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A Study of Directed Cleavage of Aziridinylcarbinyl Radicals.

by

Richard Clive Toon

A Doctoral Thesis
Submitted in Partial Fulfilment of the requirements for the award of
Doctor of Philosophy
of
Loughborough University.

December 1998

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Abstract

The work described in this thesis is an investigation into the reactivity and possible synthetic applications of aziridinylcarbinyl radicals. These radicals rapidly rearrange *via* β-cleavage, which can proceed by breakage of either the C-N or C-C bond. Cleavage of the latter has been found when the molecule has a phenyl stabilising group attached to the aziridine ring.

Chapter 1 is a review of the known radical reactions involving aziridines whilst chapter 2 discusses the various methods of aziridine syntheses.

Chapter 3 outlines the project aims with reference to the potential of directed cleavage of aziridinylcarbinyl radicals in synthesis.

Chapter 4, the main body of the work, describes the synthetic routes to aziridines derived from 3-phenyl-2-cyclohexen-1-one and indenone. The radical mediated β-cleavage reactions of these is reported and the selectivity of C-C v. C-N bond homolysis has been investigated.

Two successful approaches to the target aziridines were involved.

1) Conversion of 3-azido-3-phenylcyclohexan-1,2-diol, derived from the epoxide of 3-phenyl-2-cyclohexen-1-ol, to the aziridine *via* reaction with triphenylphosphine. Subsequent methylation and formation of the thiocarbonylimidazolide gave the radical precursor *N*-methyl-5-[imidazol-1-yl(thiocarbonyl)oxy]-1-phenyl-7-azabicylo[4.1.0]heptane. In the course of this work, several unusual cyclic thiocarbonates resulting from the reaction of 3-azido-3-phenylcyclohexan-1,2-diol and 2-azido-3-phenylcyclohexan-1,3-diol with 1,1'thiocarbonyl diimidazole were isolated.

2) Formation of *N*-(2-ethylquinazolinonyl)-1-phenyl-7-azabicyclo[4.1.0]heptan-5-ol from the reaction of 3-amino-2-ethyl-4(3*H*)-quinazolinone with 3-phenyl-2-cyclohexen-1-ol in the presence of lead tetraacetate. These aziridines show interesting acid-catalysed rearrangements to diazadioxabicyclo[2.2.2]octanes. Formation of the thiocarbonylimidazolide then gave the radical precursor. A number of other aziridines have been prepared using this methodology.

It has been found that in all cases the precursors undergo C-N bond homolysis under radical conditions. These results are discussed and conclusions are drawn. Suitable future work is also suggested.

Abbreviations

AIBN	Azoisobutyronitrile.
DCC	1,3-Dicyclohexylcarbodiimide.
DCM	Dichloromethane.
de	Diastereomeric excess.
ee	Enantiomeric excess.
DMPU	1,3-Dimethyl-3,4,5-tetrahydro-2-(1*H*)-pyrimidone.
DMSO	Dimethyl sulfoxide.
DMF	*N*,*N*-Dimethylformamide.
IR	Infrared.
LTA	Lead tetraacetate.
*m*CPBA	*meta*-Chloroperbenzoic acid.
mmol	Millimole(s).
m.p.	Melting point.
NBS	*N*-Bromosuccinimide.
NMR	Nuclear magnetic resonance.
PCC	Pyridinium chlorochromate.
PhthalNH$_2$	*N*-Aminophthalimide.
p-ClPh	*para*-Chlorophenyl.
QNH$_2$	3-Amino-2-ethyl-4(3*H*)-quinazolinone.
rt	Room temperature.
SET	Single electron transfer.
SM	Starting material.
TBAF	Tetrabutylammonium fluoride.
TBDPS	*tert*-Butyldiphenylsilyl
THF	Tetrahydrofuran.
TLC	Thin layer chromatography.

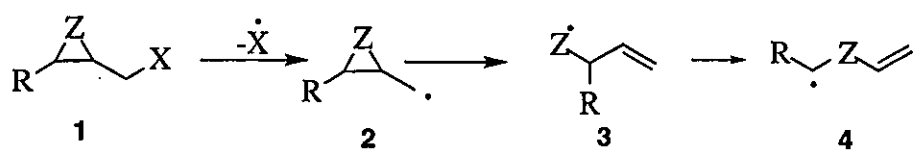
Contents.

1 A Review of the Chemistry of Aziridinylcarbinyl Radicals.

1.1 Introduction.

Over the past twenty years the use of free radical chain reactions has become much more widespread in organic chemistry and several review articles have been published in the area.[1-5] They are particularly useful in polar and hindered environments because free radicals are neutral and less prone to solvation or aggregation effects which can hinder reactions involving highly charged species. The main disadvantage with free radical reactions is that they often have several possible outcomes with the desired product being one of several. However, careful control of the reaction conditions can make the formation of less desirable products unfavourable. For example in reactions where tributyltin hydride is used as the radical chain carrier, very slow infusion of this reagent into the reaction mixture can minimise reduction of the reaction intermediate before other steps in the propagation cycle, such as rearrangement or ring closure, are complete.

1.2 Free Radical Opening of Three-membered Rings.

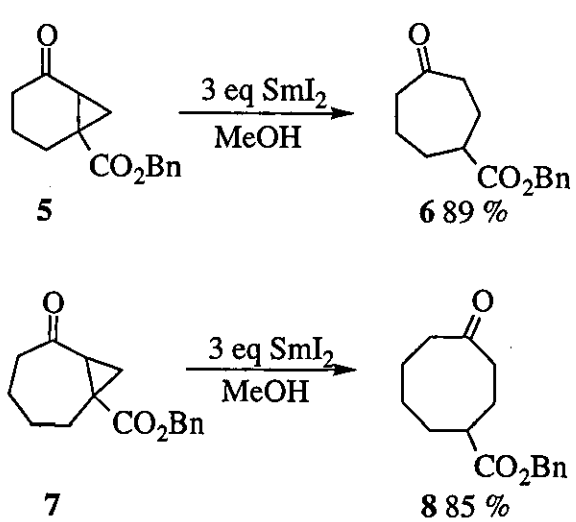


1 **2** **3** **4**

Z=CR'R", O, NR'

Scheme 1

The cyclopropylcarbinyl radical (**2**, Z=CR'R", Scheme 1) has been shown to have synthetic potential (e.g. ring expansion reactions shown in Scheme 2).[6, 7]

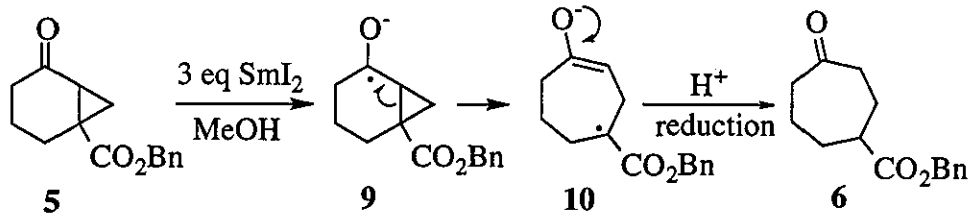


5 **6** 89 %

7 **8** 85 %

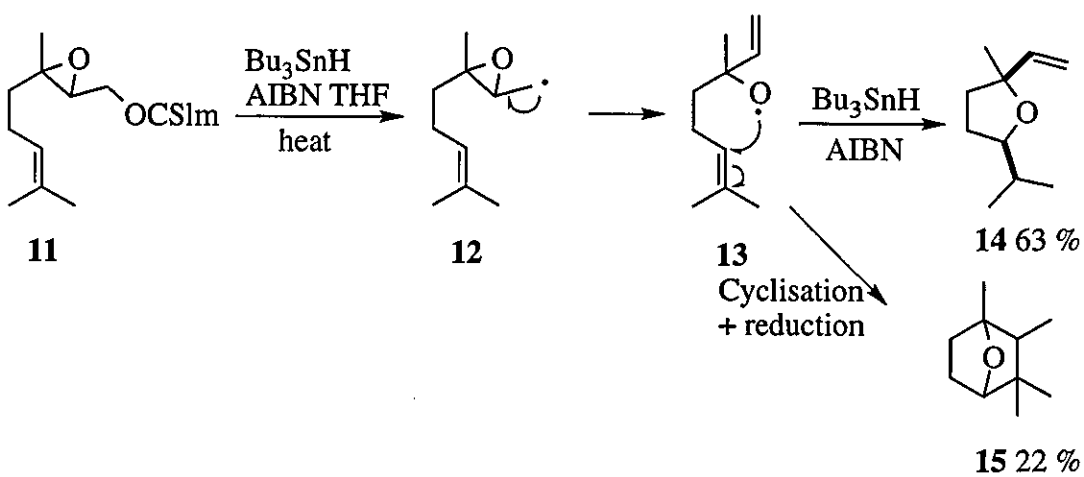
Scheme 2

Mechanistically this is shown in Scheme 3.

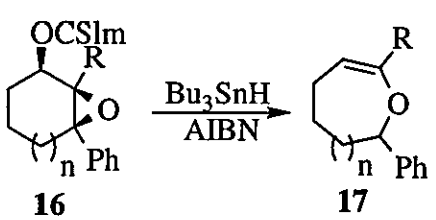


Scheme 3

The oxygen analogues i.e. 2-oxiranylcarbinyl radicals (**2**, Z=O, Scheme 1) have also been of interest particularly within these laboratories. Oxiranylcarbinyl radicals rapidly rearrange by β–cleavage in which either the C-O or C-C bond of the epoxide is broken. C-O Bond cleavage gives rise to an allylic alkoxy radical (**3**, Z=O, Scheme 1) in all cases where there is no radical stabilising group at R. C-C Bond cleavage to give (**4**) (Z=O, Scheme 1) is less common and occurs when an aryl, vinyl or in some cases, an acyl group is present at R. The ring-opening by an adjacent carbon-centred radical constitutes a useful strategy for the synthesis of heterocycles, e.g. tetrahydrofurans (**14**), tandem cyclisation to bicyclic products with bridged oxygen (**15**) (Scheme 4) and ring expansion (Scheme 5).[8,9]



Scheme 4



R=H, n=1, 62 % (normal addition)
R=Me, n=1, 53 % (normal addition)

R=H or Me, n=1 or 2

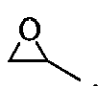
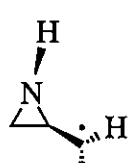
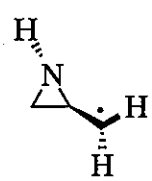
Scheme 5

In principle, the nitrogen analogues, 2-aziridinylcarbinyl radicals (**2**, Z=NR', Scheme 1) have the same synthetic potential.

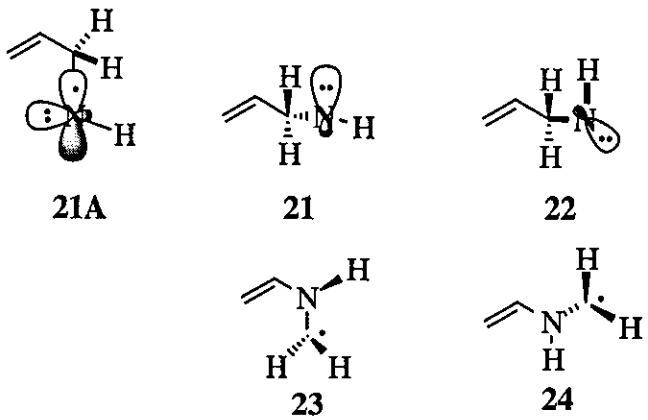
1.3 *Ab Initio* Theoretical Studies on the Ring-Opening Modes of the Aziridinylcarbinyl Radical System, Compared to the Oxiranylcarbinyl Radical and the Cyclopropylcarbinyl Radical Systems.

Table 1 below shows the energy barriers for ring opening of cyclopropylcarbinyl and heterocyclopropylcarbinyl radical systems.[10]

Table 1:Energy Barriers for the Ring-Opening of the Cyclopropylcarbinyl and Heterocyclopropylcarbinyl Radical Systems.

Radical	Bond Cleaved	Activation Energy/kcalmol^{-1} (overall energy change in brackets)
 **(18)**	C-C	7.05-7.26 (-3.7)
 **(19)**	C-O C-C	3.57 (-5.4) 14.7 (-3.51)
 *Cis*-**(20)**	C-N C-C	3.92 (-8.33) 12.27 (-11.24) (-11.58)[a]
 *Trans*-**(20)**	C-N C-C	5.20 (-9.11) (-11.21)[b] 11.87 (-12.30) (-12.64)[a]

a to form **(23)** or **(24)** (Scheme 6); b to form **(21)**, **(21a)** or **(22)** (Scheme 6).



Scheme 6

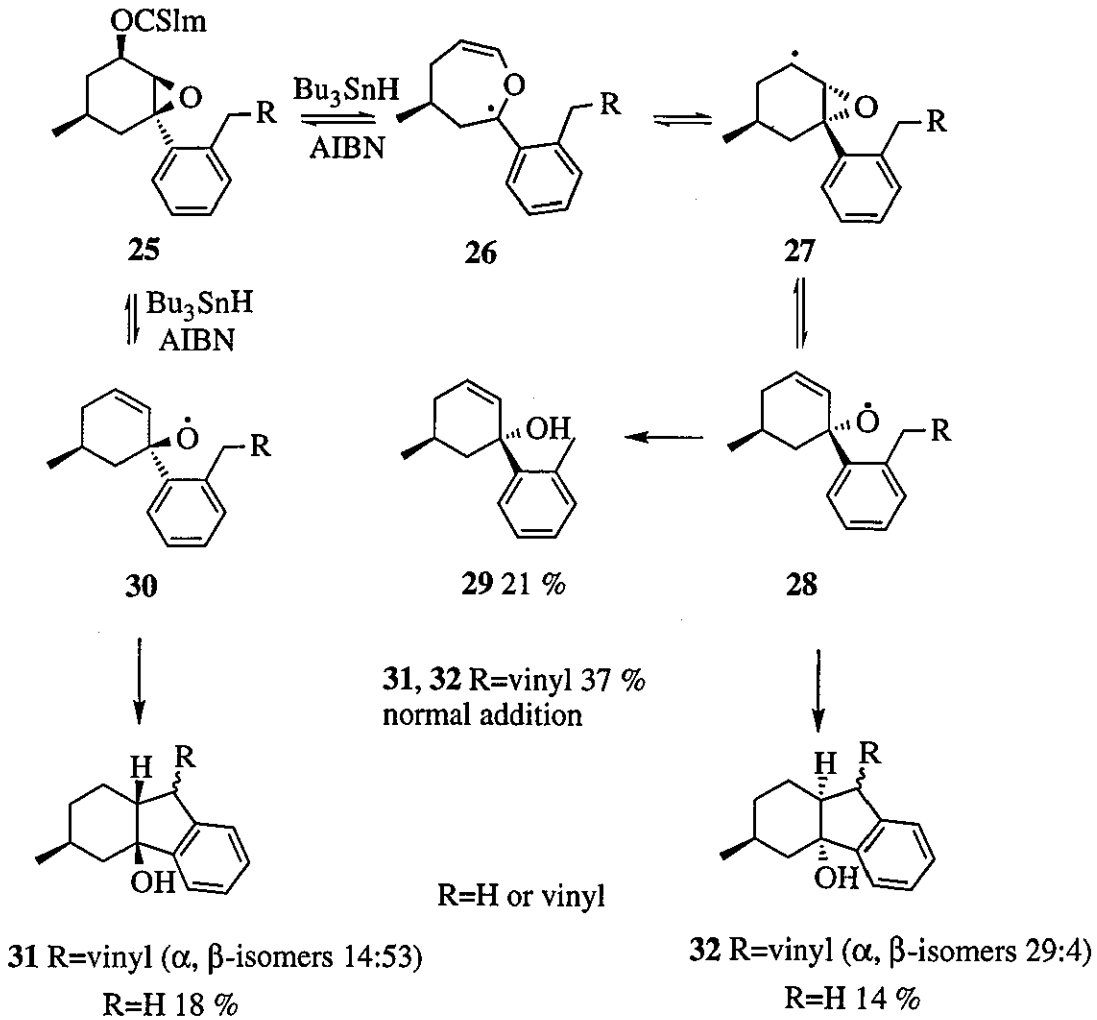
The lowest energy pathway for the ring opening of the oxiranylcarbinyl radical (**19**) is C-O bond cleavage (3.57 kcalmol^{-1}). The energy barriers for the lowest energy pathways for the *cis*- and *trans*-aziridines (**20**) (3.92 and 5.20 kcalmol^{-1}) have been calculated to be slightly greater in magnitude than the energy barrier for C-O bond cleavage in the oxiranylcarbinyl radical (and substantially less than the calculated energy barriers for ring opening of the C-C bond (12.27 and 11.87 kcalmol^{-1}). The overall reaction energies (-11.24, -11.58, -12.30 and -12.64 kcalmol^{-1}) thermodynamically favour the formation of products *via* C-C bond cleavage. This suggests the reversibility of product formation *via* (**21**), (**21A**) and (**22**) v. (**23**) and (**24**) might be readily observed by appropriate substitution to affect the energies of the ground and transition states.

In conclusion the introduction of a heteroatom into the cyclopropylcarbinyl radical results in a lowering of the energy barrier for ring opening *via* cleavage of the carbon heteroatom bond and an increase in the energy barrier for C-C bond homolysis. The overall reaction energies increase with increasing total electronegativity of the heteroatoms in the three-membered ring.

1.4 Selective Cleavage of the C-C v. the C-O Bond in Oxiranylcarbinyl Radicals.

As discussed previously, C-C bond homolysis of oxiranes can be directed by phenyl and other substituents (ref. Scheme 5).

Further studies in these laboratories showed that C-C bond homolysis is reversible (Scheme 7).[11] For example the products of the reaction of the thiocarbonylimidazolides (**25**) with tributyltin hydride and AIBN are all derived from the C-O bond cleavage. The incorporation of the cyclohexane ring methyl group as a "stereochemical probe" and the aryl ring to facilitate C-C bond cleavage provides significant insight into the reaction mechanism. The isolation of the diastereomeric fluorenols (**31**, R=H) and (**32**, R=H) and the alcohol (**29**) from (**25**, R=H) and the four diastereomeric fluorenols (**31**, R=vinyl), and (**32**, R=vinyl) from (**25**, R=vinyl) is best explained by a reversible cleavage of the C-C bond.



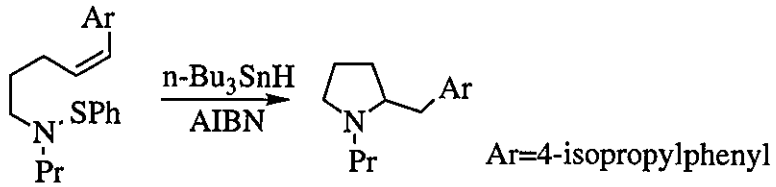
Scheme 7

Thus the C-C bond homolysis of oxiranes has been shown in this case to yield ring expanded products and the use of a stereochemical probe has proven that the homolysis is a reversible process.

1.5 C-N Bond Homolysis of Aziridines.

The C-N bond homolysis of aziridines forms the aminyl radical. Only selected reactions of aminyl radicals will be discussed in detail. Two recent reviews give comprehensive coverage in this area.[12,13]

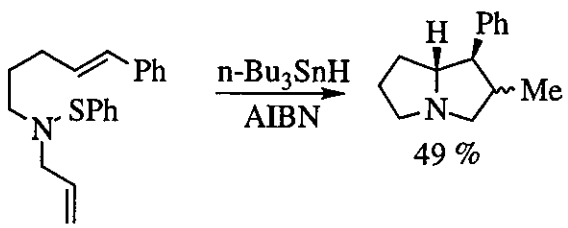
It has been demonstrated that arylsulfenamides **(33)** can be used for the generation of nitrogen-centred radicals.[14] These can react with an appropriately placed alkene group to form heterocyclic systems **(34)** (Scheme 8).



33 **34** 65 %

Scheme 8

Tandem cyclisations have also been reported in which a polycyclic system (**36**) was the final product (Scheme 9).[15]

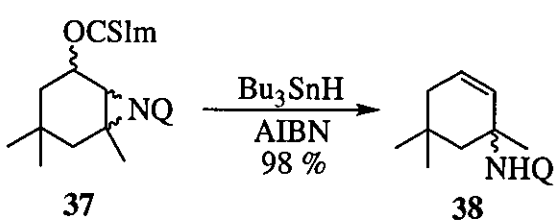


35 **36**

Scheme 9

1.5.1 Pyrrolidine Synthesis *via* C-N Bond Homolysis of *N*-Substituted Aziridines.

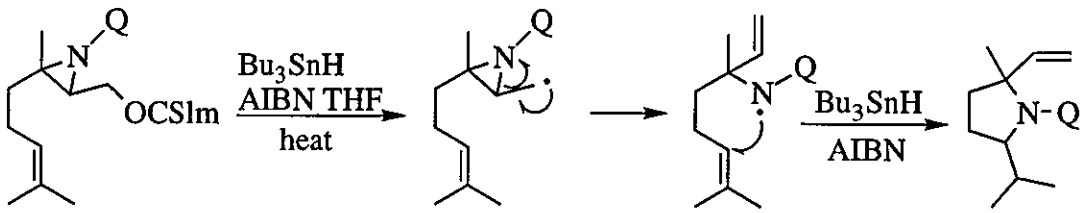
Treatment of the thiocarbonylimidazolide (**37**) with Bu3SnH and AIBN gave the allylic amine (**38**) in high yield, showing that the formation of allylic amines from allylic alcohols under free radical conditions was feasible (Scheme 10).[16]



37 **38**

Scheme 10

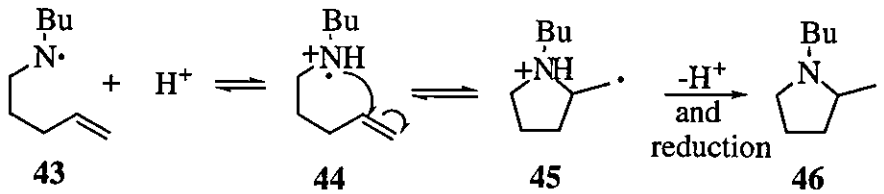
The aziridine (**39**) was treated with Bu3SnH and AIBN to afford the pyrrolidine (**42**) in 30 % yield (Scheme 11).[16]



39 **40** **41** **42** 30 %

Scheme 11

The inclusion of the mild Lewis acid-magnesium bromide etherate improved the yield to 70 %. This is in accordance with an observation that protonated aminyl radical cations (protonated with trifluoroacetic acid) cyclise much more efficiently onto alkenes than the corresponding neutral aminyl radicals (Scheme 12).[17]

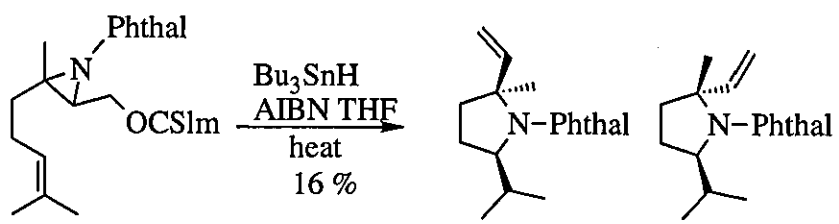


43 **44** **45** **46**

Scheme 12

Cyclisation of **(44)** to **(45)** is faster than for the unprotonated version and the equilibrium constant is also larger than for the neutral pair.

Similar radical reactions on *N*-phthalimido derivatives **(47)** gave a 1:1 mixture of isomers **(48)** and **(49)** (Scheme 13).[16]



47 **48** **49**

Scheme 13

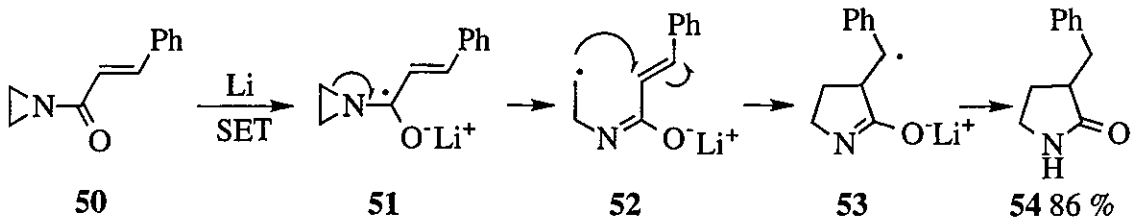
Thus aziridinylcarbinyl radicals show a synthetic potential for pyrrolidines *via* C-N bond homolysis and cyclisation onto an appropriately placed unsaturated group.

A drawback of these approaches is that this process is limited to rather special *N*-substituted aziridines e.g. *N*-phthalimido derivatives.

1.5.2 C-N Bond Homolysis of Aziridines *via* Single Electron Transfer (SET).

1.5.2.1 SET Radical Formation of Pyrrolidones.

Single electron transfer (SET) preparation of pyrrolidones has been reported.[18] Intramolecular trapping of the intermediate (**52**) derived from the aziridine (**50**) *via* the radical anion (**51**) gave the anionic pyrrolidine radical (**53**). This then undergoes hydrogen atom abstraction to give the pyrrolidone (**54**) (Scheme 14).

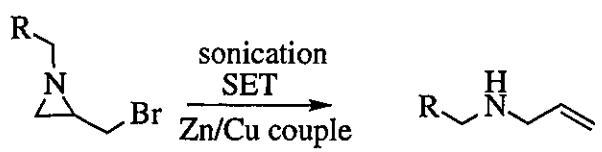


50 **51** **52** **53** **54** 86 %

Scheme 14

1.5.2.2 Radical-induced Ring Opening of 2-(Bromomethyl)aziridines *via* SET.

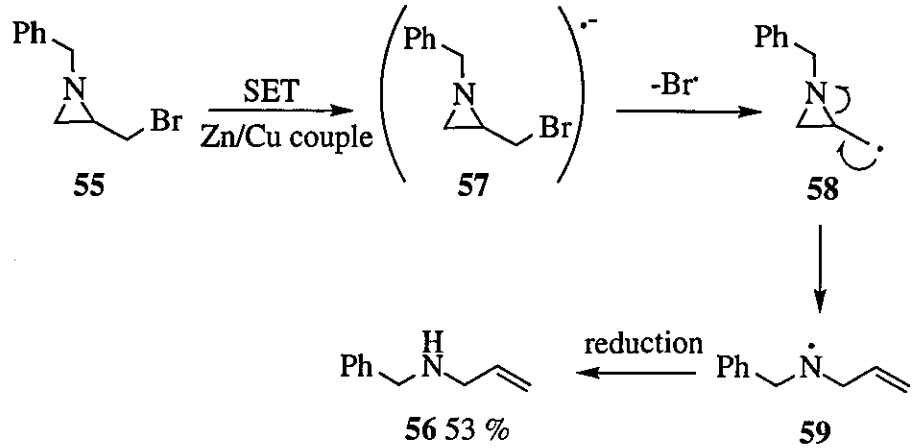
The radical-induced opening of 2-(bromomethyl)-aziridines (**55**) has been studied by DeKimpe (Scheme 15).[19]



55 **56**

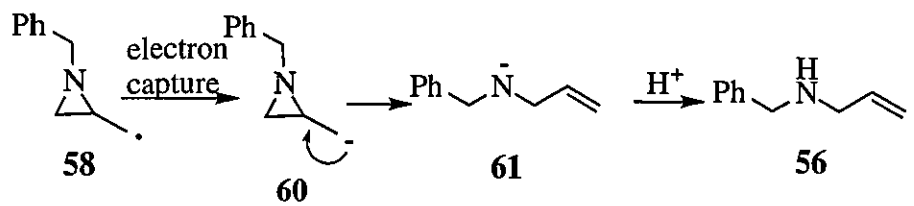
Scheme 15

Sonication of 2-(bromomethyl)aziridines (**55**) in aqueous methanol at room temperature in the presence of a zinc-copper couple resulted in a clean reaction leading to allylic amines (**56**). No C-C bond cleaved product was observed (Scheme 16). The radical opening of 2-(bromomethyl)aziridines may occur *via* SET from the metal to the substrate, followed by loss of bromide from the radical anion (**57**) to form the radical (**58**). This carbon-centred radical could then rearrange into the aminyl radical (**59**) which finally gives the allylamine (**56**).



Scheme 16

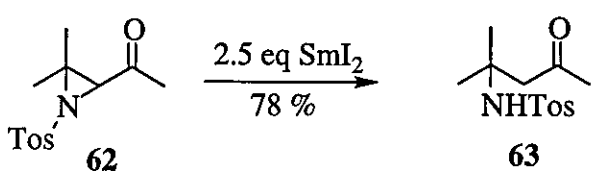
An alternative mechanism could involve the additional capture of an electron by radical (**58**) generating the corresponding carbanion (**60**), which can ring-open anionically to give the same end product (**56**) (Scheme17).



Scheme 17

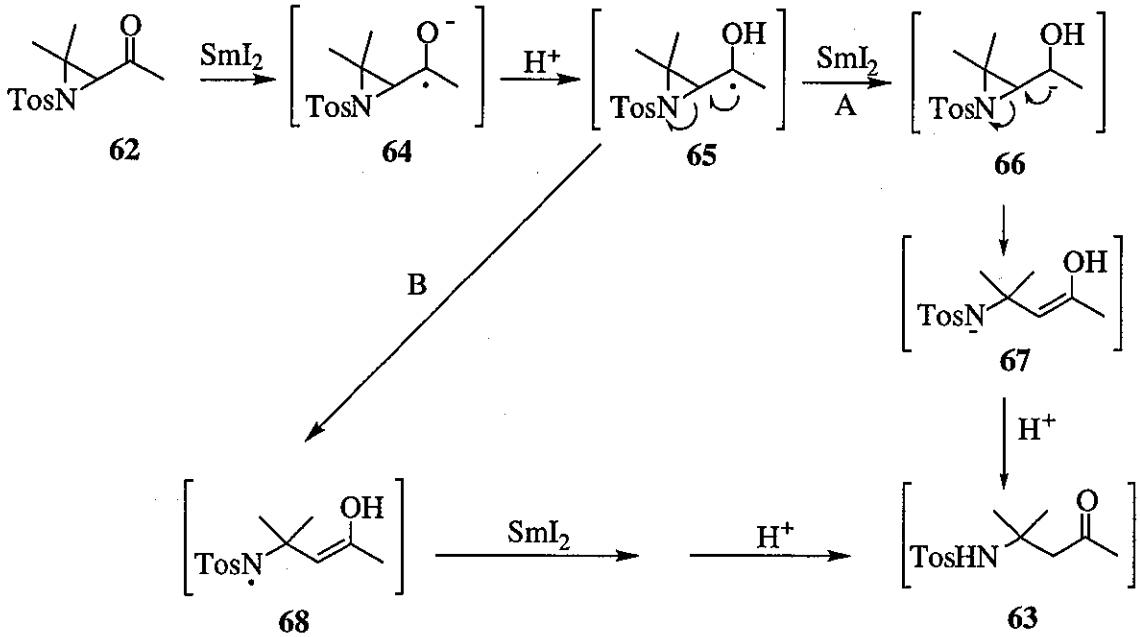
1.5.2.3 SET Reduction of 2-Acylaziridines.

Molander has studied the reduction of 2-acylaziridines by SmI_2.[20] Treatment of (**62**) with SmI_2 in THF-MeOH at -90°C provided the β-*N*-tosylamino ketone (**63**) in high yield *via* C-N bond homolysis (Scheme 18).



Scheme 18

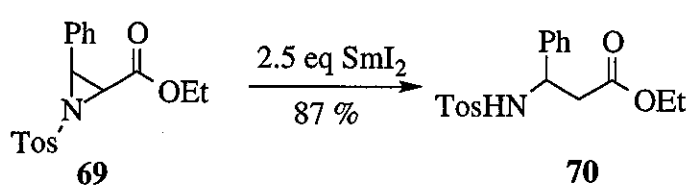
A possible mechanistic rationale is shown in Scheme 19.



Scheme 19

Reaction of the ketone carbonyl (**62**) with SmI_2 generates a ketyl radical (**64**), which is then rapidly protonated by methanol to give (**65**). Cleavage of the aziridine could occur by two distinct pathways. A carbanion (**66**) could be formed by further reduction of the ketyl radical by a second equivalent of SmI_2 and this anion would then induce the ring-opening of the aziridine (pathway A) to give (**67**). Tautomerisation of the intermediate enol could provide the observed β-amino ketone (**63**). Alternatively the protonated ketyl could undergo a radical ring scission producing the aminyl radical (**68**) (pathway B). This could be further reduced to the nitrogen anion by a further equivalent of SmI_2. Protonation would then lead to the observed product (**63**).

The reductive cleavage of *N*-tosylaziridine-2-carboxylates (**69**) was also examined (Scheme 20).



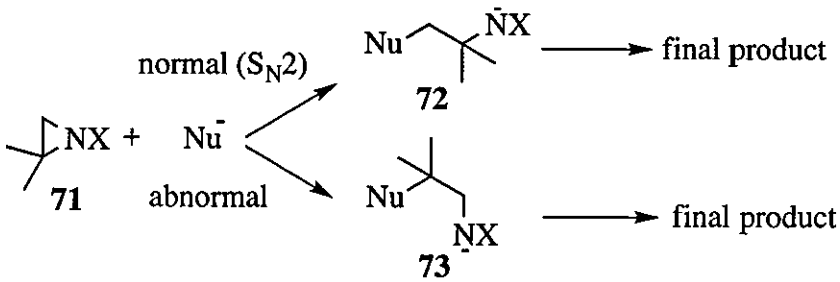
Scheme 20

Treatment of aziridine (**69**) with SmI_2 in DMEA (*N*,*N*-dimethylethanolamine) provides the β-amino esters (**70**) in excellent yields. Poor regioselectivity is observed in solvent systems such as THF-EtOH. The reduction of esters by electron transfer agents is more difficult than that of ketones. Samarium(III) Lewis acid-promoted ring opening of aziridine carboxylates competes with the reductive mode of ring cleavage leading to poor

regioselectivity. DMEA is believed to act as an effective proton source and also as an efficient chelator of the Lewis acidic samarium(III) species. It may also increase the reduction potential of the samarium(II) reductant.

1.5.2.4 Nucleophilic Cleavage of 2,2-Dimethylaziridines-Competition Between S_N2 and a Postulated SET Mechanism.

Stamm has studied the nucleophilic cleavage of 2,2-dimethylaziridines (**71**) and has found that in certain cases normal S_N2 opening is not observed; rather, an abnormal S_N1-like opening (Scheme 21) occurs.[21]



X=nitrogen substituent

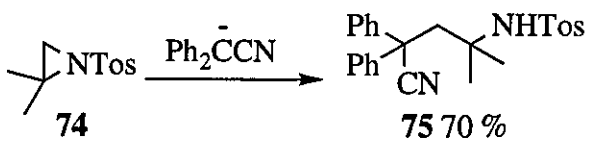
Nu^-= nucleophile

Scheme 21

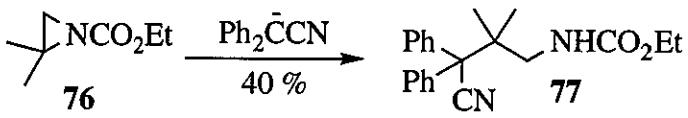
Ham has coined the term activated aziridines for aziridines that undergo S_N2-like nucleophilic ring opening even in the absence of a positive charge on nitrogen.[22] A suitable substituent (X) enhances the leaving group tendency of nitrogen by stabilisation of the negative charge that develops in the transition state. This stabilisation should be inversely reflected in the basicity of the displaced nitrogen anion (thus sulfonyl is superior to acyl activation).

The "normal" reaction of (**71**) (Scheme 21) resembles a nucleophilic substitution in the neopentyl position and will therefore be slow. It will be very slow with low activation enabling SET to occur. On the other hand, high activation accelerates the normal reaction sufficiently making it faster than SET.

Examples of reactions involving strongly activated (e.g. tosyl) and weakly activated (e.g. CO_2Et) aziridines (**74**) and (**76**) respectively are shown in Schemes 22 and 23.[21]



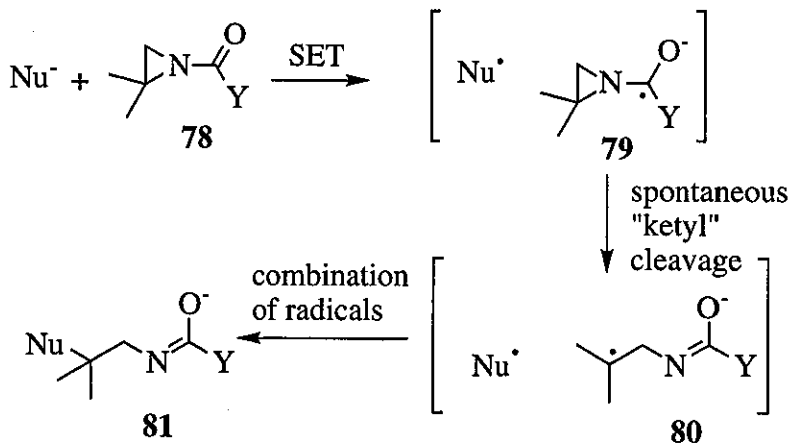
Scheme 22



76 77

Scheme 23

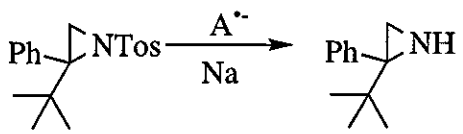
Stamm proposed a SET mechanism depicted in Scheme 24.[21] The first step (probably rate determining) may include the intermediate formation of a molecular complex **(79)**, spontaneous cleavage to **(80)** and the combination of radicals to give **(81)**.



78 79 80 81

Scheme 24

Reaction of the *N*-sulfonylaziridine **(82)** and anthracenide ($A^{\cdot -}$) shows that SET results in N-S cleavage in place of homolytic ring opening.[23] The respective radical anion **(82)** undergoes N-S cleavage faster than homolytic ring opening (Scheme 25).



82 **83** 86 %

Scheme 25

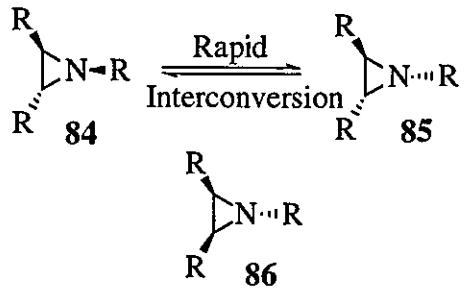
Nucleophiles can act as reducing agents for electrophiles when i) competing nucleophilic attack on the electrophile is slow and ii) the redox potentials between the nucleophile and electrophile are not too unfavourable. Nucleophilic attack on the aziridine ring of **(82)** should be slow due to steric hindrance.

1.5.2.5 SET v. Nucleophilic Ring Opening in Reactions of *Cis-Trans* Pairs of Activated 1,2-Diphenylaziridines.

Calculations and experimental evidence have been put forward which may show that a flattened nitrogen pyramid is required for nucleophilic ring opening (except when induced

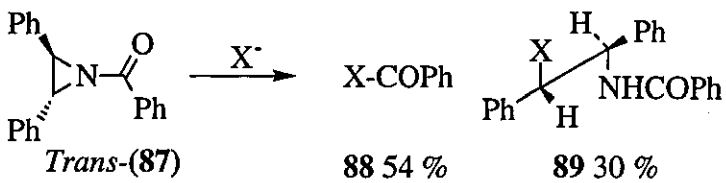
by extremely strong nucleophiles).[24,25] This is easily obtained when inversion is rapid (low inversion barrier).

Any reactivity difference should be distinct for diastereoisomers of the *cis-trans*-type. A *trans*-aziridine possesses two rapidly inverting inversional ground states (**84**) and (**85**), a *cis*-aziridine exists nearly exclusively as the *anti*-invertomer (**86**) (Scheme 26).



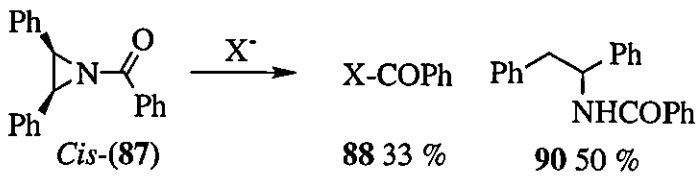
Scheme 26

Stamm carried out reactions with the xanthyl anion (X^-) and some 1,2-diphenylaziridines.[26] The investigation used the *cis-trans* pair (**87**).



Scheme 27

Trans-(**87**) gave two products of nucleophilic attack:-benzoylxanthene (**88**) and (**89**) from nucleophilic ring opening (Scheme 27). Reaction of the *cis*-isomer gave (**88**) in large quantities (but no **89**).



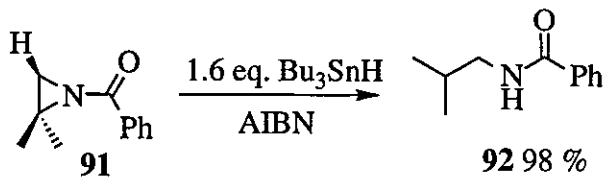
Scheme 28

The remainder of *cis*-(**87**) underwent reductive ring opening furnishing (**90**) *via* a SET mechanism (Scheme 28). Thus as expected, the *trans*-aziridine, which can obtain a flattened nitrogen pyramid undergoes nucleophilic attack whilst the *cis*-aziridine undergoes an SET reaction.

No indication of SET was detected for aziridines with carbamoyl activation. The carbamoyl group does not allow spin delocalisation in its ketyl radical anion.

1.5.2.6 Homolytic Aziridine Opening by Addition of Tributyltin Radicals to *N*-Acylaziridines.

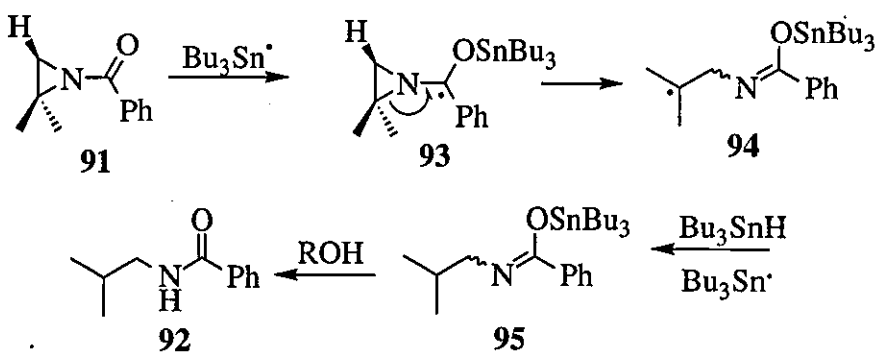
Stamm has studied the cleavage of *N*-acyl aziridines (**91**) under free radical conditions to give (**92**) (Scheme 29).[26a]



91 **92** 98 %

Scheme 29

This is represented mechanistically in scheme 30.

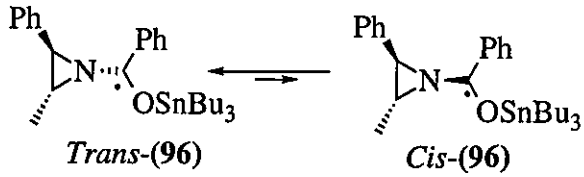


91 **93** **94** **92** **95**

Scheme 30

Usually reductive ring opening proceeds practically quantitatively unless the addition of tributyltin hydride radicals to an acyl group is sterically hindered (e.g. by *N*-pivaloyl) giving low reactivity and as a consequence, low yields. The stability of the formed radical (**94**) seems to be an important factor for the regioselectivity of ring opening. Stereoelectronic control of ring cleavage may also often favour one ring homolysis over another.

As discussed previously, *N*-acylaziridines can undergo nitrogen inversion. Unsymmetrical substitution in aziridine (**96**) makes the two ground states unequal. The preferred ground state has the large groups in a *trans*-position and the smaller methyl group in the *cis*-position relative to the *N*-substituent (Scheme 31).



Scheme 31

Steric repulsion as shown in **Fig 2** disfavours the stereoelectronic arrangement required for the cleavage of the ring N-CPh bond favouring the arrangement shown in **Fig 1**. As a consequence, some of the less stable radical **(Fig 3)** along with some of more stable radical **(Fig 4)** is formed and both reduced products are obtained in roughly equal amounts.

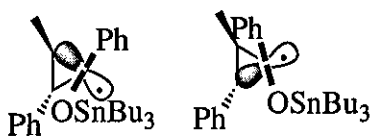


Fig 1

Fig 2

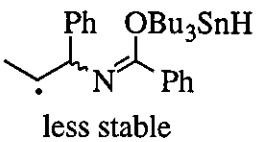


Fig 3

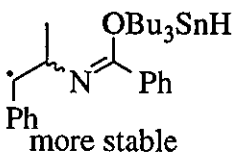


Fig 4

The isomeric *cis*-aziridine **(Fig 5)** shows no stereoelectronic difference for the two N-C bonds.

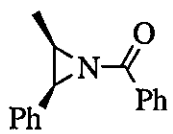
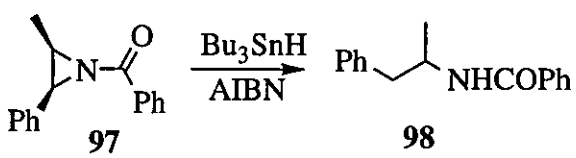


Fig 5

Here the stability of the benzylic radical seems to control the regioselectivity of the ring cleavage providing exclusively **(98)** (Scheme 32).

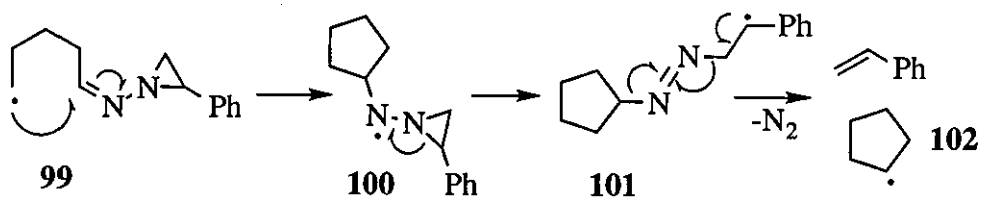


97 **98**

Scheme 32

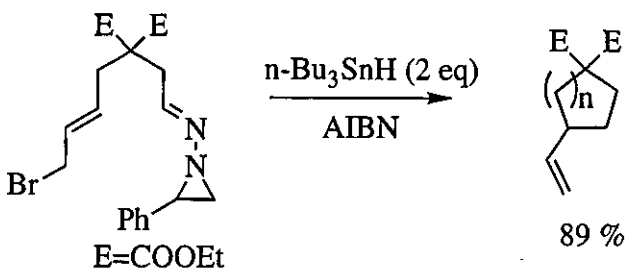
1.5.2.7 Radical Cyclisation of *N*-Aziridinyl Imines.

Kim has studied the radical cyclisation of 2-phenyl-*N*-aziridinyl imines **(99)** as outlined in Scheme 33.[27]



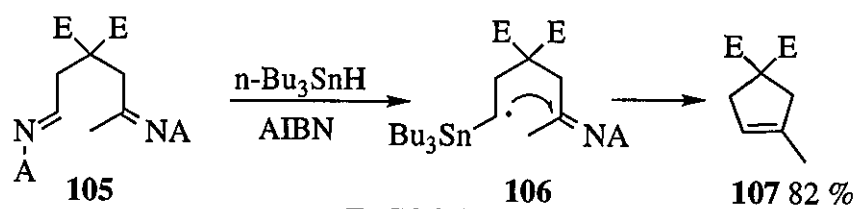
Scheme 33

Treatment of the bromide **(103)** with n-Bu3SnH and AIBN in benzene afforded 89 % of the cyclic compound **(104)** (Scheme 34).



Scheme 34

Kim also studied the use of aziridinyl imines as radical precursors and his approach relied on the intermolecular addition of tributyltin hydride radicals to an aziridinyl imine group (A) of **(105)** to generate the α-Bu3Sn-substituted carbon-centred radical **(106)**.[27] Thus the cyclised product **(107)** was obtained in 82 % yield (Scheme 35).



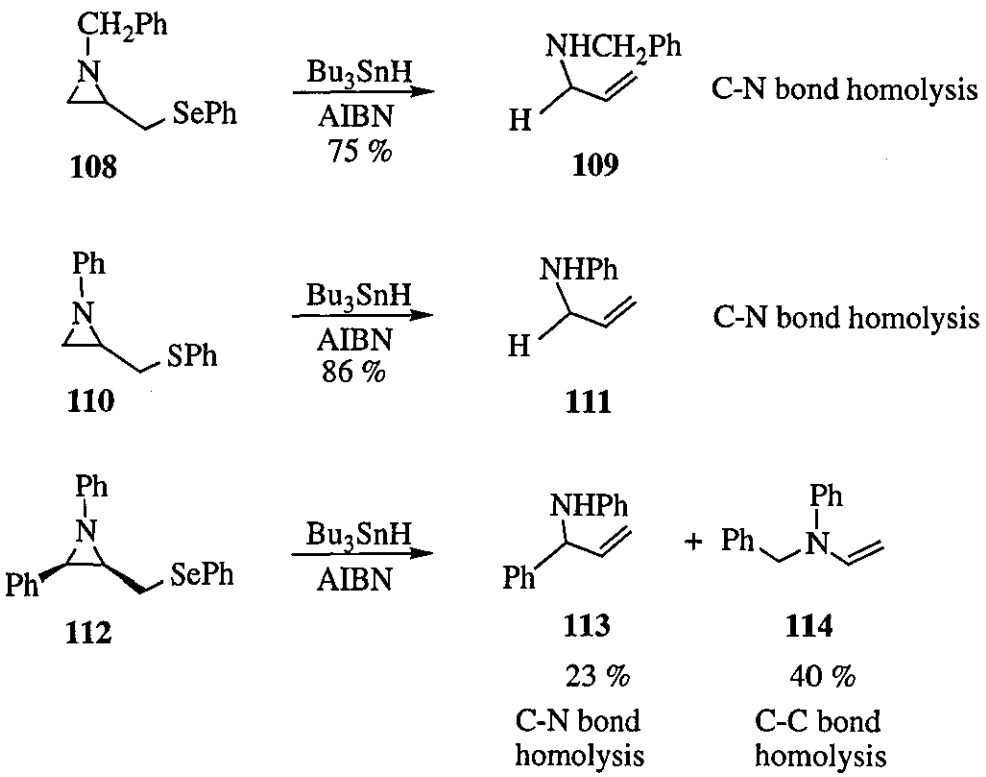
Scheme 35

This demonstrates that the aziridinyl imine group can act either as a radical precursor or a radical acceptor.

1.6 Carbon-Carbon v. Carbon-Nitrogen Bond Homolysis in Aziridines.

1.6.1 Substituent Control over the Regiochemistry of Ring-Opening of 2-Aziridinyl carbinyl Radicals.

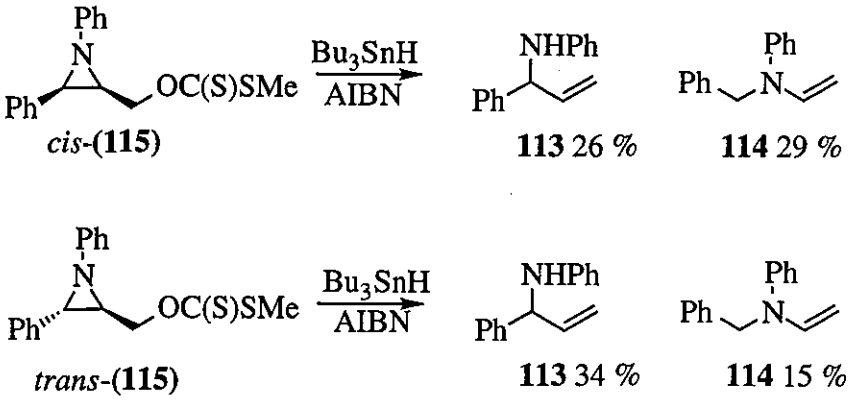
Schwan has studied the effects of substituents on the regiochemistry of the free radical ring opening of 2-aziridinylcarbinyl radicals **(108)**, **(110)** and **(112)** (Scheme 36).[28]



Scheme 36

In the *N*-benzyl compound **(108)** and the *N*-phenyl compound **(110)** products arise exclusively from C-N bond homolysis to give **(109)** and **(111)** respectively. When carbon 3 bears a phenyl group as in **(112)**, then that group increases the proportion of the C-C bond homolysis product **(114)** so that it competes with that of the C-N bond homolysis product **(113)**.

It was also found that the geometry of the carbon substituents seemed to have an effect on the regiochemistry of the ring opening (Scheme 37).



Scheme 37

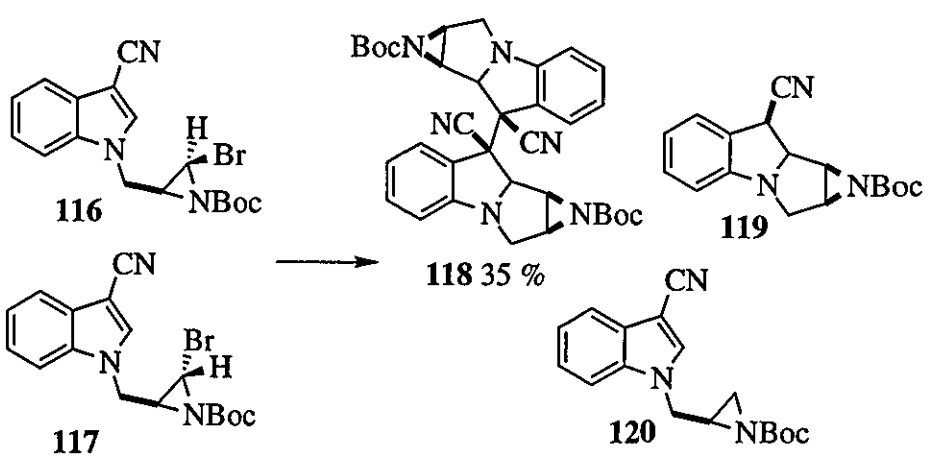
The presence of a *cis*-stereochemistry in **(115)** between the phenyl and radical leaving group apparently gives a higher yield of the C-C bond-opened product **(114)**. Possible steric release could explain this observation.

1.7 Carbon-centred Aziridine Radicals.

Although not strictly within the scope of aziridinylcarbinyl radicals some work has been performed utilising carbon-centred aziridine radicals.

1.7.1 Cyclisation of Carbon-centred Aziridinyl Radicals.

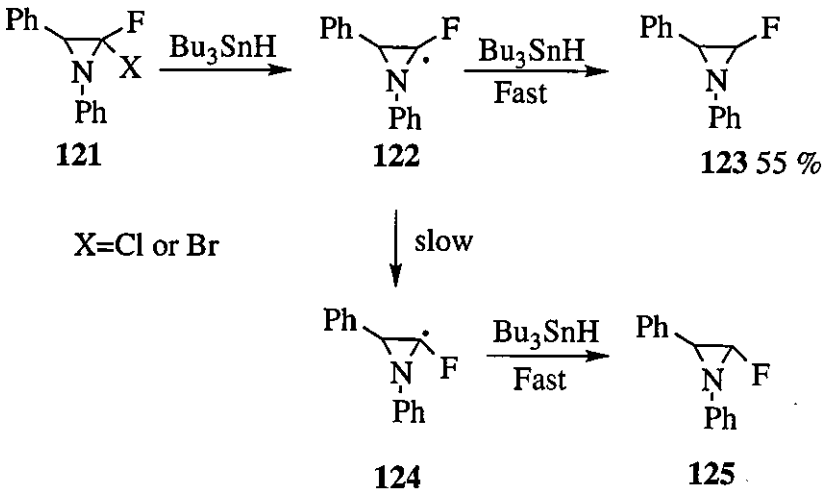
Ziegler reacted a mixture of bromoaziridines **(116)** and **(117)** with Bu3SnH and AIBN and the dimer **(118)**, dihydroindole **(119)** and uncyclised aziridine **(120)** were produced in a molar ratio 0.8 (35 %):1.5:1.1 (Scheme 38).[29]



Scheme 38

1.7.2 Reduction of 1,3-Diphenyl-2,2-dihaloaziridines with Tributyltin Hydride.

Yamanaka studied the reduction of dihaloaziridines with Bu3SnH and AIBN (Scheme 39).[30]



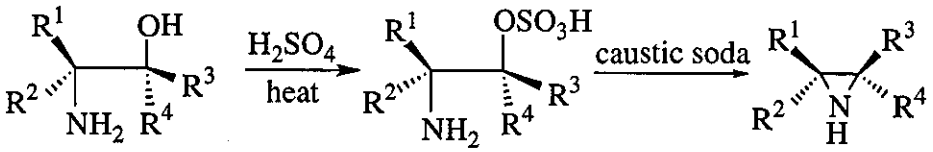
Scheme 39

The isolation of only **(123)** demonstrates that the 2-fluoro-2-aziridinyl radical **(122)** is pyramidal and abstracts hydrogen from Bu3SnH much more rapidly than inversion of configuration can occur to **(125)** *via* **(124)**.

2. A Review of the Syntheses of Aziridines.

2.1 From 1,2-Aminoalcohols.

The use of 1,2-aminoalcohols **(126)** is a common method for aziridine synthesis (Scheme 40). It can be readily achieved when the hydroxyl functional group is converted to a nucleofuge. An intramolecular nucleophilic displacement reaction by the amine lone pair then yields the aziridine ring **(128)** with inversion at carbon.

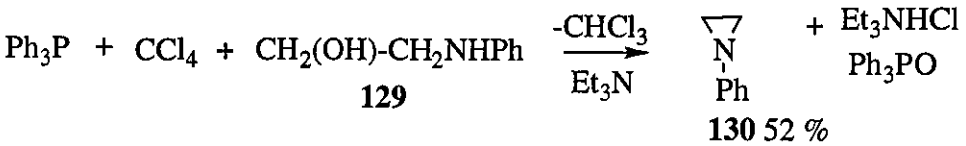


126 **127** **128**

Scheme 40

For example, the Wenker route utilises a sulfonic acid as the leaving group **(127)**.[31,32] *N*-Alkylated aziridines can be synthesised by this method, using the appropriate primary amines and methanesulfonic acid aminoesters as the leaving group.[33] This method is unsatisfactory for tertiary alcohols for which elimination occurs to produce an alkene in preference to cyclisation.

The conversion of the alcohol moiety to powerful nucleofuges is exemplified in the reaction of the aminoalcohol **(129)** with triphenylphosphine and carbon tetrachloride to give the aziridine **(130)** (Scheme 41).[34] This method is unsuitable for the synthesis of *N*-unsubstituted aziridines.

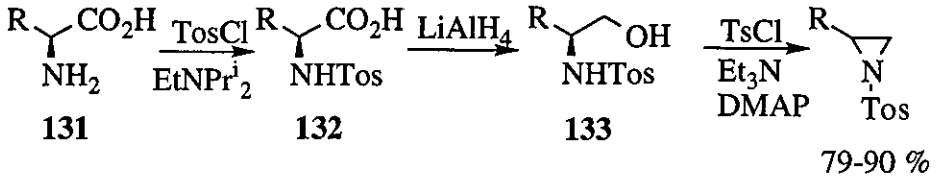


130 52 %

Scheme 41

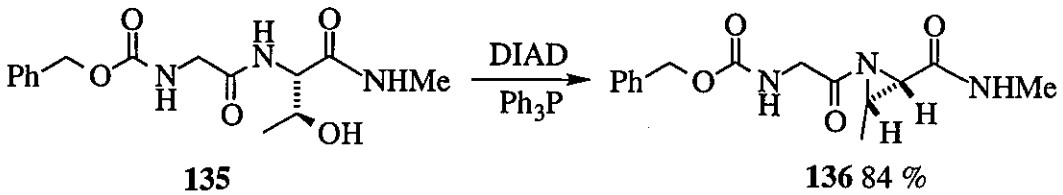
Other phosphorus reagents used are diphenylphosphinic chloride and diethoxytriphenyl phosphine.[35,36]

Enantiomerically-pure 1,2-aminoalcohols required for the asymmetric synthesis of aziridines are available *via* the reduction of enantiomerically pure 2-aminoacids. The difficulty in aziridine formation from amino acids is the isolation of the intermediate aminoalcohols, due to the formation of water soluble metal complexes. A solution to this problem has been the reduction of *N*-tosyl amino acids **(131)** in a one-pot reaction (Scheme 42).[37]



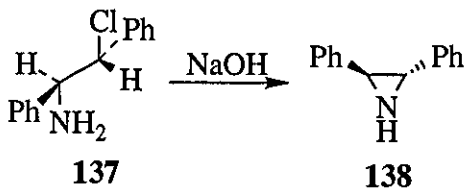
Scheme 42

Similar methodology cannot be used for *N*-acyl or *N*-carbamoyl aziridine formation as a more favourable nucleophilic attack by the carbonyl oxygen occurs on the TsO leaving group forming oxazolonium intermediates.[38] For certain peptide containing *N*-acyl aminoalcohols aziridines can be synthesised *via* a Mitsunobu reaction (Scheme 43).[39]



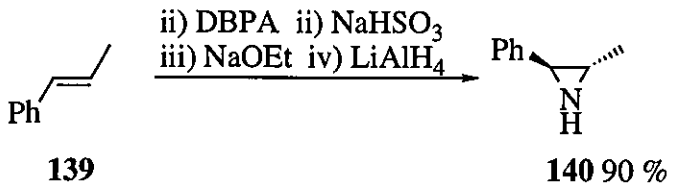
Scheme 43

The synthesis of aziridines *via* 2-haloamines (**137**) was investigated by Gabriel. (Scheme 44).[40,41]



Scheme 44

Zawadzki has described a two-step amino bromination of alkenes with diethyl *N*-dibromophosphoramidate (DBPA) (Scheme 45).[42]

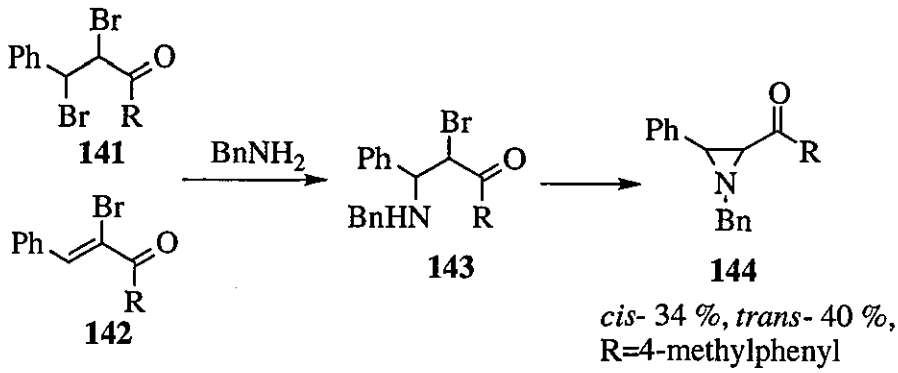


Scheme 45

A limitation in the Gabriel synthesis is the difficulty of obtaining chloroamines from highly substituted amino alcohols.

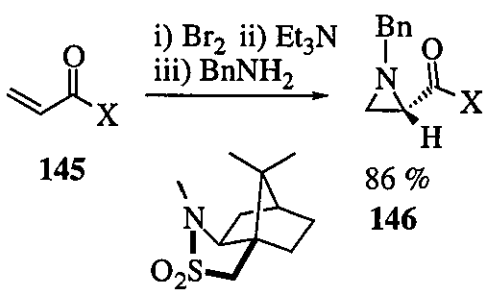
The Cromwell modification of the Gabriel synthesis involves the reaction of dihaloketones (**141**) or α-halo-α,β–unsaturated ketones (**142**) with primary amines to give 2-

acyl aziridines (**144**).[43] The probable intermediate in this reaction, a β-amino-α-haloketone (**143**) is not isolated (Scheme 46).



Scheme 46

An asymmetric version uses primary amines with enantiomerically-pure 2-bromocarboxylates, leading to *N*-alkylated aziridines (**146**). Best results have been obtained using camphorsultam as the chiral controller (Scheme 47).[44]

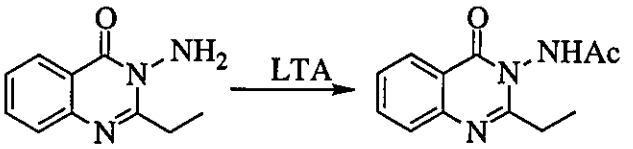


Scheme 47

2.2 From Alkenes.

2.2.1 Oxidation of Amino Compounds with Lead Tetraacetate (LTA).

Various formations of aziridines have involved the reactions of amine-type compounds with an alkene in the presence LTA. *N*-Amino-type compounds have, in some cases, been proven to react *via* an *N*-acetoxy intermediate.[45] Others have been presumed to react *via* a nitrene intermediate.[46] Atkinson has studied extensively in this area using heteroaromatic bases (e.g. 3-amino-2-ethyl-4(3*H*) quinazolinone, **147**) and LTA to form the aziridinating agent (**148**) (Scheme 48).[47]

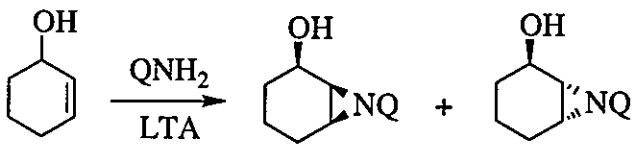


147 **148**

QNH_2 QNHAc

Scheme 48

In the presence of cyclohexenol **(149)** the product **(150)** was isolated (Scheme 49).[47] The *syn*-selectivity is due to hydrogen bonding of the alcohol group of the enol with the acetoxy group of the aziridinating agent **(148)**.



149 **150** 95:5 **151**

Scheme 49

It has been suggested that for electron-deficient alkenes (e.g. methyl acrylate) the mechanism can be represented as in **Fig 6**.[48] The acetoxyamino-substituted nitrogen acts first as a nucleophile in a Michael sense and second as an electrophile undergoing substitution of its acetoxy group in an S_N2 sense. Thus in **Fig 6**, N-Cβ bond formation runs ahead of N-Cα bond formation. The opposite is true for electron-rich alkenes **(Fig 7)**.

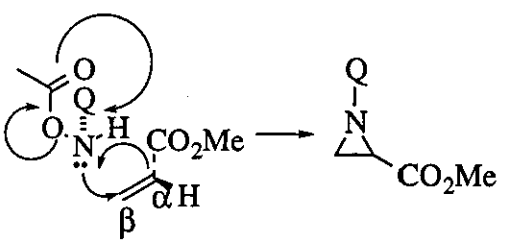


Fig 6

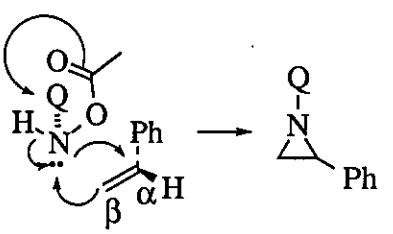
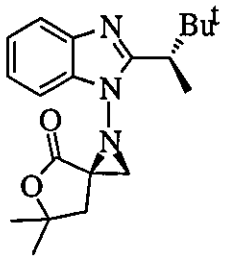


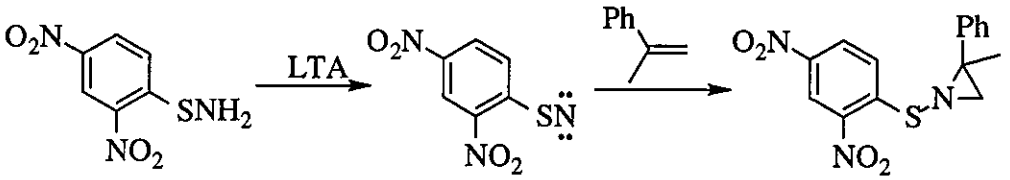
Fig 7

Applying the LTA oxidation of chiral *N*-amino heterocycles in the presence of achiral alkenes and trifluoroacetic acid leads to chiral aziridines *via* asymmetric induction giving compound **(152)** in high *de* from the appropriate starting materials.[49]



152

It has been reported that oxidation of 2,4-dinitrobenzenesulfenamide (**153**) with LTA leads to the nitrene (**154**) which can be trapped by alkenes to give the corresponding N-S bonded aziridines (**155**).[50] The presumed nitrene reacts well with electron-rich alkenes (Scheme 50).



153 **154** **155** 61 %

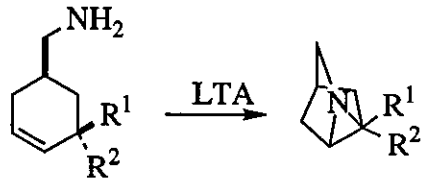
Scheme 50

Similarly Brois oxidised methoxylamine with LTA in the presence of excess tetramethylethylene at -50°C to give 1-methoxy-2,2,3,3-tetramethylaziridine (**Fig 8**) in 30 % yield *via* a presumed O-nitrene addition.[46]

Fig 8

He speculated that the O-nitrene intermediate is generated *via* LTA oxidation of methoxylamine and trapped in a singlet state. The alleged singlet nitrene can be effectively stabilised by delocalisation and adds to alkenes in a stereospecific manner.

Nagata reported LTA oxidation of the amine (**156**) to give the bridged aziridine (**157**) (Scheme 51). *N*-Chlorosuccinimide was also found to be a successful oxidant.[51]

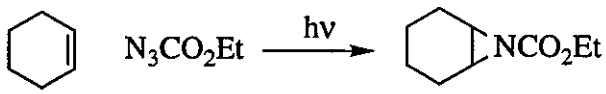


156 **157** no yield given

Scheme 51

2.2.2 Nitrene Additions Derived from Azides.

When a dilute solution of ethyl azidoformate (**159**) in cyclohexene (**158**) was irradiated at room temperature the 7-carbethoxy-7-azabicyclo[4.1.0]heptane (**160**) was formed in 50 % yield *via* addition of carboethoxy nitrene (Scheme 52).[52]

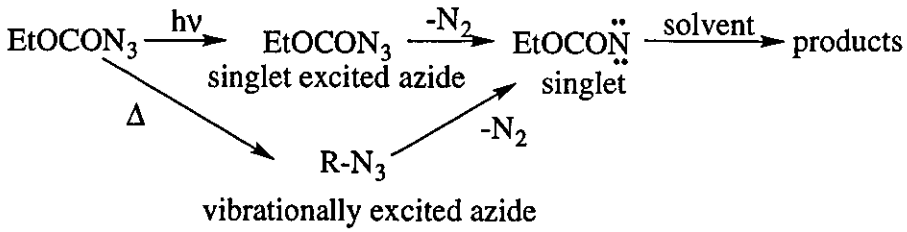


158 **159** **160**

50 % + other products

Scheme 52

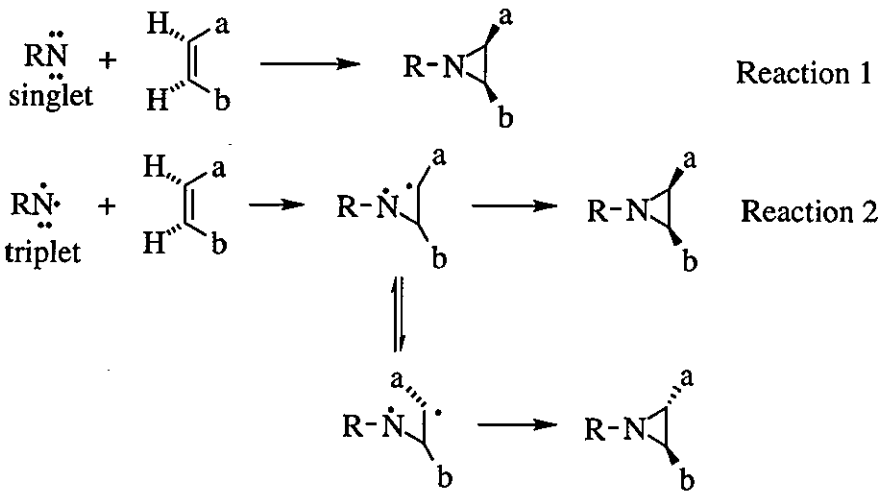
In general photolysis (and thermolysis) of the ethyl azidoformate first induces loss of nitrogen, followed by intermolecular reactions of the carboethoxy nitrene produced (Scheme 53).[52]



Scheme 53

Mechanism

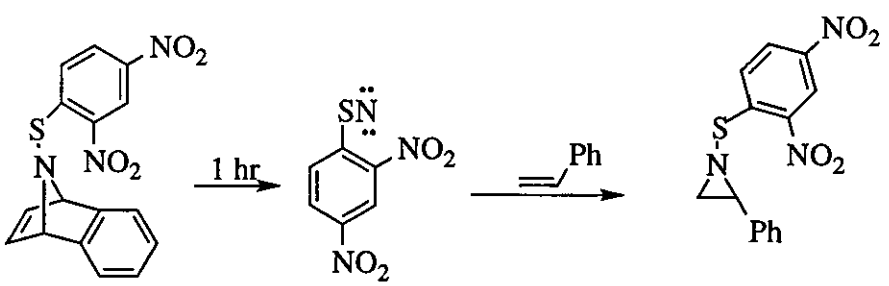
Singlet nitrene, formed by thermolysis of the azide adds stereospecifically to the alkene (reaction 1, Scheme 54). However, competitive decay of the singlet to the triplet nitrene, a 30th as fast as addition, leads to some loss of stereospecificity (reaction 2, Scheme 54). Photolysis produces two-thirds singlet and one-third triplet, which sets an upper limit to the stereospecificity of the addition (both can be optimised to give 70 % yield).[32]



Scheme 54

Barani has improved the method using ethyl *N-p*-nitrobenzenesulfonoxyurethan ($NsONHCO_2Et$) in the presence of inorganic oxides or carbonates, giving higher yields of the aziridine from cyclohexene (78 %).[53]

Arenesulfenyl nitrenes **(162)** are generated efficiently from sulphenamides on heating between 80°C and 120°C and are trapped to form aziridines. For example, the 2,4-dinitrobenzenesulfenamide **(162)** decomposes within 1 hour at 120°C in chlorobenzene and styrene (3 eq) to give a quantitative yield of the aziridine **(163)** (Scheme 55).[54]



161 **162** **163** Quantitative

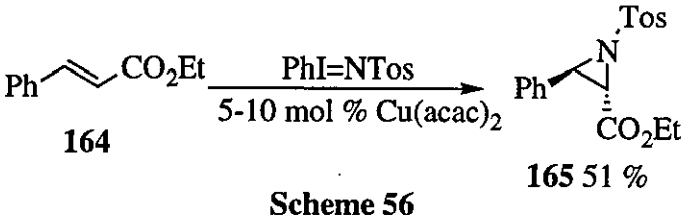
Scheme 55

Kwart has found that copper can be an effective catalyst for the decomposition of benzenesulfonyl azide forming aziridines in low yield.[55]

2.2.3 Metal-catalysed Aziridination of Alkenes.

Evans has studied the copper-catalyzed aziridination of alkenes using (*N*-(*p*-toluenesulfonyl)imino)phenyliodinane (PhI=NTos) as the nitrene precursor.[56] Various copper catalysts e.g. $Cu(acac)_2$, $Cu(OTf)_2$ and $CuClO_4$ and have been found to be successful for

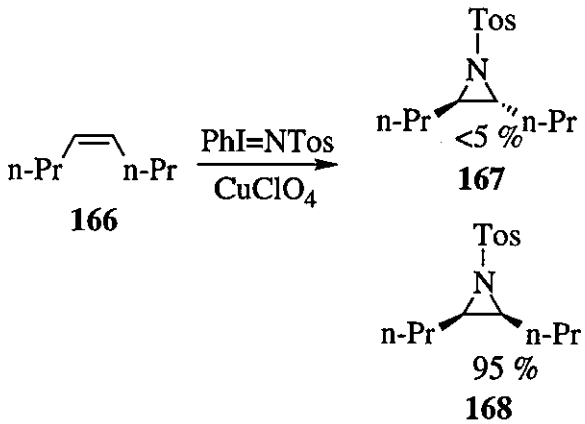
both electron-rich and electron-poor alkenes. A typical example using ethyl cinnamate **(164)** produced the aziridine **(165)** (Scheme 56).[57]



164 **165** 51 %

Scheme 56

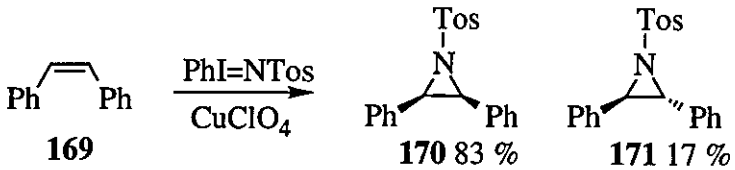
For unfunctionalised alkyl-substituted alkenes such as *cis*-4-octene **(166)**, the observed stereospecificity supports a concerted mechanism giving a 95 % yield of the *cis*-aziridine **(168)** (Scheme 57).[56]



166 **167** **168**

Scheme 57

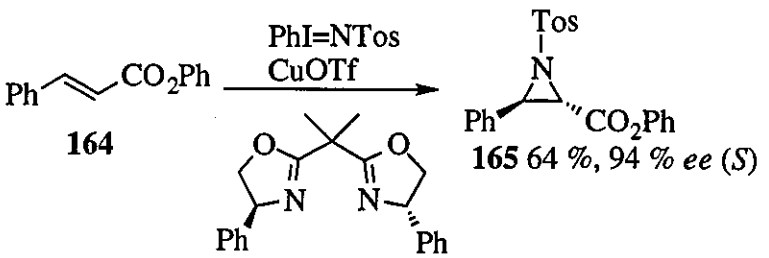
Phenyl substitution, on the other hand, seems to alter the process from a stereospecific to a non-stereospecific reaction. For example *cis*-stilbene **(169)** gave 17 % of the *trans*-aziridine **(171)** (Scheme 58).[56]



169 **170** 83 % **171** 17 %

Scheme 58

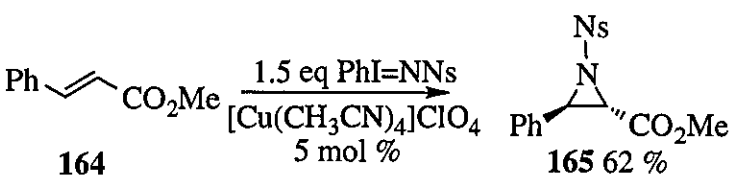
Evans has extended this method to enantioselective aziridination of alkenes using a *bis*-oxazoline ligand and copper(I) triflate (Scheme 59).[58]



Scheme 59

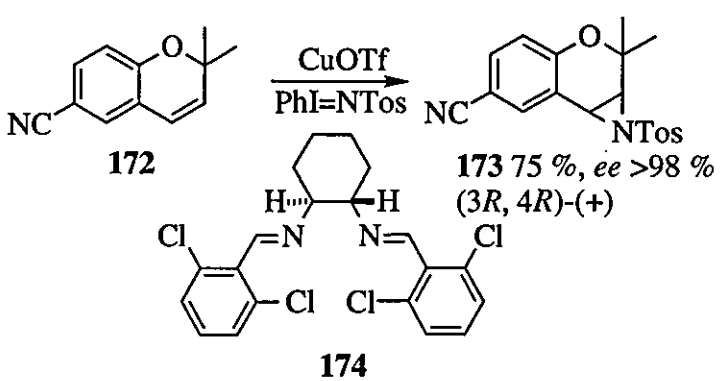
It was found that the ester (**164**) is the most synthetically useful substrate class and gave aziridine (**165**) in high yield and *ee*. Evans has speculated that the copper functions as a catalyst in the (+2) state and highly electronegative counterions are required for efficient asymmetric catalysis. A drawback of the Evans approach is that 5 equivalents of the alkene is required in the reaction.

Anderson used *N*-(*p*-nitrobenzenesulfonyl)imino)phenyliodinane (PhI=NNs), which seems to show greater reactivity than PhI=NTos and also allows the use of approximately 1 equivalent of the alkene.[59] For example the aziridine (**165**) was isolated from the alkene (**164**) under copper catalysis (Scheme 60).



Scheme 60

The chiral di-imine-based catalysts (**174**) have been employed by Jacobsen to effect asymmetric alkene aziridination.[60] For example, using the chromene (**172**) gave the aziridine (**173**) with an *ee* of 98 % (Scheme 61)



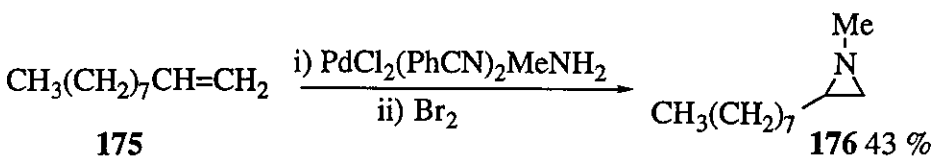
Scheme 61

Trans-stilbenes have been found to be poor substrates with regard to both selectivity and rate. Acyclic *cis*-alkenes show non-stereospecific aziridination.

Mahy has shown that the aziridination of alkenes using PhI=NTos occurs in the presence of porphyrinirons.[61]

2.2.4 Aminopalladation.

A one-pot conversion of alkenes to *N*-methylaziridines has been achieved by aminopalladation, using a palladium(II) complex and methylamine, followed by an oxidative work-up with bromine. For example, dec-1-ene (**175**) gave the *N*-methylaziridine (**176**) in 43 % yield (Scheme 62).[62]

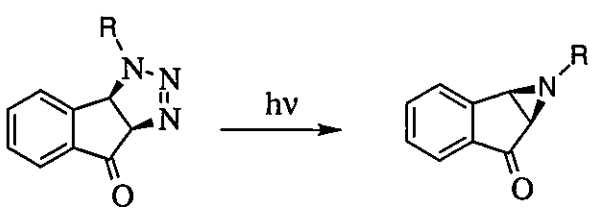


175 **176** 43 %

Scheme 62

2.2.5 Triazolines.

1,3-Dipolar cycloaddition reactions of azides with alkene-type compounds constitutes a general method for the synthesis of Δ^2-triazolines. For example, Hansen synthesised the triazoline (**177**) from indenone. The 1,2,3-triazoline was transformed into aziridine (**178**) photolytically (Scheme 63).[63]

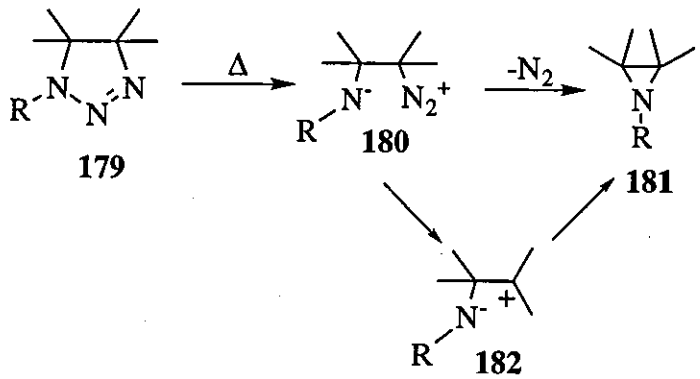


177 e.g. R=Ph (65 %) **178**

Scheme 63

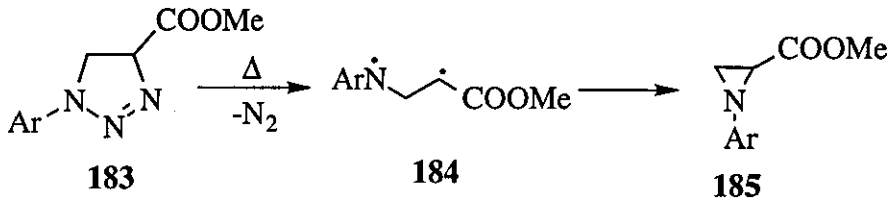
Mechanism-Thermolysis v. Photolysis.[64]

Triazoline thermolysis leads to aziridines (**181**) *via* a postulated diazonium betain (**180**) (Scheme 64).



Scheme 64

Electron-withdrawing groups on carbon 4 of the triazoline allow a homolytic decomposition to a singlet diradical (**184**) to occur (Scheme 65).



Scheme 65

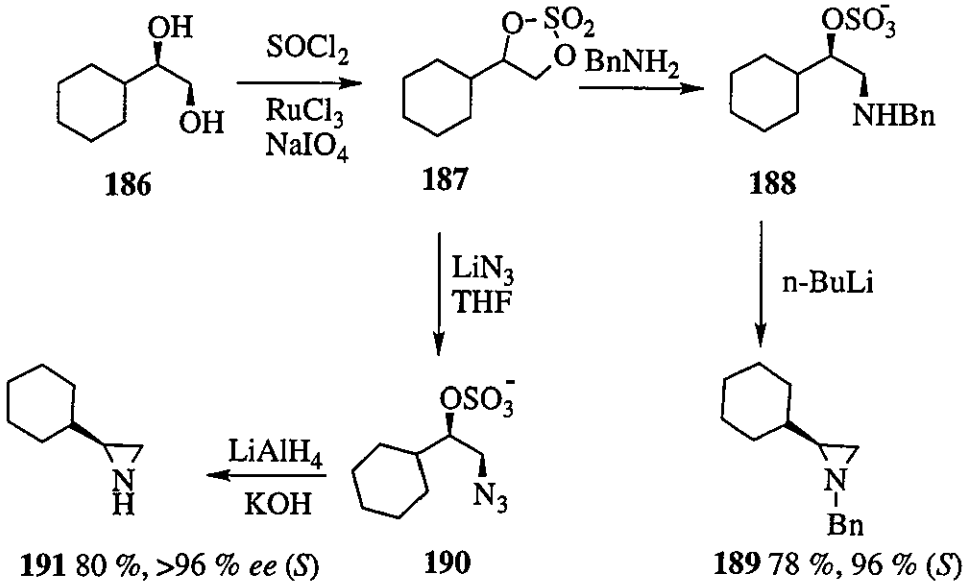
Photolysis.

The mechanism of triazoline photolysis is similar to thermal homolytic decomposition. The rotational freedom around the C-C bond determines the extent of geometrical isomerism.

The triazoline route is not a good route for *N*-unsubstituted or *N*-alkylaziridines.

2.2.6 Cyclic Sulfates.

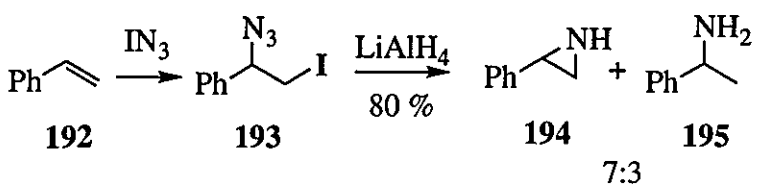
Cyclic sulfates (**187**) have been used for the synthesis of aziridines.[65] This methodology is exemplified by use of the chiral diol (**186**). Two pathways are possible for conversion into aziridines and both involve consecutive nucleophilic displacement reactions, with the final displacement being intramolecular. This offers a range of enantiopure *N*-protected (**189**) and *N*-unprotected aziridines (**191**) by using amine and azide nucleophiles respectively (Scheme 66).



Scheme 66

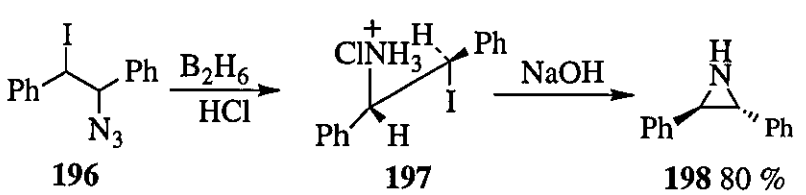
2.2.7 Pseudohalogen Intermediates.

Pseudohalogen additions to alkenes can provide the precursors for aziridine synthesis, but most of the pseudohalogen reagents possess limitations which restrict their general applications. Iodine azide has been found to be the most versatile and possesses high selectivity and high reactivity. For example, iodine azide adds to the alkene **(192)** to give **(193)** and on reduction this gives the aziridine **(194)** and the amine **(195)** (Scheme 67).[66]



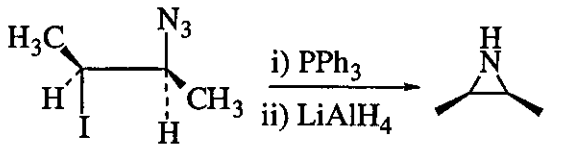
Scheme 67

Trans-diphenylaziridine **(198)** is best obtained in a two-step sequence.[66] The intermediate *erythro*-1-amino-2-iodo-1,2-diphenylethane hydrochloride **(197)** was prepared by the diborane reduction of **(196)** (Scheme 68). The use of alkyl or aryl dichloroboranes leads to the appropriate *N*-alkyl or *N*-aryl aziridines.[32]



Scheme 68

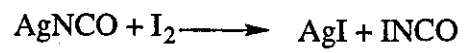
In a follow up to this procedure, Hassner discovered the synthetic use of trivalent phosphines and phosphites in the ring closure of β-iodoazides.[67] The reaction of iodo-azides **(199)** with triphenylphosphine and then reduction gave the aziridine **(200)** and triphenylphosphine (Scheme 69).

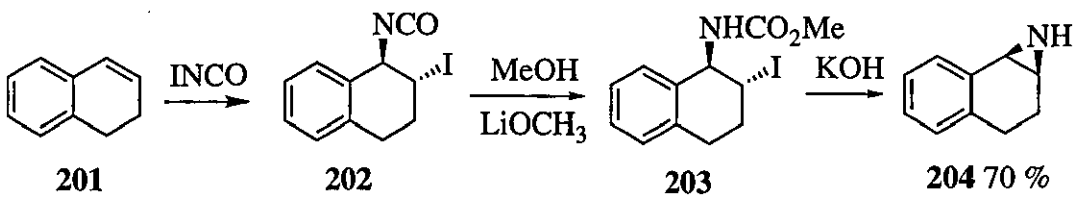


199 **200** 46 %

Scheme 69

The iodine isocyanate aziridination continues to prove useful (Scheme 70).[68,69] The reaction is similar to that of iodine azide. Both reagents are presumed to react *via* iodonium ions which cleave by rearside attack. The method is applicable to unsaturated alcohols, esters, ketones and dienes, but not to conjugated, unsaturated esters or ketones.

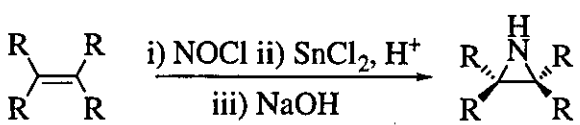




201 **202** **203** **204** 70 %

Scheme 70

An aziridinating procedure which is limited to tetra-substituted alkenes (owing to the instability of the nitroso intermediates from less substituted alkenes) is the addition of NOCl to alkenes (Scheme 71).[70]

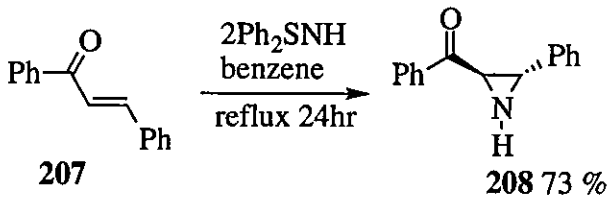


205 **206** R=Me, 79 %

Scheme 71

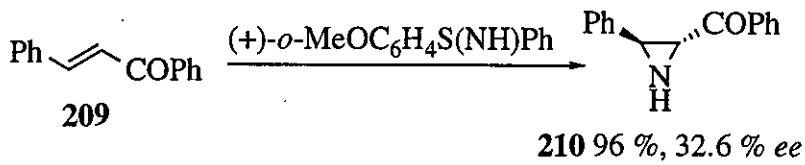
2.2.8 Michael Addition.

The use of *S*,*S*-diphenylsulfilimine for the formation of aziridines from Michael addition to α,β-unsaturated ketones has been reported by Furukawa (Scheme 72).[71]



Scheme 72

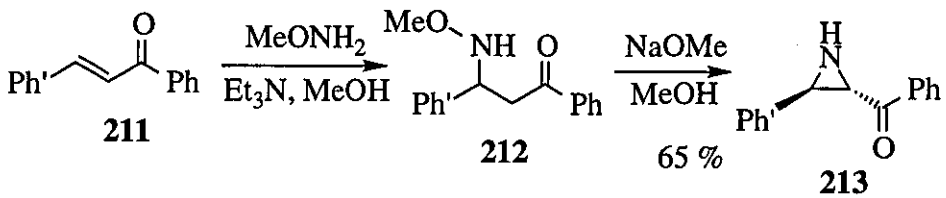
Optically-active aziridines **(210)**, albeit in low *ee* can be synthesised in one-step by treating electrophilic alkenes **(209)** with (+)-(*R*)-*o*-methoxyphenyl sulfimide (Scheme 73).[72]



Scheme 73

Reaction rates depend on the number of substituents on the alkene. The reagent has a short half-life and thus unreactive alkenes do not give high yields.

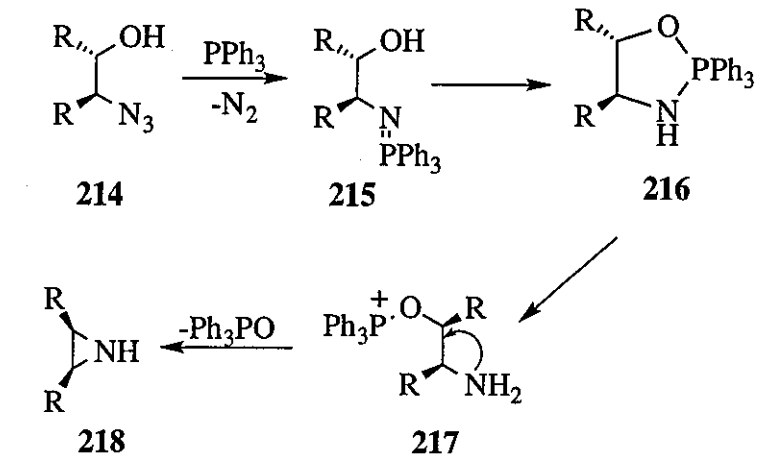
Related syntheses have employed leaving groups like halide, alkoxide or trimethylamine.[73] An example of an alkoxide as the leaving group has been detailed in Scheme 74.[74] Addition of methoxylamine to the alkene **(211)** gave the adduct **(212)** which was closed to the aziridine **(213)** using sodium methoxide. In all cases that were studied (except when Me is in place of Ph'), closure gave the *trans*-aziridine with no observed *cis*-aziridine. In the case of a methyl substituent, the aziridine was formed as a 1:1 mixture of stereoisomers.



Scheme 74

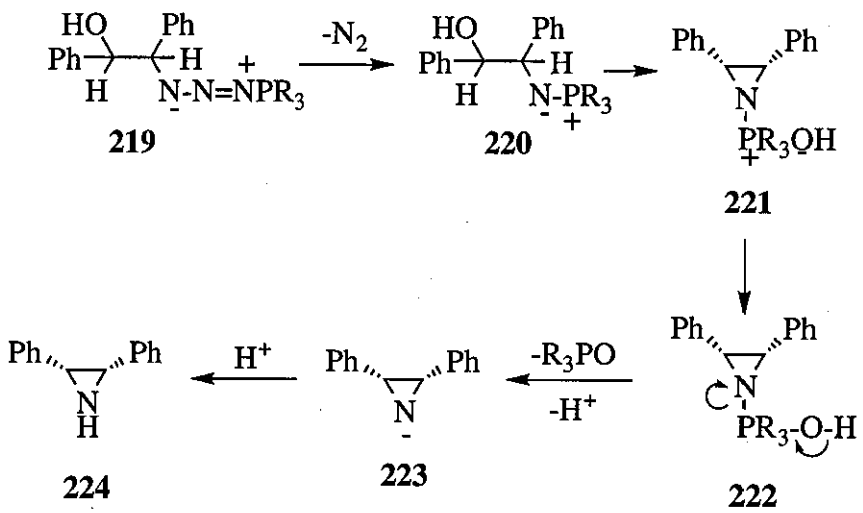
2.3 From Epoxides.

The regiospecific ring opening of epoxides by the azide ion has frequently been exploited to enable the synthesis of aziridines. Reduction of the azide moiety of the azido alcohol **(214)** for example with triphenylphosphine, *via* a Staudinger reaction, yields first the imino phosphorane **(215)** and then an oxazaphospholine **(216)** which thermally cyclises to yield an aziridine **(218)** (Scheme 75).[75]



Scheme 75

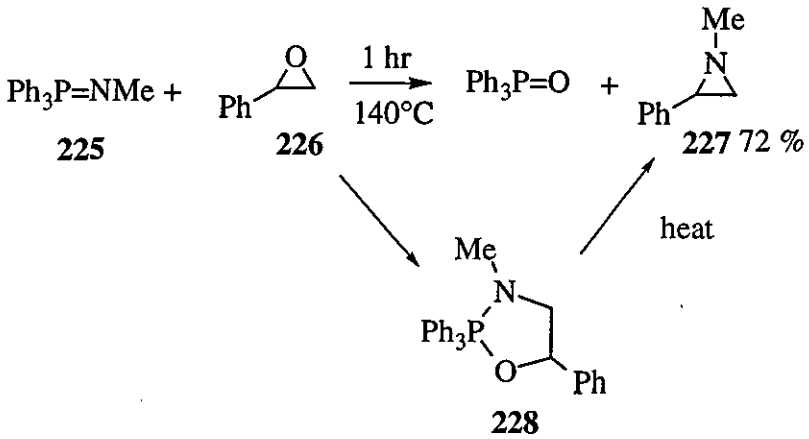
An alternative mechanism, not involving the oxazaphospholine, has been proposed by Blum (Scheme 76).[76]



Scheme 76

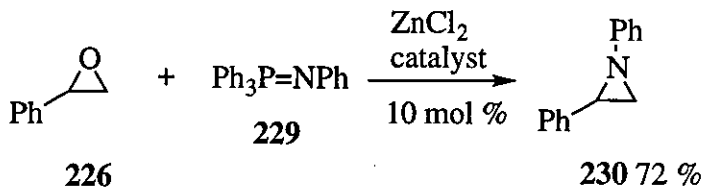
The (+/-) *threo*-azido alcohol is assumed to add the R_3P at the terminal nitrogen atom to give **(219)**. Loss of N_2 and intramolecular nucleophilic substitution would then lead to the aziridinylphosphonium hydroxide **(221)**. Elimination of Ph_3PO from **(222)** and protonation gives the *cis*-2,3-diphenylaziridine **(224)**.

Appel reported the reaction of iminophosphoranes **(225)** with epoxides to form *N*-substituted aziridines **(227)**.[77] The suggested mechanism, which involves an oxazaphospholine **(228)** is shown in Scheme 77. This reaction resembles the Wittig reaction.



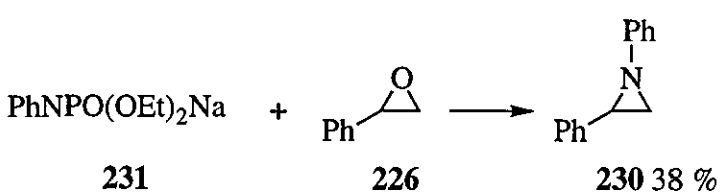
Scheme 77

The above procedure required high temperatures and in general gave low yields. Kuhnau developed a metal-catalysed version of Appel's procedure (Scheme 78).[78] Of the catalysts tried ZnX_2 (X=Cl, I, OTf) were the most effective. Use of the Me, Et, and butyl derivatives of the imine were less promising. The reaction appears to be particularly suitable for terminal and cyclic epoxides.



Scheme 78

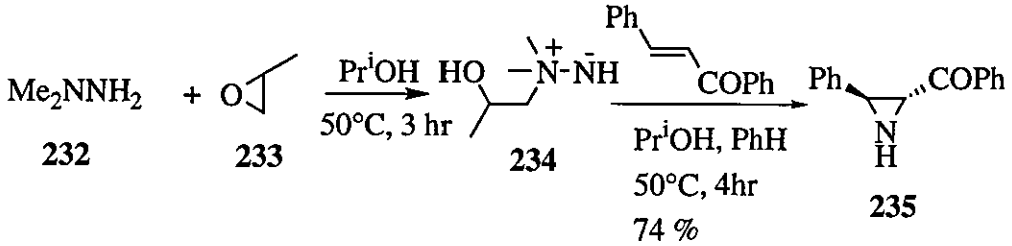
A one-step synthesis of aziridines can be achieved by simply heating the epoxide with the sodium salt of an *N*-substituted amidophosphoric ester **(231)** (Scheme 79).[79] This resembles a Horner modification of the Wittig-type reaction of Appel.



Scheme 79

The proposed mechanism involves nucleophilic attack of the amidophosphate ester anion on the less substituted epoxide carbon. The ring closure to the aziridine structure is then accompanied by phosphate ester elimination to give the aziridine.

A one-pot aziridination procedure has been reported (Scheme 80).[80]

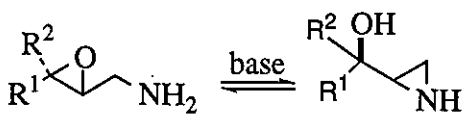


Scheme 80

The aminide **(234)** may attack the β-carbon atom of the chalcone followed by cyclisation to the *trans*-aziridine **(235)** with release of dimethyl-(2-hydroxypropyl)-amine.

2.3.1 aza-Payne Rearrangements of 2,3-Epoxyamines.

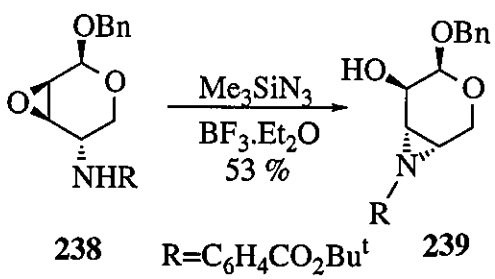
Aza-Payne rearrangements are base-induced rearrangements of epoxyamines **(236)** into the corresponding aziridino-alcohols **(237)** (Scheme 81).[81]



236 R^1, R^2=alkyl **237**

Scheme 81

Under Lewis acid conditions, the rearrangement of some epoxyamines (e.g. **238**) to yield the corresponding aziridinoalcohols **(239)** is favoured (Scheme 82).[81]

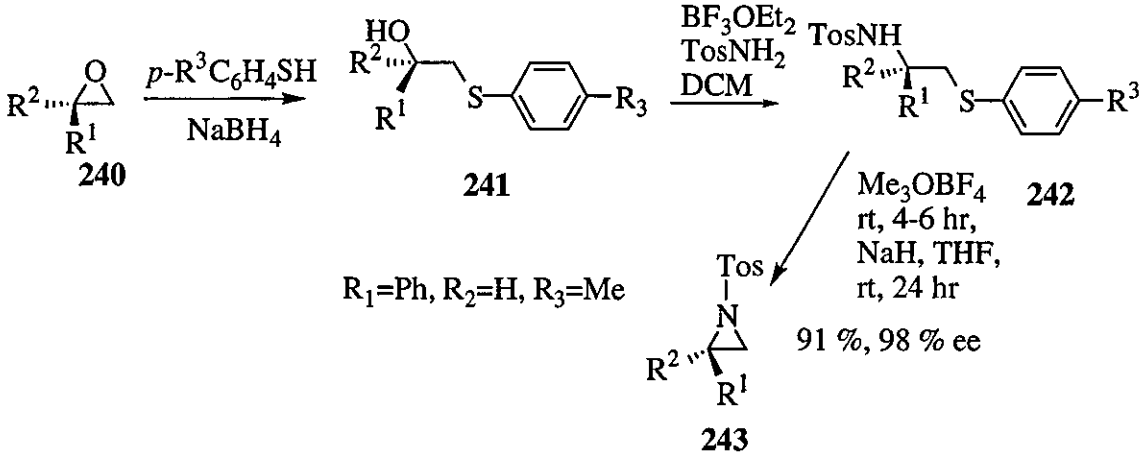


238 $R=C_6H_4CO_2Bu^t$ **239**

Scheme 82

2.3.2 Episulfonium Ions as Intermediates.

Chiral oxiranes **(240)** are converted into chiral β-hydroxyalkyl aryl sulfides **(241)**.[82] The next step involves the replacement of the hydroxy group by a tosylamino group to give **(242)**. Retention of configuration occurs through anchimeric assistance of the arylthio group and the intermediacy of the episulfonium ion **(Fig 9)**. The β-tosylamino-substituted sulfide **(242)** was converted into the sulfonium salt, which was further treated with sodium hydride to afford the tosyl-protected chiral aziridine **(243)** (Scheme 83).



Scheme 83

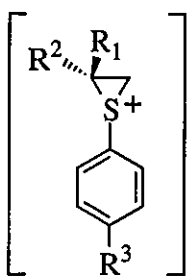
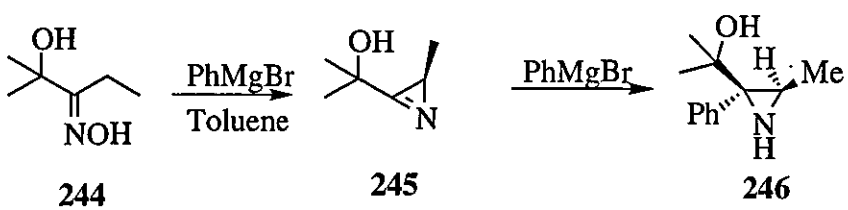


Fig 9

2.4 From Azirines.

2.4.1 Hoch-Campbell Synthesis.

Azirines are unsaturated aziridines and as such they represent potential intermediates for the synthesis of aziridines. The reaction of a α-hydroxyoximes **(244)** with excess Grignard reagent is a useful method for the preparation of 2,2-disubstituted aziridines **(246)** *via* the azirine **(245)** (Scheme 84).[83]

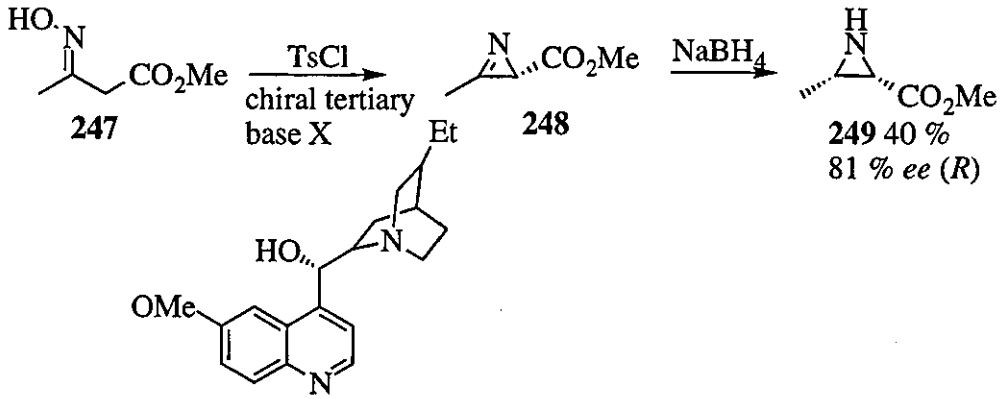


Scheme 84

The diastereofacial selectivity of this reaction was interpreted in terms of the complexation of the Grignard reagent to the alcohol function followed by intramolecular delivery of the nucleophile to the less hindered face of the C-N double bond.

2.4.2 The Neber Reaction.

A method for forming optically active aziridines employs the Neber reaction with the oxime (**247**) and a chiral tertiary base such as dihydroquinidine (**250**) in toluene (Scheme 85). Synthesis of the aziridine (**249**) is then completed by reduction of the azirine (**248**) with sodium borohydride.[84]



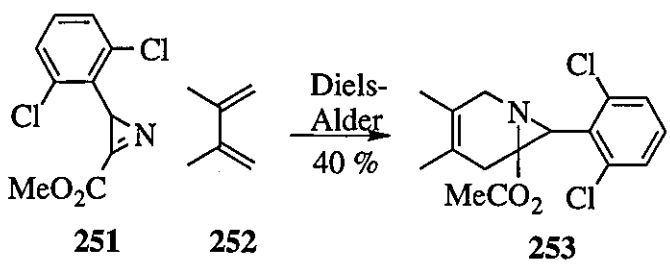
X-dihydroquinidine **250**

Scheme 85

The reaction is assumed to occur *via* a tightly-bound complex of the alkaloid base with the oxime tosylate.

2.4.3 Aziridines from Diels-Alder Reactions.

Gilchrist has used methyl 2-aryl-2*H*-azirine-3-carboxylates as dienophiles in a hetero Diels-Alder reaction (Scheme 86).[85]



251 **252** **253**

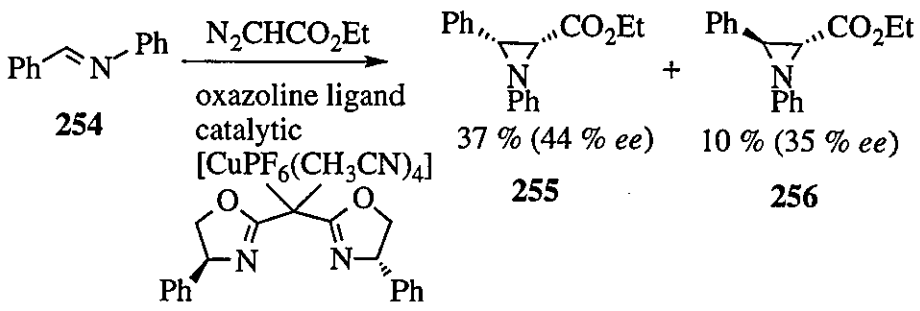
Scheme 86

The reaction of the azirine (**251**) with 2,3-dimethylbutadiene (**252**) gave the cycloadduct (**253**) in 40 % yield.

2.5 From Imines.

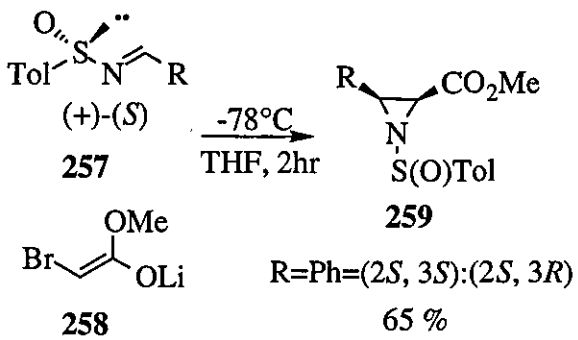
Traditional methods of synthesising racemic aziridines from imines have been elaborated to allow the asymmetric synthesis of aziridines using chiral imines, chiral nucleophiles or chiral catalysts.[86] As an example of the latter, the use of a *bis*-oxazoline

copper(I) complex as a catalyst has proved useful (Scheme 87). The combined yield of the isomeric aziridines **(255)** and **(256)** was however lower than the racemic process.[87]



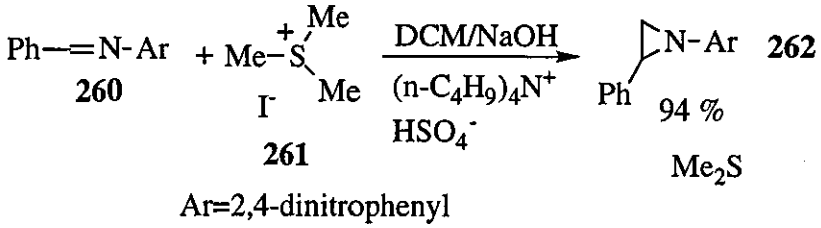
Scheme 87

Condensation of enantiopure sulfilimines **(257)** with the lithium enolate of methylbromoacetate **(258)** allows entry to *cis*-*N*-(*p*-toluenesulfinyl)aziridine-2-carboxylates **(259)** (Scheme 88).[88]



Scheme 88

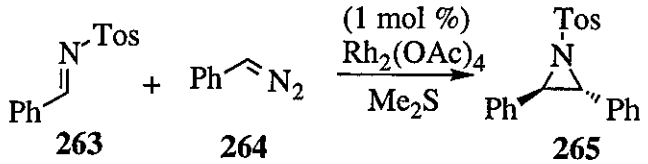
The phase transfer-catalysed production of methylenedimethylsulfurane from trimethyl sulfonium iodide **(261)** in aqueous sodium hydroxide and its interaction with *N*-arylbenzaldimines **(260)** has been utilised for the formation of aziridines **(262)** (Scheme 89).[89]



Scheme 89

A catalytic process mediated by sulfur ylides has been developed by Aggarwal.[90] The proposed catalytic cycle involves the slow addition of a diazo compound to a solution of a

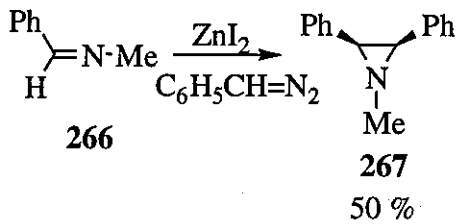
suitable metal salt, dimethylsulfide and the imine. An example includes the synthesis of the aziridine (**265**) from the imine (**263**) using the diazo compound (**264**) (Scheme 90).



90 % 4:1 *trans:cis*

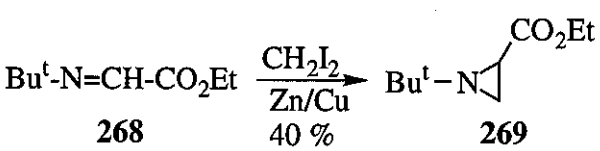
Scheme 90

N-Substituted 2-aryl-3-phenyl aziridines (**267**) were found to be the products of the reactions of imines (**266**) with phenyldiazomethane in the presence of zinc iodide (Scheme 91). *Cis*-aziridines are formed exclusively.[91]



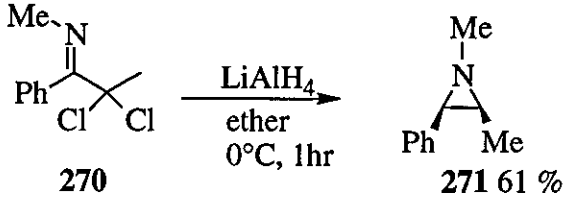
Scheme 91

The Simmons-Smith reaction using iminoesters (**268**) has been used to form aziridines (**269**).[92] The reaction seems to be specific for iminoesters as alkylimines do not appear to undergo the reaction (Scheme 92).



Scheme 92

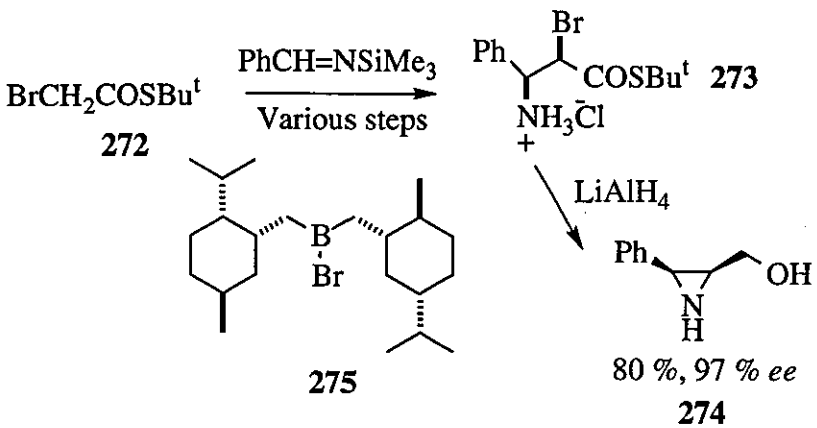
The reaction of *N*-alkyldichloroalkyl aryl ketimines (**270**) with excess $LiAlH_4$ in ether under reflux results in the stereospecific formation of exclusively *cis*-1,2-dialkyl-3-substituted aziridines (**271**) (Scheme 93).[93]



270 **271** 61 %

Scheme 93

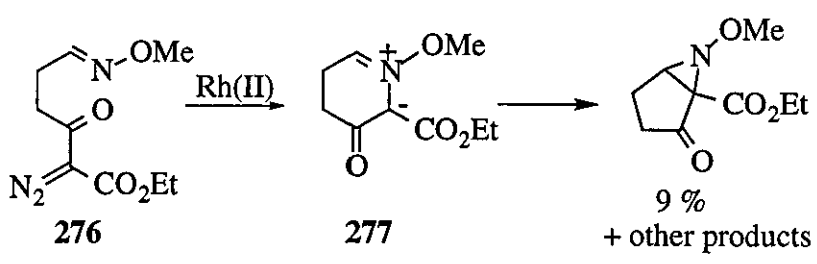
Boron enolates derived from *tert*-butyl-α-halothioacetates (**272**) and the chiral boron reagent (**275**) (derived from (+)-menthone) have been used to synthesise aziridines from *N*-trimethylsilylimines *via* a Mukaiyama-aldol reaction.[94] Reduction using LiAlH4 formed the aziridine (**274**) (Scheme 94).



272 **273** **275** 80 %, 97 % *ee* **274**

Scheme 94

It has been noted by Padwa that treatment of (**276**) with $Rh_2(OAc)_4$ formed a complex mixture from which the aziridine (**278**) was isolated in small yield (9 %) (Scheme 95).[95]

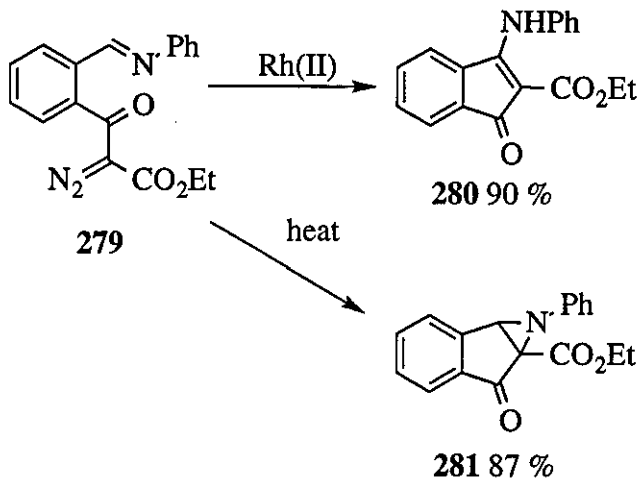


276 **277** 9 % + other products **278**

Scheme 95

The formation of these compounds is readily rationalised in terms of an initially-formed azomethine ylid (**277**) which collapses to produce aziridine (**278**) or reacts further. Padwa also found that treatment of the diazo compound (**279**) with $Rh_2(OAc)_4$ gave the indene

compound (**280**) resulting from a CH insertion of the rhodium carbenoid directly into the imine C-H bond (Scheme 96).



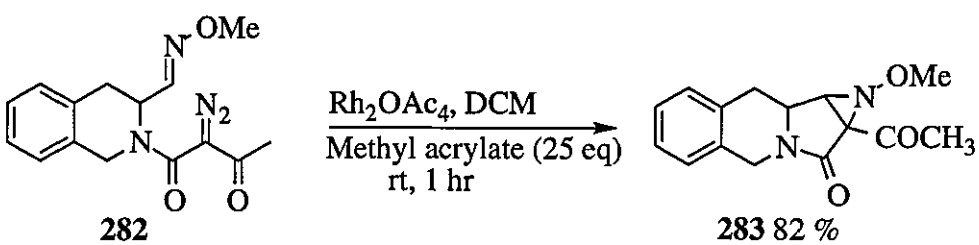
279 **280** 90 %

281 87 %

Scheme 96

Heating (**279**) formed the aziridine (**281**) *via* the intermediate triazole.

Similar results were found by McMills who formed the aziridine (**283**) from the Rh(II)-catalysed decomposition of the diazocompound (**282**) (Scheme 97).[96]

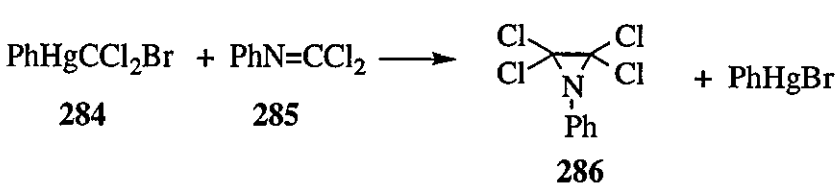


282 **283** 82 %

Scheme 97

He also found that the same compound and yield was formed without the use of a catalyst at room temperature.

The reaction of $PhN{=}CCl_2$ (**285**) with $PhHgCCl_2Br$ (**284**) afforded 1-phenyl-2,2,3,3-tetrachloroaziridine (**286**) in 53 % yield (Scheme 98).[97]

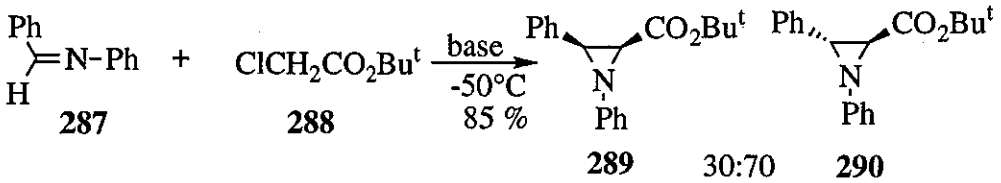


284 **285** **286**

Scheme 98

The reaction proceeds by dichlorocarbene addition to the imine double bond.

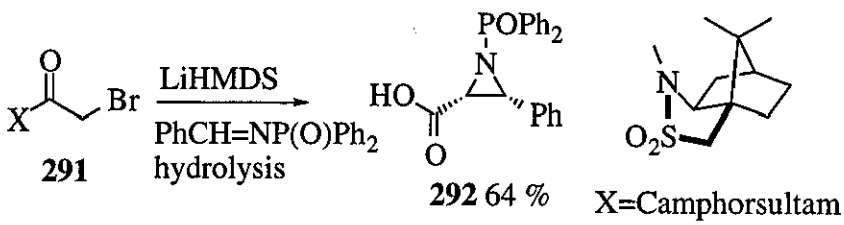
The Darzen's glycidic ester condensation has been extended to the formation of analogous aziridines by using an imine group rather than a carbonyl group. Wartski outlined the use of a variety of α-halo-*tert*-butyl esters (**288**) in producing *N*-phenyl aziridines (**289**) and (**290**) from the corresponding imine (**287**) (Scheme 99).[98] The reaction shows a preference for forming the *trans*-aziridine (**290**).



Scheme 99

Tertiary butyl esters are used instead of ethyl esters to reduce competition from Claisen condensations. The work was also extended to the nitrite derivatives.

An asymmetric aza-Darzen's reaction of the chiral enolate (**291**) derived from bromoacylcamphorsultam with *N*-(diphenylphosphinyl)arylimines has been reported for the synthesis of 2-carboxyaziridines (**292**) (Scheme 100).[99]



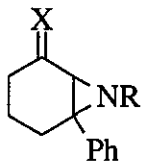
Scheme 100

Conclusion

Many methods exist for the synthesis of both *N*-substituted and *N*-unsubstituted aziridines. Many of these have been developed to allow asymmetric syntheses. Whilst covering the major synthetic routes, there are many in the literature which have not been mentioned. Some comprehensive reviews are detailed in the reference section.[32,41,86,100,101]

3 Project Aim.

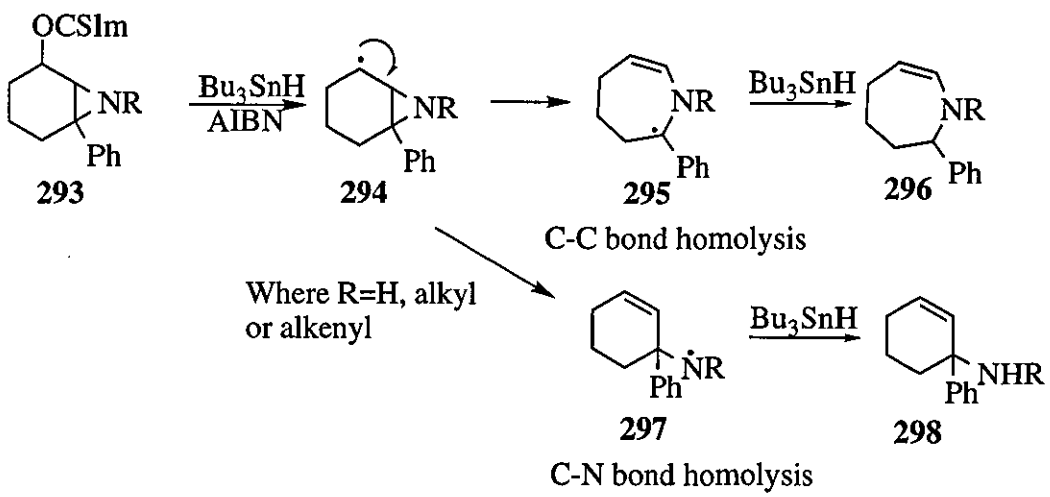
The original intention of this project was to combine the methodologies discussed in chapters 1 and 2 and use aziridines instead of epoxides or cyclopropyl rings for ring expansion reactions. An additional aim was to develop a general synthetic method for the synthesis of compounds of the type represented in **Fig 10**.



e.g. X=CSIm, H; halogen, H; or O
R=H, alkyl or alkenyl

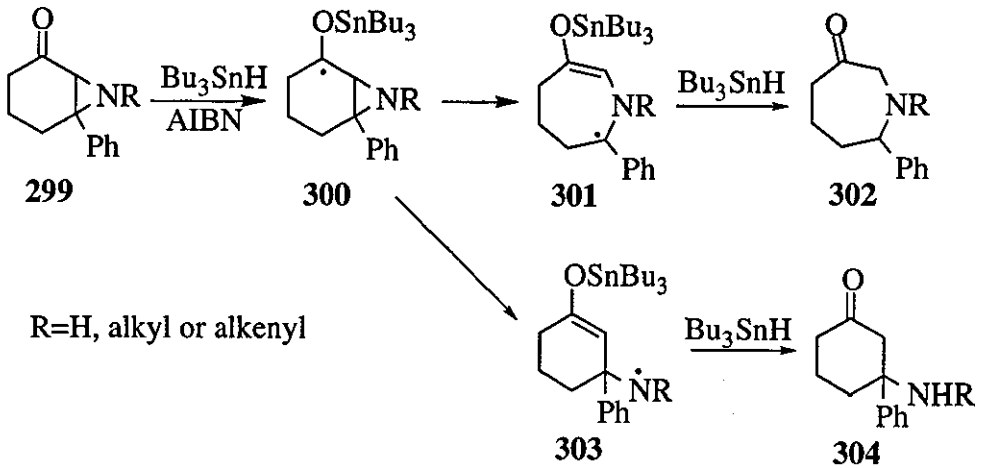
Fig 10

It was expected that the design of the aziridine would allow the study of C-C v C-N bond homolysis. C-C Bond homolysis should result in the formation of the ring expanded product (**296**). If C-N bond homolysis occurs then the allylic amine (**298**) should be formed (Scheme 101).



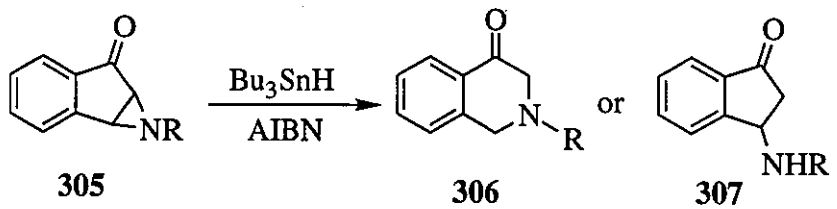
Scheme 101

Reactions of the ketoaziridines (**Fig 10**, X=O) would be expected to proceed as shown in Scheme 102.



Scheme 102

Aziridines based on indenone **(305)** should have similar reactivity and could lead to **(306)** and/or **(307)** depending on the mode of cleavage (Scheme 103).

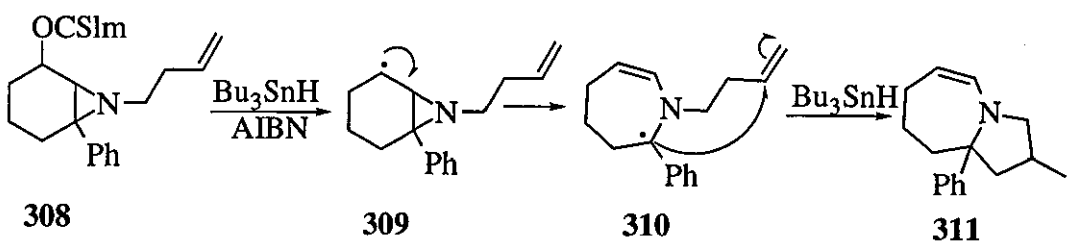


R=H, alkyl or alkenyl

Scheme 103

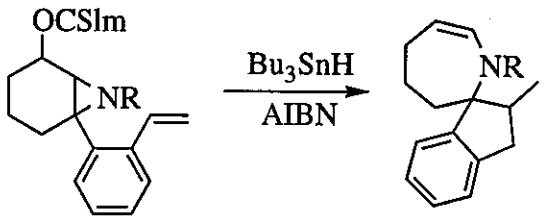
3.1 Tandem Radical Reactions.

If directed C-C bond cleavage is observed then this could open up the possibility of ring expansion and subsequent tandem reactions to give bicycles **(311)** (Scheme 104).



Scheme 104

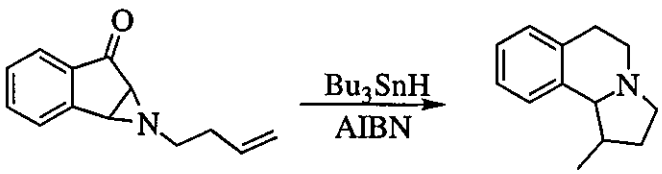
The synthesis of ring expanded *spiro* compounds **(313)** would also be possible in principle (Scheme 105).



312 **313**

Scheme 105

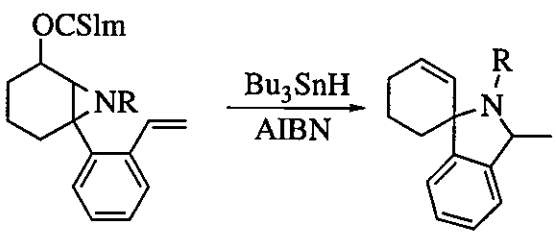
Likewise with indenone derivatives, tricycles **(315)** could be synthesised (Scheme 106).



314 **315**

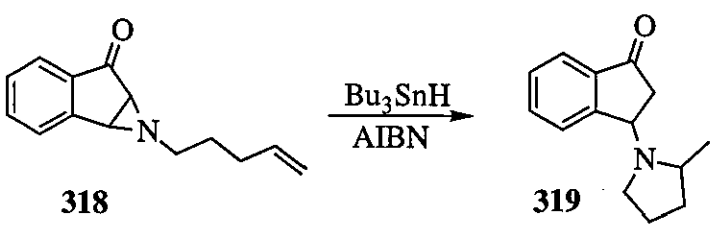
Scheme 106

If C-N bond homolysis is observed in the radical reactions of aziridines, then this could be used to form *N*-heterocycles for example **(317)** or **(319)** (Schemes 107 and 108).



316 **317**

Scheme 107



318 **319**

Scheme 108

As can be seen, directed C-C or C-N bond homolysis has potential for the synthesis of biologically active ring systems. For example, the naturally occurring (+/-)-puntarenine **(Fig 11)** shows fungicidal activity.[102]

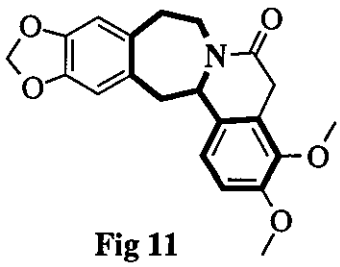


Fig 11

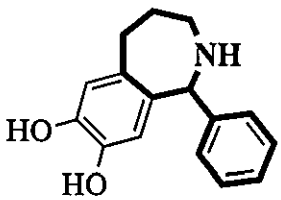


Fig 12

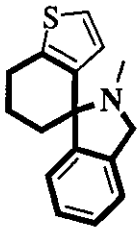


Fig 13

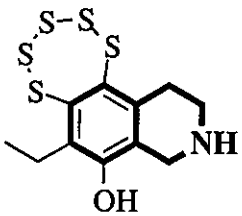


Fig 14

The synthetic benzazepin **(Fig 12)** shows anti-ulcer activity.[103] C-N Bond homolysis could be utilised to synthesise the spiropyrrole **(Fig 13)** which shows some promise in the treatment of Alzheimer's disease.[104] The elegant cyclic sulfur compound **(Fig 14)** showing antibiotic activity could be a possible target using the ring expansion of indanone-derived aziridines.[105]

The purpose of this project is to explore these possibilities.

4 Results and Discussion.

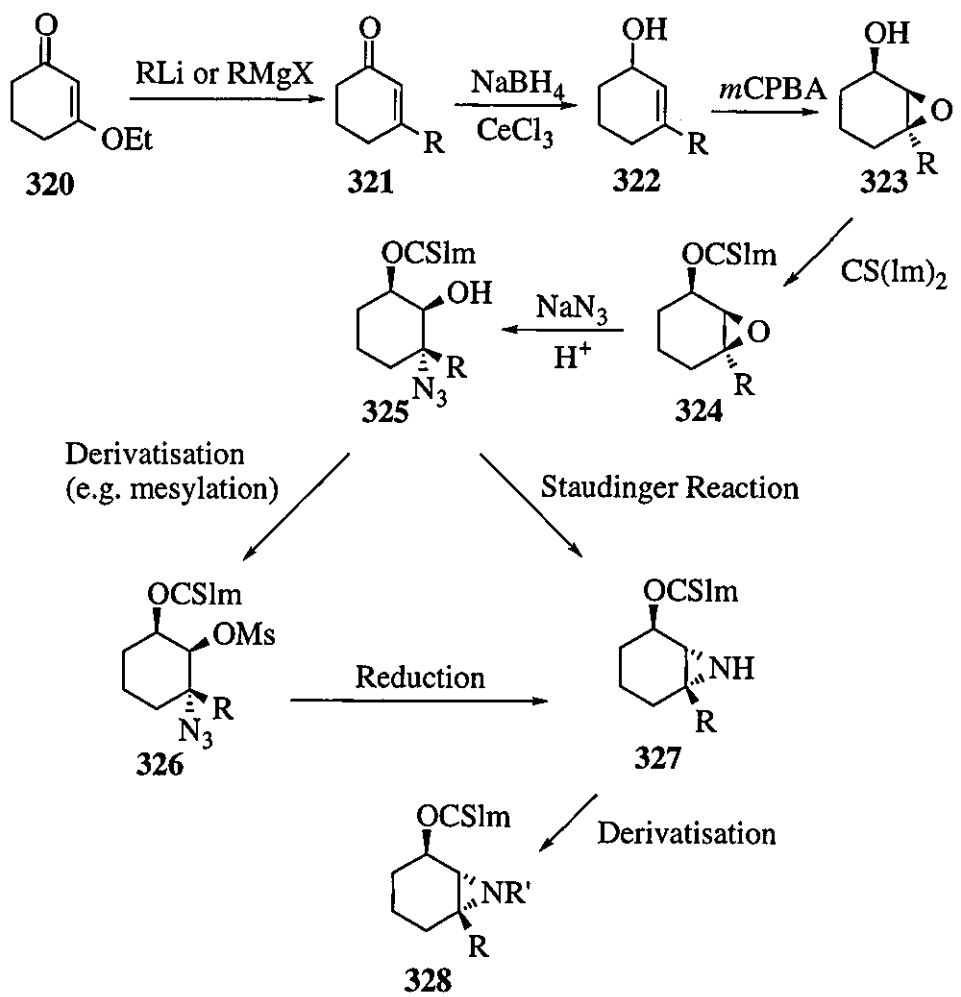
4.1 Aziridines from 2-Azidoalcohols *via* the Staudinger Reaction.

A brief strategic approach to the required free radical precursors has been detailed in Scheme 109. Reaction of the readily available 3-ethoxy-2-cyclohexen-1-one (**320**) with an aryl lithium or an aryl Grignard reagent would be expected to give the 3-aryl derivative (**321**). Luche reduction could then give the allylic alcohol (**322**) and epoxidation using *m*CPBA the 2,3-epoxyalcohol (**323**). Formation of the thiocarbonylimidazolide (**324**) and epoxide opening with sodium azide, under acidic conditions, could give the 2,3-azidoalcohol (**325**). The next step could involve two different routes.

1) Derivatisation of the azidoalcohol (**325**) (e.g. with mesylate) to give (**326**) and reduction to give the aziridine (**327**).

2) A Staudinger reaction on the azidoalcohol (**325**) to give the aziridine (**327**).

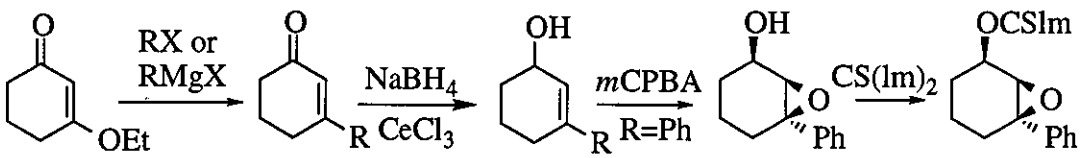
Derivatisations of the aziridine moeity could then be perfomed to give a range of *N*-alkylated aziridines (**328**).



R=aryl; R'=alkyl or alkenyl

Scheme 109

Reaction of 3-ethoxy-2-cyclohexen-1-one **(320)** with phenyl lithium followed by an acidic work up gave 3-phenyl-2-cyclohexen-1-one **(330)** (Table 2, Scheme 110). This was converted to 3-phenyl-2-cyclohexen-1-ol **(334)** by Luche reduction (Table 3). Reaction with *m*CPBA afforded 2,3-epoxy-3-phenylcyclohexan-1-ol **(338)** and then treatment with 1,1'-thiocarbonyldiimidazole afforded the thiocarbonylimidazolide **(339)** (Scheme 110). Various enones **(331)** to **(333)** and allylic alcohols **(335)** to **(337)** were synthesised (Tables 2 and 3) and these will be discussed in later sections.



320 **330-333** **334-337** **338** 89 % **339** 56 %

Scheme 110

Table 2: Results for the Syntheses of the Enone Derivatives **(330)** to **(333)**.

No.	X	R group	Yield %
330	Li	Ph	65
331	Li	Me	90
332	Li	Bu^t	37
333	Br*	*p*-ClPh**	53

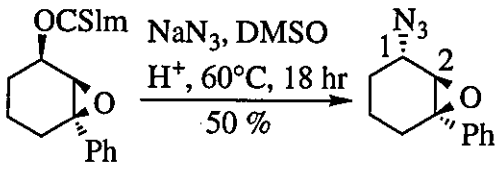
* Grignard reagent used, **p*-ClPh=*p*-Chlorophenyl

Table 3: Results for the Syntheses of the Allylic Alcohols **(334)** to **(337)**.

No.	R group	Yield %
334	Ph	98
335	Me	77
336	Bu^t	87
337	*p*-ClPh*	91

**p*-ClPh=*p*-Chlorophenyl

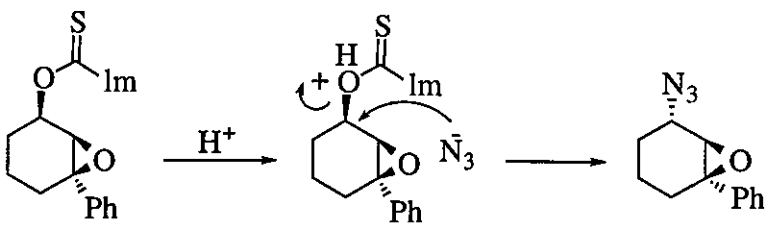
The syntheses of **(330)** **(334)** **(338)** and **(339)** have been reported by Dave Corser in these laboratories.[106] Reaction of the thiocarbonylimidazolide **(339)** with sodium azide, under acidic conditions,[107] surprisingly gave 1-azido-2,3-epoxy-3-phenylcyclohexane **(340)** (Scheme 111). Key data:- ν_{max}/cm^{-1} 2101 (N_3); δ_H 3.87 (1 H, dd, J = 9 and 6 Hz, 1-CH), 3.07 (1 H, br s, 2-CH); δ_C 61.6 (C).



339 340

Scheme 111

A proposed mechanism is shown in Scheme 112.

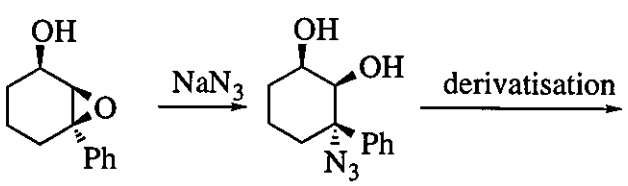


339 341 340

Scheme 112

Therefore the thiocarbonylimidazole group is insufficiently stable to acid and hydroxy group protection is required prior to opening of the epoxide.

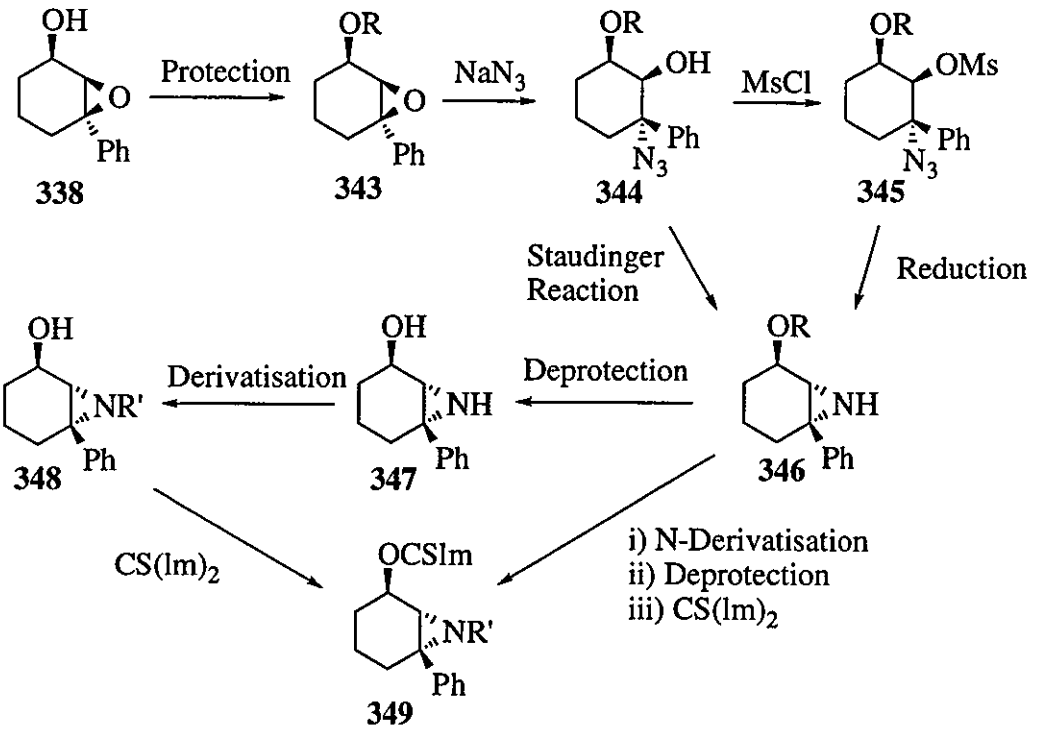
4.1.1 Hydroxy Group Protection Routes.



338 364

Scheme 113

If the diol (**364**) was formed on azide opening of the epoxyalcohol (**338**) (Scheme 113) then formation of only a mono-mesylate leaving group adjacent to the azide group, as was required for aziridine formation, would prove difficult. The other OH group was required for the formation of the thiocarbonylimidazolide and it was considered that the protection route summarised in Scheme 114 was the best way to proceed.

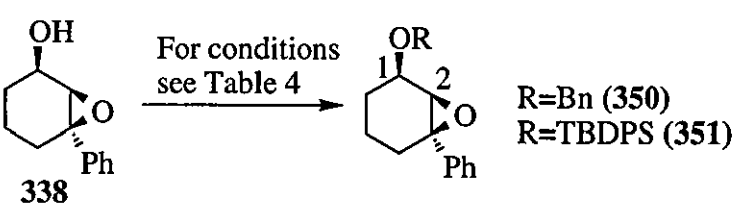


R=protecting group, R'=alkyl or alkenyl

Scheme 114

Thus the proposal involved the protection of the epoxyalcohol (**338**) to give (**343**) opening with azide to give the azidoalcohol (**344**) and reduction of the azidoalcohol or mesylate to give the aziridine (**346**). Deprotection, derivatisation and formation of the thiocarbonyl imidazolide (**349**) could be envisaged to give the required radical precursors. A similar route could involve derivatisation of the OH protected aziridine (**346**) then de-protection and formation of the required thiocarbonylimidazolide (**349**).

The epoxyalcohol (**338**) was protected using the conditions stated in Table 4 (Scheme 115).



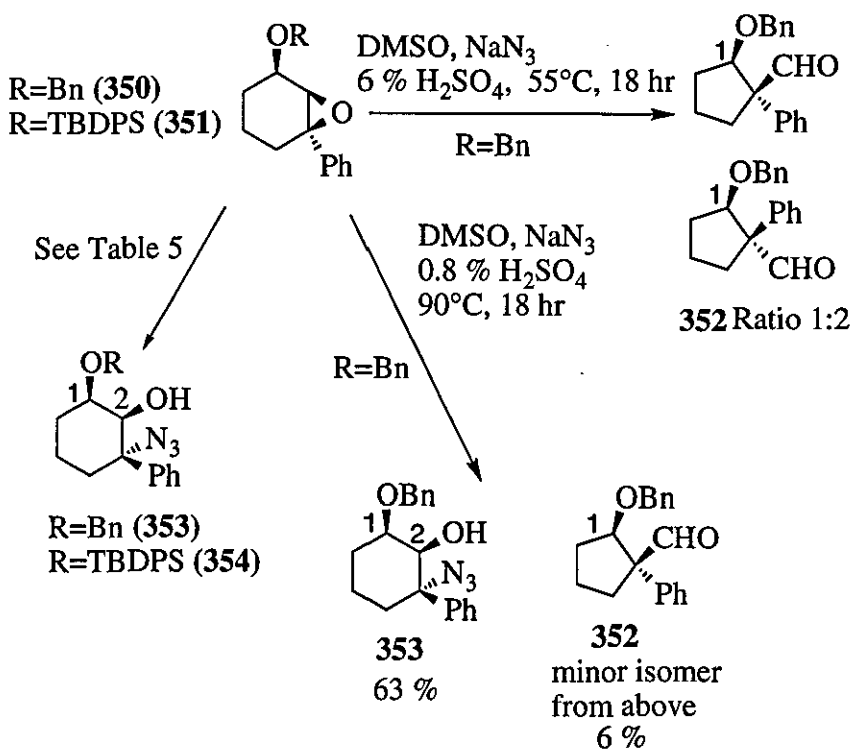
Scheme 115

Table 4: Conditions for the Hydroxy Group Protection of the Epoxy Alcohol **(338)**.

No.	Conditions	Yield %
350	BnBr, NaH, DMF, 0°C, 1 hr[108]	52
351	TBDPSCl, DMAP, Et_3N, DCM, rt, 2 days[109]	71

Key data:- **(350)** δ_H 4.71 (1 H, d, J = 12 Hz, CH_2Ph), 4.67 (1 H, d, J = 12 Hz, CH_2Ph), 3.90 (1 H, m, 1-CH), 3.24 (1 H, d, J = 2.5 Hz, 2-CH); **(351)** δ_H 4.09 (1 H, m, 1-CH), 3.00 (1 H, d, J = 2 Hz, 2-CH).

The subsequent ring opening of the benzyl ether **(350)** with sodium azide under acidic conditions proved to be very sensitive to the concentration of acid used.[107] Too much acid caused rearrangements of the ether to the aldehydes **(352)** (scheme 116). Key data:- ν_{max}/cm^{-1} 1719 (C=O); δ_H 9.39 (1 H, s, CHO, maj), 4.51 (1 H, d, J = 4.5 Hz, 1-CH, maj). The optimum acidic concentration was determined to be approximately 0.4 % sulphuric acid which gave the required azidoalcohol **(353)** cleanly without any rearrangement (Scheme 116). Key data:- ν_{max}/cm^{-1} 3460 (OH), 2099 (N_3); δ_H 4.05 (1 H, br s, 2-CH), 3.87 (1 H, m, 1-CH). The TBDPS-protected alcohol **(351)** showed a clean conversion to the required azido alcohol **(354)** using a concentration of 1 % acid. Key data:- ν_{max}/cm^{-1} 3563 (OH), 2100 (N_3); δ_H 4.15 (1 H, m, 1-CH), 3.72 (1 H, d, J = 2 Hz, 2-CH) (Table 5, Scheme 116).[107]

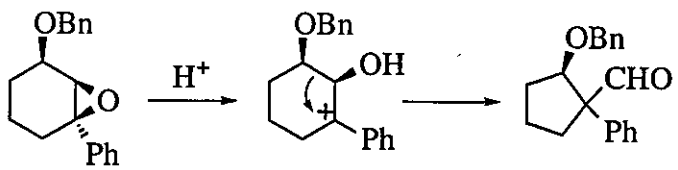


Scheme 116

Table 5: Conditions for the Synthesis of the Azidoalcohols **(353)** and **(354).**

No	Conditions	Yield %
353	DMSO, NaN_3, 0.4 % H_2SO_4, 90°C, 18 hr[107]	76
354	DMSO, NaN_3, 1 % H_2SO_4, 86°C, 72 hr[107]	94

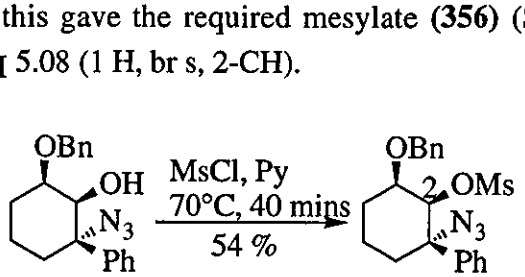
A proposed mechanism is shown in Scheme 117. It must involve a two-stage process involving i) breaking of the epoxide bond to give the benzyl cation **(355)** and ii) migration of the carbon-carbon bond to give the aldehyde **(352).**



350 **355** **352**

Scheme 117

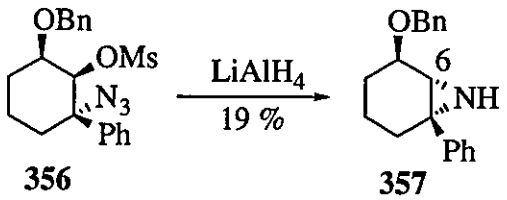
The acid-catalysed rearrangements of epoxides to aldehydes or ketones is well documented in the literature.[110] The azidoalcohol **(353)** was allowed to react with mesyl chloride in DCM containing triethylamine.[111] No formation of the required mesyl ester **(356)** was observed. Therefore a procedure by Ponsold was adopted whereby the reaction was conducted in pyridine.[112] On heating, this gave the required mesylate **(356)** (Scheme 118). Key data:- ν_{max}/cm^{-1} 2108 (N_3); δ_H 5.08 (1 H, br s, 2-CH).



353 **356**

Scheme 118

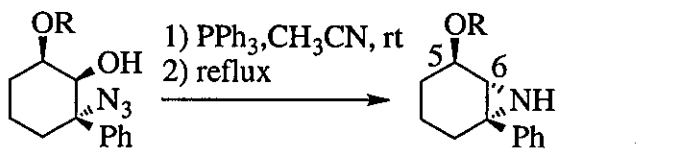
Reaction of the mesylate **(356)** with lithium aluminium hydride,[112] formed the required aziridine **(357)** (Scheme 119). Key data:- ν_{max}/cm^{-1}: N_3 absent; δ_H 2.55 (1 H, br s, 6-CH). The use of Raney nickel and hydrazine failed to form the aziridine **(357).**[107] Only a complex mixture was obtained.



356 357

Scheme 119

A Staudinger reaction was also carried out on the azidoalcohol (**353**) to determine whether the mesylation step could be omitted and gave the aziridine (**357**) in 55 % yield.[113] Key data:- ν_{max}/cm^{-1} N_3 absent; δ_H 3.76 (1 H, dd, J = 8 and 6 Hz, 5-CH), 2.55 (1 H, br s, 6-CH). The azidoalcohol (**354**) was also reacted using the Staudinger reaction to yield the aziridine (**358**) in 64 % (Scheme 120).[113] Key data:- ν_{max}/cm^{-1} N_3 absent, δ_H 4.20 (1 H, m, 5-CH), 2.52 (1 H, br s, 6-CH).

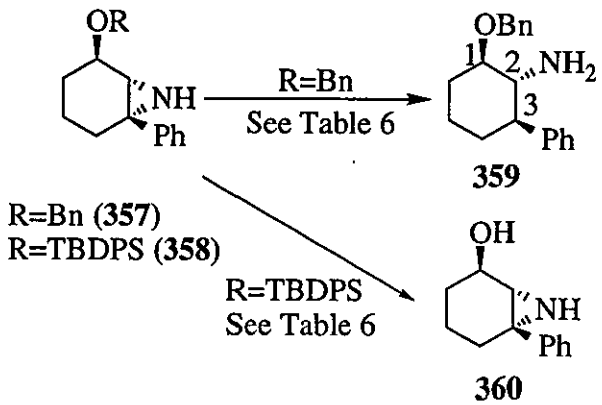


R=Bn (**353**)
R=TBDPS (**354**)

R=Bn (**357**) 55 %
R=TBDPS (**358**) 64 %

Scheme 120

Attempted deprotection of the benzyl-protected aziridine (**357**) by reduction with either (a) 10 % Pd/C and hydrogen or (b) transfer hydrogenation using 10 % Pd/C and 1,4-cyclohexadiene caused ring opening of the aziridine to yield the amine (**359**) which proved difficult to purify fully (Table 6, Scheme 121).[114,115] Key data (tentative assignment from NMR analysis of the crude product):- ν_{max}/cm^{-1} 3375 (NH_2); δ_H 3.31 (1 H, m, 1-CH), 3.01 (1 H, m, 2-CH), 2.60 (1 H, m, 3-CH). More success was found with the TBDPS protected aziridine (**358**) which, on reaction with TBAF or DMPU/NaH, removed the protecting group to give the unprotected aziridine (**360**) albeit in relatively low yield (Table 6, Scheme 121).[116,117] The aziridine was not purified further and characterisation and estimates of the yields were performed by comparison with the NMR spectra of an authentic compound (see Experimental and Data) against the spectra of the crude products.



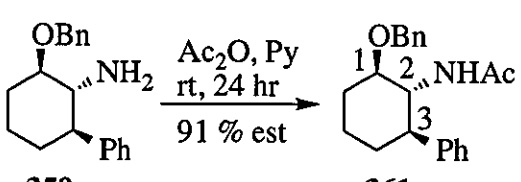
Scheme 121

Table 6: Conditions for the Deprotection of Aziridines **(357)** and **(358).**

R	Conditions	Yield %
Bn	10 % Pd/C, H_2[114]	73 (estimated)
Bn	10 % Pd/C, 1,4-cyclohexadiene, H_2[115]	36 (estimated)
TBDPS	TBAF (1 M), rt, 24 hr[116]	31 (estimated)
TBDPS	DMPU/NaH, 0°C, rt, 72 hr[117]	33 (estimated)

Czech and Bartsch have studied the affect of amines on O-benzyl group hydrogenolysis.[118] They concluded that inhibition of O-debenzylation occurs in the presence of basic non-aromatic amines. Thus, it is suggested that the benzyl-protected aziridine **(357)** is initially opened on reduction and the amine formed inhibits O-debenzylation.

In order to aid chromatographic purification of the amine **(359)** acetylation was performed to give the amide **(361)** which degraded on attempted purification and therefore characterisation is from NMR analysis of the crude product. (Scheme 122).[119] Key data (tentative):- ν_{max}/cm^{-1} 1650 (C=O); δ_H 5.07 (1 H, br d, J = 9 Hz, NHAc), 3.91 (1 H, m, 2-CH), 3.53 (1 H, m, 1-CH).



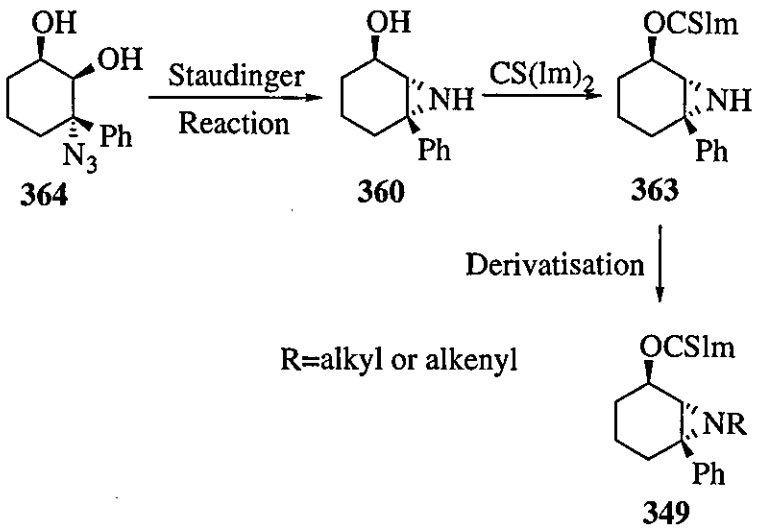
359 **361**

Scheme 122

From the two protecting groups tried, TBDPS protection appears to be the most promising. The benzyl group is difficult to remove without destroying the aziridine.

4.1.2 The Formation of Aziridines Without Hydroxy Group Protection.

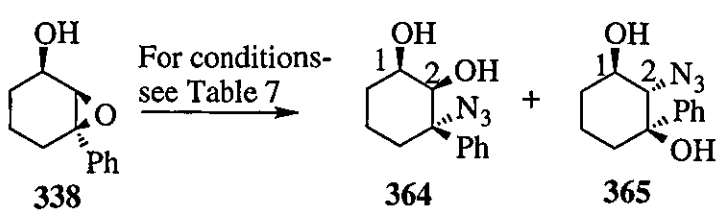
This synthetic proposal involved the synthesis the azidodiol (**364**) and subjecting this to a Staudinger reaction could give the aziridine (**360**). Reaction with 1,1'-thiocarbonyl diimidazole would then be expected to give the free-radical precursor-the *N*-unprotected aziridine (**363**) (Scheme 123). Derivatisation of this aziridine could give a range of *N*-substituted aziridines (**349**).



364 360 363 349

Scheme 123

The epoxide (**338**) was allowed to react with sodium azide in DMSO,[107] under acidic conditions to yield the two azidoalcohols (**364**) and (**365**) (Table 7, Scheme 124). Key data (**364**):- ν_{max}/cm^{-1} 2098 (N_3); δ_H 3.91 (1 H, m, 1-CH), 3.73 (1 H, br s, 2-CH), 2.54 (1 H, br s, OH), 2.39 (1 H, br s, OH); (**365**) ν_{max}/cm^{-1} 2109 (N_3); δ_H 4.04 (1 H, d, J = 6 Hz, 1-OH), 3.99 (1 H, br s, 1-CH), 3.90 (1 H, br s, 2-OH), 3.40 (1 H, br s, 2-CH). A method by Crotti using ammonium chloride as the acid and 8:1 methanol:water as the solvent system with sodium azide (5 eq) gave only one regio-isomer (**364**) in excellent yield.[113]



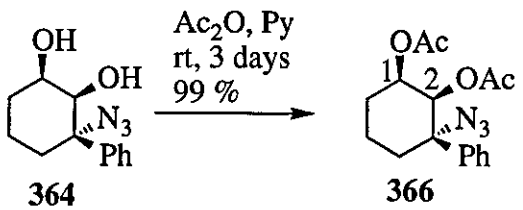
338 364 365

Scheme 124

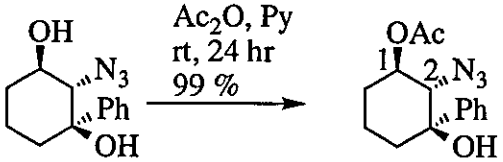
Table 7: Conditions for the Formation of the Azidoalcohols **(364)** and **(365).**

Conditions	Yield 364:365
11 NaN_3, DMSO, 0.6 % H_2SO_4, 78°C, 24 hr[107]	46:32
5 NaN_3, NH_4Cl, 8:1 MeOH:water, 70°C, 18 hr[113]	94:0

The two azidoalcohols **(364)** and **(365)** from the DMSO/NaN_3 method were then separated by flash chromatography. To aid characterisation, both were acetylated to give **(366)** and **(367)** (Scheme 125).[119]



364 **366**



365 **367**

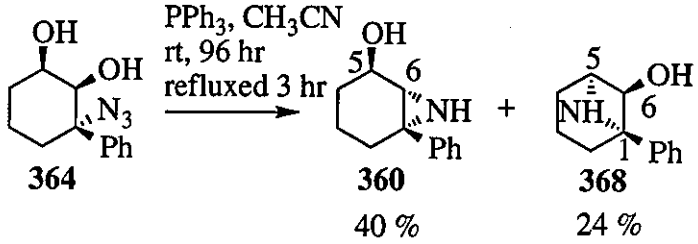
Scheme 125

Key data **(366)** :-ν_{max}/cm^{-1} 2101 (N_3), 1749 (C=O); δ_H 5.38 (1 H, br s, 2-CH), 5.30 (1 H, m, 1-CH). **(367)**:- ν_{max}/cm^{-1} 3449 (OH), 2108 (N_3), 1741 (C=O); δ_H 5.30 (1 H, m, 1-CH), 3.77 (1 H, d, J = 7 Hz, 2-CH), 3.07 (1 H, s, OH).

The two azidoalcohol regioisomers were tested separately and these have been detailed below.

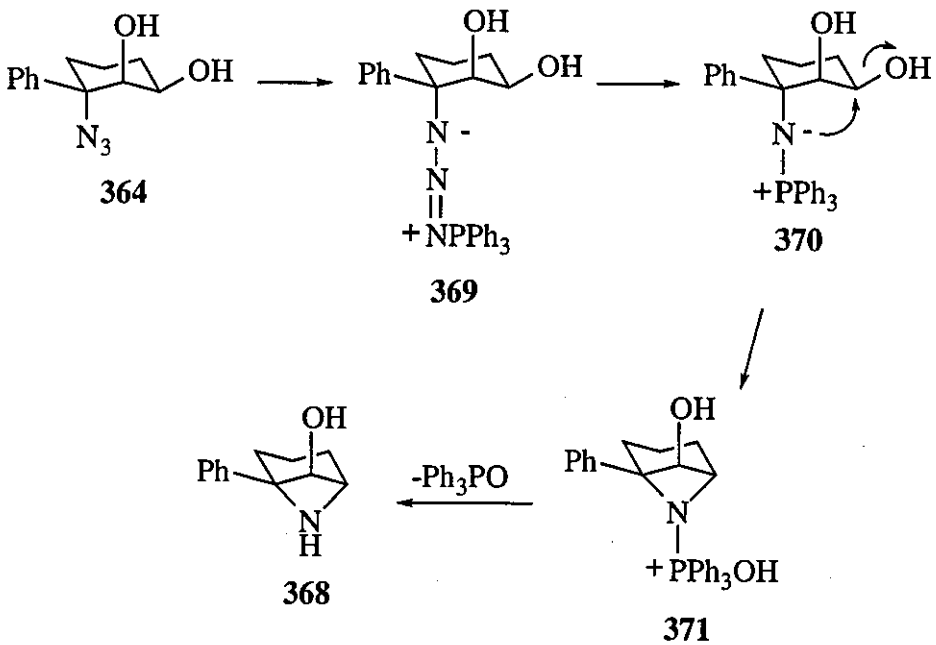
4.1.3 Reactions with 3-Azido-3-phenylcyclohexan-1,2-diol (364) and 2-Azido-3-phenyl cyclohexan-1,3-diol (365).

A Staudinger reaction on 3-azido-3-phenylcyclohexan-1,2-diol **(364)** afforded a mixture of the aziridine **(360)** and an azetidinol **(368)** (Scheme 126).[113] Key data **(360)**; ν_{max}/cm^{-1} 3289 (OH and NH); δ_H 4.00 (1 H, dd, J = 8.5 and 6 Hz, 5-CH), 2.40 (1 H, br s, 6-CH); δ_C 43.4 (1-C) **(368)**; ν_{max}/cm^{-1} 3360 (OH and NH); δ_H 4.03 (1 H, m, 5-CH), 3.80 (1 H, d, J = 2.5 Hz, 6-CH); δ_C 58.5 (1-C).

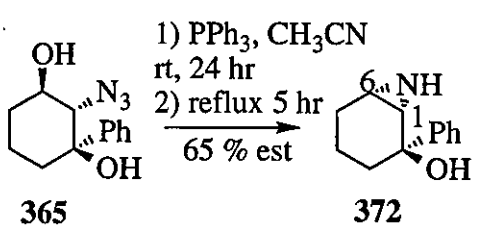


Scheme 126

The aziridine **(360)** is assumed to be formed *via* the cyclic oxazaphospholine mechanism (Chapter 2.3, page 34). This cannot explain the formation of the azetidinol **(368)**. The mechanism of Blum (Chapter 2.3, page 34) could explain its formation (Scheme 127). An intermolecular Mitsunobu-type reaction could also be possible.



Scheme 127

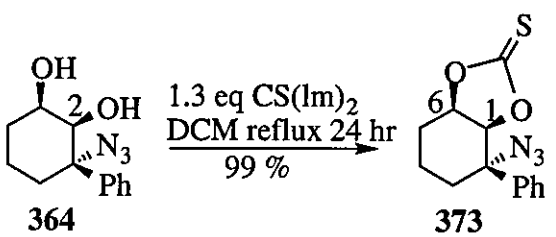


Scheme 128

A Staudinger reaction on 2-Azido-3-phenylcyclohexan-1,3-diol **(365)** gave the aziridine **(372)** (Scheme 128).[113] This presumably occurs *via* a less sterically hindered route. The aziridine degraded on attempted purification and therefore ^{1}H-NMR analysis of the

crude product was used for characterisation. Key data (tentative):- ν_{max}/cm^{-1} N_3 absent, 3301 (OH and NH); δ_H 2.28 (1 H, d, J = 6 Hz, 1-CH), 1.84 (2 H, m, 5-CH and 6-CH); δ_C 72.5 (C).

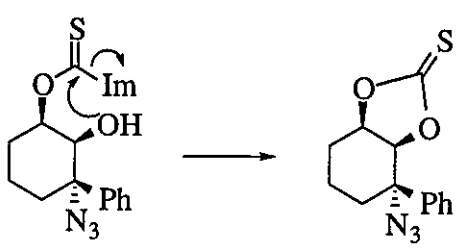
The diol **(364)** was allowed to react with approximately one equivalent of 1,1'-thiocarbonydiimidazole to determine whether any selectivity could be obtained between the two alcohol groups.[120] Instead of the required mono-thiocarbonylimidazolide in position 2 being formed for **(364)** intramolecular nucleophilic displacement of the imidazole took place to form the cyclic thiocarbonate **(373)** (Scheme 129). Key data:- ν_{max}/cm^{-1} OH absent, 2109 (N_3), δ_H 5.09 (1 H, dt, J = 13 and 6 Hz, 6-CH), 4.74 (1 H, dd, J = 6 and 1 Hz, 1-CH); δ_C 190.9 (C=S). The structure was also confirmed by X-ray crystallography-see Appendix.



364 **373**

Scheme 129

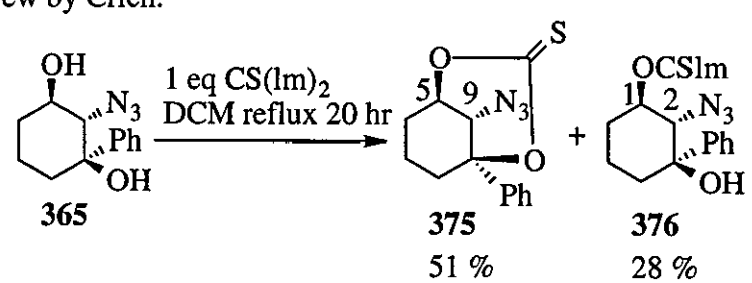
This is represented mechanistically in Scheme 130.



374 **373**

Scheme 130

The formation of cyclic thiocarbonates from diols and 1,1'-thiocarbonyldiimidazole has been reported in a review by Crich.[121]



365

375 51 %

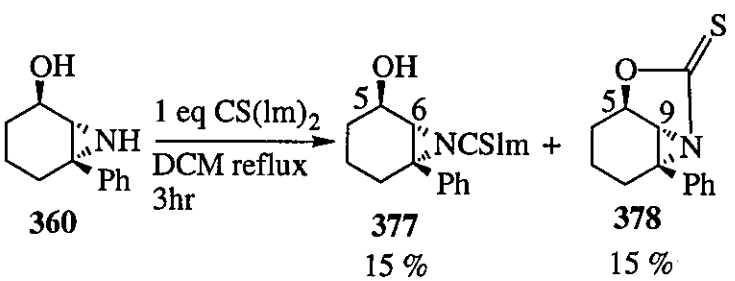
376 28 %

Scheme 131

The regioisomer **(365)** on similar reaction with 1,1'-thiocarbonyldiimidazole, gave some of the required thiocarbonylimidazolide **(376)** but the major product was the cyclic

thiocarbonate (**375**) (Scheme 131). Key data (**375**); ν_{max}/cm^{-1} 2115 (N_3); δ_H 4.08 (1 H, m, 5-CH), 4.06 (1 H, d, J = 4 Hz, 9-CH); δ_C 189.7 (C=S); structure also confirmed by X-ray crystallography-see Appendix. (**376**); ν_{max}/cm^{-1} 3237 (OH), 2111 (N_3); δ_H 5.84 (1 H, m, 1-CH), 4.03 (1 H, d, J = 5 Hz, 2-CH); δ_C 183.4 (C=S), 75.3 (C). A Staudinger reaction on the thiocarbonylimidazolide (**376**) provided no evidence for the formation of an aziridine.

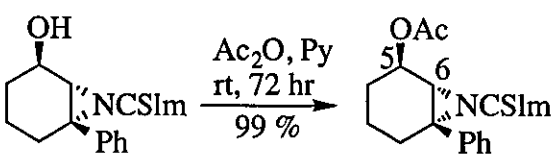
Reaction of the aziridine (**360**) with 1,1'-thiocarbonyldiimidazole was tried to determine whether the alcohol group could be selectively esterified (Scheme 132).[120] Derivatisation was found to be on the nitrogen rather than the alcohol function to give the *N*-substituted aziridine (**377**). Key data:- ν_{max}/cm^{-1} 3133 (OH); δ_H 4.62 (1 H, d, J = 7.5 Hz, 6-CH), 3.88 (1 H, m, 5-CH); δ_C 154.5 (C=S).



360 **377** 15 % **378** 15 %

Scheme 132

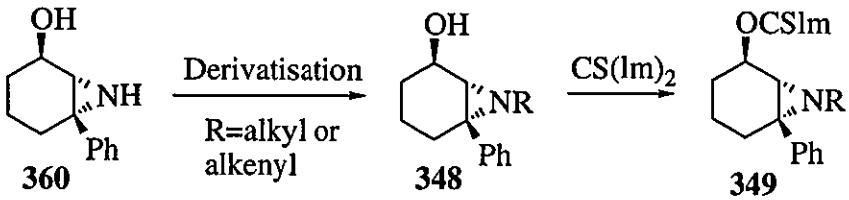
Again the alcohol function was playing a part in the formation of a by-product by nucleophilically displacing a further imidazole from (**377**) to give the ring structure (**378**). Key data:- δ_H 4.26 (1 H, d, J = 12.5 Hz, 9-CH), 4.03 (1 H, dt, J = 12.5 and 4 Hz, 5-CH); δ_C 191.4 (C=S). For characterisation purposes, the *N*-substituted aziridine (**377**) was acetylated to give the acetate (**379**) (Scheme 133).[119] Key data:- ν_{max}/cm^{-1} 1732 (C=O); δ_H 5.26 (1 H, m, 5-CH), 4.83 (1 H, d, J = 6 Hz, 6-CH); δ_C 170.2 (C=O), 154.2 (C=S).



377 **379**

Scheme 133

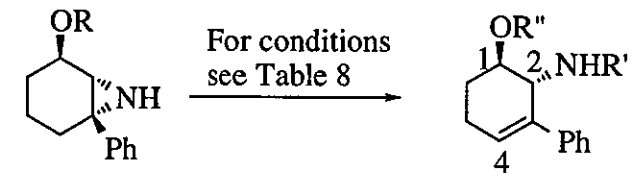
The formation of the *N*-substituted aziridine (**377**) showed that the aziridine function is more nucleophilic than the alcohol function and thus a refinement to the original synthetic strategy (Scheme 123, page 56) was required. The refinement involved the derivatisation of the aziridine moeity of (**360**) to give the *N*-substituted derivative (**348**) prior to the formation of the thiocarbonylimidazolide (**349**) (Scheme 134).



Scheme 134

4.1.4 Derivatisations of the Aziridine Nitrogen.

Various derivatisations of the aziridine moeity were tried (Scheme 135).



R=TBDPS (**358**)
R=H (**360**)

380-383

Scheme 135

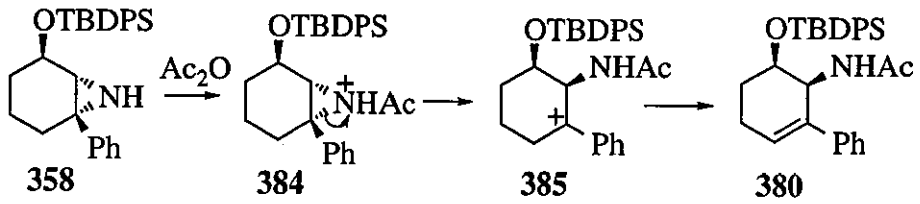
The results have been tabulated in Table 8.

Table 8: Conditions for the Derivatisations of the Aziridines (**358**) and (**360**).

No	R	R'	R"	Conditions	Yield %
380	TBDPS	Ac	TBDPS	Ac_2O, DMAP, Et_3N, DCM, 1 hr, 0°C[122]	58
380	TBDPS	Ac	TBDPS	DCC, AcOH, rt, 18 hr[123]	38
381	TBDPS	PhCO	TBDPS	PhCOCl, $NaOH_{aq}$, 2°C, 15 min[124]	86
382	TBDPS	Tos	TBDPS	TosCl*, Et_3N, reflux[125]	54
383	H	Ac	Ac	Ac_2O, Py, 5 days[119]	41

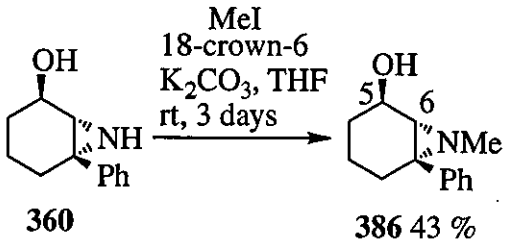
* *p*-toluenesulfonylchloride

In all cases studied, no *N*-substituted aziridines were isolated, showing instead a propensity for the formation of allylic amide derivatives. All the compounds show similar spectra-an example being for (**380**):- ν_{max}/cm^{-1} 1643 (C=O); δ_H 6.34 (1 H, t, J = 4 Hz, 4-CH), 5.14 (1 H, br d, J = 8 Hz, NH), 5.02 (1 H, br d, J = 8 Hz, 2-CH), 4.22 (1 H, m, 1-CH), structure confirmed by X-ray crystallography. The formation of the allylic amides is hardly surprising considering the propensity of the compounds on quaternisation to form the very stable tertiary benzyl cation (**385**) which on elimination of a proton gives the allylic amide (**380**).



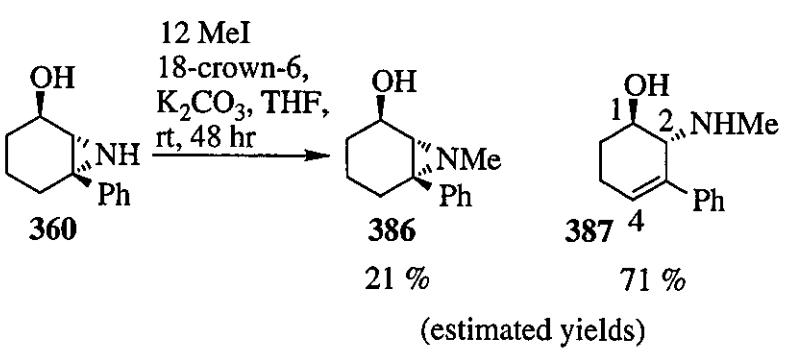
Scheme 136

Selective alkylations of the aziridine (**360**) using the conditions of Ahman were also tried (Scheme 137).[126] Alkylations using the same general method were tried with iodoheptane, allylbromide, 4-bromobutene and methyl iodide. Only methylation of (**360**) proved successful to give the *N*-methylaziridine (**386**). Key data:- ν_{max}/cm^{-1} 3357 (OH); δ_H 4.11 (1 H, dd, J = 8.5 and 6 Hz, 5-CH), 2.04 (3 H, s, Me), 2.00 (1 H, br s, 6-CH).



Scheme 137

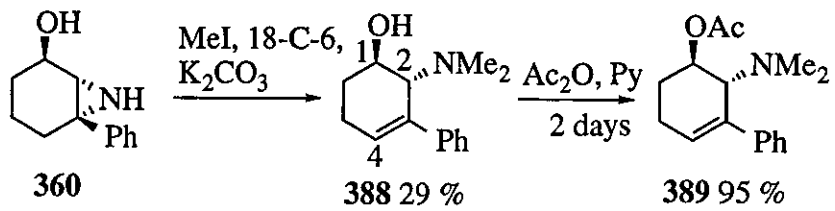
In an attempt to optimise the yield of the *N*-methylaziridine (**386**) more methyl iodide was used. This forms more of the ring opened allylic amine (**387**) than the methylated aziridine (**386**) (Scheme 138). Key data:- ν_{max}/cm^{-1} 3346 (OH/NH); δ_H 6.04 (1 H, t, J = 3 Hz, 4-CH), 4.04 (1 H, m, 1-CH), 3.71 (1 H, d, J = 4.5 Hz, 2-CH).



Scheme 138

Increasing the concentration of the reaction mixture can alter the product ratio. The allylic dimethylamine (**388**), along with other products in small yield, was isolated from a more concentrated reaction mixture (Scheme 139). Key data:- ν_{max}/cm^{-1} 3384 (OH); δ_H

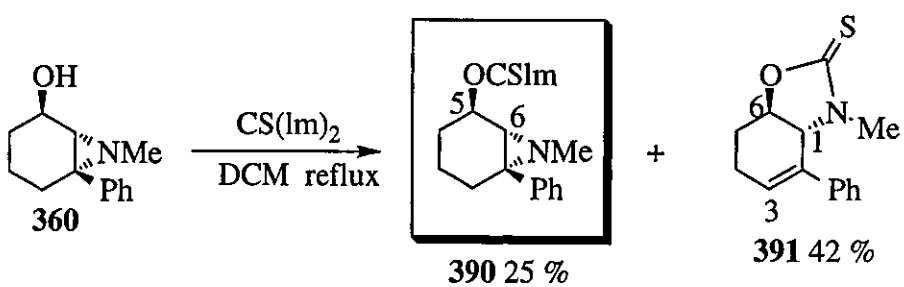
5.90 (1 H, m, 4-CH), 3.94 (1 H, ddd, J = 5.7, 3.8 and 2.1 Hz, 1-CH), 3.59 (1 H, m, 2-CH). To aid characterisation the allylic dimethylamine (**388**) was acetylated to give (**389**).[119] Key data:- ν_{max}/cm^{-1} 1732 (C=O); δ_H 6.15 (1 H, m, 4-CH), 5.36 (1 H, dd, J = 5 and 4 Hz, 1-CH), 3.70 (1 H, dd, J = 4 and 1 Hz, 2-CH); δ_C 170.6 (C=O).



Scheme 139

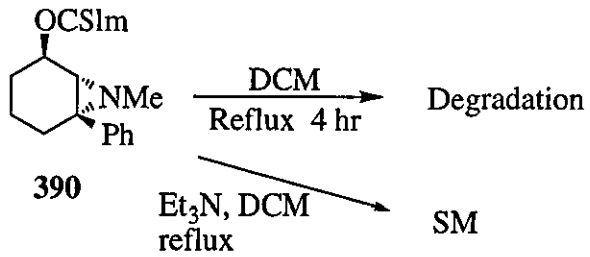
4.1.5 Formation of Free Radical Precursors.

Reaction of the aziridine (**360**) with 1,1'-thiocarbonyldiimidazole gave a small quantity of the required radical precursor- the thiocarbonylimidazolide (**390**).[120] Key data:- δ_H 5.75 (1 H, m, 5-CH), 2.10 (1 H, br s, 6-CH), 2.02 (3 H, s, Me); δ_C 183.9 (C=S) along with the cyclised product (**391**). Key data:- δ_H 5.68 (1 H, m, 3-CH), 4.55 (1 H, dq, J = 12.5 and 4 Hz, 6-CH), 4.43 (1 H, m, 1-CH), 2.89 (3 H, s, Me); δ_C 193.2 (C=S).



Scheme 140

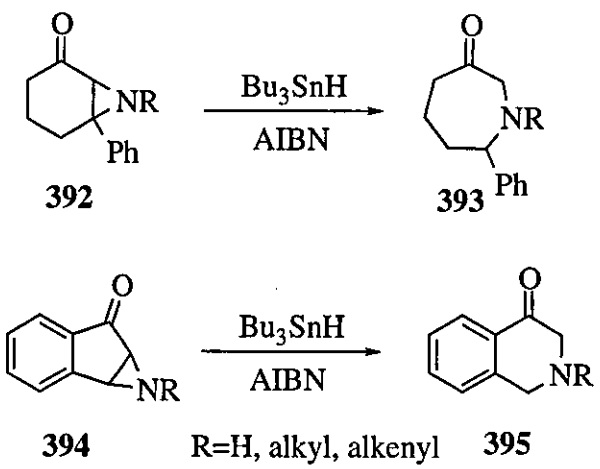
It was thought that thermal degradation of aziridine (**390**) formed the cyclic compound (**391**). Refluxing aziridine (**390**) in DCM showed that degradation occurred but not to give the cyclic compound (**391**) (Scheme 141). The presence of Et_3N allowed the solution to be heated without decomposition, suggesting that (**391**) may arise from trace acid catalysis. However, this was not investigated further.



Scheme 141

The synthesis of only the methylaziridinylcarbinyl radical precursor (**390**) *via* azidoalcohols and a Staudinger reaction shows the procedure to be of limited application. A general scheme using this approach has proven elusive, since it has not been possible to synthesise a range of acylated or alkylated derivatives.

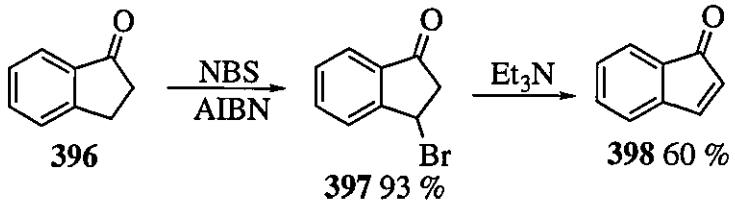
4.1.6 Formation of Aziridines Derived from Indenone *via* the Staudinger Reaction.



Scheme 142

The indenoaziridine (**394**) could be expected to follow the same radical rearrangement as the ketoaziridine (**392**) due to benzylic stabilisation (Scheme 142). In an analogous fashion, indenoaziridines could be expected to be synthesised from indenone *via* the methods described earlier i.e. azidoalcohol formation followed by a Staudinger reaction.

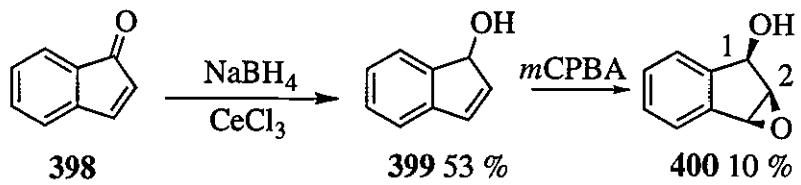
This synthesis began with the reaction of indanone (**396**) with *N*-bromosuccinimide in the presence of AIBN which gave 3-bromoindanone (**397**) *via* a literature method.[127] Reaction with triethylamine then gave indenone (**398**) again *via* a literature method (Scheme 143).[128]



396 **397** 93 % **398** 60 %

Scheme 143

Indenone (**398**) was subjected to Luche reduction to give indenol (**399**) (Scheme 144).[129]

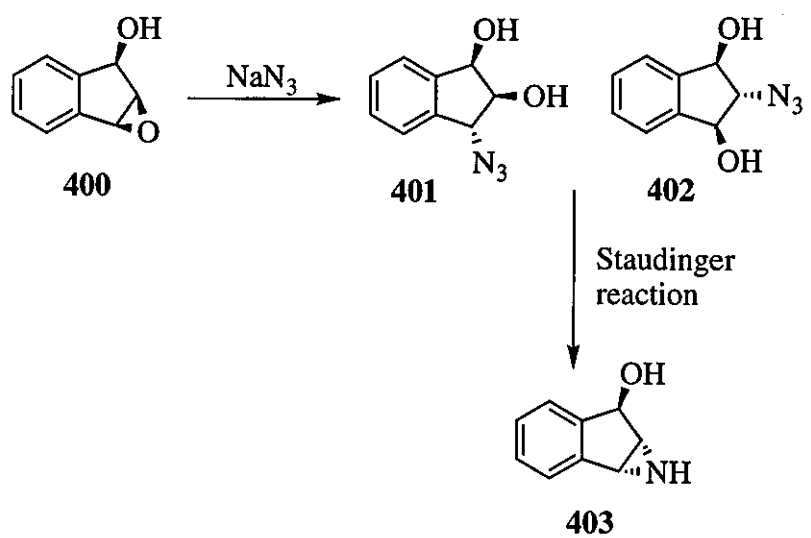


398 **399** 53 % **400** 10 %

Scheme 144

Reaction of indenol (**399**) with *m*CPBA then gave the epoxy alcohol (**400**). Key data:- ν_{max}/cm^{-1} 3420 (OH); δ_H 5.1 (1 H, dd, J = 12 and 3 Hz, 1-CH), 4.19 (1 H, dd, J = 3 and 0.5 Hz, 3-CH), 4.03 (1 H, t, J = 3 Hz, 2-CH).

The formation of the epoxyalcohol (**400**) makes the synthesis of azidoalcohols (**401**) and (**402**) and subsequent formation of the aziridine (**403**) possible by the route shown in Scheme 145.



400 **401** **402** **403**

Scheme 145

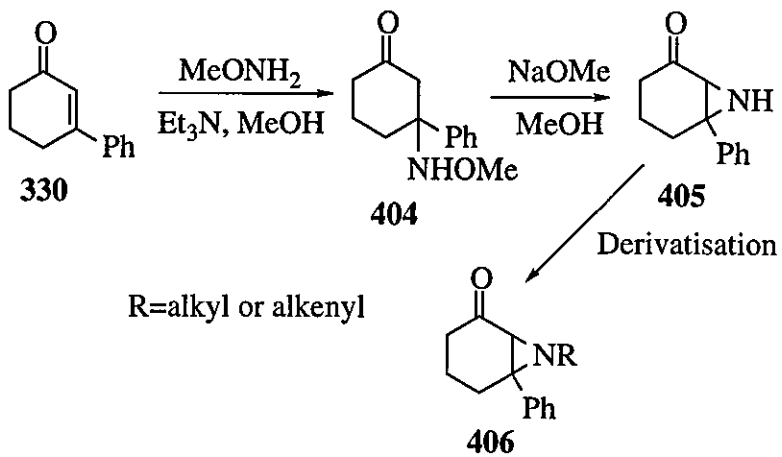
However, this was not pursued further due to other priorities.

4.2 The Formation of Aziridines *via* Methoxylamine.

The methoxylamine method of aziridine formation by Coldham has been discussed in Chapter 2.2.8 (page 33). The method involves two steps (Scheme 146):

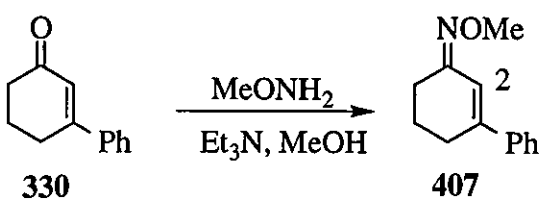
i) the formation of the 3-methoxyaminoketone (**404**) could occur *via* Michael addition of methoxylamine to the enone (**330**) and

ii) reaction of the 3-methoxy derivative (**404**) with sodium methoxide could give the aziridine (**406**) *via* methoxide elimination.



Scheme 146

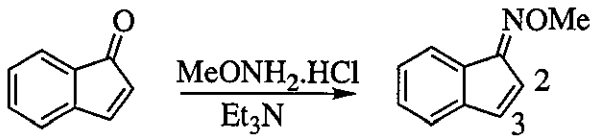
Reaction of the enone (**330**) with methoxylamine hydrochloride under basic conditions gave a mixture of imines (**407**) only (Scheme 147).[74] Key data (major isomer):- ν_{max}/cm^{-1} C=O absent; δ_H 6.59 (1 H, t, J = 1.5 Hz, 2-CH), 3.94 (3 H, s, Me); δ_C 156.6 (C). No 3-methoxyaminoketone (**404**) as required for further reaction with sodium methoxide was isolated.[74]



63 % mix of isomers in a ratio 2:1

Scheme 147

In a likewise fashion, the reaction of indenone **(398)** with methoxylamine hydrochloride also gave a mixture of imines **(408)** (Scheme 148).[74] These proved difficult to separate *via* flash chromatography and therefore the characterisation is taken from the spectra of the crude product. Key data (tentative-major isomer) δ_H 6.98 (1 H, dd, J = 6 and 0.5 Hz, 3-CH), 6.65 (1 H, d, J = 6 Hz, 2-CH), 4.11 (3 H, s, Me); δ_C 156.9 (C).



398 **408** 46 % mix of isomers 3:2

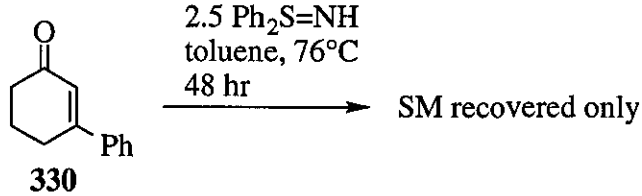
Scheme 148

The reaction of the enone **(330)** or indenone **(398)** with methoxylamine hydrochloride gave imines rather than the required 3-methoxyamine derivatives, therefore showing a preference for reaction at the carbonyl group.

4.3 The Formation of Aziridines *via* Michael Addition of Sulfilimines.

The formation of aziridines *via* Michael addition of *S,S*-diphenylsulfilimine to an α, β-unsaturated ketone has been discussed in Chapter 2.2.8 (page 33). Again the target compounds **(405)** or **(406)** are shown in Scheme 146.

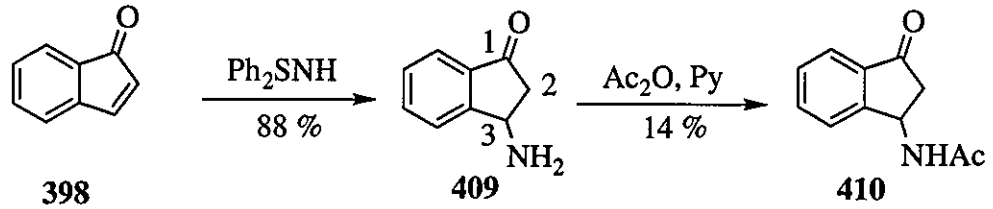
Reaction of the α,β-unsaturated ketone **(330)** with *S,S*-diphenylsulfilimine failed to produce any of the required aziridine.[71] Only starting material was isolated (Scheme 149).



330

Scheme 149

In an analogous fashion, indenone **(398)** could also undergo such an addition. On reaction with *S,S*-diphenylsulfilimine the rather unstable 3-aminoindanone **(409)** was formed (Scheme 150) which was too unstable to be purified and so key data are taken from the spectra of the crude product. Key data:- δ_H 5.04 (1 H, dd, J = 7 and 3.5 Hz, 3-CH), 2.98 (1 H, dd, J = 19 and 7 Hz, 2-CH), 2.56 (1 H, dd, J = 19 and 3.5 Hz, 2-CH). In order to purify the compound the acetamide **(410)** was synthesised.[119] Key data:- ν_{max}/cm^{-1} 1714 (C=O), 1650 (C=O); δ_H 6.37 (1 H, br d, J = 8 Hz, NH), 5.65 (1 H, ddd, J = 8, 8, and 3.5 Hz, 3-CH), 2.03 (3 H, s, Me); δ_C 203.4 (C=O), 170.3 (C=O).

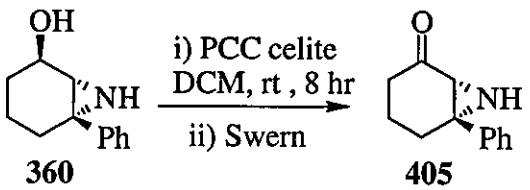


398 **409** **410**

Scheme 150

The Michael addition route to produce *N*-unsubstituted aziridines of 3-phenyl-2-cyclohexen-1-one **(330)** and indenone **(398)** using a sulfilimine, has proved unsuccessful.

An oxidative method from the aziridinoalcohol **(360)** to give the ketoaziridine **(405)** was also tried without success. Two methods were used 1) a PCC oxidation method and 2) a Swern oxidation method (Scheme 151).[130,131]



360 **405**

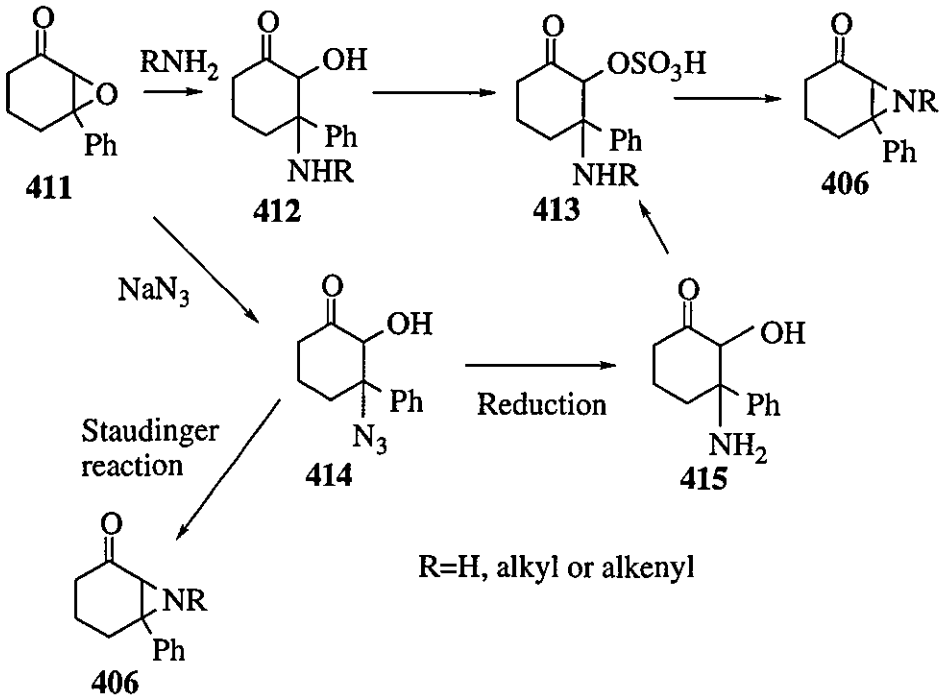
i) complex mixture
ii) SM

Scheme 151

PCC oxidation gave a complex mixture whilst only starting material was recovered using Swern oxidation.

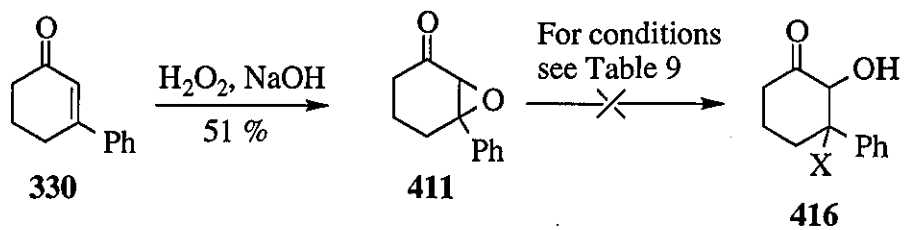
4.4 Formation of Aziridines *via* the Wenker Synthesis.

The Wenker synthesis (Chapter 2.1, page 20) involves the synthesis of aziridines *via* the formation of aminoalcohols **(412)**, conversion to a sulfonic acid ester nucleofuge **(413)** and intramolecular elimination to the aziridine **(406)**. It can be envisaged that either aminolysis or azide opening of epoxide **(411)** then derivatisation and ring closure could form the required aziridines **(406)** (Scheme 152). Again, the azidoalcohol **(414)** could form the same aziridine *via* a Staudinger reaction.



Scheme 152

The required ketoepoxide **(411)** was prepared as previously reported.[120] This involved the reaction of the enone **(330)** with hydrogen peroxide under basic conditions (Scheme 153).



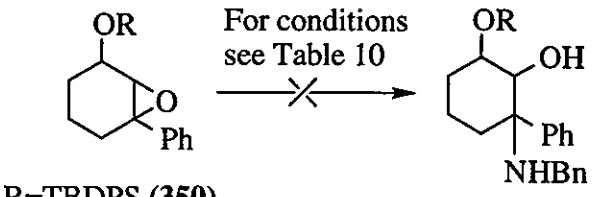
Scheme 153

Reaction of the ketoepoxide **(411)** under the conditions stated in Table 9, did not produce any of the required amino or azidoalcohols **(416)** (Scheme 153).

Table 9: Results for the Ring Opening Reactions of ketoepoxide **(411).**

X	Conditions	Observation
N_3	NaN_3, DMSO, H^+, 84°C, 3.5 hr[107]	Complex mixture
N_3	NaN_3, NH_4Cl, 8:1 MeOH:water, 58°C, 24 hr[113]	Complex mixture
PrNH	$PrNH_2$, $Zn(OTf)_2$, reflux 24 hr.[132]	Complex mixture
NH_2	NH_4OH, reflux.[133]	Starting material

The epoxide derivatives shown in Scheme 154 also failed to give the desired compounds using metal-catalysed aminolysis reactions (Table 10).



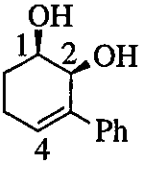
R=TBDPS (**350**),
Ac (**417**) or H (**338**)

418

Scheme 154

Table 10: Results of Metal-Catalysed Aminolysis Reactions on the Epoxides (**350**), (**417**) and (**338**).

No.	Conditions	Observations
350	$BnNH_2$, $Yb(OTf)_3$[134]	Starting material
417	$BnNH_2$, $Yb(OTf)_3$[134]	Complex mixture
338	$BnNH_2$, $Ti(OPr^i)_4$[135]	Formation of (**419**) (92 %)
338	$BnNH_2$, $Yb(OTf)_3$[134]	Complex mixture



419

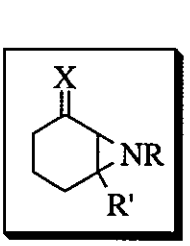
Using Sharpless conditions, the diol (**419**) was isolated. Key data:- ν_{max}/cm^{-1} 3382 (OH); δ_H 6.17 (1 H, dd, J = 5 and 3.5 Hz, 4-CH), 4.58 (1 H, d, J = 4 Hz, 2-CH), 3.85 (1 H, m, 1-CH), 2.59 (2 H, br s, OH).

In view of these disappointing results, the Wenker approach was abandoned.

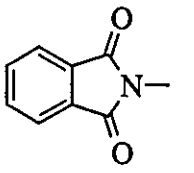
4.5 Direct Aziridinations of Alkenes.

The work of Atkinson in direct aziridination of alkenes *via* oxidation of *N*-aminoheterocycles using LTA is described in Chapter 2.2.1 (page 22).

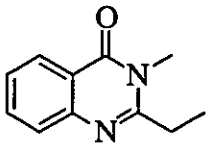
The target compound using this methodology is shown in **Fig 15.**



X=OCSIm, H; O
R=Q or Phthal, R'=aryl



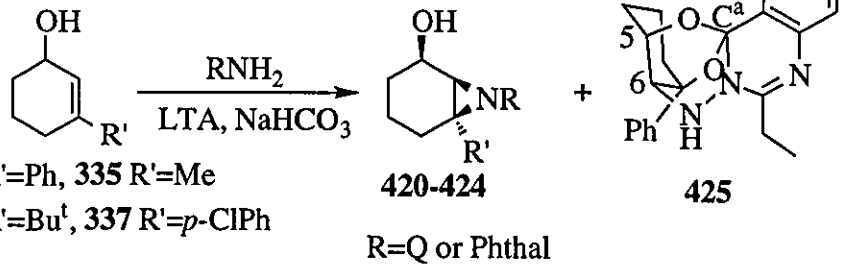
= Phthal



= Q

Fig 15

Reaction of the allylic alcohols (**334**) to (**337**) with 3-amino-2-ethyl-4(3*H*)-quinazolinone and LTA formed in most cases the required aziridines (**420**) to (**422**) and (**424**) (Scheme 155).[16] Aziridines (**420**) and (**422**) are known compounds and their spectra were consistent with those reported in the literature.[47] In the case of the formation of the aziridine (**420**) the cyclic compound (**425**) was isolated in high yield (Table 11, Scheme 155). Key data ν_{max}/cm^{-1} 3317 (NH); δ_H 4.74 (1 H, br s, 5-CH), 4.23 (1 H, s, NH), 3.36 (1 H, d, J = 2 Hz, 6-CH); δ_C 97.3 (C^a). The structure was also confirmed by X-ray crystallography-see Appendix.



334 R'=Ph, **335** R'=Me
336 R'=Bu^t, **337** R'=*p*-ClPh

420-424

R=Q or Phthal

425

Scheme 155

Table 11: Yields for *N*-substituted Aziridines Synthesised by the Direct Addition route.

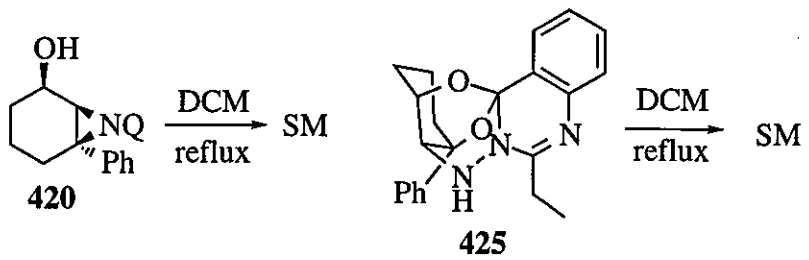
No.	R	R'	Yield %
420	Q	Ph	**420** (7), **425** (4)**
421*	Phthal	Ph	66
422	Q	Me	41
423	Q	Bu^t	0
424*	Q	*p*-ClPh***	44

*Na_2CO_3 used in reaction; ** estimated yields 17:83-ratios determined by NMR analysis of the crude product. ****p*-ClPh=*p*-chlorophenyl. Experimental procedure based on Murphy's.[16]

The formation of aziridine **(423)** did not occur possibly due to steric effects from the Bu^t group.

4.5.1 Further Investigations into the Formation of the Cyclic Compound.

Further testing was carried out on aziridine **(420)** to determine the cause of cyclisation. To test whether thermal degradation occurred to give the cyclic compound **(425)** or *vice versa*, the aziridine **(420)** and the cyclised product **(425)** were separately refluxed in DCM for a few hours (Scheme 156). No degradation occurred for either compound.

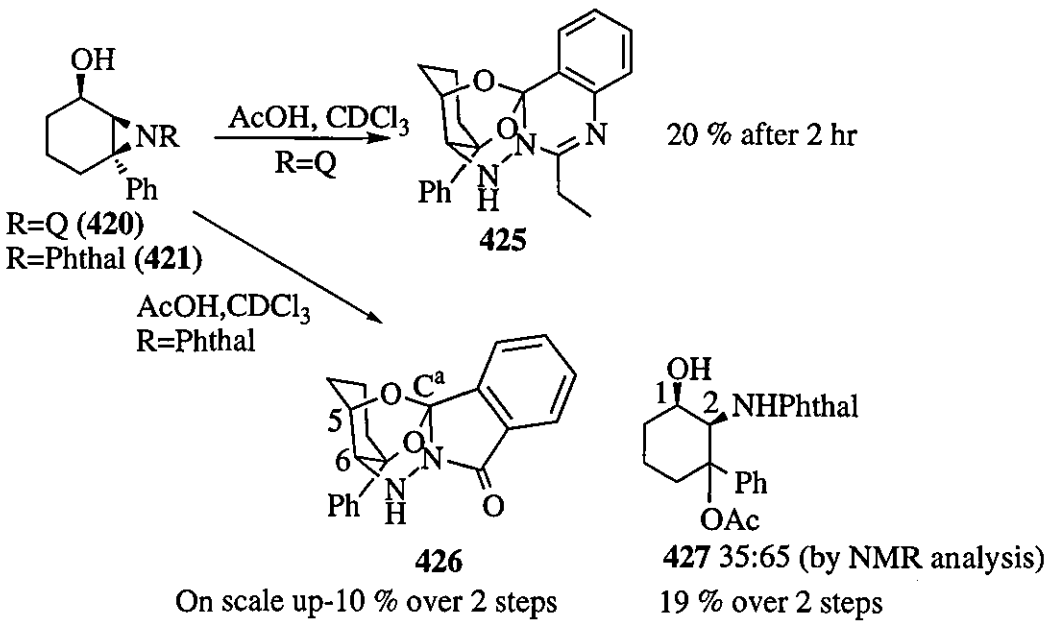


420 **425**

Scheme 156

Therefore no thermal equilibrium exists between the two products.

It was suspected that perhaps acid formed in the reaction caused the rearrangement of the aziridine **(420)** to the cyclic compound **(425)**. This was confirmed on treatment of the aziridine **(420)** with acetic acid in $CDCl_3$ (Scheme 157).



425

426

On scale up-10 % over 2 steps

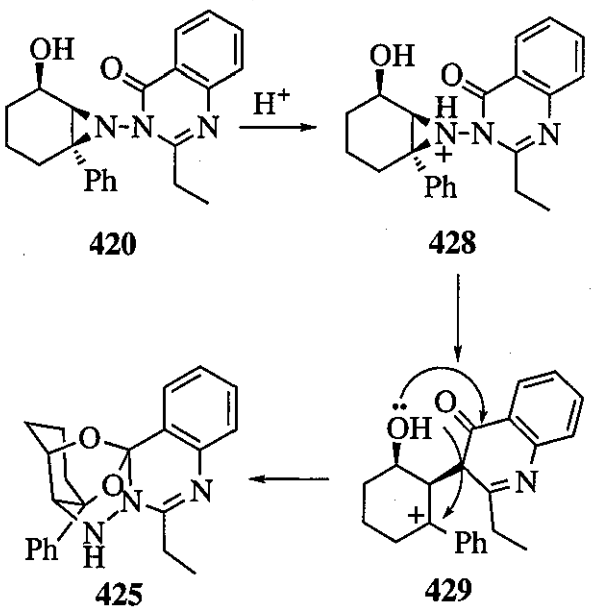
427 35:65 (by NMR analysis)

19 % over 2 steps

Scheme 157

The *N*-phthalimido aziridine **(421)** shows a similar acid-catalysed rearrangement to give the cyclic compound **(426)** and the acetate **(427)**. Key data **(426)**:- δ_H 4.83 (1 H, m, 5-CH), 4.67 (1 H, s, NH), 3.42 (1 H, d, J = 2 Hz, 6-CH); δ_C 101.0 (C^a). **(427)** ν_{max}/cm^{-1} 3425 (OH), 1720 (C=O); δ_H 4.74 (1 H, br s, OH), 4.52 (1 H, m, 1-CH), 4.23 (1 H, d, J = 3.5 Hz, 2-CH); δ_C 168.3 (C=O), 166.7 (C=O), 84.4 (C).

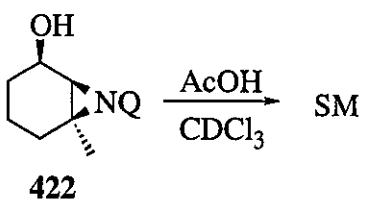
The assumed mechanism of the reaction is shown in Scheme 158.



Scheme 158

Protonation of the aziridine **(420)** to give **(428)** causes ring opening to form the benzylically stabilised, tertiary carbocation. Formation of the hemi-acetal and subsequent intramolecular attack on the cation forms the cyclic compound **(425)**.

The 3-methyl analogue **(422)** shows no rearrangement under similar acid catalysis (Scheme 159).



Scheme 159

The results for all the acid-catalysed rearrangements are shown in Table 12.

Table 12: Results for the Effects of Acid on *N*-Substituted Aziridines.

Substrate/ mmol	$CDCl_3$/ml	AcOH/mmol	Time	Ratio
(420) 0.3	1.5	1.20	2 hr	**420:425** 80:20*
(421) 0.02	0.7	1.75	3 days	**426:427** 35:65*
(422) 0.06	0.7	1.58	4 days	SM

* Peaks shift in the ^{1}H-NMR spectra in the presence of acid for **(425)** and **(427)**; ratios determined by ^{1}H-NMR analysis of the crude products.

Of particular notice was the lack of cyclic compound from the 3-methyl analogue **(422)**. It appears that the 3-phenyl substituent is vital for any rearrangement to occur.

Further investigations were carried out on the reaction depicted in Scheme 155. Reactions shown in Table 13 include the use of sodium bicarbonate as base, variations in reaction times and control experiments. Each reaction was repeated in duplicate to observe the consistency.

Table 13: Reaction (Scheme 155) using $NaHCO_3$ as Base and Varying Reaction Times.

experiment	1*	2*	3**	4**	5**	6**
Alkene/mmol	2.9	1.7	0.29	0.29	0.29	0.29
LTA/mmol	3.7	2.3	0.34	0.34	0.31	0.30
QNH_2/mmol	2.9	1.8	0.29	0.30	0.29	0.31
$NaHCO_3$/mmol	35.7	21.4	3.77	3.85	-	-
DCM/ml	15	9	1.5	1.5	1.5	1.5
Recovery %	84	95	95	98	99	99
Ratio **420:425**	23:77	22:78	89:11	89:11	90:10	86:14

*1.5 hr ** 0.5 hr reaction times. Experimental procedure based on Murphy's.[16] Ratios determined by ^{1}H-NMR analysis of the crude products.

The results clearly show that the formation of the cyclic compound is dependent on reaction time (entries 1 and 2 v. 3 and 4) and that there is no effect of added $NaHCO_3$ (Entries 3 and 4 v. 5 and 6). This is consistent with an acid-catalysed rearrangement of the aziridine. $NaHCO_3$ is not sufficiently soluble in DCM to neutralise any acid formed.

Reactions were performed in the presence of 15-C-5 to increase the solubility of sodium bicarbonate in DCM. The results (Table 14, entries 1 and 2) clearly show that the formation of the cyclic compound **(425)** is mostly inhibited. Thus 15-C-5, acting as a phase transfer catalyst, increases the solubility of $NaHCO_3$ in DCM sufficiently to neutralise any acid formed.

The use of a triethylamine (Table 14, entries 3 and 4) is most convenient and shows that no cyclic compound is formed at all. Using conditions based on Atkinson's method (i.e

pre-forming of the aziridinating agent at -20°C then the addition of 3 equivalents of the alkene) shows that larger quantities of the cyclic compound **(425)** were formed (Table 14, entries 5 and 6).[137] This is due to the increased concentration of the reaction mixture used by Atkinson.

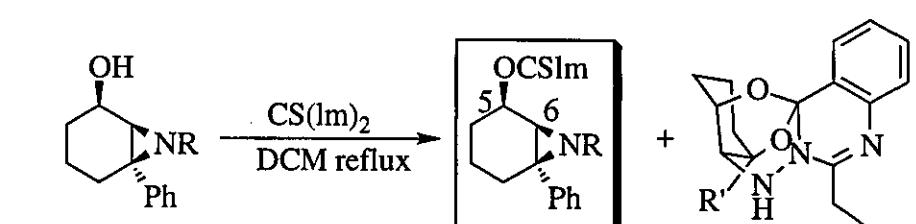
Table 14: Results using $NaHCO_3$ as Base in the Presence of 15-C-5 (Scheme 155) (Entries 1 and 2); Triethylamine as Base (Entries 3 and 4) and Pre-forming of the Aziridinating Agent (Entries 5 and 6).

experiment	1*	2*	3*	4*	5**	6**
Alkene/mmol	0.29	0.29	0.28	0.29	1.18	1.20
LTA/mmol	0.29	0.30	0.36	0.40	0.19	0.17
QNH_2/mmol	0.31	0.31	0.30	0.31	0.4	0.40
$NaHCO_3$/mmol	3.7	3.79	-	-	-	-
DCM/ml	1.5	1.5	1.5	1.5	0.7	0.7
15-C-5/mmol	0.39	0.36	-	-	-	-
Et_3N/mmol	-	-	1.18	1.18	-	-
Recovery %	100	100	87	97	100	83
Ratio **420:425**	96:4	96:6	100:0	100:0	66:34	64:36

0.5 hr reaction times; * Experimental procedure based on Murphy's method;[16] ** Experimental procedure based on Atkinson's method.[47] Ratios determined by ^{1}H-NMR analysis of the crude products.

4.5.2 Formation of Free Radical Precursors.

Reaction of the aziridine **(420)** with 1,1'-thiocarbonyldiimidazole formed some of the required radical precursor-the thiocarbonylimidazolide **(430)**.[120] Key data:- ν_{max}/cm^{-1} 1706 (C=O); δ_H 6.09 (1 H, m, 5-CH), 5.36 (1 H, br s, 6-CH); δ_C 184.5 (C=S). Some cyclic compound **(425)** was again isolated (Scheme 160). The results for a variety of substrates have been detailed in Table 15.



R=Q, R'=Ph **(420)**
R=Phthal, R'=Ph **(421)**
R=Q, R'=*p*-ClPh **(424)**

430-432

R'=Ph **(425)**
or *p*-ClPh **(433)**

Scheme 160

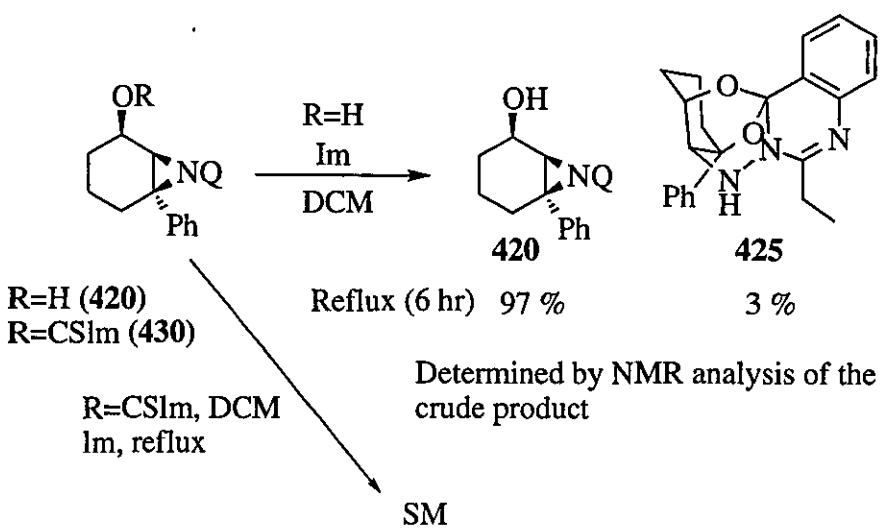
Table 15: Results for the Synthesis of the Thiocarbonylimidazolides.

No.	R	R'	Yield %	Ratio
430	Q	Ph	22	**420:425** 77:23
431	Phthal	Ph	51	-
432	Q	*p*-ClPh*	50	**421:433** 77:23

Ratios determined by ^{1}H-NMR analysis of the crude products.* *p*-ClPh=*p*-chlorophenyl

The lack of cyclic compound **(426)** from the aziridine **(421)** seems to infer greater stability of this aziridine compared to the others.

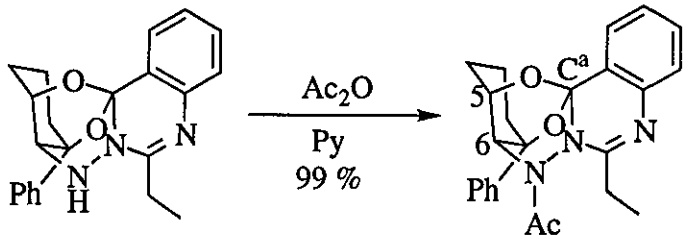
The by-product from the reaction depicted in Scheme 160 is imidazole. The reactions shown in Scheme 161 were tried to determine whether the cyclic compound **(425)** was formed by reaction of the aziridines **(420)** or **(430)** with imidazole .



Scheme 161

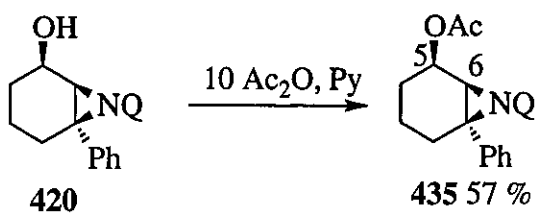
Very small quantities of the cyclic compound were obtained on refluxing the aziridine **(420)** with imidazole for 6 hours. Thus formation of the cyclic compound does not appear to be catalysed by imidazole or by the action of heat. The thiocarbonylimidazolide **(430)** was also refluxed with imidazole. Not unsurprisingly, no cyclic compound **(425)** was isolated only starting material. This also showed that the cyclic compound **(425)** was not formed from the thiocarbonylimidazolide **(430)** by the action of either heat or imidazole. It remains unclear as to what causes the rearrangement in this case.

For characterisation purposes the cyclic structure **(425)** was acetylated to give **(434)** (Scheme 162).[119] Key data:- ν_{max}/cm^{-1} 1688 (C=O); δ_H 5.16 (1 H, d, J = 3 Hz, 6-CH), 4.82 (1 H, m, 5-CH), 1.99 (3 H, s, Me); δ_C 179.3 (C=O), 99.3 (C_a).



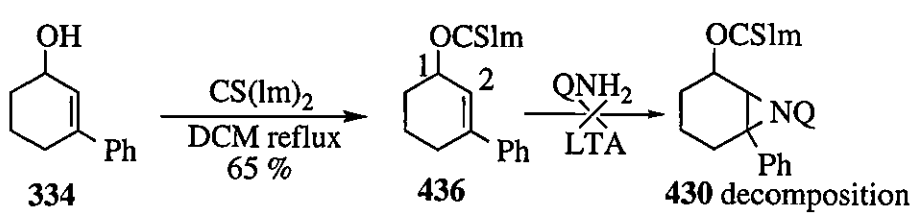
Scheme 162

Acetylation of the aziridine (**420**) gave the acetate (**435**) when 10 equivalents of acetic anhydride was used (Scheme 163).[119] Key data:- ν_{max}/cm^{-1} 1732 (C=O), 1674 (C=O); δ_H 5.38 (1 H, m, 5-CH), 5.12 (1 H, br s, 6-CH), 2.29 (3 H, s, Me); δ_C 171.6 (C=O). Smaller equivalents of acetic anhydride gave varying amounts of the cyclic compound (**425**) presumably due to acid formation and subsequent competition of the rearrangement with the acetylation.



Scheme 163

The thiocarbonylimidazolide (**436**) was synthesised in order to determine whether cyclisation could be avoided by direct aziridination. The synthesis began by reaction of the allylic alcohol (**334**) with 1,1' -thiocarbonyldiimidazole to give (**436**).[120] Key data:- δ_H 6.10 (1 H, d, J = 5 Hz, 2-CH), 4.65 (1 H, m, 1-CH); δ_C 165.9 (C=S). Reaction with 3-amino-2-ethyl-4(3*H*)-quinazolinone and LTA failed to give any of the aziridine (**430**) (Scheme 164).

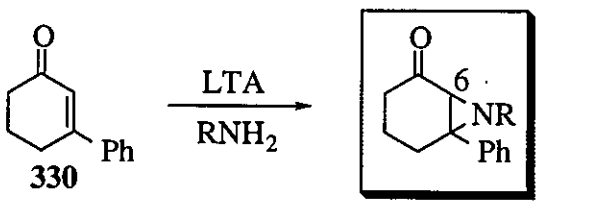


Scheme 164

4.5.3 Formation of Ketoaziridines *via* the Direct Route.

Direct aziridinations of the enone (**330**) gave fairly good yields of the required radical precursors (**437**) and (**438**) using 3-amino-2-ethyl-4(3*H*)-quinazolinone or *N*-amino phthalimide respectively (Scheme 165).[16,136] Key data (**437**):-ν_{max}/cm^{-1} 1716 (C=O), 1674 (C=O); δ_H 4.77 (1 H, s, 6-CH); δ_C 203.0 (C=O), 160.6 (C=O). (**438**) ν_{max}/cm^{-1} 1716

(C=O), δ_H 4.86 (1 H, s, 6-CH); δ_C 203.8 (C=O), 165.3 (C=O). The aziridine **(438)** proved more difficult to purify than aziridine **(437)**. For this reason, only aziridine **(437)** was purified and subjected to a radical reaction (Chapter 4.10, page 89).



330

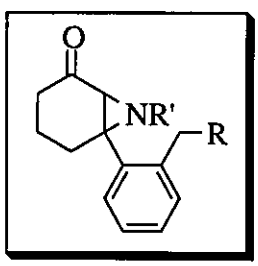
R=Q 59 % **(437)**
R=Phthal 35 % **(438)**

Scheme 165

Although the direct formation of aziridines from alkenes has proven to be successful this methodology leads to *N*-quinazolinonyl or *N*-phthalimido-substituted aziridines which limits the potential synthetic utility.

4.5.4 Direct Aziridinations of Vinyl and Allyl-substitued Enones and Enols for Tandem Radical Reactions.

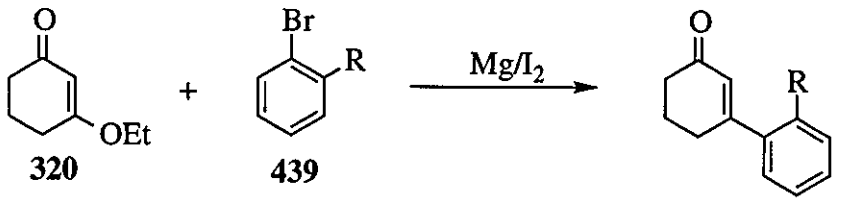
In order to study the potential tandem radical cyclisations the target molecule **(Fig 16)** was required.



R=vinyl or allyl
R'=Q or Phthal

Fig 16

By analogy to work previously reported by Rudderham,[120] the enone **(320)** was allowed to react with the Grignard reagent from vinyl bromide (**439**, R=vinyl) to give the vinyl enone **(440)** (Scheme 166). A similar reaction using the allyl bromide (**439**, R=allyl) gave the allyl-substituted enone **(441)**.[120]

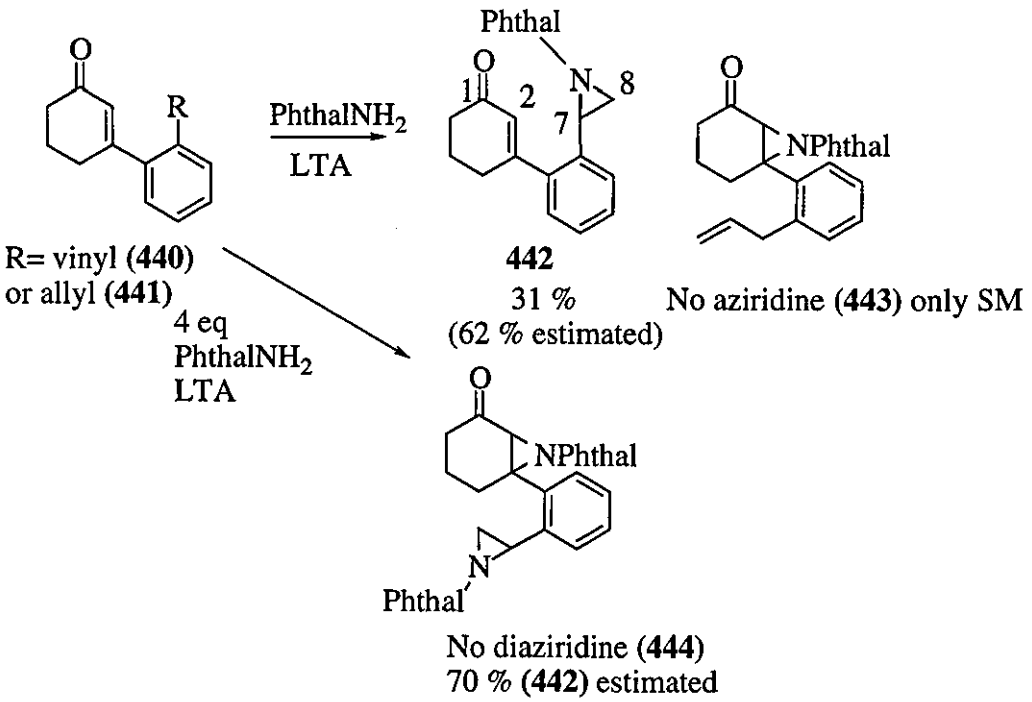


R=vinyl or allyl

R=vinyl 37 % (**440**)
R=allyl 95 % (**441**)

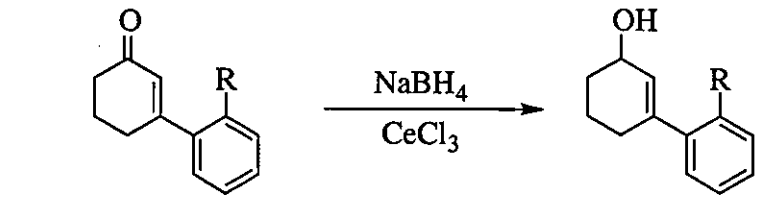
Scheme 166

Both the vinyl enones (**440**) and the allyl enone (**441**) were then allowed to react with *N*-aminophthalimide and LTA.[136] In the case of the vinyl enone (**440**) the vinylaziridine (**442**) was obtained instead of the required aziridine. Key data:- ν_{max}/cm^{-1} 1715 (C=O), 1667 (C=O), δ_H 6.09 (1 H, s, 2-CH), 3.69 (1 H, dd, J = 8 and 5.5 Hz, 7-CH), 2.94 (1 H, dd, J = 8 and 2 Hz, 8-CH), 2.60 (1 H, dd, J = 5.5 and 2 Hz, 8-CH); δ_C 199.2 (C=O), 164.9 (C=O). No reaction was observed using the allyl enone (**441**) (Scheme 167). To determine whether a di-aziridine could be synthesised, an excess of *N*-aminophthalimide and LTA were used. No di-aziridine (**444**) was isolated but the yield of the vinylaziridine (**442**) was improved by roughly 10 % (Scheme 166).



Scheme 167

The enones (**440**) and (**441**) were reduced under Luche conditions,[129] to give the allylic alcohols (**445**) and (**446**) respectively (Scheme 168) in accordance with work performed by Rudderham.[120] Their aziridinations were compared with those of the enones.

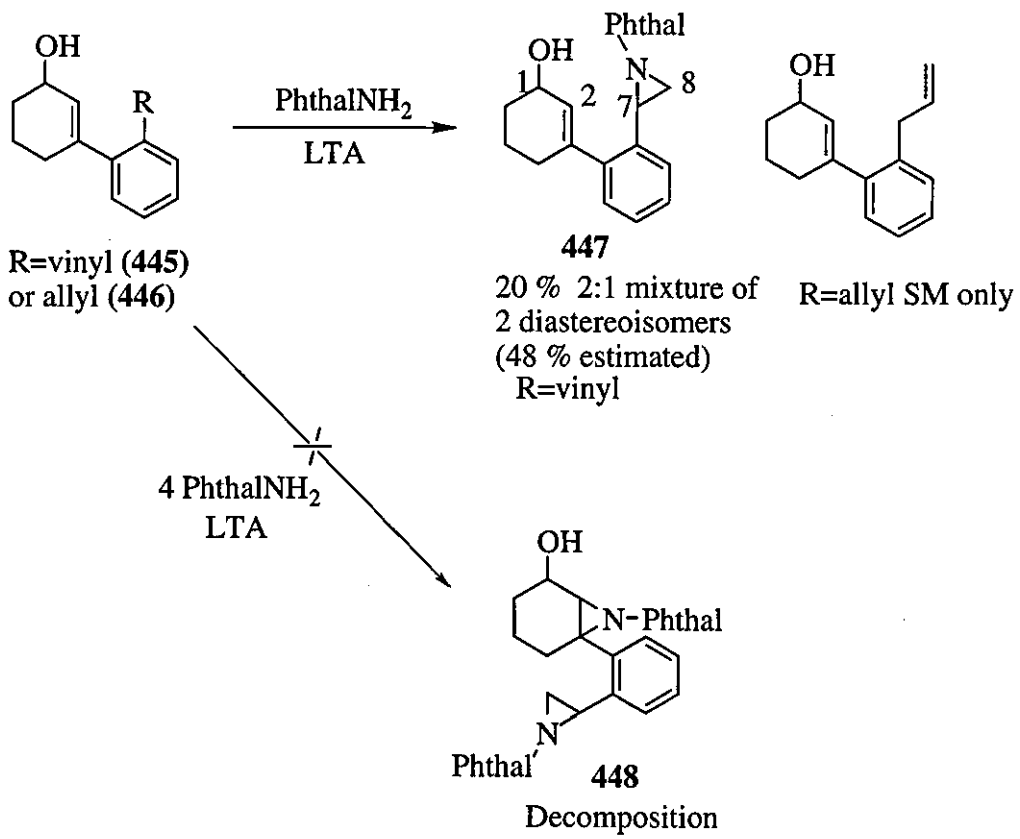


R=vinyl (**440**) or allyl (**441**)

R=vinyl 72 % (**445**),
R=allyl 53 % (**446**)

Scheme 168

Reaction of the allylic alcohol (**445**) with 1 equivalent of *N*-aminophthalimide gave the aziridine (**447**).[136] Key data-ν_{max}/cm^{-1} 3471 (OH), 1715 (C=O); δ_H 5.83 (1 H, m, 2-CH, maj), 3.79 (1 H, m, 7-CH), 2.87 (1 H, dd, J = 8 and 2 Hz, 8-CH), 2.62 (1 H, dd, J = 6 and 2 Hz, 8-CH, maj). The allylic alcohol (**446**) again showed no formation of the aziridine, only starting material being recovered. Perhaps a steric effect prevents the formation of aziridines in the allyl derivatives (Scheme 169).



Scheme 169

Again reaction of the allylic alcohol (**445**) with excess *N*-aminophthalimide and LTA in an attempt to synthesise the di-aziridine (**448**) gave a complex mixture.[136]

The direct aziridination routes have proved unsuitable for the formation of allyl and vinyl aziridines. The allylic alcohol (**445**) and enone (**440**) show reactivity on the vinyl group only. The allylic alcohol (**446**) and enone (**441**) show no reactivity whatsoever.

4.5.5 Preparation of Indenone Aziridines *via* the Direct Route.

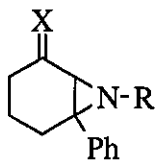


Fig 17

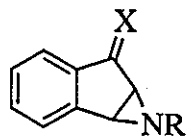
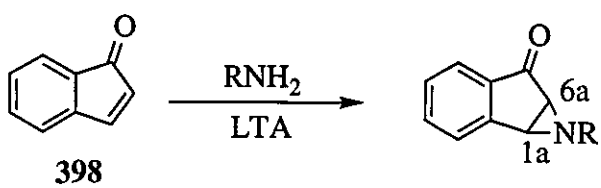


Fig 18

Where X=OCSIm, H; O
R=Phthal or Q

Formation of the indenoaziridine (**Fig 18**) could be synthesised in an analogous fashion to the aziridines shown in **Fig 17**.

Reactions of indenone (**398**) with *N*-aminophthalimide and LTA afforded the required aziridine (**449**) (Scheme 170).[136] Key data:- δ_H 4.60 (1 H, dd, J = 3.5 and 0.5 Hz, 1a-CH), 3.83 (1 H, d, J = 3.5 Hz, 6a-CH). Unfortunately this proved unstable to flash chromatography (silica and basified silica) and also recrystallisation proved difficult to perform.



398

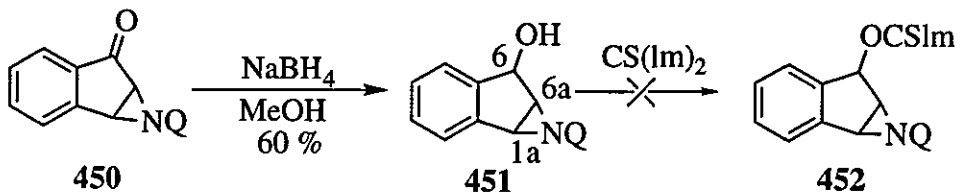
449 R=Phthal, 64 % estimated,
450 R=Q, 17 %

Scheme 170

Reaction of indenone (**398**) with 3-amino-2-ethyl-4(3*H*)-quinazolinone and LTA gave the required aziridine (**450**) in 17 % yield (Scheme 170). Key data- ν_{max}/cm^{-1} 1726 (C=O), 1674 (C=O); δ_H 5.25 (1 H, d, J = 5 Hz, 6a-CH), 4.11 (1 H, d, J = 5 Hz, 1a-CH); δ_C 196.1 (C=O). This proved easier to purify therefore further reactions were performed using this substrate. The radical reaction using the aziridine (**450**) is reported in Chapter 4.10 (page 89) and no reaction was observed.

It was thought that the thiocarbonylimidazolide (**452**) would show greater reactivity (Scheme 171). It was found that for purification purposes, the best synthetic route was to reduce the ketoaziridine (**450**) with sodium borohydride to give the aziridinoalcohol (**451**). Key data:- ν_{max}/cm^{-1} 3454 (OH), 1662 (C=O); δ_H 5.63 (1 H, dd, J = 9 and 4.5 Hz, 6-CH),

4.08 (1 H, d, J = 5.5 Hz, 1a-CH), 4.04 (1 H, dd, J = 5.5 Hz and 4.5 Hz, 6a-CH). Decomposition occurred on reaction of the aziridinoalcohol (**451**) with 1,1'-thiocarbonyldiimidazole (Scheme 171).[120]



450 **451** **452**

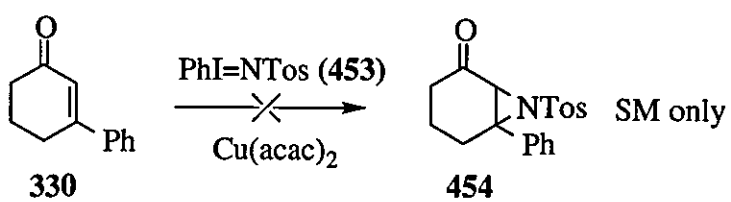
Scheme 171

The formation of radical precursors from indenone *via* the direct aziridination route of Atkinson has proven to be difficult due to decomposition either at the aziridine stage or during the formation of the thiocarbonylimidazolide. Thus the synthesis of radical precursors from indenone was abandoned.

4.6 Formation of *N*-Tosyl Aziridines using Copper-catalysed Nitrene Insertion.

The copper-catalysed aziridinations of alkenes developed by Evans has been discussed in Chapter 2.2.3 (page 26).

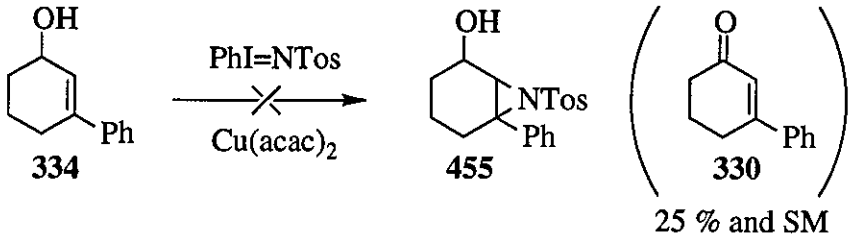
The target compound was the *N*-tosyl substituted aziridine (**454**) (Scheme 172). The reaction performed on the enone (**330**) with PhI=NTos was unsuccessful.[57] No evidence of any aziridine formation was obtained. (PhI=NTos (**453**) was prepared as in the literature).[138]



330 **454**

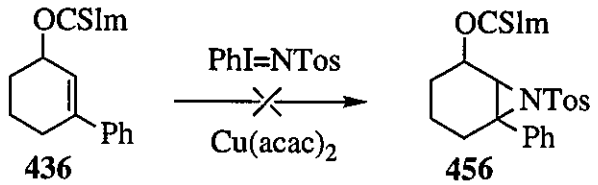
Scheme 172

The allylic alcohol (**334**) was also reacted with PhI=NTos.[57] Again no tosyl aziridine (**455**) was evident on NMR analysis of the crude. A small quantity of the enone (**330**) along with starting material was evident, showing that some oxidation of the allylic alcohol occurs under the reaction conditions (Scheme 173).



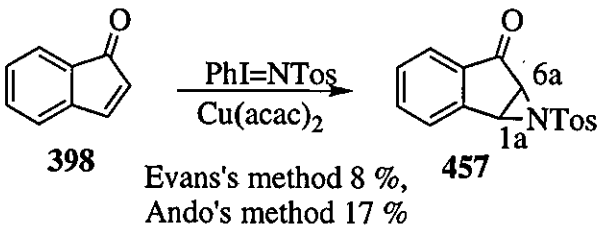
Scheme 173

The thiocarbonylimidazolide **(436)** was allowed to react with PhI=NTos.[57] No tosyl aziridine **(456)** was evident. The thiocarbonylimidazolide **(436)** appears to undergo degradation under the reaction conditions as no thiocarbonylimidazole peaks are evident in the ^{1}H-NMR spectrum of the crude product (Scheme 174).



Scheme 174

It was suspected that steric hindrance in 3-phenyl-2-cyclohexen-1-one **(330)** could be inhibiting the reaction. Reaction of indenone **(398)** with PhI=NTos in the presence of $Cu(acac)_2$ (Evans's method) gave a low yield of the *N*-Tosyl aziridine **(457)** (Scheme 175).[57]



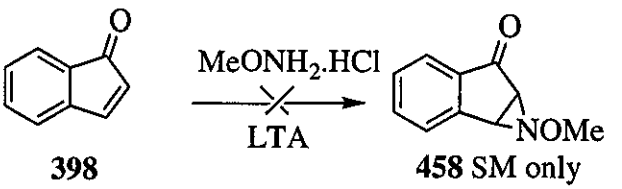
Scheme 175

Also the recent method by Ando, which uses chloramine-T as the base and copper(I) chloride as the catalyst gave the aziridine **(457)** in an estimated yield of 17 %.[139] Key data:- ν_{max}/cm^{-1} 1731 (C=O); δ_H 7.82 (2 H, d, J = 8 Hz, Tos-H), 7.34 (2 H, d, J = 8 Hz, Tos-H), 4.51 (1 H, dd, J = 5 and 0.5 Hz, 1a-CH), 3.83 (1 H, d, J = 5 Hz, 6a-CH).

The *N*-tosyl-substituted aziridines from indenone were now available and it was expected that these would be converted to the thiocarbonylimidazolide. However, owing to the low yields of the aziridination step this approach was not carried further.

4.7 Formation of Aziridines *via* Oxidation of Methoxylamine.

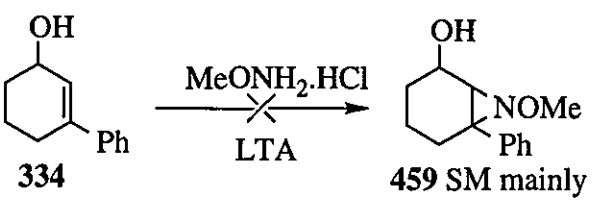
There are literature methods for the formation of aziridines *via* the oxidation of methoxylamine hydrochloride using LTA (Chapter 2.2.1, page 24). This method closely resembles the direct aziridination route used by Atkinson (Chapter 2.2.1, page 22). Reaction of indenone **(398)** with methoxylamine hydrochloride in the presence of LTA gave only unreacted starting material. No aziridine **(458)** was evident in the ^{1}H-NMR spectrum of the crude product (Scheme 176).



398 **458** SM only

Scheme 176

A similar reaction using the allylic alcohol **(334)** gave a rather complex mixture in which starting material and 3-phenyl-2-cyclohexen-1-one **(330)** were evident in the ^{1}H-NMR spectrum of the crude material (Scheme 177)



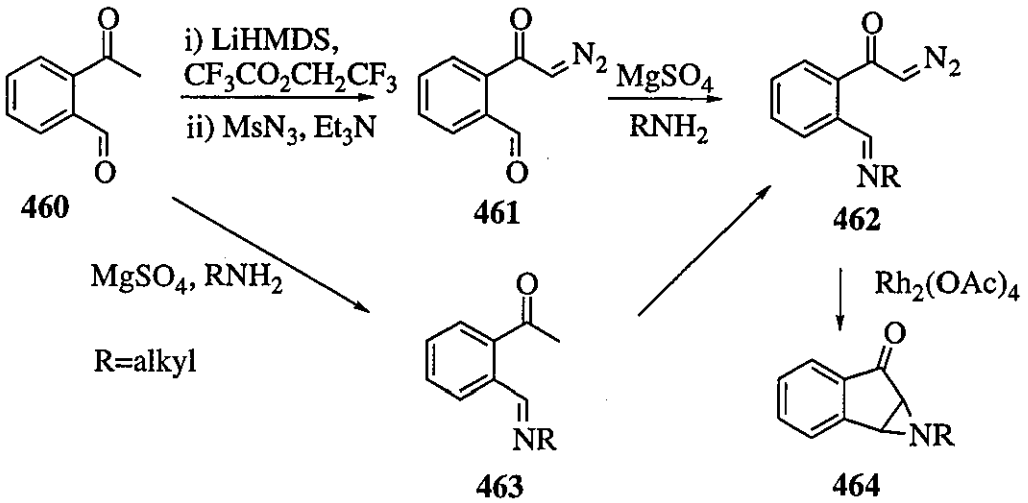
334 **459** SM mainly

Scheme 177

The oxidation of methoxylamine route to aziridines has proved to be unsuccessful. This procedure was abandoned.

4.8 Aziridines *via* Carbenoid Insertion into Imines.

A general strategy is outlined in Scheme 178 and is based on work reported by Padwa and McMills (Chapter 2.5, page 41).



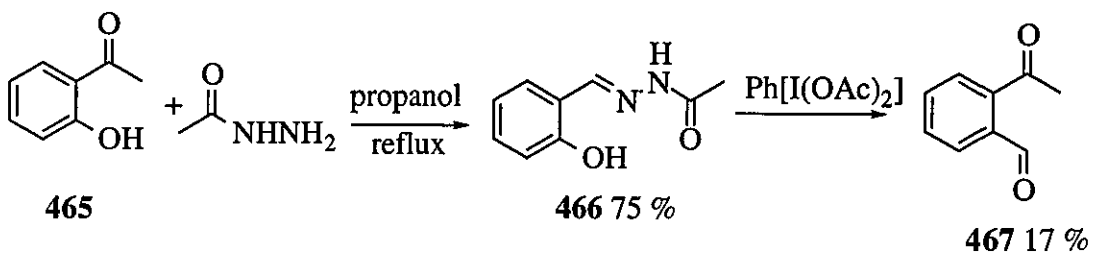
Scheme 178

Synthesis of ketoaldehyde **(460)** could be useful for the synthesis of diazoimine-type compounds **(462)** which, in principle, on reaction with $Rh_2(OAc)_4$ could undergo carbenoid insertion into imines to give aziridines **(464)** (Scheme 178). Two pathways could be envisaged.

i) Formation of the diazoketone **(461)** *via* a method by Danheiser,[140] then the diazoimine **(462)**.

ii) Formation of the imine **(463)** then the diazoimine **(462)**.

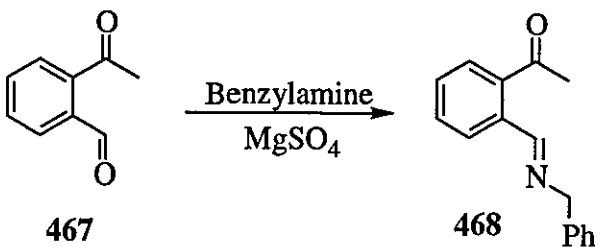
The synthesis began with the literature preparation of the ketoaldehyde **(467)** (Scheme 179). The first step involves the synthesis of the hydrazone **(466)** from salicylaldehyde **(465)** and acetic hydrazide.[140] The second step involves oxidation of the hydrazone **(466)** using [(diacetoxy)iodo]benzene to give the ketoaldehyde **(467)**.[141] A mechanism for this synthesis has been proposed by Katritzky (using LTA as oxidant).[142]



Scheme 179

The NMR data for the ketoaldehyde **(467)** corresponded with those reported in the literature, but there were anomalies with other data (m.p., mass spectrum, disappearance of the so-called CHO proton on shaking with D_2O). Diazotransfer and imine formation were both tried on **(467)** but were unsuccessful.

It was thought that perhaps the compound had degraded on work-up. The synthesis was repeated (proton signal at δ=10.22, corresponding to the aldehyde proton, did not exchange in the crude). The crude material was reacted with benzylamine in an attempt to form the imine (**468**). Key data:- δ_H:- CHO absent, Me peak unchanged) (Scheme 180).[143]

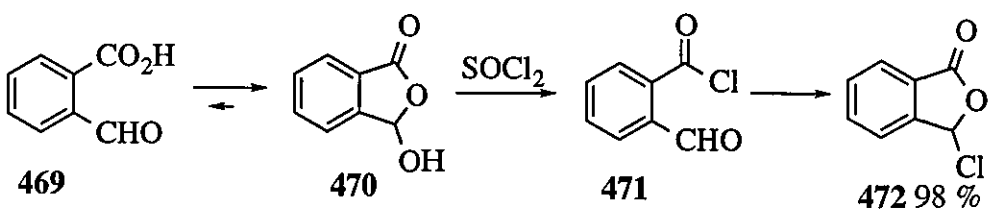


467 **468**

Scheme 180

Flash chromatography failed to isolate anything of reasonable purity.

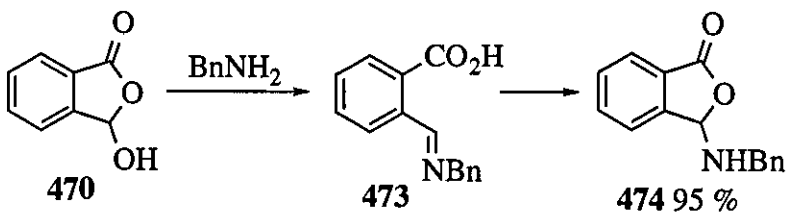
A different approach was tried using the readily available 2-carboxybenzaldehyde (**469**) which exists in equilibrium with its isomer (**470**). A known reaction of 2-carboxybenzaldehyde (**470**) with thionyl chloride is shown in (Scheme 181). No acyl chloride (**471**) is isolated; the ring closed isomer (**472**) is obtained.[144] So this route could not be used to form the acyl chloride (**471**) then further reaction with diazomethane to give the diazo derivative.



469 **470** **471** **472** 98 %

Scheme 181

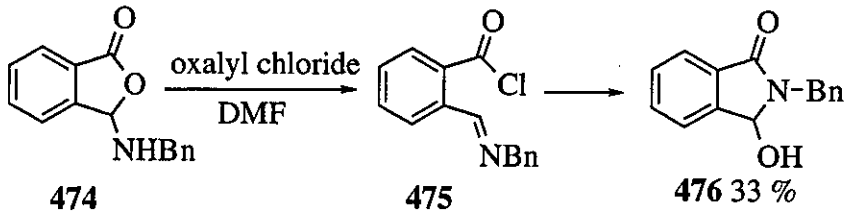
Again a known reaction of 2-carboxybenzaldehyde (**470**) with benzylamine forms the cyclised material (**474**) and not the imine (**473**) (Scheme 182).[143] Again, this ruled out the formation of a diazo compound from the imine (**473**).



470 **473** **474** 95 %

Scheme 182

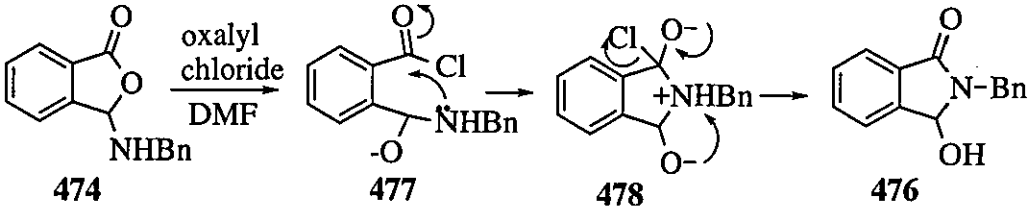
The amine (**474**) was synthesised and reacted with oxalyl chloride in DMF. No acylchloride (**475**) was isolated. The reaction proceeds to give the cyclised alcohol (**476**) (Scheme 183).



474 **475** **476** 33 %

Scheme 183

The proposed mechanism for this transformation is shown in Scheme 184.



474 **477** **478** **476**

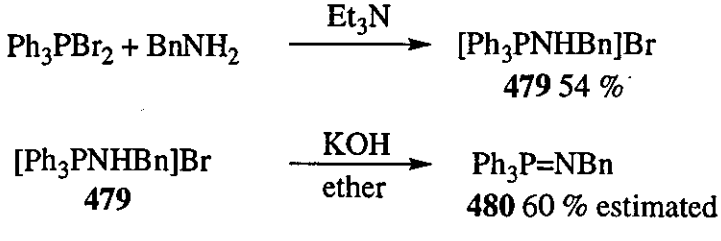
Scheme 184

The propensity of the reactions above to form ring-closed structures has made them unsuitable for the synthesis of the target diazo compound (**462**). Thus it was apparent that this route was impractical.

4.9 Aziridines *via* Reaction of Triphenylphosphoroimines with Epoxides.

The formation of aziridines *via* iminophosphoranes and epoxides using a metal catalyst has been described in Chapter 2.3 (page 35).

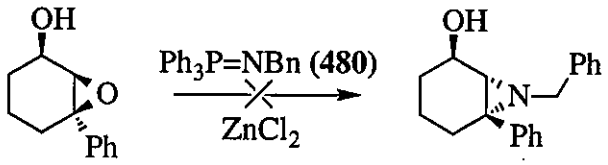
A literature method was used for the preparation of the triphenylphosphonium salt (**479**) (Scheme 185).[145] In contradiction to the literature method the reaction proceeded better at room temperature than at 0°C.



Scheme 185

Again a literature method was used to form the phosphoroimine **(480)**,[146] by simply stirring the triphenylphosphonium salt **(479)** with potassium hydroxide in ether. This proved difficult to purify and so was carried over into the next step without further purification.

Reaction of the epoxyalcohol **(338)** with the phosphoroimine **(480)** failed to form any of the required aziridine **(481)** (Scheme 186).[78]



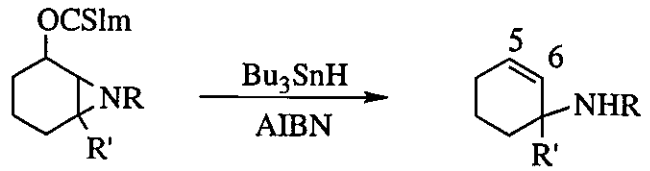
338 **481**

Scheme 186

Thus the Zn-catalysed method of forming aziridines *via* the reaction of phosphoroimines with epoxides, has proven unsuitable in this case.

4.10 Free Radical Reactions.

Reactions of the *N*-substituted aziridines **(390)**, **(431)** and **(432)** under free radical conditions gave,[16] in all cases, the C-N bond opened amine **(482)** to **(484)**. An example of the key data for **(483)** is as follows:- ν_{max}/cm^{-1} 1721 (C=O); δ_H 6.08 (1 H, m, 6-CH), 5.99 (1 H, dt, J = 10.5 and 3.5 Hz, 5-CH), 4.82 (1 H, s, NH). No C-C bond opened product was isolated in any case (Scheme 187) (Table 16).



390 R=Me, R'=Ph
431 R=Phthal, R'=Ph
432 R=Q, R'=*p*-ClPh

482-484

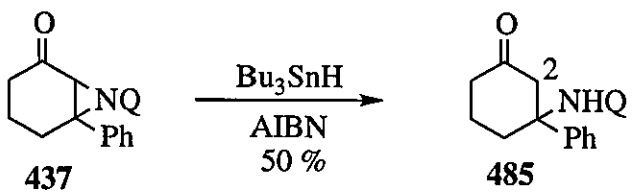
Scheme 187

Table 16: Results of the Radical Reactions on the Aziridines **(390)**, **(431)** and **(432)**.

No.	R	R'	Yield %
482	Me	Ph	15
483	Phthal	Ph	62
484	Q	*p*-ClPh*	40

*p-ClPh=p-chlorophenyl

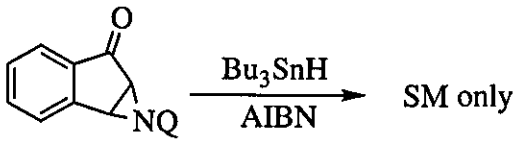
The ketoaziridine **(437)** also gave only the C-N bond opened product **(485)** using radical conditions reported by Hasegawa (Scheme 188).[147] Key data:- ν_{max}/cm^{-1} 1713 (C=O), 1681 (C=O); δ_H 6.13 (1 H, s, NH), 3.22 (1 H, d, J = 14 Hz, 2-CH), 2.92 (1 H, d, J = 14 Hz, 2-CH); δ_C 209.1 (C), 164.5 (C).[146]



437 **485**

Scheme 188

The indenoaziridine **(450)** showed no reaction under radical conditions (Scheme 189).[16] Only starting material was isolated.



450

Scheme 189

4.11 Discussion and Conclusion.

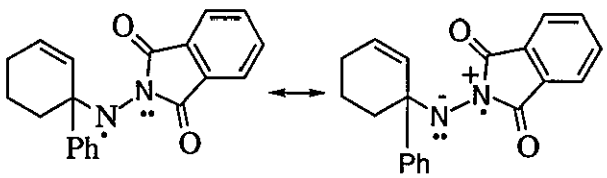


Fig 19

Fig 20

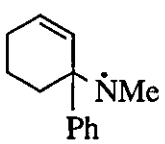


Fig 21

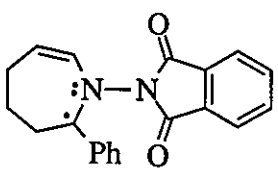


Fig 22

On C-N bond homolysis of the aziridine **(431)** to give the aminyl radical **(Fig 19)** stabilisation can be achieved by conjugation with the lone pair on the adjacent nitrogen atom **(Fig 20)**. On C-C bond homolysis of the aziridine **(431)** to give the 7-membered ring **(Fig 22)** stabilisation can occur by three methods.

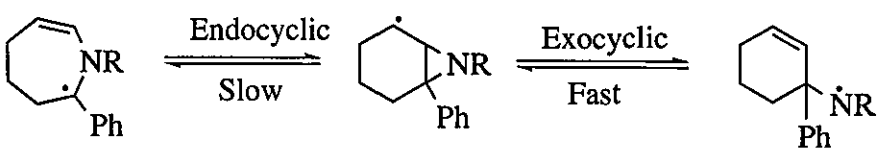
i) Conjugation with the lone pair of the adjacent nitrogen atom.

ii) Benzylic conjugation.

iii) Hyperconjugation.

The *N*-methyl radical **(Fig 21)** has no adjacent nitrogen atom and therefore no heteroatom stabilisation.

The results of calculations by Pasto (page 3) on the ring-opening modes of the aziridinylmethyl radical indicates that it kinetically prefers to ring open by cleavage of the C-N bond, but thermodynamically by cleavage of the C-C bond.



486 **487** **488**

Scheme 190

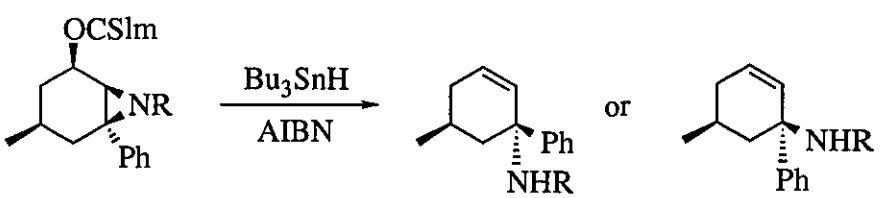
Assuming C-C and C-N bond cleavage are reversible (Scheme 190) in our system it would be reasonable to assume that some evidence of C-C bond cleavage would be detected in the products since further stabilisation of the carbon-centred radical **(486)** by the phenyl group would be anticipated. Also the reaction conditions used should favour thermodynamic control as normal addition over a relatively long time period was used, which gave a deficiency of tributyltin hydride.

Our isolation of products, in all cases, from C-N bond cleavage could be explained as follows:

i) the radical **(487)** is set up, stereoelectronically, to allow only exocyclic C-N bond homolysis and not C-C bond homolysis. This would not be the case for the aziridines considered by Pasto in his calculations or those of Schwan (page 17) which do not have the conformational restraint of the cyclohexane ring.

ii) the nitrogen substituent in the benzylic radical **(486)** can sterically hinder the approach of the Bu_3SnH, thus only allowing the reduction of the less hindered aminyl radical **(488)** and subsequent isolation of only the kinetically favoured product. No similar substituent effect would be present in the analogous epoxide work of Corser (Scheme 5, page 2) and could explain the isolation of ring expanded products in this case.

A similar experiment to that reported by Rudderham on the reversibility of epoxide C-C bond cleavage (page 5) could be used in this system in order to detect the intermediacy of the benzylic radical (Scheme 191). The isolation of two diastereoisomers **(490)** and **(491)** would confirm the intermediacy of the benzylic radical **(486)**.



489 **490** **491**

Reversible product

Non-reversible product

Scheme 191

5. Experimental.

5.1 General Information.

5.1.1 Solvents and Reagents.

Light petroleum refers to the petroleum ether fractions boiling between 40°C and 60°C and ether refers to diethyl ether. Other solvents of analytical grade were used without purification, as were commercially available reagents. Technical grade solvents were purified prior to use as follows. Dichloromethane was distilled from phosphorus pentoxide. Light petroleum and ethyl acetate were distilled form anhydrous calcium chloride. Methanol was distilled from magnesium and iodine. Tetrahydrofuran, benzene, toluene and acetonitrile were purchased from Aldrich in Sure-seal bottles.

5.1.2 Chromatographic Procedures.

Analytical TLC was performed on aluminium backed plates coated with Merck Kieselgel 60 GF_{254}. Flash chromatography was carried out using silica (Kieselgel 60 H) or alumina (Brockmann, grade 1). Basified silica refers to silica (Kieselgel 60 H) pre-washed with 5 % triethylamine in light petroleum.

5.1.3 Spectroscopic Techniques.

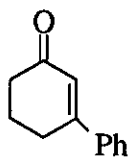
Fourier Transform infra red spectra were recorded in the range 4000-600 cm^{-1} using either a Nicolet FT-205 or a Perkin-Elmer Paragon 1000 spectrometer, with internal calibration. ^{1}H, ^{13}C and DEPT NMR spectra were recorded on either a Bruker AC-250 or a DPX-400 spectrometer in either deuteriochloroform, deuteriodimethylsulfoxide, deuterioacetone or deuteriomethanol. Chemical shifts are quoted in ppm relative to tetramethylsilane as the internal standard. Spectroscopic data are annotated with the following abbreviations, s-singlet, d-doublet, t-triplet, q-quartet, q-quintet, m-multiplet or combinations thereof. Maj and min refer to the major or minor isomers in the case of inseparable mixtures of isomers. Mass spectra were recorded on a Kratos MS80 or a VG Analytical ZAB-E spectrometer. Throughout the thesis the term "estimated" refers to yields determined by ^{1}H-NMR analysis of the crude product.

5.1.4 Other Information.

Melting points were measured on an Electrothermal digital melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400 Elemental analyser.

5.2 Experimental and Data.

Preparation of *3-Phenyl-2-cyclohexen-1-one* (330).



A solution of phenyllithium (approximately 1.8 M, 50 ml, 90.0 mmol) was added dropwise, to a stirred solution of 3-ethoxy-2-cyclohexen-1-one **(320)** (12.0 g, 85.6 mmol) in THF (40 ml) at -78°C. The resulting yellow-brown solution was then allowed to warm to room temperature. After stirring for 20 hours, HCl (2 M) was added slowly until the mixture was acidic to litmus. The mixture was then extracted with ether (4 x 20 ml) and the combined extracts were washed with saturated brine solution (2 x 20 ml), dried over magnesium sulfate, and evaporated *in vacuo* to give a yellow crystalline solid (13.0 g). Purification by recrystallisation from light petroleum gave the *title compound* as a cream crystalline solid (9.5 g, 65 %), m.p. 62-64°C (lit. 63-66°C).

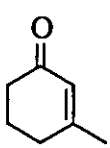
ν_{max}/cm^{-1} (Nujol), 1666 (C=O), 1604, 1453, 770 (Ph), 700 (Ph);

δ_H (250 MHz; $CDCl_3$) 7.35 (5 H, m, Ph), 6.42 (1 H, s, 2-CH), 2.79 (2 H, t, J = 6 Hz, 6-CH_2), 2.50 (2 H, t, J = 6 Hz, 4-CH_2), 2.19 (2 H, m, 5-CH_2);

δ_C (62.9 MHz; $CDCl_3$) 199.8 (C=O), 159.7 (3-C), 138.7 (Ar-C), 129.9 (2-CH), 128.7 (Ar-CH), 126.0 (Ar-CH), 125.3 (Ar-CH), 37.2 (4-CH_2), 28.0 (6-CH_2), 22.7 (5-CH_2).

Spectra are consistent with those reported in the literature.[120]

Preparation of *3-Methyl-2-cyclohexen-1-one* (331).

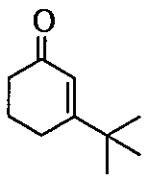


Methyllithium (13 ml, 1.5 M solution, 19.5 mmol) was added to a solution of 3-ethoxy-2-cyclohexen-1-one **(320)** (2.0 g, 14.4 mmol) in THF (20 ml) at -78 °C. The solution was then left stirring at room temperature overnight. HCl (2 M) was added until the solution was acidic to litmus. Saturated brine (100 ml) was added and the solution extracted with ethyl acetate (4 x 50 ml). The organic fractions were combined and washed with saturated brine (3 x 50 ml) dried over magnesium sulfate and evaporated *in vacuo* to give the *title compound* as an orange/red liquid (1.4 g, 90 %).

ν_{max}/cm^{-1} (neat) 2940 (CH_2), 1665 (C=O), 1430, 1380, 885;

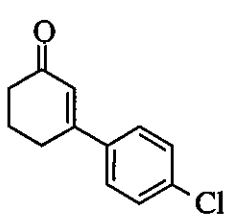
δ_H (250 MHz; $CDCl_3$) 5.88 (1 H, m, 2-CH), 2.35 (2 H, t, J = 6 Hz, 6-CH_2), 2.30 (2 H, t, J = 6 Hz, 4-CH_2), 2.00 (2 H, p, J = 6 Hz, 5-CH_2), 1.99 (3 H, s, CH_3);
δ_C (100 MHz; $CDCl_3$) 199.9 (1-C), 163.2 (3-C), 126.5 (2-CH), 37.0 (6-CH_2), 30.9 (4-CH_2), 24.5 (CH_3), 22.5 (5-CH_2).
Spectra are consistent with those reported in the literature.[148]

Preparation of *3-(tert-Butyl)-2-cyclohexen-1-one* (332).



Tert-butyllithium (7.5 ml, 1.7 M, 12.8 mmol) was added dropwise, to a solution of 3-ethoxy-2-cyclohexen-1-one **(320)** (1.0 g, 7.3 mmol) in THF (10 ml) at -60 °C. The solution was then allowed to stir at room temperature overnight. HCl (2 M) was added until the solution was acidic to litmus. Saturated brine (100 ml) was added and the solution extracted with ethyl acetate (4 x 30 ml). The organic fractions were combined and washed with saturated brine (3 x 50 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a viscous orange liquid (0.89 g). Flash chromatography (eluant 60:40 ethyl acetate:light petroleum) gave the *title compound* as a clear yellow liquid (0.41 g, 37 %).
ν_{max}/cm^{-1} (neat) 2967 (CH_2), 2871, 1669 (C=O), 1611, 1480, 1364, 1347, 890;
δ_H (250 MHz; $CDCl_3$) 5.96 (1 H, m, 2-CH), 2.36 (4 H, m, 4-CH_2 and 6-CH_2), 1.98 (2 H, m, 5-CH_2), 1.11 (9 H, s, Bu^t),
δ_C (100 MHz; $CDCl_3$) 201.1 (C=O), 174.3 (3-C), 122.9 (2-CH), 37.4 (CH_2), 36.8 (C), 28.2 (CH_3), 25.9 (CH_2), 23.2 (CH_2)
m/z (E.I) 152.1200 (M^+, 40 %, $C_{10}H_{16}O$ requires M^+, 152.1201), 137 (M^+-CH_3, 17), 124 (50), 109 (100), 96 (87), 81 (62), 57 (Bu^t, 31).

Preparation *3-(4-Chlorophenyl)-2-cyclohexen-1-one* (333).



A solution of 4-bromochlorobenzene (1.37 g, 7.1 mmol), magnesium (0.17 mg, 7.2 mmol) and iodine (1 crystal) in THF (10 ml) was left until formation of the Grignard reagent

was apparent. 3-ethoxy-2-cyclohexen-1-one (**320**) (1.0 g, 7.2 mmol) in THF (1 ml) was then added dropwise, to the pre-formed Grignard reagent. A further rinsing with THF (0.5 ml) was added dropwise. After stirring at room temperature overnight, HCl (2 M) was added until the excess magnesium was dissolved (colour changes from yellow to clear, colourless). Saturated brine (20 ml) was added and the solution extracted with DCM (2 x 20 ml). The combined organic fractions were then washed with saturated brine (3 x 20 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a beige solid (1.2 g). Flash chromatography (eluant 50:50 ethyl acetate:light petroleum) afforded the *title compound* as a clear yellow liquid (0.67 g, 53 %).

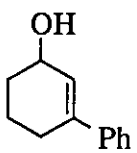
ν_{max}/cm^{-1} (DCM slurry) 3058 (Ar), 2946 (CH_2), 1665 (C=O), 1603 (Ar), 1591 (Ar), 1492 (Ar), 815 (Ar);

δ_H (250 MHz; $CDCl_3$) 7.47 (2 H, dd, J = 8 and 1 Hz, Ar-H), 7.38 (2 H, dd, J = 8 and 1 Hz, Ar-H), 6.39 (1 H, dd, J = 2 and 1.5 Hz, 2-CH), 2.74 (2 H, t, J = 6 Hz, 6-CH_2), 2.49 (2 H, t, J = 6 Hz, 4-CH_2), 2.16 (2 H, m, 5-CH_2);

δ_C (62.9 MHz; $CDCl_3$) 199.5 (C=O), 158.2 (3-C), 137.0 (C), 135.8 (C), 128.8 (CH), 127.3 (CH), 125.4 (CH), 37.0 (CH_2), 27.8 (CH_2), 22.6 (CH_2).

Known compound.[149]

Preparation *3-Phenyl-2-cyclohexen-1-ol* (334).



Sodium borohydride (2.5 g, 67.3 mmol) was added portionwise to a solution of 3-phenyl-2-cyclohexen-1-one (**330**) (7.5 g, 43.5 mmol) and cerium(III) chloride heptahydrate (16.3 g, 43.7 mmol) in methanol (75 ml) at 0°C. After stirring for 1 hour, water (100 ml) was added and the mixture was extracted with ether (3 x 80 ml). The combined extracts were washed with water (25 ml) and saturated brine (2 x 25 ml), dried over magnesium sulfate and evaporated *in vacuo* to give the *title compound* as a pale yellow, viscous liquid (7.4 g, 98 %). The liquid formed a waxy, beige solid on cooling, m.p. 60-62°C (lit. 60-61°C).[159]

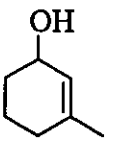
υ_{max}/cm^{-1} (Nujol), 3320 (OH), 2937 (CH_2), 2862, 1597, 1494, 1446, 1053, 974;

δ_H (250 MHz; $CDCl_3$) 7.33 (5 H, m, Ph), 6.12 (1 H, m, 2-CH), 4.40 (1 H, m, 1-CH), 2.43 (2 H, m, 4-CH_2), 2.07 (1 H, br s, OH), 1.89 (2 H, m, 6-CH_2), 1.67 (2 H, m, 5-CH_2);

δ_C (62.9 MHz; $CDCl_3$) 141.3 (Ar-C or 3-C), 139.4 (Ar-C or 3-C), 128.3 (Ar-CH), 127.9 (Ar-CH), 127.5 (2-CH), 125.3 (Ar-CH), 66.1 (1-CH), 31.5 (6-CH_2), 27.3 (4-CH_2), 19.6 (5-CH_2).

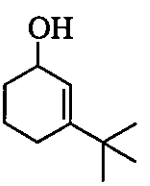
Spectra are consistent with those reported in the literature.[120]

Preparation of *3-Methyl-2-cyclohexen-1-ol* (335).



Sodium borohydride (0.70 g, 18.4 mmol) was added portionwise to a solution of 3-methyl-2-cyclohexen-1-one **(331)** (1.4 g, 12.3 mmol) and cerium(III) chloride heptahydrate (4.6 g, 12.4 mmol) in methanol (21 ml) at 0°C. After approximately 2 hours water (60 ml) was added and the solution was extracted with ethyl acetate (3 x 50 ml). The combined organic fractions were washed with saturated brine (4 x 25 ml) and dried over magnesium sulfate. Evaporation *in vacuo* afforded the *title compound* as a yellow liquid (1.1 g, 77 %).
ν_{max}/cm^{-1} (neat) 3333 (OH), 2933 (CH_2), 1672, 1448, 1377, 1294 (O-H), 1034 (C-O), 815;
δ_H (250 MHz; $CDCl_3$) 5.49 (1 H, m, 2-CH), 4.17 (1 H, m, 1-CH), 1.98 (1 H, br s, OH), 1.91 (2 H, m, 4-CH_2), 1.78 (2 H, m, 6-CH_2), 1.68 (3 H, s, CH_3), 1.57 (2 H, m, 5-CH_2);
δ_C (100 MHz; $CDCl_3$) 138.4 (3-C), 124.3 (2-CH), 65.8 (1-CH), 31.6 (CH_2), 30.1 (CH_2), 23.7 (CH_3), 19.02 (CH_2).
Spectra are consistent with those reported in the literature.[150]

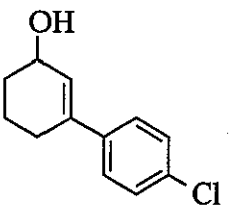
Preparation of *3-(tert-Butyl)-2-cyclohexen-1-ol* (336).



Sodium borohydride (0.13 g, 3.3 mmol) was added portionwise to a solution of 3-*(tert*-butyl)-2-cyclohexen-1-one **(332)** (0.33 g, 2.2 mmol) and cerium(III) chloride heptahydrate (1.5 g, 4.14 mmol) in methanol (5 ml) at 0°C. After an hour at room temperature, water (20 ml) was added. The solution was extracted with ethyl acetate (3 x 30 ml) and the organic fractions combined and washed with saturated brine (3 x 30 ml). The solution was dried over magnesium sulfate and evaporated *in vacuo* to give the *title compound* as a dark red liquid (0.29 g, 87 %).
ν_{max}/cm^{-1} (neat) 3332 (OH), 2936 (CH_2), 2867, 1653, 1478, 1391, 1362, 1248 (OH), 1057 (C-O), 863;
δ_H (250 MHz; $CDCl_3$) 5.54 (1 H, m, 2-CH), 4.23 (1 H, m, 1-CH), 2.00 (2 H, m, 4-CH_2), 1.80 (1 H, m, 6-CH), 1.70 (1 H, m, 5-CH), 1.56 (3 H, m, 6-CH, 5-CH and OH), 1.03 (9 H, s, Bu^t);

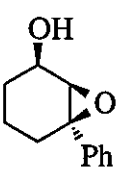
δ_C (100 MHz, $CDCl_3$) 150.0 (3-C), 120.7 (2-CH), 66.4 (1-CH), 35.3 (C), 32.0 (CH_2), 28.9 (CH_3), 24.6 (CH_2), 19.8 (CH_2);
m/z (E.I) 154.1360 (M^+, <1 %, $C_{10}H_{18}O$ requires M^+, 154.1358), 137 (M^+-CH_3, 2), 97 (M^+-Bu^t, 100), 79 (31), 57 (Bu^t, 21).

Preparation of *3-(4-Chlorophenyl)-2-cyclohexen-1-ol* (337).



Sodium borohydride (0.17 g, 4.4 mmol) was added to a solution of 3-(4-chlorophenyl)-2-cyclohexen-1-one **(333)** (0.67 g, 3.2 mmol) and cerium(III) chloride heptahydrate (1.48 g, 4.0 mmol) in methanol (8 ml) at 0°C. After stirring at room temperature for 1 hour, water (20 ml) was added and the solution extracted with ethyl acetate (3 x 20 ml). The organic fractions were combined and washed with saturated brine (3 x 20 ml), dried over magnesium sulfate and evaporated *in vacuo* to give the *title compound* as clear slightly blue liquid (0.61 g, 91 %).
ν_{max}/cm^{-1} (neat) 3334 (OH), 2936 (CH_2), 1643, 1592, 1493, 1264 (OH), 1093 (C-O), 815 (Ar);
δ_H (250 MHz; $CDCl_3$) 7.30 (2 H, d, J = 9 Hz, Ar-H), 7.25 (2 H, d, J = 9 Hz, Ar-H), 6.09 (1 H, m, 2-CH), 4.36 (1 H, m, 1-CH), 2.32 (2 H, m, 6-CH_2), 1.90 (2 H, m, 4-CH_2), 1.66 (2 H, m, 5-CH_2), 1.59 (1 H, s, OH);
δ_C (62.9 MHz; $CDCl_3$), 139.6 (C), 138.9 (C), 128.3 (CH), 127.0 (CH), 126.6 (CH), 66.2 (1-CH), 31.5 (CH_2), 27.3 (CH_2), 19.3 (CH_2).
m/z (E.I.) 208.0653 (M^+, 13 %, $C_{12}H_{14}OCl$ requires M^+, 208.0655), 173 (95), 145 (100), 115 (38).

Preparation of *2,3-Epoxy-3-phenylcyclohexanol* (338).



m-Chloroperbenzoic acid (10.0 g, 50-60 %, 30-35 mmol) was added to a stirred solution of 3-phenyl-2-cyclohexen-1-ol **(334)** (4.1 g, 23.4 mmol) and sodium carbonate (2.4 g, 23.0 mmol) in DCM (200 ml) at 0°C. After 3 hours the solution was washed with saturated

sodium carbonate solution (3 x 50 ml) and saturated brine (2 x 50 ml) dried over magnesium sulfate, and evaporated *in vacuo* to give the *title compound* as a light-beige solid (4.0 g, 89 %). m.p. 49-50°C (lit.-isolated as a liquid).[120]

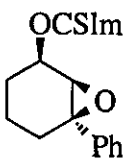
υ_{max}/cm^{-1} (Nujol) 3409 (OH), 2940 (CH_2), 1600, 1500, 1447, 1064 (OH), 874 (C-O), 758 (Ph);

δ_H (250 MHz; $CDCl_3$) 7.36 (5 H, m, Ph), 4.15 (1 H, m, 1-CH), 3.30 (1 H, d, J = 3.5 Hz, 2-CH), 2.24 (2 H, m, 4-CH and 6-CH), 1.65 (4 H, m, 5-CH_2, 6-CH and OH);

δ_C (62.9 MHz; $CDCl_3$) 141.1 (Ar-C), 128.4 (Ar-CH), 127.6 (Ar-CH), 125.3 (Ar-CH), 66.1 (1-CH), 64.3 (2-CH), 63.9 (3-C), 29.3 (6-CH_2), 28.0 (4-CH_2), 17.8 (5-CH_2).

Spectra are consistent with those reported in the literature.[120]

Preparation of *2,3-Epoxy-1-[imidazol-1-yl (thiocarbonyl)oxy]-3-phenylcyclohexane* (339).



A solution of 2,3-epoxy-3-phenylcyclohexanol (**338**) (0.82 g, 4.3 mmol) and 1,1'-thiocarbonyldiimidazole (1.2 g, 6.8 mmol) in DCM (30 ml) was stirred at a gentle reflux for 24 hours. After cooling the solution was washed with saturated brine (3 x 20 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a yellow oil (1.1 g). Purification by flash chromatography (eluant 50:50 light petroleum:ether) gave the *title compound* as a slightly yellow liquid (0.72 g, 56 %).

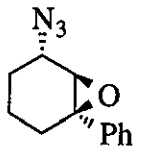
υ_{max}/cm^{-1}(neat) 2946, 1727, 1531, 1495, 1464, 1386, 1230 (C-O), 1102 (C=S), 1040 (C-O), 993;

δ_H (250 MHz; $CDCl_3$) 8.41 (1 H, d, J = 1 Hz, Im-CH), 7.69 (1 H, d, J = 1 Hz, Im-CH), 7.35 (5 H, m, Ph), 7.05 (1 H, d, J = 1 Hz, Im-CH), 6.00 (1 H, m, 1-CH), 3.48 (1 H, d, J = 2.5 Hz, 2-CH), 2.36 (1 H, m, 4-CH), 2.21 (1 H, m, 4-CH), 1.94 (3 H, m, 5-CH and 6-CH_2), 1.64 (1 H, m, 5-CH);

δ_C (62.9 MHz; $CDCl_3$) 183.6 (C=S), 140.2 (Ar-C), 137.2 (Im-CH), 130.7 (Im-CH), 128.5 (Ar-CH), 127.9 (Ar-CH), 125.3 (Ar-CH), 118.0 (Im-CH), 79.1 (1-CH), 63.1 (3-C), 60.2 (2-CH), 27.5 (4-CH_2), 24.7 (6-CH_2), 18.7 (5-CH_2).

Spectra are consistent with those reported in the literature.[120]

Preparation of *1-Azido-2,3-epoxy-3-phenylcyclohexane* (340).



Sodium azide (0.50 g, 7.0 mmol) was added to a solution of 2,3-epoxy-1-[imidazol-1-yl-(thiocarbonyl)oxy]-3-phenylcyclohexane (**339**) (0.21 g, 0.7 mmol) in DMSO (18 ml). Concentrated sulfuric acid (0.1 ml, 1.9 mmol) was added and the solution was heated to approximately 60°C for 18 hours. The solution was then cooled and sodium nitrite solution (5 ml, 20 % w/v), and saturated brine (25 ml) were added. The mixture was then extracted with DCM (3 x 25 ml) and the combined extracts washed with saturated brine (3 x 20 ml) and dried with magnesium sulfate. Evaporation *in vacuo* gave a clear colourless oil (0.21 g). This oil was then dissolved in DCM (25 ml) and re-washed with water (3 x 10 ml). The organic layer was then dried with magnesium sulfate and evaporated *in vacuo* to give a clear, colourless oil (0.13 g). Purification by flash chromatography (eluant 0.5 % methanol in DCM) afforded the *title compound* as a colourless oil (75.9 mg, 50 %).

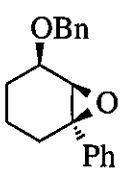
υ_{max}/cm^{-1} (neat) 2945 (CH_2), 2101 (N_3), 1495, 1447, 1253 (C-O), 756 (Ph), 699 (Ph);

δ_H (400 MHz; $CDCl_3$) 7.36 (5 H, m, Ph), 3.87 (1 H, dd, J = 9 and 6 Hz, 1-CH), 3.07 (1 H, br s, 2-CH), 2.26 (1 H, m, 4-CH), 2.18 (1 H, m, 4-CH), 2.02 (1 H, m, 6-CH), 1.66 (1 H, m, 5-CH), 1.52 (1 H, m, 5-CH), 1.39 (1 H, m, 6-CH);

δ_C (100 MHz; $CDCl_3$) 141.0 (Ar-C), 128.8 (Ar-CH), 128.1 (Ar-CH), 125.8 (Ar-CH), 63.2 (2-CH), 61.6 (C), 57.2(1-CH), 28.6 (4-CH_2), 26.7 (6-CH_2), 16.6 (5-CH_2);

m/z (C. I., ammonia) 233.1402(MNH_4^+, 9 %, $C_{12}H_{13}N_3ONH_4^+$ requires MNH_4^+ 233.1402), 215 (M^+, 1), 205 (MNH_4^+-N_2, 32), 190 (100), 188 (32), 172 (94), 160 (47), 157 (90).

Preparation of *1-(Benzyloxy)-2,3epoxy-3-phenylcyclohexane* (350).



Benzyl bromide (2.0 g, 11.7 mmol) was added to a solution of sodium hydride (1.9 g, 60 % dispersion in oil, 48.0 mmol) pre-washed with DMF (2 x 10 ml) and 2,3-epoxy-3-phenylcyclohexanol (**338**) (2.0 g, 10.5 mmol) in DMF (25 ml) at 0°C. After 1 hour water was cautiously added dropwise until fizzing ceased (approx. 25 ml). Water (65 ml) was then added and the solution extracted with DCM (5 x 20 ml). The combined extracts were then

washed with water (4 x 25 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a cloudy brown emulsion (2.6 g). Purification by flash chromatography (eluant 90:10 light petroleum:ether) gave the *title compound* as a slightly yellow oil (1.5 g, 52 %).

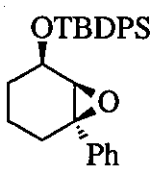
υ_{max}/cm^{-1} (neat) 2942 (CH_2), 1603, 1495, 1453, 1094 (C-O), 1074 (C-O), 737 (Ar), 698 (Ar);

δ_H (250 MHz; $CDCl_3$) 7.33 (10 H, m, Ar-H), 4.71 (1 H, d, J = 12 Hz, $\mathbf{CH_2}$Ph), 4.67 (1 H, d, J = 12 Hz, $\mathbf{CH_2}$Ph) 3.90 (1 H, m, 1-CH), 3.24 (1 H, d, J = 2.5 Hz, 2-CH), 2.26 (1 H, m, 4-CH), 2.06 (1 H, m, 4-CH), 1.74 (3 H, m, 6-CH_2 and 5-CH), 1.42 (1 H, m, 5-CH);

δ_C (62.9 MHz; $CDCl_3$) 142.1 (Ar-C), 139.1 (Ar-C), 128.8 (Ar-CH), 128.7 (Ar-CH), 128.1 (Ar-CH), 128.0 (Ar-CH), 127.8 (Ar-CH), 125.7 (Ar-CH), 73.9 (CH), 70.6 (CH_2), 63.0 (CH), 62.9 (C), 28.5 (CH_2), 25.8 (CH_2), 19.9 (CH_2).

m/z (E.I.) 280.1463(M^+, 3 %, $C_{19}H_{20}O_2$ requires M^+, 280.1463), 189 (M^+-Bn, 14), 160 (30), 105 (40), 143 (100), 77 (36).

Preparation of *1-(tert-Butyldiphenylsilyloxy)-2,3-epoxy-3-phenylcyclohexane* (351).



4-Dimethylaminopyridine (57.4 mg, 0.5 mmol), triethylamine (0.21 g, 2.1 mmol) and *tert*-butyldiphenylsilyl chloride (0.44 g, 1.6 mmol) were added to a solution of 2,3-epoxy-3-phenylcyclohexanol **(338)** (0.20 g, 1.1 mmol) in DCM (8 ml). After stirring for approximately 2 days, DCM (10 ml) was added. The mixture was then washed with water (2 x 25 ml) and saturated ammonium chloride (2 x 15 ml), dried with magnesium sulfate and evaporated *in vacuo* to give a clear yellow, viscous liquid (0.55 g). Purification by flash chromatography (eluant 90:10 light petroleum:ether) gave the *title compound* as a clear, colourless viscous oil (0.32 g, 71 %).

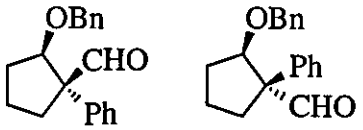
υ_{max}/cm^{-1} (neat) 2955 (CH_2), 1589 (Ar), 1495 (Ar), 1472, 1427, 1362, 1110 (Si-O or C-O), 741 (Ar), 701 (Ar);

δ_H (250 MHz, $CDCl_3$) 7.72 (4 H, m, Ar-H), 7.34 (11 H, m, Ar-H), 4.09 (1 H, m, 1-CH), 3.00 (1 H, d, J = 2 Hz, 2-CH), 2.15 (1 H, m, 4-CH), 2.00 (1 H, m, 4-CH), 1.67 (2 H, m, 5-CH and 6-CH), 1.50 (1 H, m, 6-CH), 1.28 (1 H, m, 5-CH), 1.09 (9 H, m, Bu^t);

δ_C (100 MHz, $CDCl_3$) 141.7 (Ar-C), 135.7 (Ar-CH), 134.0 (Ar-C), 129.5 (Ar-CH), 128.1 (Ar-CH), 127.4 (Ar-CH), 127.1 (Ar-CH), 125.2 (Ar-CH), 69.3 (1-CH), 64.8 (2-CH), 63.1 (C), 28.1 (6-CH_2), 27.7 (4-CH_2), 26.8 (CH_3), 19.8 (5-CH_2), 19.1 (C);

m/z (C. I., ammonia) 429.2250(MH^+, 3 %, $C_{28}H_{32}O_2SiH^+$ requires MH^+, 429.2250), 351 (MH^+-PhH, 10), 274 (8) and 157 (MNH^+ minus HOTBDPS and OH, 100).

Preparation of *1-(Benzyloxy)-2-phenylcyclopentane-2-carbaldehyde* (352).



Sodium azide (62.9 mg, 1.0 mmol) was added to a solution of 1-(benzyloxy)-2,3-epoxy-3-phenylcyclohexane (**350**) (45.9 mg, 0.2 mmol) in DMSO (5 ml). Concentrated sulfuric acid (0.3 ml, 5.6 mmol) was then added and the resulting solution was heated to 55°C for 18 hours. The solution was then cooled, sodium nitrite solution (5 ml, 20 % w/v) and saturated brine (10 ml) were added and the resulting solution was then extracted with DCM (4 x 10 ml) and dried with magnesium sulfate. Evaporation *in vacuo* afforded a yellow coloured liquid (57.0 mg, 125 %-residual DMSO). NMR analysis of the crude material showed two isomeric aldehydes (1:2). Attempted purification by flash chromatography (eluant 50:50 light petroleum:ether) failed to separate the two isomers. The separate isomers were obtained from the preparation of (**353**, minor isomer) and (**357**, major isomer). It has not been determined which isomer is the major. NOE was unable to help in this determination.

Major Isomer.

υ_{max}/cm^{-1} (neat) 2940 (CH_2), 1719 (C=O), 1495, 1192 (C-O), 1062, 735 (Ar), 697 (Ar);

δ_H (250 MHz; $CDCl_3$) 9.39 (1 H, s, CHO), 7.29 (8 H, m, Ar-H), 7.00 (2 H, t, J = 4 Hz, Ar-H), 4.51 (1 H, d, J = 4.5 Hz, 1-CH), 4.45 (1 H, d, J = 12 Hz, **CH_2**Ph), 4.25 (1 H, d, J = 12 Hz, **CH_2**Ph), 2.37 (2 H, m, 3-CH_2), 1.94 (3 H, m, 4-CH and 5-CH_2), 1.63 (1 H, m, 4-CH);

δ_C (100 MHz; $CDCl_3$) 200.0 (CHO), 138.3 (Ar-C), 135.6 (Ar-C), 129.0 (Ar-CH), 128.5 (Ar-CH), 128.1 (Ar-CH), 127.6 (Ar-CH), 127.4 (Ar-CH), 127.3 (Ar-CH), 81.4 (1-CH), 71.1 (**CH_2**Ph), 68.7 (C), 30.0 (CH_2), 28.8 (CH_2), 21.0 (CH_2);

m/z (E.I.) 280.1463(M^+, 9 %, $C_{19}H_{20}O_2$ requires M^+, 280.1463), 144 (M^+-OBn, 28), 143 (63), 91 (100), 77 (22), 65 (43).

Minor isomer.

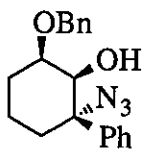
υ_{max}/cm^{-1} (neat) 2940 (CH_2), 1719 (C=O), 1599, 1495, 1453, 1071 (C-O), 735 (Ar), 698 (Ar);

δ_H (400 MHz; $CDCl_3$) 9.79 (1 H, s, CHO), 7.30 (10 H, m, Ar-H), 4.69 (1 H, d, J = 12 Hz, **CH_2**Ph), 4.52 (1 H, d, J = 12 Hz, **CH_2**Ph), 4.51 (1 H, t, J = 6 Hz, 1-CH), 2.73 (1 H, m, 3-CH), 2.05 (1 H, m, 5-CH), 1.91 (1 H, m, 4-CH), 1.83 (2 H, m, 3-CH and 5-CH), 1.64 (1 H, m, 4-CH);

δ_C (100 MHz; $CDCl_3$) 201.5 (C=O), 139.8 (Ar-C), 138.5 (Ar-C), 129.2 (Ar-CH), 128.8 (Ar-CH), 128.1 (Ar-CH), 127.9 (Ar-CH), 127.8 (Ar-CH), 127.7 (Ar-CH), 87.3 (1-CH), 72.0 (**CH_2**Ph), 65.4 (C), 30.6 (CH_2), 30.4 (CH_2), 20.8 (CH_2);

m/z (E.I.) 280.1463(M^+, 9 %, $C_{19}H_{20}O_2$ requires M^+, 280.1463), 144 (M^+-OBn and CHO, 32), 91 (100), 77 (23), 65 (47).

Preparation of *3-Azido-1-(benzyloxy)-3-phenylcyclohexan-2-ol* (353).



Procedure a : 0.8 % sulphuric acid.

Sodium azide (1.2 g, 18.2 mmol) was added to a solution of 1-(benzyloxy)-2,3-epoxy-3-phenylcyclohexane **(350)** (0.30 g, 1.0 mmol) in DMSO (30 ml). Concentrated sulfuric acid (0.25 ml, 4.7 mmol) was added and the solution heated to 90°C for 18 hours. Sodium nitrite solution (17 ml , 20 % w/v) and saturated brine (20 ml) were added. The solution was extracted with DCM (4 x 10 ml). The combined extracts were then washed with saturated brine (3 x 10 ml) dried using magnesium sulfate and evaporated *in vacuo* to give a yellow liquid (0.60 g). DCM (15 ml) was added and the solution was re-washed with saturated brine (3 x 20 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a yellow viscous liquid (0.26 g). Purification by flash chromatography (eluant 75:25 light petroleum:ether) afforded the *title compound* as a clear colourless oil (0.22 g, 63 %). An aldehyde was also isolated as a clear colourless oil (18.7 mg, 6 %) and characterised as 1-(benzyloxy)-2-phenylcyclopentane-2-carbaldehyde **(352)** (minor isomer):

Procedure b : 0.4 % sulphuric acid (optimum conditions).

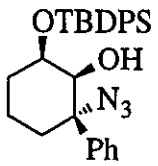
Sodium azide (2.5 g, 39.0 mmol) was added to a solution of 1-(benzyloxy)-2,3-epoxy-3-phenylcyclohexane **(350)** (0.96 g, 3.4 mmol) in DMSO (75 ml). Concentrated sulfuric acid (0.30 ml, 5.6 mmol) was added and the solution heated to 90°C for 24 hours. Sodium nitrite solution (100 ml , 20% w/v) and saturated brine (20 ml) were added. The solution was extracted with DCM (4 x 25 ml). The combined extracts were then washed with water (2 x 50 ml) dried over magnesium sulfate and evaporated *in vacuo* to give a yellow liquid. DCM (15 ml) was added and the solution was re-washed with water (2 x 25 ml), dried with magnesium sulfate and evaporated *in vacuo* to give the *title compound* as a yellow viscous liquid (0.84 g, 76 %).

υ_{max}/cm^{-1} (neat) 3460 (OH), 2099 (N_3), 1495, 1447, 1073 (C-O), 736 (Ar), 698 (Ar);

δ_H (400 MHz; $CDCl_3$) 7.38 (10 H, m, Ar-H), 4.61 (2 H, s, CH_2), 4.05 (1 H, br s, 2-CH), 3.87 (1 H, m, 1-CH), 2.37 (1 H, m, 4-CH), 2.18 (1 H, br s, OH), 1.97 (1 H, m, 4-CH), 1.82 (2 H, m, 5-CH and 6-CH), 1.66 (2 H, m, 5-CH and 6-CH);

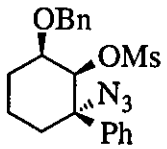
δ_C (100 MHz; $CDCl_3$) 141.3 (Ar-C), 138.6 (Ar-C), 129.0 (Ar-CH), 128.9 (Ar-CH), 128.5 (Ar-CH), 128.2 (Ar-CH), 128.1 (Ar-CH), 76.5 (CH), 72.1 (CH), 71.0 (CH_2), 69.7 (C), 26.9 (CH_2), 25.0 (CH_2), 19.7 (CH_2);
m/z (C.I., ammonia) 341.1977(MNH_4^+, 100 %, $C_{19}H_{21}N_3O_2NH_4^+$ requires MNH_4^+, 341.1977), 324 (3), 298 (38), 281 (13), 188 (14).

Preparation of *3-Azido-1-(tert-butyldiphenylsilyloxy)-3-phenylcyclohexan-2-ol* (354).



Sodium azide (2.7 g, 4.1 mmol) was added to a solution of 1-(*tert*-butyldiphenylsilyloxy)-2,3-epoxy-3-phenylcyclohexane (**351**) (1.6 g, 3.7 mmol) in anhydrous DMSO (35 ml). Concentrated sulfuric acid (0.35 ml, 7.4 mmol) was added and the solution heated to 86°C for 72 hours. The solution was cooled and sodium nitrite solution (75 ml, 20 % w/v) was added. The mixture was then extracted with DCM (3 x 20 ml) and the combined extracts were washed with water (3 x 20 ml) and dried over magnesium sulfate. Evaporation *in vacuo* afforded the *title compound* as a clear colourless liquid (1.6 g, 94 %).
υ_{max}/cm^{-1} (neat) 3563 (OH), 2932 (CH_2), 2100 (N_3), 1427, 1391, 1327, 1112 (SiO), 1077 (C-O), 739 (Ar), 700 (Ar);
δ_H (400 MHz; $CDCl_3$) 7.68 (4 H, m, Ar-H), 7.41 (11 H, m, Ar-H), 4.15 (1 H, m, 1-CH), 3.72 (1 H, d, J = 2 Hz, 2-CH), 2.46 (1 H, br s, OH), 2.27 (1 H, dt, J = 13.5 and 4 Hz, 4-CH), 1.86 (1 H, br d, J = 13 Hz, 4-CH), 1.62 (3 H, m, 5-CH and 6-CH_2), 1.50 (1 H, m, 5-CH), 1.07 (9 H, s, Bu^t);
δ_C (100 MHz; $CDCl_3$) 141.2 (Ar-C), 135.9 (Ar-CH), 135.9 (Ar-CH), 134.0 (Ar-C), 133.7 (Ar-C), 130.2 (Ar-CH), 130.1 (Ar-CH), 128.7 (Ar-CH), 128.2 (Ar-CH), 128.0 (Ar-CH), 127.9 (Ar-CH), 126.5 (Ar-CH), 73.2 (2-CH), 70.2 (1-CH), 68.4 (C), 26.7 (6-CH_2), 26.2 (CH_3), 25.5 (4-CH_2), 18.3 (5-CH_2);
δ_C (100 MHz, D_6-Acetone) 141.8 (Ar-C), 136.1 (Ar-CH), 134.6 (Ar-C), 134.4 (Ar-C), 130.2 (Ar-CH), 130.2 (Ar-CH), 128.6 (Ar-CH), 128.1 (Ar-CH), 128.0 (Ar-CH), 128.0 (Ar-CH), 127.0 (Ar-CH), 74.1(2-CH), 71.7 (1-CH), 70.4 (C), 27.7 (6-CH_2), 27.0 (CH_3), 26.6 (4-CH_2), 19.6 (5-CH_2), 19.3 (C);
m/z (C. I., ammonia) 472.2420 (MH^+, 8 %, $C_{28}H_{33}N_3O_2SiH^+$ requires MH^+, 472.2420) and 188(100, MH^+ - HOTBDPS and N_2), 444 (MH^+-N_2, 36), 366 (48), 351 (57), 274 (48), 256 (TBDPSOH, 6), 216 (MH^+-TBDPSOH, 40 %), 196 (43), 172 (52), 157 (36).

Preparation of *3-Azido-1-(benzyloxy)-2-(methanesulfonyloxy)-3-phenylcyclohexane* (356).



Methanesulfonyl chloride (3.0 g, 26 mmol) was added to a solution of 3-azido-1-(benzyloxy)-3-phenylcyclohexan-2-ol **(353)** (0.81 g, 2.5 mmol) in pyridine (10 ml). The resulting solution was then heated to approximately 70°C for 40 minutes to give a dark brown mixture. DCM (50 ml) was then added and the resulting solution was washed with 1 M HCl (4 x 50 ml), saturated sodium hydrogen carbonate solution (2 x 25 ml) and water (2 x 25 ml). The organic layer was then dried over magnesium sulfate and evaporated *in vacuo* to give a dark red coloured viscous oil (1.0 g). Crystals formed on cooling and these were separated and recrystallised using DCM to give white crystals. (0.54 g, 54 %). m.p. 104-105°C.

υ_{max}/cm^{-1} (DCM slurry) 2108 (N_3), 1495, 1449, 1360, 1175, 1100 (C-O), 759 (Ar), 700 (Ar);

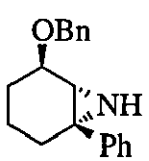
δ_H (250 MHz; $CDCl_3$) 7.42 (10 H, m, Ar-H), 5.08 (1 H, br s, 2-CH), 4.74 (1 H, d, J = 12 Hz, CH_2Ph), 4.59 (1 H, d, J = 12 Hz, CH_2Ph), 3.89 (1 H, m, 1-CH), 2.45 (3 H, s, CH_3), 2.35 (1 H, m, 4-CH), 2.04 (1 H, m, 4-CH), 1.93 (2 H, m, 5-CH and 6-CH), 1.71 (2 H, m, 5-CH and 6-CH);

δ_C (100 MHz; $CDCl_3$) 141.5 (Ar-C), 140 (Ar-C), 131.0 (Ar-CH), 130.5 (Ar-CH), 129.9 (Ar-CH), 129.8 (Ar-CH), 129.9 (Ar-CH), 84.4 (CH), 76.5 (CH), 73.1 (CH_2Ph), 70.7 (C), 40.9 (CH_3), 29.9 (CH_2), 27.5 (CH_2), 21.3 (CH_2);

m/z (C. I., ammonia) 419.1753(MNH_4^+, 100 %, $C_{20}H_{23}N_3O_4SNH_4^+$ requires MNH_4^+, 419.1753), 402 (MH^+, 3), 280 (MH^+-BnO and Me, 16), 172 (58), 157 (68), 108 (BnOH, 7).

Attempted X-ray analysis proved fruitless as the crystal stores large amounts of solvent.

Preparation of *5-(Benzyloxy)-1-phenyl-7-azabicyclo[4.1.0]heptane* (357).



Procedure a: $LiAlH_4$ Reduction.

Lithium aluminium hydride (0.10 g, 2.7 mmol) was added to a solution of 3-azido-1-(benzyloxy)-2-(methanesulfonyloxy)-3-phenylcyclohexane **(356)** (0.10 g, 0.3 mmol) in ether (15 ml). After stirring at room temperature for approximately 2 hours, potassium sodium tartrate (25 ml, 30 % w/v) and ether (20 ml) were added. The solution was washed with

saturated brine (2 x 25 ml) then dried over magnesium sulfate. Evaporation *in vacuo* gave a yellow oil (46.4 mg). Repeated purification by flash chromatography using alumina (eluant 60:40 light petroleum:ether) gave the *title compound* as a colourless oil (13.5 mg, 19 %). An aldehyde was also isolated as a clear, colourless oil (5.7 mg, 8 %) and characterised as **352** (major isomer).

Procedure b: Staudinger Reaction.

Triphenylphosphine (0.22 g, 0.8 mmol) was added to a solution of 3-azido-1-(benzyloxy)-3-phenylcyclohexan-2-ol (**353**) (0.28 g, 0.9 mmol) in acetonitrile (5 ml). The solution was stirred at room temperature for approximately 4 hours and then refluxed for approximately 18 hours, after which the acetonitrile was evaporated off *in vacuo* to give a cream coloured residue. Flash chromatography on alumina (eluant 80:20 light petroleum:ether then 100 % ethyl acetate) gave the *title compound* as a slightly yellow, viscous liquid (133 mg, 55 %).

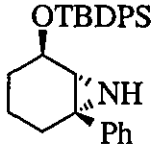
υ_{max}/cm^{-1} (neat) 3275 (NH), 2937 (CH_2), 1495, 1453, 1072 (C-O), 735 (Ar), 697 (Ar);

δ_H (250 MHz; $CDCl_3$) 7.32 (10 H, m, Ar-H), 4.66 (2 H, s, **CH_2**Ph), 3.76 (1 H, dd, J = 8 and 6 Hz, 5-CH), 2.55 (1 H, br s, 6-CH), 2.19 (1 H, dt, J = 12 and 4 Hz, 2-CH), 1.95 (2 H, m, 4-CH and 2-CH), 1.60 (1 H, m, 3-CH), 1.36 (2 H, m, 3-CH and 4-CH);

δ_C (62.9 MHz, $CDCl_3$) 144.5 (Ar-C), 138.7 (Ar-C), 128.5 (Ar-CH), 128.4 (Ar-CH), 127.6 (Ar-CH), 127.1 (Ar-CH), 127.0 (Ar-CH), 126.4 (Ar-CH), 75.1 (1-CH), 70.9 (**CH_2**Ph), 42.7 (C), 41.7 (2-CH), 30.6 (CH_2), 28.0 (CH_2), 16.6 (CH_2);

m/z (C.I., ammonia) 280.1701(MH^+, 100 %, $C_{19}H_{21}NOH^+$ requires MH^+, 280.1701), 172 (M^+-BnOH, 23), 157 (20).

Preparation of *5-(tert-Butyldiphenylsilyloxy)-1-phenyl-7-azabicyclo[4.1.0]heptane* (358).

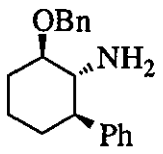


A solution of 3-azido-1-(*tert*-butyldiphenylsilyloxy)-3-phenylcyclohexan-2-ol (**354**) (0.21 g, 0.5 mmol) and triphenylphosphine (0.24 g, 0.9 mmol) in acetonitrile (10 ml) was stirred at room temperature for approximately 4 days. The solution was then refluxed for 3 hours after which evaporation *in vacuo* afforded a clear yellow viscous liquid. Flash chromatography on basified silica (eluant 80:20 light petroleum:ethyl acetate) afforded the *title compound* as a clear colourless liquid (0.12 g, 64 %).

υ_{max}/cm^{-1} (neat) 3297 (NH), 1428, 1390, 1361, 1111 (Si-O), 1079 (C-O), 821 (Si-O), 740 (Ar), 701 (Ar);

δ_H (250 MHz; $CDCl_3$) 7.79 (4 H, m, Ar-H), 7.46 (11 H, m, Ar-H), 4.20 (1 H, m, 5-CH), 2.52 (1 H, br s, 6-CH), 2.17 (1 H, dt, J = 9 and 5 Hz, 2-CH), 2.02 (1 H, m, 2-CH), 1.72 (1 H, m, 4-CH), 1.67 (1 H, m, 3-CH), 1.43 (1 H, m, 4-CH), 1.31 (1 H, m, 3-CH), 1.11 (9 H, s, Bu^t);
δ_C (100 MHz, $CDCl_3$) 145.6 (Ar-C), 136.2 (Ar-CH), 134.7 (Ar-C), 130.1 (Ar-CH), 128.9 (Ar-CH), 128.1 (Ar-CH), 128.0 (Ar-CH), 126.8 (Ar-CH), 69.7 (5-CH), 44.3 (6-CH), 43.0 (C), 30.9 (2-CH_2), 30.8 (4-CH_2), 27.5 (CH_3), 19.7 (C), 16.8 (3-CH_2);
m/z (C. I., ammonia) 428.2410(MH^+, 5 %, $C_{28}H_{33}NOSiH^+$ requires MH^+, 428.2410), 370 (M^+-Bu^t), 199 (23), 198 (19), 172 (M^+-OTBDPS, 10), 145 (100).

Preparation of *1-(Benzyloxy)-3-phenylcyclohexan-2-amine* (359).



Procedure a : Pd/C reduction.

5-(Benzyloxy)-1-phenyl-7-azabicyclo[4.1.0]heptane (**357**) (92.0 mg, 0.3 mmol) was added to ethanol (5 ml) containing 10 % palladium on carbon (24.5 mg). The resulting solution was then placed under an atmosphere of hydrogen with vigorous stirring. After approximately 24 hours further 10 % palladium on carbon (39.0 mg) was added. After approximately 19 hours the reaction mixture was filtered through celite, and the filtrate was evaporated *in vacuo* to give a cloudy liquid (87.2 mg, 73 % pure as estimated from NMR analysis of the crude material). For purification see (**361**).

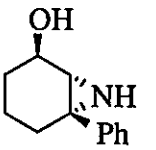
Procedure b : Transfer hydrogenation

1,4-cyclohexadiene (0.30 g, 3.7 mmol) was added to a solution of 5-(benzyloxy)-1-phenyl-7-azabicyclo[4.1.0]heptane (**357**) (50.0 mg, 0.1 mmol), 10 % palladium on carbon (91.3 mg) in ethanol (3 ml). Nitrogen was bubbled through the solution for 24 hours. Ethanol (10 ml) was then added and the solution was filtered through celite. The solution was evaporated *in vacuo* to give a cloudy grey residue (31.8 mg). NMR analysis of the crude material showed a complex mixture containing 1-(benzyloxy)-3-phenylcyclohexan-2-amine:starting material, in the ratio 3:2 (estimated 36 % yield from NMR analysis).

A tentative assignment of the *title compound* is as follows:
υ_{max}/cm^{-1} (neat) 3375 (NH), 3325 (NH), 1601, 1495, 1453, 1203, 1071 (C-O), 733 (Ar), 699 (Ar);

δ_H (250 MHz; $CDCl_3$) 7.29 (10 H, m, Ar-H), 4.72 (1 H, d, J = 11 Hz, $\mathbf{CH_2}$Ph), 4.52 (1H, d, J = 11 Hz, $\mathbf{CH_2}$Ph), 3.31 (1 H, m, 1-CH), 3.01 (1 H, m, 2-CH), 2.60 (1 H, m, 3-CH), 2.25 (1 H, m, CH), 1.78 (5 H, m, 2 x CH_2 and CH);
δ_C (62.9 MHz; $CDCl_3$) 143.3 (Ar-C), 138.8 (Ar-C), 128.6 (Ar-CH), 128.4 (Ar-CH), 127.7 (Ar-CH), 127.6 (Ar-CH), 127.5 (Ar-CH), 126.6 (Ar-CH), 83.7 (CH), 71.2 ($\mathbf{CH_2}$Ph), 59.1 (CH), 50.5 (CH), 33.4 (CH_2), 29.8 (CH_2), 24.0 (CH_2).

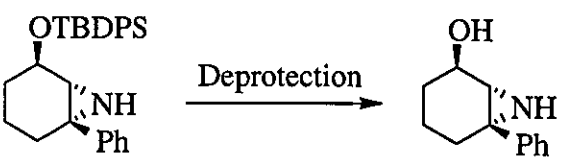
Preparation of *1-Phenyl-7-azabicyclo[4.1.0]heptan-5-ol* (360).



A solution of 3-azido-3-phenylcyclohexan-1,2-diol (**364**) (0.20 mg, 0.8 mmol) and triphenylphosphine (0.45 g, 1.7 mmol) in anhydrous acetonitrile (10 ml) was stirred at room temperature for 5 days. The solution was then refluxed for 4 hours after which the acetonitrile was evaporated *in vacuo* to give a brown viscous liquid. Purification by flash chromatography on basified silica (eluant 95:5 ethyl acetate:light petroleum) gave the *title compound* as a clear colourless liquid (52.6 mg; 40 %).
υ_{max}/cm^{-1} (neat) 3289 (OH, NH), 2939 (CH_2), 1603, 1498, 1447, 1337 (O-H), 1156 (C-O), 1048, 761 (Ph), 700 (Ph);
δ_H (400 MHz; $CDCl_3$) 7.30 (4 H, m, Ph-H), 7.21 (1 H, m, Ph-H), 4.00 (1 H, dd, J = 8.5 and 6 Hz, 5-CH), 2.40 (1 H, br s, 6-CH), 2.14 (1 H, dt, J = 14 and 4.5 Hz, 2-CH), 1.92 (2 H, m, 4-CH and 2-CH), 1.57 (1 H, m, 3-CH), 1.29 (1 H, m, 3-CH), 1.22 (1 H, m, 4-CH);
δ_C (100 MHz; $CDCl_3$) 144.9 (Ar-C), 128.9 (Ar-CH), 127.5 (Ar-CH), 126.8 (Ar-CH), 67.8 (5-CH), 44.4 (6-CH), 43.4 (C), 31.1 (4-CH_2), 30.9 (2-CH_2), 16.9 (3-CH_2);
m/z (C. I., ammonia) 190.1232(MH^+, 18 %, $C_{12}H_{15}NOH^+$ requires MH^+, 190.1232), 189 (M^+, 12), 188 (M^+-H, 20), 172 (M^+-OH, 63), 144 (60), 132(100), 119 (46), 91 (35), 77 (43).

Also isolated from the reaction mixture was a clear colourless oil, which was characterised as (**368**) (31.9 mg; 24 %).

Deprotection of *5-(tert-Butyldiphenylsilyloxy)-1-phenyl-7-azabicyclo[4.1.0]heptane*



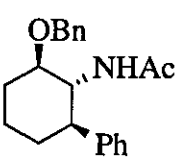
Method a: TBAF removal.

Tetrabutylammonium fluoride (120 µl, 1 M solution in THF, 0.1 mmol) was added to 5-(*tert*-butyldiphenylsilyloxy)-1-phenyl-7-azabicyclo[4.1.0]heptane **(358)** (34.0 mg, 0.08 mmol). THF (0.4 ml) was added and the solution was stirred at room temperature for 24 hours. DCM (20 ml) was added and the solution washed with saturated brine (3 x 15 ml). The organic layer was dried over magnesium sulfate and evaporated *in vacuo* to give an orange/yellow residue (60.1 mg). NMR analysis of the crude material showed the presence of **(360)** in about 31 % yield. (Crude consisted mostly of tributylamine, 83 %).

Method b: NaH/DMPU removal.

Sodium hydride (48.4 mg, 60 % dispersion in mineral oil, 2.0 mmol) was pre-washed, with petrol (approximately 3 x 5 ml). 1,3-dimethyl-3,4,5-tetrahydro-2-(1*H*)-pyrimidinone (5 ml) was added to 5-(*tert*-butyldiphenysilyloxy)-1-phenyl-7-azabicyclo[4.1.0]heptane **(358)** (90.0 mg, 0.02 mmol). The resulting mixture was cooled to 0°C, and added to the washed sodium hydride. The solution was left stirring at room temperature for 3 days, after which it was quenched with water, DCM (25 ml) was added and washed with saturated brine (3 x 25 ml). The solution was dried over magnesium sulfate and evaporation *in vacuo* afforded a large quantity of liquid. Ethyl acetate (20 ml) was added and the solution was washed with water (3 x 20 ml), dried over magnesium sulfate and evaporated *in vacuo* to yield a yellow liquid (46.1 mg). NMR analysis of the crude material showed the presence of **(360)** in approximately 33 % yield.

Preparation of *2-(Acetylamino)-1-(benzyloxy)-3-phenylcyclohexane* (361).



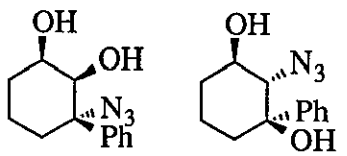
Acetic anhydride (1 ml, 10.6 mmol) was added to a mixture of 1-(benzyloxy)-3-phenylcyclohexan-2-amine **(359)** (52.7 mg, 0.2 mmol) in pyridine (1 ml). The mixture was left at room temperature for 12 hours and then evaporated *in vacuo* to give the *title compound* as a dark brown semi-solid (55.4 mg, 91 %, estimated from NMR analysis). Attempted purification by flash chromatography (eluant 2.5% ether in light petroleum) destroyed the compound. A tentative assignment is as follows:

υ_{max}/cm^{-1}(DCM slurry) 3284 (NH), 1650 (C=O), 1553, 1096 (C-O), 754 (Ar), 698 (Ar);

δ_H (400 MHz; $CDCl_3$) 7.29 (10 H, m, Ar-H), 5.07 (1 H, br d, J = 8.5 Hz, NHAc), 4.69 (1 H, d, J = 12 Hz, CH_2Ph), 4.47 (1 H, d, J = 12 Hz, CH_2Ph), 3.91 (1 H, m, 2-CH), 3.53 (1 H, m, 1-CH), 2.75 (1 H, dt, J = 12 and 3.5 Hz, 3-CH), 2.26 (1 H, m, 6-CH), 1.67 (3 H, s, CH_3), 1.49 (3 H, m, 4-CH, 5-CH and 6-CH);

δ_C (100 MHz, $CDCl_3$) 169.5 (C=O), 142.6 (Ar-C), 138.8 (Ar-C), 128.1 (Ar-CH), 128.0 (Ar-CH), 127.4 (Ar-CH), 127.2 (Ar-CH), 126.2 (Ar-CH), 125.9 (Ar-CH), 79.7 (CH), 70.4 (CH_2), 57.7 (CH), 48.5 (CH), 34.3 (CH_2), 30.9 (CH_2) , 23.6 (CH_2), 23.1 (CH_3).

Preparation of *3-Azido-3-phenylcyclohexan-1,2-diol* (364) and *2-Azido-3-phenylcyclo hexan-1,3-diol* (365).



364 **365**

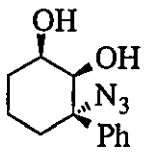
Method a: DMSO as solvent

Sodium azide (1.9 g, 29.8 mmol) was added to a solution of 2,3-epoxy-3-phenylcyclohexanol (**338**) (0.50 g, 2.6 mmol) in DMSO (35 ml). Concentrated sulfuric acid (0.2 ml, 3.7 mmol) was then added and the solution heated to approximately 78°C for 24 hours. The solution was then cooled and sodium nitrite solution (50 ml, 20 % w/v) and saturated brine (50 ml) were then added. The resulting mixture was extracted using DCM (4 x 20 ml). The combined extracts were dried over magnesium sulfate and evaporated *in vacuo* to give a crude brown mixture (0.48 g). Purification using flash chromatography (eluant 60:40 ethyl acetate:light petroleum) gave (**364**) as a yellow oil (0.24 g, 46 %) and (**365**) as a yellow crystalline solid (0.20 g, 32 %). These have been characterised separately.

Method b: 8:1 MeOH:water as solvent.

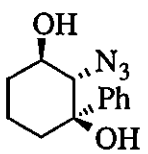
A solution of 2,3-epoxy-3-phenylcyclohexanol (**338**) (1.9 g, 10.0 mmol), sodium azide (3.08 g, 47.0 mmol) and ammonium chloride (1.07 g, 20.0 mmol) in 8:1 methanol:water (24 ml) was heated to approximately 70°C for 18 hours. After cooling sodium nitrite solution (25 ml, 20% w/v) and saturated brine (20 ml) were added and the solution extracted with ethyl acetate (4 x 20 ml). The combined extracts were washed with saturated brine (3 x 20 ml), dried over magnesium sulfate and evaporated *in vacuo* to give the *title compound* as a brown viscous liquid (2.2 g, 94 %). NMR analysis of the crude material showed this to be virtually pure.

Spectroscopic Data for *3-Azido-3-phenylcyclohexan-1,2-diol* (364).



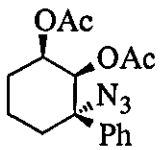
m.p. 89-91°C (solidified on cooling to give a yellow/orange solid);
Found C, 61.49; H, 6.32; N, 17.95. $C_{12}H_{15}N_3O_2$ requires C, 61.79; H, 6.48; N, 18.01.
υ_{max}/cm^{-1} (neat) 3395 (OH), 2942 (CH_2), 2098 (N_3), 1494, 1447, 1255 (O-H), 1060 (O-H), 738 (Ph), 701 (Ph);
δ_H (250 MHz; $CDCl_3$) 7.43 (5 H, m, Ph), 3.91 (1 H, m, 1-CH), 3.73 (1 H, br s, 2-CH), 2.54 (1 H, br s, OH), 2.39 (1 H, br s, OH), 2.24 (1 H, dt, J = 13 and 4.5 Hz, 4-CH), 1.89 (1H, m, 4-CH), 1.71 (3 H, m, 5-CH_2 and 6-CH), 1.54 (1 H, m, 6-CH);
δ_C (62.9 MHz, $CDCl_3$) 140.7 (Ar-C), 128.8 (Ar-CH), 128.2 (Ar-CH), 126.5 (Ar-CH), 74.2 (CH), 69.7 (C), 68.6 (CH), 27.4 (CH_2), 25.9 (CH_2), 19.3 (CH_2);
m/z (C. I., ammonia) 251.1508(MNH_4^+, 62 %, $C_{12}H_{15}N_3O_2NH_4^+$ requires MNH_4^+, 251.1508) and 208 (100), 192 (37), 190 (57), 188 (59), 172 (82), 157 (8), 52 (28).
(Ref **373** for X-ray structure).

Spectroscopic data for *2-Azido-3-phenylcyclohexan-1,3-diol* (365).



Recrystallised from DCM/light petroleum to give a white solid. m.p. 73-75°C;
Found C, 61.89; H, 6.37; N, 17.95. $C_{12}H_{15}O_2N_3$ requires C, 61.79; H, 6.48; N, 18.01.
υ_{max}/cm^{-1} (DCM slurry) 3333 (OH), 2109 (N_3), 1494, 1447, 1259 (O-H), 1109 (C-O), 960, 761 (Ph), 699 (Ph);
δ_H (250 MHz; $CDCl_3$) 7.55 (2 H, d, J = 7.5 Hz, Ph-H), 7.34 (3 H, m, Ph-H), 4.04 (1 H, d, J = 6 Hz, 1-OH), 3.99 (1 H, br s, 1-CH), 3.90 (1 H, br s, 2-OH), 3.40 (1 H, br s, 2-CH), 2.36 (1 H, dt, J = 13 and 4 Hz, 4-CH), 1.99 (1 H, m, 4-CH), 1.74 (3 H, m, 5-CH and 6-CH_2), 1.55 (1 H, m, 5-CH);
δ_C (100 MHz; $CDCl_3$) 144.9 (Ar-C), 128.8 (Ar-CH), 128.5 (Ar-CH), 126.5 (Ar-CH), 76.3 (C), 70.7 (1-CH), 68.3 (2-CH), 31.9 (5-CH_2), 28.0 (6-CH_2), 15.8 (4-CH_2).
m/z (C. I., ammonia) 251.1508(MNH_4^+, 14 %, $C_{12}H_{15}O_2N_3NH_4^+$ requires MNH_4^+, 251.1508), 233(M^+, 30), 208 (MNH_4^+-AcO, 52), 190 (55), 172 (45), 157 (40), 58 (83), 44 (100).
(Ref. **375** for X-ray structure).

Preparation of *1,2-di(Acetoxy)-3-azido-3-phenylcyclohexane* (366).



Acetic anhydride (0.2 ml, 2.1 mmol) was added to 3-azido-3-phenylcyclohexan-1,2-diol **(364)** (26 mg, 0.1 mmol) in pyridine (1 ml) and left at room temperature for 3 days. The resulting mixture was then evaporated *in vacuo* to give the *title compound* as a yellow oil (35.2 mg, 99 %).

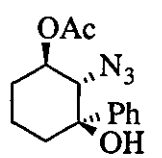
υ_{max}/cm^{-1}(neat) 2101 (N_3), 1749 (C=O), 1245 (C-O), 733 (Ph), 703 (Ph);

δ_H (400 MHz; $CDCl_3$) 7.38 (5 H, m, Ph), 5.38 (1 H, br s, 2-CH), 5.30 (1 H, m, 1-CH), 2.33 (1 H, dq, J = 17.5 and 5.5 Hz, 4-CH), 2.10 (1 H, m, 4-CH), 1.97 (3 H, s, CH_3), 1.91 (2 H, m, 5-CH_2), 1.83 (2 H, m, 6-CH_2), 1.77 (3 H, s, CH_3);

δ_C (100 MHz; $CDCl_3$) 169.7 (C=O), 168.6 (C=O), 138.9 (Ar-C), 128.3 (Ar-CH), 128.1(Ar-CH), 126.2 (Ar-CH), 71.6 (CH), 69.5 (CH), 68.1 (C), 26.9 (CH_2), 24.4 (CH_2), 20.6 (CH_3), 20.0 (CH_3), 18.9 (CH_2);

m/z (C. I., ammonia) 335.1719(MNH_4^+, 97 %, $C_{16}H_{19}N_3O_4NH_4^+$ requires MNH_4^+, 335.1719) and 275 (100), 230 (15), 215 (30), 188 (35), 187 (48), 43 (28).

Preparation of *1-(Acetoxy)-2-azido-3-phenylcyclohexan-3-ol* (367).



Acetic anhydride (0.35 ml, 3.7 mmol) was added to 2-azido-3-phenylcyclohexan-1,3-diol **(365)** (24 mg, 0.1 mmol) in pyridine (1 ml) and left at room temperature for 24 hours. The resulting mixture was then evaporated *in vacuo,* to give the *title compound* as a yellow oil (32.4 mg, 99 %).

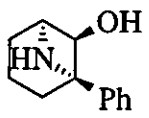
υ_{max}/cm^{-1} (neat) 3449 (OH), 2108 (N_3), 1741 (C=O), 1239 (C-O), 765 (Ph), 701(Ph);

δ_H (400 MHz; $CDCl_3$) 7.59 (2 H, m, Ph-H), 7.34 (3 H, m, Ph-H), 5.30 (1 H, m, 1-CH), 3.77 (1 H, d, J = 7 Hz, 2-CH), 3.07 (1 H, s, OH), 2.35 (1 H, dq, J = 13 and 2.5 Hz, 4-CH), 2.16 (3 H, s, CH_3), 1.98 (1 H, m, 4-CH), 1.78 (2 H, m, 5-CH_2), 1.62 (1 H, m, 6-CH), 1.36 (1 H, m, 6-CH);

δ_C (100 MHz; $CDCl_3$) 170.1 (C=O), 143.1 (Ar-C), 128.7 (Ar-CH), 128.3 (Ar-CH), 127.3 (Ar-CH), 76.3 (C), 73.2 (CH), 70.4 (CH), 35.9 (CH_2), 28.3 (CH_2), 21.6 (CH_3), 17.9 (CH_2);

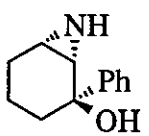
m/z (C.I., ammonia) 293.1614(MNH_4^+, 10 %, $C_{14}H_{17}N_3O_3NH_4^+$ requires MNH_4^+, 293.1614), 258 (M-OH, 10), 190 (23), 157 (37), 58 (80), 44 (100).

Spectroscopic Data for *1-Phenyl-7-azabicyclo[3.1.1]hexan-6-ol* (368).



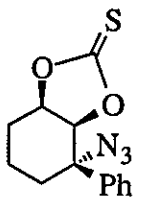
υ_{max}/cm^{-1} (neat) 3360 (OH and NH), 2939, (CH_2), 1600, 1497, 1446, 1364, 1122, 1065 (C-O), 997, 764, 731 (Ph), 699 (Ph);
δ_H (400 MHz; $CDCl_3$) 7.49 (2 H, m, Ph-H), 7.35 (2 H, m, Ph-H), 7.25 (1 H, m, Ph), 4.03 (1 H, m , 5-CH), 3.80 (1 H, d, J = 2.5 Hz, 6-CH), 2.27 (1 H, m, 2-CH), 1.75 (2 H, m, 3-CH and 4-CH), 1.67 (1 H, dt, J = 13 and 3.5 Hz, 2-CH), 1.57 (2 H, m, 3-CH and 4-CH);
δ_C (100 MHz; $CDCl_3$) 147.6 (Ar-C), 129.9 (Ar-CH), 127.5 (Ar-CH), 126.1 (Ar-CH), 76.9 (6-CH), 69.1 (5-CH), 58.5 (C), 30.1 (3-CH_2), 28.4 (2-CH_2), 19.5 (4-CH_2);
m/z (E.I.) 189.1154(M^+, 5 %, $C_{12}H_{15}NO$ requires M^+, 189.1154), 132(100), 171 (M-H_2O, 13), 119 (53), 104 (60), 91 (38), 77 (42).

Preparation of *2-Phenyl-7-azabicyclo[4.1.0]heptan-2-ol* (372).



A solution of 2-azido-3-phenylcyclohexan-1,3-diol (**365**) (0.16 g, 0.7 mmol) and triphenylphosphine (0.22 g, 0.8 mmol) in acetonitrile (15 ml) was stirred at room temperature for 24 hours. The solution was then refluxed for 5 hours after which it was evaporated *in vacuo* to yield a brown viscous liquid (0.36 g). Attempted purification using flash chromatography on basified silica (eluant 80:20 ethyl acetate:light petroleum, ethyl acetate and 90:10 ethyl acetate:methanol) gave a clear colourless oil (0.21 g, 65 % estimated from NMR analysis of the crude product). Further purification using alumina (eluant 50:50 ethyl acetate:light petroleum, ethyl acetate and 6% methanol in ethyl acetate) caused the decomposition of the compound. A tentative assignment is as follows
υ_{max}/cm^{-1} (neat) 3301 (OH, NH), 2936 (CH_2), 1591, 1484, 1438, 1312 (O-H), 1183 (C-O), 758 (Ph), 696 (Ph);
δ_H (400 MHz; $CDCl_3$) 7.31 (5 H, m Ph), 2.85 (1 H, br s, OH), 2.33 (1 H, t, J = 6 Hz, 3-CH), 2.28 (1 H, d, J = 6 Hz, 1-CH), 1.96 (1 H, m, 3-CH), 1.84 (2 H, m, 6-CH and 5-CH), 1.79 (1 H, m, 5-CH), 1.71 (1 H, m, 4-CH), 1.40 (1 H, m, 4-CH);
δ_C (100 MHz; $CDCl_3$) 148.5 (Ar-C), 128.9 (Ar-CH), 128.4 (Ar-CH), 125.7 (Ar-CH), 72.5 (C), 39.5 (CH), 33.7 (CH_2), 30.4 (CH), 22.9 (CH_2), 17.4 (CH_2).

Preparation of *2-Azido-7,9-dioxa-2-phenylbicyclo[4.3.0]nona-8-thione* (373).



A solution of 3-azido-3-phenylcyclohexan-1,2-diol (**364**) (0.10 g, 0.5 mmol) and 1,1'-thiocarbonyldiimidazole (91.0 mg, 0.5 mmol) in DCM (5 ml) was refluxed for 24 hours. The solution was then evaporated *in vacuo* to give a clear yellow viscous liquid (0.22 g). Flash chromatography (eluant 60:40 ethyl acetate:light petroleum) afforded the *title compound* as a clear yellow viscous liquid (0.13 g, 99 %) (solidified on cooling). Recrystallised using DCM/light petroleum to give a white crystalline solid. m.p. 89-90°C.

Found C, 56.87; H, 4.72; N, 15.05. $C_{13}H_{13}N_3O_2S$ requires C, 56.71; H, 4.76; N, 15.26.

υ_{max}/cm^{-1} (DCM slurry) 2953 (CH_2), 2109 (N_3), 1584, 1496, 1448, 1313, 1280 (C-O), 1170, 769 (Ph), 700 (Ph);

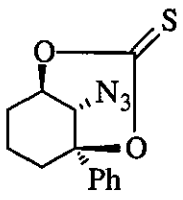
δ_H (400 MHz; $CDCl_3$) 7.46 (5 H, m, Ph), 5.09 (1 H, dt, J = 13 and 6 Hz, 6-CH), 4.74 (1 H, dd, J = 6 and 1 Hz, 1-CH), 2.29 (3 H, m, 5-CH and 3-CH_2), 1.85 (2 H, m, 4-CH_2), 1.67 (1 H, m, 5-CH);

δ_C (100 MHz; $CDCl_3$) 190.9 (C=S), 137.9 (Ar-C), 129.1 (Ar-CH), 129.0 (Ar-CH), 126.2 (Ar-CH), 82.4 (1-CH), 80.0 (6-CH), 65.8 (C), 26.6 (3-CH_2), 25.2 (5-CH_2), 16.0 (4-CH_2).

m/z (C. I., ammonia) 276.0807(MH^+, 90 %, $C_{13}H_{13}N_3O_2SH^+$ requires MH^+, 276.0807), 188 (100, MH^+), 172 (70), 170 (70), 157 (52), 143 (43).

See Appendix for X-ray structure.

Preparation of *9-Azido-6,8-dioxa-1-phenylbicyclo[3.3.1]nona-8-thione* (375)



A solution of 2-azido-3-phenylcyclohexan-1,3-diol (**365**) (0.11 g, 0.5 mmol) and 1,1'-thiocarbonyldiimidazole (0.11 g, 0.6 mmol) in DCM (5 ml) was refluxed for 20 hours. Evaporation *in vacuo* then afforded a light yellow paste (0.21 g). Flash chromatography (eluant 60:40 ethyl acetate:light petroleum) afforded the *title compound* as a cream coloured powder (64.0 mg, 51 %). Recrystallisation using DCM/light petroleum gave white crystals. m.p. 151-153°C.

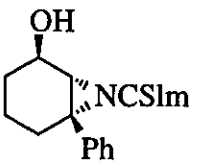
Found C, 56.56; H, 4.66; N, 15.13. $C_{13}H_{13}N_3O_2S$ requires C, 56.71; H, 4.76; N, 15.26.
υ_{max}/cm^{-1} (DCM slurry) 2956 (CH_2), 2115 (N_3), 1496, 1464, 1448, 1271 (C=S), 1219 (C-O), 763 (Ph), 702 (Ph);
δ_H (400 MHz; $CDCl_3$) 7.46 (5 H, m, Ph), 4.80 (1 H, m, 5-CH), 4.06 (1 H, d, J = 4 Hz, 9-CH), 2.62 (1 H, dq, J = 16 and 5.5 Hz, 2-CH), 2.19 (1 H, m, 2-CH), 2.15 (1 H, m, 4-CH), 1.98 (1 H, m, 4-CH), 1.85 (2 H, m, 3-CH_2);
δ_C (100 MHz; $CDCl_3$) 189.7 (C=S), 139.0 (Ar-C), 130.0 (Ar-CH), 129.4 (Ar-CH), 126.0 (Ar-CH), 87.8 (C), 78.4 (5-CH), 60.5 (9-CH), 29.4 (CH_2), 24.8 (CH_2), 16.7 (CH_2);
m/z (E. I.) 275.0728(M^+, 8 %, $C_{13}H_{13}N_3O_2S$ requires M^+, 275.0728), 198 (M-CO_2SH, 22), 170 (12), 143 (35), 130 (45), 115 (55), 104 (60), 91 (65) and 77 (100).
See Appendix for X-ray structure.

Also isolated was a clear oil (44.0 mg, 28 %) which proved to be **(376)**:

Spectroscopic Data for *2-Azido-1-[imidazol-1-yl(thiocarbonyl)oxy]-3-phenylcyclohexan-3-ol* (376).

υ_{max}/cm^{-1} (neat) 3237 (OH), 2950 (CH_2), 2111 (N_3), 1534, 1468, 1447, 1386 (C=S), 1329 (OH), 1285 (O-H), 1238 (C-O), 1112 (C-O), 732 (Ph), 700 (Ph);
δ_H (400 MHz; $CDCl_3$) 8.41 (1 H, s, Im-H), 7.70 (1 H, s, Im-H), 7.59 (2 H, m, Ph-H), 7.37 (3 H, m, Ph-H), 6.86 (1 H, s, Im-H), 5.84 (1 H, m, 1-CH), 4.03 (1 H, d, J = 5 Hz, 2-CH), 3.47 (1 H, br s, OH), 2.43 (1H, m, 4-CH), 2.02 (2 H, m, 5-CH and 6-CH), 1.90 (2 H, m, 4-CH and 6-CH), 1.56 (1 H, m, 5-CH);
δ_C (100 MHz; $CDCl_3$) 183.4 (C=S), 144.6 (Ar-C), 137.2 (Im-CH), 130.8 (Im-CH), 129.0 (Ar-CH), 128.6 (Ar-CH), 126.8 (Ar-CH), 118.8 (Im-CH), 80.6 (1-CH), 75.3 (C), 67.6 (2-CH), 33.9 (CH_2), 26.3 (CH_2), 17.4 (CH_2).
m/z (C. I., ammonia) 344.1181(MH^+, 100 %, $C_{16}H_{17}N_5O_2SH^+$ requires MH^+, 344.1181), 190 (16), 157 (56), 69 (87).

Preparation of *N-[Imidazol-1-yl(thiocarbonyl)]-1-phenyl-7-azabicyclo[4.1.0]heptan-5-ol* (377).



A solution of 1,1'-thiocarbonyldiimidazole (73.0 mg; 0.4 mmol) and 1-phenyl-7-azabicyclo[4.1.0]heptan-5-ol (**360**) (69.1 mg, 0.4 mmol) in DCM (10 ml) was refluxed for 3 hours. Evaporation *in vacuo* yielded a yellow semi-solid (0.14 mg). Flash chromatography on alumina (eluant ethyl acetate then 80:20 ethyl acetate:light petroleum) afforded a yellow viscous oil (12.4 mg, 15 %) which proved to be compound (**378**) and a cloudy yellow viscous liquid (82.5 mg). Repeated flash chromatography on the latter fraction, using alumina (eluant 95:5 ethyl acetate:methanol) afforded the *title compound* as a clear, colourless oil (15.8 mg, 15 %).

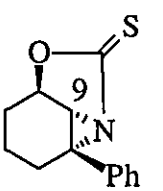
υ_{max}/cm^{-1} (neat) 3133 (OH), 2938 (CH_2), 1613, 1481, 1383, 1312, 1236, 756 (Ph), 733 (Ph);

δ_H (400 MHz; $CDCl_3$) 7.98 (1 H, br s, Im-H), 7.51 (2 H, d, J = 8 Hz, Ph-H), 7.40 (1 H, d, J = 1 Hz, Im-H), 7.34 (2 H, m, Ph-H), 7.26 (1 H, m, Ph-H), 7.05 (1 H, br s, Im-H), 4.62 (1 H, d, J = 7.5 Hz, 6-CH), 3.88 (1 H, m, 5-CH), 3.60 (1 H, br s, OH), 2.55 (1 H, m, 2-CH), 2.07 (1 H, m, 4-CH), 1.95 (1 H, m, 2-CH), 1.87 (2 H, m, 3-CH_2), 1.47 (1 H, m, 4-CH);

δ_C (100 MHz; $CDCl_3$) 154.5 (C=S), 145.1 (Ar-C), 136.9 (Im-CH), 130.9 (Im-CH), 129.0 (Ar-CH), 128.2 (Ar-CH), 125.8 (Ar-CH), 118.2 (Im-CH), 80.7 (CH), 73.8 (CH), 72.4 (C), 35.5 (CH_2), 31.0 (CH_2), 20.8 (CH_2).

m/z (E.I.) 299.1092(M^+, 30 %, $C_{16}H_{17}N_3OS$ requires M^+, 299.1092), 228 (100), 140 (38), 128 (50), 115 (50), 91 (56), 77 (33), 69 (65).

Spectroscopic Data for *6-Oxa-1-phenyl-8-azatricyclo[3.3.1.0]nona-7-thione* (378).

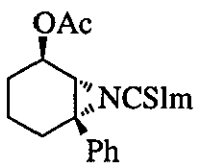


υ_{max}/cm^{-1} (neat) 2957 (CH_2), 1494, 1462, 1360, 1262, 1222, 1183, 1119 (C-O), 1095, 755 (Ph), 697 (Ph);

δ_H (400 MHz; $CDCl_3$) 7.60 (2 H, m, Ph-H), 7.38 (3 H, m, Ph-H), 4.26 (1 H, d, J = 12.5 Hz, 9-CH), 4.03 (1 H, dt, J = 12.5 and 4 Hz, 5-CH), 3.05 (1 H, dt, J = 14.5 and 3 Hz, 2-CH), 2.29

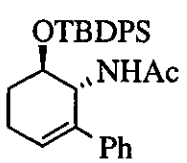
(1 H, m, 4-CH), 2.16 (1 H, dt, J = 14.5 and 5 Hz, 2-CH), 2.05 (1 H, m, 3-CH), 1.87 (1 H, m, 4-CH), 1.70 (1 H, m, 3-CH);
δ_C (100 MHz; $CDCl_3$) 191.4 (C=S), 136.7 (Ar-C), 128.7 (Ar-CH), 128.5 (Ar-CH), 127.8 (Ar-CH), 82.4 (CH), 73.7 (CH), 68.1 (C), 39.4 (CH_2), 28.7 (CH_2), 22.2 (CH_2);
m/z (E.I.) 231.0718(M^+, 11 %, $C_{13}H_{13}NOS$ requires M^+, 231.0718), 187 (M^+-C=S, 20), 172 (M-COS and H, 67), 154 (68), 129 (79), 128 (100), 115 (91), 91 (96), 77 (72).

Preparation of *N-[Imidazol-1-yl(thiocarbonyl)]-5-(acetoxy)-1-phenyl-7-azabicyclo[4.1.0] heptane* (379).



Acetic anhydride (0.2 ml, 2.1 mmol) was added to a mixture of *N*-[imidazol-1-yl(thiocarbonyl)]-1-phenyl-7-azabicyclo[4.1.0]heptan-5-ol (**377**) (10.3 mg, 0.03 mmol) in pyridine (1 ml). The resulting solution was then left at room temperature for 72 hours, after which the pyridine was removed *in vacuo* to afford the *title compound* as a yellow oil (11.5 mg, 99 %).
υ_{max}/cm^{-1}(neat) 2948 (CH_2), 1732 (C=O), 1615, 1478, 1384, 1310, 1239 (C-O), 1030, 735 (Ph), 699 (Ph);
δ_H (400 MHz; $CDCl_3$) 7.97 (1 H, br s, Im-H), 7.61 (2 H, m, Ph-H), 7.40 (1 H, d, J = 1 Hz, Im-H), 7.34 (2 H, m, Ph-H), 7.26 (1 H, m, Ph-H), 7.08 (1 H, d, J = 1 Hz, Im-H), 5.26 (1 H, m, 5-CH), 4.83 (1 H, d, J = 6 Hz, 6-CH), 2.40 (2 H, m, 2-CH_2), 2.00 (1 H, m, 4-CH), 1.90 (1 H, m, 3-CH), 1.77 (4 H, s and m, CH_3 and 3-CH), 1.62 (1 H, m, 4-CH);
δ_C (100 MHz; $CDCl_3$) 170.2 (C=O), 154.2 (C=S), 141.6 (Ar-C), 136.6 (Im-CH), 130.5 (Im-CH), 128.5 (Ar-CH), 127.8 (Ar-CH), 126.3 (Ar-CH), 117.9 (Im-CH), 76.8 (CH), 72.9 (CH), 70.3 (C), 34.5 (CH_2), 26.9 (CH_2), 20.8 (CH_3), 19.0 (CH_2),
m/z (C. I., ammonia) 342.1276(MH^+, 12 %, $C_{18}H_{19}N_3O_2SH^+$ requires MH^+, 342.1276), 287 (M-AcOH, 34), 214 (4) and 43 (100).

Preparation of *2-(Acetylamino)-1-(tert-butyldiphenylsilyloxy)-3-phenyl-3-cyclohexene* (380)



Method a-DMAP catalysis.

DCM (5 ml) was added, to a mixture of 5-(*tert*-butyldiphenylsilyloxy)-1-phenyl-7-azabicyclo[4.1.0]heptane **(358)** and 4-dimethylaminopyridine (11.5 mg, 0.09 mmol). Triethylamine (25 µl, 0.2 mmol) was added and the solution cooled in an ice bath. Acetic anhydride (9.5 µl, 0.1 mmol) was added and the solution was left stirring at 0°C for approximately 1 hour. Cooled DCM (20 ml) was added and the solution washed with cooled saturated brine (3 x 20 ml). The organic layer was dried over magnesium sulfate and evaporated *in vacuo* to give a cloudy white residue (44 mg). Flash chromatography using basified silica (eluant 60:40 light petroleum:ethyl acetate) afforded the *title compound* as a clear, slightly yellow liquid (24.0 mg, 58 %). Crystallisation occurred on cooling. Recrystallisation using DCM/light petroleum gave colourless crystals. m.p. 155-156°C

Method b: DCC coupling.

Acetic acid (3 µl, 0.05 mmol) was added to a solution of 5-(*tert*-butyldiphenylsilyloxy)-1-phenyl-7-azabicyclo[4.1.0]heptane **(358)** (24.9 mg, 0.06 mmol) and 1,3-dicyclohexylcarbodiimide (12.2 mg, 0.06 mmol) in DCM (5 ml). The solution was left stirring at room temperature for 1.5 hours afterwhich acetic acid (0.5 µl, 0.008 mmol) was added. The solution was left stirring at room temperature for 18 hours afterwhich DCM (10 ml) was added and the solution was washed with saturated brine (2 x 20 ml). The organic phase was dried over magnesium sulfate and evaporated *in vacuo* to yield a white powdery solid (36.4 mg). Flash chromatography (eluant 70:30 light petroleum:ethyl acetate) failed to separate the components. NMR analysis of the crude material shows an estimated 38 % yield of the *title compound.*

ν_{max}/cm^{-1} (DCM slurry) 3257 (NH), 3069 (Ar), 3052 (Ar), 2997 (Ar), 2930 (CH_2), 1643 (C=O), 1538, 1111 (Si-O), 759 (Ar), 735 (Si-O), 700.4 (Ar);

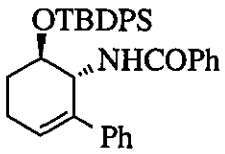
δ_H (400 MHz; $CDCl_3$) 7.71 (4 H, m, Ar-H), 7.33 (11 H, m, Ar-H), 6.34 (1 H, t, J = 4 Hz, 4-CH), 5.14 (1 H, br d, J = 8 Hz, NH), 5.02 (1 H, br d, J = 8 Hz, 2-CH), 4.22 (1 H, m, 1-CH), 2.50 (1 H, m, 5-CH), 2.07 (1 H, m, 5-CH), 1.75 (3 H, s, CH_3), 1.57 (2 H, m, 6-CH_2), 1.07 (9 H, s, Bu^t);

δ_C (100 MHz; $CDCl_3$) 169.3 (C=O), 140.0 (C), 136.4 (Ar-CH), 136.2 (Ar-CH), 134.9 (C), 134.7 (C), 134.4 (C), 130.0 (Ar-CH), 130.0 (Ar-CH), 129.1 (Ar-CH), 128.8 (Ar-CH), 128.0 (3-CH), 127.9 (Ar-CH), 127.6 (Ar-CH), 125.9 (Ar-CH), 70.3 (1-CH), 50.8 (2-CH), 27.3 (CH_3), 25.1 (6-CH_2), 23.6 (CH_3), 22.2 (5-CH_2), 19.8 (C).

m/z (C.I., ammonia) 470.2515 (MH^+, 79 %, $C_{30}H_{35}NO_2SiH^+$ requires MH^+, 470.2515), 412 (MH^+-NHAc,13), 392 (100), 157 (60), 77 (75), 60 (48), 46 (72).

See Appendix for X-ray structure.

Preparation of *2-(Benzoylamino)-1-(tert-butyldiphenylsilyloxy)-3-phenyl-3-cyclohexene* (381).



Sodium hydroxide solution (0.06 M, 2.2 ml, 0.1 mmol) was added to a solution of 5-(*tert*-butyldiphenylsilyloxy)-1-phenyl-7-azabicyclo[4.1.0]heptane **(358)** (28.4 mg, 0.07 mmol) in DCM (0.5 ml). The mixture was then cooled to 2°C. Benzoyl chloride (7.5 µl, 0.06 mmol) was then added and the resulting mixture was allowed to warm to room temperature. DCM (25 ml) was added and the solution washed with saturated brine (2 x 20 ml), dried over magnesium sulfate and evaporated *in vacuo* to give the *title compound* as a clear, slightly yellow liquid which solidified on cooling (30.3 mg, 86 %). Recrystallised using ethyl acetate/light petroleum to give a white solid. m. p. 131-133°C

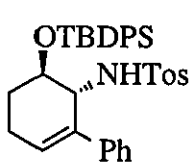
ν_{max}/cm^{-1} (DCM slurry) 3320 (NH), 3069, 3053, 3033, 2999 (CH_2), 2930, 1650 (C=O), 1601, 1580, 1507, 1483, 1112 (Si-O), 760 (Ar), 736 (Si-O), 702 (Ar).

δ_H (400 MHz; $CDCl_3$) 7.72 (4 H, m, Ar-H), 7.30 (16 H, m, Ar-H), 6.39 (1 H, t, J = 6 Hz, 4-CH), 5.72 (1 H, d, J = 8 Hz, NH), 5.25 (1 H, dd, J = 8 and 3 Hz, 2-CH), 4.33 (1 H, m, 1-CH), 2.50 (1 H, m, 5-CH), 2.13 (1 H, dq, J = 19 and 5 Hz, 5-CH), 1.63 (2 H, m, 6-CH_2), 1.09 (9 H, s, Bu^t);

δ_C (100 MHz; $CDCl_3$) 166.6 (C=O), 139.6 (C), 136.0 (Ar-CH), 135.9 (Ar-CH), 134.7 (C), 134.7 (C), 134.5 (C), 134.0 (C), 131.2 (Ar-CH), 129.6 (Ar-CH), 129.6 (Ar-CH), 128.7 (3-CH), 128.5 (Ar-CH), 128.4 (Ar-CH), 127.6 (Ar-CH), 127.6 (Ar-CH), 127.2 (Ar-CH), 126.8 (Ar-CH), 125.6 (Ar-CH), 70.2 (1-CH), 51.0 (2-CH), 27.0 (CH_3), 25.1 (6-CH_2), 22.0 (5-CH_2), 19.4 (C).

m/z (C.I., ammonia) 532.267(MH^+, 29 %, $C_{35}H_{37}NO_2SiH^+$ requires MH^+, 532.2672), 474 (MH^+-Bu^t, 5), 454 (MH^+-PhH, 13), 475 (3), 274 (14), 196 (13), 157 (67), 139 (100), 122 (95), 78 (9), 58 (14), 44 (14).

Preparation of *1-(tert-Butyldiphenylsilyloxy)-2-(tosylamino)-3-phenyl-3-cyclohexene* (382).



p-Toluenesulfonyl chloride (22.6 mg, 0.1 mmol) in DCM (1 ml) was added to a solution of 5-(*tert*-butyldiphenylsilyloxy)-1-phenyl-7-azabicyclo[4.1.0]heptane **(358)** (25.1 mg, 0.06 mmol) and triethylamine (10 µl, 0.07 mmol) in DCM (2 ml). After stirring at room

temperature for 72 hours the solution was refluxed for 18 hours and evaporated off *in vacuo* Flash chromatography on basified silica (eluant 9:1 ethyl acetate:light petroleum, then 8:1 ethyl acetate:light petroleum) gave the *title compound* as a white solid (18.1 mg, 54 %). This was recrystallised using DCM.

m.p. 175-175.9°C

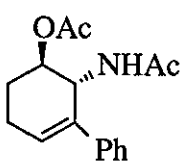
ν_{max}/cm^{-1} (DCM slurry) 3275 (NH), 3070 (Ar), 3051 (Ar), 2930 (CH_2), 1598, 1494, 1472, 1325, 1160, 1112 (Si-O), 813, 758 (Ar), 701 (Ar),

δ_H (400 MHz; $CDCl_3$) 7.67 (4 H, m, Ar-H), 7.46 (2 H, m, Ar-H), 7.39 (4 H, m, Ar-H), 7.11 (3 H, m, Ar-H), 6.96 (4 H, m, Ar-H), 6.81 (2 H, m, Ph), 6.13 (1 H, dd, J = 3 and 2.5 Hz, 4-CH), 4.53 (1 H, m, 1-CH), 4.21 (1 H, d, J = 6 Hz, NH), 3.93 (1 H, m, 2-CH), 2.49 (1 H, m, 5-CH), 2.37 (3 H, s, CH_3), 2.08 (1 H, dt, J = 19 and 5 Hz, 5-CH), 1.75 (1 H, m, 6-CH), 1.60 (1 H, dt, J = 13.5 and 5 Hz, 6-CH), 1.05 (9 H, s, Bu^t);

δ_C (100 MHz; $CDCl_3$) 142.7 (C), 139.7 (C), 136.6 (C), 136.0 (Ar-CH), 135.9 (Ar-CH), 134.4 (C), 134.1 (C), 133.7 (C), 130.8 (3-CH), 129.7 (Ar-CH), 129.7 (Ar-CH), 129.3 (Ar-CH), 128.2 (Ar-CH), 127.7 (Ar-CH), 127.0 (Ar-CH), 126.7 (Ar-CH), 126.0 (Ar-CH), 69.9 (1-CH), 53.8 (2-CH), 27.1 (Bu^t), 22.6 (6-CH_2), 21.5 (CH_3), 21.2 (5-CH_2), 19.4 (C).

m/z (C.I., ammonia) 599.276 (MNH_4^+, 3 %, $C_{35}H_{39}NO_3SiSNH_4^+$ requires MNH_4^+, 599.2763), 504 (M-Ph, 2), 428 (10), 411 (M^+-TosNH, 12), 274 (13), 256 (Bu^tSiPh_2OH, 3), 157 (100), 91 (7), 78 (10).

Preparation of *1-(Acetoxy)-2-(acetylamino)-3-phenyl-3-cyclohexene* (383).



Acetic anhydride (0.35 ml, 3.7 mmol) was added to a solution of 1-phenyl-7-azabicyclo[4.1.0]heptan-5-ol **(360)** (17.5 mg, 0.09 mmol) in pyridine (1 ml). After stirring at room temperature for 5 days the pyridine was removed *in vacuo* to afford a slightly yellow oil (20.9 mg). Purification by flash chromatography on basified silica (eluant 70:30 ethyl acetate:light petroleum) gave the *title compound* as a clear yellow liquid (10.4 mg, 41 %).

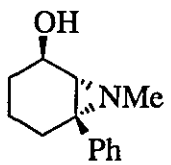
υ_{max}/cm^{-1} (neat) 3277 (NH), 3056 (NH), 1735 (C=O), 1654 (C=O), 1541, 1243 (C-O), 1048, 761 (Ph), 699 (Ph);

δ_H (400 MHz; $CDCl_3$) 7.33 (5 H, m, Ph), 6.26 (1 H, dt, J = 4 and 1 Hz, 4-CH), 5.28 (1 H, br d, J = 9 Hz, NHAc), 5.15 (1 H, m, 2-CH), 5.09 (1 H, m, 1-CH), 2.33 (2 H, m, 5-CH_2), 2.06 (4 H, m and s, CH_3 and 6-CH), 1.86 (1 H, m, 6-CH), 1.81 (3 H, s, CH_3);

δ_C (100 MHz; $CDCl_3$) 171.1 (C=O), 170.0 (C=O), 139.0 (C), 135.8 (C), 129.1 (CH), 128.8 (CH), 127.8 (CH), 126.1 (CH), 72.6 (CH), 49.4 (CH), 24.0 (CH_2), 23.6 (CH_3), 23.0 (CH_2), 21.6 (CH_3).

m/z (C.I., ammonia) 274.1443 (M^+, 1 %, $C_{16}H_{19}NO_3H^+$ requires M^+, 274.1443), 214 (MH^+-AcOH, 12), 157 (MH^+- CH_3CON, 33), 77 (100), 60 (53), 46 (41).

Preparation of *N-Methyl-1-phenyl-7-azabicyclo[4.1.0]heptan-5-ol* (386).



Methyl iodide (32 µl, 0.5 mmol) was added to a solution of 1-phenyl-7-azabicyclo[4.1.0]heptan-5-ol (**360**) (49.5 mg, 0.3 mmol), 18-crown-6 (7.0 mg, 0.03 mmol) and potassium carbonate (43.0 mg, 0.3 mmol) in THF (7 ml). The mixture was then stirred at room temperature for 3 days after which DCM (20 ml) was added and the solution washed with saturated brine (3 x 20 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a clear yellow residue (49.7 mg). Purification by flash chromatography on basified silica (eluant 90:10 ethyl acetate:light petroleum then 90:10 ethyl acetate:methanol) gave the *title compound* as a yellow oil (22.7 mg, 43 %).

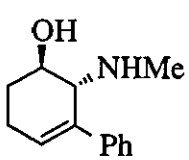
υ_{max}/cm^{-1} (neat) 3357 (OH), 2941 (CH_2), 1602, 1495, 1447, 1273 (OH), 1104, 1067 (C-O), 758 (Ph), 702 (Ph);

δ_H (400 MHz; $CDCl_3$) 7.34 (5 H, m, Ph), 4.11 (1 H, dd, J = 8.5 and 6 Hz, 5-CH), 2.25 (1 H, dt, J = 14 and 5 Hz, 2-CH), 2.04 (1 H, s, Me), 2.00 (1 H, br s, 6-CH), 1.92 (1 H, m, 4-CH), 1.71 (1 H, dq, J = 14 and 5.5 Hz, 2-CH), 1.47 (1 H, m, 3-CH), 1.42 (1 H, m, 3-CH), 1.21 (1 H, m, 4-CH);

δ_C (100 MHz; $CDCl_3$) 139.8 (Ar-C), 129.4 (Ar-CH), 128.2 (Ar-CH), 127.3 (Ar-CH), 67.6 (CH), 50.4 (CH), 48.9 (C), 41.8 (CH_3), 32.6 (CH_2), 31.2 (CH_2), 16.5 (CH_2);

m/z (E.I.) 203.1310(M^+, 24 %, $C_{13}H_{17}NO$ requires M^+, 203.1310), 202 (M^+-H, 38), 186 (M^+-OH, 25), 158 (60), 146 (58), 118 (72), 91 (46), 77 (66) and 42 (100).

Preparation of *2-(Methylamino)-3-phenyl-3-cyclohexen-1-ol* (387).



Iodomethane (150 µl, 2.4 mmol) was added to a solution of 1-phenyl-7-azabicyclo[4.1.0]heptan-5-ol **(360)** (29.0 mg, 0.2 mmol), 18-crown-6 (8.0 mg, 0.03 mmol), potassium carbonate (25.0 mg, 0.02 mmol) in THF (3 ml). The solution was then stirred at room temperature for 48 hours, after which DCM (20 ml) was added. The mixture was washed with saturated brine (3 x 10 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a cloudy yellow liquid (27.8 mg). NMR analysis on the crude material showed compound **(386)** in approximately 21 % yield and also some of the *title compound* in approximately 71 % yield. Flash chromatography (eluant 95:5 ethyl acetate:light petroleum and 90:10 ethyl acetate:methanol) gave the *title compound* as a colourless residue (8.6 mg, 28 %).

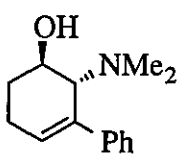
ν_{max}/cm^{-1} (neat) 3346 (OH/NH), 2928 (CH_2), 1597, 1493, 1274 (O-H), 1069 (C-O), 758 (Ph), 700 (Ph),

δ_H (400 MHz; $CDCl_3$) 7.32 (4 H, m, Ph-H), 7.26 (1 H, m, Ph-H), 6.04 (1 H, t, J = 3 Hz, 4-CH), 4.04 (1 H, m, 1-CH), 3.71 (1 H, d, J = 4.5 Hz, 2-CH), 2.79 (2 H, br s, OH and NH), 2.30 (1 H, m, 5-CH), 2.27 (1 H, m, 5-CH), 2.17 (3 H, s, Me), 2.06 (1 H, m, 6-CH), 1.77 (1 H, m, 6-CH);

δ_C (100 MHz; $CDCl_3$) 140.6 (C), 137.7 (C), 130.0 (4-CH), 129.0 (Ar-CH), 127.6 (Ar-CH), 126.6 (Ar-CH), 67.7 (CH), 62.6 (CH), 31.7 (CH_3), 27.5 (CH_2), 23.8 (CH_2)

m/z (E.I) 203.1310 (M^+, 2.5 %, $C_{13}H_{17}NO$ requires M^+, 203.1310), 159 (100), 158 (57), 144 (85), 115 (25), 57 (27).

Preparation of *2-(Dimethylamino)-3-phenyl-3-cyclohexen-1-ol* (388).

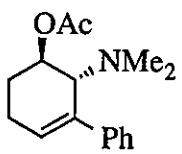


Methyl iodide (4.3 ml, 69.1 mmol) was added to a solution of 1-phenyl-7-azabicyclo[4.1.0]heptan-5-ol **(360)** (7.0 g, 36.9 mmol), 18-crown-6 (2.9 g, 10.8 mmol) and potassium carbonate (6.2 g, 44.9 mmol) in THF (100 ml). After stirring at room temperature for 4 days, the solution was washed with saturated brine (3 x 50 ml) dried over magnesium sulfate and evaporated off *in vacuo* to give a dark brown viscous liquid (4.5 g). Flash chromatography on basified silica, using 1 g of crude (eluant 80:20 ethyl acetate:methanol then 90:10 ethyl acetate:methanol) gave the *title compound* as a yellow solid (0.36 g, 29 %). m.p. 85-87°C.

ν_{max}/cm^{-1} (DCM slurry) 3384 (OH), 2931 (CH_2), 1644, 1598, 1575, 1493, 1444, 1273 (O-H), 1041 (C-O), 874, 755 (Ph), 698 (Ph);

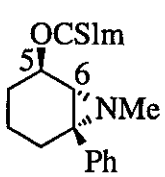
δ_H (400 MHz; $CDCl_3$) 7.30 (4 H, m, Ph-H), 7.23 (1 H, m, Ph-H), 5.90 (1 H, m, 4-CH), 3.94 (1 H, ddd, J = 5.7, 3.8 and 2.1 Hz, 1-CH), 3.59 (1 H, m, 2-CH), 2.78 (1 H, br s, OH), 2.23 (8 H, m and s, 2 x Me and 5-CH_2), 1.97 (1 H, m, 6-CH), 1.75 (1 H, m, 6-CH);
δ_C (100 MHz; $CDCl_3$) 141.8 (C), 137.9 (C), 128.7 (4-CH), 126.7 (Ar-CH), 125.9 (Ar-CH), 125.5 (Ar-CH), 67.1 (2-CH), 66.7 (1-CH), 40.9 (CH_3), 26.8 (6-CH_2), 22.1 (5-CH_2);
m/z (E. I.) 217.1467 (MH^+, 17 %, $C_{14}H_{19}NO$ requires MH^+, 217.1467), 173 (M-$N(CH_3)_2$, 90), 158 (100), 84 (90), 71 (55).

Preparation of *1-(Acetoxy)-2-(dimethylamino)-3-phenyl-3-cyclohexene* (389)



Acetic anhydride (17 µl, 0.2 mmol) was added to a solution of 2-(dimethylamino)-3-phenyl-3-cyclohexen-1-ol (**388**) (25.1 mg, 0.1 mmol) in pyridine (0.2 ml) and left stirring at room temperature for 2 days. Evaporation *in vacuo* gave the *title compound* as a viscous yellow liquid (29 mg, 95 %).
ν_{max}/cm^{-1} (neat) 2934 (CH_2), 1732 (C=O), 1646, 1599, 1494, 1444, 1243 (C-O), 756 (Ph), 697 (Ph),
δ_H (400 MHz; $CDCl_3$) 7.31 (4 H, m, Ph-H), 7.21 (1 H, m, Ph-H), 6.15 (1 H, m, 4-CH), 5.36 (1 H, dd, J = 5 and 4 Hz, 1-CH), 3.70 (1 H, dd, J = 4 and 1.5 Hz, 2-CH), 2.27 (8 H, m and s, 2 x Me and 5-CH_2), 2.05 (3 H, s, Me), 1.87 (2 H, m, 6-CH_2).
δ_C (100 MHz; $CDCl_3$) 170.6 (C=O), 142.1 (C), 137.2 (C), 129.1 (4-CH), 128.0 (Ar-CH), 126.7 (Ar-CH), 126.3 (Ar-CH), 68.8 (2-CH), 62.8 (1-CH), 41.5 (N-CH_3), 25.0 (6-CH_2), 22.1 (5-CH_2), 21.5 (CH_3).
m/z (C.I., ammonia) 260.1650 (MH^+, 28 %, $C_{16}H_{21}NO_2H^+$ requires MH^+, 260.1650), 216 (M^+-NMe_2, 2), 173 (5), 157 (53), 88 (32), 74 (38), 46 (100).

Preparation of *N-Methyl-5-[imidazol-1-yl(thiocarbonyl)oxy]-1-phenyl-7-azabicyclo[4.1.0] heptane* (390).



N-Methyl-1-phenyl-7-azabicyclo[4.1.0]heptan-5-ol (**386**) (17.8 mg, 0.09 mmol) and 1,1'-thiocarbonyldiimidazole (32.1 mg, 0.09 mmol) in DCM (8 ml) was refluxed for 13 hours.

The solution was evaporated off *in vacuo* to yield a yellow cloudy residue (51.0 mg). Flash chromatography on basified silica (eluant 95:5 ethyl acetate:methanol) afforded the *title compound* as a clear, slightly yellow liquid (6.8 mg, 25 %). Also isolated from the reaction mixture was some ringed structure **(391)** as a clear, slightly yellow liquid (9.0 mg, 42 %).

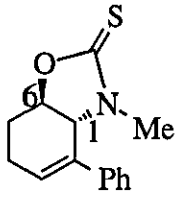
ν_{max}/cm^{-1} (neat) 3056 (Ph), 3024 (Ph), 2943 (CH_2), 1601, 1529, 1386, 1282, 1230, 969, 756 (Ph), 701 (Ph).

δ_H (400 MHz; $CDCl_3$) 8.35 (1 H, s, Im-H), 7.64 (1 H, t, J = 1.5 Hz, Im-H), 7.25 (5 H, m, Ph), 7.00 (1 H, m, Im-H), 5.75 (1 H, m, 5-CH), 2.26 (1 H, dt, J = 14.5 and 5 Hz, 2-CH), 2.10 (1 H, br s, 6-CH), 2.04 (1 H, m, 4-CH), 2.02 (3 H, s, Me), 1.77 (1 H, m, 2-CH), 1.50 (3 H, m, 4-CH and 3-CH_2).

δ_C (100 MHz; $CDCl_3$) 183.9 (C=S), 139.3 (C), 137.2 (Im-CH), 131.2 (Im-CH), 129.5 (Ar-CH), 128.8 (Ar-CH), 128.2 (Ar-CH), 118.4 (Im-CH), 80.3 (5-CH), 49.1 (C), 46.6 (6-CH), 41.8 (CH_3), 32.6 (2-CH_2), 26.6 (5-CH_2), 16.8 (3-CH_2).

m/z (C.I., ammonia) 314.1327(MH^+, 39 % , $C_{17}H_{19}N_3OSH^+$ requires MH^+, 314.1327), 204 (100).

Spectroscopic Data for *N-Methyl-9-aza-7-oxabicyclo[4.3.0]-2-nonen-8-thione* (391).



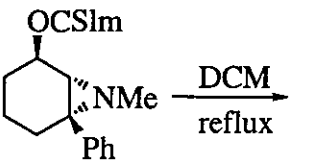
ν_{max}/cm^{-1} (neat) 3077(Ph), 3055(Ph), 3023(Ph), 2918 (CH_2), 1673, 1476, 1382, 1302, 1281, 1189, 1141, 749 (Ph), 702 (Ph).

δ_H (400 MHz; $CDCl_3$) 7.48 (3 H, m, Ph-H), 7.33 (2 H, m, Ph-H), 5.68 (1 H, m, 3-CH), 4.55 (1 H, dq, J = 12.5 and 4 Hz, 6-CH), 4.43 (1 H, m, 1-CH), 2.89 (3 H, s, Me), 2.72 (1 H, m, 4-CH), 2.66 (1 H, m, 5-CH), 2.55 (1 H, m, 4-CH), 2.19 (1 H, m, 5-CH_2).

δ_C (100 MHz; $CDCl_3$) 193.2 (C=S), 138.1 (C), 137.6 (C), 128.9 (CH), 128.7 (CH), 128.4 (CH), 128.1 (CH), 82.8 (CH), 66.4 (CH), 36.5 (CH_3), 25.8 (CH_2), 24.5 (CH_2).

m/z (E.I.) 245.0874 (M^+, 74 %; $C_{14}H_{15}NOS$ requires M^+, 245.0874), 217 (20), 184 (23), 156 (44), 128 (52), 115 (60), 91 (42) and 42 (100).

The Effects of Heat on *N-Methyl-5-[imidazol-1-yl(thiocarbonyl)oxy]-1-phenyl-7-aza bicyclo[4.1.0]heptane.*



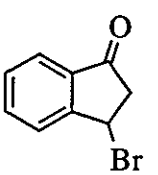
Method a.

A few mg of *N*-methyl-5-[imidazol-1-yl(thiocarbonyl)oxy]-1-phenyl-7-azabicyclo [4.1.0]heptane **(390)** in DCM (5ml) was refluxed for 3.5 hours, afterwhich TLC showed degradation had occurred (but not to the cyclised product **391**).

Method b.

A few mg of *N*-methyl-5-[imidazol-1-yl(thiocarbonyl)oxy]-1-phenyl-7-azabicyclo [4.1.0]heptane **(390)** in DCM (3ml) containing triethylamine (2.5 μl) was refluxed for 3.5 hours, afterwhich TLC showed only starting material. No degradation was evident

Preparation of *3-Bromoindanone* (397).



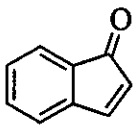
A solution of indanone (2.5 g, 19.0 mmol), *N*-bromosuccinimide (3.4 g, 19.3 mmol) and AIBN (50 mg) in carbon tetrachloride (30 ml) was refluxed for 2.5 hours. The solution was then cooled, filtered through a cotton-wool plug, and evaporated off *in vacuo* to give the *title compound* as an orange liquid (4.0 g, 93 %).

δ_H (250 MHz; $CDCl_3$) 7.69 (3 H, m, Ar-H), 7.48 (1 H, m, Ar-H), 5.59 (1 H, dd, J = 7 and 2.5 Hz, 3-CH), 3.35 (1 H, dd, J = 20 and 7 Hz, 2-CH), 3.03 (1 H, dd, J = 20 and 2.5 Hz, 2-CH);

δ_C (100 MHz; $CDCl_3$) 201.9 (C), 154.7 (C), 137.5 (C), 136.9 (CH), 130.1 (CH), 127.7 (CH), 123.75 (CH), 48.3 (CH_2), 41.1 (CH).

Spectra are consistent with those reported in the literature.[151]

Preparation of *Indenone* (398)



A solution of triethylamine (1.8 g, 17.7 mmol) in ether (1.7 ml) was added dropwise to a solution of 3-bromoindanone **(397)** (3.7 g, 17.6 mmol) in ether (18 ml) at 0°C. After 3 hours at 0°C the solution was filtered and evaporated *in vacuo* to give an orange/brown liquid (1.9 g). The liquid was extracted with hexane until the yellow colour was removed, leaving a red oil. The yellow extracts were combined and evaporated *in vacuo* to give the *title compound* as a yellow liquid (1.4 g, 60 %).

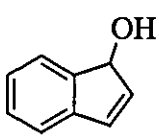
ν_{max}/cm^{-1} (neat) 3070 (Ar), 1711 (C=O), 1604, 1542, 1463, 763;

δ_H (250 MHz; $CDCl_3$) 7.56 (1 H, dd, J = 6 and 0.5 Hz, 3-CH), 7.42 (1 H, dd, J = 7 and 0.5 Hz, Ar-H), 7.34 (1 H, m, Ar-H), 7.23 (1 H, m, Ar-H), 7.05 (1 H, d, J = 7 Hz, Ar-H), 5.88 (1 H, d, J = 6 Hz, 2-CH);

δ_C (100 MHz; $CDCl_3$) 198.4 (C), 149.8 (CH), 144.6 (C), 133.7 (CH), 130.4 (C), 129.2 (CH), 127.2 (CH), 122.7 (CH), 122.3 (CH),

Spectra are consistent with those reported in the literature.[152]

Preparation of *Indenol* (399).



Sodium borohydride (24.5 mg, 0.6 mmol) was added portionwise to a solution of indenone **(398)** (48.1 mg, 0.4 mmol) and cerium(III) chloride heptahydrate (0.14 g, 0.4 mmol) in methanol (1 ml) at 0°C. After 1 hour at 0°C, water (20 ml) and DCM (20 ml) were added, shaken and separated. The organic layer was washed with saturated brine (2 x 20 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a clear yellow liquid (34.3 mg, 74 % pure by NMR analysis, estimated 53 % yield)

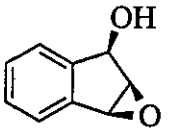
ν_{max}/cm^{-1} (neat) 3318 (OH), 3068 (Ar), 1610, 1558, 1456, 1359 (OH), 1052 (C-O), 769 (Ar);

δ_H (250 MHz; $CDCl_3$) 7.23 (4 H, m, Ar-H), 6.71 (1 H, dd, J = 6 and 1 Hz, 3-CH), 6.36 (1 H, dd, J = 6 and 2 Hz, 2-CH), 5.12 (1 H, br s, 1-CH), 1.96 (1 H, br s, OH);

δ_C (100 MHz; $CDCl_3$) 145.9 (C), 142.7 (C), 138.1 (CH), 133.1 (CH), 128.9 (CH), 126.5 (CH), 123.9 (CH), 121.8 (CH), 77.8 (CH).

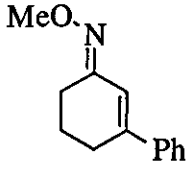
Spectra are consistent with those reported in the literature.[153]

Preparation of *2,3-Epoxyindan-1-ol* (400).



MCPBA (0.81 g, 60-86 %, 2.6 mmol) was added to a solution of indenol (**399**) (0.23 g, 1.8 mmol) and sodium carbonate (0.21 g, 1.9 mmol) in DCM (17 ml) at 0°C. The solution was stirred at 0°C for 35 minutes after which the solution was filtered and DCM (10 ml) was added. The solution was washed with saturated sodium carbonate solution (3 x 20 ml) and saturated brine (20 ml) dried over magnesium sulfate and evaporated *in vacuo* to give a clear slightly yellow liquid (0.16 g, estimated 53 %, pure by NMR analysis, 33%). Flash chromatography (eluant 85:15 light petroleum:ethyl acetate then 100% ethyl acetate) afforded the *title compound* as a white solid (27.4 mg, 10 %, NMR analysis showed 75 % purity)
ν_{max}/cm^{-1} 3420 (OH), 3056 (Ar), 1464, 1282 (O-H), 1226 (C-O), 1066 (C-O), 760 (Ar)
δ_H (250 MHz; $CDCl_3$) 7.30 (4 H, m, Ar-H), 5.1 (1 H, dd, J = 12 and 3 Hz, 1-CH), 4.19 (1 H, dd, J = 3 and 0.5 Hz, 3-CH), 4.03 (1 H, t, J = 3 Hz, 2-CH), 2.40 (1 H, br d, J = 12 Hz, OH);
δ_C (62.9 Hz; $CDCl_3$) 143.7 (C), 139.7 (C), 129.4 (CH), 128.1 (CH), 126.5 (CH), 124.9 (CH), 73.5 (CH), 57.3 (CH), 56.7 (CH).
m/z (E.I.) 148.0538 (M^+, 12 %, $C_9H_8O_2$ requires M^+, 148.0524), 147 ($M-H^+$, 10), 131 (M-OH, 15), 91 (100), 77 (60), 65 (48).

Preparation of *3-Phenyl-2-cyclohexen-1-one O1-methyloxime* (407).



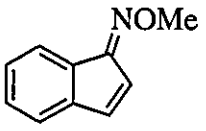
Methanol (7 ml) was added to a mixture of 3-phenyl-2-cyclohexen-1-one (**330**) (0.69 g, 4.1 mmol) and methoxylamine hydrochloride (0.42 g, 4.3 mmol). The resulting mixture was then stirred until dissolved and triethylamine (0.6 ml) was added. The solution was then refluxed overnight after which water (25 ml) was added and the resulting solution extracted with DCM (3 x 25 ml). The combined organic extracts were then washed with saturated brine (3 x 25 ml), dried over magnesium sulfate and evaporated off *in vacuo* to give a dark brown clear liquid (0.77 g). Flash chromatography using basified silica (eluant 90:10 light petroleum:ethyl acetate and ethyl acetate) afforded the *title compound* as a clear colourless

liquid (0.34 g, 42 %). The minor isomer was also isolated as a slightly off-white crystalline solid (0.17 g, 21 %).

Major Isomer.
m.p. 39.1-40.4°C.
Found C, 77.29; H, 7.45; N, 7.09. $C_{13}H_{15}NO$ requires C, 77.58; H, 7.52; N, 6.96.
ν_{max}/cm^{-1}(DCM slurry) 3082 (Ph), 3057 (Ph), 3033 (Ph), 2815, 1614, 1598, 1494, 1463 (Ph), 1053, 816, 751 (Ph), 693 (Ph);
δ_H (250 MHz; $CDCl_3$) 7.50 (2 H, m, Ph-H), 7.35 (3 H, m, Ph-H), 6.59 (1 H, t, J = 1.5 Hz, 2-CH), 3.94 (3 H, s, Me), 2.59 (4 H, m, 4-CH_2 and 6-CH_2), 1.90 (2 H, p, J = 6.5 Hz, 5-CH_2) ;
δ_C (62.9 MHz, $CDCl_3$) 156.6 (C), 145.1 (C), 140.3 (C), 128.4 (CH), 128.0 (CH), 125.2 (CH), 120.6 (CH), 61.7 (CH_3), 27.4 (4-CH_2), 22.4 (6-CH_2), 21.3 (5-CH_2).
m/z (E. I.) 201.1154 (M^+, 100 %; $C_{13}H_{15}NO$ requires M^+, 201.1154), 186 (M^+-Me, 5), 168 (62), 154 (38), 141 (60), 129 (68), 128 (75), 115 (73), 91 (36), 77 (34).

Minor Isomer.
m.p. 71.8-72.6°C.
Found C, 77.36; H, 7.38; N, 7.05. $C_{13}H_{15}NO$ requires C, 77.58; H, 7.51; N, 6.96.
ν_{max}/cm^{-1}(nujol) 1604, 1583, 1055, 876, 853, 759 (Ph), 700.1 (Ph).
δ_H (400 MHz; $CDCl_3$) 7.49 (2 H, m, Ph-H), 7.32 (3 H, m, Ph-H), 7.15 (1 H, t, J = 2 Hz, 2-CH), 3.88 (3 H, s, CH_3), 2.60 (2 H, dt, J = 6 and 2 Hz, 6-CH_2), 2.42 (2 H, m, 4-CH_2), 1.95 (2 H, p, J = 6 Hz, 5-CH_2)
δ_C (62.9 MHz; $CDCl_3$) 153.3 (C), 148.3 (C), 140.3 (C), 128.5 (Ar-CH), 128.4 (Ar-CH), 125.7 (Ar-CH), 113.5 (2-CH), 61.4 (CH_3), 28.5 (6-CH_2), 28.0 (4-CH_2), 22.6 (5-CH_2);
m/z (E. I.) 201.1154(M^+, 100 %; $C_{13}H_{15}NO$ requires M^+, 201.1154), 186 (M^+-CH_3, 5). 168 (62), 154 (38), 141 (58), 129 (68), 128 (75), 115 (72), 91 (34), 77 (34).

Preparation of *1H-Indeno-1-one O1-methyloxime* (408).



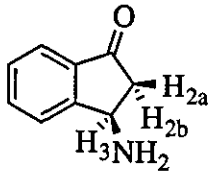
Methoxylamine hydrochloride (0.11 g, 1.3 mmol) was added portionwise to a solution of indenone **(398)** (100 mg, 0.8 mmol) and triethylamine (130 µl, 0.9 mmol) in methanol (1 ml). After being heated to approximately 50 °C for 2 hours, water (20 ml) was added. The solution was extracted with DCM (3 x 15 ml). The organic fractions were combined, washed with saturated brine (3 x 20 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a clear yellow liquid (0.11 g). Flash chromatography (eluant 90:10 light petroleum:ethyl

acetate) afforded the *title compound* as a mixture of isomers (ratio 3:2) as a clear, yellow liquid (56.6 mg, 46 %, difficult to purify fully due to co-elution of the isomers and an impurity).
ν_{max}/cm^{-1} (neat) 3066 (Ph), 2970 (Ph), 2936, 1609, 1521, 1046, 1026, 893, 758 (Ph);

Major isomer
δ_H (250 MHz; $CDCl_3$) 7.62 (1 H, m, Ar-H), 7.22 (3 H, m, Ar-H), 6.98 (1 H, dd, J = 6 and 0.5 Hz, 3-CH), 6.65 (1 H, d, J = 6 Hz, 2-CH), 4.11 (3 H , s, Me);
δ_C (100 MHz; $CDCl_3$) 156.9 (C), 142.3 (C), 138.5 (CH), 133.8 (C), 129.2 (CH), 127.1 (CH), 126.8 (CH), 121.8 (CH), 117.4 (CH), 62.9 (CH_3).
m/z (E.I.) 159.0685 (M^+, 100 %, $C_{10}H_9NO$ requires M^+, 159.0684)

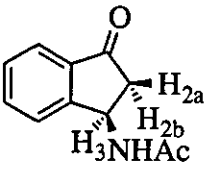
Minor isomer
δ_H (250 MHz; $CDCl_3$) 8.04 (1 H, dd, J = 7 and 1 Hz, Ar-H), 7.22 (3 H, m, Ar-H), 6.89 (1 H, dd, J = 6 and 1 Hz, 3-CH), 6.36 (1 H, d, J = 6 Hz, 2-CH), 4.17 (3 H, s, Me);
δ_C (100 MHz; $CDCl_3$) 157.3 (C), 143.7 (C), 135.9 (CH), 130.3 (CH), 127.7 (CH), 127.5 (C), 126.8 (CH), 121.3 (CH), 120.4 (CH), 63.4 (CH_3);

Preparation of *3-Aminoindanone* (409).



A solution of indenone (**398**) (0.30 mg, 2.3 mmol) and *S,S*-diphenylsulfilimine (0.56 mg, 2.8 mmol) in toluene (10 ml) was left stirring at room temperature for 3 hours, after which evaporation *in vacuo* gave a brown residue (0.87 g). NMR analysis of the crude material showed approximately 30 % of the *title compound* (88 % yield). This proved to be unstable to flash chromatography both on silica and basified silica. A tentative assignment of important peaks has been detailed below.
δ_H (250 MHz; $CDCl_3$) 5.04 (1 H, dd, J = 7 and 3.5 Hz, 3-CH), 2.98 (1 H, dd, J = 19 and 7 Hz, 2-CH_b), 2.56 (1 H, dd, J = 19 and 3.5 Hz, 2-CH_a). Aromatic signals are covered by impurity signals.
m/z (E.I.) 147 (M^+, 8 %), 29 (100).
The instability of the compound is noted in the literature.[154]

Preparation of *3-(Acetylamino)indanone* (410).



Acetic anhydride (250 µl, 2.7 mmol) was added to a solution of the crude material from 3-aminoindanone (**409**) (0.87 g containing approximately 30 % of the amine 1.8 mmol) in pyridine (3 ml). The solution was left stirring overnight. The pyridine was removed *in vacuo* to yield a brown liquid which was then subjected to flash chromatography (eluant ethyl acetate) which gave the *title compound* as an impure brown residue (33.9 mg, 86 % pure). Difficult to purify fully. Overall yield estimated to be 58.9 mg, 14 %.

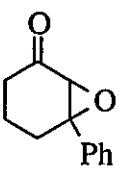
ν_{max}/cm^{-1} (neat) 3284 (N-H), 3071, 1714 (C=O), 1650 (C=O), 1544, 765 (Ar);

δ_H (250 MHz; $CDCl_3$) 7.55 (4 H, m, Ar-H), 6.37 (1 H, br d, J = 8 Hz, NH), 5.65 (1 H, ddd, J = 8, 8 and 3.5 Hz, 3-CH), 3.18 (1 H, dd, J = 19 and 7.5 Hz, 2-CH_b), 2.47 (1 H, dd, J = 19 and 3.5 Hz, 2-CH_a), 2.03 (3 H, s, Me);

δ_C (62.9 MHz; $CDCl_3$) 203.4 (C=O), 170.3 (C=O), 154.0 (Ar-C), 136.5 (Ar-C), 135.3 (Ar-CH), 129.1 (Ar-CH), 126.0 (Ar-CH), 123.1 (Ar-CH), 47.3 (CH), 44.6 (CH_2), 23.0 (CH_3);

m/z (E.I.) 189.0790 (M^+, 4 %, $C_{11}H_{11}NO_2$ requires M^+, 189.0790), 146 (30), 130 (12), 77 (32), 43 (Ac, 100).

Preparation of *2,3-Epoxy-3-Phenylcyclohexan-1-one* (411).

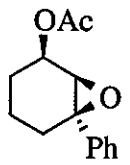


Methanol (30 ml) was added to 3-phenyl-2-cyclohexen-1-one (**330**) (3.0 g, 17.6 mmol) and the solution cooled to 0°C. Hydrogen peroxide (8.5 ml, 27.5 % w/v, 68.5 mmol) and 6 M sodium hydroxide solution (1.6 ml, 0.01 mol) were added ensuring that the temperature remained below 0°C. The solution was then left at -6°C for 20 minutes, then allowed to warm to room temperature and left stirring for approximately 4 hours. Sodium sulfite (approximately 10 g) and water (100 ml) were added with cooling. The resulting solution was then extracted with DCM (5 x 25 ml) and the combined organic extracts were washed with water (3 x 100 ml), dried over magnesium sulfate and evaporated *in vacuo* to give the *title compound* as a clear yellow liquid (1.7 g, 51 %).

ν_{max}/cm^{-1} (nujol) 1707 (C=O), 1452, 1386, 809, 792, 751, 657;

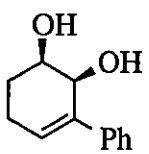
δ_H (250 MHz; $CDCl_3$) 7.36 (5 H, m, Ph), 3.26 (1 H, s, 2-CH), 2.60 (1 H, m, 4-CH), 2.43 (2 H, m, 6-CH_2), 2.15 (2 H, m, 4-CH and 5-CH), 1.81 (1 H, m, 5-CH);
δ_C (62.9 MHz; $CDCl_3$) 205.1 (C=O), 138.7 (Ar-C), 128.5 (Ar-CH), 128.2 (Ar-CH), 125.1 (Ar-CH), 64.1 (2-CH and 3-C), 35.8 (4-CH_2), 26.9 (6-CH_2), 16.7 (5-CH_2).
Spectra are consistent with those reported in the literature.[120]

Preparation of *1-(Acetoxy)-2,3-epoxy-3-phenylcyclohexane* (417).



Acetic anhydride (50 µl, 0.5 mmol) was added to a solution of 2,3-epoxy-3-phenylcyclohexanol **(338)** (35.0 mg, 0.2 mmol) in pyridine (0.5 ml). After stirring for 12 hours, evaporation *in vacuo* afforded the *title compound* as a light brown residue (36.6 mg, 85 %).
ν_{max}/cm^{-1} (neat) 3061 (Ph), 2946 (CH_2), 1733 (C=O), 1603 (Ph), 1496 (Ph), 1448 (Ph), 1241 (C-O), 761 (Ph), 699 (Ph);
δ_H (250 MHz, $CDCl_3$) 7.35 (5 H, m, Ph), 5.23 (1 H, ddd, J = 6.5, 6.5 and 2.5 Hz, 1-CH), 3.27 (1 H, d, J = 2.5 Hz, 2-CH), 2.28 (1 H, m, 4-CH), 2.13 (3 H, s, Me), 2.09 (1 H, m, 4-CH), 1.78 (1 H, m, 5-CH), 1.72 (1 H, m, 6-CH_2), 1.54 (1 H, m, 5-CH);
δ_C (62.9 MHz; $CDCl_3$) 170.8 (C), 140.9 (C), 128.3 (CH), 127.6 (CH), 125.3 (CH), 69.9 (CH), 62.8 (C), 61.6 (CH), 27.7 (CH_2), 24.9 (CH_2), 21.1 (CH_3), 19.1 (CH_2).
m/z (E.I.) 232.1079 (M^+, 1 %, $C_{14}H_{16}O_3$ requires M^+, 232.1099), 120 (21), 105 (62), 91 (25), 77 (35), 43 (100).

Preparation *3-Phenyl-3-cyclohexen-1,2-diol* (419).



Titanium(IV) isopropoxide (160 µl, 0.5 mmol) was added to a solution of 2,3-epoxy-3-phenylcyclohexanol **(338)** (49.3 mg, 0.3 mmol) and benzylamine (36 µl, 0.3 mmol) in DCM (2 ml). The solution was left stirring at room temperature for 3 days and a solution of 10 % sodium hydroxide in saturated brine (1 ml) was added. The solution was stirred for 24 hours at room temperature after which filtration through a celite plug and evaporation *in vacuo* afforded the *title compound* as a cloudy beige residue (45.5 mg, 92 %).

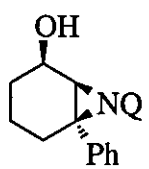
ν_{max}/cm^{-1} (neat) 3382 (OH), 2918 (CH_2), 1644, 1598, 1495, 1447, 1260 (O-H), 1070 (C-O), 732 (Ph), 698 (Ph);

δ_H (250 MHz; $CDCl_3$) 7.47 (2 H, d, J = 7 Hz, Ph-H), 7.30 (3 H, m, Ph-H), 6.17 (1 H, dd, J = 5 and 3.5 Hz, 4-CH), 4.58 (1 H, d, J = 4 Hz, 2-CH), 3.85 (1 H, m, 1-CH), 2.59 (2 H, br s, OH), 2.36 (2 H, m, 6-CH_2), 1.79 (2 H, m, 5-CH_2);

δ_C (62.9 MHz; $CDCl_3$) 139.7 (C), 137.2 (C), 128.5 (CH), 127.2 (CH), 125.8 (CH), 125.1 (C), 69.7 (CH), 67.8 (CH), 29.6 (CH_2), 24.8 (CH_2).

m/z (E.I.) 190.0996 (M^+, 4 % $C_{12}H_{14}O_2$ requires M^+, 190.0994), 117 (100)

Preparation of *N-(2-Ethylquinazolinonyl)-1-phenyl-7-azabicyclo[4.1.0]heptan-5-ol* (420).



Lead tetraacetate (1.7 g, 3.7 mmol) was added in small portions over 10 minutes, to a solution of 3-phenyl-2-cyclohexen-1-ol **(334)** (0.51 g, 2.9 mmol), 3-amino-2-ethyl-4(3*H*)-quinazolinone (0.55 g, 2.9 mmol) and sodium hydrogen carbonate (3.0 g, 35.7 mmol) in DCM (15 ml). The solution was left stirring for a further hour at room temperature, afterwhich DCM (25 ml) was added and the solution washed with saturated sodium hydrogen carbonate solution (2 x 25 ml) and saturated brine (2 x 25 ml). The organic layer was then dried over magnesium sulfate and evaporated *in vacuo* to give a brown crystalline solid (0.88 g). Flash chromatography on basified silica (eluant 70:30 ethyl acetate:light petroleum) gave the *title compound* as an impure, off-white solid (0.19 g, R_f=0.55) and another compound as a beige solid (0.48 g, R_f=0.19). Flash chromatography, on basified silica, on fraction R_f=0.19 (eluant 70:30 ethyl acetate:light petroleum and 80:20 ethyl acetate:methanol) gave compound **(425)** as a slightly impure light brown residue (0.18 g). Recrystallisation using methanol gave a pure white powder (0.04 g, 4 % very difficult to purify fully, estimated 83 % yield from NMR analysis of the crude product).

Fraction (R_f=0.55) was re-columned using basified silica (eluant 60:40 light petroleum:ethyl acetate) to give the *title compound* as a slightly yellow, clear liquid (74.3 mg, 7 %, estimated 17 %). The liquid was dissolved in DCM and allowed to evaporate slowly to give colourless crystals. The crystals were then filtered off and washed VERY CAREFULLY with small quantities of cold DCM.

ν_{max}/cm^{-1} (neat) 3440 (OH), 3064 (Ar), 3040 (Ar), 3028 (Ar), 1655 (C=O), 1593, 1569, 1500, 1450, 1299 (OH), 1068 (C-O), 911, 772 (Ph), 733 (Ar), 696 (Ph).

δ_H (400 MHz; $CDCl_3$) 8.19 (1 H, m, Q-H), 7.62 (1 H, m, Q-H), 7.40 (2 H, m, Q-H), 7.14 (5 H, m, Ph), 4.99 (1 H, br s, OH), 4.44 (1 H, m, 5-CH), 4.36 (1 H, d, J = 5 Hz, 6-CH), 2.86 (1

H, m, CH_3CH_2), 2.70 (1 H, m, 2-CH), 2.39 (1 H, m, 2-CH), 2.32 (1 H, m, CH_3CH_2), 1.92 (1 H, m, 3-CH), 1.79 (1 H, m, 4-CH), 1.67 (1 H, m, 4-CH), 1.50 (1 H, m, 3-CH), 1.14 (3 H, t, J = 7.5 Hz, CH_3).

δ_C (62.9 MHz; $CDCl_3$) 161.8 (C=O), 157.6 (C), 145.7 (C), 133.7 (Q-CH), 133.5 (C), 128.7 (Ar-CH), 128.2 (Ar-CH), 127.0 (Ar-CH), 126.7 (Q-CH), 126.1 (Q-CH), 126.0 (Q-CH), 120.3 (C), 64.3 (5-CH), 58.2 (C), 52.1 (6-CH), 28.6 (4-CH_2), 28.0 (CH_2), 27.3 (2-CH_2), 18.1 (3-CH_2), 10.4 (CH_3).

Spectra are consistent with those reported in the literature.[47]

See Appendix for X-ray structure.

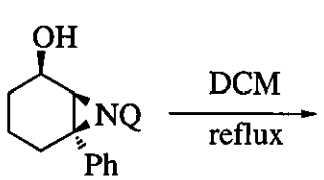
General Procedure for Tables 11, 13 and 14.

Lead tetraacetate (X, mmol) was added to a solution of 3-phenyl-2-cyclohexen-1-ol **(334)** (X, mmol), base (X, mmol) and 3-amino-2-ethyl-4(3*H*)-quinazolinone (X, mmol) in DCM (1.5 ml). After stirring at room temperature for 30 minutes, saturated sodium hydrogen carbonate solution was added (5 ml). DCM (20 ml) was added and the solution was washed with saturated sodium hydrogen carbonate solution (3 x 20 ml). The organic layer was then dried over magnesium sulfate and evaporated *in vacuo*. NMR analysis of the crude material was then performed.

General Procedure for Pre-forming of the Aziridinating Agent (Table 14, columns 5 and 6).

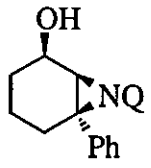
Lead tetraacetate (X, mmol) was added to a solution of 3-amino-2-ethyl-4(3*H*)-quinazolinone (X, mmol) in DCM (0.7 ml) at -25°C. 3-Phenyl-2-cyclohexen-1-one **(330)** (X, mmol, 3 eq) was added and the solution was allowed to warm to room temperature for 30 minutes, then basified with saturated sodium hydrogen carbonate solution (5 ml). DCM (20 ml) was added and the solution was washed with saturated sodium bicarbonate solution (3 x 20 ml) dried over magnesium sulfate and evaporated *in vacuo*. NMR analysis of the crude material was then performed.

Action of Heat on *N-(2-Ethylquinazolinonyl)-1-phenyl-7-azabicyclo[4.1.0]heptan-5-ol*.



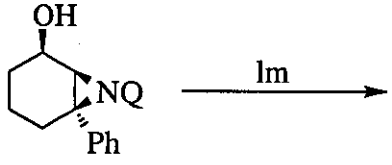
A solution of *N*-(2-ethylquinazolinonyl)-1-phenyl-7-azabicyclo[4.1.0]heptan-5-ol **(420)** (8.2 mg) in DCM (6 ml) was refluxed for 4.5 hours, after which evaporation *in vacuo* and NMR analysis of the crude material showed only starting material.

Action of acid on *N-(2-Ethylquinazolinonyl)-1-phenyl-7-azabicyclo[4.1.0]heptan-5-ol*.



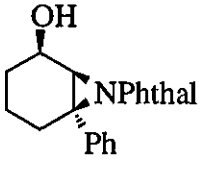
N-(2-Ethylquinazolinonyl)-1-phenyl-7-azabicyclo[4.1.0]heptan-5-ol **(420)** (98.2 mg, 0.3 mmol) was dissolved in $CDCl_3$ (1.5 ml) and acetic acid (68 µl, 1.20 mmol) was added. The solution was left for approximately 2 hours afterwhich NMR analysis showed a mixture containing starting material:cyclic compound **(425)** (80:20). (The peaks for the cyclic compound have been observed to shift in the presence of acid).

Action of Imidazole on *N-(2-Ethylquinazolinonyl)-1-phenyl-7-azabicyclo[4.1.0]heptan-5-ol.*



A solution of *N*-(2-ethylquinazolinyl)-1-phenyl-7-azabicyclo[4.1.0]heptan-5-ol **(420)** (50.2 mg, 0.1 mmol) and imidazole (13.8 mg, 0.2 mmol) in DCM (5 ml) was refluxed for 6 hours after which evaporation *in vacuo* gave an orange/white solid (64.7 mg). NMR analysis of the crude material showed mostly starting material along with 3 % of the cyclic compound **(425)**.

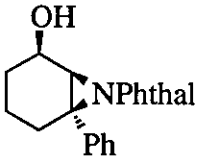
Preparation of *N-(Phthalimido)-1-phenyl-7-azabicyclo[4.1.0]heptan-5-ol* (421)



Lead tetraacetate (4.9 g, 10.5 mmol) was added portionwise, over a period of 10 minutes, to a solution of 3-phenyl-2-cyclohexen-1-ol **(334)** (1.5 g, 8.6 mmol), *N*-aminophthalimide (1.7 g, 10.4 mmol) and sodium carbonate (1.9 g, 18.0 mmol) in DCM (20 ml) at 0°C. The mixture was then allowed to stir at room temperature for 30 minutes. Saturated sodium hydrogen carbonate solution (5 ml) was added dropwise then DCM (50 ml). The organic layer was further washed with saturated sodium hydrogen carbonate

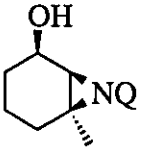
solution (8 x 50 ml), dried over magnesium sulfate and evaporated *in vacuo* to afford a beige powdery solid (1.9 g, 66 %, 86 % pure, purification difficult). m.p. 189-193°C.
ν_{max}/cm^{-1} (nujol) 3419 (OH), 1770 (C=O), 1716 (C=O), 1609, 1503, 1075 (C-O), 714 (Ar):
δ_H (400 MHz; $CDCl_3$) 7.57 (4 H, m, Phthal-H), 7.44 (2 H, m, Ph-H), 7.21 (3 H, m, Ph-H) 4.41 (1 H, d, J = 4.5 Hz, 6-CH), 4.36 (1 H, m, 5-CH), 3.20 (1 H, br s, OH), 2.77 (1 H, dq, J = 14.5 and 5 Hz, 2-CH), 2.17 (1 H, m, 2-CH), 1.77 (2 H, m, 3-CH and 4-CH), 1.63 (1 H, m, 4-CH), 1.36 (1 H, m, 3-CH).
δ_C (100 MHz; $CDCl_3$) 166.0 (C=O), 136.3 (C), 133.9 (Phthal-CH), 130.2 (C), 129.2 (Ar-CH), 128.4 (Ar-CH), 127.9 (Ar-CH), 122.8 (Phthal-CH), 65.6 (5-CH), 56.7 (C), 48.8 (6-CH), 29.5 (2-CH_2), 28.7 (4-CH_2), 18.8 (3-CH_2),
m/z (C. I., ammonia) 335.1396 (MH^+, 10 %, $C_{20}H_{18}N_2O_3H^+$ requires MH^+, 335.1396), 190 (16), 188 (M^+-Phthal, 14), 180 (64), 173 (38), 172 (21).

Action of Acid on *N-(Phthalimido)-1-phenyl-7-azabicyclo[4.1.0]heptan-5-ol* .



Crude *N*-(phthalimido)-1-phenyl-7-azabicyclo[4.1.0]heptan-5-ol **(421)** (0.27 g, 2.0 mmol) was dissolved in DCM (19 ml) and acetic acid (2.7 ml, 47.0 mmol) was added. The solution was left stirring at room temperature for three days then washed with saturated sodium bicarbonate solution (3 x 20 ml) dried over magnesium sulfate and evaporated *in vacuo* to give a beige residue (0.54 g). Flash chromatography using basified silica (eluant 50:50 ethyl acetate:light petroleum) gave the acetate **(427)** which was recrystallised in DCM/light petroleum to give a white powder (60.7 mg, 19 % over two steps). The cyclic compound **(426)** was isolated but not pure. The crude was re-columned using basified silica (eluant 70:30 ethyl acetate:light petroleum) to give cyclic compound **(426)** as a clear colourless residue (26.4 mg, 10 % over two steps).

Preparation of *N-(2-Ethylquinazolinonyl)-1-methyl-7-azabicyclo[4.1.0]heptan-5-ol* (422).



Lead tetraacetate (1.1 g, 2.4 mmol) was added portionwise, over a period of 10 minutes, to a solution of 3-methyl-2-cyclohexen-1-ol **(335)** (0.20 g, 1.8 mmol), 3-amino-2-

ethyl-4(3*H*)-quinazolinone (0.40 g, 2.1 mmol) and sodium hydrogen carbonate (1.9 g, 22.7 mmol) in DCM (11 ml). After stirring for 30 minutes at room temperature, saturated sodium hydrogen carbonate solution (5 ml) and DCM (20 ml) were added. The organic layer was washed with saturated brine (3 x 30 ml), dried over magnesium sulfate and evaporated *in vacuo* to yield an orange solid (0.49 g). Flash chromatography using basified silica (eluant 60:40 ethyl acetate:light petroleum) gave an impure mixture which was further purified by reverse recystallisation of the impurity using DCM/light petroleum to give the *title compound* as a yellow orange liquid (0.22 g, 41 %)

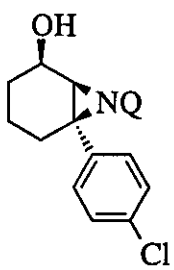
ν_{max}/cm^{-1} (neat) 3450 (OH), 2939 (CH_2), 2868, 1660 (C=O), 1593, 1471, 1284 (O-H), 1081 (C-O), 772 (Ar).

δ_H (250 MHz; $CDCl_3$) 8.17 (1 H, m, Q-H), 7.70 (2 H, m, 2 x Q-H), 7.43 (1 H, m, Q-H), 5.03 (1 H, d, J = 3 Hz, OH), 4.25 (1 H, m, 5-CH), 3.10 (1 H, d, J = 4 Hz, 6-CH), 3.09 (1 H, m, $CH_3\mathbf{CH_2}$), 2.81 (1 H, dq, J = 16 and 7.5 Hz, $CH_3\mathbf{CH_2}$), 2.05 (1 H, m, 2-CH), 1.73 (2 H, m, CH_2), 1.55 (1 H, m, $\mathbf{CH_2}$) 1.42 (3 H, t, J = 7.5 Hz, CH_3) 1.30 (1 H, m, $\mathbf{CH_2}$), 1.22 (3 H, s, CH_3);

δ_C (100 MHz; $CDCl_3$) 145.8 (C), 133.9 (Ar-CH), 126.9 (Ar-CH), 126.4 (Ar-CH), 126.1 (Ar-CH), 120.9 (C), 65.0 (CH), 54.3 (C), 53.5 (CH), 28.9 (CH_2), 28.3 (CH_2), 28.1 (CH_2), 19.8 (CH_3), 18.9 (CH_2), 10.6 (CH_3).

Spectra are consistent with those reported in the literature.[47]

Preparation of *N-(2-Ethylquinazolinonyl)-1-(4-chlorophenyl)-7-azabicyclo[4.1.0]heptan-5-ol* (424).



Lead tetraacetate (1.7 g, 3.6 mmol) was added portionwise, over 10 minutes, to a solution of 3-(4-chlorophenyl)-2-cyclohexen-1-ol (**337**) (0.61 g, 2.9 mmol), 3-amino-2-ethyl-4(3*H*)-quinazolinone (0.67 g, 3.2 mmol) and sodium carbonate (1.2 g, 11.7 mmol) in DCM (15 ml). After stirring at room temperature for 30 minutes the solid was filtered off and the filtrate washed with saturated brine (3 x 20 ml), dried over magnesium sulfate and evaporated off *in vacuo* to give the *title compound* as an orange residue (1.4 g, 44 %).

ν_{max}/cm^{-1} (neat) 3441 (OH), 3068 (Ar), 2940 (CH_2), 1657 (C=O), 1594, 1498, 1472, 1339 (O-H), 1095 (C-O), 827 (Ar), 732 (Ar);

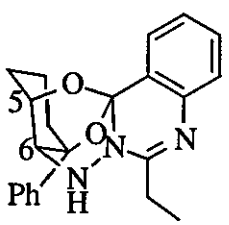
δ_H (250 MHz; $CDCl_3$) 8.19 (1 H, m, Q-H), 7.66 (1 H, m, Q-H), 7.45 (2 H, m, Q-H), 7.08 (4 H, m, Ar-H), 5.01 (1 H, br s, OH), 4.45 (1 H, m, 5-CH), 4.30 (1 H, d, J = 5 Hz, 6-CH), 2.85

(1 H, m, CH_3CH_2), 2.68 (1 H, m, 2-CH), 2.33 (2 H, m, CH_3CH_2, 2-CH), 1.92 (1 H, m, 3-CH), 1.76 (1 H, m, 4-CH), 1.68 (1 H, m, 4-CH), 1.50 (1 H, m, 3-CH), 1.18 (3 H, t, J = 7 Hz, CH_3);

δ_C (62.9 MHz; $CDCl_3$) 161.8 (C), 157.4 (C), 145.6 (C), 134.8 (C), 133.9 (CH), 132.2 (C), 128.4 (CH), 128.3 (CH), 126.8 (CH), 126.3 (CH), 126.0 (CH), 120.1 (C), 64.1 (CH), 57.5 (C), 52.3 (CH), 28.5 (CH_2), 28.0 (CH_2), 27.3 (CH_2), 18.0 (CH_2), 10.5 (CH_3).

m/z (E. I.) 395.1380 (M^+, 4 %, $C_{22}H_{22}N_3O_2Cl$ requires M^+, 395.1400), 222 (M^+-Q, 15), 200 (55), 173 (Q, 100), 130 (70), 77 (55).

Spectroscopic Data for the Cyclic Compound (425)



m.p. 167°C (decomposes).

Found C, 73.04; H, 6.56; N, 11.72. $C_{22}H_{23}N_3O_2$ requires C, 73.09; H, 6.42; N, 11.63.

ν_{max}/cm^{-1} (DCM slurry) 3317 (NH), 3240, 3062 (Ar), 3027 (Ar), 1590, 1568, 1484, 1103, 768 (Ph), 730 (Ar), 700 (Ph).

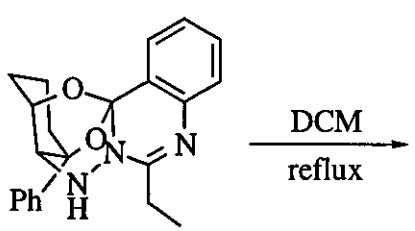
δ_H (400 MHz; $CDCl_3$) 7.77 (1 H, m, Q-H), 7.32 (7 H, m, 2 x Q-H and Ph), 7.20 (1 H, m, Q-H), 4.74 (1 H, br s, 5-CH), 4.23 (1 H, s, NH), 3.36 (1 H, d , J = 2 Hz, 6-CH), 2.32 (1 H, m, 2-CH), 2.25 (1 H, m, 4-CH), 2.18 (2 H, m, $CH_3\mathbf{CH_2}$), 1.97 (1 H, m, 3-CH), 1.80 (1 H, m, 3-CH), 1.64 (2 H, m, 4-CH and 2-CH), 1.02 (3 H, t, J = 7.5 Hz, CH_3).

δ_C (100 MHz; $CDCl_3$) 159.6 (C), 142.6 (C), 141.6 (C), 130.3 (Q-CH), 128.5 (Ar-CH), 127.5 (Ar-CH), 124.8 (Ar-CH), 124.4 (Ar-CH), 124.3 (Ar-CH), 123.9 (Q-CH), 121.3 (C), 97.3 (C), 81.4 (C), 76.3 (5-CH), 55.0 (6-CH), 37.9 (3-CH_2), 30.1 (4-CH_2), 25.6 (CH_2), 16.4 (2-CH_2), 11.1 (CH_3).

m/z (C.I., ammonia) 362.1868 (MH^+, 3 %, $C_{22}H_{23}N_3O_2H^+$ requires MH^+, 362.1868), 175 (100).

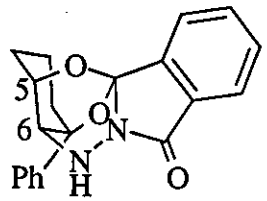
See Appendix for X-ray structure.

Action of Heat on the Cyclic Compound.



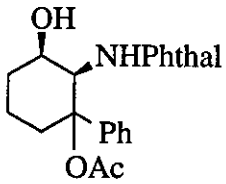
A solution of the cyclic compound **(425)** (4.8 mg) in DCM (6 ml) was refluxed for 4.5 hours after which evaporation *in vacuo*, and subsequent NMR analysis of the crude material showed only starting material.

Spectroscopic Data for the Cyclic Compound (426).



ν_{max}/cm^{-1} (neat) 3175 (NH), 3089 (Ar), 3061 (Ar), 3026 (Ar), 2937 (CH_2), 1704 (C=O), 1417, 1051, 759 (Ph), 737 (Ar), 695 (Ph);
δ_H (250 MHz; $CDCl_3$) 7.79 (1 H, m, Phthal-H), 7.72 (1 H, m, Phthal-H), 7.58 (2 H, m, Phthal-H), 7.33 (5 H, m, Ph), 4.83 (1 H, m, 5-CH), 4.67 (1 H, s, NH), 3.42 (1 H, d, J = 2 Hz, 6-CH), 2.40 (1 H, m, 2-CH), 2.23 (1 H, m, 4-CH), 2.00 (2 H, m, 2-CH and 3-CH), 1.75 (2 H, m, 3-CH and 4-CH);
δ_C (62.9 MHz, $CDCl_3$) 159.2 (C), 141.1 (C), 138.2 (C), 132.4 (C), 131.7 (CH), 130.8 (CH), 129.0 (CH), 128.0 (CH), 124.6 (CH), 123.3 (CH), 121.6 (CH), 101.0 (C), 81.1 (C), 74.3 (CH), 56.0 (CH), 37.4 (CH_2), 30.2 (CH_2), 16.3 (CH_2);
m/z (C. I.) 335.1397 (MH^+, 15 %, $C_{20}H_{18}N_2O_3$ requires MH^+, 335.1396), 281 (21), 157 (48), 94 (96), 58 (100).

Spectroscopic Data for *3-Acetoxy-3-phenyl-2-(phthalimidoamino)cyclohexan-1-ol* (427).



m.p. 217-217.8°C (decomposes).
ν_{max}/cm^{-1} (DCM slurry) 3425 (OH), 3290 (NH), 3020 (CH_2), 1781 (C=O), 1720 (C=O), 1240 (OH), 1216 (C-O), 756 (Ph), 711.6 (Ar), 669 (Ph);
δ_H (250 MHz; $CDCl_3$) 7.55 (4 H, m, Phthal-H), 7.34 (2 H, d, J = 7.5 Hz, Ph-H), 6.99 (2 H, t, J = 7.5 Hz, Ph-H), 6.75 (1 H, t , J = 7.5 Hz, Ph-H), 4.74 (1 H, br s, OH), 4.52 (1 H, m, 1-CH), 4.23 (1 H, d, J = 3.5 Hz, 2-CH), 2.90 (1 H, m, 4-CH), 2.64 (1 H, m, 4-CH), 2.50 (1 H, br s, NH), 1.93 (3 H, s, CH_3), 1.87 (3 H, m, 6-CH_2 and 5-CH), 1.50 (1 H, m, 5-CH);

δ_C (62.9 MHz; $CDCl_3$) 168.3 (C=O), 166.7 (C=O), 141.0 (C), 133.7 (CH), 129.7 (C), 127.9 (CH), 127.1 (CH), 125.8 (CH), 122.7 (CH), 84.4 (C), 68.5 (CH), 64.0 (CH), 27.2 (CH_2), 24.1 (CH_2), 22.0 (CH_3), 18.8 (CH_2)

m/z (E.I.) 334.1317 (M^+-AcOH, 100 % $C_{20}H_{18}N_2O_3$ requires M^+-AcOH, 334.1317), 130 (30), 105 (40), 76 (32), 43 (100).

Preparation of *N-(2-Ethylquinazolinonyl)-5-[imidazol-1-yl(thiocarbonyl)oxy]-1-phenyl-7-aza bicyclo[4.1.0]heptane* (430)

A solution of *N*-(2-ethylquinazolinonyl)-1-phenyl-7-azabicyclo[4.1.0]heptan-5-ol (**420**) (40.7 mg, 0.1 mmol) and 1,1'-thiocarbonyldiimidazole (34.6 mg, 0.1 mmol) in DCM (9 ml) was refluxed for 24 hours. Evaporation *in vacuo* yielded a clear yellow viscous liquid (74.8 mg). Flash chromatography on basified silica (eluant 60:40 ethyl acetate:light petroleum) gave the *title compound* as a clear, colourless oil (12.0 mg, 22 %). Also isolated was the cyclic compound (**425**) (7.4 mg, 14 %).

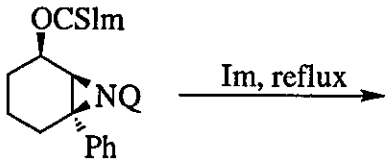
ν_{max}/cm^{-1} 3061 (Ar), 3032 (Ar), 2936 (CH_2), 1706 (C=O), 1590, 1568, 1483, 1460, 1103 (C=S), 768 (Ph), 731 (Ar), 700 (Ph).

δ_H (400 MHz; $CDCl_3$) 8.53 (1 H, br s, Im-H), 8.03 (1 H, m, Q-H), 7.83 (1 H, t, J = 1 Hz, Im-H), 7.55 (1 H, m, Q-H), 7.38 (1 H, m, Q-H), 7.29 (1 H, m, Q-H), 7.21 (2 H, m, Ph-H), 7.12 (3 H, m, Ph-H), 7.02 (1 H, d, J = 1 Hz, Im-H), 6.09 (1 H, m, 5-CH), 5.36 (1 H, br s, 6-CH), 3.10 (1 H, m, $CH_3\mathbf{CH_2}$), 2.73 (1 H, m, 2-CH), 2.60 (1 H, m, $CH_3\mathbf{CH_2}$), 2.51 (1 H, m, 2-CH), 2.12 (1 H, m, 4-CH), 2.02 (2 H, m, 3-CH and 4-CH), 1.59 (1 H, m, 3-CH), 1.30 (3 H, t, J = 7.5 Hz, CH_3).

δ_C (100 MHz; $CDCl_3$) 184.5 (C=S), 160.8 (C=O), 157.9 (C), 145.5 (C), 137.5 (Im-CH), 133.9 (C), 133.5 (Q-CH), 130.6 (Ar-CH), 128.8 (Ar-CH), 128.4 (Ar-CH), 127.5 (Ar-CH), 126.5 (Q-CH), 126.4 (Q-CH), 125.9 (Q-CH), 121.1 (C), 118.5 (Im-CH), 78.3 (5-CH), 57.2 (C), 46.8 (6-CH), 28.7 (4-CH_2), 27.3 (CH_2), 24.2 (2-CH_2), 19.5 (3-CH_2), 10.7 (CH_3).

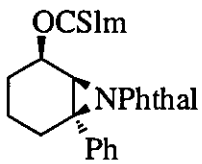
m/z (C.I., ammonia) 472.1807(MH^+, 7 %, $C_{26}H_{25}N_5O_2SH^+$ requires MH^+, 472.1807), 344 (M^+-OCSIm, 4), 190 (91), 175 (100), 172 (M^+-OCSIm and Q, 50), 157 (70), 69 (78).

Action of Imidazole on *N-(2-Ethylquinazolinonyl)-5-[imidazol-1-yl(thiocarbonyl)oxy]-1-phenyl-7-azabicyclo[4.1.0]heptane.*



A solution of *N*-(2-ethylquinazolinonyl)-5-[imidazol-1-yl(thiocarbonyl)oxy]-1-phenyl-7-azabicyclo[4.1.0]heptane (**430**) (8.8 mg, 0.02 mmol) and imidazole (2.8 mg, 0.04 mmol) in DCM (3 ml) was refluxed for 3.5 hours. Evaporation *in vacuo* and subsequent NMR analysis of the crude material showed only starting material.

Preparation of *N-(Phthalimido)-5-[imidazol-1-yl(thiocarbonyl)oxy]-1-phenyl-7-azabicyclo [4.1.0]heptane* **(431)**



A solution of *N*-(phthalimido)-1-phenyl-7-azabicyclo[4.1.0]heptan-5-ol (**421**) (32.0 mg, 0.01 mmol) and 1,1'-thiocarbonyldiimidazole (66.0 mg, 0.03 mmol) in DCM (4 ml) was refluxed for approximately 3 hours. Evaporation *in vacuo* gave a yellow residue (78.7 mg). Flash chromatography using basified silica (eluant 50:50 ethyl acetate:light petroleum) gave the *title compound* as a clear colourless residue (20.3 mg, 51 %). Recrystallisation using DCM gave clear yellow crystals. m.p. 94.6-95.8°C.

ν_{max}/cm^{-1} (DCM slurry) 3155 (Ar), 3132 (Ar), 2948 (CH_2), 1768 (C=O), 1719 (C=O), 1611, 1531, 1231, 734 (Ar), 709 (Ar).

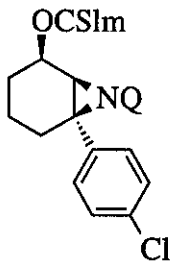
δ_H (400 MHz; $CDCl_3$) 8.48 (1 H, s, Im-H), 7.76 (1 H, s, Im-H), 7.55 (4 H, m, Phthal-H), 7.40 (2 H, d, J = 7 Hz, Ph-H), 7.20 (3 H, m, Ph-H), 7.02 (1 H, s, Im-H), 6.09 (1 H, dq, J = 9 and 3.5 Hz, 5-CH), 4.88 (1 H, d, J = 3.5 Hz, 6-CH), 2.85 (1 H, dq, J = 15 and 6 Hz, 2-CH), 2.33 (1 H, m, 2-CH), 2.08 (1 H, m, 4-CH), 1.95 (1 H, m, 4-CH), 1.89 (1 H, m, 3-CH), 1.50 (1 H, m, 3-CH).

δ_C (100 MHz; $CDCl_3$) 184.8 (C), 165.8 (C), 137.7 (Im-CH), 136.2 (C), 134.2 (Phthal-CH), 131.04 (Im-CH), 130.45 (C), 129.5 (Ar-CH), 129.0 (Ar-CH), 128.5 (Ar-CH), 123.2 (Phthal-CH), 118.8 (Im-CH), 79.3 (5-CH), 56.5 (C), 44.6 (6-CH), 29.4 (2-CH_2), 24.2 (4-CH_2), 20.3 (3-CH_2)

m/z (C.I., ammonia) 445.1334 (MH^+, 100 %, $C_{24}H_{20}N_4O_3SH^+$ requires MH^+, 445.1334), 317 (97)

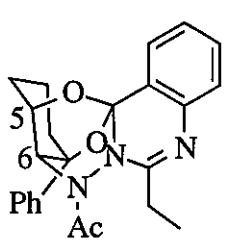
See Appendix for X-ray structure.

Preparation of *N-(2-Ethylquinazolinonyl)-5-[imidazol-1-yl(thiocarbonyl)oxy]-1-(4-chloro phenyl)-7-azabicyclo[4.1.0]heptane* (432).



A solution of *N*-(2-ethylquinazolinonyl)-1-(4-chlorophenyl)-7-azabicyclo[4.1.0] heptan-5-ol (**424**) (69.8 mg, 0.2 mmol) and 1,1'-thiocarbonyldiimidazole (50.0 mg, 0.28 mmol) in DCM (8 ml). was refluxed for 2.5 hours. Evaporation *in vacuo* gave a slightly yellow cloudy residue. Flash chromatography using basified silica (eluant 50:50 ethyl acetate:light petroleum) gave the *title compound* as a clear yellow residue (43.8 mg, 50 %).
ν_{max}/cm^{-1} (neat) 2941 (CH_2), 1674 (C=O), 1597, 1471, 1103, 772 (Ar), 733 (Ar), 693 (Ar);
δ_H (250 MHz; $CDCl_3$) 8.55 (1 H, br s, Im-H), 8.03 (1 H, m, Q-H), 7.83 (1 H, br s, Im-H), 7.55 (1 H, m, Q-H), 7.43 (1 H, m, Q-H), 7.33 (1 H, m, Q-H), 7.10 (4 H, m, Ar), 7.02 (1 H, br s, Im-H), 6.09 (1 H, m, 5-CH), 5.33 (1 H, d, J = 4 Hz, 6-CH), 3.10 (1 H, m, $CH_3\mathbf{CH_2}$), 2.70 (1 H, m, 2-CH), 2.58 (1 H, m, $CH_3\mathbf{CH_2}$), 2.44 (1 H, m, 2-CH), 2.12 (1 H, m, 4-CH), 1.99 (2 H, m, 3-CH and 4-CH), 1.60 (1 H, m, 3-CH), 1.32 (3 H, t, J = 7 Hz, CH_3);
δ_C (250 MHz, $CDCl_3$) 184.2 (C), 160.7 (C), 157.6 (C), 145.3 (C), 137.3 (C), 134.8 (C), 133.7 (CH), 132.4 (C), 130.5 (CH), 128.7 (CH), 128.6 (CH), 126.5 (CH), 126.3 (CH), 126.1 (CH), 118.4 (C), 77.9 (CH), 56.3 (C), 46.8 (CH), 28.6 (CH_2), 27.1 (CH_2), 24.0 (CH_2), 19.3 (CH_2), 10.7 (CH_3);
m/z (FAB) 506.1434 (MH^+, $C_{26}H_{24}N_5O_2ClS$ H^+ requires MH^+, 506.1417).

Preparation of the Acetylated Ring Compound (434).



Acetic anhydride (0.7 ml, 7.4 mmol) was added to a solution of the cyclic structure (**425**) (19.0 mg, 0.05 mmol) in pyridine (0.5 ml). The solution was left stirring at room

temperature for 4 days after which evaporation *in vacuo* gave the *title compound* as a clear, light yellow residue (21.5 mg, 99 %).

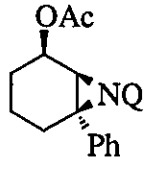
ν_{max}/cm^{-1} 3060 (Ph), 2938 (CH_2), 1688 (C=O), 1598, 1372, 1164, 1105, 998, 978, 762 (Ph), 733 (Ar), 700 (Ph).

δ_H (400 MHz; $CDCl_3$) 7.72 (1 H, m, 2 x Q-H), 7.47 (1 H, m, Q-H), 7.39 (1 H, m, Ph-H), 7.35 (2 H, m, Ph-H), 7.28 (4 H, m, 2 x Q-H and 2 x Ph-H), 5.16 (1 H, d, J = 3 Hz, 6-CH), 4.82 (1 H, m, 5-CH), 1.99 (3 H, s, CH_3), 1.87 (1 H, m, 3-CH), 1.74 (2 H, m, 4-CH and $CH_3\mathbf{CH_2}$), 1.59 (2 H, m, 3-CH and 2-CH), 0.98 (1 H, m, $CH_3\mathbf{CH_2}$), 0.81 (3 H, t, J = 7 Hz, CH_3).

δ_C (100 MHz; $CDCl_3$) 179.3 (C=O), 160.4 (C), 143.1 (C), 141.5 (C), 130.9 (Q-CH), 129.2 (Ar-CH), 128.0 (Ar-CH), 125.9 (Ar-CH), 125.6 (Ar-CH), 124.9 (Ar-CH), 123.4 (C), 123.2 (Q-CH), 99.3 (C), 79.8 (C), 75.2 (5-CH), 55.4 (6-CH), 40.8 (3-CH_2), 29.5 (4-CH_2), 23.7 (CH_2), 21.5 (CH_3), 17.0 (2-CH_2), 9.9 (CH_3).

m/z (E.I.) 403.1896 (M^+, 6 %, $C_{24}H_{25}N_3O_3$ requires M^+, 403.1896), 360 (M^+-Ac, 7), 175 (80), 174 (100), 130 (30), 105 (73), 77 (25), 43 (23).

Preparation of *N-(2-Ethylquinazolinonyl)-5-(acetoxy)-1-phenyl-7-azabicyclo[4.1.0] heptane* (435).



A solution of *N*-(2-ethylquinazolinonyl)-1-phenyl-7-azabicyclo[4.1.0]heptan-5-ol (**420**) (59.7 mg, 0.2 mmol) in pyridine (0.5 ml) and acetic anhydride (155 µl, 1.7 mmol) was left stirring at room temperature for 24 hours. The pyridine was removed *in vacuo* to yield a brown viscous liquid. Flash chromatography on basified silica (eluant 80:20 light petroleum:ethyl acetate) gave the *title compound* as a clear, colourless liquid (37.6 mg, 57 %).

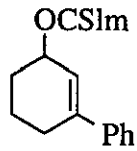
ν_{max}/cm^{-1} (neat) 3062 (Ph), 2940 (CH_2), 2873, 1732 (C=O), 1674 (C=O), 1570, 1500, 1448 , 1472, 1369, 1239 (C-O), 773 (Ar), 734 (Ar), 696 (Ph);

δ_H (250 MHz, $CDCl_3$) 8.12 (1 H, m, Q-H), 7.55 (1 H, m, Q-H), 7.34 (2 H, m, 2 x Q-H), 7.19 (2 H, m, Ph-H), 7.08 (3 H, m, Ph-H), 5.38 (1 H, m, 5-CH), 5.12 (1 H, br s, d on high temp-55°C, J = 4 Hz, 6-CH), 3.08 (1 H, dq, J = 16 and 7.5 Hz, $CH_3\mathbf{CH_2}$), 2.58 (3 H, m, $CH_3\mathbf{CH_2}$ and 2-CH_2), 2.29 (3 H, s, CH_3), 1.87 (3 H, m, 4-CH_2 and 3-CH), 1.48 (1 H, m, 3-CH), 1.26 (3 H, t, J = 7.5 Hz, CH_3);

δ_C (62.9 MHz; $CDCl_3$) 171.6 (C=O), 160.6 (C), 158.1 (C), 145.3 (C), 134.1 (C), 133.2 (CH), 128.5 (CH), 128.1 (CH), 127.5 (CH), 126.4 (CH), 126.3 (CH), 125.6 (CH), 121.1 (C), 68.6

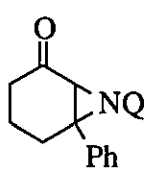
(CH), 57.3 (C), 47.3 (CH), 28.5 (CH_2), 27.1 (CH_2), 24.3 (CH_2), 21.4 (CH_3), 20.0 (CH_2), 10.6 (CH_3).
m/z (C.I., ammonia) 404.1974 (MH^+, 30 %, $C_{24}H_{25}N_3O_3H^+$ requires MH^+, 404.1974), 232 (13), 190 (40), 175 (100), 157 (90), 52 (42).

Preparation of *1-[Imidazol-1-yl(thiocarbonyl)oxy]-3-phenyl-2-cyclohexene* (436).



A solution of 3-phenylcyclohexen-1-ol **(334)** (0.25 g, 1.4 mmol) and 1,1'-thiocarbonyldiimidazole (0.57 g, 2.5 mmol) in DCM (15 ml) was refluxed for 3 hours. The solution was evaporated *in vacuo* to give a clear yellow liquid (0.75 g) Flash chromatography (eluant 70:30 light petroleum:ethyl acetate) gave the *title compound* as a clear yellow liquid (0.26 g, 65 %). m.p. 69.3-70.5°C.
Found C, 67.62; H, 5.68; N, 9.58. $C_{16}H_{16}N_2OS$ requires C, 67.58; H, 5.67; N, 9.86.
ν_{max}/cm^{-1} (DCM slurry) 3120, 3055 (Ph), 2935 (CH_2), 1689, 1213, 887, 753 (Ph), 695 (Ph)
δ_H (250 MHz; $CDCl_3$) 8.19 (1 H, br s, Im-H), 7.45 (1 H, br s, Im-H), 7.32 (5 H, m, Ph), 7.07 (1 H, d, J = 1 Hz, Im-H), 6.10 (1 H, d, J = 5 Hz, 2-CH), 4.65 (1 H, m, 1-CH), 2.49 (2 H, m, 4-CH_2), 2.14 (1 H, m, 6-CH), 2.04 (1 H, m, 6-CH), 1.91 (2 H, m, 5-CH_2),
δ_C (62.9 MHz; $CDCl_3$) 165.9 (C=S), 142.3 (C), 140.8 (C), 135.4 (Im-CH), 130.8 (Im-CH), 128.3 (Ar-CH), 127.8 (Ar-CH), 125.3 (Ar-CH), 121.04 (2-CH), 115.8 (Im-CH), 43.5 (1-CH), 28.9 (6-CH_2), 27.1 (4-CH_2), 20.1 (5-CH_2),
m/z (C.I., ammonia) 285.1062 (MH^+, 10 %, $C_{16}H_{16}N_2OSH^+$ requires MH^+, 285.1062), 225 (35), 189 (100), 157 (M^+-OCSIm, 15).

Preparation of *N-(2-Ethylquinazolinonyl)-1-phenyl-7-azabicyclo[4.1.0]heptan-5-one* (437)



Lead tetraacetate (0.82 g, 1.7 mmol) was added, over a period of 10 minutes, to a solution of 3-phenyl-2-cyclohexen-1-one **(330)** (0.21 g, 1.2 mmol), 3-amino-2-ethyl-4(3*H*)-quinazolinone (0.31 g, 1.28 mmol) and sodium carbonate (1.0 g, 9.4 mmol) in DCM (8 ml) at 0°C. The solution was left stirring at room temperature for 18 hours after which saturated sodium hydrogen carbonate solution (25 ml) and water (50 ml) were added. The solution was

extracted with DCM (3 x 20 ml). The combined extracts were then washed with saturated brine (3 x 25 ml), dried over magnesium sulfate and evaporated *in vacuo* to yield a yellow powder (0.45 g). Flash chromatography on basified silica (eluant 70:30 light petroleum:ethyl acetate) gave the *title compound* as a slightly yellow viscous liquid (0.26 g, 59 %)

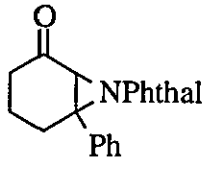
ν_{max}/cm^{-1} (DCM slurry) 3064 (Ar), 2941 (CH_2), 1716 (C=O), 1674 (C=O), 1596, 773 (Ph), 732 (Ar), 695 (Ph),

δ_H (250 MHz; $CDCl_3$) 8.09 (1 H, m, Q-H), 7.60 (1 H, m, Q-H), 7.45 (1 H, m, Q-H), 7.34 (1 H, m, Q-H), 7.18 (5 H, m, Ph), 4.77 (1 H, s, 6-CH), 3.12 (1 H, m, 4-CH), 2.96 (1 H, m, $CH_3\mathbf{CH_2}$), 2.72 (1 H, m, 2-CH), 2.54 (1 H, m, $CH_3\mathbf{CH_2}$), 2.35 (1 H, m, 3-CH), 2.28 (1 H, m, 2-CH), 2.22 (1 H, m, 4-CH), 1.97 (1 H, m, 3-CH), 1.25 (3 H, t, J = 7.5 Hz, CH_3).

δ_C (100 MHz; $CDCl_3$) 203.0 (C=O), 160.6 (C=O), 157.1 (C), 145.5 (C), 133.7 (Q-CH), 132.5 (C), 129.0 (Ar-CH), 128.4 (Ar-CH), 127.0 (Ar-CH), 126.6 (Q-CH), 126.3 (Q-CH), 126.2 (Q-CH), 120.9 (C), 56.2 (C), 53.6 (6-CH), 36.4 (2-CH_2), 28.1 (CH_2), 27.1 (4-CH_2), 17.4 (3-CH_2), 10.7 (CH_3).

m/z (C.I., ammonia) 360.1712 (MH^+, 4 %, $C_{22}H_{21}N_3O_2H^+$ requires MH^+, 360.1712), 190 (40), 175 (100), 173 (Q, 90)

Preparation of *N-(Phthalimido)-1-phenyl-7-azabicyclo[4.1.0]heptan-5-one* (438).



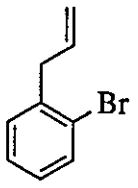
Lead tetraacetate (1.4 g, 3.2 mmol) was added to a solution of 3-phenyl-2-cyclohexen-1-one **(330)** (0.21 g, 1.2 mmol), *N*-aminophthalimide (0.45 g, 2.8 mmol) and sodium carbonate (0.51 g, 4.8 mmol) in DCM (10 ml) at 0°C. The mixture was then allowed to stir at room temperature for 1 hour. Saturated sodium hydrogen carbonate solution (5 ml) and saturated brine (20 ml) were added and then the solution was extracted using DCM (3 x 20 ml). The organic layer was then washed with saturated sodium hydrogen carbonate (4 x 30 ml), dried over magnesium sulfate and evaporated *in vacuo* to yield a light yellow solid (0.42 g). Recrystallisation using ethyl acetate/light petroleum gave a light beige powder (0.14 g, 35 %). m.p. 190°C.

ν_{max}/cm^{-1} (nujol) 3058 (Ar), 1784 (C=O), 1716 (C=O), 1609, 1499, 1467, 1376, 761 (Ph), 711 (Ar)

δ_H (400 MHz; $CDCl_3$) 7.59 (4 H, m, Phthal-H), 7.43 (2 H, dd, J = 8 and 1 Hz, Ph-H), 7.24 (3 H, m, Ph-H), 4.86 (1 H, s, 6-CH), 3.03 (1 H, m, 4-CH), 2.65 (1 H, m, 2-CH), 2.32 (1 H, m, 3-CH), 2.22 (1 H, m, 2-CH), 2.06 (1 H, m, 4-CH), 1.85 (1 H, m, 3-CH).

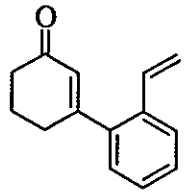
δ_C (100 MHz; $CDCl_3$) 203.8 (C=O), 165.3 (C=O),134.3 (C), 134.0 (Phthal-CH), 130.0 (C), 129.1 (Ar-CH), 129.0 (Ar-CH), 128.4 (Ar-CH), 122.9 (Phthal-CH), 56.2 (C), 48.5 (6-CH), 36.6 (2-CH_2), 29.2 (4-CH_2), 18.1 (3-CH_2),
m/z (E.I.) 332.1161 (M^+, 23 %, $C_{20}H_{16}N_2O_3$ requires M^+, 332.1161), 186 (M^+-Phthal, 38), 185 (78), 156 (50), 129 (100), 77 (30).

Preparation of 2-Allylbromobenzene (439).



Vinyl bromide (2.82 ml, 40 mmol) in THF (10 ml) was added dropwise to a stirred mixture of magnesium (2.4 g, 100 mmol), iodine (1 crystal) and THF (40 ml) under nitrogen in a flask fitted with a dry ice condenser. The resulting solution of vinylmagnesium bromide was allowed to cool, after which it was added *via* a syringe as rapidly as possible to a mixture of 2-bromobenzyl bromide (5 g, 20 mmol), copper iodide (500 mg) and 2,2'-bipyridine (420 mg) in toluene (10 ml) at 0°C. After stirring for 2 hours at room temperature, ammonium chloride (5 g) was added portionwise and after a further 10 minutes, ether (50 ml) and water (50 ml) were added. The organic fraction was separated and the aqueous fraction was further extracted with ether (3 x 50 ml). The combined organic fractions were washed with brine (150 ml) and evaporated *in vacuo* to give a brown oil. Purification by flash chromatography (eluant light petroleum) gave the *title compound* as a colourless oil (3.35 g, 85 %).
ν_{max}/cm^{-1} (neat) 3069, 3009, 2980, 2914, 1638, 1567, 1470, 1439, 1024, 994, 917, 745, 660, 640;
δ_H (250 MHz; $CDCl_3$) 7.53 (1 H, d, J = 8 Hz, Ar-CH), 7.23 (2 H, m, Ar-CH), 7.06 (1 H, m, ArCH), 5.95 (1 H, dtt, J = 5.5, 14 and 6.5 Hz, Ar**CH**=CH_2), 5.12 (1 H, dt, J = 5.5 and 1.5 Hz, RCH=**C**H_2, *cis*), 5.06 (1 H, dt, J = 14 and 1.5 Hz, RCH=**C**H_2, *trans*), 3.50 (2 H, dt, J = 6.5 and 1.5 Hz, Ar**C**H_2R);
δ_C (62.9 MHz; $CDCl_3$) 139.3 (Ar-CBr), 135.4 (Ar-CH), 132.6 (R**C**H=CH_2), 130.3 (Ar-CH), 127.7 (Ar-CH), 127.3 (Ar-CH), 124.5 (Ar-C), 116.5 (RCH=**C**H_2), 40.1 (Ar**C**H_2CH=CH_2).
Spectra consistent with those reported in the literature.[120]

Preparation of *3-(2-Vinylphenyl)-2-cyclohexen-1-one* (440)



A solution of bromostyrene (1.20 g, 6.6 mmol) was added dropwise to a stirred mixture of magnesium (0.61 g, 25.0 mmol), iodine (1 crystal) and THF (15 ml). After formation of the Grignard reagent the solution was stirred for 15 minutes and then 3-ethoxy-2-cyclohexen-1-one **(320)** (0.97 g, 7.0 mmol) was added. The solution was stirred for a further hour at room temperature after which HCl (2 M) was added (until all the excess magnesium was dissolved) and the mixture was extracted with DCM (3 x 30 ml). The combined organic fractions were washed with saturated brine (3 x 50 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a yellow oil (1.0 g). Purification by flash chromatography (eluant 75:25 light petroleum:ether) gave the *title compound* as a pale yellow oil (0.48 g, 37 %).

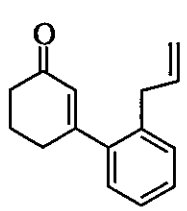
υ_{max}/cm^{-1} (DCM slurry) 2949 (CH_2), 1668 (C=O), 1613, 1326, 1245, 1189, 912, 770, 754 (Ph), 733 (Ph).

δ_H (400 MHz; $CDCl_3$) 7.56 (1 H, dd, J = 8 and 2 Hz, Ar-H), 7.30 (2 H, m, Ar-H), 7.14 (1 H, dd, J = 4 and 1 Hz, Ar-H), 6.74 (1 H, dd, J = 17.5 and 11 Hz, R**CH**=CH_2), 6.03 (1 H, t, J = 1.5 Hz, 2-CH), 5.69 (1 H, dd, J = 17.5 and 1 Hz, RCH=$\mathbf{CH_2}$), 5.28 (1 H, dd, J = 11 and 1 Hz, RCH=$\mathbf{CH_2}$), 2.59 (2 H, dt, J = 6 and 1.5 Hz, 4-CH_2), 2.47 (2 H, t, J = 6 Hz, 6-CH_2), 2.14 (2 H, quintet, J = 6 Hz, 5-CH_2),

δ_C (100 MHz; $CDCl_3$) 199.3 (C=O), 162.7 (3-C), 139.5 (Ar-C), 134.7 (R**CH**=CH_2), 129.4 (2-CH), 128.6 (Ar-CH), 127.7 (Ar-CH), 127.2 (Ar-CH), 126.2 (Ar-CH), 116.1 (RCH=$\mathbf{CH_2}$), 37.2 (6-CH_2), 31.4 (4-CH_2), 23.1 (5-CH_2).

Spectra are consistent with those reported in the literature.[120]

Preparation of *3-(2-Allylphenyl)-2-cyclohexen-1-one* (441)



A solution of 2-allylbromobenzene **(439)** (0.59 g, 3.0 mmol) was added dropwise to a stirred mixture of magnesium (0.20 g), iodine (1 crystal) and THF (5 ml). After formation of the Grignard reagent the solution was stirred for 15 minutes and then 3-ethoxy-2-cyclohexen-

1-one **(320)** (0.44 g, 3.2 mmol) was added. The solution was stirred for a further hour at room temperature after which HCl (2 M) was added (until all the excess magnesium was dissolved) and the mixture was extracted with DCM (3 x 25 ml). The combined organic fractions were washed with saturated brine (3 x 25 ml), dried over magnesium sulfate and evaporated *in vacuo* to give the *title compound* as an orange oil (0.61 g, 95 %). NMR analysis of the crude material showed this to be virtually pure.

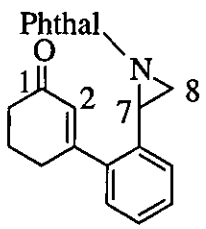
υ_{max}/cm^{-1} (neat) 2933, 1670, 1618, 1597, 1346, 1326, 1246, 1188, 758,

δ_H (250 MHz; $CDCl_3$) 7.26 (3 H, m, Ar-H), 7.11 (1 H, dt, J = 6.5 and 1.5 Hz, Ar-H), 6.00 (1 H, t, J =1.5 Hz, 2-CH), 5.90 (1 H, ddt, J = 17, 10 and 6 Hz, RC**H**=CH_2), 5.07 (1 H, dq, J = 10 and 1.5 Hz, RCH=C**H**$_2$), 4.98 (1 H, dq, J = 17 and 2 Hz, RCH=C**H**$_2$), 3.35 (2 H, dt, J = 6 and 1.5 Hz, Ar**CH**$_2$CH=CH_2), 2.58 (2 H, dt, J = 6 and 1.5 Hz, 4-CH_2), 2.49 (2 H, t, J = 6 Hz, 6-CH_2), 2.14 (2 H, quintet, J = 6 Hz, 5-CH_2).

δ_C (62.9 MHz; $CDCl_3$) 199.6 (C=O), 164.0 (3-C), 141.2 (Ar-C), 137.1 (ArCH_2**C**H=CH_2), 135.7 (Ar-C), 130.1 (Ar-CH), 128.7 (2-CH), 128.4 (Ar-CH), 127.0 (Ar-CH), 126.3 (Ar-CH), 116.2 (RCH=**C**H$_2$), 37.4 (Ar**C**H$_2$CH=CH_2), 37.2 (6-CH_2), 31.7 (4-CH_2), 23.0 (5-CH_2).

Spectra are consistent with those reported in the literature.[120]

Preparation of *3-(2-o-N-Phthalimidoaziridinylphenyl)-2-cyclohexen-1-one* (442)



Lead tetraacetate (0.44 g, 0.9 mmol) was added over a period of 10 minutes to a solution of 3-(2-vinylphenyl)-2-cyclohexen-1-one **(440)** (0.10 g, 0.5 mmol), *N*-amino phthalimide (0.10 g, 0.6 mmol) and sodium carbonate (0.11 g, 1.1 mmol) in DCM (2 ml) at 0°C. The solution was then allowed to warm to room temperature and left stirring for 40 minutes. DCM (20 ml) was added and the solution washed with saturated brine (3 x 20 ml), dried over magnesium sulfate and evaporated *in vacuo* to yield a clear yellow liquid (0.17 g). Flash chromatography using basified silica (eluant 50:50 ethyl acetate:light petroleum) gave the *title compound* as a slightly yellow liquid (56.6 mg, 31 %). Recrystallised using DCM/light petroleum to give a cream solid. m.p. 167-169°C.

υ_{max}/cm^{-1} (neat) 3059 (Ph), 2949 (CH_2), 1770 (C=O), 1715 (C=O), 1667 (C=O), 1377, 892, 759 (Ar), 735 (Ar), 709 (Ar).

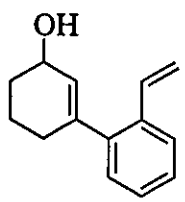
δ_H (400 MHz; $CDCl_3$) 7.77 (2 H, dd, J = 5.5 and 3 Hz, Phthal-H), 7.69 (2 H, dd, J = 5.5 and 3 Hz, Phthal-H), 7.54 (1 H, d, J = 7 Hz, Ar-H), 7.36 (2 H, m, Ar-H), 7.21 (1 H, dd, J = 7 and 1 Hz, Ar-H), 6.09 (1 H, s, 2-CH), 3.69 (1 H, dd, J = 8 and 5.5 Hz, 7-CH), 2.94 (1 H, dd, J = 8

and 2 Hz, 8-CH), 2.81 (1 H, ddt, J = 18.5 and 1 Hz, 4-CH), 2.70 (1 H, ddt, J =18.5, 6 and 1 Hz, 4-CH), 2.60 (1 H, dd, J = 5.5 and 2 Hz, 8-CH), 2.49 (2 H, t, J = 6.5 Hz, 6-CH_2), 2.17 (2 H, p, J = 6.5 Hz, 5-CH_2)

δ_C (62.9 MHz; $CDCl_3$) 199.2 (C=O), 164.9 (C=O), 161.8 (3-C), 140.5 (C), 134.1 (Phthal-CH), 133.2 (C), 130.2 (C), 129.4 (2-CH), 128.8 (Ar-CH), 127.6 (Ar-CH), 126.6 (Ar-CH), 126.5 (Ar-CH), 123.1 (Phthal-CH), 42.0 (7-CH), 41.1 (8-CH_2), 37.1 (6-CH_2), 31.5 (4-CH_2), 23.0 (5-CH_2).

m/z (C.I., ammonia) 359.1395 (MH^+, 12 %, $C_{22}H_{18}N_2O_3H^+$ requires MH^+, 359.1395), 216 (70), 214 (20), 199 (100), 182 (12), 180 (38), 52 (33).

Preparation of *3-(2-vinylphenyl)-2-cyclohexen-1-ol* (445)



Sodium borohydride (0.13 g, 3.3 mmol) was added portionwise to a stirred solution of 3-(2-vinylphenyl)-2-cyclohexen-1-one **(440)** (0.29 g, 0.1 mmol) and cerium(III) chloride heptahydrate (0.70 g, 1.9 mmol) in methanol (20 ml) at 0°C. After stirring for 1 hour, water (20 ml) was added and the mixture was extracted with DCM (3 x 50 ml). The combined organic fractions were washed with saturated brine (2 x 50 ml), dried over magnesium sulfate and evaporated *in vacuo* to give the *title compound* as a colourless oil (0.21 g, 72 %).

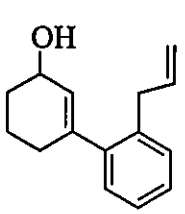
υ_{max}/cm^{-1} (neat) 3357 (OH), 2934, 2861, 1658, 1477, 1447, 1344, 1050, 972, 910, 774, 756,

δ_H (250 MHz; $CDCl_3$) 7.53 (1 H, m, Ar-H), 7.24 (2 H, m, Ar-H), 7.10 (1 H, m, Ar-H), 6.82 (1 H, dd, J = 17.5 and 11 Hz, Ar**CH**=CH_2), 5.68 (1 H, quintet, J = 1.5 Hz, 2-CH), 5.68 (1 H, dd, J = 17.5 and 1.5 Hz, ArCH=CH_2), 5.23 (1 H, dd, J = 11 and 1 Hz, ArCH=CH_2), 4.38 (1 H, m, 1-CH), 2.21 (2 H, m, 4-CH_2), 1.91 (2 H, m, 6-CH_2), 1.73 (2 H, m, 5-CH_2)

δ_C (62.9 MHz; $CDCl_3$) 142.2 (Ar-C), 141.6 (Ar-C), 135.4 (Ar**CH**=CH_2), 135.1 (3-C), 129.5 (2-CH), 128.3 (Ar-CH), 127.6 (Ar-CH), 127.2 (Ar-CH), 125.4 (Ar-CH), 114.5 (Ar-CH=CH_2), 65.6 (1-CH), 31.6 (6-CH_2), 30.7 (4-CH_2), 19.5 (5-CH_2).

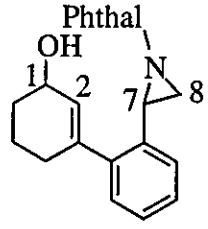
Spectra are consistent with those reported in the literature.[120]

Preparation of *3-(2-Allylphenyl)-2-Cyclohexen-2-ol* (446)



Sodium borohydride (0.13 g, 3.5 mmol) was added portionwise to a stirred solution of 3-(2-allylphenyl)-2-cyclohexen-1-one **(441)** (0.62 g, 2.9 mmol) and cerium(III) chloride heptahydrate (1.3 g, 3.5 mmol) in methanol (10 ml) at 0°C. After stirring for 1 hour, water (20 ml) was added and the mixture was extracted with DCM (3 x 20 ml). The combined organic fractions were washed with saturated brine (3 x 20 ml), dried over magnesium sulfate and evaporated *in vacuo* to give the *title compound* as a clear yellow liquid (0.33 g, 53 %).
υ_{max}/cm^{-1} (neat) 3329 (OH), 2934 (CH_2), 2861, 1637, 1598, 1485, 1443, 1431, 1342, 1290, 1153, 1051, 972, 912, 756.
δ_H (250 MHz; $CDCl_3$) 7.19 (3 H, m, Ar-H), 7.07 (1 H, m, Ar-H), 5.92 (1 H, ddt, J = 16.5, 10 and 6.5 Hz, Ar-CH_2**CH**=CH_2), 5.64 (1 H, dt, J = 3.5 and 2 Hz, 2-CH), 5.05 (1 H, ddt, J = 10, 2 and 1.5 Hz, Ar-CH_2CH=**CH_2**), 5.02 (1 H, ddt, J = 16.5, 2 and 1.5 Hz, Ar-CH_2CH=CH_2), 3.38 (2 H, dt, J = 6.5, and 1.5 Hz, Ar**CH_2**CH=CH_2), 2.22 (2 H, m, 4-CH_2), 1.93 (2 H, m, 6-CH_2), 1.74 (2 H, m, 5-CH_2),
δ_C (62.9 MHz; $CDCl_3$) 143.0 (3-C), 141.9 (Ar-C), 138.0 (Ar-CH_2**CH**=CH_2), 136.6 (Ar-C), 129.5 (Ar-CH), 128.4 (2-CH), 128.3 (Ar-CH), 127.0 (Ar-CH), 125.9 (Ar-CH), 115.7 (Ar-CH_2CH=**CH_2**), 65.8 (1-CH), 37.3 (Ar-**CH_2**CH=CH_2), 31.4 (6-CH_2), 30.9 (4-CH_2), 19.5 (5-CH_2).
Spectra consistent with that reported in the literature.[120]

Preparation of *3-(2-o-N-Phthalimidoaziridinylphenyl)-2-cyclohexen-1-ol* (447)



Lead tetraacetate (0.30 g, 0.6 mmol) was added over a period of 10 minutes to a solution of 3-(2-vinylphenyl)-2-cyclohexen-1-ol **(445)** (0.11 g, 0.5 mmol), *N*-amino phthalimide (0.11 g, 0.6 mmol) and sodium carbonate (0.12 g, 1.1 mmol) in DCM (2 ml) at 0°C. The solution was then allowed to warm to room temperature and left stirring for 40 minutes. DCM (20 ml) was added and the solution washed with saturated brine (3 x 50 ml), dried over magnesium sulfate and evaporated *in vacuo* to yield a yellow semi-solid (0.16 g). Flash chromatography using basified silica (eluant 50:50 ethyl acetate:light petroleum) gave the the *title compound* as a creamy coloured solid (37.4 mg, 20 %) (2:1 mixture of diastereoisomers).
υ_{max}/cm^{-1} (DCM slurry) 3471 (OH), 3063 (Ar), 3028 (Ar), 2938 (CH_2), 1768 (C=O), 1715 (C=O), 1611, 1488, 1467, 1378 (OH) 1159 (C-O), 911 (Ar), 732 (Ar), 709 (Ar),

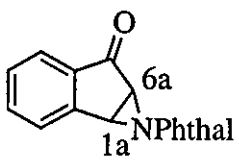
δ_H (400 MHz; $CDCl_3$) 7.76 (2 H, m, Phthal-H), 7.67 (2 H, m, Phthal-H), 7.47 (1 H, m, Ph-H, min), 7.38 (1 H, m, Ph-H, maj), 7.27 (2 H, m, Ar-H, maj), 7.14 (1 H, m, Ar-H), 5.83 (1 H, m, 2-CH, maj), 5.78 (1 H, m, 2-CH, min), 4.35 (1 H, br s, 1-CH), 3.79 (1 H, m, 7-CH), 2.87 (1 H, dd, J = 8 and 2 Hz, 8-CH), 2.62 (1 H, dd, J = 6 and 2 Hz, 8-CH, maj), 2.55 (1 H, dd, J = 5.5 and 2 Hz, 8-CH, min), 2.32 (2 H, m, 4-CH_2), 1.89 (2 H, m, 5-CH and 6-CH), 1.70 (2 H, m, 5-CH and 6-CH),

δ_C (100 MHz; $CDCl_3$) maj isomer 165.2 (C=O), 143.3 (C), 140.7 (C), 134.2 (Phthal-CH), 133.6 (3-C), 130.2 (C), 129.9 (2-CH), 127.7 (Ar-CH), 127.4 (Ar-CH), 125.7 (Ar-CH), 123.1 (Phthal-CH), 65.6 (1-CH), 41.8 (7-CH), 41.4 (8-CH_2), 31.4 (6-CH_2), 30.9 (4-CH_2), 19.4 (5-CH_2),

min isomer 165.1 (C=O), 143.0 (C), 140.7 (C), 134.1 (Phthal-CH), 133.7 (C), 130.3 (C), 129.8 (2-CH), 127.7 (Ar-CH), 127.3 (Ar-CH), 126.1 (Ar-CH), 123.1 (Phthal-CH), 65.7 (1-CH), 42.2 (7-CH), 41.2 (8-CH_2), 31.4 (6-CH_2), 30.7 (4-CH_2), 19.5 (5-CH_2).

m/z (C.I., ammonia) 361.1552 (MH^+, 2 %, $C_{22}H_{20}N_2O_3H^+$ requires MH^+, 361.1552), 343 (12), 216 (20), 200 (40), 183 (100), 180 (80).

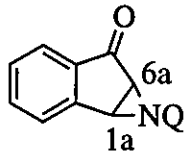
Preparation of *1-Phthalimidoindano[1, 2b]aziridin-6-one* (449).



Lead tetraacetate (0.87 g, 1.9 mmol) was added portionwise to a solution of indenone **(398)** (0.20 g, 1.5 mmol), *N*-aminophthalimide (0.32 g, 1.95 mmol) and sodium carbonate (0.51 g, 4.8 mmol) in DCM (4 ml). After an hour at room temperature, saturated sodium hydrogen carbonate solution was added (5 ml) along with DCM (20 ml). The solution was shaken and separated. The organic layer was further washed with saturated brine (3 x 20 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a yellow solid (0.54 g, estimated 64 % yield). The compound was unstable to flash chromatography (both basified and unbasified silica). A tentative assignment from NMR analysis of the crude material is as follows (the aromatic protons are covered by impurity signals).

δ_H (250 MHz; $CDCl_3$) 4.60 (1 H, dd, J = 3.5 and 0.5 Hz, 1a-CH), 3.83 (1 H, d, J = 3.5 Hz, 6a-CH).

Preparation of *1-(2-Ethylquinazolinonyl)indano-[1, 2b]aziridin-6-one* (450).



Lead tetraacetate (0.94 g, 2.12 mmol) was added portionwise, over a period of 10 minutes, to a solution of indenone **(398)** (0.25 g, 1.9 mmol), 3-amino-2-ethyl-4(3*H*)-quinazolinone (0.44 g, 2.4 mmol) in DCM (7.5 ml). After 2 hours at room temperature saturated sodium bicarbonate solution (5 ml) was added. DCM (20 ml) was added and the solution washed with saturated brine (3 x 20 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a yellow solid (0.66 g). Flash chromatography on basified silica (eluant 70:30 light petroleum:ethyl acetate) afforded the *title compound* as a yellow powdery solid (0.10 g, 17 %). m.p. 163-165 °C (decomposition).

ν_{max}/ cm^{-1} (DCM slurry) 3072 (Ar), 2982 (Ar), 2939 (Ar), 1726 (C=O), 1674 (C=O), 769 (Ar), 732 (Ar);

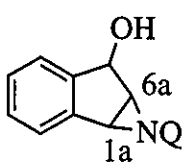
Found C, 71.63; H, 4.74; N, 13.25. $C_{19}H_{15}N_3O_2$ requires C, 71.9; H, 4.77; N, 13.25.

δ_H (250 MHz; $CDCl_3$) 8.17 (1 H, m, Q-H), 7.82 (2 H, m, Ar-H), 7.67 (3 H, m, 2 x Q-H, Ar-H), 7.51 (1 H, m, Ar-H), 7.43 (1 H, m, Ar-H), 5.25 (1 H, d, J = 5 Hz, 6a-CH), 4.11 (1 H, d, J = 5 Hz, 1a-CH), 3.03 (2 H, dq, J = 7.5 and 2 Hz, CH_2), 1.31 (3 H, t, J = 7.5 Hz, CH_3),

δ_C (100 MHz; $CDCl_3$) 196.1 (C=O), 160.8 (C), 158.5 (C), 149.2 (C), 146.4 (C), 136.3 (C), 135.3 (CH), 134.7 (CH), 130.0 (CH), 127.5 (CH), 127.0 (CH), 126.7 (CH), 126.6 (CH), 125.6 (CH), 121.8 (C), 50.6 (CH), 46.2 (CH), 28.3 (CH_2), 11.4 (CH_3).

m/z (E.I.) 317.1167 (M^+, 100 %, $C_{19}H_{15}N_3O_2$ requires M^+, 317.1164) 288 (M^+-Et, 62), 173 (Q, 75), 145 (85).

Preparation of *1-(2-Ethylquinazolinonyl)indano-[1, 2b]aziridin-6-ol* (451).



Sodium borohydride (30 mg, 0.79 mmol) was added to a solution of *N*-(2-ethyl quinazolinonyl)-10-azabicyclo[3.1.0]indan-8-one **(450)** (0.15 g, 0.49 mmol) in methanol (100 ml). After stirring at room temperature overnight, the methanol was evaporated off until approximately 5 ml remained. Saturated brine (20 ml) was added and the solution extracted with DCM (3 x 30 ml). The combined organic fractions were washed with saturated brine (3 x 20 ml), dried over magnesium sulfate and evaporated *in vacuo* to give a cream solid (0.17

g). Recrystallisation using DCM/light petroleum gave a beige powder (91.1 mg, 60 %). (Compound appears to degrade over time in DCM to give a yellow coloured solution). m.p. 189.4-190.3°C (decomposition).

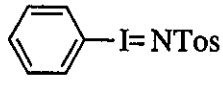
ν_{max}/cm^{-1} (nujol) 3454 (OH), 1662 (C=O), 1595, 1295 (OH), 1071 (C-O), 762 (Ar);

δ_H (250 MHz; $CDCl_3$) 8.19 (1 H, m, Q-H), 7.68 (3 H, m, Ar-H), 7.41 (4 H, m, Ar-H), 5.63 (1 H, dd, J = 9 and 4.5 Hz, 6-CH), 4.08 (1 H, d, J = 5.5 Hz, 1a-CH), 4.04 (1 H, dd, J = 5.5 and 4.5 Hz, 6a-CH), 3.16 (2 H, q, J = 7.5 Hz, CH_2), 3.02 (1 H, d, J = 9 Hz, OH), 1.40 (3 H, t, J = 7.5 Hz, CH_3);

δ_C (62.9 MHz; $CDCl_3$) 163.8 (C), 162.8 (C), 150.8 (C), 150.3 (C), 143.6 (C), 138.9 (CH), 133.9 (CH), 132.9 (CH), 131.7 (CH), 131.2 (CH), 130.9 (CH), 130.5 (CH), 130.1 (CH), 126.1 (C), 79.7 (CH), 57.9 (CH), 56.5 (CH), 31.5 (CH_2), 15.9 (CH_3)

m/z (C.I.) 320.1399 (MH^+, 5 %, $C_{19}H_{18}N_3O_2H^+$ requires MH^+, 320.1399), 190 (15), 175 (52), 130 (100).

Preparation of *(N-(p-Toluenesulfonyl)imino)phenyliodinane* (453)



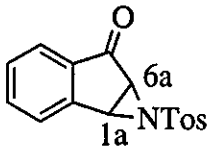
Iodobenzene diacetate (3.2 g, 9.9 mmol) was added to a solution of potassium hydroxide (1.4 g, 25.2 mmol) and *p*-toluenesulfonamide (1.7 g, 10.0 mmol) in methanol (40 ml) at 4°C. A yellow colour developed after approximately 1 minute and the solution was then allowed to warm to room temperature and stirred for a further 3 hours. Water (45 ml) was added and the mixture was refridgerated overnight. The precipitate was collected by vacuum filtration and air dried to give a light yellow powder (2.5 g). The powder was dissloved in methanol (60 ml) and water (60 ml) was added. The solution was refridgerated overnight at approximately -20°C. Filtering and air drying the precipitate gave the *title compound* as a finely divided yellow powder (1.9 g). Repeated recrystallisation gave the *title compound* as a cream precipitate (0.91 g, 25 %). m.p. 88°C (decomposition). (Lit. decomposition above 90°C).[138]

ν_{max}/cm^{-1} (nujol) 1594, 1562, 1494, 1265, 1132, 865 (Ar), 665 (Ar)

δ_H (250 MHz, D_6-DMSO) 7.67 (2 H, d, J = 8 Hz, Tos-CH), 7.44 (3 H, d, J = 8 Hz, Ph), 7.28 (2 H, t, J = 8 Hz, Ph), 7.05 (2 H, d, J = 8 Hz, Tos-CH), 2.26 (3 H, s, CH_3).

Spectra are consistent with those reported in the literature.[138]

Preparation of *1-Tosylindano[1, 2b]aziridin-6-one* (457).



Method a:PhI=NTos as base.

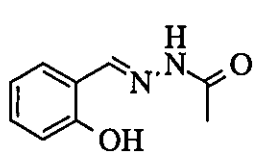
(*N*-(p-toluenesulfonyl)imino)phenyliodinane **(453)** (29.0 mg, 0.08 mmol) was added to a solution of indenone **(398)** (50.0 mg, 0.4 mmol) and copper(II) acetylacetonate (3.3 mg, 0.01 mmol) in acetonitrile (1 ml). The solution turns from brown to green. After stirring at room temperature for 6 hours the solvent was evaporated *in vacuo* to give a green coloured liquid (70 mg). Flash chromatography (eluant 80:20 light petroleum:ethyl acetate) gave the *title compound* as an orange solid (7.1 mg, 8 %).

Method b: Chloramine-T as base

Chloramine-T (36.5 mg, 0.2 mmol, pre-dried under high vacuum overnight) was added to a solution of indenone **(398)** (0.10 g, 0.8 mmol), 5A molecular sieves (powdered) (50 mg) and copper(I) chloride (0.8 mg, 0.008 mmol) in acetonitrile (1 ml). The solution immediately turns green. After stirring at room temperature for 5 hours the solvent was evaporated off *in vacuo* to give a green liquid (0.15 g). NMR analysis showed broad peaks in the expected regions (estimated yield 17 %). The *title compound* was not purified. The yield was determined by ^{1}H-NMR analysis of the crude product.

ν_{max}/cm^{-1} (DCM slurry) 3068 (Ar), 2924 (CH), 1731 (C=O), 1607, 1469, 1334, 1159, 883 (Ar), 769 (Ar).
δ_H (250 MHz; $CDCl_3$) 7.82 (2 H, d, J = 8 Hz, Tos-H), 7.70 (1 H, m, Ar-H), 7.59 (2 H, m, Ar-H), 7.44 (1 H, m, Ar-H), 7.34 (H, d, J = 8 Hz, Tos-H), 4.51 (1 H, dd, J = 5 and 0.5 Hz, 1a-CH), 3.83 (1 H, d, J = 5 Hz, 6a-CH), 2.46 (3 H, s, CH_3)
m/z (E.I) 299.0616 (M^+, 65 %, $C_{16}H_{13}NO_3S$ requires M^+, 299.0616), 155 (Tos, 32), 144 (M^+-Tos, 80), 130 (38), 91 (100)

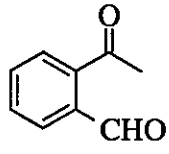
Preparation of *N'1-[(E)-1-(2-Hydroxyphenyl)methylidene]ethanohydrazide* (466).



Salicylaldehyde (1.4 g, 11.6 mmol) was added to a solution of acetic hydrazide (0.95 g, 11.5 mmol) in 1-propanol (80 ml) and the solution heated to reflux for 24 hours. The

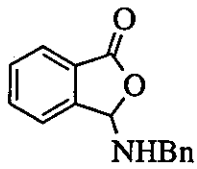
solution was then cooled and the white solid formed was filtered to give the *title compound* as a mixture of isomers (3:2), (1.6 g, 75 %). m.p. 205.5 - 206.1 °C (lit. 210°C).[155]
ν_{max}/cm^{-1} (nujol) 1682 (C=O), 1321, 1574, 1342 (O-H), 1266 (C-O), 755 (Ph);
δ_H (250 MHz; D_6-DMSO) 11.63 (1 H, s, NH, maj), 11.25 (2 H, br s, OH, maj and NH, min), 10.15 (1 H, br s, OH, min), 8.32 (1 H, s, HC=N, maj), 8.25 (1 H, s, HC=N, min), 7.60 (1 H, dd, J = 8 and 1.5 Hz, Ar-H, min), 7.47 (1 H, dd, J = 8 and 1.5 Hz, Ar-H, maj), 7.24 (3 H, m, Ar-H, min), 6.85 (3 H, m, Ar-H, maj), 2.18 (3 H, s, CH_3, min), 1.98 (3 H, s, CH_3, maj).
δ_C (100 MHz; D_6-DMSO) 171.8 (C, min), 165.6 (C, maj), 157.5 (C, maj), 156.5 (C, min), 146.5 (CH, maj), 131.5 (CH, min), 131.3 (CH, maj), 131.1 (CH, maj), 129.7 (CH, min), 126.9 (CH, min), 120.2 (C, min), 119.6 (CH, min), 119.4 (CH, maj), 118.7 (C, maj), 116.5 (CH, maj), 116.3 (CH, min), 21.5 (CH_3, maj), 20.5 (CH_3, min).

Preparation of *2-Acetylbenzaldehyde* (467).



Iodobenzene diacetate (2.9 g, 9.0 mmol) was added portionwise to a solution of *N'* 1-[(*E*)-1-(2-hydroxyphenyl)methylidene]ethanohydrazide (**466**) (0.80 g, 4.5 mmol) in DCM (45 ml). After the solution had become clear brown (approximately 1 hour) the solution was washed with saturated sodium hydrogen carbonate solution (3 x 30 ml), dried over magnesium sulfate and evaporation *in vacuo* gave a brown viscous liquid (2.5 g). Flash chromatography (eluant 60:40 light petroleum:ethyl acetate) gave a yellow viscous liquid (0.15 g). Recrystallisation using methanol and water afforded the *title compound* as a cream powder (0.46 g, 17 %). m.p. 70.5-73.6 (lit 41-42°C).[141]
ν_{max}/cm^{-1} (nujol) 1622, 1591, 1548, 1242, 1154, 833, 752 (Ar), 708 (Ar);
δ_H (250 MHz; $CDCl_3$) 10.1 (1 H, br s, should be aldehyde, exchanges with D_2O), 7.72 (1 H, ddd, J = 8, 1.5 and 0.5 Hz, Ar-H), 7.43 (1 H, dq, J = 8 and 1.5 Hz, Ar-H), 7.12 (1 H, ddd, J = 8, 1 and 0.5 Hz, Ar-H), 6.99 (1 H, dq, J = 8 and 1 Hz, Ar-H), 2.65 (3 H, s, CH_3)
δ_C (100 MHz; $CDCl_3$) 164.5 (C), 162.4 (C), 157.4 (C), 133.5 (CH), 126.3 (CH), 119.8 (CH), 117.4 (CH), 108.1 (C), 10.9 (CH_3);
m/z (E.I.) 176 (unknown, 100), 147 (M^+, 6 %), 121 (95), 105 (32), 43 (40).
Spectral data is consistent with those stated in the literature except that the signal at δ 10.1 exchanges with D_2O. Other data is inconsistent with that in the literature.[140]

Preparation of *N-[1(3H)-Isobenzofuranon-3-yl]benzylamine* (474)



Benzylamine (220 µl, 2.0 mmol) was added to a solution of 2-carboxybenzaldehyde (0.30 g, 2.0 mmol) and magnesium sulfate (0.53 g, 4.41 mmol) in DCM (12.5 ml). The solution was left stirring at room temperature for 24 hours, after which filtration and evaporation *in vacuo* gave the *title compound* as a cream solid (0.46 g, 95 %) m.p. 84-86°C (lit. 86-89°C).[156]

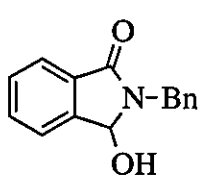
ν_{max}/cm^{-1} (DCM slurry) 3347 (NH), 3029 (Ar), 3062 (Ar), 2899 (CH_2), 2863, 1746 (C=O), 1495, 1454, 1286, 1074, 747 (Ar), 697 (Ar).

δ_H (400 MHz; $CDCl_3$) 7.84 (1 H, d, J = 7.5 Hz, Ar-H), 7.64 (1 H, dt, J = 7.5 and 1 Hz, Ar-H), 7.55 (2 H, m, Ar-H), 7.32 (4 H, m, Ar-H), 7.24 (1 H, m, Ar-H), 6.29 (1 H, s, CH), 4.00 (2 H, s, CH_2),

δ_C (100 MHz, $CDCl_3$) 170.1 (C=O), 146.2 (C), 139.2 (C), 134.4 (CH), 130.8 (CH), 129.0 (CH), 128.9 (C), 128.8 (CH), 127.9 (CH), 125.9 (CH), 124.3 (CH), 49.4 (CH_2);

Spectra are consistent with those reported in the literature.[156]

Preparation of *3-Hydroxy-2-benzylisoindolin-1-one* (476)



DMF (9 µl, 0.1 mmol) was added to a solution of *N*-[1(3*H*)-isobenzofuranon-3-yl]benzylamine (**474**) (0.40 g, 1.7 mmol) and oxalyl chloride (176 µl, 2.0 mmol) in DCM (21 ml). After approximately 1.5 hours the solution was evaporated *in vacuo* to give a slightly pink liquid containing some white crystals (0.47 g). Flash chromatography (eluant 60:40 light petroleum:ethyl acetate) gave a clear colourless liquid which crystallises on cooling (0.13 g, 33 %). Recrystallised from DCM to give a white powder. m.p. 139.7-140.2°C (lit. 141-142°C).[157]

ν_{max}/cm^{-1} (neat) 3194 (OH), 1660 (C=O), 1495, 1312 (OH), 1054 (C-O), 752 (Ar), 706 (Ar);

δ_H (400 MHz; $CDCl_3$) 7.68 (1 H, m, Ar-H), 7.54 (2 H, m, Ar-H), 7.45 (1 H, m, Ar-H), 7.27 (5 H, m, Ph), 5.58 (1 H, s, 3-CH), 4.81 (1 H, d, J = 15 Hz, CH_2), 4.21 (1 H, d, J = 15 Hz, CH_2) 4.36 (1 H, br s, OH);

δ_C (100 MHz; $CDCl_3$) 168.7 (C), 145.0 (C), 137.6 (C), 133.4 (Ar-CH), 132.0 (C), 130.7 (Ar-CH), 129.7 (Ar-CH), 129.4 (Ar-CH), 128.6 (Ar-CH), 124.5 (Ar-CH), 124.3 (Ar-CH), 81.9 (CH), 43.6 (CH_2).

Spectra are consistent with those reported in the literature.[157]

Preparation of *Benzylaminotriphenylphosphonium bromide* -[Ph_3PNHBn]Br (479).

Triethylamine (165 µl, 1.2 mmol) and benzylamine (130 µl, 1.2 mmol) were added simultaneously and dropwise to a solution of triphenylphosphine dibromide (0.58 g, 1.4 mmol) in DCM (5 ml) at room temperature. The solution was left stirring at room temperature for 1 hour, afterwhich evaporation *in vacuo* gave a white cloudy liquid which solidified on cooling (0.83 g). Recrystallisation using DCM/ethyl acetate afforded the *title compound* as a cream powder which was then washed with ether and ice-cold water and dried (0.46 g, 54 %).

m.p. 198.8-200.8°C (lit. 195-197°C).[144]

ν_{max}/cm^{-1} 3320 (NH), 1587, 724, 689 (Ar);

δ_H (250 MHz; $CDCl_3$) 7.76 (10 H, m, Ar-H), 7.58 (6 H, m, Ar-H), 7.15 (4 H, m, Ar-H), 4.29 (2 H, dd, J = 16 and 7 Hz, CH_2), 1.65 (1 H, br s, NH),

δ_C (100 MHz; D_6-DMSO) 139.0 (C), 135.9 (CH), 134.2 (CH), 131.2 (CH), 129.3 (CH), 128.2 (CH), 122.2 (C), 121.2 (C), 45.7 (CH_2);

Spectra are consistent with those reported in the literature.[158]

Preparation of *Triphenylphosphinylbenzylimine* -PPh_3=NBn (480).

A solution of benzylaminotriphenylphosphonium bromide **(479)** (200 mg, 0.5 mmol) and potassium hydroxide (72.2 mg, 1.2 mmol) in ether (5.5 ml) was left stirring at room temperature for 48 hours, after which filtration and evaporation *in vacuo* gave a clear liquid containing some crystalline material (0.15 g, 71 % pure). Flash chromatography (eluant 90:10 ethyl acetate:methanol degrades the compound). Therefore it was directly used in the next stage.

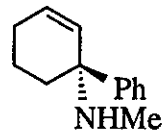
ν_{max}/cm^{-1} (neat) 3073, 3059, 3024 (Ar), 2819, 2775 (CH_2), 1603, 1589, 1492, 1487, 1437, 732 (Ar), 695 (Ar);

δ_H (250 MHz; $CDCl_3$) 7.62 (8 H, m, Ar), 7.44 (12 H, m, Ar), 4.36 (2 H, d, J = 18 Hz, CH_2);

δ_C (100 MHz; $CDCl_3$) 145.2 (C), 145.1 (C), 143.3 (C), 133.1 (C), 132.7 (CH), 132.6 (CH), 132.1 (CH), 132.0 (CH), 128.54 (CH), 128.53 (CH), 128.4 (CH), 127.8 (CH), 127.2 (CH), 48.5 (CH_2).

Spectra are consistent with those reported in the literature.[146]

Preparation of *1-Methylamino-1-phenyl-5-cyclohexene* (482)



A solution of tributyltin hydride (130 µl, 0.5 mmol) and AIBN (50 mg) in THF (10 ml) was added dropwise, over half an hour, to a refluxing solution of *N*-methyl-5-[imidazol-1-yl(thiocarbonyl)oxy]-1-phenyl-7-azabicyclo[4.1.0]heptane (**390**) (55.3 mg, 0.18 mmol) in THF (30 ml). The solution was then refluxed for 2 hours after which evaporation *in vacuo* afforded a creamy yellow liquid (0.25 g). Flash chromatography on basified silica (eluant 60:40 light petroleum:ethyl acetate) afforded the *title compound* as a clear, yellow liquid (5.0 mg, 15 %)

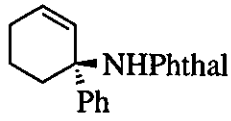
υ_{max}/cm^{-1} 3320 (NH), 3084 (Ph), 3057 (Ph), 3021 (Ph), 2937 (CH_2), 1642, 1599, 762 (Ph), 736, 701 (Ph);

δ_H (400 MHz; $CDCl_3$) 7.47 (2 H, m, Ph), 7.33 (2 H, m, Ph-H), 7.24 (1 H, m, Ph-H), 6.02 (1 H, dt, J = 10 and 3.5 Hz, 5-CH), 5.92 (1 H, br d, J = 10 Hz, 6-CH), 1.97 (5 H, m and s, CH_3 and 4-CH_2), 1.86 (1 H, m, 2-CH), 1.62 (1 H, m, 3-CH), 1.42 (1 H, m, 3-CH),

δ_C (100 MHz; $CDCl_3$) 145.9 (C), 145.2 (C), 130.6 (CH), 129.5 (CH), 128.0 (CH), 127.3 (CH), 126.5 (CH), 37.71 (CH_2), 29.1 (CH_3), 24.9 (CH_2), 19.1 (CH_2)

m/z (E.I.) 187.1361 (M^+, 11 %, $C_{13}H_{17}N$ requires M^+, 187.1361), 157 (100), 91 (72).

Preparation of *1-(Phthalimidoamino)-1-phenyl-5-cyclohexene* (483)



A solution of AIBN (30 mg) and tributyltin hydride (540 µl, 2.0 mmol) in THF (30 ml) was added dropwise, over an hour, to a refluxing solution of *N*-(phthalimido-5-[imidazol-1-yl(thiocarbonyl)oxy]-1-phenyl-7-azabicyclo[4.1.0]heptane (**431**) (0.31 g, 0.75 mmol) in THF (10 ml). The solution was then refluxed for 12 hours, after which evaporation *in vacuo* afforded a creamy yellow viscous liquid (0.94 g). Flash chromatography on basified silica (eluant 80:20 light petroleum:ethyl acetate) afforded a cream solid (0.15 g, 62 %), Re-crystallised using DCM/petrol to give a white solid. m. p. 137.5-139.5°C.

Found C, 75.05; H, 5.87; N, 9.11. $C_{20}H_{18}N_2O_2$ requires C, 75.45; H, 5.70; N, 8.80.

ν_{max}/cm^{-1} (DCM slurry) 3313 (NH), 1764 (C=O), 1721 (C=O), 1612, 883, 755 (Ph), 716 (Ar), 696 (Ph),

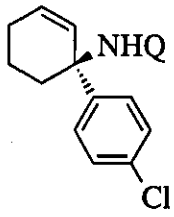
δ_H (400 MHz; $CDCl_3$) 7.80 (2 H, m, 2 x Phthal-H), 7.69 (4 H, m, 2 x Ar-H and 2 x Phthal-H), 7.35 (2 H, m, Ph-H), 7.27 (1 H, m, Ph-H), 6.08 (1 H, m, 6-CH), 5.99 (1 H, dt, J = 10.5

and 3.5 Hz, 5-CH), 4.82 (1 H, s, NH), 2.19 (1 H, m, 2-CH), 2.01 (1 H, dt, J = 10 and 3 Hz, 2-CH), 1.92 (2 H, m, 4-CH_2), 1.59 (1 H, m, 3-CH), 1.32 (1 H, m, 3-CH),

δ_C (62.9 MHz, $CDCl_3$) 167.6 (C), 143.7 (C), 134.1 (Phthal-CH), 131.6 (5-CH), 131.0 (6-CH), 130.25 (C), 128.0 (Ar-CH), 127.6 (Ar-CH), 127.4 (Ar-CH), 123.3 (Phthal-CH), 65.2 (C), 35.0 (2-CH_2), 24.7 (4-CH_2), 19.2 (3-CH_2).

m/z (E. I.) 318.1368 (M^+, <1 %, $C_{20}H_{18}N_2O_2$ requires M^+, 318.1368), 171 (M^+-Phthal, 3), 157 (M^+-PhthalNH, 100), 129 (60), 115 (58), 104 (78), 91 (100), 77 (60), 76 (55).

Preparation of *1-(2-Ethylquinazolinonylamino)-1-(4-chlorophenyl)-5-cyclohexene* (484).



A solution of tributyltin hydride (550 µl, 2.04 mmol) and AIBN (50 mg) in THF (30 ml) was added dropwise, over a period of 1 hour, to a refluxing solution of *N*-(2-ethylquinazolinonyl)-5-[imidazol-1-yl(thiocarbonyl)oxy]-1-[4-chlorophenyl]-7-azabicyclo [4.1.0]heptane (**432**) (0.41 g, 0.81 mmol) in THF (10 ml). The solution was refluxed for 1.5 hours, after which evaporation *in vacuo* afforded a yellow gelatinous residue (1.1 g). Flash chromatography (eluant 80:20 light petroleum:ethyl acetate) gave the *title compound* as an impure white crystalline material (0.22 g). Recrystallisation using DCM/light petroleum gave a white crystalline material (impurity) and the *title compound* as a colourless residue (0.12 g, 40 %).

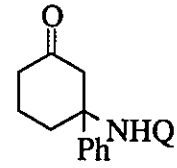
ν_{max}/cm^{-1} (neat) 3275 (NH), 2936 (CH_2), 1680 (C=O), 1592, 1489, 1471, 824 (Ph), 733 (Ph);

δ_H (250 MHz; D_6-DMSO, 80°C) 8.05 (1 H, m, Q-H), 7.77 (1 H, m, Q-H), 7.59 (1 H, m, Q-H), 7.55 (2 H, d, J = 5.5 Hz, Ph-H), 7.46 (1 H, m, Q-H), 7.37 (2 H, d, J = 5.5 Hz, Ph-H), 6.31 (1 H, s, NH), 5.94 (2 H, m, 5-CH and 6-CH), 2.87 (2 H, q, J = 7 Hz, $CH_3\mathbf{CH_2}$), 2.09 (2 H, m, 2-CH_2), 1.91 (2 H, m, 4-CH_2), 1.65 (1 H, m, 3-CH), 1.24 (1 H, m, 3-CH), 1.19 (3 H, t, J = 7 Hz, CH_3);

δ_C (62.9 MHz; D_6-DMSO, 80°C), 162.4 (C), 161.0 (C), 146.4 (C), 143.8 (C), 134.1 (Q-CH), 132.1 (C), 130.9 (5-CH), 129.6 (6-CH), 129.0 (Ar-CH), 128.0 (Ar-CH), 126.8 (Q-CH), 126.1 (Q-CH), 126.0 (Q-CH), 120.5 (C), 63.9 (C), 35.2 (2-CH_2), 27.3 (CH_2), 24.3 (4-CH_2), 18.8 (3-CH_2), 10.8 (CH_3);

m/z (C. I.) 380.1530 (MH^+, 10 %, $C_{22}H_{22}N_3OClH^+$ requires MH^+, 380.1530), 206 (M^+-Q, 47), 191 (M^+-QNH_2, 94), 190 (70), 175 (100).

Preparation of *3-(2-Ethylquinazolinonylamino)-3-phenylcyclohexan-2-one* (485).



A solution of tributyltin hydride (540 µl, 2.0 mmol) and AIBN (50 mg) in THF (40 ml) was added dropwise, over an hour, to a refluxing solution of *N*-(2-ethylquinazolinonyl)-1-phenyl-7-azabicyclo[4.1.0]heptan-5-one **(437)** (0.25 g, 0.71 mmol) in THF (20 ml). The solution was then refluxed for 12 hours after which evaporation *in vacuo* afforded a creamy yellow solid (0.84 g). Flash chromatography on basified silica (eluant 70:30 light petroleum:ethyl acetate) afforded a clear, slightly yellow liquid which solidifies on cooling to give an orange solid (0.13 g, 50 %). m.p. 137.5-139.8°C.

Found C, 73.10; H, 6.65; N, 11.66. $C_{22}H_{23}N_3O_2$ requires C, 73.11; H, 6.41; N, 11.63.

υ_{max}/cm^{-1} (neat) 3278 (NH), 1713 (C=O), 1681 (C=O), 1570, 770 (Ph), 736 (Ar), 701 (Ph),

δ_H (400 MHz; D_6-acetone, 50°C) 8.12 (1 H, m, Q-H), 7.77 (1 H, m, Q-H), 7.59 (1 H, m, Q-H), 7.53 (2 H, m, Ph-H), 7.46 (1 H, m, Q-H), 7.32 (3 H, m, Ph-H), 6.13 (1 H, s, NH), 3.22 (1 H, d, J = 14 Hz, 2-CH), 2.92 (1 H, d, J = 14 Hz, 2-CH), 2.76 (2 H, m, $CH_3\mathbf{CH_2}$ and 6-CH), 2.63 (1 H, s, 6-CH), 2.36 (2 H, m, $CH_3\mathbf{CH_2}$ and 4-CH), 2.11 (1 H, m, 4-CH), 1.93 (1 H, m, 5-CH), 1.26 (1 H, m, 5-CH), 1.16 (3 H, t, J = 7.5 Hz, CH_3),

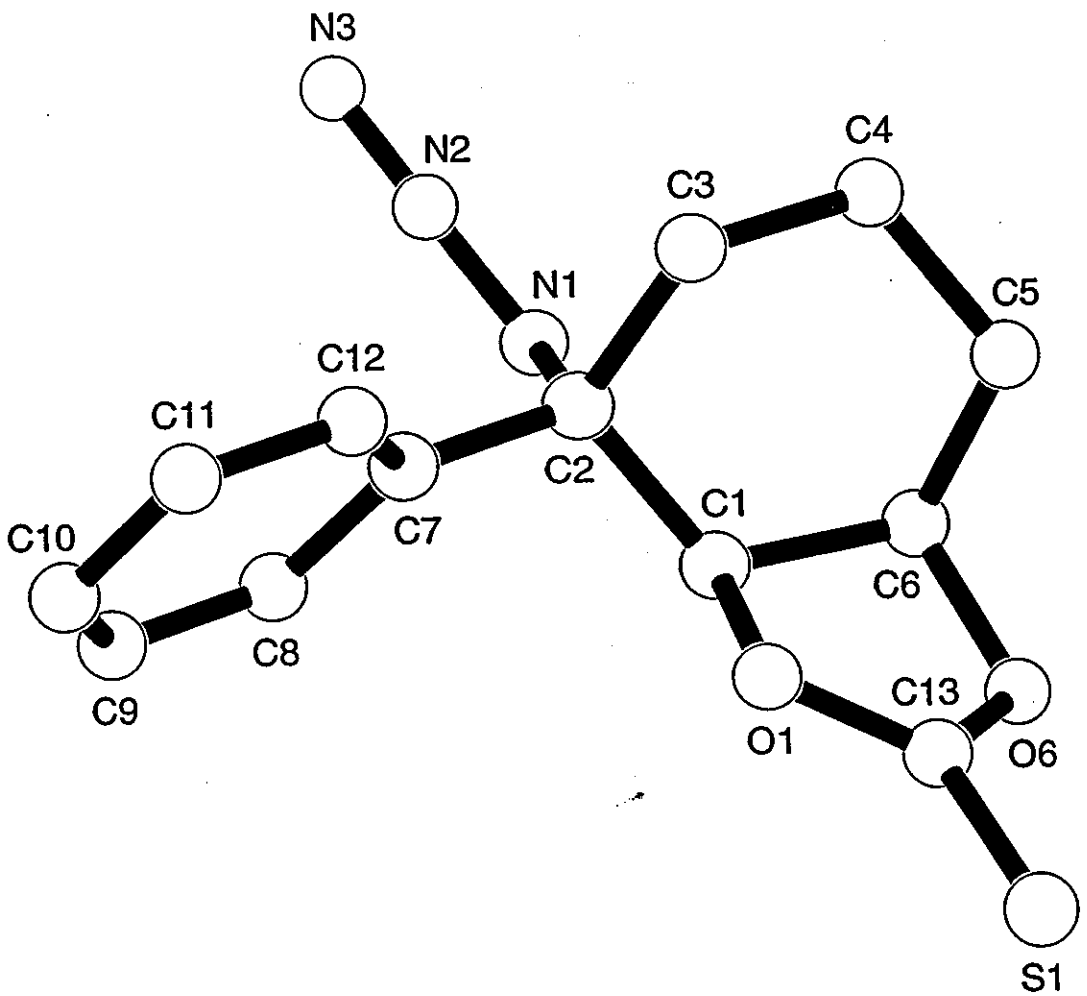
δ_C (100 MHz; D_6-acetone, 50°C) 209.1 (C), 164.5 (C), 162.5 (C=O), 148.4 (C=O), 141.9 (C), 135.6 (Ar-CH), 130.0 (Ar-CH), 129.4 (Ar-CH), 129.1 (Ar-CH), 128.4 (Ar-CH), 127.8 (Ar-CH), 127.8 (Ar-CH), 127.3 (Ar-CH), 122.2 (C), 69.3 (C), 51.2 (CH_2), 41.1 (CH_2), 36.8 (CH_2), 28.5 (CH_2), 21.8 (CH_2), 11.9 (CH_3)

m/z (C. I., ammonia) 362.1869 (MH^+, 5 %, $C_{22}H_{23}N_3O_2$ requires MH^+, 362.1869), 190 (100), 175 (30), 173 (67).

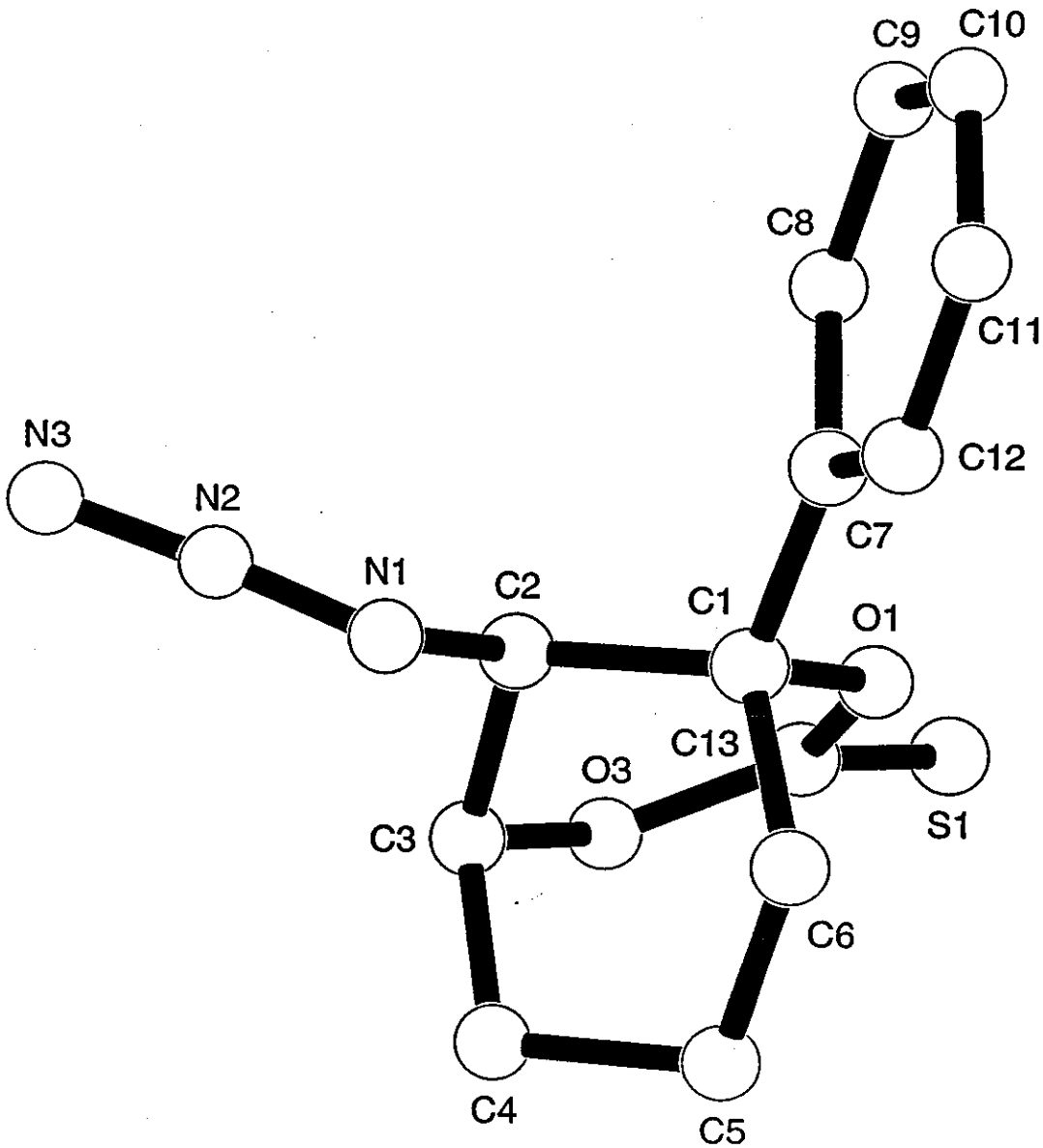
Appendix-X-ray Structures.

The numbering of the X-ray structures does not reflect the numbering sequences contained in the nomenclature.

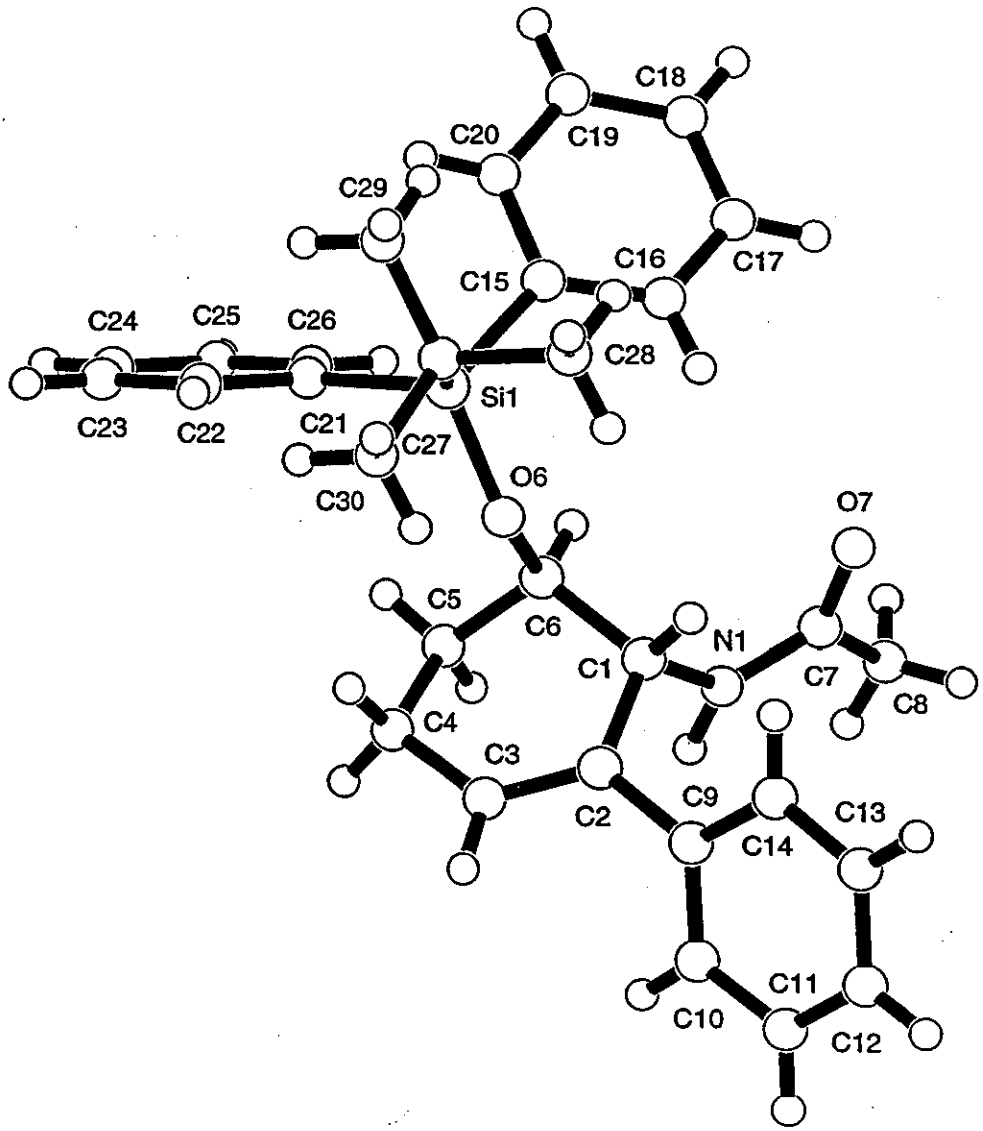
A.1. X-ray Structure for 2-Azido-7,9-dioxa-2-phenylbicyclo[4.3.0]nona-8-thione (373).



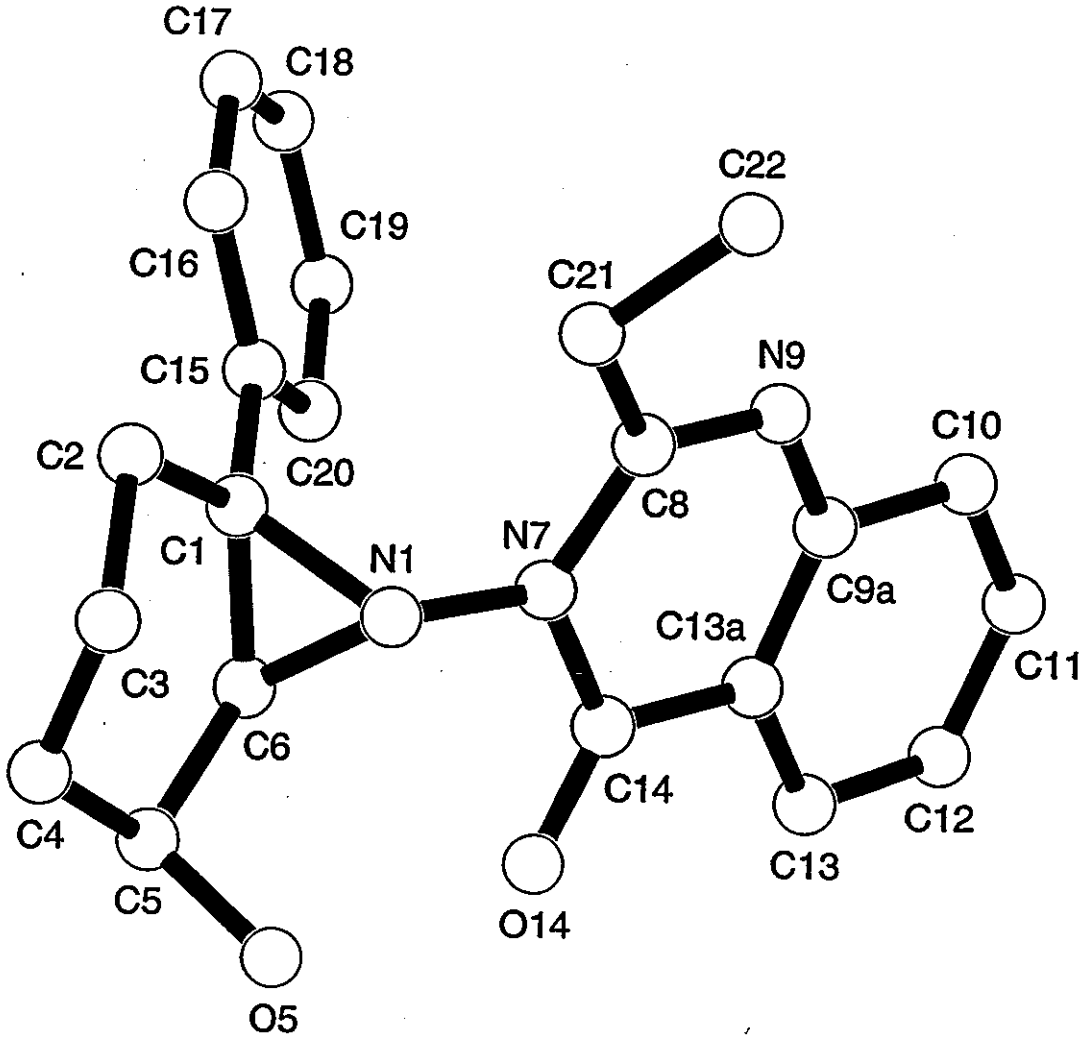
A.2. X-ray Structure for 9-Azido-6,8-dioxa-1-phenylbicyclo[3.3.1]nona-8-thione (375).



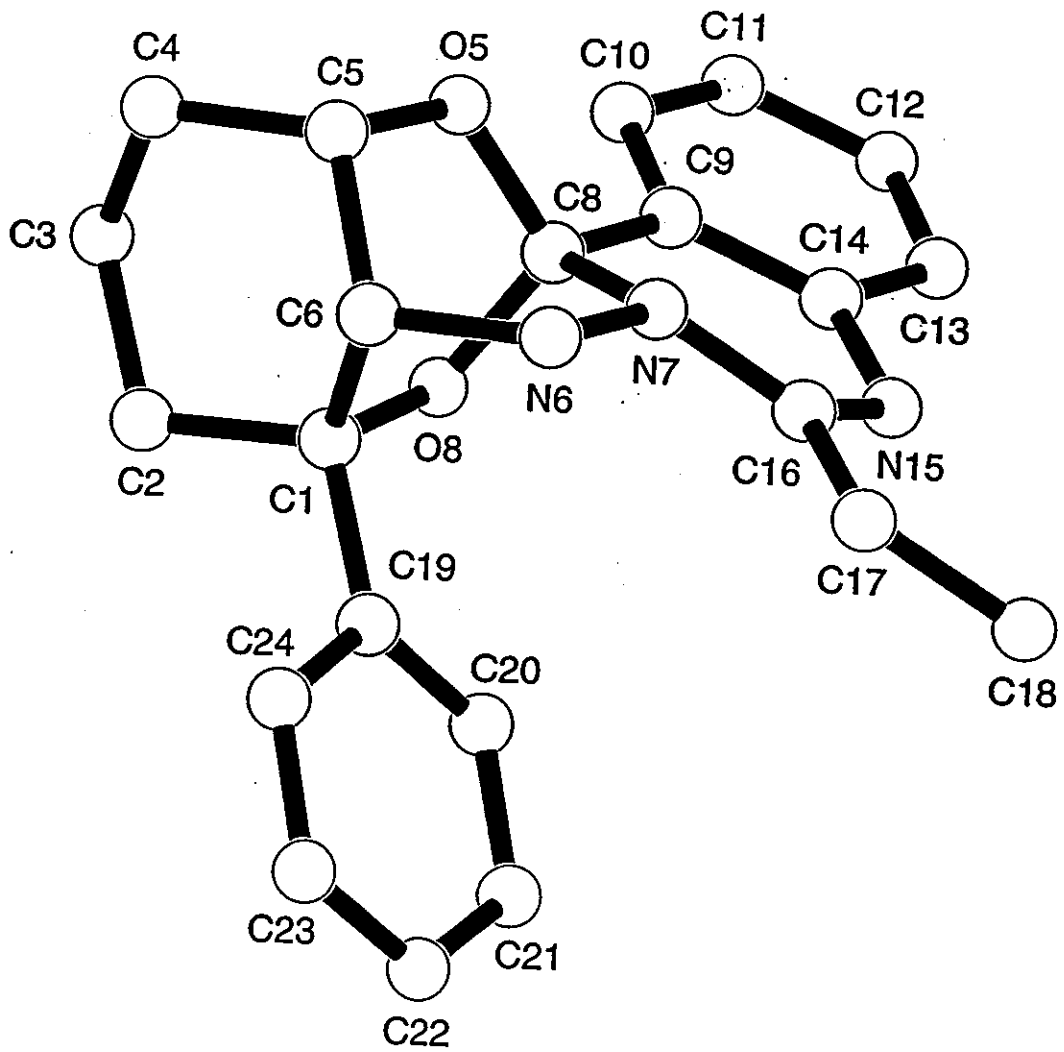
A.3. X-ray Structure for 2-(Acetylamino)-1-(*tert*-butyldiphenylsilyloxy)-3-phenyl-3-cyclo hexene (380).



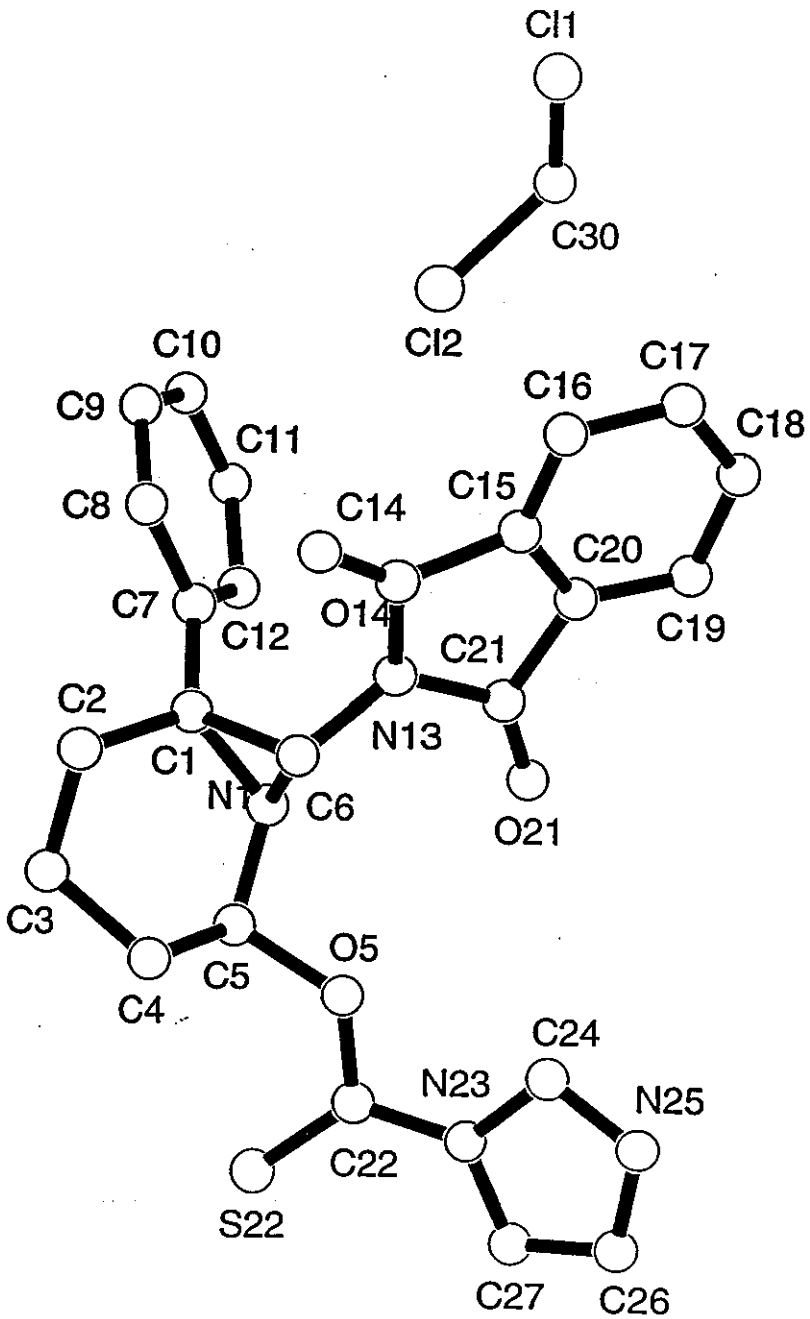
A.4. X-ray Structure for *N*-(2-Ethylquinazolinonyl)-1-phenyl-7-azabicyclo[4.1.0] heptan -5-ol (420).



A.5. X-ray Structure for the Cyclic Structure (425).



A.6. X-ray Structure for *N*-(Phthalimido)-5-[imidazol-1-yl(thiocarbonyl)oxy]-1-phenyl-7-azabicyclo[4.1.0]heptane (431).



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