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***Aziridines:***  
***Stereocontrol of Ring-Making***  
***and Ring-Breaking.***

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***A thesis submitted***  
***for the degree of***  
***Doctor of Philosophy***  
***by William Thomas Gattrell***  
***at the University of Leicester***  
***October 1997***

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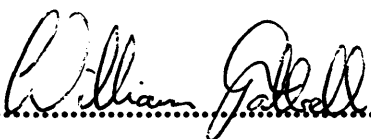
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**Statement**

*The following Thesis is submitted for the degree of Doctor of Philosophy entitled "Aziridines: stereocontrol of ring-making and ring-breaking" and is based on work conducted by William Thomas Gattrell at the Department of Chemistry, University of Leicester from October 1994 to August 1997.*

*All work is original unless otherwise acknowledged. None of this work is submitted for any other degree.*

Signed..........

Date.....18/12/97.....

## *Acknowledgements*

Firstly I would like to thank my supervisor, Dr R. S. Atkinson, for his never-ending support, help and encouragement throughout the past three years. For technical support Mick Lee, Dr Gerrald Griffith (NMR), Dr John Fawcett and Dr David Russell (X-ray structure determination) and Dr Graham Lawton (Mass Spectrometry). My gratitude also goes out to Dr Andy Ayscough (British Biotech) and Dr Tony Raynham (Roche) for helpful discussions, and to the DTI Link Asymmetric Scheme for financial support. In particular I must thank Tony for making my time spent at Roche so enjoyable.

I would like to thank the countless people who made my time at Leicester so memorable, in particular Lucy for always being there for me. For football, coffee and farcical facial hair (not necessarily in that order) I would like to thank Russ, Ian, Keith, Sabri, Chris, Erwin, Ben and the Phils: James, Last and Warrilow. I would also like to apologise to everyone who has had the misfortune to share a house with me and my Hi-Fi, in particular "Handsome" Adam who I hope holds no long-term grudges for all the practical jokes.

Finally I would like to thank my mum, dad, granddad and Martin for their tireless love and support throughout the last three years. To them I dedicate this thesis.



Strange to know nothing, never to be sure  
Of what is true or right or real,  
But forced to qualify *or so I feel*,  
Or, *Well, it does seem so*:  
*Someone must know.*

Philip Larkin, from "Ignorance"

## ***Abbreviations***

Ac - acetyl

BOC - *tert*-butoxycarbonyl

<sup>t</sup>Bu - tertiary butyl

DEPT - distortionless enhancement by polarisation transfer

DNA - deoxyribonucleic acid

DMSO - dimethyl sulfoxide

E - ester

Et - ethyl

Fig. - figure

GC - gas chromatography

h. - hour(s)

HMPA - hexamethylphosphoramide

HOMO - highest occupied molecular orbital

IR - infra-red

LTA - lead tetra-acetate

LUMO - lowest unoccupied molecular orbital

Me - methyl

min. - minute(s)

Nu - nucleophile

NMR - nuclear magnetic resonance

Ph - phenyl

Phth - phthalimide

ppm - parts per million

<sup>i</sup>Pr - isopropyl

Q - quinazolinone

s. - second(s)

TBAF - tetrabutylammonium fluoride

TFA - trifluoroacetic acid

THF - tetrahydrofuran

TLC - thin layer chromatography

**Ts - *p*-toluenesulfonyl**

**TTB - titanium (IV) tertiary-butoxide**

**UV - ultra violet**

**xs - excess**

## Abstract

(S)-3-Amino-2-(1-hydroxy-2,2-dimethylprop-1-yl)-quinazolin-4(3*H*)-one (Q\*NH<sub>2</sub>) was prepared from (L)-*tert*-leucine and its 3-acetoxycarbonyl derivative (Q\*NHOAc) used to aziridinate a range of alkenes. In the presence of titanium (IV) *tert*-butoxide, Q\*NHOAc was found to convert styrene, indene, butadiene and *tert*-butyl acrylate with complete diastereoselectivity into the corresponding *N*-Q\*-substituted aziridines in good yield; aziridination of methyl acrylate and  $\alpha$ -methylstyrene was also highly diastereoselective. In the absence of titanium (IV) *tert*-butoxide, aziridination proceeded with poor diastereoselectivity in every case.

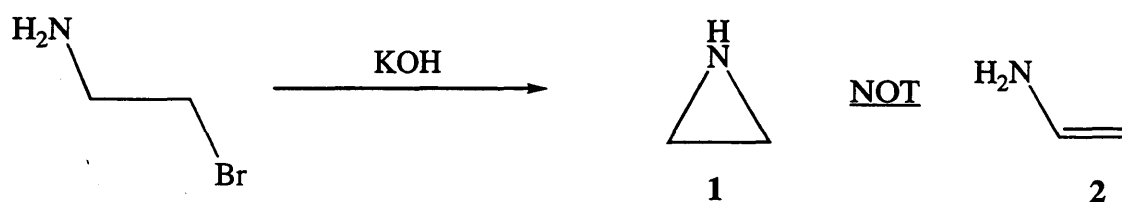
The quinazolinone (Q\*) ring has proved to be invaluable in directing or assisting the course of ring-opening of the *N*-(Q\*) aziridines produced above. Thus Q\* as a substituent on nitrogen was found to be sufficiently electron-withdrawing to activate the aziridine ring towards attack by nucleophiles in the absence of acid. The C-4 carbonyl oxygen of the quinazolinone (Q\*) was found to participate in the aziridine ring-opening under some conditions with the result that retention of configuration was found in the alcohol product; evidence for this participation was obtained by exchange of the Q\* carbonyl for a thione when the ring-opening was carried out in the presence of hydrogen sulphide. The two *N*-invertomers of the indene-derived aziridine were separately ring-opened by hydrogen chloride with very different stereochemistry, mediated by the Q\* group. Finally, the sense of regioselectivity in the ring-opening of the methyl acrylate-derived aziridine can be changed by forming a lactone tether between the aziridine and Q\* rings before ring-opening.

The *N*-Q\* bond of aziridine ring-opened products was reduced with samarium (II) iodide to NH; *N*-Q\* bond reduction could also be effected with a catalytic amount of samarium in the presence of activated magnesium. The chiral auxiliary was recovered in the form of the 3-H-quinazolinone and could be re-aminated to Q\*NH<sub>2</sub>. Overall therefore the methodology effects enantioselective and regiospecific addition of NH<sub>2</sub> and Nu across a double bond (where Nu is the nucleophile used to ring-open the aziridine intermediate) and so provide access to a range of enantiopure chiral products as has been demonstrated in three cases.

***Chapter 1 :***  
***Introduction***

## 1.1 Aziridines: Historical Background

The chemistry of aziridines dates back to the late nineteenth century when Gabriel unknowingly synthesised “ethylaziridine” **1** while attempting to prepare vinylamine **2** by treatment of 1,2-bromoethylamine with base (Scheme 1).<sup>1</sup> The correct cyclic structure was suggested by Marckwald who pointed out that the reactions of this supposed vinylamine were better explained in terms of the aziridine.<sup>2</sup> This method, intramolecular displacement of a leaving group by nitrogen, was later to become known as the Gabriel Synthesis<sup>2</sup> and represents a general method of forming this 3-membered ring system.



Scheme 1

## 1.2 Natural Products Incorporating Aziridines

Aziridines have been termed “biological alkylating agents”<sup>3</sup> and a number of natural products are known to contain this ring system, many exhibiting potent biological activity. For example, the *mitosane* family of compounds, isolated from soil extracts of *Streptomyces verticillatus*<sup>4</sup> exhibit antitumour properties ascribed to the presence of the aziridine ring.<sup>5</sup> The five members of this class are mitiromycin **3**, porfiromycin **4** and mitomycin A, B and C (**5**, **6** and **7** respectively, Fig. 1).

In particular mitomycin C shows remarkable activity against solid tumours by a mechanism that involves cross-linking of DNA; the proposed mode of action is outlined in Scheme 2.<sup>6</sup>



Another natural product shown to contain the aziridine ring system is (+)-aziridine-2,3-dicarboxylic acid **8**, isolated by Naganawa and co workers in 1975.<sup>9</sup> **8** is the only reported naturally occurring aziridine carboxylic acid and has recently been the subject of total synthesis by Zwanenberg.<sup>10</sup>

### 1.3 Bonding in Aziridines

Aziridines are highly strained heterocycles, the strain energy calculated at 113 kJ mol<sup>-1</sup> for **1**, compared with 115 and 114 kJ mol<sup>-1</sup> for ethylene oxide and cyclopropane respectively.<sup>11</sup> Being 3-membered rings they have internal ring bond angles formally of 60 °, a large divergence from natural angles between sp<sup>3</sup>-hybridised bonds. To minimise this bond-angle strain, these small rings adopt a change in hybridisation at the atoms which form the ring. Thus the orbitals comprising the endocyclic bonds are not made up of sp<sup>3</sup> hybrids but have more p character, and overlap outside the axes joining the centre of the nuclei (Fig. 2).<sup>12</sup> In this way aziridines can be considered as being constructed of bent or “banana” bonds.

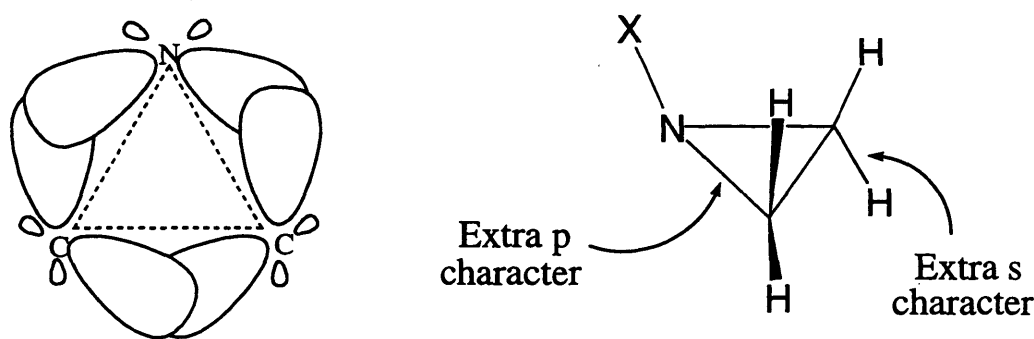


Fig. 2

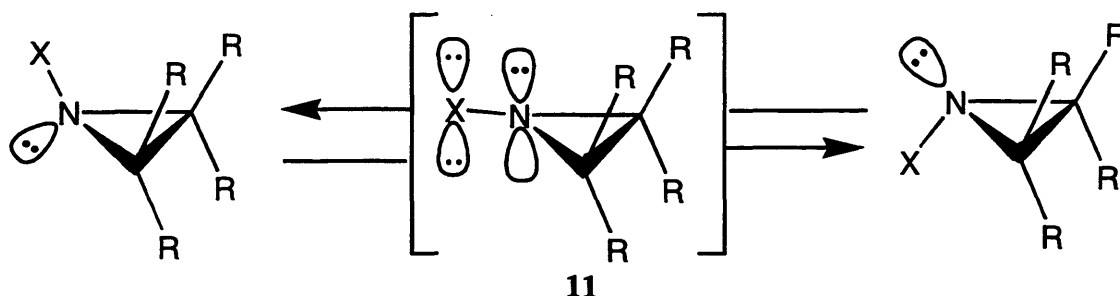
This change in ring bonding results in extra s character for the exocyclic bonds and consequently a widening of the angles between the exocyclic bonds on the ring carbons. This widening renders aziridines more susceptible toward ring-opening since it allows easier ingress of nucleophiles. <sup>13</sup>C-H Coupling constants in NMR spectra can be used to measure the percentage s character of a C-H bond: the <sup>13</sup>C-H coupling constant in **1** is 166 Hz, suggesting 32.2 % s character.<sup>13</sup> This compares with 125 Hz for the <sup>13</sup>C-H coupling constant of methane.<sup>16</sup> The lone pair on the ring nitrogen is



also in an orbital with increased s character. With increasing s character of this lone pair a corresponding decrease in basicity is observed; the  $pK_a$  of **1** is 8.04,<sup>14</sup> whereas for ammonia it is 9.5 and diethylamine 10.7.<sup>15</sup>

### 1.4 N-inversion in aziridines

As a consequence of being constrained within a small ring, the aziridine nitrogen shows retarded *N*-inversion.<sup>16</sup> The inversion process involves a change of hybridisation at nitrogen from pyramidal  $sp^3$  to the planar  $sp^2$  hybridised transition state **11** (Scheme 3) and so entails a decrease in the p character of the N-C ring bonds. The barrier to *N*-inversion is raised in aziridines since the endocyclic bonds require extra p character and oppose this change in hybridisation. Alternatively, the increased barrier can be ascribed to the greater strain in accommodating the C-N-C ring bond angle in the transition state where the *N*-hybridisation is formally  $sp^2$ .



Scheme 3

The nature of the substituent on nitrogen affects the barrier to pyramidal inversion; *N*-substituents such as an acyl group which can stabilise the trigonal transition state **11** by delocalisation of the nitrogen lone pair will lower the inversion barrier. Conversely, inductively electron withdrawing substituents enhance the barrier to inversion. The electron withdrawal of the substituent (X) can be considered to increase the p-character of the nitrogen-substituent bond<sup>17</sup> and since the inversion process involves a change of hybridisation at nitrogen from  $sp^3$  to  $sp^2$ ; the barrier to inversion is raised as the electronegative substituent resists the decrease in p-character of the N-X bond. A further increase in the barrier to inversion is observed for lone pair-containing substituents, as unfavourable lone pair (substituent)-lone pair (N) interactions will be augmented in the transition state for inversion.

In a few cases the inversion barrier has been raised sufficiently to the point where individual invertomers can be separated; the two *N*-invertomers of *N*-chloro-2-methylaziridine **12** and **13** have been separated by GC and shown to have different optical rotations (Fig. 3).<sup>18</sup> The nitrogen inversion barrier in **13** has been estimated at 83 kJ mol<sup>-1</sup>. (See also 1.11).

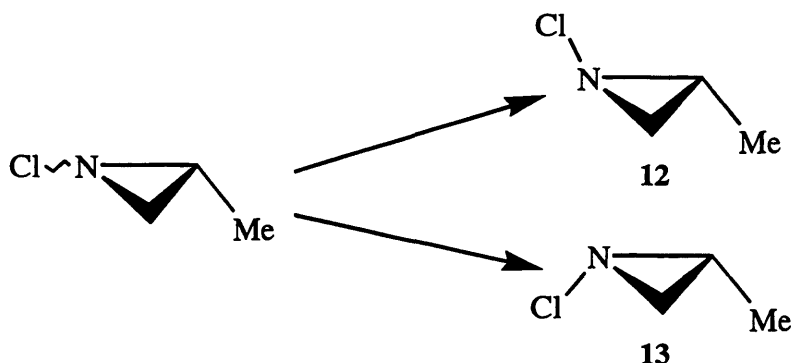
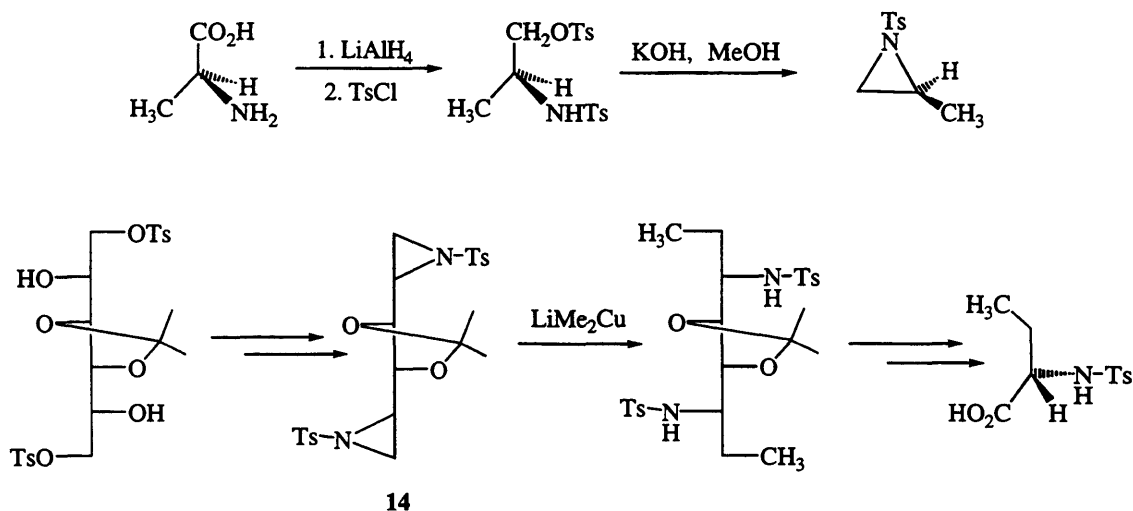


Fig. 3

### 1.5 Synthesis of aziridines from chiral pool starting materials

The Gabriel Synthesis can be extended to prepare aziridines as single enantiomers if the starting material is enantiopure, the obvious source of the required starting materials being the chiral pool. Since ring-closure of 1,2-amino alcohols affords aziridines, amino acids are convenient starting materials (Scheme 4).<sup>19</sup> Carbohydrates have also been extensively used for this purpose,<sup>20-23</sup> Depezay's ingenious synthesis of  $\alpha$ -amino acids from D-mannitol *via* bis-aziridine **14** is of particular note (Scheme 4).<sup>24</sup>



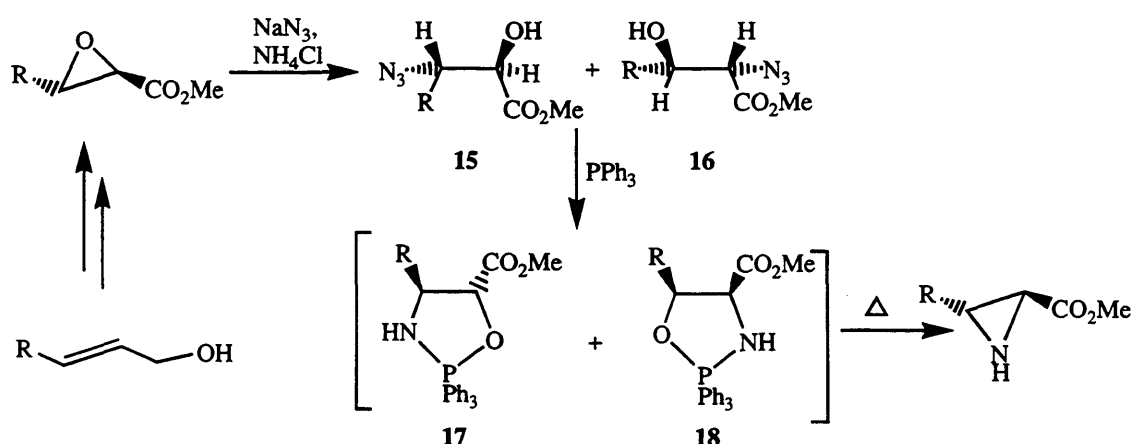
Scheme 4

## 1.6 Synthesis of Aziridines via asymmetric transformation of C-C and C-N double bonds

The range of aziridines that can be prepared by the methods described above is limited by the relatively small number of suitable chiral pool starting materials and moreover such syntheses are often lengthy multistep procedures.<sup>25</sup> These processes do not usually involve creation of new chiral centres, merely manipulation of existing chirality. Stereoselective transformations of C=N and C=C bonds into aziridines represent a more versatile alternative.

### 1.7 Preparation of aziridines from epoxides

The availability of highly enantiopure epoxides via the Sharpless asymmetric epoxidation<sup>26</sup> has led many groups to make use of these 3-membered oxygen heterocycles as substrates for conversion to their nitrogen analogues. For instance Zwanenburg<sup>27</sup> has prepared optically active aziridine-2-carboxylic acid esters from glycidic esters obtained from asymmetric epoxidation of allylic alcohols (Scheme 5). All four stereoisomers of the aziridine are accessible since all the stereoisomers of the starting glycidic esters are available from Sharpless epoxidation of the *E* and *Z* allylic

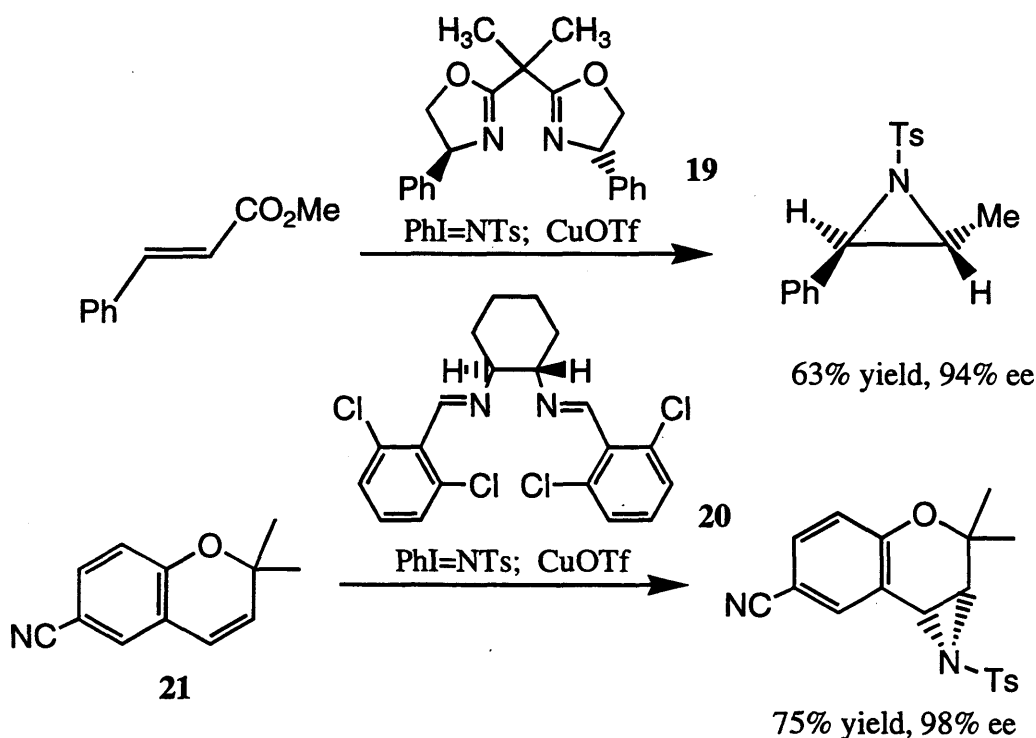


Scheme 5

alcohols. The elegance of this procedure is that the regiochemistry of ring-opening of the epoxide is unimportant; both azido alcohol regioisomers **15** and **16** ring-close via the isolable oxaphospholides **17** and **18** to give the same aziridine product.

### 1.8 Catalytic enantioselective alkene aziridination

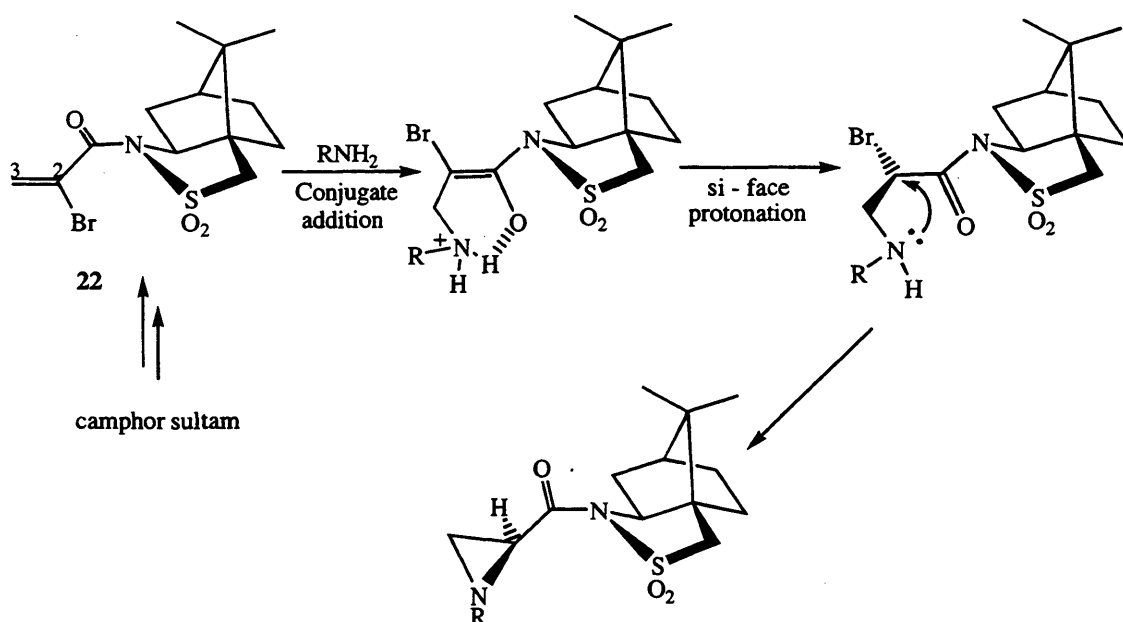
Aziridination is the direct conversion of an olefin to an aziridine. Catalytic enantioselective aziridination of alkenes has been reported independently by Evans and by Jacobsen (Scheme 6). Both studies utilise copper triflate catalysed addition of (*N*-(*p*-toluenesulfonyl)imino)phenyliodinane (PhI=NTs) to olefins<sup>28</sup> usually bearing at least one aryl group. Evans reports enantioselectivities of >95% in aziridination of some cinnamate esters using enantiopure 4,4'-disubstituted bis-oxazolinones **19**.<sup>29</sup> Jacobsen employs chiral salen catalyst **20** and attains the highest enantioselectivity with the 2,2-dimethylchromene derivative **21**.<sup>30</sup> However the non-stereospecific nature of these nitrenoid reactions means that only *trans*-alkenes or ring-contained *cis*-alkenes can be used; also only *N*-tosyl aziridine derivatives can be prepared (this is important - see 1.19.)



Scheme 6

## 1.9 Aziridination via diastereoselective Gabriel-Cromwell and aza Darzen reactions

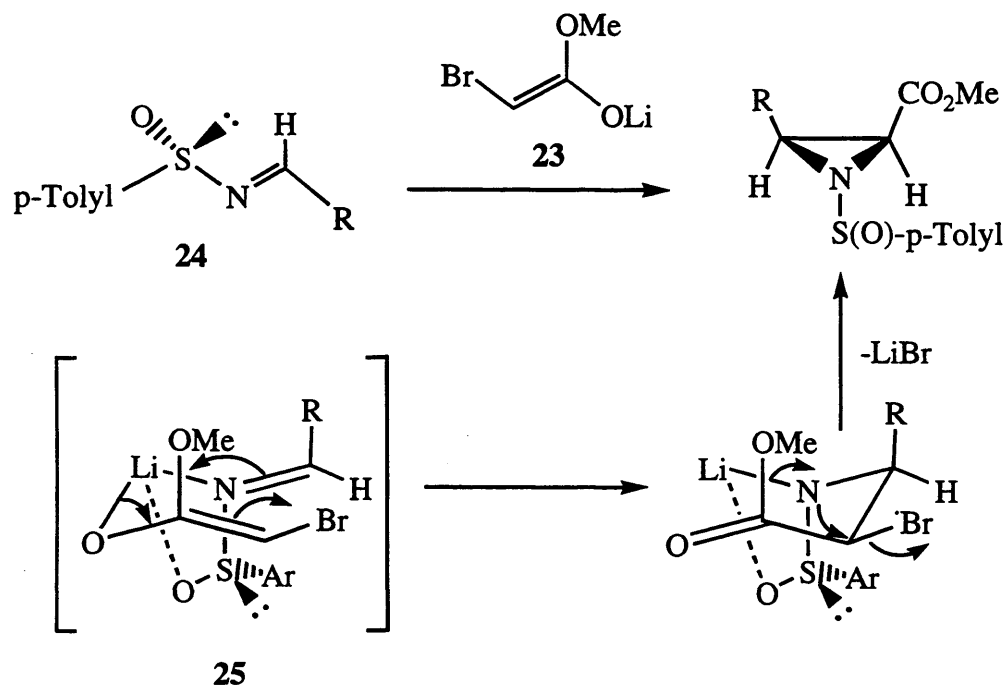
Garner<sup>31</sup> has utilised Oppolzer's camphor-derived sultam as the chiral auxiliary in substrate-controlled diastereoselective aziridination of alkenes. The Garner protocol involves synthesis of aziridine 2-carboxylates by the Gabriel-Cromwell reaction<sup>33</sup> of 2-bromo acrylic acid derivatives **22** with primary amines (Scheme 7), with the sense of asymmetric induction consistent with the model proposed by Curran and Oppolzer.<sup>32</sup> However this procedure is restricted to the preparation of monosubstituted aziridines as the conjugate addition step is non-selective and gives a mixture of products when the substrate is 2,3 disubstituted.<sup>34</sup>



Scheme 7

Applying a Darzens-type reaction<sup>35,36</sup> Davis has developed methodology allowing the asymmetric synthesis of (*cis*) disubstituted aziridine-2-carboxylic acid esters.<sup>37</sup> This simple one-pot synthesis, involving the addition of the lithium enolate of methyl bromoacetate **23** to enantiopure sulfinimines **24** is highly diastereoselective. The high *cis*-selectivity is consistent with a chair-like transition state **25**, in which lithium-sulfoxide oxygen complexing is a key feature, followed by ring-closure of the intermediate acyclic bromide (Scheme 8). Sweeney has also reported the preparation

of *cis*-disubstituted aziridine carboxylates *via* an aza-Darzens reaction, employing Oppolzers's chiral sultam as the chiral auxiliary.<sup>38</sup>



Scheme 8

### 1.10 Aziridination via oxidative addition of *N*-amino heterocycles

From these representative examples perhaps the most striking feature is the *lack* of good general methods, and particularly stereoselective ones that exist for the aziridination of alkenes,<sup>39</sup> in contrast to the epoxidation of alkenes.<sup>26</sup> It is this dearth of preparative methods that has severely limited the use of aziridines as synthetic relay intermediates in organic synthesis in comparison to their oxygen analogues.<sup>40</sup>

The most general method for the aziridination of alkenes was first discovered by Rees and co-workers in the late 1960s. Rees showed that oxidation of a range of *N*-amino heterocycles including **26-30** with lead tetra-acetate (LTA) in the presence of alkenes gave aziridines stereospecifically.<sup>41</sup> (Fig. 4). These heterocycles react with olefins of widely differing electron demand, **28** adding to  $\alpha,\beta$ -unsaturated esters,<sup>42</sup> 1,3-dienes,<sup>43</sup> aryl alkenes,<sup>44</sup> alkynes<sup>45</sup> and simple alkyl alkenes such as but-2-ene<sup>46</sup> in good yield.

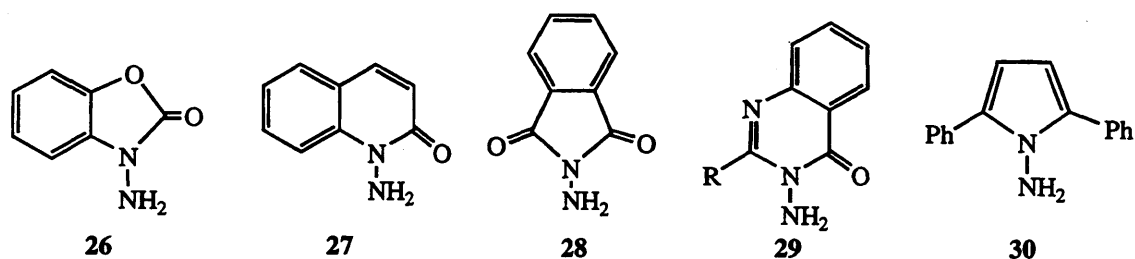


Fig. 4

### 1.11 Mechanism of aziridination

For over 20 years all evidence suggested that the intermediates in these aziridinations were the corresponding *N*-nitrenes.<sup>47</sup> However work by Kelly,<sup>48</sup> following on from an initial observation by Grimshire,<sup>49</sup> showed that the intermediates in the LTA-mediated oxidative addition of *N*-aminoquinazolinones and *N*-aminophthalimide to alkenes are in fact the *N*-acetoxyamino compounds **31** and **32** (Fig. 5) and are stable in solution at low temperature (<-10 °C for **31**).

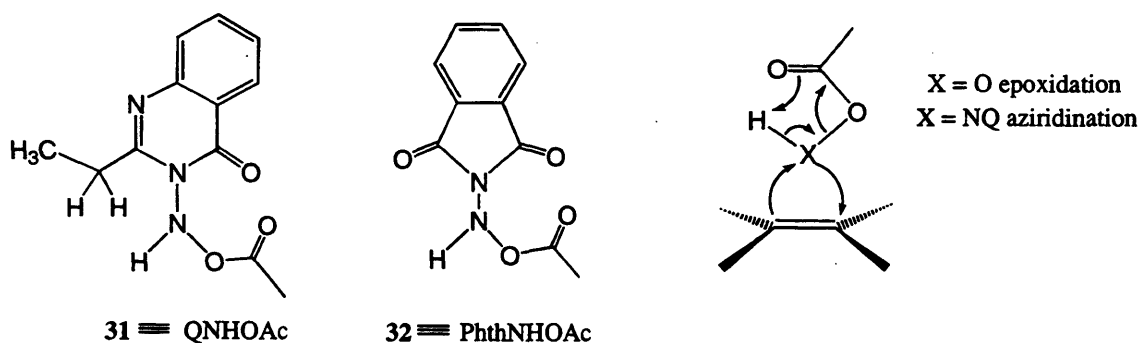


Fig. 5

The distinctive ABX<sub>3</sub> appearance of the ethyl methylene group in the low temperature NMR spectrum of **31** shows that the exocyclic nitrogen in these species is now a chiral centre; signals from diastereoisomers of 3-acetoxyaminoquinazolinones e.g. **33** (Fig. 6) are visible in the NMR spectra on incorporation of a chiral centre into the 2-position of the quinazolinone. The exocyclic nitrogen is inverting slowly on the NMR time-scale, although inversion is believed to be fast on the aziridination time-scale.<sup>50</sup> This has been established *inter alia* by preparing diastereoisomers of various 3-acetoxyaminoquinazolinones and monitoring their relative rates of aziridination of

alkenes. In every case studied there was no change in the ratio of these diastereoisomers as the aziridinations progressed, implying that the rate of interconversion between them is faster than the rates at which they react individually.

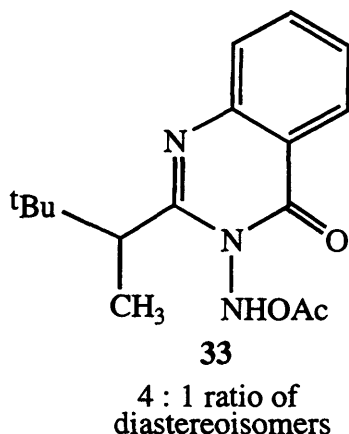
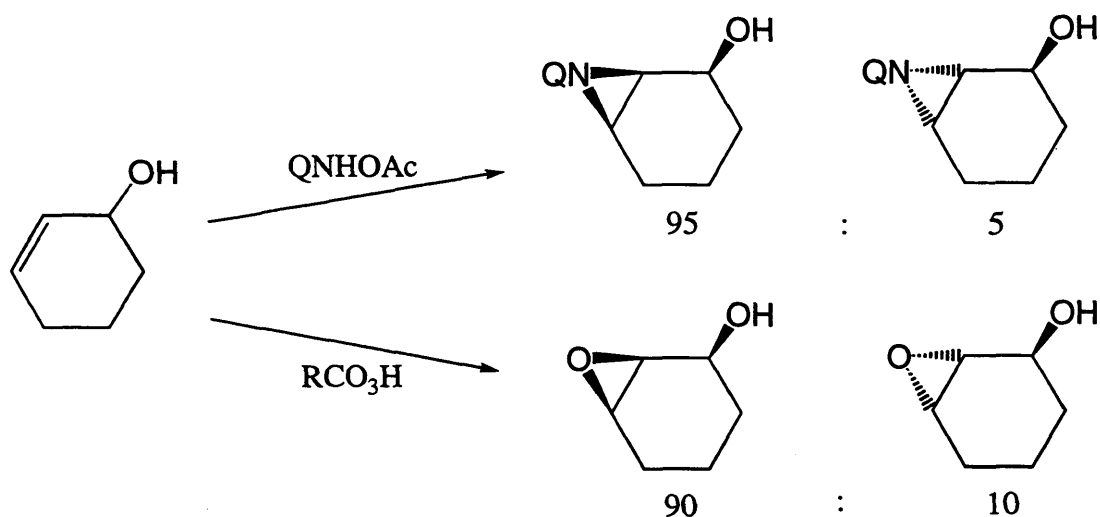


Fig. 6

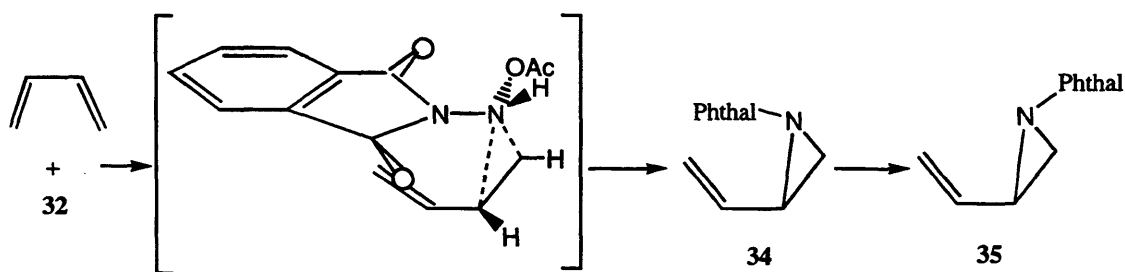
It appears that these *N*-acetoxyamino compounds e. g. **31** bring about aziridination of alkenes by a mechanism analogous to the Bartlett mechanism for epoxidation of alkenes (Fig. 5). Thus the high *syn*-stereoselectivity for peroxy acid epoxidation of cyclohex-2-enol, first reported by Henbest,<sup>51</sup> is mirrored in the corresponding aziridination using **31**<sup>52</sup> (Scheme 9). The origin of this stereoselectivity is attributed to hydrogen bonding in the transition state between the allylic alcohol and the acetoxy oxygen of the reagent.



Scheme 9



One curious feature of these aziridinations was uncovered when the low temperature reaction of what is now believed to be PhthNHOAc **32** to 1,3-butadiene was followed by NMR spectroscopy: it could be clearly seen that the (kinetically) first-formed product was the *cis*-aziridine **34** which inverts at nitrogen to the thermodynamically preferred *trans*-aziridine **35** on warming above 0° C (Scheme 10).<sup>43</sup>



Scheme 10

Subsequent studies showed that in aziridination of  $\alpha$ ,  $\beta$ -unsaturated esters and some 1,3-dienes the *s-cis* conformation is required for reaction to occur.<sup>43,53</sup> Thus  $\alpha$ -methylene- $\gamma$ -butyrolactone **36** is efficiently aziridinated by oxidative addition of *N*-aminophthalimide **28** while the *s-trans* locked analogue butenolide **37** gave no aziridine products at all (Fig. 7).<sup>42,54</sup>

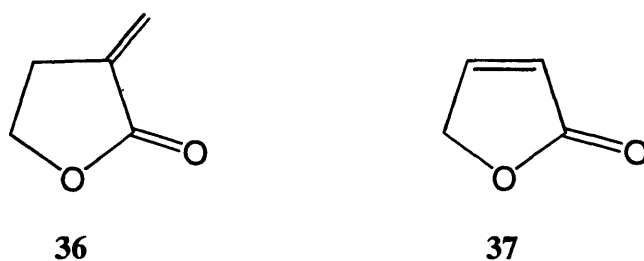


Fig. 7

These results have been rationalised in terms of an attractive secondary interaction between the heterocycle and alkene substituent in the aziridination transition state. In the *s-cis* conformation the alkene the  $\pi$  electrons of the substituent (ester, vinyl group) are placed favourably for overlap with the p-orbital lobe of a carbonyl carbon adjacent to the nitrogen of phthalimide (Fig. 8).

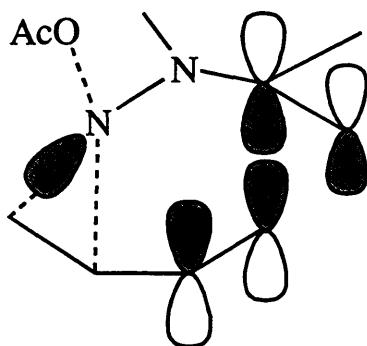


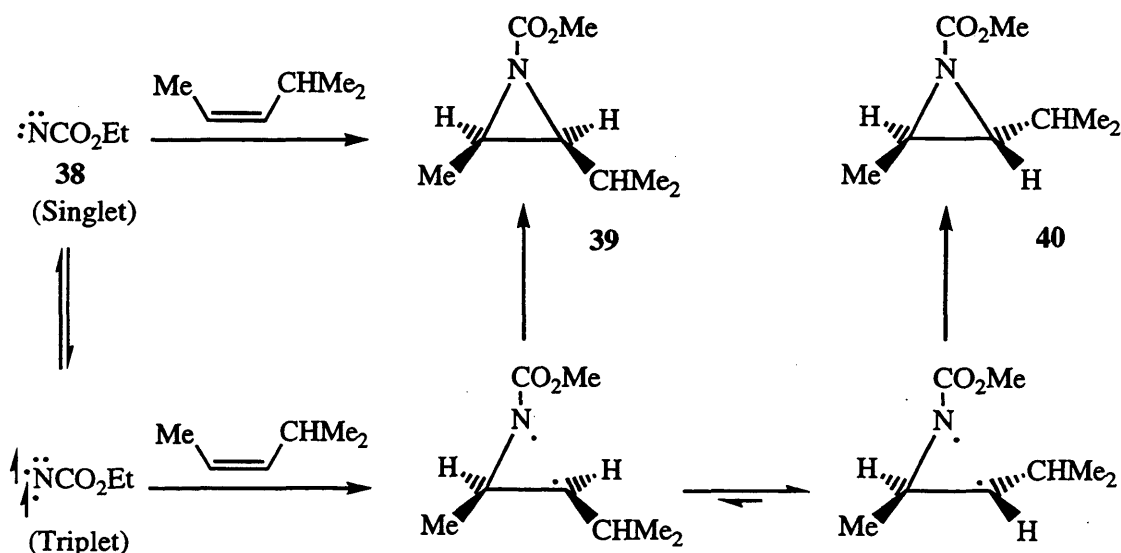
Fig. 8

The observation by NMR of signals from the *cis*-aziridine **34** is made possible by the raised barrier to inversion at the ring nitrogen which is a common feature of *N*-phthalimide aziridines: the first formed *cis*-aziridine from addition of PhthNHOAc **32** to methyl acrylate has been isolated by crystallisation at low temperature. In the crystalline state this *cis*-invertomer is converted slowly and incompletely into the *trans*-invertomer at room temperature over a period of weeks.<sup>55</sup>

Aziridination of mono-substituted alkenes such as butadiene and methyl acrylate using 3-acetoxyminoquinazolinones e. g. **31** is also believed to proceed via formation of *cis*-aziridines analogous to e.g. **34** as kinetically favoured products but the faster rate of inversion at the aziridine Q-substituted nitrogen means that it is difficult to prove this experimentally.

## 1.12 Synthesis of aziridines by addition of nitrenes to olefins

Many nitrenes can be trapped by olefins to give aziridines; however the addition of free nitrenes to alkenes is often non-stereospecific and gives mixtures of *cis* and *trans* aziridines.<sup>56</sup> This is because of rapid conversion from the singlet to the triplet nitrene state (Scheme 11); the singlet state nitrene adds stereospecifically, but the ground state of the nitrene is the triplet which adds non-stereospecifically. Even when the nitrene is generated solely in the singlet state there can be decay to the triplet nitrene leading to loss of stereospecificity. Thus in the addition of ethoxycarbonylnitrene **38** to *cis*-4-methyl-2-pentene a mixture of *cis*- **39** and *trans*- **40** aziridines is obtained.<sup>57</sup>

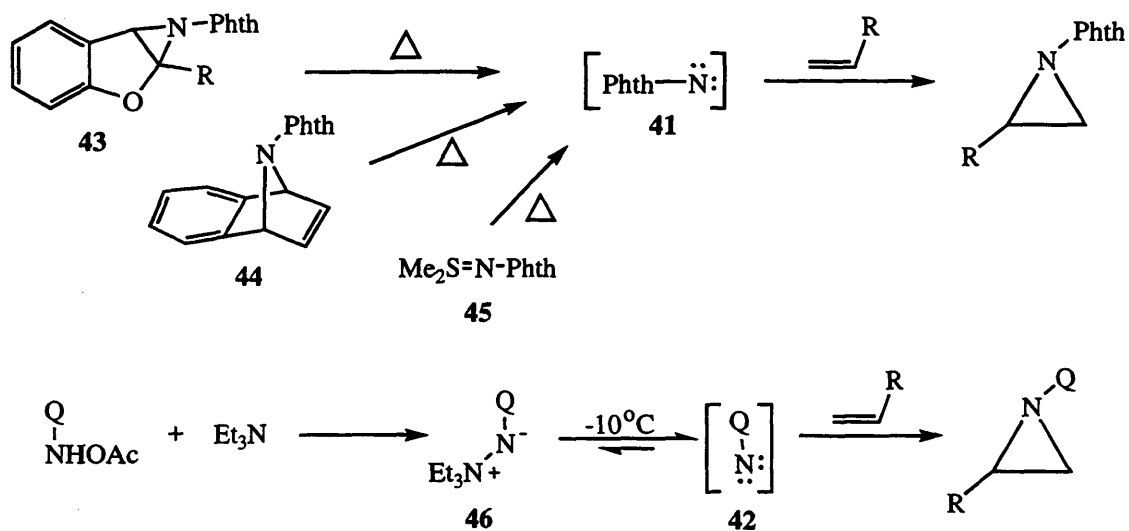


Scheme 11

When the reaction is carried out using the pure olefin as the solvent the product is mainly the *cis*-aziridine **39**. However on increasing dilution of the alkene with an inert solvent the proportion of *trans*-aziridine **40** goes up as there is more chance of the nitrene decaying to the triplet ground state which then adds non-stereospecifically.

Although the *N*-nitrenes **41** and **42** have been shown *not* to be intermediates in the LTA-mediated oxidation of *N*-aminophthalimide and *N*-aminoquinazolinone, generation and subsequent trapping of these nitrene intermediates has been recently demonstrated (Scheme 12). Thermolysis of aziridinobenzofurans **43**, the azabenzonorbornadiene **44** and sulphimide **45** gives the common intermediate

phthalimidonitrene **41** which can be trapped with olefins.<sup>58</sup> The trialkylaminium *N*-(quinazolinoyl) imides **46**, stable only at <-10 °C also act as precursors for the *N*-nitrene **42**.<sup>59</sup>



Scheme 12

### 1.13 Diastereoselective aziridination of alkenes with 3-acetoxyaminoquinazolinones

It has been demonstrated that for some of these *N*-amino heterocycles e.g. the 3-aminoquinazolinones **29**, a chiral centre can be incorporated into the 2-substituent of the heterocycle and bring about asymmetric induction in formation of the aziridine. Much work has been directed towards understanding the transition state geometry for aziridination of alkenes by 3-acetoxyaminoquinazolinones<sup>60-62</sup> with a view to rational design of the chiral group in the 2-position so as to maximise the diastereoselectivity in aziridination. The transition state geometries and mechanism for aziridination of both electron-rich and of electron-deficient alkenes suggested by the evidence are summarised below in Figs. 9 and 10 respectively.

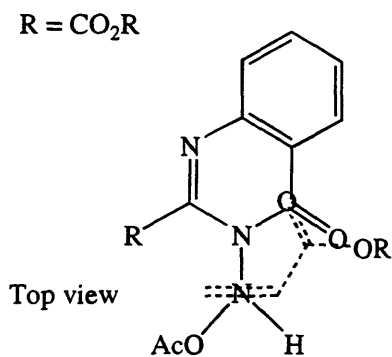
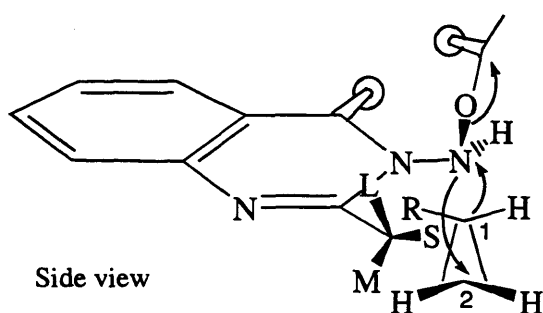


Fig. 9

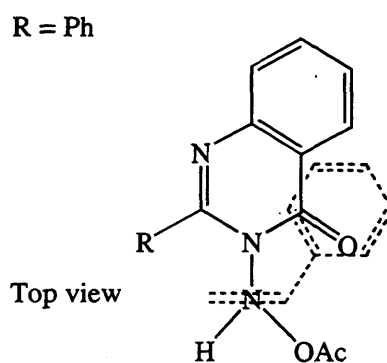
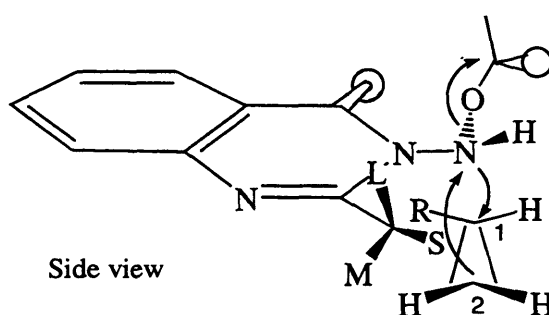
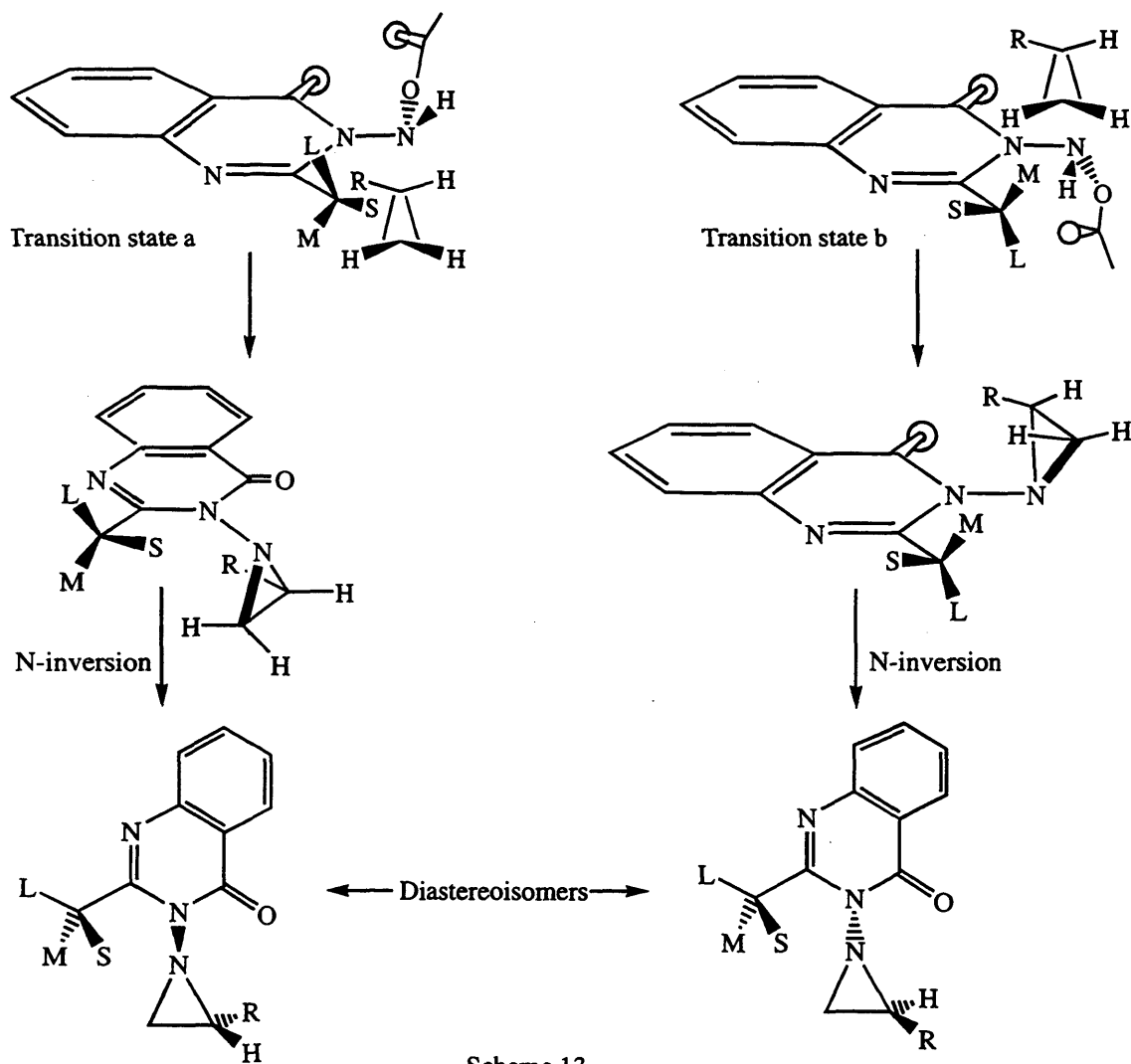


Fig. 10

In both cases the alkene and quinazolinone approach one another in approximately parallel planes, with the  $\pi$ -electron-containing substituent of the alkene lying under the C-4 carbonyl of the quinazolinone (cf. Fig. 8). For electron-deficient alkenes the exocyclic nitrogen behaves primarily as a nucleophile; N - C-2 bond formation runs

slightly ahead of C-1 - N bond formation with  $S_N2$ -type displacement of the acetoxy group.<sup>63</sup> In this case, the secondary interaction of the ester and Q serves to activate the alkene towards the initial (Michael) attack of the lone pair on  $NHOAc$ . In the case of electron-rich alkenes the electron flows are reversed, the exocyclic nitrogen behaves primarily as an electrophile with C-2 - N bond formation running slightly ahead of N - C-1 bond formation; again there is an  $S_N2$  type displacement of the acetoxy group.

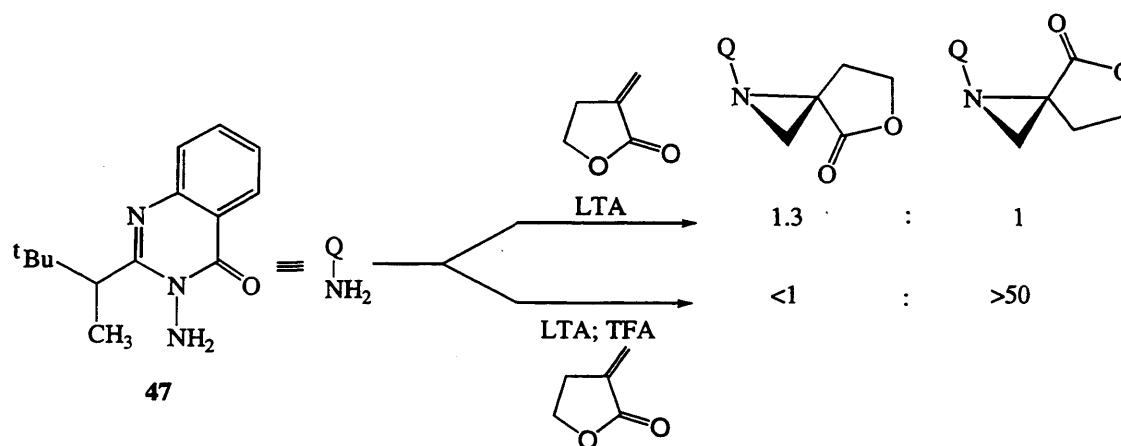


Scheme 13

If the chiral 2-substituent contains three substituents which are large (L), medium (M) and small (S) in size then an (electron-rich) alkene will approach from the face opposite to the largest group. This means that diastereoselectivity will depend on groups M and S having specific site preferences i.e. transition state a must be preferred over transition state b or *vice versa* (Scheme 13). In this way the chiral 2-

substituent will control the face of alkene attack and hence the configuration of the created chiral centre.

Previous attempts at (reagent controlled) asymmetric aziridination have had some limited success. For example the oxidative addition of (racemic) 3-aminoquinazolinone **47**<sup>64</sup> to  $\alpha$ -methylene- $\gamma$ -butyrolactone **36** has been shown to be completely diastereoselective when carried out in the presence of trifluoroacetic acid (TFA) (Scheme 14).<sup>65</sup> An identical reaction in the absence of TFA gave a 1.3 : 1 mixture of diastereoisomers. Similarly the diastereoselectivity of aziridination of other  $\alpha,\beta$ -unsaturated esters is greatly increased by the addition of TFA.<sup>66</sup>



Scheme 14

The profound enhancement of diastereoselectivity observed in the presence of TFA was ascribed to a change in the transition state geometry of that shown in Fig. 11 in the absence of TFA, to that in Fig. 12. This change in transition state geometry is presumed to be brought about by a change in the secondary interaction to that between the lactone carbonyl group and the C=N of the quinazolinone, as a result of protonation of the latter.<sup>67</sup> The consequent increase in diastereoselectivity arises from the augmented site preferences for the substituents on the C-2 chiral centre in Fig. 12 due to their proximity to the lactone.

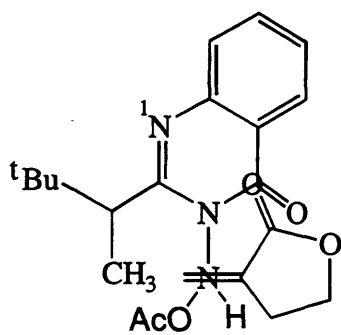


Fig. 11

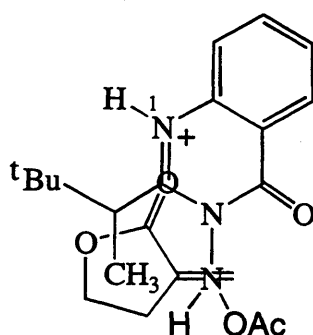
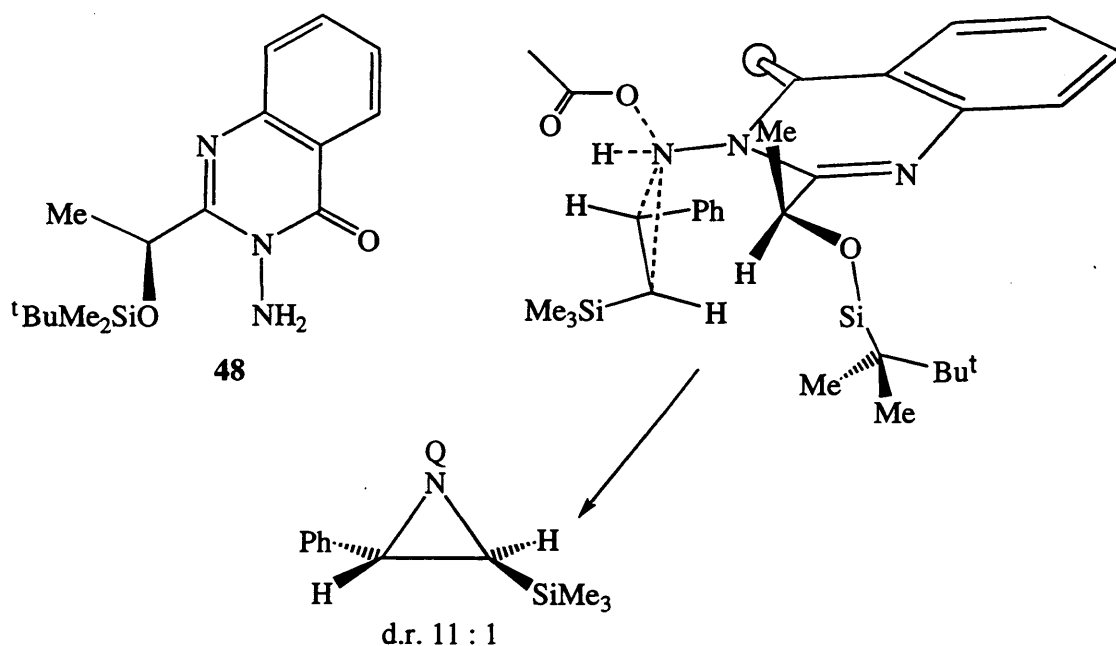


Fig. 12

High diastereoselectivity is observed in addition of 3-acetoxyquinazolinone **48** to  $\beta$ -trimethylsilylstyrene (Scheme 15). In this case high diastereoselectivity is the result of conformational preferences within the  $t\text{BuMe}_2\text{SiOCH}(\text{Me})\text{C}=\text{N}$  unit in **48** giving well defined site preferences for the three substituents H, Me and  $\text{OSiMe}_2t\text{Bu}$ .<sup>68</sup>



Scheme 15

One possible way of circumventing the problem of specific site preference (and hence increasing diastereoselectivity) is chelation control, outlined in Fig. 13. For *N*-acetoxyaminoquinazolinone **49** there exists the possibility of chelation between the hydroxy group in the 2-position and the N-1 of the quinazolinone. Chelation with a metal ion would fix the position of the substituents on the chiral centre so that attack



of the double bond on the 3-acetoxyaminoquinazolinone could reasonably only occur opposite to the *tert*-butyl group.

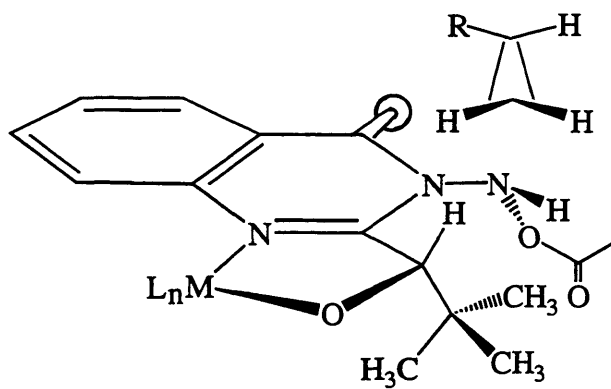
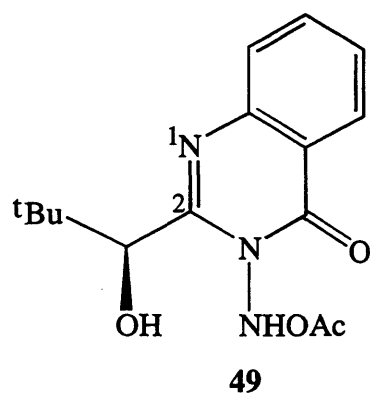
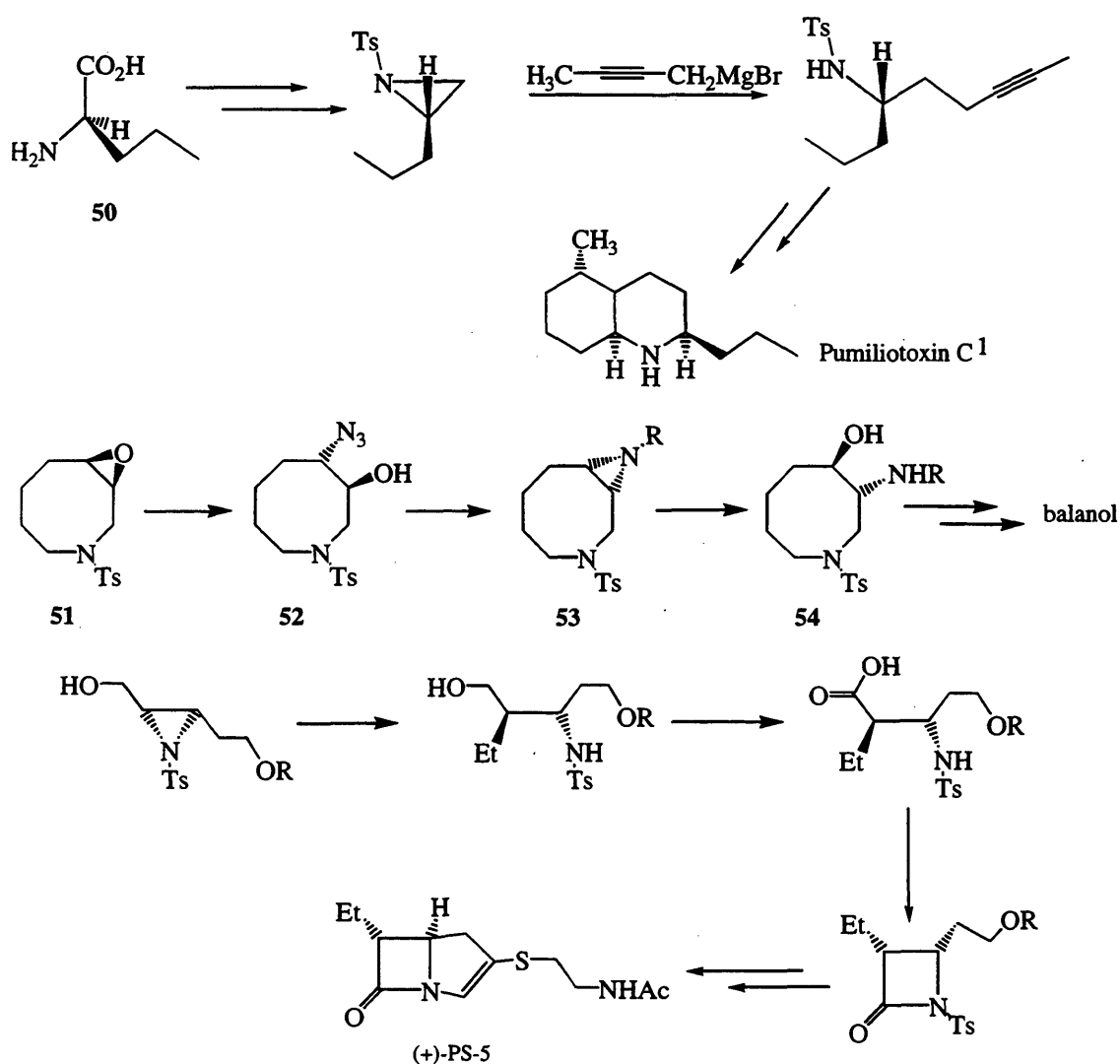


Fig. 13

## 1.14 Use of Aziridines in Total Synthesis

Despite the interest in synthesis of natural products containing the aziridine ring, the greatest value of these heterocycles lies in their potential as synthetic relay intermediates; aziridines are substrates for conversion to a range of biologically significant compounds from alkaloids, to  $\alpha$ - and  $\beta$ - amino acids and  $\beta$ -lactam antibiotics.<sup>69</sup> Examples of natural product synthesis that proceed *via* chiral aziridine intermediates are given below (Scheme 16). In the case of Oppolzer's synthesis of Pumiliotoxin-C<sup>70</sup> the starting material is the amino acid (*R*)-norvaline **50**, whereas in Tanner's synthesis of antibiotic (+)-PS-5<sup>71</sup> and of balanol<sup>72</sup> the source of enantio-generation is the Sharpless epoxidation.



Scheme 16

In Tanner's synthesis of balanol the original route to the hexahydroazepine core was directly from epoxide **51** *via* ring-opening with azide; however the reaction proceeded with the *wrong* regiochemistry to yield **52**. This problem was solved by conversion of **52** to the aziridine **53** which analogously underwent ring-opening with dilute acid giving **54**, the required regioisomer.

These syntheses illustrate that if significant use of aziridines as synthetic relay intermediates is to be made then not only is development of methodology for preparation of the 3-membered ring in enantiopure form essential, but control of subsequent ring-opening in both regio- and stereo-senses is of importance (see also Scheme 22). The same demands are made on epoxide chemistry; epoxides of high enantiopurity are readily available with the advent of Sharpless and Jacobsen epoxidation methods, however regioselective ring-opening of the products is not always dependable. Sharpless has shown that direct ring-opening of epoxides such as **55** with nucleophiles is neither very regioselective nor efficient, however in the presence of titanium (IV) isopropoxide the regioselectivity and yield are greatly enhanced.<sup>73</sup> This result has been rationalised in terms of a titanium chelated species (Fig. 14), with attack at C-3 favoured due to a better overlap of the breaking C-3 - O bond with a vacant d orbital on the metal.

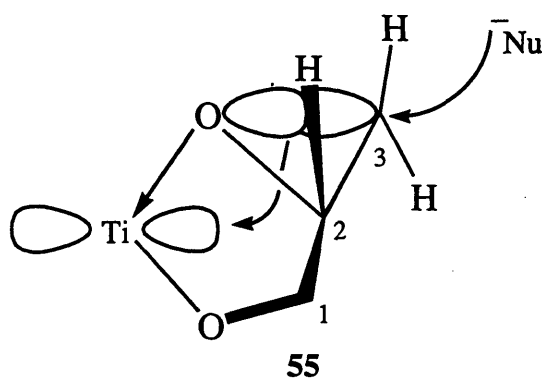


Fig. 14

### 1.15 Ring-Opening of Aziridines

As discussed earlier, aziridines are highly strained molecules and thus the dominant feature of their chemistry is ring-opening. This means that care must be taken in the handling of these compounds; many derivatives are highly toxic due to their propensity to alkylate DNA and there has been much work on the mutagenic effects of these heterocycles.<sup>3</sup>

The most obvious difference between aziridines and epoxides is the presence of an additional substituent on the aziridine ring nitrogen. This difference opens up the possibility of utilising such a group to advantage in controlling aziridine ring-opening in both regio- and stereo-senses<sup>74</sup> but in practice this possibility has yet to be explored. The identity of this substituent may be pre-determined by the method of ring formation,<sup>29,30</sup> very often the *N*-substituent is required to be electron-withdrawing to *activate* the aziridine toward ring-opening, especially in the absence of acids.

### 1.16 Ring-opening of activated and non-activated aziridines

In terms of ring-opening reactions, aziridines have been divided into two groups according to the properties of the *N*-substituent<sup>75</sup> (Fig. 15). So-called "non-activated aziridines" **56** typically only undergo ring-opening after protonation, quaternisation or formation of a Lewis acid adduct with the (weakly basic) ring nitrogen. The term "activated aziridines" **57** is used for those derivatives which contain a substituent capable of stabilising the developing negative charge formed on nitrogen when the aziridine reacts with a nucleophile; such activated aziridines have a non-basic ring nitrogen.

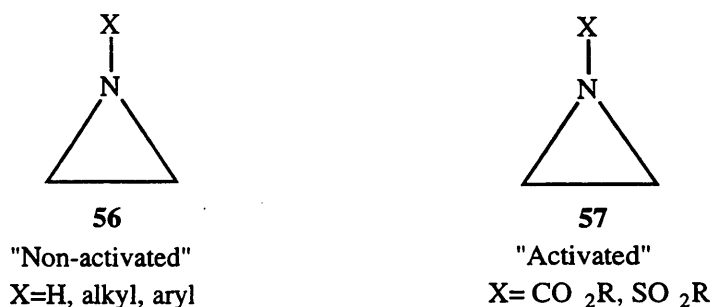
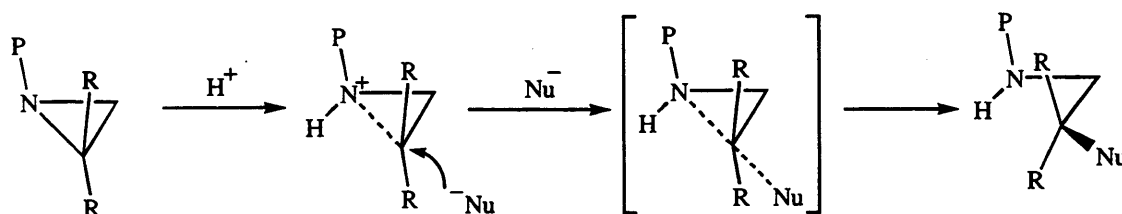


Fig. 15

### 1.17 Electrophilic and nucleophilic ring-opening of aziridines

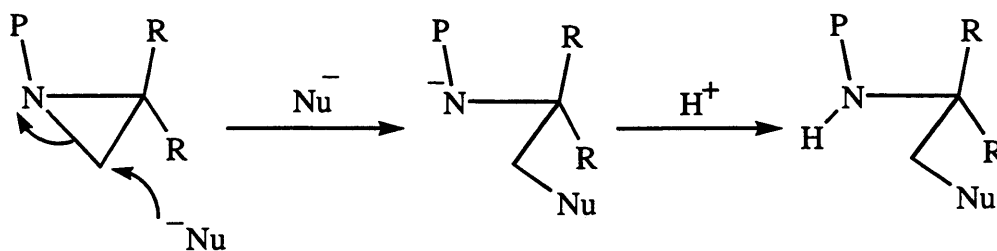
Ring-opening reactions of aziridines which proceed via heterolytic cleavage of a C-N ring bond can be divided into two types on the basis of the mechanism involved: in general, non-activated aziridines react by electrophilic ring-opening and activated aziridines by nucleophilic ring-opening.

1. Electrophilic ring-opening (typically acid-catalysed). The initial step is protonation of the ring nitrogen and the reaction proceeds through an intermediate with carbocation character (Scheme 17). Frequently ring-opening occurs with complete inversion at the ring carbon, presumably because the carbocation is not fully developed. However the scope of electrophilic ring opening is limited since it is not compatible with basic nucleophiles e.g. cuprates. Electrophilic ring-opening will, in general, proceed via the (underdeveloped) carbocation of greater stability as in Scheme 17.



Scheme 17

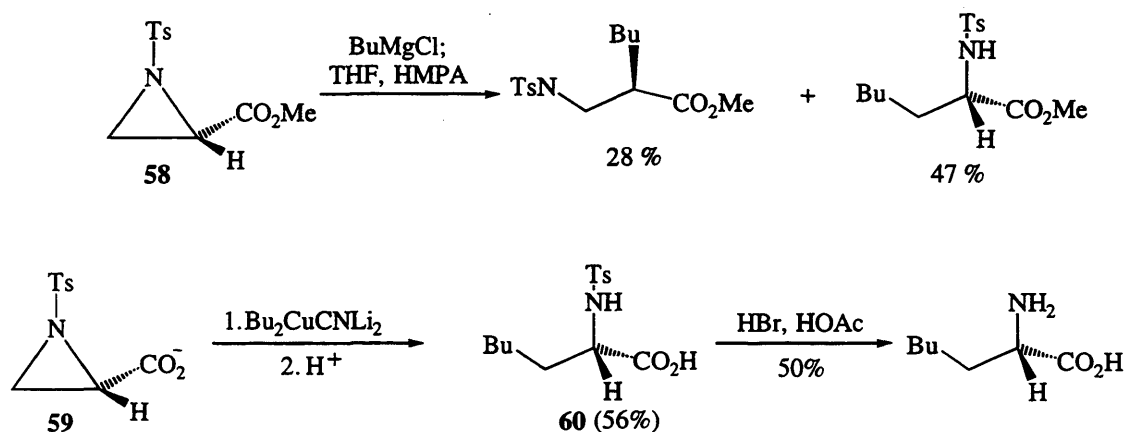
2. Nucleophilic ring-opening proceeds without protonation of the (non-basic) ring nitrogen typically *via* an  $\text{S}_{\text{N}}2$  mechanism, with inversion of configuration. In general the less sterically hindered ring carbon will be attacked preferentially, as in Scheme 18.



Scheme 18

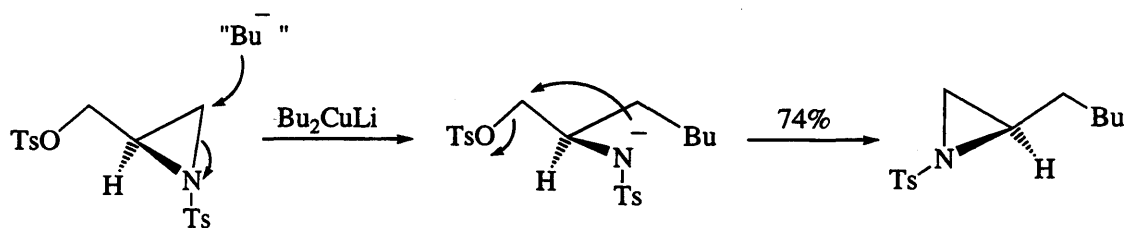
### 1.18 Activation by *N*-tosylation

*N*-Tosylation is the most frequently used means of activation, allowing ring-opening with a range of heteroatomic<sup>76</sup> and carbon nucleophiles such as Wittig reagents<sup>77</sup>, cuprates<sup>78</sup> and hydride reagents,<sup>79</sup> often in excellent yield. Studies by Baldwin<sup>77</sup> and Young<sup>78</sup> show the utility of aziridine-2-carboxylates as precursors to enantiopure  $\alpha$ -amino acids *via* ring-opening with carbon nucleophiles (Scheme 19). The poor regioselectivity experienced by Baldwin in the ring-opening of ester **58** was overcome by Young by carrying out the ring-opening on the corresponding aziridine carboxylate anion **59** with a higher order cuprate. Young attributes the improved regioselectivity to the presence of the carboxylate anion discouraging attack by the negatively charged nucleophile at C-2. The resulting *N*-protected amino acid derivative **60** was subsequently deprotected as shown.



Scheme 19

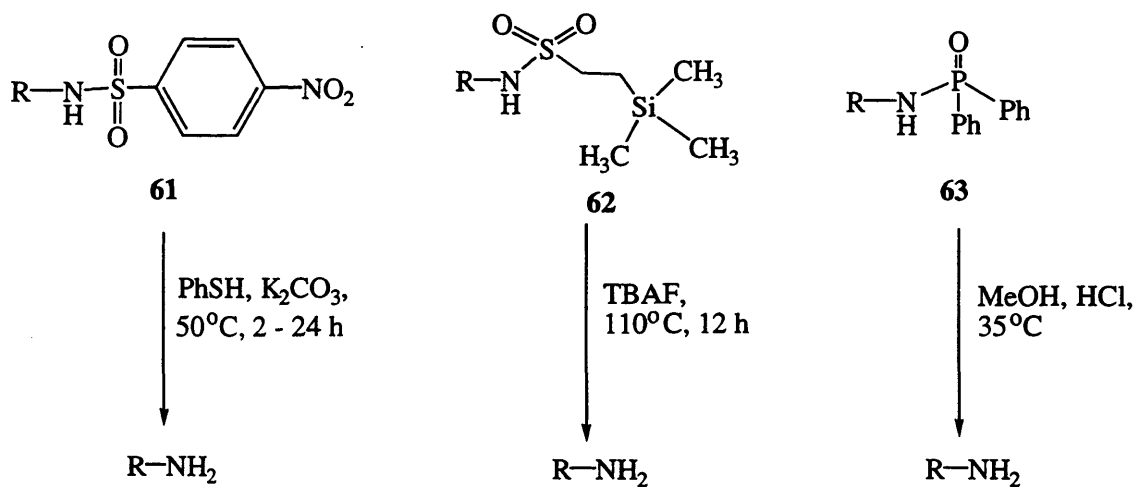
Elegant work by Bergmeier<sup>80</sup> has demonstrated the feasibility of preparing additionally substituted aziridines by reaction of aziridine tosylates with a primary organocuprate reagents using an aza-Payne rearrangement (Scheme 20). Nucleophilic attack occurs at the less substituted carbon resulting in the formation of a ring-opened intermediate which then undergoes ring closure by displacement of the tosyl ester.



Scheme 20

### 1.19 Other activating N-substituents

The harsh conditions required for deprotection of the tosyl group<sup>81</sup> have led several groups to investigate alternative methods of aziridine activation. Several other *N*-sulfonyl derivatives have been developed (Scheme 21), the 4-nitrobenzenesulfonyl<sup>82</sup> (nosyl, Ns) group **61** activates the aziridine ring to attack by a range of nucleophiles such as amines, alkoxides and cyanide and can be readily removed under mild conditions. Unfortunately it does not appear that the Evans / Jacobsen procedures are successful with  $\text{NO}_2\text{C}_6\text{H}_4\text{-N=IPh}$ . Another sulfonyl ester protecting group reported is  $\beta$ -trimethylsilylethanesulfonyl<sup>83</sup> (Ses) **62** although the authors only give one example of a ring-opening reaction (with benzyloxide), and the conditions for removal of the *N*-substituent are not particularly mild. An alternative to activation by the sulfonyl group is the use of the *N*-diphenylphosphinyl group **63**, demonstrated by Sweeney,<sup>84</sup> which is readily removed under mild acidic conditions.<sup>85</sup>



Scheme 21

## 1.20 Control of aziridine ring-opening

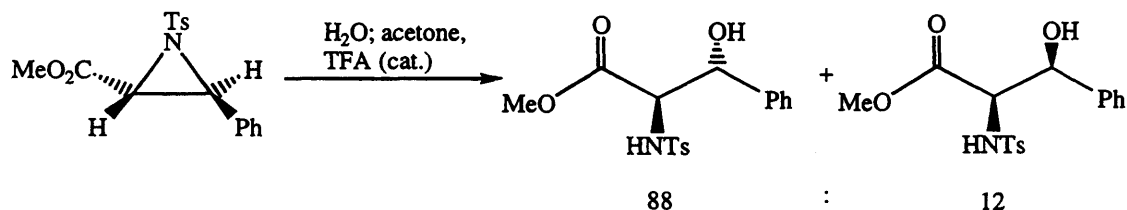
Along with the issues of aziridine activation and *N*-deprotection, in the ring-opening reactions the questions of stereo- and regio-control must also be addressed. A summary of generalisations about these aspects of aziridine ring-opening can be made as follows.

1. Nucleophilic ring-opening is expected to occur by an  $S_N2$  mechanism, with inversion of configuration.
2. Electrophilic ring-opening frequently proceeds with complete inversion of configuration: the presumed carbocation intermediate is not fully developed.
3. Monosubstituted aziridines are generally ring-opened at the less hindered unsubstituted carbon in nucleophilic ring-opening and at the more substituted carbon in electrophilic ring-opening, but regioselectivity may be poor in both cases.
4. Like epoxides, 6-membered ring-fused aziridines (7-aza-[4.1.0] heptanes) obey the Fürst-Plattner rule<sup>86</sup> (*trans*-diaxial ring opening).

In practice control of regiochemistry is often troublesome and a mixture of regioisomers results unless there is a substituent present which is strongly directing, either by electronic or steric effects. For instance the presence of carbocation stabilising substituent (e.g. aryl, allyl) on a ring carbon directs electrophilic attack  $\alpha$  to that substituent. However the carbocation stabilisation afforded by such a substituent can result in an  $S_N1$  component to the reaction and hence loss of stereospecificity *via* a fully developed carbocation<sup>29</sup> (Scheme 22). An ester substituent cannot usually be relied upon as a directing group for regiospecific ring-opening. The directing effects of an ester group are two-fold: the electron-withdrawing nature of the substituent discourages attack at the ester-bearing carbon in electrophilic ring-opening whilst stereoelectronic effects *favour* attack at this position (see Chapter 6). As a result the

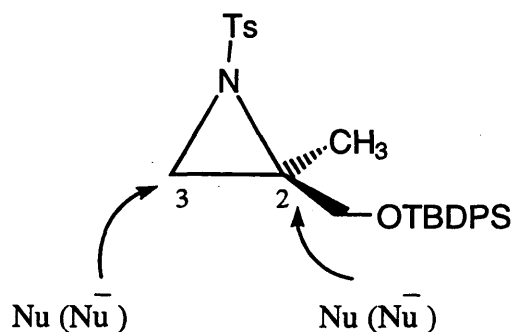


ring-opening of aziridine-2-carboxylate esters frequently show poor regioselectivity<sup>87</sup> (see Scheme 19).



Scheme 22

In developing methodology for the asymmetric synthesis of  $\alpha,\alpha$ -disubstituted amino acids, Pritchard *et al* have uncovered some contrasting regiochemistry in the ring-opening of 2,2-disubstituted aziridines with hard and soft nucleophiles.<sup>76</sup> Some representative examples are given in Table 1. What emerges is that hard (oxygen) nucleophiles reacted at C-2 while soft nucleophiles (cuprates, sulphur) attacked at C-3.



Reagent	Regiochemistry of ring-opening
HCO <sub>2</sub> H	C2 attack only
PhCH <sub>2</sub> OH	C2 attack only
PhSH	C3 attack only
PhMgBr, CuBr.SMe <sub>2</sub>	C3 attack only

Table 1

### 1.21 Chelation control of ring-opening

Regiocontrol in aziridine ring-opening in complementary senses has been reported by Tanner.<sup>79,88</sup> Reaction of **64** with lithium dimethylcuprate is completely C-2 selective, whereas reaction with trimethylaluminium results in the opposite regiochemical outcome, with attack at C-3 (Fig. 16). The regioselectivity shown by cuprates has been explained by complexation of the reagent to the hydroxyl favouring intramolecular methyl transfer to C-2. The contrasting regiochemistry shown by the aluminium reagent has been rationalised as follows. The first equivalent of the organometallic deprotonates the C-1 hydroxyl to form an aluminium alkoxide from which methyl transfer is slower than the corresponding trialkyl species.<sup>89</sup> A second equivalent of the reagent forms a Lewis acid-base complex with the C-3 benzyloxy methylene oxygen, resulting in intramolecular methyl delivery to C-3 (Fig. 17).

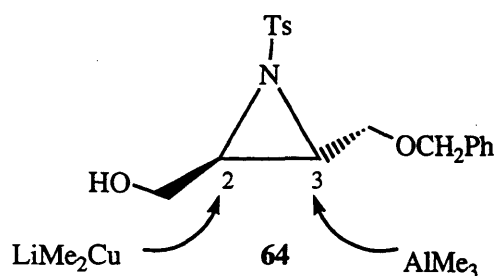


Fig. 16

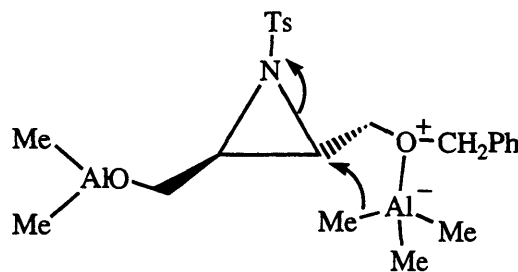


Fig. 17

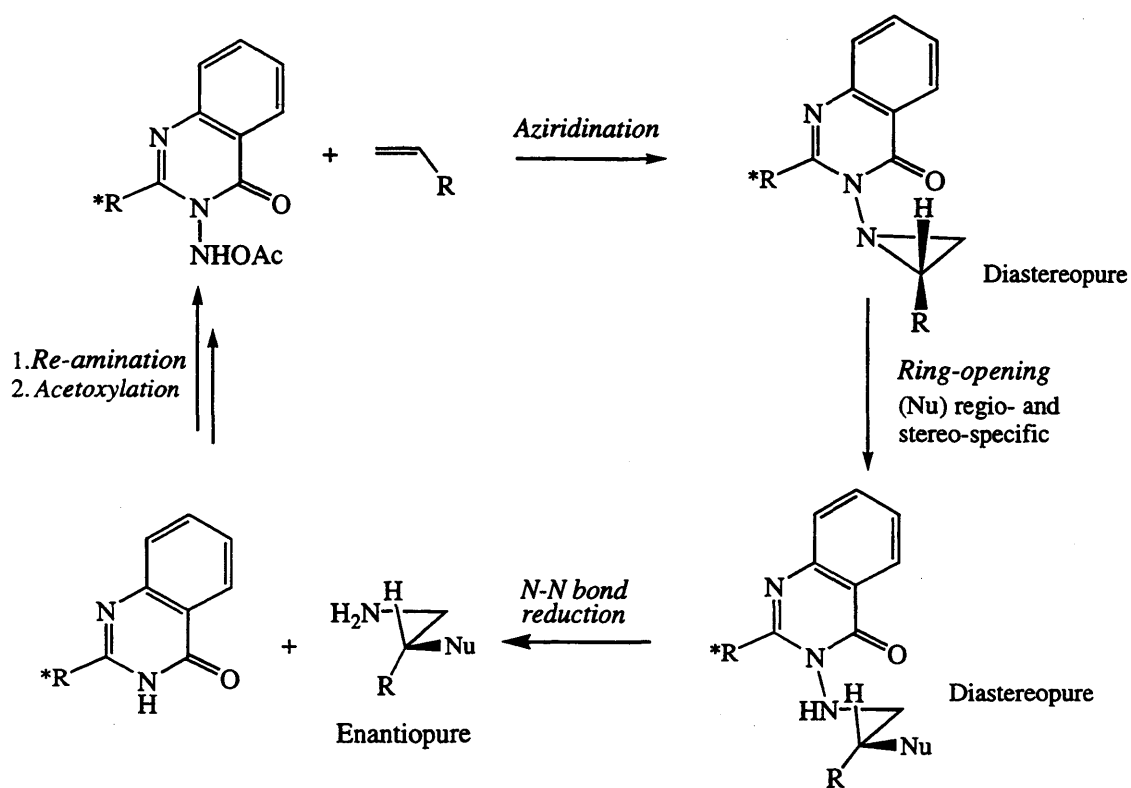
### 1.22 The aims of this study

As Heimgartner said in a recent review,<sup>90</sup> *Today, the exclusion of three-membered carbo- and heterocycles from the arsenal of the organic chemist is inconceivable.* It is clear that aziridines have great potential as synthetic relay intermediates which has yet to be fully exploited. If aziridines are to gain full acceptance in this role several issues must be addressed.

1. There must be good *general* methodology available for the preparation of chiral non-racemic aziridines, preferably from readily available achiral starting materials.
2. The aziridines so produced should undergo nucleophilic or electrophilic ring-opening, so as to increase the range of nucleophiles that can be used.
3. Ring-opening of the aziridine must be controlled, in both regio- and stereo-senses. Ideally ring-opening could be accomplished in complementary regio-senses and with either inversion *or* retention at the ring carbon.
4. The *N*-substituent must be readily removable under mild conditions, in general after ring-opening of the aziridine has been effected.

It is these problems that I have addressed during the course of my study.

The aims of the project are summarised in Scheme 23. The initial aim was to develop methodology to allow the preparation of a range of aziridines with high or complete diastereoselectivity using enantiopure 3-acetoxyminoquinazolinones. Secondly, the ring-opening reactions of the aziridines thus produced were then to be examined with a view to using the quinazolinone ring to advantage in controlling ring-opening in both regio- and stereo-senses. Because so few ring-openings of these *N*-Q-substituted aziridines had previously been examined it was not clear whether the quinazolinone ring would activate the aziridine ring toward nucleophilic attack in the absence of acid.



Scheme 23

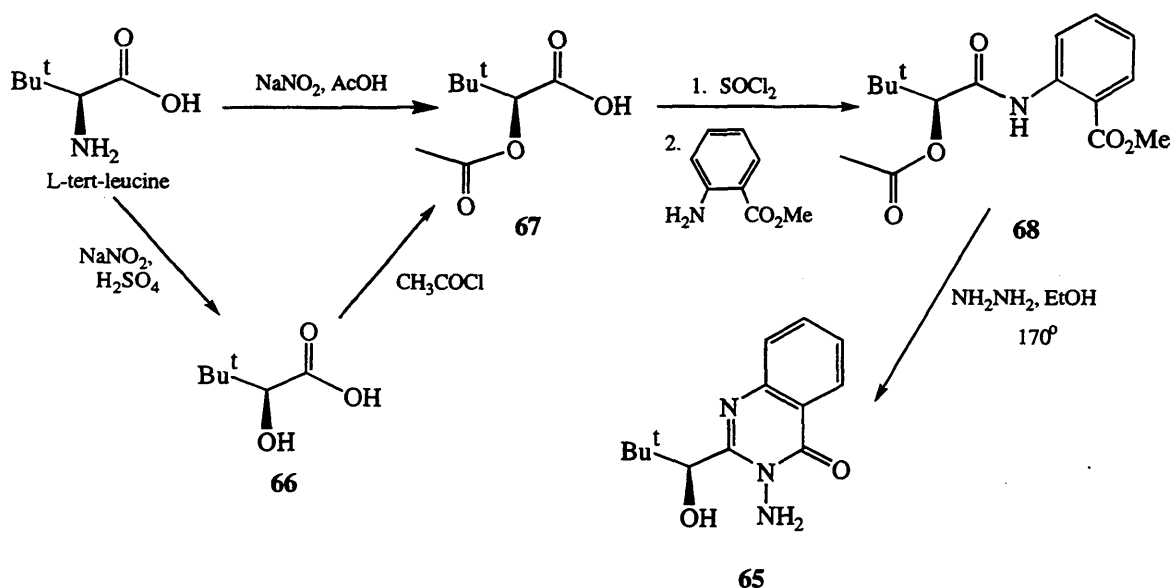
The third and final stage of the project was removal of the chiral auxiliary. Reduction of the *N*-N bond of these *N*-Q substituted ring-opened derivatives has previously been demonstrated.<sup>91</sup> Overall the conversion in Scheme 23 gives access to a range of enantiopure chirons<sup>92</sup> resulting from regio- and enantio-specific addition of NH<sub>2</sub> and Nu across the double bond of the starting alkene. In principle the chiral auxiliary can be recovered and re-used.

## ***Chapter 2 :***

### ***Aziridination of Electron-Rich Alkenes***

## 2.1 Preparation of 3-aminoquinazolinone 65

The 3-aminoquinazolinone **65** was synthesised from (L)-*tert*-leucine (Scheme 24), with only the first step, conversion of the amino functionality to hydroxyl, proving to be problematical. In the initial method employed,<sup>93</sup> treatment of the amino acid with sodium nitrite in dilute sulphuric acid afforded  $\alpha$ -hydroxy acid **66** in yields ranging from zero to 53 %; **66** could then be readily converted to (*S*)-2-acetoxy-3,3-dimethyl butyric acid **67** by treatment with acetyl chloride in 39% overall yield.



Scheme 24

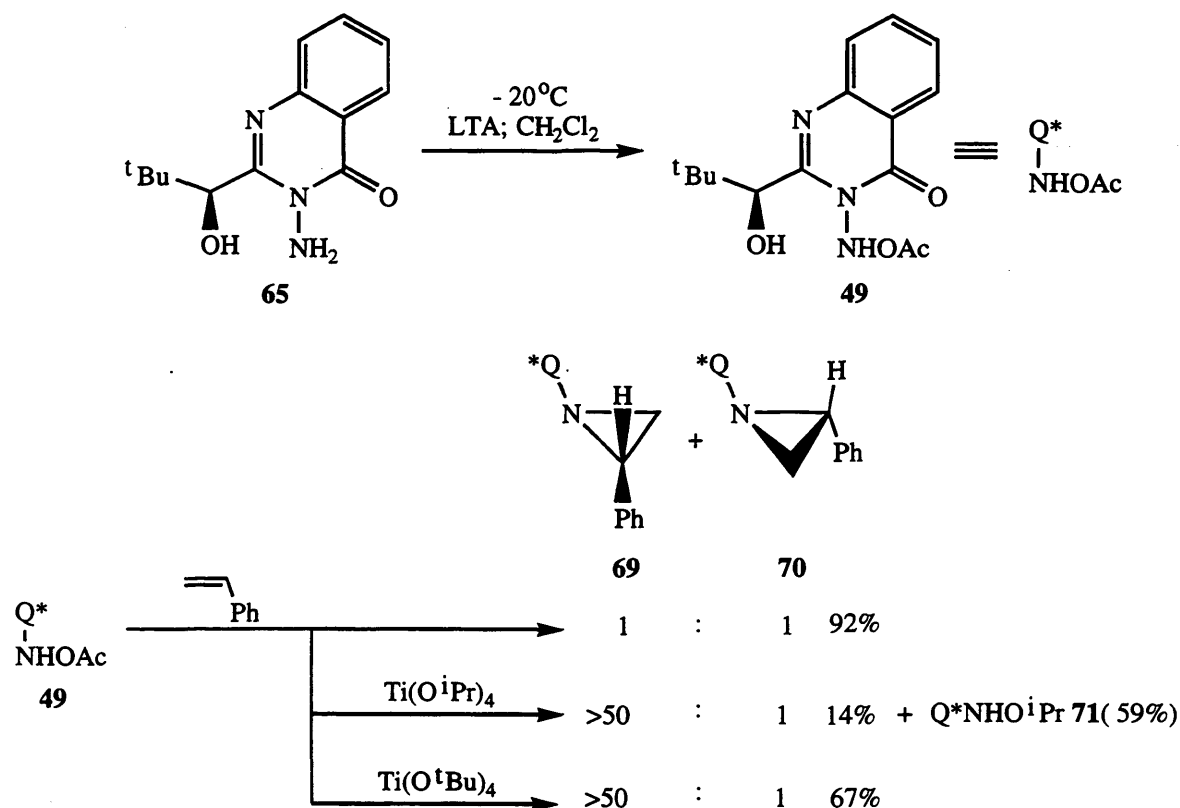
Obviously this procedure could be improved and since the cost of the starting *tert*-leucine was not insignificant, a more reliable protocol was sought. A paper by Miller<sup>94</sup> describes the direct conversion of  $\alpha$ -amino acids to  $\alpha$ -acetoxy acids by treatment with sodium nitrite in *acetic* acid. Following this procedure, (L)-*tert*-leucine could be converted directly to **67** in ~ 50% yield. When a modified procedure<sup>95</sup> was used involving addition of a 4-fold excess of nitrite without cooling of the solution, the conversion of (L)-*tert*-leucine to **67** was effected in over 60% yield and **67** showed an optical rotation that was in good agreement with that reported in the literature.<sup>96</sup>

The final two steps of the synthesis were straightforward. All of the compounds **67**, **68** and **65** were crystalline and the 3-aminoquinazolinone **65** (Q\*NH<sub>2</sub>) was prepared in 44 % yield overall without the need for chromatography at any stage. (The

enantiopurity of Q\*NH<sub>2</sub> **65** will be discussed later.) This procedure is readily applicable to the multigram scale and has been routinely carried out starting from 25 g of (L)-*tert*-leucine.

## 2.2 Aziridination of styrene

3-Aminoquinazolinone **65** was oxidised to the corresponding 3-acetoxaminoquinazolinone **49** (Q\*NHOAc) with LTA in dichloromethane at -20 °C and solutions of **49** were stable at this temperature. Using Q\*NHOAc **49** the yield and diastereoselectivity in aziridination of a range of electron-rich alkenes under various reaction conditions were examined. The first alkene to be studied was styrene and the results are shown in Scheme 25.



Scheme 25

As can be seen, the uncatalysed reaction gave virtually no diastereoselectivity: the 1:1.2 ratio of aziridines diastereoisomers present could be clearly measured from separated respective signals in the NMR spectrum of the crude reaction product. When the reaction was carried out in the presence of 2 equivalents of titanium (IV)

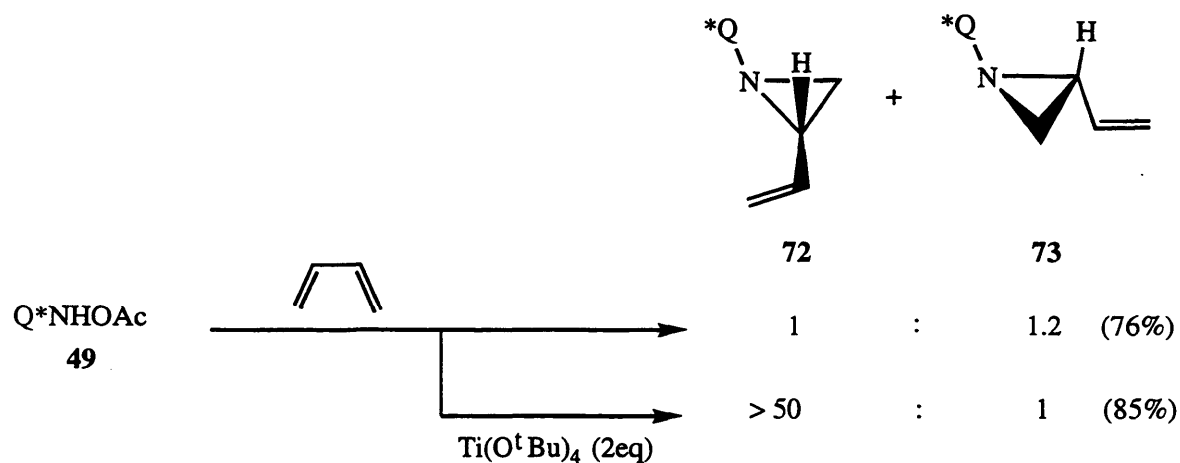
isopropoxide only the signals for a single diastereoisomer of the aziridine **69** were observed in the NMR spectrum of the crude product. The yield of aziridine was low yield (14%) and the major product from this reaction was 3-isopropoxyaminoquinazolinone **71**, formed by nucleophilic attack of the alkoxide ligand on **49**.

It was anticipated that increasing the steric bulk of the alkoxide ligand might discourage attack on Q\*NHOAc **49** and accordingly the reaction was repeated using the more hindered titanium (IV) *tert*-butoxide.<sup>97</sup> Aziridination of styrene in the presence of titanium (IV) *tert*-butoxide (TTB) (2 equivalents) was completely successful; from NMR spectroscopy of the crude product, only a single diastereoisomer of the aziridine **69** was present, and no signals attributable to 3-*tert*-butoxyaminoquinazolinone were apparent (see Appendix I). Crystallisation of the crude reaction mixture from ethanol to remove excess styrene gave the aziridine **69** in 60% yield. It is noteworthy that in this experiment and in the aziridinations of butadiene and indene which follow, the by-products from decomposition of Q\*NHOAc are lost in the work-up of the reaction i.e. apart from excess alkene the only recovered material is the aziridine.



### 2.3 Aziridination of 1,3-butadiene

With the knowledge gained previously from aziridination of styrene, the reaction of 1,3-butadiene with Q\*NHOAc **49** was examined and the results are shown in Scheme 26.

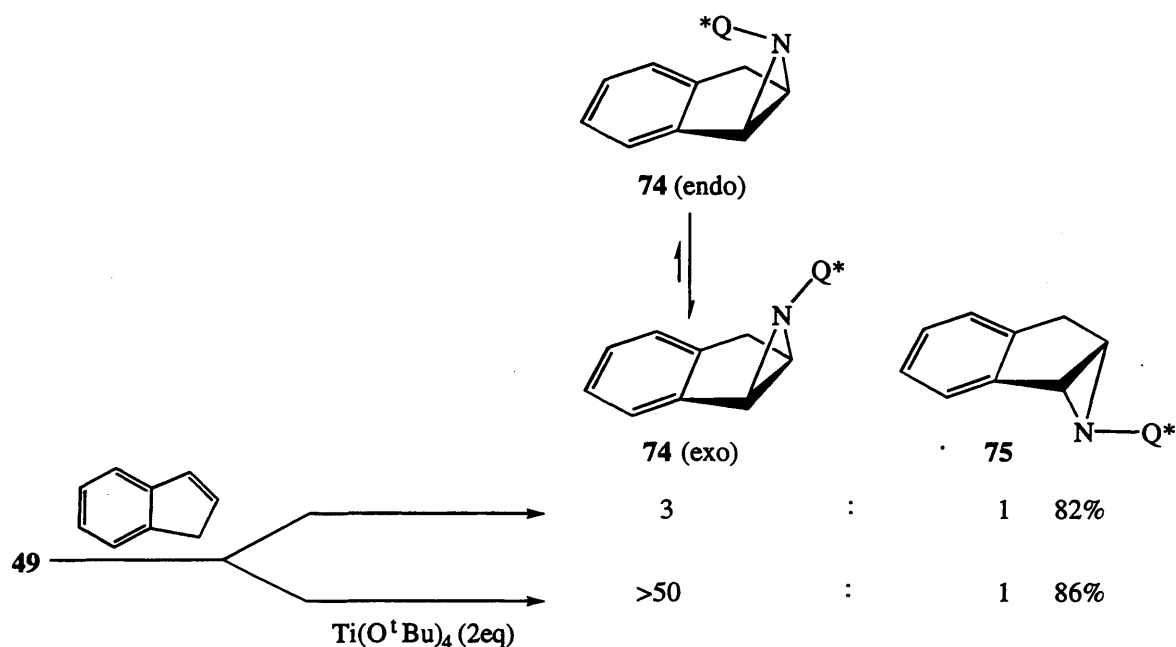


Scheme 26

Addition of Q\*NHOAc **49** to butadiene in the absence of TTB (2 equivalents) gave a mixture of aziridines **72** and **73**, with virtually no diastereoselectivity. However in the presence of TTB only a single diastereoisomer of the vinylaziridine **72** was formed; in the NMR spectrum of the crude product there were no signals visible for the other diastereoisomer or for any other species, and direct crystallisation afforded **72** in 85% yield.

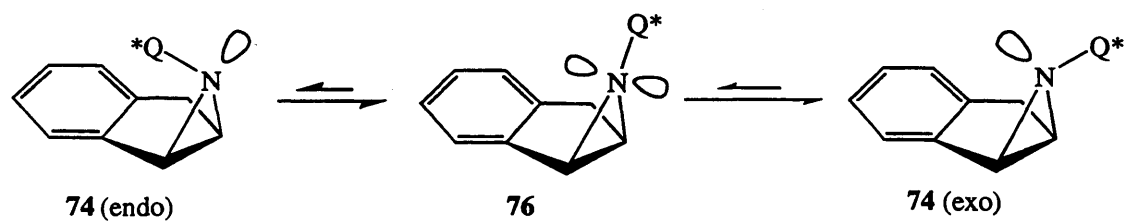
## 2.4 Aziridination of indene

The aziridination of indene with Q\*NHOAc **49** was examined next, and the results are shown below in Scheme 27.



Scheme 27

In this case the reaction in the absence of TTB gave some modest stereoselectivity, a 3 : 1 ratio of aziridine diastereoisomers **74** and **75** being produced. Again the diastereoselectivity of aziridination is greatly enhanced on the addition of TTB to the reaction mixture; the NMR spectrum of the crude product now showed only a single diastereoisomer of aziridine **74**, as an 8 : 1 mixture of *exo* : *endo* *N*-invertomers and crystallisation from ethanol gave this product in 86% yield. In the crystalline phase aziridine **74** exists only as the *exo*-*N*-invertomer; thus dissolution of a sample of **74**, crystallised from ethanol, in deuteriochloroform at -40 °C followed by the immediate recording of the room temperature NMR spectrum showed only signals for the major *exo* isomer, which equilibrated to give an 8 : 1 ratio of *exo* : *endo* *N*-invertomers over 30 min at room temperature (see Appendix I). In a further experiment, the reaction of **49** and indene in the absence of titanium alkoxide was followed by low temperature NMR spectroscopy and showed the kinetically first-formed product to be as expected<sup>43</sup> solely the *endo*-*N*-invertomer.

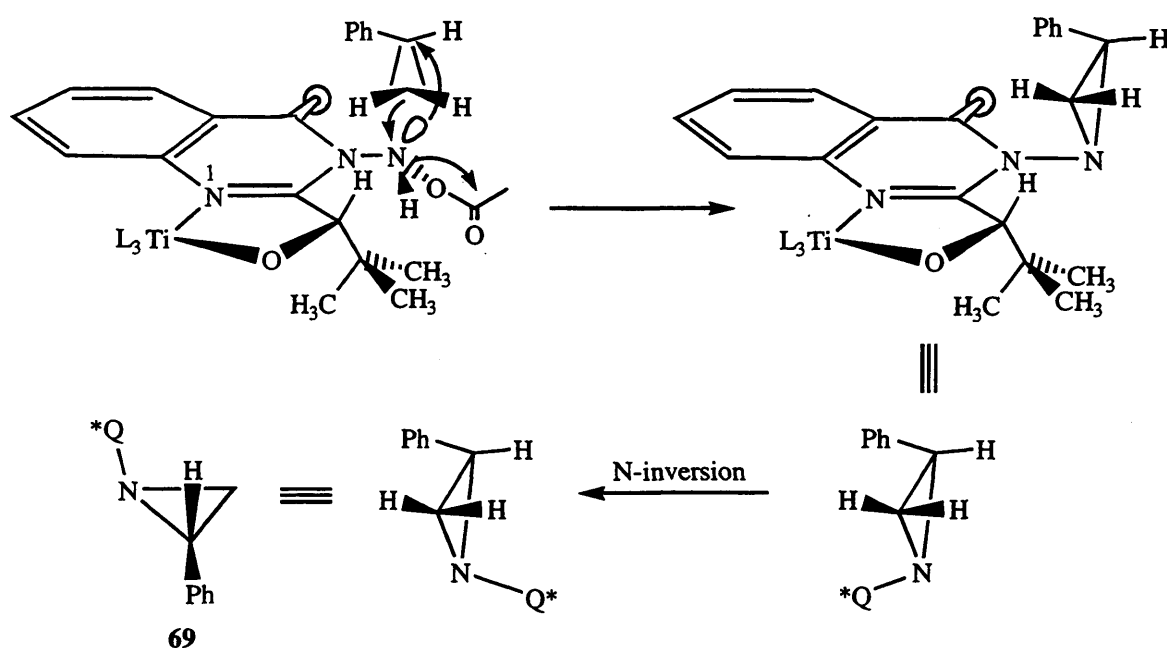


Scheme 28

Presumably the barrier to inversion at the ring nitrogen in the aziridine **74** is significantly greater than that for the styrene-derived aziridine **69** because of the greater strain associated in forming the planar 6-azabicyclo[3.1.0] intermediate **76** required for *N*-inversion (Scheme 28).

## 2.5 Transition state model for aziridination of electron-rich alkenes

As this study has shown, aziridination of styrene, butadiene and indene is completely diastereoselective in the presence of two mole equivalents of titanium (IV) *tert*-butoxide. The configuration of the newly created chiral centre in the styrene-derived aziridine **69** has been proven by X-ray structure determination and shown to be *S* (Fig. 30). The sense of diastereoselectivity is consistent with the previously described transition state model (see Introduction) together with titanium (IV) chelation between *N*-1 of the quinazolinone and the hydroxy group in the side chain (Scheme 29).



Scheme 29

In this transition state the phenyl and quinazolinone rings are *syn* (cf. addition to indene) with approach of the alkene from the face of the quinazolinone opposite to the *tert*-butyl group. Since the transition states for aziridination of indene and butadiene are presumed to be analogous the absolute configurations of aziridines **72** and **74** are assigned accordingly as shown.

## 2.6 Effect of titanium (IV) *tert*-butoxide concentration on aziridination of styrene

The concentration of titanium (IV) *tert*-butoxide was varied in order to observe the effect on the yield and diastereoselectivity in aziridination of styrene. This was done not only to find the optimum conditions for reaction, but to get some evidence for the mechanism. The results are shown in Table 2.

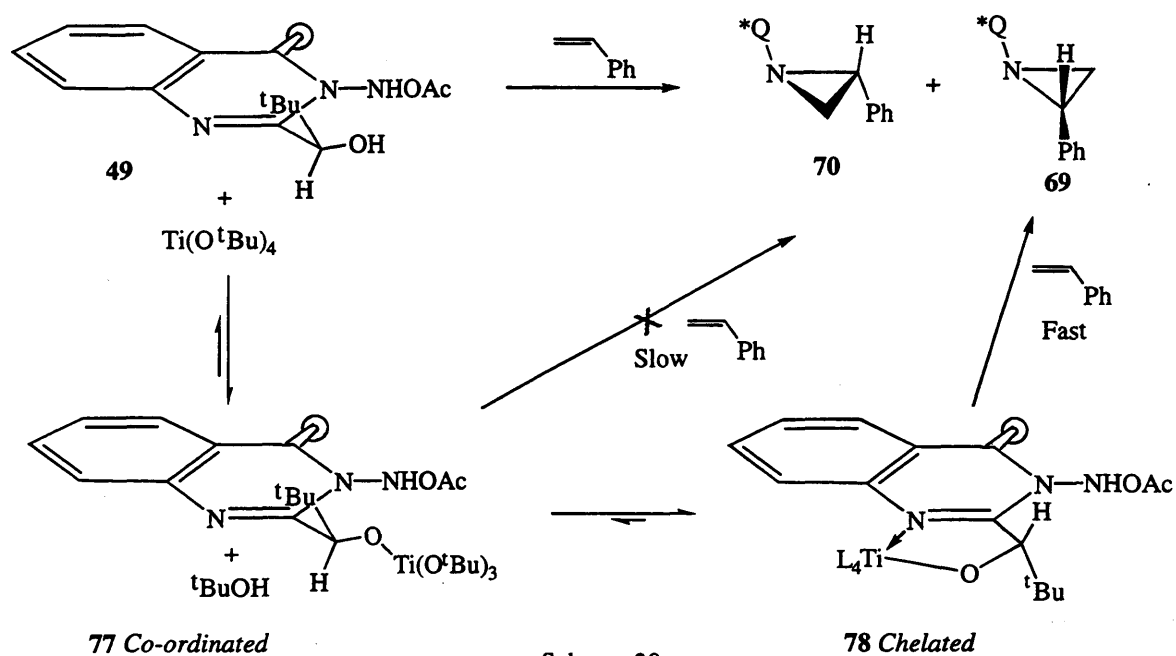
Entry	No. of Ti(O <sup><i>t</i></sup> Bu) <sub>4</sub> equivalents	Ratio of aziridine diastereoisomers	Yield of aziridine (%)
1	1.0	6.8 : 1	73
2	1.5	34 : 1	86
3	2.0	> 50 : 1	65

Table 2 - Effect of titanium concentration on yield and diastereoselectivity of aziridination

The higher yields obtained at lower concentrations of titanium are attributed to the ease of work-up; when the reaction is quenched with aqueous sodium hydrogen carbonate a white emulsion/solid forms which is difficult to separate but the corresponding reactions using lower concentrations of titanium were found to be much more readily filtered.

The increase in diastereoselectivity with increasing concentration of the titanium salt can be rationalised as follows. An increase in the concentration of TTB can be assumed to bring about a decrease in the concentration of titanium-free aziridinating agent Q\*NHOAc **49** and consequently a decrease in non-diastereoselective aziridination (see Scheme 30). In Scheme 30 it is assumed that the chelated species **78** reacts more rapidly than the co-ordinated species **77** and that the equilibrium between the two favours the former. The result of chelation would be expected to speed up the rate of aziridination; thus the relayed electron-withdrawing effect of metal chelation would make the exocyclic nitrogen (Q\*NHOAc) more reactive (electrophilic) and may also help to augment the secondary interaction between heterocycle and the  $\pi$ -

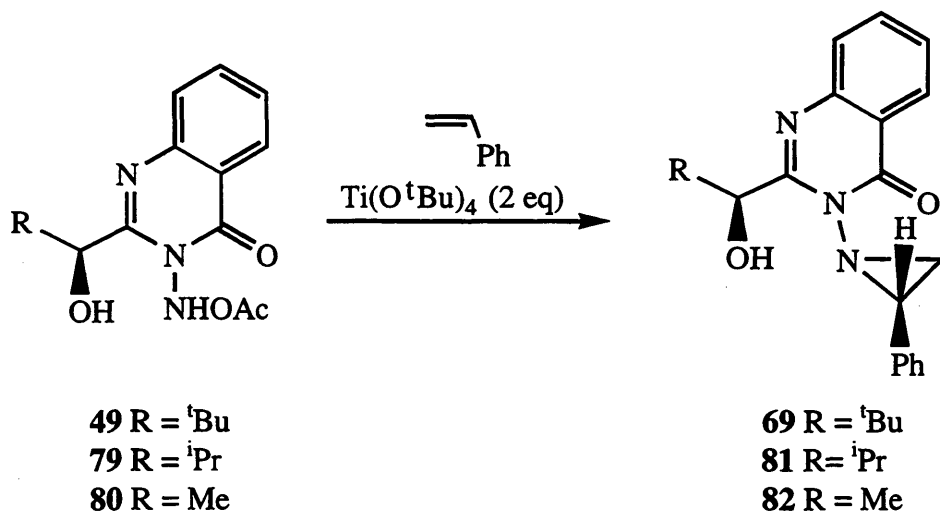
electron containing substituent on the alkene. Conversely, the co-ordinated species **77** would be expected to have a lower rate of aziridination, simply on steric grounds.



Scheme 30

## 2.7 Evidence for a chelated transition state model

Some support for the chelation model in Scheme 29 comes from the aziridination of styrene using 3-acetoxyaminoquinazolinones **79** and **80**<sup>98</sup> (Scheme 31).

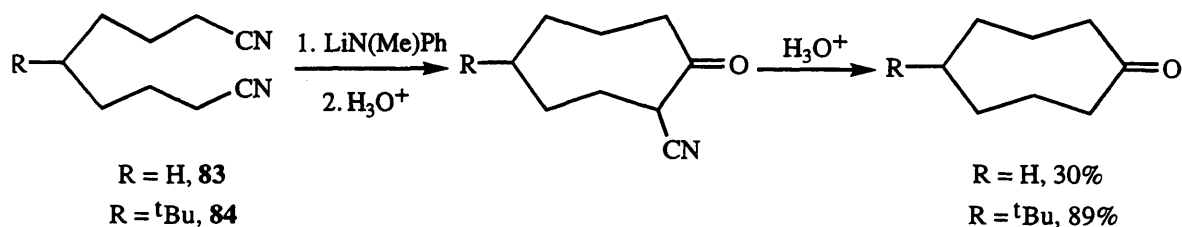


Scheme 31

There is a good correlation between diastereoselectivity in these aziridinations and the size of the R group in the side chain; when R is *tert*-butyl complete diastereoselectivity is observed, with diastereoselectivity dropping to 20 : 1 for the *iso*-propyl substituted compound and to 6 : 1 when R is methyl. The lower diastereoselectivities displayed by **79** and **80** could be explained by the chelated transition state model if, as the size of R decreases, there is increased competitive attack of the alkene from the same side as the alkyl group.

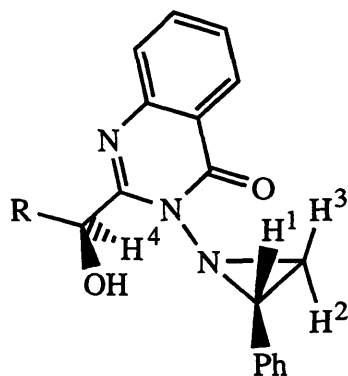
However, a further factor could be the extent to which the equilibrium between co-ordinated and chelated species might be affected by an increase in the size of the substituent. R. Allinger observed that di-nitrile **83** was cyclised to cyclooctanone in 30 % yield<sup>99</sup> via a Thorpe-Ziegler reaction, while under the same conditions the 5-*tert*-butyl derivative **84** afforded the corresponding ketone in 89% yield (Scheme 32).<sup>100</sup> The promotion of cyclisation by *gem*-substituents (methyl) on the acyclic precursor is termed the “*gem*-dimethyl effect”<sup>101</sup> and was first noted as early as 1915.<sup>102</sup> In the case of compounds **79** and **80** the smaller R group could lead to a higher concentration of

co-ordinated species (cf. Scheme 30) and hence to erosion of diastereoselectivity as a result of competitive aziridination *via* this species.



Scheme 32

The chemical shifts for the aziridine ring and  $\text{RCHOH}$  protons in the NMR spectra of compounds **69**, **81** and **82** are given in Table 3. There is a good correlation in values for the major and minor diastereoisomers suggesting that the preferred sense of diastereoselectivity is, as expected, the same in each case.



	Major diastereoisomer			Minor diastereoisomer		
	$R = \text{tBu}$	$R = \text{tPr}$	$R = \text{Me}$	$R = \text{tBu}$	$R = \text{tPr}$	$R = \text{Me}$
$\text{H}_1$	3.84	3.73	3.96	4.29	4.47	4.39
$\text{H}_2$	2.91	2.90	2.68	2.74	2.63	2.58
$\text{H}_3$	3.50	3.55	3.62	3.20	3.45	3.40
$\text{H}_4$	4.99	4.92	5.08	5.22	5.25	5.28

Table 3 Chemical shift values for selected protons in aziridines **69**, **81** and **82**.



## 2.8 Aziridination of $\alpha$ -methylstyrene

To explore the range and limitations of this method of asymmetric aziridination the effect of further substitution of the alkene was examined. Thus the aziridination of  $\alpha$ -methyl styrene with Q\*NHOAc **49** was studied, the results of which are shown in Table 4.

Entry	Reaction conditions <sup>#</sup>	Ratio of aziridine diastereoisomers	Yield (%) of aziridine <b>85</b>	Yield (%) of Q*NHO <sup>t</sup> Bu <b>86</b>
1	No Ti(O <sup>t</sup> Bu) <sub>4</sub>	1.1 : 1	77	---
2	Ti(O <sup>t</sup> Bu) <sub>4</sub> (2 eq) "normal reaction"	1.1 : 1	61	trace
3	Ti(O <sup>t</sup> Bu) <sub>4</sub> (2 eq) "premixed reaction"	9 : 1	44	8
4	NMR experiment	~20 : 1	Not calculated	Not calculated

<sup>#</sup>The "normal reaction" (entry 2) is the reaction carried out under conditions identical to those used for previous aziridinations. Reaction conditions for entries 3 and 4 are described below in the text. Yields and ratios determined from the NMR spectra of crude reaction mixtures; 2 equivalents of alkene were used in each case.

Table 4 - Aziridination of  $\alpha$ -methylstyrene

The reaction proved problematic due to the fragility of the aziridine product and alternative work-up conditions to those used previously were necessary to prevent its ring-opening. As found for other alkenes, aziridination in the absence of Ti(O<sup>t</sup>Bu)<sub>4</sub> gave very poor diastereoselectivity. Carrying out the aziridination in the presence of the titanium alkoxide under conditions identical to those used previously did *not* increase the diastereoselectivity of the reaction. However it was found, fortunately that by pre-mixing the Q\*NHOAc **49** with titanium (IV) *tert*-butoxide at low temperature (-40 °C) and leaving at this temperature for 1 h prior to addition of  $\alpha$ -methylstyrene a 9 : 1 ratio of aziridine **85** diastereoisomers was produced. Not surprisingly the yield under these conditions was lowered to 44 % since Q\*NHOAc **49** is known to decompose in the presence of titanium (IV) *tert*-butoxide to give the 3-*tert*-butoxyaminoquinazolinone **86**. In a further experiment, Q\*NHOAc **49** was pre-mixed with TTB at -40 °C for 4 h prior to addition of the alkene and the reaction followed by

NMR spectroscopy. Under these conditions no signals attributable to the minor diastereoisomer were visible.

Further work is needed to rationalise these results. The “normal” reaction in Table 3 corresponds to addition of a solution of Q\*NHOAc **49** to a solution of the alkene and TTB in dichloromethane. The possibility that  $\alpha$ -methylstyrene is sufficiently more reactive than styrene to react (non-diastereoselectively) under these conditions with titanium-free Q\*NHOAc has not been excluded.

## 2.9 Aziridination of isoprene

Since isoprene is an unsymmetrical diene, the possibility of regioisomers in the aziridination arises. The results of aziridination of isoprene with Q\*NHOAc **49** with and without titanium (IV) *tert*-butoxide are shown in Table 5.

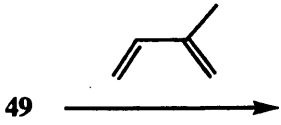
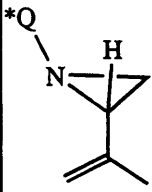
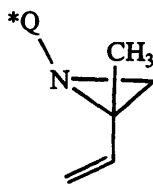
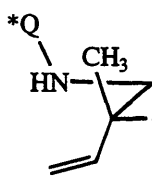

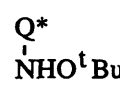
		 87	 88	 89	 90	 86
No Ti(O <sup>t</sup> Bu) <sub>4</sub>	Yield (%)	10	48	10	12	—
	Ratio of diastereoisomers	1.4 : 1	1 : 1.05	2.3 : 1	—	—
Ti(O <sup>t</sup> Bu) <sub>4</sub> (2eq)	Yield (%)	38	30	0	0	11
	Ratio of diastereoisomers	> 50 : 1	1 : 1.6	—	—	—

Table 5

As with  $\alpha$ -methylstyrene, the presence of a methyl group on the aziridine ring makes it prone to ring-opening under the reaction conditions and ring-opened product **89** derived from aziridine **88** was isolated. The double bond with a methyl group attached is more electron-rich and would be expected to be more reactive, this was indeed found to be the case. Taking the formation of the ring-opened product into account, the regioselectivity of the aziridination is biased in favour of the more electron-rich double bond by a ratio of 5.8 : 1. For aziridination of both double bonds the diastereoselectivity of the reaction was very poor.

Aziridination of isoprene with Q\*NHOAc **49** in the presence of TTB displayed less regioselectivity. Under these conditions the preferred sense of regioselectivity was inverted, the ratio of attack being 1.25 : 1 in favour of addition to the less substituted double bond. Aziridination of this less electron-rich double bond was completely diastereoselective, with no signals for the minor diastereoisomer visible in the NMR spectrum of the crude product. This is in contrast to addition to the more substituted

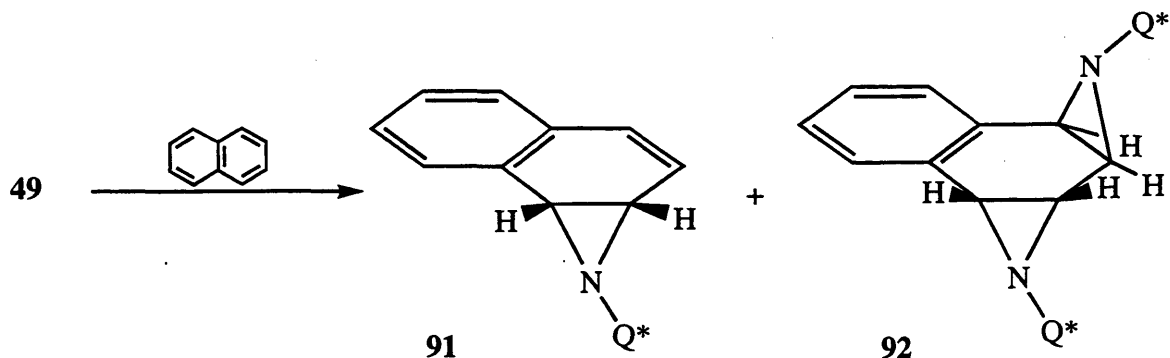
double bond which again occurred with virtually no diastereoselectivity. The single aziridine diastereoisomer **87** crystallised from the crude reaction mixture and was recovered in 38 % yield.

The reason for this gross change in regioselectivity of aziridination brought about by the presence of  $\text{Ti}(\text{O}^t\text{Bu})_4$  are not yet understood and further investigations are underway in this laboratory.

## 2.10 Enantiopurity of 3-aminoquinazolinone 65

The major goal in this project is the efficient synthesis of enantiopure  $Q^*$ -free chirons *via* ring-opening of single diastereoisomers of aziridines obtained by aziridination of alkenes with  $Q^*NHOAc$  49. For these chirons to be enantiopure the starting aziridine must not only must be a single diastereoisomer, but must also be a single enantiomer. Clearly enantiopurity of the starting 3-aminoquinazolinone 65 is required.

Evidence for the enantiopurity of  $Q^*NH_2$  65 was obtained from its aziridination products with naphthalene.<sup>103</sup> In this (low yielding) reaction two products are obtained (Scheme 33); the major product is formed by addition to a single double bond as a mixture of diastereoisomers. This mono-aziridine 91 can then go on to react with a further equivalent of  $Q^*NHOAc$  49 to yield the bis-aziridine 92.



Scheme 33

In bis-aziridine 92 if, as is believed, the two aziridine rings are *trans* to one another as shown the compound has a two-fold axis of symmetry (Fig. 18). Support for this stereostructure comes from the  $^{13}C$  NMR spectrum of 92 which shows just two resonances for the aziridine ring carbons. If however, 65 was not enantiopure then some bis-aziridine 93 would also be formed. Since the configurations of the substituents in the side chain of the quinazolinone are now no longer identical (they are R and S), they are non-superimposable and compound 93 does not have an axis (or plane) of symmetry. Thus the NMR spectrum of 93 would be different to that of 92

and could show four resonances for the aziridine ring carbons. Thus if **93** were present, additional signals from it would be visible in the  $^{13}\text{C}$  NMR spectrum.

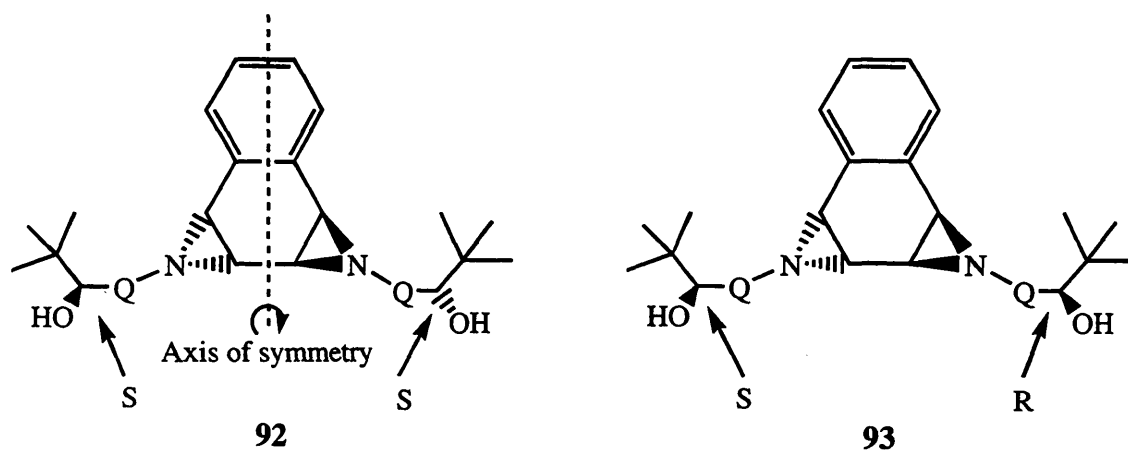


Fig. 18

## ***2.11 Summary of Chapter 2***

The 3-aminoquinazolinone **65** has been synthesised in good overall yield without the need for chromatography at any stage and shown to be of high enantiopurity by its reaction with naphthalene. Oxidation of **65** with LTA gives the corresponding 3-acetoxaminoquinazolinone **49** which aziridates styrene, butadiene, indene and the less substituted double bond of isoprene completely diastereoselectively in the presence of 2 equivalents of TTB. **49** also aziridates  $\alpha$ -methyl styrene with high but not complete diastereoselectivity in the presence of TTB.

The structure of the styrene-derived aziridine **69** has been proven by X-ray structure determination and is consistent with the chelated transition state model we propose. Since analogous transition states for aziridination of indene and butadiene are anticipated, the absolute configurations of aziridines **72** and **74** are assigned accordingly. Evidence from aziridination of styrene with 3-acetoxaminoquinazolinones **79** and **80** supports this chelated transition state model. The concentration of TTB was found to be crucial for the diastereoselectivity of aziridination of styrene with **49**.

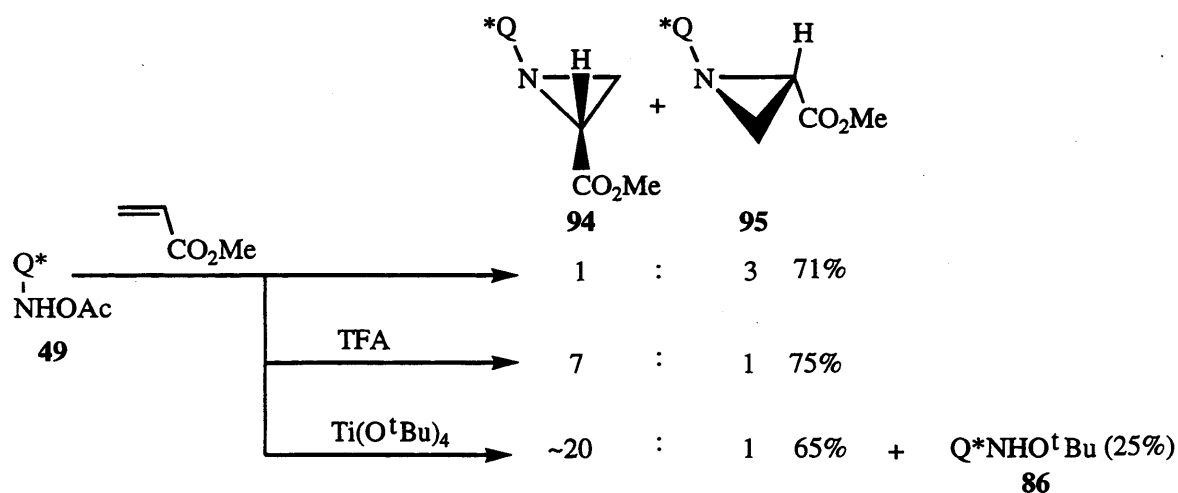
## ***Chapter 3 :***

### ***Aziridination of Electron-Deficient Alkenes***



### 3.1 Aziridination of methyl acrylate

3-Acetoxyaminoquinazolinones are also efficient aziridinating agents for electron-deficient alkenes. The diastereoselectivity of aziridination of acrylates using Q\*NHOAc **49** has been examined, not only in the presence of titanium salts, but also in the presence of TFA: the results using methyl acrylate are given in Scheme 34.



Scheme 34

Aziridination of methyl acrylate with Q\*NHOAc **49** alone gave a 1:3 ratio of aziridine diastereoisomers **94** and **95** respectively. The yield and diastereoselectivity of the aziridination of  $\alpha,\beta$ -unsaturated esters has been shown to be enhanced by the addition of TFA to the reaction mixture<sup>65,66</sup> and this was also found in the present case; in the presence of TFA the diastereoselectivity was improved to 7 : 1 and the preferred *sense* of diastereoselectivity was inverted. Thus the minor aziridine diastereoisomer **94** becomes the major product when the aziridination is carried out in the presence of TFA.

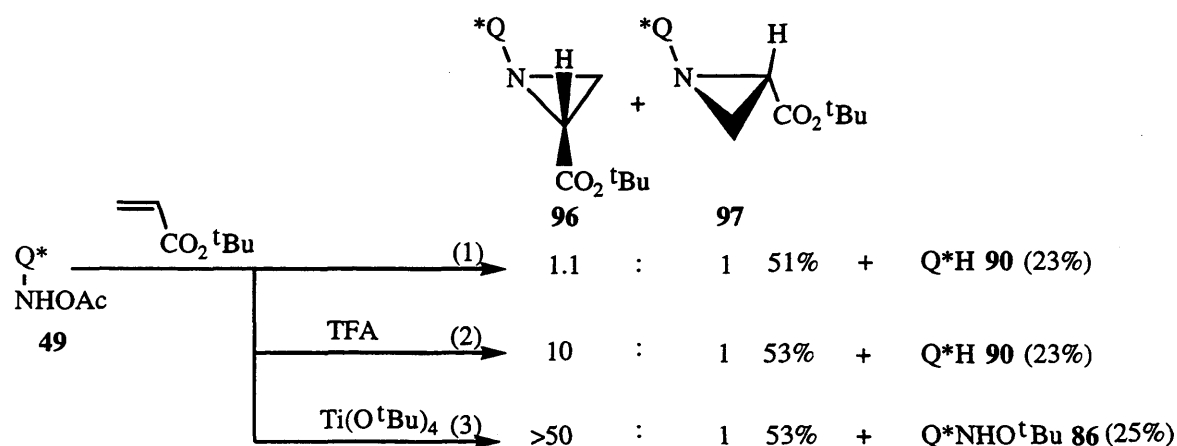
When the reaction was carried out in the presence of titanium (IV) *tert*-butoxide the diastereoselectivity is further increased to a ratio of ~20 : 1, the preferred *sense* of diastereoselectivity being the same as when the reaction was carried out in the presence of TFA. In addition, a significant amount (25%) of the 3-*tert*-

butoxyaminoquinazolinone **86** by-product was obtained, showing methyl acrylate to be a less efficient reactant with Q\*NHOAc **49** than electron-rich alkenes.

In an attempt to prevent the formation of this unwanted by-product, the aziridination was repeated in the presence of zirconium (IV) *tert*-butoxide and in the presence of triisopropylborate (both commercially available); however in both cases the sole products were the corresponding 3-alkoxyaminoquinazolinones **86** (56%) and **71** (75%).

### 3.2 Aziridination of *tert*-butyl acrylate

The aziridination of the more hindered *tert*-butyl acrylate with Q\*NHOAc **49** in the presence of TFA and in the presence of titanium (IV) *tert*-butoxide was also examined, Scheme 35.



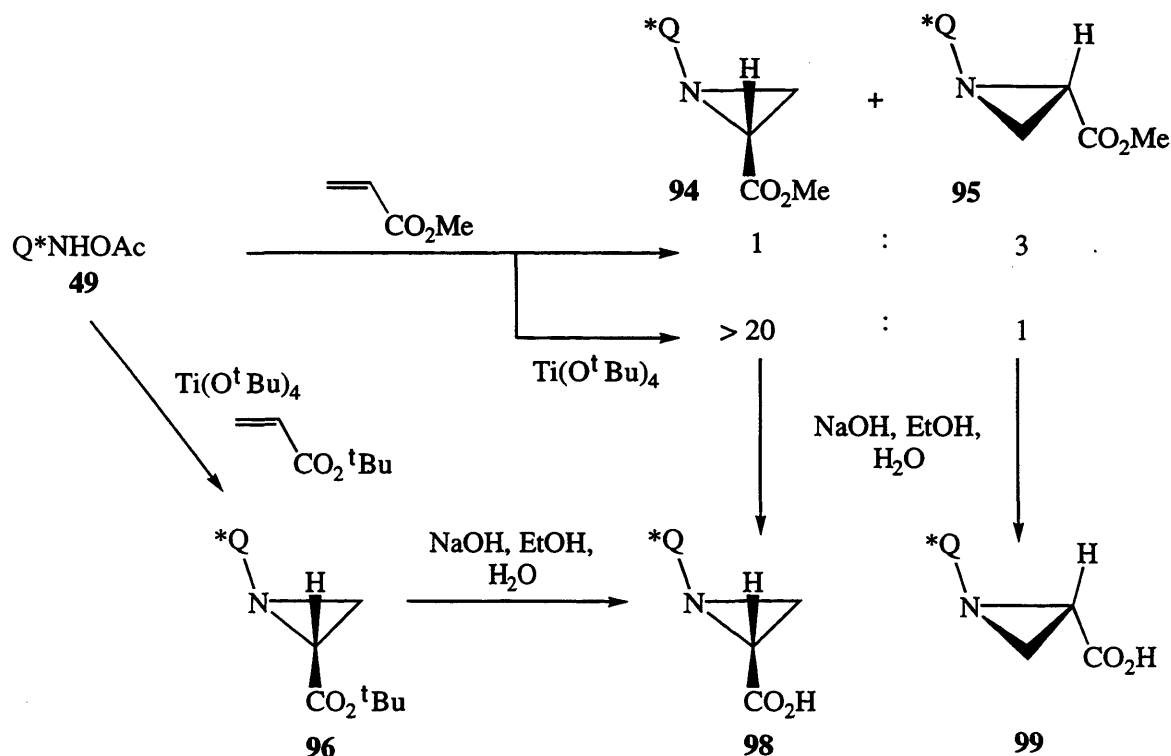
Scheme 35

In each case the yield of aziridine was lower than that obtained using methyl acrylate, as would be expected for the more hindered alkene. An additional product under conditions in entries 1 and 2 was the de-aminated quinazolinone, Q\*H **90**, now obtained in significant amounts in each case.

Thus the pattern for aziridination of *tert*-butyl acrylate was similar to that observed for methyl acrylate: diastereoselectivity was enhanced by the addition of TFA or Ti(O<sup>t</sup>Bu)<sub>4</sub> to the reaction mixture. In the presence of TTB, aziridination was

completely diastereoselective and no signals corresponding to the minor diastereoisomer were visible in the NMR spectrum of the crude product.

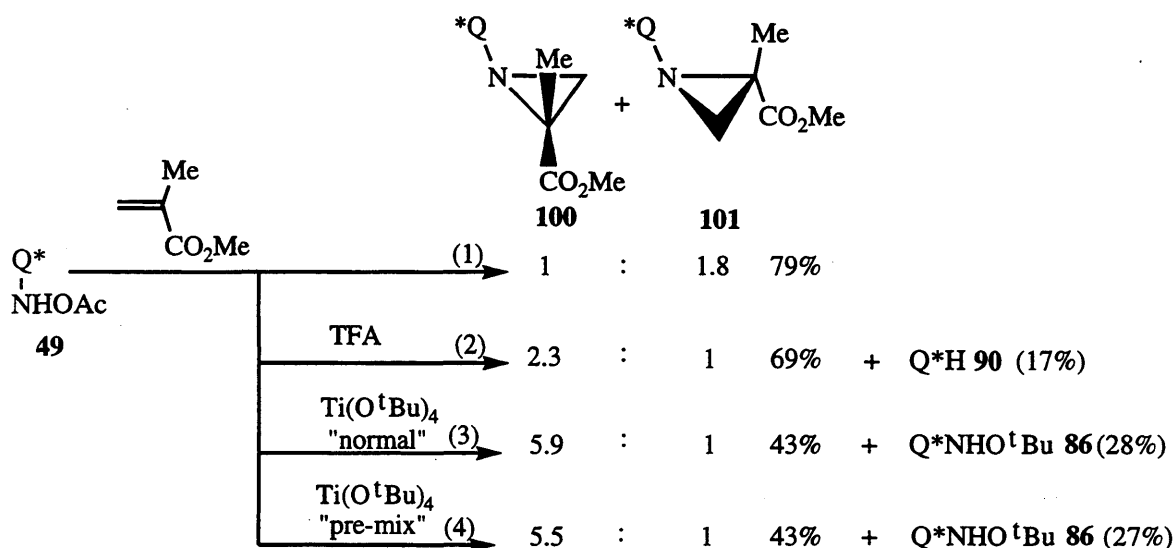
The stereostructure of the major diastereoisomer aziridine **96** was proven by X-ray structure determination (Fig. 31) and shows the configuration of the newly created chiral centre to be *S*. Hydrolysis of the aziridine *tert*-butyl ester **96** with sodium hydroxide afforded aziridine carboxylic acid **98**, (Scheme 36) identical to that obtained from hydrolysis of the major aziridine methyl ester diastereoisomer **94** obtained from aziridination of methyl acrylate in the presence of  $\text{Ti}(\text{O}^t\text{Bu})_4$  (Scheme 34). (Hydrolysis of the diastereoisomeric aziridine methyl ester **95** gave aziridine caboxylic acid **99** which was not identical to **98**). Thus the absolute configurations of both aziridine esters **94** and **96** are identical and the preferred sense of asymmetric induction in addition to both methyl acrylate and *tert*-butyl acrylate is the same.



Scheme 36

### 3.3 Aziridination of methyl methacrylate

The effect of further substitution on the double bond of an electron-deficient alkene was probed, with the aziridination of methyl methacrylate with Q\*NHOAc **49**. The results are shown below in Scheme 37.



Scheme 37

As found previously aziridination with Q\*NHOAc **49** alone (entry 1) gave virtually no diastereoselectivity. The preferred sense of diastereoselectivity was inverted but only marginally increased to 2.3 : 1 on carrying out the reaction in the presence of TFA. When the aziridination was carried out in the presence of TTB under standard conditions (entry 3) the diastereoselectivity was further enhanced, to ~6:1. The structure of the major distereoisomer **100** was proved by X-ray structure determination (Fig. 32) and thus the preferred sense of diastereoselectivity is the same as that for addition to methyl and *tert*-butyl acrylate.

However unlike aziridination of the analogous disubstituted electron-rich olefin,  $\alpha$ -methylstyrene, diastereoselectivity was not increased by carrying out the reaction under the "pre-mix" conditions. This suggests that the mechanism of addition under titanium alkoxide catalysis for electron-deficient alkenes is different to that for electron-rich alkenes (see below).

### 3.4 Mechanism of aziridination of electron-deficient alkenes

The preferred sense of diastereoselectivity in aziridination of methyl, *tert*-butyl acrylate and methyl methacrylate in the presence of TFA is the same. These results can be explained in terms of transition states analogous to those proposed for other TFA-catalysed aziridinations of acrylates (see Introduction). The TFA-free reaction in each case proceeds via the transition state shown in Fig. 19, with the ester group of the  $\alpha,\beta$ -unsaturated ester lying under the C-4 carbonyl carbon of the heterocycle. Poor diastereoselectivity is observed as there are ill-defined site preferences for the substituents on the chiral centre in the side chain.

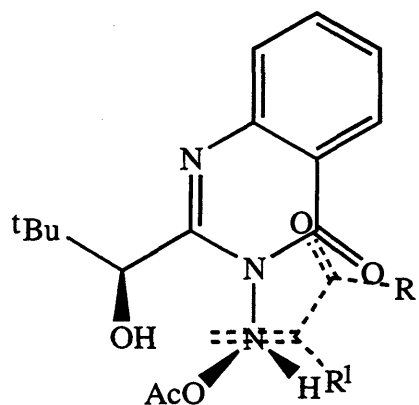


Fig. 19

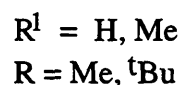
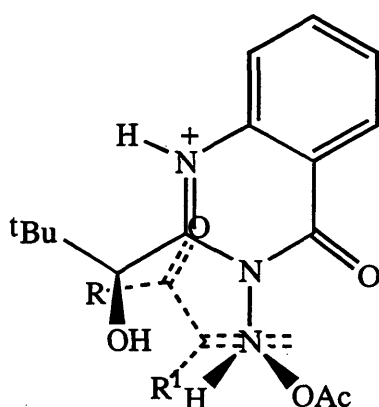
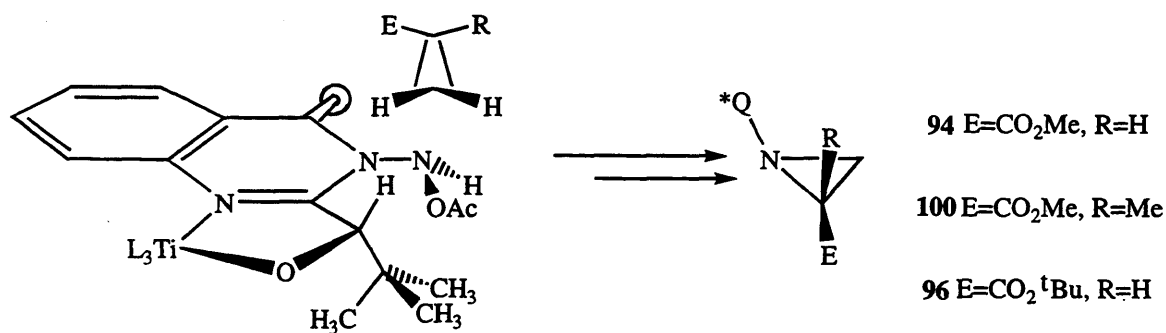


Fig. 20

The increase in diastereoselectivity observed in the presence of TFA is believed to result from a change in transition state geometry to that shown in Fig. 20.<sup>65,66</sup> This change is brought about by an augmentation of the secondary interaction between the ester and the C=N of the quinazolinone resulting from protonation of the *N*-1 nitrogen. An increase in site preferences for the substituents on the chiral centre results from their proximity to the ester group.<sup>67</sup>

The preferred sense of diastereoselectivity observed in the titanium alkoxide-catalysed reactions is the same for each of the three electron-deficient alkenes above. In these reactions the absolute configurations of the major diastereoisomers **94**, **96** and **100** are those anticipated from the transition state shown in Scheme 38, analogous to

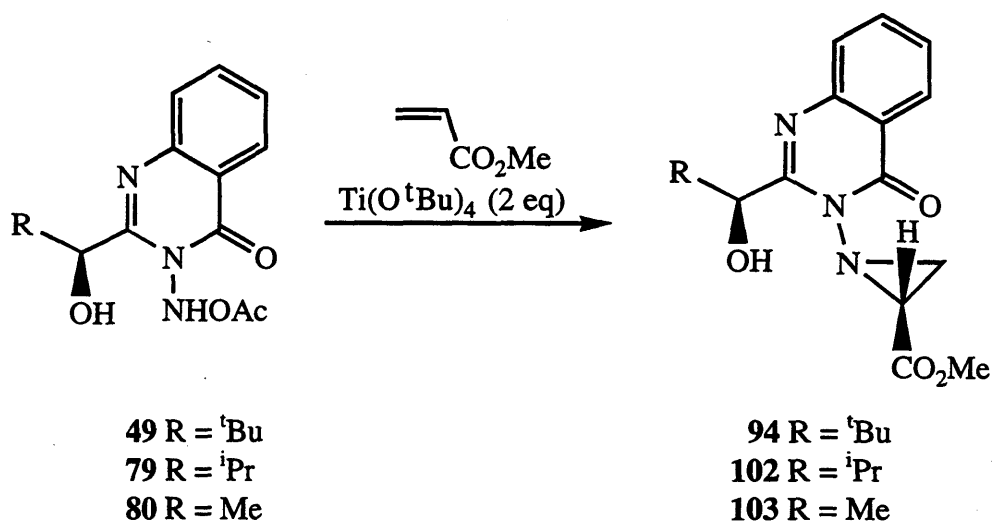
that for aziridination of electron-rich alkenes (Scheme 29) but with the configuration at the exocyclic nitrogen inverted to allow for the different mechanism of aziridination of  $\alpha,\beta$ -unsaturated esters (see Introduction).



Scheme 38

The change in diastereoselectivity in aziridination of styrene with 3-acetoxyminoquinazolinones **49**, **79** and **80** in the presence of TTB was previously used to support the transition state model proposed for reaction with electron-rich alkenes (Scheme 31). It was interesting to make the same comparison for aziridination of methyl acrylate with the 3-acetoxyminoquinazolinones **49**, **79** and **80** (Scheme 39).

The diastereoselectivity ratio decreases from ~20 : 1 to 1 : 1 on changing from R = <sup>t</sup>Bu to R = <sup>i</sup>Pr but increases to 1 : 3 on changing from R = <sup>i</sup>Pr to R = Me. Although the preferred sense of diastereoselectivity in the case of R = Me is not yet known it is likely to be opposite to that obtained for R = <sup>t</sup>Bu. These results are not consistent with the transition state model in Scheme 38 involving chelation control by titanium for all cases R = <sup>t</sup>Bu, <sup>i</sup>Pr and Me and, possibly, not for any of them.

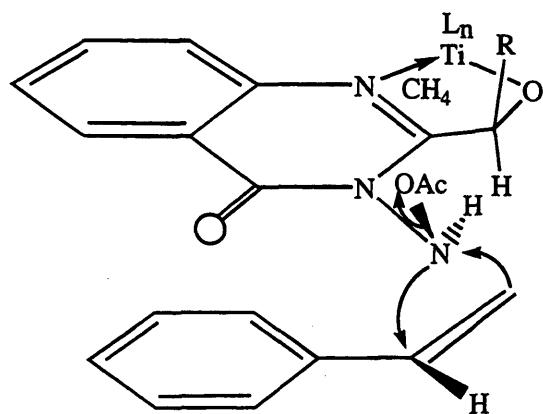


Scheme 39

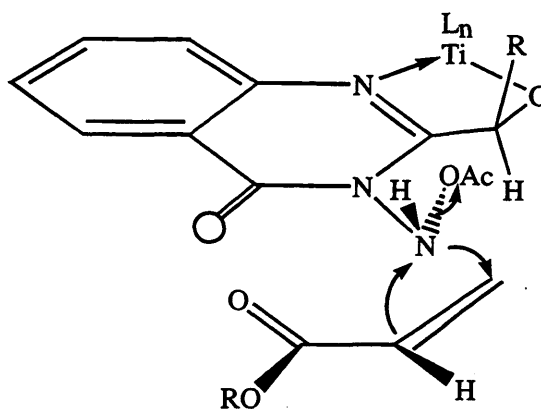
These differences in TTB-mediated aziridination of electron-deficient and electron-rich alkenes can be explained by considering the mechanisms involved. As discussed previously (see Introduction) the transition states for aziridination of styrene and of methyl acrylate by 2-alkyl-3-acetoxyaminoquinazolinones (e.g. **49**) in the absence of titanium alkoxide are believed to differ in the configuration at the exocyclic nitrogen. Applying these transition state models to  $\text{Q}^*\text{NHOAc}$  **49** with chelation of the coordinated titanium gives those illustrated in Figures 21 and 22 for the two alkenes of different electron demand. For styrene (Fig. 21) the departing acetoxy group is orientated in a position above the phenyl ring on the alkene, thus the leaving acetoxy group points *away* from the R group on the chiral centre in the reagent. For methyl acrylate (Fig. 22) the departing acetoxy group points *towards* the R group on the chiral centre in the reagent.

From Fig. 22 it is clear that when R is large (*tert*-butyl or *iso*-propyl) as in compounds **49** and **79**, for the reaction to proceed via a chelated transition state requires the acetoxy group to be in a position where it would severely clash with the R group. It seems unlikely therefore that in the presence of TTB, addition of compounds **49** and **79** to methyl acrylate could proceed easily *via* a chelated transition state. It was suggested previously in the aziridination of electron-rich alkenes that it is chelation of N-1 with titanium (and not just co-ordination) that accelerates the rate of aziridination. However, for electron-deficient alkenes, chelation would retard the rate of

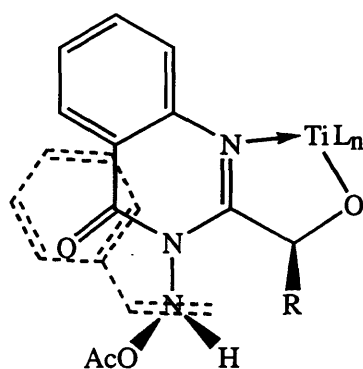
aziridination since in the transition state the exocyclic nitrogen  $Q^*NHOAc$  functions primarily as a nucleophile.



Side view

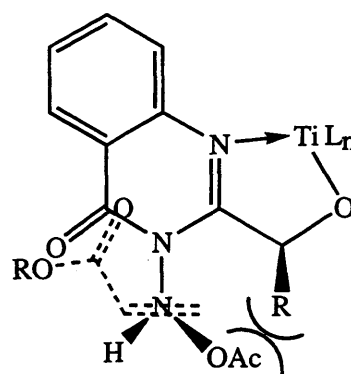


Side view



Top view

Fig. 21



Top view

Fig. 22

The high diastereoselectivities obtained in addition of **49** to methyl and *tert*-butyl acrylate in the presence of TTB can be rationalised in terms of aziridination occurring through the co-ordinated (but non-chelated) titanium species as shown in Fig. 23. Here a non-chelated species having a  $C_2 - C^*$  conformation as shown would relieve steric crowding associated with the required disposition of the acetoxy group, and would explain the magnitude and the sense of diastereoselectivity for the aziridination. Co-ordination of the titanium alkoxide increases the steric bulk of the hydroxy group, augments the site preferences for the three substituents on the chiral centre and hence enhances diastereoselectivity.



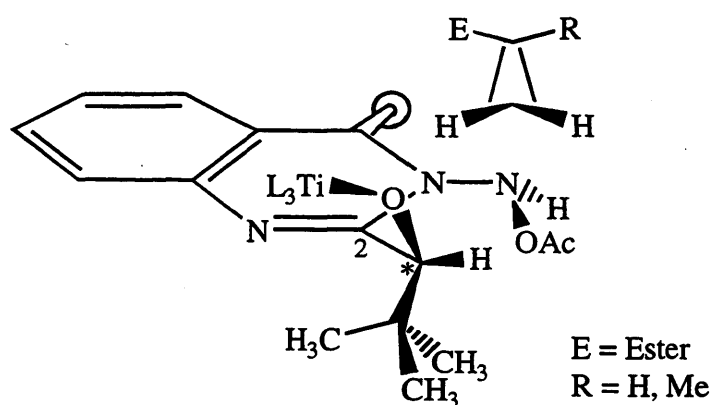


Fig. 23

In this interpretation the site preferences of the substituents on the chiral centre are critically dependent on the size of the R group. Thus there could be a change in the sense of diastereoselectivity in aziridination of methyl acrylate on changing R from *tert*-butyl to methyl that is not mirrored in aziridination of styrene (which is chelation-controlled).

The diastereoselectivity of addition of **49** to methyl acrylate is very high (> 20 : 1), therefore the rate of aziridination *via* the co-ordinated species (Fig. 23) must be much greater than that *via* the free acetoxo compound. It should be noted that the reaction of electron-rich alkenes with a TTB-co-ordinated Q\*NHOAc **49**, if it occurs, will not be by transition state analogous to that in Fig. 23 since the configuration at the exocyclic nitrogen will be opposite to that shown.

### 3.5 Effect of acetic acid on aziridination of methyl acrylate in the presence of titanium (IV) *tert*-butoxide

The acetoxylation of 3-aminoquinazolinones to 3-acetoxyaminoquinazolinones with LTA generates one equivalent of acetic acid, and no effort is made to remove it before aziridination. (A further equivalent of acetic acid is generated during the aziridination.) Since titanium (IV) *tert*-butoxide would be expected to scavenge the acid, the effect of removing it prior to addition of titanium was investigated. This was done simply by shaking the dichloromethane solution with saturated sodium hydrogen carbonate solution and drying with magnesium sulphate, entry 1, Table 6. To complement the study, the effect of adding acetic acid to the reaction mixture was probed, entries 3 to 5.

Entry	Equivalents of acetic acid present at start of reaction	Ratio of aziridine diastereoisomers	Yield (%) of aziridine <b>94</b>	Yield (%) of <b>86</b>
1	0	3 : 1	28	8
2*	1	>20 : 1	65	25
3	2	>20 : 1	57	17
4	3	3 : 1	34	37
5	4	1 : 1	17	50

\*Standard reaction, identical to 3rd entry in Scheme 34

Table 6 - Effect of acetic acid (mol equiv.) on diastereoselectivity and yields of products from aziridination of methyl acrylate with Q\*NHOAc **49** in the presence of titanium (IV) *tert*-butoxide

As shown in entry 1, scavenging the acetic acid generated during the *N*-acetoxylation prior to addition of the alkene and TTB has an adverse effect on the yield and diastereoselectivity of the reaction: under these conditions a 3:1 ratio of aziridine diastereoisomers was obtained in only 28% yield. A similar drop in yield and diastereoselectivity was obtained on the further addition of more than one equivalent of acid to the reaction (entries 4 and 5); under these conditions the major product from the reaction was 3-*tert*-butoxyaminoquinazolinone **86**. Thus the number of mol. equiv. of acetic acid present in these TTB catalysed reactions is crucial for high diastereoselectivity of aziridination and greatly affects the distribution of products.

These results suggest that the co-ordinated titanium species giving the high diastereoselectivity in these reactions must contain at least one acetate group. Although the ligands on titanium appear to be quite remote from the heterocycle (Fig. 23) it is possible that in this crowded system, reduction of the ligand size on titanium is important in controlling the site preferences of the three substituents on the existing chiral centre.

Clearly further work to establish the mechanistic details of these TTB-catalysed reactions is required; in particular the effect of the number of mol. equiv. of acetic acid present on the aziridination of electron-rich alkenes needs to be examined. However, for aziridination of electron-rich alkenes (styrene, butadiene, indene) the chelated transition model in Scheme 29 satisfactorily explains the sense of diastereoselectivity. In the case of methyl and *tert*-butyl acrylate, the present conclusion is that the same transition state is probably not involved.

### 3.6 Summary of Chapter 3

3-Acetoxyaminoquinazolinone **49** aziridinate methyl and *tert*-butyl acrylate with high diastereoselectivity in the presence of TFA. The diastereoselectivity in addition of **49** to these alkenes is further enhanced in the presence of TTB such that addition to methyl acrylate gives a ~20:1 ratio of diastereoisomers, while *tert*-butyl acrylate is aziridinated with complete diastereoselectivity.

The aziridination of methyl methacrylate with **49** displays poorer diastereoselectivity in the presence of TFA and in the presence of TTB than in the analogous reactions of methyl and *tert*-butyl acrylate. X-ray structure determination of aziridines **96** and **100** together with a chemical correlation show that for each alkene the sense of preferred diastereoselectivity of aziridination in the presence of TFA and TTB is the same. The *sense* of asymmetric induction of aziridination in the presence of TTB is consistent with a chelated transition state model however there is evidence that aziridination of electron-deficient alkenes in the presence of TTB does *not* proceed *via* a chelated transition state model.

The yield and diastereoselectivity of aziridination of methyl acrylate in the presence of TTB has been found to be critically dependent of the concentration of acetic acid present at the beginning of the reaction.

## ***Chapter 4 :***

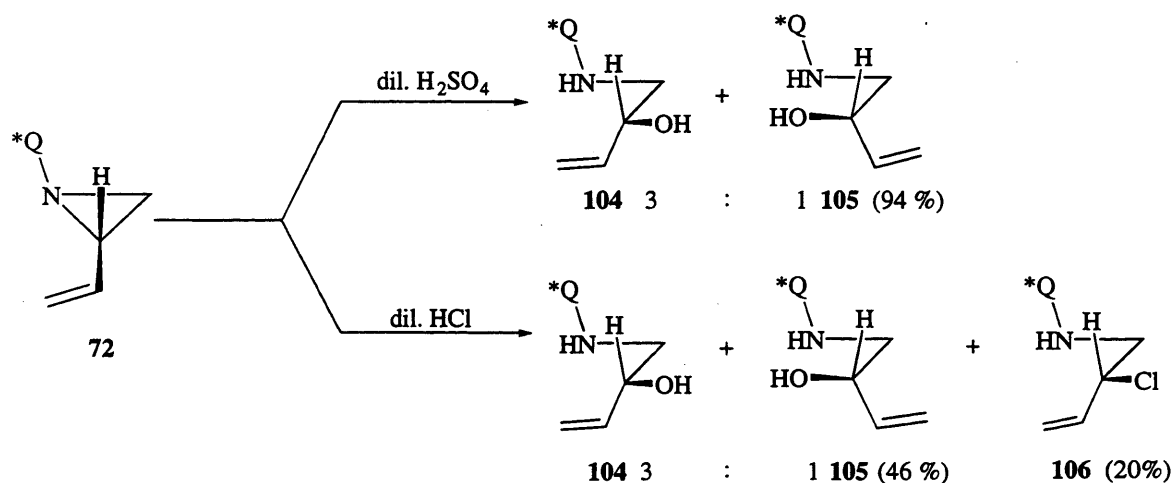
### ***Acid-Catalysed (Electrophilic) Ring-Opening of N-Q\*-Substituted Aziridines***

## 4.1 Introduction

In the previous two Chapters, methodology for the preparation of a number of aziridines with high or complete diastereoselectivity has been described. Ring-opening of these aziridines followed by  $Q^*-N$  bond reduction should give access to a range of enantiopure synthons (chirons). As mentioned in the Introduction, control of ring-breaking is as important as control of ring-making if significant use of aziridines is to be made in synthesis. There has been very little work carried out on the ring-opening of these  $N$ - $Q$ -substituted aziridines and the issues of activation, stereochemistry and regiochemistry of their ring-opening will be addressed in the following Chapters.

### 4.2 Ring-opening of vinylaziridine 72 with strong mineral acid

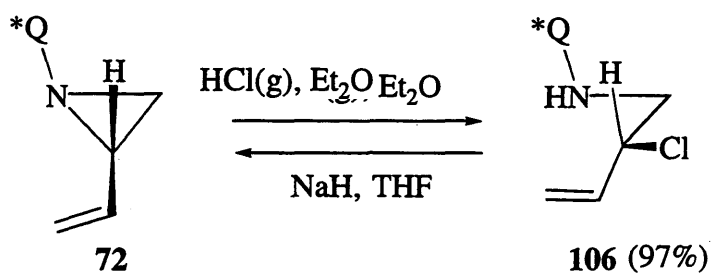
The vinylaziridine **72** was found to be readily ring-opened in dilute aqueous acid; treatment of **72** in 1,4-dioxan with dilute ( $0.2 \text{ mol dm}^{-3}$ ) sulphuric acid resulted in formation of allylic alcohol diastereoisomers **104** and **105** in a 3:1 ratio respectively (Scheme 40). This initial result seemed very disappointing; we had methodology for the preparation of **72** as a single diastereoisomer, but the subsequent ring-opening proceeded to give a mixture of diastereoisomers of the product.



Scheme 40

When the reaction was carried out in dilute hydrochloric acid, the allylic chloride **106** was isolated in addition to the allylic alcohols **104** and **105**. The allylic alcohols were obtained again as a 3:1 ratio of diastereoisomers, but the allylic chloride

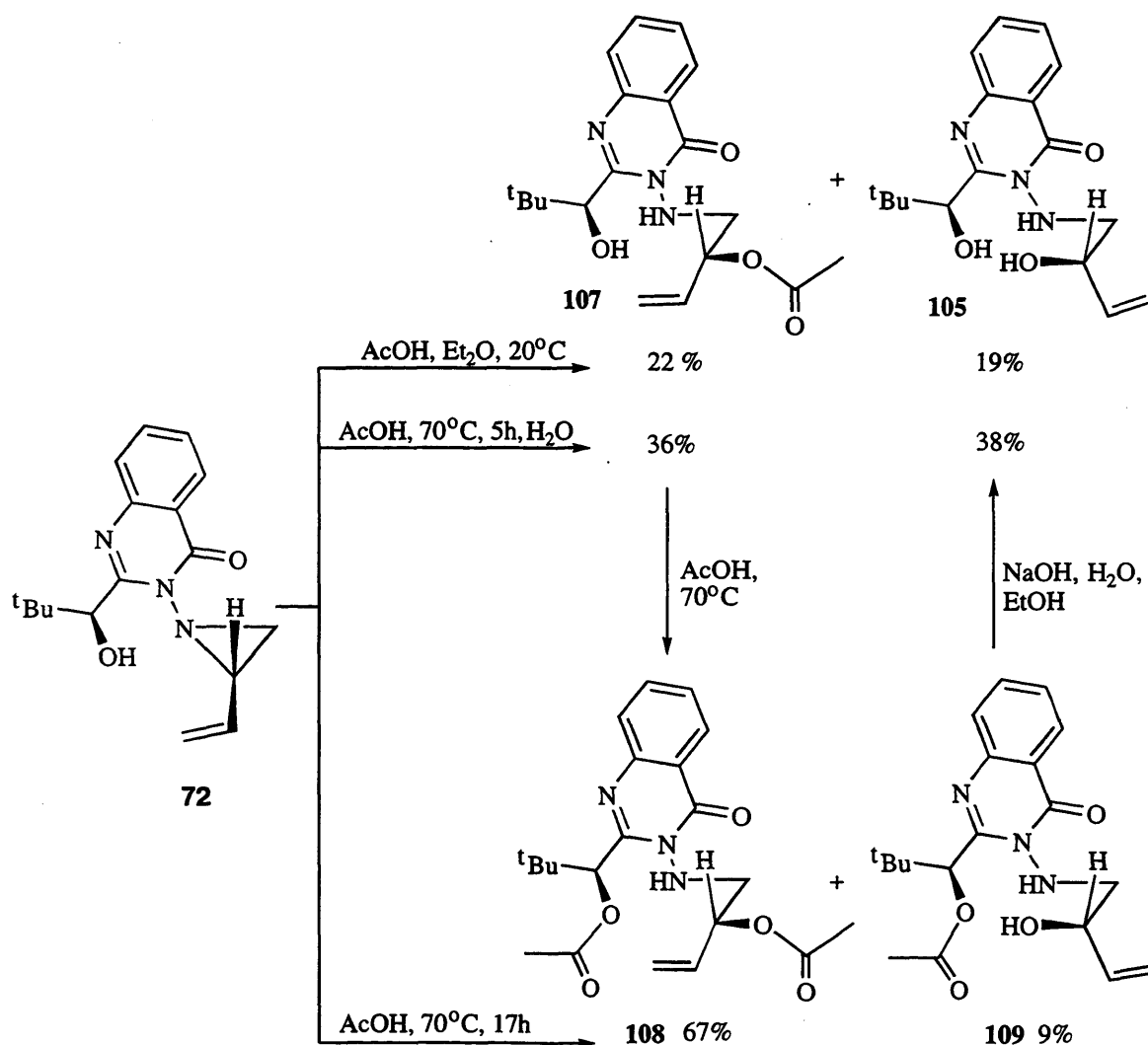
appeared to be present as a single diastereoisomer, albeit in low yield (20%). However this allylic chloride **106** could be obtained in quantitative yield when aziridine **72** was treated with hydrogen chloride gas in dry diethyl ether and was shown to be formed with inversion of configuration and as a single diastereoisomer by its conversion back to aziridine **72** in high yield on treatment with sodium hydride (Scheme 41).



Scheme 41

### 4.3 Ring-opening of vinylaziridine 72 with acetic acid

When vinylaziridine **72** was treated with acetic acid in diethyl ether, two products, allylic acetate **107** and allylic alcohol **105** were isolated in modest yield after chromatography (Scheme 42). Allylic alcohol **105** was found to be identical with the minor diastereoisomer **105** from treatment of vinylaziridine **72** with dilute sulphuric acid (Scheme 40). Carrying out the reaction in neat acetic acid at higher temperature (170 °C) again gave two products. The major product was the di-acetate **108** and the minor product the acetoxymethyl allylic alcohol **109**; under these conditions therefore the side chain hydroxy group is acetylated.

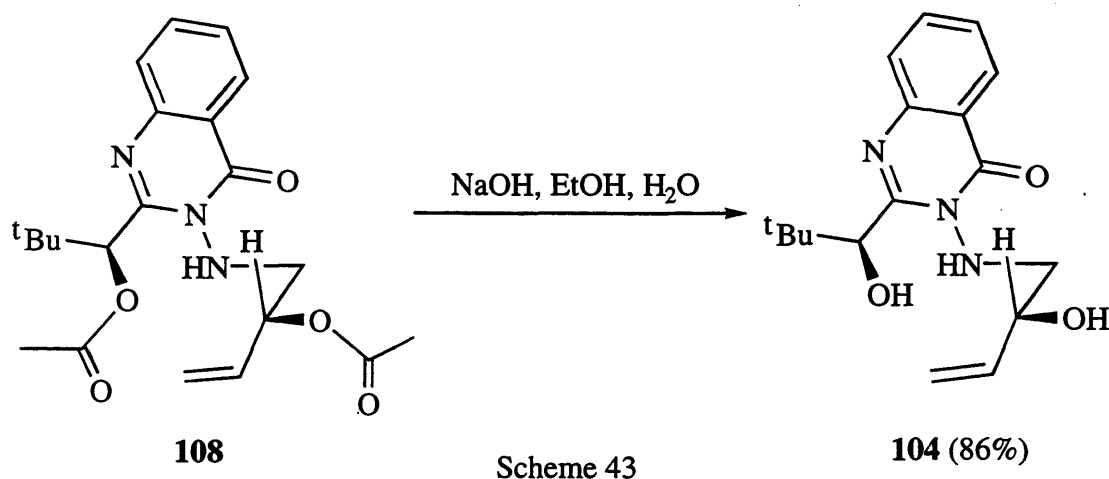


Scheme 42



Di-acetate **108** and acetoxy allylic alcohol **109** were readily separable by flash chromatography, but formation of the acetoxy allylic alcohol **109** could almost be entirely eliminated by rigorous drying of the glacial acetic acid and by carrying out the reaction in the presence of molecular sieves.

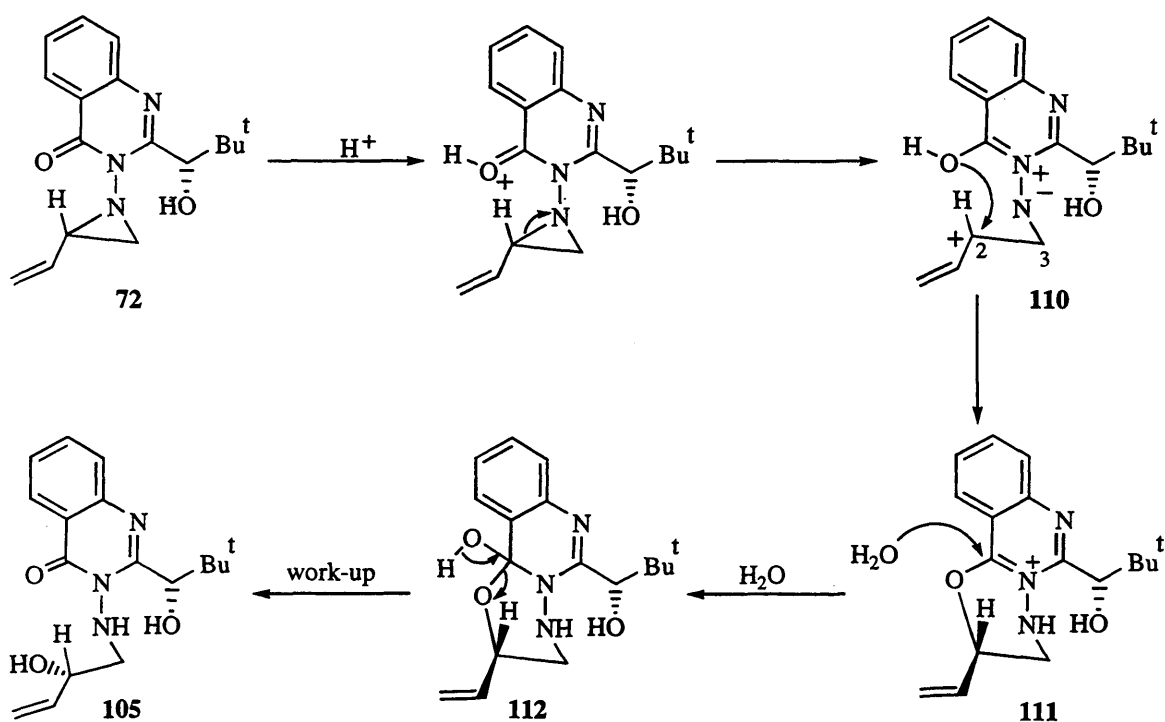
The structure of the di-acetate **108** was proven by an X-ray structure determination (Fig. 33) and shown to be formed, as expected, with inversion of configuration. Thus the stereostructures of all the products in Scheme 42 could then be determined by chemical correlation. Hydrolysis of di-acetate **108** with sodium hydroxide gave allylic alcohol **104**, showing the major product from treatment of **72** with dilute sulphuric acid was also formed with inversion of configuration (Scheme 43). However hydrolysis of acetoxy allylic alcohol **109** under the same conditions gave allylic alcohol **105** (Scheme 42) i.e. the minor acetoxy allylic alcohol product **109** from the reaction of aziridine **72** in acetic acid was formed with retention of configuration.



The yield of the allylic alcohol **105**, formed with retention of configuration, could be increased to 38 %, by carrying out the reaction in the presence of added water; a shorter reaction time at 70° C also prevented acetylation of the side chain. Further treatment of the allylic acetate **107** with this acetic acid-water mixture yielded di-acetate **108**, showing that acetoxy allylic alcohol **109** was not formed from **107** *in situ*. A proposed mechanism for this novel ring-opening is shown below in Scheme 44.

#### 4.4 Mechanism for ring-opening of aziridine 72 and formation of allylic alcohol 105

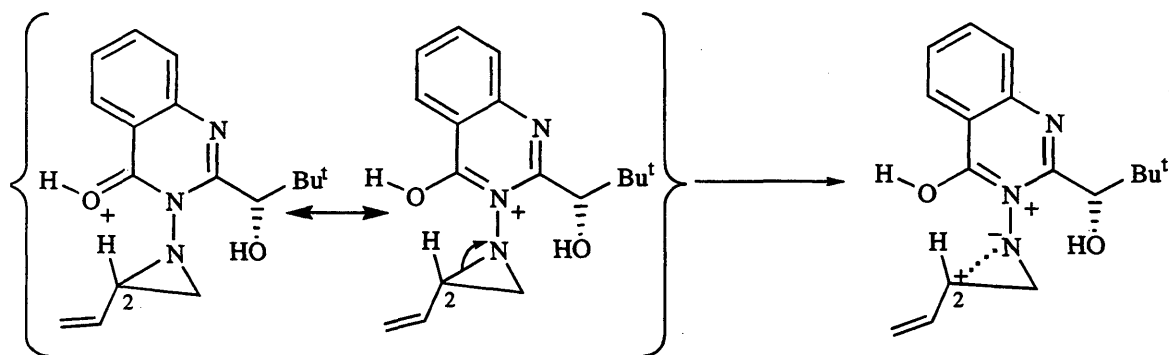
A mechanism for the formation of allylic alcohol **105** which accounts for the retention of configuration involves neighbouring group participation by the quinazolinone and is outlined in Scheme 44. The first step is protonation of the C-4 carbonyl oxygen; breakage of the C-N aziridine ring bond then occurs to yield an allylic carbocation **110**. This carbocation is apparently conformationally stable (see below) and is attacked exclusively from the *syn*-face by the quinazolinone (protonated) carbonyl oxygen to give the imidate salt **111** after protonation of the exocyclic nitrogen; water then attacks at the C-4 quinazolinone carbon to give the cyclic amide-acetal **112** which on work-up affords allylic alcohol **105** with retention of configuration. Thus the allylic alcohol hydroxy is not acetylated in the reaction as it is only liberated from the cyclic amide-acetal on work-up.



Scheme 44

The stereoselectivity of this ring-opening depends on the absence of rotation about the allylic C<sub>2</sub>-C<sub>3</sub> bond in carbocation **110** such that the face attacked by the protonated

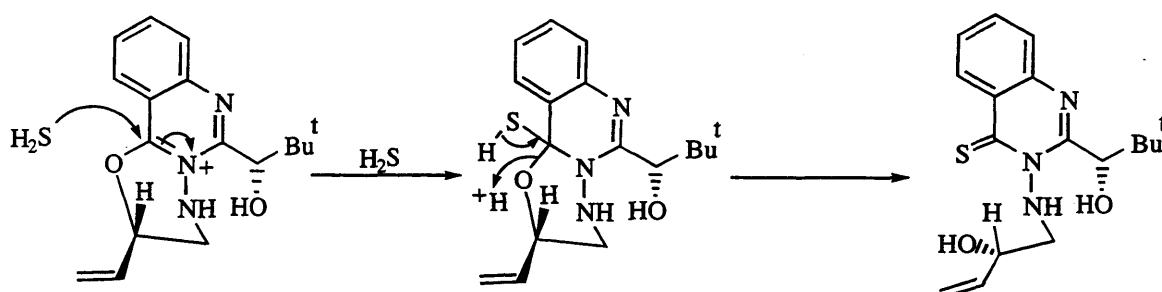
C-4 carbonyl oxygen is the same (*syn*) face originally bonded to the aziridine. It is thought that this stabilisation is a result of protonation of the carbonyl group which puts the positive charge on the amide-type ring nitrogen; cleavage of the allylic aziridine C-N bond generates a negative charge on the exocyclic nitrogen adjacent to this positive charge and hence is stabilised. The carbocation may be conformationally stable as described because of an attractive interaction between the two opposing charges on C<sub>2</sub> and the exocyclic nitrogen (Scheme 45).



Scheme 45

#### 4.5 Evidence for participation of the quinazolinone in ring-opening of aziridine 72

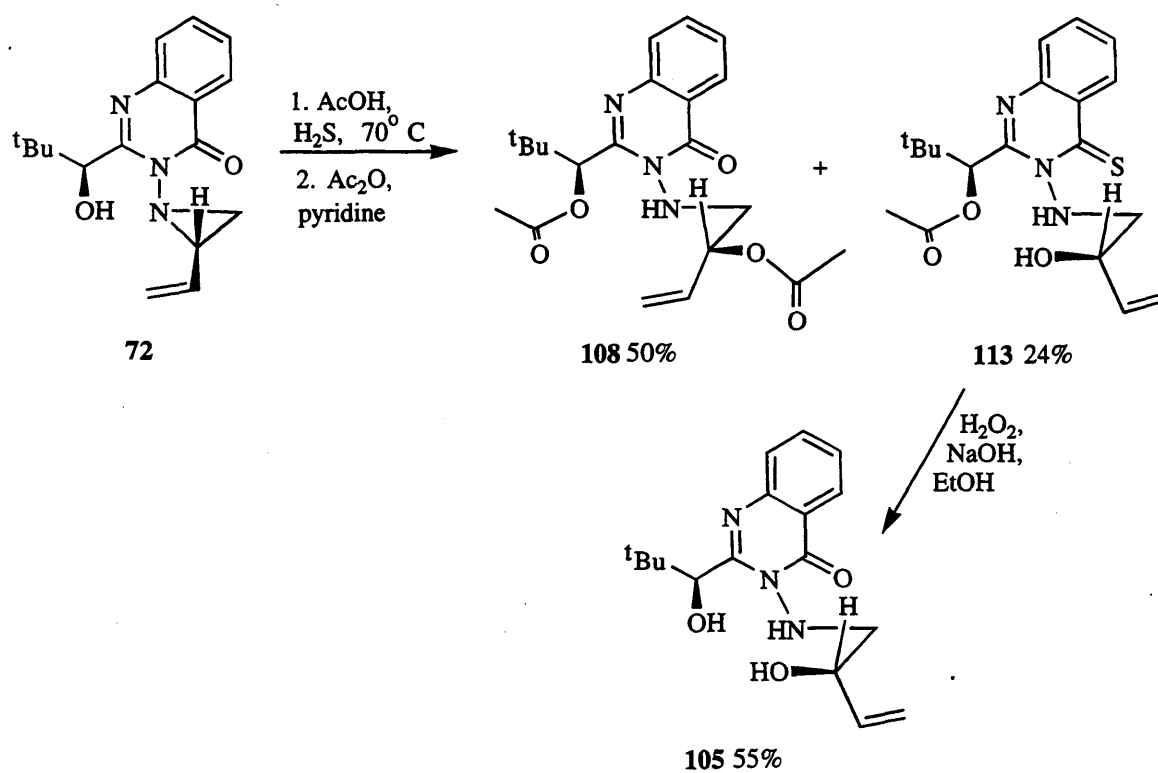
If the reaction in Scheme 44 does take place with involvement of the quinazolinone as proposed, the C-4 carbonyl oxygen is exchanged for water in the formation of allylic alcohol **105**. Carrying out the reaction in the presence of hydrogen sulphide therefore should result in the exchange of sulphur for this oxygen (Scheme 46).



Scheme 46

Heating the vinylaziridine **72** in acetic acid saturated with hydrogen sulphide followed by acetylation of the crude product gave a chromatographically separable mixture of di-acetate **108** and the (quinazolin-4-thione)-substituted allylic alcohol **113** (Scheme 47, following page). As expected **113** was formed with retention of configuration as shown by conversion to the (quinazolin-4-one)-substituted allylic alcohol **105** by treatment with basic hydrogen peroxide. The isolation of di-acetate **108** in this reaction serves as an internal control, excluding the possibility of sulphur exchange for oxygen in allylic alcohol **113** under the reaction conditions.

Considering now earlier work (see 4.2), the poor diastereoselectivity observed in the ring-opening of **72** with dilute sulphuric acid could be attributed to two competing reaction pathways: the major product, allylic alcohol **104**, formed with inversion of configuration, could result from direct S<sub>N</sub>2 attack on the aziridine ring, while the formation of minor allylic alcohol **105** could involve participation by the quinazolinone (*cf.* Scheme 46).

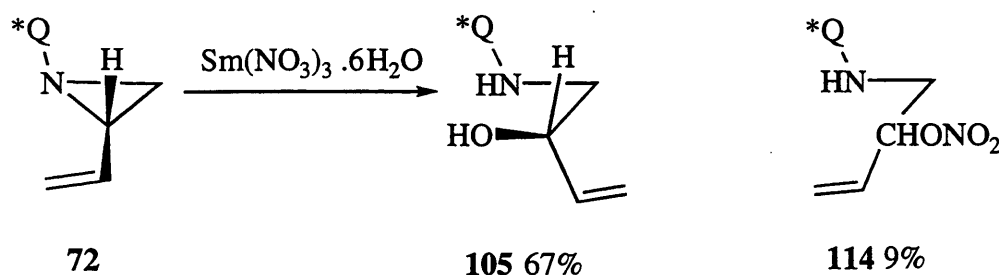


Scheme 47

#### 4.6 Samarium (III)-catalysed ring-opening of vinylaziridine **72**

Previous unpublished work in these laboratories has shown that samarium (III) salts can catalyse ring-opening reactions of these *N*-quinazolinone-substituted aziridines and it is likely that the catalytic effect of samarium results from its co-ordination to the C-4 carbonyl (see also 6.2). Since the mechanism of ring-opening with retention of configuration in Scheme 44 requires participation by the C-4 carbonyl, the effect of samarium nitrate hexahydrate ( $\text{Sm}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ ) on ring-opening of **72** was probed.

When vinylaziridine **72** was heated in acetonitrile containing this samarium (III) salt, ring-opening occurred in 45 min. to give two products (Scheme 48). The major product was identified as the allylic alcohol **105**, as a 13 : 1 ratio of diastereoisomers (previously prepared); this ring-opening therefore takes place almost exclusively with retention of configuration *and* in good yield. The minor product from the reaction was identified as the nitrate ester **114** of unknown relative configuration. (It may be possible to eliminate the formation of this by-product by carrying out the reaction in the presence of a samarium salt with a less nucleophilic counter ion).



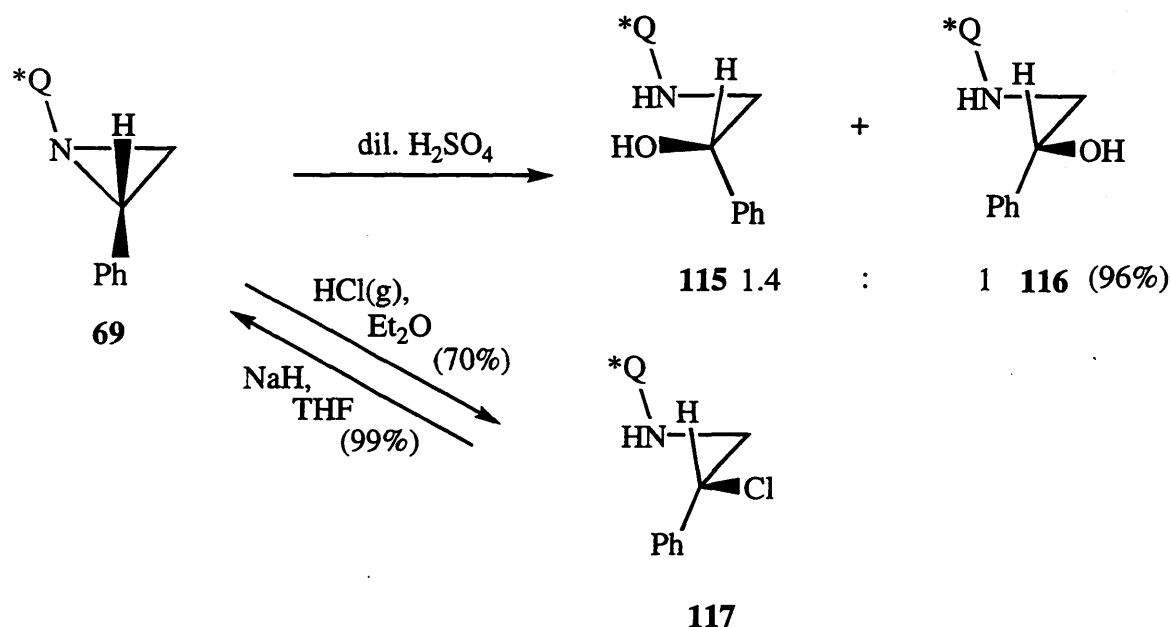
Scheme 48

The samarium-catalysed ring-opening may be proceeding *via* a mechanism analogous to that outlined in Scheme 44, with the metal taking the place of the proton. However, a possible alternative to that is shown in Scheme 49. In this mechanism samarium co-ordinates to the C-4 carbonyl oxygen and initiates C-N aziridine ring bond breaking to form the allylic carbocation; rapid intramolecular delivery of a water ligand on the metal to the carbocation from the same face as the quinazolinone

Scheme 49

#### 4.7 Ring-opening of styrene-derived aziridine **69**

The styrene-derived aziridine **69** was also subjected to some of the ring-opening conditions carried out on the vinylaziridine **72**. Treatment of **69** with dilute sulphuric acid resulted in virtually complete non-stereoselective ring-opening of the aziridine, giving both diastereoisomers **115** and **116** of the benzylic alcohol in a 1.4 :1 ratio respectively. Reaction of aziridine **69** with hydrogen chloride gas in diethyl ether, however, afforded benzylic chloride **117** as a single diastereoisomer. This chloride **117** was shown to have been formed with inversion of configuration by its conversion back to aziridine **69** on treatment with sodium hydride (Scheme 50) (compare Scheme 41).

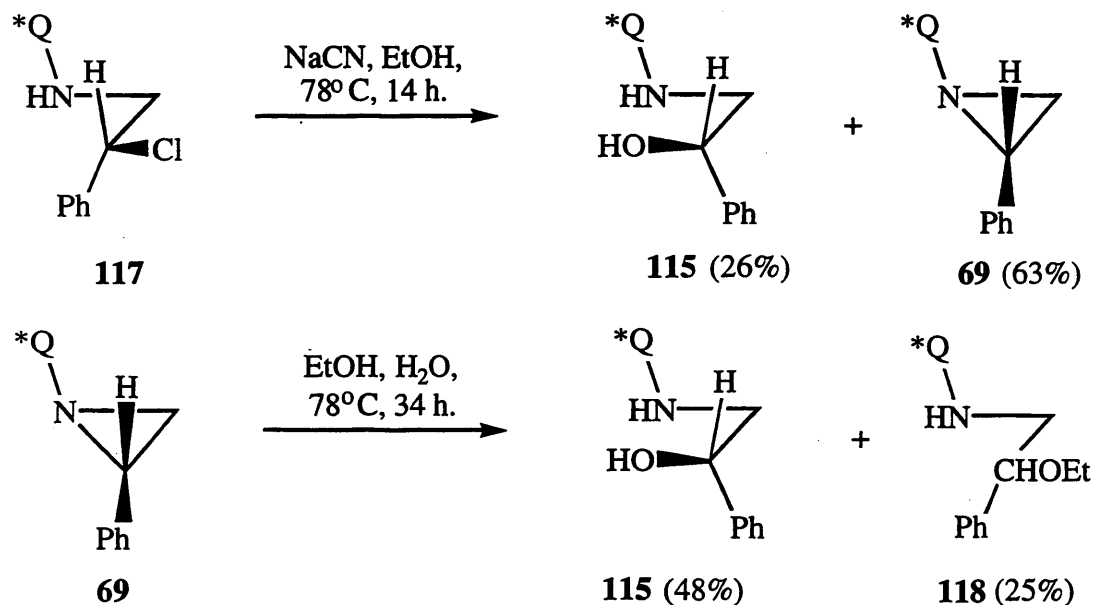


Scheme 50

Benzylic chloride **117** was heated under reflux with sodium cyanide in ethanol in an attempted nucleophilic substitution. Two products were formed: aziridine **69** and benzylic alcohol **115** as a *single diastereoisomer* (Scheme 51). It appeared that cyanide was acting as a base, re-forming the aziridine **69**. When aziridine **69** was heated for 34h. under reflux in ethanol containing a trace of water, ring-opening occurred to give the same benzylic alcohol diastereoisomer, together with benzylic ether **118** of unknown relative configuration. It is conceivable, therefore, that benzylic



alcohol **115** from the reaction of benzylic chloride **117** with cyanide is formed from the further reaction of the co-produced aziridine **69** (see however below).



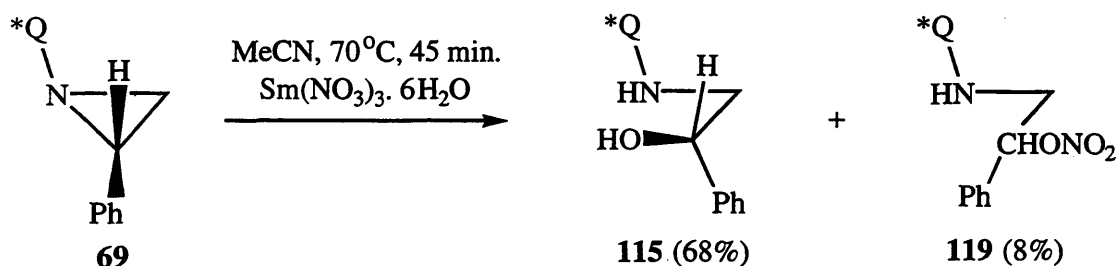
Scheme 51

In an attempt to prevent formation of the unwanted ether by-product **118**, the reaction was repeated under the same conditions in both wet isopropanol and wet 1,4-dioxan, but in each case there was no reaction and only unchanged starting material was isolated. If the ring-opening was acid-catalysed, this would explain the lack of reactivity of the aziridine under these conditions as dioxan is non-acidic and isopropanol is less acidic than ethanol. However if the acid is strong and the water concentration increased, as in the reaction of **69** with sulphuric acid, then non-stereoselective ring-opening occurs and a mixture of benzylic alcohol diastereoisomers results.

The sensitivity of the ring-opening of aziridine **69** to the acidity of the medium makes it unlikely that the alcohol in Scheme 51 is formed from the aziridine in the presence of sodium cyanide since this solution is likely to be basic (hence formation of aziridine **69**.)

#### 4.8 Ring-opening of **69** with samarium nitrate hexahydrate

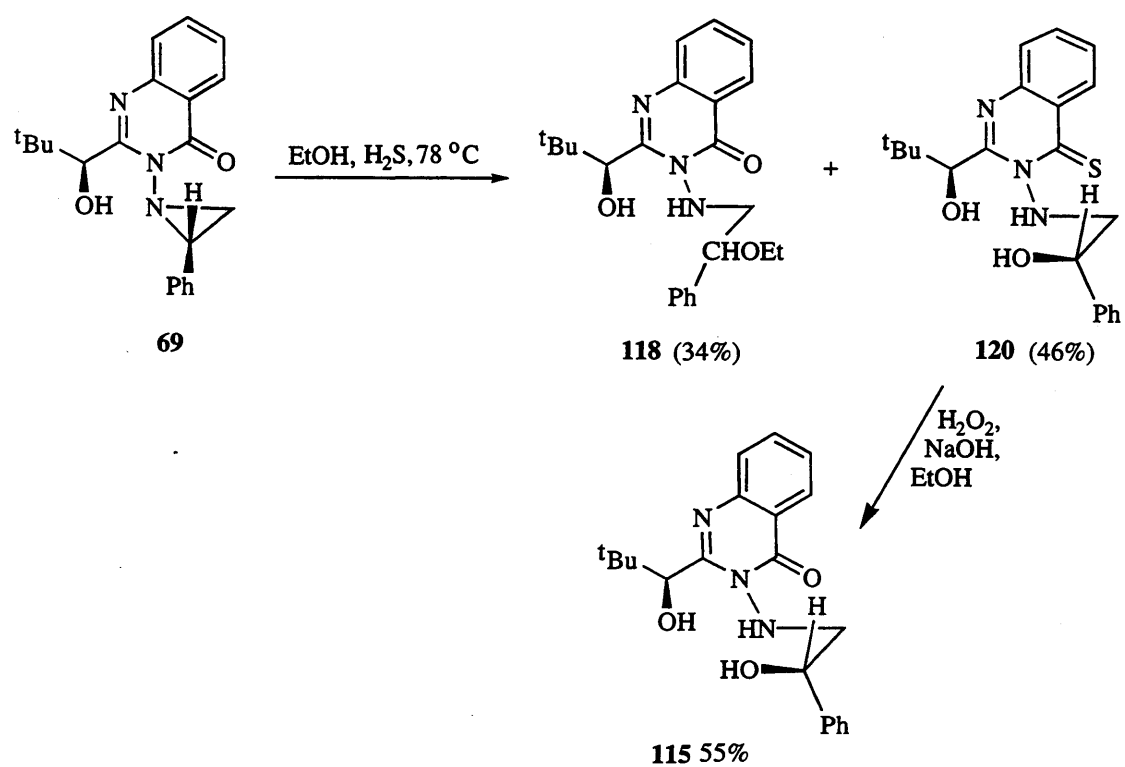
Initially it was thought that benzylic alcohol **115** in Scheme 51 was formed with inversion of configuration, by direct attack of water on the aziridine ring. However ring-opening of aziridine **69** with  $\text{Sm}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$  (Scheme 52) afforded two products, the major being the same benzylic alcohol **115** previously obtained (Scheme 51). The minor by-product from the reaction was again a nitrate ester **119** (of unknown relative configuration).



Scheme 52

Since the ring-opening of vinylaziridine **72** under the same conditions affords the allylic alcohol **105** with retention of configuration, it seemed likely that benzylic alcohol **115** is also being formed with retention of configuration, possibly by a mechanism analogous to that outlined in Scheme 44. If this mechanism was operating then the ring-opening of aziridine **69** in ethanol saturated with hydrogen sulphide should show similar incorporation of sulphur into the quinuclidinone C-4 carbonyl to that observed previously for ring-opening of the vinylaziridine **72** (*cf.* Scheme 46).

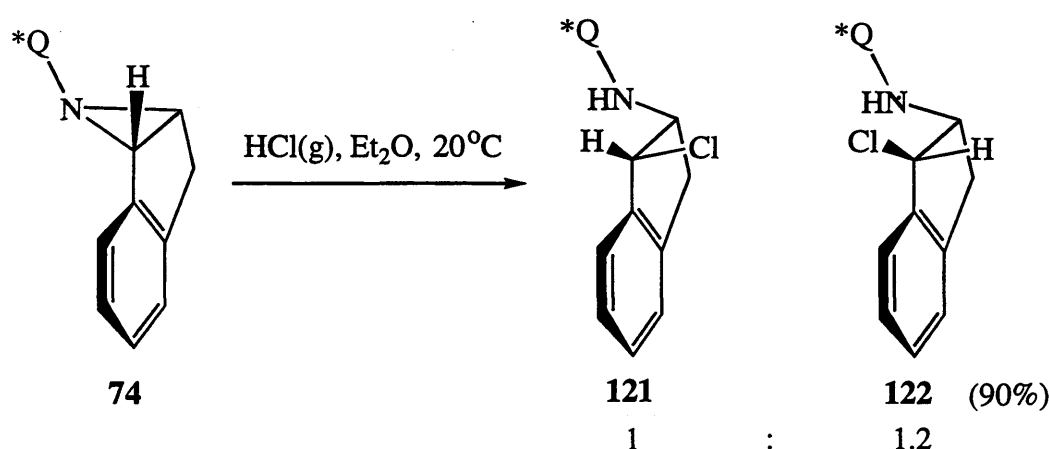
Heating aziridine **69** in a Young's tube charged with hydrogen sulphide-saturated ethanol gave a mixture of benzylic ether **118** (identical to that obtained previously) and the (quinazolin-4-thione)-substituted benzylic alcohol **120** (Scheme 53). As expected, treatment of this (quinazolin-4-thione)-substituted benzylic alcohol **120** with basic hydrogen peroxide yielded the (quinazolin-4-one)-substituted benzylic alcohol **115**. Again the isolation of benzylic ether **118** served as an internal control, excluding the possibility of sulphur exchange for oxygen in benzylic alcohol **120** under the reaction conditions.



Scheme 53

#### 4.9 Ring-opening of indene-derived aziridine **74** with hydrogen chloride

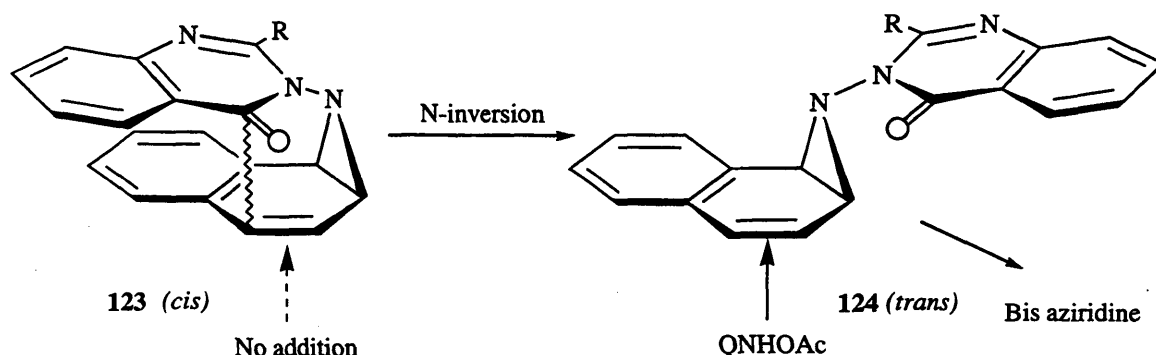
In contrast to the analogous ring-opening of the styrene- and butadiene-derived aziridines **69** and **72**, reaction of the indene-derived adduct **74** with a solution of hydrogen chloride gas in diethyl ether proceeded with no stereoselectivity, yielding a 1:1 mixture of chlorides (Scheme 54). The absence of stereoselectivity in the ring-opening was attributed to the formation of a longer-lived carbocation that could be trapped from either face by chloride to give both diastereoisomers of the same product.



Scheme 54

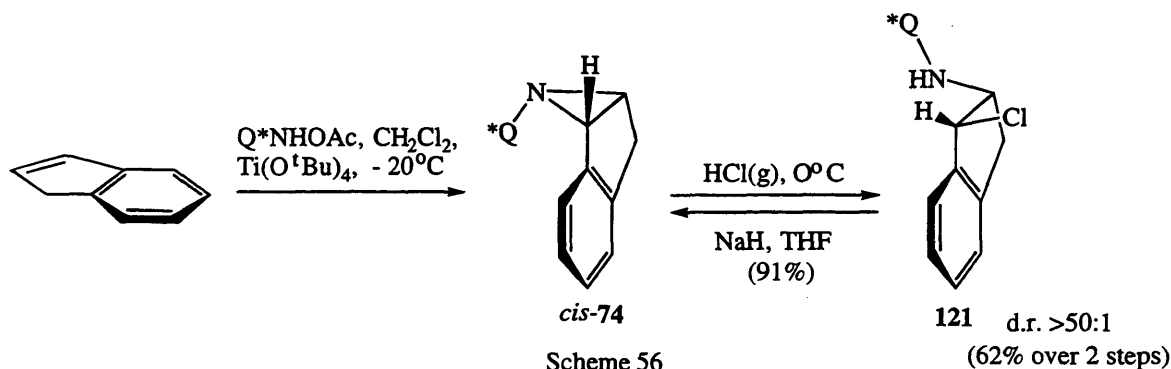
Thus it appeared that the diastereoselectivity of the ring-opening could be improved if the formation of this carbocation could be discouraged or its stability reduced. As mentioned previously (2.10) aziridination of naphthalene initially gives the mono-aziridine **91** by 1,2-addition of  $\text{Q}^*\text{NHOAc}$  **49** and then the bis-aziridination product **92** by 3,4-addition of  $\text{Q}^*\text{NHOAc}$ . It was shown using 3-acetoxyminoquinazolinones bearing smaller 2-substituents that bis-aziridination occurred only after the first formed *cis* mono-aziridine **123** had inverted to the *trans* form **124**<sup>103</sup> (Scheme 55). Since the aziridine rings in the bis-aziridine are believed to be *trans* to each other it seems unlikely that this result is attributable to the steric effect of one aziridine ring on the rate of formation of the second. Presently it is thought that the 3,4-double bond in the *cis-N*-invertomer **123** is somehow deactivated towards (*trans*) aziridination,

perhaps by an interaction with the quinazolinone ring which resembles<sup>104</sup> that which brings about formation of the *cis*-*N*-invertomer **123** initially (Scheme 55).

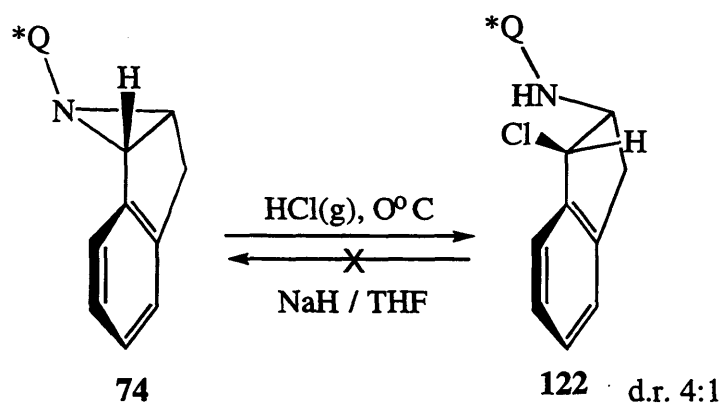


Scheme 55

As mentioned previously, the indene-derived aziridine also displays an enhanced barrier to *N*-inversion and the first-formed *cis*-aziridine can be obtained in solution free from the *trans*-invertomer. By analogy with the explanation offered above for the course of bis-aziridination of naphthalene, interaction between the Q\* group and the benzene ring in the *cis*-aziridine should reduce the stability of the derived benzylic carbocation and, it was hoped, lead to a different stereochemistry of ring-opening by comparison with its *trans* counterpart. To test this idea, the TTB-mediated aziridination was carried out as previously described in dichloromethane but the reaction allowed to warm only to 0 °C. At this temperature hydrogen chloride gas was bubbled into the reaction solution and then the reaction allowed to reach room temperature before being worked-up (Scheme 56). It was found that under these conditions ring-opening of the *cis*-aziridine proceeded to give a *single* diastereoisomer of the corresponding chloride **121**. The stereostructure of chloride **121** is assigned that shown, since it was converted to aziridine **74** in good yield on treatment with sodium hydride.



To show that the dramatic change in stereochemistry of the reaction was not caused by the change in reaction temperature and/or solvent, the *trans* invertomer of aziridine **74** was ring-opened under conditions analogous to those described above for the *cis*-aziridine. Unexpectedly, ring-opening of the *trans* invertomer in dichloromethane at 0 °C gave a 4:1 mixture of chloride diastereoisomers, the major product **122** being formed with *retention* of configuration (Scheme 57).



Scheme 57

A possible explanation for retention of configuration in the major pathway for ring-opening of the *trans*-invertomer of **74** is as follows: the first step in the reaction is protonation of the aziridine ring nitrogen by an unionised hydrogen chloride molecule and when aziridine C-N bond breakage occurs the chloride ion is thus disposed to attack the same face of the benzylic carbocation as that bearing the now protonated ring-nitrogen<sup>105</sup> (Fig. 24). This results in the formation mainly of the chloride **122** with retention of configuration.

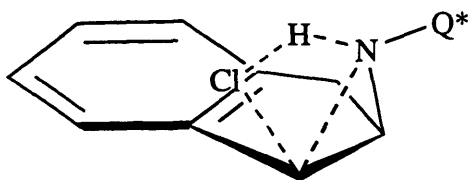


Fig. 24

In ether the solvent can become protonated and the hydrogen chloride will be appreciably more ionised. Thus a higher concentration of the chloride anion will be present which can trap the developed carbocation from both faces resulting in non-stereoselective ring-opening. For both the butadiene- and styrene-derived aziridines

ring-opening in diethyl ether is stereoselective because of the less fully-developed carbocation intermediates.

#### 4.10 Summary of Chapter 4

The styrene- and butadiene-derived aziridines **69** and **72** were ring-opened in dilute aqueous sulphuric acid with poor stereoselectivity; however ring-opening of **69** and **72** in HCl/ether was completely stereoselective with inversion of configuration at the aziridine ring carbon. Both *N*-invertomers of the indene-derived aziridine **74** were ring-opened with very different stereochemistry with HCl in dichloromethane.

The major product from ring-opening of **72** in acetic acid, di-acetate **108**, was formed by attack of acetate on the aziridine ring with inversion of configuration at the aziridine ring carbon; the structure of **108** was proven by X-ray structure determination. The minor product from this reaction was formed (formally) by attack of water on the aziridine ring with retention of configuration at the aziridine ring carbon; the structure of this product was proven by chemical correlation. A mechanism to account for this novel ring-opening, involving neighbouring group participation by the quinazolinone ring is proposed; support for this mechanism comes from a labelling experiment.

Ring-opening of aziridines **69** and **72** in the presence of samarium nitrate hexahydrate gave the alcohols **115** and **105**, formed with retention of configuration at the aziridine ring carbon, together with small amounts of nitrate esters **114** and **119** of unknown configuration. Heating aziridine **69** in wet ethanol also gave alcohol **115**; also isolated was benzylic ether **118** of unknown configuration. A labelling experiment gave evidence for participation of the quinazolinone ring in formation of alcohol **115** under these conditions.

Thus the quinazolinone ring can be used to advantage in controlling the stereochemistry of ring-opening of these *N*-Q\*-substituted aziridines such that ring-opening of the aziridine ring with retention of configuration is feasible.



## ***Chapter 5 :***

### ***Nucleophilic Ring-Opening of N-Q\*-Substituted Aziridines***

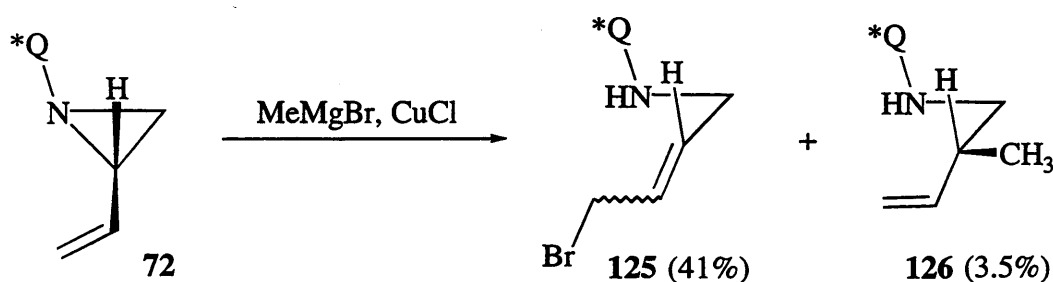
## 5.1 Introduction

As shown in the previous Chapter these *N*-(Q\*)-substituted aziridines are efficiently ring-opened with aqueous acid and the quinazolinone can be used to advantage in controlling the stereochemistry of ring-opening. However such acid-catalysed (electrophilic) ring-opening only permits attack by nucleophiles such as water and the anions of acids. In order to widen the scope of this methodology, nucleophilic ring-opening, allowing attack by carbon nucleophiles e.g. cuprates, must be explored.

Nucleophilic ring-opening of aziridines usually requires a strongly electron-withdrawing (activating) group on nitrogen to stabilise the developing negative charge, the most common group used for this purpose being the arylsulphonyl. Since ring-opening of these *N*-Q-substituted aziridines has not previously been explored it was not clear whether the Q group alone would be sufficiently electron-withdrawing to activate the aziridine ring toward nucleophilic attack. It is this issue that has been addressed in this Chapter.

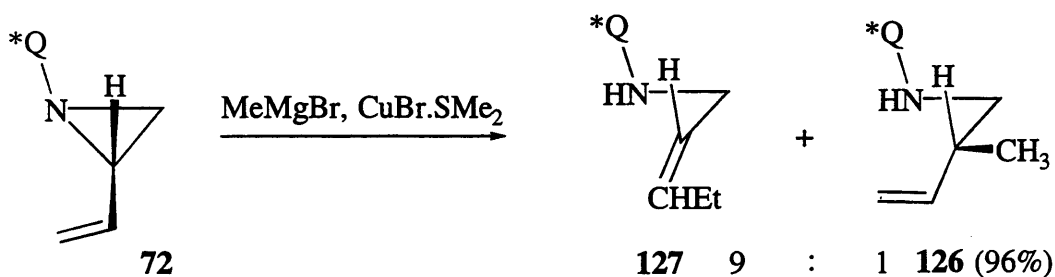
## 5.2 Ring-opening of vinylaziridine 72 with organocopper reagents

The first substrate to be examined was vinylaziridine **72** which was reacted with the organocopper generated from methylmagnesium bromide and a copper (I) salt. The first attempted reaction, employing cuprous chloride, afforded two products separable by chromatography; the major being the allylic bromide **125** (Scheme 58) formed by  $S_N2'^{106}$  attack of the halide. There was also a small amount of the directly ring-opened homoallylic amine **126**, formed apparently as a single diastereoisomer by what is assumed to be  $S_N2$  substitution by analogy with similar reactions (see below). This product is potentially more useful since the chirality of the centre created in the aziridination is conserved.



Scheme 58

Repeating the reaction in the presence of copper bromide-dimethyl sulphide complex, again afforded two products but in excellent yield (Scheme 59). The major allylic amine product **127**; formally the result of an  $\text{S}_{\text{N}}2'$  attack by  $\text{Me}^-$ , whereas the minor product **126** resulted from the same presumed  $\text{S}_{\text{N}}2$  attack of the nucleophile on the aziridine ring as above (Scheme 58). Although these two products (ratio 9:1) were inseparable by chromatography, signals from the minor homoallylic amine **126** were clearly visible in the NMR spectrum of the crude reaction mixture and were identical to those of this product isolated previously.



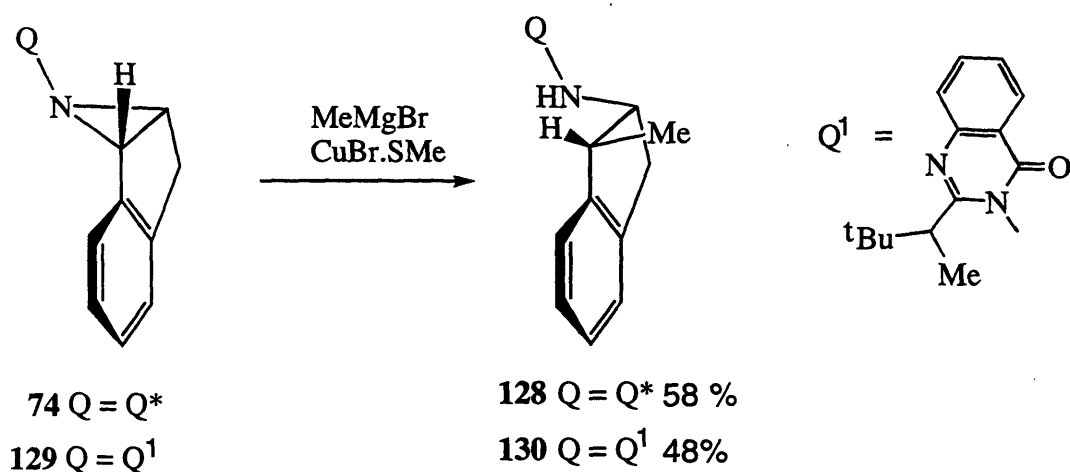
Scheme 59

It was not clear why the only methylcopper addition product isolated in the first reaction was formed *via* the desired  $\text{S}_{\text{N}}2$  pathway but this was an initial, exploratory reaction where the reaction conditions were varied; this reaction in the presence of copper (I) chloride was not repeated. The allylic amine **127** appeared to be a single double bond isomer from its  $^{13}\text{C}$  and  $^1\text{H}$  NMR spectra, although whether it was *Z*- or *E*-configured was not clear. Addition of cuprates to vinylaziridines has been reported by several groups to occur predominantly via an  $\text{S}_{\text{N}}2'$  mechanism.<sup>107</sup>

This methodology could be usefully extended to vinylaziridines in which the terminal end of the double bond is substituted e.g. a cyclohexa-1,3-diene adduct. For these substrates an  $S_N2'$  mechanism could result in stereoselective creation of one chiral centre as that on the aziridine ring was destroyed.<sup>108</sup>

### 5.3 Ring-opening of indene-derived aziridine **74** with methylcopper

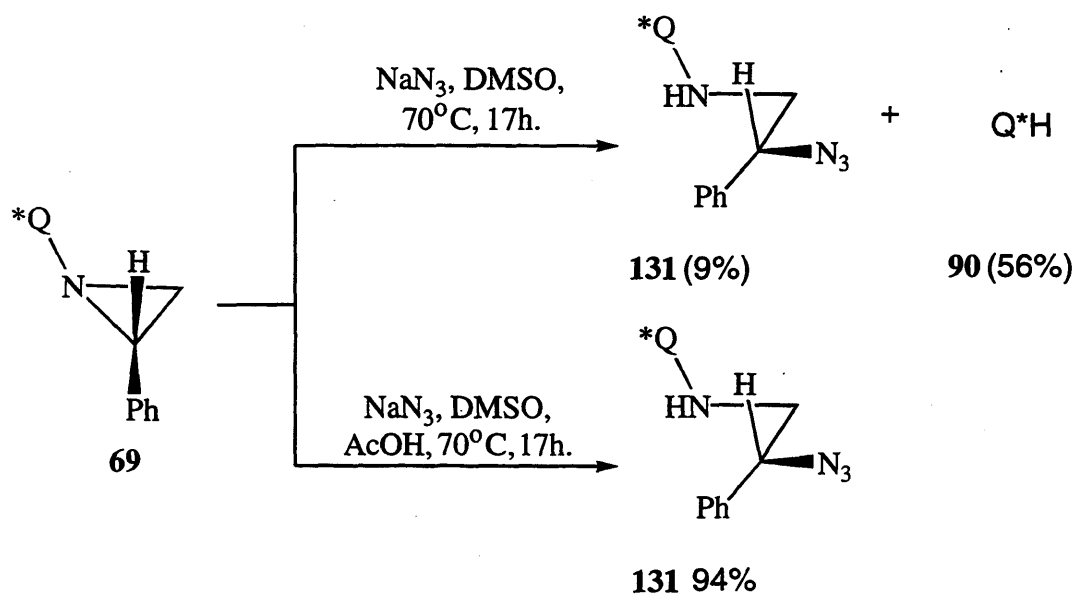
The title aziridine **74** was found to be efficiently ring opened with methylmagnesium bromide in the presence of copper bromide-dimethyl sulphide complex to give the substituted indane **128** as a single diastereoisomer (Scheme 60). Initially it was thought that this reaction was assisted by co-ordination of the aziridine ring nitrogen with a magnesium alkoxide formed from the quinazolinone 2-substituent's hydroxy group. However ring-opening of aziridine **129**<sup>109</sup> with methylcopper under the same conditions gave an analogous product **130**, albeit in lower yield. It seems therefore that chelation by magnesium in this way is not mandatory for ring-opening. X-ray structure determination of this substituted indane product **130** (Fig. 34) showed that ring-opening had taken place, as expected, with inversion of configuration.



Scheme 60

#### 5.4 Ring-opening of styrene-derived aziridine **69** with sodium azide in DMSO

The title aziridine **69** was ring-opened by heating with sodium azide in DMSO. However the azide **131** was only obtained in 9% yield, the major product being deaminated Q\*H **90** (56%) (Scheme 61); the other products were unidentified.



Scheme 61

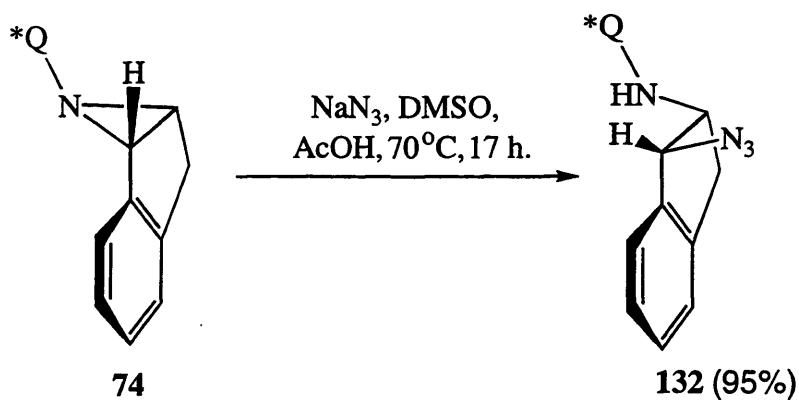
It was found that a greatly improved yield of azide **131** was obtained by inclusion of a mole equivalent of acetic acid in the reaction mixture. Despite the requirement of acetic acid for formation of azide **131** in high yield, the reaction with sodium azide appears to be nucleophilic in nature and the function of the acetic acid is simply to protonate the negative charge on nitrogen after the rate-determining ring-opening step. Support for this interpretation is shown in Table 7; three parallel reactions were set up in the same oil bath containing zero, one and two equivalents of acetic acid respectively and the reactions quenched simultaneously before complete consumption of starting material. As Table 7 shows, the rate of disappearance of starting aziridine was not significantly affected by the concentration of acetic acid present.

Entry	Equivalents of acetic acid added	Isolated unchanged aziridine (%)
1	0	34.5
2	1	30.6
3	2	31.3

Table 7

### 5.5 Ring-opening of indene-derived aziridine **74** with sodium azide in DMSO

The indene-derived aziridine **74** was ring-opened by sodium azide under conditions analogous to those applied to the styrene-derived aziridine **69**. Treatment of **74** with sodium azide and acetic acid (1 equiv.) in DMSO overnight gave azide **132** as a single diastereoisomer in virtually quantitative yield (Scheme 62).



Scheme 62

The configuration of azide **132** is not known, but presumed to be that shown by analogy with the ring-opening of styrene-derived aziridine **69**.

## 5.6 Summary of Chapter 5

The *N*-(Q\*) aziridine ring-opening reactions with sodium azide and with methylcopper show that the quinazolinone ring as a substituent on the aziridine ring nitrogen is sufficiently electron-withdrawing to allow ring-opening by nucleophiles without the necessity for prior protonation of the ring nitrogen. It is conceivable that in the ring-opening by methylcopper there could still be assistance from magnesium, chelated to the quinazolinone carbonyl oxygen (compare ring-opening of the aziridine, catalysed by samarium, Chapter 6) but ring-opening by azide above is not assisted in this way.

## ***Chapter 6 :***

### ***Ring-Opening of N-Q\*-Substituted Aziridine-2-Carboxylates***

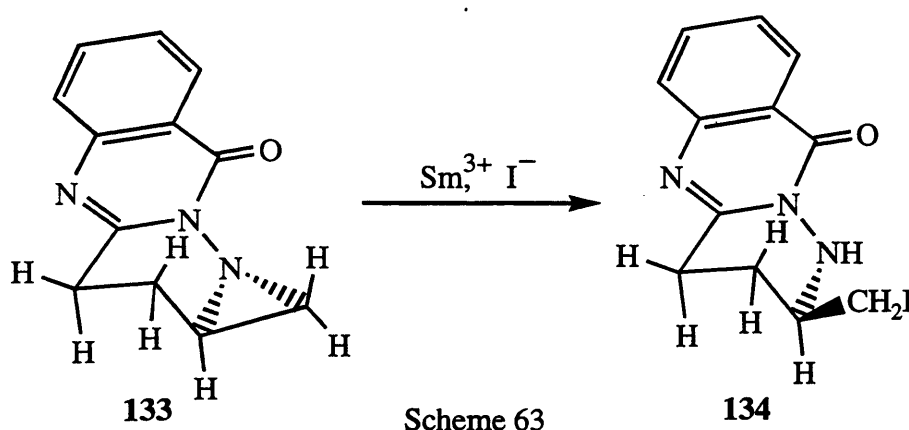


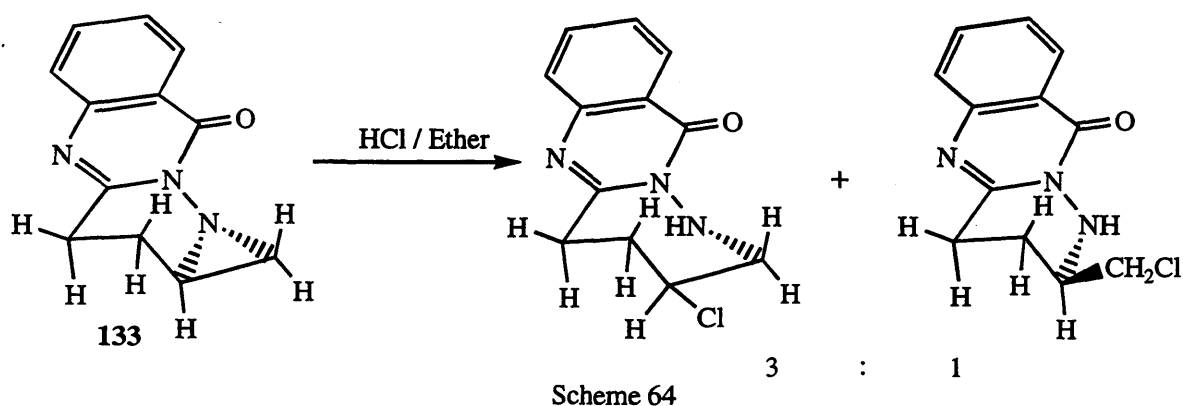
## 6.1 Introduction

The aziridines studied so far all bear a double bond or aryl group as a ring carbon substituent which efficiently directs the regiochemistry of ring-opening and reactions of **69**, **72** and **74** reported are completely regioselective. However, as discussed in the Introduction, the ring-opening of e.g. aziridine-2-carboxylates is not always highly regioselective, and the issue of regioselectivity as well as stereoselectivity must be considered.

## 6.2 Samarium (III)-catalysed ring-opening of aziridine **94**

As will be discussed in the following Chapter, samarium (II) iodide has been used to reduce the Q-N bond in N-Q-substituted amine derivatives. Previously in these laboratories<sup>110</sup> an attempt was made to reduce the N-N bond of aziridine **133** using  $\text{SmI}_2$  but the only product isolated was the ring-opened product **134**, where iodide had attacked at the less substituted aziridine ring carbon (Scheme 63). Subsequently it was found that it was the Sm (III) present in the Sm (II) iodide solution that was responsible for the ring-opening. The regioselectivity in Scheme 63 contrasts with the preferred regioselectivity in the opposite sense resulting from ring-opening by hydrogen chloride in ether.<sup>111</sup>





It was recently shown<sup>112</sup> that the effect of Sm (III) on ring-opening is catalytic and quite dramatic; reactions carried out with of Sm (III) in the presence of iodide as a nucleophile are frequently over in 2 min. or less. Samarium may be catalysing these reactions by co-ordination to the C-4 carbonyl oxygen of the quinazolinone and in such a position it may also be able to co-ordinate to the banana bonds of the aziridine ring and thus weaken them. Thus considering again the Sm (III)-mediated ring-opening of aziridine **133**, nucleophilic attack may be occurring exclusively at the less substituted carbon because it is only this ring C-N bond which is held in a position where it can be activated by co-ordination to samarium (Fig. 25).

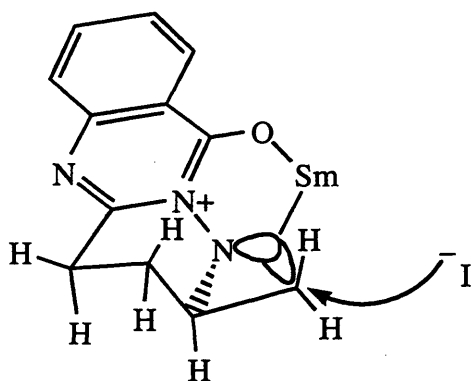
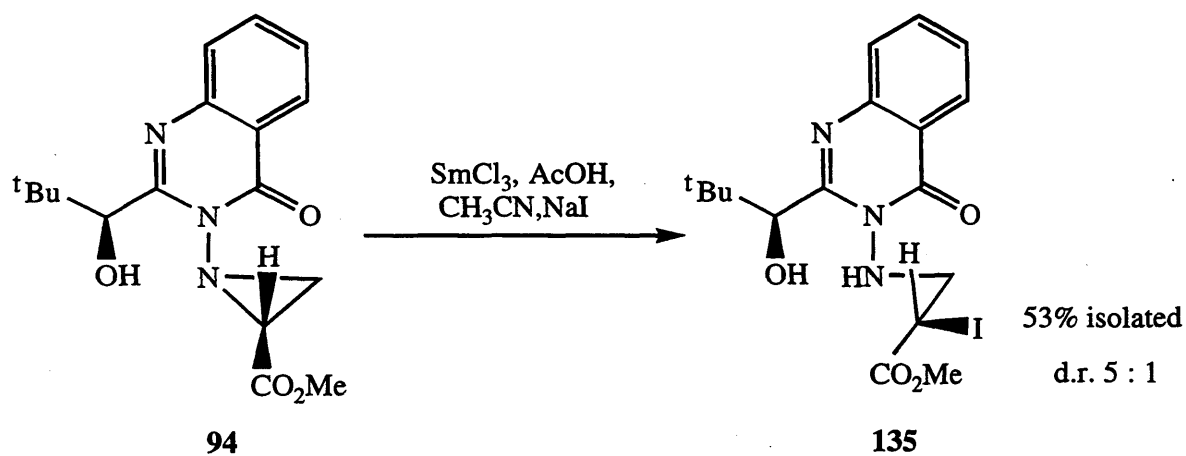


Fig. 25

Extending this methodology, Lochrie showed that aziridine **94** (prepared by the author) was efficiently ring-opened in acetonitrile containing SmCl<sub>3</sub>, sodium iodide and acetic acid (Scheme 65). Sodium iodide is the source of nucleophile while acetic acid protonates the developing negative charge on nitrogen (*cf.* Chapter 5: ring-opening by azide). The reaction was highly regioselective, with attack occurring at the

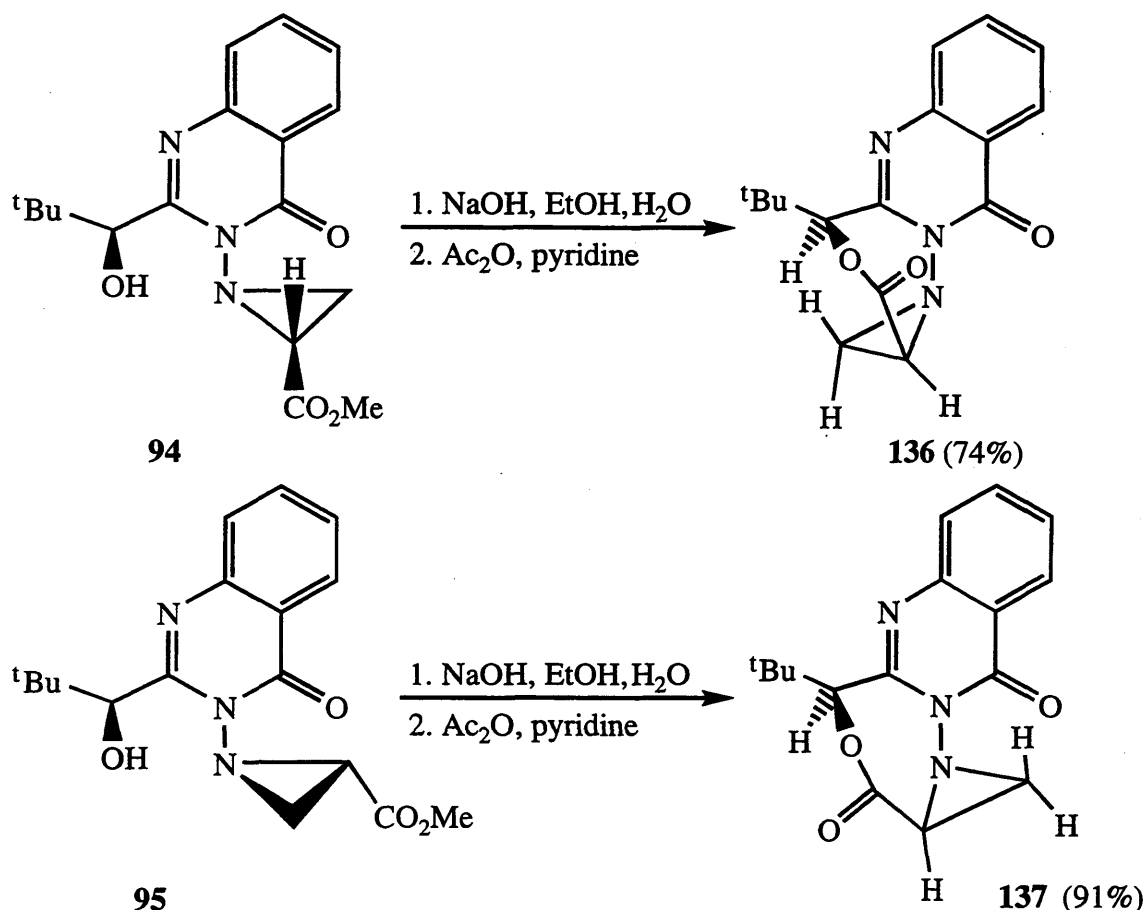
carbon bearing the ester group to give iodide **135**. There was partial epimerisation at this centre in the reaction (the result of further attack by iodide on **135**) and a 5 : 1 mixture of diastereoisomers resulted; crystallisation afforded iodide **135** as a single diastereoisomer in 53% yield.



Scheme 65

### 6.3 Lactonisation of aziridine-2-carboxylate esters **94** and **95**

Lactones **136** and **137** were readily prepared from the aziridine-2-carboxylic acid esters **94** and **95** as shown in Scheme 66; hydrolysis with sodium hydroxide afforded the corresponding acids which were lactonised with acetic anhydride - pyridine under conditions of high dilution.<sup>113</sup>



Scheme 66

As can be seen for lactone **136** in the preferred conformation there is a clash between an aziridine ring proton and the *tert*-butyl group which is absent in the preferred conformation of lactone **137** (Fig. 26). Thus lactone **136** would be expected to be less stable and less readily formed than its diastereoisomer **137** and this was indeed found to be the case; lactone **136** completely decomposed on standing overnight while **137** remained unchanged after one month under the same conditions.

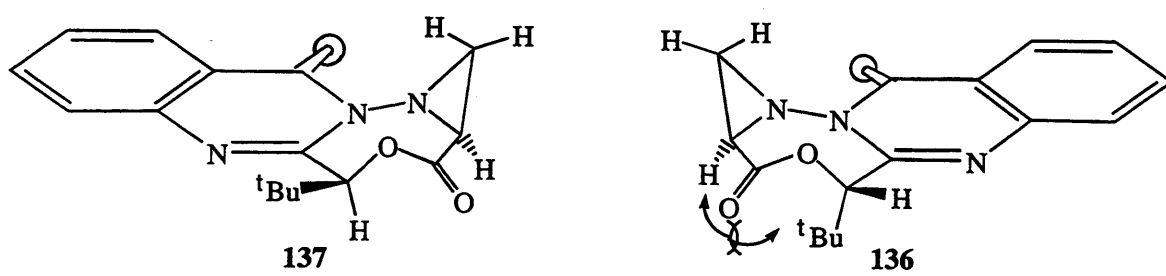
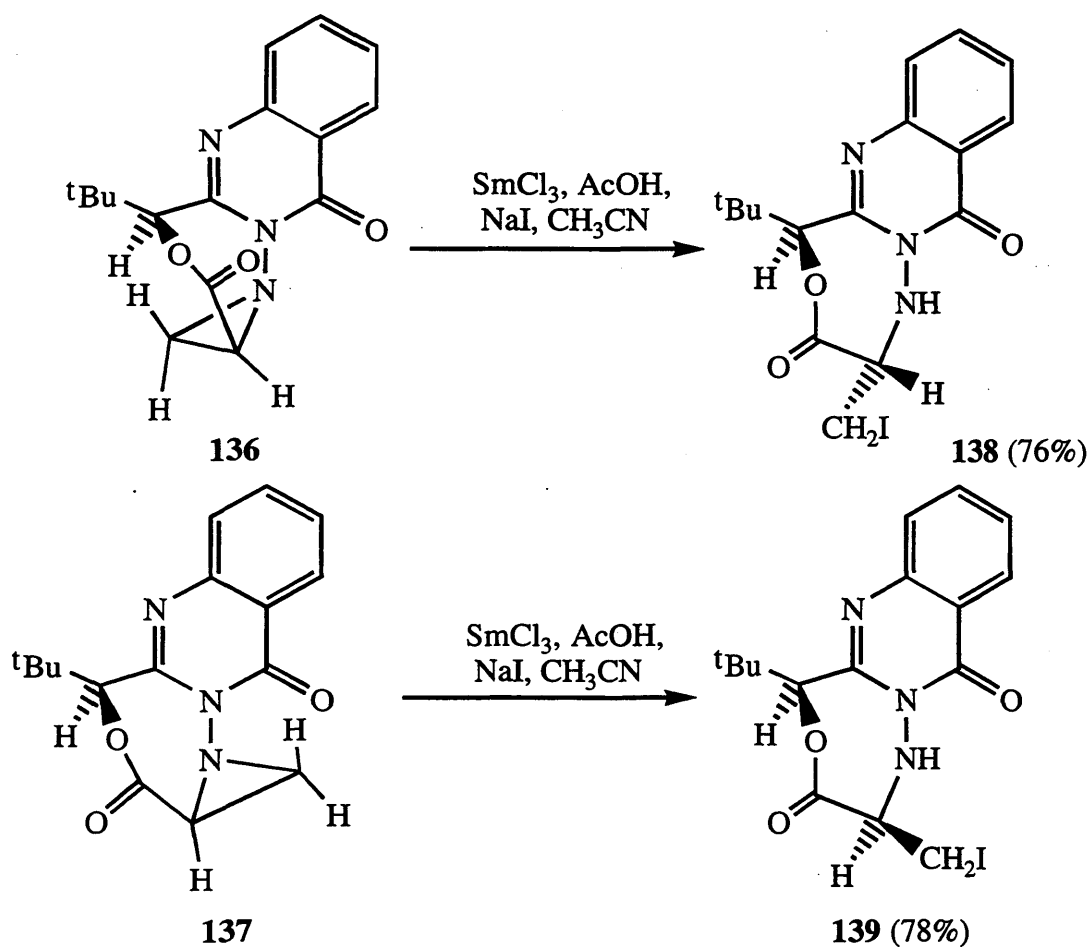


Fig. 26

#### 6.4 Samarium (III)-catalysed ring-opening of lactones 136 and 137

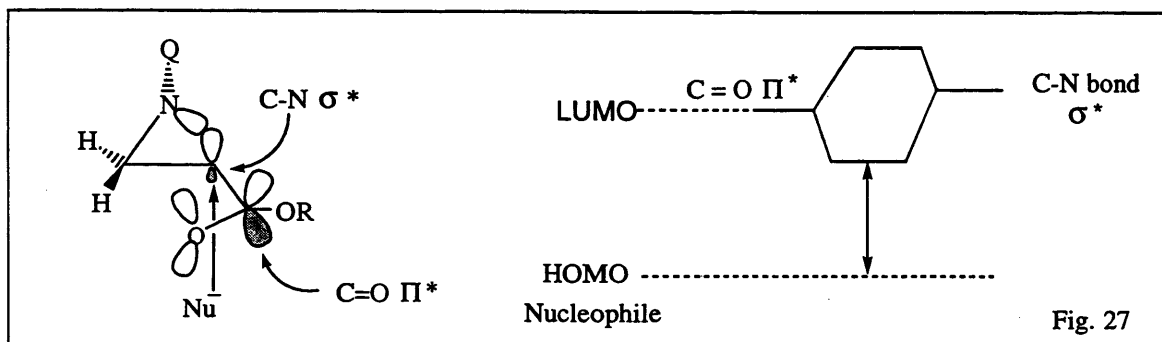
Lactones **136** and **137** were prepared in order to examine the regioselectivity of their aziridine ring-opening reactions catalysed by Sm(III). Under the same reaction conditions used for the ring-opening of aziridine **94** (Scheme 65) the products from lactones **136** and **137** were iodides **138** and **139** respectively (Scheme 67). Thus opening of the aziridine rings in these lactones takes place with exclusive attack on the unsubstituted ring carbon *in the opposite regiosense to that in Scheme 65* i.e. the quinazolinone ring can be used to bring about ring-opening of aziridine esters in complementary regiosenses.



Scheme 67

Aziridine ester **94** is ring-opened at the carbon bearing the ester group because the ester group activates this position toward attack: in this nucleophilic attack, the HOMO of the nucleophile engages the LUMO ( $\sigma^*$  orbital) of the C-N bond. If there is overlap between this  $\sigma^*$  orbital of the C-N bond and the antibonding ( $\pi^*$ ) orbital of

the C=O bond of the ester then the energy level of this C-N LUMO is lowered as shown (Fig. 27). Thus the gap between the two energy levels is reduced and the aziridine is activated towards nucleophilic attack at this ring carbon.



In the case of the lactones **136** and **137**, molecular models show that the ester group is now disposed such that it cannot activate the ester-bearing carbon towards nucleophilic attack. As can be seen in Fig. 28, there is no possibility of orbital overlap between the C=O  $\pi^*$ -orbital and the C-N  $\sigma^*$  orbital. Thus for lactones **136** and **137** the carbonyl group affords no activation toward ring-opening, and steric factors will favour attack at the unsubstituted carbon. Nucleophilic attack at this position may also be favoured for the same reasons outlined previously for aziridine **133** (Scheme 63). Thus the lactone tether in aziridines **136** and **137** permits activation of ring-opening by a Sm (III) ion co-ordinated to the quinazolinone carbonyl oxygen only at the proximate ring bond (Fig. 28).

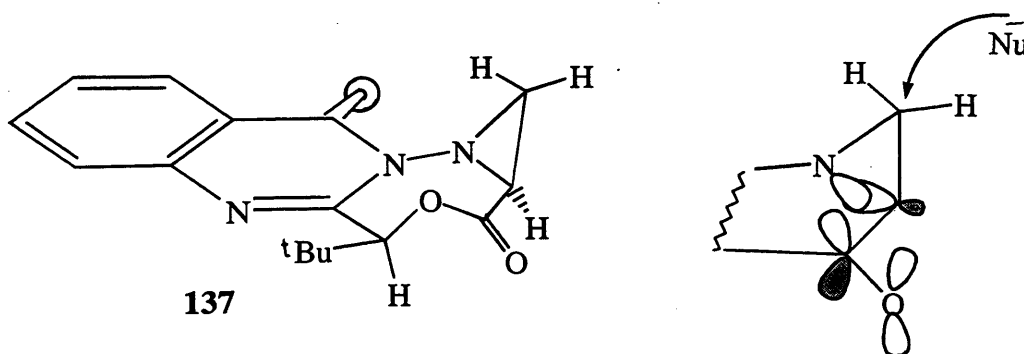
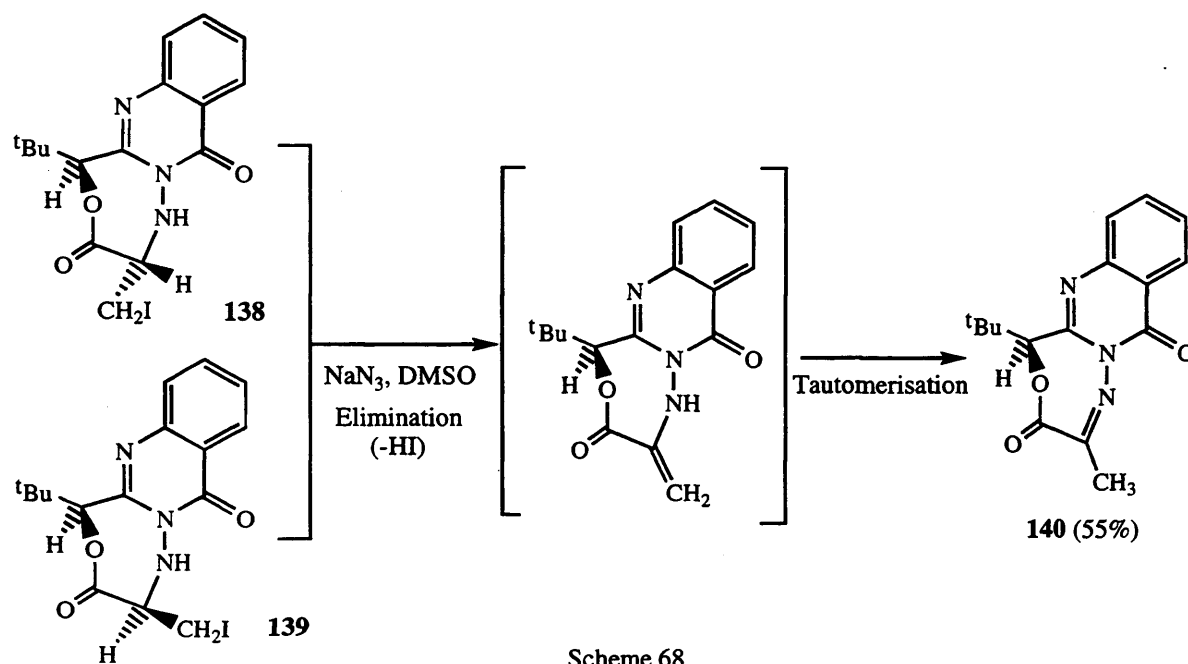


Fig. 28

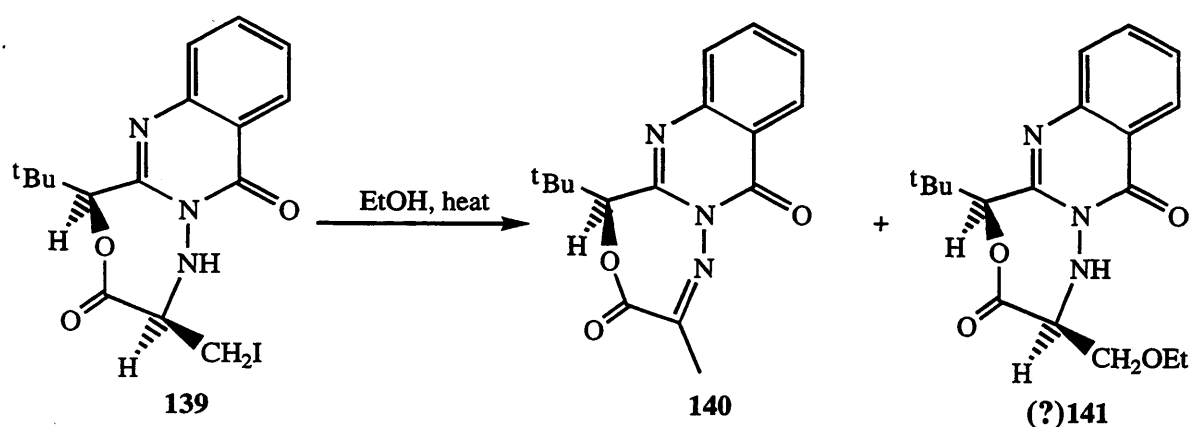
### 6.5 Attempted displacement of iodides 138 and 139 with azide

Attempts at displacing iodide by azide in compounds **138** and **139** proved unsuccessful. For each compound elimination occurred to give imine **140**, presumably as shown in (Scheme 68). The reaction was repeated in the presence of acetic acid to avoid base catalysed elimination, but even under these conditions imine **140** was the only product formed.



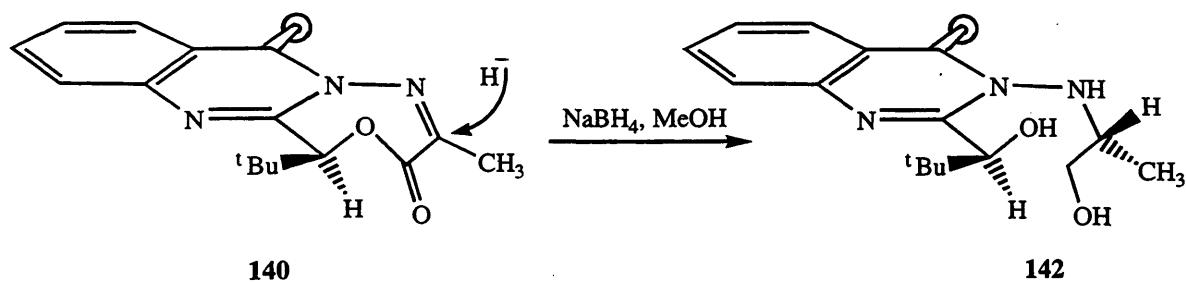
The iodide **139** was eventually obtained in crystalline form and was successfully recrystallised from ethanol to prepare an analytically pure sample. Examination of the mother liquor by NMR spectroscopy, however, showed no signals corresponding to iodide **139**; instead signals for imine **140** were present together with those of a new compound **141** in which the iodide in **139** had apparently been replaced by ethoxide (Scheme 69). (The alternative structure corresponding to addition of ethanol to the imine could be eliminated.) Although an attempt to isolate **141** by chromatography was unsuccessful, this result does indicate that under the right conditions displacement of iodide **139** may be possible without elimination and work towards this end is continuing.





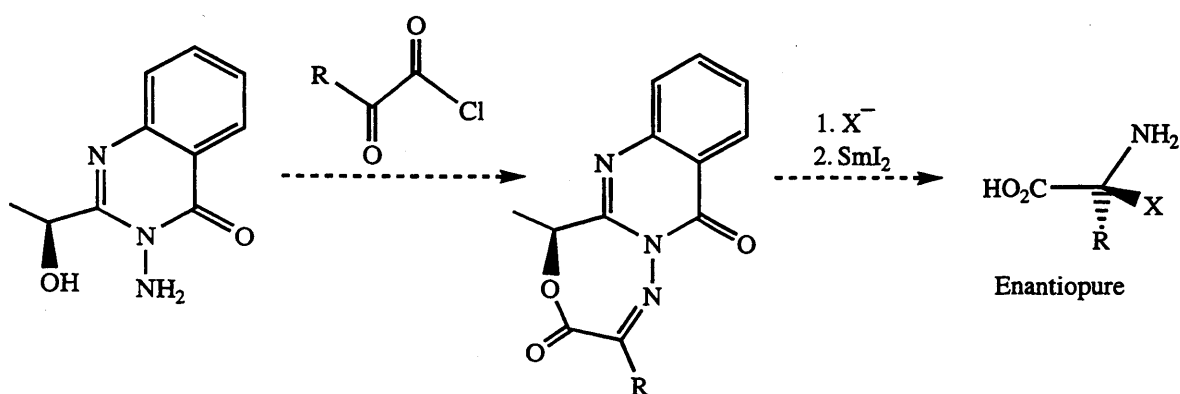
Scheme 69

Initially imine **140** seemed to be of little use since the chiral centre created in aziridination had been destroyed. However molecular models of this imine show that its preferred conformation has one face of the C=N bond shielded by the methine proton adjacent to the quinazolinone (Scheme 70) and that nucleophilic attack on this double bond should be easier from the opposite face. In practice, reduction of **140** with sodium borohydride afforded alcohol **142** as a single diastereoisomer, regenerating the chiral centre adjacent to nitrogen whose absolute configuration would be predicted to be R as shown.



Scheme 70

It would be interesting to explore the scope of this reaction as it is a possible route to a range of enantiopure  $\alpha$ -amino acids (Scheme 71). In principle, a range of imines of this type could be synthesised in a single step, as shown in Scheme 71. Nucleophilic attack at the imine followed by cleavage of the chiral auxiliary would then afford substituted amino acids.



Scheme 71

## 6.6 Summary of Chapter 6

The work outlined in this chapter has shown that Sm (III) can be used to catalyse the ring-opening of *N*-Q\*-substituted aziridine-2-carboxylates. In the case of aziridine-2-carboxylic acid ester **94** the ring-opening is highly regioselective, with attack by iodide occurring at the ester-bearing ring carbon. However when the ester is converted to the lactone **136**, ring-opening occurs exclusively at the unsubstituted ring-carbon *in the opposite regiosense to that for 94*; thus the quinazolinone ring can be used to advantage in controlling the regioselectivity of ring-opening.

## ***Chapter 7 :***

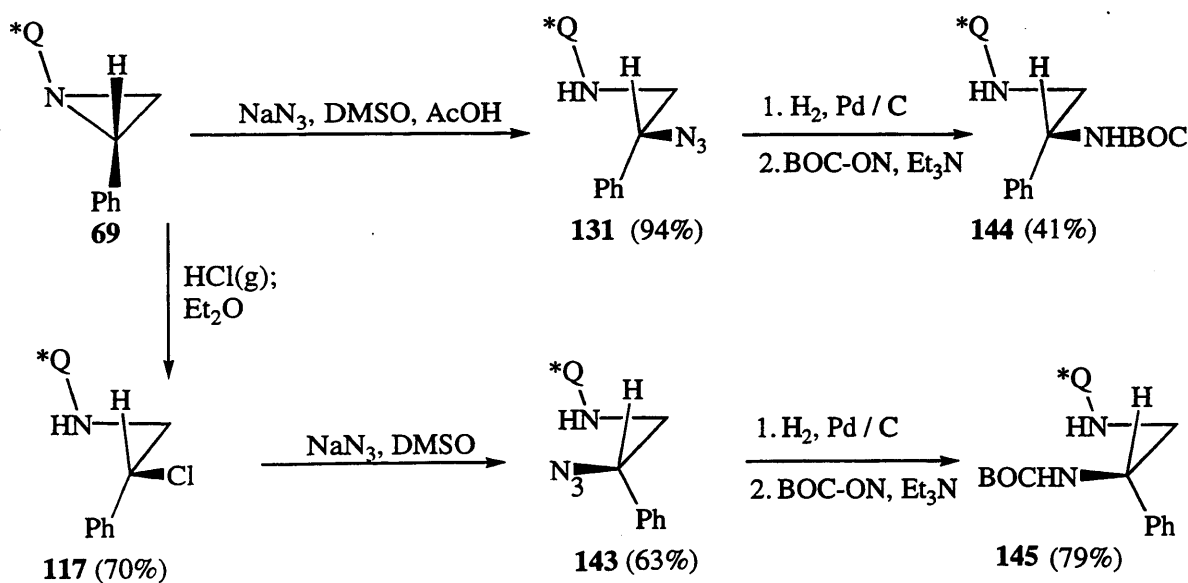
### ***N-N Bond Reduction of Aziridine Ring-Opened Derivatives***

## 7.1 Introduction

The work outlined in the previous three Chapters has shown that *N*-Q\* substituted aziridines can be ring-opened with a range of nucleophiles with excellent stereo- and regiocontrol. The final part of this project requires removal of the chiral auxiliary (Q\* group) from these ring-opened *N*-(Q\*)-aziridine products by reduction of the Q\*-N bond to provide access to enantiopure chirons. Previous work in these laboratories has shown that this *N*-N bond can be reduced under mild conditions and in excellent yield using samarium (II) iodide.<sup>91</sup>

### 7.2 *N*-N bond reduction of diamines 144 and 145

As described in Chapter 5 the styrene-derived aziridine **69** is ring-opened with sodium azide affording **131** as a single diastereoisomer in quantitative yield (Scheme 61). The other diastereoisomer of this azide **143** could also be accessed by displacement of benzylic chloride **117** with sodium azide (Scheme 72).

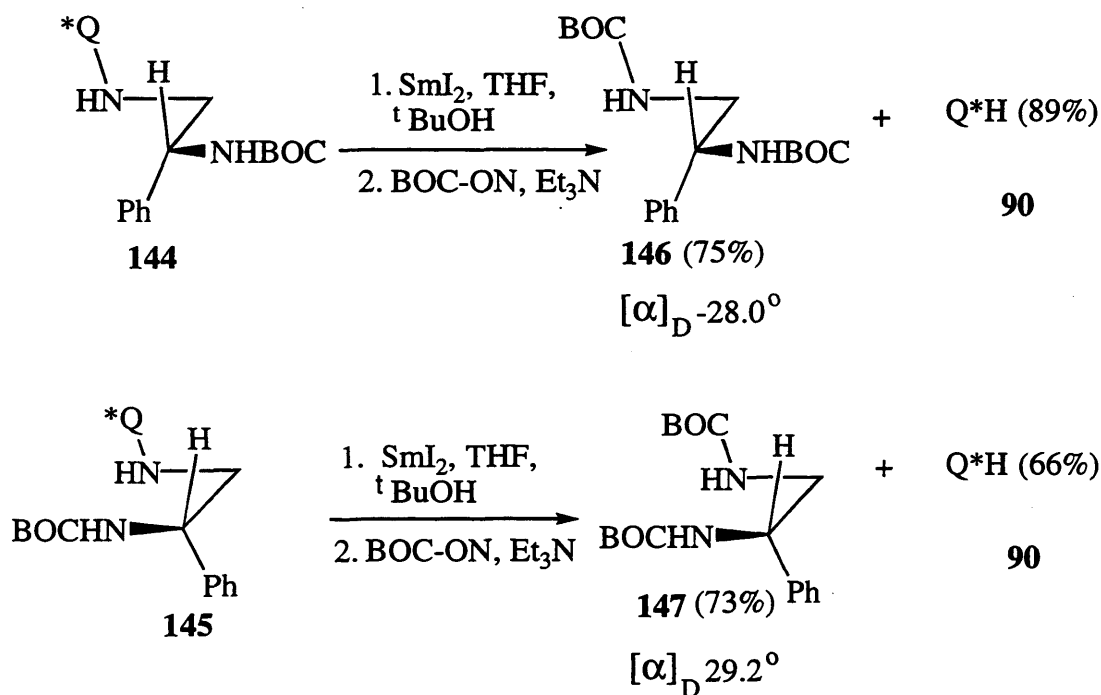


Scheme 72

Since these azides are diastereoisomers, differing in configuration at the benzylic position, their hydrogenation followed by Q\*-N bond reduction will result in the

synthesis of both (enantiopure) antipodes of the corresponding diamine derivatives from the same starting aziridine **69**. Reduction of azides **131** and **143** by catalytic hydrogenation afforded the free amines that were each protected and isolated as their *N*-BOC derivatives **144** and **145** (Scheme 72). These two diastereoisomeric *N*-BOC derivatives had very different physical properties, **145** having a melting point of 183-187 °C whereas **144** melted at 225-227 °C and showed a markedly lower solubility in organic solvents.

These two *N*-Q\* protected diamine derivatives **144** and **145** were then each converted to the corresponding bis *N*-BOC diamines **146** and **147** in good yield by treatment with samarium (II) iodide in THF (Scheme 73) followed by BOC protection. In each case the reduction was very quick and was virtually a titration; decolourisation of the deeply blue Sm (II) to pale yellow Sm (III) occurring immediately on addition of the reducing agent. The chiral auxiliary was also recovered from the reaction as the de-aminated compound Q\*H **90**.

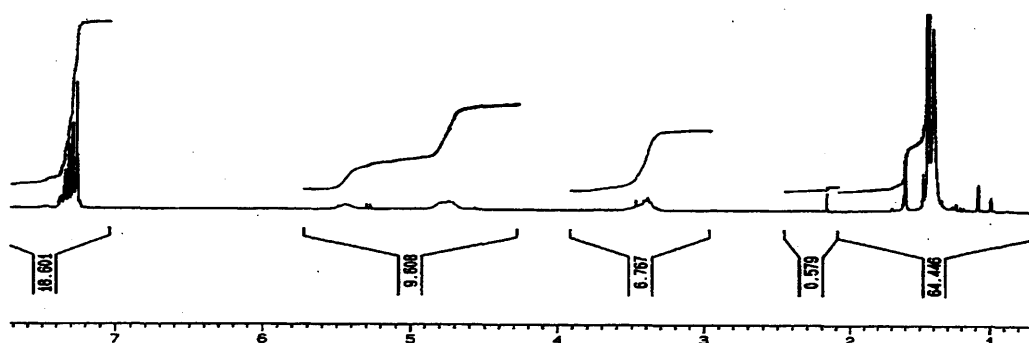


Scheme 73

The absolute configurations of these diamine enantiomers **146** and **147** are assigned as shown and follow from the known absolute configuration of aziridine **69** (proven by X-ray structure determination) and from the stereochemistry in Schemes 72 and 73.

The optical rotations of these otherwise identical diamines were, as expected, very close in magnitude but opposite in sign.

In the room temperature proton NMR spectra of these diamines the signals are broadened; on cooling to  $-40\text{ }^{\circ}\text{C}$  these signals sharpened and two species were visible in an approximately 9:1 ratio (Fig. 29). These signals are attributed to two rotameric species, interconversion between which is becoming rapid on the NMR time-scale at room temperature, but is slow at  $-40\text{ }^{\circ}\text{C}$ .



Room temperature NMR spectrum of diamine 146

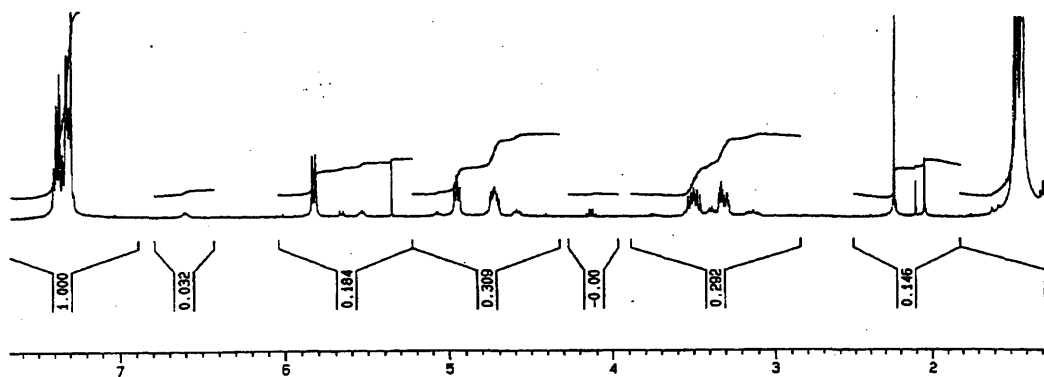
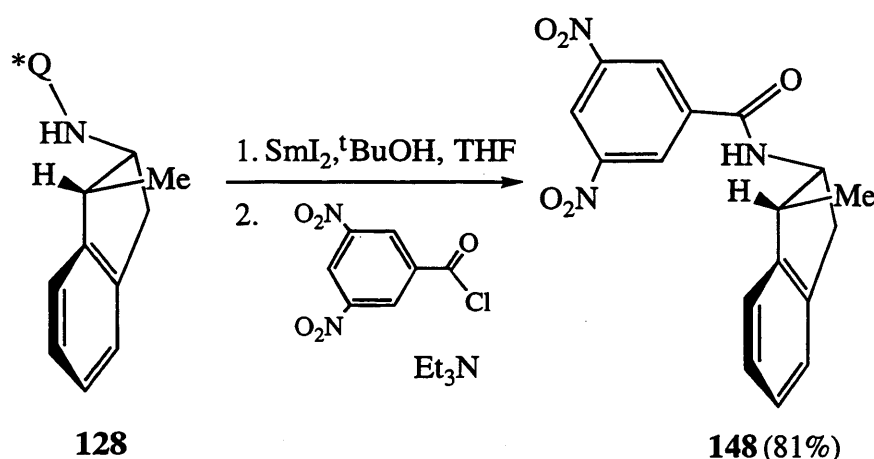


Fig. 29 NMR spectrum of diamine 146 at  $-40\text{ }^{\circ}\text{C}$

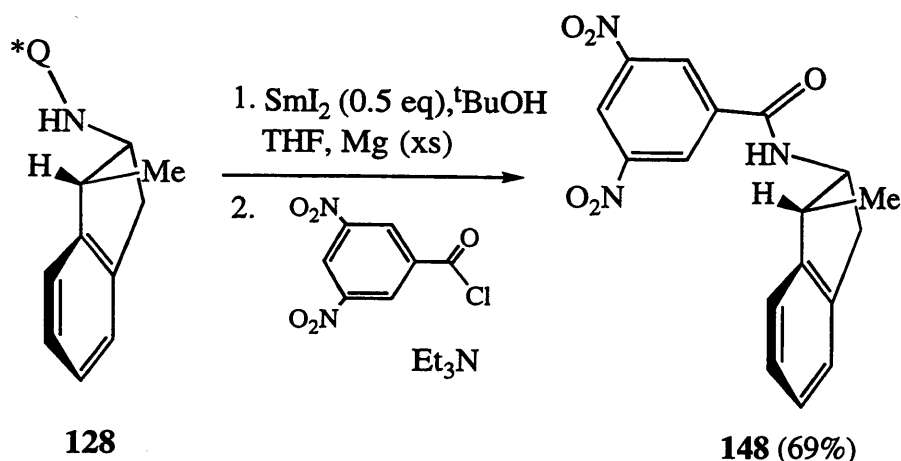
### 7.3 N-N bond reduction of 3-N(Q\*)-substituted indane 128

The Q\*-N bond reduction of amine **128** derived from methylcopper ring-opening of aziridine **74** was found to occur much more slowly than that for diamines **144** and **145**; complete decolourisation of the reaction solution and disappearance of starting material required two hours at room temperature. The free amine was converted to the 3,5-dinitrobenzoate **148** to render the product UV active and therefore easily visible by TLC, and which was isolated by chromatography in 81% yield (Scheme 74). This 3,5-dinitrobenzoate **148** has a significant optical rotation ( $\alpha_D = -40.2^\circ$ ) and is likely to be as enantiopure as the starting Q\*NHOAc since the indene-derived aziridine **74** from which the starting material **128** is derived is diastereopure.



Scheme 74

One disadvantage in using samarium (II) iodide is its cost: £16.70 for 100 cm<sup>3</sup> of 0.1 mol dm<sup>-3</sup> solution<sup>114</sup> that will reduce 5 mmol. of substrate. However Endo and co-workers<sup>115</sup> have shown that reduction of Sm(III) back to Sm(II) can be accomplished *in situ* by activated magnesium, and these authors have shown that pinacol-coupling of carbonyl compounds can be carried out catalytically in Sm(II). It was found that this *in situ* reduction of Sm(III) by magnesium could also be applied to the Q\*-N cleavage in Scheme 75 allowing a sub-molar quantity of Sm(II) to be used and with only a small loss of yield.



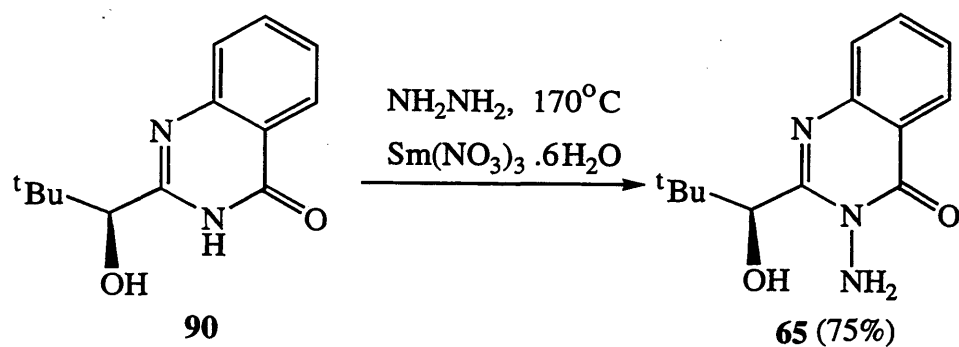
Scheme 75

#### 7.4 Re-amination of 3-H-quinazolinone 90

Since the cost of (L)-*tert*-leucine, the starting amino acid for the preparation of 3-aminoquinazolinone **65**, is not insignificant, the possibility of recycling the chiral auxiliary, recovered after  $Q^*-N$  bond reduction as  $Q^*H$  **90** (Scheme 73) was explored. In principle, simply heating a 3H-quinazolinone in the presence of hydrazine could result in re-amination to the corresponding 3-aminoquinazolinone and indeed this method succeeds when the substituent in the 2-position of the 3H-quinazolinone is a proton. However there was no reaction when  $Q^*H$  **90** was heated with hydrazine in ethanol at 170 °C for 17 h. in a sealed tube

Since samarium is oxophilic and is thought to co-ordinate with the C-4 carbonyl group of the quinazolinone (see Chapter 6), the reaction of  $Q^*H$  **90** with hydrazine was repeated in the presence of  $\text{Sm}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$  in the hope that the metal, acting as a Lewis acid, would catalyse the reaction. Under these conditions re-amination occurred and 3-aminoquinazolinone **65** ( $Q^*\text{NH}_2$ ) was isolated in good yield (Scheme 76). The optical rotation of the product  $Q^*\text{NH}_2$  was  $\alpha_D$  19.6 °, in good agreement with that found for an authentic sample ( $\alpha_D$  20.2 °) used routinely in aziridination of alkenes in this work.





Scheme 76

### 7.5 Summary of Chapter 7

The work described in this Chapter shows that the chiral auxiliary is readily removed from these ring-opened products under mild conditions to give useful chirons as exemplified by the formation of **146**, **147** and **148**. Furthermore the reduction of the *N*-Q\* bond can be accomplished with sub-molar quantities of samarium (II) iodide in the presence of activated magnesium. The chiral auxiliary can be recovered (as Q\*H **90**) and reaminated to Q\*NH<sub>2</sub>, without loss of enantiopurity.

## 7.6 Summary of Results and Discussion

As is outlined in the Summary at the end of each Chapter, the three major goals of this project have been realised so that this methodology is a viable route for conversion of alkenes into a range of enantiopure chiroins corresponding to the overall addition of  $\text{NH}_2$  and Nu (nucleophile) enantiospecifically across the double bond. The most significant findings of this study are outlined below.

1. Methodology for the conversion of a range of alkenes into aziridines with high, or in many cases complete diastereoselectivity using  $\text{Q}^*\text{NHOAc}$  **49** has been developed. The absolute configuration of three of the aziridines and two aziridine ring-opened products have been established by X-ray structure determination and is consistent with the transition state models proposed. Although a complete study of the mechanism of aziridination was not undertaken, some experimental evidence to support these proposed transition states has been gleaned.

2. Some heterolytic ring-opening reactions of the  $N\text{-Q}^*$ -substituted aziridines at carbon have been investigated. The quinazolinone as a substituent on nitrogen has been found to be sufficiently electron-withdrawing to activate the aziridine ring toward attack by nucleophiles without the need for prior protonation of the ring nitrogen.

3. These  $N\text{-Q}^*$ -substituted aziridines are efficiently ring-opened with strong acid. There is evidence that in some cases the quinazolinone C-4 carbonyl oxygen participates in ring-opening giving rise to retention of configuration at the aziridine ring carbon in several instances. Thus in addition to bringing about complete diastereoselectivity in the aziridination, the  $\text{Q}^*$  group can be subsequently used to control the stereochemistry of ring-opening of the aziridine products.

4. The two  $N$ -invertomers of the indene-derived aziridine **74** have been found to undergo very different stereochemistry of ring-opening with hydrogen chloride; thus the disposition of the  $\text{Q}^*$  can be used to control the stereoselectivity of ring-opening.

5. Ring-opening of an *N*-Q\*-aziridine-2-carboxylate ester is catalysed by Sm(III) with highly regioselective ring-opening occurring at the more substituted carbon. Regio-complementary ring-opening of the aziridine under the same conditions is found when the it is tethered in the form of a lactone to the hydroxyl adjacent to the quinazolinone; ring-opening now takes place exclusively at the less substituted aziridine ring carbon. In this way the regioselectivity of ring-opening can be controlled by making use of the substituent on the quinazolinone.

6. The Q\* group has been shown to be readily removed under mild conditions (by SmI<sub>2</sub>) from the above products of ring-opening, giving access to enantiopure chiron. *N*-Q\* bond reduction can be carried out with a catalytic amount of samarium (II) iodide in the presence of activated magnesium. The chiral auxiliary can be recovered (in the form of Q\*H **90**) and re-aminated to Q\*NH<sub>2</sub> without loss of enantiopurity.

## ***General Experimental***

## *General Experimental*

250, 300 and 400 MHz  $^1\text{H}$  (NMR) spectra were recorded on Bruker ARX 250, DPX 300 and AC 400 NMR spectrometers respectively (Bruker AC 400 courtesy of Roche products).  $^{13}\text{C}$  NMR spectra were recorded on a Bruker ARX 250 spectrometer at 75 MHz. NMR spectra were recorded at room temperature in deuterated chloroform unless otherwise stated. IR spectra of crystalline compounds were recorded as solutions in dichloromethane and of liquids as thin films using a Perkin-Elmer 298 spectrometer. Standard mass spectra were recorded on a Kratos Concept 1H Magnetic Sector Mass Spectrometer. Elemental analysis was carried out by CHN analysis, Wigston, Leicester. Melting points were determined on a Kofler hot stage and are uncorrected. Optical rotations were determined on a Perkin-Elmer 341 Polarimeter at 589 nm. All X-ray crystal structure determinations were carried out by Dr J. Fawcett and Dr D. R. Russell at the University of Leicester, except for **130** which was carried out by Dr C. Frampton (Roche). Flash chromatography was carried out on silica gel C60 (35-70) (from Prolabo). TLC was conducted on silica gel 60  $f_{254}$  (Merck 5554) on aluminium strips.

Solvents were dried by methods described by Perrin and Armarego,<sup>116</sup> dry THF was obtained by distillation from sodium / benzophenone, dichloromethane distilled from calcium hydride, and diethyl ether and toluene were sodium-dried prior to use. Light petroleum refers to the 40 - 60 °C fraction. Routine drying of organic solutions was carried out using magnesium sulphate.

Lead tetra-acetate was dried prior to use on high vacuum for 15 min. Titanium (IV) *tert*-butoxide was initially prepared by a literature method,<sup>97</sup> and subsequently purchased from Merck and used as received. (L)-*tert*-leucine was purchased from Degussa Ltd and generously donated by Roche Products. Solutions of methylmagnesium bromide in ether and samarium diiodide in THF, purchased from Aldrich, were used as received and consumed as quickly as possible after opening. Copper (I) bromide-dimethylsulphide was freshly prepared prior to use by the method

described by Taylor.<sup>117</sup> The argon used was zero grade; all other reactants were reagent grade and used as received unless otherwise stated.

All reaction products were dried on high vacuum prior to spectroscopic analysis and further use. Yields are isolated unless otherwise stated.

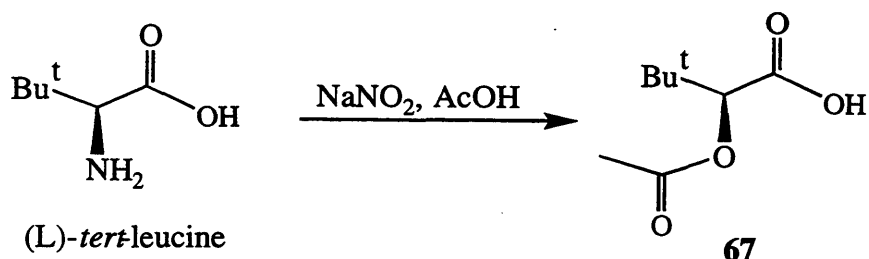
### *Physical Data*

IR spectra are measured in units of  $\text{cm}^{-1}$  and the following abbreviations are used: s - strong, m - medium and w - weak. Optical rotation values are given in units  $10^{-1} \text{deg cm}^2 \text{ g}^{-1}$ . In  $^1\text{H}$  NMR spectra, chemical shifts are expressed in ppm. relative to the internal standard tetramethylsilane; chemical shifts for  $^{13}\text{C}$  are referenced to the centre peak of the  $\text{CDCl}_3$  triplet (77.0 ppm).<sup>118</sup> Assignments of  $^{13}\text{C}$  resonances were assisted by DEPT. The following abbreviations are used: s - singlet; d - doublet; t - triplet; q - quartet; dd - doublet of doublets; ddd - doublet of doublet of doublets; m - multiplet; br - broad; struct. - structured; ariz. - aziridine; Ph - phenyl; Q - quinazolinone and J - coupling constant (Hz).

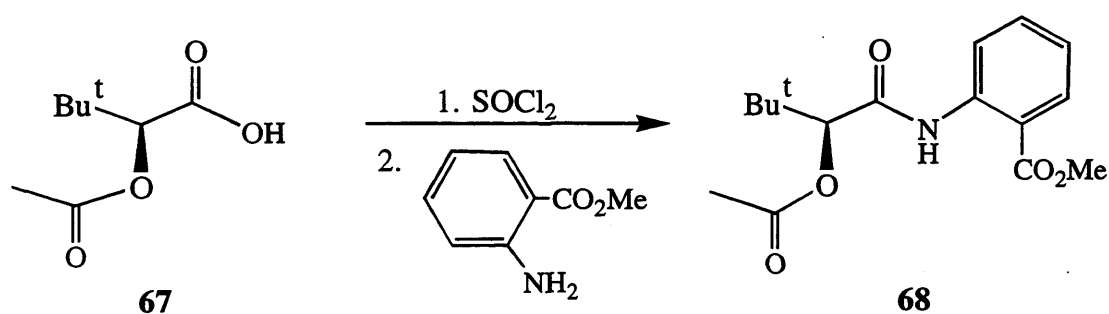
Mass spectra were determined in units of mass relative to charge ( $m/z$ ) with fast atomic bombardment (FAB) ionisation in all cases. Except for the molecular ion  $\text{MH}^+$ , only peaks  $\geq 20\%$  of the base peak are given.

## ***Experimental for Chapter 2***

**Preparation of 3-amino-2-(1-hydroxy-2,2-dimethylprop-1-yl)-  
quinazolin-4(3H)-one 65**



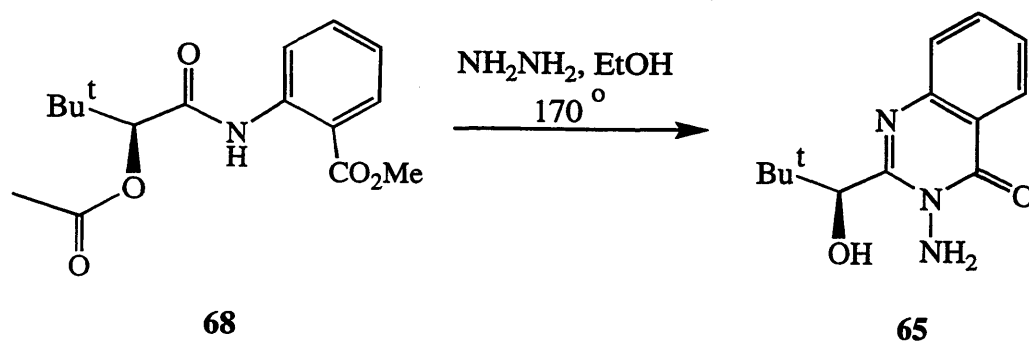
To a stirred solution of (*S*)-*tert*-leucine (25.0 g, 0.191 mol.) in glacial acetic acid (600 cm<sup>3</sup>) at room temperature was added solid sodium nitrite (52.64 g, 0.763 mol.) slowly over a period of 1 h. After addition the solution was left for a further 1 h. before the bulk of the acetic acid was removed under reduced pressure. Water (50 cm<sup>3</sup>) was added and the aqueous solution extracted with diethyl ether (3 x 70 cm<sup>3</sup>). The combined ethereal extracts were then washed with brine (50 cm<sup>3</sup>), dried and the solvent removed under reduced pressure. Trituration of the resulting greenish solid with light petroleum gave (*S*)-2-acetoxy-3,3-dimethylbutyric acid **67** (20.10 g, 60.5 %)  $\alpha_D$  (c 9.93, ethanol) -23.7 ° [lit<sup>96</sup> -22.8 ° (c 1.6, ethanol)].



(*S*)-2-Acetoxy-3,3-dimethylbutyric acid **67** (16 g, 91.9 mmol) was dissolved in sodium-dried ether and two drops of *N,N*-dimethylformamide added followed by slow dropwise addition of thionyl chloride (19 cm<sup>3</sup>, 260 mmol) to the stirred solution. The solution was left to stand overnight at room temperature and then unreacted thionyl chloride removed under reduced pressure. The resulting cloudy oil was dissolved in

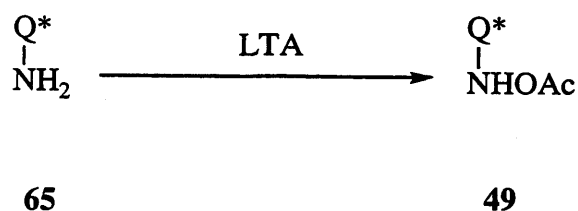


sodium-dried ether (300 cm<sup>3</sup>) and methyl anthranilate (24 cm<sup>3</sup>, 185 mmol) was added dropwise briskly with stirring; a thick white precipitate was formed over the following hour. After setting aside overnight the solid was filtered off, washed with ether, and the combined filtrates washed successively with hydrochloric acid (2M, 5 x 50 cm<sup>3</sup>), saturated aqueous sodium hydrogen carbonate and saturated brine (3 x 25cm<sup>3</sup>), then dried and the solvent removed by evaporation under reduced pressure. Crystallisation of the crude product gave the anthranilamide **68** (26.3 g, 93%) mp 61-63 °C (from ethanol) (Found: C, 62.35; H, 6.85; N, 4.55; C<sub>16</sub>H<sub>21</sub>NO<sub>5</sub> requires C, 62.55; H, 6.9; and N 4.55 %),  $\alpha_D$  -151° (c 1.0, ethanol),  $\nu_{\max}/\text{cm}^{-1}$  3290 w, 2980 m, 1750 s, 1695 s, 1590 s, 1525 s, 1450 s, 1375 m, 1270 s and 1240 m;  $\delta_H$  1.02 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 2.21 (3H, s, OCOCH<sub>3</sub>), 3.84 (3H, s, OCH<sub>3</sub>), 4.85 (1H, s, CHOAc), 7.01 (1H, ddd, *J* 0.9, 7.2 and 8.2, *ArH*), 7.46 (1H, ddd, *J* 1.6, 7.2 and 8.5, *ArH*), 7.95 (1H, dd, *J* 1.6 and 8.2, *ArH*), 8.66 (1H, dd, *J* 0.6 and 8.5, *ArH*) and 11.46 (1H, br s, *NH*);  $\delta_C$  20.5 (OCH<sub>3</sub>), 26.1 ((CH<sub>3</sub>)<sub>3</sub>), 34.1 (C(CH<sub>3</sub>)<sub>3</sub>), 52.0 (CO<sub>2</sub>CH<sub>3</sub>), 81.1 (CHC(CH<sub>3</sub>)<sub>3</sub>), 115.1 (C(*Ar*)), 120.1, 122.6, 130.6, 134.3 (4 x CH(*Ar*)), 140.4 (C(*Ar*)) and 167.6, 168.2, 169.8 (3 x C=O); *m/z* 330 (MNa<sup>+</sup>, 330, 16), 308 (MH<sup>+</sup>, 100), 216 (23), 178 (28) and 157 (83).



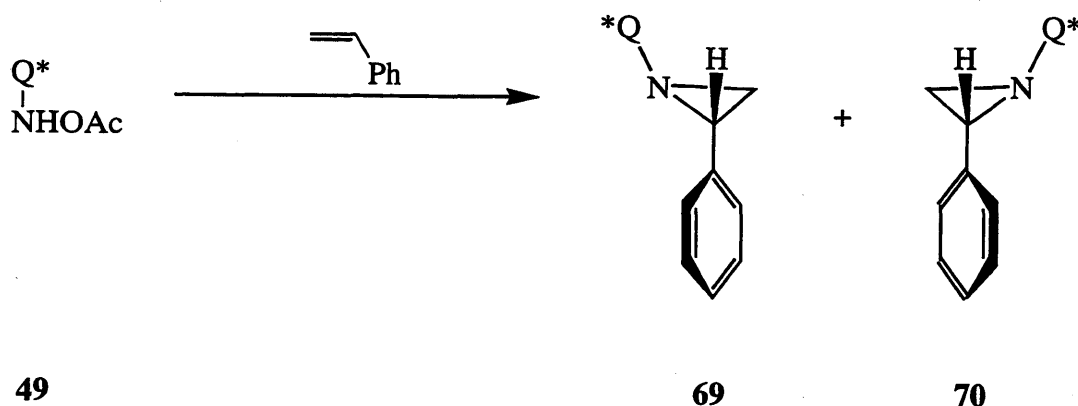
The amide **68** (16.263 g, 53.04 mmol) was dissolved in ethanol (10 cm<sup>3</sup>) and heated with hydrazine monohydrate (10 cm<sup>3</sup>, 206.15 mmol) in a steel bomb at 140 °C for 17 h. After removing the bulk of the solvent under reduced pressure, water (50 cm<sup>3</sup>) was added and the solution extracted with diethyl ether (3 x 50 cm<sup>3</sup>). The combined organic layers were washed with water (50 cm<sup>3</sup>), dried and the solvent removed by evaporation under reduced pressure. Crystallisation of the residual white solid from gave 3-amino-2-(1-hydroxy-2,2-dimethylprop-1-yl)-quinazolin-4(3H)-one **65** (10.97 g, 84%) mp 135-136 °C (from ethanol). (Found: C, 62.85; H, 6.85; N 17.0; O, 12.95. C<sub>13</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub> requires C, 63.15; H, 6.95; N, 17.0; O, 12.95%);  $\alpha_D$  20.2° (c 1.04, ethanol);  $\nu_{\text{max}}/\text{cm}^{-1}$  3500 w, 2960 m, 1680 s, 1595 s, 1475 s, 1365 m, 1180 m, 1080 m, 1045 m and 1020 m;  $\delta_H$  1.11 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 3.87 (1H, d, *J* 10, OH), 4.78 (2H, s, NH<sub>2</sub>), 5.25 (1H, d, *J* 10, CHOH), 7.54 (1H, ddd, *J* 1.6, 8.2 and 8.2, H<sub>6</sub>(Q)), 7.74 (1H, d, *J* 7.3, H<sub>8</sub>(Q)), 7.82 (1H, ddd, *J* 1.6, 6.9 and 8.2, H<sub>7</sub>(Q)) and 8.31 (1H, dd, *J* 1.0 and 8.2, H<sub>5</sub>(Q));  $\delta_C$  26.3 (3 x CH<sub>3</sub>), 37.4 (C(CH<sub>3</sub>)<sub>3</sub>), 74.6 (CHOH), 119.9 (CCO(Q)), 126.2, 126.5, 126.9, 134.1 (4 x CH(Q)), 145.6 (CN=C(Q)), 158.2 (C=N(Q)) and 161.9 (CO(Q)); *m/z* 248.13991 (MH<sup>+</sup>, 100), 230 (25).

***Low temperature NMR spectrum of 3-acetoxyamino-2-(1-hydroxy-2,2-dimethylprop-1-yl)-quinazolin-4(3H)-one 49***



To  $\text{CDCl}_3$  (2  $\text{cm}^3$ ) stirred at  $-12\text{ }^\circ\text{C}$  (bath temp.) was added powdered LTA (180 mg, 0.406 mmol). After dissolution the reaction mixture was cooled to  $-20\text{ }^\circ\text{C}$  and a solution of 3-aminoquinazolinone **65** (100 mg, 0.404 mmol in  $\text{CDCl}_3$  (2  $\text{cm}^3$ )) added dropwise with stirring over 1 minute. After stirring at this temperature for a further 20 min. the cold solution was separated from the lead salts (Pasteur pipette), washed with cold ( $0\text{ }^\circ\text{C}$ ) saturated sodium hydrogen carbonate solution, dried, and then filtered through a cooled Pasteur pipette containing a cotton wool plug directly into a cooled ( $-12\text{ }^\circ\text{C}$ ) NMR tube and the spectrum recorded at  $-20\text{ }^\circ\text{C}$ . The title compound appeared to consist of at least a 14 : 1 ratio of diastereoisomers, by comparison of two  $\text{NHOAc}$  singlets at 10.73 and 10.85 ppm (no other signals corresponding to the minor diastereoisomer were visible).  $\delta_{\text{H}}$  ( $\text{CDCl}_3$ , 300 MHz) 1.03 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 2.11 (3H, s,  $\text{OCOCH}_3$ ), 3.68 (1H, d,  $J$  10.2, OH), 5.13 (1H, d,  $J$  9.9,  $\text{CH}(\text{C}(\text{CH}_3)_3)$ ), 7.56 (1H, ddd,  $J$  1.3, 7.0 and 8.0,  $\text{H}_6(\text{Q})$ ), 7.76 (1H, d,  $J$  8.1,  $\text{H}_8(\text{Q})$ ), 7.87 (1H, ddd,  $J$  1.6, 7.0 and 8.1,  $\text{H}_7(\text{Q})$ ), 8.25 (1H, dd,  $J$  1.0 and 8.0,  $\text{H}_5(\text{Q})$ ) and 10.85 (1H, s, NH).

### Aziridination of styrene with $Q^*NHOAc$ 49



#### General procedure A

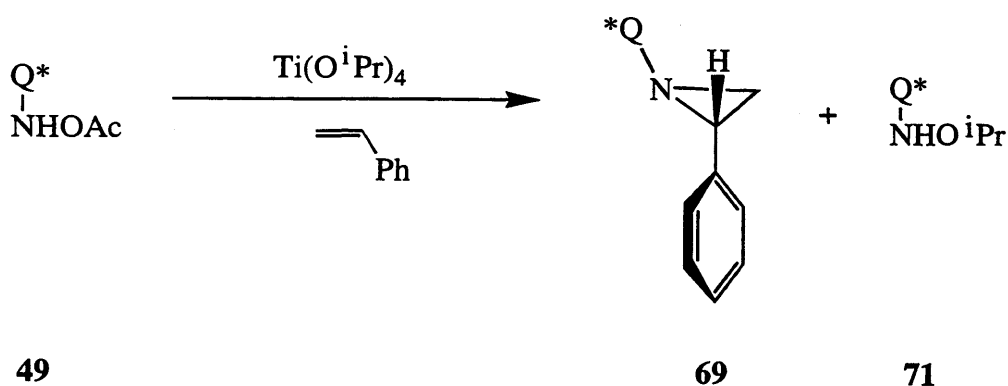
To dry dichloromethane (2 cm<sup>3</sup>) stirred at -12 °C (bath temperature) was added powdered LTA (377 mg, 0.85 mmol) in one portion. After dissolution the reaction mixture was cooled to -20 °C and 3-aminoquinazolinone **65** (200 mg, 0.81 mmol in dry dichloromethane (2 cm<sup>3</sup>)) added over 1 min. dropwise. Stirring was continued for a further 20 min (End of general procedure A) and styrene (0.11 cm<sup>3</sup>, 0.96 mmol) was added. The reaction mixture was stirred for 2 min at -20 °C before its temperature was allowed to reach ambient by removal of the cooling bath.

#### General work-up procedure B.

The solution obtained above was filtered, washed successively with aqueous saturated sodium hydrogen carbonate, saturated brine (2 x 5 cm<sup>3</sup>) and dried. Removal of solvent by evaporation under reduced pressure (end of general procedure B) gave two diastereoisomeric aziridines **70** and **69** (253 mg, 90%) in a 3:2 ratio (by integration of the signals at 2.74 and 2.91 ppm respectively (see below.)) Crystallisation gave the major aziridine diastereoisomer **70** as colourless crystals mp 124-127 °C (from ethanol.)  $\delta_H$  0.98 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 2.74 (1H, dd,  $J$  1.0, 5.0, CHH *cis* to Ph), 3.20 (1H, dd,  $J$  1.0, 8.0, CHH *trans* to Ph), 3.76 (1H, d,  $J$  10.0, OH), 4.29 (1H, dd,  $J$  5.0, 8.0,

CHPh), 5.22 (1H, d,  $J$  10.0, CHOH), 7.32 - 7.50 (6H, structured m,  $H_6(Q)$ , 5 x  $H(Ph)$ ), 7.60 to 7.78 (2H, structured m,  $H_7$ ,  $H_8(Q)$ ) and 8.22 (1H, dd,  $J$  1.0, and 7.5,  $H_5(Q)$ ).

***Aziridination of styrene with  $Q^*NHOAc$  49 in the presence of titanium (IV) isopropoxide***

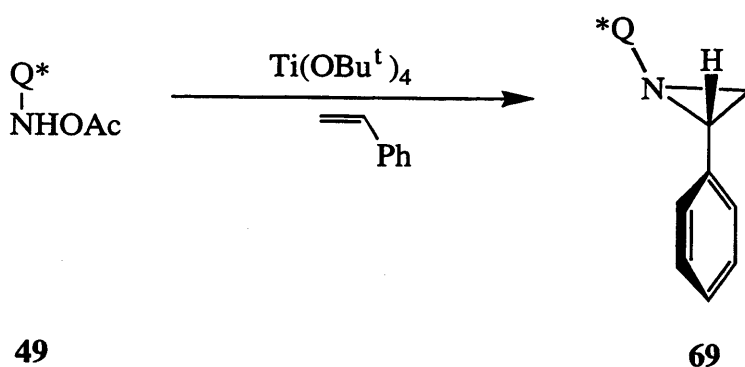


A solution of 3-acetoxaminoquinazolinone **49** in dichloromethane (4 cm<sup>3</sup>) was prepared as described (general procedure A) from **65** (200 mg, 0.81 mmol) and LTA (377 mg, 0.85 mmol) and filtered through a cotton wool-plugged Pasteur pipette into a stirred solution of titanium (IV) isopropoxide (460 mg, 1.62 mmol) and styrene (0.11 cm<sup>3</sup>, 0.96 mmol) in dry dichloromethane (1 cm<sup>3</sup>) held at -20 °C. After stirring at this temperature for 2 min the reaction temperature was allowed to reach ambient by removal of the cooling bath.

**General work-up procedure C.**

A saturated sodium hydrogen carbonate solution (5 cm<sup>3</sup>) was added to the reaction mixture and the mixture stirred vigorously until a white gelatinous precipitate formed. The solution was filtered and the organic layer of the filtrate separated, washed with saturated brine (2 x 5 cm<sup>3</sup>), dried, and the solvent evaporated under reduced pressure (end of general procedure) to give a pale yellow residue containing a single diastereoisomer of aziridine **69** (14%) and 3-isopropoxyaminoquinazolinone **71** 59% by NMR comparison of this mixture with those of authentic samples of **69** and **71** (see later).

***Aziridination of styrene with Q\*NHOAc 49 in the presence of titanium  
(IV) tert-butoxide (2 equivalents)***



A solution of 3-acetoxyaminoquinazolinone **49** in dichloromethane ( $40 \text{ cm}^3$ ) was prepared as described previously (general procedure A) from **65** (2.8 g, 11.34 mmol) and LTA (5.52 g, 12.45 mmol) and filtered through a cotton wool-plugged Pasteur pipette into a stirred mixture of titanium (IV) *tert*-butoxide (7.70 g, 22.7 mmol), styrene ( $1.6 \text{ cm}^3$ , 13.6 mmol) and dry dichloromethane ( $10 \text{ cm}^3$ ) maintained at  $-20^\circ \text{C}$ . After stirring for 2 min the temperature of the reaction mixture was allowed to reach ambient. Work-up (general procedure C) gave a pale yellow solid. Examination of the crude product by NMR spectroscopy showed it to consist of a single diastereoisomer of aziridine **69** and crystallisation gave aziridine 69 (2.56 g, 65%) mp  $127\text{--}128^\circ \text{C}$  (from ethanol). (Found: C, 72.2; H, 6.7; N, 12.  $\text{C}_{21}\text{H}_{23}\text{N}_3\text{O}_2$  requires C, 72.18; H 6.65; N 12.0 %);  $\alpha_D$   $403.0^\circ$  (c 1.00, ethanol);  $\nu_{\text{max}}/\text{cm}^{-1}$  3450 w, 2950 w, 1675 s, 1585 s, 1475 m, 1330 m, 1230 m, 1080 m and 1080 m;  $\delta_H$  0.88 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 2.91 (1H, dd,  $J$  2.5 and 5.0,  $\text{CHH}$  *cis* to Ph), 3.50 (1H, dd,  $J$  2.5 and 7.9,  $\text{CHH}$  *trans* to Ph), 3.67 (1H, d,  $J$  10.4, OH), 3.84 (1H, dd,  $J$  5.0 and 7.9,  $\text{CHPh}$ ), 4.99 (1H, d,  $J$  10.4,  $\text{CHOH}$ ), 7.37 (5H structured m, 5 x  $H(\text{Ph})$ ), 7.48 (1H, ddd,  $J$  1.0, 6.9 and 8.2,  $H_6(\text{Q})$ ), 7.66 (1H, dd,  $J$  1.0 and 8.5,  $H_8(\text{Q})$ ), 7.75 (1H, ddd,  $J$  1.6, 6.9 and 8.5  $H_7(\text{Q})$ ) and 8.24 (1H, dd,  $J$  1.6 and 8.2,  $H_5(\text{Q})$ );  $\delta_C$  25.7 ( $\text{C}(\text{CH}_3)_3$ ), 37.8 ( $\text{C}(\text{CH}_3)_3$ ), 42.1 ( $\text{CH}_2$ ), 47.3 ( $\text{CHPh}$ ), 74.4 ( $\text{CHOH}$ ), 121.4 ( $\text{CCO}(\text{Q})$ ), 126.3, 126.8, 126.9, 128.3, 128.7, 134.0 (6 x  $\text{CH}(\text{Q})$ ,  $\text{CH}(\text{Ph})$ ); 136.1 ( $\text{C}(\text{Ph})$ ), 144.8 ( $\text{CN}=\text{C}$ ) 158.1 ( $\text{C}=\text{N}(\text{Q})$ ) and 159.6 ( $\text{CO}(\text{Q})$ );  $m/z$  350 ( $\text{MH}^+$ , 100) and 215 (20). A crystal was grown from light petroleum-ethyl

acetate for X-ray structure determination which showed that the major diastereoisomer has the S configuration at the aziridine ring C-2 (Fig. 30).

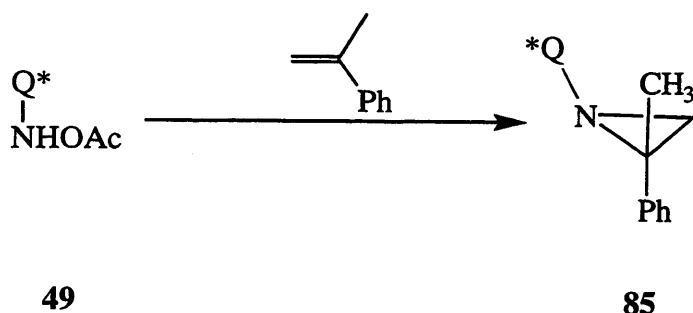
***Aziridination of styrene with Q\*NHOAc 49 in the presence of titanium  
(IV) tert-butoxide (1 and 1.5 equivalents)***

Two solutions of 3-acetoxyaminoquinazolinone **49** a and b, in dichloromethane (4 cm<sup>3</sup>) were prepared as described previously (general procedure A) from **65** (200 mg, 0.81 mmol) and LTA (377 mg, 0.85 mmol) at -20 °C. The two solutions, a and b, were then each filtered through a cotton wool-plugged Pasteur pipette into stirred solutions of styrene (0.11 cm<sup>3</sup>, 0.96 mmol) in dichloromethane (2 cm<sup>3</sup>) maintained at -20 °C containing titanium (IV) *tert*-butoxide 274 mg (0.81 mmol) and 411 mg (1.21 mmol) respectively. After stirring for 2 min the cooling baths were removed and the temperature of each reaction mixture allowed to reach ambient. Each reaction was worked-up as described previously (general procedure C), the results are given below in Table 8.

Reaction	No. of TTB equivalents	Ratio of aziridine diastereoisomer <b>69:70</b>	Yield of aziridine (%)
a	1.0	6.8: 1	73
b	1.5	34 : 1	86

Table 8

***Aziridination of  $\alpha$ -methyl styrene with  $Q^*NHOAc$  49***



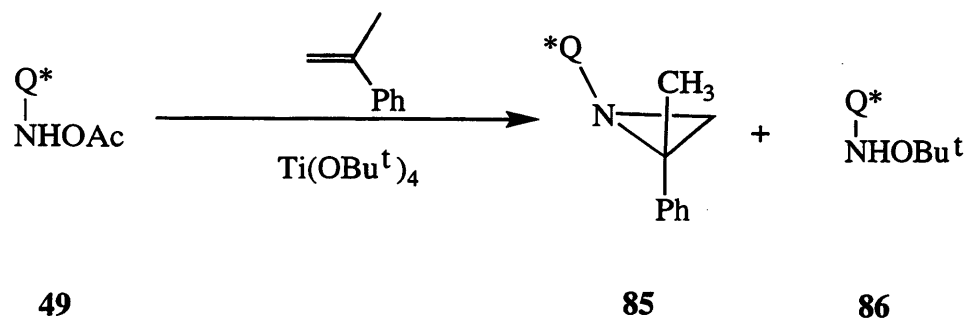
A solution of 3-acetoxycarbonylquinazolinone **49** in dry dichloromethane (4 cm<sup>3</sup>) was prepared as described previously (general procedure A) from **65** (200 mg, 0.81 mmol) and LTA (377 mg, 0.85 mmol) at -20 °C and  $\alpha$ -methyl styrene (0.21 cm<sup>3</sup>, 1.61 mmol) added to the stirred solution. After 2 min the cooling bath was removed and the temperature of the solution allowed to rise to 0 °C before being added dropwise to a vigorously stirred solution of saturated sodium bicarbonate (5 cm<sup>3</sup>). The resulting mixture was filtered, the organic layer separated washed with brine (2 x 5 cm<sup>3</sup>), dried and concentrated to give a colourless oil, 283 mg, 77%. Examination of the crude product by NMR spectroscopy showed it to be composed of a 1 : 1.1 ratio of aziridines **85** by comparison of the integration of signals at 3.03 and 3.19 respectively. ( For NMR spectrum of the major diastereoisomer see later. )

The minor diastereoisomer consisted of a 3 : 2 ratio of *N*-invertomers by comparison of the integration of *CHH* signals at 4.10 and 2.69 ppm respectively; major invertomer  $\delta$  0.95 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.54 (3H, s, CH<sub>3</sub>), 3.04 (1H, d, *J* 4.4, *CHH*), 4.10 (1H, d, *J* 4.4, *CHH*), 4.77 (1 H, br s, CHOH), 7.10 to 7.72 (8H, struct m, 5 x CH(Ph), 3 x CH(Q)) and 8.25 (1H, br d, *J* ~8, H<sub>5</sub>(Q)).

Observable signals minor invertomer at 1.00 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.54 (3H, s, CH<sub>3</sub>), 2.69 (1H, br s, *CHH*), 3.03 (1H, br s, *CHH*) and 4.83 (1H, br s, CHOH).



**Aziridination of  $\alpha$ -methyl styrene with  $Q^*NHOAc$  49 in the presence of  
titanium (IV) *tert*-butoxide**

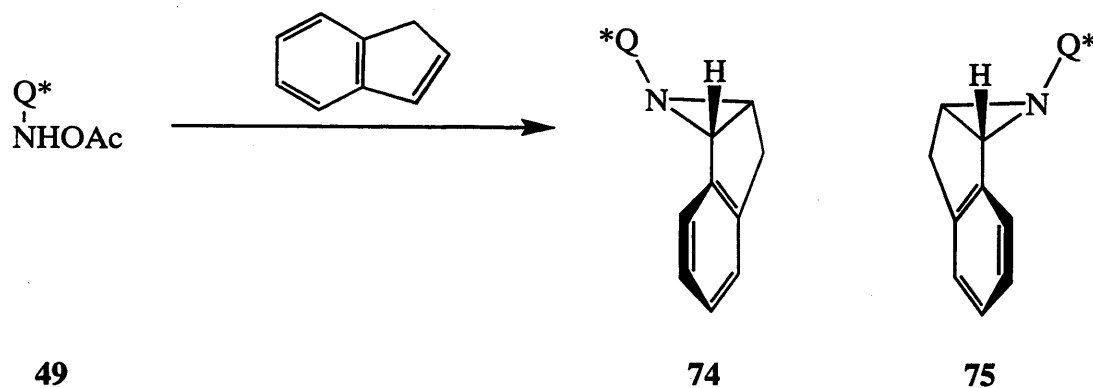


A solution of 3-acetoxyaminoquinazolinone **49** in dry dichloromethane (4 cm<sup>3</sup>) was prepared as described previously (general procedure A) from **65** (200 mg, 0.81 mmol) and LTA (377 mg, 0.85 mmol) at -20 °C and then filtered through a cotton wool-plugged Pasteur pipette into a stirred solution of titanium (IV) *tert*-butoxide (548 mg, 1.62 mmol) in dichloromethane (2 cm<sup>3</sup>) maintained at -40 °C. After 1 h at this temperature,  $\alpha$ -methyl styrene (0.21 cm<sup>3</sup>, 1.61 mmol) was added to the solution whose temperature was then allowed to rise to ambient, stirring throughout. The reaction mixture was then added dropwise to a rapidly stirred saturated sodium carbonate solution (5 cm<sup>3</sup>), the organic layer separated, washed with brine (2 x 5 cm<sup>3</sup>), dried and concentrated to give a pale brown residue (179 mg). Examination by NMR spectroscopy showed this residue to consist of a 9:1 ratio of aziridine diastereoisomers **85** (44 %) by integration comparison of signals at 3.19 and 3.03 ppm respectively, together with *tert*-butoxyaminoquinazolinone **86** (8 %).

Chromatography (eluent 4:1 light petroleum-ethyl acetate) yielded aziridine **85** (Found:  $MH^+$  364.20253. C<sub>22</sub>H<sub>26</sub>N<sub>3</sub>O<sub>2</sub> requires  $MH^+$  364.20250);  $\nu_{\max}/\text{cm}^{-1}$  3500 m, 2975 s, 1675 s, 1590 s, 1475 m, 1310 m, 1260 m, 1080 m and 1020 m;  $\delta_H$  0.79 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.59 (3H, s, CH<sub>3</sub>), 3.19 (1H, d, *J* 4.0, CHH), 3.29 (1H, d, *J* 4.0, CHH), 3.57 (1H, d, *J* 10.7, CHOH), 4.46 (1H, d, *J* 10.7, CHOH), 7.30 - 7.55 (6H, struct m, H<sub>6</sub>(Q) and CH(Ph)), 7.67 (1H, dd, *J* 1.0 and 8.2, H<sub>8</sub>(Q)), 7.74 (1H, ddd, *J* 1.2, 6.9 and

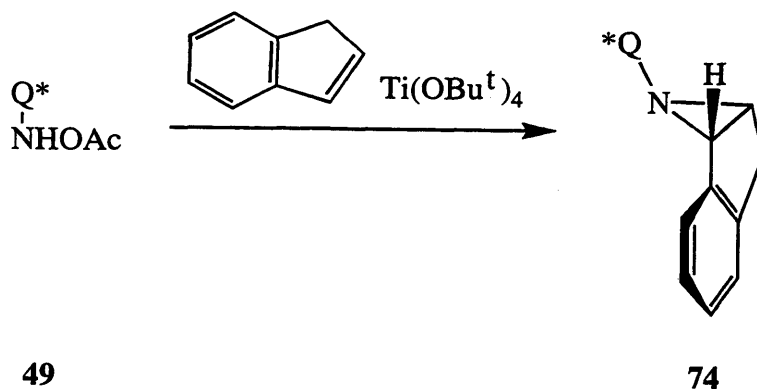
8.2,  $H_7(Q)$ ), 8.26(1H, dd,  $J$  1.2 and 7.9,  $H_5(Q)$ );  $m/z$  364 ( $MH^+$ , 100), 260 (20), 233 (31) and 215 (37).

***Aziridination of indene with Q\*NHOAc 49***



A solution of 3-acetoxyaminoquinazolinone **49** in dry dichloromethane (4 cm<sup>3</sup>) was prepared as described previously (general procedure A) from **65** (200 mg, 0.81 mmol) and LTA (377 mg, 0.85 mmol) at -20 °C and indene (0.13 cm<sup>3</sup>, 1.11 mmol) added to the stirred solution. After 2 min. the cooling bath was removed and the temperature of the solution was allowed to reach ambient. Standard work-up, described previously (general procedure B) gave a white solid (239 mg, 82%) which by NMR spectroscopy comprised a 3:1 ratio of aziridines **74** and **75** by comparison of signals at 4.09 and 4.71 ppm respectively. Signals assignable to the minor diastereoisomer were visible at  $\delta_{\text{H}}$  0.98 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 3.29 (1H, d, *J* 4.7, azir *H*  $\beta$  to CH<sub>2</sub>) and 3.88 (1H, t, *J* 5.0, azir *H*  $\alpha$  to CH<sub>2</sub>). Signals for the major diastereoisomer were identical to those given below.

**Aziridination of indene with  $Q^*NHOAc$  49 in the presence of  
titanium(IV) *tert*-butoxide**

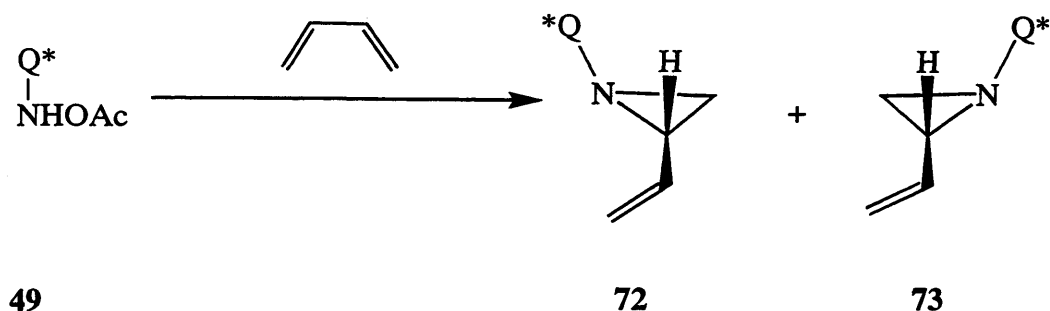


A solution of 3-acetoxyaminoquinazolinone **49** in dichloromethane (4 cm<sup>3</sup>) was prepared as described previously (general procedure A) from **65** (200 mg, 0.81 mmol) and LTA (377 mg, 0.85 mmol) and filtered dropwise but briskly through a cotton wool-plugged Pasteur pipette into a stirred solution of titanium (IV) *tert*-butoxide (548 mg, 1.62 mmol) and indene (0.13 cm<sup>3</sup>, 1.11 mmol) in dry dichloromethane (1 cm<sup>3</sup>) maintained at -20 °C. After 2 min. the cooling bath was removed and the temperature of the mixture allowed to reach ambient. Standard work-up (general procedure C) gave a white solid. Examination of the crude product by NMR spectroscopy showed it to consist of a single diastereoisomer of aziridine **74**. Crystallisation yielded aziridine 74 (251mg, 86%) as an 8:1 ratio of *N*-invertomers mp 178-180 °C (from ethanol) (Found: C, 73.0; H, 6.45; N, 11.6. C<sub>22</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub> requires C, 73.1; H, 6.4; N 11.6 %);  $\alpha_D$  228.8° (c 1.04, ethanol);  $\nu_{max}/cm^{-1}$  3500 w, 2970 m, 1680 s, 1590 s, 1470 s, 1300 m, 1230 m, 1075 m and 1020 m;  $\delta_H$  (major invertomer) 0.90 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 3.33 (1H, dd, *J* 17.9 and 5.0, CHH), 3.59 (1H, d, *J* 17.9, CHH), 3.74 (1H, d, *J* 10.6, OH), 4.09 (1H, d, *J* 5.7, aziridine *H*  $\beta$  to CH<sub>2</sub>), 4.19 (1H, pseudo t, *J* ~5.0, aziridine *H*  $\alpha$  to CH<sub>2</sub>), 5.14 (1H, d, *J* 10.6, CHOH), 7.22 - 7.37 (4H, structured m, ArH), 7.48 (1H, ddd, *J* 1.0, 6.6 and 7.9, H<sub>6</sub>(Q)), 7.60 - 7.80 (2H, structured m, H<sub>8</sub>(Q), H<sub>7</sub>(Q)) and 8.24 (1H, dd, *J* 1.0 and 7.9 H<sub>5</sub>(Q));  $\delta_C$  25.8 (C(CH<sub>3</sub>)<sub>3</sub>), 35.4 (C(CH<sub>3</sub>)<sub>3</sub>), 38.0 (CH<sub>2</sub>), 51.6, 58.3 (2 x aziridine CH), 75.3 (CHOH), 121.5 (CCO),

124.6, 125.6, 126.3, 126.6, 126.8, 126.9, 128.8, 133.9 (4 x CH(Q), 4 x CH(Ph)), 138.4, 144.1, 144.8 (2 x C(Ph), CN=C(Q)), 157.5 (C=N(Q)) and 159.3 (CO(Q)); m/z 362 (MH<sup>+</sup> 100), 307 (56) and 215 (26).

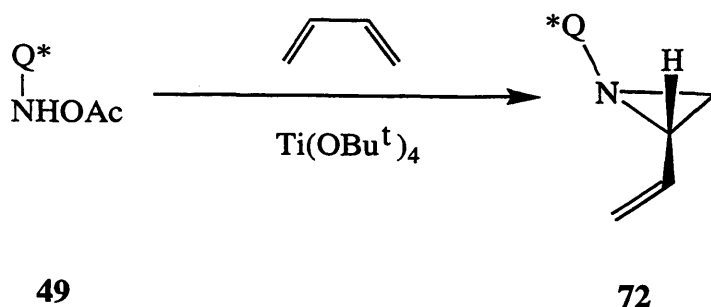
Observable signals for minor *N*-invertomer  $\delta_{\text{H}}$  1.18 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 3.38 (1H, br. s), 3.98 (1 H, s m), 4.08 (1H, d, *J* 10.4, OH), 4.87 (1H, d, *J* 4.4, H  $\beta$  to CH<sub>2</sub>), 4.97 (1H, d, *J* 10.4, CHOH), 6.86 (1H, br d, *J* 7.8), 6.99 (1H, t d, *J* 1.3, 7.5), 7.16 (1H, br t, *J* 6.9) and 7.36 (1H, s m) and  $\delta_{\text{C}}$  32.0 (CH<sub>2</sub>), 49.7 (CH), 55.8 (CH), 120.9 CCO(Q), 122.5, 128.0, 133.0 (3 x CH), 135.4, 141.2 and 157.0 (CH).

***Aziridination of 1,3-butadiene with  $Q^*NHOAc$  49***



Dichloromethane (4 cm<sup>3</sup>) was cooled to -20 °C, saturated with 1,3-butadiene and a filtered solution of 3-acetoxiaminoquinazolinone **49** in dichloromethane (4 cm<sup>3</sup>), prepared as described previously (general procedure A) from **65** (200 mg, 0.81 mmol) and LTA (377 mg, 0.85 mmol) at -20 °C added with stirring. After 2 min. the cooling bath was removed and the temperature of the solution allowed to reach ambient. Standard work-up (general procedure B) gave a colourless residue (185 mg) whose NMR spectrum showed it to comprise a 1 : 1.3 mixture of aziridine diastereoisomers **72** and **73** (76%) by integration comparison of signals at  $\delta$  2.70 and 2.51 respectively. Signals for the major diastereoisomer were visible at  $\delta$  1.03 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 2.52 (1H, dd,  $J$  1.3 and 5.3, CHH *cis* to vinyl), 2.95 (1H, dd,  $J$  1.3 and 7.9, CHH *trans* to vinyl), 3.75 (2H, struct. m, CH aziridine, OH), 5.11 (1H, d,  $J$  10.4, CHOH), 5.38 (1H, dd,  $J$  1.6 and 10.1, CH<sub>C</sub>H<sub>T</sub>=), 5.53 (1H, dd,  $J$  1.6 and 17.3, CH<sub>C</sub>H<sub>T</sub>=) and 5.82 (1H, ddd,  $J$  6.9, 10.1 and 17.3, CH=).

***Aziridination of 1,3-butadiene with  $Q^*NHOAc$  49 in the presence of  
titanium (IV) tert-butoxide***

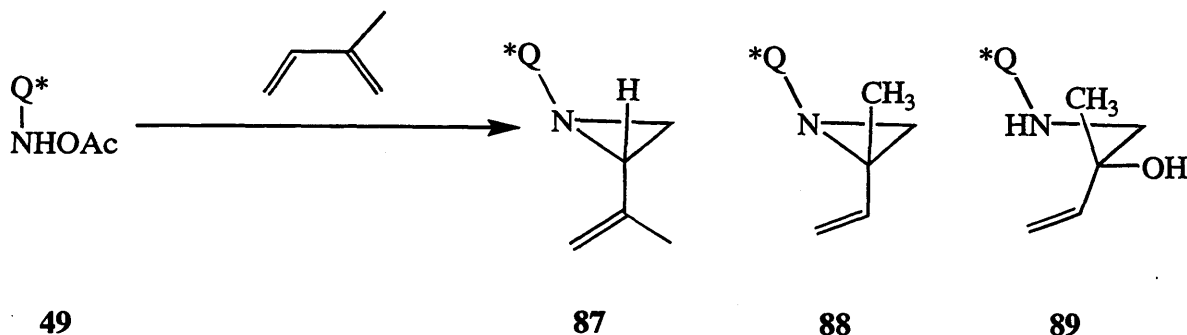


A solution of titanium (IV) *tert*-butoxide (5.50 g, 16.22 mmol) and dichloromethane (5 cm<sup>3</sup>) was cooled to -20 °C and saturated with 1,3-butadiene. A lead diacetate-freed solution of 3-acetoxyaminoquinazolinone **49** in dichloromethane (25 cm<sup>3</sup>), prepared as described previously (general procedure A) from **65** (2.0 g, 8.1 mmol) and LTA (3.77 g, 8.5 mmol) at -20 °C was then added and the resulting mixture stirred at for 2 min. before the cooling bath was removed and the temperature allowed to reach ambient. Saturated sodium hydrogen carbonate solution (30 cm<sup>3</sup>) was added to the reaction flask and the mixture stirred vigorously until a white gelatinous precipitate formed. The precipitate was filtered off and the organic layer of the filtrate separated, washed with saturated brine (2 x 20 cm<sup>3</sup>), dried and concentrated under reduced pressure to give a white crystalline solid which NMR spectroscopy showed to be a single diastereoisomer of the aziridine **72**. Crystallisation yielded 2-vinylaziridine 72 (2.05 g, 85%) mp 131-133 °C (from ethanol). (Found C, 68.0; H 7.1; N 13.9. C<sub>17</sub>H<sub>21</sub>N<sub>3</sub>O<sub>2</sub> requires C, 68.2; H 7.05; N 14.05 %);  $\alpha_D$  330.0 ° (c 1, ethanol),  $\nu_{max}/cm^{-1}$  3450 w, 3050 m, 1680 s, 1595 s, 1475 s, 1265 s and 1080 m;  $\delta_H$  1.01 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 2.70 (1H, dd,  $J$  2.6 and 5.5, CHH *cis* to vinyl), 3.14 (1H, dd,  $J$  2.6 and 7.8, CHH *trans* to vinyl), 3.27 (1H, ddd,  $J$  5.5, 7.6 and 7.8, aziridine CH), 3.72 (1H, d,  $J$  10.3, OH), 5.10 (1H, d,  $J$  10.3, CHOH), 5.41 (1H, dd,  $J$  1.7 and 9.4, CH<sub>C</sub>H<sub>T</sub>=), 5.61 (1H, dd,  $J$  1.7 and 17.2, CH<sub>C</sub>H<sub>T</sub>=), 5.72 (1H, ddd,  $J$  7.6, 9.4 and 17.2, CH=), 7.46 (1H, ddd,  $J$  1.3, 7.0 and 8.1, H<sub>6</sub>(Q)), 7.64 (1H, structured m, H<sub>8</sub>(Q)), 7.73 (1H, ddd,  $J$  1.5, 7.0 and 8.3, H<sub>7</sub>(Q)) and 8.22 (1H, structured m, H<sub>5</sub>(Q));  $\delta_C$  26.3 (C(CH<sub>3</sub>)<sub>3</sub>), 38.5

(C(CH<sub>3</sub>)<sub>3</sub>), 41.0 (CH<sub>2</sub>), 48.3 (CHC=C), 74.8 (CHOH), 120.6 (CH<sub>2</sub>=), 121.7 (CCO(Q)), 126.9, 127.1, 127.2, 134.4, 134.8 (4 x CH(Q)), CH=, 145.1 (CN=C(Q)), 158.2 (C=N(Q)) and 159.8 (CO(Q)); m/z 300 (MH<sup>+</sup>, 100) and 215 (20).



### Aziridination of isoprene with $Q^*NHOAc$ **49**



A solution of 3-acetoxyminoquinazolinone **49** in dry dichloromethane (4 cm<sup>3</sup>) was prepared as described previously (general procedure A) from **65** (200 mg, 0.81 mmol) and LTA (377 mg, 0.85 mmol) at -20 °C, and isoprene (0.16 cm<sup>3</sup>, 1.62 mmol) added to the stirred solution. After 2 min. the cooling bath was removed and the temperature of the solution was allowed to reach ambient. Standard work-up (general procedure B) gave a colourless residue whose NMR spectrum showed it to consist of aziridine **87** (10%) (1.4 : 1 mixture diastereoisomers); aziridine **88** (48%) (1 : 1.05 mixture of diastereoisomers); allylic alcohol **89** (10%) (2.3: 1 mixture of diastereoisomers) and  $Q^*H$  **90** (12%).

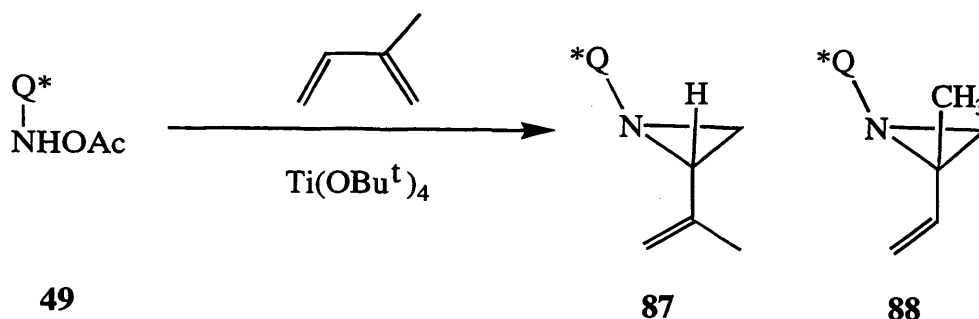
Chromatography (eluent light petroleum-ethyl acetate 2: 1) yielded aziridine **88** ( $R_f$  0.35 ) (84 mg, 33 %). Aziridine **88** (1 : 1.05 mixture of diastereoisomers) major diastereoisomer  $\delta$  1.00 (9H, s,  $C(CH_3)_3$ ), 1.67 (3H, s,  $CH_3$ ), 2.99 (1H, d,  $J$  3.7,  $CHH$ ), 3.01 (1H, d,  $J$  3.7,  $CHH$ ), 3.67 (1H, d,  $J$  10.4,  $CHOH$ ), 5.12 (1H, d,  $J$  10.4,  $CHOH$ ), 5.32 - 5.43 (3H, struct. m,  $CH_2=CH$ ), 7.46 (1H, struct. m,  $H_6(Q)$ ), 7.60 - 7.80 (2H, struct. m,  $H_8$ ,  $H_7(Q)$ ) and 8.22 (1H, struct. m,  $H_5(Q)$ ); minor diastereoisomer observable signals at 0.98 (9H, s,  $C(CH_3)_3$ ), 1.61 (3H, s,  $CH_3$ ), 2.93 (1H, d, 3.4,  $CHH$ ), 3.03 (1H, d,  $J$  3.4,  $CHH$ ), 3.64 (1H, d,  $J$  10.7,  $CHOH$ ), 5.10 (1H, d,  $J$  10.7,  $CHOH$ ), 5.40 (1H, dd,  $J$  1.0 and 10.7,  $CH_2=CH$ ), 5.50 (1H, dd,  $J$  1.0, and 17.3,  $CH_2=CH$ ), 5.79 (1H, dd,  $J$  10.7 and 17.3,  $CH=$ ), 7.46 (1H, struct. m,  $H_6(Q)$ ), 7.60 - 7.80 (2H, struct. m,  $H_8$ ,  $H_7(Q)$ ) and 8.18 (1H, struct. m,  $H_5(Q)$ ).

Aziridine **87** (1.4 :1 mixture of diastereoisomers) minor diastereoisomer observable signals at 2.59 (1H, dd,  $J$  1.2 and 7.8, CHH) and 2.85 (1 H, dd,  $J$  1.2 and 5.3, CHH). Signals for the major diastereoisomer were identical to that given below.

Further elution with the same solvent yielded allylic alcohol **89** as 2.3 : 1 mixture of diastereoisomers, ( $R_f$  0.18) (45 mg, 17 %). (Found:  $MH^+$  332.19742  $C_{18}H_{26}N_3O_3$  requires  $MH^+$  332.19742);  $\nu_{max}/cm^{-1}$  3440 m, 3300 m, 2980 m, 1660 s, 1595 s, 1475 s, 1270 m, 1235 m, 1080 m and 1020 m; major diastereoisomer  $\delta_H$  1.04 (9H, s, C(CH<sub>3</sub>)), 1.42 (3H, s, CH<sub>3</sub>), 2.84 (1H, t,  $J$  10.4, CHH), 2.90 (1H, br. s, OH), 3.26 (1H, dd,  $J$  3.8 and 10.4, CHH), 3.73 (1H, br. s, OH), 4.99 (1H, br. s, CHOH), 5.14 (1H, dd,  $J$  1.0 and 11.0, =CHC<sub>H</sub>T), 5.39 (1H, dd,  $J$  1.0 and 17.3, =CHC<sub>H</sub>T), 5.81 (1H, dd,  $J$  3.8 and 10.4, NH), 5.95 (1H, dd,  $J$  11.0 and 17.3, CH=), 7.48 (1H, struct. m,  $H_6(Q)$ ), 7.69 (1H, dd,  $J$  1.5 and 8.5,  $H_8(Q)$ ), 7.77 (1H, struct. m,  $H_7(Q)$ ), 8.22 (1H, d,  $J$  8.2,  $H_5(Q)$ );  $m/z$  332 ( $MH^+$ , 100), 260 (31), 233 (20), 215 (58) and 175 (36).

Further elution with the same solvent yielded 3-H-quinazolinone **90** (19 mg, 10 %) which crystallised as colourless plates mp 158-161 °C (from light petroleum-ethyl acetate) (Found: C 67.3, H 6.95, N 12.05.  $C_{13}H_{16}N_2O_2$  requires C 67.2, H 6.95, N 12.05 %);  $\nu_{max}/cm^{-1}$  3475 w, 2960 m, 1680 s, 1630 s, 1470 s, 1330 m, 1070 m and 1020 m;  $\delta_H$  0.99 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 4.31 (1H, s, CHOH), 7.39 (1H,  $J$  1.3, 6.9 and 7.9,  $H_6(Q)$ ), 7.58 (1H, br d,  $J$  8.2,  $H_8(Q)$ ), 7.67 (1H, ddd,  $J$  1.6, 6.9 and 8.2,  $H_7(Q)$ ), 8.17 (1H, dd,  $J$  1.2 and 7.9,  $H_5(Q)$ ) and 10.55 (1H, br s, NH);  $\delta_C$  25.9 (C(CH<sub>3</sub>)<sub>3</sub>), 36.5 (C(CH<sub>3</sub>)<sub>3</sub>), 78.8 (CHOH), 121.0 (CCO(Q)), 126.4, 126.8, 127.2, 134.8 (4 x CH(Q)), 148.2 (CN=C(Q)), 155.9 (C=N(Q)) and 162.4 (CO(Q)),  $m/z$  233 ( $MH^+$ , 100), 215 (56) and 176 (26).

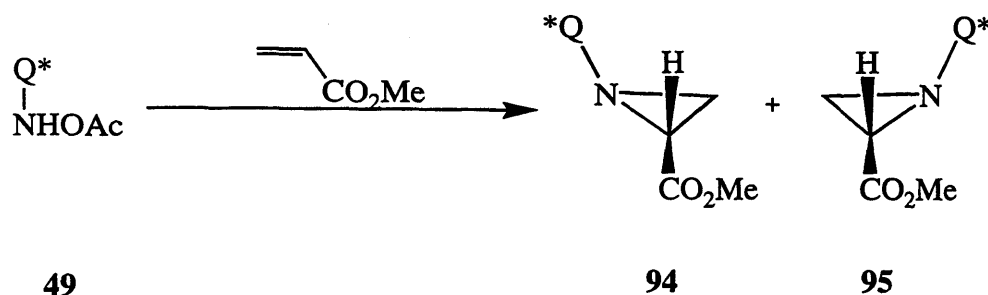
***Aziridination of isoprene with  $Q^*NHOAc$  49 in the presence of  
titanium (IV) *tert*-butoxide***



A cold solution of 3-acetoxyaminoquinazalinone **49** in dichloromethane (4 cm<sup>3</sup>) was prepared as described earlier (procedure A) from **65** (200 mg, 0.81 mmol) and LTA (377 mg, 0.85 mmol) and filtered dropwise through a cotton wool-plugged Pasteur pipette into a stirred mixture of titanium (IV) *tert*-butoxide (548 mg, 1.62 mmol) and isoprene (0.16 cm<sup>3</sup>, 1.62 mmol) in dry dichloromethane (1 cm<sup>3</sup>) maintained at -20 °C. After 2 min. the cooling bath was removed and the temperature of the reaction mixture allowed to reach ambient. Standard work-up (general procedure C) gave a white solid whose NMR spectrum showed it to be composed of a single diastereoisomer of aziridine **87** (38 %), together with aziridine **88** (30%) as a 1:1.6 ratio of diastereoisomers and 3-*tert*-butoxyaminoquinazolinone **86**, (11 %). Crystallisation yielded aziridine **87** (76 mg, 30 %) as colourless crystals mp 112-114 °C (ethanol). (Found C, 68.7; H, 7.4; N, 13.3. C<sub>18</sub>H<sub>23</sub>N<sub>3</sub>O<sub>2</sub> requires C, 69.0; H, 7.4; N, 13.4 %);  $\nu_{max}/cm^{-1}$  3060 s, 2975 w, 1680 s, 1595 s, 1470 m, 1330 w, 1310 w, 1080 m and 1020 m;  $\delta_H$  1.01 (9H, s, C(CH<sub>3</sub>)), 1.74 (3H, s, CH<sub>3</sub>), 2.77 (1H, dd  $J$  2.5 and 5.3, azir. CHH *cis* to CHMe=CH<sub>2</sub>), 3.13 (1H, dd,  $J$  2.5 and 7.9, CHH *trans* to CHMe=CH<sub>2</sub>), 3.39 (1H, dd,  $J$  5.3 and 7.9, azir. CH), 3.68 (1H, d,  $J$  10.4, OH), 5.11 (1H, d,  $J$  10.4, CHOH), 5.17 (1H, s, =CHH), 5.30 (1H, s, =CHH), 7.46 (1H, unresolved ddd,  $J$  1.3 and 8.2 visible,  $H_6(Q)$ ), 7.64 (1H, dd,  $J$  1.3 and 8.2,  $H_8(Q)$ ), 7.73 (1H, ddd,  $J$  1.2, 6.9 and 8.2,  $H_7(Q)$ ) and 8.20 (1H, dd,  $J$  1.2 and 8.2,  $H_5(Q)$ ).

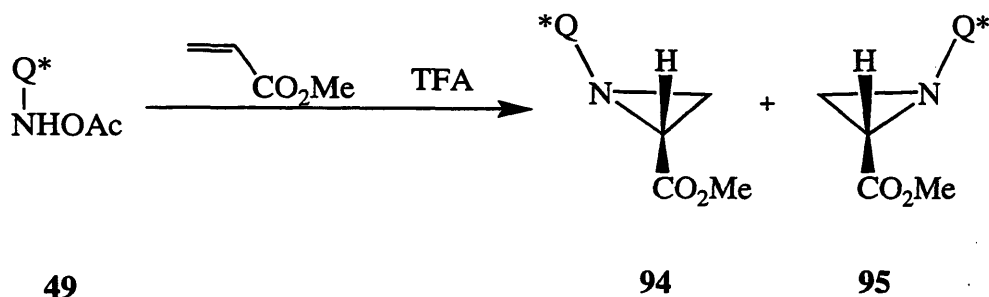
## ***Experimental for Chapter 3***

### Aziridination of methyl acrylate with $Q^*NHOAc$ **49**



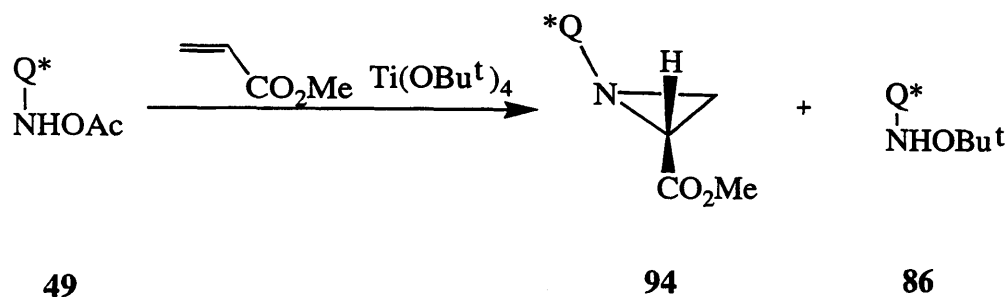
A solution of 3-acetoxyminoquinazolinone **49** in dichloromethane ( $4\text{ cm}^3$ ) was prepared as described previously (general procedure A) from **65** (200 mg, 0.81 mmol) and LTA (377 mg, 0.85 mmol) at  $-20\text{ }^\circ\text{C}$ . Methyl acrylate ( $0.1\text{ cm}^3$ , 1.1 mmol) was added and the solution stirred at  $-20\text{ }^\circ\text{C}$  for 2 min. before the cooling bath was removed and the temperature allowed to reach ambient. Standard work-up (general procedure C) gave a brown residue (199 mg) whose NMR spectrum showed it to consist of a 1 : 3 mixture of aziridine diastereoisomers **94** and **95** respectively (74%) by comparison of the signals at 2.55 and 2.68 ppm respectively (see below). Chromatography (eluent 2 : 1 light petroleum-ethyl acetate) yielded the major aziridine diastereoisomer **95** ( $R_f$  0.3)  $\delta_H$  1.03 (9H, s,  $C(CH_3)_3$ ), 2.68 (1H, d,  $J$  4.4,  $CHH$  *cis* to ester), 3.61 (1H, d,  $J$  7.2,  $CHH$  *trans* to ester), 3.83 (3H, s,  $CO_2CH_3$ ), 3.97 (1H, d,  $J$  11.0,  $OH$ ), 4.36 (1H, dd,  $J$  4.4 and 7.2,  $CHCO_2CH_3$ ), 5.18 (1H, d,  $J$  11.0,  $CHOH$ ), 7.46 (1H, ddd,  $J$  1.3, 7.0 and 7.9,  $H_6(Q)$ ), 7.65 (1H, d,  $J$  8.0,  $H_8(Q)$ ), 7.74 (1H, ddd,  $J$  1.3, 7.0 and 8.0,  $H_7(Q)$ ) and 8.16 (1H, dd,  $J$  1.3 and 7.9,  $H_5(Q)$ ). Minor diastereoisomer; see below.

***Aziridination of methyl acrylate with  $Q^*NHOAc$  **49** in the presence of trifluoroacetic acid (TFA)***



A solution of 3-acetoxyminoquinazolinone **49** in dry dichloromethane (4 cm<sup>3</sup>) was prepared as described previously (general procedure A) from **65** (200 mg, 0.81 mmol) and LTA (377 mg, 0.85 mmol) at -20 °C. The solution was filtered through a cotton wool-plugged Pasteur pipette into a stirred mixture of methyl acrylate (0.1 cm<sup>3</sup>, 1.1 mmol), TFA (0.2 cm<sup>3</sup>, 2.59 mmol) and dichloromethane (1 cm<sup>3</sup>) maintained at -20° C. After 2 min the cooling bath was removed and the temperature of the solution allowed to rise to ambient. Standard work-up (general procedure B) gave a pale brown residue (200 mg) whose NMR spectrum showed it to contain a 7 : 1 ratio of aziridines diastereoisomers **94** and **95** respectively (by comparison of the signals at  $\delta$  2.55 and 2.68 ppm respectively, see earlier).

***Aziridination of methyl acrylate with Q\*NHOAc 49 in the presence of titanium (IV) tert-butoxide***



A solution of 3-acetoxyaminoquinazolinone **49** in dichloromethane (4 cm<sup>3</sup>) was prepared as described previously (general procedure A) from **65** (200 mg, 0.81 mmol) and LTA (377 mg, 0.85 mmol) and filtered through a cotton wool-plugged Pasteur pipette into a stirred solution of titanium (IV) *tert*-butoxide (548 mg, 1.62 mmol) and methyl acrylate (0.1 cm<sup>3</sup>, 1.1 mmol) in dry dichloromethane (1 cm<sup>3</sup>) maintained at -20 °C. After 2 min. the cooling bath was removed and the temperature of the reaction mixture allowed to reach ambient. Standard work-up (general procedure C) gave a pale yellow residue whose NMR spectrum showed it consisted of aziridine **94** as a ~20:1 ratio of diastereoisomers (by comparison of the signals at  $\delta$  2.50 and 2.60 ppm respectively) together with 3-*tert*-butoxyaminoquinazolinone **86** (25%). Crystallisation of the crude product gave the aziridine diastereoisomer **94** (174 mg, 65%) mp 130-131 °C (from ethanol). (Found C, 61.95; H 6.35; N 12.55. C<sub>17</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub> requires C 61.6; H 6.4 and N 12.7 %);  $\alpha_D$  320.7 ° (c 1.16, chloroform);  $\nu_{\text{max}}/\text{cm}^{-1}$  3400 w, 2950 w, 1750 s, 1675 s, 1595, 1470 m, 1440 m and 1225 m;  $\delta_H$  1.00 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 2.55 (1H, d, *J* 4.1, CHH *cis* to ester), 3.73 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 3.80 (1H, d, *J* 10.1, OH), 3.91 (1H, d, *J* 7.23, CHH *trans* to ester), 4.18 (1H, dd, *J* 4.1 and 7.23, CHCO<sub>2</sub>CH<sub>3</sub>), 5.17 (1H, d, *J* 10.1, CHOH), 7.39 (1H, unresolved ddd, *J* 1.6 and 8.2 visible, H<sub>6</sub>(Q)), 7.59 (1H, d, *J* 7.0, H<sub>8</sub>(Q)), 7.68 (1H, ddd, *J* 1.0, 7.0 and 8.2, H<sub>7</sub>(Q)) and 8.07 (1H, dd, *J* 7.9 and 1.0, H<sub>5</sub>(Q));  $\delta_C$  25.8 (C(CH<sub>3</sub>)<sub>3</sub>), 33.3 (CH<sub>2</sub>), 36.9 (CHCO<sub>2</sub>), 37.6 (C(CH<sub>3</sub>)<sub>3</sub>), 52.5 (CO<sub>2</sub>CH<sub>3</sub>), 74.5 (CHOH), 121.4 (CCO), 126.2, 126.9, 134.5 (3 x CH(Q)), 144.8 (CN=C), 159.3 (C=N(Q)), 161.1 (CO(Q)) and 169.0 (CO<sub>2</sub>CH<sub>3</sub>) (1 CH(Q) missing); *m/z* 332 (100, MH<sup>+</sup>) and 274 (23).

***Aziridination of methyl acrylate with an acetic acid-free solution of Q\*NHOAc 49 in the presence of titanium (IV) tert-butoxide***

A solution of 3-acetoxyminoquinazolinone **49** in dichloromethane (4 cm<sup>3</sup>) was prepared as described previously (general procedure A) from **65** (200 mg, 0.81 mmol) and LTA (377 mg, 0.85 mmol) and filtered through a cotton wool-plugged Pasteur pipette. The solution was then shaken once in a separating funnel with cold (0 °C) saturated aqueous sodium hydrogen carbonate (5 cm<sup>3</sup>) and cold (0 °C) brine (5 cm<sup>3</sup>). The cold organic layer was separated and dried, keeping the temperature of the solution at ~0 °C, and then added briskly dropwise to a stirred mixture of titanium (IV) *tert*-butoxide (548 mg, 1.62 mmol) and methyl acrylate (0.1 cm<sup>3</sup>, 1.1 mmol) in dry dichloromethane (1 cm<sup>3</sup>) maintained at -20 °C. After stirring for 2 min the temperature of the reaction mixture was allowed to reach ambient. Work-up (general procedure C) gave a clear residue (98 mg). Examination of the crude product by NMR spectroscopy showed it to consist of a 3:1 mixture of aziridine diastereoisomers **94** and **95** (28%) (by comparison of the signals at  $\delta$  2.50 and 2.60 ppm respectively) together with 3-*tert*-butoxyaminoquinazolinone **86** (8%).



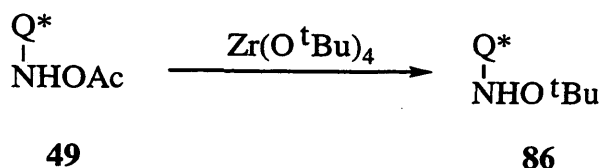
***Effect of acetic acid concentration on aziridination of methyl acrylate  
with Q\*NHOAc 49 in the presence of titanium (IV) tert-butoxide***

Three solutions of 3-acetoxylaminoquinazolinone **49** a, b and c, in dichloromethane (4 cm<sup>3</sup>), were prepared as described previously (general procedure A) from **65** (200 mg, 0.81 mmol) and LTA (377 mg, 0.85 mmol). Each solution a, b and c was filtered through a cotton wool-plugged Pasteur pipette into a stirred solution of titanium (IV) *tert*-butoxide (548 mg, 1.62 mmol) and methyl acrylate (0.1 cm<sup>3</sup>, 1.1 mmol) in dry dichloromethane (1 cm<sup>3</sup>) maintained at -20 °C, containing acetic acid 46 µl (0.81 mmol), 92 µl (1.62 mmol) and 140 µl (2.43 mmol) respectively. After 2 min. the cooling baths were removed and the temperature of each reaction mixture allowed to reach ambient. Each reaction was worked-up as described previously (general procedure C), the results are given below in Table 9.

Reaction	Equivalents of acetic acid added	Ratio of aziridine diastereoisomers	Yield (%) of aziridine	Yield (%) of <b>86</b>
a	1	>20 : 1	57	17
b	2	3 : 1	34	37
c	3	1 : 1	17	50

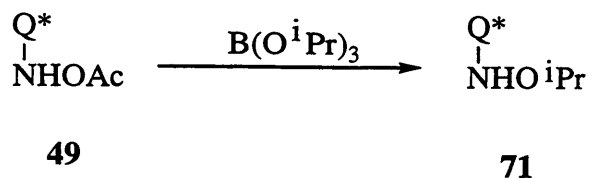
Table 9

***Attempted aziridination of methyl acrylate with Q\*NHOAc 49 in the presence of zirconium (IV) tert-butoxide***



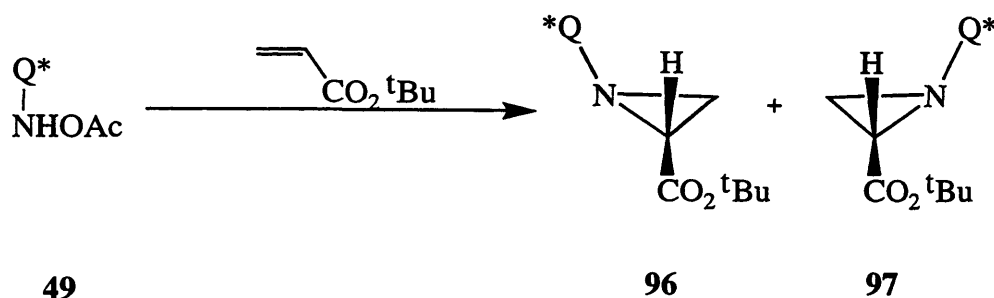
A solution of 3-acetoxyaminoquinazolinone **49** in dry dichloromethane (4 cm<sup>3</sup>) was prepared as described previously (general procedure A) from **65** (200 mg, 0.81 mmol) and LTA (377 mg, 0.85 mmol) at -20 °C. The cold solution was then filtered rapidly through a cotton wool-plugged Pasteur pipette into a solution of zirconium t-butoxide (0.53 cm<sup>3</sup>, 1.62 mmol) and methyl acrylate (0.1 cm<sup>3</sup>, 1.1 mmol) in dichloromethane stirred at -20 °C. After stirring the solution for 2 min. its temperature was allowed to reach ambient by removal of the cooling bath before it was shaken with aqueous saturated ammonium chloride (20 cm<sup>3</sup>) and the white gelatinous precipitate obtained separated. The separated organic layer was washed successively with aqueous saturated sodium hydrogen carbonate and saturated brine (2 x 5 cm<sup>3</sup>) and dried. Evaporation of solvent under reduced pressure gave **86** as a white solid (144 mg, 56 %). Crystallization yielded 3-tert-butoxyaminoquinazolinone **86** as colourless crystals (from light petroleum), mp 112-114 °C. (Found MH<sup>+</sup> 320.19740 C<sub>17</sub>H<sub>26</sub>N<sub>3</sub>O<sub>3</sub> requires MH<sup>+</sup> 320.19742);  $\nu_{\text{max}}/\text{cm}^{-1}$  2960 m, 1690 s, 1600 s, 1470 m, 1365 m, 1175 m, 1070 m and 1020 m;  $\delta_{\text{H}}$  0.91 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.27 (9H, s, OC(CH<sub>3</sub>)<sub>3</sub>), 3.65 (1H, d, *J* 9.8, OH) 5.05 (1H, d, *J* 9.8, CHOH), 7.37 (1H, unresolved ddd, *J* 1.3 and 8.2 visible, H<sub>6</sub>(Q)), 7.58 (1H, dd, *J* 7.6 and 1.3 H<sub>8</sub>(Q)), 7.66 (1H, unresolved ddd, *J* 8.2 and 1.3 visible, H<sub>7</sub>(Q)), 8.16 (1H, d, *J* 7.9, H<sub>5</sub>(Q)) and 8.78 (1H, s, NH);  $\delta_{\text{C}}$  25.8, 27.2 (2 x C(CH<sub>3</sub>)<sub>3</sub>), 37.4 (C(CH<sub>3</sub>)<sub>3</sub>), 73.9 (CHOH), 77.8 (OC(CH<sub>3</sub>)<sub>3</sub>), 120.4 (CCO(Q)), 127.0, 127.1, 127.3, 134.9 (4 x CH(Q)), 163.9 (CN=C), 157.5 (CN) and 160.8 (CO); *m/z* 320 (MH<sup>+</sup>, 22), 233 (100), 215 (31) and 160 (46).

***Attempted aziridination of methyl acrylate with Q\*NHOAc 49 in the presence of triisopropyl borate***



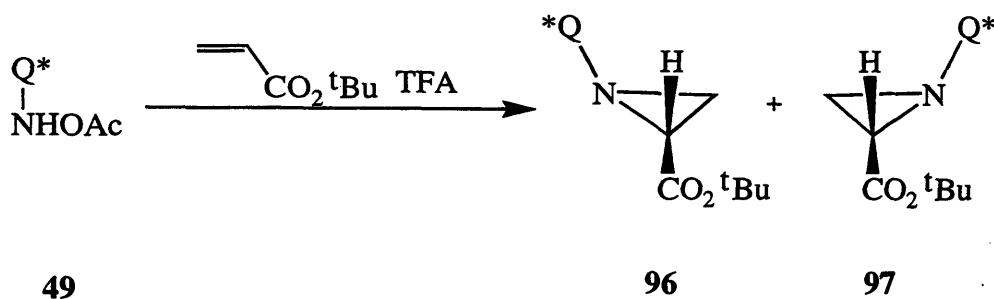
The 3-acetoxaminoquinazolinone **49** in dry dichloromethane (4 cm<sup>3</sup>) was prepared as described previously (general procedure A) from **65** (200 mg, 0.81 mmol) and LTA (377 mg, 0.85 mmol) at -20 °C. The cold solution was then filtered rapidly through a cotton wool-plugged Pasteur pipette into a solution of triisopropyl borate (304 mg, 1.62 mmol) and methyl acrylate (0.1 cm<sup>3</sup>, 1.1 mmol) in dichloromethane (1 cm<sup>3</sup>) stirred at -20 °C. After stirring the solution for 2 min. its temperature was allowed to reach ambient by removal of the cooling bath before it was shaken with aqueous saturated ammonium chloride (20 cm<sup>3</sup>) and the white gelatinous precipitate obtained separated. The separated organic layer was washed successively with aqueous saturated sodium hydrogen carbonate and saturated brine (2 x 5 cm<sup>3</sup>) and dried. Evaporation of solvent under reduced pressure gave 3-isopropoxyaminoquinazolinone **71** as a colourless residue which was not purified further (186 mg, 75%.) (Found MH<sup>+</sup> 306.18175. C<sub>16</sub>H<sub>24</sub>N<sub>3</sub>O<sub>3</sub> requires MH<sup>+</sup> 306.18177);  $\nu_{\text{max}}/\text{cm}^{-1}$  3480 m, 3230 m, 2985 m, 1690 s, 1600 s, 1470 s, 1325 m, 1065 m and 1020 m;  $\delta_{\text{H}}$  0.92 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.06 (3H, d, *J* 6.0, CH<sub>3</sub>CHCH<sub>3</sub>), 1.26 (3H, d, *J* 6.0, CH<sub>3</sub>CHCH<sub>3</sub>), 3.61 (1H, d, *J* 10.0, OH), 4.17 (1H, septet, *J* 6.0, CH(CH<sub>3</sub>)<sub>2</sub>), 5.00 (1H, d, *J* 10.0, CHOH), 7.42 (1H, unresolved ddd, *J* 1.0, 8.0 visible, H<sub>6</sub>(Q)), 7.62 (1H, dd, *J* 1.0 and 8.0, H<sub>8</sub>(Q)), 7.71 (1H, unresolved dd, *J* 1.0 and 8.0 visible, H<sub>7</sub>(Q)), 8.21 (1H, dd, *J* 1.0 and 8.0, H<sub>5</sub>(Q)) and 8.85 (1H, s, NH);  $\delta_{\text{C}}$  21.2, 21.3 (CH<sub>3</sub>CHCH<sub>3</sub>), 25.8 (C(CH<sub>3</sub>)(Q)), 36.2 (C(CH<sub>3</sub>)<sub>3</sub>), 73.7, 74.2 (CHOH, OCH(CH<sub>3</sub>)<sub>2</sub>), 120.4 (CCO(Q)), 127.0, 126.9, 126.4, 134.9 (4 x CH(Q)), 145.8 (CN=C(Q)), 157.3 (C=N(Q)) and 160.6 (CO(Q)); *m/z* 306 (MH<sup>+</sup>, 18), 233 (100), 215 (31) and 160 (41).

***Aziridination of *tert*-butyl acrylate with  $Q^*NHOAc$  49***



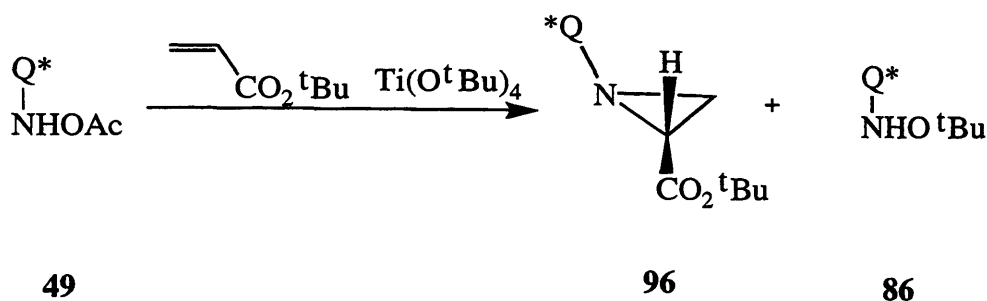
A solution of 3-acetoxyminoquinazolinone **49** in dichloromethane (4 cm<sup>3</sup>) was prepared as described previously (general procedure A) from **65** (200 mg, 0.81 mmol) and LTA (377 mg, 0.85 mmol) at -20 °C and *tert*-butyl acrylate (0.14 cm<sup>3</sup>, 0.96 mmol) added. The solution was stirred for 2 min. before the cooling bath was removed and the temperature allowed to reach ambient. Standard work-up (general procedure B) gave a brown residue (241 mg.) whose NMR spectrum showed it to consist of a 1:1.1 mixture of aziridine diastereoisomers **97** and **96** (51%), (by comparison of the integration of signals at  $\delta$  2.60 and 2.50 respectively) and 3-H-quinazolinone **90** (23%). Minor diastereoisomer observable signals  $\delta$  1.06 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.49 (9H, s, OC(CH<sub>3</sub>)<sub>3</sub>), 2.50 (1H, d,  $J$  4.1, CHH *cis* to ester), 3.76 (1H, d,  $J$  7.3, CHH *trans* to ester) and 4.44 (1H, dd,  $J$  4.1 and 7.3, CHCO<sub>2</sub>).

*Aziridination of tert-butyl acrylate with Q\*NHOAc 49 in the presence of TFA*



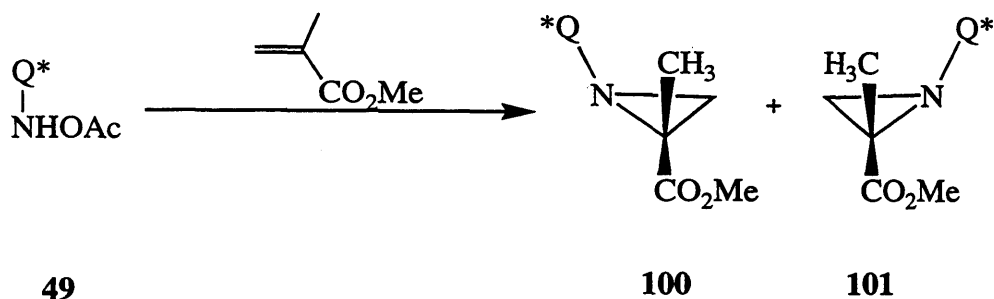
A solution of 3-acetoxyaminoquinazolinone in dichloromethane **49** (4 cm<sup>3</sup>) was prepared as described previously (general procedure A) from **65** (200 mg, 0.81 mmol) and LTA (377 mg, 0.85 mmol) at -20 °C and filtered through a cotton wool-plugged Pasteur pipette into a stirred mixture of *tert*-butyl acrylate (0.14 cm<sup>3</sup>, 0.96 mmol) and TFA (0.19 cm<sup>3</sup>, 2.46 mmol) maintained at -20 °C. After 2 min. the cooling bath was removed and the solution allowed to reach ambient temperature. Standard work-up (general procedure B) gave a brown residue (210 mg) NMR spectrum showed it to consist of a 10:1 ratio of aziridine diastereoisomers **96** and **97** (53%) by comparison of signals at 2.60 and 2.50 ppm respectively (see below), together with 3-H-quinazolinone **90** (23%).

***Aziridination of tert-butyl acrylate with Q\*NHOAc 49 in the presence  
of titanium(IV) tert-butoxide***



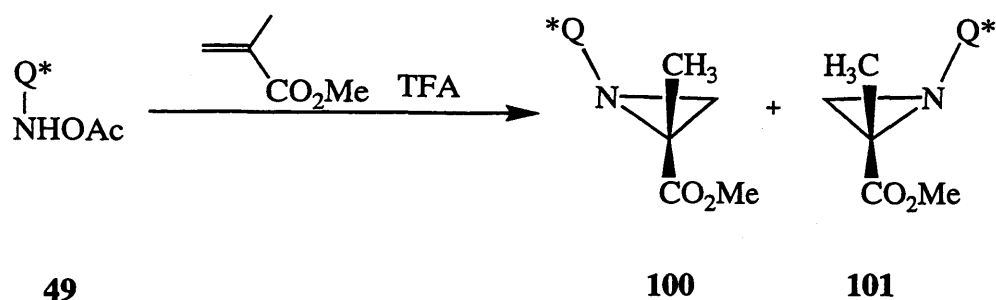
A solution of 3-acetoxyaminoquinazolinone **49** in dichloromethane (4 cm<sup>3</sup>) was prepared as described previously (general procedure A) from **65** (200 mg, 0.81 mmol) and LTA (377 mg, 0.85 mmol) and filtered through a cotton wool-plugged Pasteur pipette into a stirred solution of titanium (IV) *tert*-butoxide (548 mg, 1.62 mmol) and *tert*-butyl acrylate (0.14 cm<sup>3</sup>, 0.96 mmol) in dry dichloromethane (1 cm<sup>3</sup>) maintained at -20 °C. After stirring for 2 min. the cooling bath was removed and the temperature of the reaction mixture allowed to reach ambient. Standard work-up (general procedure C) gave a brown residue (251 mg) NMR spectrum showed it to consist of a single diastereoisomer of aziridine **96** together with 3-*tert*-butoxyaminoquinazolinone **86** (26%). Crystallization of the crude product gave the aziridine **96** (160 mg, 53%) as colourless needles, mp 156-157 °C (ethanol) (Found: C, 64.25; H, 7.3; N 11.15. C<sub>20</sub>H<sub>27</sub>N<sub>3</sub>O<sub>4</sub> requires C, 64.35; H 7.3 and N 11.25 %); α<sub>D</sub> 262.9 ° (c 1.2, chloroform); ν<sub>max</sub>/cm<sup>-1</sup> 3480 w, 2960 m, 1735 s, 1680 s, 1600 s, 1475 s, 1370 s, 1290 m, 1150 s, 1070 m and 1020 m; δ<sub>H</sub> 1.07 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.52 (9H, s, CO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>), 2.60 (1H, d, *J* 4.4 CHH *cis* to ester), 3.83 (1H, d, 7.5, CHH *trans* to ester), 4.04 (1H, dd, *J* 4.4 and 7.5, CHCO<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>), 5.22 (1H, s, CHOH), 7.45 (1H, struct. m, H<sub>6</sub>(Q)), 7.70 (2H, struct. m, H<sub>8</sub>, H<sub>7</sub>(Q)), 8.15 (1H, d, *J* 7.8, H<sub>5</sub>(Q)); δ<sub>C</sub> 26.2, 28.0 (2 x C(CH<sub>3</sub>)<sub>3</sub>), 33.7 (CH<sub>2</sub>), 37.7 (C(CH<sub>3</sub>)<sub>3</sub>), 38.8 (CHCO<sub>2</sub>), 74.7 (CHOH), 82.5 (OC(CH<sub>3</sub>)<sub>3</sub>), 121.5 (CCO(Q)), 126.3, 127.0, 127.1, 134.5 (4 x CH(Q)), 144.8 (CN=C), 159.2 (C=N(Q)), 161.0 (CO(Q)) and 167.6 (CO<sub>2</sub>.); m/z 374 (MH<sup>+</sup> 100), 318 (72), 260 (28), 215 (22), 175 (48). A crystal for X-ray structure determination was grown from ethanol and showed the absolute configuration at the aziridine ring centre to be R (Fig. 31).

***Aziridination of methyl methacrylate with  $Q^*NHOAc$  49***



Methyl methacrylate (0.11 cm<sup>3</sup>, 1.03 mmol) was added to a solution of 3-acetoxyaminoquinazolinone **49** in dichloromethane (4 cm<sup>3</sup>), prepared as described previously (general procedure A) from **65** (200 mg, 0.81 mmol) and LTA (377 mg, 0.85 mmol) at -20 °C. The solution was stirred at this temperature for a further 2 min. before being allowed to reach ambient temperature. Standard work-up (general procedure B) gave a brown residue (231 mg) whose NMR spectrum showed it consist of a 1 : 1.8 mixture of aziridine diastereoisomers **100** and **101** (79%), by comparison of signals at  $\delta$  3.05 and 2.94 ppm respectively (see below).  $\delta_H$  (major diastereoisomer) 0.93 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.68 (3H, s, CH<sub>3</sub>), 2.94 (1H, d,  $J$  3.0, CHH), 3.47 (1H, d,  $J$  3.0, CHH), 3.51 (1H, d,  $J$  10.1, OH), 3.56 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 4.49 (1H, d,  $J$  10.1, CHOH), 7.38 (1H, struct. m,  $H_6(Q)$ ), 7.61 (2H, struct. m,  $H_7, H_8(Q)$ ) and 8.16 (1H, dd,  $J$  1 and 7.9,  $H_5(Q)$ ).

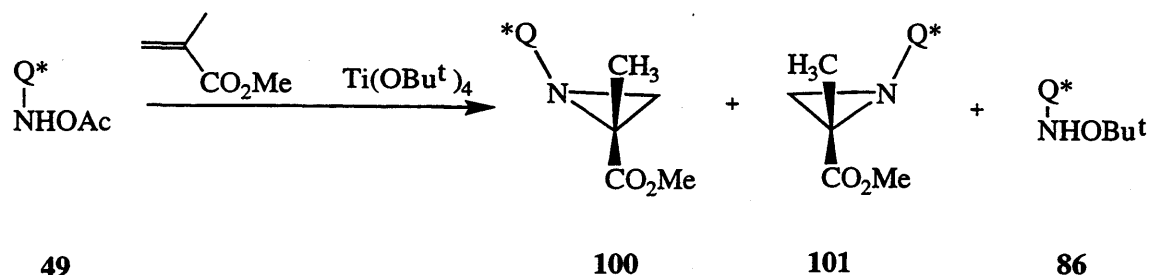
***Aziridination of methyl methacrylate with Q\*NHOAc 49 in the presence of TFA***



A solution of 3-acetoxyaminoquinazolinone **49** in dichloromethane (4 cm<sup>3</sup>) was prepared as described previously (general procedure A) from **65** (200 mg, 0.81 mmol) and LTA (377 mg, 0.85 mmol) and filtered through a cotton wool-plugged Pasteur pipette into a stirred solution of TFA (0.2 cm<sup>3</sup>, 2.59 mmol) and methyl methacrylate (0.11 cm<sup>3</sup>, 1.03 mmol) in dry dichloromethane (1 cm<sup>3</sup>) maintained at -20 °C. After stirring for 2 min. the cooling bath was removed and the temperature of the reaction mixture allowed to reach ambient. Standard work-up (general procedure B) gave a brown residue (240 mg) whose NMR spectrum showed it to consist of a 2.3:1 mixture of aziridine diastereoisomers **100** and **101** (79%), by comparison of signals at  $\delta$  3.05 and 2.94 ppm respectively together with 3-H-quinazolinone **90** (17%).

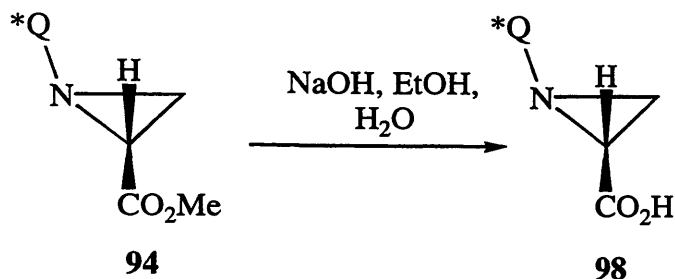


***Aziridination of methyl methacrylate with Q\*NHOAc 49 in the presence of titanium(IV) tert-butoxide***



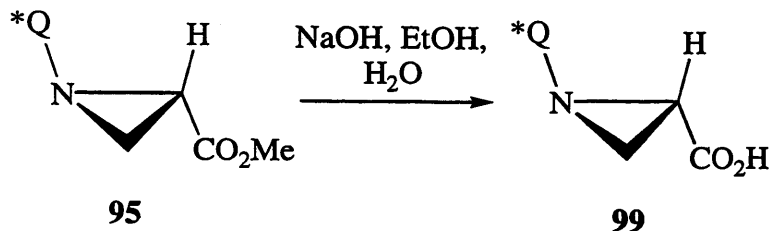
A solution of 3-acetoxyaminoquinazolinone **49** in dichloromethane (4 cm<sup>3</sup>) was prepared as described above from **65** (200 mg, 0.81 mmol) and LTA (377 mg, 0.85 mmol) and filtered through a cotton wool plugged Pasteur pipette into a stirred solution of titanium (IV) *tert*-butoxide (548 mg, 1.62 mmol), methyl methacrylate (0.11 cm<sup>3</sup>, 1.03 mmol) and dry dichloromethane (1 cm<sup>3</sup>) stirring at -20 °C. After stirring for 2 min. the cooling bath was removed and the reaction mixture allowed to reach ambient. Standard work-up (general procedure C) gave a pale brown residue (193 mg) whose NMR spectrum showed it to consist of a 5.9 : 1 ratio of aziridine diastereoisomers **100** and **101** (43%) together with 3-*tert*-butoxyaminoquinazolinone **86** (28%). Crystallization of the crude product gave the major diastereoisomer as colourless crystals, mp 169-171 °C (from ethanol). (Found C, 62.5; H, 6.7; N 12.1. C<sub>18</sub>H<sub>23</sub>N<sub>3</sub>O<sub>4</sub> requires C, 62.6; H 6.7; N 12.2 %);  $\alpha_D$  262.1 ° (c 1.03, ethanol);  $\nu_{\max}/\text{cm}^{-1}$  3400 w, 2950 w, 1740 s, 1675 s, 1590 s, 1475 m, 1330, m, 1170 m and 1080 m;  $\delta_H$  (1.3 : 1 ratio of *N*-invertomers, major *N*-invertomer) 0.91 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.35 (3H, s, CH<sub>3</sub>), 3.06 (1H, d, *J* 3.1, CHH), 3.35 (1H, d, *J* 3.1, CHH), 3.66 (1H, d, *J* 10.4, OH), 3.77 (3H, s, CO<sub>2</sub>CH<sub>3</sub>), 4.57 (1H, d, *J* 10.4, CHOH), 7.74 to 7.14 (3H, struct. m, H<sub>6</sub>,H<sub>8</sub>,H<sub>7</sub>(Q)) and 8.13 (1H, dd, *J* 1.2 and 8.5, H<sub>5</sub>(Q)); *m/z* 346 (MH<sup>+</sup>, 100) , 288 (20) and 259 (20). A crystal for X-ray structure determination was grown from ethanol and showed the absolute configuration at the aziridine ring centre to be R (Fig. 32).

### Hydrolysis of aziridine methyl ester 94



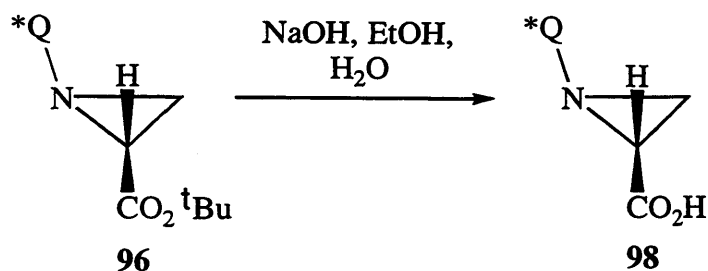
Aziridine **94** (150 mg, 0.45 mmol) was suspended in a rapidly stirred solution of 1:1 ethanol-water (4 cm<sup>3</sup>) and sodium hydroxide (18 mg, 0.45 mmol) in water (1 cm<sup>3</sup>) added. The aziridine gradually dissolved and after 15 min. the clear solution was extracted with ethyl acetate (3 x 5 cm<sup>3</sup>), the aqueous solution acidified with dilute sulphuric acid and the resulting white suspension extracted with ethyl acetate (3 x 5 cm<sup>3</sup>). The combined organic extracts were dried and the solvent removed under reduced pressure to give the aziridine 2-carboxylic acid **98** (126 mg, 88%) as a colourless oil. (Found  $MH^+$  318.14540 C<sub>16</sub>H<sub>20</sub>N<sub>3</sub>O<sub>4</sub> requires  $MH^+$  318.14538);  $\nu_{\max}/\text{cm}^{-1}$  3450 w, 2960 w, 1670 s, 1595 s, 1470 s, 1230 m, 1080 m and 1020 m;  $\delta_{\text{H}}$  1.08 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 2.63 (1H, d,  $J$  3.8, CHH *cis* to acid), 4.05 (1H, d,  $J$  7.5, CHH *trans* to acid), 4.09 (1H, dd,  $J$  3.8 and 7.5, CHCO<sub>2</sub>H), 5.38 (1H, s, CHOH), 6.70 (2H, br s, CO<sub>2</sub>H, OH), 7.45 (1H, br. ddd,  $J$  7 and 8 visible,  $H_6(\text{Q})$ ), 7.70 (2H, struct. m,  $H_8$ ,  $H_7(\text{Q})$ ) and 8.14 (1H, br d,  $J$  7.8,  $H_5(\text{Q})$ );  $m/z$  635 ((2MH<sup>+</sup>)<sup>+</sup>, 49), 318 (MH<sup>+</sup>, 100), 215 (34) and 175 (45).

### Hydrolysis of aziridine methyl ester **95**



The diastereoisomeric aziridine methyl ester **95** (150 mg, 0.45 mmol) was hydrolysed under identical conditions to those conditions above to give aziridine 2-carboxylic acid **99** (127 mg, 88%.) (Found:  $\text{MH}^+$  318.14539  $\text{C}_{16}\text{H}_{20}\text{N}_3\text{O}_4$  requires  $\text{MH}^+$  318.14538);  $\delta_{\text{H}}$  1.04 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 2.74 (1H, br d,  $J$  3.5,  $\text{CHH}$  *trans* to acid), 3.59 (1H, d,  $J$  7.3,  $\text{CHH}$  *cis* to acid), 4.23 (1H, br s,  $\text{CHCO}_2\text{H}$ ), 5.12 (1H, br s,  $\text{CHOH}$ ), 6.52 (2H, br s, 2 x OH), 7.48 (1H, br t,  $J$  7.6,  $H_6(\text{Q})$ ), 7.66 (1H, br d,  $J$  ~7.5,  $H_8(\text{Q})$ ), 7.75 (1H, br t,  $J$  ~7.5,  $H_7(\text{Q})$ ) and 8.17 (1H, d,  $J$  7.6,  $H_5(\text{Q})$ );  $\delta_{\text{C}}$  26.0 ( $\text{C}(\text{CH}_3)_3$ ), 35.3 ( $\text{CH}_2$ ), 37.4 ( $\text{C}(\text{CH}_3)_3$ ), 38.0 ( $\text{CHCO}_2\text{H}$ ), 76.6 ( $\text{CHOH}$ ), 120.9 ( $\text{CCO}(\text{Q})$ ), 126.1, 126.6, 127.0, 134.4 (4 x  $\text{CH}(\text{Q})$ ), 144.5 ( $\text{CN}=\text{C}(\text{Q})$ ), 157.5 ( $\text{C}=\text{N}(\text{Q})$ ), 160.8 ( $\text{CO}(\text{Q})$ ) and 171.2 ( $\text{CO}_2\text{H}$ );  $m/z$  635 ( $((2\text{M}+\text{H})^+$ , 9), 318 ( $\text{MH}^+$ , 100) and 260 (20).

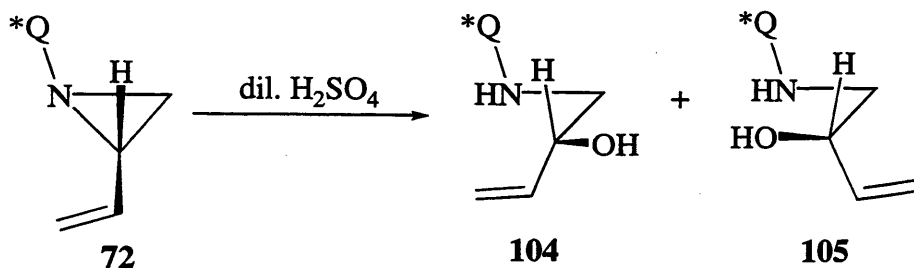
***Hydrolysis of aziridine tert-butyl ester 96***



Aziridine **96** (150 mg, 4.02 mmol) was suspended in a solution of 1:1 ethanol/water (4 cm<sup>3</sup>) and a solution of sodium hydroxide (16 mg, 4.02 mmol) in water (1 cm<sup>3</sup>) added. After stirring for 5 days at room temperature the solution was extracted with ethyl acetate (3 x 5 cm<sup>3</sup>), the aqueous solution acidified with dilute sulphuric acid and re-extracted with ethyl acetate (3 x 5 cm<sup>3</sup>). The combined organic extracts were dried and solvent removed under reduced pressure to give acid **98** (72 mg, 56%) identical with that prepared previously by comparison of their NMR spectra.

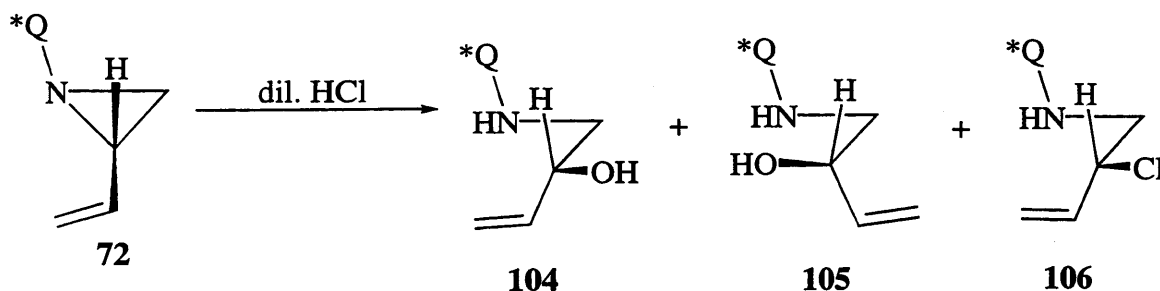
## ***Experimental for Chapter 4***

***Ring-opening of 2-vinylaziridine 72 with dilute sulphuric acid***



Aziridine **72** (50 mg, 0.167 mmol) was dissolved in 1,4-dioxane (1 cm<sup>3</sup>) and dilute sulphuric acid (1 cm<sup>3</sup>, 0.2 mol.dm<sup>-3</sup>) was added. After 15 min. the reaction solution was poured into saturated sodium hydrogen carbonate (5 cm<sup>3</sup>) and extracted with ethyl acetate (3 x 3 cm<sup>3</sup>). The combined organic extracts were dried and solvent removed under reduced pressure to give a clear residue (50 mg.) By NMR spectroscopy this residue comprised a 3 : 1 mixture of allylic alcohol diastereoisomers **104** and **105** (94 %), by comparison of the signals at  $\delta$  4.11 and 4.32 ppm respectively. (For NMR spectra of individual diastereoisomers, see later).

***Ring-opening of 2-vinylaziridine 72 with dilute hydrochloric acid***

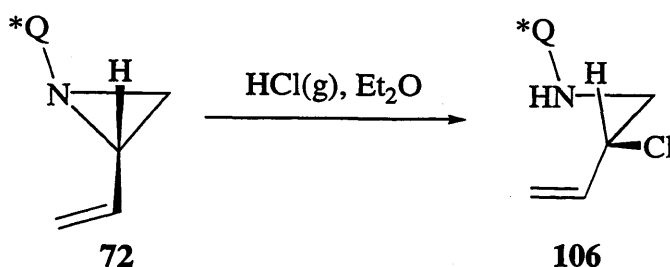


Aziridine **72** (147 mg, 0.492 mmol) was dissolved in 1,4-dioxane (4 cm<sup>3</sup>) and dilute hydrochloric acid (3 cm<sup>3</sup>, 0.2 mol.dm<sup>-3</sup>) added. After stirring for 15 min. the reaction was poured into saturated sodium hydrogen carbonate (5 cm<sup>3</sup>) and extracted with ethyl acetate (3 x 5 cm<sup>3</sup>). The organic extracts were combined, dried and solvent removed under reduced pressure to give a clear oil. Chromatography (eluent 2 : 1 light petroleum-ethyl acetate) yielded the allylic chloride **106** (R<sub>f</sub> 0.33), (32 mg, 20%)

(Found:  $MH^+$  336.14790  $C_{17}H_{23}ClN_3O_2$  requires  $MH^+$  336.14788,  $\alpha_D$  165.0 ° (c 1.0, ethanol),  $\nu_{max}/cm^{-1}$  3480 w, 3380 w, 2960 m, 1675 s, 1590 s, 1470 m, 1265 m, 1180 m, 1080 m, and 1020 m,  $\delta_H$  1.03 (9H, s,  $C(CH_3)_3$ ), 3.11 (1H, struct. m,  $CHH$ ), 3.62 (2H, struct. m,  $CHH$ ,  $OH$ ), 4.58 (1H, struct. m,  $CHCl$ ), 5.04 (1H, br. s,  $CHOH$ ), 5.32 (1H, d,  $J$  10.1,  $H_T H_C$ ), 5.46 (1H, d,  $J$  17.0,  $H_T H_C$ ), 5.64 (1H, dd,  $J$  4.1 and 9.8,  $NH$ ), 6.03 (1H, ddd,  $J$  7.9, 10.1 and 17.0,  $=CH$ ), 7.49 (1H, struct. m,  $H_6(Q)$ ), 7.69 (1H, d,  $J$  7.2,  $H_8(Q)$ ), 7.77 (1H, struct. m,  $H_7(Q)$ ) and 8.25 (1H, dd,  $J$  1.0 and 8.2,  $H_5(Q)$ );  $\delta_C$  25.8 ( $C(CH_3)_3$ ), 37.7 ( $C(CH_3)_3$ ), 55.9 ( $CH_2$ ), 59.0 ( $CHCl$ ), 74.2 ( $CHOH$ ), 118.9 ( $CH_2=$ ), 120.5 ( $CCO(Q)$ ), 126.5, 126.9, 127.3, 134.6, 135.3 (4 x  $CH(Q)$ ),  $CH=$ ), 145.8 ( $CN=C(Q)$ ), 158.1 ( $C=N(Q)$ ) and 161.0 ( $CO(Q)$ );  $m/z$  336 ( $MH^+$ , 100), 278 (20) and 215 (20).

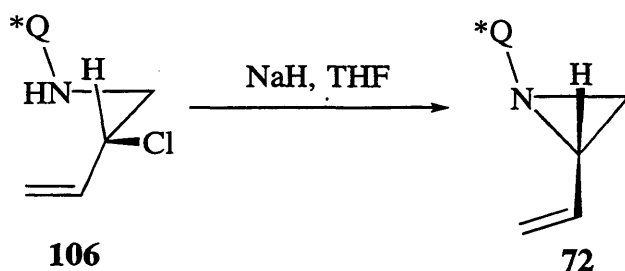
Further elution with the same solvent gave the allylic alcohol diastereoisomers **104** and **105** ( $R_f$  0.13) as a 3 : 1 mixture (69 mg, 46%) identical with that isolated previously.

***Ring-opening of 2-vinylaziridine 72 with a solution of hydrogen chloride gas in ether***



A suspension of aziridine **72** (93 mg, 0.31 mmol) was stirred rapidly in sodium-dried ether (5 cm<sup>3</sup>) whilst hydrogen chloride gas was slowly bubbled into the mixture. the suspended solid dissolved before a white solid rapidly precipitated. The reaction solution was neutralised by careful addition of excess saturated sodium hydrogen carbonate, and the organic layer separated, dried, and the solvent removed to give allylic chloride **106** (101 mg, 97%).

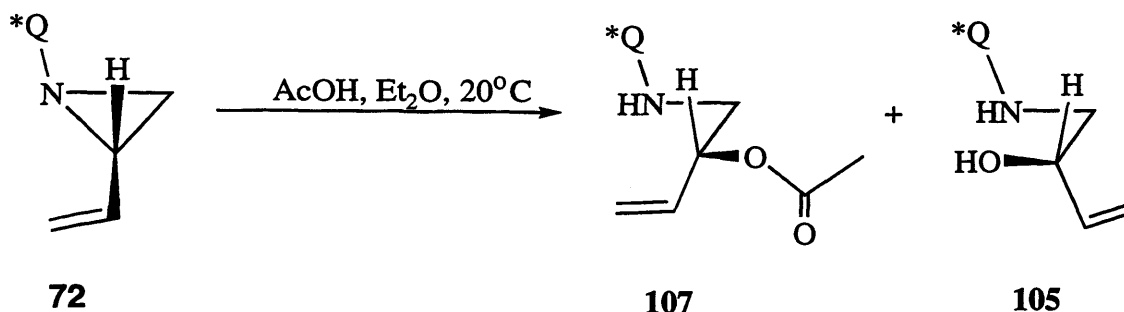
***Re-conversion of chloride 106 to aziridine 72***



To a solution of chloride **72** (175 mg, 0.52 mmol) in THF (2 cm<sup>3</sup>) was added sodium hydride (23 mg of a 60% dispersion in oil, 0.57 mmol) and the reaction stirred for 45 min. After addition of water (5 cm<sup>3</sup>) the solution was extracted with ethyl acetate (3 x 5 cm<sup>3</sup>), the organic extracts dried and solvent removed under reduced pressure to give aziridine **72** (123 mg, 79%).



### Ring-opening of 2-vinylaziridine **72** with acetic acid

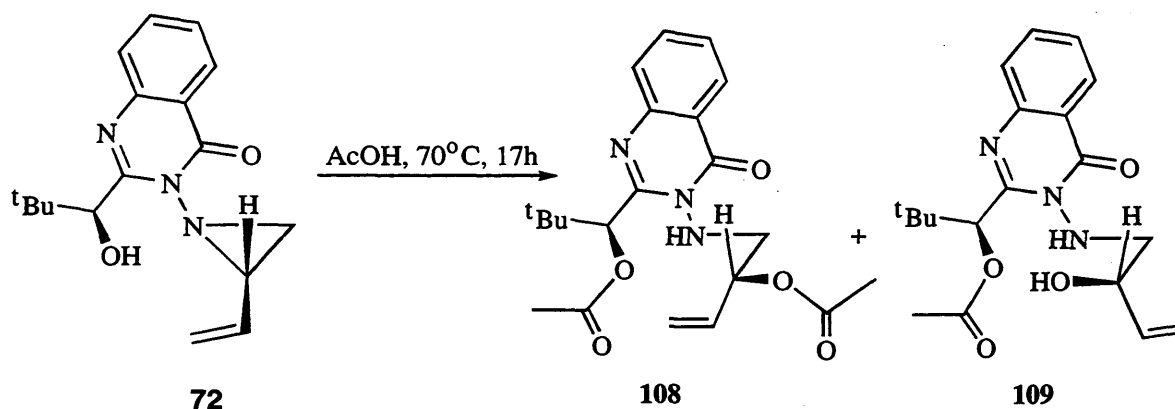


Aziridine **72** (50 mg, 0.17 mmol) was dissolved in diethyl ether (2 cm<sup>3</sup>) and glacial acetic acid (0.5 cm<sup>3</sup>) added. After 48 h. the reaction mixture was neutralised by the careful addition of excess saturated sodium hydrogen carbonate, extracted with diethyl ether (3 x 5 cm<sup>3</sup>), and the combined ether extracts dried and concentrated under reduced pressure. Chromatography (3:2 light petroleum-ethyl acetate) yielded allylic acetate **107** (*R<sub>f</sub>* 0.38), (13 mg, 22%) (Found: *MH*<sup>+</sup> 360.19236. C<sub>19</sub>H<sub>26</sub>N<sub>3</sub>O<sub>4</sub> requires *MH*<sup>+</sup> 360.19233);  $\nu_{\text{max}}/\text{cm}^{-1}$  3480 w, 3290 w, 2950 m, 1745 s, 1650 s, 1590 s, 1470 m, 1370 m, 1235 s, 1080 m and 1020 m;  $\delta_{\text{H}}$  0.94 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 2.10 (3H, s, COCH<sub>3</sub>), 2.90 (1H, struct. m, CHH), 3.40 (1H, unresolved ddd, *J* 4 and 8 visible, CHH), 3.57 (1H, br d, *J* 7.5, OH), 4.89 (1H, d, *J* 7.5, CHOH), 5.24 (1H, dd, *J* 10.7 and 1.0, H<sub>C</sub>H<sub>T</sub>C=), 5.32 (1H, dd, *J* 17.0 and 1.0, H<sub>C</sub>H<sub>T</sub>C=), 5.45 (1H, struct. m, CHOAc), 5.51 (1H, dd, *J* 4.0 and 10.4, NH), 5.82 (1H, ddd, *J* 5.9, 10.7 and 17.0, CH=), 7.43 (1H, ddd, *J* 1.0, 6.9 and 8.2, H<sub>6</sub>(Q)), 7.62 (1H, dd, *J* 1.0 and 8.2, H<sub>8</sub>(Q)), 7.71 (1H, ddd, *J* 1.6, 6.9 and 8.2, H<sub>7</sub>(Q)) and 8.18 (1H, dd, *J* 1.6 and 8.2, H<sub>5</sub>(Q));  $\delta_{\text{C}}$  21.0 (COCH<sub>3</sub>), 25.8 (C(CH<sub>3</sub>)<sub>3</sub>), 37.6 (C(CH<sub>3</sub>)<sub>3</sub>), 53.3 (CH<sub>2</sub>), 71.9, 74.3 (CHOH, CHOAc), 118.3 (CH<sub>2</sub>=), 120.5 (CCO(Q)), 126.5, 126.8, 127.2, 133.4, 134.5 (4 x CH(Q), CH=), 145.9 (CN=C), 158.2 (C=N(Q)) 161.1 (CO(Q)) and 169.9 (COCH<sub>3</sub>); *m/z* 360 (*MH*<sup>+</sup> 100) 215 (53) and 175 (37).

Further elution gave the allylic alcohol **105** (*R<sub>f</sub>* 0.22), 10 mg, 19%. (Found: *MH*<sup>+</sup> 318.18177 C<sub>17</sub>H<sub>24</sub>N<sub>3</sub>O<sub>3</sub> requires *MH*<sup>+</sup> 318.18177);  $\delta_{\text{H}}$  0.96 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 2.95 (1H, struct. m, CHH), 3.08 (1H, ddd, *J* 3.8, 8.8 and 12.0, CHH), 4.32 (1H, struct. m, CHOHCH<sub>2</sub>), 5.00 (1H, br s, Bu<sup>t</sup>CHOH), 5.13 (1H, d, *J* 10.7, H<sub>C</sub>H<sub>T</sub>C=), 5.32 (1H, d, *J* 17.3, H<sub>C</sub>H<sub>T</sub>C=), 5.73 (1H, dd, *J* 3.8, 10.4, NH), 5.80 (1H, ddd, *J* 5.0, 10.7 and 17.3,

CH=), 7.42 (1H, unresolved ddd,  $J \sim 8$  visible,  $H_6(Q)$ ), 7.63 (1H, d,  $J$  7.9,  $H_8(Q)$ ), 7.71 (1H, unresolved ddd,  $J \sim 8.2$  visible,  $H_7(Q)$ ) and 8.18 (1H, d,  $J$  8.2,  $H_5(Q)$ );  $\delta_C$  25.9 ( $C(CH_3)_3$ ), 37.6 ( $C(CH_3)_3$ ), 55.9 ( $CH_2$ ), 70.2 ( $CHOHC=$ ), 74.4 ( $CHOHC(CH_3)_3$ ), 116.0 ( $CH_2=$ ), 120.3 ( $CCO(Q)$ ), 126.5, 126.7, 127.2, 134.4 (4 x  $CH(Q)$ ), 137.8 ( $CH=$ ), 146.0 ( $CN=C(Q)$ ),  $C=N(Q)$ ) and 171.1 ( $CO(Q)$ );  $m/z$  318 ( $MH^+$ , 100), 260 (20), 215 (42) and 147 (31).

### Ring-opening of 2-vinylaziridine **72** with hot glacial acetic acid

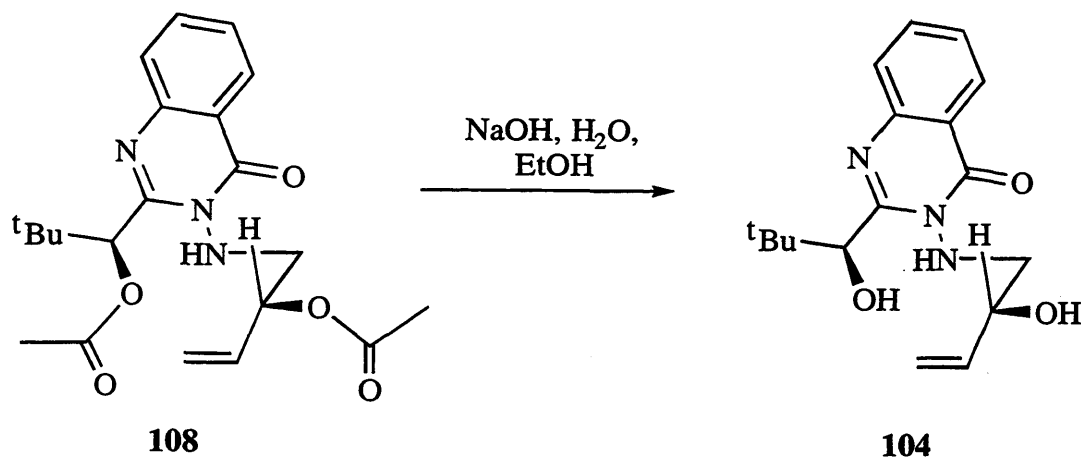


Aziridine **72** (100 mg, 0.33 mmol) was dissolved in glacial acetic ( $2\text{ cm}^3$ ) and heated at  $70^\circ\text{C}$  for 17 h. After evaporating the bulk of the acetic acid under reduced pressure, the residue dissolved in ethyl acetate ( $5\text{ cm}^3$ ) and remaining acetic acid neutralised with excess aqueous saturated sodium hydrogen carbonate. The organic layer was separated, washed with saturated brine ( $1\text{ cm}^3$ ), dried and solvent removed under reduced pressure. Chromatography (2 : 1 light petroleum-ethyl acetate) yielded diacetate **108**, ( $R_f$  0.35) (90 mg, 67%) which crystallised as a colourless solid mp  $118\text{--}121^\circ\text{C}$  (from light petroleum-ethyl acetate). (Found: C, 62.8; H, 6.8; N 10.45.  $C_{21}H_{27}N_3O_5$  requires C, 62.8; H, 6.8 and N 10.5 %);  $\alpha_D$   $154.0^\circ$  (c 1.03, ethanol);  $\nu_{\max}/\text{cm}^{-1}$  3050 m, 1740 s, 1680 s, 1595 s, 1470 m, 1370 s, 1230 s, 1080 m and 1025 m;  $\delta_H$  1.00 (9H, s,  $C(CH_3)_3$ ), 2.09 (3H, s,  $COCH_3$ ), 2.11 (3H, s,  $COCH_3$ ), 3.46 (2H, struct. m,  $CH_2$ ), 5.23 (1H, dd,  $J$  1.0 and 10.4,  $H_{CH_2C=}$ ), 5.32 (1H, dd,  $J$  1.0 and 17.3,  $H_{CH_2C=}$ ), 5.50 (2H, struct. m, NH,  $CHOAc$ ), 5.85 (1H,  $Bu^tCHOAc$ ), 5.90 (1H, ddd,  $J$  5.7, 10.4 and 17.3,  $CH=$ ), 7.39 (1H, ddd,  $J$  3.1, 5.7 and 8.0,  $H_6(Q)$ ); 7.65 (2H, struct.

m,  $H_7$ ,  $H_8(Q)$ ) and 8.16 (1H, d,  $J$  8.0,  $H_5(Q)$ );  $\delta_C$  20.9, 21.2 (2 x  $COCH_3$ ), 26.1 ( $C(CH_3)_3$ ), 35.9 ( $C(CH_3)_3$ ), 51.9 ( $CH_2$ ), 72.2, 76.5 (2 x  $CHOCO$ ), 117.8 ( $CH_2=$ ), 120.9 ( $CCO(Q)$ ), 126.4, 126.8, 127.9, 134.0, 134.3 (4 x  $CH(Q)$ ,  $CH=$ ), 146.6 ( $CN=C(Q)$ ), 154.2 ( $C=N(Q)$ ), 161.3 ( $CO(Q)$ ), 170.0 and 171.3 (2 x  $CO_2CH_3$ );  $m/z$  402 ( $MH^+$  100), 342 (47), 302 (43), 215(92) and 175 (27). A crystal was grown from light petroleum-ethyl acetate for X-ray structure determination (Fig. 33).

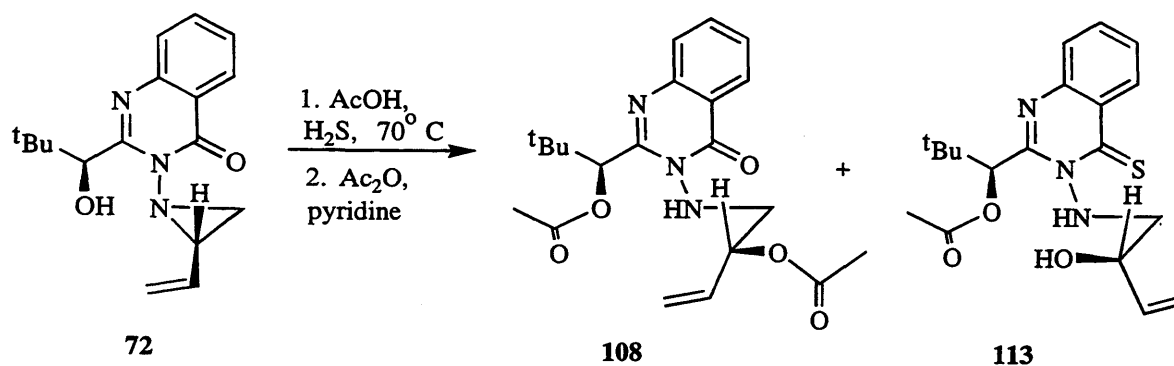
Further elution with the same solvent gave acetoxo allylic alcohol 109 ( $R_f$  0.22), (9 mg, 7 %). (Found:  $MH^+$  360.19228.  $C_{19}H_{26}N_3O_4$  requires  $MH^+$  360.19233);  $\nu_{max}/cm^{-1}$  3450 w, 3295 w, 2960 m, 1740 s, 1680 s, 1590 s, 1470 m, 1370 m, 1250 s, 1075 m and 1025 m;  $\delta_H$  1.10 (9H, s,  $C(CH_3)_3$ ), 2.18 (3H, s,  $COCH_3$ ), 3.22 (1H, ddd,  $J$  3.8, 8.5 and 11.7,  $CHH$ ), 3.45 (1H, ddd,  $J$  3.5, 10.0 and 11.7,  $CHH$ ) 4.43 (1H, struct. m,  $CHOH$ ), 5.19 (1H, ddd,  $J$  1.3, 1.6 and 10.7,  $H_C H_T C=$ ), 5.41 (1H, ddd,  $J$  1.3, 1.6 and 17.3,  $H_C H_T C=$ ), 5.70 1H, dd,  $J$  3.8 and 10.0,  $NH$ ), 5.93 (1H, ddd,  $J$  5.0, 10.7 and 17.3,  $CH=$ ), 6.11 (1H, s,  $Bu^tCHOCOCH_3$ ), 7.48 (1H, struct. m,  $H_6(Q)$ ), 7.74 (2H, struct. m,  $H_7$ ,  $H_7(Q)$ ) and 8.24 (1H, d,  $J$  7.9,  $H_5(Q)$ );  $m/z$  360 ( $MH^+$ , 100), 302 (39), 215 (73) and 175 (28).

### Hydrolysis of diacetate **108**



Di-acetate **108** (50 mg, 0.125 mmol) was dissolved in 1,4-dioxane (1 cm<sup>3</sup>), sodium hydroxide solution (2 cm<sup>3</sup>, 2.0 moldm<sup>-3</sup>) added and the resulting solution left to stand overnight. The solution was then diluted with ethyl acetate (3 cm<sup>3</sup>), washed with water (2 cm<sup>3</sup>) then brine (2 cm<sup>3</sup>), dried and evaporated under reduced pressure gave allylic alcohol **104**, (34 mg, 86%), (Found: MH<sup>+</sup> 318.18175. C<sub>17</sub>H<sub>24</sub>N<sub>3</sub>O<sub>3</sub> requires MH<sup>+</sup> 318.18177);  $\nu_{\max}/\text{cm}^{-1}$  3450 m, 3290 m, 2950 m, 1675 s, 1590 s, 1470 s, 1265 m, 1080 m, 1020 m and 740 m;  $\delta_{\text{H}}$  1.03 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 2.97 (1H, struct. m, CHH), 3.23 (1H, ddd, *J* 3.5, 7.2 and 10.8, CHH), 3.69 (2H, br s, 2 x OH), 4.25 (1H, struct. m, CHCH=), 5.03 (1H, br s, CHOH), 5.20 (1H, dd, *J* 1.3 and 11.7, CH<sub>C</sub>H<sub>T</sub>=), 5.34 (1H, dd, *J* 1.3 and 17.3, CH<sub>C</sub>H<sub>T</sub>=), 5.88 (2H, struct. m, CH=, NH), 7.49 (1H, ddd, *J* 1.3, 6.9, 8.0, H<sub>6</sub>(Q)), 7.70 (1H, br d, *J* ~8, H<sub>8</sub>(Q)), 7.78 (1H, ddd, *J* 1.0, 6.9, 8.2, H<sub>7</sub>(Q)) and 8.25 (1H, dd, *J* 1.0 and 8.2, H<sub>5</sub>(Q));  $\delta_{\text{C}}$  25.9 (C(CH<sub>3</sub>)<sub>3</sub>), 37.8 (C(CH<sub>3</sub>)<sub>3</sub>), 56.1 (CH<sub>2</sub>), 69.7, 74.6, (2 x CHOH), 116.4 (CH<sub>2</sub>=), 120.3 (CCO(Q)), 126.7, 126.9, 127.3, 134.7, 137.2 (4 x CH(Q), CH=), 146.1 (CN=C(Q)), 158.3 (C=N(Q)) and 162.1 (CO(Q)), *m/z* 318 (MH<sup>+</sup>, 100), 260 (20), 215 (42) and 147 (30).

**Ring-opening of 2-vinylaziridine 72 in acetic acid in the presence of  
hydrogen sulphide**

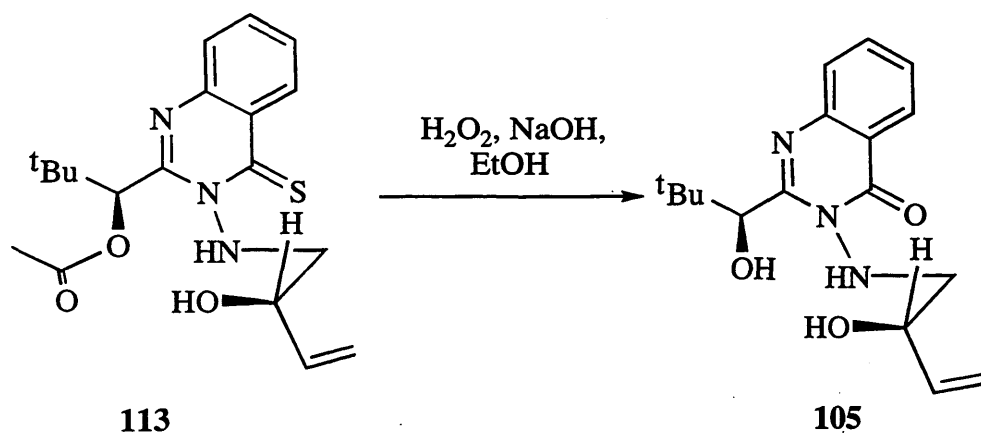


The aziridine **72** (100 mg, 0.33 mmol) was dissolved in acetic acid (2 cm<sup>3</sup>) saturated with hydrogen sulphide and the resulting solution heated at 70 °C for 17 h. After cooling the bulk of the acetic acid was removed by evaporation under reduced pressure and residual acid neutralised by addition of excess aqueous saturated sodium hydrogen carbonate. The solution was extracted with ethyl acetate (3 x 5 cm<sup>3</sup>) and the combined organic extracts washed with brine (5 cm<sup>3</sup>), dried and evaporated under reduced pressure. The resulting colourless oil was dissolved in pyridine (2 cm<sup>3</sup>), acetic anhydride (0.1 cm<sup>3</sup>, 1.06 mmol) added and the solution left to stand overnight at room temperature. After addition of saturated aqueous sodium hydrogen carbonate (5 cm<sup>3</sup>) the solution was extracted with ethyl acetate (3 x 5 cm<sup>3</sup>), the combined organic fractions washed with brine (5 cm<sup>3</sup>), dried and the solvent removed under reduced pressure. Chromatography (eluent 4 : 1 light petroleum-ethyl acetate) yielded quinazolin-4-thione di-acetate 113 (*R<sub>f</sub>* 0.31), (33 mg, 24%). (Found: *MH*<sup>+</sup> 418.18008. C<sub>21</sub>H<sub>28</sub>N<sub>3</sub>O<sub>4</sub>S requires *MH*<sup>+</sup> 418.18005);  $\nu_{\max}/\text{cm}^{-1}$  2960 m, 1740 s, 1590 s, 1470 s, 1370 s, 1240 s and 1025 s;  $\delta_{\text{H}}$  1.01 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 2.09 (3H, s, COCH<sub>3</sub>), 2.10 (3H, s, COCH<sub>3</sub>), 3.40 (1H, ddd, *J* 4.1, 11.6 and 11.6, CHH), 3.66 (1H, ddd, *J* 4.4, 7.2, 11.6, CHH), 5.23 (1H, d, *J* 10.7, H<sub>C</sub>H<sub>T</sub>C=), 5.34 (1H, d, *J* 17.3, H<sub>C</sub>H<sub>T</sub>C=), 5.54 (1H, s m, CHOCOCH<sub>3</sub>), 5.83 (1H, ddd, *J* 5.7, 10.7, 17.3, CHC=), 6.05 (1H, s, CHC(CH<sub>3</sub>)), 6.88 (1H, dd, *J* 4.4, 11.6, NH), 7.44 (1H, ddd, *J* 2.2, 6.0, 8.2, H<sub>6</sub>(Q)), 7.67 (2H, s m, H<sub>7</sub>, H<sub>8</sub>(Q)) and 8.60 (1H, d, *J* 8.5, H<sub>5</sub>(Q));  $\delta_{\text{C}}$  20.9, 21.1 (2 x CH<sub>3</sub>), 26.1 (C(CH<sub>3</sub>)<sub>3</sub>), 36.5 (C(CH<sub>3</sub>)<sub>3</sub>), 49.8 (CH<sub>2</sub>), 72.5, 77.3 (2 x CHO), 117.9 (CH<sub>2</sub>=), 128.3, 128.5 (2 x

CH(Q)), 128.7 CCS(Q)), 130.9, 133.6, 134.4 (2 x CH(Q), CH=), 141.7 (CN=C(Q)), 153.3 (C=N(Q)), 170.2, 171.3 (2 x CO) and 186.3 (CS(Q)); m/z 418 (MH<sup>+</sup>, 83), 358 (77), 305 (24), 291 (48), 231 (100), 215 (32) and 191 (36).

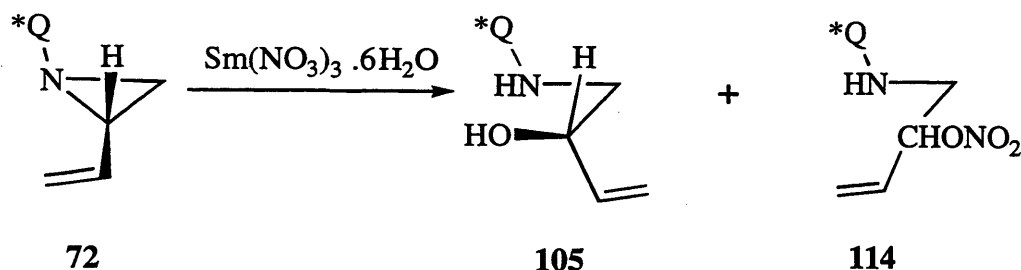
Further elution with the same solvent yielded quinazolin-4-one di-acetate **108** (R<sub>f</sub> 0.18) 67 mg, 50% identical to an authentic sample prepared previously by comparison of the NMR spectra.

***Conversion of quinazolin-4-thione di-acetate 113 to quinazolin-4-one diol 105***



The quinazolin-4-thione **113** (12 mg, 0.029 mmol) was dissolved in a mixture of ethanol (0.5 cm<sup>3</sup>) and sodium hydroxide solution (0.5 cm<sup>3</sup>, 1.0 mol.dm<sup>-3</sup>) and hydrogen peroxide (20 volume, 3 drops) added. After 30 min. the solution was extracted with ethyl acetate (10 cm<sup>3</sup>), the organic layer separated and washed successively with water (2 x 5 cm<sup>3</sup>) and brine (5 cm<sup>3</sup>), then dried and evaporated to give quinazolin-4-one diol **105** 5 mg, 55 %, identical by comparison of its NMR spectrum with that of an authentic sample prepared previously.

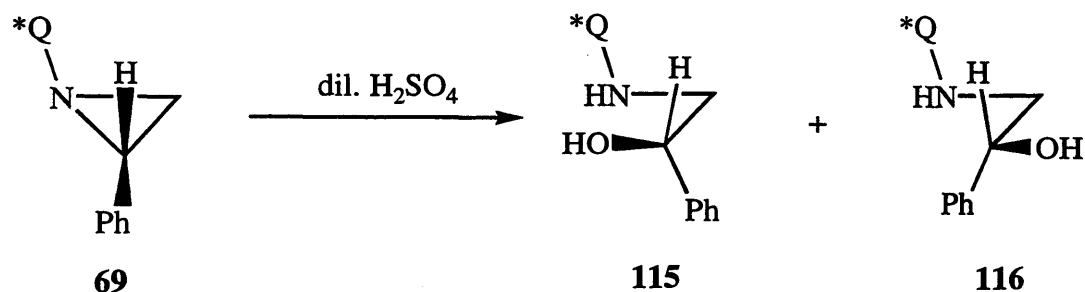
**Ring-opening of 2-vinylaziridine 72 with samarium nitrate  
hexahydrate**



The aziridine **72** (300 mg, 1.00 mmol.) was heated at 60 °C for 50 min. in acetonitrile (4 cm<sup>3</sup>) containing samarium nitrate hexahydrate (446 mg, 1.00 mmol). Water (5 cm<sup>3</sup>) was then added and the solution extracted with ethyl acetate (10 cm<sup>3</sup>). The organic layer was separated, washed with brine, dried and concentrated. Chromatography (eluent 5 : 2 light petroleum-ethyl acetate) yielded nitrate ester **114** as an oil ( $R_f$  0.30) (26 mg, 7 %). (Found:  $MH^+$  363.16681.  $\text{C}_{17}\text{H}_{23}\text{N}_4\text{O}_5$  requires  $MH^+$  363.16685);  $\delta_H$  0.93 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 3.03 (1H, struct. m,  $\text{CHH}$ ), 3.47 (2H, struct. m,  $\text{CHOH}$ ,  $\text{CHH}$ ), 5.38 (1H, d,  $J$  10.7,  $\text{H}_\text{C}\text{H}_\text{T}\text{C}=\text{}$ ), 5.46 (1H, d,  $J$  17.3,  $\text{H}_\text{C}\text{H}_\text{T}\text{C}=\text{}$ ), 5.55 (1H, s m,  $\text{CHONO}_2$ ), 5.80 (1H, ddd,  $J$  6.6, 10.7, 17.3,  $\text{CH}=\text{}$ ), 7.43 (1H, ddd,  $J$  1.0, 6.9, 8.1,  $\text{H}_6(\text{Q})$ ), 7.63 (1H, br. d,  $J \sim 8$ ,  $\text{H}_8(\text{Q})$ ), 7.71 (1H, ddd,  $J$  1.0, 6.9, 8.5,  $\text{H}_7(\text{Q})$ ) and 8.18 (1H, dd,  $J$  1.0, 8.1,  $\text{H}_5(\text{Q})$ );  $m/z$  363 ( $MH^+$ , 100), 260 (33), 233 (52), 215 (47) and 176 (96).

Further elution with the same solvent yielded a mixture of allylic alcohols **104** and **105** ( $R_f$  0.1) (242 mg, 76 %) in a 1:13 ratio by comparison of the signals at  $\delta$  4.11 and 4.32 ppm respectively with those of authentic samples.

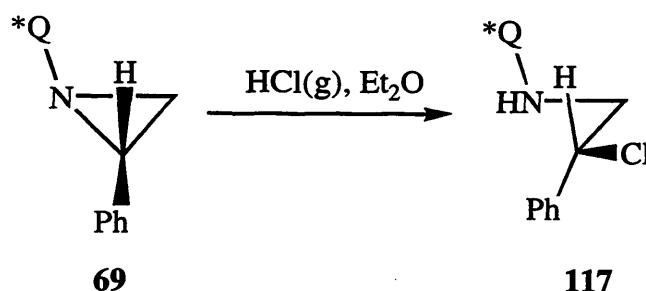
***Ring-opening of styrene-derived aziridine 69 with dilute sulphuric acid***



Aziridine **69** (100 mg, 0.28 mmol) was dissolved in 1,4-dioxane (1 cm<sup>3</sup>) and dilute sulphuric acid (1 cm<sup>3</sup>, 0.2 mol dm<sup>-3</sup>) added. After 15 min. the reaction mixture was shaken with saturated sodium hydrogen carbonate (5 cm<sup>3</sup>), extracted with ethyl acetate (3 x 5 cm<sup>3</sup>), the combined organic extracts dried and the solvent evaporated under reduced pressure to give a clear oil (101 mg) comprising a mixture of benzylic alcohol diastereoisomers **115** and **116**, (1.4 : 1), (96%), by integral comparison of the signals at  $\delta$  4.72 and 4.87 ppm respectively in its NMR spectrum. Signals for the minor diastereoisomer were visible at 0.94 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 4.87 (1H, dd,  $J$  3.4 and 9.0, NH), 4.95 (1H, br. s, Bu<sup>t</sup>CHOH) and 8.17 (1H, dd,  $J$  1.4 and 8.1, H<sub>5</sub>(Q)). (For signals due to the major diastereoisomer see later).

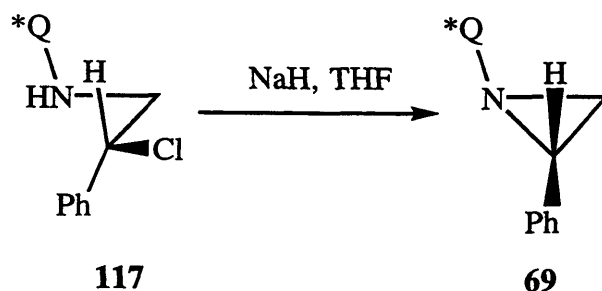


***Ring-opening of styrene-derived aziridine **69** with a solution of hydrogen chloride in ether***



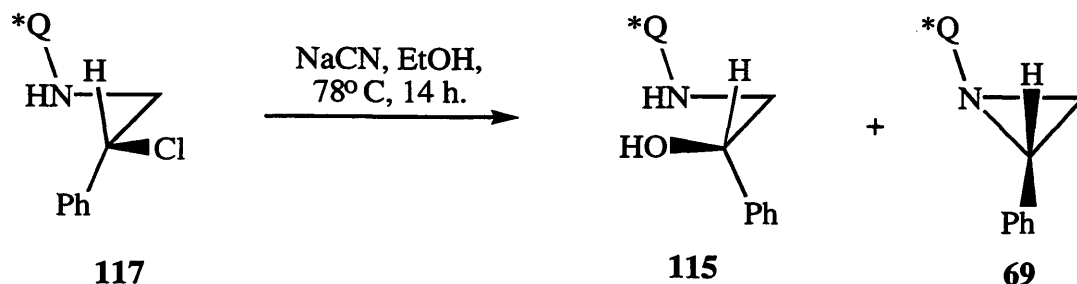
Hydrogen chloride gas was slowly bubbled into the a rapidly stirred solution of aziridine **69** (500 mg, 1.43 mmol) in diethyl ether (10 cm<sup>3</sup>) for 20 s and a white solid was immediately precipitated. The reaction mixture was carefully washed with excess saturated aqueous sodium hydrogen carbonate, the organic layer separated, dried and evaporated under reduced pressure to give a crystalline solid. Crystallisation gave chloride **117** as a colourless solid (388 mg, 70%) mp 153-155 °C (ethanol). (Found: C, 65.65; H 6.3; N 10.9. C<sub>21</sub>H<sub>24</sub>ClN<sub>3</sub>O<sub>2</sub> requires C, 65.55; H, 6.25 and N 10.9 %);  $\alpha_D$  126.0 ° (c 1.0, chloroform),  $\nu_{\text{max}}/\text{cm}^{-1}$  3500 w, 3280 w, 2950 m, 1640 s, 1590 s, 1465 s, 1320 m, 1170 m, 1070s and 1015 m;  $\delta_H$  (400 MHz) 0.95 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 3.22 (1H, struct. m, CHH), 3.59 (1H, d, *J* 10.2, OH), 3.84 (1H, struct. m, CHH), 4.91 (1H, d, *J* 10.2, CHOH), 5.09 (1H, dd, *J* 6.0 and 7.0, CHCl), 5.31 (1H, dd, *J* 4.6 and 9.8, NH), 7.29 - 7.53 (6H, struct. m, H<sub>6</sub>(Q), 5 x CH(Ph)), 7.67 (1H, br. d, *J* 7.0, H<sub>8</sub>(Q)), 7.75 (1H, ddd, *J* 1.5, 7.0 and 8.1, H<sub>7</sub>(Q)) and 8.22 (1H, dd, *J* 1.5 and 8.0, H<sub>5</sub>(Q)); *m/z* 386 (MH<sup>+</sup>, 100) and 215 (26).

***Re-conversion of chloride 117 to aziridine 69 with sodium hydride***



The chloride **117** (100 mg, 0.26 mmol) was dissolved in dry THF (2 cm<sup>3</sup>) and sodium hydride (31 mg of a 60% dispersion in oil, 0.77 mmol) added. After stirring at room temperature for 70 min. the reaction was quenched with ice/water and extracted with ethyl acetate (3 x 5 cm<sup>3</sup>). The combined organic fractions were separated, dried and solvent evaporated to give aziridine **69** (90 mg, 99%).

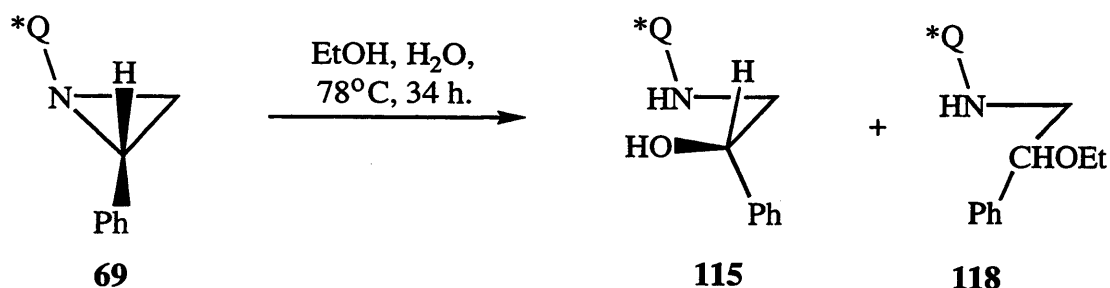
*Attempted displacement of chloride in 117 by cyanide*



Chloride **117** (100 mg, 0.26 mmol) and sodium cyanide (38 mg, 0.78 mmol) were heated together in ethanol (2 cm<sup>3</sup>) under reflux for 14h. After cooling the reaction mixture was diluted with ethyl acetate (5 cm<sup>3</sup>), washed with water (3 cm<sup>3</sup>), then saturated brine (3 cm<sup>3</sup>), dried and concentrated. Chromatography (eluent 4 : 1 light petroleum-ethyl acetate) gave aziridine **69** (*R<sub>f</sub>* 0.46) (57 mg, 63%), identical with an authentic sample.

Further elution with 2 : 1 light petroleum-ethyl acetate gave alcohol **115** (*R<sub>f</sub>* 0.1) (25 mg, 26%) as colourless crystals mp 125-128 °C (from 2 : 1 light petroleum-ethyl acetate). (Found: C, 68.75; H, 6.8; N, 11.4. C<sub>21</sub>H<sub>25</sub>N<sub>3</sub>O<sub>3</sub> requires C, 68.65; H, 6.85 and N 11.45 %);  $\nu_{\text{max}}/\text{cm}^{-1}$  3600 w, 3420 w, 3300 w, 2960 m, 1675 s, 1590 s, 1470 m, 1330 m, 1175 m, 1075 m and 1020 m.  $\delta_{\text{H}}$  0.90 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 2.86 (1H, d, *J* 4.7, CHOHPH), 3.01 (1H, struct. m, CHH), 3.30 (1H, struct. m, CHH), 3.54 (1H, d, *J* 10.4, CHOH), 4.83 (1H, struct. m, CHPh), 4.91 (1H, d, *J* 10.4, CHOH), 5.73 (1H, dd, *J* 3.7 and 9.4, NH), 7.09 to 7.30 (5H, struct. m, 5 x CH(Ph)), 7.36 (1H, ddd, *J* 1.2, 6.9 and 8.2, *H*<sub>6</sub>(Q)), 7.56 (1H, br d, *J* ~7, *H*<sub>8</sub>(Q)), 7.65 (1H, ddd, *J* 1.0, 6.9 and 8.2, *H*<sub>7</sub>(Q)) and 8.12 (1H, dd, *J* 1.0 and 8.2, *H*<sub>5</sub>(Q)); *m/z* 368 (MH<sup>+</sup>, 100), 260 (24), 215 (22) and 175 (20).

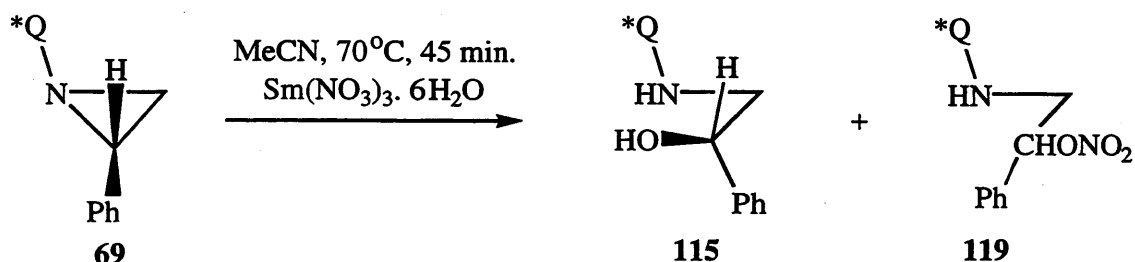
**Ring-opening of aziridine **69** by ethanol/water**



Aziridine **69** (50 mg, 0.14 mmol) was heated in a mixture of ethanol (2 cm<sup>3</sup>) and water (2 drops) under reflux for 34 h. The reaction mixture was cooled, diluted with ethanol (5 cm<sup>3</sup>), dried and evaporated under reduced pressure. Chromatography (eluent 2 : 1 light petroleum-ethyl acetate) gave the ether **118** (*R<sub>f</sub>* 0.35), (14 mg, 25%). (Found: *MH*<sup>+</sup> 396.22873. C<sub>23</sub>H<sub>30</sub>N<sub>3</sub>O<sub>3</sub> requires *MH*<sup>+</sup> 396.22872);  $\nu_{\text{max}}/\text{cm}^{-1}$  3375 w, 3290 w, 2975 m, 1680 s, 1595 s, 1470 ,1265 w, 1075 m and 1020 w;  $\delta_{\text{H}}$  (400 MHz) 0.90 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.21 (3H, t, *J* 7.0, CH<sub>3</sub>), 3.09 (1H, br s, CHH), 3.49 (3H, struct. m, CH<sub>2</sub>CH<sub>3</sub>, OH), 3.72 (1H, br. s, CHH), 4.54 (1H, dd, *J* 3.7 and 6.2, CHPh), 4.72 (1H, d, *J* 10.0, CHOH), 5.68 (1H, dd, *J* 4.8 and 8.5, NH), 7.35 (5H, s m, 5 x CH(Ar)), 7.46 (1H, br dd, *J* ~8 and ~8, H<sub>6</sub>(Q)), 7.66 (1H, d, *J* 7.5, H<sub>8</sub>(Q)), 7.74 (1H, ddd, *J* 1.3, 7.5 and 8.4, H<sub>7</sub>(Q)) and 8.24 (1H, dd, *J* 1.3 and 8.1, H<sub>5</sub>(Q));  $\delta_{\text{C}}$  15.3 (CH<sub>3</sub>), 25.9 (C(CH<sub>3</sub>)<sub>3</sub>), 37.5 (C(CH<sub>3</sub>)<sub>3</sub>), 53.4, 56.3 (2 x CH<sub>2</sub>), 74.4 (CHOH), 79.7 (CHPh), 120.7 (CCO(Q)), 126.6, 126.7, 127.3, 127.9, 128.5, 134.4 (6 x CH(Ph), Q), 139.9 (C(Ph)), 146.1 (CN=C), 158.4 (C=N(Q)) and 161.4 (CO(Q)); *m/z* 396 (100 *MH*<sup>+</sup>), 260 (39) and 215 (50).

Further elution with the same solvent gave alcohol **115** (*R<sub>f</sub>* 0.1) (25 mg, 48 %) identical to that isolated previously.

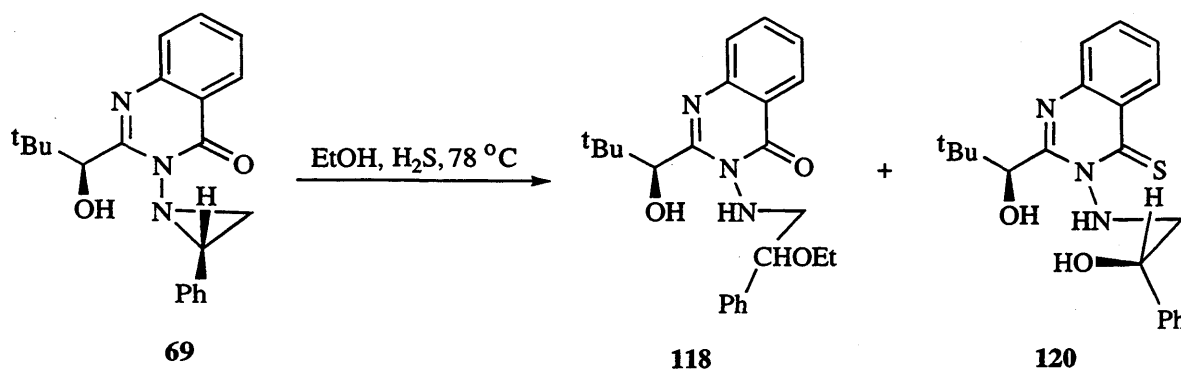
**Ring-opening of aziridine **69** with samarium nitrate hexahydrate**



The aziridine **69** (100 mg, 0.28 mmol) was heated at 60 °C for 50 min in acetonitrile (1 cm<sup>3</sup>) containing samarium nitrate hexahydrate (127 mg, 0.28 mmol). Water (5 cm<sup>3</sup>) was added and the solution extracted with ethyl acetate (5 cm<sup>3</sup>), the organic layer separated, washed with brine, dried and evaporated under reduced pressure. Chromatography (eluent 4 : 1 light petroleum-ethyl acetate) yielded nitrate ester **119** (9 mg, 8%). (Found:  $\text{MH}^+$  413.18257.  $\text{C}_{21}\text{H}_{25}\text{N}_4\text{O}_5$  requires  $\text{MH}^+$  413.18250);  $\delta_{\text{H}}$  0.90 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 3.25 (1H, s m, CHH), 3.45 (1H, d,  $J$  10.4, OH), 3.59 (1H, s m, CHH), 4.82 (1H, d,  $J$  10.4, CHOH), 5.57 (1H, dd,  $J$  5.3 and 8.2, CHPh), 5.99 (1H, dd,  $J$  3.8 and 8.5, NH), 7.61 (5H, s m, 5 x CH(Ph)), 7.43 (1H, s m,  $\text{H}_6(\text{Q})$ ), 7.70 (2H, s m,  $\text{H}_7, \text{H}_8(\text{Q})$ ) and 8.17 (1H, dd,  $J$  1.2, 7.8,  $\text{H}_5(\text{Q})$ );  $m/z$  413 ( $\text{MH}^+$ , 100), 260 (35), 233 (33), 215 (48), 176 (100) and 147 (71).

Further elution with the same solvent yielded benzylic alcohol **115** (72 mg, 68%), identical by comparison of its NMR spectrum with that of an authentic sample obtained previously.

**Ring-opening of aziridine **69** in ethanol containing hydrogen sulphide**

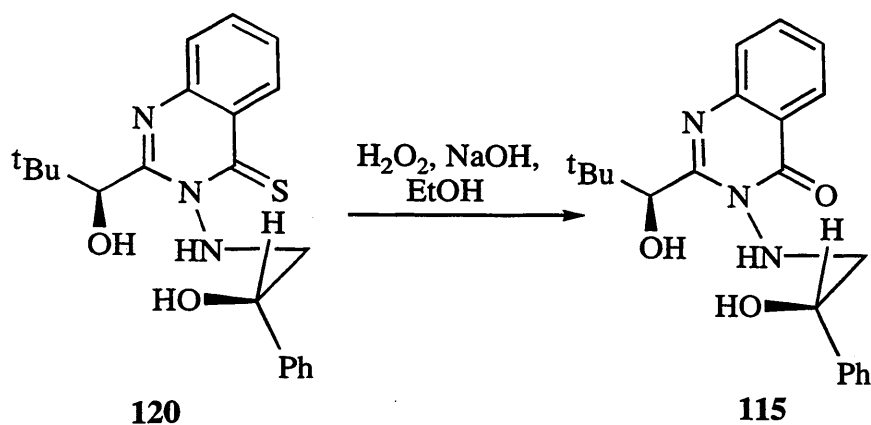


A Young's tube was charged with aziridine **69** (100 mg, 0.29 mmol) dissolved in ethanol (4 cm<sup>3</sup>). The solution was saturated with hydrogen sulphide and heated under reflux for 94 h before being evaporated under reduced pressure. Chromatography (eluent 3.5:1 light petroleum-ethyl acetate) yielded ether **118** (*R<sub>f</sub>* 0.38) (39 mg, 34 %), identical to a sample prepared previously by comparison of their NMR spectra.

Further elution with the same solvent yielded quinazolin-4-thione diol **120** (*R<sub>f</sub>* 0.25) as a yellow oil, (51 mg, 46 %). (Found: *MH*<sup>+</sup> 384.17457. C<sub>21</sub>H<sub>26</sub>N<sub>3</sub>O<sub>2</sub>S requires *MH*<sup>+</sup> 384.17457);  $\nu_{\text{max}}/\text{cm}^{-1}$  3450 s, 2960 s, 3025 w, 1735 w, 1680 s, 1590 s, 1470 s, 1400 m, 1360 s, 1215 s, 1060 m and 1015 s.  $\delta_{\text{H}}$  0.98 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 2.61 (1H, br s, CHPhOH), 3.01 (1H, ddd, *J* 3.5, 3.8 and 11.0, CHH), 3.55 (1H, d, *J* 10.0, CHOH), 3.60 (1H, ddd, *J* 3.5, 8.5 and 11.0, CHH), 4.97 (1H, dd, *J* 3.5, 8.5, CHPh), 5.14 (1H, d, *J* 10.0, CHOH), 7.18 to 7.43 (6H, s m, 5 x *H*(Ph), NH), 7.53 (1H, ddd, *J* 1.0, 6.9 and 8.2, *H*<sub>6</sub>(Q)), 7.70 (1H, d, *J* 8.2, *H*<sub>8</sub>(Q)), 7.79 (1H, ddd, *J* 1.0, 6.9 and 8.2, *H*<sub>7</sub>(Q)) and 8.69 (1H, dd, *J* 1.0 and 8.2, *H*<sub>5</sub>(Q));  $\delta_{\text{C}}$  25.8 (C(CH<sub>3</sub>)<sub>3</sub>), 38.2 (C(CH<sub>3</sub>)<sub>3</sub>), 56.0 (CH<sub>2</sub>), 72.1, 75.2 (2 x CHOH), 125.9 (CCO(Q)), 127.9, 128.3, 128.4, 128.7, 128.9, 131.0, 134.8 (7 x CH), 141.1, 141.4 (CN=C(Q), C(Ph)), 157.0 (C=N(Q)) and 185.9 (CS(Q)) (1 C missing); *m/z* 384 (*MH*<sup>+</sup>, 49), 267 (32), 231 (20) and 191 (22).

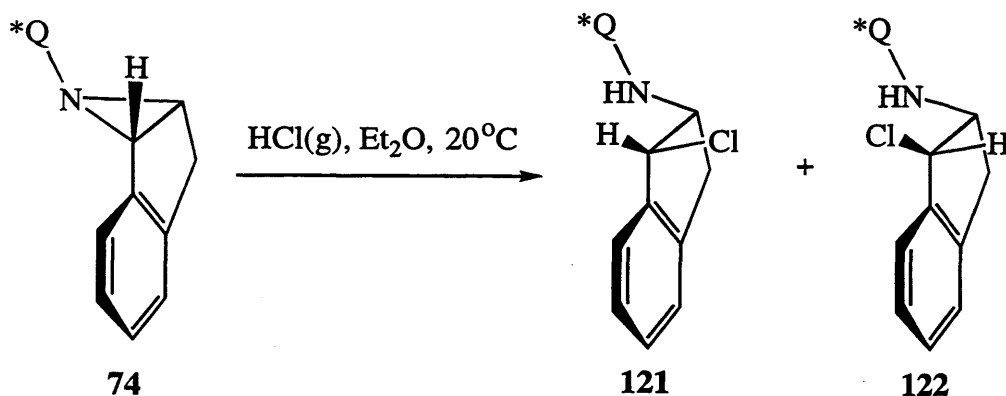
*Conversion of quinazolin-4-thione diol 120 to quinazolin-4-one diol*

**115**



The quinazolin-4-thione diol **120** (25 mg, 0.065 mmol) was dissolved in a mixture of ethanol ( $0.5 \text{ cm}^3$ ) and sodium hydroxide ( $0.5 \text{ cm}^3$ ,  $1.0 \text{ mol.dm}^{-3}$ ) and hydrogen peroxide (3 drops, 20 volume) added. After 30 min. the solution was diluted with ethyl acetate ( $10 \text{ cm}^3$ ), washed with water ( $2 \times 5 \text{ cm}^3$ ), brine ( $5 \text{ cm}^3$ ), dried and evaporated to give quinazolin-4-one diol **115** (12 mg, 50 %), identical with an NMR spectrum of an authentic sample prepared previously.

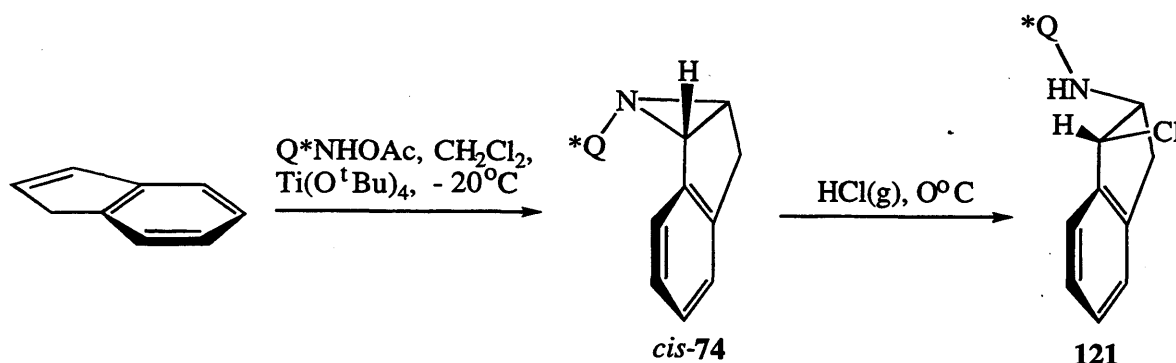
***Ring-opening of indene-derived aziridine 74 with a solution of hydrogen chloride in diethyl ether***



A suspension of aziridine (**74**, 67 mg, 0.185 mmol) in sodium dried ether ( $3\text{ cm}^3$ ) was stirred rapidly whilst hydrogen chloride gas was bubbled in. The initially cloudy solution cleared during the reaction before a white solid precipitated out. Residual acid in the solution was neutralised by careful addition of excess saturated aqueous sodium hydrogen carbonate, then more ether ( $3\text{ cm}^3$ ) added before the organic layer was separated, dried and evaporated to give a clear oil (**121** and **122**, 80 mg, 90%). Examination of the crude product by NMR spectroscopy showed it to be a 1 : 1.2 mixture of chloride diastereoisomers **121** and **122**, by comparison of the signals at  $\delta$  5.57 and 5.99 ppm respectively.  $\delta_{\text{H}}$  (major diastereoisomer) 1.06 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 3.09 (1H, dd,  $J$  6.6 and 15.4, CHH), 3.35 (1H, dd,  $J$  9.1 and 15.4, CHH), 3.62 (1H, br. d,  $J$  10.0, OH), 3.82 (1H, struct. m, CHNH), 5.15 (1H, br. d,  $J$  10.0, CHOH), 5.47 (1H, d,  $J$  5.0, CHCl), 5.99 (1H, d,  $J$  7.9, NH), 7.06 to 7.85 (7H, struct. m, 4 x CH(Ph),  $H_6$ ,  $H_7$ ,  $H_8(\text{Q})$ ) and 8.26 (1H, dd, 1.2 and 8.5,  $H_5(\text{Q})$ ). (See later for signals corresponding to minor diastereoisomer).



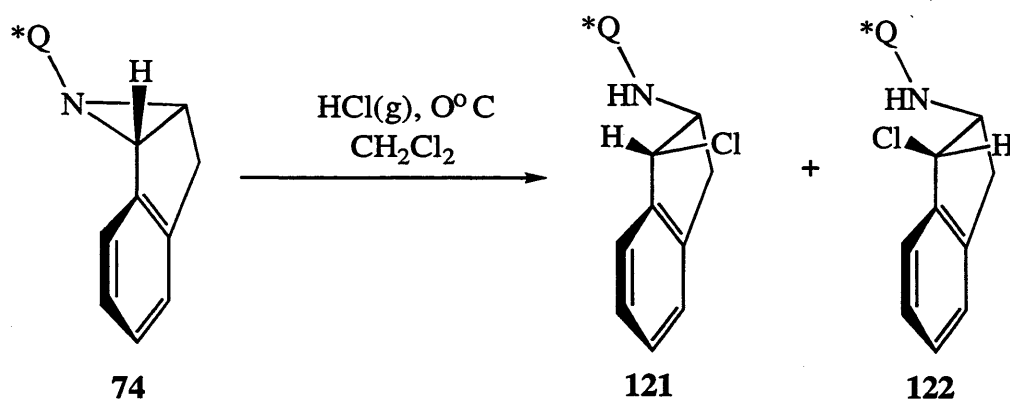
**Ring-opening of the *cis*-N-invertomer of indene-derived aziridine **74**  
with hydrogen chloride**



A lead diacetate-freed solution of 3-acetoxyaminoquinazolinone **49** in dichloromethane (4 cm<sup>3</sup>) was prepared as described previously (general procedure A) from **65** (200 mg, 0.81 mmol) and LTA (377 mg, 0.85 mmol) and added to a stirred solution of titanium (IV) *tert*-butoxide (548 mg, 1.62 mmol), indene (0.13 cm<sup>3</sup>, 1.11 mmol) and dry dichloromethane (1 cm<sup>3</sup>) at -20 °C. The temperature of the reaction mixture was held at -20 °C for 2 min. and then allowed to reach 0 °C over 10 min., stirring throughout. Hydrogen chloride gas was then bubbled into the reaction solution for 10 s. and allowed to reach ambient temperature. Excess acid was then neutralised by careful addition of excess aqueous saturated sodium hydrogen carbonate solution and the resulting white gelatinous precipitate was filtered off. The organic layer of the filtrate was separated, washed with saturated brine (2 x 5 cm<sup>3</sup>), dried, and the solvent evaporated under reduced pressure to give a white crystalline solid. Examination of the crude product by NMR spectroscopy showed it to consist of a single diastereoisomer of the chloride **121** identical to the minor diastereoisomer from the previous experiment. Crystallisation gave chloride 121 (100 mg, 62%) as colourless crystals mp 163-165 °C (from ethanol). (Found: MH<sup>+</sup> 398.16352. C<sub>22</sub>H<sub>25</sub>ClN<sub>3</sub>O<sub>2</sub> requires MH<sup>+</sup> 398.16353); α<sub>D</sub> 236.0 ° (c 0.5, ethanol); ν<sub>max</sub>/cm<sup>-1</sup> 3490 w, 3290 w, 3050 w, 2960 m, 1660 s, 1595 s, 1470 m, 1300 m, 1270 m, 1180 m, 1080 m and 1020 m; δ<sub>H</sub> 0.89 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 2.95 (1H, dd, *J* 5.7 and 16.0, CHH), 3.46 (1H, dd, *J* 6.9 and 16.0, CHH), 3.56 (1H, d, *J* 10.0, OH), 4.29 (1H, struct. m, CHNH), 4.96 (1H, d, *J* 10.0, CHOH), 5.25 (1H, d, *J* 5.0, CHCl), 5.57 (1H, d, *J* 3.8, NH), 7.20 - 7.56 (5H,

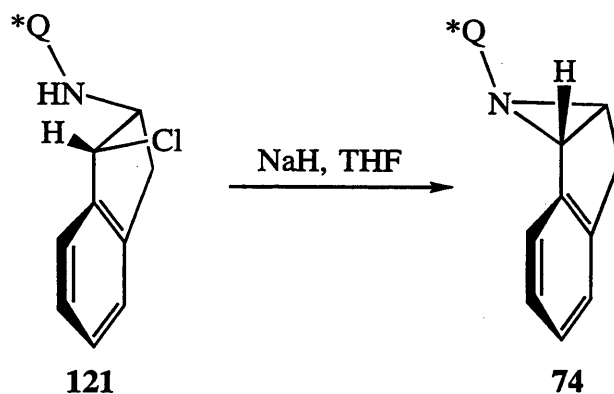
struct. m, 4 x CH(Ar),  $H_6(Q)$ ), 7.77 (2H, struct. m,  $H_8$ ,  $H_7(Q)$ ) and 8.28 (1H, dd,  $J$  1.2 and 7.9,  $H_5(Q)$ );  $m/z$  398 ( $MH^+$ , 100), 215 (21) and 175 (32).

***Ring-opening of indene-derived aziridine 74 with hydrogen chloride in dichloromethane***



The aziridine **74** (100 mg, 0.277 mmol) was dissolved in dichloromethane ( $5\text{ cm}^3$ ) and cooled to  $0^\circ C$  in an ice/water bath. Hydrogen chloride was bubbled in slowly for 20 s., the excess acid then neutralised by careful addition of excess saturated aqueous sodium hydrogen carbonate and the organic layer separated, washed with saturated brine, dried and concentrated to give a clear oil (105 mg). Examination by NMR spectroscopy showed the product to consist of a 4 : 1 ratio of chloride diastereoisomers **122** and **121** (95%) by comparison of the signals at  $\delta$  5.57 and 5.99 ppm respectively (see above).

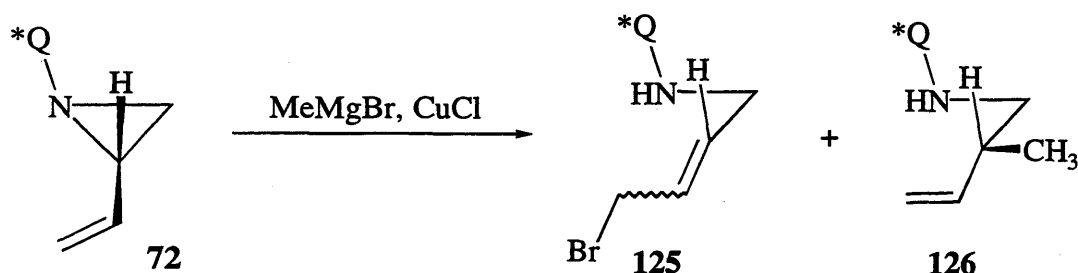
***Re-conversion of chloride 121 to aziridine 74***



To a solution of the chloride **121** (69 mg, 0.174 mmol) in THF (2 cm<sup>3</sup>) was added sodium hydride (10 mg of a 60% dispersion in oil, 0.25 mmol) and the solution stirred for 45 min. After the addition of water (5 cm<sup>3</sup>) the solution was extracted with ethyl acetate (3 x 5 cm<sup>3</sup>), the organic extracts separated, dried and solvent removed under reduced pressure to give aziridine **74**, (65 mg, 91%).

## ***Experimental for Chapter 5***

***Attempted ring-opening of 2-vinylaziridine 72 with methyl magnesium bromide***



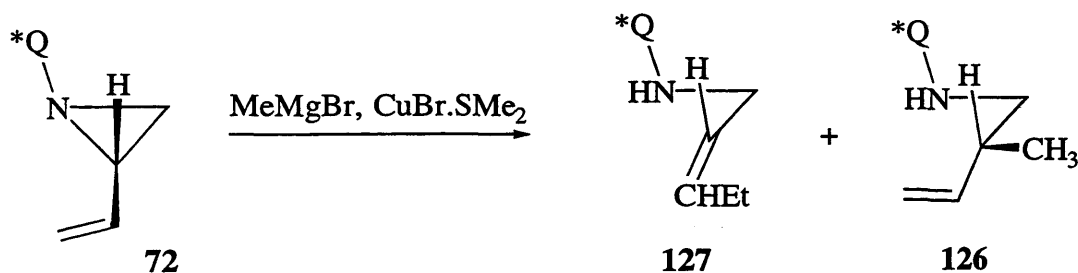
A flame-dried 3-necked flask equipped with a balloon of nitrogen was charged with magnesium turnings (18 mg, 0.75 mmol), ether (1 cm<sup>3</sup>) and bromomethane (2 drops). After the magnesium had disappeared and effervescence ceased, aziridine **72** (100 mg, 0.34 mmol) was added and the flask flushed with nitrogen. There was no reaction (monitoring by TLC) after standing overnight at room temperature. Dry THF (3 cm<sup>3</sup>) was added and the ether carefully distilled off by warming under a stream of dry nitrogen. Cuprous chloride (37 mg, 0.37 mmol) was then added and the reaction mixture heated under reflux for 18 h. The solution was quenched with saturated ammonium chloride (5 cm<sup>3</sup>), extracted with ethyl acetate (10 cm<sup>3</sup>), the organic layer separated, dried and solvent removed under reduced pressure to give a brown residue. Chromatography (eluent 2.5 : 1 light petroleum-ethyl acetate) yielded homoallylic amine 126 (*R<sub>f</sub>* 0.38) 3 mg, 3.5 % (based on recovered starting material), (Found: *MH*<sup>+</sup> 316.20251. C<sub>18</sub>H<sub>26</sub>N<sub>3</sub>O<sub>2</sub> requires *MH*<sup>+</sup> 316.20250); δ<sub>H</sub> 0.95 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.05 (3H, d, *J* 6.9, CH<sub>3</sub>), 2.42 (1H, struct. m, CHCH<sub>3</sub>), 2.62 (1H, struct. m, CHH), 2.99 (1H, struct. m, CHH), 3.58 (1H, d, *J* 9.9, OH), 4.91 (1H, d, *J* 9.9, CHOH), 5.08 (1H, d, *J* 10.4, =CHC<sub>H</sub>T), 5.14 (1H, d, *J* 17.3, =CHC<sub>H</sub>T), 5.58 (1H, dd, *J* 3.1, 11.0, NH), 5.75 (1H, ddd, *J* 7.8, 10.4, 17.3, CH=), 7.42 (1H, unresolved ddd, *J* ~8 visible, H<sub>6</sub>(Q)), 7.62 (1H, br d, *J* ~8, H<sub>8</sub>(Q)), 7.70 (1H, unresolved ddd, *J* ~7 visible, H<sub>7</sub>(Q)) and 8.18 (1H, dd, *J* 1.6, 8.2, H<sub>5</sub>(Q)); *m/z* 316 (*MH*<sup>+</sup>, 100), 215 (26) and 175 (26).

Further elution with the same solvent mixture yielded allylic bromide 125 (*R<sub>f</sub>* 0.31), (42 mg, 41 %) (based on recovered starting material). (Found: *MH*<sup>+</sup> 380.09736. C<sub>17</sub>H<sub>23</sub>BrN<sub>3</sub>O<sub>2</sub> requires *MH*<sup>+</sup> 380.09736); ν<sub>max</sub>/cm<sup>-1</sup> 3490 m, 3290 m, 2960 m, 1680

s, 1590 s, 1470 m, 1365 m, 1330 m, 1300 m, 1080 and 1020 m;  $\delta_{\text{H}}$  0.94 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 3.47 (1H, br m,  $\text{CHHNH}$ ), 3.52 (1H, d,  $J$  10.1, OH), 3.66 (1H, dt,  $J$  4.7 and 12.9,  $\text{CHHNH}$ ), 3.83 (2H, struct. m,  $\text{CH}_2\text{Br}$ ), 4.92 (1H, d,  $J$  10.1,  $\text{CHOH}$ ), 5.45 (1H, dd,  $J$  4.7 and 7.5, NH), 5.80 (1H, struct. m,  $\text{CH=}$ ), 5.82 (1H, struct. m,  $\text{CH=}$ ), 7.42 (1H, ddd,  $J$  1.0, 6.9 and 8.2,  $H_6(\text{Q})$ ), 7.61 (1H, dd,  $J$  1.0 and 8.2,  $H_8(\text{Q})$ ), 7.70 (1H, ddd,  $J$  1.6, 6.9 and 8.2,  $H_7(\text{Q})$ ) and 8.18 (1H, dd,  $J$  1.6 and 8.2,  $H_5(\text{Q})$ );  $m/z$  380 ( $\text{MH}^+$ , 100), 300 (28), 230 (27), 215 (45) and 175 (55).

Also isolated unchanged starting material, ( $R_f$  0.28), 20 mg.

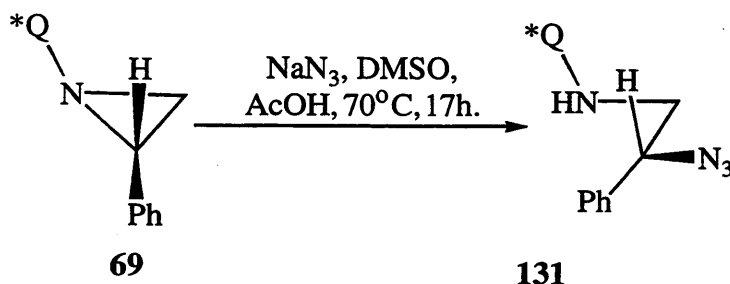
**Ring-opening of 2-vinylaziridine **72** with methyl magnesium bromide -  
copper (I) bromide - dimethylsulphide**



To a flame-dried 3-necked flask under argon was added *via* a septum cap a solution of aziridine **72** (100 mg, 0.34 mmol) in freshly distilled THF (2  $\text{cm}^3$ ) followed by a solution of methyl magnesium bromide in THF (0.4  $\text{cm}^3$ , 3.0  $\text{mol} \cdot \text{dm}^{-3}$ ). After effervescence had ceased, copper bromide-dimethyl sulphide complex (69 mg, 0.33 mmol) was added and the reaction vessel flushed with argon. The resulting deep red solution was stirred for 4 h before being quenched with saturated ammonium chloride (5  $\text{cm}^3$ ) and extracted with ethyl acetate (10  $\text{cm}^3$ ). The organic layer was separated, dried and solvent removed under reduced pressure to give a brown residue whose NMR spectrum showed it to consist of a 9 : 1 ratio of allylic amines **127** and **126**. Chromatography (eluent 3 : 1 light petroleum-ethyl acetate) yielded the allylic amines **127** and **126** (101 mg, 96 %) in the same 9 : 1 ratio. (Found:  $\text{MH}^+$  316.20250.  $\text{C}_{18}\text{H}_{26}\text{N}_3\text{O}_2$  requires  $\text{MH}^+$  316.20250);  $\nu_{\text{max}}/\text{cm}^{-1}$  (mixture) 3495 w, 3280 w, 2960 m,

2875 w, 1680 s, 1590 s, 1470 m, 1080 m, 1020 m and 770 m; for  $^{127}\delta_{\text{H}}$  0.84 (3H, t,  $J$  7.6,  $\text{CH}_3$ ), 0.93 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 1.93 (2H, quin.,  $J$  6.9,  $\text{CH}_2\text{CH}_3$ ), 3.39 (1H, struct. m,  $\text{CHHNH}$ ), 3.50 (1H, dd,  $J$  4.1 and 6.6,  $\text{CHHNH}$ ), 3.60 (1H, d,  $J$  10.0,  $\text{OH}$ ), 4.96 (1H, d,  $J$  10.0,  $\text{CHOH}$ ), 5.47 (3H, struct. m,  $\text{NH}$ , 2 x  $\text{CH=}$ ), 7.40 (1H, br t,  $J \sim 8$ ,  $H_6(\text{Q})$ ), 7.61 (1H, br d,  $J \sim 8$ ,  $H_8(\text{Q})$ ), 7.68 (1H, br t,  $J \sim 8$ ,  $H_7(\text{Q})$ ) and 8.19 (1H, dd,  $J$  1.2 and 7.9,  $H_5(\text{Q})$ );  $\delta_{\text{C}}$  13.2 ( $\text{CH}_3$ ), 25.4 ( $\text{CH}_2$ ), 25.9 ( $\text{C}(\text{CH}_3)_3$ ), 37.8 ( $\text{C}(\text{CH}_3)_3$ ), 53.2 ( $\text{CH}_2$ ), 74.6 ( $\text{CHOH}$ ), 120.7 ( $\text{CCO}(\text{Q})$ ), 121.7, 122.5, 126.6, 126.7, 127.3, 134.4, 138.8 (5 x  $\text{CH}(\text{Q})$ , 2 x  $\text{CH=}$ ), 146.0 ( $\text{CN=C}$ ), 158.5 ( $\text{C=N}(\text{Q})$ ) and 161.3 ( $\text{CO}(\text{Q})$ );  $m/z$  316 ( $\text{MH}^+$ , 100), 248 (20), 230 (26) and 175 (21).

### Ring-opening of aziridine **69** with sodium azide



To a solution of aziridine **69** (300 mg, 0.86 mmol) in DMSO (3 cm<sup>3</sup>) containing acetic acid (52 mg, 0.87 mmol) was added sodium azide (167 mg, 0.26 mmol) and the mixture heated at 70 °C for 17 h with stirring. Water (5 cm<sup>3</sup>) was then added, the solution extracted with ethyl acetate (3 x 10 cm<sup>3</sup>) and the combined organic extracts washed with water (3 x 5 cm<sup>3</sup>), then saturated brine (5 cm<sup>3</sup>), dried and the solvent removed under reduced pressure to give azide **131** (336 mg, 94%) as a colourless oil. (Found:  $\text{MH}^+$  393.20387.  $\text{C}_{21}\text{H}_{25}\text{N}_6\text{O}_2$  requires  $\text{MH}^+$  393.20390);  $\nu_{\text{max}}/\text{cm}^{-1}$  3490 w, 3290 w, 2960 m, 2100 s, 1675 s, 1595 s, 1475 s, 1265 m, 1080 m and 1020 m;  $\delta_{\text{H}}$  (400 MHz) 0.88 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 3.02 (1H, br m, CHH), 3.50 (2H, br d, OH, CHH), 4.72 (1H, dd,  $J$  5.0 and 7.3,  $\text{CHN}_3$ ), 4.78 (1H, d,  $J$  10.2, CHOH), 5.49 (1H, dd,  $J$  4.7 and 9.5, NH), 7.27 - 7.38 (5H, struct. m, 5 x CH(Ph)), 7.42 (1H, ddd,  $J$  1.2, 7.3 and 8.2,  $\text{H}_6(\text{Q})$ ), 7.61 (1H, dd,  $J$  1.0 and 7.3,  $\text{H}_8(\text{Q})$ ), 7.70 (1H, ddd,  $J$  1.5, 7.0 and 8.5,  $\text{H}_7(\text{Q})$ ), 8.17 (1H, dd,  $J$  1.4 and 7.9,  $\text{H}_5(\text{Q})$ );  $\delta_{\text{C}}$  25.6 ( $\text{C}(\text{CH}_3)_3$ ), 37.5 ( $\text{C}(\text{CH}_3)_3$ ), 55.1 ( $\text{CH}_2$ ), 64.1 ( $\text{CHN}_3$ ), 74.1 (CHOH), 120.4 ( $\text{CCO}(\text{Q})$ ), 126.4, 126.7, 126.8, 127.1, 128.6, 128.8, 134.4 ( $\text{CH}(\text{Ar})$ ,  $\text{CH}(\text{Q})$ ), 136.6 ( $\text{C}(\text{Ar})$ ), 145.8 ( $\text{CN}=\text{C}(\text{Q})$ ), 158.1 ( $\text{C}=\text{N}(\text{Q})$ ) and 161.1 ( $\text{CO}(\text{Q})$ );  $m/z$  393 ( $\text{MH}^+$ , 100), 260 (28), 215 (32) and 175 (22).



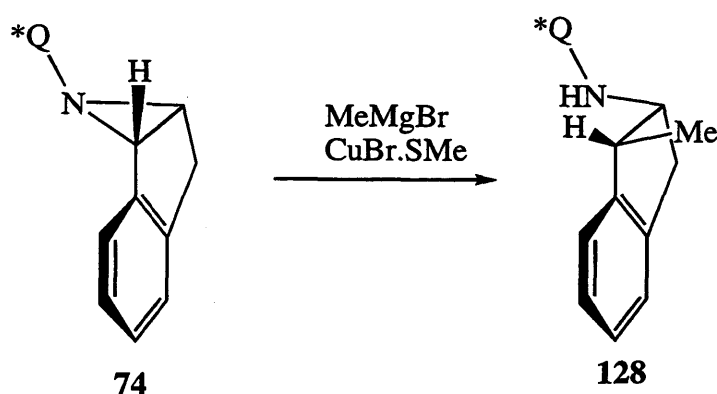
***Effect of acetic acid concentration on ring-opening of aziridine 69 with sodium azide***

Three 5 cm<sup>3</sup> round-bottom flasks a, b, and c, were each charged with aziridine **69** (100 mg, 0.286 mmol) and sodium azide (56 mg, 0.86 mmol). To flask a was added DMSO (1 cm<sup>3</sup>); to flask b, 1 cm<sup>3</sup> of a solution of acetic acid ((0.164 cm<sup>3</sup>, 2.86 mmol) made up to 10 cm<sup>3</sup> with DMSO) and to flask c 1 cm<sup>3</sup> of a solution of acetic acid ((0.33 cm<sup>3</sup>, 5.76 mmol), made up to 10 cm<sup>3</sup> with DMSO). The flasks were then heated in the same oil bath at 70 °C for 5 h. After this time the oil bath removed, each reaction poured into saturated aqueous sodium hydrogen carbonate solution (5 cm<sup>3</sup>) and worked up in the following way. The solution was extracted with ethyl acetate (3 x 5 cm<sup>3</sup>) and the combined organic extracts washed with water (3 x 5 cm<sup>3</sup>), then saturated brine (5 cm<sup>3</sup>), dried and the solvent evaporated under reduced pressure. The NMR spectra of the crude products were recorded, and the results shown in Table 10.

Flask	Equivalents of acetic acid added	Mass of crude product (mg)	Isolated unchanged aziridine <b>69</b> (%)
a	0	77	34.5
b	1	106	30.6
c	2	104	31.3

Table 10

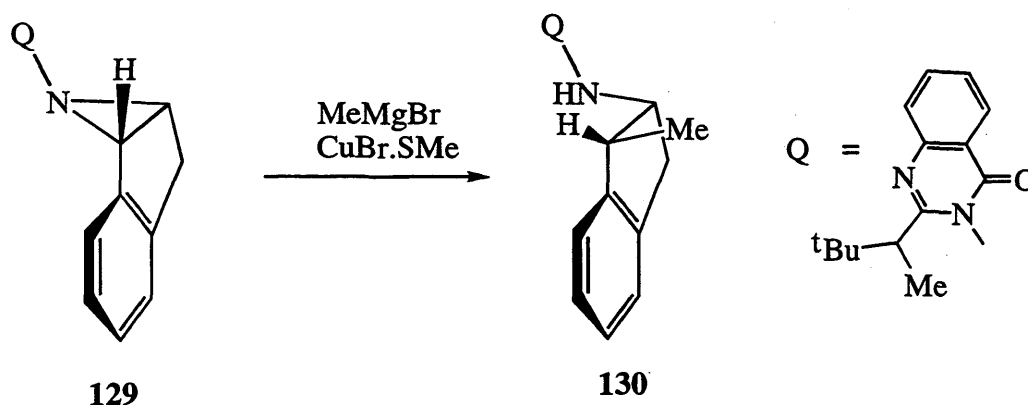
**Ring-opening of aziridine **74** with methyl magnesium bromide - copper  
(I) bromide dimethylsulphide**



To a flame-dried 3-necked flask equipped with a stirrer bar and under argon atmosphere was added a solution of aziridine **74** (100 mg, 0.277 mmol) in freshly distilled THF (2 cm<sup>3</sup>) via a septum cap, followed by a solution of methyl magnesium bromide in THF, (0.35 cm<sup>3</sup>, 3.0 mol.dm<sup>-3</sup>). After effervescence had ceased, copper bromide-dimethyl sulphide complex (57 mg, 0.33 mmol) was quickly added and then the reaction vessel again flushed with argon. The resulting deep red solution was stirred under argon for 4 h at room temperature before being syringed into a stirred saturated ammonium chloride solution (5 cm<sup>3</sup>) maintained at 0 °C. The resulting deep blue aqueous solution was extracted with ethyl acetate (10 cm<sup>3</sup>) and the organic layer separated, dried and evaporated under reduced pressure to give a brown residue. Column chromatography (eluent 4 : 1 light petroleum-ethyl acetate) yielded amine **128** (*R*<sub>f</sub> 0.35) (60 mg, 57%) as a colourless oil. (Found: *MH*<sup>+</sup> 378.21817. C<sub>23</sub>H<sub>27</sub>N<sub>3</sub>O<sub>2</sub> requires *MH*<sup>+</sup> 378.21815); α<sub>D</sub> 177.1 ° (c 3.5, ethanol); ν<sub>max</sub>/cm<sup>-1</sup> 3480 w, 3280 m, 2960 m, 1660 s, 1595 s, 1475 m, 1305 m, 1180 m, 1080 m and 1020 m; δ<sub>H</sub> (400 MHz) 0.89 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.21 (3H, d, *J* 6.9, CH<sub>3</sub>), 2.91 (1H, dd, *J* 6.2 and 15.8, CHH), 3.13 (1H, struct. m, CHCH<sub>3</sub>), 3.18 (1H, dd, *J* 6.6 and 15.8, CHH), 3.58 (1H, d, *J* 10.2, OH), 3.74 (1H, struct. m, CHNH), 4.94 (1H, d, *J* 10.2, CHOH), 5.60 (1H, d, *J* 5.6, NH), 7.18 (4H, struct. m, 4 x CH(Ar)), 7.50 (1H, ddd, *J* 1.1, 7.0 and 8.0, H<sub>6</sub>(Q)), 7.71 (1H, br. d, *J* ~8, H<sub>8</sub>(Q)), 7.78 (1H, ddd, *J* 1.5, 7.0 and 8.2, H<sub>7</sub>(Q) and 8.28 (1H, dd, *J* 1.5 and 8.0, H<sub>5</sub>(Q)); δ<sub>C</sub> 18.3 (CH<sub>3</sub>), 25.8 (C(CH<sub>3</sub>)<sub>3</sub>), 37.1 (CH<sub>2</sub>), 37.8 (C(CH<sub>3</sub>)<sub>3</sub>), 43.5

(CHNH), 69.0 (CHCH<sub>3</sub>), 74.1 (CHOH), 120.7 (CCO(Q)), 123.5, 124.5, 126.7, 126.9, 127.3, 134.6 (6 x CH(Q), CH(Ar)), 139.9, 145.7, 146.0 (2 x C(Ar), CN=C(Q)), 159.2 (C=N(Q)) and 161.7 (CO(Q)); m/z 378 (100, MH<sup>+</sup>), 248 (83) and 191 (20).

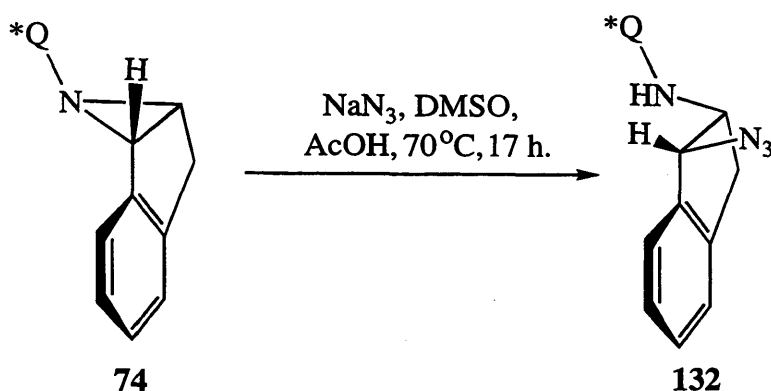
***Ring-opening of aziridine 129 with methyl magnesium bromide -  
copper (I) bromide - dimethylsulphide***



To a flame-dried, 3-necked flask equipped with a stirrer bar and under an argon atmosphere a solution of aziridine **129** (163 mg, 0.454 mmol) in THF (3 cm<sup>3</sup>) was added *via* a septum cap, followed by a solution of methyl magnesium chloride in THF (0.4 cm<sup>3</sup>, 3.0 moldm<sup>-3</sup>.) After effervescence had ceased copper bromide-dimethyl sulphide complex (93 mg, 0.45 mmol) was quickly added and the reaction vessel flushed with argon. The resulting deep red solution was stirred at room temperature for 1.5 h under argon before being syringed into a stirred saturated ammonium chloride solution (5 cm<sup>3</sup>) maintained at 0 °C. The resulting deep blue aqueous solution was extracted with ethyl acetate (10 cm<sup>3</sup>) and the organic layer separated, dried and evaporated under reduced pressure to give a brown oil. Chromatography (eluent 9:1 light petroleum-ethyl acetate) yielded amine **130** (*R<sub>f</sub>* 0.35) (82 mg, 48%) as a crystalline solid. Crystallisation gave **130** as colourless crystals mp 136-137 °C (from light petroleum-ethyl acetate.) (Found: MH<sup>+</sup> 376.23890. C<sub>24</sub>H<sub>30</sub>N<sub>3</sub>O requires MH<sup>+</sup> 376.23889);  $\nu_{\text{max}}/\text{cm}^{-1}$  3290 w, 2960 m, 1665 s, 1580 s, 1470 m, 1360 m, 1265 m and 1170 m;  $\delta_{\text{H}}$  (400 MHz) 0.91 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.30 (6H, d, *J* 6.9, 2 x CH<sub>3</sub>), 2.96 (1H, dd, *J* 6.7 and 15.7, CHH), 3.08 (1H, br. s, CHNH), 3.12 (1H, dd, *J* 6.7 and 15.7,

CHH), 3.60 (2H, struct. m, 2 x CHCH<sub>3</sub>), 5.87 (1H, d, *J* 6.6, NH), 7.13 to 7.22 (4H, struct. m, CH(Ar)), 7.45 (1H, ddd, *J* 1.6, 6.7 and 8.0, H<sub>6</sub>(Q)), 7.67 - 7.78 (2H, struct. m, H<sub>8</sub> and H<sub>7</sub>(Q)) and 8.26 (1H, dd, *J* 1.2 and 8.0, H<sub>5</sub>(Q)); δ<sub>C</sub> 14.5, 18.0 (2 x CH<sub>3</sub>), 27.4 (C(CH<sub>3</sub>)<sub>3</sub>), 35.4 (C(CH<sub>3</sub>)<sub>3</sub>), 37.2 (CH<sub>2</sub>), 42.1, 43.5, 69.1 (CHNH, CHC(CH<sub>3</sub>)<sub>3</sub>, CHCH<sub>3</sub>), 120.3 (CCO(Q)), 123.2, 124.5, 126.0, 126.4, 126.7, 126.8, 127.5, 134.0 (4 x CH(Ar), 4 x CH(Q)), 140.2, 145.5, 146.8 (2 x C(Ar), CN=C(Q)) and 161.3, 162.0 (CO(Q), C=N(Q)); *m/z* 376 (MH<sup>+</sup>, 100), 246 (21) and 189 (45). A crystal for X-ray structure determination was grown from light petroleum-ethyl acetate (Fig. 34).

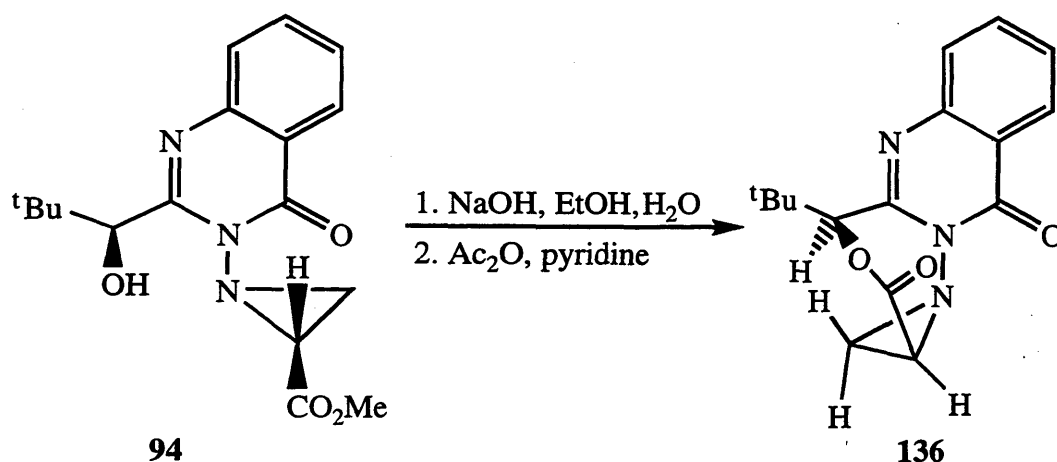
### Ring-opening of aziridine **74** with sodium azide



A mixture of aziridine **74** (100 mg, 0.277 mmol), DMSO (1 cm<sup>3</sup>), acetic acid (17 mg, 0.283 mmol) and sodium azide (54 mg, 0.83 mmol) was heated at 70 °C for 17 h. with stirring. After cooling, water (3 cm<sup>3</sup>) was added and the solution extracted with ethyl acetate (3 x 5 cm<sup>3</sup>). The organic layer was separated, washed successively with water (3 x 3 cm<sup>3</sup>) and saturated brine (3 cm<sup>3</sup>), dried and evaporated under reduced pressure to give azide **132** (106 mg, 95%) as a clear oil. (Found:  $\text{MH}^+$  405.20389.  $\text{C}_{22}\text{H}_{25}\text{N}_6\text{O}_2$  requires  $\text{MH}^+$  405.20390);  $\nu_{\text{max}}/\text{cm}^{-1}$  3500 w, 3280 m, 2950 m, 2095 s, 1680 s, 1595 s, 1475 s, 1265 m, 1180 m, 1080 m and 1020 m;  $\delta_{\text{H}}$  (400 MHz) 0.89 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 2.92 (1H, dd,  $J$  5.8 and 16.0,  $\text{CHH}$ ), 3.34 (1H, dd,  $J$  6.8 and 16.0,  $\text{CHH}$ ), 3.55 (1H, d,  $J$  10.3,  $\text{OH}$ ), 4.40 (1H, struct. m,  $\text{CHNH}$ ), 4.75 (1H, d,  $J$  5.0,  $\text{CHN}_3$ ), 4.94 (1H, d, 10.3,  $\text{CHOH}$ ), 5.60 (1H, d,  $J$  4.0,  $\text{NH}$ ), 7.26 - 7.34 (3H, struct. m, 3 x  $\text{CH}(\text{Ar})$ ), 7.39 (1H, dd,  $J$  1.1 and 7.8,  $\text{ArH}$ ), 7.51 (1H, ddd,  $J$  1.0, 7.0 and 8.0,  $\text{H}_6(\text{Q})$ ), 7.72 (1H, br d,  $J$  ~8,  $\text{H}_8(\text{Q})$ ), 7.79 (1H, ddd,  $J$  1.4, 7.0 and 8.3,  $\text{H}_7(\text{Q})$ ), 8.28 (1H, dd,  $J$  1.4 and 8.0,  $\text{H}_5(\text{Q})$ );  $\delta_{\text{C}}$  25.6 ( $\text{C}(\text{CH}_3)_3$ ), 35.9 ( $\text{CH}_2$ ), 37.6 ( $\text{C}(\text{CH}_3)_3$ ), 66.9, 68.2 ( $\text{CHNH}$ ,  $\text{CHN}_3$ ), 74.0 ( $\text{CHOH}$ ), 120.6 ( $\text{CCO}(\text{Q})$ ), 124.7, 125.1, 126.7, 126.9, 127.3, 127.4, 129.3, 134.7 (4 x  $\text{CH}(\text{Q})$ , 4 x  $\text{CH}(\text{Ph})$ ), 138.2, 140.1 (2 x  $\text{C}(\text{Ph})$ ), 145.9 ( $\text{CN}=\text{C}(\text{Q})$ ), 158.8 ( $\text{C}=\text{N}(\text{Q})$ ) and 161.5 ( $\text{CO}(\text{Q})$ );  $m/z$  405 (100  $\text{MH}^+$ ) and 215 (33).

## ***Experimental for Chapter 6***

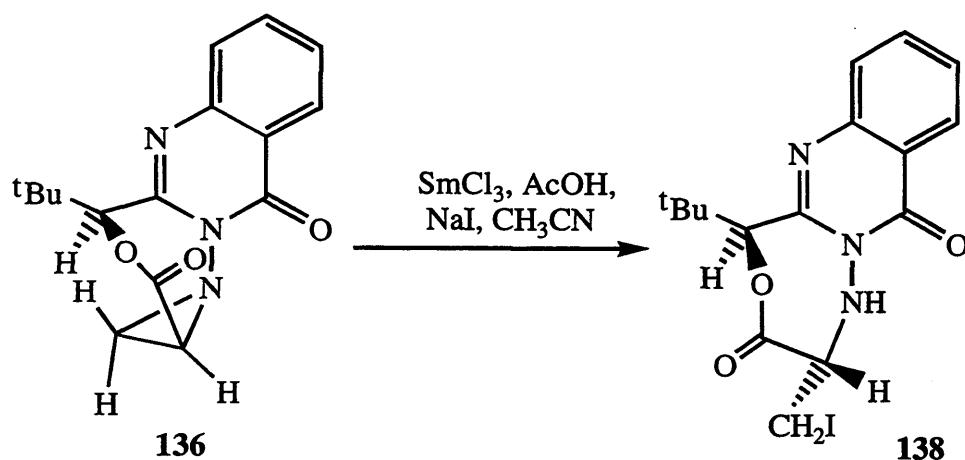
### Lactonisation of aziridine-2-carboxylic acid **94**



The aziridine 2-carboxylic acid **94** (799 mg, 2.52 mmol) was dissolved in pyridine (8 cm<sup>3</sup>) and added via a syringe pump dropwise over 4 h to a rapidly stirred mixture of pyridine (2 cm<sup>3</sup>) and acetic anhydride (0.71 cm<sup>3</sup>, 7.52 mmol) maintained at 50 °C. After a further 30 min at this temperature the solution was cooled and dichloromethane (15 cm<sup>3</sup>) added. The solution was given one shake in a separating funnel with saturated sodium bicarbonate solution (10 cm<sup>3</sup>), washed with water (10 cm<sup>3</sup>) and the organic layer separated, dried and evaporated under reduced pressure to give lactone **136** (561 mg, 74 %).  $\delta_{\text{H}}$  1.25 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 2.34 (1H, dd, *J* 2.5 and 6.9, ariz. *H* cis to C=O), 3.24 (1H, dd, *J* 2.5 and 8.0, azir. *H* trans to C=O), 3.54 (1H, dd, *J* 6.9 and 8.0, CHCO), 5.30 (1H, s, CHCO), 7.46 (1H, ddd, *J* 1.0, 6.9 and 8.2, *H*<sub>6</sub>(Q)), 7.60 (1H, dd, *J* 1.0 and 8.2, *H*<sub>8</sub>(Q)), 7.70 (1H, ddd, *J* 1.3, 6.9 and 8.2, *H*<sub>7</sub>(Q)) and 8.20 (1H, dd, *J* 1.3 and 8.2, *H*<sub>5</sub>(Q)).

The unstable lactone **136** was used directly for the ring-opening as follows.

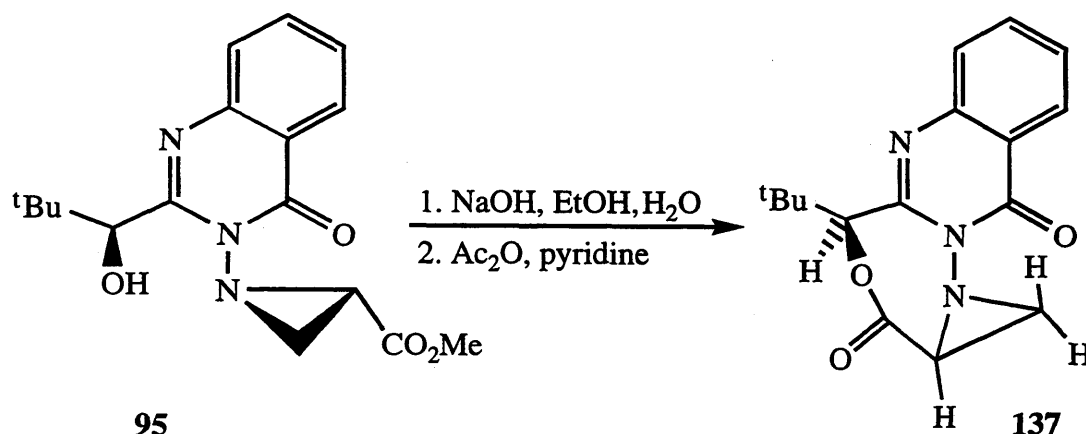
***Samarium chloride catalysed ring-opening of lactone 136***



Samarium chloride (86 mg, 0.33 mmol), sodium iodide (150 mg, 1.00 mmol) and acetic acid (60 mg, 1.00 mmol) were stirred rapidly in acetonitrile (1 cm<sup>3</sup>) for 1 min. The lactone **136** (100 mg, 0.33 mmol) in acetonitrile (1 cm<sup>3</sup>) was added and stirring continued for a further 3 min before saturated sodium hydrogen carbonate solution (5 cm<sup>3</sup>) was added. Ethyl acetate (10 cm<sup>3</sup>) was added, the organic layer separated and washed with saturated sodium thiosulphate solution (4 cm<sup>3</sup>) and brine (4 cm<sup>3</sup>) then dried and evaporated to give iodide **138** 109 mg, 76 % (Found:  $\text{MH}^+$  428. 04170.  $\text{C}_{16}\text{H}_{19}\text{IN}_3\text{O}_3$  requires  $\text{MH}^+$  428.04711);  $\nu_{\text{max}}/\text{cm}^{-1}$  2960 s, 1755 s, 1685 s, 1610 m, 1470 m, 1380 s, 1235 s, 990 m and 770 m;  $\delta_{\text{H}}$  1.30 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 3.59 (1H, dd,  $J$  3.1 and 11.0,  $\text{CHHI}$ ), 3.72 (1H, dd,  $J$  5.3 and 11.0,  $\text{CHHI}$ ), 4.11 (1H, struct. m,  $\text{CHNH}$ ), 6.09 (1H, s,  $\text{CHO}$ ), 6.58 (1H, d,  $J$  2.2,  $\text{NH}$ ), 7.43 to 7.80 (3H, struct. m,  $\text{H}_6$ ,  $\text{H}_7$ ,  $\text{H}_8(\text{Q})$ ) and 8.20 (1H, d,  $J$  8.2,  $\text{H}_5(\text{Q})$ );  $m/z$  428 ( $\text{MH}^+$ , 100), 281 (22) and 207 (38).

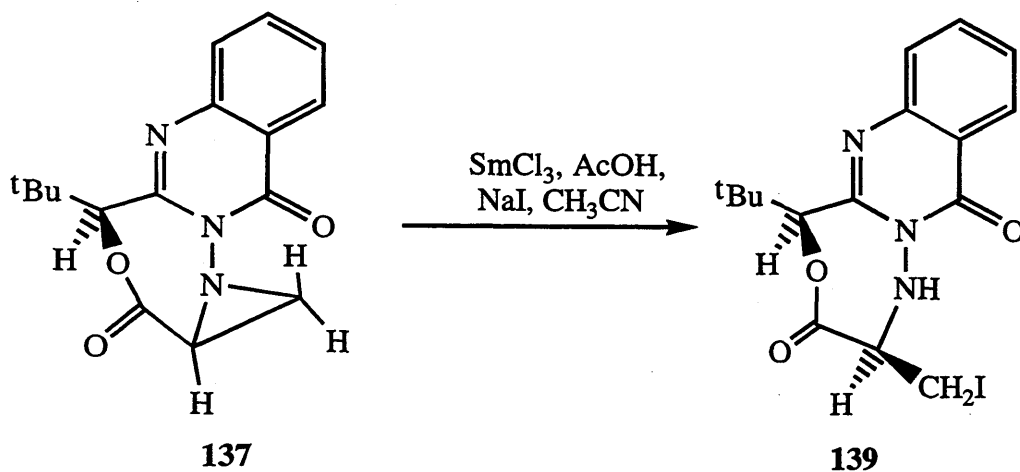


### Lactonisation of aziridine 2-carboxylic acid **95**



The aziridine 2-carboxylic acid **95** (270 mg, 0.85 mmol) was dissolved in pyridine (6 cm<sup>3</sup>) and added via a syringe pump dropwise over 4 h to a rapidly stirred mixture of pyridine (2 cm<sup>3</sup>) and acetic anhydride (0.25 cm<sup>3</sup>, 2.64 mmol) maintained at 50 °C. After a further 30 min at this temperature dichloromethane (10 cm<sup>3</sup>) was added. The solution was washed once with saturated aqueous sodium hydrogen carbonate (10 cm<sup>3</sup>), water (10 cm<sup>3</sup>), the organic layer separated, dried and evaporated under reduced pressure to give lactone **137** (231 mg, 91 %). (Found  $\text{MH}^+$  300.13482.  $\text{C}_{16}\text{N}_3\text{O}_3$  requires  $\text{MH}^+$  300.13482);  $\nu_{\text{max}}/\text{cm}^{-1}$  2960 s, 1755 s, 1685 s, 1610 s, 1470 m, 1380 s, 1235 s, 990 m and 770 m;  $\delta_{\text{H}}$  1.31 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 2.48 (1H, dd,  $J$  3.5 and 6.3, azir.  $H$  *cis* to  $\text{C}=\text{O}$ ), 3.15 (1H, dd,  $J$  3.5 and 7.6, azir.  $H$  *trans* to  $\text{C}=\text{O}$ ), 3.45 (1H, dd,  $J$  6.6 and 7.2  $\text{CHCO}$ ), 5.49 (1H, s,  $\text{CHO}$ ), 7.44 (1H, ddd,  $J$  1.9, 6.9 and 8.2,  $H_6(\text{Q})$ ), 7.64 (2H, s m,  $H_7$ ,  $H_8(\text{Q})$ ), and 8.17 (1H, dd,  $J$  1.3 and 8.2,  $H_5(\text{Q})$ );  $\delta_{\text{C}}$  24.3 ( $\text{C}(\text{CH}_3)_3$ ), 34.6 ( $\text{C}(\text{CH}_3)_3$ ), 36.5 ( $\text{CH}_2$ ), 41.1 ( $\text{CHCO}_2$ ), 78.6 ( $\text{CHOH}$ ), 119.9 ( $\text{CCO}(\text{Q})$ ), 124.4, 125.9, 126.3, 132.3 (4 x  $\text{CH}(\text{Q})$ ), 142.8, 145.4 ( $\text{CN}=\text{C}(\text{Q})$ ,  $\text{C}=\text{N}(\text{Q})$ ), 157.2 ( $\text{CO}(\text{Q})$ ) and 163.1 ( $\text{CO}_2$ );  $m/z$  300 ( $\text{MH}^+$ , 100), 221 (63), 207 (42) and 175 (22).

***Samarium chloride catalysed ring-opening of lactone 137***



Samarium chloride (86 mg, 0.33 mmol), sodium iodide (150 mg, 1.00 mmol) and acetic acid (60 mg, 1.00 mmol) were stirred rapidly in acetonitrile (1 cm<sup>3</sup>) for 1 min. The lactone **137** (100 mg, 0.33 mmol) in acetonitrile (1 cm<sup>3</sup>) was added and stirring continued for a further 3 min before water (5 cm<sup>3</sup>) was added. Ethyl acetate (10 cm<sup>3</sup>) was added, the organic layer separated and washed successively with saturated sodium hydrogen carbonate solution (5 cm<sup>3</sup>), saturated sodium thiosulphate solution (4 cm<sup>3</sup>) and brine (4 cm<sup>3</sup>), then dried and evaporated under reduced pressure to give iodide **139** (112 mg, 78 %). Crystallisation yielded iodide 139 as colourless needles mp 152-157 °C (from ethanol). (Found: C 45.1, H 4.25, N 9.8 C<sub>16</sub>H<sub>18</sub>N<sub>3</sub>O<sub>3</sub>I requires C 45.0, H 4.25 and N 9.85 %);  $\nu_{\text{max}}/\text{cm}^{-1}$  3030 m, 2990 m, 1730 s, 1680 s, 1610 s, 1470 s, 1370 s, 1235 m, 1150 m and 1020 m.  $\delta_{\text{H}}$  1.28 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 3.30 (1H, dd, *J* 8.8 and 11.0, CHHI), 3.71 (1H, dd, *J* 2.5 and 11.0, CHHI), 4.50 (1H, struct. m, CHNH), 5.79 (1H, s, CHO), 6.95 (1H, d, *J* 1.0, NH), 7.50 (1H, ddd, *J* 1.9, 6.3 and 8.2, H<sub>6</sub>(Q)), 7.71 (2H, struct. m, H<sub>7</sub>, H<sub>8</sub>(Q)) and 8.23 (1H, d, *J* 8.2, H<sub>5</sub>(Q)); *m/z* 428 (MH<sup>+</sup>, 100), 307 (85), 289 (60), 215 (24) and 176 (36).

Chemical reaction scheme showing the conversion of compound **139** to compound **140** using  $\text{NaN}_3$  in DMSO.

Compound **139** is a bicyclic hydantoin derivative. It features a phenyl ring attached to a nitrogen atom, which is part of a five-membered ring containing a carbonyl group and a nitrogen atom. This five-membered ring is fused to a six-membered ring containing a carbonyl group and a nitrogen atom. The six-membered ring also has a tert-butyl group and an iodomethyl group attached to it.

Reaction conditions:  $\text{NaN}_3$ , DMSO.

Compound **140** is the product of the reaction, where the iodomethyl group in compound **139** has been replaced by an azide group ( $\text{N}_3$ ).

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Chemical reaction scheme showing the reduction of compound **140** to compound **142** using  $\text{NaBH}_4$  in  $\text{MeOH}$ .

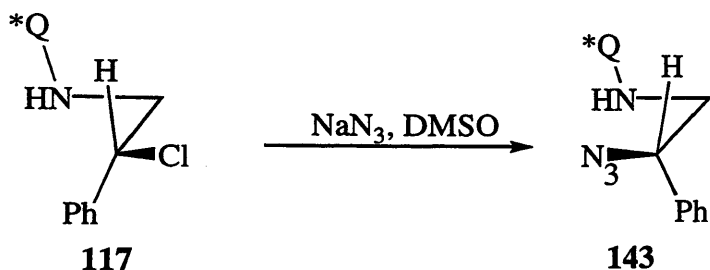
Compound **140** (left) is a bicyclic hydantoin derivative. It features a benzimidazole core. The 2-position of the benzimidazole ring is substituted with a  $\text{tert}$ -butyl group ( $\text{tBu}$ ) and a hydrogen atom ( $\text{H}$ ). The 4-position is substituted with a carbonyl group ( $\text{C=O}$ ). The 5-position is substituted with a side chain consisting of a carbonyl group ( $\text{C=O}$ ) and a methyl group ( $\text{CH}_3$ ).

Compound **142** (right) is the reduced form of **140**. The carbonyl group at the 5-position has been reduced to a secondary alcohol ( $\text{CH(OH)CH}_3$ ). The hydantoin nitrogen ( $\text{N}$ ) is now protonated ( $\text{NH}$ ).

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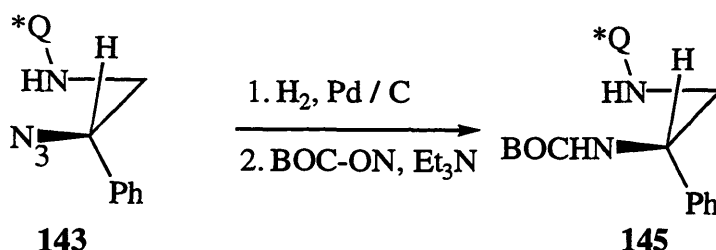
## ***Experimental for Chapter 7***

***Displacement of chloride in 117 with azide***



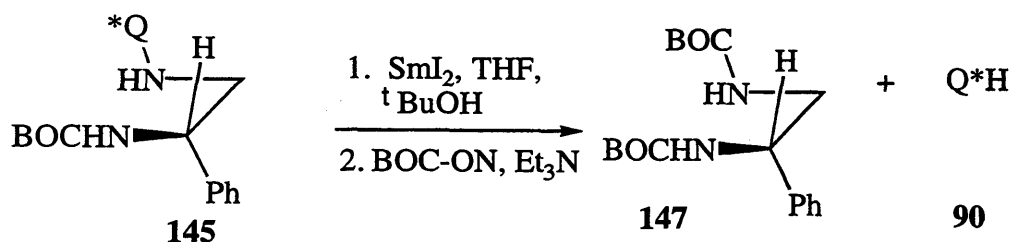
A solution of chloride **117** (381 mg, 0.99 mmol) in DMSO (3 cm<sup>3</sup>) was stirred rapidly with sodium azide (193 mg, 2.97 mmol) overnight at room temperature. The reaction mixture was then diluted with water (5 cm<sup>3</sup>), extracted with ethyl acetate (3 x 5 cm<sup>3</sup>), the combined organic extracts washed with water (3 x 5 cm<sup>3</sup>) then brine (5 cm<sup>3</sup>), dried and the solvent removed under reduced pressure to give a crystalline solid. Recrystallisation gave azide **143** as a colourless solid, (246 mg, 63 %) mp 110-112 °C (from 4 : 1 light petroleum-ethyl acetate). (Found: C, 64.35; H 6.25; N 21.15. C<sub>21</sub>H<sub>24</sub>N<sub>6</sub>O<sub>2</sub> requires C, 64.25; H, 6.15; N, 21.15 %);  $\alpha_D$  262.0 ° (c 1.0, ethanol);  $\nu_{\max}/\text{cm}^{-1}$  3480 w, 3270 m, 2960 m, 2095 s, 1675 s, 1590 s, 1470 m, 1265 m, 1075 m, 1020 m, 900 m, 770 m and 700 m;  $\delta_H$  (400 MHz) 0.90 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 2.94 (1H, br s, CHH), 3.78 (2H, br. m CHH, OH), 4.69 (1H, dd, *J* 4.7 and 8.9, CHN<sub>3</sub>), 4.83 (1H, d, CHOH), 5.64 (1H, dd, *J* 3.9 and 10.0, NH), 7.25 to 7.34 (5H, struct. m, ArH), 7.40 (1H, ddd, *J* 1.0, 7.0 and 8.1, H<sub>6</sub>(Q)), 7.59 (1H, br. d, *J* 7.5, H<sub>8</sub>(Q)), 7.68 (1H, ddd, *J* 1.5, 7.5 and 8.4, H<sub>7</sub>(Q)) and 8.17 (1H, dd, *J* 1.5 and 8.1, H<sub>5</sub>(Q)); *m/z* 393 (MH<sup>+</sup>, 100), 260 (32) and 215 (20).

### Conversion of azide **143** to *N'*-BOC, *N*-(*Q*)-diamine **145**



Azide **143** (246 mg, 0.63 mmol) was dissolved in ethyl acetate (10 cm<sup>3</sup>), 5% palladium on charcoal (25 mg) added into the mixture and stirred rapidly overnight under an atmosphere (balloon) of hydrogen. The solution was then filtered through a plug of celite, the solvent removed under reduced pressure and the residue dissolved in a mixture of 1 : 1 THF/ water (10 cm<sup>3</sup>). To the stirred solution was then added triethylamine (0.13 cm<sup>3</sup>) and BOC-ON (185 mg, 0.75 mmol). After stirring at room temperature for 2 h the solution was extracted with ethyl acetate (3 x 10 cm<sup>3</sup>), the combined extracts washed with brine (10 cm<sup>3</sup>), dried and the solvent evaporated under reduced pressure. Chromatography (eluent 4 : 1 light petroleum-ethyl acetate) yielded *N*-BOC, *N'*-(*Q*)-diamine **145** (*R*<sub>f</sub> 0.26) (230 mg, 79 %) which crystallised as colourless needles mp 183-187 °C (from ethanol). (Found: *MH*<sup>+</sup> 467.26584 C<sub>26</sub>H<sub>35</sub>N<sub>4</sub>O<sub>4</sub> requires *MH*<sup>+</sup> 467.26583); α<sub>D</sub> 151.5 ° (c 0.68, CHCl<sub>3</sub>); ν<sub>max</sub>/cm<sup>-1</sup> 3450 m, 3300 w, 2990 s, 1720, s, 1680 s, 1595, s, 1500 s, 1370 s, 1235 s, 1170 s, 1080 s, 1020 s and 900 m; δ<sub>H</sub> 0.99 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.46 (9H, s, OC(CH<sub>3</sub>)<sub>3</sub>), 3.15 (1H, ddd, *J* 5.0, 5.0 and 10.5, CHH), 3.47 (1H, br m, CHH), 3.57 (1H, d, *J* 10.0, OH), 4.89 (1H, d, *J* 10.0, CHOH), 4.99 (1H, br. s, CHPh), 5.43 (1H, br. d, *J* 7.5, NHCO), 5.57 (1H, dd, *J* 3.1 and 10.5, NH), 7.30 - 7.37 (5H, struct. m, 5 x CH(Ph)), 7.48 (1H, ddd, *J* 1.2, 6.9 and 8.0, H<sub>6</sub>(Q)), 7.67 (1H, br. d, *J* 8.1, H<sub>8</sub>(Q)), 7.76 (1H, ddd, *J* 1.2, 6.9 and 8.1, H<sub>7</sub>(Q)) and 8.23 (1H, dd, *J* 1.2 and 8.0, H<sub>5</sub>(Q)); δ<sub>C</sub> 25.9, 28.3 (2 x C(CH<sub>3</sub>)<sub>3</sub>), 37.8 (C(CH<sub>3</sub>)<sub>3</sub>), 55.3 (CH<sub>2</sub>), 74.4 (CHOH), 80.1 (OC(CH<sub>3</sub>)<sub>3</sub>), 120.6 (CCO(Q)), 126.1, 126.6, 126.9, 127.4, 127.8, 128.9, 134.6 (7 x CH), 146.0 (CN=C(Q)), 155.4, 158.3 and 161.2 (C=N(Q), CO(Q), CO) (CH, C missing); *m/z* 467 (*MH*<sup>+</sup>, 100), 411 (32), 260 (50), 215 (42), 175 and (30).

***Q-N bond reduction of N'-BOC, N-(Q)-diamine 145 using samarium  
(II) iodide***



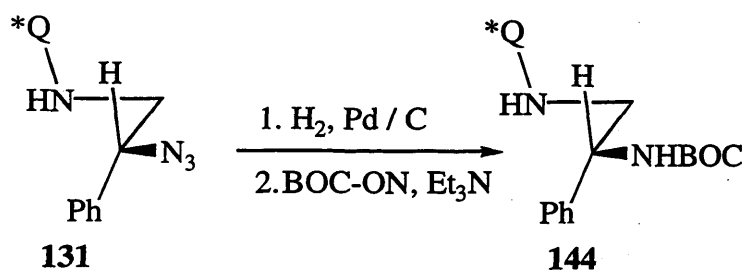
A flame-dried 3-necked flask equipped with stirrer bar under argon atmosphere was charged with amine **145** (184 mg, 0.39 mmol) dissolved in freshly distilled and dried THF (3 cm<sup>3</sup>) containing *tert*-butyl alcohol (1 cm<sup>3</sup>) *via* septum cap and the solution degassed 5 times with argon using a 3-way tap. A solution of samarium diiodide in THF (9 cm<sup>3</sup>, 0.1 moldm<sup>-3</sup>) was added slowly dropwise using a syringe *via* the septum cap with stirring; discharge of the blue colour of Sm (II) occurred almost instantaneously. Water (10 cm<sup>3</sup>) was added, followed by triethylamine (0.2 cm<sup>3</sup>) and BOC-ON (107 mg, 0.43 mmol), stirring throughout. After 2 h the solution was filtered, extracted with ethyl acetate (20 cm<sup>3</sup>), the organic layer separated, washed with brine (10 cm<sup>3</sup>), dried and evaporated to dryness under reduced pressure. Chromatography (eluent 4 : 1 light petroleum-ethyl acetate) yielded DIBOC-diamine **147** (R<sub>f</sub> 0.18, visualised with phosphomolybdic acid) (99 mg, 73 %). Crystallisation gave **147** as colourless needles mp 150-152 °C (from light petroleum-ethyl acetate). (Found: C 64.2, H 8.25, N 8.3. C<sub>18</sub>H<sub>28</sub>N<sub>2</sub>O<sub>4</sub> requires C 64.25, H 8.4 and N 8.3 %); α<sub>D</sub> 29.16 ° (c 1.20, CHCl<sub>3</sub>); ν<sub>max</sub>/cm<sup>-1</sup> 3450 m, 2980 s, 1710 s, 1455 m, 1370 s, 1250 s, 1170 s and 725 s; δ<sub>H</sub> (-40 °C, 9.4:1 ratio of rotamers) major rotamer 1.41 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.45 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 3.31 (1H, struct. m, CHH), 3.49 (1H, struct. m, CHH), 4.72 (1H, struct. m, CHAr), 4.96 (1H, t, *J* 5.7, CH<sub>2</sub>NH), 5.83 (1H, d, *J* 7.3, CHNH) and 7.27 - 7.42 (5H, struct. m, 5 x CH(Ar)); m/z 359 (MNa<sup>+</sup>, 10), 337 (MH<sup>+</sup>, 33), 281 (21), 225 (100), 181 (87), 164 (60) and 150 (39).

Minor rotamer observable signals δ<sub>H</sub> 3.12 (1H, struct. m, CHH), 4.59 (1H, struct. m, CHAr), 5.12 (1H, struct. m, CH<sub>2</sub>NH) and 5.68 (1H, d, *J* 7.3, CHNH).



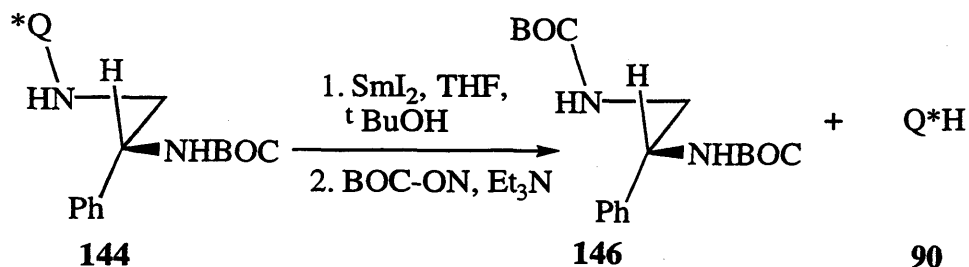
Further elution with 2 : 1 light petroleum-ethyl acetate yielded 3-H-quinazolinone **90** (60 mg, 66 %).

**Conversion of azide **131** to *N*-BOC, *N'*-(*Q*)-diamine **144****



Azide **131** (418 mg, 1.06 mmol) was dissolved in ethyl acetate (10 cm<sup>3</sup>), 5% palladium on charcoal (40 mg) added and the mixture stirred rapidly for 48 h under an atmosphere of hydrogen. The solution was then filtered through a plug of celite, the solvent removed under reduced pressure and the residue dissolved in a mixture of 1:1 THF/water (10 cm<sup>3</sup>). To the stirred solution was then added triethylamine (0.2 cm<sup>3</sup>) and BOC-ON (289 mg, 1.17 mmol). After stirring at room temperature for 45 min a solid had precipitated and was filtered off and washed with cold ethanol. Crystallisation yielded *N*-BOC, *N'*-(*Q*)-diamine **144** (206 mg, 41 %) mp 225-227 °C (from ethanol-dichloromethane) (Found C 66.5, H 7.25, N 12.2 C<sub>26</sub>H<sub>34</sub>N<sub>4</sub>O<sub>4</sub> requires C 66.9, H 7.35, N 12.0 %);  $\alpha_D$  105.55 ° (c 0.36, CHCl<sub>3</sub>);  $\nu_{\text{max}}/\text{cm}^{-1}$  2950 m, 1710 s, 1680 s, 1595 s, 1495 s, 1470 m, 1370 m, 1180 m and 1080 m;  $\delta_H$  1.00 (9H, s, C(CH<sub>3</sub>)<sub>3</sub>), 1.44 (9H, s, OC(CH<sub>3</sub>)<sub>3</sub>), 3.11 (1H, struct. m, CHH), 3.57 (1H, struct. m, CHH), 3.62 (1H, d, *J* 10.1, OH), 4.94 (1H, d, *J* 10.1, CHOH), 4.98 - 5.08 (2H, br m, CHNH, NHCO), 5.40 (1H, dd, *J* 4.1 and 10.0, NH), 7.27 - 7.41 (5H, struct. m, 5 x *H*(Ph)), 7.47 (1H, ddd, *J* 1.2, 6.9 and 7.9, *H*<sub>6</sub>(*Q*)), 7.67 (1H, br d, *J* 8.2, *H*<sub>8</sub>(*Q*)), 7.76 (1H, ddd, *J* 1.2, 6.9 and 8.2, *H*<sub>7</sub>(*Q*)) and 8.23 (1H, dd, *J* 1.2 and 7.9, *H*<sub>5</sub>(*Q*)); *m/z* 467 (MH<sup>+</sup>, 49), 260 (39) and 215 (20).

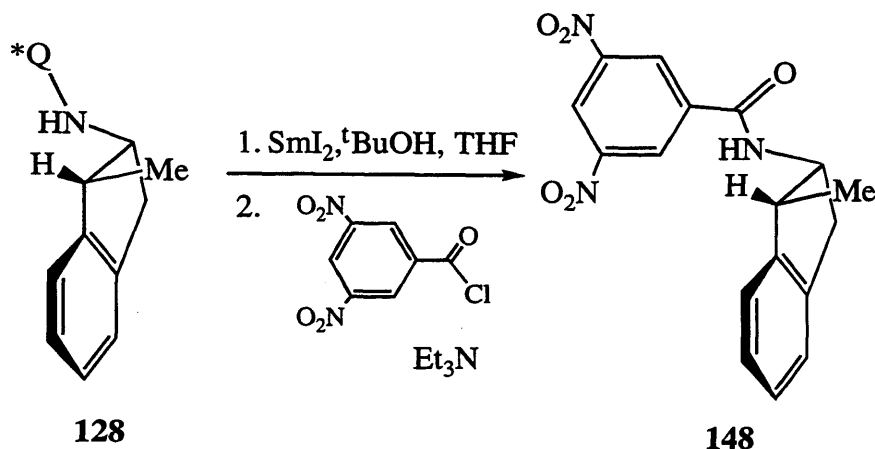
***Q-N bond reduction of N'-BOC, N-(Q)-diamine 144***



Carried out as described previously using amine **144** (196 mg, 0.42 mmol), dry distilled THF (3 cm<sup>3</sup>), *tert*-butyl alcohol (1 cm<sup>3</sup>), samarium diiodide in THF (10 cm<sup>3</sup>, 0.1 moldm<sup>-3</sup>), water (10 cm<sup>3</sup>), triethylamine (0.2 cm<sup>3</sup>) and BOC-ON (114 mg, 0.46 mmol). Chromatography (eluent 4 : 1 light petroleum-ethyl acetate) eluted unchanged starting amine ( $R_f$  0.2), (19 mg) followed by DIBOC-diamine **146** ( $R_f$  0.18, visualised with phosphomolybdic acid), 96 mg, 75 % (based on recovered starting material);  $\alpha_D$  - 28.0 ° (c 1.0, CHCl<sub>3</sub>); all other physical data i.e. mp, mass spectrometry data, NMR and IR spectra identical to that for other enantiomer **147** (see previously).

Further elution with 2 : 1 light petroleum-ethyl acetate yielded 3-H-quinazolinone **90** (78 mg, 89%) identical with that isolated previously.

***Q-N bond reduction of indene-derived N-(Q)-amine 128***

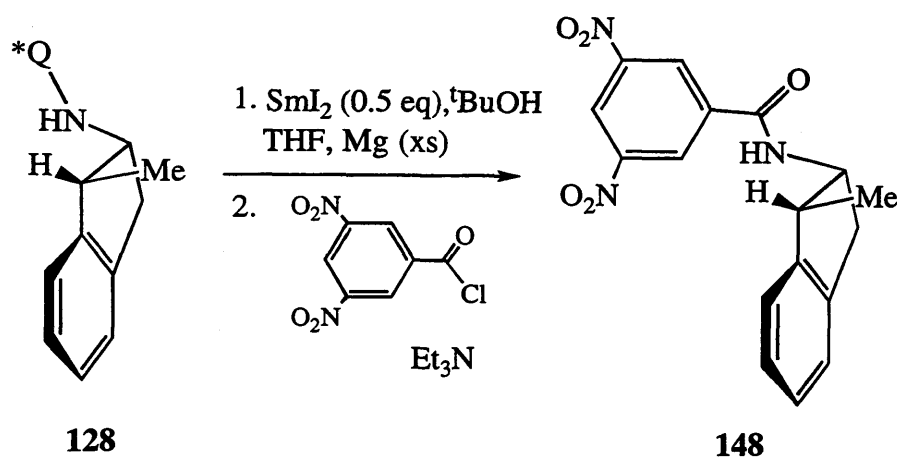


Using the procedure described above amine **128** (206 mg, 0.55 mmol) in THF (8 cm<sup>3</sup>) containing *tert*-butyl alcohol (1 cm<sup>3</sup>) was reduced with a solution of samarium diiodide in THF (33 cm<sup>3</sup>, 0.1 mol dm<sup>-3</sup>). After the solution had decolourised (~80 min), triethylamine (1 cm<sup>3</sup>) was added, followed by 3,5-dinitrobenzoylchloride (264 mg, 1.14 mmol) and the resulting red solution stirred for 2 h. Saturated sodium hydrogen carbonate solution (10 cm<sup>3</sup>) was added, the solution filtered and ethyl acetate (20 cm<sup>3</sup>) added to the filtrate. After shaking, the organic layer was separated, washed with brine (10 cm<sup>3</sup>), dried and evaporated under reduced pressure. Chromatography (eluent 5 : 1 light petroleum-ethyl acetate) yielded amide 148 ( $R_f$  0.23) (151 mg), 81 %. mp 172-174 °C (from light petroleum-ethyl acetate) (Found: C 60.1, H 4.5, N 12.2. C<sub>17</sub>H<sub>15</sub>N<sub>3</sub>O<sub>5</sub> requires C 59.8, H 4.4, N 12.3 %);  $\alpha_D$  -40.18 ° (c 1.12, CHCl<sub>3</sub>);  $\nu_{\text{max}}/\text{cm}^{-1}$  3430 w, 3100 m, 2960 m, 1735 m, 1675 s, 1545 s, 1345 s, 1275 m, 1080 m and 920 m;  $\delta_{\text{H}}$  1.41 (3H, d,  $J$  6.9, CH<sub>3</sub>), 2.89 (1H, dd,  $J$  6.3, 16.0, CHH), 3.23 (1H, quin,  $J$  6.9, CHCH<sub>3</sub>), 3.51 (1H, dd,  $J$  7.5, 16.0, CHH), 4.56 (1H, struct. m,  $J$  6.3 and 7.5 visible, CHNH), 6.56 (1H, br. d,  $J$  7.5, NH), 7.24 (4H, s, 4 x  $H(\text{Ph})$ ), 8.94 (2H, d,  $J$  2.2,  $H$ -2,  $H$ -6 ((NO<sub>2</sub>)<sub>2</sub>Ar)) and 9.16 (1H, s m,  $H$ -4 ((NO<sub>2</sub>)<sub>2</sub>Ar));  $m/z$  342 (MH<sup>+</sup>, 69), 259 (48) and 147 (33).

Further elution with the same solvent yielded OH-O-(3,5-dinitrobenzoate) 149 ( $R_f$  0.10) (72 mg, 31%). (Found: MH<sup>+</sup> 427.12539. C<sub>20</sub>H<sub>19</sub>N<sub>4</sub>O<sub>7</sub> requires MH<sup>+</sup> 427.12538);

$\nu_{\max}/\text{cm}^{-1}$  2980 w, 1740 m, 1670 s, 1610 m, 1550 s, 1470 m, 1345 s, 1270 m and 1160 m;  $\delta_{\text{H}}$  1.18 (9H, s,  $\text{C}(\text{CH}_3)_3$ ), 5.47 (1H, s,  $\text{CHO}$ ), 7.39 (1H, ddd,  $J$  1.3, 7.0 and 8.0,  $\text{H}_6(\text{Q})$ ), 7.63 (1H, dd,  $J$  1.3 and 8.2,  $\text{H}_8(\text{Q})$ ), 7.72 (1H, ddd,  $J$  1.0, 7.0 and 8.2,  $\text{H}_7(\text{Q})$ ), 8.08 (1H, dd,  $J$  1.0 and 8.0,  $\text{H}_5(\text{Q})$ ), 8.98 (1H, t,  $J$  2.2,  $\text{H}-4$  ( $(\text{NO}_2)_2\text{Ar}$ ); 9.21 (2H, d,  $J$  1.9,  $\text{H}-2$ ,  $\text{H}-6$  ( $(\text{NO}_2)_2\text{Ar}$ ); and 11.95 (1H, s,  $\text{NH}$ );  $\delta_{\text{C}}$  26.5 ( $\text{C}(\text{CH}_3)_3$ ), 35.7 ( $\text{C}(\text{CH}_3)_3$ ), 83.9 ( $\text{CHO}$ ), 120.7 ( $\text{CCO}(\text{Q})$ ), 122.6, 126.0, 127.2, 127.8, 129.7 (5 x  $\text{CH}(\text{Q})$ ,  $\text{CH}(\text{Ar})$ ), 132.8 ( $\text{C}(\text{Ar})$ ), 135.2 ( $\text{CH}(\text{Q})$ ), 148.2, 148.6, 151.5 ( $\text{CN}=\text{C}(\text{Q})$ , 2 x  $\text{C}(\text{Ar})$ ), 162.4 ( $\text{C}=\text{N}(\text{Q})$ ) and 163.9 ( $\text{CO}(\text{Q})$ ) ( $\text{CO}$ , ( $\text{CH}(\text{Ar})$  missing);  $m/z$  427 ( $\text{MH}^+$ , 51), 307 (20) and 215 (47).

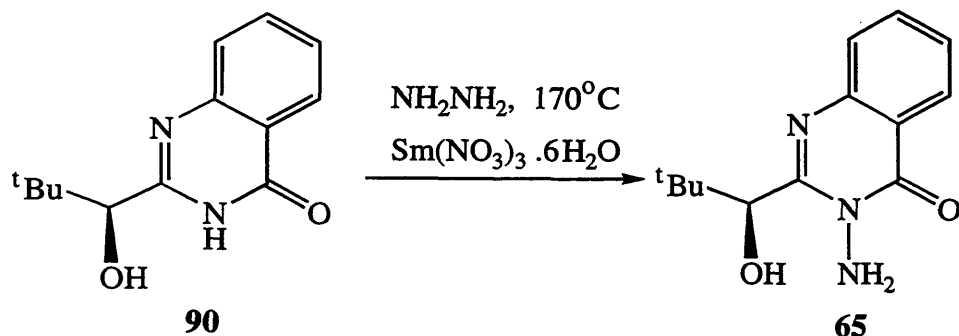
***Q-N bond reduction of indene-derived N-(Q)-amine 128 using samarium (II) iodide and magnesium***



Scheme 75

Magnesium turnings (305 mg, 12.7 mmol) were stirred vigorously overnight in a flame-dried 3-necked flask under an argon atmosphere. The amine **128** (150 mg, 0.4 mmol) dissolved in freshly distilled THF (2 cm<sup>3</sup>) and *tert*-butyl alcohol (1 cm<sup>3</sup>) were added *via* a septum cap and the solution de-gassed 5 times with argon using a 3-way tap. A solution of samarium diiodide in THF (2 cm<sup>3</sup>, 0.1 mol dm<sup>-3</sup>) was added *via* the septum cap and the disappearance of the amine monitored by TLC. After 2.5 h the solution was transferred *via* a canula into a round bottom flask under argon atmosphere and triethylamine (1 cm<sup>3</sup>) and 3,5-dinitrobenzoylchloride (193 mg, 0.84 mmol) added with stirring. After 2 h the solution was filtered, saturated sodium hydrogen carbonate solution (5 cm<sup>3</sup>) added and the mixture extracted with ethyl acetate (20 cm<sup>3</sup>). The organic layer was separated, washed with brine, dried and evaporated under reduced pressure. Chromatography of this residue (eluent 5 : 1 light-petroleum-ethyl acetate) yielded the amide **148** ( $R_f$  0.23) (94 mg, 69 %). Further elution with the same solvent yielded benzoylated QH-*O*-3,5-dinitrobenzoate **149** ( $R_f$  0.10) (87 mg, 51 %).

### Amination of 3-H-quinazolinone **90**

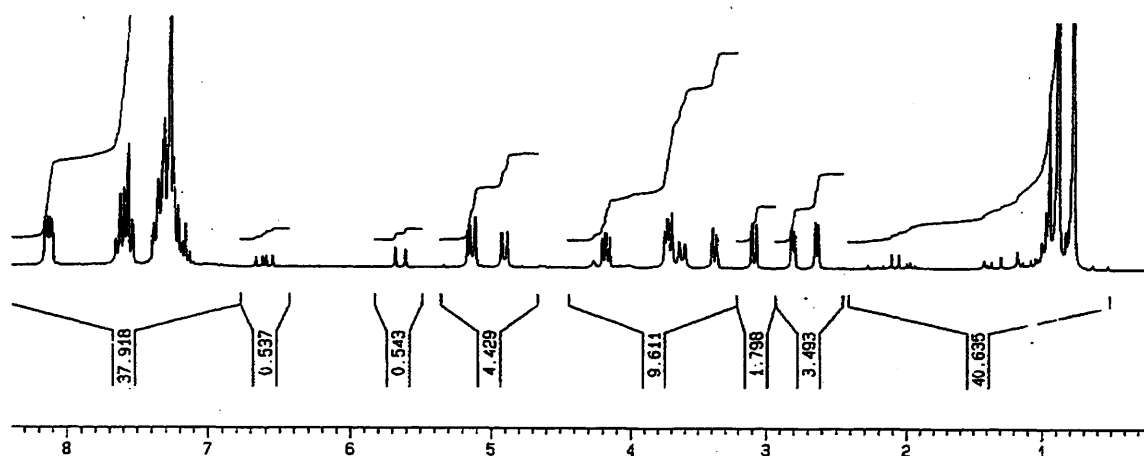


A Young's tube was charged with 3-H-quinazolinone **90** (60 mg, 0.26 mmol) in ethanol (2 cm<sup>3</sup>), hydrazine monohydrate (0.04 cm<sup>3</sup>, 0.82 mmol) and samarium nitrate hexahydrate (115 mg, 0.26 mmol) and heated at 170 °C for 24 h. After addition of water (5 cm<sup>3</sup>) the solution was filtered and extracted with ethyl acetate (10 cm<sup>3</sup>). The organic layer was separated, washed with brine (5 cm<sup>3</sup>), dried and evaporated under reduced pressure. Chromatography (eluent 2 : 1 light petroleum-ethyl acetate) yielded 3-aminoquinazolinone **65** (*R<sub>f</sub>* 0.33), (41 mg, 67%) (75% yield based on recovered starting material).  $\alpha_D$  19.58 ° (c 0.97, ethanol).

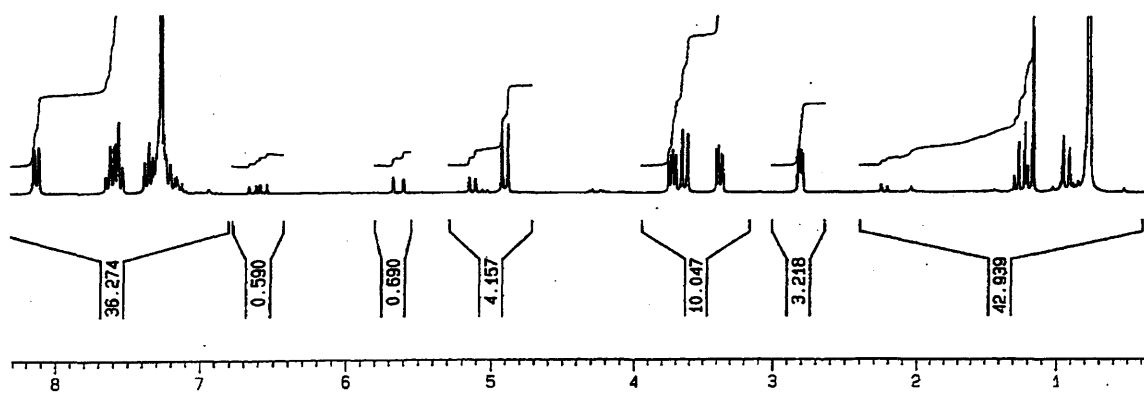
Further elution with the same solvent yielded unchanged starting material **90** (*R<sub>f</sub>* 0.15) (9 mg).

The same reaction carried out in the absence of samarium nitrate hexahydrate gave unreacted starting material (Q\*H **90**) from NMR spectroscopy of the crude reaction product.

## ***Appendix I***

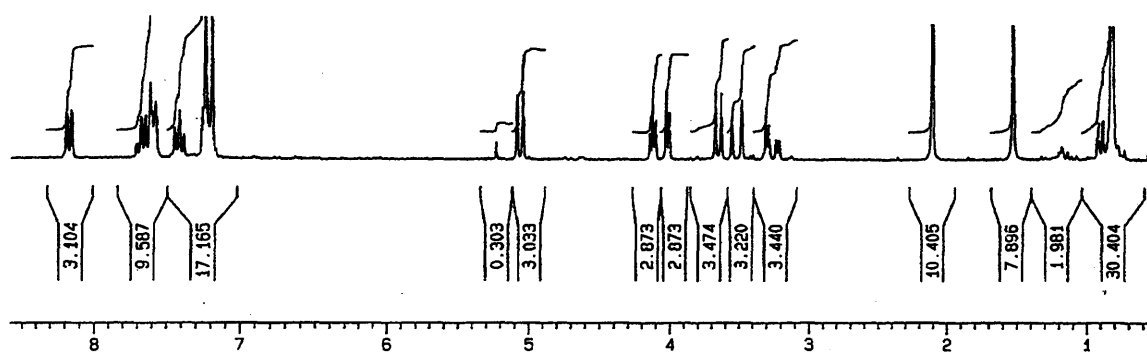


NMR spectrum of the crude product from aziridination of styrene with  
Q\*NHOAc **49**

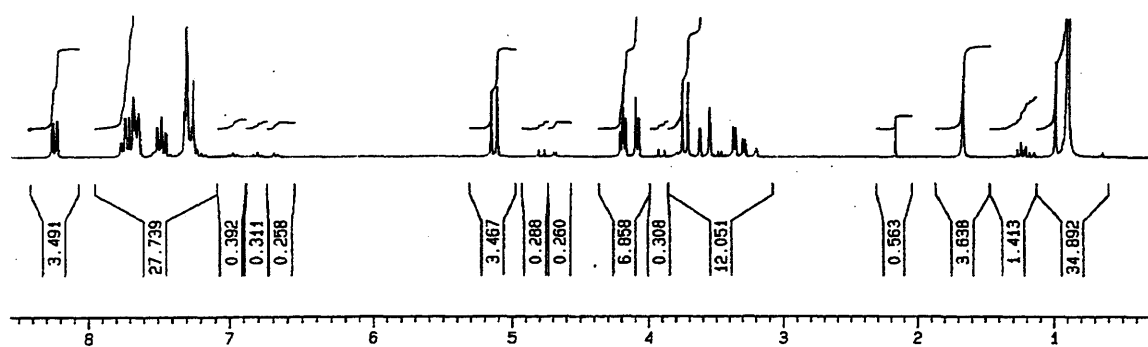


NMR spectrum of the crude product from aziridination of styrene with  
Q\*NHOAc **49** in the presence of  $\text{Ti}(\text{O}^t\text{Bu})_4$





Room temperature NMR spectrum of aziridine **74** taken after dissolution at -40 °C



Room temperature NMR spectrum of aziridine **74** after 30 min. at room temperature

## ***Appendix II***

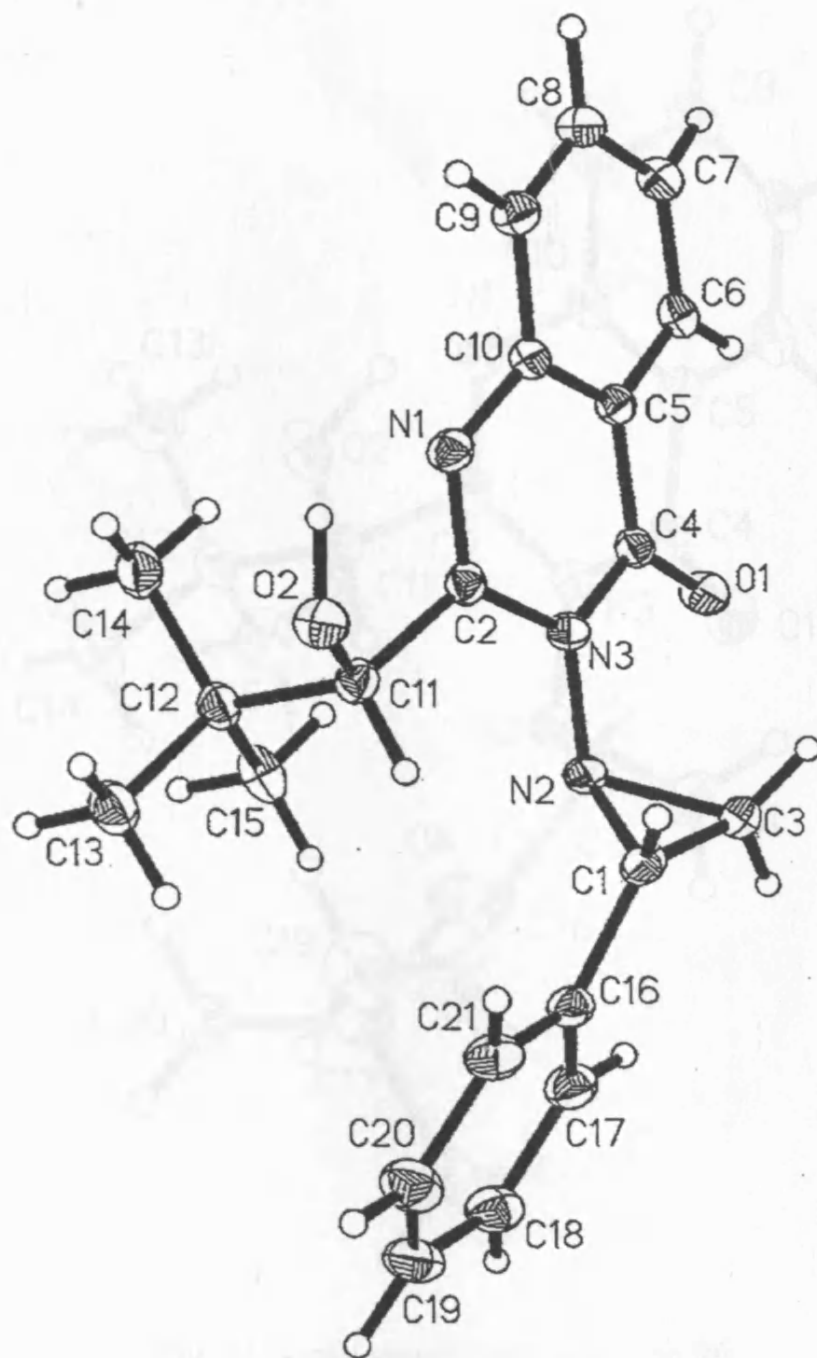


Fig. 30 X-ray structure of aziridine **69**

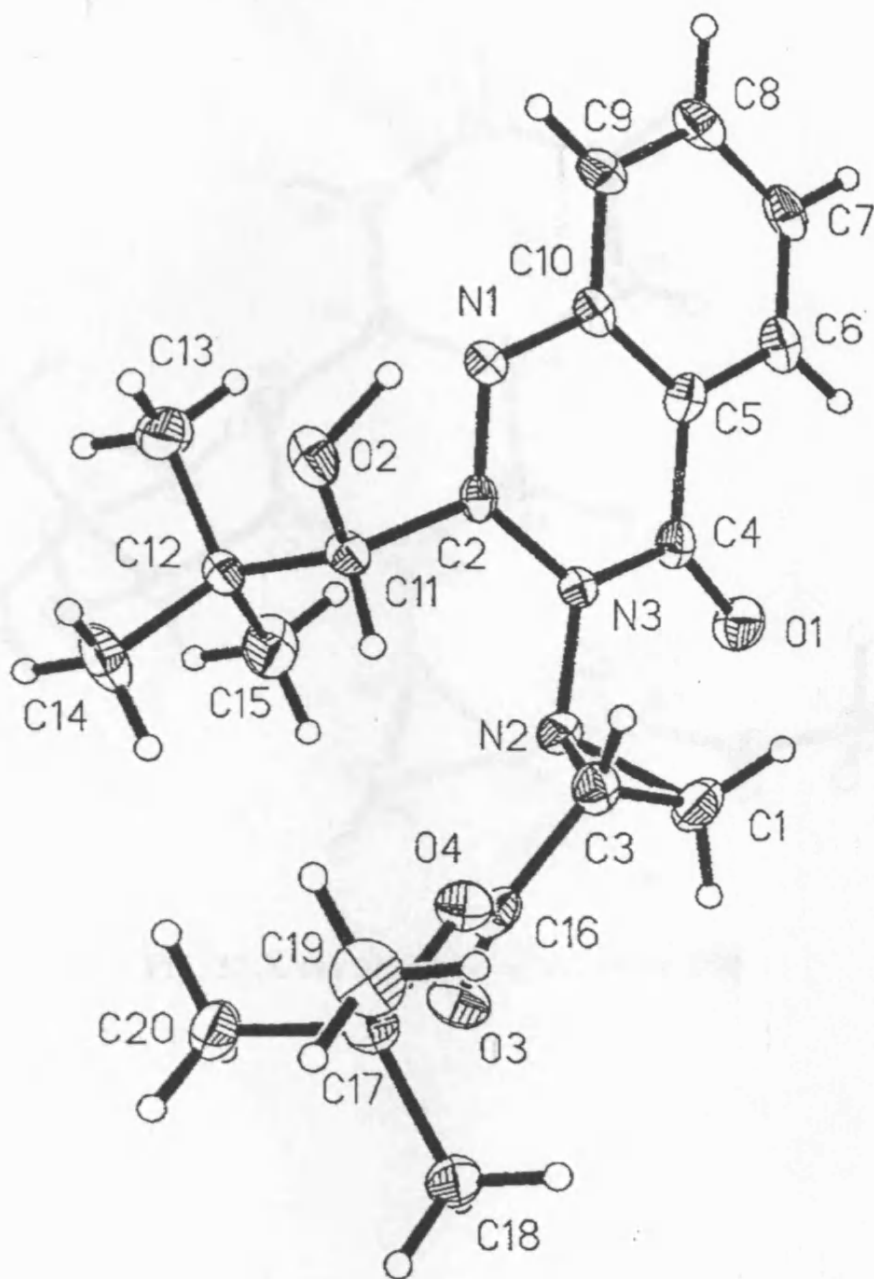


Fig. 31 X-ray structure of aziridine 96

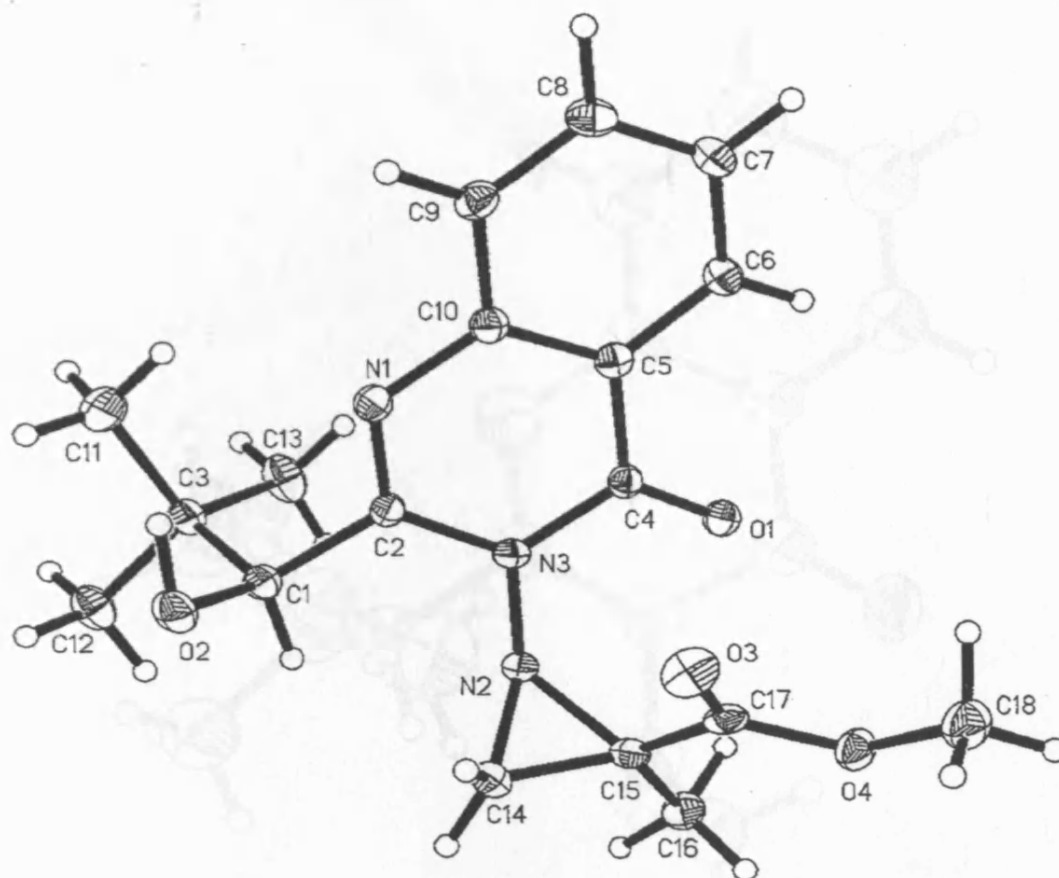


Fig. 32 X-ray structure of aziridine 100

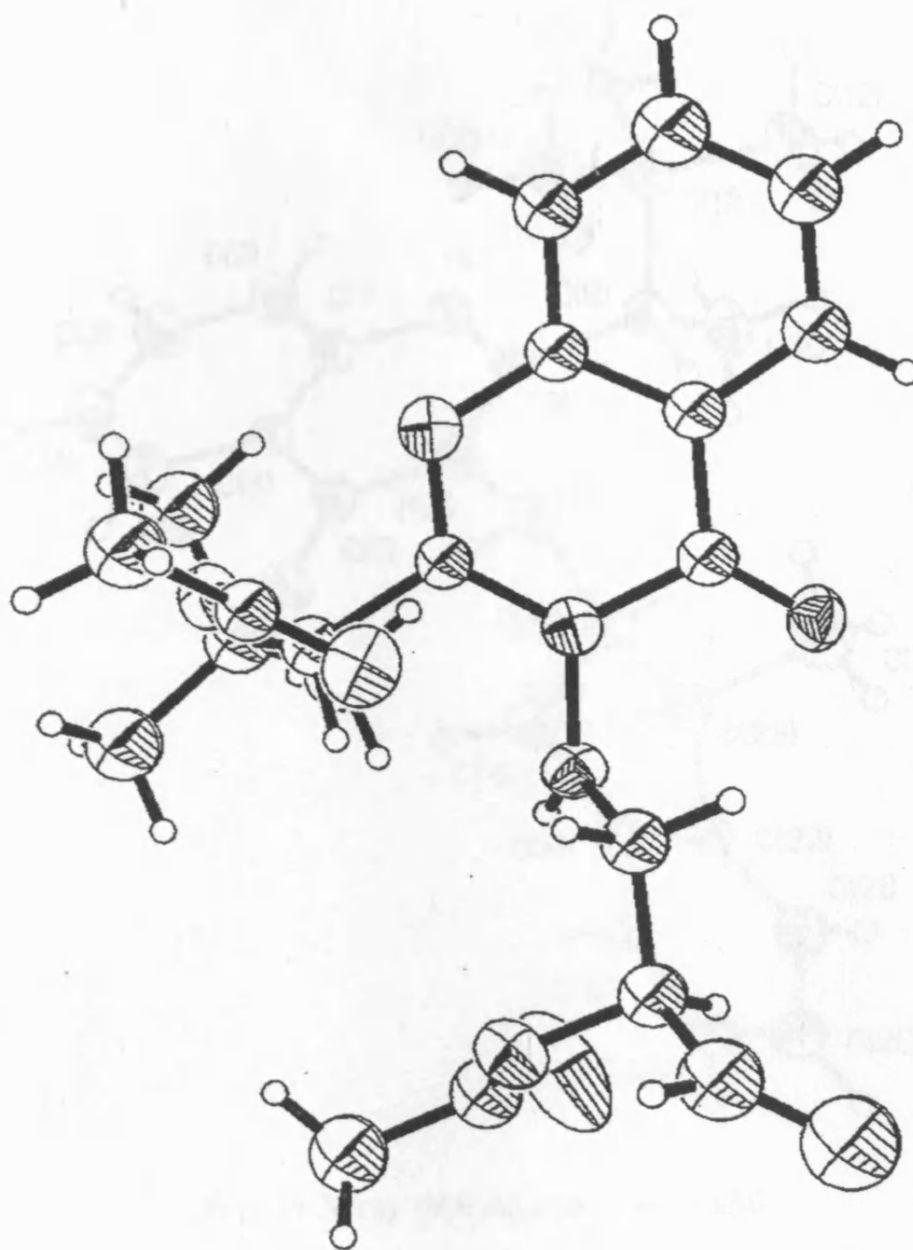


Fig. 33 X-ray structure of di-acetate **108**

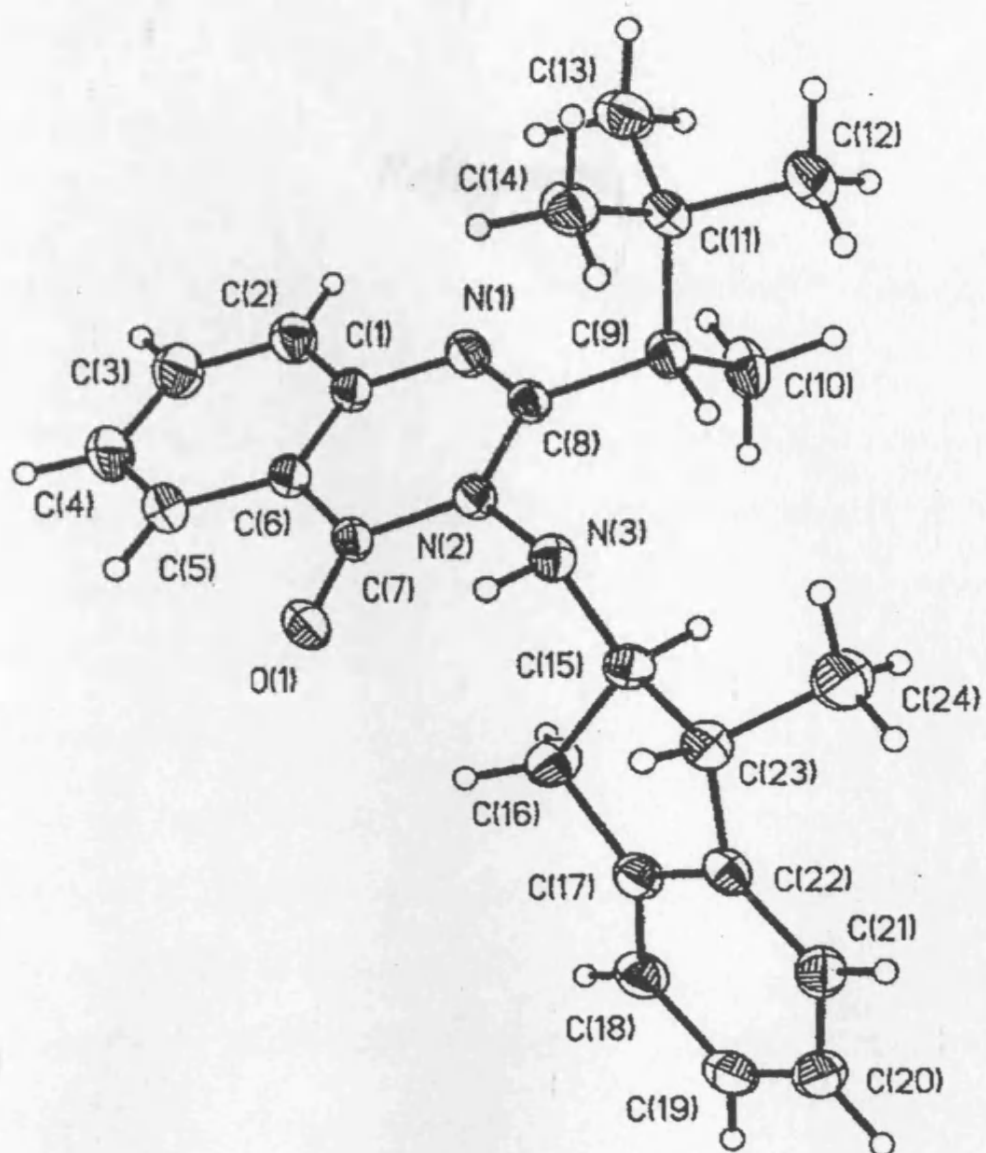


Fig. 34 X-ray structure of indane **130**

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