Novel Nitrogen Chemistry

by

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A thesis submitted to the University of Nottingham in candidature for the degree of Doctor of Philosophy

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Declaration

I declare that the work contained in this thesis has not been, nor is currently being, submitted in candidature for any other degree at this or any other university. I also declare that the substance of this thesis is a result of my own investigations. Where the work of a second party has been used, full acknowledgement of this is made in the text.

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D. W. Knight

(Director of Studies)

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Abstract

Chapter One contains a brief overview of zeolites, their structure, uses and synthesis.

Chapter Two relates to the attempted synthesis of quinuclidines *via* a novel 6-endo-trig radical cyclisation.

Chapter Three contains a review of the 'Zip reaction' and the attempted synthesis of triazacyclopentadecane derivatives.

Chapter Four relates to the synthesis of pyrrolidines *via retro*-Cope cyclisation methodology. Reviews of the Cope and *retro*-Cope reactions, nitrone synthesis and nucleophilic addition of carbon nucleophiles to nitrones are included. The synthetic work is split into three sections relating to the electron withdrawing group used to stabilise the carbanion of the nucleophile - ester, sulphone and sulphoxide - and attempts to indicate the utility of the *retro*-Cope reaction in the diastereoselective synthesis of substituted pyrrolidines.

Contents

Chapter One

Zeolites

1.1 Introduction

The term *zeolite*[1] was first used by Cronstedt[2] in 1756 as a name for an "extraordinary" aluminosilicate mineral which appeared to boil when heated. Since then, around forty naturally occurring zeolites have been identified, mostly found in sedimentary tuff deposits and also in metamorphic rocks and in the cavities of basaltic volcanic rocks. They form as a result of mineralising solutions passing through and modifying the native rock. The formation conditions of such zeolites, although probably mild (temperatures in the region of 70° to 350°C), occur over geological timescales and so, due to their rarity, they had not been investigated to any large degree until the 1940's when laboratory synthesis of zeolites was discovered and large quantities could be acquired. Since the 1970's, when zeolites were found to be economically viable as catalysts in the petrochemical industry, the field of zeolite technology has become big business.

1.2 Structure

Zeolites have framework structures which are formally constructed from $(SiO_4)^{4-}$ and $(AlO_4)^{5-}$ tetrahedra which share vertices and are termed tectosilicates. A variety of different framework structures can be formed since, although the individual tetrahedra are close to regular, the shared oxygen linkages can accommodate T-O-T angles from 130° to 180° (where T=tetrahedral[1] species, *e.g.* Si or Al). These different structures vary in size, shape and dimensions.

A general formula for the aluminosilicate zeolites can be written as;

$$M_{x/m} \cdot Al_xSi_{2-x}O_4 \cdot nH_2O \qquad 0 \geq x \geq 2$$
m=charge on M

Non-framework cations	Framework components	Sorbed water

Partial or complete isomorphous substitution of silicon or aluminium is possible: Si can be exchanged for P, Ge, Ti, Hf or Zr and Al can be exchanged for B, Fe, Cr, Sb, As or Ga, to give *e.g.* aluminophosphates, gallosilicates, *etc.* The framework is anionic and so, for charge compensation, the structure contains non-framework cations equal in total charge to the number of Al atoms (or similar) in the framework. These cations are usually mobile and may be replaced by standard ion exchange methods. As observed with Cronstedt's boiling mineral, the water in the system can be removed by heating, thus leaving an intact, open framework which will sorb water, metal vapours and a variety of other organic and inorganic molecules.[3]

Due to their structure, well-defined crystalline nature and variable stoichiometry, zeolites have sharply defined, uniform pores of one or more discrete sizes (typically between 3Å and 9Å), high acidity (when ion-exchanged with protons), a high surface area (typically >600 m^2g^{-1}) most of which is internal, good thermal stability and are able to sorb and concentrate hydrocarbons. These factors make zeolites an invaluable asset in the petrochemical industry (and others).

1.3 Industrial Uses

The three major areas where zeolites are incorporated in industrial techniques are:

1.3.1 *Ion Exchange*

The major use of zeolite ion-exchangers is in low-phosphate detergents, in which zeolite A (LTA) is used in partial replacement for sodium tripolyphosphate builders and water softeners. Zeolite ion-exchangers are also used in agriculture and in certain waste-water treatments.[1,3]

1.3.2 *As Sorbents*[3]

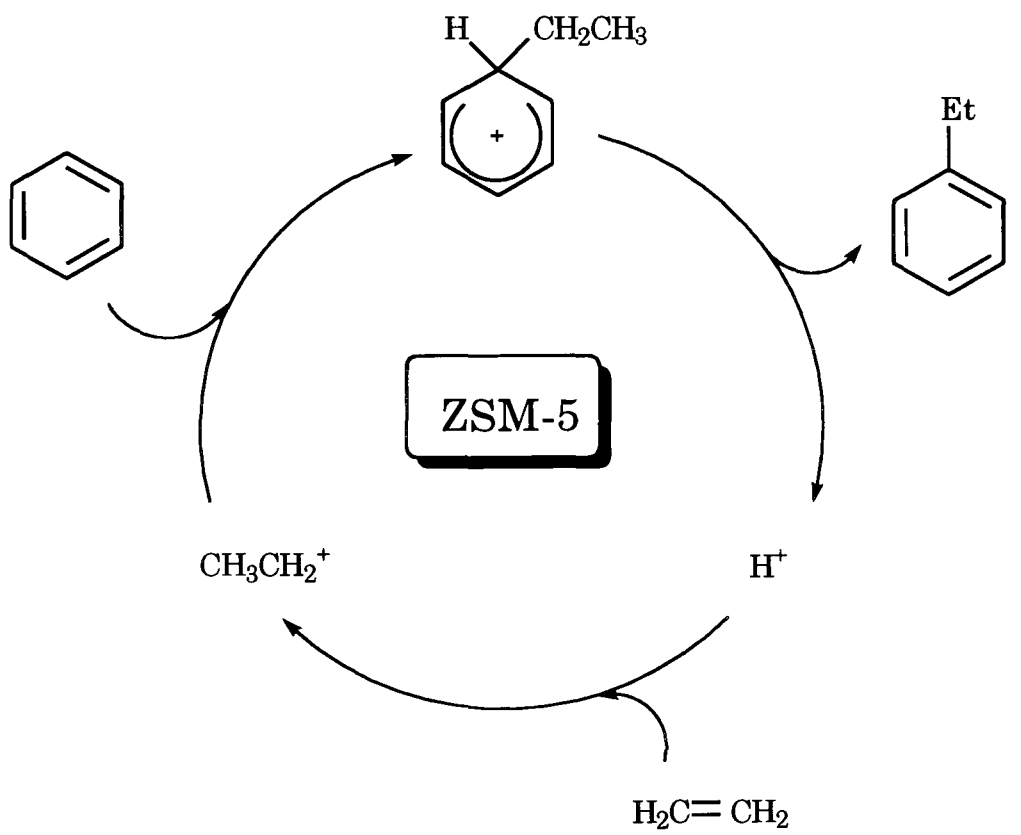
In the highly ordered structure of the zeolite framework, there are micropores of controlled dimensions and accessibility running throughout. These pores control the size of molecule which can pass into the interior of the zeolite. This can result in the selective separation of one molecule from another similar molecule (*e.g.* *n*-paraffins are separated from *iso*-paraffins using a zeolite by selectively adsorbing the *n*-paraffins, the *iso*-paraffins being too big to fit into the pores).

The use of zeolites as molecular sieves is widespread. Selective adsorption of water, oxygen, *etc.*, can be achieved by using a zeolite of specific pore size.

Zeolites tend to be hydrophilic due to their polar nature but highly silicaceous zeolites are organophilic. This means that changing the silica : alumina (or similar) ratio will affect which molecules will be adsorbed preferentially.

1.3.3 *Catalysis*

Acid catalysis by zeolites is used for the cracking and isomerisation of hydrocarbons,[4] and can also be used for several syntheses.[4-6] For example, production on an industrial scale of ethylbenzene from ethene and benzene uses zeolite ZSM-5 as catalyst (the Mobil-Badger Process,[5] Scheme 1). Using a zeolite catalyst rather than the traditional stoichiometric Friedel-Crafts method leads to highly efficient production of *mono*-ethylbenzene.



Mobil-Badger Process

Scheme 1

Zeolites also have another desirable ability. Shape selective catalysis[8] is now possible because not only are certain reactants favoured by the zeolite, because they possess the required dimensions to gain access into the pores of the zeolite, but certain products are also favoured according to their ability to diffuse back out again. In addition,

only products whose transition states are smaller than the pore diameter (or cavity size, where two or more pore cross) can be formed. For example, formation of *p*-xylene is favoured over the unwanted *o*- and *m*-xylene (in the alkylation of benzene and/or toluene and toluene disproportionation reactions) due to the ability of *p*-xylene to diffuse easily through the zeolites pores.

Zeolites can be regenerated in air by burning off the coke (which is most often the reason for deactivation); generally, the original activity is regained.

1.4 Catalytic Activity

Zeolites are members of the second of the two classes of heterogeneous catalyst,[5] which are:

1.4.1 *Non-Uniform Heterogeneous Catalysts*

This is a large class of heterogeneous catalysts which accelerate chemical conversion on the exterior surface of the catalyst (*e.g.* H_2 / N_2 conversion to NH_3 on metallic iron). The exterior surfaces of these catalysts are not uniform since they have steps, kinks, clusters and individual atoms non-uniformly distributed on the surface. Only a small portion of the surface of these catalysts are actually involved in catalysis due to these features.

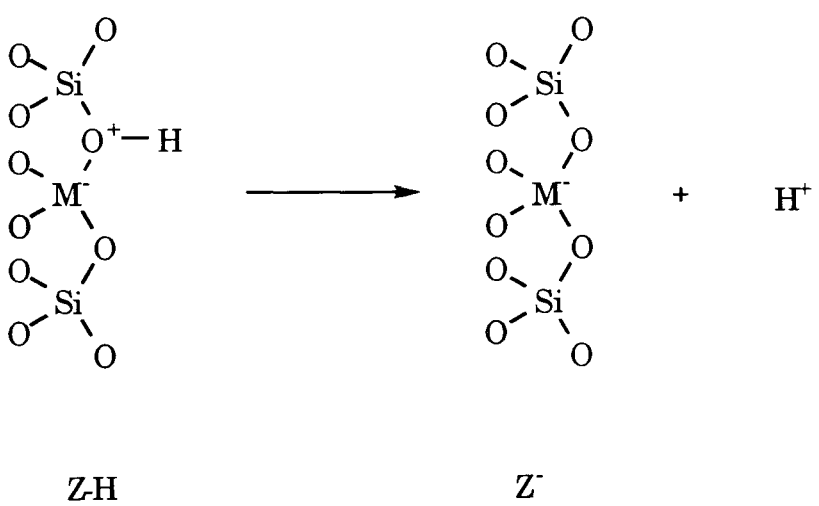
1.4.2 *Uniform Heterogeneous Catalysts*

This category is equally as large as the former category. Here, the bulk atoms of the catalyst are directly (or indirectly) responsible for catalysis. The zeolites structural framework (*i.e.* its channels (pores) and cavities) makes it possible for gaseous (or in some cases liquid) molecules

to enter into the bulk of the zeolite. Therefore, all bulk atoms are, in fact, surface atoms and, since all atoms in the framework are uniformly distributed throughout the bulk, zeolites are uniform, heterogeneous catalysts.

1.4.3 *Cause of Catalytic Activity*

There are two major types of catalytic activity. The first is based on Brønsted acidity[6] which, for example, causes generation of carbocations in the zeolite cavities and channels. One cause of Brønsted acidity is the existence of heteroatoms (Al, Ge, B, Fe, *etc.*) in the silica framework of the zeolite. Macroionic frameworks are formed when protons are freed from their bound state attached to oxygen atoms adjacent to tetrahedrally substituted heteroatoms (Scheme 2).



Scheme 2

Other causes include the presence of strongly polarising cations which can be uniformly inserted into the interzeolitic cavities. These cations facilitate hydrolysis and so, yield relatively "free" protons.

The second is based on transition metals[6,7] (or cations) which can be "doped" into the zeolite framework. These can facilitate redox reactions in the bulk of the zeolite.

1.5 Zeolite Synthesis

In a typical procedure, a solution of alumina in excess base (*e.g.* NaOH) is mixed intimately with a sol or solution of the silica component. This highly alkaline mixture forms a thick gel which crystallises over a few hours when maintained at 100°C. The product depends on gel composition, the nature of the reagents and the crystallisation conditions.

The nature of the counter cation is a critical gel parameter. Changing from sodium to lithium or potassium, for example, results in the formation of different zeolite frameworks.

In 1961, the scope of these synthetic procedures was greatly enhanced by Barrer and Denny.[9] They showed that the inorganic base could be replaced (partly or wholly) by an organic base by using tetramethylammonium hydroxide in their synthetic recipe. The gel chemistry was modified but, more importantly, this base apparently acted as a template around which the zeolite could form. This templating effect depends on the size, shape and charge distribution of the template. This work was extended to the use of other amines as well as neutral species such as alcohols, ketones, *etc.*[10,11] The organic templates are generally too large to escape from their positions in the zeolite framework and are usually removed by pyrolysis.

The structure-directing rôle of the template is, therefore, to organise oxide tetrahedra into a particular arrangement around itself, providing the initial building blocks for a particular structural type. Templating is explained by electric dipole interaction and the stereospecificity due to the size and shape of the template. Large cages[12] may be explained by the hydration of the template making the cation larger, or because more than one template is involved in formation of a

single cavity. Experimental evidence for templating action is found using X-ray crystallographic, NMR[13] and IR methods. These techniques show the presence of the template within the final zeolite.

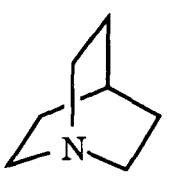
So, a great deal of interest lies in the field of zeolite templating systems. Currently, larger pore-sized zeolites are being investigated in order to incorporate more efficient use of the heavier fractions of petroleum which are, at present, not used to their full potential.

Chapter Two

Quinuclidine

2.1 Introduction

The first part of this thesis is concerned with the attempted synthesis of quinuclidine. As mentioned earlier, organic templates have been used to synthesise zeolites and quinuclidine has been used as such a template (*e.g.* aluminophosphate, $AlPO_4$-17; pore size 0.46 nm).[14]



1

It was envisaged that a functionalised quinuclidine would be more bulky than quinuclidine itself, and so may be used to create, *via* templating, a zeolite of higher pore size. Also possible would be the incorporation of polar groups which would not only make the quinuclidine more bulky, but would also be able to help in the templating ability of the molecule. These higher pore sized zeolites are of great interest in the petrochemical industry as it may be possible to use them to crack the higher fractions of crude oil which are currently used in *e.g.* bitumen.

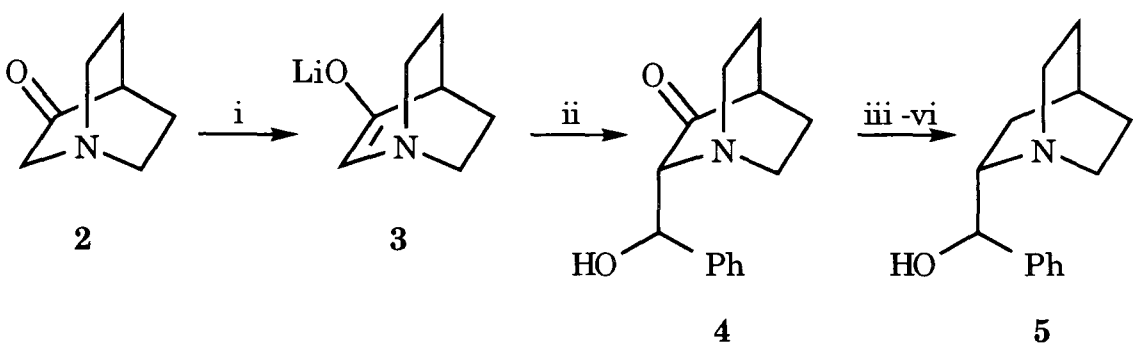
As well as the usefulness of quinuclidines in zeolite synthesis, the chemistry of quinuclidines have also been of interest in the synthesis of alkaloids which contain the quinuclidine nucleus (*e.g.* the sarpagine[15a], ajmaline[16] and cinchona[17] alkaloids) and in the pharmacological activity[18] of simple quinuclidines which may have a rôle in the treatment of *e.g.* Alzheimer's disease.[19] Quinuclidines are also of interest in the field of ligand accelerated catalysis.[20]

2.2 Previous Quinuclidine Syntheses

Routes to several substituted quinuclidines have been reported in the literature, examples of which are cited below.

2.2.1 *2-Substituted Quinuclidines*

3-Quinuclidinones have been converted to 2-substituted quinuclidines *via* enolate chemistry.[21]

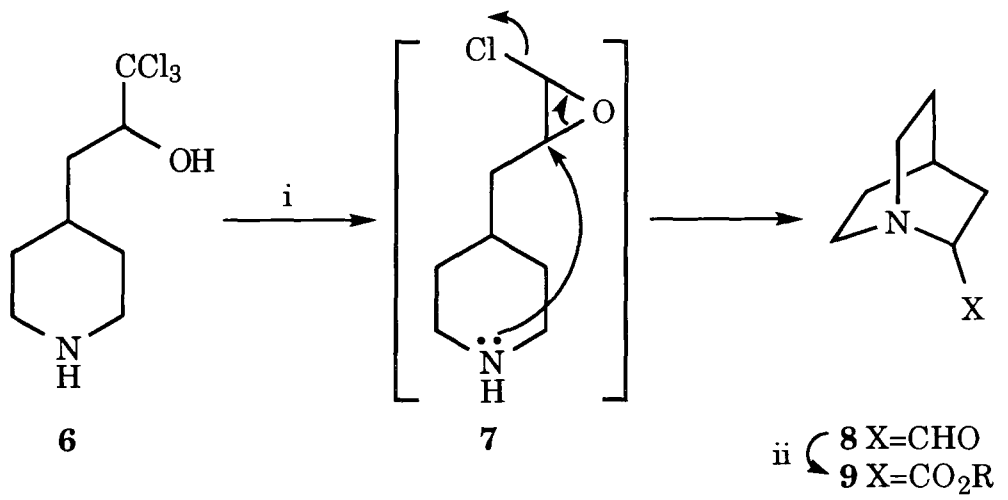


2 **3** **4** **5**

i) 2eq LDA; ii) PhCHO; iii) $NaBH_4$; iv) Ac_2O, pyridine;
v) $Im_2C{=}S$; Bu_3SnH, AIBN; vi) MeLi

Scheme 3

Also reported has been the cyclisation of piperidine chloroepoxides **7**.[22]



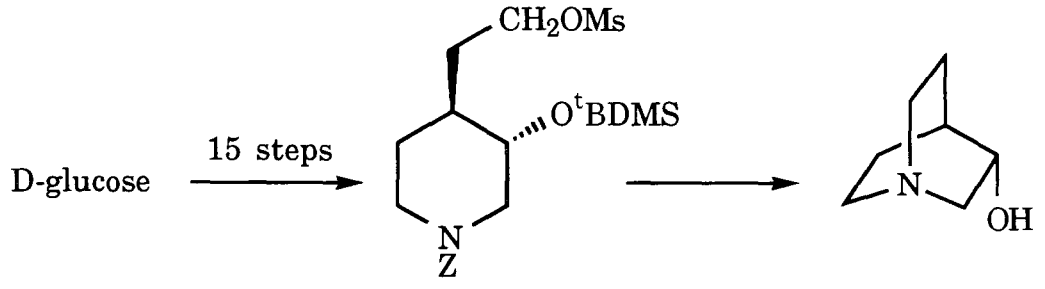
6 **7**

i) 2N aq KOH, benzene (or KOH, MeOH); ii) Ag_2O, MeOH

Scheme 4

2.2.2 *3-Substituted Quinuclidines*

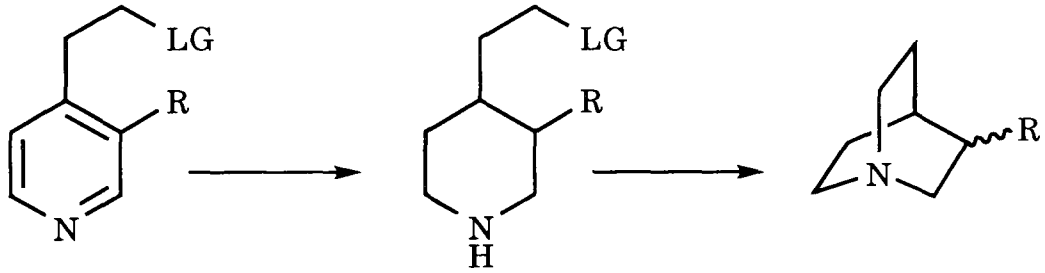
The chiral 3-substituted quinuclidine, S-quinuclidinol **11**, has been synthesised from D-glucose[15] in 15 steps using an S_N2 displacement reaction to effect the bicyclic ring closure (Scheme 5).



10 **11**

Scheme 5

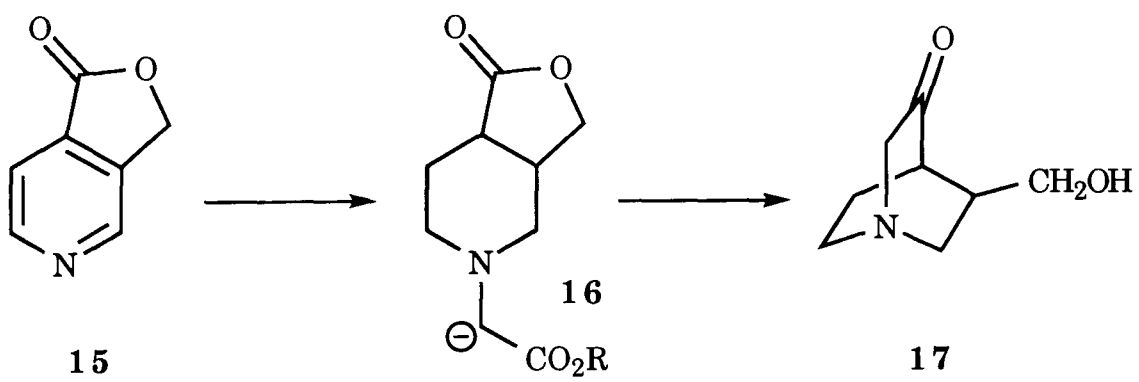
Cyclisation of other substituted piperidines produces 3-substituted quinuclidines **14** (Scheme 6).[23]



12 **13** **14**

Scheme 6

Also, the intramolecular cyclisation of the ester-stabilised anion **16** onto a lactone (Scheme 7).[24]

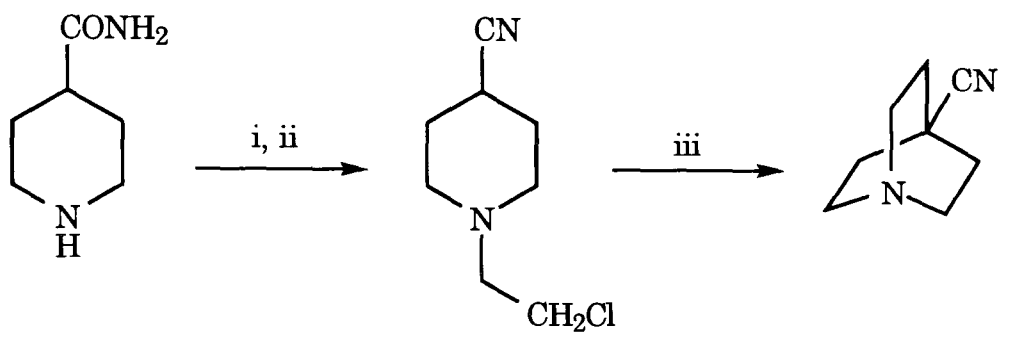


15 **16** **17**

Scheme 7

2.2.3 *4-Substituted Quinuclidines*

Quinuclidines substituted in the 4-position have been synthesised[25] using anion chemistry for the final ring closure reaction of a piperidine **19** to give quinuclidine **20** in 54% yield (Scheme 8).



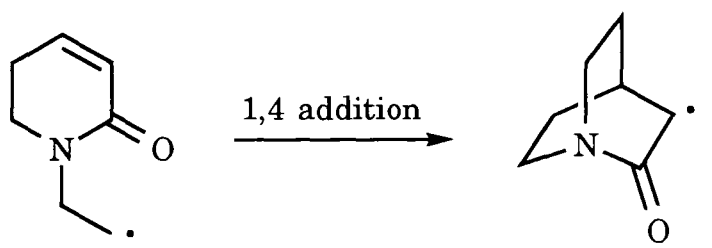
18 **19** **20**

i) 2-chloroethanol, K_2CO_3, EtOH, Δ; ii) $SOCl_2$, MeCN;
iii) $NaNH_2$, THF or LDA, THF, -78°C

Scheme 8

2.3 The Proposed Route

As a relatively small amount of synthetic routes were available, and the above syntheses were thought to be either too long or not applicable to our target molecules, it was decided that a novel route would be attempted which would allow for the synthesis of more highly functionalised quinuclidines by further manipulation of the starting materials.



21 **22**

Scheme 9

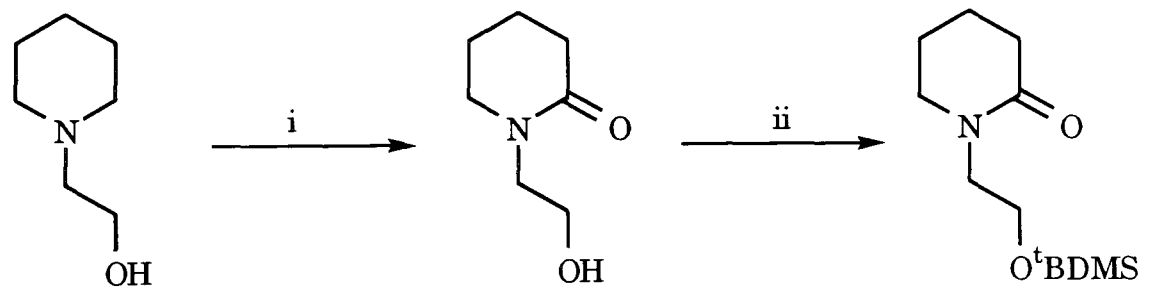
The proposed route envisaged to the quinuclidine skeleton centred around a 6-*endo*-trig radical cyclisation (Scheme 9).

Although the cyclisation would involve the formation of a strained, rigid system, it was hoped that the combination of an intramolecular cyclisation, and the fact that the cyclisation would be helped by the double bond being an electron-poor Michael acceptor, would result in the formation of the required quinuclidine system.

The advantages of this route over other syntheses of quinuclidine included the relatively short reaction sequence (6 steps, see later) and the possibility of using the reaction scheme to produce more highly substituted quinuclidines by using suitably substituted starting materials.

2.4 Results and Discussion

The proposed route began with the conversion of *N*-(2-hydroxyethyl) piperidine **23** into the piperidone **24**, in 80% yield, by oxidation using mercury(II) acetate and ethylene dinitrilo tetra acetic



23 **24** **25**

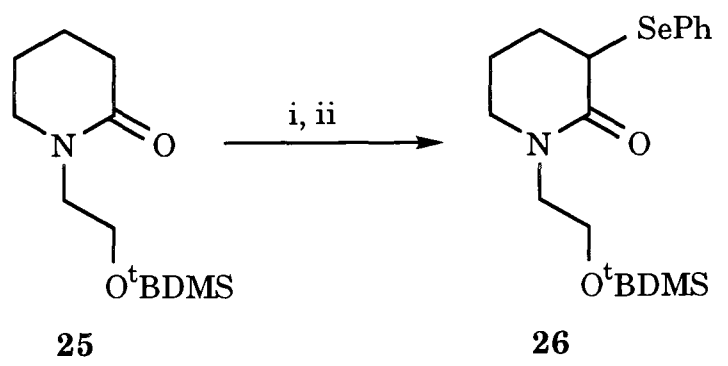
i) $Hg(OAc)_2$, EDTA, 1% AcOH; ii) ^{t}BDMSCl, Et_3N, DMAP, CH_2Cl_2.

Scheme 10

acid (EDTA).[26] The pendant hydroxyl group was then protected, under standard conditions, using *t*-butyldimethylsilyl chloride to give the silyloxy piperidone **25** in a good 80% yield (Scheme 10).

The synthesis now required the conversion of the saturated amide **25** into an α,β-unsaturated amide **28**. The route chosen was incorporation of a selenium moiety α- to the amide followed by oxidative removal of this selenium moiety to give the required α,β-unsaturation.[27]

In order to convert the amide **25** into the α-seleno-amide **26**, a carbonyl stabilised anion was required which could then be reacted with a selenium electrophile. This was achieved using 3 equivalents of lithium diisopropylamide at 0°C in tetrahydrofuran (THF). It was then found to be necessary to warm the reaction mixture to room temperature for 1h in order to complete anion formation, whereupon the reaction mixture was cooled to -78°C before adding phenyl selenenyl chloride to quench, yielding the α-seleno amide **26** in a reasonable 53% after column chromatography (Scheme 11).



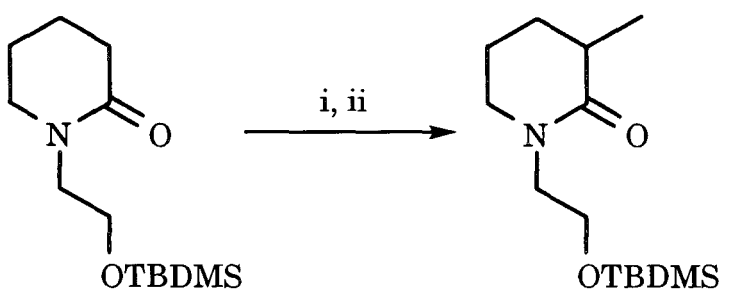
25 **26**

i) 3eq LDA, THF, 0°C to 20°C; ii) PhSeCl, -78°C

Scheme 11

Formation of the anion at temperatures below ambient resulted in much lower yields of up to 20%. The use of other bases (*e.g.* sodium hexamethyldisilazide or sodium hydride) and enol triflate formation, using dibutylboron triflate, were also found to be low yielding, as was the use of a more reactive selenium electrophile, phenyl selenenyl bromide. The use of hexamethylphosphoric triamide as co-solvent also failed to improve the yield.

To show that it was the difficulty of anion formation which was the problem here, rather than the poor reactivity of the anion once formed, the reaction was performed as above, but using methyl iodide as a much more reactive electrophile. In this case, an unoptimised 40% yield was achieved, appearing to confirm our suspicions (Scheme 12).

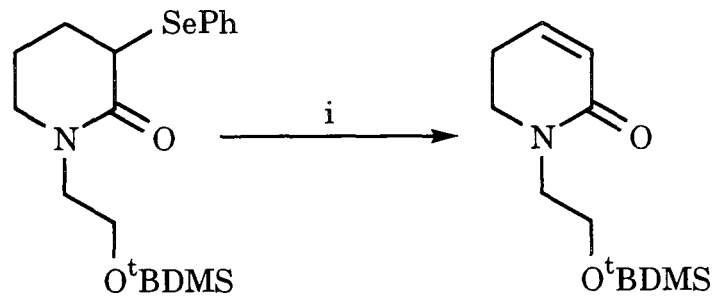


25 **27**

i) 3eq LDA, THF, 0°C to 20°C; ii) MeI, 0°C

Scheme 12

Once the α-seleno amide **26** was isolated, it was converted into the corresponding α,β-unsaturated amide **28**, using 30% aqueous hydrogen peroxide in THF at 0°C, in a 95% yield after chromatography (Scheme 13).



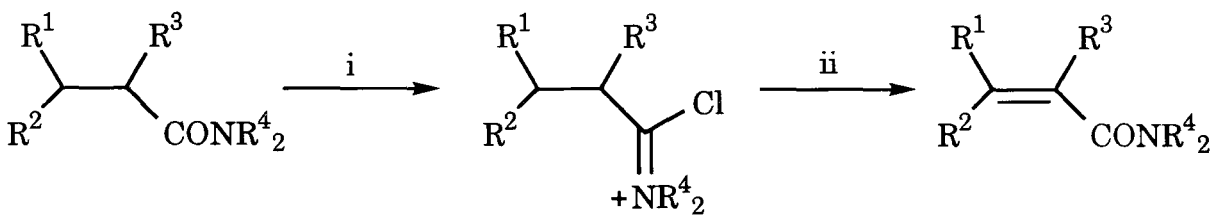
26 **28**

i) H_2O_2, THF, 0°C

Scheme 13

Here the selenium is oxidised to the selenoxide which spontaneously eliminates in a 5-membered, concerted *syn*-fashion[28] at 0°C, due to its high instability (*cf.* sulphoxides[29] which require heating to *ca.* 100°C before elimination occurs).

As incorporation of the selenium group was not as high yielding as we had hoped, other routes were examined. Another method used for the incorporation of α,β-unsaturation α- to an amide was that of phosgene in pyridine in one pot, as used by Ghosez[30] *et al*, but this was found to be unsuccessful (Scheme 14).

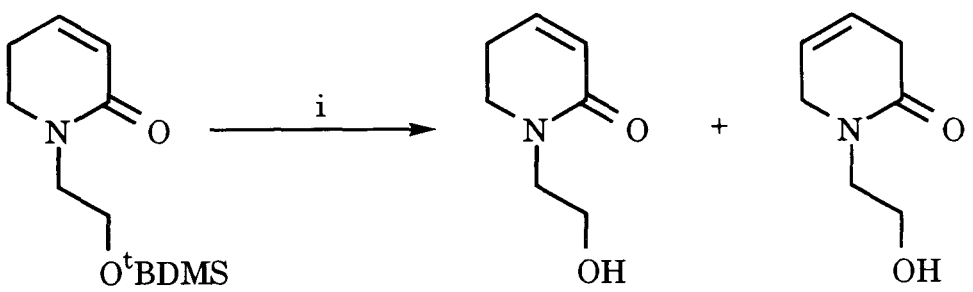


29 **30** **31**

i) $COCl_2$, CH_2Cl_2, rt; ii) pyridine *N*-oxide, Et_3N, rt

Scheme 14

Deprotection of the pendant silyloxy side chain in amide **28** was achieved using tetrabutylammonium fluoride in THF. Here, however, a 5:1 mixture of the required α,β-unsaturated **32** and β,γ-unsaturated **33** amides were isolated as an inseparable mixture, in an overall 98% yield after chromatography (Scheme 15).



28 5 : 1

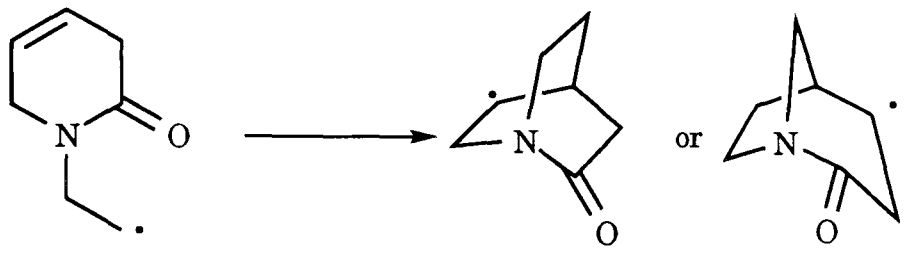
32 **33**

i) TBAF, THF, rt

Scheme 15

This was not expected to be too much of a problem as the proposed radical cyclisation would be possible with the β,γ-isomer also, although in the β,γ-case, there would now be two possible sites for the radical to

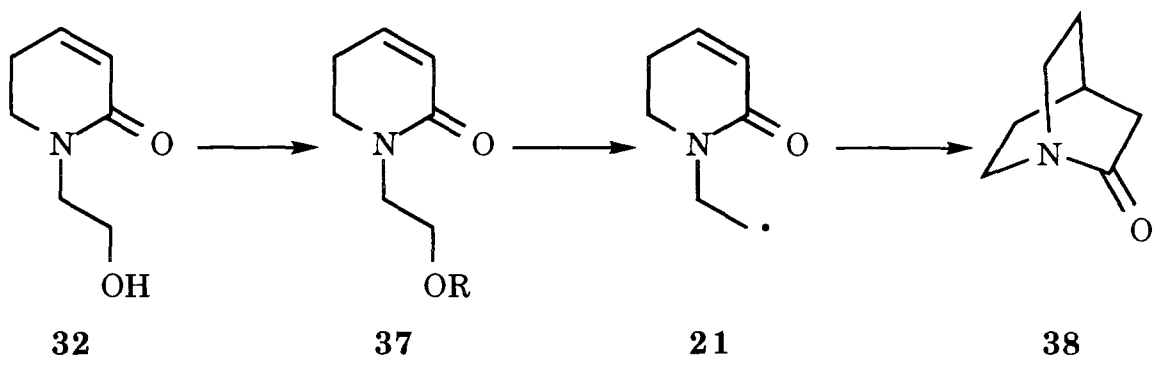
attack; *i.e.* to give a 6,6-fused quinuclidine system **35** as required, or a 5,7-fused system **36** (Scheme 16).



34 **35**; 6,6 **36**; 5,7

Scheme 16

For the final step of radical cyclisation, the now free hydroxyl group needed to be converted into a substituent which could be removed in such a way as to leave a radical in the 2' position (Scheme 17).



32 **37** **21** **38**

Scheme 17

Functionalisation of the pendant hydroxyl group to afford a thiocarbonate compound (*e.g.* **37**), followed by deoxygenation under Barton conditions,[23] using tributyltin hydride, to leave a radical in the 2' position (*e.g.* **21**), was the route chosen.

However, functionalisation of the hydroxyl group proved not to be possible. With 1,1'-thiocarbonyl diimidazole, only starting materials were recovered suggesting that the free hydroxyl may not be free at all in solution.

Since functionalisation was not observed, formation of the radical precursor to the quinuclidine system could not be attempted and the required cyclisation could not, therefore, be achieved.

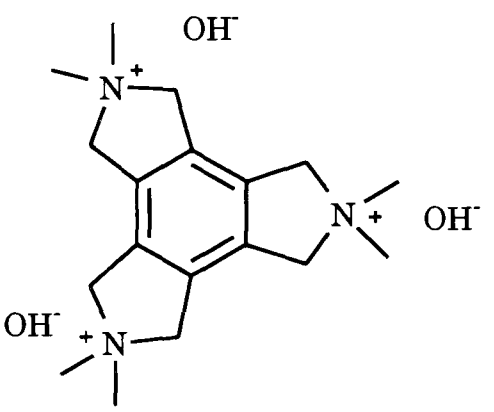
At this stage, the proposed synthesis of functionalised quinuclidines was abandoned.

Chapter Three

"Triquat" Analogue

3.1 Introduction

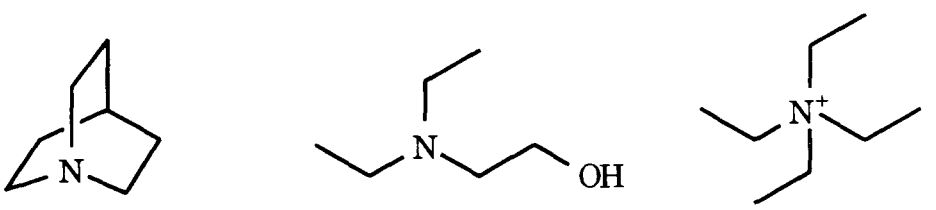
Another, already implemented, zeolite template is the "triquat" molecule **39** (1,3,4,6,7,9-hexahydro-2,2,5,5,8,8-hexamethyl-2H-benzo [1,2-C: 3,4-C': 5,6-C"] tripyrolium trihydroxide).[31]



39

This molecule has been shown to template zeolite ZSM-18, which has a pore size of 7Å and is able to sorb cyclohexane. Since this molecule appeared to be such a good template, it was decided that investigations into this molecule, and some of its analogues, would be commenced.

Molecules such as "triquat" **39** and quinuclidine **1** are good templates and are also rigid, but molecules such as diethylethanolamine **40** and the tetraethyl ammonium cation **41** are seen to be useful as well, their structures obviously not being rigid at all.

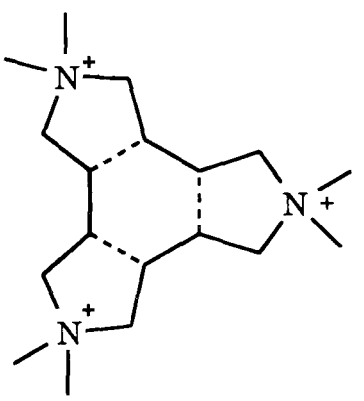


1 **40** **41**

The investigations were, therefore, to be centred around whether the rigidity of the molecule was a necessary requirement or whether it is

just the three ammonium moieties which are responsible for the observed templating ability.

The molecule **42** chosen to be examined was that resulting from the formal removal of the benzene ring from the centre of "triquat" **39**.



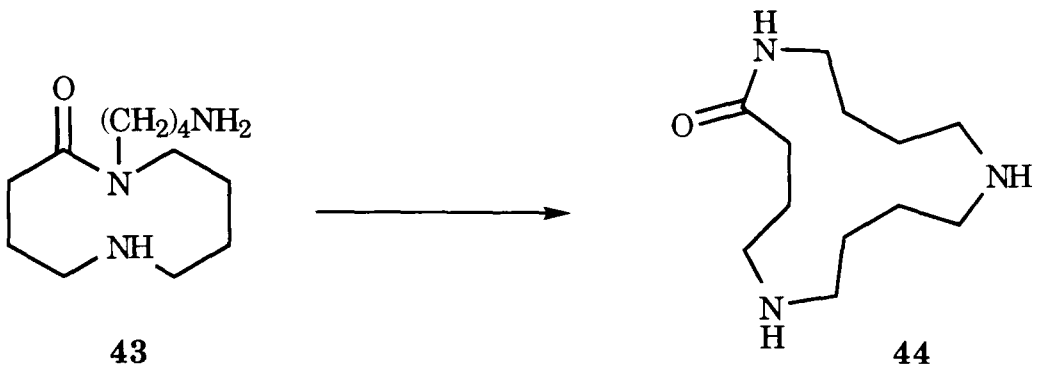
42

Here, the molecule is a simple macroheterocyclic triammonium species which is free to assume many conformations (*i.e.* not rigid) and is also not aromatic, which may be another possible reason why the template may be beneficial to zeolite synthesis.

3.2 The Proposed Route to the "Triquat" System

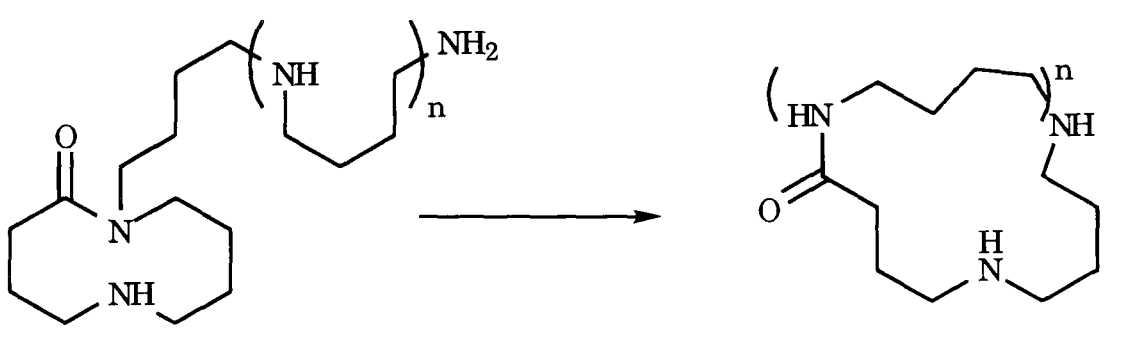
The route to the "triquat" analogue **42** was proposed to include the use of a Zip-type reaction.[32] This is, however, known to be unfavourable with a 5-membered ring due to the stability of this ring size over any other ring to be formed. It was expected, however, that a Zip-type reaction would be favourable if the Zip-precursor was an already less stable 10-membered ring system **43** (Scheme 18).

If the proposed sequence was successful, it would also be possible to increase the size of the ring system formed by using extended amino side chains (Scheme 19).



43 44

Scheme 18

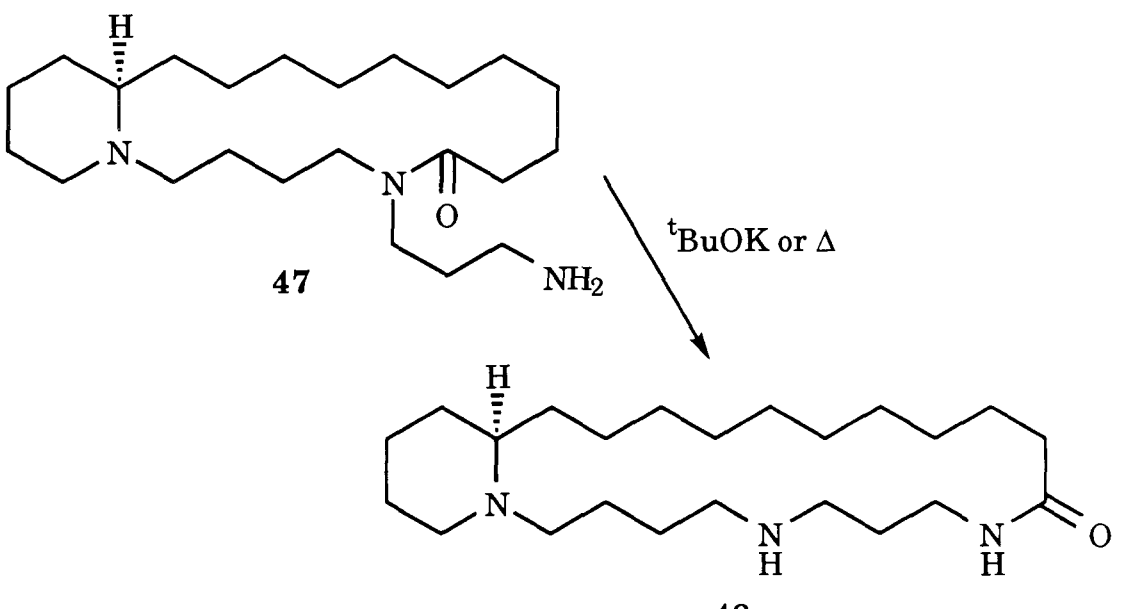


45 46

Scheme 19

3.3 The Zip Reaction

It was shown in 1978 that neooncinotine **47** could be transformed into isooncinotine **48** by either thermal or base catalysed means (Scheme 20).[33]

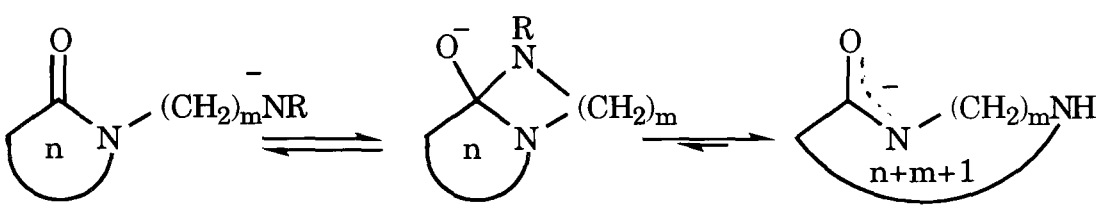


47 48

Scheme 20

This led to a series of investigations in order to generalise this process of isomerisation.

It was found that the driving force for the reaction was the conversion of the initially generated anion **49** into the relatively stable amide anion **51**, and that 8-, 9- and 11-membered lactams could be converted into the respective 12-, 13- and 15-membered lactams (where m=3 and n=8, 9, 11; Scheme 21).

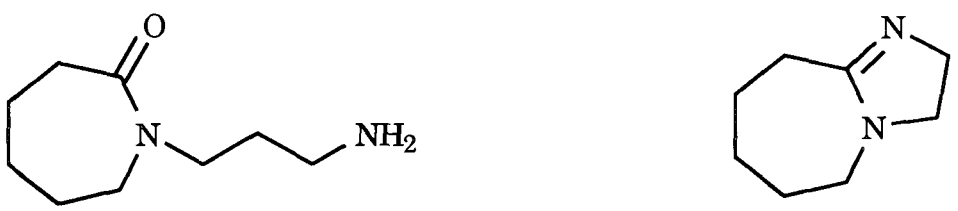


49 **50** **51**

Scheme 21

These reactions were carried out with potassium *t*-butoxide in toluene or with potassium-3-aminopropylamide (KAPA) / 1,3-diaminopropane.

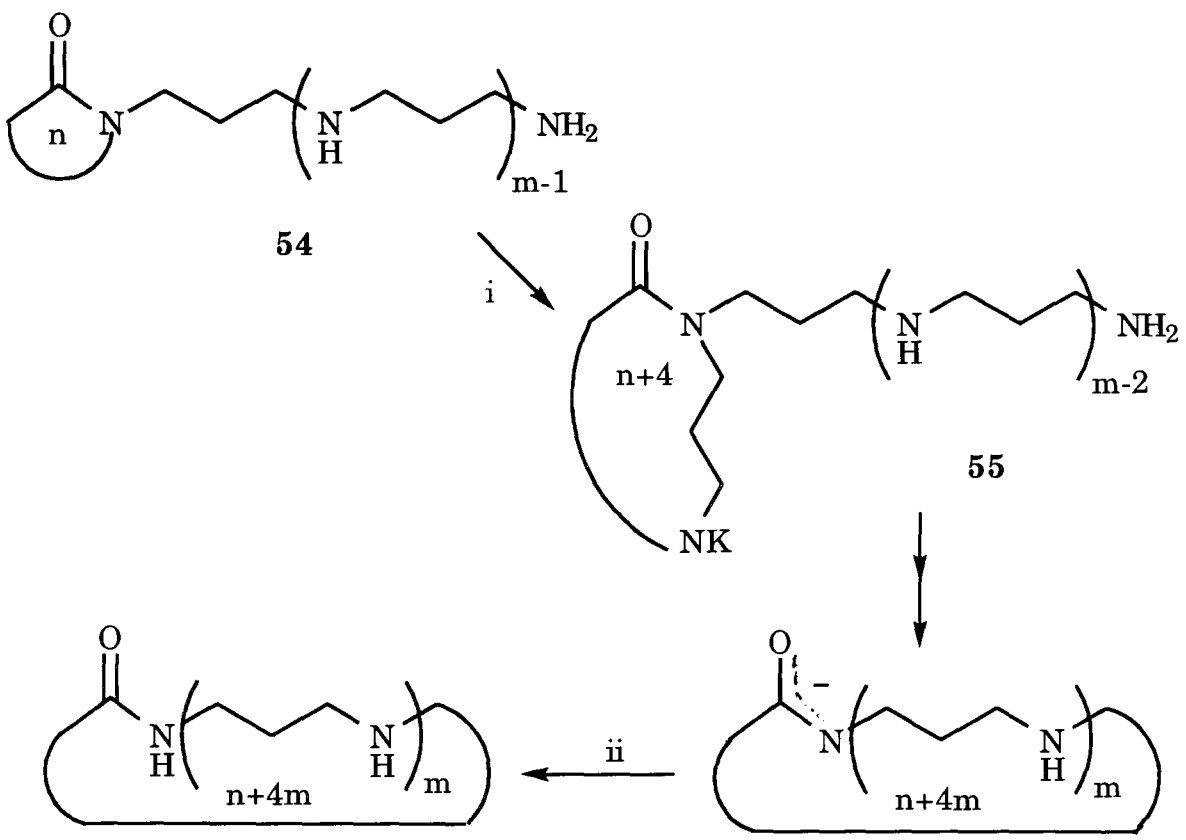
The 7-membered *N*-(3-aminopropyl)-ε-caprolactam **52** did not react in this way, however, and only the 'intermediate' amidine, 1,8-diazabicyclo [5.4.0] undec-7-ene (**53**, DBU) was isolated (Scheme 22).[34]



52 **53**

Scheme 22

Since the expanded products are also lactams, ring enlargement can be repeated stepwise (Scheme 23).



i) $NH_2(CH_2)_3NH_2$, $KNH(CH_2)_3NH_2$; ii) H_3O^+

Scheme 23

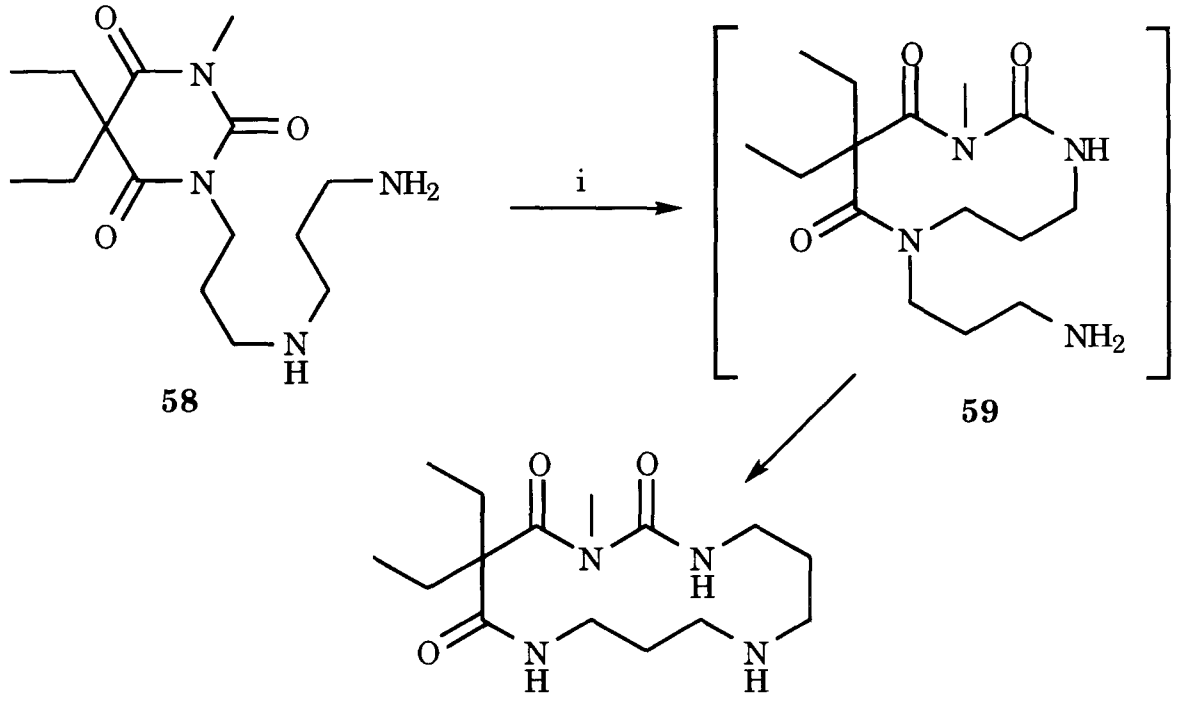
In this way, successive incorporation of aminoalkyl units produces polyazalactams in a way resembling the action of a zip; hence the so-called "Zip" reaction. Macrocycles of up to 53 ring atoms have been synthesised in this fashion.[35]

Increasing the size of the side chain in this transformation results in lower reaction rates, with three or four atoms per transamidation being the optimum.[36]

These transamidation reactions run to completion even when there is no obvious release of ring strain. This is thought to be due to the stability of the amide anion **56** (*cf.* translactonisation[37]).

Formation of strained medium sized rings (8-11 ring atoms) from smaller rings is unfavourable,[38] except from highly strained small rings, *i.e.* 3-membered rings,[39] but formation of large rings *via* these strained medium rings is entirely possible; for example, the formation of the 14-

membered ring compound **60** from the barbituric derivative **58** *via* the 10-membered ring **59** (Scheme 24).[38]

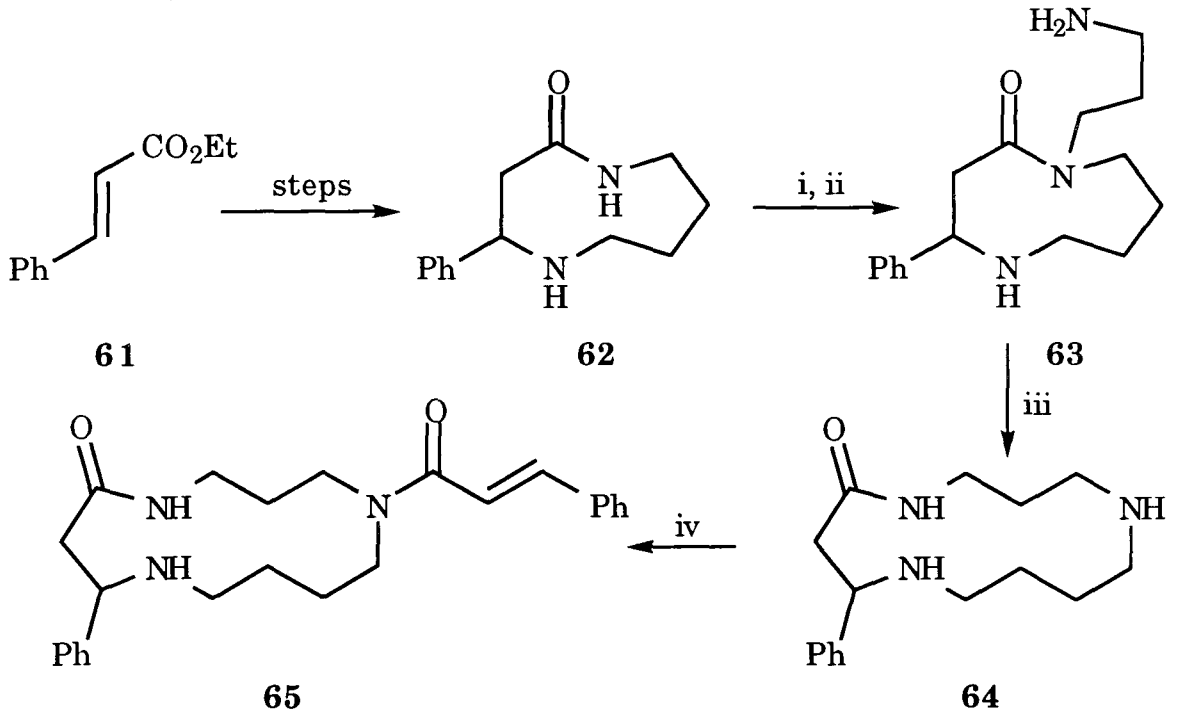


58 **59** **60**

i) KF, DMF, 18-crown-6

Scheme 24

The Zip reaction has been applied successfully in the synthesis of many polyamino alkaloids, *e.g.* celacinnine[39] **65** (Scheme 25), homaline,[40] chaenorhine,[41] verbascenine[42] and desoxoinandenine.[43]



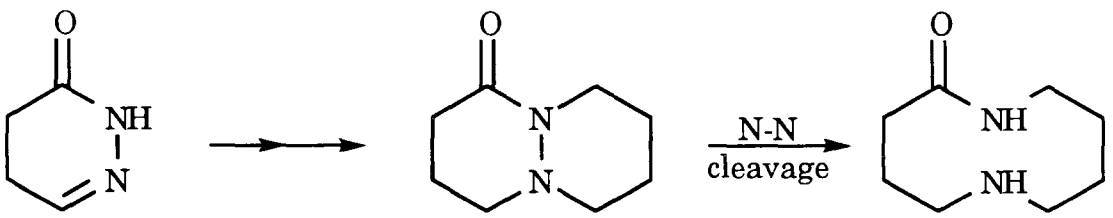
61 **62** **63** **64** **65**

i) NaH, DMF, *N*-(3-iodopropyl)-phthalimide; ii) $NH_2NH_2.H_2O$, EtOH, Δ; iii) 1M NaOH, 50°C; iv) cinnamoyl chloride

Scheme 25

3.4 Towards "Triquat" Analogue 42

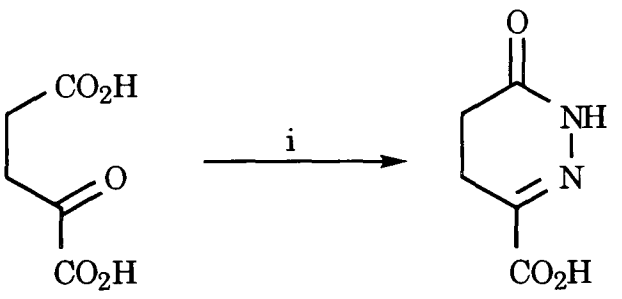
It was necessary, therefore, to first synthesise a 10-membered ring precursor to the Zip reaction. The formation of a 4,5-dihydropyridazinone **66**, followed by alkylation, cyclisation and N-N bond fission was the pathway chosen (Scheme 26).



66 **67** **68**

Scheme 26

Some crucial modifications to the literature route[44] to compound **66** were first required here. The initial step to form the pyridazinone skeleton **70** was achieved by condensing hydrazine sulphate with 2-ketoglutaric acid **69** (Scheme 27). The literature yield of 50% was much improved to 90% by simply adding the reagents together and *then* warming to *ca.* 95°C over 10 min, rather than adding the two hot solutions together.



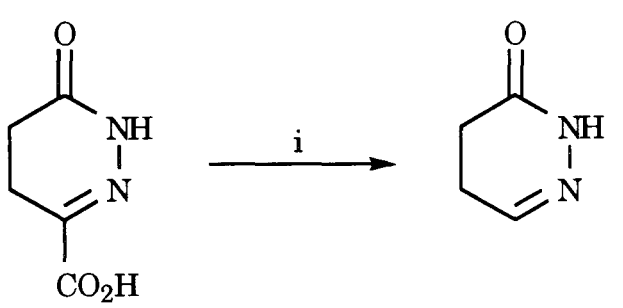
69 **70**

i) Hydrazine sulphate, NaOH aq, 95°C

Scheme 27

The second step of pyrolytic decarboxylation was performed according to literature[44] in a very disappointing yield of around 30% (lit.

23%) due to the charring of a large amount of material around the sides of the reaction flask by the Bunsen burner flame required for the conversion. The decarboxylation was optimised to an excellent 90% yield (after distillation), by using a diluent (Scheme 28). As a high temperature was required here, diphenyl ether was chosen as diluent as it has a boiling point of 259°C. When a diluent was used, it was possible to incorporate stirring and, more importantly, the heat supplied to the reaction vessel by the Bunsen burner flame was being transferred to the whole reaction mixture and not just the sides of the vessel. In this case, charring was not observed and so a much higher yield was obtained.



70 **66**

i) Ph_2O, Δ

Scheme 28

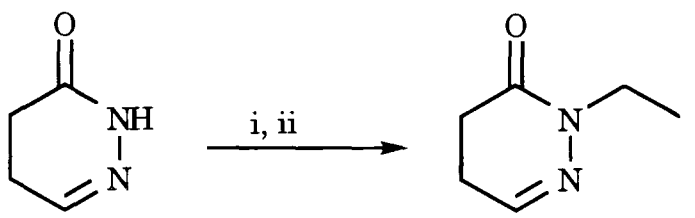
Both of the above reactions may be performed on multigram quantities but it should be noted that large amounts of carbon dioxide gas are eliminated in the decarboxylation step and suitable precautions should be taken.

Next, it was necessary to determine whether the dihydropyridazinone **66** could be alkylated. Indeed, would alkylation occur on the 2-N amide nitrogen, as it would be expected and required to be, or on the other 1-N nitrogen or the 4-C carbon α– to the amide carbonyl?

Preliminary studies involved use of an electrophile which would make ^1H NMR interpretation simple. Ethyl bromide was chosen rather

than methyl iodide as it is less reactive and so more like the electrophile which was to be used if the alkylation was successful.

Initial attempts using sodium hydride and THF at room temperature yielded only a trace amount of the required *N*-ethyl compound, along with recovered starting material.



66 **71**

i) NaH, DMF; ii) EtBr

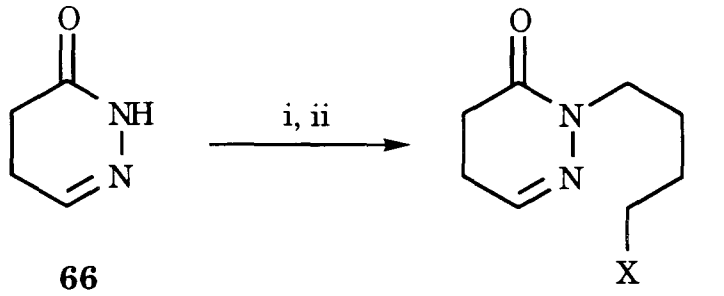
Scheme 29

Employing a change of solvent to the much more polar *N,N*-dimethylformamide at room temperature, resulted in the isolation of the *N*-ethyl compound **71** in 45% yield after column chromatography (Scheme 29).

In order to make the required ring system, it was now necessary to use a 4-carbon electrophile to alkylate the amide. This electrophile would also have to include a second electrophilic centre in order that cyclisation of the resultant side chain, to make a fused bicycle, could then be possible.

The first such electrophile chosen was 1,4-dibromobutane. Under the above conditions of sodium hydride in DMF at room temperature, the desired *N*-(4'-bromobutyl) pyridazinone **72** was isolated in a disappointing 38% yield along with polymerisation side products. This low yielding step was circumvented by using 1-bromo-4-chlorobutane as the electrophile. In this case, the preformed amide anion attacks only the bromide to give

the *N*-(4'-chlorobutyl) pyridazinone **73** in 70% yield after chromatography (Scheme 30).



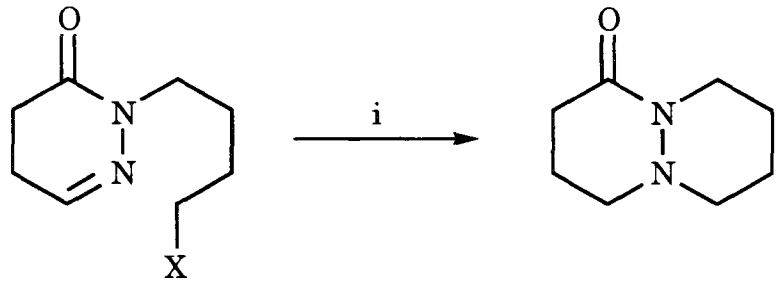
66

X = Br **72**; Cl **73**

i) NaH, THF/DMF; ii) $Br(CH_2)_4X$

Scheme 30

Cyclisation of the bromobutyl pyridazinone **72** was successfully achieved using sodium cyanoborohydride in ethanol to give bicycle **67** in 65% yield (Scheme 31).



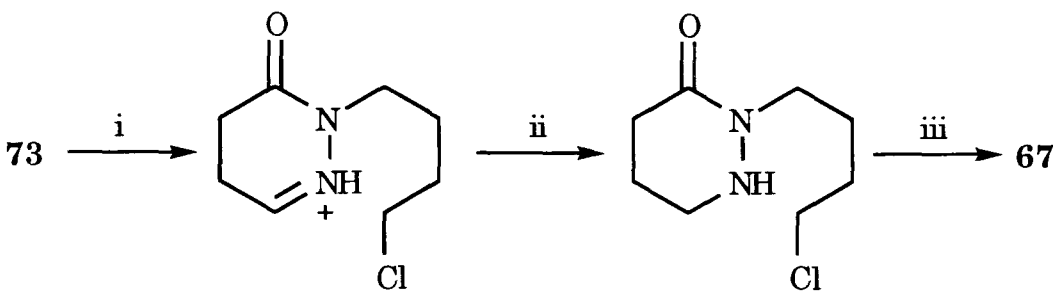
X = Br **72**; Cl **73** **67**

i) $NaBH_3CN$, cat. HCl, EtOH

Scheme 31

As expected, cyclisation of the chloro analogue **73** was found to be more difficult than with the bromo case **72**. This presented no problems, however, as the reaction rate and subsequent yield, was increased with the addition of a small quantity of acid and warming to 50°C. This process showed evidence of acid catalysed reduction of an iminium species[45] **74** in that, with the chloro analogue, the intermediate amine **75** could be isolated (Scheme 32). In the case of the bromo analogue, the

amine intermediate could not be isolated, presumably due to the higher reactivity of the bromide group with respect to the chloride.



i) HCl, EtOH; ii) $NaBH_3CN$; iii) cyclisation

Scheme 32

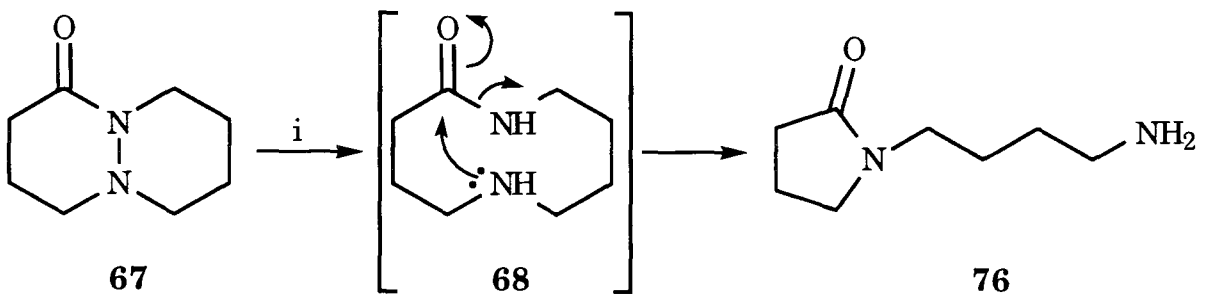
The formation of compound **67** could also be achieved from pyridazinone **66** without purification of the intermediate **73** in 66% yield.

We now had a [6,6,0] fused bicycle **67** which, in order to form the required 10-membered ring system **68**, needed to undergo N-N bond cleavage.

Initial attempts to cleave the N-N bond using hydrogenolysis were unsuccessful using the usual hydrogenation catalysts. Reaction with platinum(IV) oxide,[46] palladium on activated carbon[46,47] and Raney nickel[48] were attempted with hydrogen gas at both atmospheric and elevated (*e.g.* 100 atm) pressures. Raney nickel was also used with transfer hydrogenolysis, using hydrazine hydrate[49] as hydrogen source, and using ultrasound[50] in conjunction with hydrogen gas. Also unsuccessful was reduction using zinc and acetic acid.[48]

The N-N bond was eventually cleaved successfully using sodium in liquid ammonia[47] in around 85% yield (Scheme 33). The product was found, however, *not* to be the required 10-membered ring **68**. Comparisons of the ^1H NMR of the product with a literature compound, *N*-methyl pyrrolidinone, proved that a 5-membered pyrrolidinone system had been formed in what could, ironically, be referred to as a reverse-Zip

type reaction!! Here, the secondary amine **68** formed upon cleavage of the N-N bond reacts intramolecularly with the amide to form a more stable 5-membered ring system **76**.



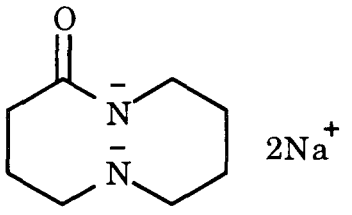
67 **68** **76**

i) Sodium/NH_3

Scheme 33

This unexpected, but hardly surprising, reactivity of the amine was, therefore, the next problem to overcome. Some sort of amine protection was required either *in situ*, after cleavage had occurred, or prior to cleavage.

In the previously described sodium in liquid ammonia reaction of compound **67**, it was proposed that an intermediate would be the dianion **77**.

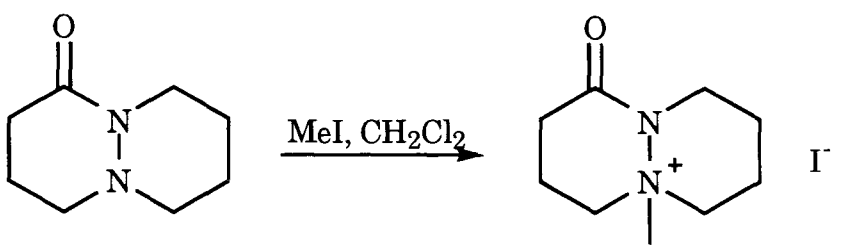


77

It was thought that it may be possible to isolate this dianion as its salt, by evaporating off the ammonia prior to quenching with, for example, methyl chloroformate, instead of the usual ammonium chloride. When attempted, however, only the pyrrolidinone **76** was isolated.

It was then decided that a protecting group for the amine nitrogen before cleavage would have to be found. As the amine to be protected was a tertiary one, protection would make the nitrogen into an ammonium

species. Obviously, the simplest alkyl group to use here would be methyl (this was also what was required in the target molecule **42**) and so bicycle **67** was treated with methyl iodide, giving the protected bicycle **78** as a white solid in 85% yield (Scheme 34).



67 **78**

Scheme 34

Purification of this compound could be achieved only by leaching away any contaminants from it using dichloromethane, as it was insoluble in most organic solvents.

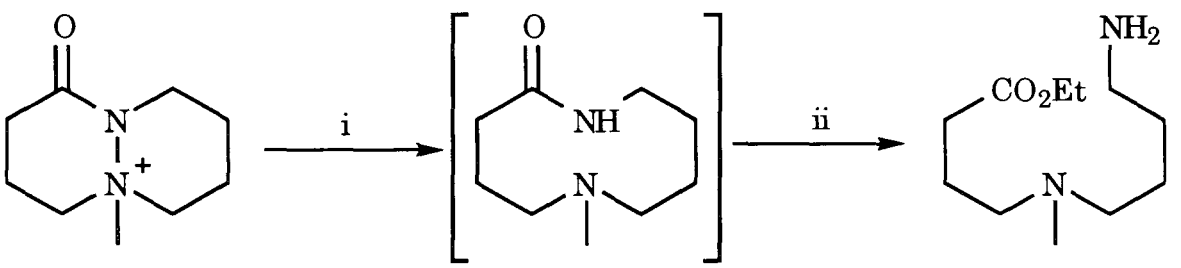
Hydrogenolysis of the bicyclic salt **78** with platinum(IV) oxide and palladium on activated carbon at hydrogen pressures of 1 atm and 100 atm were again unsuccessful. Hydrogenation with Raney nickel was somewhat more successful however, although with unexpected results. When carried out in ethanol, the product isolated was a clear oil. The IR spectrum of this compound did not, however, have the desired amide stretching vibration, but an ester stretch at 1727 cm^{-1}.

The proposed mechanism for this conversion involves ring opening of the 10-membered ring system **79** formed upon cleavage of the N-N bond with the solvent (ethanol), to give the ethyl ester **80** (Scheme 35).

Presumably, the acyclic ester **80** is more stable than the 10-membered amide **79**. It was hoped that this side reaction could be prevented by using a non-nucleophilic solvent.

When carried out in ethyl acetate under dry conditions (*i.e.* removing as much water as possible from the 50% aqueous suspension of

Raney nickel by decantation, followed by washing three times with dry ethanol and twice with dry ethyl acetate), only starting material was recovered. However, when using wet ethyl acetate, isolation of the 10-membered ring **79** was possible, but in a low 20% yield, along with unreacted starting material.

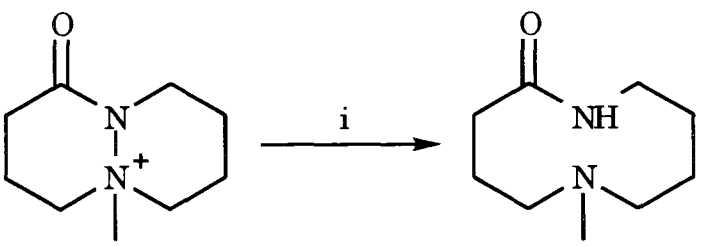


78 **79** **80**

i) Raney nickel, EtOH; ii) EtOH solvent

Scheme 35

As the sodium in liquid ammonia reduction was successful with the unprotected case **67**, it was used again with the protected hydrazide **78**. Indeed, the desired 10-membered ring system **79** was isolated in an encouraging 88% yield after chromatography, as a white solid (Scheme 36).



78 **79**

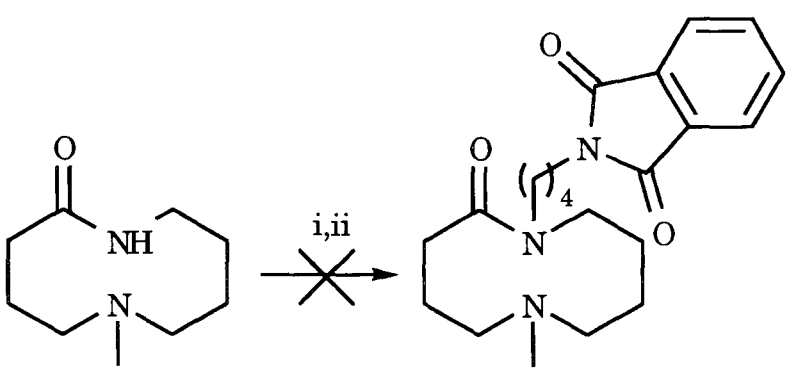
i) Sodium/NH_3

Scheme 36

It only remained, therefore, to functionalise the amide nitrogen with a suitable aminoalkyl chain in readiness for the Zip reaction. The terminal amine required for the Zip reaction would have to be incorporated onto the amide in a masked form. The most feasible

protecting group compatible with the alkylation reaction was a phthalimide group, which could be removed using *e.g.* hydrazines, sodium borohydride and methylamine.[51]

The electrophile needed was the commercially available 4-bromobutylphthalimide. Unfortunately, functionalisation was unsuccessful (Scheme 37).



79 **81**

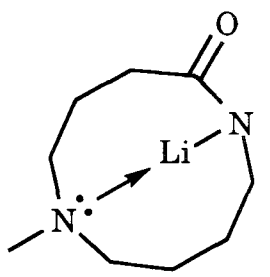
i) base; ii) 4-bromobutyl phthalimide

Scheme 37

Standard amide alkylation techniques using systems such as sodium hydride in DMF,[52] potassium hydroxide in dimethyl sulphoxide[53] and lithium diisopropylamide, and even butyllithium, at low temperatures, produced only starting materials. Phase transfer alkylation[54] using tetrabutylammonium salts was also unsuccessful.

It is thought that an intramolecular amine stabilised lithio species **82** may be responsible for the stability of what should be a reasonably reactive amide nitrogen. Such an interaction may put the molecule into a sterically hindered conformation where it is not possible for the reaction to proceed.

In any event, the starting material was recovered intact in most cases.



82

Due to this unforeseen problem, the project was brought to a close at this point.

Chapter Four

Pyrrolidine Synthesis

4.1 Introduction

The pyrrolidine system was proposed as a potential zeolite template because, like quinuclidine, and many other templates, pyrrolidines are amines. This and the incorporation of polar side chains were expected to help with the electrostatic interactions needed in templating. Making the pyrrolidines more bulky may also help in the templating ability.

There have been many synthetic methods reported for the formation of pyrrolidines and many reviews have been published.[55]

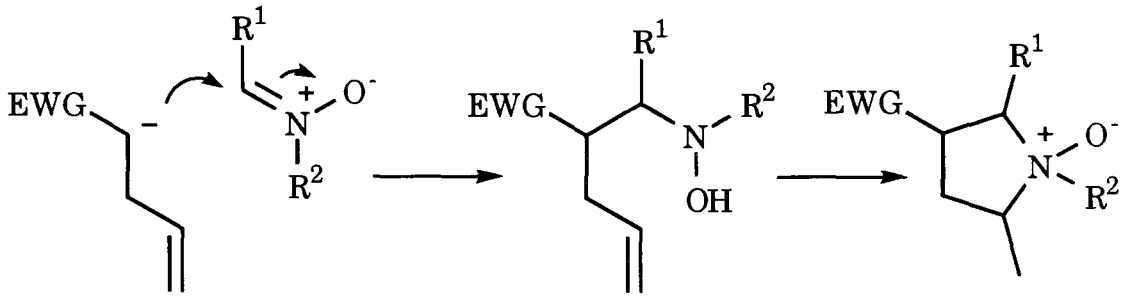
This chapter concerns the research carried out into the formation of pyrrolidines *via* a *retro*-Cope elimination reaction. The *retro*-Cope reaction is a novel process which could possibly have the advantage of the formation of functionalisable pyrrolidines, and potentially higher cyclic homologues, *via* a relatively quick and easy route. The chapter starts with an explanation of the *retro*-Cope reaction and its well known reverse reaction, the Cope elimination itself. Also, reviews of methods of nitrone synthesis and of previously reported additions of carbon nucleophiles to nitrones are included.

4.2 The Proposed Route

The proposed route consisted of the addition of a carbon-centred anion **83** containing a distal vinyl group, to a nitrone **84**, followed by the subsequent intramolecular reaction of the resultant hydroxylamine **85** with the pendant alkene, in a *retro*-Cope sense, to give a pyrrolidine system **86** (Scheme 38).

The first problem to overcome was that of nitrone synthesis. In the past, most nitrones had been formed and reacted *in situ*,

making isolation unnecessary. In this case, however, isolation and purification is intrinsically necessary because, ideally, a 1:1 reaction of carbanion and nitrone would be required so that wastage of potentially important starting materials does not occur.



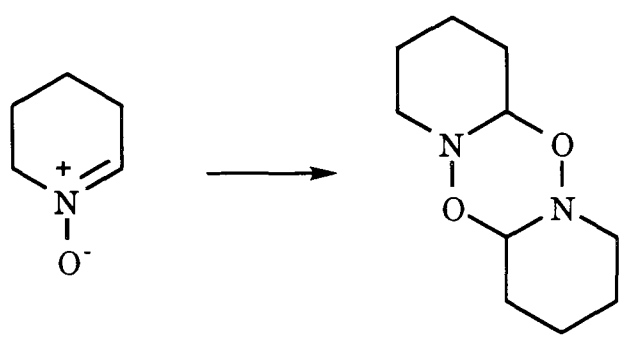
83 **84** **85** **86**

Scheme 38

In previous work carried out in our group by Thornton (see Page 54),[56] the nitrones used did not need to be dry as the nitrogen nucleophiles used were much more nucleophilic than water. In this case, however, the nitrones must, obviously, be dry in order that the carbanion is not quenched by water before it is able to react with the nitrone. Some nitrones are very hygroscopic and some also hydrolyse in wet conditions back to the respective aldehydes. Nitrones are also known to dimerise / polymerise and so this was another problem to be aware of (*e.g.* Scheme 39). All the above make nitrones difficult to work with. It was envisaged, therefore, that the nitrone would have to be made and used immediately upon isolation, with minimal purification.

The second problem was that of the carbon-centred anion. Here we would need a homoallylic anion in order that the *retro*-Cope reaction would be set up after the anion chemistry had, hopefully, produced a hydroxylamine. To form such an anion, a suitable electron withdrawing group (EWG) must be positioned α- to the carbon which

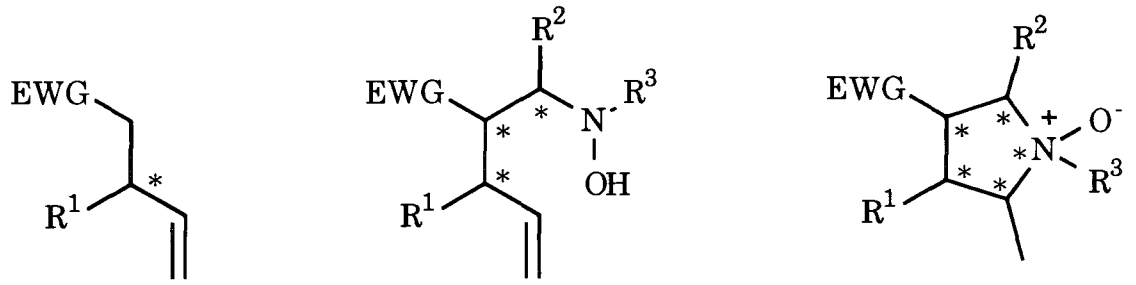
would hold the anion. Many such EWGs exist, but which ones would be stable, relatively simple to synthesise and form anions easily? More importantly, which EWGs would stabilise an anion which would also react with the electrophilic centre of the nitrone rather than, for example, reacting with the nitrone in some other way, *e.g.* deprotonation?



87 **88**

Scheme 39

Perhaps the most important stumbling block for the proposed route was that of the *retro*-Cope reaction itself. Is it possible for the hydroxylamine **85**, once formed, to undergo a *retro*-Cope



89
1 chiral centre

90
3 chiral centres

91
5 chiral centres

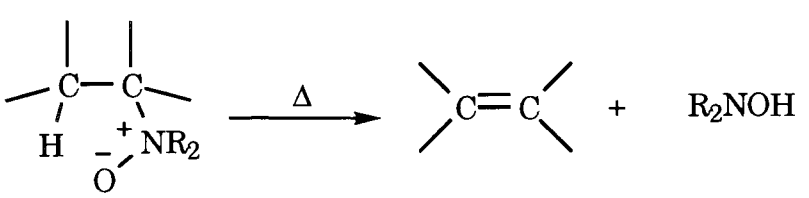
Scheme 40

process to give the required pyrrolidine system **86**? Which solvent should be used to facilitate the conversion? What, if any, stereocontrol would be seen, as potentially, up to *four* new chiral

centres would be formed upon condensation and cyclisation (Scheme 40)?

4.3 The Cope Elimination

The Cope elimination reaction[57] involves the cleavage of an amine oxide to produce an alkene and a hydroxylamine. It has been used as a method for the preparation of alkenes, substituted hydroxylamines and substituted amines (Scheme 41), usually in >80% yield.



92 **93** **94**

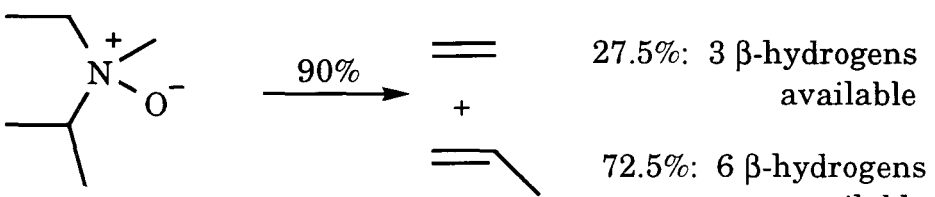
Scheme 41

This conversion is usually performed *via* oxidation of the amine without isolation of the *N*-oxide and, since the reaction conditions are relatively mild, side reactions are few and the alkenes formed do not usually isomerise. This reaction is, therefore, very useful for the preparation of many alkenes. The Cope elimination may be used to open nitrogen-containing rings of 5 and 7-10 ring atoms. Six-membered rings are not opened however (at least not in high yield (<10%) and only under forcing conditions).[58] Most early examples of the Cope elimination were carried out with neat *N*-oxide at high temperatures (*ca.* 200°C). The reaction may also be carried out in dry DMSO or THF at room temperature.[59]

The elimination is a stereoselective *syn* process with a 5-membered, E_i mechanism.[60] Evidence also indicates that the

transition state must be planar, and, indeed, this is why 6-membered rings do not react. In the acyclic case, where *cis* and *trans* alkenes are possible, the more stable *trans* isomer is preferentially formed.[57]

With simple alkyl substituted amine oxides, the direction of elimination appears to depend almost entirely on the number of β-hydrogen atoms, with rates increasing with increasing numbers of β-hydrogen atoms (Scheme 42).[57]



95

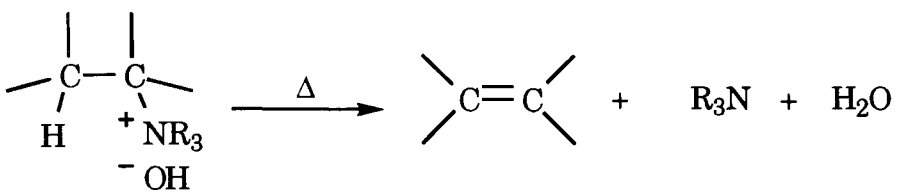
Scheme 42

Two significant variations to this appear to be the *t*-butyl and phenylethyl groups where relief of steric strain interactions and β-hydrogen acidity are also factors which favour their elimination: *t*-butyl is 2x and phenylethyl is 10x faster than ethyl with respect to the number of β-hydrogens available.

This uncertainty as to which proton is abstracted is a source of limitation for the Cope elimination *i.e.* it can be highly non-stereoselective.

The Cope elimination is also an alternative method for the formation of alkenes *via* the elimination of a nitrogen containing leaving group, *e.g.* Schemes **43** and **44**.[61,62] In Scheme 44, a mechanism similar to the Cope elimination is in evidence, where a carbon centred anion is involved, rather than the oxygen anion in the Cope elimination.

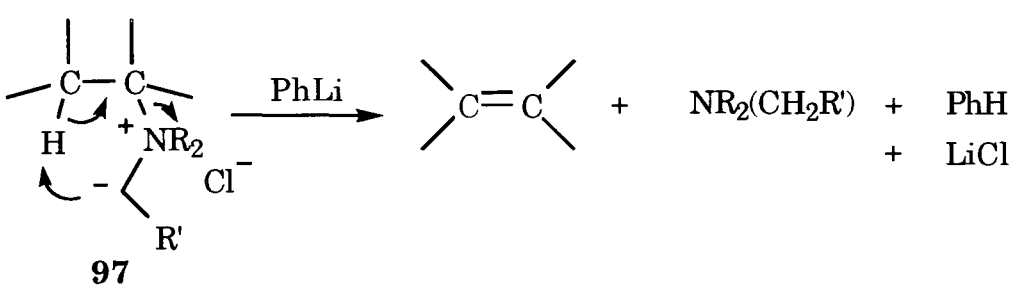
Cleavage of Ammonium Hydroxides[61]



96

Scheme 43

Cleavage of Quaternary Ammonium Salts[62]

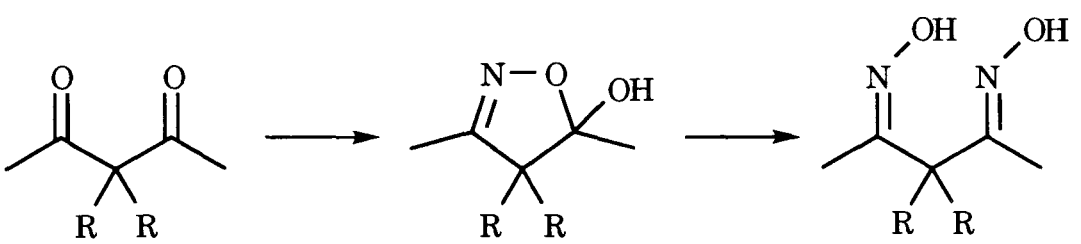


97

Scheme 44

4.4 The *retro*-Cope Elimination

In 1975, investigations by House *et al*[63] into the reaction of 3,3-disubstituted 2,4-pentadiones with excess hydroxylamine resulted in an unexpected observation. Treatment of 3,3-dimethyl-2,4-pentadione (R=Me, **98a**) with one equivalent of hydroxylamine resulted in an isoxazoline **99a** in 61% yield, which, on further treatment with hydroxylamine, could be converted to the dioxime **100a** in 48% yield. However, when 3,3-dipropargyl-2,4-pentadione (R = $CH_2C{\equiv}CH$, **98b**) was used, conversion from the isoxazoline **99b**

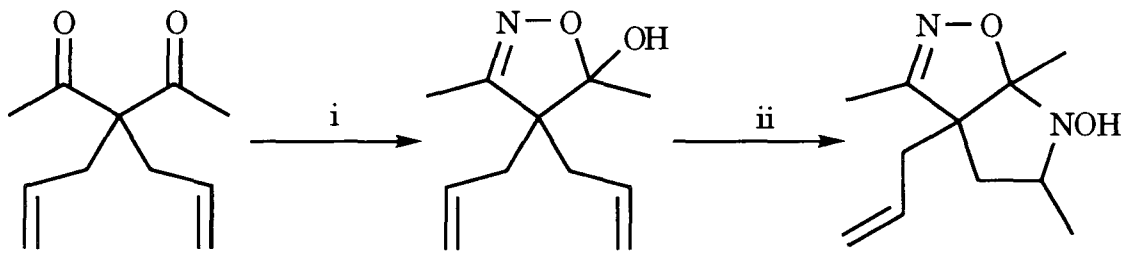


R=Me **98a**, $CH_2C{\equiv}CH$ **98b** **99a,b** **100a,b**

Scheme 45

(formed in up to 85% yield) to the respective dioxime **100b** was not possible (Scheme 45).

House's investigations continued with the diallyl (R= $CH_2CH{=}CH_2$, **98c**) substrate. Here again, the isoxazoline **99c** was easily prepared and isolated, but was again resistant to dioxime formation. Under the more vigorous conditions of refluxing ethanol or dioxane however, the unexpected product **101** mentioned above was isolated in about 7% yield (Scheme 46). This was found to have a bicyclic structure which was isomeric with the dioxime. The product was unusual in that it appeared that formation of a new C-N bond had occurred at an unactivated C=C double bond under reasonably mild conditions.



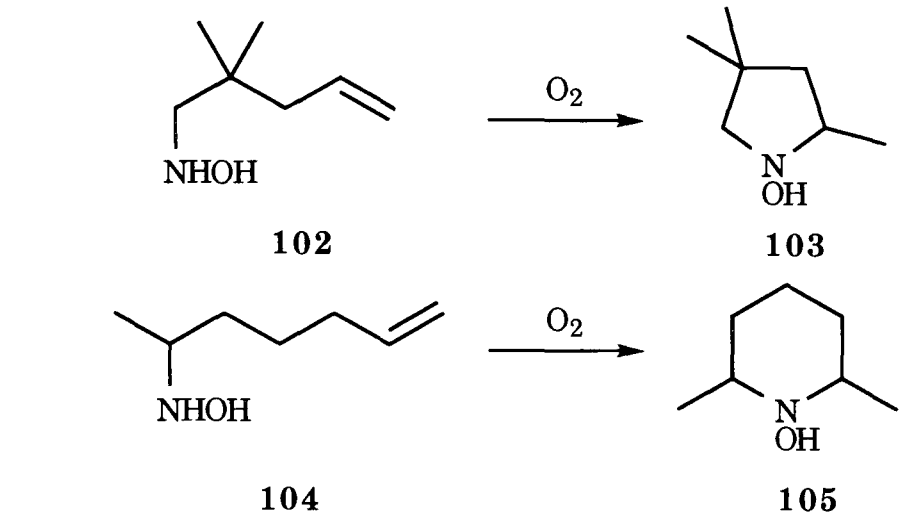
98c **99c** **101**

i) 1eq NH_2OH; ii) XS NH_2OH

Scheme 46

Further studies by House *et al*[64] with *N*-alkenyl hydroxylamine derivatives (formed by reduction of the corresponding oximes) showed that both 5- and 6-membered rings can be made using this cyclisation methodology (Scheme 47).

When *N*-(4-pentenyl) hydroxylamines **106** were used, 5- rather than 6-membered rings were observed (quantitatively), and when using *N*-(5-hexenyl) hydroxylamines, 6- rather than 7-membered

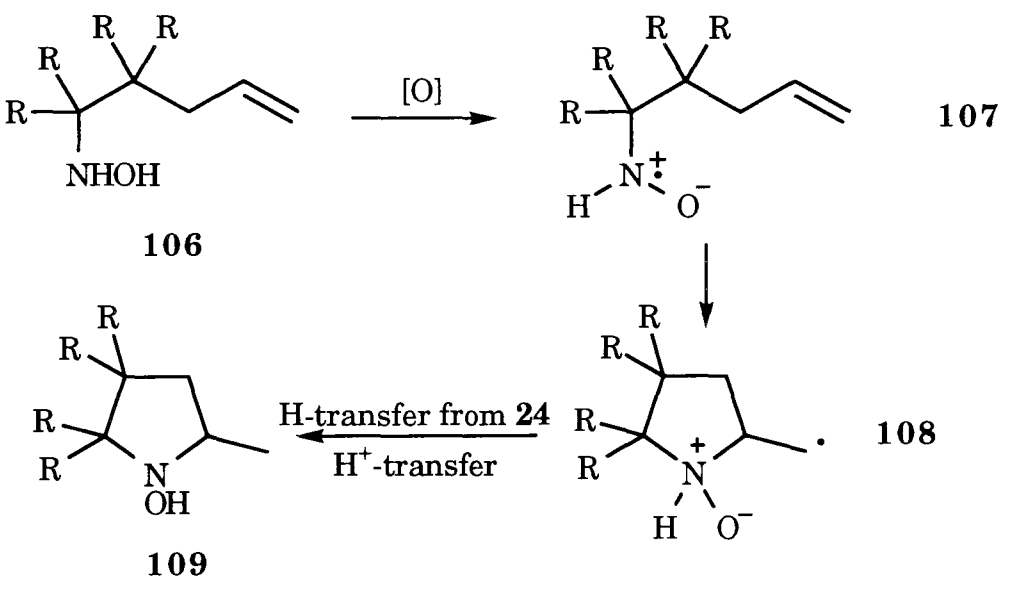


102 **103**

104 **105**

Scheme 47

rings were observed (in *ca.* 40% yield). A radical mechanism was proposed for the conversion with molecular oxygen proposed as the oxidant for the hydroxylamine (Scheme 48).

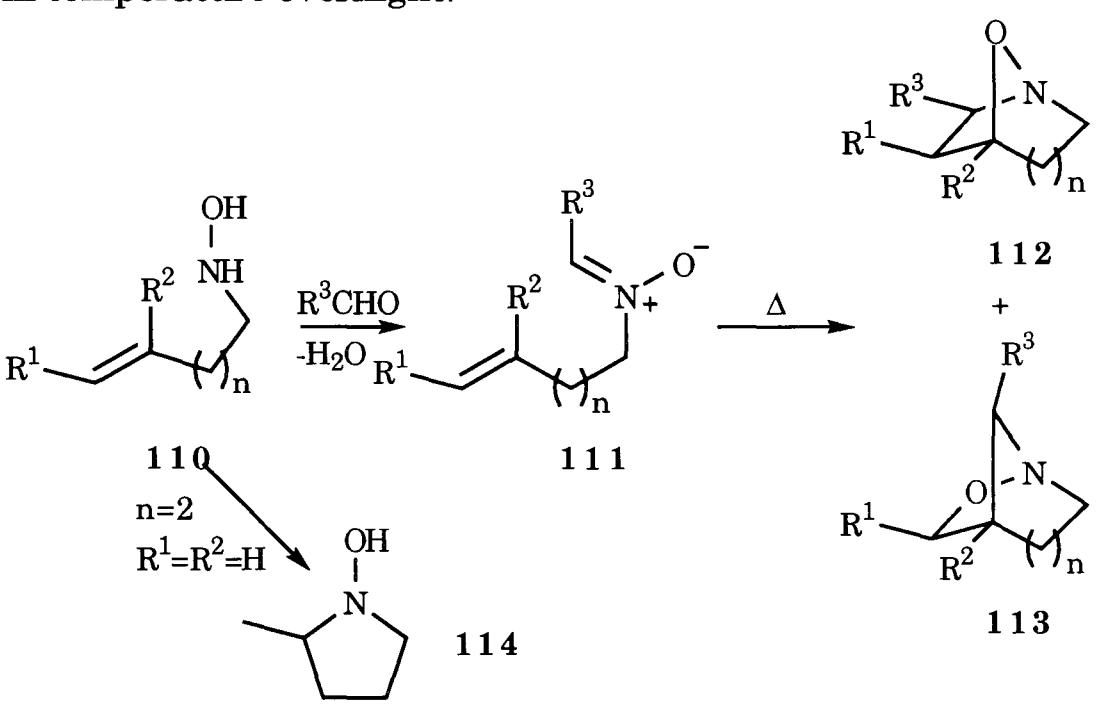


Scheme 48

The hydroxylamines used were found to be very reactive and even gentle warming of these during product isolation resulted in cyclisation.

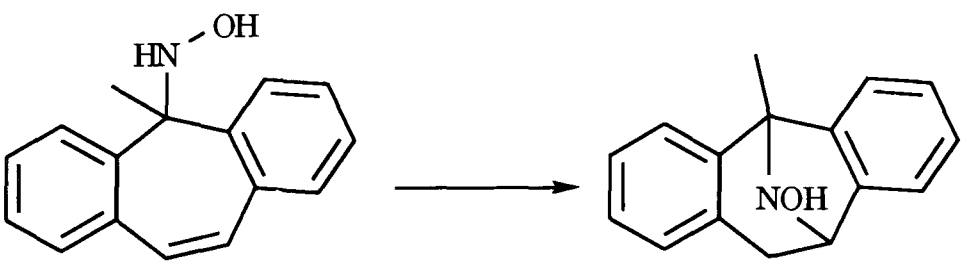
A similar result was independently observed by Oppolzer[65] *et al* in 1979, during their studies into the intramolecular 1,3-dipolar cycloaddition of nitrones onto unactivated C-C double bonds. In this case, Oppolzer's route to nitrone **111** consisted of the reaction of a

hydroxylamine **110** with an aldehyde. The hydroxylamine however, contained a C-C double bond and was perfectly set up, as above, for cyclisation (Scheme 49). It was found that these hydroxylamines would cyclise in high yield at 40°C in only a few hours ($t_{1/2}$=2h) or at room temperature overnight.



Scheme 49

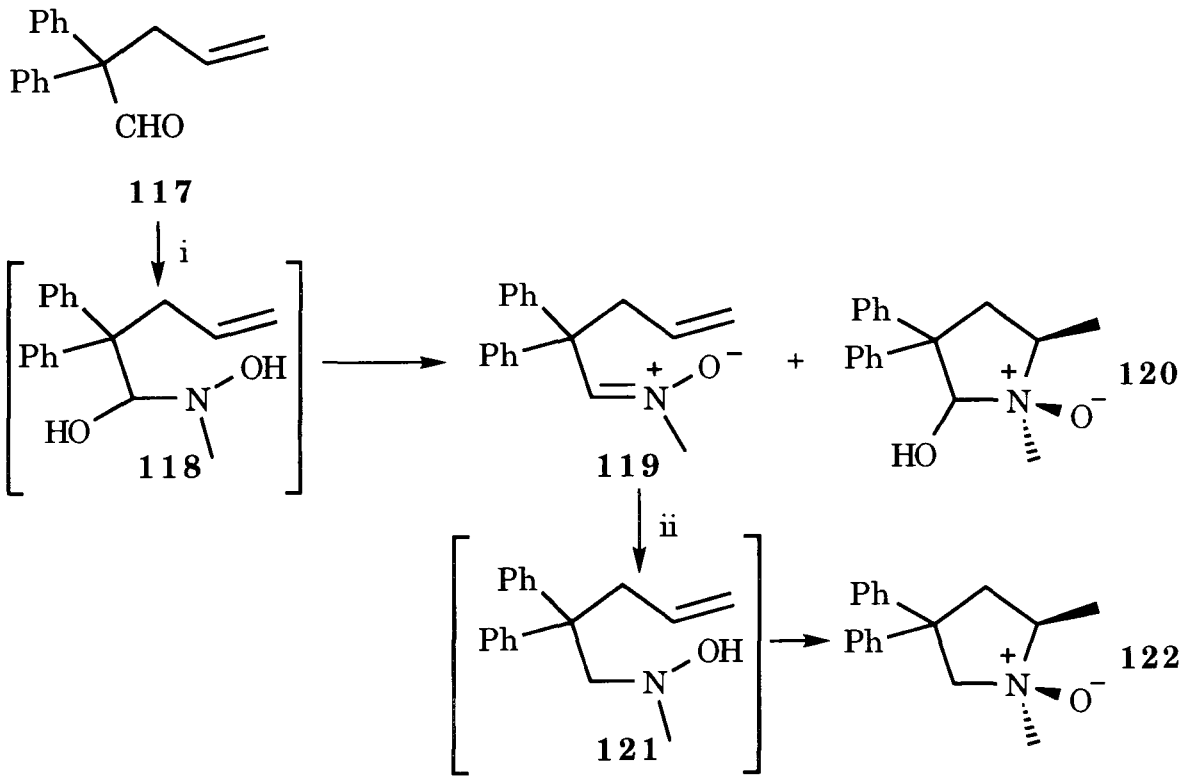
Dibenzoazabicyclic systems (*e.g.* **116**) have been elaborated from the corresponding hydroxylamines using *retro*-Cope chemistry.[66]



Scheme 50

Few further investigations[67] into this interesting reaction were reported until a paper by Ciganek[68] in 1990 indicated that this conversion was formally a reverse (or *retro*) Cope elimination.

In Ciganek's work, *N,N*-disubstituted hydroxylamines were used as the relevant reacting species, rather than the mono-substituted cases above. On reaction of 2,2-diphenyl-4-pentenal **117** with *N*-methyl hydroxylamine, only 45% of the nitrone **119** was obtained. Another product was, however, obtained in 51% yield and was shown to be the pyrrolidinol *N*-oxide **120**. This *N*-oxide was the result of a formal *retro*-Cope elimination of the initial hydroxylamine adduct **118** of the aldehyde (Scheme 51).



i) MeNHOH, EtOH, rt; ii) $LiAlH_4$

Scheme 51

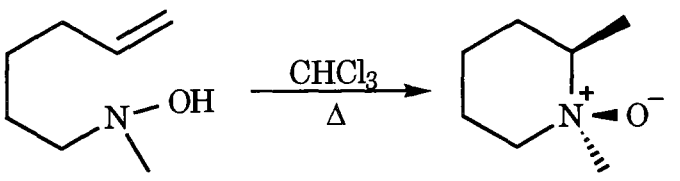
Also shown was that reduction of the nitrone **119** with lithium aluminium hydride resulted in isolation of a single *N*-oxide **122** in 89% yield. X-Ray crystallography showed the two methyl groups to be *trans*. There was no evidence in the crude product for the presence of uncyclised unsaturated hydroxylamine **118**, indicating that all the hydroxylamine had cyclised at, or below, room temperature.

Evidence for the reversibility of this reaction was obtained upon distillation of the *N*-oxide **124**. Here, partial reversion to the hydroxylamine **123** was seen, but, on cooling and standing at room temperature, the *N*-oxide was completely regenerated (Scheme 52).

123 **124**

Scheme 52

Piperidine *N*-oxides (*e.g.* **126**) were obtained using *N*-(5-hexenyl)-*N*-methyl hydroxylamines (*e.g.* **125**, Scheme 53). In this case, the reaction was much slower at room temperature, but the rate could be increased by refluxing in chloroform which resulted in complete conversion into the *N*-oxide **126** with a half-life of *ca.* 2h. Again, a *trans* dimethyl arrangement was observed.[68]



125 **126**

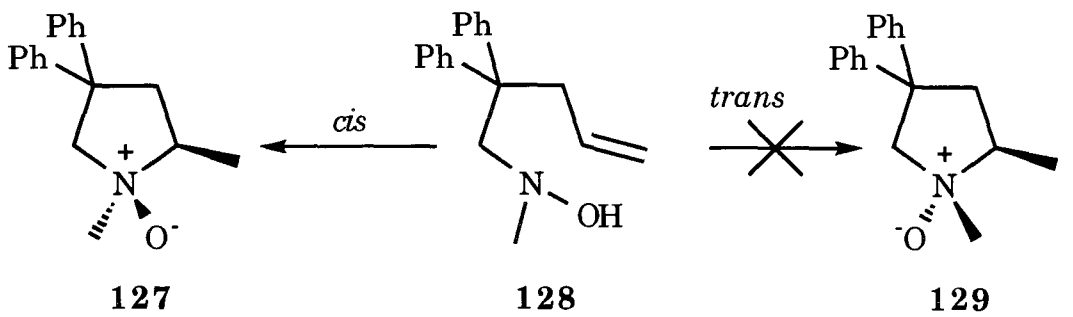
Scheme 53

Solvent studies indicated that chloroform was the optimum solvent for the *retro*-Cope elimination.[68] Ciganek then went on to observe that, as the Cope elimination is a concerted *syn* elimination involving a 5-membered transition state, then the above indicates that the reverse reaction also proceeds *via* the same mechanism, rather than the radical-chain mechanism proposed by House[64] for the mono-substituted hydroxylamines (Scheme 48).

The evidence for this was as follows:

i) Only one (**127**) of the two possible *N*-oxides is formed (Scheme 54).

e.g.



127 **128** **129**

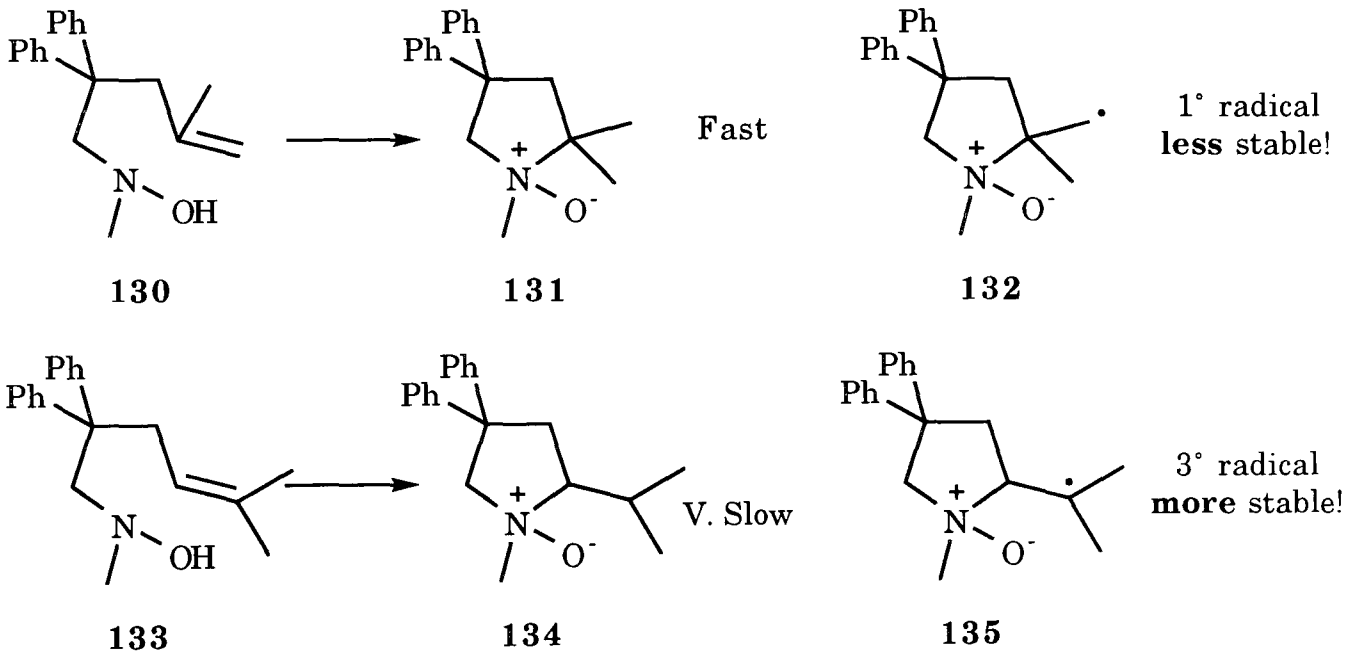
Scheme 54

In this case, the newly formed methyl group is *cis* to the *N*-oxide oxygen, as required by the concerted mechanism.

ii) The reaction is reversible at room temperature in suitably substituted substrates.

iii) The influence of double bond substitution on the rate of cyclisation is inconsistent with a radical mechanism (Scheme 55).

ie.



130 **131** **132**

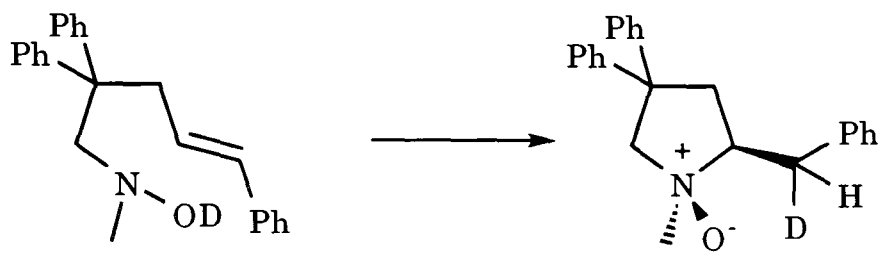
133 **134** **135**

Scheme 55

If a radical mechanism was occurring, cyclisation of hydroxylamine **133** would be expected to be more facile than cyclisation of hydroxylamine **130** because the intermediate radical would be expected to be more stable in the case of *N*-oxide **135**

(tertiary radical) than *N*-oxide **132** (primary radical) due to the stabilising effects of the alkyl groups.

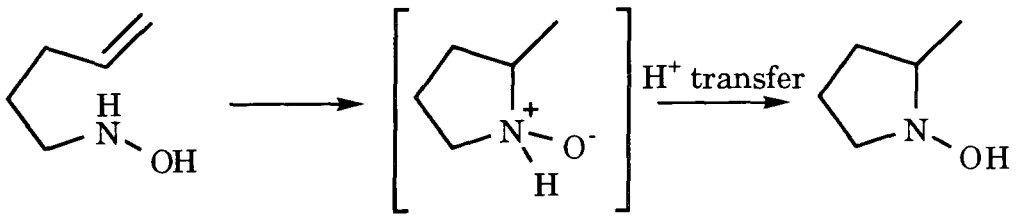
iv) The specific transfer of deuterium in the transformation shown in Scheme 56 is consistent with a concerted mechanism.



136 **137**

Scheme 56

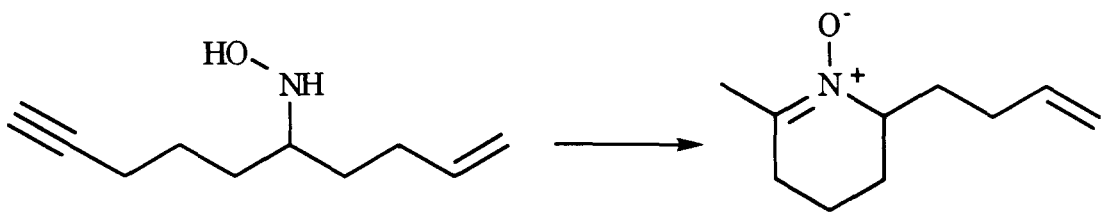
Finally, it has been subsequently shown that the rate of cyclisation of mono-substituted hydroxylamines (*cf.* House *et al*)[63,64] is unaffected by radical inhibitors.[67] It was proposed by Ciganek that this did, indeed, proceed *via* a *retro*-Cope elimination, the difference here being that the *N*-oxide **139** initially formed rearranges irreversibly to the *N*-hydroxy isomer **140** (Scheme 57).



138 **139** **140**

Scheme 57

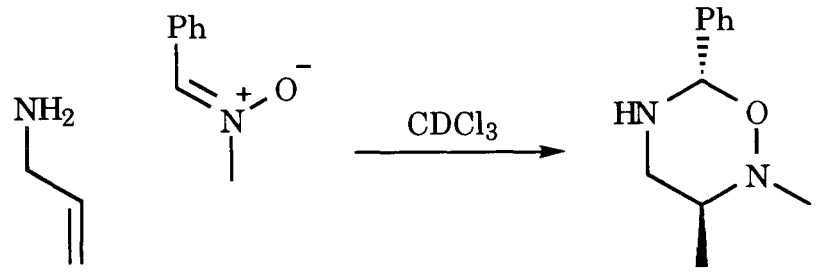
Further to this, Holmes[69] *et al* reported in 1991 that alkynes cyclise more readily than alkenes, to give nitrones (*e.g.* **142**) in around 80% yield (Scheme 58). Holmes[70-72] subsequently showed that 6-*exo*-dig cyclisations are more favoured than both 5-*exo*- and 6-*endo*-dig modes.



141 142

Scheme 58

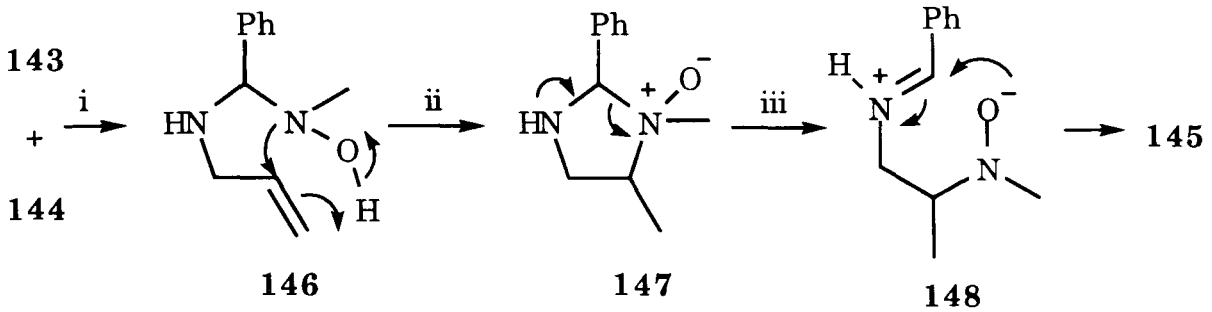
Work by Knight[56] published in 1993 indicated another use for the *retro*-Cope reaction in the synthesis of vicinal [1,2] diamines. When equivalent amounts of an allylamine **143** and a nitrone **144** were left at room temperature in chloroform for 7 days, the reactants were completely transformed into a single product **145** with only a trace of impurity (Scheme 59).



143 144 145

Scheme 59

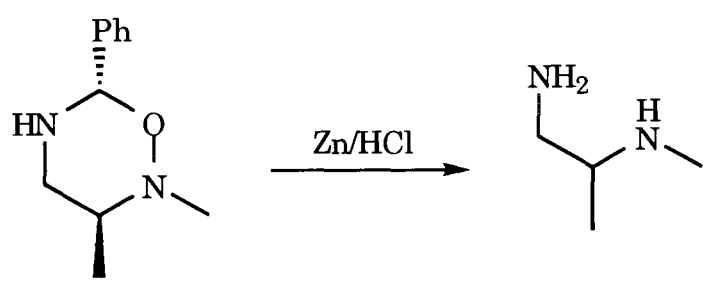
This product was not, as might be expected, a 1,3-dipolar cycloaddition product between the nitrone and the unactivated C-C double bond. It was, in fact, a compound resulting from the initial nucleophilic attack of the amine onto the nitrone, followed by *retro*-Cope elimination of the intermediate hydroxylamine **146**, this then being followed by a Meisenheimer-type rearrangement[74] (Scheme 60).



i) Addition; ii) *retro*-Cope; iii) Meisenheimer rearrangement

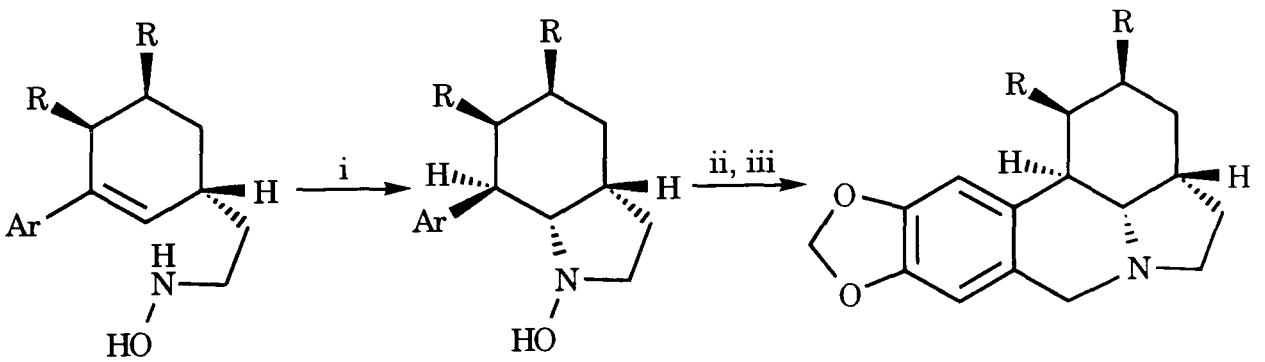
Scheme 60

Treatment of these oxadiazines (*e.g.* **145**) with zinc and hydrochloric acid resulted in the formation of 1,2-diamines in >90% yield (*e.g.* **149**, Scheme 61).



Scheme 61

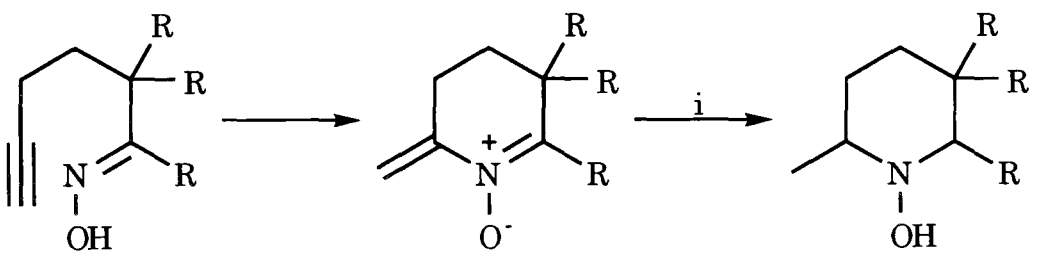
Recently, Oppolzer[75] *et al* reported the incorporation of a *retro*-Cope process in natural product synthesis, to give (±)-α-lycorane **152** and (+)-trianthine **153** (Scheme 62).



i) Δ, benzene; ii) Raney Ni; iii) Eschenmosers salt, THF, 40°C

Scheme 62

Related work, first published by Pradhan *et al* in 1982,[76] is the cyclisation of oximes in a *retro*-Cope sense. Here, oximes **154** were observed to cyclise intramolecularly with alkynes to give cyclic nitrones **155** (*ca.* 90%) which, upon reduction, gave hydroxylamines **156** (Scheme 63).

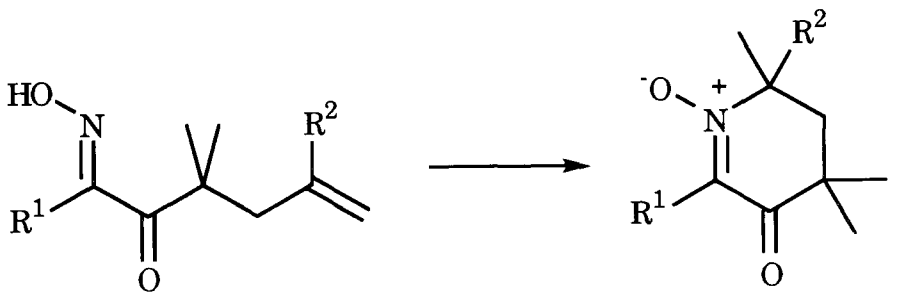


154 **155** **156**

i) $NaBH_4$

Scheme 63

This was subsequently investigated in more detail by Grigg[77] *et al* and the process was termed a 1,3-azaprotio cyclotransfer reaction.



157 **158**

Scheme 64

The *retro*-Cope reaction has recently been reviewed by Ciganek.[73]

4.5 Nitrone Synthesis

Many methods exist for the synthesis of nitrones,[89] but they all fall into one of four major subdivisions: oxidative methods, condensations with *N*-substituted hydroxylamines, *N*-alkylation of oximes and from reactions of nitroso compounds.

4.5.1 *Oxidative Methods*

4.5.1.1 Oxidation of Secondary Amines

The oxidation of both cyclic and acyclic aliphatic secondary amines has been achieved using hydrogen peroxide, catalysed by sodium tungstate.[78] The catalytic effect of other metals has also been studied, but were found to be inferior to tungsten. *C,N*-Diaryl nitrones have been synthesised by oxidation of *N*-benzylanilines using *m*CPBA in acetone.[79]

4.5.1.2 Oxidation of *N,N*-Dialkyl Hydroxylamines

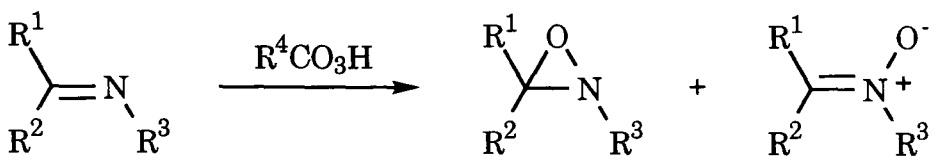
Conversion of *N,N*-dialkyl hydroxylamines into nitrones is easily achieved by mild oxidative methods. *N*-Hydroxy derivatives of cyclic amines have been oxidised to nitrones, in high yields, electrochemically, using halide ions as mediators.[80] Dialkyl and *N*-benzyl-*N*-alkyl hydroxylamines have been dehydrogenated using palladium black[81] in 60-90% yields.

Other oxidative methods include the use of hydrogen peroxide in acetic acid,[82] quinones[83] and metal oxides.[84]

4.5.1.3 Oxidation of Imines[85]

Peroxyacid oxidation of imines **159** can yield both oxaziridines **160** and nitrones **161**, the former usually being the major product

(Scheme 65). The reaction has been shown to be influenced by steric and mesomeric effects. The mechanism of formation of the nitrone is thought to be a one-step nucleophilic addition of the imine nitrogen to the peracid, whereas the oxaziridine is thought to arise from a two-step process initiated by nucleophilic attack of the peracid oxygen onto the imine carbon.



159 **160** **161**

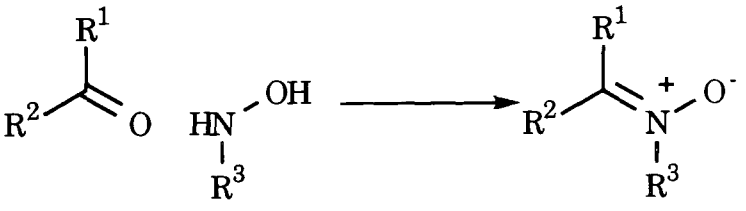
Scheme 65

It is also possible that an equilibrium exists between the oxaziridine and the nitrone.

4.5.2 *Condensation Reactions of N-Substituted Hydroxylamines*

4.5.2.1 Condensations with Aldehydes and Ketones[86]

Condensation of aldehydes or ketones with *N*-substituted hydroxylamines has been widely used in the preparation of nitrones (Scheme 66). C-Unsubstituted, mono- and di-substituted nitrones can be obtained using paraformaldehyde, an aldehyde or a ketone, respectively.



162 **163** **164**

unsubstituted: R^1=R^2=H

monosubstituted: R^1=H, R^2= *e.g.* alkyl

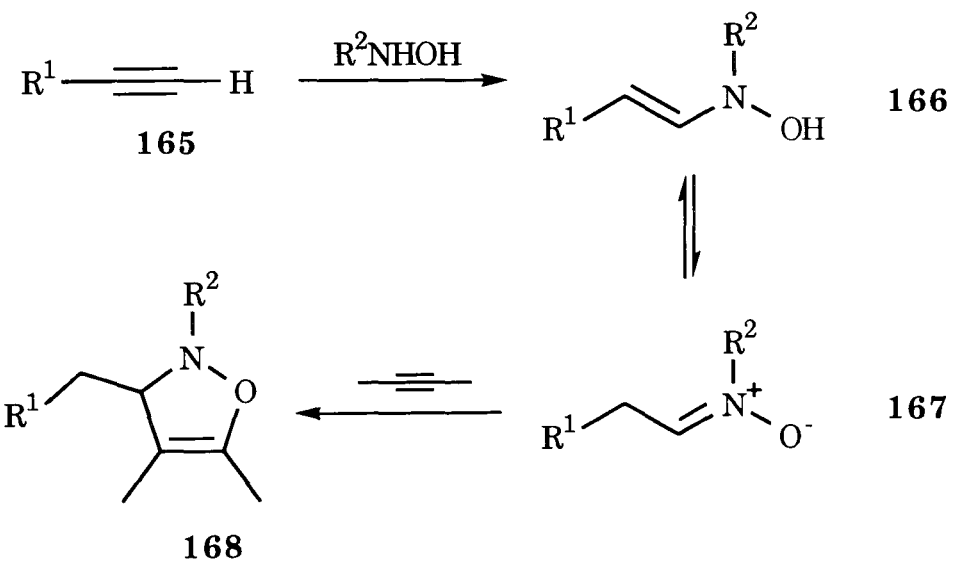
disubstituted: R^1, R^2= *e.g.* alkyl

Scheme 66

A modification to this procedure involves the use of *N*-methyl-*N,O-bis*(trimethylsilyl)hydroxylamine,[87] which results in nitrone formation and the volatile hexamethyldisiloxane byproduct rather than the usual water, which could possibly cause hydrolysis with more reactive nitrones.

4.5.2.2 Condensation with Acetylenes

Reactions of acetylenes **165** with hydroxylamines give the required nitrones **166**, but these are usually too reactive to be isolated and react with any excess acetylene present (Scheme 67).[88] Acetylenes with a suitably positioned double bond in their structure were found to produce nitrones which were trapped intramolecularly by the olefin.



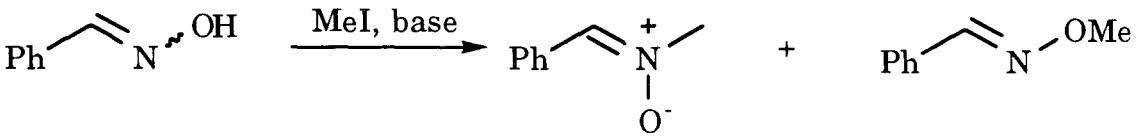
Scheme 67

4.5.2.3 Other Methods

Also reported have been the condensation of hydroxylamines with enamines[90] (the nitrone in this case was not isolated), intramolecular ketone-alkyl hydroxylamine condensations to give bicyclic nitrones,[91] and condensation of orthoesters or amide acetals to give oxazolidine *N*-oxides[92] or α-alkoxynitrones.[93]

4.5.3 N-*Alkylation of Oximes*

This is another common method for nitrone preparation. In this case, however, a mixture of *N*- and *O*-alkylated products are normally seen.[94] The position of alkylation has been found to depend on the stereochemistry of the oxime. *Z*-Oximes give predominantly *N*-alkylation, whereas *E*-oximes give *O*-alkylation preferentially (*e.g.* Scheme 68).



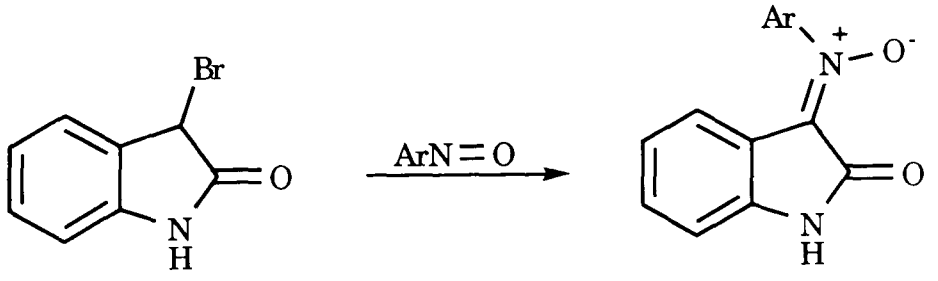
169 **170** **171**

Scheme 68

Influencing the position of alkylation by changing the reaction conditions has had some success. For example, using a two-phase system of benzene/aqueous sodium hydroxide and a phase transfer catalyst resulted in up to 80% *N*-alkylation and around 10% *O*-alkylation. Protection of the oxime as its *O*-trimethylsilyl derivative gives the *N*-alkylated product.

4.5.4 *From Nitroso Compounds*

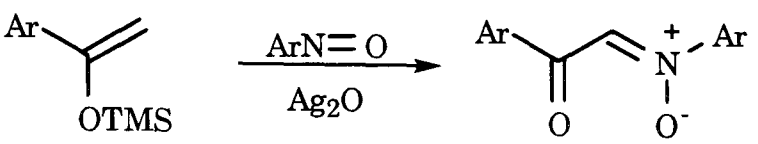
Nucleophilic addition of nitroso compounds to α-bromo-heterocyclic carbonyl compounds (*e.g.* **172**) has been shown to result in nitrone formation (Scheme 69).[95]



172 **173**

Scheme 69

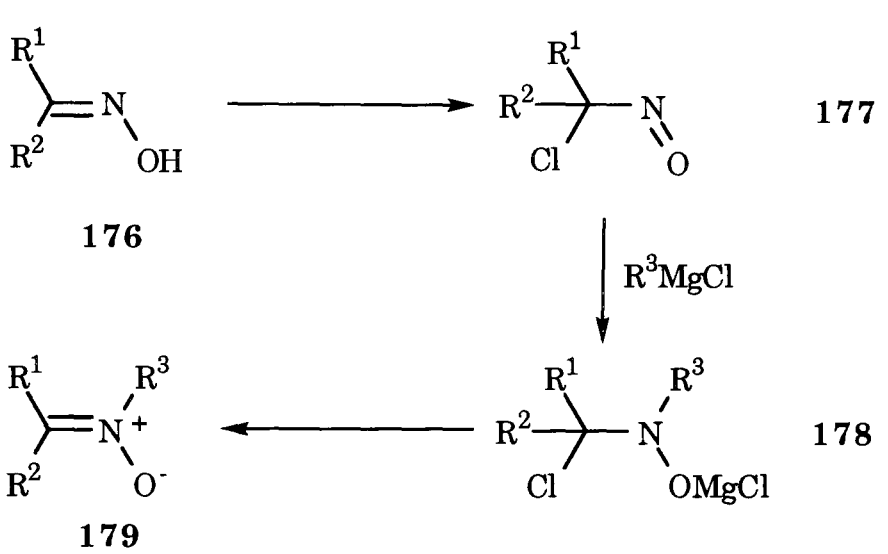
Nitrones also result from electrophilic addition of nitrosoarenes to silyl enol ethers (*e.g.* **174**), followed by silver(I) oxide oxidation (Scheme 70).[96]



174 **175**

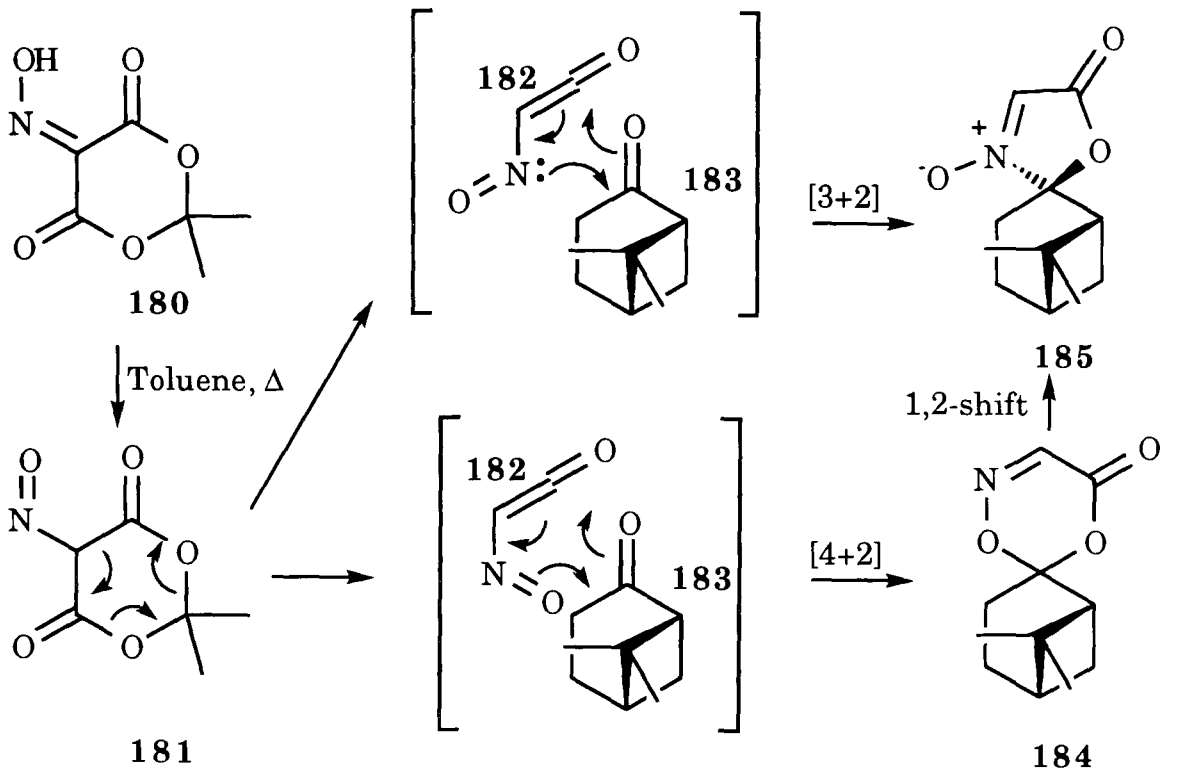
Scheme 70

Reactions of α-chloronitrosoalkanes **177** with Grignard reagents has also been reported to lead to nitrone **179** formation, usually in good yields (Scheme 71).[97]



Scheme 71

Formation of chiral cyclic nitrones **185** from nitrosoketenes **182** (generated from hydroxyimino Meldrums acid **180**) and chiral ketones (*e.g.* **183**; in around 60% yield) was reported by Katagiri[98] in 1994, probably *via* [4+2] addition followed by a 1,2-rearrangement, although direct [3+2] addition has not been dismissed (Scheme 72).



Scheme 72

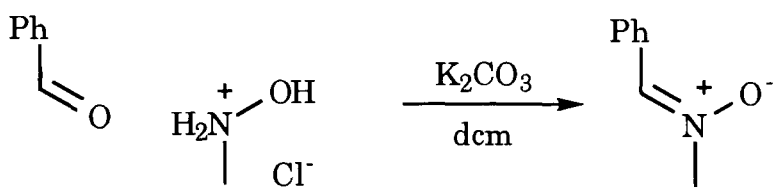
4.5.5 *Method Adopted for Nitrone Preparation*

Obviously, purification could be a problem here, as the nitrones were unlikely to be stable to chromatography on *e.g.* silica. They were also expected to be non-crystalline and so recrystallisation would not, in most cases, be possible.

The method of preparation for the nitrones would, therefore, be the one which was most likely to produce the nitrone in high yield and which would require the least purification. The method chosen was the condensation[86] of an aldehyde with a hydroxylamine in the presence of a desiccant to remove the water eliminated upon reaction.

The first nitrone to be made was that arising from the condensation of benzaldehyde **185** with *N*-methylhydroxylamine hydrochloride **186**. The base used to release the free hydroxylamine was potassium carbonate and this also acted as the desiccant, removing the water from the reaction medium and thus forcing the equilibrium over to the side of the nitrone **144** (Scheme 73).

Thus, *N*-methyl-*C*-phenyl nitrone **144** was obtained in an almost quantitative yield as a white solid, after recrystallisation. Surprisingly, this nitrone was found to be not only easily purified, but also indefinitely stable at room temperature. This fact made this nitrone ideal for our preliminary studies into the nucleophilic addition of carbanions to nitrones.



185 **186** **144**

Scheme 73

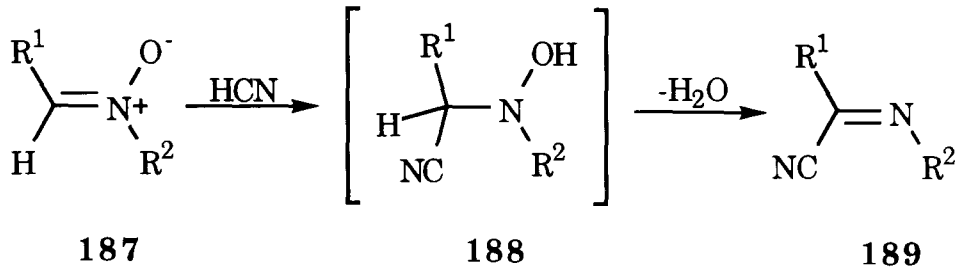
This method was used to synthesise all the nitrones dealt with in this thesis.

4.6 Nucleophilic Attack of Nitrones by Carbon Nucleophiles

Addition of carbon nucleophiles to nitrones has been studied quite extensively due to the potential for biological activity from the products which include optically active secondary amines. Some of the carbon nucleophiles[89] which have been reported to add to nitrones are shown below.

4.6.1 *Cyanide*

Cyanide[99] has been shown to add to nitrones **187** to give cyanoimines **189** upon elimination of water. The intermediate hydroxylamine has also been isolated as the silyl compound **190** by using trimethylsilyl cyanide as the nucleophile (Scheme 74).[100]



187 **188** **189**

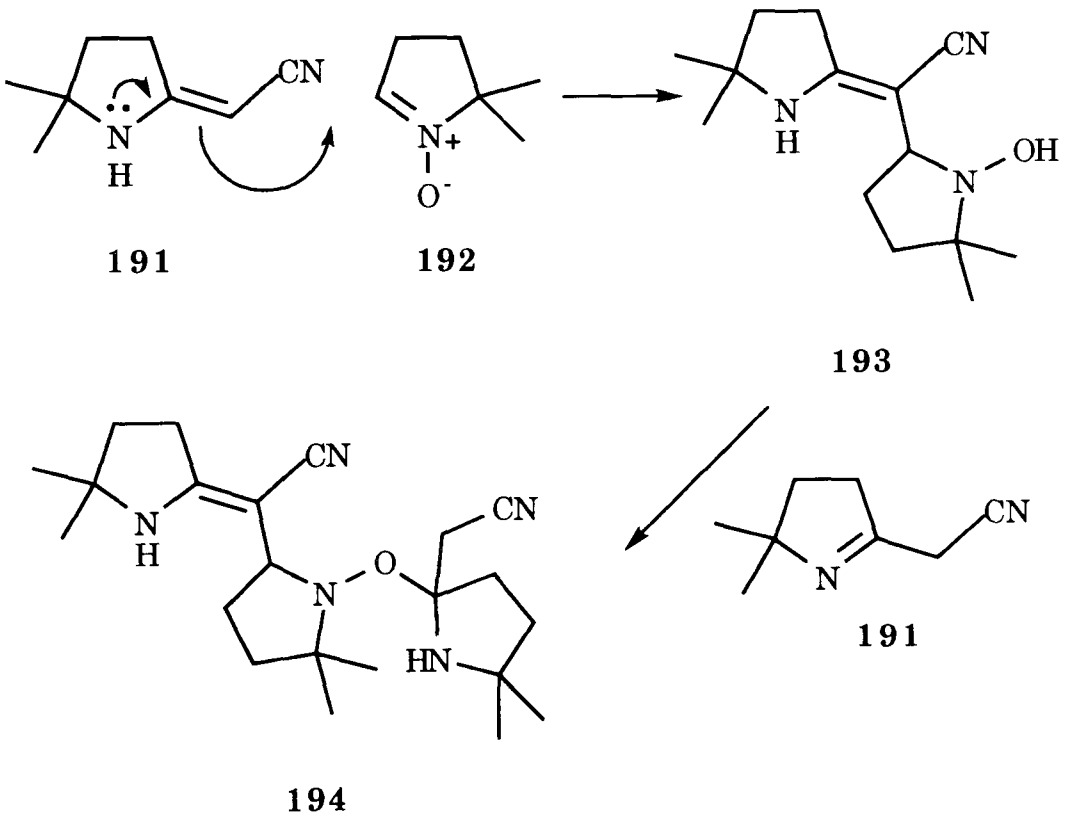
144 **190**

Scheme 74

The reverse reaction (**190** to **144**) may be accomplished by treatment with silver fluoride at 80°C.

4.6.2 *Enamines*

1,3-Dipolar cycloaddition reactions have been known with enamines,[101] but it has also been shown by Zbaida[102] that enaminonitrile **191** adds to nitrone **192** to give hydroxylamine **193**.



191 **192** **193**

191

194

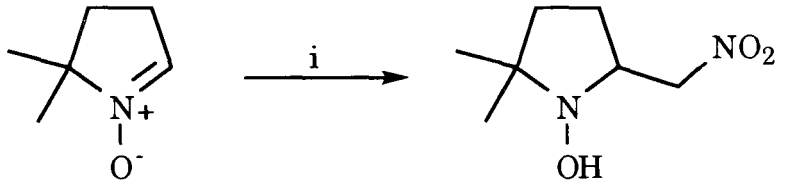
Scheme 75

The hydroxylamine **193** is also capable of adding a second time to compound **191** (in its imine form) if an excess of this starting material is used (Scheme 75).

4.6.3 *Carbanions*

Carbanions are also well documented to add to nitrones.

Nitromethane, when treated with sodium ethoxide, adds to 2-methylpyrroline-*N*-oxide **192** to give compound **195** (Scheme 76).[108]

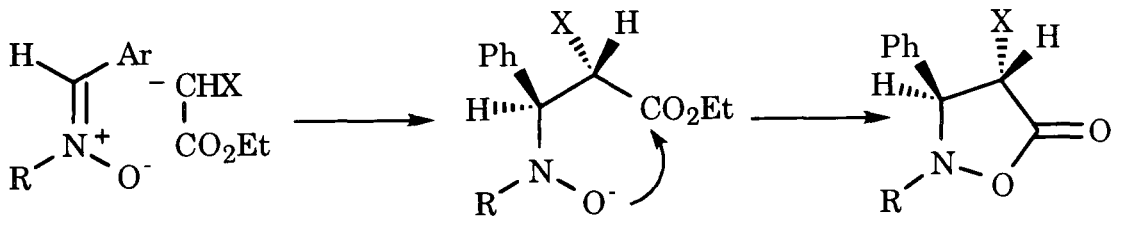


192 **195**

i) $MeNO_2$, EtO^-

Scheme 76

The carbanions derived from diethyl malonate **197a** and related species **197b-d** have been shown to result in the isoxazolidinones[103] **199a-d** when reacted with nitrones **196** (Scheme 77).



196 **197a-d** **198a-d** **199a-d**

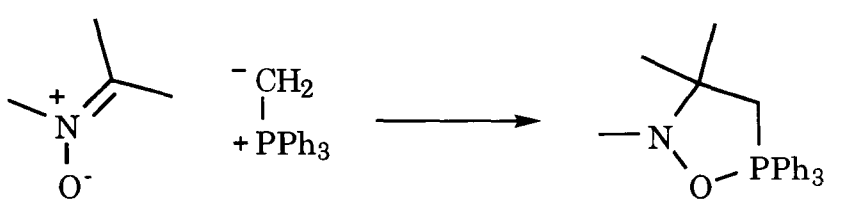
X = CO_2Et **a**, CN **b**, Ph **c**, $CONR_2$ **d**; R = alkyl

Scheme 77

The isoxazolidinones have predominantly a *trans* stereochemistry and the yields have been found to vary with the

steric requirements of the *N*-alkyl group of the nitrone and the nature of the carbanion.

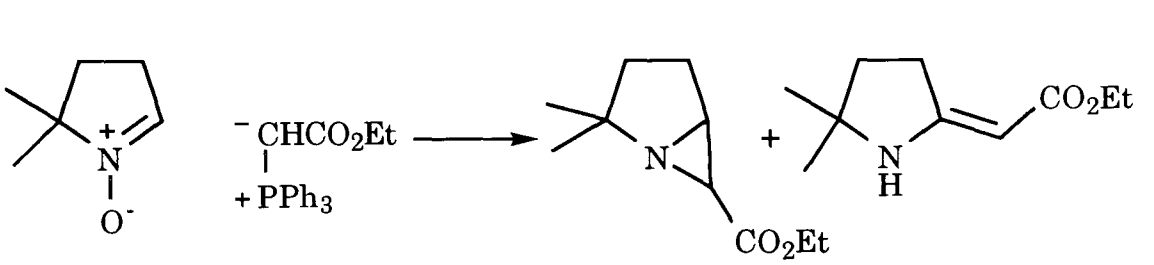
Addition reactions between nitrones and phosphorus ylides have been extensively studied. Formation of stable oxazaphospholidines **202** is observed when nitrones **200** react with triphenylphosphonium ylides **201** (Scheme 78).[105]



200 **201** **202**

Scheme 78

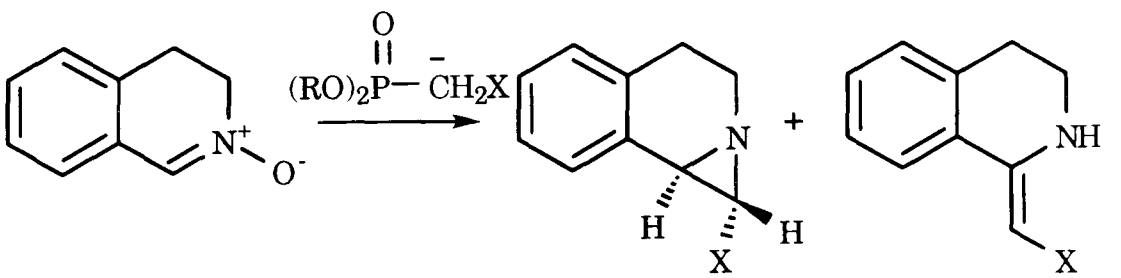
Extrusion of triphenylphosphine oxide leads to compounds **204** and **205** when ester-stabilised phosphonium ylides (*e.g.* **203**) are used (Scheme 79).[106]



192 **203** **204** **205**

Scheme 79

The addition of phosphonate stabilised anions to nitrone **206** leads to the formation of aziridines **207** or enamines **208**, depending on the reaction conditions (Scheme 80).[107]

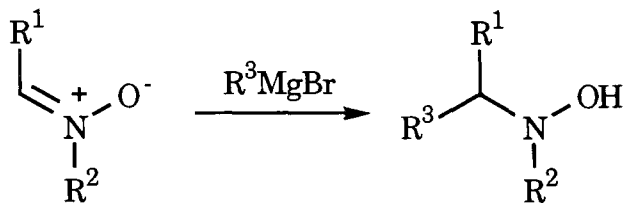


206 **207** **208**

X = CN, CO_2Et

Scheme 80

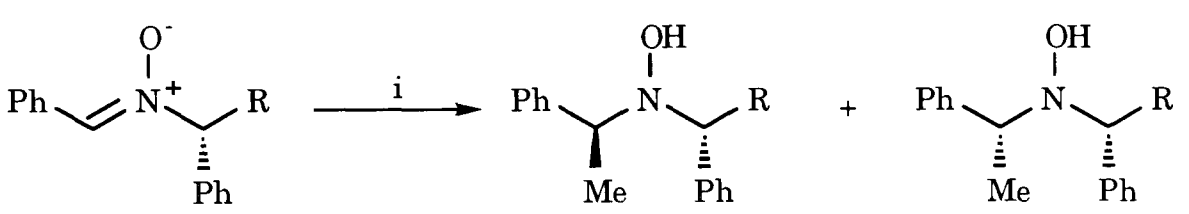
Additions of Grignard reagents[108] to nitrones **209** has been known since the 1920's, but yields are generally variable (Scheme 81).



209 **210**

Scheme 81

Diastereoselective additions of Grignards to nitrones **211** with chiral *N*-alkyl substituents have been reported by Coates,[109] with the best results obtained using chelation control of the *N*-substituent with the *N*-oxide oxygen (Scheme 82). Yields of 39-96% with diastereoselectivities of up to 95:5 were observed.



211 **212** **213**

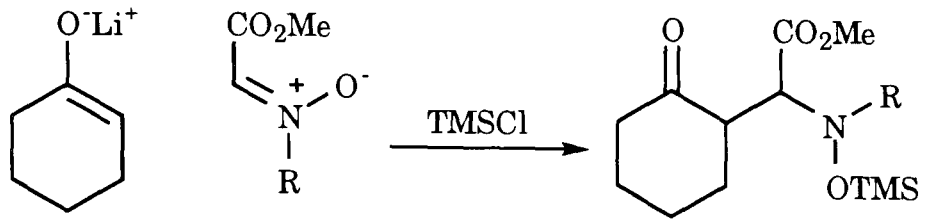
	Overall Yield		
e.g. R= Me	91 %	46	54
R = CH_2OMe	96 %	95	5

i) MeMgBr, ether, 0°C

Scheme 82

In the same way, alkyl and aryl lithium species were condensed with nitrones to give similar diastereoselectivities, but with much lower yields.

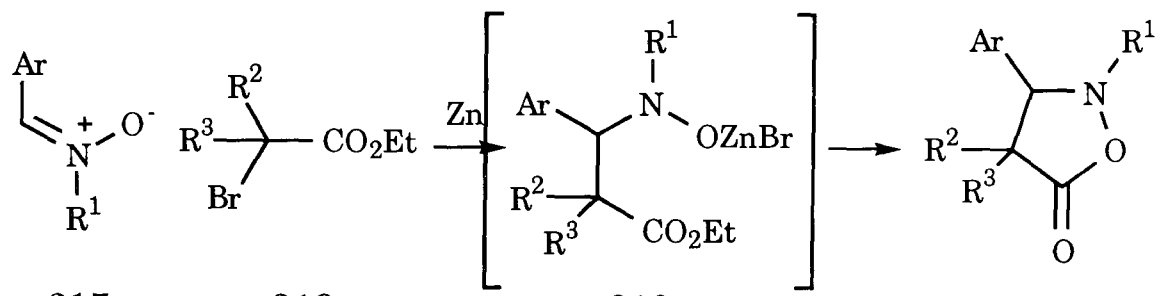
Lithium enolates (*e.g.* **214**) have been shown to add to *C*-methoxycarbonyl-*N*-alkyl nitrones **215** (Scheme 83).[110]



214 **215** **216**

Scheme 83

Reformatsky reagents,[111] such as organozinc compounds derived from α-bromoesters **218**, undergo addition reactions with *C*-aryl-*N*-alkyl nitrones **217** (Scheme 84). The resulting isoxazolidinones **220** show the similarity between this reaction and the malonate addition reactions (Scheme 77).

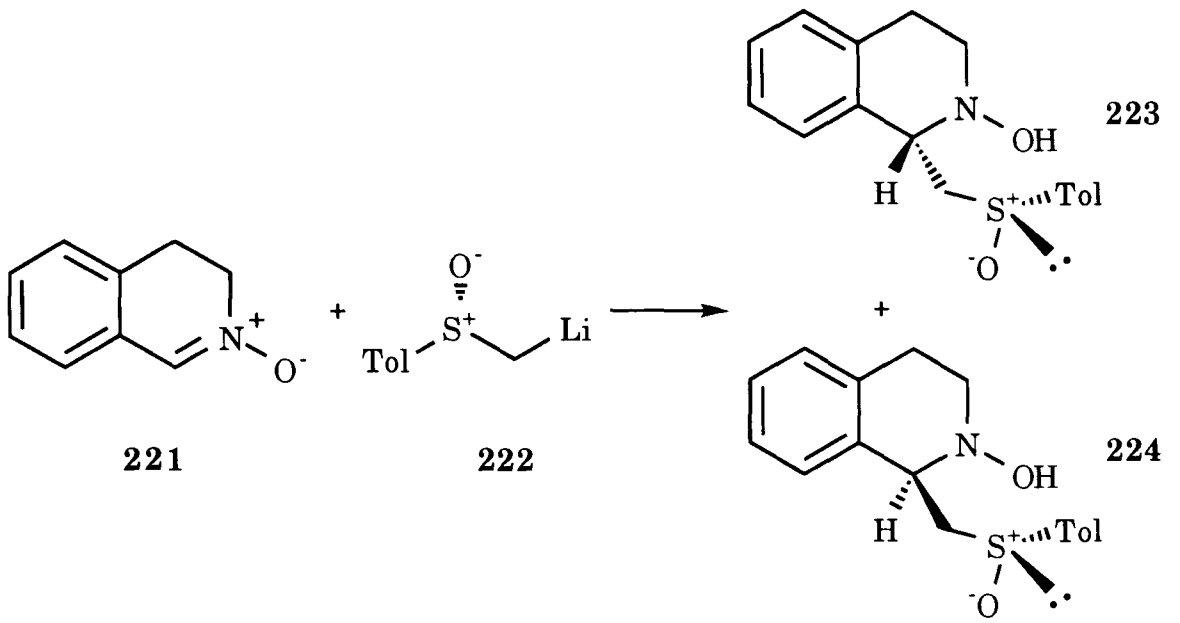


217 **218** **219** **220**

Scheme 84

Other organometallic reagents have also been reported to undergo addition reactions with nitrones.[112]

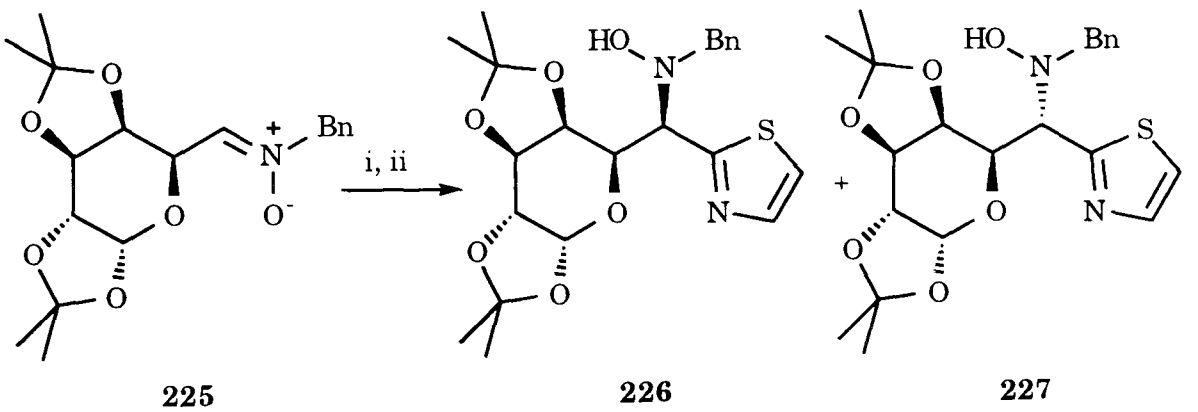
Addition of optically active methyl *p*-tolyl sulphoxide anions **222** to 3,4-dihydroxyisoquinoline *N*-oxides **221** has been extensively studied[113] as the products obtained are key intermediates in various isoquinoline alkaloid syntheses. Typically, treatment of the isoquinoline *N*-oxide **221** with the anion **222** derived from methyl *p*-tolyl sulphoxide at -78°C in THF, gave the required adduct in around 80% yield as a diastereomeric mixture (64:36) (Scheme 85).



Scheme 85

In a later paper by Murahashi *et al*,[114] the diastereomer ratio was much improved by the addition of an auxiliary (quinidine) which acts as a facial discriminating reagent. Here, an increase in diastereomer ratio to 98:2 was observed, although the yield was slightly lower (68%).

Addition of 2-metallothiazoles to nitrones (*e.g.* **225**) has been reported by Dondoni *et al*.[115] Stereoselective additions were achieved



i) Lewis acid, Et_2O, low T; ii) 2-metallothiazole (M=Li, MgX, AlR_2)

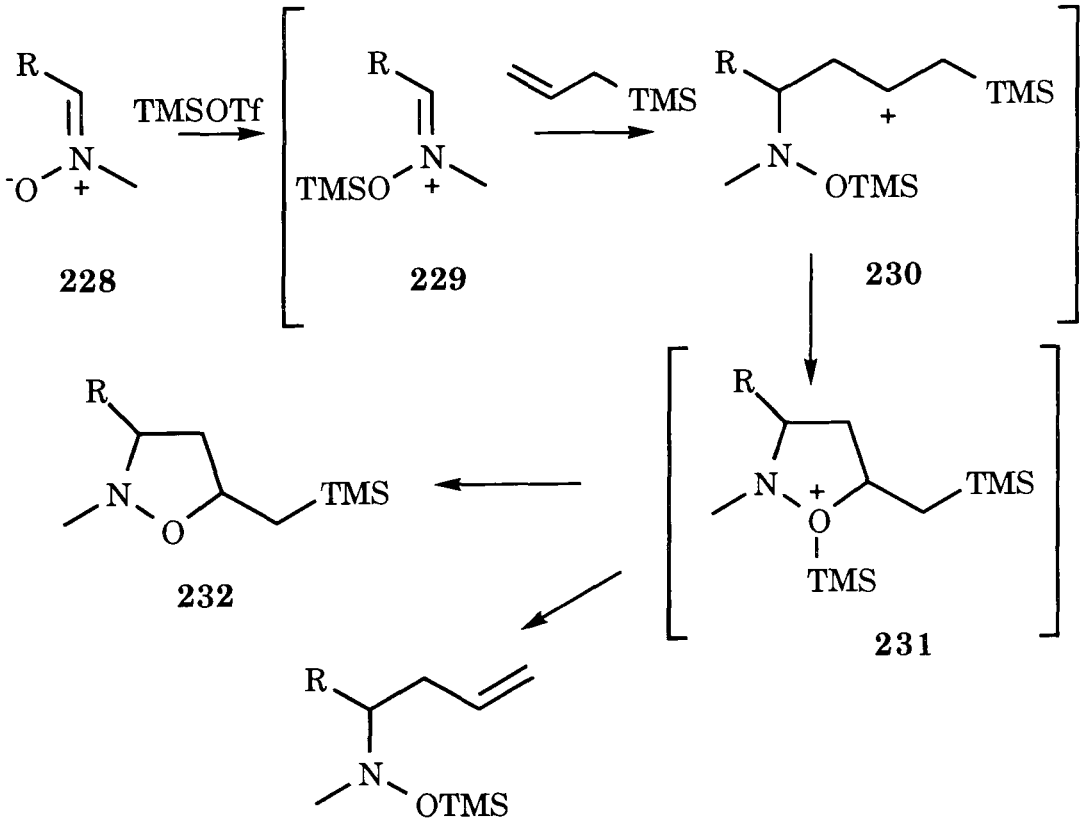
Scheme 86

using nitrones pretreated with Lewis acids in up to 90% yield (Scheme 86).[116] Here, with 2-lithiothiazole, the *syn* adduct **226** was

favoured using $MgBr_2$ (68:32; syn:anti) and $ZnBr_2$ (79:21), and the *anti* adduct **227** with Et_2AlCl (9:91) and $TiCl_4$ (11:89).

4.6.4 *Allyl Silanes*

The cycloaddition of allylsilanes with nitrones has been shown to proceed as expected to give isoxazolidines.[117] It has also been reported[118] that trimethylsilyl triflate (TMSOTf) catalysed addition of allylsilanes to nitrones is also possible. In dichloromethane at room temperature, a mixture of the addition product **233** (a homoallyl hydroxylamine) and the 1,3-dipolar cycloaddition product **232** is observed, usually with a very high selectivity and yield (70-95%) with respect to the addition. The proposed mechanism is shown in Scheme 87.



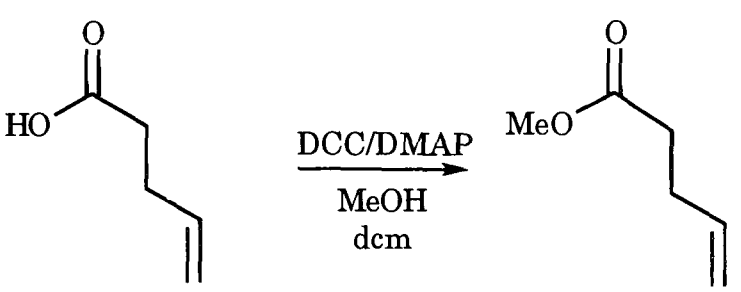
Scheme 87

TMSOTf was shown to be catalytic because it usually requires temperatures in excess of 100°C to facilitate the 1,3-dipolar

cycloaddition reaction. TMSOTf here, appears to be unique in its effect upon the reaction. Other Lewis acids, such as tin(IV) chloride and boron trifluoride etherate, were generally unsuccessful and titanium(IV) chloride, although producing the homoallyl hydroxylamine, did so in only 32% yield. The reaction may be run catalytically in TMSOTf but usually a stoichiometric amount is used since this leads to a single product in less time and better overall yield.

4.7 EWG = Ester

It was against this background that the research contained in this chapter began. It was decided that the first electron withdrawing group (EWG) to be tried was the ester group. The necessary homoallylic ester **235** was synthesised from commercially available 4-pentenoic acid **234** *via* a dicyclohexylcarbodiimide (DCC) / *N,N*-dimethylaminopyridine (DMAP)[118] esterification with methanol as nucleophile (Scheme 88). A disappointing 50% isolated yield was obtained, due to the high volatility of the ester.



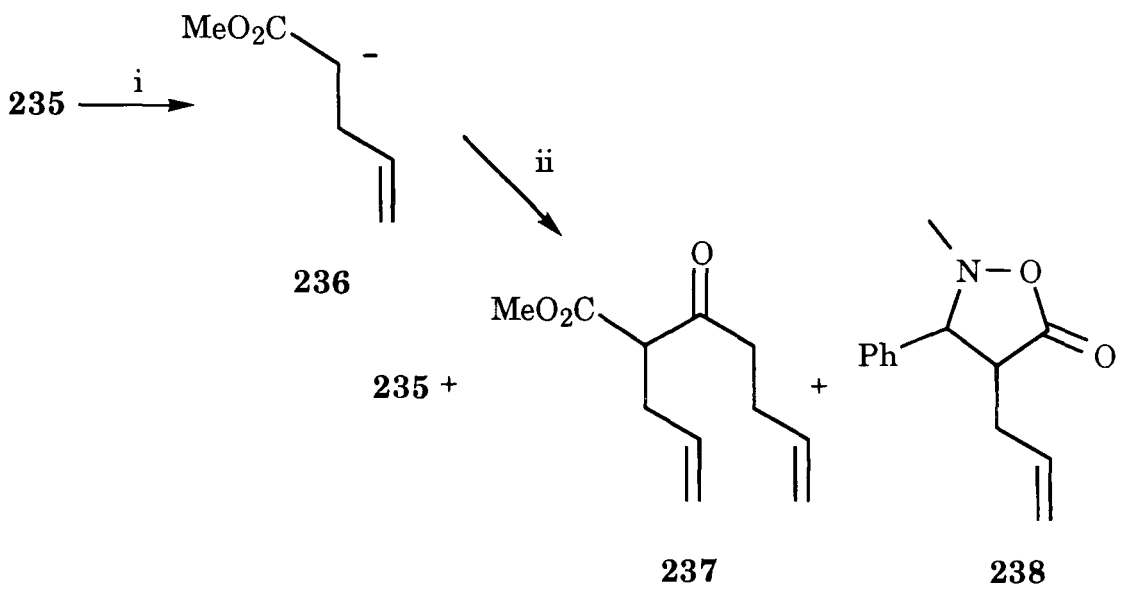
234 **235**

Scheme 88

Now, a non-nucleophilic base was needed to deprotonate α– to the ester carbonyl group. The base chosen was lithium di*iso*propylamide (LDA).

Initial attempts were very disappointing. Treatment of the ester **235** with LDA, at -78°C for 30 min, resulted in almost quantitative recovery of starting material after nitrone **144** was added to quench the anion **236** formed. Other products obtained were the Claisen condensation product **237**[119] (produced when the ester anion **236** reacts with another molecule of ester **235**) and a product **238** resulting from the condensation of the ester anion with the nitrone **144** (Scheme 89). This latter product was, however, never isolated in more than 12% yield. Also, the desired condensation of the

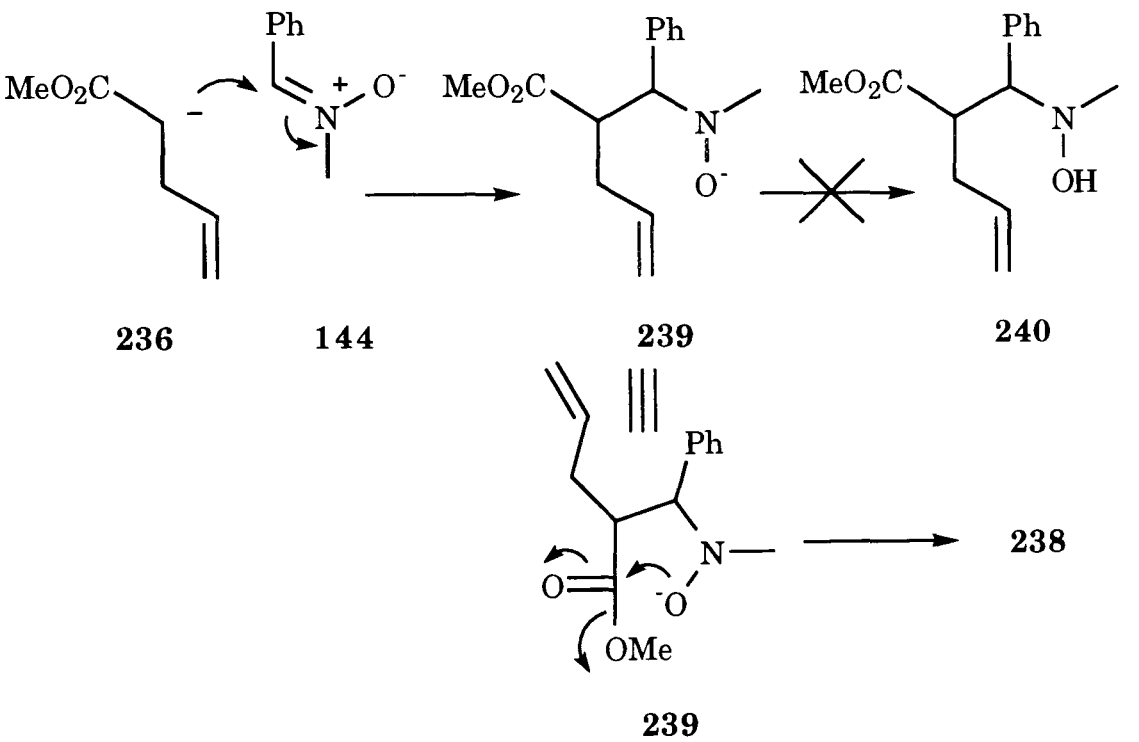
ester anion with nitrone **144** did not give the required hydroxylamine **240**, but the isoxazolidinone **238**.



i) LDA, -78°C, THF; ii) nitrone **144**

Scheme 89

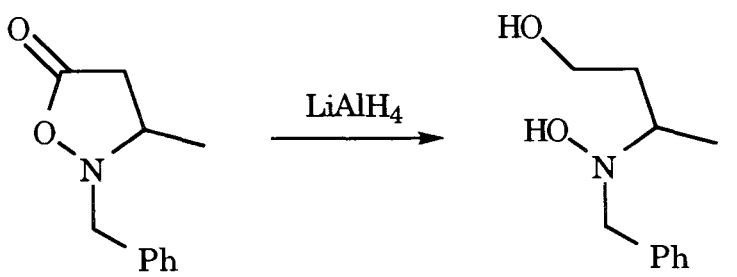
The isoxazolidinone **238** was isolated rather than the hydroxylamine **240** because the reaction intermediate **239** possesses a nucleophilic oxygen anion which reacts intramolecularly with the



Scheme 90

ester group, eliminating methoxide before the hydroxylamine is liberated upon quenching of the reaction mixture (Scheme 90, *cf.* Scheme 77).

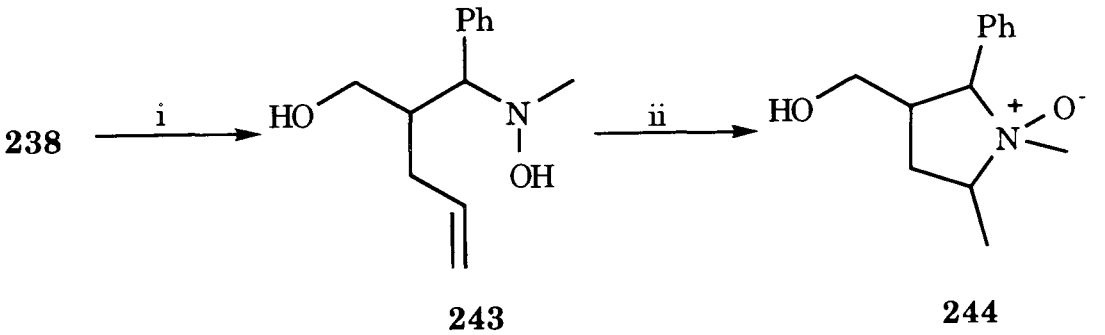
This product, at first sight, lead us to believe that the desired *retro*-Cope reaction was not possible. However, this type of reaction is not unprecedented as Baldwin and Harwood[120] have reported. They also reported that it is possible to reduce the ester function in the isoxazolidine, to give a hydroxylamine, in the presence of the N-O bond, reduction of which would give an amine. The use of lithium aluminium hydride was employed for this transformation (Scheme 91).



241 242

Scheme 91

It was, therefore, hoped that the isoxazolidine **238** could be reduced in a similar fashion to give a *retro*-Cope precursor **243** which



243 **244**

i) $LiAlH_4$; ii) $CDCl_3$

Scheme 92

could then be cyclised to give a pyrrolidine system **244** (Scheme 92).

Treatment of the isoxazolidine **238** with lithium aluminium hydride did indeed give a reduced product. The absence of a carbonyl stretch (υ_{max} 1740cm^{-1}) and the presence of an alcohol stretch (υ_{max} 3250cm^{-1}) was observed by IR spectroscopy, but the small quantity of compound isolated was not sufficient to try the *retro*-Cope reaction.

This route was then halted due to the unreliability and low yielding nature of the condensation which did not afford enough material to complete the desired sequence.

The use of a more reliable EWG was now required.

4.8 EWG = Sulphones

With the disappointing results obtained for EWG=ester, it was decided that the next EWG to be tried would be one such that intramolecular cyclisations would not be expected. The sulphone group was chosen as such a group. It was also expected that formation of an α-anion would be much cleaner.

4.8.1 *Preparation of Sulphones*

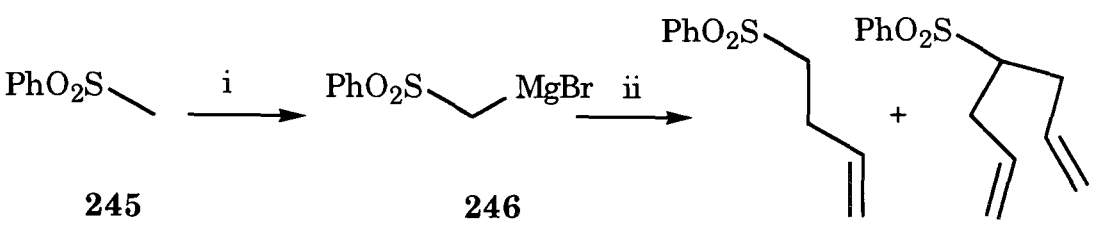
Three general methods were employed in sulphone synthesis. The method used was dependant on the price and/or commercial availability of the required starting materials.

4.8.1.1 Method A

The first method used methyl phenyl sulphone and an allylic halide. Here, the price of the allylic halide was the deciding factor.

Methyl phenyl sulphone **245** was treated with a magnesium base (ethylmagnesium bromide) in order to form an Ivanov reagent

246.[121] This was then reacted with an allylic halide and catalytic copper(I) chloride to form the required homoallylic sulphone **247** in a good (typically 70%) yield. In this case, a small quantity (*ca.* 2%) of diallylation product (*e.g.* **248**) was also isolated (Scheme 93).



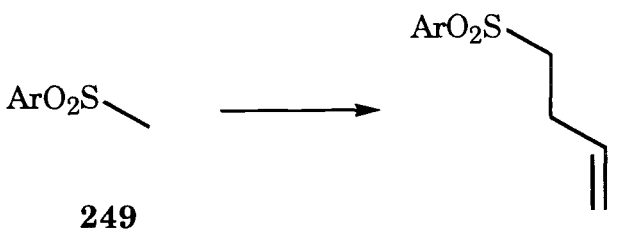
245 **246** **247** **248**

i) EtMgBr, THF, benzene; ii) allyl bromide, CuCl

Scheme 93

If, however, a lithium base is used (*e.g.* butyl lithium), only around 35% of the homoallylic sulphone **247** was isolated. The major product was found to be the diallylated methyl phenyl sulphone **248** in around 55% yield. Separation of the allylated and diallylated species was easily accomplished using column chromatography.

This method could also be used with aryl methyl sulphones in general **249** to give homoallylic aryl sulphones **250** (Scheme 94).



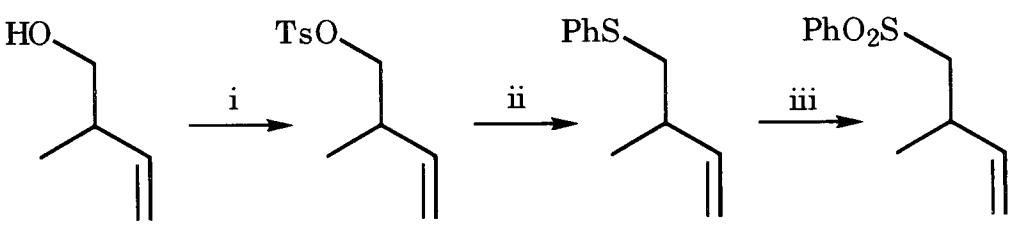
249 **250**

Scheme 94

4.8.1.2 Method B

This method was used when the allylic halide required was either too expensive or not commercially available. In this case, a

three-step route starting from the relevant homoallylic alcohol (*e.g.* **251**) was employed. Tosylation under standard conditions converted the hydroxyl into a useful leaving group in quantitative yield. The tosylate (*e.g.* **252**) was treated with sodium thiophenoxide giving the sulphide (*e.g.* **253**) typically in quantitative yield. *m*-Chloroperoxybenzoic acid (*m*CPBA) oxidation of the sulphide afforded the required sulphone (*e.g.* **254**) in around 80% yield (Scheme 95).



251 **252** **253** **254**

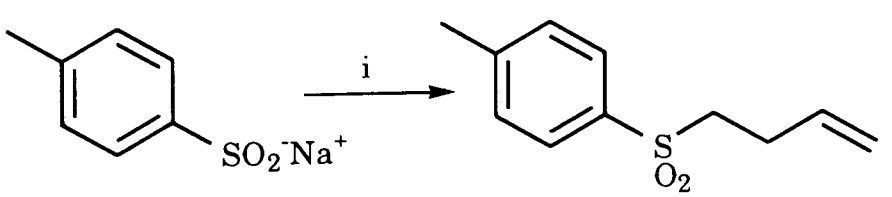
i) TsCl, Et_3N, CH_2Cl_2; ii) PhSH, NaH, THF, DMF;
iii) 2 eq *m*CPBA, CH_2Cl_2, rt

Scheme 95

This method could be carried out without any purification until that of the final sulphone.

4.8.1.3 Method C

Where the aryl methyl sulphone was not available, the third method using phase transfer catalysis was used. Sodium aryl sulphinate (*e.g.* **255**) was treated with a homoallylic halide in DME at reflux, giving sulphone (*e.g.* **256**) in about 70% yield (Scheme 96).[122]



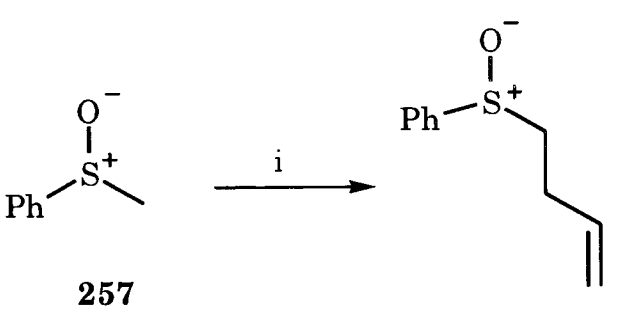
255 **256**

i) 4-Bromobut-1-ene, DME, $Bu_4N^+Br^-$, Δ

Scheme 96

4.8.2 *Preparation of Sulphoxides*

Methods A and B (above) were also compatible with sulphoxide formation. For example, method A used methyl phenyl sulphoxide **257** and butyl lithium as base (the heat required using the Grignard as base resulted in some unwanted elimination of sulphoxide) to give the required sulphoxide **258** typically in 60% yield (Scheme 97).

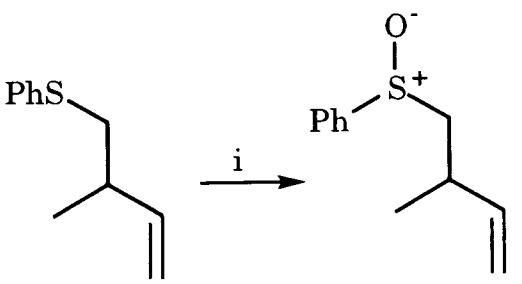


257 **258**

i) BuLi, -78°C, THF; allyl bromide

Scheme 97

Method B was adapted at the oxidation stage, where only one equivalent of *m*CPBA was required to oxidise the sulphide (*e.g.* **253**) to the sulphoxide (*e.g.* **259**, Scheme 98).



253 **259**

i) 1 eq *m*CPBA, 0°C, CH_2Cl_2

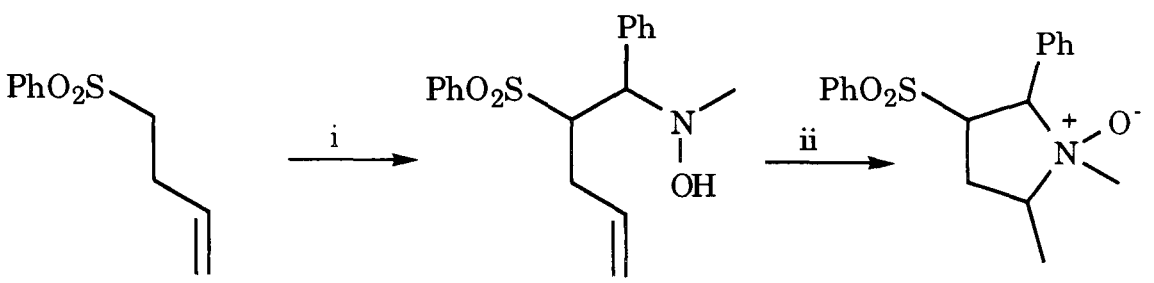
Scheme 98

4.8.3 Using *C*-Phenyl-*N*-Methyl Nitrone as Electrophile

4.8.3.1 *Preliminary Studies*

Preliminary studies began using the homoallylic sulphone **247**. Treatment of sulphone **247** with LDA, made from diisopropylamine and butyllithium, followed by addition of nitrone **144**, yielded none of the required condensation product upon work-up. However, by employing a change of base, treatment of sulphone **247** with butyllithium at -78°C resulted in formation of the required yellow sulphone stabilised carbanion. Addition of a solution of *C*-phenyl-*N*-methyl nitrone **144** in THF gave, rather disappointingly, no change in the colour of the reaction mixture. Thin layer chromatography, however, showed almost entire disappearance of the starting material sulphone **247** and, indeed, upon work-up, a crude ^{1}H NMR in $CDCl_3$ indicated almost quantitative conversion (90-100%) to the desired hydroxylamine **260**. It is not known why the use of LDA did not result in condensation, as LDA would be expected to be sufficiently basic (pK_a *ca.* 36) to deprotonate α- to a sulphone (pK_a *ca.* 30), but it may have been due to handling errors which may have occurred resulting from the small scale of the reaction. Interestingly, at this point, the ^{1}H NMR spectrum also showed a very small doublet at δ 1.4 ppm. It was thought that this might be a product resulting from a *retro*-Cope process, as previous work by Ciganek[68] on *retro*-Cope chemistry established chloroform as the best solvent for the conversion. In fact, leaving this sample at room temperature and following the reaction by ^{1}H NMR for 4 days indicated the disappearance of the hydroxylamine **260** and the formation of a compound which corresponded to a pyrrolidine *N*-oxide **261** (100%, Scheme 99).

Column chromatography of the crude *N*-oxide resulted in the loss of all material, demonstrating the instability of the *N*-oxide to silica gel chromatography.[123,172]



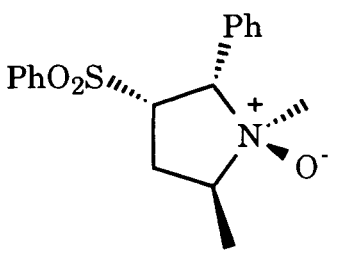
247 **260** **261**

i) a) BuLi, THF, -78°C; b) C-Ph-N-Me nitrone **144**; ii) $CDCl_3$, rt

Scheme 99

The above sequence was repeated but this time purification of the hydroxylamine **260** was attempted. Crude ^1H NMR of the condensation reaction again showed almost quantitative conversion to the hydroxylamine. Column chromatography using silica gel gave the pure hydroxylamine **260** as a foam in only around 60% yield. At this point, it was noticed that only one diastereoisomer appeared to be present, according to the NMR data.

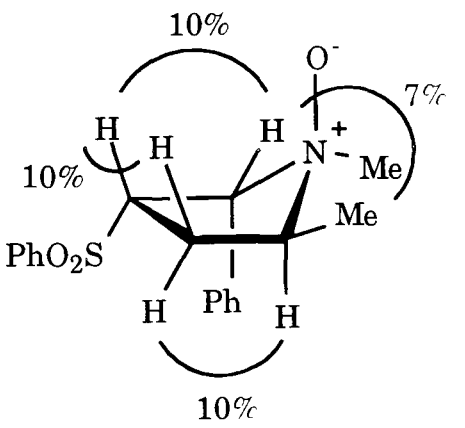
Stirring the pure hydroxylamine **260** in $CDCl_3$ and again following by ^1H NMR, afforded the pyrrolidine *N*-oxide **261** as what appeared to be largely one diastereoisomer **262** (>8:1), this being confirmed by ^{13}C NMR spectroscopy. [173]



262

The stereochemistry of the pyrrolidine *N*-oxide was established by ^{1}H (Fig. 1) and ^{13}C (Fig. 2) NMR spectroscopy. Diagnostic absorptions in the ^{1}H NMR of *N*-oxide **262** are; i) the doublet at δ 4.80 ppm is the benzylic 2-CH with a medium sized (8 Hz) coupling constant suggesting the *cis* relationship of the 2- and 3-positions, ii) the apparent double triplet at δ 5.20 ppm which has a medium sized (10.8 Hz) and two smaller (8 and 8 Hz) coupling constants, iii) a sharp singlet at δ 2.6 ppm for the *N*-methyl group, which would be expected to be around δ 3.3 ppm,[124] is probably at a higher field position due to shielding from the large phenyl and sulphonyl groups or because of the oxygen of the *N*-oxide, and iv) the high field doublet at δ 1.40 ppm due to the 5-methyl, with a small (6.3 Hz) coupling.

When subjected to structural determination by nuclear Overhauser effect (nOe) spectroscopy, the above diastereoisomer **262** was confirmed to be the major product (Fig. 3).



262

Fig. 3

The nOe experiments showed a positive enhancement between the 2-CH and the 3-CH (10%), the 3-CH and the 4-CHβ (δ 2.3 ppm) (10%), the 4-CHα (δ 3.0 ppm) and the 5-CH (10%), and the 5-CH_3 and the 2-CH (7%). Further evidence comes from the absence of nOe enhancements between the 2-CH and the 4-CHα or 5-CH

1

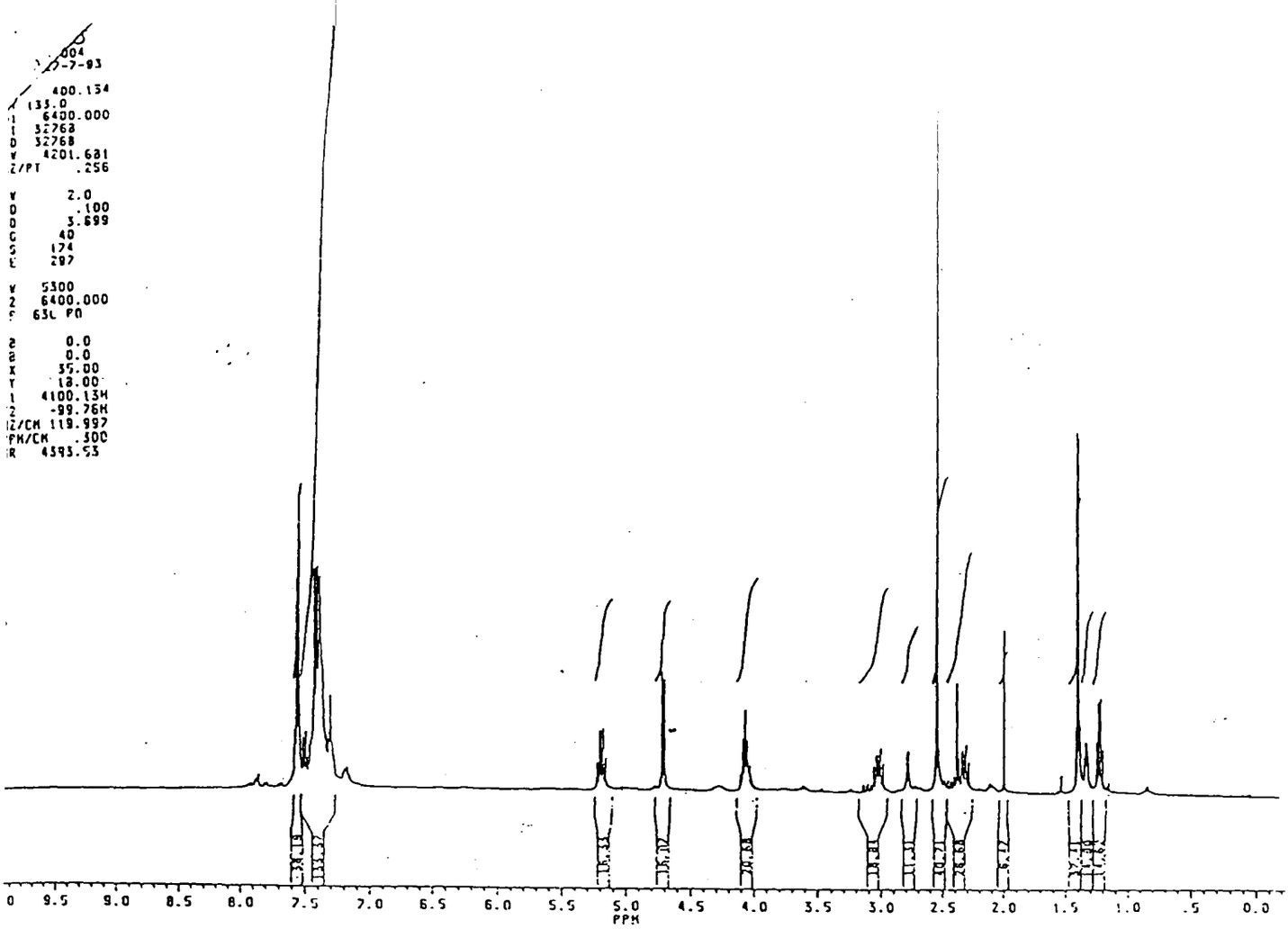


Fig. 2

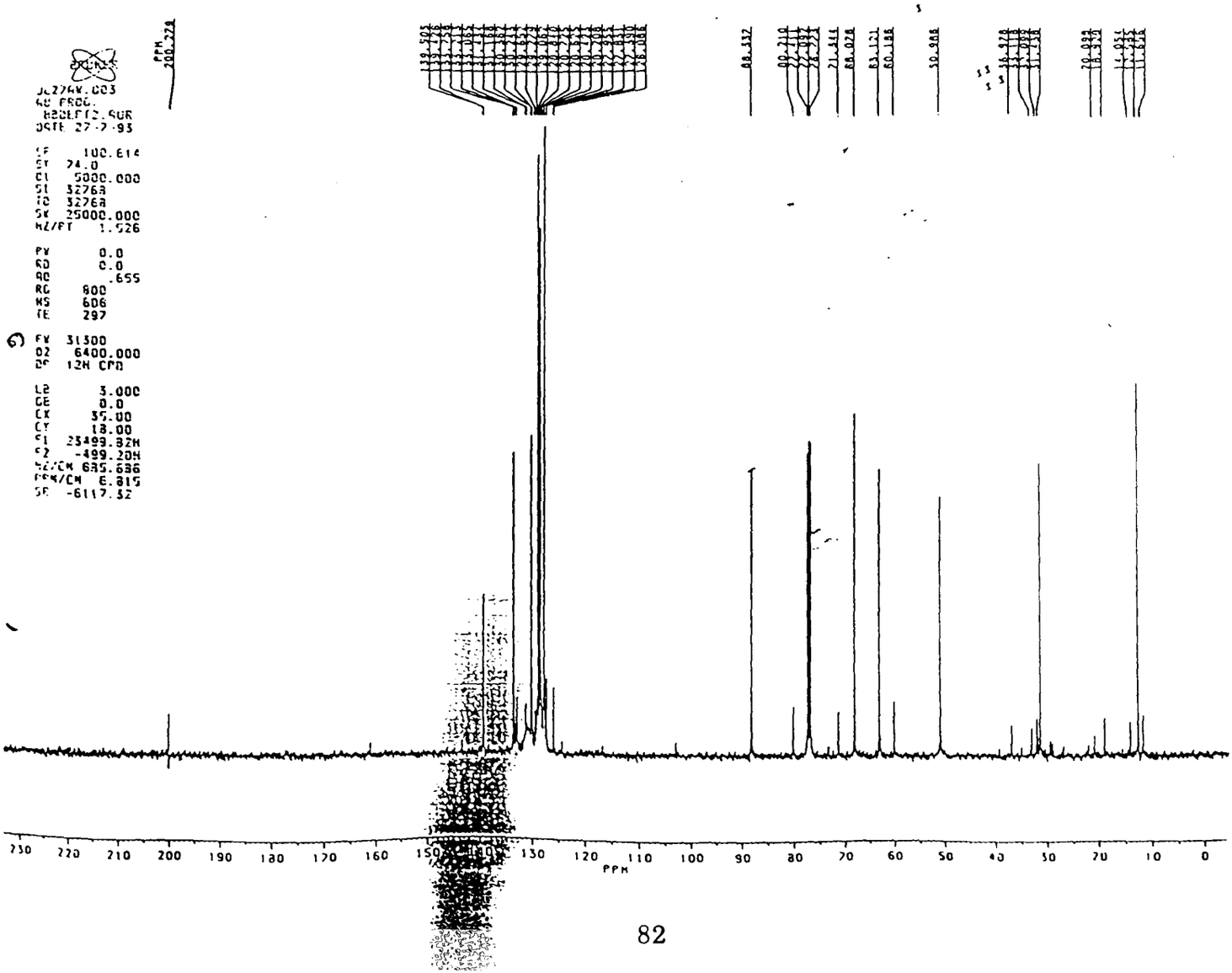
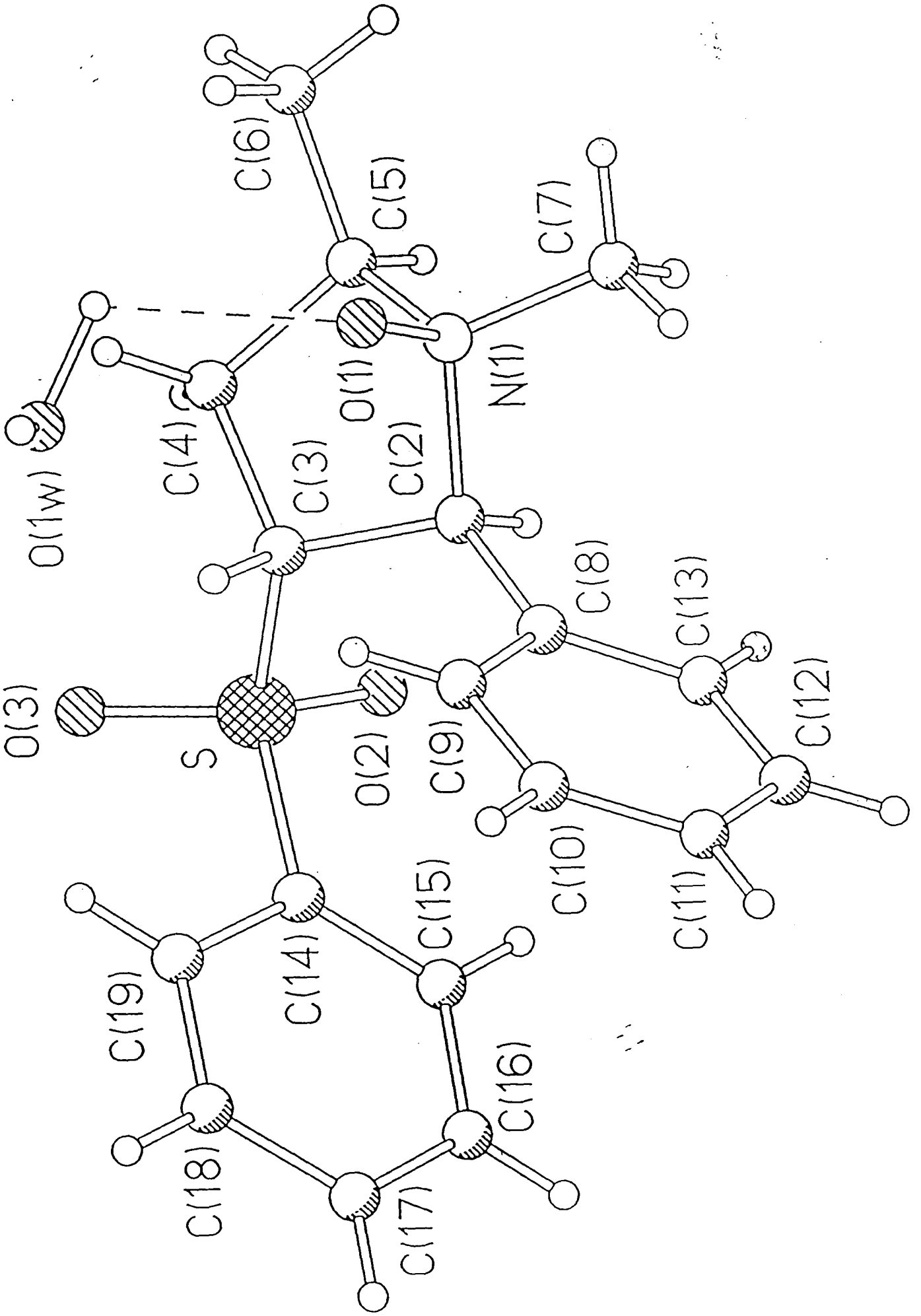


Fig. 4


O(1w)
C(4)
C(3)
C(2)
O(1)
N(1)
C(5)
C(6)
C(7)
C(8)
C(13)
C(12)
C(11)
C(10)
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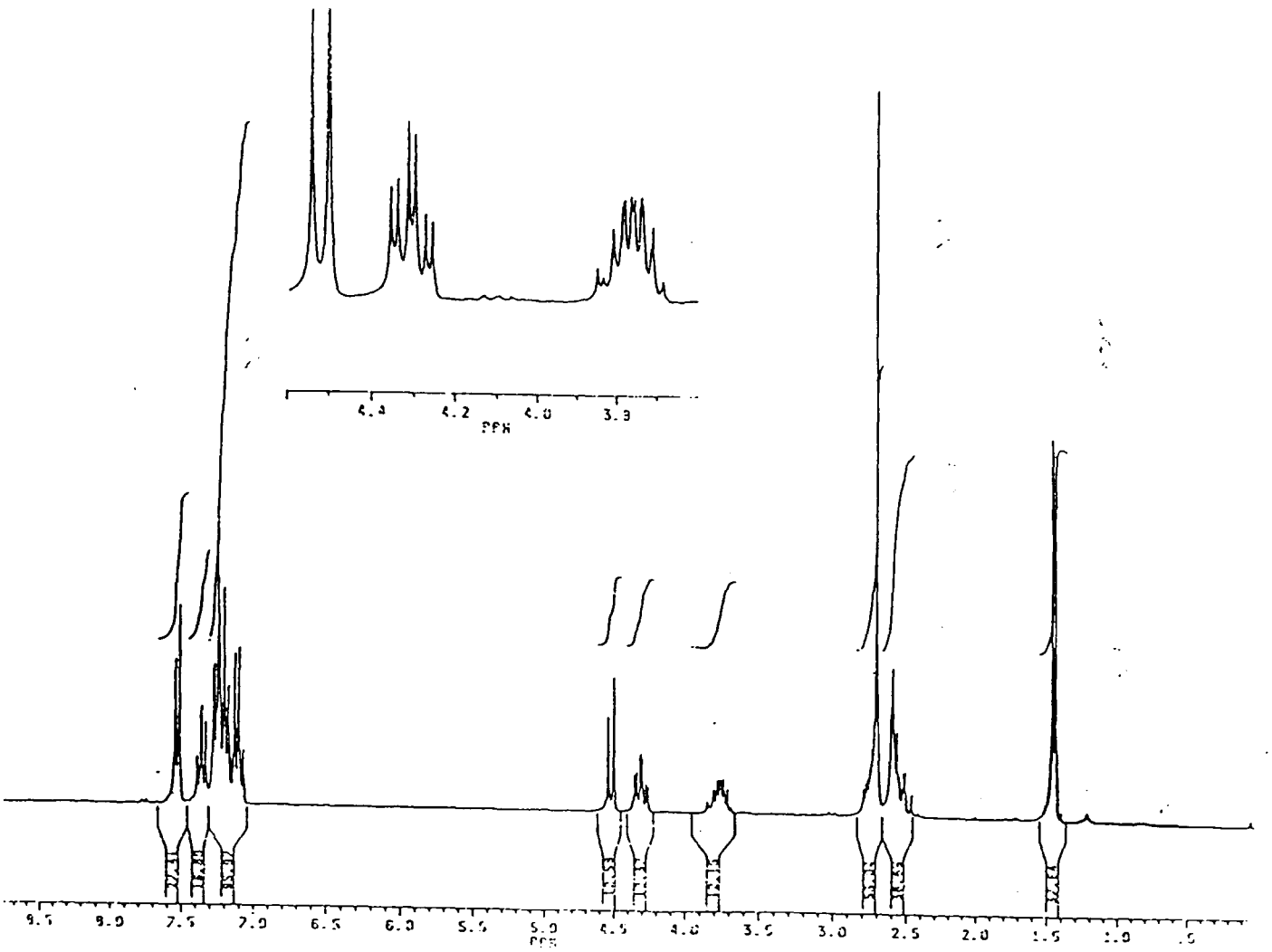
O(3)
C(14)
C(15)
C(16)
C(17)
C(18)
C(19)


4.4
4.2
4.0
3.8
PPM
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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4.0
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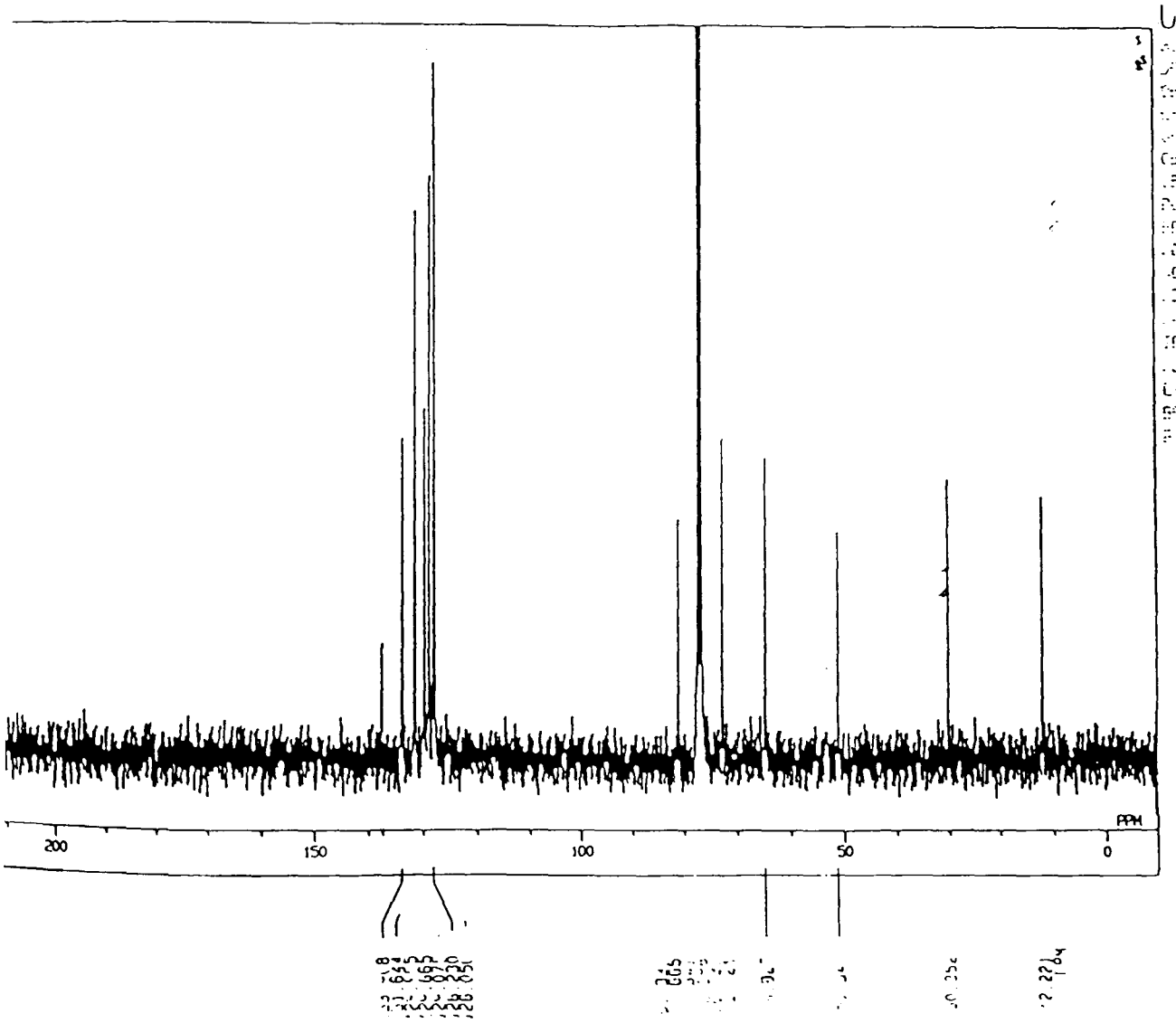
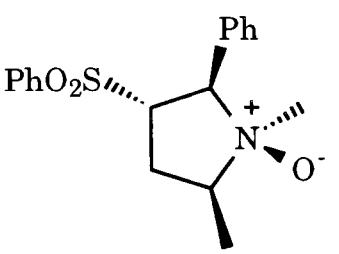
2.5
2.0
1.5
1.0
.5

Fig. 6


200
150
100
50
0
PPM

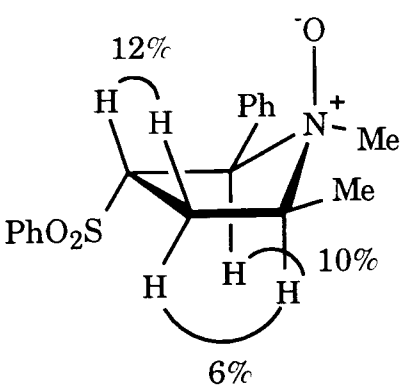
signals, and the differences between the observed effects between 3-CH and the 4-CHβ (10%) and 4-CHα (4%). This appears to confirm the assigned stereochemistry (Fig. 3). The stereochemistry of the minor isomer could not be assigned as most signals were obscured.

As the above compound **262** was a foam, recrystallisation was attempted. Allowing slow recrystallisation (*ca.* one month) from methanol, prismatic crystals were obtained which, when analysed by NMR spectroscopy, were seen to be a different compound to the initial product **262** and essentially a single diastereoisomer (see Figures 5 and 6). X-Ray crystallographic analysis showed this to be pyrrolidine *N*-oxide **264** (Fig. 4; Appendix).



264

The major changes to the ^{1}H NMR (Fig. 5) were; i) the doublet at δ 4.80 ppm (2-CH) was seen to move to δ 4.52 ppm with an increase in coupling constant (10.2 Hz) indicating a *trans* relationship of the 2- and 3-positions, and ii) the double-triplet at δ 5.20 ppm changed to a triple-doublet at δ 4.30 ppm with two medium sized (10.2 and 10.2 Hz) and a small (4 Hz) coupling constants.



264

Fig. 7

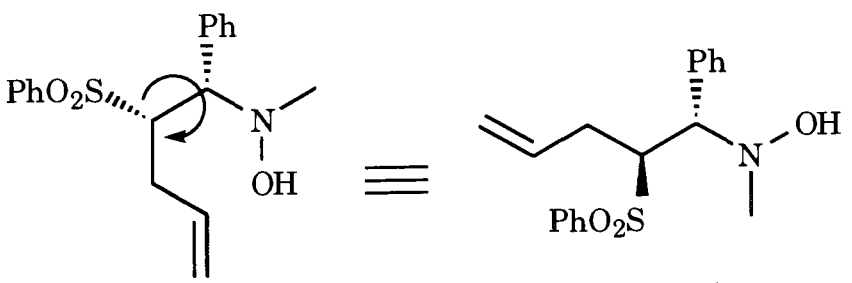
The nOe experiments showed a positive enhancement between the 3-CH and the 4-CHα (δ 2.8 ppm) (12%), the 4-CHβ (δ 2.5 ppm) and the 5-CH (6%), and the 5-CH and the 2-CH (10%). Further evidence comes from the absence of nOes between the 2-CH and the 3-CH signals. This appears to confirm the assigned stereochemistry (Fig. 7).

It should also be noted that this isomer **264** was different to the minor isomer seen in formation of *N*-oxide **262** by ^{13}C NMR spectroscopy. This indicates a separate isomerisation process during the recrystallisation period.

4.8.3.2 *Mechanistic Information*

a) <u>The Condensation Reaction</u>

It has been indicated that the addition of the anion of sulphone **247** with nitrone **144** gives only one diastereoisomer **266** (=**260**). At first sight, this seemed unlikely, but rotating around the C2-C3 bond (Scheme 100a) shows that the two bulky groups are as far away from each other as possible, and it can be seen that an *anti* addition has indeed been observed.

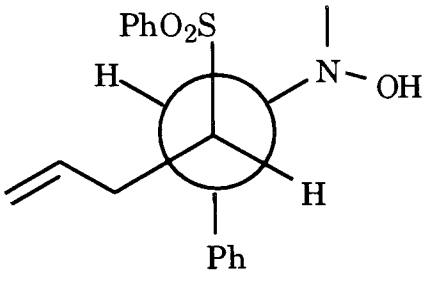


266 **267**

Scheme 100a

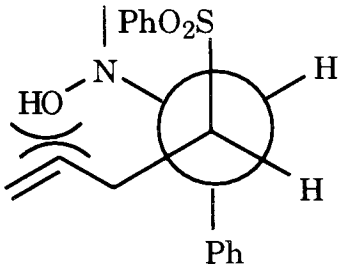
Using a Cram model (Fig. 8), this becomes more obvious. The two largest groups (sulphone and phenyl) are opposite (antiparallel) to each other, with the two medium groups (allyl and hydroxylamine),

and the two smallest groups (hydrogen and hydrogen), also antiparallel. This configuration **268** would be expected to be the most stable as no major steric interactions occur. In the case of another possible configuration **269**, a steric interaction is possible between the allyl and hydroxylamine moieties, making this conformation less likely to be adopted.



Favourable

268

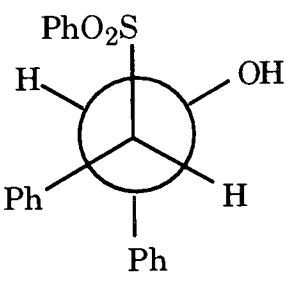


Unfavourable

269

Fig. 8

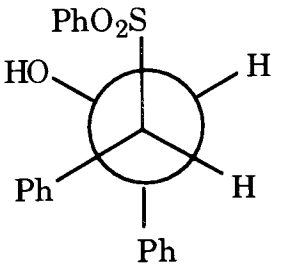
Similar results were obtained by Kingsbury[125] relating to sulphone stabilised anion additions to aldehydes. Here, two diastereoisomers (**270** and **271**, Fig. 9) were obtained with ratios of around 77:23 (threo:erythro) with overall yields of *ca.* 60%.



Favourable

threo

270



Unfavourable

erythro

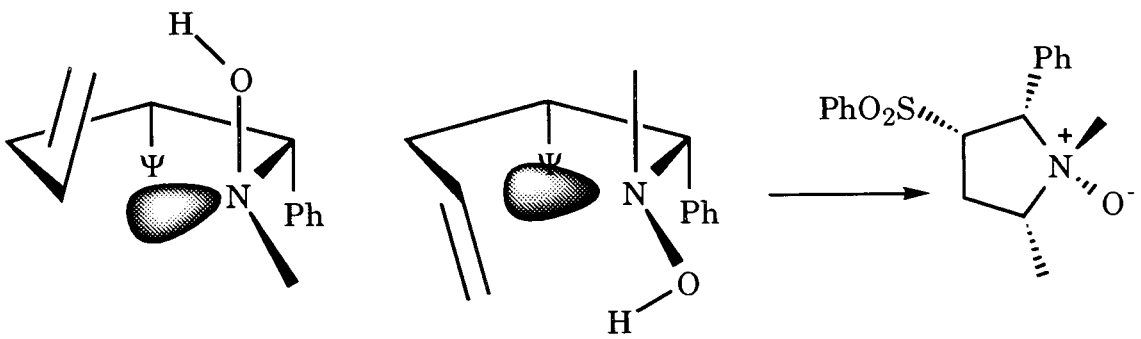
271

Fig. 9

b) The *retro*-Cope Reaction

As shown in Section 4.4, the *retro*-Cope reaction requires a 5-membered cyclic transition state, with the alkene and hydroxylamine

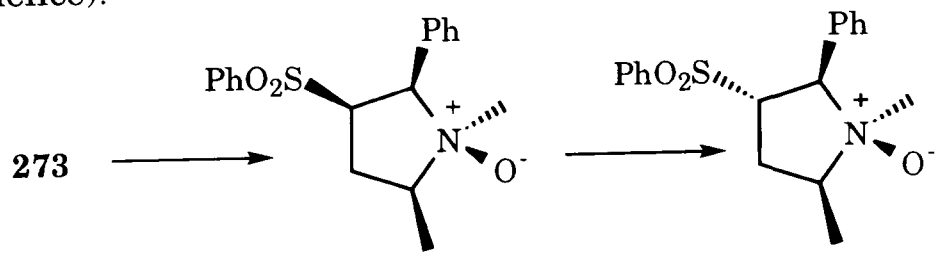
in close proximity. Therefore, in order that cyclisation of the hydroxylamine can occur, the molecule must adopt a seemingly unfavourable transition state **266** where the sulphone and phenyl group are on the same side of the molecule. Two conformations appear to be possible for the cyclisation. When the more stable transition state **272** (Fig. 10) is adopted, where the alkene is *anti* to the sulphone and phenyl groups, the major product **262**, with a 2,5-*trans* configuration, is formed. If the transition state **273** is adopted, with all the groups *syn* to each other, the steric interaction is increased and the structure proposed as the minor isomer from the cyclisation would be formed **262b** (the 2,5-*cis* product).



272 **273** **262b**

Fig. 10

A possible mechanism for the isomerisation process which gives *N*-oxide **264** may result from this "minor isomer" transition state **273** followed by isomerisation of the sulphone group (Scheme 100b). (Note. *N*-oxide **262b** is drawn as its mirror image for convenience).



262b **264**

Scheme 100b

4.8.3.3 *Solvent Studies*

Next, studies to determine the best solvent for the *retro*-Cope reaction were undertaken. Although the smooth cyclisation of hydroxylamine **266** was shown to proceed at room temperature in deuteriochloroform, it was hoped that the extended timescale of the reaction (4-5 days) could be reduced simply by warming the reaction mixture. To this end, the reaction conditions were changed such that the temperature was increased to 58°C (refluxing $CDCl_3$). Initial results showed that, indeed, the cyclisation was complete in less than 16h. Furthermore, the diastereomer ratio of products appeared to be unaffected. This was very pleasing, but unfortunately, it was found that this result was not reproducible. In subsequent studies, the diastereomeric ratio was observed to change between conversion of hydroxylamine **266** into *N*-oxide **262** as mainly one diastereoisomer (as in the room temperature case) to conversion to give at least *four* diastereoisomers in approximately equal ratios. For this reason, all subsequent *retro*-Cope reactions were carried out at room temperature to try to maximise the likelihood of obtaining high diastereoisomer ratios.

Other solvents which facilitated the *retro*-Cope reaction were also found. In toluene, the *retro*-Cope reaction went to completion in around 10 days at room temperature with a slightly lower diastereoisomer ratio. d_6-Dimethyl sulphoxide and d_6-acetone both gave mixtures of *several* diastereoisomers, along with both starting material and unidentifiable decomposition products. The use of methanol, acetonitrile and ethyl acetate all resulted in decomposition. With pentane as solvent, a 1:1 mixture of diastereoisomers was observed, and with diethyl ether, results similar to those recorded using deuteriochloroform were found. These

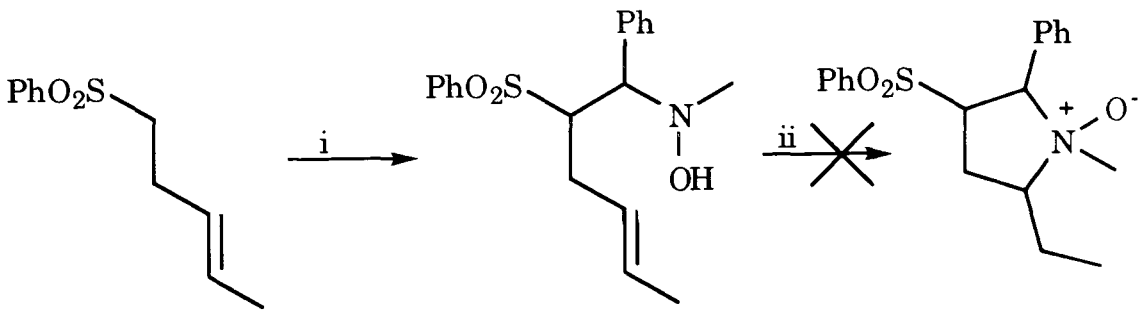
latter two results were again, however, not reproducible, possibly due to the hydroxylamine and *N*-oxide being largely insoluble in these two solvents.

It was also found that acid (*p*-toluenesulphonic acid) or base (triethylamine) catalysis of the *retro*-Cope reaction in $CDCl_3$ was not possible. When attempted, the cyclisation still took place over 4-5 days until completion was attained, and the diastereoisomer ratios were similar to those of the "uncatalysed" reaction.

4.8.3.4 *Effects of Substitution of the Double Bond*

Studies into the feasibility of using homoallylic sulphones to produce more highly substituted pyrrolidine *N*-oxides were now envisaged. Investigations were now centred around C-C double bond substituted homoallylic sulphones.

Condensation of the substituted 1-(phenylsulphonyl)-pent-3-ene **274** with *C*-phenyl-*N*-methyl nitrone **144** gave the required hydroxylamine precursor **275** (82%; 61% after chromatography), Scheme 101). The stereoselectivity of the hydroxylamine formation appeared to be as high as with the sulphone **247** by ^{1}H and ^{13}C NMR. Under the standard conditions of stirring in $CDCl_3$ solvent at room temperature, no reaction was seen to occur even after prolonged periods (1 month). Heating to 58°C in $CDCl_3$, or to 110°C in toluene,



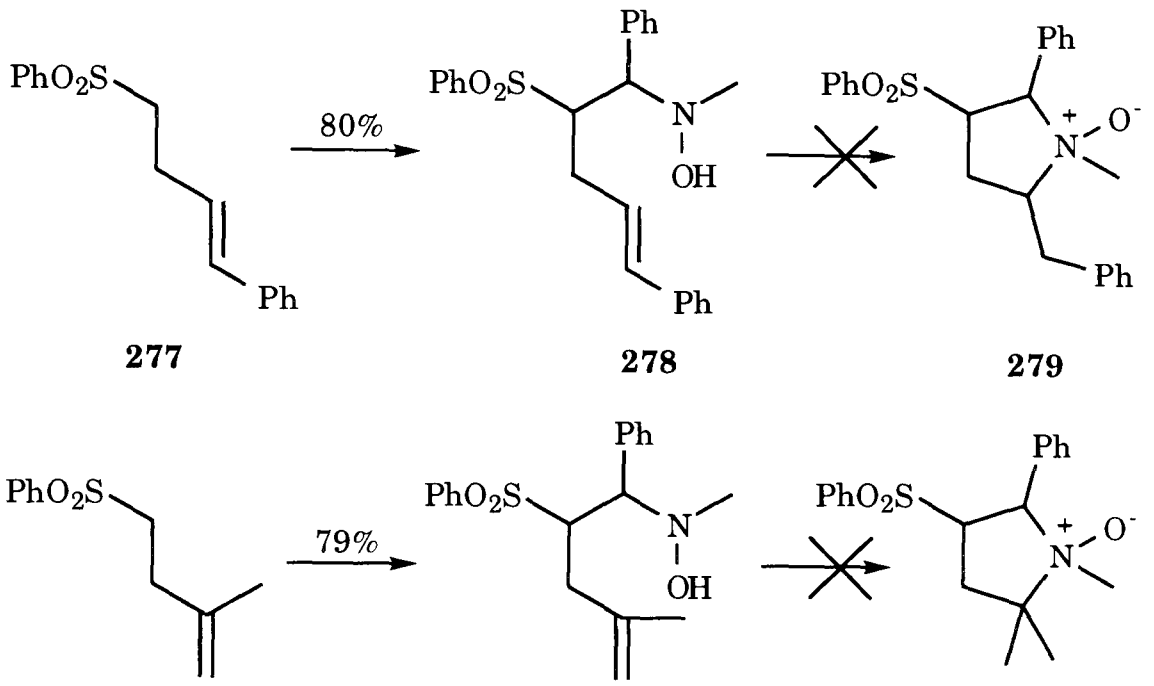
274 **275** **276**

i) a) BuLi, THF, -78°C; b) C-Ph-N-Me nitrone **144**; ii) $CDCl_3$, rt

Scheme 101

also failed to provide the required pyrrolidine *N*-oxide **276**, giving only starting material and/or decomposition products.

Similar results were obtained with the substituted 1-phenyl-4-(phenylsulphonyl)-2-butene **277** and the internally substituted 2-methyl-4-(phenylsulphonyl)-1-butene **280**, where again, no pyrrolidine *N*-oxide was seen (Scheme 102).

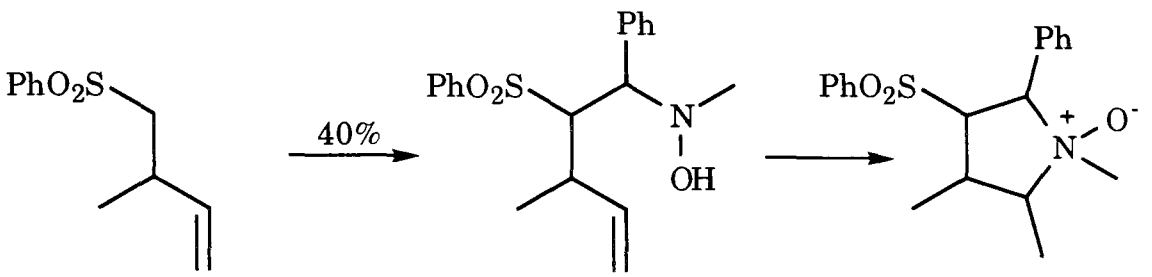


Scheme 102

With these disappointing results in hand, investigations were now turned to homoallylic sulphones substituted in the 2-position. To this end, 2-methyl-1-(phenylsulphonyl)-but-3-ene **283** was used as starting material. It was pleasing to find that, after condensation of the sulphone with *C*-phenyl-*N*-methyl nitrone **144**, cyclisation proceeded smoothly to give the required *N*-oxide **285** in around 6 days at room temperature (40% over 2 steps, Scheme 103).

The structure was not fully elucidated as nOe evidence was not available because the condensation reaction was low yielding (40%) and so most signals in the ^{1}H NMR were obscured by starting

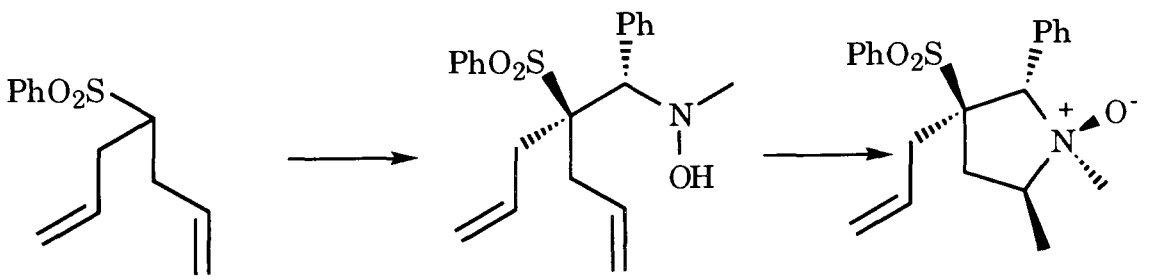
material and purification was not possible. It is expected that this poor yield can be optimised.



283 **284** **285**

Scheme 103

Further substitution α– to the sulphone was the next stage in the investigation. In this case, 4-(phenylsulphonyl)-hepta-1,6-diene **248** was used as the sulphone source. It was very surprising, therefore, to find that upon condensation of sulphone **248** with *C*-phenyl-*N*-methyl nitrone **144**, followed by work-up that, although the condensation itself was not high yielding (*ca.* 40%), all the hydroxylamine **286** formed had already cyclised into the pyrrolidine *N*-oxide **287** (Scheme 104) and, indeed, again appeared to be largely a



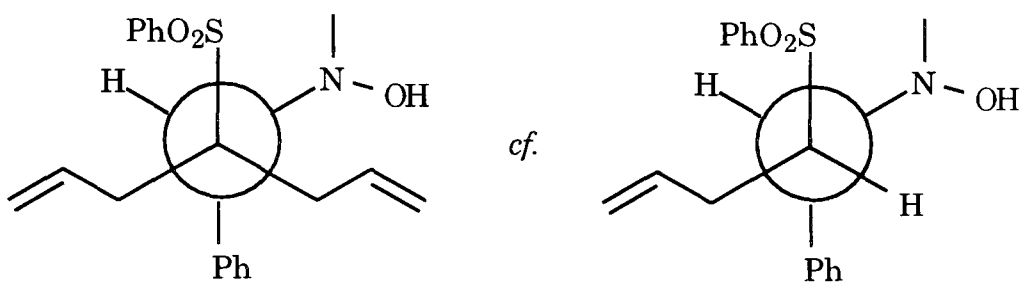
248 **286** **287**

Scheme 104

single diastereoisomer (>10:1 as shown by ^{1}H and ^{13}C NMR spectroscopy). (Due to the low yield of this condensation reaction, confirmation of the stereochemistry for compound **287** by nOe experiments was not possible. The stereochemistry shown was

inferred from the amine **334** (Page 106) resulting from reduction of the *N*-oxide).

Here, unlike previously where the *retro*-Cope reaction took a matter of days to react to completion, the process was seen to proceed in a matter of minutes! It is possible that a Thorpe-Ingold[126] effect may be being observed here. It is also possible that the reaction is quicker because there are now two similar olefinic groups



288 **268**

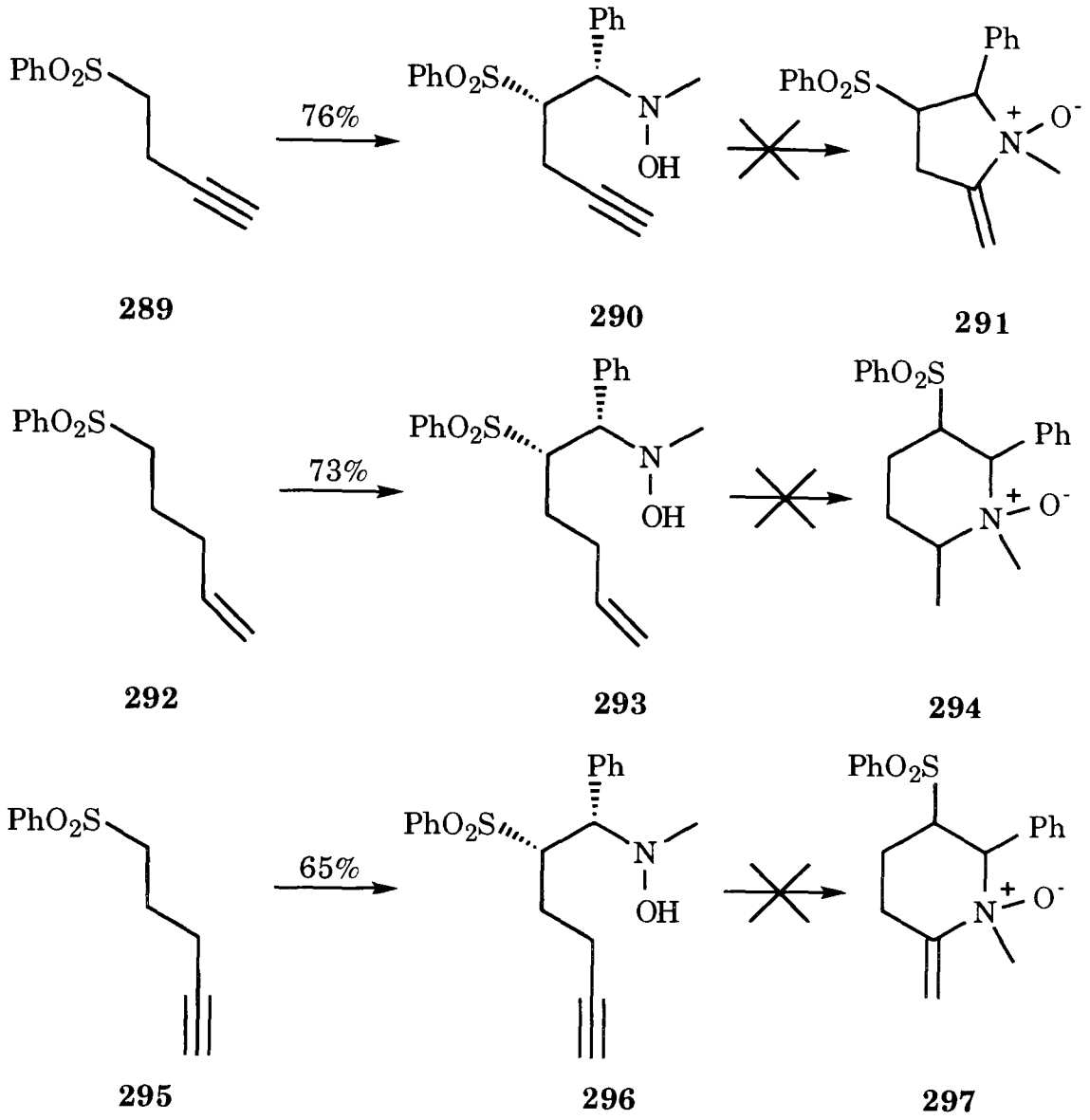
Fig. 11

in a position to undergo a *retro*-Cope elimination, although the increase in rate is not explained sufficiently by this. Another reason may be that the conformation of intermediate **288** (**=286**) now has an olefin closer in space to the hydroxylamine moiety (*cf.* intermediate **268**), making the *retro*-Cope reaction more facile because the required 5-membered transition state is attained much more easily (Fig. 11).

Investigations using alkynic sulphones and homologous sulphones was also attempted. The products here would give cyclic amines with an exocyclic double bond (from alkynic sulphones), and piperidines, rather than pyrrolidines, from higher homologue sulphones.

Here, although condensation of sulphone with *C*-phenyl-*N*-methyl nitrone **144** proceeded in good yield, and with a high degree of stereoselection, cyclisation was not observed (Scheme 105). The hydroxylamines **290**, **293** and **296** were found to be stable to

prolonged periods at room temperature and at 58°C in $CDCl_3$, and decomposition was observed at 110°C in toluene.



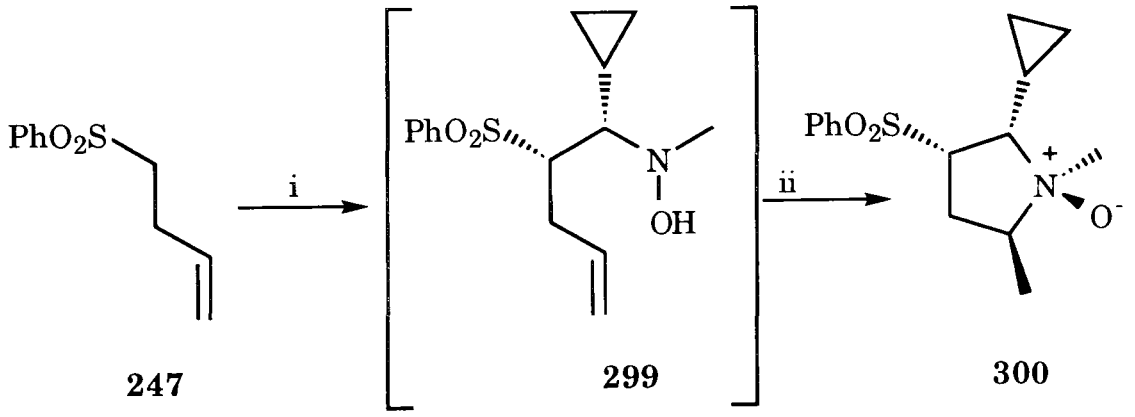
Scheme 105

4.8.4 Using *C*-Cyclopropyl-*N*-Methyl Nitrone

The phenyl nitrone **144** had been shown to be unsuitable for the *retro*-Cope reaction of substituted sulphones and so other nitrones were employed in order to identify why this was, and indeed, whether it was possible to cyclise such sulphones to give pyrrolidine *N*-oxides. The more reactive alkyl nitrone *C*-cyclopropyl-*N*-methyl nitrone **298** was used instead of the *C*-phenyl-*N*-methyl nitrone **144**.

This nitrone had been used previously in work by Thornton[56] where it had been used as a test for whether the *retro*-Cope reaction was a radical process, as cyclopropyl groups are known as radical traps. It was also found to result in easily identifiable signals in the ^{1}H NMR analysis by which the reaction would be followed. It was expected that, in this case, the nitrone would be more difficult to handle as it was found to be very hygroscopic.

Here, we were delighted to find that condensation of nitrone **298** with sulphone **247** resulted in isolation of the *N*-oxide *retro*-Cope product **300**; the expected intermediate hydroxylamine **299** was not isolable as the cyclisation had been completed quantitatively upon work-up, followed by 5 mins in $CDCl_3$ prior to ^{1}H NMR spectroscopic analysis (90% over 2 steps, Scheme 106).



247 **299** **300**

i) a) *n*BuLi, THF, -78°C; b) C-Cy-N-Me nitrone **298**; ii) $CDCl_3$, rt

Scheme 106

Again, NMR spectral data indicated the presence of largely one diastereoisomer (again *ca.* 8:1), and nOe spectroscopic evidence (Fig. 12) indicated the above structure as the major isomer.

The stereochemistry of the major pyrrolidine *N*-oxide **300** was established by ^{1}H (Fig. 13) and ^{13}C NMR (Fig. 14) spectroscopy. Diagnostic absorptions in the ^{1}H NMR of *N*-oxide **300** are; i) the double-triplet at δ 4.68 ppm which has a medium sized (10.2 Hz) and

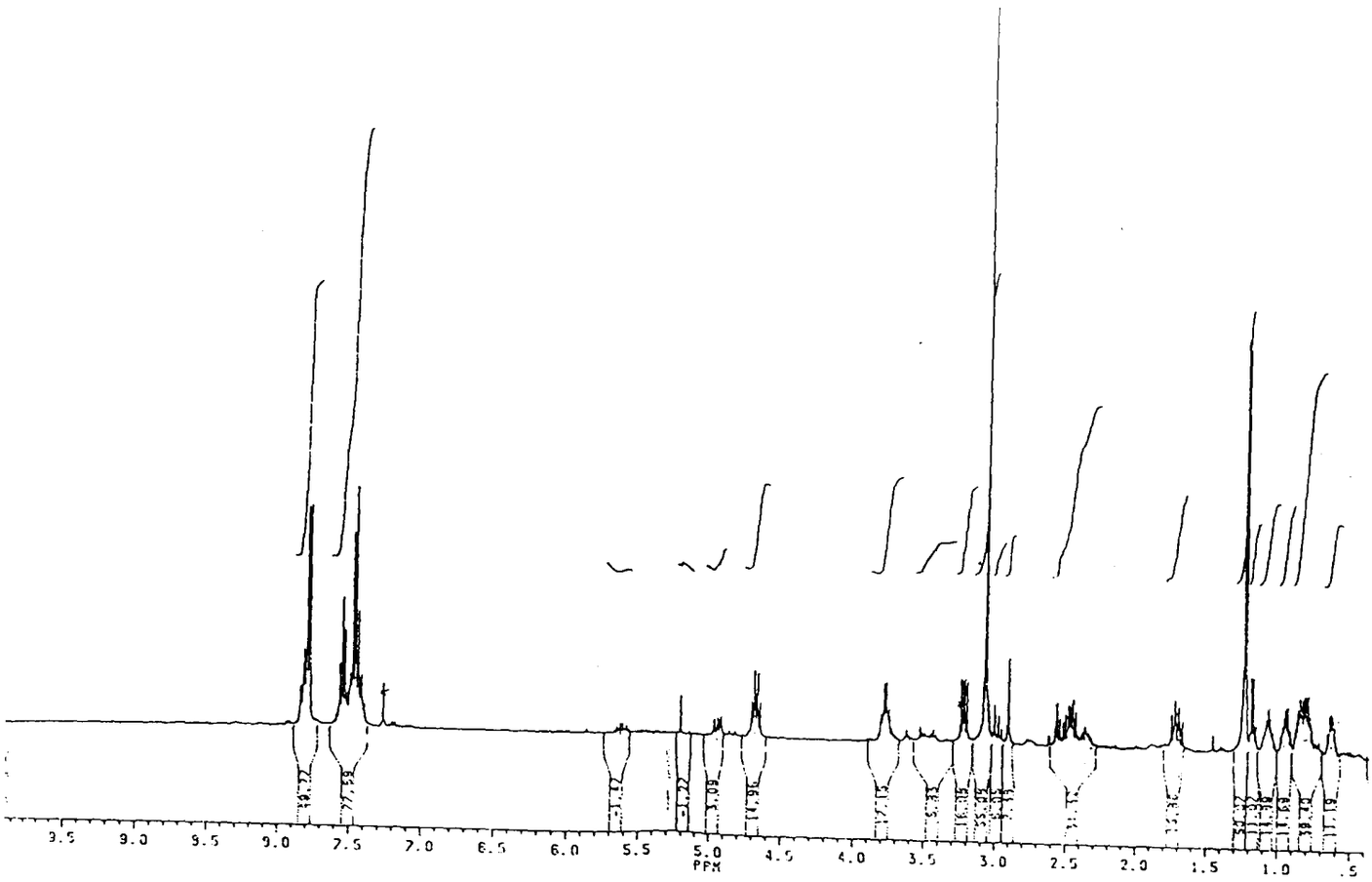


Fig. 13

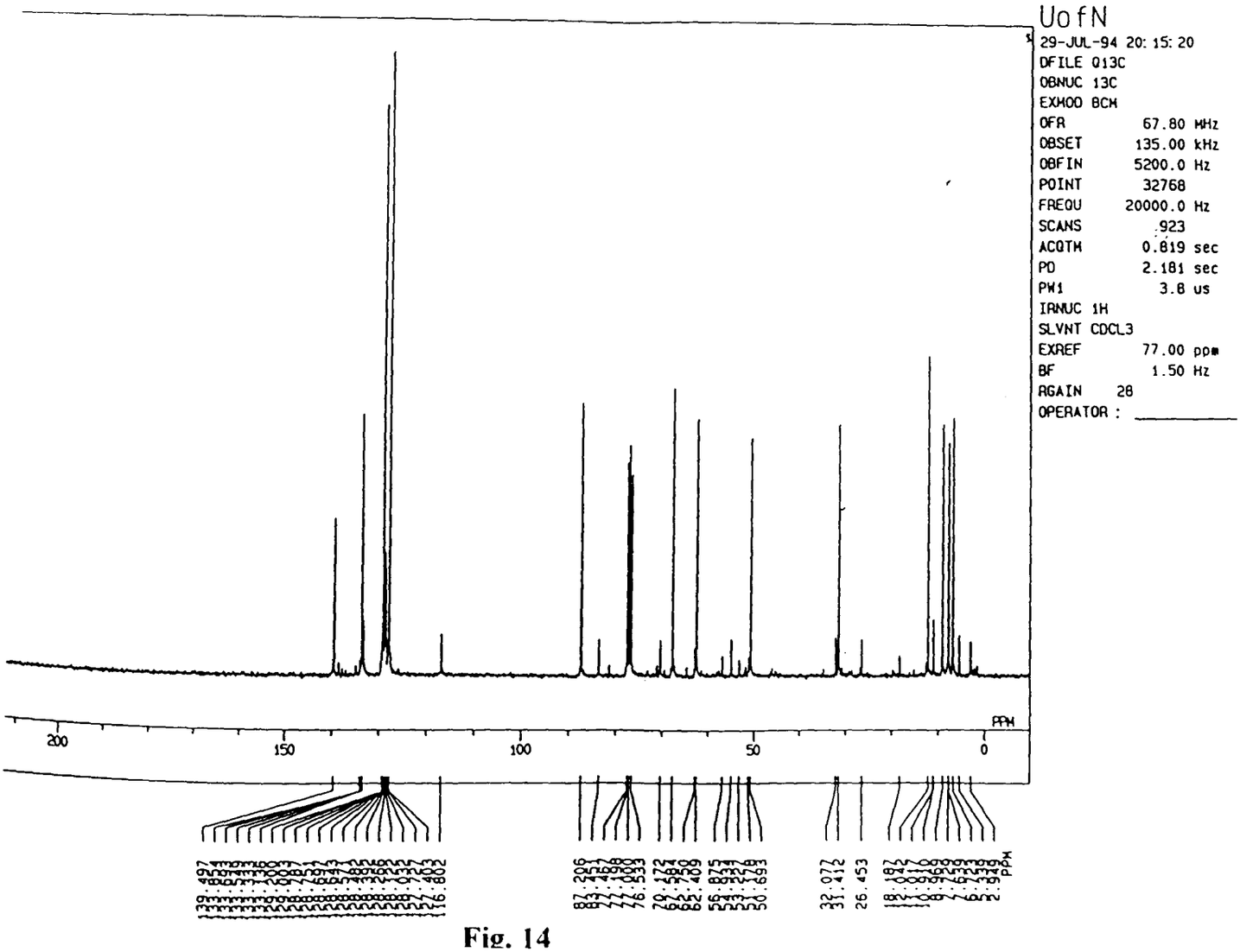
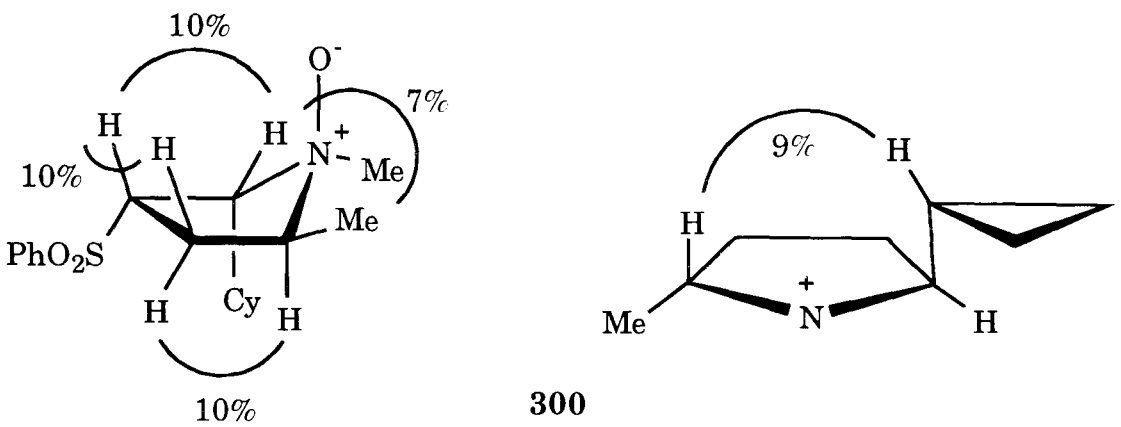

UofN
29-JUL-94 20:15:20
DFILE Q13C
OBNUC 13C
EXMOD BCM
OFR 67.80 MHz
OBSET 135.00 kHz
OBFIN 5200.0 Hz
POINT 32768
FREQU 20000.0 Hz
SCANS 923
ACQTM 0.819 sec
PD 2.181 sec
PW1 3.8 us
IRNUC 1H
SLVNT CDCL3
EXREF 77.00 ppm
BF 1.50 Hz
RGAIN 28
OPERATOR :
PPM

Fig. 14

two smaller (7.2 and 7.2 Hz) coupling constants, ii) a double doublet at δ 3.23 ppm relating to the 2-CH, iii) a sharp singlet at δ 3.10 ppm for the *N*-methyl group, which is probably at a lower field position than that of *N*-oxide **262** due to a smaller shielding effect from the other substituents, and iv) the high field doublet at δ 1.21 ppm due to the 5-methyl, with a usual (6.2 Hz) coupling.



300

Fig. 12

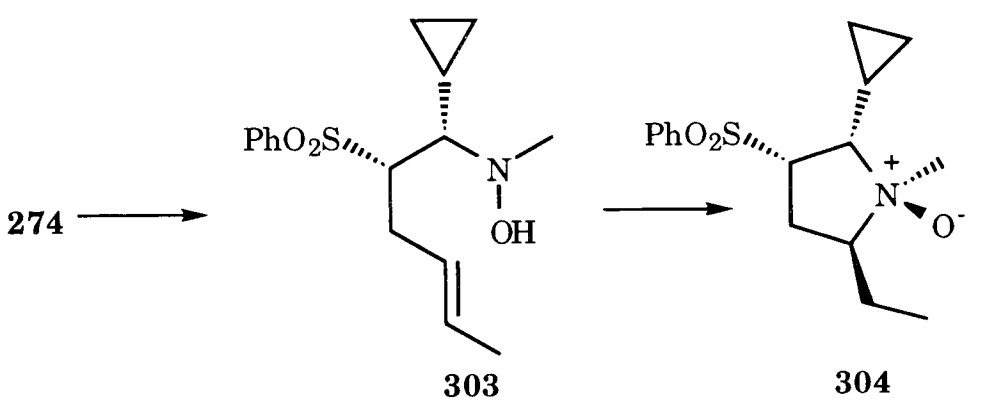
The nOe experiments showed a positive enhancement between the 2-CH and the 3-CH (10%), the 3-CH and the 4-CHβ (δ 1.7 ppm) (10%), the 4-CHα (δ 2.4 ppm) and the 5-CH (10%), the 5-CH and the 2'-CH-cyclopropyl (9%), and the 5-CH_3 and the 2-CH (7%). Further evidence comes from the absence of nOes between the 2-CH and the 4-CHα or 5-CH signals, and the differences between the observed effects between 3-CH and the 4-CHβ (10%) and 4-CHα (1%). This confirms the assigned stereochemistry (Fig. 12).

The stereochemistry of the minor isomer could not be assigned as most signals were obscured.

The speed of these *retro*-Cope conversions lead us to believe that, unlike in the *C*-phenyl-*N*-methyl nitrone case (Scheme 101 and 102), it might be possible to convert double bond substituted sulphones (*e.g.* **274**, **277** and **280**) into pyrrolidine *N*-oxides *via retro*-

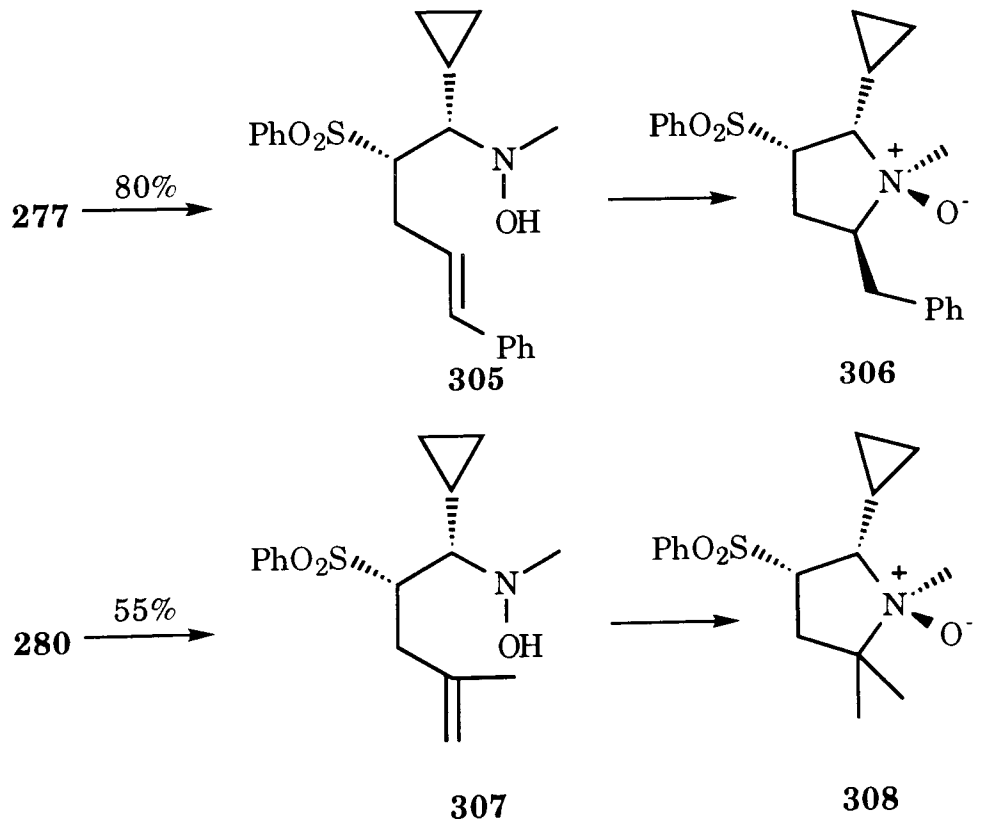
Cope methodology and, indeed, we were very happy to find that this was the case.

Using sulphone **274**, conversion into the hydroxylamine **303** was accomplished in around 55% yield (with unreacted starting material) and *N*-oxide **304** was obtained (quantitative conversion, *ca.* 55% over 2 steps; diastereoisomer ratio *ca.* 4:1) by stirring in $CDCl_3$ at ambient temperature for 3-4 days (Scheme 107).



Scheme 107

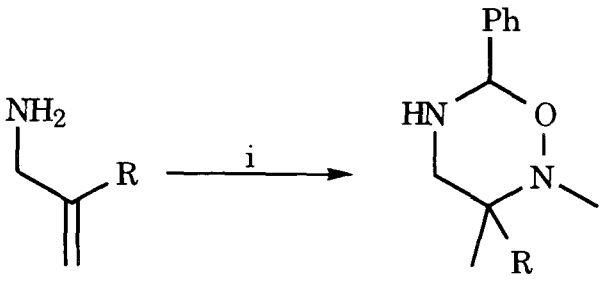
Also, conversion into the hoped for *N*-oxides (**306** [*ca.* 3:1] and **308** [*ca.* 3:1]) was accomplished using sulphones **277** and **280**, in a



Scheme 108

similar fashion, again in *ca.* 2-3 days (Scheme 108). These results were very encouraging and gave us an indication that the cyclisation was somehow dependent upon the substituent α- to the hydroxylamine.

This result was in contrast to those reported by Thornton,[56] where cyclisation times were similar for the substituted and unsubstituted allylamines **309a** and **309b** (Scheme 109).



309 **310**

a R=H, **b** R=Me

Scheme 109

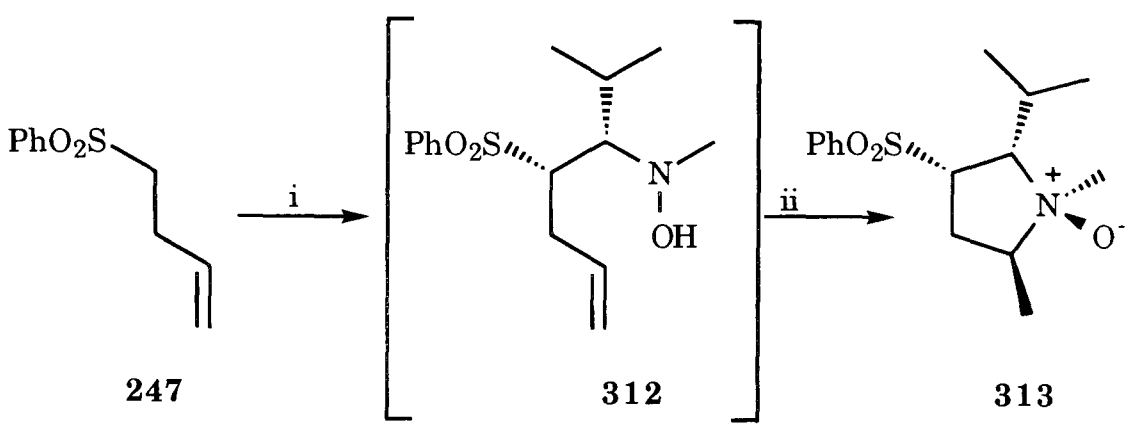
4.8.5 Cyclisation Studies

We now wondered why the *C*-phenyl-*N*-methyl nitrone gave a hydroxylamine which cyclised so slowly with respect to that resulting from the *C*-cyclopropyl-*N*-methyl nitrone. Was it, for example, the phenyl group's steric bulk, or were electronic effects responsible?

An experiment was subsequently performed using *C*-isopropyl-*N*-methyl nitrone **311** as electrophile. The intention here was to produce a *retro*-Cope precursor **312** which would have a group more sterically demanding than a phenyl group (*i.e.* an isopropyl group).

As with the *C*-cyclopropyl-*N*-methyl nitrone **298**, cyclisation of the hydroxylamine **312** to the *N*-oxide **313** occurred upon work-up after condensation (50%, Scheme 110). Here, the low yield is due to

the condensation reaction reflecting, presumably, the quality of the nitrone. Elucidation of the stereochemistry of the *N*-oxide **313** was again not possible and the stereochemistry shown was inferred from that obtained from the corresponding amine **337**.



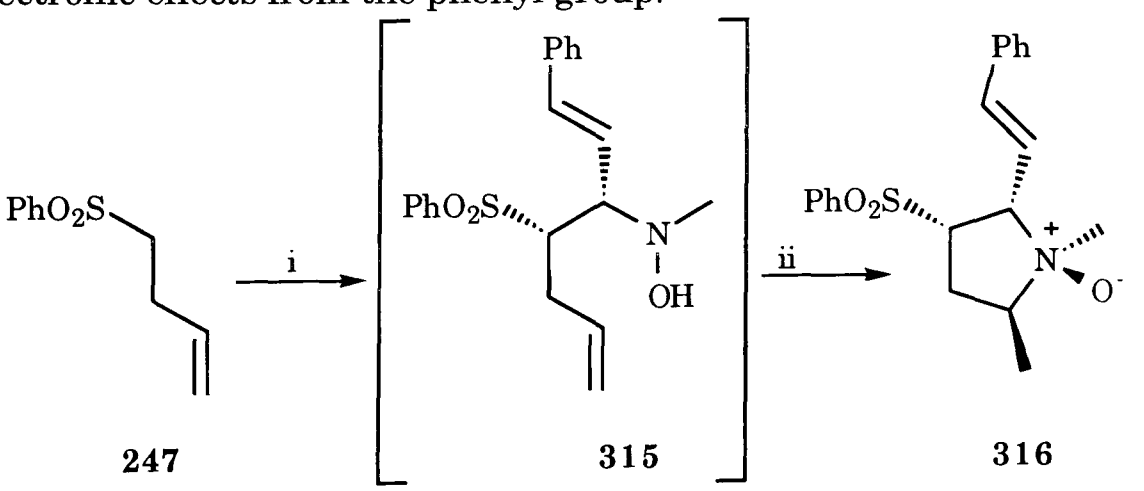
247 **312** **313**

i) a) BuLi, THF, -78°C; b) C-^{i}Pr-N-Me nitrone **311**; ii) $CDCl_3$, rt

Scheme 110

This suggested that steric bulk was *not* a factor governing cyclisation, as the isopropyl group is much more sterically demanding than the phenyl group. So, is it electronic effects which govern the cyclisation?

The next, and possibly conflicting, piece of evidence was that supplied when using *C*-cinnamyl-*N*-methyl nitrone **314** where, again, cyclisation was observed upon work-up (Scheme 111). In this case, it would be expected that the double bond would have transferred any electronic effects from the phenyl group!

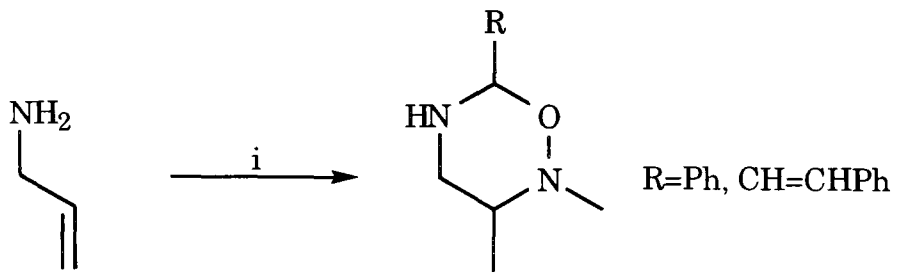


247 **315** **316**

i) a) BuLi, THF, -78°C; b) C-Cinnamyl-N-Me nitrone **314**; ii) $CDCl_3$, rt

Scheme 111

This result was again in contrast to that observed by Thornton,[56] who found that cyclisation of the hydroxylamine resulting from nitrone **144** (R=Ph) was much quicker than that resulting from nitrone **314** (R= CH=CHPh) (Scheme 112).



143 **317**

i) nitrone **144** or **314**, $CDCl_3$

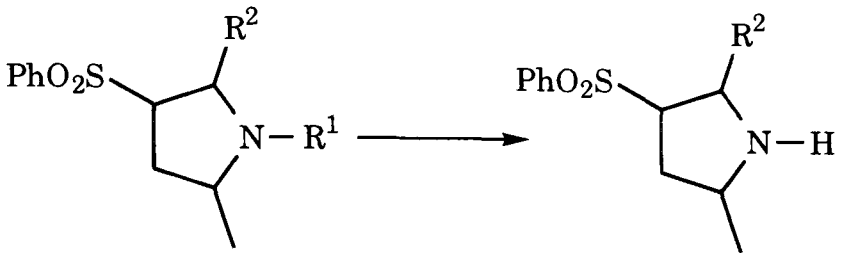
Scheme 112

The cinnamyl function is, however, less bulky than the phenyl group and it may be a combination of steric and electronic effects which govern the cyclisation here!

In the above cases, the 2-position is much more electron-rich due to alkyl or alkenyl substitution rather than the aromatic substitution in the phenyl case. This may make the nitrogen of the hydroxylamine moiety more electron-rich and so aid in the cyclisation because of its higher nucleophilicity.

4.8.6 *N-Benzyl Nitrones*

In all the cases above, the *N*-oxides formed are potential *N*-methyl pyrrolidines upon reduction (see later). It was decided to attempt to create *N*-benzyl pyrrolidines which would be expected to be more easily convertible into the corresponding free amines **319** by, for example, hydrogenolysis.

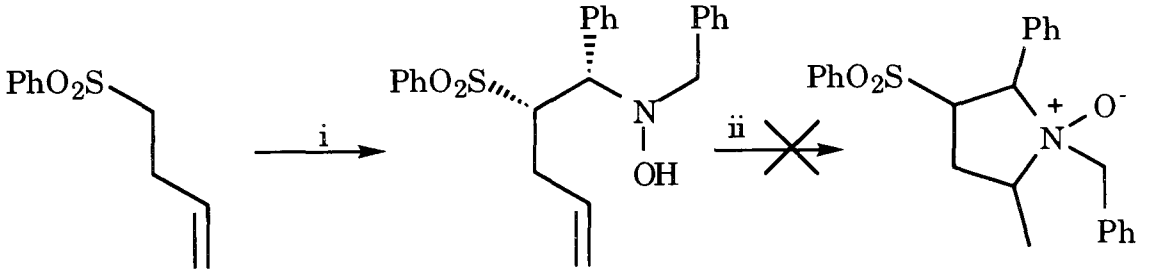


318 **319**

e.g. R^1 = Me, Bn; R^2 = Cy

Scheme 113

In order to investigate the possibilities for this, *C*-phenyl-*N*-benzyl nitrone **320** was used with the homoallylic sulphone **247**. Condensation proceeded in high yield (90%, Scheme 114) to give hydroxylamine **321** as a single diastereoisomer, but again, *retro*-Cope elimination was not observed. It is thought that the extra steric bulk or the electronics of the *N*-benzyl group effectively prevented cyclisation.

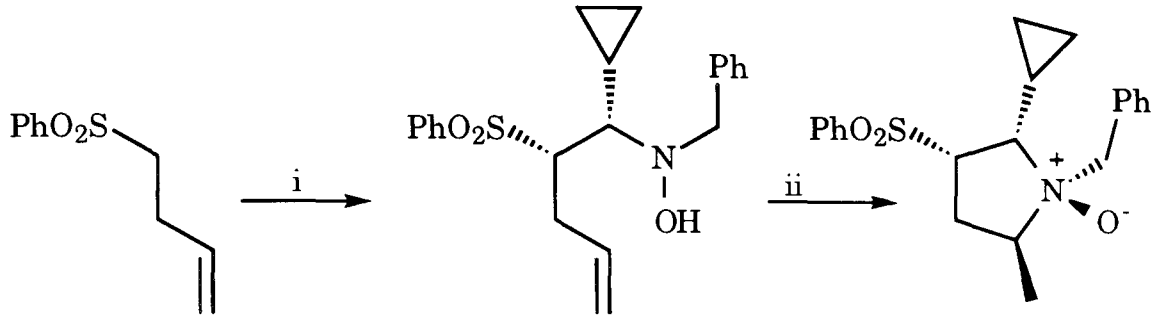


247 **321** **322**

i) a) BuLi, THF, -78°C; b) C-Ph-N-Bn nitrone **320**; ii) $CDCl_3$, rt

Scheme 114

When using *C*-cyclopropyl-*N*-benzyl nitrone **323**, however, condensation gave the hydroxylamine **324** (90%) which cyclised smoothly in 2 days at room temperature to the required *N*-oxide **325** as the major diastereoisomer (ratio *ca.* 3:1; Scheme 115). [Stereochemistry again inferred from amine **338**]



247 **324** **325**

i) a) BuLi, THF, -78°C; b) C-Cy-N-Bn nitrone **323**; ii) $CDCl_3$, rt

Scheme 115

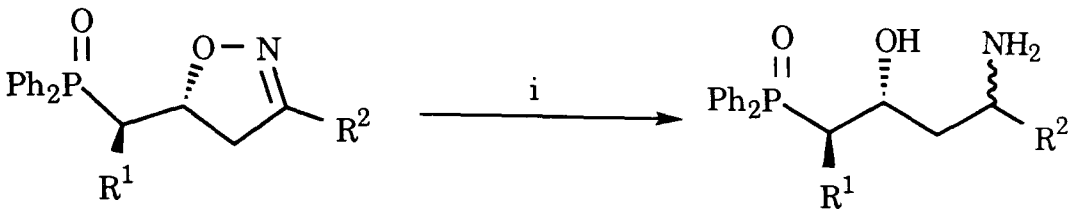
The decreased rate is, again, probably due to the increased steric bulk of the benzyl group on the nitrogen, making the 5-membered transition state required for the *retro*-Cope reaction more difficult to assume. Another possible explanation may be the reduced nucleophilicity of the hydroxylamine nitrogen due to the electron withdrawing effect of the benzyl group.

The slow rate was also thought to be possibly indicative of a slower, or non-existant, rate for cyclisations using sulphones with substituted double bonds (*i.e.* sulphones **274**, **277** and **280**). This was an effect shown when using the *C*-phenyl nitrone **144**, where cyclisation was not seen at all (Section 4.8.3.4).

4.8.7 N-O Cleavage Reactions

4.8.7.1 *"Nickel Boride"*

The system chosen to reduce the N-O bond of the *N*-oxide was that of sodium borohydride-nickel(II) chloride ("nickel boride") at -30°C in methanol, as used by Warren[127] to reduce dihydroisoxazoles **326** to hydroxyamines **327** (Scheme 116). This method appeared to be both mild and highly selective.

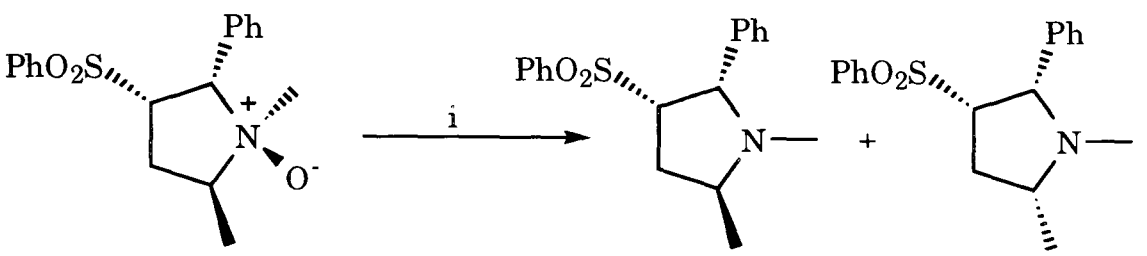


326 **327**

i) $NiCl_2.6H_2O$, $NaBH_4$, MeOH, -30°C; CH_2Cl_2, NH_3

Scheme 116

Initial studies with *N*-oxide **262** yielded the required reduced amine product in 90% yield (100% by ^1H NMR) as a 6:1 mixture of diastereoisomers **328** and **329**, which could be separated by column chromatography (Scheme 117).



262 **328** **329**

Major Minor

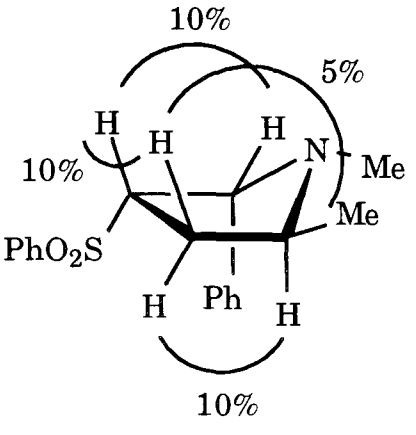
i) $NiCl_2.6H_2O$, $NaBH_4$, MeOH, -30°C; CH_2Cl_2, NH_3

Scheme 117

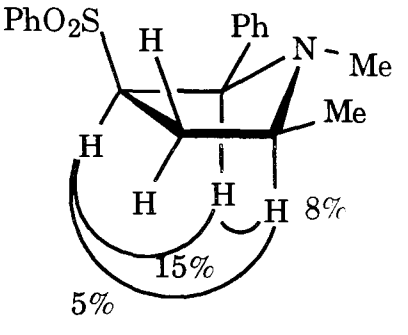
The structures were confirmed by nOe spectroscopy (Fig. 15) and the *cis* relationship of the sulphone and phenyl groups was confirmed with respect to the results obtained from the *N*-oxide **262** precursor itself (Fig. 3).

For major amine **328**, the nOe experiments showed a positive enhancement between the 2-CH and the 3-CH (10%), the 3-CH and the 4-CHβ (δ 1.90 ppm) (10%), the 4-CHα (δ 2.80 ppm) and the 5-CH (9%), and the 5-CH_3 and the 4-CHβ (5%).

For minor amine **329** the nOe experiments showed a positive enhancement between the 2-CH and the 3-CH (15%), the 3-CH and the 5-CH (5%), and the 2-CH and the 5-CH (8%).



328



329

Fig. 15

The isolation of minor isomer **329** appears to confirm that the minor isomer from the *retro*-Cope reaction is indeed the proposed *N*-oxide **262b** (see Section 4.8.3.2b, Page 88).

The presence of an increased amount of minor isomer **329** suggested that the *N*-oxide **262** was unstable to the reducing system and that epimerisation was occurring at some stage. The fact that the *N*-oxide was unstable had already been shown in the case of the X-ray crystal (*cf.* **262** to **264**), although, in this case, it was the 5-methyl group which was seen to epimerise rather than the 2-phenyl group.

This finding was unusual as it would be expected that the presence of a minor isomer would result from reduction of an *N*-oxide resulting from epimerisation of the 2-position of *N*-oxide **262**; *i.e.* from the "X-ray" *N*-oxide **264**. As this *N*-oxide **264** had already been seen, it was expected that it must be a more stable isomer and would be the one which would result if *N*-oxide **262** isomerised. The minor isomer which resulted from the reduction, however, suggested that

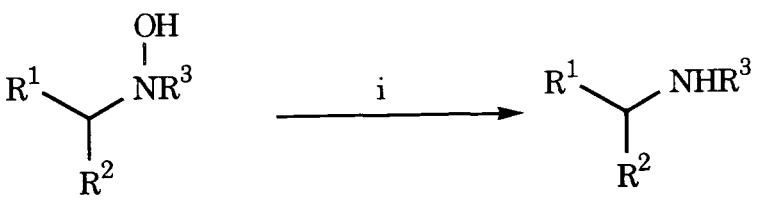
N-oxide **262** is reduced and *then* the resultant amine isomerises. Further studies are required into this isomerisation process.

4.8.7.2 *Other N-O Bond Cleavage Reagents Used*

As a decrease in diastereomer ratio was seen with the "nickel boride" reagent (*i.e.* 8:1 in *N*-oxide **262** to 6:1 in amine **328**), other routes for the conversion of *N*-oxide to amine were attempted.

The use of hydrogen with palladium on activated carbon catalyst in ethanol was first tried, and indeed this appeared to reduce the system as required. In this case, however, a much lower ratio of diastereoisomers was obtained, and indeed, other isomers appeared to be formed extra to those obtained using "nickel boride". It is thought that this is due to the prolonged reaction time required (*ca.* 18h) where the *N*-oxide and amine products are in solution for much longer and at a higher temperature (ambient temperature) and so have more time and energy to epimerise. Similar results were obtained with Raney nickel catalyst.

Also attempted was the aqueous titanium(III) chloride reduction which was reported by Murahashi[128] to reduce hydroxylamines **332** to amines **333** (Scheme 118).



332 **333**

i) $TiCl_3$, H_2O-MeOH, rt

Scheme 118

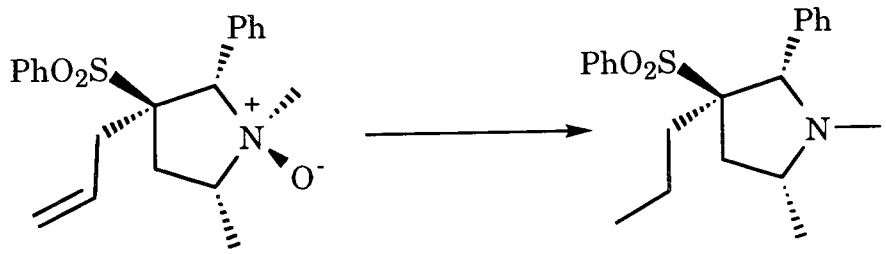
This reducing system, however, when used with *N*-oxide **262** produced only an inseparable and unidentified mixture of products.

4.8.7.3 N-O *Cleavage of Other* N-*Oxides*

Using the same "nickel boride" reducing system, *N-O* cleavage reactions were applied to other *N*-oxides.

It should be stressed at this point, that in all cases, due to the instability of the *N*-oxides to purification, the reduction processes were carried out on the crude reaction mixture of the *N*-oxide resulting from the *retro*-Cope reaction. The purity of the *N*-oxide product obviously depended upon the yield of the condensation reaction, as the *retro*-Cope process was seen, in all cases, to proceed to completion. These mixtures contained mostly *N*-oxide with unreacted starting sulphone. The C-C double bonds of the starting sulphones were reduced to give the alkyl sulphones, and although these could be isolated by column chromatography, they were not further investigated.

N-Oxide **287** was reduced to give amine **334** as only one diastereoisomer (40% over 3 steps with respect to starting sulphone, Scheme 119).



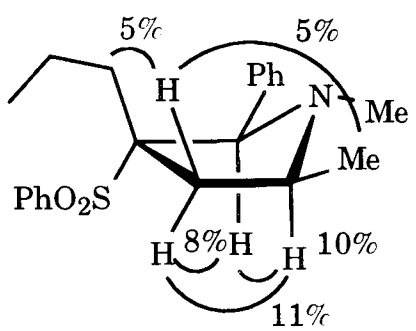
287 **334**

Scheme 119

The reduction was carried out on the crude *N*-oxide because purification of this intermediate was not possible without extensive decomposition. It can also be noted that the C-C double bond was also reduced. Indeed, the only other isolated product was that

resulting from reduction of the double bonds of the excess sulphone in **248** the crude mixture [*i.e.* 4-(phenylsulphonyl)-heptane].

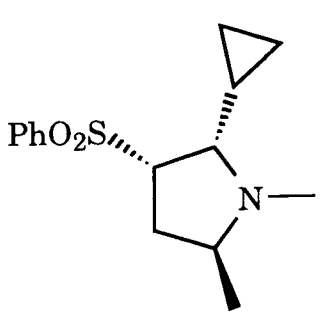
The stereochemistry was confirmed by nOe experiments (Fig. 16) and appears to confirm the transition state proposed for the cyclisation (Section 4.8.3.4, Fig. 11). The nOe experiments showed a positive enhancement between the 2-CH and the 4-CHβ (8%), the 4-CHβ and the 5-CH (11%), the 2-CH and the 5-CH (10%) and the 5-Me and the 4-CHα (5%).



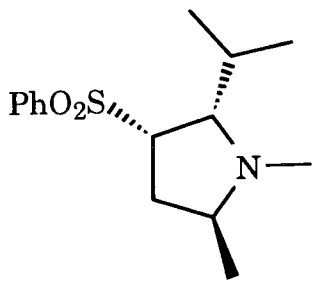
334

Fig. 16

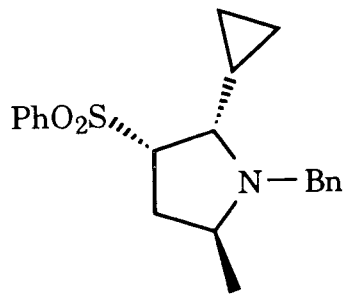
Reduction also gave the 2-cyclopropyl-pyrrolidine **336** (85%, from *N*-oxide **300**) as mainly one diastereoisomer (>6:1), the corresponding 2-isopropyl derivative **337** (90%, from *N*-oxide **313**) and the 2-cyclopropyl *N*-benzylpyrrolidine **338** (90%, from *N*-oxide **325**), as single diastereoisomers respectively.



336



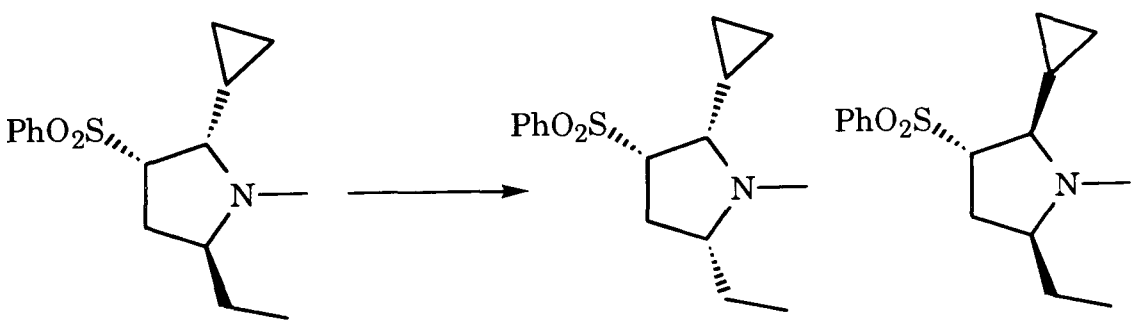
337



338

Again, the structures were confirmed by nOe experiments. For amine **337**, the observed nOe enhancements were H2~H3 (10%), H3~H4β (12%), H5~Me(^{i}Pr) (4%) and H4α~Me(^{i}Pr) (7%). No enhancements were seen for H2~H5. For amine **338**, the observed nOe enhancements were H2~H3 (10%), H3~H4β (10%), H4β~5-Me (16%), H4α~H5 (10%) and H5~H2'(Cy) (5%).

Reductions of longer chain 5-substituted examples proved to be more difficult. Reduction of the 5-ethyl *N*-oxide **304** gave, by ^{1}H NMR analysis of the crude product, the expected 2,5-*trans* compound **339** (85%), tentatively proposed with respect to the double-triplet at δ 3.74 ppm, which appears to be indicative of the 2,3-*cis*-2,5-*trans* compounds *e.g.* **328**). Purification of this crude mixture by silica column chromatography, however, resulted in isolation of not only the expected 2,5-*trans* compound, but also two other amine products as an inseparable mixture for which structures **340** and **341** are proposed but not confirmed (Scheme 120). Indeed, allowing this mixture to stand in $CDCl_3$ for two weeks at room temperature showed almost complete disappearance of the 2,5-*trans* compound in favour of the two other amine products indicated above (*i.e.* **340** and **341**). An isomerisation process would appear to be taking place here, but the mechanism by which it occurs is not, as yet, understood.

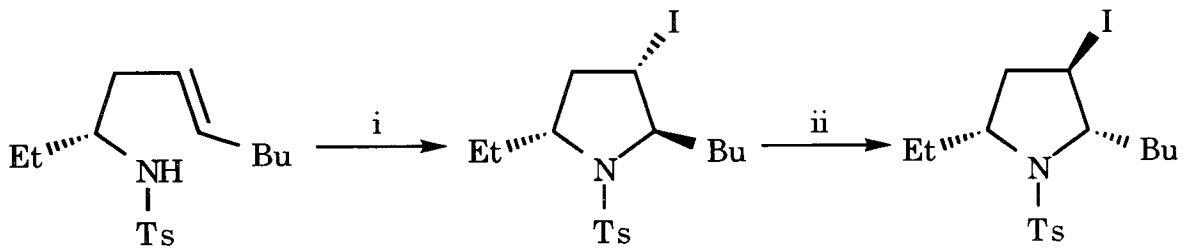


339 **340** **341**

Scheme 120

This observation appears to confirm that the isomerisation process proceeds at the amine stage *after* reduction of the *N*-oxide (see Page 104).

It has recently been noted by Knight and Jones[129] that products resulting from the iodocyclisation of homoallylic amines undergo rearrangement in the presence of acid.



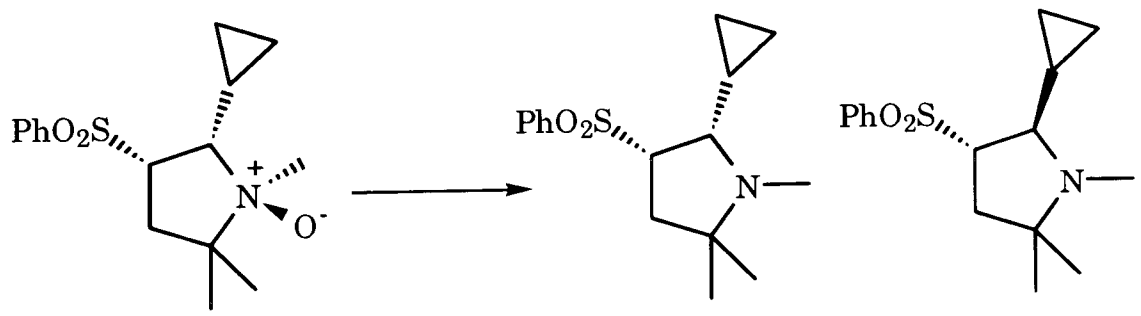
342 **343** **344**

i) I_2, K_2CO_3, MeCN; ii) HI, I_2, MeCN

Scheme 121

It may be possible that a similar rearrangement is occurring here on the acidic silica used for purification.

Reduction of *N*-oxide **308** gave, again, an inseparable mixture of diastereoisomeric amines **345** and **346** in a ratio of 2:1 (90%, Scheme 122).



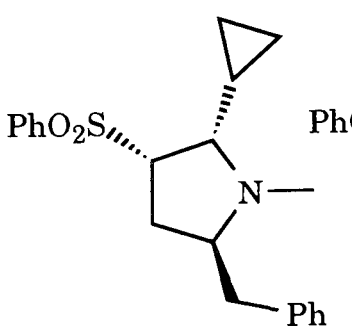
308 **345** **346**

Scheme 122

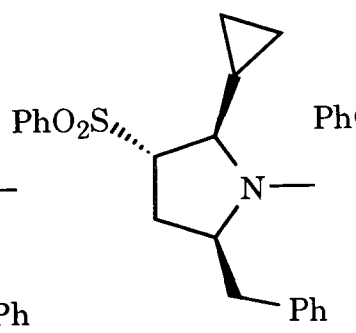
Here, it can be seen that, if no isomerisation is involved, reduction of *N*-oxide **308** would give pyrrolidine **345**. This amine could

then isomerise to give only the 2,3-*trans* compound **346** by isomerisation of either the 2- or 3-position; the 5-position is no longer an epimerisable centre. This shows that isomerisation can occur at both the 2- and 5-positions (and possibly the 3-position) whereas, with the 2-phenyl compound **328** (Section 4.8.7.1), isomerisation was observed at only the 5-position in the reduction.

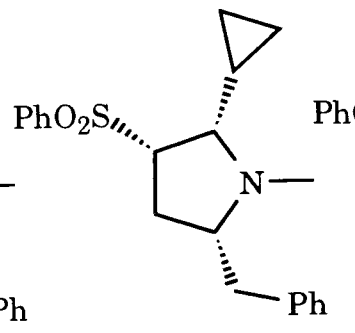
Similarly, the *N*-oxide **306** was reduced to give a mixture of pyrrolidines (60%). Purification was attempted here and two of the three amines formed were isolated in pure form; it was not possible to purify the middle of the three fractions as it was always contaminated with some of the higher and lower fractions. Confirmation of the stereochemistries has not, as yet, been completed, but structures **347**, **348** and **349** seem most likely since compound **347** would be the expected product resulting from the *retro*-Cope reaction (assuming previous results) and compounds **348** and **349** would result from isomerisation α- to the nitrogen to give the thermodynamically more favourable 2,5-*cis* compounds. Structure **350** is another possible isomer but is less likely as it involves isomerisation of the sulphone and is also a less favourable 2,5-*trans* compound.



347



348



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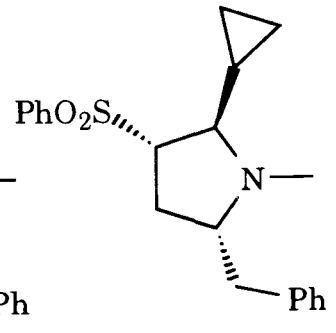
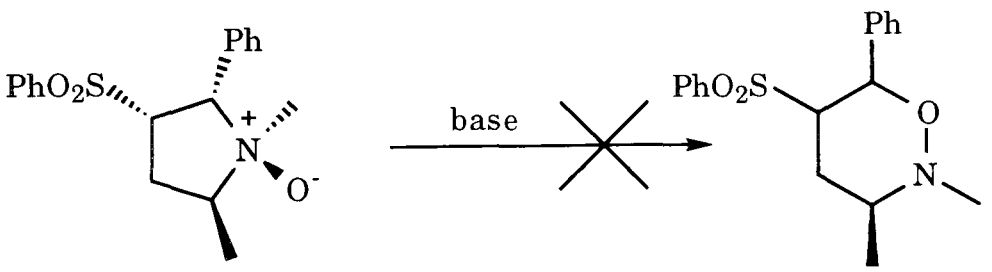


350

4.8.8 Reactions

4.8.8.1 *Of the* N-*oxide*

The stability of the *N*-oxide with respect to base was now investigated. It was thought that it may be possible to induce the *N*-oxide to undergo a Meisenheimer rearrangement, analogous to that reported by Knight[56] (Scheme 60). Thus, *N*-oxide **262** was treated with triethylamine in deuteriochloroform at room temperature in order to induce a base-catalysed Meisenheimer rearrangement (Scheme 123). After 5 days, no such rearrangement was observed. This also showed the stability of the *N*-oxide with respect to epimerisation, as no other products were seen to form either. This stability suggested that the epimerisation of the 2- and 5-positions during reduction was occurring at the amine stage rather than the *N*-oxide stage.



262 **351**

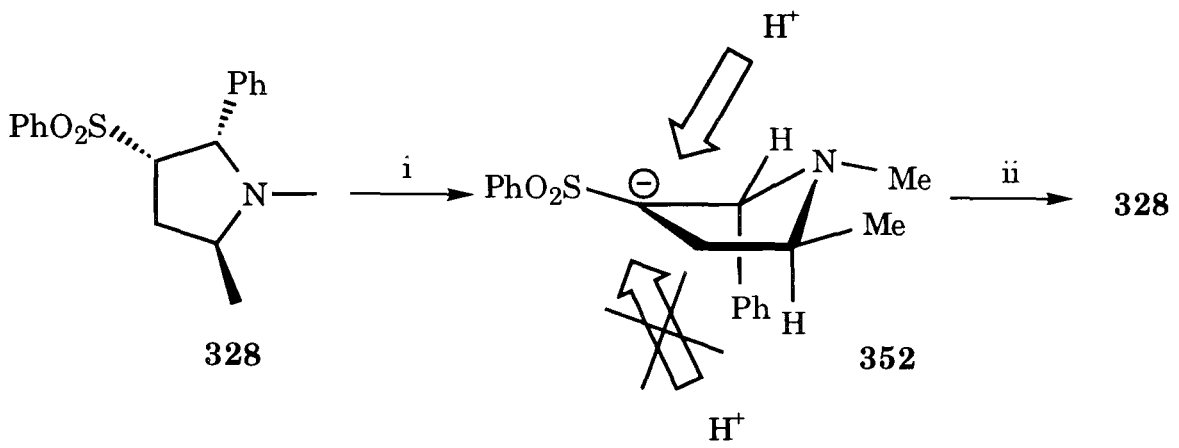
Scheme 123

Treatment of the *N*-oxide **262** with butyllithium at -78°C in THF resulted in degradation to unidentified products.

4.8.8.2 *Of the Amine*

Treatment of amine **328** with butyllithium at -78°C in THF and subsequent aqueous work-up resulted not in the expected 2,3-*trans* compound, but in starting material. This is probably due to

facial blocking by the phenyl group, making the H^+ quench the anion **352** from the less hindered face, rather than formation of the thermodynamically more stable 2,3-*trans* product (Scheme 124).



i) BuLi, -78°C, THF; ii) H^+ work up

Scheme 124

Using a methyl iodide quench in the above reaction did not, however, give the expected alkylated product; again, only starting material was recovered. No explanation has been found for this observation, but lack of deprotonation seems likely.

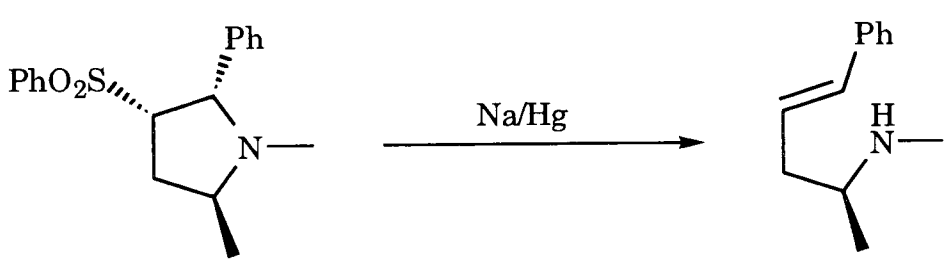
4.8.9 Desulphonylation

Having now served its purpose as an electron withdrawing group for the condensation reaction, attempts were now made to remove the sulphone group from amine **328**.

Standard hydrogenation to effect desulphurisation using Raney nickel catalyst[130] in ethanol under an atmosphere of hydrogen, resulted only in the recovery of starting material. Hydrogen transfer agents, such as cyclohexene in refluxing ethanol, were also unsuccessful.

Single electron transfer agents were examined next. Sodium[132] or lithium[133] naphthalenide in DME or THF at -78°C to ambient temperature were unsuccessful, as was magnesium in ethanol;[134] the former resulted in decomposition and the latter in recovery of starting material. Samarium iodide and HMPA in THF[135] resulted in the formation of inseparable mixtures.

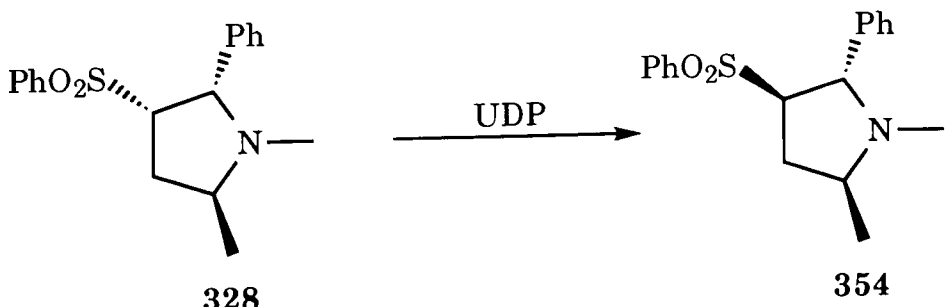
A method which was partially successful was the sodium amalgam[136] reduction of sulphone **328**, which appeared (by ^{1}H NMR analysis) to give a product resulting from a β-elimination reaction (Scheme 125), although the product could not be purified or fully characterised.



328 **353**

Scheme 125

Another method of note was the attempted desulphonylation using ultradispersed potassium[137] (UDP). Sulphone **328** was treated under ultrasonic conditions for 30 min with UDP. Instead of the required desulphurised amine, the product **354** was shown to be an isomer of sulphone **328** resulting from the quantitative epimerisation



328 **354**

Scheme 126

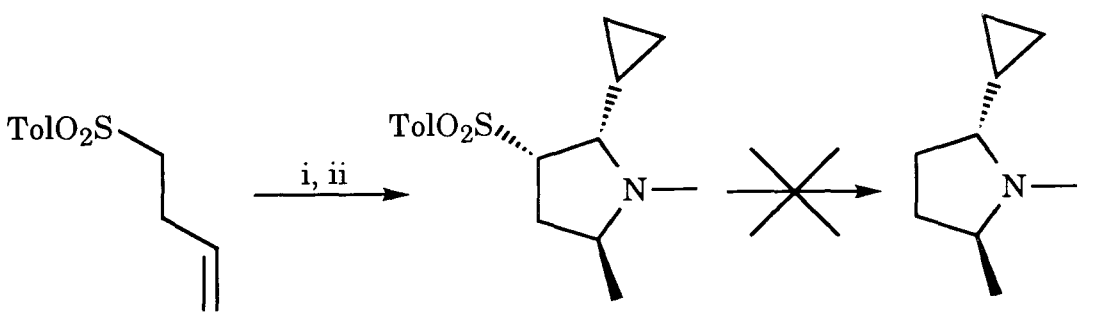
of the sulphone group to give the more stable 2,3-*trans* stereochemistry (Scheme 126).

A comparison may be made between pyrrolidines **328** and **354** with respect to nOe data. The absence of a 2,3-*cis* relationship in pyrrolidine **354** is shown by the lack of an H2~H3 enhancement. The structure shown is also implied by H3~H4α (10%) and H4α~H5 (8%) enhancements.

Radical methods, using tributyltin hydride[138] and AIBN in THF were tried, but only starting material was isolated.

Attempts to reduce the sulphone to the sulphide, which could then be removed by *e.g.* Raney nickel,[139] using lithium aluminium hydride[140] and di*iso*butylaluminium hydride[141] also failed.

As the removal of the phenylsulphonyl group was found to be unsuccessful, the use of a potentially more easily removable group was examined. The use of the *p*-toluenesulphonyl group was attempted and again conversion of sulphone **352** into amine **355** was facilitated. However, desulphonylation was not possible using sodium amlgam, sodium/lithium naphthalenide, hydrogenation (Pd/C, Raney nickel) or with potassium/ultrasound (Scheme 127).



352 **355** **356**

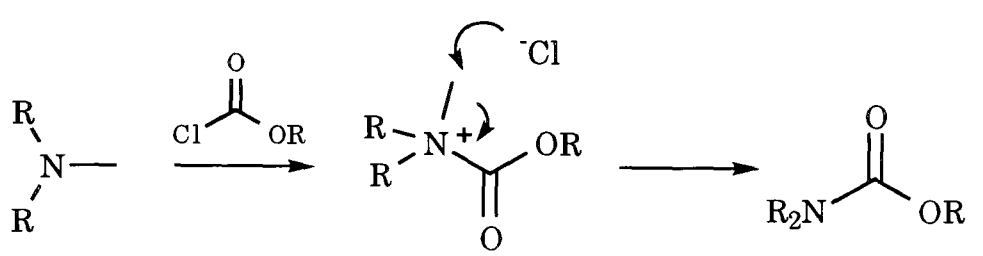
i) BuLi, nitrone **298**; ii) $NiCl_2$, $NaBH_4$, MeOH

Scheme 127

4.8.10 *N*-Dealkylation of Pyrrolidines

4.8.10.1 N-*Methyl case*

Removal of *N*-alkyl groups (usually *N*-Me) by the use of chloroformates has been reported.[142] Here, the proposed mechanism involves quaternisation of the amine by the chloroformate followed by displacement (presumably by an S_N2 mechanism) of the nitrogen alkyl substituent by chloride, resulting in a carbamate-protected secondary amine **360** and methyl chloride (Scheme 128).



358 **359** **360**

Scheme 128

Treatment of the *N*-methyl amines **328** and **336**, however, resulted in none of the expected carbamate. In reactions involving either the phenyl or benzyl chloroformate only starting material was obtained after reflux in toluene for 4 days. With ethyl and methyl chloroformate, decomposition was observed after reflux in dichloromethane for 2 days. Using vinyl chloroformate in refluxing dichloromethane (4h), a promising ^{1}H NMR of the crude product (resulting from removal of solvent and excess chloroformate) was obtained, but no identifiable products were isolated upon aqueous work-up or purification.

4.8.10.2 N-*Benzyl case*

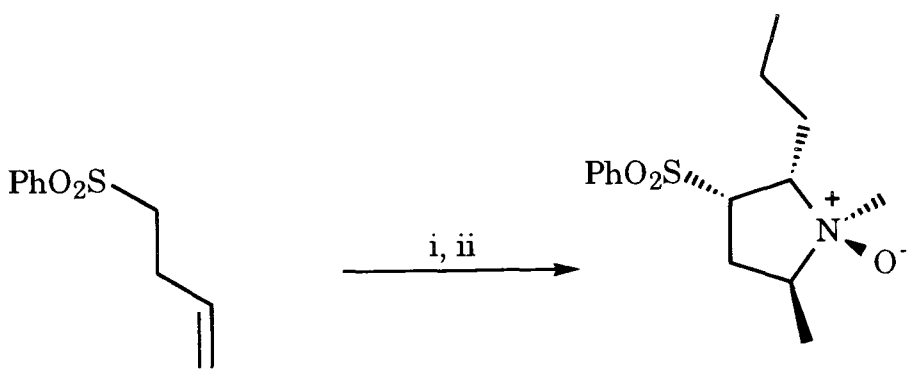
Removal of the *N*-benzyl group was expected to be much easier to facilitate. Standard hydrogenolysis of amine **338** with

palladium on activated carbon in ethanol with hydrogen gas, or with cyclohexene or formic acid as hydrogen transfer agent, however, resulted in only recovery of starting material.

4.8.11 Other Alkyl Nitrones

The use of other alkyl nitrones in the condensation reactions reported earlier proved to be more difficult. Although the cyclopropyl nitrone **298** was very hygroscopic, it was possible to store it for a number of weeks in the freezer (*ca.* -20°C) under an argon or nitrogen atmosphere. In the case of the *n*-propyl nitrone **361**, however, storage could only be achieved for around 1-2 days in the freezer, and so this intermediate was prepared and used immediately, with care in handling.

Thus, sulphone **247** was deprotonated (-78°C, THF) and condensed with nitrone **361** to give, as with the cyclopropyl case, a pyrrolidine *N*-oxide **362** upon work-up (Scheme 129). The stereochemistry was tentatively proposed as shown by comparison with other pyrrolidine *N*-oxides; other 2,3-*cis* compounds exhibit a "double-triplet" at *ca.* δ 4.5-4.9 ppm (*J ca.* 10 and 7 Hz; 3-CH) and, indeed this was observed in this case also.

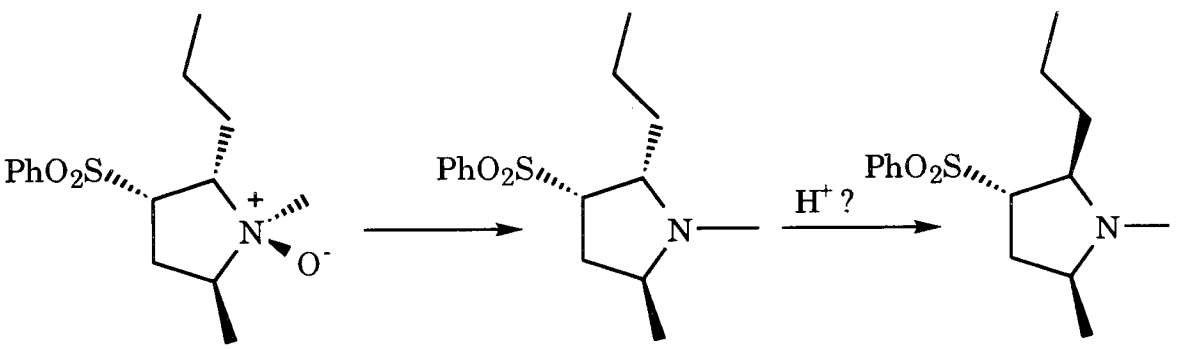


247 **362**

i) BuLi, THF, -78°C; C-propyl-N-methyl nitrone **361**; ii) $CDCl_3$

Scheme 129

Reduction of the *N*-oxide **362** gave the corresponding amine **363** according to ^{1}H NMR analysis of the crude product, but purification by column chromatography yielded two isomers and none of the expected 2,3-*cis* amine **363** shown in the initial spectrum. Again, it is thought that an isomerisation process is taking place during chromatography.



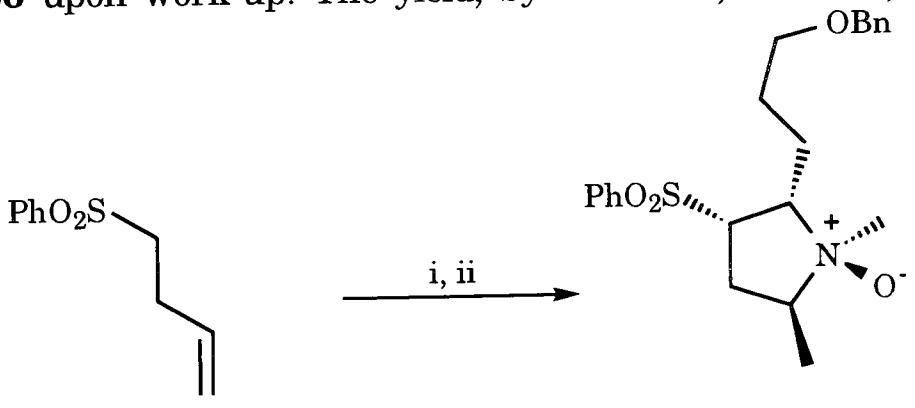
362 **363** **364**

Scheme 130

4.8.12 Heteroatom-Substituted Nitrones

Next, studies were carried out into whether heteroatoms could be incorporated into the nitrone.

Addition of the anion derived from sulphone **247** to *C*-[(3-benzyloxy)propyl]-*N*-methyl nitrone **365**, yielded a pyrrolidine *N*-oxide **366** upon work-up. The yield, by ^{1}H NMR, was low, but this



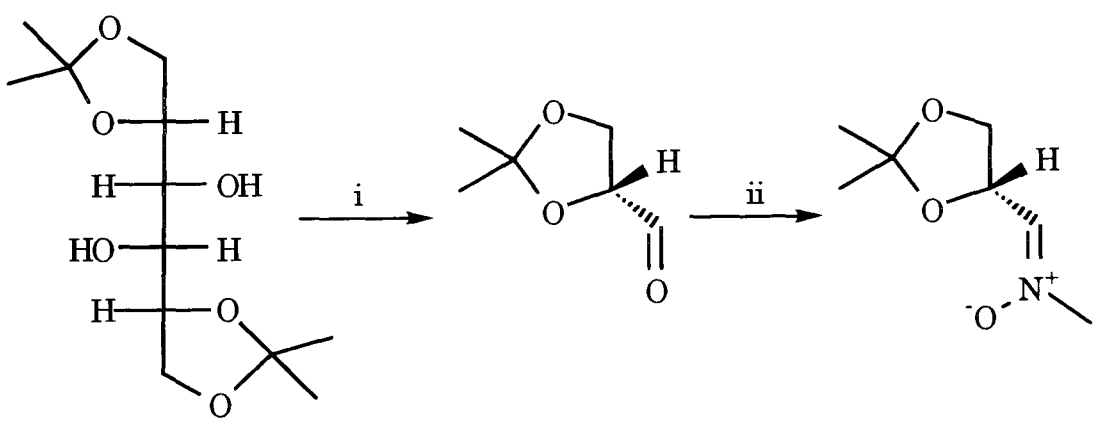
247 **366**

i) BuLi, THF, -78°C; C-3-(benzyloxy)-propyl-N-methyl nitrone **365**; ii) $CDCl_3$

Scheme 131

may be attributed to the nitrone having some aldehyde impurity and/or that it was very hygroscopic and may have become wet upon handling. As the crude product could not be purified and nOe studies were not possible due to the fact that most ^{1}H NMR resonances were obscured, a 2,5-*trans*-2,3-*cis* relationship could only be proposed with respect to the "double-triplet" at δ 4.72 ppm. It would be expected that this yield can be optimised and the structure proven, but lack of time prevented this.

A possible method for inducing chirality in the pyrrolidine *N*-oxide was envisaged using a chiral nitrone. Thus, formation of the simple isopropylidene protected diol aldehyde **368** was achieved by diol cleavage of 1,2:5,6-diisopropylidene-*D*-mannitol **367** using sodium periodate. Purification by distillation gave pure aldehyde **368** with an α_D comparable with that quoted in the literature (Scheme 132).[149] This was then converted into the corresponding nitrone **369**,[143] which was then condensed with sulphone **247** using the now established method (Scheme 133).



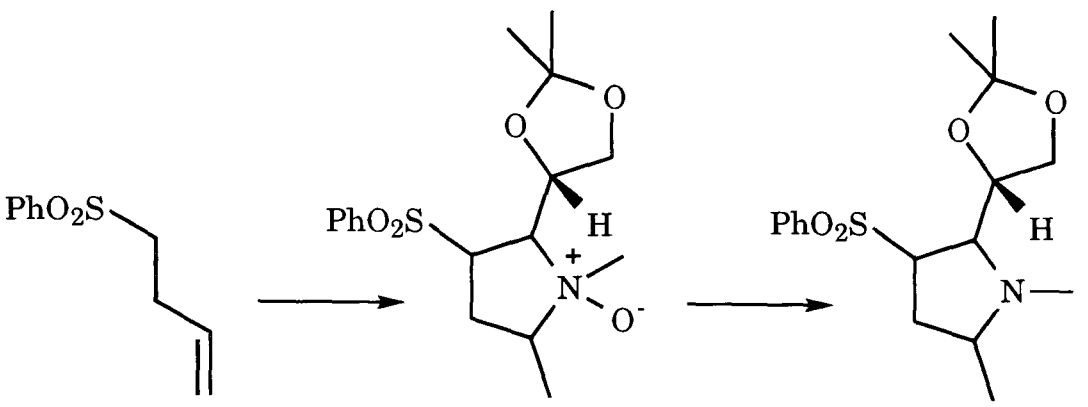
367 **368** **369**

i) $NaIO_4$, CH_2Cl_2; ii) MeNHOH, K_2CO_3, CH_2Cl_2

Scheme 132

Analysis of the crude product by ^{1}H NMR indicated formation of a pyrrolidine *N*-oxide **370** upon work-up. Reduction using "nickel

boride" resulted in the isolation of a mixture of at least 4 diastereoisomers.



247 **370** **371**

i) BuLi, THF, -78°C; nitrone **369**; ii) $CDCl_3$;
iii) $NiCl_2.6H_2O$, $NaBH_4$, MeOH, -30°C

Scheme 133

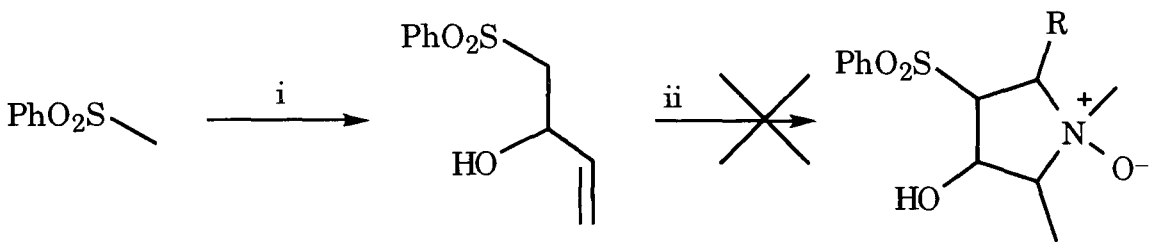
4.8.13 Miscellaneous Sulphones

With the success of the homoallylic sulphones **247**, **248** and **283**, two further functionalised sulphones with unsubstituted double bonds were synthesised.

Condensation of the methyl phenyl sulphone anion (derived from treatment of methyl phenyl sulphone **245** with butyllithium) with acrolein at -78°C, resulted in formation of homoallylic sulphone **372** in quantitative yield (by ^1H NMR analysis, Scheme 134). This sulphone possesses a heteroatom (oxygen) β– to the sulphone moiety and would, therefore, result in a functionalised pyrrolidine **373** which could undergo further elaboration.

The 2-hydroxyl group could not be protected with *e.g.* a *t*-butyldimethylsilyl group as β-elimination would become a problem and so sulphone **372** was treated with two equivalents of butyllithium in the hope of producing the corresponding dianion. When this was then quenched with a nitrone (*C*-phenyl-*N*-methyl

and *C*-cyclopropyl-*N*-methyl nitrones **144** and **298** were used), no condensation products were observed however, and starting material was recovered in high yield (some elimination products were also seen).

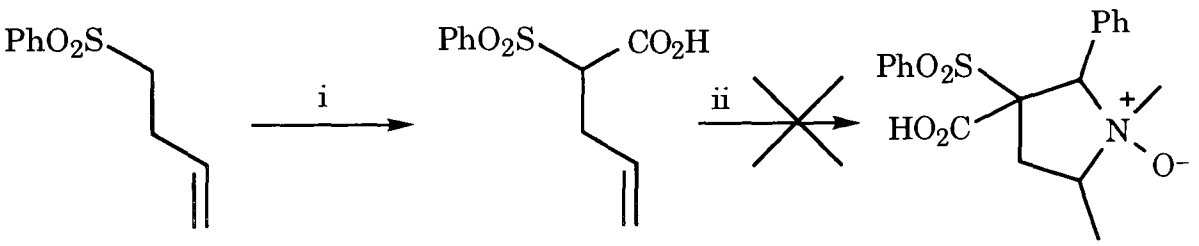


245 **372** **373**

i) BuLi, acrolein, THF, -78°C;
ii) 2eq BuLi, nitrone **144** or **298**, THF, -78°C

Scheme 134

Condensation of sulphone **247** with dry ice at -78°C resulted in formation of the α-substituted sulphone **374**. Treatment of this with 2 equivalents of butyllithium and then *C*-phenyl-*N*-methyl nitrone **144** also resulted in recovery of unreacted starting material.

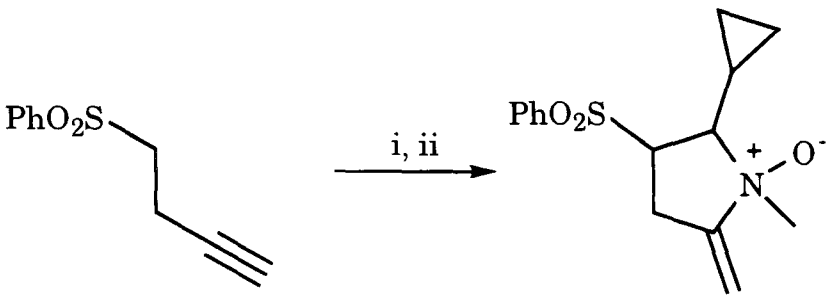


247 **374** **375**

i) BuLi, CO_2, THF, -78°C; ii) 2eq BuLi, nitrone **144**, THF, -78°C

Scheme 135

Further to the work carried out in Section 4.8.3.4 relating to similar work carried out by Holmes *et al*[70-72] on *retro*-Cope reaction of alkynes, sulphone **289** was condensed with nitrone **298** and the resulting product was proposed to be the pyrrolidine *N*-oxide **376**.



289 **376**

i) a) BuLi, THF, -78°C; b) C-Cy-N-Me nitrone **298**; ii) $CDCl_3$, rt

Scheme 136

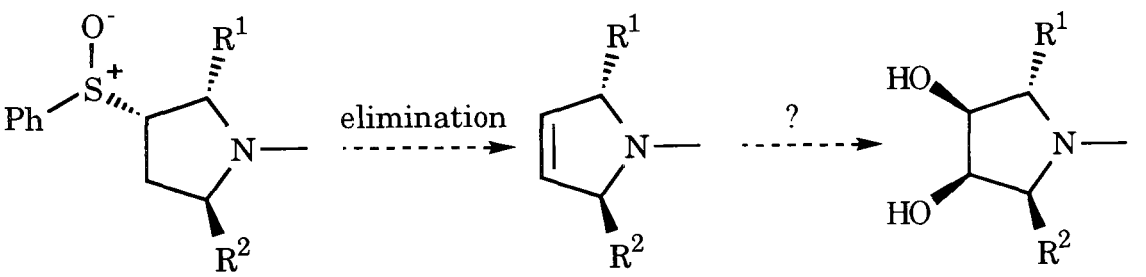
Evidence for this was given by ^1H NMR spectra which showed two broad singlets at δ 5.02 and 4.84 ppm for the exocyclic double bond and a double-triplet at δ 4.42 ppm for the 4-CH. Further elaboration was not possible as the product was unstable and decomposed in a matter of hours.

4.9 EWG = Sulphoxides

4.9.1 *Introduction*

As shown previously, sulphones have been condensed successfully with nitrones and the subsequent hydroxylamines converted *via retro*-Cope methodology into pyrrolidine *N*-oxides.

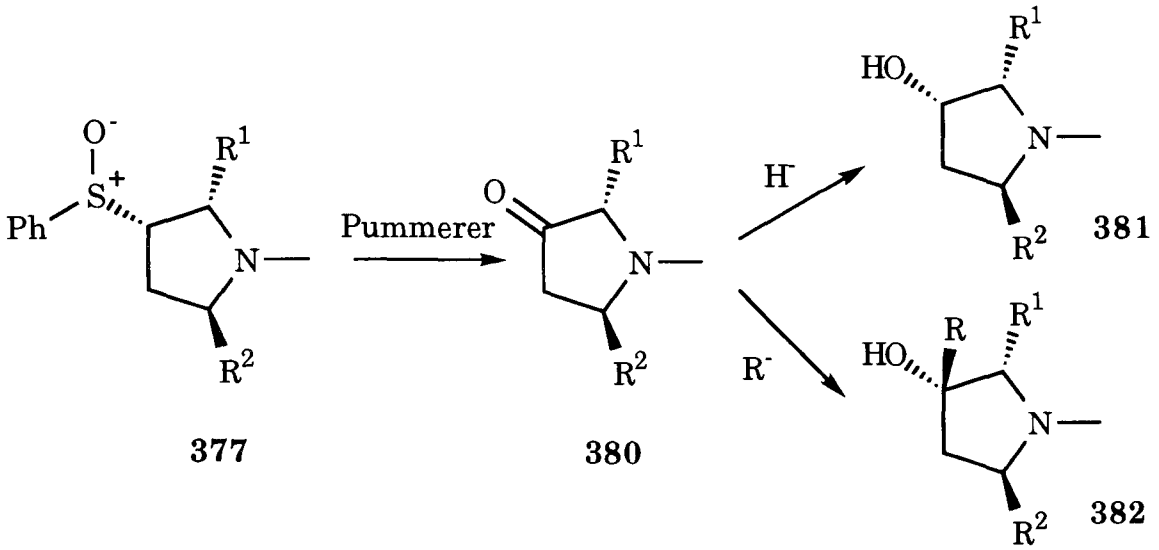
It was envisaged that a sulphoxide stabilised anion would also be suitable for this work. In this case, the resulting sulphoxide-substituted pyrrolidine **377** would open more avenues for further functionalisation. For example, elimination[29] of the sulphoxide group may yield a 3,4-unsaturated pyrrolidine **378** which could be manipulated to give products resulting from stereoselective addition to the resulting double bond, *e.g.* by osmylation, to give the diol **379** (Scheme 137). Facial selectivity may be possible due to steric differences between the substituents in the 2- and 5- positions of the unsaturated pyrrolidine.



377 **378** **379**

Scheme 137

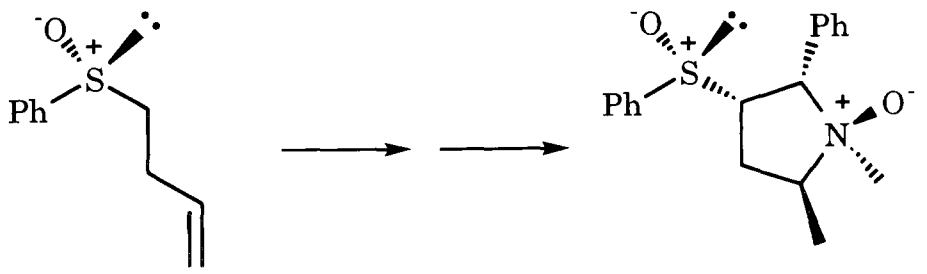
Another possibility may be the Pummerer rearrangement[145] which could yield a 3-pyrrolidinone **380** which, again, may exhibit facial selectivity when reduced to give secondary alcohol **381**, or when condensed with a suitable anion (*e.g.* R^-, CN^-, *etc.*) to give tertiary alcohol **382** (Scheme 138). Wittig-type reactions may also be possible.



377 **380** **381** **382**

Scheme 138

Another advantage of the sulphoxide moiety is that of chirality. It is possible to synthesise chiral sulphoxides by oxidation of the corresponding sulphides under, for example, Sharpless[146] conditions. It was envisaged that, as the products resulting from the sulphone work (with achiral starting materials) consisted of mainly one diastereoisomer out of a possible eight, then starting from chiral sulphoxide starting material (*e.g.* **383**), chirality may be induced into the pyrrolidine *N*-oxide products (*e.g.* **384**), producing, perhaps, one enantiomer (Scheme 139).



383 **384**

Scheme 139

The problems envisaged here consisted of:

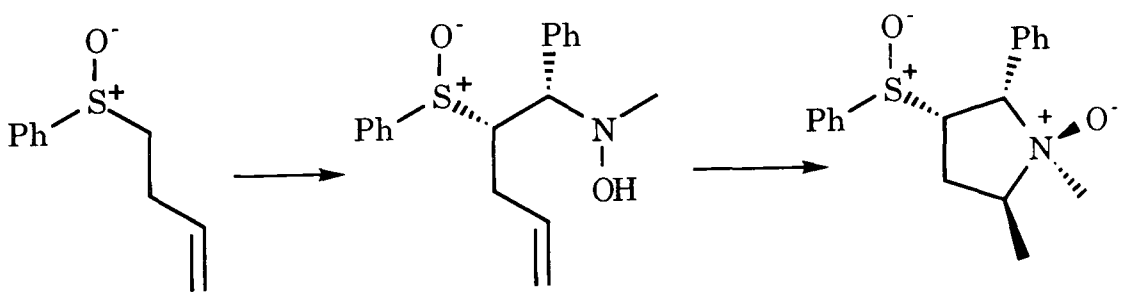
i) Synthesis of dry sulphoxides. Sulphoxides are much more hygroscopic than the corresponding sulphones, but handling problems should easily be overcome.

ii) Would it be necessary to change the conditions for the condensation with the nitrone?

iii) Would it be possible to reduce the *N*-oxide produced in the *retro*-Cope reaction in the presence of the sulphoxide, or would any chemistry involving the sulphoxide have to be carried out on the *N*-oxide? The *N*-oxides resulting from the sulphone work had already shown marked instability to any chemistry attempted, usually resulting in decomposition!

4.9.2 *Preliminary Studies*

With these thoughts in mind, initial studies were carried out. The homoallylic sulphoxide **258** was treated, as with the sulphone analogue, with butyllithium at -78°C. The resulting anion was then condensed with *C*-phenyl-*N*-methyl nitrone **144** yielding the required hydroxylamine **385** (80%, by ^{1}H NMR of the crude product), which was purified by silica column chromatography (63%). Cyclisation was effected in deuteriochloroform at room temperature over 8 days to give *N*-oxide **386** in quantitative yield as one major diastereoisomer (> 6:1; Scheme 140).



258 **385** **386**

Scheme 140

The stereochemistry was confirmed by nOe spectroscopy to be similar to that obtained from the sulphone analogue.

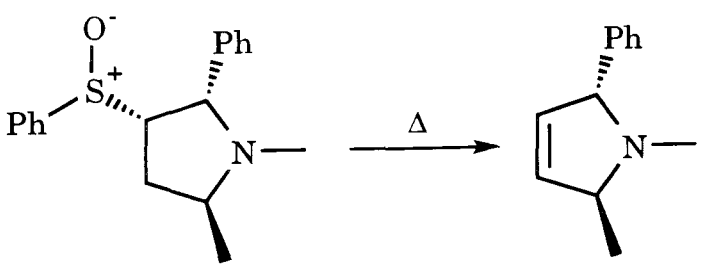
Reduction of the *N*-oxide **386** was facilitated using "nickel boride" to give the amine **387** quantitatively by ^{1}H NMR, although, again a loss was seen upon work-up (90%). Spectroscopic evidence (nOe) suggested the structure shown to be the major diastereoisomer.

The speed of the *retro*-Cope reaction was found to be comparable, but slightly slower, than with the respective sulphone; *i.e.* 8 days for the sulphoxide, 4 days for the sulphone.

4.9.3 Chemistry of the Sulphoxide

Elimination Reactions

As expected, the *N*-oxide **386** decomposed upon heating at 110°C in toluene. The reduced amine **387**, however, did undergo an elimination reaction in refluxing toluene, to give what was tentatively proposed as the 2,5-dihydropyrrole **388**, but purification was not possible (Scheme 141).



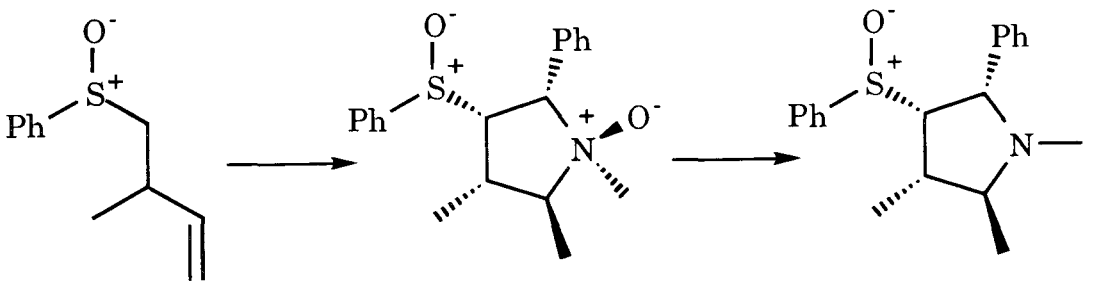
387 **388**

Scheme 141

4.9.4 A Strange Phenomenon

Perhaps the most interesting discovery in the sulphoxide investigations was that of the reactions pertaining to sulphoxide **389**. Here, as above, the corresponding sulphoxide anion (from sulphoxide **389**) was produced, condensed with nitrone **144**, and the product purified by column chromatography (58%). Cyclisation over 10 days at room temperature gave an *N*-oxide product **390**, as expected (Scheme 142). At this point it may be noticed that a substituent in the 3-position of the hydroxylamine **392** does not significantly effect the rate of cyclisation.

Reduction with "nickel boride" gave amine **391** in quantitative yield as what appeared to be one diastereoisomer (out of a possible 32 - 6 chiral centres) according to ^{1}H and ^{13}C NMR spectra, and nOe measurements indicated the structure shown.

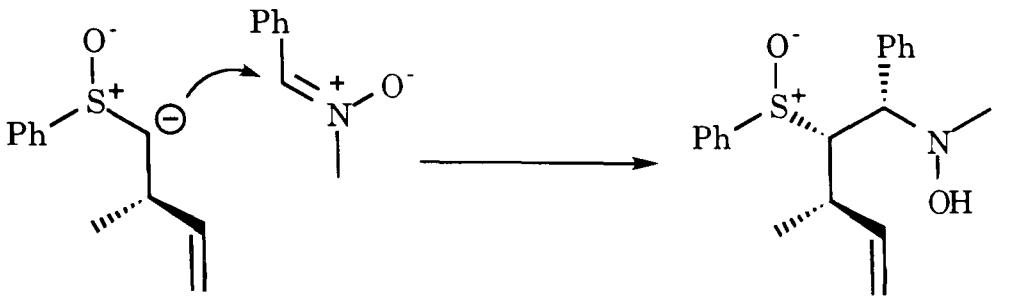


389 **390** **391**

Scheme 142

From this result, two major questions result;

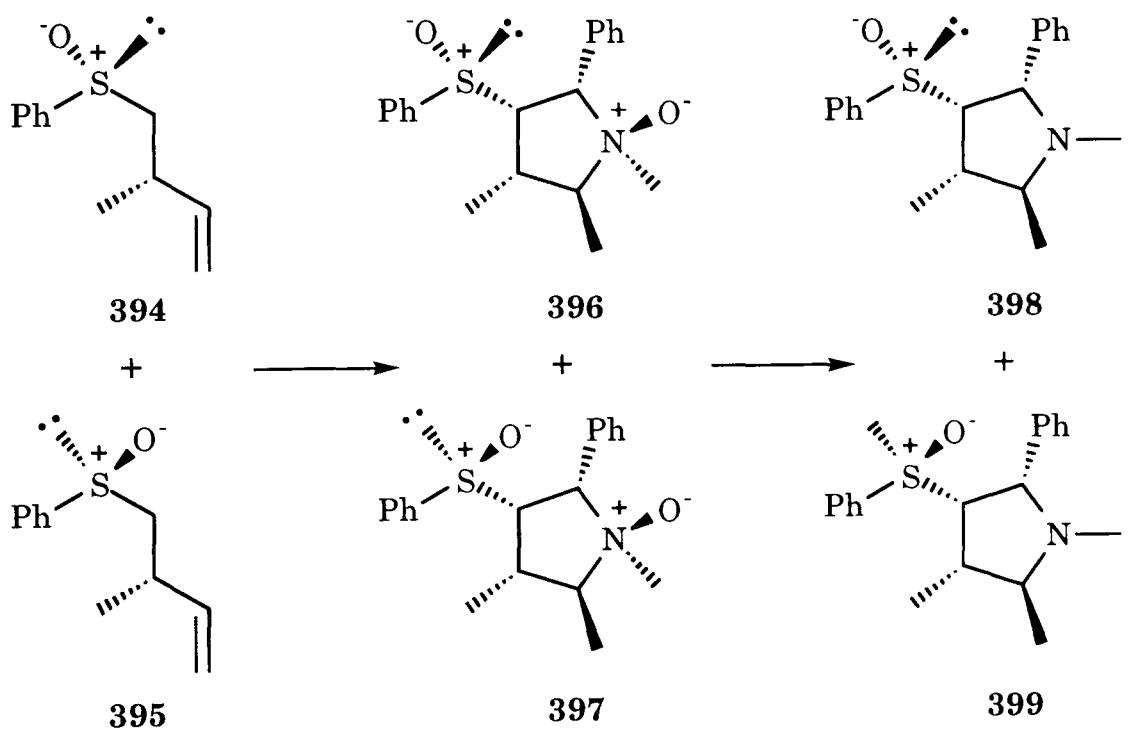
i) Why do we get a 2,3,4-*cis* relationship in the pyrrolidine? This has to come from a condensation where selectivity between a methyl group and a vinyl group is observed, suggesting that the methyl group is much more sterically demanding as no other product would appear to have been formed (Scheme 143).



392 393

Scheme 143

ii) Why is only one diastereoisomer being formed when the sulphoxide starting material is clearly **two** diastereoisomers **394** and **395** by both ^{1}H and, more importantly, ^{13}C NMR? Surely, both pyrrolidine *N*-oxides **396** and **397** would be expected to be formed (Scheme 144).



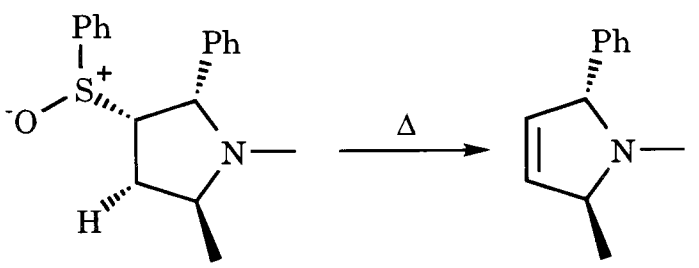
394 396 398

395 397 399

Scheme 144

The stereochemistry was further confirmed by subjecting the amine **391** to heat. In the case of sulphoxide **387**, elimination was observed to occur in toluene at 110°C, to give the 2,5-dihydropyrrole **388**. In the case of sulphoxide **391**, however, no such elimination was seen to occur (Scheme 145). This can be explained by the fact that the elimination requires a concerted, 5-membered, *syn* transition

state where the sulphoxide and the hydrogen to be eliminated are on the same side of the molecule. With sulphoxide **391**, this is not possible because the sulphoxide and hydrogen are constrained to be *trans* to each other and so cannot attain the required transition state.



387 **388**

391 **400**

Scheme 145

4.10 Further Work

Other areas of interest using the *retro*-Cope methodology are currently under investigation.

4.10.1 *Completion of Previous Studies*

Firstly, further studies need to be carried out into the isomerisation process (see Section 4.8.7.3). How and why does it occur? Can it be repressed or can it be made to go to completion to give only one diastereoisomer?

Also, it may be possible to remove the nitrogen substituent using other methods. For example, another reagent recently reported

(α-chloroethylchloroformate[147]) may be of use in the removal of the *N*-methyl group. It may also be possible to make the *N*-benzyl group more susceptible to removal by making it more electron rich. For example, changing the benzyl for a *p*-methoxybenzyl group has been shown to make the removal of the protecting group more facile and can be removed using DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone). Other substituents may also make hydrogenolysis easier.

4.10.2 *Manipulation of the Sulphone Precursor*

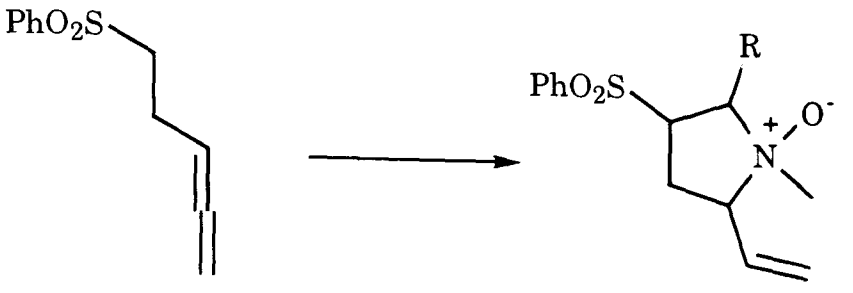
4.10.2.1 Larger Ring Sizes

As shown, alkynyl sulphones (*e.g.* **289**, Scheme 136) undergo *retro*-Cope reactions when using alkyl nitrones. The work carried out in Section 4.8.3.4 could be repeated using such an alkyl nitrone instead of the *C*-phenyl-*N*-methyl nitrone which did not undergo cyclisation. This work could also, perhaps, be used to make piperidine ring systems.

4.10.2.2 *Functionalisation of the 5-position*

As has been shown, sulphones containing a terminal double bond give the best results in the *retro*-Cope reaction. This, however, gives a methyl group in the 5-position of the pyrrolidine and so further functionalisation is not easily possible. Formation of pyrrolidines which could be manipulated further would be of greater synthetic importance.

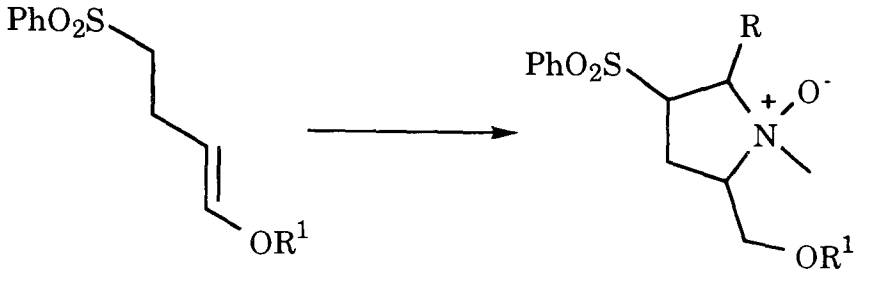
Allenes (*e.g.* **403**) could be a possible route to pyrrolidines with a functionalisable 5-position (Scheme 146).



403 404

Scheme 146

Retro-Cope reactions using heteroatom-substituted alkenyl sulphones (*e.g.* vinyl ethers such as compound **405**) could similarly result in further 5-position functionalisation (Scheme 147).



405 406

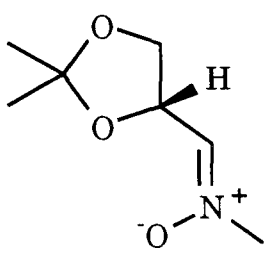
Scheme 147

4.10.3 *Manipulation of the Nitrone*

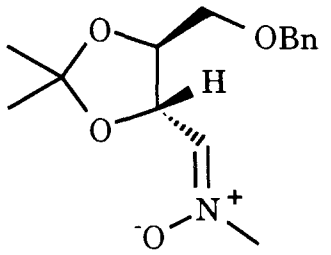
All the nitrones used in this report are those resulting from aldehydes. Nitrones resulting from ketones would also be an area of interest in the formation of 2,2-disubstituted pyrrolidines. The condensation reaction of sulphone anion with such nitrones would be expected to be more difficult due to the extra steric hindrance, but it may be possible to use this extra bulk to effect diastereoselective additions.

As indicated earlier, the chiral nitrone **369** tried did not have much success in inducing chirality, not only in our case, but also in [1,3]-dipolar cycloaddition reactions.[143] The chiral nitrone **407** which

has been used with success in [1,3]-dipolar cycloaddition reactions is that derived from tartaric acid and this may also be successful in the *retro*-Cope reaction.[148]

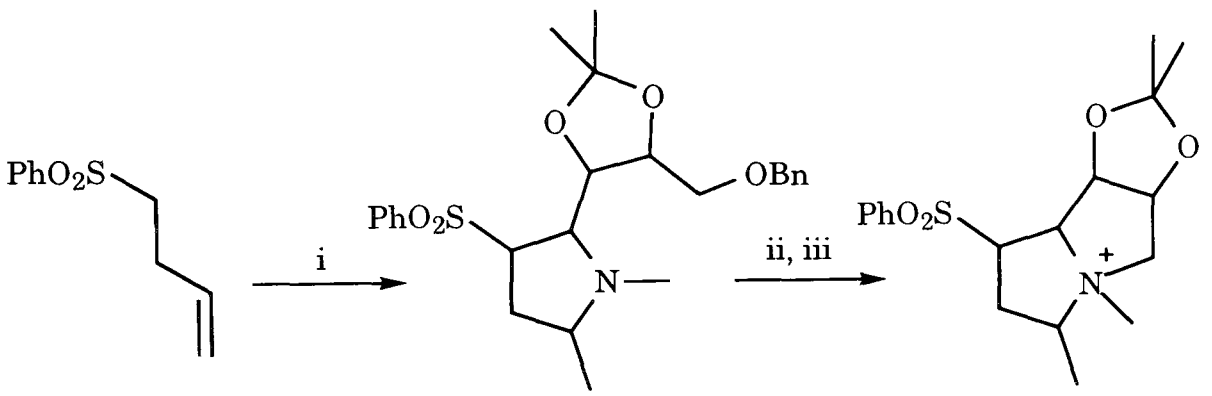


369



407

Using nitrone (**407**, Scheme 148), it may then be possible to access the pyrrolizidine system (and also the indolizidine system using a suitable C_5-nitrone).

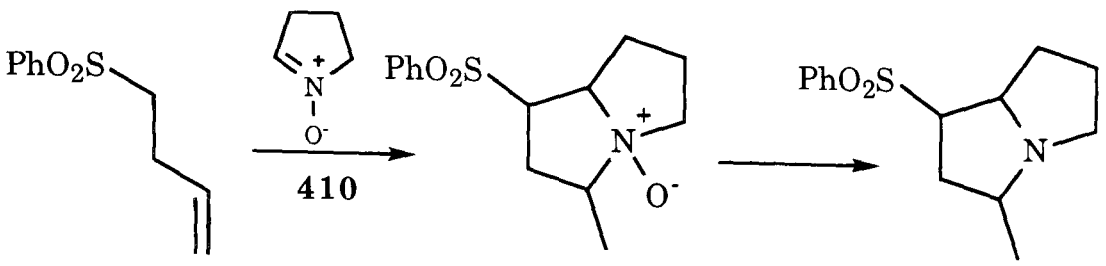


247 **408** **409**

i) BuLi, nitrone **407**, reduction; ii) deprotection & activation of OH; iii) cyclisation

Scheme 148

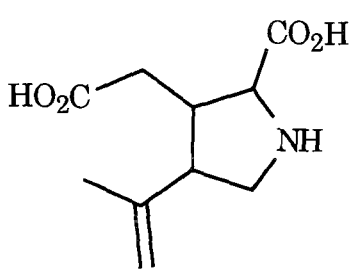
Another route to the pyrrolizidine system would involve the use of a cyclic nitrone (*e.g.* the simple unsubstituted nitrone **410**, Scheme 149).



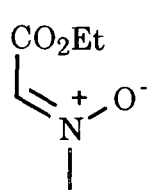
247 **411** **412**

Scheme 149

A major area of interest is the Kainic acid[150] **413** family of natural products. The 2-carboxylic acid could be introduced *via retro*-Cope methodology using, for example, nitrone **414**.[151]

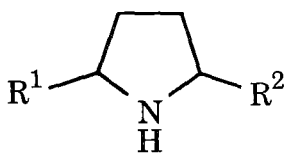


413



414

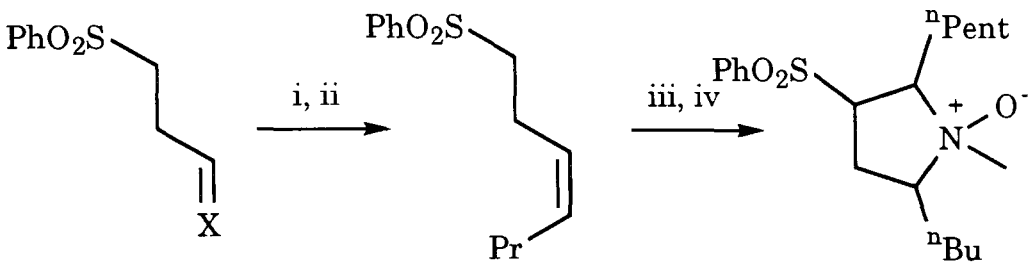
Another area of natural product chemistry is that of the ant and scorpion venoms, *i.e.* compounds **415**.[152]



415

R^1 = *n*-pentyl, *n*-heptyl;
R^2 = ethyl, *n*-butyl, *n*-hexyl

In this case, long chain aliphatic nitrones (*e.g.* nitrone **418**) could be coupled with sulphones such as compound **417**, which are easily made *via* ozonolysis of homoallylic sulphone **247**, followed by Wittig reaction of the resulting aldehyde **416** with a suitable phosphonium salt (Scheme 150). Studies have been carried out to this end, but as low yields of condensation products were obtained, more work will be necessary to establish this as a viable method.



X = CH_2 **247**
X = O **416**

417

419

i) O_3, CH_2Cl_2-MeOH; Et_3N; ii) BuP^+Ph_3, BuLi, THF;
iii) BuLi, THF; C- *n*-pentyl-N-methyl nitrone **418**; iv) $CDCl_3$

Scheme 150

Chapter Five

Experimental Section

5.1 Experimental Standards

All melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

Infrared spectra were obtained using a PE 1720 FTIR machine as a liquid film, unless otherwise stated. Ultraviolet spectra were obtained using a Philips TU 8720 spectrophotometer in ethanol solution.

^{1}H NMR spectra were recorded on either a Bruker WM 250 (250 MHz), a Jeol EX 270 (270 MHz) or a Bruker AM 400 (400 MHz) instrument. The spectra were recorded as dilute solutions in deuteriochloroform unless otherwise stated. The chemical shifts are recorded relative to an internal tetramethylsilane standard and the multiplicity of a signal is designated one of the following abbreviations:- s, singlet; d, doublet; t, triplet; q, quartet; br, broad; app, apparent; m, multiplet; and combinations of the above *e.g.* dd, double doublet; dt, double triplet; *etc.* All coupling constants, J, are reported in Hertz. ^{13}C NMR spectra were recorded on either a Jeol EX 270 (67.8 MHz) or a Bruker AM 400 (100.6 MHz) instrument. The chemical shifts are reported relative to an internal tetramethylsilane (0.00 ppm) or chloroform (77.1 ppm) signal on a broad band decoupled mode, and the multiplicities were obtained using DEPT sequences. ^{1}H and ^{13}C data were varified, where possible, with COSY and C-H Correlation sequences. Stereochemistry was confirmed where necessary using nOe spectroscopy.

Mass spectra were recorded on an AEI MS-902 or an MM-701CF instrument, using electron impact ionization at 70 eV, unless otherwise stated. Electrospray (ES) was run by Cardiff, University of Wales. CI was run by EPSRC Mass Spectroscopy Service in Swansea. Microanalytical data were obtained on a Perkin-Elmer 240B elemental analyser.

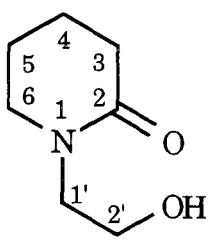
Optical rotations were obtained on a Jasco DIP-370 instrument.

Flash chromatography was performed using Flash (60 mesh) silica and the solvents were redistilled before use. All reactions were monitored by tlc using Camlab silica gel 60 F254 precoated plastic plates which were visualised with ultraviolet light or alkaline potassium permanganate solution.

Routinely, dry organic solvents were stored under nitrogen. Benzene, toluene and diethyl ether were dried over sodium wire. Other organic solvents were dried by distillation from the following:- THF (sodium, benzophenone), dichloromethane and DMF (calcium hydride), methanol and ethanol (magnesium alkoxide) and acetonitrile (phosphorus pentoxide, then potassium carbonate). Other organic solvents and reagents were purified by the accepted literature procedures.[153] Organic extracts were dried over anhydrous magnesium sulphate and the solvent was removed on a Buchi rotary evaporator. Where necessary, reactions requiring anhydrous conditions were performed in flame- or oven-dried apparatus under an argon or nitrogen atmosphere. A Buchi GKR-50 Kugelröhr was used for bulb-to-bulb distillations.

5.2 Quinuclidine (Section 2.4)

1-(2-Hydroxyethyl)-piperidin-2-one 24



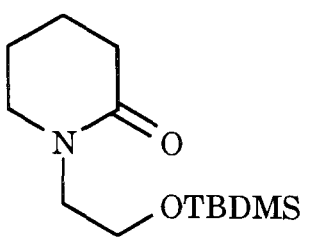
To a solution of 1-piperidineethanol (8.03 g, 62 mmol) in 2.7% aqueous acetic acid (350 ml) were added mercury(II) acetate (49.6 g, 156 mmol, 2.5 eq) and EDTA disodium salt dihydrate (57.83 g, 156 mmol, 2.5 eq). The mixture was stirred for 2.5 h on an oil bath kept at 110°C.[26]

After filtering the mercury residue, the solution was neutralised with 2M aqueous sodium hydroxide and evaporated *in vacuo* to *ca.* 50 ml. This was then extracted with chloroform (5 x 150 ml) and the combined organic extracts dried and evaporated to give a mixture of the desired piperidinone and the derived acetate (*ca.* 7%).

The crude product was then dissolved in absolute ethanol (250 ml), 50% aqueous sodium hydroxide (16 ml) was added and the solution stirred for 16h to hydrolyse the acetate. The solution was then neutralised with 2M hydrochloric acid and evaporated *in vacuo* to *ca.* 20 ml and extracted with chloroform (6 x 100 ml). The combined extracts were evaporated to dryness. The crude product was purified by filtration through a pad of alumina (50 g, $CHCl_3$ as eluent) and the combined extracts evaporated to give the *title compound* **24** (6.58 g, 74%) as a pale yellow oil, which showed υ_{max} 3371, 2945, 2873 and 1618 cm^{-1}; δ_H (250 MHz) 4.05 (1H, t, *J* 4.9, OH, disappeared with D_2O shake), 3.75-3.82 (2H, m, 2'-CH_2), 3.53 (2H, t, *J* 5.2, 1'-CH_2), 3.37-3.42 (2H, m, 6-CH_2), 2.40 (2H, t, *J* 5.9, 3-CH_2) and 1.78-1.87 (4H, m, 4- & 5-CH_2); δ_C (67.8 MHz) 171.5 (2-C), 60.4 (2'-CH_2), 50.5 & 49.4 (6- & 1'-CH_2), 30.1 (3-CH_2) and 23.1 & 21.0 (4- & 5-

CH_2); *m/z* (EI) 143 (26%, M^+), 125 (22), 124 (11), 112 (100), 100 (34), 84 (98), 56 (34) and 55 (30).

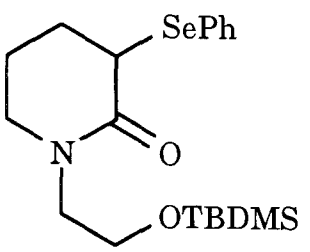
1-(2-*t*-Butyldimethylsilyloxyethyl)-piperidin-2-one 25



A solution of 1-(2-hydroxyethyl)-piperidin-2-one **24** (4.56 g, 32 mmol, 1 eq) in dry dichloromethane (20 ml) was added dropwise to an ice-cold, stirred solution of *t*-butyldimethylsilyl chloride (5.62 g, 1.1 eq, 37 mmol), dry triethylamine (4.9 ml, 1.1 eq, 37 mmol) and 4-dimethylaminopyridine (30 mg) in dry dichloromethane (200 ml). The solution was allowed to warm to room temperature and the stirring continued for 20 h.

Water (40 ml) was added and the layers separated. The aqueous layer was extracted with dichloromethane (3 x 50 ml). The combined organic extracts were washed with water (40 ml) and brine (40 ml), dried and evaporated to give a yellow oil. This was purified by column chromatography (silica; 2:1 ethyl acetate-petrol) to give the *title compound* **25** (8.13 g, 80%) as a colourless oil which showed υ_{max} 2952, 2931, 2858 and 1646 cm^{-1}; δ_H (250 MHz) 3.78 (2H, t, *J* 5.4, 2'-CH_2), 3.40-3.48 (4H, m, 6- & 1'-CH_2), 2.32-2.41 (2H, m, 3-CH_2), 1.73-1.82 (4H, m, 4- & 5-CH_2), 0.88 (9H, s, 3 x Me, ^{t}Bu) and 0.04 (6H, s, 2 x MeSi); δ_C (67.8 MHz) 169.9 (2-C), 61.5 (2'-CH_2), 50.3 & 50.2 (6- & 1'-CH_2), 32.3 (3-CH_2) 25.9 (Me, ^{t}Bu), 23.4 & 22.3 (4- & 5-CH_2) and 18.2 (C, ^{t}Bu), [Si**Me** below 0 ppm]; *m/z* (EI) 242 (9%, M^+-Me), 200 (100, M^+-^{t}Bu), 156 (14), 101 (8) and 73 (11).

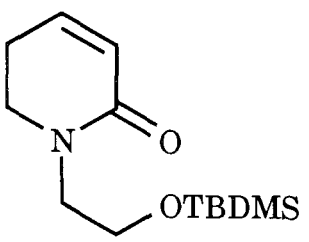
1-(2-*t*-Butyldimethylsilyloxyethyl)-3-(phenylseleno)-piperidin-2-one 26



To a stirred solution of diisopropylamine (2.3 ml, 16.4 mmol, 2.1 eq) in THF (50 ml) maintained at -10°C, was added butyllithium (1.6M in hexanes, 10.3 ml, 16.5 mmol, 2.1 eq) and the mixture stirred for 30 min. To this was added amide **25** (2.02 g, 7.8 mmol, 1 eq) and the mixture stirred for a further 1 h at -10°C, whereupon a solution of phenylselenenyl chloride (1.806 g, 9.4 mmol, 1.2 eq) in THF (10 ml) was added at 0°C and the mixture stirred for 1 h. The mixture was allowed to warm to ambient temperature and was stirred for a further 20 h.

Saturated aqueous ammonium chloride (10 ml) was then added and the mixture extracted with dichloromethane (3 x 30 ml). The combined organic extracts were dried and evaporated to give a brown oil which was purified by column chromatography (silica; 2:1 petrol-ethyl acetate) to give the *title compound* **26** (1.64 g, 51%) as a yellow-brown oil, which showed υ_{max} 3056, 2930, 2857, 1641, 1579 and 1490 cm^{-1}; δ_H (270 MHz) 7.60-7.64 (2H, m, Ar), 7.20-7.23 (3H, m, Ar), 3.96 (1H, t, *J* 5.3, 3-CH), 3.68-3.74 (2H, m, 2'-CH_2), 3.37-3.42 (4H, m, 6- & 1'-CH_2), 2.10-1.88 (3H, m, 4-CH & 5-CH_2), 1.65-1.75 (1H, m, 4-CH), 0.83 (9H, s, 3 x Me, ^tBu) and 0.00 (6H, s, 2 x MeSi); δ_C (67.8 MHz) 168.9 (2-C), 135.2 (CH), 129.3 (C), 129.0 (CH), 128.0 (CH), 61.4 (2'-CH_2), 50.7 & 50.2 (6- & 1'-CH_2), 43.0 (3-CH), 29.0 (4-CH_2), 25.9 (Me, ^tBu), 21.2 (5-CH_2), 18.2 (C, ^tBu) and 1.0 (MeSi); *m/z* (EI) 356 (37%, M^+-^tBu), 199 (100), 198 (45), 156 (16), 83 (17) and 73 (32).

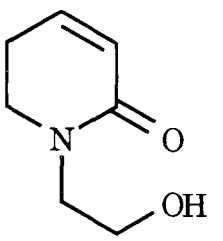
1-(2-*t*-Butyldimethylsilyloxyethyl)-5,6-dihydropyridin-2(1H)-one 28



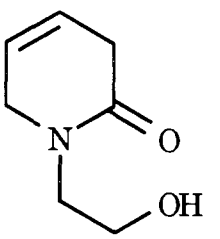
To a stirred solution of the selenide **26** (0.4273 g, 1.04 mmol, 1 eq) in THF (5 ml) at 0°C was added aqueous hydrogen peroxide (30 wt. %, 0.12 ml, 1.06 mmol, 1.02 eq) and the mixture stirred for 1.5 h. Saturated aqueous sodium sulphite (5 ml) was then added and the mixture stirred at 0°C for 10 min.

The organic layer was separated and the aqueous layer was extracted with ether (2 x 15 ml). The combined organic extracts were washed with brine (30 ml), dried and evaporated to give a crude product which was purified by column chromatography (silica; 2:1 petrol-ethyl acetate) to give the *title compound* **28** (0.224 g, 84.5%) as a colourless oil, which showed υ_{max} 1665 and 1611 cm^{-1}; λ_{max} (EtOH) 204.1 and 253.6 nm; δ_H (250 MHz) 6.55 (1H, ddd, *J* 9.8, 4.2 and 4.2, 4-CH), 5.92 (1H, ddd, *J* 9.8, 1.8 and 1.8, 3-CH), 3.78 (2H, t, *J* 5.3, 2'-CH_2), 3.55 (2H, t, *J* 7.1, 6-CH_2), 3.50 (2H, t, *J* 5.3, 1'-CH_2), 2.35 (2H, tdd, *J* 7.1, 4.2, 1.8, 5-CH_2), 0.89 (9H, s, 3 x Me, ^{t}Bu) and 0.05 (6H, s, 2 x MeSi); δ_C (67.8 MHz) 164.5 (2-C), 139.5 (4-CH), 125.6 (3-CH), 62.1 (1''-CH_2), 49.6 & 47.5 (6- & 1'-CH_2), 25.9 (Me, ^{t}Bu), 24.3 (5-CH_2) and 18.2 (C, ^{t}Bu), [Si**Me** below 0 ppm]; *m/z* (EI) 141 (8%, M^+-^{t}BDMS), 110 (100), 96 (25), 81 (79) and 53 (21).

1-(2-Hydroxyethyl)-5,6-dihydropyridin-2(1H)-one 32



32



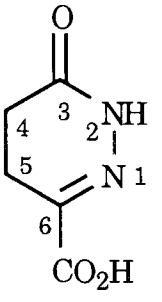
33

To a stirred solution of the silyl-protected alcohol **28** (0.054 g, 0.21 mmol, 1 eq) in THF (2 ml) at room temperature was added tetrabutylammonium fluoride (1.1M in THF, 0.20 ml, 0.22 mmol, 1.05 eq) and the mixture stirred for 1 h (followed by tlc).

Water (1 ml) was then added and the mixture extracted with dichloromethane (3 x 3 ml). The combined organic extracts were dried and evaporated and the crude product was purified by column chromatography (silica; 94:6 dichloromethane-methanol) to give a mixture of alcohols **32** and **33** (*ca.* 85:15, 0.026 g, 86%) as a colourless oil. The major product **32** showed υ_{max} 3392, 1667, 1600, 1494, 1058, 914, 817 and 732 cm^{-1}; δ_H (250 MHz) 6.58 (1H, ddd, *J* 9.8, 4.2 and 4.2, 4-CH), 5.92 (1H, ddd, *J* 9.8, 1.8 and 1.8, 3-CH), 3.78 (2H, t, *J* 5.3, 2'-CH_2), 3.55 (2H, t, *J* 5.3, 1'-CH_2), 3.51 (2H, t, *J* 7.2, 6-CH_2), 3.28 (1H, br s, OH), 2.40 (2H, tdd, *J* 7.2, 4.2, 1.8, 5-CH_2); δ_C (67.8 MHz) 166.1 (2-C), 140.0 (4-CH), 125.1 (3-CH), 61.6 (2'-CH_2), 50.6 (1'-CH_2), 47.0 (6-CH_2) and 24.2 (5-CH_2).

5.3 "Triquat" (Section 3.4)

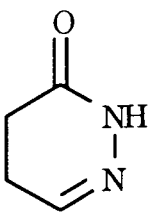
1,4,5,6-Tetrahydro-6-oxopyridazine-3-carboxylic acid 70



A solution of 2-ketoglutaric acid (82 g, 0.56 mol) in water (200 ml) at 50°C was slowly added to a solution of sodium hydroxide (49.63 g, 1.24 mol) and hydrazine sulphate (73.37 g, 0.56 mol) in water (300 ml) at 50°C. The solution was heated to 95°C whereupon precipitation was observed. The solution was kept at *ca.* 95°C for a further 2 h.

The solid was filtered and recrystallised from 2M hydrochloric acid to give the *title compound* **70** (79.3 g, 88%) as a white solid, which showed m.p. 204°C (lit[44] 194-5°C); λ_{max} 266 nm; υ_{max} (KBr) 3400-3100, 1734, 1672 and 1628 cm^{-1}; δ_H (250 MHz, acetone) 11.17 (1H, br s, CO_2H), 10.39 (1H, br s, NH), 4.70-4.20 (2H, br s, H_2O), 2.87 (2H, t, *J* 8.6, 4-CH_2) and 2.51 (2H, t, *J* 8.6, 5-CH_2); δ_C (67.8 MHz, acetone) 167.8 (C=O), 164.6 (C=O), 143.2 (3-C), 26.3 (CH_2) and 21.4 (CH_2); *m/z* (EI) 142 (100%, M^+), 124 (29), 69 (30) and 55 (57). [Found: C, 37.29; H, 5.00; N, 17.57. $C_5H_6N_2O_3.H_2O$ requires C, 37.50; H, 5.03; N, 17.50%].

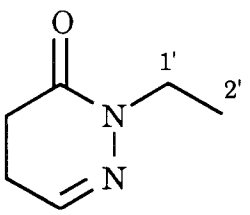
4,5-Dihydro-3(2H)-pyridazinone 66



A suspension of the carboxylic acid **70** (11.4 g, 0.07 mol) in diphenyl ether (20 ml) was carefully heated until evolution CO_2 was

observed. The suspension was heated gently until no more effervescence was observed. The product was separated from the diphenyl ether using a silica wash column. First, the diphenyl ether was removed by eluting with hexane, then the crude product was isolated by eluting with ethyl acetate. The product was purified by distillation (b.p. 82°C @ 0.5 mmHg) yielding the *title compound* **66** (5.92 g, 84.4%) as a white crystalline solid, which showed m.p. 39.5-41.5°C (lit[44] 41°C); λ_{max} 239.7 nm and inflections at 243 and 252 nm; υ_{max} (KBr) 3257, 1680 and 1636 cm^{-1}; δ_H (250 MHz) 9.12 (1H, br s, NH), 7.17 (1H, t, *J* 3.0, 6-CH) and 2.60-2.40 (4H, m, 4- & 5-CH_2); δ_C (67.8 MHz) 167.5 (3-C), 144.2 (6-CH), 25.1 (CH_2) and 22.0 (CH_2); *m/z* (EI) 98 (100%, M^+) and 55 (24). [Found: C, 48.69; H, 6.12; N, 28.42. $C_4H_6N_2O$ requires C, 48.97; H, 6.17; N, 28.56%].

2-Ethyl-4,5-dihydro-3(2H)-pyridazinone 71

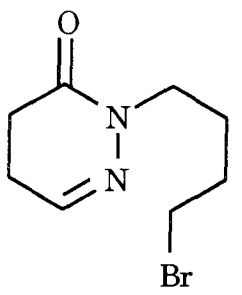


Sodium hydride (60% in mineral oil, 110 mg, 2.2 mmol, 1.1 eq) was washed with dry diethyl ether. To the resulting solid was added dry DMF (10 ml) followed by a solution of pyridazinone **66** (196 mg, 2 mmol, 1 eq) in dry DMF (5 ml) which was added dropwise with stirring. The resulting mixture was stirred for 0.5h whereupon bromoethane (280 mg, 2.2 mmol, 1.1 eq) was quickly added and the resulting mixture was stirred for a further 22 h.

Water (30 ml) was added, followed by extraction with chloroform (2 x 20 ml). The combined organic extracts were washed with water (10 ml),

dried and evaporated under reduced pressure, yielding a dark brown oil which was purified by distillation (b.p. 110°C (oven temperature) @ 0.1 mmHg, Kugelröhr) to give the *title compound* **71** (118 mg, 46%) as a colourless oil, which showed λ_{max} 247.4 nm; υ_{max} 1673 and 1387 cm^{-1}; δ_H (270 MHz) 7.16 (1H, t, *J* 3.0, 6-CH), 3.76 (2H, q, *J* 7.1, 1'-CH_2), 2.50-2.30 (4H, m, 4- & 5-CH_2) and 1.16 (3H, t, *J* 7.1, 2'-CH_3); *m/z* (EI) 126 (100%, M^+) 111 (58), 84 (53), 83 (41) and 55 (31).

2-(4-Bromobutyl)-4,5-dihydro-3(2H)-pyridazinone 72

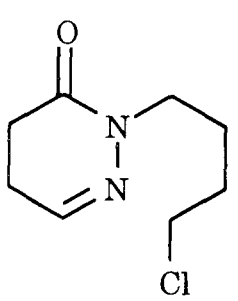


Sodium hydride (60% in mineral oil, 1.2737 g, 32 mmol, 1.1 eq) was washed with diethyl ether. To the resulting solid was added dry DMF (130 ml) and a solution of pyridazinone **66** (2.8350 g, 29 mmol, 1 eq) in dry DMF (20 ml) was then added dropwise with stirring. The mixture was stirred for 0.5h whereupon 1,4-dibromobutane (6.8635 g, 32 mmol, 1.1 eq) was quickly added and the resulting mixture was stirred for a further 22 h at ambient temperature.

Water (10 ml) was added and then the mixture was concentrated by removal of the DMF by distillation under reduced pressure using an oil pump (*ca.* 26°C @ 1 mmHg). Water (10 ml) was added to the residue followed by extraction with chloroform (3 x 20 ml). The combined organic extracts were washed with water (20 ml), dried and evaporated, yielding a dark brown oil which was separated by column chromatography (silica; 6:1 ethyl acetate-petrol) to give the *title compound* **72** (2.405 g, 36%) as a

pale yellow oil, which showed λ_{max} 248 nm; υ_{max} 1670 cm^{-1}; δ_H (270 MHz) 7.21 (1H, t, *J* 3.0, 6-CH), 3.79 (2H, t, *J* 6.6, 1'-CH_2), 3.44 (2H, t, *J* 6.3, 4'-CH_2), 2.57-2.43 (4H, m, 4-CH_2 & 5-CH_2) and 1.93-1.73 (4H, m, 2'- & 3'-CH_2); *m/z* (EI) 234 (3), 232 (4%, M^+) 153 (95), 111 (100), 98 (14), 83 (35) and 55 (11). [Found: C, 41.44; H, 6.01; N, 11.99. $C_8H_{13}BrN_2O$ requires C, 41.22; H, 5.62; N, 12.02%].

2-(4-Chlorobutyl)-4,5-dihydro-3(2H)-pyridazinone 73

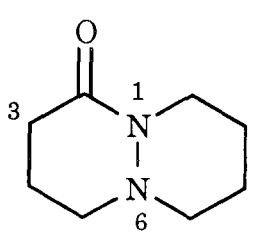


Sodium hydride (60% in mineral oil, 0.2637 g, 6.6 mmol, 1.13 eq) was washed with diethyl ether. To the resulting solid was added dry DMF (20 ml) and THF (20 ml) at 20°C followed by a solution of pyridazinone **66** (0.5739 g, 5.9 mmol, 1 eq) in dry THF (10 ml) which was added dropwise, with stirring. The resulting solution was stirred for 0.5h whereupon 1-bromo-4-chlorobutane (0.74 ml, 6.5 mmol, 1.1 eq) was quickly added and the resulting mixture stirred for a further 4.5 h.

Water (10 ml) was added and then the mixture was concentrated by removal of the DMF by distillation under reduced pressure using an oil pump (*ca.* 26°C @ 1 mmHg). Water (10 ml) was added to the mixture followed by extraction with chloroform (3 x 20 ml). The combined organic extracts were washed with water (20 ml), dried and evaporated, yielding a dark brown oil which was purified by column chromatography (silica; 6:1 ethyl acetate-petrol) to give the *title compound* **73** (0.7537 g, 68%) as a pale yellow oil, which showed λ_{max} 248.8 nm; υ_{max} 1670 cm^{-1}; δ_H (270

MHz) 7.21 (1H, t, *J* 3.0, 6-CH), 3.79 (2H, t, *J* 6.6, 1'-CH_2), 3.57 (2H, t, *J* 6.3, 4'-CH_2), 2.60-2.40 (4H, m, 4-CH_2 & 5-CH_2) and 1.90-1.70 (4H, m, 2'- & 3'-CH_2); δ_C (67.8 MHz) 165.4 (3-C), 144.7 (6-CH), 47.2 (CH_2), 44.6 (CH_2), 29.7 (CH_2), 26.4 (CH_2), 25.4 (CH_2) and 22.77 (CH_2); *m/z* (EI) 190 (4), 188 (10%, M^+) 153 (56), 111 (100), 98 (17), 83 (37) and 55 (10). [Found: C, 50.75; H, 7.14; N, 14.95. $C_8H_{13}ClN_2O$ requires C, 50.93; H, 6.94; N, 14.85%].

1,6-Diazabicyclo[4,4,0]decan-2-one 67



Method A

To a stirred solution of 2-(4-bromobutyl)-4,5-dihydro-3(2H)-pyridazinone **72** (0.7622 g, 3.3 mmol) in ethanol (34 ml) was added 2M hydrochloric acid (3 ml) at room temperature. After 5 min, sodium cyanoborohydride (0.25 g, 4 mmol, 1.2 eq) was added and the reaction mixture stirred for 4 h.

Evaporation of the solvent, followed by addition of water (2 ml) and extraction with dichloromethane (3 x 10 ml) afforded 0.4719 g of crude product which was purified by column chromatography (silica; 6:1 ethyl acetate-petrol) yielding the *title compound* **67** (0.3302 g, 66%) as a light yellow oil, which showed b.p. 96°C @ 0.5 mmHg, λ_{max} 234 and 208 nm; υ_{max} (LF) 1636 cm^{-1}; δ_H (400 MHz) 3.73 (2H, t, *J* 5.5, 10-CH_2), 3.13 (2H, t, *J* 5.6, 5-CH_2), 2.83 (2H, t, *J* 5.5, 7-CH_2), 2.46 (2H, t, *J* 6.9, 3-CH_2), 1.95-1.85 (2H, m, 4-CH_2), 1.85-1.75 (2H, m, 8-CH_2) and 1.60-1.50 (2H, m, 9-CH_2); δ_C (100.6 MHz) 166.2 (2-C), 55.1 (7-CH_2), 51.7 (5-CH_2), 43.7

(10-CH_2), 30.2 (3-CH_2), 24.8 (8-CH_2), 23.7 (9-CH_2) and 17.0 (4-CH_2); *m/z* (EI) 154 (100%, M^+) 126 (24), 125 (26), 98 (35), 97 (35) and 85 (29).

Method B

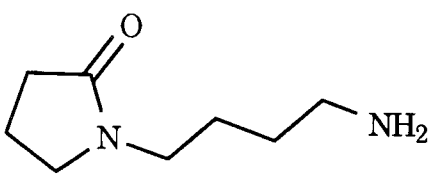
To a stirred solution of 2-(4-chlorobutyl)-4,5-dihydro-3(2H)-pyridazinone **73** (7.51 g, 40 mmol) in ethanol (200 ml) was added 2M hydrochloric acid (20 ml) and the resulting solution heated to 55°C. After 20 min, sodium cyanoborohydride (2.5 g, 40 mmol, 1 eq) was added and the reaction mixture was stirred at 55°C for 24 h. The intermediate "amine" **75** can be isolated if the reduction was carried out at room temperature.

Acetone (20 ml) was added and the solvent was evaporated. Addition of brine (20 ml) and extraction with dichloromethane (3 x 30 ml) resulted in the isolation of crude product (5.3 g) which was purified by column chromatography (silica; 6:1 ethyl acetate-petrol) yielding the *title compound* **67** (3.633 g, 59%).

Method C

The bicyclic compound **67** can also be synthesised directly from pyridazinone **66** without purification of the intermediate *N*-chlorobutyl compound **73**. Thus, pyridazinone **66** (15.985 g, 0.163 mol), sodium hydride (7.41 g, 0.185 mol, 1.14 eq) and 1-bromo-4-chlorobutane (31.044 g, 0.181 mol, 1.11 eq) in a 1:1 mixture of DMF/THF (800 ml) was reacted as above, and the solvent removed *in vacuo*. The crude alkylated product **73** was dissolved in ethanol (500 ml) and reduced using 2M hydrochloric acid (50 ml) and sodium cyanoborohydride (11.53 g, 0.183 mol, 1.13 eq). Work-up (as above) and purification by column chromatography yielded the *title compound* **67** (16.55 g, 66% over 2 steps).

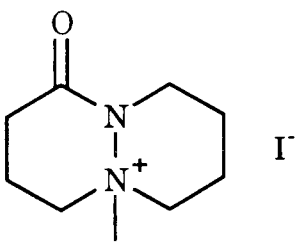
1-(4-Aminobutyl)-pyrrolidin-2-one 76



To a solution of bicycle **67** (2.829g, 0.018 mol) in THF (5 ml) at -61°C was added liquid ammonia (200 ml) and the temperature of the solution was allowed to rise such that the ammonia was at gentle reflux. Sodium (*ca.* 2 g) was added in small portions over a 2 h period such that the ammonia solution had a permanent blue colouration.

Addition of ammonium chloride (4 g, 0.08 mol) resulted in immediate decolouration. The ammonia was allowed to evaporate slowly after removal of the cooling bath. The remaining solvent was evaporated and brine (20 ml) was added to the residue. Extraction with dichloromethane (3 x 30 ml) yielded the *title compound* **76** (2.35 g, 82%), which showed υ_{max} 3363 (br) and 1680 cm^{-1}; δ_H (250 MHz) 3.39 (2H, t, *J* 7.0, 5-CH_2), 3.29 (2H, t, *J* 7.1, 1'-CH_2), 2.73 (2H, t, *J* 6.8, 4'-CH_2), 2.38 (2H, t, *J* 7.1, 3-CH_2), 1.96-2.08 (2H, m, 4-CH_2) and 1.63-1.41 (4H, m, 2'-CH_2 & 3'-CH_2).

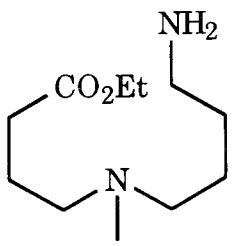
6-Methyl-1,6-diazabicyclo[4,4,0]decan-2-one iodide 78



A solution of bicycle **67** (1.91 g, 12 mmol) and methyl iodide (4.5 g, 2.6 eq, 32 mmol) in ether (5 ml) was stirred at reflux for 10 h (precipitation occurred after 10 min).

The solvent and excess methyl iodide were evaporated under reduced pressure to give an off-white solid. Any contaminants were separated by washing the largely insoluble product with dichloromethane, yielding the *title compound* **78** (2.708 g, 73.8%) as a white solid, which showed m.p. 180-181°C, υ_{max} (KBr) 1667 cm^{-1}; δ_H (400 MHz, DMSO) 4.59 (1H, ddd, *J* 14.0, 2.4 and 2.4), 4.09 (1H, ddd, *J* 12.4, 4.3 and 4.3), 4.01 (1H, ddd, *J* 12.1, 12.1 and 3.1), 3.83 (1H, m), 3.79 (1H, ddd, *J* 12.4, 12.4 and 3.2), 3.62 (3H, s, N-Me), 3.16 (1H, ddd, *J* 14.0, 14.0 and 3.0), 2.68 (1H, ddd, *J* 17.7, 10.4 and 7.4), 2.56 (1H, m), 2.39-2.00 (3H, m), 1.93-1.76 (2H, m) and 1.62-1.48 (1H, app qdd, *J* 13.3, 4.7 and 4.7); δ_C (67.8 MHz, d_6-DMSO) 167.0 (2-C), 67.3 (7-CH_2), 65.5 (5-CH_2), 48.3 (6-CH_3), 37.5 (10-CH_2), 29.5 (3-CH_2), 20.9 (CH_2), 17.9 (CH_2) and 14.7 (CH_2); *m/z* (FAB) 169 (100%, M^+-I), 154 (64), 136 (46), 107 (16), 89 (20) and 77 (22). [Found: C, 36.21; H, 6.00; N, 9.20. $C_9H_{17}IN_2O$ requires C, 36.50; H, 5.79; N, 9.46%].

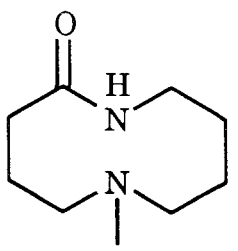
Ethyl 9-amino-5-aza-5-methyl-nonanoate 80



To a stirred solution of bicyclic salt **78** (23.9 mg, 0.08 mmol) in wet ethanol (10 ml) was added Raney nickel (90 mg) and the suspension subjected to hydrogenation at room temperature and 1 atm for 18 h.

The mixture was filtered through Kieselgühr and then dried and evaporated to give a colourless oil (16 mg, 92%), which showed υ_{max} 1727 cm^{-1}; δ_H (250 MHz) 4.15 (2H, q, *J* 7.0, $CO_2C\mathbf{H}_2$), 3.00-3.10 (2H, m, N-CH_2), 2.76-2.58 (4H, m, 2 x N-CH_2), 2.44 (3H, s, N-CH_3), 2.40 (2H, t, *J* 7, 2-CH_2), 2.07-1.72 (6H, m, 3 x CH_2) and 1.28 (3H, t, *J* 7, $CO_2CH_2C\mathbf{H}_3$).

5-Aza-5-methyl-nonanolactam 79

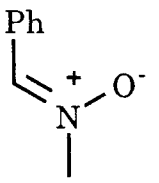


To a "damp" suspension of bicyclic salt **78** (1.9944 g, 6.7 mmol) in THF (1 ml) at -61°C was added liquid ammonia (60 ml) and the temperature of the solution allowed to rise such that the ammonia was at gentle reflux. Sodium (*ca.* 1.4 g, excess) was added in small portions over a 2 h period such that the ammonia solution had a permanent blue colouration.

Addition of ammonium chloride (0.92 g, 17 mmol, 2.6 eq) resulted in immediate decolouration. The ammonia was allowed to evaporate slowly after removal of the cooling bath. Dichloromethane (30 ml) was added to the residue, the resulting suspension filtered, the filtrate dried and the solvent removed under reduced pressure to give a crude product. This was purified by column chromatography (silica; 9:1 dichloromethane-methanol) to give the *title compound* **79** (1.007 g, 88%) as a white crystalline solid, which showed m.p. 105-106°C, υ_{max} (KBr) 3306, 1646 and 1563 cm^{-1}; δ_H (400 MHz) 8.19 (1H, br s, NH), 3.20 (2H, br s, 10-CH_2), 2.43 (2H, br s, 3-CH_2), 2.26 (7H, br s, 5- & 7-CH_2 & 6'-CH_3), 1.80 (2H, br s, 4-CH_2), 1.66 (2H, br s, 9-CH_2) and 1.61 (2H, br s, 8-CH_2); δ_C (100.6 MHz) 175.0 (2-C), 56.8 (CH_2), 56.1 (CH_2), 43.2 (CH_3), 40.2 (CH_2), 36.7 (CH_2), 29.7 (CH_2), 28.0 (CH_2) and 23.0 (CH_2); *m/z* (EI) 170 (57%, M^+), 98 (37), 84 (100), 71 (53), 70 (90), 58 (52) and 57 (94). [Found: C, 63.59; H, 10.97; N, 16.59. $C_9H_{18}N_2O$ requires C, 63.49; H, 10.65; N, 16.46%].

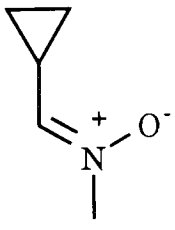
5.4 Nitrone Preparation

C-Phenyl-*N*-methyl nitrone 144



To a stirred solution of freshly distilled benzaldehyde (12.3 ml, 0.121 mol, 1.01 eq) and anhydrous potassium carbonate (18 g, 0.13 mol, 1.09 eq) in dichloromethane (100 ml) at room temperature under nitrogen was added *N*-methylhydroxylamine hydrochloride (10 g, 0.12 mol, 1 eq) and the mixture stirred for 16 h. The resulting mixture was filtered and evaporated to give an off-white solid which was recrystallised from ethyl acetate-petrol to yield the *title compound* **144** (14.51 g, 90%) as a flaky white solid, which showed m.p. 82-84°C (lit. 82-83°C[144]), υ_{max} (nujol mull) 1580, 1150, 945, 845, 770 and 715 cm^{-1} δ_H (250 MHz) 8.20-8.24 (2H, m, Ar), 7.38-7.44 (3H, m, Ar), 7.26 (1H, s, 1-CH) and 3.70 (3H, s, N-CH_3); δ_C (67.8 MHz) 134.5 (1-CH), 129.9 (C), 129.7 (CH), 127.8 (CH), 127.7 (CH) and 53.6 (N-CH_3).

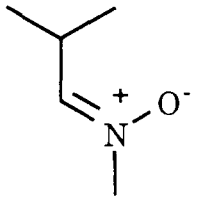
C-Cyclopropyl-*N*-methyl nitrone 298



The above procedure was followed using *N*-methyl hydroxylamine hydrochloride (1.195 g, 14.3 mmol), cyclopropylcarboxaldehyde (1.031 g, 14.7 mmol, 1.03 eq) and potassium carbonate (4 g, 28.9 mmol, 2.02 eq) in dichloromethane (50 ml) yielding the *title compound* **298** (1.35 g, 95%)[86] as a colourless oil (solidifies at *ca.* 0°C) which showed υ_{max} 1616, 1374,

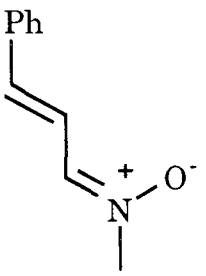
1148, 966 and 948 cm^{-1}; δ_H (400 MHz) 5.89 (1H, d, *J* 8.5, 1-CH), 3.27 (3H, s, N-CH_3), 1.97-1.99 (1H, m, 2-CH), 0.69-0.71 (2H, m, cy-CH_2) and 0.35-0.37 (2H, m, cy-CH_2); δ_C (67.8 MHz) 142.8 (1-CH), 51.2 (N-CH_3), 8.7 (2-CH) and 6.0 (3-CH_2).

_C_-Isopropyl-_N_-methyl nitrone 311



The above procedure was followed using *N*-methyl hydroxylamine hydrochloride (1.0365 g, 12.4 mmol), isobutyraldehyde (0.7 ml, 13.3 mmol, 1.07 eq) and potassium carbonate (3.47 g, 25.3 mmol, 2 eq) in dichloromethane (50 ml) yielding the *title compound* **311** (1.19 g, 95%)[144] as a colourless oil which showed υ_{max} 1606, 1410, 1206, 1124, 972 and 918 cm^{-1}; δ_H (250 MHz) 6.52 (1H, d, *J* 7.3, 1-CH), 3.63 (3H, s, N-CH_3), 3.00-3.20 (1H, m, 2-CH) and 1.07 (6H, d, *J* 7.0, 2 x 3-CH_3); δ_C (67.8 MHz) 145.4 (1-CH), 52.1 (N-CH_3), 25.6 (CH) and 18.4 (CH_3).

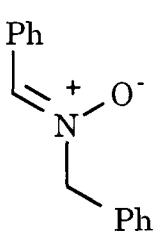
_C_-Styryl-_N_-methyl nitrone 314



The above procedure was followed using *N*-methyl hydroxylamine hydrochloride (0.42 g, 5 mmol), cinnamaldehyde (0.68 g, 5.1 mmol, 1.01 eq) and potassium carbonate (1.73 g, 12.5 mmol, 2.5 eq) in dichloromethane (40 ml) yielding the *title compound* **314** (0.74 g, 92%), as

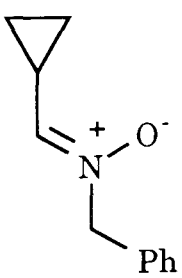
a white, needle-like, crystalline solid after recrystallisation (ethyl acetate-petrol) and showed m.p. 94-97°C, υ_{max} (soln) 1613, 1565, 1399, 1378, 1146, 970 and 952 cm^{-1}; δ_H (250 MHz) 7.49-7.51 (2H, m, Ar), 7.43 (1H, dd, *J* 16.3 and 9.5, 2-CH), 7.27-7.36 (3H, m, Ar), 7.23 (1H, d, *J* 9.5, 1-CH), 6.95 (1H, d, *J* 16.3, 3-CH) and 3.75 (3H, s, N-CH_3); δ_C (67.8 MHz) 138.0 (3-CH), 137.5 (1-CH), 135.9 (C), 129.1 (CH), 128.8 (CH), 127.2 (CH), 118.3 (2-CH) and 53.6 (CH_3).

C-Phenyl-N-benzyl nitrone 320



The above procedure was followed using *N*-benzylhydroxylamine hydrochloride (0.96 g, 6 mmol), benzaldehyde (0.62 ml, 6.1 mmol, 1.01 eq) and potassium carbonate (2.01 g, 15 mmol, 2.5 eq) in dichloromethane (40 ml) yielding the *title compound* **320** (1.14 g, 90%) as a white, needle-like, crystalline solid after recrystallisation (from ethyl acetate-petrol) and showed m.p. 82-84°C, δ_H (250 MHz) 8.30-8.20 (2H, m, Ar), 7.60-7.45 (9H, m, Ar & 1-CH) and 5.15 (2H, s, N-CH_2).

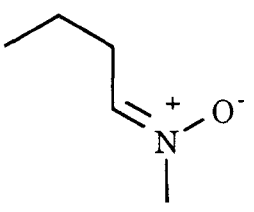
C-Cyclopropyl-N-benzyl nitrone 323



The above procedure was followed using *N*-benzyl hydroxylamine hydrochloride (1.22 g, 7.64 mmol), cyclopropylcarboxaldehyde (0.54 g, 7.7

mmol, 1.01 eq) and potassium carbonate (2.62 g, 19 mmol, 2.5 eq) in dichloromethane (50 ml) yielding the *title compound* **323** (1.3 g, 97%) as a white, crystalline solid (from ethyl acetate-petrol) which showed m.p. 131-134°C, υ_{max} 1608, 1456, 1309, 1124, 984 and 945 cm^{-1}; δ_H (250 MHz) 7.40-7.30 (5H, m, Ar), 6.05 (1H, d, *J* 8.5, 1-CH), 4.81 (2H, s, N-CH_2), 2.30-2.38 (1H, m, 2-CH), 0.96-1.01 (2H, m, cy-CH_2) and 0.58-0.62 (2H, m, cy-CH_2); δ_C (67.8 MHz) 142.1 (1-CH), 132.8 (C), 129.1 (CH), 128.8 (CH), 128.7 (CH), 68.6 (N-CH_2), 9.35 (2-CH) and 6.90 (3-CH_2). *m/z* (ES) 176 (MH^+, 100%).

C-Propyl-N-methyl nitrone 361

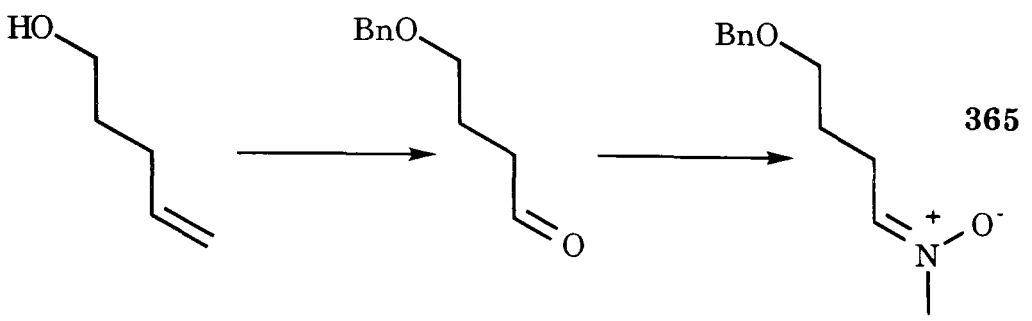


The above procedure was followed using *N*-methyl hydroxylamine hydrochloride (0.6 g, 7.2 mmol), *n*-butanal (0.65 ml, 7.3 mmol, 1.01 eq) and potassium carbonate (1.8 g, 13 mmol, 1.8 eq) in dichloromethane (30 ml) yielding the *title compound* **361** (0.62 g, 85%) as a colourless oil which showed υ_{max} 1609, 1465, 1409, 1171 and 1127 cm^{-1}; δ_H (250 MHz) 6.69 (1H, t, *J* 5.8, 1-CH), 3.65 (3H, s, N-CH_3), 2.40-2.50 (2H, m, 2-CH_2), 1.45-1.62 (2H, m, 3-CH_2) and 0.99 (2H, t, *J* 7.4, 4-CH_3); δ_C (67.8 MHz) 140.0 (1-CH), 51.9 (N-CH_3), 28.3 (2-CH_2), 18.5 (3-CH_2) and 13.6 (4-CH_3).

C-3-(Benzyloxy)propyl-N-methyl nitrone 365

A solution of pent-4-en-1-ol (2.084 g, 0.024 mol) in THF (5 ml) was added to a stirred suspension of sodium hydride (1.06 g, 0.0265 mol, 1.1 eq) in THF (45 ml) at room temperature and the mixture stirred for 1 h,

whereupon benzyl bromide (3.2 ml, 0.027 mol, 1.1 eq) and tetrabutylammonium iodide (0.1 g) were added. The resulting solution



365

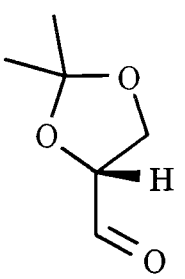
was stirred for a further 2 h at room temperature, and was then quenched with water (20 ml). The organic layer was separated and the aqueous layer was extracted with ether (3 x 25 ml). The combined organic solutions were dried and evaporated to give a yellow oil, which was purified by flash column chromatography to yield *1-(benzyloxy)-pent-4-ene*[170] (3.48 g, 82 %) as a pale yellow oil, which showed δ_H (250 MHz) 7.30-7.40 (5H, m, Ar), 5.83 (1H, dddd, *J* 17.0, 10.2, 6.6 and 6.6, 4-CH), 4.95-5.10 (2H, m, 5-CH_2), 4.52 (2H, s, O-CH_2Ph), 3.50 (2H, t, *J* 6.5, 1-CH_2), 2.09-2.20 (2H, m, 3-CH_2) and 1.65-1.80 (2H, m, 2-CH_2); δ_C (67.8 MHz) 138.6 (C), 138.2 (4-CH), 128.3 (CH), 127.6 (CH), 127.5 (CH), 114.7 (5-CH_2), 72.8 (O-CH_2), 69.7 (1-CH_2), 30.3 (3-CH_2) and 28.9 (2-CH_2).

Ozone was passed through a solution of 1-(benzyloxy)-pent-4-ene (1.07 g, 6.08 mmol) and Sudan red (indicator dye, 5 mg) in dichloromethane-methanol (100 ml, 9:1) at -78°C, until the red colouration of the dye had disappeared (*ca.* 50 min). Oxygen was passed through the solution for a further 5 min and then triethylamine (1 ml, 7.2 mmol, 1.2 eq) was added and the solution warmed to room temperature and stirred for a further 20 h. 2M Hydrochloric acid (50 ml) was added, the organic layer was separated and the aqueous layer was extracted

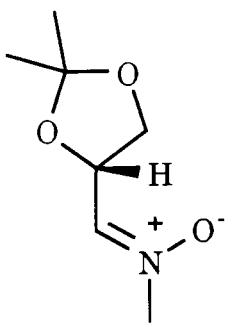
with dichloromethane (3 x 15 ml). The combined organic extracts were washed with saturated aqueous sodium hydrogencarbonate (50 ml), dried and evaporated to give *4-(benzyloxy)-butanal*[171] (1.04 g, 96 %) as a thin yellow oil which was not further purified and which showed δ_H (250 MHz) 9.80 (1H, t, *J* 1.5, 1-CH), 7.28-7.40 (5H, m, Ar), 4.50 (2H, s, O-CH_2Ph), 3.52 (2H, t, *J* 10.0, 4-CH_2), 2.57 (2H, ddd, *J* 7.1, 7.1 and 1.5, 2-CH_2) and 1.91-2.01 (2H, m, 3-CH_2); δ_C (67.8 MHz) 202.1 (1-CH), 138.0 (C), 128.2 (CH), 127.6 (CH), 127.4 (CH), 72.7 (O-CH_2), 68.9 (4-CH_2), 40.7 (2-CH_2) and 22.3 (3-CH_2).

The foregoing procedure for nitrone preparation was followed using *N*-methyl hydroxylamine hydrochloride (0.335 g, 4.01 mmol, 1.01 eq), 4-(benzyloxy)-butanal (0.71 g, 3.98 mmol, 1 eq) and potassium carbonate (1.00 g, 22 mmol, 2.2 eq) in dichloromethane (50 ml) yielding the *title compound* **365** (0.78 g, 95%) as a yellow oil, which was used without further purification and which showed δ_C (67.8 MHz) 139.8 (1-CH), 138.0 (C), 128.0 (CH), 127.3 (CH), 127.2 (CH), 72.6 (O-CH_2), 69.4 (4-CH_2), 51.9 (N-Me), 25.2 (2-CH_2) and 23.9 (3-CH_2).

D-isopropylidene glyceraldehyde nitrone 369



368



369

A solution of 1,2;5,6-diisopropylidene-D-mannitol (2.116 g, 8.07 mmol) and sodium periodate (3.49 g, 16.3 mmol, 2.02 eq) in

dichloromethane (100 ml) and water (4 ml) was stirred vigorously for 8 h.[149]

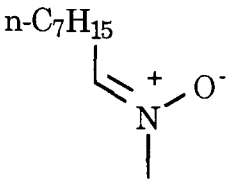
The suspension was dried and filtered and the dichloromethane was removed by distillation through a Vigreux column and the resulting oil was distilled under reduced pressure (b.p. 50-52°C @ 25 mmHg) to give *D-isopropylidene glyceraldehyde*[149] **368** (1.89 g, 90%) as a colourless oil, which showed δ_H (250 MHz) 9.73 (1H, d, *J* 1.9, 1-CH), 4.40 (1H, ddd, *J* 7.3, 4.8 and 1.9, 2-CH), 4.19 (1H, dd, *J* 8.8 and 7.3, 3-CHa), 4.11 (1H, dd, *J* 8.8 and 4.8, 3-CHb), 1.50 (3H, s, CH_3) and 1.43 (3H, s, CH_3).

The nitrone **369** was prepared using the foregoing procedure, with *N*-methylhydroxylamine hydrochloride (1.2 g, 14.3 mmol), aldehyde **368** (1.89 ml, 14.5 mmol, 1.01 eq) and potassium carbonate (8.4 g, 46 mmol, 3.2 eq) in dichloromethane (50 ml) yielding the *title compound* **369** (2.16 g, 95%) as a sensitive, colourless oil, which was sufficiently pure to be used without further purification, and which showed υ_{max} 1611, 1372, 1262, 1214, 1174, 1061, 966, 943 and 844 cm^{-1}; $[\alpha]_D^{22}$+133.2 (c 1.044 in $CHCl_3$)[143]; δ_H (250 MHz) 6.90 (1H, d, *J* 4.7, 1-CH), 5.12-5.20 (1H, m, 2-CH), 4.39 (1H, dd, *J* 8.7 and 7.0, 3-CHa), 3.95 (1H, dd, *J* 8.7 and 5.5, 3-CHb), 3.70 (3H, s, N-CH_3), 1.45 (3H, s, CH_3) and 1.39 (3H, s, CH_3); δ_C (67.8 MHz) 140.5 (1-CH), 110.2 (C, isopropylidene), 72.1 (2-CH), 68.0 (3-CH_2), 52.5 (N-CH_3), 26.6 (CH_3) and 25.3 (CH_3).

C-Heptyl-N-methyl nitrone

The above procedure was followed using *N*-methyl hydroxylamine hydrochloride (0.665 g, 7.96 mmol), *n*-octanal (1.3 ml, 8.3 mmol, 1.04 eq) and potassium carbonate (3.04 g, 22 mmol, 2.2 eq) in dichloromethane (50 ml) yielding the *title compound* (1.06 g, 85%) as a colourless oil which

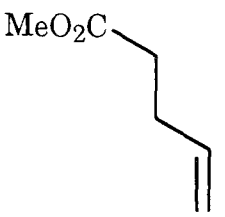
showed υ_{max} 1609, 1465, 1409, 1171, 1127, 1029 and 942 cm^{-1} δ_H (250 MHz) 6.68 (1H, t, *J* 5.8, 1-CH), 3.69 (3H, s, N-CH_3), 2.35-2.48 (2H, m, 2-



CH_2), 1.42-1.55 (2H, m, 3-CH_2), 1.24-1.00 (8H, br m, 4-, 5-, 6- & 7-CH_2) and 0.84 (2H, t, *J* 6.8, 8-CH_3); δ_C (67.8 MHz) 140.1 (1-CH), 51.7 (N-CH_3), 31.1 (2-CH_2), 28.9 (CH_2), 28.4 (CH_2), 26.3 (CH_2), 24.9 (CH_2), 22.1 (CH_2) and 13.5 (8-CH_3).

5.5 EWG = Ester (Section 4.7)

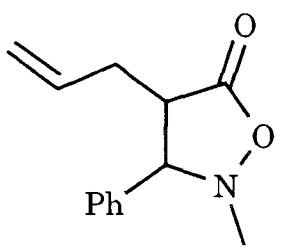
Methyl pent-4-enoate 235



To a stirred solution of pent-4-enoic acid (2.0 g, 20 mmol), methanol (0.77 ml, 0.019 mol) and 4-dimethylaminopyridine (20 mg) in dichloromethane (40 ml) at 0°C under nitrogen was added, dropwise, a solution of dicyclohexylcarbodiimide (3.93 g, 0.019 mol) in dichloromethane (40 ml) and the mixture stirred for 4 h, whereupon the cooling bath was removed and stirring continued for a further 19 h. The mixture was filtered, the solvent was reduced to *ca.* 5 ml under reduced pressure at *ca.* 0°C and pentane was added. The mixture was then filtered again and the solvent removed under reduced pressure again at *ca.* 0°C. The crude oil was distilled (b.p. 35°C, 10 mmHg) to give the *title compound* **235** (1.4 g, 58%)[158] as a colourless oil, which showed δ_H (250 MHz) 5.74-

5.92 (1H, m, 4-CH), 4.95-5.10 (2H, m, 5-CH_2), 3.69 (3H, s, CH_3) and 2.35-2.45 (4H, m, 2- & 3-CH_2).

5-Methyl-4-phenyl-3-(2-propenyl)-oxazolidin-2-one 238



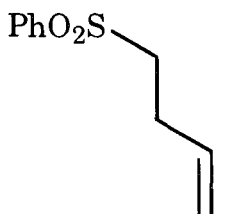
To a stirred solution of diisopropylamine (0.23 ml, 1.64 mmol, 1.1 eq) in THF (15 ml) at 0°C was added butyl lithium (1.6M, 1 ml, 1.075 eq) and the mixture stirred for 30 min. The resulting solution was cooled to -78°C and a solution of methyl pent-4-enoate **235** (0.1698g, 1.49 mmol, 1 eq) in THF (2 ml) was added over 10 min and the resulting solution stirred for a further 10 min. A solution of *C*-phenyl-*N*-methyl nitrone **144** (0.201g, 1.49 mmol, 1 eq) in THF (2 ml) was then added quickly at -78°C and stirring was continued at this temperature for a further 40 min. The reaction was quenched with saturated aqueous ammonium chloride (10 ml) and warmed to room temperature, when the organic layer was separated and the aqueous layer extracted with diethyl ether (3 x 10 ml). The combined organic solutions were dried and evaporated to give a yellow/brown oil which was separated by silica column chromatography (14:1 petrol-ethyl acetate) to give the *title compound* **238** (0.038 g, 12%) as a colourless oil, which showed δ_H (250 MHz) 7.28-7.48 (5H, m, Ar), 5.55-5.70 (1H, m, 2'-CH), 4.88-5.00 (2H, m, 3'-CH_2), 4.30-4.45 (1H, m, 4-CH), 3.00-3.14 (1H, m, 3-CH), 2.85 (3H, s, N-CH_3), 2.32-2.50 (1H, m, 1'-CHa) and 1.95-2.10 (1H, m, 1'-CHb).

No other data was obtained.

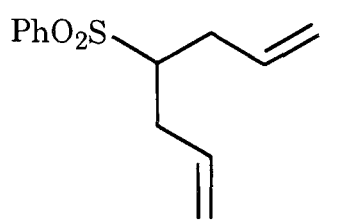
5.6 Sulphone Preparation

Method A

1-Phenylsulphonyl-but-3-ene 247 and 4-phenylsulphonyl-hepta-1,6-diene 248



247



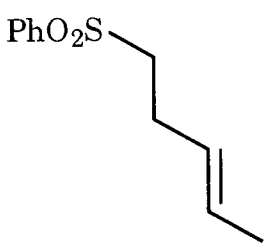
248

Method A followed the published procedure by Gaoni.[121]

To a suspension of magnesium powder (3.02 g, 120 mmol, 1.2 eq) in THF (5 ml) at room temperature were added a few drops of bromoethane until a reaction was seen to occur, whereupon more THF (55 ml) was added. The remaining bromoethane (10.3 ml, 120 mmol, 1.2 eq) was then added carefully keeping the THF at reflux. The solution was kept at reflux for a further 30 min after completion of the addition, whereupon a solution of methyl phenyl sulphone (15.63 g, 100 mmol, 1 eq) in benzene (100 ml) was quickly added. The mixture was allowed to stir for 10 min and was then brought quickly to reflux using a preheated oil bath and stirred for a further 5 min. The mixture was then cooled to around 20°C using an ice bath, whereupon allyl bromide (7.8 ml, 90 mmol, 0.9 eq) in benzene (8 ml) and a catalytic amount of copper(I) chloride (0.5 g, 5 mmol, 0.05 eq) were added. The reaction mixture was warmed to 50-60°C and stirred for a further 2 h, whereupon it was cooled to room temperature and poured into ice-cold 2M HCl (100 ml). The resulting mixture was extracted with ether (3 x 150 ml). The combined organic extracts were washed with brine (150 ml), dried and evaporated to give a yellow/brown oil which was separated by flash column

chromatography (4:1 petrol-ether) affording both monoalkylated sulphone[121] **247** (12.9 g, 73%) as a pale yellow oil which showed δ_H (250 MHz) 7.93 (2H, d, *J* 7.0, *o*-Ar), 7.70-7.50 (3H, m, Ar), 5.70 (1H, dddd, *J* 16.9, 10.3, 6.5 and 6.5, 3-CH), 4.95-5.10 (2H, m, 4-CH_2), 3.11-3.20 (2H, m, 1-CH_2) and 2.38-2.50 (2H, m, 2-CH_2); δ_C (67.8 MHz) 138.8 (C), 133.7 (3-CH), 129.2 (CH), 127.9 (CH), 117.0 (4-CH_2), 55.2 (1-CH_2) and 26.7 (2-CH_2); *m/z* (FAB) 197 (100%, M^++H), 143 (93) and 137 (58). [Found: MH^+, 197.0639. $C_{10}H_{12}O_2S$ requires MH^+, 197.0636] and the diallylated sulphone[121] **248** (0.71 g, 6.6%) as a pale yellow oil which showed υ_{max} 1641, 1313, 1135 and 992 cm^{-1}; δ_H (250 MHz) 7.90 (2H, d, *J* 6.9, *o*-Ar), 7.70-7.54 (3H, m, Ar), 5.78-5.66 (2H, m, 2 & 6-CH), 5.10-5.00 (4H, m, 1 & 7-CH_2), 3.10 (1H, pentet, *J* 4.9, 4-CH) and 2.66-2.34 (4H, m, 3- & 5-CH_2); δ_C (67.8 MHz) 137.6 (C), 133.6 (CH, Ar), 133.1 (2 & 6-CH), 129.0 (CH), 128.7 (CH), 118.3 (1 & 7-CH_2), 63.5 (4-CH) and 31.5 (3 & 5-CH_2); *m/z* (FAB) 237 (100%, MH^+), 143 (74) and 95 (79). [Found: M^++H, 237.0959. $C_{13}H_{16}O_2S$ requires MH^+, 237.0949].

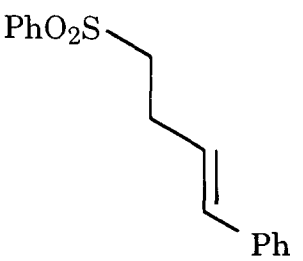
1-Phenylsulphonyl-pent-3-ene 274



The above procedure was followed using ethylmagnesium bromide (30 mmol, 1.2 eq) in THF (15 ml), methyl phenyl sulphone (3.88 g, 25 mmol, 1 eq) in benzene (25 ml), crotyl chloride (2.2 ml, 22 mmol, 0.91 eq) in benzene (2.2 ml) and copper(I) chloride (0.15 g, 0.06 eq) yielding the *title compound* **274** (3.15 g, 68%)[159] as a colourless oil, after column chromatography (silica, 3:1 petrol-ether), which showed υ_{max} 1447, 1306,

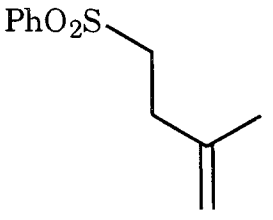
1145, 1087, 968, 736 and 690 cm^{-1}; δ_H (250 MHz) 7.90 (2H, d, *J* 7.0, *o*-Ar), 7.71-7.50 (3H, m, Ar), 5.57-5.49 (1H, m, :CH), 5.47-5.21 (1H, m, :CH), 3.02-3.12 (2H, m, 1-CH_2), 2.43-2.35 (2H, m, 2-CH_2) and 1.60 (3H, d, *J* 6.0, 5-CH_3); δ_C (67.8 MHz) 138.9 (C), 133.5 (CH), 129.1 (CH), 127.9 (CH), 127.8 (CH), 126.0 (CH), 55.8 (1-CH_2), 25.7 (2-CH_2) and 17.6 (5-CH_3).

1-Phenyl-4-phenylsulphonyl-but-1-ene 277



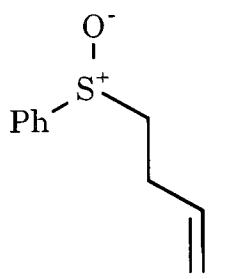
The above procedure was followed using ethylmagnesium bromide (30 mmol, 1.2 eq) in THF (15 ml), methyl phenyl sulphone (3.88 g, 25 mmol, 1 eq) in benzene (40 ml), cinnamyl chloride (3.15 ml, 23 mmol, 0.91 eq) in benzene (3.2 ml) and copper(I) chloride (0.15 g, 0.06 eq) yielding the *title compound* **277** (4.1 g, 69%)[167] after column chromatography (silica, 3:1 petrol-ether), which showed υ_{max} 1598, 1588, 1448, 1317, 1135, 1088 and 966 cm^{-1}; δ_H (250 MHz) 7.93 (2H, d, *J* 7.0, Ar), 7.67-7.51 (3H, m, Ar), 7.30-7.15 (5H, m, Ar), 6.47 (1H, d, *J* 15.8, 1-CH), 6.03 (1H, ddd, *J* 15.8, 6.85 and 6.85, 2-CH), 3.20-3.27 (2H, m, 4-CH_2) and 2.62 (2H, app q, *J* 6.9, 3-CH_2); δ_C (67.8 MHz) 138.8 (C), 136.5 (C), 133.6 (CH), 132.2 (CH), 129.2 (CH), 128.4 (CH), 127.9 (CH), 127.4 (CH), 125.9 (CH), 125.0 (CH), 55.5 (4-CH_2) and 26.2 (3-CH_2); *m/z* (FAB) 273 (81%, M^++H), 131 (89), 130 (100) and 91 (32). [Found: MH^+, 273.0956. $C_{16}H_{17}O_2S$ requires M, 273.0949].

3-Methyl-1-phenylsulphonyl-but-3-ene 280



The above procedure was followed using ethylmagnesium bromide (30 mmol, 1.2 eq) in THF (15 ml), methyl phenyl sulphone (3.88 g, 25 mmol, 1 eq) in benzene (40 ml), methallyl chloride (2.2 ml, 22 mmol, 0.91 eq) in benzene (2.2 ml) and copper(I) chloride (0.15 g, 0.06 eq) yielding the *title compound* **280** (2.85 g, 62%)[121] after column chromatography (silica, 3:1 petrol-ether), which showed υ_{max} 1651, 1586, 1448, 1318, 1132, 1088 and 899 cm^{-1}; δ_H (250 MHz) 7.87 (2H, d, *J* 6.9, *o*-Ar), 7.64-7.48 (3H, m, Ar), 4.69 (1H, app s, 4-CHa), 4.59 (1H, app s, 4-CHb), 3.13-3.20 (2H, m, 1-CH_2), 2.30-2.37 (2H, m, 2-CH_2) and 1.62 (3H, s, 3-CH_3); δ_C (67.8 MHz) 141.3 (C), 138.9 (C), 133.8 (CH, Ar), 129.3 (CH), 128.0 (CH), 111.9 (4-CH_2), 54.6 (1-CH_2), 30.3 (2-CH_2) and 22.3 (3'-CH_3); *m/z* (FAB) 211 (19%, M^++H), 143 (87), 69 (100) and 55 (59).

1-Phenylsulphinyl-but-3-ene 258

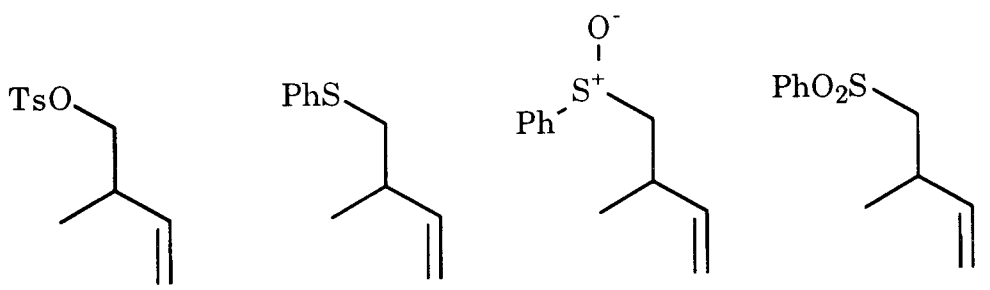


To a stirred solution of methyl phenyl sulphoxide (1.404 g, 10 mmol) in THF (30 ml) at -78°C under nitrogen, was slowly added butyl lithium (1.6M in hexanes, 6.8 ml, 10.9 mmol, 1.1 eq), and the solution

stirred at -78°C for 0.5 h. Allyl bromide (0.9 ml, 10.4 mmol, 1.04 eq) was added quickly and the mixture stirred at -78°C for a further 0.5 h, whereupon water (20 ml) was added and the reaction mixture warmed to room temperature. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dried and evaporated to give the crude product as a yellow/brown oil. This was purified by column chromatography (silica, 1:1 petrol-ether) to give *title compound* **258** (1.01 g, 56 %) as a colourless oil, which showed υ_{max} 1680, 1600, 1500, 1470, 1450, 1320, 1160, 1080, 910, 750 and 690 cm^{-1}, δ_H (250 MHz) 7.68-7.45 (5H, m, Ar), 5.80 (1H, dddd, *J* 17.0, 10.2, 6.6 and 6.6, 3-CH), 5.17-5.02 (2H, m, 4-CH_2), 2.78 (2H, t, *J* 7.0, 1-CH_2), 2.54-2.45 (1H, m, 2-CHa) and 2.42-2.25 (1H, m, 2-CHb); δ_C (67.8 MHz) 143.6 (C), 134.7 (3-CH), 130.8 (CH), 129.1 (CH), 123.8 (CH), 116.8 (4-CH_2), 55.8 (1-CH_2) and 30.0 (2-CH_2). *m/z* (ES) 181 (100%). [Found: MH^+, 181.0687. $C_{10}H_{13}OS$ requires M, 181.0687].

Method B

2-Methyl-1-phenylsulphonyl-but-3-ene 254



252 **253** **259** **254**

i) 2-Methyl-1-(toluenesulphonyl)-but-3-ene **252**

To a solution of 2-methylbut-3-en-1-ol (0.603 g, 7 mmol, 1 eq) in dichloromethane (50 ml) was added *p*-toluenesulphonyl chloride (1.87 g, 9.8 mmol, 1.4 eq), triethylamine (1.4 ml, 10 mmol, 1.4 eq) and 4-

dimethylaminopyridine (20 mg) and the mixture stirred for 24 h at room temperature. The resulting mixture was washed with 2M HCl (2 x 30 ml) and saturated aqueous sodium hydrogencarbonate (30 ml), dried and evaporated to give the *title compound* **252** (1.8 g, 100% by ^{1}H NMR)[160] as a pale yellow oil, which was used without further purification and which showed υ_{max} 1600, 1380, 1190, 950 and 810 cm^{-1}, δ_H (250 MHz) 7.70 (2H, d, *J* 8.3, Ar), 7.27 (2H, d, *J* 8.3, Ar), 5.55 (1H, ddd, *J* 17.3, 10.4 and 6.9, 3-CH), 5.00-5.1 (2H, m, 4-CH_2), 3.84 (1H, dd, *J* 9.4 and 6.4, 1-CHa), 3.76 (1H, dd, *J* 9.4 and 6.7, 1-CHb), 2.45-2.50 (1H, m, 2-CH), 2.36 (3H, s, CH_3-Ar) and 0.92 (3H, d, *J* 6.8, 2'-CH_3).

ii) 2-Methyl-1-(thiophenyl)-but-3-ene **253**

To a stirred solution of the tosylate **252** (1.8 g, 7.8 mmol) in THF (20 ml) at 0°C was added dropwise a solution of sodium thiophenoxide [9.8 mmol, 1.2 eq; made from thiophenol (1 ml) and sodium hydride (60%, 0.39 g) in DMF (10 ml) at 0°C during 5 min]. The reaction mixture was stirred for a further 10 min at 0°C and was then warmed to room temperature and stirred for a further 19 h. The reaction mixture was filtered through a pad of silica and the silica was washed with dichloromethane (20 ml). The filtrate was washed with 2M aqueous sodium hydroxide (2 x 20 ml), water (20 ml) and brine (20 ml) and then dried and evaporated to give the crude *title compound* **253** (1.31 g, 100% by ^{1}H NMR) as a yellow oil which was not further purified and which showed υ_{max} 1446, 1290, 1210, 1145, 1080 and 740 cm^{-1}, δ_H (250 MHz) 7.60-7.20 (5H, m, Ar), 5.97 (1H, ddd, *J* 17.3, 10.0 and 7.3, 3-CH), 5.18-5.26 (2H, m, 4-CH_2), 3.12 (1H, dd, *J* 12.5 and 6.8, 1-CHa), 2.99 (1H, dd, *J* 12.5 and 7.1, 1-CHb), 2.56-2.66 (1H, m, 2-CH) and 1.31 (3H, d, J 6.7, 2'-

CH_3); δ_C (67.8 MHz) 142.0 (3-CH), 136.8 (C), 128.8 (CH), 127.2 (CH), 125.5 (CH), 113.9 (4-CH_2), 40.1 (2-CH_2), 37.0 (2-CH) and 19.1 (CH_3).

iii) 2-Methyl-1-phenylsulphinyl-but-3-ene **259**

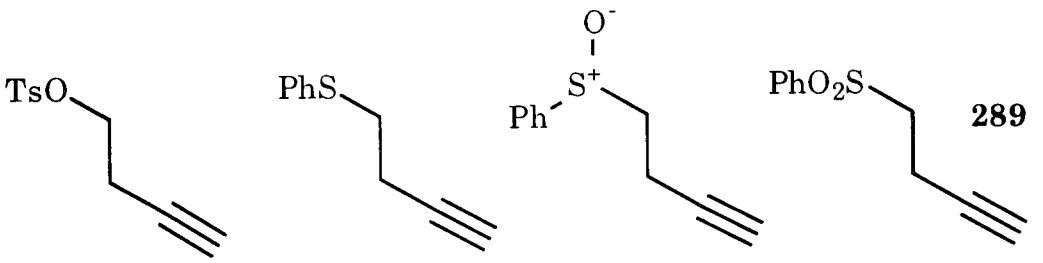
To a stirred solution of the thioether **253** (0.166 g, 0.93 mmol) in dichloromethane (10 ml) at 0°C, was slowly added, in portions, *m*-chloroperoxybenzoic acid (85%, 0.191 g, 0.94 mmol, 1.01 eq). The reaction mixture was stirred for a further 1 h at 0°C (until the thioether **253** had disappeared by tlc). The mixture was washed with 10% aqueous sodium carbonate (20 ml) and brine (20 ml) and was then dried and evaporated to give the crude product which was purified by column chromatography (silica, 1:1 petrol-ether) yielding the *title compound* **259** (*ca.* 1:1 mixture of diastereoisomers) as a pale yellow oil (0.116 g, 70%), which showed υ_{max} 1640, 1088 and 997 cm^{-1}; δ_H (250 MHz) 7.54-7.57 (2H, m, Ar), 7.41-7.46 (3H, m, Ar), 5.80-5.62 (1H, m, 3-CH), 5.20-4.91 (2H, m, 4-CH_2), 2.90-2.43 (3H, m, 1-CH_2 & 2-CH), 1.18 (1.5H, d, *J* 6.6, 2'-CH_3), 1.07 (1.5H, d, *J* 6.5, 2'-CH_3); δ_C (67.8 MHz) 144.5 & 144.1 (C), 141.0 & 140.3 (3-CH), 130.7 & 130.7 (CH), 129.3 & 125.0 (CH), 123.7 & 123.6 (CH), 114.2 & 115.4 (4-CH_2), 65.0 & 64.7 (1-CH_2), 33.1 & 32.4 (2-CH) and 20.2 & 18.6 (2'-CH_3); *m/z* (FAB) 195 (79%, MH^+), 123 (7), 77 (13) and 69 (100).

iv) 2-Methyl-1-(phenylsulphonyl)-but-3-ene **254**

To a stirred solution of thioether **253** (0.986 g, 5.53 mmol) in dichloromethane (50 ml) at 0°C, was slowly added, in portions, *m*-chloroperoxybenzoic acid (85%, 2.31 g, 11.4 mmol, 2.06 eq). The reaction mixture was stirred for a further 1.5 h at rt (until the sulphoxide intermediate **259** had all reacted according to tlc). The mixture was

washed with 10% aqueous sodium carbonate (50 ml) and brine (50 ml) and was then dried and evaporated to give the crude product which was purified by column chromatography (silica, 3:1 petrol-ether) to give the *title compound* **254** (1.09 g, 94%)[159] as a colourless oil, which showed υ_{max} 1450, 1310, 1210, 1145, 1080 and 755 cm^{-1}; δ_H (400 MHz) 7.90 (2H, d, *J* 7.2, *o*-Ar), 7.66-7.54 (3H, m, Ar), 5.71 (1H, ddd, *J* 17.3, 10.2 and 7.1, 3-CH), 4.93-5.02 (2H, m, 4-CH_2), 3.16 (1H, dd, *J* 14.1 and 6.2, 1-CHa), 3.03 (1H, dd, *J* 14.1 and 7.0, 1-CHb), 2.75-2.80 (1H, m, 2-CH) and 1.17 (3H, d, *J* 6.8, 2'-CH_3); δ_C (67.8 MHz) 140.6 (3-CH), 139.9 (C), 133.6 (CH), 129.2 (CH), 127.9 (CH), 114.5 (4-CH_2), 61.9 (1-CH_2), 32.7 (2-CH) and 19.9 (2'-CH_3); *m/z* (FAB) 211 (64%, MH^+), 143 (100), 69 (98) and 55 (57).

1-Phenylsulphonyl-but-3-yne 289



289

i) 1-(Toluenesulphonyl)-but-3-yne

The foregoing procedure was followed using but-3-yn-1-ol (2 ml, 26.4 mmol, 1 eq), *p*-toluenesulphonyl chloride (5.55 g, 29.1 mmol, 1.1 eq), triethylamine (4.1 ml, 29.4 mmol, 1.11 eq) and 4-dimethylaminopyridine (20 mg) in dichloromethane (150 ml) yielding the *title compound* (5.98g, 100% by ^1H NMR)[161] as a colourless oil, which showed υ_{max} 3307, 1600, 1300, 1150, 1080, 980, 900, 780 and 750 cm^{-1} δ_H (250 MHz) 7.81 (2H, d, *J* 8.2, *o*-Ar), 7.55 (2H, d, *J* 8.2, Ar), 4.10 (2H, dd, *J* 7.1 and 7.1, 1-CH_2), 2.56 (2H, td, *J* 7.1 and 2.6, 2-CH_2), 2.46 (3H, s, CH_3-Ar) and 1.98 (1H, t,

J 2.6, 4-CH); δ_C (67.8 MHz) 145.0 (C), 132.7 (CH), 129.8 (CH), 127.9 (CH), 78.3 (4-CH), 70.7 (3-C), 67.4 (1-CH_2), 21.6 (CH_3-Ar) and 19.4 (2-CH_2).

ii) 1-(Thiophenyl)-but-3-yne

The foregoing procedure was followed using sodium thiophenoxide (29 mmol, 1.09 eq) in DMF (10 ml) and 1-(toluenesulphonyl)-but-3-yne (5.98 g, 26 mmol) in THF (50 ml), yielding the *title compound* (4.5 g, 100% by ^{1}H NMR)[162] as a yellow oil, which showed δ_H (250 MHz) 7.60-7.10 (5H, m, Ar), 3.06 (2H, dd, *J* 7.4 and 7.4, 1-CH_2), 2.47 (2H, td, *J* 7.4 and 2.6, 2-CH_2) and 2.05 (1H, t, *J* 2.6, 4-CH).

iii) 1-Phenylsulphinyl-but-3-yne

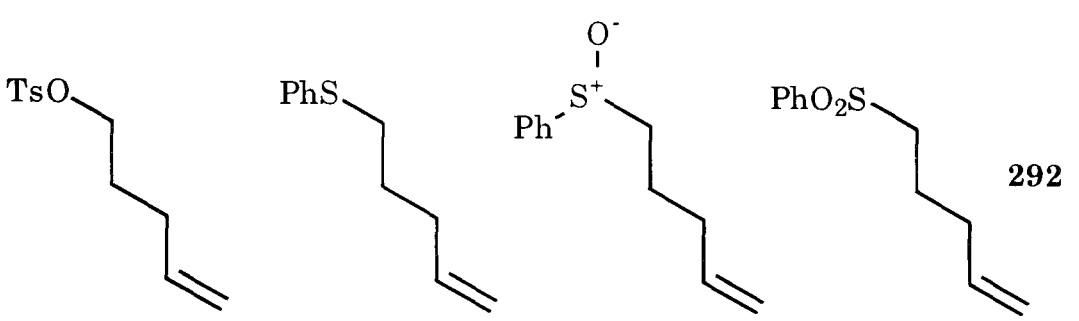
The foregoing procedure was followed using 1-(thiophenyl)-but-3-yne (0.65 g, 4 mmol) and *m*-chloroperoxybenzoic acid (85%, 0.65 g, 4.05 mmol, 1.01 eq) in dichloromethane (40 ml) yielding the *title compound* (0.35 g, 49%) as a colourless oil, which showed υ_{max} 3307, 1325 and 1086 cm^{-1}; δ_H (250 MHz) 7.60-7.64 (2H, m, Ar), 7.49-7.56 (3H, m, Ar), 3.07-2.84 (2H, m, 1-CH_2), 2.78-2.64 (1H, m, 2-CHa), 2.46-2.32 (1H, m, 2-CHb) and 2.10 (1H, t, *J* 2.6, 4-CH); δ_C (67.8 MHz) 142.6 (C), 130.8 (CH), 128.9 (CH), 123.5 (CH), 80.3 (4-CH), 70.3 (3-C), 54.6 (1-CH_2) and 11.5 (2-CH_2); *m/z* (FAB) 179 (44%, MH^+), 81 (40), 69 (61) and 55 (100).

iv) 1-Phenylsulphonyl-but-3-yne **289**

The foregoing procedure was followed using 1-(thiophenyl)-but-3-yne (0.65 g, 4 mmol) and *m*-chloroperoxybenzoic acid (85%, 1.5 g, 8.1

mmol, 2.2 eq) in dichloromethane (40 ml) yielding the *title compound* **289** (0.4 g, 51.5%) as a white solid, which showed υ_{max} 3307, 1340, 1319, 1134, 1088 and 977 cm^{-1}; δ_H (250 MHz) 7.90 (2H, d, *J* 7.1, *o*-Ar), 7.70-7.53 (3H, m, Ar), 3.28-3.34 (2H, m, 1-CH_2), 2.56-2.64 (2H, m. 2-CH_2) and 2.00 (1H, t, *J* 2.7, 4-CH); δ_C (67.8 MHz) 138.1 (C), 133.8 (CH), 129.1 (CH), 127.9 (CH), 79.1 (4-CH), 70.5 (3-C), 54.1 (1-CH_2) and 12.9 (2-CH_2); *m/z* (FAB) 195 (12%, MH^+), 81 (32), 69 (53) and 55 (85).

1-Phenylsulphonyl-pent-4-ene 292



292

i) 1-(Toluenesulphonyl)-pent-4-ene

The foregoing procedure was followed using pent-4-en-1-ol (0.244 g, 2.83 mmol, 1 eq), *p*-toluenesulphonyl chloride (0.80 g, 4.2 mmol, 1.5 eq), triethylamine (0.6 ml, 4.3 mmol, 1.5 eq) and 4-dimethylaminopyridine (20 mg) in dichloromethane (30 ml) yielding the *title compound* (0.73 g, 100% by ^1H NMR) as a colourless oil, which showed δ_H (250 MHz) 7.80 (2H, d, *J* 8.0, Ar), 7.35 (2H, d, *J* 8.0, Ar), 5.70 (1H, dddd, *J* 17.5, 9.8, 6.7 and 6.7, 4-CH), 4.91-5.00 (2H, m, 5-CH_2), 4.04 (1H, dd, *J* 6.4 and 6.4, 1-CH_2), 2.46 (3H, s, CH_3-Ar), 2.04-2.13 (2H, m, 3-CH_2) and 1.69-1.80 (2H, m, 2-CH_2).

ii) 1-(Thiophenyl)-pent-4-ene

The foregoing procedure was followed using sodium thiophenoxide (3.5 mmol, 1.2 eq) in DMF (4 ml) and 1-(toluenesulphonyl)-pent-4-ene (0.73 g, 2.8 mmol) in THF (10 ml) yielding the *title compound* (0.6 g, 100% by ^{1}H NMR) as a yellow oil, which showed υ_{max} 1640, 1600, 1490, 1450, 1080, 1030, 900, 730 and 690 cm^{-1}, δ_H (250 MHz) 7.40-7.10 (5H, m, Ar), 5.80 (1H, dddd, *J* 17.0, 10.2, 6.7 and 6.7, 4-CH), 4.98-5.10 (2H, m, 5-CH_2), 2.94 (2H, dd, *J* 7.4 and 7.4, 1-CH_2), 2.17-2.25 (2H, m, 3-CH_2) and 1.70-1.81 (2H, m, 2-CH_2); δ_C (67.8 MHz) 137.2 (4-CH), 136.6 (C), 128.6 (CH), 128.5 (CH), 125.4 (CH), 115.1 (5-CH_2), 32.5 (CH_2), 32.4 (CH_2) and 28.0 (CH_2).

iii) 1-Phenylsulphinyl-pent-4-ene

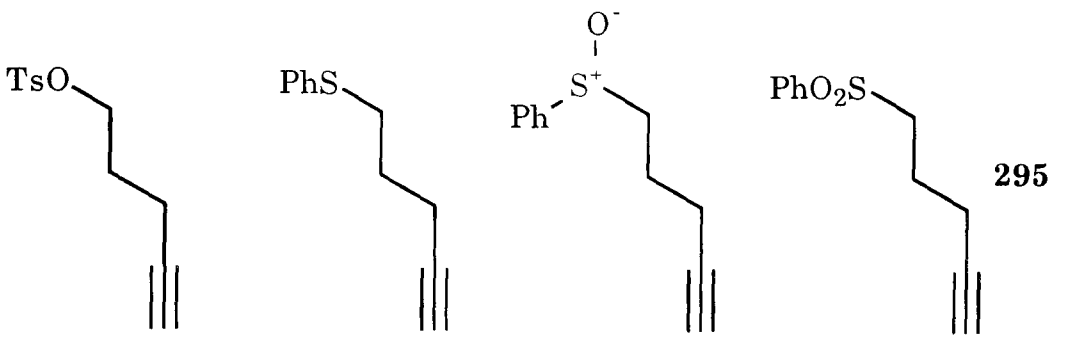
The foregoing procedure was followed using 1-(thiophenyl)-pent-4-ene (0.123 g, 0.69 mmol) and *m*-chloroperoxybenzoic acid (85%, 0.142 g, 0.70 mmol, 1.01 eq) in dichloromethane (10 ml) yielding the *title compound* (0.072 g, 54%) as a colourless oil, which showed δ_H (250 MHz) 7.61-7.64 (2H, m, Ar), 7.44-7.60 (3H, m, Ar), 5.72 (1H, dddd, *J* 17.0, 10.4, 6.7 and 6.7, 4-CH), 4.97-5.05 (2H, m, 5-CH_2), 2.75-2.84 (2H, m, 1-CH_2), 2.13-2.21 (2H, m, 3-CH_2) and 2.10-1.65 (2H, m, 2-CH_2); δ_C (67.8 MHz) 143.8 (C), 136.7 (3-CH), 130.8 (CH), 129.1 (CH), 123.9 (CH), 116.0 (5-CH_2), 56.3 (1-CH_2), 32.4 (3-CH_2) and 21.1 (2-CH_2).

iv) 1-Phenylsulphonyl-pent-4-ene **292**

The foregoing procedure was followed using 1-(thiophenyl)-pent-4-ene (0.176 g, 0.99 mmol) and *m*-chloroperoxybenzoic acid (85%, 0.444 g,

2.19 mmol, 2.2 eq) in dichloromethane (10 ml) yielding the *title compound* **292** (0.121 g, 58%)[163] as a colourless oil, which showed υ_{max} 1610, 1580, 1460, 1445, 1290, 1145, 1080, 750 and 690 cm^{-1}, δ_H (250 MHz) 7.89 (2H, d, *J* 7.0, *o*-Ar), 7.67-7.52 (3H, m, Ar), 5.66 (1H, dddd, *J* 17.7, 9.5, 6.7 and 6.7, 4-CH), 4.93-5.00 (2H, m, 5-CH_2), 3.04-3.10 (2H, m, 1-CH_2), 2.06-2.15 (2H, m, 3-CH_2) and 1.73-1.86 (2H, m, 2-CH_2); δ_C (67.8 MHz) 139.1 (C), 136.2 (3-CH), 133.6 (CH), 129.2 (CH), 128.0 (CH), 116.4 (5-CH_2), 55.4 (1-CH_2), 31.9 (3-CH_2) and 21.7 (2-CH_2). *m/z* (ES) 211(100). [Found: MH^+, 211.0793. $C_{11}H_{15}O_2S$ requires M, 211.0793].

1-Phenylsulphonyl-pent-4-yne 295



295

i) 1-(Toluenesulphonyl)-pent-4-yne

The foregoing procedure was followed using pent-4-yn-1-ol (0.331 g, 3.9 mmol, 1 eq), *p*-toluenesulphonyl chloride (1.16 g, 6.1 mmol, 1.5 eq), triethylamine (0.85 ml, 6.1 mmol, 1.5 eq) and 4-dimethylaminopyridine (20 mg) in dichloromethane (30 ml) yielding the *title compound* (1.08 g, 100% by ^1H NMR)[164] as a colourless oil, which showed υ_{max} 3310, 1600, 1330, 1150, 1080, 1005, 950, 900, 770 and 730 cm^{-1}, δ_H (250 MHz) 7.80 (2H, d, *J* 8.2, Ar), 7.34 (2H, d, *J* 8.2, Ar), 4.14 (2H, dd, *J* 6.1 and 6.1, 1-CH_2), 2.46 (3H, s, CH_3-Ar), 2.25 (2H, td, *J* 6.9 and 2.6, 3-CH_2) and 1.83-1.91 (3H, m, 2-CH_2 & 5-CH); δ_C (67.8 MHz) 144.7 (C), 132.8 (CH),

129.8 (CH), 127.8 (CH), 82.0 (5-CH), 69.4 (4-C), 68.6 (1-CH_2), 27.6 (3-CH_2), 21.5 (CH_3-Ar) and 14.6 (2-CH_2).

ii) 1-(Thiophenyl)-pent-4-yne

The foregoing procedure was followed using sodium thiophenoxide (3.4 mmol, 1.08 eq) in DMF (3 ml) and 1-(toluenesulphonyl)-pent-4-yne (0.75 g, 3.1 mmol) in THF (15 ml) yielding the crude *title compound* (0.70g, 100% by ^{1}H NMR)[162] as a colourless oil which showed υ_{max} 3310, 1600, 1460, 1440, 1145, 1090, 1030, 760 and 730 cm^{-1}, δ_H (250 MHz) 7.48-7.28 (5H, m, Ar), 3.14 (2H, dd, *J* 7.2 and 7.2, 1-CH_2), 2.45 (2H, td, *J* 6.9 and 2.6, 3-CH_2), 2.10 (1H, t, *J* 2.6, 5-CH) and 1.89-2.00 (2H, m, 2-CH_2); δ_C (67.8 MHz) 136.0 (C), 129.2 (CH), 128.8 (CH), 125.9 (CH), 83.2 (5-CH), 69.1 (4-C), 32.3 (1-CH_2), 27.7 (3-CH_2) and 17.3 (2-CH_2). m/z (ES) 172 (100).

iii) 1-Phenylsulphinyl-pent-4-yne

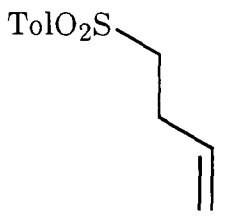
The foregoing procedure was followed using 1-(thiophenyl)-pent-4-yne (0.104 g, 0.59 mmol) and *m*-chloroperoxybenzoic acid (85%, 0.131 g, 0.64 mmol, 1.09 eq) in dichloromethane (10 ml) yielding the *title compound* (0.08 g, 70%) as a colourless oil, which showed υ_{max} 3310, 1445, 1290, 1145 and 1080 cm^{-1}, δ_H (250 MHz) 7.60-7.70 (2H, m, Ar), 7.50-7.59 (3H, m, Ar), 3.05-2.81 (2H, m, 1-CH_2), 2.29-2.37 (2H, m, 3-CH_2) and 2.07-1.79 (3H, m, 2-CH_2 & 5-CH); δ_C (67.8 MHz) 143.4 (C), 130.8 (CH), 129.1 (CH), 123.8 (CH), 82.2 (5-CH), 67.7 (4-C), 55.5 (1-CH_2), 20.8 (3-CH_2) and 17.4 (2-CH_2).

iv) 1-Phenylsulphonyl-pent-4-yne **295**

The foregoing procedure was followed using 1-(thiophenyl)-pent-4-yne (0.082 g, 0.47 mmol) and *m*-chloroperoxybenzoic acid (85%, 0.205 g, 1.01 mmol, 2.15 eq) in dichloromethane (10 ml) yielding the *title compound* **295** (0.08 g, 82%) as a colourless oil, which showed δ_H (250 MHz) 7.89 (2H, d, *J* 7.0, Ar), 7.70-7.50 (3H, m, Ar), 3.18-3.24 (2H, m, 1-CH_2), 2.28 (2H, td, *J* 6.8 and 2.6, 3-CH_2) 1.97 (1H, t, *J* 2.6, 5-CH) and 1.84-1.98 (2H, m, 2-CH_2); δ_C (67.8 MHz) 138.9 (C), 133.7 (CH), 129.3 (CH), 128.1 (CH), 81.7 (5-CH), 70.1 (4-C), 54.8 (1-CH_2), 21.6 (3-CH_2) and 17.2 (2-CH_2).

Method C

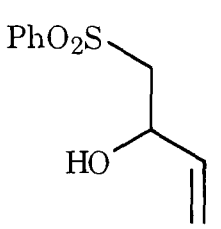
1-(Toluenesulphonyl)-but-3-ene 352



To a stirred solution of sodium *p*-toluenesulphinate (1.4 g, 6.5 mmol) in 1,2-dimethoxyethane (10 ml) under nitrogen at room temperature, were added 1-bromobut-3-ene (0.65 ml, 6.4 mmol, 0.98 eq) and tetrabutylammonium iodide (0.12 g, 0.3 mmol, 0.05 eq). The reaction mixture was then heated at reflux for 30 h. After cooling, water (20 ml) was added and the mixture was extracted with petrol (3 x 20 ml). The combined organic extracts were dried and evaporated to give a yellow/brown oil which was purified by column chromatography (silica, 3:1 petrol-ether) yielding the *title compound* **352** (1.06 g, 80%)[165] as a

colourless oil, which showed υ_{max} 1641, 1597, 1315, 1302, 1145 and 1088 cm^{-1}; δ_H (250 MHz) 7.75 (2H, d, *J* 8.1, Ar), 7.33 (2H, d, *J* 8.1, Ar), 5.69 (1H, dddd, *J* 16.9, 10.3, 6.5 and 6.5, 3-CH), 4.97-5.05 (2H, m, 4-CH_2), 3.11-3.15 (2H, m, 1-CH_2) and 2.36-2.45 (5H, m, 2-CH_2 & Me); δ_C (67.8 MHz) 144.6 (C), 135.8 (C), 133.7 (3-CH), 129.7 (CH, Ar), 127.9 (CH, Ar), 116.8 (4-CH_2), 55.2 (1-CH_2), 26.7 (2-CH_2) and 21.4 (CH_3, Ar); *m/z* (FAB) 211 (100%, MH^+), 157 (79), 137 (40) and 91 (24). [Found: MH^+, 211.0807. $C_{11}H_{14}O_2S$ requires M, 211.0793].

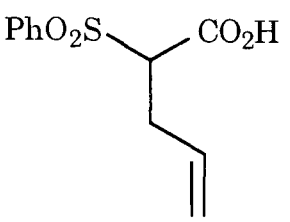
1-Phenylsulphonyl-but-3-en-2-ol 372



To a stirred solution of methyl phenyl sulphone (1.515 g, 9.7 mmol) in THF (60 ml) at -78°C under nitrogen, was slowly added butyl lithium (1.6M in hexanes, 6.7 ml, 1.1 eq), and the solution stirred at -78°C for 5 min and for a further 0.5 h at 0°C. The reaction mixture was cooled to -78°C whereupon acrolein (1 ml, 15 mmol, 1.5 eq) was added quickly and the mixture stirred at -78°C for 15 min. Water (20 ml) was added and the reaction mixture warmed to room temperature. The organic layer was separated and the aqueous layer was extracted with ether (3 x 20 ml). The combined organic extracts were dried and evaporated to give the *title compound* **372** (2.04 g, 94%)[166] as a colourless oil, which showed υ_{max} 3493 (br), 1447, 1304 and 1145 cm^{-1}; δ_H (250 MHz) 7.94 (2H, d, *J* 7.0, *o*-Ar), 7.72-7.55 (3H, m, Ar), 5.76 (1H, ddd, *J* 17.0, 10.4 and 5.5, 3-CH), 5.33 (1H, app d, *J* 17.0, 4-CHt), 5.17 (1H, app d, *J* 10.4, 4-CHc), 4.69 (1H, app br s, 2-CH), 3.41 (1H, d, *J* 1.6, OH) and 3.25-3.30 (2H, m, 1-CH_2); δ_C (67.8 MHz) 139.1 (C), 136.9 (CH), 133.8 (3-CH), 129.2 (CH),

127.7 (CH), 116.3 (4-CH_2), 66.7 (2-CH) and 61.6 (1-CH_2); *m/z* (FAB) 213 (11%, MH^+), 195 (57), 141 (53), 95 (35), 81 (41), 77 (45), 69 (70) and 55 (100).

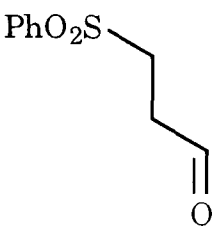
2-Phenylsulphonyl-pent-4-enoic acid 374



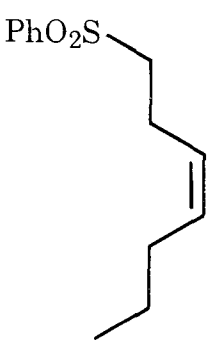
To a stirred solution of 1-(phenylsulphonyl)-but-3-ene **247** (0.196 g, 1 mmol) in THF (15 ml) at -78°C under nitrogen was slowly added butyl lithium (1.6M in hexanes, 0.69 ml, 1.1 eq), and the solution stirred at -78°C for 30 min. A dry carbon dioxide pellet (excess) was added and the mixture stirred at -78°C for 0.5 h, whereupon saturated aqueous sodium hydrogencarbonate (25 ml) and ether (15 ml) were added and the reaction mixture warmed to room temperature. The organic layer was separated. The aqueous layer was acidified with concentrated HCl (10 ml) and extracted with dichloromethane (3 x 10 ml). The combined organic extracts were dried and evaporated to give *title compound* **374** (0.205 g, 72%) as a colourless oil, which showed υ_{max} 3400-3000 (br), 1644 and 1586 cm^{-1}; δ_H (250 MHz) 10.00 (1H, br s, CO_2H), 7.88 (2H, d, *J* 7.3, Ar), 7.70-7.52 (3H, m, Ar), 5.65 (1H, dddd, *J* 16.9, 10.2, 6.9 and 6.9, 4-CH), 5.06-5.15 (2H, m, 5-CH_2), 4.04 (1H, dd, *J* 10.9 and 4.2, 2-CH) and 2.78-2.60 (2H, m, 3-CH_2); δ_C (67.8 MHz) 169.0 (1-C), 136.6 (C), 134.5 (CH), 131.3 (CH), 129.2 (CH), 129.1 (CH), 119.2 (5-CH_2), 69.9 (2-CH) and 30.8 (3-CH_2).

(Z)-1-Phenylsulphonyl-hept-3-ene 417

Ozone was passed through a solution of sulphone **247** (2 g, 0.01 mol) and Sudan red (indicator dye, 5 mg) in dichloromethane-methanol (100 ml, 9:1) at -78°C, until the red colouration of the dye had disappeared (*ca.* 1 h). Oxygen was passed through the solution for a further 5 min and then triethylamine (1.6 ml, 0.011 mmol, 1.1 eq) was added and the solution warmed to room temperature and stirred for a



416



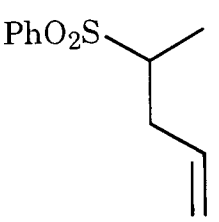
417

further 20 h. 2M Hydrochloric acid (50 ml) was added, the organic layer separated and the aqueous layer extracted with dichloromethane (3 x 15 ml). The combined organic extracts were washed with saturated aqueous sodium hydrogencarbonate (50 ml), dried and evaporated to give *3-phenylsulphonyl-propanal* **416** (1.3 g)[159] as a viscous yellow oil which was not further purified and which showed υ_{max} 1724, 1448, 1411, 1142 and 1087 cm^{-1}; δ_H (250 MHz) 9.72 (1H, app s, 1-CH_2), 7.91 (2H, d, *J* 7.5, *o*-Ar), 7.72-7.56 (3H, m, Ar), 3.44 (2H, t, *J* 7.4, 3-CH_2) and 2.95 (2H, app t, *J* 7.4, 2-CH_2); δ_C (67.8 MHz) 197.3 (1-CH), 138.6 (C), 134.2 (CH), 129.6 (CH), 128.1 (CH), 49.1 (3-CH_2) and 36.6 (2-CH_2).

To a stirred solution of butyltriphenylphosphonium bromide (1.495 g, 3.94 mmol, 1.5 eq) in THF (40 ml), at room temperature under nitrogen, was slowly added potassium hexamethyldisilazane ([KHMDS], 0.5M in toluene, 8.2 ml, 4.1 mmol, 1.1 eq), and the resulting solution

stirred at room temperature for a further 1 h. The reaction mixture was cooled to -78°C whereupon aldehyde **416** (0.5 g, 2.5 mmol, 1 eq) was added quickly and the mixture stirred at -78°C for 0.5 h and then allowed to warm to room temperature and stirring continued for a further 4 h. Water (20 ml) was added and the mixture was filtered through a pad of silica and the pad was washed with dichloromethane (2 x 20 ml). The filtrate was separated and the aqueous layer was extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dried and evaporated to give the product as a brownish semi-solid. This was purified by flash column chromatography (silica, eluting with petrol and then 3:1 petrol-ether) to give *title compound* **417** (0.303 g, 51%) as a colourless oil, which showed υ_{max} 1750, 1600, 1450, 1290, 1145, 1080, 760, 730 and 690 cm^{-1}, δ_H (250 MHz) 7.93 (2H, d, *J* 6.9, *o*-Ar), 7.72-7.54 (3H, m, Ar), 5.50-5.40 (2H, m, :CH), 5.31-5.19 (1H, m, :CH), 3.04-3.14 (2H, m, 1-CH_2), 2.41-2.50 (2H, m, 2-CH_2), 1.89-1.97 (2H, m, 5-CH_2), 1.22-1.40 (2H, m, 6-CH_2) and 0.86 (3H, t, *J* 7.3, 7-CH_3); δ_C (67.8 MHz) 139.9 (C), 133.7 (CH), 133.0 (CH), 129.3 (CH), 128.1 (CH), 124.3. (CH), 55.9 (1-CH_2), 29.1 (CH_2), 22.5 (CH_2), 20.8 (CH_2) and 13.7 (5-CH_3). *m/z* (ES) 239 (100), 195 (32). [Found: MH^+, 239.1106. $C_{13}H_{19}O_2S$ requires M, 239.1106].

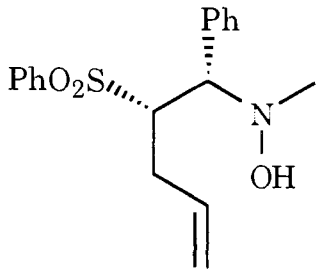
4-Phenylsulphonyl-pent-1-ene



To a stirred solution of 1-(phenylsulphonyl)-but-3-ene **247** (0.515 g, 2.62 mmol) in THF (30 ml) at -78°C under nitrogen was slowly added

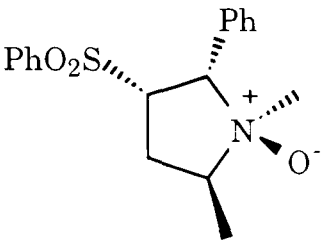
butyllithium (1.6M in hexanes, 1.8 ml, 2.9 mmol, 1.1 eq), and the solution stirred at -78°C for a further 0.5 h. Methyl iodide (0.2 ml, 3.2 mmol, 1.2 eq) was added quickly and the mixture stirred at -78°C for 15 min, whereupon water (10 ml) was added and the reaction mixture warmed to room temperature. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic extracts were dried and evaporated to give the crude product as a yellow/brown oil. This was purified by column chromatography (silica, 4:1 petrol-ether) to give the *title compound* (0.5 g, 90%)[168] as a colourless oil, which showed υ_{max} 1461, 1305, 1145, 1086 and 992 cm^{-1}; δ_H (250 MHz) 7.84 (2H, d, *J* 7.0, *o*-Ar), 7.66-7.50 (3H, m, Ar), 5.60-5.75 (1H, m, 2-CH), 5.01-5.11 (2H, m, 1-CH_2), 3.02-3.14 (1H, m, 4-CH), 2.70-2.79 (1H, m, 3-CHa), 2.08 (1H, dddt, *J* 13.9, 10.3, 8.1 and 1.0, 3-CHb) and 1.20 (3H, d, *J* 6.9, 5-CH_3); δ_C (67.8 MHz) 137.0 (C), 133.6 (3-CH), 133.0 (CH), 129.0 (CH), 128.8 (CH), 118.5 (4-CH_2), 59.3 (1-CH), 33.6 (2-CH_2) and 12.7 (1'-CH_3); *m/z* (FAB) 211 (38%, MH^+), 143 (53), 69 (100) and 55 (100).

1-(*N*-Methyl-*N*-hydroxyamino)-1-phenyl-2-(phenylsulphonyl)-pent-4-ene 260



To a stirred solution of 1-(phenylsulphonyl)-but-3-ene **247** (0.196 g, 1 mmol) in THF (15 ml) at -78°C under nitrogen, was slowly added butyllithium (0.69 ml of a 1.6M solution in hexanes, 1.1 mmol, 1.1 eq) and the solution stirred at -78°C for 30 min. A solution of *C*-phenyl-*N*-methyl nitrone **144** (0.149 g, 1.1 mmol, 1.1 eq) in THF (2 ml) was added quickly and the mixture stirred at -78°C for 0.25 h, whereupon 0.5M aqueous sodium hydroxide (10 ml) was added and the reaction mixture warmed to room temperature. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 x 10 ml). The combined organic extracts were dried and evaporated to give the crude product as a foam (0.35 g, 95% by NMR). This was purified by column chromatography (silica, 4:1 petrol-ether) to give the *title compound* **260** (0.203 g, 61%) as a foam, which showed δ_H (250 MHz) 8.04 (2H, d, *J* 7.1, *o*-Ar), 7.72-7.54 (3H, m, Ph), 7.34 (5H, br res, Ph), 5.52-5.70 (1H, m, 4-CH), 5.38 (1H, s, OH), 4.87 (1H, br d, *J* 11.4, 5-CHc), 4.57 (1H, br d, *J* 18.0, 5-CHt), 4.09-3.93 (2H, m, 1- & 2-CH), 2.37 (3H, s, N-CH_3) and 2.15-2.25 (2H, m, 3-CH_2); δ_C (67.8 MHz) 139.6 (C), 133.4 (CH), 132.5 (CH), 130.1 (CH), 129.1 (CH), 129.0 (CH), 128.8 (CH), 128.4 (CH), 128.1 (CH), 118.2 (5-CH_2), 70.7 (CH), 66.2 (CH), 44.4 (N-CH_3) and 31.6 (3-CH_2).

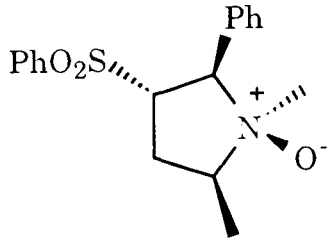
1α,5β-Dimethyl-2α-phenyl-3α-phenylsulphonyl pyrrolidine *N*-oxide 262



A solution of hydroxylamine **260** (0.203 g, 0.61 mmol) in deuteriochloroform (5 ml) was stirred at room temperature under nitrogen for 4 days yielding the *title compound* **262** (0.2 g, *ca.* 100% by ^{1}H NMR) as a foam and as largely one diastereoisomer **262**, the major isomer of which showed υ_{max} 1458, 1322, 1146, 1095 and 903 cm^{-1}; δ_H (250 MHz) 7.70-7.30 (10H, m, Ar), 5.20 (1H, ddd, *J* 10.8, 8.0 and 8.0, 3-CH), 4.80 (1H, d, *J* 8.0, 2-CH), 4.07-4.13 (1H, m, 5-CH), 3.10 (1H, ddd, *J* 13.0, 9.4 and 8.0, 4-CHα), 2.60 (3H, s, N-CH_3), 2.40 (1H, ddd, *J* 13.0, 10.8 and 8.9, 4- CHβ) and 1.40 (3H, d, *J* 6.3, 5'-CH_3); δ_C (100.6 MHz) 139.5 (C), 133.8 (CH), 130.4 (CH), 130.2 (C), 129.0 (CH), 128.6 (CH), 127.8 (CH), 128.7 (CH), 88.3 (2-CH), 68.1 (5-CH), 63.1 (3-CH), 51.0 (N-CH_3), 31.4 (4-CH_2) and 12.6 (5'-CH_3); *m/z* (FAB) 332 (32%, MH^+), 149 (100) and 57 (60).

Further manipulations were carried out on the crude material.

1α,5β-Dimethyl-2β-phenyl-3α-phenylsulphonyl pyrrolidine *N*-oxide 264 (X-ray)

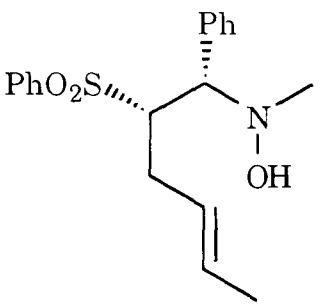


N-Oxide **262** (0.1 g) was dissolved in hot methanol and allowed to cool and stand at room temperature for *ca.* 1 month, yielding the *title*

compound **264** (0.03 g, 30%) as opaque, prismatic crystals which showed υ_{max} (soln) 1448, 1308, 1149, 1086 and 949 cm^{-1}; δ_H (250 MHz) 7.60-7.00 (10H, m, Ar), 4.52 (1H, d, *J* 10.2, 2-CH), 4.30 (1H, ddd, *J* 10.2, 10.2 and 4.0, 3-CH), 3.75-3.83 (1H, m, 5-CH), 2.78 (1H, ddd, *J* 14.0, 7.4 and 4.0, 4-CHα), 2.74 (3H, s, N-CH_3), 2.58 (1H, ddd, *J* 14.0, 10.2 and 10.2, 4-CHβ) and 1.50 (3H, d, *J* 6.2, 5'-CH_3); δ_C (67.8 MHz) 138.0 (C), 133.9 (CH), 131.6 (CH), 130.0 (C), 129.9 (CH), 129.1 (CH), 128.2 (CH), 128.1 (CH), 81.3 (2-CH), 76.7 (5-CH), 64.9 (3-CH), 51.3 (N-CH_3), 30.4 (4-CH_2) and 12.2 (5'-CH_3).

For X-ray data, see Appendix.

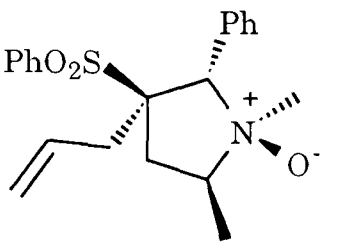
(E)-1-(*N*-Methyl-*N*-hydroxyamino)-1-phenyl-2-phenylsulphonyl hex-4-ene 275



The general procedure for the preparation of hydroxylamine **260** was followed using sulphone **274** (0.123 g, 0.58 mmol), butyl lithium (1.6M in hexanes, 0.4 ml, 0.64 mmol, 1.09 eq) and nitrone **144** (0.080 g, 0.59 mmol, 1.01 eq) in THF (15 ml) yielding the *title compound* **275** (0.164 g, 82%) as a foam after chromatography (silica, 4:1 petrol-ether), which showed δ_H (250 MHz) 8.06 (2H, d, *J* 7.0, Ar), 7.50-7.70 (3H, m, Ar), 7.34 (5H, br s, Ar), 5.61 (1H, s, OH), 5.10-5.22 (1H, m,:CH), 4.88-5.00 (1H, m, :CH), 4.18-3.96 (2H, m, 1- & 2-CH), 2.38 (3H, s, N-CH_3), 2.34-2.07 (2H, m, 3-CH_2) and 1.45 (3H, d, *J* 6.4, 6-CH_3); δ_C (67.8 MHz) 139.9 (C), 133.7 (C), 133.5 (:CH), 130.3 (CH), 129.2 (CH), 129.1 (CH), 128.9 (CH), 128.5

(CH), 128.3 (CH), 125.0 (:CH), 70.9 (CH), 66.8 (CH), 44.5 (N-CH_3), 30.8 (3-CH_2) and 17.9 (6-CH_3).

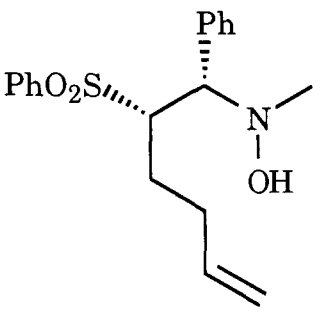
1α,5β-Dimethyl-2α-phenyl-3β-phenylsulphonyl-3α-(2-propenyl)-pyrrolidine *N*-oxide 287



The general procedure for the preparation of hydroxylamine **260** was followed using sulphone **248** (0.186 g, 0.79 mmol), butyllithium (1.6M in hexanes, 0.62 ml, 0.87 mmol, 1.1 eq) and nitrone **144** (0.12 g, 0.86 mmol, 1.1 eq) in THF (20 ml), followed by *ca.* 5 min in $CDCl_3$ (1 ml) prior to NMR studies (*ie.* upon work up), yielding the *title compound* **287** as one diastereoisomer **287** (40% by NMR, due to poor condensation reaction rather than poor *retro*-Cope) as a foam, which showed δ_H (250 MHz) 7.90-7.20 (10H, m, Ar), 3.18 (1H, dd, *J* 16.1 and 6.6), 2.82 (1H, dd, *J* 14.3 and 6.0, CH), 2.73 (3H, s, N-CH_3) and 1.40 (3H, d, *J* 6.1, 5'-CH_3) (other signals obscured); δ_C (67.8 MHz) 118.1 (3'-CH_2), 81.1 (2-CH), 72.8 (3-C), 72.0 (5-CH), 54.2 (N-CH_3), 38.6 (CH_2), 37.7 (CH_2) and 11.4 (5-CH_3) (other signals obscured by the starting material signals).

No further data was obtained and further manipulations were carried out on the crude material as purification was not possible.

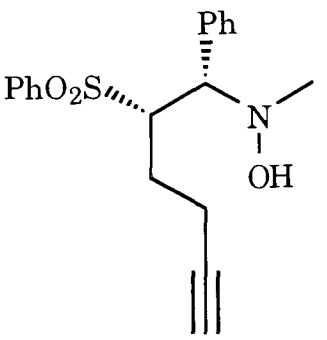
1-(*N*-Methyl-*N*-hydroxyamino)-1-phenyl-2-phenylsulphonyl-hex-5-ene 293



The general procedure for the preparation of hydroxylamine **260** was followed using sulphone **292** (0.060 g, 0.28 mmol), butyllithium (1.6M in hexanes, 0.2 ml, 0.32 mmol, 1.1 eq) and nitrone **144** (0.042 g, 0.31 mmol, 1.1 eq) in THF (10 ml) yielding the *title compound* **293** (0.071 g, 73%) as a foam after chromatography (silica, 3:1 petrol-ether), which showed δ_H (250 MHz) 8.07 (2H, d, *J* 8.0, Ar), 7.72-7.52 (3H, m, Ar), 7.33 (5H, br res, Ar), 5.40-5.22 (2H, m, 5-CH & OH), 4.39-4.20 (2H, m, 6-CH_2), 3.90-4.00 (1H, m, 2-CH), 3.34 (1H, d, *J* 11.2, 1-CH), 2.38 (3H, s, N-CH_3), 1.93-1.70 (3H, m, 3-CH_2 & 4-CH) and 1.60-1.20 (1H, m, 4-CH).

This material was then subjected to reflux in toluene to form the *retro*-Cope product. The reaction was unsuccessful.

1-(*N*-Methyl-*N*-hydroxyamino)-1-phenyl-2-phenylsulphonyl-hex-5-yne 296

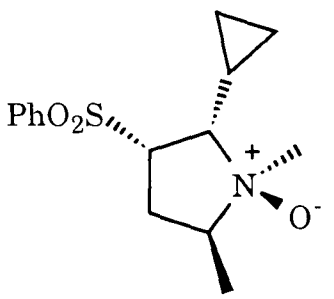


The general procedure for the preparation of hydroxylamine **260** was followed using sulphone **295** (0.080 g, 0.38 mmol), butyllithium (0.52

ml of a 1.6M solution in hexanes, 0.82 mmol, 2.1 eq) and nitrone **144** (0.06 g, 0.43 mmol, 1.1 eq) in THF (10 ml) yielding the *title compound* **296** (0.086 g, 65%) as a foam after chromatography (silica, 3:1 petrol-ether), which showed δ_H (250 MHz) 8.03 (2H, d, *J* 7.0, Ar), 7.73-7.52 (3H, m, Ar), 7.35 (5H, br res, Ar), 5.30 (1H, s, OH), 4.16 (1H, ddd, *J* 10.0, 6.7 and 3.4, 2-CH), 3.76 (1H, d, *J* 10.0, 1-CH), 2.31 (3H, s, N-CH_3), 2.28-1.94 (3H, m, 3-CH_2 & 4-CH), 1.90 (1H, t, *J* 2.5, 6-CH) and 1.72-1.50 (1H, m, 3-CH).

This material was then subjected to reflux in toluene to form the *retro*-Cope product. The reaction was unsuccessful.

2α-Cyclopropyl-1α,5β-dimethyl-3α-(phenylsulphonyl)-pyrrolidine *N*-oxide 300

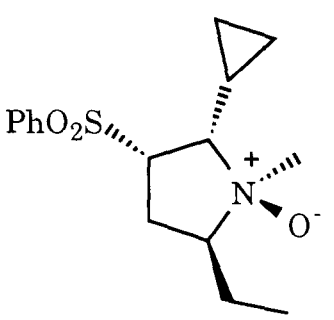


The general procedure for the preparation of hydroxylamine **260** was followed using sulphone **247** (0.35 g, 1.78 mmol), butyllithium (1.6M in hexanes, 1.2 ml, 1.92 mmol, 1.08 eq) and nitrone **298** (0.215 g, 2.17 mmol, 1.2 eq) in THF (10 ml), followed by *ca.* 5 min in $CDCl_3$ (2 ml) prior to NMR studies (*ie.* upon work up), yielding the crude *title compound* **300** as largely one diastereoisomer (0.50 g, >95% by NMR, *ca.* 8:1 ratio) as a foam, the major isomer of which showed δ_H (400 MHz) 7.90-7.40 (5H, m, Ar), 4.68 (1H, ddd, *J* 10.2, 7.0 and 7.0, 3-CH), 3.75-3.81 (1H, m, 5-CH), 3.23 (1H, dd, *J* 11.6 and 7.0, 2-CH), 3.10 (3H, s, N-CH_3), 2.47 (1H, ddd, *J* 13.1, 8.9 and 7.0, 4-CHα), 1.71 (1H, ddd, *J* 13.1, 10.2 and 10.2, 4-CHβ), 1.21 (3H, d, *J* 6.2, 5-CH_3), 1.04-1.11 (1H, m, cy-CH), 0.91-0.98 (1H, m, cy-CH), 0.77-.0.89 (2H, m, 2 x cy-CH) and 0.61-0.66 (1H, m, cy-CH); δ_C (67.8 MHz) 139.5 (C), 133.5 (CH), 129.0 (CH), 127.7 (CH), 87.2 (2-CH),

67.6 (5-CH), 62.4 (3-CH), 50.7 (N-CH_3), 31.4 (4-CH_2), 12.0 (5'-CH_3), 9.0 (2'-CH), 7.7 (2'-CH_2) and 6.7 (2'-CH_2).

Further manipulations were carried out on the crude material.

5β-Ethyl-2α-cyclopropyl-1α-methyl-3α-phenylsulphonyl-pyrrolidine *N*-oxide 304

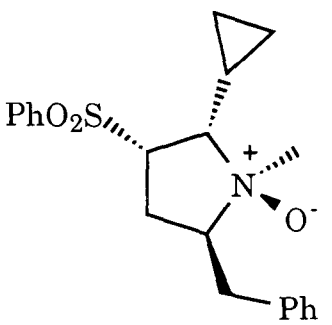


The general procedure for the preparation of hydroxylamine **260** was followed using sulphone **274** (0.20 g, 0.95 mmol), butyllithium (0.72 ml of a 1.6M solution in hexanes, 1.04 mmol, 1.1 eq) and nitrone **298** (0.10 g, 1.04 mmol, 1.1 eq) in THF (20 ml), followed by *ca.* 3-4 days at room temperature in $CDCl_3$ (2 ml), yielding the crude *title compound* **304** as largely one diastereoisomer (0.29 g, *ca.* 55% by NMR) as a foam, the major isomer of which showed υ_{max} 1450, 1300, 1220, 1145, 1085 and 755 cm^{-1}, δ_H (400 MHz) 7.88 (2H, d, *J* 7.9, Ar), 7.68-7.51 (3H, m, Ar), 4.79 (1H, ddd, *J* 10.4, 7.0 and 7.0, 3-CH), 3.58-3.63 (1H, m, 5-CH), 3.29 (1H, dd, *J* 11.3 and 7.0, 2-CH), 3.20 (3H, s, N-CH_3), 2.56 (1H, ddd, *J* 12.4, 7.9 and 7.0, 4-CHα), 1.79-1.89 (3H, m, 4-CHβ & 6-CH_2), 0.91 (3H, t, *J* 7.4, 7-CH_3), 0.94-0.99 (1H, m, cy-CH), 0.86-0.90 (2H, m, 2 x cy-CH), 0.66-0.70 (1H, m, cy-CH) and 0.50-0.54 (1H, m, cy-CH); δ_C (100.6 MHz) 139.8 (C), 133.8 (CH), 129.3 (CH), 128.0 (CH), 87.8 (2-CH), 73.7 (5-CH), 62.5 (3-CH), 51.2 (N-CH_3), 30.0 (4-CH_2), 20.6 (5-CH_2), 10.3 (5-CH_3), 9.2 (cy-CH), 8.0 (cy-CH_2) and 7.0 (cy-CH_2); *m/z* (FAB) 310 (100%, MH^+), 88

(51), 73 (56) and 55 (50). [Found: MH^+, 310.1477. $C_{16}H_{24}NO_3S$ requires M, 310.1477].

Further manipulations were carried out on the crude material.

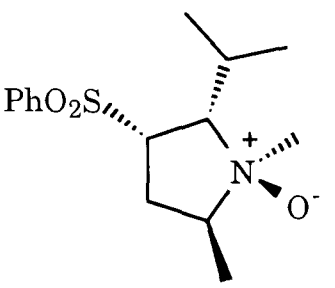
5β-Benzyl-2α-cyclopropyl-1α-methyl-3α-phenylsulphonyl-pyrrolidine *N*-oxide 306



The general procedure for the preparation of hydroxylamine **260** was followed using sulphone **277** (0.152 g, 0.56 mmol), butyllithium (1.45M in hexanes, 0.42 ml, 0.61mmol, 1.1 eq) and nitrone **298** (0.06 g, 0.61 mmol, 1.1 eq) in THF (15 ml), followed by *ca.* 2-3 days at ambient in $CDCl_3$ (2 ml), yielding the crude *title compound* **306** as largely one diastereoisomer (0.20 g, *ca.* 2:1 ratio) as a foam, the major isomer of which showed δ_H (400 MHz) 7.95-7.10 (10H, m, Ar), 4.81 (1H, ddd, *J* 9.8, 7.0 and 7.0, 3-CH), 3.96-4.00 (1H, m, 5-CH), 3.34 (1H, dd, *J* 11.9 and 7.0, 2-CH), 3.22 (3H, s, N-CH_3), 3.20-3.26 (1H, m, 5'-CHa), 3.02 (1H, dd, *J* 13.9 and 9.5, 5'-CHb), 2.33-2.43 (1H, m, 4-CHα), 1.95 (1H, ddd, *J* 13.0, 9.8 and 9.8, 4-CHβ), 1.12-1.14 (1H, m, cy-CH), 0.98-1.03 (1H, m, cy-CH), 0.96-0.85 (2H, m, 2 x cy-CH) and 0.69-0.73 (1H, m, cy-CH); δ_C (100.6 MHz) 88.3 (2-CH), 73.3 (5-CH), 62.7 (3-CH), 51.9 (N-CH_3), 34.1 (5'-CH_2), 30.5 (4-CH_2), 9.3 (cy-CH), 8.1 (cy-CH_2) and 7.1 (cy-CH_2); *m/z* (FAB) 372 (100%, MH^+).

Further manipulations were carried out on the crude material.

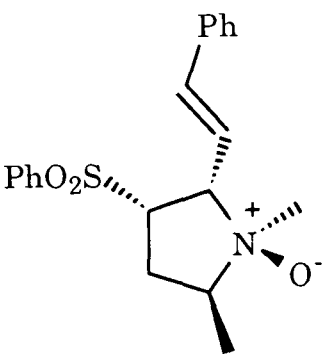
1α,5β-Dimethyl-2α-isopropyl-3α-phenylsulphonyl-pyrrolidine *N*-oxide 313



The general procedure for the preparation of hydroxylamine **260** was followed using sulphone **247** (0.284 g, 1.45 mmol), butyllithium (1.6M in hexanes, 1.1 ml, 1.6 mmol, 1.1 eq) and nitrone **311** (0.16 g, 1.58 mmol, 1.1 eq) in THF (10 ml), followed by *ca.* 5 min in $CDCl_3$ (2 ml) prior to NMR studies (*ie.* upon work up), yielding the crude *title compound* **313** as a 2:1 mixture of diastereoisomers (0.43 g) as a foam, the major isomer of which showed υ_{max} 1448, 1362, 1140, 1087 and 998 cm^{-1}; δ_H (400 MHz) 4.57 (1H, ddd, *J* 9.3, 7.3 and 7.3, 3-CH), 4.02 (1H, dd, *J* 7.3 and 5.2, 2-CH), 3.02 (3H, s, N-CH_3) and 1.40 (3H, d, *J* 7.0, 5'-CH_3); (other signals obscured by unreacted starting material); *m/z* (FAB) 298 (100%, MH^+).

Further manipulations were carried out on the crude material.

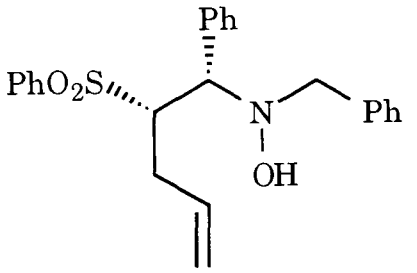
1α,5β-Dimethyl-2α-cinnamyl-3α-phenylsulphonyl pyrrolidine *N*-oxide 316



The general procedure for the preparation of hydroxylamine **260** was followed using sulphone **247** (0.20 g, 1.02 mmol), butyllithium (1.45M

in hexanes, 0.77 ml, 1.1 mmol, 1.1 eq) and nitrone **314** (0.17 g, 1.06 mmol, 1.04 eq) in THF (20 ml), followed by *ca.* 5 min in $CDCl_3$ (2 ml) prior to NMR studies (*ie.* upon work up), yielding the crude *title compound* as two diastereoisomers (0.35 g,*ca.* 2:1) as a foam, the major diastereoisomer of which showed υ_{max} 1450, 1300, 1210, 1145 and 740 cm^{-1}, δ_H (250 MHz) 7.75-7.15 (10H, m, Ar), 6.59 (1H, d, *J* 14.2, 1'-CH), 6.39 (1H, dd, *J* 14.2, 10.6, 2'-CH), 4.88 (1H, ddd, *J* 10.4, 6.8 and 6.8, 3-CH), 4.36 (1H, dd, *J* 10.6 and 6.8, 2-CH), 3.74-3.80 (1H, m, 5-CH), 2.97 (3H, s, N-CH_3), 2.82-2.90 (1H, m, 4-CHα), 2.30 (1H, ddd, *J* 14.0, 10.4 and 10.4, 4-CHβ) and 1.44 (3H, d, *J* 6.5, 5-CH_3); δ_C (100.6 MHz) 80.3 (2-CH), 71.6 (5-CH), 63.9 (3-CH), 51.3 (N-CH_3), 30.5 (4-CH_2) and 11.5 (5'-CH_3); *m/z* (FAB) 358 (93%, MH^+), 162 (30), 143 (26), 97 (37), 74 (100), 69 (56), 57 (80) and 55 (76). [Found: MH^+, 358.1484. $C_{20}H_{23}O_3S$ requires M, 358.1477].

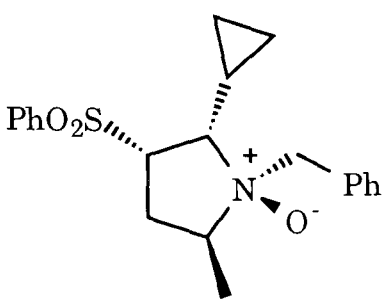
1-(*N*-Benzyl-*N*-hydroxyamino)-1-phenyl-2-phenylsulphonyl-pent-4-ene 321



The general procedure for the preparation of hydroxylamine **260** was followed using sulphone **247** (0.10 g, 0.51 mmol), butyllithium (1.6M in hexanes, 0.35 ml, 0.56 mmol, 1.09 eq) and nitrone **320** (0.119 g, 0.56 mmol, 1.09 eq) in THF (15 ml) yielding the *title compound* **321** (0.115 g, 55%) as a foam after chromatography (silica, 6:1 petrol-ether), which showed δ_H (250 MHz) 8.00 (2H, d, *J* 7.5, Ar), 7.63-7.27 (13H, m, Ar), 5.58-5.72 (1H, m, 4-CH), 4.87 (1H, app d, *J* 10.3, 5-CHc), 4.82 (1H, s, OH), 4.57 (1H, app dd, *J* 17.0 and 1.4, 5-CHt), 4.29 (1H, d, *J* 10.7, 1-CH),

4.09-4.17 (1H, m, 2-CH), 3.60 (2H, AB q, *J* 52.9, 13.5, N-CH_2) and 2.46-2.13 (2H, m, 3-CH_2); δ_C (67.8 MHz) 140.0 (C), 137.2 (C), 134.0 (C), 133.2 (CH), 132.6 (CH), 130.1 (CH), 129.2 (CH), 128.8 (CH), 128.7 (CH), 128.4 (CH), 128.2 (CH), 128.0 (CH), 118.2 (5-CH_2), 69.7 (CH), 65.9 (CH), 61.2 (N-CH_2) and 31.4 (3-CH_2).

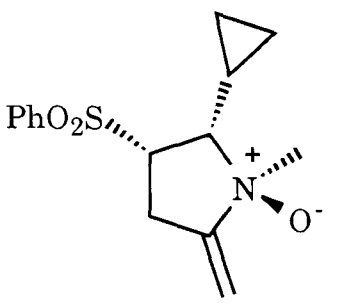
1α-Benzyl-2α-cyclopropyl-5β-methyl-3α-phenylsulphonyl-pyrrolidine *N*-oxide 325



The general procedure for the preparation of hydroxylamine **260** was followed using sulphone **247** (0.20 g, 1.04 mmol), butyllithium (1.6M in hexanes, 0.79 ml, 1.15 mmol, 1.1 eq) and nitrone **323** (0.19 g, 1.07 mmol, 1.03 eq) in THF (25 ml), followed by *ca.* 2 days at ambient in $CDCl_3$ (2 ml), yielding the crude *title compound* **325** as a mixture of diastereoisomers (0.36 g, 3:1 ratio) as a foam, the major diastereoisomer of which showed δ_H (400 MHz) 7.90-7.22 (10H, m, Ar), 4.73-4.78 (1H, m (obs), 3-CH), 4.70 & 4.38 (2H, AB q, *J* 8 and 25, N-CH_2), 4.02-3.90 (1H, m, 5-CH), 3.44 (1H, dd, *J* 11.4 and 7.1, 2-CH), 2.60 (1H, ddd, *J* 13.4, 8.0 and 8.0, 4-CHα), 1.60 (1H, ddd, *J* 13.4, 10.6 and 8.0, 4-CHβ), 1.18-1.25 (1H, m, cy-CH), 1.00-0.90 (2H, m, 2 x cy-CH), 0.76 (3H, d, *J* 6.5, 5-CH_3) and 0.53-0.60 (2H, m, 2 x cy-CH); δ_C (100.6MHz) 139.8 (C), 133.6 (CH), 131.9 (C), 131.3 (CH), 129.2 (CH), 127.9 (CH), 87.9 (2-CH), 67.9 (5-CH), 66.6 (N-CH_2), 62.7 (3-CH), 32.4 (4-CH_2), 14.5 (5-CH_3), 8.6 (cy-CH), 8.1 (cy-CH_2) and 6.8 (cy-CH_2); *m/z* (FAB) 372 (100%, MH^+), 176 (19), 150 (13), 91 (92), 69 (42), 57 (72) and 55 (54).

Further manipulations were carried out on the crude material.

2α-Cyclopropyl-1α-methyl-5-methylene-3α-(phenylsulphonyl)-pyrrolidine *N*-oxide 376



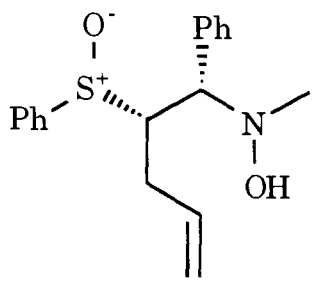
The general procedure for the preparation of hydroxylamine **260** was followed using sulphone **289** (0.193 g, 0.99 mmol), butyllithium (1.43M in hexanes, 1.46 ml, 2.09 mmol, 2.1 eq) and nitrone **298** (0.205 g, 2.07 mmol, 2.08 eq) in THF (15 ml), followed by *ca.* 5 min in $CDCl_3$ (2 ml) prior to NMR studies (*ie.* upon work up), yielding the *title compound* (0.27 g, >90% by NMR) as a yellow oil (decomposes rapidly at room temperature; <2 h), and which showed δ_H (250 MHz) 8.00-7.50 (5H, m, Ar), 5.00 (1H, br s, 2'-CHa), 4.83 (1H, br s, 2'-CHb), 4.42 (1H, ddd, *J* 10.0, 10.0 and 8.0, 4-CH), 3.79-3.84 (1H, m, 5-CH), 1.26-1.31 (1H, m, cy-CH), 1.10-0.45 (4H, m, 2 x cy-CH_2). The 3-CH_2 signal was obscured.

Due to the instability of this compound, no further data was obtained.

1-(*N*-Methyl-*N*-hydroxyamino)-1-phenyl-2-phenylsulphinyl-pent-4-ene 385

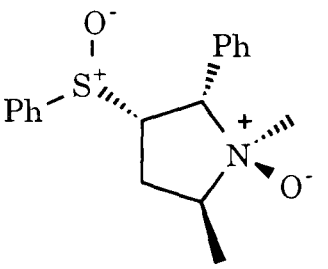
The general procedure for the preparation of hydroxylamine **260** was followed using sulphoxide **258** (0.168 g, 0.93 mmol), butyllithium (1.6M in hexanes, 0.7 ml, 0.98 mmol, 1.05 eq) and nitrone **144** (0.151 g,

1.1 mmol, 1.2 eq) in THF (10 ml) yielding the *title compound* **385** (0.185 g, 63%) as a foam after chromatography (silica, 3:1 petrol-ether), which



showed δ_H (250 MHz) 7.50-7.60 (10H, m, Ar), 5.35-5.18 (2H, m, 4-CH & OH), 4.87-4.63 (2H, m, 5-CH_2), 3.90 (1H, d, *J* 6.8, 1-CH), 2.98-3.03 (1H, m, 2-CH), 2.55-2.38 (4H, m, 3-CHa & N-CH_3) and 2.22-2.31 (1H, m, 3-CHb).

1α,5β-Dimethyl-2α-phenyl-3α-phenylsulphinyl-pyrrolidine *N*-oxide 386

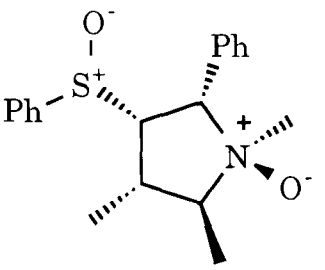


The general procedure for the preparation of *N*-oxide **262** was followed using hydroxylamine **385** (0.185 g, 0.5 mmol) in $CDCl_3$ (2 ml) for 8 days yielding the *title compound* as largely one diastereoisomer **386** (0.18 g, 100% by NMR with >6:1 ratio) as a foam, the major diastereoisomer of which showed υ_{max} (dcm)[169] 2253, 1794, 1645, 1475, 1397 and 1266 cm^{-1}, δ_H (400 MHz) 7.48-7.16 (10H, m, Ar), 4.72 (1H, d, *J* 8.5, 2-CH), 4.46 (1H, ddd, *J* 11.1, 8.5 and 6.2, 3-CH), 3.84-3.90 (1H, m, 5-CH), 3.01 (1H, ddd, *J* 14.6, 8.8 and 6.2, 4-CHα), 2.57 (3H, s, N-CH_3), 2.23-2.32 (1H, m, 4-CHβ) and 1.38 (3H, d, *J* 6.2, 5'-CH_3); δ_C (100.6 MHz) 142.7 (C), 131.6 (CH), 131.4 (CH), 131.1 (C), 130.7 (CH), 129.2 (CH),

128.4 (CH), 124.6 (CH), 88.2 (2-CH), 68.7 (5-CH), 64.6 (3-CH), 50.8 (N-CH_3), 29.3 (4-CH_2) and 12.5 (5'-CH_3).

Further manipulations were carried out on the crude material.

2α-Phenyl-3α-phenylsulphinyl-1α, 4α, 5β-trimethyl-pyrrolidine *N*-oxide 390

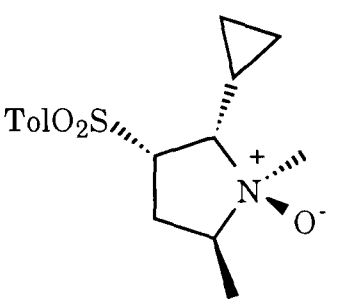


The general procedure for the preparation of hydroxylamine **260** was followed using sulphoxide **389** (0.11 g, 0.56 mmol), butyllithium (1.6M in hexanes, 0.44 ml, 0.62 mmol, 1.1 eq) and nitrone **144** (0.085 g, 0.63 mmol, 1.1 eq) in THF (10 ml), chromatography (silica, 1:1 petrol-ether, 60%), followed by the general procedure of *N*-oxide **262** using the resulting hydroxylamine **392** (0.12 g, 0.36 mmol) in $CDCl_3$ (1 ml) for 8 days yielding the *title compound* **390** as one diastereoisomer (0.12 g, 58% over 2 steps) as a foam, which showed δ_H (250 MHz) 7.65-6.91 (10H, m, Ar), 4.72 (1H, dd, *J* 12.3 and 8.5, 3-CH), 4.30 (1H, d, *J* 8.5, 2-CH), 3.48-3.60 (1H, m, 5-CH), 3.05-3.19 (1H, m, 4-CH), 2.49 (3H, s, N-CH_3), 1.82 (3H, d, *J* 7.0, 4-CH_3) and 1.44 (3H, d, *J* 6.4, 5-CH_3).

No further data was obtained on this compound and further manipulations were carried out on the crude material.

2α-Cyclopropyl-1α,5β-dimethyl-3α-(toluenesulphonyl)-pyrrolidine *N*-oxide 421

The general procedure for the preparation of hydroxylamine **260** was followed using sulphone **352** (0.50 g, 2.38 mmol), butyllithium (1.6M in hexanes, 1.6 ml, 2.56 mmol, 1.08 eq) and nitrone **298** (0.26 g,

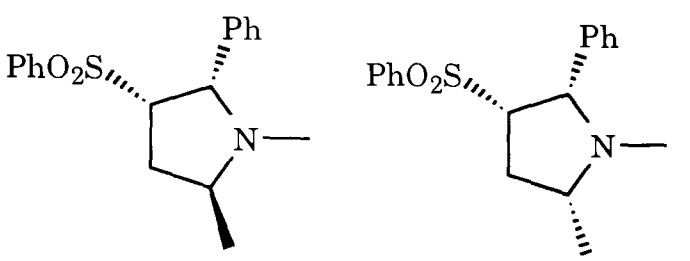


2.61 mmol, 1.1 eq) in THF (15 ml), followed by *ca.* 5 min in $CDCl_3$ (2 ml) prior to NMR studies (*ie.* upon work up), yielding the crude *title compound* **421** as largely one diastereoisomer (0.71 g, *ca.* 8:1 ratio) as a foam, the major diastereoisomer of which showed υ_{max} 1660, 1600, 1440, 1280, 1145, 1080, 1050, 900, 800 and 750 cm^{-1}, δ_H (250 MHz) 7.68 (2H, d, *J* 8.3, Ar), 7.27 (2H, d, *J* 8.3, Ar), 4.67 (1H, ddd, *J* 10.2, 7.0 and 7.0, 3-CH), 3.76-3.82 (1H, m, 5-CH), 3.23 (1H, dd, *J* 11.6 and 7.0, 2-CH), 3.10 (3H, s, N-CH_3), 2.41-2.51 (1H, m, 4-CHα), 2.37 (3H, s, CH_3-Ar), 1.72-1.78 (1H, m, 4-CHβ), 1.26 (3H, d, *J* 6.2, 5-CH_3), 1.08-1.11 (1H, m, cy-CH), 0.94-0.98 (1H, m, cy-CH), 0.90-0.75 (2H, m, 2 x cy-CH) and 0.61-0.69 (1H, m, cy-CH); δ_C (100.6 MHz) 144.8 (C), 136.9 (C), 129.8 (CH), 128.0 (CH), 87.6 (2-CH), 67.8 (5-CH), 62.7 (3-CH), 51.1 (N-CH_3), 31.8 (4-CH_2), 21.5 (CH_3, Ar), 12.3 (5'-CH_3), 9.2 (2'-CH), 8.0 (2'-CH_2) and 7.0 (2'-CH_2). *m/z* (ES) 310 (100). [Found: MH^+, 310.1477. $C_{16}H_{24}NO_3S$ requires M, 310.1477].

Further manipulations were carried out on the crude material.

5.8 Amine Preparation

1,5β-Dimethyl-2α-phenyl-3α-(phenylsulphonyl)-pyrrolidine 328 and 1,5α-Dimethyl-2α-phenyl-3α-(phenylsulphonyl)-pyrrolidine 329

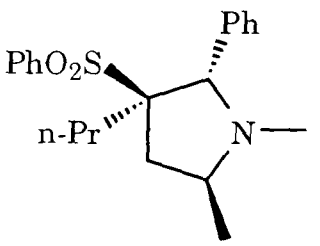


328 **329**

To a stirred solution of the *N*-oxide **262** (0.331g, 1 mmol) and nickel(II) chloride hexahydrate (0.547g, 2 mmol, 2 eq) in dry methanol (30 ml) at -30°C was added, in portions, sodium borohydride (0.189 g, 5 mmol, 5 eq) and the mixture stirred for 10 min at -30°C.[127] The solvent was then evaporated, aqueous ammonia (0.880, 30 ml) and dichloromethane (30 ml) added to the residue and the resulting two-phase mixture stirred vigorously in the presence of air until the aqueous layer had turned a purple-blue colour and the organic layer was a clear brown colour (*ca.* 1 h). The organic layer was separated and the aqueous layer extracted with dichloromethane (3 x 20 ml). The combined organic extracts were dried and evaporated to give a brown oil containing the 2 diastereoisomeric amines in a 6:1 ratio by ^{1}H NMR. These diastereoisomers were separated (90% overall isolated yield) using column chromatography (silica, 9:1 dichloromethane-methanol) to give the *title compound* (major diastereoisomer) **328** (0.243g, 77%) as a thick brown oil, which showed υ_{max} 2845, 2796, 1456, 1376, 1306, 1146 and 1087 cm^{-1}; δ_H (250 MHz) 7.60-7.10 (10H, m, Ar), 4.25 (1H, ddd, *J* 10.3, 8.3 and 8.3, 3-CH), 4.05 (1H, d, *J* 8.3, 2-CH), 3.48-3.59 (1H, m, 5-CH), 2.9 (1H, ddd, *J* 12.8, 10.3 and 8.2, 4-CHα), 2.10 (3H, s, N-CH$_3$), 1.95 (1H,

ddd, *J* 12.8, 8.3 and 2.3, 4-CHβ) and 1.10 (3H, d, *J* 6.3, 5-CH_3); δ_C (67.8 MHz) 139.3 (C), 135.0 (C), 132.9 (CH), 130.3 (CH), 128.7 (CH), 128.0 (CH), 127.9 (CH), 127.7 (CH), 68.6 (2-CH), 65.6 (3-CH), 57.4 (5-CH), 34.7 (N-CH_3), 32.9 (4-CH_2) and 16.2 (5-CH_3); *m/z* (FAB) 316 (45%, M^++H), 174 (28), 158 (20), 147 (11), 128 (14), 105 (20), 95 (32), 81 (47), 69 (63), 67 (43), 57 (53) and 55 (99). [Found: MH^+, 316.1371. $C_{18}H_{22}NO_2S$ requires M, 316.1371]; and *title compound* (minor diastereoisomer) **329** (0.040g, 13%), which showed υ_{max} 1445, 1290, 1200, 1145, 1080, 1000 and 760 cm^{-1}, δ_H (400 MHz) 7.40-7.00 (10H, m, Ar), 4.00 (1H, app q, *J* 9.0, 3-CH), 3.50 (1H, d, *J* 9.0, 2-CH), 2.43-2.48 (1H, m, 5-CH), 2.0-2.35 (2H, m, 4-CH_2), 2.10 (3H, s, N-CH_3) and 1.29 (3H, d, *J* 5.8, 5-CH_3); δ_C (67.8 MHz) 139.6 (C), 136.1 (C), 132.3 (CH), 129.9 (CH), 128.5 (CH), 127.53 (CH), 127.49 (CH), 127.4 (CH), 72.7 (2-CH), 65.0 (3-CH), 59.9 (5-CH), 38.0 (N-CH_3), 33.8 (4-CH_2) and 18.2 (5-CH_3).

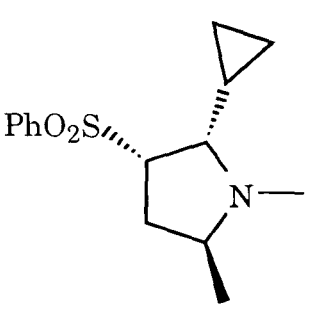
1,5β-Dimethyl-2α-phenyl-3β-(phenylsulphonyl)-3α-propyl-pyrrolidine 334



The above procedure was followed using crude *N*-oxide **287** (0.090g, containing *ca.* 0.1 mmol), nickel(II) chloride hexahydrate (0.141g, 0.52 mmol) and sodium borohydride (0.044 g, 1.16 mmol) in methanol (10 ml) yielding the *title compound* **334** (one diastereoisomer, 0.030g, 87% *wrt* **287**, *ca.* 38% *wrt* **248**) as a brown oil after chromatography (silica, 9:1 dichloromethane-methanol), which showed υ_{max} 1446, 1291, 1143, 1082, 755, 727 and 690 cm^{-1}, δ_H (400 MHz) 7.90-7.20 (10H, m, Ar), 5.06 (1H,

s, 2-CH), 3.77-3.84 (1H, m, 5-CH), 2.89 (1H, dd, *J* 14.3, 5.7, 4-CHα), 2.80 (3H, s, N-CH_3), 2.52 (1H, app t, *J* 14.3, 4-CHβ), 2.20-2.30 (1H, m, 3'-CH), 1.43 (1H, d, *J* 6.0, 5-CH_3), 1.26 (3H, br s, 3 x 3'-CH) and 0.76 (3H, t, *J* 7.0, 3'-CH_3); δ_C (100.6 MHz) 136.1 (C), 134.3 (CH), 133.5 (C), 132.2 (CH), 129.9 (CH), 129.1 (CH), 128.5 (CH), 127.6 (CH), 82.3 (2-CH), 74.1 (3-C), 72.4 (5-CH), 52.4 (N-CH_3), 36.5 (4-CH_2) 17.6 (2 x CH_2), 14.6 (5-Me) and 11.9 (3-CH_3). *m/z* (FAB) 358 (100%, MH^+). [Found: MH^+, 358.1841. $C_{21}H_{28}NO_2S$ requires M, 358.1841].

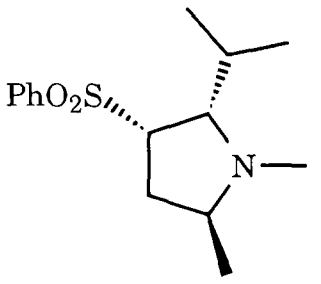
2α-Cyclopropyl-1,5β-dimethyl-3α-(phenylsulphonyl)-pyrrolidine 336



The above procedure was followed using crude *N*-oxide **300** (0.077g, containing *ca.* 0.23 mmol), nickel(II) chloride hexahydrate (0.0.143g, 0.52 mmol) and sodium borohydride (0.05 g, 1.3 mmol) in methanol (8 ml) yielding the *title compound* **336** (largely one diastereoisomer, >6:1, 0.056g, 85%) as a brown oil after chromatography (silica, 19:1 dichloromethane-methanol), the major diastereoisomer of which showed δ_H (250 MHz) 7.90 (2H, d, *J* 8.0, Ar), 7.50-7.65 (3H, m, Ar), 3.91 (1H, ddd, *J* 10.0, 10.0 and 8.0, 3-CH), 3.15-3.20 (1H, m, 5-CH), 2.75 (1H, dd, *J* 11.0 and 8.0, 2-CH), 2.61 (1H, ddd, *J* 13.0, 10.0 and 10.0, 4-CHα), 2.47 (3H, s, N-CH_3), 1.50 (1H, ddd, *J* 13.0, 10.0 and 6.0, 4-CHβ), 1.00-1.10 (4H, m, *J* 6.5, 5-CH_3 & 2'-CH), 0.75-0.81 (1H, m, 2'-CH), 0.62-0.67 (1H, m, 2'-CH) and 0.38-0.48 (2H, m, 2 x 2-CH); δ_C (67.8 MHz) 140.4 (C), 133.4 (CH), 129.2 (CH), 128.0 (CH), 70.2 (2-CH), 64.4 (3-CH),

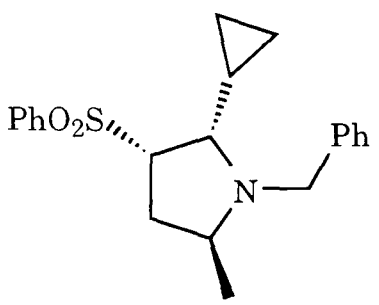
57.2 (5-CH), 35.6 (N-CH_3), 33.6 (4-CH_2), 17.8 (5'-CH_3), 7.8 (2'-CH), 6.6 (2'-CH_2) and 3.5 (2'-CH_2).

1,5β-Dimethyl-2α-isopropyl-3α-(phenylsulphonyl)-pyrrolidine 337



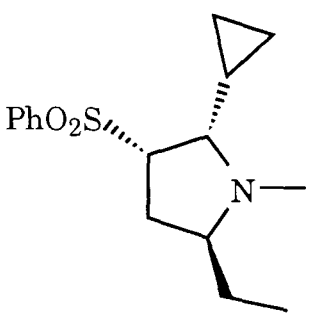
The above procedure was followed using crude *N*-oxide **313** (0.103g, *ca.* 0.17 mmol), nickel(II) chloride hexahydrate (0.19g, 0.69 mmol) and sodium borohydride (0.066 g, 1.7 mmol) in methanol (10 ml) yielding the *title compound* **337** (one diastereoisomer, 0.044g, 90%) as a brown oil after chromatography (silica, 19:1 dichloromethane-methanol), the major diastereoisomer of which showed δ_H (400 MHz) 7.90-7.50 (5H, m, Ar), 3.77 (1H, app q, *J* 8.3, 3-CH), 3.38-3.42 (1H, m, 5-CH), 3.28 (1H, dd, *J* 7.3 and 4.0, 2-CH), 2.58 (1H, ddd, *J* 13.0, 10.8 and 6.8, 4-CHα), 2.49 (3H, s, N-CH_3), 1.39 (1H, ddd, *J* 13.0, 8.4 and 4.0, 4-CHβ), 1.19-1.14 (1H, obs m, 2'-CH), 1.17 (3H, d, *J* 7.0, CH_3), 1.14 (3H, d, *J* 7.0, CH_3), 0.99 (3H, d, *J* 6.5, 5'-CH_3); δ_C (100.6 MHz) 140.9 (C), 133.4 (CH), 129.2 (CH), 128.1 (CH), 71.3 (2-CH), 65.7 (3-CH), 57.9 (5-CH), 37.5 (N-CH_3), 35.3 (4-CH_2), 29.4 (2'-CH), 23.4 (5'-CH_3), 19.6 (2'-CH_3), 18.6 (2'-CH_3). *m/z* (FAB) 282 (M^++H).

1-Benzyl-2α-cyclopropyl-5β-methyl-3α-(phenylsulphonyl)-pyrrolidine 338



The above procedure was followed using crude *N*-oxide **325** (0.335g, containing *ca.* 0.84 mmol), nickel(II) chloride hexahydrate (0.572g, 2.1 mmol) and sodium borohydride (0.20 g, 5.3 mmol) in methanol (30 ml) yielding the *title compound* **338** (one diastereoisomer, 0.244g, 90%) as a brown oil after chromatography (silica, 19:1 dichloromethane-methanol), which showed δ_H (400 MHz) 7.95 (2H, d, *J* 7.3, Ar), 7.67-7.56 (3H, m, Ar), 7.36-7.22 (5H, m, Ar), 3.95 (2H, AB q, *J* 15 and 23, 1-CH_2), 3.82 (1H, ddd, *J* 9.0, 9.0 and 6.2, 3-CH), 3.30-3.35 (1H, m, 5-CH), 2.70-2.74 (2H, m, 2-CH and 4-CHα), 1.47 (1H, ddd, *J* 13.0, 9.0 and 4.0, 4-CHβ), 1.00-1.10 (1H, m, 2'-CH), 1.00 (3H, d, *J* 6.1, 5-CH_3), 0.71-0.76 (1H, m, 2'-CH), 0.60-0.63 (1H, m, 2'-CH), 0.38-0.42 (1H, m, 2'-CH), 0.15-0.18 (1H, m, 2'-CH); δ_C (100.6 MHz) 140.7 (C), 139.9 (C), 133.2 (CH), 129.1 (CH), 128.1 (CH), 128.0 (CH), 127.8 (CH), 126.5 (CH), 66.4 (2-CH), 65.0 (3-CH), 54.2 (5-CH), 50.9 (1-CH_2), 33.5 (4-CH_2), 19.3 (5-CH_3), 6.4 (2'-CH), 6.3 (2'-CH_2) and 2.9 (2'-CH_2). *m/z* (FAB) 356 (100%, MH^+).

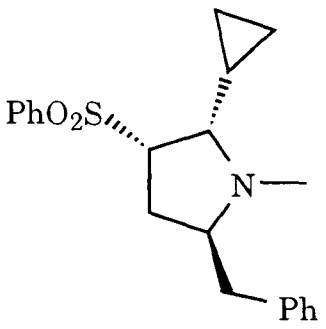
5β-Ethyl-1-methyl-2α-cyclopropyl-3α-(phenylsulphonyl)-pyrrolidine 339



The above procedure was followed using crude *N*-oxide **304** (0.245g, containing *ca.* 0.44 mmol), nickel(II) chloride hexahydrate (0.44g, 1.6 mmol) and sodium borohydride (0.15 g, 4 mmol) in methanol (30 ml) yielding the *title compound* **339** (largely one diastereoisomer, >3:1, 0.109g, 85%) as a brown oil after chromatography (silica, 19:1 dichloromethane-methanol), the major diastereoisomer of which showed υ_{max} 1450, 1290, 1145, 1080 and 750 cm^{-1}, δ_H (400 MHz) 7.90-7.20 (5H, m, Ar), 3.74 (1H, ddd, *J* 9.4, 9.4 and 6.2, 3-CH), 2.81-2.88 (1H, m, 5-CH), 2.64 (1H, dd, *J* 10.3 and 6.2, 2-CH), 2.50 (1H, ddd, *J* 13.0, 9.4 and 9.4, 4-CHα), 2.40 (3H, s, N-CH_3), 1.58-1.70 (1H, m, 5'-CH), 1.46 (1H, ddd, *J* 13.0, 9.4 and 5.0, 4-CHβ), 1.04-1.08 (1H, m, 5'-CH), 0.93-1.00 (1H, m, 2'-CH), 0.75 (3H, t, *J* 7.4, 5'-CH_3), 0.70-0.75 (1H, m, 2'-CH), 0.60-0.63 (1H, m, 2'-CH), 0.37-0.43 (1H, m, 2'-CH) and 0.28-0.33 (1H, m, 2'-CH); δ_C (100.6 MHz) 140.6 (C), 133.3 (CH), 129.1 (CH), 127.9 (CH), 70.6 (2-CH), 64.8 (3-CH), 62.9 (5-CH), 35.9 (N-CH_3), 30.9 (4-CH_2), 25.4 (5'-CH_2), 10.0 (5'-CH_3), 6.4 (2'-CH_2), 5.9 (2'-CH) and 3.2 (2'-CH_2). *m/z* (ES) 294 (100%, MH^+). [Found: MH^+, 294.1528. $C_{16}H_{24}NO_2S$ requires M, 294.1528].

When left to stand in $CDCl_3$ over *ca.* 2 days, this product was observed to isomerise to give a mixture of 3 isomers.

5β-Benzyl-1-methyl-2α-cyclopropyl-3α-(phenylsulphonyl)-pyrrolidine 347



The above procedure was followed using crude *N*-oxide **306** (0.245g, containing *ca.* 0.44 mmol), nickel(II) chloride hexahydrate (0.44g, 1.6 mmol) and sodium borohydride (0.15 g, 4 mmol) in methanol (30 ml) yielding the *title compound* **347** (largely one diastereoisomer, 0.109g, 85%) as a brown oil.

The amine **347** (100 mg) was dissolved in deuteriochloroform (10 ml) and the resulting solution was left to stand at ambient temperature for 48h. Purification by column chromatography (silica, 19:1 dichloromethane-methanol) yielded three diastereoisomers of *5-benzyl-2-cyclopropyl-1-methyl-3-(phenylsulphonyl)-pyrrolidine*, which were further separated by chromatography (silica, 19:1 dichloromethane-methanol) to give *isomer 1* and *isomer 3* as pure fractions and *isomer 2* as a crude mixture of all 3. The identity of each isomer is not known.

isomer 1

υ_{max} 1450, 1145, 1080 and 755 cm^{-1}, δ_H (400 MHz) 7.90-7.00 (10H, m, Ar), 3.43 (1H, ddd, *J* 10.0, 4.0 and 1.6, 3-CH), 2.98 (1H, dd, *J* 13.4 and 4.0, 2-CH), 2.73-2.80 (1H, m, 5-CH), 2.46 (3H, s, N-CH_3), 2.38-2.44 (2H, m, 4-CHα & 6-CHa), 2.02 (1H, ddd, *J* 14.0, 5.5 and 1.6, 6-CHb), 1.72 (1H, ddd, *J* 14.0, 10.0 and 10.0, 4-CHβ), 0.73-0.79 (1H, m, 2'-CH), 0.54-0.60 (1H, m, 2'-CH_2), 0.24-0.31 (2H, m, 2'-CH_2) and 0.05-0.10 (1H, m, 2'-CH_2);

δ_C (100.6 MHz) 138.6 (C), 138.4 (C), 133.6 (CH), 129.2 (CH), 129.1 (CH), 128.8 (CH), 128.3 (CH), 126.2 (CH), 70.4 (2-CH), 68.2 (3-CH), 66.4 (5-CH), 40.0 (5'-CH_2), 39.8 (N-CH_3), 32.7 (4-CH_2), 16.5 (2'-CH), 4.8 (2'-CH_2) and 0.7 (2'-CH_2). *m/z* (ES) 356 (100%, MH^+). [Found: MH^+, 356.1684. $C_{21}H_{26}NO_2S$ requires M, 356.1684].

isomer 2

δ_H (400 MHz) 7.90-7.00 (10H, m, Ar), 3.61 (1H, ddd, *J* 9.3, 9.3 and 6.2, 3-CH), 3.25-3.30 (1H, obs m, 5-CH), 2.63 (1H, dd, *J* 10.4 and 6.2, 2-CH), 2.38 (3H, s, N-CH_3), 2.00-2.10 (1H, m, 5'-CHa), 1.85-1.95 (1H, m, 5'-CHb), 1.50-1.60 (1H, m, 4-CHβ), 0.97-1.03 (1H, m, 2'-CH), 0.70-0.80 (1H, m, 2'-CH_2), 0.55-0.65 (1H, m, 2'-CH_2) and 0.50-0.30 (2H, m, 2'-CH_2). 4-CHα signal obscured.

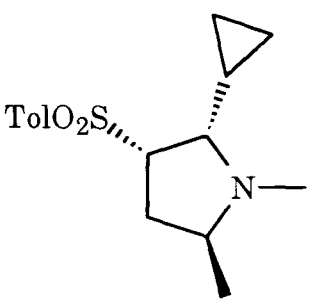
isomer 3

δ_H (400 MHz) 7.87 (2H, d, *J* 7.1, Ar), 7.63 (1H, app t, *J* 7.4, Ar), 7.54 (2H, app t, *J* 7.6, Ar), 7.23 (2H, app t, *J* 7.3, Ar), 7.16 (1H, app t, *J* 7.3, Ar), 7.03 (1H, d, *J* 7.0, Ar), 3.23 (1H, ddd, *J* 7.7, 4.8 and 3.3, 3-CH), 2.49 (1H, app t, *J* 7.5, 5-CH), 2.40 (3H, s, N-CH_3), 2.32 (1H, dd, *J* 9.2 and 3.3, 2-CH), 2.00-2.05 (1H, m), 1.80-1.90 (1H, m), 1.65-1.70 (1H, m), 1.40-1.50 (1H, m), 0.95-1.00 (1H, m), 0.58-0.63 (1H, m, 2'-CH), 0.40-0.50 (1H, m, 2'-CH) and 0.25-0.31 (2H, m, 2 x 2'-CH).

1,5β-Dimethyl-2α-cyclopropyl-3α-(toluenesulphonyl)-pyrrolidine 355

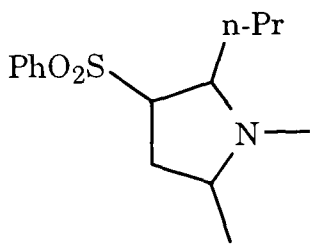
The above procedure was followed using crude *N*-oxide **421** (0.50g, containing *ca.* 1.45 mmol), nickel(II) chloride hexahydrate (0.87g, 3.2 mmol) and sodium borohydride (0.305 g, 8.1 mmol) in methanol (50 ml) yielding the *title compound* **355** (one diastereoisomer, 0.384g, 90%) as a brown oil after chromatography (silica, 19:1 dichloromethane-

methanol), which showed υ_{max} 1315, 1301 and 1145 cm^{-1}; δ_H (250 MHz) 7.75 (2H, d, *J* 8.3, Ar), 7.32 (2H, d, *J* 8.3, Ar), 3.78 (1H, ddd, *J* 9.4, 9.4 and



6.5, 3-CH), 3.06-3.11 (1H, m, 5-CH), 2.55-2.61 (2H, m, 2-CH and 4-CHα), 2.41 (3H, s, CH_3), 2.43 (3H, s, CH_3), 1.40 (1H, ddd, *J* 13.1, 9.4 and 4.5, 4-CHβ), 0.99-1.04 (1H, m, 2'-CH), 0.97 (3H, d, *J* 6.2, 5-CH_3), 0.69-0.75 (1H, m, 2'-CH), 0.60-0.65 (1H, m, 2'-CH), 0.38-0.42 (1H, m, 2'-CH) and 0.29-0.33 (1H, m, 2'-CH); δ_C (67.8 MHz) 144.2 (C), 137.9 (CH), 129.8 (CH), 128.1 (CH), 70.4 (2-CH), 64.8 (3-CH), 56.6 (5-CH), 35.8 (N-CH_3), 33.9 (4-CH_2), 21.6 (CH_3, Ar), 18.3 (5-CH_3), 6.5 (2'-CH_2), 6.4 (2'-CH) and 3.3 (2'-CH_2).

1,5-Dimethyl-2-propyl-3-(phenylsulphonyl) pyrrolidine (363/364)



The above procedure was followed using crude *N*-oxide **362** (0.219g, *ca.* 0.66 mmol), nickel(II) chloride hexahydrate (0.413g, 1.5 mmol) and sodium borohydride (0.15 g, 3.96 mmol) in methanol (20 ml) yielding the *title compound* (two diastereoisomers, 0.17 g, 87%) as brown oils after chromatography (silica, 1:1 petrol-ether), which showed

isomer 1

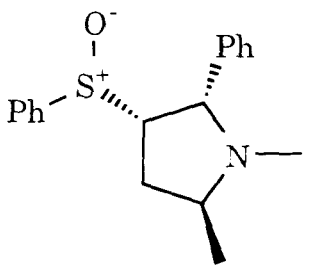
δ_H (250 MHz) 7.92 (2H, d, *J* 6.9, Ar), 7.68-7.52 (3H, m, Ar), 3.42-3.30 (2H, m, 3 & 5-CH), 2.93 (1H, app q, *J* 6.4, 2-CH), 2.26 (3H, s, N-CH_3), 2.14 (1H, ddd, *J* 13.6, 9.5 and 6.4, 4-CHa), 1.92 (1H, ddd, *J* 13.6, 7.6 and 6.6, 4-CHb), 1.50-1.60 (1H, m, 2'-CH_2), 1.33-1.06 (3H, m, 2'-CH_2), 1.03 (3H, d, *J* 6.3, 5-CH_3) and 0.81 (3H, t, *J* 7.1, 2'-CH_3);

isomer 2

δ_H (250 MHz) 7.91 (2H, d, *J* 6.9, Ar), 7.70-7.54 (3H, m, Ar), 3.29 (1H, ddd, *J* 10.2, 5.7, 1.7, 3-CH), 2.90 (1H, app q, *J* 4.7, 2-CH), 2.50-2.60 (1H, m, 5-CH), 2.27 (3H, s, N-CH_3), 2.23 (1H, ddd, *J* 13.8, 5.7 and 1.7, 4-CHa), 1.62 (1H, ddd, *J* 13.8, 10.2 and 10.6, 4-CHb), 1.48-1.10 (4H, m, 2 x 2'-CH_2), 1.04 (3H, d, *J* 7.0, 5-CH_3) and 0.84 (3H, t, *J* 7.1, 2'-CH_3).

No further data was obtained on these compounds.

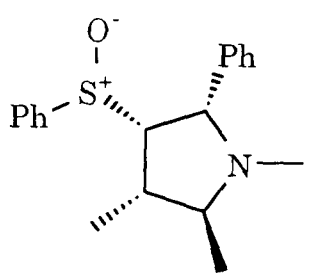
1,5β-Dimethyl-2α-phenyl-3α-(phenylsulphinyl)-pyrrolidine 387



The above procedure was followed using *N*-oxide **386** (0.031g, 0.1 mmol), nickel(II) chloride hexahydrate (0.055g, 2 mmol, 2.04 eq) and sodium borohydride (0.02 g, 5.3 mmol, 5.4 eq) in methanol (30 ml) yielding the *title compound* **387** (one diastereoisomer, 0.026 g, 88 %) as a brown oil after chromatography (silica, 9:1 dichloromethane-methanol), which showed δ_H (270 MHz) 7.50-7.10 (10H, m, Ar), 3.97 (1H, d, *J* 8.5, 2-CH), 3.44-3.61 (2H, m, 3 & 5-CH), 2.85-2.93 (1H, m, 4-CHα), 2.13 (3H, s, N-

CH_3), 1.45-1.52 (1H, m, 4-CHβ) and 1.01 (3H, d, *J* 6.6, 5-CH_3); δ_C (67.8 MHz) 144.0 (C), 137.2 (C), 130.4 (CH), 129.6 (CH), 128.8 (CH), 128.3 (CH), 128.0 (CH), 124.5 (CH), 68.7 (2-CH), 68.1 (3-CH), 57.2 (5-CH), 35.0 (N-CH_3), 28.5 (4-CH_2) and 14.2 (5-CH_3).

2α-Phenyl-3α-(phenylsulphinyl)-1, 4α, 5β-trimethyl pyrrolidine 401



The above procedure was followed using *N*-oxide **390** (0.0173 g, 0.053 mmol), nickel(II) chloride hexahydrate (0.03g, 0.11 mmol, 2.09 eq) and sodium borohydride (0.011 g, 0.29 mmol, 5.5 eq) in methanol (2 ml) yielding the *title compound* **401** (one diastereoisomer, 0.015 g, 91 %) as a brown oil, which showed δ_H (400 MHz) 7.50-6.85 (10H, m, Ar), 4.12 (1H, app t, *J* 9.0, 3-CH), 3.48 (1H, d, *J* 9.5, 2-CH), 3.00-3.07 (1H, m, 5-CH), 2.60-2.70 (1H, m, 4-CH), 1.95 (3H, s, N-CH_3), 1.75 (3H, d, *J* 7.1, 4-CH_3) and 1.08 (3H, d, *J* 6.4, 5-CH_3); δ_C (67.8 MHz) 142.4 (C), 137.6 (C), 131.3 (CH), 130.2 (CH), 128.7 (CH), 128.4 (CH), 127.9 (CH), 126.5 (CH), 69.9 (3-CH), 68.6 (2-CH), 65.2 (5-CH), 42.1 (4-CH), 34.6 (N-CH_3), 16.2 (4-CH_3) and 13.5 (5-CH_3).

5.9 Attempted Demethylation Reactions

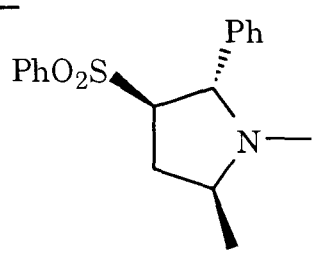
A solution of 1,5-dimethyl-2-phenyl-3-(phenylsulphonyl) pyrrolidine **328** (1 mmol) and chloroformate (2 mmol, 2 eq) [methyl, ethyl, phenyl, benzyl and vinyl chloroformates were attempted] in solvent

(5 ml) [dichloromethane, chloroform, 1,2-dichloroethane, benzene and toluene were tried] was refluxed for up to 4 days.[142]

Acid-base work-up yielded either starting material and/or unidentifiable decomposition products.

5.10 Attempted Desulphonylation Reactions

i) Ultra dispersed Potassium[137]

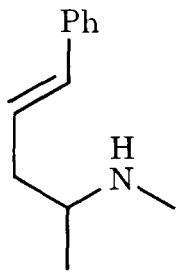


Small pieces of potassium (14 mg, 0.36 mmol, 2.8 eq) in dry toluene (0.5 ml) were subjected to ultrasound for 30 min until a purple suspension of very fine particles of ultrasonically dispersed potassium was obtained. To this was added a solution of 1,5-dimethyl-2-phenyl-3-(phenylsulphonyl)-pyrrolidine **328** (40 mg, 0.13 mmol) in dry toluene (0.5 ml) and the resulting mixture subjected to ultrasound for 30 min.

To this was added, very carefully, water (1 ml) dropwise and the mixture stirred until all the potassium had been consumed. The organic layer was separated and the aqueous layer extracted with dichloromethane (2 x 2 ml). The combined organic extracts were dried and evaporated to give *1,5-β-Dimethyl-2α-phenyl-3β-(phenylsulphonyl)-pyrrolidine* **354** (38 mg, 94%) as a brown oil, which showed υ_{max} (soln) 1456, 1307, 1146, 1087 and 998 cm^{-1}; δ_H (400 MHz) 7.80-6.90 (10H, m, Ar), 4.00 (1H, d, *J* 6.9, 2-CH), 3.77 (1H, ddd, *J* 10.8, 6.9 and 5.7, 3-CH), 3.43-3.49 (1H, m, 5-CH), 2.52 (1H, ddd, *J* 13.7, 10.8 and 7.0, 4-CHα), 2.13-2.19 (1H, m, 4-CHβ), 1.98 (3H, s, N-CH_3) and 1.13 (3H, d, *J* 6.4, 5'-CH_3); δ_C (67.8 MHz) 140.0 (C), 138.5 (C), 133.4 (CH), 128.8 (CH), 128.3

(CH), 128.2 (CH), 127.9 (CH), 127.5 (CH), 70.1 (2-CH), 67.3 (3-CH), 57.6 (5-CH), 34.4 (CH_3), 32.7 (4-CH_2) and 15.2 (5'-CH_3).

ii) Sodium Amalgam[136]



To a solution of 1,5-dimethyl-2-phenyl-3-(phenylsulphonyl)-pyrrolidine **328** (30 mg, 0.097 mmol) in dry methanol (2 ml) under nitrogen, were added sodium dihydrogen phosphate (53 mg, 0.44 mmol, 4.6 eq) and 6% sodium amalgam (77 mg, 0.2 mmol, 2.1 eq) and the mixture stirred at room temperature for 18 h.

Water (1 ml) was added, very carefully, and the mixture stirred for a further 10 min, whereupon it was filtered through Keiselguhr along with a dichloromethane wash (2 x 3 ml). The filtrate was separated and the aqueous layer was extracted with dichloromethane (2 x 2 ml). The combined organic extracts were dried and evaporated to give an inseparable product (19 mg) which appeared (by ^{13}C NMR) to contain mainly compound **353** (no starting material by NMR; proposed as *4-(methylamino)-1-phenyl-pent-1-ene*) showing δ_H (400 MHz) 7.45-7.15 (5H, m, Ar), 6.46 (1H, d, *J* 15.8, 1-CH), 6.20 (1H, dt, *J* 15.8, 7.5, 7.5, 2-CH), 2.58-2.71 (2H, m, 4-CH & NH), 2.45 (3H, s, N-CH_3), 2.42-2.15 (2H, m, 3-CH_2) and 1.13 (3H, d, *J* 6.3, 5-CH_3). *m/z* (ES) 176 (100%, MH^+). [Found: MH^+, 176.1439. $C_{12}H_{18}N$ requires M, 176.1439].

iii) Samarium Iodide[135]

To a degassed solution of 1,5-dimethyl-2-phenyl-3-(phenylsulphonyl)pyrrolidine **328** (14.5 mg, 0.05 mmol) and hexamethyl phosphoramide (46 µl, 0.26 mmol, 5.7 eq) in THF (1 ml) at room temperature under argon was added a solution of samarium(II) iodide (0.1M in THF, 0.9 ml, 0.09 mmol, 1.96 eq) and the reaction was stirred for 30 min.

The reaction mixture was diluted with hexane (3ml) and filtered through silica, yielding an inseparable mixture.

iv) Tributyltin Hydride

A solution of 1,5-dimethyl-2-phenyl-3-(phenylsulphonyl) pyrrolidine **328** (12.8 mg, 0.04 mmol) and tributyltin hydride (35 µl, 0.13 mmol, 3.2 eq) in toluene (1 ml) was degassed using the freeze-thaw method. To this was added 2,2'-azobis(2-methylpropionitrile) (AIBN, 1 mg, 15 mol%) and the solution warmed to 80°C under nitrogen. The mixture was kept at this temperature for 3 h.

The solvent was removed *in vacuo* and the resulting residue was washed with pentane (3 x 1 ml) to give starting material.

v) Hydrogenation[130,131]

A solution of 1,5-dimethyl-2-phenyl-3-(phenylsulphonyl)-pyrrolidine **328** (31 mg, 0.1 mmol) and catalyst (15 mol%) [10% palladium on activated carbon, or Raney nickel] in ethanol (1 ml) at room temperature under an atmosphere of hydrogen, was stirred for 20 h.

The suspension was filtered through Keiselgühr and the combined solution and a dichloromethane wash (3 x 2 ml) were dried and evaporated to give starting material.

Other sulphones subjected to these conditions were 1,5-dimethyl-2-cyclopropyl-3-(phenylsulphonyl)pyrrolidine **336** and 1,5-dimethyl-2-cyclopropyl-3-(*p*-toluenesulphonyl)pyrrolidine **353**, but these were also unsuccessful.

vi) Magnesium in Ethanol[134]

To a solution of 1,5-dimethyl-2-phenyl-3-(phenylsulphonyl) pyrrolidine **328** (30 mg, 0.097 mmol) in ethanol (1 ml) were added magnesium (0.4 mmol, 4 eq) and mercury(II) chloride (1 crystal, cat.), and the suspension was stirred at room temperature under nitrogen for 19 h.

Hydrochloric acid (0.5M, 2 ml) was added and the mixture stirred until no magnesium remained (*ca.* 10 min). This was then extracted with dichloromethane (3 x 2 ml) and the combined organic extracts were dried and evaporated to give only starting material.

Other sulphones subjected to these conditions were 1,5-dimethyl-2-cyclopropyl-3-(phenylsulphonyl)-pyrrolidine **336** and 1,5-dimethyl-2-cyclopropyl-3-(*p*-toluenesulphonyl)-pyrrolidine **353**, but these were also unsuccessful.

vii) Lithium / Sodium in Naphthalene[132,133]

To a green suspension of lithium powder (7.4 mg, 1.1 mmol, 17 eq) and naphthalene (2.0 mg, 0.016 mmol, 0.25 eq, cat.) in THF (5 ml) under argon at -78°C, was added a solution of 1,5-dimethyl-2-phenyl-3-

(phenylsulphonyl)-pyrrolidine **328** (21 mg, 0.06 mmol) and benzaldehyde (8 µl, 0.08 mmol, 1.2 eq) in THF (2 ml) and the solution stirred at -78°C for 45 min and then warmed to room temperature and stirred for a further 1 h.

Water (5 ml) was added, the organic layer separated and the aqueous layer extracted with dichloromethane (2 x 5 ml). The combined organic extracts were dried and evaporated to give an inseparable mixture which appeared not to contain the desired product.

A green suspension of sodium (10 mg, 0.43, 10 eq) and naphthalene (55 mg, 0.43 mmol, 10 eq) in 1,2-dimethoxyethane (0.1 ml) was added to a solution of 1,5-dimethyl-2-cyclopropyl-3-(phenylsulphonyl)-pyrrolidine **336** (12.5 mg, 0.043 mmol) in THF (1 ml) at room temperature under nitrogen, and the mixture stirred for 15 h. Again an inseparable and unidentifiable mixture was obtained.

Other sulphones subjected to these conditions were 1,5-dimethyl-2-phenyl-3-(phenylsulphonyl)-pyrrolidine *N*-oxide **328** and 1,5-dimethyl-2-cyclopropyl-3-(*p*-toluenesulphonyl)-pyrrolidine **353**, but these were also unsuccessful.

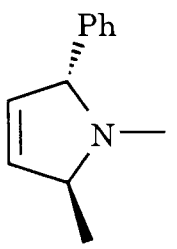
viii) Diisobutylaluminium Hydride

To a stirred solution of 1,5-dimethyl-2-phenyl-3-(phenylsulphonyl)-pyrrolidine **328** (15 mg, 0.05 mmol) in toluene (0.1 ml) was added diisobutylaluminium hydride (1.5M in toluene, 0.1 ml, 0.15 mmol, 3 eq) and the solution refluxed for 20 h.

Aqueous work-up showed an inseparable mixture of products not containing starting material.

Another sulphone subjected to these conditions was 1,5-dimethyl-2-cyclopropyl-3-(phenylsulphonyl)-pyrrolidine **336**.

5.11 Attempted Elimination Reactions of Sulphoxide



A solution of sulphoxide **387** (15 mg, 0.04 mmol) and potassium carbonate (5mg, 0.05 mmol) in toluene was heated at reflux for 7 h. The mixture was filtered and the solvent was removed *in vacuo* to give eliminated product (no starting material by NMR; proposed as alkene **388**, 12 mg) as an inseparable mixture, which contained δ_H (250 MHz) 7.10-7.60 (Ar), 5.91-5.97 (1H, m, :CH), 5.77-5.83 (1H, m, :CH), 4.68-4.72 (1H, m, 2-CH), 3.88-4.00 (1H, m, 5-CH), 2.21 (3H, s, N-Me), 2.21 (3H, d, *J* 6.5, Me).

Appendix

Crystal Structure Determination

A single crystal X-ray diffraction experiment was carried out using an Enraf-Nonius CAD4 four-circle diffractometer, at room temperature. Crystal Data: $C_{18}H_{21}NO_3S.H_2O$ (from methanol solution), M=349.43, monoclinic, space group $P2_1/c$ (No. 14), a=9.353 (5), B=12.010(5), c=16.254(6) Å, b=98.35(5)°, V=1806.4(1.4) $Å^3$ (from 25 reflections with 23 <θ<32°), Z=4, D_x=1.285 gcm^{-3}, F(000)=744, Ni-filtered Cu-K_α radiation, λ=1.54178 Å, μ=17.7 cm^{-1}, crystal size 0.1 x 0.4 x 0.8 mm, 3771 unique data with θ ≤ 76° collected by 2θ/ω scan technique. The structure was solved by direct methods using MULTAN programs,[153] expanded using CRYSTALS software.154 Final least squares refinement was performed against F^2 of 3767 data with two-term Chebyshev weighting scheme,[155] using SHELXL-93 software.[156] All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms located by difference Fourier, were included in riding positions (idealised except for water hydrogens). Methyl groups were refined as rotating bodies. The refinement of 221 variables converged at wR(F2)=0.208 for all data and conventional R(F)=0.064 for 2384 reflections with I > σ(I), goodness-of-fit 1.058, final residual electron density $\Delta\rho_{min}$=-0.46, $\Delta\rho_{max}$=0.44 $eÅ^{-3}$ (the biggest peaks on the S-C bonds, the rest being under 0.3 $eÅ^{-3}$). No absorption correction was applied. The additional material available from the Cambridge Crystallographic Data Centre comprises atomic co-ordinates and displacement parameters, bond distances and angles (see Information for Authors, Issue 1).

The molecular structure of compound **264** was determined by X-ray crystallography (Fig. 4). The heterocycle adopts an envelope conformation, with the nitrogen atom tilted 0.71 Å out of the plane of the four carbon atoms. The molecule of crystallisation water by both its hydrogen atoms

forms hydrogen bonds with the O(1) atoms of two molecules of compound **264** , related *via* an inversion centre (O...O 2.74 and 2.75 Å), thus forming an aggregate of two molecules of compound **264** and two moleclues of water.

Table 1. Crystal data and structure refinement for 1.

Identification code	aw1
Empirical formula	C18 H23 N O4 S
Formula weight	349.43
Temperature	293(2) K
Wavelength	1.54178 A
Crystal system	Monoclinic
Space group	P2(1)/c (No.14)
Unit cell dimensions	a = 9.353(5) A alpha = 90 deg. b = 12.010(5) A beta = 98.35(5) deg. c = 16.254(6) A gamma = 90 deg.
Volume	1806.4(14) A^3
Z	4
Density (calculated)	1.285 Mg/m^3
Absorption coefficient	1.770 mm^-1
F(000)	744
Crystal size	0.8 x 0.4 x 0.1 mm
Theta range for data collection	4.59 to 75.94 deg.
Index ranges	0<=h<=11, 0<=k<=15, -20<=l<=20
Reflections collected	3771
Independent reflections	3771 [R(int) = 0.0000]
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3767 / 0 / 221
Goodness-of-fit on F^2	1.058
Final R indices [I>2sigma(I)]	R1 = 0.0642, wR2 = 0.1676
R indices (all data)	R1 = 0.1116, wR2 = 0.2077
Largest diff. peak and hole	0.443 and -0.457 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 1. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
S	182(1)	4856(1)	2445(1)	45(1)
O(1)	3623(3)	6236(2)	4478(2)	51(1)
O(2)	-599(3)	5793(3)	2068(2)	65(1)
O(3)	-626(3)	3967(3)	2743(2)	66(1)
N(1)	2608(3)	6878(2)	4001(2)	37(1)
C(2)	2241(3)	6389(3)	3123(2)	36(1)
C(3)	1433(3)	5334(3)	3306(2)	38(1)
C(4)	642(4)	5634(3)	4045(2)	49(1)
C(5)	1153(4)	6792(3)	4314(2)	46(1)
C(6)	1260(6)	7002(4)	5236(3)	70(1)
C(7)	3143(4)	8040(3)	3981(3)	49(1)
C(8)	3525(3)	6291(3)	2668(2)	39(1)
C(9)	4554(4)	5451(3)	2833(3)	51(1)
C(10)	5715(4)	5402(4)	2390(3)	64(1)
C(11)	5833(5)	6184(4)	1777(3)	68(1)
C(12)	4835(5)	7016(4)	1615(3)	65(1)
C(13)	3667(4)	7063(3)	2050(2)	50(1)
C(14)	1229(3)	4288(3)	1731(2)	41(1)
C(15)	1301(5)	4832(3)	998(3)	60(1)
C(16)	2032(6)	4352(4)	416(3)	76(1)
C(17)	2712(6)	3344(4)	572(3)	71(1)
C(18)	2655(5)	2813(4)	1316(3)	63(1)
C(19)	1913(4)	3276(3)	1898(3)	51(1)
O(1W)	3524(4)	4009(3)	4838(3)	121(2)

Table 3. Bond lengths [A] and angles [deg] for 1.

S-O(2)	1.429(3)	S-O(3)	1.432(3)
S-C(14)	1.761(4)	S-C(3)	1.784(3)
O(1)-N(1)	1.372(3)	N(1)-C(7)	1.485(4)
N(1)-C(5)	1.524(5)	N(1)-C(2)	1.535(4)
C(2)-C(8)	1.504(5)	C(2)-C(3)	1.526(4)
C(3)-C(4)	1.544(5)	C(4)-C(5)	1.514(5)
C(5)-C(6)	1.508(6)	C(8)-C(13)	1.388(5)
C(8)-C(9)	1.392(5)	C(9)-C(10)	1.389(6)
C(10)-C(11)	1.384(7)	C(11)-C(12)	1.366(7)
C(12)-C(13)	1.386(6)	C(14)-C(15)	1.369(6)
C(14)-C(19)	1.382(5)	C(15)-C(16)	1.373(6)
C(16)-C(17)	1.374(7)	C(17)-C(18)	1.375(7)
C(18)-C(19)	1.370(6)		

O(2)-S-O(3)	118.0(2)	O(2)-S-C(14)	108.7(2)
O(3)-S-C(14)	107.8(2)	O(2)-S-C(3)	108.6(2)
O(3)-S-C(3)	107.1(2)	C(14)-S-C(3)	106.1(2)
O(1)-N(1)-C(7)	109.4(2)	O(1)-N(1)-C(5)	110.6(3)
C(7)-N(1)-C(5)	113.0(3)	O(1)-N(1)-C(2)	110.7(2)
C(7)-N(1)-C(2)	111.7(3)	C(5)-N(1)-C(2)	101.2(2)
C(8)-C(2)-C(3)	118.9(3)	C(8)-C(2)-N(1)	113.6(2)
C(3)-C(2)-N(1)	100.8(3)	C(2)-C(3)-C(4)	105.3(3)
C(2)-C(3)-S	113.7(2)	C(4)-C(3)-S	110.6(2)
C(5)-C(4)-C(3)	105.8(3)	C(6)-C(5)-C(4)	114.4(3)
C(6)-C(5)-N(1)	112.7(3)	C(4)-C(5)-N(1)	103.0(3)
C(13)-C(8)-C(9)	119.1(3)	C(13)-C(8)-C(2)	118.1(3)
C(9)-C(8)-C(2)	122.8(3)	C(10)-C(9)-C(8)	120.1(4)
C(11)-C(10)-C(9)	119.6(4)	C(12)-C(11)-C(10)	120.8(4)
C(11)-C(12)-C(13)	119.8(4)	C(12)-C(13)-C(8)	120.5(4)
C(15)-C(14)-C(19)	120.8(4)	C(15)-C(14)-S	119.4(3)
C(19)-C(14)-S	119.8(3)	C(14)-C(15)-C(16)	119.5(4)
C(15)-C(16)-C(17)	120.4(5)	C(16)-C(17)-C(18)	119.6(4)
C(19)-C(18)-C(17)	120.6(4)	C(18)-C(19)-C(14)	119.1(4)

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 1. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
S	28(1)	48(1)	58(1)	-13(1)	0(1)	-6(1)
O(1)	45(1)	39(1)	62(2)	6(1)	-16(1)	9(1)
O(2)	40(1)	67(2)	81(2)	-20(2)	-16(1)	20(1)
O(3)	47(2)	71(2)	83(2)	-25(2)	17(1)	-34(1)
N(1)	33(1)	27(1)	49(2)	-1(1)	-4(1)	4(1)
C(2)	26(1)	31(2)	48(2)	-1(1)	-2(1)	3(1)
C(3)	30(2)	36(2)	47(2)	-4(1)	0(1)	-4(1)
C(4)	43(2)	53(2)	54(2)	-6(2)	12(2)	-13(2)
C(5)	42(2)	43(2)	51(2)	-4(2)	5(2)	4(2)
C(6)	95(4)	63(3)	57(3)	-16(2)	23(2)	-6(3)
C(7)	50(2)	29(2)	65(2)	-1(2)	-6(2)	-2(2)
C(8)	27(1)	38(2)	50(2)	-6(1)	3(1)	-3(1)
C(9)	39(2)	40(2)	74(3)	-7(2)	8(2)	2(2)
C(10)	39(2)	61(3)	93(3)	-20(2)	14(2)	7(2)
C(11)	45(2)	85(3)	77(3)	-21(3)	21(2)	-14(2)
C(12)	60(3)	71(3)	67(3)	0(2)	20(2)	-14(2)
C(13)	43(2)	54(2)	53(2)	0(2)	7(2)	-3(2)
C(14)	35(2)	38(2)	46(2)	-7(1)	-1(1)	-4(1)
C(15)	73(3)	45(2)	61(2)	3(2)	14(2)	12(2)
C(16)	99(4)	66(3)	67(3)	8(2)	28(3)	10(3)
C(17)	76(3)	69(3)	71(3)	-12(2)	23(2)	16(2)
C(18)	58(2)	48(2)	80(3)	-4(2)	6(2)	13(2)
C(19)	49(2)	43(2)	58(2)	2(2)	1(2)	4(2)
O(1W)	76(2)	64(2)	201(5)	54(3)	-49(3)	-21(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for 1.

	x	y	z	U(eq)
H(2)	1544(3)	6890(3)	2801(2)	43
H(3)	2136(3)	4743(3)	3476(2)	46
H(4A)	-396(4)	5626(3)	3877(2)	59
H(4B)	885(4)	5108(3)	4497(2)	59
H(5)	490(4)	7339(3)	4019(2)	55
H(6A)	1585(31)	7750(9)	5356(4)	84(9)
H(6B)	1937(25)	6488(17)	5530(3)	84(9)
H(6C)	329(9)	6900(24)	5407(4)	84(9)
H(7A)	2425(11)	8495(5)	3659(12)	55(7)
H(7B)	4015(14)	8052(4)	3735(13)	55(7)
H(7C)	3337(24)	8326(7)	4538(3)	55(7)
H(9)	4462(4)	4922(3)	3239(3)	61
H(10)	6412(4)	4849(4)	2505(3)	76
H(11)	6598(5)	6142(4)	1472(3)	81
H(12)	4940(5)	7549(4)	1213(3)	78
H(13)	2974(4)	7617(3)	1927(2)	60
H(15)	858(5)	5521(3)	895(3)	71
H(16)	2071(6)	4713(4)	-87(3)	91
H(17)	3208(6)	3022(4)	176(3)	85
H(18)	3120(5)	2133(4)	1424(3)	75
H(19)	1869(4)	2913(3)	2400(3)	61
H(1W)	3359(4)	4782(3)	5180(3)	204
H(2W)	4180(4)	3775(3)	4991(3)	120

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172 Subsequent work by J. Hanrahan, Cardiff University, personal communication, has shown that purification can be effected using column chromatography by eluting quickly with ether to remove the non-polar starting materials, followed by very rapid elution with methanol to give purified material.

173 Mass spectroscopic studies showed that electron ionisation disintegrated the *N*-oxide. It was later found that fast atom bombardment techniques gave a molecular ion, as did electrospray, with very little fragmentation. Using this data,

mass spectroscopy was very useful in confirming the presence of the *N*-oxide.