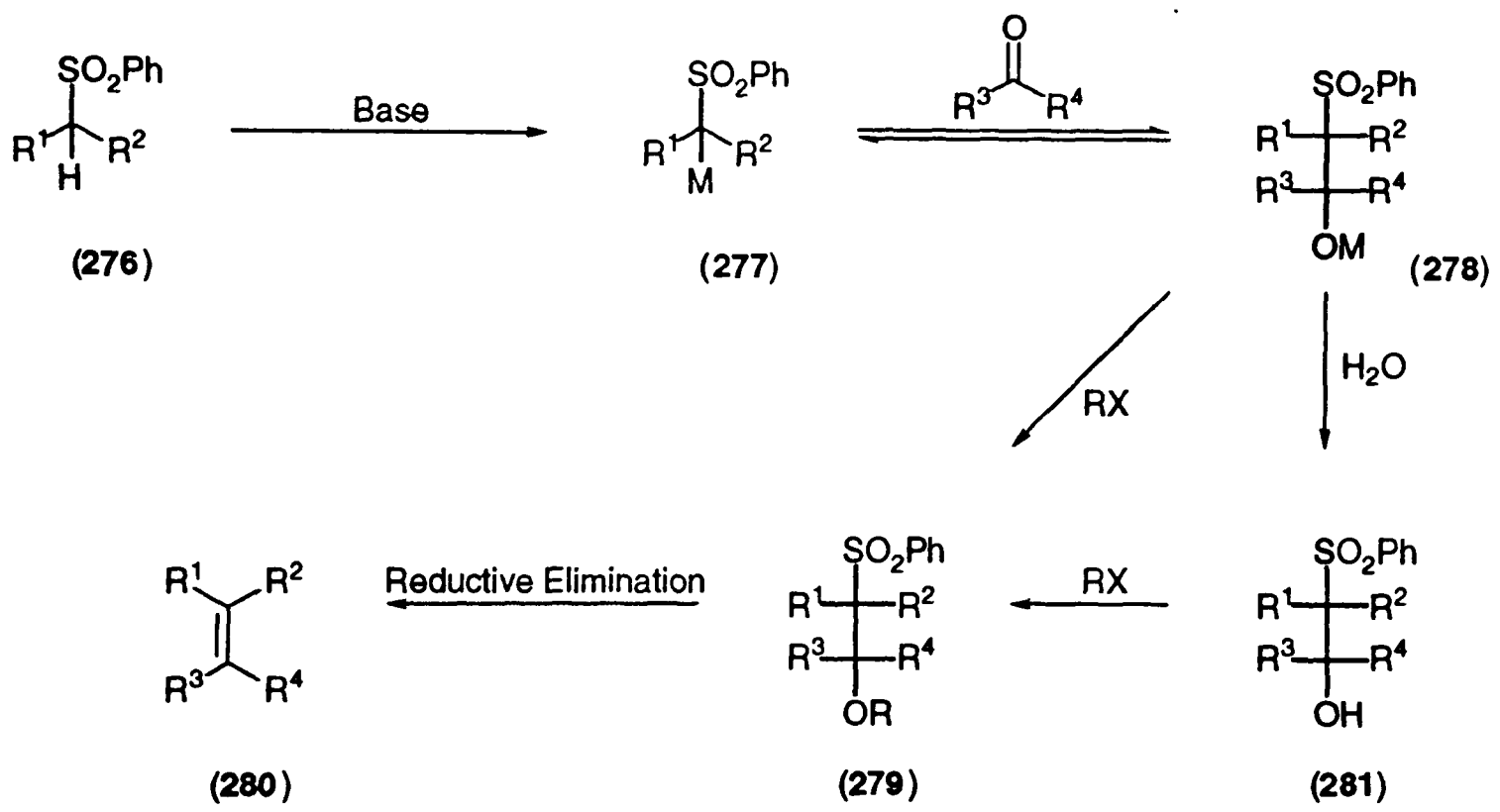
- α-Metalation of a phenyl alkyl sulfone (**276**).

- Coupling of the α-metallated sulfone (**277**) with an aldehyde or ketone to give a β-phenylsulfonyl alkoxide adduct (**278**).

- Functionalisation of the adduct (**278**) to afford β-substituted sulfone (**279**).

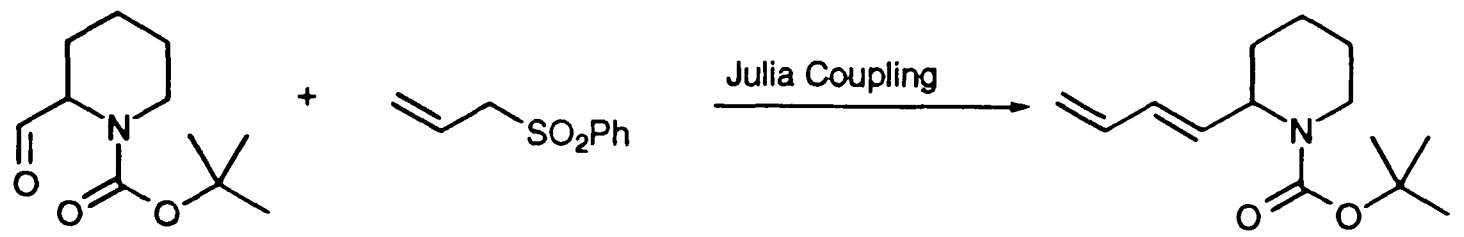
- Reductive elimination of the β-substituted sulfone (**279**) to afford *E*-alkene (**280**).

The first three stages can be performed in a single reaction vessel. However the overall efficiency of the sequence can be improved by isolation of the β-hydroxy sulfone (**281**) with functionalisation of the hydroxyl group in a separate step. The major problem with the Julia coupling is its length, it can be foiled at any of the four steps. In practice, the second step is usually the most problematic and stage four the least, however all of the steps have potential problems.



Scheme 99

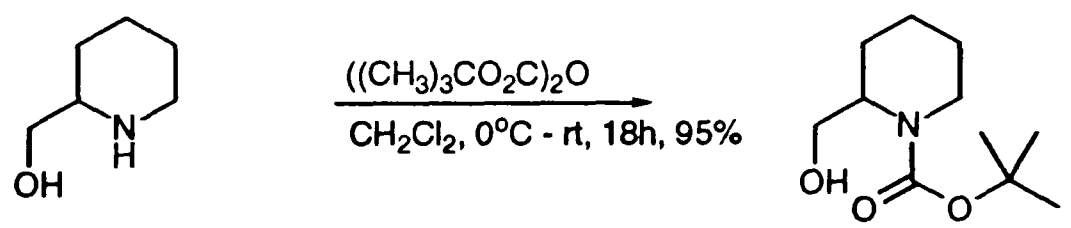
For an investigation into the Julia coupling required to join piperidine aldehyde (**160**) and allylic sulfone (**257**) it was decide to use piperidine aldehyde (**282**), derived from 2-piperidinemethanol **267**, and allyl phenyl sulfone **283** to afford piperdinediene (**284**) (Scheme 100).



(282) Allyl Phenyl Sulfone **283** **(284)**

Scheme 100

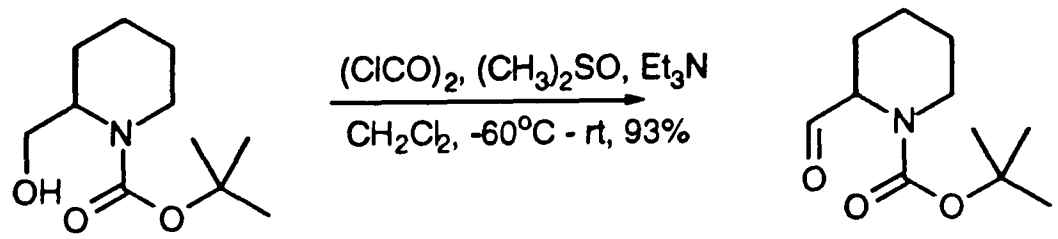
Piperidine aldehyde (**282**) was prepared from 2-piperidinemethanol **267** by a two step procedure. The first step involved *N*-BOC protection of the amine functionality in the presence of a primary alcohol. Such reactions had been demonstrated by Krapcho, using di-*tert*-butyl dicarbonate to protect 2-aminoethanol[172]. This methodology was applied to 2-piperidinemethanol **267** to afford *N*-BOC piperidinemethanol (**285**) (Scheme 101).



2-Piperidinemethanol **267** **(285)**

Scheme 101

Conversion of (**285**) to *N*-BOC piperidine aldehyde (**282**) was then completed using an oxidation with dimethyl sulfoxide activated by oxalyl chloride[173,174], using the conditions developed by Swern[175] (Scheme 102).

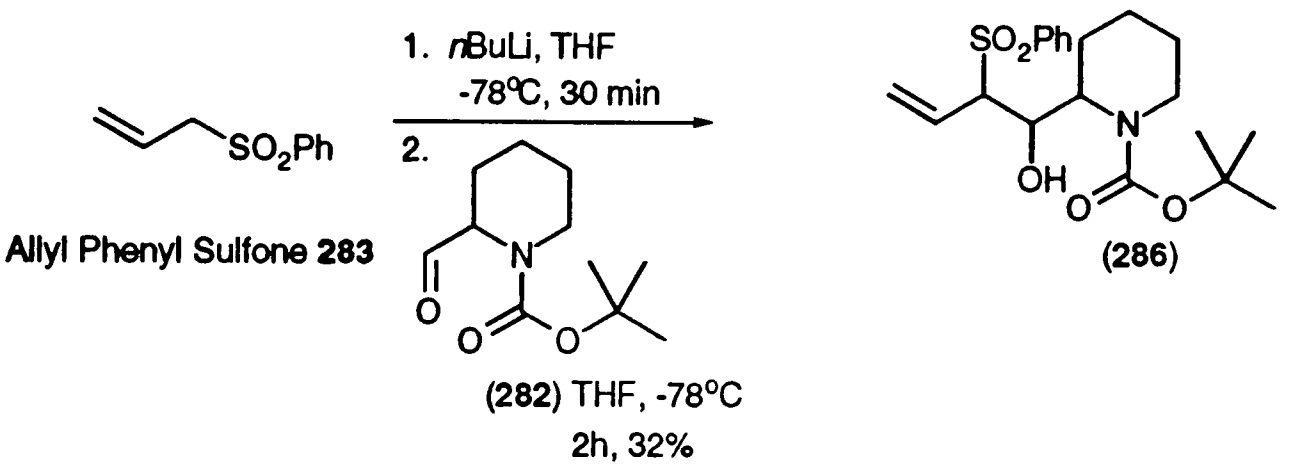


(285) **(282)**

Scheme 102

As a first investigation into the Julia coupling the conditions used by Hart were employed (Scheme 91). This involved coupling of sulfone (**165**) to piperidine aldehyde (**160**) using *n*BuLi as a base, followed by direct elimination of β-hydroxy sulfone using sodium amalgam. Reductive elimination of β-hydroxy sulfones to alkenes are known but they tend to occur rather slowly even at room temperature, however the overall yield of 46% suggested that the reaction was relatively successful in this case.

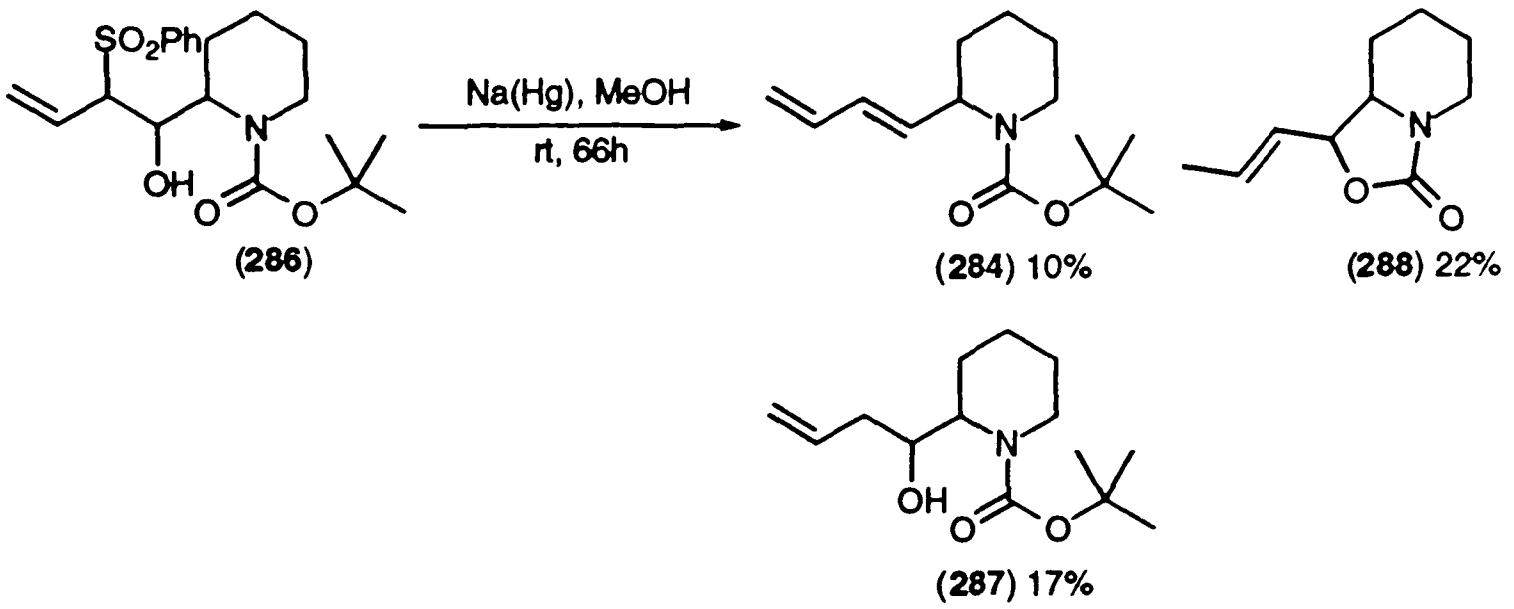
To a solution of allyl phenyl sulfone **283** in THF at -78°C was added *n*BuLi as a solution in hexanes. After stirring the sulfone anion at -78°C for 30 minutes, piperidine aldehyde (**282**) in THF was added, allowing isolation of 32% of the required β-hydroxy sulfone (**286**) (Scheme 103).



Scheme 103

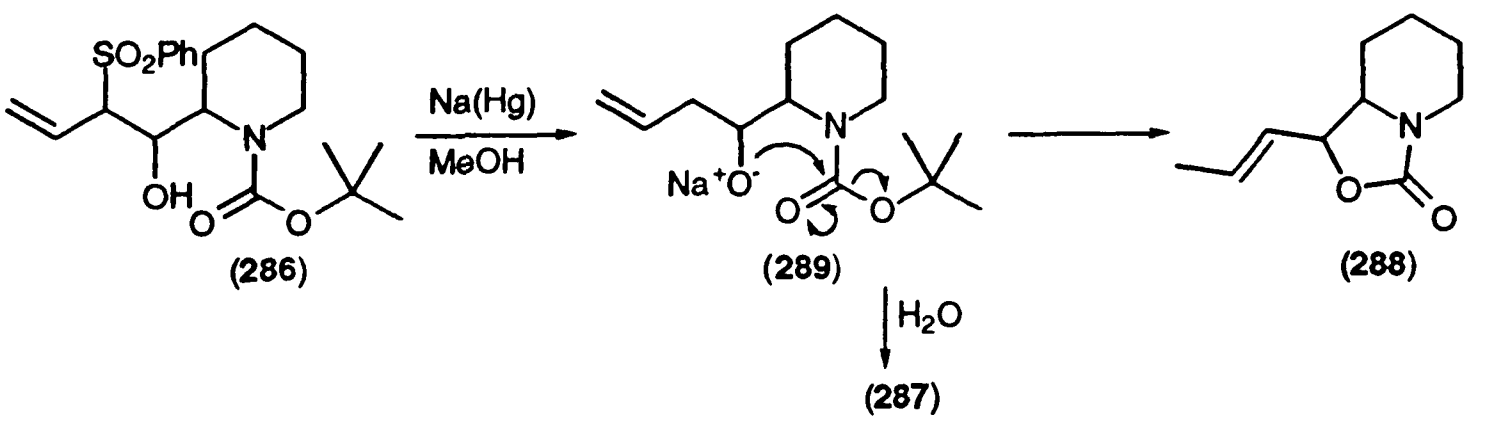
A significant analysis problem emerged at this stage, namely that the β-hydroxy sulfone (**286**) exists as a mixture of 4 diastereomers. Additionally, as the *N*-BOC group causes rotameric peak broadening, NMR analysis proved too problematic, thus many of the compounds synthesised in this study could only be characterised by mass spectrometry and infrared spectroscopy.

The elimination reaction was then completed using 6% sodium amalgam in methanol at ambient temperature which afforded a mixture of three products, piperidinediene (**284**), piperidine alcohol (**287**) and oxazolopyridinone (**288**) (Scheme 104).



Scheme 104

Formation of the piperidinediene (**284**) must occur by elimination of the sulfone and hydroxyl groups to form the alkenic bond. Formation of the piperidine alcohol (**287**) occurs by elimination of the sulfone. The basic reaction conditions are likely to have deprotonated the hydroxyl group of piperidine alcohol (**287**) which means no further elimination will occur. Formation of the oxazolopyridinone (**288**) occurs by attack of the deprotonated hydroxyl group of piperidine alcohol (**289**) on the *N*-BOC group followed by elimination of the *tert*-butoxy group (Scheme 105).



Scheme 105

The overall yield for the formation of piperidinediene (**284**) from allyl phenyl sulfone **283** was however only a disappointing 3%. Thus careful consideration of each of these four steps was required to improve the overall yield of the coupling.

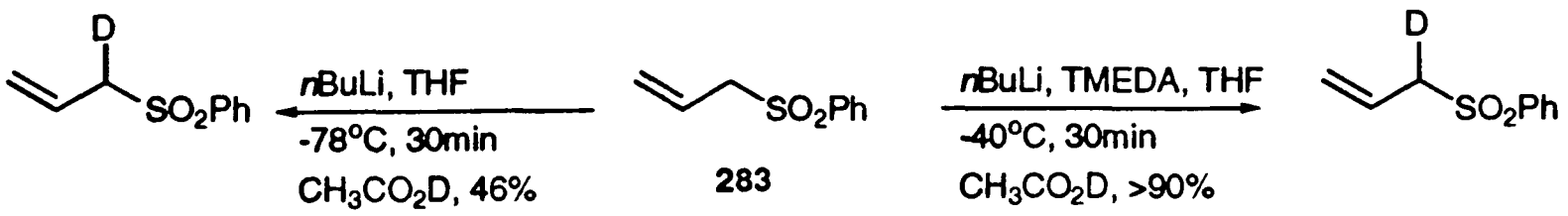
2.7.1. Metalation of the Phenyl Alkyl Sulfone

The original metallation and alkylation step to afford β-hydroxy sulfone (**286**) proceeded in a moderate 32% yield. Investigations into the first of these steps were undertaken by metallation of allyl phenyl sulfone **283** followed by deuteride quench using acetic acid. Measurement of the deuterium incorporation gave an indication of the proportion of sulfone metallated by the procedure. The conditions that had been used previously gave only a 46% deuterium inclusion (Scheme 106), thus methods of improving this result were sought. Preparation of the lithium salts of allyl phenyl sulfone **283** had been demonstrated in the synthesis of a variety of alkenes[176], and successful metallation of the sulfone had been achieved by:

- Variation in the temperature of the metallation. Raising the temperature above -78°C afforded better yields.

- The use of *N,N,N',N'*-tetramethylethylenediamine. TMEDA has been shown to promote lithiation reactions by converting alkyl lithiums, which exist as hexamers in organic solutions, to their more reactive monomeric form[177].

As well as these modifications, *ie* reaction temperature of -40°C and one equivalent of TMEDA, only freshly purchased *n*BuLi was used. The *n*BuLi was titrated using 1,3-diphenylacetone-*p*-tosylhydrazone, and was not used if the molarity had fallen below 75% of the value quoted on purchase. These reaction conditions, when tested, gave a deuterium inclusion >90%, confirming the modification to have been successful (Scheme 106).

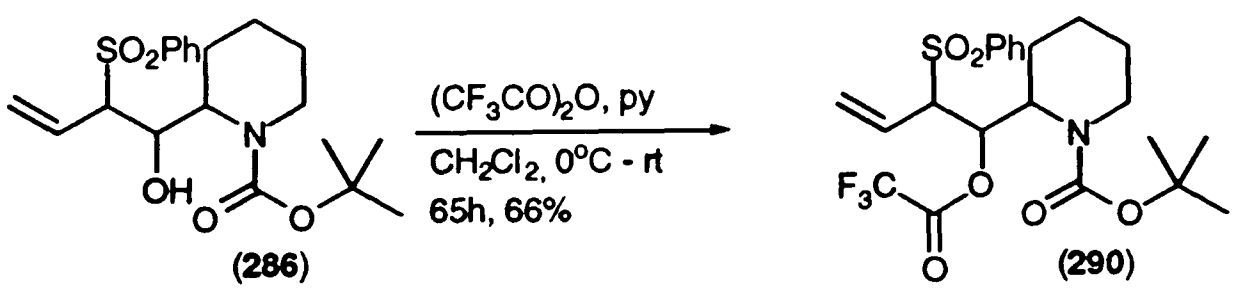


Scheme 106

2.7.2. Functionalisation of β-Hydroxy Sulfone

As was noted before, the reductive elimination of β-hydroxy sulfones (**281**) is known; however, they tend to be slow and, as was clearly demonstrated in the elimination reaction of β-hydroxy sulfone (**289**), are not always successful. Conversion of the hydroxyl group to an acetate, benzoate or methanesulfonate maximises the alkene formation pathway and hence minimises reactions such as retroaldolisation or direct reductive desulfonylation. Adducts derived from α,β-unsaturated aldehydes or sulfones are best protected as acetates or benzoates as allylic methanesulfonates are not particularly stable.

Initial investigations focused on the conversion of β-hydroxy sulfone (**286**) to an acetate, a procedure that was suggested to give the best overall yield for conversion of sulfone (**276**) to adduct (**279**). Work initially focused on the synthesis of trifluoroacetates, as these had been shown to be extremely effective in the elimination step[178]. Conversion of β-hydroxy sulfone (**286**) to trifluoroacetate (**290**) was completed using trifluoroacetic anhydride and pyridine[179]. Initially 1.1 equivalents of trifluoroacetic anhydride was used which yielded 43% of the required product (**290**). However, increasing the amount to 1.5 equivalents increased the yield to 66% (Scheme 107).

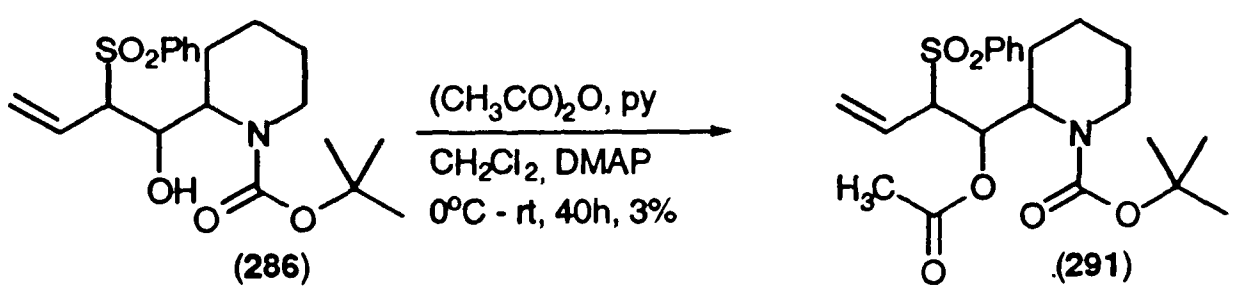


Scheme 107

The trifluoroacetate (**290**) turned out to be extremely unstable, and decomposed on flash chromatography and on standing, even if stored in a freezer at -20°C. The elimination reaction proved to be more successful, using the same conditions as

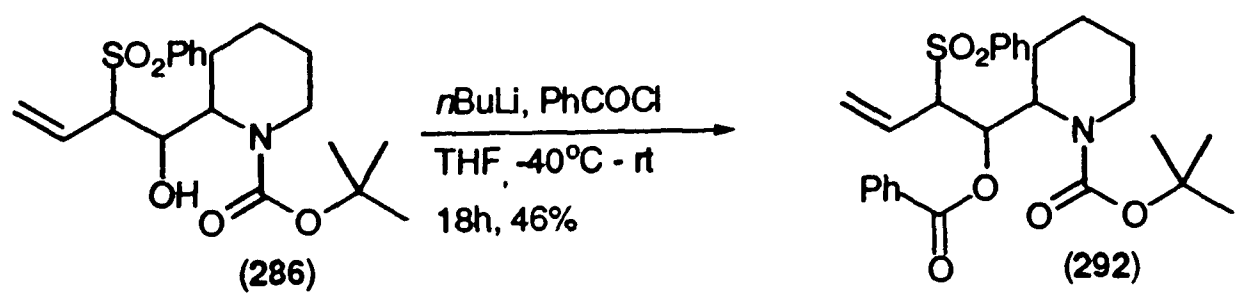
before, yielding 40% of the required piperidinediene (**284**). The instability of the trifluoroacetate (**290**) led to an investigation into alternative groups for functionalisation of the β-hydroxy sulfone (**286**).

Firstly synthesis of acetate (**291**) was attempted using acetic anhydride and pyridine[180], which afforded only a 3% yield of the required product (Scheme 108). This reaction procedure had involved the use of 4-dimethylaminopyridine , a hyperacylation catalyst, which has been shown to promote even difficult acylations[181-183], thus it was surprising that the reaction proceeded in such a poor yield.



Scheme 108

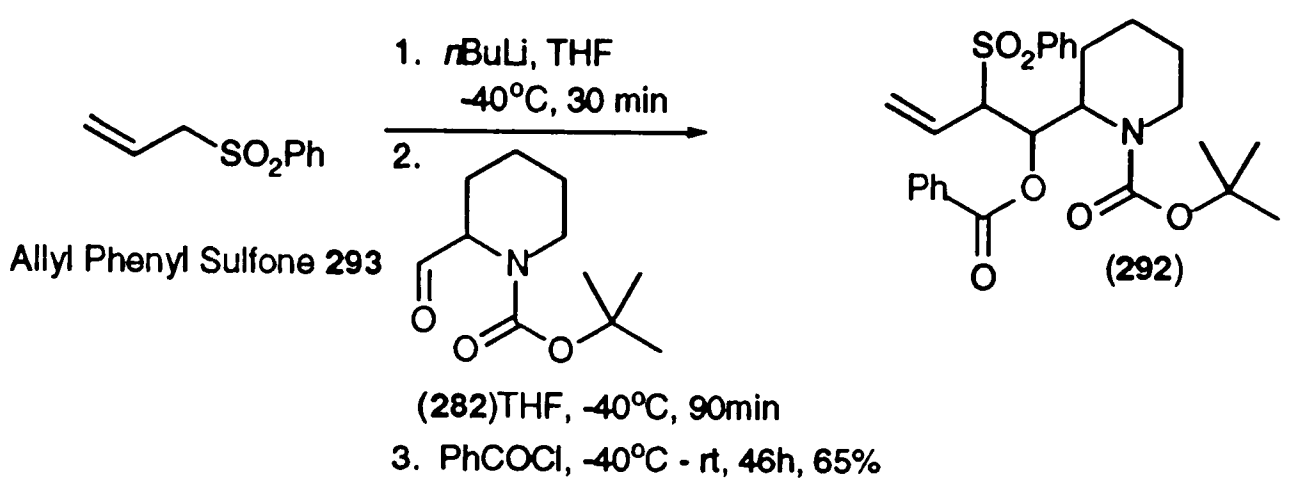
Attention then switched to synthesis of the benzoate (**292**) which was initially produced using benzoyl chloride and pyridine in a 24% yield. However work by Gannett[184] on the synthesis of the capsaicinoids suggested changing the base to *n*BuLi for the benzoylation for β-hydroxy sulfones, which improved the yield to 46% (Scheme 109).



Scheme 109

An obvious next step for the synthesis of benzoate (**292**) was to attempt a one-pot procedure, as *n*BuLi was required as the base for both the metallation and

benzoylation steps. Thus to a solution of allyl phenyl sulfone **283** at -40°C was added *n*BuLi, then after 30 minutes, piperidine aldehyde (**282**) in THF, followed by benzoyl chloride after a further 90 minutes, allowing isolation of a 65% yield of benzoate (**292**) (Scheme 110).



Scheme 110

2.7.3. Reductive Elimination of the β-Substituted Sulfone

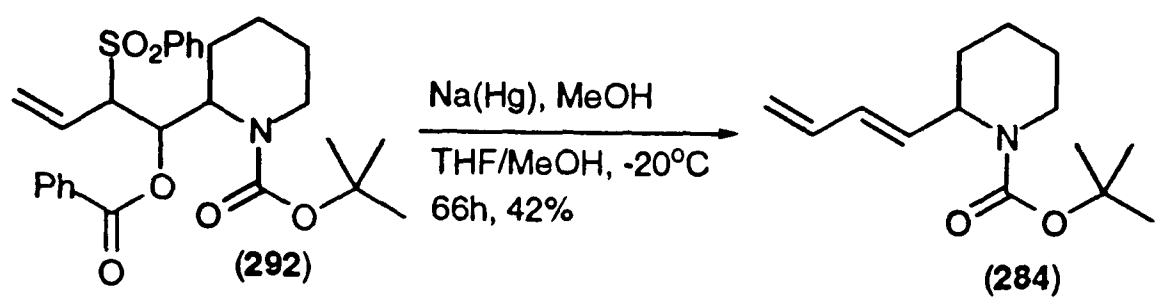
The reductive elimination step is effected by an electron donating species such as sodium amalgam in a protic solvent. The presence of the protic solvent is essential to the reaction and MeOH has been found to be superior to EtOH and *i*PrOH[111]. A number of modifications to this reaction have been suggested to slow the rate at which the MeOH reacts with the sodium amalgam, forming NaOMe which causes serious side reactions:

- The use a reaction solvent of 3:1 THF:MeOH, which reduces the amount of MeOH required, thus reducing the reaction rate with the sodium amalgam. The use of THF also improves the solubility of the organic substrates[185].

- A reaction temperature of -20°C, at which formation of NaOMe is slow[111].

- The presence of an acid phosphate buffer, to react with the produced NaOMe. Normally sodium hydrogenphosphate is used[186].

Application of all these modifications to the elimination of benzoate (**292**) using sodium amalgam (5.0eq) and sodium hydrogenphosphate (10.0eq), conditions identified by Fukumoto[187], afforded the piperidinediene (**284**) in a reproducible 40% yield (Scheme 111).

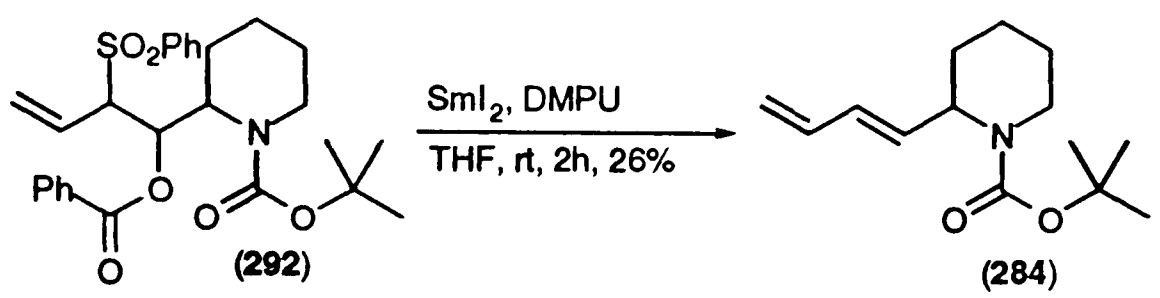


Scheme 111

A recent modification of the reductive elimination step has been the use of samarium diiodide. The use of this reagent was first reported by Kende for the reductive elimination of β-hydroxy imidazolyl sulfones only[188]. However the demonstration by Fukumoto that activation of the SmI_2 by HMPA allows elimination of all the substrates that would undergo such a reaction with sodium amalgam, has widely increased the use of this methodology[187]. Preparation of trisubstituted alkenes has been reported, during which it was demonstrated that the use of SmI_2 is a considerably milder procedure than the use of sodium amalgam[189]. Recently the use of this methodology was demonstrated in a synthesis of the rhizoxins[190].

It was decided to attempt a reductive elimination of benzoate (**292**) using this methodology; however, the use of HMPA raised some concerns. In recent years HMPA has been shown to be a carcinogen in animal tests even at low concentration and 'it was concluded that HMPA ranks in the super league of experimental carcinogens and must be considered as potentially posing a serious risk to man, even at the scale of use in the laboratory'[191]. Fortunately DMPU has been identified as an effective alternative in a variety of reactions[192], thus this reagent was substituted in the procedure.

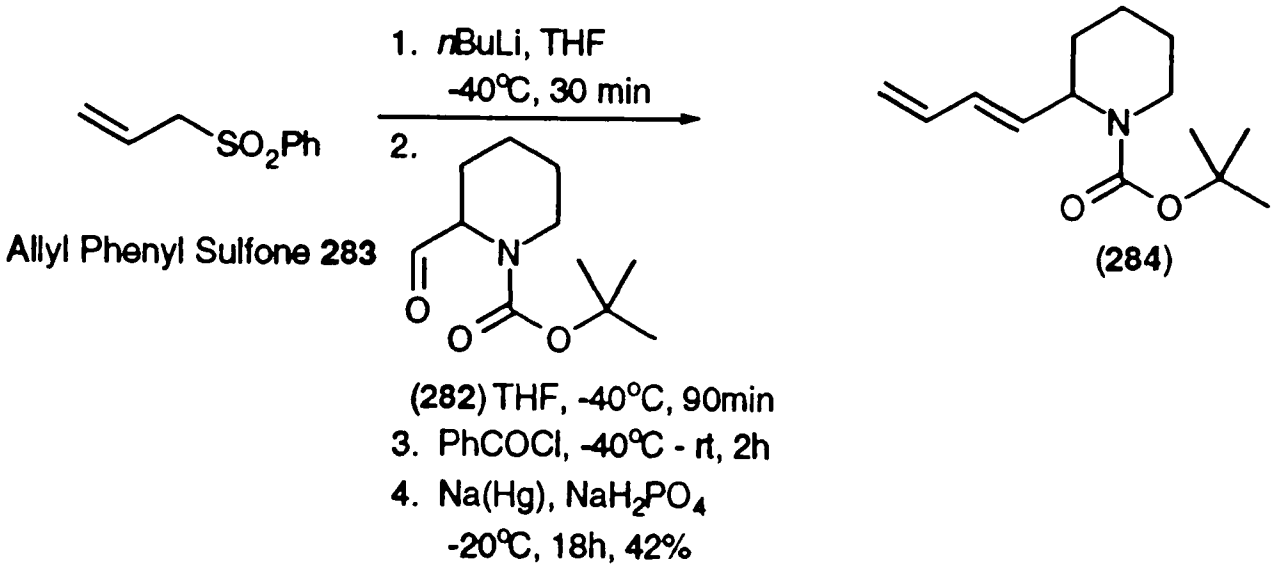
The reaction was investigated using the conditions developed by Fukumoto, starting with SmI_2 (5.0eq) as a 1.0M solution in THF. Addition of DMPU (10.0eq) turned the green/blue solution purple. Immediate addition of the benzoate (**292**) then turned the solution indigo. Work up afforded a 26% yield of the required piperidinediene (**284**) (Scheme 112).



Scheme 112

The yield was disappointing and, although no temperature control is required for the reaction, the reaction is extremely air sensitive causing practical difficulties. Thus the use of sodium amalgam seems to be a better procedure, affording a 27% yield across the four steps.

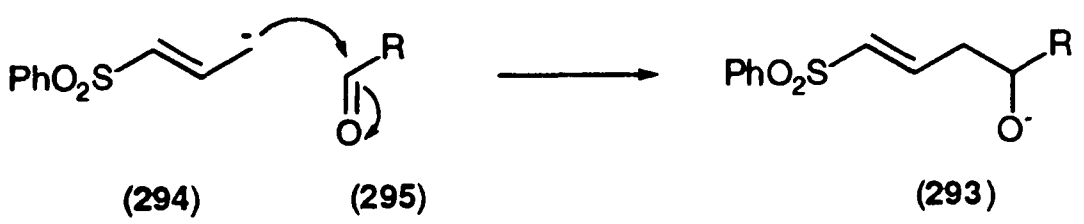
A final investigation into this step of the coupling was an attempt to complete all four steps in a single pot. The reaction procedure was carried out for the first three steps as had been previously demonstrated (Scheme 110). The reaction was then cooled to -20°C and sodium hydrogenphosphate and sodium amalgam added. This single pot reaction allowed isolation of 42% of piperidinediene (**284**) (Scheme 113).



Scheme 113

2.7.4. Coupling of the α-Metallated Sulfone with an Aldehyde or Ketone

The only step in the Julia coupling not to have been investigated was the coupling of the α-metallated sulfone (**277**) to the aldehyde or ketone to afford (**278**). Studying this reaction was problematic due to the diastereomeric and rotameric effects of the intermediate β-functionalised sulfones making NMR analysis difficult. This problem was reduced by removal of the *N*-BOC with trifluoroacetic acid, to afford secondary amines. The removal of the *N*-BOC group eliminated the rotameric effects, allowing detailed ^{1}H NMR analysis of the alkene protons in the molecules. These suggested the presence of a species containing an αβ-unsaturated sulfone. A molecule containing such a proton (**295**) could be formed by nucleophilic attack by the sulfone anion (**294**) on aldehyde (**295**) *via* its allylic stabilised resonance form (Scheme 114).

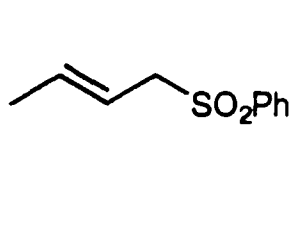


Scheme 114

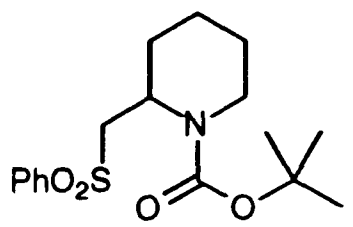
A likely reason for the occurrence of this side reaction is that the steric bulk of the *N*-BOC group prevents nucleophilic attack of the aldehyde. This effect will promote the reaction (Scheme 114), as attack through the alkene terminus is less sterically encumbered than direct attack by the centre α to the sulfone. In an attempt to reduce this effect it was decided to investigate two separate approaches:

- Increasing the steric bulk of the groups on the alkene terminus. For the coupling of piperidine aldehyde (**160**) to allylic sulfone (**257**) rather than a terminal allylic alkene (**283**), the alkene will have a carbon chain attached. This should reduce the steric difference between the two sites of nucleophilic attack. To test this hypothesis, synthesis of an allylic sulfone (**296**) with a methyl group replacing one of the hydrogen atoms was required (Figure 24).

- Reversal of the coupling partners. Coupling of a piperidine sulfone (**297**) (Figure 24) to an enal is required. This coupling reaction should be more successful as, although the sulfone might be encumbered, the enal will not be, and exclusive 1,2-addition should occur.



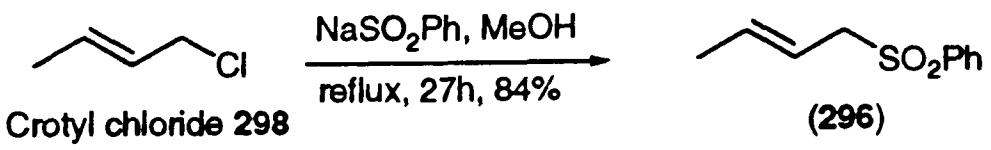
(296)



(297)

Figure 24

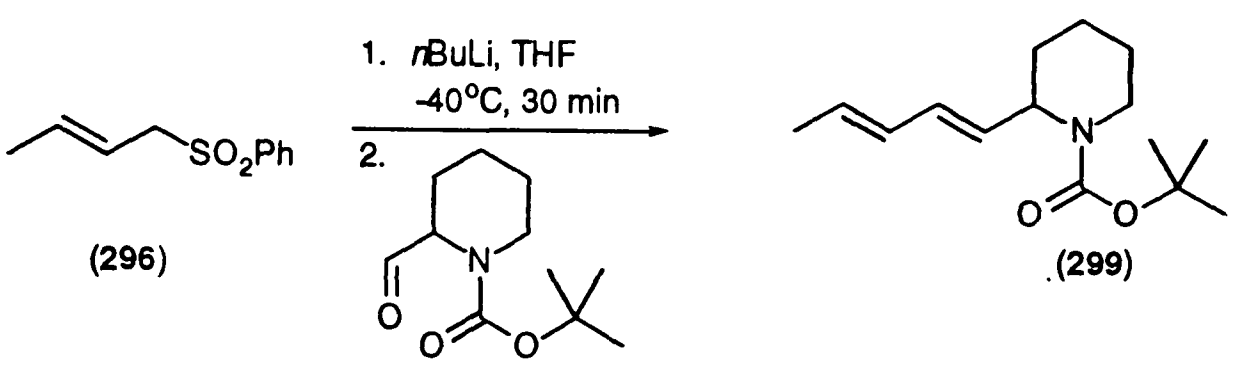
The synthesis of allylic sulfone (**296**) was completed using a reaction reported by Trost[193]. Reaction of crotyl chloride **298** with sodium benzenesulfinate in methanol afforded the required allylic sulfone (**296**) (Scheme 115).



Crotyl chloride **298** (296)

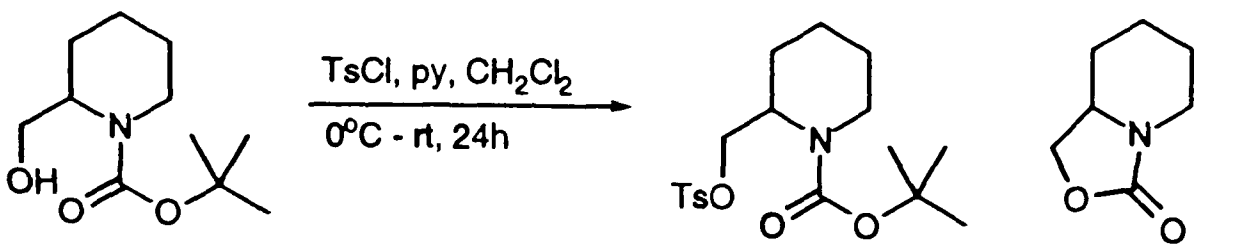
Scheme 115

This allylic sulfone (**296**) was converted to benzoate using the previously identified conditions (Scheme 110) in an improved 98% yield, suggesting that the extra methyl group strongly biases the reaction towards attack from the centre α to the sulfone. Elimination using sodium amalgam afforded piperidinediene (**299**) in a 45% yield (44% overall) and elimination using SmI_2 a 46% yield (45% overall). The best yield was achieved using the one-pot for all four steps procedure which afforded a 49% yield for the coupling (Scheme 116). However an attempt to achieve a one-pot reaction involving the use of SmI_2 failed to give any product even though oxygen free conditions were used.



Scheme 116

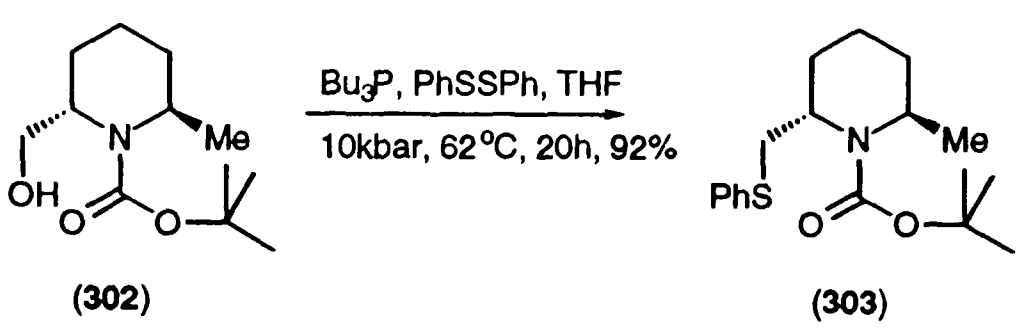
For the synthesis of piperidine sulfone (**297**), it was necessary to convert the hydroxy group of piperidine alcohol (**285**) to a sulfone. A direct method seemed to be conversion of the hydroxyl to a leaving group, followed by displacement by sodium benzenesulfinate. Thus, conversion of the alcohol (**285**) to tosylate (**300**) was investigated. Using standard conditions of TsCl and pyridine afforded only 11% of the required tosylate (**300**) with 34% of oxazolopyridinone (**301**) (Scheme 117).



(285) **(300)** 11% **(301)** 34%

Scheme 117

Obviously an alternative approach was required, and a survey of the literature uncovered work completed on conversion of alcohols to phenylsulfides using tributylphosphine and phenyldisulfide. Particularly of note was the conversion of *trans*-piperidine alcohol (**302**) to piperidine sulfide (**303**)[194] (Scheme 118).

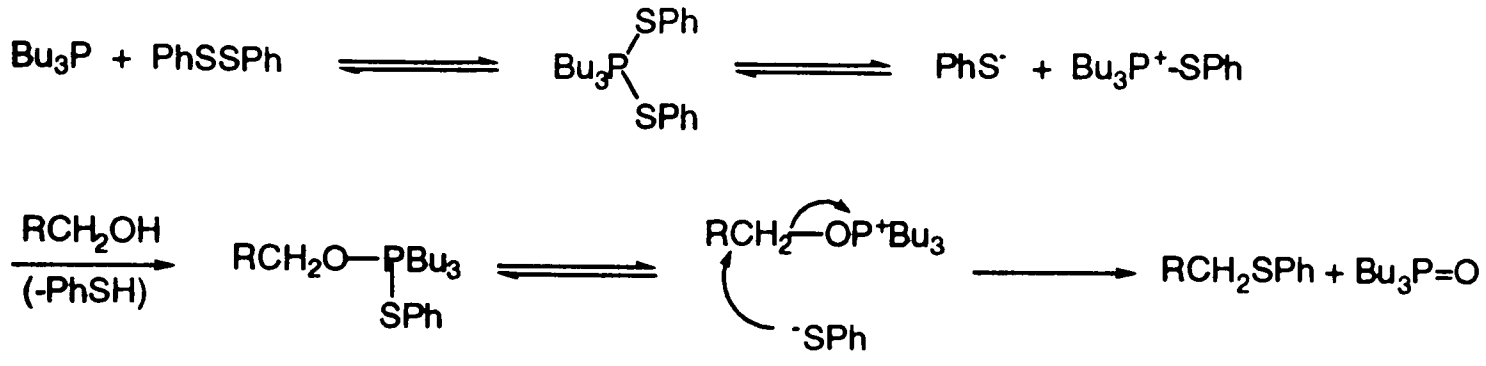


(302) **(303)**

Scheme 118

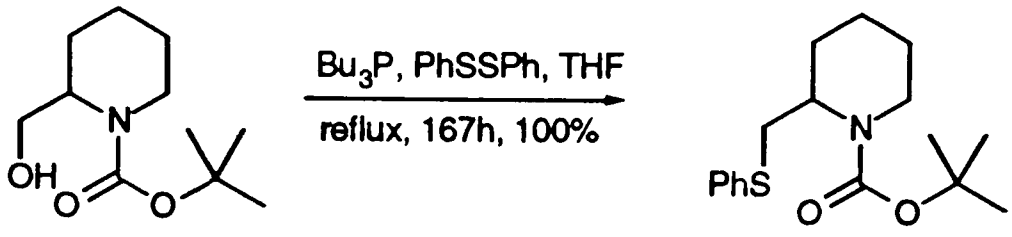
This conversion is extremely significant as it was performed on the enantiomer of *trans*-piperidine (**160**) required for the total synthesis of himbacine **1** and, if coupling of a piperidine sulfone was required in the Julia coupling, this would be an important transformation. However, with no access to the high pressure equipment of the type used in the above reaction, it was decided to use standard reaction conditions of refluxing THF at atmospheric pressure which had also been reported in the paper, with extended reaction times in an attempt to get an acceptable yield of piperidine sulfide (**304**).

The mechanism of the reaction involves a series of ionisation and bond-forming steps (Scheme 119)



Scheme 119

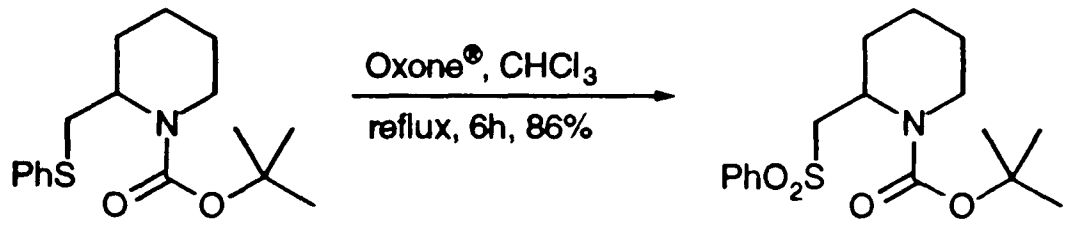
Application of this methodology to the piperidine alcohol (**285**) afforded an excellent quantitative yield of the required piperidine sulfide (**304**), proving that extending reaction times is as successful in promoting the reaction as increasing the pressure (Scheme 120).



(285) **(304)**

Scheme 120

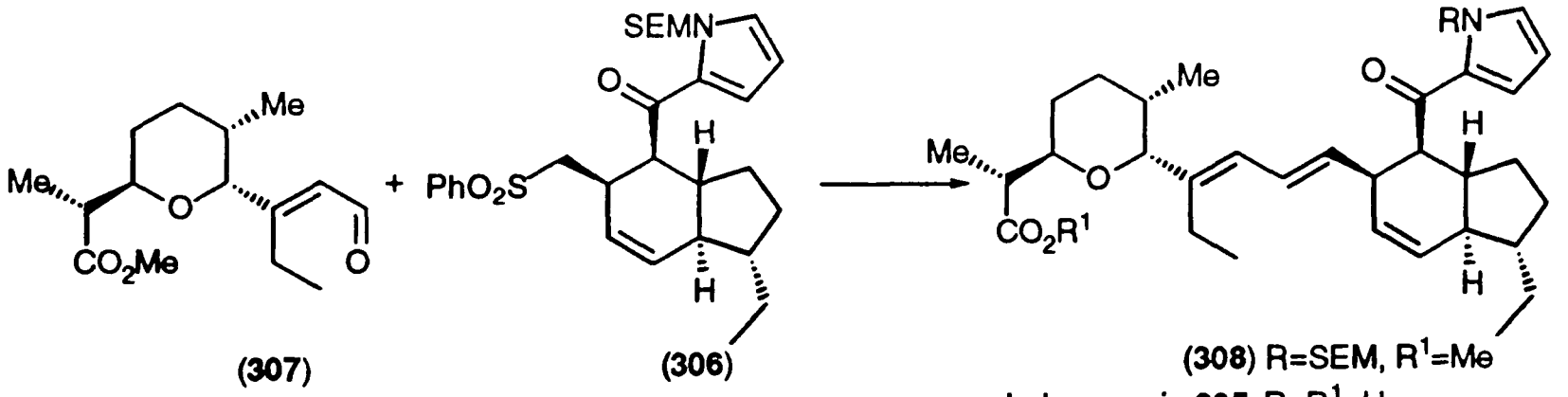
Oxidation of the sulfide (**304**) to sulfone (**297**) was completed using Oxone®, a persulfate complex widely reported for such oxidations[195]. Initially the conditions developed by Webb[196] were used, with the Oxone® and sulfide (**304**) in acetone/water buffered with sodium bicarbonate. However, this procedure was slow and required regular additions of Oxone® to reach completion. Thus, changing to the conditions reported by Greenhalgh[197], with the Oxone® and sulfide (**304**) in refluxing chloroform with wet alumina, afforded sulfone (**297**) in 86% yield (Scheme 121).



(304) (297)

Scheme 121

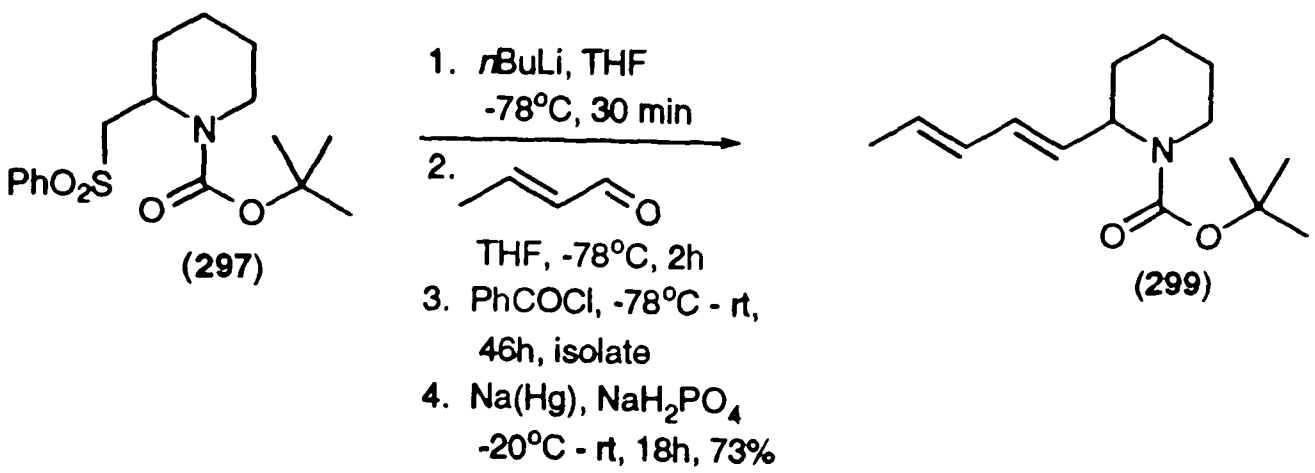
Investigations into the Julia coupling of this species (**297**) with an enal, in this case crotonaldehyde, was then undertaken. The Julia coupling of sulfones with enals has been investigated, and it has been shown that sulfone anions will exclusively attack *via* a 1,2-addition[198], unless HMPA is added to the reaction mixture when 1,4-addition is observed[199]. The initial reaction conditions were based on a synthesis of indanomycin **305**[200], where the coupling of sulfone (**306**) to enal (**307**) to afford diene (**308**) was achieved (Scheme 122).



Scheme 122

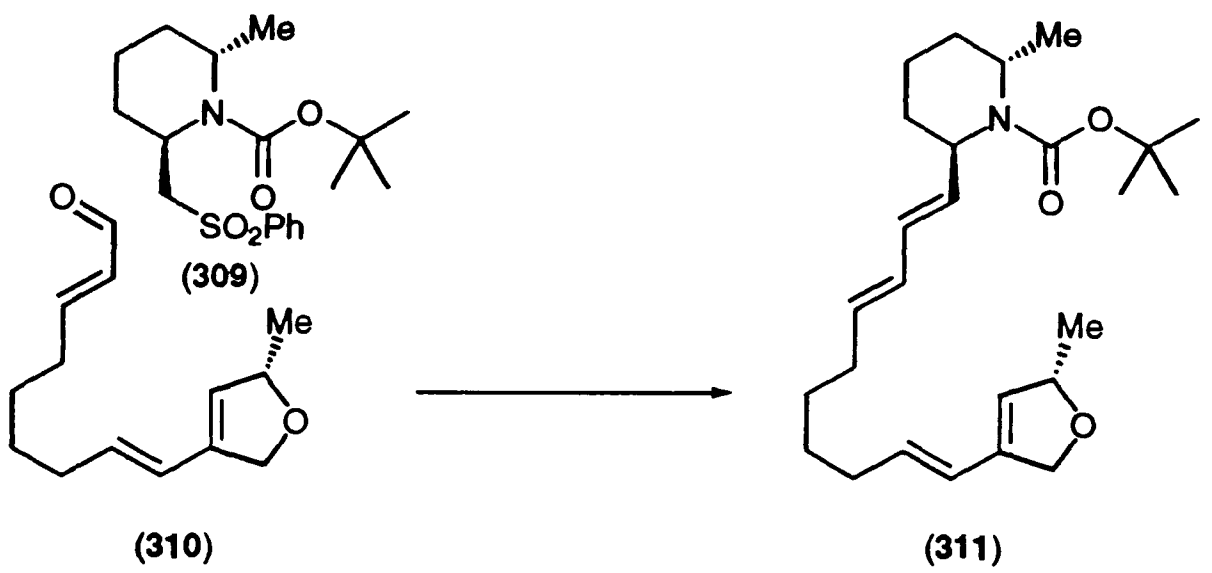
This coupling had been achieved in a 53% yield across the four steps, and had been performed with a reaction temperature of -78°C for the metallation, coupling and functionalisation steps.

Using the previously developed Julia coupling conditions, except for application of the lower reaction temperature, afforded piperidinediene (**299**) in a 58% yield across the 4 steps. If the intermediate benzoate was isolated and purified before the reductive elimination step the yield rose to 73% across the four steps (Scheme 123).



Scheme 123

In summary, careful control of the reaction conditions is required for successful coupling. After careful development, the optimum conditions for the coupling reaction appear to be reversal of the functional groups; thus, using piperidine sulfone (**309**) and an enal (**310**) (Scheme 124). Use of these conditions should allow successful coupling of piperidine sulfone (**309**) to enal (**310**), affording (**311**) which would then be converted to the precursor (**76**) for the proposed iminium ion mediated Diels-Alder reaction (Scheme 89).

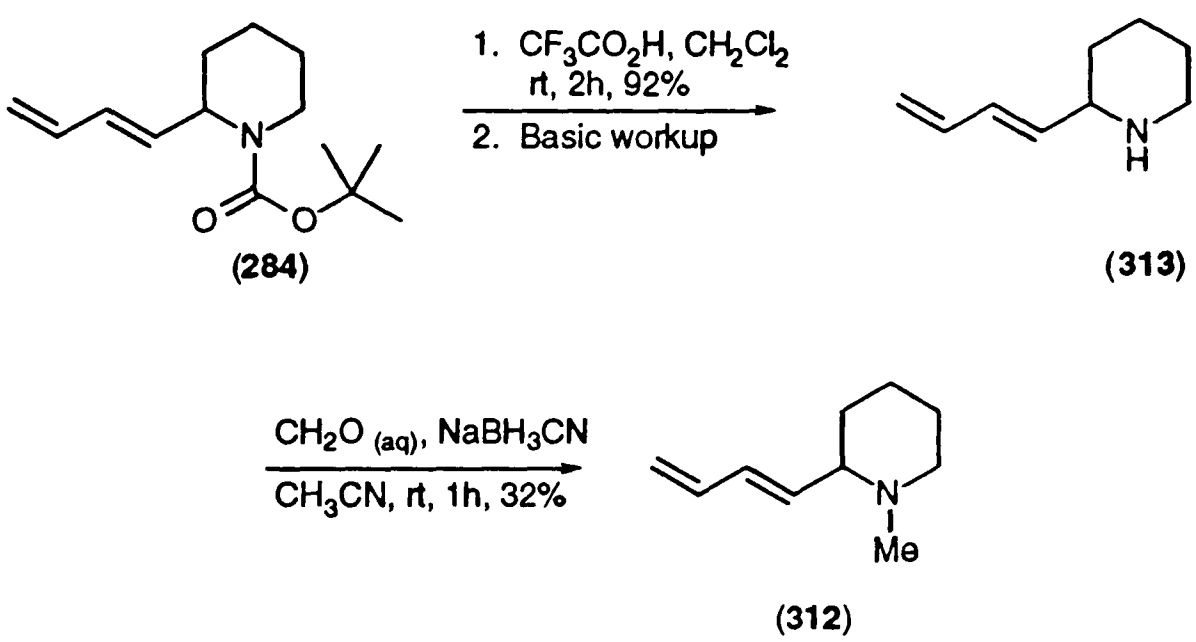


Scheme 124

2.8. Further Studies on the Polonovski Reaction

The synthesis of piperidinediene (**284**) offered an opportunity to examine the effect the diene sidechain has on the regioselectivity of the Polonovski reaction. Thus, conversion of the *N*-BOC piperidinediene (**284**) to *N*-methyl piperidinediene (**312**)

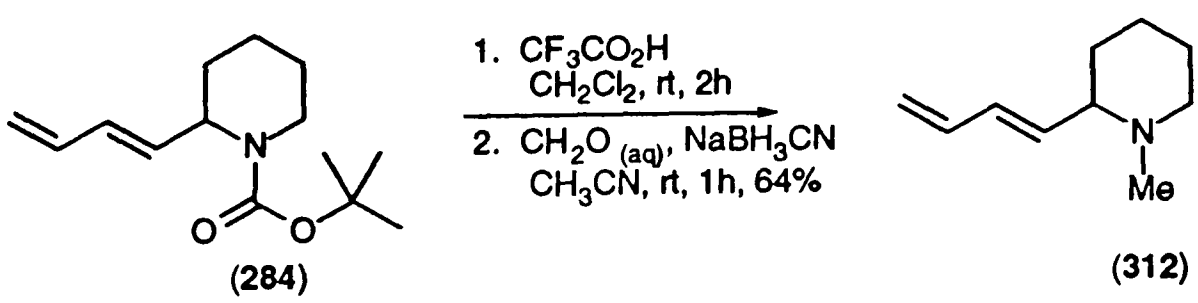
was achieved initially by deprotection to afford the amine (**313**), with trifluoroacetic acid, conditions which had been demonstrated on *N*-BOC piperidines by Coppola[201]. Isolation of the amine proved to be problematic, possibly due to the molecule having good water solubility and therefore requiring extensive extraction for the aqueous phase. A reductive methylation of amine (**313**) then afforded the *N*-methyl piperidinediene (**312**) in a disappointing 32% yield (Scheme 125).



(**284**) (**313**) (**312**)

Scheme 125

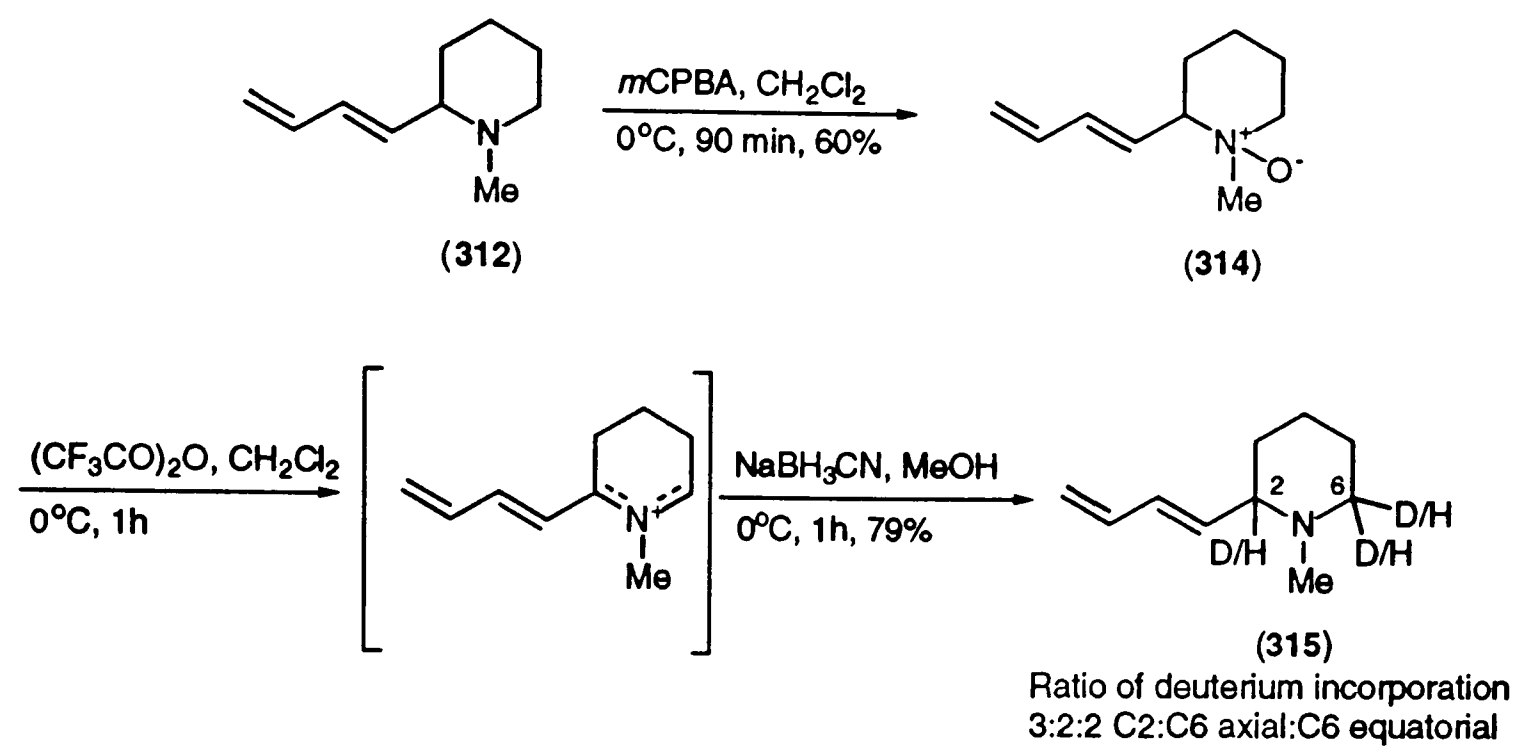
In an attempt to improve the overall yield of these two steps it was decided to change to a one-pot procedure, which had been reported to give better overall yields[202]. Thus after trifluoroacetic acid deprotection, the solvent was removed and the crude salt reductively methylated affording the *N*-methyl piperidine (**312**) in an improved 64% yield across the two steps (Scheme 126).



(**284**) (**312**)

Scheme 126

Oxidation of the *N*-methyl piperidine (**312**) to the piperidine *N*-oxide (**314**) proceeded smoothly using *m*CPBA, following which the Polonovski reaction with trifluoroacetic anhydride and sodium borodeuteride afforded a mixture of deuterated *N*-methyl piperidines (**315**) (Scheme 127).

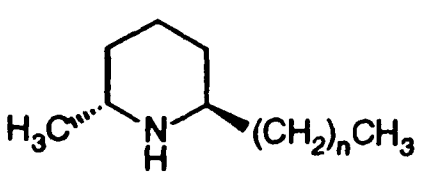


Scheme 127

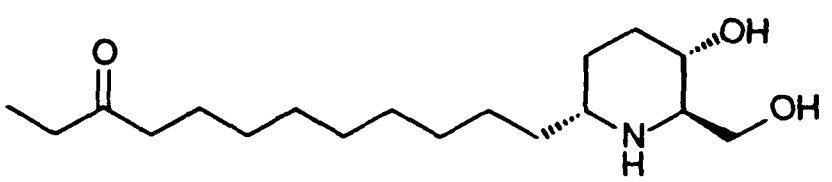
The deuterium incorporation pattern was analogous to that for *N*-methyl piperidine (**274**) (Scheme 97), strongly suggesting that the steric factors suggested earlier are the most significant affecting the course of the reaction. Thus, as increasing the acidity of the proton at the C2 position had not significantly affected the amount of deuterium incorporation at that position, investigation of the Polonovski reaction with a 2,6-disubstituted piperidine suggested itself as the next reaction to investigate factors affecting this reaction. With a substituent at C6, iminium ion formation on either side of the nitrogen would cause unfavourable 1,3-allylic interactions, hopefully further biasing the reaction towards the desired iminium ion formation by elimination of the allylic proton at C2. Total synthesis of the piperidine sulfone (**309**) required for the Julia coupling (Scheme 124) offers a substrate that could be used for this investigation. Thus attention moved to completing the synthesis of piperidine sulfone (**309**).

2.9. Synthesis of *trans*-Piperidine

The abundance of biologically active alkaloids containing a 2,6-disubstituted piperidine ring has resulted in considerable synthetic efforts to reach these systems. The majority of these approaches have been towards the synthesis of *cis*-piperidines, which are more widely found in nature[109,203]. However, a number of syntheses of *trans*-piperidines have been reported[110,204,205] as part of approaches to molecules such as the solenopsins A-C **316-318**[206,207] and prosopinine **319**[208] (Figure 25).



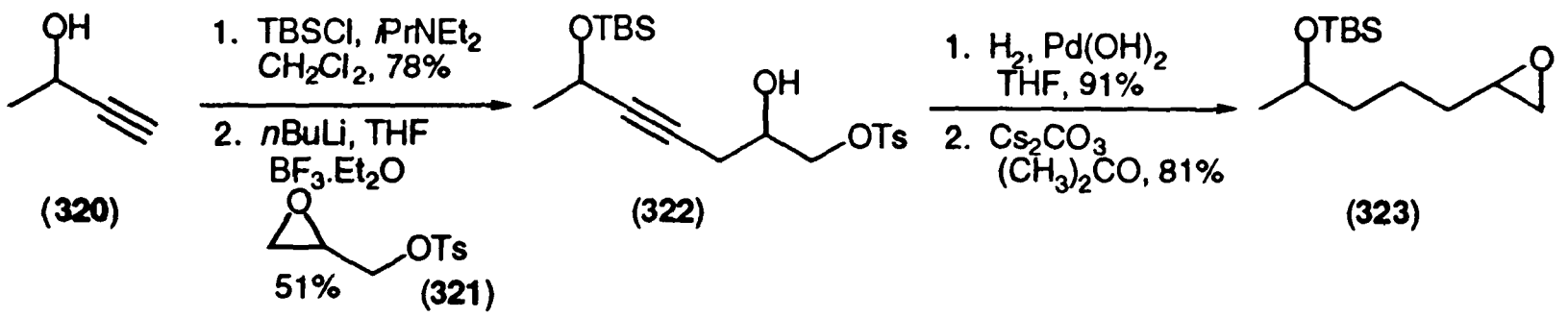
Solenopsin A **316** n=10
Solenopsin B **317** n=12
Solenopsin C **318** n=14



Prosopinine **319**

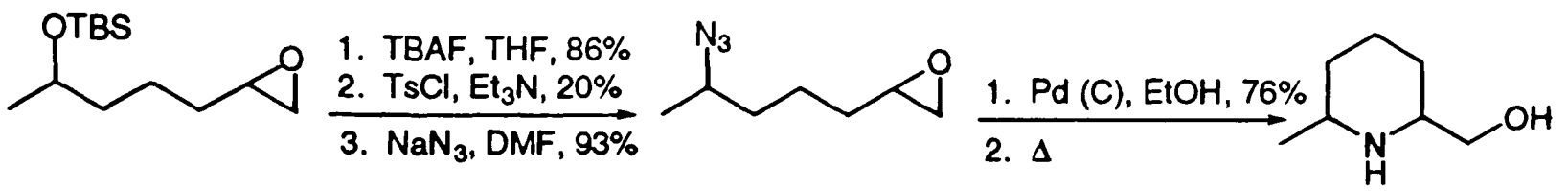
Figure 25

Previous work completed as part of this project[99] towards the synthesis of a *trans*-piperidine involved coupling of alkyne (**320**) to epoxide (**321**) to give alkyne (**322**), following which reduction and cyclisation afforded epoxide (**323**) (Scheme 128).



Scheme 128

Removal of the silyl ether, followed by tosylation and azide displacement afforded azide (**324**), which was reduced to the amine and cyclised to afford piperidine (**325**) (Scheme 129).



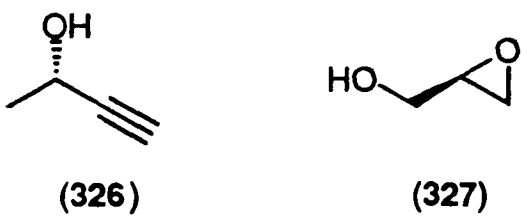
(323) **(324)** **(325)**

Scheme 129

It was decided not to use this route for two reasons:

- The overall yield of the scheme was poor. With a further five steps required (Scheme 2) to convert piperidine alcohol (**325**) to piperidine sulfone (**309**), this route involves 15 steps overall, some of which were low yielding.

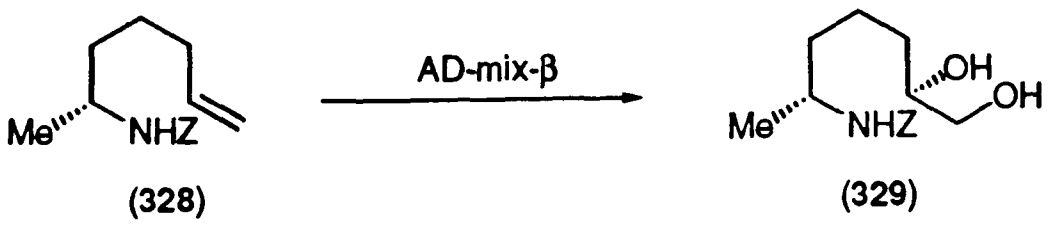
- The synthesis (Scheme 128 and 129) was completed on racemic material and the required chiral starting materials, alkyne (**326**) and epoxide (**327**) (Figure 26), are expensive.



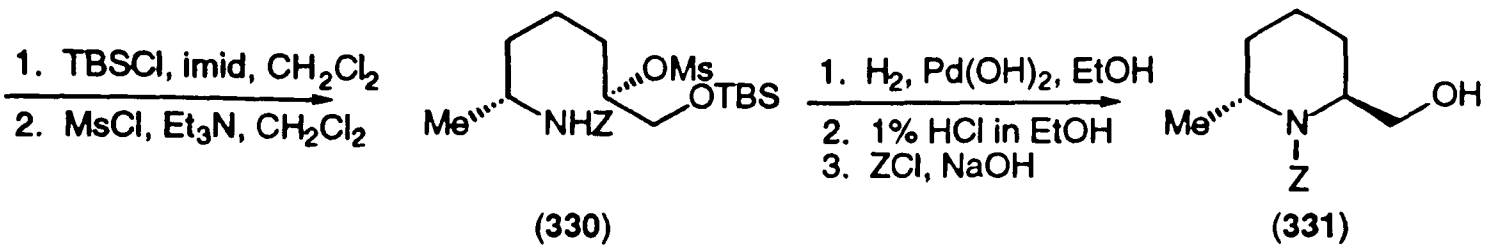
(326) **(327)**

Figure 26

Thus, it was decided to identify an alternative route to the required *trans*-piperidine which would avoid these problems. A synthesis of *trans*-piperidines was reported by Momose[209], using *R*-alanine as one of the sources of chirality, the other coming from a Sharpless asymmetric dihydroxylation. Alkene (**328**) was converted to diol (**329**) by the dihydroxylation, following which sequential functionalisation of the two hydroxyl groups afforded methanesulfonate (**330**). This was then cyclised to afford *trans*-piperidine (**331**) (Scheme 130).

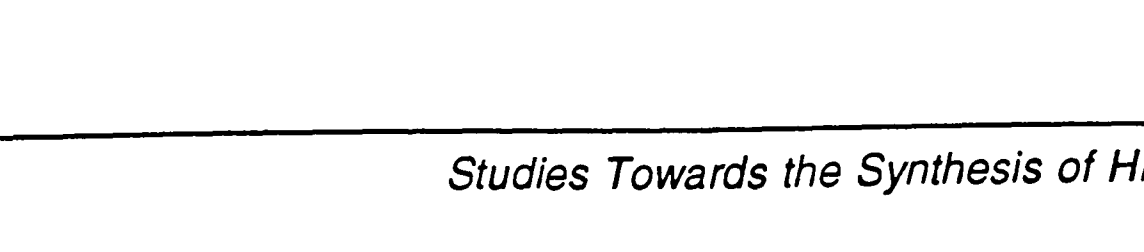


(328) **(329)**



Scheme 130

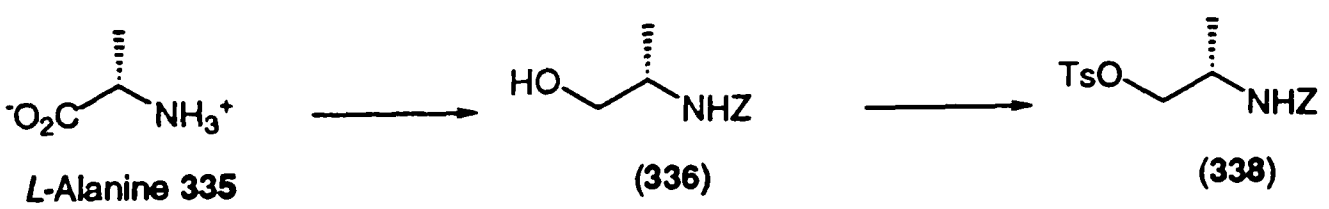
As an initial approach to the required *trans*-piperidine sulfone (**309**), it was decided to follow this work for synthesis of the diol (**332**), following which bistosylation, cyclisation and *N*-protection should afford piperidine tosylate (**333**) (Scheme 131). Conversion of the tosyl group to a phenyl sulfone could then be completed using the chemistry demonstrated by Kozikowski (Scheme 2).

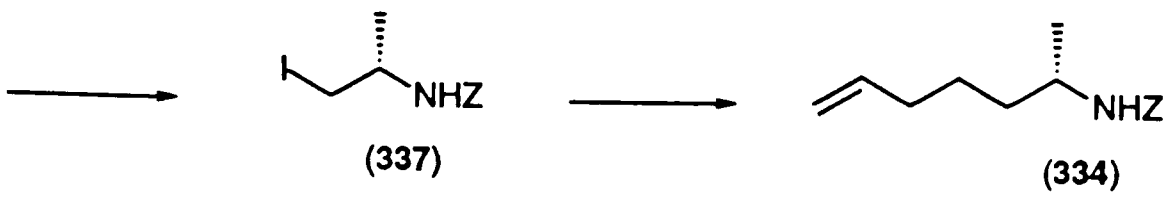


Scheme 131

2.9.1. Synthesis of Alkene (334)

A synthesis of the alkene (**334**) was initially required, which was completed using chemistry reported by Schlessinger[210]. Starting from *L*-alanine **335**, the first three steps involve reduction to alcohol (**336**), then conversion to iodide (**337**) *via* the tosylate (**338**). The carbon chain is then extended by a copper-mediated Grignard reaction using homoallylmagnesium bromide **339** to afford alkene (**334**) (Scheme 132).

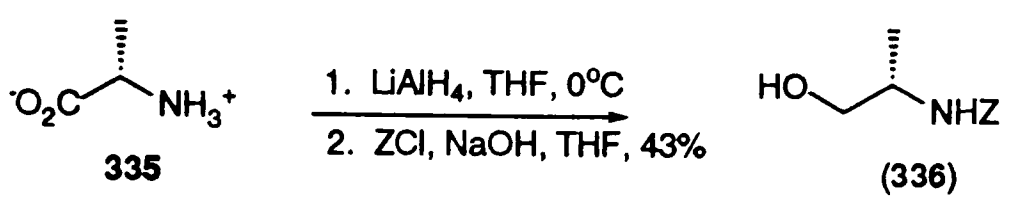




(337) (334)

Scheme 132

The reduction of *L*-alanine **335**, to the alcohol (**336**), with *N*-protection as the benzoyloxycarbamate was initially attempted using the reported conditions[210]. However, the yield of the reaction was variable, the best being a disappointing 43% (Scheme 133).

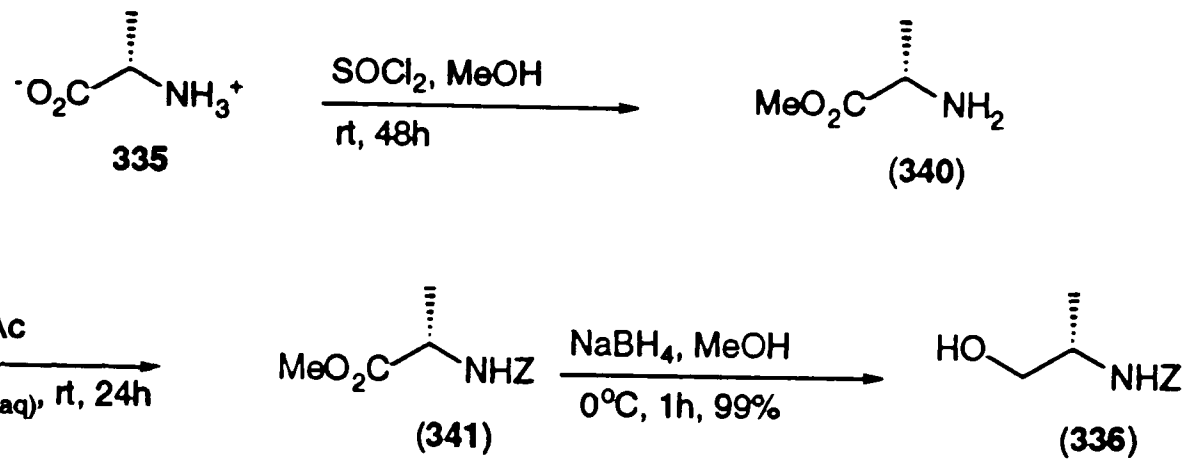


335 (**336**)

Scheme 133

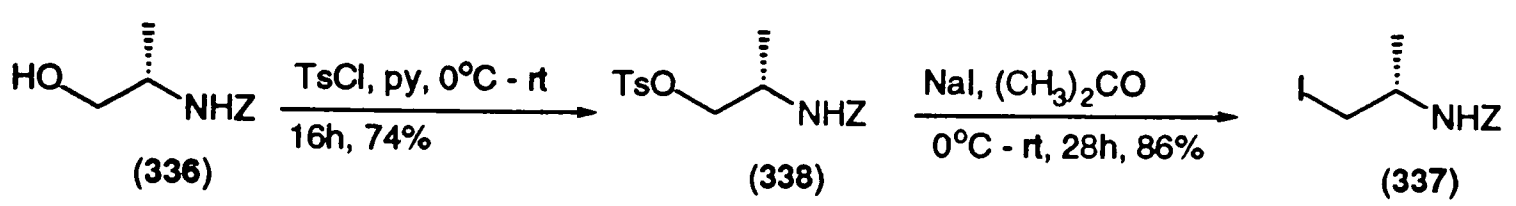
Schlessinger had reported a yield 94%, but problems with reproducing this yield had also been reported by Braekman[204], who had only been able to obtain yields of 50-55%, thus an alternative procedure was sought. Using a procedure reported by Greene[211] involving refluxing THF and *in situ N*-protection failed to improve the yield.

As the reaction remained capricious, and a large scale was required to produce a sufficient quantity of material (10g of $LiAlH_4$ each time), it was decided to investigate a more reliable and safer procedure. A three step procedure was identified, involving conversion of the amino acid to the methyl ester (**340**), followed by *N*-protection to afford carbamate (**341**) and reduction to the alcohol (**336**) using sodium borohydride. L-alanine **335** was converted to methyl ester (**340**) using thionyl chloride in methanol, then the amine protected with ZCl to give carbamate (**341**)[212]. Reduction of the carbamate[213] (**341**) to the alcohol (**336**) was achieved using sodium borohydride affording the product (**336**) in an excellent 99% yield over the three steps (Scheme 134).



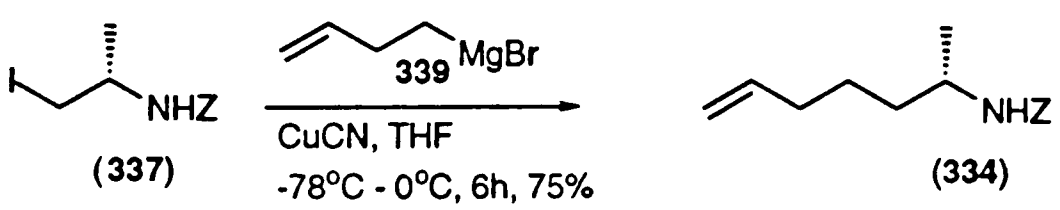
Scheme 134

The alcohol (**336**) was converted to tosylate (**338**) using tosyl chloride and pyridine. The use of a Finkelstein reaction with sodium iodide in acetone then afforded iodide (**337**) (Scheme 135).



Scheme 135

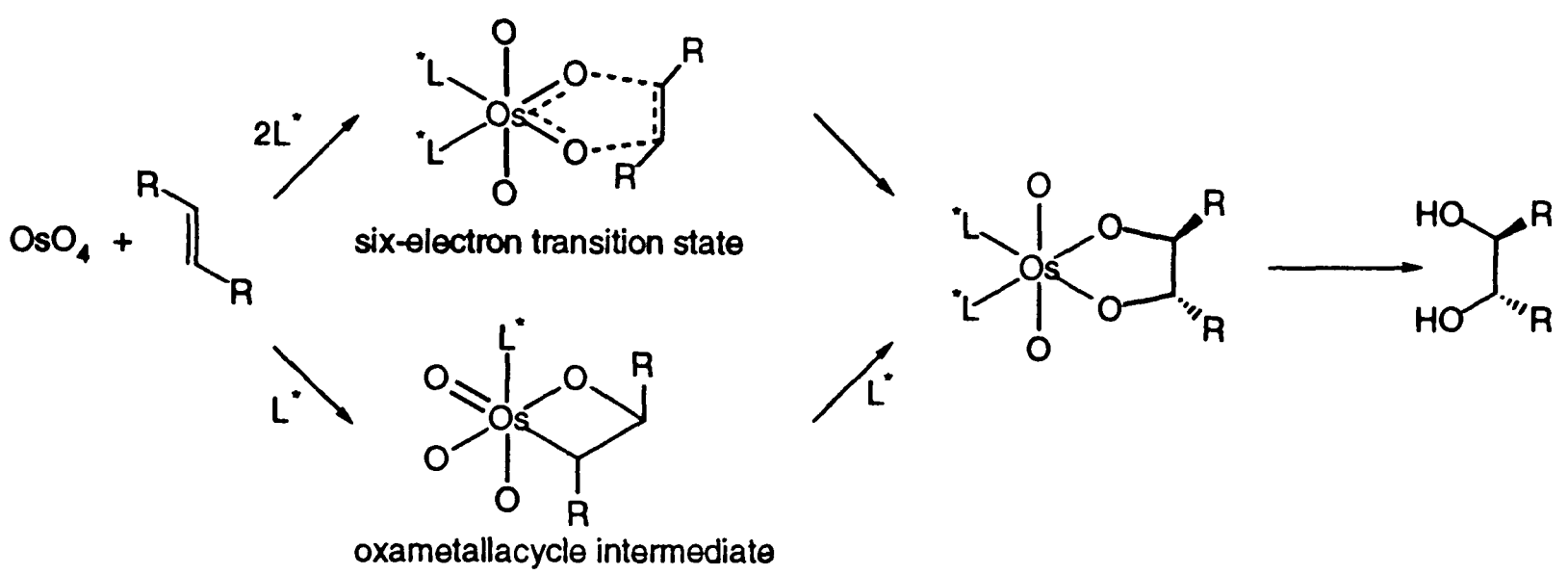
The Grignard reaction with homoallylmagnesium bromide **339** was initially completed using the original conditions reported by Momose[214]. The Grignard reagent was freshly prepared using the method of Brown[164], with careful temperature control, followed by addition of the iodide (**337**). However, this procedure, with catalytic copper iodide, afforded only a 45% yield of the required alkene (**334**). Changing the copper salt to copper cyanide and adding a stoichiometric amount improved the yield to 75% (Scheme 136).



Scheme 136

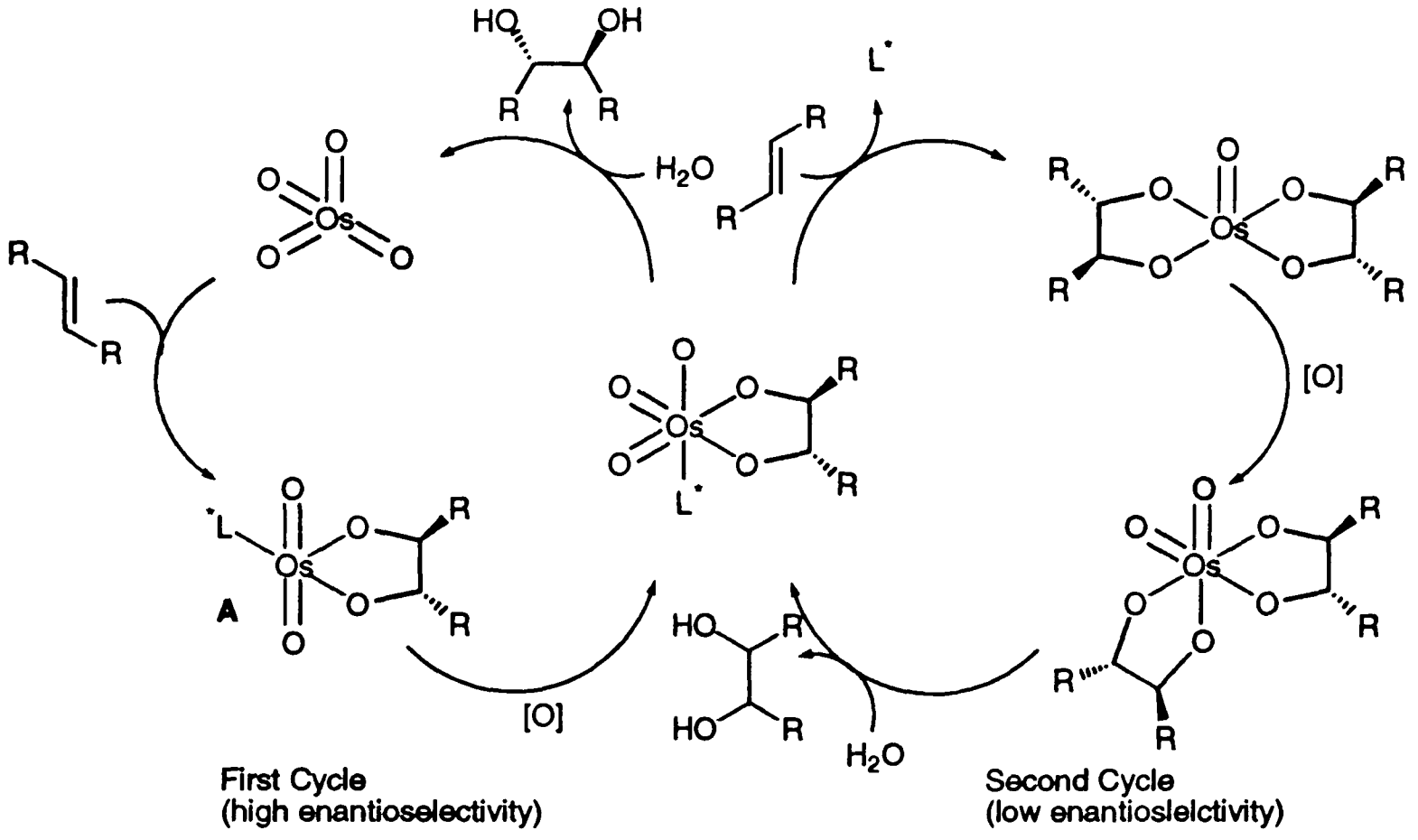
2.9.2. Dihydroxylation and Diol Functionalisation

Dihydroxylation of alkenes with osmium tetroxide stereospecifically creates *cis-vicinal*-diols in a hydrocarbon skeleton and simultaneously installs asymmetric centres at two carbon atoms. The reaction is considered to proceed either by way of a six-electron pericyclic mechanism or *via* an oxametallacycle intermediate[215] (Scheme 137).



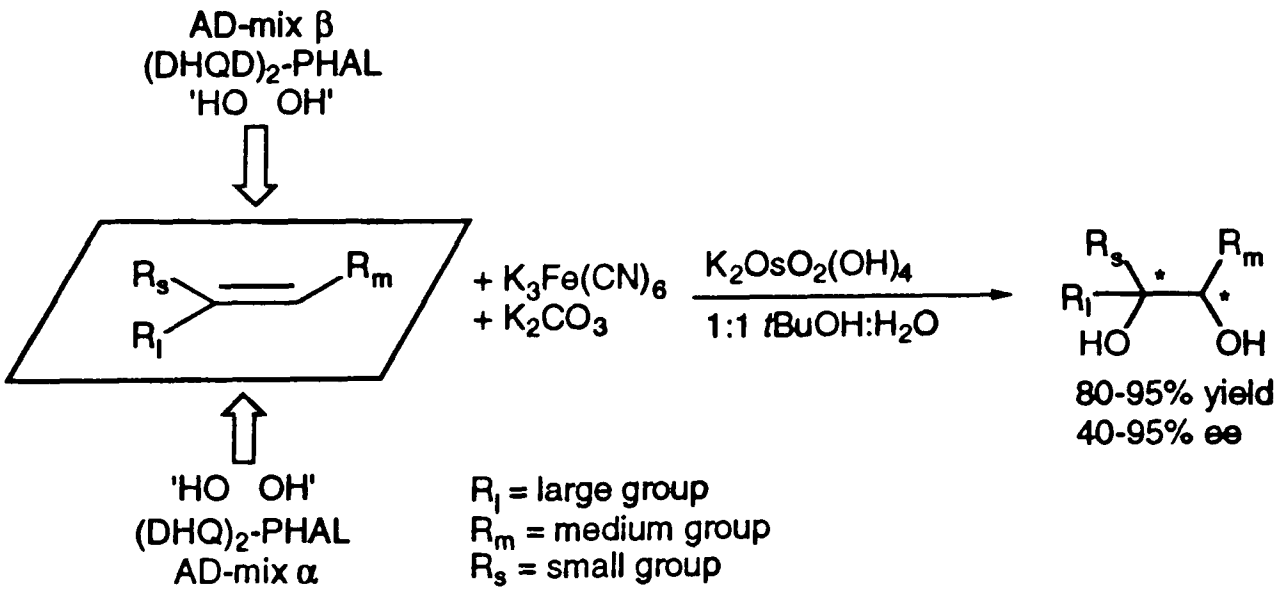
Scheme 137

Certain tertiary amines such as pyridine or α-quinuclidine accelerate the reaction, and the use of chiral ligands has been shown to be an important method of asymmetric dihydroxylation. The most important work in this area has been reported by Sharpless, who has found that the use of dihydroquinidine and dihydroquinine ligands allowed dihydroxylation reactions to proceed with an 88% enantiomeric excess[216]. According to Sharpless, two cycles operate in the catalytic reaction (Scheme 138). The first cycle is highly enantioselective, whereas the second is poorly enantioselective. Hydrolysis of the key intermediate formed from **A** and reoxidant is not very fast and osmylation of a second molecule of alkenic substrate can occur, the start of the second, undesired catalytic cycle. The use of potassium hexacyanoferrate (III) as reoxidant in a 1:1 *tert*-butyl alcohol:water two layer system suppresses the second cycle and leads to high enantioselectivity.



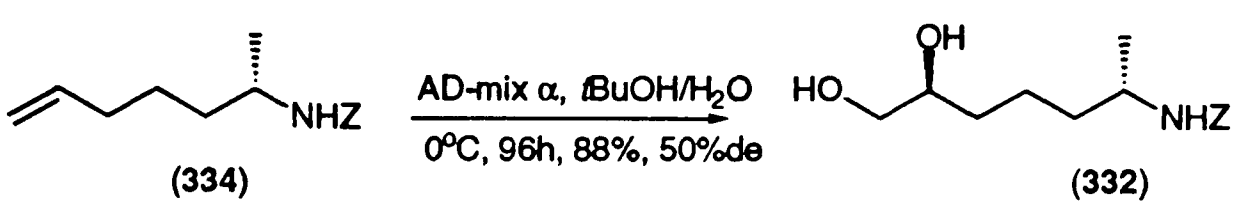
Scheme 138

Probably the most significant development in this area for the practical organic chemist has been the launch of the AD-mixes (Asymmetric Dihydroxylation)[217]. These mixes contain a catalytic amount of OsO_4, a catalytic amount of a new class of chiral cinchona alkaloid[218], and potassium hexacyanoferrate (III) as the reoxidant. The appropriate mix is purchased, suspended in *tert*-butanol:water and the alkene simply added. The particular AD-mix required can be easily identified (Scheme 139) allowing dihydroxylation to proceed in good yields with good enantiomeric excess.



Scheme 139

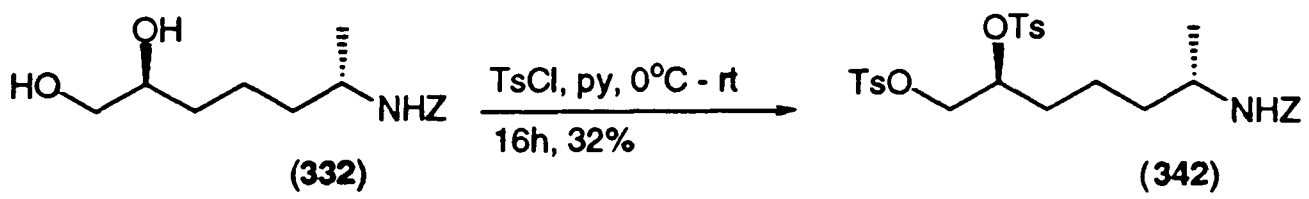
Application of this methodology to the alkene (**334**) was demonstrated by Momose, but only afforded a diastereomeric excess of 50% (3:1 5*S*:5*R*). Dihydroxylation of terminal alkenes has been reported to proceed in poorer enantiomeric excess than other substrates due to the lack of differentiation in size between the alkene substituents. New ligands have been designed to improve this reaction, but they are not readily available at the current time[219]. Thus, using the currently available AD-mix α to convert alkene (**334**) to diol (**332**) proceeded smoothly to afford the product as a 3:1 mixture of epimers (Scheme 140).



(**334**) (**332**)

Scheme 140

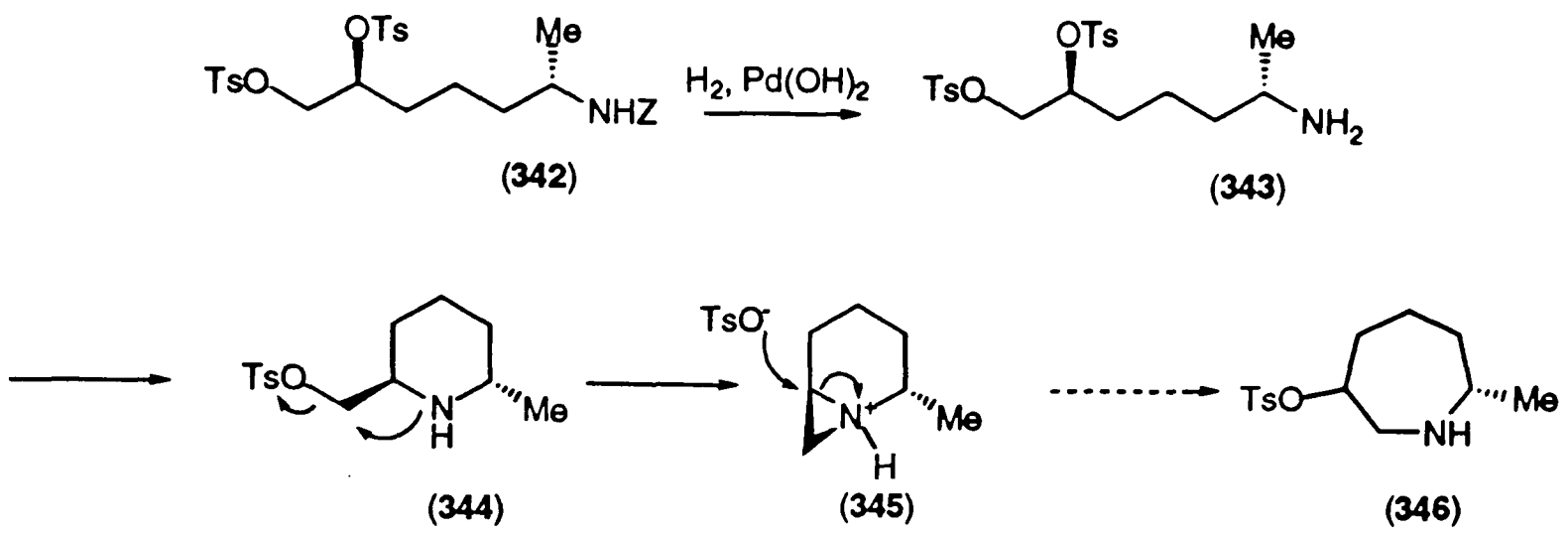
Functionalisation of the two hydroxyl groups prior to cyclisation was the next task to be completed, and initially bistosylation was investigated. Using conditions reported by Bosnich for the bistosylation of 1,2-diols[220], diol (**332**) was converted to bistosylate (**342**) (Scheme 141).



(**332**) (**342**)

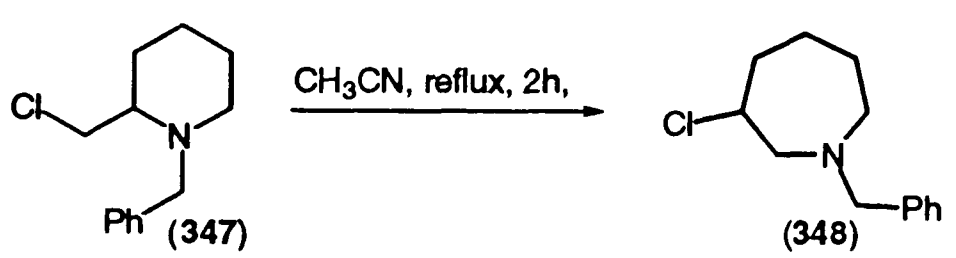
Scheme 141

The yield for the reaction was disappointing and, additionally, a further problem was identified. Removal of the *N*-Z group to afford amine (**343**) would allow cyclisation to piperidine tosylate (**344**). However, piperidine tosylate (**344**) would be likely to undergo a second cyclisation to form a aziridinium intermediate (**345**) which may then ring-open to give a seven membered ring (**346**) (Scheme 142).



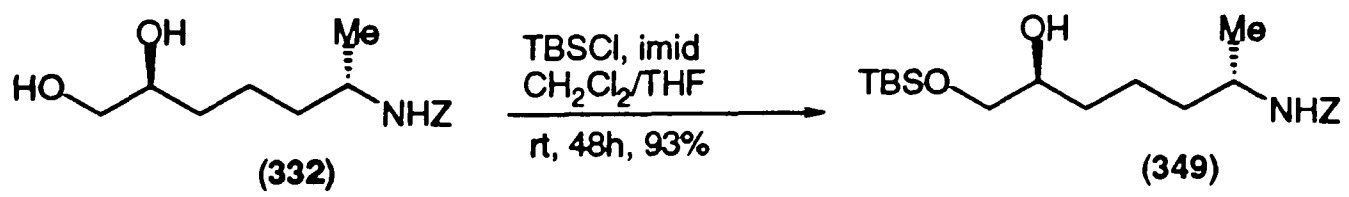
Scheme 142

Such reactions have been demonstrated by Matsumoto, as an effective method of ring-expanding nitrogen-containing heterocycles[221] such as piperidine (**347**) to seven-membered ring (**348**) (Scheme 143).



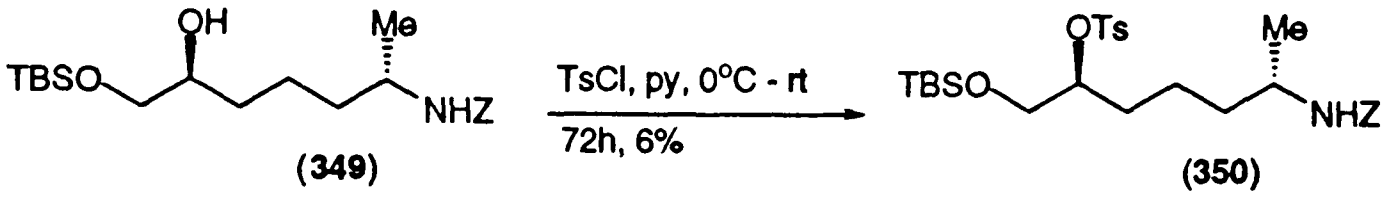
Scheme 143

To avoid the problems of the low yield and the ring-expanding side reaction it was decided to revert to the synthesis reported by Momose, with protection of the primary hydroxyl, followed by conversion of the secondary hydroxyl to a leaving group. Thus, the primary hydroxyl group was protected as a silyl ether (**349**) using the previously developed conditions (Scheme 144).



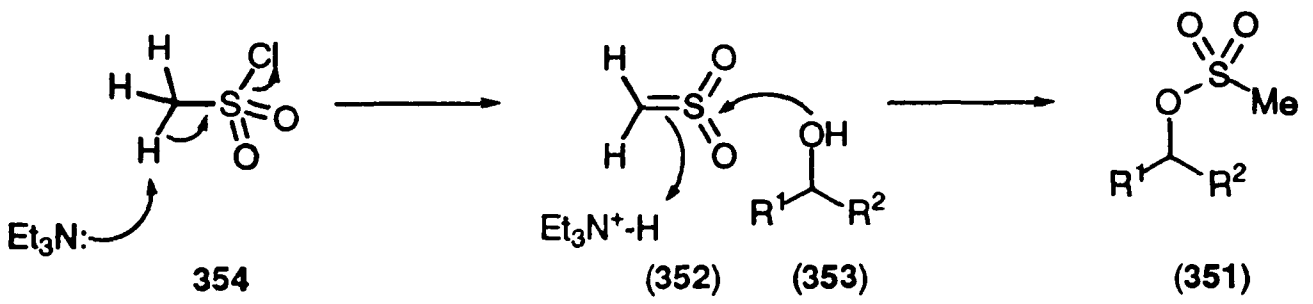
Scheme 144

Conversion of the secondary hydroxyl group to the tosylate (**350**) was initially investigated using standard conditions. However, the reaction yielded only a disappointing 6% yield, even after extended reaction times of 72 hours (Scheme 145).



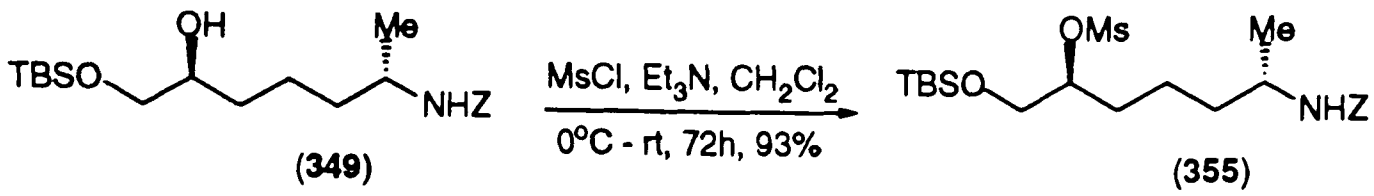
Scheme 145

Thus, again reverting to the chemistry reported by Momose, mesylation of the secondary hydroxyl group was investigated. The synthesis of mesylates (**351**) using mesyl chloride and triethylamine has been shown to be an extremely versatile procedure, which is successful for hindered and other unreactive alcohols[222]. The mechanism of the reaction has been shown to proceed *via* a sulfene intermediate (**352**), formed by the E2 elimination of hydrogen chloride from mesyl chloride **353**, followed by nucleophilic attack by the hydroxyl group of alcohol (**354**)[223] (Scheme 146).



Scheme 146

This reaction was successfully applied to the conversion of the alcohol (**349**) to the mesylate (**355**) which, compared to the low yielding tosylation, gave an excellent 93% yield (Scheme 147).

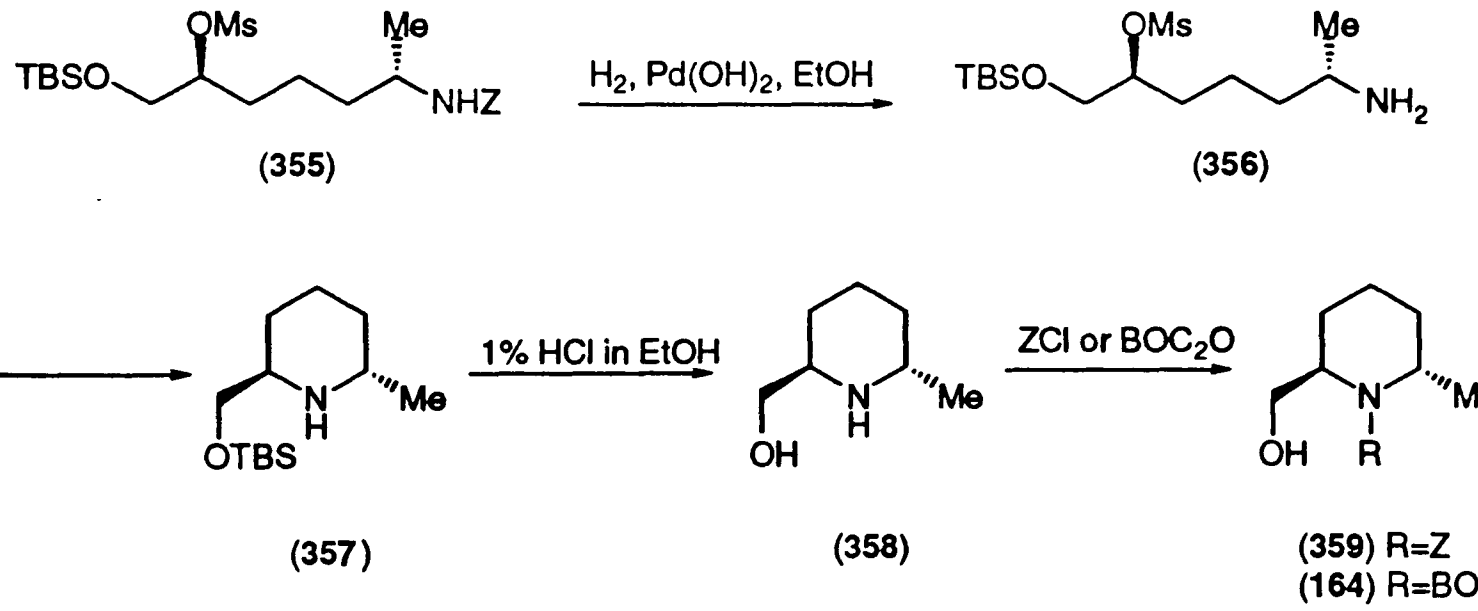


(349) **(355)**

Scheme 147

2.9.3. Piperidine Cyclisation and Functionalisation

The crucial cyclisation to form the piperidine framework was the next step on the synthetic route, and initially this reaction was attempted using the reported conditions. This involved reductive cleavage of the *N*-Z group to yield amine (**356**), followed by cyclisation to piperidine (**357**). The TBS group was then removed to yield piperidine alcohol (**358**), which could then be protected as a carbamate (either *N*-Z (**359**) or *N*-BOC (**164**)) (Scheme 148).



(355) **(356)** **(357)** **(358)** **(359)** R=Z
(164) R=BOC

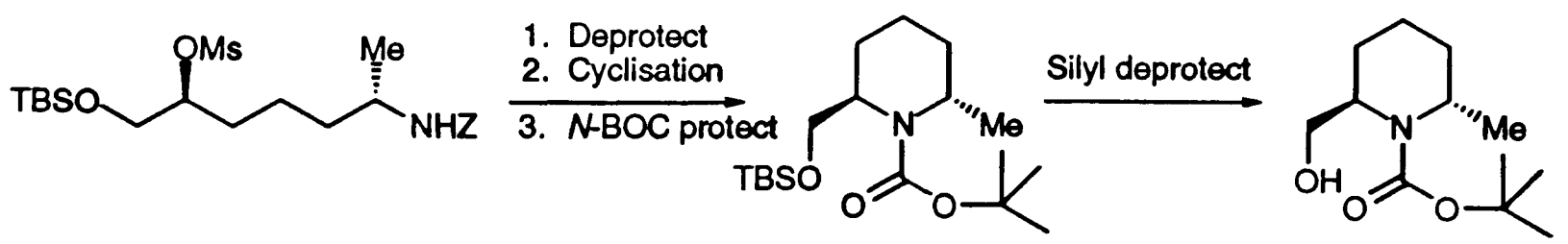
Scheme 148

Momose had quoted a 50% overall yield for the above sequence, a result that was very difficult to reproduce. Reductive cleavage of the *N*-Z group proved to be an extremely slow reaction, only reaching 50% completion at ambient temperature after 5 days. Increasing the reaction temperature to 50°C allowed the reaction to reach completion in 5 days. Isolation and purification of the piperidine (**357**) was also difficult, probably due to the amine having good water solubility. The removal of the

TBS protection using 1%HCl in EtOH proceeded smoothly in 1 hour at ambient temperature to afford piperidine alcohol (**358**), but this molecule, with free amine and hydroxyl functionalities, proved to be impossible to extract from the aqueous phase during work up.

In an attempt to avoid these isolation problems, it was decided to use the product crude through all the steps in Scheme 148 to afford *N*-BOC piperidine alcohol (**164**). However, this approach was unsuccessful allowing isolation of either a trace of, or no product. Isolation of the small amounts of the intermediate piperidine (**357**) and piperidine alcohol (**358**), and their successful conversion to piperidine alcohol (**358**) and *N*-BOC piperidine alcohol (**164**) respectively suggested that purification of the intermediates on the reaction scheme should allow an overall improvement in the yield. However, with the isolation problems encountered it was decided to investigate an alternative sequence for the transformation.

A new sequence, involving deprotection and cyclisation followed by *N*-protection should afford *N*-BOC piperidine (**163**). With both the functional groups of this molecule protected, isolation should be possible. Selective removal of the TBS protection would then allow isolation of *N*-BOC piperidine (**164**) (Scheme 149).

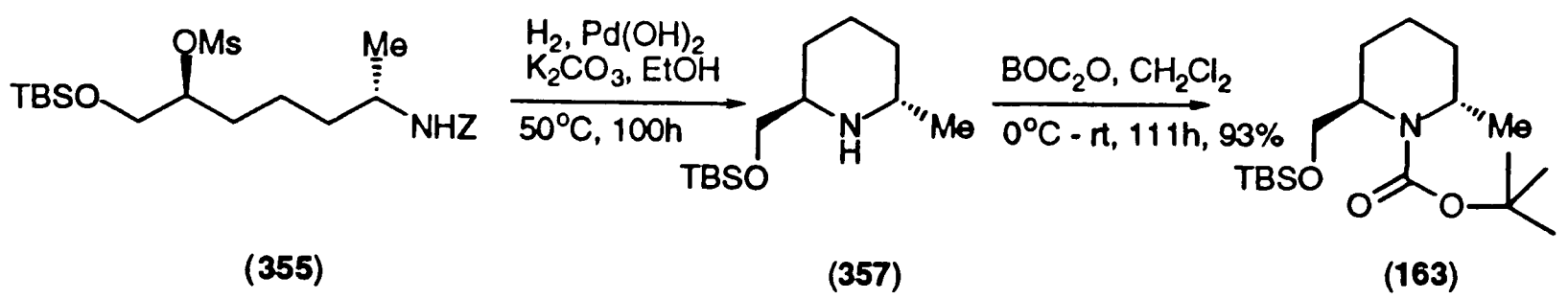


(355) **(163)** **(164)**

Scheme 149

An initial attempt at this approach *via* hydrogenolysis was unsuccessful due to acid contamination of the reaction mixture, which deactivated the palladium catalyst and removed the TBS protecting group. Thus for subsequent reactions potassium

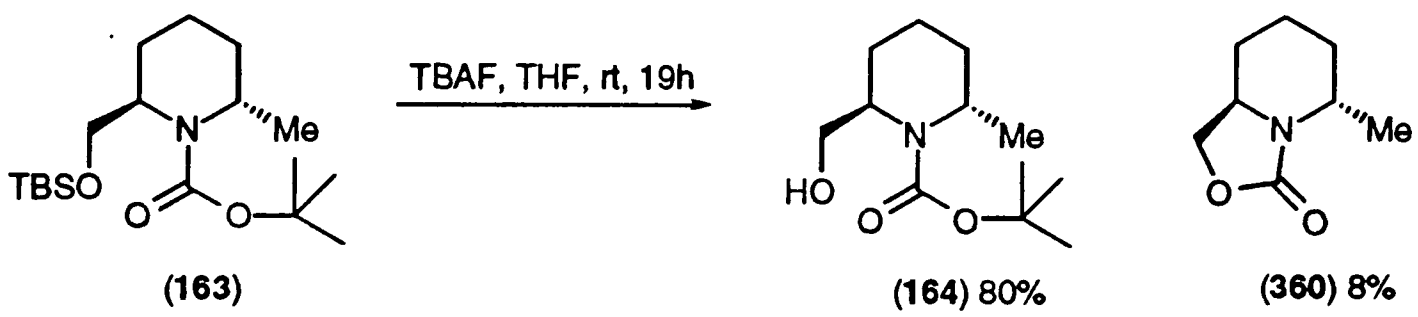
carbonate (1.0eq) was added. A one-pot procedure, without isolation of the piperidine (**357**) gave a 60% yield of the *N*-BOC piperidine (**163**). Changing the procedure to include isolation of the intermediate piperidine (**357**), which could be achieved by saturation of the aqueous phase with sodium chloride during work up, and extensive extraction, improved the yield to 93% (Scheme 150), suggesting that isolation and purification of the intermediates is important for the success of the reaction sequence.



(355) **(357)** **(163)**

Scheme 150

Selective deprotection of the TBS group was then achieved using TBAF[224] (Scheme 151). The reaction proceeded in good yield, however a trace amount of oxazolopyridinone (**360**) was isolated in each reaction.

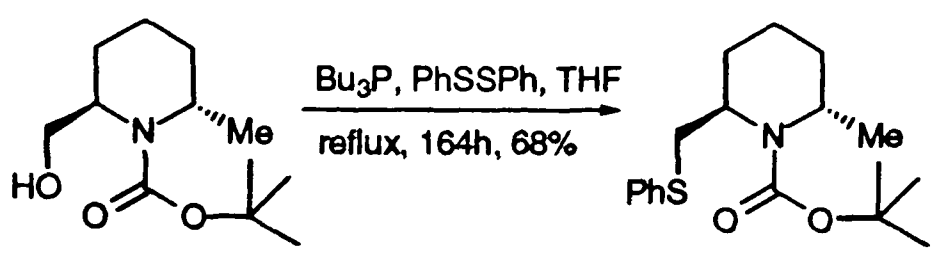


(163) **(164)** 80% **(360)** 8%

Scheme 151

The final few steps for the synthesis of the piperidine sulfone (**309**) required for the Julia coupling (Scheme 124), involves conversion of the hydroxyl group to a phenyl sulfone. This transformation was achieved using the same methodology that was used for the conversion of piperidine alcohol (**283**) to piperidine sulfone (**297**). Thus, using phenyl disulfide and tributylphosphine afforded piperidine sulfide (**361**) in a 68% yield (Scheme 152). This was a disappointment after the quantitative yield for the conversion of piperidine alcohol (**285**) to piperidine sulfide (**304**), but reflects the

problems encountered with this transformation reported by Kotsuki[194] (Scheme 118). The use of high pressure had allowed the reaction to proceed in a 92% yield, but the standard conditions of atmospheric pressure had only afforded a 56% yield. Increasing the reaction time improved the yield, but it was concluded that the extra methyl group probably increases the steric effect of the *N*-BOC group shielding the alcohol, thus reducing the effectiveness of this transformation.

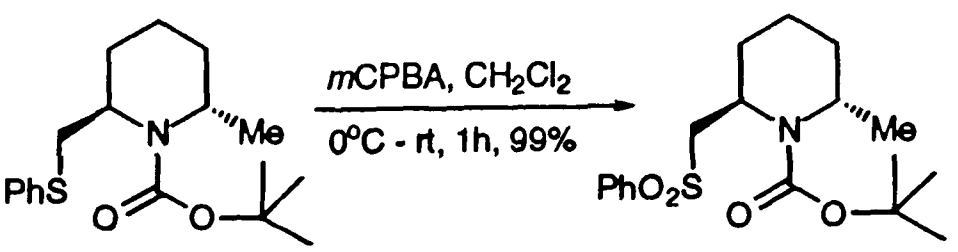


(164) **(361)**

Scheme 152

Oxidation of the piperidine sulfide (**361**) to the piperidine sulfone (**309**) was initially attempted using Oxone®. However the yield of this reaction was 50-55%, and increasing the amount of Oxone® to 5 equivalents failed to improve this result. The reduced yield could be due to the extra methyl group causing the *N*-BOC group to take up a different orientation, shielding the sulfur from oxidation.

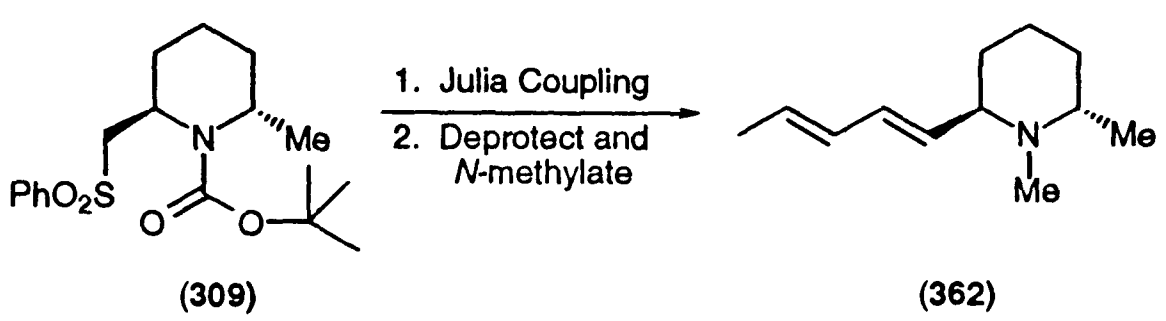
In an attempt to improve this yield the oxidant was changed from Oxone® to *m*CPBA, a method that had been reported by Hori for the oxidation of sulfides to sulfoxide and sulfones[225]. This methodology cleanly oxidised piperidine sulfide (**361**) to sulfone (**309**) in an excellent 99% yield (Scheme 153).



(361) **(309)**

Scheme 153

This transformation completed the synthesis of the piperidine sulfone (**309**) required for the Julia coupling (Scheme 124). This molecule also offered a further chance to investigate the regiochemistry of the Polonovski reaction with 2,6-disubstituted piperidines, a model considerably closer to the piperidine (**76**) required for the synthesis of himgravine **9**, than the previously used piperidinediene (**312**). Thus, it was decided to convert piperidine sulfone (**309**) to piperidinediene (**362**) (Scheme 154) using the same methodology that had been demonstrated earlier (Schemes 123 and 125) and investigate the Polonovski reaction on this molecule.



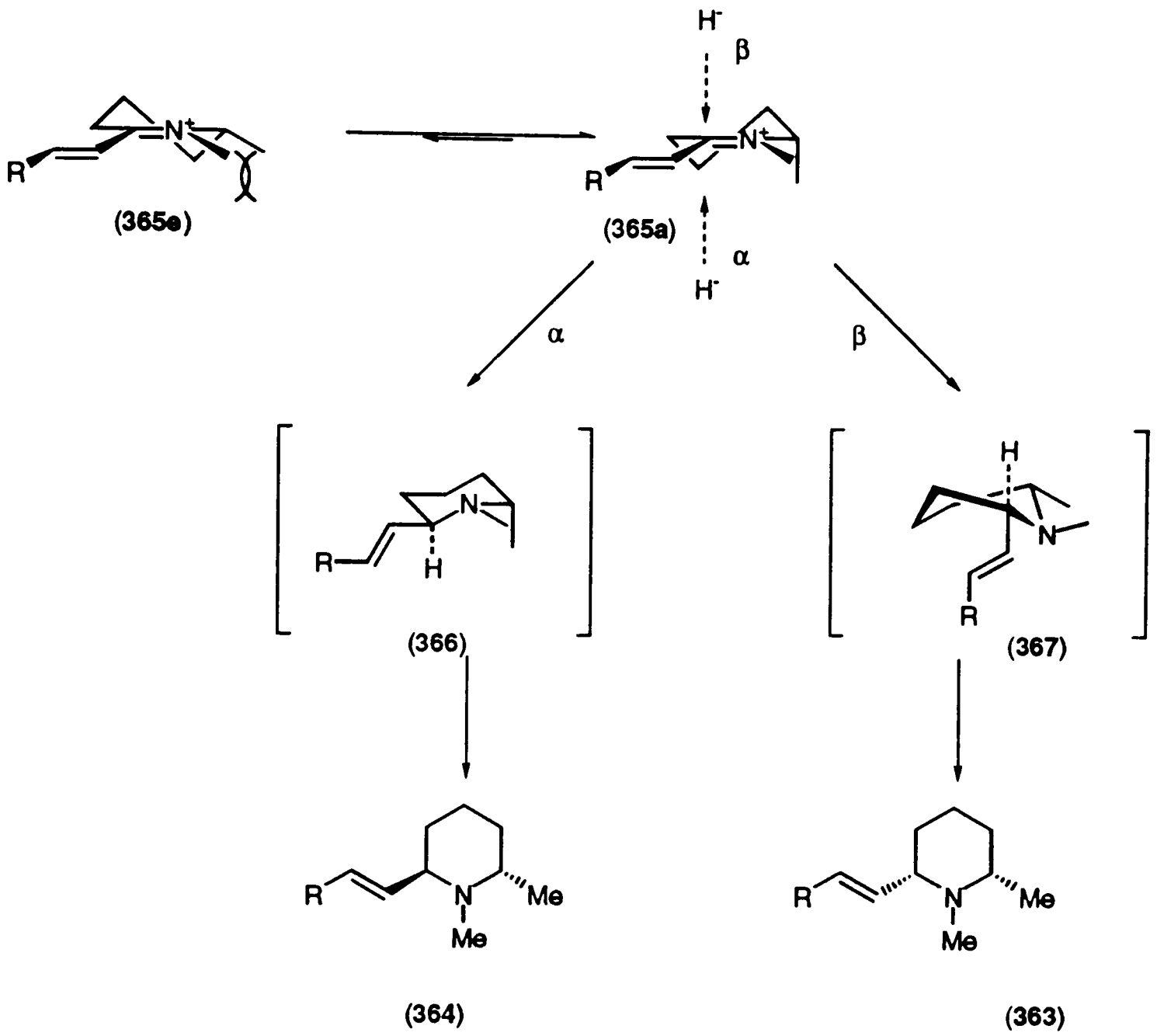
(309) (362)

Scheme 154

2.10. Polonovski Reaction of 2,6-Disubstituted Piperidines

Conversion of piperidine sulfone (**309**) to piperidinediene (**362**), as well as allowing an investigation into the regiochemistry of the Polonovski reaction, offered an opportunity to investigate the reduction step of this reaction. With 2,6-disubstituted piperidines, reduction of the iminium ion intermediate could afford either the *cis*- or *trans*-piperidine. While reduction to the *cis*-piperidine (**363**) would normally be expected[226], the presence of the *N*-methyl group may change the selectivity to favour the *trans*-isomer (**364**) (Scheme 155). The 1,3-allylic interactions between the *N*-methyl and the C6 methyl group in piperidine (**365e**) should lead to a molecule adopting a lower energy state with the C6 methyl group axial (**365a**). Reduction of piperidine (**365a**) *via* a chair transition state (**366**) (route α) would be expected to afford the *trans*-piperidine (**364**)[227]. Reduction to the *cis*-piperidine (**363**) would occur *via* a higher energy twist-boat-chair transition state (**367**) (route β). The

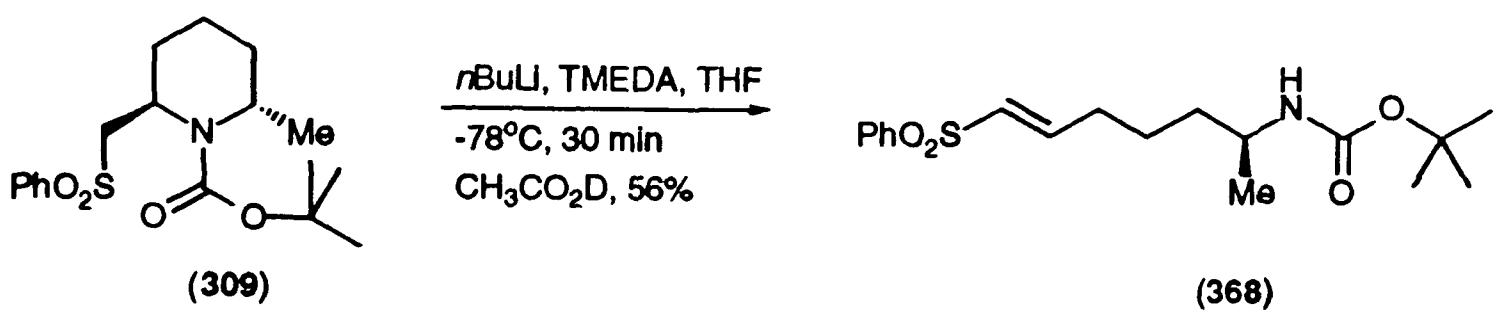
existence of himbacine **1** and himandravine **8**, identical apart from containing a *trans* and *cis*-piperidine respectively, suggests that if an iminium ion exists in the biological pathway to these molecules, reduction of the iminium ion could afford a mixture of isomers.



Scheme 155

Thus, conversion of piperidine sulfone (**309**) to piperidinediene (**362**) was initially investigated using the previously developed chemistry. The Julia coupling using the conditions developed for coupling piperidine sulfone (**297**) to crotonaldehyde was attempted twice, but no product was obtained. It was then decided to investigate the reaction in a stepwise manner to identify the problem with the coupling. Deprotonation of the piperidine sulfone (**309**), followed by deuteride quench offered a

method of measuring the efficiency of the metalation step of the sequence. The piperidine sulfone was treated with *n*BuLi at -78°C, followed by quenching with CH_3CO_2D. This reaction rather than affording the expected deuterated piperidine, allowed isolation of alkene (**368**) (Scheme 156).



(309) **(368)**

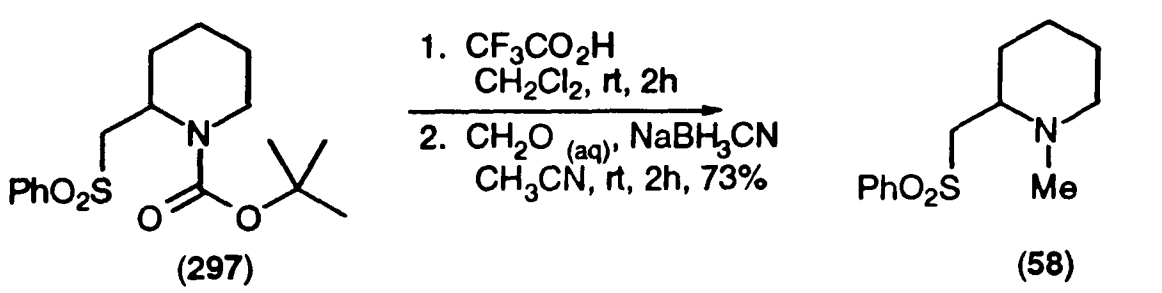
Scheme 156

The product (**368**) is presumably formed by deprotonation α to the sulfone, followed by ring opening to afford an alkene, which would then be deuterated on the nitrogen anion. An examination of the ^2D NMR showed no deuterium inclusion on the nitrogen, as this would be expected to be lost during aqueous work-up, but a trace of deuterium had been incorporated at the alkene position α to the sulfone. The ring opening could occur because of steric strain on the molecule; the extra methyl group at C6 forcing the *N*-BOC group into an orientation that interacts with phenyl sulfone causing the strain which favours the ring opening. The problem could not be simply explained by consideration of electronic factors as the model studies on piperidine sulfone (**297**) had been successful.

This reaction was a major problem as the Julia coupling reaction represents one of the key steps in the reaction sequence. Consideration of the problem led to an approach based on reducing the size of the group on the nitrogen atom; this should reduce the strain in the system, and decrease the ring opening reaction. Thus, it was decided to convert the *N*-BOC to an *N*-methyl group, which should reduce the strain in the molecule. In addition this would not increase the overall number of steps in the reaction sequence as the *N*-methyl piperidine (**76**) is required for the proposed iminium ion mediated Diels-Alder reaction (Scheme 89).

The precedent for this reaction was the work completed by Kozikowski[11] on the synthesis of simple himbacine analogs (**52**, **59-66**) (Scheme 2). This work had included a Julia coupling using an *N*-methyl piperidine (**58**), and importantly it had been noted 'that no evidence of the decomposition of the anion through a β-elimination mechanism was evident'.

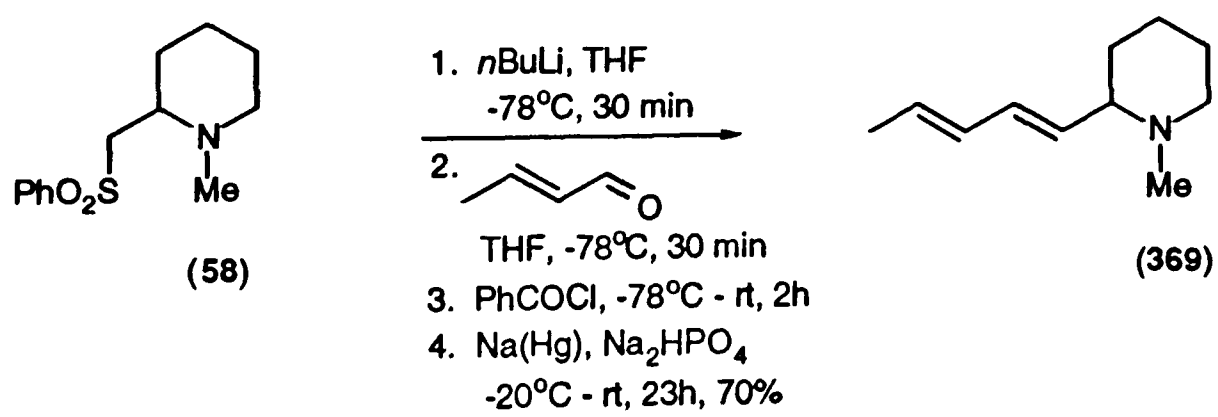
To investigate this reaction it was decided to return to the use of model systems, rather than wasting valuable late stage material. Conversion of the previously obtained piperidine sulfone (**297**) (Scheme 121) to the *N*-methyl piperidine (**58**) was completed using a one-pot deprotection and *N*-methylation procedure (Scheme 157).



(297) (58)

Scheme 157

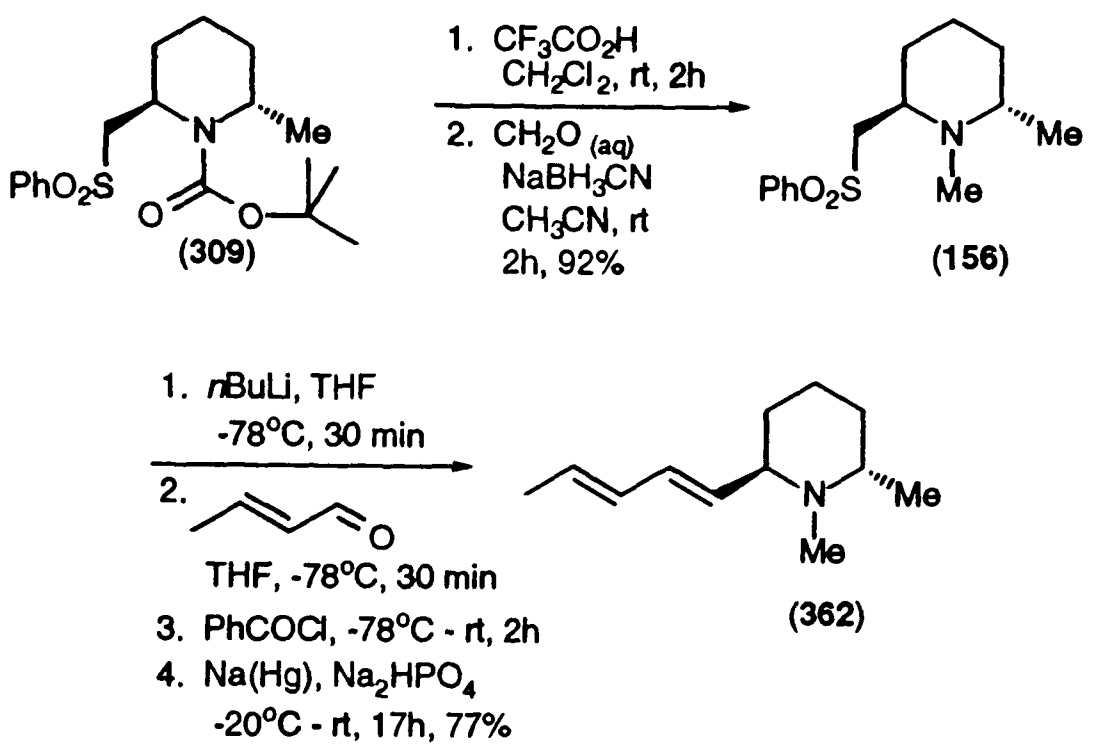
The Julia coupling of this piperidine sulfone (**58**) to crotonaldehyde was completed using the one-pot procedure previously developed in an excellent 70% yield across the four steps (Scheme 158), suggesting that the strategy of changing the *N*-BOC to an *N*-methyl group was a successful one.



(58) (369)

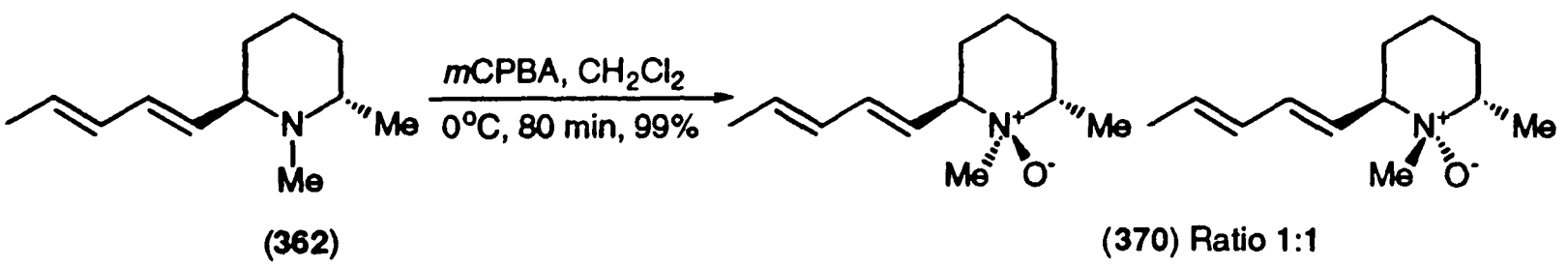
Scheme 158

Application of this chemistry to piperidine sulfone (**309**) allowed conversion to *N*-methyl piperidine (**156**) in a 92% yield, following which the Julia coupling with crotonaldehyde afforded piperidinediene (**362**) in a 77% yield (Scheme 159).



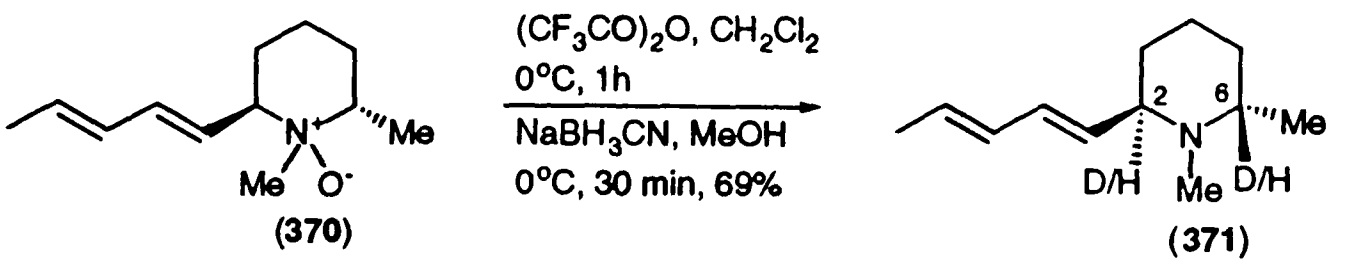
Scheme 159

Oxidation of the piperidinediene (**362**) to the piperidine *N*-oxide (**370**) proceeded smoothly in a 99% yield (Scheme 160). ^1H NMR analysis showed clearly that a 1:1 ratio of *N*-oxides had been formed, inseparable by flash chromatography, suggesting that there had been no differentiation between the two faces of the piperidine.



Scheme 160

The Polonovski reaction of this mixture of *N*-oxides (**370**) was then investigated. Using the previous conditions, the *N*-oxides were converted to iminium ions using trifluoroacetic anhydride, then reduced with sodium borodeuteride to afford deuterated piperidines (**371**) (Scheme 161).



Scheme 161

This reaction afforded two important results:

- Reduction of the iminium ion intermediate affords only the *trans*-piperidine (confirmed by comparision with the spectra of the starting piperidinediene (**362**)), in agreement with the theory that the 2,6-disubstitution pattern on the piperidine ring biases the reaction towards this isomer.

- The most important factor in influencing the regiochemistry of iminium ion formation is the mechanism of the reaction. The 1:1 ratio of *N*-oxides (**370**) affords a 1:1 ratio of iminium ions. This suggests that the reaction proceeds *via* an *E2* mechanism; acylation of the *N*-oxide with the oxygen anion on the β face, will allow *anti*-elimination only from the proton at C2 (Figure 27). Acylation of the *N*-oxide with the oxygen anion on the α face will promote elimination of the proton at C6.

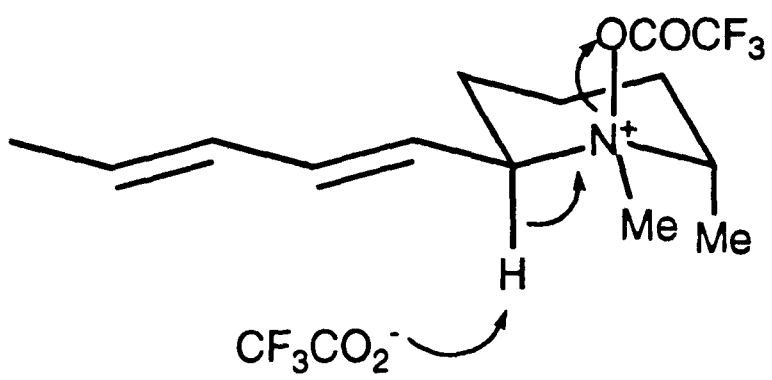
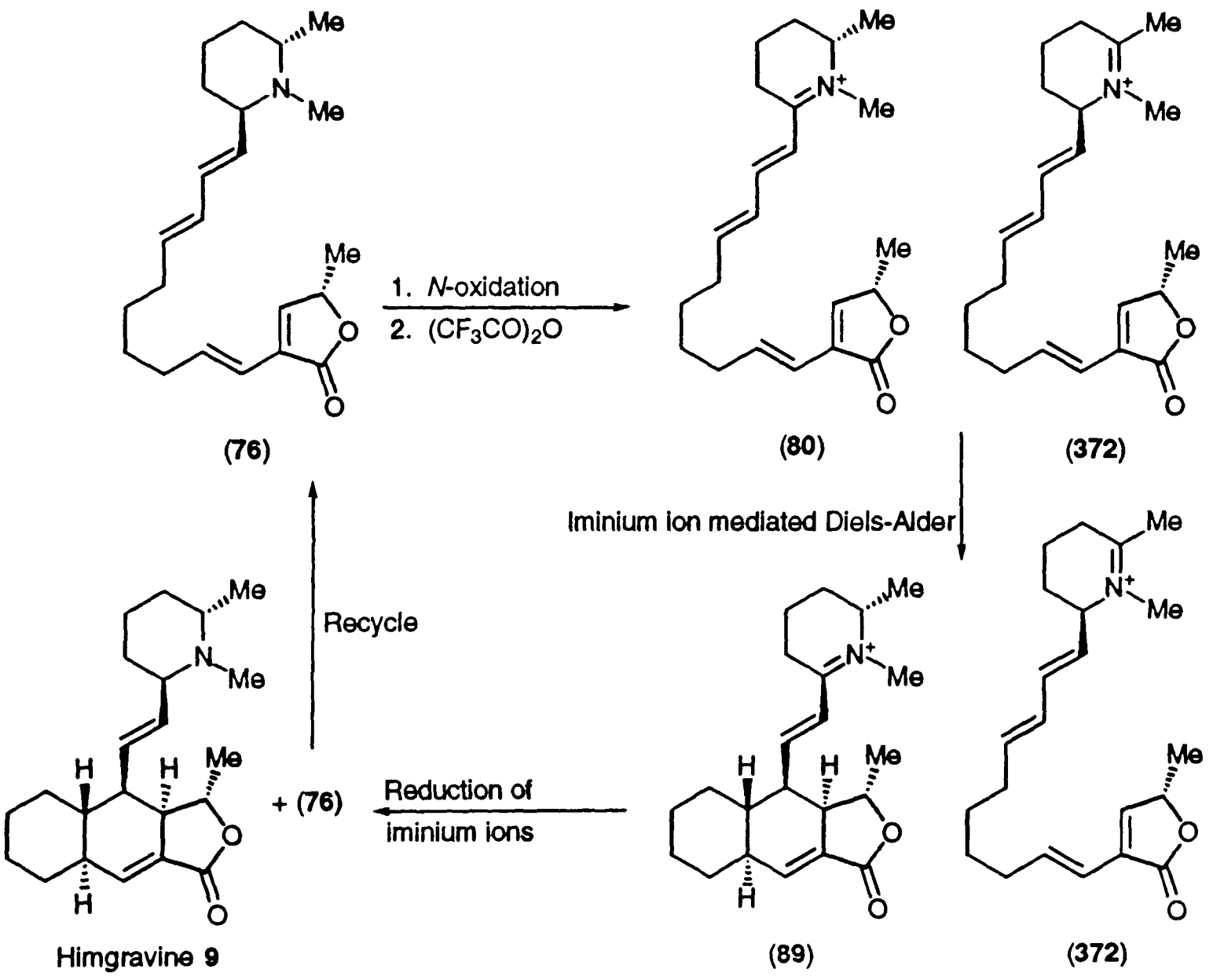


Figure 27

This result suggests that at 0°C the kinetic and thermodynamic considerations are of secondary importance, as there is no preferential elimination of the proton at C2 which is kinetically the most acidic proton. Also the product which is the most

thermodynamically stable due to conjugation to the diene side chain involves elimination of the proton at C2.

This result also has repercussions for the proposed iminium ion mediated Diels-Alder reaction (Scheme 89). Formation of the iminium ion in the piperidine ring of the *N*-methyl piperidine (**76**) is also likely to be in a 1:1 ratio, as was demonstrated for piperidinediene (**362**). Thus, only 50% of the iminium ions will be conjugated to the dienophile (**80**) promoting the Diels-Alder reaction, the other 50% will form towards the methyl group at C6 (**372**). However, if the conjugated iminium ion (**80**) under goes the Diels-Alder reaction, reduction of both iminium ions (**89** and **372**) should allow isolation of 50% of himgravine **9** and 50% of the starting *N*-methyl piperidine (**76**) which can be recycled (Scheme 162).

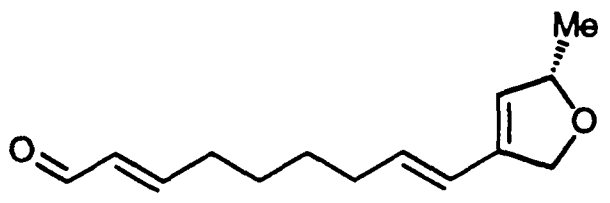


Scheme 162

This piece of work concluded the investigations into the Julia coupling and Polonovski reaction and the successful development of this chemistry should allow it to be applied to the synthesis of iminium ion (**80**) required for the proposed iminium ion mediated Diels-Alder reaction.

2.11. Studies Towards the Synthesis of Dihydrofuran (310)

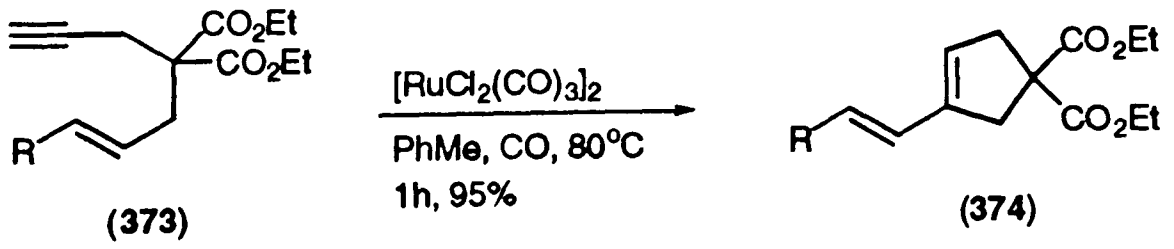
Following the studies on the Julia coupling and Polonovski reaction for the final few steps of the synthesis of iminium ion (**80**), and the completion of the synthesis of piperidine sulfone (**156**), attention turned to the synthesis of dihydrofuran (**310**) (Figure 28).



(310)

Figure 28

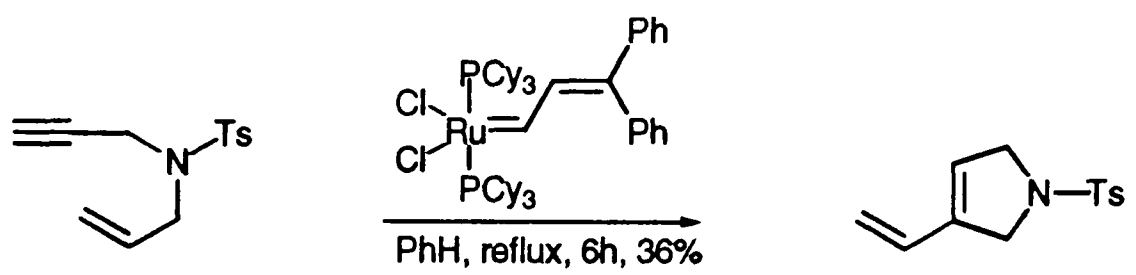
An investigation into a route to this molecule was started based on chemistry demonstrated by Murai[228]. This work had involved the conversion of 1,6-enynes (**373**) to 1-vinylcycloalkenes (**374**) using a ruthenium metathesis catalyst (Scheme 163).



(373) **(374)**

Scheme 163

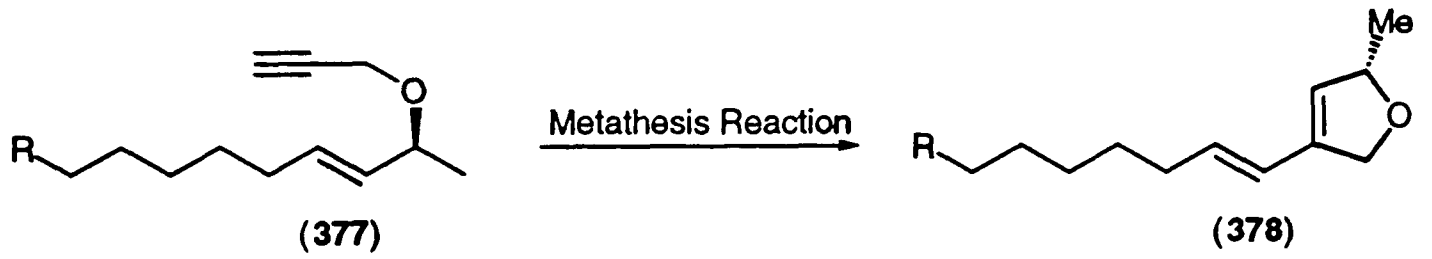
A subsequent report by Mori[229] showed that it was possible to effect such metathesis reactions with a heteroatom in the system, allowing conversion of enyne amine (**375**) to 1-vinyldihydropyrrole (**376**) (Scheme 164).



(375) **(376)**

Scheme 164

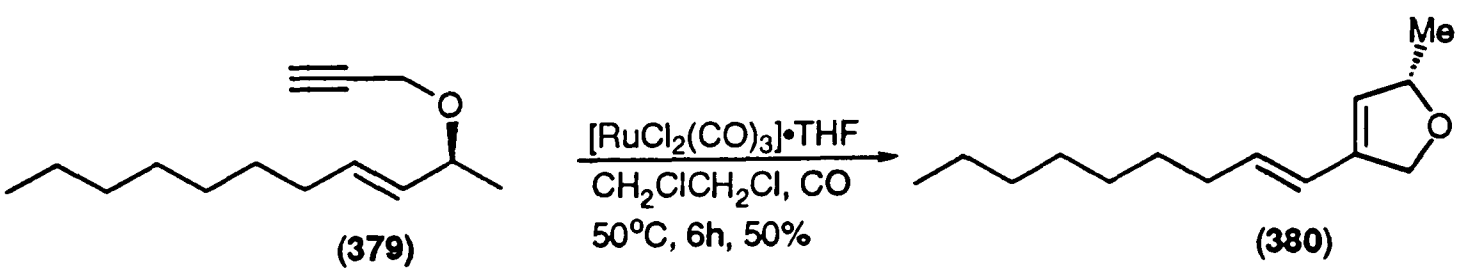
This metathesis reaction is an effective method of constructing 5-membered rings with an exocyclic 1-alkene, and it can be envisioned that such a reaction could be used for the construction of dihydrofuran (**378**) from a species such as enyne (**377**) (Scheme 165).



(377) **(378)**

Scheme 165

As an initial investigation into this proposed transformation, conversion of enyne (**379**), containing an ether linkage, to dihydrofuran (**380**) was attempted[230]. This reaction was successful, demonstrating that it is possible for the reaction to proceed with an oxygen atom in the substrate framework (Scheme 166).



(379) **(380)**

Scheme 166

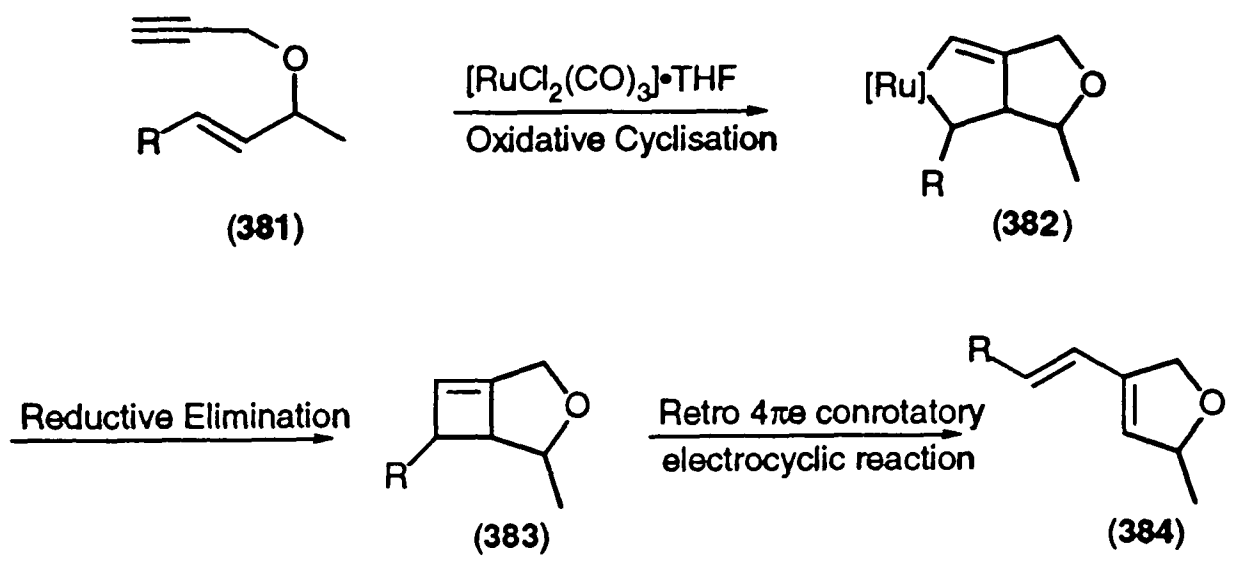
This reaction had also allowed development of optimised conditions (Scheme 166) for the transformation[230]:

- Changing the catalyst from the ruthenium dimer to the THF complex improved the procedure as the catalyst was more soluble and the reaction cleaner. The use of an acetonitrile complex was unsuccessful.

- Changing from toluene, in which the reaction was extremely slow, to THF or Et_2O, resulted in no improvement. However, the use of 1,2-dichloroethane increased the solubility of the catalyst, and allowed a fast, clean reaction.

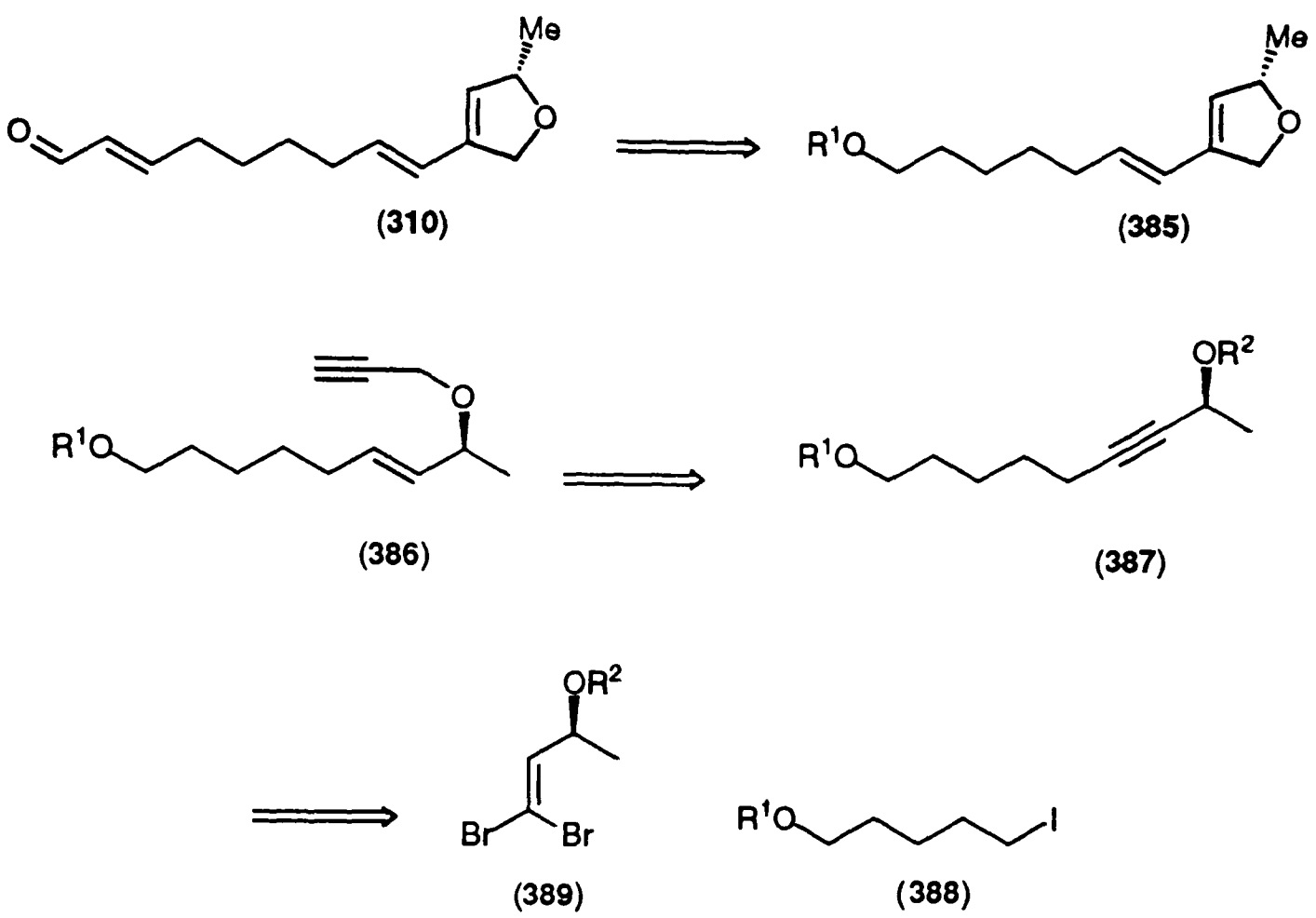
- Careful temperature control was required for the reaction. A temperature of 80°C allowed the reaction to reach completion in 1 hour, but did not give clean product. With a temperature of 20°C the reaction was extremely slow. Thus, a reaction temperature of 50°C allowed the reaction to proceed cleanly in a reasonable timescale.

The mechanism of the transformation has yet to be conclusively proven, but is thought to involve oxidative cyclisation of the ruthenium catalyst with the enyne (**381**) to form a metalocyclopentene (**382**). Reductive elimination then occurs to produce cyclobutene (**383**), following which bond isomerisation affords dihydrofuran (**384**) (Scheme 167).



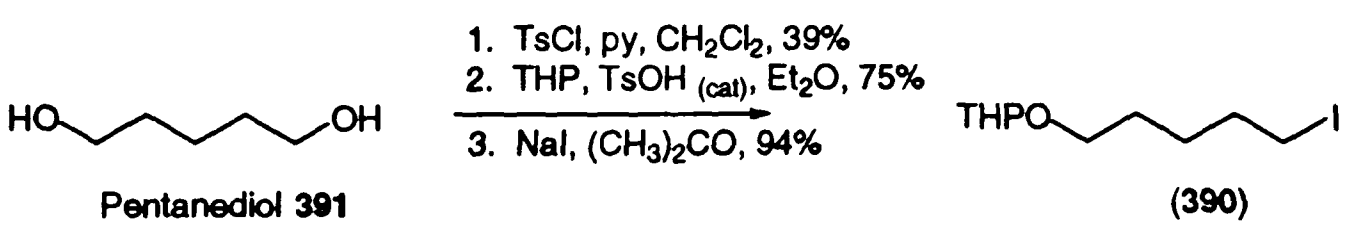
Scheme 167

The success of this methodology for the construction of dihydrofuran (**380**), led to its use for the synthesis of dihydrofuran (**310**)[230]. Retroanalysis of the dihydrofuran (**310**) involved reduction of the enal to a protected alcohol (**385**). The metathesis reaction precursor would then be enyne (**386**), which could be synthesised from alkyne (**387**). Alkyne (**387**) could be constructed from iodide (**388**) and dibromoalkene (**389**) (Scheme 168).



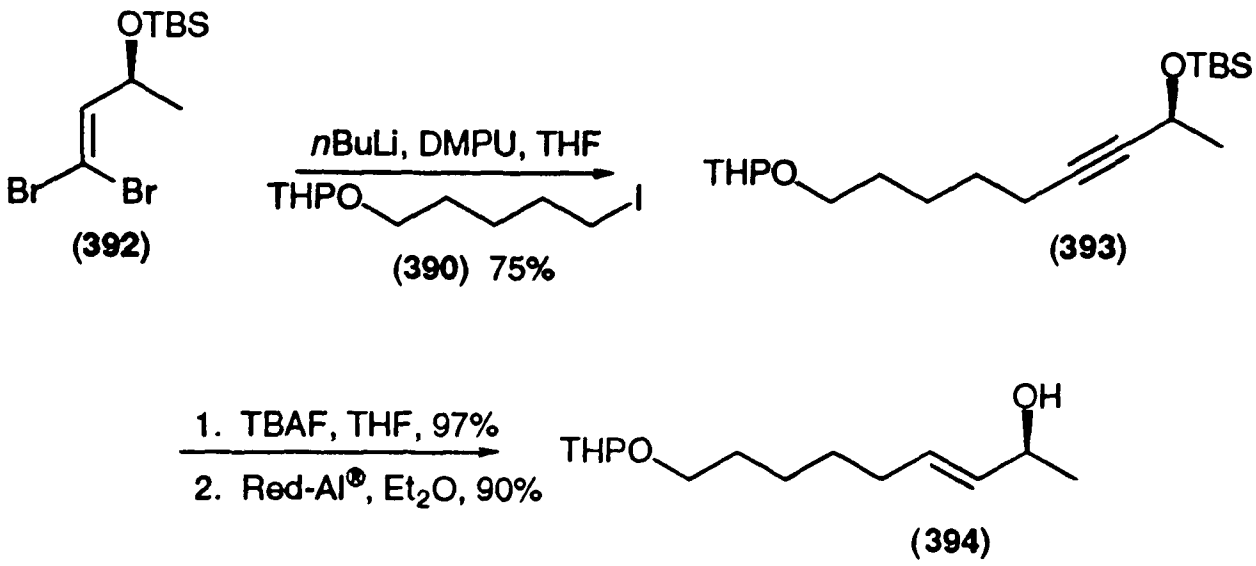
Scheme 168

Synthesis of the iodide (**390**) was completed starting from 1,5-pentanediol **391**, which was mono-tosylated to afford the alcohol. This alcohol was then THP-protected to afford the tosylate which was converted to the iodide (**390**) by a Finkelstein reaction (Scheme 169).



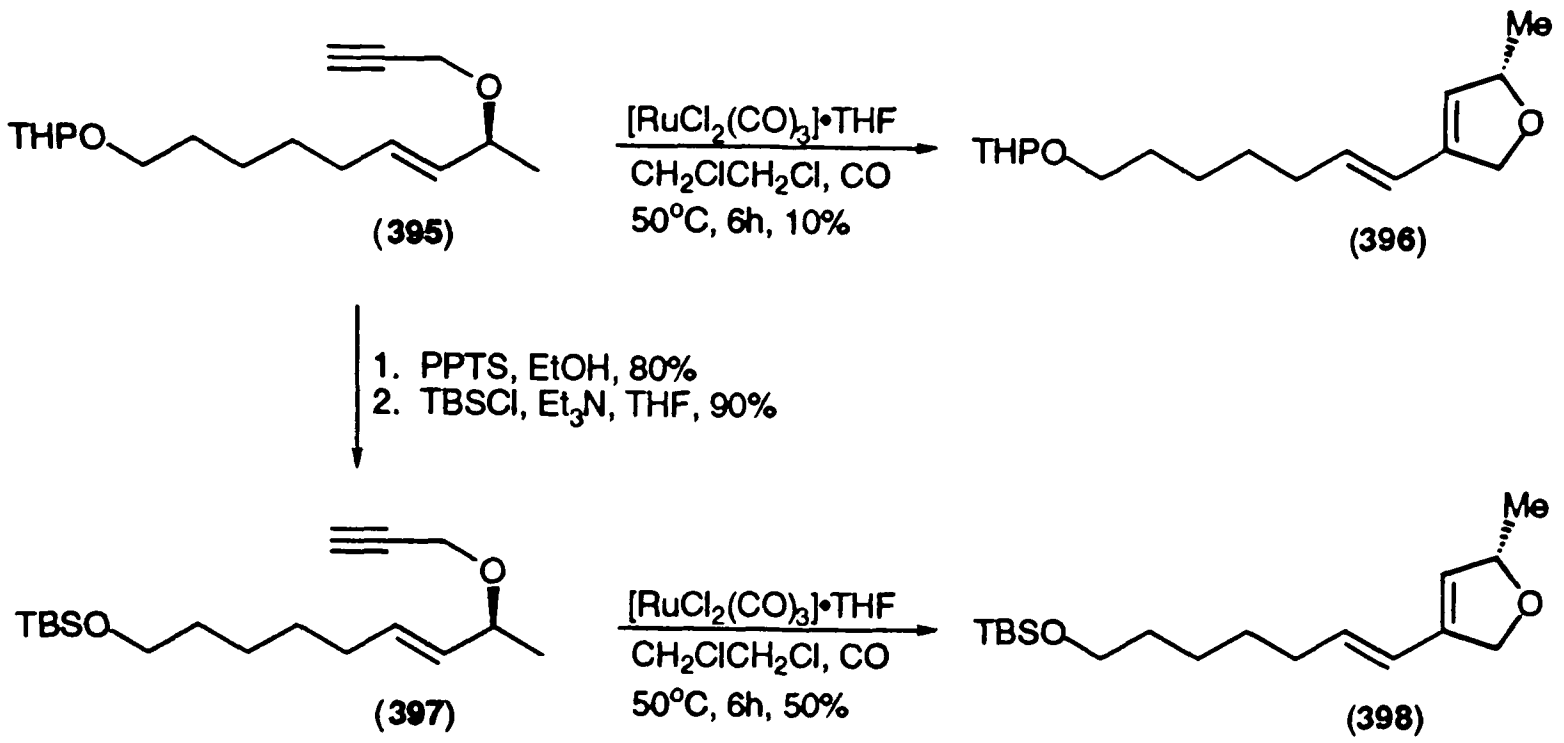
Scheme 169

The dibromoalkene (**392**) was synthesised using the chemistry demonstrated earlier (Scheme 57 and 59) to afford TBS-protected dibromoalkene (**392**) in a 68% yield across the three steps. Dibromoalkene (**392**) was then coupled to iodide (**390**) affording alkyne (**393**). The silicon protecting group then removed and the alkyne reduced to the alkene using Red-Al® affording alcohol (**394**). Propargylation of alcohol (**394**) afforded enyne (**395**) (Scheme 170).



Scheme 170

The metathesis reaction with the enyne (**395**) gave only a disappointing 10% yield of the required product (**396**). The most likely reason for this result is that the THP-group coordinates to the catalyst, hindering the reaction. Thus, conversion of the THP-enyne (**395**) to a TBS-enyne (**397**) was completed by a two step procedure. This enyne (**397**) underwent metathesis using the previously developed conditions, to afford dihydrofuran (**398**) in 50-60% yields (Scheme 171).



Scheme 171

This sequence confirmed[230] that functionalised enynes could be metathesised to dihydrofurans, thus offering a direct route for the synthesis of dihydrofuran (**310**).

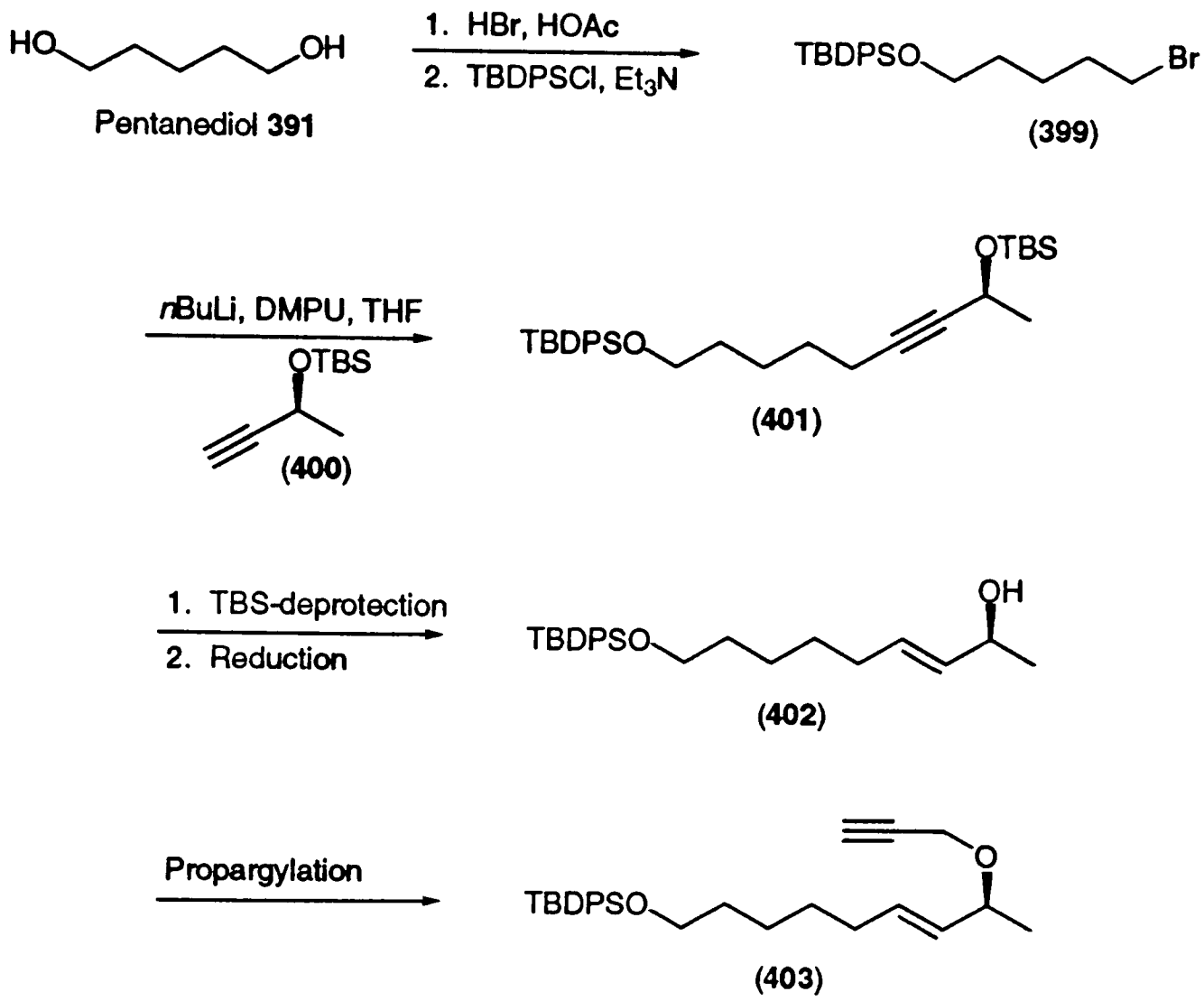
However, the overall scheme for the synthesis of enyne (**397**) that had been developed suffered from two significant problems:

- The sequence involved 15 steps. The use of the metathesis chemistry was intended to offer a short route to dihydrofuran (**310**), but in the event this route involved more steps than synthesis of enal butenolide (**182**).

- A number of steps were difficult or low yielding. Particularly of concern was the propargylation step, which is essential to reaction sequence.

In order to address the first of these problems, a new synthetic sequence was envisaged, reducing the number of steps to the enyne (**386**) from 12 to 6. This reaction sequence involved the synthesis of bromide (**399**) from 1,5-pentanediol **391**, including introduction of a silyl group for protection of the primary alcohol[231]. Coupling of chiral alkyne (**400**) to the bromide (**399**) would afford alkyne (**401**)[231] which could, as before, be selectively deprotected, the alkyne reduced to an alkene

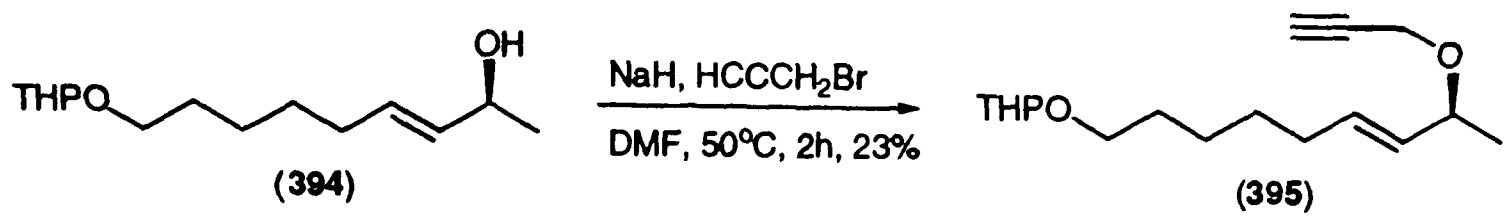
(**402**) and the hydroxyl functionality propargylated affording enyne (**403**) (Scheme 172).



Scheme 172

This sequence includes a comparable propargylation step to that in the previously developed synthesis, so before attempting to complete the new reaction scheme, the chemistry of the propargylation step needed to be improved.

Initially, the conditions that had been used previously were investigated on the THP-alcohol (**394**). Thus, using sodium hydride and neat propargyl bromide with a reaction temperature of 50°C afforded only an 23% yield of the required enyne (**395**) with a 68% recovery of starting material (**394**) (Scheme 173).



(394) (395)

Scheme 173

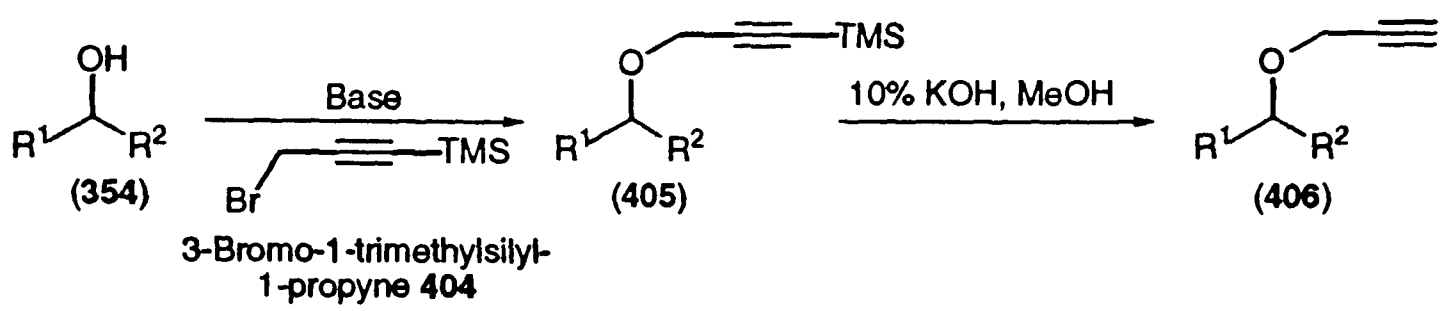
The use of reagents such as Bu_4NI, or more polar solvents such as DMPU failed to improve this result, and thus an alternative method for this transformation was sought.

The use of phase-transfer conditions have been widely reported, and using conditions reported by Fuchs[232]; a two phase system of CH_2Cl_2 and aqueous sodium hydroxide with Bu_4NI as the phase transfer catalyst, was attempted. However, this reaction yielded only starting material. Changing the base to potassium hydroxide or increasing the concentration of the organic phase, eventually using neat propargyl bromide, also failed to afford any product.

Changing the base to *n*BuLi in THF, which allowed exactly one equivalent to be added was tried. This was identified as an important experiment as the excess base used previously could be deprotonating the propargyl bromide, causing polymerisation. However, this reaction failed to allow isolation of any of the required product. The use of TMEDA, or varying the temperature of the reaction was also unsuccessful.

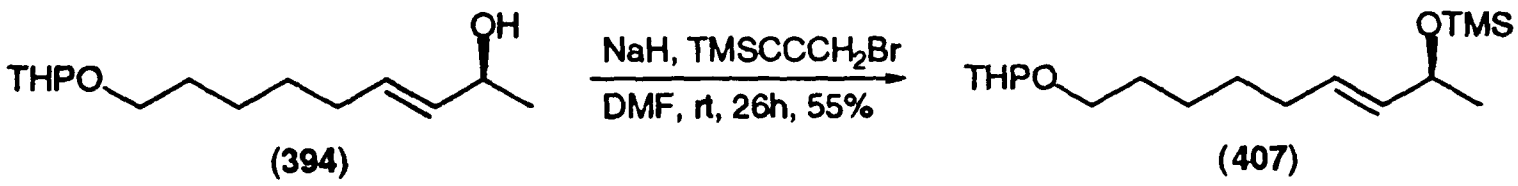
Potassium hydride with 18-crown-6 in THF had been used for deprotonation of amines[233], and this methodology was attempted under careful anaerobic and anhydrous conditions. However, the reaction only afforded a 3% yield of the required enyne (**395**), which rose to 6% on increasing the number of equivalents of propargyl bromide (1.2eq to 2.0eq).

The failure of all of these methods was disappointing, and strongly suggested that significant side reactions were taking place. One obvious concern in all these reactions had been the acidity of the alkyne proton, and a piece of methodology addressing this concern was the use of 3-bromo-1-trimethylsilyl-1-propyne **404**. This reagent had been developed by Miller[234], and could be introduced to an alcohol (**354**) using standard propargylation conditions to afford alkyne (**405**), followed by selective removal of the TMS group affording propargyl ether (**406**) (Scheme 174).



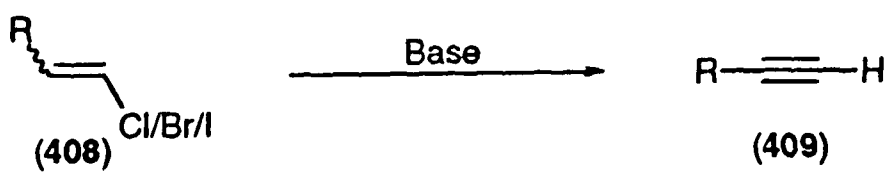
Scheme 174

However, application of this methodology to THP-alcohol (**394**) afforded only a 55% yield of TMS-protected alcohol (**407**) (Scheme 175).



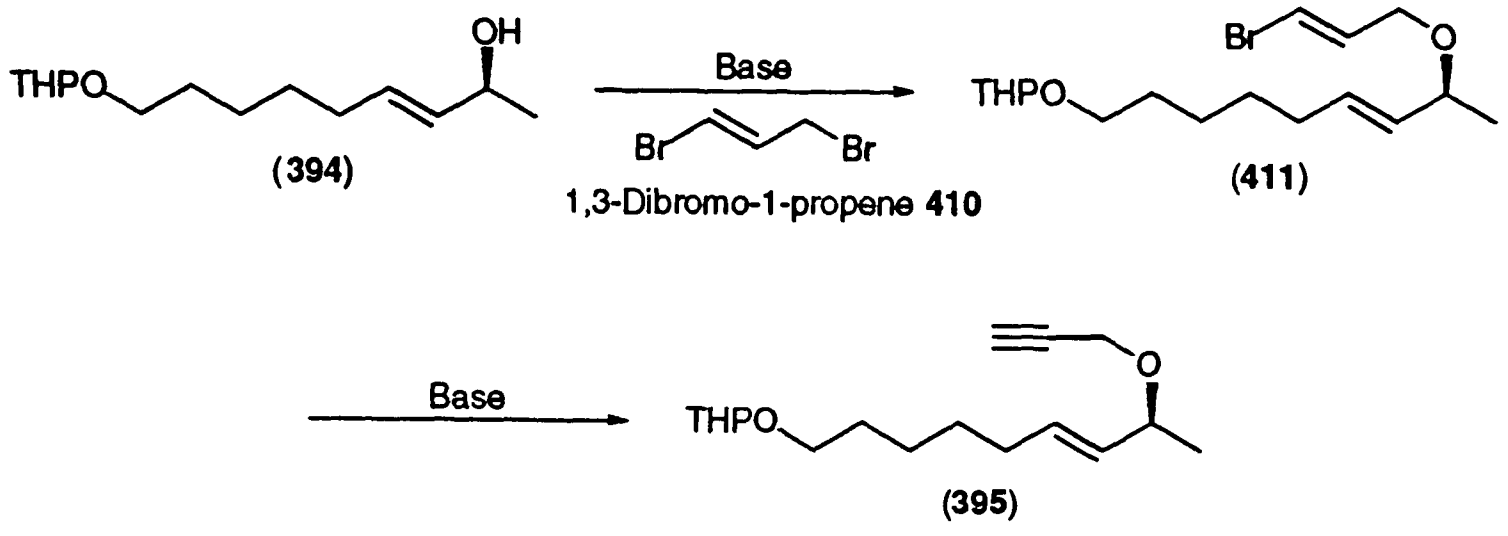
Scheme 175

The failure of this piece of methodology led to a new approach to the introduction of the propargyl group. Base mediated elimination of haloalkenes (**408**) is a well documented method of preparing alkynes (**409**)[235] (Scheme 176).



Scheme 176

Thus, introduction of 1,3-dibromo-1-propene **410** to alcohol (**394**) to afford bromoalkene (**411**) followed by elimination should yield the required enyne (**395**) (Scheme 177).



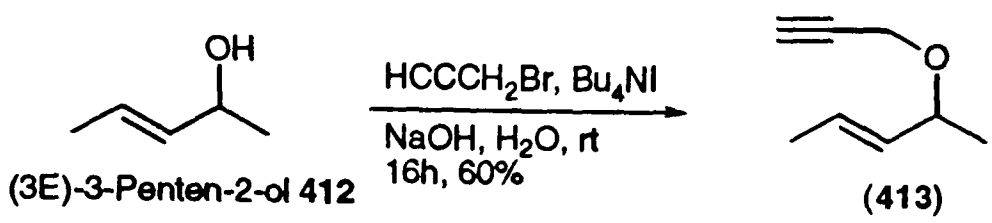
Scheme 177

Coupling of 1,3-dibromo-1-propene **410** to alcohol (**394**) was attempted using sodium hydride as the base[236,237]. However, only 10% of the required bromoalkene (**411**) was isolated, and changing the base to *n*BuLi with TMEDA failed to afford any product.

With all the reactions attempted having been unsuccessful, it was decided to investigate each step of the propargylation reaction individually. Thus, the deprotonation step was studied by quenching with methyl iodide, a simple electrophile, to investigate the extent of metallation. Using *n*BuLi as the base failed to afford any of the *O*-methylated material, suggesting this was the step causing the problems with the propargylation.

The problems with the deprotonation are possibly due to trace amounts of water getting into the reaction, quenching the alkoxide intermediate. The investigations into the propargylation had been undertaken on a small scale (0.5 - 0.2mmol), which would only require a few milligrams of water to have a significant effect on the reaction. To address this problem, the use of phase-transfer conditions were

reinvestigated, using more vigorous conditions reported by Nakai[238]. Thus, the concentration of the sodium hydroxide solution was increased to 75% (19M); neat propargyl bromide (5eq) was used as the organic layer and Bu_4NI as the phase-transfer catalyst. The reaction was investigated on (3*E*)-3-penten-2-ol **412** as supplies of the THP-alcohol (**394**) had been exhausted. These more vigorous conditions allowed isolation of a 60% yield of volatile enyne (**413**) (Scheme 178).



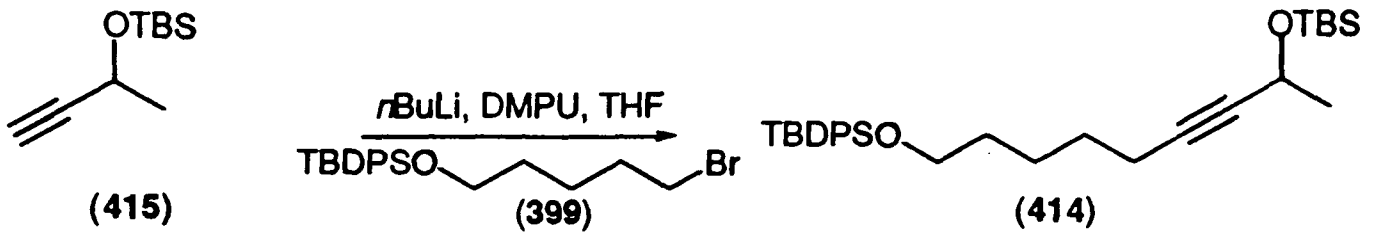
Scheme 178

The eventual identification of conditions for the propargylation increased the viability of the shortened route for the synthesis of enyne (**403**) (Scheme 172). However, two important questions regarding the route remained to be investigated to confirm its viability:

- Application of the propargylation methodology to the TBDPS-alcohol (**402**) rather than use of the model system, (3*E*)-3-propen-2-ol **412**.

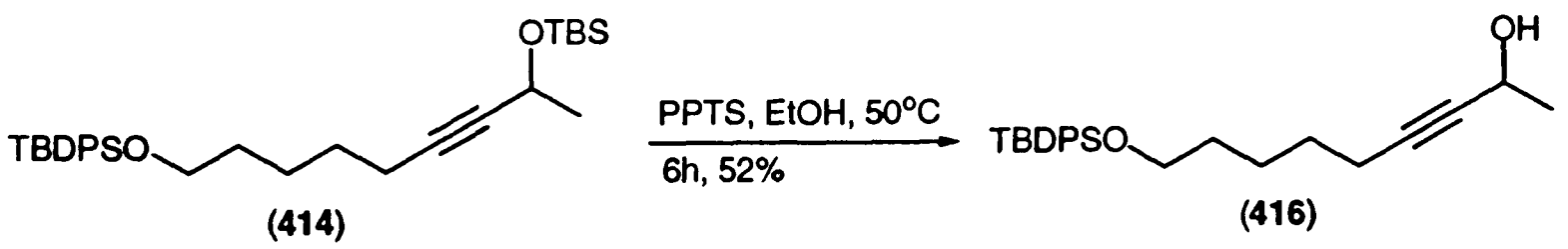
- Application of the metathesis methodology to the TBDPS-enyne (**403**). Previous work had only investigated the metathesis reaction with THP and TBS groups present.

To investigate the chemistry of these two steps, it was decide to use racemic alkyne (**414**), which had been produced during studies on the coupling of bromide (**399**) and alkyne (**415**)[231] (Scheme 179). This molecule would allow development of the chemistry needed for synthesis of dihydrofuran (**403**), following which, use of more expensive, enantiomerically pure material could be undertaken.



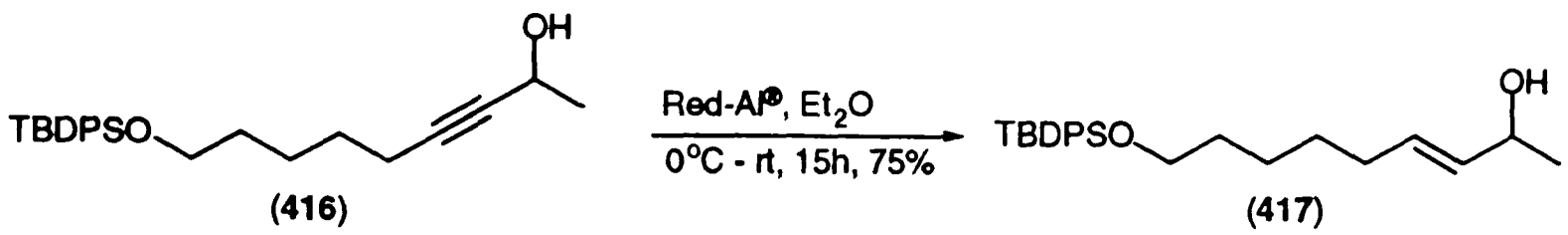
Scheme 179

Thus, selective removal of the TBS-group was required as the first step. The two silyl protecting groups had been carefully chosen, so that both were robust enough to withstand the coupling step (Scheme 179), but that one could be selectively removed in the presence of the other. The TBDPS-group[239] is relatively stable under mild acid conditions whereas the TBS-group is cleaved. Using the conditions developed by Blair[240], the TBS-group of alkyne (**414**) was selectively cleaved yielding alcohol (**416**) using PPTS as a mild acid source (Scheme 180). Interestingly, a method of selectively cleaving TBDPS-groups in the presence of TBS-groups is the use of NaH in HMPA[241], suggesting that the propargylation step of the sequence would not be possible using the previously developed conditions involving NaH, DMPU and DMF.



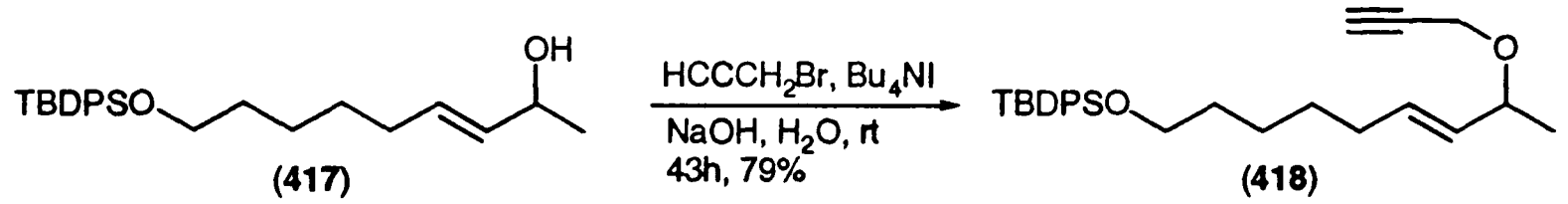
Scheme 180

Reduction of the alkyne (**416**) to a *trans*-alkene (**417**) was accomplished using Red-Al® (Scheme 181). These conditions were originally demonstrated by Denmark, who had investigated a variety of reducing reagents, and found that the presence of the alcohol and the 2-methoxyethoxy ligands were important for the reaction due to cation complexation[242].



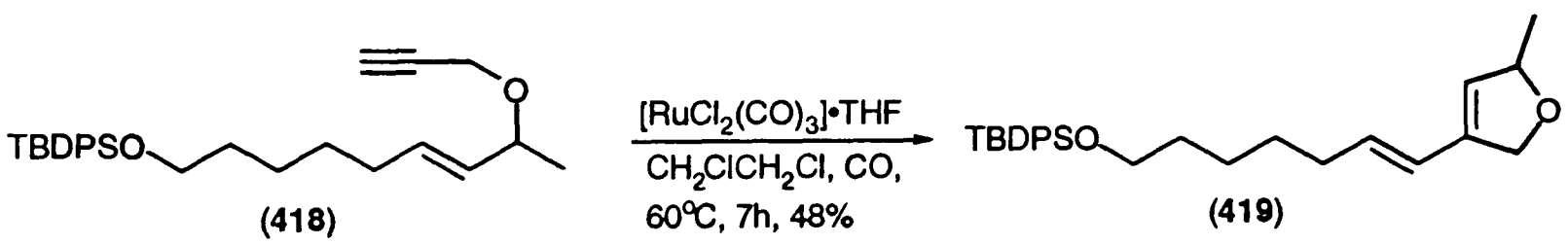
Scheme 181

The alcohol (**417**) was then successfully propargylated to afford enyne (**418**) (Scheme 182), using the conditions previously developed (Scheme 178), in an improved 79% yield.



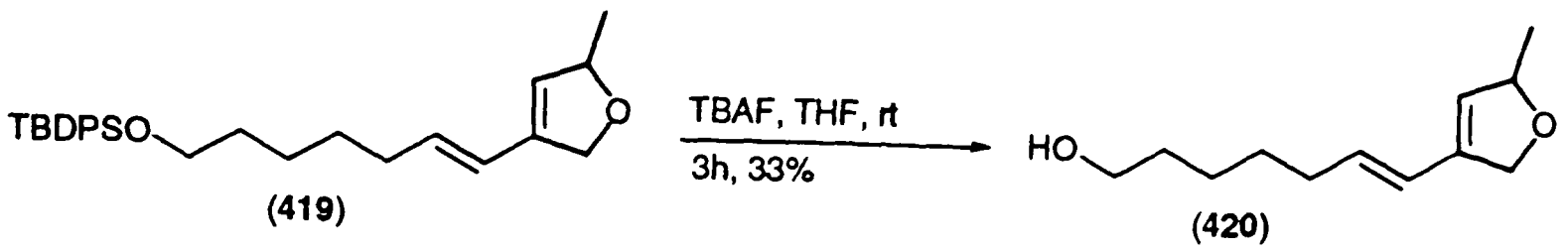
Scheme 182

Metathesis of this enyne (**418**) to dihydrofuran (**419**) was then accomplished using the standard metathesis conditions. The reaction was carefully monitored and was shown to have reached completion in 7 hours at 60°C, affording a 48% yield of the required dihydrofuran (**419**) (Scheme 183).



Scheme 183

As a final reaction in this sequence, deprotection of the silyl ether (**419**) was investigated. Using TBAF in THF allowed clean removal of the protecting group to afford alcohol (**420**) (Scheme 184). However, the single time the reaction was attempted, a slow chromatographic isolation procedure significantly reduced the yield. Subsequent work[231] has shown that with careful isolation, the reaction procedure will afford an 80% yield.



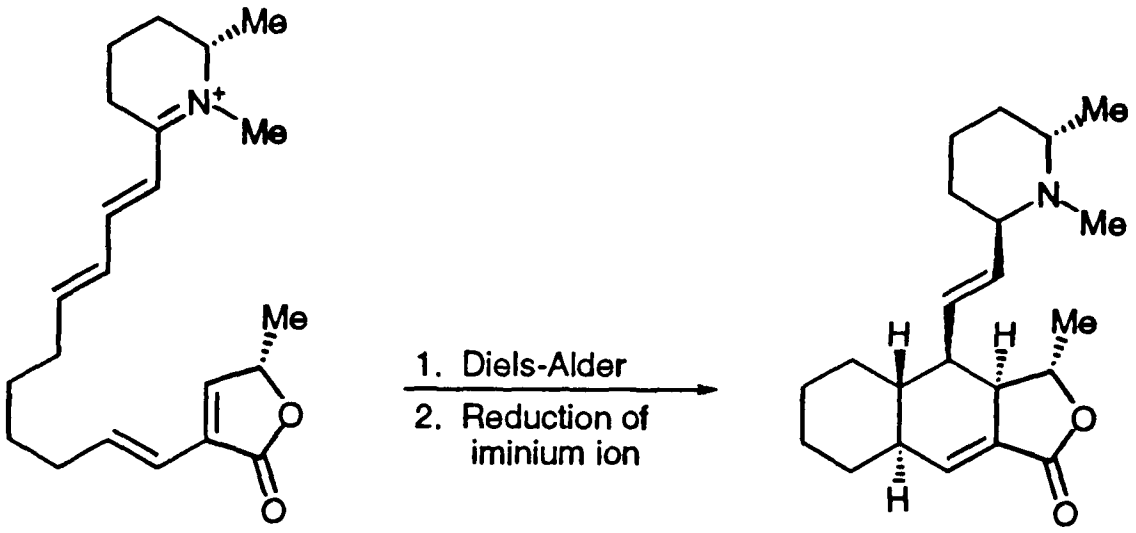
Scheme 184

Thus, the chemistry required for the synthesis of enyne (**403**) (Scheme 172), and hence dihydrofuran (**310**) has been successfully demonstrated.

Chapter 3

CONCLUSIONS

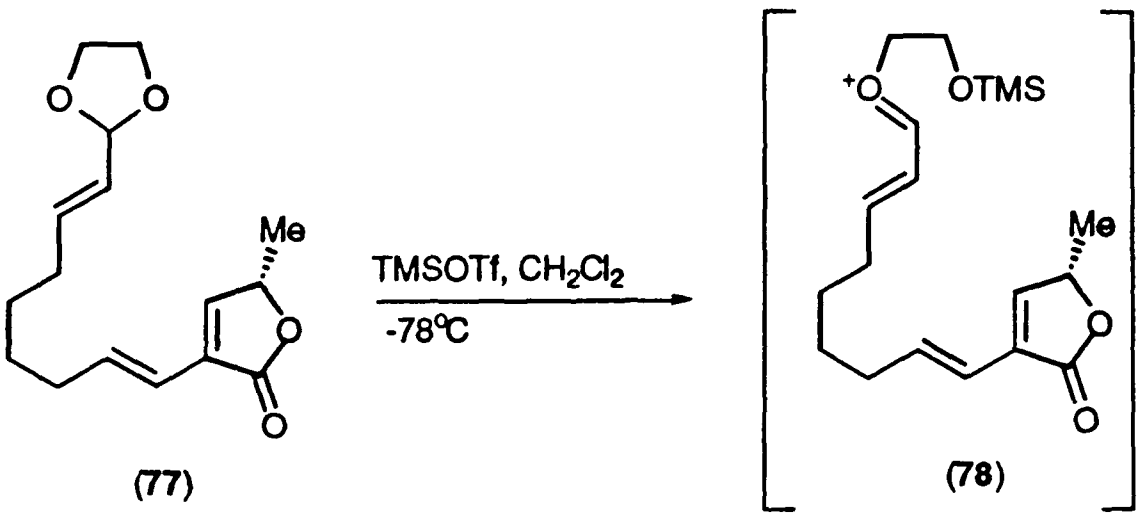
Studies towards the proposed iminium ion mediated Diels-Alder reaction (Scheme 185) for the synthesis of himgravine **9**, and hence himbacine **1**, are currently at an advanced stage.



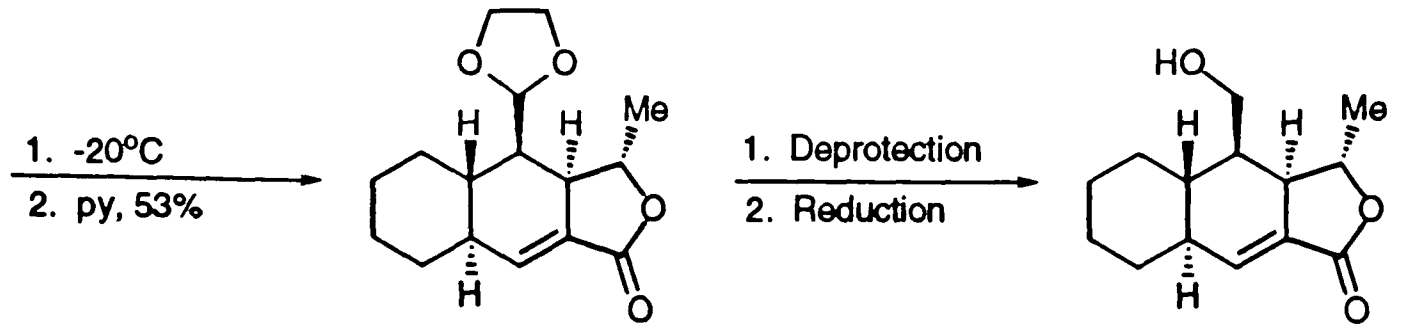
(80) **Himgravine 9**

Scheme 185

Excellent precedent for this proposal has been obtained by the oxonium ion mediated Diels-Alder reaction of acetal butenolide (**77**), yielding tricyclic acetal (**79**) (Scheme 186). The stereochemistry of the product of this cycloaddition has been confirmed by X-ray crystallography of the tricyclic alcohol (**30**).



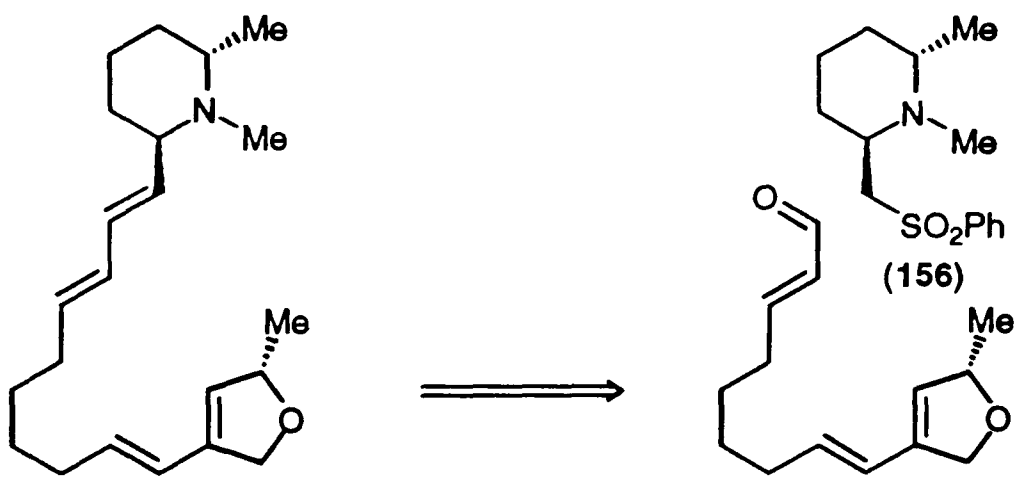
(77) **(78)**



(79) **(30)**

Scheme 186

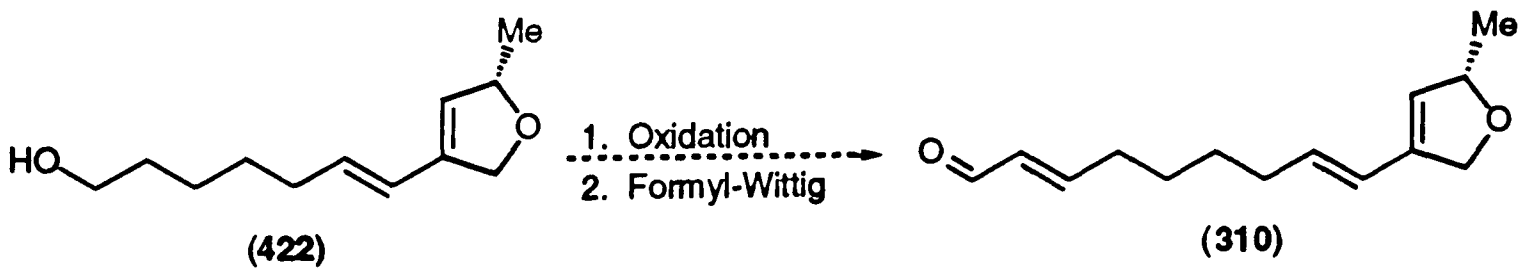
Synthesis of the piperidine (**421**) (Scheme 187) required to study the proposed iminium ion mediated Diels-Alder reaction is nearing completion.



(421) **(310)**

Scheme 187

The synthesis of enal (**310**) will be completed using metathesis chemistry, which should afford chiral alcohol (**422**). Conversion of this alcohol (**422**) to enal (**310**) should be possible by oxidation to the aldehyde, using the Dess-Martin periodinane, followed by a formyl-Wittig reaction (Scheme 188).

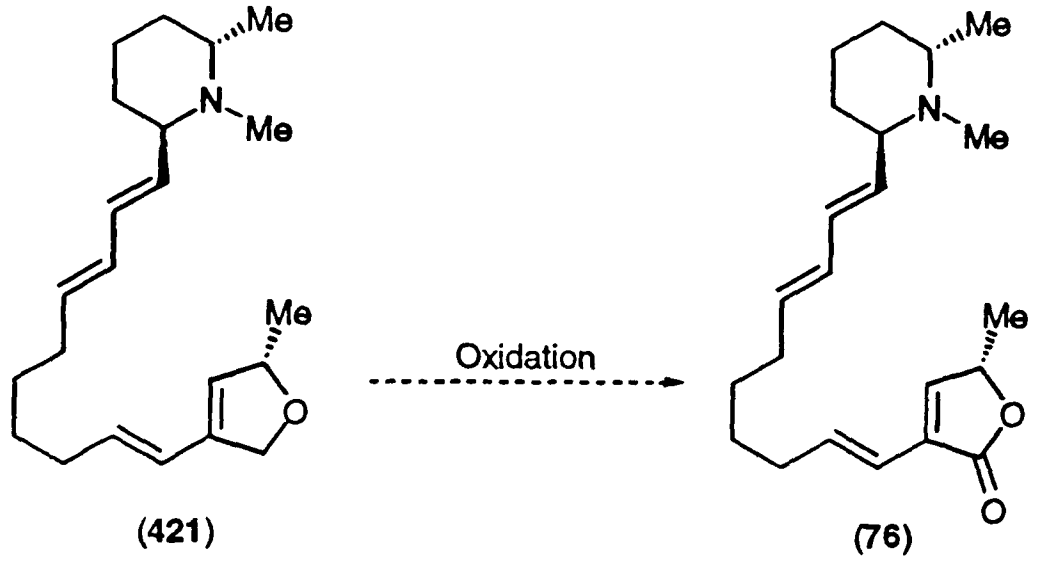


(422) **(310)**

Scheme 188

The synthesis of piperidine sulfone (**156**) has been completed starting from L-alanine in a 17% yield over 16 linear steps. This piperidine sulfone (**156**) will be coupled to enal (**310**) using the developed Julia coupling methodology to afford piperidine (**421**). Finally the iminium ion (**80**) will be generated using a Polonovski reaction, allowing an investigation as to whether this species undergoes an intramolecular Diels-Alder reaction.

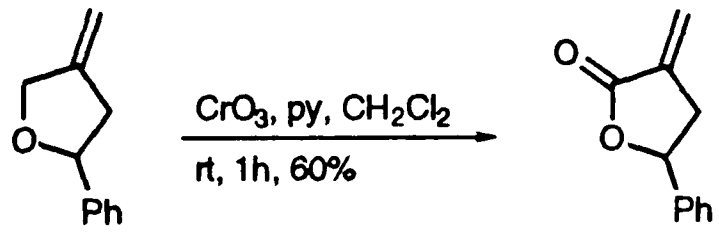
One final piece of methodology that will need to be addressed is the introduction of a carbonyl group onto the five-membered ring. This could be completed before generation of the iminium ion (Scheme 189).



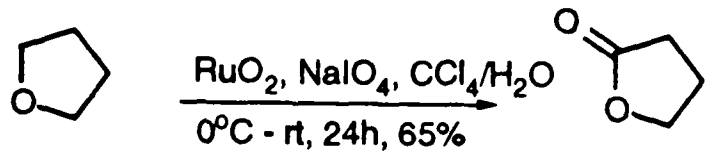
(421) (76)

Scheme 189

Chemoselective oxidation of methylene groups that are either allylic, or α to oxygen, or both, have been demonstrated using reagents such as chromium trioxide[243] (Scheme 190) and ruthenium tetroxide[244] (Scheme 191).

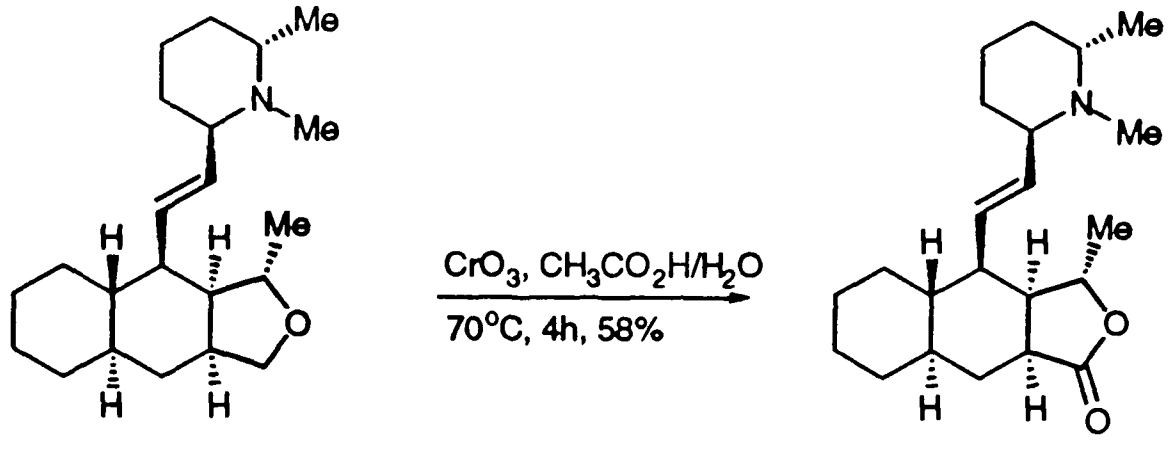


Scheme 190



Scheme 191

If introduction of the carbonyl group proves to be problematic prior to the proposed Diels-Alder reaction (Scheme 185), the oxidation could be completed afterwards. This transformation was completed by Ritchie[6] as part of the original structural elucidation of himbacine **1** (Scheme 192)



Himbacine **1**

Scheme 192

Oxidation prior to attempting the iminium ion mediated Diels-Alder reaction would be preferable, as piperidine (**76**) is the precursor to the iminium ion (**80**) in the biosynthetic proposal (Scheme 185).

In summary, the majority of the chemistry required for the synthesis of iminium ion (**80**) has either been completed, or successfully modelled. Thus, it is anticipated that the synthesis of this molecule will be completed shortly, confirming, or otherwise, the proposed iminium ion mediated Diels-Alder reaction for the synthesis of himgravine **9** and hence himbacine **1**.

Chapter 4

EXPERIMENTAL

4.1. Solvents and Reagents

The following reaction solvents and anhydrous reagents were dried and distilled prior to use:

CH_2Cl_2	Distilled from CaH_2 under nitrogen immediately prior to use.
THF Et_2O	Distilled from sodium/benophenone ketyl under nitrogen immediately prior to use.
Et_3N *i*Pr_2NEt MeOH Pyridine Quinoline CH_3CN *t*BuOH TMEDA BzCl	Distilled from CaH_2 and stored under nitrogen over 4Å molecular sieves.
DMF DMSO	Distilled from CaH_2 under reduced pressure and stored over 4Å molecular sieves.
MsCl	Distilled immediately prior to use.
Crotonaldehyde	

*n*BuLi and *s*BuLi in hexanes (unless otherwise noted) were purchased from Lancaster and Aldrich respectively and were standardised with 1,3-diphenylacetone-*p*-tosylhydrazone[245].

Molecular sieves were activated before use by heating at 200°C under reduced pressure for 24 hours.

All other reagents and solvents were used as received without further purification.

Carboethoxymethylenetriphenylphosphorane was prepared by the method of Casey[246].

Dess-Martin periodinane was prepared by the method of Ireland[247].

*m*CPBA was dissolved in CH_2Cl_2, dried over $MgSO_4$, then titrated with $KI/Na_2S_2O_3$[248].

6% Sodium Amalgam was prepared from sodium and mercury[248].

4.2. General Procedures

Reactions were normally monitored by TLC, IR and/or ^1H NMR prior to work-up. Solvents were evaporated at ≤40°C on a Büchi R110 Rotavapor. All reactions were performed in accordance with the Good Laboratory Practice.

4.2.1. Chromatography

Column chromatography was performed using Janssen silica gel 0.035-0.070mm or basic Laporte Actal UG alumina. Thin layer chromatography (TLC) was performed on glass plates pre-coated with Merck silica gel 60 F_{254} or on alumina sheets precoated with neutral aluminium oxide 60 F_{254} (type E). Visualisation was using UV fluorescence (254 and 366nm), or using iodine, ammonium molybdate (7% w/v in 1M sulfuric acid), potassium permanganate (1% w/v in 0.5M K_2CO_3/NaOH) or

Dragensdorff's reagent (0.08% bismuth subnitrate and 2% KI w/v 3M acetic acid). Petroleum ether 30-40°C was distilled prior to use as an elutant.

4.2.2. Yields

All quoted yields were isolated yields unless otherwise stated.

4.2.3. Melting Points

Melting points were determined using a Cambridge Instruments Gallen™ III Köfler Block melting point apparatus and are uncorrected

4.2.4. Optical Rotations

Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 589nm (Na D-line), and specific optical rotations $[\alpha]^D_t$ were calculated using the formula:

$$[\alpha]^D_t = \frac{100\alpha}{lc}$$

where: t = temperature (°C)

α = recorded optical rotation

l = length of cell (l = 1dm for this polarimeter)

c = concentration of sample (10mg/ml)

Solvents for optical rotations were spectrograde and were used as received.

4.2.5. Elemental Analysis

Microanalyses were determined by Mrs V. Lamburn and Mr R. Prior on a Micro Carlo-Erba Analyser, model 1106 at the Dyson Perrins Laboratory and are quoted to the

nearest 0.1% for all elements except for hydrogen which is quoted to the nearest 0.05%.

4.2.6. Infrared Spectra

Infrared spectra were recorded on a Perkin-Elmer 1750 or Perkin-Elmer Paragon 1000 Fourier Transform spectrometer with internal referencing. The samples were either prepared as thin films between NaCl plates or KBr discs as indicated. Absorption maxima are reported in wavenumbers (cm^{-1}). The following abbreviations are used: w, weak; m, medium; s, strong; vs, very strong; br, broad.

4.2.7 Nuclear Magnetic Resonance Spectra

^{1}H NMR spectra were recorded on Varian Gemini-200 (200MHz), Brüker AH-200 (200MHz), Brüker WH-300 (300MHz), Brüker AM-500 (500MHz) and Brüker AMX-500 (500MHz) spectrometers. Chemical shifts (δ_H) are quoted in parts per million (ppm) and are referenced to the appropriate residual solvent peak. The observed multiplicities are characterised as singlet (s), doublet (d), triplet (t), quartet (q), a combination of these (*eg.* dd, dt, *etc.*), or as a multiplet (m). Coupling constants (*J*) are quoted to the nearest 0.5Hz.

^{13}C NMR spectra were recorded on Brüker AH-200 (50.5MHz) and Brüker AM-500 (127.5MHz) spectrometers. Carbon spectra assignments are supported by DEPT-135 spectra and where necessary, C-H correlations. Chemical shifts (δ_C) are quoted in parts per million (ppm) and are referenced to the appropriate residual solvent peak.

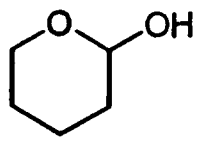
^{2}D NMR spectra were recorded on Brüker AM-250 (38MHz) and Brüker AM-500 (76MHz) spectrometers. Chemical shifts (δ_D) are quoted in parts per million (ppm) and are referenced to the appropriate residual solvent peak.

4.2.8. Mass Spectra

Low-resolution mass spectra were recorded using a TRIO-1 GCMS (GCMS CI^+/EI^+), a Micromass platform (APCI CI^+), and a Micromass ZAB 1F (Probe CI^+/EI^+), with major peaks being reported with intensity quoted as percentages of the base peak.

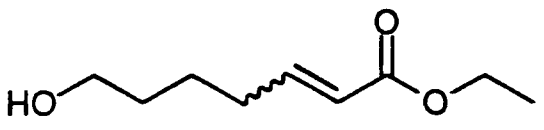
High-resolution mass spectra were recorded by the Engineering and Physical Sciences Research Council mass spectrometry service centre, Swansea.

Tetrahydropyran-2-ol **198**



To a 0.002M solution of hydrochloric acid (3000ml) was added 3,4-tetrahydropyran **138** (35.0g, 0.417mol) dropwise over a period of 60 minutes. The solution was then stirred for 12 hours at room temperature. The solution was saturated with NaCl and extracted with dichloromethane (4x800ml). The combined organic extracts were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo* to yield the product as a colourless oil (15.49g, 37%). υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3402s (O-H str), 2944s (C-H str), 2854m (C-H str), 1458m, 1443m, 1355m, 1276m, 1197m, 1138m, 1116m, 1076s (C-O str), 1028s (C-O str), 1015s, 978s, 935m, 915m, 902m, 867m, 842m and 807m; δ_H (200 MHz; $CDCl_3$) 1.52-1.54 (4H, broad m, $C\underline{H}_2C\underline{H}_2$), 1.71-1.86 (2H, broad m, $C\underline{H}_2CHOH$), 3.51-3.60 (2H, m, $C\underline{H}H'CHO\underline{H}$), 3.98-4.18 (1H, m $CH\underline{H}'CHOH$) and 4.90 (1H, broad m, $C\underline{H}OH$); δ_C (50 MHz; $CDCl_3$) 20.06 ($\underline{C}H_2CH_2CHOH$), 24.97 ($\underline{C}H_2CH_2O$), 31.67 ($\underline{C}H_2CHOH$), 63.59 ($\underline{C}H_2O$) and 94.27 ($O\underline{C}HOH$); m/z (GCMS CI^+, NH_3) 120 (4, MNH_4^+), 103 (3, MH^+), 102 (13, M^+), 86 (6), 85 (100, MH^+-H_2O), 84 (34, M^+-H_2O), 83 (4), 55 (4) and 51 (4).

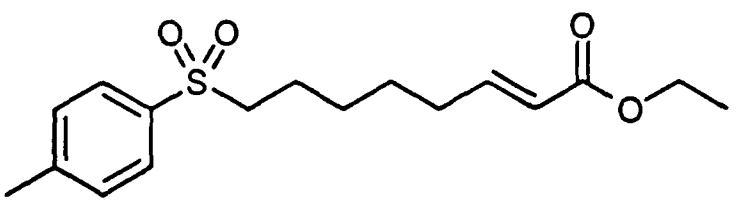
(*E,Z*)-7-Hydroxy-2-heptenoic acid ethyl ester **201**



To a solution of tetrahydropyran-2-ol **198** (10.00g, 98.0mol, 1.0eq) in tetrahydrofuran (300ml) was added carboethoxytriphenylphosphorane (81.88g, 235.0mol, 2.4eq) in a single portion. The mixture was brought to reflux at which stage the carboethoxytriphenylphosphorane dissolved affording a clear solution which was heated under reflux for 16 hours. The resultant solution was cooled and the volatiles

removed in *vacuo* affording an oily solid which was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 2:1) affording the product as an inseparable mixture of *E/Z* isomers (*E/Z* 10:1 by ^1H NMR, 15.00g, 89%). υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3248s (O-H str.), 2940s (C-H str.), 1720s (C=O str.), 1654s (C=C str.), 1445m, 1369m, 1271s, 1191s, 1097m, 1038s and 983m; δ_H (200 MHz, $CDCl_3$) 1.29 (3H, t, *J* 7.0Hz, $CO_2CH_2C\underline{H}_3$), 1.56-159 (4H, m $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 2.24 (2H, ddt, *J* 7.0, 6.5 and 1.5Hz, $C\underline{H}_2CH{=}CH$), 3.66 (2H, t, *J* 6.0Hz, $HOC\underline{H}_2$), 4.18 (2H, q, *J* 7.0Hz, $CO_2C\underline{H}_2CH_3$), 5.83 (1H, dt, *J* 14.0 and 1.5Hz, $CH{=}C\underline{H}CO_2$) and 6.96 (1H, dt, *J* 14.0 and 6.0Hz, $C\underline{H}{=}CHCO_2$); δ_C (50 MHz, $CDCl_3$) 13.94 ($CO_2CH_2\underline{C}H_3$), 23.99 ($\underline{C}H_2CH_2CH{=}CH$), 31.64 ($HOCH_2\underline{C}H_2$), 31.75 ($\underline{C}H_2CH{=}CH$), 60.07 ($CO_2\underline{C}H_2CH_3$), 61.90 ($HO\underline{C}H_2$), 121.4 ($CH{=}\underline{C}HCO_2$), 149.3 ($\underline{C}H{=}CHCO_2$) and 167.0 ($CH{=}CH\underline{C}O_2$); m/z (GCMS Cl^+, NH_3) 190 (62, MNH_4^+), 173 (100, MH^+), 127 (164), 102 (37) and 85 (26).

(*E*)-7-(Toluene-4-sulfonyloxy)-2-heptenoic acid ethyl ester **204**



To a solution of (*E,Z*)-7-hydroxy-2-heptenoic acid ethyl ester **201** (44.72g, 0.26mol, 1.0eq) in dichloromethane (500ml) cooled to 0°C under an atmosphere of argon was added pyridine (30.81g, 0.39mol, 1.5eq). The solution was stirred at 0°C for 5 minutes at which stage *para*-toluenesulphonyl chloride (74.30g, 0.39mol, 1.5eq) in dichloromethane (250ml) was added over a 15 minute period. The reaction mixture was stirred at 0°C for 15 minutes, then at room temperature for 16 hours. The resultant solution was washed with water (50ml), dilute hydrochloric acid (1M, 50ml) and water (50ml) then dried over magnesium sulphate, filtered and the volatiles removed in *vacuo* yielding an oily residue which was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 1:2) to afford

(i)

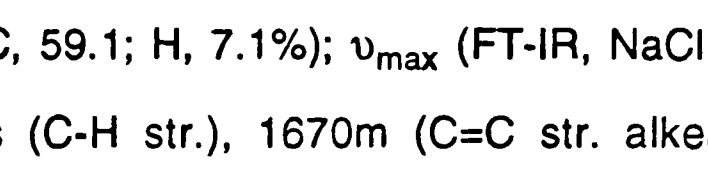
(*Z*)-7-(Toluene-4-sulfonyloxy)-2-heptenoic acid ethyl ester **204** as a colourless oil (6.78g, 8%). (Found C, 59.0; H, 6.8. $C_{16}H_{22}SO_5$ requires C, 58.9; H, 6.8%); υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2939s (C-H str.), 1718s (C=O str.), 1645s (C=C str., $\alpha\beta$-unsaturated), 1599 (C=C str., aromatic), 1496m, 1449s, 1416s, 1361s, 1292s, 1177s, 1098s, 1035s, 935s, 891s, 817s, 734s, 706m, 689m and 665s; δ_H (200 MHz; $CDCl_3$) 1.28 (3H, t, *J* 7.0Hz, $CO_2CH_2C\underline{H}_3$), 1.44-1.76 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 2.46 (3H, s, $ArC\underline{H}_3$), 2.62 (2H, dq, *J* 7.5 and 1.5Hz, $CH_2CH_2CH_2C\underline{H}_2$), 4.05 (2H, t, *J* 6.5Hz, $SOC\underline{H}_2$), 4.15 (2H, q, *J* 7.0Hz, $CO_2C\underline{H}_2CH_3$), 5.77 (1H, dt, *J* 11.5 and 1.5Hz, CH=C<u>H</u>-CO_2Et), 6.13 (1H, dt, *J* 11.5 and 7.5Hz, $CH=CHCO_2Et$), 7.35 (2H, d, *J* 8.5Hz, Ph<u>H</u>) and 7.80 (2H, d, *J* 8.5Hz, Ph<u>H</u>); δ_C (50 MHz, $CDCl_3$) 14.20 ($CO_2CH_2\underline{C}H_3$), 21.57 ($Ar\underline{C}H_3$), 24.68 ($CH_2\underline{C}H_2CH_2CH_2$), 28.00 ($CH_2CH_2\underline{C}H_2CH_2$), 28.32 ($CH_2CH_2CH_2\underline{C}H_2$), 59.78 ($CO_2\underline{C}H_2CH_3$), 70.27 ($SO\underline{C}H_2$), 120.3 ($CH=\underline{C}HCO_2Et$), 127.8 (<u>C</u>H aromatic), 129.8 (<u>C</u>H aromatic), 133.0 (ipso aromatic $\underline{C}CH_3$), 144.7 (ipso aromatic $\underline{C}SO_3$), 149.0 ($\underline{C}H=CHCO_2Et$) and 166.2 ($CH=CH\underline{C}O_2Et$); m/z (Probe CI^+, NH_3) 344 (100, MNH_4^+), 327 (25, MH^+), 298 (17), 190 (13), 155 (11), 108 (20) and 102 (14).

and (ii)

(*E*)-7-(Toluene-4-sulfonyloxy)-2-heptenoic acid ethyl ester **204** as a colourless oil. (72.89g, 86%). (Found C, 59.2; H, 6.9. $C_{16}H_{22}SO_5$ requires C, 58.9; H, 6.8%); υ_{max} (FT-IR, NaCl plates, thin film) 2942s (C-H str.), 1718s (C=O str.), 1655s (C=C str., alkene), 1599s (C=C str. aromatic), 1496m, 1458s, 1361s, 1177s, 1098s, 1042s, 931s, 817s, 778s, 736m and 664s. δ_H (200 MHz; $CDCl_3$) 1.30 (3H, t, *J* 7.0Hz, $CO_2CH_2C\underline{H}_3$), 1.45-1.72 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 2.17 (2H , dtt, *J* 7.0, 6.5 and 1.0Hz, $C\underline{H}_2CH=CH$), 2.46 (3H, s, Ar-$C\underline{H}_3$), 4.04 (2H, t, *J* 6.0Hz, $SOC\underline{H}_2$), 4.19 (2H, q, *J* 7.0, $CO_2C\underline{H}_2CH_3$), 5.77 (1H, dt, *J* 16.0 and 1.0Hz, $CH=C\underline{H}CO_2$), 6.88 (1H, dt, *J* 16.0 and 7.0Hz, $C\underline{H}=CHCO_2$), 7.36 (2H, d, *J* 8.5Hz, Ph<u>H</u>) and 7.80 (2H, d, *J* 8.5Hz, Ph<u>H</u>); δ_C (50 MHz; $CDCl_3$) 14.05 ($CO_2CH_2\underline{C}H_3$), 21.41 ($Ar\underline{C}H_3$), 23.63 ($\underline{C}H_2CH_2CH=CH$), 27.98 ($SOCH_2\underline{C}H_2$), 31.07 ($\underline{C}H_2CH=CH$), 60.02 ($CO_2\underline{C}H_2CH_3$), 69.88 ($SO\underline{C}H_2$), 121.7

($CH=\underline{C}HCO_2$), 128.0 ($\underline{C}H$ aromatic), 130.0 ($\underline{C}H$ aromatic), 133.0 ($\underline{C}CH_3$ ipso aromatic), 144.7 ($\underline{C}SO_3$ ipso aromatic), 147.8 ($C\underline{H}=CHCO_2$) and 166.3 ($CH=CH\underline{C}O_2$); m/z (Probe CI^+, NH_3) 344 (85, MNH_4^+), 327 (100, MH^+), 298 (17), 108 (27), 91 (10) and 81 (12).

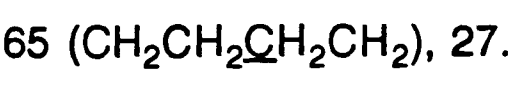
(*E*)-1-(Toluene-4-sulfonyloxy)-7-hydroxy-5-heptene **205**



To a solution of (*E*)-7-(toluene-4-sulfonyloxy)-2-heptenoic acid ethyl ester **204** (7.32g, 22.0mmol, 1.0eq) in dichloromethane (160ml) cooled to -78°C under an atmosphere of argon was added diisobutylaluminium hydride as a 1.5M solution in toluene (40ml, 60.0mmol, 2.6eq) over a period of 10 minutes. The reaction mixture was stirred at -78°C for 150 minutes at which stage the reaction was shown to be complete by TLC analysis. The reaction was quenched at -78°C by the addition of distilled water (20ml). The reaction mixture was then allowed to warm to room temperture over a period of 90 minutes. The mixture was diluted with water (20ml) and dilute hydrochloric acid (1M) was added until the white, gelatinous precipitate had fully dissolved yielding two phases. These were separated and the aqueous layer further extracted with dichloromethane (5x40ml). the organic fractions were combined, dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The obtained yellow oil was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 3:2) affording the product as a colourless oil (6.02g, 94%). (Found C, 59.2; H 7.4. $C_{14}H_{20}O_4$ requires C, 59.1; H, 7.1%); υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3377s (O-H str.), 2932s (C-H str.), 1670m (C=C str. alkene), 1599s, (C=C str. aromatic), 1496s, 1456s, 1358s, 1308m, 1293m, 1176s, 1098s, 971s, 817s and 758s; δ_H (200 MHz; $CDCl_3$) 1.42-1.70 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 2.03 (3H, m, O$\underline{H}$ and $CH_2CH_2CH_2C\underline{H}_2$), 2.46 (3H, s, $ArC\underline{H}_3$), 4.01-4.09 (4H, m, $C=CC\underline{H}_2OH$ and $SOC\underline{H}_2$), 5.60-5.64 (2H, m, $C\underline{H}=C\underline{H}CH_2OH$), 7.36 (2H, d, *J* 8.5 Hz, Ph$\underline{H}$) and 7.80 (2H, d, *J* 8.5

Hz, PhH); δ_C (50 MHz, $CDCl_3$) 21.57 ($ArCH_3$), 24.68 ($CH_2CH_2CH_2CH_2$), 28.11 ($CH_2CH_2CH_2CH_2$), 31.30 ($CH_2CH_2CH_2CH_2$), 63.20 ($SOCH_2$), 70.51 ($CH=CHCH_2OH$), 127.8 (CH aromatic), 129.7 ($CH=CHCH_2OH$), 129.9 (CH aromatic), 131.5 ($CH=CHCH_2OH$), 132.8 (ipso aromatic CCH_3) and 144.8 (ipso aromatic, CSO_3); m/z (Probe CI^+, NH_3) 302 (22, MNH_4^+), 285 (3, MH^+), 284 (M^+ for ^{32}S, 16), 112 (12), 96 (12), 95 (100) and 94 (12).

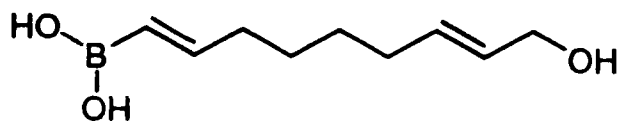
(*E*)-2-Nonen-8-yl-1-ol **206**



To a slurry of lithium acetylene diamine complex (1.66g, 18.0mmol, 2.2eq) in dimethyl sulphoxide (5ml) cooled to 10°C under an atmosphere of argon was added (*E*)-1-(toluene-4-sulfonyloxy)-7-hydroxy-5-heptene **205** (2.32g, 8.2mmol, 1.0eq) in dimethyl sulphoxide (3ml) dropwise over a period of 20 minutes. The dark solution was stirred at 12°C for 2 hours at which stage it was poured onto crushed ice. The mixture was acidified with dilute hydrochloric acid (1M, 10ml) and then extracted with diethyl ether (6x25ml). The combined organics were dried over magnesium sulphate, filtered and the volatiles carefully removed in *vacuo.* The residual dark coloured oil was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 1:2) affording the product as a colourless oil (1.10g, 69%). (Found C, 78.0; H, 10.3. $C_9H_{14}O$ requires C, 78.2; H, 10.2%); υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3302s (C-H alkyne str.), 2937s (C-H str.), 2117w (C≡C str.), 1671w (C=C str.), 1434m, 1089m, 1005m, 972s and 632w; δ_H (200 MHz; $CDCl_3$) 1.41-1.54 (4H, m, $CH_2CH_2CH_2CH_2$), 1.92 (1H, t, *J* 2.5Hz, alkyne CH), 2.06-2.21 (4H, m, $CH_2CH_2CH_2CH_2$), 2.24 (1H, s, OH), 4.09 (2H, m, $HOCH_2CH=CH$) and 5.50-5.72 (2H, m, CH=CH); δ_C (50 MHz, $CDCl_3$) 18.00 ($CH_2CH_2CH_2CH_2$), 27.65 ($CH_2CH_2CH_2CH_2$), 27.90 ($CH_2CH_2CH_2CH_2$), 31.40 ($CH_2CH_2CH_2CH_2$), 63.08 ($HOCH_2CH=CH$), 68.21 (C≡CH), 84.23 (C≡CH), 129.1 ($HOCH_2CH=CH$) and 132.1 ($HOCH_2CH=CH$); m/z (Probe CI^+, NH_3) 156 (100, MNH_4^+),

138 (75, MNH_4^+-H_2O), 121 (35), 109 (24), 107 (23), 105 (13), 95 (21), 94 (16), 93 (13), 92 (11), 91 (19), 81 (30), 79 (23), 67 (10), and 58 (14).

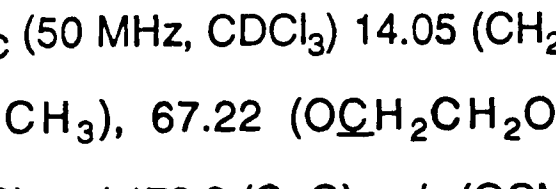
(*E,E*)-9-Hydroxy-1,7-nonadienyl boronic acid **191**



To a sample of (2*E*)-2-Nonen-8-yl-1-ol **206** (483mg, 3.5mmol, 1.0eq) in a reaction tube under an atmosphere of argon was added catecholborane (847mg, 7.7mmol, 2.2eq) dropwise. On competition of evolution of hydrogen from the reaction the mixture was was heated at 85°C for 1 hour at which stage the reaction was shown to be complete by ^1H NMR analysis. The crude product was transferred to a 100ml round bottomed flask to which was added distilled water (35ml). The flask was sealed and shaken for 1 hour on a Gallencamp Laboratory Shaker, then stirred at room temperature for 16 hours. The aqueous mixture was saturated with sodium chloride then extracted with ethyl acetate (4x25ml). The organic extracts were combined, dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The residue was purified by rapid flash chromatography (SiO_2 90x30mm; eluting with diethyl ether: petroleum ether 1:1 (400ml), dichloromethane: methanol 92:8 (200ml) and ethyl acetate: methanol 92:8 (200ml); collecting 40ml fractions; product from fractions 10-15) yielding a colourless oil which was dissolved in tetrahydrofuran containing a minimum amount of methanol. The volatiles were then removed in *vacuo* affording the product as a colourless foam (448mg, 70%). υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3414s, (O-H str.), 2928s, (C-H), 1722w (C=C str.), 1638s (C=C str.), 1474s, 1402s, 1333s, 1237s, 1094s, 996s, 971s, 810m, and 755m; δ_H (200 MHz, MeOD) 1.36-1.51 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 2.04-2.17 (4H, m, $C\underline{H}_2CH_2CH_2C\underline{H}_2$) 3.99 (2H, m, $HOC\underline{H}_2CH{=}CH$), 5.46-5.74 (3H, m, $HOCH_2C\underline{H}{=}C\underline{H}$ and $CH{=}C\underline{H}B$) and 6.57 (1H, dt, *J* 17.5 and 6.5Hz, $C\underline{H}{=}CHB$), $B(O\underline{H})_2$ not seen; δ_C (50 MHz, MeOD) 29.26 ($CH_2\underline{C}H_2CH_2CH_2$) , 29.96 ($CH_2CH_2\underline{C}H_2CH_2$), 33.20 ($\underline{C}H_2CH_2CH_2CH_2$) , 36.87

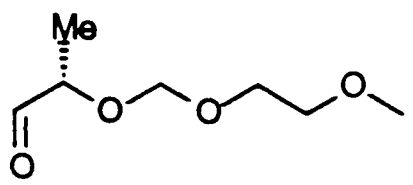
($CH_2CH_2CH_2\underline{C}H_2$), 63.78 ($HO\underline{C}H_2CH{=}CH$), 130.6 ($HOCH_2CH{=}\underline{C}H$), 133.3 ($HOCH_2\underline{C}H{=}CH$) and 153.9 ($\underline{C}H{=}CH\text{-}B$), $CH{=}\underline{C}HB$ not seen.

(*S*)-Ethyl 2-[(2-methoxyethoxy)methoxy]-propionate **209**



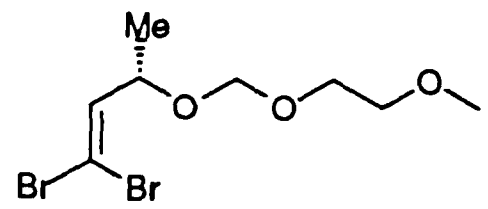
To a solution of *N,N* - di-isopropylethylamine (24.66g, 0.180mol, 1.5eq) in dichloromethane (120ml) cooled to 0°C under an atmosphere of argon was added (*S*)-ethyl lactate **193** (15.00g, 0.126mol, 1.0eq) in a single portion. The mixture was stirred at room temperature for 15 minutes at which stage (2-methoxyethoxy)methyl chloride (23.76g, 0.180mol, 1.5eq) was added dropwise over a 10 minute period. The solution was stirred for 16 hours at room temperature. The organic solution was then washed with water (3x50ml), dilute hydrochloric acid (1M, 50ml), water (50ml), dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The obtained yellow oil was purified by distillation affording the product as a colourless oil (25.52g, 98%). (b.p. 76°C / 0.7mmHg); $[\alpha]^{D}_{22}$ -44.3 (c 1, $CHCl_3$); υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2984s, 2938s, 2892s (C-H), 1748s (C=O), 1451s, 1377m, 1273m, 1202m, 1182m, 1126s, 1099s, 1024s , 935w, 851w and 758w; δ_H (200 MHz, $CDCl_3$) 1.28 (3H, t, *J* 7.0Hz, $OCH_2C\underline{H}_3$), 1.43 (3H, d, *J* 7.0Hz, $C\underline{H}_3CH$), 3.39 (3H, s, $OC\underline{H}_3$), 3.51-3.76 (4H, m, $OC\underline{H}_2C\underline{H}_2O$), 4.19 (2H, q, *J* 7.0Hz, $OC\underline{H}_2CH_3$), 4.23 (1H, q, *J* 7.0Hz, $CH_3C\underline{H}$) and 4.80 (2H, s, $OC\underline{H}_2O$); δ_C (50 MHz, $CDCl_3$) 14.05 ($CH_2\underline{C}H_3$), 18.43 ($CHC\underline{H}_3$), 58.83 ($O\underline{C}H_3$), 60.73 ($CO_2\underline{C}H_2CH_3$), 67.22 ($O\underline{C}H_2CH_2O$), 71.31 ($\underline{C}HCH_3$), 71.56 ($OCH_2\underline{C}H_2O$), 94.63 ($O\underline{C}H_2O$) and 172.9 ($\underline{C}{=}O$); m/z (GCMS CI^+, NH_3) 224 (4, MNH_4^+), 207 (6, MH^+), 132 (7), 131 (100), 94 (4), 89 (52), 59 (32) and 58 (10).

(*S*)-2-[(Methoxyethoxy)methoxy]-propanal **210**



To a solution of (*S*)-Ethyl 2-[(2-methoxyethoxy)methoxy]-propionate **209** (15.50g, 75.0mmol, 1.0eq) in dichloromethane (150ml) cooled to -78°C under an atmosphere of argon was added diisobutylaluminium hydride as a 1.0M solution in hexanes (75ml, 75.0mmol, 1.0eq) dropwise over a period of 45 minutes. The solution was stirred at -78°C for 3 hours at which stage saturated aqueous ammonium chloride (50ml) was added followed by dilute hydrochloric acid (1M, 50ml). The reaction mixture was allowed to warm to room temperature and was then stirred until the precipitated formed on the addition of the saturated aqueous ammonium chloride had fully dissolved. The mixture was extracted with dichloromethane (3x120ml), the organic extracts combined, dried over sodium sulphate, filtered and the volatiles removed in *vacuo* affording the product as a colourless oil (11.97g, 98%). $[\alpha]^{D}_{22}$ -32.3 (c 1, $CHCl_3$); (Found C, 51.6; H, 9.1. $C_7H_{14}O_4$ requires C, 51.8; H, 8.8%); υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2980m, 2932s (C-H str.), 2889s (C-H str.), 1736s (C=O str.), 1455m, 1378m, 1244 m, 1181 m, 1111s, 1042s, and 917m; δ_H (200 MHz, $CDCl_3$) 1.30 (3H, d, *J* 7.0Hz, $CHC\underline{H}_3$), 3.36 (3H, s, $OC\underline{H}_3$), 3.50-3.76 (4H, m, $OC\underline{H}_2C\underline{H}_2O$), 4.08 (1H, q, *J* 7.0Hz, $C\underline{H}CH_3$), 4.81 (2H, s, $OC\underline{H}_2O$) and 9.63 (1H, s, $H\underline{C}$=O); δ_C (50 MHz, $CDCl_3$) 14.98 ($CH\underline{C}H_3$), 58.66 ($O\underline{C}H_3$), 67.19 ($O\underline{C}H_2CH_2O$), 71.40 ($OCH_2\underline{C}H_2O$), 77.82 ($CHCH_3$), 94.78 ($O\underline{C}H_2O$) and 202.4 ($\underline{C}HO$); m/z (GCMS Cl^+, NH_3) 180 (15, MNH_4^+), 163 (22, MH^+), 162 (11, M^+), 106 (7), 94 (11), 89 (100), 87 (13), 74 (4), 59 (41) and 58 (6).

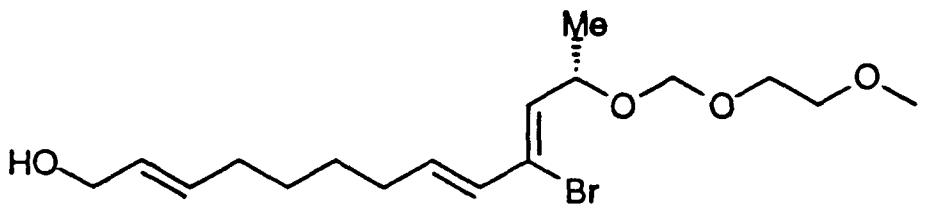
(*S*)-1,1-Dibromo-3-[(2-methoxyethoxy)methoxy]-1-butene **192**



To a suspension of zinc dust (24.3g, 0.372mol, 4.0eq) and triphenylphosphine (97.5g, 0.372mol, 4.0eq) in dichloromethane (500ml) cooled to 0°C under an atmosphere of argon was added carbon tetrabromide (123.5g, 0.372mol, 4.0eq) in dichloromethane (200ml) in such a manner that did not allow the temperature to exceed 25°C. The reaction mixture was then stirred at room temperature for 36 hours at which stage it was cooled to 0°C. (*S*)-2-[(methoxyethoxy)methoxy]-propanal **210** (15.0g, 93mmol, 1.0eq) in dichloromethane (100ml) was added dropwise and the reaction mixture was stirred at 0°C for a further 15 minutes then at ambient for 36 hours at which stage the reaction was shown to be complete by TLC analysis. The reaction mixture was poured in petroleum ether 30-40°C (2000ml) and the produced residue was filtered off. The residue was redissolved in dichloromethane (500ml) and this solution was poured into petroleum ether 30-40°C (3000ml). The obtained precipitate was filtered off, the organic extracts combined and the volatiles removed in *vacuo*. The obtained colourless oil was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 1:6) to afford the product as a colourless oil (14.97g, 51%). $[\alpha]^{D}_{22}$ -68.4 (c 1, $CHCl_3$); (Found C, 30.5; H, 4.3. $C_8H_{14}O_3Br_2$ requires C, 30.2; H, 4.4%); υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2978s (C-H str.), 2929s (C-H str.), 2887s (C-H str.), 2817s (C-H str.), 1611m (C=C str.), 1553w, 1453m 1409w, 1373m, 1282w, 1243m, 1200m, 1180s, 1137s, 1111vs, 1029vs, 985m, 935w, 859m and 779s; δ_H (200 MHz, $CDCl_3$). 1.28 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 3.40 (3H, s, $OC\underline{H}_3$), 3.54-3.77 (4H, m, $OC\underline{H}_2C\underline{H}_2O$), 4.46 (1H, dq, *J* 6.5 and 8.0Hz, $C\underline{H}CH_3$), 4.72 (2H, m, $OC\underline{H}_2O$) and 6.41 (1H, d, *J* 8.0Hz $C\underline{H}=CBr_2$); δ_C (50 MHz, $CDCl_3$) 19.48 ($CH\underline{C}H_3$), 58.84 ($O\underline{C}H_3$), 66.99 ($O\underline{C}H_2CH_2O$), 71.60 ($OCH_2\underline{C}H_2O$), 72.69 ($\underline{C}HCH_3$), 90.27 ($O\underline{C}H_2O$), 93.43 ($CH=\underline{C}Br_2$) and 140.5 ($\underline{C}H=CBr_2$); m/z (Probe CI+, NH_3) 338 (45, MNH_4^+ for $^{81/81}Br$), 336 (100,

MNH_4^+ for $^{79/81}Br$), 334 (46, MNH_4^+ for $^{79/79}Br$), 308 (25), 306 (54), 304 (27), 209 (13), 165 (10), 124 (16), 94 (57), 89(39) 73 (23) and 59 (21).

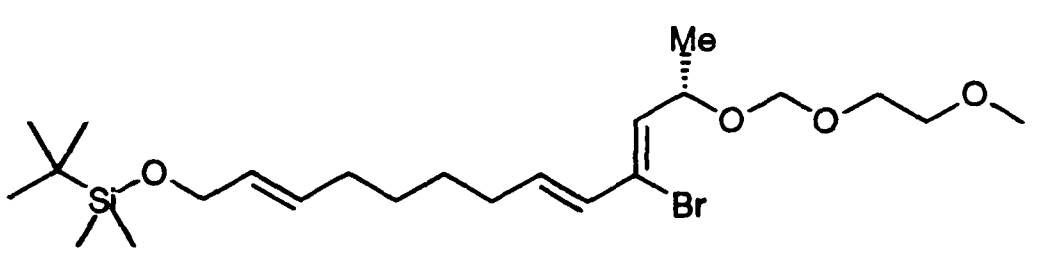
(*S*)-(3*Z*,5*E*,11*E*)-4-Bromo-13-hydroxy-2-[2-(methoxyethoxymethoxy)]-3,5,11-tridecatriene **194**



To a solution of (*E*,*E*)-9-hydroxy-1,7-nonadienyl boronic acid **191** (100mg, 0.54mmol, 1.0eq) in tetrahydrofuran:methanol (5:1, 24ml) under an atmosphere of argon was added barium hydroxide (369mg, 2.16mmol, 4.0eq) in water (4ml) yielding a yellow solution. This solution was stirred at room temperature for 2 minutes at which stage (*S*)-1,1-dibromo-3-[(2-methoxyethoxy)methoxy]-1-butene **192** (172mg, 0.54mmol, 1.0eq) and tetrakis triphenylphosphine palladium (0) (156mg, 0.13mmol, 0.25eq) were added as a solution in tetrahydrofuran (4ml) producing a cloudy, pale green solution. The reaction mixture was stirred for 30 minutes at which stage the reaction was shown to be complete by TLC analysis. The reaction mixture was diluted with dichloromethane (75ml) and water (10ml) yielding a dark green precipitate in the aqueous layer. The organic layer was separated, dried over magnesium sulphate, filtered and the organics removed in *vacuo*. The obtained pale green oil was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 3:2) affording the product as a colourless oil (0.119g, 58%). $[\alpha]^D_{22}$ -65.6 (c 1, $CHCl_3$); m/z HIRES Found 394.1593, $C_{17}H_{29}BrO_4+NH_4^+$ requires 394.1593 for ^{79}Br; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3436s (O-H str.) 2929s (C-H str.), 1646w (C=C str.), 1454w, 1370w, 1243w, 1185w, 1093m, 1035m, 971m, 913m and 850w; δ_H (500 MHz, $CDCl_3$) 1.29 (3H, d, *J* 9.0Hz, $CHC\underline{H}_3$), 1.39-1.47 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 1.70 (1H, br. s, O<u>H</u>), 2.05-2.20 (4H, m, $C\underline{H}_2CH_2CH_2C\underline{H}_2$), 3.39 (3H, s, $OC\underline{H}_3$), 3.56-3.79 (4H, m, $OC\underline{H}_2C\underline{H}_2O$), 4.10 (2H, m, $HOC\underline{H}_2CH{=}CH$), 4.74 (3H, m, $OC\underline{H}_2O$ and $C\underline{H}CH_3$), 5.67

(2H, m, $HOCH_2C\underline{H}=C\underline{H}$), 5.82 (1H, d, *J* 8.0Hz, CH=CHCBr=C$\underline{H}$), 6.01 (1H, d, *J* 15.0Hz, CH=C$\underline{H}$CBr=CH) and 6.11 (1H, dt, *J* 15.0 and 7.0Hz, C$\underline{H}$=CHCBr=CH); δ_C (125 MHz, $CDCl_3$) 20.21 ($CH\underline{C}H_3$), 28.54 ($CH_2\underline{C}H_2\underline{C}H_2CH_2$), 31.95 ($\underline{C}H_2CH_2CH_2\underline{C}H_2$), 58.93 ($O\underline{C}H_3$), 63.34 ($O\underline{C}H_2CH_2O$), 66.88 ($OCH_2\underline{C}H_2O$), 71.67 ($HO\underline{C}H_2CH=CH$), 72.04 ($\underline{C}HCH_3$), 93.31 ($O\underline{C}H_2O$), 125.2 (CH=CH$\underline{C}$Br=CH), 128.6 (CH=$\underline{C}$HCBr=CH), 129.2 ($HOCH_2\underline{C}H=CH$), 132.9 ($HOCH_2CH=\underline{C}H$), 133.0 (CH=CHCBr=$\underline{C}$H) and 136.8 ($\underline{C}H=CHCBr=CH$); m/z (Probe Cl^+, NH_3) 396 (15, MNH_4^+ for ^{81}Br), 394 (14, MNH_4^+ for ^{79}Br), 314 (6), 279 (20), 273 (26), 271 (29), 255 (17), 253 (18), 191 (100), 173 (42), 163 (13), 149 (37), 147 (10) and 133 (32).

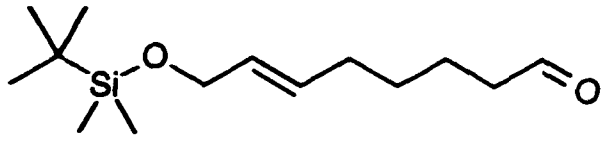
(*S*)-(3*Z*,5*E*,11*E*)-4-bromo-2-[2-(methoxyethoxymethoxy)]-13-(*tert*-butyldimethylsilyloxy)-3,5,11-tridecatriene **217**



To a solution of (*S*)-(3*Z*,5*E*,11*E*)-4-Bromo-13-hydroxy-2-[2-(methoxyethoxymethoxy)]-3,5,11-tridecatriene **194** (7.12g, 18.9mmol, 1.0eq) and imidazole (2.57g, 37.8mmol, 2.0eq) in tetrahydrofuran (120ml) under an atmosphere of argon was added *tert*-butyldimethylsilylchloride (4.26g, 28.3mmol, 1.5eq) in dichloromethane (25ml) in a single portion. The solution was stirred at room temperature for 1 minute at which stage the reaction was shown to be complete by TLC analysis. The solution was diluted with dichloromethane (100ml), washed with water (2x50ml), dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The obtained yellow oil was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 1:6) to afford

(i)

(*E*)-8-(*tert*-butyldimethylsilyloxy)-6-hexenal



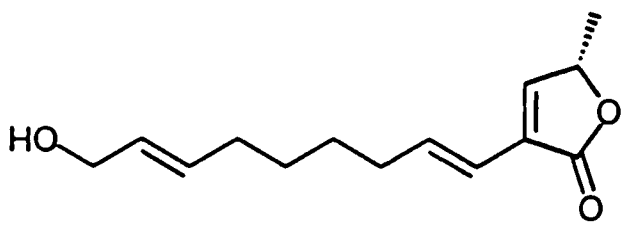
Colourless oil (17mg, 11%). υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2930s (C-H str.), 2857s (C-H str.), 2715m (C-H str.), 1728s, (C=O str.), 1472m, 1463m, 1436w, 1389w, 1361w, 1255s, 1186m, 1102s, 1056s, 971m, 837s and 777s; δ_H (200MHz, $CDCl_3$) 0.07 (6H, s, $Si(C\underline{H}_3)_2$), 0.91 (9H, s, $SiC(C\underline{H}_3)_3$), 1.18-1.47 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 1.60-1.71 (2H, m, $C\underline{H}_2CH_2CHO$), 1.99-2.08 (2H, m, $SiOCH_2CHCHC\underline{H}_2$), 2.39-2.50 (2H, dt, *J* 7.5 and 1.5Hz, $C\underline{H}_2CHO$), 4.67-4.76 (2H, m, $SiOC\underline{H}_2$), 5.46-5.63 (2H, m, $SiOCH_2C\underline{H}C\underline{H}$) and 9.77 (1H, t, *J* 1.5Hz, $C\underline{H}O$); δ_C (125 MHz, $CDCl_3$) -5.10 ($Si(\underline{C}H_3)_2$), 18.43 ($Si\underline{C}(CH_3)_3$), 21.92 ($\underline{C}H_2CH_2CH_2CHO$), 25.98 ($SiC(\underline{C}H_3)_3$), 28.65 ($CHCHCH_2\underline{C}H_2$), 28.87 ($\underline{C}H_2CH_2CHO$), 31.90 ($CHCH\underline{C}H_2CH_2$), 43.86 ($\underline{C}H_2CHO$), 63.99 ($SiO\underline{C}H_2$), 129.5 ($SiOCH_2CH\underline{C}H$), 130.9 ($SiOCH_2\underline{C}HCH$) and 202.7 ($\underline{C}HO$); m/z (GCMS EI^+) 271 (3, M^+), 253 (5), 213 (7), 156 (7), 140 (13), 139 (100), 121 (14), 92 (12) and 74 (15).

and (ii)

(*S*)-(3*Z*,5*E*,11*E*)-4-bromo-2-[2-(methoxyethoxymethoxy)]-13-(*tert*-butyldimethylsilyl oxy)-3,5,11-tridecatriene **217** as a colourless oil (7.78g, 84%). $[\alpha]^D_{22}$ -50.8 (c 1, $CHCl_3$); m/z HIRES Found 508.2460, $C_{23}H_{43}BrSiO_6+NH_4^+$ requires 508.2458 for ^{79}Br; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2929s (C-H str.), 2886s, 2857s, 1648m (C=C str.), 1463s, (C=C str.), 1362m, 1255m, 1099m, 1036m, 970m, 955w and 837m; δ_H (500 MHz, $CDCl_3$) 0.08 (6H, s, $(C\underline{H}_3)_2Si$), 0.91 (9H, s, $(C\underline{H}_3)_3CSi$), 1.30 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 1.39-1.48 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 2.05 (2H, q, *J* 6.5Hz, $CH_2CH_2CH_2C\underline{H}_2$), 2.17 (2H, q, *J* 6.5Hz, $C\underline{H}_2CH_2CH_2CH_2$), 3.40 (3H, s, $OC\underline{H}_3$), 3.55-3.77 (4H, m, $OC\underline{H}_2C\underline{H}_2O$), 4.13 (2H, m, $SiOC\underline{H}_2CH=CH$), 4.70 (1H, d, *J* 7.0Hz, one of $OC\underline{H}_2O$), 4.75

(1H, d, *J* 7.0Hz, one of OC$\underline{H}_2$O), 4.77 (1H, dq, *J* 8.0 and 6.5Hz, CHCH$_3$), 5.54 (1H, dtt, *J* 15.5 and 5.0Hz, SiOCH$_2$C$\underline{H}$=CH), 5.64 (1H, dtt, *J* 15.5, 5.0 and 2.0Hz, SiOCH$_2$CH=C$\underline{H}$), 5.82 (1H, d, *J* 8.0Hz, CH=CHCBr=C$\underline{H}$), 6.01 (1H, d, *J* 15.0Hz, CH=C$\underline{H}$CBr=CH) and 6.12 (1H, dt, *J* 15.0 and 6.5Hz, C$\underline{H}$=CHCBr=CH); δ_C (125 MHz, $CDCl_3$) -5.30 ($\underline{C}H_3)_2$Si, 18.18 ($\underline{C}H_3)_3$CSi, 20.06 (CH$\underline{C}$H$_3$), 25.77 (CH$_3)_3\underline{C}$Si, 28.38 (CH$_2\underline{C}$H$_2$CH$_2$CH$_2$), 28.48 (CH$_2$CH$_2\underline{C}$H$_2$CH$_2$), 31.76 ($\underline{C}$H$_2$CH$_2$CH$_2\underline{C}$H$_2$) 58.73 (O$\underline{C}$H$_3$), 63.76 (O$\underline{C}$H$_2$CH$_2$O), 66.72 (OCH$_2\underline{C}$H$_2$O), 71.55 ($\underline{C}$HCH$_3$) 71.84 (SiO$\underline{C}$H$_2$CH=CH), 93.15 (O$\underline{C}$H$_2$O), 125.1 (CH=CH$\underline{C}$Br=CH), 128.5 (CH=$\underline{C}$HCBr=CH), 129.2 (SiOCH$_2$CH=$\underline{C}$H), 130.7 (SiOCH$_2\underline{C}$H=CH), 132.8 (CH=CHCBr=$\underline{C}$H) and 136.7 ($\underline{C}$H=CHCBr=CH); m/z (Probe Cl$^+$,NH$_3$) 510 (8, MNH$_4^+$ for ^{81}Br), 508 (6, MNH$_4^+$ for ^{79}Br), 387 (20), 385 (18), 307 (9), 305 (30), 255 (13), 253 (12), 191 (10), 175 (27), 173 (73), 161 (17), 133 (100), 132 (23), 106 (16), 91 (22), 89 (16) and 59 (33).

(*S*)-3-[(*E*,*E*)-(9-Hydroxy-1,7-nonadienyl)]-5-methyl-*5H*-furan-2-one **219**

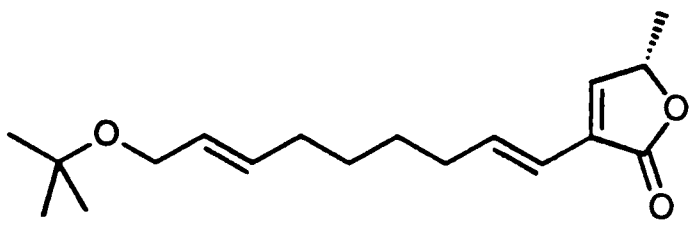


A solution of (*S*)-(3*Z*,5*E*,11*E*)-4-bromo-2-[2-(methoxyethoxymethoxy)]-13-(*tert*-butyldimethylsilyloxy)-3,5,11-tridecatriene **217** (300mg, 0.6mmol, 1.0eq) in dichloromethane (20ml) was dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The compound was then stored under high vacuum for 24 hours. The compound was then dissolved in tetrahydrofuran (5ml) and cooled to -78°C under an atmosphere of argon. *sec*-Butyl lithium as a 1M solution in cyclohexane (1.30ml, 1.3mmol, 2.2eq) was added dropwise over a period of 20 minutes. The bright yellow solution was then stirred at -78°C for 30 minutes at which stage the reaction was quenched by bubbling dried, gaseous carbon dioxide through the solution discharging the yellow colour. The bubbling was continued for 5 minutes to ensure

complete reaction. The reaction mixture was then allowed to warm slowly to room temperature under an atmosphere of carbon dioxide. The reaction mixture was then diluted with diethyl ether (20ml), washed with dilute hydrochloric acid (2M, 10ml) and water (10ml). The organic solution was dried over magnesium sulphate, filtered and the volatiles removed in *vacuo* affording the crude acid as a yellow oil. This was dissolved in *tert*-butanol (5ml) and pyridinium *para*-toluenesulphonate (1.50g, 6.0mmol, 10eq) was added in a single portion. The mixture was heated at gentle reflux under an atmosphere of argon for 16 hours. The reaction mixture was then allowed to cool to room temperature, diluted with diethyl ether (10ml) then washed with water (2x10ml). The aqueous portion was extracted with dichloromethane (10ml), the organics combined, dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The obtained dark oil was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 3:2) to afford

(i)

(*S*)-3-[(*E*,*E*)-9-*tert*-Butoxy-1,7-nonadienyl]-5-methyl-*5H*-furan-2-one



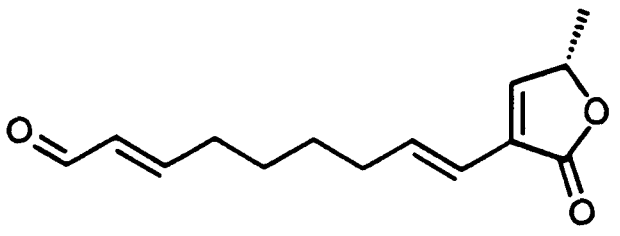
Colourless oil (29mg, 14%). $[\alpha]^{D}_{22}$ +30.1 (c 1, $CHCl_3$); υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2976m (C-H str.), 2931m (C-H str.), 2857m (C-H str.), 1756s (C=O str.), 1664w (C=C str.), 1460w, 1390m, 1363m, 1320m, 1196m, 1085m, 1056m, 1029m, 973m and 755s; δ_H (500 MHz; $CDCl_3$) 1.21 (9H, s, $C(C\underline{H}_3)_3$), 1.32-1.53 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 1.42 (3H, d, *J* 7.0Hz, $CHC\underline{H}_3$), 2.04 (2H, dt, *J* 7.0 and 6.5Hz, $CH_2CH_2CH_2C\underline{H}_2$), 2.17 (2H, ddt, *J* 7.0, 6.0 and 1.0 Hz, $C\underline{H}_2CH_2CH_2CH_2$), 3.85 (2H, m, $(CH_3)_3COC\underline{H}_2CH{=}CH$), 5.03 (1H, dq, *J* 7.0 and 1.5Hz, $C\underline{H}CH_3$), 5.54 (1H, dtt, *J* 15.5, 6.5 and 1.0Hz, $(CH_3)_3COCH_2C\underline{H}{=}CH$), 5.67 (1H, dtt, *J* 15.5, 6.0 and 1.0Hz,

$(CH_3)_3COCH_2CH=C\underline{H}$), 6.09 (1H, d, *J* 16.0Hz, $CH=C\underline{H}C(C=O)=CH$), 6.78 (1H, dt, *J* 16.0 and 7.0Hz, $C\underline{H}=CHC(C=O)=CH$) and 7.03 (1H, d, *J* 1.5Hz, $CH=CHC(C=O)=C\underline{H}$); δ_C (125 MHz, $CDCl_3$) 19.15 ($CH\underline{C}H_3$), 27.60 ($C(\underline{C}H_3)_3$), 28.29 ($CH_2CH_2\underline{C}H_2CH_2$), 28.56 ($CH_2\underline{C}H_2CH_2CH_2$), 32.10 ($\underline{C}H_2CH_2CH_2CH_2$), 33.22 ($CH_2CH_2CH_2\underline{C}H_2$), 62.85 ($(CH_3)_3CO\underline{C}H_2$), 72.96 ($(CH_3)_3\underline{C}O$), 76.88 ($\underline{C}HCH_3$), 118.4 ($CH=\underline{C}HC(C=O)=CH$), 127.8 ($(CH_3)_3COCH_2\underline{C}H$), 129.4 ($CH=CH\underline{C}(C=O)=CH$), 132.9 ($(CH_3)_3OCH_2CH=\underline{C}H$), 138.6 ($\underline{C}H=CHC(C=O)=CH$), 146.9 ($CH=CHC(C=O)=\underline{C}H$) and 172.0 ($CH=CHC(C=O)=\underline{C}H$); m/z (Probe CI^+, NH_3) 310 (2, MNH_4^+), 293 (6, MH^+), 254 (64), 236 (42), and 219 (100).

and (ii)

(*S*)-3-[(*E*,*E*)-9-Hydroxy-1,7-nonadienyl]-5-methyl-*5H*-furan-2-one **219** as a colourless oil (90.5mg, 64%). $[\alpha]^D_{22}$ +42.7 (c 1, $CHCl_3$); m/z HIRES Found 237.1491, $C_{14}H_{20}O_3+H^+$ requires 237.1491; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3422s (O-H str.), 2930m (C-H str.), 1752m (C=O str.), 1663m (C=C str.), 1454m, 1321m, 1086m, 1029m and 973m; δ_H (500 MHz, $CDCl_3$) 1.41-1.54 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 1.43 (3H, d, *J* 7.0Hz, $CHC\underline{H}_3$), 2.04 (2H, dt, *J* 7.0 and 6.5Hz, $C\underline{H}_2CH_2CH_2CH_2$), 2.16 (2H, dt, *J* 7.0 and 6.5Hz, $CH_2CH_2CH_2C\underline{H}_2$), 4.10 (2H, m, $HOC\underline{H}_2CH=CH$), 5.02 (1H, dq, *J* 7.0 and 1.0Hz, $C\underline{H}CH_3$), 5.65 (2H, m, $HOCH_2C\underline{H}=C\underline{H}$), 6.09 (1H, d, *J* 16.0Hz, $CH=C\underline{H}C(C=O)=CH$), 6.79 (1H, dt, *J* 16.0 and 7.0Hz, $C\underline{H}=CHC(C=O)=CH$) and 7.04 (1H, d, *J* 1.0Hz, $CH=CHC(C=O)=C\underline{H}$); δ_C (125 MHz, $CDCl_3$) 18.97 ($CHC\underline{H}_3$), 28.05 ($CH_2CH_2\underline{C}H_2CH_2$), 28.46 ($CH_2\underline{C}H_2CH_2CH_2$), 31.83 ($CH_2CH_2CH_2\underline{C}H_2$), 33.04 ($\underline{C}H_2CH_2CH_2CH_2$), 63.19 ($HO\underline{C}H_2$), 77.00 ($\underline{C}HCH_3$), 118.4 ($CH=\underline{C}HC(C=O)=CH$), 128.9 ($HOCH_2CH=\underline{C}H$) 129.1 ($CH=CH\underline{C}(C=O)=CH$), 132.5 ($HOCH_2\underline{C}H$), 138.2 ($\underline{C}H=CHC(C=O)=CH$), 147.2 ($CH=CHC(C=O)=\underline{C}H$) and 172.1 ($\underline{C}=O$) m/z (Probe CI^+, NH_3) 254 (7, MNH_4^+), 237 (5, MH^+), 236 (13), 221 (6), 220 (8), 219 (100), 191 (2), 173 (3), 127 (3) and 81 (2).

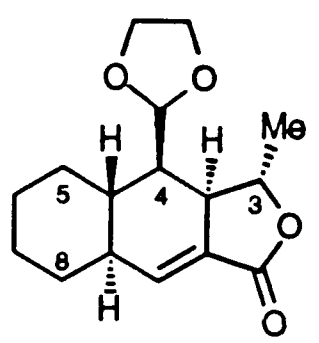
(*E,E*)-9-[(*S*)-5-Methyl-2-oxo-2,5-dihydrofuran-3-yl]-2,8-nonadienal **182**



To a solution of (*S*)-3-[(*E,E*)-9-hydroxy-1,7-nonadienyl]-5-methyl-*5H*-furan-2-one **219** (90mg, 0.38mmol, 1.0eq) in dichloromethane (20ml) under an atmosphere of argon was added Dess-Martin Periodinane (194mg, 0.46mmol, 1.2eq) in dichloromethane (10ml) in a single portion. The resultant mixture was stirred at room temperature for 2 hours at which time the reaction was shown to be complete by ^{1}H NMR analysis. The mixture was then diluted with diethyl ether (25ml), washed with 10% aqueous sodium metabisulphate:saturated aqueous sodium hydrogen carbonate (1:1, 25ml), water (25ml) and saturated aqueous sodium chloride (25ml). The aqueous portion was extracted with dichloromethane (25ml), the organics combined, dried over magnesium sulphate, filtered and the volatiles removed in *vacuo* yielding the product as a colourless oil (89mg, 100%). $[\alpha]^D_{22}$ +36.6 (c 1, $CHCl_3$); m/z HIRES Found 235.1334, $C_{14}H_{18}O_3+H^+$ requires 235.1334; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2932m (C-H str.), 2858m (C-H str.), 1753s (C=O str., lactone), 1689s (C=O str., aldehyde), 1452m (C=C str.), 1320m, 1209m, 1030m, 976m and 777m; δ_H (500 MHz, $CDCl_3$) 1.42 (3H, d, *J* 7.0Hz, $CHC\underline{H}_3$), 1.49-1.58 (4H, m, $CH_2C\underline{H}_2C\underline{H}_2CH_2$), 2.20 (2H, dt, *J* 7.0 and 7.0Hz, $CH_2CH_2CH_2C\underline{H}_2$), 2.36 (2H, ddt, *J* 7.5, 6.0 and 1.5Hz, $C\underline{H}_2CH_2CH_2CH_2$), 5.03 (1H, dq, *J* 7.0 and 1.5Hz, $C\underline{H}CH_3$), 6.11 (1H, d, *J* 16.0Hz, CH=C$\underline{H}$C(C=O)=CH), 6.13 (1H, ddt, *J* 15.5, 8.0 and 1.5Hz, CHOC$\underline{H}$), 6.79 (1H, dt, *J* 16.0 and 7.0Hz, C$\underline{H}$=CHC(C=O)=CH), 6.85 (1H, dt, *J* 15.5 and 7.5Hz, CHOCH=C$\underline{H}$), 7.04 (1H, d, *J* 1.5Hz, CH=CHC(C=O)=C$\underline{H}$) and 9.51 (1H, d, *J* 8.0Hz, C$\underline{H}$O); δ_C (125 MHz, $CDCl_3$) 19.12 ($CH\underline{C}H_3$), 27.31 ($CH_2\underline{C}H_2CH_2CH_2$), 28.19 ($CH_2CH_2\underline{C}H_2CH_2$), 32.47 ($\underline{C}H_2CH_2CH_2CH_2$), 33.01 ($CH_2CH_2CH_2\underline{C}H_2$), 76.91 ($\underline{C}HCH_3$), 118.9 (CH=$\underline{C}$HC(C=O)=CH), 129.1 (CH=CH$\underline{C}$(C=O)=CH), 133.1 (CHO$\underline{C}$H), 137.8

(CH=CHC(C=O)=CH), 147.3 (CH=CHC(C=O)=CH), 158.3 (CHOCH=CH). 171.9 (CH=CHC(C=O)=CH) and 194.0 (CHO); m/z (Probe Cl^+, NH_3) 252 (82, MNH_4^+), 235 (100, MH^+), 193 (38), 130 (36), 105 (33), 91 (25) and 73 (37).

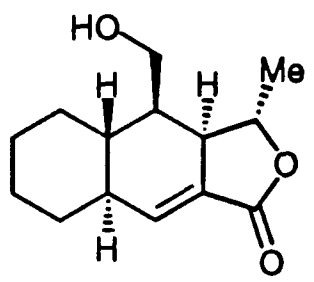
(3*S*, 3a*R*, 4*S*, 4a*S*, 8a*S*)-4-[(1,3)-Dioxolan-2-yl]-3-methyloctahydro-3H-naphtho [2,3-c]-furan-1-one **79**



To a solution of (*E*,*E*)-9-[(5*S*)-5-methyl-2-oxo-2,5-dihydrofuran-3-yl]-2,8-nonadienal **182** (88.9mg, 0.38mmol, 1.0eq) in dichloromethane (6ml) cooled to -78°C under an atmosphere of argon was added 1,2 bis-(trimethylsilyloxy)-ethane (235mg, 1.14mmol, 3.0eq). This solution was stirred at -78°C for 15 minutes at which stage trimethylsilyltrifluoromethylsulphonate (84.4mg, 0.38mmol, 1.0eq) was added dropwise. The bright yellow solution was stirred at -78°C for a further 3 hours, at which stage the temperature of the reaction mixture was rapidly increased to -20°C. The reaction mixture was stirred for 2 hours between -30°C and -20°C during which time the colour of the reaction mixture darkened considerably. Excess pyridine (0.5ml) was added to quench the reaction mixture, discharging the dark colour. The reaction mixture was then warmed to room temperature, diluted with dichloromethane (20ml) and poured into saturated aqueous sodium hydrogen carbonate (30ml). The layers were separated and the aqueous layer extracted with dichloromethane (2x20ml). The organics were combined, dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The obtained yellow oil was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 4:7) to yield the product as colourless oil (56mg, 53%). $[\alpha]^D_{22}$ -54.3 (c 1, $CHCl_3$); m/z HIRES Found 279.1596,

$C_{16}H_{22}O_4+H^+$ requires 279.1596; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2923m (C-H str.), 2854m (C-H str.), 1757s (C=O str.), 1683m (C=C str.), 1448m, 1408m, 1382m, 1333m, 1272m, 1226m, 1106m, 1039s, 979m, 947m and 917m; δ_H (500 MHz, $CDCl_3$) 1.12 (1H, m, ring hydrogen), 1.16 (1H, m, C<u>H</u>CH(CHO_2)CH), 1.26-1.46 (3H, m, ring hydrogens), 1.47 (3H, d, *J* 6.0Hz, CHC<u>H</u>$_3$), 1.72 (1H, m, C<u>H</u>CH=C), 1.75-1.80 (2H, m, ring hydrogens), 2.05-2.11 (2H, m, ring hydrogens), 2.15 (1H, ddd, *J* 9.5, 7.5 and 4.0Hz, OCH(O)C<u>H</u>CHCH(CH_3)), 2.61 (1H, ddt, *J* 9.5, 7.5 and 3.5Hz, C<u>H</u>CHCH_3), 3.81-3.83 (2H, m, OC<u>H</u>$_2$CH_2O), 3.94-3.96 (2H, m, OCH_2C<u>H</u>$_2$O), 4.78 (1H, d, *J* 4.0Hz, OC<u>H</u>O), 4.94 (1H, dq, *J* 7.5 and 6.0Hz, C<u>H</u>CH_3) and 6.71 (1H, dd, *J* 3.5 and 3.0Hz, C<u>H</u>=CC=O), δ_C (125 MHz, $CDCl_3$) 21.84 (CH<u>C</u>H_3), 26.12 (<u>C</u>H_2), 26.58 (<u>C</u>H_2), 32.24 (<u>C</u>H_2), 33.86 (<u>C</u>H_2), 41.28 (<u>C</u>HCH=CC=O), 41.35 (<u>C</u>HCH(CH($OR)_2$)CHCHCH_3), 43.51 ($(RO)_2$<u>C</u>H), 44.31 ($(RO)_2$CH<u>C</u>HCHCH_3), 64.37 (O<u>C</u>H_2CH_2O), 64.62 (OCH_2<u>C</u>H_2O), 77.47 (<u>C</u>HCH_3), 105.1 (O<u>C</u>HO), 131.4 (<u>C</u>C=O), 141.2 (<u>C</u>H=CCC=O) and 169.3 (<u>C</u>=O); m/z (Probe CI^+, NH_3) 296 (3, MNH_4^+), 279 (71, MH^+), 264 (3), 131 (49), 100 (6), 73 (100), 69 (47) and 66 (32).

<u>(3*S*, 3a*R*, 4*S*, 4a*S*, 8a*S*)-4-Hydroxymethyl-3-methyloctahydro-3H-naphtho [2,3-c]-furan-1-one **30**</u>

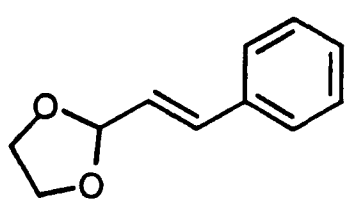


To a solution of (3*S*, 3a*R*, 4*S*, 4a*S*, 8a*S*)-4-[(1,3)-dioxolan-2-yl]-3-methyloctahydro-3H-naphtho[2,3-c]-furan-1-one **79** (56mg, 0.20mmol, 1.0eq) in acetone:water (2:1, 9ml) was added *para*-toluene sulphonic acid (103mg, 0.60mmol, 3.0eq). The solution was brought to a gentle reflux which was maintained for 5 hours. The reaction mixture was then cooled, diluted with dichloromethane (50ml) and washed with water (25ml) to remove the *para*-toluene sulphonic acid. The aqueous portion was extracted with

dichloromethane (25ml), the organics combined, dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. ^{1}H NMR analysis of the crude mixture indicated that approximately 75% of the starting material had been deprotected to the aldehyde. The crude mixture was dissolved in ethanol (7ml). To this rapidly stirred solution was added sodium borohydride (15mg, 0.40mmol, 2.0eq) in a portionwise manner. The reaction mixture was then stirred at room temperature for 20 minutes at which stage excess sodium borohydride (30mg, 0.80mmol, 4.0eq) was added in a portionwise manner. The reaction mixture was then stirred for a further 10 minutes. The reaction was quenched by the careful addition of acetone (6ml) over a period of 2 minutes. The reaction mixture was then poured into water (20ml) and which was then diluted with dichloromethane (20ml). Dilute hydrochloric acid (1M, 3ml) was added to the biphasic mixture, the layer were separated and the aqueous portion extracted with dichloromethane (20ml). The organics were combined, dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The obtained yellow oil was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 2:3) affording the product as a white crystalline solid (20mg, 42%). m/z HIRES Found 254.1756, $C_{14}H_{20}O_3$+NH_4^+ requires 254.1756; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3435s (O-H str), 2839s (C-H str), 2747s (C-H str), 1735s (C=O str), 1630m (C=C str), 1548m, 1442m, 1380m, 1280m, 1176m, 1142w, 1089m, 1060m, 1022m, 972w and 938m; δ_H (500 MHz, $CDCl_3$) 0.87 (1H, ddd, *J* 13.5, 10.0 and 3.5Hz, *4a*-H), 1.13 (1H, ddd, *J* 16.0, 12.5 and 3.5Hz, *5*-H axial), 1.25-1.39 (3H, m, one of *6*-H, *7*-H and *8*-H axial), 1.56 (3H, d, *J* 6.0Hz, $CHC\underline{H}_3$), 1.76-1.84 (3H, m, one of *6*-H, *7*-H and *8a*-H), 1.90 (1H, ddt, *J* 12.5, 9.5 and 3.5Hz, $HOCH_2C\underline{H}$), 1.97 (1H, m, *5*-H equatorial), 2.07 (1H, m, *8*-H equatorial), 2.70 (1H, ddd, *J* 12.5, 7.0 and 3.5, $CH_3CHC\underline{H}$)), 3.73 (2H, m, $HOC\underline{H}_2$), 4.80 (1H, dq, *J* 12.5 and 6.0Hz, $CH_3C\underline{H}$) and 6.65 (1H, t, *J* 3.0Hz, $C\underline{H}CCO$); δ_C (125 MHz, $CDCl_3$) 21.62 ($CH\underline{C}H_3$), 26.04 ($\underline{C}H_2$), 26.44 ($\underline{C}H_2$), 31.79 ($\underline{C}H_2$), 32.43 ($\underline{C}H_2$), 40.56 $\underline{C}HCH{=}CCO$), 40.83 $\underline{C}HCHCH_2OH$), 42.99 ($CH\underline{C}HCH_2OH$), 45.76 ($\underline{C}HCHCH_3$), 61.68 ($\underline{C}H_2OH$), 78.28 ($\underline{C}HCH_3$), 131.4 ($CH{=}\underline{C}CO$), 140.9 ($\underline{C}H{=}CCO$)

and 169.5 (C=O); m/z (Probe CI+, NH_3) 256 (18), 254 (80, MNH_4^+), 239 (30), 237 (100, MH^+), 236 (46), 219 (52), 192 (19) and 161 (11).

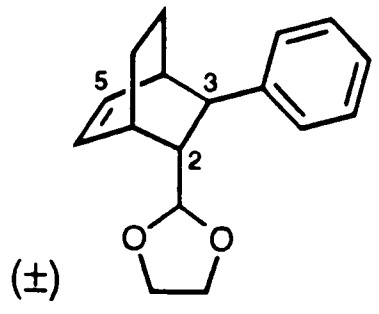
2-(*E*)-Styryl-(1,3)-dioxolane **226**



A solution of cinnamaldehyde **225** (50.00g, 0.379mol, 1.0eq), ethylene glycol (47.00g, 0.758mol, 2.0eq) and *para*-toluene sulphonic acid (0.65g, 3.79mmol, 0.01eq) in cyclohexane (200ml) was heated under reflux for 8 hours and the produced water was collected by azotropic distillation. The reaction mixture was then cooled, washed with saturated aqueous sodium hydrogen carbonate (50ml) and water (50ml). The organic solution was dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The obtained yellow oil was distilled under reduced pressure affording the product as a colourless oil (56.69g, 85%). (b.p. 120°C / 3mmHg); (Found C, 74.80; H, 7.2. $C_{11}H_{12}O_2$ requires C, 75.0; H, 6.9%); υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2958m (C-H str.), 2883s (C-H str.), 1724m, 1677s, 1627m, 1599m, 1579m, 1494s, 1452s, 1397s, 1151s, 1079s, 1063m, 956s, 839m, 750s and 694s; δ_H (200 MHz, $CDCl_3$) 3.82-3.97 (4H, m, OCH_2CH_2O), 5.33 (1H, d, *J* 6.0Hz, $CHCH(OCH)_2$), 6.07 (1H, dd, *J* 16.0 and 6.0Hz, $CHCHCH(OCH_2)$, 6.68 (1H, d, *J* 16.0Hz, PhCHCH) and 7.16-7.38 (5H, m, PhH); δ_C (50 MHz, $CDCl_3$) 64.95 (OCH_2CH_2O), 103.82 ($CHCH(OCH)_2$), 125.5 ($CHCHCH(OCH_2)$, 126.9 (CH aromatic), 128.4 (CH aromatic), 128.7 (CH aromatic), 134.6 ($CHCHCH(OCH_2)$ and 135.6 (*ipso* aromatic CCH); m/z (GCMS EI+) 177 (43), 176 (100, M^+), 175 (22), 131 (22), 117 (13), 115 (35), 104 (78), 103 (24), 77 (14) and 73 (38).

(*S, S*)-2-(1,3-Dioxolan-2-yl)-3-phenylbicyclo[2.2.2]octa-5-ene,

(*R, R*)-2-(1,3-Dioxolan-2-yl)-3-phenylbicyclo[2.2.2]octa-5-ene **227**

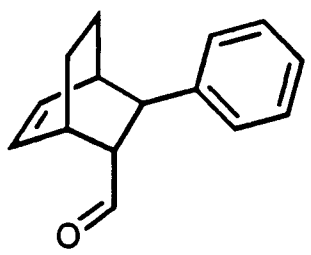


(±)

To a solution of 2-(*E*)-styryl-(1,3)-dioxolane **226** (10.00g, 57.0mmol, 1.0eq) and cyclohexadiene (9.12g, 114.0mmol, 2.0eq) in dichloromethane (100ml) cooled to -78°C under an atmosphere of argon was added trifluoromethylsulphonic acid (171mg, 1.14mmol, 0.02eq) in dichloromethane (1ml) turning the colourless solution dark blue. The reaction mixture was stirred at -78°C for 30 minutes then was allowed to warm to room temperature over a 60 minute period. The reaction mixture was stirred at room temperature for 70 hours at which stage the reaction was shown to be complete by ^{1}H NMR analysis. Triethylamine (0.5ml) was added to quench the reaction turning the mixture brown. This solution was washed with saturated aqueous sodium hydrogen carbonate (50ml), water (50ml) and saturated aqueous sodium chloride (50ml), dried over magnesium sulphate, filtered and the volatiles remove in *vacuo*. The obtained orange oil was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 1:4) to yield the product as a pale yellow crystalline solid (3.55g, 24%). (m.p. 77-78°C); (Found C, 79.8; H, 8.0. $C_{17}H_{20}O_2$ requires C, 79.65; H, 7.9%); υ_{max} (FT-IR, NaCl plates, nujol mull, cm^{-1}) 2924s (C-H str.), 2855s (C-H str.), 1717m, 1654m, 1617m, 1495m, 1465s, 1406m, 1373s, 1153s, 1086s, 1062s, 1033m, 1013m 981m, 963m, 944m, 894m, 853m, and 838m; δ_H (500 MHz, $CDCl_3$) 0.92-1.05 (1H, m, PhCHCHCHH'), 1.34-1.43 (1H, m, $(CH_2O)_2$CHCHCHCHH'), 1.55-1.72 (2H, m, PhCHCHCHH' and $(CH_2O)_2CHCHCHCHH'$), 2.20 (1H, dt, *J* 6.5 and 2.0Hz, $(CH_2O)_2$CHCH), 2.41-2.44 (1H, m, PhCHCH), 2.61-2.70 (1H, m, PhCH), 2.81-2.83 (1H, m, $(CH_2O)_2$CHCHCH), 3.65-3.93 (4H, m, OCH_2CH_2O), 4.50 (1H, d, *J* 6.5Hz,

$(CH_2O)_2C\underline{H}$), 6.27 (1H, dd, *J* 7.5 and 7.0Hz, PhCHCHC$\underline{H}$), 6.47 (1H, dd, *J* 8.0 and 7.0Hz, $(CH_2O)_2CHCHCHC\underline{H}_2$) and 7.18-7.47 (5H, m, Ph$\underline{H}$); δ_C (125 MHz, $CDCl_3$) 18.45 ($(CH_2O)_2CHCHCH\underline{C}H_2$), 25.75 (PhCHCH$\underline{C}H_2$), 31.48 ($(CH_2O)_2CHCH\underline{C}H$), 37.57 (PhCH$\underline{C}$H), 45.91 (Ph$\underline{C}$H), 46.34 ($(CH_2O)_2CH\underline{C}H$), 64.55 (O$\underline{C}H_2CH_2O$), 64.60 ($OCH_2\underline{C}H_2O$), 107.7 ($(CH_2O)_2\underline{C}H$), 125.8 (aromatic $\underline{C}$H), 128.1 (aromatic $\underline{C}$H), 128.9 (aromatic $\underline{C}$H), 132.0 (PhCHCH$\underline{C}$H), 135.4 ($(CH_2O)_2CHCHCH\underline{C}H$) and 143.4 (*ipso* aromatic $\underline{C}$CH); m/z (Probe CI+, NH_3) 274 (4, MNH_4^+), 257 (3, MH^+) 177 (10), 176 (6), 80 (7) and 73 (100).

(*R, R*)-2-Formyl-3-phenylbicyclo[2.2.2]octa-5-ene, (*S, S*)-2-Formyl-3-phenylbicyclo[2.2.2]octa-5-ene **228**

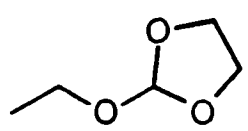


(±)

To a solution of (±)-2-(1,3-dioxolan-2-yl)-3-phenylbicyclo[2.2.2]octa-5-ene **227** (102mg, 0.4mmol, 1.0eq) in acetone:deuterium oxide (2:1 18ml) was added *para*-toluene sulphonic acid (206mg, 1.2mmol, 3.0eq). The solution was brought to a gentle reflux which was maintained for 22 hours. The reaction mixture was cooled, diluted with dichloromethane (100ml) and washed with water (100ml) The aqueous portion was extracted with dichloromethane (25ml), the organic portions combined, dried over magnesium sulphate, filtered and the volatiles remove in *vacuo*. The obtained crude material was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 1:9) affording the product as a colourless oil (39mg, 47%). (Found C, 84.8; H, 7.9. $C_{15}H_{16}O$ requires C, 84.9; H, 7.6%); υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2946s (C-H, str.), 2811s (C-H str.), 2711s (C-H str.), 1723vs (C=O str.), 1601m, 1499m, 1465m, 1451m, 1369m, 1291m, 1172m, 1050m, 925m, 752m and 702s; δ_H (500 MHz, $CDCl_3$) 1.06-1.13 (1H, m, PhCHCHC$\underline{H}$H'), 1.44-1.51 (1H, m,

CHH'CHCHCHO), 1.69-1.79 (2H, m, PhCHCHCHH' and CHH'CHCHCHO), 2.64-2.66 (1H, m, PhCHCH), 2.85 (1H, dd, *J* 6.5 and 1.0Hz, CHCHO), 3.08-3.10 (1H, m, CHCHCHO), 3.21-3.23 (1H, m, PhCH), 6.21 (1H, dd, *J* 8.0 and 7.0Hz, CHCHCHCHO) 6.52-6.56 (1H, m, CHCHCHPh), 7.22-7.37 (5H, m, PhH) and 9.52 (1H, d, *J* 1.0Hz, CHO); δ_C (125 MHz, $CDCl_3$) 18.74 (PhCHCH$\underline{C}H_2$), 25.62 (CHOCHCH$\underline{C}H_2$), 31.35 (CHOCH$\underline{C}$H), 36.63 (PhCH$\underline{C}$H), 43.18 (PhCH), 55.95 (CHOCH), 126.4 (aromatic $\underline{C}$H), 128.0 (aromatic $\underline{C}$H), 128.5 (aromatic $\underline{C}$H), 131.0 (CHCHCHPh), 137.1 (CHCHCHCHO), 142.0 (*ipso* aromatic $\underline{C}$CH) and 202.8 ($\underline{C}$HO); m/z (Probe CI^+, CH_4) 229 (26, MCH_4^+), 213 (36, MH^+), 185 (33), 184 (34), 183 (94), 161 (31), 155 (45), 133 (100), 105 (49), 91 (26), 81 (27), 80 (39) and 79 (46).

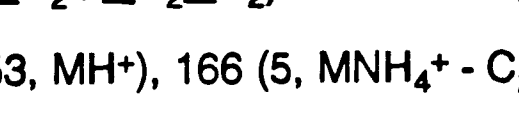
2-Ethoxy-1,3-dioxolan **230**



A solution of triethylorthoformate **229** (50.00g, 0.338mol, 1.0eq), ethylene glycol (20.95g, 0.338mol, 1.0eq) and *para*-toluene sulphonic acid (0.58g, 3.38mmol, 0.01eq) in cyclohexane (150ml) was heated and the azeotrope of cyclohexane and ethanol formed was collected for 2 hours at which time the temperature of the distillate indicated the reaction had reached completion. The reaction mixture was then cooled, washed with saturated aqueous sodium hydrogen carbonate (50ml) and water (50ml). The organic solution was dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The obtained pale yellow oil was distilled under reduced pressure affording the product as a colourless oil (16.35g, 41%). (b.p. 68°C / 60mmHg); (Found C, 50.6; H, 8.4. $C_5H_{10}O_3$ requires C, 50.8; H, 8.5%); υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2980m (C-H str.), 2903s (C-H str.), 1976w, 1478m, 1447w, 1375w, 1302w, 1120s, 1073s, 1025s, 980m, 949s, 908w, 789w and 736w; δ_H (200 MHz, $CDCl_3$) 1.24 (3H, t, *J* 7.0Hz, OCH_2CH_3), 3.60 (2H, q, *J* 7.0Hz, OCH_2CH_3), 3.92-4.15 (4H, m, OCH_2CH_2O) and 5.83 (1H, s, $OCH(OR)_2$); δ_C (50 MHz, $CDCl_3$) 14.41

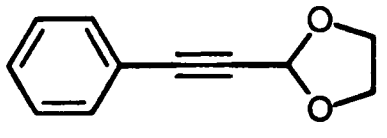
($OCH_2\underline{C}H_3$), 59.46 ($O\underline{C}H_2CH_3$), 63.27 ($O\underline{C}H_2\underline{C}H_2O$) and 114.5 ($O\underline{C}H(OR)_2$); m/z (GCMS CI^+, NH_3) 119 (32, MH^+), 90 (38), and 73 (100).

2-[2-(2-Methoxyethoxy)ethoxy]-1,3-dioxolan **237**



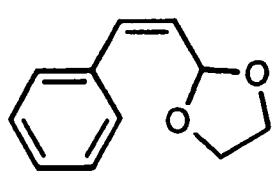
A solution of 2-ethoxy-1,3-dioxolan **230** (11.80g, 0.1mol, 1.0eq), 2-(2-methoxyethoxy)ethanol (12.00g, 0.1mol, 1.0eq) and *para*-toluene sulphonic acid (0.86g, 5mmol, 0.05eq) in cyclohexane (150ml) was heated and the azeotrope of cyclohexane and ethanol formed was collected for 2 hours at which time the temperature of the distillate indicated the reaction had reached completion. The reaction mixture was then cooled, washed with saturated aqueous sodium hydrogen carbonate (50ml) and water (50ml). The organic solution was dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The obtained pale yellow oil was distilled under reduced pressure affording the product as a colourless oil (6.65g, 35%). (b.p. 96°C / 0.3mmHg); m/z HIRES Found 193.1076, $C_8H_{16}O_5+H^+$ requires 193.1076; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2894s (C-H str.), 1724m, 1456m, 1355m, 1247m, 1078s, 948s and 851w; δ_H (500 MHz, $CDCl_3$) 3.37 (3H, s, $OC\underline{H}_3$), 3.53-3.70 (8H, m, $OC\underline{H}_2C\underline{H}_2OC\underline{H}_2C\underline{H}_2O$), 3.92-4.10 (4H, m, $OC\underline{H}_2C\underline{H}_2O$) and 5.86 (1H, s, $OC\underline{H}(OR)_2$); δ_C (50 MHz, $CDCl_3$) 58.04 ($O\underline{C}H_3$), 60.67, 63.07, 69.42, 69.62, 71.11 ($O\underline{C}H_2\underline{C}H_2$ and $O\underline{C}H_2\underline{C}H_2O\underline{C}H_2\underline{C}H_2$) and 114.5 ($O\underline{C}H(OR)_2$); m/z (Probe CI^+, NH_3) 210 (13, MNH_4^+), 193 (53, MH^+), 166 (5, $MNH_4^+ - C_2H_5O$), 149 (5, $MH^+ - C_2H_5O$), 138 (11), 121 (10), 103 (9), 87 (14) and 73 (100).

2-Phenylethynyl-(1,3)-dioxolane **240**



A solution of phenylpropargyl aldehyde diethyl acetal **239** (10.20g, 50.0mmol, 1.0eq), ethylene glycol (3.1g, 50.0mmol, 1.0eq) and *para*-toluene sulphonic acid (85mg, 0.5mmol, 0.01eq) in cyclohexane (200ml) was heated and the azeotrope of cyclohexane and ethanol formed was collected for 4 hours at which time the temperature of the distillate indicated the reaction had reached completion. The reaction mixture was then cooled, washed with saturated aqueous sodium hydrogen carbonate (50ml) and water (50ml). The organic solution was dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The obtained yellow oil was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 1:9) affording the product as a colourless oil (8.70g, 100%). (Found C, 75.55; H, 6.0. $C_{11}H_{10}O_2$ requires C, 75.85; H, 5.8%); υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2956m (C-H str.), 2893s (C-H str.), 2235m, 1599m, 1490s, 1444m, 1389s, 1344s, 1256m, 1211w, 1179w, 1104vs, 1025s, 985s, 922s, 839m and 759s; δ_H (200 MHz, $CDCl_3$) 3.97-4.20 (4H, m, $OC\underline{H}_2C\underline{H}_2O$), 5.91 (1H, s, $C\underline{H}(OR)_2$) and 7.28-7.52 (5H, m, Ph$\underline{H}$); δ_C (50 MHz, $CDCl_3$) 64.15 ($O\underline{C}H_2\underline{C}H_2O$), 84.27, 84.70 (Ph$\underline{C}\underline{C}$), 92.94 ($\underline{C}H(OR)_2$), 121.1 (*ipso* aromatic $\underline{C}$CH), 128.0, 128.6, 129.1, 131.5 and 131.7 ($\underline{C}$H aromatic); m/z (Probe CI^+, NH_3) 176 (11), 176 (100, M^+), 174 (10), 129 (10), 105 (8), 102 (18), and 73 (11).

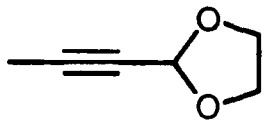
2-(*Z*)-Styryl-(1,3)-dioxolane **241**



To a stirred solution of 2-phenylethynyl-(1,3)-dioxolane **240** (870mg, 5.0mmol, 1.0eq) and quinoline (5ml) in methanol (20ml) under an atmosphere on hydrogen (1atm) was added Lindlar's catalyst (palladium on calcium carbonate poisoned with lead, 100mg). The reaction mixture was stirred for 72 hours at ambient at which stage it was filtered through a pad of Celite®. The volatiles were removed from the filtrate in

vacuo and the obtained yellow oil was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 1:9) affording the product as a colourless oil (817mg, 93%). (Found C, 74.8; H, 7.0. $C_{11}H_{12}O_2$ requires C, 75.0; H, 6.85%); υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3059w, 3028w, 2955m (C-H str.), 2886s (C-H str.), 1650m, 1601w, 1575w, 1495s, 1474w, 1450w, 1344w, 1211w, 1117vs, 1081s, 1029s, 989s, 956s, 807m, 773s, 718s and 699s; δ_H (200 MHz, $CDCl_3$) 3.90-4.13 (4H, m, $OC\underline{H}_2C\underline{H}_2O$), 5.53 (1H, d, *J* 8.0Hz, PhC<u>H</u>), 5.73 (1H, dd, *J* 8.0 and 12.0Hz, PhCHC<u>H</u>), 6.04 (1H, d, *J* 12.0Hz, C<u>H</u>$(OR)_2$) and 7.27-7.37 (5H, m, Ph<u>H</u>); δ_C (50 MHz, $CDCl_3$) 64.66 ($O\underline{C}H_2\underline{C}H_2O$), 99.22 ($\underline{C}H(OR)_2$), 127.4, 127.5, 127.8, 128.6 (<u>C</u>H Aromatic), 135.0 and 135.3 (<u>C</u>H<u>C</u>H); m/z (Probe CI^+, NH_3) 176 (40, MH^+), 175 (30), 131 (24), 115 (37), 104 (100), 103 (22), 78 (18), 77 (27) and 73 (30).

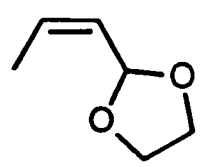
<u>2-Propenyl-(1,3)-dioxolane **245**</u>



A solution of 2-butyn-1-al diethyl acetal **244** (5.00g, 35.0mmol, 1.0eq), ethylene glycol (2.18g, 35.0mmol, 1.0eq) and *para*-toluene sulphonic acid (65mg, 0.35mmol, 0.01eq) in cyclohexane (100ml) was heated and the azeotrope of cyclohexane and ethanol formed was collected for 3 hours at which time the temperature of the distillate indicated the reaction had reached completion. The reaction mixture was then cooled, washed with saturated aqueous sodium hydrogen carbonate (50ml) and water (50ml). The organic solution was dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The obtained yellow oil was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 1:9) affording the product as a colourless oil (2.29g, 58%). m/z HIRES Found 113.0600, $C_6H_8O_2+H^+$ requires 113.0602; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2965m (C-H str.), 2894s (C-H str.), 2362m, 2265m, 1475w, 1395m, 1348w, 1181m, 1143s, 1083vs, 1024m, 924s, 918s and 832m; δ_H (200 MHz, $CDCl_3$) 1.88 (3H, s, C<u>H</u>$_3$), 3.88-4.11 (4H, m,

$OC\underline{H}_2C\underline{H}_2O$) and 5.60 (1H, s, $C\underline{H}(OR)_2$); δ_C (50 MHz, $CDCl_3$) 2.78 ($C\underline{C}H_3$), 63.84 ($O\underline{C}H_2\underline{C}H_2O$), 74.72 ($CH_3\underline{C}$), 81.64 ($CH_3C\underline{C}$) and 92.44 ($\underline{C}H(OR)_2$); m/z (GCMS CI^+, NH_3) 114 (6), 113 (100, M^+) and 68 (15).

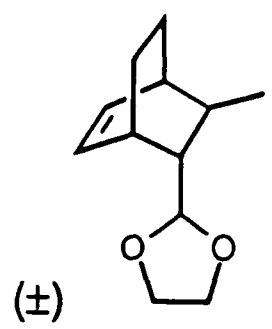
2-(*Z*)-Propenyl-(1,3)-dioxolane **236**



To a stirred solution of 2-propenyl-(1,3)-dioxolane **245** (1.68g, 15.0mmol, 1.0eq) and quinoline (2ml) in methanol (10ml) under an atmosphere on hydrogen (1atm) was added Lindlar's catalyst (palladium on calcium carbonate poisoned with lead, 100mg). The reaction mixture was stirred for 96 hours at ambient at which stage it was filtered through a pad of Celite®. The volatiles were removed from the filtrate in *vacuo* and the obtained yellow oil was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 1:9) affording the product as a colourless oil (500mg, 29%). υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2886s (C-H str.), 2360m (C-H str.), 1669w, 1502s, 1428m, 1338w, 1144s, 1106vs, 1021s, 959s, 809m, 788w and 734s; δ_H (200 MHz, $CDCl_3$) 1.78 (3H, dd, *J* 7.0 and 1.5Hz, $CHC\underline{H}_3$), 3.86-4.10 (4H, m, $OC\underline{H}_2C\underline{H}_2O$), 5.45 (1H, ddq, *J* 11.0, 7.0 and 1.5Hz, $CH_3CHC\underline{H}$), 5.57 (1H, d, *J* 7.0Hz, $C\underline{H}(OR)_2$) and 5.85 (1H, ddq, *J* 11.0, 7.0 and 1.0Hz, $CH_3C\underline{H}CH$); δ_C (50 MHz, $CDCl_3$) 13.03 ($\underline{C}H_3$), 64.43 ($O\underline{C}H_2\underline{C}H_2O$), 98.51 ($\underline{C}H(OR)_2$), 126.5 ($CH_3\underline{C}H$) and 135.5 ($CH_3CH\underline{C}H$); m/z (GCMS CI^+, NH_3) 116 (6), 115 (100, MH^+), 113 (2), 99 (5), 73 (3) and 70 (7).

(2*R*, 3*S*)-2-Formyl-3-methylbicyclo[2.2.2]octa-5-ene,

(3*S*, 2*R*)-2-Formyl-3-methylbicyclo[2.2.2]octa-5-ene **246**

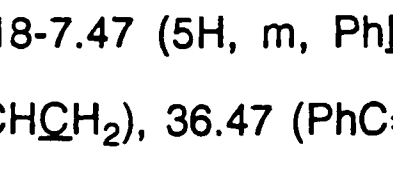


(±)

To a solution of 2-(*Z*)-propenyl-(1,3)-dioxolane **236** (0.50g, 4.4mmol, 1.0eq) and cyclohexadiene (0.70g, 8.8mmol, 2.0eq) in dichloromethane (25ml) cooled to -78°C under an atmosphere of argon was added trimethylsilyltrifluoromethyl sulphonate (19mg, 0.088mmol, 0.02eq) turning the colourless solution dark blue. The reaction mixture was stirred at -78°C for 2 hours then was allowed to warm to room temperature over a 4 hour period. The reaction mixture was stirred at room temperature for 2 hours at which stage the reaction was shown to be complete by ^{1}H NMR analysis. Triethylamine (0.1ml) was added to quench the reaction turning the mixture brown. This solution was washed with saturated aqueous sodium hydrogen carbonate (50ml), water (50ml) and saturated aqueous sodium chloride (50ml), dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The obtained orange oil was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C, 1:19) to yield the product as a pale yellow oil (123mg, 15%). (Found C, 74.1; H, 9.6. $C_{12}H_{18}O_2$ requires C, 74.2; H, 9.35%); υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3042m, 2950s (C-H str.), 2872s (C-H str.), 1733w, 1615w, 1473m, 1447m, 1402m, 1370m, 1327m, 1276w, 1230m, 1187s, 1167vs, 1129s, 1103vs, 1067s, 1023s, 1003m, 965m, 943m, 859m, 847m, 813w. 791w, 730m, 703s, 659w and 627w; δ_H (500 MHz, C_6D_6) 0.98-1.05 (1H, m, $CH_3CHCHCHCH\underline{H}$ *exo*), 1.17 (3H, d, *J* 7.0Hz, $C\underline{H}_3$), 1.20-1.27 (1H, m, $(RO)_2CHCHCHCH\underline{H}$ *exo*), 1.36-1.43 (2H, m, $(RO)_2CHC\underline{H}$ and $(RO)_2CHCHCHCH\underline{H}$ *endo*), 1.54-1.57 (1H, m, $C\underline{H}CH_3$), 1.63-1.69 (1H, m, 2.20 $CH_3CHCHCH\underline{H}$ *endo*), 2.03-2.07 (1H, m, $CH_3CHC\underline{H}$), 2.81-2.83 (1H, m, $(RO)_2CHC\underline{H}$),

3.28-3.53 (4H, m, OCH_2CH_2O), 4.44 (1H, d, *J* 7.5Hz, $(RO)_2CH$), 6.16 (1H, dd, *J* 7.0 and 7.5Hz, $(RO)_2CHCHCHCH$) and 6.32 (1H, dd, *J* 8.0 and 7.0Hz, $CH_3CHCHCH$); δ_C (125 MHz, C_6D_6) 18.70 ($CH_3CHCHCH_2$), 19.66 ($CHCH_3$), 26.26 ($(RO)_2CHCHCHCH_2$), 32.33 ($(RO)_2CHCHCH$), 34.52 (CH_3CH), 36.36 (CH_3CHCH), 51.45 ($(RO)_2CHCH$), 64.55 (OCH_2CH_2O), 108.4 ($(RO)_2CH$), 131.2 ($(RO)_2CHCHCHCH$) and 136.6 ($CH_3CHCHCH$); m/z (Probe CI^+, NH_3) 211 (7, MNH_4^+), 195 (8, MH^+) 115 (4), 113 (16), 94 (7) and 73 (100).

2-Phenylbicyclo[2.2.2]octa-2,5-diene **250**

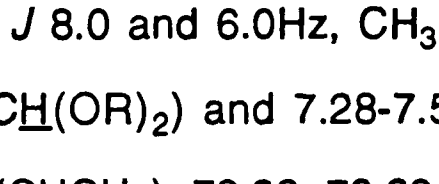


(±)

To a solution of 2-phenylethynyl-(1,3)-dioxolane **240** (448mg, 2.57mmol, 1.0eq) and cyclohexadiene (411mg, 5.14mmol, 2.0eq) in dichloromethane (20ml) cooled to -78°C under an atmosphere of argon was added trifluoromethylsulphonic acid (7.7mg, 0.051mmol, 0.02eq) turning the colourless solution dark blue. The reaction was allowed to warm to room temperature over a 60 minute period. The reaction mixture was then stirred at room temperature for 48 hours. The reaction mixture was then diluted with dichloromethane (50ml). This solution was washed with saturated aqueous sodium hydrogen carbonate (50ml), water (50ml) and saturated aqueous sodium chloride (50ml), dried over magnesium sulphate, filtered and the volatiles remove in *vacuo*. The obtained yellow oil was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C, 1:9) to yield the product as a pale yellow oil. (46mg, 10%). δ_H (200 MHz, $CDCl_3$) 1.33-1.41 (4H, m, CH_2CH_2), 3.79-3.87 (1H, m, $PhCCHCH_2$), 4.38-4.50 (1H, m, $PhC{=}CHCH$), 6.36 (1H, dd, *J* 7.5 and 7.0Hz, $PhCHCHCH$), 6.48 (1H, dd, *J* 8.0 and 7.0Hz, $PhC{=}CHCHCH$) 6.98-7.01 (1H, dd, *J* 7.5 and 3.0Hz, $PhC{=}CH$) and 7.18-7.47 (5H, m, PhH); δ_C (50 MHz, $CDCl_3$) 24.53 ($PhCCHCH_2CH_2$), 24.70 ($PhCCHCH_2$), 36.47 ($PhC{=}CHCH$), 38.15 ($PhCCH$), 128.0

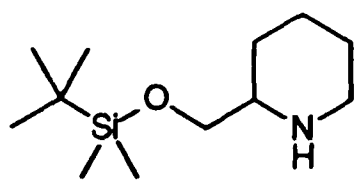
(aromatic CH), 129.1 (aromatic CH), 131.6 (PhCCHCH), 133.1 (PhC=CH), 135.4 (PhC=CHCHCH) 138.1 (PhC=CH) and 149.6 (*ipso* aromatic CCH); m/z (GCMS EI+) 183 (6), 182 (54, M+), 152 (7) 106 (6), 105 (95), 78 (10), 77 (100) and 51 (59).

(*R, R*)-2-Phenylethynyl-4,5-dimethyl-(1,3)-dioxolane **253**



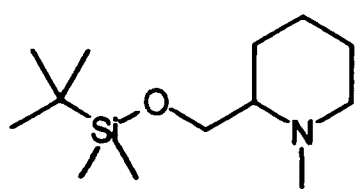
A solution of phenylpropargyl aldehyde diethyl acetal **239** (2.27g, 11.0mmol, 1.0eq), (2*R*,3*R*)-(-)-2,3-butanediol (1.00g, 11.0mmol, 1.0eq) and *para*-toluene sulphonic acid (19mg, 0.11mmol, 0.01eq) in cyclohexane (150ml) was heated and the azeotrope of cyclohexane and ethanol formed was collected for 6 hours at which time the temperature of the distillate indicated the reaction had reached completion. The reaction mixture was then cooled, washed with saturated aqueous sodium hydrogen carbonate (50ml) and water (50ml). The organic solution was dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The obtained yellow oil was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 1:9) affording the product as a colourless oil (2.01g, 90%). $[\alpha]^D_{22}$ -35.0 (c 1, $CHCl_3$); (Found C, 77.20; H, 7.05. $C_{13}H_{14}O_2$ requires C, 77.20; H, 7.0%); υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2976s (C-H str.), 2882s (C-H str.), 2238m, 1957w, 1599m, 1491s, 1444s, 1404m, 1379vs, 1324m, 1305m 1257m, 1144s, 1098vs, 1028m, 982s, 918w, 862w, 820w, 759s, 738s and 692s; δ_H (200 MHz, $CDCl_3$) 1.32-1.42 (6H, 2xd, *J* 6.0Hz, $CHCH_3$), 3.68 (1H, dq, *J* 8.0 and 6.0Hz, CH_3CH), 3.93 (1H, dq, *J* 8.0 and 6.0Hz, CH_3CH), 5.91 (1H, s, $CH(OR)_2$) and 7.28-7.52 (5H, m, PhH); δ_C (50 MHz, $CDCl_3$) 16.18 ($CHCH_3$), 16.91 ($CHCH_3$), 78.23, 73.39 ($CH_3CHCHCH_3$), 84.69, 85.33 (PhCC), 92.06 ($CH(OR)_2$), 121.5 (*ipso* aromatic CCH), 128.0, 128.6 and 131.6 (CH aromatic); m/z (GCMS EI+) 202 (100, M+) and 101 (94, M^{2+}).

2-(*tert*-Butyldimethylsilyloxy)methylpiperidine **270**



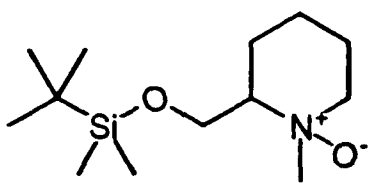
To a solution of 2-piperidinemethanol **267** (2.13g, 18.5mmol, 1.0eq) and imidazole (2.52g, 37mmol, 2.0eq) in tetrahydrofuran (20ml) under an atmosphere of argon was added *tert*-butyldimethylsilylchloride (2.78g, 18.5mmol, 1.0eq) in dichloromethane (5ml) in a single portion. After 5 minutes a white precipitate formed and the reaction mixture was stirred for 18 hours at ambient. The reaction mixture was then diluted with dichloromethane (50ml) and washed with aqueous sodium hydroxide (1M, 50ml) and saturated aqueous sodium chloride (50ml). The organic solution was dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 1:1) yielding the product as a colourless oil (3.13g, 75%). m/z HIRES Found 230.1940, $C_{12}H_{27}NOSi+H^+$ requires 230.1940; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3280s (N-H str.), 2931s (C-H str.), 2857s (C-H str.), 2801w, 1463m, 1445m, 1390w, 1361s, 1330w, 1256s, 1089s, 1007w, 930w, 838s, 778s and 666w; δ_H (500 MHz, $CDCl_3$) 0.05 (6H, s, $Si(C\underline{H}_3)_2$), 0.89 (9H, s, $SiC(C\underline{H}_3)_3$), 1.01-1.79 (6H, m, $CHC\underline{H}_2C\underline{H}_2C\underline{H}_2$), 2.56-2.65 (2H, m, $NC\underline{H}_2$), 3.08 (1H, tt, *J* 6.0 and 2.0Hz, $CH_2C\underline{H}N$), 3.39 (1H, dd, *J* 9.5 and 8.5Hz, $SiOCH\underline{H}'$) and 3.53 (1H, dd, *J* 9.5 and 4.0Hz, $SiOC\underline{H}H'$); δ_C (125 MHz, $CDCl_3$) -5.39 ($Si(\underline{C}H_3)_2$), 18.30 ($Si\underline{C}(CH_3)_3$), 24.44 ($CHCH_2\underline{C}H_2CH_2$), 25.92 ($SiC(\underline{C}H_3)_3$), 26.46 ($NCH_2\underline{C}H_2$), 28.48 ($CH\underline{C}H_2CH_2CH_2$), 46.65 ($N\underline{C}H_2$), 58.29 ($N\underline{C}H$) and 67.94 ($SiO\underline{C}H_2$); m/z (Probe CI^+, NH_3) 232 (4), 231 (13), 230 (100, MH^+), 172 (8), 98 (4), 84 (39), 69 (18) and 56 (3).

N-Methyl-2-(*tert*-butyldimethylsilyloxy)methylpiperidine **271**



To a solution of 2-(*tert*-butyldimethylsilyloxy)methylpiperidine **270** (458mg, 2.0mmol, 1.0eq) and formaldehyde (37% aqueous, 1.62ml, 20mmol, 10.0eq) in acetonitrile (12ml) under an atmosphere of argon was added sodium cyanoborohydride (378mg, 6.0mmol, 3.0eq) in a single portion. After 5 minutes acetic acid (0.2ml) was added and the reaction mixture stirred for 2 hours at ambient. Acetic acid (0.2ml) was then added and the reaction mixture stirred for a further 30 minutes. The reaction mixture was then diluted with diethyl ether (25ml), washed with aqueous sodium hydroxide (1M, 2x25ml) and saturated aqueous sodium chloride (25ml). The organic solution was dried over magnesium sulphate, filtered and the volatiles removed in *vacuo* yielding the product as a colourless oil (431mg, 87%). m/z HIRES Found 244.2097, $C_{13}H_{29}NOSi+H^+$ requires 244.2097; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2931s (C-H str.), 2857s (C-H str.), 2781m, 2711w, 1463m, 1423w, 1389w, 1373m, 1361m, 1347w, 1310m, 1283m, 1256s, 1207w, 1188w, 1156s, 1138s, 1115s, 1099s, 1066s, 1033m, 1007w, 939w, 838s, 815m, 776w and 666m; δ_H (300 MHz, $CDCl_3$) 0.03 (6H, s, $Si(C\underline{H}_3)_2$), 0.87 (9H, s, $SiC(C\underline{H}_3)_3$), 1.15-1.80 (6H, m, $CHC\underline{H}_2C\underline{H}_2C\underline{H}_2$), 1.88-2.09 (2H, m, $NC\underline{H}_2$), 2.28 (3H, s, $NC\underline{H}_3$), 3.08 (1H, m, $CH_2C\underline{H}N$), 3.42 (1H, dd, *J* 10.0 and 6.0Hz, $SiOCH\underline{H}'$) and 3.80 (1H, dd, *J* 10.0 and 5.0Hz, $SiOC\underline{H}H'$); δ_C (50 MHz, $CDCl_3$) -5.41 ($Si(\underline{C}H_3)_2$), 18.27 ($Si\underline{C}(CH_3)_3$), 23.98 ($CHCH_2\underline{C}H_2CH_2$), 25.91 ($SiC(\underline{C}H_3)_3$ and $NCH_2\underline{C}H_2$), 29.32 ($CH\underline{C}H_2CH_2CH_2$), 43.85 ($N\underline{C}H_3$), 57.48 ($N\underline{C}H_2$), 65.61 ($N\underline{C}H$) and 66.11 ($SiO\underline{C}H_2$); m/z (Probe CI^+, NH_3) 246 (3), 245 (11), 244 (52, MH^+), 130 (4), 112 (3), 99 (7), 98 (100) and 70 (3).

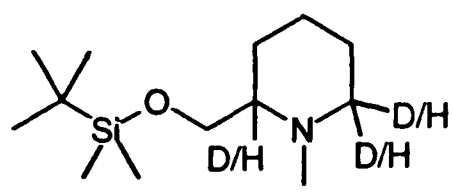
N-Methyl-2-(*tert*-butyldimethylsilyloxy)methylpiperidine *N*-oxide **272**



To a solution of *N*-methyl-2-(*tert*-butyldimethylsilyloxy)methylpiperidine **271** (117mg, 0.48mmol, 1.0eq) in dichloromethane (10ml) cooled to 0°C under an atmosphere of argon was added *meta*-chloroperbenzoic acid (87% activity, 96mg, 0.48mmol, 1.0eq). The reaction mixture was stirred at 0°C for 90 minutes then the solvent was removed in *vacuo*. The crude product was purified by flash chromatography (Al_2O_3, methanol: dichloromethane 1:49) to afford the product as a colourless oil (102mg, 82%). m/z HIRES Found 260.2046, $C_{13}H_{29}NO_2Si+H^+$ requires 260.2046; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3383s, 2954s (C-H str.), 2930s (C-H str.), 2886s (C-H str.), 2857m, 1472m, 1463m, 1446w, 1389w, 1361m, 1255s, 1161m, 1115s, 1093s, 1080s, 1029m, 1006m, 940w, 838s, 816m, 778m and 666s; δ_H (500 MHz, $CDCl_3$) 0.03 & 0.04 (6H, 2xs, $Si(C\underline{H}_3)_2$), 0.85 (9H, s, $SiC(C\underline{H}_3)_3$), 1.22-1.36 (1H, m, $NCH_2CH_2CH\underline{H}'$ equatorial), 1.47-1.55 (2H, m, $NCH\underline{H}'$ equatorial and $NCHCH\underline{H}'CH_2$ equatorial), 1.74-1.79 (1H, m, $NCH_2CH_2C\underline{H}H'$ axial), 1.97 (1H, dq, *J* 13.0 and 4.0Hz, $NCHC\underline{H}H'CH_2$ axial), 2.37 (1H, tq, *J* 13.0 and 4.0Hz, $NCH_2CH\underline{H}'$ equatorial), 2.99 (1H, tt, *J* 9.0 and 2.0Hz, $CH_2C\underline{H}N$), 3.09 (1H, dt, *J* 12.5 and 3.0Hz, $NC\underline{H}H'$ axial), 3.17 (3H, s, $NC\underline{H}_3$), 3.22-3.28 (1H, m, $NCH_2C\underline{H}H'$ axial), 3.38 (1H, dd, *J* 12.0 and 3.0Hz, $SiOCH\underline{H}'$) and 4.43 (1H, dd, *J* 12.0 and 6.0Hz, $SiOC\underline{H}H'$); δ_C (125 MHz, $CDCl_3$) -5.57 & -5.48 ($Si(\underline{C}H_3)_2$), 17.94 ($Si\underline{C}(CH_3)_3$), 20.26 ($CHCH_2\underline{C}H_2CH_2$), 22.53 ($NCH_2\underline{C}H_2$), 24.36 ($CH\underline{C}H_2CH_2CH_2$), 25.73 ($SiC(\underline{C}H_3)_3$) 59.77 ($N\underline{C}H_3$), 62.60 ($N\underline{C}H_2$), 69.23 ($SiO\underline{C}H_2$)and 76.09 ($N\underline{C}H$); m/z (Probe CI^+, NH_3) 262 (5), 261 (17) and 260 (100, MH^+).

2-*d*-*N*-Methyl-2-(*tert*-butyldimethylsilyloxy)methylpiperidine,

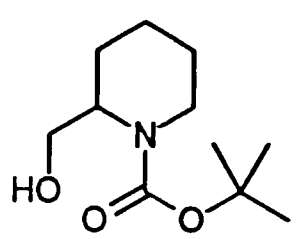
6-*d*-*N*-Methyl-2-(*tert*-butyldimethylsilyloxy)methylpiperidine **274**



To a solution of *N*-methyl-2-(*tert*-butyldimethylsilyloxy)methylpiperidine *N*-oxide **272** (720mg, 2.78mmol, 1.0eq) in dichloromethane (50ml) cooled to 0°C under an atmosphere of argon was added trifluoroacetic anhydride (5.84g, 27.8mmol, 10.0eq) dropwise. The reaction mixture was stirred at 0°C for 1 hour then allowed to warm to ambient at which time the solvent was removed in *vacuo* to give a yellow oil. The oil was dissolved in methanol (50ml), cooled to 0°C and sodium borodeuteride (584mg, 13.9mmol, 5.0eq) added in a single portion. The reaction mixture was stirred at 0°C for 1 hour, then poured into saturated aqueous sodium chloride (100ml). The mixture was extracted with dichloromethane (2x50ml) and ethyl acetate (2x50ml). The combined organic portions were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (Al_2O_3, diethyl ether: petroleum ether 1:4) to afford the product as a pale yellow oil (194mg, 29%). m/z HIRES Found 245.2158, $C_{13}H_{28}DNOSi+H^+$ requires 245.2158; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2931s (C-H str.), 2857s (C-H str.), 2780m, 1463m, 1389w, 1361m, 1256s, 1100s, 1035m, 939w, 837s, 775w and 668m; δ_H (500 MHz, $CDCl_3$) 0.03 (6H, s, $Si(C\underline{H}_3)_2$), 0.87 (9H, s, $SiC(C\underline{H}_3)_3$), 1.14-1.78 (6H, m, $CHC\underline{H}_2C\underline{H}_2C\underline{H}_2$), 1.89-1.93 (0.65H, m, $CH_2C\underline{H}N$), 2.00-2.07 (0.72H, m, NCH$\underline{H}$'), 2.28 (3H, s, $NC\underline{H}_3$), 2.76-2.80 (0.72H, m, NC$\underline{H}$H'), 3.42 (1H, dd, *J* 10.0 and 6.0Hz, SiOCH$\underline{H}$') and 3.80 (1H, dd, *J* 10.0 and 4.5Hz, SiOC$\underline{H}$H'); δ_D (38 MHz, $CDCl_3$) 1.93 ($CH_2C\underline{D}N$), 2.05 (NCH$\underline{D}$') and 2.79 (NC$\underline{D}$H') ratio 3:2:2 respectively; δ_C (125 MHz, $CDCl_3$) -5.43 ($Si(\underline{C}H_3)_2$), 18.25 ($Si\underline{C}(CH_3)_3$), 23.94 ($CHCH_2\underline{C}H_2CH_2$), 25.80 ($NCH_2\underline{C}H_2$), 25.90 ($SiC(\underline{C}H_3)_3$), 29.18 (NCH$\underline{C}$HD) & 29.31 ($NCH\underline{C}H_2$), 43.79 ($N\underline{C}H_3$),

57.11 (t, *J* 146.5Hz, N$\underline{C}$HD) & 57.45 (N$\underline{C}H_2$), 65.12 (t, *J* 146Hz, N$\underline{C}$D) & 65.61 (N$\underline{C}$H) and 66.00 (SiO$\underline{C}H_2$CD) & 66.11 (SiO$\underline{C}H_2$CH); m/z (APCI Cl^+, NH_3/Na) 246 (23), 245 (100, MH^+), 168 (5), 167 (48), 149 (95), 114 (7) and 113 (51).

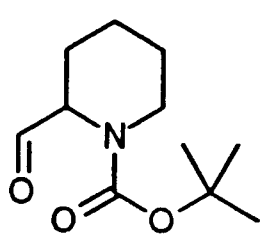
N-(*tert*-Butyloxycarbonyl)-2-hydroxymethylpiperidine **285**



To a solution of di-*tert*-butyl dicarbonate (10.90g, 5.0mmol, 1.0eq) in dichloromethane (10ml) cooled to 0°C under an atmosphere of argon was added (±)-2-piperidinemethanol **267** (5.75g, 5.0mmol, 1.0eq) in dichloromethane (10ml) over the period of 1 hour. The reaction mixture was allowed to warm to ambient at which stage it was stirred for 18 hours. The volatiles were then removed in *vacuo* to yield a brown oil which was suspended in aqueous saturated sodium chloride (100ml). The aqueous solution was extracted with ethyl acetate (2x50ml) and dichloromethane (50ml). The combined organic extracts were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The obtained yellow oil was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 1:1) yielding the product as a white crystalline solid (10.21g, 95%). (m.p. 75-76°C); (Found C, 61.1; H, 9.7; N, 6.5. $C_{11}H_{21}NO_3$ requires C, 61.4; H, 9.8; N, 6.5%); υ_{max} (FT-IR, KBr disc, cm^{-1}) 3429s (O-H str.), 3010s, 2951s (C-H str.), 2878s, 1985w, 1651s (C=O str.), 1552m, 1423m, 1368s, 1322s, 1278s, 1165s, 1112s, 1046s, 1009m, 952s, 897w, 882s, 871s, 841w and 817m; δ_H (300 MHz, $CDCl_3$) 1.43 (9H, s, C(C$\underline{H}_3$)$_3$), 1.50-1.69 (6H, m, CHC$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$), 2.37 (1H, br s, O$\underline{H}$), 2.79-2.88 (1H, m, NC$\underline{H}$), 3.58 (1H, dd, *J* 11.0 and 6.0Hz, HOC$\underline{H}$H'), 3.77 (1H, dd, *J* 11.0 and 9.0Hz, HOCH$\underline{H}$'), 3.89-3.93 (1H, m, NC$\underline{H}$H') and 4.22-4.29 (1H, m, NCH$\underline{H}$'); δ_C (50 MHz, $CDCl_3$) 19.41 (CHCH$_2\underline{C}$H$_2$CH$_2$), 24.99, 25.20 (CH$\underline{C}$H$_2$CH$_2\underline{C}$H$_2$), 28.37 (C($\underline{C}$H$_3$)$_3$), 39.85 (N$\underline{C}H_2$), 52.24 (N$\underline{C}$H), 61.10

($HO\underline{C}H_2$), 79.66 ($\underline{C}(CH_3)_3$) and 156.1 ($\underline{C}$=O); m/z (Probe CI^+, NH_3) 216 (13, MH^+), 184 (3), 177 (4), 161 (7), 160 (100), 142 (55), 117 (7), 116 (88), 98 (4) and 84 (65).

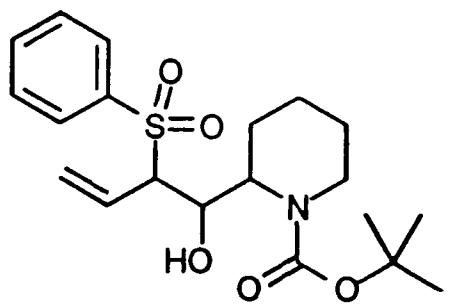
N-(*tert*-Butyloxycarbonyl)-2-formylpiperidine **282**



To a solution of oxalyl chloride (6.50g, 51.2mmol, 1.1eq) in dichloromethane (100ml) cooled to -78°C under an atmosphere of argon was added dimethyl sulphoxide (7.98g, 102.3mmol, 2.2eq) at a rate which maintained the temperature below -60°C. The reaction mixture was stirred for 2 minutes at which time *N*-(*tert*-butyloxycarbonyl)-2-hydroxymethylpiperidine **285** (10.00g, 46.5mmol, 1.0eq) in dichloromethane (15ml) was added at a rate which maintained the temperature below -50°C. The reaction mixture was stirred at -78°C for 15 minutes at which time triethylamine (23.48g, 232.5mmol, 5.0eq) was added at a rate which maintained the temperature below -50°C. The mixture was then allowed to warm to ambient and saturated aqueous sodium chloride (100ml) was added. The layers were separated and the aqueous portion extracted with dichloromethane (20ml). The organic portions were combined, dried over magnesium sulphate, filtered and the volatiles removed in *vacuo* to yield a yellow oil which was dissolved in dichloromethane (20ml). The organic solution was washed with water (20ml), dilute aqueous hydrochloric acid (20ml), water (20ml), saturated aqueous sodium hydrogen carbonate (20ml) and water (20ml). The organic solution was then dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The obtained yellow oil was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 1:4) yielding the product as a colourless oil (9.14g, 93%). (m/z HIRES Found 214.1443, $C_{11}H_{19}NO_3+H^+$ requires 214.1443; υ_{max} (FT-IR, KBr disc, cm^{-1}) 2941s (C-H str.), 2862s, 1735 (C=O str., aldehyde), 1698s (C=O str.,

carbamate), 1474m, 1456m, 1407s, 1367s, 1321m, 1277s, 1251m, 1165s, 1165s, 1128m, 1095w, 1046m, 935w, 883s, 804w and 771w; δ_H (500 MHz, $CD_3C_6D_5$, 90°C) 0.94-1.37 (5H, m, $CHC\underline{H}_2CH\underline{H}'C\underline{H}_2$), 1.38 (9H, s, $C(C\underline{H}_3)_3$), 1.73-1.79 (1H, m, $CHCH_2C\underline{H}H'CH_2$), 2.77 (1H, ddd, *J* 13.5, 11.0 and 3.5Hz, NC<u>H</u>), 3.79 (1H, d, *J* 13.5Hz, NCH<u>H</u>'), 4.33 (1H, s, NC<u>H</u>H') and 9.29 (1H, s, C<u>H</u>O); δ_C (125 MHz, $CDCl_3$) 20.92 ($CHCH_2\underline{C}H_2CH_2$), 23.57 & 24.71 ($CH\underline{C}H_2CH_2\underline{C}H_2$), 28.31 ($C(\underline{C}H_3)_3$), 43.06 ($N\underline{C}H_2$), 60.75 (N<u>C</u>H) and 201.4 (<u>C</u>HO), N<u>C</u>=O not seen; m/z (Probe CI^+, NH_3) 214 (41, MH^+), 184 (15), 175 (17), 158 (39), 114 (42), 84 (100) and 83 (13).

<u>*N*-(*tert*-Butyloxycarbonyl)-2-(1-hydroxy-2-phenylsulfonyl-3-butenyl)-piperidine **286**</u>



To a solution of allyl phenyl sulfone **283** (4.63g, 21.7mmol, 1.0eq) in tetrahydrofuran (50ml) cooled to -40°C under an atmosphere of argon was added *N,N,N',N'*-tetramethylethylenediamine (2.52g, 21.7mmol, 1.0eq). The solution was stirred at -78°C for 5 minutes at which time *n*-butyl lithium (1.30M, 16.7ml, 21.7mmol, 1.0eq) was added dropwise at a rate which maintained the temperature below -40°C. The reaction mixture was stirred at -40°C for 30 minutes, then *N*-(*tert*-butyloxycarbonyl)-2-formylpiperidine **282** (4.63g, 21.7mmol, 1.0eq) in tetrahydrofuran (10ml) was added in a single portion. The reaction mixture was stirred at -40°C for a further 90 minutes, then water (5ml) was added in a single portion. The solution was allowed to warm to ambient, diluted with water (20ml) following which the layers were separated. The aqueous portion was extracted with diethyl ether (2x25ml), neutralised by controlled addition of dilute aqueous hydrochloric acid and sodium hydrogen carbonate, then further extracted with diethyl ether (25ml). The combined organic portions were dried

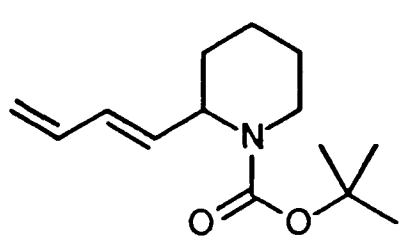
over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 7:3) to afford the product as a pale yellow oil (6.65g, 77%). m/z HIRES Found 396.1845, $C_{20}H_{29}NO_5S+H^+$ requires 396.1861; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3430s (O-H str.), 2976s (C-H str.), 2933m (C-H str.), 2869s, 2724m, 1690 (C=O str.), 1585m, 1448m, 1414s, 1367s, 1350s, 1335m, 1279s, 1253m, 1211m, 1148s, 1084s, 1028m, 998m, 975m, 931m, 868s, 805w, 772m, 759m, 724m, 713m, 691s and 667m; m/z (Probe CI^+, NH_3) 396 (22, MH^+), 357 (12), 340 (15), 297 (14), 296 (73), 278 (10), 214 (8), 200 (40), 175 (27), 158 (49), 138 (8), 114 (18) and 84 (100).

Elimination reaction of *N*-(*tert*-Butyloxycarbonyl)-2-(1-hydroxy-2-phenylsulfonyl-3-butenyl)-piperidine **286**

To a solution of *N*-(*tert*-butyloxycarbonyl)-2-(1-hydroxy-2-phenylsulfonyl-3-butenyl)-piperidine **286** (152mg, 0.38mmol, 1.0eq) and sodium hydrogenphosphate (760g, 5.32mmol, 14.0eq) in methanol (10ml) under an atmosphere of argon was added sodium amalgam (6%, 3.68g, 9.60mmol, 25.0eq). The reaction mixture was stirred at ambient for 66 hours at which time it was diluted with water (10ml) and extracted with diethyl ether (3x10ml). The combined organic extracts were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (diethyl ether: petroleum ether, gradient 1:9 to 2:1) to afford

(i)

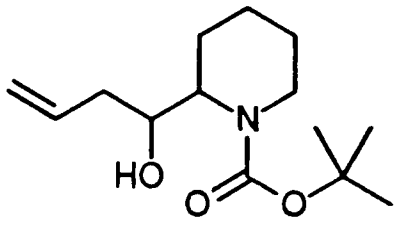
N-(*tert*-Butyloxycarbonyl)-2-[(*E*)-1,3-butadienyl]-piperidine **284**



Colourless oil (9.4mg, 10%). m/z HIRES Found 238.1807, $C_{14}H_{23}NO_2$+H+ requires 238.1807; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2976s (C-H str.), 2937m (C-H str.), 2860m, 1693s, (C=O str.), 1457m, 1410s, 1365s, 1336w, 1324w, 1271m, 1251m, 1162s, 1092m, 1036m, 1004w, 900w, 870w and 669m; δ_H (500 MHz, $CD_3C_6D_5$, 90°C) 0.84-1.60 (15H, m, $CHC\underline{H}_2C\underline{H}_2C\underline{H}_2$ and $C(C\underline{H}_3)_3$), 1.98-2.12 (1H, m, NCH<u>H</u>'), 2.58-2.83 (1H, m, NC<u>H</u>H'), 3.95-4.01 (1H, m, $CH_2C\underline{H}N$), 4.88 (1H, m, CH<u>H</u>'CHCH), 5.03 (1H, m, C<u>H</u>H'CHCH), 5.55 (1H, m, C<u>H</u>CHN), 6.20 (1H, m, $CH_2CHC\underline{H}$) and 6.78 (1H, m, $CH_2C\underline{H}CH$); m/z (Probe CI+, NH_3) 238 (8, MH+), 199 (7), 182 (48), 181 (8), 140 (10), 139 (9), 138 (100), 137 (7), 120 (6) and 84 (7).

(ii)

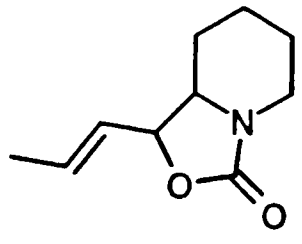
<u>*N*-(*tert*-Butyloxycarbonyl)-2-(1-hydroxy-3-butenyl)-piperidine **287**</u>



Colourless oil (21.5mg, 22%). m/z HIRES Found 256.1913, $C_{14}H_{25}NO_3$+H+ requires 256.1913; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3423 (O-H str.), 2976s (C-H str.), 2934m (C-H str.), 2865m, 1691s, (C=O str.), 1668s, 1475w, 1420s, 1392w, 1366s, 1337w, 1312m, 1275s, 1252m, 1168s, 1143m, 1092w, 1069m, 1031m, 992w, 966w, 916w, 870w, 815w and 768w; δ_H (500 MHz, $CD_3C_6D_5$, 90°C) 0.86-1.39 (5H, m, $CHC\underline{H}_2CH\underline{H}'C\underline{H}_2$), 1.40 (9H, s, $C(C\underline{H}_3)_3$), 1.90-1.96 (1H, m, $CHCH_2C\underline{H}H'CH_2$), 2.61-2.76 (2H, m, $C\underline{H}_2CHOH$), 3.76 (1H, br s, O<u>H</u>), 3.94-4.14 (3H, m, $C\underline{H}NC\underline{H}_2$), 4.97-5.01 (1H, m, CH<u>H</u>'=CHCHOH), 5.44-5.54 (1H, m, C<u>H</u>H'=CHCHOH) and 5.77 (1H, ddt, *J* 17.5, 14.0 and 7.0Hz, CH_2=C<u>H</u>CHOH); m/z (Probe CI+, NH_3) 256 (15, MH+), 201 (9), 200 (85), 183 (10), 182 (100), 156 (42), 140 (14), 138 (17) and 84 (63).

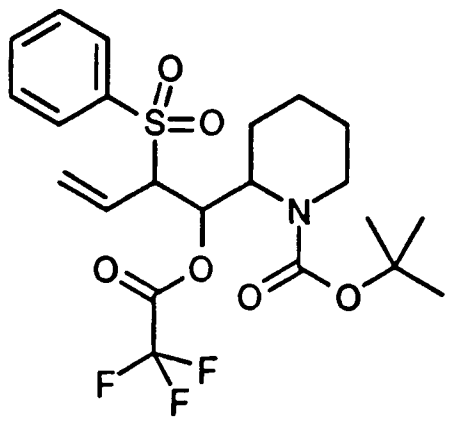
and (iii)

1-[(*E*)-1-Propenyl]-hexahydro-oxazolo(3,4-*a*)pyridin-3-one **288**



Colourless oil (11.6mg, 17%). m/z HIRES Found 182.1181, $C_{10}H_{15}NO_2$+H+ requires 182.1181; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2940s (C-H str.), 2858s, 1752vs (C=O str.), 1447m, 1418s, 1315w, 1228m, 1177w, 1063w, 1036s, 968w, 946m and 762w; δ_H (500 MHz, $CHCl_3$) 1.26-1.71 (6H, m, $CHC\underline{H}_2CH\underline{H}'C\underline{H}_2$), 1.40 (3H, dd, *J* 6.5 and 1.5Hz, $C\underline{H}_3CHCH$), 1.92-1.97 (1H, m, $CHCH_2C\underline{H}H'CH_2$), 2.83 (1H, dt, *J* 12.5 and 3.5Hz, $NCH\underline{H}'$), 3.60 (1H, ddd, *J* 11.5, 8.0 and 3.5Hz, $NC\underline{H}$), 3.87 (1H, m, $NC\underline{H}H'$), 4.87 (1H, t, *J* 8.0Hz, $CH_3CHCHC\underline{H}$), 5.50 (1H, ddq, *J* 15.5, 8.0 and 1.5Hz, $CH_3CHC\underline{H}$) and 5.86 (1H, dq, *J* 15.5 and 6.5Hz, $CH_3C\underline{H}$); δ_C (125 MHz, $CHCl_3$) 17.08 ($\underline{C}H_3$), 22.99 ($CHCH_2\underline{C}H_2CH_2$), 24.18 ($CH\underline{C}H_2CH_2CH_2$), 26.11 ($CHCH_2CH_2\underline{C}H_2$), 41.93 ($N\underline{C}H_2$), 58.28 ($N\underline{C}H$), 77.55 ($\underline{C}HOH$), 124.0 ($CH_3CH\underline{C}H$) and 132.4 ($CH_3\underline{C}HCH$); m/z (Probe CI+, NH_3) 199 (9, MNH_4+), 183 (10), 182 (100, MH+), 181 (7), 138 (7), 84 (12) and 83 (12).

N-(*tert*-Butyloxycarbonyl)-2-(1-trifluoroacetoxy-2-phenylsulfonyl-3-butenyl)-piperidine **290**

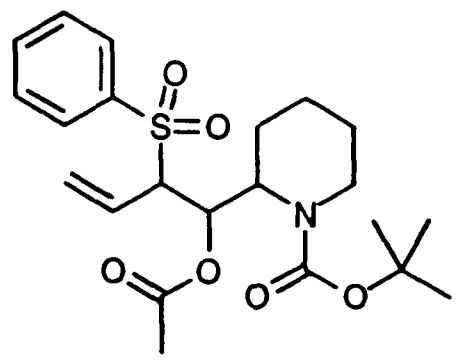


To a solution of *N*-(*tert*-butyloxycarbonyl)-2-(1-hydroxy-2-phenylsulfonyl-3-butenyl)-piperidine **286** (591mg, 1.5mmol, 1.0eq) and pyridine (237mg, 3.0mmol, 2.0eq) in dichloromethane (10ml) cooled to 0°C under an atmosphere of argon was added trifluoroacetic anhydride (473mg, 2.25mmol, 2.0eq). The reaction mixture was allowed to warm to ambient then stirred for 65 hours. The solvent was then removed in *vacuo* and the crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 1:2) to afford the product as a pale yellow oil (482g, 66%). m/z HIRES Found 492.1668, $C_{22}H_{28}F_3NO_6S+H^+$ requires 492.1668; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2943s (C-H str.), 1796s (C=O str., acetate), 1693s (C=O str., carbamate), 1451m, 1411s, 1367s, 1314m, 1225s, 1152s, 1086m, 1029m, 993m, 948w, 865w, 768m, 727s, 691s and 624m; m/z (Probe Cl^+, NH_3) 509 (5, MNH_4^+), 492 (10, MH^+), 454 (13), 453 (64), 436 (27), 395 (13), 392 (38), 341 (10), 340 (22), 339 (99), 322 (12), 280 (12), 279 (20), 278 (100), 199 (10), 183 (13), 182 (17), 160 (12), 138 (24), 136 (36) and 84 (90).

Elimination reaction of *N*-(*tert*-butyloxycarbonyl)-2-(1-trifluoroacetoxy-2-phenyl sulfonyl-3-butenyl)-piperidine **290**

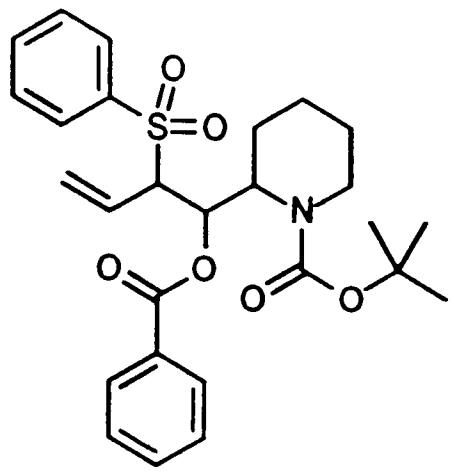
To a solution of *N*-(*tert*-butyloxycarbonyl)-2-(1-trifluoroacetoxy-2-phenylsulfonyl-3-butenyl)-piperidine **290** (229mg, 0.47mmol, 1.0eq) and sodium hydrogenphosphate (934mg, 6.7mmol, 14.0eq) in methanol (10ml) under an atmosphere of argon was added sodium amalgam (6%, 4.50g, 11.7mmol, 25.0eq). The reaction mixture was stirred at ambient for 28 hours at which time it was diluted with water (25ml) and extracted with diethyl ether (3x25ml). The combined organic extracts were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (diethyl ether: petroleum ether, gradient 1:9 to 2:1) to afford *N*-(*tert*-butyloxycarbonyl)-2-[(*E*)-1,3-butadienyl]-piperidine **284** as a colourless oil (45mg, 40%).

N-(*tert*-Butyloxycarbonyl)-2-(1-acetoxy-2-phenylsulfonyl-3-butenyl)-piperidine **291**



To a solution of *N*-(*tert*-butyloxycarbonyl)-2-(1-hydroxy-2-phenylsulfonyl-3-butenyl)-piperidine **286** (1.55g, 3.92mmol, 1.0eq), 4-dimethylaminopyridine (48mg, 0.39mmol, 0.1eq) and pyridine (3.10g, 39.2mmol, 10.0eq) in dichloromethane (20ml) cooled to 0°C under an atmosphere of argon was added acetic anhydride (0.80g, 7.84mmol, 2.0eq). The reaction mixture was allowed to warm to ambient then stirred for 40 hours. The solvent was then removed in *vacuo* and the crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether, gradient 1:2 to 2:1) to afford the product as a colourless oil (56g, 3%). m/z HIRES Found 438.1967, $C_{22}H_{31}NO_6S+H^+$ requires 438.1967; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2939s (C-H str.), 2862 (C-H str.), 1748m (C=O str., acetate), 1692s (C=O str., carbamate), 1477m, 1447s, 1412s, 1366s, 1307s, 1272m, 1154s, 1086m, 1048w, 991m, 935w, 866w, 758m, 723m and 608s; m/z (Probe CI^+, NH_3) 438 (4, MH^+), 396 (5), 395 (27), 378 (10), 338 (20), 322 (7), 279 (8), 278 (42), 277 (12), 212 (11), 192 (16), 191 (100), 136 (40), 135 (17), 134 (9) and 84 (6).

N-(*tert*-Butyloxycarbonyl)-2-(1-benzoyloxy-2-phenylsulfonyl-3-butenyl)-piperidine **292**



Method i

To a solution of *N*-(*tert*-butyloxycarbonyl)-2-(1-hydroxy-2-phenylsulfonyl-3-butenyl)-piperidine **286** (1.64g, 4.15mmol, 1.0eq) in tetrahydrofuran (20ml) cooled to -40°C under an atmosphere of argon was added *n*-butyl lithium (1.30M, 3.20ml, 4.15mmol, 1.0eq) dropwise. The reaction mixture was stirred at -40°C for 30 minutes at which time benzoyl chloride (0.64g, 4.56mmol, 1.1eq) in a single portion. The reaction mixture was allowed to warm to ambient then stirred for 19 hours. The reaction mixture was poured into satrated aqueous sodium hydrogen carbonate (50ml), diluted with ethyl acetate (50ml) and the layers separated. The aqueous portion was extracted with dichloromethane (2x25ml), then the organic portions combined, dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 1:2) to afford the product as a pale yellow foam (948mg, 46%).

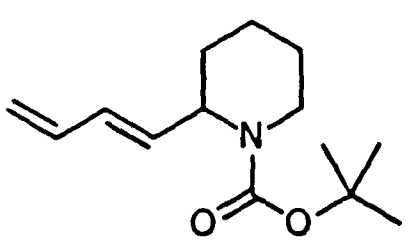
Method ii

To a solution of allyl phenyl sulphone **283** (3.64g, 20.0mmol, 1.0eq) in tetrahydrofuran (60ml) cooled to -40°C under an atmosphere of argon was added *N,N,N',N'*-tetramethylethylenediamine (2.32g, 20.0mmol, 1.0eq). The solution was

stirred at -40°C for 5 minutes at which time *n*-butyl lithium (1.10M, 18.2ml, 20.0mmol, 1.0eq) was added dropwise at a rate which maintained the temperature below -40°C. The reaction mixture was stirred at -40°C for 30 minutes, then *N*-(*tert*-butyloxycarbonyl)-2-formylpiperidine **282** (4.26g, 20.0mmol, 1.0eq) in tetrahydrofuran (10ml) was added dropwise at a rate which maintained the temperature below -40°C. The reaction mixture was stirred at -40°C for a further 90 minutes, then benzoyl chloride (3.09g, 22.0mmol, 1.1eq) was added dropwise at a rate which maintained the temperature below -40°C. The solution was allowed to warm to ambient over 2 hours, then stirred for 46 hours. The reaction mixture was then diluted with saturated aqueous sodium hydrogen carbonate (55ml) and ethyl acetate (50ml) following which the layers were separated. The aqueous portion was then extracted with dichloromethane (2x50ml). The combined organic portions were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether, gradient 1:2 to 1:0) to afford the product as a pale yellow foam (6.46g, 65%).

m/z HIRES Found 500.2110, $C_{27}H_{33}NO_6S+H^+$ requires 500.2107; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2937s (C-H str.), 2870 (C-H str.), 1728m (C=O str., acetate), 1690s (C=O str., carbamate), 1602w, 1585w, 1478m, 1449s, 1413s, 1387s, 1312s, 1270s, 1151s, 1107m, 1070m, 1028w, 990w, 938w, 869w, 759w, 712s, 689m and 624s; m/z (Probe CI^+, NH_3) 500 (8, MH^+), 461 (10), 444 (7), 402 (7), 401 (19), 400 (100), 278 (24), 240 (4), 184 (13), 136 (10) and 84 (89).

N-(*tert*-Butyloxycarbonyl)-2-[(*E*)-1,3-butadienyl]-piperidine **284**



Method i

To a solution of *N*-(*tert*-butyloxycarbonyl)-2-(1-benzoyloxy-2-phenylsulfonyl-3-butenyl)-piperidine **292** (410mg, 0.82mmol, 1.0eq) and sodium hydrogenphosphate (1.16g, 8.20mmol, 10.0eq) in tetrahydrofuran:methanol (3:1, 12ml) cooled to -20°C under an atmosphere of argon was added sodium amalgam (6%, 1.57g, 4.10mmol, 5.0eq). The reaction mixture was stirred at -20°C for 66 hours at which time it was diluted with water (20ml) and allowed to warm to ambient. The mixture was extracted with diethyl ether (3x50ml) and dichloromethane (50ml). The combined organic extracts were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether, gradient 1:9 to 1:1) to afford *N*-(*tert*-butyloxycarbonyl)-2-[(*E*)-1,3-butadienyl]-piperidine **284** as a colourless oil (81mg, 42%).

Method ii

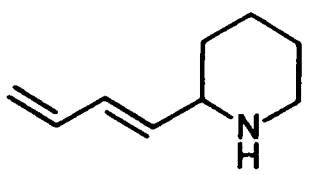
To a flask flushed with argon was transferred samarium iodide (0.1M in tetrahydrofuran, 50.0ml, 5.0mmol, 5.0eq). 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (1.92g, 15.0mmol, 15.0eq) was then added turning the blue/green solution purple. *N*-(*tert*-butyloxycarbonyl)-2-(1-benzoyloxy-2-phenylsulfonyl-3-butenyl)-piperidine **292** (499mg, 1.0mmol, 1.0eq) in tetrahydrofuran (5ml) was added immediately turning the purple solution indigo. The reaction mixture has stirred at ambient for 2 hours at which time it was diluted with diethyl ether (25ml) and washed with dilute aqueous hydrochloric acid (1M, 25ml), water (25ml), saturated aqueous sodium hydrogen carbonate (25ml) and saturated aqueous sodium chloride (25ml). The organic solution was then dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C, gradient 1:9 to 1:2) to afford *N*-(*tert*-

butyloxycarbonyl)-2-[(*E*)-1,3-butadienyl]-piperidine **284** as a colourless oil (61mg, 26%).

Method iii

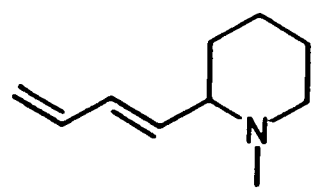
To a solution of allyl phenyl sulphone **283** (910mg, 5.0mmol, 1.0eq) in tetrahydrofuran (45ml) cooled to -40°C under an atmosphere of argon was added *N,N,N',N'*-tetramethylethylenediamine (580g, 5.0mmol, 1.0eq). The solution was stirred at -40°C for 5 minutes at which time *n*-butyl lithium (1.20M, 4.17ml, 5.0mmol, 1.0eq) was added dropwise at a rate which maintained the temperature below -40°C. The reaction mixture was stirred at -40°C for 30 minutes, then *N*-(*tert*-butyloxycarbonyl)-2-formylpiperidine **282** (1.065g, 5.0mmol, 1.0eq) in tetrahydrofuran (10ml) was added dropwise at a rate which maintained the temperature below -40°C. The reaction mixture was stirred at -40°C for a further 90 minutes, then benzoyl chloride (770mg, 5.5mmol, 1.1eq) was added dropwise at a rate which maintained the temperature below -40°C. The solution was allowed to warm to ambient over 2 hours, then cooled to -20°C and methanol (15ml) and sodium hydrogenphosphate (7.10g, 50.0mmol, 10.0eq) were added. The mixture was stirred at -20°C for 5 minutes at which time sodium amalgam (6%, 9.58g, 25.0mmol, 5.0eq) was added. The reaction mixture was stirred at -20°C for 18 hours, then allowed to warm to ambient. The reaction mixture was diluted with water (50ml) and diethyl ether (50ml) following which the layers were separated. The aqueous portion was extracted with diethyl ether (3x50ml) and dichloromethane (50ml). The combined organic portions were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 1:9) to afford *N*-(*tert*-butyloxycarbonyl)-2-[(*E*)-1,3-butadienyl]-piperidine **284** as a colourless oil (500mg, 42%).

2-[(*E*)-1,3-Butadienyl]-piperidine **313**



To a solution of *N*-(*tert*-butyloxycarbonyl)-2-[(*E*)-1,3-butadienyl]-piperidine **284** (458mg, 1.93mmol, 1.0eq) in dichloromethane (30ml) under an atmosphere of argon was added trifluoroacetic acid (2.20g, 19.3mmol, 10.0eq) in a single portion. The reaction mixture was stirred at ambient for 2 hours. The solvent was then removed in *vacuo* affording a brown oil. The oil was suspended in aqueous sodium hydroxide (1M, 50ml) then extracted with ethyl acetate (2x50ml), *tert*-butyl methyl ether (2x50ml) and dichloromethane (2x50ml). The combined organic extracts were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo* to yield the product as a yellow oil (244mg, 92%). m/z HIRES Found 138.1270, $C_9H_{15}N+H^+$ requires 138.1280; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3280m, (N-H str.), 2933s (C-H str.) 2854s (C-H str.), 1688m, 1603w, 1494w, 1452s, 1437s, 1370w, 1316s, 1279vs, 1201s, 1177m, 1071w, 1053w, 1027m, 1006m, 968m, 903m, 824w, 800m, 750m, 714s, 689m and 676m; δ_H (500 MHz, $CDCl_3$) 1.57-1.87 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$) 2.79 (1H, dt, *J* 12.5 and 4.0Hz, NCH$\underline{H}$'), 3.25 (1H, d, *J* 12.5 Hz, NC$\underline{H}$H'), 3.39 (1H, ddd, *J* 11.0, 7.5 and 3.0Hz, C$\underline{H}$N), 5.12 (1H, d, *J* 9.0Hz, CHCHCH$\underline{H}$'), 5.24 (1H, d, *J* 14.5Hz, CHCHC$\underline{H}$H'), 5.71 (1H, dd, *J* 14.5 and 7.5Hz, C$\underline{H}$CHN) and 6.26-6.32 (2H, m, $CH_2C\underline{H}C\underline{H}CH$); δ_C (125 MHz, $CDCl_3$) 22.99 ($CH_2\underline{C}H_2CH_2$), 23.22 ($\underline{C}H_2CH_2N$) 30.12 (NCH$\underline{C}H_2$), 44.90 (N$\underline{C}H_2$), 57.92 ($\underline{C}$HN), 118.8 ($\underline{C}H_2CHCHCH$), 131.4 ($CH_2CHCHC\underline{H}$), 133.9 ($CH_2\underline{C}HCHCH$) and 135.9 ($CH_2CH\underline{C}HCH$); m/z (Probe CI^+, NH_3) 140 (23), 139 (15), 138 (100, MH^+), 123 (14), 122 (8), 110 (5), 100 (6), 94 (8), 84 (53), 82 (10), 80 (10), 58 (6) and 56 (7).

N-Methyl-2-[(*E*)-1,3-butadienyl]-piperidine **312**



Method i

To a solution of 2-[(*E*)-1,3-butadienyl]-piperidine **313** (20mg, 0.146mmol, 1.0eq) and formaldehyde (37% aqueous, 0.120ml, 1.46mmol, 10.0eq) in acetonitrile (12ml) under an atmosphere of argon was added sodium cyanoborohydride (18mg, 0.292mmol, 2.0eq) in a single portion causing vigorous effervescence. The reaction mixture was stirred for 1 hour at ambient, then the solvent was removed in *vacuo*. The obtained yellow oil was suspended in aqueous sodium hydroxide (1M, 10ml) and extracted with dichloromethane (4x10ml). The combined organic extracts were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C, gradient 1:9 to 1:0) to yield the product as a colourless oil (7mg, 32%).

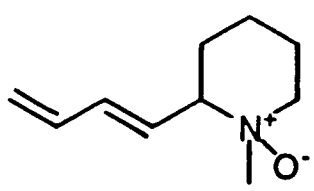
Method ii

To a solution of *N*-(*tert*-butyloxycarbonyl)-2-[(*E*)-1,3-butadienyl]-piperidine **284** (433mg, 1.83mmol, 1.0eq) in dichloromethane (30ml) under an atmosphere of argon was added trifluoroacetic acid (2.09g, 18.3mmol, 10.0eq) in a single portion. The reaction mixture was stirred at ambient for 2 hours. The solvent was then removed in *vacuo* affording a cream coloured solid. This solid was suspended in acetonitrile (12ml) and formaldehyde (37% aqueous, 1.48ml, 18.3mmol, 10.0eq) was added. The solution was stirred for 5 minutes at which time sodium cyanoborohydride (346mg, 5.49mmol, 3.0eq) was added in a single portion causing vigorous effervescence. The reaction mixture was stirred for 2 hours at ambient, then diluted with diethyl ether

(50ml). The organic solution was washed with aqueous sodium hydroxide (1M, 3x50ml) and saturated aqueous sodium chloride (50ml). The organic solution was then dried over magnesium sulphate, filtered and the volatiles removed in *vacuo.* The crude product was purified by flash chromatography (Al_2O_3, diethyl ether: petroleum ether 30-40°C, gradient 0:1 to 1:4) to yield the product as a colourless oil (176mg, 64%).

m/z HIRES Found 152.1439, $C_{10}H_{17}N+H^+$ requires 152.1439; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2937s (C-H str.), 2856m (C-H str.), 1638w, 1444m, 1306m, 1128m, 1101m, 1006m and 909m; δ_H (500 MHz, $CDCl_3$) 1.18-1.76 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 1.97 (1H, dt, *J* 11.5 and 3.0Hz, NCH$\underline{H}$'), 2.17 (3H, s, $NC\underline{H}_3$), 2.31 (1H, dt, *J* 11.0 and 3.0Hz, NC$\underline{H}$H'), 2.86 (1H, m, $CH_2C\underline{H}N$), 5.01 (1H, dd, *J* 10.0 and 1.5Hz, CH$\underline{H}$'CHCH), 5.13 (1H, dd, *J* 17.0 and 1.5Hz, C$\underline{H}$H'CHCH), 5.60 (1H, dd, *J* 15.5 and 9.0Hz, C$\underline{H}$CHN), 6.13 (1H, dd, *J* 15.5 and 10.0Hz, $CH_2CHC\underline{H}$) and 6.31 (1H, dt, *J* 17.0 and 10.0Hz, $CH_2C\underline{H}CH$); δ_C (125 MHz, $CDCl_3$) 23.82 ($CH_2\underline{C}H_2CH_2$), 25.89 ($\underline{C}H_2CH_2N$) 33.25 (NCH$\underline{C}H_2$), 44.54 ($N\underline{C}H_3$), 56.35 ($N\underline{C}H_2$), 67.54 ($\underline{C}HN$), 116.1 ($\underline{C}H_2CHCH$), 131.5 ($\underline{C}HCHN$), 136.8 ($CH_2\underline{C}HCH$) and 137.8 ($CH_2CH\underline{C}H$); m/z (GCMS CI^+, NH_3) 153 (23), 152 (100, MH^+) and 150 (43).

N-Methyl-2-[(*E*)-1,3-butadienyl]-piperidine *N*-oxide **314**

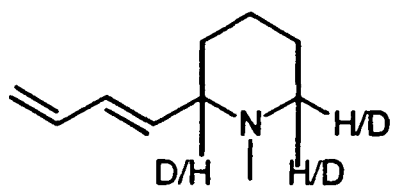


To a solution of *N*-methyl-2-[(*E*)-1,3-butadienyl]-piperidine **312** (40mg, 0.265mmol, 1.0eq) in dichloromethane (5ml) cooled to 0°C under an atmosphere of argon was added *meta*-chloroperbenzoic acid (87% activity, 52.5mg, 0.265mmol, 1.0eq). The reaction mixture was stirred at 0°C for 90 minutes then the solvent was removed in *vacuo.* The crude product was purified by flash chromatography (SiO_2, methanol:

dichloromethane 1:49) to afford the product as a colourless oil (26mg, 60%). m/z HIRES Found 168.1388, $C_{10}H_{17}NO+H^+$ requires 168.1388; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3376s, 2946s (C-H str.), 1655m, 1604m, 1449m, 1012w, 958s, 905s, 873w and 669w; δ_H (500 MHz, $CDCl_3$) 1.29-1.82 (4H, m, CH<u>H</u>'C<u>H</u>$_2$CH<u>H</u>'), 2.08-2.32 (1H, m, NCHC<u>H</u>H'), 2.70-2.92 (1H, tq, *J* 13.5 and 4.0Hz, C<u>H</u>H'CH$_2$N), 3.02 (3H, s, NC<u>H</u>$_3$), 3.03-3.09 (1H, m, NCH<u>H</u>'CH$_2$), 3.32-3.39 (2H, m, CHCHC<u>H</u>N and NC<u>H</u>H'CH$_2$) 5.14 (1H, dd, *J* 10.0 and 1.0Hz, CH<u>H</u>'CHCH), 5.21 (1H, dd, *J* 17.0 and 1.0Hz, C<u>H</u>H'CHCH), 6.08 (1H, dd, *J* 15.5 and 9.0Hz, C<u>H</u>CHN), 6.20 (1H, dd, *J* 15.5 and 10.0Hz, CH$_2$CHC<u>H</u>) and 6.36 (1H, dt, *J* 17.0 and 10.0Hz, CH$_2$C<u>H</u>CH); δ_C (125 MHz, $CDCl_3$) 20.51 (CH$_2$<u>C</u>H$_2$CH$_2$), 22.69 (<u>C</u>H$_2$CH$_2$N) 27.60 (NCH<u>C</u>H$_2$), 59.02 (N<u>C</u>H$_3$), 68.31 (N<u>C</u>H$_2$), 76.51 (<u>C</u>HN), 118.7 (<u>C</u>H$_2$CHCH), 129.7 (<u>C</u>HCHN), 135.5 (CH$_2$<u>C</u>HCH) and 136.0 (CH$_2$CH<u>C</u>H); m/z (APCI$^+$, NH_3/Na) 170 (3), 169 (9) and 168 (100, MH^+).

<u>*2-d-N*-Methyl-2-[(*E*)-1,3-butadienyl]-piperidine,</u>

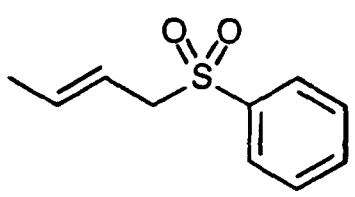
<u>*6-d-N*-Methyl-2-[(*E*)-1,3-butadienyl]-piperidine **315**</u>



To a solution of *N*-methyl-2-[(*E*)-1,3-butadienyl]-piperidine *N*-oxide **314** (25mg, 0.150mmol, 1.0eq) in dichloromethane (5ml) cooled to 0°C under an atmosphere of argon was added trifluoroacetic anhydride (315mg, 1.50mmol, 10.0eq) in a single portion. The reaction mixture was stirred at 0°C for 1 hour at which time the solvent was removed in *vacuo* to give a yellow oil. The oil was dissolved in methanol (5ml), cooled to 0°C and sodium borodeuteride (32mg, 0.750mmol, 5.0eq) added in a single portion. The reaction mixture was stirred at 0°C for a further 1 hour, then poured into saturated aqueous sodium chloride (20ml). The mixture was extracted with dichloromethane (2x10ml) and ethyl acetate (2x10ml). The combined organic extracts

were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo* to afford the product as a colourless oil (18mg, 79%). m/z HIRES Found 153.1502, $C_{10}H_{16}DN+H^+$ requires 153.1501; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2923s (C-H str.), 2850m (C-H str.), 1736w, 1702m, 1691s, 1680m, 1642w, 1415m, 1365m, 1257m and 1040m; δ_H (500 MHz, $CDCl_3$) 1.18-1.76 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 1.82-2.06 (0.8H, m, NCH$\underline{H}$'), 2.20 (3H, s, $NC\underline{H}_3$), 2.25-2.36 (0.8H, m, NC$\underline{H}$H'), 2.88-2.91 (0.7H, m, $CH_2C\underline{H}N$), 5.05 (1H, dd, *J* 10.0 and 1.5Hz, CH$\underline{H}$'CHCH), 5.17 (1H, dd, *J* 17.0 and 1.5Hz, C$\underline{H}$H'CHCH), 5.60-5.65 (1H, m, C$\underline{H}$CHN), 6.13 (1H, dd, *J* 15.5 and 10.5Hz, $CH_2CHC\underline{H}$) and 6.31 (1H, dt, *J* 17.0 and 10.5Hz, $CH_2C\underline{H}CH$); δ_D (76 MHz, $CDCl_3$) 2.08 (NCH$\underline{D}$'), 2.44 (NC$\underline{D}$H') and 2.96 ($CH_2C\underline{D}N$), relative ratio 2:2:3 respectively; δ_C (125 MHz, $CDCl_3$) 23.78 ($CH_2\underline{C}H_2CH_2$), 25.74 ($\underline{C}HDCH_2N$) & 25.85 ($\underline{C}H_2CH_2N$), 33.07 ($NCD\underline{C}H_2$) & 33.21 ($NCH\underline{C}H_2$), 44.48 ($N\underline{C}H_3$), 56.32 ($N\underline{C}H_2$), 67.59 ($\underline{C}HN$), 116.3 ($\underline{C}H_2CHCH$), 131.7 ($\underline{C}HCHN$), 136.8 ($CH_2\underline{C}HCH$) and 137.6 ($CH_2CH\underline{C}H$), N$\underline{C}$HD and C$\underline{D}$N too weak to be measured; m/z (APCI Cl^+, NH_3/Na) 155 (10), 154 (11), 153 (100, MH^+) and 152 (12).

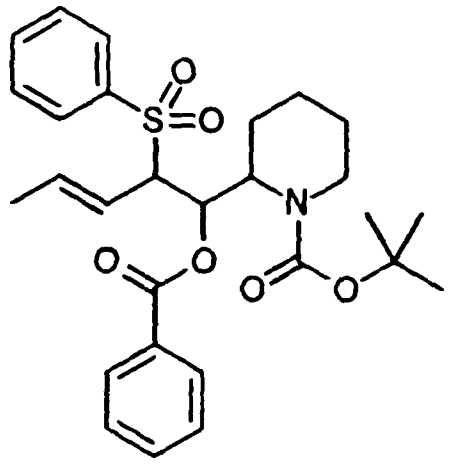
1-(Phenylsulfonyl)-2-butene **296**



To a solution of crotyl chloride **298** (20.00g, 0.22mol, 1.0eq) in methanol (200ml) under an atmosphere of argon was added sodium benzenesulphinate (65.50g, 0.40mol, 1.82eq) in a single portion. The reaction mixture was heated, then stirred under reflux for 27 hours. The solvent was removed in *vacuo* to yield a white slush. The mixture was then diluted with saturated aqueous sodium hydrogen carbonate (100ml), water (300ml) and chloroform (150ml) following which the layers were separated. The aqueous portion was then extracted with chloroform (3x150ml). The combined organic solutions were dried over magnesium sulphate, filtered and the

volatiles removed in *vacuo*. The crude product was purified distillation yielding the product as a colourless oil (36.25g, 84%). Data for *E*-isomer only: (b.p. 180°C / 6mmHg); m/z HIRES Found 197.0636, $C_{10}H_{12}OS_2+H^+$ requires 197.0636; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2918m (C-H str.), 1585w, 1478w, 1447s, 1400w, 1307s, 1239m, 1144s, 1086s, 1070m, 1025w, 999w, 966s, 931w, 867w, 762m, 731s, 713w, 690s and 674w; δ_H (300 MHz, $CDCl_3$) 1.66 (3H, dd, *J* 10.0 and 1.5Hz, $C\underline{H}_3CH$), 3.72 (2H, d, *J* 12.5Hz, $CHC\underline{H}_2S$), 5.35-5.60 (2H, m, $CH_3C\underline{H}C\underline{H}$) and 7.51 (5H, m, Ph<u>H</u>); δ_C (50 MHz, $CDCl_3$) 18.04 ($\underline{C}H_3$), 59.85 ($CH\underline{C}H_2S$), 116.9 ($C\underline{H}C\underline{H}CH_2S$), 128.3 (<u>C</u>H aromatic), 129.0 (<u>C</u>H aromatic), 133.6 (<u>C</u>H aromatic) and 138.4 (*ipso* aromatic <u>C</u>CH); m/z (APCI Cl^+, NH_3/Na) 219 (9, MNa^+), 197 (19, MH^+), 157 (6), 144 (6) and 143 (100).

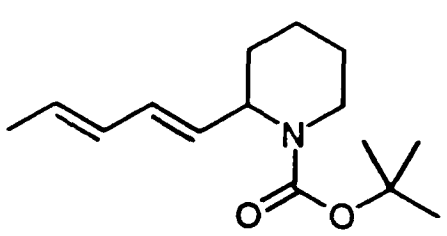
<u>*N*-(*tert*-Butyloxycarbonyl)-2-[(*E*)-1-benzoyloxy-2-phenylsulfonyl-3-pentenyl]-piperidine</u>



To a solution of 1-(phenylsulfonyl)-2-butene (980mg, 5.0mmol, 1.0eq) in tetrahydrofuran (45ml) cooled to -40°C under an atmosphere of argon was added *N,N,N',N'*-tetramethylethylenediamine (580mg, 5.0mmol, 1.0eq). The solution was stirred at -40°C for 5 minutes at which time *n*-butyl lithium (1.40M, 3.60ml, 5.0mmol, 1.0eq) was added dropwise at a rate which maintained the temperature below -40°C. The reaction mixture was stirred at -40°C for 30 minutes, then *N*-(*tert*-butyloxycarbonyl)-2-formylpiperidine **282** (1.065g, 5.0mmol, 1.0eq) in tetrahydrofuran (10ml) was added dropwise at a rate which maintained the temperature below -40°C. The reaction mixture was stirred at -40°C for a further 2 hours, then benzoyl chloride

(770mg, 5.0mmol, 1.0eq) was added dropwise at a rate which maintained the temperature below -40°C. The solution was allowed to warm to ambient, then diluted with saturated aqueous sodium hydrogencarbonate (100ml) and ethyl acetate (100ml) following which the layers were separated. The aqueous portion was extracted with dichloromethane (2x50ml). The combined organic portions were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 1:1) to afford *N*-(*tert*-butyloxycarbonyl)-2-[(3E)-1-benzoyloxy-2-phenylsulfonyl-3-pentenyl)-piperidine as a yellow foam (2.50g, 98%).

N-(*tert*-Butyloxycarbonyl)-2-[(*E,E*)-1,3-pentadienyl]-piperidine **299**



Method i

To a solution of *N*-(*tert*-butyloxycarbonyl)-2-[(*E*)-1-benzoyloxy-2-phenylsulfonyl-3-pentenyl]-piperidine (1.56g, 3.04mmol, 1.0eq) and sodium hydrogenphosphate (4.32g, 30.4mmol, 10.0eq) in tetrahydrofuran:methanol (3:1, 36ml) cooled to -20°C under an atmosphere of argon was added sodium amalgam (6%, 5.83g, 15.2mmol, 5.0eq). The reaction mixture was stirred at -20°C for 2 hours then allowed to warm to ambient as which time it was stirred for 17 hours. The reaction was quenched by addition of water (50ml) and the mixture was extracted with diethyl ether (2x50ml) and dichloromethane (50ml). The combined organic extracts were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 1:9) to afford the product as a colourless oil (344mg, 45%).

Method ii

To a flask flushed with argon was transferred samarium iodide (0.1M in tetrahydrofuran, 100.0ml, 10.0mmol, 5.0eq). 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (3.84g, 30.0mmol, 15.0eq) was then added turning the blue/green solution purple. *N*-(*tert*-Butyloxycarbonyl)-2-[(3*E*)-1-benzoyloxy-2-phenylsulfonyl-3-pentenyl)-piperidine (1.026g, 2.0mmol, 1.0eq) in tetrahydrofuran (10ml) was added immediately turning the purple solution indigo. The reaction mixture has stirred at ambient for 3 hours at which time it was diluted with diethyl ether (50ml) and washed with dilute aqueous hydrochloric acid (1M, 50ml), water (50ml), saturated aqueous sodium hydrogen carbonate (50ml) and saturated aqueous sodium chloride (50ml). The organic solution was then dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C, gradient 0:1 to 1:9) to afford the product as a colourless oil (233mg, 46%).

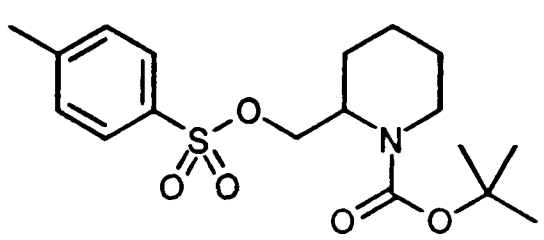
Method iii

To a solution of 1-(phenylsulfonyl)-2-butene **296** (980mg, 5.0mmol, 1.0eq) in tetrahydrofuran (45ml) cooled to -40°C under an atmosphere of argon was added *N,N,N',N'*-tetramethylethylenediamine (580mg, 5.0mmol, 1.0eq). The solution was stirred at -40°C for 5 minutes at which time *n*-butyl lithium (1.20M, 4.17ml, 5.0mmol, 1.0eq) was added dropwise at a rate which maintained the temperature below -40°C. The reaction mixture was stirred at -40°C for 30 minutes, then *N*-(*tert*-butyloxycarbonyl)-2-formylpiperidine **282** (1.065g, 5.0mmol, 1.0eq) in tetrahydrofuran was added dropwise at a rate which maintained the temperature below -40°C. The reaction mixture was stirred at -40°C for a further 90 minutes, then benzoyl chloride (770mg, 5.5mmol, 1.1eq) was added dropwise at a rate which maintained the temperature below -40°C. The solution was allowed to warm to 0°C over 2 hours,

then cooled to -20°C and methanol (15ml) and sodium hydrogenphosphate (7.10g, 50.0mmol, 10.0eq) were added. The mixture was stirred at -20°C for 5 minutes at which time sodium amalgam (6%, 9.58g, 25.0mmol, 5.0eq) was added. The reaction mixture was stirred at -20°C for 2 hours, then allowed to warm to ambient at which time it was stirred for 15 hours. The reaction mixture was then diluted with water (50ml) and diethyl ether (50ml) following which the layers were separated. The aqueous portion was extracted with diethyl ether (2x50ml) and dichloromethane (50ml). The combined organic portions were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo.* The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 1:9) to afford the product as a colourless oil (524mg, 49%).

m/z HIRES Found 252.1964, $C_{15}H_{25}NO_2+H^+$ requires 252.1963; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2935s (C-H str.), 1693s, (C=O str.), 1508w, 1411s, 1365s, 1270m, 1163s, 1035m, 988m, 870m and 668w; δ_H (500 MHz, $CDCl_3$) 1.38-1.79 (18H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$, $C(C\underline{H}_3)_3$ and $C\underline{H}_3CHCH$ (3H, d, *J* 6.5Hz)), 2.71-2.89 (3H, m, $NC\underline{H}_2$ and $NC\underline{H}$), 5.46 (1H, dd, *J* 15.0 and 5.0Hz, $C\underline{H}CHN$), 5.64 (1H, dq, *J* 13.5 and 6.5Hz, $CH_3C\underline{H}CH$) and 5.95-6.06 (2H, m, $CH_3CHC\underline{H}C\underline{H}$); δ_C (125 MHz, $CDCl_3$) 18.03 ($\underline{C}H_3CHCH$), 19.52 ($CH_2\underline{C}H_2CH_2$), 25.50 ($\underline{C}H_2CH_2N$) 28.39 ($C(\underline{C}H_3)_3$), 29.33 ($NCH\underline{C}H_2$), 39.69 ($N\underline{C}H_2$), 51.78 ($\underline{C}HN$), 128.7, 129.5, 131.1 and 131.2 ($CH_3\underline{C}H\underline{C}H\underline{C}H\underline{C}H$); m/z (Probe CI^+, NH_3) 252 (5, MH^+), 210 (10), 208 (8), 207 (41), 198 (18) and 196 (100).

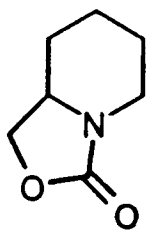
N-(*tert*-Butyloxycarbonyl)-2-(4-toluenesulfonyl)-methylpiperidine **300**



To a solution of *N*-(*tert*-butyloxycarbonyl)-2-hydroxymethylpiperidine **285** (9.20g, 42.8mmol, 1.0eq) and pyridine (6.76g, 85.6mmol, 2.0eq) in dichloromethane (50ml) cooled to 0°C under an atmosphere of argon was added *para*-toluenesulfonyl chloride (8.97g, 47.1mmol, 1.1eq) in a single portion. The reaction mixture was allowed to warm to ambient at which stage it was stirred for 24 hours. The reaction mixture was diluted with diethyl ether (200ml) then washed with dilute aqueous hydrochloric acid (1M, 2x50ml), saturated aqueous sodium hydrogen carbonate (50ml) and saturated aqueous sodium chloride (50ml). The organic solution was dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The obtained yellow oil was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 1:1) to afford

(i)

Hexahydrooxazolo(3,4-a)pyridin-3-one **301**

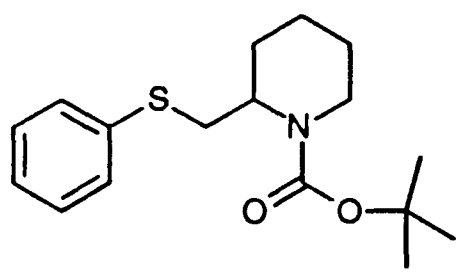


Colourless oil (2.06g, 34%). m/z HIRES Found 142.0868, $C_7H_{11}NO_2+H^+$ requires 142.0868; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2942s (C-H str.), 2859s (C-H str.), 1752 (C=O str.), 1480w 1447m, 1425s, 1358w, 1244m 1173w, 1135m, 1073w, 1043s, 993m, 944m, 850w and 763m; δ_H (500 MHz, $CDCl_3$) 1.21-1.85 (6H, m, $CHC\underline{H}_2C\underline{H}_2C\underline{H}_2$), 2.76 (1H, m, $NCH\underline{H}'$), 3.59 (1H, m, $OCH_2C\underline{H}$) 3.75-3.82 (2H, m, $NC\underline{H}H'$ and $OC\underline{H}H'$) and 4.34 (1H, m, $OCH\underline{H}'$); δ_C (125 MHz, $CDCl_3$) 23.23 ($CH_2\underline{C}H_2CH_2$), 23.76 ($\underline{C}H_2CH_2N$), 30.04 ($\underline{C}H_2CH_2CH_2$), 40.95 ($\underline{C}H_2N$), 54.00 ($OCH_2\underline{C}H$), 67.81 ($O\underline{C}H_2CH$), and 156.6 ($\underline{C}$=O); m/z (APCI Cl^+, NH_3/Na) 143 (21), 142 (100, MH^+) and 116 (5).

and (ii)

N-(*tert*-Butyloxycarbonyl)-2-(4-toluenesulfonyl)-methylpiperidine **300** as a white crystalline solid (1.70g, 11%). m/z HIRES Found 370.1688, $C_{18}H_{27}NO_5S+H^+$ requires 370.1688; υ_{max} (FT-IR, KBr disc, cm^{-1}) 2976s (C-H str.), 2868s, 1928w, 1692s (C=O str.), 1593m, 1489w, 1455m, 1413s, 1366s, 1305m, 1294m, 1277m, 1255m, 1189s, 1176s, 1145s, 1121m, 1081s, 1050m, 1016m, 952w, 889w, 844w, 812s, 702w and 655s; δ_H (500 MHz, $CDCl_3$) 1.45 (9H, s, $C(C\underline{H}_3)_3$), 1.46-1.83 (6H, m, $CHC\underline{H}_2C\underline{H}_2C\underline{H}_2$), 2.48 (3H, s, $PhC\underline{H}_3$), 2.73-2.79 (1H, m, $NC\underline{H}$), 3.35 (1H, dd, *J* 9.0 and 6.0Hz, $SOC\underline{H}H'$), 3.43 (1H, t, *J* 8.5Hz, $SOCH\underline{H}'$), 3.89-3.99 (1H, m, $NC\underline{H}H'$), 4.21-4.22 (1H, m, $NCH\underline{H}'$) 7.40 (2H, d, *J* 8.5Hz, $Ph\underline{H}$) and 7.91 (2H, d, *J* 8.5Hz, $Ph\underline{H}$); δ_C (125 MHz, $CDCl_3$) 19.17 ($CHCH_2\underline{C}H_2CH_2$), 21.73 ($Ph\underline{C}H_3$), 24.99 & 25.20 ($CH\underline{C}H_2CH_2\underline{C}H_2$), 28.43 ($C(\underline{C}H_3)_3$), 39.93 ($N\underline{C}H_2$), 50.55 ($SO\underline{C}H_2$), 59.06 ($N\underline{C}H$), 79.01 ($\underline{C}(CH_3)_3$), 127.0 ($\underline{C}H$ aromatic), 130.2 ($\underline{C}H$ aromatic), 141.6 ($\underline{C}CH_3$ ipso aromatic), 146.8 ($\underline{C}SO_3$ ipso aromatic) and 155.3 ($\underline{C}$=O); m/z (APCI Cl^+, NH_3/Na) 392 (12, MNa^+), 270 (15), 173 (12), 172 (100), 160 (17), 117 (5) and 116 (87).

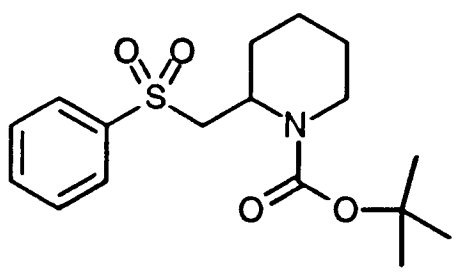
<u>*N*-(*tert*-Butyloxycarbonyl)-2-phenylsulfanylmethylpiperidine **304**</u>



To a solution of *N*-(*tert*-butyloxycarbonyl)-2-hydroxymethylpiperidine **285** (1.075g, 5.0mmol, 1.0eq) and phenyl disulphide (3.27g, 15.0mmol, 3.0eq) in tetrahydrofuran (25ml) under an atmosphere of argon was added tributylphosphine (4.04g, 20.0mmol, 4.0eq). The reaction mixture was heated under reflux for 167 hours. The solution was then diluted with diethyl ether (50ml), washed with aqueous sodium hydroxide (2x50ml) and saturated aqueous sodium chloride (50ml). The organic solution was then dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The

crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C, gradient 0:1 to 1:9) to afford the product as a colourless oil (1.54g, 100%). m/z HIRES Found 308.1684, $C_{17}H_{25}NO_2S+H^+$ requires 308.1684; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2976m (C-H str.), 2933s (C-H str.), 2859m, 1690 (C=O str.), 1584w, 1480m, 1438w, 1409s, 1364s, 1340w, 1314m, 1275m, 1244m, 1158s, 1089m, 1028m, 1005w, 937w, 873m, 738s and 691m; δ_H (500 MHz, $CDCl_3$) 1.41 (9H, s, $OC(C\underline{H}_3)_3$), 1.43-1.96 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 2.73-2.78 (1H, m, $SCH_2C\underline{H}N$), 3.05-3.16 (2H, m, $NC\underline{H}_2$), 4.01-4.03 (1H, m, PhSCH$\underline{H}$'), 4.39 (1H, m, PhSC$\underline{H}$H') and 7.16-7.38 (5H, m, Ph$\underline{H}$); δ_C (125 MHz, $CDCl_3$) 18.66 ($CH_2\underline{C}H_2CH_2$), 25.19 ($\underline{C}H_2CH_2N$) 26.37 ($CH\underline{C}H_2CH_2CH_2$), 28.47 ($OC(\underline{C}H_3)_3$), 33.28 ($N\underline{C}H_2$), 38.92 ($S\underline{C}H_2CH$), 49.47 ($SCH_2\underline{C}H$), 79.55 ($O\underline{C}(CH_3)_3$) 125.9 ($\underline{C}H$ aromatic), 128.9 ($\underline{C}H$ aromatic), 129.0 ($\underline{C}H$ aromatic), 136.3 (*ipso* aromatic $\underline{C}SCH_2$) and 154.8 ($\underline{C}$=O); m/z (Probe CI^+, NH_3) 309 (3), 308 (18, MH^+), 269 (11), 252 (32), 209 (14), 208 (100), 184 (11), 85 (5) and 84 (93).

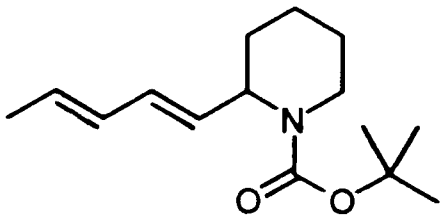
N-(*tert*-Butyloxycarbonyl)-2-phenylsulfonylmethylpiperidine **297**



A solution of *N*-(*tert*-butyloxycarbonyl)-2-phenylsulfanylmethylpiperidine **304** (153mg, 0.5mmol, 1.0eq), Oxone® ($2KHSO_5.KHSO_4.K_2SO_4$, 922mg, 1.5eq, 3.0eq) and wet alumina (10:90 w:w alumina:water, 500mg) in chloroform (5ml) was heated under reflux. The reaction mixture was stirred at reflux for 6 hours. The solution was then cooled and the organic solution decanted from the reaction flask. The remaining solids were then extracted with chloroform (3x25ml). The organic portions were combined and the volatiles removed in *vacuo* to afford the product as a colourless oil (145mg, 86%). (m.p. 95-96°C); (Found C, 60.1; H, 7.5; N, 4.1. $C_{17}H_{25}NO_4S$ requires

C, 60.1; H, 7.4; N, 4.1%); υ_{max} (FT-IR, KBr disc, cm^{-1}) 2975s (C-H str.), 2934s (C-H str.), 2864m, 1690 (C=O str.), 1585w, 1477m, 1447m, 1414s, 1365s, 1319s, 1306s, 1278m, 1248m, 1148s, 1086m, 1029w, 1001w, 873w and 750m; δ_H (500 MHz, $CDCl_3$) 1.42 (9H, s, $OC(C\underline{H}_3)_3$), 1.44-1.90 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 2.56 (1H, m, NCH$\underline{H}$'), 3.31-3.36 (2H, m, NC$\underline{H}$H' and NC$\underline{H}$), 3.91 (1H, m, SCH$\underline{H}$'), 4.79-4.80 (1H, m, SC$\underline{H}$H') and 7.55-7.96 (5H, m, Ph$\underline{H}$); δ_C (125 MHz, $CDCl_3$) 18.84 ($CH_2\underline{C}H_2CH_2$), 24.90 ($\underline{C}H_2CH_2N$) 28.04 ($CH\underline{C}H_2CH_2CH_2$), 28.28 ($OC(\underline{C}H_3)_3$), 38.96 ($N\underline{C}H_2$), 46.20 ($SCH_2\underline{C}H$), 55.70 ($S\underline{C}H_2CH$), 80.10 ($O\underline{C}(CH_3)_3$), 127.8 ($\underline{C}H$ aromatic), 129.3 ($\underline{C}H$ aromatic), 133.7 ($\underline{C}H$ aromatic), 139.7 (*ipso* aromatic $\underline{C}SCH_2$) and 154.1 ($\underline{C}$=O); m/z (APCI Cl^+, NH_3/Na) 362 (3, MNa^+), 242 (10), 241 (27) and 240 (100).

<u>*N*-(*tert*-Butyloxycarbonyl)-2-[(*E*,*E*)-1,3-pentadienyl]-piperidine **299**</u>



Method i

To a solution of *N*-(*tert*-butyloxycarbonyl)-2-phenylsulfonylmethylpiperidine **297** (1.69g, 5.0mmol, 1.0eq) in tetrahydrofuran (45ml) cooled to -78°C under an atmosphere of argon was added *N,N,N',N'*-tetramethylethylenediamine (580mg, 5.0mmol, 1.0eq). The solution was stirred at -78°C for 5 minutes at which time *n*-butyl lithium (1.35M, 3.70ml, 50.0mmol, 1.0eq) was added dropwise at a rate which maintained the temperature below -70°C. The reaction mixture was stirred at -78°C for 30 minutes, then crotonaldehyde (350mg, 5.0mmol, 1.0eq) was added dropwise at a rate which maintained the temperature below -70°C. The reaction mixture was stirred at -78°C for a further 2 hours, then benzoyl chloride (3.09g, 22.0mmol, 1.1eq) was added in a single portion. The solution was allowed to warm to ambient over 2

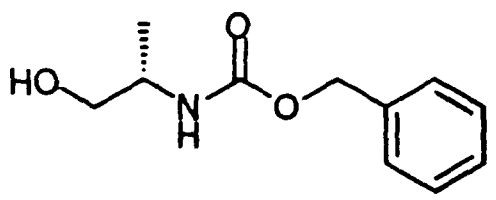
hours, then stirred for 46 hours. The reaction mixture was then diluted with saturated aqueous sodium hydrogen carbonate (100ml) and ethyl acetate (50ml) following which the layers were separated. The aqueous portion was then extracted with dichloromethane (2x50ml). The combined organic portions were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo.* The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 1:1) to afford *N*-(*tert*-butyloxycarbonyl)-2-[(*E*)-1-phenylsulfonyl-2-benzoyloxy-3-pentenyl]-piperidine as a pale yellow foam (2.43g, 95%). To this product and sodium hydrogenphosphate (6.73g, 47.7mmol, 9.54eq) in tetrahydrofuran:methanol (3:1, 60ml) cooled to -20°C under an atmosphere of argon was added sodium amalgam (6%, 9.09g, 23.7mmol, 4.74eq). The reaction mixture was stirred at -20°C for 2 hours at which time it was allowed to warm to ambient and stirred for 18 hours. The reaction mixture was quenched by addition of water (50ml), then extracted with diethyl ether (50ml), ethyl acetate (50ml), diethyl ether (50ml) and dichloromethane (50ml). The combined organic extracts were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo.* The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether, gradient 1:9 to 1:1) to afford *N*-(*tert*-butyloxycarbonyl)-2-[(*E*,*E*)-1,3-pentadienyl]-piperidine **299** as a colourless oil (864mg, 73%).

Method ii

To a solution of *N*-(*tert*-butyloxycarbonyl)-2-phenylsulfonylmethylpiperidine **297** (1.69mg, 5.0mmol, 1.0eq) in tetrahydrofuran (45ml) cooled to -78°C under an atmosphere of argon was added *N,N,N',N'*-tetramethylethylenediamine (580mg, 5.0mmol, 1.0eq). The solution was stirred at -78°C for 5 minutes at which time *n*-butyl lithium (1.20M, 4.15ml, 5.0mmol, 1.0eq) was added dropwise at a rate which maintained the temperature below -70°C. The reaction mixture was stirred at -78°C for 30 minutes, then crotonaldehyde (350mg, 5.0mmol, 1.0eq) was added in a single

portion. The reaction mixture was stirred at -78°C for a further 90 minutes, then benzoyl chloride (770mg, 5.0mmol, 1.0eq) was added in a single portion. The solution was allowed to warm to ambient over 2 hours, then cooled to -20°C and methanol (15ml) and sodium hydrogenphosphate (7.10g, 50.0mmol, 10.0eq) were added. The mixture was stirred at -20°C for 5 minutes at which time sodium amalgam (6%, 9.58g, 25.0mmol, 5.0eq) was added. The reaction mixture was stirred at -20°C for 2 hours, then allowed to warm to ambient over 2 hours at which time it was stirred for 14 hours. The reaction mixture was then diluted with water (50ml) and diethyl ether (100ml) following which the layers were separated. The aqueous portion extracted with ethyl acetate (50ml), diethyl ether (50ml) and dichloromethane (50ml). The combined organic extracts were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 1:9) to afford *N*-(*tert*-butyloxycarbonyl)-2-[(*E*,*E*)-1,3-pentadienyl]-piperidine **299** as a colourless oil (725mg, 58%).

(*S*)-*N*-(Benzyloxycarbonyl)-1-methylethan-2-olamine **336**



Method i

To a suspension of lithium aluminium hydride (10.64g, 0.280mol, 2.0eq) in tetrahydrofuran (500ml) cooled to 0°C under an atmosphere of argon was added *L*-alanine **335** (12.50g, 0.140mol, 1.0eq) in portions over a 20 minutes period. This mixture was then refluxed for 16 hours. The mixture was then cooled to 0°C and aqueous sodium hydroxide (2M, 70ml) was added. After stirring for 3 hours at ambient, the mixture was filtered and the solids washed with tetrahydrofuran (200ml). The solids were then suspended in tetrahydrofuran (100ml) and the resulting mixture

was refluxed for 1 hour. The mixture was then cooled, filtered and the solids washed with tetrahydrofuran (100ml). This procedure was repeated a further two times. To the combined tetrahydrofuran solutions was added aqueous sodium hydroxide (2M, 168ml) and benzoyl chloroformate (25.08g, 0.147mol, 1.05eq). After stirring for 1 hour at ambient the layers were separated and the aqueous layer was extracted with ethyl acetate (50ml). The combined organics were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude alcohol was titurated with petroleum ether (30-40°C, 3x25ml), then recrystallised from diethyl ether/petroleum ether 30-40°C affording the product as a white crystalline solid (12.64g, 43%).

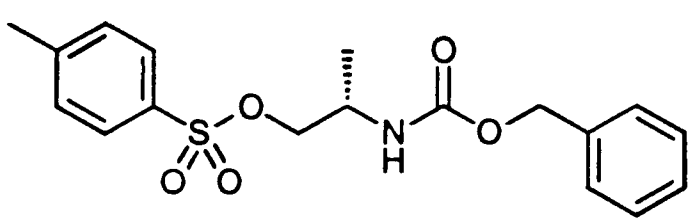
Method ii

To a solution of *L*-alanine **335** (22.25g, 0.25mol, 1.0eq) in methanol (250ml) under an atmosphere of argon was added thionyl chloride (29.75g, 0.25mol, 1.0eq) dropwise over a period of 3 hours. The reaction mixture was then stirred at ambient for 48 hours. The volatiles were removed in *vacuo* yielding (*S*)-alanine methyl ester hydrochloride as a brown solid. The crude material was suspended in ethyl acetate (100ml) and saturated aqueous sodium hydrogen carbonate (500ml) was added resulting in vigorous effervescence. To the stirred, biphasic mixture was added benzoyl chloroformate (42.62g, 0.25mol, 1.0eq) dropwise. The reaction mixture was stirred for 24 hours at which stage it was diluted with ethyl acetate (200ml). The layers were separated and the aqueous portion extracted with ethyl acetate (100ml). The combined organic extracts were washed with aqueous hydrochloric acid (1M, 2x50ml) and saturated aqueous sodium hydrogen carbonate solution (50ml), dried over magnesium sulphate, filtered and the volatiles removed in *vacuo* affording (*S*)-*N*-benzyloxycarbonyl-alanine methyl ester as a white crystalline solid. The crude material was dissolved in methanol (250ml) and cooled to 0°C under an atmosphere of argon. To this solution was added sodium borohydride (9.50g, 0.25mol, 1.0eq) portionwise over a 5 minute period. The reaction mixture was stirred for 1 hour at 0°C

at which time concentrated hydrochloric acid was added to quench the reaction. The pH was then adjusted to 7 by addition of solid sodium hydrogen carbonate, and the solvent removed in *vacuo*. The resulting white solid was suspended in dichloromethane:methanol (1:1, 450ml), filtered and the solvent removed in *vacuo* to yield a white crystalline solid. This was dissolved in dichloromethane (200ml) and water (200ml). The layers were separated and the aqueous portion was extraced with ethyl acetate (100ml) and dichloromethane (100ml). The combined organic portions were dried over magnesium sulphate, filtered and volatiles removed in *vacuo* to afford the product as a white crystalline solid (51.72g, 99%).

(m.p. 78-82°C); $[\alpha]^{D}_{22}$ -9.0 (c 1, $CHCl_3$); (Found C, 63.10; H, 7.45; N, 6.55. $C_{11}H_{15}NO_3$ requires C, 63.15; H, 7.25; N, 6.70%); υ_{max} (FT-IR, KBr disc, cm^{-1}) 3310s (O-H str.), 2974m (C-H str.) 2949m (C-H str.), 1685vs (C=O str.), 1541s, 1454m, 1342s, 1305m, 1264s, 1155w, 1075s, 1044s, 991w, 986w, 938w, 909w, 845w, 782w, 749m, 730w, 696s and 669m; δ_H (300 MHz, $CDCl_3$) 1.17 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 2.35 (1H, br s, O<u>H</u>), 3.47-3.56 (1H, m, C<u>H</u>HOH), 3.64-3.70 (1H, m, CH<u>H</u>OH), 3.80-3.88 (1H, m, C<u>H</u>CH_3), 4.91 (1H, br s, N<u>H</u>), 5.10 (2H, s, $C\underline{H}_2Ph$) and 7.35 (5H, s, Ph<u>H</u>); δ_C (50 MHz, $CDCl_3$) 17.26 ($CH\underline{C}H_3$), 48.95 ($\underline{C}HCH_3$), 66.58 ($\underline{C}H_2OH$), 66.82 ($\underline{C}H_2Ph$), 128.1, 128.5 (<u>C</u>H aromatic), 136.3 (*ipso* aromatic <u>C</u>CH) and 156.6 (<u>C</u>=O); m/z (Probe CI^+, NH_3) 227 (4, MNH_4^+), 210 (37, MH^+), 203 (3), 192 (4), 178 (2), 166 (11), 134 (8), 119 (77), 108 (22), 102 (100), 91 (43) and 58 (6).

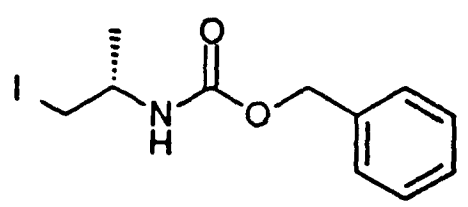
<u>(*S*)-*N*-(Benzyloxycarbonyl)-1-methyl-2-(toluene-4-sulfonyloxy)-ethylamine **338**</u>



To a solution of (*S*)-*N*-(benzyloxycarbonyl)-1-methylethan-2-olamine **336** (10.0g, 47.8mmol, 1.0eq) in pyridine (15ml) cooled to 0°C under an atmosphere of argon was

added *para*-toluenesulphonyl chloride (9.31g, 48.8mmol, 1.02eq) in a single portion. The mixture was allowed to warm to room temperature at which stage it was stirred for 16 hours. The reaction mixture was then diluted with diethyl ether (50ml), filtered and the solids washed with dichloromethane (50ml). The combined organic extracts were washed with dilute hydrochloric acid (1M, 3x50ml), saturated aqueous sodium hydrogen carbonate (50ml) and saturated aqueous sodium chloride (50ml). The organic solution was then dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The obtained yellow oil was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 1:3) yielding the product as a crystalline white solid (12.88g, 74%). (m.p. 68-69°C); $[\alpha]^{D}_{22}$ -12.4 (c 1, $CHCl_3$); (Found C, 59.25; H, 5.95; N, 4.00. $C_{18}H_{21}NO_5S$ requires C, 59.50; H, 5.80; N, 3.85%); υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3326m (N-H str.), 3034w, 2981s (C-H str.), 1703s (C=O), 1598m, 1530s, 1455m, 1360s, 1240s, 1190s, 1177s, 1097m, 1064m, 1030w, 1020w, 978s, 834s, 816s, 778m, 740m 699m and 669s; δ_H (300 MHz, $CDCl_3$) 1.17 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 2.42 (3H, s, $PhC\underline{H}_3$), 3.93-4.05 (3H, m, $C\underline{H}_2OSO_2$ and $C\underline{H}CH_3$), 4.92 (1H, br s, N<u>H</u>), 5.04 (2H, s, $C\underline{H}_2Ph$), 7.35 (7H, m, Ph<u>H</u>) and 7.76 (2H, d, *J* 8.0Hz, Ph<u>H</u>); δ_C (50 MHz, $CDCl_3$) 16.90 ($CH\underline{C}H_3$), 21.57 ($Ph\underline{C}H_3$), 45.87 ($\underline{C}HCH_3$), 66.55 ($\underline{C}H_2Ph$), 72.25 ($\underline{C}H_2OSO_2$), 127.9, 128.1, 128.5, 129.9 (<u>C</u>H aromatic), 136.4, 145.0 (*ipso* aromatic <u>C</u>CH) and 155.6 (<u>C</u>=O); m/z (Probe CI^+, NH_3) 381 (47, MH^+), 300 (12), 293 (17), 282 (25), 220 (13), 209 (33), 192 (100), 119 (28) and 91 (13).

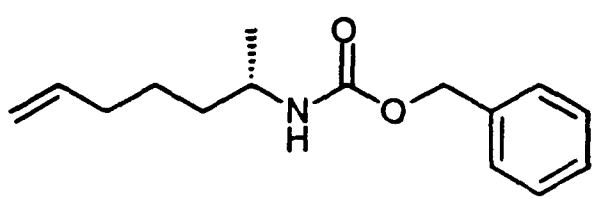
<u>(*S*)-*N*-(Benzyloxycarbonyl)-1-methyl-2-iodoethylamine **337**</u>



To a solution of (*S*)-*N*-(benzyloxycarbonyl)-1-methyl-2-(toluene-4-sulfonyloxy)-ethylamine **338** (12.88g, 35.5mmol, 1.0eq) in acetone (100ml) cooled to 0°C under an atmosphere of argon was added solid sodium iodide (53.25g, 355.0mmol, 10.0eq).

The reaction mixture was allowed to warm to room temperature at which stage it was stirred for 48 hours. The resulting orange solution was diluted with ethyl acetate (150ml), filtered and the solids were washed with additional ethyl acetate (100ml). The organic solution was washed with water (50ml), aqueous sodium thiosulphate (10%, 50ml) and aqueous saturated sodium chloride (50ml). The resulting colourless solution was dried over magnesium sulphate, filtered and the volatiles removed in *vacuo* affording the product as a white crystalline solid (90.74g, 86%). (m.p. 75-77.5°C); $[\alpha]^{D}_{22}$ -16.5 (c 1, $CHCl_3$); (Found C, 41.60; H, 4.40; N, 4.30. $C_{11}H_{14}INO_2$ requires C, 41.40; H, 4.40; N, 4.40%); υ_{max} (FT-IR, KBr disc, cm^{-1}) 3340s (N-H str.), 3061w, 3033m, 2938s (C-H str), 2935s, 2885m, 1688vs (C=O str.), 1521s, 1464m, 1452s, 1416m, 1382m, 1345s, 1312s, 1255s, 1199s, 1169m, 1095s, 1039m, 1018s, 968m, 948m, 910w, 844s, 833w, 782w, 748s, 728m, 697s and 634w; δ_H (300 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 3.27-3.60 (3H, m, $IC\underline{H}_2C\underline{H}$), 4.83 (1H, br s, N<u>H</u>), 5.08 (2H, s, $C\underline{H}_2Ph$) and 7.33 (5H, s, Ph<u>H</u>); δ_C (50 MHz, $CDCl_3$) 15.10 ($\underline{C}H_2I$), 20.80 ($CH\underline{C}H_3$), 46.33 ($\underline{C}HCH_3$), 66.46 ($\underline{C}H_2Ph$), 127.8, 127.9, 128.2 (<u>C</u>H aromatic), 136.0 (*ipso* aromatic <u>C</u>CH) and 155.1 (<u>C</u>=O); m/z (Probe CI^+, NH_3) 337 (78, MNH_4^+) 320 (100, MH^+), 276 (15), 194 (5), 119 (25), 108 (77) and 91 (50).

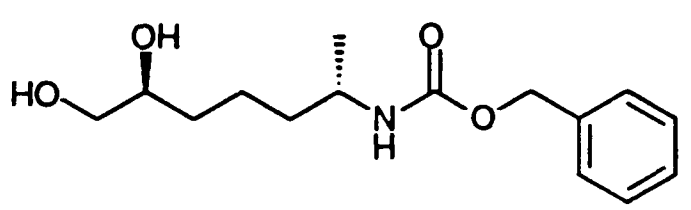
<u>(*S*)-*N*-(Benzyloxycarbonyl)-1-methyl-5-hexenylamine **334**</u>



To magnesium turnings (1.20g, 50.0mmol, 2.0eq) suspended in tetrahydrofuran (50ml) under an atmosphere of argon was added 4-bromo-1-butene (6.75g, 50.0mmol, 2.0eq) in tetrahydrofuran (20ml) over a 20 minutes period. The dark solution was stirred at room temperature until no trace of magnesium turnings remained. The solution was then cooled to -78°C at which stage copper cyanide (2.24g, 25.0mmol, 1.0eq) suspended in tetrahydrofuran (20ml) was added over a 20

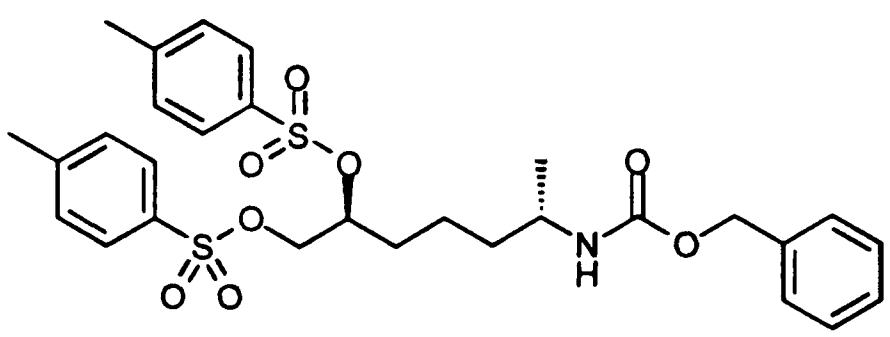
minutes period. The solution was then warmed to 0°C for 5 minutes, following which it was again cooled to -78°C. (*S*)-*N*-(benzyloxycarbonyl)-1-methyl-2-iodoethylamine **337** (7.96g, 25.0mmol, 1.0eq) in tetrahydrofuran (20ml) was then added over a period of 20 minutes at which stage the reaction was warmed to 0°C and stirred for 6 hours. Aqueous saturated ammonium chloride (50ml) was then added to the reaction mixture. The solution was diluted with diethyl ether (50ml), washed with aqueous ammonium hydroxide (1M, 3x50ml), aqueous saturated sodium chloride (50ml), dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 1:9) to yield the product as a white crystalline solid (4.61g, 75%). (m.p. 56-58°C); $[\alpha]^{D}_{22}$ +4.4 (c 1, $CHCl_3$); (Found C, 72.70; H, 8.70; N, 5.75. $C_{15}H_{21}NO_2$ requires C, 72.85; H, 8.55; N, 5.65%); υ_{max} (FT-IR, KBr disc, cm^{-1}) 3318s (N-H str.), 3067w, 2965s (C-H str), 2941m, 2858m, 1683vs (C=O str.), 1542s, 1462m, 1344m, 1276s, 1255s, 1110s, 1086m, 1009w, 927w, 846w, 779w, 754w, 729w and 698w; δ_H (500 MHz, $CDCl_3$) 1.15 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 1.43-1.46 (4H, m, $C\underline{H}_2C\underline{H}_2CHCH_3$), 1.61 (2H, s, $CH_2CHC\underline{H}_2$), 3.73 (1H, m, $CH_3C\underline{H}$), 4.53 (1H, br s, N<u>H</u>), 4.96 (1H, d, *J* 10.0Hz, *E*-C<u>H</u>HCH), 5.01 (1H, d, *J* 16.0Hz, *Z*-CH<u>H</u>CH), 5.10 (2H, s, $C\underline{H}_2Ph$), 5.78 (1H, m, $CH_2C\underline{H}$) and 7.36 (5H, s, Ph<u>H</u>); δ_C (125 MHz, $CDCl_3$) 21.22 ($CH\underline{C}H_3$), 25.20 ($\underline{C}H_2CHCH_3$), 33.48 ($\underline{C}H_2CH_2CHCH_3$), 36.57 ($CH_2CH\underline{C}H_2$), 47.04 ($\underline{C}HCH_3$), 66.47 ($\underline{C}H_2Ph$), 114.7 ($\underline{C}H_2CH$) 128.0, 128.5 (<u>C</u>H aromatic), 136.7 (*ipso* aromatic <u>C</u>CH), 138.5 ($CH_2\underline{C}H$) and 155.1 (<u>C</u>=O); m/z (Probe CI^+, NH_3) 248 (100, MH^+), 204 (13), 187 (6), 178 (5), 134 (16), 112 (7), 108 (24) and 91 (100).

<u>(*S, S*)-*N*-(Benzyloxycarbonyl)-5,6-dihydroxy-1-methylhexylamine **332**</u>



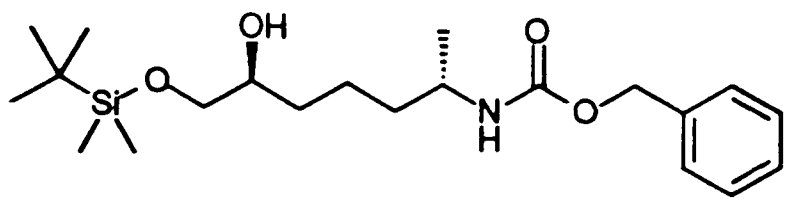
To a solution of AD-mix α (29.26g, 0.0481mmol ($OsO_2(OH)_4^{2-}$), 0.002eq ($OsO_2(OH)_4^{2-}$)) in *tert*-butanol:water 1:1 (220ml) cooled to 0°C under an atmosphere of argon was added (*S*)-*N*-(benzyloxycarbonyl)-1-methyl-5-hexenylamine **334** (5.16g, 20.9mmol, 1.0eq). The reaction mixture was stirred at 0°C for 96 hours at which stage solid sodium sulphate (20g) was added. The solution was allowed to warm to room temperature, diluted with dichloromethane (300ml) and the layers separated. The aqueous layer was extracted with dichloromethane (3x100ml). The combined organic portions were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The obtain brown oil was purified by flash chromatography (SiO_2, diethyl ether) to yield the product as a white crystalline solid (5.19g, 88%). (m.p. 54-56°C); $[\alpha]^D_{22}$ +7.4 (c 1, $CHCl_3$); (Found C, 64.25; H, 8.05; N, 4.65. $C_{15}H_{23}NO_4$ requires C, 64.05; H, 8.25; N, 4.95%); υ_{max} (FT-IR, KBr disc, cm^{-1}) 3350s (N-H str.), 3065w, 2938s (C-H str), 1685vs (C=O str.), 1537s, 1455m, 1379m, 1344m, 1256s, 1159w, 1099s, 1024m, 961w, 941w, 915w, 880w, 843w, 8.21w, 778w and 755w; δ_H (500 MHz, $CDCl_3$) 1.14 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 1.43-1.46 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2CHCH_3$), 2.87 (2H, br s, O<u>H</u>), 3.39-3.43 (1H, m, C<u>H</u>OH), 3.58-3.74 (3H, m, $C\underline{H}_2OH$ and $C\underline{H}CH_3$), 4.76 (1H, br s, N<u>H</u>), 5.07 (2H, s, $C\underline{H}_2Ph$) and 7.34 (5H, s, Ph<u>H</u>); δ_C (125 MHz, $CDCl_3$) 21.25 ($CH\underline{C}H_3$), 21.82 ($\underline{C}H_2CHCH_3$), 32.70 ($\underline{C}H_2CH_2CHCH_3$), 37.00 ($HOCH\underline{C}H_2$), 46.83 ($\underline{C}HCH_3$), 66.45 ($\underline{C}H_2Ph$), 66.57 ($HO\underline{C}H$), 72.00 ($HO\underline{C}H_2$), 128.1, 128.5 (<u>C</u>H aromatic), 136.5 (*ipso* aromatic <u>C</u>CH) and 156.0 (<u>C</u>=O); m/z (Probe CI^+, NH_3) 299 (3, MNH_4^+), 282 (50, MH^+), 238 (50), 191 (6), 174 (5), 146 (5), 134 (15), 108 (32) and 91 (100).

<u>(*S, S*)-*N*-(Benzyloxycarbonyl)-5,6-di(toluene-4-sulfonyloxy)-1-methylhexylamine **342**</u>



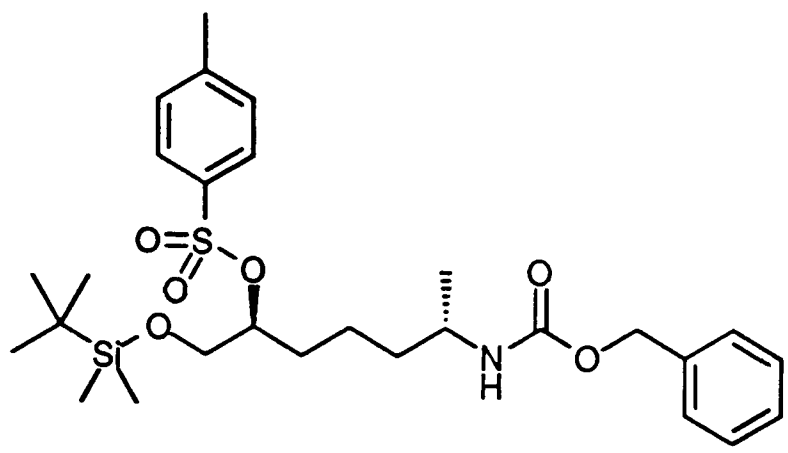
To a solution of (*S*, *S*)-*N*-(benzyloxycarbonyl)-5,6-dihydroxy-1-methylhexylamine **332** (566mg, 2.0mmol, 1.0eq) in pyridine (25ml) cooled to 0°C under an atmosphere of argon was added *para*-toluenesulphonyl chloride (777mg, 4.08eq, 2.04eq) in a single portion. the reaction mixture was allowed to warm to room temperature at which stage it was stirred for 16 hours. The mixture was then diluted with dichloromethane (50ml), washed with dilute hydrochloric acid (1M, 3x20ml), aqueous saturated sodium hydrogen carbonate (20ml), water (20ml) and aqueous saturated sodium chloride (20ml). The organic solution was dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 2:1) yielding the product as a colourless gum (381mg, 32%). $[\alpha]^D_{22}$ -38.8 (c 1, $CHCl_3$); m/z HIRES Found 590.1880, $C_{29}H_{35}NO_8S_2+H^+$ requires 590.1916; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3398s (N-H str.), 3035w, 2965s (C-H str), 23.62w, 1718vs (C=O str.), 1598m, 1525s, 1455s, 1366s, 1308w, 1293w, 1241m, 1191s, 1177s, 1097m, 1020w, 913m, 816w, 775w and 737w; δ_H (500 MHz, $CDCl_3$) 1.07 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 1.23-1.63 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2CHCH_3$), 2.43, 2.44 (2x3H, 2xs, $2xPhC\underline{H}_3$), 3.56-3.60 (1H, m, $C\underline{H}CH_3$), 4.02-4.03 (2H, d, *J* 4.5Hz, $C\underline{H}_2OSO_2$), 3.58-3.74 (2H, m, N<u>H</u> and $C\underline{H}OSO_2$), 5.09 (2H, s, $C\underline{H}_2Ph$), 7.29-7.38 (9H, m, Ph<u>H</u>), 7.71 (2H, d, *J* 8.5Hz, Ph<u>H</u>) and 7.73 (2H, d, *J* 8.0Hz, Ph<u>H</u>); δ_C (125 MHz, $CDCl_3$) 20.97 ($CH\underline{C}H_3$), 21.63 ($Ph\underline{C}H_3$ and $\underline{C}H_2CHCH_3$), 30.79 ($\underline{C}H_2CH_2CHCH_3$), 36.41 ($O_2SOCH\underline{C}H_2$), 46.71 ($\underline{C}HCH_3$), 66.53 ($\underline{C}H_2Ph$), 69.35 ($O_2SO\underline{C}H$), 78.51 ($O_2S\underline{C}H_2$), 127.9, 128.0, 128.1, 128.5, 129.8, 129.9 (<u>C</u>H aromatic), 132.3, 133.4 (*ipso* aromatic $\underline{C}CH_3$), 136.6 (*ipso* aromatic $\underline{C}CH_3$), 145.1, 145.2 (*ipso* aromatic $\underline{C}SO_3$) and 155.7 ($\underline{C}$=O); m/z (Probe CI^+, NH_3) 607 (3, MNH_4^+), 590 (8, MH^+), 499 (10), 418 (3), 310 (9), 280 (8), 246 (18), 190 (5), 178 (5), 156 (15), 134 (18), 108 (37) and 91 (100).

(*S*, *S*)-*N*-(Benzyloxycarbonyl)-5-hydroxy-1-methyl-6-(*tert*-butyldimethylsilyloxy)-hexylamine **349**



To a solution of (*S*, *S*)-*N*-(benzyloxycarbonyl)-5,6-dihydroxy-1-methylhexylamine **332** (4.42g, 15.7mmol, 1.0eq) and imidazole (2.14g, 31.4mmol, 2.0eq) in tetrahydrofuran (40ml) under an atmosphere of argon was added *tert*-butyl dimethylsilyl chloride (2.37g, 15.7mmol, 1.0eq) in dichloromethane (10ml). A white precipitate immediately formed. The reaction mixture was stirred at ambient for 48 hours at which stage it was diluted with dichloromethane (200ml). The organic solution was washed with water (2x50ml), dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 1:1) yielding the product as a colourless oil (5.75g, 93%). $[\alpha]^D_{22}$ +68.4 (c 1, $CHCl_3$); m/z HIRES Found 396.2570, $C_{21}H_{37}NO_4Si+H^+$ requires 396.2570; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3327s (N-H str.), 3066w, 2930s (C-H str), 2858s, 1698vs (C=O str.), 1536s, 1462m, 1409, 1379w, 1341w, 1254s, 1094s, 1029m, 1007w, 973w, 940w, 838s, 778s, 737m, 697w and 669w; δ_H (500 MHz, $CDCl_3$) 0.07 (6H, s, $Si(C\underline{H}_3)_2$), 0.90 (9H, s, $SiC(C\underline{H}_3)_3$), 1.15 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 1.34-1.56 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2CHCH_3$), 3.36-3.38 (1H, m, C<u>H</u>OH), 3.59-3.62 (2H, m, $C\underline{H}_2OSi$), 3.70-3.76 (1H, m, $C\underline{H}CH_3$), 4.57 (1H, br s, N<u>H</u>), 5.09 (2H, s, $C\underline{H}_2Ph$) and 7.36 (5H, s, Ph<u>H</u>); δ_C (125 MHz, $CDCl_3$) -5.40 ($Si(\underline{C}H_3)_2$), 18.28 ($Si\underline{C}(CH_3)_3$), 21.18 ($CH\underline{C}H_3$), 21.97 ($\underline{C}H_2CHCH_3$), 25.87 ($SiC(\underline{C}H_3)_3$), 32.56 ($\underline{C}H_2CH_2CHCH_3$), 37.17 ($HOCH\underline{C}H_2$), 47.05 ($\underline{C}HCH_3$), 66.48 ($\underline{C}H_2Ph$), 67.24 ($SiO\underline{C}H_2$), 71.64 ($HO\underline{C}H$), 128.0, 128.5 (<u>C</u>H aromatic), 136.7 (*ipso* aromatic $\underline{C}CH_2$) and 155.8 (<u>C</u>=O); m/z (Probe CI^+, NH_3) 396 (15, MH^+), 352 (12), 294 (4), 244 (2), 230 (3), 202 (7), 134 (6), 112 (18), 108 (16), 92 (15) and 91 (100).

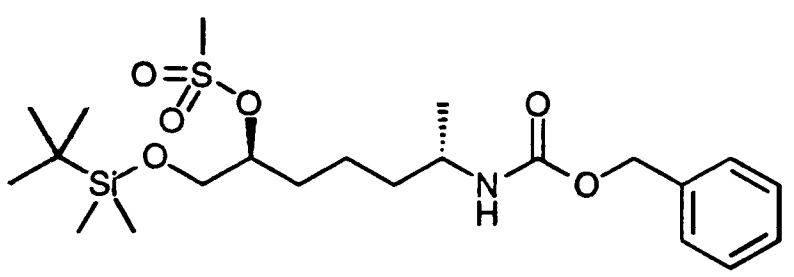
(*S, S*)-*N*-(Benzyloxycarbonyl)-1-methyl-6-(*tert*-butyldimethylsilyloxy)-5-(toluene-4-sulfonyloxy)-hexylamine **350**



To a solution of (*S, S*)-*N*-(benzyloxycarbonyl)-5-hydroxy-1-methyl-6-(*tert*-butyldimethyl silyloxy)-hexylamine **349** (74mg, 0.19mmol, 1.0eq) in pyridine (5ml) cooled to 0°C under an atmosphere of argon was added *para*-toluenesulphonyl chloride (54mg, 0.28mmol, 1.5eq) in a single portion. The solution was allowed to warm to ambient at which stage it was stirred for 72 hours. The reaction mixture was then diluted with dichloromethane (50ml), washed with dilute hydrochloric acid (1M, 3x20ml), aqueous saturated sodium hydrogen carbonate (20ml), water (20ml) and aqueous saturated sodium chloride (20ml). The organic solution was dried over magnesium sulphate, filtered and the volatiles removes in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 1:2) to yield the product as a colourless oil (6mg, 6%). m/z HIRES Found 550.2670, $C_{28}H_{43}NO_6SSi+H^+$ requires 550.2675; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3422s (N-H str.), 2975m, 2935s (C-H str), 2867s, 1686vs (C=O str.), 1670s, 1560m, 1542m, 1523m, 1508m, 1476m, 1420s, 1360s, 1341m, 1313w, 1275m, 1249w, 1166s, 1144s, 1048s, 998w, 955w, 931w, 883w, 869w, 815w and 771w; δ_H (500 MHz, $CDCl_3$) 0.02 (6H, s, $Si(C\underline{H}_3)_2$), 0.85 (9H, s, $SiC(C\underline{H}_3)_3$), 1.08 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 1.33-1.68 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2CHCH_3$), 2.48 (3H, s, $PhC\underline{H}_3$), 3.60-3.67 (3H, m, $C\underline{H}_2OSi$ and $C\underline{H}CH_3$), 4.44-4.50 (2H, m, N<u>H</u> and $C\underline{H}OSO_2$), 5.09 (2H, s, $C\underline{H}_2Ph$), 7.29-7.36 (7H, s, Ph<u>H</u>) and 7.79 (2H, d, *J* 8.5Hz, Ph<u>H</u>); δ_C (125 MHz, $CDCl_3$) -5.52 ($Si(\underline{C}H_3)_2$), 18.22 ($Si\underline{C}(CH_3)_3$), 20.94 ($CH\underline{C}H_3$), 21.04 ($\underline{C}H_2CHCH_3$), 21.56 ($PhC\underline{H}_3$), 25.78 ($Si\underline{C}(CH_3)_3$), 30.91

($\underline{C}H_2CH_2CHCH_3$), 36.67 ($O_2SOCH\underline{C}H_2$), 46.92 ($\underline{C}HCH_3$), 64.04 ($SiO\underline{C}H_2$), 66.51 ($\underline{C}H_2Ph$), 82.87 ($O_2SO\underline{C}H$), 127.8, 128.1, 128.5, 129.7 ($\underline{C}H$ aromatic), 134.4 (*ipso* aromatic $\underline{C}CH_3$), 136.6 (*ipso* aromatic $\underline{C}CH_2$), 144.6 (*ipso* aromatic $\underline{C}SO_3$) and 155.7 ($\underline{C}$=O); m/z (Probe CI+, NH_3) 550 (9, MH^+), 378 (70), 334 (15), 320 (12), 304 (27), 263 (30), 246 (100), 202 (26), 190 (28), 112 (26), 108 (60) and 91 (100).

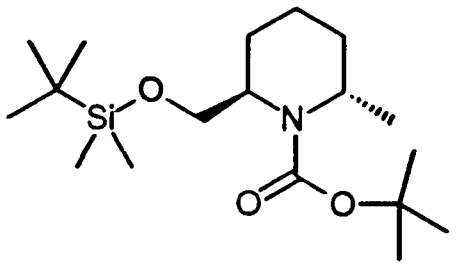
(*S, S*)-*N*-(Benzyloxycarbonyl)-1-methyl-5-(methanesulfonyloxy)-6-(*tert*-butyldimethylsilyloxy)-hexylamine **355**



To a solution of (*S, S*)-*N*-(benzyloxycarbonyl)-5-hydroxy-1-methyl-6-(*tert*-butyldimethyl silyloxy)-hexylamine **349** (5.32g, 13.5mmol, 1.0eq) and triethylamine (2.05g, 20.2mmol,1.5eq) in dichloromethane (50ml) cooled to 0°C under an atmosphere of argon was added methane sulphonyl chloride (1.70g, 14.8mmol, 1.1eq) in dichloromethane (2ml) over a period of 5 minutes. The solution was allowed to warm to ambient at which stage it was stirred for 72 hours. The reaction mixture was then diluted with dichloromethane (200ml), washed with water (100ml), dilute hydrochloric acid (1M, 100ml), aqueous saturated sodium hydrogen carbonate (100ml) and aqueous saturated sodium chloride (100ml). The organic solution was dried over magnesium sulphate, filtered and the volatiles removes in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C 1:2) to yield the product as a colourless oil (5.97g, 93%). $[\alpha]^D_{22}$ +30.5 (c 1, $CHCl_3$); m/z HIRES Found 474.2350, $C_{22}H_{39}NO_6SSi+H^+$ requires 474.2362; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3334s (N-H str.), 2954m, 2932s (C-H str), 2858s, 1719vs (C=O str.), 1528s, 1460s, 1410m, 1349s, 1252s, 1175s, 1097m, 1029w, 973w, 917s, 838s, 815w and 779m; δ_H (500 MHz, $CDCl_3$) 0.09 (6H, s, $Si(C\underline{H}_3)_2$), 0.91 (9H, s, $SiC(C\underline{H}_3)_3$),

1.16 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 1.43-1.68 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2CHCH_3$), 3.03 (3H, s, $SO_2C\underline{H}_3$), 3.70-3.74 (3H, m, $C\underline{H}_2OSi$ and $C\underline{H}CH_3$), 4.63-4.4.65 (2H, m, N<u>H</u> and $C\underline{H}OSO_2$), 5.09 (2H, s, $C\underline{H}_2Ph$) and 7.35 (5H, s, Ph<u>H</u>); δ_C (125 MHz, $CDCl_3$) -5.43 ($Si(\underline{C}H_3)_2$), 18.32 ($Si\underline{C}(CH_3)_3$), 21.09 ($CH\underline{C}H_3$), 21.21 ($\underline{C}H_2CHCH_3$), 25.85 ($Si\underline{C}(CH_3)_3$), 31.00 ($\underline{C}H_2CH_2CHCH_3$), 36.81 ($O_2SOCH\underline{C}H_2$), 38.55 ($O_2S\underline{C}H_3$), 46.83 ($\underline{C}HCH_3$), 64.87 ($SiO\underline{C}H_2$), 66.50 ($\underline{C}H_2Ph$), 83.94 ($O_2SO\underline{C}H$), 128.0, 128.5 (<u>C</u>H aromatic), 136.6 (*ipso* aromatic $\underline{C}CH_2$) and 155.8 (<u>C</u>=O); m/z (Probe CI+, NH_3) 491 (10, MNH_4^+), 474 (52), 379 (10), 320 (9), 270 (11), 264 (16), 246 (37), 230 (15), 202 (33), 186 (14), 153 (7), 134 (15), 112 (42), 108 (41) and 91 (100).

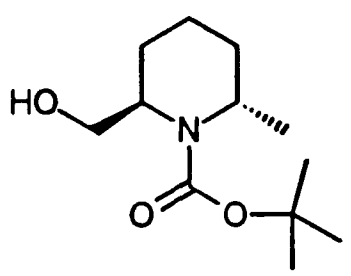
<u>(2*R*, 6*S*)-*N*-(*tert*-Butyloxycarbonyl)-2-(*tert*-butyldimethylsilyloxymethyl)-6-methylpiperidine **163**</u>



A solution of (*S*, *S*)-*N*-(benzyloxycarbonyl)-1-methyl-5-(methanesulfonyloxy)-6-(*tert*-butyldimethylsilyloxy)-hexylamine **355** (946mg, 2.0mmol, 1.0eq), potassium carbonate (276mg, 2.0mmol, 1.0eq) and palladium (II) hydroxide (20% on charcoal, 140mg, 0.2mmol, 0.1eq) in ethanol (10ml) was heated to 50°C under an atmosphere of hydrogen. The reaction mixture was stirred at 50°C for 100 hours. The solution was then cooled, and filtered though a pad of celite® and the solvent removed in *vacuo* affording a white gelatinous solid. This solid was suspended in dichloromethane (50ml) and diluted with aqueous sodium hydroxide (2M, 25ml). The layers were separated, the aqueous portion saturated with sodium chloride, extracted with ethyl acetate (25ml), diethyl ether (25ml) and dichloromethane (25ml). The combined organic extracts were then dried over magnesium sulphate, filtered and the volatiles removed in *vacuo* to afford a yellow oil. This was dissolved in

dichloromethane (20ml) and 4-dimethylaminopyridine (49mg, 0.4mmol, 0.2eq) was added. The solution was then cooled to 0°C under an atmosphere of argon. Di-*tert*-butyl dicarbonate (872mg, 4.0mmol, 2.0eq) in dichloromethane (10ml) was then added dropwise. The reaction mixture was allowed to warm to ambient, then stirred for 111hrs yielding a yellow solution. The solvent was removed in *vacuo* to afford a yellow oil which was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C, 1:9) to yield the product as a colourless oil (638mg, 93%). $[\alpha]^D_{22}$ +34.6 (c 1, $CHCl_3$); m/z HIRES Found 344.2621, $C_{18}H_{37}NO_3Si+H^+$ requires 344.2621; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2955s (C-H str.), 2857m (C-H str.), 1692 (C=O str.), 1473m, 1389s, 1364s, 1321m, 1253m, 1179m, 1089s, 1034w, 1011w, 882w, 871s, 775m; δ_H (500 MHz, $CDCl_3$) 0.07 (6H, s, $Si(C\underline{H}_3)_2$), 0.91 (9H, s, $SiC(C\underline{H}_3)_3$), 1.25 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 1.48 (9H, s, $OC(C\underline{H}_3)_3$), 1.52-1.98 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 3.51 (1H, t, *J* 9.5Hz, OC<u>H</u>H'), 3.69 (1H, dd, *J* 9.5 and 4.5Hz, OCH<u>H</u>'), 3.81 (1H, m, $OCH_2C\underline{H}$) and 4.01 (1H, m, $C\underline{H}CH_3$); δ_C (125 MHz, $CDCl_3$) -5.42 ($Si\underline{C}H_3$), -5.26 ($Si\underline{C}H_3$), 13.34 ($CH_2\underline{C}H_2CH_2$), 18.22 ($Si\underline{C}(CH_3)_3$), 20.52 ($CH\underline{C}H_3$), 20.62 ($\underline{C}H_2CHCH_3$), 25.89 ($SiC(\underline{C}H_3)_3$), 27.05 ($\underline{C}H_2CH_2CH_2$), 28.55 ($OC(\underline{C}H_3)_3$), 46.83 ($\underline{C}HCH_3$), 52.68 ($OCH_2\underline{C}H$), 63.95 ($O\underline{C}H_2CH$), 79.01 ($O\underline{C}(CH_3)_3$) and 155.2 ($\underline{C}$=O); m/z (APCI Cl^+, NH_3/Na) 366 (7, MNa^+), 344 (2, MH^+), 270 (5), 246 (12), 245 (36) and 244 (100).

<u>(2*R*, 6*S*)-*N*-(*tert*-Butyloxycarbonyl)-2-hydroxymethyl-6-methylpiperidine **164**</u>

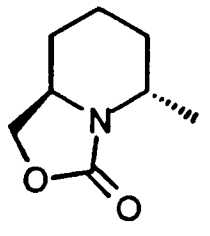


To a solution of (2*R*, 6*S*)-*N*-(*tert*-butyloxycarbonyl)-2-(*tert*-butyldimethylsilyloxymethyl)-6-methylpiperidine **163** (1.029g, 3.0mmol, 1.0eq) in tetrahydrofuran (50ml) under an atmosphere of argon was added tetrabutylammonium fluoride (1M solution in tetrahydrofuran, 4.5ml, 4.5mmol, 1.5eq). The reaction mixture was stirred at ambient

for 19 hours. The solution was then diluted with saturated aqueous sodium chloride (100ml) and ethyl acetate (50ml), the layers separated and the aqueous portion extracted with dichloromethane (50ml). The combined organic extracts were then dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C, gradient 1:1 to 9:1) to afford:

(i)

(4a*R*, 5*S*)-5-Methylhexahydrooxazolo(3,4-*a*)pyridin-3-one **360**

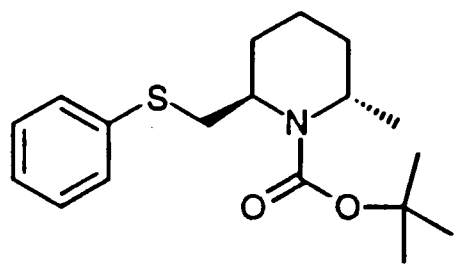


Colourless oil (37mg, 8%). $[\alpha]^{D}_{22}$ +58.3 (c 1, $CHCl_3$); m/z HIRES Found 156.1025, $C_8H_{13}NO_2+H^+$ requires 156.1025; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2936s (C-H str.), 2861m (C-H str.), 1755 (C=O str.), 1479w 1447w, 1410m, 1380s, 1360s, 1329m, 1316m, 1280m, 1260m 1233m, 1162m, 1127m, 1100w, 1087w, 1052m, 1034s, 761m; δ_H (500 MHz, $CDCl_3$) 1.32 (2H, m, $CH_3CHC\underline{H}H'$ axial and $OCH_2CHC\underline{H}H'$ axial), 1.45 (1H, ddt, *J* 13.5, 13.0 and 7.5Hz, $CH_3CHCH_2C\underline{H}H'$ equatorial), 1.59 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 1.68 (1H, m, $CH_3CHCH\underline{H}'$ equatorial), 1.82 (1H, m, $OCH_2CHCH\underline{H}'$ equatorial), 1.89 (1H, m, $CH_3CHCH_2CH\underline{H}'$ axial), 3.18 (1H, ddq, *J* 9.5, 6.5 and 3.0Hz, $C\underline{H}CH_3$), 3.53 (1H, dddd, *J* 11.5, 8.5, 8.0 and 3.0Hz, $OCH_2C\underline{H}$) 3.77 (1H, t, *J* 8.5Hz, $OC\underline{H}H'$) and 4.31 (1H, t, *J* 8.0Hz, $OCH\underline{H}'$); δ_C (125 MHz, $CDCl_3$) 18.81 ($CH\underline{C}H_3$), 23.23 ($CH_2\underline{C}H_2CH_2$), 29.65 ($\underline{C}H_2CHCH_3$), 34.19 ($\underline{C}H_2CH_2CH_2$), 52.01 ($\underline{C}HCH_3$), 57.29 ($OCH_2\underline{C}H$), 67.36 ($O\underline{C}H_2CH$), and 157.0 ($\underline{C}$=O); m/z (APCI Cl^+, NH_3/Na) 156 (100, MH^+) and 130 (30).

and (ii)

(2*R*, 6*S*)-*N*-(*tert*-butyloxycarbonyl)-2-hydroxymethyl-6-methylpiperidine **164** as a colourless oil (549mg, 80%). $[\alpha]^{D}_{22}$ +46.8 (c 1, $CHCl_3$); m/z HIRES Found 230.1756, $C_{12}H_{23}NO_3+H^+$ requires 230.1756; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3447 (O-H str.), 2938s (C-H str.), 1684 (C=O str.), 1457w, 1394s, 1363s, 1326m, 1253w, 1175m, 1125w, 1089m, 1051w, 877w, 772w; δ_H (500 MHz, $CDCl_3$) 1.20 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 1.47 (9H, s, $OC(C\underline{H}_3)_3$), 1.48-1.79 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 3.63-3.70 (2H, m, $OC\underline{H}H'$ and $OCH_2C\underline{H}$), 3.76 (1H, m, $OCH\underline{H}'$), 4.00 (1H, br s, $O\underline{H}$) and 4.23 (1H, m, $C\underline{H}CH_3$); δ_C (125 MHz, $CDCl_3$) 16.03 ($CH_2\underline{C}H_2CH_2$), 18.45 ($CH\underline{C}H_3$), 25.46 ($\underline{C}H_2CHCH_3$) 28.02 ($\underline{C}H_2CH_2CH_2$), 28.46 ($OC(\underline{C}H_3)_3$), 48.43 ($\underline{C}HCH_3$), 54.25 ($OCH_2\underline{C}H$), 66.36 ($O\underline{C}H_2CH$), 79.93 ($O\underline{C}(CH_3)_3$) and 156.5 ($\underline{C}$=O); m/z (Probe CI^+, NH_3) 230 (39, MH^+), 175 (6), 174 (66), 156 (19), 131 (10), 130 (100) and 98 (57).

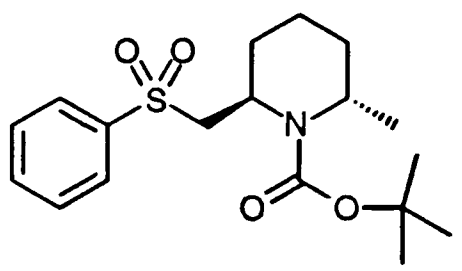
(2*R*, 6*S*)-*N*-(*tert*-Butyloxycarbonyl)-2-phenylsulfanylmethyl-6-methylpiperidine **361**



To a solution of (2*R*, 6*S*)-*N*-(*tert*-butyloxycarbonyl)-2-hydroxymethyl-6-methyl piperidine **164** (400mg, 1.75mmol, 1.0eq) and phenyl disulphide (1.145g, 5.25mmol, 3.0eq) in tetrahydrofuran (10ml) under an atmosphere of argon was added tributylphosphine (1.414g, 7.0mmol, 4.0eq). The reaction mixture was heated under reflux for 164 hours. The solution was then diluted with diethyl ether (50ml), washed with aqueous sodium hydroxide (100ml) and saturated aqueous sodium chloride (50ml). The organic solution was dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 30-40°C, gradient 0:1 to 1:1) to afford the product as a colourless oil (381mg, 68%). $[\alpha]^{D}_{22}$ +10.5 (c 1, $CHCl_3$); (Found C, 67.3; H, 8.7;

N, 4.4. $C_{18}H_{27}NO_2S$ requires C, 67.3; H, 8.5; N, 4.4%); υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2971m (C-H str.), 1685 (C=O str.), 1583w, 1480w, 1438w, 1389s, 1364s, 1321m, 1253w, 1170m, 1121w, 1087m, 1026w, 856w and 738m; δ_H (500 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 1.44 (9H, s, $OC(C\underline{H}_3)_3$), 1.48-2.09 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 2.89 (1H, dd, *J* 13.0 and 11.0Hz, $PhSCH\underline{H}'$), 3.34 (1H, dd, *J* 13.0 and 4.0Hz, $PhSC\underline{H}H'$), 3.96-4.05 (2H, m, $C\underline{H}CH_3$ and $SCH_2C\underline{H}N$) and 7.15-7.40 (5H, m, $Ph\underline{H}$); δ_C (125 MHz, $CDCl_3$) 13.04 ($CH_2\underline{C}H_2CH_2$), 20.56 ($CH\underline{C}H_3$), 21.85 ($\underline{C}H_2CHCH_3$) 26.59 ($\underline{C}H_2CH_2CH_2$), 28.51 ($OC(\underline{C}H_3)_3$), 36.85 ($S\underline{C}H_2CH$), 47.09 ($\underline{C}HCH_3$), 50.85 ($SCH_2\underline{C}H$), 79.44 ($O\underline{C}(CH_3)_3$) 125.9 ($\underline{C}H$ aromatic), 128.8 ($\underline{C}H$ aromatic), 129.3 ($\underline{C}H$ aromatic), 136.4 (*ipso* aromatic $\underline{C}SCH_2$) and 155.0 ($\underline{C}$=O); m/z (Probe CI^+, NH_3) 323 (6), 322 (33, MH^+), 266 (6), 223 (11), 222 (100), 221 (8), 156 (5), 123 (10) and 98 (60).

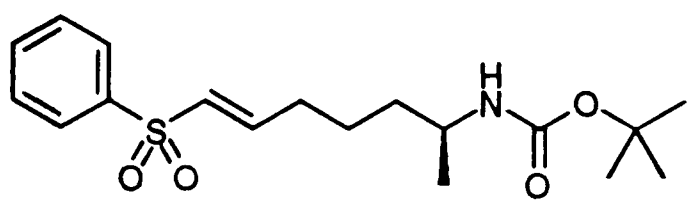
(2*R*, 6*S*)-*N*-(*tert*-Butyloxycarbonyl)-2-phenylsulfonylmethyl-6-methylpiperidine **309**



To a solution of (2*R*, 6*S*)-*N*-(*tert*-butyloxycarbonyl)-2-phenylsulfanylmethyl-6-methylpiperidine **361** (223mg, 0.69mmol, 1.0eq) in dichloromethane (10ml) cooled to 0°C under an atmosphere of argon was added *meta*-chloroperbenzoic acid (87% activity, 274mg, 1.38mmol, 2.0eq). The reaction mixture was stirred at 0°C for 10 minutes, then allowed to warm to ambient over 1 hour. The solution was then diluted with saturated aqueous sodium hydrogen carbonate (10ml) and the layer separated. The organic portion was dried over magnesium sulphate, filtered and the volatiles removed in *vacuo* to afford the product as a white crystalline solid (247mg, 99%). (m.p. 97-98°C); $[\alpha]^D_{22}$ +22.3 (c 1, $CHCl_3$); (Found C, 60.9; H, 7.9; N, 4.0. $C_{18}H_{27}NO_4S$ requires C, 61.2; H, 7.7; N, 4.0%); υ_{max} (FT-IR, KBr disc, cm^{-1}) 2973s (C-H str.), 1686 (C=O str.), 1560w, 1447w, 1392s, 1367s, 1247w, 1150s, 1086s, 867w and 750m; δ_H

(500 MHz, $CDCl_3$) 1.19 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 1.40 (9H, s, $OC(C\underline{H}_3)_3$), 1.55-2.09 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 3.32 (1H, dd, *J*14.0 and 9.5Hz, $PhSO_2CH\underline{H}'$), 3.58 (1H, dd, *J* 14.0 and 3.5Hz, $PhSO_2C\underline{H}H'$), 3.98 (1H, m, $C\underline{H}CH_3$), 4.27 (1H, m, $SCH_2C\underline{H}$) and 7.55-7.95 (5H, m, Ph<u>H</u>); δ_C (125 MHz, $CDCl_3$) 14.29 ($CH_2\underline{C}H_2CH_2$), 19.97 ($CH\underline{C}H_3$), 24.38 ($\underline{C}H_2CHCH_3$) 26.88 ($\underline{C}H_2CH_2CH_2$), 28.41 ($OC(\underline{C}H_3)_3$), 46.73 ($\underline{C}HCH_3$), 47.93 ($SCH_2\underline{C}H$), 58.90 ($S\underline{C}H_2CH$), 79.93 ($O\underline{C}(CH_3)_3$), 127.9 (<u>C</u>H aromatic), 129.3 (<u>C</u>H aromatic), 133.5 (<u>C</u>H aromatic), 139.9 (*ipso* aromatic $\underline{C}SCH_2$) and 154.7 (<u>C</u>=O); m/z (Probe CI^+, NH_3) 354 (9, MH^+), 298 (16), 255 (14), 254 (100), 253 (12), 238 (13), 156 (8), 112 (13), 111 (27) and 98 (35).

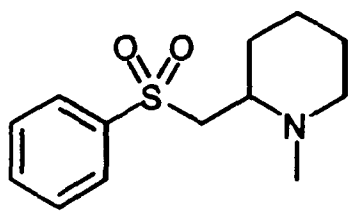
<u>(1*S*), (5*E*)-*N*-(Benzyloxycarbonyl)-1-methyl-6-phenylsulfonyl-5-hexenylamine **368**</u>



To a solution of (2*R*, 6*S*)-*N*-(*tert*-butyloxycarbonyl)-2-phenylsulfonylmethyl-6-methylpiperidine **309** (177mg, 0.5mmol, 1.0eq) in tetrahydrofuran (10ml) cooled to -78°C under an atmosphere of argon was added *N,N,N',N'*-tetramethylethylenediamine (58mg, 0.5mmol, 1.0eq). The solution was stirred at -78°C for 5 minutes at which time *n*-butyl lithium (1.20M, 0.42ml, 0.5mmol, 1.0eq) was added dropwise at a rate which maintained the temperature below -70°C. The reaction mixture was stirred at -78°C for 30 minutes, then acetic acid (acid-*d*, 61mg, 1.0mmol, 2.0eq) was added in a single portion. The solution was allowed to warm to ambient over 3 hours, then diluted with water (10ml) and diethyl ether (10ml) following which the layers were separated. The aqueous portion was extracted with diethyl ether (10ml). The combined organic portions were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 1:1) to afford the product as a colourless oil (100mg, 56%). $[\alpha]^D_{22}$ +28.9 (c 1, $CHCl_3$); m/z HIRES Found 354.1739,

$C_{18}H_{27}NO_4S+H^+$ requires 354.1739; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3378s (N-H str.), 2974s (C-H str.), 2933 (C-H str.), 1699 (C=O str.), 1520s, 1448s, 1391w, 1366s, 1306s, 1287m, 1248s, 1170s, 1147s, 1086s, 843w, 751m, 717m, 688s, 667w; δ_H (500 MHz, $CDCl_3$) 1.10 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 1.38-1.55 (13H, m, $C\underline{H}_2C\underline{H}_2CHN$ and $OC(C\underline{H}_3)_3$), 2.21-2.29 (2H, m, $CHCHC\underline{H}_2$), 3.64 (1H, m, $C\underline{H}CH_3$), 4.28 (1H, br s, N<u>H</u>), 6.31 (0.7H, dt, *J* 15.0 and 1.5Hz, SC<u>H</u>CH), 6.97 (1H, dt, *J* 15.0 and 7.0Hz, SCHC<u>H</u>) and 7.52-7.89 (5H, m, Ph<u>H</u>); δ_D (38 MHz, $CHCl_3$) 6.31 (br s, SCHC<u>D</u>); δ_C (125 MHz, $CDCl_3$) 21.31 ($CH\underline{C}H_3$), 24.11 ($CH_2\underline{C}H_2CH_2$), 28.39 ($OC(\underline{C}H_3)_3$), 31.14 ($\underline{C}H_2CHCH_3$) 26.88 ($CHCH\underline{C}H_2$), 45.95 ($\underline{C}HCH_3$), 79.13 ($O\underline{C}(CH_3)_3$), 127.6 (<u>C</u>H aromatic), 129.2 (<u>C</u>H aromatic), 130.6 (S<u>C</u>HCH), 133.2 (<u>C</u>H aromatic), 140.6 (*ipso* aromatic $\underline{C}SO_2CH_2$), 146.6 (SCH<u>C</u>H), and 155.4 (<u>C</u>=O); m/z (Probe CI^+, NH_3) 355 (8), 354 (13, MH^+), 316 (7), 315 (13), 299 (18), 298 (30), 256 (13), 255 (58), 254 (100), 144 (7), 112 (13) and 95 (8).

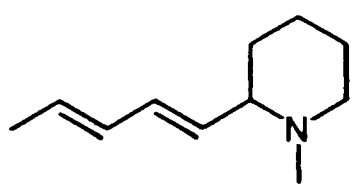
<u>*N*-Methyl-2-phenylsulfonylmethylpiperidine **58**</u>



To a solution of *N*-(*tert*-butyloxycarbonyl)-2-phenylsulfonylmethylpiperidine **297** (678mg, 2.0mmol, 1.0eq) in dichloromethane (30ml) under an atmosphere of argon was added trifluoroacetic acid (2.28g, 20.0mmol, 10.0eq) in a single portion. The reaction mixture was stirred at ambient for 2 hours. The solvent was then removed in *vacuo* affording a colourless oil. This oil was suspended in acetonitrile (12ml) and formaldehyde (37% aqueous, 1.62ml, 20.0mmol, 10.0eq) was added. The solution was stirred for 5 minutes at which time sodium cyanoborohydride (378mg, 6.0mmol, 3.0eq) was added in a single portion causing vigorous effervescence. The reaction mixture was stirred for 2 hours at ambient, then diluted with aqueous sodium

hydroxide (1M, 50ml) and diethyl ether (50ml). The layer were separated and the organic portion washed with saturated aqueous sodium chloride (50ml). The organic solution was dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (Al_2O_3, diethyl ether: petroleum ether 30-40°C 1:1) to yield the product as a colourless oil (366mg, 73%). m/z HIRES Found 254.1213, $C_{13}H_{19}NO_2S+H^+$ requires 254.1215; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2934s (C-H str.) 2858s (C-H str.), 2789s (C-H str.), 1447s, 1404w, 1375w, 1304s, 1147s, 1086s, 1028m, 999m, 951w, 923w, 878w, 747s, 741w, 689s and 610s; δ_H (500 MHz, $CDCl_3$) 1.39-1.93 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$) 2.15 (3H, s, $NC\underline{H}_3$), 2.22-2.27 (1H, m, NCH$\underline{H}$'), 2.54-2.58 (1H, m, NC$\underline{H}$H'), 2.86 (1H, m, $SCH_2C\underline{H}N$), 3.08 (1H, dd, *J* 14.5 and 8.0Hz, SCH$\underline{H}$'), 3.40 (1H, dd, *J* 14.5 and 2.0Hz, SC$\underline{H}$H') and 7.58-7.96 (5H, m, Ph$\underline{H}$); δ_C (125 MHz, $CDCl_3$) 21.65 ($CH_2\underline{C}H_2CH_2$), 25.17 ($\underline{C}H_2CH_2N$) 31.76 ($SCH_2CH\underline{C}H_2$), 42.85 ($N\underline{C}H_3$), 53.88 ($S\underline{C}H_2$), 56.05 ($N\underline{C}H_2$), 56.74 ($SCH_2\underline{C}H$), 127.9 ($\underline{C}$H aromatic), 129.3 ($\underline{C}$H aromatic), 133.7 ($\underline{C}$H aromatic) and 140.0 (*ipso* aromatic $\underline{C}SO_2CH_2$); m/z (Probe CI^+, NH_3) 256 (10), 255 (11), 254 (100, MH^+), 112 (14), 111 (13), 99 (8) and 98 (98).

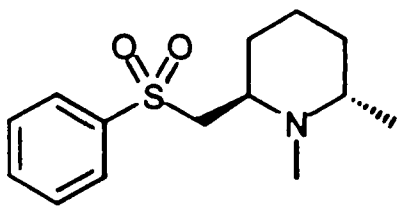
<u>*N*-Methyl-2-[(*E*,*E*)-1,3-pentadienyl]-piperidine **369**</u>



To a solution of *N*-methyl-2-phenylsulfonylmethylpiperidine **58** (253mg, 1.0mmol, 1.0eq) in tetrahydrofuran (10ml) cooled to -78°C under an atmosphere of argon was added *N,N,N',N'*-tetramethylethylenediamine (116mg, 1.0mmol, 1.0eq). The solution was stirred at -78°C for 5 minutes at which time *n*-butyl lithium (1.10M, 0.91ml, 1.0mmol, 1.0eq) was added dropwise at a rate which maintained the temperature below -70°C. The reaction mixture was stirred at -78°C for 30 minutes, then crotonaldehyde (70mg, 1.0mmol, 1.0eq) was added in a single portion. The reaction

mixture was stirred at -78°C for a further 30 minutes, then benzoyl chloride (141mg, 1.0mmol, 1.0eq) was added in a single portion. The solution was allowed to warm to ambient over 2 hours, then cooled to -20°C and methanol (3ml) and sodium hydrogenphosphate (1.42g, 10.0mmol, 10.0eq) were added. The mixture was stirred at -20°C for 5 minutes at which time sodium amalgam (6%, 1.87g, 5.0mmol, 5.0eq) was added. The reaction mixture was stirred at -20°C for 2 hours, then allowed to warm to ambient over 2 hours at which time it was stirred for 19 hours. The reaction mixture was then diluted with water (25ml) and diethyl ether (25ml) following which the layers were separated. The aqueous portion was saturated with sodium chloride and extracted with ethyl acetate (25ml) and dichloromethane (25ml). The combined organic portions were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether: diethylamine, gradient 0:1:0 to 39:60:1) to afford the product as a pale yellow oil (116mg, 70%). m/z HIRES Found 166.1596, $C_{11}H_{19}N+H^+$ requires 166.1596; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2934s (C-H str.), 2853m (C-H str.), 2775s (C-H str.), 1444m, 1370m, 1272m, 1200w, 1139w, 1111m, 1026m, 987s, 826w and 780w; δ_H (500 MHz, $CDCl_3$) 1.21-1.79 (9H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$ and $C\underline{H}_3CHCH$ (3H, d, *J* 6.5Hz)), 1.97 (1H, dt, *J* 8.0 and 3.0Hz, NCH$\underline{H}$'), 2.18 (3H, s, $NC\underline{H}_3$), 2.28 (1H, dt, *J* 8.0 and 3.0Hz, NC$\underline{H}$H'), 2.85-2.89 (1H, m, $CH_2C\underline{H}N$), 5.46 (1H, dd, *J* 14.0 and 8.5Hz, C$\underline{H}$CHN), 5.64 (1H, dq, *J* 13.5 and 6.5Hz, $CH_3C\underline{H}CH$) and 5.98-6.11 (2H, m, $CH_3CHC\underline{H}C\underline{H}$); δ_C (125 MHz, $CDCl_3$) 17.99 ($\underline{C}H_3CHCH$), 23.94 ($CH_2\underline{C}H_2CH_2$), 25.98 ($\underline{C}H_2CHN$) 33.49 ($NCH\underline{C}H_2$), 44.52 ($N\underline{C}H_3$), 56.45 ($N\underline{C}H_2$), 67.72 ($\underline{C}HN$), 128.4 ($CH_3\underline{C}HCH$), 131.0, 131.3 and 134.6 ($CH_3CH\underline{C}H\underline{C}H\underline{C}H$); m/z (GCMS CI^+, NH_3) 166 (23, MH^+), 35 (100) and 34 (15).

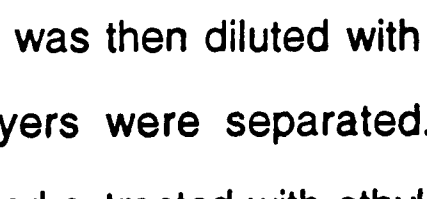
(2*R*, 6*S*)-*N*-Methyl-2-phenylsulfonylmethyl-6-methylpiperidine **156**



To a solution of (2*R*, 6*S*)-*N*-(*tert*-butyloxycarbonyl)-2-phenylsulfonylmethyl-6-methylpiperidine **309** (353mg, 1.0mmol, 1.0eq) in dichloromethane (15ml) under an atmosphere of argon was added trifluoroacetic acid (1.14g, 10.0mmol, 10.0eq) in a single portion. The reaction mixture was stirred at ambient for 2 hours. The solvent was then removed in *vacuo* affording a white gelatinous solid. This solid was suspended in acetonitrile (6ml) and formaldehyde (37% aqueous, 0.81ml, 10.0mmol, 10.0eq) was added. The solution was stirred for 5 minutes at which time sodium cyanoborohydride (189mg, 3.0mmol, 3.0eq) was added in a single portion causing vigorous effervescence. The reaction mixture was stirred for 2 hours at ambient, then diluted with aqueous sodium hydroxide (1M, 25ml) and diethyl ether (25ml). The layer were separated, the aqueous portion saturated with sodium chloride and extracted with ethyl acetate (25ml). The combined organics portions were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo.* The crude product was purified by flash chromatography (Al_2O_3, diethyl ether: petroleum ether 30-40°C, gradient 0:1 to 1:1) to yield the product as a colourless oil (245mg, 92%). $[\alpha]^D_{22}$ -1.1 (c 1, $CHCl_3$); m/z HIRES Found 268.1371, $C_{14}H_{21}NO_2S+H^+$ requires 268.1371; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2934s (C-H str.), 1447s, 1305s, 1147s, 1086m, 1036w, 996w, 918w, 788w, 751m, 689m and 631w; δ_H (500 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 1.20-1.82 (6H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$) 2.16 (3H, s, $NC\underline{H}_3$), 2.20-2.24 (1H, m, $C\underline{H}CH_3$), 3.21 (1H, dd, *J* 14.0 and 8.5Hz, SCH$\underline{H}$'), 3.31 (1H, dd, *J* 14.0 and 1.5Hz, SC$\underline{H}$H'), 3.41 (1H, m, $SCH_2C\underline{H}N$) and 7.57-7.96 (5H, m, PhC$\underline{H}$); δ_C (125 MHz, $CDCl_3$) 19.22 ($CH_2\underline{C}H_2CH_2$), 20.21 ($CH\underline{C}H_3$), 29.33 ($\underline{C}H_2CHCH_3$) 33.46 ($SCH_2CH\underline{C}H_2$), 38.99 ($N\underline{C}H_3$), 51.58 ($S\underline{C}H_2$), 52.01 ($\underline{C}HCH_3$), 55.44 ($SCH_2\underline{C}H$), 127.9 ($\underline{C}$H aromatic),

129.3 (CH aromatic), 133.6 (CH aromatic) and 140.6 (*ipso* aromatic CSO_2CH_2); m/z (Probe CI^+, NH_3) 270 (4), 269 (11), 268 (100, MH^+) and 112 (6).

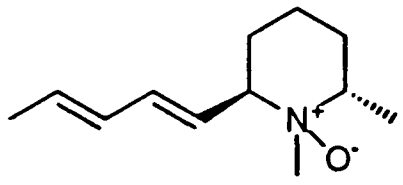
(2*R*, 6*S*)-*N*-Methyl-2-[(*E*,*E*)-1,3-pentadienyl]-6-methylpiperidine **362**



To a solution of (2*R*, 6*S*)-*N*-methyl-2-phenylsulfonylmethyl-6-methylpiperidine **156** (230mg, 0.86mmol, 1.0eq) in tetrahydrofuran (10ml) cooled to -78°C under an atmosphere of argon was added *N,N,N',N'*-tetramethylethylenediamine (100mg, 0.86mmol, 1.0eq). The solution was stirred at -78°C for 5 minutes at which time *n*-butyl lithium (1.10M, 0.78ml, 0.86mmol, 1.0eq) was added dropwise at a rate which maintained the temperature below -70°C. The reaction mixture was stirred at -78°C for 30 minutes, then crotonaldehyde (60mg, 0.86mmol, 1.0eq) was added in a single portion. The reaction mixture was stirred at -78°C for a further 30 minutes, then benzoyl chloride (133mg, 0.95mmol, 1.1eq) was added in a single portion. The solution was allowed to warm to ambient over 2 hours, then cooled to -20°C and methanol (3ml) and sodium hydrogenphosphate (1.22g, 8.6mmol, 10.0eq) were added. The mixture was stirred at -20°C for 5 minutes at which time sodium amalgam (6%, 1.65g, 4.3mmol, 5.0eq) was added. The reaction mixutre was stirred at -20°C for 2 hours, then allowed to warm to ambient over 2 hours at which time it was stirred for 15 hours. The reaction mixture was then diluted with water (25ml) and diethyl ether (25ml) following which the layers were separated. The aqueous portion was saturated with sodium chloride and extracted with ethyl acetate (25ml). The combined organic portions were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether: diethylamine, gradient 0:1:0 to 39:60:1) to afford the product as a pale yellow oil (118mg, 77%). $[\alpha]^D_{22}$ +28.5 (c 1, $CHCl_3$); m/z HIRES

Found 180.1752, $C_{12}H_{21}N+H^+$ requires 180.1752; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2932s (C-H str.), 2786m (C-H str.), 1447m, 1371m, 1341w, 1254m, 1199w, 1117m, 1069w, 1034m, 1018w, 986s, 948w and 899m; δ_H (500 MHz, $CDCl_3$) 1.00 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 1.38-1.79 (9H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$ and $C\underline{H}_3CHCH$ (3H, d, *J* 6.5Hz)), 2.22 (3H, s, $NC\underline{H}_3$), 2.78-2.83 (1H, m, $C\underline{H}CH_3$), 3.05-3.09 (1H, m, $CH_2C\underline{H}N$), 5.61-5.70 (2H, m, $CH_3C\underline{H}CHCHC\underline{H}$) and 6.02-6.11 (2H, m, $CH_3CHC\underline{H}C\underline{H}$); δ_C (125 MHz, $CDCl_3$) 15.07 ($CH\underline{C}H_3$), 17.98 ($\underline{C}H_3CHCH$), 19.16 ($CH_2\underline{C}H_2CH_2$), 32.70 ($\underline{C}H_2CHCH_3$) 33.52 ($CHCHCH_2CH\underline{C}H_2$), 40.72 ($N\underline{C}H_3$), 53.13 ($\underline{C}HCH_3$), 61.35 ($CHCHCH_2\underline{C}HN$), 128.4 ($CH_3\underline{C}HCH$), 131.3 and 131.7 ($CH_3CH\underline{C}H\underline{C}H\underline{C}H$); m/z (Probe CI^+, NH_3) 181 (4), 180 (100, MH^+), 150 (5) and 140 (4).

(2*R*, 6*S*)-*N*-Methyl-2-[(*E*,*E*)-1,3-pentadienyl]-6-methylpiperidine *N*-oxide **370**

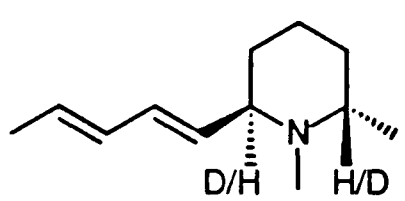


To a solution of (2*R*, 6*S*)-*N*-methyl-2-[(*E*,*E*)-1,3-pentadienyl]-6-methylpiperidine **362** (92mg, 0.51mmol, 1.0eq) in dichloromethane (5ml) cooled to 0°C under an atmosphere of argon was added *meta*-chloroperbenzoic acid (87% activity, 87mg, 0.51mmol, 1.0eq). The reaction mixture was stirred at 0°C for 80 minutes then the solvent was removed in *vacuo.* The crude product was purified by flash chromatography (Al_2O_3, methanol: dichloromethane 1:49) to afford the product as a colourless oil (98mg, 99%). $[\alpha]^D_{22}$ +57.7 (c 1, $CHCl_3$); m/z HIRES Found 196.1701, $C_{12}H_{21}NO+H^+$ requires 196.1701; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3392s, 2935s (C-H str.), 1654m, 1450m, 1376w, 1220w, 1032w, 999s and 934m; δ_H (500 MHz, $CDCl_3$) 1.31 & 1.38 (3H, 2xd, *J* 6.5 & 7.0Hz respectively, $CHC\underline{H}_3$), 1.42-1.64 (4H, m, $CH\underline{H}'C\underline{H}_2CH\underline{H}'$), 1.74 & 1.77 (3H, 2xdd, *J* 8.0 and 1.0Hz & 7.0 and 1.0Hz, $C\underline{H}_3CHCH$), 2.08-2.32 (1H, 2xm, $CHCHCHC\underline{H}H'$), 2.70-2.92 (1H, 2xm, $C\underline{H}H'CHCH_3$), 2.93 & 2.95 (3H, 2xs, $NC\underline{H}_3$), 3.23 & 3.48 (1H, 2xm, $NC\underline{H}CH_3$), 3.56 & 3.77 (1H, 2xm,

CHCHCHN) and 5.62-6.30 (4H, m, $CH_3CHCHCHCH$); δ_C (125 MHz, $CDCl_3$) 14.67 & 15.41 ($CHCH_3$), 17.17 & 18.07 ($CH_2CH_2CH_2$), 18.16 (CH_3CHCH), 26.10 & 26.79 (CH_2CHCH_3) 27.72 & 28.57 ($CHCHCH_2CHCH_2$), 55.48 & 55.63 (NCH_3), 64.60 ($CHCH_3$), 70.88 & 70.99 ($CHCHCH_2CHN$), 123.4 & 126.1 (CH_3CHCH), 130.2 & 130.6 ($CH_3CHCHCHCH$), 131.0 & 132.8 (CH_3CHCH) and 134.9 & 137.4 ($CH_3CHCHCH$); m/z (APCI$^+$, NH_3/Na) 196 (53, MH^+), 181 (7), 180 (46), 178 (20), 166 (100), 122 (7), 114 (6), 113 (6) and 112 (100).

(2*R*, 6*S*)-2-*d*-*N*-Methyl-2-[(*E*,*E*)-1,3-pentadienyl]-6-methylpiperidine,

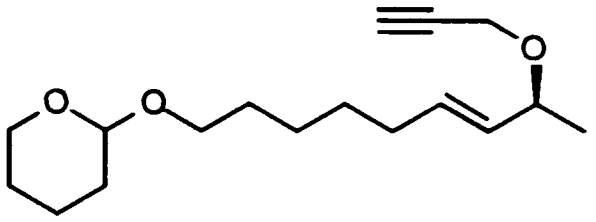
(2*R*, 6*S*)-6-*d*-*N*-Methyl-2-[(*E*,*E*)-1,3-pentadienyl]-6-methylpiperidine **371**



To a solution of (2*R*, 6*S*)-*N*-methyl-2-[(*E*,*E*)-1,3-pentadienyl]-6-methylpiperidine *N*-oxide **370** (90mg, 0.46mmol, 1.0eq) in dichloromethane (5ml) cooled to 0°C under an atmosphere of argon was added trifluoroacetic anhydride (966mg, 4.6mmol, 10.0eq) affording a pale yellow solution. The reaction mixture was stirred at 0°C for 1 hour at which time the solvent was removed in *vacuo* to give a yellow oil. The oil was dissolved in methanol (5ml), cooled to 0°C and sodium borodeuteride (97mg, 2.3mmol, 5.0eq) added in a single portion. The reaction mixture was stirred at 0°C for a further 30 minutes, then poured into saturated aqueous sodium chloride (20ml). The mixture was extracted with dichloromethane (2x10ml) then the remaining solution was saturated with sodium chloride and extracted with ethyl acetate (20ml). The combined organic portions were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (Al_2O_3, diethyl ether: petroleum ether, gradient 0:1 to 1:9) to afford the product as a pale yellow oil (57mg, 69%). $[\alpha]^D_{22}$ +20.1 (c 1, $CHCl_3$); m/z HIRES Found 181.1814, $C_{12}H_{20}DN+H^+$ requires 181.1814; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2931s (C-H

str.), 2784m (C-H str.), 1657w, 1445m, 1370m, 1260m and 988s; δ_H (500 MHz, $CDCl_3$) 1.00 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 1.38-1.80 (9H, m, $C\underline{H}_2C\underline{H}_2C\underline{H}_2$ and $C\underline{H}_3CHCH$ (3H, d, *J* 6.5Hz)), 2.23 (3H, s, $NC\underline{H}_3$), 2.79-2.82 (0.5H, m, $C\underline{H}CH_3$), 3.06-3.09 (0.5H, m, $CH_2C\underline{H}N$), 5.62-5.70 (2H, m, $CH_3C\underline{H}CHCHC\underline{H}$) and 6.03-6.12 (2H, m, $CH_3CHC\underline{H}C\underline{H}$); δ_D (38 MHz, $CHCl_3$) 2.83 (br s, $C\underline{D}CH_3$), 3.11 (br s, $CH_2C\underline{D}N$) ratio 1:1; δ_C (125 MHz, $CDCl_3$) 14.66 & 15.07 ($CD\underline{C}H_3$ & $CH\underline{C}H_3$), 18.01 ($\underline{C}H_3CHCH$), 19.10 ($CH_2\underline{C}H_2CH_2$), 32.50 & 32.69 ($\underline{C}H_2CDCH_3$ & $\underline{C}H_2CHCH_3$) 33.26 & 33.52 ($CHCHCH_2CD\underline{C}H_2$ & $CHCHCH_2CH\underline{C}H_2$), 40.68 ($N\underline{C}H_3$), 52.69 (t, *J* 39.6Hz, $\underline{C}DCH_3$), 53.07 ($\underline{C}HCH_3$), 61.24 ($CHCHCH_2\underline{C}HN$), 128.4 ($CH_3\underline{C}HCH$), 131.3 and 131.7 ($CH_3CH\underline{C}H\underline{C}H\underline{C}H$), $CHCHCH_2\underline{C}DN$ too weak to be observed; m/z (APCI Cl^+, NH_3/Na) 182 (11), 181 (100, MH^+) and 180 (4).

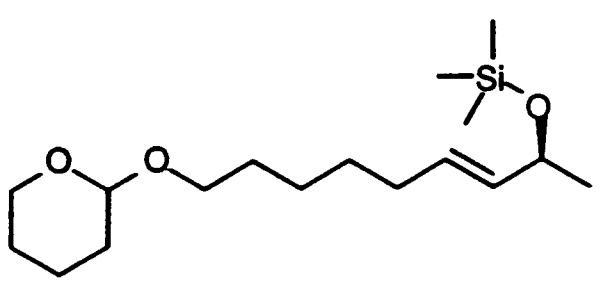
(*S*)-(*E*)-2-[(Propargyl)oxy]-9-(tetrahydropyran-2-yloy)-3-nonene **395**



To a suspension of sodium hydride (60% in oil, 30mg, 0.75mmol, 1.5eq, washed with petroleum ether 30-40°C (3x5ml)) in dimethylformamide (2ml) under an atmosphere of argon was added (*S*)-(3*E*)-2-hydroxy-9-(tetrahydropyran-2-yloy)-3-nonene **394** (122mg, 0.5mmol, 1.0eq) in dimethylformamide (2ml). The mixture was stirred at ambient for 30 minutes at which time propargyl bromide (80% in toluene, 119mg, 1.0mmol, 2.0eq) was added in a single portion. The reaction mixture was stirred at 50°C for 2 hours then at ambient for 17 hours. Saturated aqueous ammonium chloride (5ml) was then added and the mixture extracted with diethyl ether (3x25ml). The combined organic extracts were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography

(SiO_2, diethyl ether: petroleum ether, gradient 0:1 to 3:2) to afford starting material (96mg, 79% recovery) and the product as a colourless oil (33mg, 23%). $[\alpha]^D_{22}$ -15.1 (c 1, $CHCl_3$); m/z HIRES Found 298.2382, $C_{17}H_{28}O_3+NH_4^+$ requires 298.2382; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3308m (C-H alkyne str.), 2936s (C-H str.), 1441m, 1353m, 1323w, 1262m, 1200w, 1137m, 1119m, 1076s, 1034s, 972m, 906w, 869w and 814w; δ_H (500 MHz, $CDCl_3$) 1.25 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 1.29-1.66 (10H, m, $OCH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2$ and $(RO)_2CHCH\underline{H}'C\underline{H}_2CH\underline{H}'$), 1.69-1.73 (1H, m $(RO)_2CHC\underline{H}H'$), 1.81-1.84 (1H, m, $(RO)_2CHCH_2CH_2C\underline{H}H'$), 2.03-2.08 (2H, m, $C\underline{H}_2CHCH$), 2.38 (1H, t, *J* 2.5Hz, $\underline{H}CCCH_2$), 3.38 (1H, dt, *J* 13.5 and 6.5Hz, $OCHOCH\underline{H}'CH_2$), 3.48-3.51 (1H, m, $CH\underline{H}'OCHOCH_2$), 3.74 (1H, dt, *J* 14.0 and 6.5Hz, $OCHOC\underline{H}H'CH_2$), 3.84-3.88 (1H, m, $C\underline{H}H'OCHOCH_2$), 3.98-4.02 (2H, m, $C\underline{H}CH_3$ and $HCCCH\underline{H}'$), 4.12 (1H, dd, *J* 16.0 and 2.5Hz, $HCCC\underline{H}H'$), 4.57 (1H, dd, *J* 4.0 and 2.5Hz, $OC\underline{H}O$), 5.25-5.30 (1H, m, $CHC\underline{H}CHCH_3$) and 5.65 (1H, dt, *J* 15.5 and 6.5Hz, $C\underline{H}CHCHCH_3$); δ_C (125 MHz, $CDCl_3$) 19.67 ($(RO)_2CHCH_2\underline{C}H_2$), 21.50 ($CH\underline{C}H_3$), 25.48 ($OCH_2CH_2\underline{C}H_2$), 25.77 ($OCH_2\underline{C}H_2$), 28.92 ($\underline{C}H_2CH_2CHCH$), 29.54 ($(RO)_2CHCH_2CH_2\underline{C}H_2$), 30.75 ($(RO)_2CH\underline{C}H_2$), 32.03 ($\underline{C}H_2CHCH$), 54.71 ($HCC\underline{C}H_2$), 62.33 ($\underline{C}H_2OCHO$), 67.50 ($OCHOC\underline{H}_2$), 73.56 ($H\underline{C}CCH_2$), 75.51 ($\underline{C}HCH_3$), 80.41 ($HC\underline{C}CH_2$), 98.85 ($O\underline{C}HO$), 130.8 ($\underline{C}HCHCHCH_3$) and 134.3 ($CH\underline{C}HCHCH_3$); m/z (Probe CI^+, NH_3) 396 (12, MNH_4^+), 225 (22), 214 (3), 158 (24), 123 (4), 103 (5), 102 (100), 86 (5), 85 (88) and 81 (4).

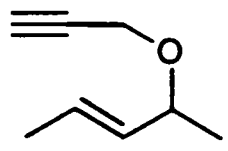
(*S*)-(*E*)-2-[Trimethylsilyloxy]-9-(tetrahydropyran-2-yloy)-3-nonene **408**



To a suspension of sodium hydride (60% in oil, 30mg, 0.75mmol, 1.5eq, washed with petroleum ether 30-40°C (3x5ml)) in dimethylformamide (2ml) under an atmosphere

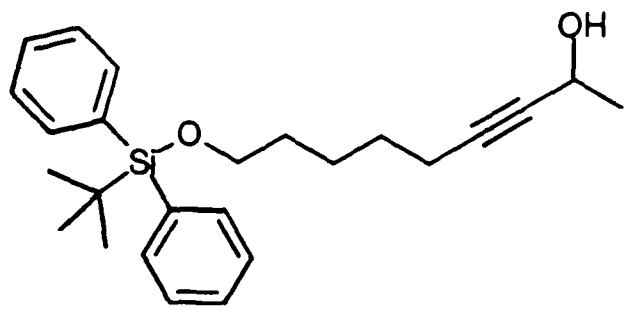
of argon was added (*S*)-(*E*)-2-hydroxy-9-(tetrahydropyran-2-yloy)-3-nonene **394** (122mg, 0.5mmol, 1.0eq) in dimethylformamide (2ml). The mixture was stirred at ambient for 30 minutes at which time 3-bromo-1-(trimethylsilyl)-1-propyne (191mg, 1.0mmol, 2.0eq) was added in a single portion. The reaction mixture was stirred ambient for 26 hours, then saturated aqueous ammonium chloride (5ml) was added and the mixture extracted with diethyl ether (3x25ml). The combined organic extracts were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether, gradient 1:9 to 1:1) to afford the product as a colourless oil (87mg, 55%). $[\alpha]^D_{22}$ -54.4 (c 1, $CHCl_3$); m/z HIRES Found 332.2620, $C_{17}H_{34}O_3Si+NH_4^+$ requires 332.2621; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2939s (C-H str.), 1441w, 1367w, 1249s, 1201w, 1137m, 1078s, 1035s, 996m, 969m, 902m and 840s; δ_H (500 MHz, $CDCl_3$) 0.11 (9H, s, $Si(C\underline{H}_3)_3$), 1.20 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 1.33-1.63 (10H, m, $OCH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2$ and $(RO)_2CHCH\underline{H}'C\underline{H}_2CH\underline{H}'$), 1.68-1.74 (1H, m $(RO)_2CHC\underline{H}H'$), 1.81-1.87 (1H, m, $(RO)_2CHCH_2CH_2C\underline{H}H'$), 1.99-2.03 (2H, m, $C\underline{H}_2CHCH$), 3.38 (1H, dt, *J* 13.5 and 6.5Hz, $OCHOCH\underline{H}'CH_2$), 3.48-3.52 (1H, m, $CH\underline{H}'OCHOCH_2$), 3.73 (1H, dt, *J* 14.0 and 6.5Hz, $OCHOC\underline{H}H'CH_2$), 3.85-3.89 (1H, m, $C\underline{H}H'OCHOCH_2$), 4.23 (1H, quintet, *J* 6.0Hz, $C\underline{H}CH_3$), 4.57 (1H, dd, *J* 4.0 and 3.0Hz, $OC\underline{H}O$), 5.42-5.58 (1H, m, $CHC\underline{H}CHCH_3$) and 5.65 (1H, dt, *J* 15.5 and 6.5Hz, $C\underline{H}CHCHCH_3$); δ_C (125 MHz, $CDCl_3$) 0.27 ($Si(\underline{C}H_3)_3$), 19.67 ($(RO)_2CHCH_2\underline{C}H_2$), 24.54 ($CH\underline{C}H_3$), 25.48 ($OCH_2CH_2\underline{C}H_2$), 25.79 ($OCH_2\underline{C}H_2$), 29.02 ($\underline{C}H_2CH_2CHCH$), 29.58 ($(RO)_2CHCH_2CH_2\underline{C}H_2$), 30.76 ($(RO)_2CH\underline{C}H_2$), 31.99 ($\underline{C}H_2CHCH$), 62.32 ($\underline{C}H_2OCHO$), 67.57 ($OCHOC\underline{H}_2$), 69.30 ($\underline{C}HCH_3$), 98.82 ($O\underline{C}HO$), 129.5 ($\underline{C}HCHCHCH_3$) and 134.5 ($CH\underline{C}HCHCH_3$); m/z (Probe CI^+, NH_3) 332 (13, MNH_4^+), 242 (14), 225 (42), 207 (6), 158 (21), 143 (7), 123 (8), 102 (100), 90 (27) and 85 (95).

(*E*)-2-[(Propargyl)oxy]-3-pentene **413**



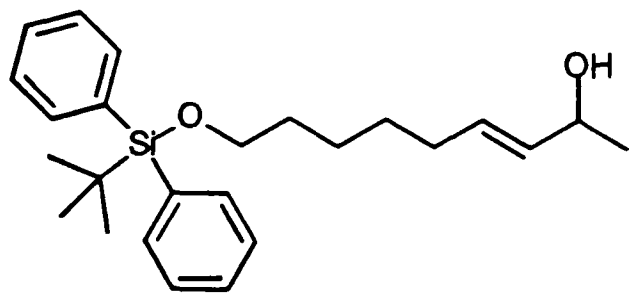
To a solution of (*E*)-3-penten-2-ol **412** (860mg, 10.0mmol, 1.0eq) and tetrabutylammonium iodide (369mg, 1.0mmol, 0.1eq) in aqueous sodium hydroxide (19M, 10ml) under an atmosphere of argon was added propargyl bromide (80% in toluene, 5.95g, 50.0mmol, 5.0eq) in a single portion. The mixture was stirred at ambient for 16 hours at which time water (10ml) and diethyl ether (10ml) were added. The layers were separated and the aqueous layer extracted with diethyl ether (2x10ml). The combined organic extracts were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether, gradient 0:1 to 1:2) to afford the product as a colourless oil (790mg, 60%). υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3310s (C-H alkyne str.), 2974s (C-H str.), 2931s (C-H str.), 2857s, 2116w (C≡C str., alkyne), 1673w (C=C str.), 1448s, 1372s, 1315w, 1258m, 1160w, 1138w, 1082s, 1059s, 1005w, 968s, 912s, 832w, 794w and 735s; δ_H (300 MHz, $CDCl_3$) 1.24 (3H, d, *J* 6.5Hz, OCHC$\underline{H}_3$), 1.71 (3H, dd, *J* 6.5 and 1.5Hz, C$\underline{H}_3$CHCH), 2.37 (1H, t, *J* 2.5Hz, $\underline{H}CCCH_2$), 4.00-4.17 (3H, m, OC$\underline{H}CH_3$ and HCCC$\underline{H}_2$), 5.42-5.58 (1H, m, $CH_3C\underline{H}CH$) and 5.65 (1H, dt, *J* 15.5 and 6.5Hz, $CH_3CHC\underline{H}$); δ_C (125 MHz, $CDCl_3$) 17.51 (OCH$\underline{C}H_3$), 21.32 ($\underline{C}H_3CHCH$), 54.60 (HCC$\underline{C}H_2$), 73.51 (H$\underline{C}CCH_2$), 75.28 (O$\underline{C}HCH_3$), 80.30 (HC$\underline{C}CH_2$), 128.8 ($CH_3\underline{C}HCH$) and 132.1 ($CH_3CH\underline{C}H$); m/z (GCMS Cl^+, NH_3) 142 (11, MNH_4^+), 125 (21, MH^+), 109 (35), 96 (10), 95 (10), 87 (6), 86 (100), 81 (17), 70 (12), 69 (72) and 67 (8).

2-Hydroxy-9-(*tert*-butyldiphenylsilyloxy)-3-nonyne **416**



To a solution of 2-(*tert*-butyldimethylsilyloxy)-9-(*tert*-butyldiphenylsilyloxy)-3-nonyne **414** (1.26g, 2.0mmol, 1.0eq) in ethanol (10ml) under an atmosphere of argon was added pyridinium *para*-toluene sulphonate (502mg, 2.0mmol, 1.0eq) in a single portion. The mixture was stirred at 50°C for 6 hours at which time ethyl acetate (50ml) was added and the mixture was washed with saturated aqueous sodium chloride (50ml) and water (50ml). The organic layer was dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 1:9) to afford the product as a colourless oil (500mg, 52%). m/z HIRES Found 412.2671, $C_{25}H_{34}O_2Si+NH_4^+$ requires 412.2672; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3393m (O-H str.), 2933s (C-H str.), 2859s, 2246w (C≡C str.), 1688m, 1589w, 1473m, 1428s, 1390w, 1365w, 1256w, 1156w, 1111s, 1007m, 939w, 823m, 740m and 703s; δ_H (500 MHz, $CDCl_3$) 1.06 (9H, s, $SiC(C\underline{H}_3)_3$), 1.42 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 1.44-1.60 (6H, m, $OCH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 2.17-2.21 (2H, dt, *J* 6.5 and 2.0Hz, $C\underline{H}_2CC$), 3.67 (2H, t, *J* 6.5Hz, $OC\underline{H}_2$), 4.51 (1H, m, $C\underline{H}CH_3$) and 7.37-7.69 (10H, m, $Ph\underline{H}$); δ_C (125 MHz, $CDCl_3$) 18.60 ($OCH_2CH_2\underline{C}H_2$), 19.19 ($\underline{C}(CH_3)_3$), 24.72 ($CH\underline{C}H_3$), 25.05 ($\underline{C}H_2CH_2CC$), 26.83 ($C(\underline{C}H_3)_3$), 28.33 ($OCH_2\underline{C}H_2$), 32.02 ($\underline{C}H_2CHCH$), 58.58 ($\underline{C}HCH_3$), 63.70 ($O\underline{C}H_2$), 82.26 ($\underline{C}CCHOH$), 84.55 ($C\underline{C}CHOH$), 127.6 ($\underline{C}H$ aromatic), 129.5 ($\underline{C}H$ aromatic), 134.0 (*ipso* aromatic $\underline{C}CH$) and 135.5 ($\underline{C}H$ aromatic); m/z (Probe CI^+, NH_3) 412 (7, MNH_4^+), 395 (10, MH^+), 379 (11), 378 (27), 377 (100), 337 (11), 317 (26), 299 (18), 216 (17), 197 (17), 165 (29), 156 (14), 138 (12), 122 (13), 121 (94), 105 (11) and 93 (16).

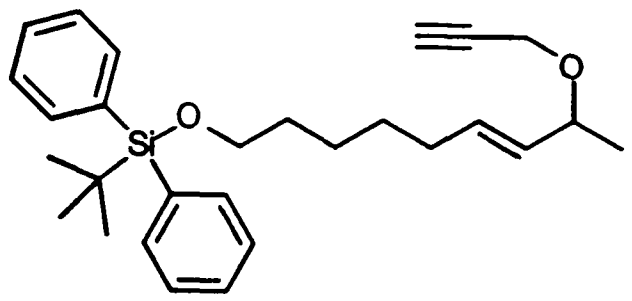
(*E*)-2-Hydroxy-9-(*tert*-butyldiphenylsilyloxy)-3-nonene **417**



To a solution of 2-hydroxy-9-(*tert*-butyldiphenylsilyloxy)-3-nonyne **416** (440mg, 1.12mmol, 1.0eq) in diethyl ether (10ml) cooled to 0°C under an atmosphere of argon was added Red-Al® (65% in toluene, 697mg, 2.24mmol, 2.0eq) in diethyl ether (10ml) *via* cannula. The mixture was allowed to warm to ambient then stirred for 15 hours at which time saturated aqueous ammonium chloride (10ml) was slowly added. The mixture was filtered through a pad of celite and saturated aqueous sodium chloride (10ml) was added. The layers were then separated, the aqueous portion saturated with sodium chloride and extracted with diethyl ether (10ml). The combined organic portions were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 1:2) to afford the product as a colourless oil (332mg, 75%). m/z HIRES Found 414.2828, $C_{25}H_{36}O_2Si+NH_4^+$ requires 414.2828; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3350m (O-H str.), 2931s (C-H str.), 2857s, 1472m, 1462w, 1428s, 1389w, 1361w, 1112s, 1007w, 998w, 969m, 938m and 823s; δ_H (500 MHz, $CDCl_3$) 1.06 (9H, s, $SiC(C\underline{H}_3)_3$), 1.26 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 1.35-1.59 (6H, m, $OCH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 2.17-2.21 (2H, m, $C\underline{H}_2CHCH$), 3.67 (2H, t, *J* 6.5Hz, $OC\underline{H}_2$), 4.26 (1H, quintet, *J* 6.5Hz, $C\underline{H}CH_3$), 5.48-5.53 (1H, m, $CHC\underline{H}CHOH$), 5.63 (1H, dt, *J* 15.5 and 6.5Hz, $C\underline{H}CHCHOH$) and 7.37-7.69 (10H, m, $Ph\underline{H}$); δ_C (125 MHz, $CDCl_3$) 19.20 ($\underline{C}(CH_3)_3$), 23.40 ($CH\underline{C}H_3$), 23.40 ($OCH_2CH_2\underline{C}H_2$), 26.85 ($C(\underline{C}H_3)_3$), 28.86 ($\underline{C}H_2CH_2CHCH$), 32.03 ($OCH_2\underline{C}H_2$), 32.38 ($\underline{C}H_2CHCH$), 63.86 ($O\underline{C}H_2$), 68.94 ($\underline{C}HCH_3$), 127.6 ($\underline{C}H$ aromatic), 129.5 ($\underline{C}H$ aromatic), 131.0 ($\underline{C}HCHCHOH$), 134.1 ($CH\underline{C}HCHOH$) and 135.6 ($\underline{C}H$ aromatic); m/z (Probe CI^+, NH_3) 414 (5, MNH_4^+), 396

(9), 380 (23), 379 (84), 377 (6), 321 (5), 256 (9), 216 (22), 199 (12), 124 (7), 123 (100), 121 (6) and 81 (43).

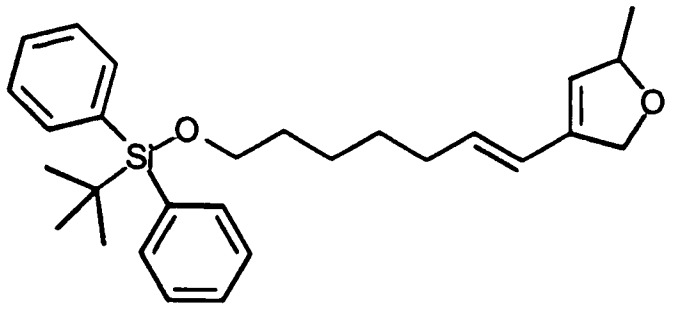
(*E*)-2-[(Propargyl)oxy]-9-(*tert*-butyldiphenylsilyloxy)-3-nonene **418**



To a solution of (*E*)-2-hydroxy-9-(*tert*-butyldiphenylsilyloxy)-3-nonene **417** (320mg, 0.81mmol, 1.0eq) and tetrabutylammonium iodide (179mg, 0.49mmol, 0.6eq) in aqueous sodium aqueous (19M, 1.5ml) under an atmosphere of argon was added propargyl bromide (80% in toluene, 1.16g, 9.72mmol, 12.0eq) in a single portion. The mixture was stirred at ambient for 43 hours at which time water (10ml) and diethyl ether (10ml) were added. The layers were separated and the aqueous layer extracted with diethyl ether (10ml). The combined organic extracts were dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 1:19) to afford the product as a colourless oil (277mg, 79%). m/z HIRES Found 452.2985, $C_{28}H_{38}O_2Si+NH_4^+$ requires 452.2985; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2930s (C-H str.), 2856s, 1472m, 1461w, 1427s, 1388m, 1360m, 1263w, 1111s, 998w, 972m, 921w, 823m, 740m, 701s and 687w; δ_H (500 MHz, $CDCl_3$) 1.07 (9H, s, $SiC(C\underline{H}_3)_3$), 1.28 (3H, d, *J* 6.5Hz, $CHC\underline{H}_3$), 1.37-1.60 (6H, m, $OCH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2$), 2.03-2.07 (2H, m, $C\underline{H}_2CHCH$), 2.39 (1H, t, *J* 2.5Hz, $\underline{H}CCCH_2$), 3.67 (2H, t, *J* 6.5Hz, $OC\underline{H}_2$), 4.00-4.16 (2H, m, $C\underline{H}CH_3$ and OCH$\underline{H}$'), 4.15 (1H, dd, *J* 15.5 and 2.5Hz, HCCC$\underline{H}$H'), 5.29 (1H, dd, *J* 15.5 And 8.5Hz, CHC$\underline{H}$CHO), 5.67 (1H, dt, *J* 15.5 and 7.0Hz, C$\underline{H}$CHCHOH) and 7.38-7.70 (10H, m, Ph$\underline{H}$); δ_C (125 MHz, $CDCl_3$) 19.21 ($\underline{C}(CH_3)_3$), 21.54 ($CH\underline{C}H_3$), 25.35 ($OCH_2CH_2\underline{C}H_2$), 26.85 ($C(\underline{C}H_3)_3$), 28.85 ($\underline{C}H_2CH_2CHCH$), 32.09 ($OCH_2\underline{C}H_2$), 32.36 ($\underline{C}H_2CHCH$), 54.70 ($HCC\underline{C}H_2$), 63.85 ($O\underline{C}H_2$), 73.58 ($H\underline{C}CCH_2$), 75.52

(<u>C</u>HCH$_3$), 80.27 (HC<u>C</u>CH$_2$), 127.6 (<u>C</u>H aromatic), 129.5 (<u>C</u>H aromatic), 130.7 (<u>C</u>HCHCHOH), 134.1 (*ipso* aromatic <u>C</u>CH), 134.4 (CH<u>C</u>HCHOH) and 135.6 (<u>C</u>H aromatic); m/z (APCI Cl$^+$, NH$_3$/Na) 452 (12, MNH$_4^+$), 451 (14), 431 (8), 396 (11), 391 (13), 380 (26), 379 (100), 357 (9), 317 (12), 279 (14), 271 (16), 257 (13), 239 (11), 166 (13), 148 (37), 123 (26), 112 (17) and 101 (10).

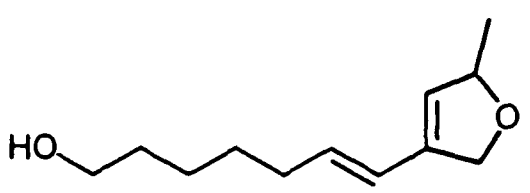
<u>4-[(*E*)-7-(*tert*-Butyldiphenylsilyloxy)-1-heptenyl]-2-methyl-2,5-dihydrofuran **419**</u>



A solution of (*E*)-2-[(propargyl)oxy]-9-(*tert*-butyldiphenylsilyloxy)-3-nonene **418** (333mg, 0.75mmol, 1.0eq) in 1,2-dichloroethane (12ml) under an atmosphere of argon was degassed by 3 freeze-pump-thaw cycles. The mixture was transferred *via* cannula to a Shlenck tube containing tricarbonyldichlororuthenium(II)-tetrahydrofuran (9.9mg, 0.03mmol, 0.04eq). The argon atmosphere was then displaced with carbon monoxide and the reaction mixture stirred at 60°C for 7 hours. The reaction mixture was then passed through a plug of silica, eluting with diethyl ether: petroleum ether 30-40°C (1:9, 25ml) following which the volatiles were removed in *vacuo*. The crude product was purified by flash chromatography (SiO$_2$, diethyl ether: petroleum ether 1:24) to afford the product as a colourless oil (159mg, 48%). m/z HIRES Found 452.2985, $C_{28}H_{38}O_2Si+NH_4^+$ requires 452.2985; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 2929s (C-H str.), 2855s, 1472m, 1427m, 1388w, 1111s, 1046w, 962m, 823m, 701s and 687w; δ_H (500 MHz, CDCl$_3$) 1.07 (9H, s, SiC(C<u>H</u>$_3$)$_3$), 1.28 (3H, d, *J* 6.5Hz, CHC<u>H</u>$_3$), 1.37-1.61 (6H, m, OCH$_2$C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$), 2.09-2.13 (2H, m, C<u>H</u>$_2$CHCH), 3.68 (2H, t, *J* 6.5Hz, OC<u>H</u>$_2$), 4.68 (1H, dt, *J* 11.5 and 2.5Hz, CH$_3$CHOCH<u>H</u>'), 4.80 (1H, ddd, *J* 11.5, 5.0 and 2.0Hz, CH$_3$CHOC<u>H</u>H'), 4.98-4.99 (1H, m, CH$_3$C<u>H</u>), 5.46 (1H, dt, *J* 16.0

and 7.0Hz, C<u>H</u>CHCCH$_2$O), 5.60 (1H, d, *J* 1.5Hz, CH$_3$CHC<u>H</u>), 6.18 (1H, d, *J* 16.0Hz, C<u>H</u>CCH$_2$O) and 7.38-7.70 (10H, m, Ph<u>H</u>); δ_C (125 MHz, $CDCl_3$) 19.19 (<u>C</u>(CH$_3$)$_3$), 21.78 (CH<u>C</u>H$_3$), 25.28 (OCH$_2$CH$_2$<u>C</u>H$_2$), 26.83 (C(<u>C</u>H$_3$)$_3$), 28.80 (<u>C</u>H$_2$CH$_2$CHCH), 32.33 (OCH$_2$<u>C</u>H$_2$), 32.90 (<u>C</u>H$_2$CHCH), 63.78 (O<u>C</u>H$_2$CH$_2$), 73.86 (<u>C</u>H$_2$OCHCH$_3$), 82.34 (<u>C</u>HCH$_3$), 122.8 (CHCH<u>C</u>H), 127.0 (CH$_2$CH$_2$CH<u>C</u>H), 127.6 (<u>C</u>H aromatic), 129.5 (<u>C</u>H aromatic), 129.5 (*ipso* aromatic <u>C</u>CH), 134.1 (CH$_2$CH$_2$<u>C</u>HCH), 135.6 (<u>C</u>H aromatic) and 137.8 (<u>C</u>CH$_2$O); m/z (APCI Cl$^+$, NH$_3$/Na) 435 (25, MH$^+$), 389 (15), 358 (14), 357 (55), 311 (22), 297 (18), 240 (13), 239 (66), 219 (14), 193 (19), 179 (92), 162 (13), 161 (100), 156 (10), 135 (11) and 121 (17).

<u>4-[(*E*)-7-Hydroxy-1-heptenyl]-2-methyl-2,5-dihydrofuran **420**</u>



To a solution of 4-[(*E*)-7-(*tert*-butyldiphenylsilyloxy)-1-heptenyl]-2-methyl-2,5-dihydrofuran **419** (150mg, 0.34mmol, 1.0eq) in tetrahydrofuran (10ml) under an atmosphere of argon was added tetrabutylammonium fluoride (1.0M solution in tetrahydrofuran, 0.68ml, 0.68mmol, 2.0eq). The reaction mixture was stirred at ambient for 3 hours. The solution was then diluted with saturated aqueous sodium chloride (20ml) and ethyl acetate (10ml), the layers separated and the aqueous portion extracted with dichloromethane (10ml). The combined organic extracts were then dried over magnesium sulphate, filtered and the volatiles removed in *vacuo*. The crude product was purified by flash chromatography (SiO_2, diethyl ether: petroleum ether 1:24) to afford the product as a colourless oil (22mg, 33%). m/z HIRES Found 197.1542, $C_{12}H_{20}O_2$+H$^+$ requires 197.1542; υ_{max} (FT-IR, NaCl plates, thin film, cm^{-1}) 3382 (O-H str.), 2930s (C-H str.), 2857s, 1459m, 1368m, 1341m, 1109w, 1082m, 1046s, 963m, 907w and 828m; δ_H (500 MHz, $CDCl_3$) 1.26 (3H, d, *J* 6.5Hz, CHC<u>H</u>$_3$), 1.33-1.60 (6H, m, OCH$_2$C<u>H</u>$_2$C<u>H</u>$_2$C<u>H</u>$_2$), 2.10-2.14 (2H, m, C<u>H</u>$_2$CHCH), 3.68 (2H, t, *J*

6.5Hz, $HOC\underline{H}_2$), 4.66 (1H, dt, *J* 11.5 and 2.5Hz, $CH_3CHOCH\underline{H}'$), 4.78 (1H, ddd, *J* 11.5, 5.0 and 2.0Hz, $CH_3CHOC\underline{H}H'$), 4.96-4.99 (1H, m, $CH_3C\underline{H}$), 5.45 (1H, dt, *J* 16.0 and 7.0Hz, $C\underline{H}CHCCH_2O$), 5.59 (1H, d, *J* 1.5Hz, $CH_3CHC\underline{H}$) and 6.18 (1H, d, *J* 16.0Hz, $C\underline{H}CCH_2O$); δ_C (125 MHz, $CDCl_3$) 21.74 ($CH\underline{C}H_3$), 25.27 ($OCH_2CH_2\underline{C}H_2$), 28.88 ($\underline{C}H_2CH_2CHCH$), 32.53 ($OCH_2\underline{C}H_2$), 32.89 ($\underline{C}H_2CHCH$), 62.84 ($O\underline{C}H_2CH_2$), 73.82 ($\underline{C}H_2OCHCH_3$), 82.33 ($\underline{C}HCH_3$), 122.9 ($CHCH\underline{C}H$), 127.1 ($CH_2CH_2CH\underline{C}H$), 133.4 ($CH_2CH_2\underline{C}HCH$) and 137.7 ($\underline{C}CH_2O$); m/z (Probe CI^+, NH_3) 214 (70), 211 (50), 197 (100, MH^+), 186 (85), 179 (42), 150 (16), 142 (25), 132 (67), 116 (14), 109 (18), 95 (18), 85 (13), 81 (13) and 58 (10).

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APPENDIX

1. Crystal Data

Experimental

$C_{14}H_{20}O_3$

M_r = 236.31

Orthorhombic

$P2_12_12_1$

a = 5.697 (1) Å

b = 11.647 (1) Å

c = 19.722 (3) Å

V = 1308.64 Å^3

Z = 4

D_x = 1.20 mg/m^3

Cu $K\alpha$ radiation

λ + 1.54180 Å

Cell parameters from 25 reflections

θ = 25-29°

μ = 0.63mm^{-1}

T = 293K

Needle fragment

0.70 x 0.30 x 0.10 mm

Colourless

Crystal source: total synthesis

Data Collection

Enraf-nonius CAD-4 diffractometer

$2\theta/\omega$ scans

Absorption correction

ψ scan

T_{min} = 0.82, T_{max} = 1.00

2074 measured reflections

1493 independent reflections

1050 observed reflections

[$I > 3.00\sigma(I)$]

R_{int} = 0.02

θ_{max} = 75.00°

h = -1 → 7

k = -1 → 14

l = -1 → 24

h = 0 → 7

k = 0 → 14

l = 0 → 24

3 standard reflections

frequency: 60 min

intensity decay: 2.74%

Refinement

Refinement of *F*

$R = 0.0386$

$\omega R = 0.0453$

$S = 1.0976$

1050 reflections

235 parameters

All H-atom parameters refined

Chebychev polynormial

Carruthers and Watkin[249]

$(\Delta/\sigma)_{max} = 0.041794$

$\Delta\rho_{max} = 0.25$ e Å^{-3}

$\Delta\rho_{min} = -0.14$ e Å^{-3}

Extinction correction: Larson 1970

Crystallographic Computing eq 22

Extrinction coefficient: 48.0 (50)

Atomic scattering factors from *International Tables for X-Ray Crystallography* (1974, Vol. IV, Table 2.2B)

Absolute configuration: from Flack enantiopole 0.000

Fractional Atomic Coordinates and equivalent isotropic displacement parameters (Å^2)

$$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i \mathbf{a}_j.$$

	x	*y*	*z*	U_{eq}
C1	-0.8819 (7)	-0.5519 (3)	-0.7470 (2)	0.0625
C3	-0.5541 (7)	-0.4341 (3)	-0.7403 (2)	0.0664
C4	-0.7294 (6)	-0.3936 (2)	-0.6864 (2)	0.0494
C5	-0.6414 (6)	-0.3454 (2)	-0.6180 (2)	0.0484
C6	-0.5513 (6)	-0.4403 (3)	-0.5704 (1)	0.0485
C7	-0.4606 (8)	-0.3935 (3)	-0.5031 (2)	0.0635
C8	-0.3877 (9)	-0.4872 (4)	-0.4538 (2)	0.0780
C9	-0.586 (1)	-0.5727 (4)	-0.4428 (2)	0.0816
C10	-0.673 (1)	-0.6204 (3)	-0.5085 (2)	0.0796

C11	-0.7490 (8)	-0.5271 (3)	-0.5585 (2)	0.0617
C12	-0.8226 (9)	-0.5790 (3)	-0.6255 (2)	0.0751
C13	-0.8835 (6)	-0.4981 (3)	-0.6781 (2)	0.0568
C15	-0.464 (1)	-0.3464 (6)	-0.7894 (2)	0.0933
C16	-0.4789 (6)	-0.2432 (2)	-0.6256 (2)	0.0534
O2	-0.6950 (5)	-0.5166 (2)	-0.7810 (1)	0.0742
O14	-1.0145 (6)	-0.6209 (2)	-0.7716 (2)	0.0813
O17	-0.2478 (5)	-0.2817 (2)	-0.6431 (1)	0.0631

Selected Geometric Parameters (Å, º)

C1 - C13	1.496 (5)	C6 - C7	1.525 (5)
C1 - O2	1.324 (5)	C6 - C11	1.532 (5)
C1 - O14	1.205 (4)	C7 - C8	1.518 (5)
C3 - C4	1.534 (5)	C8 - C9	1.523 (6)
C3 - C15	1.497 (6)	C9 - C10	1.492 (6)
C3 - O2	1.487 (4)	C10 - C11	1.531 (5)
C4 - C5	1.544 (4)	C11 - C12	1.512 (5)
C4 - C13	1.510 (4)	C12 - C13	1.445 (5)
C5 - C6	1.539 (4)	C16 - O17	1.433 (4)
C5 - C16	1.515 (4)		

Data collection: CAD-4 software (Enraf-Nonius, 1989)

Cell refinement: CAD-4 software (Enraf-Nonius, 1989)

Data Reduction: CRYSTALS (Watkin, Carruthers and Betteridge[250])

Program used to solve structure: SHELXS86 (Sheldrick[251])

Program used to refine structure: CRYSTALS

Molecular graphics: CAMERON (Pearce, Watkin and Prout[252])

Software used to prepare material for publication: CRYSTALS