New Synthetic Methods in an Approach to Huperzine A and B

By

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A Thesis submitted for the Degree of Doctor of Philosophy in the Faculty of Science at the University of Leicester

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STATEMENT

The accompanying thesis submitted for the degree of Ph.D. entitled "New Synthetic Methodology in an Approach to Huperzine A and B" is based on work conducted by the author in the Department of Chemistry of the University of Leicester between the period October 1988 and November 1991.

All the work recorded in this thesis is original unless otherwise acknowledged in the text or by references. None of the work has been submitted for any other degree in this or any other university.

Signed: Susan E Booth

Date: 12/3/92

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The Synthesis of Bicyclic and Tricyclic Ring Systems by Radical Cyclisation Reactions of Oxime Ethers: Susan E. Booth, Paul R. Jenkins and Christopher J. Swain, J. Chem. Soc., Chem. Commun., 1991, 1248.

NEW SYNTHETIC METHODS IN AN APPROACH TO HUPERZINE A

AND B

by Susan E. Booth

ABSTRACT

The aim of the research was to develop a flexible, stereocontrolled route to huperzine A and B and other lycopodium alkaloids. One of the main objectives was to investigate whether intramolecular radical cyclisation reactions on to carbon-nitrogen double bonds might provide a new method for the synthesis of key intermediates in the total synthesis.

To this end the intramolecular cyclisation reactions of vinyl and aryl radicals on to oxime ethers have been explored and these reactions have been used to prepare a number of useful bicyclic and tricyclic carbocyclic compounds and related heterocyclic compounds in good yields. This represents essentially new synthetic methodology as prior to this work there was only one reported example of the use of an oxime ether as a radical trap. The best reagent for these reactions utilising vinyl and aryl halide precursors was found to be tributyltin hydride.

Preliminary attempts to carry out tandem radical cyclisation reactions incorporating oxime ethers have not, so far, been successful on the model systems investigated.

This new synthetic strategy has been used to carry out one-carbon ring expansions of five-membered cyclic oxime ethers similar to those reported recently for carbonyl compounds. However, attempts to extend this ring expansion to the two-carbon system resulted only in cyclisation to give a bicyclic compound, rather than ring expansion.

Attempts to cleave the N-O bonds of some of the hydroxylamines resulting from these cyclisation reactions proved to be unsuccessful using SmI_2 , Zn and acetic acid or aluminium amalgam. Attempted cleavage of the N-O alkyl bond of a hydroxylamine group adjacent to an aromatic ring using lithium aluminium hydride resulted in a novel ring expansion reaction, which may occur by an unusual electron transfer process to give radical intermediates.

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ABBREVIATIONS

.

Ac	acetyl, acetate
AChE	acetylcholine esterase
AIBN	2,2'-azobisisobutyronitrile
aq.	aqueous
Bn	benzyl
b.p.	boiling point
br.	broad (i.r. and n.m.r.)
Bu	n-butyl
tBu	<i>tert</i> -butyl
c.	concentration
cat.	catalytic amount
٥C	degrees Celsius
ChAT	choline acetyl transferase
COSY	Correlation Spectroscopy
d	doublet (n.m.r.)
DEAD	diethyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
DMSO	dimethyl sulphoxide
e-	electron
Et	ethyl
glc	Gas Liquid Chromotography
HMPA	hexamethylphosphoric triamide
HPLC	High Performance Liquid Chromatography
hν	light
i.r.	infra-red
LDA	lithium diisopropylamine
m	medium (i.r.)
М	mol.dm ⁻³
Me	methyl
mol	mole
m.p.	melting point
Ms	mesyl
n.m.r.	Nuclear Magnetic Resonance
Ph	phenyl
Ру	pyridine

p.s.i.	pounds per square inch
q	quartet (n.m.r.)
S	strong (i.r.), singlet (n.m.r.)
str.	stretch (i.r.)
t	triplet (n.m.r.)
TBDMS	tert-butyldimethylsilyl
THF	tetrahydrofuran
t.l.c.	thin layer chromatography
TMS	trimethylsilyl
vib.	vibration (i.r.)
w	weak (i.r.)
Δ	heat or reflux

.

Introduction

1.1 ALZHEIMER'S DISEASE

1.1.1 Symptoms of the Disease

Over the last 10 years there has been an explosive growth of research world-wide into the problems presented by Alzheimer's disease.¹ Although Alzheimer's disease has been known for over a century it is only recently that the scale of the problem posed by this disease, and the threat to the Western World, has been fully recognised. Since the beginning of the century there has been a growing awareness that the ageing of populations was accompanied by an increase in the prevalence of a wide range of chronic and disabling diseases for which there is no medical remedy. Severe mental decay in late life constitutes the largest single problem due to the state of extreme helplessness that characterises its advanced stages. Alzheimer's disease has come to be recognised as the commonest form of such mental deterioration.

More than three-quarters of those born in Britain and the United States can now expect to reach the age of 60.2^{-5} This, coupled with the declining birth rates, has meant that the proportion of elderly people in the population is set to rise to 20% by the end of the century. At least 1 in 20 of those will suffer from Alzheimer's disease. Alzheimer's disease is most common in elderly people, the prevalence being as high as 10% in people aged over 65 years, rising to 20% in those aged over 80; in England and Wales, 700,000 people may be affected. Although it is less likely with younger people most neurologists know of some Alzheimer's disease sufferers who are in middle life.

Alzheimer's disease is marked by the disastrous failure of memory and other higher mental functions.⁶⁻⁸ Initially patients begin to lose their ability to remember whether they have carried out simple everyday tasks such as turning off the cooker or locking the front door. Routine tasks become more and more difficult as the disease progresses. They find it increasingly hard to name familiar objects or find the right

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word. They show no visual signs of illness nor signs of serious depression, stroke, brain turnour or any other specific disease likely to give rise to such symptoms. The patient becomes disoriented, confused and experiences emotional changes, most frequently those of depression. Occasionally halucinations accompany the behavioural changes. Within 3 to 10 years they will be severely demented, will be unable to speak or think or take care of themselves, and in time they will die of some complication that afflicts bedridden patients.

For a long time the disease named after Alois Alzheimer was considered to apply specifically to the presenile dementia seen in a few people in their forties and fifties.⁸ Elderly people with similar symptoms were said to suffer from 'senility' or 'hardening of the arteries'. Recently it has become clear that the brain of most old people with dementia shows all the characteristic signs of Alzheimer's disease if it is examined at autopsy.

The diagnosis of Alzheimer's disease can only be inferred during the patient's lifetime. An autopsy, however, shows characteristic pathological changes in the brain.^{1,8,9} There is a loss of neurons (nerve cells) particularly in regions essential for memory and thought processes. There are accumulations of twisted filaments (neurofibrillary tangles) and other abnormal structures within the neurons.^{10,11} There are also scattered focuses of cellular debris called neuritic plaques.¹² There is also significant loss of neurons in regions at the base of the brain.¹³ This results in a reduction in the amount of neurotransmitters (chemical messengers), normally released from the terminals of these neurons in higher brain centres.

1.1.2 Possible Causes of the Disease

Numerous models have been proposed based on the observed symptoms and the processes that might give rise to them.^{8,14} The hypothesis that has attracted the most

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interest and has given rise to the most attempts at therapy starts with the observation that the neurotransmitter acetylcholine appears to be in short supply in the brains of patients with Alzheimer's disease. Acetylcholine was the first substance to be identified as a neurotransmitter. Systems that use acetylcholine as a neurotransmitter are called cholinergic neurons or systems. The other hypotheses are more general. They propose that the death of neurons is caused by faulty genes, by abnormal accumulations of proteins, by an infectious agent, by an environmental toxin or by inadequate blood flow and energy metabolism.

The possibility that Alzheimer's disease can be inherited has been a subject of interest for some time.^{2,8,14,15} Results from several studies suggest that a genetic fault may be the cause of the disease especially in cases where the onset of the disease occurs below the age of 65 (presenile dementia). Close relatives of Alzheimer's sufferers showing this presenile dementia have a fourfold greater chance of developing the disease than the general population.

It has also been proposed recently that chromosomal abnormalities may be involved. Most patients with Down's syndrome who survive to the age of 40 years acquire dementia.^{2,8,16,17} The brains of such Down's syndrome patients show similar neurofibrillary tangles and reductions of choline acetyltransferase in the hippocampus. It is thought that close to 100% of those reaching the age of 40 will have developed Alzheimer's disease.

The presence of elevated aluminium levels in the brain tissue of Alzheimer's disease patients suggests that salts of aluminium may contribute to the development of Alzheimer's disease.^{8,18} An inorganic substance composed of aluminium and silicon is present in the neuritic plaques. Patients suffering from aluminium toxicity do not, however, exhibit the neuropathological changes characteristic of Alzheimer's disease.

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Evidence that suggests Alzheimer's disease is an infectious disease, possibly of viral origin, is based upon clinical similarities with Creutzfeldt-Jakob disease.^{8,14} This is a rare disorder consisting of progressive dementia and movement disturbances that is followed by death within 1 to 2 years from onset. Similarities with scrapie in sheep and goats is also suggested.

There is evidence to suggest that Alzheimer's disease is associated with a reduction in the amount of blood delivered to the brain, in the amount of oxygen and glucose extracted from the blood, and in the energy generated from the oxygen and glucose.

Each model is supported by some observational or experimental evidence - and each seems to be contradicted by other evidence. The acetylcholine model has attracted the most interest and offers explanations for the selective loss of the neurons from whose terminals acetylcholine is released.

In 1976 and 1977 three independent laboratories reported the first clear biochemical abnormality associated with Alzheimer's disease. They found that in post-mortem hippocampus and cerebral cortex from Alzheimer cases the level of the enzyme choline acetyltransferase was reduced by as much as 90% compared to controls.¹⁹⁻²¹ Choline acetyltransferase is confined to cholinergic neurons and since, in contrast to acetylcholine, it is relatively stable after death, it is a useful post-mortem marker of the integrity of cholinergic neurons.¹

1.1.3 The Acetylcholine Model

Cholinergic neurons are widespread within the brain and spinal chord. The cholinergic deficit in Alzheimer's disease, however, seems not to affect all cholinergic systems to the same degree, and some areas appear unchanged. The most marked reductions in choline acetyltransferase activity are seen in the temporal neocortex, the hippocampus,

- 4 -

and amygdala. This observation suggests an explanation for the most fundamental symptom of Alzheimer's disease; memory loss. If the levels of choline acetyltransferase are reduced in the hippocampus, the level of acetylcholine (which cannot be measured at autopsy) will most probably also be reduced there. Extensive research has shown that cholinergic terminals in the hippocampus are critically important for memory formation. It is therefore reasonable to suggest that some of the cognitive deficits of Alzheimer's disease are the direct result of a reduction in the acetylcholine-mediated transmission of nerve impulses. A drug that could restore the acetyl choline level in the brain may be effective in treating the disease, much as L-dopa is effective in correcting the deficit in neurotransmission caused by the loss of the transmitter dopamine in Parkinson's disease.^{22,23}

In order to develop a drug which is able to restore deficient cholinergic transmission and act only where such restoration is needed, it is necessary to consider the life cycle of the neurotransmitter acetylcholine and its mechanism for relaying messages.

The fundamental cell structure in the nervous system is the neuron (Figure 1). The neuron consists of a cell body (which has numerous extensions called dendrites), an axon, and terminal fibres. Messages in the brain are transferred as impulses which travel from the dendrites to the junction of the cell body and the axon, down the axon to the terminal fibres. The impulse in then relayed through the synapse, i.e. the specialised contact zone where one neuron communicates with another, to the next neuron, where the process begins again. Alzheimer's disease affects the transmission of nerve impulses across the synapse by the neurotransmitter, acetylcholine.

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Figure 1

A neurotransmitter is a chemical compound which is released synaptically by one neuron and subsequently affects another cell at a specific site and in a specific manner. For a substance to be a true neurotransmitter it must be synthesised by the neuron; it must be released by the neuron in sufficient amounts to exhibit an effect on another neuron; and a mechanism must exist to remove the neurotransmitter from the site of action.

The synthesis of acetylcholine occurs in the cell body of the neuron, choline acetyltransferase (ChAT) catalysing the reaction between choline and acetyl coenzyme A (Equation 1).



Once synthesised, the acetylcholine molecules are stored in the terminal until the arrival of a nerve impulse. This releases some of the acetylcholine from the presynaptic membrane into the synaptic cleft. Once in the synapse, an acetylcholine molecule can cross the cleft. Its action on the postsynaptic membrane involves binding with a receptor protein specific for acetylcholine thus transmitting the signal generated by the nerve impulse. Once acetylcholine is released into the synaptic cleft and is bound to the receptors it must be removed so that the postsynaptic neurons are not constantly affected. The acetylcholine is hydrolysed to choline and acetate ion by the enzyme acetylcholinesterase (AChE) (Equation 2).

 $AChE \\ CH_{3}COOCH_{2}CH_{2}NMe_{3} + H_{2}O \xrightarrow{+} CH_{3}CO_{2} + HOCH_{2}CH_{2}NMe_{3} \\ acetylcholine \\ acetate \\ choline \\$

Equation 2

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Most of the choline is taken up into the presynaptic membrane and is used in the synthesis of acetylcholine (Figure 2).

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Diagram of Message Transmission

Figure 2

1.1.4 <u>Treatment of the Disease</u>

For a drug to be effective it must either mimic the deficient transmitter's postsynaptic action or increase the amount of the transmitter that is present in the synapse. One approach would be to develop a drug that would simulate the effect acetylcholine has on the postsynaptic membrane. It must only be effective where the transmitter is deficient. Preliminary results suggest this may be possible. An alternative approach would be to increase the release of acetylcholine by finding a drug that selectively blocks the presynaptic acetylcholine receptors on surviving cholinergic terminals. By blocking the modulating signal from those receptors, the terminal should release more acetylcholine per firing.

Another approach would be to enhance acetylcholine synthesis in the surviving terminals by providing the enzyme choline acetyltransferase with more choline. Although administration of choline to animals have increased the amount of choline in the brain, similar tests on humans have not been conclusive.

Patients with Alzheimer's disease have significantly lower concentrations of choline acetyltransferase in the brain (the enzyme responsible for the synthesis of acetylcholine). Attempts to treat the disease by increasing the levels of acetylcholine have resulted in only minor improvements in some patients. Although Alzheimer's disease results in low levels of acetylcholine the levels of acetylcholinesterase are unaffected. It is thought that by inhibiting the generation of acetylcholinesterase, i.e. interfering in the catalysis of the conversion of acetylcholine into choline, then the relative level of acetylcholine in the synapse to the level of acetylcholinesterase in the postsynaptic membrane will be higher, thus resulting in the freer flow of messages across the synapse.

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It has recently been reported that the compounds huperzine A (1) and huperzine B (2), two new Lycopodium alkaloids isolated from a Chinese folk medicine, exhibit strong anticholinesterase activity.²⁴ The use of such inhibitors in the treatment of Alzheimer's disease has resulted in significant improvements in memory tests.²⁵ Huperzine A has also been shown to be useful in treating *myaesthenia gravis*, a rare disease affecting only 1 in 50,000 people, mostly women. The disease is characterised by a weakening in certain muscles as a result of faulty transmission of nerve impulses to the muscles they control. Huperzine A and B were isolated from a clubmoss native to China known as *Huperzia serrata* (Thunb.) Trev.=*Lycopodium serratum* Thunb., a Chinese folk medicine, Qian Ceng Ta, known to have certain memory restorative properties.²⁶ The isolation was difficult and lengthy and afforded the alkaloids in very small quantities. The total chemical synthesis of these compounds, therefore, represents an important synthetic target which several research groups throughout the world are actively engaged in. Huperzine A (1) has a similar structure to another pyridonecontaining alkaloid, selagine (3).



Мe

(3)

Selagine

1.1.5 Acetylcholinesterase Inhibitors

As previously mentioned, huperzine A has been found to function as a very potent inhibitor of acetylcholinesterase. Other well-documented acetylcholinesterase inhibitors include neostigmine (4), physostigmine (5) and pyridostigmine bromide (6) and some structural resemblance between these compounds and huperzine A can be seen.²⁴

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Neostigmine (prostigmine)



Neostigmine (4), physostigmine (5) and pyridostigmine bromide (6) work by interfering in the hydrolysis of acetylcholine to acetate ion and choline normally catalysed by the enzyme acetylcholinesterase (Equation 3).



Equation 3

They are capable of carbamylating the active serine hydroxyl group in acetylcholinesterase. Hydrolysis of acetylcholine catalysed by the carbamylated enzyme occurs much more slowly than does hydrolysis with acetylcholinesterase itself. It was suggested that huperzine A may perform a similar role in regard to its ability to bond covalently to the enzyme but this seems unlikely considering that pyridones are not particularly susceptible to nucleophilic attack.²⁷ Biological studies reinforced these doubts when no irreversible inhibition of acetylcholinesterase by huperzine A (1) was observed.

Since the discovery of huperzine A (1) numerous biological studies have been carried out, particularly in China, to assess its potential as an acetylcholinesterase inhibitor.²⁸ It was found to be a potent inhibitor, three times more active than physostigmine (5).²⁹ Huperzine B (2) was found to be less active but appeared to be less toxic than huperzine A (1). Huperzine A (1) was shown to improve animal performance in Y-maze experiments by administration of the drug 20 minutes before training.²⁵ One hundred individuals aged between 46 and 82 years suffering from memory impairment including Alzheimer's disease showed improvement 1 to 4 hours after injection with 30 mgs of huperzine A (1) compared to 600 mgs of the usual drug hydergine.³⁰ The improvement was sustained for 8 hours. In another test, 128 patients suffering from *myaesthenia gravis* were treated with huperzine A (1) instead of prostigmine (4). 99% of the cases had the clinical manifestations of their disease controlled. The duration of action of huperzine A (1) was significantly longer than neostigmine (4). The side effects observed with prostigmine i.e. dizziness, sweating and blurring of vision were much less with huperzine A.²⁴

It is thought that the ability of huperzine A (1) to function as a potent acetylcholinesterase inhibitor is due to its similarity to acetylcholine. A computergenerated overlay of huperzine A (1) with the fully extended conformation of acetylcholine shows a good coincidence of the key heteroatoms (Figure 3).²⁴

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A Computer Generated Overlay of Acetylcholine and Huperzine A Figure 3

This fully extended form of acetylcholine is the conformation thought to be relevant to recognition by acetylcholinesterase.³¹ Due to their spatial similarities huperzine A (1) may also be recognised by acetylcholinesterase. Interaction of huperzine A (1) with the enzyme would effectively reduce the amount of acetylcholine hydrolysed to choline and acetate ion as a proportion of the enzyme catalysing this reaction is interacting with huperzine A (1).²⁴

1.1.6 Structure Determination of Selagine

Huperzine A (1) and huperzine B (2) belong to a class of compounds called Lycopodium alkaloids. The pioneer in this field was Professor Karel Wiesner whose structure elucidation of annotinine, the alkaloid of *Lycopodium annotinum*, in 1956 revealed for the first time the structural type to be expected in other Lycopodium alkaloids.³²⁻³⁴ The key factor in the deduction of this structure was the identification of dehydrogenation products, and extensive systematic degradation. Since then, structures have been proposed for many alkaloids of this type including selagine (3) and the obscurines (7) and (8), 35,36 the Lycopodium alkaloids most closely related to huperzine A and B (1) and (2).



Selagine





Huperzine A



Huperzine B

The structure of selagine (3) is very similar to that of huperzine A (1) and the elucidation of its structure by Wiesner in 1960 aided the structure determination of huperzine A in 1986.

The structure of selagine (3) was derived from a simple derivative of selagine, tetrahydroselaginol (9).³⁷ Oxidation of tetrahydroselaginol gave the crystalline ketoacid (10).



The oxidation product was further characterised by its 2,4-dinitrophenylhydrazone derivative. The structure of the degradation product was confirmed by comparison with an authentic sample of 2-ethyl-3-carboxy-5-methylcyclohexanone. Although the two compounds had superimposable infrared spectra, their melting points were different. The synthetic product was the racemate of the all equatorial keto-acid while the degradation product was one of its enantiomers.

By applying similar techniques to selagine (3) itself, the structure was determined.³⁵ From infrared and ultraviolet spectroscopic data selagine was known to contain an α pyridone group. A pKa value of 7.18 showed the presence of a basic nitrogen. Reduction of the alkaloid under different conditions yielded 11,12-dihydroselagine (11) and 11,12,14,15-tetrahydroselagine (12). The fact that these two reduction products had identical ultraviolet spectra to selagine showed that selagine (3) contained two isolated double bonds in addition to the α -pyridone grouping, and was therefore tricyclic.







11,12-Dihydroselagine



(12)

11,12,14,15-Tetrahydroselagine



Selaginol

The positions of the double bonds and substitution in the pyridone ring were established by 60 MHz ¹H n.m.r. spectroscopy. This showed selagine (3) to contain a disubstituted pyridone ring with the two remaining double bonds being trisubstituted. The high field portions of the n.m.r. spectra of selagine (3), dihydroselagine (11) and tetrahydroselagine (12) revealed the relative position of the two unconjugated double bonds and the two methyl groups in selagine (3). It showed that both isolated double bonds were directly joined to a methyl group. Additional information that one of the double bonds was exocyclic was obtained by the oxidation of selagine (3), tetrahydroselagine (12) and dihydroselagine (11) followed by steam distillation and chromatography of the volatile acids. Selagine (3) gave only acetic acid, while dihydro- and tetrahydroselagine (11) and (12) yielded propionic acid and acetic acid under the same conditions. Dihydro- and tetrahydroselagine (11) and (12) must therefore contain an ethyl group while selagine (3) itself must contain an ethylidene grouping and an endocyclic double bond substituted in the way indicated above.

Information on the substitution of the pyridone ring was obtained as follows. Selagine (3) was treated with nitrous acid to give selaginol (13) which in turn was catalytically reduced to give tetrahydroselaginol (9). This was converted into the dichloro compound by treatment with phenylphosphonic dichloride, the catalytic reduction of which removed both chlorine atoms and gave the pyridine. ¹H n.m.r. spectroscopy of the pyridine showed the presence of a 2,3-disubstituted pyridine ring. It was therefore deduced that selagine (3) contains a 5,6-disubstituted α -pyridone ring.

Information on the primary amino group in selagine (3) was established firstly by treating selaginol (13) with concentrated hydrochloric acid to yield the ketone, the ultraviolet spectrum of which indicated the presence of the chromophore (14). Catalytic reduction of the ketone followed by a reduction with sodium borohydride yielded the alcohol which was not identical with tetrahydroselaginol (9). The possibility that the formation of the ketone involved a skeletal rearrangement was supported by the finding that the hydroxyl group in tetrahydroselaginol could not be oxidised or acetylated, i.e. was tertiary. The primary amino group of selagine was therefore attached to a tertiary C-atom.

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The formation of the ketone was formulated as indicated in (15). It established the relative position of the primary amino group, the α -pyridone ring and one of the two double bonds in selagine (3). The exocyclic double bond of selagine (3) is in the correct position to undergo this rearrangement. The structure proposed for selagine (3) is based upon the assumption that the endocyclic double bond is also in a suitable position to undergo rearrangement. There is no conclusive evidence to prove that the endocyclic bond should be positioned between C14 and C15 rather than between C15 and C8.

Finally, the presence of the α -pyridone group was further proved by dehydration of selagine (3) with palladium on charcoal to give 6-methyl-2-pyridone.

An unresolved stereochemical point in the structure determination of selagine (3) concerned the configuration of the ethylidene side chain; a choice between the E isomer (16) and the Z isomer (3).



In 1969 this problem was solved by Shamma and co-workers by using the rates of methiodide formation to determine the alkaloid stereochemistry.³⁸ Their results were based upon comparison with data collected for rates of methiodide formation in isomers of Yohimbine (17).³⁸⁻⁴¹









Yohimbine (17), which possesses the normal configuration, shows a moderate rate of N-methylation (4.8 x 10⁻⁴ sec⁻¹) with the tertiary nitrogen (*) being methylated. α -Yohimbine (18) possesses a hindered nitrogen and methylates very slowly (1.2 x 10⁻⁴ sec⁻¹). Pseudoyohimbine (19), however, has a very unhindered nitrogen and the quaternisation rate is very fast (7 x 10^{-2} sec⁻¹).

In the Z form of selagine (3), approach to the primary amino function at C-13 would be hindered by the methyl group on C-11 and the hydrogens at C-14 and C-3. In 11,12dihydroselagine (11), however, the primary amino function at C-13 is less hindered since the C-12 ethyl group has a chance to rotate. It was therefore expected that selagine (3) would give a very slow rate, the rate for 11,12-dihydroselagine (11) being slightly faster, given that the rates of N-methylation are usually closely related to steric hindrance about the basic nitrogen atom.

Conversely, if selagine (3) were to be represented as the E isomer (16) in which the C-13 primary amino function is not substantially hindered, a faster rate of N-methylation for selagine (3) than for 11,12-dihydroselagine (11) would be expected.

The rate of N-methylation of selagine (3) was found to be slower than that for dihydroselagine (11) suggesting the Z configuration (3) as being correct one for selagine (3). Additional support for the assignment of the Z structure was derived from the ¹H n.m.r. spectrum of the alkaloid. The C-11 methyl group which is in close proximity to the amino group appeared as a doublet at δ 1.67 whereas the C-15 methyl, being relatively distant from the amino function, appeared as a singlet at δ 1.53.

1.1.7 Structure Determination of Huperzine A

The structures of huperzine A (1) and huperzine B (2) were determined in $1986.^{26}$ The structural similarities with selagine (3) were also investigated.



As in selagine (3), infrared and ultraviolet spectra revealed the presence of an α pyridone. Dehydrogenation over palladium on charcoal afforded 6-methyl-2-pyridone further certifying this. The presence of an endocyclic double bond, as revealed in the ¹H and ¹³C n.m.r. spectra, as well as the similarity of its mass spectrum with that of selagine (3), indicated that the structure of huperzine A (1) closely resembled that of selagine (3).³⁵ The specific rotation (-99° in MeOH) of selagine (3), however, was much less than that of huperzine A (1) (-150.4° [c 0.498, MeOH]).

As mentioned earlier, the only structural differences between huperzine A (1) and selagine (3) appeared to be the E or Z stereochemistry at the exocyclic double bond and the position of the endocyclic double bond, between C8 and C15 in huperzine A (1) and between C14 and C15 in selagine (3). The olefinic proton of this endocyclic double bond in the ¹H n.m.r. spectrum of 11,12-dihydroselagine (11) was seen to appear as a singlet while in the ¹H n.m.r. spectrum of huperzine A (1) or in the ¹H n.m.r. spectrum of 11,12-dihydrohuperzine A (20), the olefinic proton appeared as a doublet. It was reasoned that in order to give a singlet the olefinic proton in 11,12dihydroselagine (11) must be adjacent to a tertiary carbon atom, i.e. the double bond between C14 and C15, whereas in huperzine A (1) and 11,12-dihydrohuperzine A (20) the double bond must lie between C8 and C15, with the olefinic proton coupling with the proton on C7. Supporting evidence for the proposed structure of huperzine A (1) was provided by ${}^{1}H{}^{1}H{}$ decoupling experiments and nuclear Overhauser enhancement measurements. Irradiation at H-7 lead to a simultaneous decoupling of H-8 and H-6 while irradiation at H-14 produced a nuclear Overhauser enhancement at H-3.



11,12-Dihydrohuperzine A

Methylation of huperzine A (1) yielded the N-monomethylhuperzine A, the N,Ndimethylhuperzine A and the N,N,N-trimethylhuperzine A. Acetylation also yielded the N-acetylhuperzine A. Examination of the ¹H n.m.r. spectra of huperzine A (1) and these derivatives showed that the signals for H-3 and H-11 were shifted upfield in Nmonomethylhuperzine A and in N-acetylhuperzine A. The remaining protons did not show any significant shift relative to the corresponding protons of huperzine A (1). This information revealed a close spatial relationship between H-3, H-11 and the Nmethyl or the N-acetyl group, i.e. the exocyclic double bond of huperzine A (1) had an E configuration. This assignment was confirmed by n.O.e. experiments. Enhancements at H-7 upon irradiation of H-10 and upon irradiation at H-6 were observed. Selagine (3) has a Z configuration of the exocyclic double bond.³⁸

1.1.8 A Comparison Between the Structures of Huperzine A and Selagine

In 1989 a paper by W.A. Ayer dedicated to the memory of Professor Wiesner, showed that selagine (3) was in fact identical to huperzine A (1).⁴² The two alkaloids were previously thought to be different mainly due to the large difference in the specific rotations of the two compounds.^{26,35} The only sample of selagine (3) remaining in Professor Wiesner's collection was in the form of a potassium bromide pellet used for an infrared spectrum. The pellet was ground and the selagine extracted with dichloromethane. This just provided sufficient material for a 360 MHz ¹H n.m.r. spectrum. An n.O.e. experiment confirmed the proximity of the C-10 methyl to the allylic C-7 hydrogen. Spin decoupling experiments revealed that this allylic hydrogen was coupled to the C-8 alkenic hydrogen. This coupling was not detected in the 60 MHz spectrum of selagine (3) recorded by the earlier workers. As previously mentioned, the stereochemistry at C-11 was not proposed in the original papers on selagine but was assigned as represented by structure (3) on the basis of the rate of methiodide formation.³⁸ Catalytic hydrogenation (over PtO₂) of the "selagine" isolated from *Lycopodium selago* provided the dihydro- derivative (11), which was identical in

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spectroscopic properties with 11,12-dihydrohuperzine A (20). Observation of an n.O.e. effect between the hydrogen at C-12 and the α -hydrogen at C-6 allowed the stereochemistry at C-12 to be assigned.



(3) Selagine



(1) Huperzine A



11,12-Dihydrohuperzine A



 $6-\beta$ -Hydroxyhuperzine A





Isoselagine

In order to confirm their conclusions that huperzine A and selagine were identical, and possessed structure (1), an authentic sample of "selagine" was prepared for comparison. Lycopodium selago was collected near Grovelsjon and near Tarna in Sweden, in the Tonquin Valley near Jasper, Alberta, and near Summit Lake in northern British Colombia. The samples collected from Summit Lake were dried and extracted with 2% aqueous tartaric acid. The crude alkaloid fraction was dissolved in chloroform and the pyridone alkaloids extracted into dilute aqueous sodium hydroxide. Separation of the crude alkaloids was achieved by preparative thin-layer chromatography. Crystallisation from acetone provided a pure compound. The specific rotation of this freshly extracted "selagine" was found to have a specific rotation of -147°. This was comparable to that of huperzine A inferring that the sample of selagine used in the original structure determination must have contained some impurities. Extracts from the other plant samples collected from different locations gave similar results. The isolation of huperzine A (= selagine) from Lycopodium selago afforded 262 mgs of the pure compound from 1.43 kg of dried plant, thus emphasising the importance of an efficient synthesis of this material.

Another sample found in Professor Wiesner's collection was found to be 6- β hydroxyhuperzine A (21). The ultraviolet spectrum was very similar to that of huperzine A (1) and the infrared spectrum showed characteristic α -pyridone absorptions. The ¹H n.m.r. spectrum showed the presence of two alkenic methyls, the two α -pyridone hydrogens, the C-8 alkenic hydrogen and the C-11 alkenic hydrogen, all with chemical shifts similar to those observed with huperzine A (1). N.O.e. experiments demonstrated the proximity of the C-10 methyl group to the allylic C-7 hydrogen. The C-7 hydrogen was also coupled to the benzylic hydrogen at C-6. This result located the hydroxyl group. The size of the coupling between H-6 and H-7 (5.5 Hz) indicated that the hydroxyl group had the β configuration. Oxidation provided the ketone (22). The signal for the hydrogen at C-7 now appeared as a

-27-

doublet. The coupling to the C-8 hydrogen was confirmed by spin decoupling, confirming the position of the endocyclic double bond.

It was thought that a compound assigned structure (23) and named isoselagine may also be identical with huperzine A (1).

1.1.9 Structure Determination of Huperzine B

The structure determination of huperzine B (2) was also included in the paper by Liu in 1986.²⁶ Huperzine B (2) was found to possess an α -pyridone and a C-8, C-15 endocyclic double bond. The notable difference between huperzine A (1) and huperzine B (2) was the absence of signals corresponding to an exocyclic double bond in the ¹H and ¹³C n.m.r. spectra of huperzine B (2). Huperzine B (2) was methylated to give N-methylhuperzine B (24), the spectral characteristics of which closely resembled those of known alkaloid β -obscurine (8).³⁶ Dehydration of huperzine B (2) gave 7-methylquinoline and 6-methyl-2(1H)-pyridone, further supporting the proposed structure of huperzine B (2).



Attempts to convert N-methylhuperzine B (24) to β -obscurine (8) by hydrogenation were unsuccessful, the product being identified as 15-epi- β -obscurine. In Nmethylhuperzine B (24), then, H-12 must be equatorial since in this configuration hydrogen addition to the C-8, C-15 double bond should produce 15-epi- β -obscurine. The stereochemistry at C-12 was verified by n.O.e. experiments.

The assignment of the absolute configuration of the bridgehead carbons, C-13 and C-7, was based upon the comparison of circular dichroism curves. The 7R, 13R, 11E configuration was assigned to huperzine A (1) and 7R, 13R, 12R to huperzine B (2).

The structural data for huperzine A (1) and B (2) are summarised below (tables 1 and 2).

HUPERZINE A

HUPERZINE B



 $C_{15}H_{18}N_2O$ (M⁺ 242.1426)

m.p. 230 °C

 $[\alpha]_{D}^{24.5}$ -150 4° (c 0.498, MeOH)

uv: $λ_{max}$ (EtOH) nm(log ε) 231 (4.01), 313 (3.89)

ir: 3180, 1650, 1615, 1550cm⁻¹

¹H nmr (100MHz)

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H-2 6.38, d, J_{2,3}=9
H-3 7.84, d, J_{2,3}=9
H-6 2.76, 2H, AB part of ABX
J_{6\alpha,6\beta}=16, J_{6\alpha}=3, J_{6\beta,7}=0
H-7 3.56, m
H-8 5.38, d, J_{7,8}=5
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H-10 1.62, 3H, d, J_{10,11}=7

H-11 5.46, q, J_{10,11}=7

H-14 2.12, 2H, s

H-16 1.46, 3H, s NH 13.20, bs (in pyridone)

(2)C₁₆H₂₀N₂O (M⁺ 256.1558) m.p. 270 - 271 °C $[\alpha]_{D}^{25}$ -52.2° (c 0.203, MeOH) uv: λ_{max} (MeOH) nm(log ϵ) 231 (3.95), 312 (3.85) ir: 3100, 1670, 1620, 1610, 1560cm⁻¹ 1 H nmr (400MHz) H-2 6.43, d, J_{2.3}=9.3 7.68, d, J_{2.3}=9.3 H-3 H-6 α 2.85, dd, J_{6 α ,6 β}=17.8, J_{6 α ,7}=5.4 H-6 β 2.43, d, J_{6 α , 6 β}=17.8, J_{6 β ,7}=0 2.34, ddd, $J_{7,12}$ =3.6, $J_{7,8}$ =4.7, $J_{6\alpha,7}$ =5.4 H-7 5.43, bd, J_{7.8}=4.7 H-8 H-9 α 2.29, ddd, J_{9 α ,9 β}=13.5, J_{9 α ,10 β}=12.5, J_{9 α ,10 α}=1.7 H-9 β 2.74, ddd, $J_{9\alpha,9\beta}=13.5$, $J_{9\alpha,10\beta}=3.3$, $J_{9\beta,10\alpha}=1.7$ H-10α 1.54 H-10 β 1.43, ddddd, J_{10 β ,10 α}=J_{10 β ,11 α}=J_{10 β ,9 α}=12.5 $J_{10\beta,9\beta} = J_{10\beta,11\beta} = 3.3$ H-11 α 1.22, dddd, J_{11 α}, 10 α =3.8, J_{11 α}, 12=J_{11 α}, 11 β =J_{11 α}, 10 β =12.5 H-11β 1.54 H-12 1.67, ddd, $J_{11\alpha,12}=12.5$, $J_{11\beta,12}=J_{7,12}=3.6$ H-14_{endo} 1.83, d, J_{14,14}=16.5 $H-14_{exo}$ 2.02, d, $J_{14,14}=16.5$ H-16 1.59, 3H, s NH 13.20, bs (in pyridone)

	HUPERZINE A	HUPERZINE B
Carbon	(22.63 MHz)	(25.18 MHz)
1	165.52 (s)	165.39 (s)
2	116.97 (d)	117.90 (d)
3	140.25 (d)	140.37 (d)
4	122.95 (s)	117.90 (s)
5	142.59 (s)	143.27 (s)
6	35.24 (t)	29.45 (t)
7	32.95 (ď)	34.59 (ď)
8	124.36 (d)	126.12 (d)
9		48.03 (t)
10	12.31 (g)	25.34 (t)
11	111.23 (d)	28.13 (t)
12	143.30 (s)	40.70 (ď)
13	54.35 (s)	53.22 (s)
14	49.25 (t)	41.67 (t)
15	134.09 (s)	132.23 (s)
16	22.57 (q)	22.68 (q)

1.1.10 Total Syntheses of Huperzine A

Over the past 15 years considerable work has gone into the synthesis of selagine (3) but based upon its original structure determination.⁴³⁻⁴⁸ Since 1989 there have been two reported total syntheses of huperzine A (1). The first, by Qian and Ji, employed the following synthetic pathway (Scheme 1).⁴⁹

Table 2



Tetrahydroquinidine (25) was used as the starting material and was prepared in several steps from 5-ethoxycarbonyl-6-methyl-2-pyridone in a 39% overall yield. The construction of bridged ring compound (26) followed a similar route to that used in the

synthesis of lycopodine.⁴⁸ Compound (25) was treated with methacrolein in methanol at -70 °C to room temperature in the presence of sodium methoxide to give (26) in 96% yield. Mesylation of (26) with methanesulphonyl chloride at 0 °C gave the mesylate (27, 62.5%). Treatment of (27) with AcOH-AcONa at 130 °C for 6 to 16 hours gave the alkene (29) (m.p. 123 °C, 30%) and the acetate (28) as the by-product, together with some unchanged (27). Wittig reaction on (29) using ethylidenetriphenylphosphorane at room temperature gave a mixture of Z and E isomers of (30). The mixture was treated with KOH-MeOH to hydrolyse the E-isomer preferentially into the acid (31, m.p. 171 °C), leaving the Z-isomer unchanged. Compound (31) was converted into the urethane (32, 72%) by a modified Curtius reaction with (PhO)₂P(O)N₃ in ethanol.⁵⁰ Cleavage of the methyl ether of (32) by Me₃SiCl/Nal/CH₃CN at 60 to 70 °C afforded the α -pyridone (33), which was heated under reflux with KOH in toluene in the presence of 18-crown-6 ether to give racemic huperzine A (1).

A second synthesis, using a different strategy, has been reported by Xia and Kozikowski using the strategy shown below (Scheme 2).⁵¹

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(40)



The pyrrolidine enamine of (34) is caused to react with acrylamide in dioxane followed by reflux with aqueous dioxane. This puts a pyridone ring onto the monoethylene ketal of 1,4-cyclohexanedione giving a mixture of the double bond regioisomers (35) and (36). The nitrogen in the ring is then protected by N-benzylation and dehydrogenation to the pyridone system (37) brought about by α -selenenylation followed by oxidative elimination and base-catalysed isomerisation. Pyridone (37) was debenzylated using palladium hydroxide in acetic acid and O-methylation brought about with silver carbonate and methyl iodide. The ketal group of (38) was removed by aqueous acid hydrolysis and the free ketone was then carbomethylated at its doublyactivated site by heating with potassium hydride and dimethyl carbonate. Methacrolein was then added across the β -keto ester (39) in a single pot reaction employing 1,1,3,3tetramethylguanidine (TMG) as the catalyst, yielding (40).⁵² Elimination of the hydroxy group was effected by refluxing the derived mesylate in acetic acid with sodium acetate for one day.⁴⁸ The alkene (41) was isolated in ca. 50% yield in addition to some of the unreacted mesylate possessing equatorial methyl and mesylate groups.

The trisubstituted alkene (42) was formed by a Wittig reaction with ethylidenetriphenylphosphorane and gave predominantly the product with Zstereochemistry. By heating with thiophenol and AIBN the Z / E mixture was isomerised to a mixture comprising predominantly the E alkene (43, 90:10 ratio). Hydrolysis of the E / Z mixture of esters was carried out to provide solely the acid of Estereochemistry, in addition to the unreacted more "sterically encumbered ester" of the Z olefin.

The acid was treated with thionyl chloride, sodium azide and methanol to give the urethane (44) via a Curtius rearrangement. Finally, both N and O deprotection was achieved by using trimethylsilyl iodide to give huperzine A as the racemate.

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Racemic huperzine A was found to be almost as potent as natural huperzine A in its inhibition of rat brain acetylcholinesterase.

In order to facilitate scale-up procedures, additional improvements were made to the synthesis in 1990.⁵³ The step thought to be particularly in need of improvement was the preparation of the fused ring intermediate (45) (Equation 4); the initial synthesis involved the use of several expensive reagents (phenylselenyl chloride and palladium hydroxide) (Equation 4).





Several different routes were examined to the pyridone (45). The first route was based upon an old procedure in the German literature (Scheme 3).⁵⁴





The Mannich base (46) of the monoethylene ketal of cyclohexane-1,4-dione was refluxed with the pyridinium salt (47) generated from α -chloroacetamide and pyridine.⁵⁵ This gave the desired pyridone (45) in 9% yield. It was thought that the reaction proceeded *via* an initial Michael addition reaction of the anion formed from the pyridinium salt (47) on the unsaturated ketone derived from the Mannich base (46) by loss of dimethylamine. Heating in dimethylformamide with acetic acid then resulted in ring closure and loss of pyridine.

The next route consisted of refluxing the pyrrolidine enamine of (34) with α chloroacrylamide in dioxane as solvent.



Varying the conditions gave at best only an 11% yield of isolated product. A variation on this theme was an improvement, but still only gave the pyridone in a 22% yield. The anion of (34) was initially reacted with methyl *cis*-3-chloroacrylate.⁵⁶



The crude product of this step was exposed to aqueous ammonium hydroxide to afford the desired pyridone.

The final route involved the reaction of the ketone (34) with a saturated solution of arrimonia in methanol and methyl propiolate in a Parr reactor where heating with stirring at 100 °C was continued for 10 hrs at an internal pressure of 200 p.s.i.. Work-up gave the pyridone (45) in a 70% yield. The overall yield of the previously published synthesis was 45%.



The reaction course was presumed to involve initial condensation of the ammonia with the ketone (34) to provide an imine (48). The enamine form (49) of the imine then reacts in a Michael fashion with the methyl propiolate. Subsequent attack of nitrogen on the ester carbonyl group completes the pyridone ring formation (Scheme 4).



1.1.11 Synthesis of (±)-Z-Huperzine A

Also in 1990, Kozikowski synthesised (\pm)-Z-huperzine A (51) in order to measure its ability to inhibit acetylcholinesterase and determine whether the E-stereochemistry of huperzine A (1) was essential to its recognition and interaction with the enzyme.

The synthesis of Z-huperzine A proceeded by methods similar to those used in his synthesis of huperzine A (1) (Scheme 5).⁵¹





The olefin (42), the major product of the Wittig reaction of the β -keto ester (41) with ethylidenetriphenylphosphorane, was converted into its acid (52) by an S_N2 type dealkylation reaction using lithium n-propylmercaptide in HMPA. The acid was then converted to the urethane (53) in a 71% overall yield. Deprotection with Me₃SiI in

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CHCl₃ at reflux followed by heating in methanol for 13hrs gave (±)-Z-huperzine A (51) as a white crystalline solid.

The compound was tested for its ability to inhibit acetylcholinesterase. The activity of (\pm) -Z-huperzine A (51) was found to be comparable to huperzine B (2). It had, however, significantly lower activity than naturally occurring huperzine A (1). It was concluded that the E-stereochemistry of huperzine A did contribute to its potency as an acetylcholinesterase inhibitor. It may, however, be less toxic than huperzine A (1). If this turns out to be the case, then (\pm)-Z-huperzine A (51) may be a better candidate for the treatment of Alzheimer's disease than the parent compound huperzine A (1).

1.2 RADICAL CHEMISTRY

1.2.1 Background

Radicals are highly reactive species with at least one unpaired electron.^{57,58,59} Unlike anions and cations they react easily with themselves by combination or disproportionation. They react rapidly with the majority of organic molecules, including alkanes which are normally resistant to the action of ions. There are two methods available for the synthesis of products using radical chemistry. The first method uses direct radical-radical combination. The reaction is very fast but has its disadvantages. Radical character is destroyed in the recombination reactions so that at least equimolar amounts of radical initiators must be used in order to continuously generate the radicals. Complications also arise due to the concentration of the radicals being so low as it is difficult to prevent reaction with non-radicals like the solvent molecules, which are present in high concentrations. Despite all the drawbacks, this method has been used successfully in the coupling reactions of electrochemically generated radicals, e.g. the Kolbe electrolysis of carboxylates (Equation 5).

$$RCO_2^- \xrightarrow{-e^-} R^- \xrightarrow{-e^-} R^-$$

Equation 5

The second method employs reactions between radicals and non-radicals and is fundamentally different. Catalytic amounts of radical initiators can be used in these reactions as the radical character is not destroyed during the course of the reaction. The concentration of the non-radicals can easily be controlled and it is possible to influence the selectivities of the radicals by variation of the substituents.

In order to apply the reactions between radicals and non-radicals to synthesis, it is desirable to maintain a low concentration of radicals over the course of the reaction. Chain reactions are ideally suited to meet this requirement. A chain reaction involves a number of different processes. Radicals are generated by an initiation process, they then undergo a series of propagation steps resulting in the generation of fresh radicals, and finally disappear, usually by mutual coupling or disproportionation. To be useful in synthesis, in a particular reaction the chain reaction must generate radicals at a specific site producing radicals that have sufficient time to react; the selectivities of the radicals involved in the chain have to differ from each other; the reactions between radicals and non-radicals must be faster than radical recombination reactions.

A reaction that illustrates all the basic requirements for a radical chain reaction is the radical addition of alkyl halides to alkenes in the presence of tributyltin hydride.



Scheme 6

A halogen atom is extracted from the alkyl halide by tributyltin (54) to provide an alkyl radical (55). Alkyl radical (55) then attacks the alkene forming the adduct radical (56). Radical (56) then abstracts a hydrogen atom from tributyltin hydride yielding the addition product and tributyltin radical (54). Tributyltin radical (54) then reacts with the alkyl halide to regenerate the alkyl radical (55).

In order that a radical chain reaction be synthetically useful, as little radical initiator as possible should be required and few side products should form. This is possible only if the chain propagating radicals meet certain conditions of reactivity and selectivity.

1.2.2 Chain Reactions

1.2.2.1 <u>Reactivity Requirements</u>

Chain reactions are terminated by combination or disproportionation of the radicals. The rate of chain propagation between radicals and non-radicals (r_p) must, therefore, be higher than that of chain termination between the radicals (r_t) . The rate constants r_p and r_t can be expressed by equation 6 and equation 7 where k_p is the rate constant for the chain propagation step and k_t the rate constant for the chain termination step; R• represents all radicals occurring in the chain, and X represents any added reagents.

$$r_{p} = k_{p} \cdot [R \cdot] \cdot [X]$$
 (Equation 6)
$$r_{t} = k_{t} \cdot [R \cdot] \cdot [R \cdot]$$
 (Equation 7)

The reactivity requirements that must be satisfied for the use of radical chains in synthesis is given by equation 8.

$$1 < \frac{r_p}{r_t} = \frac{k_p \cdot [X]}{k_t \cdot [R^*]}$$
 (Equation 8)

In most cases the rate constants k_t , are typically 10⁹ l.mol⁻¹.s⁻¹ in the liquid phase as carbon radicals react with each other in a diffusion-controlled manner. Only a very small temperature dependence is observed. The concentration of the added reagent X is dependent upon the reaction conditions, but in synthesis, these concentrations are often nearly 1 mol.l⁻¹. The concentrations of radicals in chain reactions is also dependent upon reaction conditions, such as the rate of decomposition of the initiator. In chain reactions the radical concentrations are typically around 10⁻⁷ mol.l⁻¹.60 Inserting these values of [X] and [R·] into equation 8, gives a value for k_p of greater than 10² l.mol⁻¹.s⁻¹. Rate constants greater than 10² l.mol⁻¹.s⁻¹ are required for synthetically useful reactions between carbon radicals and non-radicals. This limiting factor can be useful in the planning of a synthesis because it means that a range of functional groups can be tolerated without protection. The homolysis of O-H and N-H bonds in aliphatic alcohols and amines by alkyl radicals,⁶⁰ and the addition of alkyl radicals to C=O groups in ketones and esters takes place with k_p smaller than 10^2 l.mol⁻¹ s⁻¹ at room temperature. These functional groups are therefore not attacked in intermolecular radical C-C bond-forming reactions. Due to the high chemoselectivities exhibited by C-centred radicals, it is possible to employ them in reactions with complex molecules.

1.2.2.2 Selectivity Requirement

Synthetically useful radical chain reactions can only result when the selectivities of the radicals differ sufficiently from each other. As radicals (54), (55) and (56) are present simultaneously in the chain process represented by scheme 6, the formation of products from alkyl halides and alkenes in the presence of tributyltin hydride takes place in good yields when the selectivity of the adduct radicals (56) is significantly different from that of alkyl radical (55). This difference in selectivity allows radical (55) to add to an alkene, adduct radical (56) to abstract a hydrogen atom from tributyltin hydride, and tributyltin radical (54) to react with an alkyl halide. If adduct radicals (56) possessed the same selectivity as the alkyl radicals (55) this would lead either to polymerization of alkenes, reduction of alkyl halides or would result in a mixture of products. These problems can be prevented by choosing suitable substituents on the alkene thus changing the selectivity of radical (56) compared to radical (55).

The rates of addition of free radicals to alkenes are determined by substituents at the radical centre and by substituents on the alkene. This has been covered in detail in a paper by Giese.⁶¹ Generally, alkyl radicals substituted with electron-donating groups,

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e.g. alkyl, alkoxy, amino etc., behave like nucleophiles. They react very quickly with alkenes containing electron-withdrawing substituents, e.g. nitrile, ketone, ester etc. Conversely, radicals with electron-withdrawing substituents behave like electrophiles and react readily with electron-rich alkenes. Application of the tin method to synthesis is only possible with halides and alkenes that lead to radicals (55) and (56) with different or opposite polarity. The selectivities must differ to such an extent that the desired reaction dominates over the various competitive reactions. In order to form a C-C bond, the reaction between radical (55) and the alkene has to be faster than the reduction of (56) by tributyltin hydride. This is possible either by using an excess of alkene or by using low concentrations of tributyltin hydride. Low concentrations of tributyltin hydride can be achieved by adding the tin hydride slowly to the reaction mixture or by using a catalytic amount of tin salts and equimolar amounts of sodium borohydride, thus generating the tin hydride *in situ*.

Another synthetically important factor involved in the chain is the competition between addition to the alkene and halogen abstraction from the alkyl halide. (The competition between addition to an alkene and hydrogen capture is of no importance for the tributyltin radical (54) because (54) is regenerated upon hydrogen transfer from tributyltin hydride to (56)). As the undesired addition of tin radicals to alkenes cannot be greatly influenced by varying the concentration, it is better to use alkyl iodides which are 10-100 times more reactive than alkyl bromides.

It is possible, therefore, to evaluate whether specific reactions are synthetically useful as many of the rate constants for radical reactions have been determined. Moreover radicals have many advantages over ions in synthesis; neutral radicals, unlike ions, are little affected by a change in solvent; in radical reactions, numerous functional groups require no protection; radical reactions often show different regioselectivities than those found in ionic reactions e.g. α , β -unsaturated carbonyl compounds are attacked

exclusively at the olefinic carbon atom by carbon-centred radicals; in radical reactions the product of "umpolung" of the reactivity can be often observed.⁶²⁻⁶⁴

1.2.3 Intramolecular Formation of Aliphatic C-C Bonds

Radical cyclisation reactions have been developed to a great extent over the 1ast 10 - 20 years.^{57,59} In addition to C-C multiple bonds, a number of other functional groups can be used as radical traps including C-O and C-N multiple bonds.

A well understood intramolecular cyclisation reaction is the cyclisation of hex-5-en-1-yl radical, (57), to cyclopentylmethyl radical, (58) (Scheme 7).



Scheme 7

In this chain reaction although radicals (57) and (58) have the same nucleophilicity, the selectivity requirement is fulfilled because radical (57) reacts intramolecularly with the alkene double bond, whereas radical (58) reacts intermolecularly with tributyltin

hydride. The fact that cyclisation reactions are fast enough for a successful application to synthesis is shown by a rate constant of approximately 10^{6} .s⁻¹ at 20 °C for the cyclisation of the hex-5-en-1-yl radical (57) to cyclopentylmethyl radical (58).⁶⁵ This rate constant is increased by electron-withdrawing substituents at the double bond.

Hept-6-en-1-yl radicals cyclise to give the six-membered ring as well as the sevenmembered ring, however, simple three and four-membered rings cannot be formed in this way. The homo-allyl radical (59) rapidly cyclises to the cyclopropylmethyl radical (60) but this reverts back very rapidly to the more stable (59).



Only in a synthesis where a large proportion of the ring strain of the three-membered ring is already present in the homo-allyl radical, such as the norbornyl radical (61), can a cyclic radical such as (62) be trapped. Large rings can also be synthesised *via* radical cyclisation reactions.⁶⁶



1.2.4 <u>Regioselectivity in Intramolecular Cyclisation Reactions</u>

Hex-5-en-1-yl and hept-6-en-1-yl radicals (57) and (63) cyclise to give predominantly the less thermodynamically stable products (58) and (64).



The thermodynamically less stable primary radicals are formed much faster than the more stable secondary radicals. This is in stark contrast to the cyclisation of the analogous carbonium ions, which usually give the six-membered products and seven-membered products respectively.

The preference shown by hex-5-en-1-yl radicals for formation of five-membered rings may be a result of the geometry of the transition state.⁶⁷ The transition state for radical cyclisation probably involves interaction of the unpaired electron with the lowest unfilled orbital of the π system. As a result of this, the radical centre approaches preferentially from above (or below) the plane of the unsaturated section and along a line extending vertically from one of the carbon atoms of the double bond (Figure 4).



The carbon atom of the double bond most readily approached by the radical centre from vertically above is carbon b, resulting in formation of the cyclopentylmethyl radical (58). Also, Baldwin's rules require that five-membered ring formation (5-*exo*-trig reaction) be faster than six-membered ring formation (6-*endo*-trig reaction). This explanation is applicable to the cyclisation of hept-6-en-1-yl radicals to cyclohexylmethyl radicals and also accounts for the reluctance of pent-4-en-1-yl radicals to cyclise.

The *endo*-cyclisation could also be retarded by an unfavourable interaction between the pseudo-axial proton at C-2 and the *syn* proton at C-6. This will destabilise the transition state, (65), for ring closure to give the six-membered ring by comparison with the transition state, (66), for five-membered ring formation.⁶⁸



Less favourable entropies in the formation of cycloalkyl radicals compared to cycloalkylmethyl radicals are also a factor.

The ratio of the five- to six-membered rings depends upon the substituents on the alkene. If a methyl group is present on the double bond, this reduces the attack at this C-atom due to steric effects. Methyl groups at the radical centre, on the other hand, have only small effects.



Under thermodynamic conditions, however, the radical cyclisations are reversible and six-membered rings are formed predominantly.



1.2.5 Stereoselectivity in Intramolecular Radical Cyclisation Reactions

As well as being able to predict the regiochemistry of intramolecular cyclisation reactions, it is possible to predict the stereochemistry by applying two guidelines formulated by Beckwith.^{69,70} *Exo*-ring closure of hex-5-en-1-yl radicals and related systems monosubstituted at C-1, C-2, C-3 or C-4 gives rise to mixtures of *cis*- and *trans*- disubstituted cyclic products. Available data suggests that generally 1,5-ring closures of 1- or 3-substituted systems afford mainly *cis*-disubstituted products, whereas 2- or 4-substituted systems give mainly *trans*-products. These generalisations can be explained by consideration of the transition state structure below (Figure 5).



Figure 5

The more favourable conformer should contain the substituent in the equatorial position at C-2, C-3 and C-4. This is outlined in the series of radical cyclisation reactions below.



The preferential formation of *cis*-products from 1-substituted radicals, e.g. (67), has been ascribed to the effects of orbital symmetry. The favourable interaction between the semi-occupied orbital and the vacant π^* orbital of matching symmetry in the transition state, (68), outweighs the non-bonded repulsion between C-6 and the 1methyl substituent. If the substituent on C-1 is bulky, however, simple steric factors take precedence and the *trans*-product predominates.



In the formation of a six-membered ring from the 1-methylhept-6-en-1-yl radical, (69), the *cis*-product is again the major isomer.



1.2.6 Formation of Bicyclic and Tricyclic Fused Ring Systems

The formation of fused carbocyclic ring systems by radical cyclisation also conforms to simple guidelines. The formation of the bicyclic system (70) proceeds under the conditions of kinetic control. The ring-fusion geometry can be predicted by empirical rules.⁷¹


When n = 1 and 2 the preferred stereochemistry at the ring junction is *cis*. *Trans*-ring fusion is <u>disfavoured</u>. When n = 3 formation of the *trans*-ring junction is <u>favoured</u> and we see a mixture of *cis*- and *trans*-ring fused products.

Ring closures of the butenyl cycloalkyl radicals, (71) and (72) gives the major products (73) and (74), the all-*cis* compounds. Inspection of models shows that overlap between the semi-occupied orbital and the π^* orbital is attained most efficiently when (72) reacts through the conformer containing the substituent in a pseudo-axial position.^{69,72}



1.2.7 Radical Reactions in Synthesis

Intramolecular cyclisation reactions have been applied successfully to the synthesis of many target molecules. A vast number of methods have been developed to produce

and trap radicals and these methods are covered extensively in the many reviews on radical chemistry.^{57,64,73-76} Included are the production of radicals from thioacylated alcohols,⁷⁷ alkyl sulphides, aryl sulphides, alkylselenides, acyl selenides by the cleavage of C-S and C-Se bonds,^{78,79} nitro compounds,⁸⁰ diazonium salts,⁸¹ and azo compounds.⁸² (The fact that the catalytic cleavage of carbon - nitrogen bonds in azo compounds is so facile at the temperature of refluxing benzene has lead to their widespread use as initiators in chain reactions.) Radicals are also produced by the reduction of mercury salts,⁸³ and the cleavage of the Co-C bond of alkyl cobalamines.⁸⁴

1.2.8 Radical Cyclisation on to Carbon-Nitrogen Double Bonds

The intermolecular reaction between an oxime and alkyl radical was demonstrated as early as 1968.^{85,86}



More recently, addition of alkyl radicals to O-benzylformaldehydeoxime was achieved by Hart.⁸⁷ Iodohexane (**75**) was treated with tributyltin hydride, AIBN and Obenzylformaldehydeoxime in benzene to give the addition product (**76**) in 25% isolated yield at best . Presumably reduction of the initially formed radical by tin hydride predominated.



In an attempt to eliminate reduction, different sources of tin radicals were examined. The use of hexamethylditin provided cyclohexane carboxaldoxime (77) by addition of cyclohexyl radicals to O-benzylformaldoxime followed by fragmentation and tautomerisation of the resulting nitroso compound. This reaction went in only 8% yield.



Eventually the cyclisation was perfected using bis(trimethylstannyl)benzopinacolate (78) which, upon heating above 60 °C, affords trimethyltin radicals.⁸⁸



Thus iodocyclohexane, O-benzylformaldoxime and

bis(trimethylstannyl)benzopinacolate (78) were heated in benzene for 4 h to afford the hydroxylamine (79) in 76% yield.

$$R-X \xrightarrow{Me_{3}SnO OSnMe_{3}} | | | \\ Ph_{2}C - CPh_{2} \\ R-X \xrightarrow{R-CH_{2}NHOCH_{2}Ph} \\ CH_{2}=NOCH_{2}Ph \\ PhH, \Delta$$
(79)

There have been relatively few examples involving the intramolecular trapping of radicals by carbon-nitrogen double bonds. Corey and Pyne first demonstrated that oxime ethers were good acceptors for alkyl radicals in 1983.⁸⁹ Ring formation leading to cyclopentanol systems was achieved by the reductive activation of ketones by zinc-trimethylsilyl chloride and subsequent internal addition on to a variety of π -unsaturated functions to form the five-membered ring. The action of zinc-trimethylsilyl chloride on the unsaturated ketone generates, by electron transfer and silylation, an α -trimethylsilyloxy radical which adds to the $\delta_i \epsilon$ -multiple bond to form a five-membered ring (Scheme 8).



Cyclisation of the O-methyloxime (80) via this method produced the hydroxylamine (81) in 84% yield.



The same reaction was also achieved with alkenes, alkynes, α , β -unsaturated esters, nitriles and aldehydes as the radical traps with varying success.

In 1986, Nishiyama *et al.* described the formation of cyclopropane (82) from hydrazone (83).⁹⁰ The proposed mechanism does not, however, involve radical cyclisation on to the carbon-nitrogen double bond, but is thought to proceed by the intermediate shown below (Scheme 9).



Replacement of the tin radical occurs during formation of the cyclopropane (82).

More recently, Bartlett has reported the ready cyclisation of oxime ethers, exploring variations in chain length and substitution at both the radical centre and the oxime carbon.⁹¹



The radicals were generated by the tin hydride reduction of phenyl thionocarbonates in benzene or toluene at reflux temperature. Numerous examples were tried and it was found that on increasing the chain length from n = 1 to n = 2, the proportion of reduction prior to cyclisation increased as would be expected. For a given chain length, the oximes ethers derived from aldehydes cyclised more readily than those derived from ketones. In contrast, steric hindrance at the radical centre improved the ratio of cyclisation to reduction. The ratio of cyclisation to reduction did not, surprisingly, show a significant dependence upon concentration.

This cyclisation method was also applied to the conversion of a carbohydrate to a carbocycle (Scheme 10).





The most recent example of oxime ethers being successfully employed as radical traps was reported by Enholm *et al.*.⁹² Vinyl tin radicals were prepared from terminal alkynes and were cyclised on to oxime ethers in good yields. Subsequent protiodestannylation with acetic acid in methanol then afforded the desired product bearing an *exo*-methylene sub-unit and an O-benzylhydroxylamine group. The simplest example is shown below (Scheme 11).



Although a number of uses of oxime ethers and oximes as radical traps have been described here, there are no reported examples of the attack of vinyl or aryl radicals on such groups.

1.2.9 Tandem Radical Cyclisation Reactions

It is usual after a radical cyclisation for the adduct radical to abstract a hydrogen atom from tin hydride. If, however, the radical generated in the first reaction is used as a precursor in another, multiple radical reactions can be conducted. Such cyclisations are called tandem radical cyclisation reactions and are accomplished by generating an internal radical within bonding distance of a multiple bond to generate a new radical which in turn cyclises on to the next appropriately positioned multiple bond.

The tandem radical cyclisation strategy was developed by Stork and both alkyl and vinyl radicals were used in cyclisation reactions with both acyclic and cyclic multiple bonds. Several features of the chemistry developed by the Stork group are highlighted in the tandem cyclisation shown below (Scheme 12).⁹³



Scheme 12

A tributyltin radical abstracts the bromine atom leaving the less reactive C-Cl bond intact. The alkyl radical (86) thus formed attacks the triple bond in an *exo*-dig reaction with the formation of the vinyl radical (87),⁹⁴ which then reacts with the double bond of the cyclohexane in an *exo*-trig reaction (87 to 88) (Scheme 13). The final radical has no good intramolecular options open to it and survives until the best intermolecular option occurs, hydrogen transfer from tributyltin hydride.



Scheme 13

Selectivity is easily controlled since each intermediate radical has only one appropriately located acceptor for intramolecular addition. The formation of the *cis*-fused ring junction was in agreement with the set of rules formulated by Clive,⁷¹ mentioned previously.

In 1985, Beckwith reported an example of a triple radical cyclisation.⁹⁵



Despite it being possible to form numerous products, only eight major structural isomers were obtained. Four of these were assigned as diastereoisomers of the tricyclo[6.3.0]undecane (89) shown. If tributyltin hydride was used, even more products were obtained. In this example, some of the intermediate cyclisations were not extremely fast relative to hydrogen abstraction. As the number of cyclisations increases, it becomes more likely that intermediate radicals will be intercepted prior to the completion of the sequence.

By careful planning of regio- and stereochemical control, Curran has applied tandem radical cyclisation strategy to the synthesis of natural products. A few examples, emphasising different approaches, are outlined below.

A general route to the triquinane class of natural products was developed, the *cis*-fused rings of which were ideally suited to synthesis by radical methods.^{96,97} Hirsutene (90) and $\Delta^{9,12}$ -capnellene (91) were prepared as in scheme 14.





A central preformed cyclopentene ring was used to ensure the required stereochemical outcome of the tandem radical cyclisation. In the second cyclisation, the tertiary radical (92) cyclised to yield the vinyl radical (93). Although tertiary radicals are more stable than vinyl radicals, the cyclisation remains exothermic and occurs very quickly because a σ -bond is formed at the expense of a π -bond. This success is in contrast to anion and cation cyclisations, where the stability of the anion or cation in the product relative to the starting material often plays a central rôle in determining the rate. The generality of the strategy was established by an analogous preparation of $\Delta^{9,12}$ -capnellene (91).

Samarium diiodide was employed in place of tributyltin hydride to prepare more complicated oxygenated triquinanes. Hypnophilin (94) was prepared *via* radical (95) using the tandem radical cyclisation strategy (Scheme 15).⁹⁸



Scheme 15

In 1986, Curran devised a short route to the angular triquinane silphiperfolene (96).^{99,100} The route involved two sequential cyclisations on to olefinic bonds starting with a vinylic radical (Scheme 16).



Radical cyclisation of (97) provided a 3:1 mixture of isomers (98) in 66% yield, but in the major stereoisomer the methyl group was β , contrary to the target molecule. The stereochemistry probably resulted from the chair-like transition state (99) in which the alkene orients itself *endo* rather than *exo* relative to the existing ring, leading to the thermodynamically less stable product.



In order to disfavour transition state (99) relative to boat-like transition state (100), the carbonyl group was sterically "enlarged" by conversion to the acetal (101), which cyclised in 65% overall yield to give (102). A 1:2.5 mixture of isomers formed, with the desired α -methyl isomer predominating. The synthesis was made optically active by Meyers and Lefker.¹⁰¹

The tandem radical cyclisation involved in the formation of (102) again demonstrates the ability of radical cyclisations to generate very crowded bonds. In the first cyclisation step a quaternary centre and a tetra-substituted alkene were formed and in the second step, two tertiary centres formed. The stereochemistry of the reaction is also interesting. The thermodynamically less favoured *endo* product (102) β was formed even in the presence of the acetal, thus emphasising the bias for the chair-like transition state (99) rather than the boat-like conformer (100).

Two other applications of tandem radical reactions worth mentioning are Fraser-Reid's synthesis of (-)- α -pipitzol¹⁰² and Stork's synthesis of (+)-postaglandin F_{2 α} ¹⁰³. Since the pioneering work of Stork, however, numerous examples have appeared in the literature from several different laboratories. These include work by Kilburn,¹⁰⁴ Parsons,^{105,106,107} Ferner,¹⁰⁸ Maillard,¹⁰⁹ Corey, ¹¹⁰ and Nagano.¹¹¹

Fraser-Reid used a tandem radical cyclisation in his synthesis of (-)- α -pipitzol (103) from a carbohydrate (Scheme 17).





The pyranoside (104) was converted to (105) which reacted with tin hydride to give (103) in 65% yield. The radical was generated by a stannyl radical addition rather than abstraction of a halogen. The mechanism involves addition of tin radical to the alkyne, stereoselective cyclisation of the vinyl radical (106) and addition of the resulting alkyl radical (107) to the nitrile.

Finally, a tandem intramolecular cyclisation-intermolecular alkylation reaction was used by Stork in the synthesis of (+)-prostaglandin $F_{2\alpha}$ (108) (Scheme 18).



(109) was treated with a catalytic amount of tributyltin hydride and an excess of the α -silyl-substituted vinyl ketone, resulting in cyclisation and intermolecular trapping to produce (110). Two new alkyl groups were added across the double bond with complete control of stereochemistry.

1.2.10 The Use of Ketones as Radical Traps

Until recently, the addition of alkyl radicals to carbonyl groups has not been considered as useful for synthetic application due to the unfavourable equilibrium situation. The addition of an alkyl radical to a carbonyl is generally regarded as an endothermic or near thermoneutral transformation. This is due to the carbon-oxygen π bond being much stronger than the carbon-carbon π bond and because the oxygen-centred radical is less stable than the carbon-centred radical.



Discoveries by Fraser-Reid and Tsang have shown that carbon-oxygen π bonds can be used effectively as radical traps in synthesis.¹¹²⁻¹¹⁴



Reduction of the carbohydrate-derived aldehyde (111) by tributyltin hydride produced the cyclohexanol (112) in 85% yield. Successful cyclisation was also achieved when a non-rigid precursor (113) was used. Reaction of (113) with tributyltin hydride produced only the product of 6-*exo* cyclisation to the carbonyl (114). Rapid 5-*exo* addition to the alkene was not observed to compete.

Despite the controversy over whether carbonyl groups are good radical acceptors or not, the most exploited reaction for oxygen-centred radicals is β -bond cleavage. This transformation is very useful in ring enlargement processes (Scheme 19).



Scheme 19

Y can be either carbon, oxygen or nitrogen, giving ketones, lactones or amides respectively.

It has been independently demonstrated by both Beckwith and Dowd that α bromomethyl substituted β -keto esters can be ring expanded by one carbon upon treatment with tributyltin hydride.^{72,115}



It has since been shown that related three- and four-carbon ring expansions are also possible.^{116,117} The method allows an easy, convenient way of preparing medium-sized rings from widely distributed five- and six-membered rings.¹¹⁸ The method was most readily applied to β -keto esters whose preparation from Dieckman and Claisen condensation reactions is well established.

The simplest example is the one-carbon ring expansion of methyl 1-bromomethyl-2oxocyclopentanecarboxylate (115) to methyl 3-oxocyclohexanecarboxylate (116).



Similarly six- and seven-membered cyclic β -keto esters were expanded into seven- and eight-membered cyclic γ -keto esters in yields greater than 70%. The method can also be applied to straight chain compounds.



The ring expansion was extended to include longer chain insertions. Two-carbon ring expansions were not possible since 4-*exo* cyclisation cannot compete favourably with hydrogen atom transfer to the initial primary radical. The only product isolated from the reaction was the direct reduction product. The three-carbon and four-carbon ring expansions were more successful. A few examples are shown below.





Alkyl iodides were found to give significantly better yields as a consequence of improved chain transfer reaction.¹¹⁹

The same strategy was also used to ring expand twelve-, thirteen- and fourteenmembered carbocyclic rings. As twelve-membered rings are readily available, the method would allow access to the larger, less readily available members of the series (Scheme 20).¹²⁰





The total synthesis of (±)-muscone (117) was achieved using a similar strategy starting from a twelve-membered cyclic ketone (Scheme 21).



Scheme 21

Initial attempts to carry out the expansion in the presence of an ester group, as was the usual strategy, yielded the eleven-membered ring-contracted product (Scheme 22).





Suginome and Yamada successfully synthesised (±)-muscone (117) employing samarium iodide as an alternative to tributyltin hydride (Scheme 23).¹²¹



(118)



Intermediate (118) was isolated, again supporting the observations made by Tsang and Fraser-Reid that carbonyl groups could act effectively as radical traps.¹¹²⁻¹¹⁴

Pattenden has also applied this radical ring expansion reaction in building up the carbon skeleton for the taxane group of natural products.¹²²



The work described in the discussion section which follows is concerned with the development of a radical cyclisation strategy for the synthesis of huperzine A (1) and B (2). This strategy is based on the novel intramolecular cyclisation of alkyl and vinyl radicals on to the carbon-nitrogen double bond of an oxime ether.

Discussion

2.1 STEPS TOWARDS THE SYNTHESIS OF HUPERZINE

2.1.1 Strategy

The general aim of the project was to develop a flexible, stereocontrolled route to huperzine A (1), which could be used to prepare analogues that may have improved characteristics, and which could provide a common synthetic intermediate to other Lycopodium alkaloids e.g. β -obscurine (3).



HUPERZINE A



HUPERZINE B



The synthetic route to huperzine A (1) is based on the retrosynthetic analysis shown in Scheme 24.



The central feature of the proposed route was the synthesis of intermediates (119) and (120), which would allow simultaneous formation of the bicyclic system and tertiary amino function, either by a Lewis acid catalysed ring closure of an allyl silane on to an imine or iminium ion, 123 or by a radical addition on to an imine.

The envisaged reaction sequence to intermediates (119) and (120) is shown in Scheme 25.





The required cyclohexanecarboxylic acid starting materials could be prepared by cycloaddition chemistry.¹²⁴⁻¹³¹ Iodolactonisation,¹³¹⁻¹³⁸ followed by reaction with sodium methoxide, would result in formation of the epoxide on the same face as the

ester group. Thus, introduction of the allylic silane or vinyl bromide could then be achieved regiospecifically by organolithium or organocuprate mediated alkylation. The reformation of the lactone would ensure that the allylic silane or vinyl bromide was axial. The derived ketones would then be converted into imine derivatives and suitable conditions for their cyclisation investigated. Carbon-carbon bond formation has been effected in related systems by a variety of methods and acid catalysed ring closure of an allyl silane on to an imine is well precedented in the literature.^{123,139-142} The radical process would represent essentially new synthetic methodology,^{89,90} and so the feasibility of the trapping of radicals by carbon-nitrogen double bonds was to be investigated using model systems.

It was envisaged that the completion of the synthesis to huperzine A (1) may be accomplished using the reaction sequence shown in Scheme 26.



The initial aim of the project was to carry out the reactions outlined in the proposed synthesis of huperzine A (1) (Scheme 25), but using simplified precursors. This would give some indication of the feasibility of the proposed route and highlight any difficulties with the individual steps in the synthetic pathway.

The model reactions to be carried out are shown in Scheme 27 below.



Scheme 27

2.1.2 Attempts at Synthesis

1-Trimethylsiloxybuta-1,3-diene (121) was prepared by refluxing a centrifuged solution of triethylamine and trimethylsilyl chloride in benzene, with crotonaldehyde and anhydrous powdered zinc chloride for 72 h under an atmosphere of dry nitrogen.¹⁴³⁻¹⁴⁸ The crude product was purified by distillation under reduced pressure (b.p. 44 °C at 30 mmHg) to give a clear, colourless liquid in 46% yield. This reaction has been repeated a total of five times. In earlier preparations the solution of triethylamine and trimethylsilyl chloride in benzene was not centrifuged before addition of the crotonaldehyde and zinc chloride, and this resulted in lower yields of 40%, 27%, 33% and 36% respectively. Centrifuging removes small amounts of triethylamine hydrochloride formed by reaction of the triethylamine with any HCl formed by hydrolysis of the trimethylsilyl chloride, but it is not entirely clear why the presence of triethylamine hydrochloride has the effect of reducing the yield of the diene (121).

The diene (121) was characterised by ¹H n.m.r. spectroscopy. The 300 MHz (CDCl₃, no reference) spectrum showed characteristic bands at $\delta_{\rm H}$ (300 MHz, CDCl₃, no reference) 0.00 (s, 9 H, Si(C<u>H</u>₃)₃), 4.81 (dd, 1 H, ²J_{4a,4b} 0.5, ³J_{4a,3} 10.7 Hz, H_{4a}), 4.98 (dd, 1 H, ³J_{4b,3} 16.9 Hz, H_{4b}), 5.72 (overlapping dd, 1 H, ³J_{2,3} = ³J_{2,1} 11.9 Hz, H₂), 6.21 (complex ddd, 1 H, H₃), 6.52 (d, 1 H, H₁) ppm.



The spectrum was complicated by the presence of a small amount of crotonaldehyde and another product which was possibly a hydrolysis product. As a further complication there was additional small coupling in some of the olefinic bands which may have been due to some other geometrical isomer.

The second step in the synthetic sequence was the Diels-Alder addition of (121) to methyl acrylate.¹²⁴⁻¹²⁵



This reaction was carried out using an excess of methyl acrylate at the reflux temperature of toluene for 60 h under a nitrogen atmosphere. The crude product obtained after removal of the toluene solvent was distilled under reduced pressure to give methyl 2-trimethylsiloxycyclohex-3-ene carboxylate (122) as a clear, colourless liquid (b.p. 70 °C at 0.5 mmHg) in 68% isolated yield. This reaction has been carried out three times; once under identical conditions to those described above (isolated yield 63%), and another reaction without toluene solvent, which gave only a 45% isolated yield.

Compound (122) was characterised by ¹H n.m.r. spectroscopy. The 300 MHz spectrum revealed the presence of two isomers, a major isomer (122a) and a minor isomer (122b) in the ratio of approximately 1.85:1.



(122a)

Compound (122a): $\delta_{\rm H}$ (300 MHz, CDCl₃, no reference) -0.03 (s, 9 H, Si(CH₃)₃), 1.60-2.10 (complex m, 4 H, H_{6a}, H_{6b}, H_{5a} and H_{5b}), 2.37-2.46 (complex m, 1 H, H₁), 3.57 (s, 3 H, OCH₃), 4.37 (dd, 1 H, ³J_{2,1} 4.6 Hz, H₂), 5.40-5.85 (complex m, 2 H, H₃ and H₄) ppm.

Compound (122b): $\delta_{\rm H}$ (300 MHz, CDCl₃, no reference) 0.0 (s, 9 H, Si(CH₃)₃), 1.60-2.10 (complex m, 4 H, H_{6a}, H_{6b}, H_{5a} and H_{5b}), 2.37-2.46 (complex m, 1 H, H₁), 3.59 (s, 3 H, OCH₃; ratio of 3.57:3.59 bands 1.9:1), 4.43 (overlapping dq?, 1 H, ³J_{2,3} 2.1, ³J_{2,1} 8.4 Hz, H₂), 5.40-5.85 (complex m, 2 H, H₃ and H₄) ppm.

Reactivity in cycloaddition reactions is related to the HOMO-LUMO separation, higher reactivity being associated with a small HOMO-LUMO energy gap (Figure 6).^{149,150}


 ΔE (diene HOMO - dienophile LUMO) = 8.2 eV ΔE (diene LUMO - dienophile HOMO) = 11.4 eV

Figure 6

Thus, the most important interaction involves the diene HOMO and the dienophile LUMO.

The regioselectivity of the cycloaddition reaction is determined by the orbital coefficients.





Pairing large with large, and small with small, leads to greater stabilisation and explains the observed regioselectivity (Figure 7).

The periselectivity of the cycloaddition is predicted by the Alder *endo* rule of addition. Preference for the *endo* mode of addition, which is often sterically more congested, is due to the interaction of the frontier orbitals which are most directly involved in forming the new bonds.



Primary interactions represent the sites of the new bonds. The secondary orbital interactions do not lead directly to new bonds, but lower the energy of the *endo* transition state relative to that of the *exo* transition state, where these transitions are absent; hence, the *endo* adduct is the one obtained under kinetically controlled conditions (Figure 8).

The *endo* rule does not predict the stereochemistry of the -OSiMe₃ group, hence the formation of the two stereoisomers (**122a**) and (**122b**) seen in the 300 MHz n.m.r. spectrum, which shows compound (**122a**) as the major stereoisomer.

The next stage in the reaction sequence (see Scheme 28) was the deprotection of the $OSiMe_3$ group and hydrolysis of the methyl ester to the carboxylic acid (123).



Deprotection of the OSiMe₃ group was accomplished in 97% yield by stirring compound (122) with 3M methanolic hydrochloric acid at room temperature for 1 h to give the product (124) as a clear, colourless liquid.¹⁵¹ The ¹H n.m.r. spectrum (90 MHz, CDCl₃, no reference) showed characteristic bands at 1.8-2.3 (complex m, 4 H, H_{5ax}, H_{5eq}, H_{6ax} and H_{6eq}), 2.5-2.8 (complex m, 1 H, H₁), 3.3-3.6 (complex m, 2 H?, OH and H₂O?), 3.8 (s, 3 H, OCH₃), 4.5 (complex m, 1 H, H₂), 5.7-6.0 (complex m, 2 H, H₃ and H₄) ppm.



Hydrolysis of the product to the corresponding carboxylic acid (123) was carried out by stirring with methanolic potassium hydroxide at 100 °C on a water bath for 6 h.¹⁵¹⁻¹⁵⁵ After the usual work-up the crude product was obtained as a pale yellow liquid in 84% yield, but recrystallisation from chloroform gave the pure product as white crystals (m.p. 83-84 °C). The ¹H n.m.r. spectrum (90 MHz, CDCl₃, no reference) of the acid (123) showed the expected bands at $\delta_{\rm H}$ 1.8-2.3 (complex m, 4 H, H_{5ax}, H_{5eq}, H_{6ax} and H_{6eq}), 2.3-2.8 (complex m, 1 H, H₁), 4.5 (s, 1 H, H₂), 5.6-5.9 (complex m, 2 H, H₃ and H₄) ppm, but an unexpected feature was that both the hydroxyl proton and the carboxyl proton appear as a singlet (2 H) at the same chemical shift value of 7.4 ppm - this band disappears after shaking the solution with D₂O. Usually, a carboxylic acid proton would be expected to resonate between δ 9.5 to 13 ppm. This suggests that the hydroxyl and the carboxyl protons are exchanging rapidly in deuterochloroform solution.

From a 300 MHz ¹H n.m.r. spectrum it was possible to obtain the relevant coupling constants, and hence determine the approximate ratio of the two diastereoisomers present.



<u>Major diastereoisomer (123a)</u>: δ 1.95-2.20 (complex m, 4 H, H_{6ax}, H_{6eq}, H_{5ax} and H_{5eq}), 2.35-2.62 (overlapping dq, 1 H, H₁), 4.43 (br, 1 H, H₂), 5.75-5.88 (complex m, 2 H, H₃ and H₄), 7.40 (s, 2 H, OH and CO₂H) ppm.

Minor diastereoisomer (123b): δ 1.62-1.75 (complex m, 1 H, OH), 1.75-1.90 (complex m, 4 H, H_{6ax}, H_{6eq}, H_{5ax} and H_{5eq}), 2.38-2.47 (overlapping dq, 1 H, H₁), 4.43 (br, 1 H, H₂), 5.62-5.72 (complex m, 2 H, H₃ and H₄), 10.0 (s, 1 H, CO₂H) ppm

The ratio of the major : minor isomer was 1.69:1 in the sample.

It is interesting that in the minor diastereoisomer (123b) the hydroxyl hydrogen appears as a complex band at δ 1.62-1.75, while that of the carboxylic acid proton is at δ 10.0 and these protons do not exchange in solution as do the protons of the major isomer. This supports the assignment of the structure shown for the minor isomer in which the hydroxyl and carboxylic protons are *anti* and cannot readily exchange.

The next step in the model synthesis was the iodolactonisation of (123) to give the five-membered iodolactone (125). The iodolactonisation reaction has been attempted under both kinetically-controlled and thermodynamically-controlled conditions, but under both sets of conditions the reaction was, at best, only 12% effective.¹³⁴





The thermodynamically-controlled reaction involved stirring compound (123) with iodine in acetonitrile under nitrogen at 0 °C in the dark. Initially the reaction was carried out overnight and it has been repeated under these conditions three times giving isolated yields of (125) of 7, 7.5 and 8% respectively. Even when the reaction time was extended to 12 days at 0 °C only a 12% yield of the desired iodolactone (125) was obtained. This was identified by ¹H n.m.r. spectroscopy (90 MHz, CDCl₃, TMS) $\delta_{\rm H}$ 1.8-2.3 (complex m, 5 H, H_{5ax}, H_{5eq}, H_{6ax}, H_{6eq} and OH by D₂O shake), 2.6-2.8 (complex m, 1 H, H₁), 4.4-4.7 (complex m, 2 H, H₂ and H₄), 5.9 (s, 1 H, H₃) ppm. The five-membered lactone has a characteristic i.r. stretching vibration at 1785 cm⁻¹, and in a repeat experiment the course of the reaction was followed by i.r. spectroscopy, checking for the disappearance of the bands at 3620 (v OH), 3010 (v =CH), 1710 (v C=O), 1210 (v C-O) and 1030 (v C-O) cm⁻¹. It should be noted that it was not possible to follow this reaction using the usual t.l.c. procedure as the iodine interferes. After stirring the reaction mixture at 0 °C for 23 h the i.r. spectrum showed the formation of some lactone product, but most of the starting material remained. After 40 h at the same temperature there was still starting material present, and there was little increase in the amount of lactone formed - a new broad absorption was seen at 3440 -3520 cm⁻¹. At this point the reaction mixture was allowed to warm to room temperature, and was kept at this temperature for several hours, but there was no obvious change in the i.r. spectrum over this period. Finally, the reaction mixture was heated to reflux temperature on a water bath and maintained at this temperature for 6 h, when the i.r. spectrum still showed an appreciable quantity of the starting material, together with a new absorption at 1625 cm⁻¹ and a broad absorption in the region 3350-3650 cm⁻¹. The carbonyl absorption for the lactone (**125**) had entirely disappeared, suggesting that it is not stable under these higher temperature conditions.

The kinetically-controlled iodolactonisation reaction was carried out by stirring a solution of (123) and sodium hydrogencarbonate in water with a solution of iodine in chloroform at 0 $^{\circ}$ C in the dark for 6 h to give the desired lactone (125) in 10% isolated yield. This reaction has been repeated two further times giving yields of 7 and 8.5% respectively. So, under both kinetically- and thermodynamically-controlled conditions the yields of (125) are consistently poor.

The mechanism for iodolactonisation involves attack of the double bond on molecular iodine causing ionisation with formation of an iodonium ion and the liberation of iodide ion.¹³² The reactive iodonium ion then undergoes intramolecular nucleophilic ring opening on attack of the carboxylate anion to give two possible iodolactone products (Scheme 29).



The position of attack is controlled by electronic and stereochemical factors, and formation of the five-membered ring lactone (125) is preferred over the six-membered ring (126). In order for iodolactonisation to take place the carboxylate group must be in an axial position so that it can open the iodonium ion by a backside, S_N2 approach (i.e *anti* to the iodine atom). If the iodonium ion forms on the same face as the carboxylate ion (i.e. *syn*), or if, for some reason the carboxylate group cannot be axial, then an intramolecular iodolactonisation cannot occur.





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As mentioned earlier in the discussion the hydroxyacid (123) is formed as two diastereoisomers in the ratio 1.69:1, with the major isomer having both the hydroxyl and the carboxylate groups *cis*, while in the minor isomer these two groups are *trans*. Consider first of all the minor isomer. In order for iodolactonisation to occur the iodonium ion must form on the face *anti* to the axial carboxylate group in the 1-position, with the hydroxyl group in an axial position (see 127, Figure 9). From an examination of molecular models there appears to be considerable steric interaction between the large iodine atom and the axial hydroxyl group in the 2-position and the axial hydrogen in the 6-position. If the iodine approaches the double bond from the same face as the carboxylate ion not only will there be steric interaction with the axial carboxylate group to attack the iodonium ion from the backside. If the hydroxyl and the carboxylate groups are *trans* equatorial then, again iodolactonisation cannot occur. Therefore, if the minor diastereoisomer is unable to undergo the iodolactonisation the maximum yield of (125) becomes 62%.

Consider now the major isomer. If it is again assumed that the carboxylate group is in an axial position, then the hydroxyl group will be equatorial and does not interfere with the approach of the iodine towards the double bond from a direction *anti* to the carboxylate group, and there are only two axial hydrogens on the 2- and 6-positions which may hinder the approach (see 128, figure 9). It is difficult to see why this should inhibit iodolactonisation, particularly since compound (129), in which the isopropyl group is *cis* and pseudoequatorial to the axial carboxylate group, is reported to form the iodolactone (130) quantitatively within 8 minutes using kinetic iodolactonisation conditions.¹⁵⁶ The isomers (131) and (132) are reported by the same authors to react more slowly under the same conditions and give only partial conversion after 24 h.



This leaves two possibilities, either the preferred stereochemistry of hydroxyacid is such that the carboxylate group is never axial, or the hydroxyl group may, in some way, be interfering with the iodolactonisation, perhaps by lone pair repulsion of the approaching iodine molecule. From an examination of molecualr models the latter seems an unlikely possibility, but an examination of the literature has revealed no examples of an iodolactonisation reaction on a compound having a hydroxyl group in the 2-position, and it may be a worthwhile experiment to try to protect the hydroxyl group, although this may introduce additional steric constraints.

In an attempt to overcome the problem of the low yields from the iodolactonisation a reaction was carried out with phenylselenyl chloride. Phenylselenolactonisation is a well known reaction and is reported to work well with cyclohex-3-ene carboxylic acid, but there appear to be no reports in the literature of lactonisations of cyclohexenes having a 2-substituent.¹⁵⁷⁻¹⁶⁰ The reaction was carried out by addition of phenylselenyl chloride to a solution of (**123**) and triethylamine in dry dichloromethane at -78 °C. After stirring the mixture at this temperature for 1 h an n.m.r. spectrum showed only starting material with no evidence for lactone formation. The reaction was repeated one more time, but with the same result. The mechanism for

phenylselenolactonisation is very similar to that described above for the

iodolactonisation, and the same factors probably affect both reactions (Scheme 30).





In view of the lack of success with the iodolactonisation reaction it was decided to concentrate on the preparation of model compounds to study the radical cyclisation on to carbon-nitrogen double bonds.

2.2 <u>RADICAL CYCLISATION REACTIONS ON TO CARBON-NITROGEN</u> DOUBLE BONDS

2.2.1 Phenyl Hydrazone as a Radical Trap

In order to develop the radical cyclisation reaction on to carbon-nitrogen double bonds it was necessary to start with pure, fully characterised starting materials. Starting with unstable starting materials whose structures were unclear would only lead to problems when the radical cyclisation reactions failed. It would not have been clear whether the cyclisation fail because the carbon-nitrogen double bond species chosen were not good radical acceptors or simply because the starting materials were either so impure that the impurities were interfering with the cyclisation or because they were not, in fact, what was originally thought.

Initial attempts to prepare benzylimines of a number of aldehydes and ketones as precursors for the cyclisation reactions proved to be difficult as they were thermally and hydrolytically unstable and this lead to difficulties in isolation and purification. Phenyl hydrazones, on the other hand, were stable, crystalline solids. The phenyl hydrazone of 1-bromohexan-5-one (133) was prepared in 65% yield as bright yellow crystals by the dropwise addition of 1-bromohexan-5-one to phenyl hydrazone at 0 °C in dry ethanol, followed by stirring for 24 h at room temperature.¹⁶¹



Radical cyclisation reactions were attempted on the phenyl hydrazone of 1bromohexan-5-one (133) using a number of different experimental conditions.^{75,162,163} Under all the conditions used it is clear that the starting material disappears, and that the product is the same in all cases. However, it is not the desired cyclisation product (134), but appears to be the reduction product (135).



Under the first set of conditions the reaction was carried out in deoxygenated, sodiumdried benzene in a 0.005 M dilution. Tributyltin hydride was added in one portion to a refluxing mixture of the hydrazone, AIBN and benzene.⁸⁴ In the second reaction the tributyltin hydride was diluted with deoxygenated benzene and was added dropwise over a period of 45 minutes to the refluxing hydrazone and AIBN in benzene.¹⁶² By adding the tributyltin hydride slowly it was hoped that the effective lifetime of the PhNHN=CMe(CH₂)₃CH₂• radical would be increased sufficiently to promote cyclisation before collision with another molecule of tributyltin hydride to abstract a hydrogen atom leading to reduction. In the final reaction both the AIBN and the tributyltin hydride in benzene were added dropwise to the refluxing hydrazone in benzene over a period of 2.5 h.¹⁶³

In all cases the major product of the reaction was the same. The aromatic signals and the signals at δ 4.06, 3.06, 2.13 and 2.09 could be seen clearly, but protons in the region of δ 1.0-2.0 were impossible to interpret due to the presence of butyltin residues which obscured this region. The butyl tin residues proved extremely difficult to remove, and only after two chromatographic separations followed by preparative thin layer chromatography was it possible to obtain a small sample which contained no

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residues, and was a single spot by t.l.c.. The ¹H n.m.r. spectrum of this compound had bands at δ 1.03 (d, 3 H, H₁), 1.10-1.38 (m, 3 H, H_{4a} and H₅), 1.58 (m, 4 H, H₆ and H_{4b}), 2.08 (dt, 1 H, H_{3a}), 2.20 (dddd, 1 H, H_{3b}), 3.05 (Br. m, 1 H, H₂), 4.05 (broad, 1 H, NH - disappears on D₂O shake), 6.62 (t, 1 H, H_p), 6.80 (d, 2 H, H_o), 7.08 (t, 2 H, H_m) ppm, and was consistent with the structure shown below (Figure 10).



The hydrogens H_{3a} and H_{3b} will not be equivalent as they are next to a chiral centre, and will appear as a complex ABM₂X pattern, consistent with the multiplets at δ 2.08 and 2.20. The hydrogens H_{4a} and H_{4b} will also be diastereotopic, one proton appearing in the multiplet at δ 1.58 and the other in the multiplet at δ 1.10–1.38. The methyl group on the carbon next to the nitrogen can be seen as a doublet at δ 1.03. Thus all the hydrogens can be accounted for except there appears to be no signal for the NHPh proton.

If this is indeed the structure of the product then it is clear that the tributyltin hydride is reducing the C-Br bond, and also the C=N bond in the hydrazone. There appears to be no reports in the literature on the reduction of hydrazones by tin hydrides, but it has been shown that the carbon-nitrogen double bonds of Schiff bases can be reduced by hydrostannation followed by protolysis (Scheme 31).^{164,165}



2.2.2 Oxime Ethers as Radical Traps

2.2.2.1 Preparation of Oxime Ethers Derived From Aldehydes

Another series of stable compounds containing a carbon-nitrogen double bond that could easily be prepared were oximes and oxime ethers. Corey and Pyne had already demonstrated that oxime ethers could act as radical traps and had used this strategy in their conversion of ketones, having δ , $\varepsilon -\pi$ functions, to cyclopentanols by generation of radicals *via* zinc and trimethylsilyl chloride (Scheme 32).⁸⁹



Rather than prepare oxime ethers of 1-bromohexan-5-one as had been used in the hydrazone example, it was decided to use a more rigid system that would, on generation of the radical with tributyltin hydride, bring the radical centre in close proximity with the C=N radical acceptor. It was envisaged that the syntheses of huperzine A (1) and B (2) could incorporate the reaction between either an aryl or vinyl radical and an oxime ether. It was desirable, therefore, to use these species in the initial studies. With these two criteria in mind it was decided to use oxime ethers derived from 2-(3-bromobut-3-en-1-oxy)benzaldehyde (136). Compound (136) was prepared in 79% yield by heating 2,3-dibromoprop-1-ene, 2-hydroxybenzaldehyde and anhydrous potassium carbonate at reflux temperature in acetone for 4 h. The aldehyde decomposed on standing at room temperature but was stable for up to 2 weeks if stored below 0 $^{\circ}$ C.



(136) was characterised by preparation of its crystalline oxime. 2-(3-Bromobut-3-en-1-oxy)benzaldehyde (136) was stirred at room temperature with hydroxylamine hydrochloride and pyridine in ethanol for 24 h. This afforded the oxime (137) in 87% yield as needles, m.p. 59 °C, upon recrystallisation from petroleum ether b.r. 40-60 °C.



The product was fully characterised by microanalysis, ¹H, ¹³C n.m.r., and i.r. spectroscopy and mass spectrometry. The ¹H and ¹³C n.m.r spectra indicated that the oxime (137) had been prepared as a single isomer. Presumably the preferred conformation of the oxime will be in its E conformation, *anti* to the aromatic ring and *syn* to the smaller hydrogen atom.

Oxime ethers of 2-(3-bromobut-3-en-1-oxy)benzaldehyde (136) were prepared in an identical manner using the hydrochloride salts of the O-substituted hydroxylamines, which were commercially available. Products were obtained in higher yields, however, when pyridine was employed as both the solvent and base. Thus 2-(3-bromobut-3-en-1-oxy)benzaldehyde O-methyloxime (138), 2-(3-bromobut-3-en-1-oxy)benzaldehyde O-benzyloxime (139) and 2-(3-bromobut-3-en-1-oxy)benzaldehyde O-*tert*-butyloxime (140) were prepared as mixtures of E and Z isomers by reacting 2-(3-bromobut-3-en-1-oxy)benzaldehyde (136) with the corresponding hydroxylamine hydrochloride salts at room temperature for 24 h in pyridine. The results are summarised in table 3.



(130)	
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(138	-	140)	

	R	Yield / %	E to Z ratio	R _F (E and Z)	Physical state
(138)	CH3	94	<u>ca</u> . 95 : 1	0.38 and 0.23	oil
(139)	PhCH ₂	81	<u>ca</u> . 95 : 1	0.33 and 0.15	oil
(140)	(CH3)3C	87	100 : 0	0.54	oil

Table 3

In all cases, the minor isomer was seen in less than 5% yield. By the same reasoning as for the oxime (137), the major isomer was presumed to be the E isomer with the OR group anti to the aromatic ring. As the tert-butyl group is much bulkier than either the methyl or benzyl groups, this oxime ether exists solely as the E isomer. This preferred geometry is supported by a study of molecular models.

The olefinic protons were assigned from chemical shift tables.¹⁶⁶ H_{4'Z}, the olefinic proton syn to bromine, was calculated to be at lower field than H4E, anti to bromine. All three oxime ethers were fully characterised by ¹H and ¹³C n.m.r. and i.r. spectroscopy and mass spectrometry. In the i.r. spectrum, the strong band for the C=O stretching vibration at 1690 cm⁻¹ of the aldehyde group was absent and was replaced by a weak band for the C=N stretching vibration absorbing in the region 1620- 1645 cm^{-1} .

2.2.2.2 Radical Cyclisation of Oxime Ethers Derived From Aldehydes

The use of tributyltin hydride for radical cyclisation reactions is well precedented.^{57,64,73-75} Despite the problems associated with the use of tributyltin hydride, most noteably those of toxicity and difficulties in removal of the tin residues from products, it was decided to concentrate initial attempts at cyclisation using this reagent. Once the optimum reaction conditions had been developed for this initiator, a more "user friendly" source of radicals could be investigated. The most interesting alternative to tributyltin hydride was considered to be the new reagent developed by Giese, tris(trimethylsilyl)silane.¹⁶⁷

A number of well precedented experimental conditions were tried to effect cyclisation.^{84,75,162,163} The first set of conditions simply involved heating a 0.02 M solution of tributyltin hydride, 2-(3-bromobut-3-en-1-oxy)benzaldehyde Omethyloxime (138) and a catalytic amount of AIBN in deoxygenated benzene for 24 h at reflux temperature. Analysis of the product mixture by thin layer chromatography (t.l.c.) showed a number of products that could not be separated by column chromatography. The second set of conditions involved the slow addition of a solution of tributyltin hydride in benzene to a 0.02 M solution of the oxime ether (138) and a catalytic amount of AIBN in deoxygenated benzene over a period of 6 h.¹⁶⁶ A syringe pump was used to perform the slow addition. By adding the tributyltin hydride slowly, unwanted direct reduction products are minimised as the hydride concentration at any one time is very low. The vinyl radical is, therefore, more likely to cyclise on to the C=N group than abstract a hydrogen atom from the tin hydride. A slight variation was to add both the tributyltin hydride and the AIBN slowly over 6 h to a 0.02 M solution of the oxime ether (138) in deoxygenated benzene. The lifetime of AIBN is only a few hours at the temperature of refluxing benzene and toluene. Adding the AIBN with the tributyltin hydride ensures that the chain process is continuously being initiated. Although some radical processes have very long chains, e.g.

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chlorination, chain lengths can vary and in many cases only a very few cycles occur.⁶⁷ Both sets of conditions produced a mixture of products that again could not be separated by chromatography. Success was eventually achieved with the preparation of 4-methoxyaminochroman-3-ylidene (141) in 76% yield by the slow addition of a solution of AIBN in benzene over 18 h to a 0.02 M solution of the 2-(3-bromobut-3en-1-oxy)benzaldehyde O-methyloxime (138) and tributyltin hydride in benzene heated at reflux temperature.



The hydroxylamine product was much less polar than expected and, although it contained an aromatic ring, it was not u.v. active on the t.l.c. plate. The product could clearly be distinguished from starting material and side-products by staining the developed t.l.c. plates with an aqueous solution of potassium permanganate and potassium carbonate. The spot corresponding to the product instantly turned bright yellow without it being necessary to apply heat to the plate.

4-Methoxyaminochroman-3-ylidene (141), purified by flash column chromatography, was fully characterised and was shown to be the desired product by comparison of the ¹H and ¹³C n.m.r. spectra with those of the starting material (Table 4).





δ _H (36	0 MHz, CI	DCl3, TMS)	δ _H (3	60 MHz, (CDCl ₃ , TMS)	
3.50	S	OCH3	3.97	S	OCH ₃	
4.43	S	H ₄	8.50	S	C <u>H</u> =N	
4.52	d	H _{2ax}	4.66	dd	H _{2'}	
4.84	dd	H _{2eq}				
5.29	S	H _E	5.68	dt	$H_{4'Z}$	i
5.35	d	HZ	5.98	dt	H _{4'E}	
5.57	br. s	NHOCH3				
6.83	dd	H ₈	6.84	dd	H ₃	
6.89	td	H ₆	6.99	ddd	H ₅	
7.18	td	H ₇	7.31	ddd	H4	
7.22	dd	H5	7.81	dd	H ₆	
δ _C (90.	5 MHz, CI	OCl3, TMS)	δ _C (90).5 MHz, (CDCl3, TMS)	·
δ _C (90. 60.3	5 MHz, CI	DCl3, TMS) C4	δ _C (90 144.3).5 MHz, (CDCl ₃ , TMS) HC=N	
δ _C (90. 60.3 62.8	5 MHz, CI (DCl3, TMS) C4 DCH3	δ _C (90 144.3 61.9).5 MHz, (CDCl ₃ , TMS) HC=N OCH ₃	
δ _C (90. 60.3 62.8 67.4	5 MHz, CI ((DCl ₃ , TMS) C4 DCH ₃ C2	δ _C (90 144.3 61.9 72.0).5 MHz, (CDCl ₃ , TMS) HC=N OCH ₃ C2'	
<u>δ</u> _C (90. 60.3 62.8 67.4 115.9	5 MHz, CI	DCl ₃ , TMS) C4 DCH ₃ C2 R ₂ C= <u>C</u> H ₂	δ _C (90 144.3 61.9 72.0 118.1).5 MHz, (CDCl ₃ , TMS) HC=N OCH ₃ C2' C4'	
δ _C (90. 60.3 62.8 67.4 115.9 117.0	5 MHz, CI	DCl ₃ , TMS) C4 DCH ₃ C2 R ₂ C= <u>C</u> H ₂ C8	δ _C (90 144.3 61.9 72.0 118.1 112.6).5 MHz, (CDCl ₃ , TMS) HC=N OCH ₃ C2' C4' C3	
δ _C (90. 60.3 62.8 67.4 115.9 117.0 120.1	5 MHz, CI	DCl ₃ , TMS) C4 DCH ₃ C2 R ₂ C= <u>C</u> H ₂ C8 C4a	δ _C (90 144.3 61.9 72.0 118.1 112.6 121.3).5 MHz, (CDCl ₃ , TMS) HC=N OCH ₃ C2' C4' C3 C1	
$\begin{array}{c} & \delta_{\rm C} (90. \\ & 60.3 \\ & 62.8 \\ & 67.4 \\ & 115.9 \\ & 117.0 \\ & 120.1 \\ & 120.7 \end{array}$	5 MHz, CI	DCl ₃ , TMS) C4 DCH ₃ C2 R ₂ C= <u>C</u> H ₂ C8 C4a C6	<u>δ</u> _C (90) 144.3 61.9 72.0 118.1 112.6 121.3 121.7).5 MHz, (CDCl ₃ , TMS) HC=N OCH ₃ C2' C4' C3 C1 C5	
$\begin{array}{c} & \delta_{\rm C} (90. \\ & 60.3 \\ & 62.8 \\ & 67.4 \\ & 115.9 \\ & 117.0 \\ & 120.1 \\ & 120.7 \\ & 129.5 \end{array}$	5 MHz, CI	DCl ₃ , TMS) C4 DCH ₃ C2 $R_2C=\underline{C}H_2$ C8 C4a C6 C7	<u>δ</u> _C (90) 144.3 61.9 72.0 118.1 112.6 121.3 121.7 128.7).5 MHz, (CDCl ₃ , TMS) HC=N OCH ₃ C2' C4' C3 C1 C5 C4	
$\begin{array}{c} & \delta_{\rm C} (90. \\ & 60.3 \\ & 62.8 \\ & 67.4 \\ & 115.9 \\ & 117.0 \\ & 120.1 \\ & 120.7 \\ & 129.5 \\ & 130.1 \end{array}$	5 MHz, CI	DCl ₃ , TMS) C4 DCH ₃ C2 $R_2C=CH_2$ C8 C4a C6 C7 C5	<u>δ</u> _C (90) 144.3 61.9 72.0 118.1 112.6 121.3 121.7 128.7 130.9).5 MHz, (CDCl ₃ , TMS) HC=N OCH ₃ C2' C4' C3 C1 C5 C4 C5 C4 C6	
$\begin{array}{c} & \delta_{\rm C} (90. \\ & 60.3 \\ & 62.8 \\ & 67.4 \\ & 115.9 \\ & 117.0 \\ & 120.1 \\ & 120.7 \\ & 129.5 \\ & 130.1 \\ & 139.4 \end{array}$	5 MHz, CI	DCl ₃ , TMS) C4 DCH ₃ C2 $R_2C=CH_2$ C8 C4a C6 C7 C5 C3	<u>δ</u> _C (90) 144.3 61.9 72.0 118.1 112.6 121.3 121.7 128.7 130.9 128.6).5 MHz, (CDCl ₃ , TMS) HC=N OCH ₃ C2' C4' C3 C1 C5 C4 C5 C4 C6 C3'	
$\begin{array}{c} & \delta_{\rm C} (90. \\ & 60.3 \\ & 62.8 \\ & 67.4 \\ & 115.9 \\ & 117.0 \\ & 120.1 \\ & 120.7 \\ & 129.5 \\ & 130.1 \\ & 139.4 \\ & 155.2 \end{array}$	5 MHz, CI	DCl ₃ , TMS) C4 DCH ₃ C2 $R_2C=CH_2$ C8 C4a C6 C7 C5 C3 C8a	<u>δ</u> <u>с</u> (90) 144.3 61.9 72.0 118.1 112.6 121.3 121.7 128.7 130.9 128.6 155.6).5 MHz, (CDCl ₃ , TMS) HC=N OCH ₃ C2' C4' C3 C1 C5 C4 C5 C4 C6 C3' C2	

Table 4

The two proton singlet signal due to $H_{2'}$ at δ 4.66 in the starting material (138) became split into a doublet and a doublet of doublets at δ 4.52 and δ 4.84 respectively in the cyclised product (141) as a result of production of a new chiral centre making the two protons diastereotopic. The common geminal coupling constant was 11.8 Hz. The doublet of doublets at δ 4.84 had additional long range coupling of 1.2 Hz to the olefinic proton Hz and is therefore assigned to H_{2eq}. The signal at δ 8.50 due to the proton on the C=N group disappears and is replaced by a singlet at δ 4.43 corresponding to H₄. The olefinic protons were assigned as H_E at δ 5.29 and Hz at δ 5.35 from ¹H n.m.r. tables.¹⁶⁶



Figure 11

One olefinic hydrogen is positioned syn to a nitrogen atom four atoms away, whereas the other is positioned syn to an oxygen atom four atoms away. As oxygen has a higher molecular mass than nitrogen, and therefore a higher priority, the hydrogen synto the oxygen is assigned as H_Z (Figure 11).

Proof that cyclisation had taken place was also evident in the ¹³C n.m.r. spectrum. The sp² carbon of the C=N at δ 144.3 in the starting material becomes sp³ and appears at δ 60.3 in the cyclised product. Changes in chemical shifts were also observed with the olefinic carbon signals. C3' in the O-methyloxime (138) at δ 128.6 corresponded to C3' in the product (141) at δ 139.4, a shift to lower field due to the replacement of bromine by the carbon atom of the ring.

Despite carrying out two purifications by column chromatography, the cyclised product still contained some tributyltin residues. A number of methods are known to remove tin residues. Petroleum ether can be passed through the chromatography column to flush out the non-polar residues before using a more polar solvent to remove the desired product from the column. The crude product can be dissolved in acetonitrile and stirred vigorously with an equal quantity of petroleum ether, the non-polar tin residues are then simply removed by separating the two layers. Tributyltin resides can be removed from the product mixture as insoluble tin fluorides by dissolving the crude product in dichloromethane and stirring vigorously with aqueous potassium fluoride solution. Problems arose with the first two methods due to the solubility of the product in petroleum ether. The product was seen to come off the column before all the tin residues had been removed using the chromatographic method. With the second method, as the product was not very polar it became distributed between the two layers and could not be separated cleanly. The final method was slightly more successful but did not remove all the residues.

This purification problem was overcomeby preparing the hydrochloride salt of 4methoxyaminochroman-3-ylidine (141) in 82% yield by passing dry hydrogen chloride gas through a solution of (141) in dry diethyl ether. The resulting solid was recrystallised to give a white powder, m.p. 131-134 °C. Microanalysis was consistent with the association of 0.25 mole of water of crystallisation. The salt was hygroscopic and turned orange on standing for about 2 days. The salt was fully characterised by ¹H, ¹³C n.m.r and i.r. spectroscopy and mass spectrometry. The conversion of 2-(3-bromobut-3-en-1-oxy)benzaldehyde O-methyloxime (138) to 4-methoxyaminochroman-3-ylidene (141) *via* the tributyltin mediated radical cyclisation reaction proceeds by the chain process represented below (Scheme 33).



Scheme 33

On heating, AIBN dissociates to 2-cyanopropane radicals and nitrogen.



This then abstracts a hydrogen atom from tributyltin hydride with the production of tributyltin radicals (54). The bromine atom of the vinyl bromide is abstracted by the tributyltin radical. Vinylic radicals could either adopt a bent (142) or linear (143) structure depending on whether the carbon atom carrying the unpaired electron is sp²- or sp-hybridised, i.e. the unpaired electron would be in an sp²- or p-orbital respectively.



Analysis of ${}^{13}C$ splitting constants for the vinyl radical and proton coupling constants in the ESR spectra of vinyl radicals indicates that the radical exists with a bent structure with rapid inversion of its configuration even at -180 °C.⁶⁷



Stork and Baine have shown that the geometry of the starting vinyl halide is inconsequential for subsequent cyclisation.^{168,169} Independent reduction of either geometrical isomer of (144) results in formation of (145) in about the same yield.



Similarly (146) cyclises smoothly to give (147) in good yield.



The reactive vinyl radical has a number of options open to it. It can abstract a hydrogen atom from tributyltin hydride thus resulting in the reduction product (148); it can abstract the hydrogen atom from the carbon of the C=N; it can add to the C=N to form a new carbon-carbon bond (Scheme 34).



Abstraction of the hydrogen atom from tributyltin hydride to produce (148) is an intermolecular process and occurs at a much slower rate than an intramolecular process. The dilute reaction conditions also discourage intermolecular reactions. Abstraction of

a hydrogen atom from the carbon of the C=N is *via* a less favourable seven-membered transition state and still results in the presence of a very energetic, rapidly inverting, sp^2 hybridised radical so that there is little or no energy gain in this process. If, however, the radical attacks the C=N of the oxime ether, an sp^3 hybridised radical results which is much lower in energy. The radical on the nitrogen is flanked by an oxygen with two lone pairs of electrons. The single electron in a p-orbital on the nitrogen overlaps with one of the lone pairs of electrons on the oxygen resulting in stabilisation of the radical.



Abstraction of a hydrogen atom from tributyltin hydride then gives the desired product (141).

Identical reaction conditions were used to carry out successfully the cyclisation of 2-(3bromobut-3-en-1-oxy)benzaldehyde O-benzyloxime (139) to 4benzoxyaminochroman-3-ylidene (149) and 2-(3-bromobut-3-en-1-oxy)benzaldehyde O-*tert*-butyloxime (140) to 4-*tert*-butoxyaminochroman-3-ylidene (150) in 76% and 81% yields respectively.



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The products were characterised as their hydrochloride salts. The hydrochloride salt of 4-benzoxyaminochroman-3-ylidene (149) was so hygroscopic that a microanalysis was not possible. The microanalysis of the hydrochloride salt of 4-*tert* - butoxyaminochroman-3-ylidene (150), m.p. 129-131 °C was consistent with the presence of 0.25 mole of water of crystallisation. All of the hydrochloride salts had correct accurate masses by mass spectrometry and were further characterised by ¹H, ¹³C n.m.r. and i.r. spectroscopy and mass spectrometry.

2.2.2.3 <u>Use of Tris(trimethylsilyl)silane as an Alternative Radical Source to</u> <u>Tributyltin Hydride</u>

In an attempt to find an alternative radical source to tributyltin hydride, the radical cyclisation reaction was attempted using tris(trimethylsilyl)silane. The use of this radical precursor in organic synthesis was first reported in 1989 by Giese and Kopping.¹⁶⁷ This new reagent has advantages over the tin reagents in that it gives smaller amounts of unwanted reduction products and presents no problems in handling as it is much less toxic than tributyltin hydride. The reagent has been shown to give higher yields than tributyltin hydride in some cyclisation reactions.



Following Giese's procedure, 2-(3-bromobut-3-en-1-oxy)benzaldehyde Omethyloxime (138), tris(trimethylsilyl)silane and a catalytic amount of AIBN were heated at 70-80 °C in deoxygenated toluene for 24 h. Analysis of the product by both t.l.c. and ¹H n.m.r. spectroscopy showed that no reaction had taken place. The olefinic region in the ¹H n.m.r. spectrum was identical with that of the starting material indicating that even simple reduction of the C-Br bond had not occurred. The reaction was repeated by heating the reaction mixture to reflux temperature in toluene and also replacing the solvent with benzene so that there was no possibility of interference from stable benzyl radicals. This can sometimes be a problem when toluene is used as the solvent in radical reactions. Under both sets of conditions there was no apparent reaction.

2.2.2.4 Preparation of Oxime Ethers Derived From Ketones

Having shown that vinyl radicals add to oxime ethers derived from aldehydes in good yields, the next step was to determine whether they added equally well to oxime ethers derived from ketones. So as not to differ too much from the previous examples, a similar starting material prepared from 2-hydroxyacetophenone was chosen. Hence, 2-(3-bromobut-3-en-1-oxy)acetophenone (151) was prepared in 62% yield by heating a mixture of 2-hydroxyacetophenone, 2,3-dibromoprop-1-ene and anhydrous potassium carbonate in acetone at reflux temperature for 5 h. Recrystallisation gave the product as needles, m.p. 45-46 °C. The ketone was fully characterised by ¹H, ¹³C n.m.r. and i.r. spectroscopy, mass spectrometry and microanalysis.

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The O-methyloxime of (151) was prepared as described previously for the 2-(3bromobut-3-en-1-oxy)benzaldehyde derivatives. 2-(3-Bromobut-3-en-1oxy)acetophenone (151), O-methylhydroxylamine hydrochloride and pyridine were stirred at room temperature for 24 h to give, after purification, 2-(3-bromobut-3-en-1oxy)acetophenone O-methyloxime (152) as a clear, colourless oil in 92% yield. The oxime ether (152) was seen as a 6:1 ratio of geometrical isomers by ¹H n.m.r spectroscopy.



The major isomer had bands due to CH₃ and OCH₃ at lower field than those of the minor isomer. For oximes and hydrazones the general trend for relative chemical shifts of groups attached to the C=N of these species is shown below (Equation 9).¹⁷⁰ Syn refers to groups on the same side as a hydrogen in the case of aldoximes, and on the same side as the methyl group in this case.

$$\delta syn > \delta anti$$
 Equation 9

In aldoximes and ketoximes, the difference in the chemical shifts, $\Delta\delta$, is dependent on the dihedral angle θ (H-C-C=N).

0	θ	Δδ (ppm)
H J	0°	1
	60°	0
\bigcirc	115°	-0.3

From this generalisation the major isomer was found to have the OCH₃ and CH₃ syn to each other and was therefore assigned to the E stereochemistry assuming that the generalisation is true for oxime ethers as well as oximes. 2-(3-Bromobut-3-en-1oxy)acetophenone O-benzyloxime (153) was prepared in 74% yield following the same procedure. The product was obtained as a clear, colourless oil as a 7:1 mixture of isomers. Bands due to CH₃ and PhCH₂ in the ¹H n.m.r. spectrum were at lower field in the major isomer than in the minor isomer. The major isomer was again assigned the E stereochemistry.



2.2.2.5 Radical Cyclisation of Oxime Ethers Derived From Ketones

The method developed for the radical cyclisation of the oxime ethers derived from 2-(3bromobut-3-en-1-oxy)benzaldehyde was followed with 2-(3-bromobut-3-en-1oxy)acetophenone O-methyloxime (152). The oxime ether and tributyltin hydride in a 0.02 M solution of deoxygenated benzene was heated to reflux temperature and a catalytic amount of AIBN in benzene was added over 8 h *via* a syringe pump. Although some of the desired product was isolated, the reaction gave less than 40% yield. Again the reaction conditions were varied in an attempt to increase the yield of cyclised product. Adding both the tributyltin hydride and a catalytic amount of AIBN slowly to the oxime ether in refluxing benzene did not improve the yield,¹⁶³ but if one equivalent of AIBN was used and the reaction mixture was heated for 3 h with the oxime ether and tributyltin hydride in deoxygenated benzene under a nitrogen atmosphere, 4-methoxyamino-4-methylchroman-3-ylidene (154) was formed in 71% yield.



If this same procedure is used for the cyclisation reactions of the aldoximes (138), (139) and (140), the cyclised product is isolated only in 30% yields. This illustrates the importance of optimising the yields for each cyclisation reaction. It cannot be assumed that one set of conditions will be suitable for all reactions even when the type of reaction is apparently very similar.

4-Methoxyamino-4-methylchroman-3-ylidene (**154**) was purified by preparation of its hydrochloride salt and was obtained as a white powder, m.p. 120-123 °C. Microanalysis was consistent with the presence of 0.25 mole of water of crystallisation. The salt was very hygroscopic and was fully characterised by ¹H, ¹³C n.m.r. and i.r. spectroscopy and mass spectrometry. In an identical manner, 2-(3-bromobut-3-en-1oxy)acetophenone O-benzyloxime (153) gave 4-benzoxyamino-4-methylchroman-3ylidene (155) in 71% yield. The compound was similarly characterised as its hydrochloride salt. The salt was so hygroscopic that microanalysis was not possible but ¹H, ¹³C n.m.r. and i.r. spectroscopy and an accurate mass measured by mass spectrometry confirmed that it was the desired product.



2.2.2.6 Alkynes vs. Vinyl Bromides as Radical Precursors

It was at this stage in the investigations that a paper by Enholm *et al.* appeared in the literature reporting free radical hydrostannylation reactions of benzyloxime ethers, tethered to terminal alkynes, affording five- and six-membered rings bearing a protected amine and a vinyl stannane functionality.⁹² These products were subsequently protodestannylated to obtain the unsubstituted *exo*-methylene compounds (Scheme 35).



Scheme 35

To compare the efficiency of our method with that of Enholm's, 2-(but-3-yne-1oxy)benzaldehyde O-methyloxime (156) and 2-(but-3-yne-1-oxy)benzaldehyde Obenzyloxime (157) were prepared. Radical cyclisation following the method employed by Enholm would lead to identical products as those from the radical cyclisation reactions performed initially with 2-(3-bromobut-3-en-1-oxy)benzaldehyde O-methyloxime (138) and 2-(3-bromobut-3-en-1-oxy)benzaldehyde O-benzyloxime (139) and would make it possible to compare the two methods directly.

3-Bromopropyne (80 wt. % in toluene) and 2-hydroxybenzaldehyde were heated with anhydrous potassium carbonate in acetone for 5 h at reflux temperature to give 2-(but-3-yne-1-oxy)benzaldehyde (158) as white rhombic crystals, m.p. 68 °C, in 85% yield.



The oxime ethers were prepared by stirring the corresponding hydroxylamine hydrochloride salt with 2-(but-3-yne-1-oxy)benzaldehyde (158) and pyridine in methanol for 24 h at room temperature to yield 2-(but-3-yne-1-oxy)benzaldehyde Omethyloxime (156) and 2-(but-3-yne-1-oxy)benzaldehyde O-benzyloxime (157) in 54% and 62% yields respectively. Both oxime ethers were obtained as white prisms, the O-methyloxime (156) having m.p. 47-48 °C, and the O-benzyloxime (157), m.p. 54 °C. Both compounds were fully characterised by ¹H, ¹³C n.m.r. and i.r. spectroscopy and mass spectrometry, accurate mass measurements and microanalysis.



The radical cyclisation of 2-(but-3-yne-1-oxy)benzaldehyde O-methyloxime (**156**) to 4methoxyaminochroman-4-ylidene (**141**) was effected in 52% yield following the procedure outlined in Enholm's paper.⁹² A 0.02 M solution of 2-(but-3-yne-1oxy)benzaldehyde O-methyloxime (156) in benzene was deoxygenated and a solution of tributyltin hydride and a catalytic amount of AIBN in benzene was added to the solution heated at reflux temperature over 6 h. The crude product was dissolved in methanol and heated at reflux temperature for 12 h after addition of 3 drops of acetic acid. Purification afforded 4-methoxyaminochroman-3-ylidene (141) in 52% yield with spectroscopic data in agreement with the same compound prepared earlier. 2-(But-3-yne-1-oxy)benzaldehyde O-benzyloxime (157) was caused to react in the same way to give 4-benzoxyaminochroman-3-ylidene (142) in 56% yield (Scheme 84). The two methods, therefore, give identical products but significantly higher yields are obtained when using our method.



2.2.2.7 Radical Cyclisation of Aryl Radicals on to Oxime Ethers

With the emergence of Enholm's paper, there were now three different examples of oxime ethers acting as radical acceptors. There were, however, no examples of oxime ethers acting as radical acceptors for vinyl or aryl radicals derived from their corresponding vinyl and aryl halides. It had been established that vinyl radicals react
efficiently with oxime ethers and the next set of examples was devised to demonstrate that aryl radicals too could be effectively trapped by oxime ethers.

Model systems derived from 2-hydroxybenzaldehyde were again chosen. 2-Hydroxybenzaldehyde, 2-bromobenzyl bromide and anhydrous potassium carbonate were heated at reflux temperature in acetone to give 2-({2-bromophenyl}ethan-1oxy)benzaldehyde (**159**) in 93% yield as white rhomboids, m.p. 91-92 °C.



2-({2-Bromophenyl}ethan-1-oxy)benzaldehyde O-methyloxime (160) and 2-({2bromophenyl}ethan-1-oxy)benzaldehyde O-*tert*-butyloxime (161) were prepared in the usual manner in 87% and 84% yields respectively. The O-methyloxime ether (160) was obtained as a mixture of E and Z isomers whereas the O-*tert*-butyloxime ether (161) was formed as the E isomer only. The O-methyloxime (160) was obtained as white needles, m.p. 75.5-76 °C and was fully characterised by ¹H, ¹³C n.m.r. and i.r. spectroscopy, mass spectrometry and microanalysis. The O-*tert*-butyloxime (161) was similarly characterised and was again obtained as needles, m.p. 53-56 °C.



The cyclisation of 2-({2-bromophenyl}ethan-1-oxy)benzaldehyde O-methyloxime (160) would give rise to a seven-membered ring product (162).



Although 7-*exo-trig* ring closures are favoured according to Baldwin's rules,⁹⁴ sevenmembered rings are much less readily formed than five- or six-membered rings. It was anticipated that reduction of the aryl bromide would now compete more effectively with cyclisation in this case as cyclisation was expected to be much slower than in the previous examples where six-membered rings were formed.

The cyclisation of 2-({2-bromophenyl}ethan-1-oxy)benzaldehyde O-methyloxime (160) was attempted using two equivalents of tributyltin hydride to oxime ether; a procedure applied to radical cyclisation reactions of other aryl bromides reported in the literature.¹⁷¹ 2-({2-Bromophenyl}ethan-1-oxy)benzaldehyde O-methyloxime (160) was dissolved in dry, deoxygenated benzene (0.01 M dilution). The tributyltin

hydride and a catalytic amount of AIBN were added to the solution heated at reflux temperature over 12 h. This afforded a mixture of the cyclised product, 7methoxyamino-2,7-dihydrobenzyl[b.e]oxepin (162) in 49% yield and the reduction product 2-(phenylethan-1-oxy)benzaldehyde O-methyloxime (163) in 29% yield.



As expected, the yield of 7-methoxyamino-2,7-dihydrobenzyl[b.e]oxepin (162) was considerably lower than the cyclisation products in the previous cyclisation reactions. An attempt to improve the yield of cyclised product by adding the tributyltin hydride and AIBN over 20 h failed to give any significant improvement. The product of simple reduction of the aryl bromide (163) was isolated and fully characterised. The cyclised product was characterised by ¹H, ¹³C n.m.r. and i.r. spectroscopy and mass spectrometry. Confirmation that cyclisation had taken place was seen by ¹H n.m.r. spectroscopy. The CH₂ adjacent to oxygen in the starting material was seen as a two proton singlet at δ 5.10 whereas the corresponding CH₂ in the product was seen as two doublets with a 12.8 Hz coupling at δ 4.83 and δ 6.28. The two protons were diastereotopic due to the formation of a chiral centre in the product. The oxime proton at δ 8.54 in the starting material became H₇ at δ 4.92 in the product. Changes were also seen in the aromatic ring on removal of the bromine. In the ¹³C n.m.r. spectrum of the product, C7 at δ 70.6 replaced the oxime carbon at δ 144.5 and the most marked change in the aromatic ring was the shift of C2', at δ 121.1 in the starting material, down field to δ 138.0 for C6a in the product. The ¹H n.m.r. spectrum of the reduction product was almost identical to that of the starting material except that the

chemical shift range for the aromatic protons was much smaller due to the loss of the bromine atom.

The same procedure was followed for the cyclisation of the O-*tert*-butyloxime (161) yielding 7-*tert*-butoxyamino-2,7-dihydrobenzyl[b.e]oxepin (164) and 2-(*tert*-butylethan-1-oxy)benzaldehyde O-*tert*-butyloxime (165) in 47% and 36% yields respectively.



2.3 The Formation of Bicyclic and Tricyclic Carbocycles

2.3.1 Introduction

The radical cyclisation of aryl and vinyl radicals on to oxime ethers to form oxygen heterocycles has been shown to proceed in good to excellent yields. Numerous examples are known in which ring closure reactions involving radicals have been employed to make heterocycles but there are far fewer examples of corresponding general methods for the synthesis of carbocycles.^{57,59,74-76} The following set of examples demonstrates the potential of radical cyclisation reactions on to oxime ethers for the formation of bicyclic and tricyclic systems and, in the majority of cases, simultaneous formation of an amine group bonded to a secondary or tertiary carbon centre.

2.3.2 The formation of Bicyclic Systems

2.3.2.1 <u>Preparation of 3-(2-bromophenyl)propanal O-methyloxime</u>

The previous examples of radical cyclisation reactions on oxime ethers had been specifically designed to aid cyclisation by forcing the radical centre in to close proximity with the carbon-nitrogen double bond. Would the cyclisation work equally as well with oxime ethers tethered to the end of a flexible side-chain? This question was investigated using 3-(2-bromophenyl)propanal O-methyloxime (166) and 4-(2-bromophenyl)butan-2-one O-methyloxime (167) as the radical precursors.

A suitable route to 3-(2-bromophenyl)propanal O-methyloxime (166) depended upon the synthesis of 3-(2-bromophenyl)propanal (168) below (Scheme 36).



Scheme 36

Diethyl 2-(2-bromophenyl)-1,3-propanedicarboxylate (169) was prepared in 96% yield as a colourless liquid (b.p. 174 °C at 1mmHg) by vigorously stirring a solution of 2bromobenzyl bromide, diethyl malonate and triethylbenzylammonium chloride in dichloromethane with a 1 M sodium hydroxide solution for 1 h.¹⁷² The product was characterised by ¹H n.m.r. spectroscopy. Hydrolysis of (169) to the diacid (170) was achieved by heating with aqueous potassium hydroxide solution at 100 °C with continuous removal of the ethanol produced.¹⁷³ After acidification, compound (170) was obtained as a creamy yellow solid in 85% yield. Recrystallisation gave the product as needles, m.p. 148-150 °C. Decarboxylation to the monoacid (171) was carried out by heating the solid to 150 °C until evolution of carbon dioxide ceased. The crude product was obtained in 93% yield. This was considered sufficiently pure for use in the next stage, but a small amount was recrystallised from water to give white needles, m.p. 97-98 °C, which were characterised by ¹H n.m.r. spectroscopy, microanalysis and mass spectrometry. Conversion to the methyl ester (172) was achieved by addition of the acid to thionyl chloride in methanol and stirring the mixture at room temperature for 24 h to give the methyl ester (172) in 79% yield, after basification of the product mixture. The product was characterised by ¹H n.m.r. spectroscopy.

Reduction of the ester (172) with lithium aluminium hydride in dry diethyl ether proceeded smoothly over 15 minutes to give the desired alcohol (173) as a clear colourless oil in 97% yield, and this was characterised by ¹H n.m.r. spectroscopy.¹⁷⁴ The final step in the synthetic sequence was oxidation of the primary alcohol to the aldehyde (168). This step was achieved in 72% yield utilising the Swern oxidation procedure.¹⁷⁵⁻¹⁷⁷ The alcohol (173) was treated with dimethyl sulphoxide and oxalyl chloride in dichloromethane under nitrogen at -78 °C. Triethylamine was then added after stirring the mixture for 1.5 h at -78 °C. After work-up, ¹H n.m.r. spectroscopy revealed the desired product. The aldehyde (168) was not purified but used directly in the next stage.

The mechanism of the Swern oxidation is thought to be as shown in the following scheme (Scheme 37), in which the alcohol is converted initially in to the corresponding alkyl chloride by reaction with oxalyl chloride.

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The alcehyde (168) was easily converted into its oxime ether (166) in 84% yield by reaction with O-methyl hydroxylamine hydrochloride and pyridine. The oxime ether was obtained as a 1:1 mixture of E and Z isomers with R_F values of 0.49 and 0.54.



The E and Z isomers were distinguished from each other by comparing the chemical shifts of the oxime ether proton, H₁. The E isomer was assigned to the compound having H₁ at δ 7.39 ppm. In the Z isomer, H₁ had a chemical shift at higher field of δ 6.67 ppm.¹⁷³ The isomeric mixture was fully characterised by ¹H, ¹³C n.m.r and i.r. spectroscopy, and mass spectrometry.

2.3.2.2 Cyclisation of 3-(2-bromophenyl)propanal O-methyloxime

The reaction was found to proceed in 69% yield following the conditions found to be successful for the cyclisation of 2-({2-bromophenyl}ethan-1-oxy)benzaldehyde O-methyloxime (160) and O-*tert*-butyloxime (161), i.e. using two equivalents of tributyltin hydride. A solution of tributyltin hydride and AIBN in benzene was added over 4 h to the oxime ether (166) heated to reflux temperature in a 0.02 M solution of deoxygenated benzene. Heating was continued for a further 12 h. The product, 1-methoxyaminoindan (174), was fully characterised. Evidence that the cyclisation had been successful was especially evident in the ¹H and ¹³C n.m.r spectra with the disappearance of signals present in the starting material corresponding to the oxime ether and the aryl bromide.



2.3.2.3 Preparation of 4-(2-bromophenyl)propan-2-one O-methyloxime

The preparation and subsequent cyclisation of 4-(2-bromophenyl)propan-2-one Omethyloxime (167) would lead to simultaneous formation of a bicyclic system and the amine function on a tertiary carbon atom. 4-(2-Bromophenyl)propan-2-one (175) was prepared, following a literature procedure, in 76% yield by the reaction of 2bromobenzyl bromide, 2,4-pentanedione and anhydrous potassium carbonate in ethanol.¹⁷⁸



¹H and ¹³C n.m.r. data corresponded to those reported for authentic 4-(2bromophenyl)propan-2-one.¹⁷⁸

4-(2-Bromophenyl)butan-2-one O-methyloxime (167) was prepared as a mixture of E and Z isomers in 92% yield in the usual manner. By analogy with the mixture of isomers of 4-(2-bromophenyl)propanal O-methyloxime (166), the isomer with an R_f value of 0.36 was assigned as the E isomer and that with an R_f value of 0.31 was assigned the Z isomer. The E isomer had a band at δ 1.68 due to H₁ and one at δ 2.45 due to H₃. The Z isomer had a band for H₁ at δ 1.23 at lower field than the E isomer and a band at higher field for H₃ (δ 2.58). Although both E and Z isomers could not be completely separated from each other by column chromatography, each isomer was obtained with only slight contamination from the other isomer thus allowing bands in the ¹H and ¹³C n.m.r. spectra to be distinguished. Compound (167) was further characterised by i.r. spectroscopy and mass spectrometry as the mixture of isomers.



2.3.2.4 Cvclisation of 4-(2-bromophenyl)propan-2-one O-methyloxime

Cyclisation of 4-(2-bromophenyl)butan-2-one O-methyloxime (167) was achieved in highest yields, 74%, when further AIBN in benzene was added over 12 h to the oxime ether (167), tributyltin hydride and a catalytic amount of AIBN heated at reflux temperature in deoxygenated benzene for 24 h. 1-Methoxyamino-1-methylindan (176) was obtained as a clear colourless oil and was fully characterised by ¹H, ¹³C n.m.r. and i.r. spectroscopy and mass spectrometry.



The cyclisation of 3-(2-bromophenyl)propanal O-methyloxime (166) and 3-(2bromophenyl)butan-2-one O-methyloxime (167) to 1-methoxyaminoindan (174) and 1methoxyamino-1-methylindan (176) respectively, gave some indication of the scope of the reaction and the efficiency of oxime ethers as radical acceptors. Even when the radical was not forced in close proximity to the carbon-nitrogen double bond, the cyclisations went in very good yields without competition from direct reduction of the aryl bromide.

2.3.3 Formation of Tricyclic Systems

2.3.3.1 <u>Preparation of Ethyl 1-(2-bromobenzyl)-2-oxo-1-cyclopentanecarboxylate O-</u> methyloxime

The next set of examples illustrate the formation of tricyclic systems by the cyclisation of aryl radicals on to oxime ethers formed from cyclic ketones.

Ethyl 1-(2-bromobenzyl)-2-oxo-1-cyclopentanecarboxylate (177) was prepared by alkylation of the anion of ethyl 2-oxo-1-cyclopentanecarboxylate with 2-bromobenzyl bromide following literature precedent.¹¹⁸ The literature examples employed HMPA as the co-solvent in the alkylation reactions. This was replaced with DMPU, a reagent that had been used successfully as a replacement for HMPA in other alkylations, and exhibited none of the problems of toxicity associated with HMPA. Ethyl 1-(2-bromobenzyl)-2-oxo-1-cyclopentanecarboxylate (177) was obtained in 72% yield by the action of 2-bromobenzyl bromide on the anion of the β -keto ester. Ethyl 2-oxo-1-cyclopentanecarboxylate with 80% sodium hydride in mineral oil; the deprotonation was carried out in a solution of DMPU in THF. Addition of 2-bromobenzyl)-2-oxo-1-cyclopentanecarboxylate (177) as a clear colourless oil in 72% yield. The product was fully characterised by ¹H, ¹³C n.m.r. and i.r. spectroscopy and mass spectrometry.



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The ketone (177) was further characterised by the preparation of its crystalline oxime. Ethyl 1-(2-bromobenzyl)-2-oxo-1-cyclopentanecarboxylate (177), hydroxylamine hydrochloride and pyridine were stirred at room temperature for 48 h to give the oxime (178) in 64% yield as prisms, m.p. 77-78 °C. Accurate microanalysis was obtained on the derivative as well as full characterisation by ¹H, ¹³C n.m.r. and i.r. spectroscopy and mass spectrometry.



Similarly ethyl 1-(2-bromobenzyl)-2-oxo-1-cyclopentanecarboxylate O-methyloxime (179) was prepared as a single isomer in 84% yield. The product was fully characterised by ¹H, ¹³C n.m.r. and i.r. spectroscopy and mass spectrometry as a clear, colourless oil.



Due to the presence of a chiral centre in the alkylated product, the protons of the CH_2 in the ethyl ester and the benzylic protons were diastereotopic. The benzylic protons

were seen as two doublets at δ 3.36 and δ 3.62, and doublets of quartets at δ 4.17 and δ 4.20 corresponded to the A and B parts of an ABX₃ pattern for the CH₂ of the ester.

2.3.3.2 <u>Cyclisation of Ethyl 1-(2-bromobenzyl)-2-oxo-1-cyclopentanecarboxylate O-</u> methyloxime

Ethyl 1-(2-bromobenzyl)-2-oxo-1-cyclopentanecarboxylate O-methyloxime (**179**) was converted into ethyl 3a-methoxyaminocyclopent[a]indan-8a-carboxylate (**180**) in 68% yield by the slow addition (8 h) of a catalytic amount of AIBN in benzene to the oxime ether (**179**) and tributyltin hydride (two equivalents) in a 0.02 M solution of deoxygenated benzene heated at reflux temperature. Heating was continued for a further 8 h. By ¹H and ¹³C n.m.r. spectroscopy it could be seen that the hydroxylamine (**180**) had been obtained as a single diastereoisomer. This was assigned as having the *cis* stereochemistry on the basis of general literature precedent and similar radical cyclisations of bicyclo[3.3.0]octane derivatives which have been shown to have the expected *cis* junctions.^{92,179-182}



The cyclised product was fully characterised by ¹H, ¹³C n.m.r. and i.r. spectroscopy and mass spectrometry as a clear, colourless oil.

2.3.3.3 <u>Preparation of Ethyl 1-(2-bromobenzyl)-2-oxo-1-cyclohexanecarboxylate O-</u> methyloxime

The same procedure was used to prepare the cyclohexanone series. Ethyl 1-(2bromobenzyl)-2-oxo-1-cyclohexanecarboxylate (**181**) was prepared as white prisms, m.p. 47.5-48.5 °C, in 79% yield by the reaction of the sodium salt of ethyl 2oxocyclohexanecarboxylate with 2-bromobenzyl bromide.¹¹⁸ DMPU was again used as the co-solvent with THF instead of HMPA.



The O-methyloxime ether was prepared as a single isomer from ethyl 1-(2bromobenzyl)-2-oxo-1-cyclohexanecarboxylate (181) and O-methylhydroxylamine hydrochloride. Stirring in pyridine overnight yielded ethyl 1-(2-bromobenzyl)-2-oxo-1-cyclohexanecarboxylate O-methyloxime (182) in 67% yield as a clear, colourless oil. The product was fully characterised and had similarities with the cyclopentane derivative (179) in its ¹H and ¹³C n.m.r. spectra.



2.3.3.4 Cyclisation of Ethyl 1-(2-bromobenzyl)-2-oxo-1-cyclopentanecarboxylate Omethyloxime

Ethyl 1-(2-bromobenzyl)-2-oxo-1-cyclohexanecarboxylate O-methyloxime (182) cyclised smoothly following the same method used for the cyclisation of ethyl 1-(2-bromobenzyl)-2-oxo-1-cyclopentanecarboxylate O-methyloxime (179). Thus ethyl 4a-methoxyaminocyclohex[a]indan-9a-carboxylate (183) was prepared in 90% yield as a clear colourless oil by the dropwise addition of a catalytic amount of AIBN in benzene to a 0.02 M solution of ethyl 1-(2-bromobenzyl)-2-oxo-1-cyclohexanecarboxylate O-methyloxime (182) and tributyltin hydride (two equivalents) heated at reflux temperature in benzene. Heating was continued for a further 12 h. From the ¹H and ¹³C n.m.r. spectra it could be seen that as in the previous example, the hydroxylamine had been obtained as a single diastereoisomer. The stereochemistry of the ring junction was again assigned as *cis*.



Much work has been done, including good reviews and mechanistic discussions, on the preference for *cis* cyclisation when forming bicyclic systems.^{59,69,75} In 1986, Clive *et al.* used these studies to formulate a set of rules for the ring fusion geometry in bicyclic systems.⁷¹ 4-(Phenylseleno)butyryl esters (**184**) prepared from allylic alcohols (**185**) were converted into cyclopentanes by successive ester enolate rearrangement (**184**) to (**186**) and 5-*exo*-trigonal radical cyclisation (**187**) to (**188**).



This general process was found to be efficient with stereochemical results that were predictable. The nature of the ring fusion geometry in (188) was found to be dependent upon the value of n. The results are summarised below (Table 5).

	n	% yield	ring fusion geometry
188a	n=1	93	cis
188b	n=2	83	cis
188c	n=3	71	cis and trans



In the cyclisation producing (188a) an 80:20 mixture of two isomers (epimeric at C1) was obtained. The ring fusion was assigned as *cis* in both isomers on the basis of

strong preferences for this geometry.^{183,184} In the case of (**188b**), again only two isomers were formed in a ratio of 90:10. The *cis* nature of the ring fusion was clear from the ¹³C n.m.r. spectrum of the material by comparison with an authentic sample.¹⁸⁵ In contrast, (**188c**) was obtained as a mixture of four isomers, approximately 14:17:11:2 by ¹H n.m.r. spectroscopy. It was concluded that both *cis* and *trans*-ring fusion products were formed.

The formation of (188a-c) can be described as 5-exo-trigonal-[endo-5], 5-exotrigonal-[endo-6] and 5-exo-trigonal-[endo-7] processes, respectively, where the size of the ring originally associated with the (endocyclic) double bond is specified in brackets. Clive postulates that the kinetic barrier to the formation of trans ring-fused products gives rise to the following set of rules (Table 6).

Reaction type	trans ring fusion				
5-exo-[endo-5]	disfavoured				
5-exo-[endo-6]	disfavoured				
5-exo-[endo-7]	favoured				



Two other cases of radical cyclisation were attempted in the paper. Radical cyclisation of (189) produced the corresponding *cis*-fused bicyclic product. Compound (190) was subjected to the radical cyclisation conditions but ring closure was not efficient.



Force-field calculations using the MM2 method applied to model transition structures for radical ring closure were carried out by Beckwith.⁷⁰



For *exo* ring closure of either the hexenyl system (191) or the heptenyl system (192) the calculated strain energies of the *cis*-transition structures are much less than those of the *trans* (Table 7).

Radical	E _s (ground)	$\Delta E_{s}(cis)$	ΔE_{s} (trans)		
191 .	15.7	5.1	30.6		
192	16.2	9.5	21.6		

There is a similarly large energetic advantage for formation of *cis* products from ring closures of the aryl radicals (193).

Numerous examples to illustrate the preference for formation of *cis* products by radical cyclisation reactions were provided by Beckwith.^{72,186} Some of these examples are illustrated below.



The stereochemistry of the newly formed ring junction in all cases proved to be *cis* (this was rigorously determined in two cases). Preparation of these compounds was part of a study to determine the effects of substituents on the rate of cyclisation.

The corresponding *trans*-ring fused compounds are best prepared by reactions in which the last bond to be made in the ring forming process is <u>not</u> a bond to one of the ring junction atoms.¹⁸⁷

Preparation of *trans*-ring fused compounds therefore involves the sequence given in scheme 38, demonstrated by Clive.





The *trans* geometry of the side chain was set up by conjugate addition and aldol condensation. Treatment with triphenyltin hydride and AIBN generated the desired radical (194) which cyclised. The mode of closure [5-exo (shown in scheme 38) or 6-endo] depended upon the substitution pattern of the double bond.

Despite there being very good literature precedent for the assignment of the *cis* stereochemistry of ethyl 4a-methoxyaminocyclohex[a]indan-9a-carboxylate (**183**) it was decided to try and confirm these predictions by n.m.r. spectroscopy experiments.

By carrying out n.O.e. experiments, it was hoped to be able to show that the ester group and the hydroxylamine were on the same face of the molecule (Figure 12).



Figure 12

It was hoped that by irradiating the methoxy group at δ 2.90, or the NH at δ 6.27, some enhancement of the signals for the OCH₂ and the CH₃ of the ester would be seen. In practice, no enhancement was observed upon irradiation of the NH or the OCH₃. Similarly no enhancement was seen in the NH or OCH₃ signals when irradiating the OCH₂ and CH₃ of the ester group.

It was thought that the failure of the n.O.e. experiment may be due to the hydroxylamine and the ester group being too distanced from each other. It was decided to prepare 9b-methoxyaminocyclohex[a]indan (195) and try an n.O.e. experiment on this system.



The ester group has been replaced by a hydrogen on the ring junction. An n.O.e. between this hydrogen and the NH or OCH₃ in the hydroxylamine function would be expected to be more likely as they are in closer proximity than in the previous example.

2.3.3.5 Preparation of 2-(2-Bromobenzyl)cyclohexanone O-methyloxime

The preparation of 9b-methoxyaminocyclohex[a]indan (195) depended upon the synthesis of 2-(2-bromobenzyl)cyclohexanone O-methyloxime (196). Alkylation of the cyclohexanone with 2-bromobenzyl bromide could not be accomplished by deprotonation with sodium hydride as in the previous examples, as no ester functionality was present to direct enolate formation. This problem can be overcome by the preparation of an enamine prior to alkylation (Scheme 39).



Scheme 39

2-(2-Bromobenzyl)cyclohexanone (179) was thus prepared by heating 1-pyrrolidino-1-cyclohexene and 2-bromobenzyl bromide in benzene at reflux temperature for 6 h. 1-Pyrrolidino-1-cyclohexene is commercially available although it can be synthesised easily from cyclohexanone and pyrrolidine by heating in benzene.¹⁸⁸⁻¹⁹⁰ The intermediate (198) was cleaved by heating with a 1:2:2 solution of sodium acetate:acetic acid:water,¹⁸⁹ yielding the ketone (197) in 70% yield as a clear, colourless oil. The mechanism of the reaction is shown below (Scheme 40).





2-(2-Bromobenzyl)cyclohexanone (197) was fully characterised by ¹H, ¹³C n.m.r. and i.r. spectroscopy and mass spectrometry. 2-(2-Bromobenzyl)cyclohexanone (197), O-methylhydroxylamine hydrochloride and pyridine were stirred overnight to afford a mixture of E and Z isomers of the O-methyloxime (196) as a clear, colourless oil in 78% yield. The E and Z isomers were not separated but could be distinguished from each other by ¹H and ¹³C n.m.r. spectroscopy. 2-(2-

Bromobenzyl)cyclohexanone O-methyloxime (196) was further characterised by i.r. spectroscopy and mass spectrometry.



2.3.3.6 Cyclisation of 2-(2-Bromobenzyl)cyclohexanone O-methyloxime

The mixture of E and Z isomers of 2-(2-bromobenzyl)cyclohexanone O-methyloxime (196) was subjected to conditions for radical cyclisation to yield 9bmethoxyaminocyclohex[a]indan (195) in 58% yield. To a solution of the oxime ether (196) and tributyltin hydride in a 0.02 M dilution of benzene was added the AIBN in benzene over 8 h. Heating at reflux temperature for a further 10 h yielded the cyclised product as a pale yellow oil.



The product was characterised by ¹H, ¹³C n.m.r and i.r. spectroscopy and mass spectrometry. The assignment of the protons in the ¹H n.m.r. spectrum was confirmed by a COSY experiment (shown below).



The results of the n.O.e. experiment are summarised in table 8.



irradia	tion pt.	% n.O.e.												
δ	group	1ax	1eq	2ax	2eq	3ax	3eq	4ax	4eq	4a	5x	5y	NH	CH ₃
2.48	4a	0.5	0.5	/	/	0.5	0.5	1.1	1.9	/	9.6	/	/	0.8
3.48	OCH ₃	/	/	/	/	/	/	/	/	/	/	0.4	0.8	/
5.47	NH	1.8	1.8	1	/	/	1	/	1	1.2	1.2	/	1	1.5

Table 8

Although the results were not very conclusive, they did show that a small enhancement at H_{4a} and H_{5x} could be observed upon irradiation at NH. Irradiating H_{4a} also resulted in a small enhancement of the OCH₃ signal. These results suggest that the stereochemistry at the ring junction is *cis* supporting the assignment arrived at earlier based on literature precedent.

2.3.3.7 <u>Attempted Preparation of Methyl 1-(2-bromobenzyl)-2-oxo-1-</u> cycloheptanecarboxylate O-methyloxime

As methyl 2-oxo-1-cycloheptanecarboxylate was also commercially available, the same sequence was applied to this. Methyl 2-oxo-1-cycloheptanecarboxylate was deprotonated with sodium hydride in a THF/DMPU solvent. Addition of 2-bromobenzyl bromide and heating at reflux temperature for 5 h afforded the alkylation product, methyl 1-(2-bromobenzyl)-2-oxo-1-cycloheptanecarboxylate (**199**) as a white powder, m.p. 67-68 °C, in 84% yield. A satisfactory microanalysis was obtained in addition to full characterisation by ¹H, ¹³C n.m.r. and i.r. spectroscopy and mass spectrometry.



Preparation of the O-methyloxime was attempted three times by the reaction of methyl 1-(2-bromobenzyl)-2-oxo-1-cycloheptanecarboxylate (**199**), O-methylhydroxylamine hydrochloride and pyridine both at room temperature and heating to 100 °C. On all occasions only starting material was recovered. At first glance there seems to be no reason why the oxime ether does not form in the cycloheptane derivative, but forms readily with the cyclohexane derivative. However, a study of molecular models shows that attack from both faces in the seven-membered case appears to be more hindered than in the six-membered case.

Nucleophilic attack on a carbonyl group involves approach of the nucleophile along a vector at an angle close to 109° with the carbon-oxygen double bond. As the

nucleophile approaches the carbonyl carbon, the oxygen atom and the allyl substituents bend out of the plane and the carbon-oxygen bond length increases [cf. (200) to (201)].¹⁹¹



If we consider methyl 1-(2-bromobenzyl)-2-oxo-1-cycloheptanecarboxylate (**199**) (Figure 13), it can be seen that attack by the nucleophile across face a is blocked by the bromobenzyl group and by two axial hydrogens. Attack from face b encounters three axial hydrogens rather than the two seen in the cyclohexanone case (Figure 14). These three axial hydrogens are slightly angled underneath the seven-membered ring, unlike the six-membered case where the axial hydrogen atoms are perpendicular. This is the only obvious explanation for the lack of formation of the oxime ether.



2.3.2.8 System Related to Huperzine

Having developed the method of radical cyclisation on to oxime ethers to form heterocyclic systems and bicyclic and tricyclic carbocycles, it was decided to use this methodology to synthesise a bridged tricyclic system related to the skeleton of huperzine B.

The huperzine B framework could be built up *via* two possible radical cyclisation reactions. (Scheme 41)



Scheme 41

A simplified version of the starting material for route a is 3-(2bromobenzyl)cyclohexanone O-methyloxime (202).



If cyclisation were successful, this would result in the formation of a similar bridged tricyclic system (203) to that found in huperzine.

3-(2-Bromobenzyl)cyclohexanone (204) was prepared by making the cuprate of 2bromobenzyl bromide and reacting this with 2-cyclohexen-1-one. The Grignard reagent, 2-bromobenzylmagnesium bromide was prepared and copper (I) cyanide added at -78 °C. The reaction mixture was warmed to -30 °C and 2-cyclohexen-1-one added. This afforded the ketone (204) as a clear colourless oil in 67% yield, b.p. 200 °C at 0.4 mmHg. The oil was fully characterised by microanalysis, ¹H, ¹³C n.m.r and i.r. spectrometry and mass spectrometry.



As an aside, 2-bromobenzylmagnesium bromide was reacted directly with 2cyclohexen-1-one to determine the proportion of 1,2-addition and 1,4-addition products in the product mixture. Surprisingly to us it was found that the ratio of 1,4-addition product to 1,2-addition product was 71:29.

Grignard reagents normally add to α,β -unsaturated carbonyl compounds to give 1,2addition products. Addition of a catalytic amount of a copper (I) salt, however, results in conjugate addition (Scheme 42).¹⁹²



The product of addition of a Grignard reagent to an α , β -unsaturated carbonyl compound is often controlled by steric factors. Thus (205) with phenylmagnesium bromide gives 100% 1,4-addition, while (206) gives 100% 1,2-addition.



In general, substitution at the carbonyl group increases 1,4-addition, while substitution at the double bond increases 1,2-addition. In most cases, both products are obtained. It has been postulated that the 1,4-addition of Grignard reagents proceeds by a sixcentred cyclic mechanism.



This would be in accord with the decrease in the amount of 1,2-addition with increased substitution at the 4 position. The transition state for the 1,2-addition of Grignard reagents is often represented as a cyclic array containing the carbonyl group and two molecules of Grignard reagent.¹⁹³



In the case of the reaction of 2-bromobenzylmagnesium bromide with 2-cyclohexen-1one, the major product was 3-(2-bromobenzyl)cyclohexanone (**204**), the product of 1,4-addition, despite the fact that there were no bulky substituents blocking attack at the carbonyl group.

The 3-(2-bromobenzyl)cyclohexanone (204) and 1-(2-bromobenzyl)cyclohex-2-en-1ol (207) in the product mixture could not be separated by column chromatography as their R_F values were identical. 3-(2-Bromobenzyl)cyclohexanone (204) was separated from the mixture and characterised by preparation of its 2,2dimethylpropylidene acetal (208).



The 71:29 mixture of products was heated in a Dean-Stark apparatus with 2,2dimethylpropane-1,3-diol and *p*-toluenesulphonic acid in toluene for 24 h. This gave 3-(2-bromobenzyl)cyclohexan-1-one 2,2-dimethylpropylidene acetal (208) as a clear colourless oil in 89% yield, based up on the percentage of ketone (204) present in the original mixture. The acetal (208) was fully characterised and the ¹H n.m.r. spectrum showed some interesting characteristics. The majority of the ring protons could be assigned and their coupling constants were measured. The presence of the chiral centre makes all the aliphatic protons diastereotopic. The benzylic protons, although adjacent to the chiral centre, were equivalent and were seen as a doublet, coupling with H_{3ax}. H₁ⁿ and H₃ⁿ, the two methylenes in the acetal group, gave different signals. One of the CH₂ groups was seen as a two proton singlet at δ 3.50 whereas the protons on the other CH₂ group were diastereotopic giving rise to two doublets at δ 3.35 and δ 3.41, the geminal coupling being of the order of 11.4 Hz.

For comparative purposes identical reactions were carried out with 2chlorobenzylmagnesium bromide, 2-fluorobenzylmagnesium bromide and benzylmagnesium bromide. The results are summarised in table 9 below.

GRIGNARD	yield of mixture	1,4-addition : 1,2 addition
BrC ₆ H ₄ CH ₂ MgBr	72%	71 : 29
ClC ₆ H ₄ CH ₂ MgBr	73%	99:1
FC ₆ H ₄ CH ₂ MgBr	79%	59 : 41
C ₆ H ₅ CH ₂ MgBr	76%	64 : 36

Table 9

2-Fluorobenzylmagnesium bromide and benzylmagnesium bromide gave large amounts of the 1,2-addition products whereas 2-chlorobenzylmagnesium bromide reacted with 2-cyclohexen-1-one to give almost exclusively the product of 1,4-addition. The fact that 2-bromobenzylmagnesium bromide and 2-chlorobenzylmagnesium bromide react to give mainly the 1,4-addition product could simply be due to the larger size of the substituent on the aromatic ring making it harder for the Grignard reagent to react with the carbonyl group at the tetrahedral angle. This would not be the case with the smaller benzyl and 2-fluoro derivatives. Another explanation would involve looking at the Grignard reagents themselves. Hydrogen and fluorine atoms are small and <u>hard</u> whereas chlorine and bromine atoms are large and <u>soft</u>. The chlorine and the bromine atoms in the *ortho*-position on the aromatic ring could coordinate with the magnesium thus softening the <u>hard</u> magnesium making it act more like a <u>soft</u> cuprate (Figure 15).



Figure 15

There seems to be no obvious reason why 2-chlorobenzylmagnesium bromide should give more 1,4-addition than 2-bromobenzylmagnesium bromide unless the bromine atom is simply too large making it less effective than chlorine in coordinating to the magnesium atom.

The ratio of 1,4-addition to 1,2-addition products was measured in two ways, by gas chromatography and by ¹H n.m.r. spectroscopy. The ¹H n.m.r. spectra of the product mixtures were very complicated but, in each case, the benzylic protons belonging to the 1,4- and 1,2-addition products were well separated from other signals. The relative integration of these two peaks allowed the ratio of products to be determined. G.l.c. measurements were made on the product mixtures using a BP10 column after initially removing baseline material from the product mixtures by flash
column chromatography. The column needed heating to a temperature of 240 °C which resulted in traces containing four peaks. Small samples of pure alcohol and pure ketone were obtained by column chromatography in the cases of the benzyl and fluorobenzyl derivatives and by HPLC in the case of the bromobenzyl derivative. The retention times of the peaks seen in each case are shown in table 10.



x		retention times (min)
	1	7.48 ^a
Br	2	5.09, 5.67 and 5.77 ^a
	product mixture	4.74, 5.29, 5.38 and 9.17 b
Cl	1	7.37 b
	2	
	product mixture	7.37 b
F	1	4.98 ^a
	2	3.23 and 3.63 b
	product mixture	3.26, 3.68 and 5.02 b
н	1	5.17 ^a
	2	3.28, 3.69 and 3.74 b
	product mixture	3.30. 3.69, 3.77 and 5.15 ^a

a) BP10; 240 °C; air, 0.49 kg/cm²; He, 1.06 kg/cm²; H₂, 1.06 kg/cm²
b) BP10; 240 °C; air, 0.53 kg/cm²; He, 0.99 kg/cm²; H₂, 0.92 kg/cm²

Table 10

As the pure alcohols gave three peaks in the g.l.c. it was obvious that two of the peaks were not just an impurity. Due to the high temperature of the column, the alcohol was most probably dehydrating to give three possible dienes (209), (210) and (211).



To confirm that this was indeed the case, the samples were analysed by g.c. / mass spectrometry. To confuse matters these analyses which were carried out at the SERC centre at Swansea University were done using a BP5 column. This resulted in poor separation of the peaks corresponding to the decomposition products and in some cases there seemed to be no separation at all. For the mixture of 3-(2-bromobenzyl)cyclohexan-1-one (204) and 1-(2-bromobenzyl)cyclohex-2-en-1-ol (207), two peaks were seen with retention times of 7.44 and 8.22 minutes having molecular masses of 248/250 corresponding to loss of water from the alcohol, and another peak at 12.38 minutes for the ketone. Only one peak was seen for the chloro derivative at 12.08 minutes with the correct mass of 222 for 3-(2-chlorobenzyl)cyclohexan-1-one (212). The product mixture when X = F had two peaks, 7.50 and 8.48 minutes, corresponding to masses of 188 (for loss of water) and 206 [for 3-(2-fluorobenzyl)cyclohexan-1-one (213)] respectively. Finally, when X = H, two peaks were seen at 7.45 and 8.50 minutes with molecular masses of 172 (for the dehydration product) and 188 [for 3-benzylcyclohexan-1-one (214)].

The proportion of 1,4-addition product to 1,2-addition product in the product mixtures were calculated by taking the sum of the areas of the peaks thought to correspond to the dehydration products from the original g.l.c. traces. These results were compared to those obtained by integration measurements in the ¹H n.m.r. spectra of the mixtures and are tabulated below (Table 11).

х	g.l.c	¹ H n.m.r.
	1,4-addition : 1,2-addition	1,4-addition : 1,2-addition
Br	74.8 : 25.2	71 : 29
CI	98.9 : 1.1	99:1
F	59.7 : 40.3	59 : 4 1
Н	62.4 : 37.6	64.4 : 35.6

I AUIC II	Ta	ble	11	
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The results from the two measurements corresponded very well. The ratios obtained by integration measurements in the ¹H n.m.r. spectra were more accurate. The product ratios could be measured accurately from the integration whereas with g.l.c., as the response factors for the degradation products were unknown, a quantitative determination was not possible. It would have been possible to obtain the response factors, but this would have involved a lenghthy separation of each component of the product mixture by preparative g.l.c. and this did not seem justified in view of the relatively close agreement between the g.l.c. and n.m.r. results.

All the products of 1,4-addition were characterised fully after separation by either flash column chromatography or HPLC. 1-(2-Bromobenzyl)cyclohex-2-en-1-ol (**207**) was characterised by ¹H and ¹³C n.m.r. spectroscopy and 1-(2-fluorobenzyl)cyclohex-2-en-1-ol (**215**) and 1-(2-benzyl)cyclohex-2-en-1-ol (**216**) were fully characterised by ¹H, ¹³C n.m.r. and i.r. spectroscopy and mass spectrometry. As 1-(2-chlorobenzyl)cyclohex-2-en-1-ol was formed as a very minor product, it was not isolated. All the ketones were further characterised and separated from their product mixtures by preparation of their 2,2-dimethylpropylidene acetals, formed by the reaction of 2,2-dimethyl-1,3-propanediol and *p*-toluenesulphonic acid in toluene heated at reflux temperature. Yields are shown below (Scheme 43) based on the percentage of ketone present in the mixture of ketone and alcohol reacted.





The reaction of 2-fluoromagnesium bromide with 2-cyclohexen-1-one had given a 59:41 ratio of 3-(2-fluorobenzyl)cyclohexan-1-one (213):1-(2-fluorobenzyl) cyclohex-2-en-1-ol (215). As this had produced the highest proportion of 1,2-addition product, it was decided to prepare the cuprate of the Grignard reagent, react it with 2-cyclohex-1-one, and see if 1,2-addition was still seen to compete with the formation of 3-(2-fluorobenzyl)cyclohexan-1-one (213). Two copper (I) salts were used, copper (I) cyanide, as used with the analogous reaction with 2-bromobenzylmagnesium bromide, and copper (I) iodide. If the reaction with copper (I) iodide was successful, this method was preferable to having to handle copper (I) cyanide. The copper (I) salt was added to 2-fluoromagnesium bromide at -78 °C. The reaction mixture was warmed to -30 °C followed by addition of 2-cyclohexen-1-one. This afforded 3-(2-fluorobenzyl)cyclohexan-1-one (213) exclusively in both cases, the yields being 92% with copper (I) cyanide and 89% with copper (I) iodide.



Exclusive 1,4-addition can, therefore, be achieved by carrying out the Grignard reactions in the presence of copper (I) salts. Good yields of 1,4-addition products were obtained when 2-bromobenzylmagnesium bromide and 2-chlorobenzylmagnesium bromide were reacted with 2-cyclohexen-1-one in the absence of copper (I) salts. In the latter case, 3-(2-chlorobenzyl)cyclohexan-1-one (**212**) was formed almost exclusively.

Having investigated the preparation of 3-(2-bromobenzyl)cyclohexan-1-one (204), the next step was to prepare the O-methyloxime. 3-(2-Bromobenzyl)cyclohexan-1-one (204), O-methylhydroxylamine hydrochloride and pyridine were stirred overnight at room temperature in methanol. In addition to the E and Z isomers of the desired oxime ether (220), another product could be seen. This was identified as 3-(2-bromobenzyl)cyclohexan-1-one dimethylacetal (221). Despite pyridine being present in the reaction mixture to mop up the HCl from the O-methylhydroxylamine hydrochloride, it would appear that enough free acid was present to catalyse the reaction between the ketone and methanol, resulting in acetal formation.



Support for this conclusion was obtained by the preparation of an authentic sample of 3-(2-bromobenzyl)cyclohexan-1-one dimethylacetal (**221**) in 83% yield from the

reaction of 3-(2-bromobenzyl)cyclohexan-1-one (204) with methanol in the presence of a catalytic amount of pyridinium toluene-4-sulphonate. The ¹H and ¹³C n.m.r. spectra were identical to the contaminant in the previous reaction.



3-(2-Bromobenzyl)cyclohexan-1-one O-methyloxime (**220**) was prepared in 95% yield by simply reacting the ketone with O-methylhydroxylamine hydrochloride in pyridine at room temperature. Pyridine worked successfully as both the base and the solvent in the reaction making the use of methanol as the solvent unnecessary.



The radical cyclisation of (220) was attempted following the usual procedure. 3-(2-Bromobenzyl)cyclohexan-1-one O-methyloxime (220) and tributyltin hydride (two equivalents) in deoxygenated benzene were heated to reflux temperature and a solution of AIBN in benzene added slowly (8 h). Heating was continued for a further 10 h. This gave a mixture of products, none of which appeared to be the cyclised product by ¹H n.m.r. spectroscopy. The carbon-nitrogen double bond was still present in the i.r. spectrum.



In order for cyclisation to take place, the 2-bromobenzyl group must be in an axial position. The bond to be made by radical addition to the C=N bond is also an axial bond.



Figure 16

Under normal circumstances the bromobenzyl group would prefer to occupy an equatorial position and, on looking at the desired orientation of the starting material (Figure 16), it seems very unlikely that cyclisation will take place unless some way can be found to force the bromobenzyl group to be axial. This could be done by preparing the starting material with a *tert*-butyl group or a trimethylsilyl group on the ring. This large group will presumably prefer to be equatorial and will thus force the bromobenzyl group to be axial (Figure 17).





Figure 17

-169-

The cyclisation was also attempted using hexabutylditin. This would give the cyclisation a reasonable chance of working without having to compete with direct reduction of the aryl bromide due to the presence of tributyltin hydride. A few variations on reaction conditions were tried.¹⁹⁴⁻¹⁹⁷ A solution of 3-(2-bromobenzyl)cyclohexan-1-one O-methyloxime (**220**) and hexabutylditin in benzene was degassed in a Pyrex tube. The tube was irradiated to initiate the reaction. Light with wavelengths of 300 nm and 350 nm were tried, both with and without cooling of the Pyrex tube, without any success. Starting material was retrieved from the reaction indicating that the bromine atom had not been removed by the hexabutylditin.

2.4 Radical Cyclisation on to Chiral Oxime Ethers

2.4.1 Chiral Oxime Ethers Having a Chiral Auxillary on the Oxime O-atom

2.4.1.1 <u>Preparation of 2-(3-Bromobut-3-en-1-oxy)benzaldehyde O-(2-menthyl-2-oxyethyl)oxime</u>

In 1991, J. Marco-Contelles *et al.* reported the synthesis of polyfunctionalised cyclohexane rings from sugar intermediates.¹⁹⁸ Annulated furanoses (222) were prepared by radical cyclisation of intermediates (223) obtained from diacetone glucose (224) (Scheme 44).



In some cases a new chiral centre was formed showing good diastereoselectivity.





Rather than use a chiral template as had been used here, it was decided to prepare chiral oxime ethers and investigate whether any diastereoselectivity was observed upon radical cyclisation.

Analogues of the previous model systems prepared from 2-hydroxybezaldehyde were used as these were easily prepared and radical cyclisation on such compounds was known to be successful.

The first chiral oxime ether prepared was 2-(3-bromobut-3-en-1-oxy)benzaldehyde O-(2-menthyl-2-oxyethyl)oxime (225). This was prepared as a single isomer in 82% yield by deprotonation of 2-(3-bromobut-3-en-1-oxy)benzaldehyde oxime (137) with sodium hydride in THF and DMPU and subsequent reaction with chloromethylmenthyl ether, at room temperature for 1 h.



¹H n.m.r. spectroscopy showed characteristic menthyl peaks between δ 0.71 and δ 2.08 ppm, the proton on the same carbon as the ether linkage in the menthyl group at δ 3.47 ppm and the OCH₂ as an AB quartet at δ 5.26 and δ 5.30 ppm.

2.4.1.2 <u>Cyclisation of 2-(3-Bromobut-3-en-1-oxy)benzaldehyde O-(2-menthyl-2-oxyethyl)oxime</u>

Radical cyclisation went smoothly in 78% yield by the slow addition of a solution of AIBN in benzene to the oxime ether (225) and tributyltin hydride in a 0.02 M dilution of benzene over 10 h. Heating was continued for a further 12 h. Unfortunately, the cyclised product, 4-(2-menthyl-2-oxyethoxyamino)chroman-3-ylidene (226) was obtained as a 1:1 mixture of diastereoisomers. The ratio was calculated from the ¹H n.m.r. spectrum by integration measurements on the H₃ and OCH₂O signals in both diastereoisomers.



In 2-(3-bromobut-3-en-1-oxy)benzaldehyde O-(2-menthyl-2-oxyethyl)oxime (225), the chiral centre is five atoms away from the site of radical attack. It is, therefore, not too surprising that this did not have any effect on diastereoselectivity.

2.4.1.3 Preparation of 2-(3-Bromobut-3-en-1-oxy)benzaldehyde O-camphanic oxime

The next example tried was 2-(3-bromobut-3-en-1-oxy)benzaldehyde O-camphanic oxime (227). Although the chiral centre is still far removed from the site of radical attack, unlike the flexible side chain in the previous case, the side chain is rigid. 2-(3-Bromobut-3-en-1-oxy)benzaldehyde O-camphanic oxime (227) was prepared as needles, m.p. 88-89 °C, by causing the deprotonated 2-(3-bromobut-3-en-1-oxy)benzaldehyde oxime (227) to react with camphanic chloride for 30 min at room temperature.¹⁹⁹ The oxime ether was obtained as a single diastereoisomer in 93% yield.



The oxime ether was characterised by ¹H, ¹³C n.m.r. and i.r. spectroscopy, mass spectrometry and microanalysis.

2.4.1.4 Cvclisation 2-(3-Bromobut-3-en-1-oxy)benzaldehyde O-camphanic oxime

The radical cyclisation of 2-(3-bromobut-3-en-1-oxy)benzaldehyde O-camphanic oxime (227) was attempted in the usual way, by the slow addition of the AIBN (8 h) to a solution of the oxime ether (227) and tributyltin hydride in benzene heated at reflux

temperature. Heating was continued for a further 5 h. The reaction gave numerous products that could not be isolated, none of which corresponded to starting material. One possibility was that a Beckmann rearrangement could have taken place.

Upon heating it is possible that the nitrogen-oxygen bond could have been broken as the camphanate ion (228) is a very good leaving group. This could lose carbon dioxide to give (229) or remain as the carboxylate anion (228). Migration of the aryl group could then take place resulting in the formation of a nitrilium salt (230). This could then undergo nucleophilic attack either by (228) or (229) to yield the imidates (231) and (232) (Scheme 45).







2.4.2 Preparation of Chiral Oxime Ethers From Chiral Hydroxylamines

2.4.2.1 <u>Preparation of 2-(3-Bromobut-3-en-1-oxy)benzaldehyde O-(α -methyl)benzyloxime</u>

In order to prepare chiral oxime ethers with chiral centres close to the site of radical attack, it was necessary to be able to prepare chiral O-alkyl hydroxylamines. These could then be reacted with the aldehyde or ketone directly without the need to prepare its oxime, deprotonate, and react with a chiral alkyl halide. There were no examples of chiral O-alkyl hydroxylamines reported in the literature.

O-Alkyl hydroxylamines had been prepared by reaction of the sodium salt of Nhydroxyphthalimide, by reaction with sodium acetate in dimethylsulphoxide, with an alkyl halide.²⁰⁰ The O-alkyl hydroxylamines were then cleaved from the phthalimide by reaction with hydrazine (Scheme 46).



This procedure was attempted using (-)-menthylchloride as the alkyl halide. (-)-Menthyl chloride was added to a solution of N-hydroxyphthalimide and sodium acetate in dimethylsulphoxide. The reaction mixture was heated for 30 min to give a product mixture containing in excess of ten inseparable spots by t.l.c..



An alternative synthesis of O-alkyl hydroxylamines by Grochowski involved the reaction of betaine (233), formed from triphenylphosphine and diethyl azodicarboxylate, with N-hydroxyphthalimide and an alcohol (Scheme 47).²⁰¹



N-Alkoxyphthalimides (234) were formed in very good yields. The free O-alkyl hydroxylamines (235) were obtained by reaction with hydrazine as in the former method.

The mechanism of the reaction is thought to be as follows (Scheme 48).





Grochowski tried the reaction on a number of different alcohols, i.e. $R = CH_3CH_2CH_2CH_2$, $CH_3CH_2CH(CH_3)$, $CH_2=CHCH_2$, $PhCH_2$ and Ph_2CH , with yields varying between 73 and 92%.

Using this method, N-(2-phenylpropan-1-oxy)phthalimide (236) was prepared in our work as white plates, m.p. 89-91 °C, in 62% yield from 1-methylbenzylalcohol. Although the alcohol used was racemic, eventual cyclisation would tell us if we were achieving any diastereoselectivity even though the products themselves would not be optically active.



The free O-alkyl hydroxylamine (237) was obtained by reaction with hydrazine monohydrate in ethanol. The hydroxylamine was reacted directly with 2-(3-bromobut-3-en-1-oxy)benzaldehyde (136) without purification or characterisation. 2-(3-Bromobut-3-en-1-oxy)benzaldehyde (136), O-(α -methyl)benzylhydroxylamine (237) and pyridine were stirred overnight. This afforded a single isomer of 2-(3-bromobut-3-en-1-oxy)benzaldehyde O-(α -methyl)benzyloxime (238) as a clear, colourless oil in 73% overall yield from N-(2-phenylpropan-1-oxy)phthalimide (236).



2.4.2.2 <u>Cyclisation of 2-(3-Bromobut-3-en-1-oxy)benzaldehyde O-(α -methyl)benzyloxime</u>

2-(3-Bromobut-3-en-1-oxy)benzaldehyde O-(α -methyl)benzyloxime (238) was converted into 4-(α -methylbenzoxyamino)chroman-3-ylidene (239) by the slow addition of AIBN in benzene to a 0.02 M solution of oxime ether (238) and tributyltin hydride in benzene heated at reflux temperature. Heating was continued for a further 18 h.



It was hoped that the oxime ether (238) would be in a preferred conformation such that the radical centre could attack the C=N bond from one face preferentially. For example, if the two aromatic rings preferred to lie on top of each other through a π stacking effect then radical attack is only possible from the top face.

In the event, the cyclisation was found to give a 1:1 mixture of diastereoisomers in a 61% yield, as measured from the integrations of the two methyl doublets in the ¹H n.m.r. spectrum. It is clear from this result that there is no diastereoselection and from an examination of molecular models it is apparent that if an E stereochemistry is presumed for the oxime ether the system is so rigid that π -stacking of the two aromatic rings is impossible.

2.4.2.3 <u>Preparation of 2-(3-Bromobut-3-en-1-oxy)benzaldehyde O-(R)-(α -methyl-2naphthalene)methyloxime</u>

It was decided to try the same reaction, but this time with 2-(3-bromobut-3-en-1oxy)benzaldehyde O-(R)-(α -methyl-2-naphthalene)methyloxime (240). By using optically active (S)- α -methyl-2-naphthalenemethanol [optical rotation [α]^D -40° (c = 5, EtOH)²⁰²], the oxime ether is optically active rather than racemic as in the previous example. The naphthyl group is also larger than the phenyl group and may be more effective in blocking one face to radical attack. (R)-N-(2-(2-naphthyl)propan-1-oxy)phthalimide (241) was prepared in 57% yield as white needles by the reaction of N-hydroxyphthalimide, (S)-(α -methyl-2-naphthalene)methanol, diethyl azodicarboxylate and triphenylphosphine. The stereochemistry of the chiral centre is inverted due to S_N2 attack of N-hydroxyphthalimide on the intermediate complex of the alcohol (Scheme 49).





The free O-alkyl hydroxylamine was again obtained by heating the phthalimide (241) with hydrazine monohydrate in ethanol. O-(α -methyl-2naphthalene)methylhydroxylamine (242) was used directly in the next step to form the oxime ether without characterisation or purification.



Reaction of O-(R)-(α -methyl-2-naphthalene)methylhydroxylamine (242) with 2-(3bromobut-3-en-1-oxy)benzaldehyde (136) and pyridine at room temperature overnight afforded 2-(3-bromobut-3-en-1-oxy)benzaldehyde O-(R)-(α -methyl-2naphthalene)methyloxime (240) as a clear, colourless oil in 93% yield.



The optical rotation of 2-(3-bromobut-3-en-1-oxy)benzaldehyde O-(R)-(α -methyl-2naphthalene)methyloxime (240) was found to be $[\alpha]^D$ +7.42° (c = 4.58, CH₂Cl₂). It could be seen from the ¹H and ¹³C n.m.r. spectra that the chiral centre in the product had not been racemised and that the oxime ether existed as a single isomer, presumably the E isomer. 2.4.2.4 <u>Cyclisation of 2-(3-Bromobut-3-en-1-oxy)benzaldehyde O-(R)-(α-methyl-2-</u> naphthalene)methyloxime

The cyclisation of (240) proceeded smoothly under the usual experimental conditions to yield 4-[(R)-(α -methyl-2-naphthalene)methoxyamino]chroman-3-ylidene (243) in 68% yield. Examination of the ¹H and ¹³C n.m.r. spectra showed the product to be a 1:1 mixture of diastereoisomers. Again no diastereoselectivity had been shown in the radical cyclisation reaction.



The ratio was calculated from the ¹H n.m.r. spectrum by measurement of the integrations of the methyl doublets at δ 1.36 and δ 1.43 ppm in both diastereoisomers.

2.4.2.5 Conclusions

No diastereoselectivity was observed in the radical cyclisation reactions even when the chiral centre was brought in as close to the site of radical attack as possible. These results are not conclusive and may simply be due to an incorrect choice of model

systems. Presuming that in each case the geometry of the oxime ether is E (only one isomer is observed by ¹H n.m.r. spectroscopy in each case), the system is very rigid (Figure 18).



The chiral group in the oxime ether will have no preferential geometry as no other groups are close enough to interfere. The oxime ether could be chosen in such a way that intramolecular bonding would hold the oxime ether in a fixed geometry (Figure 19).



Figure 19

Attack by the radical may then be forced to proceed on the opposite face to the large R group thus giving some diastereoselectivity. One possibility would be to try using (S)-1-amino-2-(methoxymethyl)-pyrrolidine (244), a reagent used extensively by Enders.²⁰³ Reaction with 2-(3-bromobut-2-en-1-oxy)benzaldehyde (136) would result in the formation of hydrazone (245). It would be necessary to modify the radical cyclisation reaction so that it could be applied to hydrazones; earlier attempts using the phenyl hydrazone of 1-bromohexan-5-one resulted only in reduction of the C=N and C-Br bonds.



Unfortunately, there was no time to explore these reactions and this, and other ideas for chiral induction, will need to be investigated in the future.

2.5 Tandem Radical Cyclisation Reaction

2.5.1 Preparation of 2-(2-Bromobenzyl)pent-4-enal O-methyloxime

Tandem radical cyclisation reactions, i.e. formation of two or more consecutive ring closures from alkyl radicals, have been used successfully to prepare a number of natural products.^{93,96-100,102-111} These reactions are accomplished by generating an internal radical within bonding distance of a multiple bond to generate a new radical which again should be able to bond to the next multiple bond. These cyclisations have involved alkenes, alkynes and in one case the final cyclisation has been on to a nitrile.¹⁰² There have been no examples, however, of the involvement of carbon-nitrogen double bonds in tandem radical cyclisation reactions.

A model system with which to attempt such a radical cyclisation reaction could be prepared relatively simply by adapting the synthesis of 2-(2-bromobenzyl)pent-4-enal O-methyloxime (166) used to prepare 1-methoxyaminoindan (177) previously. The proposed synthesis of the model system is outlined below (Scheme 50).





It was hoped that the reaction of the oxime ether (246) with tributyltin hydride would afford compund (247) *via* a tandem radical cyclisation (Scheme 51).





The initial cyclisation would involve a 5-*exo*-trig cyclisation onto the oxime ether. This would be preferred to the 6-*exo*-trig cyclisation that would be the result of cyclisation on to the alkene. It was hoped that a second 5-*exo*-trig cyclisation would follow by attack by the nitrogen radical on the alkene. Diethyl 2-(2-bromobenzyl)-1,3-propanedicarboxylate was used as the starting material. This was converted into diethyl 5-(2-bromophenyl)pent-1-en-4,4-dicarboxylate (**248**) in 88% yield by deprotonation with sodium hydride and subsequent reaction with allyl bromide, heating at reflux temperature in THF for 4 h.¹¹⁸ The resulting clear, colourless oil was fully characterised by ¹H, ¹³C n.m.r. and i.r. spectroscopy and mass spectrometry. In the ¹H n.m.r. spectrum, H_{1Z} at δ 5.09 and H_{1E} δ 5.10 were assigned by their coupling constants, H_{1Z} having a larger *trans* coupling (17.5 Hz) to H₂ than the *cis* coupling (10.3 Hz) between H_{1E} and H₂. A small coupling could also be seen between H_{1E} and H₃ (Figure 20).



Figure 20

The diester (248) was hydrolysed to the diacid (249) by heating with aqueous potassium hydroxide at 100 °C for 6 h.¹⁷³ After acidification 5-(2-bromophenyl)pent-1-en-4,4-dicarboxylic acid (249) was obtained as a white solid in 81% yield. The product was considered pure enough to be used directly in the next reaction without the need for characterisation. Decarboxylation to the monocarboxylic acid was carried out by heating to 240 °C until the evolution of carbon dioxide had ceased (4 h). The monocarboxylic acid was not purified but was converted directly into its ethyl ester in 78% yield by heating with ethanol and two drops of sulphuric acid at reflux temperature for 2 h. Ethyl 5-(2-bromophenyl)pent-1-en-4-carboxylate (250) was obtained as a clear, colourless oil and was characterised by ¹H, ¹³C n.m.r. and i.r. spectroscopy and mass spectrometry. Reduction of ethyl 5-(2-bromophenyl)pent-1-en-4-carboxylate (250) with lithium aluminium hydride proceeded smoothly to afford 2-(2-bromophenyl)pent-4-en-1-ol (251) as a clear, colourless oil in 94% yield.¹⁷⁴ This was characterised by ¹H, ¹³C n.m.r. and i.r. spectroscopy and mass spectrometry. 2-(2-Bromobenzyl)pent-4-en-1ol (251) was oxidised to the aldehyde (252) using the Swern oxidation procedure.¹⁷⁵⁻ ¹⁷⁷ The alcohol (251) was treated with dimethylsulphoxide and oxalyl chloride in dichloromethane at -78 °C under a nitrogen atmosphere. After stirring the mixture for 1 h, triethylamine was added. After work-up, the aldehyde (252) was reacted directly with O-methylhydroxylamine hydrochloride in pyridine at room temperature to give a mixture of E and Z isomers of 2-(2-bromobenzyl)pent-4-enal O-methyloxime (246) in 81% overall yield. The two isomers were not separated but were characterised as a mixture by ¹H, ¹³C n.m.r. and i.r. spectroscopy and mass spectrometry. As the ratio of isomers was not 1:1, bands belonging to each isomer could easily be identified in the ¹H and ¹³C n.m.r. spectra. The signal corresponding to the oxime proton in the minor isomer was seen at δ 6.51 whereas that for the major isomer was seen further down field at δ 7.27. A study of ¹H n.m.r. tables indicates that the E isomer is the major isomer and that the Z isomer is the minor isomer.¹⁷⁰

2.5.2 Attempted Tandem Radical Cyclisation

As it was critical that abstraction of hydrogen did not occur before the two successive radical cyclisations had taken place, it was decided to keep the concentration of tributyltin hydride as low as possible throughout the course of the reaction.¹⁶³ Thus tributyltin hydride and AIBN in benzene were added dropwise over 20 h to a 0.02 M deoxygenated solution of 2-(2-bromobenzyl)pent-4-enal O-methyloxime (246) in benzene heated at reflux temperature under a nitrogen atmosphere. A number of products were seen on analysis of the product mixture by t.l.c.. The major spot, with an R_F value of 0.48, was isolated by column chromatography in 49% yield. Interpretation of the ¹H and ¹³C n.m.r. spectra of this product showed it to be 1-

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methoxyamino-2-(prop-2-enyl)indan (253). Varying the conditions by adding the tributyltin hydride all in one portion and adding the AIBN slowly, or by altering the addition time of the tributyltin hydride, still produced a number of products.75,^{84,162} The major product was always 1-methoxyamino-2-(prop-2-enyl)indan (253) but was obtained in lower yields.



The ¹H and ¹³C n.m.r spectra showed that 1-methoxyamino-2-(prop-2-enyl)indan (253) had been prepared as a single diastereoisomer.

Guidelines governing the ring closures of substituted hexenyl radicals were formulated by Beckwith and are as follows.⁶⁹

a) 1- or 2-substituted radicals preferentially give *cis*-disubstituted cyclopentyl products;

b) 2- or 4-substituted radicals give mainly *trans*-disubstituted cyclopentyl derivatives.

The explanation of these guidelines lies in the transition state structure. The more favourable conformer contains the substituents in the equatorial position. The transition state structure formed upon reaction of 2-(2-bromobenzyl)pent-4-enal O-methyloxime (246) with tributyltin hydride is shown in figure 21.



Thus cyclisation should lead mainly to the *trans*-disubstituted cyclopentyl derivative (Figure 22).



Figure 21

In a simple hexenyl system, the ratio of *trans* product to *cis* product is 83:17.



It is likely, therefore, that rather than the *trans* product being formed exclusively, the *cis* product is also formed and is seen as one of the minor products in the product mixture shown by t.l.c..

The lack of success of the tandem radical cyclisation reaction could be due to a number of factors. The radical formed as a result of the first cyclisation could be too stable to react further by cyclising on to the alkene; the radical in a p-orbital on the nitrogen is stabilised by overlap with one of the lone pairs in a p-orbital on the adjacent oxygen. Another reason could be that on cyclising on to the alkene an unstable primary radical results. In Curran's synthesis of hirsutene (90) and $\Delta^{9,12}$ -capnellene (91),^{96,97} however, a relatively stable tertiary radical was seen to cyclise on to an alkyne producing a vinyl radical which is relatively more unstable than a primary radical. The cyclisation remained exothermic and took place very quickly because a σ bond was formed at the expense of a π bond.





hirsutene (90)

Scheme 52

This would also be the case had the the second cyclisation taken place by attack of the nitrogen radical on the alkene; a σ bond would have been formed and a π bond broken.

It would be relatively easy to test whether the formation of a primary radical is the cause of the failure of the cyclisation reaction by preparation of the model compounds (254) and (255) by a simple adaptation of the route to 2-(2-bromobenzyl)pent-4-enal Omethyloxime (246). Cyclisation in compound (254) would lead to the more stable tertiary radical, whereas the similar reaction of (255) would give a resonance stabilised benzyl radical.



By far the most likely reason that the second cyclisation step in the tandem cyclisation does not take place is that the stereochemistry of the molecule after the first cyclisation makes it impossible for it to do so. If, after the first cyclisation, the stereochemistry of the major product observed is indeed as in figure 22, as would be suggested by Beckwith's guidelines, formation of the next five-membered ring is simply impossible because the allyl group and the radical on the nitrogen are *trans* to each other (Figure 23).



Figure 23

More careful planning of a suitable model needs to be taken to ensure that cyclisation is possible. In previous successful tandem radical cyclisations, the first cyclisation is usually on to an endocyclic double bond. The resulting radical is then neither *cis* or *trans* to the next group for the second cyclisation. Also, by employing this strategy, the stereochemistry of the product can be predicted.⁷¹

2.6 Oxime Ethers versus Ketones as Radical Acceptors

2.6.1 <u>Preparation of Ethyl 1-bromomethyl-2-oxocyclopentanecarboxylate O-</u> methyloxime

The usual reaction for oxygen-centred radicals is rapid β -bond cleavage, a process that is very useful in ring enlargement processes. This phenomenon has been utilised by Dowd to prepare medium and large rings by radical ring expansion reactions.^{115,116,118,120} The simplest one carbon ring expansion involves conversion of methyl 1-bromomethyl-2-oxocyclopentanecarboxylate (**256**) to methyl 3oxocyclohexanecarboxylate (**257**).



To compare the properties of carbonyl groups and oxime ethers towards these ring expansion reactions, it was decided to prepare ethyl 1-bromomethyl-2oxocyclopentanecarboxylate O-methyloxime (258). Reaction of (258) with tributyltin hydride using the conditions employed by Dowd would allow a direct comparison to be made with the ring expansion of ethyl 1-bromomethyl-2-oxocyclopentanecarboxylate, a reaction already done by Dowd.

Following Dowd's procedure,¹¹⁸ ethyl 1-bromomethyl-2-oxocyclopentanecarboxylate (259) was prepared in 59% yield by the deprotonation of ethyl 2-oxocyclopentanecarboxylate with sodium hydride followed by reaction with

dibromomethane. The ¹H n.m.r. spectrum corresponded with the literature data. DMPU was used as the co-solvent in place of the HMPA used by Dowd.



Ethyl 1-bromomethyl-2-oxocyclopentanecarboxylate (259) was caused to react with Omethylhydroxylamine hydrochloride and pyridine at room temperature overnight to yield a single isomer of ethyl 1-bromomethyl-2-oxocyclopentanecarboxylate Omethyloxime (258) as a pale yellow oil in 81% yield. The product was fully characterised by ¹H, ¹³C n.m.r. and i.r. spectroscopy and mass spectrometry.



2.6.2 <u>Reaction of Ethyl 1-bromomethyl-2-oxocyclopentanecarboxylate O-</u> methyloxime with Tributyltin Hydride

In order to maximise the yield of rearranged product at the expense of direct reduction products, AIBN and tributyltin hydride were added over 10 h *via* a syringe pump. Ethyl 1-bromomethyl-2-oxocyclopentanecarboxylate O-methyloxime (258) in benzene was deoxygenated and heated to reflux temperature. The tributyltin hydride and AIBN in benzene were added over a period of 10 h. Heating was continued for a further 14 h. The ring expanded product, ethyl 3-oxocyclohexanecarboxylate O-methyloxime
(260) was isolated as a clear, colourless oil in 95% yield and was seen as a 1:1 mixture of isomers. The product was fully characterised by ¹H, ¹³C n.m.r. and i.r. spectroscopy and mass spectrometry.



The ¹H.and ¹³C n.m.r. data for the ethyl 1-bromomethyl-2oxocyclopentanecarboxylate O-methyloxime (241) and the product of radical rearrangement, ethyl 3-oxocyclohexanecarboxylate O-methyloxime (243), were compared with the analogous β -keto esters prepared by Dowd (Table 12).

δ _H	3 4 5 Br CO ₂ Me	MeON Br 3 4 5 CO ₂ Et	δ _H	4 5 6 1 CO ₂ Me	$ \frac{4}{5} \frac{3}{6} \frac{2}{1} \frac{1}{CO_2Et} $
			H ₁	2.80	3.07 and 3.30
H ₃	ן	1.77-2.03	H ₂	2.55	J
H4	2.62-1.93	2.40-2.65	H4	2.43-2.26	Ļ
H ₅	J	1.77-2.65	H5	2.11-1.97	1.39-2.62
CH ₂ Br	3.75 and 3.60	3.49 and 3.98	Н ₆	1.90-1.64	J
OCH ₃		3.85	OCH ₃	/	3.82 and 3.824
δ _C			δ _C		
C1	60.9	57.0	C1	42.2	42.16 and 43.33
C2	167.9	162.9	C2	42.4	31.35 and 34.01
C3	38.1	36.6	C3	173.6	157.37 and 157.68
C4	19.2	21.7	C4	40.3	28.49 and 28.60
C5	33.6	34.9	C5	23.8	24.11 and 24.38
OCH ₃	/	61.9	C 6	27.1	25.24 and 26.87
C=0	211.2	170.5	OCH3	1	61.11 and 61.13
CH ₂ Br	32.2	27.9	C=0	208.4	174.24 and 174.34

Table 12

The i.r. spectrum of the rearranged oxime ether still showed a C=N absorption at 1640 cm⁻¹.

In the ¹H n.m.r. spectrum the CH₂Br, seen as two doublets in the starting material, disappeared and was not replaced by a methyl singlet as would be expected had direct reduction of the alkyl bromide taken place. Instead a one proton singlet was seen for H_1 .

The mechanism for radical ring expansion is thought to be as follows (Scheme 53).¹¹⁸



Scheme 53

The first-formed primary radical attacks the carbonyl carbon resulting in an oxy radical. This then forces the internal cyclopropane ring bond to cleave. The radical centre is shifted to the carbon adjacent to the ester where it is stabilised through conjugation.

According to Dowd the ester plays a critical rôle in the rearrangement. Not only does it provide a useful activation for the bromomethylation reaction, it also appears to activate the ketone towards attack by the nucleophilic methylene radical. Once the bond to the carbonyl carbon is formed, the ester provides the driving force for cyclopropane ring cleavage, thus resulting in ring expansion.

A suggested alternative to this mechanism is a fragmentation pathway (Scheme 54).



Scheme 54

If the ring carbonyl-carbon bond is cleaved, an aryl radical and an acrylate would be formed. These could recombine by the acyl radical adding to the β -bond of the acrylate.

Evidence in favour of the first mechanism comes from an examination of the twocarbon ring expansion shown in scheme 55. The only product isolated was the reduction product and there was no product of ring expansion, as anticipated for an unfavourable bicyclic 5, 4-membered ring intermediate. In contrast, when the alkyl chain length was extended to three and four carbon atoms ring expansion proceeded smoothly *via* the five- and six-membered ring oxy radicals respectively.



It will be recalled that a reaction carried out previously in our work was the cyclisation of ethyl 1-(2-bromobenzyl)-2-oxocyclopentanecarboxylate O-methyloxime (179), to

give ethyl 3a-methoxyaminocyclopent[a]indan-8a-carboxylate (180). Under none of the conditions studied, including addition of the tributyltin hydride and AIBN slowly over 20 h to a solution of (179) in refluxing benzene, was there any evidence for the ring expansion product (261) (Scheme 56).





Thus, on the basis of this rather limited evidence it would appear that ring opening of a five-membered ring adjacent to an aminyl radical does not occur. This can be rationalised by consideration of the energy differences between the intermediates (262) and (263) (Scheme 57)



Scheme 57

In intermediate (262), although the N-centred radical is more stable than the corresponding O-centred radical, the high ring strain in thecyclopropane ring is sufficient to ensure that ring expansion is thermodynamically favoured. However, in intermediate (263) the combination of a more stable N-centred radical and a comparatively strain free five-membered ring means that there is no driving force for ring expansion to occur, and instead H atom abstraction takes place preferentially to give the hydroxylamine. If this analysis is correct it implies that only one-carbon ring expansions are possible in radical additions to oxime ethers. This does not necessarily imply that three- or four-carbon ring expansions may not occur with other types of C=N bonds e.g.imines.

2.7 Attempted Cleavage of the N-OR Bond in the Hydroxylamines

Several methods are available for the reduction of the N-O bond of the hydroxylamines resulting from the radical cyclisation reactions mentioned in previous sections including catalytic hydrogenation and lithium aluminium hydride reduction.²⁰⁴⁻²¹²

Initial attempts at reduction were carried out on 4-methoxyaminochroman-3-ylidene (141). Due to the other functional groups present in this molecule it was not considered prudent to use either hydrogenation or lithium aluminium hydride and a metal reducing agent was chosen. The first attempt was carried out using aluminium amalgam, a reagent used successfully for the cleavage of N-O bonds by Malpass.²¹⁰ The aluminium amalgam was prepared by treating thin strips of aluminium foil with aqueous potassium hydroxide, water, aqueous mercury (II) chloride, water, and finally washing with THF. The freshly prepared amalgam was then added to the hydroxylamine (141) in a solution of aqueous THF at 0 °C under an atmosphere of nitrogen. Stirring was continued at 0°C for 24 h. The reaction was repeated on four separate occasions but in each case no reaction was observed by t.l.c.. Work-up afforded only unreacted starting material.

Reduction of N-O bonds by samarium diiodide is well precedented²¹² and this reagent was used in the next instance. A solution of 4-methoxyaminochroman-3-ylidene (141) in dry THF was added to a solution of samarium diiodide in THF under a nitrogen atmosphere. The solution was stirred at room temperature for 30 mins until the deep blue colour changed to yellow. T.l.c. still revealed only starting material. This reaction is very sensitive to moisture and it may be worth repeating the reaction under rigorously dry conditions.

Finally the reduction was attempted with zinc and acetic acid, again without success. Zinc powder was added to (141) in glacial acetic acid at 0 °C followed by heating between 50 and 60 °C for 24 h.

Due to the lack of success in the N-O bond reduction of 4-methoxyaminochroman-3ylidene (141) it was decided to concentrate on a different model system and attempt the reduction with lithium aluminium hydride.

Thus 4a-methoxyaminocyclohex[a]indan (195) in dry diethyl ether was caused to react with lithium aluminium hydride at reflux temperature for 2 h. Chromatography of the product mixture gave two pure solids (19:6 ratio) in 96% overall yield. Mass spectrometry indicated that the two products were isomers (<u>M</u> 147), but neither of the products were the expected 4a-aminocyclohex[a]indan. The i.r. spectra showed, in each case, only a single N-H stretching vibration instead of the expected two strong bands for a primary amine. The ¹H n.m.r. spectra showed marked changes in the aromatic proton region with all the aromatic protons appearing to higher field than those of the starting material. This strongly suggested that a rearrangement had occurred bringing the nitrogen atom into conjugation with the aromatic ring. The spectroscopic evidence indicated that the products were *trans* and *cis* 1,2,3,4,4a,9,9a,10octahydroacridine (264) with the *trans* isomer as the major product. This conclusion was confirmed by melting point determination on the *trans* compound which agreed with that reported in the literature.²¹³



This was a totally unexpected result. Lithium aluminium hydride usually behaves as a hydride donor when used as a reducing agent for carbonyl groups. However, it is not widely appreciated that lithium aluminium hydride (as well as other hydride donor reagents) can also effect the replacement of halogen groups by hydrogen. A mechanistic study of such reactions indicates that these are not simple S_N2 substitution reactions as reaction occurs with aryl and bridgehead halides which cannot react in this way.²¹⁴

Reduction of vinyl halides can result in a loss of stereochemistry which would suggest the involvement of a radical intermediate.²¹⁵ It is thought that formation and subsequent decomposition of a radical anion by one-electron transfer is the most likely mechanism for the reductive dehalogenation of halides which cannot react by the S_N^2 mechanism (Scheme 58).





The involvement of radical intermediates was demonstrated by reaction of 5-hexenyl iodide and 2,2-dimethyl-5-hexenyl iodide with lithium aluminium hydride. Whilst no cyclisation was seen with the former reagent, 2,2-dimethyl-5-hexenyl iodide gave mainly cyclic product (Scheme 59).²¹⁶



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This result indicates the involvement of radical intermediates, at least in the branched chain system.

If we consider the reaction of 4a-methoxyaminocyclohex[a]indan (195) with lithium aluminium hydride, a similar electron transfer process could take place. The radical anion could be formed by one electron transfer, subsequent decomposition leading to an aminyl radical (265) and a methoxy group (Scheme 60).



The aminyl radical (265) could either react with hydride to give an amino group or it can attack the aromatic ring resulting in a rearrangement reaction (Scheme 61).





Closure of the aminyl radical (265) on to the aromatic ring would give rise to the intermediate (266). Ring opening of the strained three-membered ring would either reproduce the aminyl radical or result in ring expansion to the six-membered ring with production of a tertiary radical and re-aromatisation of the aromatic ring. Reaction with hydride would then give 1,2,3,4,4a,9,9a,10-octahydroacridine (264) as a mixture of *cis* and *trans* isomers as the tertiary radical (267) can be attacked by the hydride from either face. This mechanism offers a rational explanation of the observed reaction, but it can only be regarded as speculative in the absence of definitive evidence.

In order to assess whether this rearrangement was a general phenomenon, 1methoxyamino-1-methylindan (176) and ethyl 3a-methoxyaminocyclopent[a]indan (180) were caused to react with lithium aluminium hydride in the same manner.

1-Methoxyamino-1-methylindan (176) and lithium aluminium hydride were heated at reflux temperature in diethyl ether for 2 h. This afforded 2-methyl-1,2,3,4tetrahydroquinoline (268) in 92% yield. A single absorption in the i.r. spectrum at 3090 cm⁻¹ corresponded to the single N-H stretching frequency. The compound was

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further characterised by 1 H and 13 C n.m.r. spectroscopy. In the 1 H n.m.r. spectrum the aromatic protons were again seen to be shifted to higher field.



Ethyl 3a-methoxyaminocyclopent[a]indan (180) was heated to reflux temperature for 2 h with lithium aluminium hydride in diethyl ether to afford a 21:4 mixture of 1,1a,1b,3tetrahydro-1b-hydroxymethylcyclopent[b]quinoline (269) and 8b-amino-3ahydroxymethylcyclopent[a]indan (270) in 94% overall yield. The two compounds were very close running by t.l.c. and only small analytical samples of each could be completely separated from one another.



The lithium aluminium hydride had also reduced the ethyl ester to the alcohol. The two compounds were characterised by ¹H and ¹³C n.m.r. spectroscopy, and in the case of 1,1a,1b,3-tetrahydro-1b-hydroxymethylcyclopent[b]quinoline (269), additional data was obtained by i.r. spectroscopy and mass spectrometry. That rearrangement had taken place to give the major isomer was evident from the n.m.r. spectra. In the ¹H n.m.r. spectrum, the aromatic protons had been shifted significantly upfield due to the now adjacent nitrogen atom. This was not observed in the case of the minor isomer.

In the ¹³C n.m.r. spectrum of the major product, a CH was seen at δ 57.3 due to the bridgehead proton, C1a. This was seen as C8b in the minor isomer at δ 81.8 due to C-NH₂.

A somewhat related reaction has been reported in a paper by Curran in 1991,²¹⁷ in which he describes the first example of a 4+1 radical annulation. Radical annulations provide direct entries to functionalised five-membered rings from acyclic precursors and involve an addition reaction prior to cyclisation. All previously described radical annulation reactions were of the 3+2 or 4+2 class.



4 + 2 Radical Annulations

This retrosynthetic notation was devised by Curran.²¹⁸ Closed dots (•) represent radical donor sites and open dots (o) represent radical acceptor sites.

In preliminary experiments Curran showed that by heating iodopentyne (271), phenyl isocyanite and tributyltin hydride the results were not encouraging but small amounts of a highly u.v. active product were isolated. This was identified as being the known quinoline (272).



Reaction conditions were varied and eventually the quinoline (272) was prepared in greater than 63% yield by employing hexamethylditin and *tert*-butylbenzene as solvent. The generality of this procedure was surveyed by reacting several iodopentynes with phenyl isocyanide, *p*-fluorophenyl isocyanide, *p*-methoxyphenyl isocyanide and *m*-fluorophenyl isocyanide. The results which Curran obtained are shown below.



With *p*-fluorophenyl isocyanide, two separable regioisomers (273) and (274) were formed in ratios that varied slightly as a function of the alkyne substituent. The minor regioisomer (274) was a rearranged product; the orientation of the C-N bond and the fluorine had changed from *para* to *meta*. Similar results were obtained with *p*methoxyphenyl isocyanide. The use of *m*-fluorophenyl isocyanide gave rise to a mixture of four products, two unrearranged and two rearranged products. Again the unrearranged products predominated.

The new quinoline synthesis reported by Curran consisted of a sequence of radical reactions of which the 4+1 radical annulation was an integral part. Radical generation was followed by three successive carbon-carbon bond forming reactions; addition of an alkyl radical to an isonitrile; cyclisation of an imidoyl radical to an alkyne; and cyclisation of a vinyl radical on to a phenyl ring.

Addition of (278) to the isonitrile gives (279) which further cyclises on to the alkyne to give vinyl radical (280).



The cyclic vinyl radical (280) can cyclise to either of two positions on the aromatic ring, closure to the *ortho* position formed a six-membered ring product (281) which was ultimately converted to the unrearranged product (282).



The rearranged product (283) must have arisen from the cyclisation of (280) to the *ipso* position to form the five-membered ring product (284).

Two ways were envisaged by which radical (284) could isomerise to (285), the probable precursor of rearranged product (283).



The first possibility was that (284) may suffer ring opening with cleavage of the C-N bond. Closure of the iminyl radical (286) at the *ortho* position would give rise to the rearranged radical (285). The closest current precedent for the reverse cyclisation of radical (284) to give radical (286) was provided by Newcomb who has shown that aminyl radical cyclisations can be easily reversed.²¹⁹

The second possibility is that radical (284) underwent a 3-*exo* closure to give the strained intermediate (287). (285) was then formed by cleavage of the intra-annular bond *via* 3-*exo* opening. Such ring expansions are well precedented for simple β multiply bonded alkyl radicals, although no examples are reported where allyl or dienyl radicals participate.

Curran tentatively predicted that the radical (286) was the intermediate in the conversion of (284) to (285). This was derived from a simple experiment that proved that if (286) were formed, it would ultimately be converted to (285) under the reaction conditions.



Under the standard conditions, the cyclisation of bromide (288) provided a 6:1 mixture of the quinoline (289) and the reduced product (290). It was decided that it was highly probable that the vinyl radical derived from bromine abstraction of (288) would cyclise to form (286) (R = Ph, X = H).

The rearrangement observed by the action of lithium aluminium hydride on 4amethoxyaminocyclohex[a]indan to yield (195) *cis* and *trans* 1,2,3,4,4a,9,9a,10octahydroacridine (264), on ethyl 3a-methoxyaminocyclopent[a]indan-8a-carboxylate (180) to give 1,1a,1b,2-tetrahydro-1b-hydroxymethylcyclopent[b]quinoline (269) and finally on 1-methoxyamino-1-methylindan (176) to provide 2-methyl-1,2,3,4tetrahydroquinoline (268) could only follow one of the possible mechanisms described by Curran.



As the aminyl radical is exocyclic, ring opening by cleavage of the C-N bond followed by closure on to the aryl ring is not a possibility.

2.8 <u>Conclusions</u>

In this work it has been demonstrated that intramolecular radical cyclisation reactions onto oxime ethers occur in high yields. This synthetic strategy has been used to make a number of useful heterocyclic and bicyclic and tricyclic carbocyclic intermediates. Tributyltin hydride was found to be a good catalyst for these reactions and attempts to carry out these reactions using tris(trimethylsilyl)silane and hexabutylditin proving to be unsuccessful.

Preliminary attempts to carry out tandem radical cyclisation reactions incorporating oxime ethers were unsuccessful but there is a good possibility that by changing the model systems such reactions can be accomplished and this is a suitable area for further development.

Intramolecular radical cyclisation reactions onto oxime ethers can also be used to carry out one-carbon ring expansions, but so far this method has been found to be unsuccessful for two-carbon ring expansions. This reaction could be investigated further for larger three- and four-carbon ring expansions.

Attempted cleavage by lithium aluminium hydride of the N-O alkyl bonds of a hydroxylamine adjacent to an aromatic ring resulted in a novel ring expansion. The mechanism of this reaction needs to be investigated in more detail and the scope of the reaction for organic synthesis needs to be explored further.

Although this work has not resulted in a viable synthesis for either huperzine A or B, it has opened up new synthetic methods which could be applied to the synthesis of these compounds and related alkaloids.

Experimental

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Experimental Techniques

All 90 MHz ¹H n.m.r. spectra were recorded on a Varian EM-390 spectrometer. High-field ¹H n.m.r. (300 MHz) and ¹³C n.m.r. (75.5 MHz) spectra were recorded on a Bruker AM-300 spectrometer at the University of Leicester. High-field ¹H n.m.r. (360 MHz and 250 MHz) and ¹³C n.m.r. (90.5 MHz and 63.5 MHz) spectra were recorded on Bruker AM-360 and Bruker AM-250 spectrometers at Merck, Sharp and Dohme, Harlow. COSY and n.O.e. experiments were recorded using the high-field (400 MHz) n.m.r. service at the University of Warwick. Standard mass spectra and accurate mass measurements were made at either the SERC mass Spectrometry centre, University College of Swansea or at Merck Sharp and Dohme, Harlow. Elemental analysis was carried out by Butterworth Laboratories, Teddington, Middlesex. Infrared spectra were recorded on a Perkin-Elmer 298 spectrometer. Melting points were determined on a Kofler hotstage and are uncorrected.

Flash chromatography was carried out according to the method of Still *et al.*²⁰⁰ using silica gel [Kiesel 60].manufactured by Merck and Co. T.l.c. was conducted on precoated aluminium sheets (60-254) with a 0.2 mm thickness, manufactured by Merck and Co.

Petroleum ether b.r. 40-60 °C and ethyl acetate were distilled prior to use. THF was distilled from sodium metal in the presence of benzophenone. Diethyl ether was distilled from lithium aluminium hydride. Methanol and ethanol were distilled from magnesium and iodine.

3.1.1 Preparation of 1-Trimethylsiloxybuta-1,3-diene (121)¹⁴³⁻¹⁴⁸



Triethylamine (428 cm³, 2.99 mmol), trimethylsilyl chloride (148 cm³, 1.16 mmol) and benzene (225 cm³) were mixed together and the solution centrifuged at 3000 r.p.m.; copious white fumes were evolved during this procedure. The solution was decanted from the solid and was poured into a 3-necked flask fitted with a dropping funnel and a mechanical stirrer. Anhydrous zinc chloride (1.5 g) was added to the reaction mixture, which was then stirred at RT for 30-40 min under a nitrogen atmosphere. Crotonaldehyde (70 cm³, 0.84 mol) was added dropwise over 30 min. The mixture was heated at reflux temperature for 72h. The triethylamine hydrochloride precipitate was filtered off under nitrogen and the benzene was removed under reduced pressure to give a residual oil which was distilled under reduced pressure to give 1trimethylsiloxybuta-1,3-diene (121) (55.2 g, 0.39 mmol, 46%), as a clear colourless oil, b.p. 131 °C; δ_H (300 MHz, CDCl₃, no reference) 0.00 (s, 9 H, Si(CH₃)₃), 4.81 (dd, 1 H, ${}^{2}\underline{J}_{4a,4b}$ 0.5, ${}^{3}\underline{J}_{4a,3}$ 10.7 Hz, H_{4a}), 4.98 (dd, 1 H, ${}^{3}\underline{J}_{4b,3}$ 16.9 Hz, H_{4b}), 5.72 (overlapping dd, 1 H, ${}^{3}J_{2,3} = {}^{3}J_{2,1}$ 11.9 Hz, H₂), 6.21 (complex ddd, 1 H, H₃), 6.52 $(d, 1 H, H_1)$ ppm. There was also some additional coupling probably due to another geometrical isomer.

3.1.2 Preparation of Methyl 2-Trimethylsiloxycyclohex-3-ene carboxylate

(122)124,125



Methyl acrylate (67.0 g, 0.77 mol) and 1-trimethylsiloxybuta-1,3-diene (121) (55.0 g, 0.39 mol) in toluene (50 cm³) were heated at reflux temperature for 60 h under a nitrogen atmosphere. Toluene was evaporated *in vacuo* and the crude residual oil was distilled to give methyl 2-trimethylsiloxycyclohex-3-ene carboxylate (122) (60.25 g, 0.26 mol) as a clear colourless oil, b.p. 70 °C/0.5 mmHg; <u>RF</u> (diethyl ether-petroleum ether b.r. 40-60 °C, 2:3) 0.67; $\delta_{\rm H}$ (300 MHz, CDCl₃, no reference) -0.03 (s, 9 H, Si(CH₃)₃ of major isomer), 0.0 (s, 9 H, Si(CH₃)₃ of minor isomer), 1.60-2.10 (complex m, 4 H, H_{6a}, H_{6b}, H_{5a} and H_{5b}), 2.37-2.46 (complex m, 1 H, H₁), 3.57 (s, 3 H, OCH₃ of major isomer), 3.57 (s, 3 H, OCH₃ of minor isomer), 4.37 (dd, 1 H, ³J_{2,1} 4.6 Hz, H₂ of major isomer), 4.43 (overlapping m, 1 H, ³J_{2,3} 2.1, ³J_{2,1} 8.4 Hz, H₂ of minor isomer), 5.4-5.85 (complex m, 2 H, H₃ and H₄) ppm.

3.1.3 Preparation of Methyl 2-Hydroxycyclohex-3-enecarboxylate (124)¹⁵¹



Methyl 2-trimethylsiloxycyclohex-3-ene carboxylate (122) (9.1 g, 0.4 mol) was stirred for 1 h at RT with aqueous hydrochloric acid (3 M, 10 cm³) in methanol (100 cm³). Methanol was evaporated *in vacuo* and the concentrated aqueous product mixture was extracted with diethyl ether (3 x 25 cm³). The combined organic extracts were dried (MgSO₄), and the diethyl ether was then removed under reduced pressure to give the product (124) as a clear colourless liquid (6.13 g, 0.039 mol, 97%); <u>RF</u> (diethyl etherpetroleum ether b.r. 40-60 °C, 2:3) 0.24; $\delta_{\rm H}$ (90 MHz, CDCl₃, no reference) 1.8-2.3 (complex m, 4 H, H_{5ax}, H_{5eq}, H_{6ax} and H_{6eq}), 2.5-2.8 (complex m, 1 H, H₁), 3.3-3.6 (complex m, 2 H?, OH and H₂O?), 3.8 (s, 3 H, OCH₃), 4.5 (complex m, 1 H, H₂), 5.7-6.0 (complex m, 2 H, H₃ and H₄) ppm.

3.1.4 Preparation of 2-Hydroxycyclohex-3-ene carboxylic acid (123)¹⁵¹⁻¹⁵⁵



Methyl 2-hydroxycyclohex-3-ene carboxylate (124) (3.49 g, 0.022 mol) was stirred with a solution of aqueous potassium hydroxide solution (1 M, 10 cm³) in methanol (50 cm³) at water bath temperature for 6 h. The methanol was removed under reduced pressure and the resulting solution was acidified with aqueous hydrochloric acid (3 M) until neutral to litmus. The product was extracted with diethyl ether (3 x 25 cm³), and the organic phase was dried (MgSO₄) and concentrated by removal of the solvent to give a pale orange liquid (2.63 g, 18.5 mmol, 84%). The product was crystallised from chloroform to give needles, m.p. 83-84 °C; (Found: C, 59.45; H, 6.98; N, 0.02. C₇H₁₀O₃ requires C, 59.14; H, 7.09; N, 0.00%); <u>R</u>_F (ethyl acetate-petroleum ether b.r. 40-60 °C, 1:1) 0.23; v_{max} (CHCl₃) 3700-3600 w (O-H str.), 2021-3010 s (=C-H, C-H str.), 2900-2840 m (C-H str.), 3000-2500 w (O-H str. of CO₂H), 1700 m (C=O str.), 1250 s (O-H bending) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.62-1.75 (complex m, 1 H, OH in minor isomer), 1.75-1.90 (complex m, 4 H, H_{6ax}, H_{6eq}, H_{5ax} and H_{5eq} in minor isomer), 1.95-2.20 (complex m, 4 H, H_{6ax}, H_{6eq}, H_{5ax} and H_{5eq} in major isomer), 2.38-2.62 (complex m, 2 H, H₁ in both isomers), 4.43 (br., 2 H, H₂ in both isomers), 5.62-5.72 (complex m, 2 H, H₃ and H₄ in minor isomer), 5.75-5.88 (complex m, 2 H, H₃ and H₄ in major isomer), 7.40 (s, 2 H, OH and CO₂H in major isomer), 10.0 (s, 1 H, CO₂H in minor isomer) ppm.

3.1.5 Iodolactonisation of 2-Hydroxycyclohex-3-ene carboxylic acid (123)¹³⁴

(a) Under kinetic conditions



2-Hydroxycyclohex-3-ene carboxylic acid (123) (0.5 g, 3.52 mmol) and sodium hydrogencarbonate (0.57 g, 6.8 mmol) in water (15 cm³) were stirred until a homogenous solution was obtained. Chloroform (15 cm³) was added and the mixture was cooled to 0 °C. Iodine (1.8 g, 6.9 mmol) was added and the mixture was stirred at 0 °C for 6 h in the dark. The organic layer was then separated, and washed with 10% aqueous sodium thiosulphate solution until colourless, followed by water and brine. The organic phase was dried (MgSO₄) and the chloroform removed under reduced pressure yielding the crude product as a waxy solid (0.1 g, 0.35 mmol, 10%). The crude product was recrystallised from diethyl ether to give the <u>iodolactone</u> (**125**) as needles. v_{max} (CHCl₃) 1785 s (C=O str. of 5-membered lactone) cm⁻¹; δ_{H} (90 MHz, CDCl₃, TMS) 1.8-2.3 (complex m, 5 H, H_{5ax}, H_{5eq}, H_{6ax}, H_{6eq} and OH), 2.6-2.8 (complex m, 1 H, H₁), 4.4-4.7 (complex m, 2 H, H₂ and H₄), 5.9 (s, 1 H, H₃) ppm - shaking the sample with D₂O reduced the integration of the band at δ 1.8-2.3 to 4 H.

(b) Under thermodynamic conditions



The acid (123) (0.5 g, 3.5 mmol), iodine (3.0 g, 11.8 mmol) and acetonitrile (20 cm³) were stirred at 4 $^{\circ}$ C for 12 days under nitrogen. The reaction mixture was then acidified and extracted with diethyl ether. The organic layer was washed with aqueous sodium hydrogen carbonate and dried (MgSO₄). The removal of diethyl ether under reduced pressure yielded the crude product as a pale orange oil (0.21 g, 0.045 mmol, 12%) having identical ¹H n.m.r. and i.r. spectra to those of the compound described previously.

3.1.6 <u>Phenylselenolactonisation of 2-Hydroxycyclohex-3-ene carboxylic acid</u> (123)¹⁵⁷



Triethylamine (0.3 g, 2.82 mmol) was added to a solution of the acid (**123**) (0.4 g, 2.82 mmol) in dry dichloromethane (50 cm³), and the mixture was stirred at RT for 30 min and then cooled to -78 °C. To the stirred solution at this temperature was added dropwise over 30 min a solution of phenylselenyl chloride (0.6 g, 3.1 mmol) and after 30 min stirring the reaction mixture was allowed to warm up to RT. The solvent was removed under reduced pressure. ¹H n.m.r. spectroscopy showed only starting materials to be present. A further 1 molar equivalent of triethylamine and phenylselenyl chloride in dichloromethane (20 cm³) was added and the reaction mixture was heated under reflux for 3 h, but after work-up ¹H n.m.r. spectroscopy again revealed only starting materials.

3.2.1 <u>Preparation of the Phenylhydrazone Derivative of 1-Bromohexan-5-one</u> (133)¹⁶¹



1-Bromohexan-5-one (10.0 g, 0.5mol) was added dropwise at 0 °C to phenylhydrazine (6.04 g, 0.056 mol), followed by shaking to give an orange solution. Absolute ethanol (20 cm³) was then added and the solution was stirred at RT for 2 h, and then allowed to stand, whereupon yellow-orange crystals precipitated. The product (**133**) was recrystallised from ethanol to give bright yellow rhombic crystals (9.82 g, 0.36 mol, 65%), m.p. 150-151 °C; (Found: C, 53.56; H, 6.34; N, 10.44; Br, 29.70. C₁₂H₁₇BrN₂ requires C, 53.54; H, 6.37; N, 10.41; Br, 29.68%); $\delta_{\rm H}$ (360 MHz, CDCl₃, TMS) 1.99 (m, 2 H, H₃), 2.13 (m, 2 H, H₂), 2.77 (s, 3 H, CH₃), 3.25 (q, 2 H, ³J_{4,3} 9.0 Hz, H₄), 4.10 (broad, 2 H, H₁), 6.95-7.00 (m, 2 H, H_o), 7.04-7.09 (m, 1 H, H_p), 7.34-7.29 (td, 2 H, ⁴J 2.0, ³J 8.0 Hz, H_m), 9.70 (s, 1 H, NHPh) ppm; m/z (CI⁺) 268/270 ([M-H]⁺, 20%), 189 (M-Br, 100%).

3.2.2 <u>Reaction between the Phenylhydrazone Derivative of 1-Bromonexan-5-one</u> (133) and Tributyltin hydride



Dry benzene was deoxygenated by passing a steady stream of nitrogen through it for 15 min. To the deoxygenated benzene (150 cm^3) was added the hydrazone (133) (0.337 g, 1.25 mmol) and AIBN (0.02 g, 0.125 mmol) under an atmosphere of nitrogen. The solution was heated to reflux temperature and a solution of tributyltin hydride $(0.336 \text{ cm}^3, 1.25 \text{ mmol})$ in benzene (100 cm^3) was added over a period of 45 min. Heating was continued for a further 3 h. Benzene was evaporated under reduced pressure and the residue purified by column chromatography (silica, 60 mesh, ethyl acetate-hexane, 1:49). The product was further purified by preparative t.l.c. (ethyl

acetate-hexane, 1:49) to give the product (135) (~10 mg) as a single spot. <u>R</u>_F (ethyl acetate-hexane, 1:49) 0.33; $\delta_{\rm H}$ (360 MHz, CDCl₃, TMS) 1.03 (d, 3 H, H₁), 1.10-1.38 (m, 3 H, H_{4a} and H₅), 1.58 (m, 4 H, H₆ and H_{4a}), 2.08 (td, 1 H, H_{3a}), 2.20 (dddd, 1 H, H_{3b}), 3.05 (br.m, 1 H, H₂), 4.05 (broad, 1 H, NH - disappears on D₂O shake), 6.62 (t, 1 H, H_p), 6.80 (d, 2 H, H_o), 7.08 (t, 2 H, H_m) ppm

3.2.3 Preparation of 2-(3-Bromobut-3-en-1-oxy)benzaldehyde (136)



A solution of 2,3-dibromoprop-1-ene (9.82 g, 49.1 mmol) and 2hydroxybenzaldehyde (5.00 g, 40.9 mmol) in acetone (20 cm³) was heated at reflux temperature with anhydrous potassium carbonate (11.32 g, 81.9 mmol) for 4 h. After this time, the reaction mixture was poured into water (50 cm³) and extracted with diethyl ether (3 x 100 cm³). The organic extracts were dried (MgSO₄) and evaporated under reduced pressure. The residue was purified by column chromatography (silica, 60 mesh, dichloromethane-petroleum ether b.r. 40-60 °C, 1:1) to give the product (**136**) (10.09 g, 32.31 mmol, 79%) as a clear colourless oil which turned brown on standing at RT. <u>RF</u> (dichloromethane-petroleum ether b.r. 40-60 °C, 3:7) 0.24; v_{max} (CH₂Cl₂) 3070-3015 w (=C-H and Ar-H, C-H str.), 2990-2910 w (sat. C-H str.), 2860 w (-OCH₂, C-H str.), 1690 s (C=O str.), 1600 s, 1580 m and 1480 s (Ar ring vib.), 1450 s (C-H def.) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 4.76 (t, 2 H, ⁴J₂, 4^rE = ⁴J_{2',4'Z} 1.1 Hz, H₂'), 5.74 (dt, 1 H, ²J_{4'Z,4'E} 2.2 Hz, H_{4'Z}), 6.10 (dt, 1 H, H_{4'E}), 6.87 (d, 1 H, ³J_{3,4} 8.5 Hz, H₃), 7.02 (t, 1 H, ³J_{5,4} = ³J_{5,6} 7.6 Hz, H₅), 7.42 (dt, 1 H, ⁴J_{4,6} 1.8 Hz, H₄), 7.73 (dd, 1 H, H₆), 10.59 (s, 1 H, R<u>H</u>C=O) ppm.

3.2.4 Preparation of 2-(3-Bromobut-3-en-1-oxy)benzaldehyde Oxime (137)¹⁵¹



2-(3-Bromobut-3-en-1-oxy)benzaldehyde (**136**) (1.00 g, 4.15 mmol), hydroxylamine hydrochloride (0.35 g, 4.98 mmol) and pyridine (1.68 cm³, 20.77 mmol) were stirred in ethanol (10 cm³) for 24 h at RT. Ethanol was evaporated *in vacuo*, the residue diluted with diethyl ether and washed with water (2 x 20 cm³). The organic phase was dried (MgSO₄) and solvent removed under reduced pressure. Flash chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 60-80 °C, 3:7)) gave a single isomer of the <u>oxime</u> (**137**) (0.92 g, 3.61 mmol, 87%) as needles, m.p. 59 °C (from petroleum ether b.r. 40-60 °C); (Found: C, 46.98; H, 3.95; N, 5.39. C₁₀H₁₀BrNO₂ requires C, 46.90; H, 3.94; N, 5.47%); <u>RF</u> (diethyl ether-petroleum ether b.r. 40-60 °C, 3:7) 0.33; v_{max} (CH₂Cl₂) 3565 s (free O-H, O-H str.), 3450-3200 br.s. (H-bonded O-H, O-H str.), 3040 w (=C-H and Ar-H, C-H str.), 1640-1620 w (C=N str.), 1640 m, 1575 w and 1480 s (Ar ring vib.), 1450 m (C-H def), 1225 s (C-O str.), 1044 s (C-O str.) cm⁻¹; $\delta_{\rm H}$ (360 MHz, CDCl₃, TMS) 4.67 (dd, ⁴J₂, 4^rZ and ⁴J₂, 4^rE <1.0 Hz, H₂'), 5.67 (dt, 1H, ²J₄'Z, 4^rE 1.9 Hz, H₄'Z), 5.97 (dt, 1 H, H₄'E), 6.84 (d, 1 H, ³J₃, 4

8.2 Hz, H₃), 6.99 (t, 1 H, 3 <u>J_{5,6}</u> = 3 <u>J_{5,4}</u> 7.7 Hz, H₅), 7.31 (ddd, 1 H, 4 <u>J_{4,6}</u> 1.5 Hz, H₄), 7.72 (dd, 1 H, H₆), 8.57 (s, 1 H, C<u>H</u>=NOH), 9.46 (bs, 1 H, O<u>H</u>) ppm; δ_{C} (90.5 MHz, CDCl₃, TMS) 71.9 (C2'), 112.7 (C3), 118.1 (C4'), 121.0 (C1), 121.8 (C5), 126.5 (C3'), 127.0 (C4), 131.2 (C6), 146.2 (<u>C</u>H=NOH), 155.6 (C2) ppm; m/z (EI+) 255/257 (<u>M</u>+, 3%), 238/240 (<u>M</u>-OH, 12%), 176 (<u>M</u>-Br, 21%), 159 (<u>M</u>-OH and Br, 16%), 119 (<u>M</u>-CH₂C(Br)=CH₂ and OH, 21%), 91 (<u>M</u>-CH₂C(Br)=CH₂ and H₂C=NOH, 47%), 77 (C₆H₅+, 28%), 63 (27%), 51(27%), 39(100%); (Found: <u>MH</u>+, 255.9957. C₁₀H₁₀BrNO₂ requires <u>MH</u>+, 255.9973).

3.2.5 Preparation of 2-(3-Bromobut-3-en-1-oxy)benzaldehvde O-methyloxime (138)



2-(3-Bromobut-3-en-1-oxy)benzaldehyde (136) (2.00 g, 7.84 mmol) and Omethylhydroxylamine hydrochloride (0.98 g, 11.8 mmol) were stirred for 24 h at RT in pyridine (20 cm³). Pyridine was removed under reduced pressure and the residue diluted with diethyl ether (50 cm³). The organic phase was washed with water (2 x 50 cm³), dried (MgSO₄), and evaporated under reduced pressure to leave a yellow oil. Flash chromatography (silica, 60 mesh, dichloromethane-petroleum ether b.r. 40-60 °C, 7:3) gave a mixture of E and Z isomers of the <u>oxime ether</u> (138) as a clear colourless oil (2.11 g, 7.37 mmol, 94%); <u>RF</u> (dichloromethane-petroleum ether b.r. 40-60 °C, 3:7) 0.38 and 0.23; v_{max} (film) 3080 w (=C-H, C-H str.), 3005 w (Ar-H, C-H str.), 2960-2900 m (sat. C-H str.), 2810 w (-O-CH₂-, C-H str.), 1645 m (C=N str.), 1600 m, 1570 w and 1480 s (Ar ring vib.), 1260-1230 s (C-O str), 1055 s (C-O str.), 920 s cm⁻¹

MAJOR E ISOMER

 $\delta_{\rm H}$ (360 MHz, CDCl₃, TMS) 3.97 (s, 3 H, C<u>H</u>₃), 4.66 (dd, 2 H, ⁴J_{2',4'Z} 1.2, ⁴J_{2',4'E} 1.6 Hz, H_{2'}), 5.68 (dt, 1 H, ²J_{4'Z,4'E} 2.1 Hz, H_{4'Z}), 5.98 (dt, 1 H, H_{4'E}), 6.84 (dd, 1 H, ⁴J_{3,5} 0.6, ³J_{3,4} 8.3 Hz, H₃), 6.99 (ddd, 1 H, ³J_{5,4} 7.5, ³J_{5,6} 7.8 Hz, H₅), 7.31 (ddd, 1 H, ⁴J_{4,6} 1.7 Hz, H₄), 7.81 (dd, 1 H, H₆), 8.50 (s, 1 H, C<u>H</u>=NOCH₃) ppm; $\delta_{\rm C}$ (CDCl₃, 90.5 MHz, TMS) 61.9 (O<u>C</u>H₃), 72.0 (C2'), 112.6 (C3), 118.1 (C4'), 121.3 (C1), 121.7 (C5), 128.6 (C3'), 128.7 (C4), 130.9 (C6), 144.3 (<u>C</u>H=NOCH₃), 155.6 (C2) ppm; m/z (EI⁺) 269/271 (<u>M</u>⁺, 29%), 240/242 (38%), 221/223 (90%), 190 (<u>M</u>-Br, 72%), 159 (<u>M</u>-CH₃O and Br, 100%), 144 (39%), 119 (CH₂C(Br)=CH₂, 80%), 91 (<u>M</u>-CH₃ON=CH₂ and CH₂C(Br)=CH₂, 90%), 77 (C₆H₅⁺, 31%); (Found: <u>M⁺</u>, 269.0025. C₁₁H₁₂BrNO₂ requires <u>M⁺</u>, 269.0051).

3.2.6 Preparation of 2-(3-Bromobut-3-en-1-oxy)benzaldehyde O-benzyloxime (139)



2-(3-Bromobut-3-en-1-oxy)benzaldehyde (136) (1.00 g, 4.15 mmol) and Obenzylhydroxylamine hydrochloride (0.79 g, 4.98 mmol) in pyridine (20 cm³) were

stirred at RT for 24 h. Pyridine was removed under reduced pressure and diethyl ether (50 cm^3) added to the residue. The organic phase was washed with water (2 x 50 cm³), dried (MgSO₄) and evaporated *in vacuo* to give a yellow oil. Flash chromatography (silica, 60 mesh, dichloromethane-petroleum ether b.r. 60-80 °C, 3:2) gave a mixture of E and Z isomers of the <u>oxime ether</u> (**139**) (1.16 g, 3.36 mmol, 81%) as a clear, colourless oil. <u>RF</u> (dichloromethane-petroleum ether b.r. 60-80 °C, 3:7) 0.33 and 0.15; v_{max} (film) 3060 w (=C-H, C-H str.), 3023 m (Ar-H, C-H str.), 2920 m (sat. C-H str.), 2862 m (-O-CH₂, C-H str.), 1634 m (C=N str.), 1598 s, 1570 w and 1480 s (Ar ring vib.), 1360 s, 1335 m, 1250-1220 s (C-O str.) cm⁻¹

MAJOR E ISOMER (R_E 0.33)

 $\delta_{\rm H}$ (360 MHz, CDCl₃, TMS) 4.64 (t, 2 H, ${}^{4}J_{2',4'E} = {}^{4}J_{2',4'Z}$ 1.2 Hz, H_{2'}), 5.21 (s, 2 H, OC<u>H</u>₂Ph), 5.67 (dt, 1 H, ${}^{2}J_{4'Z,4'E}$ 3.4 Hz, H_{4'Z}), 5.97 (dt, 1 H, H_{4'E}), 6.83 (d, 1 H, ${}^{3}J_{3,4}$ 8.4 Hz, H₃), 6.98 (dd, 1 H, ${}^{3}J_{5,4}$ 7.5, ${}^{3}J_{5,6}$ 7.8 Hz, H₅), 7.25-7.38 (complex m, 4 H, H₄ and H_m and H_p in PhCH₂), 7.42 (dd, 2 H, ${}^{4}J_{o,p}$ 1.6, ${}^{3}J_{o,m}$ 7.7 Hz, H_o in PhCH₂), 7.82 (dd, 1 H, ${}^{4}J_{6,4}$ 1.7 Hz, H₆), 8.58 (s, 1 H, C<u>H</u>=NOCH₂Ph) ppm; δ_C (90.5 MHz, CDCl₃, TMS) 72.0 (C2'), 76.4 (Ph<u>C</u>H₂), 112.6 (C3), 118.1 (C4'), 121.3 (C1), 121.7 (C5), 126.6 (C3'), 126.8 (C4), 127.6 (C_p in PhCH₂), 128.4 (C_m and C_o in PhCH₂), 131.0 (C6), 137.6 (C' in PhCH₂), 144.8 (<u>C</u>H=NOCH₂Ph), 155.6 (C2) ppm;

MINOR Z ISOMER (R_F 0.15)

 $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 4.58 (dd, 2 H, ${}^{4}J_{2',4'Z}$ 1.2, ${}^{4}J_{2',4'E}$ 1.6 Hz, H_{2'}), 5.20 (s, 2 H, OC<u>H</u>₂Ph), 5.63 (dt, 1 H, ${}^{2}J_{4'Z,4'E}$ 3.7 Hz, H_{4'Z}), 5.93 (dt, 1 H, H_{4'E}), 6.77 (dd, 1 H, ${}^{4}J_{3,5}$ 0.6, ${}^{3}J_{3,4}$ 8.3 Hz, H₃), 6.94 (td, 1 H, ${}^{3}J_{5,4} = {}^{3}J_{5,6}$ 7.6 Hz, H₅), 7.22-7.42 (complex m, 6 H, H₄ and H_o, H_m and H_p in PhCH₂), 7.81 (dd, 1 H, ${}^{4}J_{6,4}$ 1.7 Hz, H₆), 8.57 (s, 1 H, C<u>H</u>=NOCH₂Ph) ppm; $\delta_{\rm C}$ (CDCl₃, 75.5 MHz) 71.8 (C2'), 76.2 (Ph<u>C</u>H₂), 112.5 (C3), 118.1 (C4'), 121.2 (C1), 121.6 (C5), 126.5 (C3'), 126.6 (C4), 127.8 (C_p in PhCH₂), 128.27 (C_m in PhCH₂), 128.31(C_o in PhCH₂), 130.9
(C6), 137.5 (C' in PhCH₂), 144.7 (<u>C</u>H=NOCH₂Ph), 155.5 (C2) ppm;
m/z (EI⁺) 346/348 (<u>M</u>⁺, 25%), 91 (<u>M</u>-H₂C=NOCH₂Ph and CH₂C(Br)=CH₂, 100%),
77 (C₆H₅⁺, 10%); (Found: <u>M</u>⁺, 345.0364. C₁₇H₁₆BrNO₂ requires <u>M</u>⁺,
345.0364).

3.2.7 <u>Preparation of 2-(3-Bromobut-3-en-1-oxy)benzaldehyde O-tert-butyl oxime</u> (140)



2-(3-Bromobut-3-en-1-oxy)benzaldehyde (136) (1.00 g, 4.15 mmol) was stirred with O-*tert*-butylhydroxylamine hydrochloride (0.62 g, 4.98 mmol) and pyridine (20 cm³) for 24 h at RT. Pyridine was removed under reduced pressure, the residue diluted with diethyl ether (50 cm³) and washed with water (2 x 20 cm³). The organic phase was dried (MgSO₄) and evaporated *in vacuo* to give a yellow oil. Flash chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 60-80 °C, 3:7) gave one isomer of the <u>oxime ether</u> (140) as a clear colourless oil (1.13 g, 3.16 mmol, 87%); <u>RF</u> (diethyl ether-petroleum ether b.r. 60-80 °C, 1:4) 0.54; v_{max} (film) 3070 w (=C-H, C-H str.), 3018 w (Ar-H, C-H str.), 2970-2900 m (sat. C-H str.), 2860 w (-O-CH₂-, C-H str.), 1640 m (C=N str.), 1600 m, 1570 w and 1480 s (Ar ring vib.), 1260-1230 s (C-O str.), 1055 s (C-O str.), 920 s cm⁻¹; $\delta_{\rm H}$ (360 MHz, CDCl₃, TMS)

1.29 (s, 9 H, C(C<u>H</u>₃)₃), 4.58 (dd, 2 H, ${}^{4}J_{2',4'Z}$ and ${}^{4}J_{2',4'E}$ <1.0 Hz, H₂'), 5.60 (dt, 1 H, ${}^{3}J_{4'Z,4'E}$ 3.1 Hz, H_{4'Z}), 5.91 (dt, 1 H, H_{4'E}), 6.76 (d, 1 H, ${}^{3}J_{3,4}$ 8.3 Hz, H₃), 6.91 (dd, 1 H, ${}^{3}J_{5,4}$ 7.5, ${}^{3}J_{5,6}$ 7.7 Hz, H₅), 7.21 (ddd, 1 H, ${}^{4}J_{4,6}$ 1.6 Hz, H₄), 7.79 (dd, 1 H, H₆), 8.40 (s, 1 H, C<u>H</u>=NOCH₃) ppm; δ_{C} (90.5 MHz, CDCl₃, TMS) 27.6 (C(<u>C</u>H₃)₃), 72.0 (C2'), 79.0 (-<u>C</u>(CH₃)₃), 112.6 (C3), 118.0 (C4'), 121.6 (C5), 122.3 (C1), 128.5 (C4), 128.7 (C3'), 130.4 (C6), 142.7 (<u>C</u>H=NOC(CH₃)₃), 155.4 (C2) ppm; m/z (EI⁺) 311/313 (<u>M</u>⁺, 3%), 255/257 (<u>M</u>-C(CH₃)₃, 3%), 238/240 (<u>M</u>-OC(CH₃)₃, 10%), 176 (<u>M</u>-OCH₂C(Br)=CH₂, 13%), 159 (<u>M</u>-OC(CH₃)₃ and Br, 5%), 131(<u>M</u>-H₂C=NOC(CH₃)₃ and Br, 3%), 119 (<u>M</u>-OC(CH₃)₃ and CH₂C(Br)=CH₂, 5%), 91 (<u>M</u>-H₂C=NOC(CH₃)₃ and CH₂C(Br)=CH₂, 10%), 77 (C₆H₅⁺, 5%), 57 (-C(CH₃)₃, 100%), 41 (20%); (Found: <u>MH</u>⁺, 312.0599. C₁₄H₁₈BrNO₂ requires <u>MH</u>⁺, 312.0599).

3.2.8 Preparation of 4-Methoxyaminochroman-3-ylidene (141)



A solution of 2-(3-bromobut-3-en-1-oxy)benzaldehyde O-methyloxime (138) (2.00 g, 7.37 mmol) and tributyltin hydride (2.59 g, 8.90 mmol) in benzene (370 cm³, 0.02 M dilution of (138)) was degassed by bubbling nitrogen through the solution for 1 h. The reaction mixture was heated to reflux temperature under a nitrogen atmosphere and the AIBN (240 mg, 1.46 mmol) in degassed benzene (10 cm³) was added to the solution over 18 h (syringe pump). After 24 h the benzene was evaporated *in vacuo*. Flash chromatography (silica, 60 mesh, 500 cm³ petroleum ether b.r. 40-60 °C then

diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) afforded the <u>hydroxylamine</u> (141) as a pale yellow oil (1.07 g, 5.63 mmol, 76%); <u>R</u>_E (diethyl ether-petroleum ether b.r. 40-60 °C, 1:9) 0.27; $\delta_{\rm H}$ (360 MHz, CDCl₃, TMS) 3.50 (s, 3 H, OC<u>H₃</u>), 4.43 (s, 1 H, H₄), 4.52 (d, 1 H, ²J_{2ax,2eq} 11.8 Hz, H_{2ax}), 4.84 (dd, 1 H, ⁴J_{2eq,Z} 1.2 Hz, H_{2eq}), 5.29 (s, 1 H, H_E), 5.35 (d, 1 H, H_Z), 5.57 (broad s, 1 H, N<u>H</u>), 6.83 (dd, ⁴J_{8,6} 0.6, ³J_{8,7} 7.5 Hz, H₈), 6.89 (td, 1 H, ³J_{6,5} = ³J_{6,7} 7.5 Hz, H₆), 7.18 (td, 1 H, ⁴J_{7,5} 1.6 Hz, H₇), 7.22 (dd, 1 H, H₅) ppm; $\delta_{\rm C}$ (90.5 MHz, CDCl₃, TMS) 60.3 (C4), 62.8 (O<u>C</u>H₃), 67.4 (C2), 115.9 (R₂C=<u>C</u>H₂), 117.0 (C8), 120.1 (C4a), 120.7 (C6), 129.5 (C7), 130.1 (C5), 139.4 (C3), 155.2 (C8a) ppm.

The hydrochloride salt of (141) was prepared by passing dry hydrogen chloride gas through a solution of (141) in dry diethyl ether. This gave the hydrochloride salt (1.05 g, 4.62 mmol, 82 %) as a powder, m.p. 131-134 °C (from chloroformmethanol); (Found: C, 56.90; H, 6.23; N, 5.67. C₁₁H₁₄ClNO₂.¹/₄ H₂O requires C, 56.90; H, 6.29; N, 6.03%); v_{max} (CH₂Cl₂) 3940 w, 3045 s, 2980 m (C-H str.), 2690 w (N-H str.), 2300 m, 1650 m, 1580 m and 1570 m (Ar ring vib.), 1040 w (=C-O, C-O str.), 895 s (R₂C=CH₂ out of plane def.) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 3.91 (s, 3 H, OCH₃), 4.60 (d, 1 H, ²J_{2ax,2eq} 12.8 Hz, H_{2ax}), 4.76 (s, 1 H, H₄), 5.11 $(dd, 1 H, {}^{4}J_{2ea,E} 1.1 Hz, H_{2ea}), 5.61 (s, 1 H, H_E), 5.66 (d, 1 H, H_Z), 6.87 (dd, {}^{4}J_{8.6})$ 1.1, ${}^{3}J_{8,7}$ 8.3 Hz, H₈), 6.95 (ddd, 1 H, ${}^{3}J_{6,5}$ 7.7, ${}^{3}J_{6,7}$ 8.6 Hz, H₆), 7.23 (ddd, 1 H, 4 <u>J_{7,5}</u> 1.4 Hz, H₇), 7.77 (dd, 1 H, H₅), 12.01 (broad s, 2 H, +N<u>H₂</u>Cl⁻) ppm; δ_{C} (75.5 MHz, CDCl₃, TMS) 58.8 (C4), 62.7 (OCH₃), 67.6 (C2), 112.2 (C4a), 117.6 (C8), 120.9 (C6), 123.4 (R₂C=<u>C</u>H₂), 131.5 (C7), 131.71 (C3), 132.0 (C5), 155.9 (C8a) ppm; m/z (EI+) 160 (M-CH₃O, 2%), 145 (M-CH₃ONH, 100%), 115 (20%), 91 (PhCH₂, 8%), 77 (C₆H₅+, 2%); (Found: <u>M-Cl</u>+, 192.1025. C₁₁H₁₄ClNO₂ requires <u>M-Cl</u>+, 192.1025).
3.2.9 Preparation of 4-Benzoxyaminochroman-3-ylidene (149)



2-(3-Bromobut-3-en-1-oxy)benzaldehyde O-benzyloxime (139) (300 mg, 0.87 mmol) and tributyltin hydride (303 mg, 1.04 mmol) were dissolved in benzene (43 cm³ (0.02 M dilution of (139)) and degassed by bubbling nitrogen through the solution for 1 h. The solution was heated to reflux temperature and AIBN (25 mg, 0.17 mmol) in benzene (10 cm^3) added over 9 h (syringe pump). The reaction mixture was heated at reflux temperature under a nitrogen atmosphere for 24 h. Benzene was removed under reduced pressure. Flash chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) afforded the hydroxylamine (149) as a pale yellow oil (176 mg, 0.66 mmol, 76 %); RF (diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) 0.39; v_{max} (film) 3080 w (=C-H, C-H str.), 3005 w (Ar-H, C-H str.), 2960-2900 m (sat. C-H str.), 2805 w (-O-CH₂-, C-H str.), 1640 m, 1610 m, 1570 w and 1485 s (Ar ring vib.), 1240 s (C-O str.) cm⁻¹; $\delta_{\rm H}$ (360 MHz, CDCl₃, TMS) 4.43 (d, 1 H, ${}^{3}J_{4,\rm NH}$ 4.8 Hz, H4), 4.47 (d, 1 H, ²J_{2ax,2eq} 11.7 Hz, H_{2ax}), 4.65 and 4.72 (AB quartet, 2 H, ²J 11.7 Hz, PhCH₂), 4.78 (dd, 1 H, ⁴J_{2ea,Z} 1.2 Hz, H_{2ea}), 5.28 (s, 1 H, H_E), 5.35 (d, 1 H, H_Z), 5.54 (d, 1 H, NH), 6.83 (dd, 1 H, ${}^{4}J_{8,6}$ 1.1, ${}^{3}J_{8,7}$ 8.1 Hz, H₈), 6.87 (td, 1 H, ${}^{3}\underline{J}_{6,5} = {}^{3}\underline{J}_{6,7}$ 7.4 Hz, H₆), 7.15 (dd, 1 H, ${}^{4}\underline{J}_{5,7}$ 1.7 Hz, H₅), 7.18 (ddd, 1 H, H₇), 7.25-7.34 (complex m, 5 H, H_o, H_m and H_p in PhCH₂) ppm; δ_{C} (90.5 MHz, CDCl₃, TMS) 60.4 (C4), 67.4 (C2), 77.1 (PhCH₂), 116.0 (R₂C=CH₂), 117.0 (C8), 120.1 (C4a), 120.6 (C6), 127.9 (C_p in PhCH₂), 128.3 (C_m in PhCH₂), 128.8 (C_o in PhCH₂), 129.5 (C7), 130.2 (C5), 137.7 (C' in PhCH₂), 139.5 (C3), 155.3 (C8a) ppm.

The hydrochloride salt of (149) was prepared by passing dry hydrogen chloride gas through a sloution of the hydroxylamine (149) in dry diethyl ether. This gave the hydrochloride salt (164 mg, 0.54 mmol, 82 %) as a very hygroscopic powder; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 4.58 (d, 1 H, ${}^{2}J_{2ax,2eq}$ 12.7 Hz, H_{2ax}), 4.80 (s, 1 H, H₄), 5.04 (d, 1 H, ${}^{2}J$ 9.1 Hz, PhCH₂), 5.15 (d, 1 H, PhCH₂), 5.17 (d, 1 H, H_{2eq}), 5.58 (s, 1 H, H_E), 5.61 (s, 1 H, H_Z), 6.81 (dd, 1 H, ${}^{4}J_{8,6}$ 1.0, ${}^{3}J_{8,7}$ 8.3 Hz, H₈), 6.87 (ddd, 1 H, ${}^{3}J_{6,5}$ 7.2, ${}^{3}J_{6,7}$ 7.5 Hz, H₆), 7.06 (ddd, 1 H, ${}^{4}J_{7,5}$ 1.4 Hz, H₇), 7.24 - 7.40 (complex m, 5 H, H_o, H_m and H_p in PhCH₂), 7.78 (dd, 1 H, H₅) ppm; $\delta_{\rm C}$ (75.5 MHz, CDCl₃, TMS) 59.2 (C4), 67.5 (C2), 77.0 (PhCH₂), 112.3 (C4a), 117.5 (C8), 120.9 (C6), 123.3 (R₂C=<u>C</u>H₂), 128.5 (C_m in PhCH₂), 129.2 (C_p in PhCH₂), 129.6 (C_o in PhCH₂), 131.6 (C7), 131.9 (C' in PhCH₂), 132.0 (C5), 132.8 (C3), 155.8 (C8a) ppm; m/z (CI⁺) 268 (M-Cl, 8%), 160 (M-PhCH₂O and HCl, 12%), 145 (M-PhCH₂ONH and HCl, 100%), 131 ([PhCH₂C(CH₃)=CH₂]⁺, 2%), 115 (6%), 91 (PhCH₂, 21%), 77 (C₆H₅⁺, 2%); (Found: M-Cl⁺, 268.1337. C₁₇H₁₈CINO₂ requires M-Cl⁺, 268.1337).

3.2.10 <u>Preparation of 4-tert-Butoxyaminochroman-3-ylidene(150)</u>



A solution of 2-(3-bromobut-3-en-1-oxy)benzaldehyde O-*tert*-butyloxime (140) (400 mg, 1.28 mmol) and tributyltin hydride (450 mg, 1.54 mmol) in benzene (64 cm³, 0.02 M dilution of (140)) was degassed for 1 h. The reaction mixture was heated to

reflux temperature under a nitrogen atmosphere and AIBN (40 mg, 0.26 mmol) in degassed benzene (10 cm³) was added over 8 h (syringe pump). Heating was continued for 24 h. Benzene was evaporated under reduced pressure. Flash chromatography (silica, 60 mesh, 500 cm³ petroleum ether b.r. 40-60 °C then diethyl ether-petroleum ether b.r. 40-60 °C, 1:9) gave the <u>hydroxylamine</u> (**150**) as a pale yellow oil (242 mg, 1.04 mmol, 81%); <u>R</u>_E (diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) 0.43; $\delta_{\rm H}$ (360 MHz, CDCl₃, TMS) 1.07 (s, 9 H, (C<u>H₃)₃C-), 4.25 (s, 1 H,</u> H₄), 4.41 (d, 1 H, ²<u>J_{2ax,2eq} 11.7 Hz</u>, H_{2ax}), 4.70 (dd, 1 H, ⁴<u>J_{2eq,Z} 1.2 Hz</u>, H_{2eq}), 4.85 (broad s, 1 H, N<u>H</u>), 5.19 (s, 1 H, H_E), 5.23 (d, 1 H, H_Z), 6.75 (dd, 1H, ⁴<u>J_{8,6}</u> 1.0, ³<u>J_{8,7} 8.9 Hz</u>, H₈), 6.82 (td, 1 H, ³<u>J_{6,5} = ³J_{6,7} 7.6 Hz}, H₆), 7.10 (ddd, 1 H, ⁴<u>J_{7,5}</u> 1.5 Hz, H₇), 7.21 (dd, 1H, H₅) ppm.</u>

The hydrochloride salt was prepared by bubbling dry hydrogen chloride gas through a solution of the hydroxylamine (150) in dry diethyl ether. This afforded the salt (238 mg, 0.88 mmol, 85%) as a powder, m.p. 129-131 °C (from ethyl acetate-petroleum ether b.r. 40-60 °C) (Found C, 61.28; H, 7.75; N, 5.15. C₁₄H₂₀ClNO₂.¹/₄ H₂O requires C, 61.31; H, 7.45; N, 5.11%); v_{max} (CH₂Cl₂) 3940 w, 3045 s (Ar-H, C-H str.), 2980-2 860 s (C-H str.), 2690 w (N-H str.), 2300 m, 1720 w (N-H def.), 1605 m, 1580 m and 1570 m (Ar ring vib.), 1040 m (=C-O-, C-O str.), 895 m (R₂C=CH₂ out of plane def.) cm⁻¹; δ_{H} (360 MHz, CDCl₃, TMS) 1.37 (s, 9 H, (C<u>H</u>₃)₃C), 4.62 (d, 1 H, ²J_{2ax,2eq} 12.4 Hz, H_{2ax}), 4.97 (d, 1 H, H_{2eq}), 5.05 (s, 1 H, H₄), 5.67 (s, 1 H, H_E), 5.95 (s, 1 H, H_Z), 6.88 (d, ${}^{3}J_{8,7}$ 8.2 Hz, H₈), 6.99 (dd, 1 H, ${}^{3}J_{6,7}$ 7.2, ${}^{3}J_{6,5}$ 7.7 Hz, H₆), 7.24 (dd, 1 H, H₇), 8.17 (d, 1 H, H₅), 11.69 (broad s, 2 H, +NH₂Cl⁻) ppm; δ_C (63.5 MHz, CDCl₃, TMS) 27.0 ((<u>C</u>H₃)₃C), 58.2 (C4), 69.2 (C2), 84.5 ((CH₃)₃<u>C</u>), 113.6 (C4a), 117.3 (R₂C=<u>C</u>H₂), 121.3 (C8), 123.8 (C6), 131.3 (C7), 131.9 (C5), 132.8 (C3), 156.4 (C8a) ppm; m/z 177 (M-(CH₃)₃C and Cl, 5%), 160 (M-(CH₃)₃CO and HCl, 5%), 145 (M-(CH₃)₃CONH₂.HCl, 100%), 115 (15%), 91 (5%), 77 ($C_6H_5^+$, 2%); (Found: <u>M-Cl</u>⁺, 234.1494. $C_{14}H_{20}CINO_2$ requires <u>M-Cl</u>⁺, 234.1494).





2-(3-Bromobut-3-en-1-oxy)benzaldehyde O-methyloxime (138) (250 mg, 0.93 mmol), tris(trimethylsilyl)silane (230 mg, 0.93 mmol) and a catalytic amount of AIBN were dissolved in toluene (18.6 cm³, 0.05 M dilution of (138)) that had been degassed for 30 min. The reaction mixture was heated at 70-80 $^{\circ}$ C under a nitrogen atmosphere for 20 h. Analysis of the reaction mixture by thin layer chromatography revealed no reaction. Toluene was evaporated under reduced pressure and the residue was purified by column chromatography (silica, 60 mesh, dichloromethane-petroleum ether b.r. 60-80 $^{\circ}$ C, 7:3). ¹H data corresponded to starting materials.

3.2.12 Preparation of 2-(3-Bromobut-3-en-1-oxy)acetophenone (151)



2-Hydroxyacetophenone (2.00 g, 14.69 mmol), 2,3-dibromopropene (3.52 g, 17.63 mmol) and anhydrous potassium carbonate (4.06 g, 29.38 mmol) were heated at reflux temperature in anhydrous acetone (20 cm^3) for 5 h. The reaction mixture was poured into water (100 cm^3) and extracted into diethyl ether $(2 \times 100 \text{ cm}^3)$. The organic phase was dried (MgSO₄) and evaporated in vacuo. Column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:9) gave the ketone (151) (2.32 g, 9.11 mmol, 62%) as needles, m.p. 45-46 °C (from petroleum ether b.r. 60-80 °C) (Found: C, 51.68; H, 4.40. C₁₁H₁₁BrO₂ requires C, 51.79; H, 4.35%); <u>R</u>_F (diethyl ether-petroleum ether b.r. 40-60 °C, 1:9) 0.29; v_{max} (CH₂Cl₂) 3070 w-3010 w (=C-H and Ar-H, C-H str.), 2990 w-2910 w (sat. C-H str.), 2860 w (-O-CH₂, C-H str.), 1670 s (C=O str.), 1595 s, 1575 m and 1480 s (Ar ring vib.), 1445 s (C-H def.), 1050 s (C-O str.), 895 s cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 2.66 (s, 3 H, CH₃), 4.73 (t, 2 H, ${}^{4}J_{2',4'E} = {}^{4}J_{2',4'Z}$ 1.1 Hz, H₂'), 5.72 (dt, 1 H, ${}^{2}J_{4'Z,4'E}$ 2.2 Hz, H_{4'Z}), 6.02 (dt, 1 H, H_{4'E}), 6.89 (dd, 1 H, ${}^{4}J_{3,5}$ 0.9, ${}^{3}J_{3,4}$ 8.4 Hz, H₃), 7.02 (td, 1 H, ${}^{3}J_{5,4} = {}^{3}J_{5,6}$ 7.6 Hz, H₅), 7.42 (ddd, 1 H, ${}^{4}J_{4,6}$ 1.8 Hz, H₄), 7.73 (dd, 1 H, H₆) ppm; δ_{C} (75.5 MHz, CDCl₃, TMS) 32.0 (<u>C</u>H₃), 72.2 (C2'), 112.7 (C3), 119.2 (C4'), 121.4 (C5), 126.4 (C1), 128.6 (C3'), 130.5 (C6), 133.5 (C4), 156.7 (C2), 119.3 (<u>C</u>=O) ppm; m/z (CI⁺) 254/256 (M⁺, 79%), 238/240 (M-O, 3%), 175 (M-Br, 100%), 160 (M-Br and CH₃, 3%), 147 (M-Br and CH₂=CH₂, 6%), 131 (M-Br and CH₃CHO, 8%), 121 (34%), 92

(M-CH₃C=O and CH₂C(Br)=CH₂, 8%), 77 (C₆H₅+, 8%); (Found: MH+, 255.0021. C₁₁H₁₁BrO₂ requires MH+, 255.0021).

3.2.13 <u>The Preparation of 2-(3-Bromobut-3-en-1-oxy)acetophenone O-</u> methyloxime (152)



2-(3-Bromobut-3-en-1-oxy)acetophenone (151) (2.00 g, 7.84 mmol) and Omethylhydroxylamine hydrochloride (0.79 g, 9.41 mmol) was stirred for 24 h at RT in pyridine (20 cm³). Pyridine was evaporated under reduced pressure, the residue diluted with diethyl ether (50 cm³) and the organic phase washed with water (2 x 50 cm³). The organic layer was separated, dried (MgSO₄) and solvent evaporated *in vacuo* to afford a yellow oil. Chromatography (silica, 60 mesh, diethyl etherpetroleum ether b.r. 40-60 °C, 1:9) gave a 6:1 ratio of E to Z isomers of the <u>oxime</u> <u>ether</u> (152) as a clear colourless oil (2.05 g, 7.21 mmol, 92%); <u>R_F</u> (diethyl etherpetroleum ether b.r. 40-60 °C, 3:7) 0.43; v_{max} (film) 3065 m (=C-H, C-H str.), 3020 w (Ar-H, C-H str.), 2960 - 2910 m (sat. C-H str.), 2860 w (-O-CH₂-, C-H str.), 1645 w (C=N str.), 1600 s, 1575 w and 1485 s (Ar ring vib.), 1440 s (C-H def.), 1230 s and 1040 s (C-O str.), 885 s, 750 s (*o*-disubstituted Ar) cm⁻¹

MAJOR E ISOMER

 $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 2.20 (s, 3 H, C<u>H</u>₃), 3.93 (s, 3 H, C<u>H</u>₃O), 4.55 (dd, 2 H, ⁴J_{2',4'Z} and ⁴J_{2',4'E} <1.0 Hz, H_{2'}), 5.60 (dt, 1 H, ²J_{4'Z,4'E} 1.9 Hz, H_{4'Z}), 5.91 (dt, 1H, H_{4'E}), 6.76 (dd, 1 H, ⁴J_{3,5} 0.7, ³J_{3,4} 8.1 Hz, H₃), 6.92 (ddd, 1 H, ³J_{5,6} 7.5, ³J_{5,4} 7.7 Hz, H₅), 7.22 (ddd, 1 H, ⁴J_{4,6} 1.7 Hz, H₄), 7.31 (dd, 1 H, H₆) ppm; $\delta_{\rm C}$ (75.5 MHz, CDCl₃, TMS) 16.1 (CH₃), 61.5 (OCH₃), 71.8 (C2'), 112.3 (C3), 118.0 (C4'), 121.4 (C5), 126.7 (C1), 127.3 (C3'), 129.8 (C4), 130.0 (C6), 155.3 (C(CH₃)=NOCH₃), 155.6 (C2) ppm

MINOR Z ISOMER

 $δ_{\rm H}$ (300 MHz, CDCl₃, TMS) 2.17 (s, 3 H, CH₃), 3.78 (s, 3 H, CH₃O), 4.55 (dd, 2 H, H_{2'} masked by E isomer), 5.60 (m, 1 H, H_{4'Z} masked by E isomer), 5.98 (dt, 1 H, ⁴J_{4'E,2'} <1, ²J_{4'Z,4'E} 1.9 Hz, H_{4'E}), 6.80-7.35 (complex m, H₃, H₄, H₅ and H₆ masked by E isomer) ppm; $δ_{\rm C}$ (75.5 MHz, CDCl₃, TMS) 21.4 (CH₃), 61.4 (OCH₃), 71.6 (C2'), 112.5 (C3), 117.5 (C4'), 121.3 (C5), 125.4 (C1), 126.6 (C3'), 128.3 (C4), 129.6 (C6), 152.8 (C(CH₃)=NOCH₃), 153.4 (C2) ppm; m/z (CI⁺) 284/286 (M⁺, 100%), 204 (M-HBr, 4%), 174 (M-Br and CH₃OH, 10%); (EI⁺) 239/241 (M-CH₃ON, 4%), 204 (M-HBr, 4%), 172 (M-HBr and CH₃OH, 10%), 133 (M-CH₃ON=CCH₃ and Br, 4%), 119 (CH₂C(Br)=CH₂, 4%), 105 (M-CH₃ON, CH₃ and CH₂C(Br)=CH₂, 8%), 91 (M-CH₃ON=C(CH₃) and CH₂C(Br)=CH₂, 100%), 77 (C₆H₅⁺, 8%), 39 (73%); (Found: MH⁺, 284.0286. C₁2H₁₄BrNO₂ requires MH⁺, 286.0286).

3.2.14 <u>The Preparation of 2-(3-Bromobut-3-en-1-oxy)acetophenone O-</u>

benzyloxime (153)



2-(3-Bromobut-3-en-1-oxy)acetophenone (151) (2.00 g, 7.84 mmol) and Obenzylhydroxylamine hydrochloride (1.50 g, 9.40 mmol) were stirred at RT in pyridine (20 cm³) for 24 h. Pyridine was evaporated *in vacuo* and the residue diluted with diethyl ether (50 cm³). The organic phase was washed with water (2 x 50 cm³), dried (MgSO₄) and solvent removed under reduced pressure to give a yellow oil. Flash chromatography (silica, 60 mesh, dichloromethane-petroleum ether b.r. 40-60 °C, 3:2) gave a 7:1 mixture of E to Z isomers of the <u>oxime ether</u> (153) (2.10 g, 5.83 mmol, 74%) as needles, m.p. 53-53.5 °C (from petroleum ether b.r. 40-60 °C); (Found: C, 59.97; H, 5.13; N, 3.97. C₁₈H₁₈BrNO₂ requires C, 60.01; H, 5.04; N, 3.89%); <u>RF</u> (diethyl ether-petroleum ether b.r. 40-60 °C, 3:7) 0.47; v_{max} (film) 3060 m (=C-H, C-H str.), 3013 m (Ar-H, C-H str.), 2980-2905 s (sat. C-H str.), 2860 s (-O-CH₂-, C-H str.), 1640-1630 w (C=N str.), 1595 s, 1575 w and 1482 s (Ar ring vib.), 1440 s (C-H def). cm⁻¹

MAJOR E ISOMER

 $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 2.27 (s, 3 H, C<u>H</u>₃), 4.58 (dd, 2 H, ⁴J_{2',4'Z} 1.2, ⁴J_{2',4'E} 1.6 Hz, H_{2'}), 5.22 (s, 2 H, PhCH₂), 5.62 (dt, 1 H, ²J_{4'Z,4'E} 2.1 Hz, H_{4'Z}), 5.92 (dt, 1 H, H_{4'E}), 6.79 (dd, 1 H, ⁴J_{3,5} 1.0, ³J_{3,4} 7.8 Hz, H₃), 6.94 (td, 1 H, ³J_{5,4} = ³J_{5,6} 7.5 Hz, H₅), 7.22-7.41 (complex m, 7 H, H₄, H₆ and H_o, H_m and H_p in PhCH₂) ppm; δ_C (75.5 MHz, CDCl₃, TMS) 16.5 (<u>C</u>H₃), 71.9 (C2'), 75.8 (Ph<u>C</u>H₂), 112.5 (C3), 117.9 (C4'), 121.5 (C5), 126.6 (C1), 127.4 (C3'), 127.5 (C_p in PhCH₂), 127.8 (C_o or C_m in PhCH₂), 128.2 (C_o or C_m in PhCH₂), 129.8 (C4), 130.0 (C6), 138.1 (C' in PhCH₂), 155.4 (<u>C(</u>CH₃)=NOCH₂Ph), 156.4 (C2) ppm

MINOR Z ISOMER

 $\delta_{\rm H}$ (360 MHz, CDCl₃, TMS) 2.16 (s, 3 H, C<u>H</u>₃), 4.57 (dd, 2 H, ⁴J_{2',4'Z} 1.4, ⁴J_{2',4'E} 1.6 Hz, H_{2'}), 5.05 (s, 2 H, PhCH₂), 5.57 (dt, 1 H, ²J_{4'Z,4'E} 2.1 Hz, H_{4'Z}), 5.90 (m, 1 H, H_{4'E} masked by E isomer), 6.75-7.50 (complex m, masked by E isomer) ppm; $\delta_{\rm C}$ (75.5 MHz, CDCl₃, TMS) 21.5 (<u>C</u>H₃), 71.6 (C2'), 75.3 (Ph<u>C</u>H₂), 112.5 (C3), 117.5 (C4'), 121.3 (C5), 126.6 (C1), 127.27 (C_p in PhCH₂ or C3'), 127.34 (C_p in PhCH₂ or C3'), 128.1 (C_o or C_m in PhCH₂), 128.3 (C_o or C_m in PhCH₂), 129.5 (C4), 130.0 (C6) ppm. Peaks due to C2, <u>C</u>(CH₃)=NOCH₂Ph and C' are too small to be assigned;

m/z (CI⁺) 360/362 (<u>M</u>⁺, 100%), 280 (<u>M</u>-HBr, 4%), 224 (<u>M</u>-HOCH₂C(Br)=CH₂, 10%), 174 (<u>M</u>-Br and PhCH₂O, 10%), 159 (<u>M</u>-Br and PhCH₂ONH, 10%), 91 (<u>M</u>-PhCH₂ON=C(CH₃) and CH₂C(Br)=CH₂, 16%); (Found: <u>MH</u>⁺, 360.0599. C₁₈H₁₈NO₂Br requires <u>MH</u>⁺, 360.0599).

3.2.15 <u>Preparation of 4-Methoxyamino-4-methylchroman-3-ylidene (154)</u>



A solution of 2-(3-bromobut-3-en-1-oxy)acetophenone O-methyloxime (152) (265 mg, 0.93 mmol), tributyltin hydride (330 mg, 1.12 mmol) and AIBN (150 mg, 1.93 mmol) in benzene (47 cm³, 0.02 M) was degassed by bubbling nitrogen through the solution for 1h. The reaction mixture was heated at 80 °C for 3 h under a nitrogen atmosphere. Benzene was evaporated *in vacuo*. Flash chromatography (silica, 60 mesh, 500 cm³ petroleum ether b.r. 40-60 °C then diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) gave the <u>hydroxylamine</u> (154) as a pale yellow oil (135 mg, 0.66 mmol, 71%); <u>R</u>_F (diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) 0.23.

The hydrochloride salt was prepared by bubbling dry hydrogen chloride gas through a solution of (154) in dry diethyl ether. This gave the hydrochloride salt (137 mg, 0.57 mmol, 86%) as a powder, m.p. 120-123 °C (ethyl acetate-petroleum ether b.r. 40-60 ^oC); (Found: C, 58.16; H, 6.93; N, 5.62. $C_{12}H_{16}CINO_2$.¹/₄ H₂O requires C, 58.53; H, 6.76; N, 5.69%); v_{max} (CH₂Cl₂) 3940 w, 3045 s, 2980-2860 s (C-H str.), 2690 w (N-H str.), 2300 m, 1710 w (N-H def), 1605 w, 1580 m and 1560 m (Ar ring vib.), 1320-1300 s and 1040 w (=C-O-, C-O str.), 895 s (R₂C=CH₂ out of plane def.) cm⁻¹; $\delta_{\rm H}$ (360 MHz, CDCl₃, TMS) 1.98 (s, 3 H, C<u>H₃</u>), 3.99 (s, 3 H, OCH3), 4.58 (d, 1 H, ²J_{2ax,2eq} 12.6 Hz, H_{2ax}), 4.87 (d, 1 H, H_{2eq}), 5.66 (s, 1 H, H_E), 5.94 (s, 1 H, H_Z), 6.90 (dd, 1 H, ${}^{4}\underline{J}_{8,6}$ 0.7, ${}^{3}\underline{J}_{8,7}$ 7.7 Hz, H_8), 7.05 (ddd, 1 H, 3 J_{6.7} 7.0, 3 J_{6.5} 7.8 Hz, H₆), 7.25 (ddd, 1 H, 4 J_{7.5} 1.1 Hz, H₇), 8.09 (dd, 1 H, H₅), 12.47 (broad s, 2 H, $+NH_2Cl^-$) ppm; δ_c (63.5 MHz, CDCl₃, TMS) 23.61 (<u>CH</u>₃), 62.67 (C4), 63.11 (OCH₃), 69.55 (C2), 117.93 (R₂C=CH₂), 119.35 (C4a), 119.92 (C8), 122.00 (C6), 128.71 (C7), 130.84 (C5), 137.84 (C3), 155.95 (C8a) ppm; m/z (EI+) 159 (M-HCl and CH₃ONH₂, 100%), 144 (M-HCl,CH₃ONH₂ and CH₃, 15%), 131 ([PhCH₂C(CH₃)=CH₂]+, 14%), 115 (12%), 91 (PhCH₂, 8%), 77 (C₆H₅+); (Found: <u>M-Cl</u>⁺, 206.1181. $C_{12}H_{16}CINO_2$ requires <u>M-Cl</u>⁺, 206.1181).

3.2.16 <u>Preparation of 4-Benzyloxyamino-4-methylchroman-3-ylidene (155)</u>



2-(3-Bromobut-3-en-1-oxy)acetophenone O-benzyloxime (**153**) (660 mg, 1.9 mmol), tributyltin hydride (660 mg, 2.3 mmol) and AIBN (310 mg, 1.9 mmol) were dissolved in benzene (95 cm³, 0.02 M dilution of (**153**)) and the solution degassed with a stream of nitrogen for 1 h. The reaction mixture was heated at reflux temperature under a nitrogen atmosphere for 4 h. Benzene was evaporated *in vacuo*. Flash chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) gave the <u>hydroxylamine</u> (**155**) as a pale yellow oil (360 mg, 1.3 mmol, 71%); <u>R</u>_F (diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) 0.38.

The hydrochloride of (155) was prepared by bubbling dry hydrogen chloride gas through a solution of the hydroxylamine (155) in dry diethyl ether. This afforded the salt (335 mg, 1.1 mmol, 86 %) as a very hygroscopic powder; v_{max} (CH₂Cl₂) 3045 s (Ar-H, C-H str.), 2990 s (C-H str.), 2690 m (N-H str.), 2300 m, 1710 br. (N-H def.), 1605-1570 w (Ar ring vib.), 1480-1420 m (C-H def.), 1260 s (=C-O, C-O str.), 895 m (R₂C=CH₂ out of plane def.) cm⁻¹; δ_{H} (360 MHz, CDCl₃, TMS) 1.97 (s, 3 H, CH₃), 4.56 (d, 1 H, ²J_{2ax,2eq} 12.5 Hz, H_{2ax}), 4.83 (d, 1 H, H_{2eq}), 5.07 (d, 1 H, ²J 9.8 Hz, PhC<u>H</u>₂O), 5.31 (d, 1 H, PhC<u>H</u>₂O), 5.60 (s, 1 H, H_E), 5.75 (s, 1 H, H_Z), 6.69 (d, 1 H, ³J_{8,7} 7.3 Hz, H₈), 7.06 (dd, 1 H, ³J_{6,5} 7.0, ³J_{6,7} 7.2 Hz, H₆), 7.20 -7.30 (complex m, 6 H, H₇ and H_o, H_m, H_p in PhCH₂), 8.05 (d, 1 H, H₅), 12.30 (broad s, 2 H, +NH₂Cl⁻) ppm; δ_{C} (63.5 MHz, CDCl₃, TMS) 22.6 (CH₃), 61.7 (C4), 69.9 (C2), 76.8 (PhCH₂), 117.6 (C8), 119.5 (C4a), 121.6 (C6), 128.5 - 130.6 (C3,

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C5, C7, $R_2C=\underline{C}H_2$ and C', C_o, C_m, C_p in PhCH₂), 155.7 (C8a) ppm; m/z (EI⁺) 174 (<u>M</u>-HCl and PhCH₂OH, 4%), 159 (<u>M</u>-PhCH₂ONH₂.HCl, 100%), 144 (<u>M</u>-PhCH₂ONH₂.HCl and CH₃, 6%), 131 ([PhCH₂C(CH₃)=CH₂]⁺, 7%), 115 (6%), 91 (PhCH₂, 29%), 77 (C₆H₅⁺, 6%); (Found: <u>M-Cl</u>⁺, 282.1494. C₁₈H₂₀ClNO₂ requires <u>M-Cl</u>⁺, 282.1494).

3.2.17 <u>Preparation of 2-(But-3-yne-1-oxy)benzaldehyde (158)</u>



A solution of 3-bromopropyne (1.17 g, 9.84 mmol, 80 wt % in toluene) and 2hydroxybenzaldehyde (1.00 g, 8.20 mmol) in acetone (20 cm³) was heated at reflux temperature with anhydrous potassium carbonate (2.26 g, 1.64 mmol). After 5 h the reaction mixture was poured into water (50 cm³) and extracted with diethyl ether (3 x 50 cm³). The organic extracts were dried (MgSO₄) and evaporated under reduced pressure. The residue was purified by column chromatography (silica, 60 mesh, dichloromethane-petroleum ether b.r. 40-60 °C, 1:1) to give the product (**158**) as rhombic crystals (1.11 g, 6.94 mmol, 85%), m.p. 68 °C (petroleum ether b.r. 60-80 °C); (Found: C, 74.83; H, 4.80. C₁₀H₈O₂ requires C, 74.99; H, 5.03%); <u>RF</u> (dichloromethane-petroleum ether b.r. 40-60 °C, 1:1) 0.30; v_{max} (CH₂Cl₂) 3300 s (=C-H, C-H str.), 3070-3015 w (Ar-H, C-H str.), 2915 w and 2870 m (C-H str.), 1685 s (C=O str.), 1600 s, 1580 m and 1480 s (Ar ring vib.), 1450 s (C-H def.) cm⁻¹; $\delta_{\rm H}$ (360 MHz, CDCl₃, TMS) 2.58 (t, 1 H, ⁴<u>I</u>₄',₂' 2.3 Hz, H₄'), 4.83 (d, 2 H, H₂'), 7.07 (dd, 1 H, ⁴<u>I</u>_{3,5} 1.7, ³<u>I</u>_{3,4} 7.0 Hz, H₃), 7.12 (ddd, ³<u>I</u>_{5,6} 7.7, ³<u>I</u>_{5,4} 9.0 Hz, H₅), 7.56 (ddd, 1 H, ${}^{4}J_{4,6}$ 1.8 Hz, H₄), 7.85 (dd, 1 H, H₆), 10.47 (s, 1 H, <u>H</u>COR) ppm; δ_{C} (90.5 MHz, CDCl₃, TMS) 56.4 (C2'), 76.5 (C4'), 77.7 (C3'), 113.2 (C3), 121.7 (C5), 125.5 (C1), 128.5 (C6), 135.7 (C4), 159.7 (C2), 189.4 (H<u>C</u>OR) ppm; m/z (CI⁺) 178 ([<u>M</u>+NH₄]⁺, 10%), 161 (<u>MH</u>⁺, 100%), 132 (<u>M</u>-CHO, 3%), 58 (3%), 44 (7%), 36 (11%); (Found: [<u>M</u>+NH₄]⁺, 178.0868. C₁₀H₈O₂ requires [<u>M</u>+NH₄]⁺, 178.0868).



2-(But-3-yne-1-oxy)benzaldehyde (158) (270 mg, 1.69 mmol), Omethylhydroxylamine hydrochloride (225 mg, 2.70 mmol) and pyridine (293 mg, 3.71 mmol) were stirred at RT in methanol (20 cm³) for 4 h. Methanol was evaporated *in vacuo*, the residue dissolved in diethyl ether (50 cm³) and the solution was washed with water (2 x 20 cm³). The organic phase was dried (MgSO₄) and diethyl ether was removed under reduced pressure. Column chromatography (silica, 60 mesh, dichloromethane-petroleum ether b.r. 40-60 °C, 1:1) afforded the <u>oxime ether</u> (156) (173 mg, 0.91 mmol, 54%) as prisms, m.p. 47-48 °C (petroleum ether b.r. 40-60 °C);.(Found: C, 69.63; H, 6.04; N, 7.25. C₁₁H₁₁NO₂ requires C, 69.82; H, 5.86; N, 7.40%); <u>R_F</u> (dichloromethane-petroleum ether b.r. 40-60 °C, 7:3) 0.63; v_{max} (CH₂Cl₂) 3300 s (-C=C-H and Ar-H, C-H str.), 2940 s, 2900 w and 2860 w (C-H str.), 1600 m, 1570 m and 1480 s (Ar ring vib.), 1450 s (C-H def.) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 2.50 (t, 1 H, ${}^{4}J_{4',2'}$ 2.4 Hz, H_{4'}), 3.95 (s, 3 H, OC<u>H</u>₃), 4.68 (d, 2 H, H_{2'}), 6.95 (dd, 1 H, ${}^{4}J_{3,5}$ 1.1, ${}^{3}J_{3,4}$ 8.4 Hz, H₃), 6.98 (ddd, 1 H, ${}^{3}J_{5,6}$ 8.0, ${}^{3}J_{5,4}$ 7.4 Hz, H₅), 7.31 (ddd, 1 H, ${}^{4}J_{4,6}$ 1.7 Hz, H₄), 7.80 (dd, 1 H, H₆), 8.45 (s, 1 H, <u>H</u>C=NOCH₃) ppm; $\delta_{\rm C}$ (75.5 MHz, CDCl₃, TMS) 56.3 (C2'), 61.9 (OCH₃), 75.9 (C3'), 78.2 (C4'), 112.8 (C3), 121.5 (C1), 121.7 (C5), 126.5 (C4), 130.8 (C6), 144.4 (H<u>C</u>=NOCH₃), 155.4 (C2) ppm; m/z (EI⁺) 189 (<u>M</u>⁺, 22%), 158 (<u>M</u>-OCH₃, 22%), 143 (<u>M</u>-CH₃ONH, 100%), 130 (15%), 115 (22%), 103 (15%), 91 (C7H7⁺, 33%), 77 (C₆H₅⁺, 21%); (Found: <u>M</u>⁺, 189.0790. C₁₁H₁₁NO₂ requires <u>M</u>⁺, 189.0790).

3.2.19 <u>Preparation of 2-(But-3-yne-1-oxy)benzaldehyde O-benzyloxime</u> (157)⁹²



2-(But-3-yne-1-oxy)benzaldehyde (158) (1.00 g, 6.24 mmol), O-

benzylhydroxylamine hydrochloride (1.59 g, 9.99 mmol) and pyridine (1.09 g, 13.70 mmol) were stirred at RT overnight in methanol (20 cm³). Methanol was evaporated *in vacuo*, the residue was diluted with diethyl ether (100 cm³) and washed with water (2 x 100 cm³). The organic phase was dried (MgSO₄) and solvent was removed under reduced pressure. Column chromatography (silica, 60 mesh, dichloromethanepetroleum ether b.r. 40-60 °C, 7:3) gave the <u>oxime ether</u> (157) as prisms (1.03 g, 3.87 mmol, 62%), m.p. 54 °C (from petroleum ether b.r. 40-60 °C);.(Found: C, 76.89; H, 5.84; N, 5.22. $C_{17}H_{15}NO_2$ requires C, 76.96; H, 5.70; N, 5.28%); <u>RF</u> (dichloromethane-petroleum ether b.r. 40-60 °C, 7:3) 0.69; v_{max} (CH₂Cl₂) 3300 s (-C=C-H, C-H str.), 2940 s, 2910 w and 2860 w (C-H str.), 1600 m, 1570 m (Ar ring vib.), 1450 s (C-H def.) cm⁻¹; δ_H (300 MHz, CDCl₃, TMS) 2.44 (t, 1 H, $^{4}J_{4',2'}$ 2.4 Hz, H₄'), 4.60 (d, 2 H, H₂'), 5.18 (s, 2 H, PhCH₂), 6.91 (d, 1 H, $^{3}J_{3,4}$ 8.3 Hz, H₃), 6.93 (t, 1 H, $^{3}J_{5,6} = ^{3}J_{5,4}$ 7.7 Hz, H₅), 7.23-7.41 (complex m, 6 H, H₄, H_o , H_m and H_p in PhCH₂O), 7.82 (dd, 1 H, $^{4}J_{6,4}$ 1.6 Hz, H₆), 8.54 (s, 1 H, <u>HC</u>=N) ppm; δ_C (75.5 MHz, CDCl₃, TMS) 56.2 (C2'), 75.8 (C3'), 76.2 (PhCH₂), 78.1 (C4'), 112.7 (C3), 121.5 (C1), 121.6 (C5), 126.5 (C4), 127.8 (C_p in PhCH₂O), 128.23 and 128.28 (C_o and C_m in PhCH₂O), 130.8 (C6), 137.6 (C' in PhCH₂O), 144.4 (H<u>C</u>=NOCH₂Ph), 155.4 (C2) ppm; m/z (CI⁺) 266 (<u>MH</u>⁺, 100%), 175 (<u>M</u>-PhCH, 2%), 160 (<u>M</u>-PhCO, 5%), 122 (2%), 108 (5%),91 (8%); (Found: <u>MH</u>⁺, 266.1181. C₁₇H₁₅NO₂ requires <u>MH</u>⁺, 266.1181).

3.2.20 <u>Preparation of 4-Methoxyaminochroman-3-ylidene (141) from 2-(But-</u> 3-yne-1-oxy)benzaldehyde O-methyloxime (**156**)



2-(But-3-yne-1-oxy)benzaldehyde O-methyloxime (156) (200 mg, 1.06 mmol) was dissolved in benzene (53 cm³, 0.02 M dilution of (156)) and the solution degassed by bubbling a steady stream of nitrogen through the solution for 30 min. The solution was heated at reflux temperature under a nitrogen atmosphere and a solution of tributyltin hydride (369 mg, 1.27 mmol) and AIBN (35 mg, 0.21 mmol) in benzene

(10 cm³) was added to the solution over 6 h. Heating was continued for a further 6 h. Benzene was removed *in vacuo* and the residue was diluted with methanol (2 cm³). A few drops of glacial acetic acid were added and the reaction mixture heated at reflux temperature for 12 h. Methanol and acetic acid were evaporated under reduced pressure and the residue was purified by column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40 - 60 °C, 1:4). This afforded the <u>hydroxylamine</u> (141) (105 mg, 0.55 mmol, 52%) as a pale yellow oil. <u>R_F</u> (diethyl ether-petroleum ether b.r. 40-60 °C, 1:9) 0.27;

¹H and ¹³C data corresponded to the preparation of (141) in experiment 3.2.6.

3.2.21 <u>Preparation of 4-Benzoxyaminochroman-3-ylidene (142) from 2-(But-</u> 3-yne-1-oxy)benzaldehyde O-benzyloxime (157)



2-(But-3-yne-1-oxy)benzaldehyde O-methyloxime (157) (320 mg, 1.26 mmol) was dissolved in benzene (63 cm^3 , 0.02 M dilution of (157)) and the solution degassed for 1 h. The solution was heated at reflux temperature under a nitrogen atmosphere and a solution of tributyltin hydride (442 mg, 1.52 mmol) and AIBN (40 mg, 0.25 mmol) in benzene (10 cm^3) was added to the solution dropwise over 10 h. Heating was continued for a further 4 h. Benzene was evaporated *in vacuo* and the residue was diluted with methanol (2.5 cm^3). Three drops of glacial acetic acid were added and the reaction mixture heated at reflux temperature for 12 h. Methanol and acetic acid were

evaporated under reduced pressure and the crude product was purified by column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:4). This yielded the <u>hydroxylamine</u> (142) (188 mg, 0.71 mmol, 56%) as a pale yellow oil. <u>RF</u> (diethyl ether-petroleum ether b.r. 40-60 °C, 1:9) 0.39;

¹H and ¹³C data corresponded to the preparation of (142) in experiment 3.2.7.

3.2.22 Preparation of 2-({2-Bromophenyl}ethan-1-oxy)benzaldehyde (159)



2-Hydroxybenzaldehyde (1.00 g, 8.19 mmol), 2-bromobenzyl bromide (2.46 g, 9.83 mmol) and anhydrous potassium carbonate (2.26 g, 16.4 mmol) were heated at reflux temperature in dry acetone (30 cm³) for 3 h. The reaction mixture was diluted with diethyl ether (200 cm³) and washed with water (2 x 200 cm³). The organic layer was dried (MgSO₄) and solvent removed *in vacuo*. Flash chromatography (silica, 60 mesh, dichloromethane-petroleum ether b.r. 40-60 °C, 1:1) gave the product (**159**) (2.22 g, 7.62 mmol, 93 %) as rhomboids, m.p. 91-92 °C (from petroleum ether b.r. 60-80 °C);(Found: C, 57.74; H, 3.82. C₁₄H₁₁BrO₂ requires C, 57.75; H, 3.81%); R_F (dichloromethane-petroleum ether b.r. 40-60 °C, 1:1) 0.43; v_{max} (CH₂Cl₂) 3050 w (Ar-H, C-H str.), 2890-2860 w (C-H str.), 1735 s (C=O str.), 1600 s, 1580 w and 1480 s (Ar ring vib.), 765 s (*o*-disubstituted Ar) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 5.23 (s, 2 H, OCH₂), 7.03-7.08 (complex m, 2 H, H₃ and H₅), 7.20 (ddd, 1 H, ⁴J₄',6'

1.7, ${}^{3}I_{4',5'}$ 7.5, ${}^{3}I_{4',3'}$ 7.9 Hz, H_{4'}), 7.35 (dt, 1 H, ${}^{4}I_{5',3'}$ 1.2, ${}^{3}I_{5',6'}$ 7.5 Hz, H_{5'}), 7.51 - 7.57 (complex m, 2 H, H_{6'} and H₄), 7.59 (dd, 1 H, H_{3'}), 7.87 (dd, 1 H, ${}^{4}I_{6,4}$ 1.6, ${}^{3}I_{6,5}$ 7.6 Hz, H₆), 10.58 (s, 1 H, Ar<u>H</u>C=O) ppm; δ_{C} (75.5 MHz, CDCl₃, TMS) 69.9 (CH₂O), 113.03 (C3), 121.2 (C5), 122.3 (C2'), 125.3 (C1), 127.7 (C5'), 128.7 (C6'), 128.8 (C4'), 129.6 (C6), 132.8 (C3'), 135.3 (C1'), 135.9 (C4), 160.6 (C2), 189.4 (C=O) ppm; m/z (CI+) 290/292 (MH+, 100%), 262/264 (M-CO, 8%), 211 (M-Br, 8%), 185/187 (BrC₆H₄CH₂OH, 79%), 168/170 (BrC₆H₄CH₂, 12%), 121 (M-BrC₆H₄CH₂, 9%), 106 (M-BrC₆H₄CH₂O, 2%), 89 (3%); (Found: MH+, 291.0021). C₁₄H₁₁BrO₂ requires MH+, 291.0021).

3.2.23 <u>Preparation of 2-({2-Bromophenyl}ethan-1-oxy)benzaldehyde O-</u> methyloxime (160)



2-({2-Bromophenyl}ethan-1-oxy)benzaldehyde (**159**) (1.00 g, 3.43 mmol) was stirred overnight at RT with O-methylhydroxylamine hydrochloride (0.46 g, 5.50 mmol) in pyridine (10 cm³). Pyridine was removed under reduced pressure and the residue diluted with water (100 cm³). The product was extracted from the aqueous phase with diethyl ether (2 x 100 cm³). The organic layers were dried (MgSO₄) and the diethyl ether removed *in vacuo*. Column chromotography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:9) gave a mixture of the E and Z isomers of the <u>oxime</u>

<u>ether</u> (160) (0.96 g, 2.98 mmol, 87%) as needles, m.p. 75.5-76 °C (from petroleum ether b.r. 60-80 °C) (Found: C, 55.97; H, 4.44; N, 4.34. $C_{15}H_{14}BrNO_2$ requires C, 56.21; H, 4.40; N, 4.37%); <u>R</u> (diethyl ether-petroleum ether b.r. 40-60 °C) 0.46 and 0.35; v_{max} (CH₂Cl₂) 3000 w (Ar-H, C-H str.), 2940 m and 2810 m (C-H str.), 1605 s (C=N str.), 1595 s, 1570 m and 1485 s (Ar ring vib.) cm⁻¹

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 $δ_{\rm H}$ (300 MHz, CDCl₃, TMS) 3.96 (s, 3 H, OC<u>H</u>₃), 5.10 (s, 2 H, CH₂O), 6.90 (d, 1 H, ³J_{3,4} 8.2 Hz, H₃), 6.95 (t, 1 H, ³J_{5,6} = ³J_{5,4} 7.6 Hz, H₅), 7.14 (ddd, 1 H, ⁴J_{4',6'} 1.7, ³J_{4',5'} 7.5, ³J_{4',3'} 7.9 Hz, H_{4'}), 7.26-7.32 (complex m, 2 H, H₄ and H_{5'}), 7.49 (dd, 1 H, ³J_{6',5'} 7.7 Hz, H_{6'}), 7.54 (dd, 1 H, ⁴J_{3',5'} 1.1 Hz, H_{3'}), 7.81 (dd, 1 H, ⁴J_{6,4} 1.7 Hz, H₆), 8.54 (s, 1 H, R<u>H</u>C=N) ppm; $δ_{\rm C}$ (75.5 MHz, CDCl₃, TMS) 61.8 (O<u>C</u>H₃), 72.5 (OCH₂), 112.5 (C3), 121.1 (C2'), 121.3 (C5), 122.2 (C1), 126.6 (C5'), 127.5 (C6'), 128.7 (C4'), 129.3 (C6), 131.0 (C3'), 132.6 (C4), 135.8 (C1'), 144.5 (<u>C</u>=N), 156.2 (C2) ppm; m/z (EI+) 287/289 (<u>M</u>-CH₃O, 10%), 272/274 (<u>M</u>-CH₃ONH, 5%), 168/170 (BrC₆H₄CH₂, 100%), 119 (<u>M</u>-CH₃O and BrC₆H₄CH₂, 4%), 91 (<u>M</u>-BrC₆H₄CH₂ and H₂C=NOCH₃, 98%), 77 (C₆H₅+, 7%); (Found: <u>MH</u>+, 320.0286. C₁₅H₁₄BrNO₂ requires <u>MH</u>+, 320.0286).

3.2.24 <u>Preparation of 2-({2-Bromophenyl}ethan-1-oxy)benzaldehyde O-*tert*butyloxime (161)</u>



2-({2-Bromophenyl}ethan-1-oxy)benzaldehyde (159) (1.00 g, 3.43 mmol) and O-tertbutylhydroxylamine hydrochloride (0.52 g, 4.12 mmol) were stirred at RT overnight in pyridine. Pyridine was removed in vacuo. Flash chromatography (diethyl etherpetroleum ether b.r. 40-60 °C, 1:9) afforded the oxime ether (161) (1.04 g, 2.88 mmol, 84%) as needles, m.p. 53-56 °C (from petroleum ether b.r. 60-80 °C) (Found: C, 59.25; H, 5.48; N, 3.92. C₁₈H₂₀BrNO₂ requires C, 59.67; H, 5.57; N, 3.87%); <u>R</u>_F (diethyl ether-petroleum ether b.r. 40-60 °C, 1:9) 0.48; v_{max} (CH₂Cl₂) 3060 w (Ar-H, C-H str.), 2960 m, 2920 m and 2890 w (C-H str.), 1600 m (C=N str.), 1565 w (Ar ring vib.), 1480 m and 1445 m (C-H def.), 1230 s (C-O str.) cm⁻¹; <u>R</u>_F (diethyl ether-petroleum ether b.r. 40-60 °C, 1:9) 0.48; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.37 (s, 9 H, (CH₃)₃C), 5.11 (s, 2 H, OCH₂), 6.90 (d, 1 H, ³J_{3.4} 8.3 Hz, H₃), 6.96 (t, 1 H, 3 <u>J</u>_{5,4} = 3 <u>J</u>_{5,6} 7.5 Hz, H₅), 7.16 (dd, 1 H, 3 <u>J</u>_{4',5'} 7.4, 3 <u>J</u>_{4',3'} 8.0 Hz, H_{4'}), 7.26 (dd, 1 H, H₄), 7.31 (dd, 1 H, ³<u>J</u>5',6' 7.6 Hz, H₅'), 7.50 (d, 1 H, H₆'), 7.55 (d, 1 H, H₃'), 7.88 (d, 1 H, H₆), 8.52 (s, 1 H, R<u>H</u>C=N) ppm; δ_C (75.5 MHz, CDCl₃, TMS) 27.6 ((<u>C</u>H₃)₃C), 69.6 (OCH₂), 78.9 ((CH₃)₃C), 112.4 (C3), 121.1 (C5), 122.1 (C2'), 122.1 (C1), 126.4 (C5'), 127.5 (C6'), 128.8 (C4'), 129.2 (C6), 130.4 (C3'), 132.5 (C4), 135.9 (C1'), 142.8 (C=N), 156.0 (C2) ppm; m/z (CI+) 361/363 (M+, 100%), 287/289 (M-(CH3)3COH, 5%), 226 (M-Br and (CH3)3C, 2%), 210 (M-Br and

(CH₃)₃CO, 4%), 194 (<u>M</u>-BrC₆H₄CH₂, 10%), 169 (BrC₆H₄CH₂, 1%); (Found <u>MH</u>+ 362.0756. C₁₈H₂₀BrNO₂ requires <u>MH</u>+ 362.0755).

3.2.25 Preparation of 7-Methoxyamino-2,7-dihydrobenzyl[b.e]oxepin (162)



A solution of 2-({2-bromophenyl}ethan-1-oxy)benzaldehyde O-methyloxime (160) (300 mg, 0.94 mmol)in dry benzene (95 cm³, 0.01 M dilution of (160)) was degassed by passing a steady stream of nitrogen through the solution for 1h. The solution was heated to reflux temperature and a solution of tributyltin hydride (327 mg, 1.12 mmol)) and AIBN (30 mg, 0.19 mmol) in dry benzene (10 cm³) was added to the reaction mixture over 12h via a syringe pump. Heating was continued for a further 12h. Benzene was removed under reduced pressure and the product was purified by column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:9). This gave the <u>hydroxylamine</u> (162) (111 mg, 0.46 mmol, 49%) and the reduction product (163) (66 mg, 0.27 mmol, 29%) as pale yellow oils.

7-Methoxyamino-2,7-dihydrobenzyl[b.e]oxepin (162)

<u>R_F</u> (diethyl ether-petroleum ether b.r. 40-60 °C, 1:9) 0.31; v_{max} (film) 3240 w (N-H str.), 3040 w (Ar-H, C-H str.), 2950 s, 2920 s, and 2890 m (C-H str.), 2800 w (C-H str. of O-CH₃), 1600 m, 1540 m and 1480 s (Ar ring vib.), 1440 s (C-H def.) cm⁻¹;

 $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 3.24 (s, 3 H, OCH₃), 4.83 (d, 1 H, ${}^{2}J_{2x,2y}$ 12.8 Hz, H_{2x}) 4.92 (s, 1 H, H₇), 5.90 (br.s, 1 H, NH), 6.28 (d, 1 H, H_{2y}), 6.89 (dd, 1 H, ${}^{4}J_{11,9}$ 1.2, ${}^{3}J_{11,10}$ 8.2 Hz, H₁₁), 6.92 (td, 1 H, ${}^{3}J_{9,8} = {}^{3}J_{9,10}$ 7.4 Hz, H₉), 7.16 -7.36 (complex m, 6 H, H₃, H₄, H₅, H₆, H₈ and H₁₀) ppm; $\delta_{\rm C}$ (75.5 MHz, CDCl₃, TMS) 62.5 (OCH₃), 70.6 (C7), 71.0 (C2), 120.5 (C10), 121.5 (C11), 124.1 (C7a), 128.4 (C4 and C8), 129.8 (C3), 130.4 (C6), 132.9 (C5), 136.4 (C2a), 138.0 (C6a), 158.1 (C11a) ppm; m/z (CI⁺) 240 ([M-H]⁺, 38%), 225 ([M-H]⁺-CH₃, 2%), 210 ([M-H]⁺-CH₂O, 8%), 195 ([M-H]⁺-CH₂ON; 100%); (Found: [M-H]⁺, 240.1025).

2-(phenylethan-1-oxy)benzaldehyde O-methyloxime (163)

<u>R</u>_E (diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) 0.26; v_{max} (film) 3040 w (Ar-H str.), 3000 w, 2960 s, 2940 s, and 2900 m (C-H str.), 2820m (C-H str. of O-CH₃), 1600 s, 1590 m and 1570 m (C=C, Ar), 1480 s and 1450 s (C-H def.), 1380 s (C-O str.) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 3.95 (s, 3 H, OCH₃), 5.05 (s, 2 H, OCH₂), 6.91 (d, 1 H, ³J_{3,4} 8.6 Hz, H₃), 6.94 (t, 1 H, ³J_{5,4} = ³J_{5,6} 7.6 Hz, H₅), 7.25 - 7.41 (complex m, 6 H, H₄, H_o, H_m, and H_p in PhCH₂), 7.82 (dd, 1 H, ⁴J_{6,4} 1.8, ³J_{6,5} 7.7 Hz, H₆), 8.52 (s, 1 H, RHC=N) ppm; $\delta_{\rm C}$ (75.5 MHz, CDCl₃, TMS) 61.8 (OCH₃), 70.2 (OCH₂), 112.4 (C3), 121.0 (C1 and C5), 126.4 (Cp), 127.2 (Co), 127.9 (C6), 128.5 (Cm), 131.0 (C4), 136.5 (C'), 144.6 (HC=N), 156.6 (C2) ppm; m/z (EI+) 241 (<u>M</u>+, 3%), 210 (<u>M</u>-CH₃O, 48%), 195 (<u>M</u>-CH₂ONH, 15%), 91 (C₉H₇+; 100%); (Found: <u>M</u>+, 241.1100. C₁₅H₁₅NO₂ requires <u>M</u>+, 241.1103).

3.2.26 <u>Preparation of 7-(tert-Butoxyamino)-2,7-</u>

dihydrodibenzyl[b,e]oxepin(164)



2-({2-Bromophenyl}ethan-1-oxy)benzaldehyde O-*tert*-butyloxime (161) (250 mg, 0.69 mmol) was dissolved in dry benzene (35 cm^3 , 0.02 M dilution of (161)) and nitrogen bubbled through the solution for 1 h. The solution was heated at reflux temperature under a nitrogen atmosphere. A solution of tributyltin hydride (400 mg, 1.37 mmol) and AIBN (25 mg, 0.14 mmol) in dry benzene (10 cm^3) was added to the oxime ether (161) over 12 h (syringe pump). Heating was continued for a further 8 h. Benzene was removed under reduced pressure. Flash chromatography (silica, 60 mesh, 500 cm³ petroleum ether b.r. 40-60 °C then diethyl ether-petroleum ether b.r. 40-60 °C, 1:9) gave the cyclised product (164) (92 mg, 0.32 mmol, 47%) as a clear colourless oil and the reduction product (165) (70 mg, 0.25 mmol, 36%) as needles, m.p. 88-89 °C (from petroleum ether b.r. 40-60 °C)

7-(tert-Butoxyamino)-2,7 dihydrodibenzyl[b,e]oxepin(164)

<u>R</u>_F (diethyl ether-petroleum ether b.r. 40-60 °C, 1:9) 0.33; v_{max} (CH₂Cl₂) 3010 w (Ar-H, C-H str.), 2980 s, 2910 m and 2890 m (C-H str.), 1600 m and 1570 m (Ar ring vib.), 1480 s (C-H def.), 1360 s, 1310 m and 1230 s (C-O str.) cm⁻¹; δ_{H} (300 MHz, CDCl₃, TMS) 0.88 (s, 9 H, C(C<u>H</u>₃)₃), 4.81 (d, 1 H, ³J_{2x,2y} 12.4 Hz, H_{2x}), 4.86 (s, 1 H, H₇), 5.27 (br.s., 1 H, NH), 6.34 (d, 1 H, H_{2y}), 6.85 (dd, 1 H, ⁴J_{11,9}

1.3, ${}^{3}J_{11,10}$ 8.4 Hz, H₁₁), 6.90 (td, ${}^{3}J_{9,8} = {}^{3}J_{9,10}$ 7.5 Hz, H9), 7.15-7.33 (complex m, 6 H, H3, H4, H5, H6, H8 and H10) ppm; δ_{C} (75.5 MHz, CDCl3, TMS) 26.8 (C(<u>C</u>H3)3), 70.68 (C7), 70.72 (C2), 76.9 (<u>C</u>(CH3)3), 120.3 (C10), 121.1 (C11), 123.3 (C7a), 128.2 (C4), 128.4 (C8), 129.8 (C3), 130.6 (C6), 133.7 (C5), 136.4 (C2a), 138.7 (C6a), 158.2 (C11a) ppm; m/z (EI+) 284 (<u>MH</u>+, 2%), 210 (<u>M</u>-(CH3)3CO, 3%), 195 (<u>M</u>-(CH3)3CONH, 100%), 90 (7%); (Found: <u>MH</u>+, 284.1651. C₁₈H₂₁NO₂ requires <u>MH</u>+, 284.1650)

2-(Phenylethan-1-oxy)benzaldehyde O-tert-butyloxime (165)

(Found: C, 76.43; H, 7.66; N, 5.05. $C_{18}H_{20}BrNO_2$ requires C, 76.29; H, 7.47; N, 4.94%); \underline{R}_E (diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) 0.40; v_{max} (CH₂Cl₂) 3020 w (Ar-H, C-H str.), 2960 m, 2910 w and 2860 w (C-H str.), 1600 m, 1570 w (Ar ring vib.), 1480 m (C-H def.), 1360 m (C-O str.) cm⁻¹; δ_H (300 MHz, CDCl₃, TMS) 1.35 (s, 9 H, (CH₃)₃C), 5.00 (s, 2 H, CH₂O), 6.87 (d, 1 H, ${}^{3}\underline{J}_{3,4}$ 8.4 Hz, H₃), 6.92 (t, 1 H, ${}^{3}\underline{J}_{5,4} = {}^{3}\underline{J}_{5,6}$ 7.7 Hz, H₅), 7.23 (ddd, 1 H, ${}^{4}\underline{J}_{4,6}$, 1.8 Hz, H₄), 7.27 - 7.38 (complex m, 5 H, H₀, H_m, H_p in PhCH₂), 7.88 (dd, 1 H, H₆), 8.50 (s, 1 H, RCH=N) ppm; δ_C (75.5 MHz, CDCl₃, TMS) 27.6 (CH₃), 70.2 (OCH₂), 78.8 (Me₃C), 112.3 (C3), 120.9 (C5), 122.0 (C1), 126.2 (Cp), 127.3 (Co), 128.5 (Cm), 130.4 (C4), 136.6 (C'), 142.9 (C=N), 156.4 (C2) ppm; m/z (CI⁺), 284 (MH⁺, 100%), 242 (24%), 228 (MH⁺- Me₃C, 5%), 210 (M- Me₃CO, 14%), 194 (M-Me₃CONH₂, 5%), 122 (22%), 108 (12%), 91 (18%); (Found: MH⁺, 284.1651. C₁₈H₂₁NO₂ requires MH⁺, 284.1651).

3.3.1 Preparation of diethyl 2-(2-bromobenzyl)-1,3-propanedicarboxylate (169)¹⁷²



2-Bromobenzylbromide (2.00 g, 8.00 mmol) and diethyl malonate (1.54 g, 9.60 mmol) were dissolved in dichloromethane (10 cm³). Triethylbenzylammonium chloride (0.20 g) was added and the solution stirred vigorously. Sodium hydroxide (1 M, 10 cm³) was poured into the vigorously stirring solution. Stirring was continued for 1 h. The reaction mixture was diluted with dichloromethane (100 cm³), the organic phase separated, dried and evaporated *in vacuo*. This afforded the <u>diester</u> (169) as a clear colourless oil (2.53 g, 7.68 mmol, 96%) without need of purification. <u>R</u>_E (diethyl ether-petroleum ether b.r. 40-60 °C, 3:7) 0.48; $\delta_{\rm H}$ (360 MHz, CDCl₃,TMS) 1.20 (t, 6 H, ³J 7.1 Hz, CH₃), 3.85 (d, 2 H, ³J_{ArCH,2} 7.8 Hz, ArCH₂), 3.85 (t, 1 H, H₂), 4.15 (ABX₃ multiplet, 4 H, OCH₂), 7.08 (td, 1 H, ⁴J_{4',6'} 1.9, ³J_{4',5'} = ³J_{4',3'} 7.9 Hz, H_{4'}), 7.23 (ddd, 1 H, ⁴J_{5',3'} 1.2, ³J_{5',6'} 7.5 Hz, H_{5'}), 7.19 (dd, 1 H, H₆), 7.52 (dd, 1 H, H_{3'}) ppm; m/z (EI⁺) 329 (<u>M</u>⁺, 31%), 283 (10%), 249 (<u>M</u>-Br, 100%), 221 (20%), 175 (43%), 147 (58%), 103 (29%), 77 (18%).

3.3.2 Preparation of 2-(2-Bromobenzyl)-1,3-propanedicarboxylic acid (170)¹⁷³



To a warm solution of potassium hydroxide (6.45 g) in water (6.5 cm³) was added diethyl 2-(2-bromobenzyl)-1,3-propanedicarboxylate (169) (10.00 g, 30.40 mmol) dropwise over a period of 10 min. The reaction mixture was heated at 100 °C and the ethanol produced distilled off and collected. Water was added from time to time to prevent the reaction mixture from solidifying. After 4 h the reaction mixture was cooled in an ice bath and conc. hydrochloric acid added with stirring until the solution was acidic. The product was extracted into diethyl ether (4 x 50 cm³) and the organic phase dried (MgSO₄). Diethyl ether was removed under reduced pressure to give the product (**170**) (7.75 g, 25.84 mmol, 85%) as needles, m.p. 148-150 °C (from H₂O). $\delta_{\rm H}$ (250 MHz, CD₃OD, TMS) 3.29 (d, 2 H, ArC<u>H₂</u>), 3.77 (t, 1 H, H₂), 5.05 (broad, 2 H, CO₂<u>H</u>), 7.14 (ddd, 1 H, H₄·), 7.23 (ddd, 1 H, H₅·), 7.31 (dd, 1 H, H₆·), 7.56 (dd, 1 H, H₃·) ppm.

3.3.3 Preparation of 3-(2-bromophenyl)propanoic acid (171)¹⁷³



2-(2-Bromobenzyl)-1,3-propanedicarboxylic acid (170) (7.00 g, 25.65 mmol) was heated at 150 °C for 4 h. The crude product was used without purification in the next step (5.46 g, 23.85 mmol, 93%). A small sample was recrystallised and was seen as needles, m.p. 97-98 °C (from H₂O). (Found: C, 47.04; H, 3.98; N, 0.03. C9H9BrNO₂ requires C, 47.18; H, 3.97; N, 0.00%); $\delta_{\rm H}$ (360 MHz, CD₃OD, TMS) 2.60 (t, 2 H, ${}^{3}J_{2,3}$ 7.8 Hz, H₂), 3.03 (t, 2 H, H₃), 7.10 (ddd, 1 H, ${}^{4}J_{4',6'}$ 1.8, ${}^{3}J_{4',5'}$ 7.3, ${}^{3}J_{4',3'}$ 8.0 Hz, H_{4'}), 7.26 (ddd, 1 H, ${}^{4}J_{5',3'}$ 1.0, ${}^{3}J_{5',6'}$ 7.6 Hz, H_{5'}), 7.31 (dd, 1 H, H_{6'}), 7.54 (dd, 1 H, H_{3'}) ppm; m/z (EI⁺) 169/171 (24%), 149 (100%), 107 (39%), 90 (15%), 77 (38%); (CI⁺) 246/248 ([M+NH₄]⁺, 100%), 211/213 (30%), 169/171 (68%), 149 (43%), 131 (18%), 107 (49%), 77 (32%).

3.3.4 Preparation of Methyl 3-(2-bromophenyl)propanoate (172)



Thionyl chloride (1.42 cm³, 0.196 mol) was added dropwise to methanol (13.5 cm³) at -20 °C with stirring. Finely-powdered 3-(2-bromophenyl)propanoic acid (171) (4.6 g, 20 mmol) was added in portions and the reaction mixture was stirred at RT for 24h. The solvent was removed under reduced pressure and the residue was dissolved in water (30 cm³), and dichloromethane (30 cm³) was added. The aqueous solution was basified cautiously to pH 10 using potassium carbonate. The organic layer was separated and the aqueous layer was re-extracted with dichloromethane (3 x 30 cm³). The organic phase was dried (MgSO₄) and the solvent was removed under reduced pressure to give the crude product as a brown liquid. This was distilled in a kugelrohr oven to give the <u>ester</u> (172) as a clear colourless liquid (3.84 g, 16 mmol, 79%), b.p. 155 °C/0.5 mmHg. <u>R_F</u> (diethyl ether-petroleum ether b.r. 40-60 °C, 1:1) 0.40; $\delta_{\rm H}$ (250 MHz, CDCl₃, TMS) 2.65 (t, 2 H, H₂), 3.07 (t, 2 H, H₃), 3.66 (s, 3 H, OCH₃), 7.06-7.14 (m, 1 H, H₄), 7.17-7.26 (m, 2 H, H₅⁻ and H₆), 7.53 (d, 1 H, H₃) ppm.

3.3.5 Preparation of 3-(2-Bromophenyl)propan-1-ol (173)¹⁷⁴



Methyl 3-(2-bromophenyl)propanecarboxylate (172) (1.6 g, 6.6 mmol) in dry diethyl ether (10 cm³) was added dropwise to a solution of lithium aluminium hydride (1 M in THF, 3.95 cm³, 3.95 mmol) in dry diethyl ether (10 cm³) under nitrogen. After addition, the reaction mixture was heated at reflux temperature for 15 min. Water (0.15 cm³) was slowly added to the reaction mixture followed by 15% aqueous sodium hydroxide solution (0.15 cm³). More water (0.45 cm³) was added to give a white precipitate, which was filtered off and was washed with ethyl acetate. The organic layer from the filtrate was separated , dried (MgSO₄), and the solvent evaporated *in vacuo* to yield the <u>alcohol</u> (173) as a clear colourless oil (1.37 g, 6.3 mmol, 97%); <u>R_F</u> (diethyl ether-petroleum ether b.r. 40-60 °C, 1:1) 0.23; $\delta_{\rm H}$ (250 MHz, CDCl₃, TMS) 1.87 - 2.00 (m, 3 H, H₂ and OH), 2.84 (m, 2 H, H₃), 3.69 (t, 2 H, H₁), 7.06 (m, 1 H, H₄·), 7.24 (m, 2 H, H₅[·] and H₆·), 7.53 (d, 1 H, H₃·) ppm.

3.3.6 Preparation of 3-(2-Bromophenyl)propanal (168)¹⁷⁵⁻¹⁷⁷



Dimethyl sulphoxide (3.76 g, 48.12 mmol) was dissolved in dichloromethane (10 cm³) and was added dropwise to a solution of oxalyl chloride (4.58 g, 36.10 mmol) in dichloromethane (40 cm³) cooled to -78 °C under a nitrogen atmosphere. 3-(2-Bromophenyl)propan-1-ol (173) (3.45 g, 16.04 mmol) in dichloromethane (10 cm³) was added dropwise to the reaction mixture and stirring was continued for 1 h at -78 °C. After this time triethylamine (4.86 g, 48.12 mmol) was added and the reaction mixture allowed to warm to room temperature. The reaction mixture was poured into 2 M hydrochloric acid (100 cm³) and extracted with diethyl ether (3 x 100 cm³). The

combined organic extracts were washed with saturated sodium bicarbonate solution, dried (MgSO₄) and solvent evaporated *in vacuo*. Column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 2:3) afforded the <u>aldehyde</u> (**168**) (2.46 g, 11,55 mmol, 72%) as a clear colourless oil. <u>R_F</u> (diethyl ether-hexane, 3:7) 0.35; $\delta_{\rm H}$ (250 MHz, CDCl₃, TMS) 2.79 (t, 2 H, H₃), 3.06 (t, 2 H, H₂), 7.04 - 7.12 (m, 1 H, H₄), 7.23 (d, 2 H, H_{5'} and H_{6'}), 7.53 (d, 1 H, H_{3'}), 9.81 (s, 1 H, H₁) ppm.

3.3.7 Preparation of 3-(2-Bromophenyl)propanal O-methyloxime (166)



3-(2-Bromophenyl)propanal (168) (0.49 g, 2.32 mmol) and O-methylhydroxylamine hydrochloride (0.23 g, 2.78 mmol) were stirred in pyridine (5 cm³) at RT overnight. Pyridine was removed under reduced pressure. The residue was diluted with diethyl ether (50 cm³), washed with water (2 x 50 cm³) and the organic layer dried (MgSO₄). Diethyl ether was removed *in vacuo*. Column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 3:7) afforded a 1:1 mixture of E and Z isomers of the <u>oxime ether</u> (166) (0.47 g, 1.94 mmol, 84%) as a clear colourless oil. R_E (diethyl ether-petroleum ether b.r. 40-60 °C, 3:7) 0.54 and 0.49; v_{max} (film) 3050 m (Ar-H, C-H str.), 2930 s, 2900 s and 2810 m (C-H str.), 1630 w (C=N str.), 1590 w and 1565 m (Ar ring vib.), 1470 s and 1440 s (C-H def.), 1280-1020 s (C-O str.), 750 s (*o*-disubstituted Ar) cm⁻¹

<u>E ISOMER</u>

 $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 2.49 (td, 2 H, ${}^{3}J_{2,1}$ 5.9, ${}^{3}J_{2,3}$ 8.8 Hz, H₂), 2.91 (t, 2 H, H₃), 3.80 (s, 3 H, OC<u>H₃</u>), 7.04 (ddd overlapping with Z isomer, 1 H, H₄'), 7.21 (complex overlapping with Z isomer, 2 H, H₅' and H₆'), 7.39 (t, 1 H, H₁), 7.51 (d, 1 H, ${}^{3}J_{3',4'}$ 7.7 Hz, H_{3'}) ppm; $\delta_{\rm C}$ (75.5 MHz, CDCl₃, TMS) 29.6 (C2), 33.2 (C3), 61.2 (O<u>C</u>H₃), 127.3 (C2'), 127.5 (C5'), 127.9 (C4'), 130.3 (C6'), 132.8 (C3'), 139.8 (C1'), 149.3 (C1) ppm

Z ISOMER

 $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 2.64 (dt, 2 H, ${}^{3}J_{2,1}$ 5.4, ${}^{3}J_{2,3}$ 8.8 Hz, H₂), 2.89 (t, 2 H, H₃), 3.85 (s, 3 H, OCH₃), 6.67 (t, 1 H, H₁), 7.04 (ddd overlapping with E isomer, 1 H, H₄·), 7.21 (complex overlapping with E isomer, 2 H, H₅· and H₆·), 7.39 (t, 1 H, H₁), 7.51 (d, 1 H, ${}^{3}J_{3',4'}$ 7.7 Hz, H₃·) ppm; $\delta_{\rm C}$ (75.5 MHz, CDCl₃, TMS) 25.5 (C2), 32.4 (C3), 61.6 (OCH₃), 127.3 (C2'), 127.5 (C5'), 127.9 (C4'), 130.1 (C6'), 132.6 (C3'), 139.8 (C1'), 150.0 (C1) ppm; m/z (CI+) 241/243 (MH+, 100%), 211/213 (MH+-CH₃O, 3%), 181/183 (M-CH₃ON=CH₂, 2%), 162 (M-Br, 25%), 132 (MH+-Br and CH₃O, 20%), 117 (M-Br and CH₃ON, 2%); (Found: MH+, 242.011. C₁₀H₁₂BrNO requires MH+, 242.0180).

3.3.8 Preparation of 1-Methoxyaminoindan (174)



3-(2-Bromophenyl)propanal O-methyloxime (166) (100 mg, 0.41 mmol) and tributyltin hydride (240 mg, 0.83 mmol) were dissolved in dry benzene (42 cm³, 0.02 M dilution of (166)) and degassed by bubbling a steady stream of nitrogen through the solution for 1 h. The solution was heated to reflux temperature under a nitrogen atmosphere and a solution of AIBN (80 mg, 0.08 mmol) in benzene (10 cm³) was added dropwise to the refluxing solution over 4 h via a syringe pump. Heating was continued for a further 12 h. Benzene was removed in vacuo. Column chromatography (silica, 60 mesh, 500 cm³ petroleum ether b.r. 40-60 °C then diethyl ether-petroleum ether b.r. 40-60 °C, 3:7) gave the hydroxylamine (174) as a colourless oil (93 mg, 0.57 mmol, 69%). <u>R</u>_F (diethyl ether-petroleum ether b.r. 40-60 °C, 3:7) 0.34; v_{max} (film) 3010 m (Ar-H, C-H str.), 2940 s, 2890 m and 2840 m (C-H str.), 1450 s (C-H def.), 1210 s (C-O str.) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 2.02 (dddd, 1 H, ${}^{3}J_{2x,1x}$ 4.8, ${}^{3}J_{2x,3x}$ 5.4, ${}^{3}J_{2x,3y}$ 8.8, ${}^{2}J_{2x,2y}$ 13.3 Hz, H_{2x}), 2.32 (dddd, 1 H, ${}^{3}\underline{J}_{2y,3y}$ 6.5, ${}^{3}\underline{J}_{2y,1}$ 7.3, ${}^{3}\underline{J}_{2y,3x}$ 8.8 Hz, H_{2y}), 2.84 (ddd, 1 H, ${}^{2}\underline{J}_{3x,3y}$ 15.1 Hz, H_{3x}), 3.04 (ddd, 1 H, H_{3v}), 3.55 (s, 3 H, OCH₃), 4.59 (dd, 1 H, H₁), 5.05 (br.s., 1 H, NHOCH₃), 7.15-7.24 (complex m, 3 H, H₅, H₆ and H₇), 7.40 (d, 1 H, ³J_{4,5} 6.5 Hz, H₄) ppm; δ_C (75.5 MHz, CDCl₃, TMS) 30.2 (C2 or C3), 30.4 (C2 or C3), 62.1 (OCH₃), 65.6 (C1), 124.8 (C6), 124.9 (C7), 126.2 (C5), 127.9 (C4), 142.1 (C3a), 144.3 (C7a) ppm; m/z (CI+) 164 (MH+, 100%), 132 (M-CH₃O, 21%), 117 (M-CH₃ONH, 67%), 91 (C₇H₇+, 2%); (Found: <u>MH</u>+, 164.1075. C₁₀H₁₃NO requires <u>MH</u>+, 164.1075).

3.3.9 Preparation of 4-(2-Bromophenyl)propan-2-one (175)¹⁷⁸



2-Bromobenzyl bromide (10.00 g, 40.00 mmol), 2,4-pentanedione (3.64 g, 36.40 mmol) and anhydrous potassium carbonate (5.02 g, 36.40 mmol) in anhydrous ethanol (50 cm³) were heated at reflux temperature for 15 h. Solvent was evaporated *in vacuo*, the residue was diluted with water (100 cm³) and extracted with diethyl ether (2 x 100 cm³). The organic phase was dried (MgSO₄) and the diethyl ether was removed under reduced pressure. The resulting oil was purified by distillation under reduced pressure, b.p. 122 °C/5 mmHg. This afforded the <u>ketone</u> (175) as a clear colourless oil (6.28 g, 27.66 mmol, 76%).

¹H and ¹³C data corresponded to those of authentic 4-(2-bromophenyl)propan-2one.¹⁷⁵



4-(2-Bromophenyl)butan-2-one (175) (3.00g, 13.22 mmol) and Omethylhydroxylamine hydrochloride (1.65 g, 19.82 mmol) were stirred at RT in pyridine (10 cm³) for 24h. Pyridine was evaporated under reduced pressure, the residue was diluted with water (20 cm³) and the product extracted into diethyl ether. The organic solution was dried (MgSO₄) and the solvent was evaporated under vacuum. Column chromatography (silica 60, mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:9) yielded a mixture of the E and Z isomers of the <u>oxime ether</u> (167) as a clear, colourless oil (3.11 g, 12.16 mmol, 92%). <u>R_F</u> (diethyl ether-petroleum ether b.r. 40-60 °C, 1:9) 0.36 and 0.31; v_{max} (film) 3050 w (Ar-H, C-H str.), 2980 w, 2930 s and 2890 m (C-H str.), 2810 m (C-H str. of O-CH₃), 1640 w, (C=N str.), 1560 w (Ar ring vib.), 1470 s (C-H def.), 1440 s, 750 s (*o*-dibstubstituted Ar) cm⁻¹.

<u>E ISOMER ($R_F = 0.36$)</u>

 $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.68 (s, 3 H, H₁), 2.45 (m, 2 H, H₃), 2.93 (m, 2 H, H₄), 3.83 (s, 3 H, OCH₃), 7.04 (ddd, overlapping with bands from the other isomer, 1 H, H₄'), 7.21 (complex m, overlapping with bands from the other isomer, 2 H, H₅' and H₆'), 7.51 (d, 1 H, ³J_{3',4'} 8.1 Hz, H₃') ppm; $\delta_{\rm C}$ (75.5 MHz, CDCl₃, TMS) 14.1 (C1), 33.2 (C3), 36.0 (C4), 61.0 (OCH₃), 124.2 (C2'), 127.4 (C5'), 127.7 (C4'), 130.3 (C6'), 132.7 (C3'), 140.3 (C1'), 156.2 (C2) ppm.

<u>Z ISOMER ($R_F = 0.31$)</u>

 $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.23 (s, 3 H, H₁), 2.58 (m, 2 H, H₃), 2.93 (m, 2 H H₄), 3.80 (s, 3 H, OCH₃), 7.04 (ddd, overlapping with bands from the other isomer, 1 H, H₄), 7.21 (complex m, overlapping with bands from the other isomer, 2 H, H₅⁻ and H₆), 7.51 (d, 1 H, ³J_{3',4'} 8.1 Hz, H_{3'}) ppm; $\delta_{\rm C}$ (75.5 MHz, CDCl₃, TMS) 20.1 (C1), 29.4 (C3), 31.9 (C4), 61.0 (OCH₃), 124.2 (C2'), 127.4 (C5'), 127.7 (C4'), 130.2 (C6'), 132.6 (C3'), 140.2 (C1'), 156.8 (C2) ppm; m/z (CI+) 256/258 (<u>MH</u>+, 100%), 226/228 (<u>MH</u>-CH₂O, 10%), 176 (<u>M</u>-Br, 18%), 162 (<u>M</u>-Br and CH₂, 3%), 146 (<u>M</u>-Br and CH₂O, 15%), 131 (<u>M</u>-Br and CH₂ON, 20%); (Found: <u>MH</u>+, 256.0337, C₁₁H₁₄BrNO requires <u>MH</u>+, 256.0337).

3.3.11 Preparation of 1-Methoxyamino-1-methylindan (176)



A solution of 4-(2-bromophenyl)butan-2-one O-methyloxime (167) (1.70g, 6.66 mmol), tributyltin hydride (3.87g, 13.31 mmol)) and AIBN (0.11g, 0.67 mmol) dissolved in dry benzene (133 cm³, 0.05 M dilution of (167)) was degassed with a steady stream of nitrogen for 1h. The reaction mixture was heated to reflux temperature under a nitrogen atmosphere and a solution of AIBN (0.22g, 1.33 mmol) in benzene (10 cm^3) added dropwise over 12h. The reaction mixture was heated for a further 12 h. Benzene was evaporated under reduced pressure and the residue was purified by column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:9). This afforded the hydroxylamine (176) as a clear, colourless oil (0.87g, 4.93 mmol, 74%). <u>R</u>_F (diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) 0.17; v_{max} (film) 3230 br.w (NHOCH₃), 3060 w and 3010 w (Ar-H, C-H str.), 2960 s, 2910 s, 2880 s and 2840 m (C-H str.), 2800 m (C-H str. of O-CH₃), 1600 w, 1580 w (Ar ring vib.), 1450 s (C-H def.), 1370 m, 750 s (o-disubstituted Ar) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.43 (s, 3 H, CH₃), 1.93 (ddd, 1 H, ³J_{2x,3x} 6.6, ³J_{2x,3y} 8.6, ${}^{2}J_{2x,2y}$ 13.1 Hz, H_{2x}), 2.27 (ddd, 1 H, ${}^{3}J_{2y,3y}$ 5.0, ${}^{3}J_{2y,3x}$ 8.4 Hz, H_{2y}), 2.82 (ddd, 1 H, ${}^{3}J_{3x,3y}$ 15.9 Hz, H_{3x}), 2.97 (ddd, 1 H, H_{3y}), 3.47 (s, 3 H, OCH₃), 5.26 (br. s, 1 H, NH OCH₃), 7.13-7.19 (complex m, 3 H, H₅, H₆ and H₇), 7.28 (m, 1 H, H₄) ppm; δ_C (75.5 MHz, CDCl₃, TMS) 23.9 (CH₃), 29.7 (C2 or C3), 36.6 (C2 or C3), 62.9 (OCH₃), 69.3 (C1), 123.3 (C6), 124.7 (C7), 126.2 (C5), 127.7 (C4), 143.6

(C3a), 146.2 (C7a) ppm; m/z (CI⁺) 178 (<u>MH</u>⁺, 12%), 146 (<u>M</u>-CH₃O, 15%), 131 (<u>M</u>-CH₃ONH, 100%); (Found: <u>MH</u>⁺, 178.1232. C₁₁H₁₅NO requires <u>MH</u>⁺, 178.1232).

3.3.12 <u>Preparation of Ethyl 1-(2-bromobenzyl)-2-oxo-1-</u> cyclopentanecarboxylate (177)¹¹⁸



Ethyl 2-oxo-1-cyclopentanecarboxylate (2.00g, 12.82 mmol) in dry THF (10 cm³) was added dropwise to sodium hydride (370 mg, 15.42 mmol, 80 % dispersion in mineral oil) suspended in a solution of DMPU (1.97 g, 15.42 mmol) and dry THF (20 cm³). After stirring at RT for 1 h, 2-bromobenzyl bromide (3.85 g, 15.42 mmol) in dry THF (10 cm³) was added in one portion and the reaction mixture was heated at reflux temperature for 4 h. The reaction mixture was poured into water (100 cm³) and the product was extracted with diethyl ether (3×100 cm³). The organic phase was dried (MgSO₄) and the diethyl ether removed under reduced pressure. Column chromatography (silica, 60 mesh, ethyl acetate-petroleum ether b.r. 40-60 °C, 1:9) gave the product (**177**) as a clear colourless oil (3.01 g, 9.23 mmol, 72 %); <u>R_F</u> (ethyl acetate-petroleum ether b.r. 40-60 °C, 1:9) gave the product (**177**) as a clear colourless oil (3.01 g, 9.23 mmol, 72 %); <u>R_F</u> (ethyl acetate-petroleum ether b.r. 40-60 °C, 1:3) 0.48; ν_{max} (film) 3025 w (Ar-H, C-H str.), 2980-2860 s (C-H str.), 1740 s (C=O str.), 1720 s (CO₂Et, C=O str.), 1560 w (Ar ring vib.), 1465 s and 1435 s (C-H def.), 1230 s (C-O str.), 750 m (*o*-disubstituted Ar) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.25 (t, 3 H, ${}^{3}_{\rm J}$ 7.1 Hz, CO₂CH₂CH₃), 1.66-2.08 (complex m, 4 H, H4 and H₅), 2.31-2.53 (complex m, 2 H, H₃), 3.31 (d, 1 H,

²<u>J</u> 14.2 Hz, ArC<u>Ha</u>), 3.54 (d, 1 H, ArC<u>Hb</u>), 4.17 (dq (AB system), 1 H, ²<u>J</u> 11.8 Hz, CO₂C<u>Ha</u>), 4.21 (dq (AB system), 1 H, CO₂C<u>Hb</u>), 7.02-7.09 (complex m, 1 H, H4'), 7.10-7.24 (complex m, 2 H, H5' and H6'), 7.53 (d, ³J_{3',4'} 7.8 Hz, H3') ppm; $\delta_{\rm C}$ (75.5 MHz, CDCl₃, TMS) 14.0 (<u>C</u>H₃), 19.7 (C4), 31.7 (BrC₆H₄<u>C</u>H₂), 37.5 (C5), 38.2 (C3), 61.4 (C1), 61.6 (O<u>C</u>H₂), 126.3 (C2'), 127.5 (C5'), 128.4 (C4'), 131.4 (C6'), 132.9 (C3'), 136.7 (C1'), 170.8 (<u>CO₂Et</u>), 214.7 (C2) ppm; m/z (CI+) 341/343 (<u>IM</u>+NH₃]+, 100%), 324/326 (<u>M</u>+, 78%), 295/297 (<u>M</u>-CH₂CH₃, 2%), 278/280 (<u>M</u>-EtOH, 5%), 261/263 (3%), 245 (<u>M</u>-Br, 27%), 185/187 (2%), 172 (<u>M</u>-Br and CO₂CH₂CH₃, 31%), 155 (<u>M</u>-BrC₆H₄CH₂, 27%), 128 (<u>M</u>-BrC₆H₄CH₂ and CH₂CH₃, 3%), 91 (PhCH₂, 2%); (Found: <u>M</u>+, 325.0439. C₁₅H₁₇BrO₃ requires <u>M</u>+, 325.0439).

3.3.13 Preparation of Ethyl 1-(2-bromobenzyl)-2-oxo-1 cyclopentanecarboxylate Oxime (178)¹⁵¹



Ethyl 1-(2-bromobenzyl)-2-oxo-1-cyclopentanecarboxylate (177) (2.00 g, 6.39 mmol) and hydroxylamine hydrochloride (0.53 g, 7.66 mmol) were stirred for 48 h at RT in triethylamine (10 cm^3). The reaction mixture was diluted with diethyl ether and the triethylamine hydrochloride side product was removed by filtration. Solvent was evaporated *in vacuo* and the residue was purified by column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 3:7) to yield the <u>oxime</u> (178) as
prisms (1.38 g, 4.06 mmol, 64%), m.p. 77-78 °C (from petroleum ether b.r. 60-80 °C); (Found: C, 53.04; H,5.33; N, 4.14. C₁₅H₁₈BrNO₃ requires C, 52.95; H, 5.33; N, 4.12%); <u>R</u>_F (diethyl ether-petroleum ether b.r. 40-60 °C, 3:7) 0.12; v_{max} (CH₂Cl₂) 3050 w (Ar-H, C-H str.), 2980m, 2940s and 2810 s (C-H str.), 1720 s (CO2Et, C=O str.), 1640 w (C=N str.), 1560 w (Ar ring vib.), 1465 and 1440 s (C-H def.), 1230 s (C-O str.), 750 m (o-disubstituted Ar) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.26 (t, 3 H, 3J 7.1 Hz, CH3), 1.62-1.89 (complex m, 3 H, H5 and H4a), 2.36 (m, 1 H, H_{4b}), 2.40 (dt, 1 H, ${}^{3}J_{3a,4a} = {}^{3}J_{3a,4b}$ 8.0, ${}^{2}J_{3a,3b}$ 18.7 Hz, H_{3a}), 2.61 (ddd, 1 H, ${}^{3}J_{3b,4b}$ 6.2, ${}^{3}J_{3b,4a}$ 8.0 Hz, H_{3b}), 3.35 (d, 1 H, ${}^{2}J$ 14.3 Hz, ArC<u>H</u>_aH_b), 3.60 (d, 1 H, ArCH_aH_b), 4.17 (dq, 1 H, ²J 18.0 Hz, OCH_aH_b), 4.23 (dq, 1H, OCH_aH_b), 7.04 (ddd, 1 H, ${}^{4}J_{4',6'}$ 1.7, ${}^{3}J_{4',5'}$ 7.3, ${}^{3}J_{4',3'}$ 8.0 Hz, H_{4'}), 7.17 (ddd, 1H, ${}^{4}J_{5',3'}$ 1.2, 3 J_{5',6'} 7.7 Hz, H_{5'}), 7.30 (dd, 1H, H_{6'}), 7.52 (dd, 1H, H_{3'}), 9.77 (br.s., 1 H, OH) ppm; δ_C (75.5 MHz, CDCl₃, TMS) 14.0 (<u>C</u>H₃), 22.0 (C4), 27.7 (Ar<u>C</u>H₂), 33.7 (C5), 40.4 (C3), 57.3 (C1), 61.6 (OCH₂), 61.6 (OCH₃), 126.2 (C2'), 127.2 (C5'), 128.2 (C4'), 131.2 (C6'), 132.8 (C3'), 137.2 (C1'), 165.3 (C2), 172.8 (<u>C</u>O₂CH₂CH₃) ppm; m/z (CI⁺) 340/342 (<u>MH</u>⁺, 100%), 324/326 (14%), 260 (<u>M</u>-Br, 22%), 244 (<u>M</u>-O, 12%), 170 (8%); (Found: <u>MH</u>⁺, 340.0548. C₁₅H₁₈BrNO₃ requires <u>MH</u>⁺, 340.0548).

3.3.14 Preparation of Ethyl 1-(2-bromobenzyl)-2-oxo-1-

cyclopentanecarboxylate O-methyloxime (179)



Ethyl 1-(2-bromobenzyl)-2-oxo-1-cyclopentanecarboxylate (177) (2.80 g, 8.94 mmol) and O-methylhydroxylamine hydrochloride (0.90 g, 10.73 mmol) were stirred overnight at RT in pyridine (10 cm³). Pyridine was removed under reduced pressure and the residue was diluted with diethyl ether (50 cm^3) . The organic phase was washed with water, dried (MgSO₄) and the diethyl ether evaporated in vacuo. Flash chromatography (silica, 60 mesh, ethyl acetate-petroleum ether b.r. 40-60 °C, 1:3) gave the oxime ether (179) as a clear, colourless oil (2.57 g, 7.51 mmol, 84 %); RF (ethyl acetate-petroleum ether b.r. 40-60 °C, 1:3) 0.53; v_{max} (film) 3060 w (Ar-H, C-H str.), 2980-2810 s (C-H str.), 1725 s (CO₂Et, C=O str.), 1645 w (C=N str.), 1565 w (Ar ring vib.), 1465 and 1440 s (C-H def.), 1230 s (C-O str.), 750 m (odisubstituted Ar) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.24 (t, 3 H, 3 <u>J</u> 7.1 Hz, C<u>H</u>₃), 1.56-2.56 (complex m, 6 H, H₃, H₄ and H₅), 3.36 (d, 1 H, ²J 14.2 Hz, ArCH₂), 3.62 (d, 1 H, ArCH_b), 3.91 (s, 3 H, OCH₃), 4.17 (dq (ABX₃ system), 1 H, ²J 11.7 Hz, $OCH_{x}H_{y}$, 4.20 (dq (ABX₃ system), 1 H, $OCH_{x}H_{y}$), 7.03 (ddd, 1 H, ${}^{4}J_{4',6'}$ 1.7, ³J_{4',5'} 7.7, ³J_{4',3'} 8.0 Hz, H_{4'}), 7.17 (td, 1 H, ⁴J_{5',3'} 1.3, ³J_{5',6'} 7.7 Hz, H_{5'}), 7.36 (dd, 1 H, H₆'), 7.51 (dd, 1 H, H₃') ppm; δ_C (75.5 MHz, CDCl₃, TMS) 14.1 (<u>C</u>H₃), 22.0 (C4), 27.9 (BrC₆H₄CH₂), 34.1 (C5), 39.4 (C3), 57.3 (C1), 61.2 (OCH₂), 61.9 (OCH₃), 126.5 (C2'), 127.1 (C5'), 128.1 (C4'), 131.7 (C6'), 132.7 (C3'), 137.5 (C1'), 164.6 (C2), 173.2 (<u>C</u>O₂CH₂CH₃) ppm; m/z (CI⁺) 353/355 (<u>M</u>⁺, 100%), 339/341 (M-CH2, 8%), 323/325 (M-CH2CH3, 2%), 274 (M-Br, 27%), 260 (M-Br and CH₂, 2%), 244 (M-Br and CH₂CH₃, 15%), 170 (11%), 128 (M-BrC₆H₄CH₂ and CH₂CH₃, 2%); (Found: <u>M</u>⁺, 354.0704. C₁₆H₂₀BrNO₃ requires <u>M</u>⁺, 374.0704).

3.3.15 <u>Preparation of Ethyl 3a-methoxyaminocyclopent[alindan-8a-carboxylate</u> (180)



Ethyl 1-(2-bromobenzyl)-2-oxo-1-cyclopentanecarboxylate (179) (200 mg, 0.56 mmol) and tributyltin hydride (330 mg, 0.56 mmol) were dissolved in dry benzene (57 cm^3 , 0.02 M dilution of (179)) and degassed for 1 h. The reaction mixture was heated to reflux temperature and the AIBN (20 mg, 0.11 mmol) in benzene (10 cm^3) was added dropwise over 8 h (syringe pump). Heating was continued for a further 8 h. Benzene was removed under reduced pressure. Flash chromatography (silica, 60 mesh, 500 cm³ petroleum ether b.r. 40-60 °C then ethyl acetate-petroleum ether b.r. 40-60 °C, 1:9) gave the hydroxylamine (180) as one diastereoisomer as a clear colourless oil (105 mg, 0.38 mmol, 68 %); RF (ethyl acetate-petroleum ether b.r. 40-60 °C, 1:9) 0.39; v_{max} (CH₂Cl₂) 3010 w (Ar-H, C-H str.), 960 s, 2900 m and 2860 m (C-H str.), 2810 w (C-H str. of OCH₃), 1710 s (CO₂Et, C=O str.), 1590 w (Ar ring vib.), 1470-1430 m (C-H def.), 1230 (C-O str.) cm⁻¹; δ_H (300 MHz, CDCl₃, TMS) 1.29 (t, 3 H, ³J 7.1 Hz, CH₃), 1.33-1.42 (complex m, 1 H, H_{2x}), 1.70-1.84 (complex m, 2 H, H_{3x} and H_{2y}), 1.95-2.09 (complex m, 2 H, H_{1x} and H_{3y}), 2.27-2.37 (m, 1 H, H_{1y}), 2.84 (d, 1 H, ${}^{2}J_{8x,8y}$ 16.2 Hz, H_{8x}), 3.74 (d, 1 H, H_{8y}), 4.21 (q, 2 H, ${}^{3}J$ 7.1 Hz, OCH₂), 6.49 (br. s., 1 H, NH), 7.14-7.26 (complex m, 3 H, H₄, H₇ and H₅ or H₆), 7.33-7.38 (complex m, 1 H, H₅ or H₆) ppm; δ_C (75.5 MHz, CDCl₃, TMS) 14.2 (<u>CH</u>₃), 23.3 (C2), 37.3 (C3), 41.0 (C1), 43.9 (C8), 58.8 (C8a), 60.7 (O<u>C</u>H₂), 62.4 (OCH₃), 84.4 (C3a), 124.2 (C6), 124.5 (C7), 126.8 (C5), 128.1 (C4), 142.3

(C3b), 144.5 (C7a), 176.3 (C=O) ppm; m/z (CI+) 276 (<u>MH</u>+, 100 %), 244 (<u>M</u>-CH₃O, 37 %), 229 (<u>M</u>-CH₃ONH, 40 %), 170 (<u>M</u>-CH₃OH and CO₂CH₂CH₃, 4 %), 155 (<u>M</u>-CH₃ONH and CO₂CH₂CH₃, 11 %); (Found <u>MH</u>+ 276.1600. C₁₆H₂₁NO₃ requires <u>MH</u>+ 276.1600).

3.3.16 <u>Preparation of Ethyl 1-(2-bromobenzyl)-2-oxo-1-</u> cyclohexanecarboxylate (**181**)¹¹⁸



To a suspension of sodium hydride (0.84 g, 34.83 mmol, 80% dispersion in mineral oil) in a solution of dry THF (50 cm³) and DMPU (4.46 g, 34.83 mmol) was slowly added a solution of ethyl 2-oxocyclohexanecarboxylate (4.94 g, 29.02 mmol) in dry THF (10 cm³). After stirring the mixture at RT for 1h, 2-bromobenzyl bromide (7.98 g, 31.92 mmol) in dry THF (10 cm³) was added in one portion and the reaction mixture was heated at reflux temperature for 6h. The mixture was then poured into water (100 cm³) and the product was extracted into diethyl ether (3 x 100 cm³). The organic phase was dried (MgSO₄) and the solvent was evaporated under reduced pressure. Flash chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) afforded the product (**181**) (7.77 g, 22.93 mmol, 79%) as prisms, m.p. 47.5-48.5 °C (from MeOH/H₂O) (Found: C, 56.65; H, 5.67. C₁₆H₁₉BrO₃ requires C, 56.65; H, 5.65%); <u>RF</u> (diethyl ether-petroleum ether b.r. 40-60 °C, 1:4)

0.33; $v_{max.}$ (CH₂Cl₂) 3030 w (Ar-H, C-H str.), 2980 m, 2940 s and 2860 m (C-H str.), 1760-1700 s (C=O and C=O str. of CO₂Et), 1560 w (Ar ring vib.), 1465 s and 1430 s (C-H def.) cm⁻¹; δ_{H} (300 MHz, CDCl₃, TMS) 1.20 (t, 3 H, ³J 7.1 Hz, CH₃), 1.52-1.80 (complex m, 4 H, H₄ and H₅), 2.00 (complex m, 1 H, H_{6a}), 2.41-2.52 (complex m, 3 H, H₃ and H_{6b}), 3.28 (d, 1 H, ²J 14.3 Hz, ArCH_aH_b), 3.46 (d, 1 H, ArCH_bH_a), 4.13 (dq, 1 H (ABX₃ system), ²J 10.8 Hz, OCH_xH_yCH₃), 4.17 (dq, 1 H (ABX₃ system), OCH_xH_yCH₃), 7.05 (ddd, 1 H, ⁴J_{4',6'} 2.8, ³J_{4',5'} 6.0, ³J_{4',3'} 8.0 Hz, H_{4'}), 7.14-7.28 (complex m, 2 H, H_{5'} and H_{6'}), 7.50 (d, 1 H, H_{3'}) ppm; δ_{C} (75.5 MHz, CDCl₃, TMS) 13.9 (CH₃), 22.5 (C5), 27.5 (BrC₆H₄CH₂), 35.3 (C4), 38.6 (C6), 41.1 (C3), 61.4 (OCH₂), 61.9 (C1), 125.9 (C2'), 127.0 (C5'), 128.2 (C4'), 132.0 (C6'), 132.8 (C3'), 136.5 (C1'),170.8 (C=O of ester), 206.9 (C2) ppm; m/z (CI+) 356/358 ([M+NH₄]+, 11%), 339/341 (MH+, 100%), 259 (M-Br, 25%), 232 (2%), 185 (13%), 169 (M-BrC₆H₄CH₂, 13%); (Found: MH+, 339.0596. C₁₆H₁₉BrO₃ requires MH+, 339.0596).

3.3.17 <u>Preparation of Ethyl 1-(2-bromobenzyl)-2-oxo-1-</u> cyclohexanecarboxylate O-methyloxime (**182**)



Ethyl 1-(2-bromobenzyl)-2-oxo-1-cyclohexanecarboxylate (181) (1.00 g, 2.95 mmol) and O-methylhydroxylamine hydrochloride (0.30 g, 3.54 mmol) were stirred at RT

overnight in pyridine (10 cm³). The reaction mixture was poured into water (50 cm³) and the product was extracted into diethyl ether $(2 \times 50 \text{ cm}^3)$. The organic phase was dried (MgSO₄) and the solvent was removed under reduced pressure. Flash chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) of the residue gave the <u>oxime ether (182)</u> (0.73 g, 1.98 mmol, 67%) as a clear, colourless oil; <u>R</u>_F (diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) 0.47; v_{max} (film) 3050 w (Ar-H, C-H str.), 2930 s, 2895 m and 2880 m (C-H str.), 2810 w (C-H str. of OCH₃), 1720 s (CO₂Et, C=O str.), 1645 w (C=N str.), 1460 s and 1430 s (C-H def.), 750 s (o-disubstituted Ar) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.18 (t, 3 H, ³J 7.1 Hz, CH₃), 1.23-1.78 (complex m, 6 H, H₄, H₅ and H₆), 2.30 (ddd, 1 H, H_{3a}), 3.31 (ddd, 1 H, H_{3b}), 3.35 (d, 1 H, ²J 14.3 Hz, ArCH_aH_b), 3.53 (d, 1 H, ArCH_aH_b), 4.10 (dq, 1 H (ABX₃ system), ²J 15.6 Hz, OCH_xH_yCH₃), 4.13 (dq, 1 H (ABX₃ system), $OCH_{x}H_{v}CH_{3}$), 7.03 (ddd, 1 H, ${}^{4}J_{4',6'}$ 2.3, ${}^{3}J_{4',5'}$ 6.8, ${}^{3}J_{4',3'}$ 7.9 Hz, H_{4'}), 7.19 (complex m, 2 H, H_{5'} and H_{6'}), 7.51 (dd, 1 H, ${}^{4}J_{3',5'}$ 1.1 Hz, H_{3'}) ppm; δ_{C} (75.5.MHz, CDCl₃, TMS) 14.0 (<u>C</u>H₃), 22.8 (C5), 24.0 (BrC₆H₄<u>C</u>H₂), 25.6 (C4), 35.1 (C6), 39.4 (C3), 54.7 (C1), 61.0 (OCH₂), 61.5 (OCH₃), 126.2 (C2'), 126.7 (C5'), 127.9 (C4'), 132.1 (C6'), 132.7 (C3'), 137.3 (C1'), 158.8 (C2), 172.6 (C=O of ester) ppm; m/z (CI+), 368/370 (M+, 100%), 338/340 (M-CH₂O, 4%), 228 (M-HBr, 15%), 258 (M-HBr and CH₂O, 15%), 243 (M-HBr and MeON, 8%), 217 (3%), 184 (8%); (Found: <u>MH</u>+, 368.0861. C₁₇H₂₂BrNO₃ requires <u>MH</u>+, 368.0861).

3.3.18 <u>Preparation of Ethyl 4a-methoxyaminocyclohex[a]indan-9a-carboxylate</u> (183)



Ethyl 2-oxo-1-(2-bromobenzyl)cyclohexane carboxylate (182) (300 mg, 0.82 mmol) and tributyltinhydride (475 mg, 1.63 mmol) were dissolved in dry benzene (40 cm³, 0.02M dilution of (182)) and degassed by passing a stream of nitrogen through the solution for 30 min. The solution was heated to reflux temperature under a nitrogen atmosphere and a solution of AIBN (30 mg, 0.18 mmol) in dry benzene (10 cm³) was added over 8h (syringe pump). Heating was continued for a further 12 h. Benzene was evaporated under reduced pressure and the product was isolated by column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:4). This afforded the hydroxylamine (183) as a clear, colourless oil (214 mg, 0.74 mmol, 90%). <u>R</u>_F (diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) 0.32; v_{max} (CH₂Cl₂) 3262 w (N-H), 3010 w (Ar-H, C-H str.), 2920 s, 2850 s and 2800 w (C-H str.), 1710 s (CO₂Et, C=O str.), 1600 w, 1560 w, 1500 m (Ar ring vib.), 1480-1440 s (C-H def.), 1230 m (C-O str.) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.07 (qt, 1 H, ${}^{2}J_{3ax,3eq}$ = ${}^{3}J_{3ax,4ax} = {}^{3}J_{3ax,2ax}$ 13.6, ${}^{3}J_{3ax,4eq} = {}^{3}J_{3ax,2eq}$ 3.7 Hz, H_{3ax}), 1.27 (td, 1 H, ${}^{2}J_{4ax,4eq}$ 13.6, ³J_{4ax,3eq} 4.0 Hz, H_{4ax}), 1.31 (t, 3 H, CH₃), 1.37 (overlapping ddddd, 1 H, H_{2eq}), 1.48 (qt, 1 H, ${}^{2}J_{2ax,2eq} = {}^{3}J_{2ax,1ax}$ 13.6, ${}^{3}J_{2ax,1eq} = {}^{3}J_{2ax,3eq}$ 4.0 Hz, H_{2ax}), 1.67 (br. m, 1 H, H_{3eq}), 1.84 (td, 1 H, ²J_{1ax,1eq} 13.6, ³J_{1ax,2eq} 4.2 Hz, H_{1ax}), 1.93 (ddd, 1 H, ${}^{3}J_{4eq,3eq}$ 4.8 Hz, H_{4eq}), 2.39 (br. ddd, 1 H, H_{1eq}), 2.61 (d, 1 H, ${}^{2}J_{9x,9y}$

15.3 Hz, H_{9x}), 2.90 (s, 1 H, OCH₃), 3.67 (d, 1 H, H_{9y}), 4.23 (q, 2 H, OCH₂), 6.27 (br., 1 H, NH), 7.16-7.34 (complex m, 4 H, H₅, H₆, H₇ and H₈) ppm; δ_{C} (75.5 MHz, CDCl₃, TMS) 14.1 (CH₃), 21.8 (C3), 21.9 (C2), 28.4 (C4), 35.7 (C1), 42.8 (C9), 54.7 (C9a), 60.2 (OCH₂), 62.3 (OCH₃), 70.9 (C4a), 124.2 (C7), 125.0 (C8), 126.1 (C6), 127.8 (C5), 142.2 (C4b), 142.8 (C8a), 175.0 (C=O) ppm; m/z (EI+) 290 (<u>MH</u>+, 80%), 260 (<u>M</u>-CH₃CH₂, 32%), 243 (<u>M</u>-CH₃CH₂OH, 100%), 199 (<u>M</u> - CH₃CH₂O and CH₃ONH, 3%), 169 (<u>M</u>- CH₃ONH and CH₃CH₂CO₂H, 36%); (Found: <u>MH</u>+, 290.1756. C₁₇H₂₃NO₃ requires <u>MH</u>+, 290.1756).





1-Pyrrolidino-1-cyclohexene (2.57 g, 17.00 mmol) and 2-bromobenzyl bromide (4.25 g, 17.00 mmol) were heated at reflux temperature in benzene (30 cm³) for 6 h. A solution of sodium acetate/acetic acid/water (1:2:2) (25 cm³) was added and the reaction mixture was heated at reflux temperature for a further 2 h. The reaction mixture was diluted with water (50 cm³) and extracted with diethyl ether (2 x 50 cm³). The solvent was evaporated under reduced pressure. Column chromatography (silica 60, mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) afforded the ketone (197) as a clear colourless oil (3.16 g, 11.84 mmol, 70 %). <u>R_F</u> (diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) 0.34; v_{max}(film) 3025 w (Ar-H, C-H str.), 2930 s and 2860 s (C-H str.), 1700 s (C=O str.), 1560 w (Ar ring vib.), 1465 s and 1440 s (C-H def.), 745 s (*o*-

disub. Ar) cm⁻¹; δ_{H} (300 MHz, CDCl₃, TMS) 1.39 (complex dddd, 1 H, ${}^{3}J_{3ax,2ax}$ ${}^{3}J_{3ax,4eq}$ 3.6, ${}^{2}J_{3ax,3eq}$ 12.0 Hz, H_{3ax}), 1.60 (complex m, 2 H, H_{4ax} and H_{5ax}), 1.80 (complex dddd, 1 H, H_{2ax}), 2.04 (complex m, 2 H, H_{5eq} and H_{3eq}), 2.30 (complex ddd, 1 H, ${}^{3}J_{6ax,5ax}$ 10.2, ${}^{3}J_{6ax,5eq}$ 5.8, ${}^{2}J_{6ax,6eq}$ 12.9 Hz, H_{6ax}), 2.39 (complex m, 1 H, H_{4eq}), 2.54 (dd, 1 H, ${}^{3}J_{a,2ax}$ 8.1, ${}^{3}J_{a,b}$ 13.7 Hz, ArCH_aCH_b), 2.66 (complex m, 1 H, H_{6eq}), 3.34 (dd, 1 H, ${}^{3}J_{b,2ax}$ 5.2 Hz, ArCH_aCH_b), 7.03 (ddd, 1 H, ${}^{4}J_{4',6'}$ 2.1, ${}^{3}J_{4',5'}$ 7.0, ${}^{3}J_{4',3'}$ 7.9 Hz, H_{4'}), 7.18 (ddd, 1 H, ${}^{4}J_{5',3'}$ 1.1, ${}^{3}J_{5',6'}$ 7.6 Hz, H_{5'}), 7.23 (dd, 1 H, H₆), 7.49 (dd, 1 H, H_{3'}) ppm; δ_{C} (75.5 MHz, CDCl₃, TMS) 25.2 (C5), 28.1 (C4), 33.6 (C3), 35.6 (ArCH₂), 42.2 (C6), 50.5 (C2), 124.6 (C2'), 127.1 (C5'), 127.7 (C4'), 131.7 (C6'), 132.6 (C3'), 139.6 (C1'), 211.8 (C1) ppm; m/z (CI⁺) 284/286 ([M+NH₄]⁺, 100 %), 267/269 (MH⁺, 31 %), 187 (M-Br, 53 %), 169/171 (C₇H₆Br⁺, 2 %); (Found: [M+NH₄]⁺, 284.0650. C₁₃H₁₅BrO requires [M+NH₄]⁺, 284.0650).

3.3.20 <u>Preparation of 2-(2-Bromobenzyl)cyclohexanone O-methyloxime (196)</u> \xrightarrow{O} \xrightarrow{Br} $\xrightarrow{CH_3ONH_2.HCl}$ \xrightarrow{O} $\xrightarrow{VOCH_3}$ \xrightarrow{Br} $\xrightarrow{VOCH_3}$ $\xrightarrow{Preparation}$ $\xrightarrow{VOCH_3}$ $\xrightarrow{Preparation}$ $\xrightarrow{VOCH_3}$ $\xrightarrow{Preparation}$ $\xrightarrow{VOCH_3}$ $\xrightarrow{VOCH_3$

2-(2-Bromobenzyl)cyclohexanone (197) (1.00 g, 3.75 mmol) and Omethylhydroxylamine hydrochloride (0.47 g, 5.62 mmol) were stirred overnight at RT in pyridine (10 cm³). Pyridine was removed under reduced pressure. Column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:9) gave a mixture of isomers of the <u>oxime ether</u> (196) as a clear colourless oil (0.86 g, 2.93 mmol, 78%). <u>RF</u> (diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) 0.31 and 0.28; v_{max} (film) 3030 w (Ar-H, C-H str.), 2980 w, 2930 s and 2880 s (C-H str.), 2805 w (C-H str. of O-CH₃), 1650 w (C=N str.), 1560 w (Ar ring vib.), 1465 s and 1440 s (C-H def.), 1050 s, 1020 s, 750 s (*o*-disubstituted Ar) cm⁻¹

<u>MAJOR ISOMER ($R_F = 0.31$)</u>

 $δ_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.26-1.79 (complex m, 6 H, H_{2ax}, H_{3ax}, H_{3eq}, H_{4ax}, H_{5ax} and H_{5eq}), 2.04 (ddd, 1 H, ³J_{6ax,5eq} 4.4, ³J_{6ax,5ax} 9.9, ²J_{6ax,6eq} 14.0 Hz, H_{6ax}), 2.56 (br. m, 1 H, H_{4eq}), 2.74 (dd, 1 H, ³J_{x,2ax} 8.7, ²J_{x,y} 13.7 Hz, ArCH_xH_y), 2.91 (m overlapping with minor isomer, 1 H, H_{6eq}), 3.26 (dd, 1 H, ³J_{y,2ax} 5.5 Hz, ArCH_xH_y), 3.82 (s, 3 H, OCH₃), 7.03 (ddd, 1 H, ⁴J_{4',6'} 2.3, ³J_{4',5'} 6.9, ³J_{4',3'} 7.8 Hz, H_{4'}), 7.16-7.23 (m, 2 H, H_{5'} and H_{6'}), 7.50 (d, 1 H, H_{3'}) ppm; $δ_{\rm C}$ (75 5 MHz, CDCl₃, TMS) 24.3 (C5), 24.5 (C4), 26.2 (C3), 32.4 (ArCH₂), 37.1 (C6), 42.2 (C2), 61.0 (OCH₃), 124.9 (C2'), 126.9 (C5'), 127.5 (C4'), 131.7 (C6'), 132.7 (C3'), 140.2 (C1'), 160.9 (C1) ppm.

<u>MINOR ISOMER ($R_F = 0.28$)</u>

 $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.26-1.79 (complex m, 6 H, H_{2ax}, H_{3ax}, H_{3eq}, H_{4ax}, H_{5ax} and H_{5eq}), 1.96 (m, 1 H, H_{6ax}), 2.30 (dd, 2 H, ArC<u>H</u>₂), 2.90 (m, 2 H, H_{4eq} and H_{6eq}), 3.56 (s, 3 H, OCH₃), 7.03 (ddd, 1 H, ⁴J_{4',6'} 2.3, ³J_{4',5'} 6.9, ³J_{4',3'} 7.8 Hz, H_{4'}), 7.16-7.23 (m, 2 H, H_{5'} and H_{6'}), 7.50 (d, 1 H, H_{3'}) ppm; $\delta_{\rm C}$ (75.5 MHz, CDCl₃, TMS) 21.0 (C5), 26.8 (C4), 28.8 (C3), 28.9 (ArCH₂), 33.6 (C2), 36.4 (C6), 60.6 (OCH₃), 124.9 (C2'), 127.0 (C5'), 127.7 (C4'), 130.9 (C6'), 132.5 (C3'), 139.2 (C1'), 161.4 (C1) ppm. m/z (CI+) 296/298 (<u>MH</u>+, 100%), 266 (5%), 216 (<u>M</u> - Br, 45%), 186 (<u>M</u> - Br and CH₂O, 12%), 171 (<u>M</u> - Br and CH₂ONH, 5%); (Found: <u>MH</u>+, 296.0650. C₁₄H₁₈BrNO requires <u>MH</u>+, 296.0650).

3.3.21 <u>Preparation of 9b-Methoxyaminocyclohex[a]indan (195)</u>



2-(2-Bromobenzyl)cyclohexanone O-methyloxime (196) (300 mg, 1.01 mmol) and tributyltin hydride (590 mg, 2.03 mmol) were dissolved in benzene (51 cm³, 0.02 M dilution of (196)) and the solution degassed for 1 h. The AIBN (33 mg, 0.02 mmol) in benzene (10 cm^3) was added to the solution heated at reflux temperature under a nitrogen atmosphere over 8 h. Heating was continued for a further 10 h. Benzene was evaporated in vacuo and the crude product purified by column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:9) yielding the hvdroxylamine (195) (127 mg, 0.59 mmol, 58%) as a pale yellow oil. R_F (diethyl ether-petroleum ether b.r. 40-60 °C, 1:9) 0.31; v_{max} (film) 3400 br. (H₂O), 3210 Br. w (NH), 3030 w (Ar-H, C-H str.), 2910 s and 2850 s (C-H str.), 2800 m (O-CH₃ C-H str.), 1630-1580 w (Ar ring vib.), 1450 m (C-H def.), 760 s (o-disubstituted Ar) cm^{-1} ; δ_{H} (400 MHz and COSY, CDCl₃, TMS) 1.15 (m, 1 H, H_{4ax}), 1.20 (m, 1 H, H_{2ax}), 1.36 (dtt, 1 H, ${}^{3}J_{3ax,4eq} = {}^{3}J_{3ax,2eq}$ 3.5, ${}^{3}J_{3ax,4ax} = {}^{3}J_{3ax,2ax}$ 9.4, ${}^{2}J_{3ax,3eq}$ 13.0 Hz, H_{3ax}), 1.47 (dtt, 1 H, ${}^{3}J_{3eq,2eq} = {}^{3}J_{3eq,4eq}$ 3.4, ${}^{3}J_{3eq,4ax} = {}^{3}J_{3eq,2ax}$ 6.7 Hz, H_{3eq}), 1.60 (m, 1 H, H_{2eq}), 1.79 (m, 1 H, H_{4eq}), 1.88 (ddd, 1 H, ³J_{1ax,2eq} 4.1, ³J_{1ax,2ax} 9.6, ²J_{1ax,1eq} 13.9 Hz, H_{1ax}), 1.96 (ddd, 1 H, ³J_{1eq,2eq} 4.2, ³J_{1eq,2ax} 6.8 Hz, H_{1eq}), 2.48 (m, 1 H, H_{4a}), 2.52 (dd, 1 H, ³J_{5x,4a} 4.5, ²J_{5x,5y} 15.0 Hz, H_{5x}), 3.09 (dd, 1 H, ³L_{5y,4a} 6.1 Hz, H_{5y}), 3.48 (s, 3 H, OCH₃), 5.47 (br. s, 1 H, NH), 7.17-7.30 (complex m, 4 H, H₆, H₇, H₈ and H₉) ppm; δ_C (75.5 MHz, CDCl₃, TMS) 22.1 (C3), 23.3 (C4), 28.3 (C2), 30.2 (C1), 36.0 (C5), 41.0 (C4a), 62.9 (OCH₃), 70.5 (C9b),
123.1 (C7), 125.7 (C6), 126.1 (C8), 127.6 (C9), 143.4 (C9a), 145.3 (C5a) ppm; m/z
(CI⁺) 218 (MH⁺, 15%), 186 (M-MeO, 15%), 171 (M-MeONH, 100%), 129 (12%);
(Found: MH⁺, 218.1545. C₁₄H₁₉NO requires MH⁺, 218.1545).

3.3.22 <u>Preparation of Methyl 1-(2-bromobenzyl)-2-oxo-1-</u> cycloheptanecarboxylate (**199**)¹¹⁸



Methyl 2-oxo-1-cycloheptanecarboxylate (2.00 g, 11.75 mmol) in dry THF (5 cm³) was added dropwise to a suspension of sodium hydride (0.34 g, 80% dispersion in oil) in THF (20 cm³) and DMPU (1.80 g, 12.10 mmol). The reaction mixture was left stirring at RT for 1 h. 2-Bromobenzyl bromide (3.23 g, 12.93 mmol) in THF (5 cm³) was added and the reaction was mixture heated at reflux temperature for 5 h. The reaction mixture was poured into water (100 cm³) and the product extracted into diethyl ether (2 x 100 cm³). The organic layer was dried (MgSO₄) and solvent removed *in vacuo*. Column chromatography (silica, 60 mesh, diethyl ether - petroleum ether b.r. 40 - 60 °C, 1:4) gave the product (**199**) (3.53 g, 9.87 mmol, 84%) as a powder, m.p. 67-68 °C (from petroleum ether b.r. 40-60 °C); (Found: C, 56.47; H, 5.70. C₁₆H₁₉BrO₃ requires C, 56.65; H, 5.65%); <u>RF</u> (diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) 0.24; v_{max} (CH₂Cl₂) 3030 w (Ar-H, C-H str.), 2900 s and 2860 m (C-H str.), 1760 s (C=O str.), 1710 s (CO₂Me, C=O str.), 1560 w (Ar ring vib.), 1470 m

and 1430 m (C-H def.), 1230 m (C-O str.); $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.35-1.81 (complex m, 6 H, H₄, H₅ and H₆), 1.91 (ddd, 1 H, ³J 1.7, ³J 9.5, ²J_{7a,7b} 14.8 Hz, H_{7a} or H_{7b}), 2.01 (ddd, 1 H, ³J 1.4, ³J 8.5 Hz, H_{7a} or H_{7b}), 2.46 (ddd, 1 H, ³J 3.7, ³J 10.3, ²J_{3a,3b} 11.9 Hz, H_{3a} or H_{3b}), 2.61 (ddd, 1 H, ³J 2.9, ³J 9.7 Hz, H_{3a} or H_{3b}), 3.29 (d, 1 H, ²J 14.3 Hz, BrC₆H₄CH₂), 3.52 (d, 1 H, BrC₆H₄CH₂), 3.72 (s, 3 H, OC<u>H</u>₃), 7.06 (ddd, 1 H, ⁴J_{4',6'} 1.8, ³J_{4',5'} 7.5, ³J_{4',3'} 7.9 Hz, H_{4'}), 7.07 (dd, 1 H, ³J_{6',5'} 7.5 Hz, H_{6'}), 7.19 (dt, 1 H, ⁴J_{5',3'} 1.3 Hz, H_{5'}), 7.53 (dd, 1 H, H_{3'}) ppm; $\delta_{\rm C}$ (75.5 MHz, CDCl₃) 24.7 (C5), 26.1 (C4), 30.0 (C6), 30.5 (BrC₆H₄<u>C</u>H₂), 38.3 (C7), 41.8 (C3), 52.4 (CO₂<u>C</u>H₃), 64.1 (C1), 126.2 (C2'), 127.1 (C5'), 128.3 (C4'), 131.6 (C6'), 133.0 (C3'), 136.7 (C1'), 172.1 (<u>CO</u>₂CH₃), 208.5 (C2) ppm; m/z (CI⁺) 339/341 (<u>MH</u>⁺, 100%), 307/309 (<u>MH</u>⁺-CH₃OH, 10%), 259 (<u>M</u>-Br, 67%), 199 (<u>M</u>-CH₃OCO, 21%), 171 (BrC₆H₄CH₃, 6%), 115 (C₈H₁₃O, 8%), 91 (PhCH₂, 5%); (Found: <u>MH</u>⁺, 339.0595. C₁₆H₁₉BrO₃ requires <u>MH</u>⁺, 339.0595).

3.3.23 <u>Preparation of 3-(2-Bromobenzyl)cyclohexanone (204)</u>²²¹ + $\underbrace{\bigcirc}_{H_2O}^{Br}$ $\underbrace{\bigcirc}_{Et_2O}^{O}$ $\underbrace{\bigcirc}_{f_2O}^{O}$ $\underbrace{\bigcirc}_{f_2O}^$

2-Bromobenzylmagnesium bromide was prepared by the dropwise addition of 2bromobenzylbromide (3.25 g, 13.01 mmol) in diethyl ether (10 cm³) to magnesium turnings (0.51 g, 20.81 mmol) in diethyl ether (5 cm³). The reaction mixture was cooled to -78 °C (acetone/Cardice) for 20 min. Copper (1) cyanide (2.27 g, 25.35 mmol) was added in one portion. The internal temperature of the reaction was allowed to warm slowly, under a nitrogen atmosphere, to -30 °C over 90 min. 2-Cyclohexen-1-one (1.00 g, 10.40 mmol) in diethyl ether (20 cm³) was added dropwise

to the cuprate at -30 °C and stirring was continued at this temperature for a further 30 min. A solution of saturated ammonium chloride (30 cm³) in water (30 cm³) was added dropwise to the reaction mixture over 20 min and stirring was continued for a further 90 min. The reaction mixture was filtered and the filtrate was extracted with diethyl ether. The organic phase was dried (MgSO₄) and the diethyl ether was removed in vacuo. Column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 2:3) afforded the ketone (204) as a clear colourless oil (1.86 g, 6.97 mmol, 67%). The oil was further purified by a kugelrohr distillation, b.p. 200 ^oC, 0.4 mmHg; (Found: C, 58.66; H, 5.69. C₁₃H₁₅BrO requires C, 58.44; H, 5.66%); <u>R</u>_F (diethyl ether-petroleum ether b.r. 40-60 °C, 1:1) 0.50; v_{max} (film) 3050 w (Ar-H, C-H str.), 2915 s, 2860 s and 2810 w (C-H str.), 1705 s (C=O str.), 1590 w, 1560 m and 1555 w (Ar ring vib.), 1470 s (C-H def.), 1440 m, 750 s (odisubstituted Ar) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.44 (qd, 1 H, ³J_{4ax,5eq} 3.0 Hz, H_{4ax}), 1.61 (qdd, 1 H, ${}^{3}\underline{J}$ 3.5, ${}^{3}\underline{J}$ 4.3, ${}^{2}\underline{J}_{5ax,5eq} = {}^{3}\underline{J}_{5ax,6ax} = {}^{3}\underline{J}_{5ax,4ax}$ 12.0 Hz, H_{5ax}), 1.87 (m, 1 H, H_{4eq}), 1.97-2.42 (complex m, 6 H, H_{2ax}, H_{2eq}, H_{3ax}, H_{5eq}, H_{6ax} and H_{6eq}), 2.72 (dd, 1 H, ${}^{3}J_{x,3ax}$ 6.6, ${}^{2}J_{x,y}$ 13.4 Hz, ArC $\underline{H}_{x}H_{y}$), 2.79 (dd, 1 H, ${}^{3}J_{y,3ax}$ 6.6Hz, ArCH_xH_v), 7.05 (ddd, 1 H, ${}^{3}J_{4',6'}$ 1.9, ${}^{3}J_{4',3'}$ 7.4, ${}^{3}J_{4',5'}$ 7.9 Hz, H_{4'}), 7.13 $(dd, 1 H, {}^{3}\underline{J}_{6',5'}, 7.6 Hz, H_{6'}), 7.20 (ddd, 1 H, {}^{4}\underline{J}_{5',3'}, 1.1 Hz, H_{5'}), 7.51 (dd, 1 H, H_{3'})$ ppm; δ_C (75.5 MHz, CDCl₃, TMS) 25.0 (C5), 30.1 (C4), 39.3 (C3), 41.3 (C6), 42.7 (ArCH₂), 47.5 (C2), 124.6 (C2'), 127.2 (C5'), 127.9 (C4'), 131.2 (C6'), 132.9 (C3'), 138.8 (C1'), 211.0 (C1) ppm; m/z (EI+) 266/268 (M+, 19%), 248/250 (M-H₂O, 6%), 209/211 (M - C₃H₅O, 12%), 187 (M - Br, 100%), 168/170 (C₇H₆Br, 14%), 129 (M - HBr and C₃H₅O, 15%), 129 (18%), 115 (25%), 97 (C₆H₉O, 98%), 91 (C₇C₇, 21%), 77 (C₆H₅, 2%), 69 (C₄H₅O, 72%), 63 (10%), 55 (C₄H₇, 53%); (Found: $[M+NH_4]^+$, 284.0650. $C_{13}H_{15}BrO$ requires $[M+NH_4]^+$, 284.0650).

3.3.24 Reaction of Cyclohex-2-en-1-one with 2-Bromobenzylmagnesium

bromide



2-Bromobenzyl bromide (2.00 g, 8.01 mmol) in dry diethyl ether (10 cm³) was added dropwise to magnesium turnings (0.31 g, 12.81 mmol) covered by diethyl ether under a nitrogen atmosphere to prepare the Grignard reagent, 2-bromobenzylmagnesium bromide. After stirring for 1 h at RT, cyclohex-2-en-1-one (0.92 g, 9.61 mmol) in diethyl ether (10 cm^3) was added dropwise and the reaction mixture was heated at reflux temperature for 2 h. The reaction mixture was quenched with saturated ammonium chloride solution (100 cm^3) and the aqueous mixture was extracted with diethyl ether $(2 \times 100 \text{ cm}^3)$. The organic phase was dried (MgSO₄) and the solvent was evaporated under reduced pressure. Column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:1) afforded a 71:29 mixture of 3-(2bromobenzyl)cyclohexan-1-one (204):1-(2-bromobenzyl)cyclohex-2-en-1-ol (207) as a clear, colourless oil (1.54 g, 5.77 mmol, 72%). g.l.c. (BP10; 240 °C; atten. 16; air, 0.53 kg/cm²; He, 0.99 kg/cm²; H₂, 0.92 kg/cm²) RT (area %) 4.74 (20.2%), 5.29 (3.7%), 5.38 (6.4%), 9.17 (69.7%) min. Analytical samples of the two components were separated by HPLC chromatography (methyl *tert*-butyl ether-hexane, 1:9; flow, 1.5 cm³/in; detector, 254 nm).

3-(2-Bromobenzyl)cyclohexan-1-one (204)

<u>R</u>_F (dichloromethane) 0.52; HPLC (methyl *tert*-butyl ether-hexane, 1:9; flow, 1.5 cm³/in; detector, 254 nm) 11.26 min; g.l.c.(BP10; 240 °C; atten. 16; air, 0.49 kg/cm²;

He, 1.06 kg/cm²; H₂, 1.06 kg/cm²) RT (area %) 7.48 min; (Found: C, 58.66; H, 5.69. C₁₃H₁₅BrO requires C, 58.44; H, 5.66%); v_{max} (film) 3050 w (Ar-H, C-H str.), 2915 s, 2860 s and 2810 w (C-H str.), 1705 s (C=O str.), 1590 w, 1560 m and 1555 w (Ar ring vib.), 1470 s (C-H def.), 1440 m, 750 s (o-disubstituted Ar) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.44 (qd, 1 H, 3 J_{4ax,5eq} 3.0 Hz, H_{4ax}), 1.61 (qdd, 1 H, ${}^{3}\underline{J}$ 3.5, ${}^{3}\underline{J}$ 4.3, ${}^{2}\underline{J}_{5ax,5eq} = {}^{3}\underline{J}_{5ax,6ax} = {}^{3}\underline{J}_{5ax,4ax}$ 12.0 Hz, H_{5ax}), 1.87 (m, 1 H, H_{4eq}), 1.97-2.42 (complex m, 6 H, H_{2ax}, H_{2eq}, H_{3ax}, H_{5eq}, H_{6ax} and H_{6eq}), 2.72 (dd, 1 H, ${}^{3}J_{x,3ax}$ 6.6, ${}^{2}J_{x,y}$ 13.4 Hz, ArCH_xH_y), 2.79 (dd, 1 H, ${}^{3}J_{y,3ax}$ 6.6Hz, ArCH_xH_y), 7.05 (ddd, 1 H, ${}^{3}\underline{I}_{4',6'}$ 1.9, ${}^{3}\underline{I}_{4',3'}$ 7.4, ${}^{3}\underline{I}_{4',5'}$ 7.9 Hz, H_{4'}), 7.13 (dd, 1 H, ${}^{3}\underline{I}_{6',5'}$ 7.6 Hz, H_{6'}), 7.20 (ddd, 1 H, 4 <u>J</u>_{5',3'} 1.1 Hz, H_{5'}), 7.51 (dd, 1 H, H_{3'}) ppm; δ_{C} (75.5 MHz, CDCl₃, TMS) 25.0 (C5), 30.1 (C4), 39.3 (C3), 41.3 (C6), 42.7 (ArCH₂), 47.5 (C2), 124.6 (C2'), 127.2 (C5'), 127.9 (C4'), 131.2 (C6'), 132.9 (C3'), 138.8 (C1'), 211.0 (C1) ppm; m/z (EI+) 266/268 (M+, 19%), 248/250 (M-H₂O, 6%), 209/211 (M -C₃H₅O, 12%), 187 (M - Br, 100%), 168/170 (C₇H₆Br, 14%), 129 (M - HBr and C₃H₅O, 15%), 129 (18%), 115 (25%), 97 (C₆H₉O, 98%), 91 (C₇C₇, 21%), 77 $(C_{6}H_{5}, 2\%), 69 (C_{4}H_{5}O, 72\%), 63 (10\%), 55 (C_{4}H_{7}, 53\%); (Found: [M+NH_{4}]+,$ 284.0650. C₁₃H₁₅BrO requires [M+NH₄]+, 284.0650).

1-(2-Bromobenzyl)cyclohex-2-en-1-ol (207)

<u>R</u>_E (dichloromethane) 0.39; HPLC (methyl *tert*-butyl ether-hexane, 1:9; flow, 1.5 cm³/in; detector, 254 nm) 8.43 min; g.l.c.(BP10; 240 °C; atten. 16; air, 0.49 kg/cm²; He, 1.06 kg/cm²; H₂, 1.06 kg/cm²) RT (area %) 5.09 (67%), 5.67 (10%), 5.77 (23%) min [compound dehydrates under the glc conditions to give a mixture of dienes]; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.52 (br. s, 1 H, OH), 1.67-1.80 (complex m, 4 H, H₅ and H), 1.98-2.03 (complex m, 2 H, H₄), 3.05 and 3.10 (AB quartet, 2 H, ²J_{X,Y} 13.7 Hz, ArCH_xH_y), 5.59 (dt, 1 H, ⁴J_{2,4a} = ⁴J_{2,4a} 1.8 Hz, ³J_{2,3} 10.0 Hz, H₂), 5.82 (ddd, 1 H, ³J_{3,4a} 3.3 Hz, ³J_{3,4b} 4.1 Hz, H₃), 7.07 (ddd, 1 H, ⁴J_{4',6'} 1.7 Hz, ³J_{4',3'} 7.5 Hz,

 ${}^{3}\underline{J}_{4',5'}$ 8.0 Hz, H_{4'}), 7.24 (ddd, 1 H, ${}^{4}\underline{J}_{5',3'}$ 1.2Hz, ${}^{3}\underline{J}_{5',6'}$ 7.6 Hz, H_{5'}), 7.42 (dd, 1 H, H_{6'}), 7.55 (dd, 1 H, H_{3'}) ppm.

3.3.25 <u>Preparation of 3-(2-Bromobenzyl)cyclohexan-1-one 2,2-</u> Dimethylpropylidene acetal (**208**)¹⁵¹



A solution of the 71:29 mixture of 3-(2-bromobenzyl)cyclohexan-1-one (204):1-(2bromobenzyl)cyclohex-2-en-1-ol (207) (13.9 g, 52 mmol), 2,2-dimethylpropane-1,3diol (5.96 g, 57 mmol) and p-toluenesulphonic acid (0.95 g, 0.50 mmol) in toluene (100 cm^3) were heated at reflux temperature in a Dean-Stark apparatus for 24 h. Toluene was evaporated in vacuo and the residue was purified by column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:4). This yielded the <u>acetal</u> (208) (11.6 g, 33 mmol, 89% based on the % of ketone (204))as a clear colourless oil. <u>R</u>_F (diethyl ether-petroleum ether b.r. 40-60 °C, 1:1) 0.69; v_{max} (film) 3060 s (Ar-H, C-H str.), 2990 s, 2960 m and 2860 m (C-H str.), 1600 w and 1550 w (Ar ring vib.), 1420 s (C-H def.), 1370 w and 1390 w (C(CH₃)₂) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 0.90 (s, 3 H, C<u>H₃</u>), 0.94 (s, 3 H, C<u>H₃</u>), 1.00 (qd, 1 H overlapping with CH₃ signals, ${}^{3}J_{4ax,5eq}$ 3.8 Hz, H_{4ax}), 1.07 (t, 1 H, ${}^{2}J_{2ax,2eq}$ = 3 <u>J</u>_{2ax,3ax} 12.7 Hz, H_{2ax}), 1.23 (td, 1 H, 2 <u>J</u>_{6ax,6eq} = 3 <u>J</u>_{6ax,5ax} 13.0, 3 <u>J</u>_{6ax,5eq} 4.0 Hz, H_{6ax}), 1.40 (qt, 1 H, ${}^{2}J_{5ax,5eq} = {}^{3}J_{5ax,4ax}$ 13.0, ${}^{3}J_{5ax,4eq} = {}^{3}J_{5ax,6eq}$ 3.3 Hz, H_{5ax}), 1.57-1.70 (complex m, 2 H, H_{5eq} and H_{4eq}), 1.91 (ddddt, 1 H, H_{3ax}), 2.19-2.34 (complex m, 2 H, H_{2eq} and H_{6eq}), 2.66 (d, 2 H, ³J_{ArCH,3ax} 7.2 Hz, ArCH₂), 3.35 (d, 1 H, 2 <u>J</u> 11.4 Hz, H_{3a}" or H_{1a}"), 3.41 (d, 1 H, H_{3b}" or H_{1b}"), 3.50 (s, 2 H, H₁" or H₃"), 7.03 (ddd, 1 H, 3 <u>J</u>_{4',3'} 7.8, 3 <u>J</u>_{4',5'} 6.6, 4 <u>J</u>_{4',6'} 2.5 Hz, H₄'), 7.16 (dd, 1 H overlapping with H₅', H₆'), 7.20 (ddd, 1 H overlapping with H₆', H₅'), 7.51 (dd, 1 H, 4 <u>J</u>_{3',5'} 1.1 Hz, H₃') ppm; δ_{C} (75.5 MHz, CDCl₃, TMS) 21.8 (C5), 22.8 (2 x CH₃), 30.1 (C2"), 32.0 (C2 or C6), 32.4 (C2 or C6), 34.6 (C3), 38.6 (C4), 43.0 (Ar<u>C</u>H₂), 69.7 (C1" or C3"), 69.9 (C1" or C3"), 98.0 (C1), 124.9 (C2'), 127.0 (C5'), 127.4 (C4'), 131.2 (C6'), 132.7 (C3'), 140.0 (C1') ppm; m/z (CI⁺) 353/355 (<u>MH</u>⁺, 95%), 273 (<u>M</u>-Br, 18%), 183 (<u>M</u>-C₇H₇Br, 100%), 141 (37%), 129 (6%); (Found: <u>MH</u>⁺, 353.1116. C₁₈H₂₅BrO₂ requires <u>MH</u>⁺, 353.1116).

3.3.26 Reaction of Cyclohex-2-en-1-one with 2-Chlorobenzylmagnesium bromide



The Grignard reagent, 2-chlorobenzylmagnesium bromide was prepared by the dropwise addition of 2-chlorobenzyl bromide (3.53 g, 17.17 mmol) in diethyl ether (10 cm³) to magnesium turnings (0.67 g, 27.69 mmol) just covered with diethyl ether. The reaction was carried out under a nitrogen atmosphere. After stirring for 1h at RT, cyclohex-2-en-1-one (1.32g, 13.73 mmol) was added and the reaction mixture was heated at reflux temperature for 2h. A saturated aqueous solution of ammonium chloride (50 cm³) was added and the product was extracted into diethyl ether (2 x 100 cm³). The organic phase was dried (MgSO₄) and the solvent was evaporated under reduced pressure. Column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:7) afforded a 99:1 mixture of 3-(2-chlorobenzyl)cyclohexanone

(212):1-(2-chlorobenzyl)cyclohex-2-en-1-ol (2.23 g, 10.02 mmol, 73%) as a clear, colourless oil. Pure 3-(2-chlorobenzyl)cyclohexanone (212) was obtained by kugelröhr distillation (150 °C, 0.1 mm Hg) as a clear, colourless oil (Found: C, 69.75; H, 7.09; Cl, 16.07. C₁₃H₁₅ClO requires C, 70.11; H, 6.79; Cl, 15.92%); <u>R</u>_F (dichloromethane) 0.45; glc (BP 10; 240 °C; attenuation 32; air, 0.53 kg/cm²; He, 0.99 kg/cm²; H₂, 0.92 kg/cm²) 7.37 min; v_{max} (film) 3060 w (Ar-H, C-H str.), 2930 s and 2860 s (C-H str.), 1700 s (C=O str.), 1590 w and 1570 w (Ar ring vib.), 1470 m and 1440 m (C-H def.),1220 m, 1050 m cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.43 (qd, 1 H, H_{4ax}), 1.60 (qdd, 1 H, 3 <u>J</u> 3.0, 3 <u>J</u> 5.0, 2 <u>J</u>_{5ax,5eq} = 3 <u>J</u>_{5ax,6ax} = 3 <u>J</u>_{5ax,4ax} 12.2 Hz, H_{5ax}), 1.88 (complex m, 1 H, H_{4eq}), 2.10-2.40 (complex m, 6 H, H_{2ax}, H_{2eq}, H_{3ax}, H_{5eq} , H_{6ax} and H_{6eq}), 2.70 and 2.77 (AB part of an ABX pattern, 2 H, ${}^{3}J_{Ha,3}$ 6.6,³J_{Hb,3} 6.7, ²J_{Ha,Hb} 13.3 Hz, ArCH_aH_b), 7.16 (complex m, 3 H, H₄', H₅' and H_{6'}), 7.53 (dd. 1 H, 4 <u>J</u>_{3',5'} 1.9, 3 <u>J</u>_{3',4'} 7.4 Hz, H_{3'}) ppm; δ_{C} (75.5 MHz, CDCl₃, TMS) 25.0 (C5), 30.9 (C4), 39.3 (C3), 40.3 (ArCH₂),41.3 (C6), 47.6 (C2), 126.6 (C5'), 127.6 (C4'), 129.5 (C3'), 131.2 (C6'), 134.0 (C2'), 137.1 (C1'), 211.0 (C1) ppm; m/z (EI+) 221 (M-H+, 11%), 187 (M-Cl, 28%), 172 (21%), 141 (79%), 125 (ClC₆H₄CH₂, 20%) 97 (<u>M</u>-ClC₆H₄CH₂, 100%).

3.3.27

Reaction of Cyclohex-2-en-1-one with 2-Fluorobenzylmagnesium

bromide



2-Fluorobenzylmagnesium bromide was prepared by the dropwise addition of 2fluorobenzyl bromide (2.46 g, 13.01 mmol) in dry diethyl ether (10 cm³) to magnesium turnings (0.51 g, 20.98 mmol) covered by diethyl ether under a nitrogen atmosphere. After stirring for 1 h at RT, cyclohex-2-en-1-one (1.00 g, 10.40 mmol) in diethyl ether (10 cm³) was added and the reaction mixture was heated at reflux temperature for 2 h. The reaction mixture was poured into saturated ammonium chloride solution (50 cm³) and the product mixture was extracted into diethyl ether (2 x 100 cm³), dried (MgSO₄) and the solvent was removed *in vacuo*. Column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:1) afforded a 59:41 mixture of 3-(2-fluorobenzyl)cyclohexan-1-one (213):1-(2fluorobenzyl)cyclohex-2-en-1-ol (215) as a clear, colourless oil (1.69 g, 8.17 mmol, 79%); g.l.c. (BP10; 240 °C; atten. 16; air, 0.53 kg/cm²; He, 0.99 kg/cm²; H₂, 0.92 kg/cm²) RT (area %) 3.26 (21.7%), 3.68 (18.6%), 5.02 (59%) min. The components were separated by column chromatography (silica, 60 mesh, dichloromethane).

3-(2-fluorobenzyl)cyclohexan-1-one (213)

<u>R</u>_E (dichloromethane) 0.44; g.1.c.(BP10; 240 °C; atten. 16; air, 0.49 kg/cm²; He, 1.06 kg/cm²; H₂, 1.06 kg/cm²) RT (area %) 4.98 min; v_{max} (film) 3060 s (Ar-H, C-H str.), 2990 s, 2940 s and 2870 m (C-H str.), 1705 s (C=O str.), 1600 w, 1580 m and 1550 w (Ar ring vib.), 1490 s (C-H def.) cm⁻¹; δ_{H} (360 MHz, CDCl₃, TMS) 1.41 (qd, 1 H, ²J_{4ax,4eq} = ³J_{4ax,3ax} = ³J_{4ax,5ax} 12.3 Hz, H_{4ax}), 1.62 (qdd, 1 H, ³J 1.2, ³J 3.6, ²J_{5ax,5eq} = ³J_{5ax,6ax} 12.3 Hz, H_{5ax}), 1.89 (m, 1 H, H_{4eq}), 2.02-2.12 (complex m, 3 H, H_{2ax}, H_{3ax} and H_{6ax}), 2.21-2.40 (complex m, 3 H, H_{2eq}, H_{5eq} and H_{6eq}), 2.64 and 2.69 (AB part of ABX₂, 2 H, ³J_{x,3ax} 5.4, ³J_{y,3ax} 5.6, ²J_{x,y} 13.4 Hz, ArCH_xH_y), 6.99 (dd, 1 H, ⁴J_{3',5'} 1.0, ³J_{3',4'} 9.6 Hz, H_{3'}), 7.05 (td, 1 H, ³J_{5',4'} = ³J_{5',6'} 7.4 Hz, H_{5'}), 7.09-7.22 (complex m, 2 H, H_{4'} and H_{6'}) ppm; δ_{C} (90.5 MHz, CDCl₃, TMS) 25.1 (C5), 31.0 (C4), 35.9 (ArCH₂), 39.9 (C3), 41.3 (C6), 47.7 (C2), 115.3 (d, J_{F,3'} 22.5 Hz, C3'), 123.9 (d, J_{F,5'} 3.6 Hz, C5'), 126.5 (d, J_{F,1'} 20.0 Hz, C1'), 128.0 (d,

<u>J_{F,4'} 8.1 Hz, C4'</u>), 131.3 (d, <u>J_{F,6'} 4.7 Hz, C6'</u>), 161.3 (d, <u>J_{F,2'} 245.0 Hz, C2'</u>), 211.2 (C1) ppm; m/z (EI⁺) 206 (<u>M</u>⁺, 14%), 186 (<u>M</u>-HF, 20%), 148 (52%), 109 (C₇H₆F, 52%), 97 (C₆H₉O, 90%); (Found: <u>M</u>⁺, 206.1027. C₁₃H₁₅FO requires <u>M</u>⁺ 206.1107).

1-(2-fluorobenzyl)cyclohex-2-en-1-ol (215)

RF (dichloromethane) 0.23; g.l.c.(BP10; 240 °C; atten. 16; air, 0.53 kg/cm²; He, 0.99 kg/cm²; H₂, 0.92 kg/cm²) RT (area %) 3.23 (55.7%), 3.63 (44.3%) min [the compound decomposes on the glc column to give a mixture of dienes]; v_{max} (film) 3460 br. w. (O-H str.), 3050 s (Ar-H, C-H str.), 2990-2800 s (C-H str.), 1600 w and 1580 w (Ar ring vib.), 1490 s (C-H def.), 1440 s, 1420 s, 1380 s cm⁻¹; $\delta_{\rm H}$ (360 MHz, CDCl₃, TMS) 1.54 (br. s, 1 H, OH), 1.53-1.74 (complex m, 4 H, H_{4ax}, H_{5ax}, H_{5eq} and H_{6ax}), 1.91-2.03 (complex m, 2 H, H_{4eq} and H_{6eq}), 2.89 and 2.91 (AB quartet, 2 H, ${}^{2}J_{x,y}$ 13.5 Hz, ArCH_xH_y), 5.62 (d, 1 H, ${}^{3}J_{2,3}$ 10.0 Hz, H₂), 5.82 (dt, 1 H, ${}^{3}J_{3,4ax} = {}^{3}J_{3,4eq}$ 3.7 Hz, H₃), 7.02 (dd, 1 H, ${}^{4}J_{3',5'}$ 1.0 Hz, ${}^{3}J_{3',4'}$ 8.6 Hz, H_{3'}), 7.07 (td, 1 H, ${}^{3}J_{5',4'} = {}^{3}J_{5',6'}$ 7.5 Hz, H_{5'}), 7.18-7.32 (complex m, 2 H, H_{4'} and H_{6'}) ppm; δ_C (90.5 MHz, CDCl₃, TMS) 19.0 (C4), 25.2 (C5), 35.5 (C6), 40.6 (ArCH₂), 70.0 (C1), 115.2 (d, J_{F3'} 23.0 Hz, C3'), 123.6 (d, J_{F5'} 3.4 Hz, C5'), 124.0 (d, J_{F1'} 15.8 Hz, C1'), 128.19 (d, J_{F.4}' 8.2 Hz, C4'), 128.24 (C2), 131.9 (C3), 133.0 (d, J_{F,6}' 4.7 Hz, C6'), 161.6 (d, J_{F,2}' 244.5 Hz, C2') ppm; m/z (EI+) 206 (M+, 25%), 188 (M-H₂O, 62%), 148 (21%), 109 (C₇H₆F, 83%), 97 (C₆H₉O, 100%), 79 (C₆H₇+, 89%); (Found: <u>M</u>⁺, 206.1086. $C_{13}H_{15}FO$ requires <u>M</u>⁺ 206.1107).



Benzylmagnesium bromide was prepared by the dropwise addition of benzyl bromide (2.22 g, 12.98 mmol) in dry diethyl ether (10 cm³) to magnesium turnings (0.50 g, 20.77 mmol) covered by diethyl ether under a nitrogen atmosphere. After stirring at RT for 1 h, cyclohex-2-en-1-one (1.00 g, 10.40 mmol) in diethyl ether (5 cm³) was added and the reaction mixture was heated at reflux temperature for 3 h. An aqueous solution of saturated ammonium chloride (50 cm³) was added and the product mixture was extracted into diethyl ether (2 x 100 cm³). The organic phase was dried (MgSO₄) and solvent removed *in vacuo*. Column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:1) afforded a 64.4:35.6 mixture of 3-benzylcyclohexan-1-one (**214**):1-benzylcyclohex-2-en-1-ol (**216**) as a clear, colourless oil (1.48 g, 7.89 mmol, 76%). g.l.c. (BP10; 240 °C; atten. 16; air, 0.49 kg/cm²; He, 1.06 kg/cm²; H₂, 1.06 kg/cm²) RT (area %) 3.30 (23.9%), 3.69 (1.7%), 3.77 (12.0%), 5.15 (62.4%) min.

Analytical samples were separated by column chromatography (silica, 60 mesh, dichloromethane).

3-benzylcyclohexan-1-one (214)

<u>R</u>_F (dichloromethane) 0.36; g.l.c.(BP10; 240 °C; air, 0.49 kg/cm²; He, 1.06 kg/cm²; H₂, 1.06 kg/cm²) RT (area %) 5.17 min; v_{max} (film) 3050 s (Ar-H, C-H str.), 2980 s, 2940 m and 2880 m (C-H str.), 1705 s (C=O str.), 1600 w and 1550 w (Ar ring vib.), 1440 s (C-H def.) cm⁻¹; $\delta_{\rm H}$ (360 MHz, CDCl₃, TMS) 1.36 (m, 1 H, H_{4ax}), 1.66 (m, 1 H, H_{5ax}), 1.88 (m, 1 H, H_{4eq}), 1.99-2.12 (complex m, 3 H, H_{2ax}, H_{3ax} and H_{6ax}), 2.20-2.40 (complex m, 3 H, H_{2eq}, H_{5eq} and H_{6eq}), 2.59 and 2.66 (AB part of ABX₂, 2 H, ${}^{3}J_{x,3ax}$ 6.5 Hz, ${}^{3}J_{y,3ax}$ 6.8 Hz, ${}^{2}J_{x,y}$ 13.0 Hz, ArCH_xH_y), 7.12 (d, 2 H, ${}^{3}J$ 7.4 Hz, H_o), 7.20 (t, 1 H, ${}^{3}J$ 7.4 Hz, H_p), 7.26 (t, 2 H, H_m) ppm; δ_{C} (90.5 MHz, CDCl₃, TMS) 25.1 (C5), 30.9 (C4), 40.9 (C3), 41.4 (C6), 43.0 (ArCH₂), 47.9 (C2), 120.2 (C_p), 128.3 (C_m), 129.1 (C_o). 139.4 (C'), 211.5 (C1) ppm; m/z (EI⁺) 189 (<u>MH</u>⁺, 100%), 109 (18%), 97 (C₆H₉O, 72%); (Found: <u>M</u>⁺, 188.1223. C₁₃H₁₆O requires <u>M</u>⁺ 188.1201).

1-benzylcyclohex-2-en-1-ol (216)

<u>R</u>_E (dichloromethane) 0.24; g.l.c.(BP10; 240 °C; air, 0.53 kg/cm²; He, 0.99 kg/cm²; H₂, 0.92 kg/cm²) RT (area %) 3.28 (63.5%), 3.69 (4.5%), 3.74 (31.9%) min [sample dehydrates to give a mixture of dienes on the glc column]; v_{max} (film) 3460 br. w (O-H), 3050 s (Ar-H), 2990 s and 2940 s (C-H str.), 1600 w and 1550 w (C=C, Ar), 1440 s (R₃C-H def.) cm⁻¹; $\delta_{\rm H}$ (360 MHz, CDCl₃, TMS) 1.55 (br. s, 1 H, OH), 1.60-1.75 (complex m, 4 H, H₅ and H₆), 1.90-2.08 (complex m, 2 H, H₄), 2.83 (s, 2 H, ArCH₂), 5.60 (dt, 1 H, $^{4}J_{2,4}$ 2.1 Hz, $^{3}J_{2,3}$ 10.1 Hz, H₂), 5.81 (ddd, 1 H, $^{3}J_{3.2}$ Hz, $^{3}J_{3.7}$ Hz, H₃), 7.18-7.31 (complex m, 5 H, H_o, H_m and H_p) ppm; $\delta_{\rm C}$ (90.5 MHz, CDCl₃, TMS) 19.1 (C4), 25.2 (C5), 35.7 (C6), 48.2 (ArCH₂), 89.6 (C1), 126.4 (C_p), 128.0 (C_m), 129.9 (C3), 130.7 (C_o), 132.1 (C2), 137.0 (C') ppm; m/z (EI⁺) 189 (<u>MH</u>⁺, 100%), 109 (25%), 97 (C₆H₉O, 39%); (Found: <u>M</u>⁺, 188.1223. C₁₃H₁₆O requires <u>MH</u>⁺ 188.1201).

3.3.29 <u>Preparation of 3-(2-Chlorobenzyl)cyclohexan-1-one 2,2-</u> Dimethylpropylidene acetal (**217**)¹⁵¹



3-(2-Chlorobenzyl)cyclohexan-1-one (212) (2.00 g, 8.81 mmol), 2,2dimethylpropane-1,3-diol (1.10 g, 10.57 mmol) and pyridinium toluene-4-sulphonate (168 mg, 0.88 mmol) in toluene (100 cm³) were heated at reflux temperature in a Dean-Stark apparatus until the evolution of water had ceased, 6 h. Toluene was evaporated in vacuo and the residue was purified by column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:9) to yield the acetal (217) as a clear colourless oil (2.31 g, 7.49 mmol, 85%). RF (diethyl ether-petroleum ether b.r. 40-60 ^oC, 1:1) 0.64; (Found; C, 69.92; H, 8.65; Cl, 11.31. C₁₈H₂₅ClO₂ requires C, 70.0; H, 8.16; Cl, 11.48%); v_{max} (film) 3060 s (Ar-H, C-H str.), 2980 s and 2860 m (C-H str.), 1590 w and 1570 w (Ar ring vib.), 1470 s and 1440 s (C-H def.), 750 s (o-disubstituted Ar), 740 s (C-Cl str.) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 0.91 (s, 3 H, CH₃), 0.93 (s, 3 H, CH₃), 0.96 (qd, 1 H overlapping with CH₃ signals, ${}^{3}J_{4ax,5eq}$ 3.9 Hz, H_{4ax}), 1.07 (t, 1 H, ${}^{2}J_{2ax,2eg} = {}^{3}J_{2ax,3ax}$ 12.7 Hz, H_{2ax}), 1.22 (td, 1 H, ${}^{2}J_{6ax,6eq} = {}^{3}J_{6ax,5ax}$ 13.1, ${}^{3}J_{6ax,5eq}$ 4.0 Hz, H_{6ax}), 1.40 (qt, 1 H, ${}^{2}J_{5ax,5eq} = {}^{3}J_{5ax,4ax}$ $13.1, {}^{3}J_{5ax,4eq} = {}^{3}J_{5ax,6eq} 3.1 \text{ Hz}, H_{5ax}$, 1.55-1.70 (complex m, 2 H, H_{5eq} and H_{4eq}), 1.90 (ddddt, 1 H, H_{3ax}), 2.23-2.27 (complex m, 2 H, H_{2eq} and H_{6eq}), 2.65 (d, 2 H, 3 <u>J_{ArCH,3ax}</u> 7.2 Hz, ArC<u>H</u>₂), 3.34 (d, 1 H, 2 <u>J</u> 11.4 Hz, H_{3a}" or H_{1a}"), 3.42 (d, 1 H, H_{3b}" or H_{1b}"), 3.50 (s, 2 H, H₁" or H₃"), 7.08-7.19 (complex m, 3 H, H₄', H₅' and $H_{6'}$), 7.32 (dd, 1 H, ${}^{4}\underline{J}_{3',5'}$ 1.7, ${}^{3}\underline{J}_{3',4'}$ 6.9 Hz, $H_{3'}$) ppm; δ_{C} (75.5 MHz, CDCl₃,

TMS) 21.8 (C5), 22.8 (2 x CH₃), 30.1 (C2"), 32.0 (C2 or C6), 32.2 (C2 or C6), 34.6 (C3), 38.9 (C4), 40.5 (Ar<u>C</u>H₂), 69.7 (C1" or C3"), 69.9 (C1" or C3"), 98.0 (C1), 126.3 (C5'), 127.2 (C4'), 129.4 (C3'), 131.2 (C6'), 134.3 (C2'), 138.3 (C1') ppm; m/z (CI⁺) 309/311 (<u>MH</u>⁺, 100%), 273 (<u>M</u>-Cl, 8%), 183 (<u>M</u>-C₇H₇Cl, 29%), 141 (27%); (Found: <u>MH</u>⁺, 309.1621. C₁₈H₂₅ClO₂ requires <u>MH</u>⁺, 309.1621).

3.3.30 <u>Preparation of 3-(2-Fluorobenzyl)cyclohexan-1-one 2.2</u> Dimethylpropylidene acetal (218)¹⁵¹



3-(2-Fluorobenzyl)cyclohexanone (213) (500 mg, 2.25 mmol), 2,2-dimethylpropane-1,3-diol (258 mg, 2.47 mmol) and a catalytic amount of pyridinium toluene-4sulphonate were heated at reflux temperature in toluene (100 cm^3) in a Dean-Stark apparatus. After evolution of water had ceased, 8h, toluene was removed under reduced pressure and the residue was purified by column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:9). This yielded the acetal (218) (596 mg, 1.94 mmol, 86%), as a clear colourless oil. <u>R</u>F (diethyl ether-petroleum ether b.r. 40-60 °C, 1:1) 0.53; v_{max} (film) 3020 s (Ar-H, C-H str.), 2940 s and 2860 s (C-H str.), 1610 w, 1580 w and 1490 w (Ar ring vib.), 1470 s and 1450 s (C-H def.), 760 s (o-disubstituted Ar) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 0.90 (s, 3 H, C<u>H</u>₃), 0.93 (s, 3 H, CH₃), 0.95 (qd, 1 H overlapping with CH₃ signals, ³J_{4ax,5eq} 3.1 Hz, H_{4ax}), 1.05 (t, 1 H, ${}^{2}J_{2ax,2eq} = {}^{3}J_{2ax,3ax}$ 12.7 Hz, H_{2ax}), 1.18 (td, 1 H, ${}^{2}J_{6ax,6eq} =$ 3 <u>J</u>_{6ax,5ax} 13.1, 3 <u>J</u>_{6ax,5eq} 4.0 Hz, H_{6ax}), 1.39 (qt, 1 H, 2 <u>J</u>_{5ax,5eq} = 3 <u>J</u>_{5ax,4ax} 13.1, 3 J_{5ax,4eq} = 3 J_{5ax,6eq} 3.4 Hz, H_{5ax}), 1.54-1.66 (complex, 2 H, H_{5eq} and H_{4eq}), 1.85 (ddddt, 1 H, H_{3ax}), 2.20-2.56 (complex m, 2 H, H_{2eq} and H_{6eq}), 2.55 (d, 2 H, 3 <u>JArCH,3ax</u> 7.1 Hz, ArC<u>H</u>₂), 3.33 (d, 1 H, 2 <u>J</u> 10.6 Hz, H_{3a}" or H_{1a}"), 3.42 (d, 1 H, H_{3b}" or H_{1b}"), 3.46 (d, 1 H, ²J 11.7 Hz, H_{1a}" or H_{3a}"), 3.49 (d, 1 H, H_{1b}" or H_{3b}"), 6.93-7.25 (complex m, 4 H, H₃', H₄', H₅' and H₆') ppm; δ_{C} (75.5 MHz, CDCl₃,

TMS) 21.8 (C5), 22.7 (CH₃), 22.8 (CH₃), 30.0 (C2"), 31.7 (C2 or C6), 31.9 (C2 or C6), 34.9 (C3), 35.9 (C4), 39.2 (Ar<u>C</u>H₂), 69.7 (C1" or C3"), 69.8 (C1" or C3"), 98.0 (C1), 115.0 (d, $J_{F,3'}$ 22.6 Hz, C3'), 123.6 (d, $J_{F,5'}$ 3.4 Hz, C5'), 127.3 (d, $J_{F,1'}$ 16.5 Hz, C1'), 127.4 (d, $J_{F,6'}$ 8.0 Hz, C6'), 131.4 (d, $J_{F,4'}$ 5.1 Hz, C4'), 161.2 (d, $J_{F,2'}$ 244.2 Hz, C2') ppm; m/z (CI+) 293 (MH+, 100%), 183 (M-C₇H₇F, 13%), 141 (8%); (Found: MH+, 292.183 9. C₁₈H₂₅FO₂ requires MH+, 292.183 9).

3.3.31 <u>Preparation of 3-Benzylcyclohexan-1-one 2,2-Dimethylpropylidene</u> acetal (219)¹⁵¹



The 64.4:35.6 mixture of 3-benzylcyclohexanone (214):1-benzylcyclohexen-1-ol (216) (300 mg, 1.59 mmol), 2,2-dimethylpropane-1,3-diol (183 mg, 1.75 mmol) and a catalytic amount of pyridinium toluene-4-sulphonate were heated at reflux temperature in toluene (50 cm³) in a Dean-Stark apparatus. When evolution of water had ceased, 8h, toluene was evaporated under reduced pressure. The residue was purified by column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:9) afforded the <u>acetal</u> (219) as a clear colourless oil (227 mg, 0.83 mmol, 81% based on % of ketone (214) present in the mixture); <u>RF</u> (diethyl ether-petroleum ether b.r. 40-60 °C, 1:1) 0.48; v_{max} (film) 3010 s (Ar-H, C-H str.), 2 940 s and 2 860 s (C-H str.), 1 600 w, 1 580 w and 1 490 w (Ar ring vib.), 1 450 s (C-H def.), 750 s (*o*-disubstituted Ar) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 0.86 (qd, 1 H overlapping with

CH₃ signals, ${}^{3}J_{4ax,5eq}$ 3.1 Hz, H_{4ax}), 0.91 (s, 3 H, C<u>H</u>₃), 0.93 (s, 3 H, C<u>H</u>₃), 1.02 (t, 1 H, ${}^{2}J_{2ax,2eq} = {}^{3}J_{2ax,3ax}$ 12.6 Hz, H_{2ax}), 1.18 (td, 1 H, ${}^{2}J_{6ax,6eq} = {}^{3}J_{6ax,5ax}$ 13.2, ${}^{3}J_{6ax,5eq}$ 4.1 Hz, H_{6ax}), 1.38 (qt, 1 H, ${}^{2}J_{5ax,5eq} = {}^{3}J_{5ax,4ax}$ 13.2, ${}^{3}J_{5ax,4eq} = {}^{3}J_{5ax,6eq}$ 3.3 Hz, H_{5ax}), 1.55-1.65 (complex m, 2 H, H_{5eq} and H_{4eq}), 1.82 (dddddd, 1 H, H_{3ax}), 2.20-2.30 (complex, 2 H, H_{2eq} and H_{6eq}), 2.46 (dd, 1 H, ${}^{2}J_{13.3}$, ${}^{3}J_{ArCHa,3ax}$ 7.7 Hz, ArC<u>Ha</u>CH_b), 2.55 (dd, 1 H, ${}^{3}J_{ArCHb,3ax}$ 6.6 Hz, ArCHa<u>CH_b</u>), 3.33 (d, 1 H, ${}^{2}J_{11.0}$ Hz, H_{3a}" or H_{1a}"), 3.42 (d, 1 H, H_{3b}" or H_{1b}"), 3.45 (d, 1 H, ${}^{2}J_{11.3}$ Hz, H_{1a}" or H_{3a}"), 3.52 (d, 1 H, H_{1b}" or H_{3b}"), 7.10-7.28 (complex m, 5 H_o, H_m and H_p in PhCH₂) ppm; δ_{C} (75.5 MHz, CDCl₃, TMS) 21.8 (C5), 22.7 (CH₃), 22.8 (CH₃), 30.1 (C2"), 31.8 (C2 or C6), 32.0 (C2 or C6), 35.7 (C3), 39.3 (C4), 43.4 (ArCH₂), 69.7 (C1" or C3"), 69.8 (C1" or C3"), 98.1 (C1), 125.7 (C_p), 128.0 (C_o), 129.1 (C_m), 140.5 (C') ppm; m/z (CI⁺) 275 (<u>MH</u>⁺, 100%), 183 (<u>M</u>-C₇H₈, 13%), 141 (7%); (Found: <u>M</u>⁺, 274.193 3. C₁₈H₂₆O₂ requires <u>M</u>⁺, 274.193 3).

3.3.32 <u>Preparation of 3-(2-Fluorobenzyl)cyclohexanone (213)</u>²²¹



2-Fluorobenzylmagnesium bromide was prepared by the dropwise addition of 2fluorobenzylbromide (2.46 g, 13.03 mmol) in diethyl ether (10 cm^3) to magnesium turnings (0.51 g, 20.99 mmol) in diethyl ether (5 cm^3). The reaction mixture was cooled to -78 °C (acetone/Cardice) for 20 min. Copper (1) cyanide (2.26 g, 25.28 mmol) was added in one portion. The internal temperature of the reaction was allowed to warm slowly, under a nitrogen atmosphere, to -30 °C over 90 min. 2-Cyclohexen-1-one (1.00 g, 10.38 mmol) in diethyl ether (20 cm³) was added dropwise to the cuprate at -30 °C and stirring was continued at this temperature for a further 30 min. A solution of saturated ammonium chloride (30 cm³) in water (30 cm³) was added dropwise to the reaction mixture over 20 min and stirring was continued for a further 90 min. The reaction mixture was filtered and the filtrate was extracted with diethyl ether. The organic phase was dried (MgSO₄) and the diethyl ether was removed *in vacuo*. Column chromatography (silica, 60 mesh, diethyl etherpetroleum ether b.r. 40-60 °C, 2:3) afforded the <u>ketone</u> (213) as a clear colourless oil (1.97 g, 9.55 mmol, 92%); <u>R_F</u> (dichloromethane) 0.44; g.l.c.(BP10; 240 °C; atten. 16; air, 0.49 kg/cm²; He, 1.06 kg/cm²; H₂, 1.06 kg/cm²) RT (area %) 4.99 min; ¹H and ¹³C data corresponded to those of 3-(2-Fluorobenzyl)cyclohexanone (213) in experiment 3.3.27.

3.3.33Preparation of 3-(2-Fluorobenzyl)cyclohexanone (213) from 2-Fluorobenzylmagnesium bromide and Copper (1) Iodide²²¹



2-Fluorobenzylmagnesium bromide was prepared by the dropwise addition of 2fluorobenzylbromide (2.46 g, 13.02 mmol) covered in diethyl ether (10 cm^3) to magnesium turnings (0.51 g, 20.99 mmol) in diethyl ether (5 cm^3). The reaction mixture was cooled to -78 °C (acetone/Cardice) for 20 min and the copper (1) iodide (4.82 g, 25.31 mmol) was added in one portion. The internal temperature of the reaction was allowed to warm slowly, under a nitrogen atmosphere, to -30 °C over 90 min. 2-Cyclohexen-1-one (1.00 g, 10.38 mmol) in diethyl ether (20 cm^3) was added dropwise to the cuprate at -30 °C and stirring was continued at this temperature for a further 30 min. A solution of saturated ammonium chloride (30 cm³) in water (30 cm³) was added dropwise to the reaction mixture over 20 min and stirring was continued for a further 90 min. The reaction mixture was filtered and the filtrate was extracted with diethyl ether. The organic phase was dried (MgSO₄) and the diethyl ether was removed *in vacuo*. Column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 2:3) afforded the ketone (213) as a clear colourless oil (1.91 g, 9.24 mmol, 89%); $R_{\rm E}$ (dichloromethane) 0.44; g.l.c.(BP10; 240 °C; atten. 16; air, 0.49 kg/cm²; He, 1.06 kg/cm²; H₂, 1.06 kg/cm²) RT (area %) 4.96 min; ¹H and ¹³C data corresponded to those of 3-(2-Fluorobenzyl)cyclohexanone (213) in experiment 3.3.27.

3.3.34 Reaction of 3-(2-Brombenzyl)cyclohexan-1-one (204) with O Methylhydroxylamine hydrochloride



3-(2-Brombenzyl)cyclohexan-1-one (204) (730 mg, 2.73 mmol), O-

methylhydroxylamine hydrochloride (274 mg, 3.28 mmol) and pyridine (432 mg, 5.46 mmol) were stirred at RT in methanol (10 cm^3) overnight. Methanol was evaporated *in vacuo*, the residue was diluted with water (20 cm^3) and the aqueous solution

extracted with diethyl ether (2 x 50 cm³). The organic phases were dried (MgSO₄) and solvent removed under reduced pressure. The product was purified by column chromatography (silica, 60 mesh, dichloromethane) to afford a clear colourless oil (663 mg). The product was found to be a 1:2 mixture of 3-(2-brombenzyl)cyclohexan-1- one dimethyl acetal (221):E and Z isomers of 3-(2-brombenzyl)cyclohexan-1-one O- methyloxime (220). ¹H and ¹³C nmr data corresponded to those of authentic samples prepared in experiments 3.3.35 and 3.3.36.





3-(2-Bromobenzyl)cyclohexan-1-one (204) (200 mg, 0.75 mmol) and a catalytic amount of pyridinium toluene-4-sulphonate were heated at reflux temperature in methanol (20 cm³) for 2 h. Methanol was evaporated under reduced pressure and the product was purified by column chromatography (silica, 60 mesh, diethyl etherpetroleum ether b.r. 40-60 °C, 1:4). This gave the <u>acetal</u> (221) as a clear colourless oil (195 mg, 0.62 mmol, 83%); <u>R</u>_E (diethyl ether-petroleum ether b.r. 40-60 °C, 3:7) 0.57; v_{max} (film) 3060 s (Ar-H, C-H str.), 2920 s and 2860 m (C-H str.), 2810 s (C-H str. of O-CH₃), 1600 w and 1565 w (Ar ring vib.), 1470 s and 1440 s (C-H def.), 750 s (*o*-disubstituted Ar) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 0.97 (qd, 1 H, ³J_{4ax,5eq} 3.8, ²J_{4ax,4eq} = ³J_{4ax,3ax} = ³J_{4ax,5ax} 12.2 Hz, H_{4ax}), 1.07 (t, 1 H, ²J_{2ax,2eq} = ³J_{2ax,3ax} 12.7 Hz, H_{2ax}), 1.22 (ddd, 1 H, ³J_{5ax,6eq} 3.9, ³J_{6ax,5ax} 12.5, ²J_{6ax,6eq} 13.5 Hz, H_{6ax}), 1.37 (dddt, 1 H, ³J_{5ax,4eq} = ³J_{5ax,6eq} 3.4, ²J_{5ax,5eq} 13.0 Hz, H_{5ax}), 1.65 (complex m, 2 H, H_{5eq} and H_{4eq}), 1.87 (ddddt, 1 H, H_{3ax}), 2.03 (complex m, 2 H, H_{2eq} and H_{6eq}), 2.66 (d, 2 H, ${}^{3}J_{ArCH,3ax}$ 7.2 Hz, ArCH₂), 3.05 (s, 3 H, OCH₃), 3.17 (s, 3 H, OCH₃), 7.02 (ddd, 1 H, ${}^{4}J_{4',6'}$ 2.3, ${}^{3}J_{4',5'}$ 7.6, ${}^{3}J_{4',3'}$ 8.0 Hz, H_{4'}), 7.15 (dd, 1 H, ${}^{3}J_{6',5'}$ 7.6 Hz, H_{6'}), 7.19 (td, 1 H, ${}^{4}J_{5',3'}$ 1.2 Hz, H_{5'}), 7.51 (dd, 1 H, H_{3'}) ppm; δ_{C} (75.5 MHz, CDCl₃, TMS) 22.2 (C5), 32.0 (C6), 32.6 (C2), 34.9 (C3), 38.4 (C4), 43.1 (Ar<u>C</u>H₂), 47.3 (OCH₃), 47.4 (OCH₃), 100.3 (C1), 124.8 (C2'), 127.0 (C5'), 127.5 (C4'), 131.2 (C6'), 132.8 (C3'), 140.0 (C1') ppm; m/z (EI+) 281/283 (M - OCH₃, 12%), 233 (M - Br, 3%), 201 (M - Br and CH₃OH, 33%), 187 (M - Br, CH₃ and CH₃O, 5%), 169 (M - Br and 2 x CH₃OH, 12%), 143 (C₈H₁₅O₂,35%), 111 (C₇H₁₁O, 25%), 91 (C₇H₇, 11%), 70 (12%), 69 (C₄H₅O, 9%); (Found: <u>M</u>+, 312.0725. C₁₅H₂₁BrO₂ requires <u>M</u>+, 312.0725).

3.3.36 <u>Preparation of 3-(2-Bromobenzyl)cyclohexan-1-one O-methyloxime</u> (220)



3-(2-Bromobenzyl)cyclohexan-1-one (204) (230 mg, 0.86 mmol) and Omethylhydroxylamine hydrochloride (90 mg, 1.03 mmol) were stirred at RT in pyridine (2 cm³) overnight. Pyridine was removed under reduced pressure and the residue purified by column chromatography (silica, 60 mesh, dichloromethane). This afforded a mixture of E and Z isomers of the <u>oxime ether</u> (220) as a clear colourless oil (242 mg, 0.82 mmol, 95%). The product was characterised as a mixture of E and Z isomers. <u>R_F</u> (dichloromethane) 0.50 and 0.43; v_{max} (film) 3050 w (Ar-H, C-H str.), 2900 m, 2940 s and 2860 s (C-H str.), 2810 m (O-CH₃, C-H str.), 1635 w (C=N str.), 1590 w, 1570 w and 1560 w (Ar ring vib.), 1470 s and 1440 s (C-H def.), 750 s (*o*-disubstituted Ar ring) cm⁻¹; $\delta_{\rm H}$ (360 MHz, CDCl₃, TMS) 1.23-2.05 (complex m, 14 H, H_{2ax}, H_{3ax}, H4, H5, and H_{6ax} in both isomers), 2.31-2.39 (complex m, 2 H, H_{2eq} or H_{6eq} in both isomers), 2.65-2.79 (complex m, 4 H, ArCH_aH_b in both isomers), 3.07-3.12 (complex m, 2 H, H_{2eq} or H_{6eq} in both isomers), 3.792 (s, 3 H, OCH₃), 3.798 (s, 3 H, OCH₃), 7.02-7.08 (complex m, 2 H, H_{4'} in both isomers), 7.13-7.16 (complex m, 4 H, H_{5'} and H_{6'} in both isomers), 7.50-7.54 (complex m, 2 H, H_{3'} in both isomers) ppm; $\delta_{\rm C}$ (90.5 MHz, CDCl₃, TMS) 24.4 (C5 in isomer A), 24.8 (C4 in A), 25.4 (C5 in B), 30.9 (C4 in B), 31.6 (C6 in A), 31.9 (C2 in A), 32.0 (C6 in B), 37.5 (C3 in A and B), 37.9 (C2 in B), 38.8 (CH₃ in A), 42.8 (ArCH₂ in B), 42.9 (ArCH₂ in A), 61.0 (CH₃ in B), 125.0 (C2' in B), 125.1 (C2' in A), 127.1 (C5' in A and B), 127.7 (C4' in A and B), 131.3 (C6' in A and B), 132.9 (C3' in A and B), 159.5 (C1' in A), 139.7 (C1' in B), 159.1 (C=N in B), 159.8 (C=N in A) ppm; m/z (CI+ 295/297 (M+, 15%), 264/266 (M-OCH₃), 216 (M-Br, 100%), 169/171 (BrC₆H₄CH₂, 62%), 126 (36%), 87 (100%).

 3.3.37
 Attempted cyclisation of 3-(2-Bromobenzyl)cyclohexan-1-one O

 methyloxime (220) with Tributyltin Hydride



3-(2-Bromobenzyl)cyclohexan-1-one O-methyloxime (220) (180 mg, 0.61 mmol) and tributyltin hydride (354 mg, 1.22 mmol) were dissolved in dry benzene (30.5 cm³, 0.02 M dilution of (220))and the solution degassed for 1 h. The solution was heated to reflux temperature under a nitrogen atmosphere and the AIBN (20 mg, 0.12 mmol)

in benzene (10 cm³) was added over 8 h. Heating was continued for a further 10 h. Benzene was evaporated *in vacuo* but a tlc of the reaction mixture revealed a number of products that could not be isolated. ¹H nmr of the crude mixture did not reveal any peaks that could be associated with the desired product.

3.3.38 <u>Attempted cyclisation of 3-(2-Bromobenzyl)cyclohexan-1-one O-</u> methyloxime (220) with Hexabutlyditin¹⁹⁴⁻¹⁹⁷



3-(2-Bromobenzyl)cyclohexan-1-one O-methyloxime (220) (425 mg, 1.44 mmol) and hexabutylditin (833 mg, 1.44 mmol) were dissolved in benzene (28.8 cm³, 0.05 M dilution) and placed in a Pyrex irradiation vessel. The solution was degassed for 1 h. The vessel was placed in the Rayonet Photochemical Reactor and kept under a nitrogen atmosphere. The reaction was irradiated for 2 h with light having a wavelength of 350 nm (blue tubes) with cooling of the reactor. T.1.c. revealed no reaction so the tubes were replaced by ones having a wavelength of 300 nm (white tubes). The reaction was irradiated for a further 2 h with cooling. Benzene was evaporated under reduced pressure and the residue purified by column chromatography (silica, 60 mesh, dichloromethane). The ¹H nmr spectrum revealed starting material.

3.4.1 <u>Preparation of 2-(3-Bromobut-3-en-1-oxy)benzaldehyde O-(2-menthyl-2-oxyethyl)oxime (225)</u>[†]



2-(3-Bromobut-3-en-1-oxy)benzaldehyde oxime (137) (500 mg, 1.95 mmol) in dry THF (1 cm³) was added dropwise to a suspension of sodium hydride (56 mg, 2.34 mmol, 80% dispersion in mineral oil) in dry THF (10 cm³) and DMPU (300 mg, 2.34 mmol). The solution was stirred at RT for 1h and chloromethylmenthyl ether (600 mg, 2.93 mmol) was added. Stirring was continued at RT for 1h and the reaction mixture was then quenched with water and the crude product was extracted into diethyl ether. The organic phase was dried (MgSO₄) and the solvent was evaporated under reduced pressure. Column chromatography of the residue (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:9) afforded the oxime ether (225) as a clear, colourless oil (678 mg, 1.60 mmol, 82%); RF (diethyl ether-petroleum ether b.r. 40-60 °C, 1:1) 0.35; $[\alpha]_D$ -64° (c. 6.5, CH₂Cl₂); v_{max} (film) 3060 w (Ar-H and C=C-H, C-H str.), 2940 s, 2910 s and 2860 s (C-H str.), 1635 w (C=N str.), 1600 m, 1570 w and 1560 w (Ar ring vib.), 1480 m and 1450 s (C-H str.), 750 s (o-disubstituted Ar) cm⁻¹; δ_H (300 MHz, CDCl₃, TMS) 0.71-1.04 (complex m, 12 H, H₆", H₇", H₈",H₉" and H_{10"}), 1.17-1.42 (complex m, 2 H, H_{1"} and H_{4"}), 1.62 (complex m, 2 H, H_{5"}), 2.08-2.28 (complex m, 2 H, H_{2"}), 3.47 (td, 1 H, ³J 4.2, ³J 10.6 Hz, H_{3"}), 4.64 (dd, 2 H, ${}^{4}J_{2',4'E}$ and ${}^{4}J_{2',4'Z} < 1.0$ Hz, H_{2'}), 5.26 and 5.30 (AB quartet, 2 H, ${}^{2}J$ 7.7 Hz, OCH₂O), 5.66 (dt, 1 H, ²J_{4'Z,4'E} 2.0 Hz, H_{4'Z}), 5.96 (dt, 1 H, H_{4'E}), 6.81 (d, 1 H,

³J_{3.4} 8.1 Hz, H₃), 6.97 (dd, 1 H, ³J_{5,4} 7.4, ³J_{5,6} 7.7 Hz, H₅), 7.29 (td, 1 H, ⁴J_{4,6} 1.6 Hz, H₄), 7.85 (dd, 1 H, H₆), 8.56 (s, 1 H, C<u>H</u>=N) ppm; $\delta_{\rm C}$ (75.5 MHz, CDCl₃, TMS) 15.8 (C7"), 21.1 (C10"), 22.3 (C9"), 23.1 (C6"), 25.0 (C8"), 31.5 (C1"), 34.4 (C5"), 41.3 (C2"), 48.1 (C4"), 71.9 (C2'), 77.6 (C3"), 95.9 (OCH₂O), 112.4 (C3), 118.0 (C4'), 121.1 (C1), 121.6 (C5), 126.6 (C3'), 126.8 (C4), 131.1 (C6), 145.5 (CH=N), 155.6 (C2) ppm; m/z (EI⁺) 424/426 (<u>MH⁺</u>, 2%), 256/258 (<u>M</u>-MenthOCH, 2%), 240/242 (<u>M</u>-MenthOCHO, 4%), 169 (MenthOCH₂, 8%), 139 (Menth, 48%), 97 (22%), 83 (100%), 69 (40%), 55 (58%); (Found: <u>MH⁺</u>, 424.1487. C₂₁H₃₄BrNO₃ requires <u>MH⁺</u>, 424.1487).

† Chloromethylmenthyl ether was prepared by David Dawkins, Leicester University.

3.4.2 Preparation of 4-(2-menthyl-2-oxyethoxyamino)chroman-3-ylidene (226)



2-(3-Bromobut-3-en-1-oxy)benzaldehyde O-(2-menthyl-2-oxyethyl) oxime (225) (250 mg, 0.59 mmol) and tributyltin hydride (206 mg, 0.71 mmol) were dissolved in benzene (30 cm³, 0.02 M dilution of (225)) and the solution degassed by bubbling a steady stream of nitrogen through it for 1 h. The solution was heated to reflux temperature under a nitrogen atmosphere and AIBN (20 mg, 0.12 mmol) in benzene (10 cm³) added over 10 h. Heating at reflux temperature was continued for a further 12 h. Benzene was evaporated *in vacuo* and the residue purified by column
chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) yielding a 1:1 mixture of diastereoisomers of the hydroxylamine (226) (159 mg, 0.46 mmol, 78%) as a pale yellow oil. <u>R</u>_F (diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) 0.47; v_{max} (film) 3200 br, w (N-H), 3010 w (Ar-H, C-H str.), 2960 m, 2920 w and 2860 w (C-H str.), 1650 (C=N str.), 1600 w, 1590 m and 1580 w (Ar ring vib.), 1480 m (C-H def.) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 0.68-1.04 (complex m, 24 H, $H_{6'}$, $H_{7'}$, $H_{8'}$, $H_{9'}$ and $H_{10'}$ in both diastereoisomers), 1.18-1.43 (complex m, 4 H, $H_{1'}$ and $H_{4'}$ in both diastereoisomers), 1.62 (complex m, 4 H, $H_{5'}$ in both diastereoisomers), 1.98-2.31 (complex m, 4 H, H_{2'} in both diastereoisomers), 3.29 (td, 1 H, ${}^{4}J$ 4.2, ${}^{3}J$ 10.6 Hz, H_{3'} in diastereoisomer A), 3.35 (td, 1 H, ${}^{4}J$ 4.3, ${}^{3}J$ 10.6 Hz, H_{3'} in diastereoisomer B), 4.44 (s, 1 H, H₄ in diastereoisomer B), 4.47 (s, 1 H, H₄ in diastereoisomer A), 4.49 (d, 2 H, ${}^{2}\underline{J}_{2x,2y}$ 12.0 Hz, H_{2x} in both diastereoisomers), 4.70 and 4.84 (AB quartet, 2 H, ²J 7.6 Hz, OCH₂O in diastereoisomer B), 4.75 and 4.86 (AB quartet, 2 H, ²J 7.5 Hz, OCH₂O in diastereoisomer A), 4.85 (d, 2 H, H_{2v} in both diastereoisomers), 5.28 (s, 2 H, H_E in both diastereoisomers), 5.33 (s, 2 H, H_Z in both diastereoisomers), 6,84 (d, 2 H, ${}^{3}J_{8,7}$ 8.2 Hz, H₈ in both diastereoisomers), 6.90 (t, 2 H, ${}^{3}J_{6,5} = {}^{3}J_{6,7}$ 7.5 Hz, H₆ in both diastereoisomers), 7.15-7.27 (complex m, 4 H, H₅ and H₇ in both diastereoisomers) ppm; δ_C (75.5 MHz, CDCl₃, TMS) 15.9 (C7'), 21.1 (C10'), 22.3 (C9'), 22.96 and 23.02 (C6'), 25.3 (C8'), 31.49 and 31.55 (C1'), 34.31 and 34.35 (C5'), 41.2 and 42.3 (C2'), 48.1 and 48.2 (C4'), 60.1 (C4), 67.3 (C2), 76.9 (C3"), 96.5 and 98.0 (OCH₂O), 115.8 and 115.9 (R₂C=<u>C</u>H₂), 116.9 and 117.0 (C8), 119.87 and 119.93 (C4a), 120.6 (C6), 129.42 and 129.45 (C7), 129.9 and 130.1 (C5), 139.3 and 139.4 (C3), 155.19 and 155.25 (C8a); m/z (CI+) 346 (MH+, 7%), 160 (M - menthOCH₂O, 6%), 145 (<u>M</u> - menthOCH₂ONH₂, 100%), 122 (4%); (Found: <u>MH</u>+, 346.2382. C₂₁H₃₁NO₃ requires <u>MH</u>⁺, 346.2382).

3.4.3 <u>Preparation of 2-(3-Bromobut-3-en-1-oxy)benzaldehyde O-camphanic oxime</u> (227)¹⁹⁹



2-(3-Bromobut-3-en-1-oxy)benzaldehyde oxime (137) (500 mg, 1.95 mmol) and camphanic chloride (507 mg, 2.34 mmol) were stirred for 30 min at RT in pyridine (2 cm^3). The reaction mixture was diluted with water (10 cm³) and the product was extracted into diethyl ether. The organic phase was washed with hydrochloric acid $(2M, 10 \text{ cm}^3)$ and water (10 cm^3) and dried (MgSO₄). Column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 7:3) yielded the oxime ether (227) (791 mg, 1.81 mmol, 93%) as needles, m.p. 88-89 °C (from ethanol). (Found: C, 55.01; H, 5.19; N, 3.32. C₂₀H₂₂BrNO₅ requires C, 55.04; H, 5.09; N, 3.21%); $[\alpha]_D$ -6° 9c. 2.24, CH₂Cl₂); <u>R</u>_F (diethyl ether-petroleum ether b.r. 40-60 °C, 7:3) 0.38; vmax. (CH2Cl2) 2860 w - 2990 w (Ar-H and C-H str.), 1780 s and 1710 s (C=O str.), 1630 w (C-H def.) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.67 (s, 3 H, CH₃), 1.14 (s, 3 H, CH₃), 1.15 (s, 3 H, CH₃), 1.74 (ddd, 1 H, ³J_{3a}, 2a⁺ 4.1, ³J_{3a}, 2b" 9.3, ²J_{3a}", 3b" 13.3 Hz, H_{3a}"), 1.99 (ddd, 1 H, ³J_{2b}", 3b" 4.5, ²J_{2b}", 2a" 15.0 Hz, H_{2b} "), 2.15 (ddd, 1 H, ${}^{3}J_{3b}$ ",2a" 10.7 Hz, H_{3b} "), 2.55 (ddd, 1 H, H_{2a} "), 4.72 (s, 2H, H_{3'}), 5.73 (d, 1 H, ³J_{4'E,4'Z} 1.8 Hz, H_{4'Z}), 6.01 (d, 1 H, ³J_{3,4} 8.4 Hz, H₃), 7.04 (dd, 1 H, 3 <u>J</u> 5,4 7.4, 3 <u>J</u> 5,6 7.8 Hz, H5), 7.45 (ddd, 1 H, 4 <u>J</u> 4,6 1.6 Hz, H4), 8.00 (dd, 1 H, H₆), 8.93 (s, 1 H, CH=NOR) ppm; δ_C (75.5 MHz, CDCl₃, TMS) 9.7 (CH₃), 16.68

(CH₃), 16.72 (CH₃), 28.9 (C3"), 30.9 (C2"), 54.66 (<u>C</u>Me₂), 54.7 (C4"), 72.1 (C2'), 90.5 (C1"), 112.7 (C3), 118.5 (C1), 118.8 (C4'),121.8 (C5), 126.1 (C3'), 128.0 (C4), 133.5 (C6), 153.7 (CH=N), 156.7 (C2), 164.9 (C5"), 178.0 (C(O)O-N) ppm; m/z (CI⁺) 436 (<u>MH</u>⁺, 2%), 255 (12%), 216 (100%), 160 (38%), 137 (5%), 120 (15%), 109 (8%) (Found: <u>MH</u>⁺, 436.076. C₂₀H₂₂BrNO₅ requires <u>MH</u>⁺ 436.076).

3.4.4 <u>Attempted Cyclisation of 2-(3-Bromobut-3-en-1-oxy)benzaldehyde O-</u> camphanic oxime (227)



A solution of AIBN (23 mg, 0.014 mmol) in benzene (10 cm³) was added dropwise over 8 h to a solution of 2-(3-Bromobut-3-en-1-oxy)benzaldehyde O-camphanic oxime (227) (300 mg, 0.68 mmol) and tributyltin hydride (240 mg, 0.83 mmol) in dry deoxygenated benzene (34.4 cm³, 0.02 M dilution of (227)) heated at reflux temperature. Heating was continued for a further 5 h. Benzene was evaporated under reduced pressure but analysis of the crude product mixture revealed approximately 10 spots that could not be isolated. None of the spots in the product mixture corresponded to starting material.

3.4.5 Attempted preparation of N-(menthyl-3-oxo)phthalimide²⁰⁰



Anhydrous sodium acetate (250 mg, 3.07 mmol) was slowly added to a solution of Nhydroxyphthalimide (500 mg, 3.07 mmol) in dimethylsulphoxide (5 cm³). The reaction mixture was stirred at RT for 15 min. (-)-Menthyl chloride (640 mg, 3.66 mmol) was added and the reaction mixture heated at reflux temperature until the red colouration disappeared (30 min). Analysis by thin later chromatography revealed in excess of ten products that could not be isolated.

3.4.6 Preparation of N-(2-Phenylpropan-1-oxy)phthalimide (236)²⁰¹



To a stirred solution of N-hydroxyphthalimide (1.00 g, 6.13 mmol), triphenylphosphine (1.61 g, 6.13 mmol) and α -methylbenzylalcohol (0.75 g, 6.13 mmol) in THF (30 cm³) under a nitrogen atmosphere was slowly added diethylazodicarboxylate (1.17 g, 6.74 mmol). The reaction mixture was stirred at RT for 24 h. THF was evaporated *in vacuo* and the crude product purified by column chromatography (silica, 60 mesh, dichloromethane-petroleum ether b.r. 40-60 °C, 1:1) to give the <u>phthalimide</u> (236) (1.01 g, 3.78 mmol, 62%) as plates, m.p. 89-91 °C (from petroleum ether b.r. 60-80 °C); (Found: C, 71.86; H, 4.92; N, 5.27. C₁₆H₁₃NO₃ requires C, 71.90; H, 4.92; N, 5.24%); <u>R</u>_E (dichloromethane-petroleum ether b.r. 40-60 °C, 1:1) 0.43; v_{max} (CH₂Cl₂) 3080-2820 w (Ar-H and C-H str.), 1785 s and 1725 s (cyclic 5-ring imide), 1460 m (C-H def.), 1370 s, 1185 s (C-O str.) cm⁻¹; δ_{H} (300 MHz, CDCl₃, TMS) 1.70 (d, 3 H, ³J₃, 2, 6.5 Hz, H₃), 5.49 (q, 1 H, H₂), 7.26-7.36 (complex m, 3 H, H_o and H_p in PhCH(CH₃)O-), 7.50 (complex m, 2 H, H_m in PhCH(CH₃)O-), 7.69 (complex m, 4 H, H4, H5, H6 and H7) ppm; δ_{C} (75.5 MHz, CDCl₃, TMS) 20.4 (C3'), 85.0 (C2'), 123.3 (C4 and C7), 127.5 (C_o in PhCH(CH₃)O-), 128.3 (C_m in PhCH(CH₃)O-), 128.7 (C3a and C7a), 128.9 (C_p in PhCH(CH₃)O-), 134.2 (C5 and C6), 138.9 (C' in PhCH(CH₃)O-), 163.7 (C1 and C3) ppm; m/z (EI⁺) 268 (<u>MH⁺</u>, 13%), 164 (<u>MH</u>-PhCHCH₃, 13%), 105 (PhCHCH₃, 100%), 90 (C₆H₅+, 31%); (Found: [<u>M</u>+NH₄]⁺, 285.1239. C₁₆H₁₃NO₃ requires [<u>M</u>+NH₄]⁺, 285.1239.

3.4.7 <u>Preparation of O-(α -Methyl)benzylhydroxylamine (237)</u>²⁰¹



N-(2-Phenylpropan-1-oxy)phthalimide (236) (290 mg, 1.09 mmol) and hydrazine monohydrate (54 mg, 1.09 mmol) were heated at reflux temperature in ethanol (5 cm³) for 2 h. The reaction mixture was poured into 3% sodium carbonate solution and the

product extracted with diethyl ether. <u>R</u>_F (dichloromethane-petroleum ether b.r 40-60 °C, 1:1) 0.20. The <u>hydroxylamine</u> (237) was used without purification or characterisation in the next experiment.

3.4.8 <u>Preparation of 2-(3-Bromobut-3-en-1-oxy)benzaldehyde O-(α-</u> <u>Methyl)benzyloxime (238)</u>



2-(3-Bromobut-3-en-1-oxy)benzaldehyde (136) (225 mg, 0.93 mmol) and unpurified O-(α-methyl)benzylhydroxylamine (137) (150 mg, 1.12 mmol) were stirred overnight at RT in pyridine (5 cm³). Pyridine was removed under reduced pressure and column chromatography (silica 60 mesh, dichloromethane-petroleum ether b.r. 40-60 °C, 1:1) yielded one isomer of the <u>oxime ether</u> (238) as a clear colourless oil (246 mg, 0.68 mmol, 73%); <u>R</u>_E (dichloromethane-petroleum ether b.r. 40-60 °C, 1:1) 0.52; v_{max} (film) 3060 w (=C-H, C-H str.), 3010 w (Ar-H, C-H str.), 2990 m, 2910 w and 2860 w (sat. C-H str.), 1635 m, 1600 s, 1570 w and 1480 s (Ar ring vib.), 1450 s (C-H def.) cm⁻¹; δ_H (300 MHz, CDCl₃,TMS) 1.61 (d, 3 H, ³J 6.6 Hz, CH₃), 4.60 (t, 2 H, ⁴J₂, _{4'Z} = ⁴J₂, _{4'E} 1.3 Hz, H₂), 5.35 (q, 1 H, OC<u>H</u>(CH₃)Ph), 5.64 (dt, 1 H, ²J_{4'Z,4'E} 2.2 Hz, H_{4'Z}), 5.94 (dt, 1 H, H_{4'E}), 6.77 (d, 1 H, ³J_{3,4} 8.4 Hz, H₃), 6.91 (dd, 1 H, ³J_{5,4} 7.5, ³J_{5,6} 7.7 Hz, H₅), 7.20-7.40 (complex m, 6 H, H4 and H_o, H_m and H_p in OCH(CH₃)Ph), 7.74 (dd, 1 H, ⁴J_{6,4} 1.7 Hz, H₆) ppm; δ_C (75.5 MHz, CDCl₃, TMS) 21.9 (CH₃), 71.9 (C2'), 81.2 (OCH(CH₃)Ph), 112.5 (C3), 118.0 (C4'), 121.5 (C1),

121.6 (C5), 126.4 (C_m in PhCH(CH₃)), 126.5 (C3'), 126.7 (C4), 127.4 (C_p in PhCH(CH₃)), 128.2 (C_o in PhCH(CH₃)), 130.8 (C6), 143.1 (C' in PhCH(CH₃)). 144.3 (<u>CH=NOR</u>), 155.4 (C2) ppm; m/z (CI+) 360/362 (<u>MH</u>+, 100%), 256/258 (<u>M-PhCHCH₃, 7%), 242 (<u>M-CH₂=C(Br)CH₃, 28%)</u>, 160 (15%), 145 (15%), 122 (HOC₆H₄CHO, 23%), 105 (C₆H₄CHO, 22%), 94 (C₆H₅OH, 2%); (Found: <u>MH</u>+, 360.0599. C₁₈H₁₈BrNO₂ requires <u>MH</u>+, 360.0599).</u>

3.4.9 Preparation of 4-(α-Methylbenzoxyamino)chroman-3-ylidene (239)



2-(3-Bromobut-3-en-1-oxy)benzaldehyde O-(α -methyl)benzyloxime (238) (125 mg, 0.35 mmol) and tributyltin hydride (122 mg, 0.42 mmol) were dissolved in dry benzene (18 cm³, 0.02 M dilution of (238)) and the solution degassed for 1 h. The reaction mixture was heated to reflux temperature and a solution of AIBN (12 mg, 0.07 mmol) in dry benzene (10 cm³) added over 8 h. Heating was continued for 18 h. Benzene was removed under reduced pressure and the residue purified by column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:9). This afforded a 1:1 mixture of diastereoisomers of the <u>hydroxylamine</u> (239) as a pale yellow oil (59 mg, 0.21 mmol, 61%); <u>RF</u> (diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) 0.36; v_{max} 3080 w (=C-H, C-H str.), 2960-2900 m (sat. C-H str.), 2805 w (O-CH₂, C-H str.), 1640 m, 1610 m, 1570 w and 1485 s (Ar ring vib.), 1240 s (C-O str.) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.44 (d, 3 H, ³<u>J</u> 6.6 Hz, CH₃ in isomer A), 1.52 (d, 3 H, ³<u>J</u> 6.6 Hz, CH₃ in isomer B),4.30 (d, 1 H, ²<u>J_{2ax,2eq}</u> 11.5 Hz, H_{2ax} in

isomer B), 4.40 (s, 1 H, H₄ in isomer A), 4.48 (s, 1 H, H₄ in isomer A), 4.50-4.55 (complex m, 2 H, H_{2eq} in isomer B and H_{2ax} in isomer A), 4.76-4.84 (complex m, 2 H, C<u>H</u>CH₃ in isomers A and B), 4.88 (dd, 1 H, ${}^{4}J_{2eq,Z} 1.1$, ${}^{2}J_{2eq,2ax} 11.7$ Hz, H_{2eq} in isomer A), 5.23 (s, 1 H, H_E in isomer B), 5.34 (complex m, 2 H, H_E in isomer A and H₂ in isomer B), 5.41 (d, 1 H, H₂ in isomer A), 6.77-6.90 (complex m, 2 H, H₈ in isomers A and B), 7.07-7.29 (complex m, 2 H, H₆ in isomers A and B), 7.40-7.48 (complex m, 4 H, H₅ and H₇ in isomers A and B), 7.70-7.83 (complex m, 10 H, H_o, H_m and H_p in PhCH₂ in isomers A and B) ppm; δ_C (75.5 MHz, CDCI3, TMS) 23.9 and 24.9 (CH₃), 58.6 and 58.7 (C4), 69.3 and 69.9 (C2), 81.5 and 81.6 (CH(Me)Ph), 116.9 and 117.1 (C=CH₂), 120.7 and 120.8 (C8), 120.8 and 121.1 (C4a), 126.0 and 126.2 (C6), 127.1 and 127.2 (C_p in PhCH₂), 127.8 and 127.9 (Cm in PhCH₂), 128.1 and 128.2 (Co in PhCH₂), 128.5 and 128.6 (C7), 129.7 and 129.8 (C5), 143.5 and 143.8 (C' in PhCH₂), 145.0 and 145.1 (C3), 155.1 and 155.4 (C8a) ppm.

3.4.10 <u>Preparation of (R)-N-(2-(2-naphthyl)propan-1-oxy)phthalimide</u> (241)²⁰¹



Diethylazodicarboxylate (2.22 g, 12.75 mmol) was added dropwise to a stirred solution of (S)- α -methyl-2-naphthalenemethanol (2.00 g, 11.61 mmol), N-hydroxyphthalimide (1.89 g, 11.61 mmol) and triphenylphosphine (3.05 g, 11.61 mmol) in THF (50 cm³)

under a nitrogen atmosphere. The reaction was left stirring at RT for 72 h. THF was evaporated under reduced pressure. Column chromatography (silica, 60 mesh, dichloromethane-petroleum ether b.r. 40-60 °C, 2:1) afforded the phthalimide (241) (2.10 g, 6.62 mmol, 57%) as needles, m.p. 105-106 °C (from diethyl ether); (Found: C, 75.84; H, 4.89; N, 4.45. C₂₀H₁₅NO₃ requires C, 75.69; H, 4.76; N, 4.41%); <u>R</u>_F (dichloromethane-petroleum ether b.r. 40-60 °C, 1:1) 0.38; vmax (CH2Cl2) 3080 -2820 w (Ar-H and C-H str.), 1780 s and 1720 s (cyclic 5-ring imide), 1460 m (C-H def.), 1370 s (CH₃, C-H sym. def.), 1180 s (C-O str.) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.77 (d, 3 H, ${}^{3}J_{3',2'}$ 6.5 Hz, H_{3'}), 5.67 (q, 1 H, H_{2'}), 7.41 (complex m, 2 H, H_{7"} and H_{6"}), 7.60 (complex m, 4 H, H₄, H₅, H₆ and H₇), 7.80 (complex m, 5 H, H₁", H₃", H₄", H₅", and H₈") ppm; δ_C (75.5 MHz, CDCl₃, TMS) 20.6 (C3'), 85.1 (C2'), 123.1 (C4 and C7), 124.7 (C3"), 126.0 (C6"), 126.2 (C7"), 127.9 (C4"), 127.5 (C1"), 127.9 (C5"), 128.1 (C8"), 128.6 (C3a and C7a), 132.7 (C8a"), 133.4 (C4a"), 134.1 (C5 and C6), 136.4 (C2"), 163.6 (C1 and C3) ppm; m/z (EI+) 317 (M⁺, 1%), 155 ([naphthCHCH₃]⁺, 100%), 127 (naphth⁺, 12%), 115 (8%), 104 (10%), 76 (13%); (Found: <u>M</u>⁺, 317.1050. C₂₀H₁₅NO₃ requires <u>M</u>⁺, 317.1050).

3.4.11 <u>Preparation of O-(α -methyl-2-naphthalene)methylhydroxylamine</u>





(R)-N-(2-(2-naphthyl)propan-1-oxy)phthalimide (241) (670 mg, 2.11 mmol) and hydrazine monohydrate (106 mg, 2.11 mmol) were heated at reflux temperature in ethanol (5 cm³) for 2 h. The reaction mixture was poured into 3% sodium carbonate solution and the product extracted with diethyl ether. <u>R_F</u> (dichloromethane-petroleum ether b.r 40-60 °C, 1:1) 0.38. The <u>hydroxylamine</u> (242) was used without purification or characterisation in the next experiment.

3.4.12Preparation of 2-(3-Bromobut-3-en-1-oxy)benzaldehyde O-(α-methyl-
2-naphthalene)methyloxime (240)



O-(R)-(α -Methyl-2-naphthalene)methylhydroxylamine (186) (400 mg, 2.14 mmol) and 2-(3-bromobut-3-en-1-oxy)benzaldehyde (242) (430 mg, 1.78 mmol) were stirred in pyridine (5 cm³) at RT overnight. Pyridine was removed under reduced pressure and the residue purified by column chromatography (silica, 60 mesh, dichloromethanepetroleum ether b.r. 40-60 °C, 1:1). This afforded the <u>oxime ether</u> (240) as a clear, colourless oil (677 mg, 1.65 mmol, 93%); <u>RF</u> (dichloromethane-petroleum ether b.r.

40-60 °C, 1:1) 0.51; $[\alpha]^D$ +7.42° (c. 4.58, CH₂Cl₂); v_{max} (film) 3045 w (=C-H and Ar-H, C-H str.), 2970 s, 2910 m and 2860 w (sat. C-H str.), 1635 m (C=C str.), 1600 s, 1540 w and 1480 s (Ar ring vib.), 750 s (o-disubstituted Ar) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.68(d, 3 H, ³J 6.6 Hz, CH₃), 4.55 (t, 2 H, ⁴J_{2',4'Z}=⁴J_{2',4'E} 1.2 Hz, H_{2'}), 5.51 (q, 1 H, OCH(CH₃)naphth), 5.64 (dt, 1 H, ²J_{4'Z,4'E} 2.1 Hz, H_{4'Z}), 5.90 (dt, 1 H, H_{4'E}), 6.69 (d, 1 H, 3 <u>J</u>_{3,4} 8.2 Hz, H₃), 6.87 (dd, 1 H, 3 <u>J</u>_{5,4} 7.5, 3 <u>J</u>_{5,6} 7.7 Hz, H₅), 7.19 (ddd, 1 H, ${}^{4}J_{4,6}$ 1.7 Hz, H₄), 7.41 (complex m, 2 H, H_{6"} and H_{7"}), 7.51 (dd, 1 H, H₆), 7.771-7.81 (complex m, 5 H, H_{1"}, H_{3"}, H_{4"}, H_{5"} and H_{8"}), 8.60 (s, 1 H, <u>H</u>C=N) ppm; δ_C (75.5 MHz, CDCl₃, TMS) 21.9 (CH₃), 71.8 (C2'), 81.3 (OCH(CH₃)naphth), 112.4 (C3), 118.0 (C4'), 121.4 (C1), 121.4 (C5), 124.6 (C3"), 125.1 (C6"), 125.6 (C7"), 125.9 (C4"), 126.5 (C3'), 126.7 (C4), 127.6 (C1"), 127.9 (C5"), 128.0 (C8"), 130.8 (C6), 132.8 (C8a"), 133.2 (C4a"), 140.6 (C2"), 144.4 (C=N), 155.4 (C2) ppm; m/z (EI+) 410/412 (MH+, 2%), 256/258 (MnaphthCH(CH₃), 2%, 155 (naphthCH(CH₃), 100%), 141 (naphthCH₂, 2%), 127 (naphth+, 15%); (Found: <u>MH</u>+, 410.0756. C₂₂H₂₀BrNO₂ requires <u>MH</u>+, 410.0756).

3.4.13 Preparation of $4-[(R)-(\alpha-methyl-2-$

naphthalene)methoxyamino]chroman-3-ylidene (243)



2-(3-Bromobut-3-en-1-oxy)benzaldehyde O-(R)-(α methyl-2-naphthalene)methyloxime (240) (300 mg, 0.73 mmol) and tributyltin hydride (256 mg, 0.88 mmol) were dissolved in benzene (37 cm³, 0.02 M dilution of (240)) and the solution was degassed with a steady stream of nitrogen for 1h. The solution was heated to reflux temperature and a solution of AIBN (24 mg, 0.15 mmol) in benzene (10 cm³) was added over 8h *via* a syringe pump. Benzene was evaporated *in vacuo* and the crude product was purified by column chromatography (silica, 60 mesh, diethyl etherpetroleum ether b.r. 40-60 °C, 1:9). This afforded the <u>hydroxylamine</u> (243) (165 mg, 0,50 mmol, 68%) as a 1:1 mixture of diastereoisomers A and B, seen as a clear, colourless oil. <u>R_F</u> (diethyl ether-petroleum ether b.r. 40-60 °C, 1:9) 0.17; v_{max}. (CH₂Cl₂) 3250 br. w (N-H), 1600 m, 1580 s and 1480 s (Ar ring vib.), 1460 s (C-H def.), 1240 s (=C-O-C, C-O str.), 1070 s (=C-O-C, C-O str.) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.36 (d, 3 H, ³J 6.6 Hz, CH₃ in diastereoisomer A), 1.43 (d, 3 H, ³J 6.5 Hz, CH₃ in B), 4.35 (d, 1 H, ²J_{2ax,2eq} 11.6 Hz, H_{2ax} in A), 4.37 (s, 1 H, H₄ in

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A), 4.43 (s, 1 H, H₄ in B), 4.51 (d,1 H, ${}^{2}J_{2ax,2eg}$ 11.6 Hz, H_{2ax} in B), 4.55 (d, 1 H, H_{2eq} in A), 4.62 (2 overlapping q, 2 H, CH₃C<u>H</u> in A and B), 4.84 (d, 1 H, H_{2eq} in B), 5.22 (s, 1 H, RC=CH_aH_b in A), 5.30 (2 x s, 2 H, RC=CH_aH_b in A and $RC=CH_{a}H_{b}$ in B), 5.32 (br. s, 2 H, NH in A and B), 6.78 (complex m, 4 H, H₃ and H₅ in A and B), 7.00-7.23 (complex m, 4 H, H₄ and H₆ in A and B), 7.42 (complex m, 6 H, $H_{7'}$, $H_{6'}$ and $H_{3'}$ in A and B), 7.75 (complex m, 8 H, $H_{1'}$, $H_{4'}$, $H_{5'}$ and $H_{8'}$ in A and B) ppm; δ_C (75.5 MHz, CDCl₃, TMS) 21.0 (CH₃), 21.6 (CH₃O, 60.1 and 10.4 (C4), 67.2 and 67.3 (C2), 81.0 and 81.9 (CHCH₃), 115.7 and 116.1 (C=CH₂), 116.8 (C8), 119.8 and 120.3 (C4a), 120.4 and 120.5 (C6), 126.3 (C5), 126.7 and 127.3 (C7), 127.4 (CH), 127.5 (CH), 128.1 (2 x CH), 128.3 (CH), 128.5 (CH), 129.4 (2 x CH), 130.0 (CH), 132.7 (CH), 132.9 (CH), 137.0 (C3), 139.1 (C), 139.6 (C), 143.0(C), 143.6 (C), 155.1 and 155.2 (C4a), 168.6 (2 x C8a) ppm [NOTE: the C atoms in the naphthyl group could not be assigned unambiguously]; m/z (CI+) 332 (<u>MH</u>+,22%) 188 (8%), 171 (naphthCH(CH₃)O, 5%), 155 (naphthCH(CH₃), 39%), 145 (M-naphthCH(CH₃)ONH, 100%), 128 (naphthH, 2%); (Found: <u>MH</u>+, 332.1651. C₂₂H₂₁NO₂ requires <u>MH</u>+, 332.1651).

3.5.1 Preparation of Diethyl 5-(2-bromophenyl)pent-1-en-4,4-dicarboxylate (248)¹¹⁸



Diethyl 2-(2-bromobenzyl)-1,3-propanedicarboxylate (500 mg, 1.52 mmol) in dry THF (2 cm³) was added dropwise to a suspension of sodium hydride (54 mg, 1.82 mmol, 80% by wt. in oil) in DMPU (235 mg, 1.82 mmol) and dry THF (2cm³). The reaction mixture was stirred at RT for 30 min. Allyl bromide (275 mg, 2.28 mmol) in THF (2 cm^3) was added dropwise and the reaction mixture was heated at reflux temperature for 4h. The mixture was then poured into water (50 cm^3) and the product was extracted into diethyl ether $(2 \times 50 \text{ cm}^3)$. The organic layers were combined, dried (MgSO₄) and the solvent was removed under vacuum. Column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:9) afforded the diester (248) as a clear, colourless oil (494 mg, 1.34 mmol, 88%); RF (diethyl etherpetroleum ether b.r. 40-60 °C, 1:9) 0.31; v_{max} (film) 3060 w (Ar-H, C-H str.), 2980s, 2930 m, 2900w (C-H str.), 1725 s (CO₂Et, C=O str.), 1670 w (C=C str.), 1470 s and 1440 s (C-H def.) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.19 (t, 6 H, ²<u>J</u> 7.2 Hz, C<u>H</u>₃), 2.66 (dd, 1 H, ${}^{4}J_{3,1E}$ <1, ${}^{3}J_{3,2}$ 7.2 Hz, H₃), 3.49 (s, 2 H, H₅), 4.15 (complex AB part of an ABX₃ pattern, 4 H, OCH₂), 5.09 (d, 1 H, ³J_{1Z,2} 17.5 Hz, H_{1Z}), 5.10 (dt, 1 H, ³J_{1E.2} 10.3 Hz, H_{1E}), 5.85 (ddt, 1 H, H₂), 7.04 (ddd, 1 H, ⁴J_{4',3'} 1.8, ³J_{4',5'} 7.4, 3 J_{4',3'} 8.0 Hz, H_{4'}), 7.18 (ddd,1 H, 4 J_{5',3'} 1.3, 3 J_{5',6'} 7.7 Hz, H_{5'}), 7.28 (dd, 1 H, H₆'), 7.51 (dd, 1 H, H₃') ppm; δ_C (75.5 MHz, CDCl₃, TMS) 13.9 (CH₃), 37.7 (C3), 37.9 (C5), 58.7 (C4), 61.3 (OCH₂), 118.8 (C1), 126.0 (C2'), 127.1 (C5'), 128.3 (C4'), 131.4 (C6'), 132.8 (C2), 132.9 (C3'), 136.3 (C1'), 170.5 (C=O) ppm; m/z (CI+) 369/371 (MH+, 100%), 289 (M-Br, 14%), 278/280 (M-2 x EtO, 3%), 217

(11%), 199 (<u>M</u>-Br and 2 x EtO, 13%); (Found: <u>MH</u>+, 369.0701. C₁₇H₂₁BrO₄ requires <u>MH</u>+, 369.0701).

3.5.2 Preparation of 5-(2-Bromophenyl)pent-1-en-4,4-dicarboxylic acid (249)¹⁷³



The diester (248) (3.00 g, 8.13 mmol) was heated at 100 °C with potassium hydroxide (1.80 g, 32.08 mmol) in water (5cm³) for 6h. The reaction mixture was cooled and poured into a beaker surrounded by ice. Ice was added to the mixture and concentrated hydrochloric acid was then added dropwise until the mixture was acidic to litmus paper. The product was extracted into diethyl ether ($3 \times 100 \text{ cm}^3$) and the combined organic extracts were dried (MgSO₄) before evaporation of the solvent to give the crude <u>diacid</u> (249) as a white solid (2.06 g, 6.59 mmol, 81%). This was used without further purification or characterisation.

3.5.3 Preparation of Ethyl 5-(2-bromophenyl)pent-1-en-4-carboxylate (250)



The diacid (249) (2.06 g, 6.59 mmol) was heated to 240 °C and maintained at this temperature until the evolution of carbon dioxide had ceased (approx. 4h). The flask

was cooled and ethanol (20 cm^3) and sulphuric acid (2 drops) were added. The reaction mixture was heated at reflux temperature for 2h. Ethanol was removed under reduced pressure, the residue was diluted with diethyl ether and washed with 10% sodium bicarbonate solution. The organic phase was dried (MgSO₄) and the diethyl ether was evaporated in vacuo. Column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:5) yielded the ester (250) (1.53 g, 5.14 mmol, 78%) as a clear, colourless oil. \underline{R}_{F} (diethyl ether-petroleum ether b.r. 40-60 °C, 3:10) 0.55; v_{max} (film) 3060 w (C=CH₂ and Ar-H, C-H str.), 2975 m, 2950 m, 2915 m and 2860 w (C-H str.), 1720 s (CO₂Et, C=O str.), 1640 m (C=C str.), 1440 m, 1370 m, and 750 s (o-dibstustituted Ar-H) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.12 (t, 6 H, ²J 7.1 Hz, CH₃), 2.32 (dtt, 1 H, ${}^{4}J_{3a,1E}$ 1.0, ${}^{4}J_{3a,1Z}$ 1.4, ${}^{3}J_{3a,2} = {}^{3}J_{3a,4}$ 7.0, ${}^{2}J_{3a,3b}$ 12.6 Hz, H_{3a}), 2.43 (dtt, 1 H, ${}^{4}J_{3b,1E}$ 1.0, ${}^{4}J_{3b,1Z}$ 1.4, ${}^{3}J_{3b,2} = {}^{3}J_{3b,4}$ 7.0 Hz, H_{3b}), 2.85-3.05 (complex m, 3 H, H₅ and H₄), 3.98-4.09 (complex AB part of an ABX₃ pattern, 2 H, OCH₂), 5.05 (ddt, 1 H, ${}^{2}J_{1E,1Z}$ 3.3 Hz, ${}^{3}J_{1E,2}$ 10.1 Hz, H_{1E}), 5.09 (ddt, 1 H, 3 J_{1Z,2} 17.0 Hz, H_{1Z}), 5.79 (ddt, 1 H, 3 J_{2,3} 7.0 Hz, H₂), 7.05 (dd, 1 H, H₄) 7.20 (complex m, 2 H, H_{6'} and H_{5'}), 7.51 (d, 1 H, ${}^{3}J_{3',4'}$ 7.7 Hz, H_{3'}) ppm ; δ_{C} (75.5 MHz, CDCl₃, TMS) 14.2 (CH₃), 36.8 (C3), 38.0 (C5), 45.1 (C4), 60.2 (OCH₂), 117.2 (C1), 124.6 (C2'), 127.2 (C5'), 128.1 (C4'), 131.2 (C6'), 132.8 (C2), 134.9 (C3'), 138.6 (C1'), 174.5 (C=O) ppm; m/z (CI+) 297/299 (MH+, 18%), 217 (M-Br, 100%), 189 (M-Br and Et, 22%), 169/171 (BrC₆H₄CH₂+, 23%), 127 (15%), 115 (10%), 90 (C₇H₆+, 12%), 77 (C₆H₅+, 5%); (Found: [M+NH₄]+, 314.076. $C_{14}H_{17}BrO_2$ requires [M+NH4]+, 314.076).

3.5.4 Preparation of 2-(2-Bromobenzyl)pent-4-en-1-ol (251)¹⁷⁴



The ester (250) (750 mg, 2.53 mmol) in dry diethyl ether (2 cm³) was added dropwise to a stirred suspension of lithium aluminium hydride (60 mg, 1.58 mmol) in diethyl ether (5 cm^3) under a nitrogen atmosphere. The reaction mixture was heated at reflux temperature for 2h before quenching by cautious addition of wet diethyl ether. The mixture was diluted with diethyl ether, then dried (MgSO₄), and the solvent was removed under reduced pressure to give the crude <u>alcohol</u> (251). This was purified by column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:1) to give the product (251) as a clear, colourless oil (606 mg, 2.38 mmol, 94%); <u>R</u>F (diethyl ether-petroleum ether b.r. 40-60 °C, 1:1) 0.33; v_{max} (film) 3590 w (free O-H, O-H str.), 3460 br. (intermolecular and weakly H-bonded O-H, O-H str.), 3070 m (C=CH₂, C-H str.), 2970 m, 2910 s and 2860 m (C-H str.), 1640 m (C=C str.), 1590 w and 1565 w (Ar ring vib.), 1470 s (C-H def.), 1440 s (C-O str.), 990 m (RCH=CH₂ out of plane def.), 910 s (RCH=CH₂ out of plane def.), 750 s (odisubstituted Ar) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 2.00 (complex m, 2 H, H₂ and OH), 2.09-2.26 (complex m, 2 H, H₃), 2.73 (AB dd, 1 H, ³J_{3a,2} 6.7, ²J_{3a,3b} 13.6 Hz, H_{3a}), 2.76 (AB dd, 1 H, ³J_{3b,2} 7.9 Hz, H_{3b}), 3.52 (AB dd, 1 H, ³J_{ArCHa,2} 5.2 Hz, ²JArCHa, ArCHb 10.9 Hz, ArCHa, Hb), 3.54 (AB dd, 1 H, ³JArCHb, 2 4.7 Hz, ArCH_aH_b), 5.04 (ddt, 1 H, ⁴J_{5E,3} 1.0, ³J_{5E,4} 10.0 Hz, H_{5E}), 5.08 (ddt, 1 H, ³J_{5Z,4} 17.1 Hz, H_{5Z}), 5.83 (ddt, 1 H, ³J_{4,3} 7.1 Hz, H₄), 7.02 (dd, 1 H, H₄), 7.20 (complex m, 2 H, H_{6'} and H_{5'}), 7.51 (d, 1 H, ³J_{3',4'} 7.8 Hz, H_{3'}) ppm; δ_C (75.5 MHz, CDCl₃, TMS) 35.5 (C3), 37.3 (ArCH₂), 40.7 (C2), 64.1 (C1), 116.6 (C5), 124.7 (C2'), 127.2 (C5'), 127.7 (C4'), 131.4 (C6'), 132.8 (C3'), 136.6 (C4), 140.0 (C1') ppm;

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m/z (CI⁺) 272/274 ([<u>M</u>+NH₄]⁺, 100%), 254/256 (<u>M</u>⁺, 3%), 236/238 (<u>M</u>-H₂O, 20%), 223/225 (<u>M</u>-CH₂=OH⁺, 3%), 175 (<u>M</u>-Br, 20%), 157 (<u>M</u>-Br and H₂O, 32%), 116 (15%); (Found: <u>M</u>⁺, 254.0306. C₁₂H₁₅BrO requires <u>M</u>⁺, 254.0306).

3.5.5 Preparation of 2-(2-Bromobenzyl)pent-4-enal O-methyloxime (246)¹⁷⁵⁻¹⁷⁷



Oxalyl chloride (400 mg, 1.78 mmol) in dichloromethane (6 cm³) was cooled to -78 °C with stirring under a nitrogen atmosphere. A solution of dimethyl sulphoxide (420 mg, 5.38 mmol) in dichloromethane (5 cm³) was added and the solution was stirred at -78 °C for 10 min. The alcohol (251) in dichloromethane (2 cm³) was added dropwise and the reaction mixture was allowed to stir at -78 °C for 1h before addition of triethylamine (575 mg, 5.69 mmol). The mixture was then allowed to warm to room temperature before pouring it into hydrochloric acid (2M, 20 cm³) and extracting the product with diethyl ether. The organic phase was dried (MgSO₄) and the solvent was removed under vacuum to afford the crude aldehvde (252). This was not isolated or purified, but was treated directly with O-methyl hydroxylamine hydrochloride (200 mg, 2.40 mmol) in pyridine (5 cm^3) and stirred at RT overnight. The pyridine was removed under reduced pressure and the residue was diluted with water (20 cm^3). The crude oxime ether was extracted into diethyl ether and the organic phase was dried (MgSO₄) before removal of the ether. Column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:9) of the crude residue gave a mixture of the <u>E</u>- and <u>Z</u>- isomers of the <u>oxime ether</u> (246) (407 mg, 1.44 mmol, 81% overall) as a clear, colourless oil; RF (diethyl ether-petroleum ether b.r. 40-60 °C, 1:9) 0.45 and

0.27; v_{max} (film) 3060 w (Ar-H, C-H str.), 3000-2840 m (C-H str.), 2810 w (C-H str.of OCH₃), 1640 w (C=N str.), 1560 w (Ar ring vib.), 1470 s and 1430 s (C-H def.), 750 s (o-disubstituted Ar) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 2.25 (complex m, 2 H in major isomer and 2 H in minor isomer, H₃), 2.77 (complex m, 1 H in major isomer and 1 H in minor isomer, H₂), 2.92 (complex m, 2 H in major isomer and 2 H in minor isomer, ArCH₂), 3.67 (s, 3 H in minor isomer, OCH₃), 3.75 (s, 3 H in major isomer, OCH₃), 5.02-5.11 (complex m, 2 H in major isomer and 2 H in major isomer, H_{5E} and H_{5Z}), 5.78 (2 overlapping ddt, 1 H in major isomer and 1 H in minor isomer, H₄), 6.51 (d, 1 H in minor isomer, ${}^{3}J_{1,2}$ 7.8 Hz, H₁), 7.04 (2 overlapping ddd, 1 H in major isomer and 1 H in minor isomer, H₄'), 7.18 (complex m, 2 H in major isomer and 2 H in minor isomer, $H_{5'}$ and $H_{6'}$), 7.27 (d, 1 H in major isomer, ${}^{3}J_{1,2}$ 6.9 Hz, H₁), 7.51 (2 overlapping dd, 1 H in major isomer and 1 H in minor isomer, H_{3'}) ppm; δ_C (75.5 MHz, CDCl₃, TMS) 35.5 (C2 minor), 36.5 (C3 minor), 36.9 (C3 major), 38.1 (ArCH₂ minor), 38.6 (ArCH₂ major), 39.6 (C2 major), 61.2 (CH₃ major), 61.4 (CH₃ minor), 116.9 (C5 minor), 117.3 (C5 major), 124.7 (C2' major and C2' minor), 127.1 (C5' minor), 127.15 (C5' major), 127.8 (C4' minor), 127.9 (C4' major), 130.8 (C6' minor), 131.4 (C6' major), 132.7 (C3' minor), 132.8 (C3' major), 135.12 (C4 major), 135.2 (C4 minor), 138.6 (C1' major), 138.7 (C1' minor), 152.3 (C1 major), 153.3 (C1 minor) ppm; m/z (EI+) 282/284 (MH+, 100%), 202 (M-Br, 41%), 188 (M-Br and CH₂, 2%), 172 (M-Br and CH₂O, 23%). 143 (M-Br and CH₂=NOCH₃, 5%), 130 (15%), 112 (10%); (Found: <u>MH</u>+, 282.0494. C₁₃H₁₆BrNO requires <u>MH</u>+, 282.0494).

3.5.6 Preparation of 1-methoxyamino-2-(prop-2-envl)indan (253)



2-(2-Bromobenzyl)pent-4-enal O-methyloxime (246) (700 mg, 2.48 mmol) was dissolved in benzene (125 cm^3 , 0.02M dilution of (246)) and the solution was degassed for 30 min. before heating to reflux temperature under a nitrogen atmosphere. A solution of tributyltin hydride (1.44 g, 4.96 mmol) and AIBN (81 mg, 0.50 mmol) in benzene (10 cm³) was added dropwise over 20h. Heating was continued for a further 6h. The benzene was evaporated under reduced pressure and the hydroxylamine (253) (247 mg, 1.22 mmol, 49%) was isolated by column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) as a pale yellow oil; <u>R</u>_F (diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) 0.48; v_{max} 3240 w (N-H str.), 3060 m (Ar-H, C-H str.), 2970 m, 2910 s, 2820 m (C-H str.), 2800 m (C-H str. of OCH₃), 1640 m (C=C str.), 1600 w, 1580 w (Ar ring vib.), 1460 s and 1430 s (C-H def.), 990 s and 910 s (RCH=CH₂ out of plane def.), 740 s (odibsubstituted Ar) cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 2.19 (complex m, 1 H, H₂), 2.40 (complex m, 2 H, H₁), 2.58 (dd, 1 H, ${}^{3}\underline{J}_{3b,2}$ 5.6, ${}^{3}\underline{J}_{3b,3a}$ 16.0 Hz, H_{3b}), 3.15 (dd, 1 H, ${}^{3}J_{3a,2}$ 7.8 Hz, H_{3a}), 3.54 (s, 3 H, OCH₃), 4.24 (d, 1 H, ${}^{3}J_{1,2}$ 4.8 Hz, H₁), 5.04 (ddt, 1 H, ${}^{4}J_{3'E,1'} < 1.0$, ${}^{2}J_{3'E,3'Z} 2.0$, ${}^{3}J_{3'E,2'} 10.2$ Hz, H_{3'E}), 5.08 (ddt, 1 H, ${}^{4}J_{3'Z,1'} < 1.0, {}^{3}J_{3'Z,2'}$ 17.1 Hz, H_{3'Z}), 5.87 (ddt, 1 H, ${}^{3}J_{2',1'}$ 6.8 Hz, H_{2'}), 7.20 (complex m, 3 H, H₅, H₆ and H₇), 7.39 (complex m, 1 H, H₄?) ppm; δ_C (75.5 MHz, CDCl₃, TMS) 36.4 (C1'), 38.5 (C3), 42.4 (C2), 62.2 (OCH₃), 70.8 (C1), 116.1 (C3'), 124.8 (C6), 124.9 (C7), 126.4 (C5), 127.9 (C2'), 136.9 (C4), 142.0 (C3a), 143.0 (C7a) ppm; m/z (EI+), 204 (MH+, 15%), 172 (M-MeO, 25%), 157 (M-

MeONH, 100%), 142 (<u>M</u>-MeONH and CH₃, 12%), 129 (<u>M</u>-MeONH and C₂H₄, 100%), 115 (<u>M</u>-MeONH and MeCH=CH₂, 67%), 91 (C₇H₇+, 18%); (Found: <u>MH</u>+, 204.1388. C₁₃H₁₇NO requires: <u>MH</u>+, 204.1388).

3.5.7 Preparation of Ethyl 1-bromomethyl-2-oxocyclopentanecarboxylate (259)¹¹⁸



Ethyl 2-oxocyclopentanecarboxylate (1.00 g, 6.98 mmol) in dry THF (5 cm³) was added dropwise to a suspension of sodium hydride (251 mg, 8.37 mmol, 80% suspension in mineral oil) in THF (5 cm³) containing DMPU (1.07 g, 8.57 mmol) at RT under nitrogen. The reaction mixture was stirred at RT for 1h and was then treated with dibromomethane (6.05 g, 34.9 mmol) before heating at reflux temperature for 6h. The reaction mixture was diluted with diethyl ether (100 cm³), washed with water (3 x 10 cm³) and dried (K₂CO₃). The solvent was then removed under reduced pressure and the residue was chromatographed (silica, 60 mesh, ethyl acetate-petroleum ether b.r. 40-60 °C, 1:4) to yield the <u>bromide</u> (259) as a clear, colourless oil (891 mg, 4.12 mmol, 59%); <u>R_E</u> (ethyl acetate-petroleum ether b.r. 40-60 °C, 1:3) 0.41; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.28 (t, 3 H, CH₃), 1.91-2.64 (complex m, 6 H, H₃, H₄ and H₅), 3.60 and 3.75 (AB quartet, 2 H, ²J 10.4 Hz, C<u>H</u>₂Br), 4.21 (AB part of an ABX₃ pattern, 2 H, OCH₂) ppm.

3.5.8 <u>Preparation of Ethyl 1-bromomethyl-2-oxocyclopentanecarboxylate O-</u> methyloxime (258)



Ethyl 1-bromomethyl-2-oxocyclopentanecarboxylate (259) (500 mg, 2.01 mmol) and O-methylhydroxylamine hydrochloride (201 mg, 2.41 mmol) were stirred overnight at RT in pyridine (10 cm^3). The pyridine was then removed under reduced pressure, the residue was diluted with water (50 cm³), and the product was extracted into diethyl ether $(2 \times 50 \text{ cm}^3)$. The organic phase was dried (MgSO₄) and the solvent was evaporated in vacuo. Flash chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) yielded the oxime ether (258) as a pale yellow oil (435 mg, 1.63 mmol, 81%); \underline{R}_{F} (diethyl ether-petroleum ether b.r. 40-60 °C, 1:4) 0.40; v_{max} . (film) 2960 s, 2930 m, and 2890 m (C-H str.), 2810 m (C-H str. of OCH₃), 1720 s (C=O str.), 1640 w (C=N str.), 1460 m and 1440 m (C-H def.), 1420 m, 1360 m cm⁻¹; δ_H (300 MHz, CDCl₃, TMS) 1.28 (t, 3 H, ³J 7.1 Hz, CH₃), 1.77-2.03 (complex m, 3 H, H₃ and H_{5ax} or H_{5eq}), 2.40-2.65 (complex m, 3 H, H₄ and H_{5ax} or H_{5eq}), 3.49 (d, 1 H, ²J 10.2 Hz, CH₂H_bBr), 3.85 (s, 3 H, OCH₃), 3.98 (d, 1 H, CH_aH_bBr), 4.18 and 4.25 (AB dq, 2 H, ²J 17.8 Hz, OCH₂) ppm; δ_C (75.5 MHz, CDCl₃, TMS) 13.9 (CH₃), 21.7 (C4), 27.9 (CH₂Br), 34.9 (C5), 36.6 (C3), 57.0 (C1), 61.4 (OCH₂), 61.9 (OCH₃), 162.9 (C2), 170.5 (C=O) ppm; m/z (CI⁺) 391 (100%), 278/280 (MH+, 58%), 94 (25%), 72 (25%), 72 (5%), 58 (30%), 44 (45%); (Found: <u>MH</u>⁺, 278.0392. C₁₀H₁₆BrNO₂ requires <u>MH</u>⁺, 278.0392).

3.5.9 <u>Ring Expansion of Ethyl 1-bromomethyl-2-oxocyclopentanecarboxylate O-</u> methyloxime to Ethyl 3-oxocyclohexanoate O-methyloxime (260)



Ethyl 1-bromomethyl-2-oxocyclopentanecarboxylate O-methyloxime (258) (100 mg, 0.36 mmol) was dissolved in benzene (18 cm^3) and the solution was degassed by the passage of a steady stream of nitrogen through it for 30 min. The solution was heated to reflux temperature under a nitrogen atmosphere and a solution of tributyltin hydride (115 mg, 0.40 mmol) and AIBN (6 mg, 0.04 mmol) in benzene (5 cm³) were added over 10 h using a syringe pump. Heating was continued for a further 14 h until all the starting material had disappeared as evidenced by TLC. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 1:1) to yield a 1:1 mixture of isomers of the rearranged product (260) as a clear, colourless oil (53 mg, 0.27 mmol, 95%); \underline{R}_F (diethyl ether-petroleum ether b.r. 40-60 °C, 1:1) 0.48; v_{max} (film) 2950 s, 2900 s and 2860 s (C-H str.), 2810 m (C-H str. of an OCH₃), 1740 s (C=O str.), 1640 w (C=N str.), 1450 s (C-H def.), 1370 s cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.25 (t, 3 H, CH₃ isomer A), 1.26 (t, 3 H, CH₃ isomer B), 1.39-2.62 (complex m, 16 H, H₂, H₄, H₅ and H₆ in both isomers), 3.07 (complex m, 1 H, H₁ in isomer A), 3.30 (complex m, 1 H, H₁ in isomer B), 3.82 (s, 3 H, OCH₃ in isomer A), 3.824 (s, 3 H, OCH₃ in isomer B), 4.141 (q, 2 H, OCH₂ in isomer A), 4.144 (q, 2 H, OCH₃ in isomer B) ppm; δ_C (75.5 MHz, CDCl₃, TMS) 14.21 (2 x CH₃), 24.11 (C5 in isomer A), 24.38 (C5 in isomer B), 25.24 (C6 in isomer B), 26.87 (C6 in isomer A), 28.49 (C4 in isomer A), 28.60 (C4 in isomer B), 31.35 (C2 in isomer B), 34.01 (C2 in isomer A), 42.16 (C1 in isomer B), 43.33 (C1 in isomer A), 60.54 (OCH₂ in

isomer B), 60.59 (OCH₂ in isomer A), 61.11 (OCH₃ in isomer B), 61.13 (OCH₃ in isomer A), 157.37 (C3 in isomer A), 157.68 (C3 in isomer B), 174.24 (C=O in isomer A), 174.34 (C=O in isomer B) ppm; m/z (CI⁺) 200 (<u>MH</u>⁺, 100%), 168 (<u>M</u>-CH₃O, 5%), 126 (4%), 94 (8%); (Found: <u>MH</u>⁺, 200.1287. C₁₀H₁₇NO₃ requires <u>MH</u>⁺, 200.1287).

3.6.1 <u>Attempted Cleavage of the N-O Bond in 4-Methoxyaminochroman-3-ylidene</u> (141) by Aluminium Amalgam²¹⁰



4-Methoxyaminochroman-3-ylidene (141) (250 mg, 1.31 mmol) was dissolved in a solution of THF (10 cm³) and water (1 cm³) and cooled to 0 °C under a nitrogen atmosphere. The aluminium amalgam was prepared by sequentially dipping pieces of aluminium foil (350 mg, 13.1 mmol) in aqueous potassium hydroxide (1 M), water, aqueous mercury (II) chloride (0.5%), water and finally THF. The amalgam was then added to the reaction mixture. The reaction mixture was stirred at 4 °C for 12 h. Analysis of the reaction mixture by thin layer chromatography showed no reaction. Further amalgam was added (prepared from 1,25 g, 6.54 mmol aluminium) and the reaction stirred at 4 °C for 48 h. Thin layer chromatography still showed no reaction. The reaction mixture was diluted with THF (100 cm³) and the resultant slurry was filtered. THF and water was evaporated under reduced pressure. ¹H nmr of the crude material revealed unreacted starting material.

3.6.2 Attempted N-O Bond Cleavage with Samarium Diiodide²¹²



4-Methoxyaminochroman-3-ylidene (141) (100 mg, 0.52 mmol) in dry THF (2 cm³) was added to a solution of samarium diiodide (420 mg, 1.04 mmol, 0.1 M solution in THF) under an Argon atmosphere. The solution was stirred at room temperature for 30 min, turning from a deep blue colour to yellow within that time. Analysis of the reaction mixture by thin layer chromatography revealed only starting materials.

3.6.3 Attempted N-O Bond Cleavage with Zinc and Acetic Acid



Zinc powder (1.28 g, 19.6 mmol) was added to a solution of 4-

methoxyaminochroman-3-ylidene (141) (250 mg, 1.31 mmol) in glacial acetic acid (5 cm^3) at 0 °C. The reaction was heated at 50 - 60 °C for 24 h. Analysis of the reaction mixture by thin layer chromatography revealed no reaction.

3.6.4 Preparation of 1,2,3,4,4a,9,9a,10-octahydroacridine (264).



4a-Methoxyaminocyclohex[a]indan (195) (160mg, 0.74 mmol) in diethyl ether dried over sodium (2 cm³) was added dropwise to a suspension of lithium aluminium hydride (30 mg, 0.75 mmol) in diethyl ether (2 cm³) under a nitrogen atmosphere. The reaction mixture was heated at reflux temperature for 2h. Excess lithium aluminium hydride was quenched with diethyl ether (50 cm³), dried (MgSO₄), filtered and solvent evaporated *in vacuo*. Column chromatography (silica, 60 mesh, dichloromethane-petroleum ether b.r. 60-80 °C, 1:1) afforded a mixture of *trans*-1,2,3,4,4a,9,9a,10-octahydroacridine (164a) (102 mg, 0.55 mmol, 73%) and *cis* -1,2,3,4,4a,9,9a,10-octahydroacridine (164b) (32 mg, 0.17 mmol), 23%) as plates.

trans-1,2.3.4.4a,9.9a,10-octahydroacridine (164a)



M.p. 80 - 82 °C (from petroleum ether, b.r. 60-80 °C).²¹³ R_F (dichloromethane-petroleum ether b.r. 60-80 °C) 0.30; v_{max} (CH₂Cl₂) 3400 m (N-H str.), 3010 m (Ar-H, C-H str.), 2910 s, 2880 s and 2840 s (C-H str.), 1600 s and 1580 s (Ar ring vib.), 1480 s (C-H def.), cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.25 - 1.56 (complex m, 5 H, H_{1ax}, H_{2ax}, H_{3ax}, H_{4ax}, and H_{9a}), 1.71-1.87 (complex m, 4 H, H_{1eq}, H_{2eq}, H_{3eq} and H_{4eq}), 2.45 (dd, 1 H, ${}^{3}J_{9ax,9a,ax}$ 11.8, ${}^{2}J_{9ax,9eq}$ 16.1 Hz, H_{9ax}), 2.64 (dd, 1 H, ${}^{3}J_{9eq,9a,ax}$ 4.9 Hz, H_{9eq}), 2.81 (td, 1 H, ${}^{3}J_{4a ax, 3ax} = {}^{3}J_{4a ax,9a}$ ax 10.1, ${}^{3}J_{4a ax, 4eq}$ 3.7 Hz, H_{4a ax}), 3.56 (br.s, 1 H, NH), 6.43 (dd, 1 H, ${}^{4}J_{5,7}$ 1.1, ${}^{3}J_{5,6}$ 8.0 Hz, H₅), 6.58 (ddd, 1 H, ${}^{3}J_{7,6}$ 7.3, ${}^{3}J_{7,8}$ 7.6 Hz, H₇), 6.91 (d, 1 H, H₈), 6.92 (t, 1 H, H₆) ppm; δ_{C} (75.5 MHz, CDCl₃, TMS) 24.6 (C2), 25.9 (C3), 31.9 (C1), 33.5 (C4), 34.6 (C9), 37.6 (C9a), 56.0 (C4a), 113.6 (C5), 116.9 (C7), 121.4 (C8a), 126.6 (C6), 129.1 (C8), 144.5 (C10a) ppm.

cis-1,2,3,4,4a,9,9a,10-octahydroacridine (164b)



 $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.26-1.54 (complex m, 5 H, H_{1ax}, H_{2ax}, H_{3ax}, H_{4ax}, and H_{9a}), 1.57-1.71 (complex m, 4 H, H_{1eq}, H_{2eq}, H_{3eq} and H_{4eq}), 1.96 (ddd, 1 H,³J_{4a,4eq} 4.3, ³J_{4a,4ax} 9.3, ³J_{4a,9a} 13.6 Hz, H_{4a}), 2.51 (dd, 1 H, ³J_{9eq,9a} 4.1, ²J_{9eq,9ax} 16.3 Hz, H_{9eq}), 2.90 (dd, 1 H, ³J_{9ax}, 9a 5.7 Hz, H_{9ax}), 3.50 (br.dd, 1 H, NH), 6.44 (dd, 1 H, ⁴J_{5,7} 1.1, ⁴J_{5,6} 8.0 Hz, H₅), 6.56 (td, 1 H, ³J_{7,6} = ³J_{7,8} 7.3 Hz, H₇), 6.94 (complex m, 2 H, H₆ and H₈) ppm; $\delta_{\rm C}$ (75.5 MHz, CDCl₃, TMS) 20.6 (C2), 24.6 (C3), 27.1 (C1), 31.6 (C4), 32.4 (C9), 32.8 (C9a), 49.9 (C4a), 113.1 (C5), 116.3 (C7), 119.1 (C8a), 126.4 (C6), 129.5 (C8), 143.7 (C10a) ppm.; m/z (CI⁺), 187 (<u>M</u>⁺, 40%), 186 (M-H, 42%), 144 (82%), 130 (100%), 117 (17%), 91 (C₇H₇⁺, 36%).

3.6.5 Preparation of 2-Methyl-1,2,3,4-tetrahydroquinoline (268)^{213,222}



1-Methoxyamino-1-methylindan (176) (440 mg, 2.49 mmol) in diethyl ether (2 cm³) was added dropwise to a stirred suspension of lithium aluminium hydride (94 mg, 2.49 mmol) in dry diethyl ether (5 cm³). The reaction was heated at reflux temperature for 2h after which time the reaction was cooled and then quenched with wet diethyl ether. The solution was diluted with more diethyl ether, dried (MgSO₄), and the solvent was then removed under reduced pressure. The residue was purified by column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 2:3) to give the product (268) as a clear, colourless oil (337 mg, 2.29 mmol, 92%), which on standing gradually turned brown. R_F (diethyl ether-petroleum ether b.r. 40-60 °C; v_{max} (film) 3090 m (N-H str.), 3020 w (Ar-H, C-H str.), 2960 s, 2910 s and 2840 s (C-H str.), 1600 s, 1580 s and 1490 s (Ar ring vib.), 1450 m (C-H def.),1370 m (CH3 sym. def.), 740 s (*o*-disubstituted Ar) cm⁻¹; δ_{H} (300 MHz, CDCl₃, TMS) 1.18 (d, 3 H, ³J_CH_{3,2} 6.3 Hz, CH₃), 1.56 (dddd, 1 H, ³J_{3b,2} 2.9, ³J_{3b,4b} 3.6, ³J_{3b,4a} 5.6 Hz, H_{3b}), 2.70 (ddd, 1 H, ²J_{4b,4a} 16.5 Hz, H_{4b}), 2.81 (ddd, 1 H, H_{4a}), 3.36 (dq, 1 H, H₂), 3.46 (br.s, 1 H, NH), 6.43 (dd, 1H, ${}^{4}J_{8,6}$ 1.2, ${}^{3}J_{8,7}$ 8.4 Hz, H₈), 6.58 (td, 1 H, ${}^{3}J_{6,5}$ = ${}^{3}J_{6,7}$ 7.4 Hz, H₆), 6.94 (complex m, 2 H, H₅ and H₇) ppm; δ_{C} (75.5 MHz, CDCl₃, TMS) 22.5 (CH₃), 26.5 (C3), 30.1 (C4), 47.1 (C2), 113.9 (C8),116.9 (C6), 121.0 (C4a), 126.6 (C7), 129.2 (C5), 144.6 (C8a) ppm.

3.6.6 <u>Preparation of Ethyl 3a-methoxyaminocyclopent[a]indan-8a-carboxylate (180)</u> with Lithium Aluminium Hydride



Ethyl 3a-methoxyaminocyclopent[a]indan-8a-carboxylate (180) (500 mg, 1.82 mmol) in diethyl ether (2 cm³) was added dropwise to a suspension of lithium aluminium hydride (100 mg, 2.73 mmol) in diethyl ether (10 cm³) under a nitrogen atmosphere. The reaction mixture was heated at reflux temperature for 2 h. The reaction was quenched with wet diethyl ether, diluted with further diethyl ether (20 cm³) and dried (MgSO₄). Solvent was evaporated *in vacuo* and the product purified by column chromatography (silica, 60 mesh, diethyl ether-petroleum ether b.r. 40-60 °C, 9:1). This afforded an 84:16 mixture of 1,1a,1b,2-tetrahydro-1bhydroxymethylcyclopent[b]quinoline (269):8b-amino-3ahydroxymethylcyclopent[a]indan (270) (340 mg, 17.11 mmol, 94%) as a clear colourless oil. An analytical sample of (269) was separated by column

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1,1a,1b,2-tetrahydro-1b-hydroxymethylcyclopent[b]quinoline (269)

<u>R</u>_E (diethyl ether-petroleum ether b.r. 40-60 °C, 1:1) 0.18; v_{max} (film) 3610-3150 br. s. (O-H and N-H str.), 3040 w and 3000 w (Ar-H, C-H str.), 2940 s and 2860 s (C-H str.), 1600 s and 1580 m (Ar ring vib.), 1490 s (C-H def.) 1300 m, 1260 m cm⁻¹; $\delta_{\rm H}$ (300 MHz, CDCl₃, TMS) 1.46-2.02 (complex m, 7 H, H₇, H₈, H₉ and OH), 2.56 and 2.70 (AB quartet, 2 H, ²J_{8ax,8eq} 15.6 Hz, H_{8ax} and H_{8eq}), 3.41 and 3.47 (AB quartet, 2 H, ²J 10.7 Hz, CH₂OH), 3.46 (dd, 1 H, ³J_{1a,7eq} 3.1, ³J_{1a,7ax} 5.6 Hz, H_{1a}), 6.59 (dd, 1 H, ⁴J_{6,7} 1.1, ³J_{6,5} 7.3 Hz, H₆), 6.68 (dt, 1 H, ³J_{7,6} = ³J_{7,8} 7.4 Hz, H₇), 6.99 -7.03 (complex m, 2 H, H₆ and H₈) ppm; $\delta_{\rm C}$ (75.5 MHz, CDCl₃, TMS) 20.5 (C8), 32.5 (C9), 33.5 (C7), 34.0 (C2), 45.0 (C9a), 57.3 (C1a), 67.9 (CH₂OH), 113.5 (C6), 117.1 (C4), 121.6 (C2a), 126.7 (C5), 129.1 (C3), 143.6 (C6a) ppm; m/z (EI⁺) 203 (M⁺, 100%), 187 (10%), 172 (M - CH₃O, 58%), 160 (28%), 144 (30%), 130 (15%); (Found: M⁺, 203.1310. C₁₃H₁₇NO requires M⁺, 203.1310).

8b-amino-3a-hydroxymethylcyclopent[a]indan (270)

<u>R</u>_E (diethyl ether-petroleum ether b.r. 40-60 °C, 1:1) 0.21; δ_{H} (300 MHz, CDCl₃, TMS) 1.39-1.74 (complex m, 4 H, H_{2ax}, H_{2eq}, OH and H_{3ax} or H_{3eq}), 1.80-2.01 (complex m, 3 H, H_{1ax}, H_{1eq} and H_{3ax} or H_{3eq}), 2.65 (d, 1 H, ²J_{4ax,4eq} 16.7 Hz, H_{4ax} or H_{4eq}), 3.12 (d, 1 H, H_{4ax} or H_{4eq}), 3.65 and 3.69 (AB quartet, 2 H, ²J 11.7 Hz, C<u>H₂OH</u>), 7.11-7.29 (complex m, 4 H, H4, H5,H6 and H7) ppm; δ_{C} (75.5 MHz, CDCl₃, TMS) 22.6 (C2), 38.1 (C3), 38.5 (C1), 42.6 (C4), 55.1 (C3a), 66.6 (<u>C</u>H₂OH), 81.8 (C8b), 123.8 (C6), 124.2 (C5), 126.6 (C7), 127.9 (C8), 145.1 (C4a) ppm. References

REFERENCES

- 1) Sir M. Roth, Br. Med. Bull., 1986, 42, 1.
- 2) A. S. Henderson, Br. Med. Bull., 1986, 42, 3.
- 3) G. Ferry, New Scientist, 1988, 44.
- 4) G. Ferry, New Scientist, 1989, 27.
- 5) C. N. Martyn, D. J. P. Barker, C. Osmond, E. C. Harris, J. A. Edwardson and R. F. Lacey, *The Lancet*, 1989, 59.
- 6) W. K. Summers, L. V. Majovski, G. M. Marsh, K. Tachiki and A. Kling, The New England Journal of Medicine, 1986, 315, 1242.
- 7) J. T. Coyle, D. L. Price and M. R. DeLong, Science, 1983, 219, 1184.
- 8) R. J. Wurtman, Scientific American, 1985, 48.
- 9) E. Hollander, R. C. Mohs and K. L. Davis, Br. Med. Bull., 1986, 42, 97.
- 10) E. M. Kidd, Nature (London), 1963, 197, 192.
- H. M. Wisniewski, H. K. Narang and R. D. Terry, J. Neurol. Sci., 1976, 27, 173.
- 12) R. D. Terry and P. Davies, Annu. Rev. Neurosci., 1980, 3, 77.
- P. J. Whitehouse, D. L. Price, A. W. Clark, J. T. Coyle and M. R. DeLong, Ann. Neurol., 1981, 10, 122.
- 14) F. M. Hershenson and W. H. Moos, J. Med. Chem., 1986, 29, 1125.
- 15) J. Williamson, I. H. Stokoe, S. Gray et al., The Lancet, 1964, 1, 1117.
- 16) L. H. Heston, Science, 1977, 196, 322.
- C. M. Yates, I. M. Ritchie, J. Simpson, A. F. J. Maloney and A. Gordon, *The Lancet*, 1981, 39.
- 18) D.R. Crapper, S.S. Krishnan and A.J. Dalton, Science, 1973, 180, 511.
- 19) P. Davies and A. J. F. Maloney, *The Lancet*, 1976, 1403.
- E. K. Perry, B. E. Tomlinson, G. Blessed, K. Bergmann, P. H. Gibson and
 R. H. Perry, Br. Med. J., 1978, 1457.

- N. R. Sims, D. M. Bowen, S. J. Allen, C. C. T. Smith, D. Neary, D. J.
 Thomas and A. N. Davidson, J. Neurochem., 1983, 40, 503.
- 22) R. H. Perry, D. Irving, G. Blessed, E. K. Perry and A. F. Fairbairn, *The Lancet*, 1989, 166.
- 23) A. Barbeau, G. F. Murphy and T. S. Sourkes, Science, 1961, 133, 1706.
- 24) A. P. Kozikowski, J. Heterocycl. Chem., 1990, 27, 97.
- 25) X.-C. Tang, Y.-F. Han, X.-P. Chen and X.-D. Zhu, Acta Pharm. Sin., 1986,
 7, 507.
- J.-S. Liu, Y.-L. Zhu, C.-M. Yu, Y.-Z. Zhou, Y.-Y. Han, F.-W. Wu and B. F. Qi, Can. J. Chem., 1986, 64, 837.
- A. R. Katritzky, "Handbook of Heterocyclic Chemistry", Pergamon Press,
 Oxford, 1985, 168.
- 28) H. Xu, X.-C. Tang, Acta Pharm. Sin., 1987, 8, 18.
- 29) Y. Wang, D.-X. Yue and X.-C. Tang, Acta Pharm. Sin., 1986, 7, 110.
- 30) S.-L. Zhang, New Drugs and Clinical Remedies, 1986, 5, 260.
- 31) D. L. Beveridge and R. J. Radna, J. Am. Chem. Soc., 1971, 93, 3759.
- 32) C. Bankiewicz, Chem. Ind., 1956, 1019.
- 33) K. Wiesner, W. A. Ayer. L. R. Fowler and Z. Valenta, *Chem. Ind.*, 1957, 564.
- 34) K. Wiesner, Z. Valenta, W. A. Ayer, L. R. Fowler and J. E. Francis, *Tetrahedron*, 1958, 4, 87.
- Z. Valenta, H. Yoshimura, E. F. Rogers, M. Ternbah and K. Wiesner, *Tetrahedron Lett.*, 1960, no. 10, 26.
- W. A. Ayer, J. A. Berezowsky and G. G. Iverach, *Tetrahedron*, 1962, 18, 567.
- 37) H. Yoshimura, Z. Valenta and K. Wiesner, *Tetrahedron Lett.*, 1960, no. 12, 14.
- 38) M. Shamma, C. D. Jones and J. A. Weiss, *Tetrahedron*, 1969, 25, 4347.
- 39) M. Shamma and J. B. Moss, J. Am. Chem. Soc., 1961, 83, 5038.

- 40) M. Shamma and J. M. Richey, J. Am. Chem. Soc., 1962, 84, 1739.
- 41) M. Shamma and J. M. Richey, J. Am. Chem. Soc., 1963, 85, 2507.
- W. A. Ayer, L. M. Browne, H. Orszanska, Z. Valenta and J.-S. Liu, Can. J.
 Chem., 1989, 67, 1539.
- 43) D. Gravel, L. Bordeleau, G. Ladouceur, J. Rancourt and D. Thoraval, *Can. J. Chem.*, 1984, 62, 2945.
- 44) A. S. Kende and J. A. Schneider, Synth. Commun., 1979, 9, 419.
- 45) D. Gravel, R. Deziel and L. Bordeleau, Tetrahedron Lett., 1983, 24, 699.
- A. S. Kende, F. H. Ebetino, R. Battista, R. J. Boatman, D. P. Lorah and E.
 Lodge, *Heterocycles*, 1984, 22, 91.
- 47) A. S. Kende, R. Battista and S. B. Sandoval, *Tetrahedron Lett.*, 1984, 25, 1341.
- 48) E. W. Colvin, J. Martin, W. Parker, R. A. Raphael, B. Shroot and M. Doyle,
 J. Chem. Soc., Perkin Trans. 1, 1972, 860.
- 49) L. Qian and R. Ji, Tetrahedron Lett., 1989, 30, 2089.
- T. Shiori, K. Ninomiya and S. I. Yamada, J. Am. Chem. Soc., 1972, 94, 6203.
- 51) Y. Xia and A. P. Kozikowski, J. Am. Chem. Soc., 1989, 111, 4116.
- 52) G. P. Pollini, A. Barco and G. DeGiuli, Synthesis, 1972, 44
- 53) A. P. Kozikowski, E. R. Reddy and C. P. Miller, J. Chem. Soc., Perkin Trans. 1, 1990, 195.
- 54) J. Thesing and A. Miller, Chem. Ber., 1957, 90, 711.
- 55) S. Danishefsky, T. Kitahara, R. McKee and P. F. Schuda, J. Am. Chem. Soc., 1976, 98, 6715.
- 56) R. K. Boeckman, J. P. Bershas, J. Clardy and B. Solheim, J. Org. Chem., 1977, 42, 3630.
- 57) B. Giese, "Radicals in Organic Synthesis : Formation of Carbon-Carbon Bonds", Pergamon Press, New York, 1986.
- 58) C. Walling, Tetrahedron, 1985, 41, 3887.

- 59) B. Giese, Angew. Chem., Int. Ed. Engl., 1985, 24, 553.
- K. U. Ingold in J. Kochi (Ed.): "Free Radicals", vol. 1, Wiley, New York, 1973, p37.
- 61) B. Giese, Angew. Chem., Int. Ed. Engl., 1983, 22, 753.
- 62) B. Giese and H. Horler, Tetrahedron Lett., 1983, 24, 3221.
- 63) B. Giese and H. Horler, Tetrahedron, 1985, 41, 4025.
- 64) D. J. Hart, Science, 1984, 223, 883.
- 65) S. U. Park, S.-K. Chung and M. Newcomb, J. Am. Chem. Soc., 1986, 108, 240.
- N. A. Porter, D. R. Magnin and B. T. Wright, J. Am. Chem. Soc., 1986, 108, 2787.
- D. C. Nonhebel, J. M. Tedder and J. C. Walton, "Radicals", Cambridge University Press, 1979.
- 68) M. Julia, C. Descoins, M. Baillarge, B. Jacquet, D. Uguen and F. A. Groeger, Tetrahedron, 1975, 31, 1737.
- 69) A. L. J. Beckwith, Tetrahedron, 1981, 37, 3073.
- 70) A. L. J. Beckwith and C. H. Schiesser, Tetrahedron, 1985, 41, 3925.
- A. Y. Mohammed and D. L. J. Clive, J. Chem. Soc., Chem. Commun., 1986, 588.
- 72) A. L. J. Beckwith, D. M. O'Shea and D. H. Roberts, J. Chem. Soc., Chem. Commun., 1983, 1445.
- 73) M. Ramaiah, Tetrahedron, 1987, 43, 3541.
- 74) D. P. Curran, Synthesis, 1988, 417 and 489.
- 75) W. P. Neumann, Synthesis, 1987, 665.
- 76) C. P. Jasperse, D. P. Curran and T. L. Fevig, Chem. Rev., 1991, 91, 1237.
- D. H. R. Barton and S. W. McCombi, J. Chem. Soc., Perkin Trans. 1, 1975, 1574.
- 78) J. Dupuis, B. Giese, D. Rüegge, H. Fischer, H. G. Korth and R. Sustmann, Angew. Chem., Int. Ed. Engl., 1984, 23, 896.

- 79) J. K. Choi and D. J. Hart, Tetrahedron, 1985, 41, 3959.
- N. Ono, H. Miyake, R. Tamura and A. Kaji, *Tetrahedron Lett.*, 1981, 22, 1705.
- 81) J. I. G. Cadogan, Pure Appl. Chem., 1967, 15, 153.
- 82) D. H. Hey, M. J. Perkins and G. H. Williams, J. Chem. Soc., 1965, 110.
- 83) B. Giese, K. Gröninger, Tetrahedron Lett., 1984, 25, 2743
- 84) M. Ladlow and G. Pattenden, Tetrahedron Lett., 1984, 25, 4317
- 85) W. G. Bentrude and K. R. Darnall, J. Am. Chem. Soc., 1968, 90, 3588.
- F. Minisci, R. Galli, M. Cecere, V. Malatasta and T. Caronna, *Tetrahedron Lett.*, 1968, 9, 5609.
- 87) D. J. Hart and F. L. Seely, J. Am. Chem. Soc., 1988, 110, 1631.
- 88) H. Hillgärtner, W. P. Neumann and B. Schroeder, *Liebigs Ann. Chem.*, 1975, 586.
- 89) E. J. Corey and S. G. Pyne, Tetrahedron Lett., 1983, 24, 2821
- 90) H. Nishiyama, H. Arai, Y. Kanai, H. Kawashima and K. Itoh, *Tetrahedron Lett.*, 1986, 27, 361.
- P. A. Bartlett, K. L. McLaren and P. C. Ting, J. Am. Chem. Soc., 1988, 110, 1633.
- 92) E. J. Enholm, J. A. Burroff and L. M. Jaramillo, *Tetrahedron Lett.*, 1990, *31*, 3727.
- 93) G. Stork and R. Mook, J. Am. Chem. Soc., 1983, 105, 3721.
- 94) J. E. Baldwin, J. Chem. Soc., Chem. Commun., 1976, 734.
- 95) A. L. J. Beckwith, D. H. Roberts, C. H. Schiesser and A. Wallner, *Tetrahedron Lett.*, 1985, 26, 3349.
- 96) D. P. Curran and D. M. Rakiewicz, J. Am. Chem. Soc., 1985, 107, 1448.
- 97) D. P. Curran and M.-H. Chen, Tetrahedron Lett., 1985, 26, 4991.
- 98) T. L. Fevig, R. L. Elliott and D. P. Curran, J. Am. Chem. Soc., 1988, 110, 5064.
- 99) D. P. Curran and S.-C. Kuo, J. Am. Chem. Soc., 1986, 108, 1106.
- 100) D. P. Curran and S.-C. Kuo, Tetrahedron, 1987, 43, 5653.
- 101) A. I. Meyers and B. A. Lefker, Tetrahedron, 1987, 43, 5663.
- 102) H. Pak, I. I. Canalda and B. Fraser-Reid, J. Org. Chem., 1990, 55, 3009.
- 103) G. Stork and P. M. Sher, J. Am. Chem. Soc., 1986, 108, 303.
- 104) J. D. Kilburn, Tertrahedron Lett., 1990, 31, 2193.
- 105) D. C. Lathbury, P. J. Parsons and I. Pinto, J. Chem. Soc., Chem. Commun., 1988, 81.
- 106) P. J. Parsons, P. A. Willis and S. C. Eyley, J. Chem. Soc., Chem. Commun., 1988, 283.
- 107) D. E. Cladingboel and P. J. Parsons, J. Chem. Soc., Chem. Commun., 1990, 1543.
- 108) R. J. Ferrier, P. M. Petersen and M. A. Taylor, J. Chem. Soc., Chem. Commun., 1989, 1247.
- B. A. San Miguel, B. Maillard and B. Delmond, *Tetrahedron Lett.*, 1987, 28, 1247.
- 110) E. J. Corey, K. Shimoji and C. Shih, J. Am. Chem. Soc., 1984, 106, 6425.
- 111) H. Nagano, Y. Seko and K. Nakai, J. Chem. Soc., Perkin Trans. 1, 1990, 2153.
- 112) R. Tsang and B. Fraser-Reid, J. Am. Chem. Soc., 1986, 108, 2116.
- 113) R. Tsang and B. Fraser-Reid, J. Am. Chem. Soc., 1986, 108, 8102.
- 114) R. Tsang, J. K. Dickson, H. Pak, R. Walton and B. Fraser-Reid, J. Am. Chem. Soc., 1987, 109, 3484.
- 115) P. Dowd and S.-C. Choi, J. Am. Chem. Soc., 1987, 109, 3493.
- 116) P. Dowd and S.-C. Choi, J. Am. Chem. Soc., 1987, 109, 6548.
- 117) A. L. J. Beckwith, D. M. O'Shea and S. W. Westwood, J. Am. Chem. Soc., 1988, 110, 2565.
- 118) P. Dowd and S.-C. Choi, Tetrahedron, 1989, 45, 77.
- 119) N. A. Porter, D. R. Magnin and B. T. Wright, J. Am. Chem. Soc., 1986, 108, 2787.

- 120) P. Dowd and S.-C. Choi, Tetrahedron Lett., 1991, 32, 565.
- 121) H. Suginome and S. Yamada, Tetrahedron Lett., 1987, 28, 3963.
- 122) C. W. Ellwood and G. Pattenden, Tetrahedron Lett., 1991, 32, 1591.
- 123) H. Hiemstra, H. P. Fortgens and W. Spekamp, *Tetrahedron Lett.*, 1985, 26, 3155.
- 124) P. Cazeau and E. Frainnet, Bull. Soc. Chim. Fr., 1972, 1658.
- 125) M. Petrzilka and J.I. Grayson, Synthesis, 1981, 753.
- 126) S. Danishefsky, M. P. Prisbylla and S. Hiner, J. Am. Chem. Soc., 1978, 100, 2918.
- 127) G.H. Posner, A. Haces, W. Harrison and C.M. Kinter, J. Org. Chem., 1987, 52, 4836
- 128) K. Yamamoto, S. Suzuki and T. Tsiji, Chem. Letters, 1978, 649.
- 129) R. Grewe and I. Hinrichs, Chem. Ber., 1964, 97, 443.
- J. C. Barrish, H. L. Lee, T. Mitt, G. Pizzolato, E. G. Baggiolini and M. R. Uskokvic, J. Org. Chem., 1988, 53, 4282.
- 131) M. M. Campbell, A. D. Kaye, M. Sainsbury and R. Yavarzadeh, *Tetrahedron Lett.*, 1984, 25, 1629.
- 132) M. D. Dowle and D. I. Davies, Chem. Soc. Rev., 1979, 8, 171.
- R. C. Cambie, P. S. Rutledge, R. F. Somerville and P. D. Woodgate, Synthesis, 1988, 1009.
- 134) F. B. Gonzalez and P. A. Bartlett, Org. Synth., 1985, 64, 175.
- B. M. Trost, J. M. Timko and J. L. Stanton, J. Chem. Soc., Chem.
 Commun., 1978, 436.
- 136) S. Danishefsky, P. F. Schuda, T. Kitahara and S. J. Etheredge, J. Am. Chem. Soc., 1977, 99, 6066.
- 137) R. Grewe, A. Heinke and C. Sommer, Chem. Ber., 1956, 89, 1978.
- 138) M. Kato, M. Kageyama, R. Tanaka, K. Kuwahara and A. Yoshikoshi, J. Org. Chem., 1975, 40, 1932.

- 139) L. E. Overman, T. C. Malone and G. P. Meier, J. Am. Chem. Soc., 1983, 105, 6993.
- 140) L. C. Tu and P. S. Mariano, J. Am. Chem. Soc., 1987, 109, 5287.
- 141) J. C. Gremain and R. Remuson, Tetrahedron Lett., 1985, 26, 4083.
- 142) S. D. Larsen, P. A. Greico and W. F. Fobare, J. Am. Chem. Soc., 1986, 108, 3512.
- 143) P. Brownbridge, Synthesis, 1983, 1 and references therein
- 144) E. W. Colvin, "Silicon Reagents in Organic Synthesis", Academic Press, 1988, Chapter 15.
- 145) Rhône-Poulenc S.A., Belgian Patent 670769/1966; Chem. Abs., 1966, 65, 5487.
- 146) Rhône-Poulenc S.A., French Patent 1436568/1966; Chem. Abs., 1974, 80, 15062.
- 147) M. E. Jung, C. A. McCombs, Tetrahedron Lett., 1976, 17, 2935.
- 148) H. O. House, L. J. Czuba, M. Gall and H. D. Olmstead, J. Org. Chem., 1969, 34, 2324.
- 149) T. L. Gilchrist and R. C. Storr, "Organic Reactions and Orbital Symmetry", Cambridge University Press, 1979.
- 150) I. Fleming, "Frontier Orbitals and Organic Chemical Reactions", John Wiley and Sons, 1987.
- 151) T. W. Greene, "Protective Groups in Organic Synthesis", J. Wiley and Sons, 1981.
- 152) H. C. Cunningham and A. R. Day, J. Org. Chem., 1973, 38, 1223.
- 153) D. H. Miles and E. J. Parish, Tetrahedron Lett., 1972, 13, 3987.
- 154) E. J. Corey, I Székely and C. S. Shiner, Tetrahedron Lett., 1977, 18, 3529.
- 155) E. J. Parish and D. H. Miles, J. Org. Chem., 1973, 38, 1223.
- P. R. Brook and J. M. Harrison, J. Chem. Soc., Chem. Commun., 1972, 997.
- 157) K. C. Nicolau and Zhysenko, J. Am. Chem. Soc., 1977, 99, 3185.

- 158) K. C. Nicolau, S. P. Seitz, W. J. Sipio and J. F. Blount, J. Am. Chem. Soc., 1979, 101, 3884.
- 159) D. L. J. Clive and G. Chittattu, J. Chem. Soc., Chem. Commun., 1977, 484.
- 160) D. L. J. Clive, C. G. Russell, G. Chittattu and A Singh, *Tetrahedron*, 1980, 36, 1399.
- 161) D. Todd, J. Am. Chem. Soc., 1949, 71, 1353.
- 162) Y. Ueno, R. K. Khare and M. Okawara, J. Chem. Soc., Perkin Trans. 1, 1983, 2637.
- 163) A. L. J. Beckwith and S. W. Westwood, Tetrahedron, 1989, 45, 5269.
- 164) W. P. Neumann and E. Heymann, Angew. Chem., Int. Ed. Engl., 1963, 2, 160.
- 165) W. P. Neumann and E. Heymann, Liebigs Ann. Chem., 1965, 683, 24.
- 166) D. H. Williams and I. Fleming, "Spectroscopic Methods in Organic Chemistry", Fourth Edition Revised, McGraw-Hill, London, 1989, p.137.
- 167) B. Giese and B. Kopping, Tetrahedron Lett., 1989, 30, 681.
- 168) G. Stork and N. H. Baine, J. Am. Chem. Soc., 1982, 104, 2321.
- 169) G. Stork and N. H. Baine, Tetrahedron Lett., 1985, 26, 5927.
- 170) E. Pretsch, J. Clerc, J. Seibl and W. Simon, "Tables of Spectral Data for Structure Determination of Organic Compounds", Springer-Verlag, 1983, p.H175.
- 171) Y. Ueno, K. Chino and M. Okawara, Tetrahedron Lett., 1982, 23, 2575.
- 172) R. K. Singh and S. Danishefsky, J. Org. Chem., 1975, 40, 2969.
- 173) C. S. Marvel, Organic Syntheses, Coll. Vol. 3, Second Edition, p. 705.
- 174) N. G. Gaylord, "Complex Metal Hydrides", Interscience, 1956, 107.
- 175) A. J. Mancuso and D. Swern, Synthesis, 1981, 165.
- 176) K. Omara and D. Swern, Tetrahedron, 1978, 34, 165.
- 177) M. Marx 2nd T. T. Tidewell, J. Org. Chem., 1984, 49, 788.
- 178) S. Boatman, T. M. Harris and C. R. Hauser, Synthesis, 1965, 3321.

- 179) E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, 1962, p.273.
- 180) S.-J. Chang, D. McNally, S. Shary-Tehrany, Sister M. J. Hickey and R. H. Boyd, J. Am. Chem. Soc., 1970, 92, 3109.
- 182) M. Nagai, J. Lazor and C. S. Wilcox, J. Org. Chem., 1990, 55, 3400.
- 183) J. F. Liebman and A. Greenberg, Chem. Rev., 1976, 76, 311.
- 184) W. C. Agosta and S. Wolff, J. Org. Chem., 1975, 40, 1699.
- 185) H. O. House and G. A. Frank, J. Org. Chem., 1965, 30, 2948.
- 186) A. L. J. Beckwith and D. H. Roberts, J. Am. Chem. Soc., 1986, 108, 5893.
- 187) D. L. J. Clive, D. R. Cheshire and L. Set, J. Chem. Soc., Chem. Commun., 1987, 353.
- 188) R. B. Woodward, I. J. Pachter and M. L. Scheinbaum, Org. Synth., 1974, 54, 39.
- 189) J. K. Whitesell and M. A. Whitesell, Synthesis, 1983, 517.
- G. Stork, A. Brizzolata, H. Landesman, J. Szmuszkovicz and R. Terrel, J.
 Am. Chem. Soc., 1963, 85, 207.
- P. Deslongchamps, "Stereochemical Effects in Organic Chemistry", Pergamon Press, 1983, p.32.
- H. O. House, W. L. Respess and G. M. Whitesides, J. Org. Chem., 1966, 31, 3128.
- 193) E. C. Ashby, Pure Appl. Chem., 1980, 52, 545.
- 194) G. Stork and P. M. Sher, J. Am. Chem. Soc., 1983, 105, 6765.
- 195) D. P. Curran and C.-T. Chang, Tetrahedron Lett., 1987, 28, 2477.
- 196) D. P. Curran and M.-H. Chen, J. Am. Chem. Soc., 1987, 109, 6558.
- 197) G. E. Keck and J. H. Byers, J. Org. Chem., 1985, 50, 5442.
- 198) J. Marco-Contelles, A. Martinez-Grau, M. Bernabé, N. Martin and C. Seoane, SynLett., 1991, 165.
- 199) T. S. Wheeler, Org. Synth., Collective Volume IV, 478.
- 200) A. Rougny and M. Daudon, Bull. Soc. Chim. Fr., 1976, 883.

- 201) E. Grochowski and J. Jurczak, Synthesis, 1976, 682.
- 202) Aldrich Catalogue Handbook of Fine Chemicals.
- 203) D. Enders, H. Eichenauer, U. Baus, H. Schubert and K. A. M. Kremer, Tetrahedron, 1984, 40, 1345.
- 204) J. M. Lalancette and J. R. Brindle, Can. J. Chem., 1970, 48, 735.
- 205) H. Feuer and D. M. Braunstein, J. Org. Chem., 1969, 34, 1817.
- 206) S. Karady, E. G. Corley, N. L. Abramson, J. S. Amato and L. M. Weinstock, *Tetrahedron*, 1991, 47, 757.
- 207) H. Iida, Y. Watanabe and C. Kibayashi, J. Org. Chem., 1985, 50, 1818.
- 208) J. Firl and G. Kresze, Chem. Ber., 1966, 99, 3695.
- 209) G. E. Keck, S. Fleming, D. Nichell and P. Weider, Synth. Commun., 1979, 9, 281.
- 210) A. Bathgate and J. R. Malpass, Tetrahedron Lett., 1987, 28, 5937.
- P. N. Rylander, "Catalytic Hydrogenation Over Platinum Metals", Academic Press, New York, 1967, p.139.
- 212) N. R. Natale, Tetrahedron Lett., 1982, 23, 5009
- 213) J. Buckingham (Ed.), "Dictionary of Organic Compounds", 1982, 5th. Edition, Chapman and Hall.
- 214) C. W. Jefford, D. Kirkpatrick and F. Delay, J. Am. Chem. Soc., 1972, 94, 8905.
- 215) S.-K. Chung, J. Org. Chem., 1980, 45, 3513.
- 216) E. C. Ashby, R. N. DePriest and A. B. Goel, Tetrahedron Lett., 1981, 1763.
- 217) D. P. Curran and H. Liu, J. Am. Chem. Soc., 1991, 113, 2127.
- 218) D. P. Curran, SynLett., 1991, 63.
- 219) M. Newcomb, T. M. Deeb and D. J. Marquardt, Tetrahedron, 1990, 46, 2317.
- 220) W. C. Still, M. Kahn and A. Mitra, J. Org. Chem., 1978, 43, 2923.
- 221) W. A. Nugent and F. W. Hobbs, Jr., Org. Synth., 66, 52.
- 222) G. H. Fisher and H.P. Schultz, J. Org. Chem., 1974, 39, 635.