SYNTHETIC APPLICATIONS OF SOME CHIRAL CYCLIC IMINIUM SALTS

by

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بِسْمِ اللّٰهِ الرَّحْمٰنِ الرَّحِيْمِ

اللہ کے نام سے جو بڑا مہربان اور رحم کرنے والا ہے

In the name of Allah (swt),
the most compassionate, the most merciful

DEDICATION

To my parents

in affection, gratitude and respect

A man would do nothing, if he waited until he could do it so well that no one would find fault with what he has done.

CARDINAL NEWMAN

Declaration

I, Karamat Ali, hereby certify that this thesis has been composed by myself, it is a record of my own work and has not been accepted in partial or complete fulfilment of any other degree of professional qualification.

Signed .... Date .....7.6.1996.

I was admitted to the Faculty of Science of the University of St. Andrews under Ordinance General No. 12 on 1st October 1992 and as a candidate for the degree of Ph.D. on 1st October 1993.

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I hereby certify that the candidate has fulfilled the conditions of the Resolution and Regulations appropriate to the Degree of Ph.D.

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Lecture Courses

The following is a statement of the courses attended during the period of research:

Organic Research Seminars	3 years attendance
Asymmetric Synthesis	Dr. R. A. Aitken
Heterocyclic Chemistry	Dr. D. M. Smith
Advanced NMR	Dr. R. K. Mackie
Ligand Design	Professor R. W. Hay
Organic Synthesis	Professor D. Gani
Intoduction to Instrumentation	Dr. R. K. Mackie
Case Studies of Reaction Mechanism	Dr. A. R. Butler
Current Topics in Bioinorganic Chemistry	Dr. D. T. Richens
Advanced NMR	Dr. F. G. Riddell
Pharmaceutical Chemistry	Dr. R. A. Aitken and Dr. A. R. Butler

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Finally, I thank the Government of Pakistan for financial support and for granting me study leave.

ABSTRACT

Attempts are made to optimise the kinetic resolution of 1-phenylethanol using a proline-derived chiral bicyclic iminium salt. A wide range of counter cations are examined and also the influence of changing the reaction temperature and solvent. It is clear from these studies that the original conditions using the sodium salt in toluene at RT are the best.

The reactions of bicyclic iminium salts with silylating agents and bulky alkoxides are examined in the hope of generating more hindered and thus more selective iminium salts. The reactions do not take the expected course, failing in the first case and resulting in nucleophilic dealkylation in the second. In the course of preparing one of the starting materials, a novel 1,3,6-oxadiazocane-2-thione was obtained.

Four new monocyclic chiral iminium salts are prepared starting from phenylalaninol and the two enantiomers of ephedrine. These are evaluated for kinetic resolution of sodium 1-phenylethoxide and give e.e.s in the range 3–7%.

Reaction of a bicyclic iminium salt with the sodium salts of 1,2- and 1,3-diols are examined. In most cases a novel monothioorthocarbamate is obtained but in one case the reaction takes the desired course to form a spiro dioxane-thiazolidine system. Reaction of the iminium salt with the anions of glycerol and pentaerythritol also gives the simple monothioorthocarbamate and an attempt to alkylate this revealed an unexpected S to O methyl transfer. With the anion of phenylalaninol, a 2-iminothiazolidine is formed, and isolation of the product of initial alkoxide attack in this case points to an indirect mechanism for its formation involving a spiro intermediate.

By base induced reaction of a thiazolidine-based iminium salt with acidic methylene compounds five new highly polarised double bond

compounds are obtained. Attempts to prepare the corresponding oxazolidine-based polarised double bond compounds are frustrated by unexpected ring opening of the iminium salts by iodide, but one example of a chiral imidazolidine-based polarised double bond compound is obtained. The structure of the polarised double bond compounds is examined by means of ^{13}C NMR shifts for all six compounds, variable temperature NMR studies in two cases, and an X-ray structure determination in one case. As a result of these studies it is clear that the compounds exist to quite a large extent in a charge-separated delocalised form with essentially free rotation about the "double bond" and this is borne out by reactivity studies in the thiazolidine series where the compounds are unreactive towards common nucleophiles and electrophiles.

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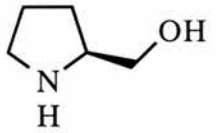
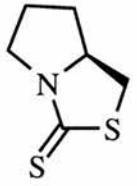
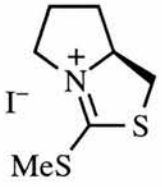
a. Preparation of **175**  29

b. Preparation of **169**  29

c. Preparation of **147**  30

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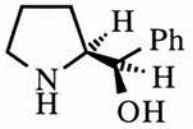
1. Attempted preparation of **194**  40

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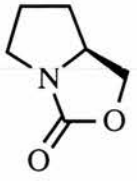
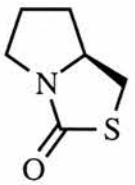
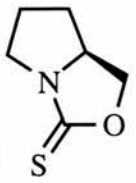
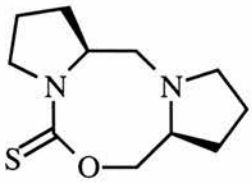
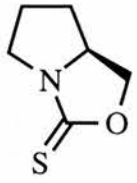
a. Preparation of **195**  41

b. Preparation of **149**  42

c.(i) Preparation of **196**  also **197**  42



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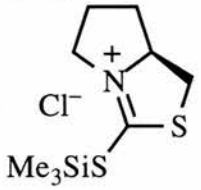
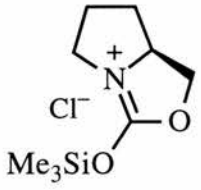
a. Attempted preparation of **205**  44

b. Attempted preparation of **206**  44

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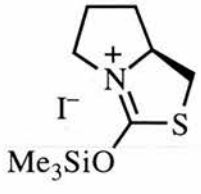
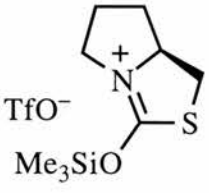
d. Attempted preparation of **208**  45

e. Attempted preparation of **209**  45

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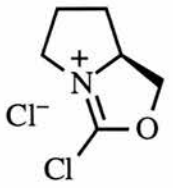
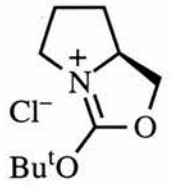
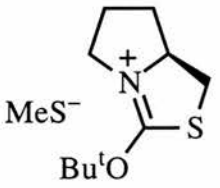
a. Attempted preparation of **212**  46

b. Attempted preparation of **213**  46

c. Attempted preparation of **216**  47

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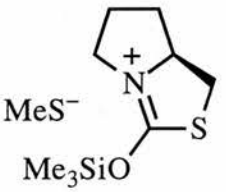
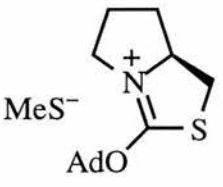
f. Attempted preparation of **218**  48

g. Attempted preparation of **219**  48

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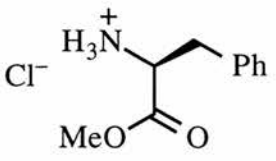
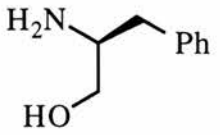
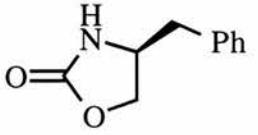
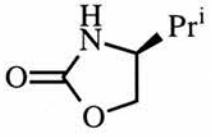
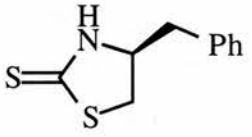
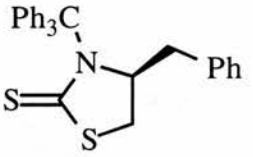
a. Preparation of **225**  49

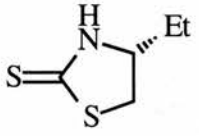
b. Preparation of **226**  50

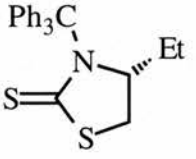
c. Preparation of **233**  50

d. Preparation of **234**  51

e. Preparation of **235**  51

f. Attempted preparation of **239**  52

g. Preparation of **236**  52

h. Attempted preparation of **240**  53

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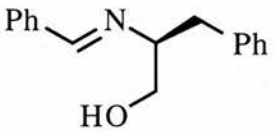
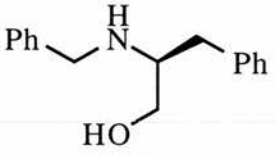
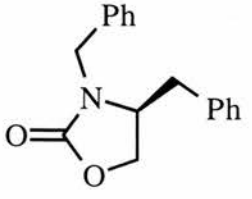
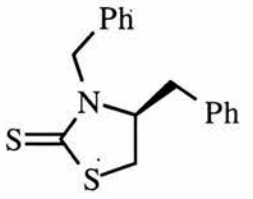
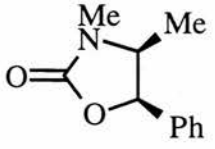
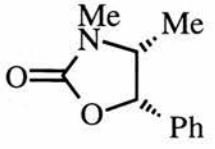
a. Preparation of **241**  53

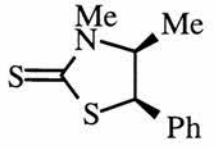
b. Preparation of **242**  54

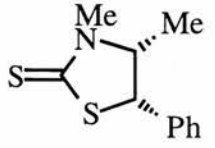
c. Preparation of **243**  54

d. Preparation of **248**  55

e. Preparation of **245**  56

f. Preparation of **247**  56

g. Preparation of **249**  57

h. Preparation of **250**  57

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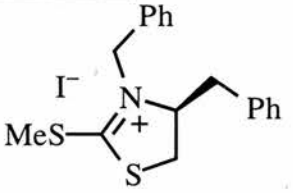
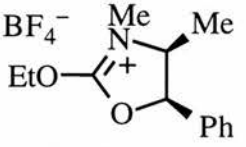
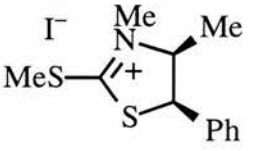
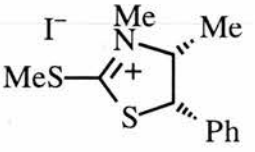
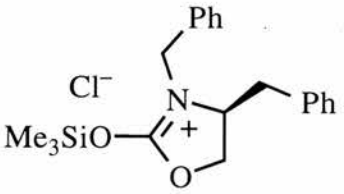
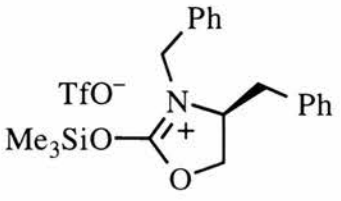
a. Preparation of **251**  58

b. Preparation of **252**  59

c. Preparation of **253**  59

d. Preparation of **254**  60

e. Attempted preparation of **255**  61

f. Attempted preparation of **256**  61

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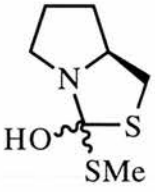
a. Reaction of **147** with the sodium salt of ethanediol leading to **263**  63

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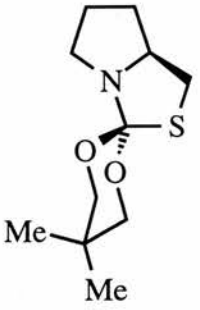

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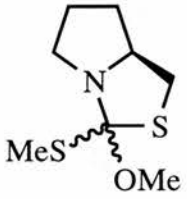

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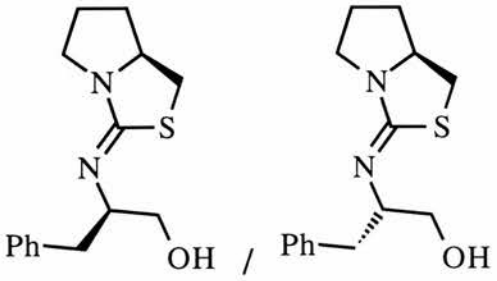
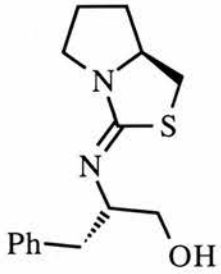
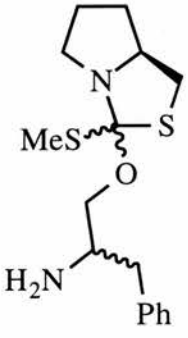
e. Preparation of **283/284**  69

f. Preparation of **284**  70

g. Preparation of **285**  70

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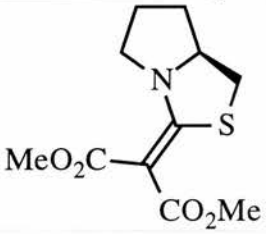
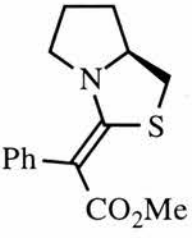
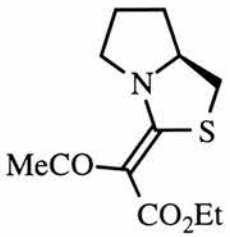
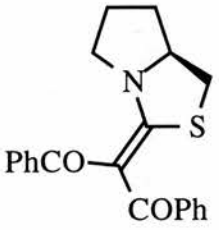
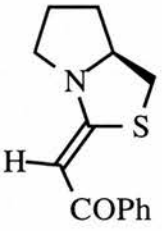
a. Preparation of **291**  71

b. Preparation of **294**  72

c. Preparation of **295**  73

d. Preparation of **298**  and **299**  73

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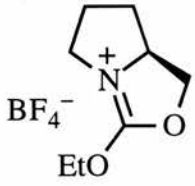
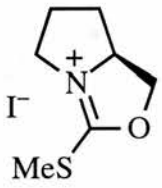
a. Preparation of **185**  75

b. Preparation of **186**  75

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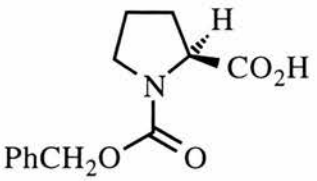
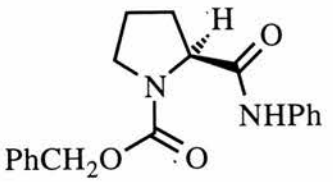
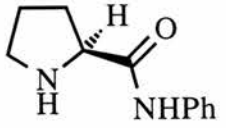
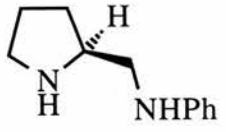
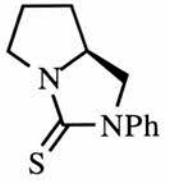
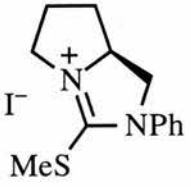
a. Preparation of **309**  78

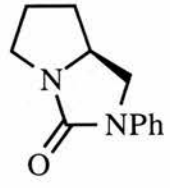
b. Preparation of **310**  79

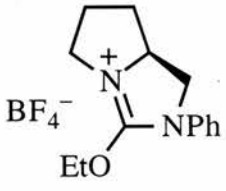
c. Preparation of **311**  80

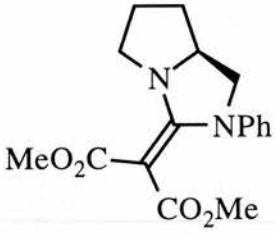
d. Preparation of **312**  80

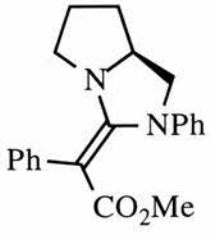
e. Preparation of **313**  81

f. Preparation of **315**  82

g. Preparation of **314**  82

h. Preparation of **316**  83

i. Preparation of **317**  84

j. Attempted preparation of  85

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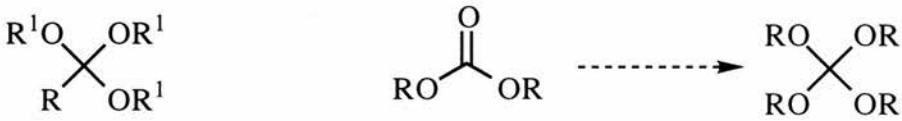
INTRODUCTION

A. Ortho Derivatives of Carbamates and Ureas and their Thio Analogues

1. Ortho Derivatives of Acids in General

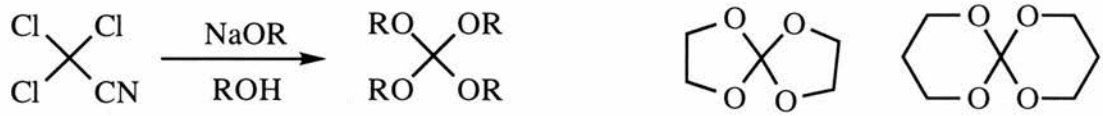
An ortho acid has the structure **2** formally derived by replacing the C=O function in a carboxylic acid **1** by $C(OH)_2$. Although the compounds **2** are not stable, their esters are and trialkyl orthocarboxylates **3** are a well

1 **2**



3 **4** **5**

known class of compound. The same formal transformation may be carried out on dialkyl carbonates **4** to obtain tetraalkyl orthocarbonates **5** which are also well known. An example of the preparation of these compounds is the reaction of trichloroacetonitrile with an excess of sodium alkoxide to give the products **6** and **7**.[1] Once they have been prepared, the

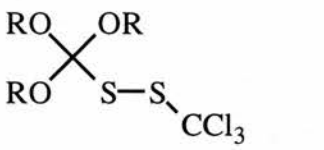


6 R = Me
7 R = Et

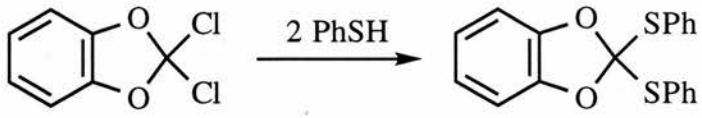
8 **9**

alkoxy groups may be substituted by others and by using 1,2- and 1,3-diols, spiro orthocarbonates such as **8** and **9** may be obtained.[2]

Examples of thio analogues of orthocarbonates are rare but both monothio analogues such as **10**[3] and dithio analogues such as **12**[4] have been described. The latter was prepared, as shown, by reaction of the corresponding dichloride **11** with thiophenol.



10 R = $CH_2CF(NO_2)_2$

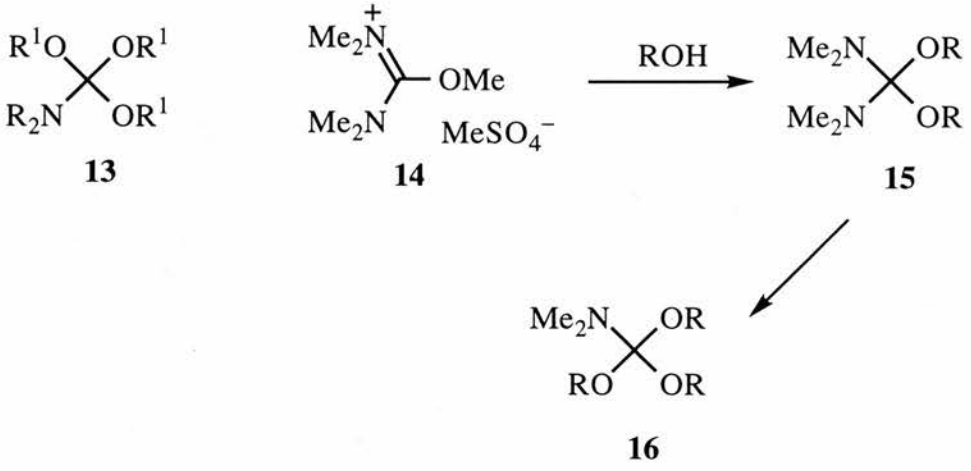


11 **12**

In the following sections the corresponding classes of compounds containing one or two nitrogens are considered.

2. Orthocarbamates

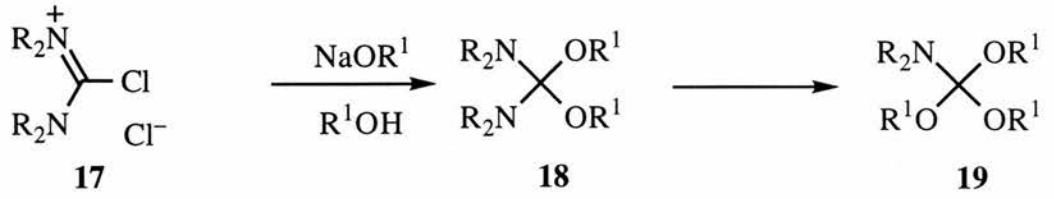
Orthocarbamates, which have the general structure **13** have been obtained by a variety of methods. One of the earliest methods begins from



13 **14** **15** **16**

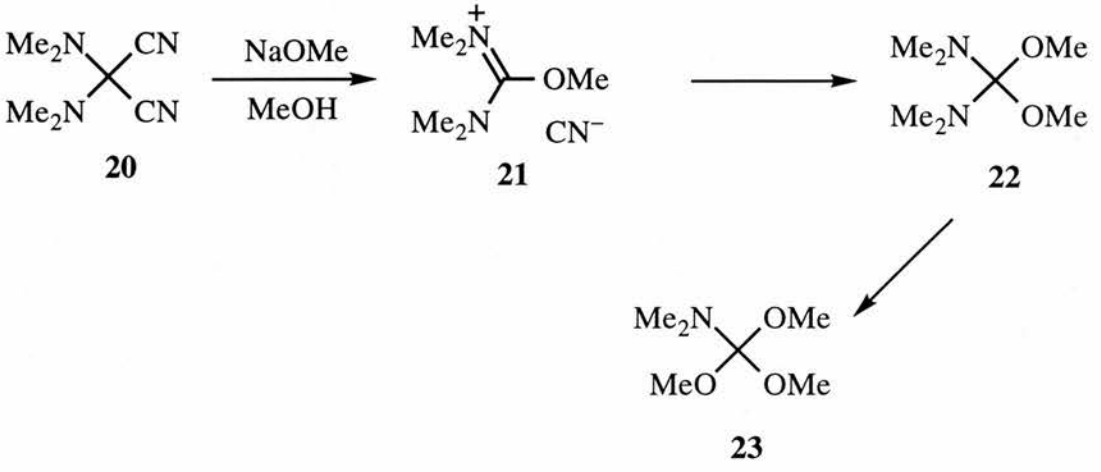
O-alkyl uronium salts such as **14** formed by alkylation of ureas with dimethyl sulphate. When this is treated with an alcohol the orthourea **15** is formed (see Section 6) but this reacts with a further alcohol molecule to

give the orthocarbamate **16**.[5] A similar sequence is observed upon



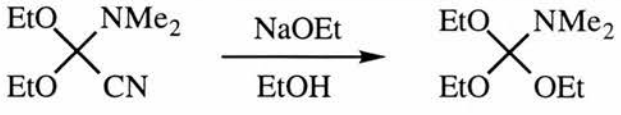
17 **18** **19**

treatment of the chloroamidinium salts **17** with sodium alkoxide to give first the orthoureas **18** and then the orthocarbamates **19**.[6,7,8] Reaction of diaminomalononitriles such as **20** with NaOMe results in stepwise displacement to give **21**, **22** and finally **23**.[9] Other starting materials such



20 **21** **22** **23**

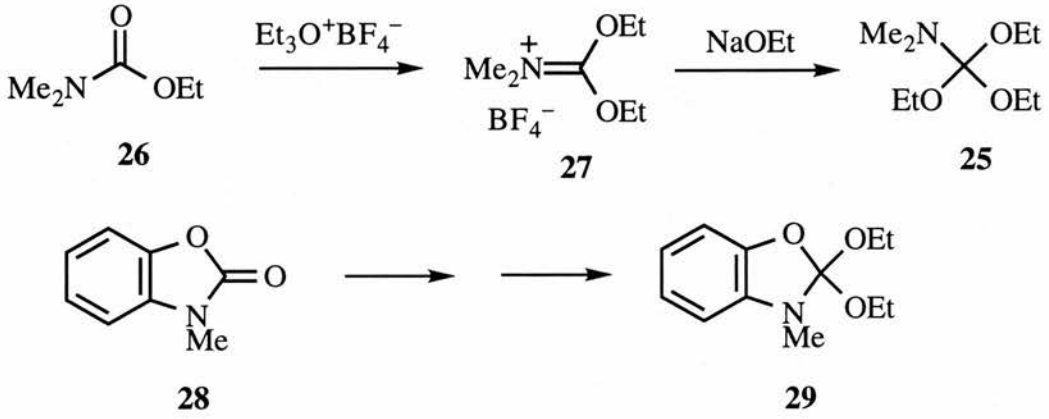
as **24** undergo a similar process to give **25**,[2] and reaction of orthoureas from other sources with alcohols to give orthocarbamates has been described.[10,11]



24 **25**

A second important method of access to compounds of this type was reported at an early stage by Meerwein and coworkers.[10] This involves *O*-

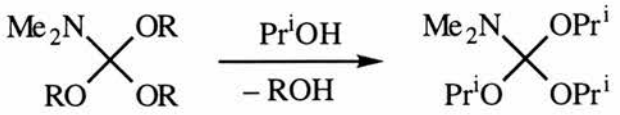
alkylation of a carbamate such as **26** with triethyloxonium fluoroborate ("Meerwein reagent") to give the iminium salt **27** followed by nucleophilic



addition of an alkoxide to afford the orthocarbamate **25**.[10,11] This method has also been applied to cyclic carbamates such as the benzoxazolone **28** to obtain **29**.[10]

An interesting and novel method of orthocarbonate formation involves treatment of a cyclic thiocarbonate **30** with an organotin reagent **31** to give the spiro product **32**.[12]

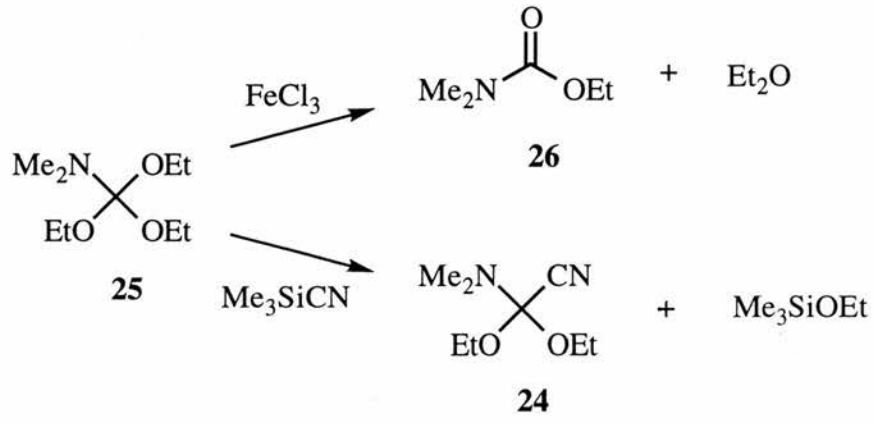
Once the orthocarbamates have been obtained they undergo a variety of reactions. The alkoxy groups may be exchanged by heating with a higher boiling alcohol as illustrated by the conversion of **23** or **25** into **33**.[2,13]



23 R = Me
25 R = Et

33

Treatment with $FeCl_3$ results in reversion to the carbamate with elimination of an ether as shown for **25**.[6,7] Exchange of one of the alkoxy groups for cyano to give products such as **24** can be achieved by treatment with trimethylsilyl cyanide.[14]



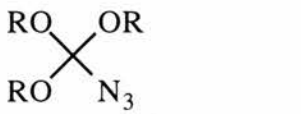
25

26

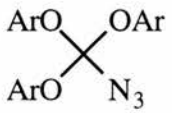
24

In addition to the stable compounds mentioned above, many orthocarbamic acid derivatives have been involved as intermediates in such processes as hydrolysis of carbamates and aminolysis of carbonates.[15]

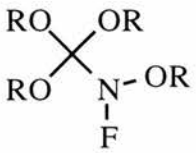
Other compounds are known which contain the $(RO)_3C–N$ function but with the nitrogen not in the form of an amine such as the azides **34**[3] and **35**[16] and the *N*–fluoro compound **36**.[17]



34 R = $CH_2CF(NO_2)_2$



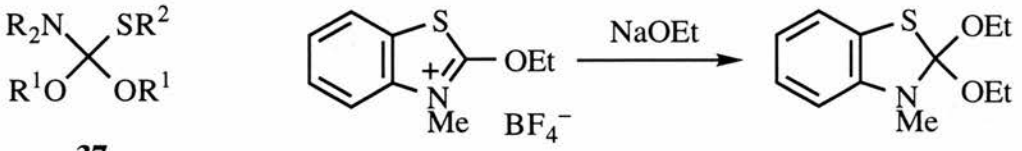
35



36 R = SO_2F

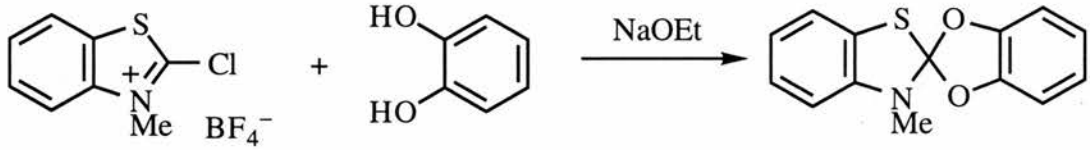
3. Orthothiocarbamates

The monothio derivatives of orthocarbamates with the general structure **37** are an almost unknown class of compounds. Only two papers describing compounds of this type have been located. The first was Meerwein's report in 1961 that the salt **38**, derived from the corresponding benzothiazolone exactly as for **28**, reacted with NaOEt to



37 **38** **39**

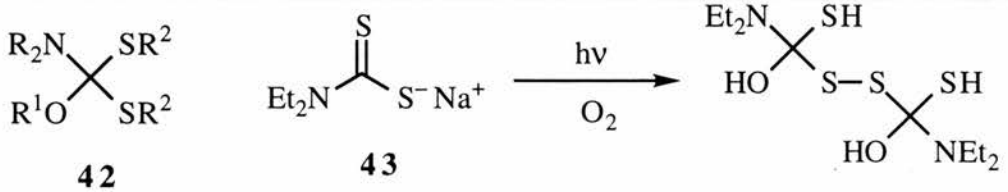
afford **39** in 75% yield as a colourless oil.[10] The closely related iminium salt **40** reacts with catechol to give an excellent yield of the spiro compound **41**.[18]



40 **41**

4. Orthodithiocarbamates

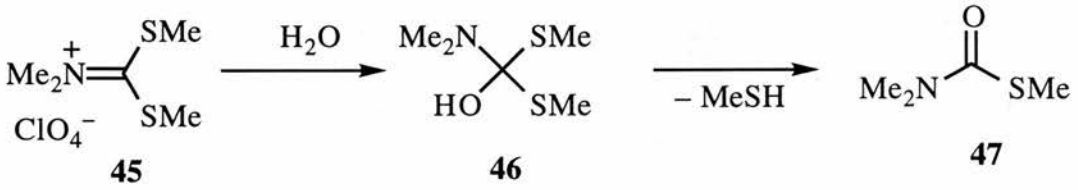
The dithio derivatives of orthocarbamates **42** are also a virtually unknown class of compounds. The only isolable compound reported



42 **43** **44**

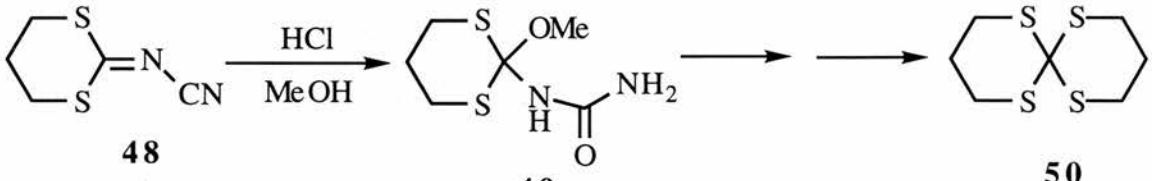
appears to be the unusual dimer **44**, obtained by photochemical oxidation of sodium diethyldithiocarbamate **43** in a phosphate buffer in the presence of formate anions.[19] Hydrogen peroxide can also be used to convert **43** into **44**.[19]

Hydrolysis of the salt **45**, obtained by *S*-alkylation of the dithiocarbamate, proceeds via the intermediate **46** which readily loses



45 **46** **47**

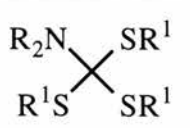
methanethiol to give the thiocarbamate **47**.[20] The acid catalysed methanolysis of **48** which eventually gives **50** is thought to involve initial formation of **49**.[21]



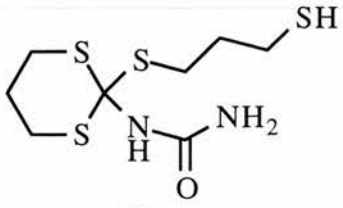
48 **49** **50**

5. Trithioorthocarbamates

The trithio derivatives **51** of orthocarbamates are again fairly uncommon. One example is **52** which is postulated as an intermediate in

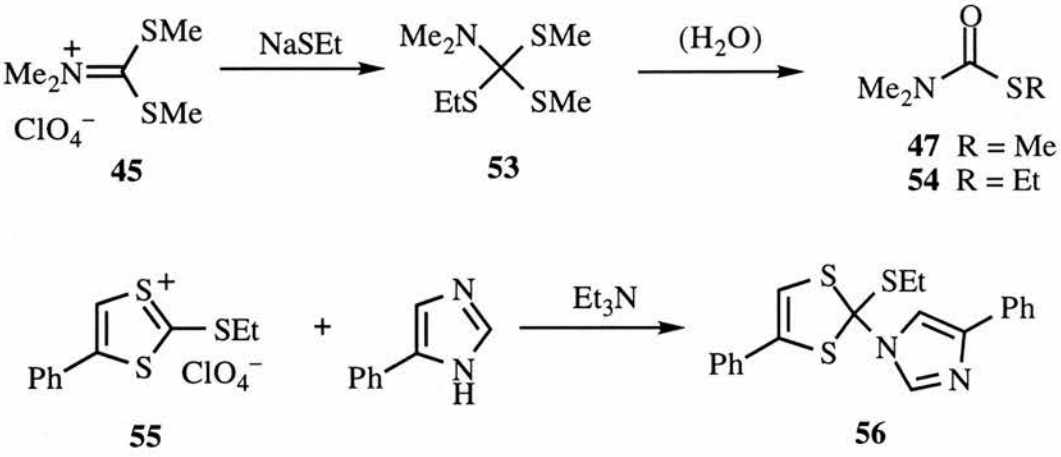


51

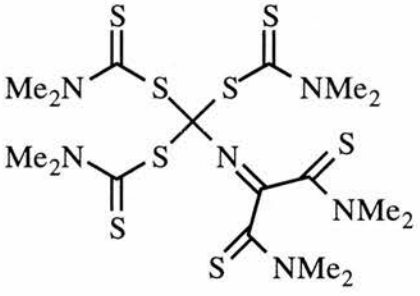


52

the conversion **49** to **50** mentioned above.[21] Reaction of the salt **45** with sodium ethanethiolate followed by aqueous work-up gave a mixture of **53** and its hydrolysis products **47** and **54**.[20] Treatment of the dithiolium salt **55** with 4-phenylimidazole in the presence of triethylamine gave the product **56**.[22]

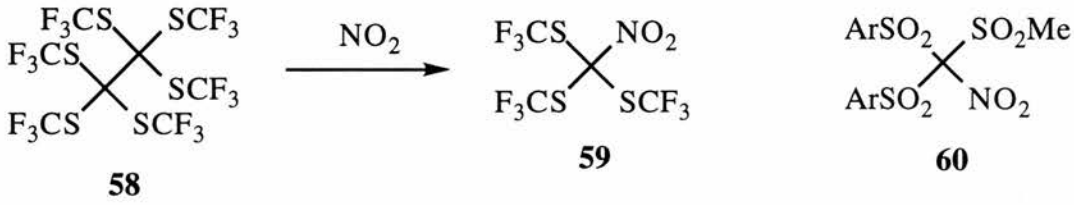


Reaction of $Cl_3C–N=CCl_2$ with a sodium dithiocarbamate gives the fungicidal compound **57**.[23]



57

Other compounds containing the $(RS)_3C–N$ function include the nitro compound **59** formed by treatment of **58** with NO_2,[24] and the trisulfonyl

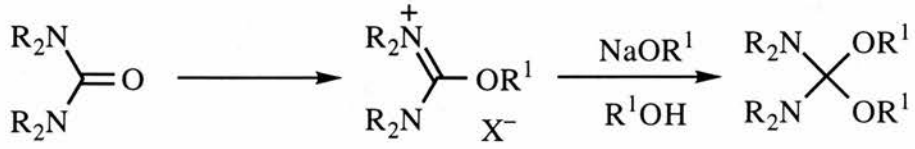


58 **59** **60**

nitromethane **60**, formed by nitration of the corresponding trisulfonylmethane using HNO_3/H_2SO_4.[25]

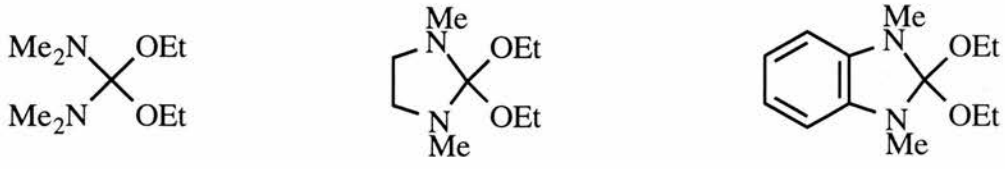
6. Orthoureas

The orthoureas with general structure **18** are somewhat better known than the compounds of previous sections. The simplest method to prepare them involves treatment of a tetraalkylurea with an alkylating agent to give the *O*-alkyluronium salt **61** which is then treated with an alkoxide or alcohol to give **18**. The salts can be formed using either dimethyl sulphate[5] or triethyloxonium fluoroborate[10] as the alkylating agent.



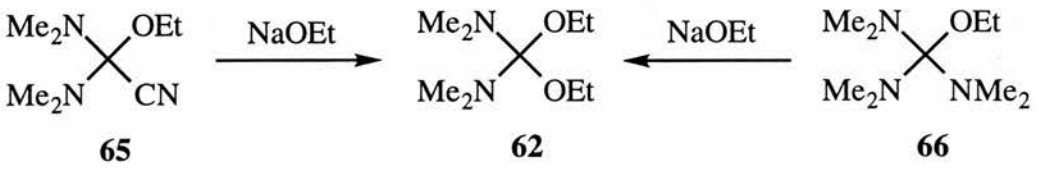
61 **18**

The latter method has been used to obtain not only acyclic examples such as **62** but also the cyclic compounds **63** and **64**.[10] Reaction of chloroamidinium salts **17** with a sodium alkoxide initially gives the



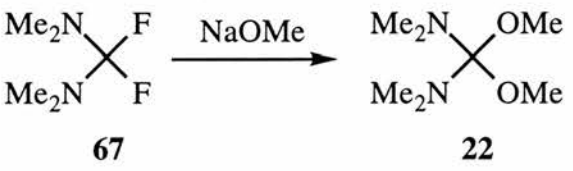
62 **63** **64**

orthoureas **18**, although as noted in section 2, these may react further to give the orthocarbamates.[6,7,8] If the salts **17** are instead reacted with cyanide, the diaminomalononitriles **20** are produced which undergo stepwise displacement of CN^- by various alkoxides to give orthoureas **22**.[9] Treatment of **65** with NaOEt similarly affords **62**,[2] as does the same reaction of **66**.[8]

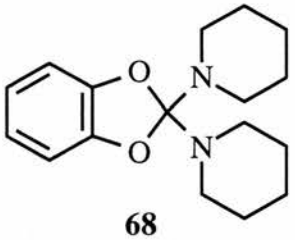


65 **62** **66**

The difluoro compound **67** is formed by reaction of tetramethylurea with COF_2 and reacts with NaOMe to give **22**.[26]

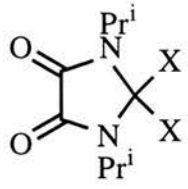


67 **22**

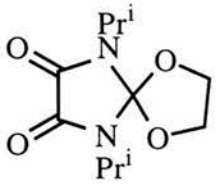


68

Reaction of dichlorobenzodioxole **11** with amines results in substitution of both chlorines, e.g. the reaction with piperidine gives **68**.[4] The interesting heterocyclic examples **70** and **71** were obtained by alcohol treatment of the dichloride **69**, itself derived from direct addition of oxalyl chloride to diisopropylcarbodiimide. The spiro example **72** was similarly

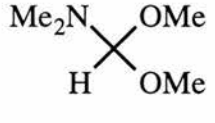


69 X = Cl
70 X = OMe
71 X = OEt

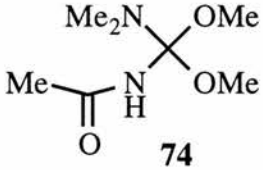


72

obtained using ethanediol.[27] Reaction of **73** with *N*-chloroacetamide gives **74** in addition to several other products.[28] The heterocyclic example **76**



73



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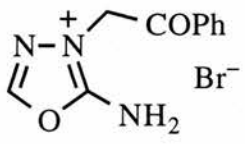

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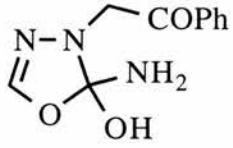
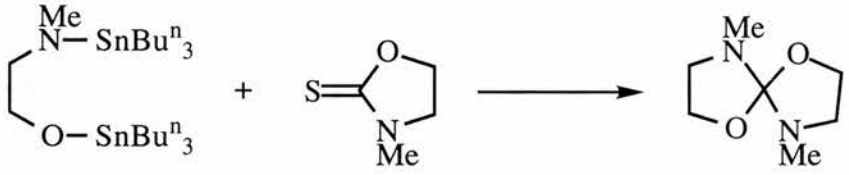


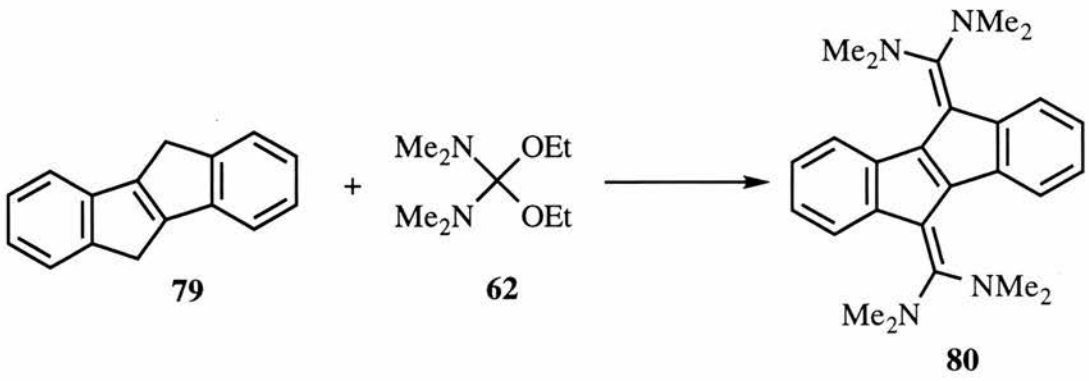
76

has been obtained as an intermediate in the reaction of **75** with hydrazine hydrate.[29] As described earlier for **30**, the oxazolidinethione **77** reacts with **31** to afford the spiro product **78**.[30]



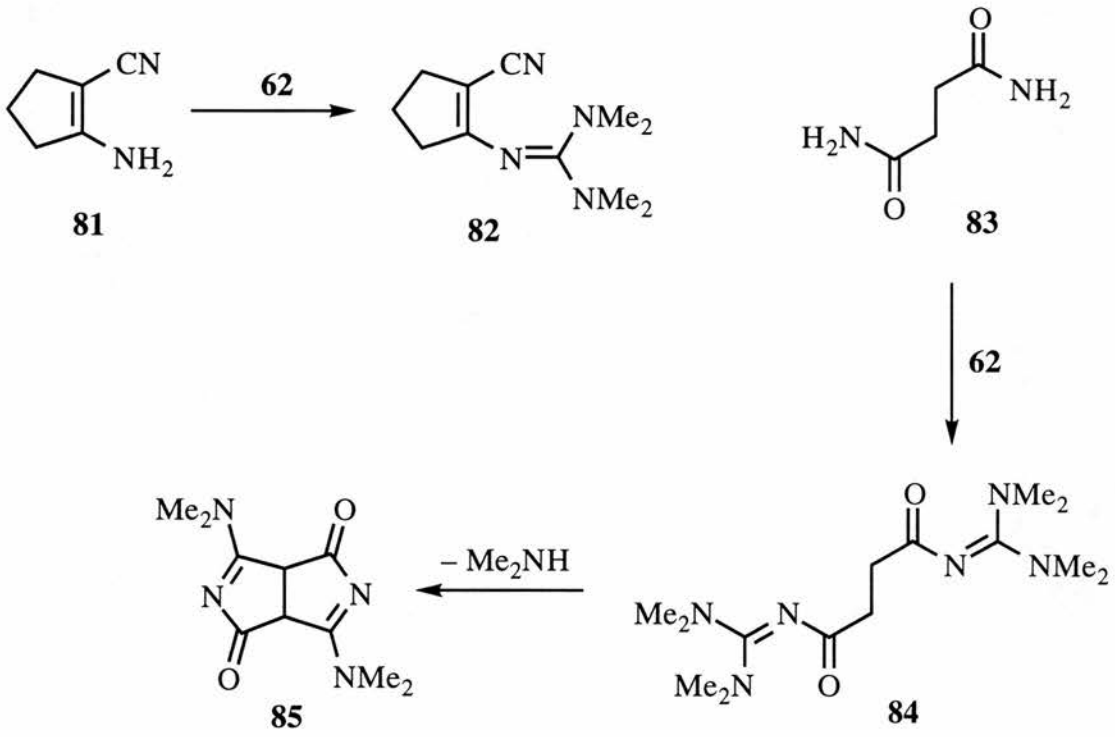
31 **77** **78**

A variety of reactions have been described for the orthoureas involving displacement of either the amino or alkoxy groups. Acidic hydrocarbons such as indenoindene **79** react with **62** with loss of ethanol to



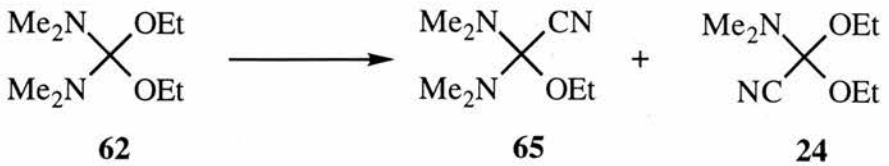
79 **62** **80**

give **80**.[31] Reaction of **62** with enamines such as **81**[32] and amides such as **83**[33] also results in loss of ethanol to give **82** and **84** respectively and the latter goes on to give **85**.



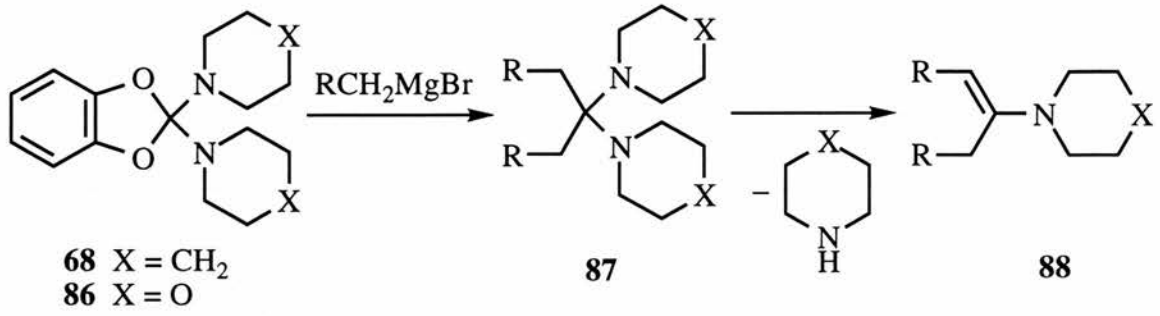
81 **82** **83** **85** **84**

Reaction of **62** with either MeCOCN or PhCOCN,[1] or Me_3SiCN[14] results in displacement of both amino and ethoxy groups by CN to give a



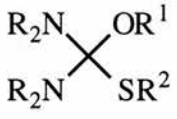
62 **65** **24**

mixture of **65** and **24**. Treatment of **68** or the morpholine analogue **86** with a Grignard reagent, RCH_2MgBr, results in displacement of catechol to give **87** which then loses piperidine or morpholine to afford the enamine **88**.[34]

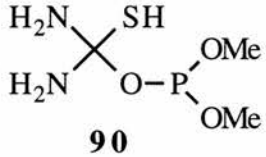


7. Orthothioureas

Replacement of one oxygen by sulfur in the orthoureas gives the orthothioureas with general structure **89**. Only a few examples of this type

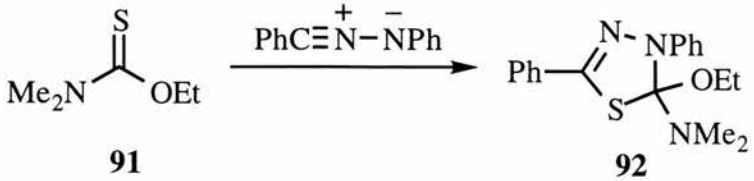


89

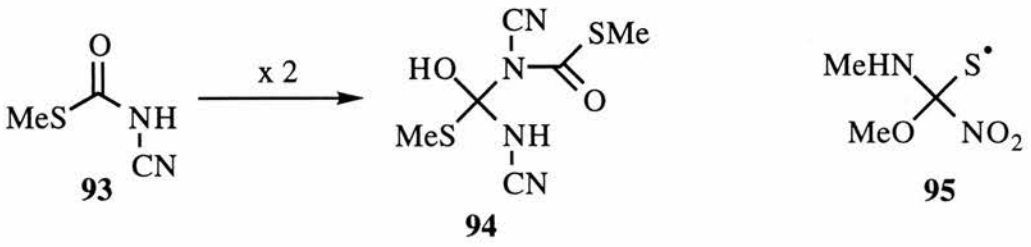


90

of compound have been described. Reaction of dimethyl phosphite with thiourea gives **90**.[35] The 1,3-dipolar cycloaddition of diphenylnitrile imine to the thiocarbamate **91** gives the thiadiazoline product **92**.[36] The intermediate **94** is implicated in the the disproportionation of **93**,[37] and



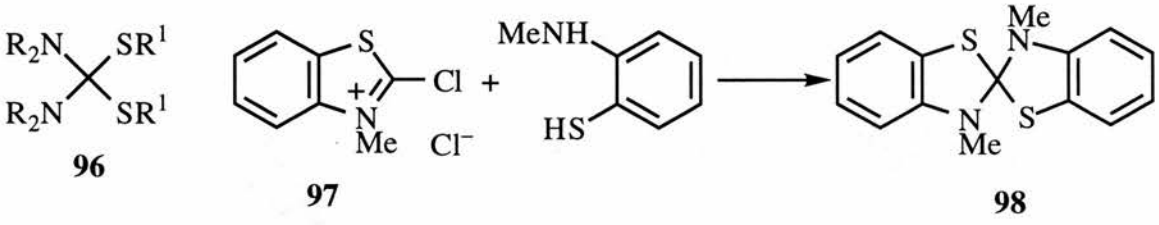
91 **92**



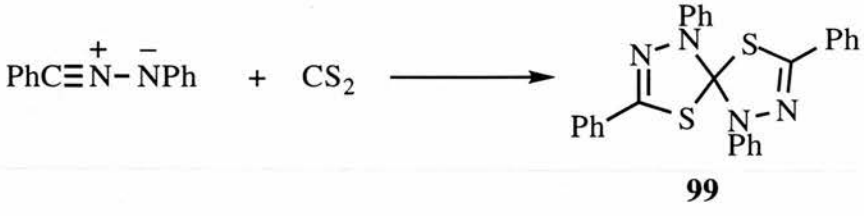
radical **95** has been detected during a study of radiation damage of carnidazole.[38]

8. Dithioorthoureas

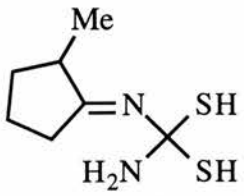
The dithio analogues of orthoureas with general structure **96**, are also fairly uncommon. Reaction of the salt **97** with 2-mercapto-*N*-



methylaniline gives the spiro compound **98**.[18] Twofold addition of diphenylnitrile imine to carbon disulfide affords the spiro bis(thiadiazoline) **99**.[36] Treatment of 2-methylcyclopentanone with CS_2 and

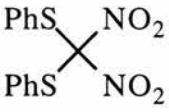


aqueous ammonia below 0°C gives the isolable compound **100**.[39] The product **101** was obtained by reaction of *N*,*N*´-diacetylthiourea with



100

101



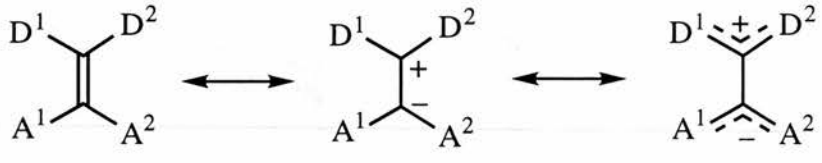
102

N-nitrosoacetanilide.[40] The dinitro compound **102** has been obtained by treatment of sulfonium,[41] iodonium,[42,43] and selenonium[44] dinitromethylides with benzenesulfenyl chloride.

B. Polarised Double Bond Compounds

1. Introduction

The lack of free rotation about the C=C double bond is one of the most well established phenomena in organic chemistry. The existence of E and Z isomers which are not easily interconverted provides ready evidence of this. In certain special cases however, the presence of donor groups on one end of the double bond and acceptors on the other may lead to polarisation and a degree of charge separation which lowers the barrier to rotation considerably. This situation can be represented diagramatically as **103** existing to some extent in the fully charge-separated form **104** and is



103 **104** **105**

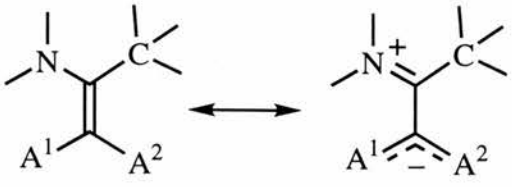
particularly favoured in cases where the charges can be extensively delocalised into the donor and acceptor groups as in **105**.

Double bond polarisation can be quantified by a range of physical techniques. Dipole moment measurements provide an obvious measure of the extent of polarisation and determination of the ionisation energies by photoelectron spectroscopy is also useful. The charge density at the two carbon atoms is reflected in the chemical shifts observed in ^{13}C NMR with the donor-substituted atom being moved to higher frequency (deshielded) and the acceptor-substituted atom being moved to lower frequency. In some cases this effect can be very pronounced with a difference of over 100 ppm between the two atoms being not uncommon. The reduced barrier to rotation about the bond can be examined directly by variable-temperature NMR methods and this method has been particularly useful in deriving values for the free energy barrier to rotation from observed coalescence temperature data. Finally the contribution from a charge-separated single bond form is reflected in a lengthening of the bond and this can be observed directly by X-ray diffraction.

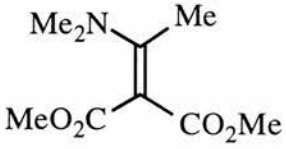
A comprehensive review in this area was published by Sandström in 1983.[45] In the remainder of this section, the most important classes of compound of this type are discussed with emphasis on more recent examples.

2. Acceptor Substituted Enamines

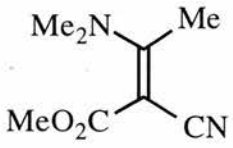
These compounds represented by the general structure **106**, are well known and have been studied by variable-temperature NMR.[45] This



106 **107**



108

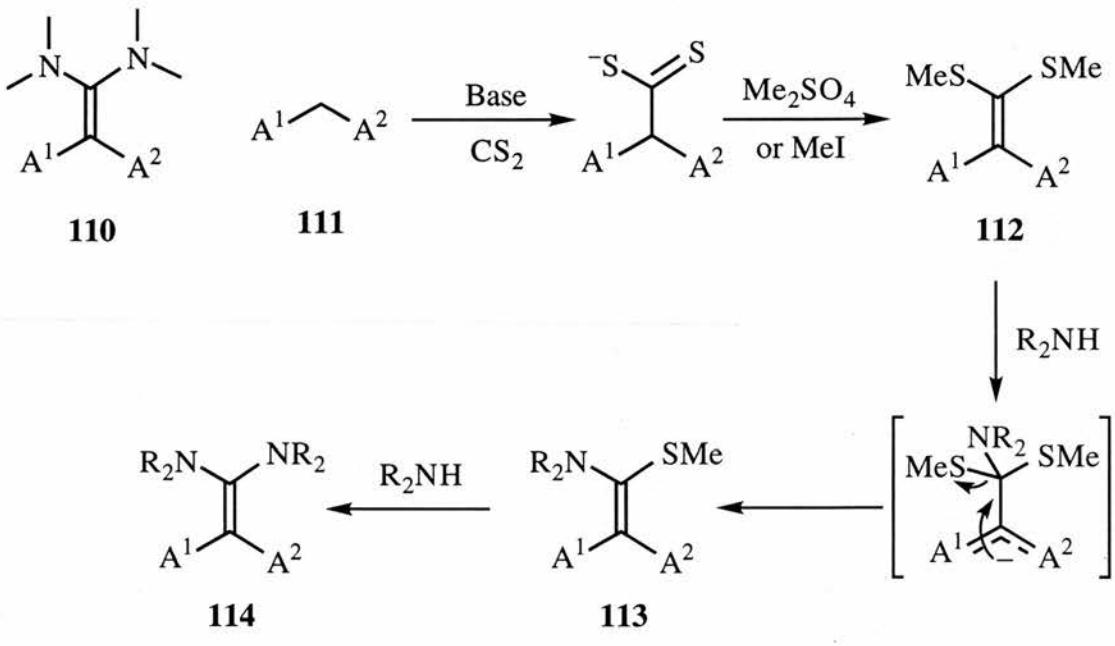


109

shows not only a reduced barrier to rotation about the double bond, but also an increased barrier to rotation about the C-N bond due to involvement of the form **107**. Typical examples include **108** and **109**.

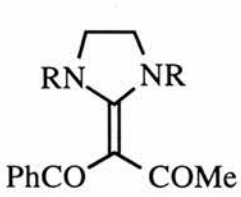
3. Ketene Aminals

A variety of routes to these compounds of general structure **110** have been reported. If we start from an active methylene compound **111**,



110 **111** **112** **113** **114**

treatment with CS_2 and base followed by methylation gives the ketene dithioacetal **112**. The methylthio groups can then be displaced stepwise by an amine to give first **113** and then **114**. This process is clearly assisted by the favourable intermediate shown in which the acceptor groups stabilise the negative charge. Typical examples prepared by this route include **115** and **116**,[46] **117**,[47] **118**,[48] **119**,[49] **120**,[50] and **121**.[51] The



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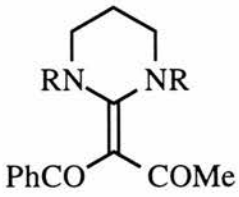

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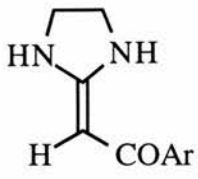

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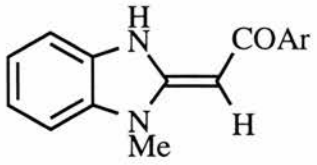

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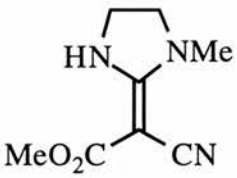

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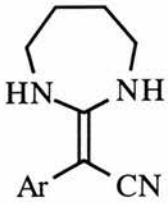

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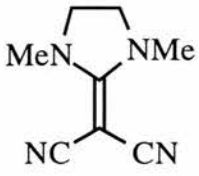
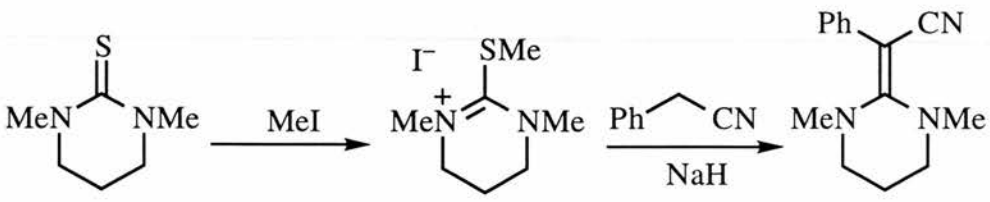


121

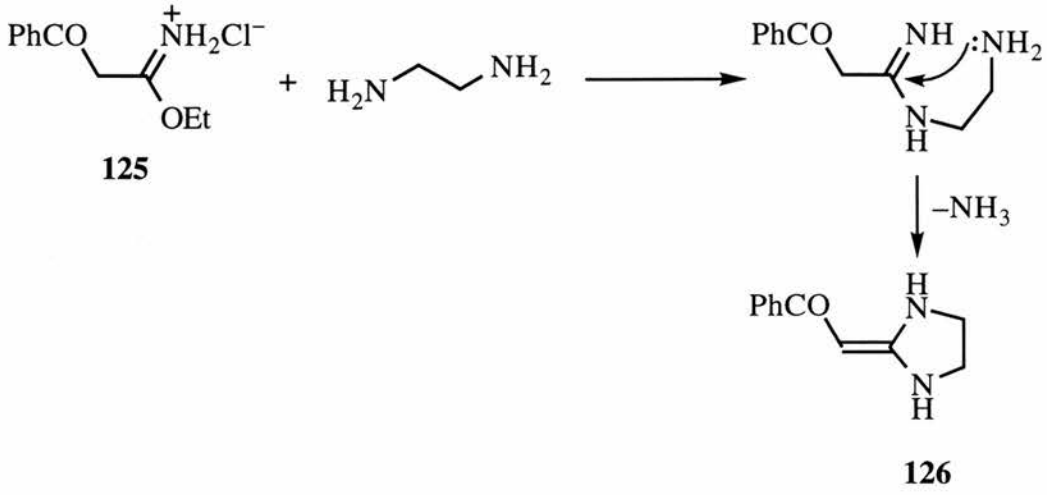
charge separation is well illustrated by the ^{13}C NMR values for the "double bond" carbons of δ_C 164 and 53 for **119** and δ_C 165.5 and 28 for **121**. An X-ray structure determination was also carried out for **119** giving a bond length for "C=C" of 1.418 Å. Free energy barriers to rotation estimated by variable temperature NMR are typically 75.6 kJ mol^{-1} for **115** (R = Pr^i) and 99.5 kJ mol^{-1} for **116** (R = Pr^i).[52] These figures should be compared with 260-275 kJ mol^{-1} for simple alkenes.[45]

A second route for preparation of compounds of this type is the reaction of acidic methylene compound **111** with a thiouronium salt as illustrated by the synthesis of **124** from the iminium salt **123**, derived from

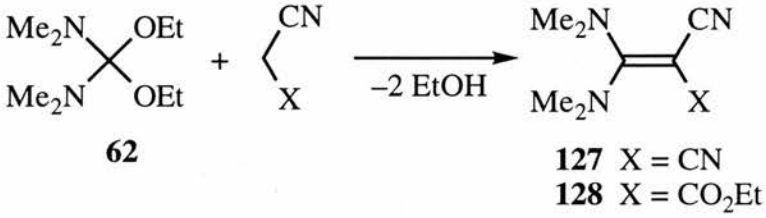


122 **123** **124**

methylation of thiourea **122**, and the anion of phenylacetonitrile.[52] In a related method, compounds such as **126** can be prepared by treatment of an iminium salt **125** with a 1,2-(or 1,3-) diamine.[53]

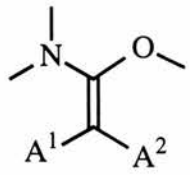


A quite different method starts from **111** and an orthourea derivative of the type described in Section A.[13] Reaction of **62** with malononitrile or ethyl cyanoacetate, for example, proceeds readily with loss of ethanol to give **127** or **128**.

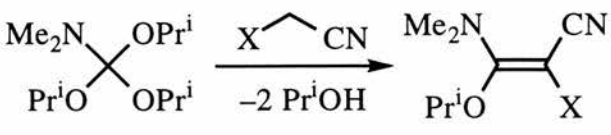


4. Ketene Oxo Aminals

These compounds have the general structure **129**. The preparative method corresponding to that shown for **127** and **128** above can be used. Thus, the orthocarbamate **33** can be used to obtain either **130** or **131**.[8,13]



129

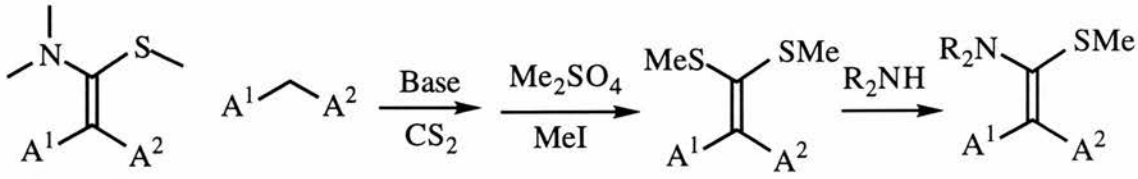


33

130 X = CN
131 X = CO_2Et

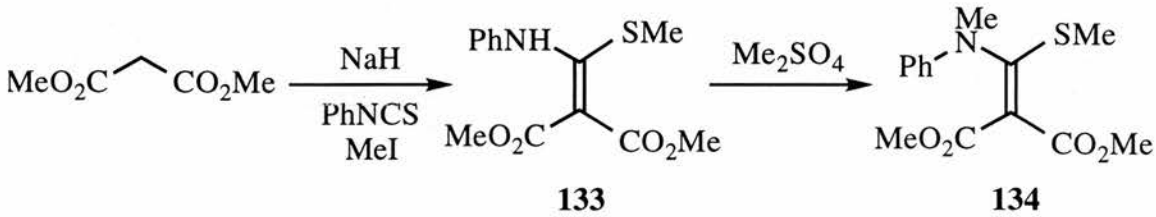
5. Ketene Mercapto Aminals

One preparative method for compounds of the type **132** has already



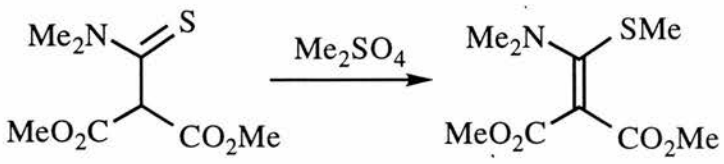
132 **111** **112** **113**

been mentioned:— reaction of acidic methylene compounds **111** with carbon disulphide and base followed by methylation to give the ketene dithioacetals **112**, which then react with a secondary amine to afford **113**.[54] While this is effective for aliphatic amines and aniline, *N*-methylaniline failed to react, so an alternative route to **134** had to be found. This involves reaction of dimethyl malonate and base with phenyl isothiocyanate in the presence of methyl iodide to afford **133**, which can be



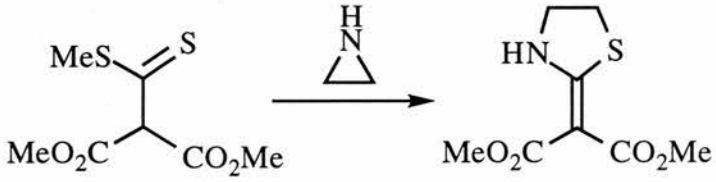
133 **134**

methylated as shown.[54] The thioamide **135** can be converted into **136** by



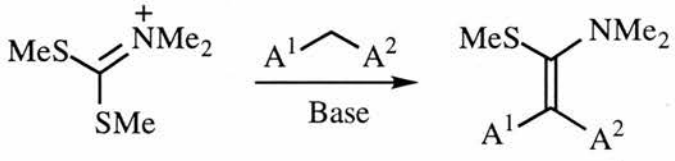
135 **136**

methylation using dimethyl sulphate. In a related process, reaction of **137** with aziridine gives the cyclic compound **138**.[54] A final important method



137 **138**

in this area is the reaction of the dithiocarbamate derived iminium salt **139** with an acidic methylene compound and base to give **140**.[20]

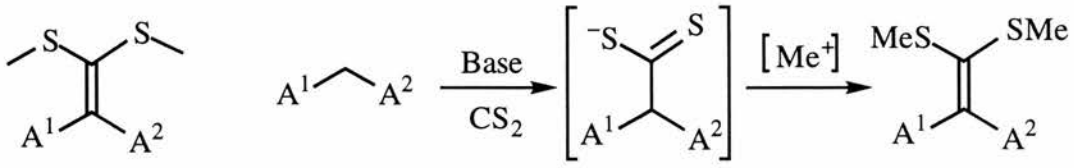


139 **140**

Typical energy barriers for compounds of this type determined by variable temperature NMR methods are: < 39.5 kJ mol^{-1} for **136**, 50.4 kJ mol^{-1} for **133**, < 35.7 kJ mol^{-1} for **134**, and 93.7 kJ mol^{-1} for **138**.[54]

6. Ketene Dithioacetals

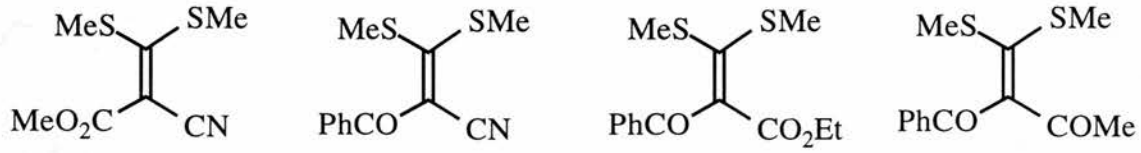
The main method of access to compounds of general structure **141** has already been described: reaction of an appropriate acidic methylene



141 **111** **142** **112**

compound **111** with base and CS_2 to afford **142** which can then be methylated to give **112**. Since these products are valuable precursors to ketene mercaptoaminals and ketene aminals a wide variety of examples have been prepared as already mentioned.[47, 49–51]

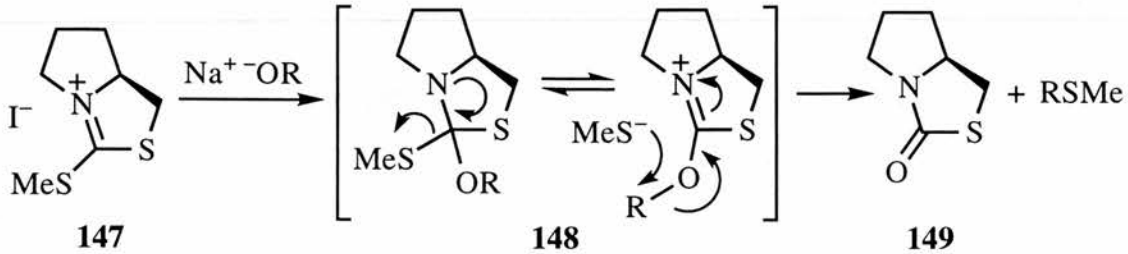
Typical energy barriers to rotation in this type of compound are 104 kJ mol^{-1} for **143**, 86.5 kJ mol^{-1} for **144**, 81.5 kJ mol^{-1} for **145**, and 75.6 kJ mol^{-1} for **146**.[55]



143 **144** **145** **146**

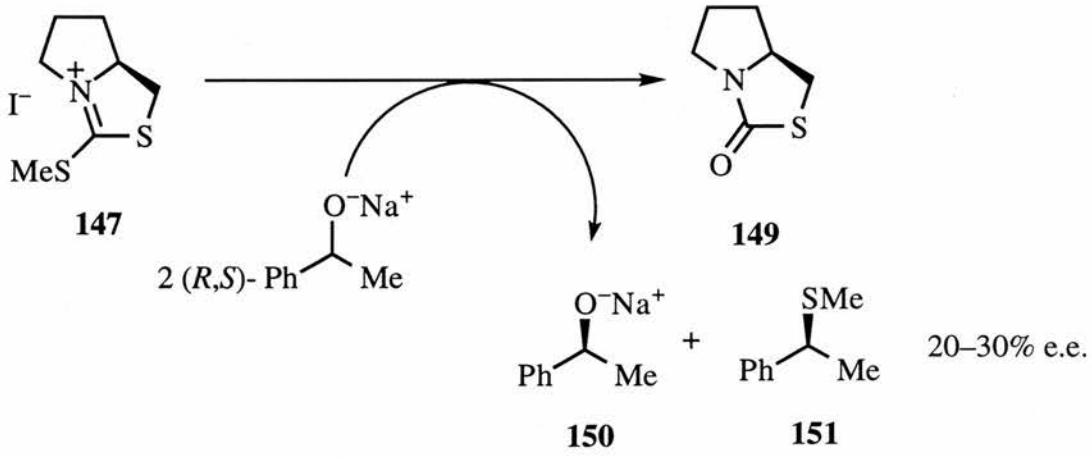
C. Programme of Research

In the course of previous work in this laboratory,[56] the chiral bicyclic iminium salt **147** was prepared in three steps from (*S*)-proline. This was found to react in a rather unexpected way with sodium alkoxides,



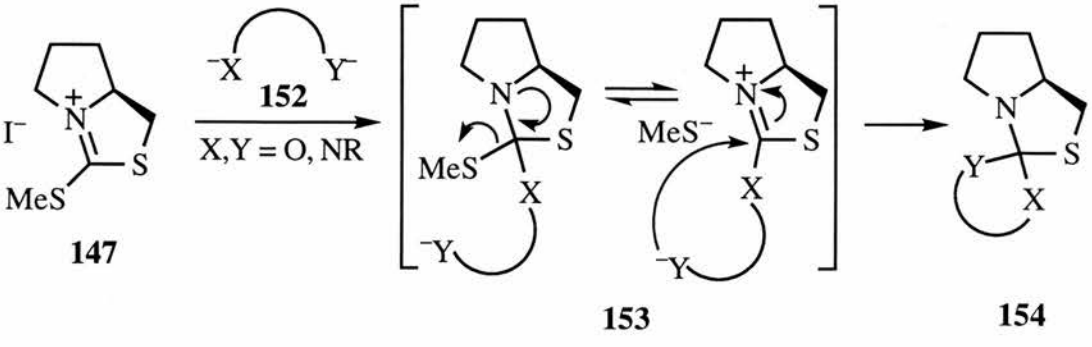
147 **148** **149**

to give the thiazolidinone **149** and a methyl sulphide by way of the intermediates **148** as shown. It was realised that, since **147** is chiral, this might form the basis of a useful method for kinetic resolution of secondary alcohols. In a preliminary study, reaction of **147** with two equivalents of sodium 1-phenylethoxide in toluene at room temperature proceeded as



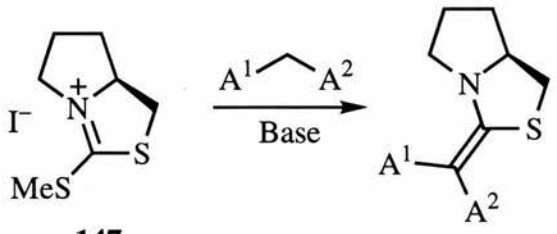
shown to afford the unreacted (*S*)-alkoxide **150** and the (*S*)-sulphide **151** each in 20–30% e.e.[56] The initial aim was therefore to optimise this procedure by varying such parameters as the nature of the counter-cation, the solvent and temperature in the hope of improving the e.e. Variation in the structure of the resolving agent also seemed worthwhile and, in particular, a range of monocyclic chiral iminium salts were to be examined for this application.

The possibility of reacting **147** with a bidentate nucleophile **152** was also of interest, since reaction by way of the intermediates **153** was



expected to afford access to the interesting and novel spiro compounds **154** and, as noted in Section A, these monothio derivatives of orthocarbamates and orthoureas are little known.

While the work was in progress, an important paper appeared in which reaction of **147** with acidic methylene compounds in the presence of base was reported to result in condensation to give the polarised double



147 **155**

bond compounds **155**.[57] However, this was only reported for two examples ($A^1 = A^2 = CO_2Me$ or CN) and the products were not fully characterised. In view of the considerable interest in compounds of this type as described in Section B, a detailed study of the structure and reactivity of a range of analogues of **155** seemed in order. In particular, the chiral nature of **155** meant that reaction with nucleophiles or electrophiles might proceed with significant diastereoselectivity and thus form the basis of a useful method of asymmetric synthesis.

EXPERIMENTAL

A. Symbols and Abbreviations

mmol	millimoles
M	mol dm^{-3}
min	minutes
h	hours
NMR	nuclear magnetic resonance
δ	chemical shift in ppm
J	spin spin coupling constant
s, d, t, q, m, br	singlet, doublet, triplet, quartet, multiplet, broad
ν_{max}	infrared absorption frequency in cm^{-1}
m/z	mass to charge ratio
M^+	mass of molecular ion
RT	room temperature
m.p.	melting point
b.p.	boiling point
eq	equivalent
e.e.	enantiomeric excess
THF	tetrahydrofuran
TLC	thin layer chromatography

B. Instrumentation and General Techniques

1. N.M.R. Spectroscopy

a. ^{1}H NMR

Routine spectra were obtained at 200 MHz on a Varian Gemini 200 spectrometer. Spectra of new compounds and variable temperature spectra were obtained at 300 MHz on a Bruker AM-300 spectrometer operated by Mrs M. Smith. Chiral shift reagent spectra were also obtained both at 200 MHz on a Varian Gemini 200 spectrometer and 300 MHz on a Bruker AM-300 spectrometer operated by the author and Mrs M. Smith.

b. ^{13}C NMR

Routine spectra were obtained at 50 MHz on a Varian Gemini 200 and spectra of new compounds were obtained at 75 MHz on a Bruker AM-300 spectrometer operated by the author and Mrs M. Smith.

All ^{1}H and ^{13}C spectra were obtained from solutions in deuteriochloroform, except when stated otherwise, and chemical shifts are expressed in parts per million to high frequency of tetramethylsilane.

2. Infrared Spectroscopy

Spectra were obtained on a Perkin-Elmer 1420 ratio recording spectrophotometer or Perkin-Elmer 1710 Fourier transform spectrophotometer. Solids were run as nujol mulls and liquids as thin films using matched sodium chloride cells. Spectra were calibrated with the polystyrene peak at 1603 cm^{-1}.

3. Mass Spectrometry

Mass spectra and high resolution measurements were obtained on an AEI MS50 instrument operated by Mr C. Millar.

4. Gas Chromatography-Mass Spectrometry

Gas chromatography-mass spectrometry studies were carried out on a Hewlett-Packard 5890A gas chromatograph coupled to a Finngan Incos 50 mass spectrometer operated by Mr C. Millar.

5. Elemental Analysis

Microanalyses for carbon, hydrogen and nitrogen were carried out on a Carlo-Erba 1106 elemental analyser operated by Mrs S. Williamson.

6. Melting Points

Routine melting points were determined using an Electrothermal melting point apparatus while melting points of new compounds were determined on a Reichert hot-stage microscope. All melting points are uncorrected.

7. Thin Layer Chromatography

This was carried out using 0.2 mm layers of silica (Merck, Kieselgel $60F_{254}$) or of alumina (Merck, Aluminium oxide $60F_{254}$) on aluminium sheets The components were observed under ultraviolet light.

8. Preparative Thin Layer Chromatography

This was carried out using 1.0 mm layers of silica (Merck, Kieselgel 60-80 mesh), containing 0.5% Woelm fluorescent green indicator, on glass plates. After locating the components with ultraviolet light, the bands were scraped off and the products removed from the support by soaking in dichloromethane for 3 h.

9. Column Chromatography

This was carried out using Fisons silica gel for chromatography (60-

120 mesh) or alumina (100-250 mesh).

10. Drying and Evaporation of Organic Solutions

Organic solutions were dried by standing over anhydrous magnesium sulfate and were evaporated under reduced pressure on a Büchi rotary evaporator.

11. Drying and Purification of Solvents

Commercially available solvents were used without further purification unless otherwise indicated. Dry ether and toluene were prepared by the addition of sodium wire. Dry THF was prepared by preliminary drying with sodium wire and then distilling from potassium benzophenone ketyl. ''Pet. ether'' refers to light petroleum, the redistilled 40-60°C boiling fraction being used for chromatography.

12. Optical Rotation

Optical rotation measurements were performed with an Optical Activity AA-1000 polarimeter operating at 589 nm using a 5 cm^3 solution cell with a 10 cm path length or a 1 cm^3 solution cell with a 20 cm path length.

13. Chiral Lanthanide NMR Shift Reagent Studies

The experiments were carried out at both 200 and 300 MHz on standard NMR samples using tris(3-heptafluoropropylhydroxymethylene-(1*R*)-camphorato)europium (III), by the author and Mrs M. Smith.

The enantiomerically enriched samples were run after the racemic analogues had been used to optimise the experimental conditions in each case.

C. Optimisation of the kinetic resolution of (*R*,*S*)-1-phenylethanol using (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide 147

1. Preparation of the iminium salt

a. Preparation of (S)-prolinol[58] (2-hydroxymethylpyrrolidine) **175**

(*S*)-Proline **174** (20.0 g, 174 mmol) was added slowly (2 g portions) to a well stirred boiling suspension of $LiAlH_4$ (11.0 g, 290 mmol) in anhydrous THF (400 cm^3) under nitrogen. The mixture was heated under reflux for 1 h. Excess $LiAlH_4$ was destroyed by cautiously adding a solution of KOH (4.76 g) in water (20 cm^3).The mixture was heated for a further 15 min. The hot solution was filtered and the filtrate dried and evaporated at 30 °C to give the amino alcohol **175** (11.3 g, 64%) as a faintly orange oil; ν_{max} (neat) 3286 (NH and OH), 2952, 1541, 1412, 1047, 814 and 665 cm^{-1}; δ_H (200 MHz) 4.25 (2H, br s), 3.58 (1 H, half of AB pattern of d, J_{AB} 11, J_{AX} 4 Hz), 3.40 (1 H, half of AB pattern of d, J_{AB} 11, J_{BX} 7 Hz), 3.30-3.10 (1 H, m), 3.05-2.80 (2 H, m), 1.95-1.60 (3 H, m) and 1.55-1.30 (1 H, m); δ_C (50 MHz) 63.9 (CH_2OH), 59.6 (CH), 45.8 (CH_2), 27.0 (CH_2) and 25.1 (CH_2).

b. Preparation of (*S*)-3-thia-1-azabicyclo[3.3.0]octane-2-thione **169**

A modification of the method of Roth[59] was used. (*S*)-Prolinol **175** (10.0 g, 99 mmol) was dissolved in 2 M NaOH (150 cm^3) at room temperature and carbon disulfide (9.8 cm^3, 12.4 g, 163 mmol) was added to the stirred suspension. After stirring for 20 h, a further portion of CS_2 (5 cm^3, 6.3 g, 83 mmol) was added and the solution stirred for an additional 4 h. The solution was extracted with CH_2Cl_2 and the organic layer washed with water, dried and evaporated to afford (*S*)-3-thia-1-

azabicyclo[3.3.0]octane-2-thione **169** (9.05 g, 48%) as colourless crystals, m.p. 131-132 °C (lit.,[56] 130-131 °C; lit.,[57] 132-133 °C); $[\alpha]_D^{20}$ –155.4° (c 0.98, CH_2Cl_2) [lit.,[56] $[\alpha]_D^{20}$ –159.8° (c 1.0, CH_2Cl_2)]; δ_H (200 MHz) 4.55 (1 H, m), 3.52 (1 H, m), 3.40 (1 H, m), 3.25 (2 H, m), 2.45-2.20 (2 H, m), 2.15 (1 H, m) and 1.70 (1 H, m); δ_C (50 MHz) 191.2 (CS), 72.5 (CH), 46.8 (CH_2), 36.3 (CH_2), 31.8 (CH_2) and 29.3 (CH_2).

c. Preparation of (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147**

Based on a procedure by Roussel et al.,[60] a mixture of thiazolidinethione **169** (4.36 g, 27.4 mmol), acetone (110 cm^3) and methyl iodide (15.6 cm^3, 35.5 g, 250 mmol) was stirred for 16 h at room temperature. The resulting precipitate was filtered off and washed with ether (50 cm^3). The filtrate was concentrated and a second crop of the product filtered off and washed with ether (50 cm^3). The solids were combined to yield (*S*)-2-methylthio-3-thia-1-azabicyclo[3.3.0]oct-1-enium iodide **147** (7.2 g, 87%) as colourless crystals , m.p. 107-109 °C (lit.,[56] 111-112 °C; lit.,[57] 104-105 °C); $[\alpha]_D^{20}$ –248.7° (c 1.53, CH_2Cl_2) [lit.,[56] $[\alpha]_D^{20}$ –256.5° (c 1.66, CH_2Cl_2)]; ν_{max} 1560 (C=N), 1302, 1201, 1169, 1049, 1026 and 948 cm^{-1}; δ_H (200 MHz) 5.40 (1 H, m), 4.15-4.05 (2 H, m), 4.00-3.70 (2 H, m), 2.98 (3 H, s), 2.68 (2 H, m) and 2.40 (2 H, m); δ_C (50 MHz) 186.3 (4^{ry}), 77.0 (CH), 48.8 (CH_2), 38.0 (CH_2), 29.0 (CH_2), 28.9 (CH_2) and 19.3 (Me).

2. Examination of different metal alkoxides in toluene

a. Resolution of sodium (*R*,*S*)-1-phenylethoxide

A solution of (*R*,*S*)-1-phenylethanol (1.62 g, 13.3 mmol) and sodium metal (1.15 g, 50 mmol) in dry toluene (25 cm^3) was heated under reflux

for 24 h under nitrogen. The solution was cooled, excess sodium removed and the solution used immediately.

To the solution of sodium (*R*,*S*)-1-phenylethoxide (13.3 mmol) in toluene was added (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (2.0 g, 6.65 mmol) at room temperature under nitrogen. After stirring for 16 h, water (400 cm^3) was added, and the mixture extracted with CH_2Cl_2 (300 cm^3) which was dried and evaporated to give an orange brown oil (1.57 g). Kugelrohr distillation of this afforded a colourless oil (0.39 g), b.p. 110-150 °C/ 5 mmHg, containing 1-phenylethanol **178** and methyl 1-phenylethyl sulfide **151** in a molar ratio of 7 : 2. Further distillation (155-175 °C/ 5 mmHg) gave an oil (0.24 g) which contained a mixture of all three products, **178**, **151** and (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one **149** in a molar ratio of 19 : 5 : 15. The overall recovery of **178** was 0.40 g (50%) and of **151** 0.13 g (16%).

Spectroscopic data:

178 δ_H 7.40–7.15 (5 H, m), 4.85 (1 H, q, *J* 7), 2.28 (1 H, br s) and 1.45 (3 H, d, *J* 7); δ_C 145.7 (4ry), 128.2 (2 CH), 127.4 (CH), 125.3 (2 CH), 70.3 (CH) and 25.1 (Me).

151 δ_H 7.40–7.15 (5 H, m), 3.83 (1 H, q, *J* 7), 1.88 (3 H, s) and 1.55 (3 H, d, *J* 7); δ_C 133.1 (4ry), 128.5 (CH), 128.2 (2 CH), 127.1 (2 CH), 45.6 (CH), 22.0 (SMe) and 14.5 (Me).

149 See p. 42.

The e.e. of the alcohol was determined by ^{1}H NMR using the chiral shift reagent, tris(3-heptafluoropropylhydroxymethylene-(1*R*)-camphor--ato)europium (III) [Eu(hfc)$_3$].[61] For this purpose the samples were prepared by the gradual addition of chiral lanthanide shift reagent (C.L.S.R.) to the alcohol in $CDCl_3$ solution until the 200 MHz ^{1}H NMR spectrum showed optimum separation of enantiomer peaks. The C.L.S.R. added was normally 9-12.5% molar equivalent and the peak separation was

greatest for the proton bonded to the stereogenic centre. The quartets due to PhC<u>H</u>(Me)OH shifted from 4.85 to 10.58 for the (*S*)-enantiomer and to 10.80 for the (*R*)-enantiomer. The assignment of the lower frequency signal to the (*S*)-enantiomer relies on the previous work[56] in which a pure sample with 29% e.e. in favour of the lower frequency signal gave a rotation of $[\alpha]_D$ –12.0° [lit.,[62] –40.95° for (*S*)-enantiomer]. The alcohol obtained in this case was found to have an e.e. of 21% in favour of the (*S*)-enantiomer.

b. <u>Resolution of potassium (*R*,*S*)-1-phenylethoxide</u>

Using the same conditions as above but with potassium metal (1.17 g, 30 mmol), potassium (*R*,*S*)-1-phenylethoxide was prepared and used immediately.

To the solution of potassium (*R*,*S*)-1-phenylethoxide (13.3 mmol) in toluene (25 cm^3) was added (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (2.0 g, 6.65 mmol) at room temperature under nitrogen. After stirring for 16 h, water (400 cm^3) was added and the mixture extracted with CH_2Cl_2 (300 cm^3) which was dried and evaporated to give an orange brown oil (1.27 g). Kugelrohr distillation of this afforded a colourless oil (0.37 g), b.p. 110-150 °C/ 5 mmHg containing PhCH(Me)OH **178** and PhCH(Me)SMe **151** in a molar ratio of 17 : 2. Further distillation (155-175 °C/ 5 mmHg) gave an oil (0.12 g) which was a mixture of **178**, **151** and (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one **149** in a molar ratio of 5 : 1 : 7. The overall recovery of **178** was 0.36 g (44%) and of **151** 0.06 g (8%).

The alcohol was determined to have an e.e. of 6% in favour of the (*S*)-enantiomer using the chiral lanthanide NMR shift reagent.

c Resolution of lithium (*R*,*S*)-1-phenylethoxide

Using the same conditions as above but with lithium metal (0.35 g, 50 mmol), lithium (*R*,*S*)-1-phenylethoxide was prepared and used immediately.

To the solution of lithium (*R*,*S*)-1-phenylethoxide (13.3 mmol) in toluene (25 cm^3) was added (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (2.0 g, 6.65 mmol) at room temperature under nitrogen. After stirring for 16 h, water (400 cm^3) was added and the mixture extracted with CH_2Cl_2 (300 cm^3) which was dried and evaporated to give an orange brown oil (2.56 g). Kugelrohr distillation of this afforded a colourless oil (0.77 g), b.p. 110-120 °C/ 5 mmHg, containing PhCH(Me)OH **178** and PhCH(Me)SMe **151** in a molar ratio of 19 : 8. Further distillation (155-175 °C/ 5 mmHg) gave an oil (0.25 g) which was a mixture of **178**, **151** and (*S*)-3-thia-1-azabicyclo [3.3.0]octan-2-one **149** in a ratio of 19 : 8 : 1. The overall recovery of **178** was 0.67 g (82%) and of **151** 0.34 g (42%).

^1H NMR analysis using chiral shift reagent showed the alcohol to have an e.e. of 2% in favour of the (*S*)-enantiomer.

d. Resolution of caesium (*R*,*S*)-1-phenylethoxide **179**

A mixture of (*R*,*S*)-1-phenylethanol (1.62 g, 13.3 mmol) and sodium metal (1.15 g, 50 mmol) in dry toluene (25 cm^3) was heated under reflux for 24 h under nitrogen. The solution was cooled and excess sodium removed. Caesium chloride (2.24 g, 13.3 mmol) was added to the resulting sodium alkoxide solution which was heated under reflux for 2 h to afford the caesium alkoxide solution.

To the freshly prepared solution of caesium (*R*,*S*)-1-phenylethoxide (13.3 mmol) in toluene (25 cm^3) was added (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (2.0 g, 6.65 mmol) at room

temperature under nitrogen. After stirring for 16 h, water (400 cm^3) was added and the mixture extracted with CH_2Cl_2 (300 cm^3) which was dried and evaporated to give an orange brown oil (2.73 g). Kugelrohr distillation of this gave a colourless oil (0.31 g), b.p. 100-120 °C/ 2 mmHg, containing PhCH(Me)OH **178** and PhCH(Me)SMe **151** in a molar ratio of 7 : 3. Further distillation (150-175 °C/ 2 mmHg) gave an oil (0.29 g) which was a mixture of **178**, **151** and (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one **149** in a molar ratio of 25 : 8 : 1. The overall recovery of **178** was 0.40 g (50%) and of **151** 0.19 g (24%).

^1H NMR analysis using chiral shift reagent showed the alcohol to have an e.e. of 7% in favour of the (*S*)-enantiomer.

e. Attempted resolution of bromomagnesium (*R,S*)-1-phenylethoxide **167**

i) *Using Grignard reagent*

A mixture of magnesium turnings (0.53 g, 21.8 mmol) and a few crystals of iodine in dry ether (20 cm^3) was stirred under nitrogen. A few drops of a solution of ethyl bromide (0.99 cm^3, 13.3 mmol) in dry ether (30 cm^3) were added from a pressure equalising funnel to start the reaction. The remainder of the ethyl bromide solution was added over a period of 15-20 min and mixture stirred for half an hour under nitrogen to afford the Grignard reagent (13.3 mmol).

(*R,S*)-1-phenylethanol (1.62 g, 13.3 mmol) was added with stirring. Reaction took place immediately and a yellow precipitate was formed. The mixture was stirred for an additional 2 h to afford the bromomagnesium alkoxide **167**. Toluene (25 cm^3) was added and the solution used immediately.

To the freshly prepared solution of bromomagnesium alkoxide **167** (13.3 mmol) was added (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-

enium iodide **147** (2.0 g, 6.65 mmol) at room temperature under nitrogen. After stirring for 16 h, water (400 cm^3) was added and the mixture extracted with CH_2Cl_2 (300 cm^3) which was dried and evaporated to give an orange brown oil (1.20 g). Kugelrohr distillation of this afforded (*R,S*)-1-phenylethanol (0.57 g) as a colourless oil, b.p. 50-70 °C/ 2 mmHg. Further distillation (80-115 °C/ 2 mmHg) gave a liquid (0.41 g) which was shown by ^1H NMR to also consist mainly of the alcohol with none of the desired sulfide **151**.

ii) *Using magnesium bromide etherate at room temperature*

A mixture of magnesium dust (0.65 g, 27 mmol) and mercury (II) bromide (4.79 g, 13.3 mmol) in dry ether (120 cm^3) and toluene (60 cm^3) was heated under reflux for 2 h under a nitrogen atmosphere to afford anhydrous magnesium bromide etherate (13.3 mmol). The solution of $MgBr_2.Et_2O$ was added to a solution of sodium alkoxide (13.3 mmol) in toluene prepared as in (a). Reaction took place immediately and a yellow precipitate was formed. The mixture was stirred for 30 min to afford the bromomagnesium alkoxide **167** (13.3 mmol).

To the freshly prepared solution of bromomagnesium alkoxide **167** (13.3 mmol) was added (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (2.0 g, 6.65 mmol) at room temperature under nitrogen. After stirring for 16 h, water (400 cm^3) was added and the mixture extracted with CH_2Cl_2 (300 cm^3) which was dried and evaporated to give an orange brown oil. Kugelrohr distillation of this afforded (*R,S*)-1-phenylethanol (0.79 g) as a colourless oil, b.p. 80-100 °C/ 2 mmHg. Further distillation (110-150 °C/ 2 mmHg) gave a liquid (0.25 g) which was shown by ^1H NMR to also consist mainly of the alcohol with none of the desired sulfide **151**.

iii) *Using magnesium bromide etherate and heating under reflux*

Reaction as in e(ii). above using (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (2.0 g, 6.65 mmol) but heating under reflux for 24 h under nitrogen gave an orange brown oil (1.68 g). Kugelrohr distillation of this afforded (*R,S*)-1-phenylethanol (0.57 g) as a colourless oil, b.p. 60-80 °C/ 2 mmHg. Further distillation (90-110 °C/ 2 mmHg) again gave a liquid (0.21 g) which contained no sulfide.

3. Resolution of quaternary ammonium and phosphonium (*R,S*)-1-phenylethoxides

a. Attempted resolution of benzyltriethylammonium (*R,S*)-1-phenylethoxide **180**

A mixture of (*R,S*)-1-phenylethanol (1.62 g, 13.3 mmol) and sodium metal (1.15 g, 50 mmol) in dry toluene (25 cm^3) was heated under reflux for 24 h under nitrogen. The solution was cooled and excess sodium removed to give the sodium alkoxide (13.3 mmol). A solution of benzyltriethylammonium chloride (3.03 g, 13.3 mmol) in acetonitrile (40 cm^3) was added and the mixture stirred for 2 h at room temperature to afford the product **180** (13.3 mmol) which was used immediately.

To the freshly prepared alkoxide solution was added (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (2.0 g, 6.65 mmol) at room temperature under nitrogen. After stirring for 24 h, water (400 cm^3) was added and the mixture extracted with CH_2Cl_2 (300 cm^3) which was dried and evaporated to give an orange brown oil (5.11 g). Kugelrohr distillation of this gave benzyldiethylamine **181** (2.49 g) as a colourless oil, b.p. 60-120 °C/ 2 mmHg; δ_H (200 MHz) 7.45 (5 H, m) 3.55 (2 H, s), 2.50 (4 H, q, *J* 8 Hz) and 1.05 (6 H, t, *J* 8 Hz) and 1-phenylethanol; δ_H (200 MHz) 7.45 (5 H, m) 4.88 (1 H, q, *J* 8 Hz), 2.15 (1 H, br s) and 1.50 (3 H, d, *J* 8 Hz) and no sulfide was formed.

NMR analysis showed the residue to be mainly the thiazolidinone **149.**

b Resolution of tetramethylammonium (*R*,*S*)-1-phenylethoxide **182**

The salt was prepared in an identical manner to alkoxide **180** using solid tetramethylammonium chloride (1.46 g, 13.3 mmol) and stirring for 20 h at room temperature and used immediately.

This was reacted in an analogous manner to that described for benzyltriethylammonium (*R*,*S*)-1-phenylethoxide **180** to give an orange brown oil (1.6 g). Kugelrohr distillation of this afforded a colourless oil (0.45 g), b.p. 90-120 °C/ 2 mmHg, containing PhCH(Me)OH **178** and PhCH(Me)SMe **151** in a molar ratio of 27 : 7. Further distillation (150-175 °C/ 2 mmHg) gave an oil (0.16 g) which was a mixture of **178**, **151** and (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one **149** in a molar ratio of 27 : 7 : 1. The overall recovery of **178** was 0.46 g (56%) and of **151** 0.15 g (18%).

The alcohol was determined to have an e.e. of < 2% in favour of the (*R*)-enantiomer using ^{1}H NMR in the presence of the chiral shift reagent as described above.

c. Attempted resolution of tetraphenylphosphonium (*R*,*S*)-1-phenylethoxide **183**

The salt was prepared in an identical manner to alkoxide **180** using tetraphenylphosphonium bromide (5.58 g, 13.3 mmol) solution in acetonitrile (30 cm^3) and stirring for 2 h at room temperature and used immediately.

This was reacted in an analogous manner to that described for benzyltriethylammonium (*R*,*S*)-1-phenylethoxide **180** to give orange coloured oil (1.35 g). Kugelrohr distillation of this afforded (*R*,*S*)-1-phenylethanol (0.48 g) as a colourless oil, b.p. 100-120 °C/ 2 mmHg.

Further distillation (130-170 °C/ 2 mmHg) also gave the same product (0.31 g) and no sulfide **151** was formed.

4. Effect of solvent and temperature on resolution of sodium (*R*,*S*)-1-phenylethoxide

a. Resolution in dichloromethane at RT

A solution of (*R*,*S*)-1-phenylethanol (1.62 g, 13.3 mmol) and sodium metal (1.15 g, 50 mmol) in toluene (25 cm^3) was heated under reflux for 24 h. The solution was cooled and excess sodium removed. Toluene was evaporated to afford light yellow sodium alkoxide. This was taken up in CH_2Cl_2 (25 cm^3), (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (2.0 g, 6.65 mmol) added and the solution stirred for 24 h at room temperature.

The solution was diluted with hexane (25 cm^3) and filtered to give a light brown solid (0.99 g). The solid was partitioned in a mixture of water and CH_2Cl_2 (200 cm^3) (1 : 1). The organic phase was separated and aqueous phase extracted with CH_2Cl_2 (200 cm^3). The combined organic layers were washed with water (400 cm^3), dried and evaporated to give amber oil (0.26 g). The filtrate was washed with water (200 cm^3), dried and evaporated to afford a yellow oil (2.1 g). Kugelrohr distillation of this (110-150 °C/ 15 mmHg) gave a colourless oil (0.58 g) containing PhCH(Me)OH **178** and PhCH(Me)SMe **151** in a molar ratio of 4 : 5. Further distillation (155-175 °C/ 15 mmHg) gave an oil (0.16 g) which was a mixture of **178**, **151** and (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one **149** in a molar ratio of 1 : 2 : 1. The overall recovery of **178** was 0.20 g (24%) and of **151** 0.37 g (46%).

The alcohol **178** was found to have an e.e. of 18% in favour of the (*S*)-enantiomer using the chiral shift reagent.

b. Resolution in toluene at –78 °C

A solution of (*R*,*S*)-1-phenylethanol (1.62 g, 13.3 mmol) and sodium metal (1.15 g, 50 mmol) in dry toluene (25 cm^3) was heated under reflux for 24 h under nitrogen. The solution was cooled, excess sodium removed and the solution used immediately.

To the solution of sodium (*R*,*S*)-1-phenylethoxide (13.3 mmol) in toluene was added (*S*)-2-methylthio-3-thia-1λ⁴-azabicyclo[3.3.0]oct-1-enium iodide **147** (2.0 g, 6.65 mmol) at –78 °C under nitrogen. After stirring for 16 h, water (400 cm^3) was added and the mixture extracted with CH_2Cl_2 (300 cm^3) which was dried and evaporated to give an orange brown oil (1.57 g). Kugelrohr distillation of this afforded a colourless oil (0.39 g), b.p. 110-150 °C/ 15 mmHg, containing PhCH(Me)OH **178** and PhCH(Me)SMe **151** in a molar ratio of 6 : 1. Further distillation (155-175 °C/ 15 mmHg) gave an oil (0.24 g) which was a mixture of **178**, **151** and (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one **149** in a molar ratio of 7 : 1 : 6. The overall recovery of **178** was 0.43 g (54%) and of **151** 0.09 g (12%).

The alcohol was found to have an e.e. of 15% in favour of the (*S*)-enantiomer using the chiral shift reagent.

c. Resolution in dichloromethane at –78 °C

A solution of (*R*,*S*)-1-phenylethanol (1.62 g, 13.3 mmol) and sodium metal (1.15 g, 50 mmol) in toluene (25 cm^3) was heated under reflux for 24 h. The solution was cooled and excess sodium removed. Toluene was evaporated to afford light yellow sodium alkoxide. This was taken up in CH_2Cl_2 (25 cm^3), (*S*)-2-methylthio-3-thia-1λ⁴-azabicyclo[3.3.0]oct-1-enium iodide **147** (2.0 g, 6.65 mmol) added and the solution stirred for 24 h at –78 °C under nitrogen.

The solution was diluted with hexane (25 cm^3) and filtered to give a light brown solid (1.10 g). The solid was partitioned in a mixture of water

and CH_2Cl_2 (200 cm^3) (1 : 1). The organic phase was separated and aqueous phase extracted with CH_2Cl_2 (200 cm^3). The combined organic layers were washed with water (400 cm^3), dried and evaporated to give an amber oil (1.00 g). Kugelrohr distillation of this (110-150 °C/ 15 mmHg) gave a colourless oil (0.52 g) containing PhCH(Me)OH **178** and PhCH(Me)SMe **151** in a molar ratio of 4 : 3. Further distillation (155-175 °C/ 15 mmHg) gave an oil (0.37 g) which was a mixture of **178**, **151** and (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one **149** in a molar ratio of 5 : 4 : 2. The overall recovery of **178** was 0.42 g (52%) and of **151** 0.40 g (50%).

The alcohol **178** was found to have an e.e. of 20% in favour of the (*S*)-enantiomer using the chiral shift reagent.

D. Preparation of other bicyclic iminium salts and their evaluation for kinetic resolution

1. Attempted preparation of 2-(*S*)-[(*R*)-α-hydroxybenzyl]pyrrolidine 194

Following a method by Ookawa[63], (*S*)-proline (6.67 g, 57.9 mmol) was added to a cooled (0 °C) suspension of PCl_5 (12.06 g, 57.9 mmol) in CH_2Cl_2 (170 cm^3) and the mixture stirred for 16 h allowing it to warm to room temperature. The solution was concentrated to 50 cm^3 under reduced pressure and used for acylation of benzene.

Dry benzene (170 cm^3) and $AlCl_3$ (23 g, 173.7 mmol) were then added and the mixture heated under reflux for 4 h. After cooling to room temperature the mixture was poured into 1 M HCl (75 cm^3) containing crushed ice. The aqueous phase was washed with ethyl acetate and then neutralised with Na_2CO_3 until a solid precipitated out of solution. The resulting viscous mixture was first extracted with CH_2Cl_2 (3 x 100 cm^3)

and then filtered. The filter cake was thoroughly washed with CH_2Cl_2 (200 cm^3) and the extracts were combined with the filtrate which was washed with water (400 cm^3) and dried.

The dried organic layer was concentrated to 100 cm^3 and methanolic hydrogen chloride (3%, 100 cm^3) was added. The resulting brown solution was evaporated to give deep brown coloured oil. The residue was redissolved in ethanol (50 cm^3) which was cooled to 0 °C. Sodium borohydride (0.40 g, 10.4 mmol, 4 eq) was slowly added to the stirred solution over 30 minutes. The mixture was stirred at room temperature for 16 h and then poured into 3 M HCl (100 cm^3), and the ethanol evaporated off under reduced pressure. The aqueous layer was washed with ethyl acetate and then made alkaline with solid NaOH. The alkaline solution was extracted with CH_2Cl_2 which was dried and evaporated to yield a dark brown product (1.81 g, 5%). ^1H NMR analysis showed little if any of the desired compound to be present.

2. Preparation of bicyclic carbamates and thiocarbamates

a. Preparation of (*S*)-3-oxa-1-azabicyclo[3.3.0]octan-2-one **195**

Based on a method by Kaneko,[64] (*S*)-prolinol **175** (5.0 g, 50 mmol) was dissolved in a mixture of water (85 cm^3) and 40% aqueous potassium hydroxide (12.5 cm^3) and cooled to –5 °C. A solution of phosgene in toluene (1.93 M, 6.53 g, 34.2 cm^3, 66 mmol) was added concurrently with a solution of 40% aqueous potassium hydroxide (25 cm^3) over a period of 15 min to the stirred solution and resulting mixture allowed to warm to room temperature. After stirring for 16 h, the reaction mixture was extracted with CH_2Cl_2 (400 cm^3) which was washed with water (300 cm^3), dried and evaporated to afford a reddish brown oil (2.42 g, 39%). Kugelrohr distillation afforded (*S*)-3-oxa-1-azabicyclo[3.3.0]octan-2-one

195 (1.50 g, 24%) as a colourless oil, b.p. 165 °C/ 0.1 mmHg (lit.,[65] 120 °C/ 12 mmHg); $[\alpha]_D^{20}$ –36.2° (c 1.16, CH_2Cl_2) [lit.,[65] $[\alpha]_D^{20}$ –35.1° (c 0.702, $CHCl_3$)]; δ_H (200 MHz) 4.50 (1 H, dd, *J* 9, 8 Hz), 4.18 (1 H, dd, *J* 9, 4 Hz), 3.95 (1 H, m), 3.65 (1 H, m), 3.20 (1 H, m), 2.15-1.75 (3 H, m) and 1.65-1.35 (1 H, m); δ_C (50 MHz) 161.4 (CO), 67.5 (CH_2), 59.1 (CH), 45.4 (CH_2), 30.3 (CH_2) and 25.3 (CH_2).

b. Preparation of (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one **149**

Based on a procedure by Roussel,[60] (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (5 g, 16.6 mmol) was added to a solution of sodium methoxide (16.6 mmol) in methanol (50 cm^3) and stirred for 16 h at room temperature. Water (100 cm^3) was added and the mixture extracted with CH_2Cl_2 (3x100 cm^3). The combined organic layers were washed with water (300 cm^3), dried and evaporated to yield a colourless solid (2.26 g, 95%). Recrystallisation from ethyl acetate (50 cm^3) with cooling (0 °C) afforded (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one **149** (2.04 g, 86%) as colourless crystals, m.p. 69-70 °C (lit.,[56] 70-71 °C); $[\alpha]_D^{20}$ –34.2° (c 1.12, CH_2Cl_2) [lit.,[56] $[\alpha]_D^{20}$ –35.4° (c 1.0, CH_2Cl_2)]; ν_{max} (nujol) 1697 (CO), 1664, 1334, 1315, 1300, 1285, 1239, 1211, 1170, 883, 656, 593 cm^{-1}; δ_H (300 MHz) 4.24 (1 H, m), 3.58 (1 H, m), 3.35 (1 H, half of AB pattern of d, J_{AB} 10, J_{AX} 8 Hz), 3.25 (1 H, half of AB pattern of d, J_{AB} 10, J_{BX} 9 Hz), 3.25-3.15 (1 H, m), 2.35-2.00 (3 H, m) and 1.60 (1 H, m); δ_C (75 MHz) 170.0 (CO), 63.0 (CH), 43.3 (CH_2), 33.2 (CH_2), 30.9 (CH_2) and 27.2 (CH_2); *m/z* 143 (M^+, 100%), 128 (70), 115 (12), 74 (16), 70 (20) and 55 (31).

c.(i) Preparation of (*S*)-3-oxa-1-azabicyclo[3.3.0]octane-2-thione **196**

Based on a method by Sharma,[66] a stirred solution of triethylamine (3.95 g, 5.4 cm^3, 39 mmol) and (*S*)-prolinol **175** (2.0 g, 19.8 mmol) in

CH_2Cl_2 (100 cm^3) was cooled down to 0 °C and a solution of thiophosgene (2.0 cm^3, 2.99 g, 26 mmol) in CH_2Cl_2 (50 cm^3) was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred overnight. The mixture was then washed with water (2 x) and 0.5 M sodium hydroxide, dried and evaporated to afford a reddish brown semi-solid (1.61 g, 57%). Column chromatography on alumina using ether : pet. ether (70:30) gave, at R_f 0.28, (*S*)-3-oxa-1-azabicyclo[3.3.0]octane-2-thione **196** (1.07 g, 38%) as fine colourless crystals, m.p. 58.5-59 °C (lit.,[56] 58-59 °C); $[\alpha]_D^{20}$ +72.7° (c 1.15, CH_2Cl_2) [lit.,[56] $[\alpha]_D^{20}$ +69° (c 1.02, CH_2Cl_2)]; (Found: C, 50.5; H, 6.4, N, 9.8. C_6H_9NOS requires C, 50.3; H, 6.3; N, 9.8%); ν_{max} (nujol) 1501, 1327, 1318, 1293, 1247, 1171, 1143, 924 and 647 cm^{-1}; δ_H (200 MHz) 4.80-4.70 (1 H, m), 4.35-4.20 (2 H, m), 3.95-3.75 (1 H, m), 3.55-3.40 (1 H, m), 2.35-2.00 (3 H, m) and 1.85-1.55 (1 H, m); δ_C (50 MHz) 189.5 (CS), 72.9 (CH_2), 62.8 (CH), 47.2 (CH_2), 30.5 (CH_2) and 26.3 (CH_2).

A second minor component at R_f 0.64 was identified by NMR and high resolution mass spectra to be (*S*,*S*)-dipyrrolidino[3,4-a:6,7-a′]1,3,6-oxadiazocane-2-thione **197** (0.02 g, 1%); (Found: M^+, 226.1142. $C_{11}H_{18}N_2OS$ requires *M*, 226.1140); δ_H (300 MHz) 4.55 (2 H, m), 4.25-4.05 (2 H, m), 3.85-3.75 (2 H, m), 3.72-3.60 (2 H, m), 3.15-2.95 (2 H, m), 2.20-1.95 (4 H, m) and 1.95-1.60 (4 H, m); δ_C (75 MHz) 190.6 (CS), 78.9 (CH_2), 62.6 (CH), 60.0 (CH), 58.3 (CH_2), 56.7 (CH_2), 50.1 (CH_2), 28.6 (CH_2), 27.2 (CH_2), 24.4 (CH_2) and 22.4 (CH_2); *m/z* 226 (M^+, 100%), 193 (28), 163 (16), 149 (12), 110 (32), 97 (73), 82 (38), 69 (58) and 55 (48).

c.(ii) Repeat preparation of **196** using more solvent

The method as in c(i) using (*S*)-prolinol (9.95 g, 98.5 mmol) and excess of solvent (1200 cm^3) afforded the desired product only. Column chromatography on alumina using ether : pet. ether (70:30) gave, at R_f

0.28, (*S*)-3-oxa-1-azabicyclo[3.3.0]octane-2-thione **196** (6.33 g, 45%) as colourless crystals; m.p., δ_H and δ_C as in c(i) above.

3. Preparation of iminium salts by silylation

a. Attempted preparation of (*S*)-2-trimethylsilylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium chloride **205**

A mixture of (*S*)-3-thia-1-azabicyclo[3.3.0]octane-2-thione **169** (4.0 g, 25 mmol), CH_2Cl_2 (110 cm^3) and trimethylsilyl chloride (31.73 cm^3, 27.16 g, 250 mmol) was stirred for 16 h at room temperature. The resulting light brown solution was evaporated to yield a light brown solid product. The ^{1}H NMR spectrum did not show any peaks corresponding to the iminium salt **205** and the starting material was recovered; δ_H and δ_C identical to thiazolidine-2-thione **169**.

b. Attempted preparation of (*S*)-2-trimethylsilyloxy-3-oxa-1λ^4-azabicyclo[3.3.0]oct-1-enium chloride **206**

A mixture of (*S*)-3-oxa-1-azabicyclo[3.3.0]octan-2-one **195** (0.57 g, 4.48 mmol), CH_2Cl_2 (25 cm^3) and trimethylsilyl chloride (5.69 cm^3, 4.87 g, 44.8 mmol) was stirred for 16 h at room temperature. The resulting light brown solution was evaporated *in vacuo* to afford brown oil (0.49 g, 46%). The ^{1}H NMR spectrum did not show any peaks corresponding to iminium salt **206** and starting material was recovered; δ_H and δ_C as in Section D2a.

c. Attempted preparation of (*S*)-2-trimethylsilyloxy-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium chloride **207**

i) *in dichloromethane at room temperature*

A mixture of (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one **149** (0.48 g, 3.35 mmol), CH_2Cl_2 (25 cm^3) and trimethylsilyl chloride (3.64 g, 44.8 mmol) was stirred for 16 h at room temperature. The resulting yellow solution was evaporated to afford yellow crystals (0.41 g). The ^1H NMR spectrum did not show any peaks corresponding to iminium salt **207** and starting material was recovered.

ii) *in toluene on heating under reflux*

The reaction as in c(i). using toluene and heating under reflux also gave unreacted starting material.

d. Attempted preparation of (*S*)-2-trimethylsilyloxy-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **208**

Trimethylsilyl chloride (4.25 cm^3, 3.64 g, 33.5mmol) was added to a stirred mixture of (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one **149** (0.48 g, 3,35 mmol) and sodium iodide (5.02, 33.5 mmol) in acetonitrile (25 cm^3). After stirring for 16 h at room temperature under nitrogen, the resulting precipitate was filtered off and the filtrate evaporated to afford a brown solid (0.45 g). The ^1H NMR spectrum did not show any peaks corresponding to iminium salt **208** and starting material was recovered.

e. Attempted preparation of (*S*)-2-trimethylsilyloxy-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium triflate **209**

A mixture of (*S*)-3-thia-1-azabicyclo[3.3.0]octan-2-one **149** (0.43 g, 3.0 mmol), toluene (35 cm^3) and trimethylsilyl trifluoromethanesulfonate (3.33 g, 15 mmol, 2.9 cm^3) was stirred at room temperature for 16 h. The resulting dark brown solution was evaporated to afford a dark brown solid (0.27 g); ν_{max} (nujol) 1654 (CO), 1252 and 1027 cm^{-1}; δ_H (200 MHz) 4.75 (1 H, m), 3.75-3.45 (4 H, m), 2.55-2.20 (3 H, m) and 1.85 (1 H, m);

δ_C (50 MHz) 157.6 (CO), 67.7 (CH), 46.4 (CH_2) 35.1 (CH_2), 30.0 (CH_2) and 28.1 (CH_2); *m/z* 143 (M^+, 75%) (for starting material), 114 (10), 74 (23), 69 (55) and 55 (100).

4. Preparation of derivatives by nucleophilic attack at C-2

a. Attempted preparation of (*S*)-2-chloro-3-oxa-1λ^4-azabicyclo[3.3.0]oct-1-enium chloride **212**

A mixture of (*S*)-3-oxa-1-azabicyclo[3.3.0]octane-2-one **195** (2.2 g, 17.3 mmol), phosphorus pentachloride (3.60 g, 17.3 mmol) and phosphorus oxychloride (40 cm^3) was heated under reflux for 4 h. The mixture was evaporated to give reddish brown oil (3.55 g). ^1H and ^{13}C NMR spectra were not taken due to instability of the compound.

The experiment was repeated by heating the reactants in the absence of $POCl_3$. The $POCl_3$ formed was evaporated and the product used immediately for the preparation of its corresponding t-butoxy salt **213**. ^1H and ^{13}C NMR spectra were not taken due to instability of the compound.

b. Attempted preparation of (*S*)-2-t-butoxy-3-oxa-1λ^4-azabicyclo[3.3.0]oct-1-enium chloride **213**

A mixture of crude (*S*)-2-chloro-3-oxa-1λ^4-azabicyclo[3.3.0]oct-1-enium chloride **212** (2.56 g, 14.08 mmol), dry CH_2Cl_2 (30 cm^3) and potassium t-butoxide (1.58 g, 14.08 mmol) was stirred for 4 h at room temperature. The mixture was evaporated to give a brown solid (3.09 g) Reaction had not taken place as no peak due to the Bu^t group was observed in the ^1H NMR spectrum.

c. Attempted preparation of (*S*)-2-t-butoxy-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium methanethiolate **216**

A mixture of (*S*)-2-methylthio-3-thia-1λ4-azabicyclo[3.3.0]oct-1-enium iodide **147** (1.0 g, 3.32 mmol), THF (100 cm^3) and potassium t-butoxide (0.37 g, 3.32 mmol) was heated under reflux for 24 h. The resulting mixture was distilled at atmospheric pressure to give THF containing t-butyl methyl sulfide (10 mg, 3%); δ_H 2.40 (3 H, s) and 1.23 (9 H, s); δ_C 30.5 (C*Me*$_3$). The residue consisted mainly of thiazolidinethione **169** and thiazolidinone **149** in a molar ratio of 2 : 1; δ_H and δ_C as in Sections C1b. and D2b. respectively.

d. Reaction of (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** with sodium phenoxide

A solution of phenol (0.63 g, 6.65 mmol) in toluene (40 cm^3) was heated under reflux with sodium metal (1.15 g, 25 mmol) for 24 h. The solution was cooled and excess sodium removed. (*S*)-2-Methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (1.0 g, 3.33 mmol) was added. After stirring at room temperature under nitrogen for 24 h, water (300 cm^3) was added and the mixture extracted with CH_2Cl_2 (300 cm^3) which was dried and evaporated to give a reddish brown oil (1.20 g). Kugelrohr distillation of this afforded a colourless oil (0.10 g) b.p. 90-110 °C/ 2 mmHg, that crystallised into the starting phenol; δ_H (200 MHz) 7.27-7.19 (2 H, m), 7.00-6.75 (3 H, m) and 5.70-5.35 (1 H, br s); δ_C 155.2 (4^{ry}), 129.6 (2 CH), 120.7 (CH) and 115.2 (2 CH).

Further distillation (150-180 °C/ 2 mmHg) gave a brown oil (0.60 g) which turned to a semi-solid. NMR analysis of this showed the presence of a 2 : 5 ratio of phenol; δ_H and δ_C as above, and the thiazolidinone **149**; δ_H (200 MHz) 4.20 (1 H, m), 3.60-3.45 (1 H, m), 3.45-3.10 (3 H, m),

2.30-1.85 (3 H, m) and 1.60 (1 H, m); δ_C (50 MHz) 169.8 (CO), 62.9 (CH), 42.9 (CH_2), 33.0 (CH_2), 30.6 (CH_2) and 27.0 (CH_2).

e. Reaction of (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** with sodium phenoxide on heating

The reaction as in d. above on heating under reflux for 24 h followed by addition of pet. ether (400 cm^3), filtering of the resulting suspension and evaporation of the mixture afforded a dark brown oil. GC-MS showed the thiazolidinethione **169**; δ_H and δ_C as in C1b; *m/z* 159, anisole; δ_H 3.80 (3 H, s); *m/z* 108 and phenol; *m/z* 94 to be present in a molar ratio of 13 : 2 : 7.

f. Attempted preparation of (*S*)-2-trimethylsilyloxy-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium methanethiolate **218**

A mixture of (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (1.0 g, 3.32 mmol), potassium trimethylsilanolate (0.43 g, 3.32 mmol) and CH_2Cl_2 (50 cm^3) was heated under reflux for 8 h. The resulting precipitate was filtered off and the filtrate evaporated to give an orange coloured oil (0.85 g). After chromatographic separation this proved to be a mixture of the thiazolidinone **149** and thiazolidinethione **169** in a molar ratio of 3 : 1 by ^{1}H and ^{13}C NMR.

In a repeat experiment, the solvent was distilled off at atmospheric pressure and shown to contain some trimethylsilyl methyl sulfide; δ_H 2.42 (3 H, s) and 0.07 (9 H, s); δ_C 1.9 ($SiMe_3$).

g. Attempted preparation of (*S*)-2-adamantoxy-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium methanethiolate **219**

A mixture of 1-adamantanol (1.01 g, 6.65 mmol) and sodium metal (1.15 g, 50 mmol) in dry toluene (40 cm^3) was heated under reflux for 24 h under nitrogen. The solution was cooled and excess sodium removed.

(*S*)-2-Methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (2.0 g, 6.65 mmol) was added. After heating the mixture under reflux under nitrogen for 24 h, the solid was filtered off and the filtrate evaporated to give reddish brown solid (2.01 g).

The experiment was repeated and after heating under reflux for 8 h, water (200 cm^3) was added, the mixture extracted with CH_2Cl_2 (300 cm^3), dried and evaporated to give a brown oil (0.97 g). NMR showed it to be a mixture of adamantanol; δ_H (200 MHz) 2.15 (3 H, s), 1.72 (6 H, s) and 1.61 (6 H, s) [OH not apparent]; δ_C (50 MHz) 68.2 (COH), 45.3 (3 CH), 36.0 (3 CH_2) and 30.6 (3 CH_2) and the thiazolidinone **149**; δ_H and δ_C as in Section D2b in a molar ratio of 8 : 3.

E. Kinetic resolution of (*R*,*S*)-1-phenylethanol using monocyclic iminium salts

1. Preparation of 3-unsubstituted thiazolidine-2-thiones and their oxygen analogues

a Preparation of (*S*)-phenylalanine methyl ester hydrochloride **225**

This was prepared by a modification of the method of Meyers.[67] Thionyl chloride (95 cm^3, 154 g, 1.3 mol) was added to a stirred suspension of (*S*)-phenylalanine (100 g, 0.606 mol) in A.R. methanol (500 cm^3) at 0 °C over 20 min. Evaporation followed by removal of remaining traces of the thionyl chloride under reduced pressure gave a colourless solid. This was washed with ether to give methyl ester hydrochloride **225** (121.6 g, 93%) as colourless crystals, m.p. 156-160 °C (lit.,[67] 177-181 °C); δ_H (200 MHz; CD_3SOCD_3) 8.85 (3 H, br s), 7.35 (5 H, m), 4.25 (1 H, m), 3.65 (3 H, s) and 3.50-3.05 (2 H, m); δ_C (50 MHz; CD_3SOCD_3) 169.5 (CO), 134.9 (4^{ry}), 129.6 (2 CH), 128.7 (2 CH), 127.4 (CH), 53.4 (CH), 52.7 (CH_2) and 36.0 (Me).

b. Preparation of 2-(*S*)-amino-3-phenylpropan-1-ol **226**

A solution of (*S*)-phenylalanine methyl ester hydrochloride (43.3 g, 200.5 mmol) in 50% aqueous ethanol (375 cm^3) was added over 20 min to a solution of sodium borohydride (37.85 g, 100 mmol) in 50% aqueous ethanol (375 cm^3) at 0 °C. The mixture was heated under reflux for 144 h. Ethanol was evaporated off and 2 M sodium hydroxide (150 cm^3) was added to dissolve the borate salts. Extraction using ethyl acetate (400 cm^3) followed by drying and evaporation gave 2-(*S*)-amino-3-phenylpropan-1-ol **226** (23.6 g, 78%) as colourless crystals, m.p. 90-91 °C (lit.,[67] 89-91 °C); $[\alpha]_D^{20}$ –24.5° (c 1.57, EtOH) [lit.,[67] $[\alpha]_D^{20}$ –24.2° (c 1.5, EtOH)]; ν_{max} (nujol) 3350 (NH_2), 3300 (NH_2), 3060 (br, OH), 1570, 1490, 1340, 1110, 1080, 1060, 970, 900, 820, 750 and 690 cm^{-1}; δ_H (300 MHz) 7.35-7.25 (2 H, m), 7.25-7.15 (3 H, m), 3.64 (1 H, half of AB pattern of d, J_{AB} 12, J_{AX} 4 Hz), 3.41 (1 H, half of AB pattern of d, J_{AB} 12, J_{BX} 8 Hz), 3.11 (1 H, m), 2.80 (1 H, half of AB pattern of d, J_{AB} 13, J_{AX} 5 Hz) and 2.52 (1 H, half of AB pattern of d, J_{AB} 13, J_{BX} 9 Hz) and 2.35 (3 H, br s); δ_C (75 MHz) 138.7 (4^{ry}), 129.2 (2 CH), 128.6 (2 CH), 126.4 (CH), 66.2 (CH_2), 54.2 (CH) and 40.8 (CH_2).

c. Preparation of 4-(*S*)-benzyloxazolidin-2-one **233**

A modification of the method of Newman[68] was used. Potassium t-butoxide (0.5 g, 4.5 mmol) was added to a stirred suspension of 2-(*S*)-amino-3-phenylpropan-1-ol **226** (6.10 g, 40 mmol) in diethyl carbonate (85 cm^3, 82.7 g, 700 mmol) at room temperature. Distillation using a fractionating column gave a few cm^3 of ethanol (b.p. 78-80 °C) and then an azeotrope of ethanol/ diethyl carbonate for 90 min, until a temperature of 122 °C was reached. The remaining diethyl carbonate was evaporated off under reduced pressure and the residue dissolved in water and extracted with CH_2Cl_2 (300 cm^3). The organic layer was washed with water (200

cm^3), dried and evaporate to afford an orange oil. Crystallisation using ether gave 4-(*S*)-benzyloxazolidin-2-one **233** (5.48 g, 77%) as colourless crystals, m.p. 87-88 °C (lit.,[68] m.p. 87-88.5 °C); $[\alpha]_D^{20}$ –61.5° (c 0.79, CH_2Cl_2); δ_H (300 MHz) 7.50-7.25 (3 H, m), 7.23-7.10 (2 H, m), 5.35 (1 H, br s), 4.48 (1 H, t, *J* 8 Hz), 4.20-4.05 (2 H, m) and 2.90 (2 H, d, *J* 8 Hz); δ_C (75 MHz) 159.1 (CO), 136.0 (4^{ry}), 129.1 (2 CH), 129.0 (2 CH), 127.3 (CH), 69.7 (CH_2), 53.8 (CH) and 41.5 (CH_2).

d. Preparation of 4-(*S*)-isopropyloxazolidin-2-one **234**

This was prepared in an identical method to **233** starting from 2-(*S*)-amino-3-methylbutan-1-ol **227** (4.0 g, 38.8 mmol) to yield an orange oil (3.38 g, 67%). Kugelrohr distillation (150-200 °C/ 5 mmHg) afforded 4-(*S*)-isopropyloxazolidin-2-one **234** as a faintly yellow oil (2.70 g, 54%); $[\alpha]_D^{20}$ –10.3° (c 0.41, CH_2Cl_2) [lit.,[69] $[\alpha]_D^{20}$ –16.6° (c 5.81, EtOH)]; δ_H (200 MHz) 7.32 (1 H, br s), 4.45 (1 H, t, *J* 8 Hz), 4.12 (1 H, dd, *J* 8, 7 Hz), 3.64 (1 H, q, *J* 7 Hz), 1.72 (1 H, m), 0.95 (3 H, d, *J* 7 Hz) and 0.90 (3 H, d, *J* 7 Hz); δ_C (50 MHz) 160.4 (CO), 68.2 (CH), 58.0 (CH_2), 32.3 (CH), 17.6 (Me) and 17.3 (Me).

e. Preparation of 4-(*S*)-benzylthiazolidine-2-thione **235**

A modification of the method of Roth[59] was used. Carbon disulfide (8 cm^3, 10.1 g, 133 mmol) was added with stirring to a suspension of 2-(*S*)-amino-3-phenylpropan-1-ol **226** (4.0 g, 26.5 mmol) in 2 M NaOH (75 cm^3) at room temperature. The solution was stirred for 22 h and extracted with CH_2Cl_2 which was dried and evaporated to give colourless crystals (1.70 g) which proved to be a 1:1 mixture of 4-(*S*)-benzyloxazolidine-2-thione; δ_H and δ_C in agreement with literature data,[72] and the desired 4-(*S*)-benzylthiazolidine-2-thione **235**; δ_H (300 MHz) 8.05 (1 H, br s), 7.40-7.25 (3 H, m), 7.25-7.15 (2 H, m), 4.45 (1 H, quintet, *J* 10 Hz), 3.57 and 3.31 (2 H, AB pattern of d, *J* 14, 10 Hz) and 3.05 and 2.97 (2 H, AB

pattern of d, *J* 16, 10 Hz); δ_C (75 MHz) 200.9 (CS), 135.9 (4^{ry}), 129.1 (2 CH), 129.0 (2 CH), 127.4 (CH), 65.1 (CH), 40.0 (CH_2) and 38.1 (CH_2). The spectra for **235** were in full agreement with the literature data.[72]

f. Attempted preparation of 4-(*S*)-benzyl-3-triphenylmethylthiaz--olidine-2-thione **239**

Sodium hydride (0.06 g, 2.39 mmol) was added to a solution of 4-(*S*)-benzylthiazolidine-2-thione **235** (0.5 g, 2.39 mmol) and trityl chloride (0.67 g, 2.39 mmol) in THF (50 cm^3) at room temperature and the mixture stirred for 24 h. Evaporation of the mixture gave a brown semi-solid. The reaction did not gave the desired product and a complex mixture was formed as shown by ^1H and ^{13}C NMR.

g. Preparation of 4-(*R*)-ethylthiazolidine-2-thione **236**

A modification of the method of Roth[59] was used. Carbon disulfide (35.2 cm^3, 44.54 g, 0.59 mol) was added with stirring to a suspension of 2-(*R*)-aminobutan-1-ol **228** (12.0 g, 134.6 mmol) in 2 M NaOH (200 cm^3) at room temperature. After stirring for 40 h, a further portion of carbon disulfide (5 cm^3, 6.3 g, 83 mmol) was added and the solution stirred for an additional 4 h. The solution was extracted with CH_2Cl_2 which was dried and evaporated to give the crude 4-(*R*)-ethylthiazolidine-2-thione **236** as a yellow oil.

^{13}C NMR showed some 4-(*R*)-ethyloxazolidine-2-thione **237** to be present with the product, so it was redissolved in toluene (100 cm^3), phosphorus pentasulfide (16.0 g 36 mmol) was added and the mixture heated under reflux for 10 h. The solution was filtered and the filtrate evaporated to give an orange coloured oil (9.2 g, 46%). Column chromatography on silica using pet. ether : ether (1:1) gave a yellow oil which crystallised on standing Washing the crystals with ether gave the

product **236** (3.5 g, 18%) as colourless crystals, m.p. 44-46 °C (lit.,[70] 41 °C for opposite enantiomer); $[\alpha]_D^{20}$ +19.9° (c 1.84, $CHCl_3$) [lit.,[70] $[\alpha]_D^{23}$ –35.4° (c 0.64, $CHCl_3$) for opposite enantiomer]; (Found: M^+, 147.0168. $C_5H_9NS_2$ requires *M*, 147.0176); ν_{max} 3140 (NH), 1500, 1428, 1378, 1288, 1265, 1144, 1020, 951 and 669; δ_H (200 MHz) 8.42 (1 H, br s), 4.20 (1 H, m), 3.58 and 3.22 (2 H, AB pattern of d, *J* 10, 7 Hz), 1.75 (2 H, m) and 1.00 (3 H, t, *J* 7 Hz); δ_C (50 MHz) 200.9 (CS), 65.7 (CH), 38.2 (CH_2), 27.1 (CH_2) and 10.1 (Me); *m/z* 147 (M^+, 100%), 118 (36), 100 (31), 73 (10), 59 (26), 55 (28) and 46 (15).

h. Attempted preparation of 4-(*R*)-ethyl-3-triphenylmethylthiazolidine-2-thione **240**

Sodium hydride (0.26 g, 10.86 mmol) was added to a solution of 4-(*R*)-ethylthiazolidine-2-thione **236** (1.6 g, 10.86 mmol) and trityl chloride (3.03g, 10.86 mmol) in THF (50 cm^3) at room temperature and the mixture stirred for 24 h. Evaporation of the solvent gave a brown semi-solid. The reaction did not gave the desired product and a complex mixture was formed as shown by TLC.

2. Preparation of 3-substituted oxazolidinones and thiazolidinethiones

a. Preparation of 2-(*S*)-benzylideneamino-3-phenylpropan-1-ol **241**

A modification of the method of Freifelder[71] was used. Benzaldehyde (15.33 g, 144.5 mmol, 14.69 cm^3) was added to a stirred suspension of 2-(*S*)-amino-3-phenylpropan-1-ol **226** (21.85 g, 144.5 mmol) in toluene (350 cm^3) at room temperature. After heating under reflux for 1 h using a Dean-Stark separator, evaporation gave a light yellow solid (33.1 g, 96%). Recrystallisation from ethyl acetate and

hexane (200 cm^3) (5:1) gave 2-(*S*)-benzylideneamino-3-phenylpropan-1-ol **241** (22.6 g, 66%) as colourless prisms, m.p. 76-78 °C (lit.,[72] 78-80 °C); $[\alpha]_D^{20}$ –208.9° (c 1.85, $CHCl_3$) [lit.,[72] $[\alpha]_D^{20}$ –215.6° (c 2.0, $CHCl_3$)]; δ_H (300 MHz) 7.85 (1 H, s, CH=N), 7.55 (2 H, m), 7.30 (4 H, m), 7.20 (4 H, m), 3.85 (1 H, half of AB pattern of d, J_{AB} 14, J_{AX} 6 Hz), 3.80 (1 H, half of AB pattern of d, J_{AB} 14, J_{BX} 4 Hz), 3.50 (1 H, m), 2.95 (1 H, half of AB pattern of d, J_{AB} 14, J_{AX} 5 Hz), 2.85 (1 H, half of AB pattern of d, J_{AB} 14, J_{BX} 8 Hz) and 2.95-2.85 (1 H, br s); δ_C (75 MHz) 162.4 (C=N), 138.5 (4^{ry}), 135.7 (4^{ry}), 130.7 (CH), 129.7 (2 CH), 128.5 (2 CH), 128.2 (4 CH), 126.1 (CH), 74.2 (CH), 65.8 (CH_2) and 39.0 (CH_2).

b. Preparation of 2-(*S*)-benzylamino-3-phenylpropan-1-ol **242**

Hydrogen gas (28.0 mmol, 627 cm^3) was absorbed into a stirred solution of 2-(*S*)-benzylideneamino-3-phenylpropan-1-ol **241** (6.70 g, 28.0 mmol) in ethyl acetate (85 cm^3) in the presence of 5% palladium-charcoal catalyst (1.1 g). Filtration and evaporation gave yellow oil which crystallised out to give 2-(*S*)-benzylamino-3-phenylpropan-1-ol **242** (6.50 g, 96 %) as colourless crystals, m.p. 57-59 °C; $[\alpha]_D^{20}$ –50.5° (c 2.14, $CHCl_3$) [lit.,[72] 124–126 °C, $[\alpha]_D^{25}$ –49.8° (c 2.0, $CHCl_3$)]; ν_{max} (nujol) 3250 (NH), 3060 (OH, br), 1590, 1570, 1480, 1230, 1140, 1100, 1050, 850, 720 and 690 cm^{-1}; δ_H (300 MHz) 7.35-7.10 (10 H, m), 3.75 (2 H, s), 3.62 (1 H, half of AB pattern of d, J_{AB} 10, J_{AX} 4 Hz), 3.35 (1 H, half of AB pattern of d, J_{AB} 10, J_{BX} 5 Hz), 2.95 (1 H, m), 2.85-2.70 (2 H, m) and 2.25 (2 H, br s); δ_C (75 MHz) 140.0 (4^{ry}), 138.5 (4^{ry}), 129.2 (2 CH), 128.6 (2 CH), 128.5 (2 CH), 128.0 (2 CH), 127.1 (CH), 126.4 (CH), 62.5 (CH_2), 59.4 (CH), 51.1 (CH_2) and 38.1 (CH_2).

c. Preparation of 3,4-(*S*)-dibenzyloxazolidin-2-one **243**

A modification of the method of Newman[68] was used. Potassium t-

butoxide (0.25 g, 2.25 mmol) was added to a stirred suspension of 2-(*S*)-benzylamino-3-phenylpropan-1-ol **242** (3.1 g, 13.5mmol) in diethyl carbonate (42.5 cm^3, 41.35 g, 350 mmol) at room temperature. Distillation using a fractionating column gave a few cm^3 of ethanol (b.p. 78-80 °C) and then an azeotrope of ethanol/ diethyl carbonate for 90 min, until a temperature of 122 °C was reached. The remaining diethyl carbonate was evaporated under reduced pressure and the residue dissolved in water and extracted with CH_2Cl_2 (300 cm^3). The organic layer was washed with water (200 cm^3), dried and evaporated to afford **243** (3.35 g, 92%) as a faint yellow semi-solid; $[\alpha]_D^{20}$ –7.2° (c 0.482, CH_2Cl_2); δ_H (300 MHz) 7.45-7.15 (8 H, m), 7.12-7.00 (2 H, m), 4.90 and 4.15 (2 H, AB pattern, *J* 15 Hz), 4.12 (1 H, half of AB pattern of d, J_{AB} 10, J_{AX} 8 Hz), 4.05 (1 H, half of AB pattern of d, J_{AB} 10, J_{BX} 6 Hz), 3.80 (1 H, m), 3.10 (1 H, half of AB pattern of d, J_{AB} 12, J_{AX} 4 Hz) and 2.65 (1 H, half of AB pattern of d, J_{AB} 12, J_{BX} 8 Hz); δ_C (75 MHz) 158.3 (CO), 135.8 (4^{ry}), 135.5 (4^{ry}), 129.0 (2 CH), 128.9 (2 CH), 128.8 (2 CH), 128.2 (2 CH), 128.0 (CH), 127.2 (CH), 66.9 (CH_2), 55.3 (CH), 46.3 (CH_2) and 38.4 (CH_2). The spectroscopic data for **243** were in full agreement with the literature.[72]

d. <u>Preparation of 3,4-(*S*)-dibenzylthiazolidine-2-thione **248**</u>

A modification of the method of Roth[59] was used. Carbon disulfide (2.4 cm^3, 3.05 g, 40 mmol) was added with stirring to a suspension of 2-(*S*)-benzylamino-3-phenylpropan-1-ol **242** (4.8 g, 20.26 mmol) in 2 M sodium hydroxide (100 cm^3) at room temperature. After stirring for 20 h, a further portion of carbon disulfide (1 cm^3, 1.266 g, 16.63 mmol) was added and the solution stirred for an additional 4 h. The solution was extracted with CH_2Cl_2 and organic layer washed with water, dried and evaporated to afford dibenzylthiazolidin-2-thione **248** (4.07 g, 68%) as colourless crystals, m.p. 136-137 °C (lit.,[72] 137-139 °C); $[\alpha]_D^{20}$ –44.5° (c

1.54, CH_2Cl_2); δ_H (300 MHz) 7.45-7.20 (8 H, m), 7.15-7.00 (2 H, m), 5.83 and 4.22 (2 H, AB pattern, *J* 15 Hz), 4.30-4.20 (1 H, m), 3.25 (1 H, half of AB pattern of d, J_{AB} 12, J_{AX} 8 Hz), 3.15 (1 H, half of AB pattern of d, J_{AB} 14, J_{BX} 5 Hz), 2.95 (1 H, half of AB pattern of d, J_{AB} 12, J_{AX} 10 Hz) and 2.90 (1 H, half of AB pattern of d, J_{AB} 14, J_{BX} 10 Hz); δ_C (75 MHz) 196.7 (CS), 135.8 (4^{ry}), 135.3 (4^{ry}), 129.0 (2 CH), 128.9 (2 CH), 128.8 (2 CH), 128.1 (CH), 127.9 (2 CH), 127.1 (CH), 67.4 (CH), 50.6 (CH_2), 36.2 (CH_2) and 32.1 (CH_2).

e. Preparation of 3,4-(*S*)-dimethyl-5-(*R*)-phenyloxazolidin-2-one **245**

The method of c. above using potassium t-butoxide (0.25 g, 2.25 mmol), (1*R*,2*S*)-(–)-ephedrine **244** (6.61 g, 40 mmol) and diethyl carbonate (85 cm^3, 87.7 g, 700 mmol), gave 3,4-(*S*)-dimethyl-5-(*R*)-phenyloxazolidin-2-one **245** (7.10 g, 93%) as a yellowish white solid, m.p. 88-90 °C (lit.,[73] 91-92 °C); $[\alpha]_D^{20}$ –119.4° (c 1.12, $CHCl_3$) [lit.,[73] $[\alpha]_D^{20}$ –125° (c 1, $CHCl_3$) and lit.,[74] $[\alpha]_D^{20}$ –110.6° (c 1, $CHCl_3$)]; ν_{max} (nujol) 1735 (CO), 1238, 1104, 1089, 1063, 995, 766, 728 and 704 cm^{-1}; δ_H (200 MHz) 7.45-7.25 (5 H, m), 5.60 (1 H, d, *J* 7 Hz) 4.05 (1 H, m), 2.88 (3 H, s) and 0.80 (3 H, d, *J* 7 Hz); δ_C (50 MHz) 158.0 (CO), 135.2 (4^{ry}), 128.5 (3 CH), 126.1 (2 CH), 78.3 (CH), 57.0 (CH), 29.0 (Me) and 14.3 (Me); *m/z* 191 (M^+, 2%), 148 (8), 132 (4), 117 (6), 105 (9), 91 (10), 85 (30), 77 (20) and 58 (100).

f. Preparation of 3,4-(*R*)-dimethyl-5-(*S*)-phenyloxazolidin-2-one **247**

The method of c. above using potassium t-butoxide (0.25 g, 2.25 mmol), (1*S*,2*R*)-(+)-ephedrine **246** (6.61 g, 40 mmol) and diethyl carbonate (85 cm^3, 87.7 g, 700 mmol), gave 3,4-(*R*)-dimethyl-5-(*S*)-phenyloxazolidin-2-one **247**, obtained after recrystallisation from ethyl acetate (50 cm^3) as colourless crystals (4.46 g, 58%), m.p. 89-90 °C (lit.,[73]

91-92 °C for opposite enantiomer); $[\alpha]_D^{20}$ +116.7° (c 1.09, $CHCl_3$) [lit.,[73] $[\alpha]_D^{20}$ –125° (c 1, $CHCl_3$) for opposite enantiomer]; ν_{max} (nujol) 1742, 1238, 1104, 1089, 1064, 995, 767, 728 and 704 cm^{-1}; δ_H (200 MHz) 7.40-7.25 (5 H, m), 5.60 (1 H, d, *J* 7.5 Hz) 4.05 (1 H, m), 2.89 (3 H, s) and 0.81 (3 H, d, *J* 7.5 Hz); δ_C (50 MHz) 158.0 (CO), 135.1 (4^{ry}), 128.5 (3 CH), 126.1 (2 CH), 78.3 (CH), 57.1 (Me), 29.0 (CH) and 14.3 (Me); *m/z* 191 (M^+, 20%), 176 (5), 148 (9), 132 (10), 117 (11), 105 (15), 91 (14), 77 (20), 63 (8) and 57 (100).

g. Preparation of 3,4-(*S*)-dimethyl-5-(*R*)-phenylthiazolidine-2-thione **249**

Reaction as in d. above using (1*R*,2*S*)-(–)-ephedrine **244** (5.0 g, 30.3 mmol) in 2 M NaOH (150 cm^3) and carbon disulfide (3.6 cm^3, 4.57 g, 60 mmol) gave a light yellow oil which crystallised out to afford 3,4-(*S*)-dimethyl-5-(*R*)-phenylthiazolidine-2-thione **249** (4.4 g, 65%) as colourless crystals, m.p. 64-66 °C (lit.,[75] 65-66 °C); $[\alpha]_D^{20}$ –163.7° (c 1.01, EtOH) [(lit.,[75] $[\alpha]_D^{20}$ –155° (c 1, EtOH)]; R_f 0.84 (ether, silica); ν_{max} (nujol) 1320, 1250, 1225, 1150, 1075, 975, 950 and 850 cm^{-1}; δ_H (300 MHz) 7.35 (5 H, s), 4.35 (1 H, d, *J* 7 Hz), 4.15 (1 H, quintet, *J* 7Hz), 3.28 (3 H, s) and 1.50 (3 H, d, *J* 7 Hz); δ_C (75 MHz) 195.0 (CS), 138.5 (4^{ry}), 129.1 (2 CH), 128.5 (CH), 127.5 (2 CH), 73.1 (CH), 54.6 (CH), 34.8 (Me) and 17.9 (Me); *m/z* 223 (M^+, 100), 166 (10), 150 (8), 135 (9), 118 (75), 100 (10) and 91 (30).

h. Preparation of 3,4-(*R*)-dimethyl-5-(*S*)-phenylthiazolidine-2-thione **250**

Reaction as in d. above using (1*S*,2*R*)-(+)-ephedrine **246** (10 g, 60.5 mmol) in 2 M NaOH (200 cm^3) and carbon disulfide (7.2 cm^3, 9.14 g, 120 mmol) gave a light yellow oil which crystallised out to afford 3,4-(*R*)-

dimethyl-5-(*S*)-phenylthiazolidine-2-thione **250** (10.1 g, 75%) as colourless crystals, m.p. 64.5-65.5 °C (lit.,[75] 65-66 °C for opposite enantiomer); $[\alpha]_D^{20}$ +166.3° (c 1.06, EtOH) [lit.,[75] $[\alpha]_D^{20}$ –155° (c 1, EtOH) for opposite enantiomer]; (Found: C, 59.7; H, 5.7; N, 6.3. $C_{11}H_{13}NS_2$ requires C, 59.2; H, 5.9; N, 6.3%); ν_{max} (nujol) 1310, 1240, 1210, 1130, 1070, 1050, 970, 930, 840 and 740 cm^{-1}; δ_H (200 MHz) 7.45 (5 H, m), 4.35 (1 H, d, *J* 7 Hz), 4.15 (1 H, quintet, *J* 7 Hz), 3.30 (3 H, s) and 1.48 (3 H, d, *J* 7 Hz); δ_C (50 MHz) 195.0 (CS), 138.5 (4^{ry}), 129.1 (2 CH), 128.6 (CH), 127.5 (2 CH), 73.2 (CH), 54.7 (CH), 34.8 (Me) and 18.0 (Me); *m/z* 223 (M^+, 35%), 208 (2), 166 (4), 150 (3), 118 (5), 103 (100), 86 (10) and 61 (35).

3. Preparation of monocyclic iminium salts

a. Preparation of 3,4-(*S*)-dibenzyl-2-methylthiothiazolinium iodide **251**

A mixture of 3,4-(*S*)-dibenzylthiazolidine-2-thione **248** (1.15 g, 3.84 mmol), acetone (50 cm^3) and methyl iodide (2.39 cm^3, 5.54 g, 38.4 mmol) was stirred at room temperature for 16 h. The resulting yellow solution was evaporated to yield a mixture of **248** and 3,4-(*S*)-dibenzyl-2-methylthiothiazolinium iodide **251** (1.5 g) as an orange solid, m.p. 135-137 °C; $[\alpha]_D^{20}$ –24.7° (c 0.66, CH_2Cl_2); for **251;** δ_H (200 MHz) 7.45-7.20 (8 H, m), 7.12 (2 H, m), 5.25 and 4.88 (2 H, AB pattern, *J* 15 Hz), 5.05 (1 H, m), 4.05 (1 H, half of AB pattern of d, J_{AB} 15, J_{AX} 10 Hz), 3.60 (1 H, half of AB pattern of d, J_{AB} 15, J_{BX} 5 Hz) 3.20-2.80 (2 H, m), and 2.96 (3 H, s); δ_C (50 MHz) 182.0 (CS), 133.8 (4^{ry}), 130.9 (4^{ry}), 129.6 (2 CH), 129.4 (CH), 129.3 (2 CH), 128.7 (CH), 128.1 (2 CH), 127.2 (2 CH), 73.2 (CH), 55.8 (CH_2), 36.7 (CH_2), 36.4 (CH_2) and 19.8 (Me).

b. Preparation of 3,4-(*S*)-dimethyl-2-ethoxy-5-(*R*)-phenyloxazolinium tetrafluoroborate **252**

Following a method by Meerwein[10] 3,4-(*S*)-dimethyl-5-(*R*)-phenyloxazolidin-2-one **245** (1.00 g, 5.23 mmol) was added to a solution of triethyloxonium tetrafluoroborate (1.19 g, 6.28 mmol) in CH_2Cl_2 (15 cm^3) and the mixture stirred for 4 h at room temperature. The mixture was evaporated to afford an orange coloured oil which crystallised to give 3,4-(*S*)-dimethyl-2-ethoxy-5-(*R*)-phenyloxazolinium tetrafluoroborate **252** (1.37 g, 85%) as colourless crystals, m.p. 72-74 °C; $[\alpha]_D^{20}$ –93.9° (c 2.09, acetone); (Found: C, 51.1; H, 5.8; N, 4.7. $C_{13}H_{18}BF_4NO_2$ requires C, 50.8; H, 5.9; N, 4.6%); ν_{max} (neat) 3480, 2950, 1650, 1500, 1430, 1080-990, 830 and 710 cm^{-1}; δ_H (200 MHz) 7.55-7.15 (5 H, m), 6.50 (1 H, d, *J* 10 Hz), 4.85-4.65 (3 H, m), 3.15 (3 H, s), 1.55 (3 H, t, *J* 8 Hz) and 1.00 (3 H, d, *J* 8 Hz); δ_C (50 MHz) 161.8 (NCO), 131.0 (4^{ry}), 129.9 (CH), 129.0 (2 CH), 126.4 (2 CH), 87.8 (CH), 73.7 (OCH_2), 60.2 (CHN), 29.9 (Me) 14.3 (Me) and 13.9 (Me); *m/z* 219 (M^+–HBF_4, 1%), 191 (16), 176 (3), 132 (7), 105 (8), 77 (12), 57 (100) and 42 (69).

c. Preparation of 3,4-(*S*)-dimethyl-2-methylthio-5-(*R*)-phenylthiazolinium iodide **253**

A mixture of 3,4-(*S*)-dimethyl-5-(*R*)-phenylthiazolidine-2-thione **249** (1.50 g, 6.72 mmol), acetone (35 cm^3) and methyl iodide (5 cm^3, 80 mmol) was stirred for 16 h at room temperature. The resulting precipitate was filtered off and washed with ether (25 cm^3). The filtrate was concentrated and a second crop of the product filtered off and washed with ether (25 cm^3). The solids were combined to yield 3,4-(*S*)-dimethyl-2-methylthio-5-(*R*)-phenylthiazolinium iodide **253** (2.35 g, 96%) as colourless crystals, m.p. 116-118 °C; $[\alpha]_D^{20}$ –105.1° (c 2.15, CH_2Cl_2); (Found: C, 39.45; H, 4.4; N, 3.8. $C_{12}H_{16}INS_2$ requires C, 39.4; H, 4.4;

N, 3.8%); ν_{max} (nujol) 1300, 1200, 1120, 1050, 1000, 960, 840 and 750 cm^{-1}; δ_H (200 MHz) 7.65 (2 H, m), 7.50-7.30 (3 H, m), 5.35 (1 H, d, *J* 10 Hz), 5.20 (1 H, m), 3.58 (3 H, s), 2.95 (3 H, s) and 1.68 (3 H, d, *J* 8 Hz); δ_C (50 MHz) 191.6 (CS), 133.3 (4^{ry}), 129.9 (CH), 129.6 (2 CH), 128.9 (2 CH), 76.3 (CH), 58.7 (CH), 38.4 (Me), 19.0 (Me) and 16.9 (Me); *m/z* 222 (M^+–MeI–1, 77%), 165 (12), 141 (100), 117 (54), 91 (23), 77 (12) and 39 (15).

d. Preparation of 3,4-(*R*)-dimethyl-2-methylthio-5-(*S*)-phenylthiazolinium iodide **254**

A mixture of 3,4-(*R*)-dimethyl-5-(*S*)-phenylthiazolidine-2-thione **250** (1.50 g, 6.72 mmol), acetone (35 cm^3) and methyl iodide (5 cm^3, 80 mmol) was stirred for 16 h at room temperature. The resulting precipitate was filtered off and washed with ether (25 cm^3). The filtrate was concentrated and a second crop of the product filtered off and washed with ether (25 cm^3). The solids were combined to yield 3,4-(*R*)-dimethyl-2-methylthio-5-(*S*)-phenylthiazolinium iodide **254** (2.35 g, 96%) as colourless crystals, m.p. 118-120 °C; $[\alpha]_D^{20}$ +100.3° (c 0.89, CH_2Cl_2); (Found: C, 39.2; H, 4.4; N, 3.8. $C_{12}H_{16}INS_2$ requires C, 39.4; H, 4.4; N, 3.8%); ν_{max} (nujol) 1540, 1310, 1240, 1210, 1150, 1130, 1065, 1010, 965 and 750 cm^{-1}; δ_H (200 MHz) 7.65 (2 H, m), 7.50-7.30 (3 H, m), 5.38 (1 H, d, *J* 10 Hz), 5.18 (1 H, m), 3.57 (3 H, s), 2.92 (3 H, s) and 1.68 (3 H, d, *J* 8 Hz); δ_C (50 MHz;) 191.7 (SCN), 133.2 (4^{ry}), 130.0 (CH), 129.6 (2 CH), 129.0 (2 CH), 76.4 (CH), 58.9 (CH), 38.5 (Me), 19.0 (Me) and 16.9 (Me); *m/z* 223 (M^+–MeI, 67%), 166 (12), 135 (10), 118 (44), 100 (12), 91 (20), 77 (12), 64 (8) and 39 (12).

e. Attempted preparation of 3,4-(*S*)-dibenzyl-2-trimethylsilyloxy oxazolinium chloride **255**

A mixture of 3,4-(*S*)-dibenzyloxazolidin-2-one **243** (3.32 g, 12.42 mmol), CH_2Cl_2 (25 cm^3) and trimethylsilyl chloride (13.04 g, 120 mmol) was stirred for 16 h at room temperature. The resulting yellow solution was evaporated to afford a yellow oil (3.30 g). The ^1H and ^{13}C NMR spectra did not show any peaks corresponding to the iminium salt **255** and starting material was recovered.

f. Attempted preparation of 3,4-(*S*)-dibenzyl-2-trimethylsilyloxy oxazolinium triflate **256**

A mixture of 3,4-(*S*)-dibenzyloxazolidin-2-one **243** (3.32 g, 12.42 mmol), toluene (35 cm^3) and trimethylsilyl trifluoromethanesulfonate (6.67 g, 30 mmol, 5.79 cm^3) was stirred for 16 h at room temperature. The resulting brown solution was evaporated to afford a reddish brown semi-solid (2.5 g). The spectra suggested that this might be the trifluoromethanesulfonic acid salt of the starting oxazolidinone **257**; δ_H (200 MHz) 7.50-7.10 (8 H, m), 7.05 (2 H, m), 4.85 and 4.22 (2 H, AB pattern, *J* 12 Hz), 4.37 (1 H, half of AB pattern of d, J_{AB} 8, J_{AX} 7 Hz), 4.25 (1 H, half of AB pattern of d, J_{AB} 8, J_{BX} 5 Hz), 4.05 (1 H, m), 3.15 (1 H, half of AB pattern of d, J_{AB} 12, J_{AX} 5 Hz) and 2.78 (1 H, half of AB pattern of d, J_{AB} 12, J_{BX} 8 Hz); δ_C (50 MHz) 162.5 (CO), 134.0 (4^{ry}), 132.9 (4^{ry}), 129.4 (2 CH), 129.3 (2 CH), 129.1 (CH), 129.0 (2 CH), 128.4 (2 CH), 127.8 (CH), 71.5 (CH_2), 57.3 (CH), 47.2 (CH_2) and 37.8 (CH_2); *m/z* 176 (M^+–TfOH, 30%), 139 (2), 121 (9), 106 (30), 91 (100), 77 (32), 65 (18) and 32 (15).

4. Resolution using monocyclic iminium salts

a. Reaction of 3,4-(*S*)-dimethyl-2-ethoxy-5-(*R*)-phenyloxazolinium tetrafluoroborate **252** with 2 eq sodium (*R*,*S*)-1-phenylethoxide

To a freshly prepared solution of sodium (*R*,*S*)-1-phenylethoxide (1.92 g, 13.3 mmol) in toluene (25 cm^3) was added 3,4-(*S*)-dimethyl-2-ethoxy-5-(*R*)-phenyloxazolinium tetrafluoroborate **252** (2.04 g, 6.65 mmol) at room temperature under nitrogen. After stirring for 16 h, water (400 cm^3) was added and the mixture extracted with CH_2Cl_2 (300 cm^3) which was dried and evaporated to give an orange brown oil (1.57 g). Kugelrohr distillation of this afforded 1-phenylethanol **178** (0.43 g, 54%) as a colourless oil, b.p. 50-70 °C/ 2 mmHg. This was found by ^1H NMR analysis using chiral shift reagent to have an e.e. of 4.6% in favour of the (*S*)-enantiomer.

b. Reaction of 3,4-(*S*)-dimethyl-2-methylthio-5-(*R*)-phenylthiazolinium iodide **253** with 2 eq of sodium (*R*,*S*)-1-phenylethoxide

To a freshly prepared solution of sodium (*R*,*S*)-1-phenylethoxide (1.92 g, 13.3 mmol) in toluene (25 cm^3) was added 3,4-(*S*)-dimethyl-2-methylthio-5-(*R*)-phenylthiazolinium iodide **253** (2.43 g, 6.65 mmol) at room temperature under nitrogen. After stirring for 16 h, water (400 cm^3) was added and the mixture extracted with CH_2Cl_2 (300 cm^3) which was dried and evaporated to give an orange brown oil (1.2 g). Kugelrohr distillation of this afforded a colourless oil (0.45 g), b.p. 60-95 °C/ 2 mmHg, containing PhCH(Me)OH **259** and methyl PhCH(Me)SMe **260** in a molar ratio of 25 : 12. Further distillation (100-115 °C/ 2 mmHg) gave an oil (0.30 g) which was a mixture of **259** and **260** in a molar ratio of 1 : 1. The overall recovery of **259** was 0.41 g (50%) and of **260** 0.34 g (42%). The 3,4-(*S*)-dimethyl-5-(*R*)-phenylthiazolidin-2-one **261** was assumed to be left in the involatile residue.

The alcohol was found to have an e.e. of 7% in favour of the (*R*)-enantiomer.

c. Reaction of 3,4-(*R*)-dimethyl-2-methylthio-5-(*S*)-phenylthiazolinium iodide **254** with 2 eq of sodium (*R*,*S*)-1-phenylethoxide

To a freshly prepared solution of sodium (*R*,*S*)-1-phenylethoxide (1.34 g, 10.95 mmol) in toluene (25 cm^3) was added 3,4-(*R*)-dimethyl-2-methylthio-5-(*S*)-phenylthiazolinium iodide **254** (2.0 g, 5.47 mmol) at room temperature under nitrogen. After stirring for 16 h, water (400 cm^3) was added and the mixture extracted with CH_2Cl_2 (300 cm^3) which was dried and evaporated to give an orange brown oil (0.72 g). Kugelrohr distillation of this afforded a colourless oil (0.27 g), b.p. 70-90 °C/ 2 mmHg which contained PhCH(Me)OH **178** and PhCH(Me)SMe **151** in a molar ratio of 3 : 1. Further distillation (100-150 °C/ 2 mmHg) gave a product (0.25 g) which appeared to consist mainly of the two diastereomers of di(1-phenylethyl) ether; δ_H 7.50–7.15 (10 H, m), 4.55 and 4.28 (2 H, q, *J* 7) and 1.50 and 1.45 (6 H, d, *J* 7); δ_C 74.6/74.3 (CHOH) and 24.7/23.0 (Me). The overall recovery of **178** was 0.19 g (24%) and of **151** 0.08 g (10%).

Using ^1H NMR in the presence of the chiral shift reagent, the alcohol was found to have an e.e. of 3% in favour of the (*S*)-enantiomer.

F. Reaction of the bicyclic iminium salt 147 with bidentate nucleophiles

1. Reaction with the disodium salts of diols

a. Reaction of (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** with the disodium salt of ethanediol

i) A mixture of ethanediol (0.21 g, 3.33 mmol) and sodium metal (1.15 g, 50 mmol) in dry toluene (40 cm^3) was heated under reflux for 24 h under nitrogen. The solution was cooled and excess sodium removed. (*S*)-

2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (2.0 g, 6.65 mmol) was added. After stirring at room temperature under nitrogen for 24 h, water (200 cm^3) was added and the mixture extracted with CH_2Cl_2 (300 cm^3) which was dried and evaporated to give a brown oil (0.31 g). Kugelrohr distillation of this afforded a 1:1 mixture of diastereomers of (*S*)-2-methylthio-3-thia-1-azabicyclo[3.3.0]octan-2-ol **263** (0.06 g, 19%) as a brown oil, b.p.170-180 °C/ 2 mmHg; (Found: C, 43.1; H, 6.65, N, 7.6. $C_7H_{13}NOS_2$ requires C, 43.9; H, 6.9; N, 7.3%); ν_{max} (neat) 3340 (OH), 2880, 1390, 1170, 1080, 940 and 740 cm^{-1}; δ_H (200 MHz) 4.23 (1 H, m), 3.35 (1 H, m), 3.18 (1 H, half of AB pattern of d, J_{AB} 10, J_{AX} 7 Hz), 3.02 (2 H, m), 2.83 (1 H, half of AB pattern of d, J_{AB} 10, J_{BX} 8 Hz), 2.26 and 2.17 (3 H, Me), 2.02 (2 H, m), 1.75 (1 H, m) and 1.27 (1 H, br s); δ_C (75 MHz) 97.9 (4^{ry}), 70.1 (CH), 47.7 (CH_2), 39.1 (CH_2), 30.1 (CH_2), 24.9 (CH_2), 16.09 (Me) and 16.06 (Me).

ii) The reaction as above using NaH (0.04 g, 1.66 mmol) and ethanediol (0.103 g, 1.66 mmol) and the iminium salt **147** did not give the desired spiro compound **264**. NMR spectra showed the formation of the methylthiohydroxy compound **263**. The experiment was also carried out using 1 eq of NaH and either water or saturated ammonium chloride for work up. NMR spectra showed the presence of the methylthiohydroxy compound **263**.

b. <u>Reaction of (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** with the disodium salt of propane-1,2-diol</u>

A mixture of propane-1,2-diol (0.51 g, 6.65 mmol) and sodium metal (1.15 g, 50 mmol) in dry toluene (40 cm^3) was heated under reflux for 24 h under nitrogen. The solution was cooled and excess sodium removed. (*S*)-2-Methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (2.0 g, 6.65 mmol) was added. After stirring at room temperature under nitrogen for 24 h, water (400 cm^3) was added and the mixture

extracted with CH_2Cl_2 (300 cm^3) which was dried and evaporated to give a brown oil (1.15 g). NMR showed that the methylthiohydroxy compound **263** was formed; δ_H and δ_C as in a. Attempted purification by Kugelrohr distillation gave a mixture of the thiazolidinone **149** and thiazolidinethione **169**.

c. Reaction of (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** with the disodium salt of meso hydrobenzoin

The method of b. using meso hydrobenzoin (0.43 g, 1.66 mmol) and (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (0.50 g, 1.66 mmol) gave a brown oil (0.17 g). Attempted separation by preparative TLC gave the thiazolidinone **149**, the thiazolidinethione **169** and a complex mixture of compounds derived from the starting diol.

d. Reaction of (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** with the disodium salt of 2,2-dimethylpropane-1,3-diol

A mixture of 2,2-dimethylpropane-1,3-diol (0.17 g, 1.66 mmol) and sodium hydride (0.079 g, 3.32 mmol) in dry toluene (40 cm^3) was heated under reflux for 1 h under N_2. (*S*)-2-Methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (0.50 g, 1.66 mmol) was added. After stirring at room temperature under nitrogen for 24 , water (200 cm^3) was added and the mixture extracted with ether (300 cm^3) which was dried and evaporated to give a brown oil (0.33 g) which was triturated with pet. ether to give oily crystals (0.18 g). This proved to be 1:1 mixture of the methylthiohydroxy compound **263**; δ_H and δ_C as in a. and spiro compound (*S*)-3-thia-1-azabicyclo[3.3.0]octane-2-spiro-2′-5′,5′-dimethyl-1′,3′-dioxane **267**; δ_H (300 MHz) 3.90 (1 H, m), 3.90 and 3.54 (2 H, AB pattern, *J* 11 Hz), 3.68 and 3.53 (2 H, AB pattern of d, *J* 11, 3 Hz), 3.10 (1 H, m), 3.00 (2 H, m) 2.80 (1 H, m), 2.05-1.80 (3 H, m),

1.80-1.50 (1 H, m), 1.19 (3 H, s) and 0.82 (3 H, s); δ_C (75 MHz) 129.2 (4^{ry}), 76.6 (CH_2), 72.7 (CH_2), 65.9 (CH), 46.7 (CH_2), 36.8 (CH_2), 30.6 (CH_2), 29.5 (4^{ry}), 23.6 (CH_2), 23.1 (Me) and 21.7 (Me).

e. Reaction of (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** with the disodium salt of 2-butyl-2-ethylpropane-1,3-diol

The method of d. using 2-butyl-2-ethyl-1,3-propanediol (0.27 g, 1.66 mmol) and (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (0.50 g, 1.66 mmol) gave a brown oil (0.37g) which proved to be the methylthiohydroxy compound **263**; δ_H and δ_C as in a., together with the unreacted diol.

f. Reaction of (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** with the disodium salt of 2-ethylhexane-1,3-diol

The method of d. using 2-ethylhexane-1,3-diol (0.24 g, 1.66 mmol) and (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (0.50 g, 1.66 mmol) gave a brown oil (0.31 g). This proved by NMR to consist mainly of the methylthiohydroxy compound **263**; δ_H and δ_C as in a., and the starting diol.

g. Reaction of (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** with the disodium salt of 1-glyceryl monostearate **273**

The method of b. using 1-glyceryl monostearate (1.19 g, 3.33 mmol) and (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (1.0 g, 3.33 mmol) gave a brown semi-solid product (0.28 g). NMR spectra showed the presence of the thiazolidinone **149**, thiazolidinethione **169** and unreacted glyceryl stearate.

h. Reaction of (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** with the trisodium salt of propane-1,2,3-triol

The method of b. using propane-1,2,3-triol (0.31 g, 3.33 mmol) and (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (1.0 g, 3.33 mmol) gave a brown oil (0.35 g). Kugelrohr distillation of this afforded a clear brown oil, b.p.230-240 °C/ 2 mmHg. NMR spectra showed the formation of the methylthiohydroxy compound **263**; δ_H and δ_C as in a. and the expected spiro compound **275** was not formed.

The experiment was repeated using NaH (0.08 g, 3.3 mmol) for the preparation of the sodium alkoxide but the expected spiro compound **275** could not be observed. NMR spectra again showed the formation of the methylthiohydroxy compound **263**.

i. Reaction of (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** with the tetrasodium salt of pentaerythritol

The method of b. using pentaerythritol (0.45 g, 3.33 mmol) and (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (2.0 g, 6.65 mmol) gave a clear brown oil (0.53 g). Kugelrohr distillation of this afforded a brown oil, b.p.170-180 °C/ 2 mmHg which proved to be the methylthiohydroxy compound **263**; δ_H and δ_C as in a.

j. Attempted preparation of (*S*)-2-methoxy-2-methylthio-3-thia-1-azabicyclo[3.3.0]octane **173**

A mixture of methylthiohydroxy compound **263** (0.25 g, 1.30 mmol) and sodium hydride (0.03 g, 1.30 mmol) in dry toluene was stirred for 1 h under nitrogen. Methyl iodide (0.40 cm^3, 0.92 g, 6.50 mmol) was added and the mixture stirred at room temperature under nitrogen for 24 h. Water (200 cm^3) was added and the mixture extracted with CH_2Cl_2 (300 cm^3) which was dried and evaporated to give a brown oil (0.15 g).

TLC showed, at R_f (ether) 0.50, the presence of the thiazolidinethione **169** as the major compound and this was confirmed by ^1H and ^{13}C NMR.

2. Reaction with the anions of amino alcohols

a. Reaction of (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** with the disodium salt of ethanolamine

The method of 1d. using ethanolamine (0.10 g, 1.66 mmol) and (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (0.50 g, 1.66 mmol) gave a brown oil (0.21 g).

A mixture of two diastereomers of the methylthiohydroxy compound **263**; δ_H and δ_C as in 1a. and the thiazolidinone **149** in a molar ratio of 1 : 8 was formed.

b. Reaction of (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** with the disodium salt of 2-(*R*)-benzylaminobutan-1-ol **282**

The method of 1d. using 2-(*R*)-benzylaminobutan-1-ol (0.29 g, 1.66 mmol) and (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (0.50 g, 1.66 mmol) gave a brown oil (0.29 g).

NMR and TLC showed that the product consisted of a complex mixture of products with none of the methylthiohydroxy compound **263** present.

c. Reaction of (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** with the disodium salt of (*S*)-prolinol **175**

The method of 1d. using (*S*)-prolinol (0.17 g, 1.66 mmol) and (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (0.50 g, 1.66 mmol) gave the methylthiohydroxy compound **263** (0.10g) as a brown oil; δ_H and δ_C as in 1a.

The experiment was repeated using THF as a solvent and saturated ammonium chloride solution (200 cm^3) for work up. NMR showed the presence of the thiazolidinone **149** and the thiazolidinethione **169** and the absence of the methylthiohydroxy compound **263**.

d. Reaction of (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** with the disodium salt of (1*R*,2*S*)-(–)-ephedrine **244**

The method of 1b. using (1*R*,2*S*)-(–)-ephedrine **244** (0.27 g, 1.66 mmol) and (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (0.50g, 1.66 mmol) gave a brown oil (0.31 g). NMR spectra showed the presence of the methylthiohydroxy **263** compound and the expected spiro compound was not formed.

The experiment was repeated and in order to discover the fate of ephedrine the mixture of products was subjected to acid/base separation. It was dissolved in 1M HCl (20 cm^3) and extracted with CH_2Cl_2. The organic layer was separated and concentrated to give acidic component as a brown oil (0.27 g). NMR spectra showed this to be a complex mixture of many products which could not be identified. The aqueous layer was neutralised with 1M NaOH (20 cm^3) and extracted with CH_2Cl_2. The organic layer was separated and evaporated to give the basic component as a brown oil (0.04 g). NMR analysis of this showed the main compounds present to be the thiazolidinethione **169** and recovered ephedrine.

e. Preparation of (*S*)-2-(1-hydroxy-3-phenyl-2-(*R*,*S*)-propylimino)-3-thia-1-azabicyclo[3.3.0]octane **283/284**

The method of 1d. using (*R*,*S*)-2-amino-3-phenylpropan-1-ol (0.50 g, 3.32 mmol) and (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (0.50 g, 1.66 mmol) gave the title compound **283/284**

(0.41 g, 45%) as a brown oil; (Found: M^+–1, 275.1211. $C_{15}H_{20}N_2OS$ requires *M*–H, 275.1218); ν_{max} (neat) 3300 (OH), 3020, 3010, 2900, 1610, 1490, 1400, 1070, 960, 725 and 690 cm^{-1}; δ_H (200 MHz) 7.45-7.10 (5 H, m), 4.25 (1 H, m), 4.20-3.90 (2 H, m), 3.42 (2 H, m), 3.14 (2 H, m), 2.62 (2 H, m), 2.35 (1 H, s) and 2.05-1.80 (4 H, m) [OH not apparent]; δ_C (50 MHz) (double signals due to two diastereomers) 138.4/138.3 (4^{ry}), 138.3/138.2 (C=N), 129.1 (2 CH), 128.3 (2 CH), 126.2 (CH), 72.3/72.2 (CH_2), 65.7/65.5 (CH), 57.9/57.8 (CH), 48.2 (CH_2), 42.7/42.6 (CH_2), 42.0/41.8 (CH_2), 29.7/29.6 (CH_2) and 23.5/23.4 (CH_2); *m/z* 276 (M^+, 3%), 275 (18), 260 (20), 259 (27), 231 (10), 143 (81) and 91 (100).

f. Preparation of (*S*)-2-(1-hydroxy-3-phenyl-2-(*S*)-propylimino)-3-thia-1-azabicyclo[3.3.0]octane **284**

The method of 1d. using (*S*)-2-amino-3-phenylpropan-1-ol (0.25 g, 1.66 mmol) and (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (0.50 g, 1.66 mmol) gave the condensation product **284** (0.37 g, 40%) as a brown oil; ν_{max} (neat) 3300 (OH), 3000, 2900, 1620, 1400, 1340, 1170, 1020, 950, 720 and 690 cm^{-1}; δ_H (200 MHz) 7.45-7.10 (5 H, m), 4.25 (1 H, m), 4.20-3.90 (2 H, m), 3.42 (2 H, m), 3.14 (2 H, m), 2.62 (2 H, m), 2.35 (1 H, s) and 2.05-1.80 (4 H, m) [OH not apparent]; δ_C (50 MHz) 138.3 (4^{ry}), 137.5 (C=N), 129.0 (2 CH), 128.1 (2 CH), 126.0 (CH), 72.0 (CH_2), 65.6 (CH), 57.6 (CH), 48.0 (CH_2), 42.7 (CH_2), 41.7 (CH_2), 29.6 (CH_2) and 23.4 (CH_2). The spectroscopic data are identical to those for the mixture of diastereomers in e. above.

g. Preparation of (*S*)-2-(2-amino-3-phenylpropoxy)-2-methylthio-3-thia-1-azabicyclo[3.3.0]octane **285**

Reaction as in e. above using the (*R*,*S*)-amino alcohol and 1 eq of iminium salt **147** afforded the title addition product **285** (0.31 g, 57%) as a brown oil; (Found: C, 59.5; H, 6.3; N, 7.8. $C_{16}H_{24}N_2OS_2$ requires C,

59.2; H, 7.4; N, 8.6%); δ_H (200 MHz) 7.40-7.10 (5 H, m), 4.35-4.05 (1 H, m), 4.05-3.90 (2 H, m), 3.65-3.35 (2 H, m), 3.35-3.00 (2 H, m), 2.60 (1 H, m), 2.40/2.35 (3 H, s) and 2.10-1.85 (6 H, m) [NH_2 not apparent]. The compound was unstable and converted spontaneously into the imine **283/284** over the course of two days at room temperature; δ_C as in e.

G. Synthesis and reactivity of polarised double bond compounds

1. Preparation of thiazolidine based condensation products

a. Preparation of (*S*)-2-(bis(methoxycarbonyl)methylene)-3-thia-1-azabicyclo[3.3.0]octane **291**

A mixture of dimethyl malonate (0.88 g, 6.64 mmol) and sodium hydride (0.17 g, 6.96 mmol) in dry THF (60 cm^3) was stirred for 30 min under nitrogen. (*S*)-2-Methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (2.00 g, 6.64 mmol) was added and the mixture stirred at room temperature under nitrogen for 24 h. The mixture was evaporated, water (400 cm^3) was added and the mixture was extracted with CH_2Cl_2 (300 cm^3) which was dried and evaporated to give a brown oil. This crystallised out on standing overnight as off-white solid (1.54 g). Column chromatography of this on silica using ether gave, at R_f 0.23, (*S*)-2-(bis(methoxycarbonyl)methylene)-3-thia-1-azabicyclo[3.3.0]octane **291** (1.38 g, 81%) as colourless needles, m.p. 79-79.5 °C (lit.,[57] 71-72 °C); $[\alpha]_D^{20}$ –311.5° (c 1.58, MeOH) [lit.,[57] $[\alpha]_D^{24}$ –286.9° (c 1.57, MeOH)]; (Found: C, 51.3; H, 5.55; N, 5.3. $C_{11}H_{15}NO_4S$ requires C, 51.4; H, 5.9; N, 5.4%); ν_{max} (nujol) 1715, 1668, 1530, 1290, 1220, 1190, 1150 and 1080 cm^{-1}; δ_H (300 MHz) 4.39 (1 H, m), 3.76 (6 H, s), 3.37 (1 H, m), 3.10 (2 H, m), 2.82 (1 H, t, *J* 11 Hz), 2.20-2.00 (3 H, m) and 1.70 (1 H,

m); δ_C (75 MHz) 167.4 (2 x CO), 166.7 (4^{ry}), 90.8 (4^{ry}) 69.2 (CH), 51.6 (2 x Me), 49.8 (CH_2), 32.8 (CH_2), 29.5 (CH_2) and 27.3 (CH_2); *m/z* 257 (M^+, 8%), 226 (16), 167 (8), 159 (100), 126 (9), 118 (12), 99 (5) and 86 (48).

b. Preparation of (*S*)-2-(α-methoxycarbonylbenzylidene)-3-thia-1-azabicyclo[3.3.0]octane **294**

A mixture of methyl phenylacetate (1.0 g, 6.64 mmol) and sodium hydride (0.17 g, 6.96 mmol) in dry THF (40 cm^3) was stirred for 1 h under nitrogen. (*S*)-2-Methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (2.0 g, 6.64 mmol) was added. After heating under reflux for 6 h, the THF was evaporated and water (400 cm^3) was added. The mixture was extracted with CH_2Cl_2 (400 cm^3) which was dried and evaporated to give a brown oil (1.80g). Column chromatography of this on silica using pet. ether 40/60 : ether (30:70) gave a light brown oil which crystallised out on standing overnight to afford (*S*)-2-(α-methoxycarbonyl benzylidene)-3-thia-1-azabicyclo[3.3.0]octane **294** (1.08 g, 59%) as colourless crystals, m.p. 81-82 °C; $[\alpha]_D^{20}$ −147.5° (c 1.69, MeOH); (Found: C, 65.4; H, 6.3; N, 5.0. $C_{15}H_{17}NO_2S$ requires C, 65.4; H, 6.2; N, 5.1%); ν_{max} (nujol) 1663, 1510, 1294, 1188, 1141 and 641 cm^{-1}; δ_H (200 MHz;) 7.30-7.15 (5 H, m), 4.18 (1 H, m), 3.62 (3 H, s), 3.08 (1 H, dd, *J* 11, 7 Hz), 2.77 (1 H, t, *J* 10 Hz), 2.65 (1 H, m), 2.35 (1 H, m), 2.00-1.70 (3 H, m) and 1.58 (1 H, m); δ_C (75 MHz) 169.4 (CO), 161.9 (4^{ry}), 137.6 (4^{ry}), 132.1 (2 CH), 127.5 (2 CH), 126.7 (CH), 98.2 (4^{ry}) 68.2 (CH), 51.2 (Me), 50.6 (CH_2), 33.8 (CH_2), 30.0 (CH_2) and 27.3 (CH_2); *m/z* 275 (M^+, 2%), 205 (5), 150 (50), 144 (45), 128 (15), 116 (40), 105 (8) and 91 (100).

c. Preparation of (*S*)-2-(α-acetyl(ethoxycarbonylmethylene))-3-thia-1-azabicyclo[3.3.0]octane **295**

A mixture of ethyl acetoacetate (1.72 g, 13.3 mmol) and sodium hydride (0.34 g, 13.9 mmol) in dry THF (150 cm^3) was stirred for 1 h under N_2. (*S*)-2-Methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (4.0 g, 13.3 mmol) was added. After stirring at room temperature under nitrogen for 24 h, the mixture was evaporated, water (400 cm^3) was added and the mixture extracted with CH_2Cl_2 (500 cm^3) which was dried and evaporated to give a brown oil (3.30 g). Column chromatography of this on silica using ether gave, at R_f 0.15, (*S*)-2-(α-acetyl(ethoxycarbonylmethylene))-3-thia-1-azabicyclo[3.3.0]octane **295** as a light brown oil (1.88 g, 56%); (Found: C, 56.0; H, 6.7, N, 5.3. $C_{12}H_{17}NO_3S$ requires C, 56.4; H, 6.7; N, 5.5%); ν_{max} (neat) 2950, 2800, 1680, 1600, 1550, 1500, 1450, 1380, 1300, 1205, 1160 and 1050 cm^{-1}; δ_H (200 MHz) 4.50-4.20 (3 H, m), 3.44 (1 H, m), 3.15-2.95 (2 H, m), 2.80 (1 H, t, *J* 11 Hz), 2.31 (3 H, s), 2.20-2.05 (3 H, m), 1.70 (1 H, m) and 1.34 (3 H, t, *J* 7 Hz); δ_C (50 MHz) 192.4 (CO), 168.2 (4^{ry}), 167.7 (CO), 101.8 (4^{ry}), 68.4 (CH), 60.0 (CH_2), 50.7 (CH_2), 31.9 (CH_2), 29.3 (Me), 29.1 (CH_2), 26.7 (CH_2) and 14.1 (Me); *m/z* 255 (M^+, 95%), 240 (65), 226 (5), 212 (22), 210 (40), 194 (30), 181 (35), 168 (100), 153 (8) and 126 (10).

d. Attempted preparation of (*S*)-2-(dibenzoylmethylene)-3-thia-1-azabicyclo[3.3.0]octane **298**

A mixture of dibenzoylmethane (0.37 g, 1.66 mmol) and sodium hydride (0.04g, 1.74 mmol) in dry toluene (40 cm^3) was stirred for 1 h under nitrogen. (*S*)-2-Methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **147** (0.50 g, 1.66 mmol) was added. After stirring at room temperature under nitrogen for 24 h, water (300 cm^3) was added and the

mixture extracted with CH_2Cl_2 (300 cm^3) which was dried and evaporated to give a brown oil (0.59g). Column chromatography of this on silica using pet. ether : ether (95:5) gave the following products: 2,2-dibenzoylpropane **297**; δ_H (200 MHz) 8.10-7.30 (10 H, m) and 2.49 (6 H, s); δ_C (75 MHz) 192.4 (2 CO), 137.1 (2 x 4^{ry}), 133.3 (2 CH), 128.6 (4 CH), 127.1 (4 CH) and 11.7 (2 Me) [C-2 (4^{ry}) not apparent], unreacted dibenzoylmethane, 1,1-dibenzoylethane **296**; δ_H (200 MHz) 8.10-7.40 (10 H, m), 5.28 (1 H, q, *J* 7 Hz) and 1.60 (3 H, d, *J* 7 Hz); δ_C (75 MHz) 197.2 (2 CO), 135.7 (2 x 4^{ry}), 133.5 (2 CH), 128.9 (4 CH), 128.6 (4 CH), 51.1 (CH) and 14.4 (Me), the thiazolidinethione **169**; δ_C as in C1b, and a fraction containing two additional products in a 2 : 1 ratio. This was further separated using preparative TLC (SiO_2, ether) to give, as the major product, a small quantity of the desired (*S*)-2-(dibenzoylmethylene)-3-thia-1-azabicyclo[3.3.0] octane **298**; δ_H (200 MHz) 7.50 (4 H, m), 7.25-7.05 (6 H, m), 4.48 (1 H, m), 3.30-3.10 (2 H, m), 3.10-2.90 (2 H, m), 2.20-2.10 (3 H, m) and 1.80-1.65 (1 H, m); δ_C (75 MHz) 194.0 (2 CO), 168.8 (4^{ry}), 142.0 (2 4^{ry}), 131.0 (2 CH), 128.9 (4 CH), 127.9 (4 CH), 108.9 (4^{ry}), 70.0 (CH), 50.7 (CH_2), 32.5 (CH_2), 29.7 (CH_2) and 27.5 (CH_2); *m/z* 349 (M^+, 30%), 320 (26), 279 (10), 272 (5), 244 (6), 167 (20), 149 (50) and 105 (100), together with a second minor component which appeared to be (*S*)-2-(benzoylmethylene)-3-thia-1-azabicyclo[3.3.0]octane **299**; δ_H (200 MHz) 8.00-7.90 (2 H, m), 7.50-7.40 (3 H, m), 5.98 (1 H, s), 4.30 (1 H, m), 3.40 (2 H, m), 3.16 (1 H, m), 2.92 (1 H, t, *J* 11 Hz), 2.45-2.25 (2 H, m) and 2.25-2.10 (2 H, m); δ_C (75 MHz) (CO and C-1 (Ph) not apparent), 162.8 (4^{ry}), 130.7 (CH), 128.1 (2 CH), 127.3 (2 CH), 88.7 (=CH), 67.4 (CH), 45.4 (CH_2), 33.6 (CH_2), 30.6 (CH_2) and 28.3 (CH_2); *m/z* 245 (M^+, 100%), 228 (14), 204 (25), 172 (68), 168 (82), 140 (35) and 105 (92).

2. Attempted preparation of oxazolidine-based condensation products

a. Preparation of (*S*)-2-ethoxy-3-oxa-1λ^4-azabicyclo[3.3.0]oct-1-enium tetrafluoroborate **185**

Following a method by Meerwein[10] the oxazolidinone **195** (1.21 g, 9.52 mmol) was added to a solution of triethyloxonium tetrafluoroborate (2.72 g, 14.3 mmol) in dry CH_2Cl_2 (50 cm^3) and the mixture heated under reflux for 4 h under nitrogen. The solvent was evaporated to afford (*S*)-2-ethoxy-3-oxa-1λ^4-azabicyclo[3.3.0]oct-1-enium tetrafluoroborate **185** (1.87 g, 81%) as an orange coloured oil which had identical spectroscopic data to those reported earlier[56]; δ_H (200 MHz) 5.25 (1 H, m), 4.95 (1 H, m), 4.85-4.55 (3 H, m), 3.80 (1 H, m), 3.45 (1 H, m), 2.45 (1 H, m), 2.27-2.12 (3 H, m) and 1.50 (3 H, t, *J* 8 Hz); δ_C (50 MHz) 163.2 (4^{ry}), 77.7 (CH_2O), 73.5 (CH_2O), 62.8 (CH), 44.4 (CH_2), 29.0 (CH_2), 26.6 (CH_2) and 13.7 (Me).

b. Preparation of (*S*)-2-methylthio-3-oxa-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **186**

A mixture of oxazolidinethione **196** (0.65 g, 4.54 mmol), acetone (60 cm^3) and methyl iodide (2.5 cm^3, 5.68 g, 40 mmol) was stirred for 24 h at room temperature. The resulting solution was evaporated to yield (*S*)-2-methylthio-3-oxa-1-azabicyclo[3.3.0]oct-1-enium iodide **186** (0.89g, 69%) as an orange oil; $[\alpha]_D^{20}$ –44.3° (c 1.67, CH_2Cl_2); ν_{max} (neat) 2920, 2870, 1630, 1415, 1350, 1300, 1280, 1160 and 970 cm^{-1}; δ_H (200 MHz) 4.15 (1 H, m), 3.75-3.25 (4 H, m), 2.34 (3 H, s) and 2.20-1.80 (4 H, m); δ_C (50 MHz) 166.7 (4^{ry}), 58.9 (CH), 46.9 (CH_2), 30.5 (CH_2), 23.2 (CH_2), 12.4 (Me) and 9.3 (CH_2); *m/z* 285 (M^+, 37%), 238 (M^+–SMe, 83), 195 (10), 144 (100), 116 (23), 75 (18), 67 (28) and 55 (10). The spectroscopic data were identical to those reported earlier.[56]

c. Reaction of (*S*)-2-ethoxy-3-oxa-1λ^4-azabicyclo[3.3.0]oct-1-enium tetrafluoroborate **185** with the sodium salt of methyl phenylacetate

Sodium hydride (0.04 g, 1.74 mmol) was added to a solution of methyl phenylacetate (0.25 g, 1.66 mmol) in dry toluene (40 cm^3) at 0 °C and the mixture was stirred for 1 h under nitrogen. (*S*)-2-Ethoxy-3-oxa-1λ^4-azabicyclo[3.3.0]oct-1-enium tetrafluoroborate **185** (0.40 g, 1.66 mmol) was added. After stirring at room temperature under nitrogen for 24 h, water (200 cm^3) was added. The organic layer was separated, dried and evaporated to give a brown oil (0.32 g). The NMR spectra showed the presence of the oxazolidinone **195** and unreacted methyl phenylacetate.

d. Reaction of (*S*)-2-methylthio-3-oxa-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **186** with the sodium salt of methyl phenylacetate

A mixture of methyl phenylacetate (0.50 g, 3.32 mmol) and sodium hydride (0.08 g, 3.48 mmol) in dry THF (30 cm^3) was stirred for 1 h under nitrogen. (*S*)-2-Methylthio-3-oxa-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **186** (0.95 g, 3.32 mmol) was added. After heating under reflux under nitrogen for 6 h, the mixture was evaporated and water (400 cm^3) was added. The mixture was extracted with CH_2Cl_2 (300 cm^3) which was dried and evaporated to give the crude product as an orange oil (0.72 g). Column chromatography of this on alumina using pet. ether 40/60 : ether (95:5) gave, at R_f 0.45, a fraction which contained mainly 2-(*S*)-iodomethyl-1-(methylthiocarbonyl)pyrrolidine **302**; δ_H and δ_C as in f. below.

e. Reaction of (*S*)-2-ethoxy-3-oxa-1λ^4-azabicyclo[3.3.0]oct-1-enium tetrafluoroborate **185** with the sodium salt of dimethyl malonate

Sodium hydride (0.04 g, 1.74 mmol) was added to a solution of dimethyl malonate (0.22 g, 1.66 mmol) in dry toluene (40 cm^3) at 0 °C and

the mixture was stirred for 1 h under nitrogen. (*S*)-2-Ethoxy-3-oxa-1λ^4-azabicyclo[3.3.0]oct-1-enium tetrafluoroborate **185** (0.40 g, 1.66 mmol) was added. After stirring at room temperature under nitrogen for 24 h, the mixture was evaporated and water (200 cm^3) was added. The mixture was extracted with CH_2Cl_2 (300 cm^3) which was dried and evaporated to give an orange oil (0.29 g). This was shown by ^{1}H and ^{13}C NMR to consist of the oxazolidinone **195** and unreacted dimethyl malonate.

f. Reaction of (*S*)-2-methylthio-3-oxa-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **186** with the sodium salt of dimethyl malonate

Sodium hydride (0.08 g, 3.48 mmol) was added to a solution of dimethyl malonate (0.44 g, 3.32 mmol) in dry THF (40 cm^3) at 0 °C and the mixture was stirred for 1 h under nitrogen. (*S*)-2-Methylthio-3-oxa-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide **186** (0.95 g, 3.32 mmol) was added. After stirring at room temperature under nitrogen for 24 h, the mixture was evaporated and water (400 cm^3) was added. The mixture was extracted with CH_2Cl_2 (300 cm^3) which was dried and evaporated to give an orange oil (0.94 g). Column chromatography of this on alumina using pet. ether 40/60 : ether (95:5) gave, at R_f 0.24, 2-(*S*)-iodomethyl-1-(methylthiocarbonyl)pyrrolidine **302** (0.31 g, 33%) as a colourless oil; (Found: M$^+$, 284.9679. $C_7H_{12}INOS$ requires *M*, 284.9684); ν_{max} (neat) 2927, 2872, 2365, 1724, 1651 (CO), 1362, 1302, 1283, 1178 and 1153 cm^{-1}; δ_H (300 MHz) 4.25-4.10 (1 H, m), 3.55-3.40 (3 H, m), 3.32 (1 H, m), 2.35 (3 H, s) and 2.18-1.85 (4 H, m); δ_C (75 MHz) 167.0 (CO), 59.2 (CH), 47.2 (CH_2), 30.8 (CH_2) 23.5 (CH_2), 12.7 (Me) and 9.5 (CH_2I); *m/z* 285 (M$^+$, 30%), 238 (M$^+$–SMe, 71), 195 (17), 158 (M$^+$–I, 15), 149 (24), 144 (100), 116 (40), 75 (33), 67 (41), 55 (26) and 47 (19).

g. Reaction of (*S*)-2-ethoxy-3-oxa-1λ^4-azabicyclo[3.3.0]oct-1-enium tetrafluoroborate **185** with the sodium salt of ethyl acetoacetate

Sodium hydride (0.04 g, 1.74 mmol) was added to ethyl acetoacetate (0.22 g, 1.66 mmol) in dry toluene (40 cm^3) at 0 °C and mixture was stirred for 1 h under nitrogen. (*S*)-2-Ethoxy-3-oxa-1λ^4-azabicyclo[3.3.0] oct-1-enium tetrafluoroborate **185** (0.40 g, 1.66 mmol) was added. After heating under reflux under nitrogen for 6 h, water (200 cm^3) was added and the mixture extracted with CH_2Cl_2 (300 cm^3) which was dried and evaporated give a brown oil (0.28 g). The NMR spectra did not show any peaks corresponding to the desired condensation product. Once again, the oxazolidinone **195** was present together with many other products.

3. Preparation of imidazolidine based condensation products

a. Preparation of *N*-benzyloxycarbonyl-(*S*)-proline **309**

Based on a method by Bergmann[76] and modified by Cooper[77] (*S*)-proline (40 g, 347 mmol) was dissolved in 2 M sodium hydroxide (117.5 cm^3, 355 mmol) and stirred at 0 °C while benzyl chloroformate (51.6 cm^3, 61.62 g, 361 mmol) and 2 M sodium hydroxide (117.5 cm^3, 355 mmol) were added dropwise over 15 min. The solution was stirred for 10 min, then neutralised with 2 M hydrochloric acid (183.5 cm^3, 367 mmol) and allowed to warm to room temperature. The mixture was then extracted with ethyl acetate (2 x 300 cm^3) which was washed with water (500 cm^3), 2 M hydrochloric acid (120 cm^3) and water (2 x 500 cm^3), then dried. Evaporation gave a transparent thick oil which crystallised over three days into a white solid. It was recrystallised from ethyl acetate : pet. ether 60/80 (1:1) to give *N*-benzyloxycarbonyl-(*S*)-proline **309** (79.5 g, 92%) as colourless crystals, m.p.77-78 °C (lit.,[78] 77 °C); $[\alpha]_D^{20}$ –41.1° (c 2.12, EtOH) [lit.,[78] $[\alpha]_D^{20}$ –40.6° (c 2.0, EtOH); (Found: C, 62.6; H, 6.2, N,

5.6. $C_{13}H_{15}NO_4$ requires C, 62.6; H, 6.1; N, 5.6%); ν_{max} (nujol) 2000, 1750 (CO), 1630 (CO), 1430, 1350, 1330, 1310, 1210, 1180, 1120, 1080, 980, 850, 750 and 700 cm^{-1}; δ_H (200 MHz) 8.0 (1 H, br s), 7.45-7.20 (5 H, m), 5.15 (2 H, s), 4.40 (1 H, m), 3.65-3.40 (2 H, m), and 2.30-1.80 (4 H, m); δ_C (50 MHz) (double signals due to two isomers) 177.6 and 176.8 (COOH), 155.3 and 154.4 (CO), 136.2 (4^{ry}), 128.3 and 128.2 (2 CH), 127.9 (1 CH), 127.7 and 127.4 (2 CH), 67.0 and 64.2 (CH_2), 59.0 and 58.5 (CH), 46.8 and 46.4 (CH_2), 30.7 and 29.5 (CH_2), 24.0 and 23.2 (CH_2).

b. Preparation of 1-benzyloxycarbonyl-(*S*)-pyrrolidine-2-carboxanilide **310**

Following a method by Mukaiyama,[79] *N*-benzyloxycarbonyl-(*S*)-proline **309** (35.7 g, 143 mmol) was dissolved in ethyl acetate (200 cm^3) and the solution cooled to 0 °C. Under a nitrogen atmosphere, *N*-methylmorpholine (15.7 cm^3, 143 mmol) in ethyl acetate (200 cm^3) was added. The mixture was cooled to –15 °C, and ethyl chloroformate (13.7 cm^3, 143 mmol) in ethyl acetate (50 cm^3) was added slowly to the solution over during 5 min.

Aniline (13 cm^3, 13.3 g, 143 mmol) in ethyl acetate (50 cm^3) was added to the mixture which was kept at –15 °C for 1 h and at 0 °C for 1 h, then the temperature was gradually raised up to room temperature and it was stirred overnight. To the mixture was added ethyl acetate (100 cm^3) and water (200 cm^3). Then the organic layer was separated, washed with 4% $NaHCO_3$ (200 cm^3), brine (200 cm^3), 2% HCl (200 cm^3) and brine successively. Drying and evaporation gave the crude product (42.8 g, 92%) which was recrystallised from acetone (160 cm^3) to afford 1-benzyloxycarbonyl-(*S*)-pyrrolidine-2-carboxanilide **310** (31.3 g, 67%) as colourless crystals , m.p. 142.5-143 °C (lit.,[79] 141-141.5 °C); $[\alpha]_D^{20}$ –60.0°(c 1.224, EtOH) [lit.,[79] $[\alpha]_D^{20}$ –63.2° (c 0.997, EtOH)]; ν_{max} (nujol)

3250 (NH), 1650, 1590, 1530, 1480, 1420, 1350, 1300, 1230, 1170, 1110, 730 and 690 cm^{-1}; δ_H (300 MHz) 9.25 (1 H, br s), 7.55-7.00 (10 H, m), 5.25 (2 H, s), 4.55 (1 H, m), 3.75-3.40 (2 H, m) and 2.50-1.80 (4 H, m); δ_C (75 MHz) 169.5 (CO), 156.5 (CO), 138.0 (4^{ry}), 136.1 (4^{ry}), 128.7 (2 CH), 128.4 (2 CH), 128.0 (CH), 127.8 (2 CH), 123.8 (CH), 119.7 (2 CH), 67.4 (CH_2), 61.0 (CH), 47.0 (CH_2), 27.7 (CH_2) and 24.5 (CH_2).

c. Preparation of (*S*)-pyrrolidine-2-carboxanilide **311**

Following a method by Mukaiyama,[79] 1-benzyloxycarbonyl-(*S*)-pyrrolidine-2-carboxanilide **310** (5.5 g 17.0 mmol) and 5% Pd/C (0.7 g) were stirred vigorously in MeOH (150 cm^3) under hydrogen atmosphere for 3 h until the calculated volume (380 cm^3, 17.0 mmol) had been absorbed. The mixture was filtered through celite and filtrate evaporated to give the crude product as a white solid. This was recrystallised from cyclohexane (70 cm^3) to afford the title compound **311** (3.10 g, 96%) as colourless crystals, m.p. 78-79 °C (lit.,[79] m.p. 76-77 °C); $[\alpha]_D^{20}$ –68.6° (c 1.014, EtOH) [lit.,[79] $[\alpha]_D^{27}$ –71.0°, (c 1.025, EtOH)]; (Found: C, 69.6; H, 7.5; N, 14.8. $C_{11}H_{14}N_2O$ requires C, 69.4; H, 7.4; N, 14.7%); ν_{max} (nujol) 3460 (NH), 3260 (NH), 2965, 1670 (CO), 1592, 1495, 1440, 1380, 1302, 1142, 754 and 696 cm^{-1}; δ_H (300 MHz) 9.74 (1H, br s), 7.62 (2 H, m), 7.32 (2 H, m), 7.09 (1 H, m), 3.86 (1 H, dd, *J* 8, 5 Hz), 3.10-2.90 (2 H, m), 2.25-2.10 (2 H, m), 2.03 (1H, m) and 1.74 (2 H, m); δ_C (75 MHz) 173.3 (CO), 137.8 (4^{ry}), 128.8 (2 CH), 123.7 (CH), 119.1 (2 CH), 60.9 (CH), 47.2 (CH_2), 30.6 (CH_2) and 26.2 (CH_2).

d. Preparation of (*S*)-2-(anilinomethyl)pyrrolidine **312**

Following a method by Mukaiyama,[79] a solution of the anilide **311** (4.60 g, 24.2 mmol) in dry THF (50 cm^3) was added to a suspension of $LiAlH_4$ (1.99 g, 52.7 mmol) in dry THF (150 cm^3) at 0 °C under nitrogen.

The mixture was stirred overnight at 0 °C and then cautiously hydrolysed with saturated aqueous Na_2SO_4. The inorganic salts were filtered off and the filtrate evaporated. Fractional distillation of the residue under reduced pressure afforded (*S*)-2-(anilinomethyl)pyrrolidine **312** (3.51 g, 82%) as a light brown oil, b.p. 170–190 °C/ 2 mmHg (lit.,[79] 111–112 °C/ 0.55 mmHg); $[\alpha]_D^{20}$ +18.9° (c 0.987, EtOH) [lit.,[79] $[\alpha]_D^{24}$ +19.7° (c 1.087, EtOH)]; ν_{max} (neat) 3327 (NH), 3050 (NH), 2959, 2869, 1604, 1505, 1322, 1260, 1180, 749 and 694 cm^{-1}; δ_H (300 MHz) 7.20-7.10 (2 H, m), 6.75-6.55 (3 H, m), 4.20 (1 H, br s), 3.28 (1 H, m), 3.08 (1 H, m), 2.90-2.80 (3 H, m), 2.25 (1 H, br s), 1.95-1.55 (3 H, m) and 1.45-1.30 (1 H, m); δ_C (75 MHz) 148.2 (4^{ry}), 128.8 (2 CH), 116.7 (CH), 112.5 (2 CH), 57.3 (CH), 48.2 (CH_2), 46.1 (CH_2), 29.2 (CH_2) and 25.4 (CH_2); *m/z* 176 (M^+, 7%), 108 (8), 107 (44), 106 (13), 84 (7), 77 (9) and 70 (100).

e. Preparation of (*S*)-3-phenyl-1,3-diazabicyclo[3.3.0]octane-2-thione **313**

Based on a method by Sharma,[66] a stirred solution of triethylamine (4.67 g, 6.4 cm^3, 46.2 mmol) and (*S*)-2-(anilinomethyl)pyrrolidine **312** (4.07 g, 23.1 mmol) in CH_2Cl_2 (800 cm^3) was cooled down to 0 °C and a solution of thiophosgene (2.7 cm^3, 4.02 g, 35 mmol) in CH_2Cl_2 (100 cm^3) was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred overnight. The mixture was then washed with water (2 x) and 0.5 M sodium hydroxide (200 cm^3), dried and evaporated to afford a reddish brown semi-solid. The crude product was purified by chromatography using ether : pet. ether (80:20) on alumina to afford, at R_f 0.34, the title product **313** (1.99 g, 34%) as colourless crystals, m.p. 126-127 °C; $[\alpha]_D^{20}$ –163.5° (c 1.02 g, CH_2Cl_2); (Found: C, 66.3; H, 6.5; N, 12.9; M^+, 218.0870. $C_{12}H_{14}N_2S$ requires C, 66.0; H, 6.5; N, 12.8%; *M*, 218.0878); ν_{max} (nujol) 1594, 1581, 1498, 1489, 1332, 1314, 1296,

1255 and 1230 cm^{-1}; δ_H (300 MHz) 7.56 (2 H, m), 7.41 (2 H, m), 7.23 (1 H, m), 4.20-4.00 (3 H, m), 3.98 (1 H, m), 3.47 (1 H, m), 2.25-2.10 (2 H, m), 2.02 (1 H, m) and 1.65-1.50 (1 H, m); δ_C (75 MHz) 183.7 (CS), 140.7 (4^{ry}), 128.8 (2 CH), 126.0 (CH), 124.3 (2 CH), 59.5 (CH), 55.2 (CH_2), 47.8 (CH_2), 31.3 (CH_2) and 25.2 (CH_2); *m/z* 218 (M^+, 45%), 202 (100), 174 (42), 160 (8), 119 (20), 105 (49), 91 (15), 77 (52), 70 (15), 55 (54), 51 (23) and 41 (26).

f. Preparation of (*S*)-2-methylthio-3-phenyl-1λ^4,3-diazabicyclo[3.3.0]oct-1-enium iodide **315**

Based on a procedure by Roussel et al.,[60] a mixture of the imidazolidinethione **313** (0.50 g, 2.29 mmol), acetone (60 cm^3) and methyl iodide (1.9 cm^3, 4.26 g, 30 mmol) was stirred for 16 h at room temperature. The mixture was evaporated to afford the crude (*S*)-2-methylthio-3-phenyl-1λ^4,3-diazabicyclo[3.3.0]oct-1-enium iodide **315** in quantitative yield (0.83 g) as an orange oil; $[\alpha]_D^{20}$ −143.7° (c 0.992, CH_2Cl_2); δ_H (300 MHz) 7.70-7.60 (2 H, m), 7.55-7.40 (3 H, m), 4.95 (1 H, m), 4.60 (1 H, t, *J* 8 Hz), 4.53 (1 H, t, *J* 8 Hz), 4.00 (1 H, m), 3.78 (1 H, m), 2.55 (3 H, s), 2.55-2.40 (2 H, m) and 2.38-2.25 (2 H, m); δ_C (75 MHz) 169.7 (C=N^+), 135.7 (4^{ry}), 129.2 (2 CH), 128.8 (CH), 125.2 (2 CH), 63.7 (CH), 58.3 (CH_2N^+), 48.2 (CH_2NPh), 29.4 (CH_2), 26.4 (CH_2) and 16.1 (Me).

g. Preparation of (*S*)-3-phenyl-1,3-diazabicyclo[3.3.0]octan-2-one **314**

Based on a method by Sharma,[66] a stirred solution of triethylamine (1.72 g, 2.37 cm^3, 17.02 mmol and (*S*)-2-(anilinomethyl)pyrrolidine **312** (1.5 g, 8.51 mmol) in CH_2Cl_2 (400 cm^3) was cooled to 0 °C and a solution of phosgene (11.3 cm^3, 1.29 g, 13 mmol) in CH_2Cl_2 (50 cm^3) was added dropwise. The resulting mixture was allowed to warm to room

temperature and stirred overnight. The mixture was then washed with water (2 x) and 0.5 M sodium hydroxide, dried and evaporated to afford a reddish brown semi-solid. The crude product was purified by chromatography on alumina using ether : pet. ether (40:60) to afford, at R_f 0.15, the title product **314** (0.60 g, 35%) as colourless crystals, m.p. 92-93 °C; $[\alpha]_D^{20}$ –94.5° (c 1.11, CH_2Cl_2); (Found: C, 71.35; H, 7.2; N, 13.7. $C_{12}H_{14}N_2O$ requires C, 71.3; H, 7.0; N, 13.9%); ν_{max} (nujol) 1691 (CO), 1592 (C=C in Ph), 1492, 1400, 1322, 1286 and 1250 cm^{-1}; δ_H (300 MHz) 7.65-7.55 (2 H, m), 7.40-7.25 (2 H, m), 7.10-6.90 (1 H, m), 4.00 (1 H, t, *J* 8 Hz), 3.85-3.70 (3 H, m), 3.18 (1 H, m), 2.15-1.80 (3 H, m) and 1.45 (1 H, m); δ_C (75 MHz) 160.8 (CO), 140.3 (4^{ry}), 128.8 (2 CH), 122.6 (CH), 117.6 (2 CH), 55.5 (CH), 48.0 (CH_2), 45.7 (CH_2), 31.4 (CH_2) and 25.1 (CH_2); *m/z* 202 (M^+, 100%), 174 (28), 112 (13), 105 (38), 104 (17), 86 (40), 84 (70), 77 (25), 70 (15) and 55 (55).

h. Preparation of (*S*)-2-ethoxy-3-phenyl-1λ^4,3-diazabicyclo[3.3.0]oct-1-enium tetrafluoroborate **316**

Following a method by Meerwein[10] the bicyclic urea derivative **314** (0.30 g, 1.48 mmol) was added to a solution of triethyloxonium tetrafluoroborate (0.42 g, 2.22 mmol) in dry CH_2Cl_2 (10 cm^3) and the mixture heated under reflux for 4 h under nitrogen. The solvent was evaporated to afford a colourless oily solid (0.42 g) which proved to be a mixture of the imidizolidinone; δ_H and δ_C as in g., and (*S*)-2-ethoxy-3-phenyl-1λ^4-1,3-diazabicyclo[3.3.0]oct-1-enium tetrafluoroborate **316** (0.52 g); δ_H (200 MHz, CD_3SOCD_3) 7.80-7.40 (5 H, m), 4.78 (1 H, m), 4.58 (1 H, dd, *J* 8, 6 Hz), 4.25 (1 H, m), 4.17 (1 H, dd, *J* 8, 3 Hz), 3.75-3.45 (3 H, m), 2.30 (1 H, m), 2.05-1.85 (3 H, m) and 1.47 (3 H, t, *J* 7 Hz); δ_C (75 MHz, CD_3SOCD_3) 151.5 (4^{ry}), 135.9 (4^{ry}), 129.4 (2 CH), 127.6 (CH), 121.7 (2 CH), 63.0 (CH_2O), 62.5 (CH), 57.2 (CH_2N^+), 49.8 (CH_2NPh),

31.6 (CH_2), 23.4 (CH_2) and 9.2 (Me); *m/z* 230 (M^+–HBF_4, 15%), 215 (6), 202 (94), 189 (83), 174 (30), 178 (22), 105 (52), 89 (100), 77 (48), 55 (80), and 49 (41). Additional NMR signals were present due to the Meerwein reagent; δ_H 4.45 (6 H, q, *J* 8 Hz) and 1.20 (9 H, t, *J* 8 Hz); δ_C 72.8 (CH_2) and 15.3 (Me).

i. Preparation of (*S*)-2-(bis(methoxycarbonyl)methylene)-3-phenyl-1,3-diazabicyclo[3.3.0]octane **317**

A mixture of dimethyl malonate (0.30 g, 2.29 mmol) and sodium hydride (0.06g, 2.41 mmol) in dry THF (60 cm^3) was stirred for 30 min under nitrogen. (*S*)-2-Methylthio-3-phenyl-1λ^4,3-diazabicyclo[3.3.0]oct-1-enium iodide **315** (0.83 g, 2.29 mmol) was added. After heating under reflux under nitrogen for 6 h, the mixture was evaporated and water (400 cm^3) was added and the mixture extracted with CH_2Cl_2 (300 cm^3) which was dried and evaporated to give (*S*)-2-(bis-(methoxycarbonyl)methylene)-3-phenyl-1,3-diazabicyclo[3.3.0]octane **317** (0.60 g, 84%) as an off white solid, m.p. 135-137 °C; $[\alpha]_D^{20}$ –19.4° (c 1.766, CH_2Cl_2); (Found: M^+, 316.1418. $C_{17}H_{20}N_2O_4$ requires *M*, 316.1423); ν_{max} (nujol) 1702, 1595, 1499, 1332, 1296, 1257, 1165, 1081, 1047, 765 and 694 cm^{-1}; δ_H (300 MHz) 7.35-7.28 (2 H, m), 7.25-7.15 (2 H, m), 7.09 (1 H, m), 4.38 (1 H, m), 4.12 (1 H, t, *J* 7 Hz), 3.90 (1 H, t, *J* 7 Hz), 3.57 (1 H, m), 3.34 (6 H, s), 3.22 (1 H, m), 2.30-2.00 (3 H, m) and 1.75 (1 H, m); δ_C (75 MHz) 167.5 (2 x CO), 165.0 (=C-N), 142.2 (4^{ry}), 129.1 (2 CH), 124.8 (CH), 121.1 (2 CH), 75.5 (=$\underline{C}CO_2Me$), 59.4 (CH), 56.2 (CH_2), 50.5 (2 Me), 48.4 (CH_2), 31.6 (CH_2) and 26.7 (CH_2); *m/z* 316 (M^+, 60%), 285 (15), 257 (30), 218 (98), 202 (23), 149 (30), 84 (88) and 49 (100).

j. Attempted preparation of (*S*)-2-(α-methoxycarbonylbenzylidene)-3-phenyl-1,3-diazabicyclo[3.3.0]octane

A mixture of methyl phenylacetate (0.34 g, 2.29 mmol) and sodium hydride (0.06 g, 2.41 mmol) in dry THF (30 cm^3) was stirred for 1 h under nitrogen. (*S*)-2-Methylthio-3-phenyl-1λ⁴,3-diazabicyclo[3.3.0]oct-1-enium iodide **315** (0.83 g, 2.29 mmol) was added. After heating under reflux under nitrogen for 6 h, the mixture was evaporated and water (400 cm^3) was added and the mixture extracted with CH_2Cl_2 (300 cm^3) which was dried and evaporated to give a brown oily solid (0.64 g) which was shown by NMR to be a mixture of imidazolidinethione **313**; δ_H and δ_C as in e., the imidazolidinone **314**; δ_H and δ_C as in g., and unreacted methyl phenylacetate.

4. Reactions of thiazolidine based condensation products

a. Reaction of the condensation product of dimethyl malonate **291** with methyl iodide

A mixture of the condensation product **291** (0.25 g, 0.97 mmol) and methyl iodide (0.14 g, 0.97 mmol) in dry CH_2Cl_2 (50 cm^3) was stirred at room temperature for 24 h. The solvent was evaporated to give a white solid (0.26 g). NMR spectra did not show any peaks corresponding to the desired electrophilic addition product and only the starting material was present.

The experiment was repeated using 2 eq of MeI, and by heating under reflux for 8 h, but reaction still did not take place.

b. Reaction of the condensation product of ethyl acetoacetate **295** with methyl iodide

A mixture of the condensation product **295** (0.25 g, 0.97 mmol) and

methyl iodide (0.14 g, 0.97 mmol) in dry CH_2Cl_2 (50 cm^3) was stirred at room temperature for 24 h. The solvent was evaporated to give a brown oil (0.27 g). NMR spectra did not show any peaks corresponding to the desired electrophilic addition product and only the starting material was present.

The experiment was repeated using 2 eq of methyl iodide, and by heating under reflux for 8 h, but reaction still did not take place.

c. Reaction of the condensation product of dimethyl malonate **291** with methyl trifluoromethanesulfonate

A mixture of the condensation product **291** (0.25 g, 0.97 mmol) and methyl trifluoromethanesulfonate (0.21 cm^3, 1.94 mmol) in dry toluene (50 cm^3) was stirred at room temperature for 24 h. The solvent was evaporated to give a brown product (0.26 g). The ^{13}C NMR spectrum of this showed some indication of the presence of the protonated starting material, (*S*)-2-(bis(methoxycarbonyl)methyl)-3-thia-1λ^4-azabicyclo[3.3.0] oct-1-enium trifluoromethanesulfonate **339**; δ_C (50 MHz) 76.6 (CH), 54.4, 54.2 and 54.1 (2 $CO_2\underline{Me}$ and $\underline{C}H(CO_2Me)_2$), 49.1 (CH_2N^+), 35.1 (CH_2), 28.4 (CH_2) and 28.0 (CH_2) (CO not apparent).

d. Reaction of the condensation product of ethyl acetoacetate **295** with methyl trifluoromethanesulfonate

A mixture of the condensation product **295** (0.25 g, 0.97 mmol) and methyl trifluoromethanesulfonate (0.21 cm^3, 1.94 mmol) in dry toluene (50 cm^3) was stirred at room temperature for 24 h. The solvent was evaporated to give a brown product (0.26 g). NMR spectra did not show any peaks corresponding to the desired electrophilic addition product and the starting material had apparently been destroyed.

e. Reaction of the condensation product of dimethyl malonate **291** with BuLi followed by methyl iodide

A mixture of the condensation product **291** (0.20 g, 0.78 mmol) and BuLi (1.6 M, 0.55 cm^3, 0.88 mmol) in dry THF (25 cm^3) was stirred at room temperature for 6 h under nitrogen. Then methyl iodide (0.22 g, 0.1 cm^3, 1.56 mmol) was added and the mixture stirred overnight. The solution was evaporated and saturated NH_4Cl solution was added and the mixture extracted with CH_2Cl_2 which was dried and evaporated to give a brown solid (0.24 g). NMR spectra did not show any peaks corresponding to the desired nucleophilic and electrophilic additions and only the starting material was present.

f. Reaction of the condensation product of dimethyl malonate **291** with ethyl magnesium bromide followed by methyl iodide

To a mixture of magnesium turnings (0.06 g, 2.34 mmol) and a few crystals of iodine in dry ether (10 cm^3) under nitrogen, ethyl bromide (0.09 cm^3, 0.13g, 1.17 mmol) in dry ether (10 cm^3) was added slowly from a pressure equalising funnel and the mixture stirred for half an hour under nitrogen to afford the Grignard reagent. The dimethyl malonate condensation product **291** (0.2 g, 0.78 mmol) was added and the mixture stirred for 8 h.

Then methyl iodide (0.16 g, 0.07 cm^3, 1.5 mmol) was added and the solution stirred overnight. Saturated NH_4Cl solution was added and the ether layer separated, dried and evaporated to give a brown solid (0.24 g). NMR spectra did not show any peaks corresponding to the desired nucleophilic and electrophilic additions and only the starting material was present.

H. X-Ray Structure Determination

The structure of **294** was determined by Dr P. Lightfoot, School of Chemistry, University of St. Andrews.

(*S*)-2-(α-methoxycarbonylbenzylidene)-3-thia-1-azabicyclo[3.3.0]octane **294**

A colourless crystal suitable for X-ray diffraction was obtained by recrystallisation from n-hexane - ethanol. The following data were obtained:—

$C_{15}H_{17}NO_2S$, M = 275.36, monoclinic space group $P2_1$ (#4); a = 8.555(3), b = 15.555(3), c = 10.663(2) Å, β = 91.23(2)°, V = 1418.7(5) $Å^3$, Z = 4, D_C = 1.289 g cm^{-3}, R = 0.037, R_W = 0.030 for 1930 data with $I>3\sigma(I)$ and 342 parameters. Data were recorded at 293 K using Mo-Kα radiation and the structure was solved by direct methods and refined using full-matrix least square analysis. The structure is illustrated in the Discussion and selected data are given in the Appendix.

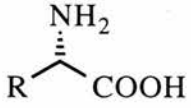
DISCUSSION

A. Kinetic Resolution using (*S*)-2-methylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium iodide 147

1. Background

The aim of part of our work was to examine a range of simple chiral heterocyclic iminium salts as effective chemical reagents for kinetic resolution of racemic nucleophilic compounds. Up to now most kinetic resolution has involved the use of enzymes but our work involved the development of simple heterocyclic reagents capable of achieving the same goal. Before going on to describe the results in detail the meaning and significance of kinetic resolution will be outlined.

In the recent years it has become very important to prepare the desired enantiomer of a chiral compound exclusively or predominantly, avoiding the undesired enantiomer due to economic and environmental reasons. Two enantiomers of a compound may have quite different properties. For example, α-amino acids exhibit striking dissimilarities in their taste properties. The (*S*)-enantiomers **156** of leucine, phenylalanine, tyrosine and tryptophan taste bitter, whereas their corresponding (*R*)-enantiomers **157** are sweet.



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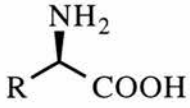
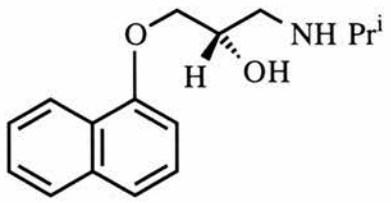


157

Two enantiomers of a chiral drug may have quite distinct biological activities and may lead to different effects. (–)-Propranolol **158** is used for the treatment of heart disease while (+)-propranolol **159** acts as a contraceptive.



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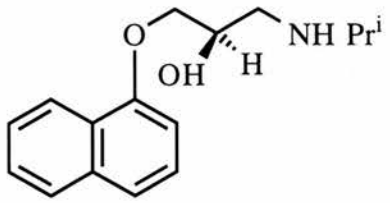
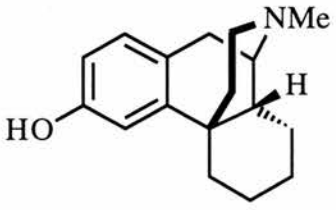


159

The alkaloid (–)-levorphanol **160** is a powerful narcotic analgaesic with an activity 5–6 times stronger than morphine. Its enantiomer, (+)-dextrophan **161**, is totally devoid of this activity, but acts as a cough suppressant.



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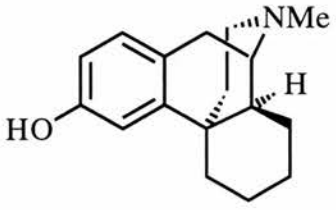

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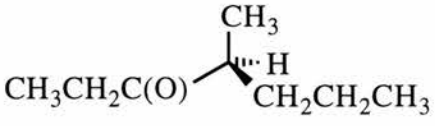
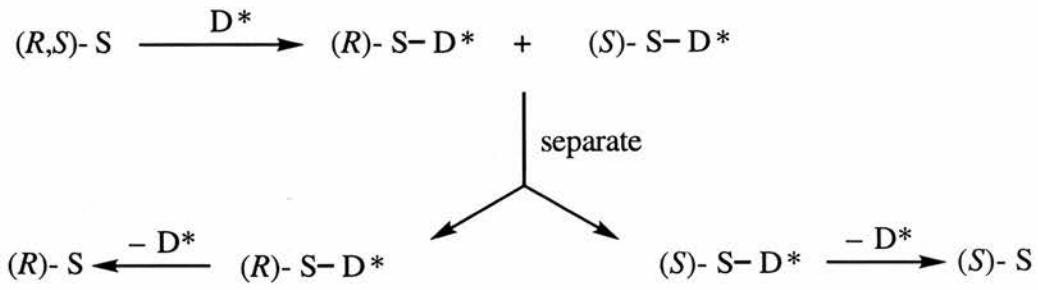
The principal alarm pheromone of leaf cutting ant is (*S*)-4-methyl-3-heptanone **162** while its (*R*)-enantiomer does not possess this characteristic.



162

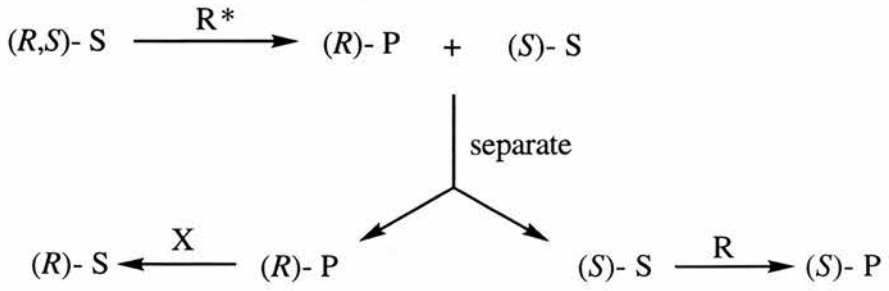
Practical resolution methods are of great importance in large scale fine chemical manufacture.[80] The procedure of resolution depends upon the fact that diastereomers, in contrast to enantiomers, may have different physical properties. If we take racemic substrate S and react it with an enantiomerically pure derivatising agent D*, the resulting products are

diastereomeric. They can therefore be separated, commonly by fractional



crystallisation, and treated separately to remove the resolving agent D*. This then gives the two separate enantiomers of S and also liberates the resolving agent which can be resued. Although effective resolving agents have been developed for very many compounds,[81] this classical resolution is still very much a matter of trial and error.

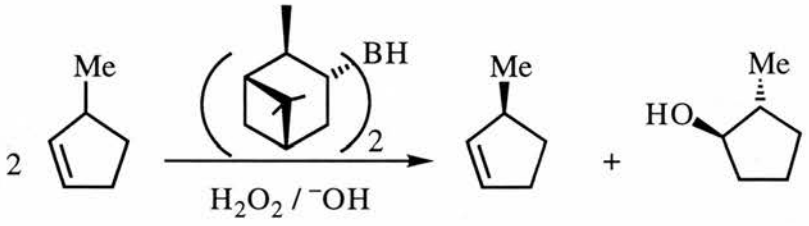
Kinetic resolution differs from the classical resolution procedure described above in that the enantiomers of the substrate are separated by their rates of reaction with a chiral reagent R*. In the ideal situation one enantiomer reacts to give the chiral product P while the other remains



completely unreacted. These compounds can then be separated directly and if necessary the unreacted enantiomer can be converted into the corresponding product by reaction with an achiral equivalent of R*. Alternatively the enantiomer which did react can be converted back to the non-racemic starting material by an achiral reagent X which brings about the reverse reaction to R. The advantages of kinetic resolution over

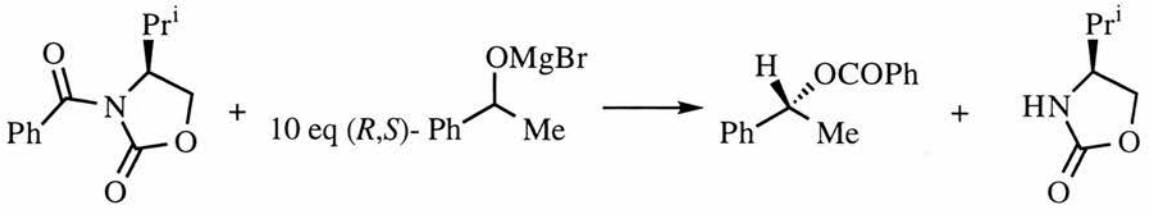
classical resolution are twofold. First, fewer steps are involved and at least one enantiomer of the substrate can be obtained directly. Secondly, the separation is usually easier since the two materials involved contain different functional groups rather than being stereoisomers. A detailed review of kinetic resolution methods has been published.[82]

An important early example of kinetic resolution is the stoichiometric asymmetric hydroboration of racemic 3-methylcyclopentene **163** by treatment with optically active diisopinocampheylborane[83] in which the (*S*)-enantiomer **164** is less reactive and is recovered at the end of the reaction in 30% e.e. The (*R*)-enantiomer having a more favourable conformation to react with the chiral reagent is consumed faster to produce the optically enriched alcohol **165**.



163 **164** **165**

A more recent example which is of particular relevance to the work involved here is the development of chiral *N*-benzoyloxazolidinones such as **166** by Evans for resolution of secondary alcohols.[84] As shown, benzoylation of the racemic alcohol in the form of its bromomagnesium

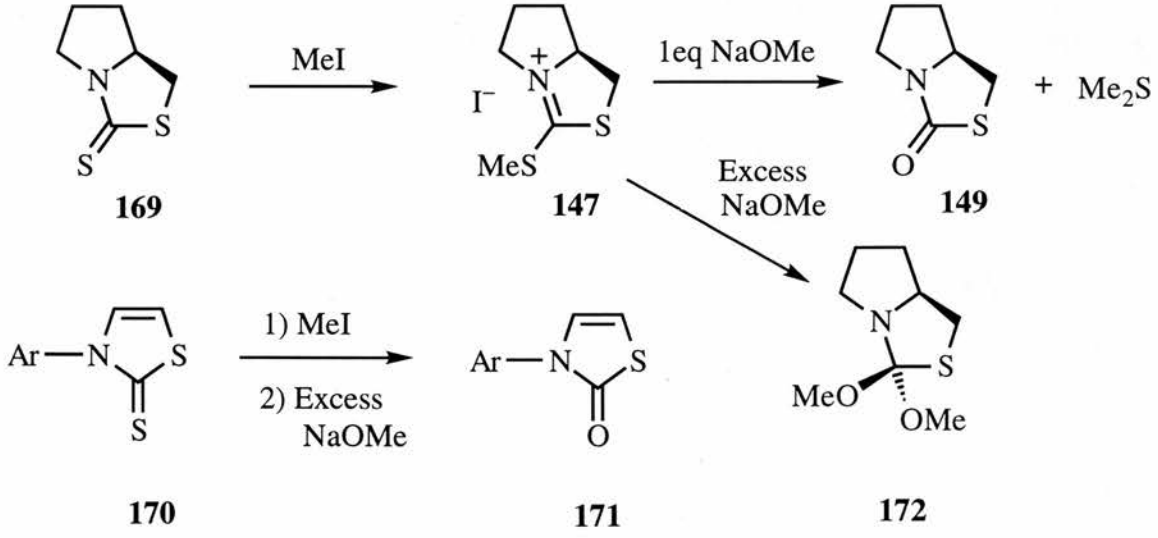


166 **167** **168**

salt **167** proceeds with excellent selectivity to give the (*R*)-benzoate **168**. Although Evans used a large excess of **167**, use of just two equivalents would in principle produce **168** and the unreacted (*S*)-alcohol.

2. Previous work

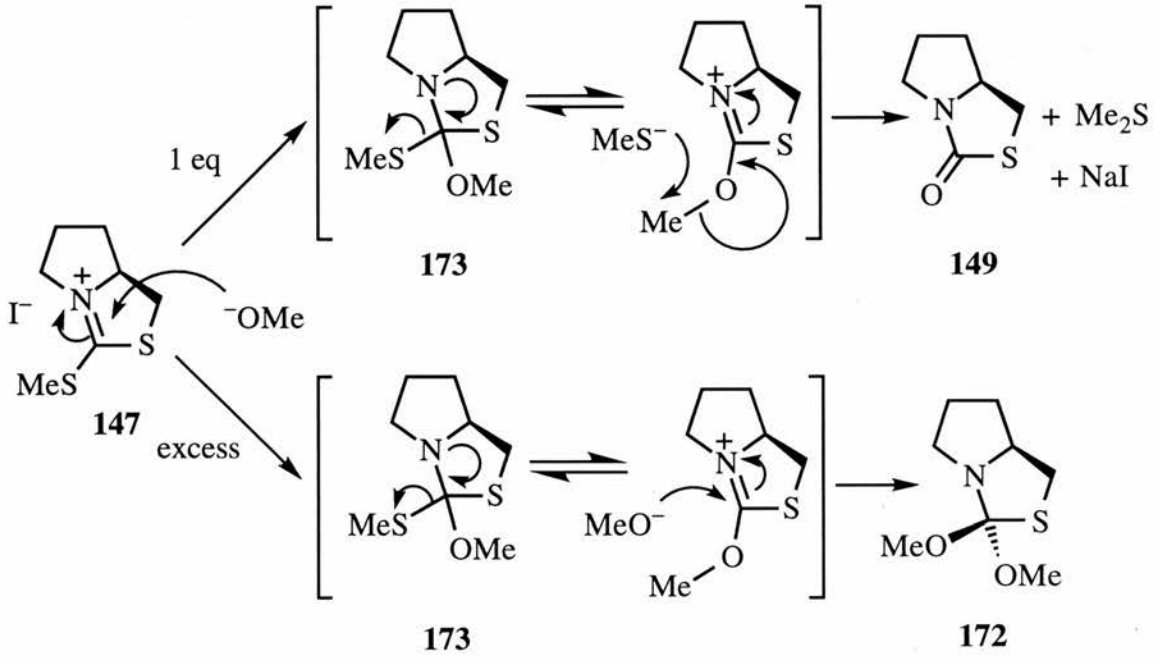
In the course of a previous study in this laboratory,[56] it was required to convert the chiral bicyclic dithiocarbamate **169** into thiocarbamate **149**. Based on a recently reported method of Roussel and coworkers[60] treatment with MeI to form the salt **147** followed by reaction with excess NaOMe was expected to give **149**. While this was reported to be successful for a variety of monocyclic thiazolinethiones (e.g. **170** ⟶ **171**),[60] in the bicyclic case the use of excess of NaOMe resulted in the displacement of the methylthio group to give orthothiocarbamate derivative **172**.[56]



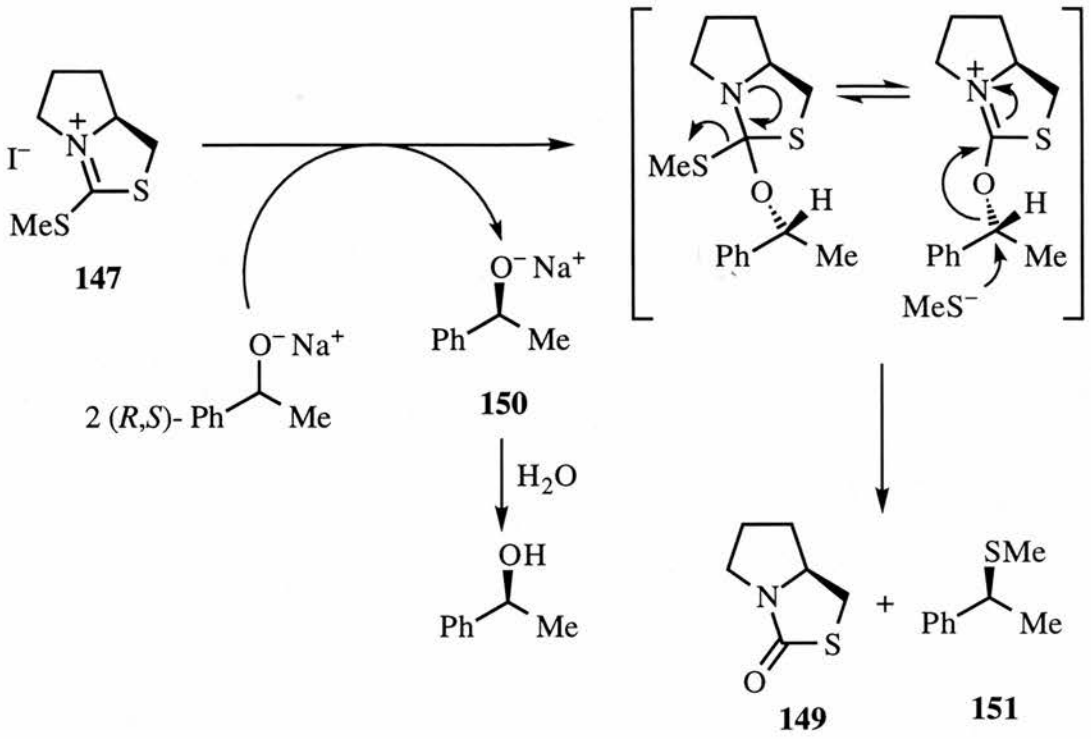
169 **147** **149** **170** **171** **172**

This compound proved to be extraordinarily stable, distilling without decomposition at nearly 200 °C. The thiazolidinone **149** was later obtained from **147** either by the use of only 1 eq. of NaOMe or more satisfactorily by using a bulkier alkoxide such as KOBu^t in Bu^{t}OH. However it was the

spectroscopic properties of **172** and in particular the large differentiation between the two methoxy groups (δ_H 3.30 vs 3.45, δ_C 50.7 vs 53.3) which led to the realisation that these reactions might be adapted to form the basis of an important new method to obtain enantiomerically pure compounds. The mechanism proposed for the reaction of **147** with 1 eq and excess of the alkoxide was explained as shown below:

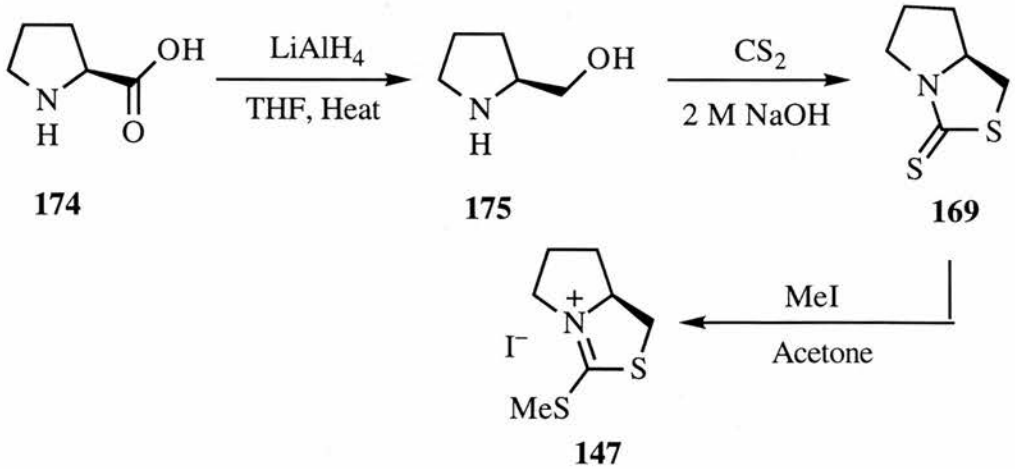


The bicyclic iminium salt **147** was then examined as a reagent for kinetic resolution of racemic 1-phenylethanol. Treatment of the alcohol with sodium metal gave the alkoxide which was reacted with **147** at room temperature in toluene. The desired reaction took place to give **149**, the methyl sulphide **151**, and the unreacted alkoxide **150**. Upon work up the last compound was converted to the corresponding alcohol and this was found to have an e.e. of 20-30% in favour of the (*S*)-enantiomer as shown. The sulfide **151** is also expected to be the (*S*)-enantiomer due to the inversion involved in the reaction, although this could not be confirmed since this compound has never been prepared in non-racemic form before.



3. Preparation of the iminium salt 147 i.e. (*S*)-2-methylthio-3-thia-1λ⁴-azabicyclo[3.3.0]oct-1-enium iodide

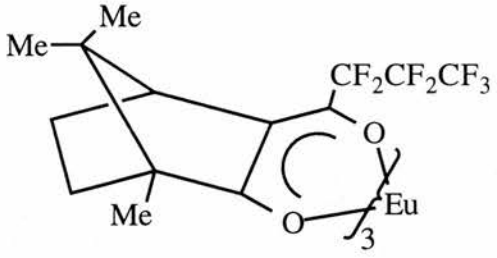
(*S*)-Prolinol **175** was prepared following a literature procedure,[58] by reduction of (*S*)-proline **174** using $LiAlH_4$ in dry THF. Based on the method of Roth, the chiral bicyclic dithiocarbamate **169** was prepared from (*S*)-prolinol **175** by condensation with carbon disulfide in the



presence of sodium hydroxide.[59] This was then converted, using the method of Roussel and coworkers,[60] into the iminium salt **147** by reaction with methyl iodide. The overall conversion from **174** through to **147** proceeded in 27% yield but could be performed readily and reproducibly to provide the large quantities of **147** required for further study.

4. Standard procedure of determination of enantiomeric excess

The enantiomeric excess of the alcohol produced in the kinetic resolution experiments was determined by ^{1}H NMR using a chiral lanthanide shift reagent (C.L.S.R.). These are hexacoordinate complexes of trivalent lanthanide metals with chiral 1,3-diketones.[61] The C.L.S.R. used in the e.e. measurement of 1-phenylethanol was tris[3-heptafluoropropylhydroxymethylene-(1*R*)-camphorato]europium(III) [Eu(hfc)$_3$] **176**.



176

C.L.S.R. complexes are known to be Lewis acids and therefore the most probable binding site on the 1-phenylethanol would be the alcoholic oxygen. The C.L.S.R. binds one enantiomer satisfactorily and complexes poorly with the other due to different steric hindrance.

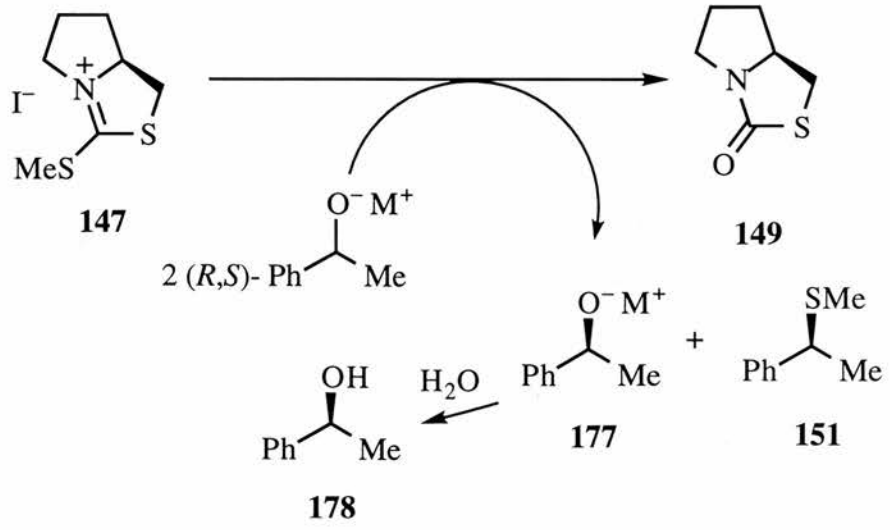
The samples were prepared by the gradual addition of **176** to the alcohol in $CDCl_3$ solution until the 200 MHz ^{1}H NMR spectrum showed optimum separation of enantiomeric peaks. The C.L.S.R. added was

normally 9-12.5% molar equivalent and the peak separation was greatest for the proton bonded to the stereogenic centre. The quartets due to PhC<u>H</u>(Me)OH shifted from 4.85 to 10.58 for the (*S*)-enantiomer and to 10.80 for the (*R*)-enantiomer. The assignment of the lower frequency signal to the (*S*)-enantiomer relies on the previous work[56] in which a pure sample with 29% e.e. in favour of the lower frequency signal gave a rotation of $[\alpha]_D$ –12.0° [lit.,[62] –40.95° for (*S*)-enantiomer].

5. Counter cation effects

We expected that changing the counter cation for the alkoxide could have an effect on its reactivity, with the possibility of increasing the enantioselectivity of the reaction.

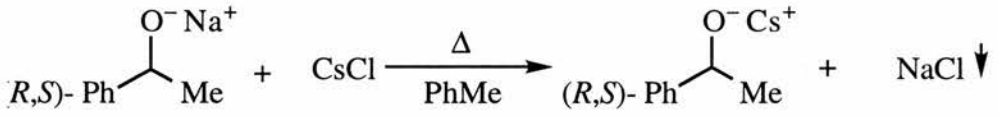
In the previous work, it was found that attempts to isolate the sodium salt of (*R*,*S*)-1-phenylethanol led to partial decomposition as indicated by darkening of the solid. This observation is consistent with an early literature report.[85] It was therefore found to be preferable to generate it *in situ* as a solution in toluene by heating the toluene solution of 1-phenylethanol with a large piece of sodium metal for several hours and then removing the excess sodium manually.



Preparation of the sodium alkoxide in this way followed by reaction with **147** gave products **149**, **150** and **151** and the alcohol derived from hydrolysis of **150** had an e.e. of 21% as determined by the C.L.S.R. method, thus confirming the previous results.[56]

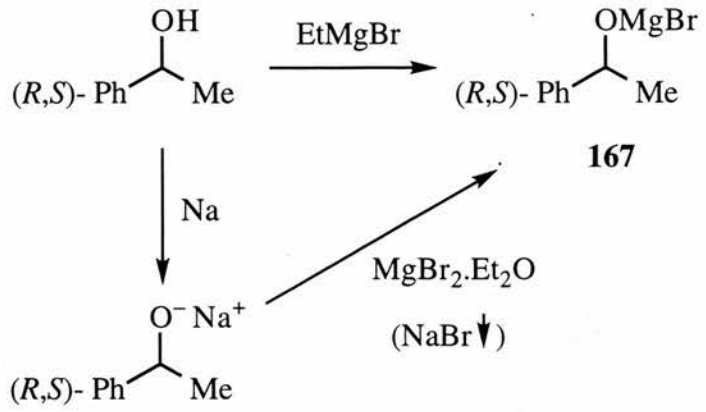
Direct reaction of the alcohol with the appropriate metal was found to be suitable for the preparation of the potassium and lithium alkoxides. When these were reacted with **147** and the unreacted alkoxides **177** hydrolysed, the alcohol **178** was obtained with e.e. values of 6% and 2% respectively.

For the caesium alkoxide the extreme reactivity of the metal made direct reaction to give **179** impracticable and so this was generated by exchange of the sodium alkoxide prepared as above with caesium chloride. The desired exchange did occur as indicated by the formation of a precipitate of sodium chloride. When the caesium alkoxide solution was reacted with **147**, theresulting alcohol **178** was found to have an e.e. of 7%.



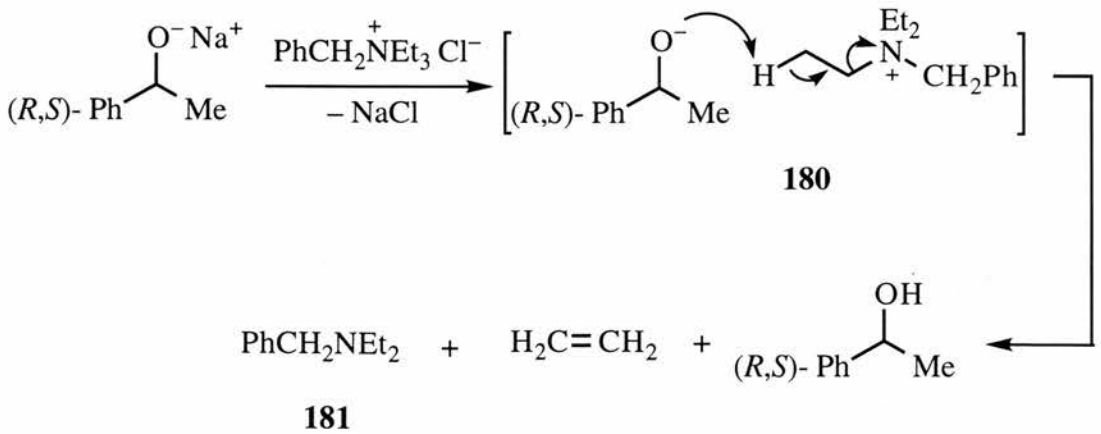
179

The successful work of Evans[84] mentioned in Section 1 suggested that use of the bromomagnesium alkoxide might be worthwhile. Two different ways were examined to prepare the required alkoxide **167**. Direct reaction of the alcohol with ethylmagnesium bromide in ether proceeded with elimination of ethane and toluene was then added prior to reaction with **147**. Alternatively an exchange reaction of the sodium alkoxide with an anhydrous solution of magnesium bromide in ether could be used. Surprisingly **167** prepared by either method failed to react with

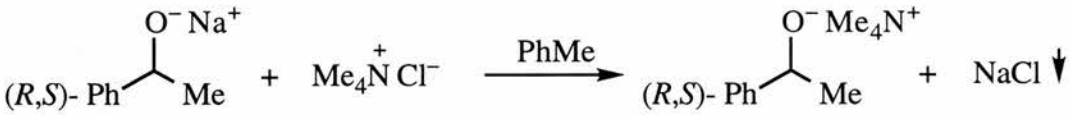


147 in the desired sense. Work up gave 1-phenylethanol and also some thiazolidinone **149** due to hydrolysis of the salt, but most significantly none of the sulphide **151**. This was also the case when the reaction mixture was heated under reflux for 24 h.

Since the small size and high covalent character of the lithium and magnesium derivatives had obviously led to poor results, it was decided to examine large non-coordinating counter ions such as quaternary ammonium and phosphonium. The first attempt was made by treating the sodium salt, prepared as usual in toluene, with a solution of benzyltriethylammonium chloride in acetonitrile. The desired exchange seemed to have occurred as indicated by precipation of sodium chloride. However, reaction with **147** followed by the usual work up gave 1-phenylethanol, the thiazolidinone **149** and none of the sulphide **151**. An

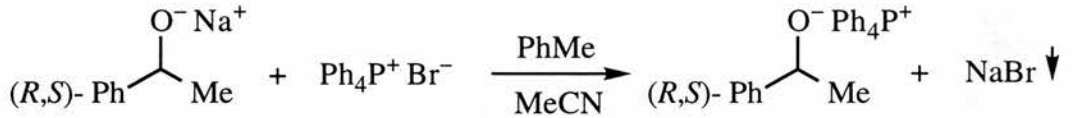


unexpected product was benzyldiethylamine **181**, isolated in moderate yield by distillation. This indicated that a β-elimination process had taken place in the initially formed salt **180** with elimination of ethene and formation of **181**. In order to avoid this, the same procedure was repeated using tetramethylammonium chloride. In this case the desired salt **182** was formed and the reaction with **147** did proceed to give **149** and the sulphide **151**. However the alcohol **178** obtained had an e.e. of < 2% apparently in favour of the opposite (*R*)-enantiomer.



182

A final attempt in this area involved the formation of the tetraphenylphosphonium salt **183** formed as shown. The salt seemed to



183

have formed as expected, but when the solution was reacted with **147**, no sulfide was formed indicating that the reaction had failed.

6. Effect of different solvents and temperatures on kinetic resolution of sodium 1-phenylethoxide

As a result of the foregoing studies it appeared that sodium as the counter-ion gave by far the best results. A brief study was now carried out

to see whether changing the solvent or temperature could bring about a further improvement in e.e.

When the reaction of sodium (*R*,*S*)-1-phenylethoxide with **147** was carried out in toluene at –78 °C for 16 h, the desired products were formed, but the alcohol **178** had an e.e. of 15%, slightly worse than at room temperature.

For reaction in dichloromethane, the sodium salt was first prepared in toluene as usual and this was then evaporated to dryness. As already noted the dry salt was rather unstable and and so was quickly dissolved in CH_2Cl_2 and used for reaction with **147**. Reaction at room temperature proceeded in the desired sense to give (*S*)-1-phenylethanol of 18% e.e. while at –78 °C a similar value of 20% e.e. was achieved.

The results obtained in this section are summarised in Table 1.

Table 1. Enantiomeric excess of (*S*)-1-phenylethanol from kinetic resolution with salt **147**

counter-ion	solvent	temperature	e.e. (%)
Na^+	toluene	RT	21
K^+	toluene	RT	6
Li^+	toluene	RT	2
Cs^+	toluene	RT	7
$MgBr^+$	toluene/ether	RT	-*
$PhCH_2NEt_3^+$	toluene	RT	-†
Me_4N^+	toluene	RT	< 2 (*R*)
Ph_4P^+	toluene/acetonitrile	RT	-*
Na^+	toluene	–78 °C	15
Na^+	dichloromethane	RT	18
Na^+	dichloromethane	–78 °C	20

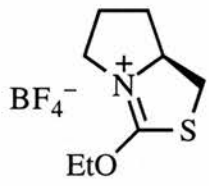
*failed to react †salt decomposed

From these it is clear that the use of the sodium salt in toluene at room temperature gives the best result for reaction of **147** and attempts to improve on this value were not successful. It was therefore decided to investigate different iminium salts which might be more highly selective in their kinetic resolution of alkoxides.

B. Preparation of other bicyclic iminium salts and their evaluation for kinetic resolution

1. Background

In the previous work[56] the five iminium salts **184-188** were prepared and evaluated for kinetic resolution of sodium (*R*,*S*)-1-phenylethoxide



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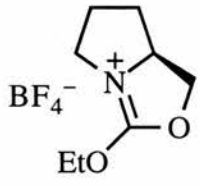

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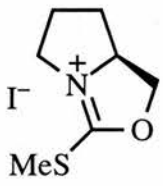

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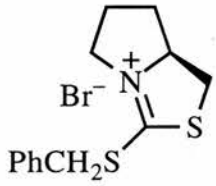

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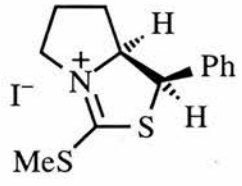


188

As shown in Table 2, these proved disappointing in that all the changes made either led to no major improvement in e.e. or to failure of the reaction. Exchange of the exocyclic sulfur atom by oxygen gave a slight improvement in e.e., but the enantiomer of the alkoxide which did react formed a stable orthocarbamate and so could not be recovered. In the case of **185** where both sulfurs have been replaced by oxygen the reaction failed completely and an unidentified ring-opening product was obtained. For **186** where the endocyclic sulfur atom has been replaced by oxygen, the reaction did proceed as expected to give the sulfide and alcohol

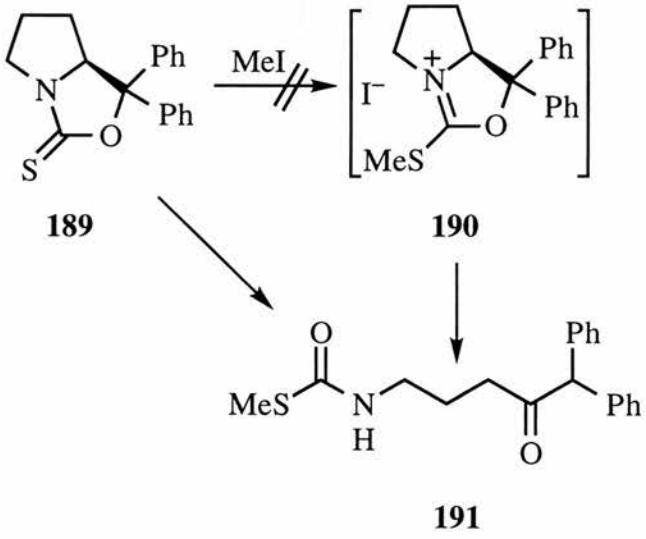
but the latter was racemic. Replacement of the SMe of **147** by SCH_2Ph as in **187** did not give a significant improvement in e.e. either.

Table 2. Enantiomeric excess of (S)-1-phenylethanol from kinetic resolution with salts **184-188**.[56]

salt	e.e. (%)
147	20-30
184	25
185	—*
186	0
187	29
188	6

*salt decomposed

Attempts were then made to increase the steric bulk and thus, hopefully, the selectivity by using a more hindered derivative of prolinol. The salt **188** was obtained in low yield and appeared to give a lower e.e. but this reaction was carried out on too small a scale to be reliable and was to be repeated. Finally, attempts to prepare the more hindered salt **190**



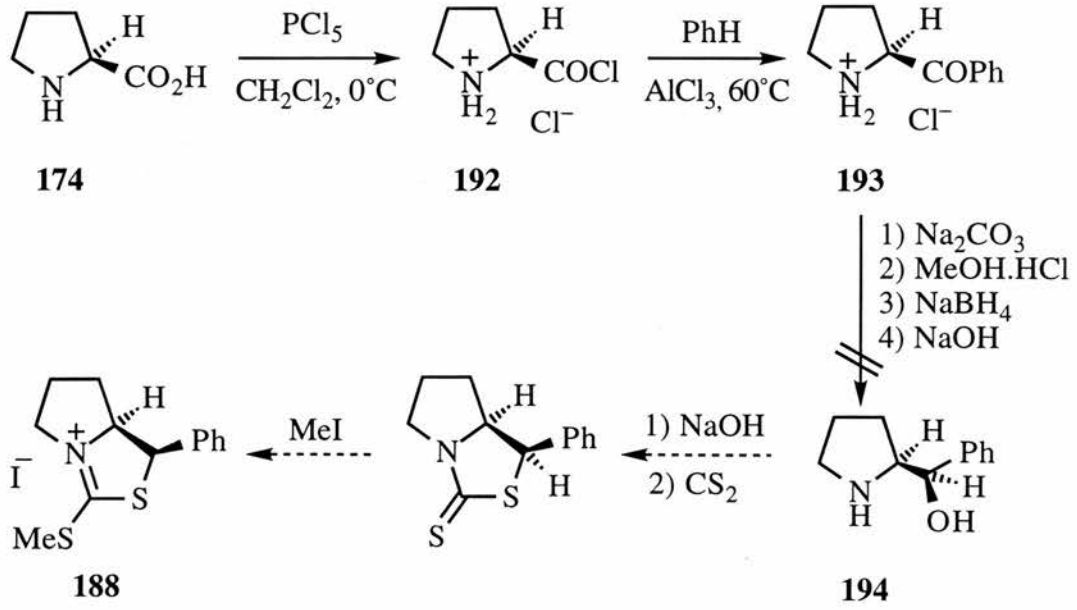
189 **190**

191

were unsuccessful, since treatment of the oxazolidinethione **189** with methyl iodide resulted in an unexpected ring-opening reaction to afford **191**.

2. Attempted preparation of the more selective iminium salt 188 for kinetic resolution

In order to improve the selectivity of resolution an attempt was made to prepare the sterically hindered phenyl substituted thiazolidinethione and its iminium salt **188**. The preparation of the required amino alcohol **194** has been reported in the literature,[63] but was carried out on a very small scale and had previously been found to be problematic.[56] (*S*)-Proline **174** was converted into its chloride hydrochloride **192** by reaction with phosphorus pentachloride in dichloromethane. The resulting acid chloride was used for Friedel-Crafts acylation of benzene in CH_2Cl_2 in presence of $AlCl_3$ which afforded the corresponding phenyl ketone hydrochloride **193**. Since the free amino

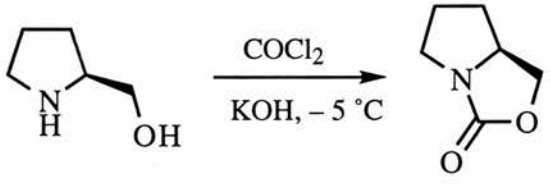


phenyl ketone of **193** was unstable,[63] the hydrochloride was reduced directly with sodium borohydride. In our case the ^{1}H NMR spectrum did not show any peaks corresponding to the amino alcohol, 2-(*S*)-[(*R*)-α-hydroxybenzyl] pyrrolidine **194**. The Friedel-Crafts reaction might not have taken place, or else the unstable amino ketone may have polymerised. This reaction was repeated many times but the desired amino alcohol **194** could not be obtained.

3. Preparation of bicyclic carbamates and thiocarbamates

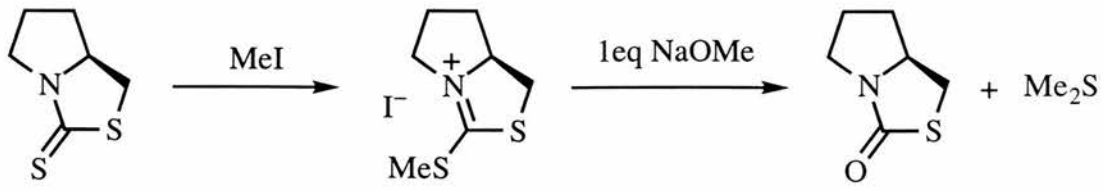
It was then decided to revert to the prolinol-derived heterocycles and examine other ways of modifying their structure to obtain more selective iminium salts.

The oxazolidinone **195** was readily prepared, albeit in disappointing yield, by direct reaction of prolinol **175** with phosgene following a literature procedure.[64]



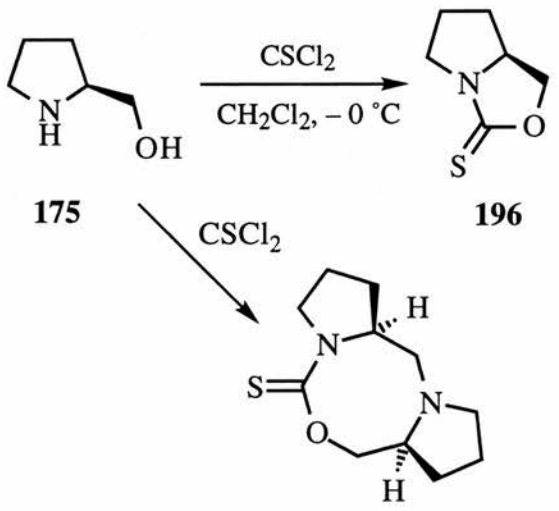
175 **195**

The best preparation of the thiazolidinone **149** was found to be the one already described: conversion of the thiazolidinethione **169** into iminium salt **147**, followed by reaction with one equivalent of NaOMe.



169 **147** **149**

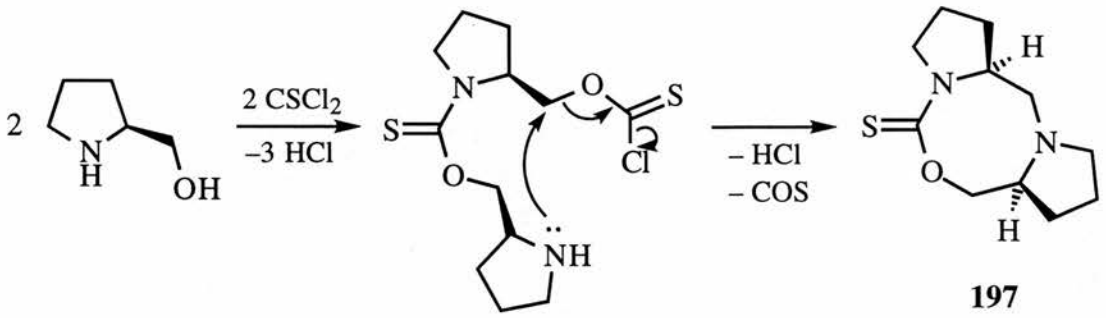
For the oxazolidinethione **196**, reaction of prolinol with thiophosgene in the presence of triethylamine following the general procedure of Sharma,[66] produced the desired product in moderate yield. The first run of this reaction was carried out with less solvent than usual



197

and, under these conditions, careful chromatographic separation of the product allowed isolation of a very interesting by-product. This was determined by high resolution mass spectrometry to have the formula $C_{11}H_{18}N_2OS$ which corresponds to $CSCl_2$ reacting with two molecules of prolinol with elimination of 2 HCl and then further loss of H_2O. This was confirmed by the ^{13}C NMR spectrum which showed 11 signals. Detailed comparison with the spectrum of the major product **196** showed that a thiocarbamate signal was present (δ_C 190.6 -cf 189.5 for **196**) and that most of the other signals were doubled. An important exception, however, was that there was only one signal in the range expected for CH_2O (δ_C 78.9) but three signals in the range expected for CH_2N (δ_C 58.3, 56.7 and 50.1). This led to assignment of the structure as the dipyrrolidino-1,3,6-oxadiazocane-2-thione **197**.

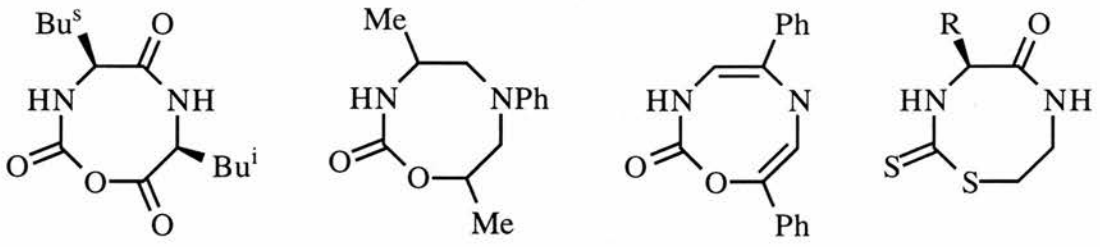
The formation of this product is rationalised, as shown below, by reaction of two molecules of prolinol with two molecules of $CSCl_2$ to give the intermediate **198** in which the alcohol OH has been activated towards



198 **197**

nucleophilic attack by formation of the chlorothioformate. This then allows ring closure with elimination of HCl and COS to give **197**.

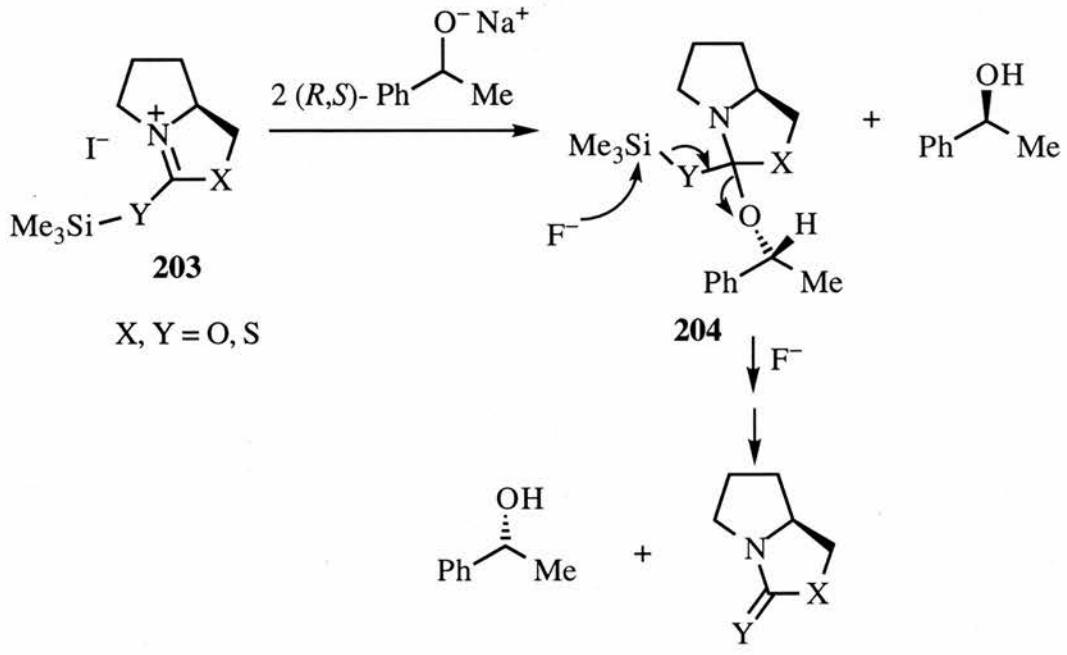
Although it was only obtained as a minor by-product, this compound is of considerable interest since it is the first 1,3,6-oxadiazocanethione ever to be reported. A search of the literature revealed that the 1,3,6-oxadiazocane system itself is virtually unknown with only three examples being located, the dipeptide-derived trione **199**,[86] the oxadiazocan-2-one **200**,[87] and the partly unsaturated -2-one **201**.[88] The related 1,3,6-thiadiazocane-2-thiones **202** have also been described.[89]



199 **200** **201** **202**

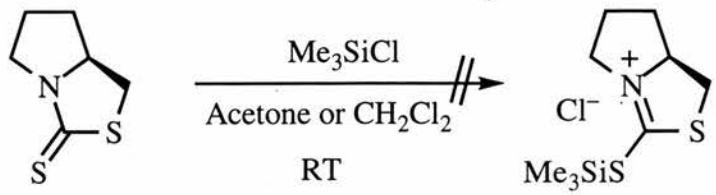
4. Attempted formation of silylated bicyclic iminium salts

One drawback of the kinetic resolution strategy already described is that only one enantiomer of the alcohol can be recovered. The other is converted into the methyl sulfide which can not be converted back to the alcohol very easily. It appeared to us that a modified method using the



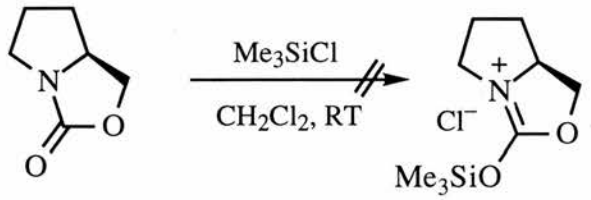
silyl iminium salts of general structure **203** would offer two major advantages. First, the reacting enantiomer of the alkoxide would form the orthocarbamate derivative **204**, which at least for Y = O should be stable, but could be liberated as the alcohol by treatment with F^-. Secondly, the silyl group offers another opportunity to vary the structure for increased selectivity and bulky groups such as Bu^tMe_2Si and Bu^tPh_2Si are readily accessible. The preparation of (*S*)-2-trimethylsilylthio-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium chloride **205** was attempted. Bicyclic thiazolidinethione **169** was stirred with trimethylsilyl chloride at room temperature in both acetone and dichloromethane. In each case, the ^1H

NMR spectrum showed there had been no reaction and the starting material was recovered.



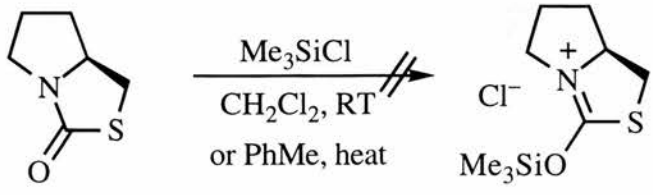
169 **205**

Attempted formation of the iminium salt, (*S*)-2-trimethylsilyloxy-3-oxa-1λ^4-azabicyclo[3.3.0]oct-1-enium chloride **206**, by stirring **195** with Me_3SiCl at room temperature was also unsuccessful, the starting material being recovered unchanged.



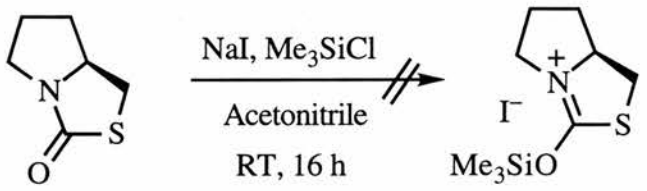
195 **206**

The preparation of (*S*)-2-trimethylsilyloxy-3-thia-1λ^4-azabicyclo [3.3.0]oct-1-enium chloride **207** was attempted in both CH_2Cl_2 and toluene. Bicyclic thiazolidinone **149** was stirred with trimethylsilyl chloride at room temperature in CH_2Cl_2 and in boiling toluene. In each case the reaction did not work and starting material was recovered.



149 **207**

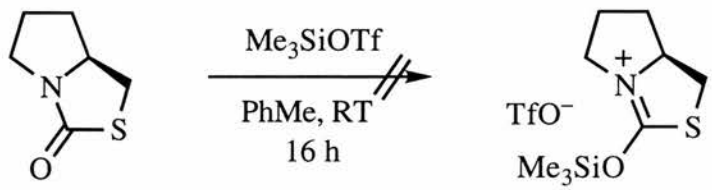
Trimethylsilyl iodide is known to be a stronger silylating agent in many reactions,[90] and can be conveniently generated in situ from Me_3SiCl and NaI. Thiazolidinone **149** was stirred with sodium iodide and trimethylsilyl chloride in acetonitrile for 16 h at room temperature in the hope of forming (*S*)-2-trimethylsilyloxy-3-thia-1λ4-azabicyclo[3.3.0]oct-1-enium iodide **208** but no ^1H NMR peaks corresponding to the iminium salt could be observed.



149 **208**

$$[\ NaI + Me_3SiCl \longrightarrow Me_3SiI + NaCl\ ]$$

Perhaps the most powerful common silylating agent is Me_3SiOTf. An attempt was made to prepare (*S*)-2-trimethylsilyloxy-3-thia-1λ4-azabicyclo[3.3.0]oct-1-enium triflate **209** by stirring bicyclic thiazolidinone **149** with trimethylsilyl trifluoromethanesulphonate in toluene for 16 h. The desired product was not formed but instead a new

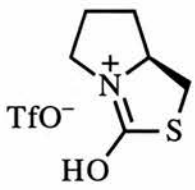


149 **209**

Tf = SO_2CF_3

product was obtained in impure form. This was shown spectroscopically not to contain the $SiMe_3$ group but the substantial shift of the ring-junction CH to higher frequency (δ_H 4.75, δ_C 67.7) compared to the starting

material (δ_H 4.24, δ_C 63.0) suggested formation of a protonated species. The ^{13}C NMR shift of the C-2 carbon (δ_C 157.6) is clearly too low for the O-protonated structure **210** by comparison with **184** (δ_C 177.6)[56] and so we favour the *N*-protonated structure **211**. Although this is far from



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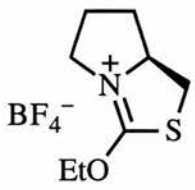

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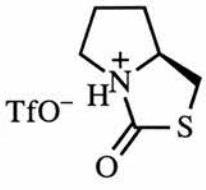
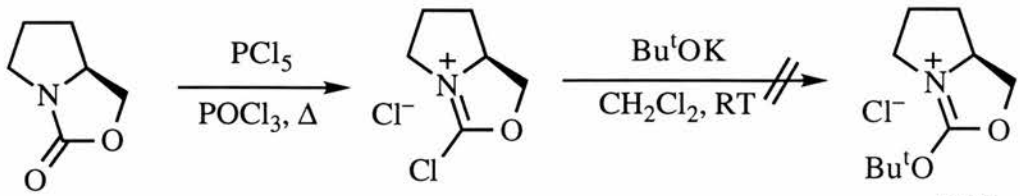


211

certain it seems a good possibility since Me_3SiOTf can readily give rise to tetrafluoromethanesulfonic acid upon hydrolysis and this is a very strong acid, perhaps strong enough to protonate the thiocarbamate nitrogen.

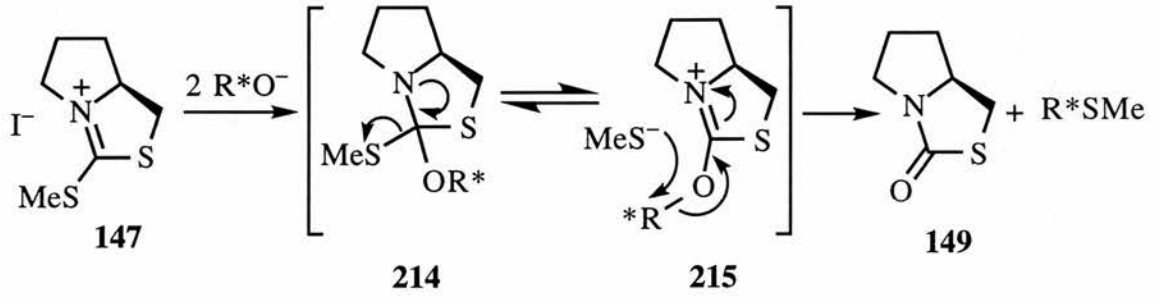
5. Attempted formation of iminium salts by nucleophilic attack at C-2

In an attempt to obtain iminium salts with bulkier substituents at C-2 the oxazolidinone **195** was treated with PCl_5 either neat or in $POCl_3$. Since the product **212** was expected to be highly reactive no attempt was made to analyse it, but it was used directly for the next stage. In each case the crude product was reacted with potassium t-butoxide in CH_2Cl_2 at room temperature in the hope of obtaining **213**. The ^1H NMR showed there had been no reaction as no peaks due to a Bu^t group were observed.



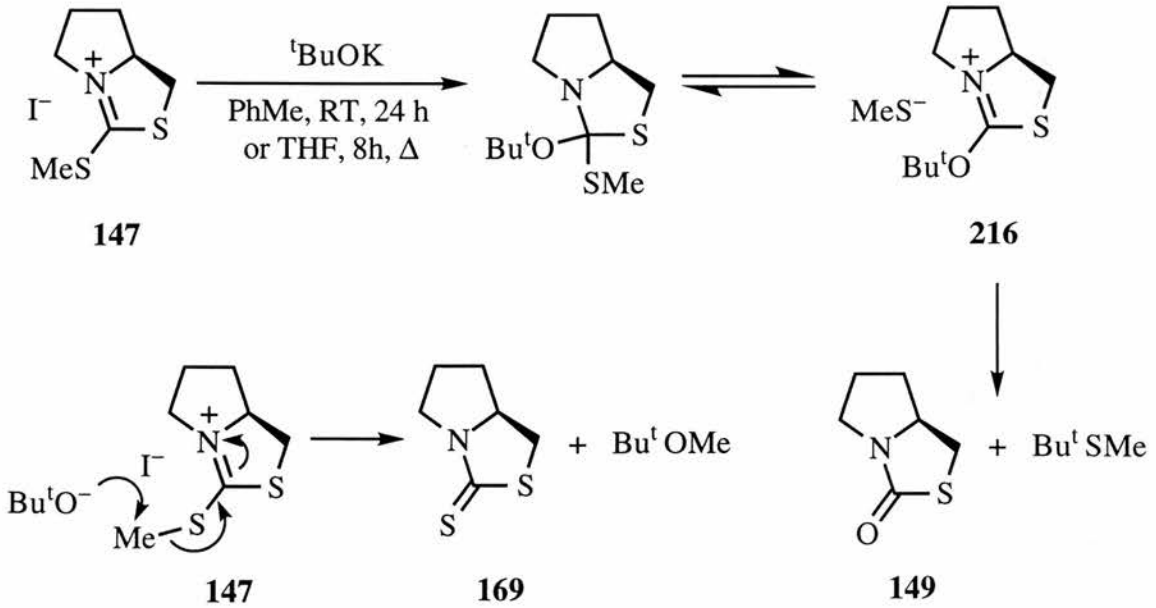
195 **212** **213**

In the basic strategy for kinetic resolution the iminium salt **147** reacts with one enantiomer of the alkoxide to give the dithiocarbamate **214**. This then undergoes loss of MeS^- as shown to give the iminium salt **215** and MeS^- finally attacks the R* group in this to give **149** and the



sulphide. It occurred to us that by using a group R* in which nucleophilic substitution was impossible, the new salts **215** with a bulky R* group might be isolated and used for kinetic resolution

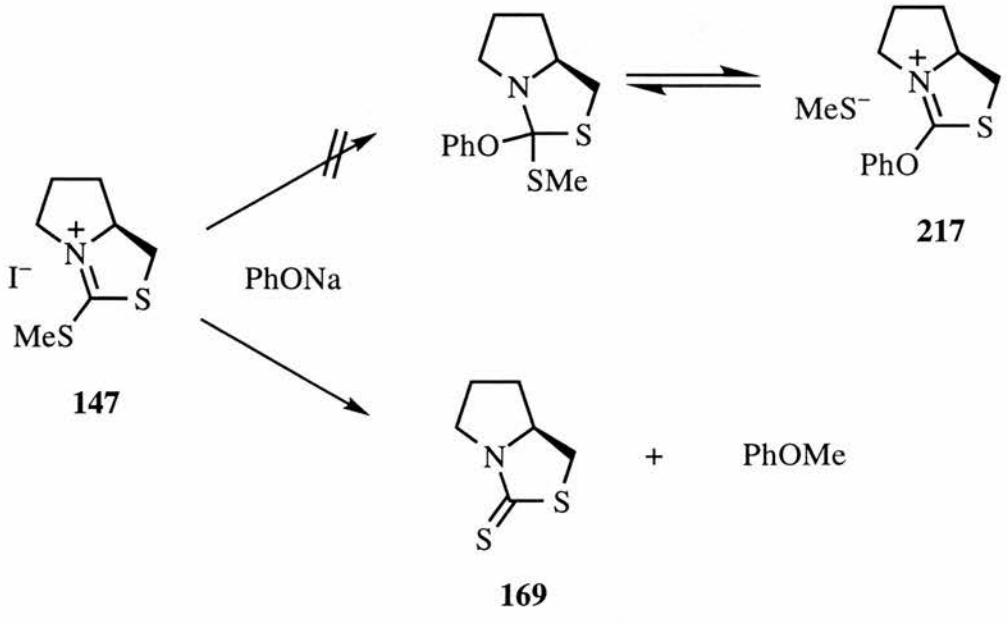
In the first example, the preparation of (*S*)-2-t-butoxy-3-thia-1λ^4-azabicyclo[3.3.0]oct-1-enium methanethiolate **216** was attempted. Iminium salt **147** was reacted with potassium t-butoxide in toluene or THF.



The products were rather unexpected. Spectroscopic evidence was obtained for the formation of t-butyl methyl sulphide, the thiazolidinone **149**, and the thiazolidinethione **169**. As shown the first two of these products indicate that the reaction has taken the expected course despite the bulk of the t-butyl group, probably via an S_N1 mechanism. The thione **169** may be formed by demethylation of the initial salt **147** by t-butoxide although no t-butyl methyl ether was detected.

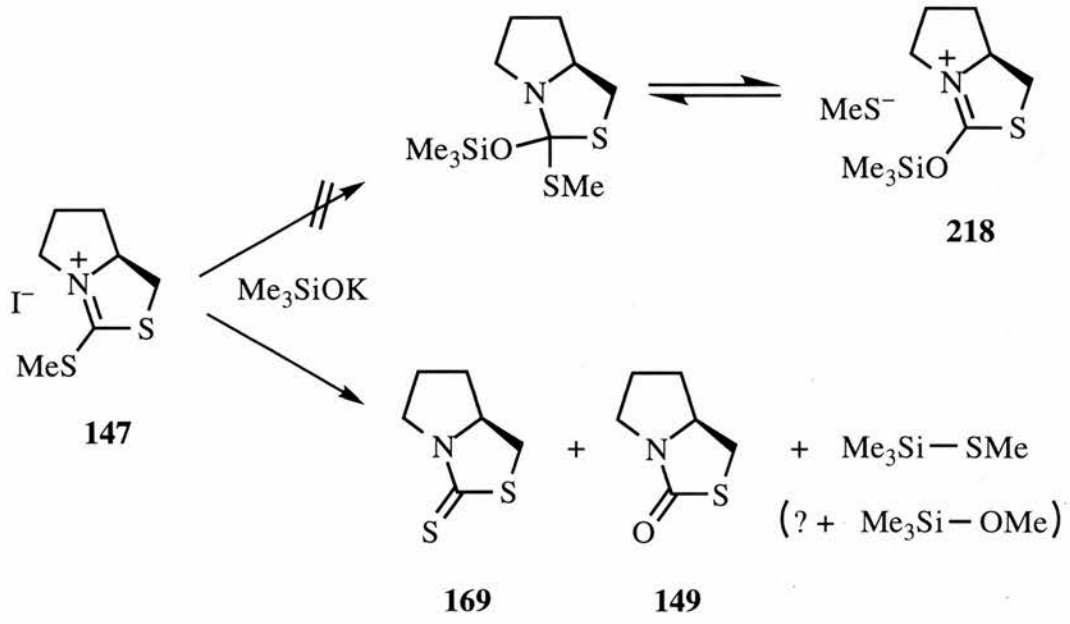
In an attempt to stabilise **216** methyl iodide was added to the reaction mixture in the hope of converting **216** to the corresponding iodide salt but this was not successful and the main products were still **149** and **169**.

A second attempt at this strategy was made using sodium phenoxide. Treatment of **147** with sodium phenoxide at room temperature followed by aqueous work up gave phenol together with the thiazolidinone **149**, presumably resulting from hydrolysis of **147** during the basic work up. When the same reaction was carried out in boiling toluene, these two products were again formed but they were now accompanied by anisole

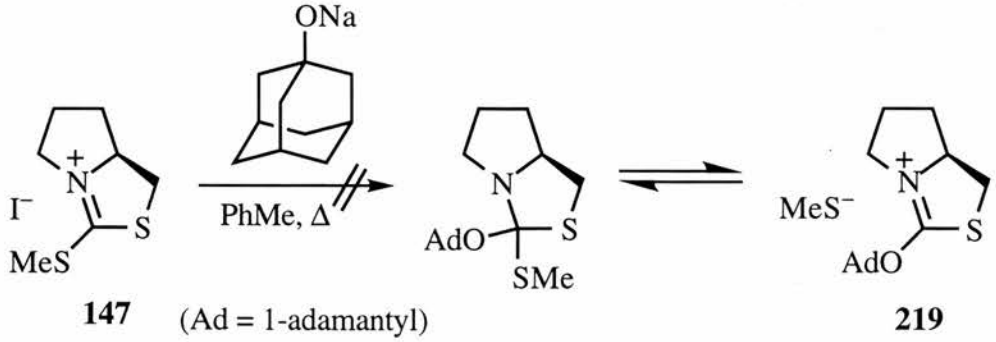


and the thiazolidinethione **169**. Again it appears that nucleophilic demethylation of the initial salt has intervened.

It was expected that silyl salt **218** might be more useful for kinetic resolution purposes. Its preparation was attempted by reacting iminium salt **147** with potassium trimethylsilanolate in CH_2Cl_2 both at room temperature and on heating. Analysis showed the product to be a mixture of thiazolidinone **149** and thiazolidinethione **169** by ^1H and ^{13}C NMR. In a repeat experiment some trimethylsilyl sulphide was also observed.



In another reaction, the sodium salt of 1-adamantanol was reacted with the iminium salt **147**. Work up only gave a mixture of unreacted adamantanol and the thiazolidinethione **169**.

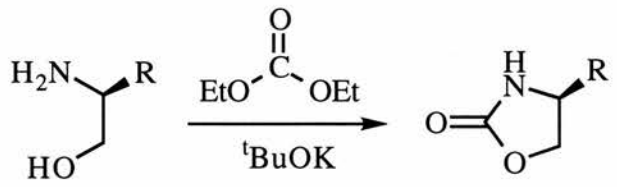


C. Kinetic resolution of (*R*,*S*)-1-phenylethanol using monocyclic iminium salts

1. Background

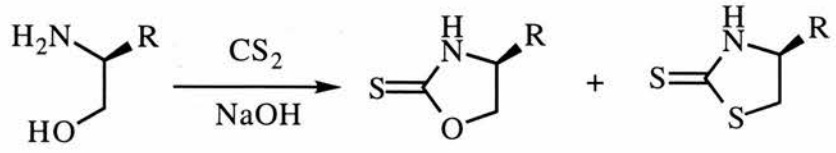
It was realised that the bicyclic structure might not be necessary and that suitably substituted monocyclic iminium salts could also be useful for the kinetic resolution. Previous work in this laboratory by Armstrong[72] and Mesher[56] outlined the direct synthesis of a variety of chiral oxazolidinones and their sulphur analogues starting from amino alcohols derived from (*S*)-phenylalanine and (*S*)-valine.

The main precursors to chiral oxazolidinones in the literature are amino alcohols **220**. These react directly with diethyl carbonate in the presence of potassium t-butoxide to give the oxazolidinones of the general formula **221**.



220 **221**

The main route to thiazolidine-2-thiones is via cyclisation of amino alcohols **220** using carbon disulphide to give either the oxazolidine-2-thione **222** or the thiazolidine-2-thione **223** depending upon the substitution at the amino bearing carbon atom.

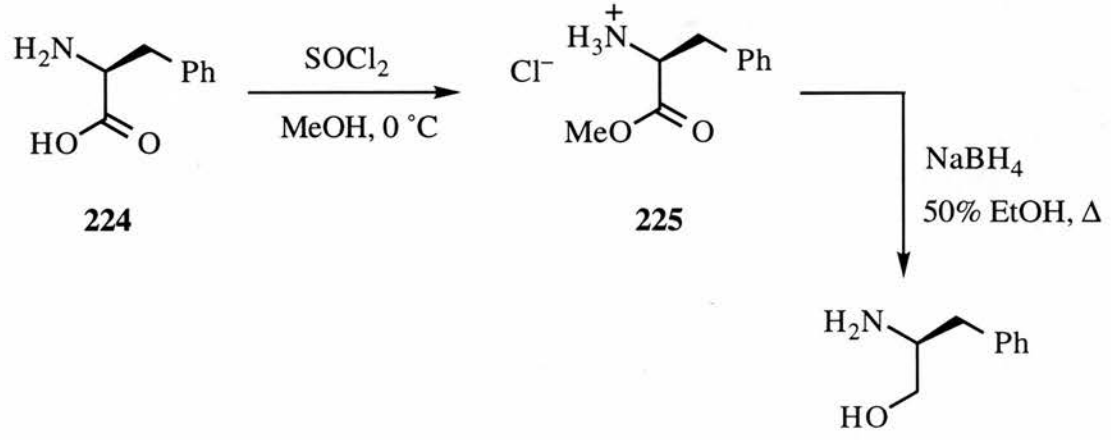


220 **222** **223**

2. Synthesis of amino alcohols

The preparation of (*S*)-prolinol **175** by $LiAlH_4$ reduction of (*S*)-proline has already been described in Section A.

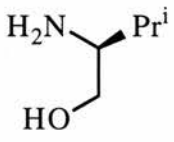
Reaction of the methyl ester hydrochloride salt **225** of (*S*)-phenylalanine **224** with sodium borohydride gave the derived amino alcohol, 2-(*S*)-amino-3-phenylpropan-1-ol **226**, in good yield.[67]



224 **225** **226**

The preparation of 2-(*S*)-amino-3-methylbutan-1-ol **227** was accomplished by $LiAlH_4$ reduction of (*S*)-valine using the same procedure as for proline.

The commercially available 2-(*R*)-aminobutan-1-ol **228** was used directly as received.



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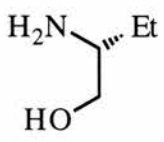
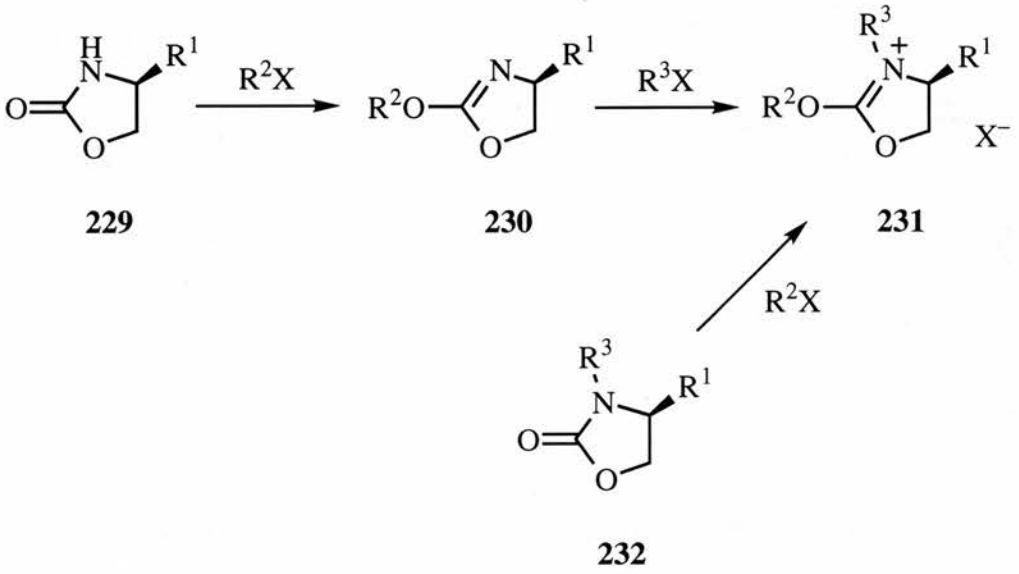


228

3. Synthesis of 3-unsubstituted oxazolidinones and attempted silylation

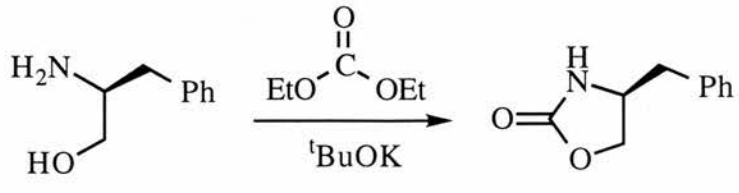
Two possible approaches to the target oxazolidine-derived iminium salts **231** were considered. First an *N*-unsubstituted oxazolidinone could



229 **230** **231** **232**

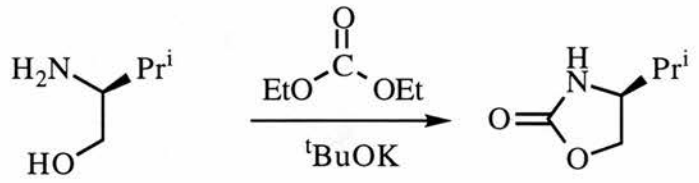
be *O*-alkylated to give **230** and then subsequently alkylated on nitrogen. Alternatively we could start from an *N*-substituted oxazolidinone **232** and alkylate it on oxygen. Since the compounds **229** could be made simply, two examples were prepared.

2-(*S*)-Amino-3-phenylpropan-1-ol **226** was reacted with diethyl carbonate in presence of potassium t-butoxide as a catalyst at room temperature.[68] 4-(*S*)-Benzyloxazolidin-2-one **233** was obtained in 77% yield.



226 **233**

Similarly 2-(*S*)-amino-3-methylbutan-1-ol **227** on reaction with diethyl carbonate gave 4-(*S*)-isopropyloxazolidin-2-one **234** in 67% yield.

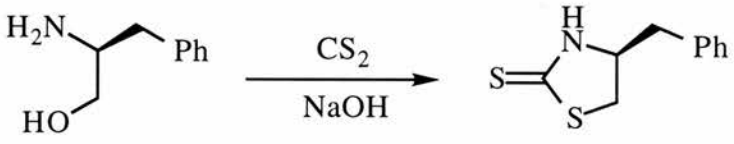


227 **234**

Unfortunately, at this stage results were obtained from the thiazolidine series which suggested that it would be better to begin with *N*-substituted heterocycles (see next section) and so this line of investigation was abandoned.

4. Synthesis of 3-unsubstituted thiazolidine-2-thiones and attempted 3-alkylation

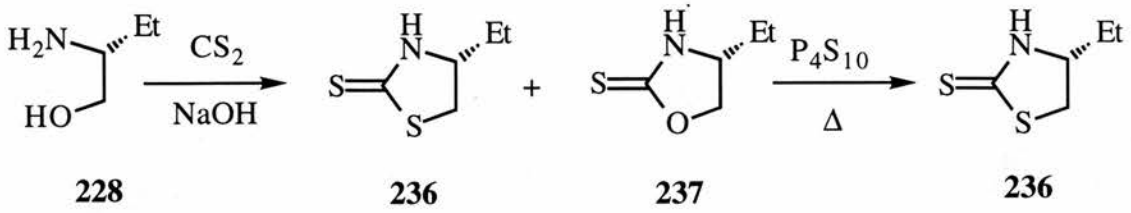
Based on the method of Roth,[59] the amino alcohol **226** and was reacted with carbon disulphide in aqueous alkali to form the the thiazolidine-2-thione **235**.



226 **235**

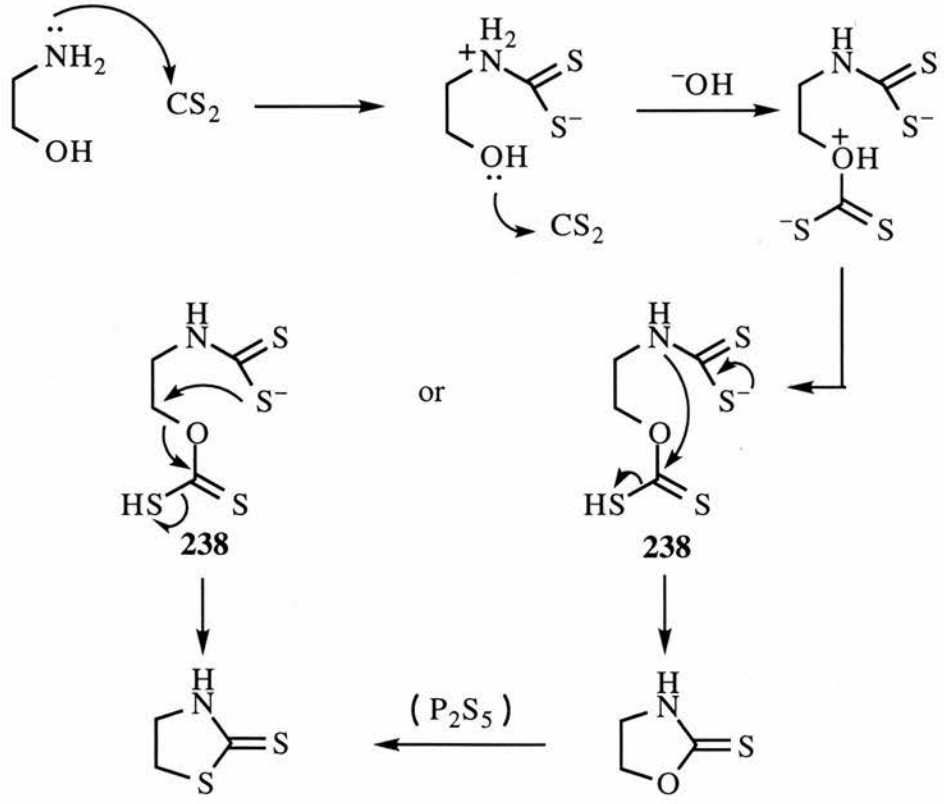
4-(*R*)-Ethylthiazolidine-2-thione **236** was prepared by reacting 2-(–)-(*R*)-aminobutan-1-ol **228** with CS_2. ^{13}C NMR showed 4-(*R*)-ethyloxazolidine-2-thione **237** also to be present with the product and the

mixture was converted entirely into thiazolidinethione **236** by heating with phosphorus pentasulfide in toluene.

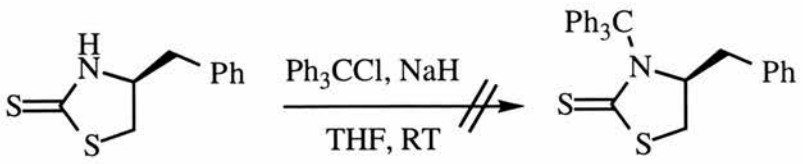


228 **236** **237** **236**

The mechanism of formation of these two products is consistent with literature precedent, involving the xanthate ester/dithiocarbamate **238**[91, 92] and can be generalised as:

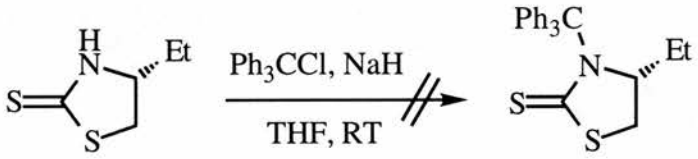


With the two thiazolidinethiones in hand it was decided to prepare highly hindered *N*-substituted iminium salts. 4-(*S*)-Benzylthiazolidine-2-thione **235** was reacted with sodium hydride and trityl chloride in THF, but the reaction did not give the desired product.



235 **239**

Similarly the reaction of thiazolidinethione **236** with NaH and trityl chloride in THF did not result in the formation of **240**.

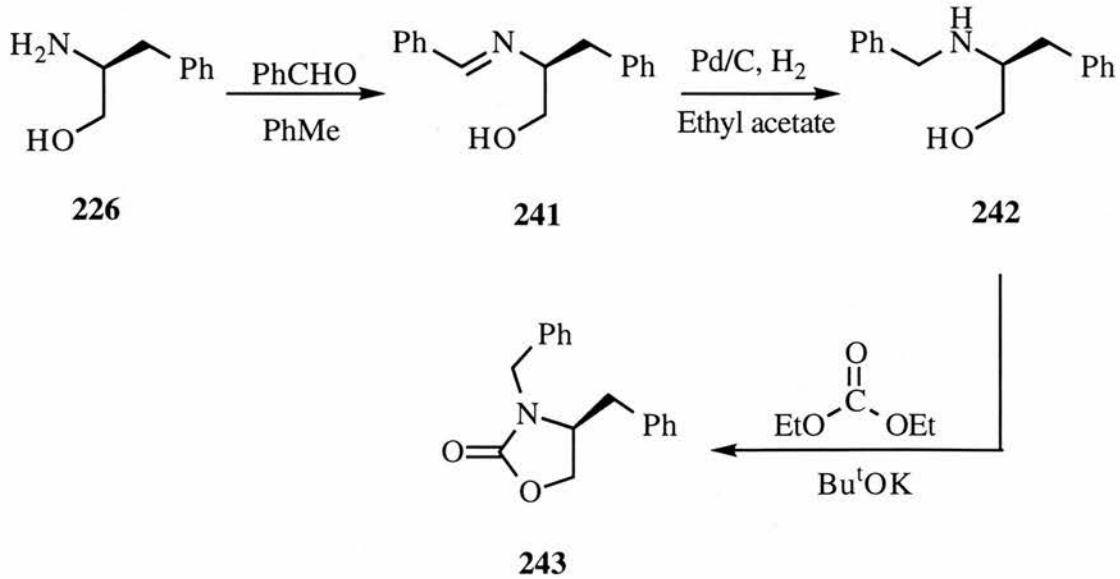


236 **240**

In view of these results, it was decided to adopt the second strategy and to begin with *N*-substituted heterocycles.

5. Synthesis of 3-substituted oxazolidin-2-ones

The amino alcohol **226** was condensed with freshly distilled benzaldehyde, with azeotropic removal of water to give the imine **241**, reduction of which with hydrogen in the presence of palladium on charcoal

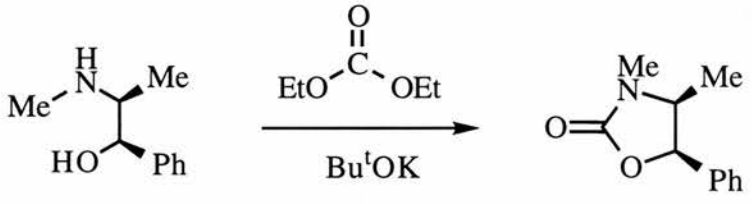


226 **241** **242**

243

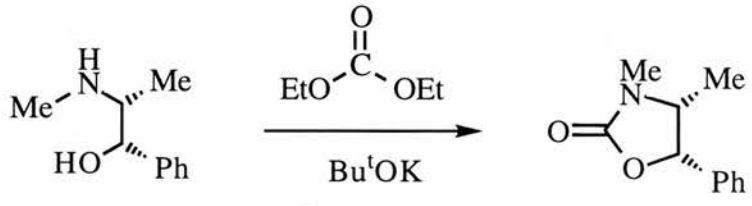
catalyst provided the *N*-benzylamino alcohol **242**. Based on the method of Newman[68] condensation of benzylamino alcohol **242** with diethyl carbonate afforded the oxazolidin-2-one ring system **243**.

An attractive amino alcohol for this purpose was the commercially available ephedrine which already has a methyl group on nitrogen. Using the same method as above, **244** was reacted with diethyl carbonate in the presence of potassium t-butoxide as a catalyst to form 3,4-(*S*)-dimethyl-5-(*R*)-phenyloxazolidin-2-one **245**.



244 **245**

Similarly reaction of the opposite enantiomer, (1*S*,2*R*)-(+)-ephedrine **246** with diethyl carbonate in the presence of potassium t-butoxide at room temperature afforded 3,4-(*R*)-dimethyl-5-(*S*)-phenyloxazolidin-2-one **247**.

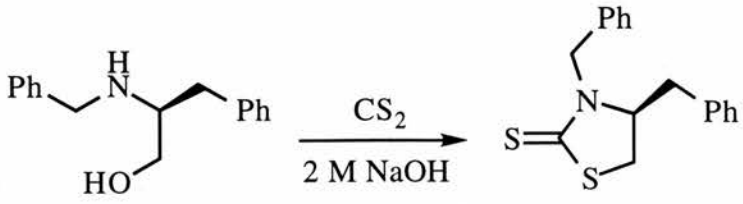


246 **247**

6. Synthesis of 3-substituted thiazolidine-2-thiones

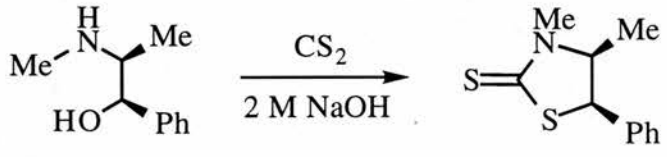
These were again prepared by reaction of the appropriate amino alcohol with CS_2 and aqueous NaOH. Thus, 2-(*S*)-benzylamino-3-

phenylpropan-1-ol **242** was reacted with CS_2 to form the thiazolidine-2-thione **248**.



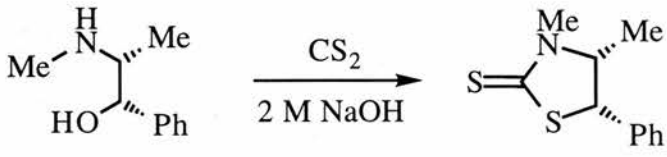
242 **248**

As before, the two enantiomers of ephedrine with an *N*-methyl group already present were convenient precursors for this reaction. Thus, (1*R*,2*S*)-(–)-ephedrine **244** was reacted with carbon disulphide to form 3,4-(*S*)-dimethyl-5-(*R*)-phenylthiazolidine-2-thione **249**.



244 **249**

Similarly 3,4-(*R*)-dimethyl-5-(*S*)-phenylthiazolidine-2-thione **250** was prepared by reacting (1*S*,2*R*)-(+)-ephedrine **246** with carbon disulphide at room temperature.

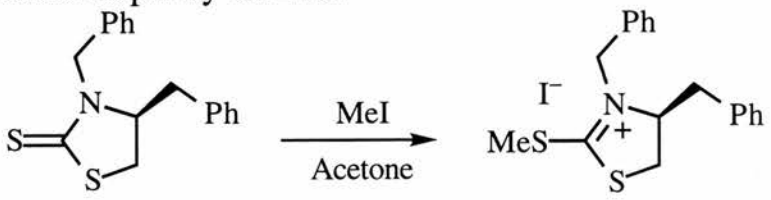


246 **250**

7. Formation of monocyclic iminium salts by alkylation

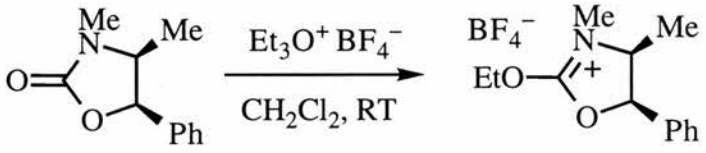
Based on the method of Roussel et al.,[60] the thiazolidinethione **248** was reacted with methyl iodide to form the iminium salt **251**. The

reaction did not go to completion and the sample of **251** obtained still contained a small impurity of **248**.



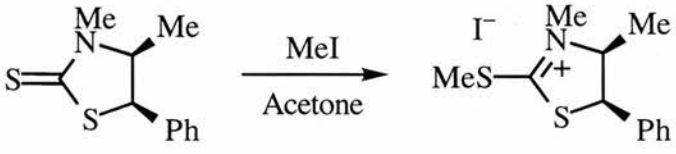
248 **251**

Based on the method of Meerwein,[10] oxazolidinone **245** was reacted with triethyloxonium fluoroborate at room temperature to afford 3,4-(*S*)-dimethyl-2-ethoxy-5-(*R*)-phenyloxazolinium tetrafluoroborate **252**.

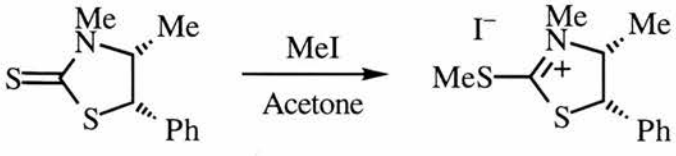


245 **252**

The ephedrine derived iminium salts **253** and **254** were also prepared along similar lines, from **249** and **250**, respectively.



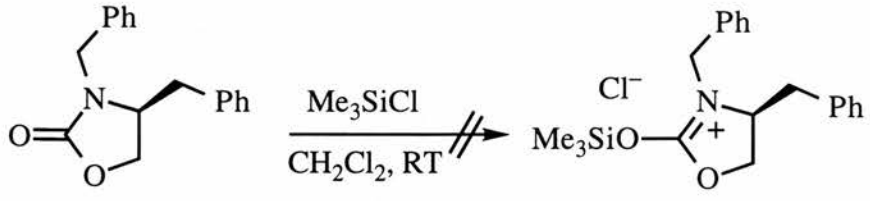
249 **253**



250 **254**

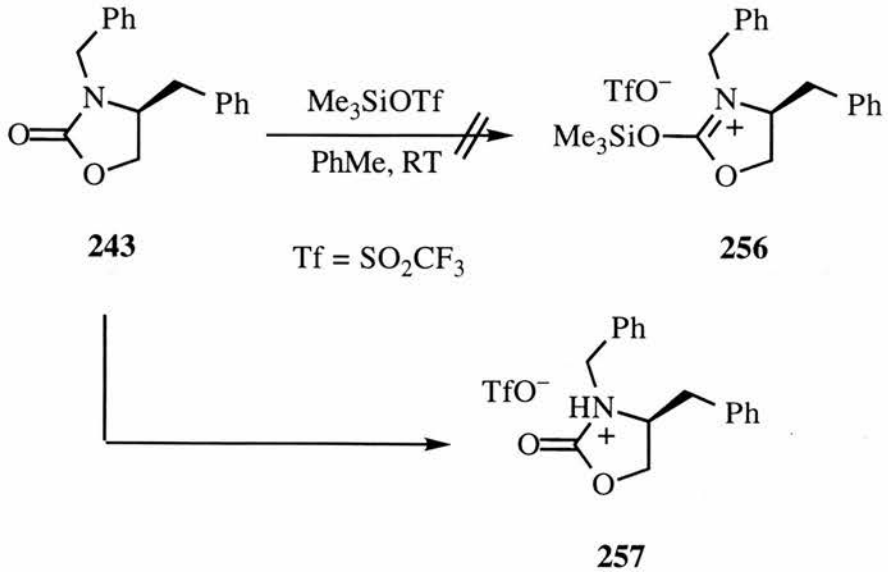
8. Attempted formation of monocyclic iminium salts by silylation

In a further attempt to gain access to 2-trimethylsilyloxy iminium salts, the *N*-substituted oxazolidinone **243** was treated with trimethylsilyl chloride. After reaction at room temperature for 16 h evaporation simply gave unchanged **243** with no trace of the desired salt **255**.



243 **255**

Perhaps the most powerful common silylating reagent is Me_3SiOTf. An attempt was made to prepare 3,4-(*S*)-dibenzyl-2-trimethylsilyloxy oxazolinium triflate **256** by reacting 3,4-(*S*)-dibenzyloxazolidin-2-one **243** with trimethylsilyl trifluoromethanesulphonate in toluene for 16 h. The starting material was consumed but the desired product was not formed.



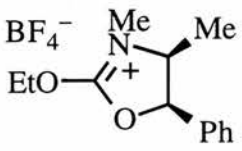
243 **256**

257

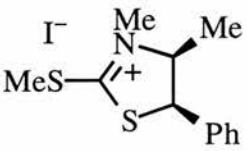
Spectra suggested that the product might be the trifluoromethanesulphonic acid salt of the starting oxazolidinone **257**.

9. Resolution using monocyclic iminium salts

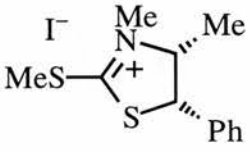
As a result of the work described in the previous sections, the following monocyclic iminium salts were available for attempted kinetic resolution.



252

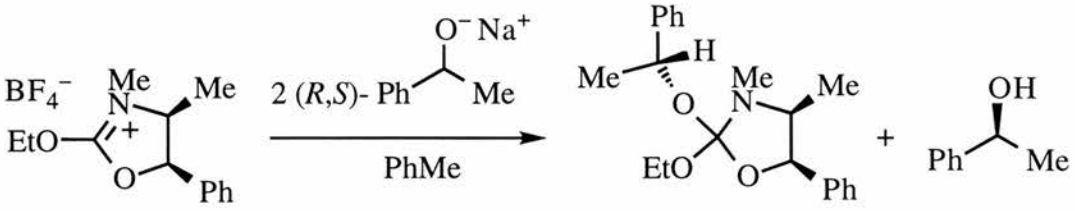


253



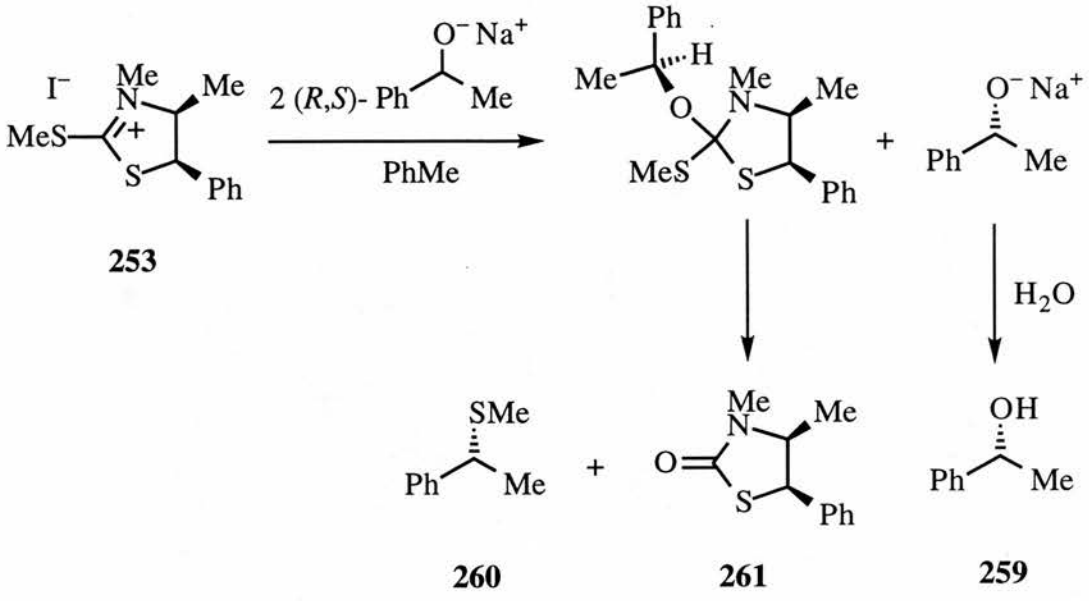
254

Kinetic resolution of racemic sodium 1-phenylethoxide using the iminium salt **252** gave the (*S*)-alcohol in 4.6% e.e. In agreement with the previous work,[56] the reacted enantiomer formed the stable orthocarbamate **258**.

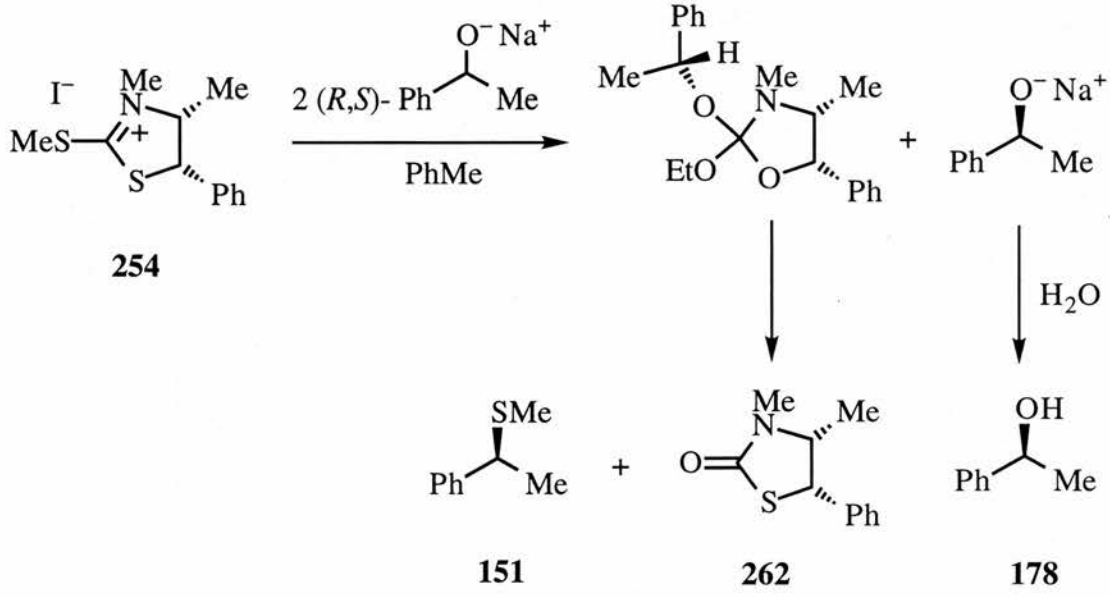


252 **258**

When the same racemic alkoxide was reacted with the salt **253** the (*R*)-alcohol **259** was obtained in 7% e.e. This time the corresponding methyl sulphide **260** was formed, together with the thiazolidinone **261**.



The enantiomeric iminium salt **254** on reaction with 2 eq of the sodium alkoxide and subsequent showed a somewhat lower e.e. of 3% in



favour of the (S)-enantiomer. While the results obtained here are clearly disappointing, it is pleasing to see that the enantiomeric salts **253** and **254** do give opposite enantiomers of the products confirming that the e.e. values obtained are significant, and not merely within experimental error of zero. The results are summarised in Table 3.

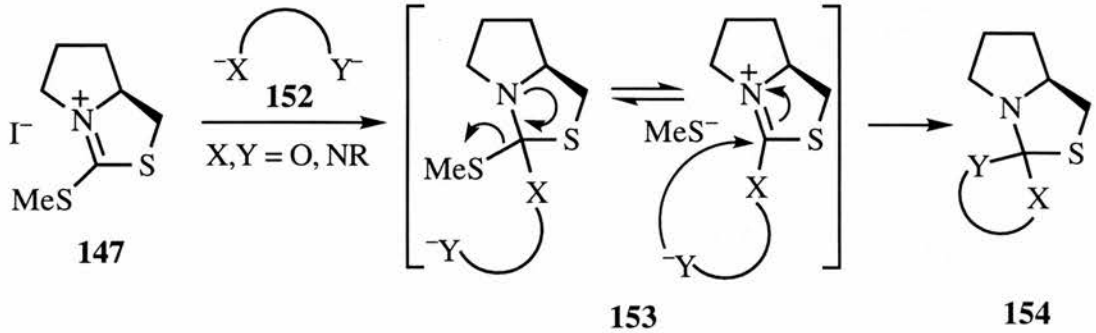
Table 3. Summary of kinetic resolution results with monocyclic iminium salts

salt	e.e. of alcohol (%)	enantiomer
252	4.6	*S*
253	7	*R*
254	3	*S*

D. Reactions of bicyclic iminium salt 147 with bidentate nucleophiles

1. Background

As described briefly in the Programme of Research, reaction of the iminium salt **147** with a bidentate nucleophile, such as the disodium salt of a diol or amino alcohol **152** was expected to initially result in addition of one end of the nucleophile. The intermediate could then undergo ring

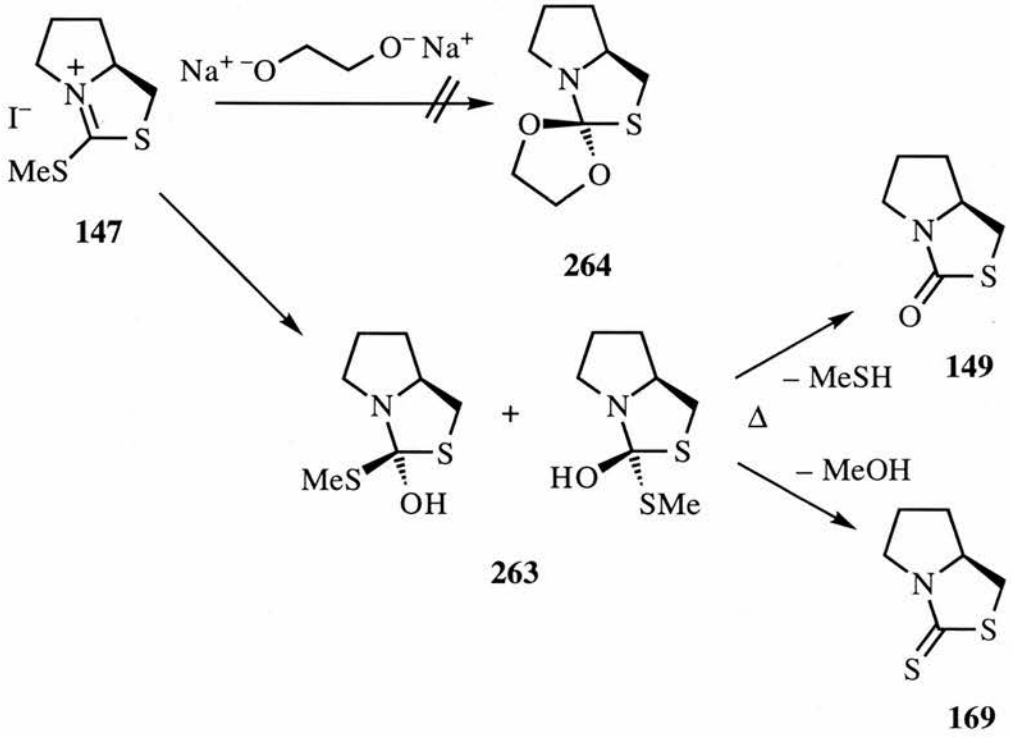


closure by the two step mechanism shown to give the chiral spiro compounds **154** which are novel examples of the monothioortho-carbamates and -ureas. Because of the particular stability of five and six

membered rings, 1,2- and 1,3-diols and the corresponding amino alcohols seemed most promising for this application.

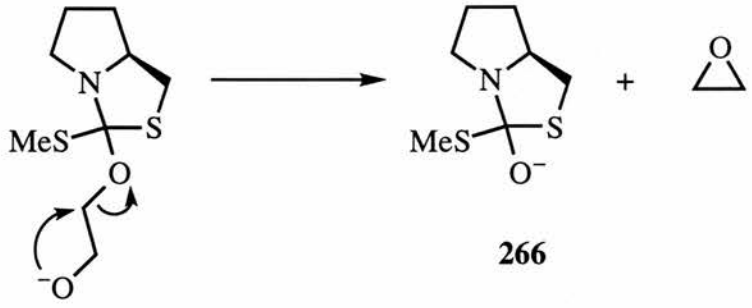
2. Reactions of iminium salt 147 with the disodium salts of 1,2-diols

The disodium salt of ethane-1,2-diol was generated by reaction with either sodium metal or sodium hydride and reacted with iminium salt **147** in toluene. Upon aqueous work up and Kugelrohr distillation the expected spiro compound **264** was not obtained and instead the novel dithioorthiocarbamic acid derivative **263** was produced. This was found to be rather unstable towards heat, losing either methanol to give the thiazolidinethione **169** or methanethiol to give the thiazolidinone **149**. Despite this, the compound gave elemental analysis results in reasonable agreement with expectation (Found: C, 43.1. cf. expected C, 43.9%). The



structure was also supported by an IR absorption at 3340 cm^{-1} (OH). The NMR spectra provided conclusive evidence for the orthodithiocarbamic acid structure with a signal at δ_C 97.9 for the quaternary carbon and also showed the compound to consist of 1 : 1 mixture of the two possible diastereomers [δ_C 16.09 and 16.06; δ_H 2.26 and 2.17 (Me)].

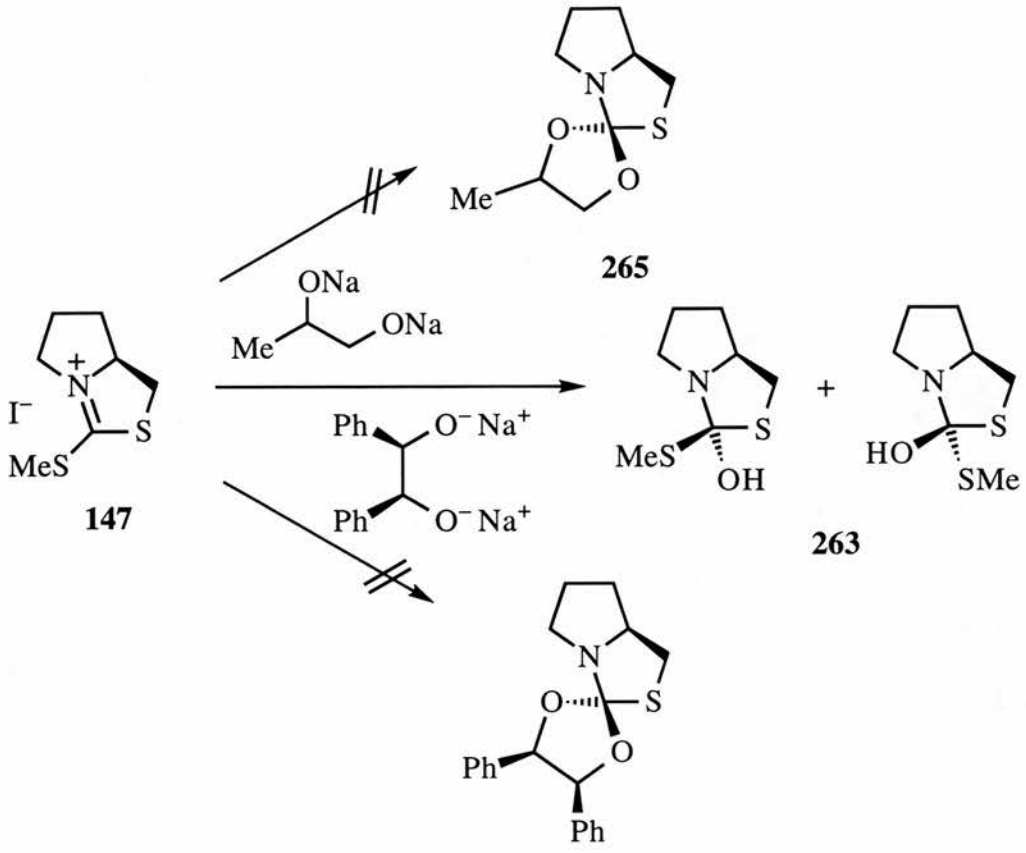
It was initially thought this product might have arisen from elimination of ethylene oxide from the expected intermediate **265** as shown



265 **266**

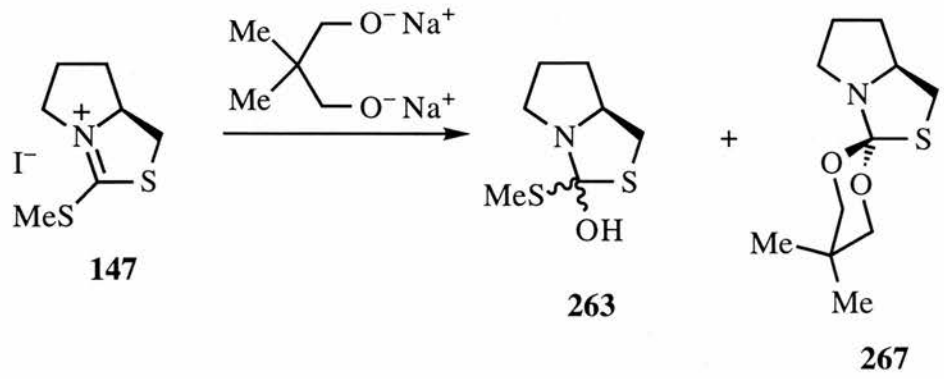
to give **266** which was then protonated. However no epoxide was ever detected in this or the subsequent experiments involving more highly substituted diols from which the epoxide should have been readily isolated. It therefore appears that the diol anion has failed to add irreversibly to **147** and that **263** is produced by simple attack of ^{-}OH on the salt during the work-up where alkaline conditions are produced by hydrolysis of the sodium alkoxide. An attempt to avoid this by adding the reaction mixture to aqueous ammonium chloride rather than water had no effect.

Essentially the same result was obtained for the two other 1,2-diols examined, propane-1,2-diol and *meso*-dihydrobenzoin. No sign of the expected spiro compounds **265** and **266** was seen and the main product in each case was again **263** or its thermal degradation products **149** and **169**. Attention was therefore turned to 1,3-diols.



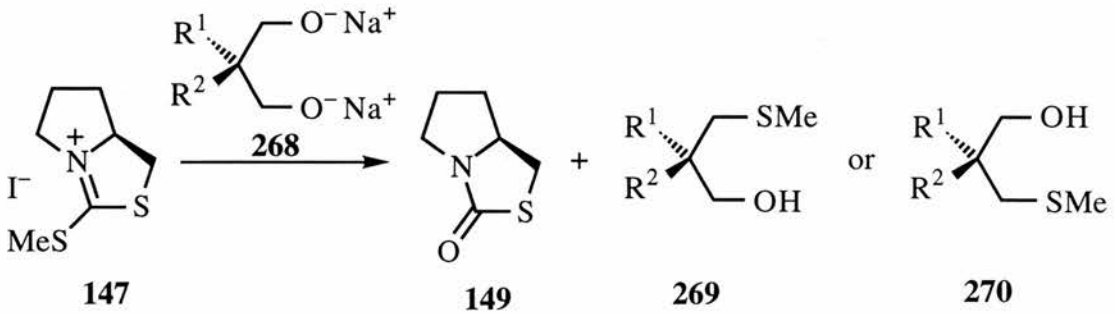
3. Reactions of iminium salt 147 with the disodium salts of 1,3-diols

Reaction of the iminium salt **147** with the disodium salt of 2,2-dimethylpropane-1,3-diol gave a 1:1 mixture of methylthiohydroxy compound **263** and the desired spiro compound **267**. The identity of the

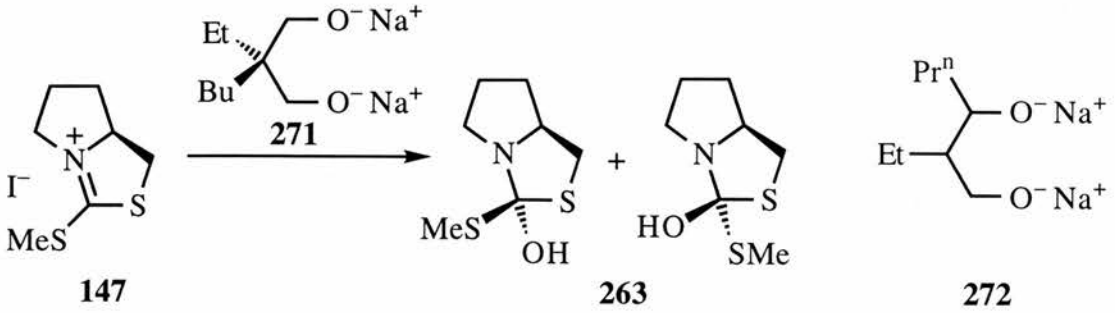


spiro compound was proved by its NMR spectra although it could not be obtained in pure form. Most characteristic was a small ^{13}C NMR signal at δ_C 129.2 corresponding to the quaternary spiro centre connected to four heteroatoms. This value compares well with that of δ_C 131.7 for the dimethoxy analogue **172** and δ_C 130.9 for the corresponding diethoxy compound.[56] The slightly non-equivalent CH_2O groups gave rise to signals at δ_C 76.6 and 72.7, the quaternary CMe_2 centre gave a signal at δ_C 29.5, and the two non-equivalent methyl groups gave signals at δ_C 23.1 and 21.7 and at δ_H 1.19 and 0.82.

Another interesting possibility for the reaction of **147** with diols which has not been mentioned up to now is that it could proceed as for simple alkoxides. Thus a 1,3-diol such as **268** for example could react to give either **269** or **270**. For cases in which $R^1 \neq R^2$, these are opposite



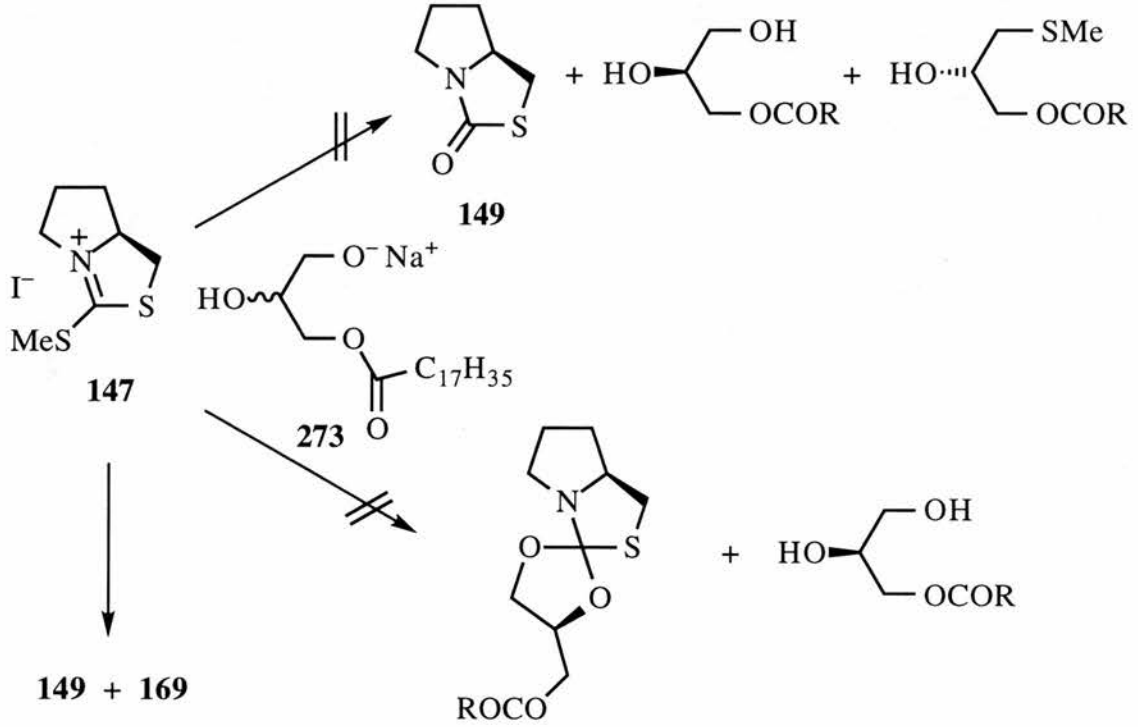
enantiomers and so there was some interest to discover whether this "internal kinetic resolution" might be possible. With this in mind **147** was reacted with the disodium salt of 2-butyl-2-ethylpropane-1,3-diol **271**.



Unfortunately the product again proved to be only the SMe/OH compound **263**. The disodium salt of 2-ethylhexane-1,3-diol **272**, for which more complex issues of stereochemistry arise, also reacted with **147** to give only **263**.

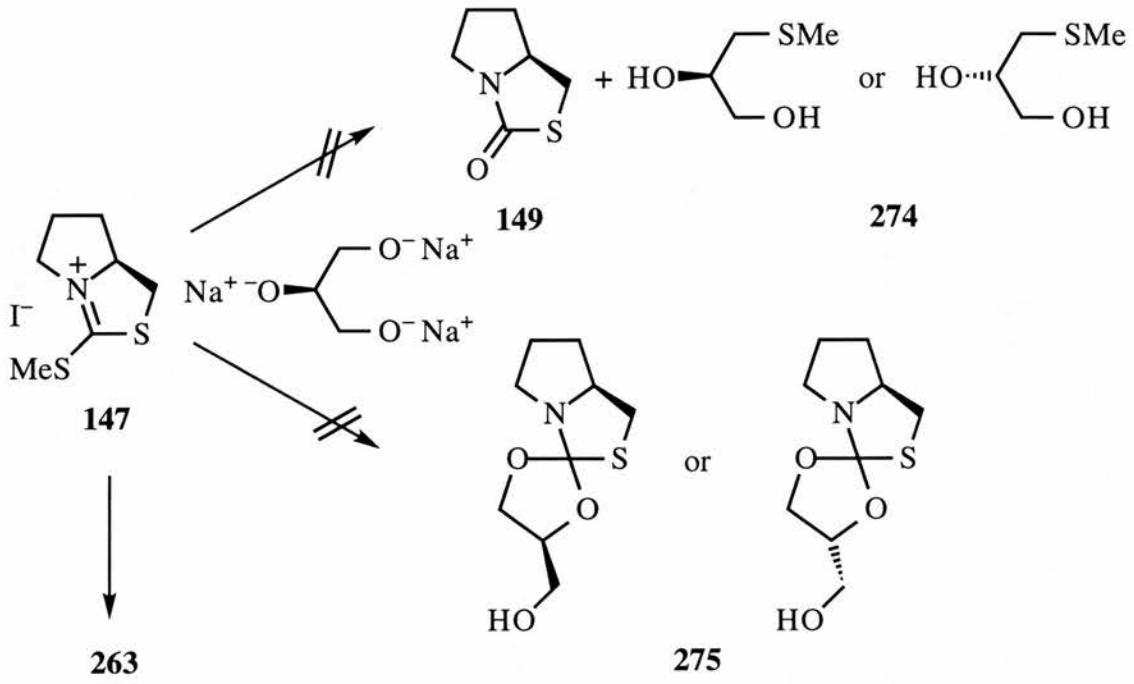
4. Reaction of iminium salt 147 with the sodium salts of other alcohols

Another type of kinetic resolution is possible with the salt of a monoacylglycerol such as 1-glyceryl monostearate **273**. As shown below, either mode of reaction could be used to achieve kinetic resolution. In the event this reaction again only gave the degradation products of **263**, namely **149** and **169**, together with recovered glyceryl stearate.

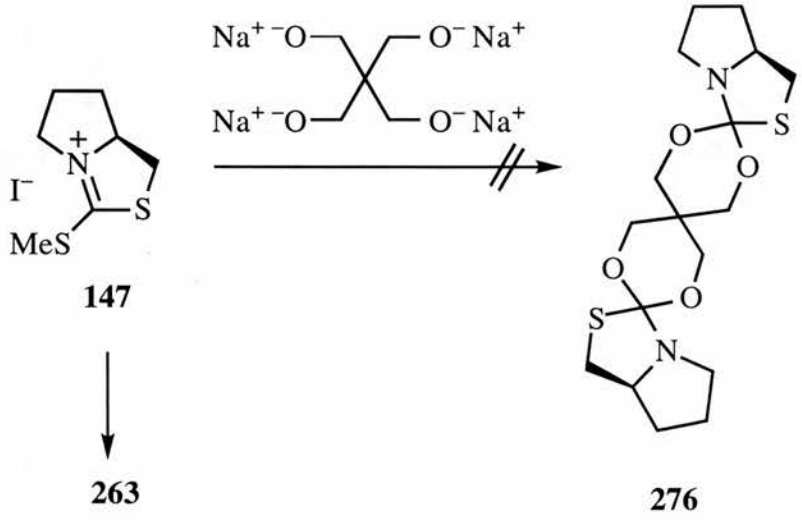


Reaction of **147** with the trisodium salt of glycerol itself also raises various possibilities such as formation of enantiomeric sulphides **274** or

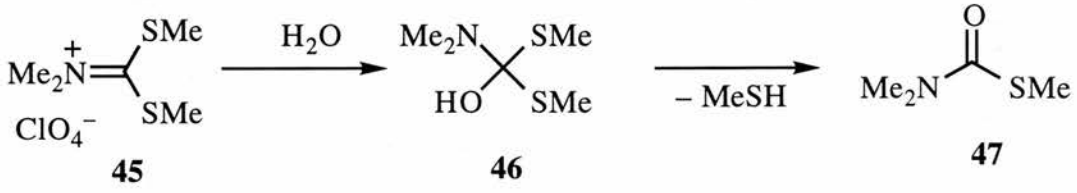
the diastereomeric spiro compounds **275**. Again the reaction was rather disappointing in that only **263** was formed.



A final reaction attempted in this area was that of the salt **147** with the tetrasodium salt of pentaerythritol. No sign of the possible trispiro product **276** was seen and instead **263** was isolated.

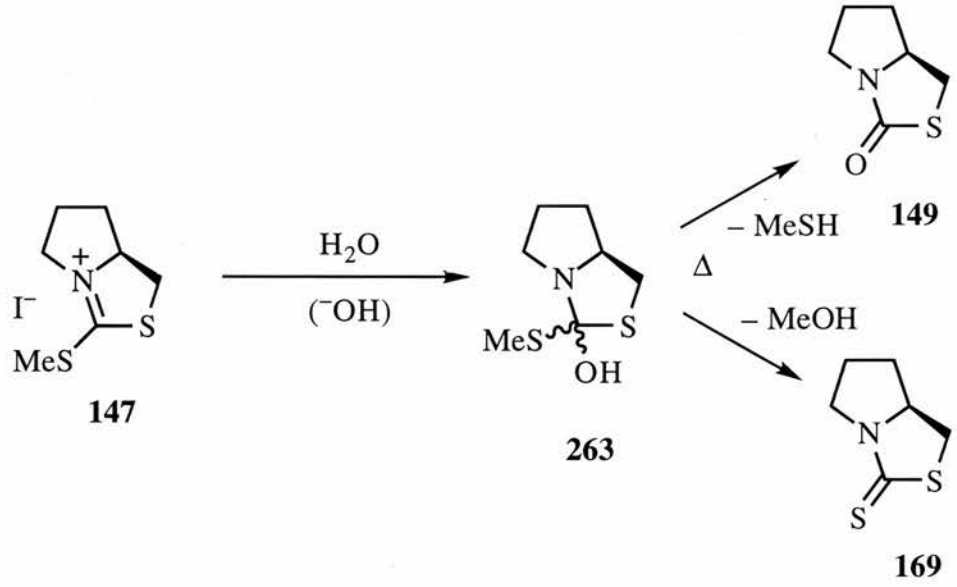


Although the work of this section generally produced disappointing results in that only one spiro compound **267** was formed, the alternative product **263** formed in most cases was of considerable interest. As described in Section A4 of the Introduction, only one isolable dithioorthocarbamate derivative **44** has been reported before. The intermediate **46** postulated in the hydrolysis of **45** lost methanethiol to give **47**.[20] On the other hand, as already noted earlier in this section, the



45 **46** **47**

closely related dithioorthocarbamic acid **263** could be isolated by careful distillation but at a higher temperature degraded both by loss of

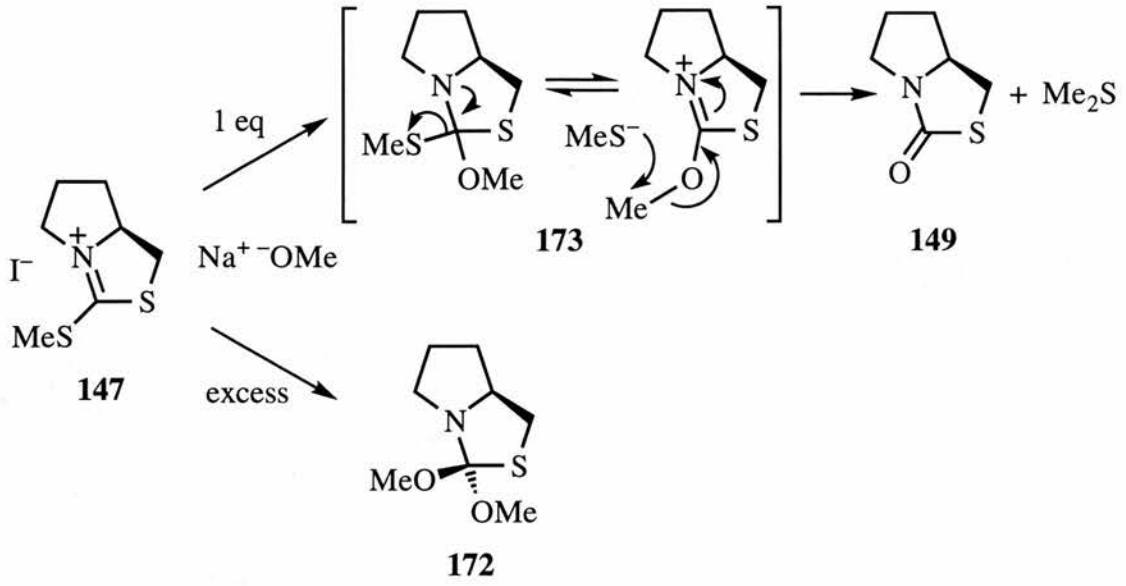


147 **263** **149** **169**

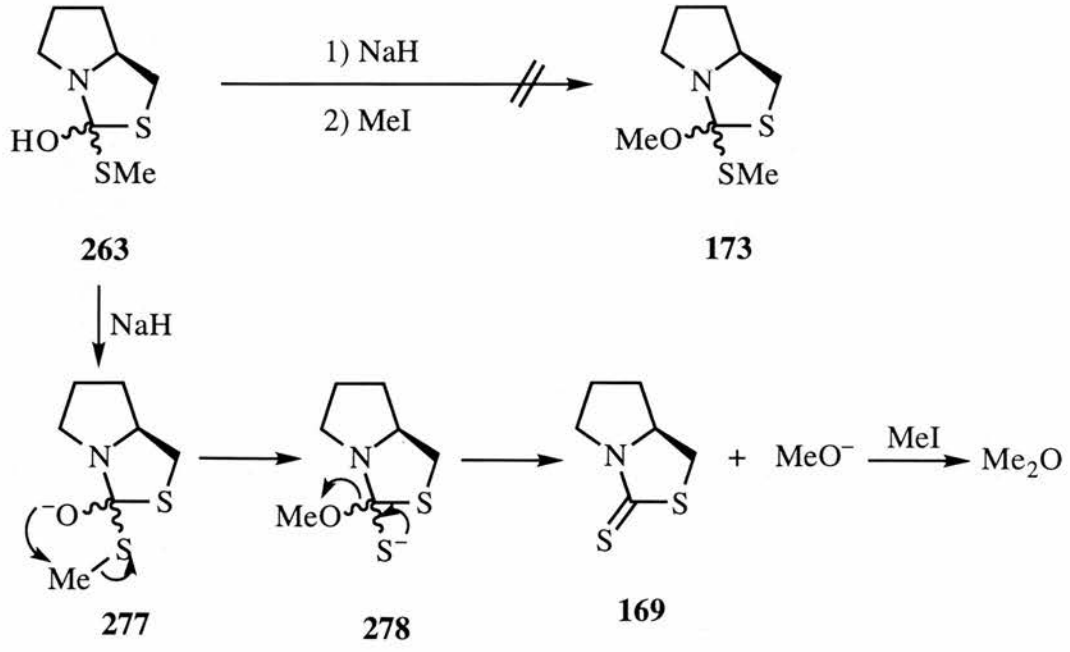
methanethiol to give the thiazolidinone **149** and by loss of methanol to give the thiazolidinethione **169**.

As described in Section A of this Discussion, reaction of **147** with sodium methoxide resulted in formation of **149** in high yield by loss of

dimethyl sulfide from the intermediate **173** as shown. Since **263** had



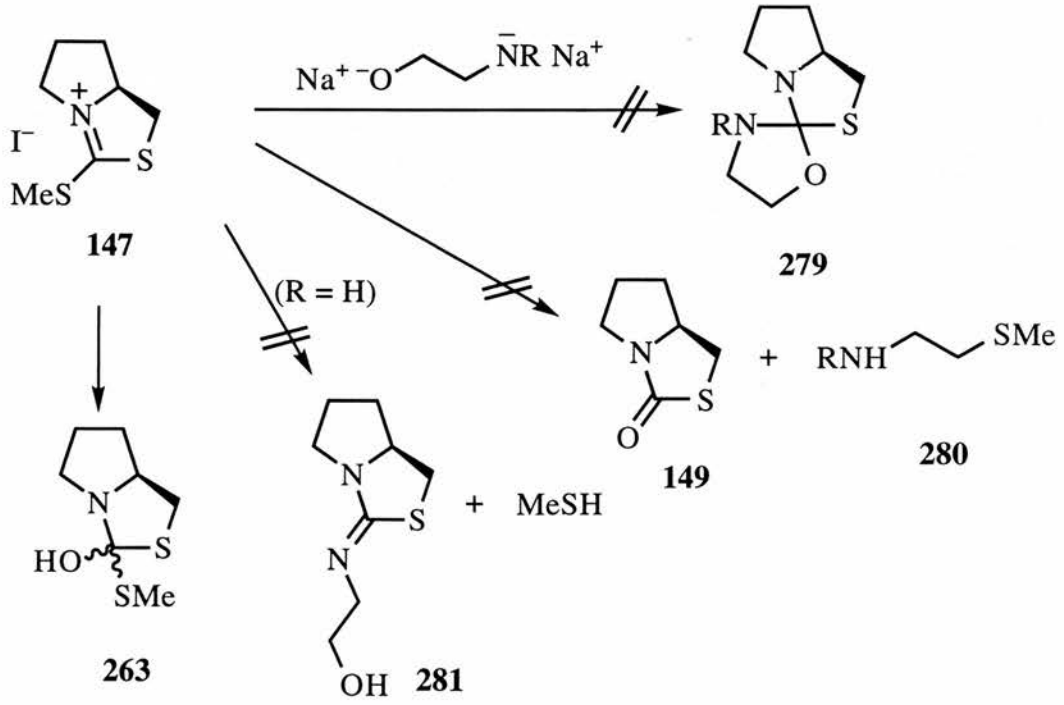
unexpectedly been isolated and since the monothio-analogue **172** formed by reaction of **147** with excess NaOMe was also stable,[56] it was considered worth attempting to prepare and isolate **173**. With this in mind, **263** was treated with one equivalent of sodium hydride and methyl iodide in toluene at room temperature. At first sight this gave a most surprising result— the



only product was the thiazolidinethione **169** together with, presumably, dimethyl ether, although the latter was not isolated. We believe that the explanation for this lies in the process shown above where the initially formed alkoxide anion **277** abstracts the methyl group from the adjacent atom to give the thiolate anion **278**. This can then readily lose methoxide to give **169** as observed and, although the methyl transfer postulated is unusual, it should be favoured by the greater basicity of O^- as compared to S^- making **278** more thermodynamically stable than **277**. It is perhaps surprising that no trace of **149** was formed in this reaction — i.e **277** showes no tendency to lose MeS^-, in contrast to **46**, **263** and **173** where in each case cleavage of the C-S bond occurs.

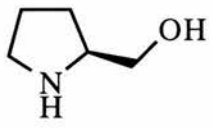
5. Reaction of iminium salt 147 with the disodium salts of amino alcohols

We decided to change the nucleophilicity of one end of the bidentate nucleophiles by using primary and secondary amino alcohols. This could



result in a variety of different processes as shown on the last page. First, a spiro compound **279** could be formed. If the reaction proceeds as for simple alkoxides, the amino sulfide **280** would result. For primary amines, a further possibility is formation of 2-iminothiazolidine **281**.

In the event, reaction of **147** with the disodium salt of ethanolamine again gave only the SMe/OH compound **263** together with some thiazolidinone **149** from its degradation. This pattern was also followed for the anions derived from (*S*)-prolinol **175** and (1*R*,2*S*)-ephedrine **244**.



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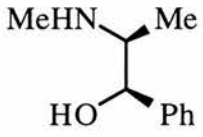

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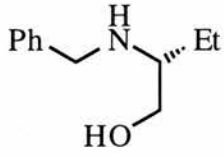
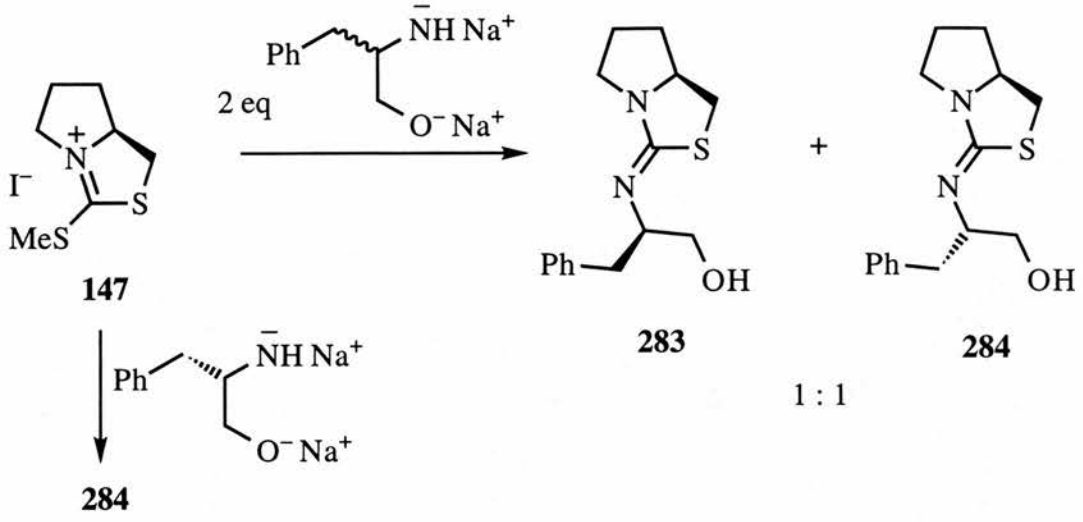


282

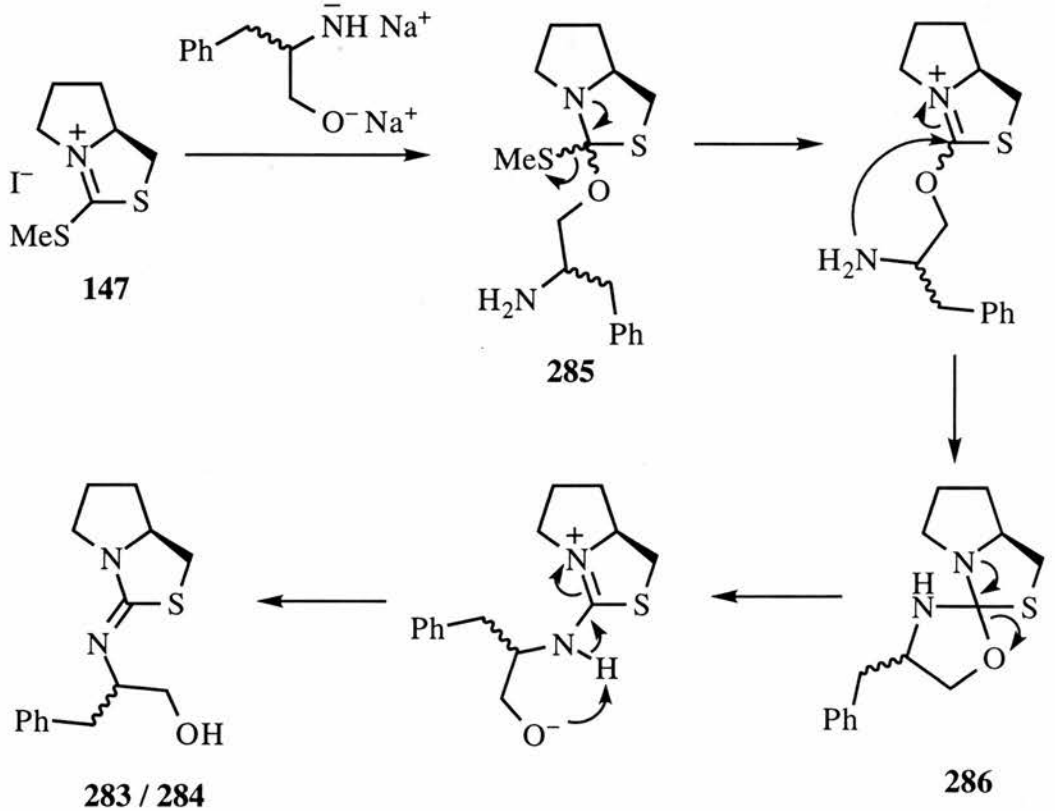
In each case the SMe/OH compound **263** could be isolated from the normal basic work up, whereas use of aqueous ammonium chloride led to its degradation and isolation of the thiazolidinone **149** and thiazolidinethione **169**. With the *N*-benzylamino alcohol **282**, the identity of the products remains unknown since a complex mixture was produced.

Much better results were produced by using the anion of (S)-phenylalaninol **226**. When **147** was treated with two equivalents of the racemic amino alcohol and NaH, the imine was formed as a 1:1 mixture of diastereomers **283** and **284**. The lack of any kinetic resolution in this case is disappointing. By using one equivalent of the (*S*)-amino alcohol, only **284** was obtained thus allowing assignment of the NMR signals to each diastereomer in the mixture. Since the compounds were oils correct elemental analysis could not be obtained but the high resolution mass spectrum did confirm the formula. The most conclusive evidence for the

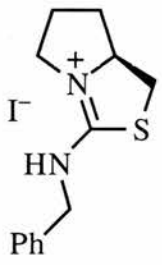


structures came from IR absorptions at 3300 (OH) and 1610 (C=N) cm^{-1} and a ^{13}C NMR signal at 138.3 for C-2 of the thiazolidine ring.

An interesting insight into the mechanism of formation of these products came from a further experiment. In one run of the reaction of **147** with one equivalent of the racemic amino alcohol a different product was obtained by chance and this proved to be the product of initial alkoxide



addition **285**. The presence of SMe was demonstrated by elemental analysis results in reasonable agreement with expectation and, more conclusively, by double ^1H NMR signals at δ_H 2.40 and 2.35 indicating two diastereomers in a 1:1 ratio. Unfortunately the compound **285** proved to be unstable in solution and by the time the ^{13}C NMR spectrum could be run, it had rearranged to the imine **283/284**. This observation is of great significance since it indicates that **285** is an intermediate in the formation of the imines **283/284**. The mechanism for the overall reaction shown above, which also involves the spiro compound **286** as an intermediate, seems quite plausible. Thus it appears that **283/284** is only the final product in a rather complex sequence involving both **285** and **286**. The only precedent for the reaction of **147** with amines comes from the publication of Yadav and coworkers,[57] where the complication of a competing oxygen nucleophile is not present. As they reported while our work was in progress, **147** reacts with benzylamine under neutral conditions or ethyl glycinate in the presence of triethylamine to afford **287** and **288** respectively.



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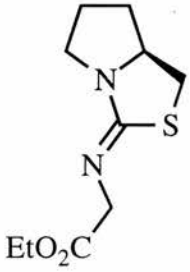
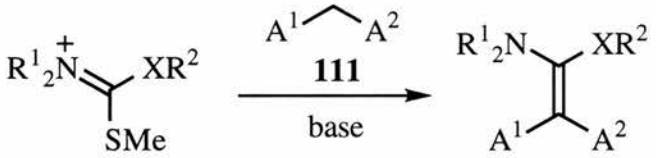


288

E. Synthesis, structure and reactivity of highly polarised double bond compounds

1. Background

As described in Section B of the Introduction, one of the most important routes to both ketene aminals and ketene mercapto aminals is reaction of an appropriate iminium salt **289** with an acidic methylene

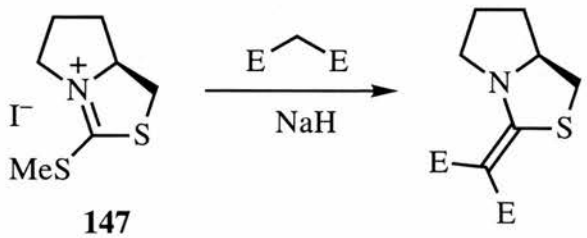


289

X = S, NR^2

290

compound **111** under basic conditions to give the products **290**. Since a range of chiral iminium salts were available from the work described earlier, it was considered of interest to examine the formation of polarised double bond compounds from these. While our work was in progress a short communication from Yadav and coworkers reported the formation of **291** and **292** from **147**.[57]

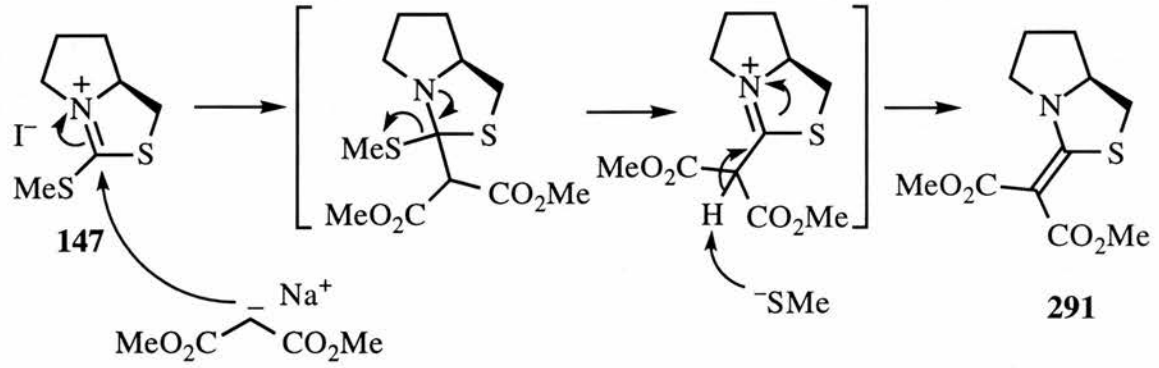


147

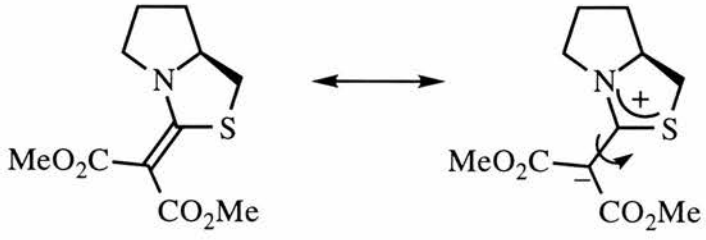
291 E = CO_2Me
292 E = CN

2. Preparation of thiazolidine-based condensation products

The preparation of **291** was first repeated by reaction of **147** with the anion of dimethyl malonate in THF at room temperature. As shown below, the reaction involves addition of the anion at C-2 followed by loss of MeS^- which then abstracts a proton to give the product. This was



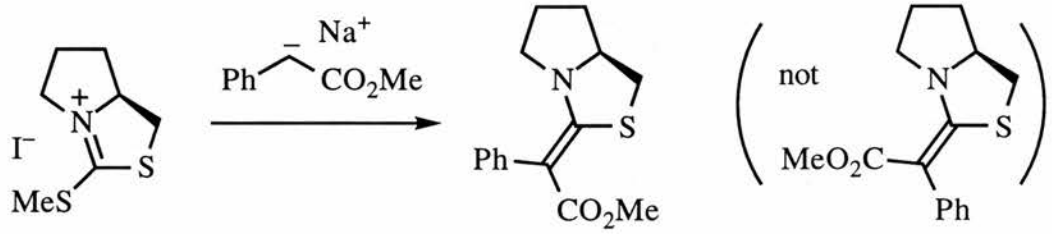
obtained as colourless crystals with melting point and optical rotation values in good agreement with the reported data.[57] A somewhat surprising observation which was also noted by the previous workers without comment, was that the ester methyl groups appeared to be equivalent, giving a single ^1H NMR peak at δ_H 3.76. This was also the case in the ^{13}C NMR spectrum with single signals at δ_C 167.4 and 51.6. The explanation for this is that the polarisation of the double bond in **291** results in such a large reduction in the energy barrier to rotation that it undergoes free rotation at room temperature as represented in formula **293**, making the



291 **293**

ester groups equivalent on the NMR time-scale. The quantification of this effect by means of a variable temperature NMR study is described in detail in Section E5. The polarisation of the "double bond" was also confirmed by the ^{13}C NMR values of 166.7 and 90.8.

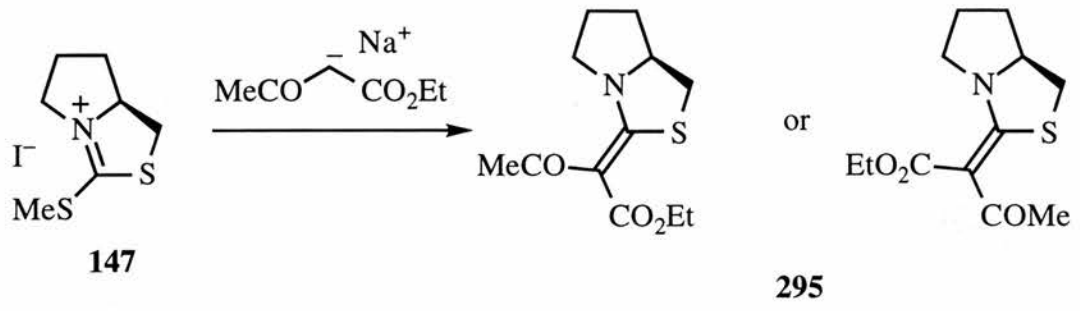
The reaction of **147** with the anion of methyl phenylacetate was now examined. Again it took the expected course to afford a crystalline product. In this case two geometrical isomers are possible but it was clear



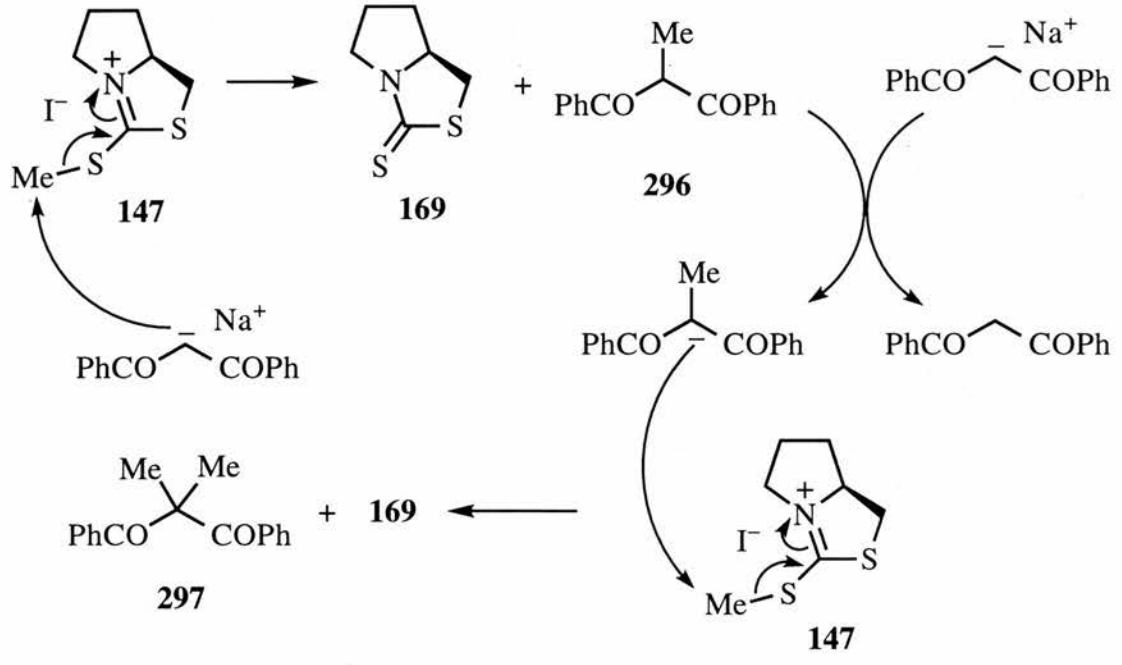
147 **294**

from the spectra that only one methyl environment was present (δ_H 3.62; δ_C 169.4, 51.2). In principle, this could again be due to free rotation allowing rapid interconversion of the isomers but a variable temperature NMR study showed this not to be the case. Instead the condensation had taken place with complete selectivity to give exclusively the *Z*-isomer **294**. This was conclusively demonstrated by an X-ray structure determination, as discussed in detail in Section E5. The ^{13}C NMR values of δ_C 161.9 and 98.2 for the "double bond" in this case showed a slightly lower degree of polarisation than for **291**.

The reaction of **147** with the anion of ethyl acetoacetate proceeded similarly to give the adduct **295**, this time as an oil. Again this was formed as a single geometrical isomer although it was not possible to say which. The ^{13}C NMR signals for the "double bond", δ_C 168.2 and 101.8 showed a lower degree of polarisation than for **291**.

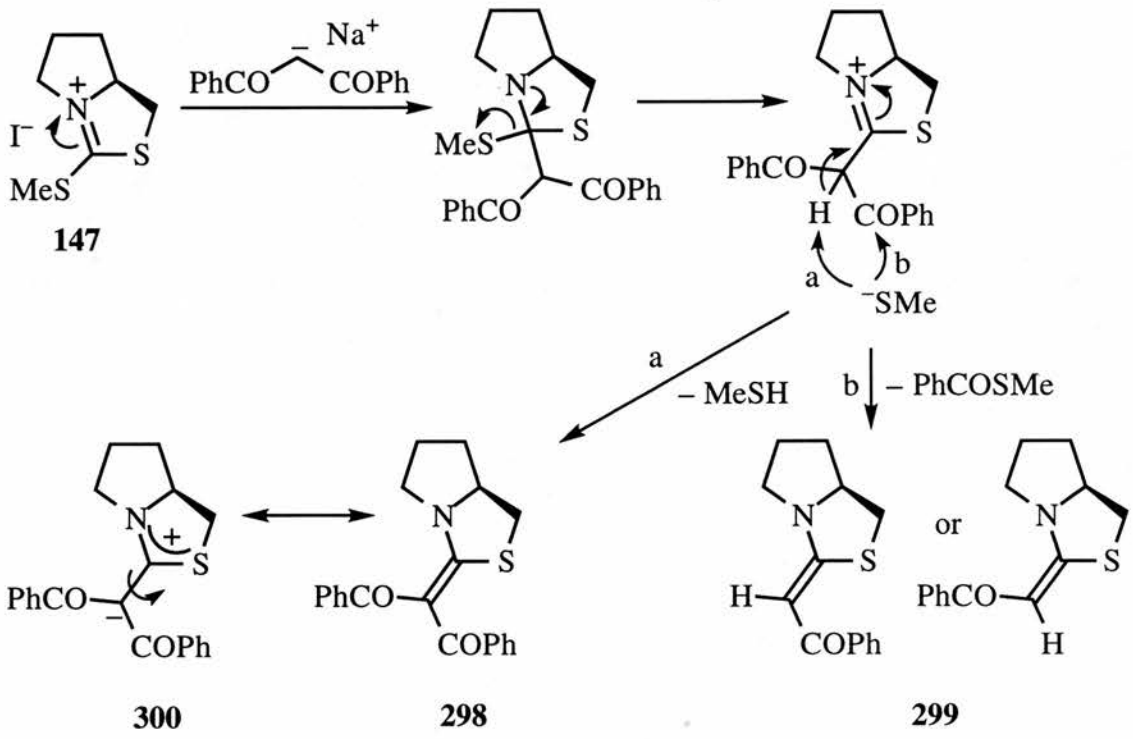


The reaction of **147** with the anion of dibenzoylmethane took a more complex course. Careful chromatography allowed separation of five separate products in addition to some unreacted dibenzoylmethane. The first three of these, the thiazolidinone **169**, 1,1-dibenzoylethane **296** and 2,2-dibenzoylpropane **297** indicated the occurrence of an unexpected side-reaction: *S*-demethylation of the salt **147** by the anion.



Despite this competing process, a low yield of the desired product **298** was obtained and characterised spectroscopically. Even the condensation process with this anion was not without complication however, since the final product was a second polarised double bond compound **299**. As shown below this results from competing abstraction of a benzoyl group

rather than a proton by MeS^- in the intermediate. The spectra indicated **299** to be a single geometrical isomer although it was not possible to tell

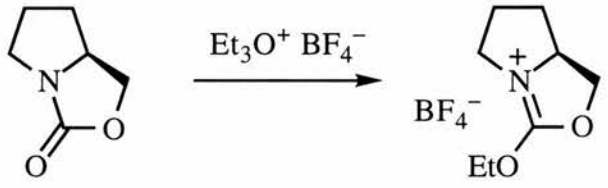


which one. The polarisation in both these was again confirmed by the ^{13}C NMR signals for the "double bond" carbons, **298** δ_C 168.8 and 108.9, **299** δ_C 162.8 and 88.7. Once again, as in the case of **291**, the two benzoyl groups of **298** were magnetically equivalent, leading to only one set of ^{13}C NMR signals and this indicates a high contribution of the charge separated form **300** with free rotation at room temperature. In the case of **299** the single NMR signals observed could either be due to formation of a single geometrical isomer or free rotation in a charge-separated form. Unfortunately due to the small quantities of these compounds available variable temperature NMR studies which might have clarified the situation were not carried out.

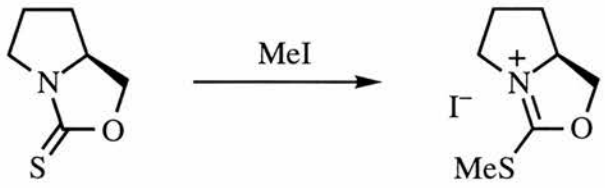
3. Attempted preparation of oxazolidine-based condensation products

In view of the success achieved in preparation of the thiazolidine based polarised double bond compounds, it was decided to investigate the formation of the corresponding oxazolidine based compounds.

The required iminium salts **185** and **186** had already been prepared previously,[56] and were obtained in good yield from the oxazolidinone **195** and the oxazolidinethione **196** as shown below.

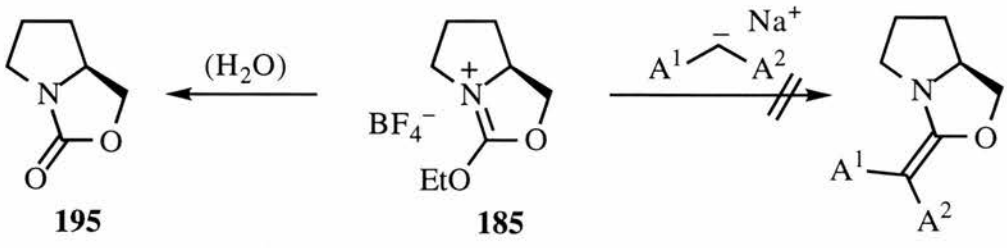


195 **185**



196 **186**

When **185** was reacted with the anions of methyl phenylacetate, dimethyl malonate and ethyl acetoacetate rather disappointing results were obtained. In each case none of the expected condensation products **301**

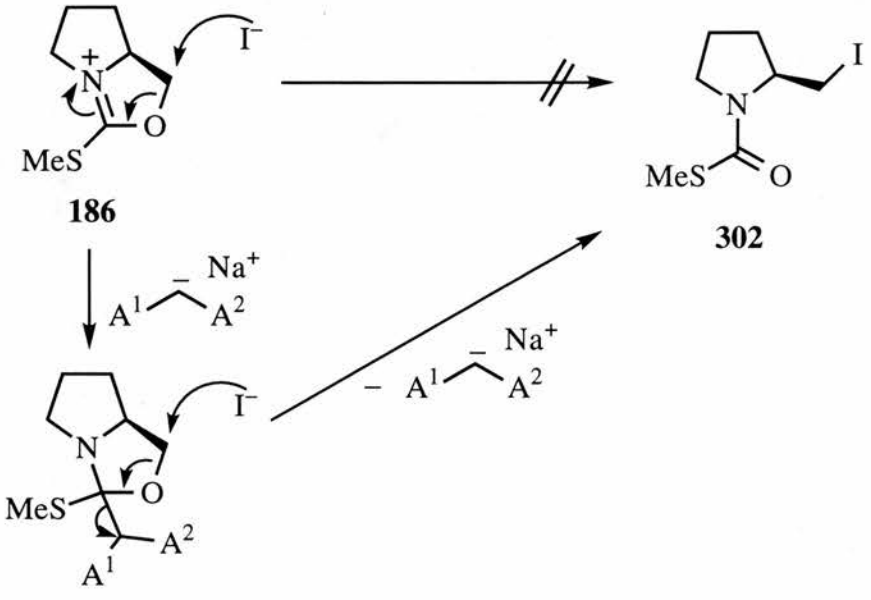


195 **185** **301**

were formed and only the oxazolidinone **195** was isolated presumably resulting from hydrolysis of **185** during work up.

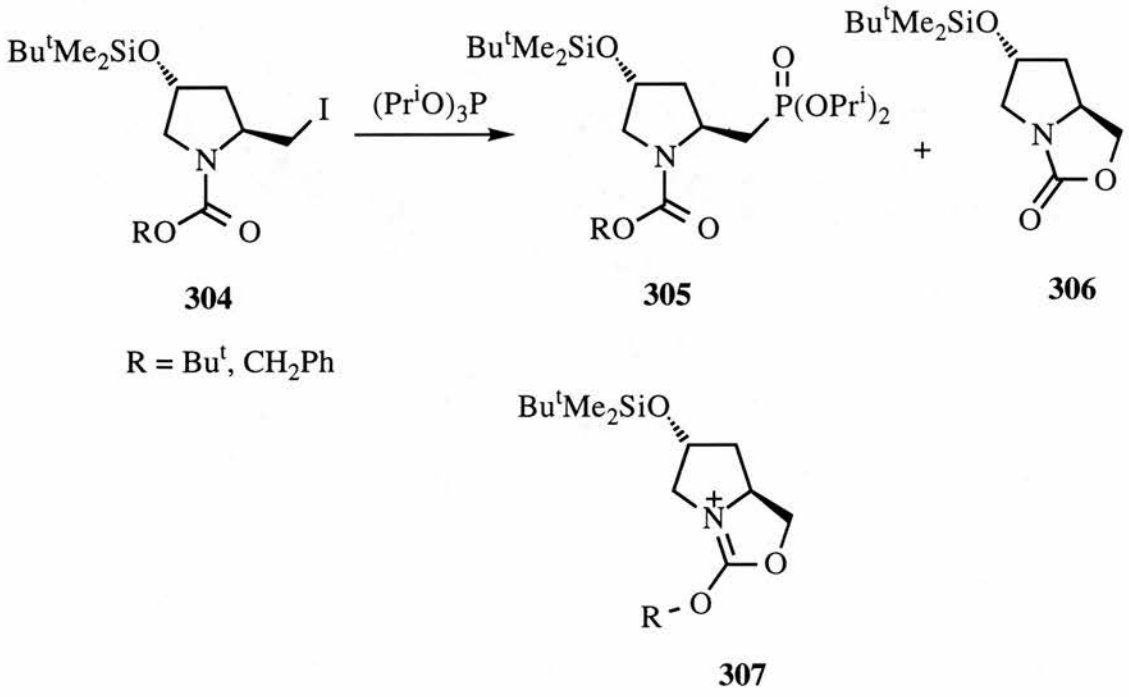
With the oxazolidinethione derived salt **186**, more interesting results were obtained. Treatment of this with the anion of either methyl phenylacetate or dimethyl malonate gave a new product which was identified as the 2-iodomethyl compound **302**. This gave a correct high resolution mass spectrum measurement and the structure was further confirmed by NMR signals at δ_C 167.0 (thiocarbamate C=O), δ_C 12.7 and δ_H 2.35 (SMe) and δ_C 9.5 (CH_2I). The low frequency of the last signal is particularly characteristic for carbon joined to iodine.

The formation of **302** could in principle involve direct attack of I^-



on C-4 of the salt **186** as shown to give the product. This does not seem likely however, since **186** has previously been found to be perfectly stable in solution even in the presence of alkoxides.[56] A possible explanation is that the carbanion catalyses the isomerisation by addition to give **303** which is then attacked by I^- to give **302** and regenerate the carbanion.

It is interesting to note that a recent publication by Tanaka and coworkers describes a process which is essentially the reverse of this.[93] Upon treatment of the iodomethyl compounds **304** with



304 **305** **306**

R = Bu^t, CH_2Ph

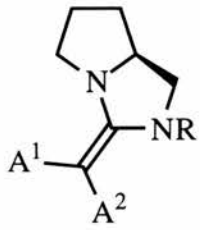
307

triisopropyl phosphite, the desired product **305** was accompanied by the oxazolidinone **306** which was explained by the intermediacy of **307** which could be nucleophilically dealkylated.

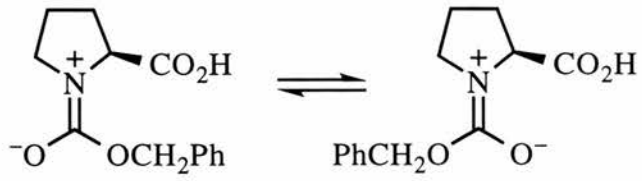
4. Preparation of imidazolidine based condensation products

In view of the differing results obtained in the previous two sections, it was of interest to see whether polarised double bond compounds of the general type **308** could be prepared and, if so, what the extent of polarisation of their double bond would be.

A suitable diamine precursor **312** was already known from the work of Mukaiyama,[79] and this was prepared in four steps using the literature



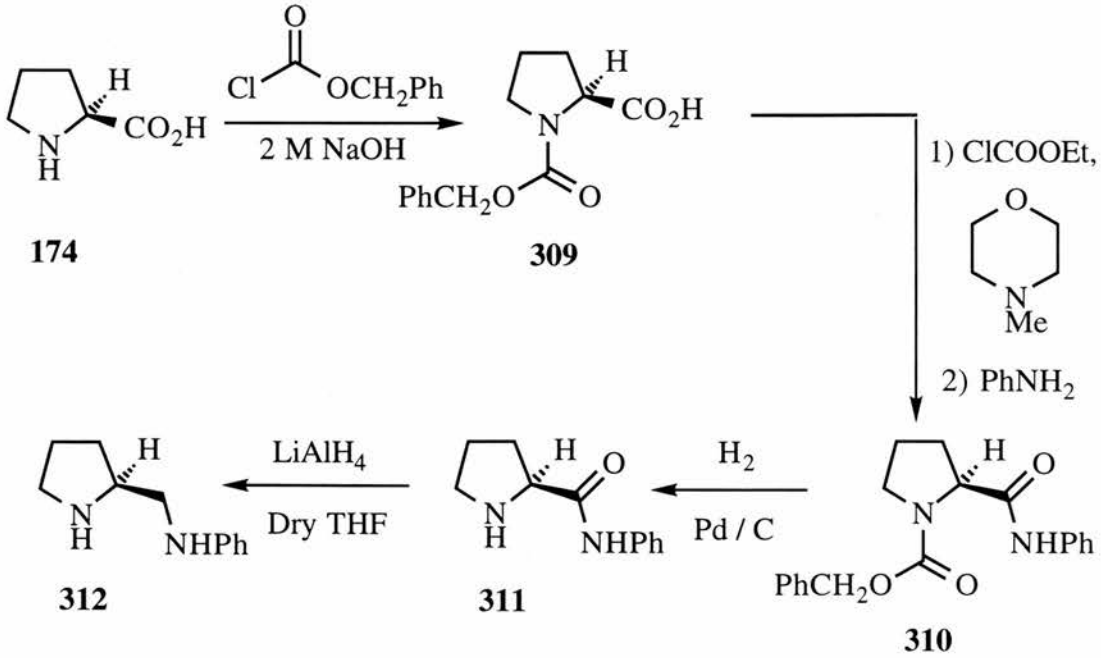
308



309

procedure. (S)-proline **174** was first protected on nitrogen by formation of the N-benzyloxycarbonyl derivative **309**. The ^{13}C NMR spectrum clearly showed this to exist as a mixture of two isomers due to restricted rotation about the carbamate function as represented by the two extreme structures shown above.

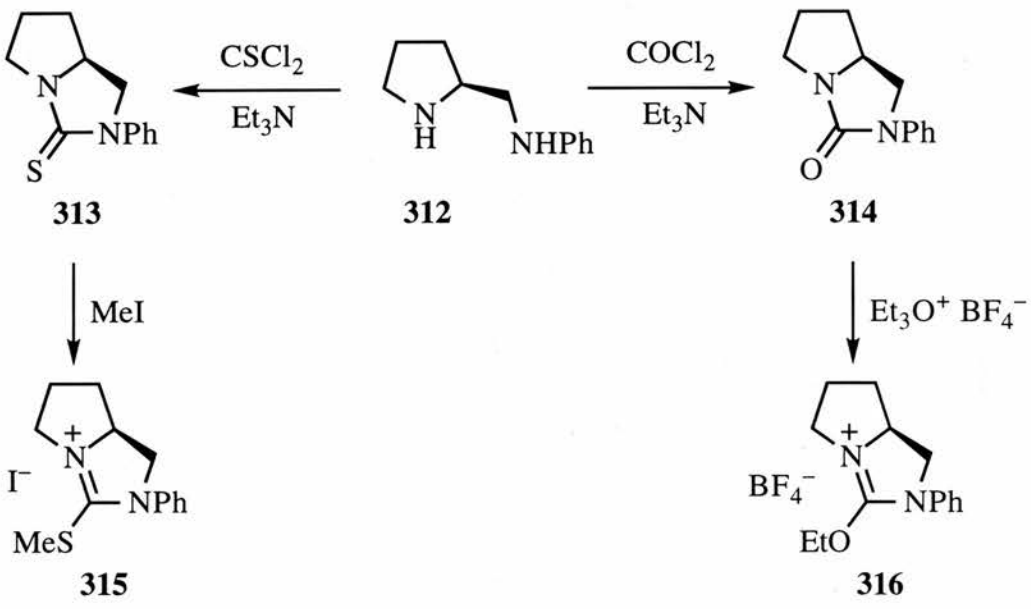
This was then reacted with ethyl chloroformate in the presence of *N*-methylmorpholine as a base to form the mixed anhydride. Keeping the mixture at low temperature to avoid racemisation, aniline was added to form the *N*-protected-(*S*)-pyrrolidine-2-carboxanilide **310**. Deprotection by hydrogenation in the presence of Pd/C gave (*S*)-pyrrolidine-2-



174 **309** **310** **311** **312**

carboxanilide **311**. This was finally reduced to the diamine **312** using lithium aluminium hydride. The sequence was achieved in a good overall yield of 49% for the four steps.

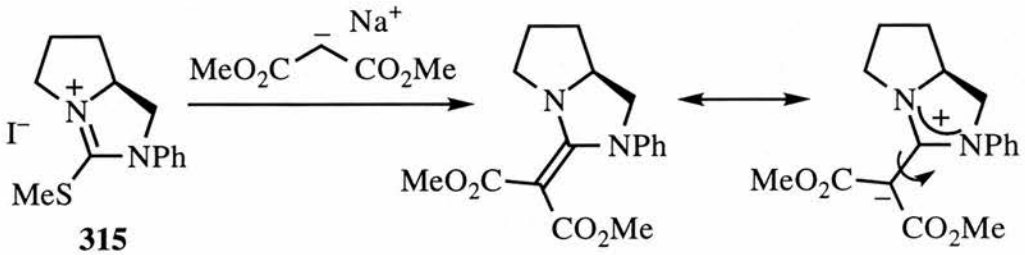
The diamine **312** was now used to prepare two new chiral heterocyclic compounds, the imidazolidinethione **313** and the imidazolidinone **314**. These were readily obtained in moderate yield by reaction with thiophosgene and phosgene, respectively, using the standard



methods already described. The two heterocyclic compounds were fully characterised and gave all the expected analytical and spectroscopic data including ^{13}C NMR signals for C=S in **313** at δ_C 183.7 and for C=O in **314** at δ_C 160.8.

These were then converted into the iminium salts **315** and **316** using the normal methods as shown. Unfortunately these were both obtained as oils and could not readily be purified but they did give the expected spectroscopic data in each case, including ^{13}C NMR signals for C-2 showing the expected shift to lower frequency (**315** δ_C 169.7, **316** δ_C 151.5).

With these compounds in hand, the formation of polarised double bond systems could now be attempted. Reaction of **315** with the anion of dimethyl malonate proceeded in the desired sense to afford **317** in good yield as colourless crystals. This gave a correct high resolution mass



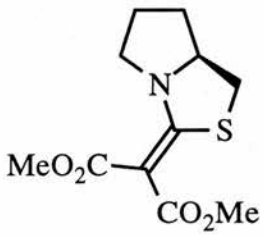
315 **317** **318**

spectrum value and the structure was confirmed by the spectra. The most striking feature of these was that once again, as in the case of the sulfur analogue **291**, the ester groups were magnetically equivalent giving only one set of signals (δ_H 3.34, δ_C 167.5 and 50.5) indicating a high contribution from the fully charge separated form **318** with free rotation at room temperature. As described in detail in the next section, a variable temperature NMR study confirmed this. The high degree of polarisation was also confirmed by the ^{13}C NMR values for the "double bond"of δ_C 165.0 and 75.5.

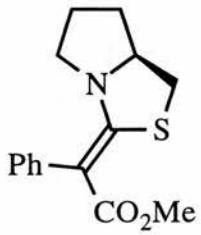
A preliminary attempt to prepare a second example of this type by reaction of **315** with the anion of methyl phenylacetate was not successful and this could not be pursued further due to lack of time, but there is no reason why **315** should not be used to gain access to a whole range of examples as for **147**. This is a promising area for future work.

5. Structure of the polarised double bond compounds

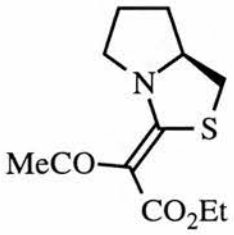
As a result of the work describe in Section E2 and E4, the six polarised double bond compounds, **291**, **294**, **295**, **298**, **299** and **317**



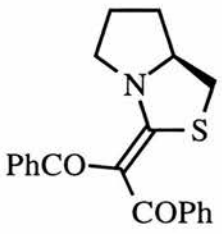
291



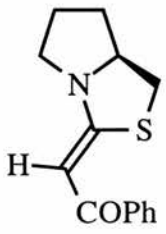
294



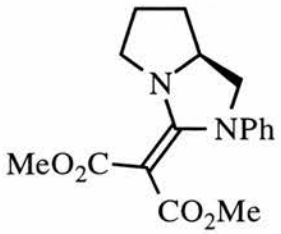
295



298



299



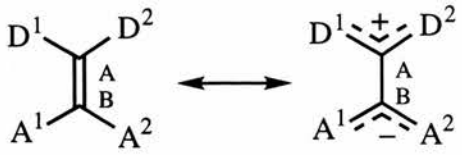
317

were available. In this section a detailed comparison of their structure as revealed by ^{13}C NMR shifts, variable temperature NMR studies and an X-ray diffraction study is made. Where appropriate the data is also compared with literature data for similar compounds.

As mentioned in Section B of the Introducton, the observed ^{13}C NMR shifts for the "double bond" carbons in compounds of this type have been used as a direct measure of the degree of polarisation.[45] The values obtained here are listed in Table 4, together with the values for comparable compounds from the literature.

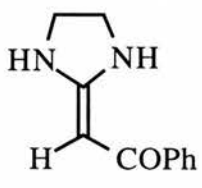
From these data various trends can be seen. First it appears that the difference in chemical shifts, $\Delta\delta$, is generally greater for ketene aminals

Table 4. ^{13}C NMR shifts of double bond carbons in compounds of the type:—

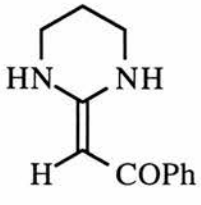


compound	δ_C C(A)	δ_C C(B)	$\Delta\delta$	ref.
291	166.7	90.8	75.9	a
294	161.9	98.2	63.7	a
295	168.2	101.8	66.4	a
298	168.8	108.9	59.9	a
299	162.8	88.7	74.1	a
317	165.0	75.5	89.5	a
126	165.1	73.0	92.1	53
319	159.2	76.1	83.1	53
320	165.1	51.7	93.4	49
321	158.8	56.0	102.8	49
322	167.4	87.7	79.6	51
323	166.4	81.1	85.3	51
324	163.8	99.5	64.3	51
325	173.0	97.3	75.7	51

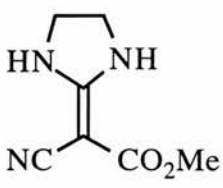
[a] This work



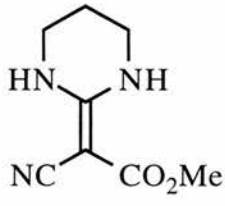
126



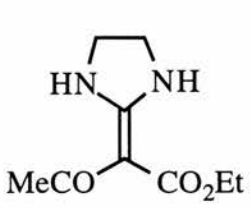
319



320



321



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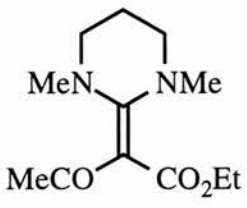
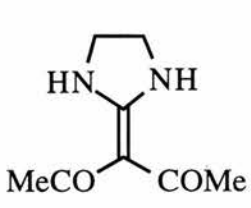
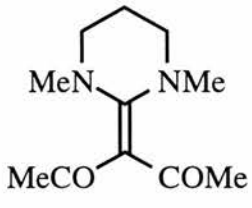


323



324



325

than for ketene thioaminals. Interestingly, this does not correlate with a reduced energy barrier to rotation, since, as will be seen below, the energy barrier for **317** is almost the same as for **291**. By comparing the series **126**, **322** and **324** where the donor groups remain the same it can be seen that the value of $\Delta\delta$ decreases steadily in going from H/COPh to MeCO/CO_2Et to MeCO/MeCO as the acceptor groups. This agrees well with the similar trend for the directly comparable examples from our work, **299**, **295** and **298**. The highest values of $\Delta\delta$ are associated with the presence of a cyano acceptor group, and as mentioned in the introduction, a second cyano group can take the value of $\Delta\delta$ to nearly 140 for **121**. It is also significant that, among our compounds, the two showing the highest $\Delta\delta$, **291** and **317**, were the two for which definite evidence for free rotation about the "double bond" at room temperature was obtained.

In an attempt to quantify this effect, variable temperature ^{1}H NMR studies were carried out on **291** and **317**. The resulting spectra (CO_2Me region) are shown in Figures 1 and 2, respectively. From these the coalescence temperatures T_c can be estimated as -50 ± 2 °C for **291** and -27 ± 1 °C for **317**. The low temperature separations of the signals $\Delta\nu$ are 17 Hz and 280 Hz respectively. From these values it is possible to calculate the free energy barriers to rotation, ΔG^* by using the equation:

$$\Delta G^* = RT_c [22.96 + \ln (T_c / \Delta\nu)]$$

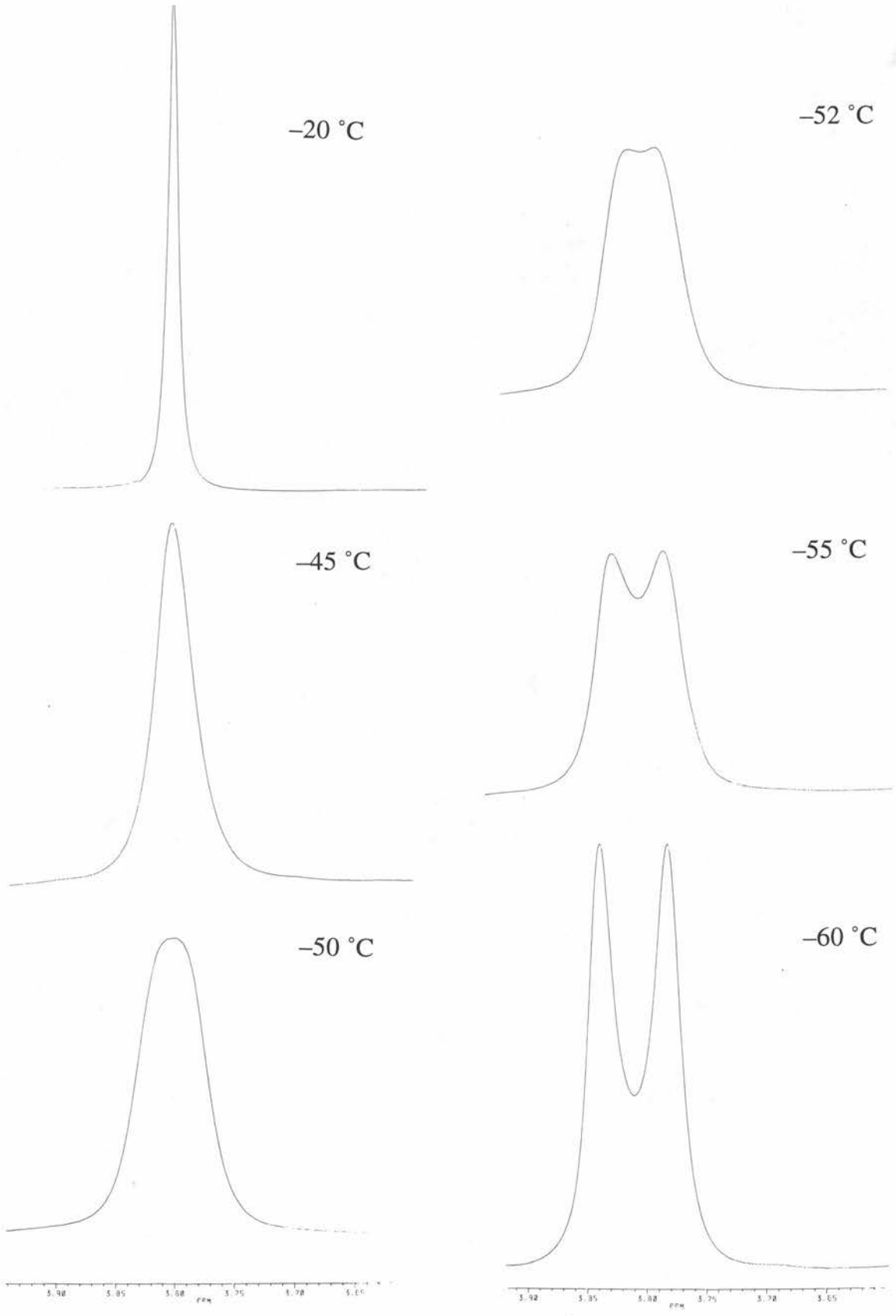


Figure 1. Variable temperature ^{1}H NMR study of **291**

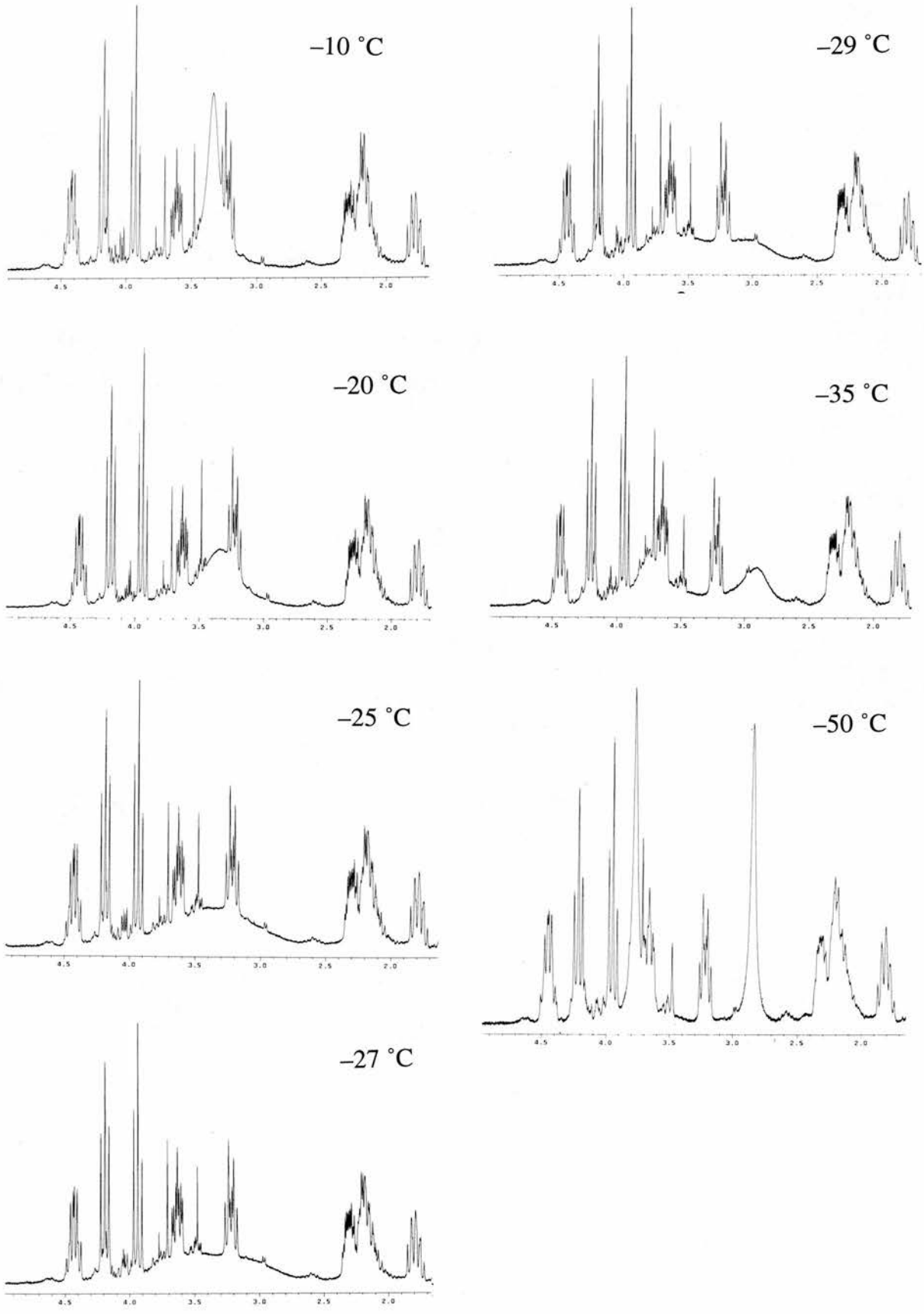
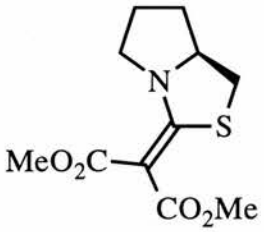


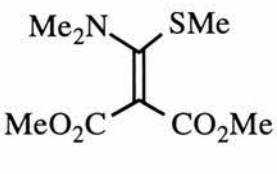
Figure 2. Variable temperature ^{1}H NMR study of **317**

This gives values of $\Delta G^* = 47.4 \pm 0.5$ kJ mol^{-1} for **291** and $\Delta G^* = 46.7 \pm 0.2$ kJ mol^{-1} for **317**. It is interesting to note that the energy barriers for the two compounds are almost identical despite the widely differing coalescence temperatures. This is because the frequency difference between the signals is much larger in the latter case. Comparison of the measured energy barrier for **291** with those for the model compounds **136**, **138** and **326**,[54] shows it to be within the expected range, although



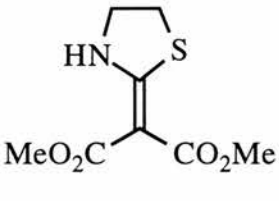
291

47.4 kJ mol^{-1}



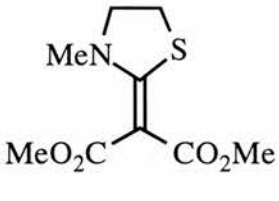
136

< 39.5 kJ mol^{-1}



138

93.7 kJ mol^{-1}

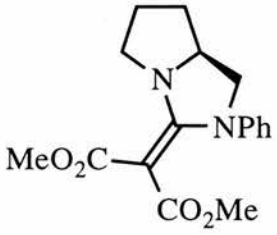


326

< 39.5 kJ mol^{-1}

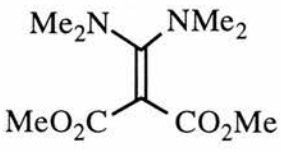
somewhat higher than for **326** which is most similar in structure. The higher value for **138** was attributed to hydrogen bonding between the NH and an ester CO.[54]

Good models for **317** are harder to find, but the energy barrier can be compared with those for **327**,[94] **328** and **329**.[52]



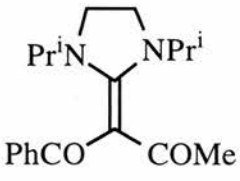
317

46.7 kJ mol^{-1}



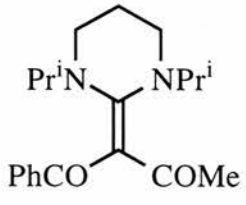
327

< 33.65 kJ mol^{-1}



328

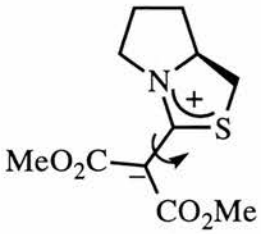
75.6 kJ mol^{-1}



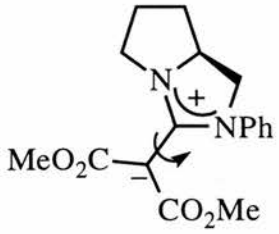
329

99.5 kJ mol^{-1}

From these studies it is clear that both **291** and **317** are most accurately represented by the charge separated structures **293** and **318** with free rotation about the single bond at room temperature.



293



318

One of the most powerful methods available to examine the state of bonding and electron distribution in compounds of this type is X-ray crystallography. A suitable single crystal of the methyl phenylacetate condensation product **294** was obtained and the structure was determined by Dr P. Lightfoot of this Department. Unfortunately crystals of **291** obtained from a wide variety of solvents proved unsuitable for X-ray diffraction.

The structure consisted of two slightly different molecules in each unit cell. The ORTEP diagram for one of these is shown in Figure 3 with selected bond lengths and angles noted. The full atomic coordinates and other data are given in Appendix 1.

The most important value is the length of the polarised double bond from which the extent of π-character can be estimated directly. The length of a typical sp^2–sp^2 double bond is 1.34 Å while for a single bond the value increases to 1.50 Å.[46] The observed value here of 1.37 Å would indicate around 80% double bond character.

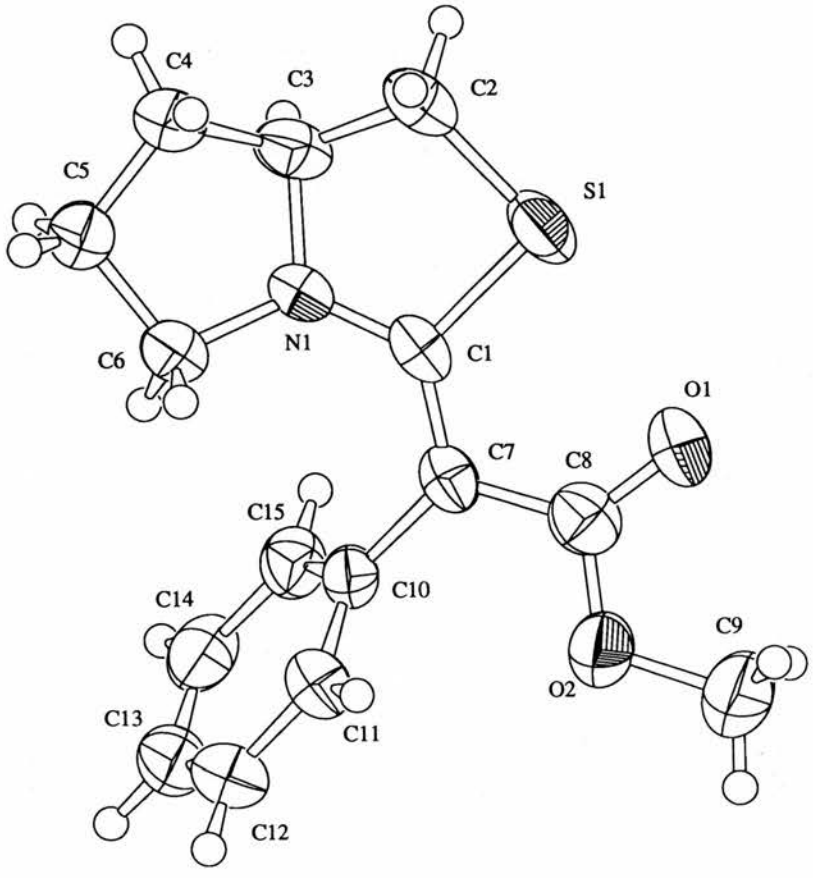
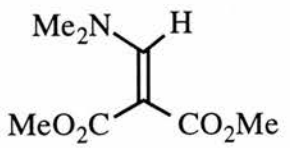


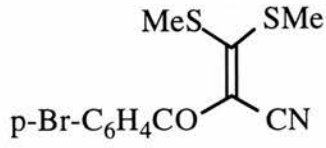
Figure 3: X-ray structure of **294.** Selected bond lengths; C(1)–S(1) 1.778, C(2)–S(1) 1.803, C(1)–N(1) 1.346, C(1)–C(7) 1.370, C(7)–C(10) 1.497, C(7)–C(8) 1.445, C(8)–O(1) 1.217 and C(8)–O(2) 1.351 Å; dihedral angles S(1)–C(1)–C(7)–C(8) 5.8, S(1)–C(1)–C(7)–C(10) 167.5, C(1)–C(7)–C(8)–O(1) 7.5 and C(1)–C(7)–C(8)–O(2) 173.3°; angle sum at C(1) 360.0 and C(7) 359.6°.

The value can also be compared with those of **330**,[95] **331**,[96] **332**,[97] **333**[98] and **334**.[99] The expected shortening of the C(1)–S(1) and C(1)–N(1)



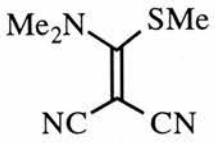
330

C=C 1.38 Å



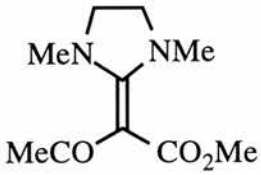
331

C=C 1.369 Å



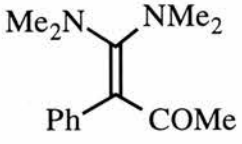
332

C=C 1.39 Å



333

C=C 1.466 Å



334

C=C 1.412 Å

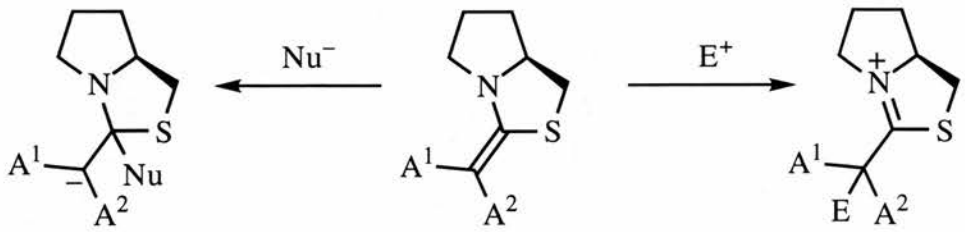
bonds can be seen by comparing them with C(2)–S(1) and C(6)–N(1) respectively when shortenings of 0.027 and 0.120 Å are evident.

The other prominant feature of the structure is the existence of the compound as the apparently more hindered *Z*-isomer. This phenomenon has been observed previously and rationalised by Sandström,[45] in terms of the relative *E* relationship of the stronger donor and stronger acceptor allowing more efficient conjugation.

6. Reactivity of thiazolidine based polarised double bond compounds

As revealed in the previous section the double bond of the compounds **335** has a highly polar character and this suggested that they could react either with nucleophiles to give **336** or with electrophiles to

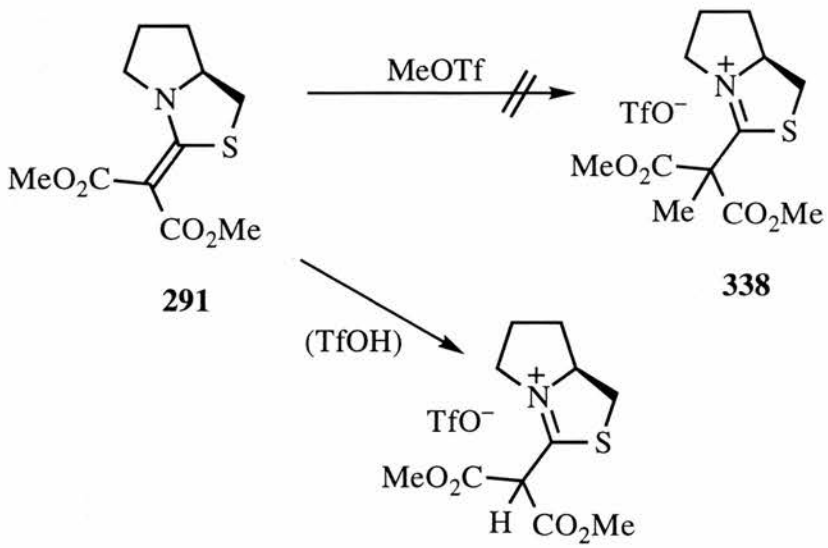
give **337**. Because of the chiral nature of **335** either of these processes



336 **335** **337**

might be expected to proceed with significant diastereoselectivity and thus form the basis of a useful method of asymmetric synthesis.

The dimethyl malonate adduct **291** was treated with methyl iodide but was recovered unchanged both at room temperature and upon heating. The same result was observed with the ethyl acetoacetate derived compound **295**. The methylation of **291** was then tried by treatment with methyl triflate at room temperature. Again the desired product **338** was not obtained but the starting material had changed. Evaporation gave oil



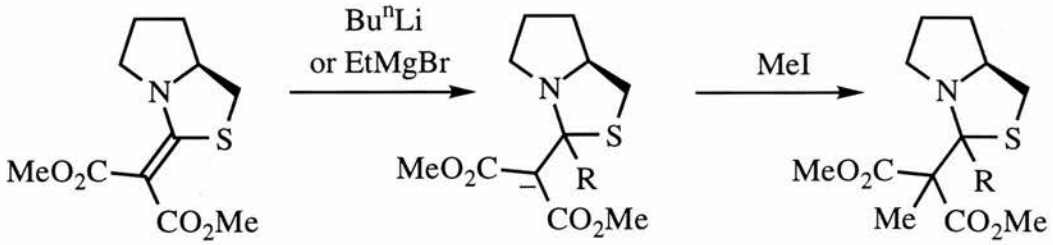
291 **338**

339

which showed some spectroscopic evidence for the protonated salt structure **339**. The ring CH gave a signal at δ_C 76.6 and, most significantly, there

was a third signal in the range δ_C 54–55 corresponding to the position expected for $CH(CO_2Me)_2$. This had apparently been formed by decomposition of the methyl triflate to give some free triflic acid which reacted with **291**. The corresponding reaction of **295** with methyl triflate also gave some reaction but the complex mixture of products could not be identified.

It was thought that addition of an organometallic reagent to **291** might occur at C-2 to give the anion **340** which could then be trapped by



291 **340** **341**

R = Bu^n, Et

an electrophile such methyl iodide to give **341**. In the event, both these attempts met with failure and **291** was recovered unchanged in each case. The degree of delocalisation of both the positive and negative charges in **291** is clearly too great to permit high reactivity with either nucleophiles or electrophiles. The corresponding reactions of the related systems such as **294** where this delocalisation is not so great may be a fruitful area for future study.

APPENDIX

X-Ray Structural Data for Compound **294**

Table 5. Atomic coordinates and B_{iso}/B_{eq} for **294**

atom	x	y	z	B_{eq}
S(1)	0.1024(2)	0.3777	-0.0683(1)	5.03(4)
O(1)	-0.0719(4)	0.3521(4)	-0.2731(3)	6.6(1)
O(2)	0.0088(4)	0.3377(3)	-0.4691(3)	5.1(1)
N(1)	0.3850(4)	0.3896(3)	-0.1420(3)	3.8(1)
C(1)	0.2397(5)	0.3802(4)	-0.1912(4)	3.5(1)
C(2)	0.2537(6)	0.3718(6)	0.0516(5)	6.3(2)
C(3)	0.4025(6)	0.4061(4)	-0.0064(5)	4.5(1)
C(4)	0.5515(6)	0.3583(5)	0.0304(5)	5.1(2)
C(5)	0.6494(6)	0.3634(5)	-0.0856(4)	4.8(1)
C(6)	0.5331(5)	0.3630(4)	-0.1967(4)	4.1(1)
C(7)	0.1976(5)	0.3722(4)	-0.3153(4)	3.5(1)
C(8)	0.0355(6)	0.3535(4)	-0.3460(5)	4.4(1)
C(9)	-0.1529(6)	0.3226(5)	-0.5055(5)	6.8(2)
C(10)	0.3088(5)	0.3912(4)	-0.4181(4)	3.7(1)
C(11)	0.3432(6)	0.3315(4)	-0.5087(5)	4.7(1)
C(12)	0.4426(7)	0.3523(5)	-0.6057(5)	5.8(2)
C(13)	0.5089(6)	0.4320(5)	-0.6125(5)	5.9(2)
C(14)	0.4769(6)	0.4918(4)	-0.5219(5)	5.1(2)
C(15)	0.3757(6)	0.4724(4)	-0.4263(5)	4.2(1)

Table 5. Atomic coordinates and B_{iso}/B_{eq} for **294** (contd.)

atom	x	y	z	B_{eq}
H(1)	0.2266	0.4059	0.1218	7.5190
H(2)	0.2685	0.3138	0.0777	7.5190
H(3)	0.6031	0.3855	0.0995	6.1180
H(4)	0.5296	0.3003	0.0512	6.1180
H(5)	0.7093	0.4147	-0.0853	5.7292
H(6)	0.7173	0.3152	-0.0899	5.7292
H(7)	0.5244	0.3071	-0.2321	4.9525
H(8)	0.5643	0.4025	-0.2594	4.9525
H(17)	0.4136	0.4659	0.0094	5.3600
H(19)	0.2986	0.2756	-0.5050	5.6576
H(20)	0.4646	0.3106	-0.6680	6.9293
H(21)	0.5763	0.4459	-0.6792	7.0313
H(22)	0.5247	0.5469	-0.5247	6.1345
H(23)	0.3518	0.5150	-0.3658	5.0812
H(29)	-0.2134	0.3719	-0.4860	8.1744
H(30)	-0.1600	0.3118	-0.5931	8.1744
H(31)	-0.1913	0.2743	-0.4612	8.1744

Table 6. Bond Lengths (Å) for **294**

atom	atom	distance	atom	atom	distance
S(1)	C(1)	1.779(4)	S(1)	C(2)	1.803(5)
O(1)	C(8)	1.217(5)	O(2)	C(8)	1.350(6)
O(2)	C(9)	1.447(6)	N(1)	C(1)	1.347(6)
N(1)	C(3)	1.474(6)	N(1)	C(6)	1.465(6)
C(1)	C(7)	1.370(6)	C(2)	C(3)	1.524(7)
C(3)	C(4)	1.520(7)	C(4)	C(5)	1.511(6)
C(5)	C(6)	1.530(6)	C(7)	C(8)	1.447(7)
C(7)	C(10)	1.497(6)	C(10)	C(11)	1.377(7)
C(10)	C(15)	1.390(8)	C(11)	C(12)	1.391(7)
C(12)	C(13)	1.366(9)	C(13)	C(14)	1.374(9)
C(14)	C(15)	1.385(7)			

Table 7. Bond Angles (°) for **294**

atom	atom	atom	angle	atom	atom	atom	angle
C(1)	S(1)	C(2)	92.7(2)	C(8)	O(2)	C(9)	115.6(4)
C(1)	N(1)	C(3)	118.3(4)	C(1)	N(1)	C(6)	127.8(4)
C(3)	N(1)	C(6)	111.7(4)	S(1)	C(1)	C(7)	123.0(4)
S(1)	C(1)	N(1)	109.5(3)	S(1)	C(2)	C(3)	106.7(4)
N(1)	C(1)	C(7)	127.4(4)	N(1)	C(3)	C(4)	103.6(4)
N(1)	C(3)	C(2)	105.6(4)	C(2)	C(3)	C(4)	115.3(5)
C(3)	C(4)	C(5)	103.9(4)	C(4)	C(5)	C(6)	105.7(4)
N(1)	C(6)	C(5)	104.1(4)	C(1)	C(7)	C(8)	117.9(4)
C(1)	C(7)	C(10)	122.1(4)	C(8)	C(7)	C(10)	119.7(4)
O(1)	C(8)	O(2)	120.2(5)	O(1)	C(8)	C(7)	126.3(5)
O(2)	C(8)	C(7)	113.5(4)	C(7)	C(10)	C(11)	122.0(5)
C(7)	C(10)	C(15)	119.7(5)	C(11)	C(10)	C(15)	118.3(5)
C(10)	C(11)	C(12)	120.5(6)	C(11)	C(12)	C(13)	120.8(6)
C(12)	C(13)	C(14)	119.2(5)	C(13)	C(14)	C(15)	120.5(6)
C(10)	C(15)	C(14)	120.6(5)				

Table 8. Torsion Angles (°) for **294**

atom	atom	atom	atom	angle	atom	atom	atom	atom	angle
S(1)	C(1)	N(1)	C(3)	-7.2(6)	S(1)	C(1)	N(1)	C(6)	154.5(5)
S(1)	C(1)	C(7)	C(8)	-5.4(8)	S(1)	C(1)	C(7)	C(10)	167.9(4)
S(1)	C(2)	C(3)	N(1)	-27.1(6)	S(1)	C(2)	C(3)	C(4)	-140.8(4)
O(1)	C(8)	O(2)	C(9)	2.1(8)	O(1)	C(8)	C(7)	C(1)	7.5(10)
O(1)	C(8)	C(7)	C(10)	-166.0(6)	O(2)	C(8)	C(7)	C(1)	-173.3(5)
O(2)	C(8)	C(7)	C(10)	13.2(8)	O(3)	C(23)	O(4)	C(24)	2.7(9)
N(1)	C(1)	S(1)	C(2)	-9.1(5)	N(1)	C(1)	C(7)	C(8)	173.5(5)
N(1)	C(1)	C(7)	C(10)	-13.2(10)	N(1)	C(3)	C(4)	C(5)	31.5(6)
N(1)	C(6)	C(5)	C(4)	20.1(7)	C(1)	S(1)	C(2)	C(3)	21.4(5)
C(1)	N(1)	C(3)	C(4)	144.7(5)	C(1)	N(1)	C(3)	C(2)	23.1(7)
C(1)	C(7)	C(10)	C(11)	124.1(6)	C(1)	N(1)	C(6)	C(5)	-162.7(6)
C(2)	S(1)	C(1)	C(7)	170.0(6)	C(1)	C(7)	C(10)	C(15)	-58.4(7)
C(2)	C(3)	C(4)	C(5)	146.3(5)	C(2)	C(3)	N(1)	C(6)	-141.5(5)
C(3)	N(1)	C(6)	C(5)	0.0(6)	C(3)	N(1)	C(1)	C(7)	173.8(6)
C(4)	C(3)	N(1)	C(6)	-19.9(6)	C(3)	C(4)	C(5)	C(6)	-32.2(7)
C(7)	C(8)	O(2)	C(9)	-177.3(5)	C(6)	N(1)	C(1)	C(7)	-24.5(9)
C(7)	C(10)	C(15)	C(14)	-179.0(4)	C(7)	C(10)	C(11)	C(12)	177.6(5)
C(8)	C(7)	C(10)	C(15)	114.8(6)	C(8)	C(7)	C(10)	C(11)	-62.7(7)
C(10)	C(15)	C(14)	C(13)	2.1(8)	C(10)	C(11)	C(12)	C(13)	0.5(9)
C(11)	C(12)	C(13)	C(14)	0.3(10)	C(11)	C(10)	C(15)	C(14)	-1.3(8)
C(12)	C(13)	C(14)	C(15)	-1.6(9)	C(12)	C(11)	C(10)	C(15)	0.0(8)

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