SYNTHESIS OF FUSED MEDIUM-RING HETEROCYCLES
BY THE REARRANGEMENT OF
QUATERNARY AMMONIUM DERIVATIVES

by

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HOBART

DECEMBER, 1994.

To my parents

and my wife

(i)

This thesis contains no material which has been accepted for the award of any other degree or diploma in any University, nor, to the best of my knowledge and belief does it contain any copy or paraphrase of material previously published or written by another person, except where due reference is included in the text.

ABSTRACT

The general aim of this study was to develop new modes of access to benz-fused medium-ring heterocycles. The approach adopted was to utilise the rearrangements, with concurrent ring expansion, of heterocyclic quaternary ammonium *N*-ylides and *N*-oxides. Of particular interest were new applications of the [2,3] rearrangements of these systems.

Base promoted [2,3] sigmatropic rearrangement of 1-vinyl-2-ethoxycarbonylmethyl-1,2,3,4-tetrahydroisoquinolinium salts at room temperature in acetonitrile afforded functionalised 2,3,4,5-tetrahydro-*1H*-3-benzazonine derivatives, as mixtures of the olefinic isomers, in high yields. This is the first application of this rearrangement to the synthesis of benz-fused aza-heterocycles. A stereoselective preference for the formation of the *E*-benzazonines was observed. The *E*-benzazonines degraded to polar material on p.t.l.c. and acid-catalysed transannular interactions were proposed. The rearrangement reaction at high temperature also provided 1-vinyl-2,3,4,5-tetrahydro-*1H*-benzazepines, the products of [1,2] Stevens rearrangement. The mechanisms and product distributions of these rearrangements are discussed, with reference to models of the expected concerted transition states.

Application of the [2,3] sigmatropic rearrangement to 1-vinyl-tetrahydroisoquinolinium salts with nitrile or phenacyl ylide stabilising groups provided the appropriate 4-substituted-2,3,4,5-tetrahydro-*1H*-3-benzazonine derivatives in good yields. Successful [2,3] rearrangement of the phenacyl stabilised ylide was limited to low temperatures, with Stevens rearrangement products being isolated selectively at high temperature. Rearrangement of an unstabilised methylene ylide, generated by fluorodesilylation, gave a 4-unsubstituted 3-benzazonine in low yield. Base-promoted rearrangement of *N*-methyl-tetrahydro-isoquinolinium salts with no ylide stabilising group afforded Hofmann elimination

products and demonstrated a limitation on the potential synthetic uses of the [2,3] rearrangement.

Rearrangement of vinyl substituted 2-ethoxycarbonylmethyl-tetrahydro-isoquinolinium salts gave, in most cases, 6- or 7-substituted-2,3,4,5-tetrahydro-*1H*-3-benzazonine derivatives via the [2,3] rearrangement. A decrease in the *E*-stereoselectivity of the rearrangement was observed from C1'-substituted salts and probably reflected changes in the preferred concerted transition state geometry. Limitations to the potential uses of the [2,3] rearrangement were exemplified by the rearrangements of the 2',2'-dimethyl and *trans*-2'-dimethoxyphenyl salts at room temperature. The former provided a mixture of the [1,2] and [2,3] rearrangement products, indicative of steric interference by the *cis*-2'-methyl group with the concerted transition state, while the latter gave the Stevens rearrangement product selectively, indicative of promotion of the [1,2] radical pathway by the radical stabilising group at C2'.

Hydrogenation of the *E*-2,3,4,5-tetrahydro-*1H*-3-benzazonines gave 2,3,4,5,6,7-hexahydro-derivatives, while the *Z*-2,3,4,5-tetrahydro-*1H*-3-benzazonines were unaffected. Hydrogenation of a 6-methyl-2,3,4,5-tetrahydro-*1H*-3-benzazonine derivative was accompanied by a [1,3] hydrogen shift to an endocyclic olefinic 3-benzazonine. Hydrogenolysis of an *N*-benzyl-tetrahydro-3-benzazonine could not be obtained preferentially without concurrent hydrogenation. The reaction afforded a secondary amine derivative of the 3-benzazonine system.

The [2,3] rearrangement of a 2-(tetrahydro-2'-furanon-3'-yl)-1-vinyl-tetrahydroisoquinolinium salt afforded the first example of the 2,3,4,5-tetrahydro-1*H*-3-benzazonine-4-spiro-3'-tetrahydro-2'-furanone ring system in low yield.

An effort to extend the [2,3] rearrangement to the synthesis of unsaturated 3-benzazonines from a 1-ethynyl-tetrahydroisoquinolinium salt gave only the Stevens rearrangement product in poor yield.

Thermolysis of 1-vinylic-tetrahydroisoquinolinium *N*-oxides unsubstituted at C1' failed to provide [2,3] rearrangement and afforded 1-vinylic-1,3,4,5-tetrahydro-

2,3-benzoxazepines in good yield by the Meisenheimer rearrangement. Neat pyrolysis of the 1-vinyl-benzoxazepines gave an unexpected isomerisation to 1,3,3a,4,9,9a-hexahydroisoxazolo[3,4-b]naphthalene derivatives. This isomerisation may involve the formation and reaction of a nitrone intermediate.

Thermolysis of 1'-substituted-1-vinylic-tetrahydroisoquinolinium N-oxides gave the first representatives of the 4,3-benzoxazonine system in mixtures with the Meisenheimer rearrangement products. The Z-olefinic 1,2,3,5-tetrahydro-4,3-benzoxazonines were formed selectively. A stereoselective concerted [2,3] rearrangement of the cis-N-oxides was indicated as thermolysis in refluxing dichloromethane gave the 4,3-benzoxazonines with unchanged trans-N-oxides. The structure of a 4,3-benzoxazonine was unequivocally established by X-ray structural analysis. The 4,3-benzoxazonines were thermally labile and in refluxing xylene gave equilibrium mixtures with, and favouring, the less-strained 1-vinylic-2,3-benzoxazepines.

Meisenheimer rearrangement of a 5,6-dihydro-4H-s-triazolo[4,3-a]-1,4-benzodiazepine N-oxide afforded a 4,5-dihydro-7H-s-triazolo[4,3-a]-5,1,4-benzoxadiazocine, the first representative of this ring system, with structural similarities to the CNS active agent 'Alprazolam'.

Further extension of the Meisenheimer rearrangement to tricyclic bridgehead N-oxides of the 10b-vinyl-pyrrolo[2,1-a]isoquinoline and 11b-vinyl-benzo[a]quinolizine systems gave, in low yield, the first examples of the 3,7-epoxy-3-benzazonine and 2H-3,8-epoxy-3-benzazecine ring systems.

Modification of the Meisenheimer and Stevens rearrangement to give a four atom ring expansion by the inclusion of an α-cyclopropyl substituent was also investigated. Thermolysis of a 1-cyclopropyltetrahydroisoquinoline N-oxide gave the 2,3-benzoxazepine product of the Meisenheimer rearrangement. Thermolysis of a 1-(2'-phenylcyclopropyl)tetrahydroisoquinoline N-oxide derivative gave the Meisenheimer rearrangement product and, in low yield, a 2,3,5,6-tetrahydro-5-phenyl-1H-4,3-benzoxazecine derivative. Formation of the 4,3-benzoxazecine

system, the first example of this ring system, confirmed the plausibility of a modified rearrangement pathway. The 4,3-benzoxazecine structure was confirmed by X-ray crystallography. Base promoted rearrangement of the analogous 1-cyclopropyl or 1-(2'-phenylcyclopropyl)-*N*-ethoxycarbonylmethyl salts afforded only 3-benzazepine derivatives by the Stevens rearrangement.

N-Alkylation of a 1-(2'-phenylcyclopropyl)-3,4-dihydroisoquinoline at moderate temperatures with iodomethane gave an unexpected Cloke rearrangement and a new route to the pyrrolo[2,1-*a*]isoquinoline system. The structure of the *N*-methyl-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolinium iodide product was unequivocally established by X-ray structural analysis.

The global minima and low energy conformations of the 2,3,4,5-tetrahydro-*1H*-3-benzazonine, 1,2,3,5-tetrahydro-4,3-benzoxazonine, and 2,3,5,6-tetrahydro-*1H*-4,3-benzoxazecine systems were determined with the molecular mechanics-based program PCModel and, where possible, compared with X-ray crystallographic results. The implications of the conformers found for the properties of these compounds are discussed. It is envisaged that these studies may allow the future assessment of the potential of these compounds as CNS active agents.

The present study has provided the synthesis of many novel isoquinoline derivatives necessary for the investigations described above and has established new synthetic routes to five known and six new benz-fused medium ring heterocyclic systems.

ACKNOWLEDGEMENTS

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CHAPTER 1

INTRODUCTION

1.1   General Introduction

The past thirty years have seen a tremendous drive towards the synthesis of novel nitrogen-containing heterocycles. This has occurred due to the large demand for synthetic access to natural alkaloids and the recognised commercial potential of many heterocyclic compounds as, typically, agricultural chemicals, dyes, or pharmaceuticals. In particular many nitrogen heterocycles containing aromatic moieties have found application as central nervous system (CNS)-active pharmaceutical agents.

Although benz-fused medium-sized (8- to 11-membered) heterocycles containing nitrogen, or both nitrogen and oxygen, have a high potential for CNS activity, research in this area has been limited and sporadic. The CNS potential of the benz-fused medium-sized nitrogen heterocycles arises from the presence of the aromatic and nitrogen atom moieties. Lloyd and Andrews proposed[1] a primary pharmacophore for activity over all CNS receptor types using these two moieties. In particular, medium-sized rings may be used to provide constrained analogues of known drugs with less side-effects. Nefopam hydrochloride, a 2,5-benzoxazocine (Figure 1.1) is a non-narcotic analgesic with muscle relaxant, anti-cholinergic and anti-histaminic properties[2] which acts as a cyclised, constrained, analogue of the parent antihistamine diphenhydramine.[3,4,5] It is also possible that a medium-sized ring may substitute for a rigid combination of smaller rings. For example, the structure of the dopamine agonist apomorphine (Figure 1.1), known for its emetic effect,[6] suggests that a 6,7- or 7,8-unsaturated 3-benzazecine derivative would have a high potential for CNS activity.

Considerable scope remains for the synthesis of new benz-fused medium-sized nitrogen heterocycles. For example, only 18 of the 100 possible medium-sized

benzoxaza- skeletons are presently known.[7] In addition, alternate methods of access to those already known are required to enable detailed structure-pharmacological property relationship studies incorporating new functionalities.

Nefopam   Apomorphine
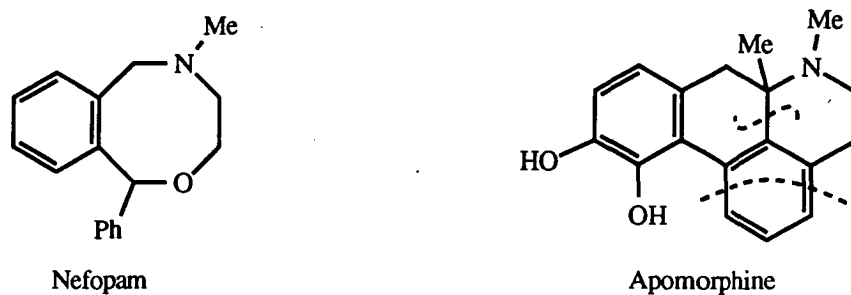
Figure 1.1

1.1.1 Project Aims

The aims of this project were to examine a set of ring interconversion reactions involving the rearrangements of N-ylides and N-oxides, and to develop their application to the syntheses of benz-fused medium-sized nitrogen heterocycles. The reactions to be investigated are outlined schematically in Figure 1.2.

N-ylides, Y = CHR^2 aza-heterocycles, Y = CHR^2
N-oxides, Y = O   oxaza-heterocycles, Y = O
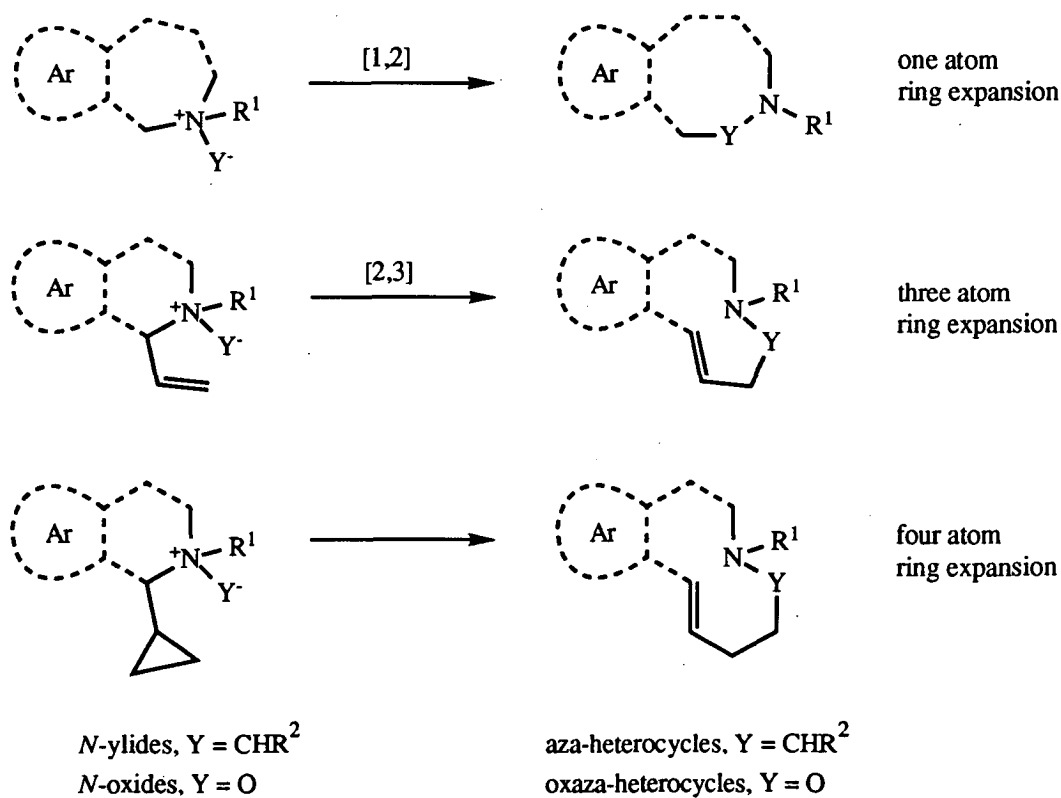
Figure 1.2 Ring Interconversions of N-Ylides and N-Oxides

1.2   Introduction to [1,2] Rearrangements

The [1,2] rearrangements of *N*-ylides and *N*-oxides, termed the Stevens and Meisenheimer rearrangements respectively, have been extensively studied and are the subject of several reviews.[8,9,10,11] The rearrangement may be viewed formally as a nucleophilic substitution at the migrating carbon with an anionic centre replacing the electron deficient nitrogen. The Meisenheimer rearrangement occurs thermally from an *N*-oxide. The Stevens rearrangement proceeds via *in situ* generation of an *N*-ylide, typically in the presence of a base. The [1,2] rearrangement may provide a one atom ring expansion and 1,2-oxaza heterocycles (Figure 1.2).

1.2.1   Mechanism

A radical-pair mechanism is currently accepted for these rearrangements, with homolytic cleavage of the C-N bond prior to radical rearrangement and recombination in a solvent cage (Figure 1.3). The radical-pair mechanism was adopted, rather than a comparable ion-pair mechanism, as chemically induced dynamic nuclear polarization (CIDNP) spectra, indicative of free-radicals, were observed during the rearrangements.[12] Experiments showing retention of configuration in the migrating group (R[1]), contrary to orbital symmetry principles, have precluded a concerted mechanism. In practice, electron delocalising migrating groups have provided the highest rearrangement yields. Benzylic and allylic groups are most often used.

N-ylides, Y = CHR[4]
N-oxides, Y = O
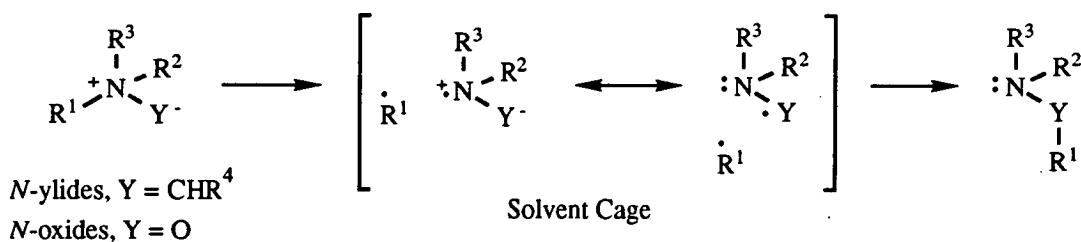
Figure 1.3

1.2.2 Competing Reactions

The Hofmann and Cope eliminations of quaternary ammonium salts and *N*-oxides (Figure 1.4) containing a *beta*-hydrogen atom can interfere with other rearrangements. The Hofmann elimination may compete with *N*-ylide generation when the prevalent technique of ylide generation by the removal of an *alpha*-hydrogen with a strong base is used. The elimination may be prevented by selection of the appropriate base and incorporation of an electron-withdrawing group (R^4) to provide an acidic *alpha*-hydrogen. The Cope elimination requires a five-membered transition state and may not be possible from many rigid systems.
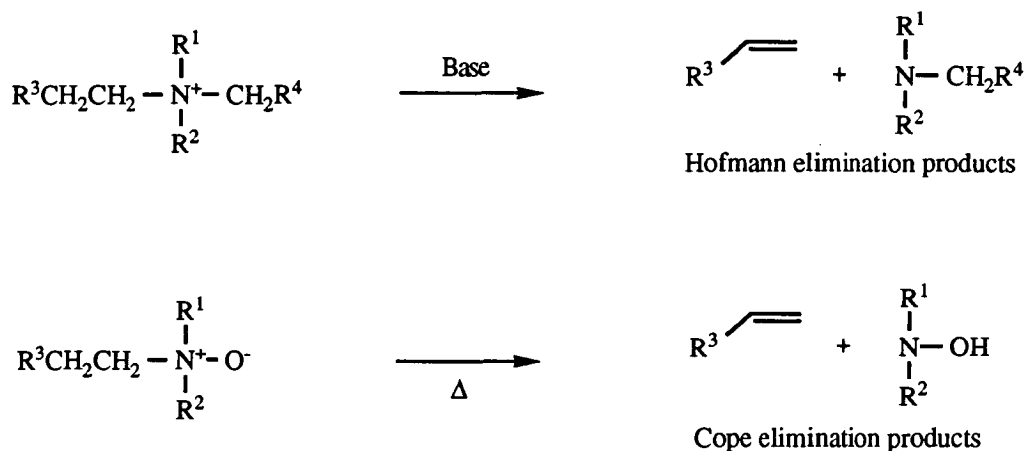
Figure 1.4

The Sommelet-Hauser rearrangement[13] (Figure 1.5) often competes with the Stevens rearrangement of benzylammonium salts and under the appropriate conditions may provide the major product. Non-polar solvents and increased reaction temperatures favour the Stevens rearrangement.[9] The rearrangement provides migration of a group to the *ortho* position of the benzene ring. The mechanism may involve a concerted [2,3] shift followed by aromatisation.
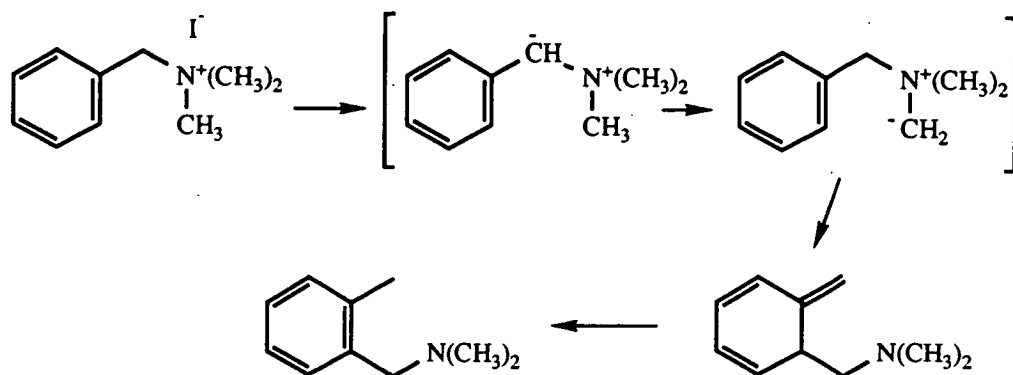
Figure 1.5 Proposed Mechanism of the Sommelet-Hauser Rearrangement

The Sommelet-Hauser rearrangement has been exploited for the synthesis of medium-sized heterocycles.[14,15,16] For example, the rearrangement of the 2-aryl heterocycles 1 afforded the benzaza-derivatives 2. Derivatives of the 2,5-benzoxazocine[17] and 5,2-benzoxazonine[18] systems were obtained in a similar manner.

1   n = 1, 2, 3.   2
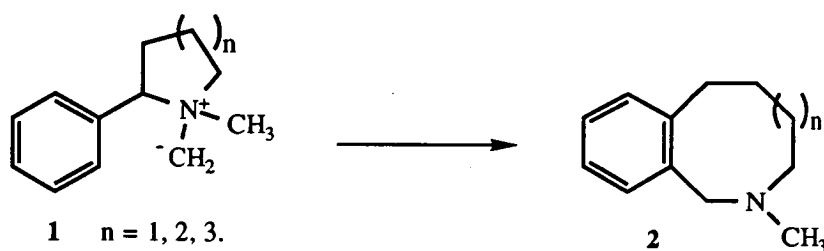
1.2.3 Ring Expansion via [1,2] Rearrangements

[1,2] Rearrangements have provided the one atom expansion of simple 4-, 5-, and 6-membered heterocyclic rings. The initial investigations of pyrrolidine and piperidine salts[9] and N-oxides[19,20,21] showed that beta-aryl substituents were necessary to prevent the prevalence of eliminations or non-expansive rearrangements, however, beta-unsubstituted azetidinium[22] salts and unsaturated pyrrolidine derivatives[23] underwent ring expansion readily. The relief of ring strain promoted the ring expansion in the latter cases. Recently the Meisenheimer rearrangement was used

to provide access to 1,5,2-dioxazine[24] and 1,6,2-dioxazepine[25] derivatives from the appropriate 5- and 6-membered cyclic *N*-oxide precursors.

The Meisenheimer rearrangement has afforded access to a number of benz-fused heterocycles. The 2,3-benzoxaza medium ring heterocycles **4** were obtained in high yields from the 1-phenyl-2-benzaza precursors **3**.[26,27] Rearrangement without the additional 1-phenyl substituent provided a lower yield and substantial deoxygenation.[28] Replacement of the benzene ring of **3** (n = 1) by [2,3]indolo, [3,2]thieno or [2,3][1]benzothieno moieties[29] provided the respective analogues of **4** (n = 1). The Meisenheimer rearrangement was also extended to the production of the benzodioxaza derivatives[30] **5** and benzoxadiaza derivatives[31,32] **6**.

3 n = 1, 2, 3.

4

5 n = 1, 2.

6 n = 1, 2.
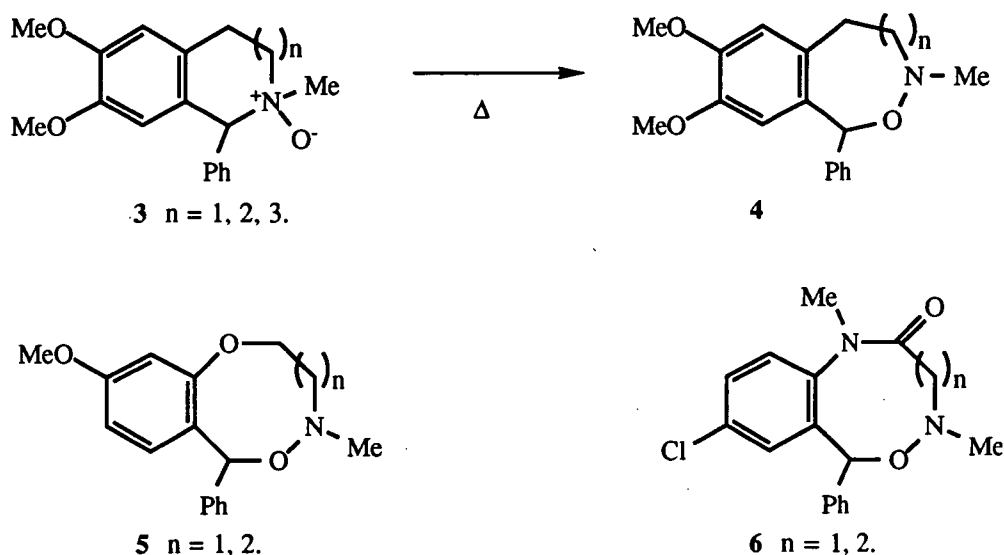
The Stevens rearrangement has provided few benz-fused medium-sized aza heterocycles. The *N*-allyl salts[33] **7** rearranged to the 3-benzazonine and 3-benzazecine derivatives **8** in good yield. Otherwise only the metacyclophane[34] **9** and the 3-benzazecine[35] **10** were reported to be produced by the Stevens rearrangement. These compounds were observed as minor byproducts during investigations of the Sommelet-Hauser rearrangement.

7 n = 1, 2.   NaNH₂/NH₃ (l)   8

9   10
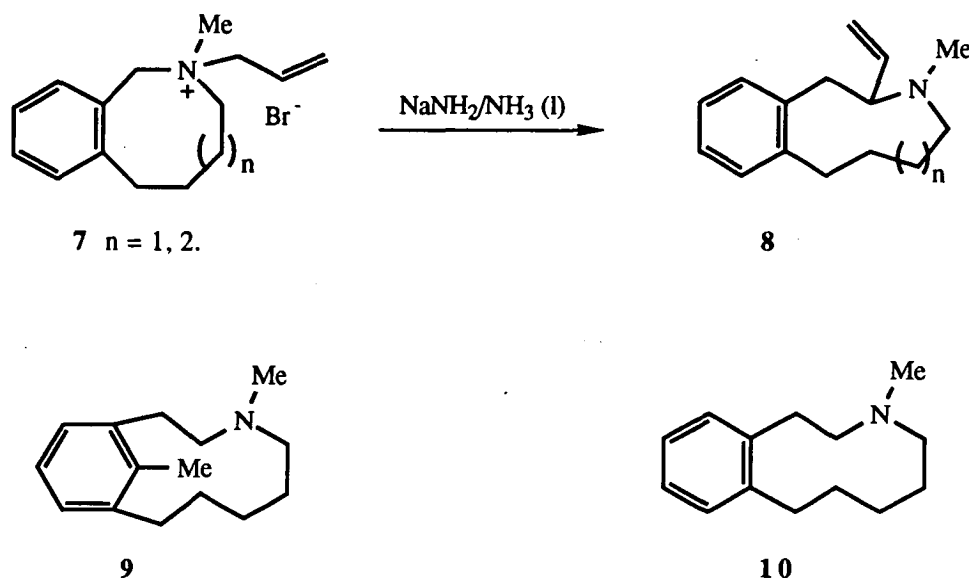
1.3   Introduction to [2,3] Rearrangements

The [2,3] rearrangements of sulfur-ylides have attracted considerable interest and are now an established technique for the formation of C-C bonds.[10,36] The [2,3] rearrangements of *N*-ylides and *N*-oxides have attracted less interest, although they are well documented in acyclic cases.[10] The rearrangement may provide a three atom ring expansion from a precursor with both the vinylic and anionic groups exocyclic to the original ring (Figure 1.2). Two reviews examining the production of medium rings via [2,3] sigmatropic rearrangements are available.[10,37] The reaction has found particular application to the synthesis of macrocyclic sulfur heterocycles by a series of [2,3] shifts.[38,39]

1.3.1   Mechanism

A concerted mechanism is currently accepted for the [2,3] rearrangement. The high regio-, diastereo- and enantioselectivities observed in these rearrangements, and the lack of evidence for other mechanisms, led to the proposition of a concerted symmetry-allowed[40] transition state (Figure 1.6, shown for *N*-ylides). The rearrangement is thermally allowed via suprafacial-suprafacial attack of the ylide on

the allylic group. Six electrons participate from the olefin π-orbital, the carbanion, and the N-C σ-bond of the precursor.

concerted transition state
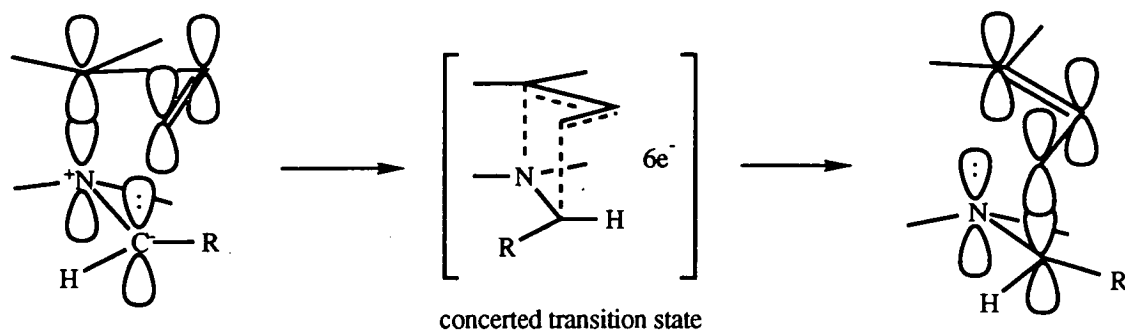
Figure 1.6

1.3.2 Ring Expansion via [2,3] Sigmatropic Rearrangements

The [2,3] rearrangement of small-ring N-ylides has allowed access to medium-sized heterocycles. The 2-vinylpyrrolidine[41] and piperidine[42] salts **11** provided the azocine and azonine products **12** in high yields. Mixtures of the E and Z geometric isomers were obtained. The E/Z ratio was dependent on both the ring size and the stereochemistry of the initial salts. These factors were postulated to alter the preferred transition state geometry and thus the product ratio. Rearrangement of a carbanion generated α to an amide nitrogen, rather than an N-ylide, produced ring expansion[43] of the highly strained 4-vinyl-2-azetidinone **13** to the seven-membered lactam **14**.
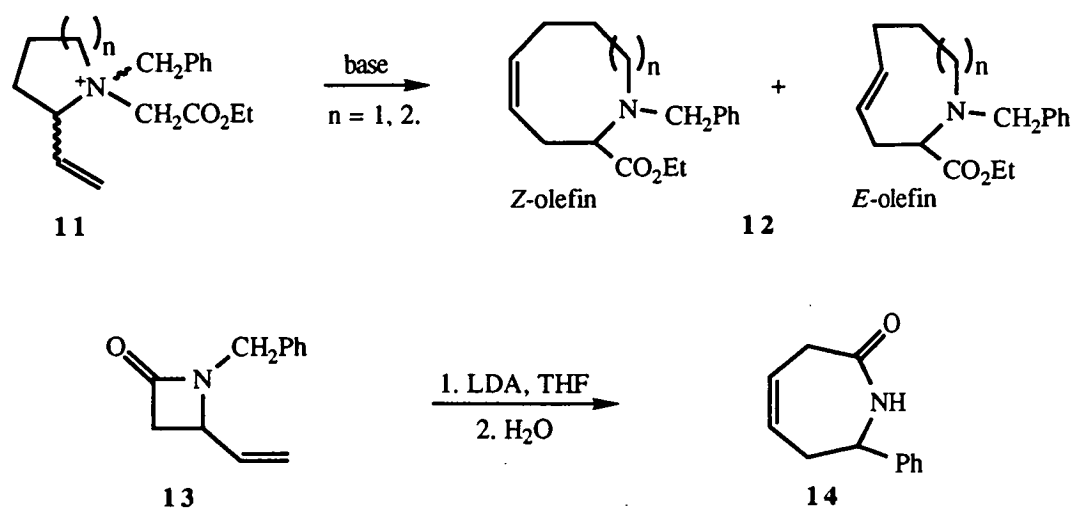
The ethynyl group may replace the vinyl group in [2,3] sigmatropic rearrangements. This type of rearrangement afforded ring expansion of the ethynylpiperidine N-ylide derivatives **15** to the unstable allenic azonines[44] **16** in moderate yields. The allenic products may in some cases undergo rapid isomerisation to stable conjugated dienes prior to isolation. Thus rearrangement of the N-imides analogous to **15** gave conjugated trienes directly.[44]
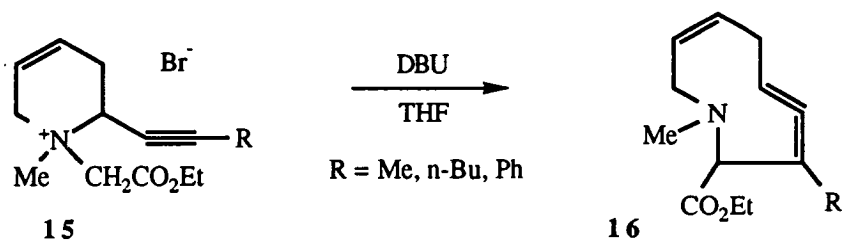
Although the 1-vinylisothiochroman[45] S-imide **17** and 1-ethynylisothiochroman[46] S-ylides **19** are known to undergo [2,3] rearrangements to the medium-sized benz-fused derivatives **18** and **20**, the similar [2,3] rearrangements of N-ylides to benz-fused nitrogen-containing heterocycles have not been investigated. Much scope remains for investigations in this field.
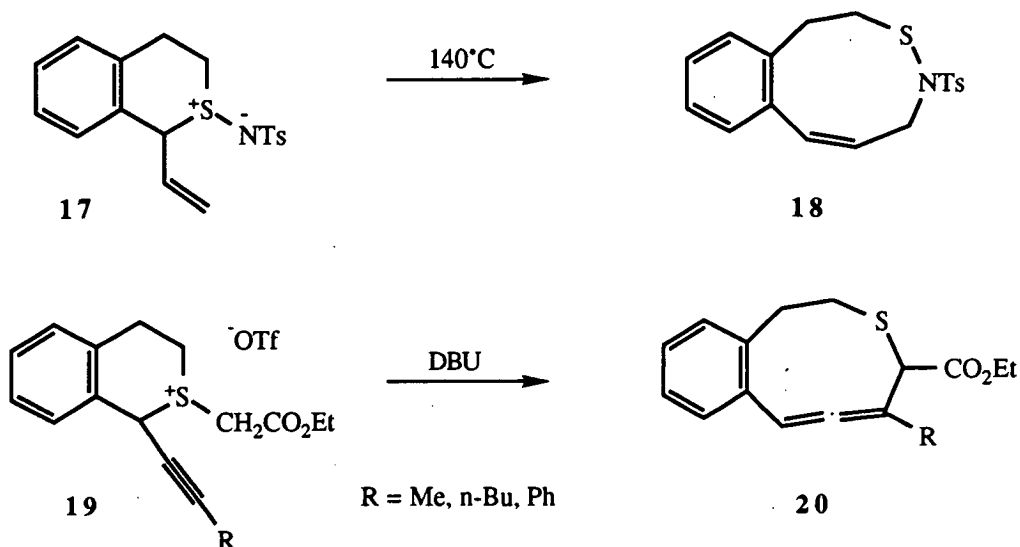
Few attempts have been made to develop the ring expansion of allylic N-oxides via [2,3] rearrangement. An examination of the rearrangements of 2-

vinylpiperidine N-oxides[47,48] found that only the 1,2-oxazepine derivatives were formed via the Meisenheimer rearrangement. This behaviour, in contrast to that of 13 (n=2), suggested the [2,3] shift was less favourable for N-oxides. Two successful cases were, however, reported from more complex ring systems containing allylic N-oxides. The catharanthine N-oxide 21 rearranged quantitatively[49] to 22 at 40°C. The azetopyrido[3,4-b]indole 23, upon treatment with *meta*-chloroperoxybenzoic acid (*m*-CPBA) at 0°C in dichloromethane, gave[50,51] the oxazepine derivative 24 in high yield via the preferential formation and rearrangement of the N-oxide with the oxygen and vinyl moieties *cis* to each other in the azetidine ring.

21 R = CO2Me, CH2O2CMe

22

23 R = H, Et

24
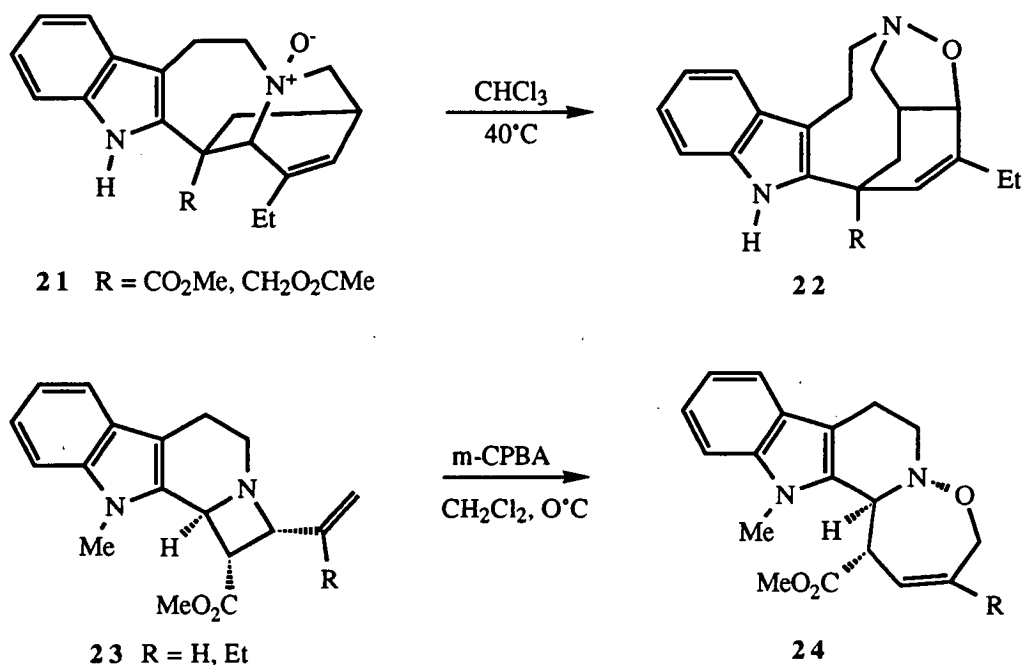
1.4 Introduction to a Cyclopropylcarbinyl Rearrangement

Cyclopropylcarbinyl radicals are known to undergo rapid ring opening to give homoallylic radicals. It was thus proposed that the incorporation of a cyclopropyl group would allow the modification of the Meisenheimer or Stevens rearrangements and a four atom ring expansion (Figure 1.2) via a diradical mechanism (Figure 1.7). A concerted mechanism may also be possible.

Y = CHR^4, O.

Solvent Cage
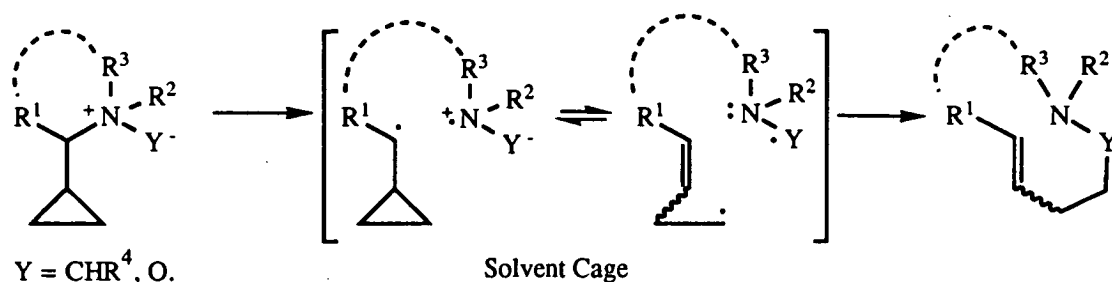
Figure 1.7

A single report[52] of an acyclic rearrangement of this type was revealed in the literature. The rearrangement conditions were not specified. Thermal treatment of the N-oxide **25** provided mainly deoxygenation with the hydroxylamine **26** isolated in low yield. No further investigations of this rearrangement are known. An examination of the Sommelet-Hauser rearrangement[53] of N-ylides did, however, indicate that the cyclopropyl group could promote the reaction in the same way as an allylic double bond. No products of cyclopropyl ring opening were observed.
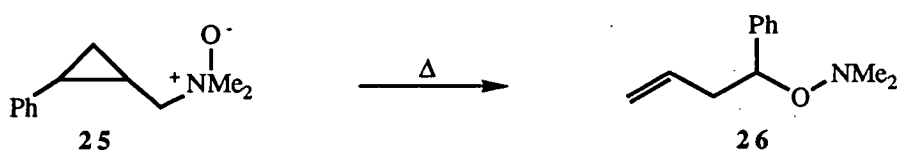
A recent report[54] involved a cyclopropylcarbinyl radical rearrangement and highlighted the potential for the investigation of the rearrangement proposed above. Photolysis of the α-keto ester **27** produced the 1,4-diradical which underwent cyclopropylcarbinyl radical rearrangement then radical recombination to give the 7-membered lactone **28** in 25% yield.
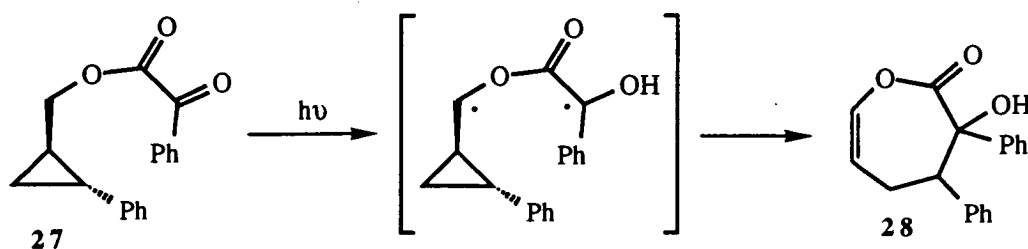
1.5   Thesis Outline

The results of studies aimed at developing the syntheses of 3-benzazonines and 4,3-benzoxazonines via the [2,3] rearrangements of 1-vinylic isoquinoline-N-ylides and N-oxides are presented in Chapters 2 and 3 respectively. These investigations form the core of this work.

Further applications of the [1,2] rearrangements in heterocyclic synthesis are examined in Chapter 4. These include the production of an 8-membered ring analogue of the potent benzodiazepine therapeutic Alprazolam[55] and epoxy-bridged benzazonine and benzazecine derivatives.

Studies on the development of a four atom ring expansion by the rearrangement of 1-cyclopropylisoquinoline N-ylides and N-oxides are presented in Chapter 5.

CHAPTER 2

REARRANGEMENTS OF 1-VINYLIC
TETRAHYDROISOQUINOLINE *N*-YLIDES

2.1 Introduction

The absence of reported work on the synthesis of benz-fused *N*-heterocycles by ring expansion technology utilising the [2,3] sigmatropic rearrangement of allylic *N*-ylides was noted in Chapter 1. In view of this deficiency it was decided to investigate the rearrangements of 1-vinylic-tetrahydroisoquinoline *N*-ylides (Figure 2.1). It was anticipated that the results of this study would be applicable to the rearrangements of many benz- or other aromatic- ring-fused aza-heterocycles and the development of a new synthetic technique for the production of aromatic ring-fused medium sized aza heterocycles.

The isoquinoline-based system was investigated due to the synthetic accessibility of the necessary 1-substituted tetrahydroisoquinolines and the potential for the development of a new route to highly functionalised 3-benzazonine derivatives. The present methods available for the synthesis of 3-benzazonines are limited and are summarised in Section 2.2. Functionalised 3-benzazonines are desirable as precursors for the synthesis of other 3-benzazonine derivatives and the full evaluation of the pharmaceutical potential of this heterocyclic system. In addition, it was anticipated that the 1-vinylic isoquinoline system would allow the investigation of the competition between the [2,3] and [1,2] rearrangement pathways. It was reasoned that this competition would provide a sensitive indicator of the reaction variables either beneficial or detrimental to the [2,3] rearrangement and aid in the development of this synthetic approach.

In this study it was proposed to investigate, in particular, the effects of the reaction temperature, olefinic substituents, $R^{1,2}$, and ylide stabilising groups, R^3, on the course of the *N*-ylide rearrangements (Figure 2.1). The olefinic and ylide

substituents shown were suggested for study. It was anticipated that this series would be modified according to the synthetic accessibility of the required compounds. The olefinic substituents were selected to allow the investigation of stereoelectronic effects on the [2,3] sigmatropic transition state. The ylide substituents were selected primarily to examine the effect of the electron delocalising, and thus radical stabilising, nature of these groups.

$R^{1,2}$ from H, Me, Br, I, CN, CO$_2$Et or Ph.
R^3 from H, CO$_2$Et, COPh or CN.
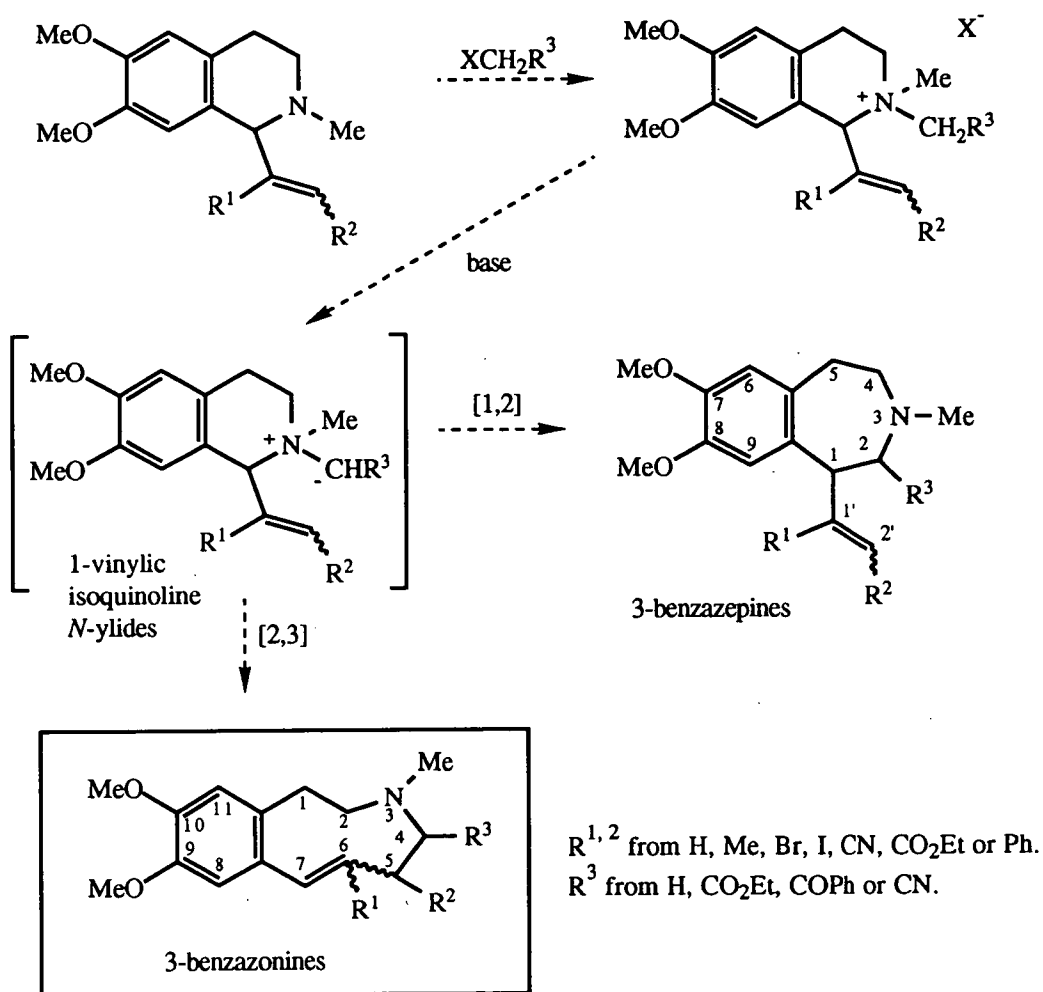
Figure 2.1

2.2   Review of 3-Benzazonines

Derivatives of the 3-benzazonine ring system were first reported[56] upon the degradation of alkaloids from the seeds of *Erythrina* species. The vast majority of the limited subsequent synthetic reports[57,58,59] have used the ring destruction of reduced pyrrolo[2,1-*a*]isoquinolines to provide access to this system. A variety of techniques were developed that provided the necessary heterolytic cleavage of the benzylic C-N bond. The Emde-type reduction[60,61,62] of pyrroloisoquinolinium salts with sodium or lithium and liquid ammonia, as exemplified by the conversion[63] of **29** to **30**, provided 3-benzazonines in good yields. The similar treatment of the *N*-oxide **31** with an alcohol as the proton source gave[64] the secondary amine **32**.

29 R, R₁ = Me, H
         Ph, H
         Ph, OMe

30

Li, NH₃ (l)

31

Li, NH₃ (l)
ROH

32
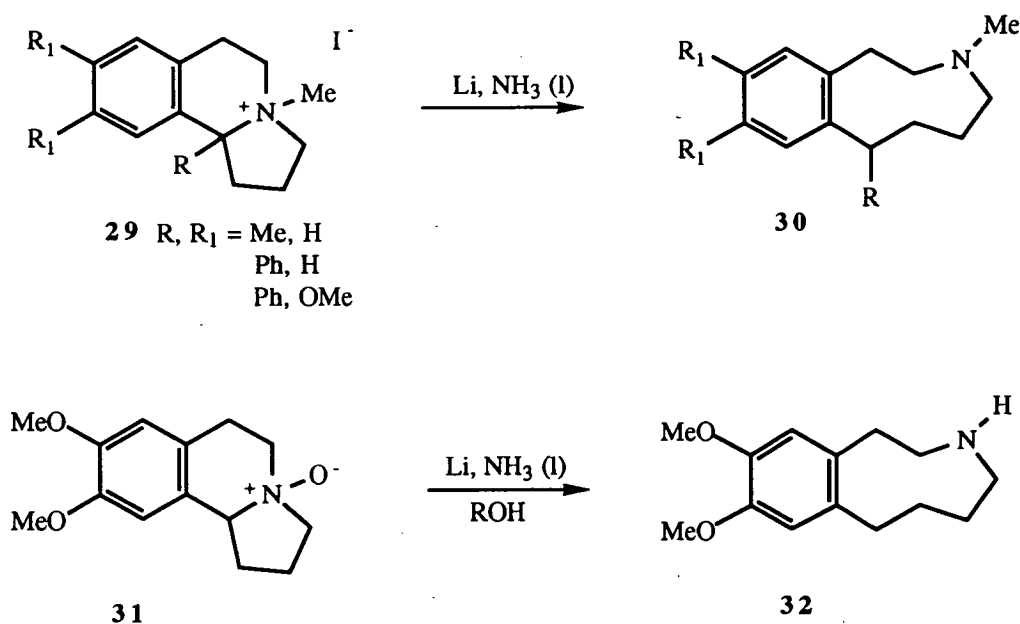
Cleavage of the pyrroloisoquinolines **33** was achieved photolytically[65] with concurrent solvolysis, allowing the synthesis of the 7-methoxy or 7-hydroxy derivatives **34**. In a similar technique, cyanogen bromide in the presence of a hydroxylic solvent promoted the ring cleavage and solvolysis of the quaternary salts **35** to the 3-carbonitriles **36** in good yields.[66] These induced-solvolysis methods

were extended to the production of benzoxazonine and benzoxazecine derivatives in good yields (Sections 3.2 and 5.2).

33 → **34**

R and R^1 = H or Me

35 → **36**

R = H, Me
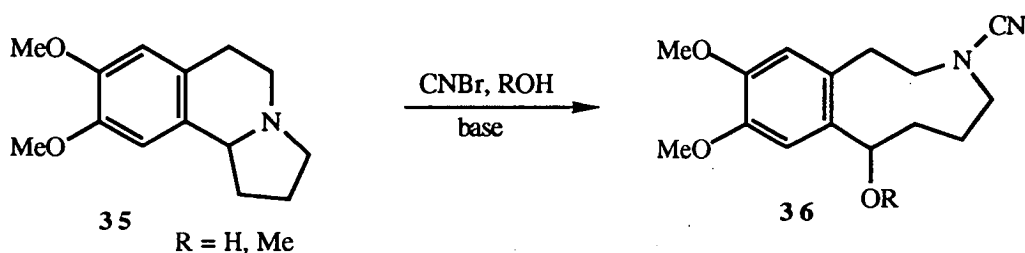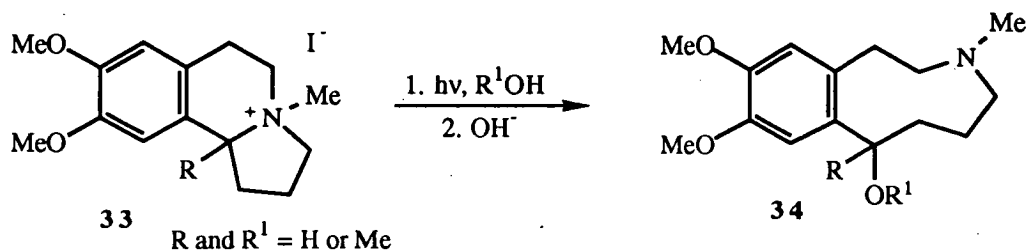
The elimination reactions of pyrroloisoquinolinium salts, such as the Hofmann elimination[67], have provided several examples of unsaturated 3-benzazonines. The chloroformate ester-induced elimination of the 10b-methyl derivative **37** gave selectively the exocyclic olefin **38**.[62] Cyanogen bromide-induced elimination of the 10b-phenyl derivative **39** gave **40**, the only reported 2,3,4,5-tetrahydro-1H-3-benzazonine.[68]

37 → **38** + 37.HCl

39 → **40**
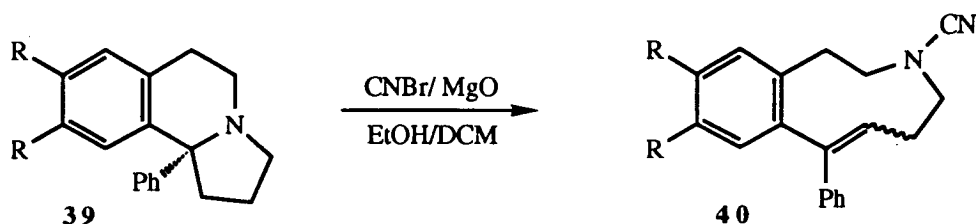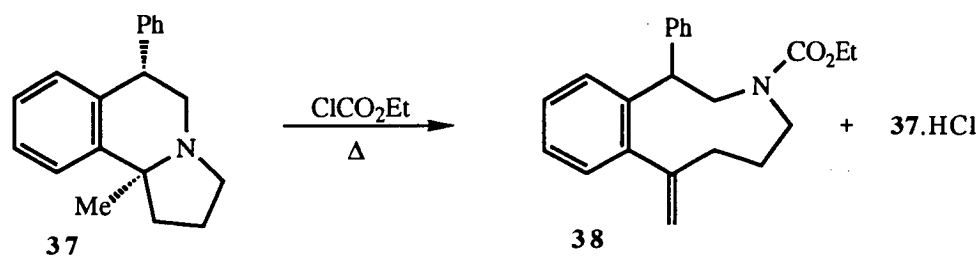
Only three reports have appeared on accessing the 3-benzazonine system by non-ring destruction methods. The N-chloroacetamide **41** cyclised[69] to the lactam **42** on photolysis in low yield. The scope of this reaction appears limited. Similarly, ring expansion[70] of the secondary amino acid **43** gave the 1,2-dihydro-3-benzazonine **44** in only low yield. The Stevens rearrangement afforded the successful ring expansion of the 2-benzazocines **45** to the 3-benzazonines **46** in good yield.[29]
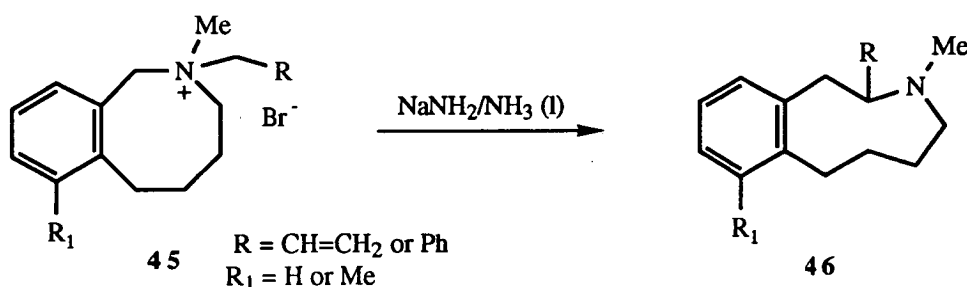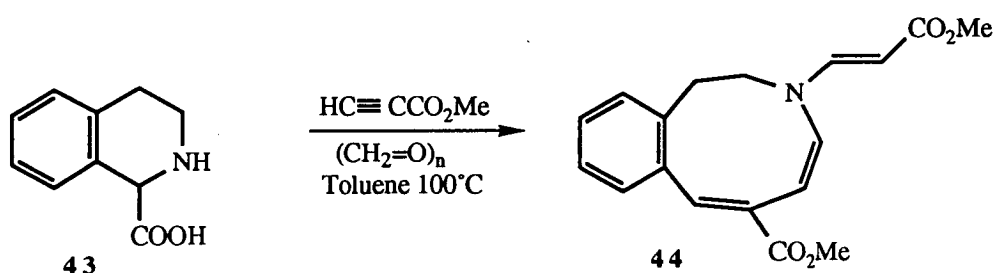
2.3 Rearrangement of 2-Ethoxycarbonylmethyl-1-vinyl-tetrahydroisoquinoline Derivatives

A preliminary investigation of the rearrangement of simple 1-vinyltetrahydroisoquinolines N-ylides was conducted in the presence of an ester ylide stabilising group. The N-ylides were derived from N-methyl derivatives by

deprotonation with base. The ester ylide stabilising group was adopted as the 'standard' ylide substituent throughout this work due to its synthetic availability, via the N-alkylation of the appropriate amines with ethyl bromoacetate, and the acidity of the methylene protons of the N-ethoxycarbonylmethylene group. The rearrangement was investigated with both N-methyl and N-benzyl derivatives. The latter system was investigated for the purpose of examining the subsequent hydrogenolysis of any N-benzyl-3-benzazonines formed, a reaction which would provide access to 3-benzazonines with the synthetically useful secondary amino group present.

2.3.1 Synthesis of the Precursor Quaternary Salts

The 3,4-dihydroisoquinoline **47** was prepared by a modification of the standard Bischler-Napieralski cyclisation technique[71] and then converted to the iminium halides **48**. Conducting the Grignard reaction of **48a** with vinylmagnesium bromide by the conditions published[72] for the reaction of vinylmagnesium bromide with 6,7-methylenedioxy-3,4-dihydroisoquinolinium iodide, involving refluxing in tetrahydrofuran, gave the 1-vinylisoquinoline **49a** in only 38% yield. A 1:1 mixture of the isomeric 6-hydroxy-7-methoxy- and 7-hydroxy-6-methoxy-2-methyl-1-vinyl-1,2,3,4-tetrahydroisoquinoline compounds was also isolated in 31% yield. This mixture was identified by spectroscopic means and by conversion to **49a** on reaction with diazomethane. Conducting the Grignard reaction at low temperature avoided the O-demethylation. Thus, adding **48** to a solution of four equivalents of the Grignard reagent in tetrahydrofuran at low temperature ($\leq$-50°C) then stirring the mixture for 10-20 hours with warming to room temperature provided, after workup, the 1-vinylisoquinolines **49** as crystalline solids in high yields.

Compounds **49** were fully characterised by elemental analysis and spectroscopic techniques. The presence of the 1-vinyl group was clearly indicated by a base peak at $(M-27)^+$ in the mass spectrum and a set of characteristic signals in the ^{1}H and ^{13}C NMR spectra (Figure 2.2).
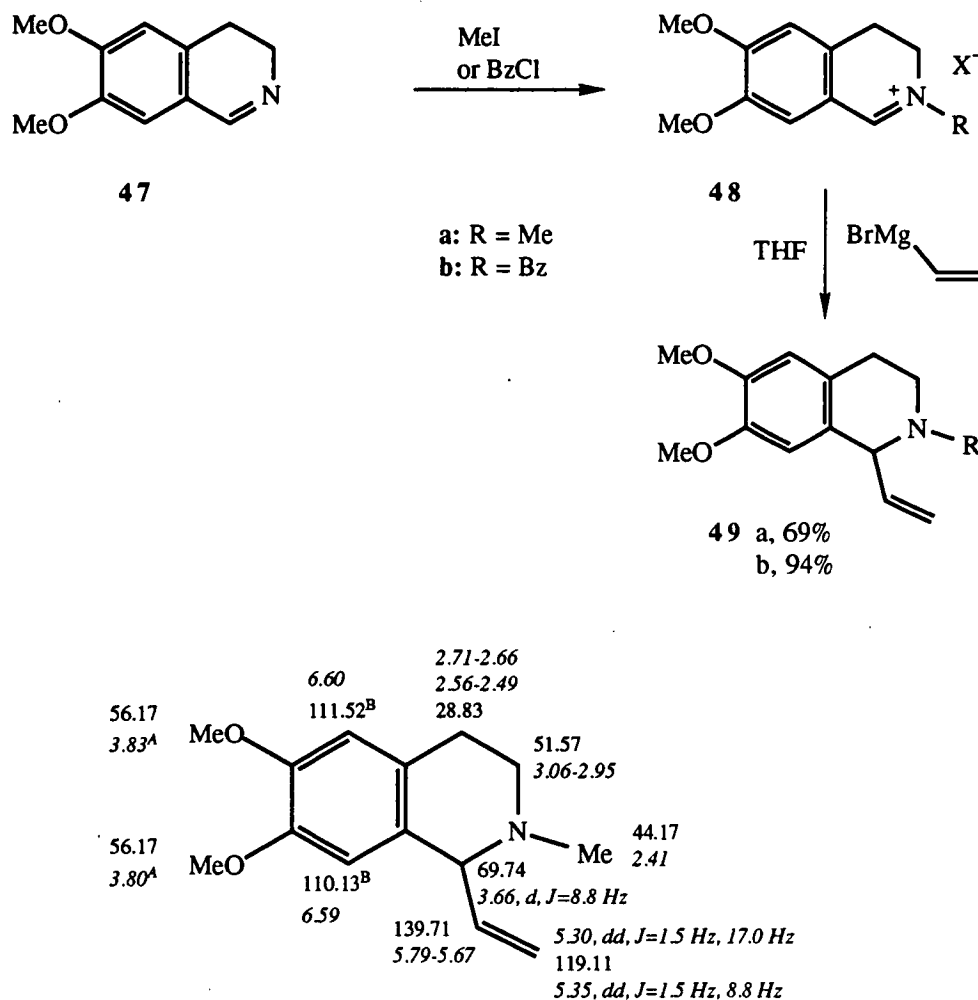
Figure 2.2 ^{13}C and ^{1}H (italics) NMR spectral assignments for **49a**

Alkylation of **49** with ethyl bromoacetate at room temperature provided, in good yields, the quaternary amine salts **50** as hygroscopic solids. The alkylation of **49a** proceeded very rapidly in neat ethyl bromoacetate, while the alkylation of **49b** at room temperature required nineteen days for the satisfactory conversion of **49b** to **50b**. Although this reaction was very slow a clean crystalline product was obtained. The attempted quaternization of **49b** at elevated temperatures, or with ethyl iodoacetate in acetonitrile, provided either no reaction or degradation of the amine to highly coloured material.

The quaternary salts **50** were mixtures of the possible *trans* and *cis* B-ring diastereomers and were identified primarily by NMR analyses. The ^{1}H NMR spectra

of the diastereomeric mixtures were complex and difficult to interpret, however, the ^{13}C NMR spectra afforded rapid confirmation of the proposed structures. Two-dimensional COSY experiments and the examination of materials containing different levels of the *trans* and *cis* isomers enabled the assignment of the respective NMR signals for the isomers of **50a** (Table 2.1). The proportions of the isomers were determined by comparing the ^1H NMR peak areas of the corresponding protons. A considerable preference, approximately 2.3-3:1, was observed for the formation of one isomer at room temperature.

$$49 \quad \xrightarrow[\text{20-25°C}]{\text{BrCH}_2\text{CO}_2\text{Et}}$$

50 a: R = Me   70:30 dr
b: R = Bz   75:25 dr
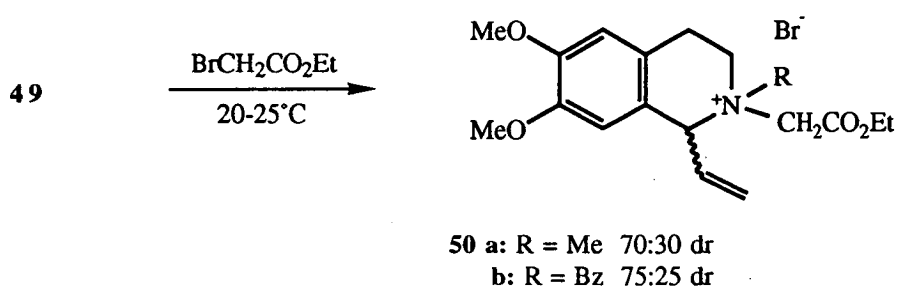
Table 2.1 NMR Shifts of the *Trans* and *Cis* Diastereoisomers of **50a**

^1H NMR	*trans*	*cis*	^{13}C NMR	*trans*	*cis*
H1	6.05-6.01	5.73-5.64	C1	73.50	73.31
H1'	6.05-6.01	6.10-6.01	C1'	129.79	131.06
H2'	6.26-6.24	5.73-5.64	C2'	130.15	127.48
H2'	5.85-5.81	5.73-5.64	NCH$_2$CO	58.44	60.76
NCH$_2$CO	5.11 d	5.37 d	NCH$_3$	47.52	46.41
NCH$_2$CO	4.69 d	4.39 d	C3	54.83	55.69
NCH$_3$	3.55	3.70			
H3	4.49-4.41	4.83-4.75			
H8	6.53	6.44			

The quaternization of 1-substituted-1,2,3,4-tetrahydroisoquinolines was reported[73,74] to proceed preferentially by attack *trans* to the 1-substituent. The chemical shifts of the *N*-methyl groups on the resultant *trans* 2-alkyl-2-methyl-1-phenyl-1,2,3,4-tetrahydroisoquinolinium salts were upfield of the *cis* isomers. As the

major isomer of **50a** exhibited a chemical shift for the *N*-methyl protons upfield of that for the minor isomer (3.55 δ cf. 3.70 δ), the major isomer was assigned the *trans* configuration. This assignment was supported by experiments which confirmed that the *N*-methyl group in the *trans*-*N*-oxide **128a** had a chemical shift upfield of the *cis*-*N*-oxide. Definitive assignment of the identity of the diastereomers of **50a** was sought, however, as piperidine derivatives were reported[75] to undergo *N*-alkylation preferentially by axial approach of the alkylating agent, a process which would provide predominantly the *cis* isomer of **50** by alkylation of the low energy conformer of **49** with the vinyl group equatorial. Nuclear Overhauser experiments were conducted on **50a** but the complexity of the proton spectra prevented the confident assignment of the interactions observed. Similar experiments on the methiodide salt **54a** failed to determine conclusively the position of the *N*-methyl signals *cis* and *trans* to the vinyl group. Compound **54a** was only slightly soluble in the common deuterated solvents and residual non-deuterated solvent peaks interfered with the *N*-methyl signals.

As the *trans* and *cis N*-ylides of many heterocyclic systems undergo contrasting sigmatropic rearrangements the separation of the diastereomers of **50a** was attempted. Recrystallisation of a diastereomeric mixture of **50a** was examined. It was hoped that the *trans* isomer would be enriched in the crystalline solid. Recrystallisation of **50a** (*trans/cis*=1.70) from ethanol/tetrahydrofuran instead provided a crystalline solid (62%, *trans/cis*=1.33) and mother liquor (*trans/cis*=0.67) in which both were depleted in the *trans* isomer. Recrystallisation of the first crop provided a similar result with the level of the *trans* isomer reduced in both the crystalline solid (65%, *trans/cis*=1.12) and mother liquor (*trans/cis*=0.60). These results were replicated over several experiments and indicated a mechanism for the conversion of *trans*-**50a** to *cis*-**50a** existed, with the *cis* isomer favoured as the thermodynamic product. The interconversion of the isomers was rationalised by proposing a reversible *N*-dealkylation promoted by the bromide ion.

The selectivity of the *N*-alkylation of **49a** in neat ethyl bromoacetate was examined. The reaction was temperature dependent, but neither diastereomer could be produced selectively. At -15°C and 110°C respectively 4:1 and 1:1 mixtures of *trans* and *cis*-**50a** were obtained. It was reasoned that the elevated temperature increased the population of a high energy conformer of **49a**, from which the *cis* isomer was formed by attack with the alkylating agent. The reaction of **49a** with ethyl bromoacetate in acetonitrile at room temperature afforded a precipitate which was found to be enriched in *trans*-**50a** (*trans/cis*=9.0) to a degree sufficient for the analysis of later rearrangements.

2.3.2   Modelling of the Concerted Transition States

The concerted transition states possible for the *N*-ylides **51** and the analogous *N*-oxides **123** were modelled to predict: (i) whether the *cis* and *trans* isomeric salts could both attain a concerted transition state, (ii) the likely stereochemistry of any concerted rearrangement products, and (iii) the effect, if any, of substituents on the allylic group.

Two types of conformers were identified for each diastereomer of **51** by consideration of the normal axial/axial, equatorial/equatorial, and axial/equatorial arrangements of the low-energy distorted chair conformation for the isoquinoline ring. An additional criterion, the rotation of the 1-vinyl group, provided four conformational minima for each diastereomer of **51** (Figure 2.3). Clearly, the axial/axial *trans*-systems **I** and **II** were unsuitable for the formation of a five-centre concerted transition state. The energy and geometry of the remaining conformers **III-VIII** were modelled using PCModel (Table 2.2), a molecular mechanics based computer modelling system.[76] The *cis*-conformer **V**, in which the ylide component was axial, possessed both the lowest energy and the lowest minimum distance between the ylide carbanion and C2', making this the most favoured conformation for a concerted rearrangement. The *trans*-conformer **III** by comparison attained a less favourable geometry. As **III** was not significantly different to the structure achievable

in the *trans*-2-vinylpiperidine-*N*-ylides, which were reported[42] to undergo the [2,3] rearrangement, it was proposed that both the *cis* and *trans* diastereomers of **51** would undergo the [2,3] sigmatropic rearrangement. It should be noted, however, that the PCModel studies were for the molecules *in vacuo* and no solvent interactions were modelled.

Table 2.2 Data from PCModel for the *N*-Ylide Conformers of **51a**

Structure	H_f [a]	$D_{X-C2'}$ [b]	min.$_{X-C2'}$ [c]
III	1.36	3.56	2.90
IV	1.75	3.89	-
V	0.00	3.98	2.55
VI	1.06	3.63	2.63
VII	1.98	3.32	-
VIII	2.28	3.72	-

[a] energy above that of **V** at H_f=79.58 (kcal)

[b] distance from C^- to C2' at the energy minimum (Å)

[c] the minimum distance between C^- to C2' upon rotation of C1-C1' (Å)

The configuration of the developing olefinic bond and stereoselectivity of the [2,3] sigmatropic rearrangement of α-substituted-allylic-*N*-ylides was discussed by Marko.[10] The five-centred transition state was assumed to adopt a conformation similar to the 'folded envelope' conformation of cyclopentane. In this system the *E*-isomer will be formed if the α-substituent is in a psuedo-equatorial position, and the *Z*-isomer if the α-substituent is psuedo-axial (Figure 2.4). Following this technique the conformers **III-VIII** were assigned as pro-*E* or pro-*Z* structures (Figure 2.3).

These results clearly indicated that the major products of the *N*-alkylation, the *trans*-salts **50**, would undergo base promoted concerted rearrangements stereoselectively to the *E* double bond derivatives via the conformers **III** and **IV**. The stereoselectively of the [2,3] rearrangement of the *trans*-salts, although possibly not the rearrangement type, would be independent of the substituents present on the vinyl

I

II

III pro-*E*
trans- conformers IV

V pro-*E*
cis-conformers VI

VII pro-Z
cis-conformers VIII
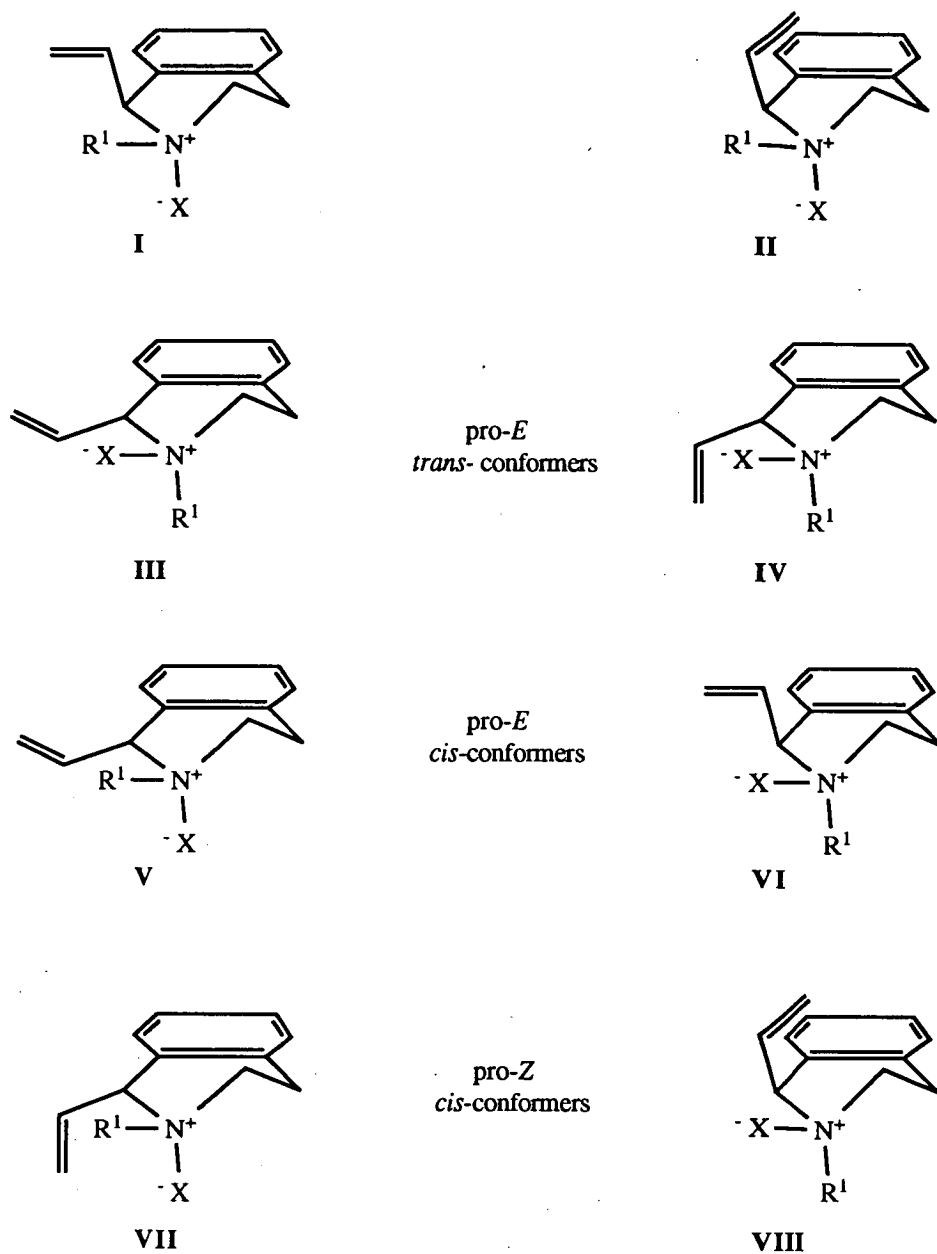
Figure 2.3 Conformational minima for 1-vinylisoquinoline *N*-ylides **51** (X=CHR)
and *N*-oxides **123** (X=O). The 6,7-methoxy groups are omitted for clarity

pro-*E*
transition
state

pro-Z
transition
state
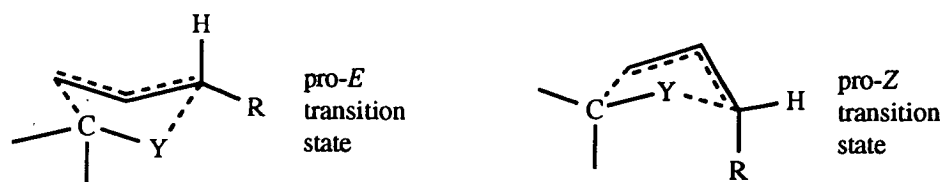
Figure 2.4 Folded cyclopentane geometry of the allylic-*N*-ylide (Y=NR$_2$) transition state

group. The *cis*-salts of **50** were also expected to undergo preferentially a [2,3] rearrangement to the *E*-benzazonines, as the lower energy pro-*E* conformers, particularly **V** in which the equatorial nature of the vinyl group was maximised, would predominate over the higher energy pro-*Z* conformers.

After consideration of the conformers **V** and **VII** it was proposed that a substituent on the olefinic group at C1' would reverse the relative energies of these conformers, allowing access to significant amounts of the *Z*-benzazonine derivatives from the *cis*-salts. The bulky C1' substituents in the *cis*-salts could be accommodated preferentially in the equatorial position provided by conformer **VII**. This proposal was supported by modelling several C1'-substituted-*N*-ylide derivatives in conformations analogous to **V** and **VII** (Figure 2.5).
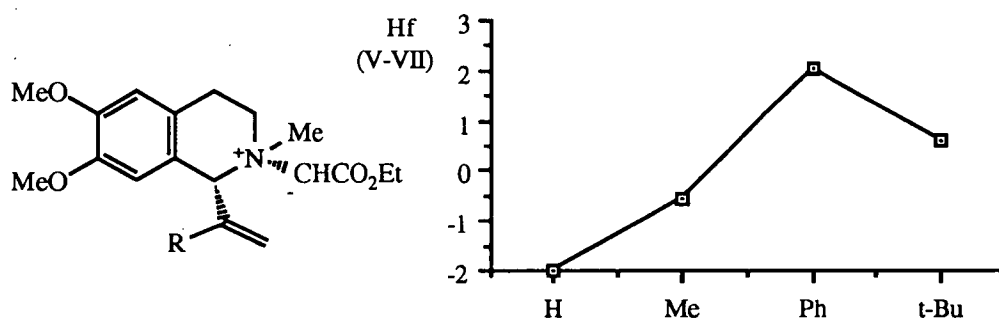
Figure 2.5 The energy difference between conformer types V and VII with C1' substituents (R)

2.3.3 Formation and Characterisation of 3-Benzazonine Derivatives

The detection of all possible rearrangement products from this rearrangement, and others examined in this work, was ensured by an initial purification to a 'rearranged fraction', containing the non-polar compounds which eluted rapidly through an alumina column with dichloromethane/20% light petroleum. This fraction was then analysed by t.l.c., NMR and GC-MS techniques. Where mixtures were present the proportions of the compounds were determined from ^{1}H NMR peak areas. Residual polar salts were retained on the column while traces of the precursor bases **49**, if present, generally eluted with dichloromethane/5% light petroleum.

Treatment of the 1-vinylisoquinolinium compounds **50** in acetonitrile at room temperature with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), a non-nucleophilic base, gave the [2,3] sigmatropic rearrangement products, the 2,3,4,5-tetrahydro-1*H*-3-benzazonines **52**, in excellent yields (Table 2.3). The rearrangement was assumed to proceed via the allylic-*N*-ylides **51**. The *E*-benzazonines were obtained almost stereoselectively, as predicted (Section 2.3.2). The *N*-benzyl derivative *E*-**52b** was a colourless oil which required no further purification as the *Z*-isomer was not detected. In contrast, NMR analysis of the *N*-methyl benzazonine fraction **52a** revealed the presence of a minor amount of the *Z*-isomer (*E/Z* ratio = 19). The isomers of **52a** were separated to give *E*-**52a** as a colourless waxy solid and *Z*-**52a** as a colourless oil. The structures were confirmed primarily by spectroscopic means. All data was consistent with the proposed structures.

Over a temperature range between -40°C and 82°C the rearrangement products from **50a** were almost unchanged (Table 2.3), with the [2,3] sigmatropic rearrangement occurring preferentially. The results confirmed the anticipated low energy requirement of the [2,3] concerted pathway when compared to the diradical mechanism of the [1,2] rearrangement. At the highest temperature the Stevens rearrangement product, the 1-vinyl-3-benzazepine **53a**, was observed in low yield. The stereoselectivity of the [2,3] rearrangement was slightly reduced at high temperature (*E/Z* = 10.0). At -40°C the reaction was complete in six hours. The rearrangement of **50a** to **52a** proceeded satisfactorily in tetrahydrofuran, however, the precursor salts were only partially soluble in this solvent. Acetonitrile was used subsequently.

The observed stereoselectivity of the [2,3] rearrangement was rationalised in Section 2.3.2. The yields of **52** apparently confirmed that both the diastereomeric salts of **50** could undergo the concerted rearrangement. However, in one reaction of **50a** (*trans/cis*=3.0) where DBU was the limiting reagent (0.7 equivalents) the alumina

50

DBU

51

a: R = Me
b: R = Bz

E-52

Z-52

53

Table 2.3 Rearrangement Conditions and Products from **50**

Reactant	Reaction Temp (°C)	Total % Yield[a]	Product Distribution[b] (%)		
			E-52	*Z*-52	53
50a	-40	86	95	5	-
"	0	90	95	5	-
"	82	70	87	9	4
50b	25	93	100	-	-

[a] yield to a non-polar rearranged fraction

[b] from ^{1}H NMR integrals

column was stripped with ethanol and the residual salts examined. The *cis* diastereomer of **50a** was recovered exclusively, suggesting either a substantial difference in the reaction rates of the diastereomeric salts or the rapid interconversion of *trans*-**50a** to *cis*-**50a** by reversible deprotonation at the benzylic C1 position. The interconversion of α-vinyl-*S*-allyl sulfonium salts[39,42] by DBU is known, while conversion of *trans*-**50a** to *cis*-**50a** occurred during the recrystallisation of **50a**

(Section 2.3.1). Thus the [2,3] rearrangement could conceivably have occurred solely via *cis*-**50a**. Some support for this proposition was provided by the observation that, although a variety of diastereomeric mixtures of **50a** (from *trans/cis*=9.0 to *trans/cis*=1.0) were rearranged in this work, the product ratio of *E* to *Z*-**52a** was constant. The accuracy of the measurement technique, using ^{1}H NMR integrals with low levels of the *Z*-isomer, however, suggests caution in the interpretation of these results.

The ^{1}H NMR (Figures 2.6 and 2.7) and ^{13}C NMR (Figure 2.8) spectra of *E* and *Z*-**52a** were assigned unambiguously by nuclear Overhauser and two dimensional homo- and heteronuclear decoupling experiments. The magnitude of the H6-H7 coupling constant gave the identification of each isomer. Compound *E*-**52a** displayed a doublet for H7 at 6.43 δ, with a coupling constant of 16.1 Hz, while the *Z*-**52a** isomer displayed a doublet for H7 at 6.67 δ, with a coupling constant of 10.7 Hz. The assignment of the isomers was confirmed by a nuclear Overhauser effect (nOe) between H5 and H7 for *E*-**52a**, and not *Z*-**52a**, and the upfield position of C5 at 32.63 δ, compared to 36.32 δ, in the *Z*-isomer. The 3-benzazonines displayed characteristic multiplets at 5.8-5.5 δ and 3.6-3.4 δ, for H6 and H4, and two olefinic ^{13}CH peaks between 135-130 δ for C6 and C7.

The mass spectra of **52** displayed a base peak at M-73 as the only prominent ion, apart from the benzyl ion at m/z 91 for **52b**. The base peak was consistent with the loss of the ethoxycarbonyl side chain and formation of a cyclic iminium ion.

Substantial difficulties were encountered in this work with the separation and purification of the *E* and *Z* 3-benzazonine isomers. Although analytical t.l.c. demonstrated separation of the isomers of **52a** the *E*-benzazonine was degraded by p.t.l.c. or column chromatography on silica, with the formation of polar material. The *Z*-benzazonine was, however, recovered successfully. Analysis of the ^{1}H NMR spectrum of the polar material indicated several quaternary salts were formed by the degradation of *E*-**52**. It was proposed that the pyrrolo[2,1-*a*]isoquinolinium salts **54**,
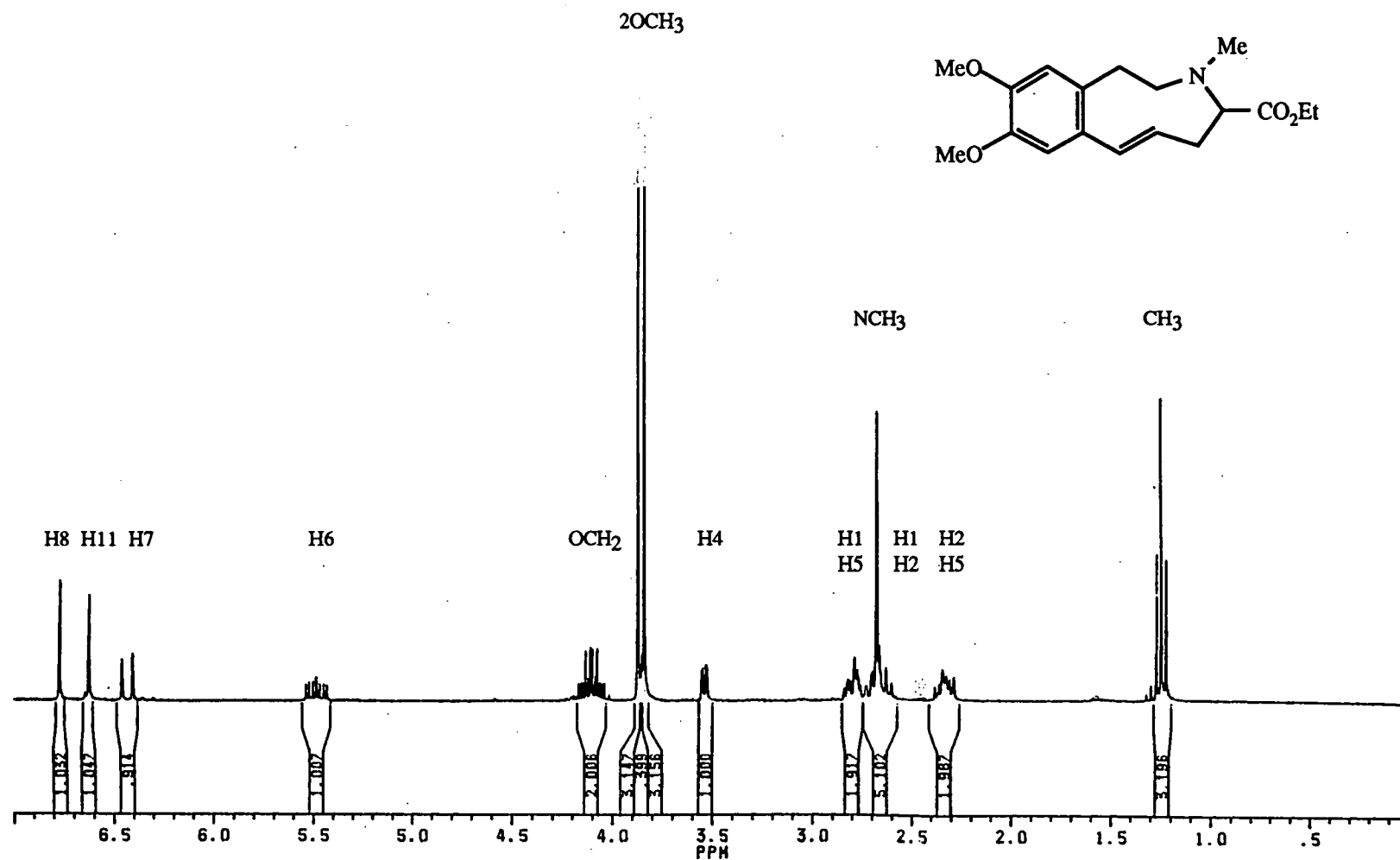
Figure 2.6 ^{1}H NMR spectrum and assignments for the *E*-isomer of **52a** in CDCl$_3$
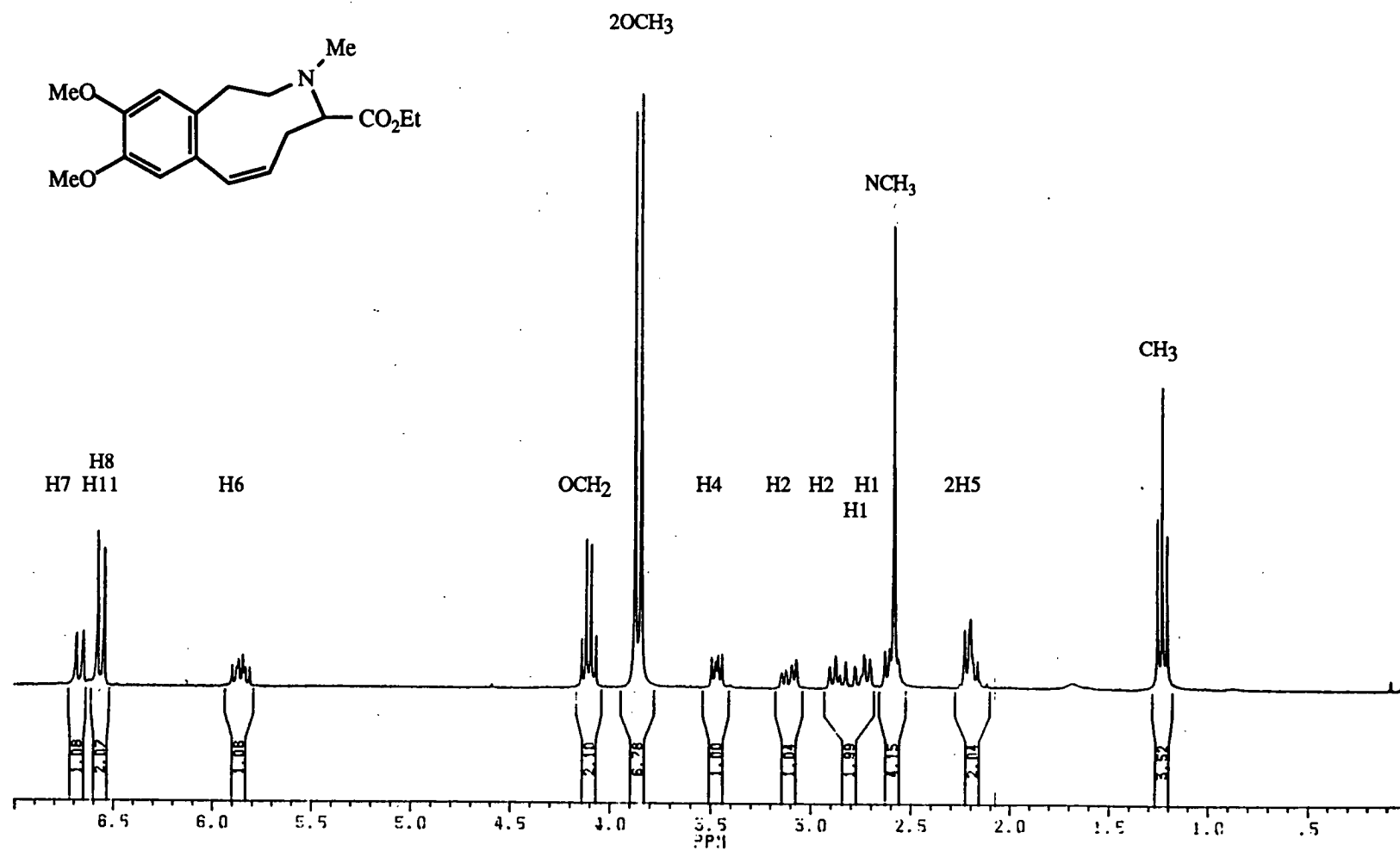
Figure 2.7 ^{1}H NMR spectrum and assignments for the Z-isomer of **52a** in CDCl$_3$
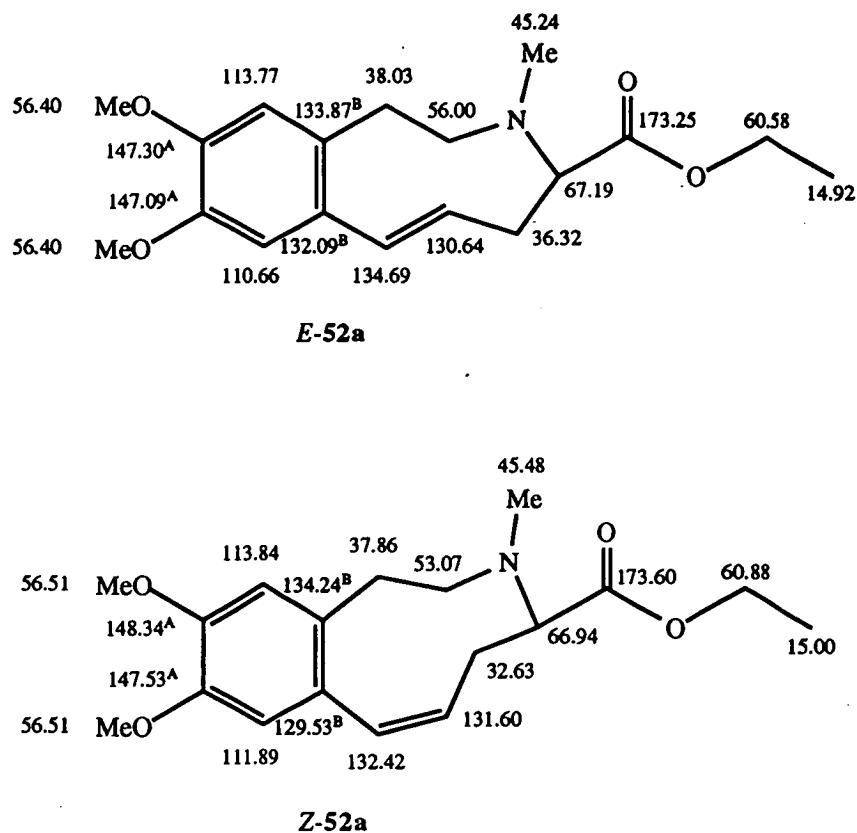
Figure 2.8 ^{13}C NMR Assignments for the Isomers of 52a

were formed by a transannular reaction of the nitrogen and olefin groups under the acidic conditions. Attempted purification of **52a** by p.t.l.c. on alumina, or silica slurried with 0.5M potassium hydroxide, however, also resulted in the degradation of *E*-**52a**.
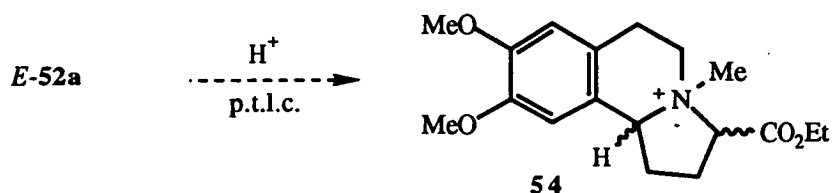
With the failure of the standard chromatographic techniques to provide purified *E*-**52a**, several alternative methods of purification were examined. Sublimation under high vacuum at 95°C proved an effective means for providing highly purified **52a**,

but the product, a colourless waxy solid (m.p. 90-92°C), remained a mixture of the isomers.

The reverse phase HPLC analysis of **52a** on a C18 column with an unbuffered system of acetonitrile/20% H_2O provided baseline resolution of the E and Z isomers. The Z-isomer exhibited a more polar nature and eluted prior to the E-isomer. The method was scaled-up to a semi-preparative scale (50-100 mg applications) and successfully provided the pure E and Z isomers of **52a**, with an excellent recovery of material. The isolated yields were in agreement with the proportions determined by ^{1}H NMR analysis. Modifications of this preparative HPLC method were invaluable for the isolation of the isomeric, often unstable, unsaturated 3-benzazonines, or other medium-ring heterocycles, produced from the various rearrangements throughout this work.

The present results clearly indicated the rearrangement of 2-ethoxycarbonylmethyl-1-vinylisoquinoline-N-ylides **51** could provide a good route to 2,3,4,5-tetrahydro-1H-3-benzazonine derivatives.

2.3.4 Conformational Modelling of 2,3,4,5-Tetrahydro-1H-3-Benzazonines

The large difference in the stability of the E and Z-isomers of **52a** reflected differences in the ring strain incurred by the double bond. The inclusion of a E double bond in a medium-ring heterocycle would be expected to become difficult as the ring size decreases. Derivatives of the eight-membered azacyclooct-4-ene system[41] exhibited a similar behaviour to the tetrahydro-3-benzazonines with the E-isomers, but not the Z-isomers, degraded on silica gel. Derivatives of the larger nine-membered E-azacyclonon-4-ene system[42] were stable on silica, indicating that, as expected, the fused aromatic ring of E-**52a** must also contribute to ring-strain. Hand-held models confirmed E-**52a** would experience substantial ring strain.

The conformations available to the parent E- and Z-2,3,4,5-tetrahydro-1H-3-benzazonines were investigated with PCModel.[76] It was envisaged that a knowledge

of these conformers would aid in the rationalisation of the chemical behaviour and the possible CNS activity of derivatives based on these systems. It should be noted that substituents on these parent derivatives, such as the *N*-methyl and 4- groups of **52a**, would be expected to affect the relative energies and populations of these conformers. It was assumed, however, that the global minimum would still be based on one of the identified conformers.

Five low energy conformations were identified for each of the *E*- and *Z*-2,3,4,5-tetrahydro-1*H*-3-benzazonines (Tables 2.4 and 2.5). The structures which are not shown in either Figures 2.9, 2.11 or 2.12 are included in Appendix A. The Boltzmann distribution afforded the expected populations of the respective conformers at 293 K. The relative positions of the aromatic and nitrogen moieties were calculated to describe each conformer.

The five conformers identified for the parent *E*-benzazonine were within 3 kcal of the global minimum (Table 2.4). Conformer 1 (Figure 2.9) would be predominant (85%) at room temperature, however, any of the five conformers could contribute significantly to the chemical and potential CNS activity. These conformers generally possessed structures in which the medium ring adopted a non-folded, planar, conformation, as expected for a medium-ring incorporating a *trans*-double bond. In conformers 1, 3, and 4 the nitrogen atom was only slightly removed (< 0.8 Å) from the plane of the aromatic ring. The *E*-benzazonine system therefore may be useful as an alternative to other ring systems, such as that in the serotonin receptor ligands (+)-lysergic acid diethylamide (LSD) and R-(-)-10-methyl-11-hydroxyaporphine (MHA) (Figure 2.10), which constrain the nitrogen atom near the aromatic ring plane by a composite of small rings.[77] In support of the proposed transannular degradation of *E*-**52a** to **54** both conformers 1 and 2 possessed structures in which the nitrogen and C7 olefin atoms were in close proximity.

The ^{1}H NMR analysis of the 3,4,5-trisubstituted-3-benzazonine *E*-**87b** (pg. 63-64) in chloroform suggested that conformer 4 (Figure 2.9) was adopted by the *E*-benzazonine system in this relatively non-polar solvent.

(a)

(b)
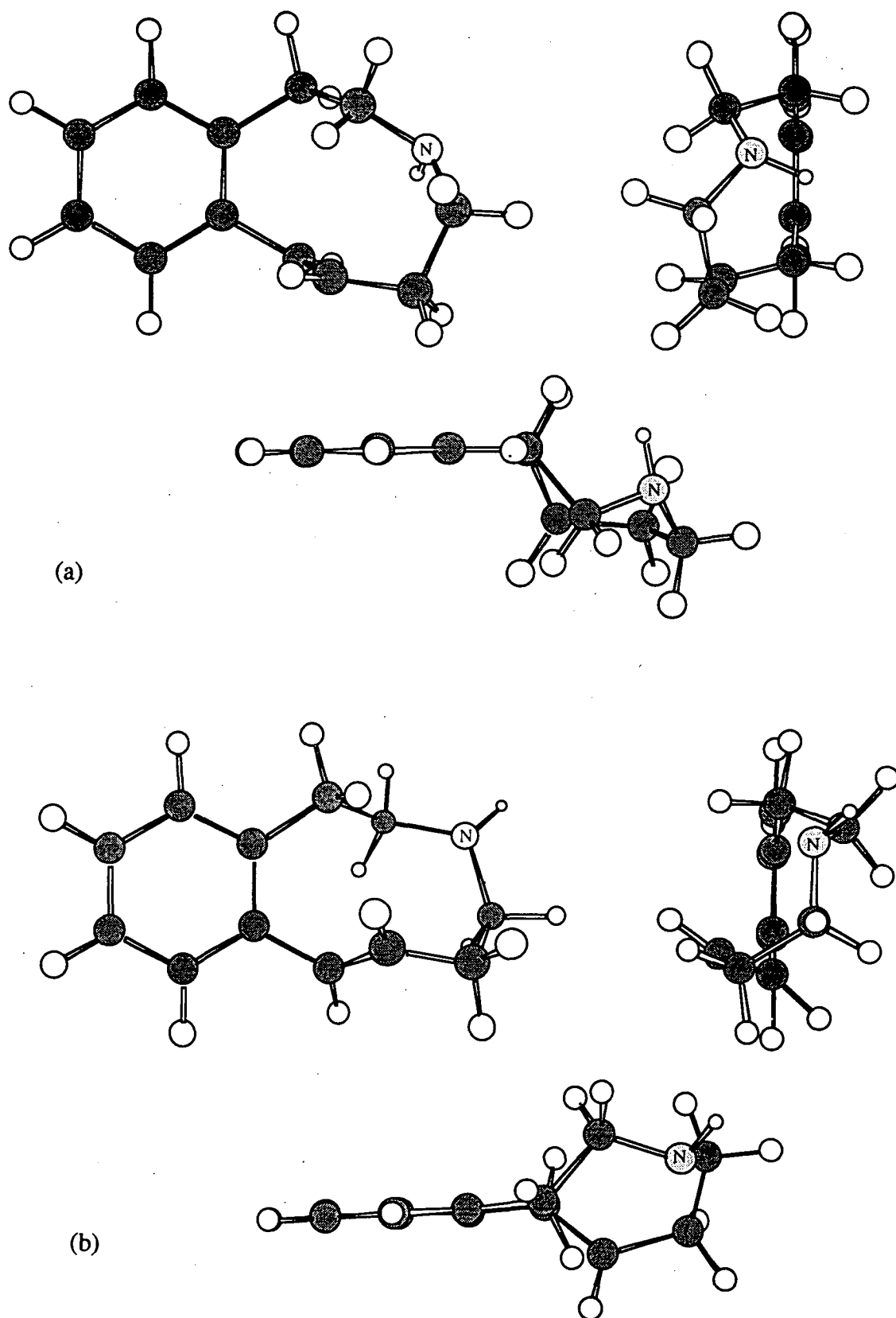
Figure 2.9 Three perspectives of (a) conformer 1 and (b) conformer 4 for the

E-benzazonine system

<u>Table 2.4</u> Low energy conformations of the E-benzazonine system

conformer	E (kcal)	Hf	Population[a]	N-elevation[b]	N-Ar planar[c]
1	34.02	47.92	85.3%	0.74	4.73
2	35.48	47.69	7.3%	1.49	4.24
3	35.90	49.28	3.6%	0.79	5.08
4	36.22	48.50	2.0%	0.70	4.95
5	36.31	50.57	1.8%	2.09	3.72

[a] from the Boltzmann distribution at 293 K

[b] distance of N above the aromatic plane (Å)

[c] distance of N from the aromatic centre in the aromatic plane (Å)
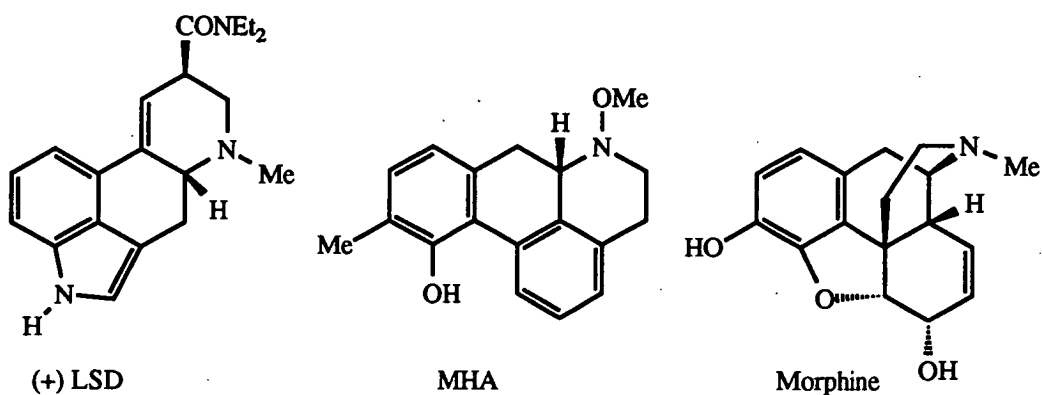
Figure 2.10 Several CNS active agents with constrained phenylethylamine components

Of the five lowest energy conformers identified for the parent Z-benzazonine system three were within 1 kcal of the global minima (Table 2.5). These conformers (Figures 2.11 and 2.12) may all be significantly populated at room temperature, however, only one conformer of Z-**52a** was observed on NMR analysis. It was assumed that solvent or substituents effects had produced a preference for one of these conformers. The X-ray crystallographic analysis of the 3,4,6-trisubstituted Z-benzazonine Z-**75b** (Figure 2.14, pg. 53) confirmed that a structure based on conformer 1 was adopted in the solid state for the Z-benzazonine system.

The low energy conformers identified for the Z-benzazonine system were comparatively folded structures, with the nitrogen atom displaced from the aromatic

plane by 1.7-2.4 Å. The Z-benzazonine system therefore may be useful as an alternative to other ring systems, such as that of morphine[6] (Figure 2.10), which place the nitrogen atom out of the aromatic ring plane.

Table 2.5 Low energy conformations of the Z-benzazonine system

conformer	E (kcal)	H_f	Population[a]	N-elevation[b]	N-Ar planar[c]
1	27.35	41.16	61.3%	1.75	4.36
2	27.95	42.30	22.2%	2.24	3.54
3	28.13	42.56	16.4%	2.41	3.04
4	31.94	45.40	<0.1%	1.91	4.50
5	32.34	46.22	<0.1%	2.42	2.58

[a] from the Boltzmann distribution at 293 K

[b] distance of N above the aromatic plane (Å)

[c] distance of N from the aromatic centre in the aromatic plane (Å)
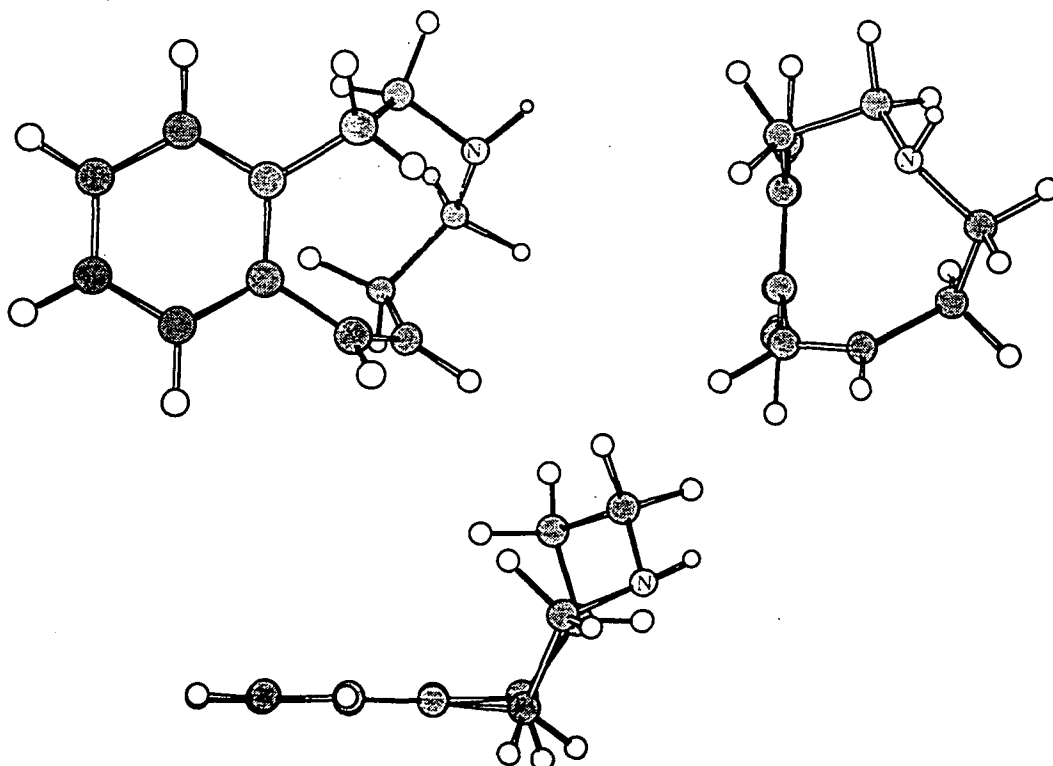
Figure 2.11 Three perspectives of conformer 1 for the Z-benzazonine system
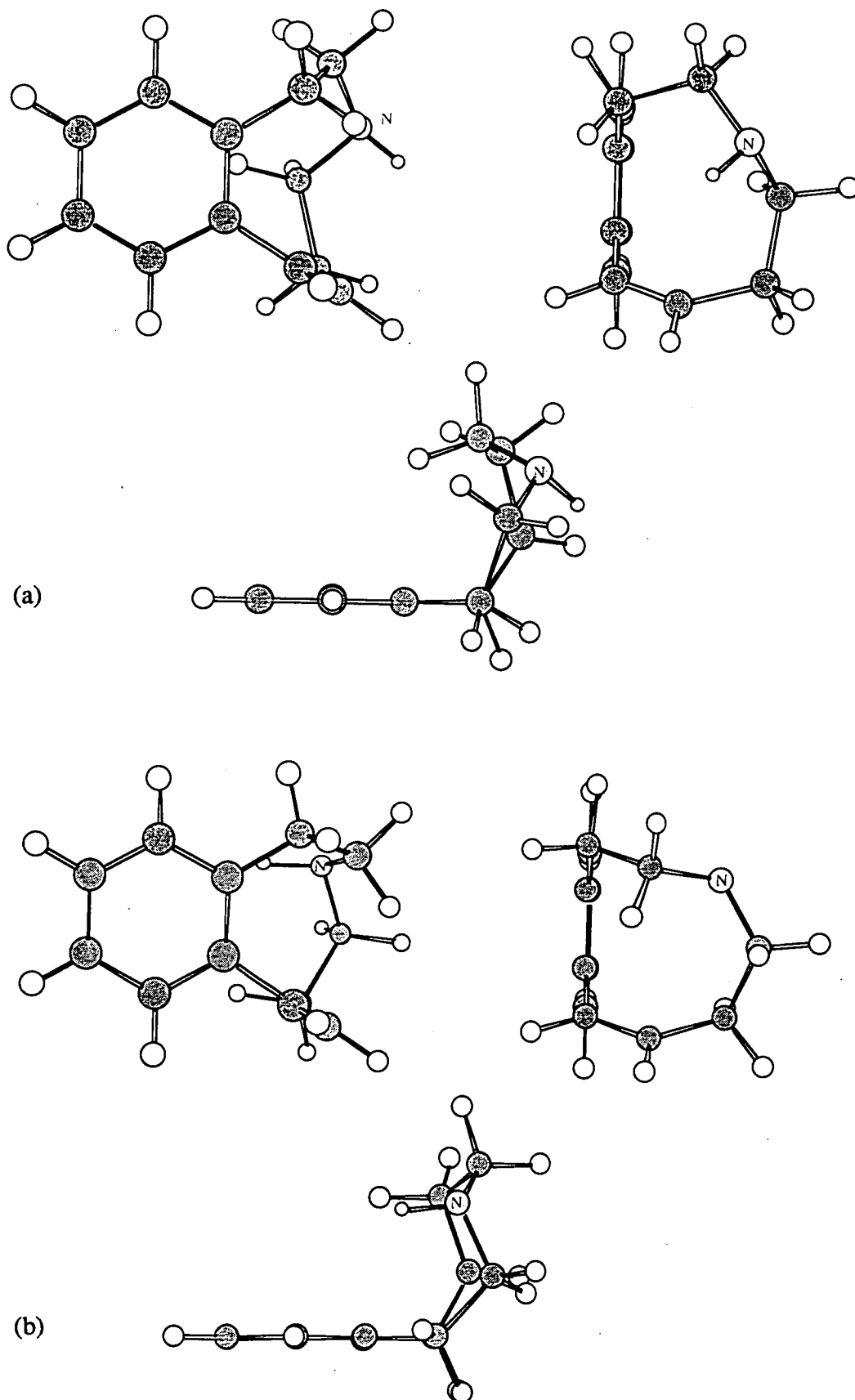
Figure 2.12 Three perspectives of (a) conformer 2 and (b) conformer 3 for the
Z-benzazonine system

The isomers of **52a** were examined exhaustively by NMR techniques, including two-dimensional nOe analysis (NOESY), in an attempt to determine the conformations adopted by these derivatives in solution. The H1 and H2 protons, however, were not resolved to a degree permitting the confident assignment of transannular nOe effects with the H5, H6 or H7 protons, and the conformers of *E* and *Z* **52a** were not identified.

2.4   Effect of the Ylide Stabilising Group on the [2,3] Rearrangement

2.4.1 Attempted Generation and Rearrangement of *N*-Methylene Ylides with Lithium Diisopropylamide

Although electron-withdrawing, potentially ylide-stabilising, groups are typically incorporated to facilitate the formation of *N*-ylides, strong bases have promoted the formation and rearrangement of the unstabilised methylene *N*-ylides. The reaction of *N*-benzyl-*N*-methyl-2-vinylpiperidinium iodide with lithium diisopropylamide (LDA) afforded[42] the [2,3] and [1,2] rearrangement products via a methylene *N*-ylide. The analogous reactions of the isoquinolinium salts **55** were investigated in this work.

a: R = Me
b: R = Bz
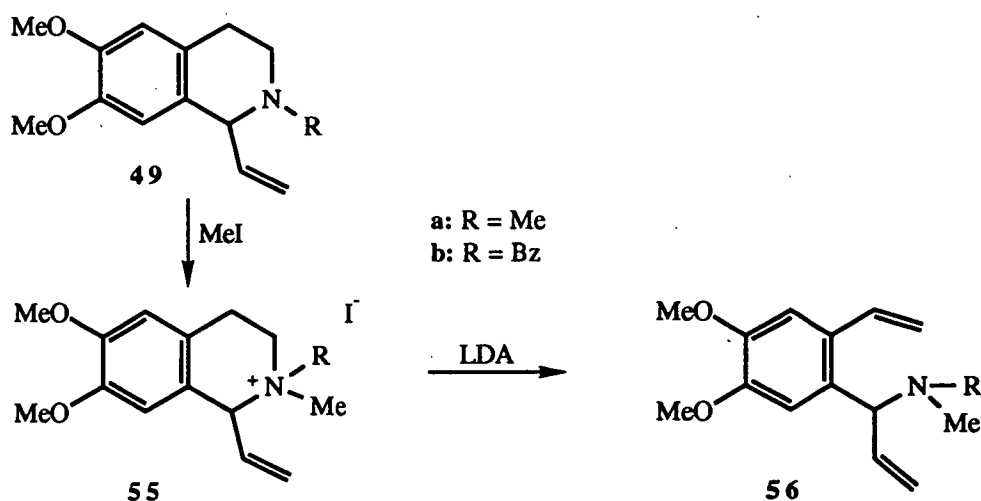
The N-alkylation of **49** with iodomethane afforded **55a,b**. Compound **55a** exhibited signals for the two N-methyl groups at 3.59 and 3.36 δ in the ^{1}H NMR spectrum. The signals were attributed to the N-methyl groups occupying the *cis* and *trans* positions with respect to the 1-vinyl substituent. Compound **55b** was a 54:46 mixture of the B-ring diastereomers.

Treatment of **55** with LDA at -20°C in tetrahydrofuran afforded the Hofmann elimination products, the ring-opened diolefins **56**, in good yield. No [2,3] or [1,2] rearrangement products were detected. The spectroscopic characteristics of the diolefins were consistent with the proposed structures. Two-dimensional NMR correlation experiments confirmed the presence of the separate vinylic and allylic moieties of **56**.

2.4.2 Rearrangement of an N-Methylene Ylide Generated by a Fluoride-Catalyzed Desilylation

Alternatives to the generation of N-ylides by the deprotonation of ammonium salts are known.[10] In particular, the direct generation of N-ylides from the reaction of a carbene, typically from a diazonium salt, with an amine lone-pair has attracted widespread use.[78] A method for the specific generation of methylene N-ylides by the desilylation of trimethylsilylmethyl ammonium salts with cesium fluoride was developed[79,80] and applied recently[81-83] in investigations of the Sommelet-Hauser rearrangement. The application of this method to the synthesis of the 4-unsubstituted 3-benzazonine **61**, via the methylene N-ylide **60**, was investigated.

Preparation of the trimethylsilylmethyl ammonium precursor **59** was attempted via treatment of the N-methyl amine **49a** with iodomethyltrimethylsilane, but without success. Little reaction was observed. It was concluded that the large steric bulk of the alkylating agent prevented access of the reagent to the lone-pair of the tertiary amine. An alternative approach to **59**, via the reaction of trimethylsilylmethyl trifluoromethanesulfonate with the secondary amine **57** and alkylation of the resultant trimethylsilylmethyl amine **58** with iodomethane, was examined.
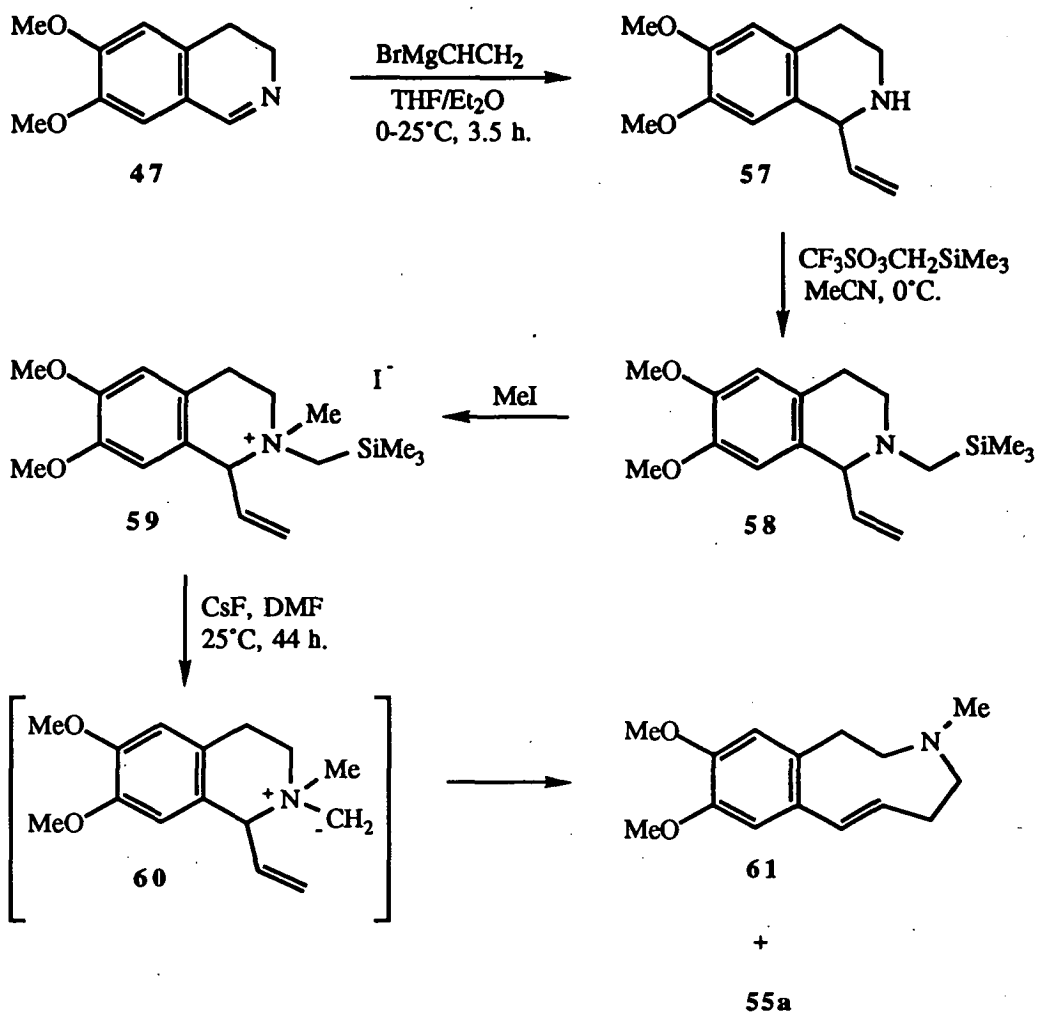
Compound **57** was obtained in moderate yield by the direct action of vinylmagnesium bromide on the imine **47**. Other examples of the direct reaction of alkenylmagnesium halides with Schiff's bases of type $C_6H_5CH{=}NR$, rather than their iminium salts, are known[84] but are rare. The reaction was conducted in a diethyl ether/tetrahydrofuran mixture as the basicity of tetrahydrofuran was reported[84] to provide reduced yields in reactions of this type, but **47** was insoluble in diethyl ether alone. Reaction at room temperature over 24 hours gave, surprisingly, a 1.4:1.0 mixture of **57** and the *N*-methyl compound **49a**. Subsequent experiments confirmed the formation of **49a** reached significant levels only with reaction times above four hours. A reaction time of 3.5 hours afforded **57** in 33% yield free of **49a** and eliminated the need for a lengthy purification of **57**.

The reaction of trimethylsilylmethyl trifluoromethanesulfonate with **57** in acetonitrile at room temperature afforded **58** in good yield. ^{1}H NMR analysis revealed the NCH$_2$Si protons at 2.39 and 1.78 δ with geminal coupling (14.7 Hz) while the silylmethyl protons absorbed at 0.07 δ. Quaternization of **58** with iodomethane in acetonitrile at 60°C afforded **59**, a crystalline solid, as a 51:49 mixture of the *cis* and *trans* B-ring diastereomers.

The reaction of **59** with cesium fluoride was conducted in dimethylformamide at room temperature. The method was adapted from that described by Sato *et. al.*[81] A single non-polar product was isolated and identified by spectral analyses as the desired [2,3] rearrangement product, the *E*-2,3,4,5-tetrahydro-*1H*-3-benzazonine **61** (30% yield). The 4-unsubstituted 3-benzazonine derivative exhibited a ^{13}C NMR resonance at 61.08 δ for C4.

A polar solid was also isolated from the reaction of **59** with cesium fluoride. The compound was identified as the *N,N*-dimethyl salt **55a** (59% yield), assumed to be formed by the reaction of moisture with the intermediate *N*-ylide **60**. The high yield of **55a** was surprising as all efforts were made to exclude moisture from the reaction. Time constraints prevented the repetition of the experiment to obtain an improved yield of **61**.

2.4.3 Rearrangements of Nitrile and Benzoyl Stabilised *N*-Ylides

Quaternization of the tertiary amine **49a** with iodoacetonitrile or phenacyl bromide in butanone at room temperature afforded the isoquinolinium salts **62a,b** possessing the electron-withdrawing nitrile and benzoyl groups. Mixtures of the possible B-ring diastereomers were obtained. The stereoselectivity of the reaction was greater to **62b** (78:22 d.r.) than **62a** (53:47 d.r.). In each case the major isomer exhibited a more upfield shift of the *N*-methyl signal in the ^{1}H NMR spectrum and was assigned the *trans*-stereochemistry.

The DBU-promoted rearrangements of **62** were examined at a variety of temperatures in acetonitrile. The results are summarised in Table 2.6.
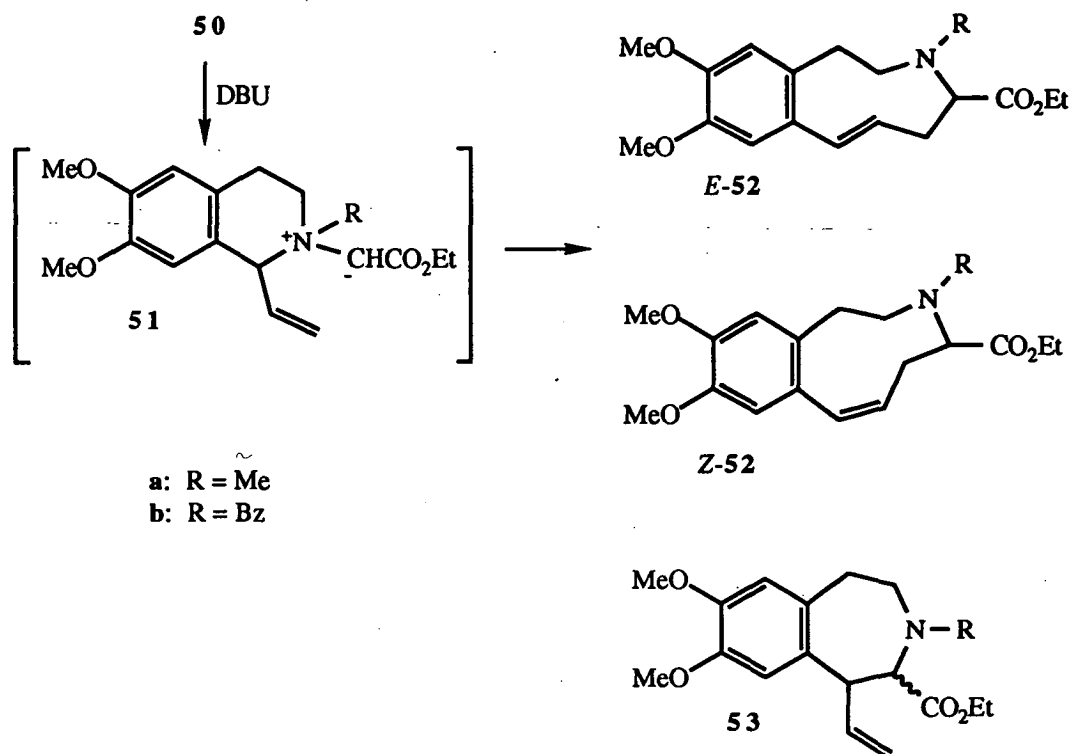
Table 2.6 Rearrangement Conditions and Products from **62**

Reactant	Reaction Temp (°C)	Total % Yield[a]	Product Distribution[b] (%)			
			E-63	Z-63	64 major	64 minor
62a	25	84	78	16	6	-
"	82	62	80	8	12	-
62b	-30	71	94	6	-	-
"	0	84	91	7	2	-
"	25	66	89	3	8	-
"	65	54	-	-	78	22

[a] yield of a non-polar rearranged fraction

[b] from ^{1}H NMR integrals

The treatment of **62a** with DBU at room temperature provided, in high yield, a rearranged fraction which contained three components observed by ^{1}H NMR analysis. The major component was isolated by preparative reverse-phase HPLC and identified as the E-benzazonine **63a**. Compound E-**63a** exhibited behaviour similar to E-**52a** and degraded upon silica gel. The two minor components were not isolated but, by analogy with the rearrangement of **50a**, were tentatively attributed to Z-**63a** and the Stevens rearrangement product **64a**. Compound Z-**63a** exhibited a multiplet at 5.69 δ, consistent with H6 of the proposed structure, while **64a** exhibited a ^{1}H NMR

pattern indicative of the 1-vinyl substituent with H1', H2' and H2' assigned to peaks at 6.08, 5.11, and 4.78 δ respectively. The rearrangement of **62a** with DBU in refluxing acetonitrile provided a slight increase in the level of the Stevens rearrangement product **64a**, however, *E*-**63a** remained the dominant product.

The rearrangements of **62b** with DBU in acetonitrile were significantly different to those observed from either **50a** or **62a**. The rearrangement was greatly effected by the reaction temperature. At room temperature the reaction afforded the *E*-benzazonine **63b** as the major product, while at 65°C the B-ring diastereomers of the 3-benzazepine **64b** (3.5:1 d.r.) were obtained. A reaction temperature of -30°C was necessary for the completely selective rearrangement of **62b** to the isomers of **63b**. The selective formation of **64b** from **62b** at high temperature suggested this compound was the thermodynamic product, with the less strained 3-benzazepine system favoured over the unsaturated 3-benzazonine system. This was confirmed by the conversion of **63b** to **64b** as described in Section 2.9.4.

The *E* and *Z* isomers of **63b** were isolated by preparative reverse-phase HPLC and characterised spectroscopically. The isomers, yellow oils which darkened on storage, exhibited identical mass spectra in which the molecular ion was not observed. A base peak at M^{+}·-105 was consistent with the loss of the benzoyl fragment from the molecular ion. The *E*-isomer of **63b** exhibited two equally populated conformations in the ^{1}H and ^{13}C NMR spectra at 25°C. The conformers reflected hindered rotation of the C4-CO bond, rather than conformational flexibility of the medium-ring. Hand-held models of the 4-benzoyl-*E*-benzazonine indicated the bulky conjugated benzoyl group would adopt a position with the H4-C4-C-O dihedral angle at either approximately 180° or between 0-30°. The latter angle would place the benzoyl ring over one face of the heterocycle, at 90° to the molecular plane, and produce the downfield shifts of the heterocyclic protons observed in one conformer. Compound *E*-**63b** was degraded on silica p.t.l.c.

The diastereomers of **64b** could not be separated, however, NMR and MS analyses of a purified mixture were consistent with the proposed structures and

comparable with the other 3-benzazepines prepared in this work. Typical vinyl signals were observed in the NMR spectra. The major isomer of **64b** exhibited H1 and H2 at 4.10 and 4.48 δ in the ^{1}H NMR spectrum, while C1 and C2 appeared at 50.33 and 69.18 δ in the ^{13}C NMR spectrum.

2.4.4 Rearrangement of an *N*-Butyrolactone Salt

The [2,3] or [1,2] rearrangements of allylic bis(methoxycarbonyl)methyl-*N*-ylide derivatives are known,[10] however, the rearrangements of few other ylides possessing a tertiary carbanionic centre have been investigated. In this work the commercial availability of α-bromo-γ-butyrolactone, and the possibility of further functional group manipulations, prompted an investigation of the potential for the synthesis of the unusual spirocyclic 3-benzazonine derivative **66** via the [2,3] rearrangement of the butyrolactone salt **65**. The rearrangements of *N*-butyrolactone salts do not appear to have been investigated.
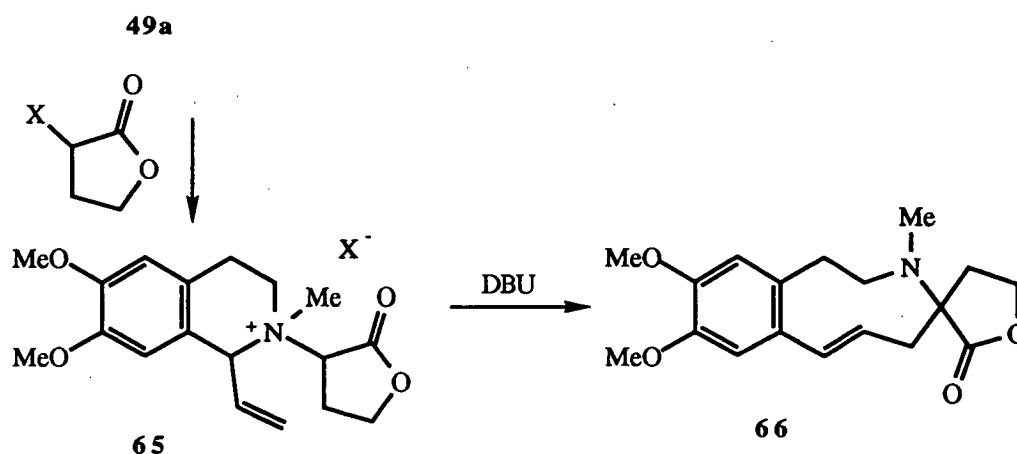
The synthesis of **65** proved difficult. Treatment of **49a** with α-bromo-γ-butyrolactone in butanone at 50°C for 40 hours provided a tan powder which displayed only broad resonances in the ^{1}H and ^{13}C NMR spectra, possibly due to a number of diastereomers being present, and could not be identified. Treatment of this material with DBU afforded the precursor **49a** and **66**, suggesting the original alkylation was incomplete. Alkylation of **49a** with α-iodo-γ-butyrolactone afforded,

after column chromatographic purification, a polar fraction attributed to the iodide salt of **65** in low (19%) yield.

Treatment of **65** with DBU gave the lactone derivative **66**, the first example of this unusual spiro-annulated medium ring heterocyclic system, in low (29%) yield. The molecular formula of **66** was confirmed by high-resolution mass spectrometry while the NMR spectra were consistent with the proposed structure. The resonances of the C5 and NMe carbons in the ^{13}C NMR spectrum (Figure 2.13) were shifted respectively 6.1 δ upfield and 5.9 δ downfield compared to those of *E*-**52a** (Figure 2.8) by the proximity of the constrained lactone ring. In several attempts to purify **66** by preparative reverse-phase HPLC the compound was not recovered, suggesting the material was degraded by aqueous solvent mixtures.
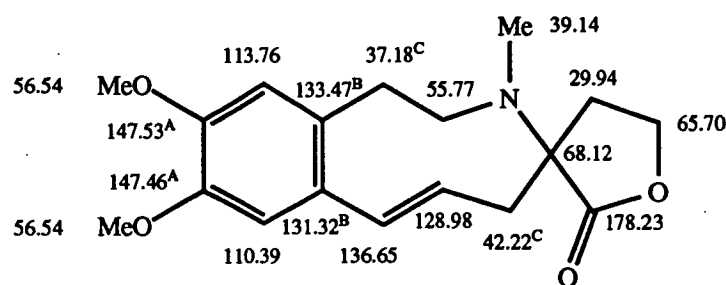
Figure 2.13 ^{13}C NMR Assignments for **66**

2.4.5 Attempted Formation of a Spiro-ammonium Salt

Numerous cases of the Stevens rearrangement of spiro ammonium salts are reported in the literature. The [2,3] rearrangement of these systems, however, appear to be unknown. It was proposed that the [2,3] rearrangement of the ylide derived from the spiro ammonium salt **68** may provide the unknown 1,4-oxazino-3-benzazonine derivative **69**. The preparation of **68** was thus investigated.

2-Chloroethyl bromoacetate was synthesised by the reaction of bromoacetic acid with 2-chloroethanol. The reaction of this ester with **57** gave the proposed precursor amine **67** in moderate yield. It was envisaged that an intramolecular quaternization of **67** to **68** would occur over potassium or sodium iodide, following

halide exchange. The synthesis of **68**, however, was not achieved despite investigation of the reaction in acetone, butanone, or acetonitrile, at temperatures between 25°C and the boiling points of these solvents. In each case the majority of **67** was recovered. Any polar material formed contained many components. The failure to achieve the synthesis of **68** prevented the proposed examination of the rearrangements of this spiro ammonium salt. .
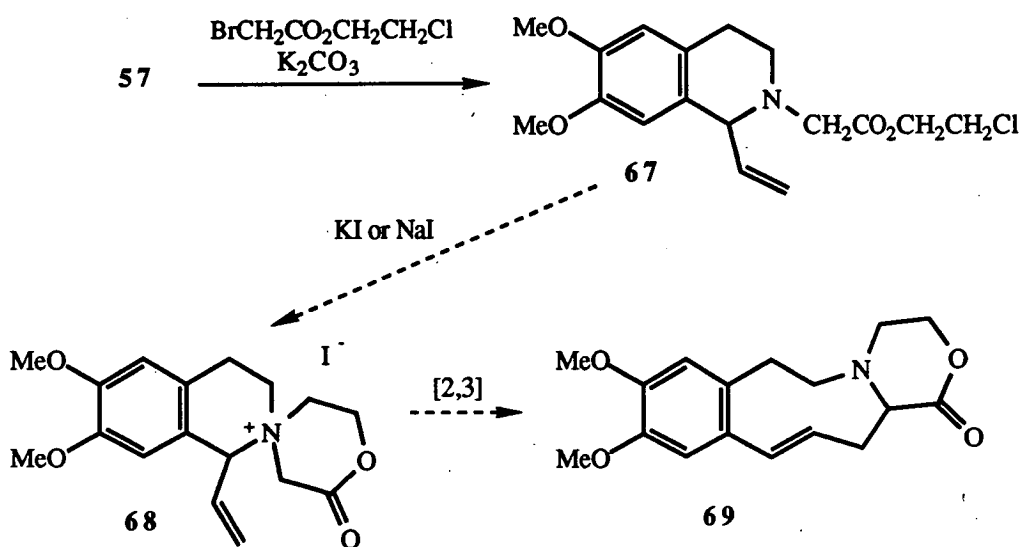
2.4.6 Discussion of the Effect of the Ylide Stabilising Group

The ylide-stabilising group had little effect on the rearrangement pathway adopted at room temperature, but a substantial effect on the reaction pathway at higher temperatures. The results were consistent with the currently accepted concerted and diradical mechanisms for the [2,3] and [1,2] rearrangements respectively. In all cases the low-energy concerted [2,3] rearrangement occurred preferentially at low temperature. Clearly none of the ylide substituents investigated (hydrogen, ester, nitrile, benzoyl, lactone) lowered the activation energy of the high-energy [1,2] rearrangement sufficiently to allow substantial rearrangement via this pathway at low temperature. At high temperature, however, the selectivity of the rearrangement reflected the radical stabilisation offered by the ylide substituent. Thus the extra radical stabilisation offered by the benzoyl substituent in **62b** enabled the selective

[1,2] rearrangement of this derivative. The nitrile and ester substituents did not afford significant [1,2] rearrangement, even at high temperatures, and should be used preferentially in future applications of the [2,3] rearrangement to the synthesis of fused medium-ring aza-heterocycles.

The Hofmann elimination from **55** with LDA reflected the acidic nature of the C4 benzylic proton β to the amino group in this fused aromatic derivative. The results were not surprising given the acidic nature of H4, the strong base used, and the absence of a group promoting the formation of the desired N-ylide. Similar results are likely to be encountered with other aromatic-fused systems, particularly those containing an arylethylamino component. The present results indicated that an ylide-stabilising group was necessary for the successful [2,3] rearrangement of an aromatic-fused system when generating the N-ylide by deprotonation of a precursor salt.

The [2,3] rearrangements of the various ylide-substituted 1-vinylisoquinoline derivatives demonstrated the synthetic potential of this pathway to the 3-benzazonine system. A variety of functionalised 4-substituted 3-benzazonines were prepared which could be useful for the preparation of further derivatives. In addition, the fluoride-catalysed desilylation of **59** demonstrated that, with the exclusion of water, 4-unsubstituted 3-benzazonines could be obtained in high yield. Finally, the rearrangement of the N-butyrolactone salt **65** confirmed the potential for the formation of 4,4-disubstituted 3-benzazonines, including spiro derivatives, in moderate yields.

2.5 Effect of 1'-Substituents on the [2,3] Rearrangement

2.5.1 Synthesis of the 1'-Substituted Precursors

The three 1'-substituted precursor amines **70a-c**, possessing respectively the methyl, phenyl, and trimethylsilyl substituents, were prepared by the treatment of **48a** with the appropriate Grignard reagent. No negative effect on the Grignard reaction was observed despite the presence of the 1'-substituent in the alkenylmagnesium

bromide reagents. Compounds **70a-c** were obtained in excellent yields and were fully characterised by their spectroscopic data and elemental analyses.

Vinylsilane derivatives may be converted to vinylhalide derivatives by iodo- or bromo-desilylation.[85,86] The reaction proceeds via the formation of an intermediate dihalide then dehydrohalogenation. The reaction of **70c** with iodine or bromine in dichloromethane, however, failed to provide the 1'-iodovinyl derivative **70d** or the analogous 1'-bromo compound. The alternative synthesis of **70d** via the 1-ethynyl amine **71** was then investigated. A recent report described the clean conversion of alkynes to internal alkenyliodides under mild conditions by the addition of hydrogen iodide, generated *in situ* from a chlorotrimethylsilane/sodium iodide/water system in acetonitrile.[87]

The reaction of **48a** with commercial ethynylmagnesium bromide gave **71** in good yield. The compound exhibited characteristic ethynyl NMR resonances for H2' at 2.42 δ, for C2' at 82.31, and for C1' at 74.57 δ. A significant byproduct was also isolated from this reaction. The material, a crystalline solid, on ^{1}H and ^{13}C NMR spectral analysis appeared almost identical to **71** but lacked the terminal ethynyl signals. The detection of an MH[+] ion at 437 by LSIMS-MS was consistent with the bis-acetylene structure **73**. The formation of **73** was rationalised by assuming the generation of the ethynyl anion of **71** in the presence of the basic Grignard reagent, then the attack of this anion on **48a**.

The treatment of **71** with chlorotrimethylsilane/sodium iodide/water in acetonitrile at room temperature afforded only the hydroiodide salt of **71**. Increasing the reaction temperature to 80°C gave, after four hours, the partial conversion of **71** to a mixture of the Markovnikov product **70d** and the 1-(*cis*-2'-iodo)ethenyl product of *anti*-Markovnikov addition. Surprisingly, only **70d** and **71** were detected after eight hours. Column chromatography afforded the isolation of **70d** in moderate yield.

		trans:cis
a:	R = Me	46:54
b:	R = Ph	58:42
c:	R = SiMe$_3$	100:0
d:	R = I	100:0
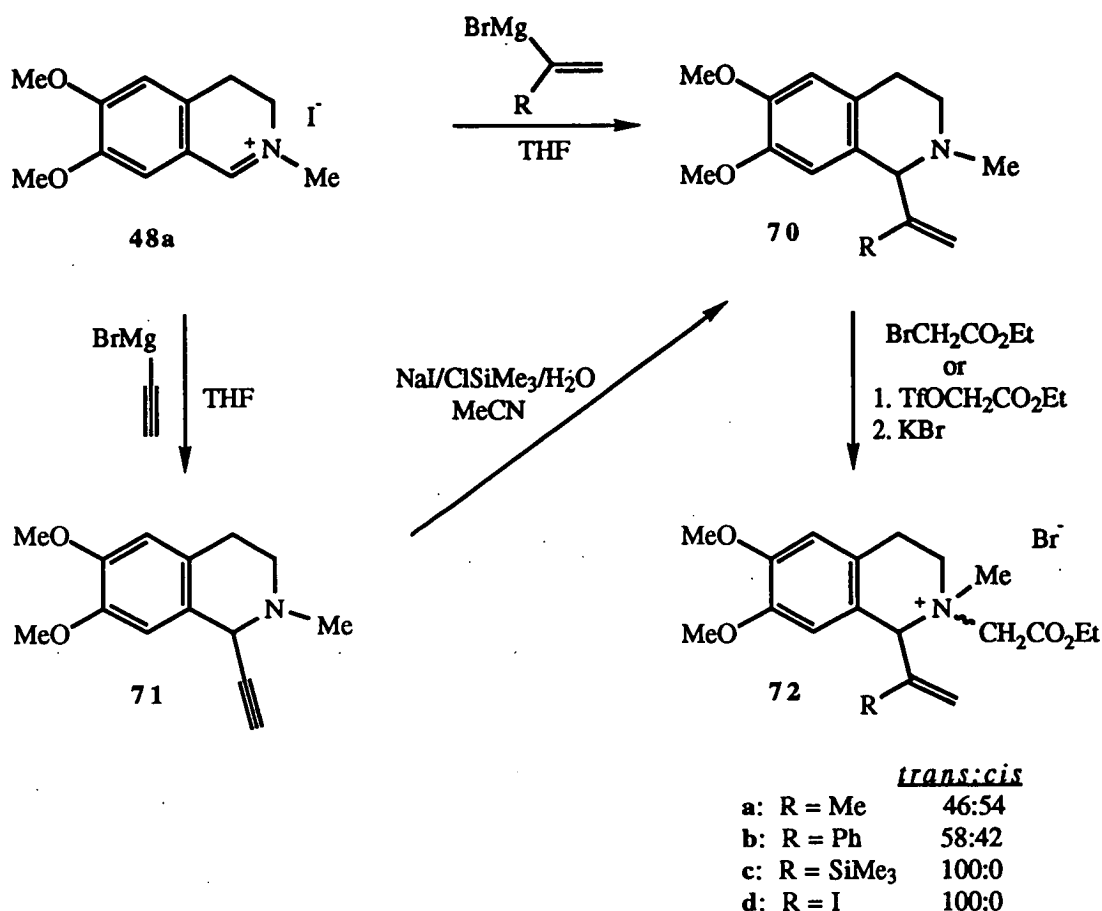
Compounds **70a** and **70b** were N-alkylated by warming the amines with ethyl bromoacetate in butanone. The products **72a,b** were mixtures of the expected B-ring diastereomers. In contrast, **70c** and **70d** failed to react, or gave significant byproducts, on warming with ethyl bromoacetate. The action of ethyl bromoacetate on **70c** is discussed in Section 2.8. The N-alkylation of **70c** and **70d** was achieved by the reaction of the amines with the more reactive triflate alkylating agent, ethoxycarbonylmethyltriflate,[88,89] under mild conditions. Anion exchange of the crude triflate salts afforded the bromide salts **72c,d**. In each case only a single B-ring diastereomer, assumed to have the *trans* configuration, was obtained.

Attempts were made to synthesize the 1-(1'-cyano)vinyl derivative **74a**. The necessary Grignard reagent, however, was not formed by the reaction of 2-chloroacrylonitrile with magnesium under a variety of conditions, including the use of magnesium activated by 'dry-stirring' under nitrogen.[90] Similarly, the formation of

the 1-cyclopentenyl derivative **74b** failed, as the literature preparation[91] of cyclopent-1-enyl lithium from lithium and 1-chlorocyclopentene could not be reproduced. The [2,3] rearrangements of acyclic α-cyclopentenyl[92] and α-cyclohexenyl[92-94] sulfur-ylides are known. The [2,3] rearrangement of an *N*-ylide based on **74b** would afford an unusual fused cyclopentyl[5,6]-3-benzazonine derivative.

MeO, MeO — N—Me

73

MeO, MeO — N — Me

48a

CLMg NC   Li

MeO, MeO — N—Me

74 R

R =   NC   a   b
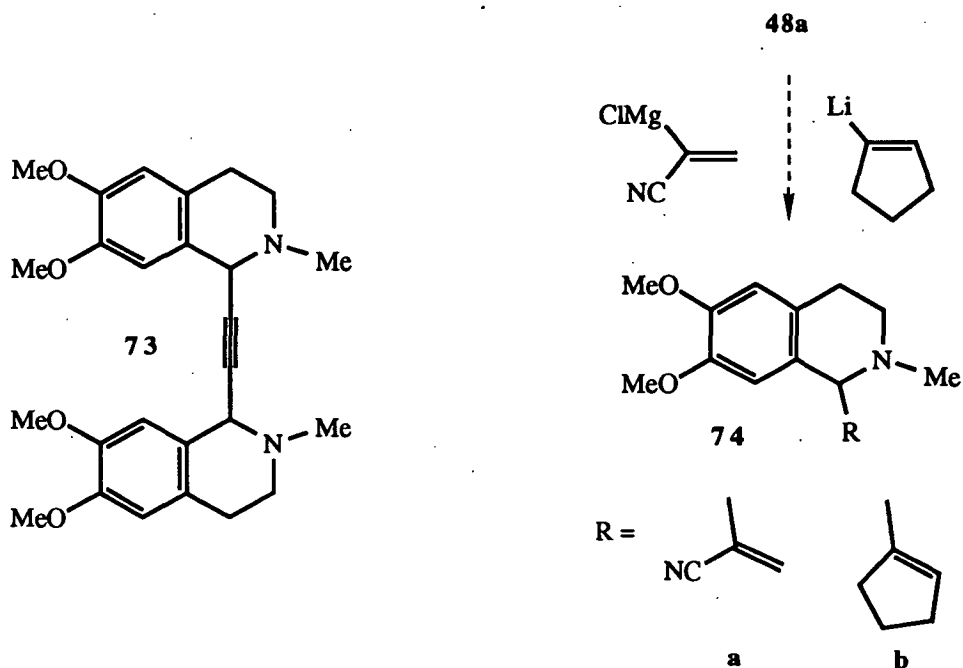
2.5.2   Rearrangement of the 1'-Substituted *N*-Ylides

The DBU-promoted rearrangements of **72** were examined at a variety of temperatures in acetonitrile. The results are summarised in Table 2.7.

The reaction of **72a** at both high and low temperatures afforded exclusively the isomers of the 3-benzazonine derivative **75a** in excellent yield. The 1'-methyl substituent reduced the stereoselectivity of the [2,3] rearrangement to the *E*-benzazonine isomer and substantial levels of the *Z*-benzazonine were formed (*E/Z*=1.9).

The reactions of **72b** gave primarily the 3-benzazonine products **75b**, however, some promotion of the Stevens rearrangement by the 1'-phenyl substituent was evident with the formation of significant amounts of **76b**, even at low

temperatures. With the 1'-phenyl substituent the stereoselectivity of the [2,3] rearrangement was reversed to afford preferentially the Z-benzazonine isomer (E/Z=0.7).

At high temperature the reaction of **72b** afforded a byproduct tentatively identified as **77**, which could not be separated from **76b**. The identification of **77** was dependant on the NMR spectra and GC-MS analysis of a mixture of these compounds. Compound **77** provided resonances in the NMR spectra consistent with an isolated vinyl group, an isolated olefinic proton, and two isolated N-methylene groups (singlets at 3.61 and 3.15 δ in the ^{1}H NMR and 58.25 and 55.19 δ in the ^{13}C NMR). The yields suggested the formation of **77** from Z-**75b**, however, this conversion would appear unlikely mechanistically. The amino ester **77** may arise from the conversion of **72b** to a 5-phenyl-3-benzazocinium salt (cf. Section 2.8) at the high temperature, then the Hofmann elimination from this salt.

The rearrangement of the 1'-trimethylsilyl derivative **72c** at room temperature afforded selectively the E-benzazonine E-**75c** in good yield. No other rearrangement products were detected. Repeating the rearrangement at high temperature failed to afford any of the expected products. An unidentified mixture of many components was obtained in low yield.

Treatment of the 1'-iodovinyl derivative **72d** with DBU at room temperature provided a complex mixture of polar components. None of the expected [2,3] or [1,2] rearrangement products were formed with only traces of any non-polar material.

Each of the E and Z-isomers of **75a,b** were identified unambiguously by their preparative HPLC isolation then nOe difference experiments. Two-dimensional heteronuclear decoupling experiments afforded the positive identification of H7 for the nOe experiments. The NMR spectra for **75b** were obtained in deuterated benzene which enabled the discrimination of the various aromatic and olefinic protons present. The Z-isomers gave nuclear Overhauser interactions between the 6-methyl and H7

a: R = Me
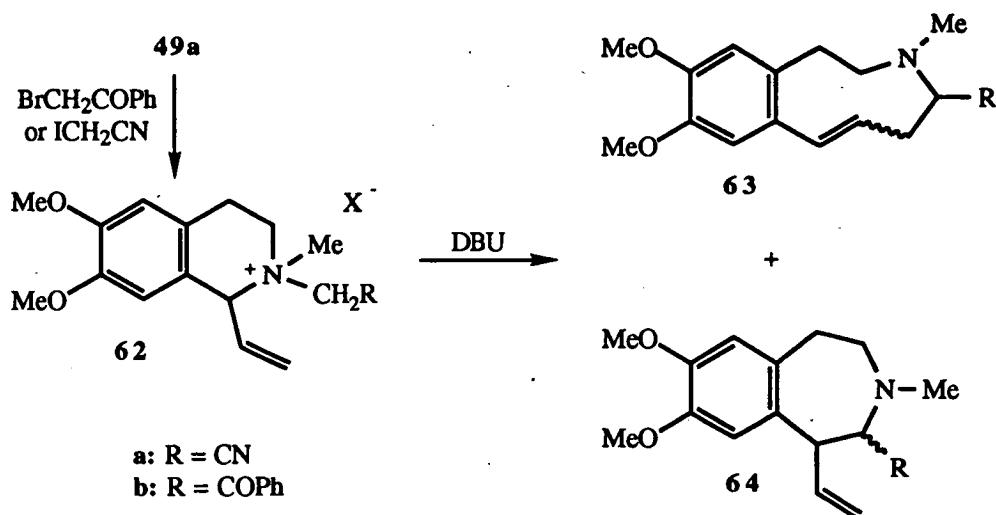**b:** R = Ph
c: R = SiMe₃
d: R = I
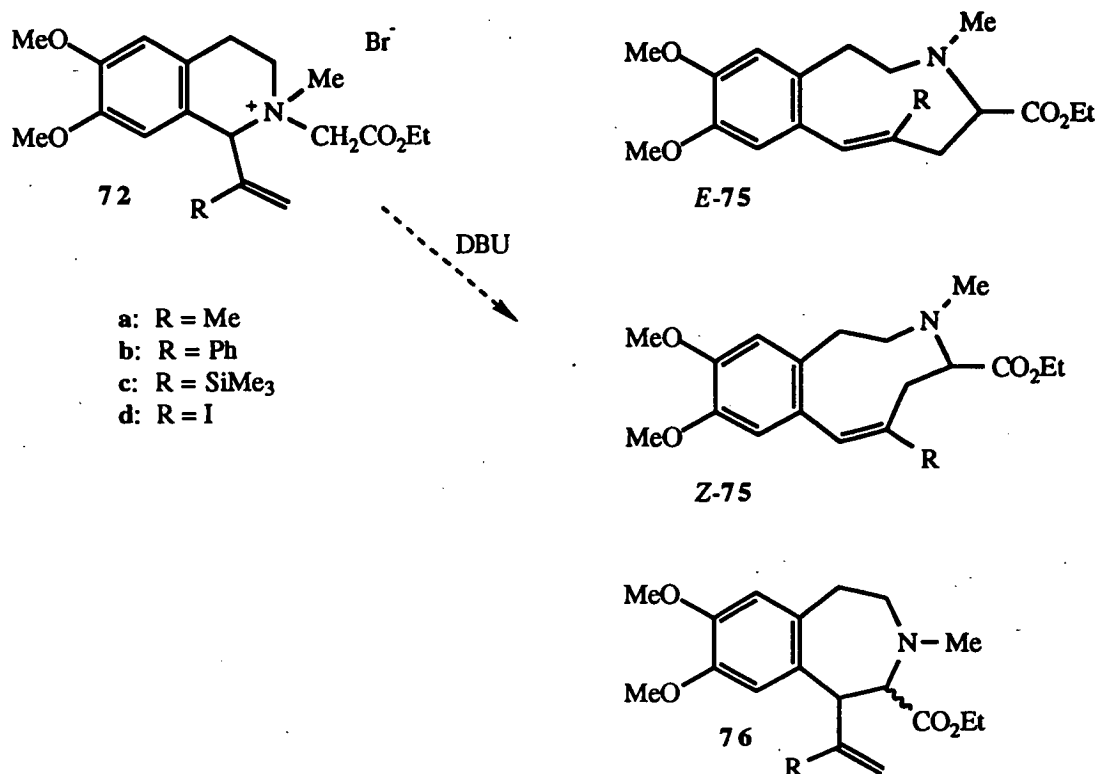
Table 2.7 Rearrangement Conditions and Products from **72**

| Reactant | Reaction Temp (°C) | Total % Yield[a] | Product Distribution[b] (%) | | | |
			E-75	Z-75	76	Other
72a	-40	97	63	37	-	-
"	25	93	66	34	-	-
"	82	93	76	24	-	-
72b	-15	81	38	54	8	-
"	25	81	37	53	8	2 (**77**)
"	82	84	36	35	11	18 (**77**)
72c	25	67	100	-	-	-
"	82	<10[c]	-	-	-	-
72d	25	4	-	-	-	100 (**70d**)

[a] yield to a non-polar rearranged fraction

[b] from ¹H NMR integrals

[c] unidentifiable mixture
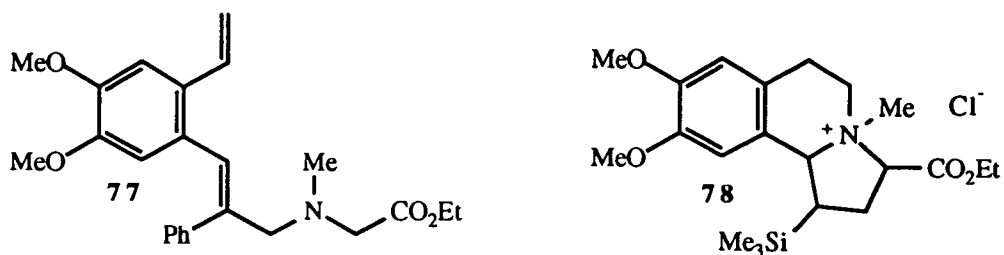
protons for Z-**75a**, and between the *ortho*-6-phenyl and H7 protons for Z-**75b**. No interactions were observed for the *E*-isomers. The assignments of these isomers were consistent with their stability on silica t.l.c; the *E*-isomers were not observed if the t.l.c. plate was aged prior to elution. This simple test provided a rapid, although not conclusive, means of discriminating the isomers. It should be noted that the *E*-isomer of **75b** eluted prior to the Z-isomer on HPLC analysis, the opposite order to all other examples in this work.

The isomers of **75b** were crystalline solids. Unequivocal evidence for the structure of Z-**75b** was obtained by X-ray crystallographic analysis[95] (Figure 2.14). Suitable crystals for an X-ray crystal structure of *E*-**75b** could not be obtained.
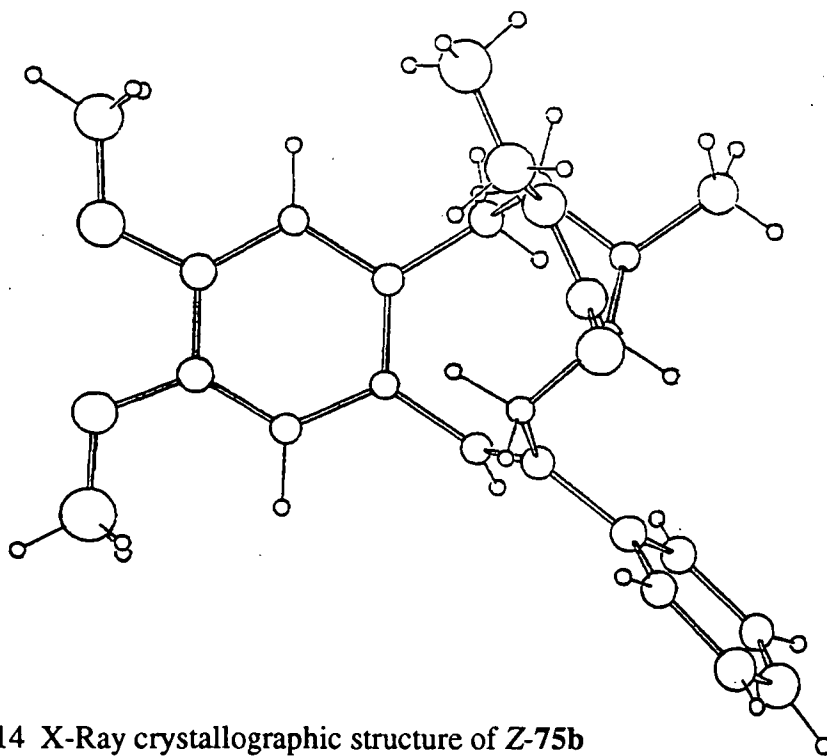
Figure 2.14 X-Ray crystallographic structure of Z-**75b**

Compound *E*-**75b** exhibited conformational flexibility upon NMR spectral analysis at room temperature in either deuterated benzene or chloroform. Broad peaks lacking definition were observed. At 75°C in benzene a single set of signals was obtained which afforded confirmation of the proposed structure. At this temperature only the H5 and the ethyl ester protons exhibited poor peak shape. At -50°C in chloroform two sets of signals were observed, confirming the presence of two conformers for this strained system. The relative populations were approximately 1.94:1. The shifts of the *N*-methyl protons, at 2.36 and 2.69 δ, and the ester methyl protons, at 1.37 and 0.83 δ, were substantially different between the conformers.

The NMR analysis of *E*-**75c** at -20°C in deuterated toluene afforded two sets of signals indicating that, as for *E*-**75b**, two conformers existed. The relative populations were 1.56:1. The shifts of the *N*-methyl protons, at 2.60 and 2.46 δ, and the trimethylsilyl protons, at 0.25 and 0.04 δ, were the major differences between the conformers. The conformers of **75b,c** may reflect transannular interference between the bulky C6 substituents and the C1 or C2 atoms, causing the molecule to favour a more strained conformation of the ring, able to separate these moieties, for a proportion of the time.

The NMR analysis of *E*-**75c** at 75°C in deuterated tetrachloroethane afforded a single set of signals and confirmation of the proposed structure. Extended analysis times under these conditions, however, resulted in the conversion of *E*-**75c** to a mixture consistent with two diastereomeric quaternary salts. The reaction had a half-life of 20 minutes, reflecting the strained nature of the 6-trimethylsilyl-*E*-benzazonine. The products, which were not isolated, were tentatively attributed to diastereomers of the pyrrolo[2,1-*a*]isoquinoline **78**, formed by a transannular reaction in the presence of traces of acid in the chlorinated solvent. Both the ^{1}H and ^{13}C DEPT NMR data appeared consistent with these structures. Similar derivatives were proposed to occur by the degradation of the *E*-benzazonines on silica p.t.l.c. Compound *E*-**75c** was degraded by silica t.l.c.

2.5.3 Discussion of the Effect of the 1'-Substituent

The results indicated that a 1'-substituent had only a marginal effect on the selectivity of the rearrangement of the 1-vinylic tetrahydroisoquinolines. Each of the methyl, phenyl, and silyl substituents were successfully accommodated in the [2,3] rearrangement to provide the 3-benzazonine products **75a-c** in good to excellent yields. The 1'-methyl derivative **72a** afforded the highest yield of the 3-benzazonines and the reaction occurred selectively, even at high temperature, suggesting that the 1-alkyl group hindered the [1,2] rearrangement. In contrast, some Stevens rearrangement occurred from the 1'-phenyl derivative **72b** at low temperature. As the 1'-phenyl group may not contribute to the promotion of the radical pathway by radical delocalisation it was proposed that the concerted transition state was less favoured in this case, due to steric interference. The failure of the 1'-silyl derivative **72c** to afford rearrangement products at high temperature may be attributed to the degradation of the strained E-6-trimethylsilyl-3-benzazonine product, as evidenced by the high temperature NMR experiments on **75c**.

The 1'-iodo derivative **72d** failed to undergo the desired rearrangements. It was proposed that **72d** underwent dehydrohalogenation to a 1-ethynyl derivative which was then degraded by the basic conditions to a variety of products. The promotion of the dehydrohalogenation of alkenyl halides by DBU was previously reported.[96]

The results for **72a,b** demonstrated that the stereoselectivity of the [2,3] rearrangement of the 1-vinylic-isoquinoline N-ylides may be controlled by the selection of the 1'-substituent. Whereas the 1'-unsubstituted derivative **50a** underwent almost stereoselective rearrangement (E/Z=19) to the 3-benzazonines at room temperature the selectivity was reduced by a 1'-methyl substituent (E/Z=1.9) and reversed by the 1'-phenyl substituent (E/Z=0.7). This behaviour was rationalised and predicted in Section 2.3.2 (pg. 25). An alternative explanation proposing the thermodynamic control of the stereoselectivity was considered, as the bulky 6-substituents would increase the ring strain in the E isomers of **75a, b**, but this would

predict a decrease in the *E*-benzazonines at high temperatures. The level of the *E*-benzazonine was increased with the rearrangement of **72a** at high temperature (Table 2.7), consistent with an increased population of the high-energy pro-*E* conformers of **72a** at high temperature.

The stereoselective formation of *E*-**75c** from **72c**, in contrast to the behaviour of **72a** and **72b**, was consistent with the assignment of *trans*-stereochemistry to the single diastereomer observed for **72c**. The results indicated that the *Z*-isomers of **75a,b** were formed predominantly, if not exclusively, from the *cis*-diastereomers of the precursor salts, in agreement with the conclusions in Section 2.3.2. The results suggest that the stereospecific control of the [2,3] rearrangement could be achieved by the appropriate selection of a 1'-substituent and control of the stereochemistry of the precursor salt.

The results confirmed that the [2,3] rearrangement of 1-vinylic isoquinoline *N*-ylides could provide a good pathway to a variety of 6'-substituted 3-benzazonine derivatives.

2.6   Effect of 2'-Substituents on the [2,3] Rearrangement

2.6.1   Synthesis of the 2'-Substituted Precursors

The reaction of alkenyl Grignard reagents with **48a** provided the 2'-(2-methylpropenyl) and 2'-propenyl precursor amines **81a,b**. The synthesis of **81a** gave the lowest yield (61%) for a reaction of this type; the formation of 2-methylpropenylmagnesium bromide occurred slowly and was clearly hindered by the methyl group *cis* to the halide. A mixture of the *cis*- and *trans*-1-propenyl derivatives, **81b1** and **81b2**, was obtained from the commercial mixture of 1-bromo-1-propene isomers. The major isomer was assigned the *cis*-geometry on the basis of nuclear Overhauser experiments and ^{13}C chemical shift data for the terminal methyl group; in the *cis* derivative the methyl signal was at 13.9 δ, approximately 4.5 δ upfield of the

same signal in the *trans*-isomer. Efforts to separate the isomers **81b1** and **81b2** by recrystallisation, p.t.l.c., or preparative HPLC were not successful, so the isomeric mixture was used in subsequent reactions.

1. 170°C, 3 hr.
2. POCl₃
   Δ toluene
3. NaOH

	R^1	R^2	X
a:	Me	Me	Br
b: 75% b1	H	Me	Br
25% b2	Me	H	Br
c:	C₆H₄(OMe)₂	H	I
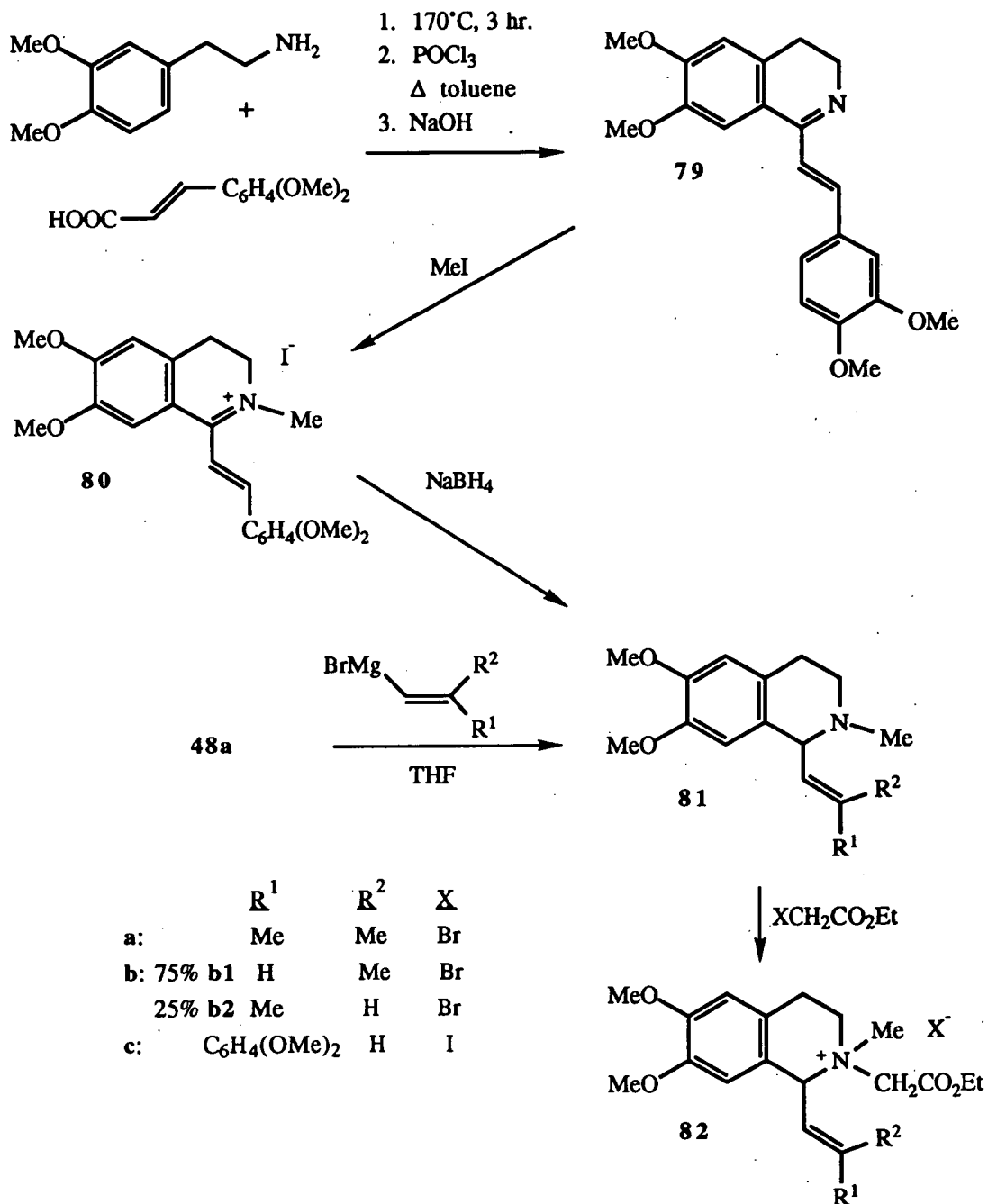
Synthesis of the 2'-dimethoxyphenyl derivative **81c** was achieved by the Bischler-Napieralski cyclisation. This approach allowed the incorporation of the 1-vinylic substituent prior to construction of the isoquinoline ring. The modification of

a published method[97] afforded the free base **79** which was then converted to the methiodide salt **80**. The reduction of **80** with sodium borohydride gave **81c**.

The reaction of the amines **81a,b** with ethyl bromoacetate at 0-25°C in acetonitrile afforded the quaternary salts **82a,b**. Under these conditions **81c** was unaffected. The formation of **82c** was achieved by the treatment of **81c** with ethyl iodoacetate at high temperature in a sealed tube. The quaternary salts **82a-c** were mixtures of the B-ring diastereomers.
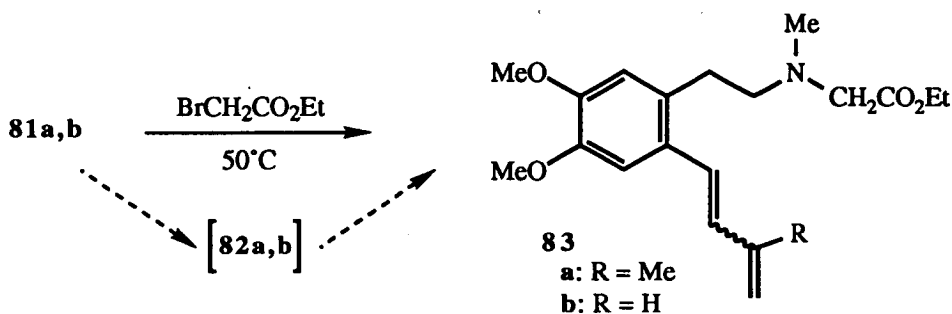
The reactions of **81a,b** with ethylbromoacetate at 50°C in butanone, or acetone, afforded the ring-opened dienes **83a,b**. All spectra were consistent with the proposed structures. Both the geometric isomers of **83b** were isolated, with the *cis* isomer formed preferentially (*cis/trans*=4.2). The reaction of the 1-propenyl isomers of **81b** (*cis/trans*=3) confirmed that the elimination occurred only from the amine possessing the *cis* 2'-methyl group, as the *trans*-propenyl salt **82b2** was obtained with **83b**. A similar elimination process was observed from a 1-cyclopropyl salt (Section 5.7.1), which gave the isomers of **83b** in low yield as byproducts to the Stevens rearrangement at high temperature.

The mechanism for the formation of the dienes is unclear, but was assumed to proceed via the initial formation of **82**. The salt **82b1** was converted to the diolefin **83b** by refluxing in acetone. The formation of an *N*-ylide from **82** by bromide ion induced deprotonation, then a concerted or diradical α-rearrangement may afford **83** (Figure 2.14). However, the intermediacy of the *N*-ylide appears unlikely as the

dienes were not observed from the high temperature rearrangements of **82a,b** with DBU. An alternative pathway may involve the tautomer (β) (Figure 2.15).
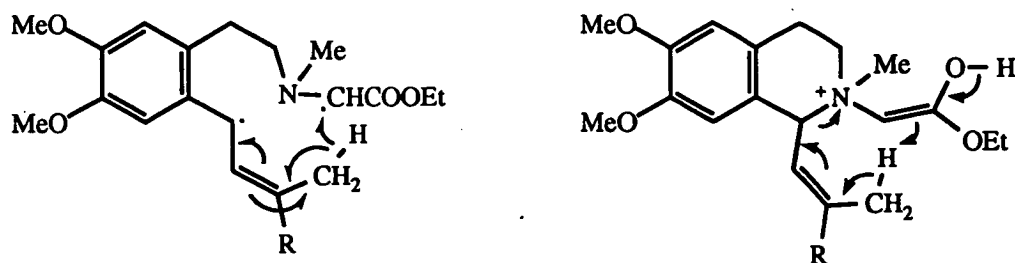
Figure 2.15 Possible Intermediates in the Formation of the Dienes **83**

An alternative route with the potential to provide selectively the *trans*-1-propenyl isomer **81b2** was investigated. The synthesis[98] of the 1-propenyl-dihydroisoquinoline **85** by the Bischler-Napieralski cyclisation of the crotonamide **84a**, in benzene with a large excess of phosphorus oxychloride, could not be reproduced despite exhaustive trials. Several additional experiments in toluene or acetonitrile, with either phosphorus oxychloride or phosphorus pentoxide, failed to provide **85**. In each case only complex mixtures of many components were obtained.

8 4 a: R = Me
b: R = COOEt

8 5

48a → THF → **8 6**
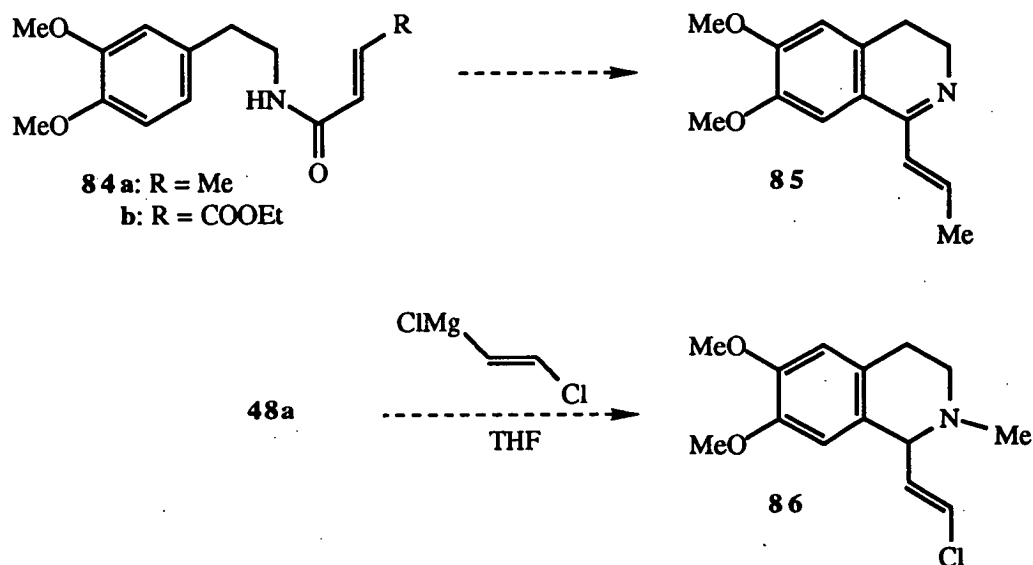
The synthesis of *trans*-2'-ethoxycarbonyl- and *trans*-2'-chloro-1-vinyl-isoquinoline derivatives was also investigated but without success. The reaction of

homoveratrylamine and fumaric acid monoethyl ester failed to provide the amide **84b**, the potential precursor for a 2'-ethoxycarbonyl derivative via the Bischler-Napieralski cyclisation. Similarly, the Grignard reaction of *trans*-2-chlorovinylmagnesium chloride with **48a** failed to give the desired 2'-chloro derivative **86**. The incomplete formation of the Grignard reagent or its rapid degradation may have occurred. Some reaction of the magnesium with *trans*-1,2-dichloroethylene was evident as the magnesium was consumed.

2.6.2 Rearrangement of the 2'-Substituted *N*-Ylides

The DBU-promoted rearrangements of **82** were examined at a variety of temperatures in acetonitrile. The results are detailed in Table 2.8.

At low temperatures the reaction of the 1-(2'-methylpropenyl) salt **82a** gave predominantly the 3-benzazonine *E*-**87a**, however, even at -20°C the diastereomers of the 3-benzazepine **88a** were also formed. The selectivity was 2.3:1 in favour of the [2,3] rearrangement at -20°C and 1.4:1 at 25°C. The reaction of compound **82a** at high temperature gave exclusively the Stevens rearrangement products.

Two different mixtures of the 1-propenyl salts **82b** were examined in these rearrangements. The first contained predominantly the diastereomers of the *cis*-propenyl salt **82b1** (*cis:trans* propenyl=70:30) and was obtained by the alkylation of **81b** at room temperature. The rearrangement of this mixture, at either 0°C or 82°C, afforded a complex mixture of products with diastereomers present for each of the *E* and *Z* 3-benzazonines **87b** and the *cis*-1-propenylbenzazepine **88b1**. The additional chiral centre at C5 enabled the formation of the diastereomers of **87b**. The *E*-benzazonine diastereomers were the major products of the reaction but large amounts of the benzazepines were also formed. The selectivity of the rearrangement was 2.4:1 in favour of the [2,3] rearrangement at 0°C and 1.3:1 at 82°C. Only traces of the *Z*-benzazonines were observed.

MeO— ... (structure **82**) ... CH₂CO₂Et, Me, N⁺, X⁻, R², R¹

82

- - → DBU

E-87 (structure) CO₂Et, R², R¹

Z-87 (structure) CO₂Et, R¹, R², Me, N

88 (structure) N—Me, CO₂Et, R², R¹

	R¹	R²
a:	Me	Me
b: b1	H	Me
b2	Me	H
c:	C₆H₄(OMe)₂	H
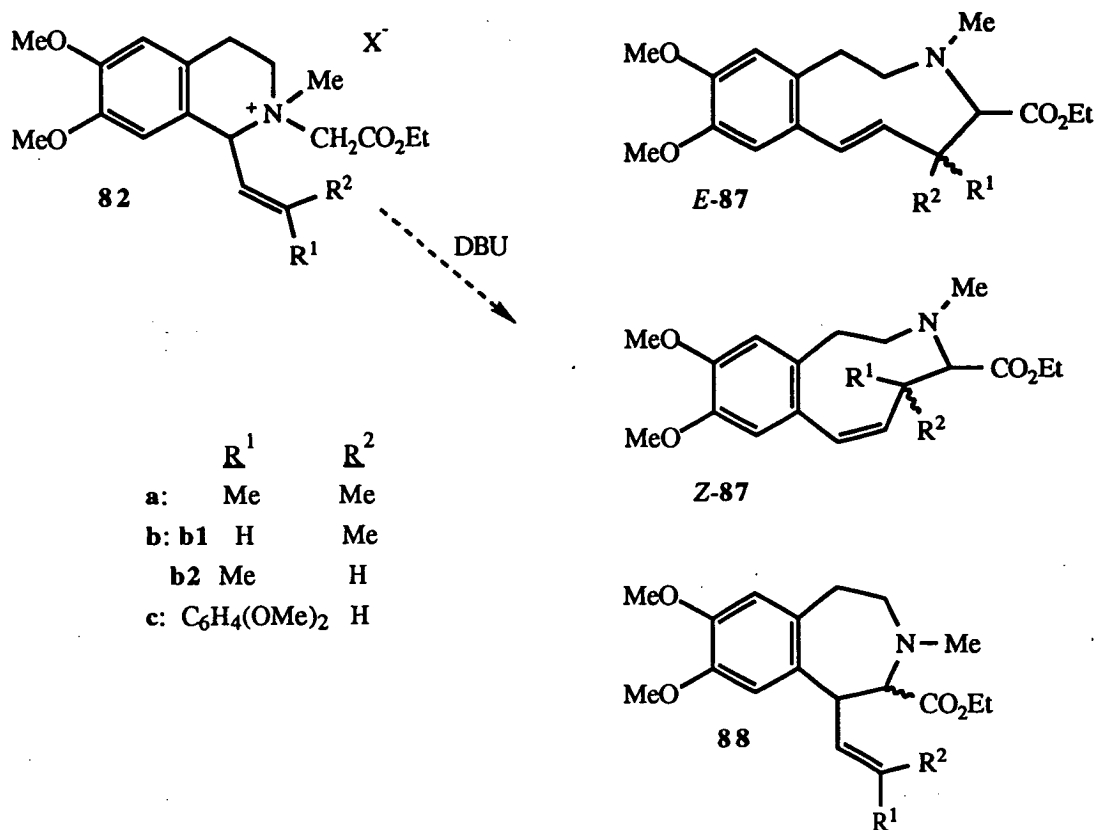
Table 2.8 Rearrangement Conditions and Products from **82**

			Product Distribution[b] (%)			
Reactant	Reaction Temp (°C)	Total % Yield[a]	*E*-87	*Z*-87	**88** trans, cis	Other
82a	-20	65	70	-	27, 3	-
"	25	86	58	-	37, 5	-
"	82	71	-	-	84, 16	-
82b[c]	0	80	42, 23	3, 3	27, 2	-
"	82	72	39, 14	2, 3	37, 5	-
82b[d]	0	65	40, 30	13, 11	4, 2	-
82c	-45	72	-	-	83, 17	-
"	25	63	-	-	80, 16	4 (90)

[a] yield to a non-polar rearranged fraction

[b] from ¹H NMR integrals

[c] from a 73:23 mixture of **82b1** and **82b2**

[d] from a 10:90 mixture of **82b1** and **82b2**

The second mixture of the 1-propenyl salts **82b** was obtained fortuitously following the alkylation of **81b** at 50°C and the removal of the dienes **83b**. The

mixture contained predominantly the diastereomers of the *trans*-propenyl salt **82b2** (*cis:trans* propenyl=10:90). The rearrangement of this mixture at low temperature gave a greatly increased preference (15.7:1) for the [2,3] rearrangement and a higher proportion of the Z-benzazonines.

The base-promoted rearrangement of the 1-styrylic derivative **82c** afforded the diastereomers of the 3-benzazepine **88c** at both 25°C and -45°C, the only selective Stevens rearrangement of a 1-vinylic-isoquinoline derivative observed at room temperature in this work.

The separation of the isomers of **87a** and **88a** was not achieved, however, they could be detected by the ^{1}H NMR analysis of a mixture in deuterated benzene. The olefin coupling constant (16.6 Hz) for the single isomer of **87a** confirmed the compound possessed the *E* stereochemistry. Compound **87a** was not isolated, however, the skeletal structure was confirmed by the hydrogenation of the reaction mixture of **87a** and **88a**, then the separation of the hexahydro-3-benzazonine **101c** (Section 2.9) from the unchanged **88a**.

A combination of alumina column chromatography, to obtain enriched fractions, and preparative HPLC chromatography afforded the isolation of four of the six isomers, at least one from each pair of diastereomers, from the rearrangements of **82b**. The major isomer of *E*-**87b**, the two Z-**87b** isomers, and the major isomer of **88b** were isolated. All spectral data was consistent with the proposed structures. Each type of isomer provided the doublet methyl signal at a characteristic shift in the ^{1}H NMR spectrum; for the *E*-**87b** diastereomers it was 1.25-1.15 δ, for the Z-**87b** diastereomers 0.95-0.75 δ, and for the **88b** diastereomers 1.65-1.50 δ. The H1'-H2' coupling constant (10.9 Hz) of the major diastereomer of **88b** confirmed the compound possessed the *cis* geometry of the 1-propenyl group.

In Z-**87b** the magnitude of the H4-H5 coupling constant was substantially different between the diastereomers (11.45 Hz cf. 4.18 Hz). This allowed the assignment of stereochemistry to the compounds. The consideration of the X-ray structure for Z-**75b** (Figure 2.14, pg. 53) indicated the higher vicinal coupling was

consistent with the *trans*-B-ring diastereomer of Z-**87b**, with a dihedral angle between H4 and H5 of approximately 180°, while the smaller coupling was consistent with the *cis*-B-ring diastereomer. It was proposed that the diastereomers resulted from the inversion of C4 as both exhibited identical vicinal coupling between H6 and H5.
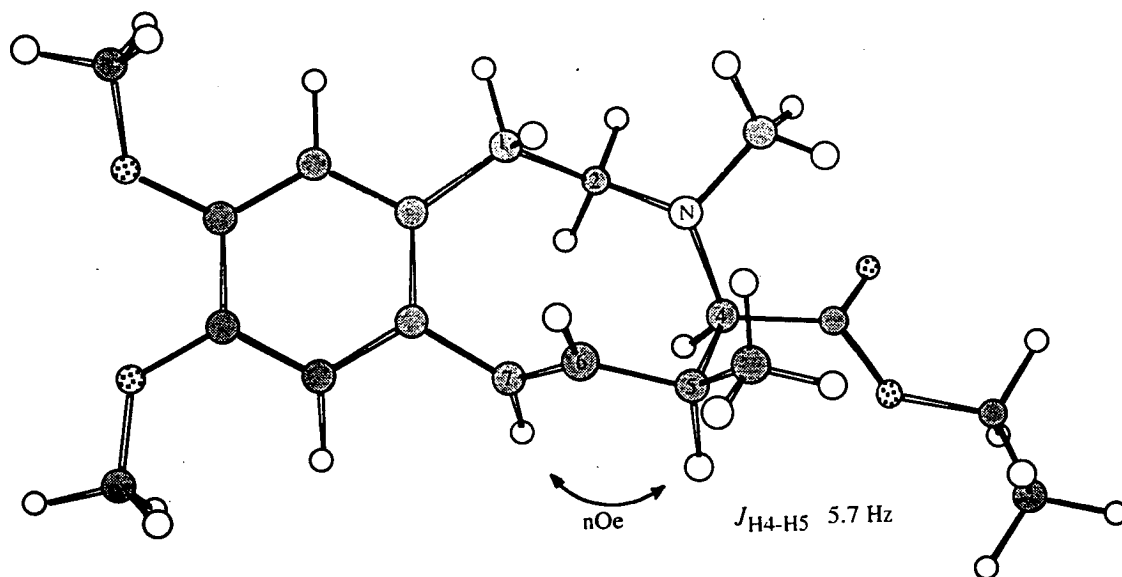
Figure 2.16 Proposed Conformation and Stereochemistry of the Major Diastereomer of *E*-**87b**

The major diastereomer of *E*-**87b** was recovered intact from p.t.l.c. on alumina while the minor diastereomer was degraded. This suggested that a stable *E*-benzazonine may be obtained by the inclusion of substituents with the appropriate stereochemistry. The stereochemistry of the major diastereomer of *E*-**87b** was investigated by the consideration of ^{1}H NMR data. The stereochemistry of the C6 centre was identified by an nOe between H5 and H7, and the coupling constant between H5 and H6 (9.95 Hz). Clearly the C5 to C7 portion of the molecule adopted the geometry shown (Figure 2.16). The H4-H5 vicinal coupling constants for the major (5.76 Hz) and minor (1.28 Hz) diastereomers of *E*-**87b** were consistent with the inversion of C4 in conformer 4 (Figure 2.9, pg. 34), previously identified by the molecular modelling of the *E*-benzazonine system (Section 2.3.4); values of 5.72 Hz

(42°) and 1.01 Hz (72°) were predicted for the *cis* and *trans* diastereomers. The results were not consistent with the other low-energy conformers identified for the *E*-benzazonine system. Values of 11.8-12.2 Hz were predicted for the H4-H5 coupling constant in the *trans* diastereomers of these conformers. It was concluded that the major diastereomer of *E*-87b possessed the *cis* B-ring stereochemistry and that derivatives of the *E*-benzazonine system adopted structures based on conformer 4 in solution.

The crystalline diastereomers of 88c were isolated by p.t.l.c. on silica with dichloromethane/ethanol. P.t.l.c. with dichloromethane/methanol afforded facile ester exchange to the diastereomers of 89. Compounds 88c and 89 were characterised by spectral and elemental analysis. As some doubt existed over the ability of spectral analyses to differentiate between the isomers of 87c and 88c nuclear Overhauser difference experiments were conducted to provided the confirmation of the molecular geometry. The proton assigned to H1 in 88c (or H5 in 87c) interacted with an aromatic proton on the fused ring, while that assigned to H2' in 88c (or H7' in 87c) interacted with the *ortho* protons of the phenyl ring. The results (Figure 2.17) were consistent with the benzazepine structure of 88c.
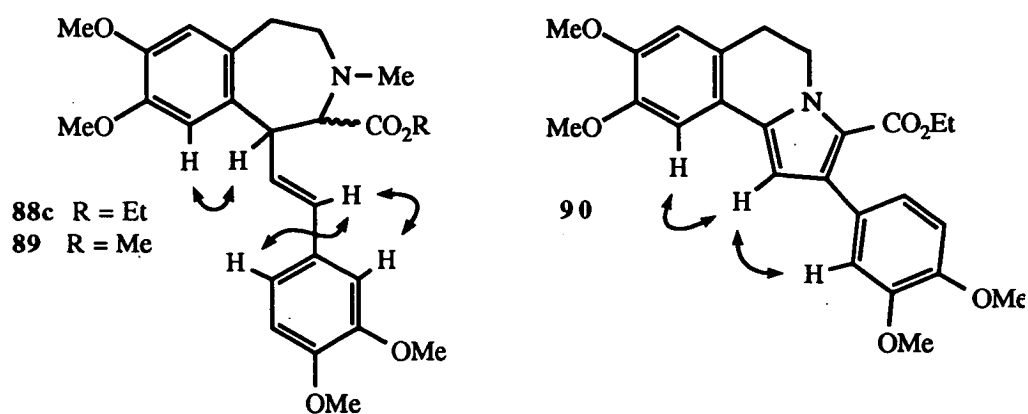
Figure 2.17 nOe Interactions Observed for 88c, 89, and 90

The diastereomers of 88c were identified by nuclear Overhauser difference experiments and the examination of hand-held models; the major isomer was assigned the *trans* B-ring stereochemistry. Both diastereomers exhibited a strong nOe between

H1 and H2' indicating a dihedral angle of 180° for H1-H1'. The *trans* diastereomer adopted a conformation with the vinylic group axial in which there was an nOe between H2 and H2', no nOe between H9 and H1', and a moderate H1-H2 coupling constant (5.8 Hz). The *cis* diastereomer adopted a conformation with the vinylic group equatorial in which there was no nOe between H2 and H2', an nOe between H9 and H1', and a low H1-H2 coupling constant (1 Hz) indicating a dihedral angle of 90°.

A byproduct from the treatment of **82c** with DBU at 25°C was isolated in low yield and identified as the 5,6-dihydropyrrolo[2,1-*a*]isoquinoline **90**. The resonances in the ^{1}H NMR spectrum for H1 (6.45 δ) and H5 (4.61 δ) were consistent with those observed in similar 2-phenyl- or 3-ethoxycarbonyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline derivatives.[99,100] Additional support for this structure was obtained by nuclear Overhauser experiments which located the lone olefinic proton between, and interacting with, an aromatic proton of the fused ring and the *ortho* protons of the pendant phenyl ring (Figure 2.17).

The formation of **90** may involve an intermediate iminium salt. The similar formation of an iminium salt by the butyl lithium-induced deprotonation with *N*-deoxygenation of a tetrahydroisoquinolinium-*N*-oxide was implicated in the synthesis of an oxazolidine derivative.[101] The deprotonation of the iminium salt would give a dipolar structure which may undergo ring closure and oxidation to **90** (Figure 2.18). The 1,3-dipolar cycloaddition of dipolarophiles with isoquinoline derivatives has often provided access to 5,6-dihydropyrrolo[2,1-*a*]isoquinoline derivatives,[102-104] but the intramolecular rearrangement apparently occurring in the formation of **90** does not appear to have been reported previously. This rearrangement could provide a new route to derivatives of the 5,6-dihydropyrrolo[2,1-*a*]isoquinoline system. The further development of this reaction was deemed outside the scope of this work.

82c

Ar = C₆H₄(OMe)₂
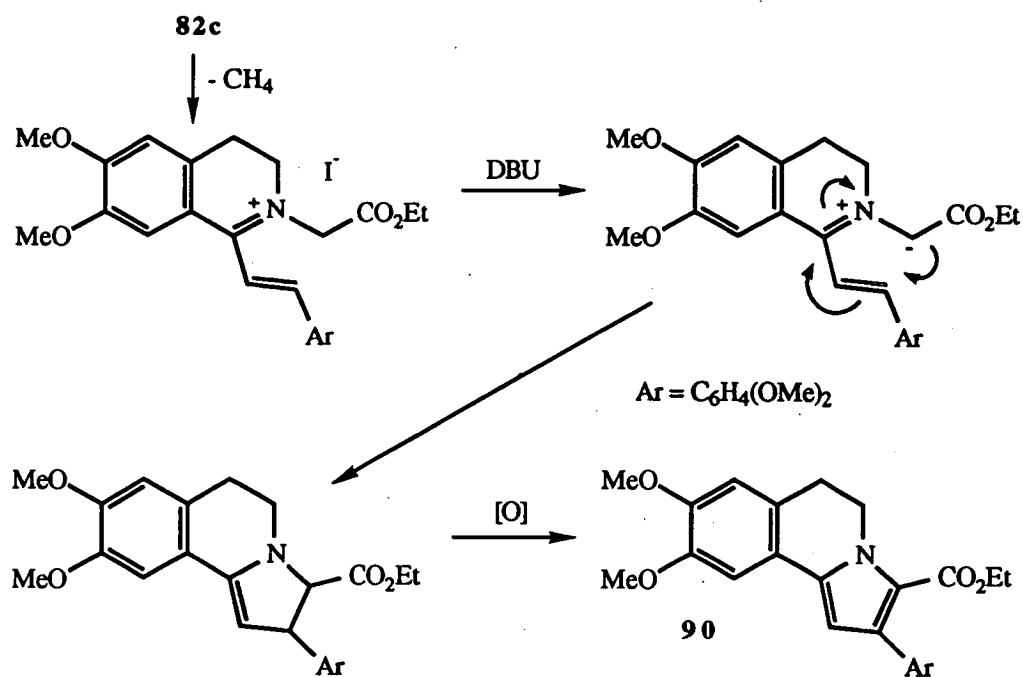
Figure 2.18 Proposed Mechanism for the Conversion of **82c** to **90**

2.6.3 Discussion of the Effect of the 2'-Substituent

As only the *cis*-1-propenylbenzazepine diastereomers were detected from the rearrangement of **82b** (*cis/trans*=3.2) it was assumed that the *trans*-1-propenyl salt underwent a selective [2,3] rearrangement. This assumption was consistent with the low levels of the benzazepines formed by the reaction of the predominantly *trans*-1-propenyl salt (*cis/trans*=0.11). The results indicated a relatively non-bulky alkyl substituent could be accommodated at C2' in the *trans* position without a detrimental effect on the [2,3] rearrangement. The decrease in the *E*-stereoselectivity (*E/Z*=2.92) of the [2,3] rearrangement from **82b2** was attributed to the minimisation of 1,3-substituent effects across the pseudo-cyclopentane transition state (refer Figure 2.4, pg. 24).

A substituent at C2' in the *cis* position clearly decreased the yields of the 3-benzazonines. Thus the preference for the [2,3] rearrangement over the [1,2] rearrangement was reduced to approximately 2:1 for both the *cis*-1-propenyl salt **82b1** and the 1-(2'-methylpropenyl) salt **82a** at low temperature. This behaviour

was assumed to reflect steric interference of the *cis*-2'-substituent with the concerted transition state.

Both compounds **82a** and **82b1** possessed a *cis* 2'-methyl group hindering the [2,3] rearrangement and exhibited similar behaviour at room temperature. At high temperature **82a** provided the Stevens rearrangement exclusively, while **82b1** afforded a 1.4:1 preference for the Stevens rearrangement. The additional 2'-methyl group in **82a** was assumed to promote the [1,2] rearrangement by increasing the stabilisation of the allylic radical through hyperconjugation.

The results for the *trans*-2'-dimethoxyphenyl salt **82c** confirmed that electron delocalising, radical stabilising, groups at C2' promoted the [1,2] rearrangement. Only the Stevens rearrangement products were observed from **82c**, reflecting the high electron delocalising nature of the dimethoxyphenyl group. This high electronic activation allowed the [1,2] rearrangement to occur at low temperature (-45°C). The complete lack of any [2,3] rearrangement products from **82c**, however, suggested that other factors may have contributed to the deactivation of the concerted rearrangement. Some steric hindrance of the concerted state may occur with the bulky aromatic group while electronic factors could include, for instance, a reduction in the molecular orbital coefficient of the π^* acceptor orbital (LUMO) at C2' due to the extension of the conjugating system. These factors would decrease the efficacy of the orbital overlap necessary for a concerted transition state. In addition, the conjugation of the vinyl and aromatic groups would hinder the migration of the double bond.

The *trans* stereoselectivity of the Stevens rearrangement of **82c** to **88c** (*trans/cis*=4.9) was rationalised by the consideration of the diradical transition states leading to each diastereomer (Figure 2.19); clearly steric interactions would be minimised in the pro-*trans* state. It was assumed that the *trans* diastereomers were the major products in the other Stevens rearrangements observed throughout this work.
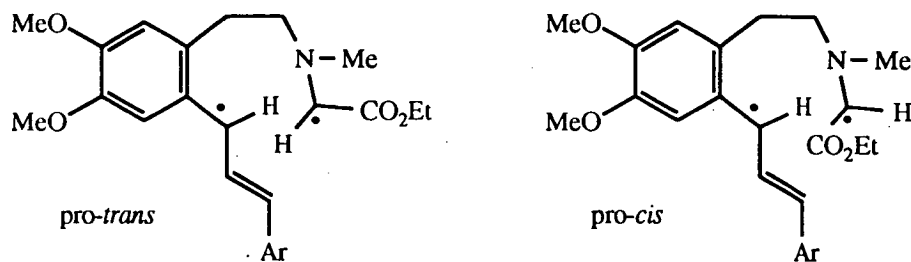
Figure 2.19 Diradical Transition States for the Stevens Rearrangement

2.7   Rearrangement of a 1-Ethynylisoquinoline
N-ylide Derivative

The rearrangement of α-ethynyl-N-ylides may be viewed as an extension of the behaviour of α-vinyl-N-ylides. The successful [2,3] rearrangements of the α-ethynylpiperidinium salt **15** and 1-ethynylisothiochroman sulfonium salt **19** were noted in Section 1.3.2. The ready availability of the 1-ethynyltetrahydroisoquinoline **71** prompted an investigation of the potential [2,3] rearrangement of an N-ylide based on this derivative.

The reaction of **71** with ethyl bromoacetate gave **91** as a crystalline mixture (*trans/cis*=3.5) of the B-ring diastereomers. Treatment of the salt mixture suspended in acetonitrile at 0°C with DBU afforded the rapid dissolution of the solid but no significant non-polar rearrangement products. When the reaction was repeated at reflux more non-polar material was obtained. At least five components were present in this fraction. The three major components were isolated by preparative HPLC and characterised by spectroscopic analysis. The two largest components were each isolated in 7% yield and identified as the 3-benzazepine **92** and the isoquinoline derivative **93**. Compound **93** may be formed by the deprotonation of **91** at C1 and a subsequent Stevens rearrangement. The third component, isolated in 3% yield, was assigned the isoquinoline structure **94**. This compound was an intense yellow colour, consistent with the extensive conjugation. A resonance at 3.11 δ for the N-methyl group in the ¹H NMR spectrum supported the enamine structure. The alternative 2,3-

dihydro-3-benzazonine structure **95** was considered less likely on the basis of calculations of the chemical shifts expected[105] for the olefinic protons. A large downfield shift observed for the central olefinic proton, at 7.97 δ, was reasonably consistent with the predicted value of 7.69 δ for H2' in **94** with the geometry shown. Chemical shifts of 6.73 or 6.26 δ were predicted for H6 in **95** with the E or Z C6-C7 geometry. Compound **94** may form by the deprotonation of **91** at C1 then a [1,4] shift of the ethoxycarbonylmethyl group by a diradical or symmetry allowed concerted process. The benzazonine **95** could arise from the [2,3] rearrangement followed by a [1,3] hydrogen shift of the initial strained allenic system.
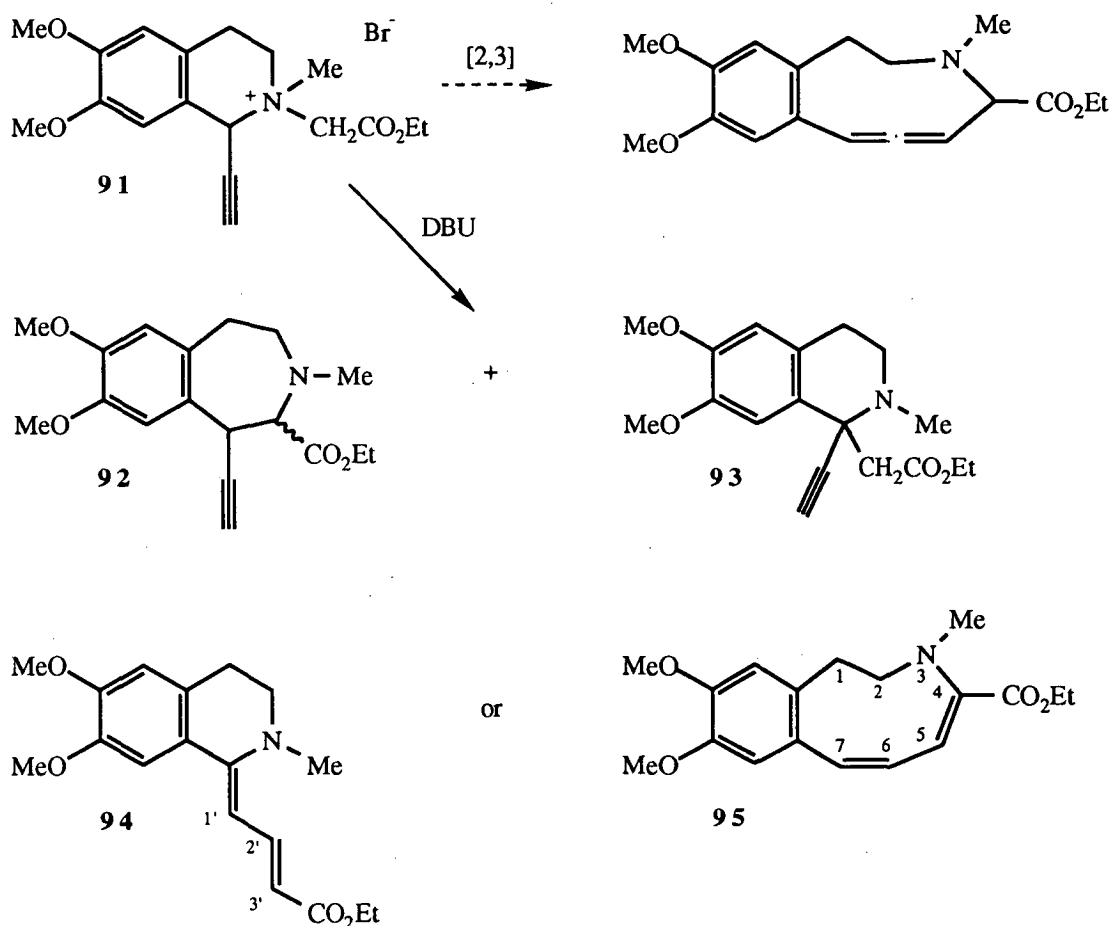
The low yield of the non-polar material from **91** suggested that deprotonation had occurred to provide the ethynyl anion. It was noted that in the rearrangements of both **15** and **19** 2'-substituents were present, which would negate this problem, although a previous report[106] by the same authors had indicated the successful [2,3]

rearrangement of a simple 2-ethynyltetrahydrothiophene-S-ylide. Several attempts were made to synthesize the 1'-propynyl amine **96** from **71**, but without success. The selective generation of the ethynyl anion and subsequent attack with iodomethane was not achieved without concurrent attack at either C1 or the nitrogen lone pair. Thus the reaction of **71** at -78°C in tetrahydrofuran with sodamide then iodomethane afforded only the recovery of a substantial amount of **71** and a crude salt, tentatively assigned as **97** by NMR analysis.
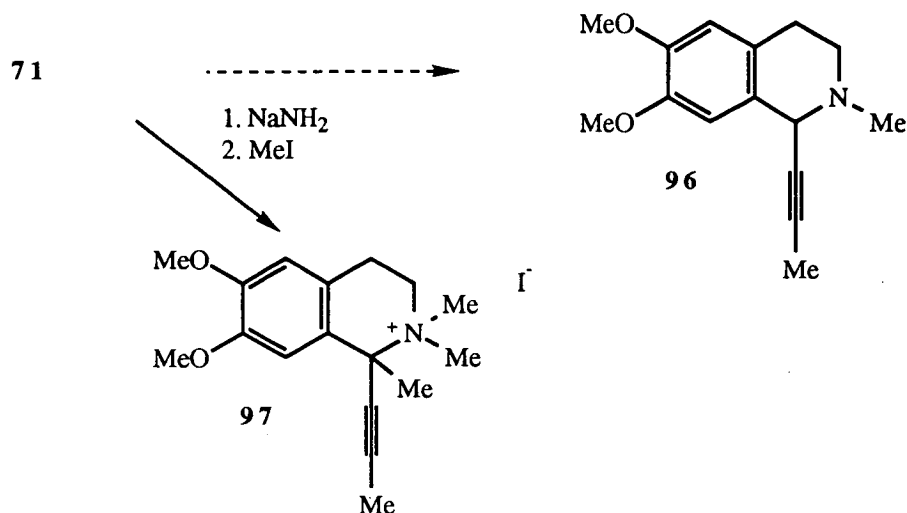
The results indicated that the [2,3] rearrangement of 1-ethynyl-tetrahydroisoquinoline-N-ylides would not provide an effective route to 2,3-dihydro-1H-3-benzazonine derivatives.

2.8　　Thermal [1,3] Ring Expansion of a 2'-Silyl Substituted Quaternary Salt

Treatment of the 1-(2'-trimethylsilylvinyl) amine **70c** in butanone with ethyl bromoacetate at elevated temperatures afforded an isomer of the expected salt **72c** in moderate yield. The compound was identified as the 3-benzazocinium salt **98** by spectroscopic and elemental analysis. The olefinic proton, H6, appeared as a singlet at 7.25 δ in the ^{1}H NMR spectrum. The Z-geometry of the olefin bond was

confirmed by an nuclear Overhauser effect between H6 and the trimethylsilyl group. Compound **98** may have formed by a [1,3] C-N bond shift in **72c**. The partial conversion of **72c** to **98** was achieved by refluxing the former in butanone for several hours.

The formation of **98** was avoided by the *N*-alkylation of **70c** with ethoxycarbonylmethyltriflate at 0°C. The reaction of **70c** with ethyl bromoacetate at 25°C gave a mixture (**98/72c**=1.5) of the isomeric salts.
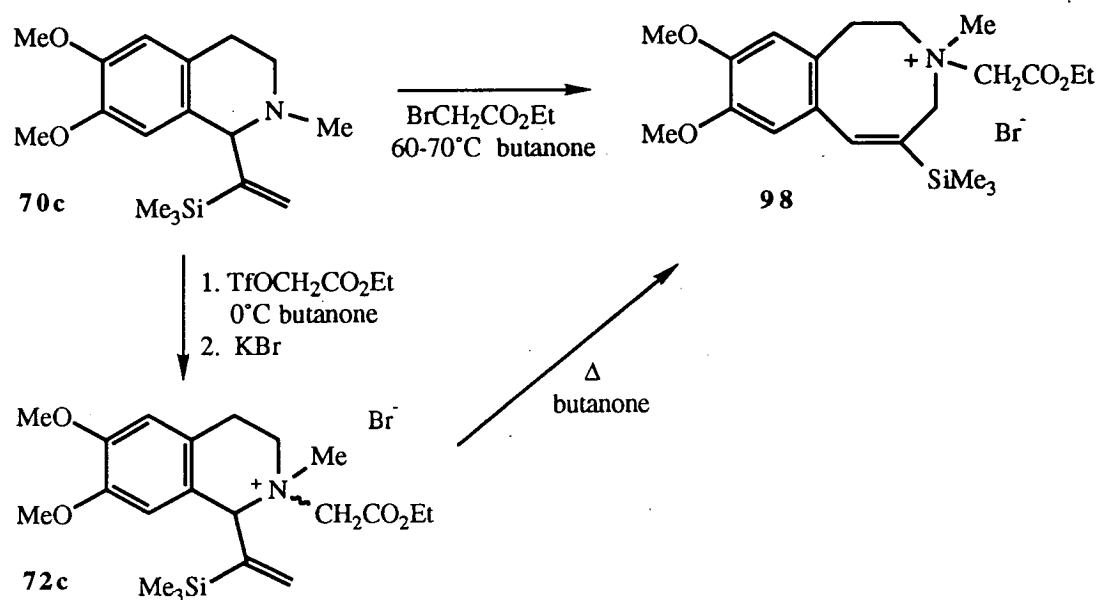
The [1,3] isomerisation of 1-aryl-1-vinyl-tetrahydroisoquinolines to 3-benzazocine derivatives was reported previously by Bersch *et. al.*[72,107] The isomerisation was achieved thermally, by heating the free bases neat at temperatures of 170-200°C, or during quaternisation of the amines with iodomethane in refluxing acetone. In the present work no isomerisation of **72c** was observed on thermolysis of the compound in a sealed, evacuated tube at 170-200°C. It was also noted that the *N*-alkylation of **49a** to **55a** in refluxing acetone with iodomethane proceeded without isomerisation (Section 2.4.1) while **49a** was unchanged by thermolysis at 180°C.

The conversion of **70c** to **98** represents the first rearrangement of this type without a 1-aryl substituent and with an alkylating agent other than iodomethane. The

further investigation of this rearrangement could lead to the development of an alternative route to functionalised 3-benzazocine derivatives.

2.9 Behaviour of the 2,3,4,5-Tetrahydro-1*H*-3-Benzazonine Derivatives

2.9.1 Attempted *N*-Alkylation with Iodomethane

Several attempts were made to synthesize the quaternary salt **99** for X-ray structural analysis and confirmation of the medium ring skeleton. The reaction of **52a** with excess iodomethane in refluxing butanone or neat at room temperature, however, afforded the ring opened salt **100**. The molecular formula of the cation was confirmed by mass spectrometry (LSIMS). All other spectra were consistent with the proposed structure. The formation of **100** indicated that **99** was formed initially but then underwent nucleophilic attack by the iodide ion at the electron deficient C4 position. Nucleophilic substitution followed by *N*-alkylation would provide **100** from **99**.
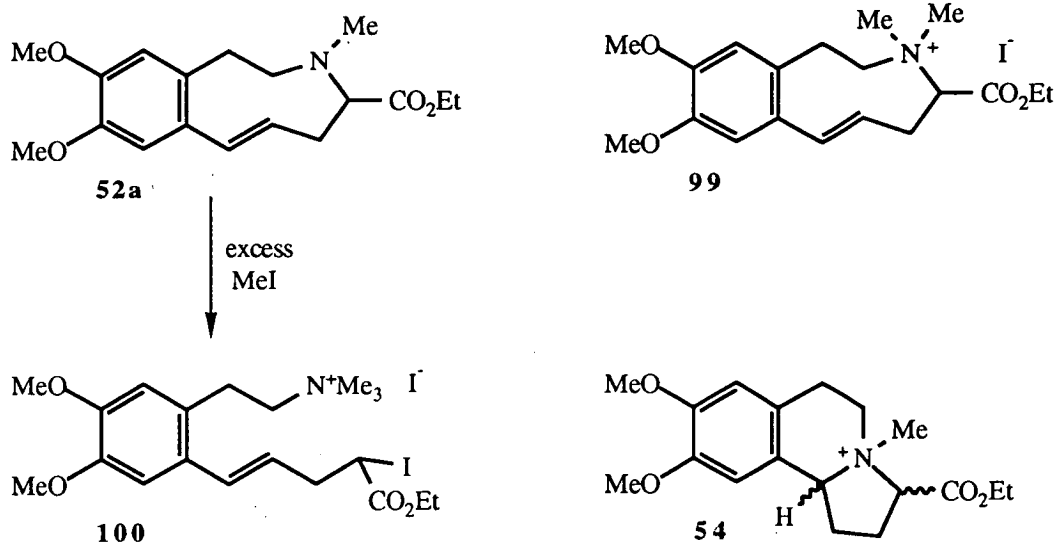
When **52a** was reacted with 1.2-1.5 equivalents of iodomethane in butanone at 25°C a crystalline solid was isolated in very low yield. The product was identified as **54** and neither **99** or **100** were detected. Compound **54** showed a single *N*-methyl

resonance at a quaternary position in the ^{1}H NMR spectrum with triplets for the H10b and H3 protons at 6.18 δ and 6.02 δ. The ^{13}C NMR spectrum showed five methylene carbons, none olefinic, and two downfield CH signals. The formation of **54** could occur with the generation of trace amounts of hydroiodic acid during the reaction (see also Section 2.3.3), as iodomethane freshly distilled from potassium carbonate and dry solvents did not prevent its formation.

The present results indicated that the *N*-alkylation of the 3-benzazonines was hindered and complicated by both the potential transannular degradation of the precursors and nucleophilic attack of the products at C4. It was envisaged that a successful *N*-alkylation might be achieved using an alkylating agent which provided a less nucleophilic anion, but this reaction was not investigated.

2.9.2   Hydrogenation to 2,3,4,5,6,7-Hexahydro-3-Benzazonines

As part of the structural confirmation work and to make further derivatives the hydrogenation of several tetrahydro-3-benzazonine derivatives was investigated. Hydrogenation of the tetrahydro-3-benzazonines (Table 2.9) over palladium on carbon, in ethanol at 1 atmosphere with heating, afforded the hexahydro-3-benzazonines **101a-c** by the selective reaction of the *E*-benzazonine isomers. The *Z*-isomers, and any 1-vinylic-3-benzazepine isomers present, were not effected and could be recovered.

Two diastereomers of **101b** were isolated. Compounds **101a**, the diastereomers of **101b**, and **101c** were characterised by spectroscopic analysis. One of the diastereomers of **101b** exhibited unusual chemical shifts in the ^{1}H NMR spectrum with the aromatic H8 proton (5.52 δ) and one methoxy group (3.34 δ) shifted substantially upfield. The results suggested the system adopted a conformation with the pendant phenyl ring positioned over, and shielding, the H8 and methoxy protons. Hand-held models confirmed this conformation was possible for **101b**.

52a, 75b, 87a → 101
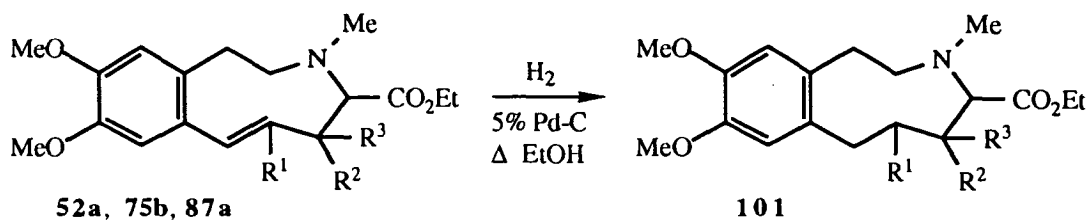
Table 2.9 Hydrogenations to hexahydro-3-benzazonines 101

Reactant	R^1	R^2	R^3	Product	Yield^c (%)
E-52a [a]	H	H	H	101a	66
E-75b [a]	Ph	H	H	101b	81
E-87a [b]	H	Me	Me	101c	58

[a] mixture with the Z isomer which did not react

[b] mixture with 88a which did not react

[c] calculated from the unrecovered E-isomer

The relief of ring strain appeared to be the important factor influencing the reactivity of the E-benzazonines compared to the Z-benzazonines in the hydrogenation. This proposition was supported by the hydrogenation of E-75a. This compound gave a mixture of the reduced compound 101d and the two alternative products of a [1,3] hydrogen shift, compounds 102 and 103. Both 102 and 103 exhibited the same stability as the Z-benzazonines once formed and were not hydrogenated. Apparently the removal of the E-olefinic bond from the medium ring afforded a large increase in the stability of the unsaturated derivatives.

The spectroscopic data of 102 and 103 were consistent with the proposed structures. Both exhibited AX patterns in the ^{1}H NMR spectra for the geminal protons at H7, with one proton at 4.20-4.15 δ and the other at 3.3-2.7 δ. The exocyclic 6-methylene group in 102 afforded resonances at 4.99 and 4.79 δ for the geminal protons and at 112.63 δ for the olefinic carbon. The related compound 38, with a 7-methylene group, was previously reported.[62] Compound 103 was assumed to be the Z-benzazonine but the geometry was not confirmed. Compound 101d was not isolated, but its presence was inferred from the NMR spectra of the mixture. The selective conversion of E-75a to either 101d or 102 was not achieved by lowering

the hydrogenation temperature. At -10°C no reaction occurred. At 25°C the reaction afforded a mixture (7.7:6.0:1.0) of **101d**, **102** and **103**. In an additional test the presence of hydrogen was found to be unnecessary and the selective isomerisation of *E*-**75a** to **102** was achieved in ethanol at reflux over the palladium catalyst.
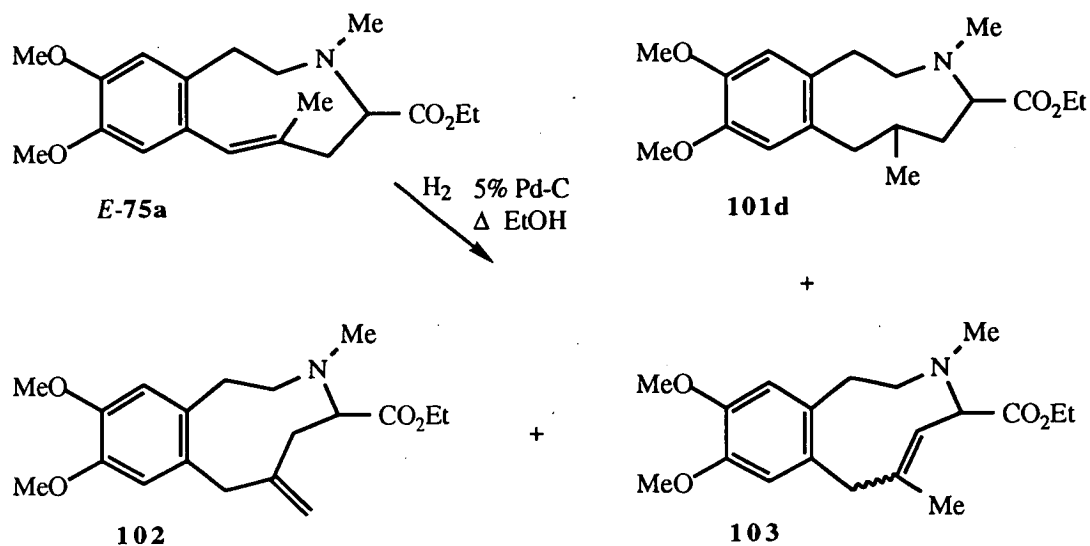
The equipment was not available for the investigation of the hydrogenation of the *Z*-benzazonines at elevated temperatures and pressures. The compounds were not affected by high hydrogen pressures (≤ 4 atm.) at room temperature with a palladium catalyst. The hydrogenation of these derivatives remains to be investigated with other catalysts and conditions.

2.9.3   Hydrogenation and Hydrogenolysis of an *N*-Benzyl Derivative

The hydrogenolysis of tertiary amines containing a benzyl group can provide a useful approach to secondary amines,[108] from which a range of other substituents may be introduced. Thus the hydrogenolysis of the *N*-benzyl-3-benzazonine *E*-**52b** was investigated. It was anticipated that the secondary 3-benzazonine **104b** would serve as a useful synthetic intermediate for the future production of a variety of *N*-substituted 3-benzazonines.

The reaction of **52b** with hydrogen in refluxing ethanol afforded **104b** in only moderate yields. Monitoring the reaction by GC-MS analysis confirmed that the

hydrogenation of **52b** to **104a** occurred rapidly then was followed by the slow hydrogenolysis of **104a** to **104b**, reaching 23% after 16 hours. Only traces of the product of the direct hydrogenolysis of **52b**, a secondary tetrahydro-3-benzazonine, were detected.
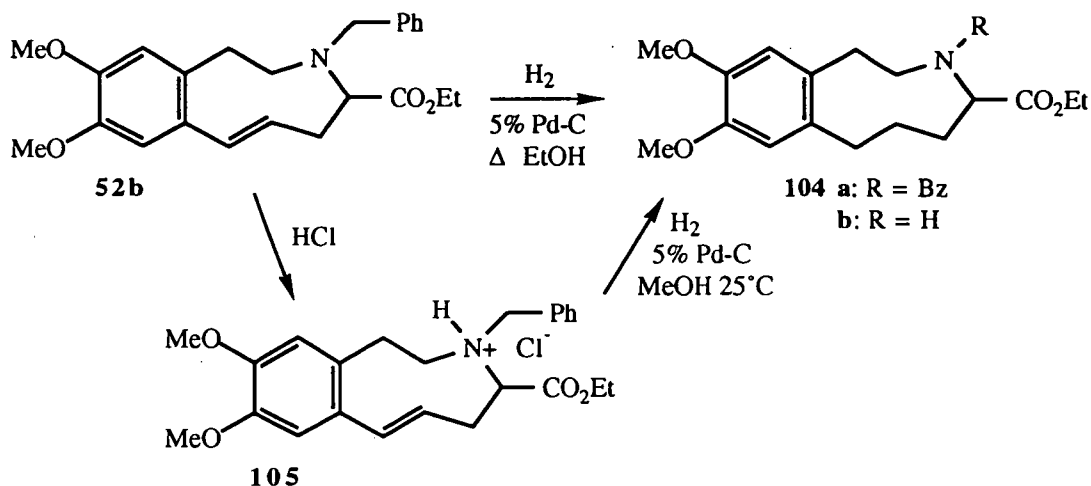
An improved pathway to **104b** was developed with the reaction of the hydrochloride salt **105** with hydrogen in methanol. The acidic system catalysed both the hydrogenation and hydrogenolysis reactions and enabled these steps to occur rapidly at low temperatures. At 0°C the hydrogenation was complete within 30 minutes and the hydrogenolysis within 2 hours. The secondary amine was obtained in good yield as a colourless oil which was characterised by spectroscopic analysis.

2.9.4 Thermolysis of Tetrahydro-3-Benzazonine Derivatives

Mass spectral analysis failed to differentiate between the 3-benzazonine and 3-benzazepine isomers, which afforded identical fragmentation patterns. In addition, when analysed by GC-MS the isomers typically afforded identical chromatographs, complete with other minor isomers apparently formed on injection or on-column; the technique was misleading and should not be used for the analysis of these mixtures. It was proposed that the 3-benzazonines were thermally labile and rearranged to the 3-benzazepines on MS analysis. This proposition was tested with the thermolysis of several 4-substituted-3-benzazonines (Table 2.10) in solution.

MeO. Me R → Δ MeO. N—Me R

52, 63   **53, 64**
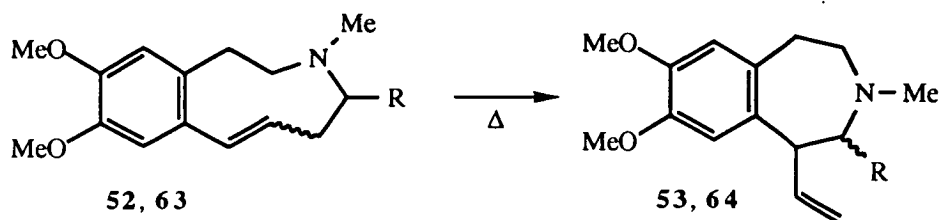
Table 2.10 Thermolysis of 3-Benzazonines

Reactant mixture[a]	R	Solvent[b]	Time (hrs)	Product mixture	Conversion of E-isomer
E-52a:Z-52a:53 87:9:4	CO₂Et	PrCN	11.5	E-52a:Z-52a:53 40:9:51	55%
E-63a:64a[c] 87:13	CN	PrCN	18	E-63a:64a:106 51:30:19	41%
E-63b	COPh	MeCN	1.25	64b	100%

[a] ratios from ^{1}H NMR integrations

[b] MeCN and PrCN refluxed at 82°C and 115°C respectively

[c] compound **64a** was not isolated

The results confirmed the E-benzazonines were thermally labile and rearranged to 3-benzazepine derivatives with prolonged heating. The Z-benzazonine Z-**52a**, however, was stable at elevated temperatures. The 4-benzoyl derivative **63b** rearranged rapidly in refluxing acetonitrile, while the 4-ethoxycarbonyl and 4-cyano derivatives **52a** and **63a** required extended times in refluxing butyronitrile.

Although the 1-vinyl-3-benzazepine **64a** was observed as an intermediate in the pyrolysis of E-**63a** the 2,3-dihydro-3-benzazepine **106** was obtained as the sole product after 66 hours. Compound **106** exhibited characteristic signals in the ^{1}H NMR spectrum for the N-methyl enamine function at 2.87 δ and 6.31 δ and for the propionitrile substituent at 3.79 δ and 1.50 δ. Compound **106** may form by the loss of the cyanide anion and a [1,3] hydrogen shift prior to its reuptake (Figure 2.20).
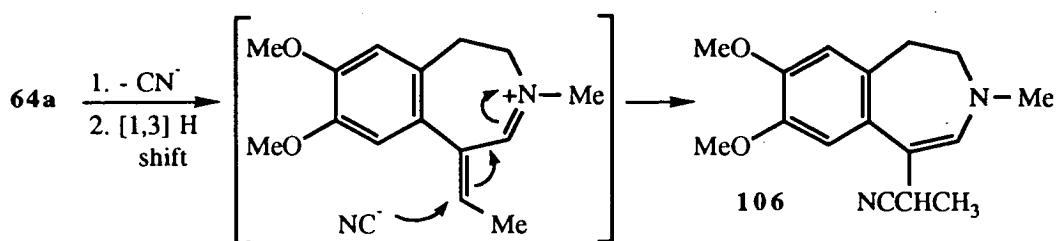
Figure 2.20 Mechanism for the formation of 106

The isomerisation of the E-3-benzazonines to 3-benzazepines confirmed the latter was the more thermodynamically stable system, or thermodynamic product, and that the interconversion between the two was possible by a [1,3] allylic shift. The observed order of reactivity, greatest with the benzoyl substituent and least with the nitrile, was consistent with the expected promotion of a C4-C5 homolytic cleavage by these substituents, and a radical pathway for this interconversion. The results suggest that the chemical manipulation of the 4-substituents to provide less radical-stabilising functions would afford E-benzazonines of greater stability.

2.9.5   Reduction of an Ester Derivative

The reduction of the ester function of **52a** was investigated in a single experiment. The treatment of **52a** with lithium aluminium hydride in ether afforded a crude solid which was examined by ^{1}H NMR analysis prior to purification. The material displayed conformational flexibility with two sets of broad peaks at 25°C in deuterated chloroform. At 60°C a single set of broad signals was obtained. The signals appeared consistent with the expected alcohol **107**, but the poor peak shapes were insufficient for the positive identification of this compound. The purification of this solid by p.t.l.c. on alumina with ethyl acetate/5% hexane surprisingly afforded the pyrrolidine derivatives **108** which were not present prior to the p.t.l.c. treatment. Compound **108b** was attributed to the esterification of **108a** with ethyl acetate, catalysed by the basic alumina. The formation of **108** can be rationalised by proposing the conversion of **107** to a pyrrolo[2,1-a]isoquinolinium salt which underwent Hofmann elimination under the basic conditions. The results suggested the

reduction of the ester function was achieved, but afforded further evidence for the proposed transannular degradation of the strained E-benzazonines.

52a → **107** → **108 a**: R = H, **b**: R = COMe
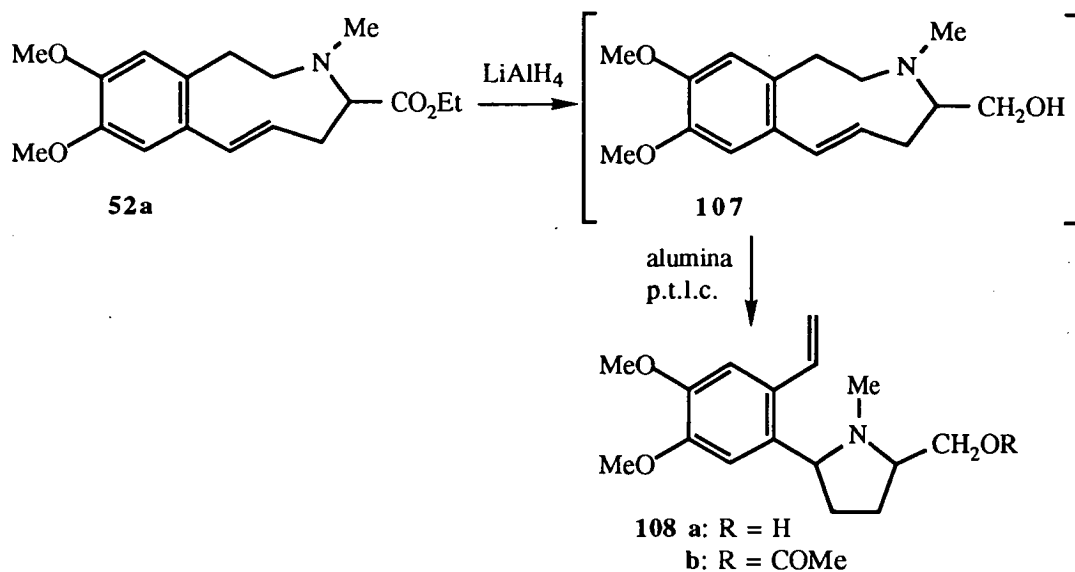
2.10   Conclusion

The present results demonstrated that the rearrangement of 1-vinylic-tetrahydroisoquinoline N-ylides could afford a good new route to functionalised 2,3,4,5-tetrahydro-1H-3-benzazonines. The N-ylides typically underwent the concerted [2,3] rearrangement preferentially at room temperature, the first application of this type of rearrangement to the synthesis of benz-fused aza-heterocycles, to give mixtures of the E and Z-benzazonine isomers in high yields.

The [2,3] rearrangement generally afforded the E-benzazonine isomers almost stereoselectivity. With bulky substituents at the 1'-position, however, the levels of the Z-benzazonine isomers were increased. The 1'-substituent acted by favouring the appropriate pro-Z concerted transition state geometry in the *cis* B-ring diastereomer of the precursor salt. The development of a method for the selective synthesis of the *cis*-salt may enable the stereoselective synthesis of Z-benzazonine derivatives. The control of the stereoselectivity of the rearrangement would be useful as the E or Z isomers may be expected to afford different types of pharmacological activity. The E-

benzazonine derivatives may be active at CNS receptors requiring the nitrogen and aromatic moieties in the same plane, while the Z-benzazonines may be active at receptors in which the nitrogen moiety is removed from the aromatic plane.

The [2,3] rearrangement of the isoquinoline N-ylides tolerated a variety of functional groups on both the ylide and 1'-vinyl positions. The Stevens rearrangement products became significant only when the rearrangements were conducted at high temperatures and were easily avoided. Each of the ester, nitrile, benzoyl and lactone ylide-stabilised derivatives, and the 1'-methyl, 1'-trimethylsilyl, and 1'-phenyl substituted derivatives, afforded the [2,3] rearrangement preferentially. The rearrangement of a methylene N-ylide confirmed that an ylide stabilising group was unnecessary for the selective [2,3] rearrangement. The presence of an ylide-stabilising group was, however, beneficial and afforded higher yields as the N-ylides were easily formed from the precursor salts with a mild base; a strong base promoted the Hofmann elimination of the salts. These results demonstrated that a wide variety of functional groups may be incorporated in the 3-benzazonine system, or others, by this rearrangement methodology.

The presence of 2'-substituents was generally detrimental to the [2,3] rearrangement. A simple methyl group could be accommodated in the trans-2'-position, however, radical stabilising groups in this position promoted the Stevens rearrangement; with the trans-2'-dimethoxyphenyl group the Stevens rearrangement was obtained selectively. A methyl substituent in the cis-2'-position interfered with the formation of the concerted transition state and reduced the selectivity of the rearrangement. These results suggested that only simple alkyl groups, at the trans-position, could be tolerated at C2' for the [2,3] rearrangement. The effects of these groups may, however, be less pronounced for systems without the activation of the Stevens rearrangement afforded by the fused ring of the isoquinoline system.

The E-2,3,4,5-tetrahydro-1H-3-benzazonine derivatives prepared in this work experienced substantial ring-strain and appeared to degrade to pyrrolo[1,2-a]isoquinoline derivatives under a variety of conditions. This degradation may limit

the further chemical manipulation of these derivatives. The hydrogenation of these derivatives could be achieved and these compounds may serve as useful intermediates in the synthesis of stable, substituted 2,3,4,5,6,7-hexahydro-3-benzazonines.

CHAPTER 3

REARRANGEMENTS OF 1-VINYLIC
TETRAHYDROISOQUINOLINE *N*-OXIDES

3.1 Introduction

The absence of literature investigating the synthesis of benz-fused *N*-heterocycles by the [2,3] sigmatropic rearrangement of allylic *N*-oxides was noted in Section 1.3.2. It was proposed to investigate the rearrangements of 1-vinylic isoquinoline *N*-oxides (Figure 3.1) and the synthesis of derivatives of the unknown 4,3-benzoxazonine system. Derivatives of this type were desired for evaluation of their pharmaceutical properties. It was anticipated this study would afford information relevant to the preparation of other fused oxaza-heterocycles by the same ring-expansion technique.
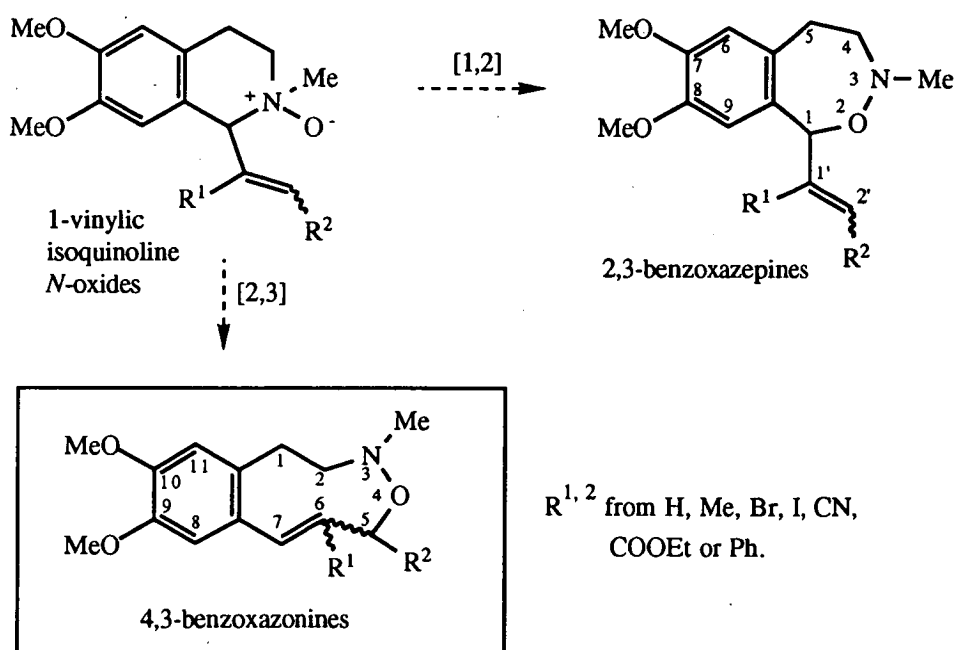
Figure 3.1

3.2 Review of Benzoxazonines

Of the twenty one possible benzoxazonine skeletons only five, the 1,4-, 2,3-, 2,5-, 2,6-, and 4,1-benzoxazonines, are known (prior to *Chem. Abs.* 119).

Ring destructive strategies provided access to three of the known skeletons. The 1,4-benzoxazonine **110** was prepared[109] in low yield by the oxidative removal of the thioether group of **109**, attack on the resultant carbocation by water, and rearrangement of the hydroxyamide intermediate. Oxidative cleavage of the pyrano[3,4-*b*]indole **111** with periodate ion gave the 4,1-benzoxazonine[110] **112** in high yield. The photosolvolysis and cyanogen bromide-induced solvolysis techniques used to produce 3-benzazonines were extended to the production of 2,5-benzoxazonine derivatives in good yields from oxazolo[2,3-*a*]-isoquinolines.[66,111,112]

109   R = Me, Et, *i*-Pr   110

111   H   112   H   O
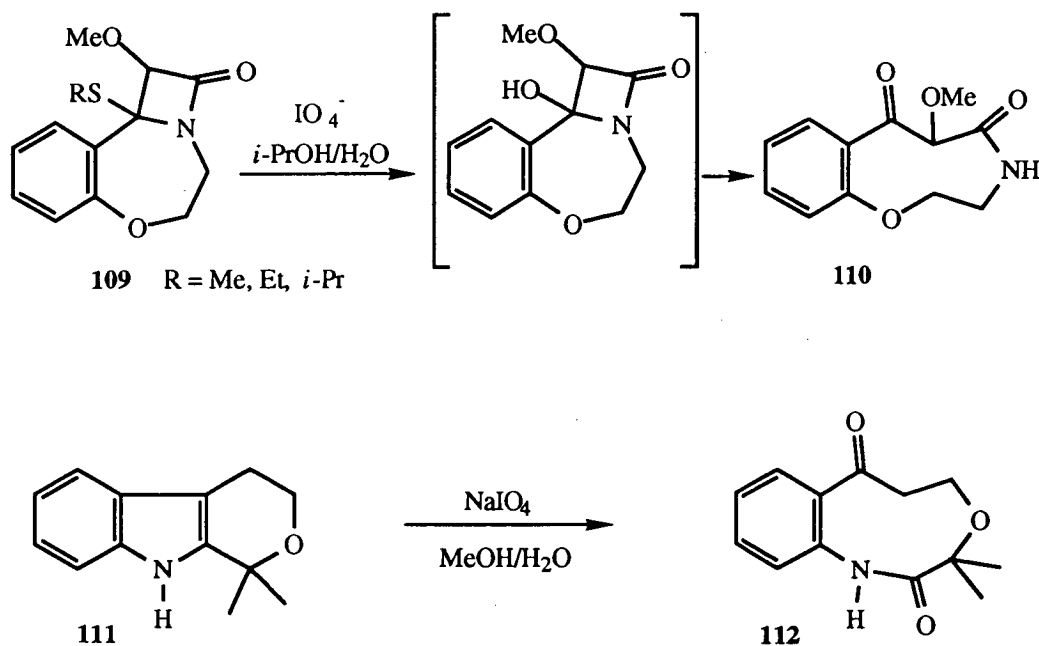
The 1,4- and 4,1- benzoxazonine systems were also accessed via ring construction strategies. Condensation of the phenolic propionaldehyde **113** with L-alanine gave the 1,4-benzoxazonine[113] **114**, while an intramolecular Michael

addition in the α,β-unsaturated ester **115** provided[114] the 4,1-benzoxazonine **116** in low yield.
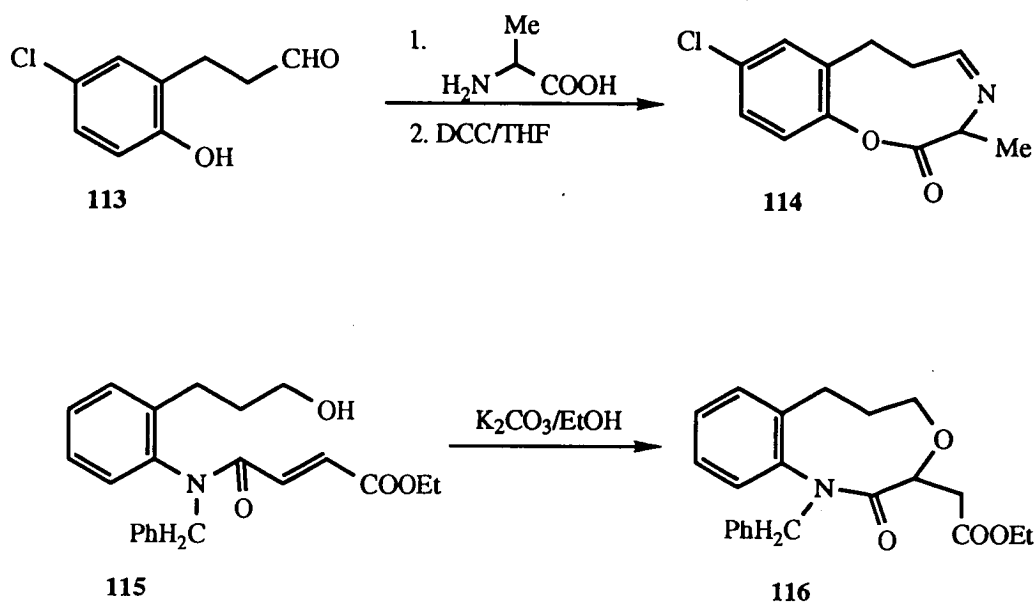
The 2,6-benzoxazonine system was first prepared[115] by a ring construction method involving the dehydration of the amino-alcohol **117** to the 2,6-benzoxazonine **118**. Compound **118** was reported to have activity as a diuretic, skeletal muscle relaxant, and CNS stimulant. The 2,6-benzoxazonine **120** was also prepared[116] by a cyanogen bromide-induced four atom ring expansion directly from the isoindole **119**.

121 R, R$_1$, R$_2$ = H, H, H
H, Me, H
OMe, H, Ph

122
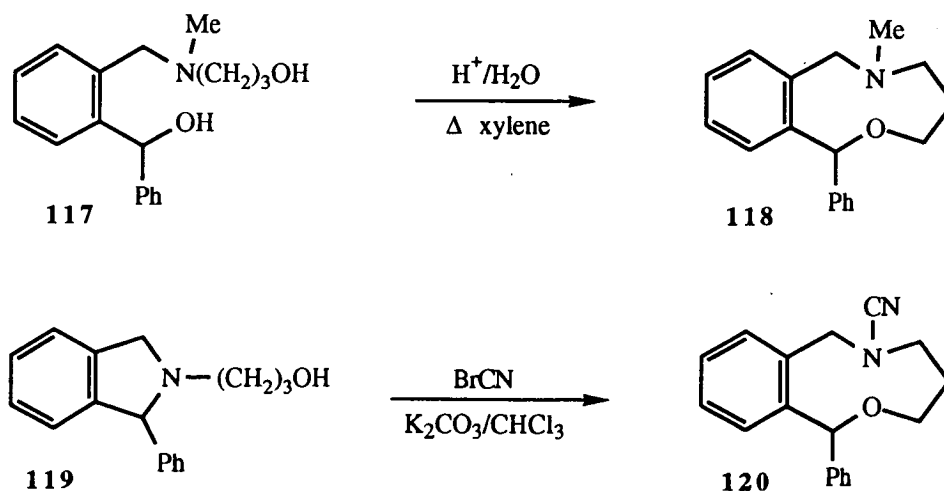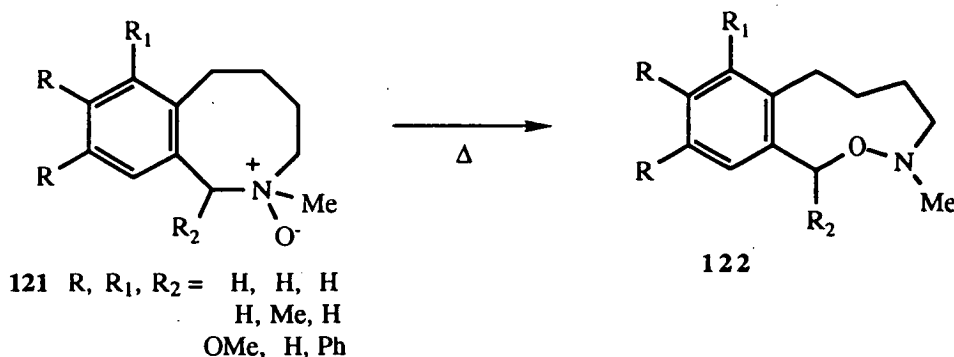
The synthetic applications of the Meisenheimer rearrangement were extended to the synthesis[27,117] of the 2,3-benzoxazonines **122** from the 2-benzazocine *N*-oxides **121** in low yields.

3.3   Rearrangement of Vinyl Unsubstituted and 2'-Substituted *N*-Oxides

The vinyl unsubstituted and 2'-substituted bases (Table 3.1) were converted to the corresponding *N*-oxides **123a-d** by *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane at room temperature. No competing epoxidation of the olefin was observed. Later experiments (see Section 5.3) failed to achieve epoxidation of this system even under forcing conditions. The *N*-oxides were mixtures of the *cis* and *trans B*-ring diastereomers and were used without further purification. The compounds possessed characteristic downfield NMR shifts of the atoms alpha to the electron-deficient quaternary nitrogen, with H1 and C1 at 4.6-5.1 δ and 74.7-84.8 δ respectively. The *cis* diastereomers were formed preferentially and identified by the more downfield positions[26] of H1 in the ^{1}H NMR.

Thermolysis of the *N*-oxides in refluxing acetonitrile afforded the 2,3-benzoxazepines **124a-d** in good yield (Table 3.1). No other rearrangement products, such as the [2,3] rearrangement products **125a-d**, were detected by NMR or HPLC analysis of the crude material.

	R¹	R²	R³
a:	H	H	Me
b:	H	H	Bz
c: 75% **c1**	H	Me	Me
25% **c2**	Me	H	Me
d:	C₆H₄(OMe)₂	H	Me
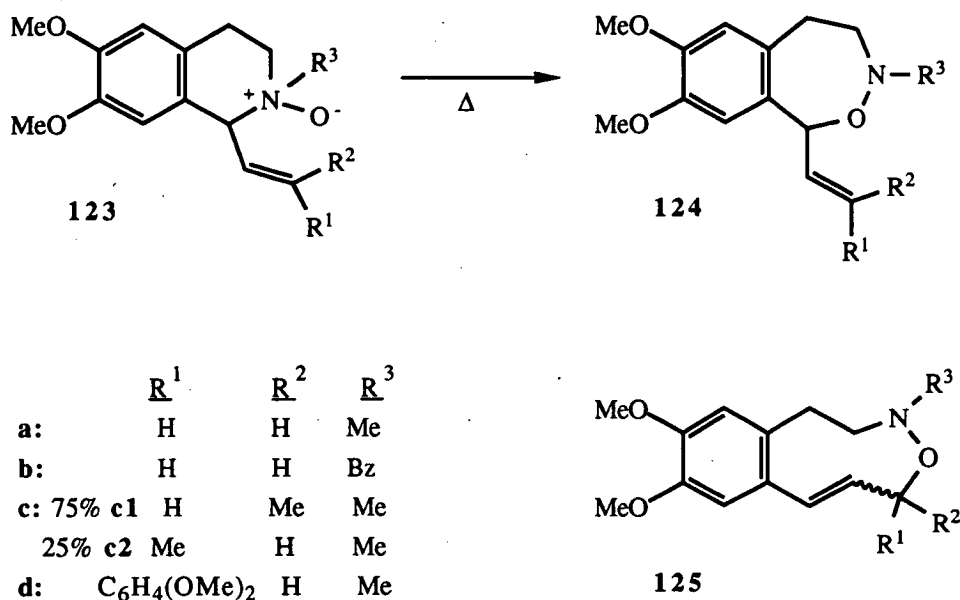
Table 3.1 Thermolyses of **123** in Acetonitrile[a].

Precursor Amine	N-Oxide (trans:cis)	Product	% Yield
49a	**123a** (35:65)	**124a**	73
49b	**123b** (19:81)	**124b**	71
81b[b]	**123c**[b] (31:69)	**124c**[b]	87[b]
81c	**123d** (32:68)	**124d**	58[c]

[a] conducted at reflux over 45-60 min.

[b] mixtures of the 1-propenyl isomers (Z:E=3:1)

[c] compound **123d** (22%) was recovered

The spectroscopic data of the 2,3-benzoxazepines was consistent with the proposed structures. The compounds exhibited NMR resonances characteristic of this system with H1 at 5.1-5.8 δ and C1 typically at 87.1-87.4 δ. The C1 resonance was shifted upfield to 81.6 δ in the Z-propenyl derivative **124c1**.

Further NMR experiments were conducted to confirm the compounds assigned as **124c1** and **124d** possessed the benzoxazepine rather than benzoxazonine structures; these isomers could provide similar spectra. An X-H correlation experiment on **124c1** placed the proton vicinal to the methyl group on an olefinic carbon, consistent with the proposed structure. The nOe interactions detected on

analysis of **124d** (Figure 3.2) were consistent only with the proposed structure. Compound **125d** would not exhibit the required nOe interaction between H5 and H8.
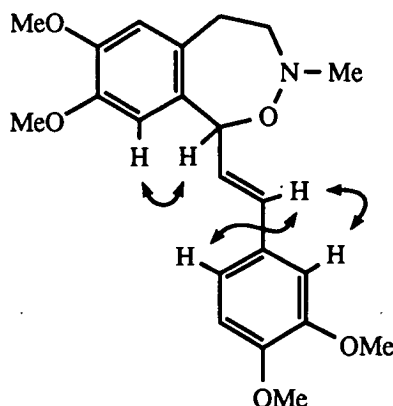
Figure 3.2 nOe Interactions observed for **124d**

Table 3.2 Other Treatments of the *N*-Oxides **123**

N-Oxide	Solvent	Temp. (°C)	Time	Product/s[a]	% Yield
123a	Mesitylene	162	25 min.	**124a**	15
"	PrCN	115	30 min.	**124a**	-
"	CHCl₃	55	7 days	**124a**	-
"	DCM	42	6 days	**123a:124a** (36:64)	-
"	MeCN	20	3.5 months	**123a:124a** (21:79)	-
123c[b]	DCM	42	5 days	**124c**[b]	54
"	-	microwave[c]	5 min.	**124c**[b]	70
123d	MeCN	photolysis[d]	30 min.	complex mixture	-

[a] from ^{1}H NMR integrals

[b] mixtures of the 1-propenyl isomers ($Z:E$=3:1)

[c] microwaved on an alumina support at medium power

[d] Hg arc lamp filtered to >225 nm at 5-10°C

A variety of other rearrangement conditions (Table 3.2) were investigated. In higher boiling solvents at reflux the rearrangement occurred rapidly but afforded no new products. Substantial degradation occurred in refluxing mesitylene. At low temperatures in either chloroform, dichloromethane or acetonitrile the Meisenheimer rearrangement occurred slowly. After several months at room temperature in

acetonitrile 79% conversion of **123a** to **124a** had occurred. No other products were observed. The photolysis of **123d** for 30 minutes gave a complex mixture of products, which were not isolated. In a single experiment, the microwave-induced rearrangement of **123c** on an alumina support was investigated. Microwave heating on silica or alumina supports[118-120] has previously altered the course or yields of various thermal reactions. The reaction afforded no change in selectivity but provided the 2,3-benzoxazepine rapidly and in good yield. These conditions may prove useful in future for specific applications of the Meisenheimer rearrangement. The dispersal of the compounds on alumina may minimise intermolecular reactions.

The exclusive [1,2] rearrangement of the 1-vinyl-N-oxides **123a,b**, compared to the [2,3] rearrangement of the analogous 1-vinyl-N-ylides **51a,b**, was consistent with the behaviour described[47,48] for the 2-vinylpiperidine derivatives (Section 1.3.2). The results reflected the greater stability of the N-oxides. The molecular orbital energy levels for the N-ylide **51a** and N-oxide **123a** (Table 3.3) were calculated[121] with MNDO and confirmed a substantially higher energy difference between the HOMO-LUMO orbitals in the N-oxide, due primarily to the greater stability of the donor HOMO orbital with the anionic charge on the electronegative oxygen atom. The increased energy difference would reduce the efficiency of any orbital overlap and inhibit the formation of a concerted [2,3] transition state from the N-oxides at low temperature.

Table 3.3 Calculated Orbital Energies (Hartree) for **51a** and **123a**

	X⁻ (HOMO)	π* (LUMO)	ΔE
N-ylide **51a**	-7.305	0.245	7.550
N-oxide **123a**	-8.889	0.625	9.543

3.4   Pyrolysis of the 1-Vinyl-2,3-Benzoxazepines to Isoxazolo[3,4-b]naphthalene Derivatives

The 1-vinylbenzoxazepines **124a,b** exhibited minor isomeric peaks on GC-MS analysis, which appeared to be artefacts of the thermal analytical technique. It was proposed originally that these isomers were the desired 4,3-benzoxazonines and the pyrolyses of the benzoxazepines were thus investigated.

Pyrolysis of the *N*-methylbenzoxazepine **124a** neat in an evacuated vessel at 180°C afforded no reaction. The compound could be purified by vacuum distillation at this temperature. Pyrolysis at 210°C afforded isomerisation of **124a** to a single product in moderate yield. Isomerisation of the *N*-benzylbenzoxazepine **124b** at the lower temperature of 180°C afforded two products (1.89:1.0) in low yield. The major isomerisation products were isolated in each case and identified as the isoxazolo[3,4-b]naphthalene derivatives **126a,b**. Only two previous examples of this ring system are known,[122,123] both with a 4,9-dione structure. The present synthesis provided the first 1,3,3a,4,9,9a-hexahydro derivatives of this rare system. The derivatives were proposed to form via homolysis of the carbon-oxygen bond then [1,5] hydrogen abstraction to afford a nitrone intermediate (Figure 3.3). The intramolecular 1,3-dipolar cycloaddition of the nitrone and olefin functions would afford the isoxazolo[3,4-b]naphthalenes.

a: R = Me
b: R = Bz

124   **126**
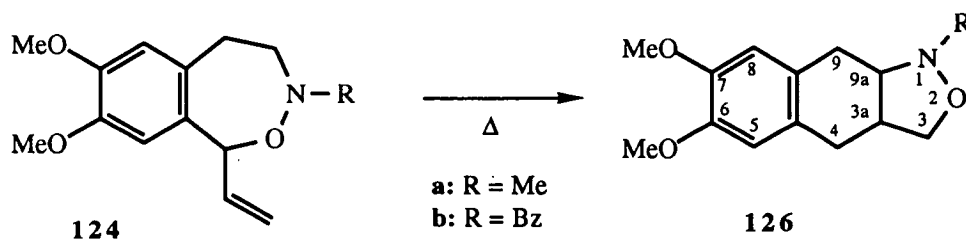
The isoxazolo[3,4-b]naphthalenes were characterised spectroscopically. The analysis of **126b** with heteronuclear, short-range homonuclear, and long-range

homonuclear NMR correlation experiments gave a conclusive identification of the structure and the complete assignment of the NMR spectra (Figure 3.4).

Figure 3.3

a: R = Me
b: R = Bz

[1,5] H shift

nitrone cycloaddition

124

126
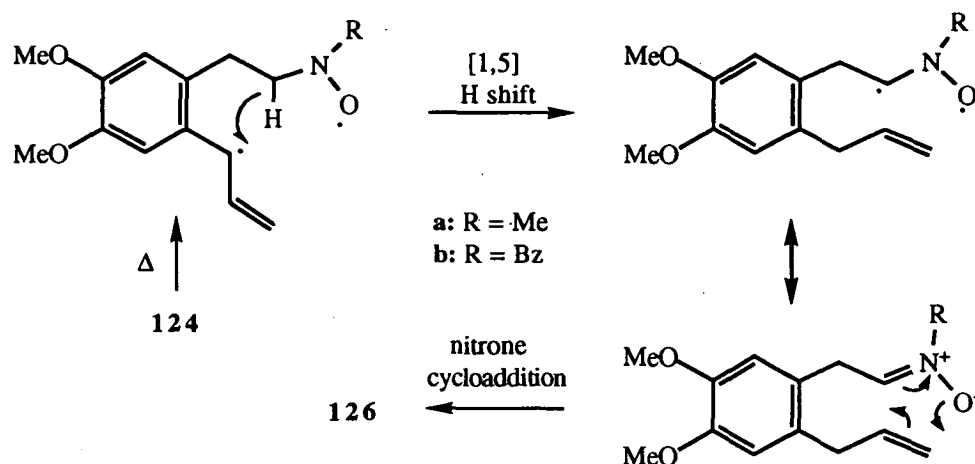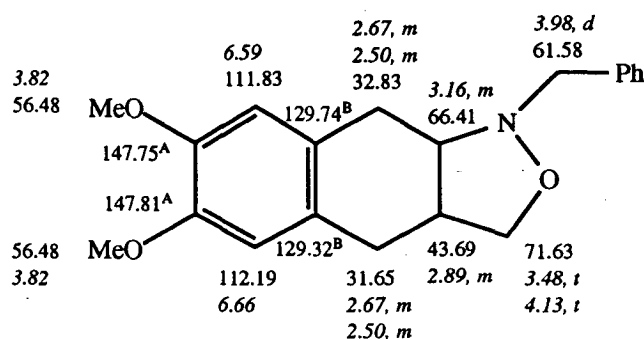
Figure 3.4 ^{13}C and ^{1}H (italics) NMR spectral assignments for **126b**

The second pyrolysis product from **124b**, a crystalline solid, was identified as the isoquinoline isomer **127**. This compound exhibited chemical shifts in the NMR spectra at 4.35 δ for H1 and 70.76 δ for C1, downfield of those for the precursor **49b** and upfield of those for **124b**. Compound **127** would arise by the reversion of the benzoxazepine to the precursor N-oxide, then a Meisenheimer rearrangement with the migration of the stabilised benzyl radical.

127
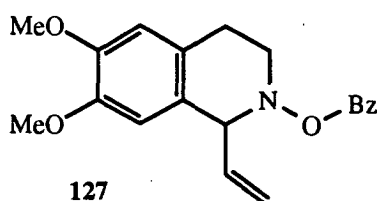
3.5   Rearrangement of 1'-Substituted *N*-Oxides

3.5.1 Synthesis and Thermolysis

Treatment of the 1'-substituted bases **70** with *m*-chloroperbenzoic acid at room temperature and workup in the usual manner afforded the *N*-oxides **128**. Substantial (≤ 25%) rearranged material was also isolated from **70a-c** (Table 3.4). Subsequent experiments confirmed the rearranged components were the 4,3-benzoxazonines **129a-c**. Only the *Z* isomers of the benzoxazonines were observed. The formation of the benzoxazonines was minimised by cooling the solutions during the workup of the *N*-oxides, however, the formation of **129b** in particular could not be eliminated. The benzoxazonines were formed by the selective rearrangement of the *cis-N*-oxides at low temperature; these were present in significant levels only when the solutions were cooled during the workup. The stereoselectivity of the *N*-oxidation was altered by the bulky 1'-substituents, with the *trans* diastereomers favoured in their presence and *cis* diastereomers in their absence.

a: R = Me
b: R = Ph
c: R = SiMe₃
d: R = I
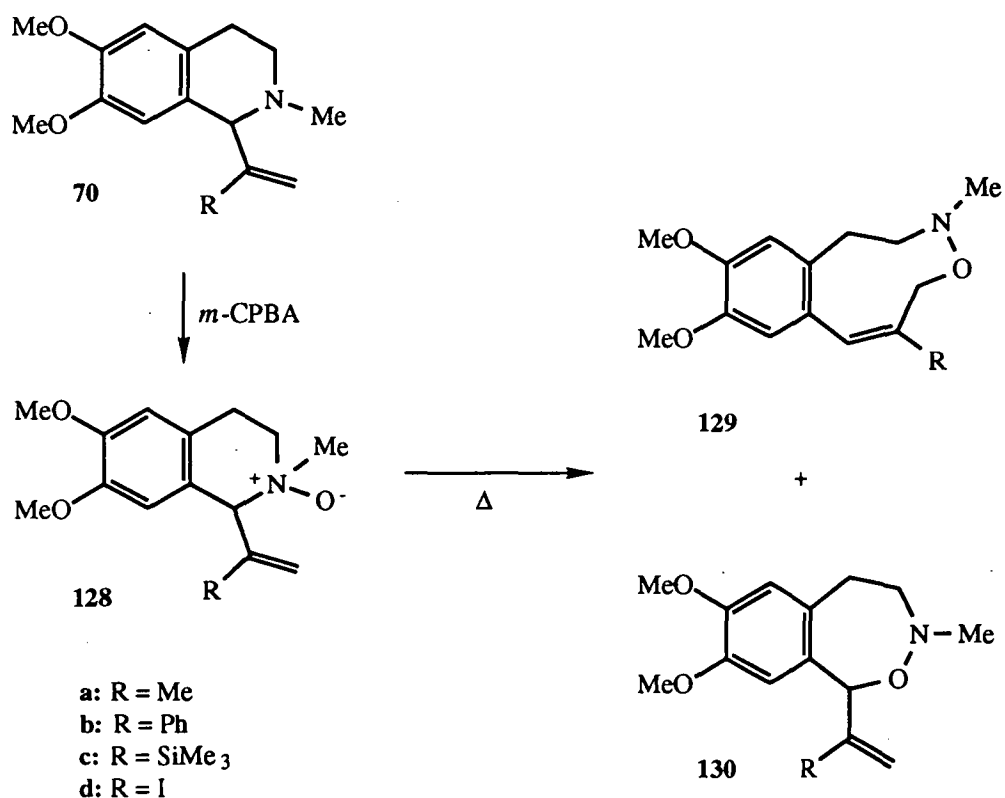
<u>Table 3.4</u> Products from Treatment of **70a-d** with *m*-CPBA

Input	Workup[a]	*N*-Oxides **128**		Non-polar Fraction	
		cis:trans[b]	% Yield	Components[b]	% Yield
70a	normal	17:83	29	**129a**	25
"	cooled	50:50	64	-	-
70b	normal	0:100	53	**129b:130b** (44:56)	24
"	cooled	0:100	47	**129b:130b** (78:22)	14
70c	cooled	34:66	61	**70c:129c** (74:26)	26
70d	normal	0:100	82	-	-

[a] details given in Section 6.6

[b] from ^{1}H NMR integrals

<u>Table 3.5</u> Thermolyses of the *N*-Oxides **128a-d**

N-Oxide (*cis:trans*)[a]	Conditions		Product Mixture[a] (%)				% Yield 129+130+70
	Solvent[b]	Time	*trans*-**128**	129	130	70	
128a (50:50)	MeCN	1 h.	-	58	42	-	-
" "	CHCl₃	7.5 h.	39	53	8	-	-
" "	DCM	34 h.	53	46	1	-	41
" (0:100)	MeCN	1 h.	-	34	66	-	-
" "	DCM	6 days	85	5	10	-	-
128b (0:100)	MeCN	1 h.	-	23	77	-	-
" "	DCM	24 h.	26	13	61	-	69
" "	DCM*	15 days	88	-	12	-	-
128c (34:66)	DCM	36 h.	-	62	38	-	81
128d (0:100)	MeCN	1 h.	-	11	30	59	27[c]
" "	DCM	24 h.	-	8	-	92	28[c]

[a] from ^{1}H NMR integrals

[b] solvents at reflux, except * at 20°C

[c] the majority was degraded low R_f material

The thermal rearrangements of the isolated *N*-oxides were examined (Table 3.5). The 1'-methyl, 1'-phenyl and 1'-trimethylsilyl-*N*-oxides **128a-c** afforded mixtures of the Meisenheimer and [2,3] rearrangement products, with a high combined yield based on the unrecovered *N*-oxides. The 1'-iodoethenyl-*N*-oxide

128d provided mainly dark degraded material and substantial N-deoxygenation to the precursor amine **70d**; the rearrangement products were obtained in low yield.

The course of the rearrangement was dependant on the stereochemistry of the precursor N-oxide and the thermolysis temperature. Rearrangement of the cis N-oxide **128a** occurred stereoselectively to give the 4,3-benzoxazonine **129a** in refluxing dichloromethane. Under these mild conditions, with moderate reaction times, the trans-N-oxide was unaffected. The benzoxazonine was separated from the unreacted trans-N-oxide and isolated in high yield. The cis-N-oxides **128b** and **128c** were assumed to undergo a similar stereoselective rearrangement at low temperatures. The formation and low temperature rearrangement of cis-**128b** during the N-oxidation would account for the observed level of **129b**. This assumption could not be confirmed. In refluxing acetonitrile the selectivity of the rearrangement of the cis-N-oxide **128a** was decreased (Table 3.6).

Table 3.6 Selectivity (**130/129**) of the N-Oxide Rearrangements

N-Oxide	DCM (42°C)	MeCN (82°C)
cis-**128a**	0.02	0.22
trans-**128a**	2.00	1.94
trans-**128b**	4.69	3.35
trans-**128c**	1.36[a]	-
trans-**128d**	1.00	2.33

[a] calculated assuming selective conversion of cis-**128c** to **129**

The trans-N-oxides rearranged preferentially to the 2,3-benzoxazepines **130a-d** at both low and high temperatures. No consistent change in selectivity with temperature was observed. The 1'-substituent on the N-oxides **129a-d** had a large effect on the stereoselectivity of the rearrangement (Table 3.6). The phenyl substituent afforded the greatest proportion of the Meisenheimer rearrangement, consistent with its electron delocalising nature, while the trimethylsilyl substituent provided the least. The temperature at which the rearrangement of the trans-N-oxides occurred was also effected by the 1'-substituent and could be placed in the

order phenyl<trimethylsilyl<methyl. The 1'-phenyl and 1'-trimethylsilyl compounds both gave >80% conversion in refluxing dichloromethane after 36 hours, while the 1'-methyl derivative had not rearranged significantly after 6 days. The 1'-phenyl derivative underwent a slow Meisenheimer rearrangement at room temperature.

3.5.2 Isolation and Characterisation of the 4,3-Benzoxazonines

Preparative reverse-phase HPLC with acetonitrile/water mixtures enabled the isolation of the 4,3-benzoxazonine derivatives **129b,d** and the isomeric benzoxazepines **130b,d** from the crude rearrangement mixtures. The benzoxazepines eluted more rapidly and baseline resolution was achieved. In contrast, the isomeric forms of **129a,c** and **130a,c** were not separated by HPLC analysis. Compound **129a** was, however, easily isolated following the selective rearrangement of *cis*-**128a**. Compound **129c** recrystallised preferentially from a mixture with **130c** in methanol. Successive recrystallisations afforded pure material. The benzoxazepine **130c** could not be isolated independently.

Compounds **129a,d** were respectively colourless and yellow oils, while **129b,c** were colourless crystalline solids. Unequivocal evidence for the structure of the 4,3-benzoxazonines was obtained by the X-ray crystallographic analysis[124] of **129b** (Figure 3.5).

Variable-temperature experiments were necessary to provide the confirmation of the benzoxazonine structures by NMR analysis. At 25°C in deuterated chloroform the 4,3-benzoxazonines exhibited two broad singlets for the ring protons; at 4.1-4.5 δ for H5 and at 2.8-2.9 δ for H1 with H2 (Figure 3.6). The latter peak typically integrated as only 2-3 protons. The olefinic H7 proton absorbed between 7.44 δ, for **129d**, and 6.46 δ for **129a**. The measurement of an nOe interaction between H7 and the 6-methyl group of **129a** supported the Z-olefin geometry. Improved ^{1}H NMR integrations and ^{13}C NMR spectra (Table 3.7) were obtained at 50°C. At -30°C the broad NMR peaks of **129a** resolved to two distinct forms of equal population (Figures 3.6 and 3.7). The two populations were proposed to

reflect the presence of two conformers related by the inversion, or "flipping", of the N3-O4-C5 segment of the structure (see Section 3.7). The displacement of the oxygen atom relative to the *N*-methyl and 6-methyl groups would explain the large differences in the chemical shifts observed for these groups in the conformers of **129a**.

Figure 3.5 The X-Ray crystallographic structure of **129b**

Table 3.7 Characteristic ^{13}C NMR Resonances for the 4,3-Benzoxazonines[a]

	129a	129b	129c	134
C1	33.24	32.91	33.44	33.15
*N*Me	47.41	47.94	47.29	47.35
C2	62.81	63.00	62.87	62.62
C5	74.77	74.55	71.42	69.37
C6	131.10	142.39	145.11	122.71
C7	127.93	131.32	141.83	144.06
6-Me	24.36	-	-	-
6-SiMe$_3$	-	-	-1.17	-

[a] ppm at 25°C in CDCl$_3$

Figure 3.6 ^{1}H NMR spectra for **129a** in CDCl$_3$ at -30°C and 25°C
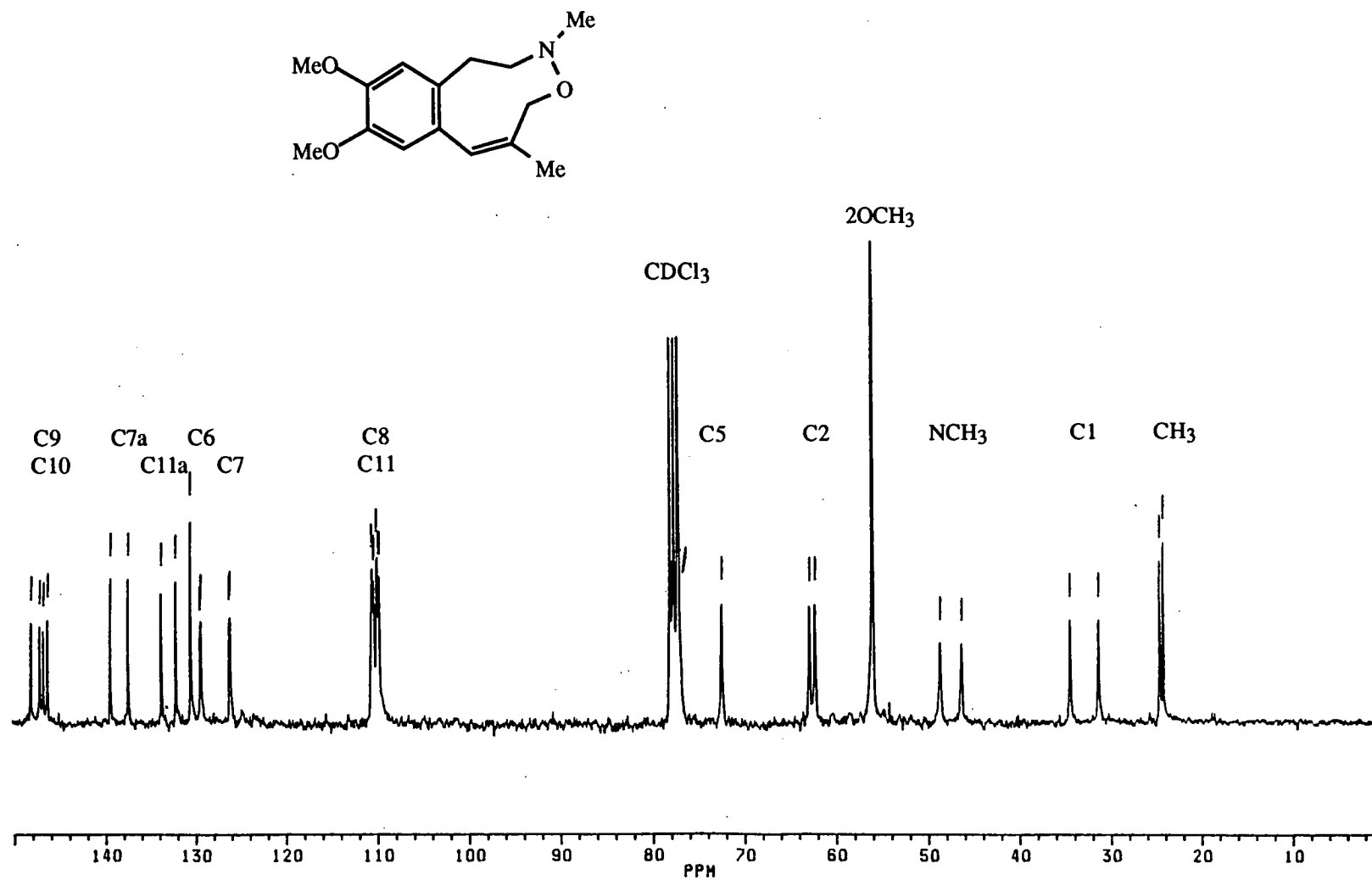
Figure 3.7 ^{13}C NMR spectrum for **129a** in CDCl$_3$ at -30°C with two conformers

The mass spectra of the 4,3-benzoxazonines displayed significant ions at M-59 and M-74. These fragments were consistent with the formation of a highly conjugated radical cation (Figure 3.8). The base peak was either at m/z 206 or 204.
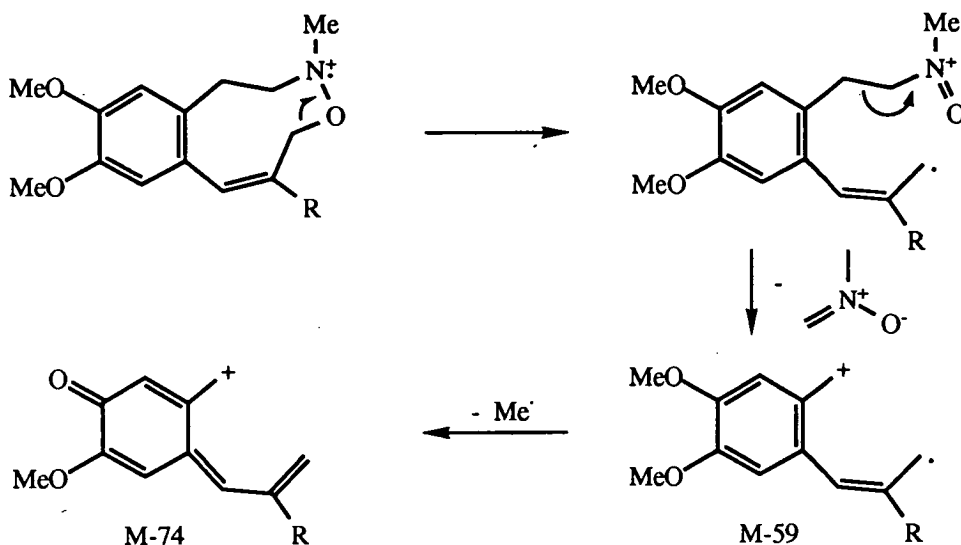
Figure 3.8 Proposed mass spectral fragmentation of the benzoxazonines

3.5.3 Thermal Behaviour of 4,3-Benzoxazonine Derivatives

The isomers **129b** and **130b** exhibited almost identical mass-spectral fragmentation patterns. This behaviour was rationalised by proposing either an initial cleavage of the O-C bond, in each case to a common delocalised radical cation, or thermal equilibration of the isomers during volatilisation. The thermolyses of the 6-methyl and 6-phenyl benzoxazonines **129a,b** were thus investigated.

In refluxing acetonitrile the benzoxazonines **129a,b** isomerised slowly by a [1,3] shift to the benzoxazepines **130a,b** (Table 3.8). The isomerisation rate was increased in refluxing xylene, affording mixtures of the 9- and 7-membered ring derivatives which were unchanged by longer reaction times. The isomerisation of **130b** to an identical mixture of **129b** and **130b** confirmed an equilibrium was established between the benzoxazonines and benzoxazepines at high temperatures. The equilibrium favoured the benzoxazepines and was consistent with the expected thermodynamic preference for the less strained 7-membered ring. A higher level of

the 6-phenylbenzoxazonine derivative at equilibrium reflected the additional conjugation in this derivative.

129   ⇌   130

Δ
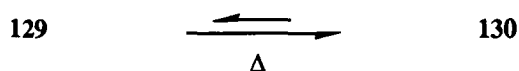
Table 3.8 Thermal Interconversion of 129 and 130

Precursor	Solvent[a]	Time (h.)	Product ratio[b] 129:130
129a	MeCN	1	93:7
"	Xylene	"	5:95
129b	MeCN	1	89:11
"	"	4	54:46
"	Xylene	1	24:76
130b	"	1	22:78

[a] solvents at reflux; MeCN (82°C), Xylene (137-142°C)

[b] from ^{1}H NMR integrals.

Literature precedents exist for the thermal [1,3] isomerisation of 2-butenylhydroxylamine derivatives to 2-propenylhydroxylamine derivatives in both acyclic[125] and cyclic[51] systems. A radical pair mechanism was proposed[125] due to the observed extent (20%) of racemisation.

3.5.4 Discussion

Modelling studies (Section 2.3.2) predicted that only the cis-N-oxides would undergo a concerted rearrangement to the Z-benzoxazonines. Consequently, the promotion of the concerted rearrangement by the 1'-substituents was linked to the factors able to effect the rearrangement of the cis-N-oxides to the stable Z-4,3-benzoxazonines. The 1'-substituents were proposed to act by lowering the conformational energy of conformer VII below that of conformer V (Figure 2.3, pg. 24). With conformer VII as the global minimum, the activation energy required to achieve the pro-Z concerted state (Figure 3.9) would be lowered, and the [2,3]

rearrangement would be promoted. This behaviour was supported by the observed increase in the proportion of Z-benzazonine isomers formed with the rearrangement of the 1'-substituted salts **72a-c**.
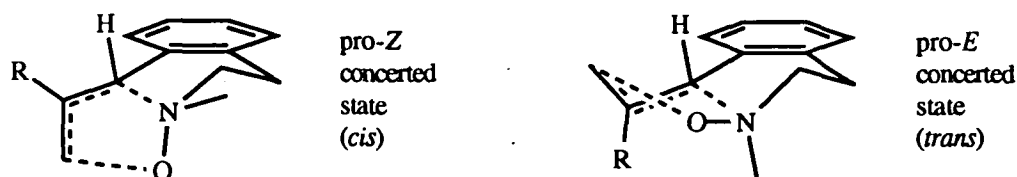
Figure 3.9 Proposed concerted transition states for **128a-d**

The failure of the 1'-substituted N-oxides to afford any traces of the E-4,3-benzoxazonine isomers, while the Z-benzoxazonines were obtained, clearly indicated that either (i) a concerted pro-E transition state (Figure 3.9) could not be achieved, or (ii) the E-benzoxazonines were not thermodynamically favoured. The latter appeared likely given the strained nature of the similar E-benzazonine derivatives isolated in this work. Considerable ring strain in the E-benzoxazonine system would prevent the rearrangement of the comparatively stable N-oxides at low temperatures and explain the total lack of [2,3] rearrangement from the 1-vinyl and 2'-substituted N-oxides **123a-d**, for which the E-benzoxazonine derivatives were the expected major products. It should be noted that in the only previous examples of the [2,3] rearrangement with ring expansion, Z double bond derivatives were formed (Section 1.3.2, pg. 10).

The [1,3] isomerisation of the benzoxazonines afforded the possibility that the benzoxazepines **130a-d** (Table 3.5) were formed by a [2,3] rearrangement then [1,3] shift, rather than a direct Meisenheimer rearrangement. The slow rate of the [1,3] shift from **129a,b** ruled out this mechanism for these derivatives. It was noted, however, that the isomerisation[125] of the 2-butenyl-1-phenylhydroxylamine (Figure 3.10) to the more conjugated product occurred under mild conditions. Thus the isolation of the 5-(dimethoxyphenyl)benzoxazonine **125d** (pg. 86), and any other 5-arylbenzoxazonines, would be unlikely from the present thermal rearrangements.
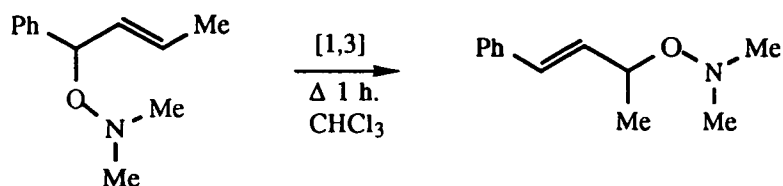
Figure 3.10

Substantial quantities of the Z-benzoxazonines **129a-d** were formed on rearrangement of the *trans-N*-oxides **128a-d** (Table 3.6), however, it was predicted (Section 2.3.2) that only a pro-*E* concerted state could be formed from the *trans-N*-oxides. Reexamination of the molecular models suggested that, with the rapid formation of the *E*-benzoxazonines blocked, a pro-*Z* concerted state might be plausible with the rotation of the olefin group in conformer **IV** (Figure 2.3, pg. 24) toward the fused ring. The distance between the O⁻ and C2' centres in this geometry, however, would be on the borderline for a successful concerted interaction. An alternative pathway to the Z-benzoxazonines from the *trans-N*-oxides was proposed by assuming the *E*-benzoxazonine derivatives formed briefly but reverted, by a radical process, to mixtures of the *cis-N*-oxides, *trans-N*-oxides and the 2,3-benzoxazepines. The *cis-N*-oxide would then undergo a rapid concerted rearrangement to the Z-benzoxazonine. No evidence could be obtained for this proposition.

3.6 Synthesis and Rearrangement of a 1-Aryl *N*-Oxide

The availability, from another project, of the imine precursor of the 1-fluorophenyl imine salt **131**, prompted the investigation of the synthesis and rearrangement of a 1-aryl-1-vinyl-*N*-oxide. The reaction of **131** with vinylmagnesium bromide afforded the tetrahydroisoquinoline base **132** in excellent yield despite the steric crowding at the C1 centre.

The *N*-oxidation of **132** with *m*-CPBA in dichloromethane at 20°C afforded substantial rearrangement (≤70%) directly without isolation of the *N*-oxide **133**. The major component was isolated by p.t.l.c. in moderate yield and identified as the 7-fluorophenyl-4,3-benzoxazonine **134** by spectroscopic and elemental analysis. The compound, a crystalline solid, behaved similarly to the previously described benzoxazonines and exhibited two sets of signals on NMR analysis at -30°C. At 25°C in the ^{13}C (Table 3.7, pg. 95) and ^{1}H NMR spectra, a single set of well resolved signals was observed with the H5 protons at 4.35 and 3.99 δ, and H6 at 6.52 δ. The Z-stereochemistry of the benzoxazonine was confirmed by the detection of an nOe between H6 and the *ortho*-protons of the pendant aryl group.
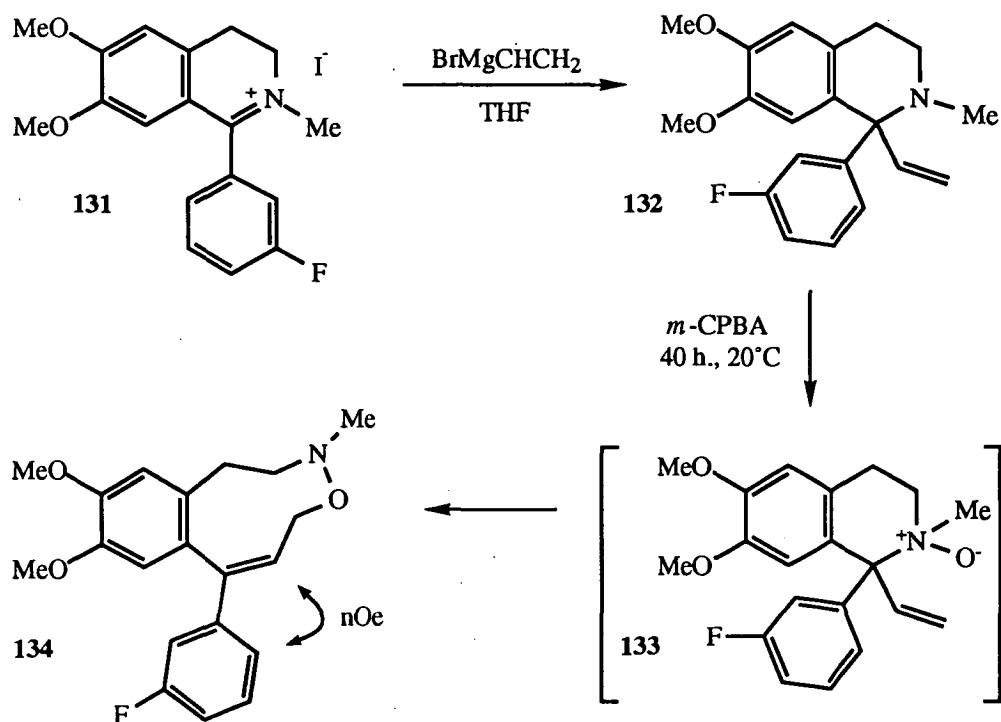
The facile [2,3] rearrangement of **133** may be due to the relief of steric crowding at the C1 position, together with the increased conjugative stabilisation in **134**.

3.7   Molecular Modelling of the Z-1,2,3,5-Tetrahydro-4,3-benzoxazonine System

In order to obtain a better understanding of the conformational preferences of the 4,3-benzoxazonine derivatives the parent Z-1,2,3,5-tetrahydro-4,3-benzoxazonine was investigated with PCModel.[76]   The five lowest energy conformations were identified (Table 3.9). These structures are included in either Figure 3.11 or Appendix A. Several of the conformers (2, 3, and 4) were analogous to those previously identified for the Z-benzazonine system (conformers 2, 5, and 4, Table 2.5, pg. 36). The lower energy conformers adopted a folded structure with the nitrogen atom displaced from the aromatic ring plane by 1.8-2.5 Å.

Conformers 1 and 2 were significantly lower in energy than the others. The Boltzmann distribution predicted a 2:1 mixture at 25°C. These conformers possessed almost the same basic structure, however, in conformer 1 the oxygen occupied an endocyclic position, over the fused aromatic ring, while in conformer 2 the oxygen was exocyclic (Figure 3.11). The presence of these two closely related conformers would explain the observed conformational flexibility of the 4,3-benzoxazonines during NMR analyses (Section 3.5.2). The two conformers may exchange rapidly with the inversion of the N3-O4-C5 portion of the structure.

Table 3.9 Low energy conformations of the Z-benzoxazonine system

conformer	E (kcal)	inc H_f	Population[a]	N-elevation[b]	N-Ar planar[c]
1	23.56	20.34	66.3%	2.28	3.51
2	23.96	19.65	33.6%	2.45	2.99
3	30.34	25.77	<0.1%	1.81	4.50
4	32.19	28.03	<0.1%	2.45	2.59
5	33.66	30.44	<0.1%	0.82	4.41

[a] from the Boltzmann distribution at 293 K

[b] distance of N above the aromatic plane (Å)

[c] distance of N from the aromatic centre in the aromatic plane (Å)
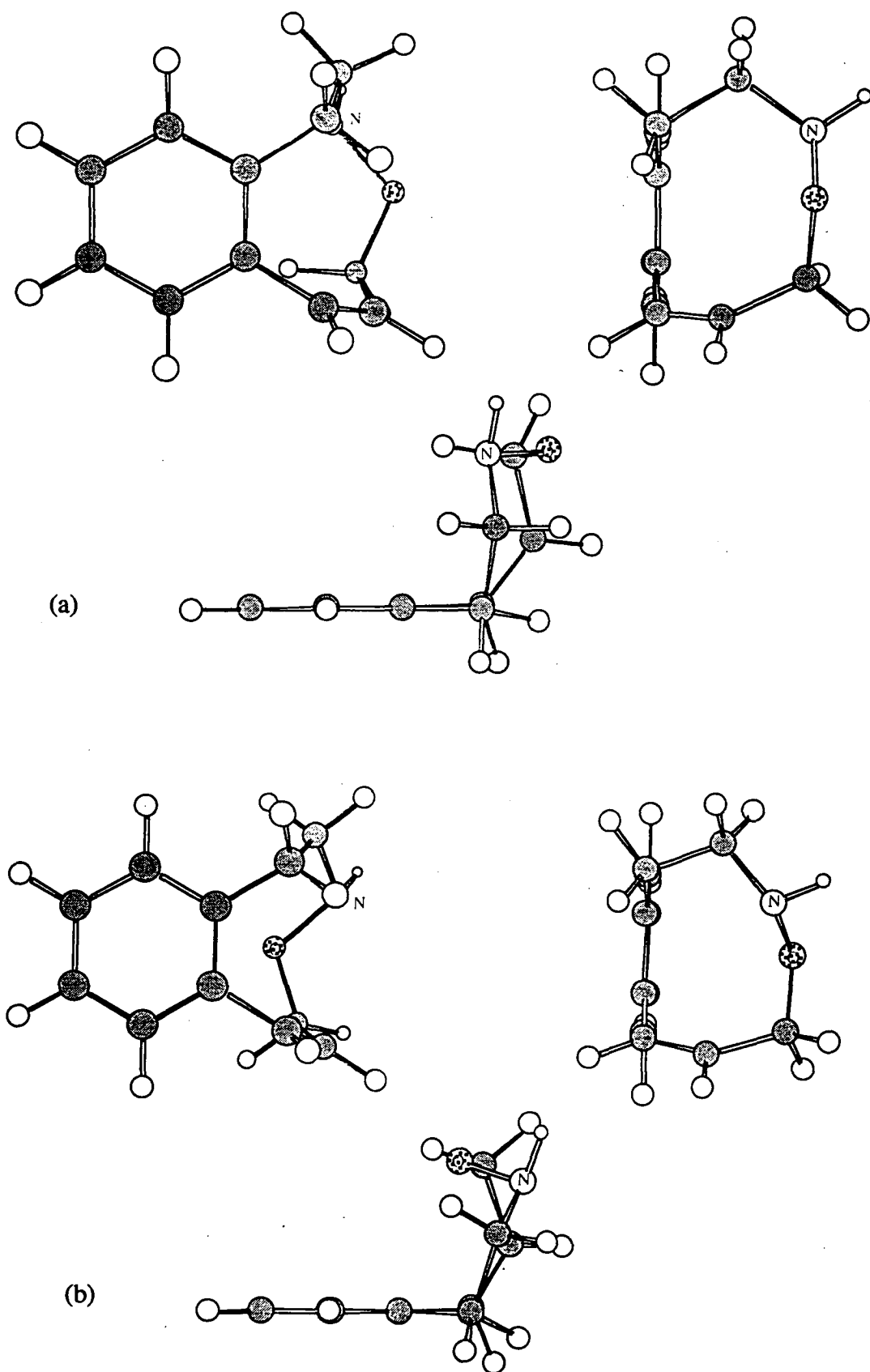
Figure 3.11 Three perspectives of (a) conformer 1 and (b) conformer 2 for the
Z-benzoxazonine system

The X-ray crystallographic analysis of the substituted 4,3-benzoxazonine **129b** confirmed the modelling predictions and afforded a structure based on conformer 2 of the Z-1,2,3,5-tetrahydro-4,3-benzoxazonine system (Figure 3.5, pg. 95).

3.8   Conclusion

The 1-vinylic-tetrahydroisoquinoline N-oxides generally displayed a lower propensity for the concerted [2,3] rearrangement than the analogous N-ylides examined in Chapter 2. This behaviour reflected the additional stability of the N-oxides and an inability to form the expected E-4,3-benzoxazonine derivatives. Derivatives of the E-4,3-benzoxazonine system are unlikely to be achieved due to the strained nature of the ring and the potential facile homolytic cleavage of the oxygen-carbon bond, enabling isomerisation to the stable 2,3-benzoxazepine derivatives.

The successful [2,3] rearrangement of the 1-vinylic-tetrahydroisoquinoline N-oxides required the presence of a 1-aryl or 1'-substituent. The 1'-substituent acted by favouring the appropriate pro-Z concerted transition state geometry in the cis-N-oxides, while the 1-aryl group promoted the formation of a more highly conjugated product. With these substituents, a route was developed which afforded the first examples of the Z-4,3-benzoxazonine system, in moderate yield, via the [2,3] rearrangement. The Z-4,3-benzoxazonines isomerised to equilibrium mixtures favouring the 2,3-benzoxazepine isomers at high temperatures, and any future reactions of these compounds should be conducted at low temperatures.

The appropriately substituted cis-N-oxides afforded exclusively the Z-4,3-benzoxazonines at low temperatures (<40°C). In this work, however, the trans-N-oxides were formed preferentially during the N-oxidation. The rearrangements with these diastereomers present afforded, except from a 1-isopropenyl derivative, mixtures of the 2,3-benzoxazepines and Z-4,3-benzoxazonines. The development of a method able to afford selectively the cis-N-oxides would enable the present

synthesis to be optimised and afford a high-yielding, convenient route to the Z-4,3-benzoxazonine system.

CHAPTER 4

FURTHER APPLICATIONS OF
[1,2] REARRANGEMENTS

4.1   Introduction

4.1.1   General Introduction

The Stevens and Meisenheimer rearrangements have provided the one atom ring

expansion of a limited number of heterocyclic systems (Section 1.2.3). Many

applications of these rearrangements to the synthesis of medium-sized aza- or oxaza-

heterocyclic systems remain to be examined. It was proposed to investigate the

rearrangements of the 5,6-dihydro-s-triazolo[4,3-a]-1,4-benzodiazepine derivatives

(Figure 4.1) and the tricyclic bridgehead N-ylides and N-oxides (Figure 4.2). The

former may afford access to the unknown triazolo[4,3-a]-1,4-benzodiazocine and

triazolo[4,3-a]-5,1,4-benzoxadiazocine systems, while the latter would give the novel

fused methylene or oxa-bridged medium-sized heterocyclic systems.
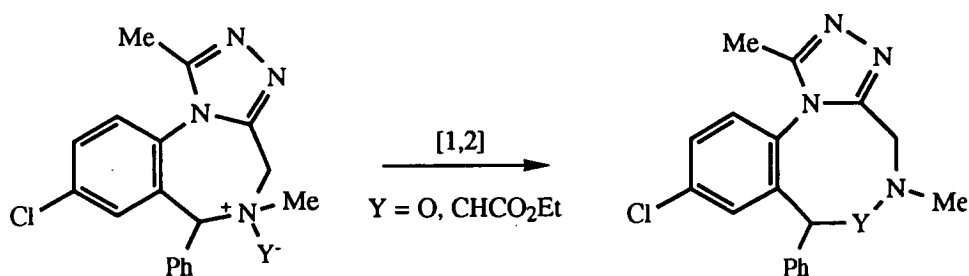
Figure 4.1
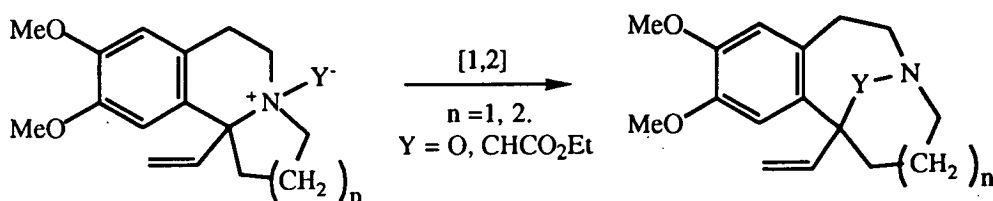
Figure 4.2

4.1.2 Introduction to 5,1,4-Benzoxadiazocines

Many potent CNS active therapeutics have been developed based on the 1,4-benzodiazepine heterocyclic system,[126-129] including Nitrazepam[130] **135a** and Diazepam[131] ("Valium") **135b**. The addition of a fused triazolo[4,3-a] ring, as in Alprazolam[55] **136**, provided therapeutics of higher activity. As a class these compounds typically possessed potent anxiolytic, anticonvulsant, muscle-relaxant and sedative activity. Derivatives of the 1,4-benzodiazepine system, or other compounds active at the benzodiazepine receptor, remain the subject of intense investigation[132] as the multiple clinical actions, habituation, and addiction of many of the known drugs are undesirable.

135 a: X=NO$_2$, R=H
b: X=Cl, R=Me

136

137,139 a: X=H, R=H
b: X=H, R=Me
c: X=Cl, R=Me
d: X=NO$_2$, R=Me
138,140 a: X=Cl, R=Me

137 n=1
138 n=2

139 n=1
140 n=2
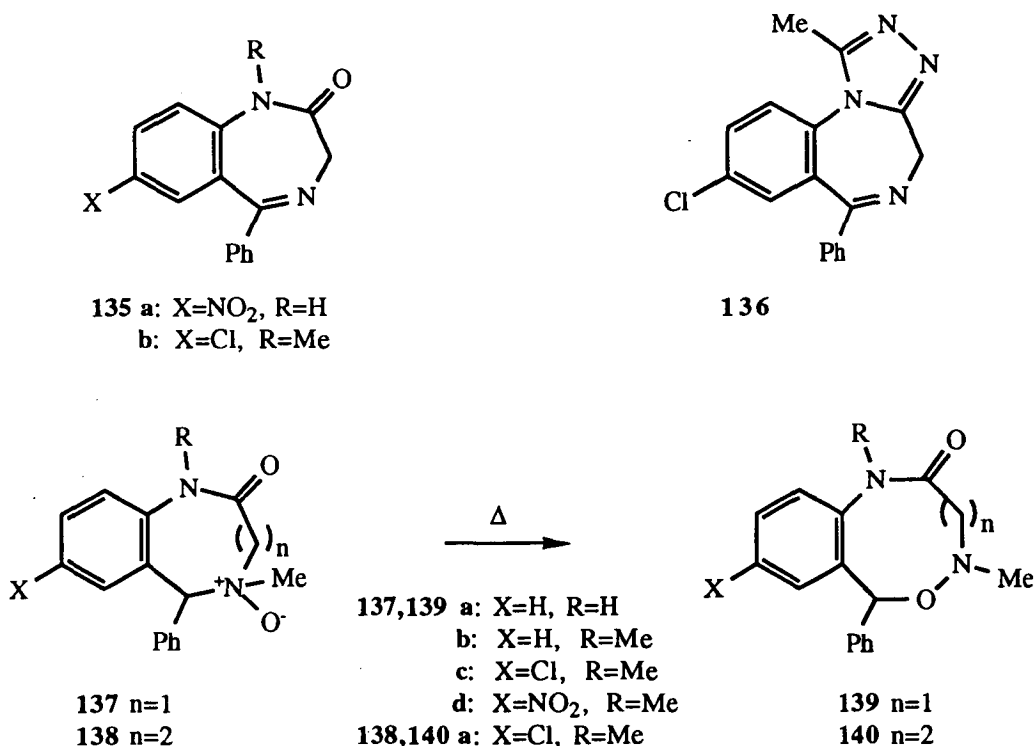
The ring-expanded analogues of the 1,4-benzodiazepines, the 5,1,4-benzoxadiazocines[31,32] **139** and the 2,3,7-benzoxadiazonine[32] **140**, were synthesized via the Meisenheimer rearrangement of the N-oxides **137** and **138**. These medium-ring heterocyclic derivatives demonstrated CNS activity in preliminary pharmacological tests. Compound **139d** exhibited some possible antagonistic activity

at the 5-HT₃ receptor site and may represent a new lead compound of novel structural type for this receptor. Consequently, the proposed synthesis of triazolo[4,3-*a*]-1,4-benzodiazocine and triazolo[4,3-*a*]-5,1,4-benzoxadiazocine derivatives (Figure 4.1) was of interest for the further development of this series. It was reasoned that, as in the 1,4-benzodiazepines, the addition of a fused triazolo[4,3-*a*] ring may provide 5,1,4-benzoxadiazocine derivatives of increased CNS activity.

4.1.3 Introduction to Fused Methylene or Oxa-bridged Medium-sized Heterocyclic Systems

Bridged fused medium-sized heterocyclic systems have attracted considerable attention, with particular interest in the pharmaceutical applications of derivatives of this class. Some examples include the methylene bridged systems of the analgesic eptazocine,[133] a 1,6-methano-4-benzazonine, and the antitumour alkaloid vinblastine[134] (Figure 4.3), one of the most often used compounds in cancer chemotherapy.[135] Oxa-bridged systems, such as the antitumour antibiotic FR-900482 (Figure 4.3) and its derivatives[136-138] which possess a 1,5-epoxy-1-benzazocine core, are also of great interest.

Eptazocine

Vinblastine
(V=Vindoline)

FR-900482
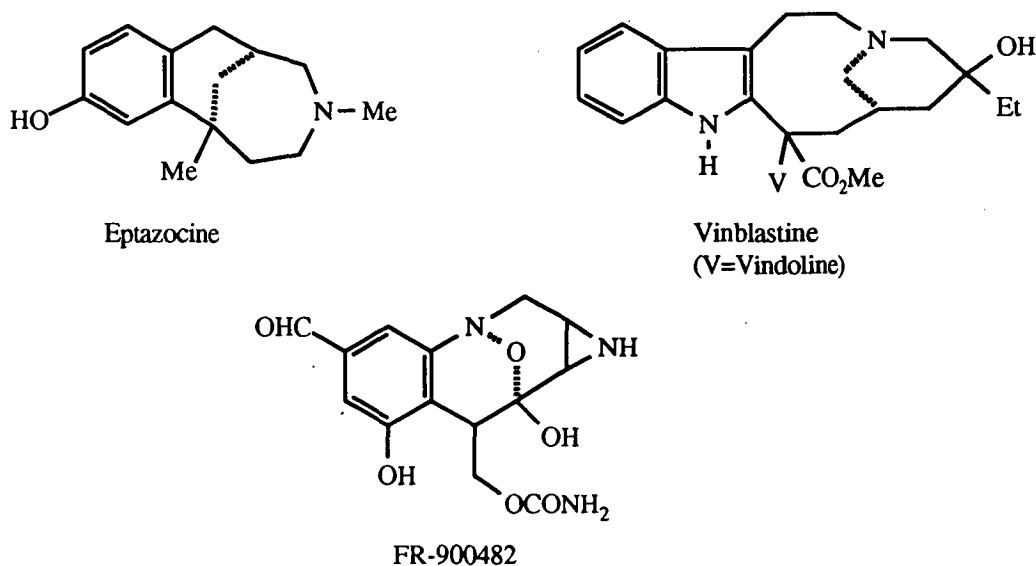
Figure 4.3

It was proposed that the [1,2] rearrangements of the tricyclic bridgehead *N*-oxides and *N*-ylides (Figure 4.2) may afford the new oxa- or methylene-bridged

heterocyclic systems of pharmaceutical interest. In addition, the potential [2,3] rearrangements of these derivatives (Figure 4.4), although considered unlikely, were of interest.
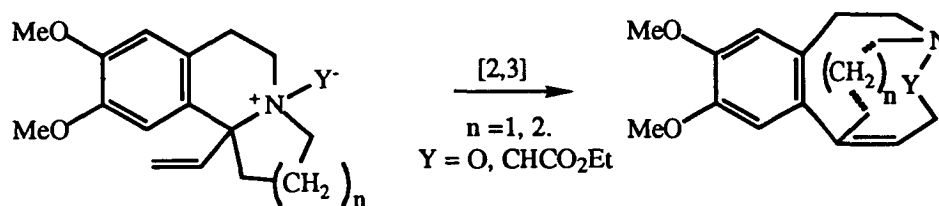
Figure 4.4

Few investigations have been made of the potential for [1,2] rearrangements to provide access to oxa- and methylene-bridged heterocycles. One report of the synthesis of an oxa-bridged heterocycle by the Meisenheimer rearrangement has been published,[139] in which the tetrahydro-2H-azetopyrido[3,4-b]indole N-oxide **141a** rearranged to the 3,6-epoxyhexahydroazocino[5,6-b]indole derivative **142a** at room temperature, while the 1-hydroxymethyl N-oxide **141b** rearranged to **142b** only on heating in tetrahydrofuran to 55°C, and was obtained along with a substantial amount of the Cope elimination product.

a: R=CO$_2$Me
b: R=CH$_2$OH

141   **142**
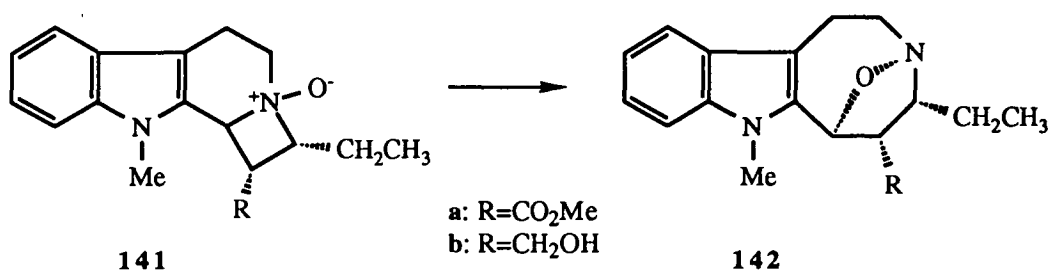
4.2 Rearrangements of 5,6-Dihydro-s-triazolo[4,3-a]-1,4-Benzodiazepine Derivatives

4.2.1 Synthesis of N-Methyldihydroalprazolam

Initially it was thought that N-methyldihydroalprazolam **147**, required as the precursor for the rearrangement studies, could be made by the N5-methylation of

Alprazolam to the iminium salt **143**, followed by reduction. The treatment of

Alprazolam with iodomethane at 50°C, however, provided a mixture of at least two

isomeric methiodide salts (ratio=2.24:1). The major isomer possessed a 1-methyl

signal at 3.19 δ, downfield of that for Alprazolam (2.64 δ) and consistent with the

1,2-dimethyl iminium salt **144**. The reduction of this crude alkylated material with

sodium borohydride afforded the known[140] 1,2-dimethyl derivative **145** as the major

product. Compound **145** possessed a characteristic doublet in the ^{1}H NMR spectrum

for the 1-methyl signal at 1.52 δ, and a quartet for H1 at 4.75 δ. The results were

consistent with previous studies which reported the preferential *N*-alkylation[140] or

protonation[141] of Alprazolam at the triazolo nitrogen atom *N*2.

Alprazolam

136

143

144

145
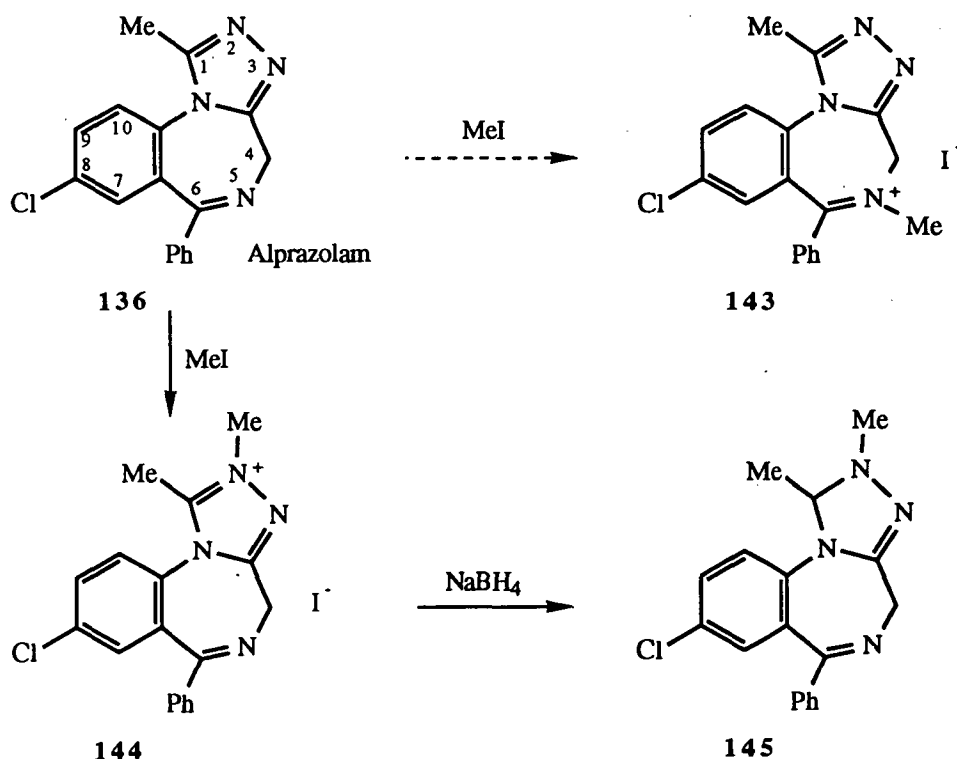
The development of an alternative route to *N*-methyldihydroalprazolam from

Alprazolam via dihydroalprazolam **146** was then investigated. It was reasoned that

under acidic conditions the protonated 2-, 3- or 5-iminium salts of Alprazolam would

exist in equilibrium. The reduction of the non-aromatic 5,6 site may then occur

preferentially to give **146**. Dihydroalprazolam had been prepared previously,[142-145]

but only as the direct product of benzazepine ring construction and not from Alprazolam.

Me—N—N / N
Cl
Ph
136

NaBH₃CN
MeOH/HCl
→

Me—N—N / N
Cl
Ph
N—H
Dihydroalprazolam
146

1. H₂CO, MeOH
2. HCl/NaBH₃CN

Me—N—N
Cl
Ph
N—R
148 a: R = CH₂CH₃
b: R = (CO)CH₃

Me—N—N
Cl
Ph
N—Me
N-Methyldihydroalprazolam
147
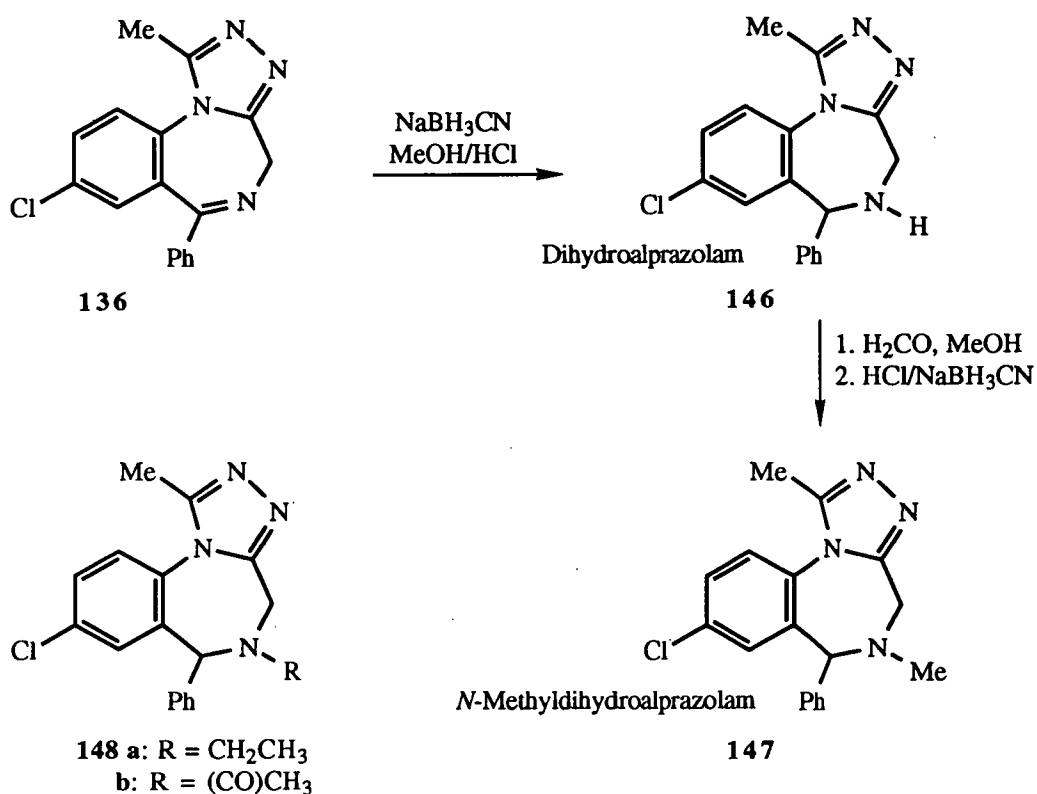
The treatment of Alprazolam at room temperature with either sodium borohydride in ethanol, sodium cyanoborohydride in methanol/acetic acid, or sodium cyanoborohydride in glacial acetic acid, gave no reaction. The latter system at 50°C afforded three products from which dihydroalprazolam **146**, the major component, was isolated in 36% yield. Compound **146** exhibited a ¹H NMR resonance for H6 at 4.95 δ as a singlet, consistent with the proposed 4H-5,6-dihydro- structure but not the alternative potential 1H-2,4- or 3H-3a,4-dihydro- isomers. The two minor products, 25% and 11% respectively of the crude product mixture, were tentatively identified as the N-ethyl **148a** and N-acetamide **148b** compounds by GC-MS analysis. The formation of **148b** reflected the condensation of **146** with acetic acid and suggested that the acidification of the mixture with a mineral acid, rather than an organic acid, would provide an increased yield of **146**. The subsequent reduction of Alprazolam by sodium cyanoborohydride in methanol acidified with hydrochloric acid afforded **146**

in excellent yield and provided an efficient and mild route from Alprazolam to dihydroalprazolam. The use of sodium cyanoborohydride, a more stable and selective reagent under acidic conditions than sodium borohydride, was critical to the success of this reaction.

The treatment of **146** with formaldehyde and sodium borohydride afforded the expected reductive methylation product, together with several minor byproducts. The purification of **147** by p.t.l.c. on silica failed, however, with the material being degraded to a mixture of four components. The ^{1}H NMR spectrum of the mixture indicated the formation of quaternary amine or iminium salts with the signals for the methyl groups between 3.3 and 3.5 δ, downfield of their positions in **146**. The impurities in the reductive methylation of **146**, and thus the complications inherent in purifying **147**, were avoided by conducting the reaction with sodium cyanoborohydride in acidic solution. Under these conditions **147** was formed in almost quantitative yield. No impurities were detected by GC-MS. The NMR (Figure 4.5) and mass spectral data for *N*-methyldihydroalprazolam were consistent with the proposed structure. The present method appeared to be the first preparation of this potentially CNS active 1,4-benzodiazepine derivative.
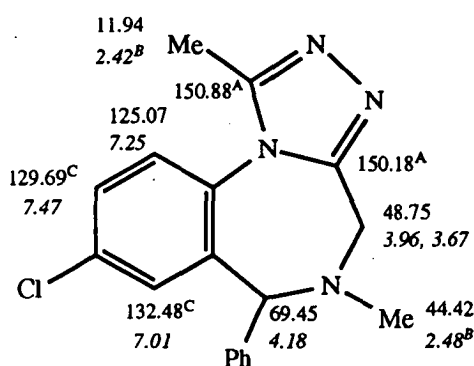
Figure 4.5 ^{13}C and ^{1}H (italics) NMR assignments for **147**

Prior to the successful preparation of **147** described above, the one-pot conversion of **136** to **147** was investigated. The reduction with *N*-alkylation of indole, quinoline, and isoquinoline, by a combination of sodium borohydride and the

appropriate carboxylic acid, was described by Gribble *et. al.*[147,148] The mechanism was proposed[148] to involve the generation of the free aldehyde from the carboxylic acid, via an acyloxyborohydride species, with the subsequent reductive amination of the saturated amine formed *in situ*. The formation of *N*-ethyldihydroalprazolam **148a** in previous experiments suggested this methodology may be applicable to the direct generation of *N*-methyldihydroalprazolam from Alprazolam.

The treatment of Alprazolam with sodium borohydride and formic acid at 0°C produced mixtures of **147** and the formamide derivative **149**. Compound **149** was identified by MS and NMR spectral analysis. The compound exhibited two conformers in deuterated chloroform at room temperature, reflecting hindered rotation of the amide bond. The ratio of **149** to **147** was dependant on the rate of addition of the formic acid to the reaction mixture. The addition of the acid in one dose produced mainly the amide **149** (**149/147**=13.3), while the slow dropwise addition of the acid produced a significant improvement in the yield of **147** (**149/147**=1.0). The results were consistent with the reaction of **146**, generated *in situ*, with either formic acid or formaldehyde. The rate of addition was assumed to control the relative concentrations of these species. A previous study[146] of this type noted the formation of an amide byproduct and demonstrated this compound was not an intermediate in the one-pot reaction.
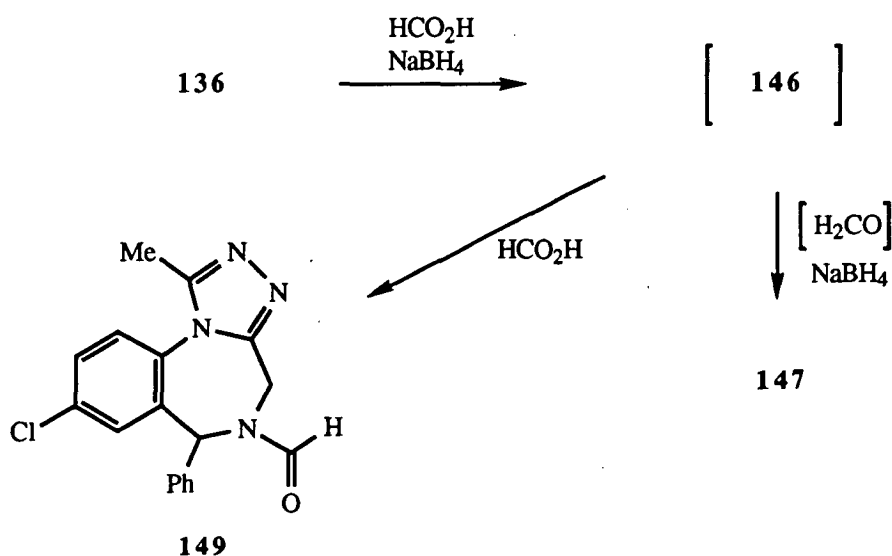
The further development of the one-pot reaction of **136** to **147** was prevented by time constraints. It appeared likely that the complete optimisation of reaction variables, such as reactant stoichiometry, concentration, and method of addition, would allow the successful one-pot conversion of Alprazolam to *N*-methyldihydroalprazolam.

4.2.2 Attempted Synthesis of a Quaternary *N*-Ylide Precursor

In several reactions the selective *N*-alkylation of **147** to the immediate ylide precursor, the ethoxycarbonylmethyl salt **150**, was pursued, but ultimately without success. The treatment of **147** with ethyl bromoacetate in acetone at elevated temperatures failed to provide any alkylation, while the reaction of **147** with ethoxycarbonylmethyltriflate at room temperature afforded a mixture of several salts. Numerous signals were present in the ^{1}H NMR spectrum of the material between 2.96 and 2.45 δ, consistent with a downfield shift of the 1-methyl groups' signal by the formation of 2- or 3- iminium salts. These results suggested that, as for Alprazolam, the triazole ring nitrogens of **147** were the preferred nucleophilic sites for *N*-alkylation.
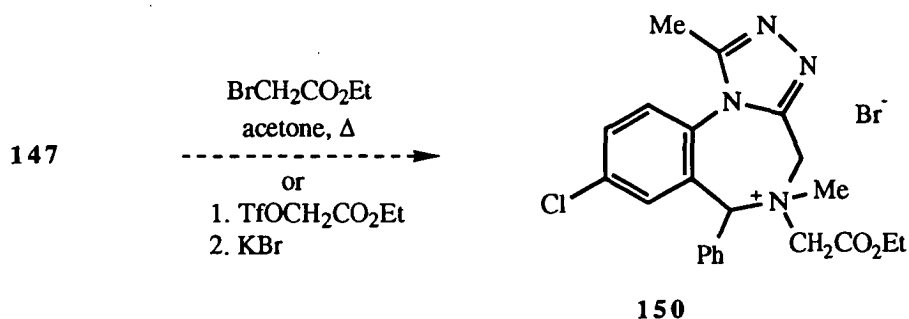
With the planned synthesis of **150** found to be unsuccessful, the intended synthesis of a triazolo[4,3-*a*]-1,4-benzodiazocine derivative (Figure 4.1) via the Stevens rearrangement of an *N*-ylide was abandoned.

4.2.3 Synthesis and Rearrangement of an *N*-Oxide to a Triazolo[4,3-*a*]-5,1,4-benzoxadiazocine Derivative

Alprazolam is known[148] to react selectively with peracids to produce the 5-oxide, in contrast to the reaction of Alprazolam with alkylating agents. The treatment of **147** with *m*-CPBA, however, gave a mixture of compounds. Analysis of the material by GC-MS indicated the major component possessed a molecular weight of 322 mass units, consistent with the triazolobenzodiazepin-4-one structure **151**. It was proposed that the potential for a highly stabilised radical at C4 allowed hydrogen abstraction and attack by a chlorobenzoate radical, with the formation of a 4-chlorobenzoate derivative. The hydrolysis of this and then oxidation would give **151**. A 3-chlorobenzoate-4,1,5-benzoxadiazocine was isolated after treatment of a 1,3,4,5-tetrahydro-1,4-benzodiazepinone with *m*-CPBA.[32] The hydrolysis and tautomerism of 4-acetoxy-4*H*-triazolo[4,3-*a*]-1,4-benzodiazepine derivatives to 4*H*-triazolo-benzodiazepin-4-ones has been reported.[148]
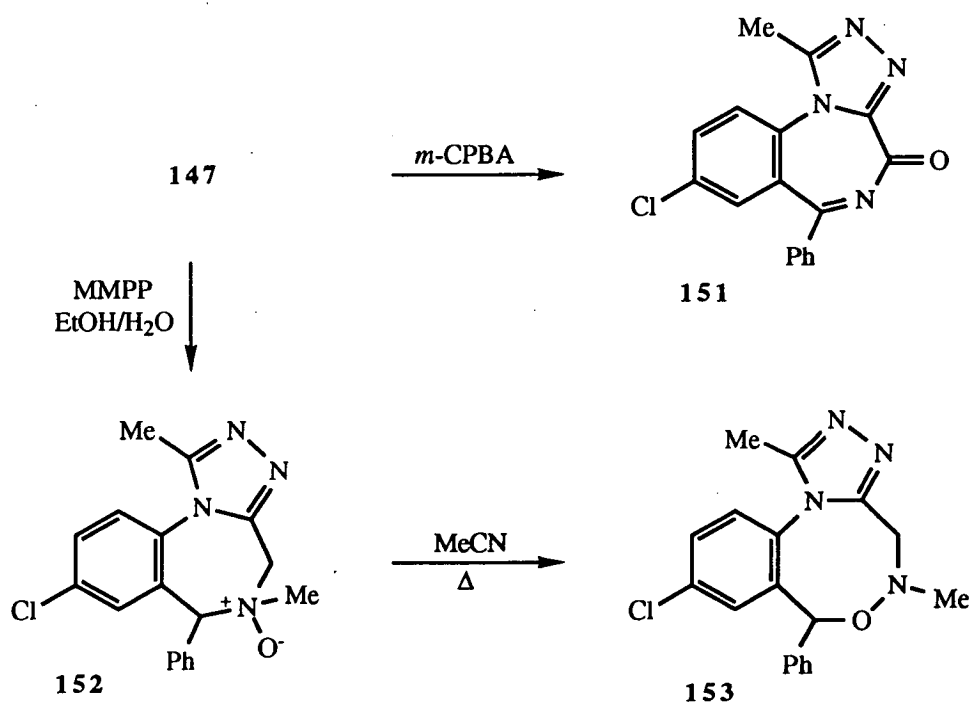
The relatively new oxidation agent, magnesium monoperoxyphthalate[149] (MMPP), demonstrated a clear superiority over *m*-CPBA for the *N*-oxidation of **147**.

This reagent reacted selectively with **147** at room temperature to give a mixture of the N-oxide **152** and the desired Meisenheimer rearrangement product, the triazolo[4,3-a]-5,1,4-benzoxadiazocine **153** (**152/153**=1.9). No other products were observed. The N-oxide was not isolated but signals at 80.63 δ for C6 and 5.61 δ for H6 in the ^{13}C and ^1H NMR spectra were consistent with the expected structure. The compound exhibited broad peaks in the ^1H NMR spectrum and individual signals for the expected *cis* and *trans* diastereomers were not observed.

It should be noted that **147** and **153** were not distinguished by t.l.c. with common solvent mixtures on silica. Consequently, monitoring the N-oxidation of **147** by t.l.c. gave misleading results, as the formation of **153** gave the appearance of incomplete oxidation. A long reaction time was adopted to ensure the removal of **147**. In addition, on-column reactions during GC-MS provided a mixture of **147** and **153** from pure **153**, preventing analysis by this technique.

The Meisenheimer rearrangement of N-oxides at room temperature is typically associated[26-32] with the formation of nine membered, or larger, heterocycles, and was not observed during the N-oxidation of the 1,4-benzodiazepinones **137**. The low temperature rearrangement of **152** reflected the presence of additional ring strain in the triazolo[4,3-a]-1,4-benzodiazepine ring system when compared to the 1,4-benzodiazepinone system.

Heating the N-oxidation mixture of **152** and **153** in acetonitrile at reflux promoted the facile Meisenheimer rearrangement of the remaining **152** to **153**. The purification of this crude reaction mixture by p.t.l.c. on silica gave the triazolo[4,3-a]-5,1,4-benzoxadiazocine **153**, the first example of this ring system, as a colourless powder in 50% yield from N-methyldihydroalprazolam.

Compound **153** was characterised principally by ^{13}C NMR (Figure 4.6), ^1H NMR (Figure 4.7) and MS analysis. The downfield positions of H7 and C7 in the NMR spectra, at 5.98 δ and 86.43 δ respectively, supported the proposed structure, with the deshielding caused by the adjacent electronegative oxygen exceeding that

present in the *N*-oxide. The alternative rearrangement of the *N*-oxide toward C4 was precluded by the comparatively high-field chemical shifts for H4.
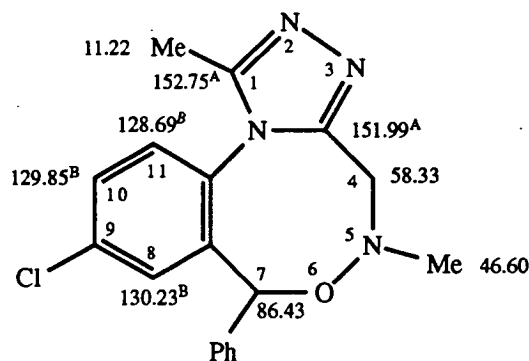
Figure 4.6 ^{13}C NMR assignments for 153

The H4 methylene protons of 153 demonstrated chemical shift nonequivalence and geminal coupling in the ^{1}H NMR spectrum. This behaviour is characteristic of the 1,4-benzodiazepine pharmacueticals[150] and was exhibited by the triazolobenzodiazepine precursors, 146 and 147, and the 5,1,4-benzoxadiazocin-2-ones[32] 139. The appearance of the chemical shift nonequivalent protons confirmed that only one conformation of 153 was important at room temperature, with a large energy barrier preventing ring inversion. The shifts of the methylene protons, at 4.43 δ and 4.22 δ, were assumed to reflect the position of each proton in the shielding region of the anisotropic aromatic ring. In the 1,4-benzodiazepinone therapeutics a much larger shift difference, for example 5.50 δ and 4.09 δ for Alprazolam, was observed. The results indicated that 153 did not adopt a folded chair-like conformation in which one proton was significantly nearer the aromatic ring. The upfield position of the 1-methyl signal at 1.79 δ, compared to those for Alprazolam (2.65 δ) and for dihydroalprazolam (2.54 δ), suggested that 153 adopted a conformation with the triazole ring at a greater angle to the aromatic ring, removing the 1-methyl group from the deshielding region in the plane of the aromatic ring.
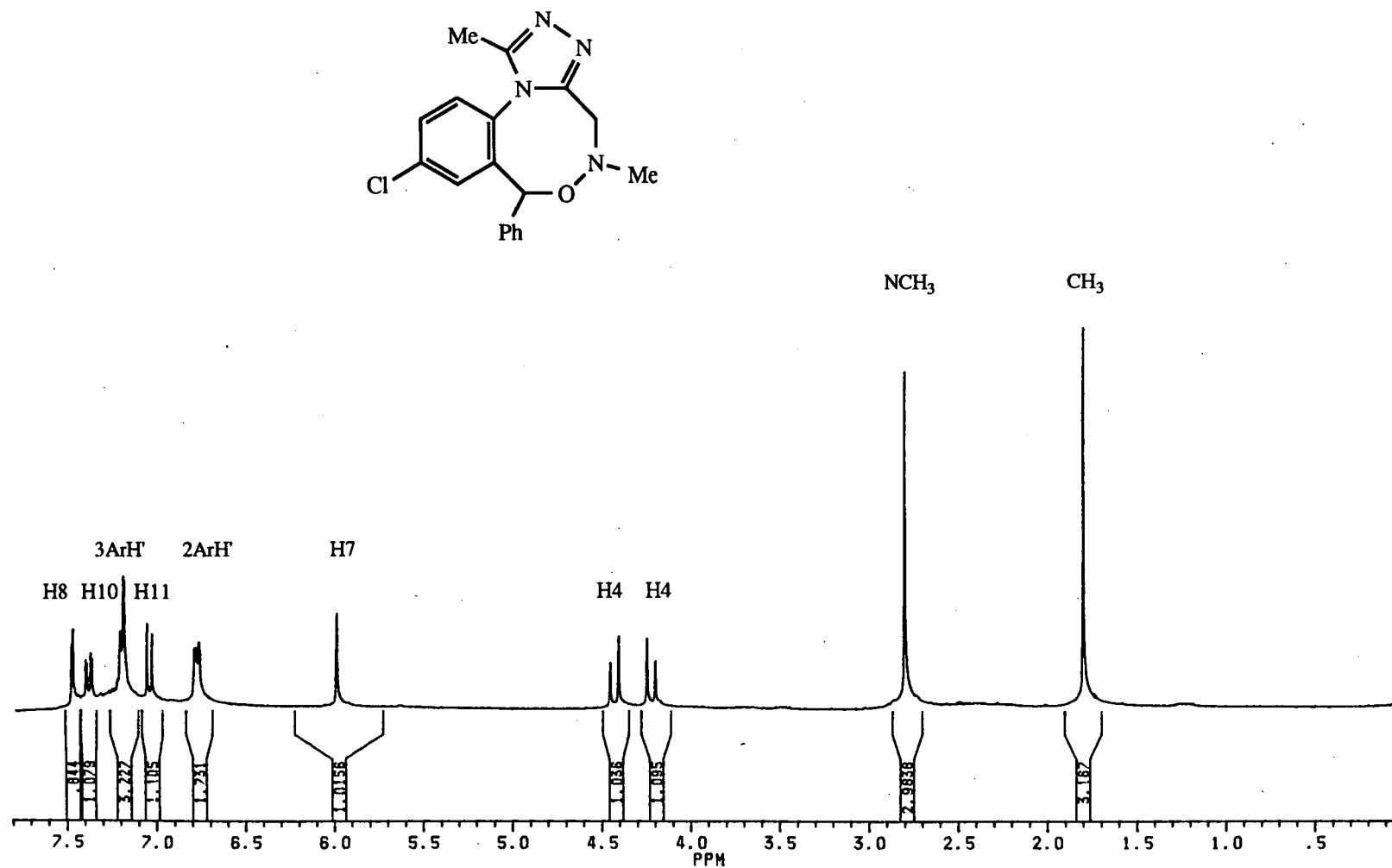
Figure 4.7 ^{1}H NMR spectrum and assignments for **153** in CDCl$_3$

4.3   Rearrangements of Tricyclic Bridgehead
N-Ylides and *N*-Oxides

4.3.1   Synthesis of the Pyrrolo[2,1-*a*]isoquinoline and Benzo[*a*]quinolizine Precursors

The vinyl substituted pyrrolo[2,1-*a*]isoquinoline and benzo[*a*]quinolizine precursors **158a** and **158b**, required to test the proposed rearrangements (Figure 4.2, pg. 107), were prepared from the known iminium salts[151,152] **154** and **156**. The Grignard reaction of vinylmagnesium bromide in tetrahydrofuran with **156** did not proceed at room temperature. Refluxing the reaction mixture, however, provided **158b** in low yield. In contrast **154** failed to react with vinylmagnesium bromide even in tetrahydrofuran at reflux. The low reactivities of **154** and **156** toward vinylmagnesium bromide reflected the steric crowding around the electrophilic 10b- and 11b-carbon centres of the tricyclic iminium salts. The planar nature of the pyrrole ring in **154** may result in the more efficient shielding of the electrophilic carbon by the α-protons, and thus the lower reactivity of **154**. Methylmagnesium iodide reacted with **154** in refluxing diethyl ether.[153]

The conversion of hindered 1-alkyl-3,4-dihydroisoquinolinium salts to 1-alkyl-1-vinyl-3,4-dihydroisoquinoline derivatives via 1-cyano adducts and their reaction with vinylmagnesium bromide was achieved.[105] The application of this technique to the present work allowed the synthesis of the previously unattainable **158a** under surprisingly mild conditions. The reaction of the pyrrolo[2,1-*a*]isoquinoline cyanide adduct **155** with vinylmagnesium bromide gave **158a** in good yield at room temperature. The mechanism involved is unclear. The reaction of the benzo[*a*]quinolizinium cyanide adduct **157** with vinylmagnesium bromide was not attempted, but would be expected to provide an improved yield from **156** to **158b**.

The cyanide adducts **155** and **157** were formed by the reaction of the iminium salts with cyanide ion in water/methanol. The benzo[*a*]quinolizinium salt reacted more readily with this reagent than the pyrrolo[2,1-*a*]isoquinolinium salt. Thus, elevated

temperatures were required for the conversion of **154** to **155**, while **156** gave **157** at room temperature. Both **155**, a pale yellow oil, and **157**, an off-white solid, developed a red colour on storage and were degraded by heating. The compounds lost HCN on mass spectral analysis and afforded spectra identical with those of the resultant enamines. The molecular ions were not observed. The ^1H and ^{13}C NMR spectra of **155** and **157** were consistent with the proposed structures. A quaternary ^{13}C NMR signal in the 118-127 δ region confirmed the presence of the cyano group.

MeO

MeO

154

I⁻

N⁺

MeO

MeO

156

X=Cl or I

X⁻

N⁺

NaCN
H₂O/MeOH

Δ

BrMgCH=CH₂

KCN
H₂O/MeOH

MeO

MeO

155

NC

N

MeO

MeO

157

NC

N

BrMgCH=CH₂

a: n=1
b: n=2

MeO

MeO

158

N

(CH₂)ₙ

MeO

MeO

159

Ph

N

(CH₂)ₙ
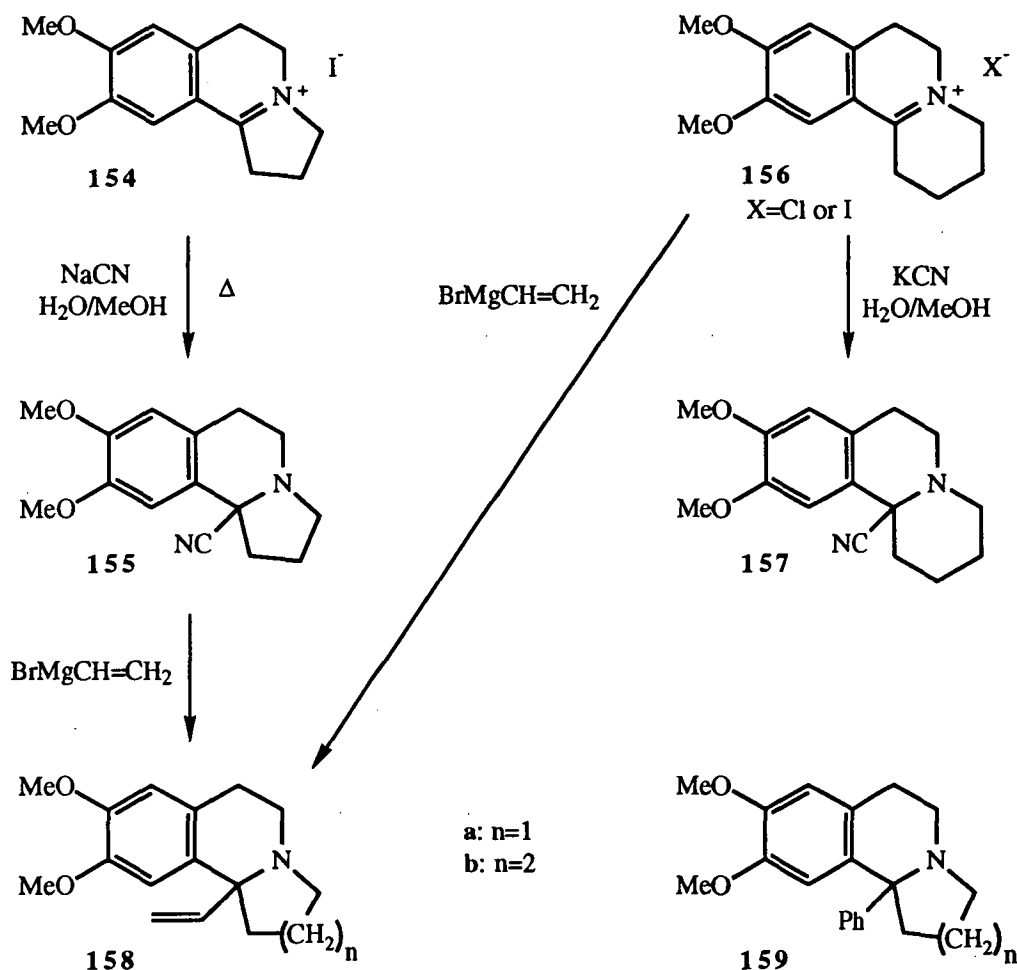
The 10b- and 11b-vinyl substituted bases **158a,b** were isolated as oils. High resolution MS analyses confirmed the molecular formulae. The loss of the vinyl group provided the base peak (M-27) in the mass spectra of **158a,b**. The ^1H NMR spectra confirmed the presence of the vinylic group, while two-dimensional homonuclear correlation experiments afforded the assignment of the methylene spin

systems. The quaternary carbons alpha to the aromatic, vinyl, and amino moieties in **158a** and **158b** were shifted downfield to 67.55 and 62.22 δ respectively in the ^{13}C NMR spectra.

Several attempts were made to synthesise the 10b- and 11b-phenyl substituted tricyclic derivatives **159a,b** from the iminium salts or cyanide adducts. It was reasoned that the phenyl substituent would provide extra resonance stabilisation of the radical pathway for later *N*-oxide or *N*-ylide [1,2] rearrangements. An earlier attempt[31] to add a phenyl Grignard reagent to the chloride salt of **154** was unsuccessful. The conversion of **154** to the cyanide adduct **155** failed to promote any reaction with phenylmagnesium bromide and **159a** was not obtained. Similarly, the reactions of phenylmagnesium bromide or phenyllithium with **157** failed to produce **159b**. Compound **159a** is known,[61,63] however, time did not permit its synthesis via the published technique involving the formation and reduction of a 10b-phenylpyrrolo[2,1-*a*]isoquinoline-3-one derivative.

4.3.2 Synthesis and Base-Promoted Behaviour of Quaternary Salts

The tricyclic amines **158a,b** were alkylated with ethoxycarbonylmethyl triflate in acetonitrile to provide, after treatment with potassium bromide, the *N*-ethoxycarbonylmethyl salts **160a,b.** Compound **160a** was obtained as a single diastereomer which displayed the expected downfield shift of the 10b-carbon signal to 83.88 δ in the ^{13}C NMR spectrum. It is thought likely that **160a** was the *trans* B/C fused diastereomer, as hexahydropyrrolo[2,1-*a*]isoquinolines typically adopt a low energy *trans* B/C fused conformation, and the *N*-alkylation of this conformation would be less sterically hindered than for the *cis* B/C fused conformers in the presence of the 10b-vinyl group. In contrast, **160b** was a mixture (3.3:1) of two conformationally flexible diastereomers. The *N*-Alkylation to a *cis* B/C fused diastereomer of **160b** may have occurred as the dihedral angle adopted in *cis* B/C fused **158b**, between the nitrogen lone-pair and the vinyl-substituent, would be considerably larger than that in **158a**, decreasing the steric hindrance of the reaction.

The base promoted reactions of **160a,b** were tested initially at mild temperatures. No reaction occurred upon treatment of **160a,b** with DBU in acetonitrile at temperatures below the refluxing point of the solvent. In refluxing acetonitrile minor amounts of non-polar rearrangement products were observed after 10 to 20 hours. Lengthier reaction times failed to increase the level of this material. Similarly, conducting the reactions in refluxing butyronitrile provided no significant increase in the non-polar material and led to darkening of the reaction solution.

158 $\xrightarrow{\text{1. TfOCH}_2\text{CO}_2\text{Et} \quad \text{2. KBr}}$

a: n=1
b: n=2

160

DBU
MeCN

161 R = CO$_2$Et
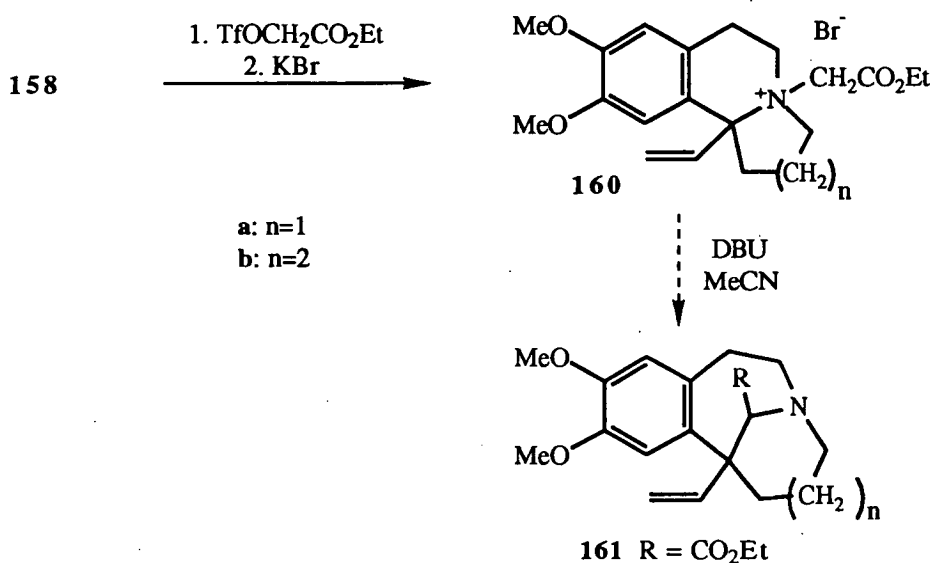
The small amount of non-polar material from the reaction of **160a** in refluxing acetonitrile was purified by reverse-phase preparative HPLC to give a fraction with approximately 95% purity. The major component was tentatively attributed to the desired 3,7-methano-3-benzazonine **161a** and represented at best a 1% yield. The small amount of **161a** obtained prevented its unequivocal identification, however, the ^{1}H NMR and ^{13}C DEPT NMR (Figure 4.8) spectra were consistent with the proposed structure. The presence of a vinyl group and a downfield ^{13}C NMR signal at 64.48 δ, attributed to the bridging carbon, were indicative of **161a** and eliminated the obvious alternative products from either the Hofmann elimination or the [2,3] sigmatropic rearrangement.
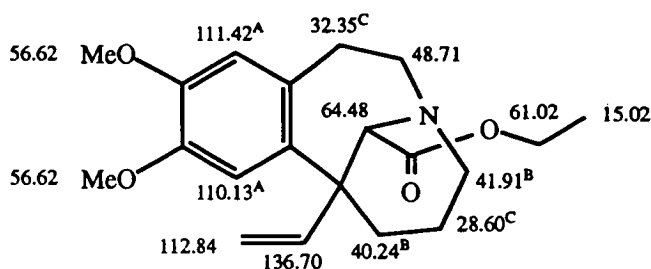
Figure 4.8 ^{13}C NMR spectral assignments for **161a**

The non-polar material from the reaction of **160b** in refluxing acetonitrile represented at best a 7% total yield of products. The GC-MS and ^{1}H NMR spectral analysis of the material revealed the presence of the precursor **158b** (33% of the material), assumed to be present as an impurity in **160b** or formed by bromide catalysed N-dealkylation, and three isomers (10%, 36%, and 11% of the material) with the correct molecular weight for **161b** and almost identical mass spectra. In view of the low yields no attempts were made to purify the material further.

4.3.3 Synthesis and Thermolyses of the N-Oxides to Fused Oxa-Bridged Medium-Sized Systems

The oxidation of **158a,b** with m-CPBA in dichloromethane gave the N-oxides **162a,b** as mixtures of the cis- and trans-diastereomers which, after isolation, were utilised without further purification. The N-oxidation was considerably more diastereoselective from **158a** than **158b**, with a ratio of 13.3:1.0 for the diastereomers of **162a** and 5.7:1.0 for the diastereomers of **162b**. The ^{1}H and ^{13}C NMR spectra of **162a,b** confirmed the proposed structures, with the vinyl group intact and the C10b and C11b signals shifted downfield to 82.24 δ and 77.69 δ for the major diastereomers of **162a** and **162b** respectively.

The N-oxides **162a,b** were unchanged on refluxing in acetonitrile for 48 hours. Refluxing **162a,b** in butyronitrile for 1-2 hours, however, gave a small non-polar fraction in each case which was isolated from the largely intact N-oxide. The reverse phase HPLC purification of these fractions gave the Meisenheimer

rearrangement products, the 3,7-epoxy-3-benzazonine **163a** and 2*H*-3,8-epoxy-3-benzazecine **163b** derivatives, in low yields of 5-6%. The formation of these new oxa-bridged systems was confirmed by the downfield positions of the quaternary carbons, C7 at δ 82.87 for **163a** and C8 at δ 87.89 for **163b**, in the ^{13}C NMR spectra (Figure 4.9). Two dimensional homonuclear and heteronuclear correlation experiments afforded the assignment of the ^{1}H NMR spectra for **163a** (Figure 4.10) and **163b** (Figure 4.11).

158 → m-CPBA / Δ →

162

a: n=1
b: n=2

Δ / PrCN

163
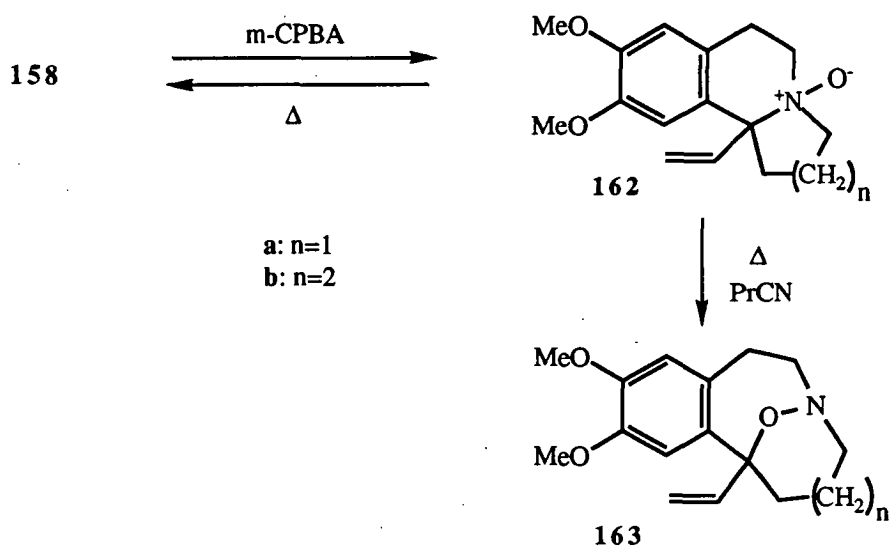
No evidence was obtained for the formation of the other possible Meisenheimer or [2,3] sigmatropic rearrangement products. The precursors **158a,b** were, however, detected in the non-polar thermolysis fractions by ^{1}H NMR, at yields about half those of **163a,b**. Compounds **158a,b** may arise either directly from **163a,b** or by the deoxygenation of **162a,b** prior to, or after reversal of, the Meisenheimer rearrangement. The stability of **163a** was thus tested by refluxing a sample in butyronitrile for 1 hour. After this time traces of **158a** were evident in the ^{1}H NMR of the mixture, indicating that the direct deoxygenation and recyclization of the oxa-bridged derivatives could occur, however, the majority of **163a** was unchanged. This confirmed the precursors were formed mainly by the deoxygenation of the corresponding *N*-oxides in the thermolytic reactions. Small amounts of deoxygenation products were previously noted[154] to accompany the Meisenheimer

rearrangement, with several mechanisms proposed for the thermal deoxygenation.[154,155]

(a)

(b)
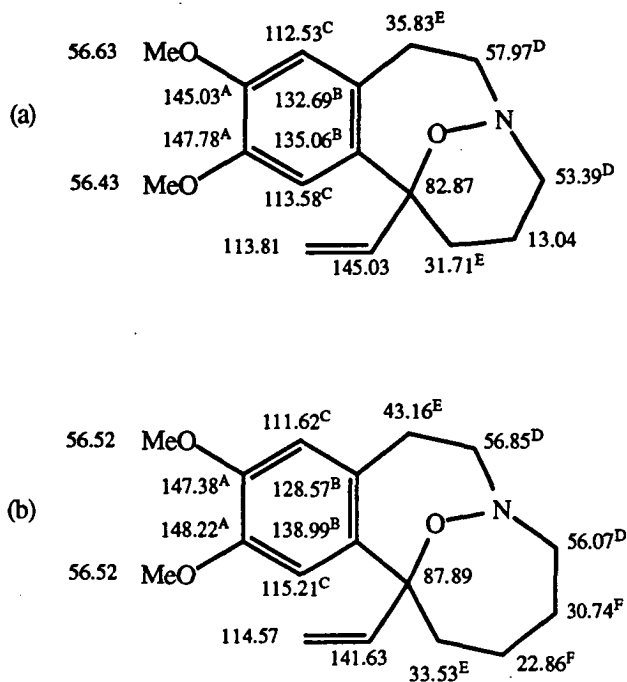
Figure 4.9 ^{13}C NMR spectral assignments for (a) 163a and (b) 163b

A variety of conditions were tested in attempts to improve the yield of 163a, but without success. These included longer reaction times in butyronitrile, thermolysis in DMSO at 130°C, and thermolysis neat in an evacuated tube at 120°C. In each case the deoxygenated precursor 158a became the major product, with no significant increase in the yield of 163a.

The reaction temperature necessary for any significant Meisenheimer rearrangement of the bridgehead N-oxides 162a,b was higher than that required for the rearrangement of the simpler 1-vinylic tetrahydroisoquinoline N-oxide derivatives 123a-d and contrasted greatly with the reported formation[139] of 142a (pg. 110) from the tetrahydro-2H-azetopyrido[3,4-b]indole N-oxide 141a at room temperature in dichloromethane. Clearly the relief of the azetidine ring strain promotes the low temperature Meisenheimer rearrangement of 141a. The less facile rearrangement of 141b also indicated a role in the activation of the [1,2] rearrangement by the β-ester substituent of 141a.
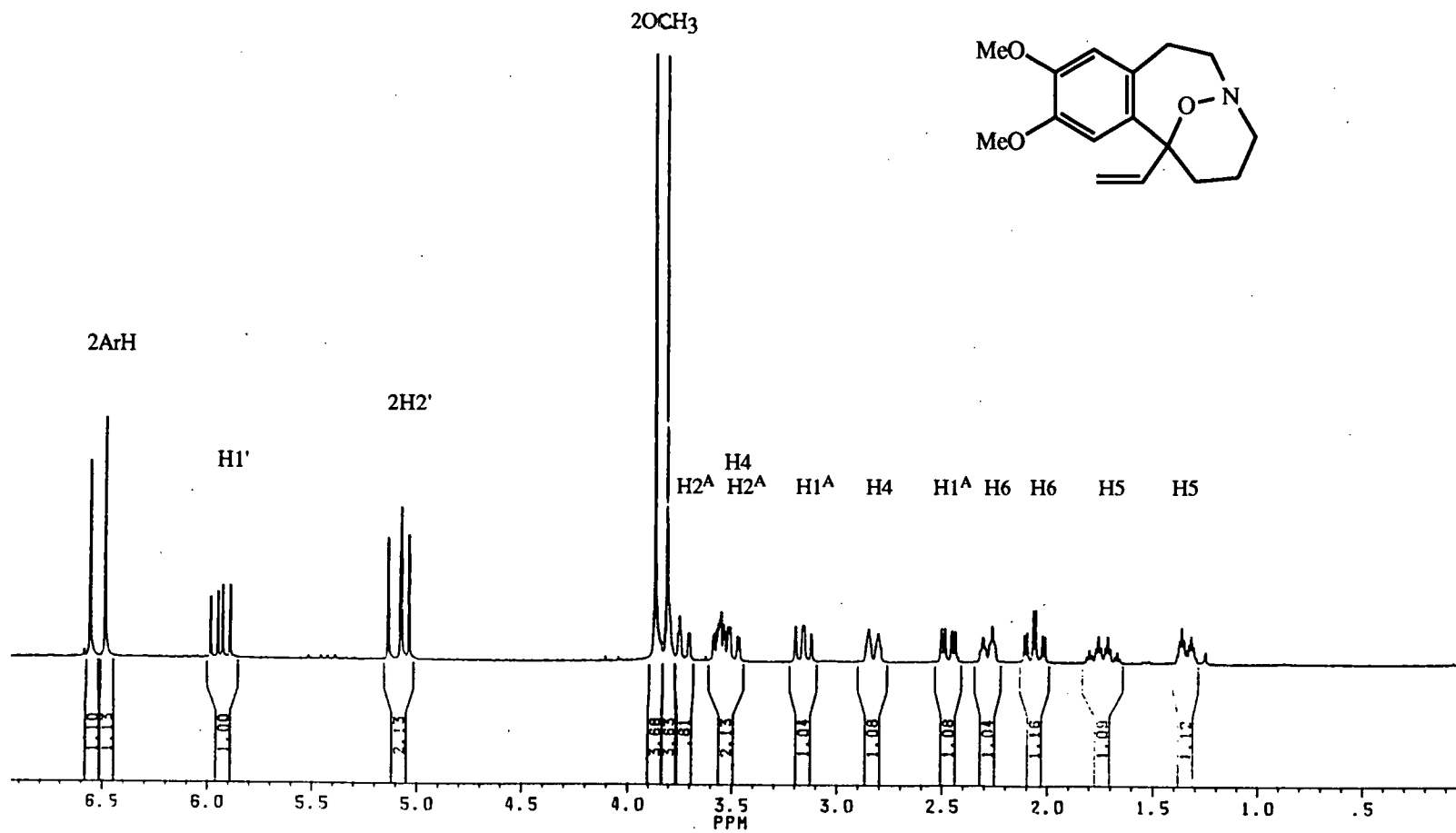
Figure 4.10 ^{1}H NMR spectrum and assignments for **163a** in CDCl$_3$
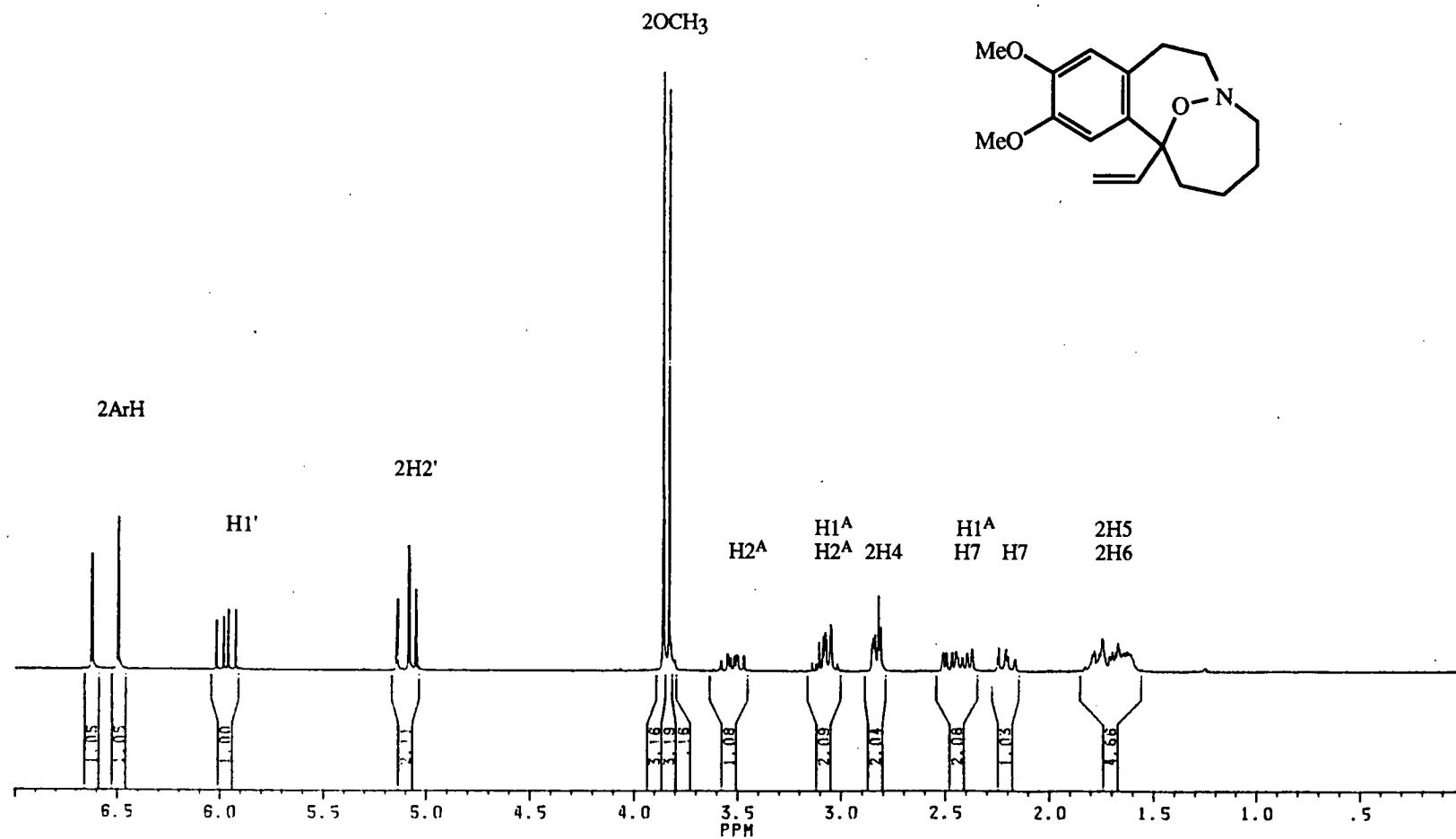
Figure 4.11 ^{1}H NMR spectrum and assignments for **163b** in CDCl$_3$

...
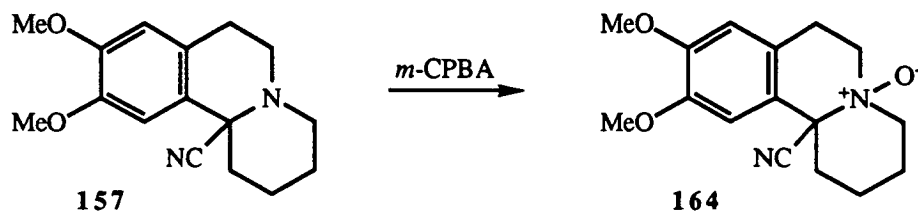
As the 10b-unsubstituted pyrrolo[2,1-a]isoquinoline N-oxide analogue of **162a** did not undergo Meisenheimer rearrangement,[31] the vinylic group of **162a** apparently promoted the rearrangement by providing additional stabilisation of the radical intermediate. It was reasoned that a cyano group may also provide radical stabilisation and, as the cyano adduct **157** was accessible in higher yields than **158b**, the thermolysis of the 11b-cyanobenzo[a]quinolizine N-oxide **164** was investigated. The N-oxidation of **157** with m-CPBA occurred stereospecifically to give one diastereomer of **164**, assumed to be the *trans* B/C fused diastereomer. The thermolysis of **164** in refluxing butyronitrile afforded an ether soluble fraction, in approximately 37% yield, but failed to provide the desired 3,8-epoxy-3-benzazecine derivative. The analysis of this material by GC-MS indicated the presence of two significant components (4.5:1.0), with molecular ions at 246 (N-oxide **164** - O; CN) and 272 (N-oxide **164** - O). Thermolysis of **164** in refluxing dimethylformamide produced a complex mixture with the $M^{+\cdot}$ 272 compound the only significant component present. No attempts were made to purify the material further in view of the low yields.

4.4 Conclusion

The applications of the Meisenheimer rearrangement in organic synthesis were extended to the synthesis of the first example of the triazolo[4,3-a]-5,1,4-benzoxadiazocine ring system, compound **153**, with the successful [1,2] rearrangement of the triazolo[4,3-a]-1,4-benzodiazepine N-oxide **152**. The synthesis

of **153** was achieved in excellent yield overall from the known 1,4-benzodiazepine therapeutic, Alprazolam, via the novel derivative *N*-methyldihydroalprazolam **147**.

The similar extension of the Stevens rearrangement to the production of a triazolo[4,3-*a*]-1,4-benzodiazocine derivative was not achieved, as the necessary precursor triazolo[4,3-*a*]-1,4-benzodiazepine salt **150** could not be obtained. The successful preparation of this, or a similar *N*-ylide precursor, and the subsequent Stevens rearrangement remains to be investigated.

The first examples of the 3,7-epoxy-3-benzazonine and 2*H*-3,8-epoxy-3-benzazecine systems, derivatives **163a** and **163b**, were prepared by the Meisenheimer rearrangements of the tricyclic bridgehead *N*-oxides **162a,b**. The compounds, however, were obtained in low yield and the deoxygenation of the *N*-oxides was often preferred to the formation of the strained oxa-bridged heterocyclic systems. The results suggested that the Meisenheimer rearrangement may provide only limited access to oxa-bridged, fused aza-heterocycles.

The tricyclic bridgehead quaternary salts **160a,b** failed to undergo any significant Stevens rearrangement. The novel 3,7-methano-3-benzazonine derivative **161a** was tentatively identified but not fully characterised due to the very low ($\leq 1\%$) yield. The results indicated that the Stevens rearrangement will not be applicable to the synthesis of methylene-bridged, fused aza-heterocycles.

CHAPTER 5

REARRANGEMENTS OF 1-CYCLOPROPYL-ISOQUINOLINE *N*-OXIDES AND *N*-YLIDES

5.1   Introduction

It was proposed that the presence of a cyclopropyl group may modify the Stevens or Meisenheimer rearrangements, allowing a four atom ring expansion (Section 1.4). To evaluate the synthetic potential of this proposition the synthesis and behaviour of 1-cyclopropyl-substituted tetrahydroisoquinoline *N*-ylide and *N*-oxide derivatives were examined in this work. The rearrangement had the potential to provide direct access to derivatives of the 3-benzazecine system and the novel 4,3-benzoxazecine system from easily preparable tetrahydroisoquinoline precursors (Figure 5.1). There is a need for new approaches to these fused ten-membered ring systems, either to incorporate new functionality in the known rings or to synthesize new oxaza systems.
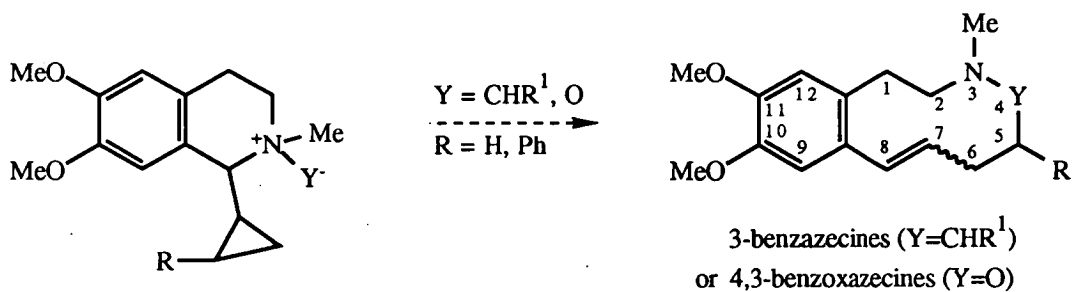
Figure 5.1

5.2   Review of Benzoxazecines and 3-Benzazecines

Although twenty eight different benzoxazecine ring skeletons are possible only the 2,6- and 3,6-benzoxazecine systems have been reported (prior to *Chem. Abs.* **119**). Both were prepared by the extension of photosolvolysis and cyanogen bromide-induced solvolysis ring destruction techniques.[156,157] Thus the

[1,3]oxazino[2,3-a]isoquinoline and [1,4]oxazino[3,4-a]isoquinoline precursors, **165** and **167**, gave the benzoxazecines **166** and **168** in moderate yields. A 2,6-benzoxazecine derivative was prepared[97] by the cyanogen bromide-induced four atom ring expansion of an isoquinoline derivative, analogous to the conversion of **119** to **120** (pg. 84).

a. X=O,   Y=CH₂
b. X=CH₂, Y=O

A variety of methods are known for the preparation of derivatives of the 3-benzazecine system. The majority involve ring destruction techniques with the same reagents and techniques used for the production of 3-benzazonines[60,61,64] and 3-benzoxazecines,[156] but from the appropriate benzo[a]quinolizine precursors. Thus Emde reduction of **169** gave the 3-benzazecine **170** in high yield. Compound **170** demonstrated antiinflammatory activity when injected intraperitoneally in the rat.[158] Elimination accompanied the cyanogen bromide-induced ring opening[159] of the amino alcohols **171** to afford the 7,8-unsaturated products **172**. The stereochemistry about the double bond in **172** was not determined.

A ring construction approach, analogous to the conversion of **41** to **42** (pg. 17), afforded 3-benzazecines in low yield,[69] while the Stevens rearrangement of 2-benzazonines to 3-benzazecines was noted[33,35] previously (Section 1.2.3).

5.3 Synthesis of 1-Cyclopropyl Rearrangement Precursors

No reports of the preparation of cyclopropylisoquinolines were found in the literature, however, it was envisaged that the cyclopropanation of the 1-vinyltetrahydroisoquinoline **49a** would afford access to the necessary 1-cyclopropylisoquinoline precursors (Figure 5.2) . As it was originally proposed that 1-oxiranyl-substituted tetrahydroisoquinoline *N*-ylides and *N*-oxides may also rearrange to benzoxazecine and benzodioxazecine products the epoxidation of **49a** was also investigated.
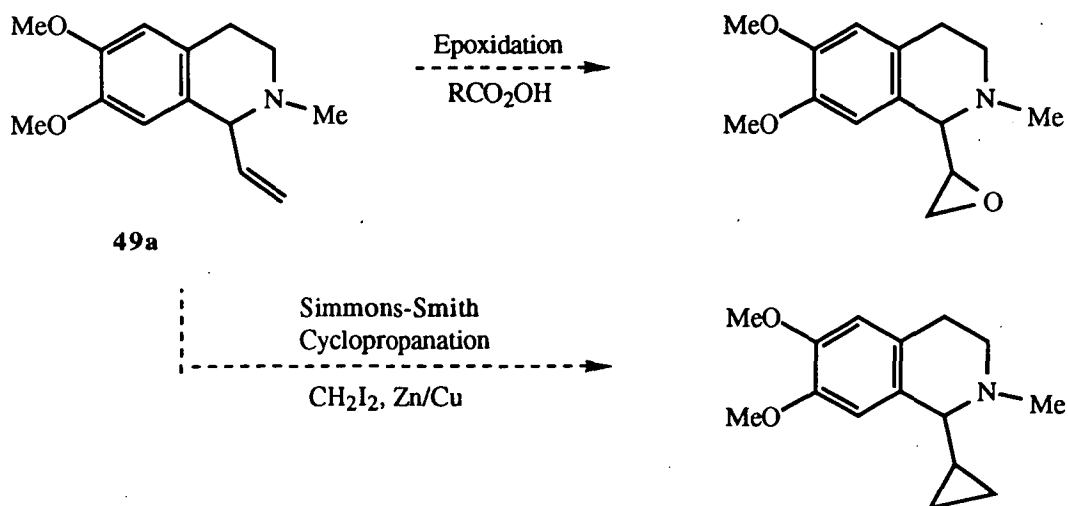
Figure 5.2

Both allylamine[160] and 2-methyl-3-amino-propene[161] were reported to undergo Simmons-Smith cyclopropanation in high yields, however, the reaction of **49a** with methylene iodide over a Zn/Cu couple in diethyl ether at reflux provided only an unidentified salt, presumed to be the methiodide salt of **49a**. It is possible that the inductive effect of the nitrogen prevented attack of the olefin by the electrophilic carbene. A recent paper[162] reported the successful cyclopropanation of substituted *N*-allyl compounds, without competing *N*-methylation, using diazomethane and bis(benzonitrile)palladium dichloride, but the cyclopropanation of **49a** was not investigated further.

The treatment of **49a** with three equivalents of *m*-CPBA in a variety of solvents at reflux, including dichloromethane, chloroform, and 1,2-dichloroethane, yielded only the *N*-oxide **123a**. The similar treatment of the methiodide and hydrochloride salt of **49a** failed to produce any epoxidation; the salts or the free base were recovered after basification. As above, the results indicated that a decrease in the nucleophilicity of the olefin by the inductive effect of the nitrogen had prevented attack by the electrophilic peracid reagent. These problems have been noted previously[163,164] and epoxidation was achieved by converting the allyl amine derivatives to their trifluoroacetate salts, which were then treated with trifluoroperacetic acid. Chemical restrictions precluded the preparation of trifluoroperacetic acid in the normal manner[165] in this work. However, several experiments in which the new hydrogen-bonded adduct, urea-hydrogen peroxide[166] (UHP), was reacted with trifluoroacetic anhydride and the trifluoroacetate salt of **49a** were conducted. No epoxidation was observed and the synthesis of 1-oxiranyl-substituted tetrahydroisoquinolines was not pursued further.

The commercial availability of cyclopropanecarboxylic acid, **173a**, and *trans*-2-phenyl-1-cyclopropane carboxylic acid, **173b**, prompted the investigation of the synthesis of 1-cyclopropyltetrahydroisoquinolines by the Bischler-Napieralski cyclisation[167] of the cyclopropanecarboxamides **174**.

a: R = H
b: R = Ph
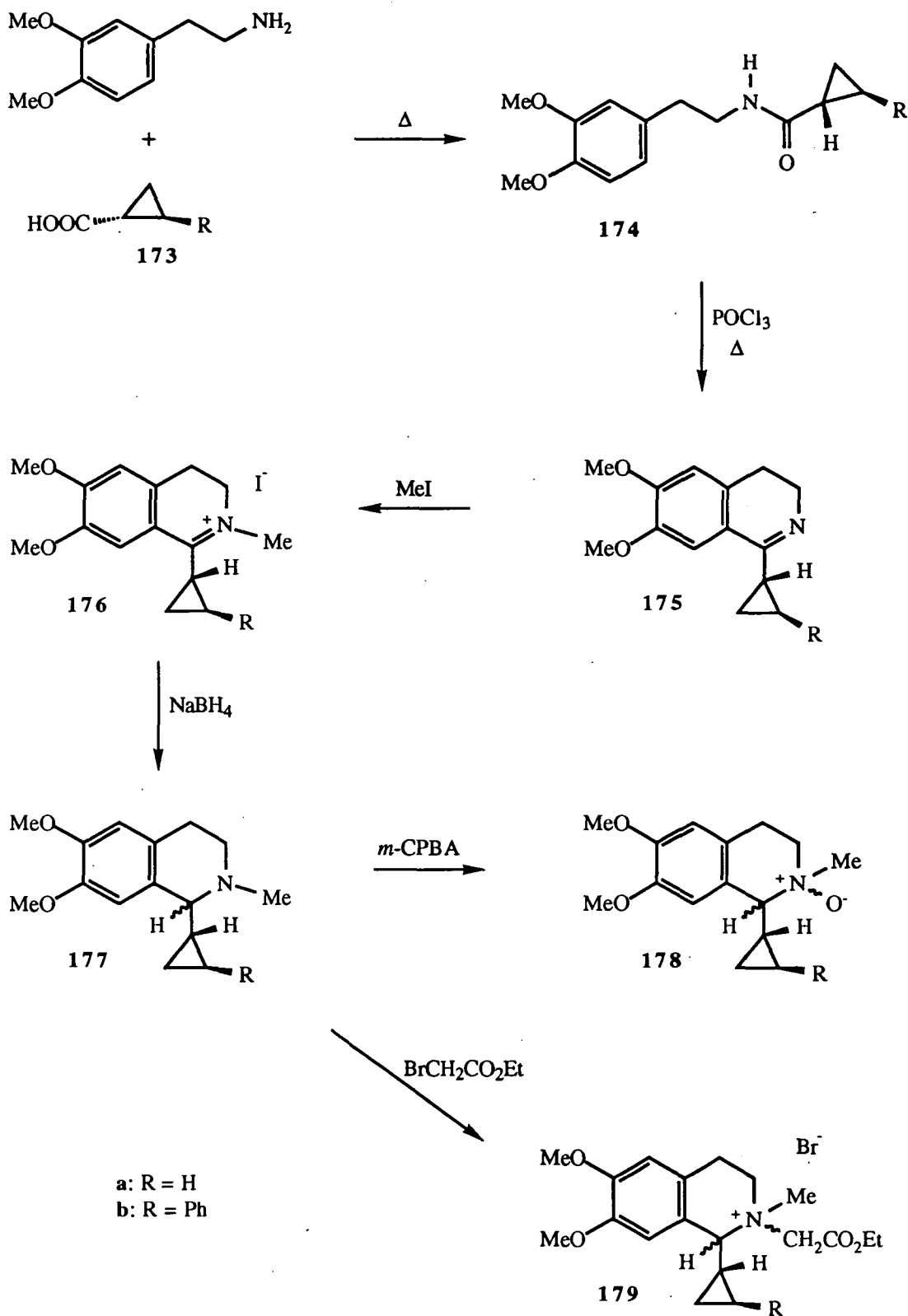
The treatment of homoveratrylamine with **173a,b** at elevated temperatures, between 140 and 170°C, gave the cyclopropanecarboxamides **174a,b** in good yield. The Bischler-Napieralski cyclisation of **174a,b** proceeded smoothly with phosphorus

oxychloride in refluxing acetonitrile to afford the 1-cyclopropyldihydroisoquinolines **175a,b** in excellent yields, the first example of the Bischler-Napieralski cyclisation of cyclopropanecarboxamide derivatives. All spectroscopic data was consistent with the proposed structures. The imines were converted to the crystalline iminium salts **176a,b** by *N*-alkylation with iodomethane in acetone and satisfactory elemental analyses were obtained. While the *N*-alkylation of **175a** was conducted in refluxing acetone, the *N*-alkylation of **175b** proceeded to the desired salt only at or below room temperature. At higher temperatures an isomer of **176b** was formed. The identification of this isomer is discussed in Section 5.4.

The sodium borohydride reduction of **176a,b** in ethanol gave the tetrahydroisoquinoline derivatives **177a,b**. Two diastereomers of the *t*-(2'-phenylcyclopropyl) compound **177b** were obtained (*SSS/RSS*=0.82) with the formation of the chiral centre at C1. The diastereomers of **177b** were separated by p.t.l.c. on silica for characterisation purposes and identified by n.O.e. experiments. One diastereomer possessed a 7-methoxy signal considerably upfield of the other (3.57 δ cf. 3.83 δ) consistent with shielding of the methoxy group by an appropriately positioned 2'-phenyl substituent. The examination of hand-held models and computer-aided molecular modelling (PCModel) confirmed the *RSS* and *SSS* diastereomers must adopt considerably different conformations to enable shielding of the 7-methoxy protons. In the *RSS* form H2' would point to the same side of the isoquinoline plane as H1, while in the *SSS* form H2' and H1 would be on opposite sides of the isoquinoline plane (Figure 5.3). NMR n.O.e. difference experiments confirmed an effect between H2' and H1, and H2' and H8, for the diastereomer with the shielded 7-methoxy signal, allowing this to be assigned the *RSS* configuration.

The *N*-oxide rearrangement precursors **178a,b** were generated in the usual manner by the reaction of **177a** and **177b** (*SSS/RSS*=0.47) with *m*-CPBA in dichloromethane at room temperature. No rearrangement products were isolated during the workup of the reaction mixture. The *N*-oxides were obtained as complex

6-OCH₃   7-OCH₃

NCH₃

(c)
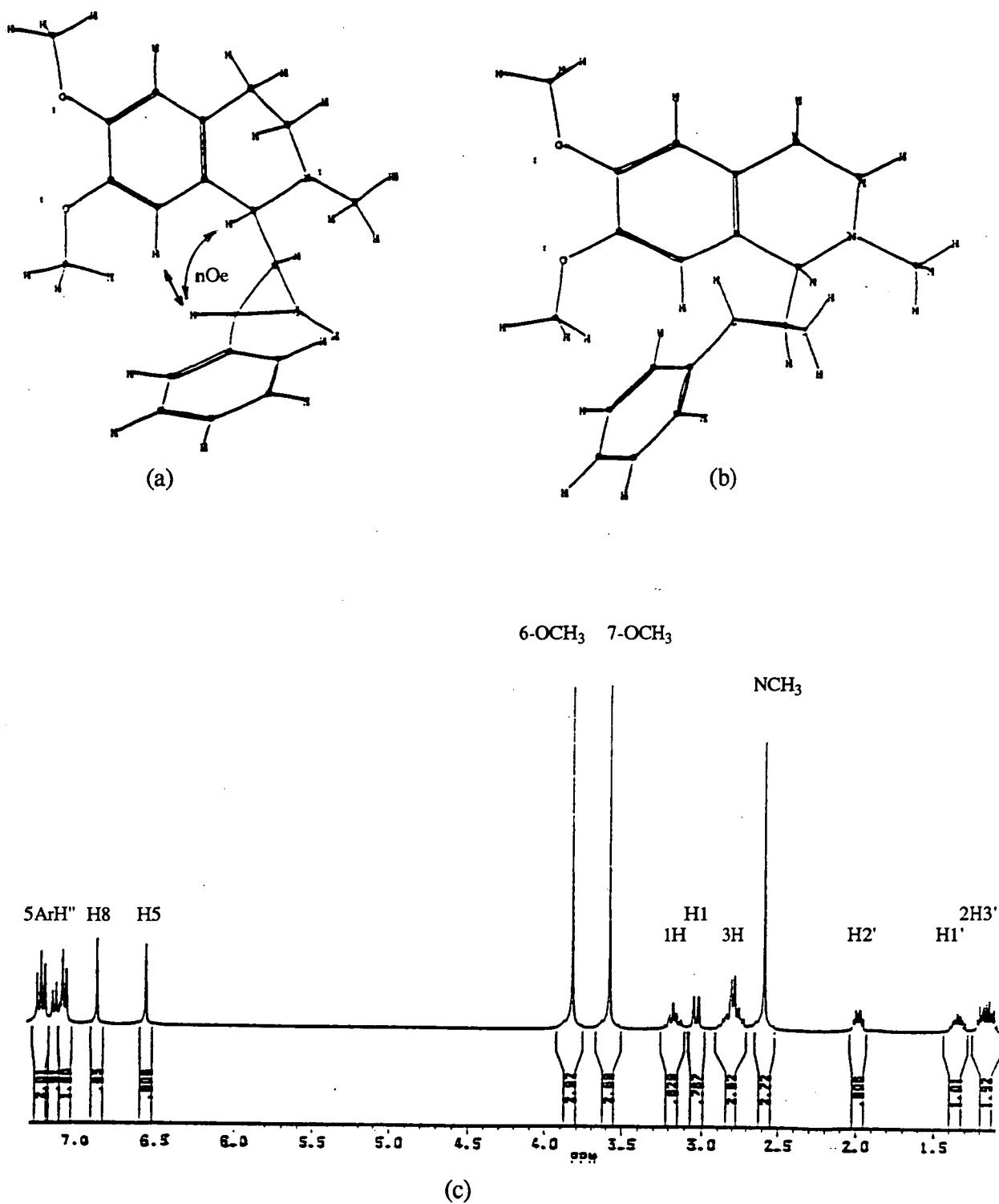
Figure 5.3 The conformers of (a) *RSS*-**177b** and (b) *SSS*-**177b** able to produce deshielding of the

7-methoxy group, and (c) the ¹H NMR spectrum of *RSS*-**177b**.

mixtures of the possible diastereomers, observable by ^{1}H NMR, and were utilised as crude oils.

On consideration of the proposed rearrangements of the quaternary salts **179b**, generated from **177b**, it was apparent that a diastereomeric mixture of **177b** would provide a complex mixture of four diastereomeric benzoxazepines, two diastereomeric *E*-benzazecines and two diastereomeric *Z*-benzazecines. To reduce the difficulty of later analyses, particularly the detection of small amounts of benzazecines, a fraction of almost pure *SSS* **177b** (*SSS/RSS*=19) was obtained by column chromatography on flash silica and this fraction was used in the subsequent *N*-alkylation. Ethyl bromoacetate in refluxing acetone *N*-alkylated **177a,b** to give the quaternary salts **179a,b**, which were used as crude oils. The salts were mixtures of the B-ring diastereomers.

5.4   A Modified Cloke Rearrangement

The *N*-alkylation of the imine **175b** with iodomethane in refluxing acetone produced a precipitate in moderate yield which proved to be an isomer of the expected methiodide salt **176b**. Compound **176b** was present in the filtrate. The molecular weight of the isomer was confirmed by LSIMS-MS in glycerol, with an ion at m/z 322 for the cationic component. The pyrrolo[2,1-*a*]isoquinoline enamine structure **180** was proposed after examination of the ^{1}H and ^{13}C NMR spectra and consideration of the likely reaction mechanisms. An alternative 2-phenyl-2,3-unsaturated enamine, however, appeared consistent with the appearance of the single olefinic proton as a singlet, at 7.18 δ. An n.O.e. difference experiment demonstrated an effect between H10 and the olefinic signal and this supported structure **180**. Two-dimensional homonuclear and heteronuclear correlation NMR experiments (COSY and X-H correlation) were consistent with this structure and afforded the complete assignment of the NMR signals (Figure 5.4).
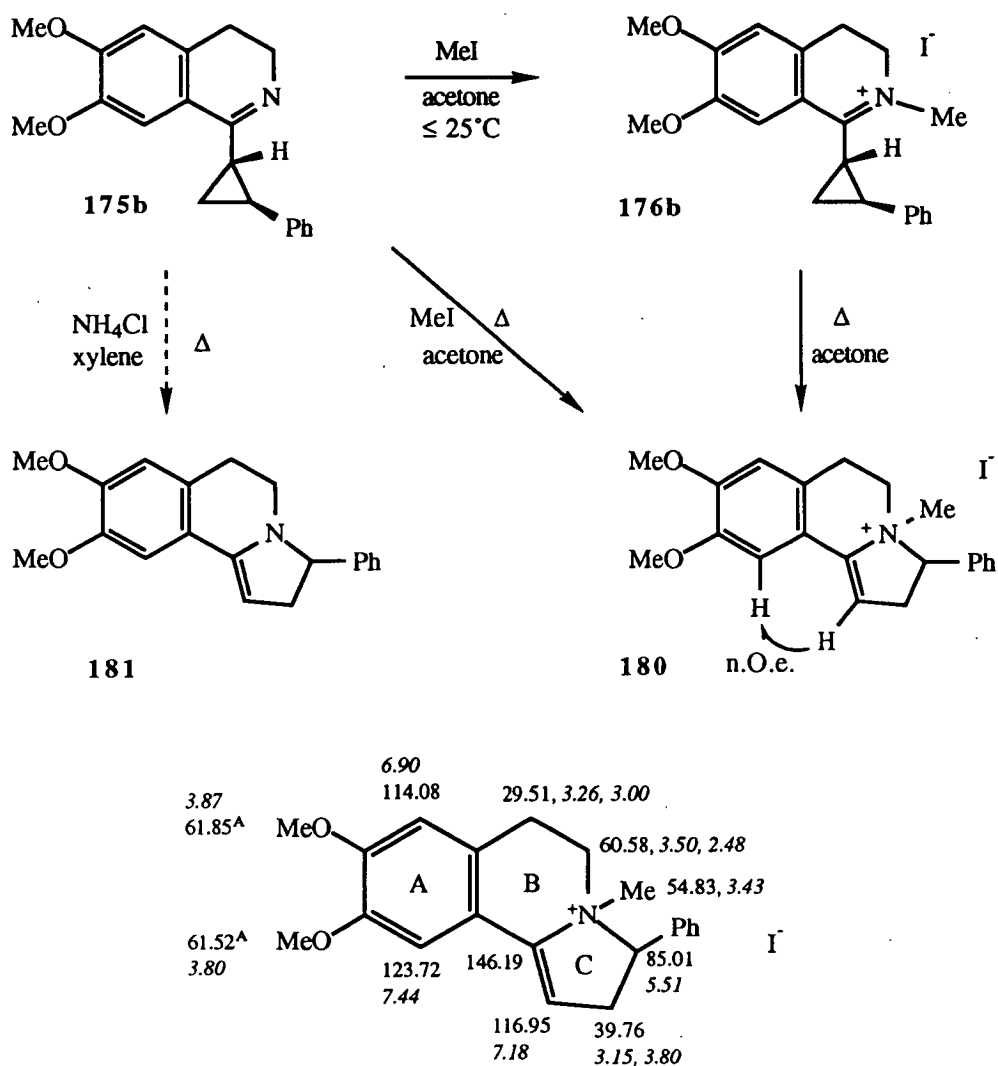
Figure 5.4 ^{13}C and ^{1}H (italics) NMR assignments for **180**

Elemental microanalyses on crystals of **180** from either acetonitrile or methanol failed to provide satisfactory results, despite repeated attempts. The unusual enamine structure of **180** was, however, confirmed unambiguously by a single crystal X-ray structure determination.[168] The compound was identified as the diastereomer of **180** with the 3-phenyl and 4-methyl substituents *trans* to each other across the C-ring (Figure 5.5).

Further experiments demonstrated that **180** was formed via the initial conversion of **175b** to **176b**, then a subsequent cyclopropane ring opening and rearrangement, rather than the alternate sequence. At low temperatures the alkylation of **175b** proceeded selectively to **176b**. This material, after isolation and removal of

excess iodomethane, was isomerised to **180** in good yield by refluxing in acetone for 24 hours. Attempts to dry **176b** at elevated temperatures also produced the partial isomerisation of **176b** to **180**.
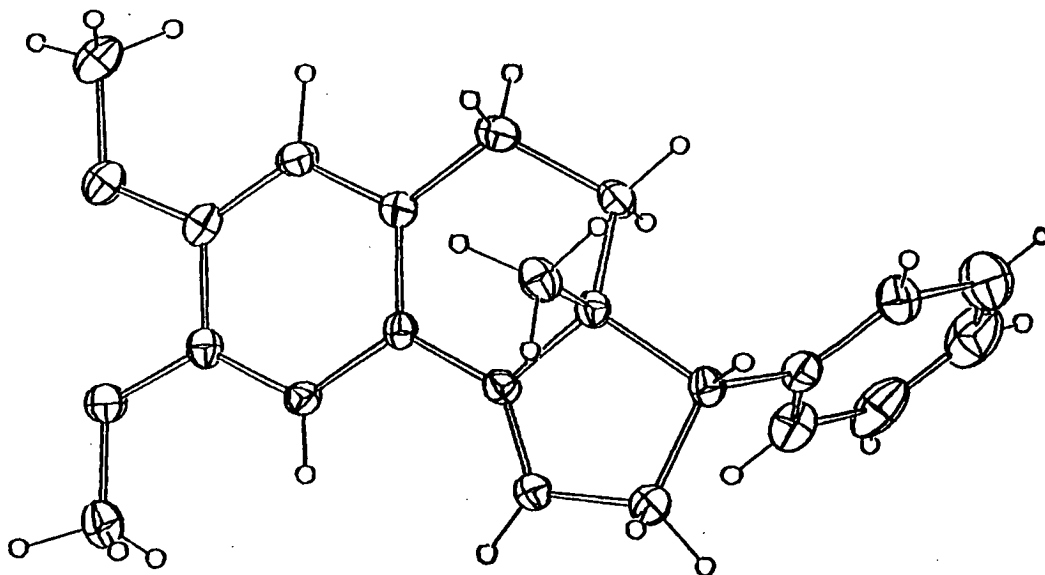
Figure 5.5 X-Ray Crystallographic structure of **180**

The formation of **180** is a variation of the Cloke rearrangement[169] of cyclopropylimines. In this rearrangement the heteroatom may act as either a nucleophile or electrophile to initiate ring opening of the cyclopropane ring and formation of a pyrroline. The promotion of this rearrangement by iodomethane does not appear to have been reported. The Cloke rearrangement normally proceeds from an imine with acid catalysis at elevated temperatures, typically by heating the substrate as a melt, or in xylene, with ammonium chloride above 130°C. The treatment of **175b** under these conditions, at temperatures up to 195°C, failed to afford the expected enamine base **181**. In each case a complex mixture of products was obtained. The Cloke rearrangement of 1-(1'-methyl)cyclopropylisoquinoline hydrochloride salts was reported[170] during the course of this work, although neither

the immediate products of the rearrangement, analogous to **181**, or the subsequent hexahydropyrrolo[2,1-*a*]isoquinoline derivatives were isolated and characterised.

The present results suggest potential for the development of a new route to pyrrolo[2,1-*a*-isoquinoline derivatives via the Cloke rearrangement of 1-cyclopropylisoquinolines.

5.5 Rearrangements of the *N*-Oxides

5.5.1 Treatment of the 1-Cyclopropyl-*N*-oxide

A variety of conditions were tested to investigate the rearrangement of the 1-cyclopropyl *N*-oxide **178a**, as summarised in Table 5.1.

Surprisingly high temperatures and long reaction times were required to produce the rearrangement of **178a**. In acetonitrile at reflux **178a** was unaffected. At 130°C in a butyronitrile/xylene mixture some rearrangement was observed, but a temperature of 143°C in a butyronitrile/mesitylene mixture was necessary to afford substantial rearrangement of **178a**. Butyronitrile was used to dissolve the polar *N*-oxides. It was apparent from these results that the cyclopropyl group was substantially less efficient in promoting the Meisenheimer rearrangement than a vinyl group, reflecting a poor capacity for radical stabilisation.

The crude ether extracts from reactions 2, 3 and 4 (Table 5.1) each contained the same single major component. The p.t.l.c. purification of the product from reaction 4 provided, in good yield, a colourless oil identified as the 1-cyclopropyl-2,3-benzoxazepine **182a**. All spectra were consistent with the proposed structure. The ^{1}H and ^{13}C NMR spectra displayed peaks characteristic of the 1-cyclopropyl group (Table 5.3).

Compound **178a** was also pyrolysed neat in an evacuated vessel at 215°C to determine whether higher temperatures would promote the formation of the 4,3-benzoxazecine **183a**. Two components resulted (1.5:1), with the major component being **182a**. The NMR spectrum of the mixture indicated the second component was

not **183a**. This compound lacked an olefinic peak and possessed the characteristic cyclopropyl signals, and was tentatively assigned as the 1-cyclopropyl-3,2-benzoxazepine formed by the alternate orientation of the Meisenheimer rearrangement towards C3.

MeO (structure **178**)

a: R = H
b: R = Ph

Δ

→

MeO (structure **182**)

+

MeO (structure **183**)
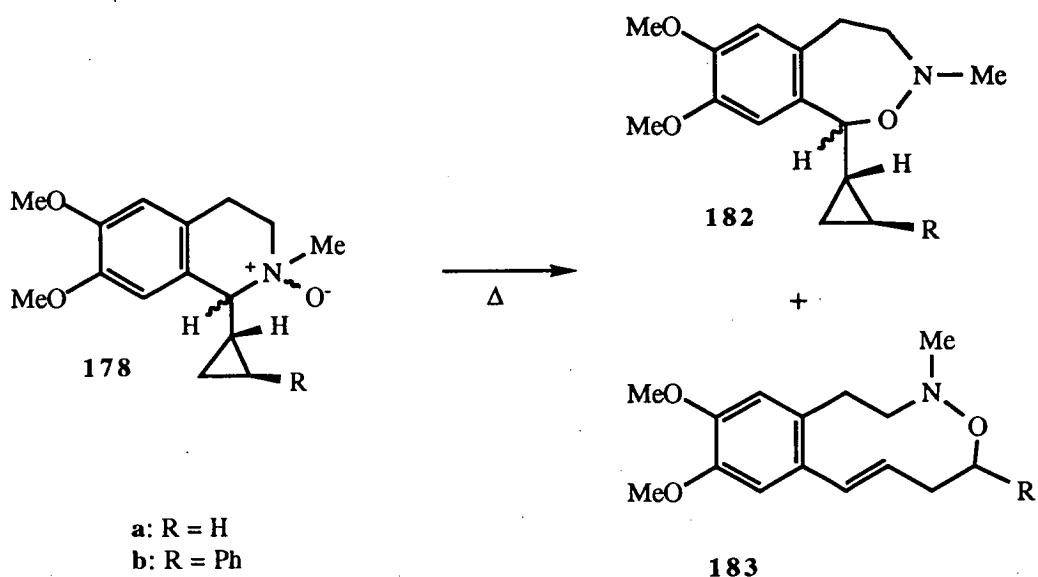
Table 5.1 Treatment of the 1-cyclopropyl *N*-oxide **178a**

Conditions	Temp.°C	time	Result [a]
1. MeCN	82	3 hr	no reaction
2. MeCN, sealed tube	111	6 hr	2%
3. PrCN/Xylene (1:5)	130	5 hr	18%
4. PrCN/Mesitylene (1:5)	143	12 hr	78% [b]
5. neat, evacuated tube	215	15 min.	42%, 2 components
6. MeCN, hv, duran filter	25	1 hr	no change
7. MeCN, hv, vycor filter	25	50 min.	15%, 3 components

[a] yields are for crude ether extracts

[b] p.t.l.c. gave **182a**, 51% yield.

The effect of UV irradiation on **178a** in acetonitrile at room temperature was investigated as an alternative to the thermolytic activation of the reaction. Irradiation at wavelengths above 300 nm were ineffective. Irradiation with light filtered to a lower

minimum of 230 nm promoted the formation of tarry material. The diethyl ether extract of this material showed several components by GC-MS and ^{1}H NMR, one being **182a**. No peaks indicative of **183a** were observed. The major component detected by GC-MS had a molecular weight of 231, a loss of 32 mass units from the *N*-oxide. The mass spectrum of this component was identical to that of the imine **175a**. The conversion of **178a** to **175a** may have occurred by rearrangement and homolytic cleavage (Figure 5.6).
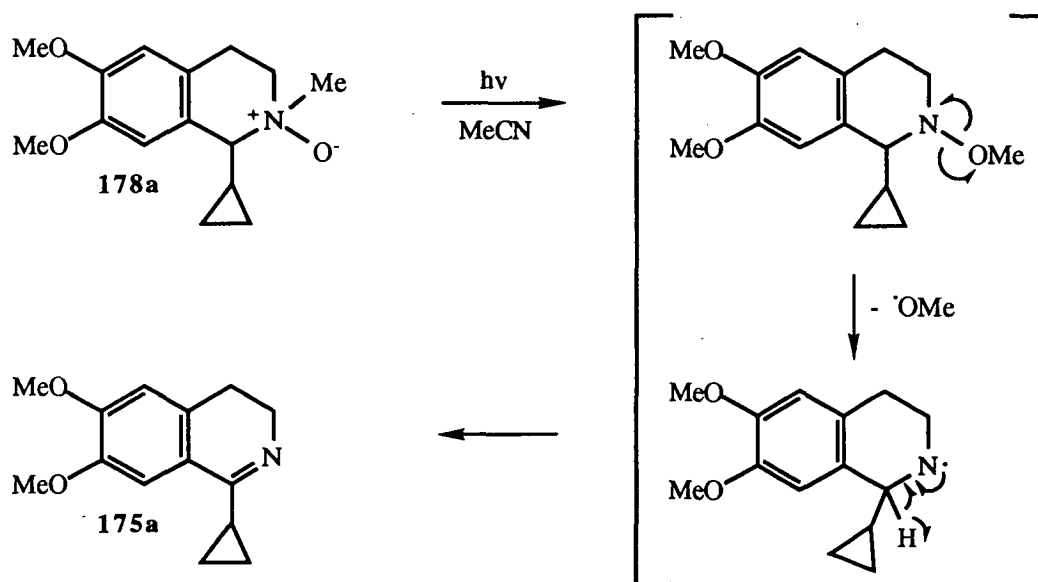
Figure 5.6

5.5.2 Thermolysis of the 1-(*t*-2'-Phenylcyclopropyl)-*N*-oxide to a 4,3-Benzoxazecine Derivative

The thermal rearrangements of **178b** (*SSS/RSS*=0.47) were examined under a variety of conditions, as summarised in Table 5.2.

The behaviour of **178b** was substantially different to that of **178a**. In the presence of the 2'-phenyl substituent the rearrangement was more facile and occurred at lower temperatures. Thus **178b** underwent a slow rearrangement in acetonitrile at reflux and a rapid rearrangement in a butyronitrile/mesitylene mixture at 143°C, affording the complete removal of the *N*-oxide after only 1.5 hours. The extra phenyl

group clearly enhanced the radical stabilising nature of the cyclopropyl substituent by additional electron delocalisation, promoting the cleavage of the C1-N bond in **178b**.

The ^{1}H NMR spectra of the crude rearrangement mixtures from **178b** indicated the presence of three components. The ratio of the components was 55:33:12 from the rearrangement in butyronitrile/mesitylene. The proportion of these compounds was, within the accuracy of this technique, unchanged in the two experiments at lower temperatures. The minor component exhibited a complex multiplet at 5.74 δ consistent with the expected position of the olefinic H7 in the benzoxazecine **183b**. Preparative reverse phase HPLC afforded the isolation of each of the three components. The minor component exhibited the least polar nature and eluted with a retention time 35% greater than the nearest component.

Table 5.2 Thermolysis of the 1-(t-2'-Phenylcyclopropyl)-N-oxide **178b**

Conditions	Temp.°C	time	Result [a]
1. MeCN	82	60 hr	49%
2. PrCN	115	2.5 hr	48%
3. PrCN/Mesitylene (1:5)	143	1.5 hr	84% [b]

[a] yields are for crude ether extracts

[b] HPLC gave **182b**, 23% (*RSS*) and 27% (*SSS*), and **183b**, 9% yield.

Table 5.3 Characteristic NMR Signals for the 1-Cyclopropylbenzoxazepines **182**

	182a	**182b** (*RSS*)	**182b** (*SSS*)
H1, C1	*4.34*, 89.93	*4.53*, 88.78	*4.77*, 87.00
H1', C1'	*1.23*, 15.74	*1.55*, 22.72	*1.57*, 21.53
H2', C2'	*0.65*[a], 4.11[b]	*1.95*, 27.94	*2.05*, 26.99
H3', C3'	*0.52*[a]+*0.42*[a], 3.78[b]	*1.22*, 14.69	*1.13*, 14.07

[a,b] assignments are interchangeable

The two major rearrangement products from **178b**, isolated in 27% and 23% yields respectively from the HPLC purification, were identified as the diastereomeric 2,3-benzoxazepine derivatives **182b** by spectroscopic and elemental analyses. The compounds were crystalline solids and exhibited characteristic cyclopropane, C1, and H1 NMR signals (Table 5.3).

The minor rearrangement product, a crystalline solid, was isolated in 9% yield from the HPLC purification and identified as the desired 4,3-benzoxazecine **183b**, the first example of this ten-membered benz-fused oxaza heterocyclic system. The molecular formula of **183b** ($C_{21}H_{25}NO_3$) was confirmed by elemental microanalysis. All other spectral data were consistent with the proposed structure. The ^{13}C (Figure 5.7) and ^1H (Figure 5.8) NMR spectra confirmed the presence of the olefinic carbon atoms, at 132.25 and 134.45 δ, and the olefinic hydrogen atoms, at 5.74 and 6.65 δ. The magnitude of the H7-H8 coupling constant across the double bond (16 Hz) afforded the identification of the material as the *E* isomer of **183b**.
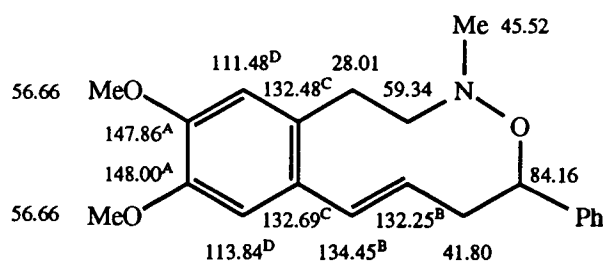
Figure 5.7 ^{13}C NMR assignments for **183b**

The *E*-benzoxazecine **183b** was stable on silica and could be isolated from the diastereomers of **182b** by p.t.l.c. with dichloromethane/1% methanol. This behaviour, in contrast to that of the *E*-benzazonine derivatives (e.g. Section 2.3.3), reflected the greater ability of the 10-membered ring to accommodate a *trans*-double bond without incurring serious ring strain.

The thermal isomerisations of the 2,3-benzoxazepine and 4,3-benzoxazonine derivatives were previously noted (Section 3.5.3) so consequently the thermal behaviour of the 1-cyclopropylbenzoxazepine **182b** was briefly examined. It was
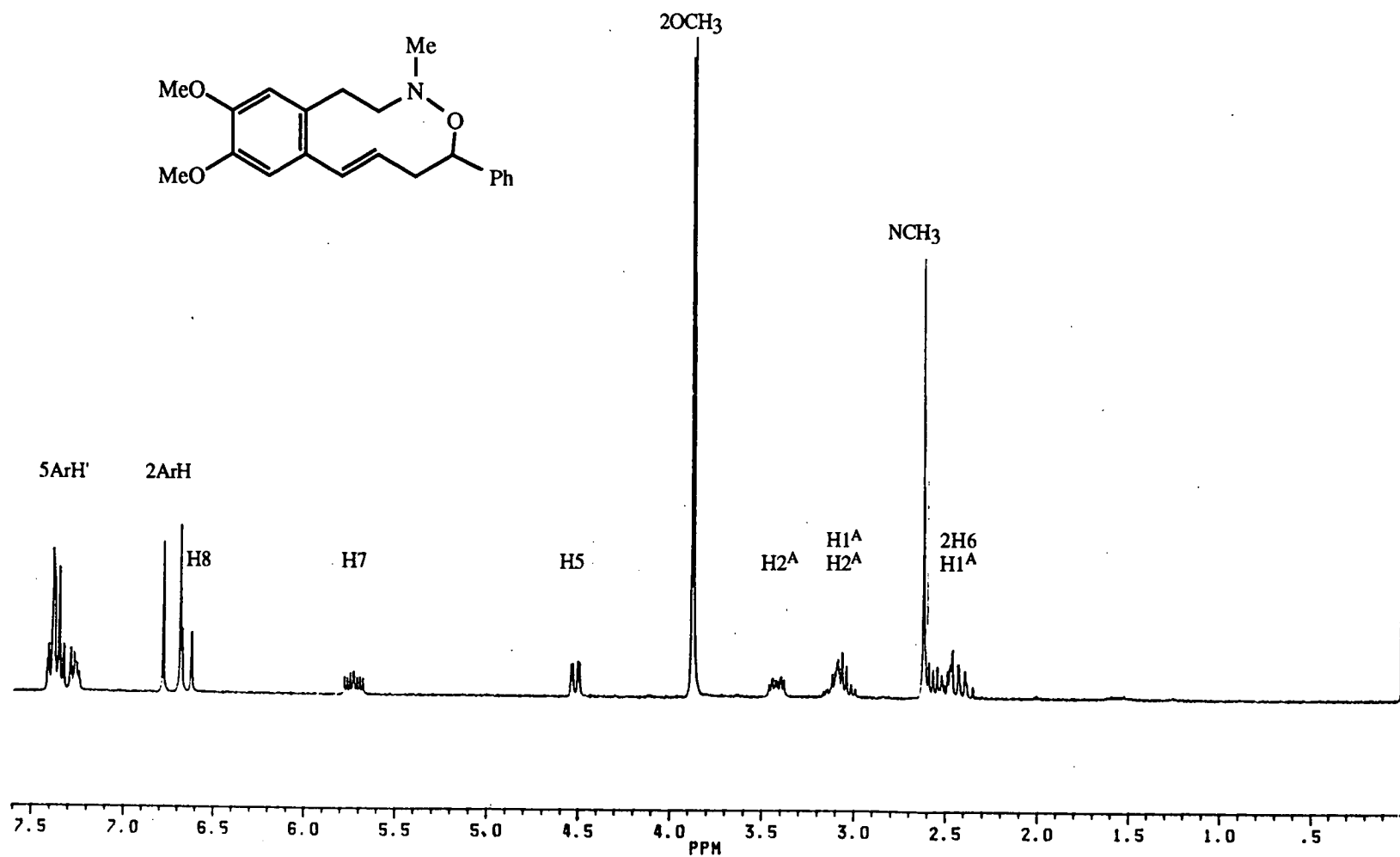
Figure 5.8 ^{1}H NMR spectrum and assignments for **183b** in CDCl$_3$

thought that at high temperatures some isomerisation of **182b** to **183b** may occur, although the benzoxazepines were likely to remain the thermodynamically favoured products. The treatment of a diastereomeric mixture of **182b** at 210°C in an evacuated sealed tube for 30 minutes, however, produced only slight degradation. No evidence for the presence of **183b**, or any other new rearranged isomer, was observed in the ^{1}H NMR spectrum of the thermolysate.

5.6 Modelling and X-Ray Crystal Structure of a 4,3-Benzoxazecine

The low energy conformations available for the 4,3-benzoxazecine **183b** were investigated with PCModel.[76] It was envisaged that the results would aid in any future development of derivatives of the 4,3-benzoxazecine system as CNS active agents. Four low energy conformations within a 5 kcal range were identified for **183b** (Table 5.4). The global minimum, conformer 1, was predicted to have a relatively folded structure (Figure 5.9) in which the nitrogen atom was removed from the aromatic plane by 2.35 Å. The Boltzmann distribution predicted that 79% of **183b** would adopt this conformation at 25°C. The structures of conformers 2, 3, and 4 are included in Appendix A.

<u>Table 5.4</u> Low energy conformations of **183b** predicted by PCModel

conformer	E (kcal)	inc H$_f$	Population[a]	N-elevation[b]	N-Ar planar[c]
1	47.78	-29.71	79.3%	2.35	3.43
2	48.84	-29.64	13.2%	1.83	3.92
3	49.18	-28.25	7.5%	1.54	4.64
4	52.33	-24.97	<0.1%	1.88	4.28

[a] from the Boltzmann distribution at 293 K

[b] distance of N above the aromatic plane (Å)

[c] distance of N from the aromatic centre in the aromatic plane (Å)
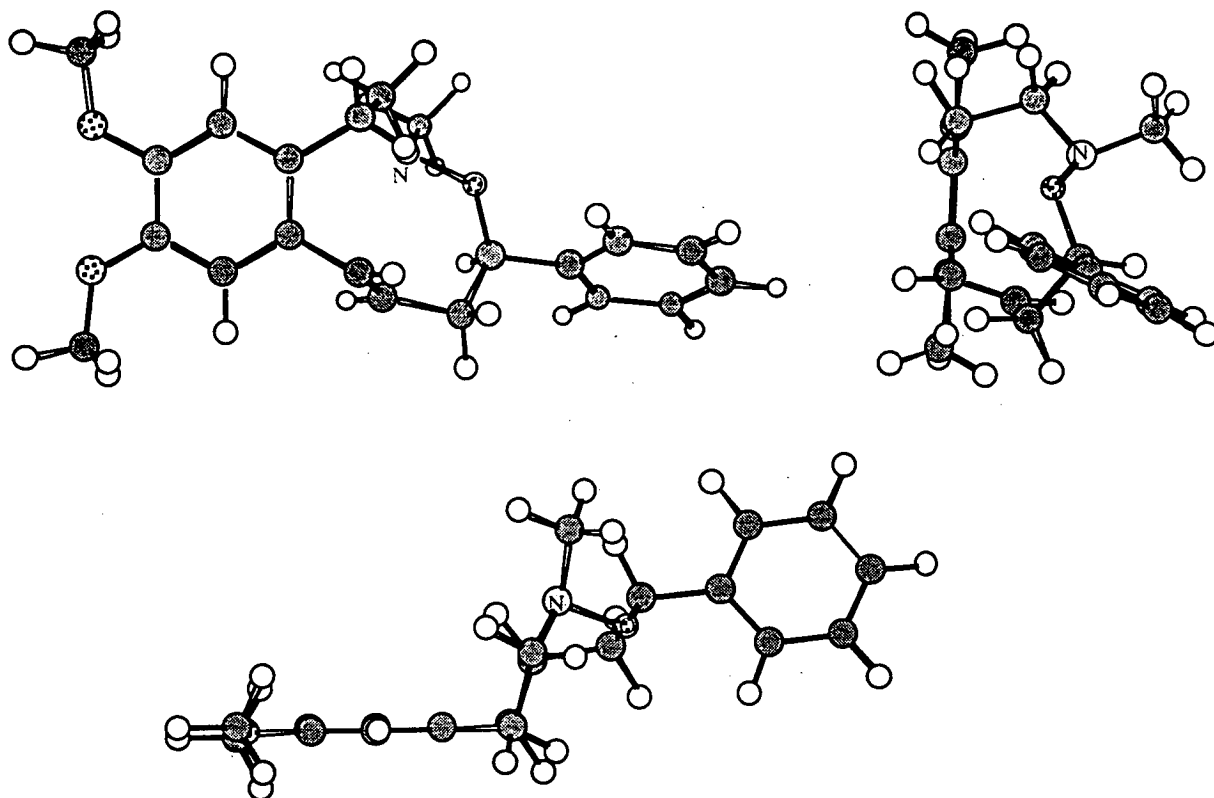
Figure 5.9 Three perspectives of the global minimum predicted for **183b** by PCModel
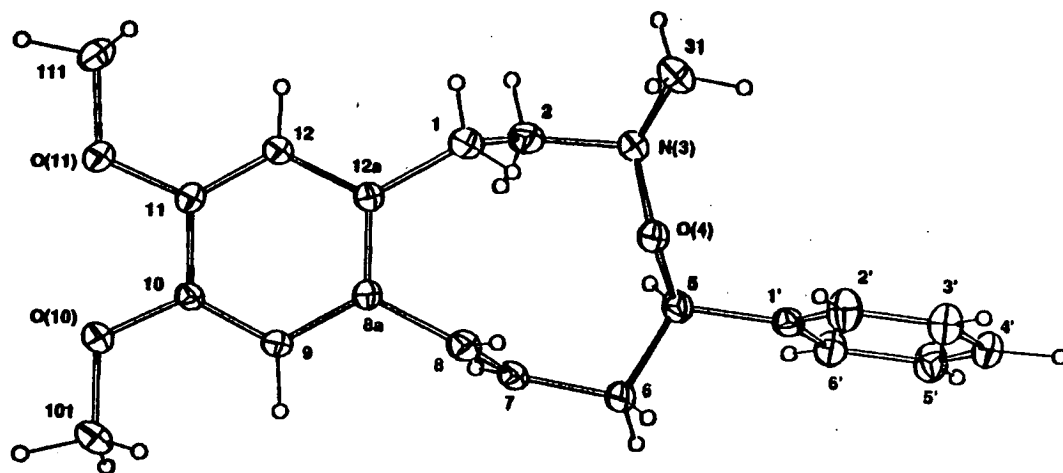
Figure 5.10 X-Ray Crystallographic structure of **183b**

The structure of **183b** was confirmed unequivocally by a single crystal X-ray structure determination.[168] The unsaturated benzoxazecine formed triclinic crystals with a less-folded conformation (Figure 5.10) than that predicted by PCModel. The X-ray structure corresponded to conformer 3 (Table 5.4) identified by PCModel, with the nitrogen atom only 1.54 Å above the aromatic plane and further from the aromatic centre than in conformer 1.

The discrepancy between the conformation predicted by PCModel and that determined by X-ray techniques may indicate a real difference between the conformers preferred in the solid state, or in solution, and the theoretical vacuum assumed by PCModel. The comparison of several bond lengths predicted by PCModel with those determined by the X-ray analysis (Table 5.5), however, suggested that the parameters used to define the PCModel forcefield were not accurate for the strained medium ring system. These differences may have altered the calculated conformational energies, and thus their order, for the confined medium ring. The results highlighted the limitations of molecular mechanics based modelling programs when applied to strained medium-ring systems and emphasised that care must be taken in interpreting studies of this type. Conformers 1 and 3 of **183b** would be predicted to have substantially different CNS activity. Time did not permit further conformational assessments using other modelling programs and the incorporation of solvent (water) molecules.

Table 5.5 Bond Lengths Determined for Conformer 3 of **183b** (Å)

bond	PCModel	X-Ray
C1-C2	1.544	1.519
N-O	1.483	1.458
C7=C8	1.342	1.299
C8a-C12a	1.406	1.390

5.7   Rearrangements of the *N*-Ylides

5.7.1 Behaviour of the 1-Cyclopropyl Salt

A variety of conditions were examined to determine those necessary to provide the rearrangement of **179a**. These are summarised in Table 5.6.

At room temperature in acetonitrile with DBU no rearrangement of **179a** occurred. It was necessary to conduct the reaction in refluxing butyronitrile or acetonitrile to obtain substantial rearranged fractions. The results reflected the poor radical stabilisation offered by the cyclopropane group. The ^{1}H NMR spectra of the rearranged fractions suggested the major products were the diastereomers of the 3-benzazepine **184a**, however, additional olefinic peaks were observed. The fractions were purified by p.t.l.c. on silica with dichloromethane/5% ethanol to give, in each case, four components (Table 5.6).

The two major components isolated by p.t.l.c. were shown by their characteristic NMR spectra to be the products of the Stevens rearrangement, the B-ring diastereomers of the 1-cyclopropyl-3-benzazepine **184a**. The two remaining components contained olefinic protons with signals in the ^{1}H and ^{13}C NMR (with DEPT editing) characteristic of a terminal methylene group. Further examination confirmed the compounds were the geometric isomers of the ring opened diene **83b** previously isolated in this work (Section 2.6.1). The dienes were formed at approximately the same level relative to the benzazepines in both refluxing acetonitrile and butyronitrile. No trace of the desired 3-benzazecine **185a** was detected from these reactions.

A radical pathway involving hydrogen abstraction via the intermediate **186** may account for the formation of the dienes, however, a concerted pathway directly from the *N*-ylide **187** cannot be excluded. The cyclopropane ring is known to participate in place of double bonds in sigmatropic reactions[171] such as the homodienyl [1,5] hydrogen shift.

a: R = H
b: R = Ph

179 → **184** (Base)

185

83b
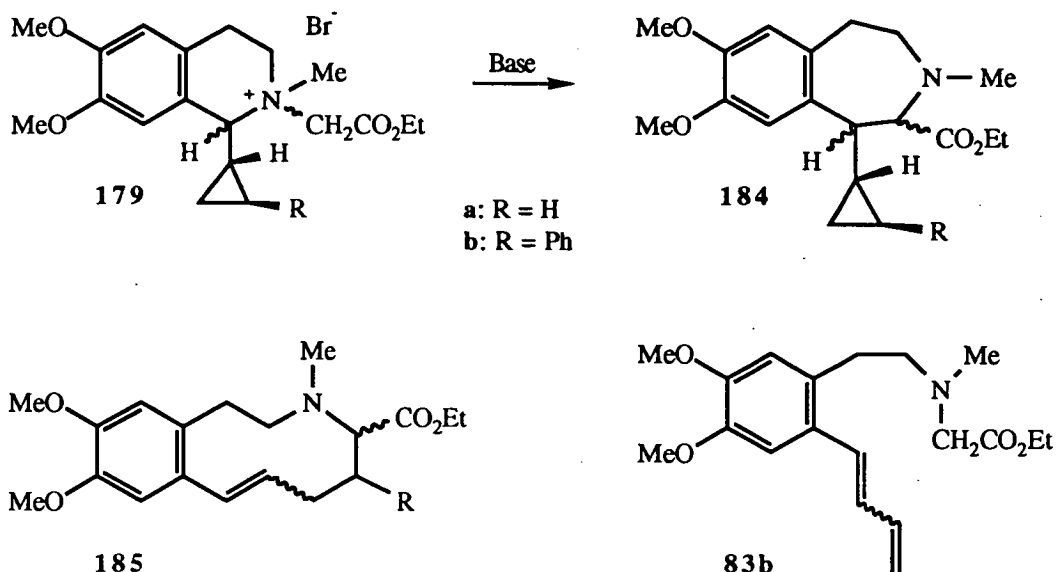
Table 5.6 Treatment of the 1-cyclopropyl salt **179a**

Conditions	Temp.°C	time	Result [a]
1. MeCN, 1.3 equiv. DBU	25	60 hr	no reaction
2. MeCN, 1.3 equiv. BuLi	40	44 hr	26%
3. MeCN, 4.6 equiv. DBU	40	48 hr	12%
4. CHCl₃, 1.3 equiv. DBU	62	67 hr	50%
5. MeCN, " " "	82	5 hr	48%[b], 4 components
6. PrCN, " " "	115	8.5 hr	90%[c], 4 components

[a] crude fractions obtained by passage through alumina with DCM/10% L.P.

[b] p.t.l.c. gave diastereomers of **184a**, 32% and 9%, and **83b**, 8% and 4%

[c] p.t.l.c. gave diastereomers of **184a**, 45% and 17%, and **83b**, 14% and 5%

186

187
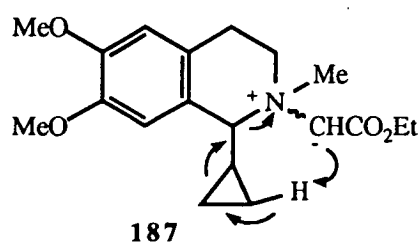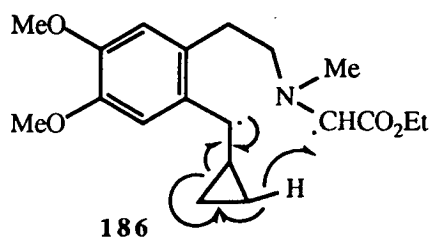
As the proposed modified Stevens rearrangement may occur by a concerted mechanism the products obtained from lower temperature reactions (2, 3, and 4 in Table 5.6) were examined. In each case NMR analysis confirmed the benzazepines were the major products with traces of the dienes. No peaks attributable to **185a** were observed. A large excess of DBU failed to afford the substantial rearrangement of **179a** at 40°C. It was reasoned that the reversible base may hinder the rate of any rearrangement by allowing the formation of an equilibrium between the ylide and salt forms of **179a**. The reaction rate was increased with the use of the non-reversible base butyl lithium, but no change in the product distribution was observed. The reaction in refluxing chloroform afforded the same products.

5.7.2 Behaviour of the 1-(*t*-2'-Phenylcyclopropyl) Salt

Compound **179b** was synthesized for this examination from almost pure *SSS* **177b** (*SSS/RSS*=19), thus reducing the number of potential diastereomeric products and minimising the complexity of the expected reaction mixture.

The treatment of **179b** with DBU in refluxing butyronitrile for 8.5 hours provided, after preliminary purification on an alumina column, a rearranged fraction in 67% yield. The analysis of this material by NMR spectroscopy suggested the B-ring diastereomers of the 1-(*t*-2'-phenylcyclopropyl)-3-benzazepine **184b** were present. No peaks were observed in the ^{1}H NMR spectrum between 6.5 and 4.5 δ, precluding the presence of either the desired 3-benzazecine **185b** or any undesired ring-opened dienes. Preparative HPLC purification afforded a mixture (1.66:1) of the diastereomers of **185b** in moderate yield. The diastereomers could not be separated and were identified on the basis of the ^{1}H and ^{13}C NMR spectra of the mixture. Although three very minor components were isolated by the preparative HPLC analysis each contained substantial impurities and none possessed NMR spectra consistent with the desired 3-benzazecine derivative.

5.8   Discussion

The 1-cyclopropylisoquinoline *N*-oxides and *N*-ylides were found to undergo predominantly the normal Meisenheimer and Stevens rearrangements. The cyclopropane substituent provided only weak activation in these rearrangements. Higher temperatures were necessary than for the rearrangements of the 1-vinylisoquinoline analogues. Clearly, however, the cyclopropane ring was able to act in a similar manner to an olefin and partake in a π bonding system, as the addition of a 2' phenyl substituent significantly increasing the rate of the rearrangement of **178b** over **178a**, consistent with increased stabilisation of the initial C1-N homolytic cleavage.

The present results supported the formation of the 4,3-benzoxazecine **183b** by the proposed radical mechanism (Figure 1.7, pg. 11), with C1-N homolysis followed by ring opening of the substituted cyclopropylcarbinyl radical prior to radical recombination. The 2-phenyl substituent is known to increase the rate constant[172,173] for cyclopropylcarbinyl radical ring opening by a factor of approximately 10^3, from 1.2×10^8 s^{-1} at 37°C for the unsubstituted radical to 4×10^{11} s^{-1} at 45°C, and can account for the formation of **183** from **178b** and not **178a**. At this faster rate significant cyclopropylcarbinyl ring opening apparently occurred before the normal radical recombination of the Meisenheimer rearrangement.

pro-*trans*   pro-*cis*

Figure 5.11   Cyclopropylcarbinyl Radical Geometries.

The observed selectivity of the four atom ring expansion to the *E*-4,3-benzoxazecine may be rationalised by considering the non-bonded interactions[174] in the α-substituted cyclopropylcarbinyl radical. The Walsh model[171] of cyclopropane

bonding proposed the existence of p orbitals in the plane of the cyclopropane ring able to participate in π bonding. Thus for ring opening the radical would adopt either of the conformers shown in Figure 5.11. Non-bonded interactions will be minimised in the geometry leading to the *trans*-olefin and the simple α-methylcyclopropylcarbinyl radical produced[172] predominantly the *E*-olefin (E/Z=1.88) at 37°C. The stereoselective rearrangement of the cyclopropylcarbinyl radicals to *E*-olefin products may limit the applications of this new ring expansion, as the formation of smaller medium-sized rings with an endocyclic *E*-olefin will be energetically unfavourable.

The failure of the *N*-ylide **179b** to undergo any four atom ring expansion suggested the Stevens rearrangement occurred with greater rapidity than the Meisenheimer rearrangement, possibly due to the lower stability of the carbon radical and a more concerted-like transition state, possessing less radical nature. The experiments described herein (Chapters 2 and 3) highlighted the greater preference for *N*-ylides to rearrange via a concerted pathway. The formation of the diene **83b** from **179a** and not **179b** contradicted expectations based on a diradical pathway, for which the phenyl substituent of **179b** should promote 2'-hydrogen abstraction. This behaviour may be rationalised by proposing that the less stabilised 1-cyclopropyl **179a** adopted a low energy concerted pathway for the formation of the diene, while the greater resonance stabilisation of 1-(2'-phenylcyclopropyl) **179b** allowed the diradical Stevens rearrangement to occur at a lower energy than any concerted pathway.

5.9   Conclusion

Although the Meisenheimer and Stevens rearrangements predominated from the reactions of the 1-cyclopropylisoquinoline *N*-ylides and *N*-oxides a single example of the proposed four atom ring expansion was observed. Thus it was demonstrated that the proposed reaction was mechanistically feasible and may, with the appropriate modification of the substrate, find synthetic applications in the production of medium

ring heterocycles. The rearrangement provided the first example of the 4,3-benzoxazecine ring system, compound **183b**.

The present results suggested two strategies for the future development of the four atom ring expansion and its applications in organic synthesis. Firstly, the further acceleration of the cyclopropylcarbinyl radical ring opening by the appropriate placement of substituents either on the cyclopropane ring, the fused aromatic ring, or at C1, should be examined. A *cis*-2'-substituent for example may increase the cyclopropylcarbinyl ring opening rate due to the relief of additional steric strain. Secondly, the retardation of the radical attack on the α carbon by the presence of a bulky α substituent, or tailoring the ring system to prevent [1,2] radical recombination, could be examined. It should be noted that an α-phenyl group, effectively present in these 1-cyclopropylisoquinoline rearrangements, reduced the cyclopropylcarbinyl ring opening rate constant.[175] Consequently the rearrangements of other non-benz fused ring systems should be investigated.

CHAPTER 6

EXPERIMENTAL

6.1   General Procedures

Microanalyses were carried out by the Central Science Laboratory, University of Tasmania, Hobart.

Melting points were determined on a Yanagimoto Seisakusho micromelting point apparatus, and are uncorrected.

Infra-red spectra were recorded on a Digilab FTS-20E Fourier transform spectrometer.

The ultra-violet spectra were recorded on a Varian DMS 100 UV-Visible spectrophotometer. Analyses were conducted on solutions in acetonitrile.

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer at 300 and 75 MHz respectively. The DEPT.AUR microprogram was used routinely to determine the degree of protonation of the carbon resonances. The standard two-dimensional programs, COSY.AUR and XHCORR.AUR, were used when necessary to afford the unambiguous assignment of the resonances. The NOEDIFF.AUR pulse program was used for the measurement of nuclear Overhauser effects by the difference technique. Chemical shifts in ppm (δ) were measured relative to tetramethylsilane. Unless otherwise stated, the NMR spectra were measured in deuterated chloroform. Peaks are reported as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q) or multiplet (m). The ^{13}C NMR assignments indicated by superscript letters may be interchanged as defined by those letters. Where samples in the ^{13}C NMR exhibited several conformers, or isomers, the chemical shift for the major form is given first for each signal type; different forms are denoted with superscripts a,b or x,y in the ^{1}H NMR spectra.

The mass spectra were recorded on either a VG MM 7070F or a Kratos Concept ISQ mass spectrometer operating at 70 eV. Peak intensities in parentheses

are expressed as a percentage of the base peak. GC-MS analyses were performed on a Hewlett Packard 5790 Mass Selective Detector coupled to an HP 5890 gas chromatograph fitted with a direct capillary interface and an HP-1 capillary column.

Analytical thin layer chromatography (t.l.c.) and preparative thin layer chromatography (p.t.l.c.) were performed on either Merck silica gel 60 F_{254} or Camag DSF-5 aluminium oxide. All column chromatography was performed under medium-pressure ("flash chromatography") on either Merck silica gel 60, 230-400 mesh, or on type H aluminium oxide, 100-200 mesh. Preparative HPLC utilised a Dynamax-60A C18 reverse-phase column with a Waters 600 multisolvent delivery system and Waters 486 tunable UV detector. Samples were eluted at 10ml/min and monitored at 254 nm. Mixtures of the chromatography solvents were made up by volume.

Ultraviolet irradiation was conducted at 5-10°C under nitrogen in a water-cooled, immersion-type photochemical reactor (quartz inner vessel) using a Hanovia 450-Watt medium-pressure mercury arc lamp with glass filter sleeves. The solution was stirred magnetically during the irradiation.

Organic solvent extracts were dried with anhydrous sodium sulfate. Where reaction mixture solutions or solvent extracts were concentrated this refers to evaporation under reduced pressure on a rotary evaporator.

Organic solvents and reagents were purified and dried by standard techniques.[176] When anhydrous conditions were necessary the glassware and solvents were dried and the additions or transfers were made via gas-tight syringes or stainless steel tubing, under a positive pressure of nitrogen. Light petroleum refers to a fraction boiling between 60-80°C. Vinylmagnesium bromide was prepared in tetrahydrofuran as described by Normant,[84] with a low temperature condensor (acetone/dry ice) to contain the vinyl bromide. Ethoxycarbonylmethyltriflate was prepared by the method of Vedejs et. al.[88,89]

Abbreviations for hours (h.), minutes (min.), days (d.), 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), and *meta*-chloroperoxybenzoic acid (*m*-CPBA) are adopted throughout the experimental.

6.2   Experimental for Chapter Two

6,7-Dimethoxy-3,4-dihydroisoquinoline 47

Homoveratrylamine (32.22 g, 0.178 mol) and formic acid (12.81 g, 0.278 mol) were heated at 170°C under nitrogen for 2 h. The melt was maintained at this temperature for a further 2 h. under a slow stream of nitrogen, to remove the majority of water and excess formic acid, then further dried under oil-pump vacuum at 140°C for 1 h. The melt was allowed to cool below 100°C and dry toluene (375 ml) was added before the melt solidified. The resultant solution was treated with phosphorus oxychloride (98.7 g, 0.644 mol) then refluxed for 2 h. under nitrogen. Upon cooling a dark oil separated. The toluene layer was decanted onto a mixture of ice (50 g) and water (50 ml) while to the residual oil was added ice (150 g). After 45 min. the aqueous solutions were combined and basified by the slow addition of 80% aqueous sodium hydroxide to pH 11, then extracted with chloroform (4 x 150 ml). The organic extracts were concentrated to a volume of approximately 70 ml and extracted with 12% aqueous hydrochloric acid (3 x 45 ml) and water (50 ml). The aqueous extracts were again basified to pH 11, then extracted with chloroform (4 x 75 ml). The organic extracts were dried and then concentrated to give the imine[71] 47 (25.69 g, 75%) as a yellow oil which was used without further purification. ^{1}H NMR δ: 8.23 (s, H1), 6.81 (s, ArH), 6.68 (s, ArH), 3.92 (s, OCH₃), 3.90 (s, OCH₃), 3.73 (t, H3), 2.68 (t, H4); MS m/z: 191 (M⁺, 100%), 176 (78), 146 (13), 91 (16), 77 (25).

6,7-Dimethoxy-2-methyl-3,4-dihydroisoquinolinium Iodide 48a

To 47 (13.05 g, 68.25 mmol) in dry toluene (50 ml) was added iodomethane (31.98 g, 227 mmol). After 30 min. the deposited solid was collected and dried

Abbreviations for hours (h.), minutes (min.), days (d.), 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), and *meta*-chloroperoxybenzoic acid (*m*-CPBA) are adopted throughout the experimental.

6.2   Experimental for Chapter Two

6,7-Dimethoxy-3,4-dihydroisoquinoline 47

Homoveratrylamine (32.22 g, 0.178 mol) and formic acid (12.81 g, 0.278 mol) were heated at 170°C under nitrogen for 2 h. The melt was maintained at this temperature for a further 2 h. under a slow stream of nitrogen, to remove the majority of water and excess formic acid, then further dried under oil-pump vacuum at 140°C for 1 h. The melt was allowed to cool below 100°C and dry toluene (375 ml) was added before the melt solidified. The resultant solution was treated with phosphorus oxychloride (98.7 g, 0.644 mol) then refluxed for 2 h. under nitrogen. Upon cooling a dark oil separated. The toluene layer was decanted onto a mixture of ice (50 g) and water (50 ml) while to the residual oil was added ice (150 g). After 45 min. the aqueous solutions were combined and basified by the slow addition of 80% aqueous sodium hydroxide to pH 11, then extracted with chloroform (4 x 150 ml). The organic extracts were concentrated to a volume of approximately 70 ml and extracted with 12% aqueous hydrochloric acid (3 x 45 ml) and water (50 ml). The aqueous extracts were again basified to pH 11, then extracted with chloroform (4 x 75 ml). The organic extracts were dried and then concentrated to give the imine[71] 47 (25.69 g, 75%) as a yellow oil which was used without further purification. ^{1}H NMR δ: 8.23 (s, H1), 6.81 (s, ArH), 6.68 (s, ArH), 3.92 (s, OCH_3), 3.90 (s, OCH_3), 3.73 (t, H3), 2.68 (t, H4); MS m/z: 191 (M⁺, 100%), 176 (78), 146 (13), 91 (16), 77 (25).

6,7-Dimethoxy-2-methyl-3,4-dihydroisoquinolinium Iodide 48a

To 47 (13.05 g, 68.25 mmol) in dry toluene (50 ml) was added iodomethane (31.98 g, 227 mmol). After 30 min. the deposited solid was collected and dried

briefly under vacuum. Recrystallisation of the solid from ethanol gave the salt[71] **48a** (19.61 g, 86%) as yellow crystals with m.p. 201-202°C. ^{1}H NMR δ: 9.82 (s, H1), 7.62 (s, H8), 6.87 (s, H5), 4.03 (t, H3), 4.01 (s, NCH3), 3.93 (s, OCH3), 3.94 (s, OCH3), 3.32 (t, H4).

2-Benzyl-6,7-dimethoxy-3,4-dihydroisoquinolinium Chloride **48b**

To **47** (12.17 g, 63.64 mmol) in dry toluene (50 ml) was added benzyl chloride (25.24 g, 199 mmol). After stirring for 12 h. the deposited solid was collected. The filtrate was warmed at 60°C for 2 h. then concentrated to approximately 20 ml. After cooling a second batch of crystals was collected. The solids were combined and recrystallised from acetonitrile to give the salt **48b** (17.93 g, 89%) as a yellow solid with m.p. 181-183°C. ^{1}H NMR δ: 10.84 (s, H1), 7.67 (s, H8), 7.60 (s, 2ArH'), 7.36 (s, 3ArH), 6.86 (s, H5), 5.54 (s, NCH2Ar), 3.99 (s, OCH3), 3.93 (t, H3), 3.90 (s, OCH3), 3.17 (t, H4); ^{13}C NMR δ: 166.05 (C1), 157.85 (C7), 149.07 (C6), 132.24 (C1'^{A}), 132.05 (C8a^A), 129.86-129.66 (5C'), 117.65 (C4a^A), 116.28 (C5^B), 111.10 (C8^B), 63.30 (NCH2Ar), 56.91 (OCH3), 56.83 (OCH3), 47.47 (C3), 25.84 (C4).

6,7-Dimethoxy-2-methyl-1-vinyl-1,2,3,4-tetrahydroisoquinoline **49a**

(i) Vinylmagnesium bromide in dry tetrahydrofuran (190 ml) under nitrogen was prepared from vinyl bromide (25.8 g, 0.241 mol). The solution was cooled in an acetone/liquid nitrogen slush bath to -78°C, with the deposition of some solid, and then the iminium salt **48a** (19.60 g, 58.8 mmol) was added portionwise over 30 min. The mixture was allowed to warm slowly to room temperature with stirring for 12 h. and then ice was added carefully to decompose the excess Grignard reagent. The mixture was then basified by the addition of 40% aqueous potassium hydroxide and the tetrahydrofuran solution was decanted from the resultant inorganic salts. The tetrahydrofuran solution was treated with diethyl ether (100 ml) and water (50 ml) and the organic layer was collected. The inorganic salts and the aqueous solution

were extracted successively with further portions of diethyl ether (3 x 100 ml). All the organic solutions were then combined and washed with water (2 x 20 ml), then dried and concentrated. Passage of a dichloromethane solution of the crude solid through an alumina plug, then evaporation of the solvent and recrystallisation of the residue from ethanol, gave the *1-vinylisoquinoline* **49a** (9.46 g, 69%) as an off-white solid with m.p. 69-70°C. ^{1}H NMR δ: 6.60 (s, ArH), 6.59 (s, ArH), 5.79-5.67 (m, H1'), 5.35 (dd, *J* 1.5 Hz, 8.8 Hz, H2'), 5.30 (dd, *J* 1.5 Hz, 17.0 Hz, H2'), 3.83 (s, OCH$_3$), 3.80 (s, OCH$_3$), 3.66 (d, *J* 8.8 Hz, H1), 3.06-2.95 (m, 2H), 2.71-2.66 (m, H), 2.56-2.49 (m, H), 2.41 (s, NCH$_3$); ^{13}C NMR δ: 148.02 (C6^A), 147.42 (C7^A), 139.77 (C1'), 127.88 (C4a^B), 126.51 (C8a^B), 119.11 (C2'), 111.52 (C5^C), 111.06 (C8^C), 69.74 (C1), 56.17 (2OCH$_3$), 51.57 (C3), 44.17 (NCH$_3$), 28.83 (C4); MS m/z: 233 (M$^+$, 29%; Calcd. for C$_{14}$H$_{19}$NO$_2$ 233.1415, found 233.140), 232 (19), 207 (40), 206 (100), 190 (43), 103 (16); Anal. Calcd for C$_{14}$H$_{19}$NO$_2$: C, 72.07; H, 8.21; N, 6.01%, found: C, 72.10; H, 8.27; N, 5.95%.

(ii) Vinylmagnesium bromide in dry tetrahydrofuran (100 ml) under nitrogen was prepared from vinyl bromide (11.8 g, 0.111 mol). To this solution at room temperature was added the iminium salt **48a** (9.07 g, 27.2 mmol) portionwise over 30 min. A mild exotherm occurred. The mixture was refluxed for 3 h. then cooled and worked up (as for (i)) to give, on concentration of the dichloromethane solution, a tan solid (5.93 g). A portion of this solid (0.772 g) was purified by p.t.l.c. on silica with dichloromethane/12% methanol to give **49a** (0.313 g) and a mixture (46:54) of the phenolic compounds *6-hydroxy-7-methoxy-2-methyl-1-vinyl-1,2,3,4-tetrahydroisoquinoline* and *7-hydroxy-6-methoxy-2-methyl-1-vinyl-1,2,3,4-tetra-hydroisoquinoline* as a yellow oil (0.244 g) from a single band. ^{1}H NMR δ: 6.58 (s, ArH), 6.54 (s, ArH), 6.51 (s, ArH), 6.46 (s, ArH), 6.19 (bs, ArOH), 5.82-5.67 (m, 2H), 5.34-5.18 (m, 4H), 3.82 (s, OCH$_3$), 3.80 (s, OCH$_3$), 3.73-3.57 (m, 2H), 3.08-2.91 (m, 4H), 2.69-2.48 (m, 4H), 2.40 (s, 2NCH$_3$); ^{13}C NMR δ: 146.52 and 146.00 (C6^A), 145.24 and 144.54 (C7^A), 139.79 and 139.41 (C1'), 128.40 and 127.01 (C4a^B), 126.84 and 125.50 (C8a^B), 119.34 (C2'), 115.20 and 114.68 (C5^C), 111.20

and 110.77 (C8^C), 69.95 and 69.69 (C1), 56.21 (OCH$_3$), 51.66 (C3), 44.26 (NCH$_3$),

28.78 and 28.44 (C4); MS m/z: 219 (M$^+$, 8%), 218 (6), 192 (100), 177 (20), 162 (6).

The treatment of this phenolic mixture in the minimum of dry methanol at 0°C with

excess diazomethane in diethyl ether provided, after stirring at 0°C for 12 h., **49a**

(0.205 g, 79%).

2-Benzyl-6,7-dimethoxy-1-vinyl-1,2,3,4-tetrahydroisoquinoline 49b

A solution of vinylmagnesium bromide in dry tetrahydrofuran (195 ml) under

nitrogen was prepared from vinyl bromide (22.7 g, 0.213 mol). The solution was

cooled in an acetone/liquid nitrogen slush bath to -78°C, with the deposition of some

solid, and then the iminium salt **48b** (16.98 g, 53.43 mmol) was added portionwise

over 30 min. The mixture was allowed to warm slowly to room temperature with

stirring for 18 h. and then worked up (as for compound **49a**) to give the *1-*

vinylisoquinoline **49b** (15.72 g, 95%) as an off-white solid from ethanol with m.p.

106-107°C. ^{1}H NMR δ: 7.39-7.23 (m, 5ArH), 6.61 (s, ArH), 6.58 (s, ArH), 5.96-

5.84 (m, H1'), 5.34-5.23 (m, H2'), 4.06 (d, *J* 13.6 Hz, H of CH$_2$Ph), 4.00 (d, *J* 8.4 Hz,

H1), 3.83 (s, OCH$_3$), 3.80 (s, OCH$_3$), 3.42 (d, *J* 13.6 Hz, H of CH$_2$Ph), 3.06-2.98 (m,

H), 2.77-2.69 (m, 2H), 2.52-2.44 (m, H); ^{13}C NMR δ: 148.18 (C6^A), 147.62 (C7^A),

140.72 (C1'), 140.06 (C1"^{A}), 129.42 (C4a^B and 2C"), 128.77 (2C"), 127.52 (C8a^B),

127.40 (C"), 118.58 (C2'), 111.78 (C5^C), 111.72 (C8^C), 67.16 (C1), 59.30 (CH$_2$Ph),

56.44 (2OCH$_3$), 46.99 (C3), 29.07 (C4); MS m/z: 309 (M$^+$, 8%), 282 (100), 218 (3),

190 (5), 91 (48), 65 (6); Anal. Calcd for C$_{20}$H$_{23}$NO$_2$: C, 77.64; H, 7.49; N, 4.53%,

found: C, 77.64; H, 7.53; N, 4.51%.

2-Ethoxycarbonylmethyl-6,7-dimethoxy-2-methyl-1-vinyl-1,2,3,4-tetrahydroisoquinolinium Bromide 50a

(i) The *N*-methyl base **49a** (0.392 g, 1.68 mmol) was stirred in ethyl bromoacetate

(2.0 ml, 18 mmol) at 20-25°C for 16 h. The mixture was applied to a short silica

column and the column was eluted with dichloromethane/5% light petroleum, and

then ethanol. Concentration of the ethanolic washings gave a mixture (*trans:cis*=70:30) of the B-ring diastereomers of the *N-methyl-N-ethoxycarbonylmethyl salt* **50a** (0.481 g, 72%) as an off-white hygroscopic powder. *trans diastereomer*: ^{1}H NMR δ: 6.70 (s, ArH), 6.53 (s, ArH), 6.26-6.24 (m, H2'), 6.05-6.01 (m, H1 and H1'), 5.85-5.81 (m, H2'), 5.11 (d, J 17.4 Hz, H of NCH_2CO), 4.69 (d, J 17.3 Hz, H of NCH_2CO), 4.49-4.41 (m, H), 4.24 (q, CH_2 of Et), 3.97-3.88 (m, H), 3.90 (s, OCH_3), 3.87 (s, OCH_3), 3.55 (s, NCH_3), 3.25-3.06 (m, 2H), 1.28 (t, CH_3 of Et); ^{13}C NMR δ: 165.50 (CO), 150.23 (C6^A), 149.37 (C7^A), 130.15 (C2'), 129.79 (C1'), 120.98 (C4a and C8a), 111.39 (C5 and C8), 73.50 (C1), 63.35 (CH_2 of Et), 58.44 (NCH_2CO^B), 56.59 (2OCH_3), 54.83 (C3^B), 47.52 (NCH_3), 24.22 (C4), 14.32 (CH_3 of Et); IR (thin film from CH_2Cl_2): 1742, 1520, 1258, 1229, 1117, 924, 731 cm^{-1}. *cis diastereomer*: ^{1}H NMR δ: 6.69 (s, ArH), 6.44 (s, ArH), 6.10-6.01 (m, H1'), 5.73-5.64 (m, H1 and H2'), 5.37 (d, J 17.5 Hz, H of NCH_2CO), 4.83-4.75 (m, H), 4.39 (d, J 17.1 Hz, H of NCH_2CO), 4.26 (q, CH_2 of Et), 3.83 (s, OCH_3), 3.80 (s, OCH_3), 3.76-3.71 (m, H), 3.70 (s, NCH_3), 3.29-3.06 (m, 2H), 1.25 (t, CH_3 of Et); ^{13}C NMR δ: 165.33 (CO), 150.24 (C6^A), 149.28 (C7^A), 131.06 (C1'), 127.48 (C2'), 120.95 (C4a^B), 120.67 (C8a^B), 111.40 (C5^C), 110.97 (C8^C), 73.31 (C1), 63.30 (CH_2 of Et), 60.76 (NCH_2CO^D), 56.56 (2OCH_3), 55.69 (C3^D), 46.41 (NCH_3), 23.64 (C4), 14.38 (CH_3 of Et); IR (thin film from CH_2Cl_2): 1744, 1520, 1260, 1230, 1119 cm^{-1}.

(ii) Treatment of **49a** (0.105 g, 0.450 mmol) as for (i), except with stirring at 110°C for 1 h., gave a 50:50 mixture of the B-ring diastereomers of **50a** (0.121 g, 67%).

(iii) Treatment of **49a** (0.364 g, 1.56 mmol) as for (i), except with stirring at -15°C for 60 h., gave an 80:20 mixture of the B-ring diastereomers of **50a** (0.441 g, 71%).

(iv) Treatment of **49a** (0.759 g, 3.25 mmol) as for (i), except with stirring at 37°C for 11 h., gave a 63:37 mixture of the B-ring diastereomers of **50a** (0.713 g, 55%). The recrystallisation of this material from ethanol/tetrahydrofuran gave a 57:43 diastereomeric mixture of **50a** (0.442 g) as a solid, while the concentration and analysis of the mother liquor showed a 40:60 diastereomeric mixture of **50a**. Repeating the recrystallisation from the new solid provided a 53:47 diastereomeric

mixture of crystalline **50a** (0.288 g), while the concentration and analysis of the mother liquor showed a 38:62 diastereomeric mixture of **50a**.

(v) Compound **49a** (3.054 g, 13.10 mmol) was stirred in acetonitrile (6 ml) with ethyl bromoacetate (2.8 ml, 25 mmol) at 20-25°C for 20 h. with the precipitation of a solid. The mixture was stored for 24 h. at -5°C and then filtered while cold. The solid was slurried twice with hexane then dried to give a 90:10 diastereomeric mixture of **50a** (3.367 g, 64%) as a cream hygroscopic solid. Concentration of the filtrate and trituration of the oily residue with hexane (4 x 20 ml) afforded, after drying, a second batch of **50a** (1.397 g, 27%) as a tan hygroscopic powder.

2-Benzyl-2-ethoxycarbonylmethyl-6,7-dimethoxy-1-vinyl-1,2,3,4-tetrahydroisoquinolinium Bromide 50b

(i) Compound **49b** (3.010 g, 9.729 mmol) was dissolved in ethyl bromoacetate (13.0 ml, 117 mmol) by warming the mixture briefly at 50°C, then the solution was stored under nitrogen protected from light at 15-25°C for 19 days. The precipitate was collected and washed with several portions of diethyl ether to give, after drying, a mixture (*trans:cis*=3:1) of the B-ring diastereomers of the *N-benzyl-N-ethoxycarbonylmethyl salt* **50b** (2.718 g, 59%) as an off-white powder. *trans diastereomer*: ^{1}H NMR δ: 6.67 (s, ArH), 6.60 (s, ArH), 1.14 (t, CH_3 of Et); ^{13}C NMR δ: 164.84 (CO), 150.09 (C6^A), 149.12 (C7^A), 133.63 (C2"^{B}), 132.58 (C3"^{B}), 131.78 (C1'), 131.21 (C4"^{B}), 130.16 (C5"^{B}), 129.45 (C6"^{B}), 127.65 (C2'), 121.56 (C4a^C), 121.33 (C8a^C), 111.49 (C1"), 111.15 (C5 and C8), 74.79 (C1), 66.49 (NCH$_2$Ph^D), 62.59 (CH$_2$ of Et^D), 56.53 (2OCH$_3$), 54.51 (NCH$_2$CO^D), 51.40 (C3^D), 24.15 (C4), 14.05 (CH$_3$ of Et). *cis diastereomer*: ^{1}H NMR δ: 6.78 (s, ArH), 6.53 (s, ArH), 1.31 (t, CH_3 of Et); ^{13}C NMR δ: 165.18 (CO), 150.21 (C6^A), 149.12 (C7^A), 133.63 (C2"^{B}), 132.58 (C3"^{B}), 131.40 (C1'), 131.21 (C4"^{B}), 130.16 (C5"^{B}), 129.45 (C6"^{B}), 126.94 (C2'), 121.01 (C4a^C), 120.41 (C8a^C), 110.76 (C1"), 111.15 (C5 and C8), 73.25 (C1), 63.20 (NCH$_2$Ph^D), 61.56 (CH$_2$ of Et^D), 57.37 (NCH$_2$CO^D), 56.53 (2OCH$_3$), 53.66 (C3^D), 23.86 (C4), 14.26 (CH$_3$ of Et).

(ii)   The *N*-benzyl base **49b** (0.444 g, 1.44 mmol) was dissolved in ethyl bromoacetate (1.5 ml, 13 mmol) by warming the mixture briefly at 50°C, then the solution was stirred at 25°C for 11 h. No reaction was detected by t.l.c. analysis. The solution was then heated at 60°C for 5 h. A dark colour developed, however, no significant reaction was detected by t.l.c. analysis.

(iii)   To **49b** (0.427 g, 1.38 mmol) in acetonitrile (4 ml) was added ethyl bromoacetate (1.2 g, 7.1 mmol) and potassium iodide (1.25 g, 7.50 mmol). No reaction was detected after the agitation of this mixture at 25°C for 24 h. The mixture was then heated under nitrogen at 90°C for 3 days. A dark tar formed.

Ethyl 9,10-Dimethoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-
3-benzazonine-4-carboxylate **52a**

(i)   To the salt **50a** (4.617 g, 11.54 mmol) in dry acetonitrile (125 ml) under nitrogen at 0°C was added DBU (2.14 g, 14.1 mmol) dropwise. After stirring at 0°C for 6 h. the solution was then concentrated and the residue was purified by column chromatography on alumina (100 g) with dichloromethane/20% light petroleum. Concentration of the early fraction (250 ml) gave a mixture (*E/Z*=19.0) of the *3-benzazonine isomers* **52a** (3.309 g, 90%) as a colourless, amorphous, waxy solid. A portion (160 mg) of this mixture was purified by preparative reverse phase HPLC with acetonitrile/20% water to give:

(a) after 10.94 min., the *Z-benzazonine* Z-**52a** (8 mg) as a colourless oil. ^{1}H NMR δ: 6.67 (d, *J* 10.7 Hz, H7), 6.58 (s, ArH), 6.54 (s, ArH), 5.90-5.81 (m, H6), 4.10 (q, CH$_2$ of Et), 3.87 (s, OCH$_3$), 3.84 (s, OCH$_3$), 3.49-3.44 (m, H4), 3.14-3.07 (m, H2), 2.90-2.82 (m, H2), 2.77-2.70 (m, H1), 2.62-2.56 (m, H1), 2.58 (s, NCH$_3$), 2.22-2.12 (m, H5), 1.23 (t, CH$_3$ of Et); ^{13}C NMR δ: 173.60 (COO), 148.34 (C9^A), 147.53 (C10^A), 134.24 (C11a^B), 132.42 (C6^C), 131.60 (C7^C), 129.53 (C7a^B), 113.84 (C8^D), 111.89 (C11^D), 66.94 (C4), 60.88 (CH$_2$ of Et), 56.51 (2OCH$_3$), 53.07 (C2), 45.48 (NCH$_3$), 37.86 (C1), 32.63 (C5), 15.00 (CH$_3$ of Et); MS m/z: 319 (M$^+$, 14%; Calcd. for C$_{18}$H$_{25}$NO$_4$ 319.1783, found 319.1778), 246 (100), 215 (2), 203 (3), 189 (6).

(b) after 14.23 min., the *E-benzazonine E-52a* (135 mg) as a colourless waxy solid. ^{1}H NMR δ: 6.77 (s, H8), 6.62 (s, H11), 6.43 (d, *J* 16.1 Hz, H7), 5.53-5.42 (m, H6), 4.17-4.04 (m, CH_2 of Et), 3.87 (s, OCH_3), 3.84 (s, OCH_3), 3.54 (dd, *J* 1.7 Hz, 6.3 Hz, H4), 2.84-2.76 (m, H1 and H5), 2.70 (s, NCH_3), 2.73-2.60 (m, H1 and H2), 2.38-2.28 (m, H2 and H5), 1.25 (t, CH_3 of Et); ^{13}C NMR δ: 173.25 (COO), 147.30 ($C9^A$), 147.09 ($C10^A$), 134.69 (C7), 133.87 ($C11a^B$), 132.09 ($C7a^B$), 130.64 (C6), 113.77 (C11), 110.66 (C8), 67.19 (C4), 60.58 (CH_2 of Et), 56.40 ($2OCH_3$), 56.00 (C2), 45.24 (NCH_3), 38.03 (C1), 36.32 (C5), 14.92 (CH_3 of Et); MS m/z: 319 (M^+, 8%; Calcd. for $C_{18}H_{25}NO_4$ 319.178, found 319.178), 246 (100), 215 (7), 204 (7), 189 (12); IR (thin film from CH_2Cl_2): 1717, 1508, 1462, 1265, 1221, 1197, 1101 cm^{-1}.

(ii) To **50a** (0.308 g, 0.770 mmol) in dry acetonitrile (15 ml) under nitrogen at -45°C was added DBU (0.14 g, 9.2 mmol). The solution was stirred between -45°C and -40°C for 6 h. and then allowed to warm slowly to room temperature. Concentration and then column chromatography of the residue on alumina with dichloromethane/20% light petroleum gave a mixture of the isomers of **52a** (0.211 g, 86%, *E/Z*=19.0).

(iii) To **50a** (0.295 g, 0.737 mmol) in dry acetonitrile (15 ml) at reflux, under nitrogen, was added DBU (0.14 g, 9.2 mmol). The solution was refluxed for 1 h. then concentrated and purified as for (i) to give a mixture (0.164 g, 70%) of the isomers *E*-**52a**:*Z*-**52a**:**53a** in the ratio 19.3:1.9:1.0.

(iv) To **50a** (0.508 g, 1.27 mmol) in dry acetonitrile (20 ml) under nitrogen at room temperature was added DBU (0.13 g, 0.87 mmol). The solution was stirred for 4.5 h. then concentrated. Column chromatographic purification of the residue on alumina with dichloromethane/20% light petroleum gave a mixture of the isomers of **52a** (0.251 g, 90%, *E/Z* =19.0). The column was then eluted with ethanol. Concentration of the ethanol solution gave a residue (0.391 g) which was partitioned between 1% aqueous hydrochloric acid (10 ml) and dichloromethane (10 ml). The aqueous layer was extracted with dichloromethane (2 x 5 ml) and then the organic

extracts were combined, dried, and then concentrated to give *cis*-**50a** (0.109 g).

Sublimation of the initial mixture of **52a** by heating at 95°C for 7 h. under oil-pump

vacuum afforded **52a** (0.215 g, 86% recovery) as a colourless noncrystalline solid

with m.p. 90-92°C, and an unchanged isomer ratio.

(v) To **50a** (0.481 g, 1.20 mmol) suspended in dry tetrahydrofuran (30 ml) under

nitrogen at room temperature was added DBU (0.18 g, 1.18 mmol). The solution

was stirred for 1 h. and then concentrated. Passage of the residue through a silica

plug with dichloromethane gave, upon concentration, a mixture of the isomers of

52a (0.283 g, 74%) as a pale oil. The attempted purification of this oil by p.t.l.c. on

a silica plate with dichloromethane/4% ethanol gave:

(a) several unidentified impure high R_f bands of < 3 mg.

(b) at R_f 0.6, *Z*-**52a** (7 mg) as a pale yellow oil.

(c) at R_f<0.3, unidentified polar material.

Ethyl 3-Benzyl-9,10-dimethoxy-2,3,4,5-tetrahydro-1*H*-3-benzazonine-4-carboxylate 52b

To **50b** (0.519 g, 1.09 mmol) in dry acetonitrile under nitrogen was added

DBU (0.18 ml, 1.2 mmol). The mixture was stirred for 3 h. and then concentrated.

The column chromatographic purification of the residue on alumina (17 g) with

dichloromethane/20% light petroleum gave, on concentration, the *E-3-benzyl-3-*

benzazonine **52b** (0.401 g, 93%) as a colourless oil. ^{1}H NMR δ: 7.47-7.45 (m,

2ArH'), 7.38-7.26 (m, 3ArH'), 6.79 (s, H8), 6.63 (s, H11), 6.57 (d, *J* 16.2 Hz, H7),

5.56-5.46 (m, H6), 4.19-4.05 (m, CH$_2$ of Et and H of CH$_2$Ph), 3.96 (d, *J* 13.9 Hz, H

of CH$_2$Ph), 3.88 (s, OCH$_3$), 3.85 (s, OCH$_3$), 3.52 (dd, *J* 1.3 Hz, 6.2 Hz, H4), 2.98-

2.90 (m, H2^A), 2.76-2.66 (m, H1^A and H5), 2.41-2.34 (m, H1^A), 2.06-2.00 (m, H5),

1.26 (t, CH$_3$ of Et); ^{13}C NMR δ: 173.79 (COO), 147.45 (C9^A), 147.25 (C10^A),

140.34 (C1'), 134.84 (C7^B), 133.99 (C7a^C), 132.09 (C11a^C), 131.02 (C6^B), 129.66

(2C''), 128.89 (2C''), 127.81 (C''), 113.85 (C11), 110.81 (C8), 62.25 (C4), 60.80

(CH$_2$ of Et and CH$_2$Ph), 56.59 (2OCH$_3$), 55.13 (C2), 38.53 (C1), 36.62 (C5), 15.08

(CH$_3$ of Et);   MS m/z: 395 (M$^+$, 7%; Calcd. for C$_{24}$H$_{29}$NO$_4$ 395.209, found 395.211), 322 (84), 282 (18), 230 (14), 189 (14), 115 (11), 91 (100).

Ethyl 7,8-Dimethoxy-3-methyl-1-vinyl-2,3,4,5-tetrahydro-1H-
3-benzazepine-4-carboxylate 53

An 87:9:4 mixture (0.164 g) of E-52a, Z-52a, and a component attributed to 53, was refluxed in butyronitrile (10 ml) for 11.5 h. to produce, after concentration, a 40:9:51 mixture of the same isomers. Purification of a portion (0.103 g) of this material by p.t.l.c. on silica with dichloromethane/5% ethanol afforded a mixture (82:18) of the B-ring diastereomers of the *3-benzazepine* 53 (0.042 g) as a pale yellow oil. *trans diastereomer* ^{1}H NMR δ: 6.62 (s, ArH), 6.61 (s, ArH), 6.21-6.18 (m, H1'), 5.18 (d, *J* 10.3 Hz, H2'), 4.91 (d, *J* 17.2 Hz, H2'), 4.11-3.98 (q, CH$_2$ of Et), 3.95-3.91 (m, H1), 3.85 (s, OCH$_3$), 3.83 (s, OCH$_3$), 3.67 (d, *J* 5.7 Hz, H2), 3.38-3.31 (m, H), 3.19-3.10 (m, H), 2.77-2.59 (m, H), 2.54 (s, NCH$_3$), 1.17 (t, CH$_3$ of Et); ^{13}C NMR δ: 171.99 (COO), 148.03 (C7^A), 147.39 (C8^A), 138.72 (C1'), 133.90 (C5a^B), 130.91 (C9a^B), 116.77 (C2'), 114.40 (C6^C), 113.86 (C9^C), 69.28 (C2), 60.45 (CH$_2$ of Et), 56.59 (2OCH$_3$), 52.11 (C1), 51.22 (C2), 46.92 (NCH$_3$), 35.40 (C5), 15.08 (CH$_3$ of Et); *cis diastereomer* ^{1}H NMR δ: 5.82-5.83 (m, H1'), 2.58 (s, NCH$_3$), 1.23 (t, CH$_3$ of Et); ^{13}C NMR δ: 173.88 (COO), 66.95 (C2), 60.71 (CH$_2$ of Et), 52.87 (C4), 45.37 (NCH$_3$), 38.15 (C5);   MS m/z: 319 (M$^+$, 12%; Calcd. for C$_{18}$H$_{25}$NO$_4$ 319.1783, found 319.1786), 246 (100), 230 (3), 204 (4), 189 (6).

Conversion of 52a to the Proposed Pyrrolo[2,1-a]isoquinolinium Derivative 54

(i) The reaction of 52a (0.294 g, 0.920 mmol) with iodomethane (0.157 g, 1.11 mmol) in dry butanone (2 ml) at room temperature in a sealed vessel protected from light over 3 days gave the precipitation of colourless needles tentatively attributed to the *3-ethoxycarbonyl-8,9-dimethoxy-4-methyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolinium iodide* 54 (0.015 g, 3%) with m.p. 206-207°C. Satisfactory microanalytical results could not be obtained from this material. ^{1}H NMR δ: 6.19 (t,

H10b^A), 6.02 (t, H3^A), 3.58 (s, NCH$_3$); ^{1}H NMR (d$_6$-DMSO) δ: 6.95 (s, ArH), 6.83 (s, ArH), 5.04 (t, H10b^A), 4.84 (t, H3^A), 4.34 (q, CH$_2$ of Et), 3.79 (s, OCH$_3$), 3.77 (s, OCH$_3$), 3.71-3.64 (m, 2H), 3.27 (s, NCH$_3$), 3.21-3.17 (m, H), 3.04-2.98 (m, H), 2.77-2.69 (m, H), 2.53-2.43 (m, 2H), 2.03-1.96 (m, H), 1.34 (t, CH$_3$ of Et); ^{13}C (d$_6$-DMSO) NMR δ: 169.05 (COO), 152.73 (C8^A), 152.05 (C9^A), 125.31 (C6a^B), 123.84 (C10a^B), 115.59 (C7^C), 113.89 (C10^C), 78.38 (C10b^D), 76.94 (C3^D), 66.62 (CH$_2$ of Et), 59.67 (OCH$_3$), 59.56 (OCH$_3$), 51.87 (C5), 50.16 (NCH$_3$), 33.10 (C6), 26.59 (C1^E), 26.02 (C2^E), 17.75 (CH$_3$ of Et); Anal. Calcd for C$_{18}$H$_{26}$NO$_4$I: C, 48.33; H, 5.86; N, 3.13%, found: C, 47.19; H, 5.83; N, 3.15%.

(ii) The reaction of **52a** (0.231 g, 0.724 mmol) with iodomethane (0.156 g, 1.11 mmol) in refluxing dry butanone (2 ml) for 2 h. afforded, after aging at -5°C, a precipitate which was collected to give **54** (0.027 g, 8%).

6,7-Dimethoxy-2,2-dimethyl-1-vinyl-1,2,3,4-tetrahydroisoquinolinium Iodide 55a

The 1-vinylisoquinoline **49a** (0.461 g, 1.98 mmol) was refluxed in acetone (10 ml) with iodomethane (2.1 g, 14 mmol) for 1 h. The solution was then cooled and concentrated. Recrystallisation of the residue from methanol gave the *isoquinolinium iodide* **55a** (0.612 g, 83%) as pale yellow prisms with m.p. 231-232°C. ^{1}H NMR δ: 6.72 (s, ArH), 6.55 (s, ArH), 6.03-5.82 (m, H1' and H2'), 5.66 (d, *J* 7.9 Hz, H1), 4.13-4.06 (m, H3), 4.00-3.92 (m, H3), 3.89 (s, OCH$_3$), 3.83 (s, OCH$_3$), 3.59 (s, NCH$_3$), 3.36 (s, NCH$_3$), 3.20 (t, H4); ^{1}H NMR (CD$_3$CN) δ: 6.68 (s, ArH), 6.43 (s, ArH), 5.89-5.76 (m, H1'), 5.64-5.59 (m, H2'), 4.88 (d, *J* 8.8 Hz, H1), 3.65 (s, OCH$_3$), 3.59 (s, OCH$_3$), 3.55-3.41 (m, H3), 2.99-2.92 (m, H4 and NCH$_3$), 2.85 (s, NCH$_3$); ^{13}C NMR δ: 150.04 (C6^A), 149.05 (C7^A), 129.91 (C1'), 129.36 (C2'), 121.61 (C4a^B), 121.44 (C8a^B), 111.46 (C5^C), 110.97 (C8^C), 74.34 (C1), 57.88 (C3), 56.55 (2OCH$_3$), 51.58 (NCH$_3$), 48.37 (NCH$_3$), 24.31 (C4); Anal. Calcd for C$_{15}$H$_{22}$NO$_2$I: C, 48.01; H, 5.91; N, 3.73%, found: C, 48.13; H, 5.93; N, 3.83%; IR (KBr): 1520, 1238, 1119, 1111, 783 cm^{-1}.

2-Benzyl-6,7-dimethoxy-2-methyl-1-vinyl-1,2,3,4-tetrahydroisoquinolinium Iodide 55b

The 1-vinylisoquinoline **49b** (1.012 g, 3.271 mmol) was refluxed in acetone (10 ml) with iodomethane (4.3 g, 31 mmol) for 2 h. The solution was then cooled and concentrated. Recrystallisation of the residue from methanol gave a mixture (54:46) of the B-ring diastereomers of the *isoquinolinium iodide* **55b** (1.146 g, 78%) as pale yellow prisms with m.p. 209-210°C. ^{1}H NMR (superscripts[a,b] denote those attributed to each diastereomer) δ: 7.79-7.76 (m, 2ArH"[b]), 7.64-7.62 (m, 2ArH"[a]), 7.50-7.33 (m, 3ArH"), 6.76 (s, ArH[a]), 6.67 (s, ArH[b]), 6.62 (s, ArH[b]), 6.56 (s, ArH[a]), 6.35-6.01 (m, H1' and H2'[b]), 5.92-5.82 (m, H2'[a]), 5.71 (d, J 9.2 Hz, H1[b]), 5.63 (d, J 8.6 Hz, H1[a]), 5.50 (d, J 12.8 Hz, NCH[b]Ph), 5.30 (d, J 12.8 Hz, NCH[a]Ph), 4.83 (d, J 12.8 Hz, NCH[a]Ph), 4.52 (d, J 12.9 Hz, NCH[b]Ph), 4.27-4.19 (m, H3[a]), 3.90-3.84 (m, 2OCH$_3$ and H3[b]), 3.77-3.61 (m, H), 3.38-3.27 (m, H), 3.20 (s, NCH$_3$[b]), 3.14 (s, NCH$_3$[a]), 3.07-2.98 (m, H4); Anal. Calcd for $C_{21}H_{26}NO_2I$: C, 55.88; H, 5.81; N, 3.10%, found: C, 55.75; H, 5.82; N, 3.18%; IR (KBr): 1522, 1227, 1119, 1113, 706 cm^{-1}.

N,N-Dimethyl-α-vinyl-4,5-dimethoxy-2-vinylbenzylamine 56a

To **55a** (0.475 g, 1.27 mmol) suspended in dry tetrahydrofuran (20 ml) at -20°C under nitrogen was added dropwise a 0.98M solution of lithium diisopropylamide (1.5 ml, 1.5 mmol) in a tetrahydrofuran/hexane mixture. The mixture was stirred at -20°C for 30 min. and then allowed to warm with stirring for a further 30 min. before the addition of water (15 ml) and diethyl ether (25 ml). The aqueous layer was extracted with further diethyl ether (2 x 20 ml) and the ether extracts were then combined and washed with water (10 ml), and then saturated brine (10 ml). Drying and then concentration of the ether solution gave the *benzylamine* **56a** (0.079 mg, 25%) as a yellow oil. ^{1}H NMR δ: 7.19 (dd, J 10.0 Hz, 17.2 Hz, H1'''), 7.00 (s, ArH), 6.93 (s, ArH), 5.90 (m, H1'), 5.49 (dd, J 1.2 Hz, 17.2 Hz, H2'''), 5.24-5.14 (m, H2' and H2'''), 5.02 (dd, J 1.3 Hz, 10.1 Hz, H2'), 3.89 (s, OCH$_3$), 3.87

(s, OCH$_3$), 3.76 (d, J 8.7 Hz, H1), 2.19 (s, 2NCH$_3$); ^{13}C NMR δ: 149.34 (C4"^{A}),

148.23 (C5"^{A}), 141.02 (C2^B), 134.13 (C1'''^{B}), 133.50 (C1"^{C}), 129.34 (C2"^{C}), 115.89

(C2'^{D}), 114.63 (C2'''^{D}), 110.88 (C3"^{E}), 109.04 (C6"^{E}), 72.16 (C1), 56.62 (OCH$_3$),

56.40 (OCH$_3$), 44.58 (NCH$_3$); MS m/z: 247 (M$^+$, 60%; Calcd. for C$_{15}$H$_{21}$NO$_2$

247.157, found 247.159), 232 (62), 203 (100), 188 (25), 172 (47), 84 (47), 58 (55).

The aqueous washings were concentrated and the residue was then extracted

with hot chloroform. Concentration of these extracts afforded **55a** (0.305 g, 64%).

N-Benzyl-*N*-methyl-α-vinyl-4,5-dimethoxy-2-vinylbenzylamine 56b

To **55b** (0.518 g, 1.15 mmol) suspended in dry tetrahydrofuran (20 ml) at

-20°C under nitrogen was added dropwise a 0.98M solution of lithium

diisopropylamide (1.4 ml, 1.4 mmol) in a tetrahydrofuran/hexane mixture. The

mixture was stirred at -20°C for 20 min. and then allowed to warm with stirring for a

further 40 min. before the addition of water (15 ml) and diethyl ether (25 ml). The

aqueous layer was extracted with further diethyl ether (2 x 20 ml) and the extracts

were then combined and washed with water (10 ml), and then saturated brine (10

ml). Drying and then concentration of the ether solution gave a yellow oil which

was purified by passage through an alumina plug with dichloromethane to give the

benzylamine **56b** (0.244 mg, 55%) as a pale yellow oil. ^{1}H NMR δ: 7.39-7.19 (m,

5ArH and H1'''), 7.16 (s, ArH), 6.99 (s, ArH), 5.99 (m, H1'), 5.53 (dd, J 1.2 Hz, 17.3

Hz, H2'''), 5.27-5.20 (m, H2' and H2'''), 5.07 (dd, J 1.4 Hz, 10.0 Hz, H2'), 4.09 (d, J

8.9 Hz, H1), 3.91 (s, OCH$_3$), 3.89 (s, OCH$_3$), 3.56 (d, J 13.3 Hz, NCHPh), 3.33 (d, J

13.3 Hz, NCHPh), 2.12 (s, NCH$_3$); ^{13}C NMR δ: 149.72 (C4"^{A}), 148.50 (C5"^{A}),

140.51 (C1'^{B}), 140.38 (C1^{+C}), 134.98 (C1'''^{B}), 133.30 (C1"^{C}), 129.94 (C2"^{C}),

129.30 (2C$^+$), 128.77 (2C$^+$), 127.35 (C4$^+$), 116.39 (C2'^{D}), 114.57 (C2'''^{D}), 111.04

(C3"^{E}), 109.51 (C6"^{E}), 70.84 (C1), 59.92 (NCH$_2$Ph), 56.58 (OCH$_3$), 56.44 (OCH$_3$),

40.58 (NCH$_3$); MS m/z: 323 (M$^+$, 25%; Calcd. for C$_{21}$H$_{25}$NO$_2$ 323.188, found

323.188), 308 (16), 232 (37), 203 (63), 172 (29), 134 (43), 91 (100).

The aqueous solutions were combined and extracted with chloroform (3 x 20 ml). Concentration of the extracts afforded a mixture (70:30) of the B-ring diastereomers of **55b** (0.198 g, 38%).

6,7-Dimethoxy-1-vinyl-1,2,3,4-tetrahydroisoquinoline 57

A solution of vinylmagnesium bromide in dry tetrahydrofuran (130 ml) under nitrogen was prepared from vinyl bromide (22.2 g, 0.208 mol). The solution was cooled to 0°C and dry diethyl ether (160 ml) was added prior to the addition of the imine **47** (13.24 g, 69.25 mmol) as a solution in dry tetrahydrofuran (100 ml) over 30 min. The mixture was allowed to warm to room temperature with stirring for 3.5 h. and then the excess Grignard reagent was hydrolysed by the addition of saturated aqueous ammonium chloride. The organic solvents were decanted and the residual solids were rinsed with diethyl ether (30 ml). The solids were dissolved in 3M aqueous hydrochloric acid (250 ml) and the solution was then basified with 80% aqueous sodium hydroxide. The solids which precipitated were collected by centrifuging the mixture, while the supernatant liquid was decanted and extracted with chloroform (4 x 50 ml); centrifugation was necessary to break the emulsions formed during the extractions. The solid was then dissolved in the chloroform extracts. The resultant solution was washed with water (20 ml) then saturated brine (20 ml), and then dried and concentrated to a dark solid (6.355 g) which was purified by column chromatography on silica with dichloromethane/0-2% methanol to give the secondary amine **57** (5.009, 33%) as a pale tan powder. ^{1}H NMR δ: 6.59 (s, ArH), 6.58 (s, ArH), 6.00-5.88 (m, H1'), 5.29-5.22 (m, H2'), 4.40 (d, J 7.8 Hz, H1), 3.85 (s, OCH$_3$), 3.82 (s, OCH$_3$), 3.26-3.20 (m, H), 3.06-2.98 (m, H), 2.88-2.75 (m, H), 2.72-2.62 (m, H), 1.85 (bs, NH); ^{13}C NMR δ: 148.27 (C6^A), 147.72 (C7^A), 141.31 (C1'), 129.25 (C4a^B), 127.60 (C8a^B), 117.71 (C2'), 112.39 (C5^C), 110.93 (C8^C), 60.60 (C1), 56.49 (2OCH$_3$), 42.25 (C3), 29.78 (C4); MS m/z: 219 (M$^+$, 28%; Calcd. for C$_{13}$H$_{17}$NO$_2$ 219.1259, found 219.1269), 218 (34), 204 (13), 192 (100), 188 (12), 178 (13), 176 (16).

6,7-Dimethoxy-2-trimethylsilylmethyl-1-vinyl-1,2,3,4-tetrahydroisoquinoline 58

The secondary amine **57** (0.926 g, 4.22 mmol) was stirred in dry acetonitrile (5 ml) with trimethylsilylmethyl trifluoromethanesulfonate (0.992 g, 4.20 mmol) under nitrogen for 6 h. at room temperature, then water (5 ml) and diethyl ether (10 ml) were added. The aqueous layer was extracted with further diethyl ether (4 ml) and then the ether extracts were combined and washed with water (3 x 2 ml), and then saturated brine (2 x 2 ml). The ether solution was then dried and concentrated to a tan solid which was purified by column chromatography on alumina (30 g) with hexane/40% dichloromethane. The residual **57** was retained on the column and the *2-trimethylsilylmethylisoquinoline* **58** (0.801 g, 63%) was obtained as a pale yellow oil on concentration of the early fractions. ^{1}H NMR δ: 6.58 (s, ArH), 6.54 (s, ArH), 5.77-5.66 (m, H1'), 5.27-5.17 (m, H2'), 3.79 (s, OCH$_3$), 3.77 (s, OCH$_3$), 3.68 (d, J 8.4 Hz, H1), 3.02-2.97 (m, H), 2.85-2.78 (m, H), 2.69-2.62 (m, H), 2.47-2.36 (m, H and H of NCH$_2$Si), 1.78 (d, J 14.7 Hz, H of NCH$_2$Si), 0.07 (s, Si(CH$_3$)$_3$); ^{13}C NMR δ: 147.82 (C6^A), 147.26 (C7^A), 141.30 (C1'), 128.77 (C4a^B), 127.01 (C8a^B), 117.90 (C2'), 111.53 (C5 and C8), 71.15 (C1), 56.09 (2OCH$_3$), 50.65 (NCH$_2$Si^C), 46.43 (C3^C), 29.00 (C4), -0.95 (Si(CH$_3$)$_3$).

6,7-Dimethoxy-2-methyl-2-trimethylsilylmethyl-1-vinyl-1,2,3,4-tetrahydroisoquinolinium Iodide 59

The amine **58** (0.682 g, 2.23 mmol) was stirred in dry acetonitrile (4 ml) with iodomethane (1.9 g, 13 mmol) at 60°C for 1 h. Concentration of the mixture and recrystallisation of the residue from methanol/ethyl acetate gave a mixture (51:49) of the B-ring diastereomers of the *isoquinolinium salt* **59** (0.917 g, 92%) as off-white prisms. ^{1}H NMR (superscripts[a,b] denote those attributed to each diastereomer) δ: 6.74 (s, ArH[a]), 6.73 (s, ArH[b]), 6.60 (s, ArH[b]), 6.54 (s, ArH[a]), 6.09-5.76 (m, 3H and H1[b]), 5.49 (d, J 8.6 Hz, H1[a]), 4.01-3.92 (m, H), 3.88 (s, OCH$_3$), 3.82 (s, OCH$_3$), 3.57 (d, J 14.9 Hz, NCH[a]Si), 3.50-3.10 (m, 3H), 3.45 (s, NCH$_3$[b]), 3.31 (s, NCH$_3$[a]), 2.98 (d, J 14.7 Hz, NCH[b]Si), 0.37 (s, Si(CH$_3$)$_3$[b]), 0.35 (s, Si(CH$_3$)$_3$[a]); ^{13}C NMR δ:

150.30 (C6^A), 149.35 (C7^A), 130.91 (C1'), 129.27 (C2'), 121.83-121.06 (C4a and C8a), 111.75-111.38 (C5 and C8), 76.88 and 76.64 (C1), 58.45 and 57.81 (NCH$_2$Si^B), 56.82 (2OCH$_3$), 55.84 and 54.53 (C3^B), 51.32 and 50.51 (NCH$_3$), 24.92 and 24.73 (C4), 0.83 and 0.68 (Si(CH$_3$)$_3$).

9,10-Dimethoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazonine 61

All traces of moisture were excluded from this procedure. The cesium fluoride was dried immediately prior to use under vacuum at 170-190°C over phosphorus pentoxide. Dry dimethylformamide was obtained by distillation from barium oxide, under reduced pressure, onto 4A molecular sieves and then storage. The glassware was dried at 120°C prior to use.

The salt **59** (0.408 g, 0.912 mmol) was placed in a two-necked flask to which a test-tube containing dry cesium fluoride (0.698 g, 4.60 mmol) was attached by rubber tubing and the apparatus was flushed with nitrogen. Dry dimethylformamide (3 ml) was added via syringe to **59**, then the cesium fluoride was added and the mixture was stirred sealed under nitrogen, protected from light, for 44 h. The resultant mixture was treated with 2.5% aqueous sodium bicarbonate (25 ml) and then extracted with diethyl ether (4 x 10 ml). The organic extracts were washed with 2.5% sodium bicarbonate (5 ml), then saturated brine (5 ml), and then dried and concentrated to give the *E-3-benzazonine* **61** (0.063 g, 30%) as a colourless oil. ^{1}H NMR δ: 6.69 (s, H8), 6.55 (s, H11), 6.34 (d, *J* 16.2 Hz, H7), 5.26-5.15 (m, H6), 3.79 (s, OCH$_3$), 3.76 (s, OCH$_3$), 2.79-2.57 (m, 4H), 2.39 (s, NCH$_3$), 2.35-2.16 (m, 4H); ^{13}C NMR δ: 147.40 (C9^A), 147.21 (C10^A), 134.15 (C7a^B), 133.56 (C7^C), 132.23 (C6^C), 134.15 (C11a^B), 114.13 (C11), 110.90 (C8), 61.08 (C4^D), 57.96 (C2^D), 56.58 (2OCH$_3$), 45.38 (NCH$_3$), 38.31 (C1), 35.76 (C5); MS m/z: 247 (M$^+$, 100%; Calcd. for C$_{15}$H$_{21}$NO$_2$ 247.1572, found 247.1578), 246 (35), 232 (29), 204 (15), 189 (13), 149 (14); IR (thin film from CH$_2$Cl$_2$): 1508, 1463, 1328, 1264, 1219, 1196, 1104 cm^{-1}.

The various aqueous washings were combined and saturated with sodium chloride then extracted with chloroform (4 x 10 ml). Concentration of these extracts, after drying, afforded **55a** (0.201 g, 59%).

2-Cyanomethyl-6,7-dimethoxy-2-methyl-1-vinyl-1,2,3,4-tetrahydroisoquinolinium Iodide 62a

Iodoacetonitrile was prepared for this synthesis by stirring a mixture of sodium iodide (75.0 g, 0.500 mole), chloroacetonitrile (20.0 ml, 0.316 mole) and dry acetonitrile (150 ml) at room temperature for 24 h. The mixture was filtered and the filtrate was then concentrated at 50°C. The residue was taken up in dichloromethane and the solution was again filtered and then concentrated at 50°C. The vacuum distillation of the residual liquid afforded iodoacetonitrile (19.82 g, 37%) at approximately 110°C. ^{1}H NMR δ: 3.54.

The amine **49a** (1.022 g, 4.381 mmol) was stirred in dry butanone (3 ml) with iodoacetonitrile (1.10 g, 6.59 mmol) for 40 h. at room temperature protected from light. The mixture was then cooled to -10°C and a first crop of solid (0.548 g) was collected. The concentration of the filtrate afforded a second crop (1.276 g). The solids were combined and recrystallised from methanol/ethyl acetate to give a mixture (*trans:cis*=53:47) of the B-ring diastereomers of the *N-cyanomethyl salt* **62a** (1.090 g, 62%) as an off-white powder. The characteristic NMR peaks were: *trans diastereomer* ^{1}H NMR δ: 3.51 (s, NCH$_3$); ^{13}C NMR δ: 132.33 (C2'), 128.77 (C1'), 111.99 (C5^A), 111.01 (C8^A), 74.66 (C1), 58.19 (NCH$_2$CN), 56.95 (2OCH$_3$), 50.88 (C3), 47.14 (NCH$_3$), 24.43 (C4); *cis diastereomer* ^{1}H NMR δ: 3.66 (s, NCH$_3$); ^{13}C NMR δ: 130.23 (C1'), 130.15 (C2'), 111.87 (C5^A), 111.26 (C8^A), 74.93 (C1), 56.19 (NCH$_2$CN), 56.95 (2OCH$_3$), 51.73 (C3), 48.74 (NCH$_3$), 24.43 (C4).

6,7-Dimethoxy-2-methyl-2-phenacyl-1-vinyl-1,2,3,4-tetrahydroisoquinolinium Bromide 62b

To the *N*-methyl base **49a** (2.015 g, 8.641 mmol) in dry butanone (6.0 ml) was added phenacyl bromide (2.623 g, 13.18 mmol). The mixture was warmed briefly to

dissolve all the solids and was then stirred at room temperature for 12 h. with the formation of a solid. The mixture was aged at -10°C for 2 h. then filtered while cold. The addition of diethyl ether (10 ml) to the filtrate gave a small second crop of solid. The solids were combined and reslurried with diethyl ether (3 x 30 ml) then dried to give a mixture (*trans:cis*=78:22) of the B-ring diastereomers of the *N-phenacyl salt* **62b** (3.062 g, 82%) as a pale yellow powder. *trans diastereomer* ^{1}H NMR δ: 8.35-8.31 (m, *o*-ArH"), 7.66-7.61 (m, *p*-ArH"), 7.53-7.48 (m, *m*-ArH"), 6.63 (s, ArH), 6.59 (s, ArH), 6.65-6.58 (m, H2'), 6.25-6.15 (bd, NCHCO), 6.18-6.00 (m, H1' and H2'), 5.84 (d, *J* 10.8 Hz, H1), 5.60-5.48 (bd, NCHCO), 4.79-4.75 (m, H), 3.93-3.78 (m, H), 3.88 (s, OCH$_3$), 3.85 (s, OCH$_3$), 3.60 (s, NCH$_3$), 3.15-3.11 (m, 2H); ^{13}C NMR δ: 192.10 (CO), 150.05 (C6^A), 149.21 (C7^A), 135.40 (C1'), 134.53 (C1"), 129.90 (C2'), 129.54 (2C"), 129.24 (C"), 128.95 (2C"), 121.06 (C4a^B), 120.69 (C8a^B), 111.27 (C5^C), 110.73 (C8^C), 73.72 (C1), 62.88 (NCH$_2$CO), 56.47 (2OCH$_3$), 54.93 (C3), 47.71 (NCH$_3$), 24.29 (C4); *cis diastereomer* distinguishable peaks ^{1}H NMR δ: 8.01-7.97 (m, *o*-ArH"), 4.98-4.92 (m, H), 3.69 (s, NCH$_3$); ^{13}C NMR δ: 72.68 (C1), 45.92 (NCH$_3$), 23.59 (C4).

Recrystallisation of this material from methanol gave a mixture (95:5) of the B-ring diastereomers as a cream powder (1.257 g, 34%) with m.p. 198-201°C. Anal. Calcd for C$_{22}$H$_{26}$NO$_3$Br: C, 61.12; H, 6.06; N, 3.24%, found: C, 60.80; H, 6.23; N, 3.34%; IR (KBr): 1697, 1519, 1258, 1225, 1115, 860 cm^{-1}.

9,10-Dimethoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazonine-4-carbonitrile **63a**

(i) To the salt **62a** (0.395 g, 0.987 mmol) in dry acetonitrile (15 ml) at room temperature under nitrogen was added DBU (0.195 g, 1.28 mmol). After stirring for 5 h. the solution was then concentrated and the residue was purified by column chromatography on alumina (25 g) with dichloromethane/20% light petroleum. Concentration of the early fraction (100 ml) gave a pale yellow oil (0.227 g, 84%) which upon ^{1}H NMR analysis indicated 3 components in the ratio of 11.4:2.3:1.0. The purification of this oil by preparative reverse phase HPLC with acetonitrile/24%

water afforded at 8.89 min. the major component, the E-*4-cyano-benzazonine* **63a**

(0.133 g, 49%), as a colourless oil. ^{1}H NMR δ: 6.69 (s, H8), 6.58 (s, H11), 6.40 (d, *J*

16.1 Hz, H7), 5.43-5.33 (m, H6), 3.78 (s, OCH$_3$), 3.75 (s, OCH$_3$), 3.67-3.64 (m, H4),

2.75-2.54 (m, 6H), 2.46 (s, NCH$_3$); ^{13}C NMR δ: 147.66 (C9 and C10), 137.19 (C7),

133.05 (C11a^A), 131.35 (C7a^A), 128.33 (C6), 118.82 (CN), 114.01 (C11), 110.66

(C8), 57.03 (C2), 56.65 (2OCH$_3$), 56.44 (C4), 45.34 (NCH$_3$), 39.17 (C1), 37.55

(C5); MS m/z: 272 (M$^+$, 25%; Calcd. for C$_{16}$H$_{20}$N$_2$O$_2$ 272.1524, found 272.1540),

257 (17), 245 (100), 230 (65), 204 (37), 189 (53), 188 (66).

(ii) To **62a** (0.631 g, 1.58 mmol) in dry acetonitrile (30 ml) at reflux under nitrogen

was added DBU (0.337 g, 2.21 mmol). The solution was refluxed for 1 h.

Concentration and purification as for (i) gave a pale yellow oil (0.265 g, 62%) which

contained the same 3 components as for (i), but in the ratio of 10.0:1.0:1.5.

4-Benzoyl-9,10-dimethoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazonine 63b

(i) To the salt **62b** (1.507 g, 3.486 mmol) suspended in dry acetonitrile (50 ml)

under nitrogen at 0°C was added DBU (0.69 g, 4.53 mmol). After stirring at 0°C for

5 h. the solution was then concentrated and the residue was purified by column

chromatography on alumina with dichloromethane/20% light petroleum.

Concentration of the early fraction gave a yellow oil (1.026 g, 84%). Analysis by ^{1}H

NMR revealed a 91:7:2 mixture of *E*-**63b**:*Z*-**63b**:**64b**. Purification of a portion of

this mixture by preparative reverse phase HPLC with acetonitrile/20% water gave:

(a) the *Z-benzazonine Z*-**63b** as a yellow oil. ^{1}H NMR δ: 7.84 (dd, *J* 1.0 Hz, 7.6 Hz,

o-ArH"), 7.55-7.50 (m, *p*-ArH"), 7.45-7.40 (m, *m*-ArH"), 6.67 (d, *J* 11.0 Hz, H7),

6.65 (s, ArH), 6.54 (s, ArH), 6.04-5.95 (m, H6), 4.33 (dd, *J* 3.5 Hz, 10.9 Hz, H4),

3.88 (s, OCH$_3$), 3.83 (s, OCH$_3$), 3.14-3.06 (m, H2), 2.76-2.67 (m, H1), 2.53 (s,

NCH$_3$), 2.43-2.32 (m, H5), 2.18-2.14 (m, H5); ^{13}C NMR δ: 200.46 (CO), 148.54

(C9^A), 147.70 (C10^A), 137.71 (C11a^B), 134.28 (C7a^B), 133.30 (C6^C), 132.37 (C7^C),

132.06 (C4"^{C}), 130.11 (C1"^{B}), 129.17 (2C"), 128.77 (2C"), 113.61 (C8^D), 111.83

(C11^D), 65.96 (C4), 56.56 (2OCH$_3$), 53.54 (C2), 42.90 (NCH$_3$), 36.10 (C1), 30.93

(C5); MS m/z: 349 (M-2$^+$, 2%; Calcd. for $C_{22}H_{23}NO_3$ 349.1675, found 349.168), 246 (100), 215 (7), 206 (12), 160 (12), 105, (14), 77 (16).

(b) the *E-benzazonine E*-**63b** as a yellow oil. The compound showed 2 conformers (51:49) on NMR analysis at room temperature. ^{1}H NMR (superscripts[a,b] denote signals for each conformer) δ: 7.84-7.77 (m, *o*-ArH"), 7.54-7.51 (m, *p*-ArH"), 7.47-7.37 (m, *m*-ArH"), 6.84 (s, ArH[a]), 6.78 (s, ArH[a]), 6.67 (s, ArH[b]), 6.58 (s, ArH[b]), 6.41 (d, *J* 16.4 Hz, H4[b]), 6.23 (d, *J* 16.1 Hz, H4[a]), 5.82-5.71 (m, H6[b]), 5.42-5.32 (m, H6[a]), 4.40-4.37 (m, H[b]), 3.91-3.83 (m, 2OCH$_3$ and H), 3.71-3.56 (m, H), 3.11-3.06 (m, H[a]), 2.84-2.67 (m, 2H), 2.53 (s, NCH$_3$[b]), 2.50-2.32 (m, 2H), 2.25 (s, NCH$_3$[a]); ^{13}C NMR δ: 201.14 and 200.92 (CO), 147.75 and 147.53 (C9[A]), 147.28 (C10[A]), 139.07 and 137.68 (C11a[B]), 133.89 (C7a[B]), 135.68 and 133.70 (C6[C]), 133.31 and 133.02 (C7[C]), 132.79 and 132.30 (C1"[B]), 131.76 and 130.94 (C4"[C]), 129.07-128.61 (4C"), 114.21 (C8[D]), 111.06 and 109.81 (C11[D]), 70.34 and 70.02 (C4), 56.52 (2OCH$_3$), 59.62 and 55.56 (C2), 41.40 (NCH$_3$), 35.94 and 34.88 (C1), 33.37 and 33.26 (C5); MS m/z: 349 (M-2$^+$, 2%; Calcd. for $C_{22}H_{23}NO_3$ 349.1675, found 349.168), 246 (100), 215 (7), 206 (12), 160 (12), 105, (14), 77 (16). IR (thin film from CH_2Cl_2): 2934, 1678, 1512, 1259, 1221, 1105, 735, 698 cm^{-1}.

(ii) To **62b** (0.125 g, 0.289 mmol) suspended in dry acetonitrile (5 ml) under nitrogen at -30°C was added DBU (0.053 g, 0.35 mmol). After stirring between -20°C and -30°C for 5 h. the solution was worked up as for (i) to give a 94:6 mixture of *E*-**63b**:*Z*-**63b** (0.071 g, 71%).

(iii) To **62b** (0.521 g, 1.205 mmol) suspended in dry acetonitrile (20 ml) under nitrogen at room temperature was added DBU (0.204 g, 1.34 mmol). After stirring for 3 h. the solution was worked up as for (i) to give a 89:3:8 mixture of *E*-**63b**:*Z*-**63b**:**64b** (0.280 g, 66%).

2-Benzoyl-7,8-dimethoxy-3-methyl-1-vinyl-2,3,4,5-tetrahydro-*1H*-3-benzazepine
64b

(i)   To the salt **62b** (0.122 g, 0.282 mmol) suspended in dry acetonitrile (5 ml) at 65°C was added DBU (0.052 g, 0.35 mmol), producing the immediate removal of the solid.   After stirring at 65°C for 1 h. the solution was then concentrated and the residue was purified by column chromatography on alumina with dichloromethane/20% light petroleum.   Concentration of the early fraction gave a yellow oil (0.053 g, 54%).   Analysis by ^{1}H NMR revealed a mixture (3.6:1.0) of the B-ring diastereomers of the *3-benzazepine* **64b**.   P.t.l.c. on silica with dichloromethane/3% methanol failed to separate the diastereomers.   *trans diastereomer* ^{1}H NMR δ: 7.88-7.83 (m, *o*-ArH"), 7.57-7.52 (m, *p*-ArH"), 7.48-7.42 (m, *m*-ArH"), 6.66 (s, ArH), 6.37 (s, ArH), 6.27-6.16 (m, H1'), 5.12 (dd, *J* 1.5 Hz, 10.3 Hz, H2'), 4.91 (dd, *J* 1.5 Hz, 17.7 Hz, H2'), 4.48 (d, *J* 6.8 Hz, H2), 4.12-4.08 (m, H1), 3.86 (s, OCH$_3$), 3.76 (s, OCH$_3$), 3.42-3.35 (m, H3), 3.14-3.07 (m, H3), 2.88-2.80 (m, H4), 2.43 (s, NCH$_3$); ^{13}C NMR δ: 201.97 (CO), 148.05 (C7^A), 147.54 (C8^A), 138.60 (C1'), 137.35 (C9a^B), 133.30 (C4"), 133.13 (C5a^B), 131.19 (C1"^{B}), 129.21 (2C"), 128.53 (2C"), 117.30 (C2'), 113.65 (C6^C), 111.38 (C9^C), 69.18 (C2), 56.56 (2OCH$_3$), 51.82 (C4), 50.33 (C1), 45.71 (NCH$_3$), 34.60 (C5);   MS m/z: 351 (M$^+$,100%), 335 (26), 322 (33), 247 (20), 217 (24), 161, (20);   *cis diastereomer* ^{1}H NMR (discernible peaks) δ: 8.00-7.98 (m, *o*-ArH"), 6.65 (s, ArH), 6.53 (s, ArH), 6.48-6.39 (m, H1'), 4.76 (dd, *J* 1.5 Hz, 17.7 Hz, H2'), 4.37 (d, *J* 1.3 Hz, H2), 3.88 (s, OCH$_3$), 3.80 (s, OCH$_3$), 2.41 (s, NCH$_3$); ^{13}C NMR δ 138.80 (C1'), 133.74 (C4"), 117.30 (C2'), 114.34 (C6^A), 114.18 (C9^A), 72.20 (C2), 51.63 (C1), 44.58 (NCH$_3$).

(ii)   The 3-benzazonine *E*-**63b** (0.072 g) in dry acetonitrile (10 ml) was refluxed for 75 min.   Concentration and then passage of the residue through an alumina plug with dichloromethane/20% light petroleum afforded a mixture (4.8:1.0) of the B-ring diastereomers of **64b** (0.043 g, 60%).

E-9,10-Dimethoxy-3-methyl-2,3,4,5-tetrahydro-1H-3-benzazonine-4-spiro-3'-tetrahydro-2'-furanone **66**

(i) The base **49a** (1.049 g, 4.502 mmol) was stirred in dry butanone (4 ml) at 50°C with α-bromo-γ-butyrolactone (1.40 g, 8.48 mmol) for 40 h. then the solution was cooled and diethyl ether (10 ml) was added. The resultant gummy solid was triturated with diethyl ether (4 x 10 ml) then taken-up and concentrated from dichloromethane to give a pale tan hygroscopic powder (1.219 g) of crude **65**.

A portion of the above solid (0.870 g) in dry acetonitrile (45 ml) at 0°C was treated with DBU (0.415 g, 2.72 mmol). After stirring at 0°C for 5 h. the solution was then concentrated and the residue was purified by column chromatography on alumina (15 g) with dichloromethane/10% light petroleum. Concentration of the early fraction (100 ml) gave a yellow oil (0.377) which contained mainly **49a**. This fraction was further purified by column chromatography on alumina (20 g) with light petroleum/15% ethyl acetate to give **49a** (0.210 g, 28%) followed by the E-_benzazonine_ **66** (0.118 g, 12%) as a colourless oil. ^{1}H NMR δ: 6.78 (s, H8), 6.66 (s, H11), 6.54 (d, _J_ 15.8 Hz, H7), 5.42-5.35 (m, H6), 4.26-4.21 (m, H3'), 3.87 (s, OCH$_3$), 3.85 (s, OCH$_3$), 2.96-2.88 (m, H), 2.75-2.72 (m, H), 2.69-2.61 (m, H5), 2.57-2.55 (m, H), 2.49 (s, NCH$_3$), 2.43-2.41 (m, H), 2.37-2.28 (m, H4'), 2.04-1.96 (m, H4'); ^{13}C NMR δ: 178.23 (CO), 147.53 (C9^A), 147.46 (C10^A), 136.65 (C7), 133.47 (C11a^B), 131.32 (C7a^B), 128.98 (C6), 113.76 (C11), 110.39 (C8), 68.12 (C4), 65.70 (C3'), 56.54 (2OCH$_3$), 55.77 (C2), 42.22 (C5^C), 39.14 (NCH$_3$), 37.18 (C1^C), 29.94 (C4'); MS m/z: 317 (M$^+$, 71%; Calcd. for C$_{18}$H$_{23}$NO$_4$ 317.1626, found 317.1640), 258 (16), 204 (53), 189 (50), 173 (26), 126 (100).

(ii) A mixture of α-bromo-γ-butyrolactone (13.29 g, 82.6 mmol) and sodium iodide (19.0 g, 127 mmol) in acetonitrile was stirred sealed at room temperature for 4 days protected from light. The solution was then filtered and the acetonitrile was removed by distillation at atmospheric pressure. The vacuum distillation of the dark residue provided the removal of residual α-bromo-γ-butyrolactone at 130°C and then α-iodo-γ-butyrolactone (12.4 g, 72%) as a yellow liquid with b.p. 165-170°C (1 mmHg).

The base **49a** (1.007 g, 4.316 mmol) was stirred in dry butanone (3 ml) protected from light with α-iodo-γ-butyrolactone (1.64 g, 7.74 mmol) for 40 h. at 50°C. The solution was then concentrated and the residue was triturated with diethyl ether (2 x 20 ml). Column chromatography of the residue on silica with chloroform/10% acetonitrile afforded unreacted **49a**. Elution of the column with chloroform/50% acetonitrile gave crude **65** (0.359, 19%) as a tan powder which was then stirred with DBU (0.171 g, 1.13 mmol) in dry acetonitrile (20 ml) at room temperature for 5 h. Concentration of the solution and then purification of the residue by column chromatography on alumina with dichloromethane/40% hexane afforded **66** (0.075 g, 29%) as a clear oil.

2-(2"-Chloroethoxycarbonyl)methyl-6,7-dimethoxy-1-vinyl-1,2,3,4-tetrahydroisoquinoline 67

2-Chloroethyl bromoacetate was prepared by the reaction of bromoacetic acid (17.2 g, 0.132 mol) with 2-chloroethanol (19.0 g, 0.236 mol) and concentrated sulfuric acid (0.5 ml) in toluene (20 ml). The mixture was refluxed for 5 h. connected to a Dean-Stark condenser then cooled. The organic liquid was extracted with water (40 ml) then 1% aqueous sodium bicarbonate (2 x 20 ml) and water (30 ml) again before drying over sodium sulfate. The residual water and toluene were evaporated from the crude 2-chloroethyl bromoacetate at 150°C under atmospheric pressure, and then the liquid was distilled under reduced pressure to give *2-chloroethylbromoacetate* (18.7 g, 75%) as a clear liquid with b.p. 102-104°C (80 mm).

To the secondary amine **57** (3.01 g, 13.7 mmol) in dichloromethane (85 ml) with potassium carbonate (15 g) was added 2-chloroethyl bromoacetate (4.20 g, 20.7 mmol). The mixture was stirred for 16 h. Filtration of the mixture and washing of the solids with dichloromethane (2 x 10 ml) gave an organic filtrate which was extracted with 5% aqueous sodium bicarbonate (40 ml), then dried and concentrated. The residue was purified by column chromatography on silica (60 g), with a gradient

from dichloromethane/25% hexane to dichloromethane/2.5% ethanol, to give *2-(2"-chloroethoxycarbonyl)methylisoquinoline* **67** (2.52 g, 54%) as a pale tan oil. ^{1}H NMR δ: 6.59 (s, ArH), 6.56 (s, ArH), 5.83-5.71 (m, H1'), 5.35-5.29 (m, H2'), 4.39 (H1"), 4.20 (d, H1), 3.85 (s, OCH$_3$), 3.80 (s, OCH$_3$), 3.70 (t, H2"), 3.64 (d, *J* 17.1 Hz, H of NCH$_2$CO), 3.50 (d, *J* 17.1 Hz, H of NCH$_2$CO), 3.15-3.09 (m, H), 2.94-2.83 (m, 2H), 2.76-2.70 (m, H); ^{13}C NMR δ: 171.36 (CO), 148.14 (C6^A), 147.59 (C7^A), 139.85 (C1'), 128.07 (C4a^B), 126.90 (C8a^B), 119.52 (C2'), 111.70 (C5^C), 111.34 (C8^C), 66.34 (C1), 64.47 (CH$_2$ of NCH$_2$CO^D), 56.38 (2OCH$_3$), 56.23 (C1"^{D}), 48.65 (C3), 42.15 (C2"), 29.26 (C4); MS m/z: 339 (M$^+$, 6%; Calcd. for C$_{17}$H$_{22}$NO$_4$Cl 339.1233, found 339.1225), 338 (7), 314 (34), 312 (100), 250 (11), 232 (61), 218 (42).

Attempted cyclisation of 67 to the Spiro Salt 68

(i) The amine **67** (0.628 g, 1.84 mmol) was stirred in dry butanone (20 ml) with potassium iodide (0.349 g, 2.10 mmol) under nitrogen at room temperature for 1 h. with no reaction.

(ii) Compound **67** (0.622 g, 1.82 mmol) was stirred in dry acetonitrile (20 ml) with potassium iodide (0.352 g, 2.12 mmol) under nitrogen at room temperature for 12 h., with no reaction. The mixture was heated at 55°C and then concentrated. Extraction of the residue with dichloromethane then concentration of the extracts gave unchanged **67** (0.578 g, 93%).

(iii) Compound **67** (0.550 g, 1.62 mmol) was refluxed in dry acetonitrile (15 ml) with potassium iodide (0.364 g, 2.19 mmol) for 12 h. Concentration and then treatment of the residue on a silica column gave the elution of unchanged **67** with dichloromethane. Elution of the column with acetonitrile afforded a dark powder (0.222 g) containing numerous components.

(iv) Compound **67** (0.623 g, 1.83 mmol) was refluxed in dry acetone (15 ml) with sodium iodide (1.0 g, 6.6 mmol) for 48 h. protected by a drying tube. The solution was then concentrated and the residue was extracted with dichloromethane (3 x 20

ml). The extracts were filtered then concentrated to afford a tan foam (0.688 g) which on analysis by ^{1}H NMR indicated many components.

6,7-Dimethoxy-1-isopropenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline 70a

A solution of isopropenylmagnesium bromide was prepared by the slow addition of 2-bromopropene (10.25 g, 84.7 mmol) to magnesium turnings (2.30 g, 94.6 mmol) in dry tetrahydrofuran (100 ml) under nitrogen. The reaction was initiated by heating the solution to reflux in the presence of an iodine crystal. The addition rate was controlled to maintain a gentle reflux. The mixture was refluxed for 30 min. after the completion of the addition.

The solution of isopropenylmagnesium bromide in tetrahydrofuran was cooled to <-50°C in an acetone/liquid nitrogen slush bath, with the deposition of some solid, and then the iminium salt 48a (9.51 g, 28.5 mmol) was added portionwise over 30 min. The mixture was allowed to warm slowly to room temperature with stirring for 20 h. and then warmed to 40°C for 1 h. The mixture was then cooled and ice was added carefully to decompose the excess Grignard reagent. The mixture was basified by the addition of 40% aqueous potassium hydroxide and diethyl ether (100 ml) was added. The organic layer was decanted from the precipitated inorganic salts and washed with water (50 ml). The inorganic salts and aqueous layer were extracted with further portions of diethyl ether (3 x 50 ml). The ether extracts were combined and then concentrated. The residue was taken up in dichloromethane (100 ml) and the organic solution was washed with water (6 x 20 ml). Drying and then concentration of the organic solution gave the *1-isopropenylisoquinoline* 70a (6.595 g, 94%) as a pale tan oil of >99% purity by GC-MS analysis. The oil formed a solid on storage at -5°C. ^{1}H NMR δ: 6.64 (s, ArH), 6.58 (s, ArH), 5.08 (d, *J* 1.5 Hz, H2'), 3.84 (s, OCH$_3$), 3.79 (s, OCH$_3$), 3.61 (s, H1), 3.06-3.00 (m, 2H), 2.62-2.56 (m, H), 2.49-2.40 (m, H), 2.32 (s, NCH$_3$), 1.50 (CH$_3$); ^{13}C NMR δ: 148.02 (C6^A), 147.82 (C7^A), 147.22 (C1'), 128.32 (C4a^B), 127.77 (C8a^B), 116.18 (C2'), 111.59 (C5^C), 110.25 (C8^C), 74.18 (C1), 56.46 (OCH$_3$), 56.35

(OCH3), 53.08 (C3), 44.66 (NCH3), 29.75 (C4), 17.56 (CH3); MS m/z: 247 (M+,

2%; Calcd. for C15H21NO2 247.1570, found 247.156), 207 (14), 206 (100), 191 (6),

190 (14), 162 (6); IR (thin film from CH2Cl2): 2945, 2833, 2781, 1516, 1259, 1219,

1142 cm^{-1}.

6,7-Dimethoxy-2-methyl-1-(α-phenylethenyl)-1,2,3,4-tetrahydroisoquinoline 70b

A solution of α-phenylethenylmagnesium bromide was prepared by the

dropwise addition of α-bromostyrene (15.0 g, 81.9 mmol) to magnesium turnings

(2.22 g, 91.3 mmol) in dry tetrahydrofuran (200 ml) under nitrogen over 45 min.

The mixture was heated briefly to initiate the reaction at the start of the addition with

an iodine crystal present. The reaction temperature was then kept below 35°C. The

solution was stirred for 30 min. after the addition had ceased.

The solution of α-phenylethenylmagnesium bromide in tetrahydrofuran was

cooled to <-50°C in an acetone/liquid nitrogen slush bath and then the iminium salt

48a (13.52 g, 40.6 mmol) was added. The mixture was stirred at <-50°C for 90 min.

and then allowed to warm slowly to room temperature with stirring for 16 h. before

the careful addition of ice to decompose excess Grignard reagent. The mixture was

basified by the addition of 40% aqueous potassium hydroxide and diethyl ether (150

ml) was added. The organic layer was decanted from the precipitated inorganic salts

then centrifuged to remove any residual solids, washed with water (150 ml), and then

concentrated. The residue was dissolved in diethyl ether (240 ml) which had been

used, in three portions, to extract the inorganic solids and then the aqueous wash.

The ether solution was washed with water (30 ml) then saturated brine (2 x 20 ml),

and then dried and passed through a silica plug. Concentration of the solution

afforded a solid which recrystallised from ethanol to give the *1-(α-*

phenylethenyl)isoquinoline 70b (11.11 g, 88%) as a pale yellow powder with m.p.

80-82°C. ^{1}H NMR δ: 7.33-7.28 (m, 2ArH"), 7.22-7.17 (m, 3ArH"), 6.72 (s, ArH),

6.59 (s, ArH), 5.60 (d, *J* 1.6 Hz, H2'), 5.34 (d, *J* 1.6 Hz, H2'), 4.09 (s, H1), 3.84 (s,

OCH3), 3.72 (s, OCH3), 3.10-3.02 (m, 2H), 2.66-2.45 (m, 2H), 2.33 (s, NCH3); ^{13}C

NMR δ: 149.93 (C1'), 147.94 (C6^A), 147.78 (C7^A), 140.30 (C1"^{B}), 128.91 (C4a^B), 128.48 (2C"), 128.18 (2C"), 127.96 (C"), 127.23 (C8a^B), 119.10 (C2'), 111.63 (C5^C), 110.55 (C8^C), 73.69 (C1), 56.34 (2OCH$_3$), 52.98 (C3), 44.74 (NCH$_3$), 29.38 (C4); MS m/z: 308 (M-H$^+$, 0.5%; Calcd. for C$_{20}$H$_{22}$NO$_2$ 308.1650, found 308.1647), 206 (100), 190 (8), 162 (4), 132 (2), 103 (2), 77 (4); IR (KBr disc): 2768, 1514, 1256, 1217, 1143, 783 cm^{-1}; Anal. Calcd for C$_{20}$H$_{23}$NO$_2$: C, 77.64; H, 7.49; N, 4.53%, found : C, 77.67; H, 7.64; N, 4.42%.

6,7-Dimethoxy-2-methyl-1-(1'-trimethylsilylethenyl)-1,2,3,4-tetrahydroisoquinoline 70c

The 1-(bromovinyl)trimethylsilane required for this procedure was prepared[177] from commercial (Aldrich) vinyltrimethylsilane. A solution of 1-trimethylsilylethenylmagnesium bromide in dry tetrahydrofuran (60 ml) under nitrogen was then prepared from the 1-(bromovinyl)trimethylsilane (9.03 g, 50.4 mmol) by the method of Ottolenghi *et. al.*[178]

The solution of 1-trimethylsilyethenylmagnesium bromide in tetrahydrofuran was cooled to <-50°C in an acetone/liquid nitrogen slush bath and then additional dry tetrahydrofuran (50 ml) was added followed by the iminium salt **48a** (8.404 g, 25.22 mmol). The mixture was allowed to warm slowly to room temperature with stirring for 19 h. The reaction was worked up (as for **70b**) to give a solid upon concentration of the ether solution. Recrystallisation of the solid from ethanol afforded *1-(1'-trimethylsilylethenyl)isoquinoline* **70c** (6.231 g, 81%) as a colourless solid with m.p. 89-90°C. ^{1}H NMR δ: 6.55 (s, 2ArH), 5.79 (d, *J* 3.3 Hz, H2'), 5.62 (d, *J* 3.1 Hz, H2'), 3.85 (s, OCH$_3$), 3.78 (s, OCH$_3$), 3.67 (s, H1), 3.03-2.95 (m, 2H), 2.62-2.54 (m, H), 2.42-2.36 (m, H), 2.27 (s, NCH$_3$), -0.12 (Si(CH$_3$)$_3$); ^{13}C NMR δ: 156.03 (C1'), 147.86 (C6^A), 147.42 (C7^A), 129.66 (C4a^B), 128.95 (C2'), 127.36 (C8a^B), 111.53 (C5 and C8), 76.56 (C1), 56.46 (2OCH$_3$), 52.97 (C3), 45.30 (NCH$_3$), 29.70 (C4), 0.44 (Si(CH$_3$)$_3$); MS m/z: 305 (M$^+$, 0.4%), 304 (1), 290 (2), 206 (100), 190 (8), 162

(3); Anal. Calcd for $C_{17}H_{27}NO_2Si$: C, 66.84; H, 8.91; N, 4.59%, found : C, 66.94; H, 8.78; N, 4.57%.

6.7-Dimethoxy-1-(1'-iodoethenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline 70d

(i) To a stirred mixture of sodium iodide (1.301 g, 8.68 mmol) in acetonitrile (6 ml) was added trimethylchlorosilane (0.934 g, 8.60 mmol) then a solution of water (85 mg, 4.7 mmol) in acetonitrile (4 ml). After 10 min. the 1-ethynyl base 71 (0.503 g, 2.17 mmol) was added. The mixture was stirred in an oil bath at 80°C for 4 h. then cooled and treated with 2M aqueous sodium hydroxide (5 ml). The solution was extracted with diethyl ether (3 x 10 ml) and the ether extracts were then combined and washed with water (5 ml), and then saturated brine (5 ml). Drying and then concentration of the extracts gave a tan powder (0.569 g) which contained 71 (41%), the 1-(1'-iodoethenyl) product 70d (27%), and a component tentatively identified as 6,7-dimethoxy-1-(*cis*-2'-iodoethenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (32%) due to the following signals: ^{1}H NMR δ: 6.58 (d, *J* 7.4 Hz, H2'), 6.18 (dd, *J* 7.6 Hz, 8.8 Hz, H1'), 4.23 (d, *J* 8.8 Hz, H1), 2.31 (NCH$_3$); ^{13}C NMR δ: 142.31 (C1'), 86.59 (C2'), 68.96 (C1). Purification of this material by p.t.l.c. on silica with hexane/50% ethyl acetate provided, from R$_f$ 0.92, the *1-(1'-iodoethenyl)isoquinoline* 70d (0.149 g, 19%) which recrystallised from ethanol as a pale tan powder with m.p. 89-90°C. ^{1}H NMR δ: 6.59 (s, ArH), 6.57 (s, ArH), 6.53 (d, *J* 0.8 Hz, H2'), 6.09 (d, *J* 0.8 Hz, H2'), 3.85 (s, OCH$_3$), 3.82 (s, OCH$_3$), 3.18 (s, H1), 3.12-3.05 (m, 2H), 2.67-2.59 (m, 2H); 2.38 (s, NCH$_3$); ^{13}C NMR δ: 148.43 (C6^A), 147.85 (C7^A), 128.92 (C2'), 128.08 (C4a^B), 126.70 (C8a^B), 120.92 (C1'^{B}), 111.42 (C5^C), 110.24 (C8^C), 75.96 (C1), 56.47 (OCH$_3$), 56.23 (OCH$_3$), 51.71 (C3), 44.26 (NCH$_3$), 29.23 (C4); MS m/z: 359 (M$^+$, 4%; Calcd. for $C_{14}H_{18}NO_2I$ 359.0382, found 359.0382), 230 (2), 206 (100), 190 (5), 142 (4); Anal. Calcd for $C_{14}H_{18}NO_2I$: C, 46.81; H, 5.05; N, 3.90%, found : C, 46.72; H, 5.16; N, 3.94%.

(ii) To a stirred mixture of sodium iodide (15.54 g, 103.7 mmol) in acetonitrile (53 ml) was added trimethylchlorosilane (11.23 g, 103.4 mmol) then a solution of water

(0.938 g, 52.1 mmol) in acetonitrile (35 ml). After 10 min. the 1-ethynyl base **71** (4.046 g, 17.49 mmol) was added. The mixture was stirred in an oil bath at 80°C for 8.5 h. then cooled and concentrated. The residue was partitioned between 2M aqueous sodium hydroxide (50 ml) and diethyl ether (150 ml) and the aqueous layer was then extracted with further diethyl ether (2 x 60 ml). The ether extracts were combined and washed with water (3 x 30 ml) then saturated brine (2 x 30 ml), and then dried and passed through a silica plug, removing much yellow colour. Concentration of the solution gave a yellow solid (3.123 g) which, after applying the material in the minimum of dichloromethane/25% hexane, was purified by column chromatography on silica with hexane/30% ethyl acetate to afford **70d** (1.885 g, 30%). Elution of the column with hexane/60% ethyl acetate afforded **71** (1.190 g, 29%).

Attempted Preparation of **70d**, or a 1-(1'-Bromoethenyl)- Analogue, from **70c**

(i) The 1-(1'-trimethylsilylethenyl)isoquinoline **70c** (0.646 g, 1.939 mmol) was stirred in dichloromethane (35 ml) with iodine (0.40 g, 1.6 mmol) at room temperature for 4 h. The organic solution was washed with 5% aqueous sodium bicarbonate (2 x 10 ml) then dried and concentrated to give a dark solid (0.548 g). The material contained many components, all with signals between 3.96 δ and 3.65 δ for the N-methyl group in the ^{1}H NMR spectrum.

(ii) To **70c** (0.527 g, 1.725 mmol) in dichloromethane (2 ml) at -78°C was added dropwise a solution of bromine (0.294 g, 1.86 mmol) in dichloromethane (2 ml), with the rapid removal of colour and the formation of a colourless precipitate. The mixture was stirred for 40 min. at -78°C then warmed to room temperature. The solid dissolved. Concentration of the solution gave a pale yellow powder comprising two approximately equal components. The compounds were tentatively identified as 6,7-dimethoxy-2-methyl-1-(1'-trimethylsilylethenyl)-3,4-dihydroisoquinolinium bromide and 6,7-dimethoxy-2-methyl-1-(1'-trimethylsilylethenyl)-1,2,3,4-tetrahydro-isoquinolinium bromide by NMR analysis of the mixture.

6,7-Dimethoxy-1-ethynyl-2-methyl-1,2,3,4-tetrahydroisoquinoline 71

A commercial (Aldrich) solution of 0.5M ethynylmagnesium bromide in tetrahydrofuran (180 ml, 90 mmol) under nitrogen was cooled in an acetone/liquid nitrogen slush bath to <-50°C and then the iminium salt **48a** (15.00 g, 45.04 mmol) was added. The mixture was allowed to warm slowly to room temperature with stirring for 16 h. then worked up (as for **70b**) to give a solid upon concentration of the ether solution. Recrystallisation of the solid from ethanol afforded *1-ethynylisoquinoline* **71** (6.88 g, 66%) as a pale yellow solid of >99% purity by GC-MS analysis. ^{1}H NMR δ: 6.75 (s, ArH), 6.57 (s, ArH), 4.42 (s, H1), 3.85 (s, OCH$_3$), 3.83 (s, OCH$_3$), 2.94-2.63 (m, 4H), 2.54 (s, NCH$_3$), 2.42 (d, *J* 2.3 Hz, H2'); ^{13}C NMR δ: 148.75 (C6[A]), 147.93 (C7[A]), 127.15 (C4a[B]), 126.02 (C8a[B]), 111.79 (C5[C]), 110.58 (C8[C]), 82.31 (C2'), 74.57 (C1'[D]), 56.47 (C1[D]), 56.34 (OCH$_3$), 56.28 (OCH$_3$), 48.79 (C3), 43.99 (NCH$_3$), 28.89 (C4); MS m/z: 231 (M[+], 84%; Calcd. for C$_{14}$H$_{17}$NO$_2$ 231.1259, found 231.1250), 230 (100), 216 (30), 200 (37), 188 (50), 145 (53), 115 (34); IR (KBr disc): 3239, 2943, 1519, 1256, 1225, 1136, 1010, 702 cm^{-1}.

2-Ethoxycarbonylmethyl-6,7-dimethoxy-1-isopropenyl-2-methyl-1,2,3,4-tetrahydroisoquinolinium Bromide 72a

The base **70a** (1.498 g, 6.059 mmol) was stirred in dry butanone (10 ml) under nitrogen with ethyl bromoacetate (2 ml, 18 mmol) for 10 h. at 55°C. Concentration of the solution and trituration of the residue with diethyl ether (4 x 15 ml) gave, after drying, a pale foam (2.452 g) which upon recrystallisation from ethanol/tetrahydrofuran afforded a mixture (*trans:cis*=46:54) of the B-ring diastereomers of the *2-ethoxycarbonylmethylisoquinolinium salt* **72a** (1.183 g, 47%) as an off-white powder. *trans diastereomer* (assignable signals) ^{1}H NMR δ: 6.70 (s, ArH), 6.49 (s, ArH), 5.91 (s, H1), 5.38 (d, *J* 17.4 Hz, H of NCH$_2$CO), 4.38 (d, *J* 17.3 Hz, H of NCH$_2$CO), 4.25 (q, CH$_2$ of Et), 3.97-3.88 (m, H), 3.89 (s, OCH$_3$), 3.83 (s, OCH$_3$), 3.60 (s, NCH$_3$), 1.82 (s, CH$_3$), 1.29 (t, CH$_3$ of Et); ^{13}C NMR δ: 137.57 (C1'), 130.00 (C2'), 76.13 (C1), 63.47 (CH$_2$ of Et), 58.28 (NCH$_2$CO[A]), 56.69

(2OCH$_3$), 54.84 (C3^A), 49.47 (NCH$_3$), 24.20 (C4), 22.09 (CH$_3$), 14.48 (CH$_3$ of Et);

cis diastereomer (assignable signals) ^{1}H NMR δ: 6.72 (s, ArH), 6.43 (s, ArH), 6.20

(s, H1), 5.37 (d, *J* 17.3 Hz, H of NCH$_2$CO), 4.95-4.4.89 (m, H), 4.64 (d, *J* 17.1 Hz, H

of NCH$_2$CO), 4.25 (q, CH$_2$ of Et), 3.90 (s, OCH$_3$), 3.83 (s, OCH$_3$), 3.78 (s, NCH$_3$),

1.71 (s, CH$_3$), 1.33 (t, CH$_3$ of Et); ^{13}C NMR δ: 138.49 (C1'), 128.05 (C2'), 76.13

(C1), 63.47 (CH$_2$ of Et), 61.52 (NCH$_2$CO^A), 56.69 (2OCH$_3$), 56.10 (C3^A), 47.35

(NCH$_3$), 23.58 (C4), 20.83 (CH$_3$), 14.48 (CH$_3$ of Et); IR of mixture (thin film from

CDCl$_3$): 1744, 1520, 1257, 1229, 1123 cm^{-1}.

2-Ethoxycarbonylmethyl-6,7-dimethoxy-2-methyl-1-(α-phenylethenyl)-1,2,3,4-tetrahydroisoquinolinium Bromide 72b

The base **70b** (2.224 g, 7.188 mmol) was stirred in dry butanone (7 ml) under

nitrogen with ethyl bromoacetate (1.81 g, 10.8 mmol) for 10 h. at 50°C.

Concentration of the solution and trituration of the residue with diethyl ether (4 x 20

ml) afforded a gum which on concentration from a solution in dichloromethane gave

a mixture (*trans:cis*=58:42) of the B-ring diastereomers of the *2-*

ethoxycarbonylmethylisoquinolinium salt **72b** (1.183 g, 47%) as a tan hygroscopic

powder. *trans diastereomer* (assignable signals) ^{13}C NMR δ: 165.36 (COO), 143.44

(C1"^{A}), 139.60 (C1'^{A}), 131.41 (C2'), 74.2-73.6 (bs, C1), 63.19 (CH$_2$ of Et), 61.20

(NCH$_2$CO^B), 56.52 (2OCH$_3$), 53.81 (C3^B), 47.11 (NCH$_3$), 23.76 (C4), 14.10 (CH$_3$

of Et); *cis diastereomer* (assignable signals) ^{13}C NMR δ: 165.17 (COO), 142.49

(C1"^{A}), 138.60 (C1'^{A}), 130.65 (C2'), 74.2-73.6 (bs, C1), 63.03 (CH$_2$ of Et), 58.17

(NCH$_2$CO^B), 56.52 (2OCH$_3$), 54.84 (C3^B), 49.79 (NCH$_3$), 23.05 (C4), 14.10 (CH$_3$

of Et).

2-Ethoxycarbonylmethyl-6,7-dimethoxy-2-methyl-1-(1'-trimethylsilylethenyl)-1,2,3,4-tetrahydroisoquinolinium Bromide 72c

To the base **70c** (0.520 g, 1.70 mmol) in dry acetonitrile (4 ml) under nitrogen

at 0°C was added a solution of ethoxycarbonylmethyltriflate (0.528 g, 2.24 mmol) in

acetonitrile (2 ml). Stirring at 0°C for 45 min. and 25°C for 4 h. provided a homogeneous solution which was then concentrated. Trituration of the residue with diethyl ether (4 x 15 ml) afforded a white powder which was stirred in ethanol (10 ml) with potassium bromide (1.43 g) for 3 h. Concentration of the mixture and extraction of the residue with dichloromethane (4 x 10 ml) gave, after concentration of the organic extracts, a single B-ring diastereomer of the *2-ethoxycarbonylmethyl salt* **72c** (0.781 g, 80%) as a white powder. ^{1}H NMR δ: 6.67 (s, ArH), 6.30 (s, ArH^A), 6.24 (s, H2'^{A}), 6.18 (bs, H2'^{A}), 5.64 (s, H1), 4.44 (d, J 16.9 Hz, H of NCH$_2$CO), 4.37 (d, J 16.9 Hz, H of NCH$_2$CO), 4.29-4.19 (m, CH$_2$ of Et and H3), 3.85 (s, OCH$_3$), 3.76 (s, OCH$_3$), 3.71-3.56 (m, H3), 3.27 (s, NCH$_3$), 3.17-3.09 (m, H4), 1.25 (t, CH$_3$ of Et), 0.11 (s, Si(CH$_3$)$_3$); ^{13}C NMR δ: 165.55 (COO), 150.37 (C6^A), 149.67 (C7^A), 146.64 (C1'), 143.99 (C2'), 122.14 (C4a^B), 120.64 (C8a^B), 111.19 (C5^C), 110.93 (C8^C), 74.43 (bs, C1), 63.62 (CH$_2$ of Et), 58.41 (NCH$_2$CO^D), 56.62 (2OCH$_3$), 54.52 (C3^D), 49.66 (NCH$_3$), 24.00 (C4), 14.32 (CH$_3$ of Et), 0.58 (Si(CH$_3$)$_3$).

2-Ethoxycarbonylmethyl-6,7-dimethoxy-1-iodo-2-methyl-1,2,3,4-tetrahydroisoquinolinium Bromide 72d

To the base **70d** (0.602 g, 1.68 mmol) in dry acetonitrile (4 ml) under nitrogen at 0°C was added a solution of ethoxycarbonylmethyltriflate (0.524 g, 2.22 mmol) in acetonitrile (3 ml). Stirring at 0°C for 1 h. and 25°C for 4 h. provided a homogeneous solution which was then concentrated. Trituration of the residue with diethyl ether (3 x 20 ml) afforded a gum which was stirred in ethanol (10 ml) with potassium bromide (1.00 g) for 3 h. Concentration of the mixture and extraction of the residue with dichloromethane (4 x 7 ml) gave, after concentration of the organic extracts, a yellow powder from which residual **70d** was then removed by column chromatography on silica with dichloromethane/0-20% ethanol to give a single B-ring diastereomer of the *2-ethoxycarbonylmethyl salt* **72d** (0.781 g, 89%) as an off-white powder. ^{1}H NMR δ: 7.46 (s, H2'), 6.71 (s, H2'^{A}), 6.63 (s, ArH^A), 6.51 (s,

ArH^A), 5.56 (s, H1), 4.63-4.56 (m, H3), 4.33-4.20 (m, 5H), 3.90 (s, OCH$_3$), 3.85 (s, OCH$_3$), 3.52 (s, NCH$_3$), 3.15-3.07 (m, H4), 1.28 (t, CH$_3$ of Et); ^{13}C NMR δ: 165.13 (COO), 151.02 (C6^A), 150.05 (C7^A), 143.53 (C2'), 121.35 (4a^B), 120.93 (8a^B), 111.29 (C5^C), 110.94 (C8^C), 100.94 (C1'), 77.44 (C1), 63.90 (CH$_2$ of Et), 59.36 (NCH$_2$CO), 56.83 (OCH$_3$), 56.67 (OCH$_3$), 53.93 (C3), 50.31 (NCH$_3$), 23.93 (C4), 14.38 (CH$_3$ of Et).

1-[2'-(6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline)ethynyl]-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline 73

The crystallisation mother liquor from the formation of **71** was concentrated and the residue was then submitted to column chromatography on alumina (45 g) with a gradient from dichloromethane/5%hexane to dichloromethane/5% methanol. Residual **71** eluted in the early fractions. Concentration of the late fractions provided the *title compound* **73** (0.76 g, 8%) as a pale yellow powder. Recrystallisation of a portion from dichloromethane/hexane gave off-white needles with m.p. 178-179°C. Two conformers (ratio 71:29) gave the signals marked with superscripts^{X,Y} in the ^{1}H NMR spectrum of this material. ^{1}H NMR δ: 6.78^X and 6.73^Y (s, ArH), 6.56 (s, ArH), 4.41 (s, H1), 3.83 (s, OCH$_3$), 3.78^X and 3.71^Y (s, OCH$_3$), 2.98-2.90 (m, H), 2.83-2.79 (m, 2H), 2.63-2.57 (m, H), 2.56^Y and 2.52^X (s, NCH$_3$); ^{13}C NMR δ 148.56 (C6^A), 147.82 (C7^A), 127.94 (C4a^B), 126.02 (C8a^B), 111.67 (C5^C), 110.78 (C8^C), 85.02 (C1'), 57.03 (C1), 56.40 (2OCH$_3$), 49.79 (C3), 44.42 (NCH$_3$), 29.02 (C4); MS (LSIMS in a glycerol matrix) m/z: 437 (MH$^+$, 33%), 406 (3), 277 (9), 230 (13), 219 (8), 206 (100), 204 (28); IR (KBr disc): 3239, 2943, 1522, 1254, 1223, 1132, 1009 cm^{-1}.

Attempted Preparation of 1-Cyanoethenylmagnesium Chloride for Synthesis of 74a

(i) To magnesium turnings (1.71 g, 70.2 mmol) in dry tetrahydrofuran under nitrogen was added an iodine crystal and 2-chloroacrylonitrile (5.12 g, 58.5 mmol) portionwise. The mixture was heated to reflux for 10 min. No reaction initiated.

The mixture was cooled and submitted to ultrasound irradiation, then a small amount of iodomethane was added and the mixture was returned to reflux. No reaction occurred.

(ii) Magnesium turnings (3.40 g, 142 mmol) were activated[90] by stirring the turnings vigorously under nitrogen for 2.5 days. The magnesium became very dark and a 'mirror' of metal formed on the glass vessel. Dry tetrahydrofuran (10 ml) was added and the mixture was cooled to 0°C then 2-chloroacrylonitrile (2.20 g, 25.1 mmol) was added as a solution in dry tetrahydrofuran (25 ml) dropwise over 80 min. The mixture was stirred at 0°C for a further 5 h. No reaction occurred.

Attempted Preparation of 6,7-Dimethoxy-1-(1'-cyclopentenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline 74b

The method of Braude and Forbes[91] was modified to generate 1-cyclopentenyllithium in tetrahydrofuran rather than diethyl ether. Thus freshly distilled 1-chlorocyclopentene (4.056 g, 39.54 mmol) in dry tetrahydrofuran (8 ml) was added to a stirred suspension of finely cut lithium wire (0.61 g, 88 mmol) in dry tetrahydrofuran (70 ml) under argon. The mixture was heated for 6 h. in an oil bath at 45-50°C then 18 h. at 63-65°C. No reaction occurred at the lower temperature. After heating at the higher temperature the solution was a grey/green colour with a white precipitate. The solution was transferred via cannula to a new reaction vessel, leaving residual lithium (0.31 g), then cooled to -78°C under nitrogen and the iminium salt **48a** (6.164 g, 18.50 mmol) was added. After 1 h. at -78°C the mixture was allowed to warm to room temperature with stirring over 18 h. Ice was added cautiously until the vigorous reaction ceased then water (30 ml) and diethyl ether (60 ml) were added. The aqueous layer was made basic with 2M aqueous sodium hydroxide then the layers were separated and the aqueous layer was extracted with diethyl ether (2 x 30 ml) then chloroform (3 x 30 ml). The ether extracts were combined and washed with water (2 x 20 ml) then saturated brine (20 ml), and then dried and concentrated to a yellow oil (0.994 g) which displayed many components

on ^{1}H NMR spectral analysis. Concentration of the chloroform extracts and recrystallisation of the residue from ethanol afforded the recovery of **48a** (3.554 g, 58%).

Ethyl 9,10-Dimethoxy-3,6-dimethyl-2,3,4,5-tetrahydro-1*H*-3-benzazonine-4-carboxylate 75a

(i) The salt **72a** (0.302 g, 0.729 mmol) was stirred in dry acetonitrile (10 ml) under nitrogen at room temperature with DBU (0.14 g, 0.94 mmol) for 5 h. then the solution was concentrated. Purification of the residue by column chromatography on alumina (6 g) with dichloromethane/20% light petroleum afforded, from the early fraction (100 ml), a mixture (*E/Z* = 1.83) of the *3-benzazonine isomers* **75a** (0.226 g, 93%) as a pale yellow oil. A portion (148 mg) of this mixture was purified by preparative reverse phase HPLC with acetonitrile/20% water to give:

(a) after 20.8 min., the *Z-benzazonine Z-75a* (37 mg) as a colourless oil. ^{1}H NMR δ: 6.56 (s, ArH), 6.53 (s, ArH), 6.38 (s, H7), 4.09 (q, CH$_2$ of Et), 3.86 (s, OCH$_3$), 3.83 (s, OCH$_3$), 3.59 (dd, *J* 4.0 Hz, 12.6 Hz, H4), 3.06-2.99 (m, H), 2.90-2.82 (m, H), 2.71-2.57 (m, 2H), 2.60 (s, NCH$_3$), 2.27 (dd, *J* 13.3 Hz, 13.3 Hz, H5), 2.03 (dd, *J* 3.9 Hz, 14.0 Hz, H5), 1.90 (s, CH$_3$), 1.23 (t, CH$_3$ of Et); ^{13}C NMR δ: 174.31 (COO), 148.07 (C9^A), 147.20 (C10^A), 138.59 (C7a^B), 135.04 (C11a^B), 130.70 (C6^B), 127.53 (C7), 113.63 (C8^C), 112.10 (C11^C), 65.04 (C4), 60.65 (CH$_2$ of Et), 56.43 (2OCH$_3$), 52.95 (C2), 45.57 (NCH$_3$), 38.35 (C5), 36.65 (C1), 22.31 (CH$_3$), 15.01 (CH$_3$ of Et); MS m/z: 333 (M$^+$, 21%; Calcd. for C$_{19}$H$_{27}$NO$_4$ 333.1940, found 333.1951), 260 (100), 229 (4), 203 (10), 130 (4).

(b) after 24.5 min., the *E-benzazonine E-75a* (52 mg) as a colourless oil. ^{1}H NMR δ: 6.71 (s, ArH), 6.67 (s, ArH), 6.28 (s, H7), 4.12 (q, CH$_2$ of Et), 3.87 (s, OCH$_3$), 3.85 (s, OCH$_3$), 3.54 (d, *J* 6.3 Hz, H4), 2.88-2.70 (m, 4H), 2.65 (s, NCH$_3$), 2.59-2.53 (m, H5), 1.99-1.94 (m, H5), 1.45 (s, CH$_3$), 1.26 (t, CH$_3$ of Et); ^{13}C NMR δ: 174.34 (COO), 147.29 (C9^A), 147.03 (C10^A), 133.87 (C7a^B), 132.48 (C11a^B), 131.64 (C6^B), 129.66 (C7), 113.84 (C8^C), 111.89 (C11^C), 65.92 (C4), 60.82 (CH$_2$ of Et),

56.67 (OCH$_3$), 56.51 (OCH$_3$), 55.22 (C2), 45.64 (NCH$_3$), 41.56 (C1^D), 39.00 (C5^D), 18.91 (CH$_3$), 14.99 (CH$_3$ of Et); MS m/z: 333 (M$^+$, 23%; Calcd. for C$_{19}$H$_{27}$NO$_4$ 333.1940, found 333.1922), 276 (10), 260 (100), 217 (5), 203 (10).

(ii) The salt **72a** (0.282 g, 0.682 mmol) was stirred in dry acetonitrile (15 ml) under nitrogen (10 ml) with DBU (0.13 g, 0.87 mmol) between -45°C and -40°C for 6 h. then allowed to warm slowly to room temperature before workup as for (i) to afford a mixture (*E/Z* = 1.72) of the isomers of **75a** (0.221 g, 97%).

(iii) The salt **72a** (0.290 g, 0.700 mmol) was refluxed in dry acetonitrile (10 ml) with DBU (0.13 g, 0.87 mmol) for 1 h. before workup as for (i) to afford a mixture (*E/Z* = 3.10) of the isomers of **75a** (0.217 g, 93%).

Ethyl 9,10-Dimethoxy-3-methyl-6-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazonine-4-carboxylate **75b**

(i) The salt **72b** (0.307 g, 0.644 mmol) was stirred in dry acetonitrile (15 ml) under nitrogen at room temperature with DBU (0.17 g, 0.84 mmol) for 5 h. then the solution was concentrated. Purification of the residue by column chromatography on alumina with dichloromethane/20% light petroleum afforded a pale yellow oil (0.206 g, 81%). ^{1}H NMR analysis indicated a mixture of 4 components attributed to *E*-**75b**:*Z*-**75b**:**76b**:**77** in the ratio of 37:53:8:2. A portion (160 mg) of this mixture was purified by preparative reverse phase HPLC with acetonitrile/36% water to give:

(a) after 27.0 min., a mixture (9 mg) of two components (67:33) attributed to **76b** and **77**. *Compound* **76b** ^{1}H NMR δ: 7.42-7.25 (m, 5ArH"), 6.72 (s, ArH), 6.63 (s, ArH), 5.33 (s, H2'), 4.91 (s, H2'), 4.50 (d, *J* 6.5 Hz, H2), 4.03 (q, CH$_2$ of Et), 3.86 (s, OCH$_3$), 3.82 (s, OCH$_3$), 3.66 (d, *J* 6.5 Hz, H1), 3.30-3.15 (m, 2H), 2.75-2.65 (m, 2H), 2.29 (s, NCH$_3$), 1.15 (t, CH$_3$ of Et); ^{13}C NMR δ: 172.61 (COO), 116.52 (C2'), 66.98 (C2), 60.48 (CH$_2$ of Et), 53.29 (C1), 50.44 (C4), 46.61 (NCH$_3$), 35.81 (C5), 15.11 (CH$_3$ of Et). *Compound* **77** ^{1}H NMR δ: 7.64 (dd, *J* 1.4 Hz, 7.6 Hz, *o*-ArH"), 7.42-7.25 (m, 3ArH"), 7.06 (s, H), 6.96 (s, H), 6.89 (s, H), 6.80 (dd, *J* 11.0 Hz, 17.0, H), 5.57 (dd, *J* 1.0 Hz, 17.0, H), 5.17 (dd, *J* 1.0 Hz, 11.0, H), 4.03 (q, CH$_2$ of Et),

3.94 (s, OCH$_3$), 3.91 (s, OCH$_3$), 3.61 (s, 2H), 3.15 (s, 2H), 2.25 (s, NCH$_3$), 1.17 (t, CH$_3$ of Et); ^{13}C NMR δ: 171.60 (COO), 113.83 (=CH$_2$), 60.81 (CH$_2$ of Et), 58.25 (NCH$_2$), 55.19 (NCH$_2$), 42.72 (NCH$_3$), 14.79 (CH$_3$ of Et).

(b) after 32.8 min., the *benzazonine isomer*[*] *E*-75b (50 mg) which recrystallised from ethanol as colourless needles with m.p. 101-102°C. ^{1}H NMR (d$_6$-benzene at 75°C) δ: 7.56 (d, *J* 7.3 Hz, *o*-ArH"), 7.01-6.91 (m, 3ArH"), 6.74 (s, H7^A), 6.60 (s, H8^A), 6.56 (s, H11^A), 4.10-3.82 (bs, CH$_2$ of Et), 3.53 (s, OCH$_3$), 3.45 (s, OCH$_3$), 3.36 (t, H4), 3.01-2.94 (m, 4H), 2.66-2.57 (bs, H), 2.48 (s, NCH$_3$), 2.42-2.36 (bs, H), 0.94 (t, CH$_3$ of Et); ^{13}C NMR (d$_6$-benzene) δ: 173.00 (COO), 150.04 (C9^A), 149.65 (C10^A), 141.27 (C1"^{B}), 133.40 (C7a^B), 132.62 (C11a^B or C6^B), 131.47 (C7), 117.56 (C11), 114.66 (C8), 65.95 (C4), 60.78 (CH$_2$ of Et), 57.96 (bs, C2), 57.11 (OCH$_3$), 56.99 (OCH$_3$), 41.47 (C5), 37.53 (bs, C1), 14.93 (CH$_3$ of Et), NCH$_3$ not observed; ^{1}H NMR (CDCl$_3$ at -50°C): *conformer 1* δ: 6.88 (s, H7^A), 6.54 (s, H8^A), 6.38 (s, H11^A), 3.98 (s, OCH$_3$), 3.83 (s, OCH$_3$), 2.36 (s, CH$_3$), 1.38 (t, CH$_3$ of Et). *conformer 2* δ: 6.82 (s, H7^A), 6.67 (s, H8^A), 6.45 (s, H11^A), 3.93 (s, OCH$_3$), 3.64 (s, OCH$_3$), 2.69 (s, CH$_3$), 0.84 (t, CH$_3$ of Et); MS m/z: 395 (M$^+$, 27%; Calcd. for C$_{24}$H$_{29}$NO$_4$ 395.2096, found 395.2098), 377 (6), 322 (100), 291 (14), 265 (10); Anal. Calcd for C$_{24}$H$_{29}$NO$_4$: C, 72.88; H, 7.39; N, 3.54%, found: C, 72.69; H, 7.40; N, 3.36%.

(c) after 38.8 min., the *benzazonine isomer*[*] *Z*-75b (54 mg) which recrystallised from ethanol as colourless prisms with m.p. 124-125°C. ^{1}H NMR δ: 7.52-7.49 (m, *o*-ArH"), 7.41-7.31 (m, 3ArH"), 6.78 (s, ArH), 6.61 (s, ArH and H7), 4.06 (q, CH$_2$ of Et), 3.88 (s, OCH$_3$), 3.83 (s, OCH$_3$), 3.32 (dd, *J* 3.3 Hz, 12.4 Hz, H4), 2.96-2.91 (m, 2H), 2.80-2.69 (m, 3H), 2.56-2.46 (m, H), 2.41 (s, NCH$_3$), 1.21 (t, CH$_3$ of Et); ^{13}C NMR δ: 174.30 (COO), 148.39 (C9^A), 147.41 (C10^A), 143.45 (C1"^{B}), 141.67 (C7a^B), 134.66 (C11a^B), 130.32 (C6^B), 130.00 (C7^C), 129.05 (2C"), 128.04 (C"^{C}), 127.41 (2C"), 113.89 (C8^D), 112.44 (C11^D), 65.21 (C4), 60.67 (CH$_2$ of Et), 56.51 (2OCH$_3$), 52.76 (C2), 45.11 (NCH$_3$), 38.28 (C5), 34.83 (C1), 15.04 (CH$_3$ of Et); ^{1}H NMR (d$_6$-benzene) δ: 7.56 (d, *J* 8.4 Hz, *o*-ArH"), 7.30-7.17 (m, 3ArH"), 6.91 (s, H7), 6.65 (s, H8), 6.59 (s, H11), 3.92 (q, CH$_2$ of Et), 3.56 (dd, *J* 4.1 Hz, 12.0 Hz, H4),

3.49 (s, OCH$_3$), 3.48 (s, OCH$_3$), 3.35 (dd, J 3.3 Hz, 15.5 Hz, H), 3.07-2.88 (m, 4H),

2.78-2.70 (m, H), 2.47 (s, NCH$_3$), 0.93 (t, CH$_3$ of Et); ^{13}C NMR (d$_6$-benzene) δ:

173.81 (COO), 149.56 (C9^A), 148.62 (C10^A), 143.45 (C1"^{B}), 142.04 (C7a^B), 134.68

(C11a^B or C6^B), 130.48 (C7), 113.89 (C11), 112.44 (C8), 65.45 (C4), 60.20 (CH$_2$ of

Et), 55.94 (2OCH$_3$), 53.15 (C2), 45.15 (NCH$_3$), 38.84 (C5), 35.09 (C1), 14.70 (CH$_3$

of Et); MS m/z: 395 (M$^+$, 29%; Calcd. for C$_{24}$H$_{29}$NO$_4$ 395.2096, found 395.2099),

377 (6), 322 (100), 291 (11), 265 (9); Anal. Calcd for C$_{24}$H$_{29}$NO$_4$: C, 72.88; H,

7.39; N, 3.54%, found: C, 72.99; H, 7.58; N, 3.62%.

* For consistency with the other olefinic benzazonines in this work the E and Z

isomers of **75b** are named according to the structures pictured for **75**. IUPAC rules

would reverse the naming of these geometric isomers of **75b**.

(ii) The salt **72b** (0.297 g, 0.623 mmol) was stirred in dry acetonitrile (15 ml) under

nitrogen (10 ml) with DBU (0.12 g, 0.81 mmol) between -15°C and -20°C for 6 h.

Workup as for (i) afforded a mixture (0.200 g, 81%) of E-**75b**:Z-**75b**:**76b** in the ratio

of 38:54:8.

(iii) To the salt **72b** (0.401 g, 0.842 mmol) in refluxing dry acetonitrile (15 ml) was

added DBU (0.17 g, 1.1 mmol). The solution was refluxed for 1 h. Workup as for

(i) afforded a mixture (0.281 g, 84%) of 4 components attributed to E-**75b**:Z-

75b:**76b**:**77** in the ratio of 36:35:11:18. Preparative reverse phase HPLC as for (i)

afforded, after 27.0 min., a mixture (45 mg) of two components (37:63) attributed to

76b and **77**.

Ethyl 9,10-Dimethoxy-3-methyl-6-trimethylsilyl-2,3,4,5-tetrahydro-1H-

3-benzazonine-4-carboxylate **75c**

(i) The salt **72c** (0.306 g, 0.648 mmol) was stirred in dry acetonitrile (10 ml) under

nitrogen at room temperature with DBU (0.13 g, 0.84 mmol) for 5 h. then the

solution was concentrated. Purification of the residue by column chromatography on

alumina with dichloromethane/25% light petroleum afforded the *3-benzazonine E*-

75c (0.171 g, 67%) as a colourless oil. ^{1}H NMR δ: 7.2-7.1 (bs, H7), 6.78 (s, ArH),

6.64 (s, ArH), 4.25-4.15 (bs, CH_2 of Et), 3.88 (s, OCH_3), 3.86 (s, OCH_3), 3.1-2.6 (bm, 6H), 2.45-2.25 (bs, 4H), 1.30 (t, CH_3 of Et), -0.10 (s, $Si(CH_3)_3$); ^1H NMR ($C_2D_2Cl_4$ at 75°C*) δ: 6.89 (bs, H7), 6.73 (s, ArH), 6.59 (s, ArH), 4.13 (q, CH_2 of Et), 3.79 (s, OCH_3), 3.77 (s, OCH_3), 3.15-2.91 (bs, 2H), 2.69-2.58 (m, 4H), 2.48-2.36 (m, H), 2.43 (s, NCH_3), 1.24 (t, CH_3 of Et), -0.13 (s, $Si(CH_3)_3$); ^1H NMR (d_8-toluene at -20°C, two conformers in 61:39 ratio) δ: 7.52[a] and 7.22[b] (bs, H7), 7.06[b] and 6.95[a] (s, ArH), 6.58[a] and 6.53[b] (s, ArH), 4.05[a] and 3.90[b] (q, CH_2 of Et), 2.60[a] and 2.46[b] (NCH_3), 0.25[a] and 0.04[b] (s, $Si(CH_3)_3$); ^{13}C NMR (d_8-toluene at -20°C) δ: 173.89 (COO), 148.41 (C9[A]), 147.83 (C10[A]), 147.38 (C7), 136.47 (C7a[B]), 133.43 (C11a[B]), 130.36 (C6[B]), 115.01 and 114.41 (C8[C]), 112.44 and 111.83 (C11[C]), 66.23 (C4), 61.29 and 60.89 (CH_2 of Et), 55.99 (2OCH_3), 53.93 (C2), 44.86 (NCH_3), 40.13 (C5[D]), 38.78 (C1[D]), 15.34 (CH_3 of Et), 1.86 ($Si(CH_3)_3$); MS m/z: 391 (M[+], 5%; Calcd. for $C_{21}H_{33}NO_4Si$ 391.2170, found 391.2174), 389 (45), 318 (26), 246 (100), 230 (20), 206 (15), 73 (55).

* The rapid collection of spectral data (within 5 min.) was necessary to prevent the reaction of **75c** under these conditions.

(ii) To the salt **72c** (0.150 g, 0.317 mmol) in dry acetonitrile (8 ml) at reflux was added DBU (0.063 g, 0.41 mmol). The solution was refluxed for 1 h. then concentrated. Purification of the residue by column chromatography on alumina with dichloromethane/20% light petroleum afforded an unidentified mixture (0.012 g).

Attempted Base-Promoted Rearrangement of **72d** to **75d**

The salt **72d** (0.336 g, 0.639 mmol) was stirred in dry acetonitrile (10 ml) under nitrogen and protected from light for 5 h. at room temperature with DBU (0.13 g, 0.85 mmol). The solution was then concentrated and the residue was purified by column chromatography on alumina. Elution with dichloromethane/25% light petroleum afforded only the precursor base **70d** (0.008 g). Elution with dichloromethane/5-10% ethanol afforded a mixture (0.300 g) which was found to

contain protonated DBU salts (~75%) and impure material inconsistent with either 72d, 75d or 76d upon ^{1}H NMR spectral analysis.

<u>Degradation of 75c to the Proposed Pyrrolo[2,1-*a*]isoquinolinium Salt 78</u>

The NMR analysis of 75c in $C_2D_2Cl_4$ at 75°C afforded, after 115 min., the total removal of 75c and the formation of signals tentatively attributed to a mixture (58:42) of the diastereomers of *3-ethoxycarbonyl-8,9-dimethoxy-4-methyl-1-trimethylsilyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinolinium chloride* 78. *major diastereomer* ^{1}H NMR* δ: 6.15 (d, *J* 11.6 Hz, H10b), 4.95-4.87 (m, H3), 3.42 (s, NCH$_3$), -0.29 (s, Si(CH$_3$)$_3$); ^{13}C DEPT NMR* δ: 113.30 (C7^A), 111.62 (C10^A), 74.70 (C10b^B), 73.85 (C3^B), 63.29 (CH$_2$ of Et), 56.58 (2OCH$_3$), 48.03 (C5), 45.86 (NCH$_3$), 27.98 (C6^C), 27.29 (C1), 23.25 (C2^C), 14.30 (CH$_3$ of Et), -1.21 (Si(CH$_3$)$_3$); *minor diastereomer* ^{1}H NMR* δ: 5.56 (d, *J* 7.8 Hz, H10b), 5.34 (d, *J* 8.6 Hz, H3), 3.28 (s, NCH$_3$), -0.26 (s, Si(CH$_3$)$_3$); ^{13}C DEPT NMR* δ: 113.30 (C7^A), 112.02 (C10^A), 73.76 (C10b^B), 72.99 (C3^B), 63.57 (CH$_2$ of Et), 56.58 (2OCH$_3$), 54.46 (C5), 43.28 (NCH$_3$), 29.79 (C6^C), 29.21 (C1), 23.45 (C2^C), 14.30 (CH$_3$ of Et), -1.21 (Si(CH$_3$)$_3$).

* in $C_2D_2Cl_4$ at 75°C.

<u>6,7-Dimethoxy-1-[2'-(3,4-dimethoxyphenyl)ethenyl]-3,4-dihydroisoquinoline 79</u>

Homoveratrylamine (5.30 g, 29.2 mmol) and 3,4-dimethoxycinnamic acid (7.45 g, 35.8 mmol) were heated at 170°C under nitrogen for 3 h. The solid product was taken up in chloroform (100 ml) and the organic solution was washed with 2.5 M sodium hydroxide (30 ml), 2.5 M hydrochloric acid (30 ml), water (30 ml) and then saturated brine (30 ml). The solution was then concentrated to give crude *N*-(3,4-dimethoxyphenethyl)-3,4-dimethoxycinnamide[97] (9.39 g) as a yellow solid.

The crude amide was refluxed in dry toluene (80 ml) with phosphorus oxychloride (14.8 g, 96.6 mmol) for 2 h, then the solution was allowed to cool to room temperature. The yellow precipitate was collected by filtration and rinsed with

light petroleum then dried briefly under vacuum. Recrystallisation of this solid from methanol gave the hydrochloride salt[97] of the title compound (6.56 g). The salt was dissolved in chloroform (200 ml) and then 2 M sodium hydroxide (30 ml) was added and the mixture was stirred vigorously for 5 min. The organic layer was then separated and washed with water (2 x 30 ml). Drying and concentration of the solution afforded *1-[2'-(3,4-dimethoxyphenyl)ethenyl]isoquinoline* **79** (4.56 g, 44%) as a pale yellow solid. ^{1}H NMR δ: 7.36 (d, *J* 16.0 Hz, H1'^{A}), 7.15-7.10 (m, 3ArH), 7.07 (d, *J* 16.0 Hz, H2'^{A}), 6.68 (d, *J* 8.8 Hz, H4"), 6.76 (s, ArH), 3.91 (s, OCH$_3$), 3.88 (s, OCH$_3$), 3.87 (s, OCH$_3$), 3.86 (s, OCH$_3$), 3.74 (t, H3), 2.67 (t, H4); ^{13}C NMR δ: 163.67 (C1), 151.45 (C6^A), 150.42 (C7^A), 149.72 (C3"^{A}), 147.98 (C4"^{A}), 136.74 (C1'^{B}), 132.89 (C1"^{C}), 130.15 (C4a^C), 124.45 (C2'^{B}), 122.63 (C8a^C), 121.61 (C6"^{D}), 111.72 (C5"^{D}), 111.01 (C2"^{D}), 110.33 (C5^D), 110.00 (C8^D), 57.03-56.59 (4OCH$_3$), 48.01 (C3), 26.76 (C4); MS m/z: 353 (M$^+$, 38%), 352 (100), 338 (23), 336 (16), 322 (11).

6,7-Dimethoxy-1-[2'-(3,4-dimethoxyphenyl)ethenyl]-2-methyl-3,4-dihydroisoquinolinium Iodide 80

The imine **79** (3.96 g, 11.2 mmol) was heated at 70°C in dry butanone (20 ml) with iodomethane (22.8 g, 161 mmol) for 30 min. The removal of the solvents *in vacuo* and then recrystallisation of the residue twice from methanol gave the *isoquinolinium salt* **80** (3.87 g, 70%) as yellow needles with m.p. 193-195°C. ^{1}H NMR δ: 7.62 (d, *J* 16.0 Hz, H1'^{A}), 7.48 (d, *J* 1.8 Hz, H2"), 7.29-7.18 (m, 2ArH), 7.13 (s, ArH), 6.99 (s, ArH), 6.91 (d, *J* 8.3 Hz, H4"), 4.12 (t, H3), 4.08 (s, OCH$_3$), 4.06 (s, OCH$_3$), 4.04 (s, OCH$_3$), 3.94 (s, OCH$_3$), 3.80 (NCH$_3$), 3.26 (t, H4); ^{13}C NMR δ: 171.03 (C1), 156.47 (C6^A), 153.58 (C7^A), 151.79 (C1'^{B}), 150.41 (C3"^{A}), 148.65 (C4"^{A}), 134.43 (C1"^{C}), 127.24 (C4a^C), 125.58 (C2'^{B}), 119.72 (C8a^C), 116.04 (C6"^{D} and C5"^{D}), 111.63 (C2"^{D} and C2"^{D}), 110.77 (C5^D), 57.97-56.75 (4OCH$_3$), 53.24 (C3), 47.38 (NCH$_3$), 26.76 (C4).

6,7-Dimethoxy-2-methyl-1-(2'-methylpropenyl)-1,2,3,4-tetrahydroisoquinoline **81a**

A solution of 2-methylpropenylmagnesium bromide was prepared by the slow addition of 1-bromo-2-methylpropene (9.711 g, 71.93 mmol) to magnesium turnings (1.90 g, 78.0 mmol) in dry tetrahydrofuran (100 ml) under nitrogen. The reaction was initiated by heating the solution to reflux in the presence of an iodine crystal and was then maintained at a gentle reflux for 90 min., with the slow consumption of the magnesium.

The solution of 2-methylpropenylmagnesium bromide in tetrahydrofuran was cooled to <-50°C in an acetone/liquid nitrogen slush bath and then additional dry tetrahydrofuran (50 ml) was added, followed by **48a** (9.855 g, 29.58 mmol). The mixture was allowed to warm slowly to room temperature with stirring for 21 h. before workup (as for **70b**) to give, upon concentration of the ether solution, the *1-(2-methylpropenyl)isoquinoline* **81a** (4.731 g, 61%) as a pale oil of >99% purity by GC-MS analysis. The oil formed a solid, which melted on exposure to room temperatures, when stored at -5°C. ^{1}H NMR δ: 6.48 (s, ArH), 6.41 (s, ArH), 5.06 (d, J 9.7 Hz, H1'), 3.84 (d, J 9.6 Hz, H1), 3.74 (s, OCH$_3$), 3.70 (s, OCH$_3$), 2.97-2.93 (m, 2H), 2.59-2.53 (m, H), 2.47-2.40 (m, H), 2.29 (s, NCH$_3$), 1.75 (CH$_3$), 1.74 (CH$_3$); ^{13}C NMR δ: 147.91 (C6^A), 147.53 (C7^A), 135.28 (C4a^B), 130.07 (C2'^{B}), 127.54 (C1'), 126.83 (C8a^B), 111.59 (C5^C), 111.05 (C8^C), 63.55 (C1), 56.33 (OCH$_3$), 56.29 (OCH$_3$), 52.55 (C3), 44.42 (NCH$_3$), 29.45 (C4), 26.38 (*E*-CH$_3$), 18.89 (Z-CH$_3$); MS m/z: 261 (M$^+$, 18%; Calcd. for C$_{16}$H$_{23}$NO$_2$ 261.1728, found 261.1730), 260 (16), 246 (5), 218 (12), 206 (100), 203 (19), 190 (7); IR (thin film from CH$_2$Cl$_2$): 1510, 1259, 1217, 1139, 829 cm^{-1}.

The methiodide salt of **81a** crystallised from methanol as pale yellow needles with m.p. 207-209°C. ^{1}H NMR δ: 6.72 (s, ArH), 6.46 (s, ArH), 5.56 (d, J 10.3 Hz, H1), 5.21 (d, J 10.3 Hz, H1'), 4.39-4.32 (m, H3), 4.16-4.08 (m, H3), 3.88 (s, OCH$_3$), 3.82 (s, OCH$_3$), 3.56 (s, NCH$_3$), 3.21-3.15 (m, NCH$_3$ and H4), 2.13 (CH$_3$), 1.98 (CH$_3$); Anal. Calcd for C$_{17}$H$_{26}$NO$_2$I: C, 50.63; H, 6.50; N, 3.47%, found: C, 50.76; H, 6.54; N, 3.53%.

Mixture of 6,7-Dimethoxy-2-methyl-1-propenyl-1,2,3,4-tetrahydroisoquinoline 81b Isomers

A solution of propenylmagnesium bromide was prepared by the slow addition of 1-bromo-1-propene (28.97 g, 239.4 mmol, a mixture of Z and E isomers) to magnesium turnings (6.45 g, 265 mmol) in dry tetrahydrofuran (180 ml) under nitrogen. The reaction was initiated by heating the solution to reflux in the presence of an iodine crystal. The addition rate was controlled to maintain a gentle reflux. The mixture was refluxed for 30 min. after the completion of the addition.

The solution of propenylmagnesium bromide in tetrahydrofuran was cooled to $<-50°C$ in an acetone/liquid nitrogen slush bath and then **48a** (20.00 g, 60.03 mmol) was added. The mixture was allowed to warm slowly to room temperature with stirring for 21 h. before workup (as for **70b**) to give, upon concentration of the ether solution, a mixture ($Z:E=3:1$) of the isomers of *1-propenylisoquinoline* **81b** (12.72 g, 86%) as a tan oil with >99% purity upon GC-MS analysis. ^1H NMR* δ: 6.55 (s, ArH), 6.51 (s, ArH), 5.82-5.78 (m, H2'^{X}), 5.20-5.12 (m, H2'^{Y}), 5.39-5.31 (m, H1'), 4.02 (d, J 9.7 Hz, H1^X), 3.81 (s, OCH$_3$), 3.77 (s, OCH$_3$), 3.63 (d, J 8.6 Hz, H1^Y), 3.03-2.97 (m, 2H), 2.65-2.59 (m, H), 2.51-2.47 (m, H), 2.37 (s, NCH$_3$), 1.81 (dd, J 1.8 Hz, 6.9 Hz, CH$_3^X$), 1.76 (dd, J 1.6 Hz, 6.4 Hz, CH$_3^Y$); ^{13}C NMR* δ: 147.99 (C6^A), 147.62 (C7^A), 133.41 (C1'^{BY}), 133.15 (C1'^{BX}), 129.70 (C2'^{BY}), 129.31 (C5a^C), 126.83 (C8a^C), 126.91 (C2'^{BX}), 111.65 (C5^D), 110.85 (C8^D), 68.89 (C1^Y), 62.15 (C1^X), 56.36 (2OCH$_3$), 52.71 (C3^X), 51.85 (C3^Y), 44.54 (NCH$_3$), 29.54 (C4^X), 29.31 (C4^Y), 18.23 (CH$_3^Y$), 13.91 (CH$_3^X$); MS m/z: 247 (M$^+$, 14%; Calcd. for C$_{15}$H$_{21}$NO$_2$ 247.1572, found 247.1565), 246 (11), 246 (5), 232 (5), 206 (100), 190 (12), 189 (15).

* Signals attributed to the Z and E isomers are marked with superscripts X and Y respectively.

<u>6,7-Dimethoxy-1-[2'-(3,4-dimethoxyphenyl)ethenyl]-2-methyl-1,2,3,4-</u>

<u>tetrahydroisoquinoline 81c</u>

The methiodide salt **80** (3.83 g, 7.73 mmol) was suspended in ethanol (100

ml) at 0°C and then treated with sodium borohydride (0.84 g, 22 mmol) portionwise

over 30 min. The mixture was stirred for 1 h. then concentrated and the residue was

partitioned between 5% aqueous sodium bicarbonate (50 ml) and dichloromethane

(50 ml). The organic layer was separated and washed with water (2 x 10 ml), then

dried and concentrated. Column chromatographic purification of the residue on

silica (35 g) with a gradient from dichloromethane/5% light petroleum to

dichloromethane/8% methanol gave:

(a) the desired *1-[2'-(3,4-dimethoxyphenyl)ethenyl]isoquinoline* **81c** (2.495 g, 86%)

as a pale yellow powder from the late fractions. ^{1}H NMR δ: 7.01 (d, *J* 1.4 Hz, H2"),

6.96 (dd, *J* 1.4 Hz, 8.6 Hz, H6"), 6.83 (d, *J* 8.6 Hz, H5"), 6.64 (s, ArH), 6.62 (s,

ArH), 6.57 (d, *J* 15.7 Hz, H2'), 6.02 (dd, *J* 8.9 Hz, 15.7 Hz, H1'), 3.88 (s, 2OCH$_3$),

3.86 (s, OCH$_3$), 3.81 (d, *J* 8.9 Hz, H1), 3.76 (s, OCH$_3$), 3.10-3.03 (m, 2H), 2.76-2.66

(m, H), 2.58-2.54 (m, H), 2.48 (s, NCH$_3$); ^{13}C NMR δ: 149.57 (C6^A), 149.33 (C7^A),

148.16 (C3"^{A}), 147.62 (C4"^{A}), 133.41 (C1'^{B}), 130.37 (C1"^{C}), 130.11 (C2'^{B}),128.89

(C4a^C), 126.99 (C8a^C), 120.26 (C2"^{D}), 111.70 (C5"^{D}), 111.58 (C6"^{D}), 111.44

(C5^D), 109.04 (C8^D), 69.09 (C1), 56.45-56.34 (4OCH$_3$), 51.92 (C3), 44.73 (NCH$_3$),

29.42 (C4); MS m/z: 369 (M$^+$, 47%; Calcd. for C$_{22}$H$_{27}$NO$_4$ 369.1939, found

369.193), 368 (20), 354 (48), 218 (22), 206 (100), 190 (16), 151 (26); IR (thin film

from CH$_2$Cl$_2$): 2936, 2833, 2783, 1516, 1265, 1142, 1028 cm^{-1}.

(b) an unidentified isomer of **81c** (0.123 g, 4%) as a pale yellow oil from an early

fraction. The material showed two sets of signals (a/b=1.21) on NMR analysis. ^{1}H

NMR δ: 6.98-6.91 (m, 2ArH"), 6.85-6.81 (m, H2"), 6.67-6.65 (m, ArH), 6.62-6.57

(m, H1'^{a} and H2'^{b}), 6.55-6.52 (m, ArH), 6.10 (d, *J* 15.9 Hz, H2'^{a}), 6.04 (dd, *J* 9.4 Hz,

15.6 Hz, H1'^{b}), 4.61 (d, *J* 9.4 Hz, H1^b), 4.34 (d, *J* 7.5 Hz, H1^a), 3.90-3.87 (m,

3OCH$_3$), 3.82 (s, OCH$_3$), 3.37-2.85 (m, 8H), 2.72 (s, NCH$_3$^{a}), 2.64 (s, NCH$_3$^{b}); ^{13}C

NMR δ: 150.21-148.34 (6 peaks; C7, C8, C3", and C4"), 137.07 and 136.61 (C1'^{A}),

129.94 and 129.43 (C1"^{B}), 126.63 and 125.46 (C4a^B), 125.84 and 123.38 (C2'^{A}), 124.53 and 123.96 (C8a^B), 120.84 (C2"^{C}), 111.77 (C5"^{C}), 111.63 (C6"^{C}), 111.47 (C5^C), 109.77 (C6^C), 71.81 and 71.09 (C1), 56.57 (4OCH$_3$), 55.83 and 54.69 (C3), 50.83 and 49.85 (NCH$_3$), 25.99 and 25.48 (C4); MS m/z: 369 (M$^+$, 46%), 368 (17), 354 (44), 218 (19), 206 (100), 190 (16), 151 (23); MS (LSIMS in *m*-nitrobenzyl alcohol) m/z: 370 (MH$^+$, 71%), 206 (100); IR (thin film from CH$_2$Cl$_2$): 2936, 2835, 1516, 1263, 1258, 1140, 1130, 1026 cm^{-1}.

2-Ethoxycarbonylmethyl-6,7-dimethoxy-2-methyl-1-(2'-methylpropenyl)-1,2,3,4-tetrahydroisoquinolinium Bromide 82a

To the base **81a** (1.295 g, 4.955 mmol) in dry acetonitrile (3 ml) at 0°C was added ethyl bromoacetate (1.06 g, 6.34 mmol). The mixture was stirred at room temperature for 24 h. and then concentrated to afford a gum which was triturated with diethyl ether (3 x 10 ml), then taken-up in dichloromethane and reconcentrated. Further trituration of the resultant powder with diethyl ether (3 x 10 ml) and drying afforded a mixture (*trans:cis*=58:42) of the B-ring diastereomers of the *2-ethoxycarbonylmethylisoquinolinium salt* **82a** (1.869 g, 88%) as an off-white powder. *trans diastereomer* (assignable signals) ^{1}H NMR δ: 6.72 (s, ArH), 6.43 (s, ArH), 6.10 (d, *J* 10.2 Hz, H1'), 5.31 (d, *J* 10.7 Hz, H1), 3.41 (s, NCH$_3$), 2.14 (s, CH$_3$), 1.97 (s, CH$_3$); ^{13}C NMR δ: 165.39 (COO), 149.78 (C6^A), 148.90 (C7^A), 122.34 (C4a^B), 120.88 (C8a^B), 116.52 (C2'), 111.47 (C5^C), 110.71 (C8^C), 69.21 (C1), 62.96 (CH$_2$ of Et), 58.53 (NCH$_2$CO), 56.31 (2OCH$_3$), 55.39 (C3^A), 46.88 (NCH$_3$), 26.75 (CH$_3$), 23.86 (C4), 20.16 (CH$_3$), 14.09 (CH$_3$ of Et); *cis diastereomer* (assignable signals) ^{1}H NMR δ: 6.74 (s, ArH), 6.44 (s, ArH), 5.86 (d, *J* 10.5 Hz, H1'), 5.42 (d, *J* 10.5 Hz, H1), 3.70 (s, NCH$_3$), 2.04 (s, CH$_3$), 1.91 (s, CH$_3$); ^{13}C NMR δ: 164.89 (COO), 148.28 (C6^A), 146.04 (C7^A), 122.46 (C4a^B), 120.68 (C8a^B), 117.30 (C2'), 111.31 (C5^C), 110.30 (C8^C), 69.81 (C1), 62.85 (CH$_2$ of Et), 58.53 (NCH$_2$CO), 56.31 (2OCH$_3$), 55.39 (C3^A), 45.63 (NCH$_3$), 26.75 (CH$_3$), 23.44 (C4), 19.91 (CH$_3$), 14.21 (CH$_3$ of Et).

2-Ethoxycarbonylmethyl-6,7-dimethoxy-2-methyl-1-propenyl-1,2,3,4-
tetrahydroisoquinolinium Bromide **82b**

(i)   To the base **81b** (0.860 g, 3.48 mmol, 3:1 mixture of the Z and E olefinic isomers) was added ethyl bromoacetate (0.72 ml, 6.47 mmol). The mildly exothermic reaction was cooled and the solution was then left to sit for 16 h. at room temperature. Trituration of the resultant gel with diethyl ether (5 x 20 ml) afforded a mixture (A:B:C:D=51:18:19:12) of the four possible isomers of the 2-*ethoxycarbonylmethylisoquinolinium salt* **82b** (1.42 g, 98%) as a tan powder. Isomers A and B were attributed to the Z-olefinic diastereomers and isomers C and D to the E-olefinic diastereomers. *Isomer A* ^{1}H NMR δ: 3.37 (s, NCH$_3$), 2.07 (d, J 7.1 Hz, CH$_3$); *Isomer B* ^{1}H NMR δ: 3.69 (s, NCH$_3$), 1.96 (d, J 7.0 Hz, CH$_3$); *Isomer C* ^{1}H NMR δ: 3.60 (s, NCH$_3$), 1.82 (d, J 6.3 Hz, CH$_3$); *Isomer D* ^{1}H NMR δ: 3.45 (s, NCH$_3$), 1.77 (d, J 6.5 Hz, CH$_3$).

(ii)   To **81b** (1.984 g, 8.023 mmol, a 3:1 mixture of the Z and E olefinic isomers) in dry acetonitrile (3.5 ml) at room temperature was added ethyl bromoacetate (1.7 ml, 15 mmol). The solution was stirred for 24 h. then concentrated and the residue was triturated with diethyl ether (5 x 20 ml) to afford a mixture (A:B:C:D=55:18:17:9) of the isomers of **82b** (3.19 g, 96%).

2-Ethoxycarbonylmethyl-6,7-dimethoxy-1-[2'-(3,4-dimethoxyphenyl)ethenyl]-2-
methyl-1,2,3,4-tetrahydroisoquinolinium Iodide **82c**

Potassium iodide (1.38 g, 8.31 mmol), dry acetonitrile (50 ml) and ethyl bromoacetate (0.90 ml, 8.1 mmol) were combined and stirred under nitrogen, protected from light, for 24 h. Filtration of the mixture afforded a solution, assumed to contain ethyl iodoacetate, which was added to **81c** (1.00 g, 2.71 mmol). The mixture was heated in a sealed tube at 100-110°C for 3.5 h. then concentrated. The residue was dissolved in chloroform and the solution was filtered then reconcentrated. Trituration of the residue with diethyl ether (3 x 20 ml) and then recrystallisation of the gum from ethanol/tetrahydrofuran gave a mixture

(*trans:cis*=46:54) of the B-ring diastereomers of the *2-ethoxycarbonyl-methylisoquinolinium salt* **82c** (0.977 g, 62%) as a pale yellow powder. *trans diastereomer* ^{1}H NMR δ: 6.37 (d, *J* 9.4 Hz, H1), 3.59 (s, NCH$_3$); *cis diastereomer* ^{1}H NMR δ: 7.30 (d, *J* 15.4 Hz, H2'), 5.84 (d, *J* 9.6 Hz, H1), 3.66 (s, NCH$_3$); ^{13}C NMR *of mixture* δ: 165.14 (COO), 142.71 and 140.70 (C2'[A]), 122.60 and 122.35 (C1'[A]), 118.36 and 117.49 (C6"[A]), 78.19 and 74.53 (C1), 63.60 and 63.47 (CH$_2$ of Et), 60.99 and 58.29 (NCH$_2$CO), 56.17 and 55.02 (C3[A]), 48.35 and 46.70 (NCH$_3$), 24.16 and 23.84 (C4), 14.64 and 14.54 (CH$_3$ of Et).

<u>Ethyl *N*-{2-[4',5'-Dimethoxy-2'-(3"-methyl-1"*E*,3"-butadienyl)phenyl]ethyl}-*N*-methyl-aminoethanoate **83a**</u>

To the base **81a** (1.710 g, 4.955 mmol) in dry butanone (5 ml) was added ethyl bromoacetate (1.06 g, 6.34 mmol). The solution was stirred at 50°C for 10 h. then concentrated. The residue was triturated with diethyl ether (3 x 15 ml) then taken-up in dichloromethane. Concentration and then further trituration of the residue with diethyl ether (3 x 10 ml) afforded a gum which, upon purification by column chromatography on silica (30 g) with dichloromethane/0-4% ethanol, gave the *title compound* **83a** (1.407 g, 62%) as a yellow oil. ^{1}H NMR δ: 7.03 (s, ArH), 6.72 (s, H1"[A]), 6.71 (s, H2"[A]), 6.68 (s, ArH), 5.10 (s, H4"), 5.05 (s, H4"), 4.17 (q, CH$_2$ of Et), 3.89 (s, OCH$_3$), 3.87 (s, OCH$_3$), 3.30 (s, NCH$_2$CO), 2.88-2.83 (m, 2H), 2.69-2.64 (m, 2H), 2.48 (s, NCH$_3$), 2.00 (s, CH$_3$), 1.26 (t, CH$_3$ of Et); ^{13}C NMR δ: 171.12 (COO), 149.00 (C4'[A]), 147.98 (C5'[A]), 142.60 (C3"), 131.68 (C1"[B]), 130.76 (C1'[C]), 128.56 (C2'[C]), 125.91 (C2"[B]), 116.92 (C4"), 113.33 (C3'[D]), 108.75 (C6'[D]), 60.73 (CH$_2$ of Et), 58.89 (NCH$_2$CO and C1), 56.20 (2OCH$_3$), 42.68 (NCH$_3$), 31.66 (C2), 19.05 (CH$_3$), 14.58 (CH$_3$ of Et). ^{1}H NMR (d$_6$-benzene) δ: 7.35 (s, ArH), 7.23 (d, *J* 15.9 Hz, H1"[A]), 7.10 (d, *J* 15.9 Hz, H2"[A]), 6.68 (s, ArH).

Ethyl <u>*N*-{2-[4',5'-Dimethoxy-2'-(1",3"-butadienyl)phenyl]ethyl}-</u>

<u>*N*-methylamino-ethanoate **83b**</u>

(i) To **81b** (5.20 g, 21.0 mmol, a 3:1 mixture of the *Z* and *E* olefinic isomers) in dry acetone (3.5 ml) was added ethyl bromoacetate (5.3 ml, 48 mmol). The solution was refluxed for 5 h. then concentrated. The oily residue was purified by column chromatography on silica with dichloromethane/0-6% ethanol to give successively:

(a) the *1E,3-butadienyl isomer* of **83b** (0.88 g, 13%) as a yellow oil. ^{1}H NMR δ: 7.02 (s, ArH), 6.77 (d, *J* 14.6 Hz, H1"), 6.68 (s, ArH), 6.63-6.52 (m, H2" and H3"), 5.31 (d, *J* 17.4 Hz, H4"), 5.16 (d, *J* 9.1 Hz, H4"), 4.20 (q, CH$_2$ of Et), 3.90 (s, OCH$_3$), 3.88 (s, OCH$_3$), 3.37 (s, NCH$_2$CO), 2.90-2.85 (m, 2H), 2.75-2.70 (m, 2H), 2.52 (s, NCH$_3$), 1.28 (t, CH$_3$ of Et); ^{13}C NMR δ: 170.98 (COO), 149.48 (C4'^{A}), 148.38 (C5'^{A}), 138.10 (C1"^{B}), 130.67 (C1'^{C}), 130.21 (C2" and C3"^{B}), 128.64 (C2'^{C}), 117.53 (C4"), 113.65 (C3'^{D}), 108.87 (C6'^{D}), 61.44 (CH$_2$ of Et), 58.99 (NCH$_2$CO^E), 58.79 (C1^E), 56.60 (2OCH$_3$), 42.97 (NCH$_3$), 31.72 (C2), 14.92 (CH$_3$ of Et); MS m/z: 333 (M$^+$, 12%; Calcd. for C$_{19}$H$_{27}$NO$_4$ 333.1940, found 333.194), 260 (7), 190 (2), 130 (100), 102 (10).

(b) the *1Z,3-butadienyl isomer* of **83b** (3.88 g, 55%) as a yellow oil. ^{1}H NMR δ: 6.99 (s, ArH), 6.86-6.80 (m, ArH and H1"), 6.68-6.60 (m, H2" and H3"), 5.32 (d, *J* 17.4 Hz, H4"), 5.17 (d, *J* 9.1 Hz, H4"), 4.26 (q, CH$_2$ of Et), 3.97 (s, NCH$_2$CO), 3.97 (s, 2OCH$_3$), 3.40-3.37 (m, 2H), 3.27-3.23 (m, 2H), 3.01 (s, NCH$_3$), 1.30 (t, CH$_3$ of Et); ^{13}C NMR δ: 165.57 (COO), 149.68 (C4'^{A}), 149.07 (C5'^{A}), 137.98 (C1"^{B}), 131.21 (C2"^{B}), 129.27 (C3"^{B}), 129.01 (C1'^{C}), 128.64 (C2'^{C}), 118.20 (C4"), 113.79 (C3'^{D}), 108.96 (C6'^{D}), 63.26 (CH$_2$ of Et), 56.78 (NCH$_2$CO^E), 56.57 (2OCH$_3$), 54.56 (C1^E), 41.72 (NCH$_3$), 29.24 (C2), 14.62 (CH$_3$ of Et); MS m/z: 333 (M$^+$, 13%; Calcd. for C$_{19}$H$_{27}$NO$_4$ 333.1940, found 333.194), 260 (7), 190 (2), 130 (100), 102 (13).

(c) a mixture (A:B:C:D=4:6:25:65) of the isomers of **82b** (0.77 g, 9%).

(ii) A mixture (A:B:C:D=55:18:17:9) of the isomers of **82b** (0.273 g, 0.659 mmol) was refluxed in dry acetone for 7 h. then worked-up as for (i) to afford a mixture (*Z/E*=8.8) of the isomers of **83b** (0.137 g, 62%).

N-(3,4-dimethoxyphenylethyl)crotonamide **84a**

Homoveratrylamine (10.00 g, 55.2 mmol) and crotonic acid (5.70 g, 66.2 mmol) were heated at 170°C, under a slow flow of nitrogen to remove water, for 2 h. The mixture was allowed to cool to 80°C then chloroform (150 ml) was added, preventing the formation of a difficult to dissolve glassy solid. The organic solution was washed with 2.0 M sodium hydroxide (2 x 30 ml), 2.5 M hydrochloric acid (4 x 30 ml) and water (2 x 30 ml) then dried and concentrated. The residue was purified by column chromatography on silica (80 g) with dichloromethane/2-4% methanol, leaving residual homoveratrylamine on the column. The eluant was concentrated and the residue was recrystallised from ethyl acetate to give the crotonamide **84a** (2.59 g, 19%) as an off-white powder. ^{1}H NMR δ: 6.85-6.71 (m, 3ArH and NH), 5.96-5.89 (m, H3), 5.78 (dd, *J* 1.6 Hz, 15.2 Hz, H2), 3.85 (s, 2OCH$_3$), 3.57-3.50 (m, 2H), 2.78 (t, 2H), 1.82 (dd, *J* 1.6 Hz, 6.9 Hz, CH$_3$); ^{13}C NMR δ: 166.55 (CO), 149.51 (C3"^{A}), 1478.14 (C4"^{A}), 140.14 (C2^B), 132.05 (C1"), 125.70 (C3^B), 121.15 (C6"^{B}), 112.48 (C2"^{C}), 111.90 (C5"^{C}), 56.41 (2OCH$_3$), 41.27 (C1'), 35.77 (C2'), 18.19 (C4); MS m/z: 249 (M$^+$, 5%; Calcd. for C$_{14}$H$_{19}$NO$_3$ 249.1363, found 249.137), 164 (100), 151 (33), 149 (10), 69 (37); IR (thin film from CH$_2$Cl$_2$): 3306, 2940, 1516, 1263, 1236 cm^{-1}.

Attempted *N*-[2-(3,4-Dimethoxyphenyl)ethyl]fumaramide Ethyl Ester **84b**

(i) Homoveratrylamine (3.409 g, 18.81 mmol) and fumaric acid monoethyl ester (4.027 g, 27.94 mmol) were heated at 155°C under a slow flow of nitrogen, to remove water, for 4 h. Some solid was present throughout the reaction. Upon cooling the mixture was taken up in chloroform (50 ml) and washed with 2M sodium hydroxide (4 x 10 ml) then 5% hydrochloric acid (3 x 10 ml) and water (10 ml).

Drying and then concentration of the solution gave a tan solid (2.755 g). Analysis by GC-MS showed fumaric acid monoethyl ester (86%) and a second component (14%) with MS m/z: 261 (M$^+$, 15%), 164 (43), 151 (100), 149 (9), 107 (17).

(ii) To fumaric acid monoethyl ester (1.515 g, 10.50 mmol) as a melt at 90°C under nitrogen was added homoveratrylamine (2.093 g, 11.55 mmol). The mixture was then heated to 185-190°C. A solid formed rapidly in the liquid melt and then dissolved as the temperature exceeded 170°C. After 20 min. at 185-190°C under a steady flow of nitrogen the evolution of water from the brown liquid mixture ceased. The reaction was allowed to cool slowly to room temperature under oil pump vacuum and the solid was taken up in chloroform (30 ml). The solution was washed with 1M sodium hydroxide (4 x 6 ml), 1M hydrochloric acid (3 x 6 ml), and then water (10 ml). Drying and then concentration of the solution gave a tan solid (2.360 g). Analysis by GC-MS showed 3 components with molecular ions at 261 (65%, as for (i)), 429 (17%) and 442 (18%).

Attempted Preparation of 6,7-Dimethoxy-1-(1'-propenyl)-3,4-dihydroisoquinoline 85

(i) The technique of Markaryan and Airapetyan,[98] reported to provide the hydrochloride of 85 in 75-87% yield via 85 as a crude oil, was followed. A mixture of the amide 84a (11.79 g, 47.27 mmol) in dry benzene (150 ml) with phosphorus oxychloride (76.0 g, 496 mmol) was refluxed for 6.5 h. then cooled to room temperature. The mixture was then concentrated and the residue was dissolved in water (150 ml). The solution was cooled and 10% aqueous sodium carbonate was added carefully to provide a pH of 9-10. The mixture which resulted was extracted with benzene (3 x 100 ml) and the extracts were then combined and washed with water (2 x 50 ml). Drying and then concentration of the organic solution afforded a dark yellow powder (6.735 g). Analysis by t.l.c., GC-MS and ^{1}H NMR techniques showed many components.

(ii) Compound 84a (0.614 g, 2.46 mmol) was refluxed in dry toluene (12 ml) with phosphorus oxychloride (3.29 g, 21.5 mmol) for 2.5 h. then the mixture was cooled

and the dark toluene layer was decanted from the resultant oil. The toluene was extracted with water (5 ml) while ice/water (30 g) was added to the oil. The aqueous layers were combined and washed with diethyl ether then cooled and basified to pH 9-10 by the slow addition of 80% aqueous sodium hydroxide. The mixture was extracted with chloroform (4 x 20 ml) and the extracts were then dried and concentrated to a dark film (0.606 g). Analysis by t.l.c., GC-MS and ^{1}H NMR techniques showed many components.

(iii) Compound **84a** (0.944 g, 3.79 mmol) was refluxed in dry toluene (25 ml) with phosphorus pentoxide (5.12 g, 36.1 mmol) for 1.5 h. then the mixture was cooled to room temperature. The dark toluene layer was decanted and extracted with water (5 ml), while the solid was dissolved in ice/water (30 g). The aqueous layers were combined and washed with diethyl ether (3 x 10 ml) then cooled and basified to pH 9-10 by the slow addition of 80% aqueous sodium hydroxide. The mixture was extracted with diethyl ether (3 x 20 ml) and the extracts were then dried and concentrated to give a yellow oil. Analysis by t.l.c., GC-MS and ^{1}H NMR techniques showed many components.

(iv) Compound **84a** (0.605 g, 2.43 mmol) was refluxed in dry acetonitrile (20 ml) with phosphorus oxychloride (3.29 g, 21.5 mmol) for 2 h. over 4A molecular sieves. The molecular sieves were removed by filtration and the solution was then washed with light petroleum (3 x 10 ml), and then concentrated. The residue was treated with methanol (30 ml) and sodium cyanoborohydride portionwise until the yellow colour was removed, then stirred for 3 h. The mixture was then concentrated and 5% aqueous sodium bicarbonate was added to produce an alkaline solution which was extracted with dichloromethane (30 ml). The dichloromethane extracts were washed with 5% aqueous sodium bicarbonate (3 x 10 ml) then dried and concentrated. Analysis of the residual powder (0.519 g) by t.l.c. and GC-MS showed many components inconsistent with 6,7-dimethoxy-1-(1'-propenyl)-1,2,3,4-tetrahydroisoquinoline.

Attempted Preparation of 2-Chloroethenylmagnesium Chloride and 1-(*trans*-2'-Chloroethenyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline **86**

A solution of *trans*-1,2-dichloroethene (7.59 g, 78.3 mmol) in dry tetrahydrofuran (10 ml) was added to magnesium turnings (1.96 g, 80.6 mmol) in dry tetrahydrofuran (70 ml) under nitrogen. An iodine crystal was added and the mixture was refluxed for 2.5 h. The magnesium was consumed and a pale tan solid formed in the dark solution. The mixture was cooled to -50°C and then the iminium salt **48a** (6.01 g, 18.0 mmol) was added. The mixture was allowed to warm to room temperature with stirring for 16 h. then worked up (as for **70b**) to provide an ether solution which on concentration gave a yellow oil (0.43 g). The oil contained many components.

Ethyl 9,10-Dimethoxy-3,5,5-trimethyl-2,3,4,5-tetrahydro-1*H*-3-benzazonine-4-carboxylate **87a**

(i) The salt **82a** (0.104 g, 0.243 mmol) was stirred in dry acetonitrile (10 ml) under nitrogen at -20°C with DBU (0.048 g, 0.32 mmol) for 5 h. then the solution was concentrated. Purification of the residue by column chromatography on alumina with dichloromethane/20% light petroleum afforded a mixture (0.053 g, 65%) of the isomers *E*-**87a**:*t*-**88a**:*c*-**88a** in the ratio 70:27:3 as a colourless oil. The *E*-*benzazonine E*-**87a** could not be isolated separately. NMR signals attributed to **87a** were: ^{1}H NMR (d_6-benzene) δ: 7.08 (s, ArH), 6.82 (s, ArH), 6.73 (d, J 16.6 Hz, H6[A]), 6.73 (d, J 16.6 Hz, H7[A]), 4.18 (q, CH_2 of Et), 3.76 (s, OCH_3), 3.68 (s, OCH_3), 3.22-3.13 (m, H), 3.12 (s, H4), 3.05-2.98 (m, H), 2.82-2.71 (m, H), 2.80 (s, NCH_3), 2.64-2.57 (m, H), 1.52 (s, CH_3), 1.42 (s, CH_3), 1.19 (t, CH_3 of Et); ^{13}C NMR (CDCl$_3$) δ: 170.87 (COO), 147.44 (C9[A]), 147.02 (C10[A]), 139.18 (C6[B]), 134.34 (C7a[C]), 132.17 (C11a[C]), 130.62 (C7[B]), 113.74 (C8[D]), 110.81 (C11[D]), 77.18 (C4), 60.14 (CH_2 of Et), 56.54 (OCH_3), 54.97 (C2), 46.39 (NCH_3), 41.71 (C5), 38.22 (C1), 25.57 (CH_3), 24.80 (CH_3), 15.18 (CH_3 of Et).

(ii) The salt **82a** (0.433 g, 1.011 mmol) was stirred in dry acetonitrile (15 ml) under nitrogen at room temperature with DBU (0.048 g, 0.32 mmol) for 5 h. then worked-up as for (i) to give a mixture (0.293 g, 86%) of the isomers *E*-**87a**:*t*-**88a**:*c*-**88a** in the ratio 58:37:5 as a colourless oil.

Ethyl 9,10-Dimethoxy-3,5-dimethyl-2,3,4,5-tetrahydro-1*H*-

3-benzazonine-4-carboxylate **87b**

(i) A mixture (A:B:C:D=55:18:17:9) of the isomers of **82b** (2.450 g, 5.913 mmol), in dry acetonitrile (100 ml) under nitrogen at 0°C, was treated with DBU (1.08 g, 7.09 mmol) then allowed to warm to room temperature with stirring for 12 h. Concentration and then purification of the residue by column chromatography on alumina with dichloromethane/40% light petroleum afforded a colourless oil (1.578 g, 80%) containing a mixture of the isomers* *E*-**87bA**:*E*-**87bB**:*Z*-**76bA**:*Z*-**87bB**:**88bA**:**88bB** in the ratio 42:23:3:3:27:2.

A portion (1.26 g) of the above oil was purified by column chromatography on alumina (57 g) with light petroleum/0-50% dichloromethane to afford successively:

(a) a fraction (0.712 g) enriched in *E*-**87bA**. Purification of a portion (0.150 g) of this material by preparative reverse phase HPLC with acetonitrile/26% water gave, after 20.7 min., the *E-benzazonine E*-**87bA** (0.102 g) as a colourless oil. ^{1}H NMR δ: 6.81 (s, ArH), 6.61 (s, ArH), 6.41 (d, *J* 16.1 Hz, H7), 5.51 (dd, *J* 9.9 Hz, 16.1 Hz, H6), 4.18-4.10 (m, CH$_2$ of Et), 3.86 (s, OCH$_3$), 3.83 (s, OCH$_3$), 3.32 (d, *J* 5.8 Hz, H4), 2.74-2.57 (m, 4H), 2.63 (s, NCH$_3$), 2.41-2.32 (m, H), 1.24 (t, CH$_3$ of Et), 1.16 (d, *J* 7.0 Hz, CH$_3$); ^{13}C NMR δ: 171.00 (COO), 147.44 (C9[A]), 147.13 (C10[A]), 135.75 (C7[B]), 133.83 (C11a[C]), 132.73 (C6[B]), 132.01 (C7a[C]), 113.78 (C8[D]), 110.69 (C11[D]), 72.08 (C4), 60.19 (CH$_2$ of Et), 56.52 (2OCH$_3$), 54.58 (C2), 45.47 (NCH$_3$[E]), 43.93 (C5[E]), 38.18 (C1), 15.83 (CH$_3$[F]), 15.19 (CH$_3$ of Et[F]); MS m/z: 333 (M$^+$, 4%; Calcd. for C$_{19}$H$_{27}$NO$_4$ 333.1940, found 333.1939), 260 (100), 203 (12), 189 (6), 115 (4).

(b) a mixture (0.130 g) of *E*-**87bA**, Z-**87bB** and **88bA**.

(c) a fraction which when crystallised from ethanol afforded **88bA** (0.219 g).

(d) a mixture (0.068 g) of **88bA**, **88bB** and Z-**87bA**.

(ii) A mixture (A:B:C:D=55:18:17:9) of the isomers of **82b** (0.100 g, 0.241 mmol) in dry acetonitrile (100 ml) at reflux was treated with DBU (0.10 ml, 0.67 mmol). The solution was refluxed for 50 min. A preliminary work-up as for (i) afforded a colourless oil (0.058 g, 72%) with *E*-**87bA**:*E*-**87bB**:Z-**87bA**:Z-**87bB**:**88bA**:**88bB** in the ratio 39:14:2:3:37:5.

(iii) A mixture (A:B:C:D=4:6:25:65) of the isomers of **82b** (0.198 g, 0.478 mmol), in dry acetonitrile (100 ml) under nitrogen at 0°C, was treated with DBU (0.10 ml, 0.67 mmol) then allowed to warm to room temperature with stirring for 12 h. A preliminary work-up as for (i) afforded a colourless oil (0.104 g, 65%), with *E*-**87bA**:*E*-**87bB**:Z-**87bA**:Z-**76bB**:**88bA**:**88bB** in the ratio 40:30:13:11:4, which was purified by preparative reverse phase HPLC with acetonitrile/26% water to give:

(a) after 11.4 min., the *Z-benzazonine* Z-**87bA** (0.010 g), attributed to the *cis* B-ring diastereomer, as a colourless oil. ^{1}H NMR δ: 6.61 (s, ArH), 6.56 (d, *J* 10.5 Hz, H7), 6.54 (s, ArH), 6.41 (dd, *J* 10.5 Hz, 10.6 Hz, H6), 4.26 (q, CH$_2$ of Et), 3.89 (s, OCH$_3$), 3.85 (s, OCH$_3$), 3.34-3.26 (m, H), 2.96 (d, *J* 4.2 Hz, H4), 2.89-2.79 (m, 2H), 2.63-2.44 (m, 2H), 2.41 (s, NCH$_3$), 1.32 (t, CH$_3$ of Et), 0.90 (d, *J* 7.0 Hz, CH$_3$); ^{13}C NMR δ: 172.82 (COO), 148.23 (C9^A), 147.53 (C10^A), 137.00 (C7^B), 133.42 (C11a^C), 130.63 (C7a^C), 129.77 (C6^B), 113.94 (C8^D), 111.87 (C11^D), 75.56 (C4), 60.94 (CH$_2$ of Et), 56.59 (2OCH$_3$), 55.61 (C2), 46.93 (NCH$_3$), 37.08 (C1), 36.93 (C5), 19.38 (CH$_3$), 15.16 (CH$_3$ of Et); MS m/z: 333 (M$^+$, 5%; Calcd. for C$_{19}$H$_{27}$NO$_4$ 333.1940, found 333.1951), 260 (100), 203 (11), 189 (5), 115 (3).

(b) after 13.4 min., the *Z-benzazonine*, Z-**87b** (0.004 g), attributed to the *trans* B-ring diastereomer, as a colourless oil. ^{1}H NMR δ: 6.59 (d, *J* 10.5 Hz, H7), 6.57 (s, ArH), 6.56 (s, ArH), 5.60 (dd, *J* 10.5 Hz, 10.6 Hz, H6), 4.13 (q, CH$_2$ of Et), 3.87 (s, OCH$_3$), 3.85 (s, OCH$_3$), 3.28-3.22 (m, H), 3.06 (d, *J* 11.4 Hz, H4), 2.71-2.57 (m, 3H), 2.54 (s, NCH$_3$), 2.43-2.33 (m, H5), 1.25 (t, CH$_3$ of Et), 0.81 (d, *J* 6.5 Hz, CH$_3$);

^{13}C NMR δ: 173.29 (COO), 148.33 (C9^A), 147.40 (C10^A), 138.71 (C7^B), 134.80 (C11a^C), 129.79 (C7a^C and C6^B), 113.96 (C8^D), 111.97 (C11^D), 73.04 (C4), 60.49 (CH$_2$ of Et), 56.55 (2OCH$_3$), 51.98 (C2), 45.75 (NCH$_3$), 38.48 (C1), 36.35 (C5), 18.17 (CH$_3$), 15.22 (CH$_3$ of Et); MS m/z: 333 (M$^+$, 9%; Calcd. for C$_{19}$H$_{27}$NO$_4$ 333.1940, found 333.1954), 260 (100), 203 (9), 189 (5), 115 (4).

* suffixes A and B denote B-ring diastereomers. Compound *E*-87bB could not be isolated. ^{1}H NMR δ: 5.65 (dd, *J* 5.3 Hz, 16.8 Hz, H6), 2.68 (s, NCH$_3$).

<u>Ethyl 7,8-Dimethoxy-3-methyl-1-(2'-methyl)propenyl-2,3,4,5-tetrahydro-*1H*-3-benzazepine-4-carboxylate 88a</u>

(i) To a solution of DBU (0.048 g, 0.32 mmol) in refluxing dry acetonitrile (10 ml) was added a solution of **82a** (0.105 g, 0.245 mmol) in acetonitrile (1 ml). The solution was refluxed for 1 h. then concentrated. Purification of the residue by column chromatography on alumina with dichloromethane/20% light petroleum afforded a mixture (84:16) of the B-ring diastereomers of the *3-benzazepine* **88a** (0.058 g, 71%) as a colourless oil. Characteristic ^{1}H NMR signals were: *trans*-**88a** ^{1}H NMR (d$_6$-benzene) δ:7.08 (s, ArH), 6.73 (s, ArH), 6.38 (d, *J* 8.3 Hz, H1'), 4.61 (t, H2), 2.77 (s, NCH$_3$), 1.92 (s, CH$_3$), 1.85 (s, CH$_3$), 1.15 (t, CH$_3$ of Et); *cis*-**88a** ^{1}H NMR (d$_6$-benzene) δ:7.18 (s, ArH), 6.78 (s, ArH), 6.52 (d, *J* 8.1 Hz, H1'), 4.68 (d, *J* 7.5 Hz, H2), 2.73 (s, NCH$_3$), 2.02 (s, CH$_3$), 1.72 (s, CH$_3$), 1.07 (t, CH$_3$ of Et).

(ii) The *trans* B-ring diastereomer of **88a** was isolated from the synthesis of **101c**. ^{1}H NMR δ: 6.69 (s, ArH), 6.64 (s, ArH), 5.70 (d, *J* 9.1 Hz, H1'), 4.13-4.06 (m, CH$_2$ of Et and H1), 3.84 (s, OCH$_3$), 3.83 (s, OCH$_3$), 3.30 (d, *J* 7.4 Hz, H2), 3.26-3.23 (m, H), 3.03-2.92 (m, 2H), 2.69-2.59 (m, H), 2.43 (s, NCH$_3$), 1.78 (d, *J* 0.8 Hz, CH$_3$), 1.63 (d, *J* 1.1 Hz, CH$_3$), 1.21 (t, CH$_3$ of Et); ^{13}C NMR δ: 172.74 (COO), 147.78 (C7^A), 147.42 (C8^A), 134.80 (C2'^{B}), 133.18 (C5a^B), 132.98 (C9a^B), 123.85 (C1'), 113.37 (C6^C), 112.79 (C9^C), 70.65 (C2), 60.44 (CH$_2$ of Et), 56.65 (OCH$_3$), 56.42 (OCH$_3$), 51.61 (C4), 46.25 (C1), 45.38 (NCH$_3$), 34.71 (C5), 26.63 (CH$_3$), 18.82

(CH$_3$), 15.05 (CH$_3$ of Et); MS m/z: 347 (M$^+$, 3%; Calcd. for C$_{20}$H$_{29}$NO$_4$ 347.2096, found 347.2111), 274 (100), 258 (3), 217 (15), 203 (5).

<u>Ethyl 7,8-Dimethoxy-3-methyl-1-propenyl-2,3,4,5-tetrahydro-*1H*-3-benzazepine-4-carboxylate **88b**</u>

The synthesis and purification described for **87b** afforded the *3-benzazepine*, **88bA** (0.219 g), attributed to the diastereomer* with the Z-geometry of the double bond, as an off-white solid with m.p. 83-84°C. ^{1}H NMR δ: 6.71 (s, ArH), 6.64 (s, ArH), 5.98-5.92 (m, H1'), 5.70-5.66 (m, H2'), 4.23 (dd, *J* 7.3 Hz, 7.9 Hz, H1), 4.16-4.03 (m, CH$_2$ of Et), 3.87 (s, OCH$_3$), 3.86 (s, OCH$_3$), 3.35 (d, *J* 7.7 Hz, H2), 3.28-3.23 (m, H), 3.00-2.92 (m, 2H), 2.72-2.63 (m, H), 2.45 (s, NCH$_3$), 1.62 (dd, *J* 1.7 Hz, 6.8 Hz, CH$_3$), 1.22 (t, CH$_3$ of Et); ^{13}C NMR δ: 172.37 (COO), 147.65 (C7^A), 147.27 (C8^A), 133.05 (C5a^B), 132.20 (C9a^B), 129.69 (C2'^{C}) 123.85 (C1'^{C}), 113.21 (C6^D), 112.50 (C9^D), 70.10 (C2), 60.43 (CH$_2$ of Et), 56.45 (OCH$_3$), 56.27 (OCH$_3$), 51.37 (C4), 46.24 (C1^E), 44.19 (NCH$_3$^{E}), 34.63 (C5), 14.94 (C3'), 13.71 (CH$_3$ of Et); MS m/z: 333 (M$^+$, 5%; Calcd. for C$_{19}$H$_{27}$NO$_4$ 333.1940, found 333.1945), 260 (100), 203 (10), 189 (4), 115 (3).

* The isomer **88bB** could not be isolated. ^{1}H NMR δ: 6.21-6.15 (m, H), 2.51 (s, NCH$_3$), 1.58 (dd, *J* 1.7 Hz, 6.8 Hz, CH$_3$), 1.10 (t, CH$_3$ of Et).

<u>Ethyl 7,8-Dimethoxy-1-[2'-(3,4-dimethoxyphenyl)ethenyl]-3-methyl-2,3,4,5-tetrahydro-*1H*-3-benzazepine-4-carboxylate **88c**</u>

(i) The salt **82c** (0.215 g, 0.368 mmol) as a suspension in dry tetrahydrofuran (13 ml) under nitrogen at room temperature was treated with DBU (0.073 g, 0.48 mmol). After 45 min. the solution was then concentrated. Purification of the residue by p.t.l.c. on silica with dichloromethane/3% ethanol gave:

(a) at R$_f$ 0.91, compound **89** (0.007 g, 4%).

(b) at R$_f$ 0.56, the *trans* B-ring diastereomer of the *3-benzazepine* **88c** (0.081 g, 48%) which crystallised from ethanol as colourless needles with m.p. 106-108°C. ^{1}H

NMR δ: 6.90 (d, *J* 1.8 Hz, H2"), 6.89 (dd, *J* 1.8 Hz, 8.3 Hz, H6"), 6.79 (d, *J* 8.3 Hz H5"), 6.66 (s, H9), 6.64 (s, H6), 6.50 (dd, *J* 5.8 Hz, 15.9 Hz, H1'), 6.16 (dd, *J* 1.3 Hz, 15.9 Hz, H2'), 4.12-3.96 (m, H1 and CH_2 of Et), 3.89 (s, OCH_3), 3.87 (s, $2OCH_3$), 3.84 (s, OCH_3), 3.74 (d, *J* 5.8 Hz, H2), 3.39-3.33 (m, H4), 3.21-3.14 (m, H4), 2.76-2.62 (m, H5), 2.56 (s, NCH_3), 1.16 (t, CH_3 of Et); ^{13}C NMR δ: 172.20 (COO), 149.56 (C7^A), 149.10 (C8^A), 148.03 (C3"^{A}), 147.41 (C4"^{A}), 134.07 (C1"^{B}), 131.64 (C5a^B), 131.28 (C1'^{C}), 131.16 (C9a^B), 128.89 (C2'^{C}), 119.83 (C2"^{D}), 114.50 (C5"^{D}), 113.96 (C6"^{D}), 111.72 (C6^D), 109.65 (C9^D), 69.61 (C2), 60.48 (CH_2 of Et), 56.69-56.51 ($4OCH_3$), 51.54 (C1), 51.34 (C4), 46.89 (NCH_3), 35.53 (C5), 15.10 (CH_3 of Et); MS m/z: 455 (M$^+$, 23%), 383 (38), 382 (100), 366 (4), 309 (3), 151 (6); Anal. Calcd for $C_{26}H_{33}NO_6$: C, 68.55; H, 7.30; N, 3.08%, found: C, 68.61; H, 7.32; N, 3.04%.

(c) at R_f 0.42, the *cis* B-ring diastereomer of the *3-benzazepine* **88c** (0.019 g, 11%) as a colourless solid. ^1H NMR δ: 6.96 (d, *J* 1.9 Hz, H2"), 6.95 (dd, *J* 1.9 Hz, 6.2 Hz, H6"), 6.86-6.79 (m, H1' and H5"), 6.70 (s, H9), 6.66 (s, H6), 6.38 (d, *J* 15.8 Hz, H2'), 4.13 (d, *J* 8.1 Hz, H1), 4.09-4.00 (q, CH_2 of Et), 3.91 (s, OCH_3), 3.88 (s, OCH_3), 3.86 (s, OCH_3), 3.82 (s, OCH_3), 3.61 (s, H2), 3.36-3.30 (m, H), 3.13-3.08 (m, H), 2.89-2.82 (m, H), 2.76-2.70 (m, H), 2.52 (s, NCH_3), 1.21 (t, CH_3 of Et); ^{13}C NMR δ: 172.23 (COO), 149.64 (C7^A), 149.34 (C8^A), 148.02 (C3"^{A}), 147.54 (C4"^{A}), 133.92 (C1"^{B}), 133.29 (C5a^B), 132.13 (C1'^{C}), 131.17 (C9a^B), 128.30 (C2'^{C}), 120.00 (C2"^{D}), 113.56 (C5"^{D}), 112.67 (C6"^{D}), 111.82 (C6^D), 109.76 (C9^D), 70.85 (C2), 60.61 (CH_2 of Et), 56.87-56.58 ($4OCH_3$), 53.23 (C4), 50.85 (C1), 45.89 (NCH_3), 35.28 (C5), 14.99 (CH_3 of Et); MS m/z: 455 (M$^+$, 25%), 383 (36), 382 (100), 366 (5), 309 (4), 151 (6).

(ii) To **82c** (0.299 g, 0.513 mmol) in dry acetonitrile (15 ml) under nitrogen at -45°C was added DBU (0.094 g, 0.62 mmol). The solution was stirred between -45°C and -40°C for 6 h. then allowed to warm slowly to -10°C over 1.5 h. Concentration and then column chromatography of the residue on alumina with dichloromethane/20% light petroleum gave a mixture (*trans/cis*=4.8) of the isomers of **88c** (0.168 g, 72%).

Methyl 7,8-Dimethoxy-1-[2'-(3,4-dimethoxyphenyl)ethenyl]-3-methyl-2,3,4,5-tetrahydro-*1H*-3-benzazepine-4-carboxylate **89**

(i) A portion of **82c** was crystallised from methanol/diethyl ether to afford a pale yellow powder (0.080 g, 0.14 mmol) which was treated, as a suspension in dry tetrahydrofuran (5 ml) under nitrogen at room temperature, with DBU (0.027 g, 0.18 mmol). After 30 min. the solution was then concentrated. Purification of the residue by p.t.l.c. on silica with dichloromethane/4% methanol gave:

(a) at R_f 0.94, the *trans* B-ring diastereomer of the *3-benzazepine* **89** (0.039 g, 65%) which crystallised from methanol as colourless needles with m.p. 123-124°C. ^{1}H NMR δ: 6.90-6.87 (m, H2" and H6"), 6.79 (d, *J* 8.8 Hz H5"), 6.66 (s, H9), 6.64 (s, H6), 6.50 (dd, *J* 5.9 Hz, 15.9 Hz, H1'), 6.16 (dd, *J* 1.4 Hz, 15.9 Hz, H2'), 4.12-4.08 (m, H1), 3.90 (s, OCH$_3$), 3.87 (s, 2OCH$_3$), 3.85 (s, OCH$_3$), 3.75 (d, *J* 5.9 Hz, H2), 3.57 (CO$_2$CH$_3$), 3.36-3.29 (m, H4), 3.20-3.16 (m, H4), 2.74-2.65 (m, H5), 2.55 (s, NCH$_3$); ^{13}C NMR δ: 172.53 (COO), 149.51 (C7^A), 149.08 (C8^A), 148.03 (C3"^{A}), 147.41 (C4"^{A}), 133.95 (C1"^{B}), 131.59 (C5a^B), 131.28 (C1'^{C}), 131.07 (C9a^B), 128.70 (C2'^{C}), 119.79 (C2"^{D}), 114.25 (C5"^{D}), 113.65 (C6"^{D}), 111.66 (C6^D), 109.57 (C9^D), 69.70 (C2), 56.72 (OCH$_3$), 56.49 (4OCH$_3$), 51.49 (C1), 51.45 (C4), 46.86 (NCH$_3$), 35.43 (C5); MS m/z: 441 (M$^+$, 39%; Calcd. for C$_{25}$H$_{31}$NO$_6$ 441.215, found 441.214), 382 (100), 309 (9), 206 (13), 189 (8), 151 (23).

(b) at R_f 0.86, the *cis* B-ring diastereomer of the *3-benzazepine* **89** (0.010 g, 16%) as a pale yellow oil. ^{1}H NMR δ: 6.97-6.94 (m, H2" and H6"), 6.81 (d, *J* 8.0 Hz H5"), 6.78 (dd, *J* 7.9 Hz, 15.8 Hz, H1'), 6.69 (s, H9), 6.65 (s, H6), 6.34 (d, *J* 15.8 Hz, H2'), 4.12-4.06 (m, H1), 3.91 (s, OCH$_3$), 3.88 (s, OCH$_3$), 3.87 (s, OCH$_3$), 3.83 (s, OCH$_3$), 3.62 (d, *J* 6.2 Hz, H2), 3.61 (CO$_2$CH$_3$), 3.36-3.28 (m, H4), 3.10-3.02 (m, H4), 2.91-2.84 (m, H5), 2.76-2.70 (m, H5), 2.51 (s, NCH$_3$); ^{13}C NMR δ: 172.73 (COO), 149.60 (C7^A), 149.32 (C8^A), 147.98 (C3"^{A}), 147.55 (C4"^{A}), 133.83 (C1"^{B}), 133.22 (C5a^B), 132.23 (C1'^{C}), 131.10 (C9a^B), 128.08 (C2'^{C}), 119.99 (C2"^{D}), 113.50 (C5"^{D}), 112.73 (C6"^{D}), 111.74 (C6^D), 109.91 (C9^D), 70.95 (C2), 56.91 (OCH$_3$), 56.59 (3OCH$_3$), 53.53 (C4), 51.94 (CO$_2$CH$_3$), 50.92 (C1), 45.79 (NCH$_3$), 34.90 (C5); MS

m/z: 441 (M$^+$, 37%; Calcd. for C$_{25}$H$_{31}$NO$_6$ 441.215, found 441.215), 382 (100), 309 (10), 206 (18), 189 (11), 151 (36).

3-Ethoxycarbonyl-2-(3,4-dimethoxy)phenyl-8,9-dimethoxy-5,6-dihydropyrrolo [2,1-a]isoquinoline 90

The preparation of **88c** described above afforded the *pyrrolo[2,1-a]isoquinoline* **90** (0.007 g, 4%) as a pale yellow oil. ^{1}H NMR δ: 7.06 (s, H10), 7.01-6.98 (m, H2' and H6'), 6.88 (d, *J* 8.3 Hz, H5'), 6.75 (s, H7), 6.45 (s, H1), 4.61 (t, H5), 4.16 (q, CH$_2$ of Et), 3.92 (s, 3OCH$_3$), 3.90 (s, OCH$_3$), 3.05 (t, H6), 1.11 (t, CH$_3$ of Et); ^{13}C NMR δ: 162.20 (COO), 149.47 (C8^A), 148.94 (C9^A), 148.62 (C3'^{A} and C4'^{A}), 147.41 (C4"^{A}), 135.57 (C2a^B), 135.00 (C3a^B), 130.35 (C1'^{B}), 125.46 (C10b^B), 122.48 (C1), 121.38 (C6a^B), 118.83 (C10a^B), 113.88 (C7^C), 111.59 (C10^C), 111.04 (C2'^{C}), 107.49 (C5'^{C}), 106.57 (C6'^{C}), 60.44 (CH$_2$ of Et), 56.71 (4OCH$_3$), 43.54 (C5), 29.35 (C6), 14.77 (CH$_3$ of Et); MS m/z: 437 (M$^+$, 100%; Calcd. for C$_{25}$H$_{27}$NO$_6$ 437.1837, found 437.184), 422 (15), 364 (8), 218 (8), 204 (6); IR (thin film from CH$_2$Cl$_2$): 1684, 1504, 1418, 1265, 1134, 1055, 1028 cm^{-1}.

2-Ethoxycarbonylmethyl-6,7-dimethoxy-1-ethynyl-2-methyl-1,2,3,4-tetrahydroisoquinolinium Bromide 91

The reaction of the base **71** (1.515 g, 6.551 mmol) with ethyl bromoacetate (1.81 g, 10.8 mmol) in dry butanone (5 ml) at 50°C for 3 h. afforded a solid which was collected, after aging at 5°C for 1 h., to give a mixture (*trans:cis*=78:22) of the B-ring diastereomers of the *2-ethoxycarbonylmethylisoquinolinium salt* **91** (2.172 g, 83%) as an off-white powder. *trans diastereomer* ^{1}H NMR δ: 6.94 (d, *J* 1.7 Hz, H1), 6.90 (s, ArH), 6.75 (s, ArH), 5.14 (q, NCH$_2$CO), 4.71-4.62 (m, H3), 4.40-4.34 (m, H3), 4.29 (q, CH$_2$ of Et), 3.89 (s, OCH$_3$), 3.88 (s, OCH$_3$), 3.59 (s, NCH$_3$), 3.40 (d, *J* 2.2 Hz, H2'), 3.28-3.10 (m, H4), 1.32 (s, CH$_3$); ^{13}C NMR δ: 165.13 (COO), 150.69 (C6^A), 149.40 (C7^A), 120.92 (C4a^B), 118.58 (C8a^B), 111.51 (C5^C), 110.82 (C8^C), 84.42 (C1), 74.52 (C1'), 64.55 (C2'), 63.55 (CH$_2$ of Et), 59.31 (NCH$_2$CO), 56.60

(2OCH$_3$), 55.94 (C3), 46.07 (NCH$_3$), 24.08 (C4), 14.27 (CH$_3$ of Et); *cis diastereomer* (assignable signals) ^{1}H NMR δ: 6.80 (s, ArH), 6.57 (s, H1), 3.79 (s, NCH$_3$); ^{13}C NMR δ: 84.56 (C1), 64.33 (C2'), 46.75 (NCH$_3$), 23.75 (C4).

<u>Ethyl 7,8-Dimethoxy-1-ethynyl-3-methyl-2,3,4,5-tetrahydro-*1H*-3-benzazepine-4-carboxylate **92**</u>

(i) To the salt **91** (0.323 g, 0.811) in refluxing dry acetonitrile (10 ml) was added DBU (0.160 g, 1.05 mmol). The mixture was refluxed for 1 h. Concentration and then purification of the residue by column chromatography on alumina with dichloromethane/20% light petroleum afforded a yellow oil (0.090 g, 35%) which was further purified by preparative reverse phase HPLC with H$_2$O/44% acetonitrile to give:

(a) at 15.9 min, the *3-benzazepine* **92** (0.018 g, 7%) as a yellow oil. ^{1}H NMR δ: 6.89 (s, ArH), 6.64 (s, ArH), 4.34 (dd, *J* 2.6 Hz, 7.0 Hz, H1), 4.11 (q, CH$_2$ of Et), 3.86 (s, 2OCH$_3$), 3.62 (d, *J* 6.9 Hz, H2), 3.25-3.20 (m, 2H), 2.83-2.72 (m, 2H), 2.53 (s, NCH$_3$), 2.43 (d, *J* 2.6 Hz, CH$_3$), 1.22 (t, CH$_3$ of Et); ^{13}C NMR δ: 171.26 (COO), 148.23 (C7[A]), 147.62 (C8[A]), 133.58 (C5a[B]), 128.25 (C9a[B]), 113.48 (C6[C]), 113.15 (C9[C]), 83.25 (C1'), 73.66 (C2[D]), 69.45 (C2'[D]), 60.97 (CH$_2$ of Et), 56.63 (OCH$_3$), 56.53 (OCH$_3$), 51.45 (C4), 46.47 (NCH$_3$[E]), 39.99 (C1[E]), 34.60 (C5), 15.03 (CH$_3$ of Et); MS m/z: 317 (M$^+$, 56%; Calcd. for C$_{18}$H$_{23}$NO$_4$ 317.1627, found 317.1633), 302 (31), 288 (9), 244 (100), 228 (11), 201 (21), 115 (14).

(b) at 18.2 min, compound **93** (0.018 g, 7%).

(c) at 29.1 min, compound **94** (0.007 g, 3%).

(ii) To **91** (0.534 g, 1.34 mmol) suspended in dry acetonitrile (5 ml) at 0°C was added DBU (0.35 g, 2.3 mmol). The mixture was stirred for 80 min. while allowed to warm to room temperature. Water (10 ml) and dichloromethane (15 ml) were then added. The layers were partitioned and the aqueous layer was extracted with further dichloromethane (2 x 5 ml). Drying and then concentration of the organic extracts

afforded a dark oil (0.099 g) in which no rearrangement products were detected by t.l.c. or ^{1}H NMR analysis.

1-Ethoxycarbonyl-6,7-dimethoxy-1-ethynyl-2-methyl-1,2,3,4-tetrahydroisoquinoline 93

The preparation of **92** described above afforded the *1-ethoxycarbonylmethyl-isoquinoline* **93** (0.018 g) as a yellow oil. ^{1}H NMR (d$_6$-benzene) δ: 7.04 (s, ArH), 6.31 (s, ArH), 3.92-3.74 (m, CH$_2$ of Et), 3.49 (s, OCH$_3$), 3.39 (s, OCH$_3$), 3.26 (d, *J* 14.0 Hz, H of CH$_2$COO), 3.13 (d, *J* 13.9 Hz, H of CH$_2$COO), 2.98-2.83 (m, H3 and H4), 2.62 (s, NCH$_3$), 2.60-2.55 (m, H3), 2.30-2.25 (m, H4), 2.20 (s, H2'), 0.78 (t, CH$_3$ of Et); ^{13}C NMR (d$_6$-benzene) δ: 169.01 (COO), 149.85 (C6^A), 149.38 (C7^A), 130.96 (C4a^B), 129.01 (C8a^B), 112.77 (C5^C), 112.49 (C8^C), 84.38 (C1'), 75.40 (C2'), 61.14 (C1), 60.40 (CH$_2$ of Et), 56.60 (OCH$_3$), 56.15 (OCH$_3$), 50.12 (C3), 46.78 (CH$_2$CO$_2$), 40.91 (NCH$_3$), 30.28 (C4), 14.63 (CH$_3$ of Et); MS m/z: 317 (M$^+$, 2%; Calcd. for C$_{18}$H$_{23}$NO$_4$ 317.1627, found 317.1649), 291 (3), 244 (3), 230 (100), 214 (8), 115 (6).

1-[*E*-3-Ethoxycarbonyl-*Z*-2-propenylidene]-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline 94

The preparation of **92** described above afforded an intensely yellow coloured oil tentatively attributed to the *isoquinoline* **94** (0.007 g). ^{1}H NMR δ: 7.97 (dd, *J* 12.1 Hz, 14.5 Hz, H2'), 7.15 (s, ArH), 6.68 (s, ArH), 5.57 (d, *J* 14.5 Hz, H3'^{A}), 5.37 (d, *J* 12.1 Hz, H1'^{A}), 4.13 (q, CH$_2$ of Et), 3.92 (s, 2OCH$_3$), 3.35 (t, H3), 3.11 (s, CH$_3$), 2.75 (t, H4), 1.24 (t, CH$_3$ of Et); ^{13}C NMR δ: 169.60 (COO), 152.23 (C3'^{A}), 150.32 (C7^A), 147.50 (C6^A), 147.09 (C1'), 131.12 (C8a^B), 123.56 (C4a^B), 114.78 (C2'^{C}), 110.86 (C8^C), 108.46 (C5^C), 94.51 (C3'), 59.83 (CH$_2$ of Et), 56.86 (OCH$_3$), 56.67 (OCH$_3$), 51.01 (C3), 40.72 (NCH$_3$), 30.49 (C4), 15.27 (CH$_3$ of Et); MS m/z: 317 (M$^+$, 49%; Calcd. for C$_{18}$H$_{23}$NO$_4$ 317.1627, found 317.1624), 302 (11), 288 (6), 272 (31), 244 (100), 230 (60), 214 (20), 199 (12).

Attempted Preparation of 6,7-Dimethoxy-2-methyl-1-(1'-propynyl)-1,2,3,4-tetrahydroisoquinoline **96**

(i) A solution of the 1-ethynyl base **71** (3.019 g, 13.05 mmol) in dry tetrahydrofuran (25 ml) was added dropwise to a suspension of sodium amide (0.584 g, 90% technical grade, $\geq$ 13.5 mmol) in dry tetrahydrofuran (25 ml) at -78°C under nitrogen. The mixture was allowed to warm to room temperature with stirring over 1 h. then the resultant solution was cooled to -78°C and iodomethane (1.86 g, 13.2 mmol) was added dropwise. The solution was maintained at -70°C for 15 min. then allowed to warm to room temperature and stirred for 2 h. with the deposition of a tan solid. Ammonium chloride (0.5 g) and water (30 ml) were added cautiously and the solution was extracted with diethyl ether (4 x 20 ml). The ether extracts were combined and washed with water (2 x 10 ml) then saturated brine (10 ml), and then dried and passed through a silica plug. Concentration afforded **71** (1.501 g, 50%). The original aqueous layer was then concentrated and extracted with chloroform (3 x 25 ml). Concentration of the chloroform extracts afforded a dark powder (2.326 g) which was taken up in hot methanol. Ethyl acetate was added and the mother liquor was decanted from the resultant dark oil. The concentration of the mother liquor gave a tan powder tentatively identified as crude 6,7-Dimethoxy-1,2,2-trimethyl-1-(1'-propynyl)-1,2,3,4-tetrahydro-isoquinolinium iodide **97** (1.424 g). ^{1}H NMR δ: 6.93 (s, ArH), 6.70 (s, ArH), 4.50-4.42 (s, H), 4.13-4.01 (m, H), 3.91 (s, OCH$_3$), 3.89 (s, OCH$_3$), 3.56 (s, NCH$_3$), 3.47 (s, NCH$_3$), 3.32-3.21 (m, 2H), 2.06 (s, CH$_3$), 2.05 (s, CH$_3$); ^{13}C NMR δ: 149.95 (C6^A), 148.87 (C7^A), 125.46 (C4a^B), 120.04 (C8a^B), 111.35 (C5^C), 110.00 (C8^C), 90.07 (C1^D), 74.42 (C1'^{D}), 71.75 (C2'^{D}), 56.51 (OCH$_3$), 56.23 (OCH$_3$), 56.06 (C3), 49.81 (NCH$_3$), 49.01 (NCH$_3$), 29.01 (CH$_3$), 23.80 (C4), 4.50 (C3'); MS (LSIMS) m/z: 274 (M-I$^+$, 100%), 258 (5), 246 (5), 232 (6), 220 (9).

(ii) Compound **71** (0.964 g, 4.17 mmol) was added to a suspension of sodium amide (0.197 g, 90% technical grade, $\geq$ 4.54 mmol) in dry tetrahydrofuran (25 ml) at -78°C under nitrogen. The mixture was allowed to warm to 0°C with stirring over 1 h. then

stirred at this temperature for 8 h. The brown solution was cooled to -78°C and a solution of iodomethane (0.604 g, 4.28 mmol) in dry tetrahydrofuran (20 ml) was added dropwise over 1 h. The solution was then stirred at 25°C for 24 h. Work up as for (i) gave, from the ether solution, **71** (0.342 g, 35%).

3-Ethoxycarbonylmethyl-8,9-dimethoxy-3-methyl-5-trimethylsilyl-1,2,3,4-tetrahydro-3-benzazocinium Bromide 98

(i) A solution of the base **70c** (0.506 g, 1.66 mmol) and ethyl bromoacetate (0.75 g, 4.5 mmol) in dry butanone (8 ml) under nitrogen was stirred for 24 h. at 60-70°C then aged at 0°C for 12 h. Collection of the precipitate and recrystallisation of this material from dichloromethane/butanone afforded the *3-benzazocinium salt* **9 8** (0.254 g, 32%) as a pale yellow powder with m.p. 140-142°C. ^{1}H NMR δ: 7.25 (s, H6), 6.64 (s, H10), 6.39 (s, H7), 5.08 (d, *J* 17.0 Hz, H of NCH$_2$CO), 4.73 (d, *J* 17.0 Hz, H of NCH$_2$CO), 4.40-4.28 (m, H2), 4.13 (d, *J* 13.0 Hz, H4), 3.79 (d, *J* 13.3 Hz, H4), 4.02 (m, CH$_2$ of Et), 3.71 (s, OCH$_3$), 3.68-3.59 (m, H2), 3.66 (s, OCH$_3$), 3.37 (s, NCH$_3$), 2.95-2.87 (m, H1), 2.78-2.69 (m, H1), 1.07 (t, CH$_3$ of Et), 0.15 (s, Si(CH$_3$)$_3$); ^{13}C NMR δ: 164.93 (COO), 151.74 (C6), 150.21 (C8^A), 148.10 (C9^A), 132.85 (C5), 129.09 (C6a^B), 127.56 (C10a^B), 112.92 (C7^C), 110.89 (C10^C), 64.12 (CH$_2$ of Et^D), 63.83 (NCH$_2$CO^D), 62.82 (C4^D), 62.38 (C2^D), 56.31 (OCH$_3$), 56.19 (OCH$_3$), 48.26 (NCH$_3$), 28.25 (C1), 14.10 (CH$_3$ of Et), 0.05 (Si(CH$_3$)$_3$); Anal. Calcd for C$_{21}$H$_{34}$NO$_4$SiBr: C, 53.38; H, 7.25; N, 2.97%, found: C, 53.30; H, 7.30; N, 3.06%.

(ii) A solution of the base **70c** (0.498 g, 1.63 mmol) and ethyl bromoacetate (0.75 g, 4.5 mmol) in dry butanone (2.5 ml) under nitrogen was stirred for 48 h. at room temperature. Concentration of the solution and trituration of the residue with diethyl ether (3 x 20 ml) afforded a 60:40 mixture (0.125 g, 16%) of **98** and **72c**. The diethyl ether washings contained unchanged **70c**.

(iii) A solution of the salt **72c** (0.196 g, 0.415 mmol) in dry butanone (6 ml) was refluxed for 24 h. Concentration and then ^{1}H NMR spectral analysis of the residue

indicated a 2:1:1 mixture of **72c**, **98**, and a component attributed to the previously unobserved B-ring diastereomer of **72c** with the following characteristic NMR signals: ^{1}H NMR δ: 5.44 (s, H1), 3.30 (s, NCH₃), -0.01 (s, Si(CH₃)₃); ^{13}C NMR δ: 142.62 (C2'), 46.99 (NCH₃).

N-{2-[4,5-Dimethoxy-2-(4-ethoxycarbonyl-4-iodo-1(*E*)-butenyl)phenyl]ethyl}-*N,N,N*-trimethylammonium iodide **100**

(i) Treatment of **52a** (0.246 g, 0.771 mmol) with iodomethane (0.156 g, 3.47 mmol) in dry butanone (2 ml) at reflux for 3 h. gave the precipitation of a solid which, after cooling, was collected and recrystallised from butanone to afford *the title compound* **100** (0.170 g, 37%) as a colourless powder with m.p. 167-169°C. ^{1}H NMR δ: 6.95 (s, ArH), 6.73 (d, *J* 15.6 Hz, H1"), 6.63 (s, ArH), 6.08-5.98 (m, H2"), 4.79 (dd, *J* 3.9 Hz, 10.8 Hz, H4"), 4.26 (q, CH₂ of Et), 3.91 (s, OCH₃), 3.88 (s, OCH₃), 3.67 (s, 3NCH₃), 3.30-3.23 (m, 3H), 3.18-3.13 (m, 2H), 2.95-2.84 (m, H), 1.22 (t, CH₃ of Et); ^{13}C NMR δ: 167.40 (COO), 149.76 (C4'^{A}), 148.81 (C5'^{A}), 133.13 (C1"^{B}), 131.60 (C1'^{C}), 127.47 (C2'^{C}), 120.74 (C2"^{B}), 113.31 (C3'^{D}), 109.65 (C6'^{D}), 74.51 (C4"), 63.87 (CH₂ of Et), 56.93 (OCH₃), 56.60 (OCH₃), 53.92 (3NCH₃), 37.76 (C1), 31.96 (C2), 14.78 (CH₃ of Et), 6.41 (C3"); MS (LSIMS) m/z: 476 ([M-I]$^+$, 100%), 417 (26), 366 (11), 348 (7); IR (thin film from CHCl₃): 1740, 1512, 1271, 1215, 731 cm^{-1}.

(ii) The reaction of **52a** (0.183 g, 0.573 mmol) in iodomethane (2.0 ml, 32 mmol) at room temperature under nitrogen over 16 h. gave a solid which was collected and recrystallised three times from dichloromethane/toluene to afford **100** (0.107 g, 31%) as a colourless powder with m.p. 163-164°C. Anal. Calcd for C₂₀H₃₁NO₄I₂: C, 39.82; H, 5.18; N, 2.32%, found: C, 40.23; H, 5.22; N, 2.47%.

Ethyl 9,10-Dimethoxy-3-methyl-2,3,4,5,6,7-hexahydro-1*H*-
3-benzazonine-4-carboxylate **101a**

Compound **52a** (0.178 g, 0.558 mmol, *E/Z*=19) was refluxed in ethanol (15 ml) under hydrogen at atmospheric pressure with 5% Pd-C (0.025 g) for 3 h. Concentration and then purification of the residue by p.t.l.c. on silica with dichloromethane/3% ethanol afforded:

(a) at R_f 0.95, the *hexahydro-3-benzazonine* **101a** (0.102 g, 66% from unrecovered **52a**) as a colourless oil. ^{1}H NMR δ: 6.63 (s, ArH), 6.54 (s, ArH), 4.08 (q, CH$_2$ of Et), 3.85 (s, 2OCH$_3$), 3.55-3.45 (m, H), 3.23 (dd, *J* 2.8 Hz, 12.1 Hz, H4), 2.87-2.73 (m, 3H), 2.61-2.57 (m, H), 2.57 (s, NCH$_3$), 2.48-2.40 (m, H), 1.83-1.76 (m, 2H), 1.54-1.47 (m, H), 1.22 (t, CH$_3$ of Et), 1.18-1.11 (m, H); ^{13}C NMR δ: 174.07 (COO), 147.90 (C9^A), 147.23 (C10^A), 135.00 (C7a^B), 133.24 (C11a^B), 114.15 (C8^C), 113.19 (C11^C), 68.75 (C4), 60.41 (CH$_2$ of Et), 56.50 (2OCH$_3$), 53.40 (C2), 44.05 (NCH$_3$), 36.78 (C7^D), 32.08 (C1^D), 31.91 (C5^D), 26.27 (C6^D), 15.06 (CH$_3$ of Et); MS m/z: 321 (M$^+$, 2%; Calcd. for C$_{18}$H$_{27}$NO$_4$ 321.1939, found 321.1948), 248 (100), 205 (13), 164 (4), 124 (5).

(b) at R_f 0.88, compound Z-**52a** (0.024 g).

Ethyl 9,10-Dimethoxy-3-methyl-6-phenyl-2,3,4,5,6,7-hexahydro-1*H*-
3-benzazonine-4-carboxylate **101b**

A 38:54:8 mixture of the isomers *E*-**75b**, *Z*-**75b**, and **76b** (0.200 g, 0.504 mmol) was refluxed in ethanol (15 ml) under hydrogen at atmospheric pressure with 5% Pd-C (0.030 g) for 3 h. and was then concentrated. The residue was passed through an alumina plug with dichloromethane/5% light petroleum to give a colourless oil (0.143 g). Purification of a portion (0.067 g) of this oil by preparative reverse phase HPLC with acetonitrile/29% water gave:

(a) after 30.0 min., unchanged *Z*-**75b** (0.011 g).

(b) after 37.5 min., the *hexahydro-3-benzazonine* **101b** (0.029 g) as a colourless oil. ^{1}H NMR δ: 7.39-7.36 (m, 4ArH'), 7.27-7.25 (m, ArH'), 6.70 (s, ArH), 6.59 (s, ArH),

4.15 (t, H7), 4.13 (q, CH_2 of Et), 3.87 (s, OCH_3), 3.86 (s, OCH_3), 3.18-3.12 (m, H6),

3.02-2.97 (m, H4 and H1), 2.81-2.78 (m, H2), 2.72 (dd, J 4.3 Hz, 12.3 Hz, H7), 2.55

(s, NCH_3), 2.54-2.50 (m, H1), 1.67-1.60 (m, H5), 1.15 (t, CH_3 of Et); ^{13}C NMR δ:

174.23 (COO), 148.09 ($C9^A$), 147.63 ($C10^A$), 145.31 ($C1'^B$), 134.93 ($C7a^B$), 132.98

($C11a^B$), 129.05 (2C'), 128.73 (2C'), 126.93 (C'), 114.41 ($C8^C$), 113.49 ($C11^C$),

63.07 (C4), 60.47 (CH_2 of Et), 56.61 ($2OCH_3$), 54.09 (C2), 46.91 (C6), 43.86

(NCH_3), 38.86 ($C7^D$), 36.13 ($C1^D$), 33.02 (C5), 15.09 (CH_3 of Et); MS m/z: 397

(M^+, 3%; Calcd. for $C_{24}H_{31}NO_4$ 397.2253, found 397.2281), 324 (100), 267 (9), 220

(4), 165 (5), 91 (6), 70 (6).

(c) after 42.5 min., an unidentified isomer of **101b** as a colourless oil (0.008 g). ^1H

NMR δ: 7.37-7.26 (m, 2ArH'), 7.22-7.19 (m, ArH'), 7.07-7.05 (m, 2ArH'), 6.54 (s,

ArH), 5.52 (s, ArH), 4.14-4.00 (m, CH_2 of Et and H), 3.83 (s, OCH_3), 3.40-3.34 (m,

OCH_3 and H), 3.28-3.20 (m, H), 3.04-2.99 (m, H), 2.85-2.77 (m, 3H), 2.66 (s,

NCH_3), 2.55-2.50 (m, H), 1.86-1.81 (m, H), 1.66-1.57 (m, H), 1.23 (t, CH_3 of Et);

MS m/z: 397 (M^+, 7%; Calcd. for $C_{24}H_{31}NO_4$ 397.2253, found 397.2247), 324

(100), 267 (10), 220 (5), 165 (8), 91 (12), 70 (5).

Ethyl 9,10-Dimethoxy-3,5,5-trimethyl-2,3,4,5,6,7-hexahydro-1*H*-
3-benzazonine-4-carboxylate **101c**

A 58:37:5 mixture of the isomers *E*-**87a**, *trans*-**88a**, and *cis*-**88a** (0.259 g,

0.772 mmol) was refluxed in ethanol (15 ml) under hydrogen at atmospheric

pressure with 5% Pd-C (0.030 g) for 3 h. and was then concentrated. The residue

was passed through an alumina plug with dichloromethane/5% light petroleum to

give a pale yellow oil (0.236 g). Purification of the oil by preparative reverse phase

HPLC with acetonitrile/36% water gave:

(a) after 17.2 min., unchanged *trans*-**88a** (0.057 g).

(b) after 34.7 min., the *hexahydro-3-benzazonine* **101c** (0.088 g, 58% based on

original *E*-**87a**) as a colourless oil. ^1H NMR δ: 6.62 (s, ArH), 6.60 (s, ArH), 4.18 (q,

CH_2 of Et), 3.85 (s, $2OCH_3$), 3.60 (s, H4), 3.09-3.04 (m, H1 and H2), 2.50-2.42 (m,

H1, H2 and H7), 2.23 (s, NCH$_3$), 1.75-1.62 (m, H6), 1.31 (t, CH$_3$ of Et), 1.10 (s,

CH$_3$), 1.00 (s, CH$_3$); ^{13}C NMR δ: 171.96 (COO), 147.80 (C9^A), 147.32 (C10^A),

137.54 (C7a^B), 130.75 (C11a^B), 113.69 (C8^C), 113.11 (C11^C), 64.10 (C4), 59.96

(CH$_2$ of Et), 59.05 (C2), 56.47 (OCH$_3$), 56.35 (OCH$_3$), 44.14 (C6), 42.48 (NCH$_3$),

38.72 (C5), 32.48 (C1), 26.58 (C7), 26.24 (CH$_3$), 25.82 (CH$_3$), 15.28 (CH$_3$ of Et);

MS m/z: 349 (M$^+$, 27%; Calcd. for C$_{20}$H$_{31}$NO$_4$ 349.2253, found 349.2246), 276

(100), 220 (98), 206 (8), 177 (10), 130 (93), 110 (10).

Ethyl 9,10-Dimethoxy-3-methyl-6-methylene-2,3,4,5,6,7-hexahydro-1*H*-
3-benzazonine-4-carboxylate 102

A 66:34 mixture of *E*-75a and *Z*-75a (0.185 g, 0.555 mmol) was refluxed in

ethanol (10 ml) under hydrogen at atmospheric pressure with 5% Pd-C (0.030 g) for

2.5 h. Concentration and then purification of the residue by p.t.l.c. on silica with

dichloromethane/5% methanol afforded, at R$_f$ 0.55, compound 103 (0.007 g) and, at

R$_f$ 0.92, a mixture (0.131 g) which was further purified by p.t.l.c. on silica with

dichloromethane to give:

(a) at R$_f$ 0.12, a mixture with predominantly *Z*-75a (0.044 g).

(b) at R$_f$ 0.23, a mixture (0.054 g) attributed to compounds 101d and 102.

Purification by preparative reverse phase HPLC with acetonitrile/20% water gave,

after 22.15 min., the *6-methylene-3-benzazonine* 102 (0.030 g) as a colourless oil.

^{1}H NMR δ: 6.63 (s, ArH), 6.55 (s, ArH), 4.99 (s, H of =CH$_2$), 4.79 (s, H of =CH$_2$),

4.20 (d, *J* 13.2 Hz, H7), 4.10 (q, CH$_2$ of Et), 3.85 (s, OCH$_3$), 3.83 (s, OCH$_3$), 3.32-

2.25 (H4 and H7), 2.89-2.80 (m, 3H), 2.55 (s, NCH$_3$), 2.51-2.45 (m, H), 2.18 (dd, *J*

3.2 Hz, 14.0 Hz, H5), 1.90 (dd, *J* 13.1 Hz, 14.0 Hz), 1.24 (t, CH$_3$ of Et); ^{13}C NMR

δ: 173.50 (CO), 150.65 (C6), 147.81 (C9^A), 147.69 (C10^A), 134.19 (C7a^B), 131.60

(C11a^B), 114.12 (C8^C), 113.51 (C11^C), 112.60 (=CH$_2$), 67.92 (C4), 60.64 (CH$_2$ of

Et), 56.50 (2OCH$_3$), 53.63 (C2), 43.74 (NCH$_3$), 41.91 (C7^D), 36.65 (C1^D), 36.05

(C5^D), 15.15 (CH$_3$ of Et); MS m/z: 333 (M$^+$, 12%; Calcd. for C$_{19}$H$_{27}$NO$_4$

333.1940, found 333.1950), 260 (100), 217 (13), 203 (4), 168 (3), 130 (5).

Ethyl 9,10-Dimethoxy-3,6-dimethyl-2,3,4,7-tetrahydro-1*H*-
3-benzazonine-4-carboxylate **103**

The synthesis described for the preparation of **102** afforded the *2,3,4,7-
tetrahydro-3-benzazonine* **103** (0.007 g) as a colourless oil. ^{1}H NMR δ: 6.70 (s,
ArH), 6.55 (s, ArH), 5.21 (d, *J* 9.8 Hz, H5), 4.50 (d, *J* 9.9 Hz, H4), 4.23 (q, CH$_2$ of
Et), 4.18 (d, *J* 13.2 Hz, H7), 3.87 (s, OCH$_3$), 3.84 (s, OCH$_3$), 3.14-3.08 (m, 2H),
2.97-2.91 (m, H), 2.75 (d, *J* 13.3 Hz, H7), 2.49-2.23 (m, H), 2.39 (s, NCH$_3$), 1.82 (d,
J 1.2 Hz, CH$_3$), 1.32 (t, CH$_3$ of Et); ^{13}C NMR δ: 173.79 (CO), 148.10 (C9^A), 147.64
(C10^A), 140.34 (C6), 134.00 (C7a^B), 129.15 (C11a^B), 119.88 (C5), 115.54 (C8^C),
114.14 (C11^C), 63.89 (C4), 61.89 (CH$_2$ of Et), 56.80 (OCH$_3$), 56.58 (OCH$_3$), 54.70
(C2), 40.63 (NCH$_3$), 37.42 (C7^D), 26.42 (C1^D), 24.15 (CH$_3$), 14.95 (CH$_3$ of Et); MS
m/z: 333 (M$^+$, 28%; Calcd. for C$_{19}$H$_{27}$NO$_4$ 333.1940, found 333.1917), 290 (30),
260 (100), 246 (13), 217 (47), 206 (31), 202 (23).

Ethyl 9,10-Dimethoxy-2,3,4,5,6,7-hexahydro-1*H*-3-benzazonine-4-carboxylate **104b**

(i) Compound **52b** (0.193 g) was refluxed in ethanol (10 ml) under hydrogen at
atmospheric pressure with 5% Pd-C (0.020 g) for 16 h. Samples analysed by GC-MS
after 1.5 h., 3.5 h. and 16 h. showed mixtures attributed to **52b**, **104a**, and **104b** in the
ratios 8:88:4, 1:88:11, and 0:77:23.

(ii) Compound **105** (0.101 g, 0.233 mmol) was stirred in methanol (5 ml) at room
temperature with 5% Pd-C (0.015 g) under hydrogen for 3 h. The solution was
filtered and then concentrated. Treatment of the residue with 1M aqueous sodium
hydroxide (5 ml) and extraction of the aqueous mixture with diethyl ether (3 x 5 ml)
afforded, after drying and then concentration of the ether extracts, the *hexahydro-3-
benzazonine* **104b** (0.051 g, 71%) as a colourless oil. ^{1}H NMR δ: 6.63 (s, ArH), 6.57
(s, ArH), 4.13 (q, CH$_2$ of Et), 3.85 (s, 2OCH$_3$), 3.83-3.74 (m, H), 3.45 (dd, *J* 4.4 Hz,
7.9 Hz, H4), 2.98-2.63 (m, 5H), 1.97 (bs, NH), 1.81-1.69 (m, 2H), 1.62-1.48 (m, 2H),
1.24 (t, CH$_3$ of Et); ^{13}C NMR δ: 175.53 (COO), 148.05 (C9^A), 147.48 (C10^A),
134.43 (C7a^B), 133.15 (C11a^B), 113.68 (C8^C), 112.94 (C11^C), 61.19 (CH$_2$ of Et),

60.82 (C4), 56.45 (2OCH$_3$), 48.02 (C2), 37.83 (C7^D), 31.77 (C1^D), 28.66 (C5^D),

27.54 (C6^D), 14.85 (CH$_3$ of Et); MS m/z: 307 (M$^+$, 20%; Calcd. for C$_{17}$H$_{25}$NO$_4$

307.1782, found 307.1787), 234 (100), 217 (11), 165 (17), 117 (7).

(iii) Compound **105** (0.101 g, 0.233 mmol) was stirred in methanol (5 ml) at 0°C

with 5% Pd-C under hydrogen. Samples analysed by GC-MS after 10 min., 30 min.,

1 h. and 2 h. showed mixtures attributed to **52b**, **104a**, and **104b** in the ratios 46:53:1,

0:84:16, 0:7:93, and 0:0:100.

3-Benzyl-9,10-Dimethoxy-4-ethoxycarbonyl-2,3,4,5-tetrahydro-1*H*-3-benzazoninium Hydrochloride 105

Hydrogen chloride gas from a Kipps' apparatus was passed through a solution

of **52b** (1.123 g, 2.839 mmol) in diethyl ether (20 ml) for 5 min. The precipitate was

collected and recrystallised from methanol/diethyl ether to give the *title compound*

105 (0.613 g, 50%) as fine colourless prisms with m.p. 102-103°C. ^{1}H NMR δ:

11.70 (s, NH), 8.08 (s, 2ArH'), 7.49 (bs, 3ArH'), 6.71 (s, ArH), 6.34 (s, ArH), 5.51-

5.42 (m, H6), 5.03-4.98 (m, H7), 4.45-4.29 (m, CH$_2$ of Et and NCH$_2$), 3.89 (s,

OCH$_3$), 3.75 (s, OCH$_3$), 3.30-3.11 (m, 3H), 1.78-1.72 (m, H), 1.36 (t, CH$_3$ of Et);

^{13}C NMR δ: 167.66 (COO), 148.15 (C9^A), 147.61 (C10^A), 137.82 (C6^B), 133.26

(C7 and C4'^{B}), 132.80 (C7a^C), 130.68 (2C'), 130.00 (C11a^C), 129.61 (2C'), 128.77

(C1'^{C}), 113.37 (C8^D), 110.22 (C11^D), 69.05 (C4), 63.51 (CH$_2$ of Et), 62.56 (NCH$_2$),

58.09 (C2), 56.48 (2OCH$_3$), 33.40 (C1^E), 33.16 (C5^E), 14.60 (CH$_3$ of Et).

7,8-Dimethoxy-5-isopropionitrile-3-methyl-2,3-dihydro-*1H*-3-benzazepine 106

A pale yellow oil (0.265 g) containing 3 components in the ratio 10.0:1.0:1.5,

with **63a** the major component (from the rearrangement of **62a** in refluxing

acetonitrile), was refluxed in dry butyronitrile (20 ml) for 66 h. Concentration and

then purification of the residue by passage through an alumina plug with

dichloromethane/25% light petroleum afforded an oil (109 mg). A portion of the oil

(0.074 mg) was purified by preparative reverse phase HPLC with acetonitrile/41%

water to give the *5-isopropionitrile-3-benzazepine* **106** (0.037 g) as a yellow oil. ^{1}H NMR δ: 6.69 (s, ArH), 6.57 (s, ArH), 6.31 (s, H4), 3.87 (s, OCH$_3$), 3.86 (s, OCH$_3$), 3.78 (q, H2'), 3.41 (t, H2), 2.88 (t, H1), 2.86 (s, NCH$_3$), 1.50 (d, *J* 7.1 Hz, CH$_3$); ^{13}C NMR δ: 148.03 (C7^A), 146.88 (C8^A), 137.19 (C4), 133.89 (C9a^B), 129.74 (C5a^B), 123.95 (CN^C), 113.09 (C6^D), 109.23 (C9^D), 102.16 (C5^C), 57.54 (C2), 56.72 (OCH$_3$), 56.55 (OCH$_3$), 45.64 (NCH$_3$), 36.13 (C1), 31.55 (C2$^{'E}$), 21.23 (C3$^{'E}$); MS m/z: 272 (M$^+$, 75%; Calcd. for C$_{16}$H$_{20}$N$_2$O$_2$ 272.1524, found 272.1517), 257 (100), 243 (7), 230 (3), 218 (10), 199 (4), 175 (4).

Attempted Preparation of *E*-9,10-Dimethoxy-3-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazonine-4-methanol 107

A suspension of lithium aluminium hydride (0.289 g, 7.61 mmol) in dry diethyl ether (6 ml) was refluxed for 10 min. and then a solution of **52a** (1.029 g, 3.222 mmol, *E/Z* = 19) in diethyl ether (10 ml) was added dropwise to maintain reflux. Substantial solid formed. After refluxing for 30 min. the mixture was stirred for 1 h. at 25°C and then cooled and water was added cautiously until the hydrogen evolution ceased. Diethyl ether (10 ml) was added and the solution was filtered. The solid was extracted with further diethyl ether (2 x 10 ml) and then the ether solutions were combined and washed with water (5 ml), and then saturated brine (5 ml). Drying and then concentration of the extracts afforded a colourless solid tentatively attributed to **107** (0.864 g, 95%). ^{1}H NMR (CDCl$_3$ at 60°C) δ: 6.72 (s, ArH), 6.63 (s, ArH), 6.32 (bs, H7), 5.53 (bs, H6), 3.82 (s, OCH$_3$), 3.81 (s, OCH$_3$), 3.46 (bs, 3H), 3.11 (bs, 2H), 2.70 (bs, 2H), 2.55 (dd, *J* 15.8 Hz, 7.8 Hz, H), 2.44 (s, NCH$_3$), 2.32-2.05 (m, 2H).

Purification of a portion (0.260 g) of the above solid by p.t.l.c. on alumina with ethyl acetate/5% hexane gave:

(i) at R$_f$ 0.92, the pyrrolidine **108b** (0.113 g, 36%).

(ii) at R$_f$ 0.40, the pyrrolidine **108a** (0.034 g, 12%).

<u>5-(2-Ethenyl-4,5-dimethoxyphenyl)-1-methyl-2-pyrrolidinemethanol **108a**</u>

The procedure described for the preparation of **107** afforded *the title compound* **108a** (0.034 g, 12%) as a colourless oil. ^{1}H NMR δ: 7.08 (dd, *J* 17.3 Hz, 10.9 Hz, H1"), 6.99 (s, ArH'), 6.83 (s, ArH'), 5.51 (dd, *J* 17.3 Hz, 1.3 Hz, H2"), 5.22 (dd, *J* 10.9 Hz, 1.3 Hz, H2"), 4.36 (t, H5), 3.88 (s, OCH$_3$), 3.86 (s, OCH$_3$), 3.67 (t, CH$_2$ of CH$_2$OH), 3.30-3.26 (m, H2), 2.23 (s, NCH$_3$), 2.29-2.11 (m, 2H), 1.87-1.74 (m, 2H); ^{13}C NMR δ: 149.52 (C4'^{A}), 148.26 (C5'^{A}), 134.84 (C1"), 133.73 (C1'^{B}), 130.25 (C2'^{B}), 114.72 (C2"), 110.20 (C3'^{C}), 109.44 (C6'^{C}), 65.04 (C5^D), 63.35 (C2^D), 62.74 (CH$_2$OH), 56.60 (OCH$_3$), 56.48 (OCH$_3$), 35.84 (NCH$_3$), 32.98 (C4^E), 27.60 (C3^E); MS m/z: 277 (M$^+$, 12%; Calcd. for C$_{16}$H$_{23}$NO$_3$ 277.1677, found 277.1669), 246 (100), 215 (13), 189 (32), 70 (30).

<u>5-(2-Ethenyl-4,5-dimethoxyphenyl)-1-methyl-2-pyrrolidinemethanol acetate **108b**</u>

The procedure described for the preparation of **107** afforded *the title compound* **108b** (0.113 g, 36%) as a colourless oil. ^{1}H NMR δ: 7.05 (dd, *J* 17.3 Hz, 10.9 Hz, H1"), 7.00 (s, ArH'), 6.97 (s, ArH'), 5.51 (dd, *J* 17.3 Hz, 1.3 Hz, H2"), 5.20 (dd, *J* 10.9 Hz, 1.3 Hz, H2"), 4.26 (dd, *J* 11.2 Hz, 4.9 Hz, H of CH$_2$OAc), 4.15-4.06 (m, H5 and H of CH$_2$OAc), 3.90 (s, 2OCH$_3$), 3.59-3.53 (m, H2), 2.32 (s, NCH$_3$), 2.29-2.24 (m, H), 2.12 (s, CH$_3$), 2.10-2.01 (m, H), 1.72-1.53 (m, 2H); ^{13}C NMR δ: 171.51 (CO), 149.71 (C4'^{A}), 148.05 (C5'^{A}), 134.42 (C1"), 129.58 (C1' and C2'), 114.34 (C2"), 109.54 (C3'^{C}), 109.16 (C6'^{C}), 64.60 (CH$_2$ of CH$_2$OAc), 63.10 (C5^D), 61.68 (C2^D), 56.43 (OCH$_3$), 56.34 (OCH$_3$), 35.43 (NCH$_3$), 33.78 (C4^E), 27.42 (C3^E), 21.60 (CH$_3$); MS m/z: 319 (M$^+$, 17%; Calcd. for C$_{18}$H$_{25}$NO$_4$ 319.1783, found 317.1775), 246 (100), 215 (12), 189 (26), 70 (24).

6.3 Experimental for Chapter Three

6,7-Dimethoxy-2-methyl-1-vinyl-1,2,3,4-tetrahydroisoquinoline *N*-oxide 123a

To **49a** (2.116 g, 9.07 mmol) in dichloromethane (40 ml) at 0°C was added a solution of *m*-CPBA (1.9 g, 11 mmol) in dichloromethane (30 ml). The solution was allowed to warm to room temperature and stirred for 24 h. before the addition of 5% aqueous sodium bicarbonate (40 ml) and removal of the organic solvent *in vacuo*. The aqueous solution was washed with diethyl ether (3 x 15 ml) then made acidic to litmus with 3M aqueous hydrochloric acid and washed with further diethyl ether (3 x 15 ml). The solution was basified with saturated aqueous sodium bicarbonate then saturated with sodium chloride and extracted with chloroform (3 x 25 ml). Drying and then concentration of the organic extracts afforded a mixture (65:35) of the B-ring diastereomers of *1-vinyltetrahydroisoquinoline N-oxide* **123a** (1.647 g, 73%) as a tan hygroscopic solid. ^{1}H NMR δ: 6.68 (s, H5), 6.55 (s, H8^a), 6.60-6.51 (m, H1'^{a}), 6.48 (s, H8^b), 5.93-5.81 (m, H1^b), 5.67 (d, *J* 10.1 Hz, H2'^{a}), 5.57 (d, *J* 17.8 Hz, H2'^{b}), 5.52 (d, *J* 10.1 Hz, H2'^{b}), 5.28 (d, *J* 16.8 Hz, H2'^{a}), 4.75 (d, *J* 9.0 Hz, H1^b), 4.67 (d, *J* 7.5 Hz, H1^a), 3.87 (s, OCH$_3$), 3.73 (s, OCH$_3$), 3.74-3.38 (m, 3H), 3.28 (s, NCH$_3$^{a}), 3.22 (s, NCH$_3$^{b}), 2.93-2.81 (m, H); ^{13}C NMR δ: 149.31 (C6^A), 148.38 (C7^A), 134.51 and 134.03 (C1'), 124.33 and 124.56 (C2'), 123.68 (C4a and C8a), 111.57 (C5^B), 111.67 and 111.14 (C8^B), 78.41 and 77.95 (C1), 63.26 and 60.89 (C3), 58.13 and 57.23 (NCH$_3$), 56.51 (2OCH$_3$), 26.02 and 25.66 (C4); .MS m/z: 249 (M$^+$, 24%; Calcd. for C$_{14}$H$_{19}$NO$_3$ 249.136, found 249.135), 232 (7), 203 (12), 190 (100), 175 (43), 159 (24).

2-Benzyl-6,7-dimethoxy-1-vinyl-1,2,3,4-tetrahydroisoquinoline *N*-oxide 123b

To **49b** (2.109 g, 6.817 mmol) in dichloromethane (40 ml) at 0°C was added a solution of *m*-CPBA (1.42 g, 8.26 mmol) in dichloromethane (30 ml). The solution was allowed to warm to room temperature and stirred for 24 h. before the addition of 5% aqueous sodium bicarbonate (40 ml) and removal of the organic solvent *in*

vacuo. The aqueous solution was washed with diethyl ether (3 x 15 ml) then made acidic to litmus with 3M aqueous hydrochloric acid and washed with further diethyl ether (3 x 15 ml). The solution was basified with saturated aqueous sodium bicarbonate then saturated with sodium chloride and extracted with chloroform (3 x 25 ml). Drying and then concentration of the organic extracts afforded a mixture (81:19) of the B-ring diastereomers of *1-vinyltetrahydroisoquinoline N-oxide* **123b** (1.778 g, 80%) as a tan hygroscopic solid. ^{1}H NMR δ: 7.57-7.26 (m, 5ArH"), 6.73-6.62 (m, H5 and H1^a), 6.53 (s, H8^a), 6.44 (s, H8^b), 6.11-5.98 (m, H1^b), 5.67 (d, J 10.4 Hz, H2'^{a}), 5.57 (d, J 10.3 Hz, H2'^{b}), 5.48 (d, J 10.1 Hz, H2'^{b}), 5.19 (d, J 17.5 Hz, H2'^{a}), 5.03 (d, J 9.1 Hz, H1^b), 4.85 (d, J 6.5 Hz, H1^a), 4.69-4.51 (m, NCH$_2$Ph), 3.88 (s, OCH$_3$^{a}), 3.86 (s, OCH$_3$^{b}), 3.77 (s, OCH$_3$^{a}), 3.71 (s, OCH$_3$), 3.73-3.32 (m, 3H), 2.99-2.74 (m, H); ^{13}C NMR δ: 149.55 (C6^A), 148.51 (C7^A), 134.16-128.28 (6C", C1', C4a and C8a), 123.97 and 125.26 (C2'), 111.57 (C8^B), 111.35 (C8^B), 74.69 and 79.40 (C1), 71.46 and 70.21 (NCH$_2$Ph), 59.21 and 57.17 (C3), 56.68 (2OCH$_3$), 26.04 and 25.38 (C4).

Mixture of 6,7-Dimethoxy-2-methyl-1-propenyl-1,2,3,4-tetrahydroisoquinoline *N*-oxide isomers **123c**

To a mixture (Z:E=3:1) of the 1-propenyl isomers of **81b** (1.282 g, 5.18 mmol) in dichloromethane (25 ml) at 0°C was added a solution of *m*-CPBA (1.079 g, 6.27 mmol) in dichloromethane (25 ml). The solution was allowed to warm to room temperature and stirred for 20 h. before the addition of 5% aqueous sodium bicarbonate (25 ml) and removal of the organic solvent *in vacuo*. The aqueous solution was washed with diethyl ether (3 x 10 ml) then made acidic to litmus with 3M aqueous hydrochloric acid and washed with diethyl ether (3 x 10 ml). The solution was basified with saturated aqueous sodium bicarbonate then saturated with sodium chloride and extracted with chloroform (3 x 25 ml). Drying and then concentration of the organic extracts afforded a mixture (51:24:16:9) attributed to the two *Z* and two *E* B-ring diastereomers of *1-propenyltetrahydroisoquinoline N-oxide*

123c (1.243 g, 91%) as a tan hygroscopic solid. ^{1}H NMR characteristic peaks δ: 6.54[c], 6.52[a], 6.48[d] and 6.42[b] (s, H8), 5.14[b], 5.08[a], 4.70[d] and 4.63[c] (d, J 9.6 Hz, H1), 3.27[a], 3.25[c], 3.21[b] and 3.19[d] (s, NCH₃).

<u>6,7-Dimethoxy-1-[2'-(3,4-dimethoxyphenyl)ethenyl]-2-methyl-1,2,3,4-tetrahydroisoquinoline *N*-oxide **123d**</u>

To **81c** (0.301 g, 0.781 mmol) in dichloromethane (10 ml) at 0°C was added a solution of *m*-CPBA (0.263 g, 1.53 mmol) in dichloromethane (15 ml). The solution was allowed to warm to room temperature and stirred for 21 h. then washed with 0.5M aqueous sodium bicarbonate (3 x 5 ml). Drying and then concentration of the organic layer afforded a residue which was purified by p.t.l.c. on silica with dichloromethane/10% methanol to afford a mixture (68:32) of the B-ring diastereomers of *tetrahydroisoquinoline N-oxide* **123d** (0.259 g, 82%) as a tan hygroscopic solid. ^{1}H NMR δ: 7.10-6.74 (m, 3ArH", H1'[a], and H2'[b]), 6.72 (s, H5), 6.60 (s, H8[a]), 6.52 (s, H8[b]), 6.41 (d, J 16.1 Hz, H2'[a]), 6.01 (dd, J 15.5 Hz, 9.3 Hz, H1'[b]), 4.98 (d, J 9.3 Hz, H1[b]), 4.87 (d, J 7.5 Hz, H1[a]), 3.89-3.88 (m, 3OCH₃), 3.78 (s, OCH₃), 3.72-3.49 (m, 3H), 3.34 (s, NCH₃[a]), 3.32 (s, NCH₃[b]), 2.94-2.85 (m, H); ^{13}C NMR δ: 138.24 and 138.47 (C1'), 122.76 (C2'[A]), 121.17 (C6[A]), 78.09 and 80.70 (C1), 63.02 and 59.83 (C3), 57.78 and 57.41 (NCH₃), 56.42-56.25 (4OCH₃), 25.82 and 25.28 (C4); MS m/z: 385 (M[+], 43%), 354 (43), 326 (16), 206 (100), 204 (45), 151 (53).

<u>7,8-Dimethoxy-3-methyl-1-vinyl-1,3,4,5-tetrahydro-2,3-benzoxazepine **124a**</u>

(i) The *N*-oxide **123a** (1.647 g) was refluxed in dry acetonitrile (50 ml) for 1 h. Concentration and then purification of the residue by column chromatography on alumina with dichloromethane/2% light petroleum afforded the *2,3-benzoxazepine* **124a** (1.197 g, 73%) as a pale tan oil. ^{1}H NMR δ: 6.67 (s, ArH), 6.58 (s, ArH), 6.01-6.10 (m, H1'), 5.45 (d, J 6.8 Hz, H1), 5.29 (d, J 17.9 Hz, H2'), 5.24 (d, J 10.8 Hz, H2'), 3.86 (s, OCH₃), 3.83 (bs, OCH₃ and H), 3.28-3.24 (m, H), 3.10-3.02 (m, H),

2.92-2.85 (m, H), 2.72 (s, NCH$_3$); ^{13}C NMR δ: 148.03 (C7^A), 147.89 (C8^A), 137.17 (C1'), 132.81 (C5a^B), 129.63 (C9a^B), 117.78 (C2'), 114.39 (C6^C), 111.16 (C9^C), 87.12 (C1), 60.69 (C4), 56.57 (2OCH$_3$), 47.39 (NCH$_3$), 33.25 (C5); MS m/z: 249 (M$^+$, 22%; Calcd. for C$_{14}$H$_{19}$NO$_3$ 249.1363, found 249.135), 232 (10), 203 (11), 190 (100), 175 (44), 159 (22), 147 (17).

(ii) A solution of **123a** (0.219 g) in acetonitrile (15 ml) was stored sealed under nitrogen and protected from light at 20-25°C for 3.5 months. ^{1}H NMR analysis indicated a 79:21 mixture of **124a:123a.**

(iii) A solution of **123a** (0.419 g) in dichloromethane (30 ml) was refluxed for 6 days. ^{1}H NMR analysis indicated a 64:36 mixture of **124a:123a.**

(iv) A solution of **123a** (0.109 g) in mesitylene (10 ml) was refluxed for 25 min. then concentrated. The residue was purified by passage through an alumina plug with dichloromethane to give **124a** (0.016 g, 15%).

3-Benzyl-7,8-dimethoxy-1-vinyl-1,3,4,5-tetrahydro-2,3-benzoxazepine 124b

The *N*-oxide **123b** (1.778 g) was refluxed in dry acetonitrile (50 ml) for 1 h. Concentration and then purification of the residue by column chromatography on alumina with dichloromethane/2% light petroleum afforded the *2,3-benzoxazepine* **124b** (1.260 g, 71%) as a pale yellow oil. ^{1}H NMR δ: 7.45-7.25 (5ArH"), 6.66 (s, ArH), 6.49 (s, ArH), 5.97-5.85 (m, H1'), 5.12-5.00 (m, 2H2' and H1), 3.92-3.77 (m, 2OCH$_3$ and NCH$_2$Ph), 3.37-3.29 (m, H), 3.21-3.13 (m, H), 3.04-2.96 (m, H), 2.79-2.71 (m, H); ^{13}C NMR δ: 147.86 (C7^A), 147.70 (C8^A), 138.25 (C1"), 136.94 (C1'), 133.20 (C5a^B), 132.54 (C9a^B), 130.11 (2C"), 128.60 (2C"), 127.68 (C4"), 117.61 (C2'), 114.33 (C6^C), 111.09 (C9^C), 87.40 (C1), 63.96 (C4), 58.69 (NCH$_2$Ph), 56.55 (2OCH$_3$), 33.42 (C5); MS m/z: 325 (M$^+$, 14%; Calcd. for C$_{20}$H$_{23}$NO$_3$ 325.1677, found 325.1692), 308 (10), 282 (14), 203 (15), 190 (100), 175 (30), 159 (16), 147 (11), 91 (61); IR: 2934, 2832, 1516, 1258, 1109, 1030, 700 cm^{-1}; UV: 286, 240, 215 nm.

7,8-Dimethoxy-3-methyl-1-propenyl-1,3,4,5-tetrahydro-2,3-benzoxazepine 124c

(i) A mixture (Z:E=3:1) of the isomers of the 1-propenyl-N-oxide **123c** (0.411 g) was refluxed in dry acetonitrile (25 ml) for 1 h. Concentration and then purification of the residue by column chromatography on alumina with dichloromethane/2% light petroleum afforded a mixture (Z:E=3:1) of the isomers of the *2,3-benzoxazepine* **124c** (0.358 g, 87%) as a colourless oil. The isomers could not be separated by p.t.l.c. or HPLC techniques. *Z-isomer* ^{1}H NMR δ: 6.67 (s, ArH), 6.59 (s, ArH), 5.82 (d, J 8.6 Hz, H1), 5.75-5.68 (m, H1' and H2'), 3.86 (s, OCH$_3$), 3.82 (s, OCH$_3$), 3.32-3.22 (m, H), 3.12-3.04 (m, H), 2.90-2.86 (m, 2H), 2.71 (s, NCH$_3$), 1.83 (dd, J 6.6 Hz, 1.4 Hz, CH$_3$); ^{1}H NMR (d$_6$ Benzene) δ: 6.00 (d, J 8.7 Hz, H1), 5.93-5.87 (m, H1), 5.61-5.57 (m, H2'), 1.61 (dd, J 6.9 Hz, 1.6 Hz, CH$_3$); ^{13}C NMR (d$_6$ benzene) δ: 149.13 (C7[A]), 149.07 (C8[A]), 135.61 (C5a[B]), 131.52 (C9a[B]), 131.04 (C1'), 126.92 (C2'), 116.26 (C6[C]), 112.56 (C9[C]), 81.57 (C1), 61.13 (C4), 56.68 (2OCH$_3$), 47.82 (NCH$_3$), 34.93 (C5), 14.30 (CH$_3$). Signals attributed to the *E-isomer* ^{1}H NMR δ: 6.65 (s, ArH), 6.55 (s, ArH), 5.41 (d, J 7.0 Hz, H1), 2.70 (s, NCH$_3$), 1.73 (d, J 5.3 Hz, CH$_3$); ^{13}C NMR (d$_6$ benzene) δ: 87.21 (C1), 62.83 (C4), 56.36 (2OCH$_3$), 47.53 (NCH$_3$), 34.01 (C5), 18.48 (CH$_3$).

(ii) A mixture (Z:E=3:1) of the isomers of **123c** (0.221 g) was refluxed in dichloromethane (12 ml) for 5 days then worked up as for (i) to give a mixture (Z:E=3:1) of the isomers of **124c** (0.118 g, 53%).

(iii) A mixture (Z:E=3:1) of the isomers of **123c** (0.033 g) was absorbed onto 60HF$_{254}$ basic alumina type E (0.22 g) from dichloromethane. The residual solvent was removed under vacuum. The solid was irradiated on medium power for 5 min. in a standard microwave (high power=750W) then extracted with dichloromethane to give a mixture (Z:E=1.9:1) of the isomers of **124c** (0.023 g, 70%).

7,8-Dimethoxy-1-[2'-(3,4-dimethoxyphenyl)ethenyl]-3-methyl-1,3,4,5-tetrahydro-2,3-benzoxazepine 124d

(i) The *N*-oxide **123d** (0.192 g) was refluxed in dry acetonitrile (10 ml) for 1 h. Concentration and then purification of the residue by p.t.l.c. with dichloromethane/5% methanol afforded:

(a) at R_f 0.15, recovered **123d** (0.042 g, 22%).

(b) at R_f 0.40, the precursor amine **81c** (0.003 g, 2%).

(c) at R_f 0.80, the *2,3-benzoxazepine* **124d** (0.112 g, 58%) as a pale yellow oil. ^{1}H NMR δ: 6.97-6.92 (m, *o*-ArH"), 6.80 (d, *J* 8.2 Hz, H5"), 6.69 (s, H6), 6.61 (s, H9), 6.57 (d, *J* 15.9 Hz, H2'), 6.26 (dd, *J* 15.8 Hz, 7.5 Hz, H1'), 5.62 (d, *J* 7.4 Hz, H1), 3.88 (s, 3OCH$_3$), 3.82 (s, OCH$_3$), 3.46-3.38 (m, H), 3.14-3.07 (m, H), 2.96-2.90 (m, H), 2.75 (s, NCH$_3$), 2.73-2.67 (m, H); ^{13}C NMR δ: 149.55 (C7 and C2"^{A}), 148.07 (C8 and C3"^{A}), 133.11 (C1'), 132.94 (C5a^B), 130.15 (C1"^{B}), 129.04 (C9a^B), 126.16 (C2'), 120.83 (C6"^{C}), 114.32 (C6^C), 111.47 (C9^C), 111.27 (C5"^{C}), 109.36 (C2"^{C}), 87.29 (C1), 60.66 (C4), 56.56 (4OCH$_3$), 47.28 (NCH$_3$), 32.88 (C5); MS m/z: 385 (M$^+$, 9%; Calcd. for C$_{22}$H$_{27}$NO$_5$ 385.189, found 385.188), 369 (62), 354 (50), 326 (16), 206 (100), 204 (25), 190 (12), 151 (43); IR: 1516, 1464, 1265, 1227, 1140, 1026, 914, 802, 731 cm^{-1}.

(ii) Photolysis of **123d** (0.259 g) in dry acetonitrile (200 ml) at ≥225 nm for 30 min. afforded a mixture with numerous components.

6,7-Dimethoxy-1-methyl-1,3,3a,4,9,9a-hexahydroisoxazolo[3,4-*b*]naphthalene 126a

The benzoxazepine **124a** (1.050 g) was heated in an evacuated sealed tube at an internal temperature of 210°C for 30 min. Passage of the resultant oil through an alumina plug with dichloromethane afforded a colourless residue (0.868 g). Purification of this residue by column chromatography on silica, with a gradient from dichloromethane/5% light petroleum to dichloromethane/1% methanol, afforded **124a** (0.070 g, 7%) followed by the *isoxazolo[3,4-b]naphthalene* **126a** (0.450 g, 43%) as a colourless oil. ^{1}H NMR δ: 6.68 (s, ArH), 6.67 (s, ArH), 4.09 (t,

H3), 3.83 (s, OCH$_3$), 3.82 (s, OCH$_3$), 3.40 (t, H3), 2.97-2.92 (m, H3a and H), 2.80-2.72 (m, H), 2.70 (s, NCH$_3$), 2.66-2.45 (m, 3H); ^{13}C NMR δ: 147.66 (C6^A), 147.51 (C7^A), 129.10 (C4a^B), 128.81 (C8a^B), 111.90 (C5 and C8), 71.23 (C3), 68.18 (C9a), 56.23 (OCH$_3$), 56.05 (OCH$_3$), 43.92 (C3a^C), 43.44 (NCH$_3$^{C}), 31.70 (C9^D), 30.83 (C4^D); MS m/z: 249 (M$^+$, 100%; Calcd. for C$_{14}$H$_{19}$NO$_3$ 249.1364, found 249.1378), 232 (16), 218 (52), 204 (55), 189 (56), 164 (63); IR: 1514, 1464, 1452, 1258, 1229, 1115.

1-Benzyl-6,7-Dimethoxy-1,3,3a,4,9,9a-hexahydroisoxazolo[3,4-*b*]naphthalene 126b

The benzoxazepine **124b** (0.890 g) was heated in an evacuated Buchi bulb-to-bulb apparatus at an internal temperature of 180°C for 150 min. with the distillation of a 67:25:8 mixture of **124b:127:126** (0.190 g, 21%). The residual dark oil was purified by passage through a silica plug with dichloromethane to afford a pale yellow oil (0.508 g) which was then further purified by preparative reverse phase HPLC with acetonitrile/41% H$_2$O to give:

(a) at 21.9 min., the *isoxazolo[3,4-b]naphthalene* **126b** (0.210 g, 24%) as a colourless oil. ^{1}H NMR δ: 7.39-7.25 (m, 5ArH'), 6.66 (s, ArH), 6.59 (s, ArH), 4.13 (t, H3), 3.98 (d, *J* 3.9 Hz, NCH$_2$Ph), 3.82 (s, 2OCH$_3$), 3.48 (t, H3), 3.19-3.13 (m, H9a), 2.93-2.85 (m, H3a), 2.72-2.62 (m, H4 and H9), 2.56-2.45 (m, H4 and H9); ^{13}C NMR δ: 147.81 (C6^A), 147.75 (C7^A), 137.86 (C1'), 129.74 (C4a^B), 129.51 (2C'), 129.32 (C8a^B), 128.74 (2C'), 127.78 (C4'), 112.19 (C5^C), 111.83 (C8^C), 71.63 (C3), 66.41 (C9a), 61.58 (NCH$_2$Ph), 56.48 (2OCH$_3$), 43.69 (C3a), 32.83 (C9^D), 31.65 (C4^D); MS m/z: 325 (M$^+$, 46%; Calcd. for C$_{14}$H$_{19}$NO$_3$ 249.1364, found 249.1378), 294 (20), 204 (35), 189 (60), 165 (41), 106 (22), 91 (100); IR: 1516, 1464, 1452, 1223, 1113.

(b) at 42.5 min., compound **124b** (0.005 g, 1%)

(c) at 45.9 min., compound **127** (0.076 g, 9%).

<u>2-Benzyloxy-6,7-dimethoxy-1-vinyl-1,2,3,4-tetrahydroisoquinoline 127</u>

The preparation of **126b** described above gave the *2-benzyloxyisoquinoline* **127** (0.076 g, 9%) which crystallised from methanol as a colourless solid with m.p. 67-68°C. ^{1}H NMR δ: 7.40-7.24 (m, 5ArH"), 6.60 (s, ArH), 6.57 (s, ArH), 5.98-5.87 (m, H1'), 5.39 (dd *J* 9.7 Hz, H2'), 5.35 (d, *J* 15.7 Hz, H2'), 4.78 (d, *J* 10.7 Hz, H of OCH$_2$Ph), 4.73 (d, *J* 10.7 Hz, H of OCH$_2$Ph), 4.34 (d, *J* 7.8 Hz, H1), 3.83 (s, OCH$_3$), 3.80 (s, OCH$_3$), 3.44-3.36 (m, H), 3.04-2.93 (m, 2H), 2.85-2.77 (m, H); ^{13}C NMR δ: 148.47 (C6^A), 147.91 (C7^A), 139.44 (C1'), 138.19 (C1"), 129.56 (2C"), 128.88 (2C"), 128.45 (C"), 127.70 (C4a^B), 126.35 (C8a^B), 119.83 (C2'), 111.43 (C5^C), 111.30 (C8^C), 75.85 (OCH$_2$Ph), 56.50 (2OCH$_3$), 52.07 (C3), 28.81 (C4); MS m/z: 325 (M$^+$, 18%; Calcd. for C$_{20}$H$_{23}$NO$_2$ 325.1677, found 325.1670), 308 (9), 254 (32), 234 (77), 204 (13), 189 (100), 176 (27), 91 (71).

<u>6,7-Dimethoxy-1-isopropenyl-2-methyl-1,2,3,4-tetrahydroisoquinoline *N*-oxide 128a</u>

To **70a** (1.020 g, 4.378 mmol) in dichloromethane (30 ml) at 0°C was added a solution of *m*-CPBA (0.904 g, 5.25 mmol) in dichloromethane (30 ml). The solution was stirred for 30 h. while allowed to warm to room temperature then 5% aqueous sodium bicarbonate (25 ml) was added and the organic solvent was removed *in vacuo*. The aqueous solution was washed with diethyl ether (3 x 10 ml) then made acidic to litmus with 3M aqueous hydrochloric acid and washed with further diethyl ether (3 x 15 ml). The solution was basified with saturated aqueous sodium bicarbonate then saturated with sodium chloride and extracted with chloroform (3 x 25 ml). Drying and then concentration of the organic extracts afforded a mixture (50:50) of the B-ring diastereomers of *1-isopropenyltetrahydroisoquinoline N-oxide* **128a** (0.693 g, 64%) as a tan hygroscopic solid. *trans isomer** ^{1}H NMR δ: 6.60 (s, ArH), 6.36 (s, ArH), 5.25 (m, H2'), 4.84 (s, H1), 3.79 (s, OCH$_3$), 3.72 (s, OCH$_3$), 3.61-3.45 (m, 2H), 3.42-3.31 (m, H), 3.16 (s, NCH$_3$), 2.73-2.66 (m, H), 1.61 (s, CH$_3$); ^{13}C NMR δ: 148.84 (C6^A), 148.46 (C7^A), 141.43 (C1'), 124.03 (C4a^B), 123.93 (C2'), 123.31 (C8a^B), 111.24 (C5^C), 110.83 (C8^C), 84.83 (C1), 60.62 (C3),

58.28 (NCH$_3$), 56.40 (2OCH$_3$), 24.96 (C4), 20.49 (CH$_3$); IR: 1520, 1256, 1229, 1124, 918, 729. *Peaks attributed to the cis isomer* ^{1}H NMR δ: 6.40 (s, ArH), 5.48 (s, H2'), 5.09 (s, H2'), 4.76 (s, H1), 3.29 (s, NCH$_3$), 2.03 (s, CH$_3$); ^{13}C NMR δ: 80.75 (C1), 63.79 (C3), 58.49 (NCH$_3$), 25.87 (C4), 22.26 (CH$_3$).

* The *trans* isomer was obtained separately as described in the formation of **129a**.

6,7-Dimethoxy-2-methyl-1-(α-phenylethenyl)-1,2,3,4-tetrahydroisoquinoline *N*-oxide **128b**

Whenever possible solutions were cooled in ice throughout this procedure. To **70b** (1.486 g, 4.803 mmol) in dichloromethane (25 ml) at 0°C was added a solution of *m*-CPBA (1.021 g, 5.936 mmol) in dichloromethane (25 ml). The solution was stirred at 0°C for 20 h. then 5% aqueous sodium bicarbonate (30 ml) was added and the organic solvent was removed *in vacuo*. The cooled aqueous solution was washed with diethyl ether (3 x 10 ml) then made acidic to litmus with 3M aqueous hydrochloric acid and washed with further diethyl ether (3 x 15 ml). The solution was basified with saturated aqueous sodium bicarbonate then saturated with sodium chloride and extracted with chloroform (3 x 25 ml). Drying and then concentration of the organic extracts afforded a 4:1 mixture of **128b** and **129b** (1.525 g). Purification of a portion (1.161 g) of this mixture by column chromatography on alumina with dichloromethane/0-10% methanol gave:

(a) a 78:22 mixture of **129b** and **130b** (0.156 g, 14%).

(b) the *trans*-B-ring diastereomer of the *tetrahydroisoquinoline N-oxide* **128b** (0.547 g, 47%) as a cream hygroscopic solid. ^{1}H NMR δ: 7.30 (s, 3ArH"), 7.07 (bs, *o*-ArH"), 6.71 (s, ArH), 6.62 (s, ArH), 5.61 (s, H1^A), 5.30 (s, 2H2'^{A}), 3.91 (s, OCH$_3$), 3.83 (s, OCH$_3$), 3.73-3.60 (m, 2H), 3.18-3.11 (m, H), 3.12 (s, NCH$_3$), 2.65-2.58 (m, H); ^{13}C NMR δ: 149.28 (C6^A), 148.92 (C7^A), 147.83 (C1'^{A}), 140.53 (C1"), 129.43 (2C"), 129.03 (2C"), 127.95 (C4"), 126.14 (C2'), 124.75 (C4a^B), 124.28 (C8a^B), 111.56 (C5 and C8), 82.45 (C1), 59.76 (NCH$_3$), 58.66 (C3), 56.67 (OCH$_3$), 56.56 (OCH$_3$), 24.91 (C4).

6,7-Dimethoxy-2-methyl-1-(1'-trimethylsilylethenyl)-1,2,3,4-tetrahydroisoquinoline N-oxide 128c

To **70c** (0.506 g, 1.66 mmol) in dichloromethane (10 ml) at 0°C was added a solution of m-CPBA (0.310 g, 1.80 mmol) in dichloromethane (10 ml). The solution was allowed to warm to room temperature and stirred for 20 h. then washed with 5% aqueous sodium bicarbonate (2 x 7 ml). Drying and then concentration of the organic solution afforded a hygroscopic foam that was purified by column chromatography on alumina, with a gradient from dichloromethane/5% hexane to dichloromethane/10% methanol, to give:

(a) a 74:26 mixture (0.134 g) of **70c** (20%) and **129c** (6%).

(b) a mixture ($trans:cis$=66:34) of the B-ring diastereomers of the *tetrahydroisoquinoline N-oxide* **128c** (0.325 g, 61%) as a yellow oil. ^{1}H NMR δ: 6.49 (s, H5^a), 6.47 (s, H5^b), 6.26 (s, H8^b), 6.15 (s, H8^a), 5.83-5.78 (m, 2H2'^{a} and H2'^{b}), 5.62 (d, J 2.5 Hz, H2'^{b}) 4.88 (s, H1^a), 4.58 (s, H1^b), 3.69 (s, OCH$_3$), 3.60 (s, OCH$_3$), 3.48-3.32 (m, 2H), 3.24-3.17 (m, H), 2.99 (s, NCH$_3$^{b}), 2.96 (s, NCH$_3$^{a}), 2.64-2.53 (m, H), -0.03 (s, Si(CH$_3$)$_3$^{a}), -0.17 (s, Si(CH$_3$)$_3$^{b}); ^{13}C NMR δ: 138.08 and 134.58 (C2'), 111.49-110.95 (C5 and C8), 82.67 and 82.24 (C1), 59.70 and 63.42 (C3), 57.88 and 58.66 (NCH$_3$), 56.30 (2OCH$_3$), 25.25 and 25.39 (C4), 0.50 and 1.87 (Si(CH$_3$)$_3$).

6,7-Dimethoxy-1-(1'-iodoethenyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline N-oxide 128d

To **70d** (0.953 g, 2.65 mmol) in dichloromethane (20 ml) at 0°C was added a solution of m-CPBA (0.545 g, 3.17 mmol) in dichloromethane (15 ml). The solution was allowed to warm to room temperature and stirred for 26 h. then 5% aqueous sodium bicarbonate (25 ml) was added and the organic solvent was removed *in vacuo*. The aqueous solution was washed with diethyl ether (3 x 10 ml). Concentration of the ether washings gave **70d** (0.129 g, 14%). The aqueous solution was made acidic to litmus with 3M aqueous hydrochloric acid and washed with diethyl ether (3 x 10 ml) then basified with saturated aqueous sodium bicarbonate.

Saturation of the solution with sodium chloride and extraction with chloroform (3 x 25 ml), then drying and concentration of the extracts, afforded a single B-ring diastereomer of *1-(1'-iodoethenyl)tetrahydroisoquinoline N-oxide* **128d** (0.814 g, 82%) as a red hygroscopic solid. ^{1}H NMR δ: 7.46 (s, H2'), 6.66 (ArH^A), 6.52 (s, ArH^A), 6.47 (s, H2'^{A}), 5.34 (s, H1), 4.23-4.10 (m, H), 3.91 (s, OCH$_3$), 3.83 (s, OCH$_3$), 3.70-3.62 (m, H), 3.52 (s, NCH$_3$), 3.45-3.33 (m, H), 2.89-2.84 (m, H); ^{13}C NMR δ: 141.34 (C2'), 111.18 (C8^A), 110.87 (C4a^A), 83.25 (C1), 60.45 (C3), 57.36 (NCH$_3$^{B}), 57.01 (OCH$_3$^{B}), 56.64 (OCH$_3$^{B}), 24.74 (C4).

Z-9,10-Dimethoxy-3,6-dimethyl-1,2,3,5-tetrahydro-4,3-benzoxazonine 129a

A mixture (50:50) of the diastereomers of *N*-oxide **128a** (0.544 g) was refluxed in dry dichloromethane (25 ml) for 34 h. Concentration and then purification of the residue by passage through an alumina column with dichloromethane afforded the *4,3-benzoxazonine* **129a** (0.223 g, 41%) as a colourless oil. ^{1}H NMR δ: 6.67 (s, ArH), 6.52 (s, ArH), 6.46 (s, H7), 4.06 (bs, H5), 3.86 (s, OCH$_3$), 3.82 (s, OCH$_3$), 2.88 (bs, 2H), 2.57 (s, NCH$_3$), 1.90 (s, CH$_3$), 2H of CH$_2$CH$_2$ not detected; ^{13}C NMR δ: 148.25 (C9^A), 147.13 (C10^A), 138.68 (C7a^B), 133.58 (C11a^B), 131.10 (C6), 127.93 (bs, C7), 111.58 (C8^C), 111.16 (C11^C), 74.77 (bs, C5), 62.81 (C2), 56.28 (OCH$_3$), 56.20 (OCH$_3$), 47.41 (bs, NCH$_3$), 33.24 (bs, C1), 24.36 (CH$_3$); MS m/z: 263 (M$^+$, 12%; Calcd. for C$_{15}$H$_{21}$NO$_3$ 263.1521, found 263.1532), 246 (5), 204 (100), 189 (37), 175 (11); IR: 1516, 1258, 1231, 1117, 986, 871, 763 cm^{-1}; UV: 290, 221 nm.

NMR analyses at -30°C displayed two conformers in a 50:50 ratio. Assignable signals were: ^{1}H NMR δ: 6.78 and 6.65 (s, ArH^A), 6.56 and 6.54 (s, ArH^A), 6.49 (s, H7), 4.25-3.95 (4 d, *J* 12.4 Hz, H5), 3.92 and 3.89 (s, OCH$_3$), 3.85 (s, OCH$_3$), 2.67 and 2.57 (s, NCH$_3$), 1.98 and 1.87 (s, CH$_3$); ^{13}C NMR δ: 147.95 and 146.98 (C9^A), 146.59 and 146.13 (C10^A), 139.25 and 137.30 (C7a^B), 133.65 and 132.08 (C11a^B), 130.48 (C6), 129.37 and 126.18 (C7), 110.66 and 110.49 (C8^C), 110.11 and 109.85 (C11^C), 77.25 and 72.46 (C5), 62.80 and 62.20 (C2),

55.99 (2OCH$_3$), 48.64 and 46.29 (NCH$_3$), 34.44 and 31.35 (C1), 24.64 and 24.24 (CH$_3$).

Elution of the alumina column with dichloromethane/20% methanol afforded the recovery of the pure *trans* diastereomer of N-oxide **128a** (0.117 g, 22%).

Z-9,10-Dimethoxy-3-methyl-6-phenyl-1,2,3,5-tetrahydro-4,3-benzoxazonine 129b

To **70b** (2.056 g, 6.626 mmol) in dichloromethane (40 ml) at 0°C was added a solution of *m*-CPBA (1.40 g, 8.14 mmol) in dichloromethane (60 ml). The solution was stirred at 0°C for 40 h. then 5% aqueous sodium bicarbonate (40 ml) was added and the organic solvent was removed *in vacuo*. The aqueous solution was washed with diethyl ether (3 x 25 ml) then made acidic to litmus with 3M aqueous hydrochloric acid and washed with further diethyl ether (3 x 15 ml). The solution was basified with saturated aqueous sodium bicarbonate then saturated with sodium chloride and extracted with chloroform (3 x 25 ml). Drying and then concentration of the organic extracts, then column chromatography of the residue on alumina with dichloromethane/0-10% methanol, gave a 44:56 mixture of **129b** and **130b** (0.522 g, 24%) and the *trans* diastereomer of N-oxide **128b** (1.142 g, 53%). Preparative reverse phase HPLC of this mixture with acetonitrile/37% H$_2$O gave:

(a) at 14.3 min., the 2,3-benzoxazepine **130b**.

(b) at 17.1 min., the *4,3-benzoxazonine* **129b** as colourless prisms from methanol with m.p. 111-112°C. ^{1}H NMR δ: 7.55-7.52 (m, *o*-ArH'), 7.40-7.24 (3ArH'), 7.00 (s, H7), 6.75 (s, ArH), 6.63 (s, ArH), 4.51 (bs, H5), 3.89 (s, OCH$_3$), 3.85 (s, OCH$_3$), 2.94 (bs, 2H), 2.65 (s, NCH$_3$), 2H of CH$_2$CH$_2$ not detected; ^{13}C NMR δ: 148.84 (C9^A), 147.49 (C10^A), 142.39 (C6^B), 142.05 (C1'^{B}), 133.56 (C7a^C), 131.32 (C7), 130.75 (C11a^C), 129.06 (2C'), 127.88 (C4'), 126.82 (2C'), 111.75 (C8^D), 111.06 (C11^D), 74.55 (C5), 63.00 (C2), 56.51 (OCH$_3$), 56.35 (OCH$_3$), 47.94 (NCH$_3$), 32.91 (C1); MS m/z: 325 (M$^+$, 13%; Calcd. for C$_{20}$H$_{23}$NO$_3$ 325.1677, found 325.1670), 266 (93), 251 (18), 235 (7), 206 (100), 178 (12), 165 (17); Anal. Calcd for

$C_{20}H_{23}NO_3$: C, 73.87; H, 7.13; N, 4.31%, found: C, 73.84; H, 7.10; N, 4.44%; UV: 293, 235, 220 nm.

NMR analyses at -30°C displayed two conformers in a 78:22 ratio. Assignable signals were: ^{1}H NMR δ: 7.11 and 6.92 (s, H7), 6.83 and 6.70 (s, ArH), 6.67 and 6.63 (s, ArH), 4.87 (d, J 12.7 Hz, H5[a]), 4.47 (s, 2H5[b]), 4.32 (d, J 12.7 Hz, H5[a]), 2.73 and 2.63 (s, NCH3); ^{13}C NMR δ: 132.44 and 131.66 (C7), 75.76 and 71.74 (C5), 63.02 and 62.98 (C2), 48.77 and 46.53 (NCH3), 31.71 and 34.34 (C1).

Z-9,10-Dimethoxy-3-methyl-6-trimethylsilyl-1,2,3,5-tetrahydro-4,3-benzoxazonine 129c

A mixture (*trans:cis*=66:34) of the diastereomers of *N*-oxide **128c** (0.325 g, 1.01 mmol) was refluxed in dichloromethane (20 ml) for 36 h. Concentration and then purification of the residue by passage through an alumina column with dichloromethane/5% hexane gave a 62:38 mixture of **129c** and **130c** (0.262 g, 81%). The components were not separated by HPLC. Recrystallisation twice from methanol, with the collection of the early solid, afforded the *4,3-benzoxazonine* **129c** (0.044 g, 14%) as colourless prisms with m.p. 132-133°C. ^{1}H NMR (50°C) δ: 6.95 (s, H7), 6.66 (s, ArH), 6.49 (s, ArH), 4.17 (s, H5), 3.84 (s, OCH3), 3.80 (s, OCH3), 2.82-2.73 (m, 4H), 2.51 (s, NCH3), 0.17 (s, Si(CH3)3); ^{13}C NMR (50°C) δ: 148.75 (C9[A]), 147.58 (C10[A]), 145.11 (C6), 141.83 (C7), 133.42 (C7a[B]), 132.87 (C11a[B]), 112.53 (C8[C]), 110.95 (C11[C]), 71.42 (C5), 62.87 (C2), 56.63 (OCH3), 56.48 (OCH3), 47.29 (NCH3), 33.44 (C1), -1.17 (Si(CH3)3); MS m/z: 321 (M[+], 3%; Calcd. for $C_{17}H_{27}NO_3Si$ 321.1759, found 321.1761), 290 (4), 262 (10), 247 (30), 206 (100), 178 (16); Anal. Calcd for $C_{17}H_{27}NO_3Si$: C, 63.51; H, 8.47; N, 4.36%, found: C, 63.53; H, 8.44; N, 4.33%.

NMR analyses at -30°C displayed two conformers in a 74:26 ratio. Assignable signals were: ^{13}C NMR δ: 143.15 and 139.33 (C7), 110.06 and 110.68 (C8[A]), 109.65 and 108.52 (C11[A]), 73.50 and 69.17 (C5), 62.76 and 62.04 (C2),

55.95 (2OCH$_3$), 48.64 and 46.15 (NCH$_3$), 31.48 and 34.24 (C1), -1.27 and -1.50 (Si(CH$_3$)$_3$).

Z-9,10-Dimethoxy-6-iodo-3-methyl-1,2,3,5-tetrahydro-4,3-benzoxazonine 129d

The *N*-oxide **128d** (0.301 g, 0.803 mmol) was refluxed in dichloromethane (13 ml) for 24 h. Concentration and then purification of the residue by passage through an alumina column with dichloromethane/25% hexane gave an oil (0.084 g). Analysis of the oil by HPLC at 254 nm indicated a 90:10 mixture of **70d** and **129d**. Preparative reverse phase HPLC purification of this mixture with acetonitrile/33% H$_2$O gave:

(a) at 12.9 min., the precursor amine **70d** (0.055 g, 19%).

(b) at 15.4 min., the *4,3-benzoxazonine* **129d** (0.005 g, 2%) as a yellow oil. ^{1}H NMR δ: 7.44 (s, H7), 6.66 (s, ArH), 6.51 (s, ArH), 4.50 (s, H5), 3.87 (s, OCH$_3$), 3.83 (s, OCH$_3$), 2.92 (bs, 3H), 2.57 (bs, NCH$_3$ and H); MS m/z: 375 (M$^+$, 2%; Calcd. for C$_{14}$H$_{18}$NO$_3$I 375.0331, found 375.0353), 358 (4), 316 (15), 248 (10), 206 (100), 189 (90).

7,8-Dimethoxy-1-isopropenyl-3-methyl-1,3,4,5-tetrahydro-2,3-benzoxazepine 130a

(i) The benzoxazonine **129a** (0.027 g) was refluxed in dry xylene (5 ml) for 1 h. Concentration and then purification of the residue by passage through an alumina plug with dichloromethane gave a 5:95 mixture (0.023 g, 85%) of **129a** and the *2,3-benzoxazepine* **130a** as a pale tan oil. ^{1}H NMR δ: 6.65 (s, ArH), 6.53 (s, ArH), 5.39 (s, H1^A), 4.97 (s, H2'^{A}), 4.94 (s, H2'^{A}), 3.86 (s, OCH$_3$), 3.81 (s, OCH$_3$), 3.47-3.42 (m, H), 3.14-3.06 (m, H), 2.95-2.88 (m, H), 2.72 (s, NCH$_3$), 2.62-2.55 (m, H); ^{13}C NMR δ: 147.98 (C7^A), 145.47 (C8 and C1'^{A}), 132.71 (C5a^B), 129.72 (C9a^B), 115.18 (C6^C), 114.12 (C9^C), 111.34 (C2'), 90.49 (C1), 60.81 (C4), 56.63 (OCH$_3$), 56.55 (OCH$_3$), 47.25 (NCH$_3$), 33.29 (C5), 19.46 (CH$_3$); IR: 1516, 1258, 1227, 1209, 1119, 1036, 905, 864, 781 cm^{-1}; UV: 286, 240, 220 nm.

(ii) The *trans-N*-oxide **128a** (0.028 g) was refluxed in dry acetonitrile (5 ml) for 50 min. Concentration and then purification of the residue by passage through an alumina column with dichloromethane/5% hexane gave a 34:66 mixture of **129a** and **130a** (0.023, 82%).

(iii) A mixture (50:50) of the diastereomers of *N*-oxide **128a** (0.076 g) was treated as for (ii) to give a 58:42 mixture of **129a** and **130a** (0.067, 88%).

7,8-Dimethoxy-3-methyl-1-(α-phenylethenyl)-1,3,4,5-tetrahydro-2,3-benzoxazepine 130b

The preparation of **129b** described above afforded the *2,3-benzoxazepine* **130b** as colourless prisms from methanol with m.p. 96-97°C. ^{1}H NMR δ: 7.48-7.45 (m, *o*-ArH"), 7.33-7.25 (m, 3ArH"), 6.65 (s, ArH), 6.50 (s, ArH), 5.98 (s, H2'), 5.53 (s, H2'), 5.15 (s, H1), 3.85 (s, OCH$_3$), 3.69 (s, OCH$_3$), 3.45-3.37 (m, H), 3.12-3.04 (m, H), 2.91-2.86 (m, H), 2.72-2.67 (m, H), 2.66 (s, NCH$_3$); ^{13}C NMR δ: 148.14 (C7^A), 147.86 (C8^A), 147.61 (C1'^{A}), 140.58 (C1"), 132.81 (C5a^B), 130.43 (C9a^B), 128.69 (2C"), 128.01 (C4"), 127.31 (2C"), 117.25 (C2'), 114.21 (C6^C), 111.71 (C9^C), 87.18 (C1), 60.64 (C4), 56.46 (OCH$_3$), 56.30 (OCH$_3$), 47.24 (NCH$_3$), 33.74 (C5); MS m/z: 325 (M$^+$, 12%; Calcd. for C$_{20}$H$_{23}$NO$_3$ 325.1677, found 325.1670), 308 (3), 266 (100), 251 (16), 237 (10), 206 (47); Anal. Calcd for C$_{20}$H$_{23}$NO$_3$: C, 73.87; H, 7.13; N, 4.31%, found: C, 73.98; H, 7.29; N, 4.48%; UV: 284, 237, 220 nm.

7,8-Dimethoxy-1-(1'-trimethylsilylethenyl)-3-methyl-1,3,4,5-tetrahydro-2,3-benzoxazepine 130c

The preparation of **129c** described above afforded a 62:38 mixture (81%) of **129c** and **130c**. Compound **130c** could not be isolated separately. The signals attributed to **130c** were: ^{1}H NMR δ: 6.65 (s, ArH), 6.46 (s, ArH), 5.66 (s, H1), 5.56 (d, *J* 2.6 Hz, H2'), 5.50 (d, *J* 2.6 Hz, H2'), 3.84 (s, OCH$_3$), 3.82 (s, OCH$_3$), 3.38-3.12

(m, 2H), 2.95-2.87 (m, H), 2.70 (s, NCH$_3$), 2.2.68-2.62 (m, H); ^{13}C NMR δ: 128.37 (C2'), 89.26 (C1).

7,8-Dimethoxy-1-(1'-iodoethenyl)-3-methyl-1,3,4,5-tetrahydro-2,3-benzoxazepine 130d

The *N*-oxide **128d** (0.210 g, 0.560 mmol) was refluxed in dry acetonitrile (12 ml) for 50 min. Concentration and then purification of the residue by passage through an alumina column with dichloromethane/25% hexane gave an oil (0.056 g). Analysis by HPLC at 254 nm indicated a 59:30:11 mixture of **70d**, **130d** and **129d**. Preparative reverse phase HPLC purification of this mixture with acetonitrile/33% H$_2$O gave, at 11.9 min., the *2,3-benzoxazepine* **130d** (0.010 g, 5%) as a yellow oil. ^{1}H NMR δ: 6.66 (s, ArH), 6.57 (s, ArH), 6.27 (bs, H1), 6.00 (s, H2'), 5.30 (s, H2'), 3.88 (s, OCH$_3$), 3.83 (s, OCH$_3$), 3.63-3.52 (m, H), 3.12-3.03 (m, H), 2.99-2.92 (m, H), 2.78 (s, NCH$_3$), 2.65-2.57 (m, H); ^{13}C NMR δ: 148.59 (C7^A), 148.06 (C8^A), 130.99 (C5a^B), 130.58 (C9a^B), 129.53 (C2'), 114.66 (C6^C), 111.85 (C9^C), 110.79 (C1'), 91.83 (C1), 60.65 (C4), 56.66 (2OCH$_3$), 47.60 (NCH$_3$), 33.73 (C5); MS m/z: 375 (M$^+$, 2%; Calcd. for C$_{14}$H$_{18}$NO$_3$I 375.0331, found 375.0344), 358 (2), 316 (11), 248 (12), 206 (19), 189 (100), 145 (23), 115 (16), 60 (28).

6,7-Dimethoxy-1-(3"-fluorophenyl)-2-methyl-1-vinyl-1,2,3,4-tetrahydroisoquinoline 132

6,7-Dimethoxy-1-(3'-fluorophenyl)-3,4-dihydroisoquinoline (7.70 g, 27.9 mmol) was refluxed for 1.5 h. in dry acetone (60 ml) with iodomethane (16.0 g, 112 mmol). The solution was then cooled and the yellow solid was collected, washed with cold acetone, and then dried to give 6,7-dimethoxy-1-(3'-fluorophenyl)-2-methyl-3,4-dihydroisoquinolinium iodide **131** (11.52, 99%). m.p. 215-217°C.

A solution of vinylmagnesium bromide in dry tetrahydrofuran (120 ml) under nitrogen was prepared from vinyl bromide (5.02 g, 47.0 mmol). The solution was cooled to 0°C and the imine salt **131** (5.02 g, 11.7 mmol) was then added portionwise

over 30 min. The mixture was refluxed for 3.5 h. then stirred at room temperature for 12 h. before workup (as for **70b**) to give, upon concentration of the ether solution, the *1-(3"-fluorophenyl)isoquinoline* **132** (3.73 g, 97%) as a pale yellow oil. ^{1}H NMR δ: 7.28-7.22 (m, 3ArH"), 6.95-6.88 (m, H2"), 6.56 (s, ArH), 6.34 (dd, *J* 10.6 Hz, *J* 17.2 Hz, H1'), 6.04 (s, ArH), 5.54 (dd, *J* 1.7 Hz, *J* 10.6 Hz, H2'), 4.67 (dd, *J* 1.7 Hz, *J* 17.2 Hz, H2'), 3.84 (s, OCH$_3$), 3.58 (s, OCH$_3$), 3.13-3.05 (m, H), 2.82-2.63 (m, 3H), 2.16 (s, NCH$_3$); ^{13}C NMR displayed two conformers δ: 165.13 and 161.89 (C3"), 150.01 (C6^A), 148.01 and 147.04 (C7^A), 138.32 (C1'), 131.44 (C4a^B), 129.70 (C6"^{C}), 128.07 (C8a^B), 126.05 (C1"^{B}), 124.78 (C5"^{C}), 121.54 (C2'), 116.36 and 116.06 (C4"^{D}), 114.50 and 114.21 (C2"^{D}), 113.89 (C5^E), 111.13 (C8^E), 71.10 and 69.45 (C1), 56.38 (2OCH$_3$), 47.36 (C3), 39.77 (NCH$_3$), 29.90 (C4); MS m/z: 327 (M$^+$, 12%; Calcd. for C$_{20}$H$_{22}$NO$_2$F 327.1634, found 327.1615), 300 (100), 286 (23), 284 (10), 232 (53), 218 (12).

Z-9,10-Dimethoxy-3-methyl-7-(3'-fluorophenyl)-1,2,3,5-tetrahydro-4,3-benzoxazonine 134

To the amine **132** (0.771 g, 2.35 mmol) in dichloromethane (23 ml) at 0°C was added a solution of *m*-CPBA (0.485 g, 2.82 mmol) in dichloromethane (20 ml). The solution was allowed to warm to room temperature and stirred for 40 h. then 5% aqueous sodium bicarbonate (20 ml) was added and the organic solvent was removed *in vacuo*. The aqueous solution was extracted with diethyl ether (10 ml and 3 x 5 ml). The ether extracts were washed with saturated brine (5 ml) then dried and concentrated to afford a tan solid (0.567 g). Purification of a portion (0.371 g) of this material by p.t.l.c. on silica with dichloromethane/7% methanol afforded a band, at R$_f$ 0.95, which was collected (0.220 g) and subjected to further p.t.l.c. on silica with two developments by dichloromethane/1% methanol. The front third of the resultant broad band, at R$_f$ 0.69, gave the *4,3-benzoxazonine* **134** (0.125 g, 24%) as colourless prisms from methanol with m.p. 131-132°C. ^{1}H NMR δ: 7.24-7.17 (m, H6'), 7.05 (d, *J* 7.8 Hz, H2'), 6.94-6.88 (m, 2ArH'), 6.78 (s, ArH), 6.52 (t, H6), 6.45 (s, ArH), 4.35

(dd, J 13.4 Hz, 5.9 Hz, H5), 3.99 (dd, J 13.7 Hz, 6.0 Hz, H5), 3.92 (s, OCH_3), 3.76 (s, OCH_3), 3.01-2.94 (m, H), 2.92-2.85 (m, 2H), 2.66-2.61 (m, H), 2.57 (s, NCH_3); ^{13}C NMR δ: 165.04 and 161.78 (C3'), 149.00 (C9^A), 147.65 (C10^A), 144.80 (C1'^{B}), 144.06 (C7^B), 134.30 (C7a^C), 131.07 (C11a^C), 130.07 (C6'^{D}), 127.61 (C5'^{D}), 122.71 (C6^D), 114.89 and 114.61 (C8^D), 114.10 and 113.81 (C11^D), 111.48 (C2' and C4^D), 69.37 (C5), 62.62 (C2), 56.41 (OCH_3), 56.19 (OCH_3), 47.35 (NCH_3), 33.15 (C1); MS m/z: 343 (M$^+$, 18%; Calcd. for $C_{20}H_{22}NO_3F$ 343.1583, found 343.1600), 326 (14), 297 (20), 284 (100), 271 (15), 253 (12); Anal. Calcd for $C_{20}H_{22}NO_3F$: C, 69.95; H, 6.46; N, 4.08%, found: C, 69.90; H, 6.58; N, 4.12%.

NMR analysis at -30°C displayed two conformers in a 69:31 ratio. Assignable signals were: ^{13}C NMR δ: 66.26 and 73.01 (C5), 61.96 and 62.81 (C2), 46.43 and 48.78 (NCH_3), 33.93 and 30.94 (C1).

6.4   Experimental for Chapter Four

8-Chloro-1,2-dimethyl-6-phenyl-2,4-dihydro-1*H*-s-triazolo[4,3 *a*]-[1,4]benzodiazepine 145

Alprazolam **136** (0.216 g, 0.701 mmol) in dry butanone (10 ml) at 50°C was stirred with iodomethane (0.11 g, 0.80 mmol) under nitrogen for 20 h. The solution was then concentrated to a pale yellow solid. ^1H NMR analysis of the material indicated two isomers (2.24:1) were present with characteristic peaks for: (a) compound **144**.[140] ^1H NMR δ: 5.42 (d, J 13.3 Hz, H4), 4.25 (d, J 13.4 Hz, H4), 4.11 (s, NCH_3), 3.19 (s, CH_3); (b) an unknown isomer ^1H NMR δ: 5.46 (d, J 14.4 Hz, H4), 4.66 (d, J 14.4 Hz, H4), 4.18 (s, NCH_3), 2.77 (s, CH_3).

The crude solid above in dry ethanol (10 ml) at 0°C was treated with sodium borohydride (0.025 g, 0.66 mmol) added portionwise over 1 h. The solution was then concentrated and the residue was extracted with dichloromethane (3 x 5 ml). Concentration of the extracts afforded a pale yellow powder which was purified by p.t.l.c. on silica with dichloromethane/10% methanol to give the triazolo[4,3-

a][1,4]benzodiazepine[140] **145** (0.058 g, 26%). ^{1}H NMR δ: 7.53-7.39 (m, 6ArH), 7.17 (d, *J* 2.5 Hz, H7), 6.86 (d, *J* 8.8 Hz, H10), 4.85 (d, *J* 12.4 Hz, H4), 4.75 (q, H1), 3.92 (d, *J* 12.4 Hz, H4), 2.77 (s, NCH₃), 1.52 (d, *J* 5.2 Hz, CH₃).

8-Chloro-1-methyl-6-phenyl-5,6-dihydro-4*H*-s-triazolo[4,3-*a*][1,4]benzodiazepine **146**

A solution of alprazolam **136** (1.976 g, 6.399 mmol) in methanol (40 ml) was acidified to a pH of 3 to 4 with a mixture of concentrated hydrochloric acid/methanol (1:4) and then sodium cyanoborohydride (0.46 g, 7.3 mmol) was added. A solid precipitated after 2 min. The solution was returned to a pH of 3 to 4 by the further addition of the acid mixture and then stirred for 20 min. Aqueous 0.5 M sodium bicarbonate (40 ml) was added and the mixture was then extracted with dichloromethane (4 x 40 ml), with poor separation. The extracts were combined and washed with water (4 x 15 ml). The aqueous washings were combined and back-extracted with dichloromethane (2 x 20 ml). All the dichloromethane layers were then combined, dried, and concentrated to give the 5,6-dihydrotriazolo-benzodiazepine[142-145] **146** (1.872 g, 94%) as a colourless solid. ^{1}H NMR δ: 7.46 (dd, *J* 2.4 Hz, 8.4 Hz, H9), 7.35-7.28 (m, 5ArH), 7.26 (d, *J* 8.4 Hz, H10), 6.95 (d, *J* 2.3 Hz, H7), 4.95 (s, H6), 4.27 (d, *J* 15.0 Hz, H4), 3.77 (d, *J* 15.0 Hz, H4), 2.54 (s, CH₃), 2.50-2.25 (bs, NH); ^{13}C NMR δ: 153.88 (C1[A]), 150.65 (C3a[A]), 140.03 (C1'[B]), 138.35 (C6a[B]), 135.57 (C10a[B]), 132.84 (C8[B]), 131.71 (C7[C]), 129.70 (C9[C]), 129.37 (2C'), 129.03 (C'[C]), 128.46 (2C'), 124.97 (C10[C]), 60.35 (C6), 40.71 (C4), 12.07 (CH₃); MS m/z: 310 (M⁺·, 73%; Calcd. for $C_{17}H_{15}N_4Cl$ 310.0984, found 310.098), 294 (8), 282 (20), 232 (100), 205 (36), 179 (22).

Other Attempted Reductions of **136** to **146**

(i)   To **136** (0.263 g, 0.850 mmol) in dry ethanol (35 ml) was added sodium borohydride (0 033 g, 0.88 mmol). After 90 min. additional sodium borohydride

(0.037 g, 0.98 mmol) was added. After a further 30 min. t.l.c. analysis confirmed that **136** remained unchanged.

(ii) To **136** (0.263 g, 0.850 mmol) in dry methanol (25 ml) with glacial acetic acid (1.25 ml) was added sodium cyanoborohydride (0 053 g, 0.84 mmol). After 1 h. t.l.c. analysis confirmed that **136** remained unchanged.

(iii) To **136** (0.263 g, 0.850 mmol) in glacial acetic acid (12 ml) was added sodium cyanoborohydride (0 214 g, 3.41 mmol). After 18 h. t.l.c. analysis indicated that **136** remained almost unchanged. The solution was then warmed to 50°C for 3 h. The solution was cooled and water (30 ml) and concentrated aqueous ammonia were added to afford a basic mixture which was then extracted with dichloromethane (4 x 30 ml). The extracts were washed with saturated brine (15 ml) then dried and concentrated. Analysis of the residual yellow solid by GC-MS indicated the presence of **146** (64%) and components attributed to: (a) **148a** (25%), MS m/z: 338 (M$^+$·, 71%), 323 (41), 282 (63), 261 (100), 207 (14); and (b) **148b** (11%), MS m/z: 352 (M$^+$·, 36%), 337 (100), 295 (29), 282 (45), 275 (36). Purification of this material by p.t.l.c. on silica with dichloromethane/4% methanol gave **146** (0.083 g, 36%).

8-Chloro-1,5-dimethyl-6-phenyl-5,6-dihydro-4*H*-s-triazolo[4,3-*a*] [1,4]benzodiazepine **147**

(i) A solution of dihydroalprazolam **146** (1.872, 6.024 mmol) in methanol (80 ml) was treated with 37% aqueous formaldehyde (0.80 ml, 10 mmol) then stirred for 15 min., and then acidified to a pH of 4 with a concentrated hydrochloric acid/methanol (1:1) mixture. After 5 min. sodium cyanoborohydride (0.475 g, 7.56 mmol) was added and the solution was then stirred for 4 h. The pH was then readjusted to 4 with the acid mixture and the stirring was continued for 1 h. Aqueous 0.25 M potassium hydroxide (40 ml) was then added and the organic solvent was removed *in vacuo*. The extraction of the aqueous mixture with dichloromethane (70 ml, 3 x 40 ml), then drying and concentration of the extracts gave the 1,5-dimethyl-5,6-

dihydro-triazolobenzodiazepine **147** (1.950 g, 100%) as a colourless solid of purity
>99% upon GC-MS analysis. ^{1}H NMR δ: 7.47 (dd, J 2.3 Hz, 8.4 Hz, H9), 7.30 (bs,
5ArH'), 7.25 (d, J 8.4 Hz, H10), 7.01 (d, J 2.3 Hz, H7), 4.18 (s, H6), 3.96 (d, J 14.1
Hz, H4), 3.67 (d, J 14.1 Hz, H4), 2.48 (s, NCH$_3$^{A}), 2.42 (s, CH$_3$^{A}); ^{13}C NMR δ:
150.88 (C1^A), 150.18 (C3a^A), 139.90 (C1'^{B}), 137.66 (C6a^B), 135.03 (C10a^B),
132.86 (C8^B), 132.48 (C7^C), 129.69 (C9^C), 129.16 (2C'), 128.61 (C'^{C}), 128.26 (2C'),
125.07 (C10^C), 69.45 (C6), 48.75 (C4), 44.42 (NCH$_3$), 11.94 (CH$_3$); MS m/z: 324
(M$^{+\cdot}$, 41%; Calcd. for C$_{18}$H$_{17}$N$_4$Cl 324.1142, found 324.1140), 282 (16), 247 (100),
219 (21), 193 (15); IR (KBr): 1491, 1105, 1094, 723, 536 cm^{-1}.

(ii) A solution of **146** (0.192 g, 0.619 mmol) in methanol (35 ml) and 37% aqueous
formaldehyde (10 ml) was stirred for 1 h. and then cooled to 0°C. Sodium
borohydride (0.45 g, 12 mmol) was added portionwise over 1.5 h. The solution was
then concentrated to a gummy residue which was partitioned between
dichloromethane (25 ml) and 0.5 M aqueous sodium bicarbonate (10 ml). The
aqueous layer was extracted with further dichloromethane (2 x 25 ml) and the
extracts were then dried and concentrated to afford a pale yellow oil which displayed
a single major spot on t.l.c. analysis. The purification of this oil by p.t.l.c. on silica
with dichloromethane/10% methanol gave a single band. The recovery of this
material from the silica with dichloromethane/10% methanol afforded a white
powder (0.210 g) which displayed four components on t.l.c. analysis.

Attempted One-Pot Reduction of **136** to **147** with Formic Acid and Sodium Borohydride

(i) To **136** (0.299 g, 0.970 mmol) and powdered sodium borohydride (0.206 g, 5.45
mmol) in dry tetrahydrofuran (4 ml) at 0°C under nitrogen was added freshly
distilled formic acid (2.8 ml, 80 mmol). A vigorous reaction ensued. The mixture
was allowed to warm slowly to room temperature with stirring for 12 h. then cooled
to 0°C and water (7 ml) was added. The mixture was made basic with 50% aqueous
sodium hydroxide and then extracted with dichloromethane (4 x 10 ml). The

extracts were washed with saturated brine (7 ml) then dried and concentrated to give a white powder (0.296 g). Analysis of this material by GC-MS, with peak integration, indicated the presence of **147** (7%) and the *formamide* **149** (93%). Compound **149** displayed the following characteristic peaks with 2 conformers at approximately equal levels in CDCl$_3$ at room temperature. ^{1}H NMR δ: 8.47 and 8.34 (s, CHO), 7.80-6.65 (m, 8ArH), 6.62 and 5.92 (s, H6), 5.69 (d, J 15.3 Hz) and 5.18 (d, J 14.2 Hz, H4), 4.20 (d, J 14.2 Hz) and 3.87 (d, J 15.3 Hz, H4), 2.08 and 2.03 (s, CH$_3$); ^{13}C NMR δ: 162.28 and 161.68 (CHO), 63.25 and 58.46 (C6), 41.07 and 37.49 (C4), 11.30 and 11.06 (CH$_3$); MS m/z: 338 (M$^{+\cdot}$, 71%; Calcd. for C$_{18}$H$_{15}$N$_4$OCl 338.0932, found 338.095), 309 (95), 295 (100), 207 (54), 206 (63).

(ii) To **136** (0.203 g, 0.659 mmol) and powdered sodium borohydride (0.230 g, 6.07 mmol) in dry tetrahydrofuran (4 ml) at 0°C under nitrogen was added freshly distilled formic acid (1.9 ml, 54 mmol) dropwise over 3 h. The mixture was allowed to warm slowly to room temperature with stirring for 8 h. and then worked up as for (i) to afford a white powder (0.233 g). Analysis of this material by GC-MS, with peak integration, indicated the presence of **147** (47%), **136** (6%) and **149** (47%).

Investigation of the Proposed *N*-alkylation of **147** to **150**

(i) The base **147** (99.2 mg, 0.305 mmol) was refluxed in acetone (3 ml) with ethylbromoacetate for 12 h. The solution was then cooled and concentrated. The residue was triturated with diethyl ether (4 x 2 ml) and dried to give a white powder (10.0 mg) which remained at the origin upon t.l.c. analysis with dichloromethane/10% methanol on silica. This material was unchanged when treated with DBU in acetonitrile.

(ii) The base **147** (0.623 g, 1.92 mmol) in dry dimethylformamide (20 ml) at 0°C was treated with ethoxycarbonylmethyltriflate (0.596 g, 2.51 mmol) dropwise. The solution was stirred for 1 h. at 0°C and then for 5 days at room temperature sealed and protected from light. The removal of the solvent under oil pump vacuum and trituration of the residue with hexane (4 x 5 ml) gave a white waxy oil which was

taken up in ethanol (7 ml) and stirred with potassium bromide (1.28 g, 10.8 mmol) for 2 h. Filtration of this mixture and concentration of the filtrate gave an off-white powder (0.921 g) which on ^{1}H NMR analysis displayed many peaks between 2.96 and 2.40 δ.

Attempted *N*-oxidation of 147 to 152 with *m*-Chloroperoxybenzoic Acid.

To the base 147 (53.0 mg, 0.163 mmol) in dichloromethane (5 ml) at 0°C was added a solution of *m*-chloroperoxybenzoic acid (51.7 mg, 0.300 mmol) in dichloromethane (2 ml) portionwise over 1 h. The solution was allowed to warm slowly to room temperature with stirring for 40 h. and then washed with 0.5M aqueous sodium bicarbonate (3 x 3 ml). The aqueous washings were concentrated and the residue was extracted with dichloromethane (5 ml). The dichloromethane solutions were then combined, dried, and concentrated to give a pale yellow powder (42.5 mg). The analysis of this material by GC-MS revealed many components. The major components had molecular ions at 322 (attributed to 151), 325, 296, 338 and 354 mass units.

8-Chloro-1,5-dimethyl-6-phenyl-5,6-dihydro-4*H*-s-triazolo[4,3-*a*]-[1,4]benzodiazepine *N*-Oxide 152 and 9-Chloro-1,5-dimethyl-7-phenyl-4,5-dihydro-7*H*-s-triazolo[4,3-*a*][5,1,4]benzoxadiazocine 153

To the base 147 (0.611 g, 1.88 mmol) in ethanol (50 ml) at 0°C was added a solution of monomagnesiumperoxyphthalate hexahydrate (0.71 g, 80% technical grade, 1.15 mmol) in water (20 ml). The solution was allowed to warm slowly with stirring for 35 h. and then 0.5M aqueous sodium bicarbonate (30 ml) was added. The mixture was then concentrated and the residue was extracted with dichloromethane (3 x 25 ml). The extracts were dried, filtered, and then concentrated to afford a mixture (65:35) of *N-oxide* 152 and *triazolo[4,3-a][5,1,4]benzoxadiazocine* 153, as a colourless hygroscopic solid (0.525 g). Compound 152 displayed the following discernible characteristic peaks. ^{1}H NMR

δ: 5.61 (bs, H6), 4.38-4.31 (m, H4), 3.72-3.64 (m, H4), 2.87 (bs, NCH$_3$), 2.45 (CH$_3$); ^{13}C NMR δ: 80.86 (C6), 57.27 (C4), 47.86 (NCH$_3$), 12.26 (CH$_3$).

The solid above was refluxed in dry acetonitrile (50 ml) for 50 min. Concentration and then purification of the residue by p.t.l.c. on silica with dichloromethane/10% methanol gave *triazolo[4,3-a][5,1,4]benzoxadiazocine* **153** (0.304 g, 50%) as a colourless solid. ^{1}H NMR δ: 7.46 (d, *J* 2.4 Hz, H8), 7.37 (dd, *J* 2.3 Hz, 8.3 Hz, H10), 7.20-7.17 (m, 3ArH'), 7.02 (d, *J* 8.3 Hz, H11), 6.78-6.75 (m, 2ArH'), 5.97 (s, H7), 4.43 (d, *J* 14.1 Hz, H4), 4.22 (d, *J* 14.1 Hz, H4), 2.80 (s, NCH$_3$), 1.80 (s, CH$_3$); ^{13}C NMR δ: 152.75 (C1^A), 151.99 (C3a^A), 142.35 (C1'^{B}), 138.68 (C7a^B), 136.10 (C11a^B), 130.80 (C9^B), 130.23 (C8^C), 129.85 (C10^C), 129.14 (2C'), 128.89 (C'^{C}), 128.69 (C11^C), 125.83 (2C'), 86.43 (C7), 58.33 (C4), 46.60 (NCH$_3$), 11.22 (CH$_3$); MS m/z: 340 (M$^{+\cdot}$, 15%; Calcd. for C$_{18}$H$_{17}$N$_4$OCl 340.1091, found 340.1080), 323 (24), 310 (22), 295 (36), 281 (100), 253 (51), 233 (39), 218 (78).

10b-Cyano-8,9-dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline 155

To a solution of the pyrrolo[2,1-a]isoquinolinium iodide[151] **154** (15.13 g, 42.12 mmol) in methanol (100 ml) and water (200 ml), made slightly alkaline with sodium bicarbonate, was added sodium cyanide (7.0 g, 143 mmol). The solution was heated for 2 h. with slow evaporation to a volume of 190 ml then cooled and extracted with diethyl ether (3 x 100 ml) and chloroform (3 x 100 ml). The ether and chloroform solutions were each dried and evaporated to provide the *10b-cyanopyrrolo[2,1-a]isoquinoline derivative* **155** (5.07 g and 5.01 g respectively, total 93%) as an oil. ^{1}H NMR δ: 6.70 (s, ArH), 6.62 (s, ArH), 3.88 (s, OCH$_3$), 3.85 (s, OCH$_3$), 3.22-3.16 (m, 2H), 3.17-2.93 (m, 2H), 2.85-2.70 (m, 3H), 2.08-2.00 (m, 3H); ^{13}C NMR δ: 149.59 (C8^A), 148.34 (C9^A), 127.23 (C6a^B), 126.96 (C10a^B), 120.24 (CN^B), 112.12 (C10^C), 109.02 (C7^C), 64.12 (C10b), 56.63 (OCH$_3$), 56.43 (OCH$_3$), 50.96 (C5^D), 45.07 (C3^D), 37.69 (C6), 27.66 (C1), 21.27 (C2); MS m/z: 231 (M$^{+\cdot}$-HCN, 64%), 230 (100), 219 (28), 199 (15), 187 (11).

11b-Cyano-9,10-dimethoxy-1,2,3,4,5,6,7,11b-octahydrobenzo[a]quinolizine 157

The benzo[a]quinolizinium iodide[152] **156** (X=I) (2.324 g, 6.227 mmol) was dissolved in water (60 ml) made slightly alkaline with sodium bicarbonate by mild warming, and potassium cyanide (1.42 g, 21.8 mmol) was then added. The solution was allowed to cool while stirring for 2 h. A precipitate was observed after 5 min. The suspension was extracted with diethyl ether (3 x 50 ml). Drying and then concentration of the ether extracts gave a solid which was recrystallised from ethanol/H_2O to give the *11b-cyanobenzo[a]quinolizine* **157** (1.094 g, 64%) as an off-white powder. ^{1}H NMR δ: 6.80 (s, ArH), 6.58 (s, ArH), 3.86 (s, OCH_3), 3.84 (s, OCH_3), 3.12-3.00 (m, H), 2.89-2.50 (m, 6H), 1.87-1.58 (m, 5H); ^{13}C NMR δ: 149.28 (C9^A), 148.10 (C10^A), 127.47 (C7a^B), 126.90 (C11a^B), 118.86 (CN^B), 111.91 (C11^C), 108.22 (C8^C), 62.00 (C11b), 56.43 (OCH_3), 56.21 (OCH_3), 52.93 (C6^D), 50.11 (C4^D), 36.48 (C7), 28.84 (C1^E), 25.09 (C3^E), 22.34 (C2^E); MS m/z: 245 (M$^+$·-HCN, 95%), 244 (100), 230 (35), 216 (10), 123 (12).

8,9-Dimethoxy-10b-vinyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-a]isoquinoline 158a

A solution of vinylmagnesium bromide in dry tetrahydrofuran (90 ml) was prepared from vinyl bromide (9.9 g, 93 mmol). To this solution at 0°C under nitrogen was added dropwise a solution of the cyano derivative **155** (5.98 g, 23.1 mmol) in tetrahydrofuran (50 ml). The mixture was stirred for 24 h. at room temperature then treated with ice and basified with 40% aqueous potassium hydroxide. The supernatant liquor was decanted from the deposited solids which were then extracted with tetrahydrofuran (3 x 75 ml). The tetrahydrofuran extracts were centrifuged to remove the solids then concentrated. The residue was treated with 0.5 M aqueous sodium hydroxide (50 ml) and extracted with diethyl ether (3 x 100 ml). The ether extracts were washed with saturated brine (30 ml) then dried and concentrated. Purification of the residue by column chromatography on silica with dichloromethane/5% methanol gave the *10b-vinylpyrrolo[2,1-a]isoquinoline* **158a** (3.54 g, 59%) as a pale yellow oil. ^{1}H NMR δ: 6.59 (s, ArH), 6.55 (s, ArH), 5.95

(dd, *J* 17.2 Hz, 10.3 Hz, H1'), 5.07 (dd, *J* 10.3 Hz, 1.5 Hz, H2'), 4.73 (dd, *J* 17.2 Hz,

1.5 Hz, H2'), 3.85 (s, OCH$_3$), 3.84 (s, OCH$_3$), 3.15-3.08 (m, 1H), 3.05-2.86 (m, H3

and 2H), 2.46-2.38 (m, 1H), 2.22-2.13 (m, H1), 1.92-1.81 (m, 1H2), 1.72-1.64 (m,

1H2); ^{13}C NMR δ: 147.79 (C8^A), 147.61 (C9^A), 146.15 (C1'), 131.52 (C6a^B),

127.66 (C10a^B), 115.00 (C2'), 111.61 (C10^C), 111.52 (C7^C), 67.55 (C10b), 56.49

(OCH$_3$), 56.26 (OCH$_3$), 50.04 (C5^D), 42.84 (C3^D), 39.20 (C6), 23.82 (C1^E), 23.13

(C2^E); MS m/z: 259 (M$^{+\cdot}$, 7%; Calcd. for C$_{16}$H$_{21}$NO$_2$ 259.1572, found 259.1565),

244 (4), 232 (100), 230 (18), 216 (12).

9,10-Dimethoxy-11b-vinyl-1,2,3,4,5,6,7,11b-octahydrobenzo[*a*]quinolizine 158b

A solution of vinylmagnesium bromide in dry tetrahydrofuran (80 ml) was

prepared from vinyl bromide (15.9 g, 149 mmol). To this solution at 0°C under

nitrogen was added dry tetrahydrofuran (70 ml) and the iminium salt **156** (X=Cl)

(10.02 g, 35.6 mmol). The mixture was refluxed for 5 h. then cooled, treated with

ice, and then basified with 40% aqueous potassium hydroxide. The supernatant

tetrahydrofuran solution was decanted from the deposited solids then treated with

water (30 ml) and diethyl ether (100 ml). The organic layer was separated and

diethyl ether (3 x 100 ml) then used to further extract the solids and the aqueous

solution. The organic extracts were combined and then concentrated. The residue

was taken up in diethyl ether (100 ml) and washed with water (4 x 20 ml), saturated

brine (20 ml), and then dried. Concentration and then column chromatography of

the residue on silica with dichloromethane/5% methanol gave the *11b-*

vinylbenzo[a]quinolizine **158b** (1.60 g, 16%) as a pale yellow oil. ^{1}H NMR δ: 6.66

(s, ArH), 6.57 (s, ArH), 6.08 (dd, *J* 17.4 Hz, 10.7 Hz, H1'), 5.16 (dd, *J* 10.7 Hz, 1.5

Hz, H2'), 4.63 (dd, *J* 17.4 Hz, 1.5 Hz, H2'), 3.84 (s, OCH$_3$), 3.82 (s, OCH$_3$), 3.28-

3.18 (m, H), 3.04-2.93 (m, H), 2.83-2.77 (m, H4 and H), 2.70-2.60 (m, H4), 2.55-

2.47 (m, H), 2.00-1.96 (m, 2H), 1.73-1.58 (m, H3 and H), 1.52-1.46 (m, H); ^{13}C

NMR δ: 148.25 (C9^A), 147.46 (C10^A), 144.67 (C1'), 131.54 (C7a^B), 127.88

(C11a^B), 117.12 (C2'), 112.12 (C11^C), 110.94 (C8^C), 62.22 (C11b), 56.67 (OCH$_3$),

56.33 (OCH$_3$), 49.41 (C6^D), 47.01 (C4^D), 35.59 (C7), 26.64 (C1^E), 25.87 (C3^E),

21.45 (C2^E); MS m/z: 273 (M$^{+ \cdot}$, 39%; Calcd. for C$_{17}$H$_{23}$NO$_2$ 273.1727, found

273.174), 272 (38), 246 (100), 244 (40), 230 (35), 205 (18).

Attempted Preparation of 8.9-Dimethoxy-10b-phenyl-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-a]isoquinoline 159a

To a solution of phenylmagnesium bromide [from bromobenzene (9.8 ml, 94

mmol)], in dry tetrahydrofuran (30 ml) and dry diethyl ether (60 ml), under nitrogen

at 0°C, was added dropwise a solution of 155 (5.85 g, 22.6 mmol) in tetrahydrofuran

(50 ml). The mixture was allowed to warm to room temperature with stirring

overnight then worked-up as for 158a. Examination of the crude product by GC-MS

indicated many components were present. None had the desired molecular weight

for 159a.

Attempted Preparation of 9.10-Dimethoxy-11b-phenyl-1,2,3,4,5,6,7,11b-octahydro-benzo[a]quinolizine 159b

(i) To a solution of phenylmagnesium bromide [from bromobenzene (3.5 g, 22

mmol)], in dry tetrahydrofuran (25 ml), under nitrogen at 0°C, was added dropwise a

solution of 157 (1.520 g, 5.581 mmol) in tetrahydrofuran (50 ml). The mixture was

allowed to warm to room temperature with stirring overnight then worked-up as for

158b. The cyano compound was recovered. No other products were evident.

(ii) The procedure of (i) was repeated, but with the reaction mixture instead refluxed

for 4 h. The GC-MS analysis of the product residue indicated only traces of a

compound with the desired molecular weight.

(iii) To 157 (0.965 g, 3.54 mmol) in tetrahydrofuran (30 ml) under nitrogen was

added a solution of phenyl lithium (4 equiv.) in diethyl ether (20 ml). The mixture

was stirred for 2 h. then ice water (20 ml) and diethyl ether (50 ml) were added. The

ether layer was washed with water (4 x 20 ml) and saturated brine (2 x 15 ml) then

dried and concentrated to an oil which was triturated with hexane to remove

bromobenzene. The residue was purified by column chromatography on silica to provide a fraction containing the major product. The GC-MS analysis of this fraction suggested the major product was the reduced compound 9,10-dimethoxy-1,3,4,6,7,11b-hexahydro-2*H*-benzo[*a*]quinolizine.[156]

8,9-Dimethoxy-4-ethoxycarbonylmethyl-10b-vinyl-1,2,3,5,6,10b-hexahydro-pyrrolo[2,1-*a*]isoquinolinium Bromide 160a

To the base **158a** (0.665 g, 2.56 mmol) in dry acetonitrile (3 ml) at 0°C under nitrogen was added dropwise a solution of ethoxycarbonylmethyltriflate (0.78 g, 3.3 mmol) in dry acetonitrile (3 ml). The solution was stirred for 1 h. at 0°C then 4 h. at room temperature, then concentrated. The residue was triturated with hexane (4 x 5 ml) then taken up in ethanol (6 ml) and stirred with potassium bromide (1.50 g, 12.6 mmol) for 2 h. before the addition of activated charcoal and filtration of the solution. The filtrate was concentrated and the residue then redissolved in dichloromethane and the filtration was repeated. Concentration of the filtrate gave the *4-ethoxycarbonylmethylpyrrolo[2,1-a]isoquinolinium salt* **160a** (1.014 g, 93%) as a tan solid. ^{1}H NMR δ: 6.74 (s, ArH), 6.47 (s, ArH), 6.17 (dd, *J* 17.1 Hz, 10.6 Hz, H1'), 5.91 (d, *J* 10.6 Hz, H2'), 5.69 (d, *J* 17.1 Hz, H2'), 4.35 (d, *J* 16.5 Hz, H of CH_2CO), 4.27 (q, CH_2 of Et), 4.13-3.92 (m, 5H), 3.88 (s, OCH_3), 3.81 (s, OCH_3), 3.20-3.13 (m, 2H), 2.92-2.84 (m, H), 2.58-2.50 (m, H), 2.42-2.32 (m, H), 2.30-2.22 (m, H), 1.72-1.64 (m, 1H2), 1.31 (t, CH_3 of Et); ^{13}C NMR δ: 164.73 (CO), 149.59 (C8[A]), 148.99 (C9[A]), 133.43 (C1'), 126.38 (C2'), 124.45 (C6a[B]), 121.18 (C10a[B]), 111.27 (C10[C]), 110.24 (C7[C]), 83.88 (C10b), 63.24 (CH_2 of Et[D]), 59.94 (NCH_2CO[D]), 56.84 (C3[D]), 56.30 (OCH_3), 56.24 (OCH_3), 51.96 (C5[D]), 34.23 (C6), 23.55 (C1[E]), 20.21 (C2[E]), 13.86 (CH_3 of Et).

9,10-Dimethoxy-5-ethoxycarbonylmethyl-11b-vinyl-1,2,3,4,5,6,7,11b-octahydro-benzo[*a*]quinolizinium Bromide **160b**

To the base **158b** (0.700 g, 2.56 mmol) in dry acetonitrile (3 ml) at 0°C under nitrogen was added dropwise a solution of ethoxycarbonylmethyltriflate (0.80 g, 3.4 mmol) in dry acetonitrile (3 ml). The solution was stirred for 1 h. at 0°C then 4 h. at room temperature, then concentrated. The residue was triturated with hexane (4 x 5 ml) then taken up in ethanol (6 ml) and stirred with potassium bromide (1.58 g, 13.3 mmol) for 2 h. before the addition of activated charcoal and filtration of the solution. The filtrate was concentrated then the residue redissolved in dichloromethane and refiltered. Concentration of the filtrate gave the *5-ethoxycarbonylmethyl-benzo[a]quinolizinium salt* **160b** (0.908 g, 80%) as a tan solid. Two conformationally flexible diastereomers (ratio 3.3:1.0) were evident in the NMR spectra of this material. Discernible NMR peaks were: ^{1}H NMR δ: 6.80 and 6.78 (s, ArH), 6.62 and 6.53 (s, ArH), 4.32-4.27 (m, CH_2 of Et'), 3.91 and 3.90 (s, OCH_3), 3.87-3.83 (s, OCH_3), 1.36-1.30 (m, CH_3 of Et); ^{13}C NMR δ: 164.91 (CO), 150.49 and 150.17 (C9[A]), 149.63 and 149.20 (C10[A]), 135.25 and 133.54 (C1'), 128.46 and 127.90 (C2'), 112.14 and 112.02 (C11[B]), 110.11 and 109.38 (C8[B]), 623.75 (CH_2 of Et), 56.83 (OCH_3), 56.58 (OCH_3), 14.25 (CH_3 of Et).

Ethyl 9,10-Dimethoxy-7-vinyl-1,2,4,5,6,7-hexahydro-3,7-methano-3-benzazonine-12-carboxylate **161a**

To the salt **160a** (0.961, 2.25 mmol) in dry acetonitrile (30 ml) was added DBU (0.54 g, 3.5 mmol). The solution was refluxed for 20 h. then cooled and concentrated. Purification of the residue by column chromatography on alumina (25 g) with dichloromethane/33% hexane gave an impure yellow oil (36 mg) from the first eluted fraction. Further purification of this oil by preparative reverse phase HPLC with acetonitrile/20% water gave a colourless oil tentatively attributed to the *3,7-methano-3-benzazonine* **161a** (8 mg, 1%). ^{1}H NMR δ: 7.51 (s, ArH), 7.10 and 7.01 (m, H1' and ArH), 5.52 (dd, *J* 17.2, 1.1 Hz, H2'), 5.18 (dd, *J* 10.9, 1.1 Hz, H2'),

4.19 (q, CH$_2$ of Et), 3.90 (s, OCH$_3$), 3.89 (s, OCH$_3$), 3.94-3.84 (m, 2H), 3.09-3.03 (m, H), 2.86-2.77 (m, H), 2.38-2.30 (m, H), 2.17-1.93 (m, 5H), 1.70-1.62 (m, H), 1.29 (t, CH$_3$ of Et); ^{13}C DEPT NMR δ: 136.70 (C1'), 112.83 (C2'), 111.42 (C8^A), 110.13 (C11^A), 64.48 (C12), 61.02 (CH$_2$ of Et), 56.62 (2OCH$_3$), 48.71 (C2), 41.91 (C4^B), 40.24 (C6^B), 32.35 (C1^C) 28.60 (C5^C), 15.02 (CH$_3$ of Et).

Attempted Base-Promoted Rearrangement of 160b to 161b

(i) To the salt 160b (0.323, 0.733 mmol) in dry acetonitrile (20 ml) was added DBU (0.15 g, 0.99 mmol). The solution was stirred at 45°C for 18 h. then cooled and concentrated. The non-polar fraction of the residue was obtained by column chromatography on alumina (25 g) with dichloromethane/10% light petroleum and then purified by passage of the crude oil through an alumina plug with diethyl ether. Concentration of the ether solution gave an impure oil (5 mg) found to contain the precursor 158b as the major component (≥50%) upon GC-MS and ^{1}H NMR spectral analysis.

(ii) To the salt 160b (0.203, 0.461 mmol) in dry acetonitrile (20 ml) at reflux under nitrogen was added DBU (0.10 g, 0.66 mmol). The solution was refluxed for 10 h. then cooled and concentrated. Workup as for (i) gave an impure oil (11 mg). GC-MS analysis of the oil revealed the presence of 158b (33%) and three isomers (10%, 36%, and 11%) possessing almost identical mass spectra, and consistent with the desired 3,8-methano-benzazecine 161b. MS m/z: 359 (M$^{+\cdot}$, 24%), 316 (15), 305 (69), 286 (100, M-CO$_2$Et), 246 (13), 188 (40).

(iii) To the salt 160b (0.147, 0.334 mmol) in dry butyronitrile (25 ml) at reflux under nitrogen was added DBU (0.080 g, 0.0.52 mmol). The solution was refluxed for 4 h. then cooled and concentrated to a dark residue. Workup as for (i) gave an impure oil (16 mg). GC-MS analysis of the oil gave a similar result to (ii).

8,9-Dimethoxy-10b-vinyl-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline
N-Oxide **162a**

The pyrrolo[2,1-*a*]isoquinoline **158a** (3.54 g, 13.7 mmol) in dichloromethane
(50 ml) at 0°C was treated with *m*-CPBA (3.28 g, 19.1 mmol) in dichloromethane
(50 ml). The resultant solution was stirred for 40 h., while allowed to warm to 20°C,
then water (100 ml) was added and the dichloromethane was removed *in vacuo*. The
aqueous solution was basified with solid potassium carbonate and washed with
diethyl ether (3 x 30 ml), then acidified with 3 M aqueous hydrochloric acid and
again washed with diethyl ether (3 x 30 ml). The solution was rebasified and
saturated with sodium chloride then extracted with chloroform (3 x 40 ml). The
extracts were dried and then concentrated. Elution of the residue through an alumina
plug with chloroform/20% methanol gave the *pyrrolo[2,1-a]isoquinoline* N-*oxide*
162a (2.92 g, 78%) as a mixture of the B-ring diastereomers (13.3:1) with the
following diagnostic peaks. Major diastereomer: ^{1}H NMR δ: 6.68 (dd, *J* 17.5 Hz,
10.6 Hz, H1'), 6.60 (s, ArH), 6.55 (s, ArH), 5.46 (d, *J* 10.6 Hz, H2'), 4.78 (d, *J* 17.5
Hz, H2'), 3.88 (s, OCH$_3$), 3.84 (s, OCH$_3$), 3.66-3.46 (m, 4H), 3.12-2.93 (m, 3H),
2.44-2.39 (m, 2H), 1.81-1.70 (m, H); ^{13}C NMR δ: 149.08 (C8^A), 148.27 (C9^A),
139.78 (C1'), 127.28 (C6a^B), 123.48 (C10a^B), 121.67 (C2'), 111.06 (C7 and C10),
82.24 (C10b), 63.96 (C5^C), 57.29 (C3^C), 56.44 (OCH$_3$), 56.28 (OCH$_3$), 34.80 (C6),
26.83 (C1), 19.87 (C2). Minor diastereomer: ^{1}H NMR δ: 6.02 (dd, *J* 17.5 Hz, 10.6
Hz, H1'), 5.29 (d, *J* 10.6 Hz, H2').

9,10-Dimethoxy-11b-vinyl-1,2,3,4,5,6,7,11b-octahydrobenzo[*a*]quinolizine *N*-Oxide
162b

The benzo[*a*]quinolizine **158b** (0.827 g, 3.03 mmol) in dichloromethane (30
ml) at 0°C was treated with *m*-CPBA (0.632 g, 3.67 mmol) in dichloromethane (15
ml). The resultant solution was stirred for 40 h., while allowed to warm to 20°C,
then washed with 0.5 M aqueous sodium bicarbonate (3 x 10 ml). Drying and then
concentration gave the crude *benzo[a]quinolizine* N-*oxide* **162b** (0.723 g, 83%) as a

mixture of the B-ring diastereomers (5.7:1) with the following diagnostic peaks. Major diastereomer: ^{1}H NMR δ: 5.35 (d, *J* 10.7 Hz, H2'), 4.49 (d, *J* 15.5 Hz, H2'); ^{13}C NMR δ: 141.01 (C1'), 121.88 (C2'), 111.98 (C8[A]), 110.70 (C11[A]), 77.69 (C11b). Minor diastereomer: ^{1}H NMR δ: 5.50 (d, *J* 10.7 Hz, H2'), 4.87 (d, *J* 12.4 Hz, H2'); ^{13}C NMR δ: 136.52 (C1'), 125.10 (C2'), 111.66 (C8[A]), 109.83 (C11[A]), 76.09 (C11b).

9,10-Dimethoxy-7-vinyl-1,2,4,5,6,7-hexahydro-3,7-epoxy-3-benzazonine 163a

A solution of the *N*-oxide **162a** (0.365 g, 1.33 mmol) in dry butyronitrile (20 ml) was refluxed for 1 h. then concentrated and the residue was extracted with diethyl ether. Concentration of the extracts and ^{1}H NMR analysis of the residue (41 mg) indicated a mixture (1.9:1) of the 3,7-epoxy-3-benzazonine **163a** and pyrrolo[2,1-*a*]isoquinoline **158a**. Preparative reverse-phase HPLC purification of the mixture with methanol/20%water afforded the *3,7-epoxy-3-benzazonine* **163a** (22 mg, 6%) as a pale yellow oil. ^{1}H NMR δ: 6.56 (s, ArH), 6.49 (s, ArH), 5.94 (dd, *J* 17.4 Hz, 10.7 Hz, H1'), 5.11 (dd, *J* 17.4 Hz, 1.1 Hz, H2'), 5.05 (dd, *J* 10.7 Hz, 1.1 Hz, H2'), 3.87 (s, OCH$_3$), 3.81 (s, OCH$_3$), 3.80-3.70 (m, H2[A]), 3.59-3.47 (m, H4 and H2[A]), 3.20-3.12 (m, H1[A]), 2.86-2.79 (m, H4), 2.51-2.42 (m, H1[A]), 2.32-2.25 (m, H6), 2.12-2.01 (m, H6), 1.81-1.66 (m, H5), 1.39-1.30 (m, H5); ^{13}C NMR δ: 147.78 (C9[A]), 147.37 (C10[A]), 145.03 (C1'), 135.06 (C7a[B]), 132.69 (C11a[B]), 113.81 (C2'), 113.58 (C8[C]), 112.53 (C11[C]), 82.87 (C7), 57.97 (C2[D]), 56.63 (OCH$_3$), 56.43 (OCH$_3$), 53.39 (C4[D]), 35.83 (C1[E]), 31.71 (C6[E]), 13.04 (C5); MS m/z: 275 (M[+•], 5%; Calcd. for C$_{16}$H$_{21}$NO$_3$ 275.1521, found 275.1513), 258 (27), 245 (6), 232 (100), 215 (35), 199 (14).

Other Thermolyses of 162a and 163a

(i) To dimethyl sulfoxide (10 ml) at 130°C was added **162a** (105 mg). The solution was stirred for 50 min at 130°C then cooled and extracted with diethyl ether (3 x 15 ml). The combined ether extracts were washed with water (2 x 7 ml) and saturated

brine (5 ml), then dried and concentrated. ^{1}H NMR analysis of the residue (29 mg) indicated a mixture (7.3:1) of **158a** and **163a**.

(ii) The *N*-oxide **162a** (273 mg) was heated in an evacuated sealed tube for 1 h. at 120°C, then cooled and the residue was extracted with diethyl ether (5 x 2 ml). Concentration of the extracts and ^{1}H NMR analysis of the residue (104 mg) indicated a mixture (2.9:1.4:1.0) of **158a** and **162a** and **163a**.

(iii) The 3,7-epoxy-3-benzazonine **163a** (12 mg) was refluxed in dry butyronitrile (2 ml) for 1 h. then the solution was cooled and concentrated. ^{1}H NMR analysis of the residue showed the majority of the material was unchanged **163a** (≥90%) although some **158a** (≤10%) was detected.

10,11-Dimethoxy-8-vinyl-1,4,5,6,7,8-hexahydro-2*H*-3,8-epoxy-3-benzazecine **163b**

A solution of the *N*-oxide **162b** (0.846 g, 2.92 mmol) in dry butyronitrile (40 ml) was refluxed for 2 h. then cooled and concentrated. The residue was purified by column chromatography on silica with dichloromethane/0-2% methanol to give 2*H*-*3,8-epoxy-3-benzazecine* **163b** (46 mg, 5%) as a colourless oil. ^{1}H NMR δ: 6.63 (s, ArH), 6.50 (s, ArH), 5.97 (dd, *J* 17.4 Hz, 10.7 Hz, H1'), 5.12 (dd, *J* 17.4 Hz, 1.5 Hz, H2'), 5.07 (dd, *J* 10.7 Hz, 1.5 Hz, H2'), 3.86 (s, OCH$_3$), 3.83 (s, OCH$_3$), 3.58-3.47 (m, H2^A), 3.11-3.05 (m, H2^A and H1^A), 2.86-2.82 (m, H4), 2.51-2.38 (m, H7 and H1^A), 2.25-2.16 (m, H7), 1.80-1.60 (m, H5 and H6); ^{13}C NMR δ: 148.22 (C10^A), 147.38 (C11^A), 141.63 (C1'), 138.99 (C8a^B), 128.57 (C12a^B), 115.21 (C9^C), 114.57 (C2'), 111.62 (C12^C), 87.89 (C8), 56.85 (C2^D), 56.52 (2OCH$_3$), 56.07 (C4^D), 43.16 (C1^E), 33.53 (C7^E), 30.74 (C5), 22.86 (C6); MS m/z: 289 (M$^{+\cdot}$, 7%; Calcd. for C$_{17}$H$_{23}$NO$_3$ 289.1678, found 289.1684), 272 (100), 256 (5), 246 (7), 244 (7), 230 (6).

9,10-Dimethoxy-11b-cyano-1,2,3,4,5,6,7,11b-octahydrobenzo[a]quinolizine

N-Oxide 164

The 11b-cyanobenzo[a]quinolizine **157** (0.961 g, 3.53 mmol) in dichloromethane (20 ml) at 0°C was treated with a solution of *m*-CPBA (0.760 g, 4.42 mmol) in dichloromethane (15 ml). The resultant solution was stirred for 24 h. while allowed to warm to 20°C. The organic solution was washed with 5% aqueous sodium bicarbonate (5 x 20 ml) then dried and concentrated to a residual solid. The aqueous washings were combined and saturated with sodium chloride then back-extracted with chloroform (4 x 15 ml). Drying and then concentration of the extracts gave a second crop of solid. The solids were combined and then purified by column chromatography on alumina with dichloromethane/10% methanol to give the *benzo[a]quinolizine* N-*oxide* **164** (0.741 g, 73%) as a light tan powder. ^{1}H NMR δ: 6.70 (s, ArH), 6.69 (s, ArH), 4.14-4.04 (m, H), 3.92-3.78 (m, 2H), 3.88 (s, OCH$_3$), 3.85 (s, OCH$_3$), 3.50-3.44 (m, H), 3.39-3.34 (m, H), 2.88-2.73 (m, 3H), 2.49-2.44 (m, H), 2.04-1.96 (m, 2H), 1.74-1.70 (m, H); ^{13}C NMR δ: 150.49 (C9[A]), 149.07 (C10[A]), 125.49 (C7a[B]), 122.56 (CN[B]), 119.02 (C11a[B]), 112.60 (C11[C]), 109.06 (C8[C]), 69.75 (C11b), 66.69 (C4[D]), 63.32 (C6[D]), 56.91 (OCH$_3$), 56.67 (OCH$_3$), 29.55 (C7), 25.21 (C1[E]), 20.86 (C3[E]), 19.95 (C2[E]); MS m/z: 288 (M$^{+\cdot}$, 6%; Calcd. for C$_{16}$H$_{20}$N$_2$O$_3$ 288.1472, found 288.149), 271 (50), 245 (56), 244 (100), 230 (20), 164 (12); IR (thin film from CDCl$_3$): 2940, 2864, 2837, 1524, 1263, 1140, 729 cm^{-1}.

Thermolyses of Compound **164**

(i) The *N*-oxide **164** (214 mg) was refluxed in dry acetonitrile (20 ml) for 18 h. then the solution was cooled and concentrated. Analysis of the residue by t.l.c. showed the majority of the *N*-oxide remained. The residue was partitioned between diethyl ether (30 ml) and water (10 ml) and the ether layer then washed with further water (2 x 5 ml). Drying and then concentration gave an impure oil (2 mg).

(ii) The *N*-oxide **164** (201 mg) was refluxed in dry butyronitrile (20 ml) for 10 h. then the solution was cooled and concentrated. Analysis of the residue by t.l.c. with

dichloromethane/10% methanol showed mainly material at the origin. The treatment of the residue as for (i) gave an orange oil (75 mg). Analysis of this material by GC-MS revealed two components (82% and 18%) with molecular ions at 246 and 272 mass units.

(iii) The N-oxide **164** (187 mg) was refluxed in dry dimethylformamide (20 ml) for 1 h. then the solution was cooled and concentrated. Treatment of the residue as for (i) gave a dark oil (100 mg). Analysis of this material by GC-MS revealed numerous minor components with a single significant component (40%) with MS: 272 (96%), 256 (31), 232 (100), 203 (32), 82 (69).

6.5   Experimental for Chapter Five

<u>Investigation of the Epoxidation of 1-Vinylisoquinoline **49a** and Derivatives with _m_-CPBA</u>

(i) To **49a** (117 mg, 0.501 mmol) in dichloromethane (10 ml) was added _m_-CPBA (258 mg, 1.50 mmol). The solution was stirred for 48 h. then extracted with 0.5 M aqueous sodium bicarbonate (2 x 5 ml). The aqueous washings were concentrated and the residue was extracted with dichloromethane (5 ml). The dichloromethane portions were combined then dried and concentrated to afford a yellow solid (97 mg). The NMR spectra confirmed the material was the N-oxide **123a**.

(ii) To **49a** (93 mg, 0.40 mmol) in chloroform (10 ml) was added _m_-CPBA (206 mg, 1.20 mmol). The solution was refluxed for 12 h. before workup as for (i) to afford a solid residue. The NMR spectra confirmed the material was the N-oxide **123a** contaminated with some _m_-chlorobenzoic acid.

(iii) To **49a** (113 mg, 0.484 mmol) in chloroform (10 ml) was added _m_-CPBA (250 mg, 1.45 mmol). The solution was refluxed for 1 h. before the addition of further _m_-CPBA (250 mg, 1.45 mmol) and continuation of reflux for 5 h. Workup as for (i) gave a dark solid residue. The NMR spectra confirmed the material was the N-oxide **123a** contaminated with some _m_-chlorobenzoic acid.

(iv) To the hydrochloride salt **49a.HCl** (54 mg, 0.20 mmol) in chloroform (6 ml) was added *m*-CPBA (79 mg, 0.46 mmol). The solution was stirred for 16 h. before workup as for (i) to afford a solid residue. The NMR spectra confirmed the material was the *N*-oxide **123a**.

(v) To the methiodide salt **55a** (147 mg, 0.392 mmol) suspended in chloroform (10 ml) was added a solution of *m*-CPBA (191 mg, 0.702 mmol) in chloroform (5 ml) dropwise, providing dissolution of the initial salt. After stirring for 15 h. a sample was withdrawn and then concentrated for analysis. The NMR spectra confirmed that **55a** remained, along with *m*-chlorobenzoic acid.

(vi) To the methiodide salt **55a** (53 mg, 0.14 mmol) in 1,2-dichloroethane (5 ml) at reflux was added *m*-CPBA (74 mg, 0.43 mmol). After refluxing for 3 h. a sample was withdrawn and then concentrated for analysis. The NMR spectra confirmed that **55a** remained, along with *m*-chlorobenzoic acid.

Investigation of the Epoxidation of 1-Vinylisoquinoline **49a** and Derivatives with Urea-Hydrogen Peroxide

(i) To the trifluoroacetic acid salt of **49a** (379 mg, 1.09 mmol) with disodium hydrogen phosphate (1.352 g, 9.52 mmol) and urea-hydrogen peroxide (1.040 g, 11.1 mmol) in dry dichloromethane (8 ml) under nitrogen was added trifluoroacetic anhydride (0.40 ml, 2.83 mmol) dropwise. The mixture, with solid present, was refluxed for 1 h. then saturated aqueous sodium bicarbonate was added carefully to give a basic mixture. The organic layer was separated and the aqueous layer was extracted with dichloromethane (4 x 10 ml). The organic extracts were combined and washed with 5% aqueous sodium bicarbonate (5 ml) then water (5 ml). Drying and then concentration of the organic solution afforded only the free base **49a** (98 mg, 39%).

(ii) To **49a** (345 mg, 1.48 mmol) in dry acetonitrile (5 ml) under nitrogen was added trifluoroacetic acid (169 mg, 1.48 mmol) then a solution of urea-hydrogen peroxide (561 mg, 5.96 mmol) and trifluoroacetic anhydride (0.40 ml, 2.83 mmol) in dry

dichloromethane (8 ml). The mixture was stirred for 5 h. then saturated aqueous sodium bicarbonate (10 ml) and dichloromethane (15 ml) were added. The organic layer was separated and the aqueous layer was extracted with dichloromethane (2 x 5 ml). The organic extracts were combined and washed with 5% aqueous sodium bicarbonate (5 ml) then water (5 ml). Drying and then concentration of the organic solution afforded only **49a** (268 mg, 78%).

Investigation of the Simmons-Smith Cyclopropanation of 1-Vinyltetrahydroisoquinoline **49a**

A zinc-copper couple was prepared[179] by the addition of zinc dust (3.0 g, 45.9 mmol) to a hot rapidly stirred solution of cupric acetate monohydrate (0.173 g, 0.866 mmol) in glacial acetic acid (5 ml), followed by stirring for 1 min. The mixture was briefly allowed to settle and then the acetic acid was decanted. The solid was washed with glacial acetic acid (2 x 5 ml) then diethyl ether (3 x 10 ml) and was used immediately.

To the zinc-copper couple (0.30 g, 4.6 mmol) and **49a** (0.418 mg, 1.80 mmol) in dry diethyl ether (5 ml) under nitrogen was added a crystal of iodine. Methylene iodide (0.997 g, 3.72 mmol) was then added in three portions over 50 min. while the solution was brought to reflux. The mixture was refluxed for 10 h. with the deposition of a tan precipitate. Saturated aqueous ammonium chloride (5 ml) was then added. The supernatant liquor was decanted from the solids, which were then extracted with diethyl ether (3 x 5 ml). The ether extracts were washed with saturated aqueous sodium bicarbonate (2 x 5 ml) then dried and concentrated to afford only a trace of material (0.1 mg). The ether insoluble solid was extracted with chloroform (4 x 5 ml). These extracts were filtered then washed with saturated aqueous sodium bicarbonate (2 x 5 ml). Drying and concentration of the extracts afforded a tan powder assumed to be the methiodide salt **55a** (0.468 g, 70%).

N-[2-(3,4-Dimethoxyphenyl)ethyl]cyclopropyl carboxamide 174a

Homoveratrylamine (30.03 g, 165.7 mmol) and cyclopropane carboxylic acid 173a (20.40 g, 237.0 mmol) were combined and stirred as a melt at 160°C for 4.25 h. under a slow stream of nitrogen to remove water vapour, then allowed to cool to a solid which was taken up in chloroform (300 ml). This solution was washed with 2M sodium hydroxide (3 x 80 ml), 3M hydrochloric acid (2 x 80 ml), 0.5M hydrochloric acid (3 x 60 ml), and water (60 ml) then dried and concentrated. The residue was recrystallised from ethyl acetate to give the *cyclopropyl carboxamide* 174a (28.59 g, 69%) as a colourless powder, m.p. 94-95°C. ^{1}H NMR δ: 6.82 (d, *J* 8.4 Hz, ArH), 6.74 (d, *J* 8.2 Hz, ArH), 6.73 (s, ArH), 5.84 (bs, NH), 3.87 (s, OCH$_3$), 3.86 (s, OCH$_3$), 3.50 (q, H1), 2.77 (t, H2), 1.32-1.27 (m, H1'), 0.98-0.93 (m, 2H'), 0.74-0.67 (m, 2H'); ^{13}C NMR δ: 174.15 (CO), 149.63 (C3"^{A}), 148.26 (C4"^{A}), 132.12 (C1"), 121.24 (C6"^{B}), 112.55 (C2"^{B}), 111.95 (C5"^{B}), 56.50 (2OCH$_3$), 41.55 (C1), 35.96 (C2), 15.31 (C1'), 7.63 (C2', C3'); MS m/z: 249 (M$^+$, 9%; Calcd. for C$_{14}$H$_{19}$NO$_3$ 249.1364, found 249.1357), 165 (11), 164 (100), 151 (25), 149 (10), 69 (17); Anal. Calcd for C$_{14}$H$_{19}$NO$_3$: C, 67.44; H, 7.68; N, 5.62%, found: C, 67.66; H, 7.85; N, 5.72%; IR (thin film from CDCl$_3$): 3309 (NH), 1636 (CO), 1028 cm^{-1}.

N-[2-(3,4-Dimethoxyphenyl)ethyl]-*trans*-2'-phenylcyclopropyl carboxamide 174b

Homoveratrylamine (12.2 g, 67.3 mmol) and *trans*-2'-phenylcyclopropane carboxylic acid 173b (13.14 g, 81.02 mmol) were combined and stirred as a melt between 140°C and 160°C for 5 h. under a slow stream of nitrogen to remove water vapour, then allowed to cool to a solid which was taken up in chloroform (150 ml). This solution was washed with 2M sodium hydroxide (3 x 35 ml), 3M hydrochloric acid (3 x 30 ml), water (20 ml), and saturated aqueous sodium chloride (20 ml) then dried and concentrated. The residue was recrystallised from ethyl acetate to give the t-*phenylcyclopropyl carboxamide* 174b (16.51 g, 75%) as a colourless powder, m.p. 116-117°C. ^{1}H NMR δ: 7.27-7.17 (m, 3ArH), 7.06-7.03 (m, 2ArH), 6.80-6.70 (m, 3ArH), 5.85 (bs, NH), 3.84 (s, OCH$_3$), 3.82 (s, OCH$_3$), 3.50 (q, H1), 2.76 (t, H2),

2.48-2.42 (m, H2'), 1.60-1.52 (m, H1' and 1H3'), 1.23-1.17 (m, 1H3'); ^{13}C NMR δ:

172.53 (CO), 149.58 (C3"^{A}), 148.23 (C4"^{A}), 141.43 (C1"^{B}), 131.92 (C1"'^{B}), 129.03

(2C"'^{C}), 126.84 (1C"'^{C}), 126.55 (2C"'^{C}), 121.21 (C6"^{D}), 112.43 (C2"^{D}), 111.91

(C5"^{D}), 56.47 (OCH$_3$), 56.39 (OCH$_3$), 41.64 (C1), 35.87 (C2), 27.31 (C2'^{E}), 25.58

(C1'^{E}), 16.52 (C3'); MS m/z: 325 (M$^+$, 15%; Calcd. for C$_{20}$H$_{23}$NO$_3$ 325.1677,

found 325.1674), 165 (12), 164 (100), 151 (16), 91 (6); IR (KBr disk): 3323 (NH),

1638 (CO), 1028 cm^{-1}.

1-Cyclopropyl-6,7-dimethoxy-3,4-dihydroisoquinoline 175a

The carboxamide **174a** (32.44 g, 130.1 mmol) was refluxed in dry acetonitrile

(500 ml) with phosphorus oxychloride (48 ml, 510 mmol) for 3 h. Ice was then

added to decompose the excess reagent. The resultant solution was concentrated *in*

vacuo until the majority of the organic solvent was removed, then water (700 ml)

was added and the aqueous solution was washed with diethyl ether (3 x 100 ml). The

aqueous solution was made basic with concentrated ammonia and then extracted with

chloroform (4 x 300 ml). The extracts were dried and then concentrated to give the

crude *1-cyclopropylimine* **175a** (26.50 g, 88%) as a grey solid. Recrystallisation of a

portion of this material from ethanol gave a colourless powder, m.p. 80-81°C. ^{1}H

NMR δ: 7.31 (s, ArH), 6.70 (s, ArH), 3.94 (s, OCH$_3$), 3.93 (s, OCH$_3$), 3.56 (t, H3),

2.60 (t, H4), 2.02-1.90 (m, H1'), 1.01-0.97 (m, H2'), 0.91-0.86 (m, H3'); ^{13}C NMR δ:

167.22 (C1), 151.33 (C6^A), 148.09 (C7^A), 131.80 (C4a^B), 123.59 (C8a^B), 110.74

(C5^C), 109.52 (C8^C), 56.83 (OCH$_3$), 56.58 (OCH$_3$), 47.41 (C3), 26.48 (C4), 15.24

(C1'), 7.66 (C2', C3'); MS m/z: 231 (M$^+$, 88%; Calcd. for C$_{14}$H$_{17}$NO$_2$ 231.1259,

found 231.1241), 230 (100), 216 (28), 214 (14), 200 (37), 184 (13); IR (thin film

from CDCl$_3$): 3001, 2936, 2832, 1512, 1281, 1142 cm^{-1}.

6,7-Dimethoxy-1-(t-2-phenylcyclopropyl)-3,4-dihydroisoquinoline 175b

The carboxamide **174b** (16.50 g, 50.70 mmol) was refluxed in dry acetonitrile

(300 ml) with phosphorus oxychloride (20 ml) for 3 h. Ice (50 g) was then added to

decompose the excess reagent. The resultant solution was concentrated until the majority of the organic solvent was removed, then water (300 ml) was added and the aqueous solution was washed with diethyl ether (3 x 75 ml). The solution was made basic with concentrated ammonia and then extracted with chloroform (3 x 75 ml). The yellow extracts developed a red colour. The extracts were dried and then concentrated to afford the crude *1-(2'-phenylcyclopropyl)imine* **175b** (15.50 g, 98%) as a red oil which was used without further purification. ^{1}H NMR δ: 7.32-7.16 (m, 5ArH"), 7.07 (s, ArH), 6.68 (s, ArH), 3.89 (s, OCH$_3$), 3.81-3.74 (m, 1H3), 3.64 (s, OCH$_3$), 3.51-3.42 (m, 1H3), 2.68-2.58 (m, H4), 2.29-2.19 (m, 2H'), 1.86-1.80 (m, 1H'), 1.39-1.33 (m, 1H'); ^{13}C NMR δ: 165.90 (C1), 151.29 (C6^A), 148.05 (C7^A), 142.60 (C4a^B), 131.56 (C8a^B), 129.03 (2C"), 127.94 (C4"), 126.39 (2C"), 123.23 (C1"^{B}), 110.69 (C5^C), 109.36 (C8^C), 56.52 (OCH$_3$), 56.39 (OCH$_3$), 47.58 (C3), 28.32 (C1'^{D}), 26.68 (C2'^{D}), 26.39 (C4), 15.55 (C3'); MS m/z: 307 (M$^+$, 50%; Calcd. for C$_{20}$H$_{22}$NO$_3$ 307.1572, found 307.1586), 306 (83), 305 (100), 304 (63), 290 (21), 276 (12), 201 (18).

1-Cyclopropyl-6,7-dimethoxy-2-methyl-3,4-dihydroisoquinolinium Iodide 176a

To the crude 1-cyclopropylimine **175a** (21.3 g, 92.1 mmol) in dry acetone (140 ml) was added iodomethane (39.0 g, 280 mmol). The solution was refluxed for 3 h. with the formation of a yellow precipitate. A further portion of iodomethane (11.5 g, 81.6 mmol) was then added and the refluxing was continued for 1 h. The mixture was then cooled and concentrated to approximately 100 ml. The precipitate was collected and rinsed with cold acetone, then recrystallised from ethanol to afford the *1-cyclopropylmethiodide salt* **176a** (32.04 g, 93%) as yellow prisms, m.p. 212-213°C. ^{1}H NMR δ: 7.58 (s, ArH), 6.89 (s, ArH), 4.09 (t, H3), 4.03 (s, NCH$_3$), 4.00 (s, OCH$_3$), 3.94 (s, OCH$_3$), 3.30 (t, H4), 2.57-2.48 (m, H1'), 1.52-1.44 (m, H2'), 1.21-1.13 (m, H3'); ^{13}C NMR δ: 176.21 (C1), 156.48 (C6^A), 148.47 (C7^A), 133.56 (C4a^B), 120.03 (C8a^B), 113.81 (C5^C), 111.06 (C8^C), 57.32 (OCH$_3$), 57.05 (OCH$_3$), 53.07 (C3), 46.21 (NCH$_3$), 26.31 (C4), 14.42 (C1'), 9.89 (C2', C3'); Anal. Calcd for

$C_{15}H_{20}NO_2I$: C, 48.27; H, 5.40; N, 3.75%, found: C, 48.24; H, 5.57; N, 3.85%; IR (thin film from $CDCl_3$): 2941, 1602, 1560, 1521, 1394, 1007, 920, 731 cm^{-1}.

6,7-Dimethoxy-2-methyl-1-(t-2-phenylcyclopropyl)-3,4-dihydroisoquinolinium Iodide 176b

Heating must be avoided at all stages in this preparation. The crude 1-(2'-phenylcyclopropyl) imine 175b (0.664 g, 2.16 mmol) was stirred at room temperature in dry acetone (6 ml) with iodomethane (0.32 g, 2.3 mmol), protected from light, for 3 days. Concentration and then recrystallisation of the residue from acetone/ethyl acetate gave the *1-(2'-phenylcyclopropyl) methiodide salt* 176b (0.498 g, 51%) as yellow needles, m.p. 159-160°C. ^{1}H NMR δ: 7.35-7.22 (m, 5ArH", ArH), 6.85 (s, ArH), 4.11 (t, H3), 3.99 (s, NCH$_3$), 3.98 (s, OCH$_3$), 3.60 (s, OCH$_3$), 3.51-3.39 (m, 1H'), 3.37-3.25 (m, 1H'), 2.67 (t, H4), 2.02-1.96 (m, 1H'), 1.86-1.78 (m, 1H'); ^{13}C NMR δ: 174.84 (C1), 156.74 (C6^A), 148.76 (C7^A), 139.16 (C4a^B), 133.67 (C8a^B), 129.54 (2C"), 127.81 (1C"), 126.51 (2C"), 120.44 (C1"^{B}), 113.67 (C5^C), 111.23 (C8^C), 57.45 (OCH$_3$), 56.68 (OCH$_3$), 53.38 (C3), 47.00 (NCH$_3$), 27.67 (C1'^{D}), 26.48 (C4), 24.78 (C2'^{D}), 20.23 (C3'); Anal. Calcd for $C_{21}H_{24}NO_2I$: C, 56.13; H, 5.38; N, 3.12%, found: C, 56.41; H, 5.40; N, 3.02%; IR (KBr disc): 2932, 1603, 1563, 1521, 1292, 1265, 1219, 1010 cm^{-1}.

1-Cyclopropyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline 177a

To the 1-cyclopropyl imine salt 176a (30.45 g, 81.59 mmol) suspended in ethanol (600 ml) at 0°C was added sodium borohydride (8.74 g, 230 mmol) portionwise over 35 min. The solution was allowed to warm to room temperature with stirring over 2 h, then concentrated. The residue was partitioned between water (100 ml) and chloroform (400 ml). The chloroform layer was separated and washed with water (3 x 50 ml), then dried and concentrated to give the *1-cyclopropyltetrahydroisoquinoline* 177a (19.24 g, 95%) as a colourless solid. Recrystallisation of a portion of this solid from 2-methyl-1-propanol gave a

colourless powder, m.p. 70-71°C. ^{1}H NMR δ: 6.92 (s, ArH), 6.58 (s, ArH), 3.85 (s, 2OCH$_3$), 3.22-3.17 (m, H1), 2.83-2.72 (m, H3, H4), 2.55 (s, NCH$_3$), 1.02-0.96 (m, H1'), 0.71-0.66 (m, H2'), 0.48-0.44 (m, H3'); ^{13}C NMR δ: 148.10 (C6^A), 147.37 (C7^A), 130.63 (C4a^B), 126.85 (C8a^B), 111.78 (C5^C), 111.12 (C8^C), 67.86 (C1), 56.47 (OCH$_3$), 56.34 (OCH$_3$), 49.66 (C3), 43.23 (NCH$_3$), 26.80 (C4), 15.76 (C1'), 5.21 (C2'), 4.47 (C3'); MS m/z: 247 (M$^+$, 1%; Calcd. for C$_{15}$H$_{21}$NO$_2$ 247.1572, found 247.1579), 207 (13), 206 (100), 190 (8), 162 (3), 145 (2); Anal. Calcd for C$_{15}$H$_{21}$NO$_2$: C, 72.84; H, 8.56; N, 5.66%, found: C, 72.59; H, 8.51; N, 5.69%; IR: 2932, 1516, 1256, 1016 cm^{-1}. The *methiodide salt* of **177a** recrystallised from methanol with m.p. 212-213°C. Anal. Calcd for C$_{16}$H$_{24}$NO$_2$I: C, 49.37; H, 6.21; N, 3.60%, found: C, 49.36; H, 6.34; N, 3.70%.

6,7-Dimethoxy-2-methyl-1-(*t*-2-phenylcyclopropyl)-1,2,3,4-tetrahydroisoquinoline 177b

The 1-(2'-phenylcyclopropyl) imine **175b** (1.140 g, 3.709 mmol) was stirred at room temperature in dry acetone (10 ml) with iodomethane (0.576 g, 4.06 mmol) protected from light for 3 days. Concentration of the solution gave a dark residue which was suspended in dry ethanol (20 ml) at 0°C and treated with sodium borohydride (0.42 g, 11 mmol) portionwise over 30 min. The solution was allowed to warm with stirring over 2 h. then concentrated. The residue was partitioned between water (7 ml) and chloroform (30 ml). The chloroform layer was separated and washed with water (3 x 6 ml), then dried and concentrated to give a tan oil (1.121 g). Purification of this oil by column chromatography on silica with chloroform/0-2% methanol gave a mixture (55:45) of the *SSS* and *RSS* diastereomers of **177b** (0.628 g, 52%). Further purification of a portion (268 mg) of this mixture by p.t.l.c. on silica with dichloromethane/10% methanol gave:

(a) *SSS-1-(2'-phenylcyclopropyl)tetrahydroisoquinoline* **177b** (87 mg) as colourless needles from hexane, with m.p. 109-110°C. ^{1}H NMR δ: 7.27-7.22 (m, 2ArH"), 7.17-7.14 (m, ArH"), 7.07-7.03 (m, 2ArH"), 6.90 (s, ArH), 6.59 (s, ArH), 3.85 (s,

OCH$_3$), 3.84 (s, OCH$_3$), 3.10-3.06 (m, 1H, H1), 2.79 (t, 2H), 2.81-2.77 (m, 1H), 2.53 (s, NCH$_3$), 1.97-1.92 (m, H2'), 1.47-1.40 (m, H1'), 1.17-1.11 (m, H3'); ^{13}C NMR δ: 148.25 (C6^A), 147.42 (C7^A), 143.09 (C8a^B), 130.43 (C4a^B), 128.86 (2C"), 126.99 (C1"^{B}), 126.14 (3C"), 111.86 (C5^C), 110.98 (C8^C), 67.15 (C1), 56.53 (OCH$_3$), 56.32 (OCH$_3$), 49.79 (C3), 43.81 (NCH$_3$), 27.81 (C4), 27.44 (C1'^{D}), 23.75 (C2'^{D}), 15.34 (C3'); MS m/z: 323 (M$^+$, 2%; Calcd. for C$_{21}$H$_{25}$NO$_2$ 323.1885, found 323.1879), 305 (8), 219 (14), 206 (100), 190 (8); Anal. Calcd for C$_{21}$H$_{25}$NO$_2$: C, 77.98; H, 7.79; N, 4.33 %, found: C, 78.33; H, 7.7.78; N, 4.26.

(b) *RSS-1-(2'-phenylcyclopropyl)tetrahydroisoquinoline* **177b** (69 mg) as colourless needles from hexane, with m.p. 100-101°C. ^{1}H NMR δ: 7.26-7.20 (m, 2ArH"), 7.15-7.13 (m, ArH"), 7.10-7.06 (m, 2ArH"), 6.88 (s, ArH), 6.55 (s, ArH), 3.82 (s, OCH$_3$), 3.57 (s, OCH$_3$), 3.19-3.14 (m, 1H), 3.03 (d, J 8.6 Hz, H1), 2.83-2.74 (m, 3H), 2.58 (s, NCH$_3$), 2.01-1.97 (m, H2'), 1.37-1.33 (m, H1'), 1.21-1.10 (m, H3'); ^{13}C NMR δ: 148.14 (C6^A), 147.53 (C7^A), 143.01 (C8a^B), 129.90 (C4a^B), 128.97 (2C"), 126.78 (C1"^{B}), 126.42 (3C"), 111.79 (C5^C), 110.82 (C8^C), 67.74 (C1), 56.36 (OCH$_3$), 56.24 (OCH$_3$), 50.72 (C3), 42.98 (NCH$_3$), 27.85 (C1'^{D}), 26.83 (C4), 23.51 (C2'^{D}), 16.24 (C3'); MS m/z: 323 (M$^+$, 1%; Calcd. for C$_{21}$H$_{25}$NO$_2$ 323.1885, found 323.1875), 305 (3), 219 (8), 206 (100), 190 (9); Anal. Calcd for C$_{21}$H$_{25}$NO$_2$: C, 77.98; H, 7.79; N, 4.33 %, found: C, 78.24; H, 7.82; N, 4.34.

1-Cyclopropyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline N-oxide 178a

To the 1-cyclopropyltetrahydroisoquinoline **177a** (1.46 g, 5.90 mmol) in dichloromethane (25 ml) at 0°C was added a solution of *m*-CPBA (1.40 g, 8.14 mmol) in dichloromethane (15 ml) dropwise. The solution was allowed to warm and stirred for 21 h. before the addition of 5% aqueous sodium bicarbonate (45 ml) and removal of the organic solvent *in vacuo*. The aqueous solution was washed with diethyl ether (3 x 20 ml) then concentrated to 10 ml and extracted with chloroform (3 x 30 ml). Drying and then concentration of the ether extracts provided a yellow

solid (32.6 mg). Drying and then concentration of the chloroform extracts gave a mixture (53:47) of the B-ring diastereomers of *1-cyclopropyltetrahydroisoquinoline N-oxide* **178a** (1.38 g, 89%) as a pale yellow hygroscopic solid. ^{1}H NMR δ: 3.42 and 3.24 (s, NCH_3); ^{13}C NMR δ: 149.71 and 149.19 (C6^A), 148.14 and 147.94 (C7^A), 125.68 (C4a^B), 123.35 and 123.08 (C8a^B), 111.62 (C5^C), 111.49 (C8^C), 81.43 and 78.12 (C1), 60.79 and 60.30 (C3), 56.87 (NCH_3), 56.61 (OCH_3), 56.48 (OCH_3), 26.95 and 25.78 (C4), 15.58 and 11.45 (C1'), 7.42 and 4.84 (C2'), 2.88 and 2.74 (C3').

6,7-Dimethoxy-2-methyl-1-(*t*-2-phenylcyclopropyl)-1,2,3,4-tetrahydroisoquinoline *N*-oxide **178b**

To a mixture (*SSS/RSS*=0.47) of the 1-(2'-phenylcyclopropyl)tetrahydro-isoquinoline diastereomers of **177b** (0.947 g, 2.93 mmol) in dichloromethane (30 ml) at 0°C was added a solution of *m*-CPBA (0.70 g, 4.1 mmol) in dichloromethane (25 ml) dropwise. The solution was allowed to warm and stirred for 40 h. before the addition of water (20 ml) and the removal of the organic solvent *in vacuo*. The residual aqueous mixture was basified with potassium carbonate then washed with diethyl ether (4 x 10 ml). Drying and then concentration of the ether washes provided a yellow solid (0.041 g) containing mainly **177b**. The aqueous layer was made just acidic to litmus with 3M aqueous hydrochloric acid and washed with diethyl ether (4 x 10 ml), then rebasified with potassium carbonate, saturated with sodium chloride, and extracted with chloroform (4 x 10 ml). The extracts were dried and then concentrated to give a crude mixture of the four possible diastereomers of the *1-(2'-phenylcyclopropyl) N-oxide* **178b** (0.834 g, 84%) as a pale yellow hygroscopic solid. ^{13}C NMR δ: four peaks between 81-76 ppm (C1), four peaks between 65-60 ppm (C3), four peaks between 17-12 ppm (C2').

1-Cyclopropyl-6,7-dimethoxy-2-ethoxycarbonylmethyl-2-methyl-1,2,3,4-tetrahydroisoquinolinium Bromide 179a

To the 1-cyclopropyltetrahydroisoquinoline **177a** (2.027 g, 8.195 mmol) in dry acetone (15 ml) was added ethyl bromoacetate (4.2 g, 25 mmol). The solution was refluxed for 8 h. then concentrated. The gummy residue was triturated with diethyl ether (3 x 10 ml) then dissolved in ethanol (20 ml), concentrated, and triturated with further diethyl ether (2 x 10 ml). The residue was dried at 80°C under oil pump vacuum to afford a mixture (55:45) of the B-ring diastereomers of the *isoquinolinium salt* **179a** (2.95 g, 87%), as an off-white powder. ^{1}H NMR δ: 3.82 and 3.59 (s, NCH$_3$); ^{13}C NMR δ: 165.75 and 165.46 (CO), 150.05 (C6^A), 148.72 and 148.51 (C7^A), 122.53 and 121.98 (C4a^B), 121.06 and 120.84 (C8a^B), 111.35 (C5 and C8), 75.16 and 74.65 (C1), 63.18 (CH$_2$ of CH$_2$CH$_3$), 60.36 and 56.79 (CH$_2^C$ of CH$_2$CO), 56.45 (2OCH$_3$), 55.13 and 54.28 (C3^C), 49.03 and 47.19 (NCH$_3$), 24.12 and 23.60 (C4), 14.28 (CH$_3$ of CH$_2$CH$_3$), 13.87 and 13.43 (C1'), 8.67 and 7.81 (C2'), 4.66 and 4.47 (C3').

6,7-Dimethoxy-2-ethoxycarbonylmethyl-2-methyl-1-(t-2-phenylcyclopropyl)-1,2,3,4-tetrahydroisoquinolinium Bromide 179b

To the predominantly *SSS* diastereomer of **177b** (172 mg, 0.532 mmol, *SSS/RSS*=19) in dry acetone (2 ml) was added ethyl bromoacetate (0.75 g, 4.5 mmol). The solution was refluxed for 6 h. then concentrated. The gummy residue was triturated with diethyl ether (3 x 3 ml) then dissolved in water (5 ml). The aqueous solution was washed with diethyl ether (2 x 3 ml), removing some yellow colour. The aqueous solution was then saturated with sodium chloride and extracted with chloroform (3 x 3 ml). Drying and then concentration of the extracts gave the crude *isoquinolinium salt* **178b** (225 mg, 90%), as a tan powder. ^{1}H and ^{13}C NMR analyses generally supported the presence of two B-ring diastereomers, however, the peaks were broad and often overlapping, preventing their assignment.

8,9-Dimethoxy-4-methyl-3-phenyl-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinolinium Iodide **180**

(i) To the crude 1-(2'-phenylcyclopropyl) imine **175b** (8.11 g, 26.4 mmol) in dry acetone (70 ml) was added iodomethane (11.2 g, 79.4 mmol). The mixture was refluxed for 4 h. The resultant yellow precipitate was collected and washed with cold acetone, then dried to give the *tetrahydropyrrolo[2,1-a]isoquinolinium salt* **180** (3.82 g, 32%). Concentration of the filtrate afforded crude **176b** (7.37 g, 62%). The recrystallisation of **180** gave colourless needles from methanol, m.p. 168-170°C, or pale yellow prisms from acetonitrile, m.p. 175-178°C. Satisfactory elemental microanalysis results could not be obtained from either crystal type. ^{1}H NMR δ (d_6-DMSO): 7.58-7.49 (m, 5ArH'), 7.44 (s, H10), 7.18 (s, H1), 6.90 (s, H7), 5.52 (d, *J* 7.2 Hz, H3), 3.87 (s, OCH$_3$), 3.80 (s, OCH$_3$), 3.87-3.76 (m, H2), 3.50-3.43 (m, H5), 3.43 (s, NCH$_3$), 3.32-3.22 (m, H6), 3.15 (dd, *J* 3.8 Hz, 18.4 Hz, H2), 3.00 (dd, *J* 4.1 Hz, 18.3 Hz, H6), 2.55-2.46 (m, H5); ^{13}C NMR δ (d_6-DMSO): 156.39 (C8^A), 154.40 (C9^A), 146.19 (C10b^B), 138.90 (C10a^B), 136.50 (C'), 135.08 (4C'), 129.04 (C1^B), 123.72 (C10), 121.14 (C6a^B), 116.95 (C1), 114.08 (C7), 85.01 (C3), 61.85 (OCH$_3$), 61.52 (OCH$_3$), 60.58 (C5), 54.83 (NCH$_3$), 39.76 (C2), 29.51 (C6); MS m/z: 322 (M$^+$-I, 5%), 321 (25), 307 (M$^+$-CH$_3$I, 88; Calcd. for C$_{20}$H$_{21}$NO$_2$ 307.1572, found 307.1565), 306 (100), 290 (13), 230 (27), 142 (33); IR (KBr disc): 1609, 1512, 1265, 1018 cm^{-1}.

(ii) The 1-(*t*-2-phenylcyclopropyl)isoquinoline salt **176b** (110 mg) was refluxed in dry acetone (5 ml) for 24 h. then the solution was cooled. Collection of the precipitate afforded **180** (74 mg, 64%).

Investigation of the Cloke Rearrangement of the 1-(2'-Phenylcyclopropyl) Imine **175b** to **181**

(i) To crude **175b** (0.890 g, 2.89 mmol) in dry xylene (50 ml) was added ammonium chloride (2.0 g, 38 mmol). The mixture was refluxed for 2.6 h. then cooled and water (10 ml) and solid potassium carbonate were added to afford a basic aqueous

layer. The xylene layer was separated and washed with water (2 x 5 ml) then saturated aqueous sodium chloride (5 ml). Concentration of the xylene solution afforded a tan film (0.582 g) which, when analysed by t.l.c. and GC-MS, showed the presence of numerous compounds.

(ii) A mixture of crude **175b** (0.355 g, 1.15 mmol) and ammonium chloride (0.090 g, 1.7 mmol) was heated at 160-170°C for 3 h. under a slow flow of nitrogen. The residue was then extracted with dichloromethane. The extracts were filtered and then concentrated to afford a film which, when analysed by t.l.c. and GC-MS, showed the presence of numerous unidentified compounds.

(iii) A mixture of crude **175b** (0.371 g, 1.21 mmol) and ammonium chloride (0.090 g, 1.7 mmol) was heated at 195-200°C for 40 min. in a sealed tube under nitrogen. Work-up of the reaction as for (ii) afforded an unidentified mixture of numerous compounds.

1-Cyclopropyl-7,8-dimethoxy-3-methyl-1,3,4,5-tetrahydro-2,3-benzoxazepine 182a

A solution of N-oxide **178a** (188 mg, 0.714 mmol) in butyronitrile/mesitylene (1:5 mixture, 25 ml) was refluxed at 143°C for 12 h. then concentrated. Passage of the residue through an alumina plug as a diethyl ether solution afforded, after concentration, a yellow oil (147 mg) which was purified by p.t.l.c. on silica with dichloromethane/5% ethanol to give the *1-cyclopropyl-2,3-benzoxazepine* **182a** (96 mg, 51%) as a colourless oil. ^{1}H NMR δ: 6.77 (s, ArH), 6.67 (s, ArH), 4.35 (d, J 8.5 Hz, H1), 3.87 (s, OCH$_3$), 3.85 (s, OCH$_3$), 3.30-3.27 (m, 1H), 3.09-3.01 (m, 1H), 2.89-2.74 (m, 2H), 2.70 (s, NCH$_3$), 1.26-1.19 (m, H1'), 0.69-0.60 (m, 2H'), 0.56-0.50 (m, 1H'), 0.45-0.41 (m, 1H'); ^{13}C NMR δ: 148.00 (C7^A), 147.71 (C8^A), 134.35 (C9a^B), 129.81 (C5a^B), 114.38 (C6^C), 110.99 (C9^C), 89.93 (C1), 60.54 (C4), 56.66 (OCH$_3$), 56.60 (OCH$_3$), 47.25 (NCH$_3$), 33.72 (C5), 15.74 (C1'), 4.11 (C2'^{D}), 3.78 (C3'^{D}); MS m/z: 263 (M$^+$, 57%; Calcd. for C$_{15}$H$_{20}$NO$_3$ 263.1521, found 263.1516), 246 (18), 217 (14), 204 (100), 189 (75), 173 (57).

Investigation of the Conditions Necessary for the Rearrangement of *N*-Oxide **178a**

(i) A solution of **178a** (310 mg) in dry acetonitrile (25 ml) was refluxed under nitrogen for 3 h. then concentrated. Examination of the residue by t.l.c. and ^{1}H NMR techniques showed the material was unchanged **178a**.

(ii) A solution of **178a** (310 mg) in dry acetonitrile (25 ml) was heated in a sealed tube at 111°C for 6 h. then concentrated. The residue was extracted with diethyl ether (3 x 10 ml). The ether extracts were washed with water (2 x 5 ml) then dried and concentrated to afford **182a** (7 mg, 2%).

(iii) Compound **178a** (303 mg) was heated in a butyronitrile (4 ml) and xylene (20 ml) mixture at 130°C for 5 h. Workup as for (ii) gave **182a** (54 mg, 18%).

(iv) Compound **178a** (110 mg) was heated at 215°C in an evacuated sealed tube for 15 min. The resultant dark oil was taken up in diethyl ether and eluted through an alumina plug. Concentration of the eluant afforded an oil (0.047 g, 42%) which contained **182a** and an unidentified isomer (ratio 60:40) with the following distinctive spectral peaks. ^{1}H NMR δ: 6.87 (s, ArH), 6.55 (s, ArH), 4.93 (d, *J* 4.7 Hz, 1H), 2.52 (s, NCH$_3$); ^{13}C NMR δ: 15.20 (C1'), 5.01 (C2'A), 4.51 (C3'A); MS m/z: 263 (M$^+$, 1%), 248 (3), 206 (100), 190 (16), 162 (4), 103 (2).

(v) A solution of **178a** (159 mg) in acetonitrile (200 ml) was irradiated with UV light passed through a duran glass sleeve (≥300 nm) for 1 h. Concentration and then examination of the residue by t.l.c. and ^{1}H NMR analysis showed the original material was unchanged.

(vi) A solution of **178a** (159 mg) in acetonitrile (220 ml) was irradiated with UV light passed through a vycor glass sleeve (≥230 nm) for 50 min. then concentrated. The resultant dark solid was taken up in diethyl ether and eluted through an alumina plug. Concentration afforded a solid (24 mg, 15%) which contained **182a** (18%) and two other components detected by GC-MS analysis. The major component (65%) had a MS pattern identical to that of **175a**.

<u>7,8-Dimethoxy-3-methyl-1-(*t*-2-phenylcyclopropyl)-1,3,4,5-tetrahydro-2,3-</u>

<u>benzoxazepine **182b**</u>

A solution of *N*-oxide **178b** (303 mg, 0.894 mmol) in butyronitrile (5 ml) and

mesitylene (25 ml) was refluxed at 143°C for 90 min. then concentrated and the dark

residue taken up in diethyl ether (30 ml). The organic solution was washed with

water (3 x 7 ml) then saturated aqueous sodium chloride (7 ml). Drying and then

concentration of the ether solution afforded a mixture (55:33:12) of three

components (0.256 g). Purification of this mixture by preparative reverse phase

HPLC with acetonitrile/25% water gave:

(a) at 17.04 min., the *SSS 1-(2'-phenylcyclopropyl)-2,3-benzoxazepine* **182b** (71 mg,

23%) as a colourless solid which crystallised from methanol, m.p. 102-103°C. ^{1}H

NMR δ: 7.28-7.23 (m, 2ArH"), 7.17-7.11 (m, 3ArH"), 6.78 (s, ArH), 6.68 (s, ArH),

4.78 (d, *J* 6.7 Hz, H1), 3.86 (s, OCH$_3$), 3.71 (s, OCH$_3$), 3.20-3.10 (m, 1H), 3.08-

2.98 (m, 1H), 2.96-2.86 (m, 1H), 2.85-2.78 (m, 1H), 2.67 (s, NCH$_3$), 2.08-2.01 (m,

H2'), 1.62-1.54 (m, H1'), 1.17-1.06 (m, 2H3'); ^{13}C NMR δ: 148.05 (C7^A), 147.66

(C8^A), 143.37 (C1"), 134.34 (C5a^B), 130.89 (C9a^B), 128.95 (2C"), 126.53 (2C"),

126.21 (1C"), 114.46 (C6^C), 110.90 (C9^C), 86.97 (C1), 60.67 (C4), 56.64 (OCH$_3$),

56.42 (OCH$_3$), 47.43 (NCH$_3$), 34.47 (C5), 26.99 (C2'^{D}), 21.54 (C1'^{D}), 14.07 (C3');

MS m/z: 339 (M$^+$, 3%), 305 (4), 280 (98), 249 (15), 206 (44), 189 (100); Anal.

Calcd for C$_{21}$H$_{25}$NO$_3$: C, 74.31; H, 7.42; N, 4.13%, found: C, 74.21; H, 7.35; N,

4.37%.

(b) at 19.34 min., the *RSS 1-(2'-phenylcyclopropyl)-2,3-benzoxazepine* **182b** (83 mg,

27%) as a colourless solid which crystallised from methanol, m.p. 90-91°C. ^{1}H

NMR δ: 7.25-7.20 (m, 2ArH"), 7.15-7.05 (m, 3ArH"), 6.76 (s, ArH), 6.66 (s, ArH),

4.53 (d, *J* 8.6 Hz, H1), 3.84 (s, OCH$_3$), 3.55 (s, OCH$_3$), 3.12-2.89 (m, 3H), 2.88-

2.79 (m, 1H), 2.74 (s, NCH$_3$), 1.97-1.94 (m, H2'), 1.60-1.50 (m, H1'), 1.27-1.16 (m,

2H3'); ^{13}C NMR δ: 147.91 (C7^A), 147.58 (C8^A), 142.62 (C1"), 134.35 (C5a^B),

130.56 (C9a^B), 128.98 (2C"), 126.38 (3C"), 114.40 (C6^C), 110.66 (C9^C), 88.78

(C1), 60.59 (C4), 56.58 (OCH$_3$), 56.10 (OCH$_3$), 47.61 (NCH$_3$), 34.61 (C5), 27.95

(C2'^{D}), 22.72 (C1'^{D}), 14.89 (C3'); Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13%, found: C, 74.30; H, 7.33; N, 4.37.%.

(c) at 26.98 min., the 4,3-benzoxazecine **183b** (27 mg, 9%) described below.

10,11-Dimethoxy-3-methyl-5-phenyl-*1H*-2,3,5,6-tetrahydro-4,3-benzoxazecine **183b**

The preparation of **182b** described above gave the *4,3-benzoxazecine* **183b** (27 mg, 9%) as a colourless solid which crystallised from methanol, m.p. 146-148°C. ^{1}H NMR δ: 7.42-7.26 (m, 5ArH'), 6.78 (s, ArH), 6.69 (s, ArH), 6.65 (d, *J* 16.0 Hz, H8), 5.80-5.65 (m, H7), 4.52 (dd, *J* 3.2 Hz, 11.1 Hz, H5), 3.88 (s, OCH$_3$), 3.86 (s, OCH$_3$), 3.45-3.35 (m, 1H), 3.12-3.04 (m, 2H), 2.62 (s, NCH$_3$), 2.59-2.39 (m, 1H and 2H6); ^{13}C NMR δ: 148.00 (C10^A), 147.86 (C11^A), 143.90 (C1'), 134.45 (C8^B), 132.69 (C8a^C), 132.48 (C12a^C), 132.25 (C7^B), 128.97 (2C'), 127.83 (1C'), 126.59 (2C'), 113.84 (C9^D), 111.48 (C12^D), 84.16 (C5), 59.34 (C2), 56.66 (2OCH$_3$), 45.52 (NCH$_3$), 41.80 (C6), 28.01 (C1); MS m/z: 339 (M$^+$, 6%; Calcd. for $C_{21}H_{25}NO_3$ 339.1834 found 339.1815), 322 (2), 280 (54), 232 (10), 206 (100), 189 (73); Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13%, found: C, 74.27; H, 7.41; N, 4.33%; IR (thin film from CDCl$_3$): 1508, 1109, 700 cm^{-1}.

Other Thermolyses of the *N*-Oxide **178b**

(i) A solution of **178b** (288 mg) in dry acetonitrile (25 ml) was refluxed under nitrogen for 60 h. then concentrated. The residue was taken up in diethyl ether (30 ml) and the solution was washed with water (3 x 7 ml) and saturated aqueous sodium chloride (7 ml) then dried and concentrated to afford a yellow oil (141 mg, 49%). ^{1}H NMR analysis confirmed the oil contained *RSS*-**182b**, *SSS*-**182b** and **183b** (56:33:11).

(ii) A solution of **178b** (267 mg) in dry butyronitrile (25 ml) was refluxed under nitrogen for 2.5 h. Workup as for (i) afforded a yellow oil (129 mg, 48%) which contained *RSS*-**182b**, *SSS*-**182b** and **183b** (52:35:13).

Thermolysis of the 1-(2'-Phenylcyclopropyl)-2,3-benzoxazepine 182b

A diastereomeric mixture (*SRR/SSS*=1.5) of **182b** (0.168 g, 0.495 mmol) was heated in an evacuated sealed tube at 210°C for 30 min. ^{1}H NMR analysis of the resultant oil confirmed the original material was unchanged.

Ethyl 1-Cyclopropyl-7,8-dimethoxy-3-methyl-1,2,4,5-tetrahydro-*3H*-
3-benzazepine-2-carboxylate 184a

To the 1-cyclopropyl salt **179a** (243 mg, 0.586 mmol) in butyronitrile (25 ml) at reflux was added DBU (0.13 ml, 0.87 mmol). The solution was refluxed for 8.5 h. then concentrated. Application of the residue to an alumina column and elution with dichloromethane/10% light petroleum (100 ml) gave, upon concentration, a dark oil (176 mg). Purification of this oil by p.t.l.c. on silica with dichloromethane/5% ethanol gave:

(a) the *trans*-butadiene isomer of **83b** (9 mg, 5%).

(b) the major B-ring diastereomer of the *1-cyclopropyl-3-benzazepine* **184a** (88 mg, 45%) as a white waxy solid. ^{1}H NMR δ: 6.75 (s, ArH), 6.64 (s, ArH), 4.08 (q, CH$_2$ of CH$_2$CH$_3$), 3.85 (s, 2OCH$_3$), 3.51 (d, *J* 6.9 Hz, H2), 3.24-3.18 (m, 1H), 3.03-2.94 (m, 1H), 2.86-2.78 (m, 1H), 2.74-2.66 (m, 1H), 2.49 (s, NCH$_3$), 2.36-2.28 (m, 1H), 1.43-1.38 (m, H1'), 1.22 (t, CH$_3$ of CH$_2$CH$_3$), 0.68-0.64 (m, H2'), 0.59-0.52 (m, H2'), 0.30-0.50 (m, H3'), 0.17-0.10 (m, H3'); ^{13}C NMR δ: 173.01 (CO), 147.89 (C7^A), 147.50 (C8^A), 133.17 (C9a^B), 132.89 (C5a^B), 113.43 (C6^C), 113.18 (C9^C), 70.06 (C2), 60.51 (CH$_2$ of CH$_2$CH$_3$), 56.74 (OCH$_3$), 56.51 (OCH$_3$), 53.00 (C1), 51.05 (C4), 46.47 (NCH$_3$), 34.76 (C5), 15.18 (CH$_3$ of CH$_2$CH$_3$), 13.84 (C1'), 6.76 (C2'^{D}), 5.44 (C3'^{D}); MS m/z: 333 (M$^+$, 5%; Calcd. for C$_{19}$H$_{27}$NO$_4$ 333.1940, found 333.1929), 260 (100), 204 (5), 189 (4), 130 (8).

(c) the *cis*-butadiene isomer of **83b** (28 mg, 14%).

(d) the minor B-ring diastereomer of the *1-cyclopropyl-3-benzazepine* **184a** (34 mg, 17%) as a white waxy solid. ^{1}H NMR δ: 7.00 (s, ArH), 6.63 (s, ArH), 3.89 (q, CH$_2$ of CH$_2$CH$_3$), 3.86 (bs, 2OCH$_3$ and 1H), 3.31 (t, 1H), 3.06 (t, 1H), 2.79-2.72 (m, 1H),

2.65-2.56 (m, 1H), 2.54 (s, NCH$_3$), 2.41 (d, J 10.3 Hz, 1H), 1.71-1.64 (m, H1'), 1.07 (t, CH$_3$ of CH$_2$CH$_3$), 0.77-0.72 (m, H2'), 0.47-0.43 (m, H3'), 0.18-0.13 (m, H3'); ^{13}C NMR δ: 171.99 (CO), 147.74 (C7^A), 147.46 (C8^A), 134.03 (C9a^B), 133.13 (C5a^B), 113.00 (C6^C), 111.62 (C9^C), 70.04 (C2), 60.28 (CH$_2$ of CH$_2$CH$_3$), 56.83 (OCH$_3$), 56.55 (OCH$_3$), 52.33 (C1), 51.19 (C4), 45.76 (NCH$_3$), 35.92 (C5), 15.06 (CH$_3$ of CH$_2$CH$_3$), 14.58 (C1'), 7.06 (C2'^{D}), 6.60 (C3'^{D}); MS m/z: 333 (M$^+$, 4%; Calcd. for C$_{19}$H$_{27}$NO$_4$ 333.1940, found 333.1929), 260 (100), 204 (5), 189 (5), 130 (10).

Other Treatments of the 1-Cyclopropyl-2-ethoxycarbonylmethyl Salt **179a** by Base

(i) To **179a** (347 mg, 0.837 mmol) in dry acetonitrile (25 ml) under nitrogen was added DBU (0.15 ml, 1.0 mmol). The solution was stirred for 60 h. then concentrated. Analysis of the residue by t.l.c. and GC-MS techniques confirmed no reaction had occurred.

(ii) To **179a** (360 mg, 0.869 mmol) in dry acetonitrile (25 ml) under nitrogen at 40°C was added dropwise a solution of 1.6M butyl lithium in hexane (0.70 ml, 1.1 mmol). A small amount of solid formed. The mixture was stirred for 44 h. at 40°C then concentrated and the residue was extracted with diethyl ether (4 x 10 ml). Concentration of the extracts gave a dark oil (72 mg, 26%). Analysis of the oil by ^{1}H NMR and GC-MS techniques confirmed that only the diastereomers of **184a** and **83b** were present.

(iii) To **179a** (303 mg, 0.731 mmol) in dry acetonitrile (25 ml) at 40°C was added DBU (0.52 ml, 3.4 mmol). The solution was stirred for 48 h. at 40°C before workup as for (ii) to give a dark oil (30 mg, 12%). Analysis of the oil by ^{1}H NMR and GC-MS techniques confirmed that only the diastereomers of **184a** and **83b** were present.

(iv) To **179a** (265 mg, 0.639 mmol) in chloroform (25 ml) at reflux under nitrogen was added DBU (0.12 ml, 0.83 mmol). The solution was refluxed for 67 h. before workup as for (ii) to give a dark oil (107 mg, 50%). Analysis of the oil by ^{1}H NMR

and GC-MS techniques confirmed that only the diastereomers of **184a** and **83b** were present.

(v) To **178a** (317 mg, 0.765 mmol) in dry acetonitrile (25 ml) at reflux under nitrogen was added DBU (0.15 ml, 0.99 mmol). The solution was refluxed for 5 h. then concentrated. Application of the residue to an alumina column and elution with dichloromethane/10% light petroleum (100 ml) gave, after concentration, a colourless oil (123 mg). Purification of this oil by p.t.l.c. on silica with dichloromethane/5% ethanol gave the diastereomers of **184a** (82 mg, 32%; 23 mg, 9%) and **83b** (21 mg, 8%; 10 mg, 4%).

Ethyl 7,8-Dimethoxy-3-methyl-1-(t-2-phenylcyclopropyl)-1,2,4,5-tetrahydro-*3H*-3-benzazepine-2-carboxylate **184b**

To the 1-(2'-phenylcyclopropyl) salt **179b** (225 mg, 0.459 mmol) in dry butyronitrile (25 ml) at reflux was added DBU (0.10 g, 0.66 mmol). The solution was refluxed for 8.5 h. then concentrated. Application of the residue to an alumina column and elution with dichloromethane/10% light petroleum (130 ml) gave, upon concentration, a dark oil (132 mg, 67%). Purification of this oil by preparative reverse phase HPLC with acetonitrile/25% water gave:

(a) at 14.12 min., a colourless film (2 mg, 1%) approximately 90% pure. The material was not identified. The ^1H NMR spectrum was inconsistent with that expected for **185b**.

(b) at 19.20 min., a mixture (1.66:1) of the B-ring diastereomers of *1-(2'-phenylcyclopropyl)-3-benzazepine* **184b** (60 mg, 31%) as a colourless oil with the following distinguishable NMR peaks. ^1H NMR δ: 7.27-7.11 (m, 4ArH"), 7.02-7.01 (m, ArH"), 6.82 and 6.66 (s, ArH), 6.64 (s, ArH), 3.88 and 3.86 (s, OCH$_3$), 3.84 (s, OCH$_3$), 2.43 and 2.42 (s, NCH$_3$), 1.32 and 1.08 (t, CH$_3$ of CH$_2$CH$_3$); ^{13}C NMR δ: 173.15 and 172.89 (CO), 147.77 (C7^A), 147.60 (C8^A), 133.02 and 132.75 (C9a^B), 143.38 (C1"), 132.49 and 132.33 (C5a^B), 128.92 (2C"), 126.87 (C"), 126.19 (2C"), 113.41 and 113.00 (C6^C), 112.84 and 112.01 (C9^C), 70.55 and 69.86 (C2), 60.79

and 60.64 (CH_2 of CH_2CH_3), 56.78 and 55.96 (OCH_3), 56.48 (OCH_3), 52.06 (C1), 51.21 and 50.80 (C4), 46.29 and 45.92 (NCH_3), 34.59 and 33.94 (C5), 26.98 and 25.59 (C2"D), 25.08 and 23.59 (C1"D), 17.85 and 16.15 (C3"), 15.22 and 14.92 (CH_3 of CH_2CH_3).

(c) at 29.94 min., a colourless film (4 mg, 2%) approximately 90% pure. The material was not identified. The ^{1}H NMR spectrum was inconsistent with that expected for **185b**.

(d) at 37.70 min., a colourless film (9 mg, 4%) approximately 90% pure. The material was not identified. The ^{1}H NMR spectrum was inconsistent with that expected for **185b**.

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APPENDIX

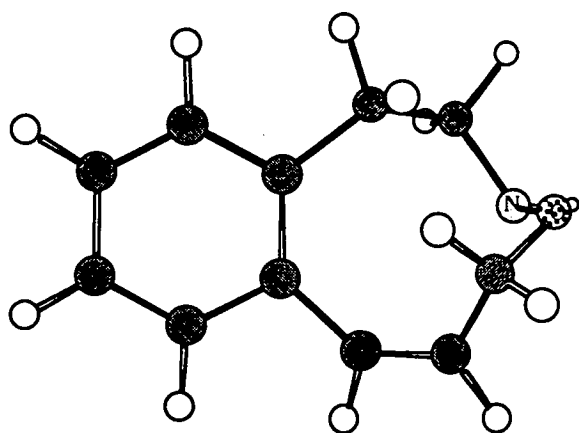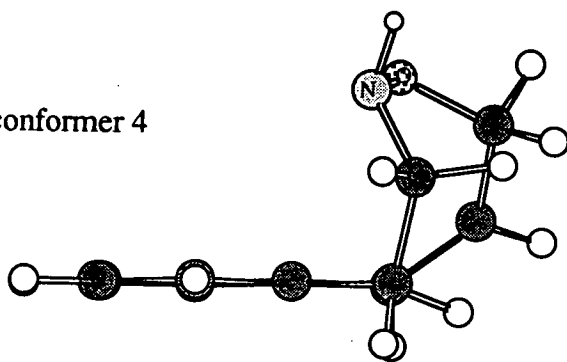## 1. Conformational Modelling of the *E*-2,3,4,5-Tetrahydro-1*H*-3-Benzazonines

The molecular modelling of the parent *E*-2,3,4,5-tetrahydro-1*H*-3-benzazonine derivative (Section 2.3.4) afforded five low energy conformations, described in Table 2.4. The structures determined for conformers 2, 3, and 5 are shown below, with three perspectives of each conformation.
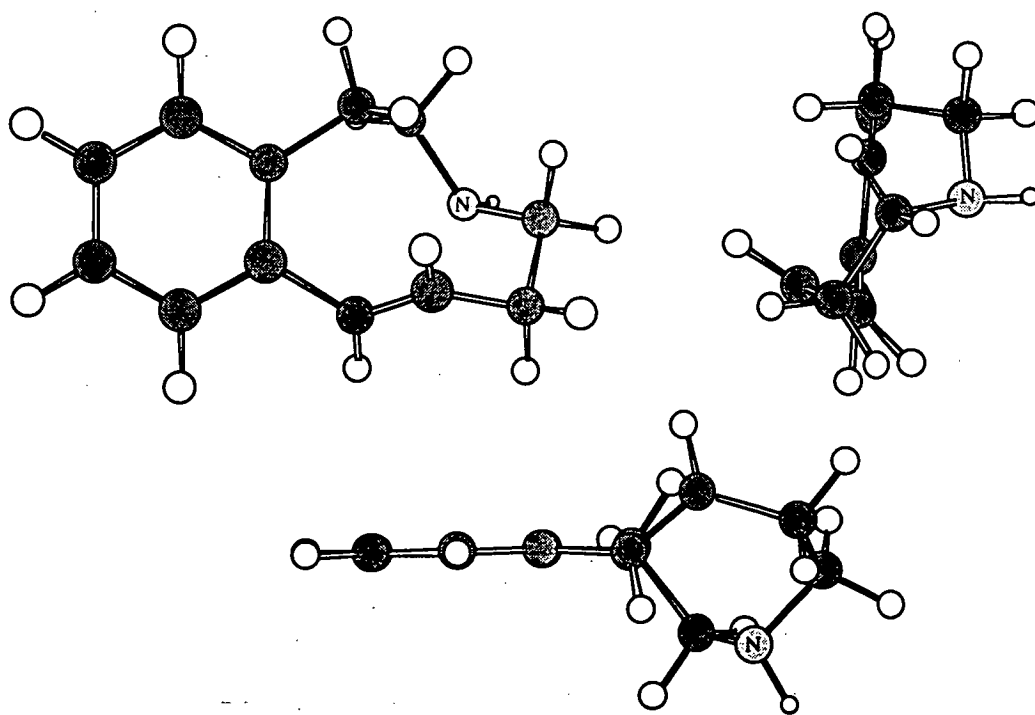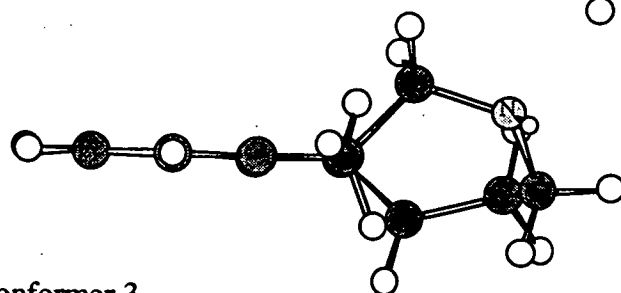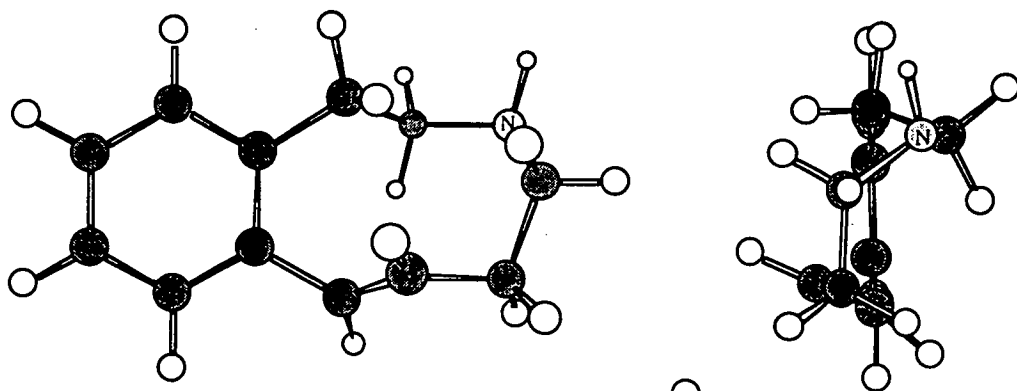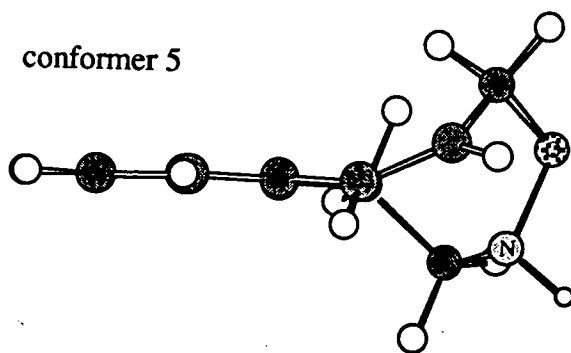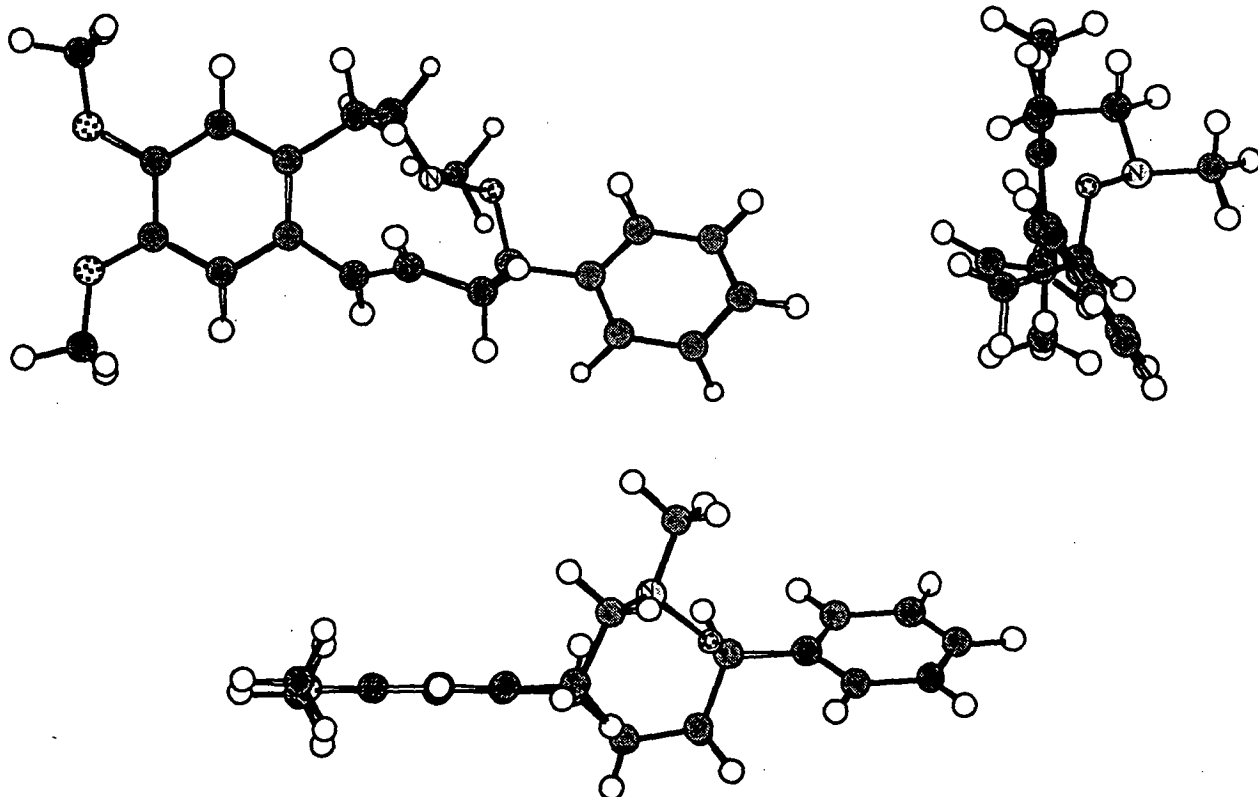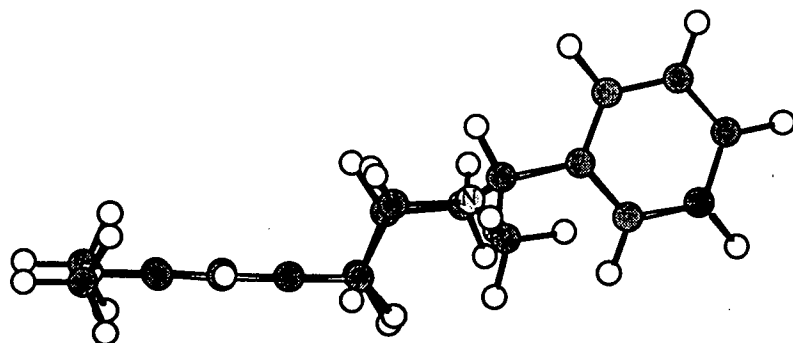

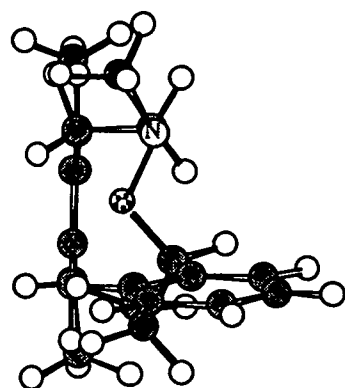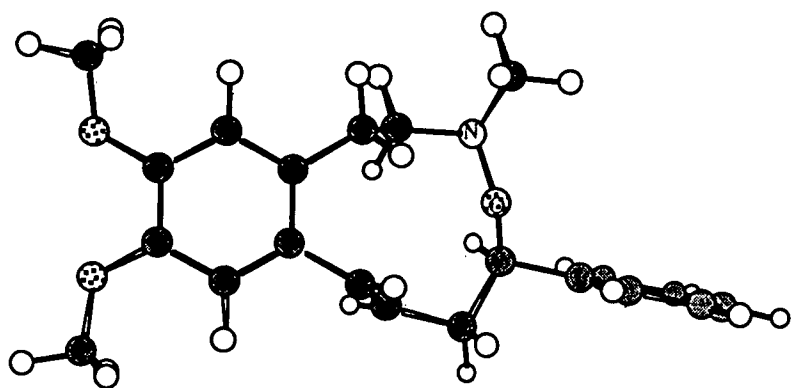conformer 2
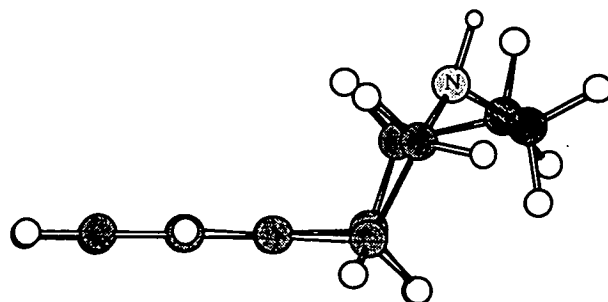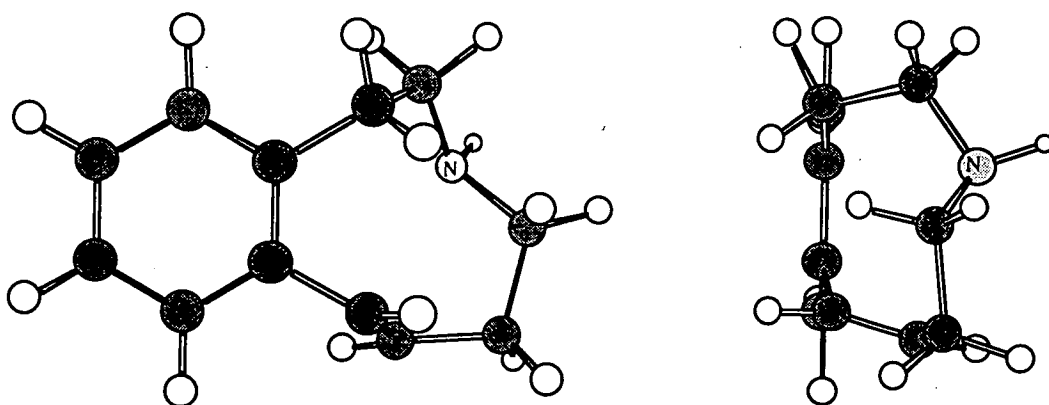
conformer 3

conformer 5

2. Conformational Modelling of the Z-2,3,4,5-Tetrahydro-1H-3-Benzazonines

The molecular modelling of the parent Z-2,3,4,5-tetrahydro-1H-3-benzazonine derivative (Section 2.3.4) afforded five low energy conformations, described in Table 2.5. The structures determined for conformers 4 and 5 are shown below, with three perspectives of each conformation.
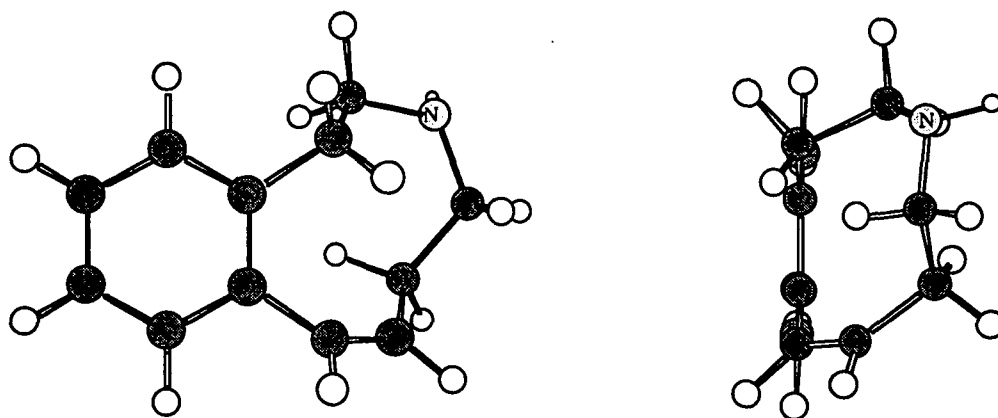
conformer 4
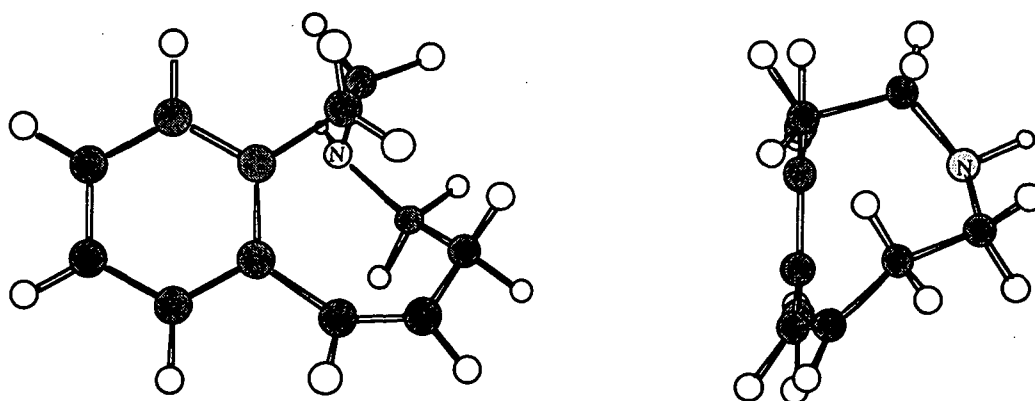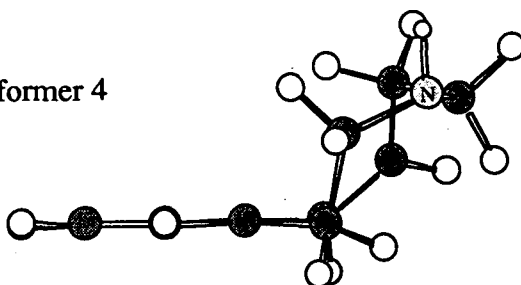
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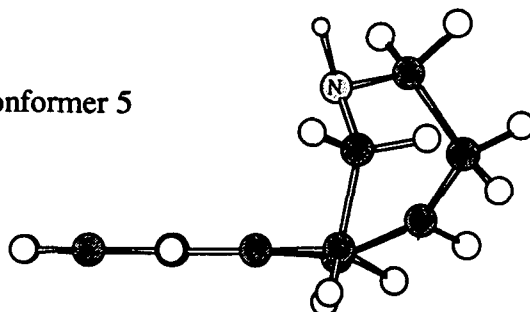
3. Molecular Modelling of the *Z*-1,2,3,5-Tetrahydro-4,3-Benzoxazonine System

The molecular modelling of the parent *Z*-1,2,3,5-tetrahydro-4,3-benzoxazonine derivative (Section 3.7) afforded five low energy conformations, described in Table 3.9. The structures determined for conformers 3, 4, and 5 are shown below, with three perspectives of each conformation.
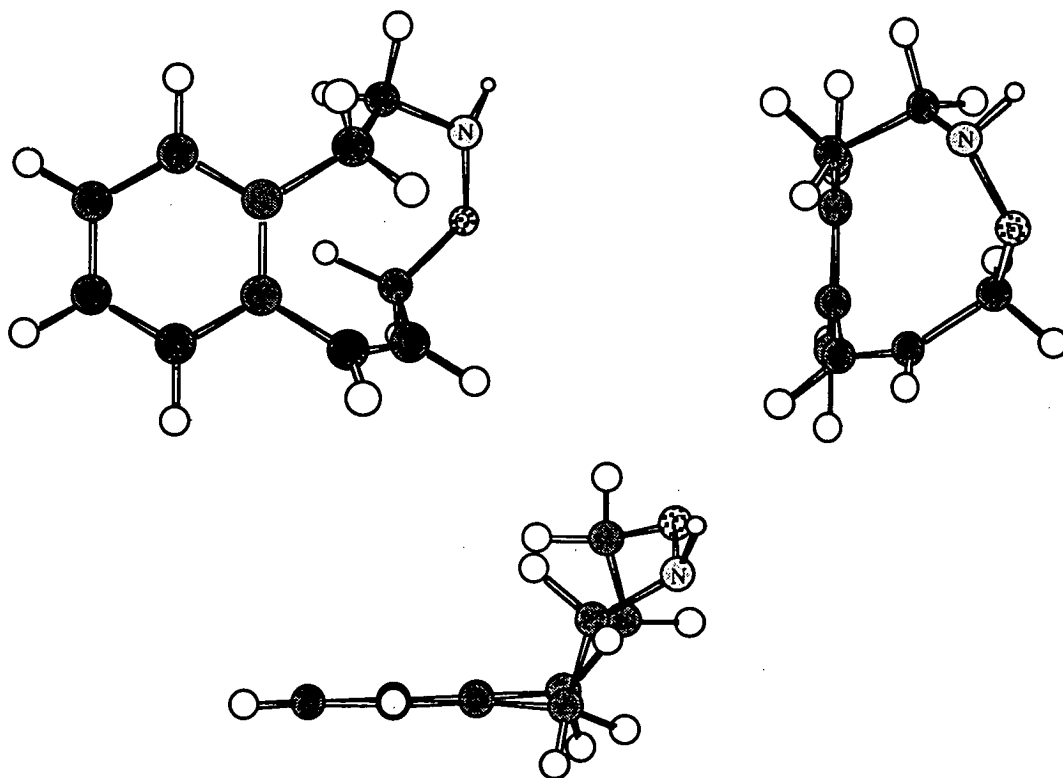
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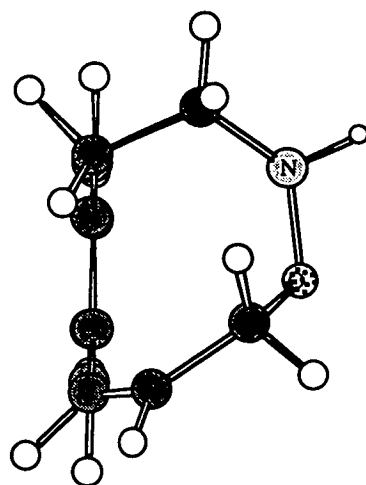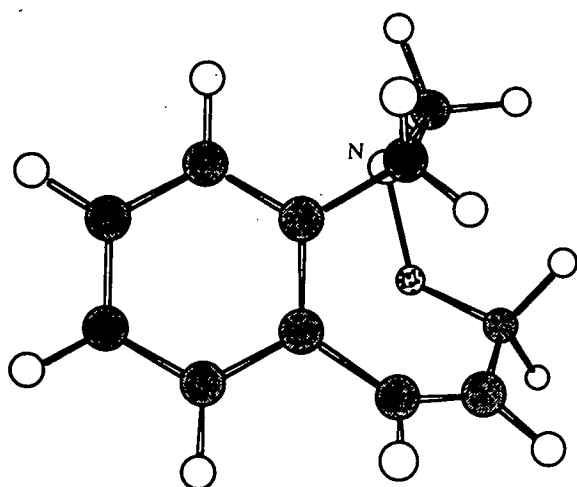
conformer 4
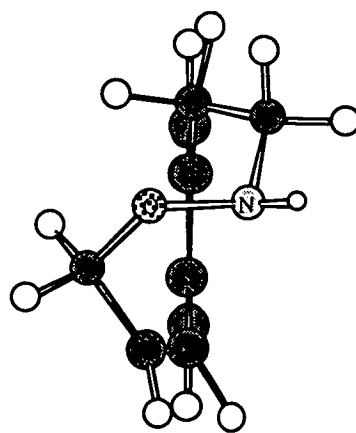
conformer 5

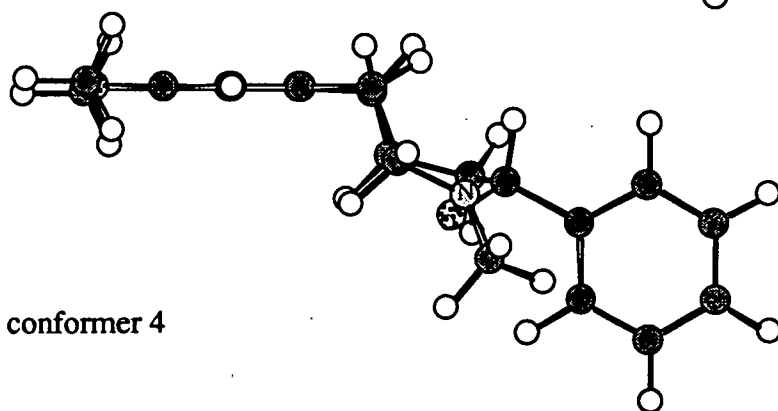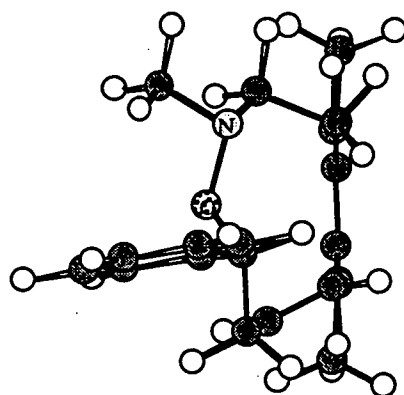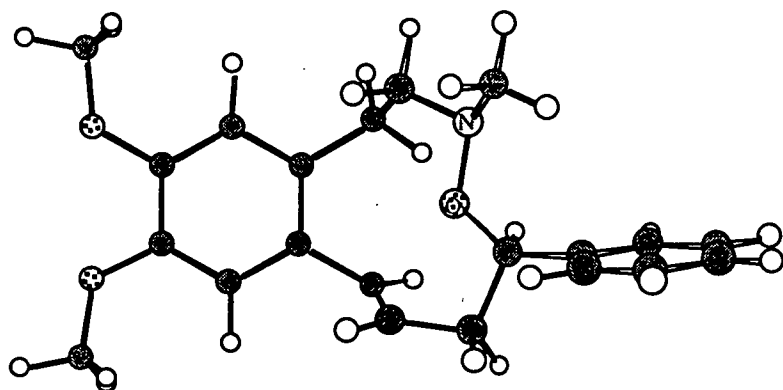# 4. Conformational Modelling of the *E*-2,3,5,6-Tetrahydro-1*H*-4,3-Benzoxazecine 183b

The molecular modelling of the substituted *E*-2,3,5,6-1*H*-4,3-benzoxazecine derivative **183b** (Section 5.6) afforded four low energy conformations, described in Table 5.4. The structures determined for conformers 2, 3 and 4 are shown below, with three perspectives of each conformation.

conformer 2

conformer 3

conformer 4