Synthetic studies towards methylene cyclic sulfamidites and sulfamidates

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METHYLENE CYCLIC SULFAMIDITES

AND

SULFAMIDATES

By

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for the award of

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Abstract

Chapter one provides a general introduction, which reviews relevant literature concerning the preparation and chemistry of cyclic sulfamidites and sulfamidates. A comparison is drawn between these compounds and the analogous cyclic sulfites, cyclic sulfates, epoxides and aziridines, in terms of their chemistry. Work undertaken by other members of the research group in this area is discussed and a review of the preparation of allene oxides and methyleneaziridines is given. Project aims, in terms of the preparation of a methylene cyclic sulfamidate are discussed in relation to the successful preparation of a methylene cyclic sulfite within our group.

Chapter two describes the preparation of a simple cyclic sulfamidate and goes on to detail three routes undertaken towards the synthesis of novel 4-methylene cyclic sulfamidates. The first approach involved subjecting a β-hydroxy imine to the conditions used to convert an amino alcohol to a cyclic sulfite, which unexpectedly did not result in formation of the desired 4-methylene cyclic sulfamidite. An alternative route for the preparation of 4-methylene cyclic sulfamidites was explored using an elimination reaction employing selenoxides to introduce the double bond as the final synthetic step. We successfully completed the synthesis of two precursors possessing different substituents attached to the selenium atom, although neither could be successfully eliminated to the desired methylene cyclic sulfamidite.

Chapter three describes the detailed experimental work undertaken in this thesis.

Acknowledgements

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Contents

Abbreviations

Ar	aryl
Bn	benzyl
C.I.	chemical ionisation
CSA	camphor-10-sulphonic acid
DME	dimethoxy ethane
DMF	dimethyl formamide
e.e.	enantiomeric excess
E.I.	electron impact
^{i}Pr	isopropyl
IR	infra red
m-CPBA	3-chloroperoxybenzoic acid
Me	methyl
M.P.	melting point
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
RT	room temperature
^{t}Bu	*tert*-butyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetra-*n*-propyl ammonium perruthenate
Ts	Tosyl
PTC	phase transfer catalyst

CHAPTER 1

INTRODUCTION

1.1 An Introduction to Cyclic Sulfamidites and Sulfamidates

Cyclic sulfamidites (oxathiazolidine-S-oxides) **1** and cyclic sulfamidates

(oxathiazolidine-S,S-dioxides) **2** are closely related in structure to cyclic sulfites

(oxathiolanes) **3** and cyclic sulfates (dioxathiolanes) **4**. This relationship has been

exploited during attempts to prepare 4-methylene cyclic sulfamidites using the same

basic chemistry as that employed to successfully prepare methylene cyclic sulfites.
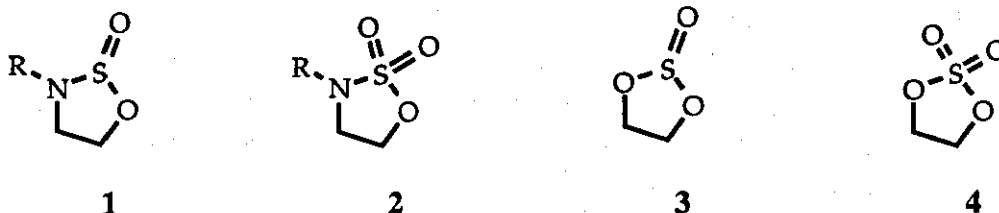
The first reported preparation and analysis of cyclic sulfamidates came in 1968 when

Deyrup and Moyer isolated a range of different analogues, whilst trying to prepare

aziridines.[1]   The basic method of preparation set out then is still the most commonly

used route to simple cyclic sulfamidates. Despite the fact that they were first isolated

nearly 30 years ago they have only recently begun to be recognised as a versatile and

important class of compounds.

1.2 Synthesis of Cyclic Sulfamidites and Sulfamidates

The most common route to cyclic sulfamidates is to first make the corresponding

cyclic sulfamidite **1**, and then oxidised it to the cyclic sulfamidate **2**. Direct routes to

the dioxygen species **2** have been investigated, but none have yet proved as generally

effective as the route *via* the sulfamidite. Cyclic sulfamidites can be formed in very

good yields from an amino alcohol and thionyl chloride using a slight excess of

triethylamine at -78 °C, [1,2,3,4,5] or another proton acceptor such as pyridine at 0°C

(Scheme 1). [6,7,8] Various solvents have been utilised, such as hexane, benzene, THF,

and more recently, dichloromethane.
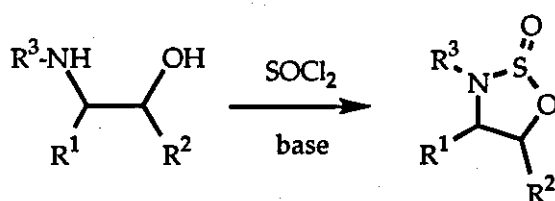
Scheme 1

Gautun and Carlson used an optically active amino alcohol to generate the optically active serinol based cyclic sulfamidite **8** (Scheme 2). Homochiral glycidol was reacted with benzyl isocyanate to produce optically active cyclic carbamate **5**. Unfortunately they were unable to determine the e.e of **5**, but comparison with optical data reported by Katsumura showed there to be little or no racemisation.[9] Mild benzylation conditions were required for the preparation of **6** because racemisation was observed when sodium hydride was employed. Alkaline hydrolysis of the oxazolidine **6** gave the amino alcohol **7**, which upon treatment with thionyl chloride gave two diastereomeric sulfamidites **8** which were inseparable by column chromatography. The overall yield for this sequence was good (60-66%) although the optically purity of **8** was not determined.[5]
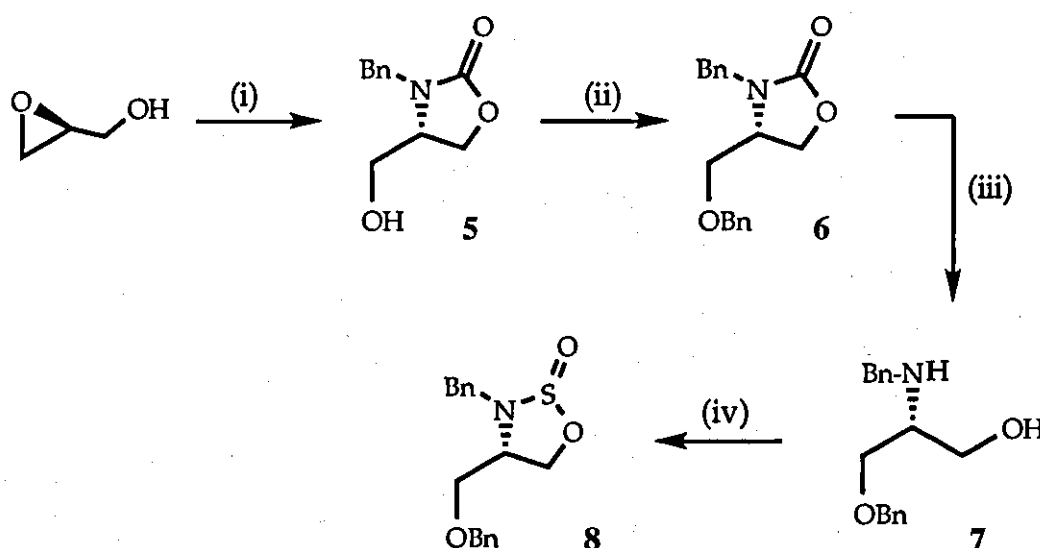
Scheme 2. *Reagents and Conditions*: (i) BnNCO, Et$_3$N, CH$_2$Cl$_2$, reflux, 18h, 78%; (ii) Et$_3$N, BnBr, DMF, 120°C, 93%; (iii) NaOH, H$_2$O, EtOH, reflux, 87%; (iv) SOCl$_2$, CH$_2$Cl$_2$, -78°C, 95%.

The formation of cyclic sulfamidite is presumed to proceed *via* the chlorosulfinyl derivative shown in Scheme 3. It seems likely that the amine lone pair attacks first, rather than the hydroxyl group since the secondary amine is the more nucleophilic.
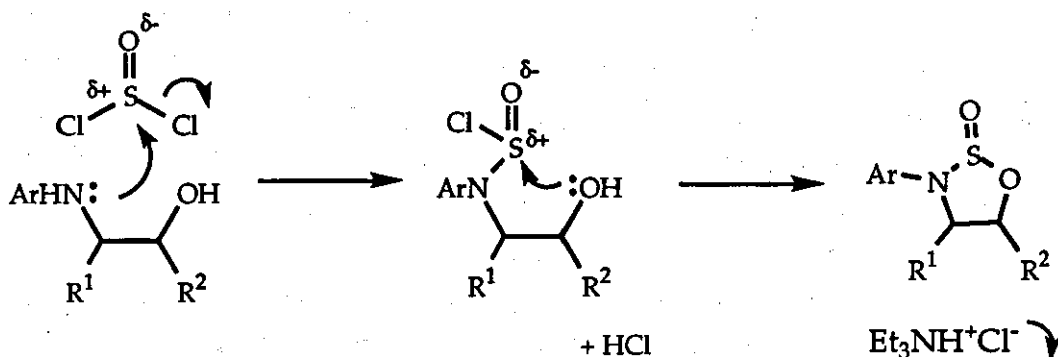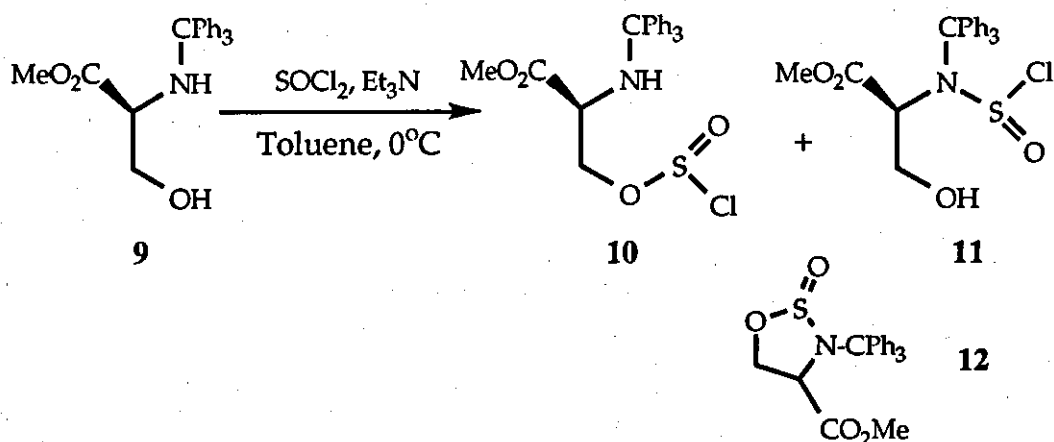

Scheme 3

However, Pilkington and Wallis found that when they used a system of $SOCl_2$ and Et_3N in toluene at 0^oC to convert the *N*-trityl serine methyl ester **9** into the corresponding cyclic sulfamidite **12**, they formed a mixture of three products **10, 11,** and **12**, instead of just the desired cyclic sulfamidite **12** (Scheme 4).[7] Interestingly, when a system of $SOCl_2$ and pyridine in THF at 0^oC was used **12** was formed as the sole product. The individual products were not completely separable by chromatography, but it was established that they corresponded to the *O*-chlorosulfinyl derivative **10**, *N*-chlorosulfinyl derivative **11**, and the cyclic sulfamidite **12** in a ratio of 2:2:1. This result suggests that, at least in this instance, when the N atom is sufficiently sterically hindered, initial attack on the thionyl chloride may involve the hydroxyl group.
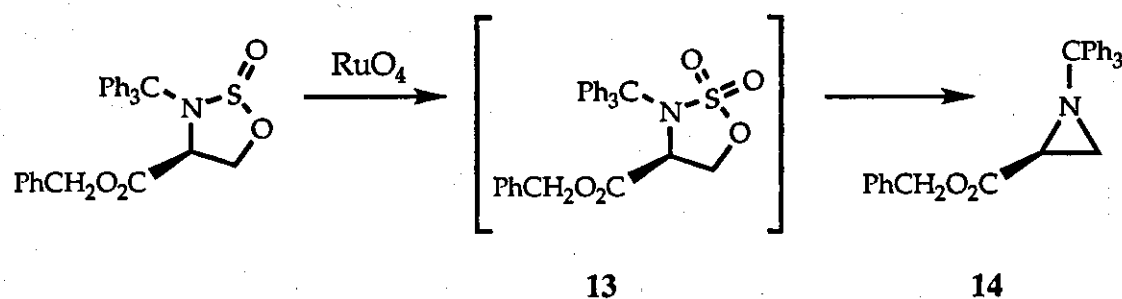
Scheme 4

Cyclic sulfamidites are formed as mixtures of two diastereoisomers, as a result of asymmetry at sulfur, when the molecule contains an additional stereocentre at one of the ring positions. Oxidation of a mixture of the diastereomeric sulfamidites to the corresponding sulfamidate results in the formation of a single product.

Oxidation of cyclic sulfamidites has been examined using many different reagents, the most successful seeming to be a procedure developed by Sharpless [10] involving RuCl$_3$ and sodium periodate as used by White and Garst, [4] Alker *et al*, [2] and Pilkington and Wallis. [7] Other oxidants have been used including *m*-CPBA and TPAP/NMO,[4] but these give substantially lower yields than the ruthenium (III)/periodate system.[4] Potassium permanganate has been successfully used.[2] Interestingly it is reported that this oxidant gives poor yields and impure products when used to oxidise the corresponding cyclic sulfites to sulfates.[10] In 1981, Denmark (1,3-cyclic sulfites), [11] and in 1983, Lowe (1,2-cyclic sulfites)[12] reported that the oxidation step was much cleaner when a stoichiometric amount of RuO$_4$ was used, but unfortunately this system was too expensive for preparative work. In 1981, Gao and Sharpless reported that, for cyclic sulfites, a catalytic RuO$_4$ system was highly active for the same transformation, involving as little as 1 part in 1500 of the ruthenium catalyst, and as short as 1 hour reaction time (this catalytic system involves the *in situ* generation of RuO$_4$ from RuCl$_3$.H$_2$O and sodium periodate).[11]

RuCl$_3$.3H$_2$O / sodium periodate seems to be the most common system currently being used to successfully oxidise many cyclic sulfamidites, however this oxidation is not

always feasible either due to the presence of other oxidisable groups in the substrate, or because the resulting sulfamidate is too reactive, or too unstable to be isolated. For instance, the benzyl ester substituted cyclic sulfamidate **13** is often unstable to loss of SO_3 during preparation from the cyclic sulfamidite by ruthenium (VIII) oxidation and gives the aziridine **14** (Scheme 5).[7]

Scheme 5. *Reagents and Conditions*: $Ru(III)Cl_3.xH_2O$, $NaIO_4$, H_2O, Acetonitrile, 0^oC, RT.

There have been many attempts to devise a one step synthesis in which the dioxide is formed directly using sulfuryl chloride.[4] The successful attempts include the formation of the cyclic sulfamidate of (*S*)-prolinol **15**, by Alker *et al*, [2] which was formed in 63% yield (Scheme 6), which compared favourably to 57% overall yield for the two step process *via* the cyclic sulfamidite.
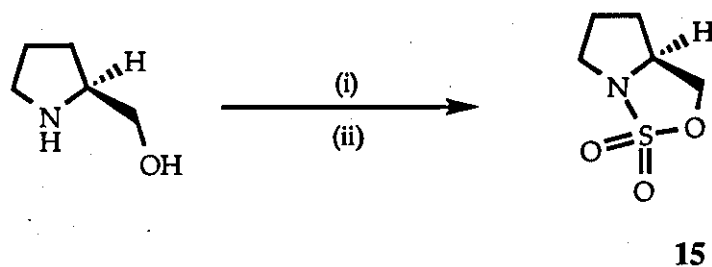
Scheme 6. *Reagents and Conditions*: (i) Et_3N, SO_2Cl_2, CH_2Cl_2, -78^oC, 3h (ii) RT, 10h

1.3 Synthesis of Cyclic Sulfites and Sulfates

1,2-diols are converted to the corresponding cyclic sulfite *via* the same route that 1,2-amino alcohols are converted to the corresponding cyclic sulfamidite (Scheme 7).[13,14] Dichloromethane is the favoured solvent to improve the yield.[15] Many cyclic sulfites

have been conveniently prepared by this method, using thionyl chloride, [13, 14, 16, 17] or

sulfur tetrafluoride.[18, 19, 20, 21, 22] The mechanism is the same as that for the

formation of the cyclic sulfamidites, with triethylamine being present to remove the

HCl generated, especially when there are acid labile substituents present. The

favoured oxidant for the formation of the cyclic sulfate is $RuCl_3.H_2O$ / $NaIO_4$ as used

for the oxidation of cyclic sulfamidites to sulfamidates.[13, 14]
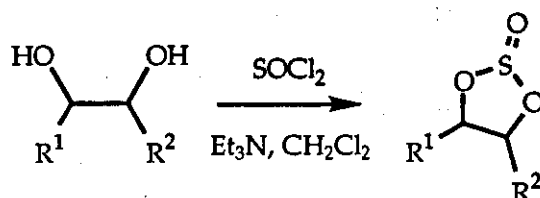
Scheme 7

1.4 Physical and Spectroscopic Characteristics of Cyclic Sulfamidites and Sulfamidates

Cyclic sulfamidites and sulfamidates are generally stable oils. Cyclic sulfamidites

show the characteristic intense S=O stretch at 1150-1165 cm^{-1}. The bicyclic

analogues reported by Cuthbert and Lowe have their S=O stretch at a slightly higher

value of 1165 and 1170 cm^{-1}, which they attributed to the strain caused by the ring

fusion.[6] The S=O stretching band is intense due to the large dipole moment of the

S=O bond. Cyclic sulfamidates posses the characteristic SO_2 symmetric and

asymmetric stretching frequencies around 1340 and 1180 cm^{-1}, which are not, of

course, observed in the cyclic sulfamidites. Cyclic sulfamidites often show weak

molecular ions in their mass spectrum, because of the facile loss of SO_2.

It should be noted that cyclic sulfamidites contain a stereocentre and can exist as

diastereoisomers when the molecule possesses another stereocentre (Fig. 1).

The observed diastereoisomerism in cyclic sulfamidites can be attributed solely to the

anisotropy of sulfur, rather than nitrogen, since mixtures of the diastereoisomers,

when oxidised to the sulfamidate, are always converted into a single product, as

expected. This diastereoisomerism is also observed in cyclic sulfites.
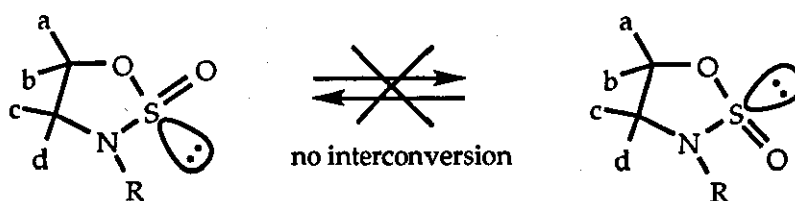
Fig. 1 Diastereoisomerism in cyclic sulfamidites.

This diastereoisomerism has a marked effect on the ^{1}H NMR spectrum of cyclic sulfamidites. Ring substituents which lie *cis* to the sulfoxide (S=O) bond are deshielded and so will appear further downfield than *trans* substituents.[1, 23] Deyrup and Moyer were able to make assignments for a range of analogues of the cyclic sulfamidite **16**.[1] ^{1}H NMR data for cyclic sulfamidites **16a** and **16b** are shown in Table 1. Deyrup and Moyer assigned the *cis* configuration of the methyl group to the isomer which showed the most deshielded methyl protons, *i.e.* the isomer with the methyl protons furthest downfield. This is supported by the position of the H_b proton, which must be *trans* if the methyl is *cis*, *i.e.* further upfield.
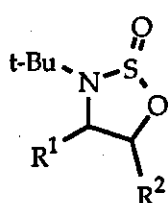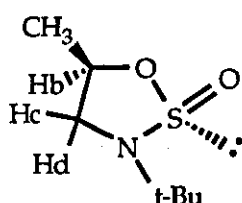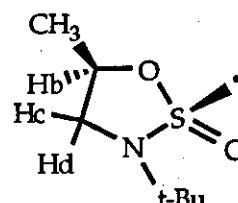
| **16** | **16a (methyl *cis*)** | **16b (methyl *trans*)** |

Compound	δ/ppm H_b	δ/ppm CH_3	δ/ppm H_c/H_d	δ/ppm t-Bu	Assignment of CH_3
16a	4.53	1.53	2.7-3.7	1.33	*cis*
16b	5.08	1.37	2.7-3.7	1.33	*trans*

Table 1

1.5 Reactions of Cyclic Sulfamidites and Sulfamidates

1.5.1 Nucleophilic Ring Opening

The chemistry of cyclic sulfamidates is dominated by regiospecific nucleophilic

attack at one of the ring positions leading to ring opening (Scheme 8). Subsequent

removal of the SO_3 moiety is often accomplished by hydrolysis with 20% H_2SO_4,[4, 25]

although aqueous base has been used.[2, 26]
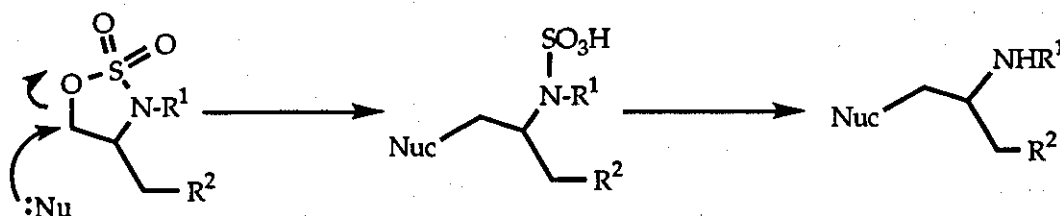
Scheme 8

For monosubstituted cyclic sulfamidates attack usually occurs at the unsubstituted

ring position. Gautun and Carlson investigated nucleophilic attack on optically active

cyclic sulfamidite **8**, with cyanide anions.[5] In each case, nitrile **19a** was produced as

a result of ring opening. With NaCN, or LiCN in DMF complete racemization of the

product was observed. The formation of the racemate was assumed to be due to the

involvement of the relatively acidic protons α to the electron withdrawing nitrile

group (Scheme 9).
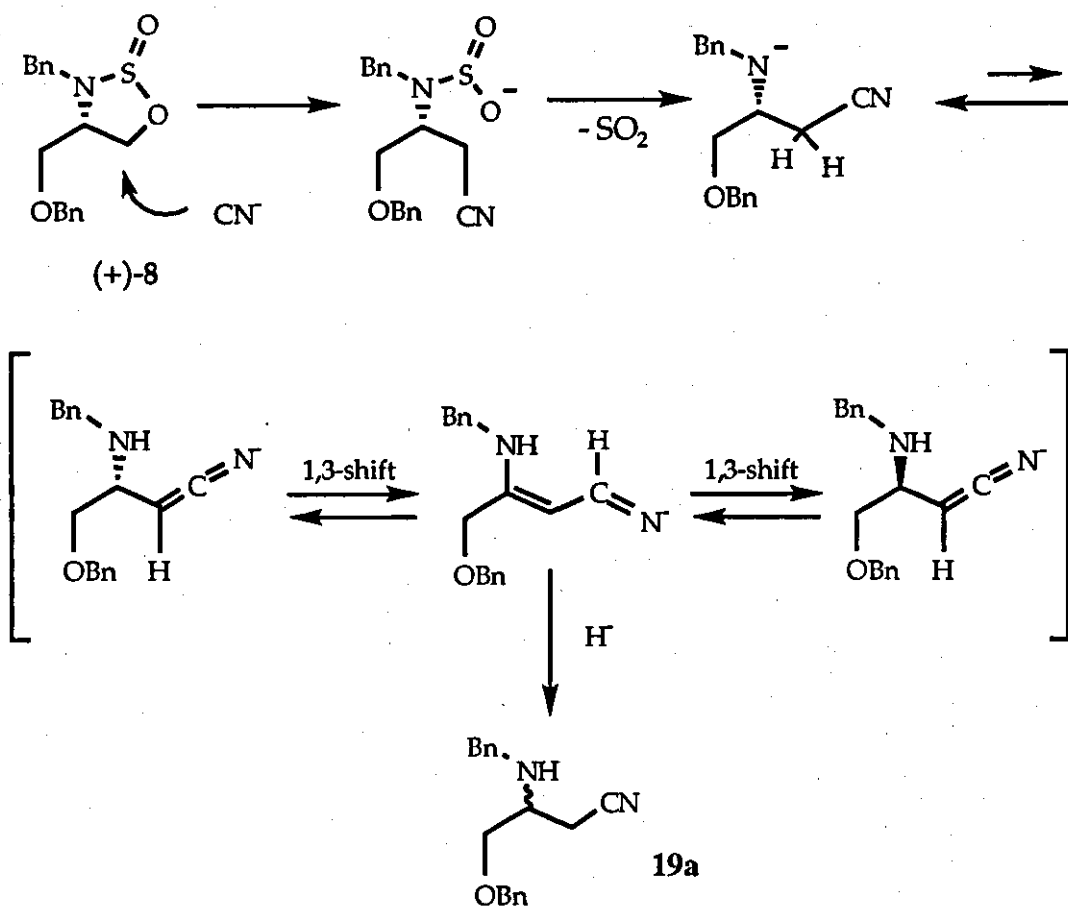
Scheme 9. *Reagents and Conditions*: NaCN or LiCN, DMF, 110°C.

1.5.2 Nucleophilic attack at the Sulfur Atom

Cyclic sulfamidites and sulfamidates contain another electrophilic centre susceptible

to attack by nucleophiles, the electropositive sulfur atom. Gautun and Carlson

studied the regioselectivity of nucleophilic attack on cyclic sulfamidites (Scheme

10).[5] Cyclic sulfamidite **17** was reacted with a range of nucleophiles to give a

mixture of products, **18** and **19**, resulting from attack at the sulfur position, or the C-5

position of the sulfamidite ring, respectively. Cyanide and azide anions which are

relatively soft nucleophiles attack regioselectively at the C-5 position to give

exclusively products **19a** and **19b** respectively, in high yield, whereas benzyloxy

anion gave a mixture of **18** and **19c** in a 68:32 ratio, indicating a degree of attack at

the sulfur atom. Similar selectivity has been observed in cyclic sulfites, where harder,

less polarizable nucleophiles have demonstrated an increased reactivity towards the

harder sulfur atom, relative to the softer carbon atom.[5]
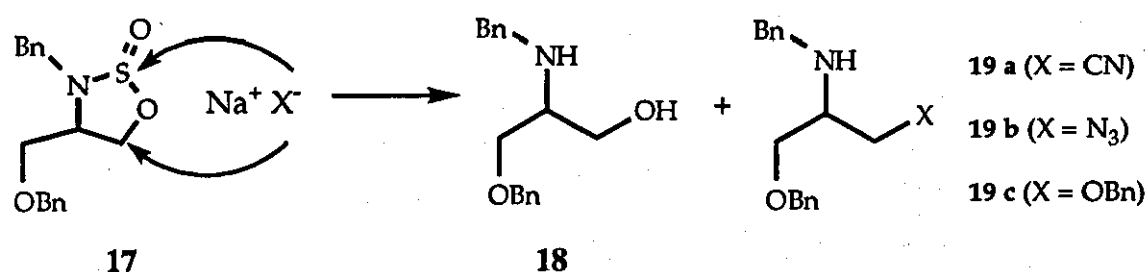
Scheme 10. *Reagents and Conditions*: **19a**: NaCN, DMF, 120°C, 10h, 80%; **19b**: NaN3, DMF,

120°C, 6h, 90%; **18** and **19c**: BnOH, NaH, DMF, 120°C, 8h, 24% .

Anderson *et al* reacted cyclic sulfamidate **20** with sodium hydroxide in aqueous

acetonitrile (Scheme 11).[24] Partial saponification gave a mixture of **20** and the

disodium salt **21**, which upon treatment with aqueous acid transformed **21** to

sulfonamide **22** by loss of sulfate ion. In this particular case, they found that the

initial cleavage occurred at the endocyclic S-N bond, the tosyl group being capable of

accepting negative charge in the transition state, thus forming a more stable

intermediate than if the endocyclic S-O bond were to cleave.[24] However, when the

tosyl is replaced with a methyl group the rate of reaction is decreased by more than

1700 fold, and presumably, in this instance, the endocyclic S-O cleavage occurs first,

since a phenoxide ion is a better leaving group than an anilide ion. In reactions

involving other bicyclic sulfamidates such as **23**, it was found that no reaction would

occur with nucleophiles such as phenyl magnesium bromide or lithium aluminium

hydride, however *N*-sulfonation transforms the nitrogen into a much better leaving

group and so *N*-benzenesulfonated **23** undergoes endocyclic S-N bond cleavage, with

the exocyclic S-N bond remaining intact.

20 → (i) → **21** → (ii) → **22**
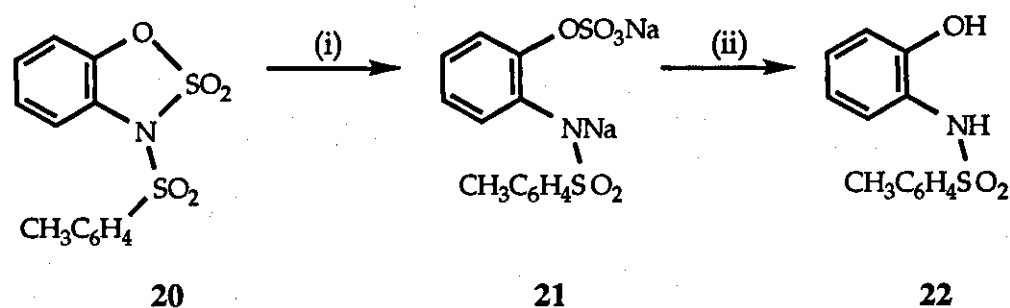
Scheme 11. *Reagents and Conditions*: (i) NaOH, acetonitrile/95% EtOH (3:2 v/v), 3h; (ii) HCl, H_2O
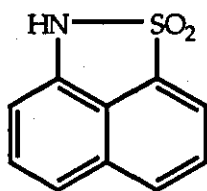
23

Anderson *et al* found that when cyclic sulfamidate **20**, was treated with various nucleophiles there were two observed reaction sites.[24] Some nucleophiles attacked the endocyclic sulfonyl sulfur, resulting in cleavage of the endocyclic N-SO_2 bond, and some attacked the exocyclic tosyl sulfur atom, resulting in cleavage of the exocyclic N-SO_2 bond (Table 2).

Nucleophile	Observed Reaction Site
HO^-	endocyclic sulfonyl sulfur
$MeNH_2$	endocyclic sulfonyl sulfur
$^tBuNH_2$	endocyclic sulfonyl sulfur
PhLi	exocyclic sulfonyl sulfur
MeLi	exocyclic sulfonyl sulfur
F^-	exocyclic sulfonyl sulfur
MeO^-	endocyclic and exocyclic sulfur

Table 2

Attack at the exocyclic sulfonyl sulfur was explained as a product of the relative acidity of the sulfamidate unit **24**, which is expected to be quite acidic, thus it's

conjugate base would act as a good leaving group, hence promoting attack at the exocyclic sulfonyl sulfur.
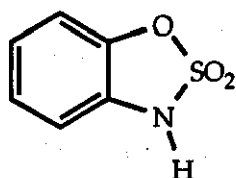
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1.6 Synthetic Applications of Cyclic Sulfamidites and Sulfamidates

Returning to the chemistry of saturated cyclic sulfamidates, the main areas of interest have been regiospecific nucleophilic ring opening, which can lead to a variety of products, depending on the substitution of the starting sulfamidate. One of the more useful of these, involves sulfamidates containing a carboxylic acid derivative, leading to the formation of β-functionalised α-amino acids.

Baldwin, Spivey and Schofield examined the ring opening of the cyclic sulfamidate **25**, derived from serine, using several nucleophiles, such as H_2O (**26a**), N_3^- (**26b**), SCN^- (**26c**), pyrazole (**26d**), and CN^- (**26e**), and found that substitutions occurred best under acidic or neutral conditions and resulted in the formation of a number of β-functionalised α-amino acids **26**, with yields ranging from 55 % (pyrazole) to 93 % (N_3^-) (Scheme 12).[25]

25   **26**
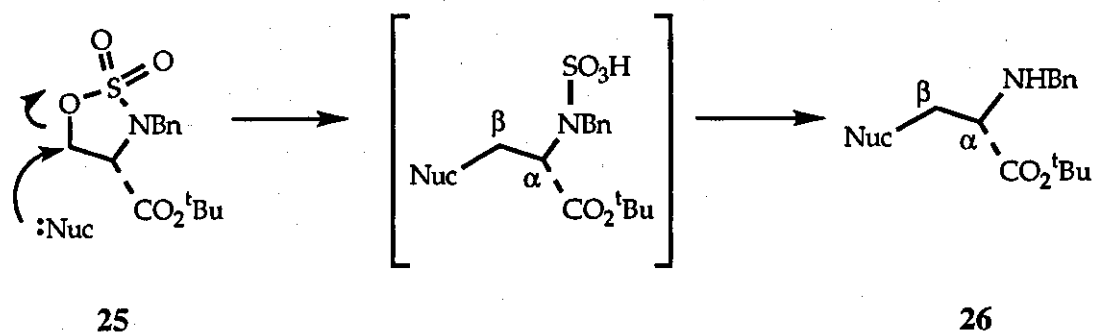
Scheme 12. *Reagents and Conditions*: **26a**: 2.0 M HCl:dioxane (1:1), 14h, 0-20°C, 63%; **26b**: NaN_3 (2 eq), acetone:water (1:1), 12h, 20°C, 93%; **26c**: NH_4SCN (2 eq), DMF, 12h, 20°C, 91%; **26d**: pyrazole (5 eq), DMF, 11h, 60°C, 55%; **26e**: NaCN (2eq), DMF, 12h, 20°C, 82%.

Zubovics *et al* reported the nucleophilic substitution of cyclic sulfamidates with secondary amines, under forcing conditions to yield diamines (Scheme 13).[26]
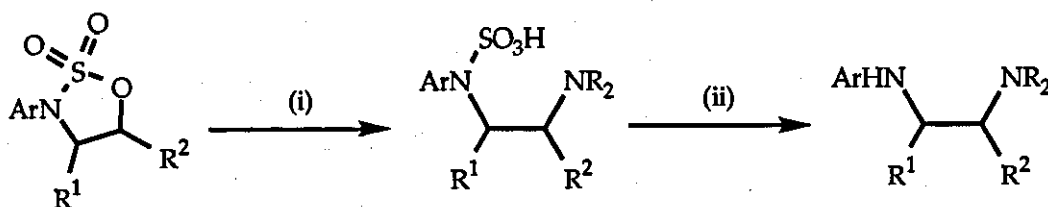

Scheme 13 *Reagents and Conditions*: (i) EtOH, R_2NH, 130°C, steel bomb, 3h; (ii) aq. NaOH

Alker *et al*, whilst investigating the reactions of the cyclic sulfamidate derived from S-prolinol **15**, found that attack by a range of nucleophiles such as MeMgBr, PhLi, MeONa, under a variety of conditions were unsuccessful.[2] However, refluxing **15** with a secondary amine in chloroform afforded a selection of diamines **27a-d** which have found useful applications as chiral bases, and also for complexation with hydride reagents to obtain enantioselective reducing agents. (Scheme 14).[2] Alker *et al* extended this procedure to successfully prepare 2-(methoxymethyl)pyrrolidine **28**.

27a (R = Et);

27b (R = -(CH$_2$)$_4$-);

27c (R = -(CH$_2$)$_5$-);

27d (R = -(CH$_2$)$_2$O(CH$_2$)$_2$-)
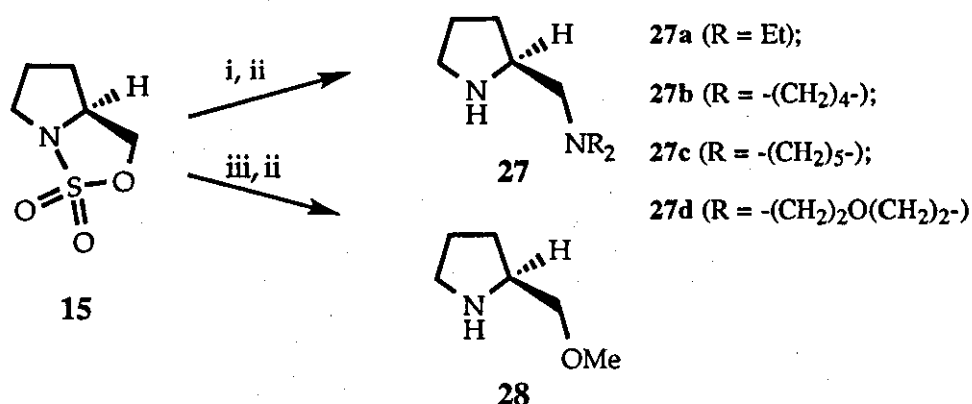
Scheme 14. *Reagents and Conditions*: (i) R_2NH, CHCl$_3$, TFA (1 drop), reflux 24h; (ii) 2M aq. NaOH, 90°C, 1h; (iii) MeOH, TFA (1 drop), reflux 48h.

Cyclic Sulfamidites have found useful applications, as antibiotics. In the search for new families of antibacterial agents, a lot of interest was shown in the late 1980's and early 1990's in the possibility of replacing the β-lactam ring in the β-lactam

antibiotics with some other functionality. Diastereomeric analogues of penicillanic acid **29** have been synthesised in which the β-lactam ring has been replaced with a basic cyclic sulfamidite ring **30**.[6, 8] The cyclic sulfamidate was not prepared as it was likely that the presence of the two oxygen atoms outside the ring would probably sterically preclude the molecule from binding effectively to the enzyme active site. Unfortunately these compounds proved to be unstable in aqueous solution, and so are unsuitable for use as antibacterial agents. The ring fusion in the bicyclic analogues greatly increases their reactivity, which must be moderated if they are to be useful antibacterial agents. Monocyclic sulfamidites, however, are stable in neutral aqueous solution (although hydrolysed in acidic or basic media). It has been shown, that monocyclic sulfamidites **31** and **32** are effective inhibitors of the growth of the growth of a number of bacteria, including *Staphylococcus aureus* and *Escherichia coli*, among others.[6, 27]
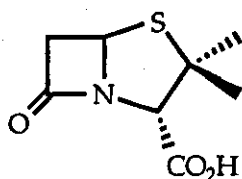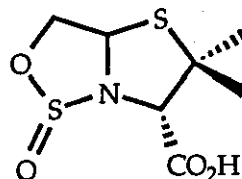
29   **30**
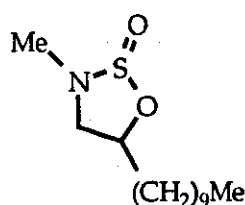
31   **32**

1.7 The Relationship Between Aziridines, Epoxides, Cyclic Sulfates and Cyclic Sulfamidates.

Aziridines are saturated three-membered hetrocycles containing one nitrogen atom. They were first synthesised in 1888 by Gabriel.[28] Like other three-membered rings such as cyclopropanes and epoxides, aziridines are highly strained. This fact,

combined with the fact that the carbon-nitrogen bonds are polarised, renders them susceptible to the ring opening reactions that dominate their chemistry, and 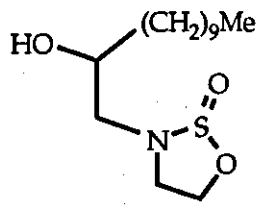that of the chemistry of the epoxides. Given the relationship between epoxides and cyclic sulfates there is an analogous relationship between aziridines and cyclic sulfamidates. The ring opening reactions of all four classes of compounds having marked similarities.

1.7.1 Cyclic Sulfates as Epoxide like Synthons

As with cyclic sulfamidates, cyclic sulfates have been investigated extensively recently, and it has been discovered that they and epoxides have many similarities in their properties.[10, 13, 29] Cyclic sulfites have become popular because of developments in the asymmetric synthesis of diols.[30] Both cyclic sulfates and epoxides are highly susceptible to nucleophilic attack, and offer protection of the functionalised carbon atom, since nucleophilic attack is usually directed at the least hindered position. These two properties have led to significant roles in organic synthesis.

In all cyclic sulfate ring openings, the first formed product is the β-sulfate **33**, which can be hydrolysed to the β-hydroxy compound **34** by treatment with a two phase mixture of ether and 20% sulphuric acid or a catalytic amount of H_2SO_4 (Scheme 15).[14, 10] In this sense, cyclic sulfates are synthetically equivalent to epoxides. Attack by a nucleophilic species giving the same product **34**. Nucleophilic attack occurs, usually, at the least hindered or unsubstituted carbon atom for both epoxides and cyclic sulfates, although there are exceptions to this rule.
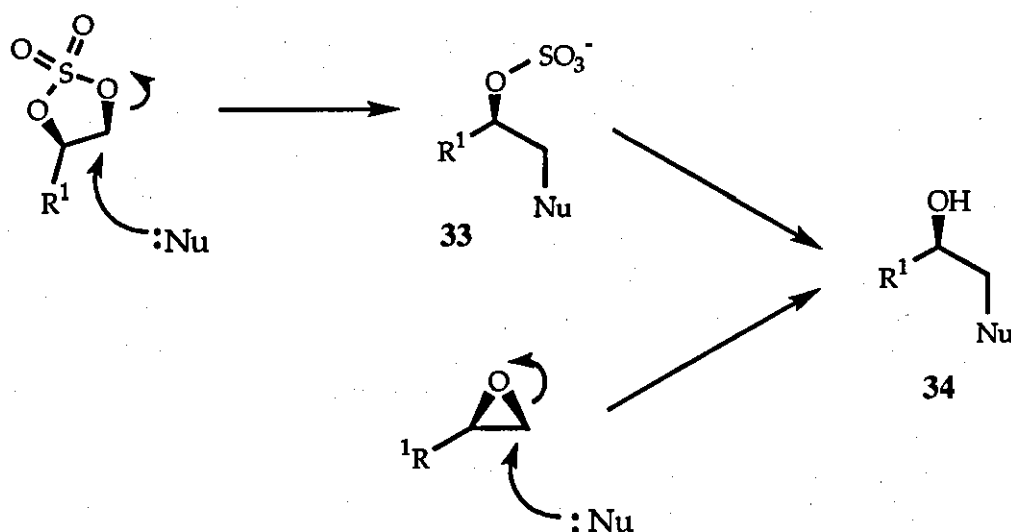
Scheme 15

Unlike the β-hydroxyl group generated in epoxide openings, the corresponding β-sulfate moiety, as in **33** is still a leaving group and, in certain situations double substitutions occur. For example cyclic sulfate **35** affords the cyclopropane **36** as a consequence of this double nucleophilic displacement, when treated with malonate anion (Scheme 16).[10] This suggests a variety of useful transformations for cyclic sulfates that cannot be accomplished using the corresponding epoxide.
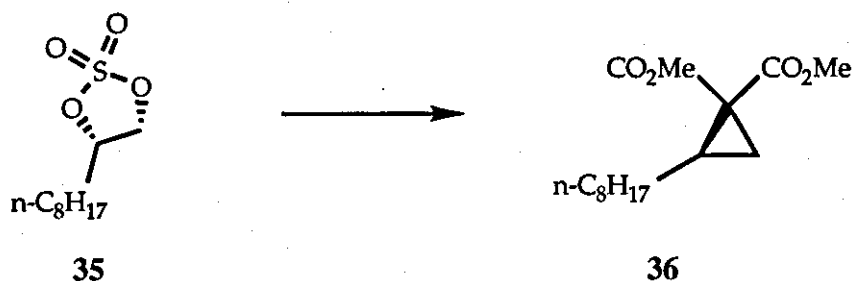
Scheme 16. *Reagents and Conditions:* NaH, $CH_2(CO_2Me)_2$, DME, reflux.

Whilst the reactivity of cyclic sulfates and epoxides towards nucleophiles is similar in nature, it can be very different in selectivity. Nucleophilic attack at the unfunctionalised β-carbon does not always follow for either species. Cyclic sulfates such as **37**, that have an α-carbonyl substituent, can react with a variety of nucleophiles with apparent complete selectivity for attack at the α-position (Scheme 17), even in cases where there is no substitution at the β-position.[10, 29] This is in

contrast to epoxides, which show no preference in such circumstances. It should be noted that cyclic sulfate **37**, when treated with R₄NX nucleophile in acetone gives a mixture of regioisomers.
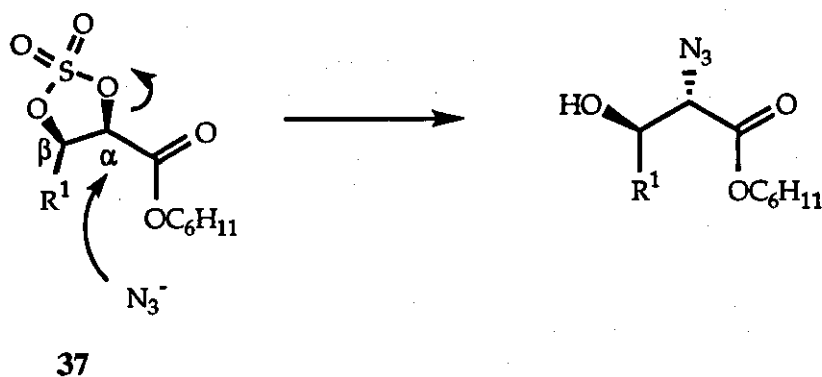
Scheme 17. *Reagents and Conditions*: (i) NaN_3, acetone/H_2O; (ii)H_2SO_4.

By contrast, the ethyl ester of the corresponding epoxide, under different conditions reacts with azide exclusively at the β-position (Scheme 18).[29]
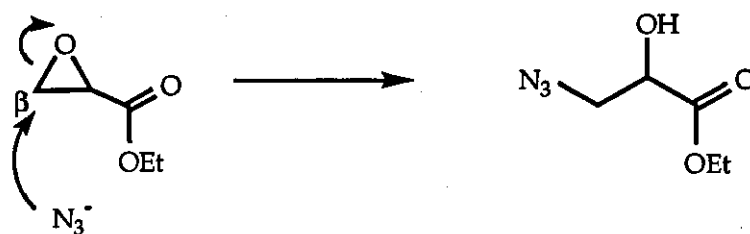
Scheme 18. *Reagents and Conditions*: NaN_3, H_2O, PTC.

It can be seen that in certain cases there are no hard and fast rules for either epoxides or cyclic sulfates regarding selectivity, the stereochemistry of the product depending on the type of attacking nucleophile, the substitution on the ring, and the conditions used, but generally, they are more susceptible to nucleophilic attack at the unfunctionalised carbon atom. Berridge *et al* observed that substitution reactions on cyclic sulfates were stereospecific, and remarkably regiospecific.[31] Whilst both epoxides and cyclic sulfates are very susceptible to nucleophilic attack, both are also thermally stable. Cyclic sulfates are much more reactive than epoxides and have been

described by Gao and Sharpless as "like epoxides only more reactive".[10] The ring

opening reactions of cyclic sulfates and epoxides are very similar in nature to those of

cyclic sulfamidates and aziridines.

1.7.2 Cyclic sulfamidates as aziridine like synthons

Most of the reactions of both cyclic sulfamidates and aziridines involve ring opening

(Scheme 19), leading to the same product.
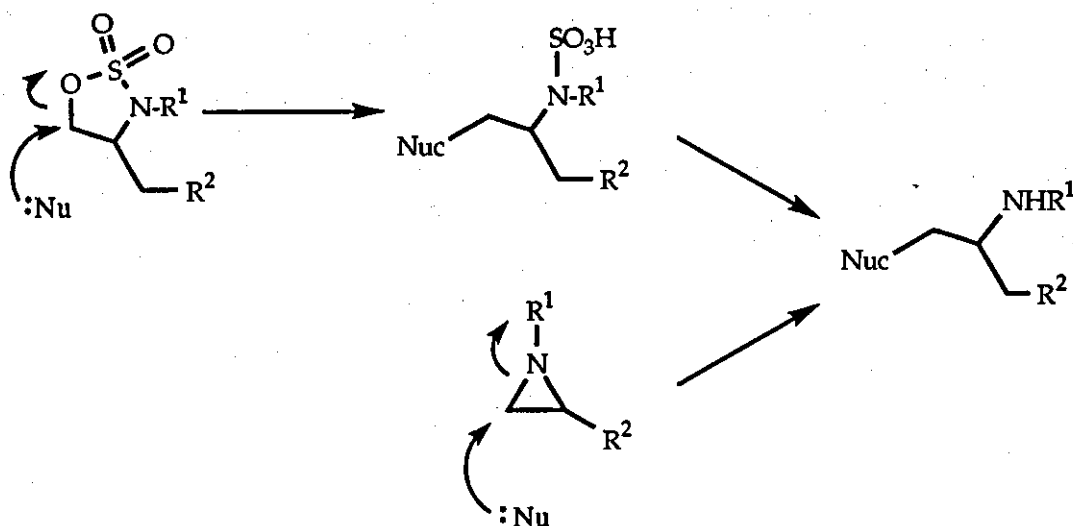
Scheme 19

In respect of these ring opening reactions, aziridines can be divided into two groups

according to the nature of the substituent on the nitrogen atom, those which are "non-

activated" **38** and those which are "activated" **39** aziridines.[28]

"non-activated"
R= H, alkyl, aryl

38

"activated"
G= COR, CO_2R, SO_2R
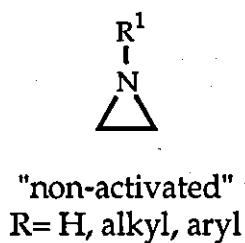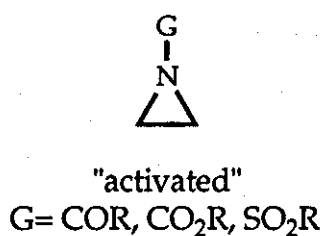
39

Non-activated aziridines **38** contain a basic nitrogen atom and ring opening reactions

usually occur only after protonation, quaternization, or formation of a Lewis acid

adduct.[28] Activated aziridines **39**, however, contain a substituent which can stabilise

the negative charge that develops on the nitrogen atom in the transition state when

ring opened by a nucleophile.[28] The mechanism for ring opening of this latter type of

aziridine is more clear cut than for the non-activated type and some generalisations

can be made. For monocyclic activated aziridines, nucleophilic attack is expected to

occur via an S_N2-like mechanism with inversion, and monosubstituted aziridines are

known to be attacked predominantly, or exclusively, at the methylene carbon atom.[28]

For example, the *cis / trans* isomers **40** and **41** undergo clean S_N2 reactions with

complete Walden Inversion (Scheme 20). Furthermore, the monosubstituted

derivative **42** was attacked exclusively at the less hindered site (Scheme 21).[28]
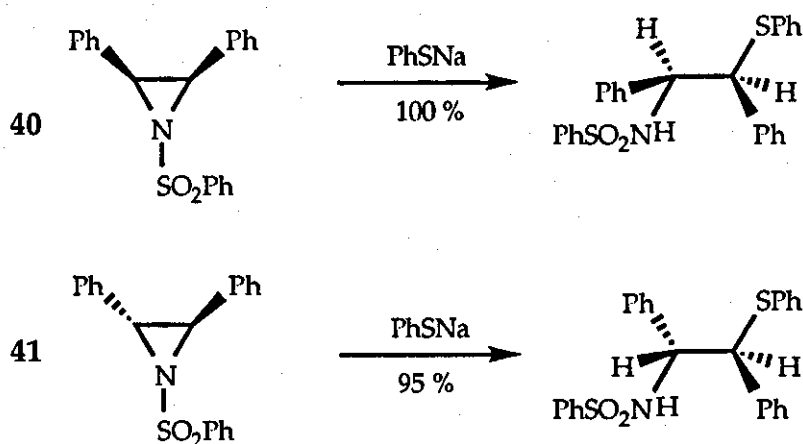
Scheme 20
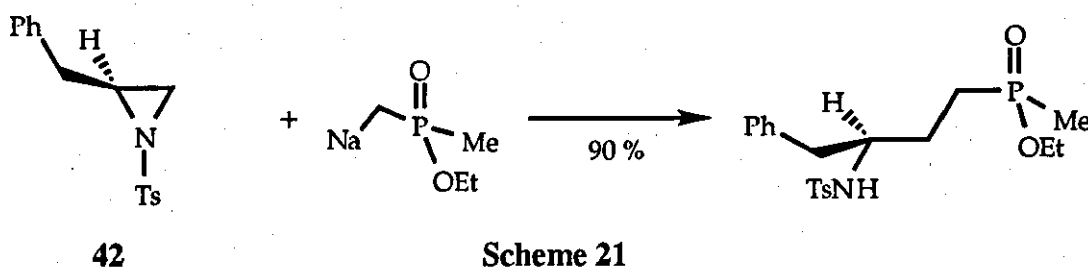
42   **Scheme 21**

There are, of course "abnormal" nucleophilic ring openings which do not give the

expected products. For example, Scheme 22 shows nucleophilic attack at both the

substituted and the unsubstituted position, giving two regiochemically different

products.[28]
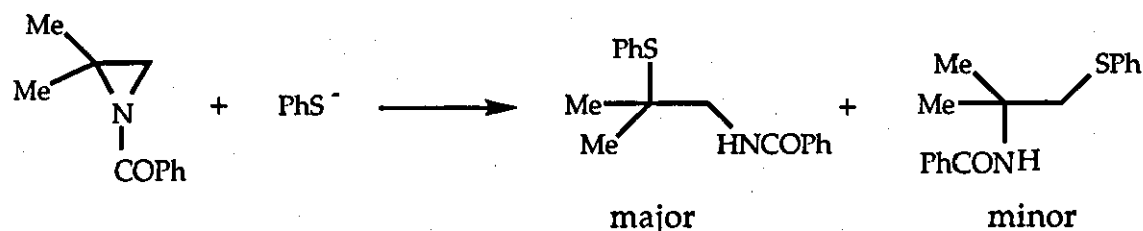
Scheme 22

The choice of substituent on the nitrogen can be used to control the stereochemistry of a reaction, for instance a strongly activating group, such as COOR or COR, will promote an S_N2-type attack under mild conditions. Regiochemistry can be affected by the nature of the substituents attached to the aziridine ring. For example, alcohol **43a** (R^2 = H) and the corresponding ether **43b** (R^2 = X) give different regioisomeric products. In **43a**, the incoming nucleophile is directed to C-2 by complexation with the attacking species. In **43b** R^2 is sterically blocking C-2 and so the nucleophile is directed to C-3.[28]
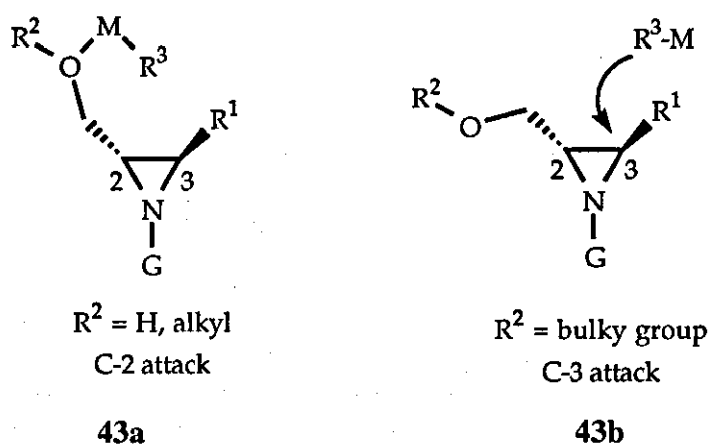
One common reaction of both aziridines, such as **44** and cyclic sulfamidates, such as **45** is the stereo- and regio-selective nucleophilic ring opening of derivatives containing a carboxylate group as a route to β-functionalised α-amino acids (Scheme 23).[25, 28] Baldwin *et al*, found that with a range of nucleophiles cyclic sulfamidate **45** only gave products resulting from attack at the position β to the ester moiety, which is consistent with the activated aziridines.[25] It should be noted that the mechanism and regioselectivity of non-activated aziridines, like **46** may vary, depending on the exact conditions used (Scheme 24). Sharpless, however, noted a bias for attack at the

position α to the ester moiety in the nucleophilic ring opening of analogous cyclic sulfates (Scheme 17).[10] Cyclic sulfamidates are obviously similar to activated aziridines with regard to ring opening reactions.

44

Cyclic Sulfamidate

45   **Scheme 23**

Non-activated aziridine

46   **Scheme 24**
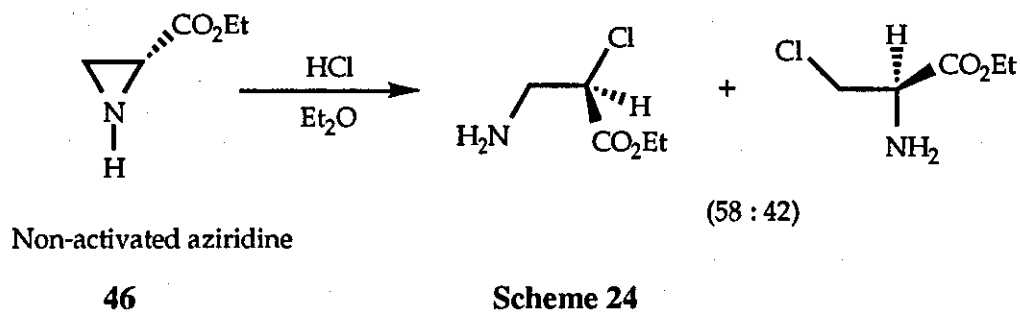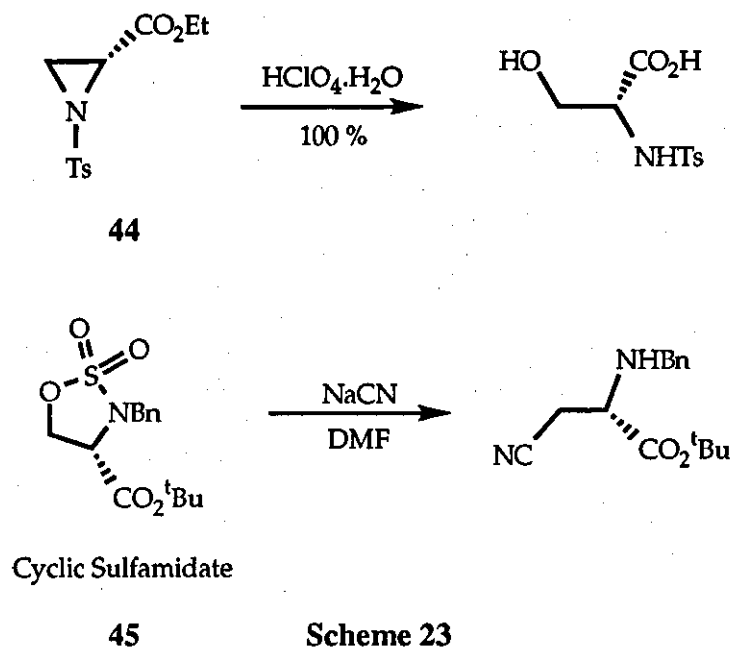
1.8 Background to the Project.

Work undertaken by other members of the research group has provided convenient routes to allene oxides **47**, methyleneaziridines **48** and methylene cyclic sulfite **49**.[32, 33]

47   **48**   **49**
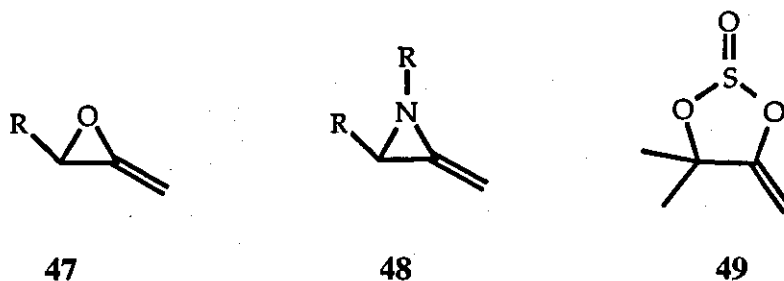
Until now the only practical procedure for the synthesis of methyleneaziridines has been that used by Pollard and Parcell.[34]   Unfortunately, the forcing conditions used to generate the aziridine (sodium amide in liquid ammonia) means that only derivatives containing relatively simple alkyl substituents have been prepared (Scheme 25).[35]
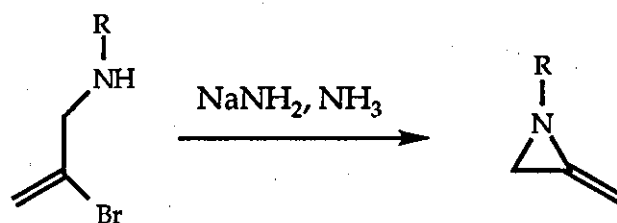
Scheme 25

Ince *et al* [36] successfully synthesised methylene aziridine **51**, by first preparing the amine precursor **50** and using the Pollard and Parcell methodology to cyclise to the methylene aziridine (Scheme 26).

50   **Scheme 26**   **51**
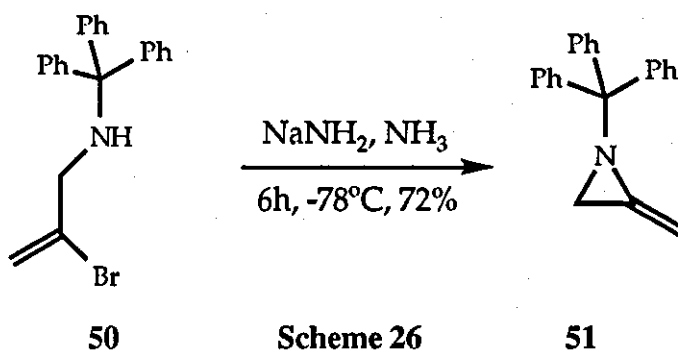
Chiral, non-racemic methyleneaziridines (52a-e) have been successfully synthesised from commercially available homochiral β-amino alcohols.[37] Ince *et al* devised a simple three step protocol for the preparation of these methyleneaziridines, in yields ranging from 68-93 %, with no significant racemisation (Scheme 27).[36]
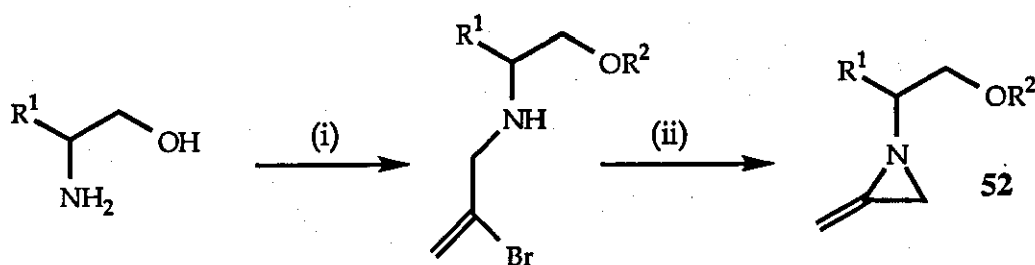
52a (R^1 = CH_3, R^2 = CH_2Ph); **52b** (R^1 = ^iPr, R^2 = CH_2Ph);
52c (R^1 = $CH_2CH(CH_3)_2$, R^2 = CH_2Ph); **52d** (R^1 = Ph, R^2 = CH_2Ph);
52e (R^1 = ^iPr, R^2 = Si^tBuPh_2)

Scheme 27

In conjunction with the synthesis of the methyleneaziridines, studies have been undertaken into the synthesis of the analogous allene oxides. It is known that allene oxides, being extremely reactive molecules, have considerable potential as intermediates in a variety of novel chemical transformations.[37] Allene oxides without a bulky substituent are not isolable by column chromatography, due to their volatility, other allene oxides can simply be too reactive to be stable and can exist only for a short time as reaction intermediates.[37] Shipman and Thorpe studied elimination reactions of appropriately functionalised epoxides to generate allene oxides in situ.[32] This approach involved elimination of silyl substituted epoxides with alkoxide anion, a further equivalent of alkoxide being added to trap the allene oxide *in situ*, leading to the corresponding α-alkoxyketone (Scheme 28).[32]
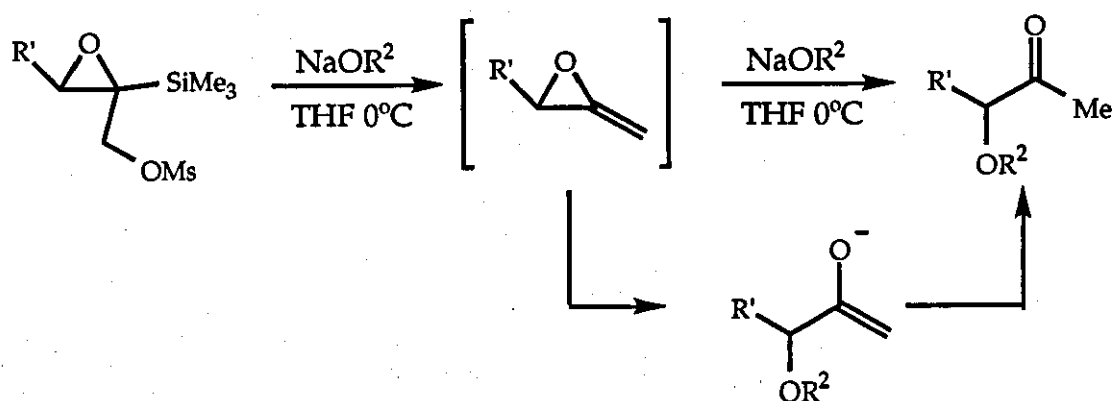
Scheme 28

Given the problems associated with instability of allene oxides an attractive goal

seemed to be the development of compounds that would react in a similar manner and

be easier to prepare and handle, *i.e.*, methylene cyclic sulfites and sulfates. This was

achieved *via* two different routes. The first route involved the reaction of a

β-hydroxy ketone with thionyl chloride (Scheme 29) to prepare methylene cyclic

sulfites **49** and **53**.[32] Unfortunately this chemistry only works when tertiary alcohols

are employed.
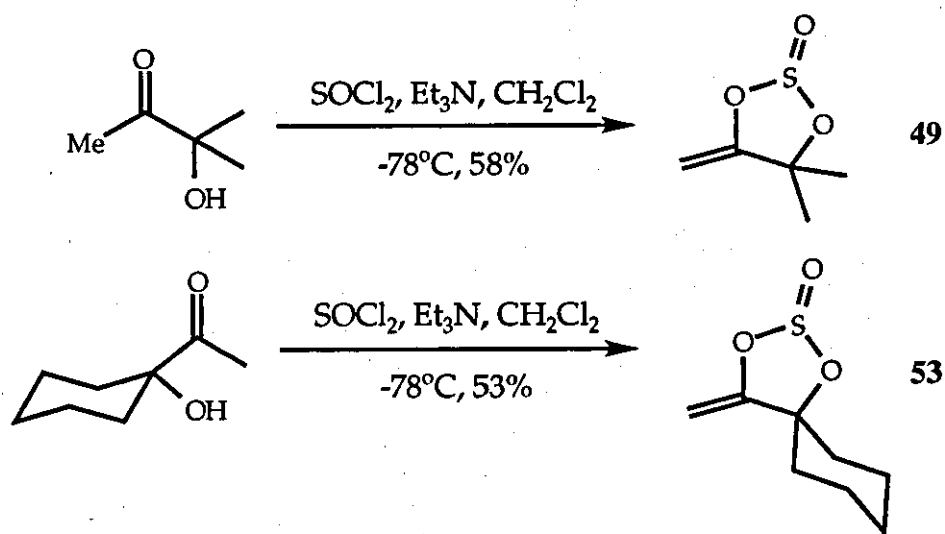
Scheme 29

Alternatively, methylene cyclic sulfites can be made using a selenoxide elimination

strategy. For example, sulfite **49** was prepared from the corresponding aryl selenide

by oxidation and spontaneous elimination (Scheme 30).[32]
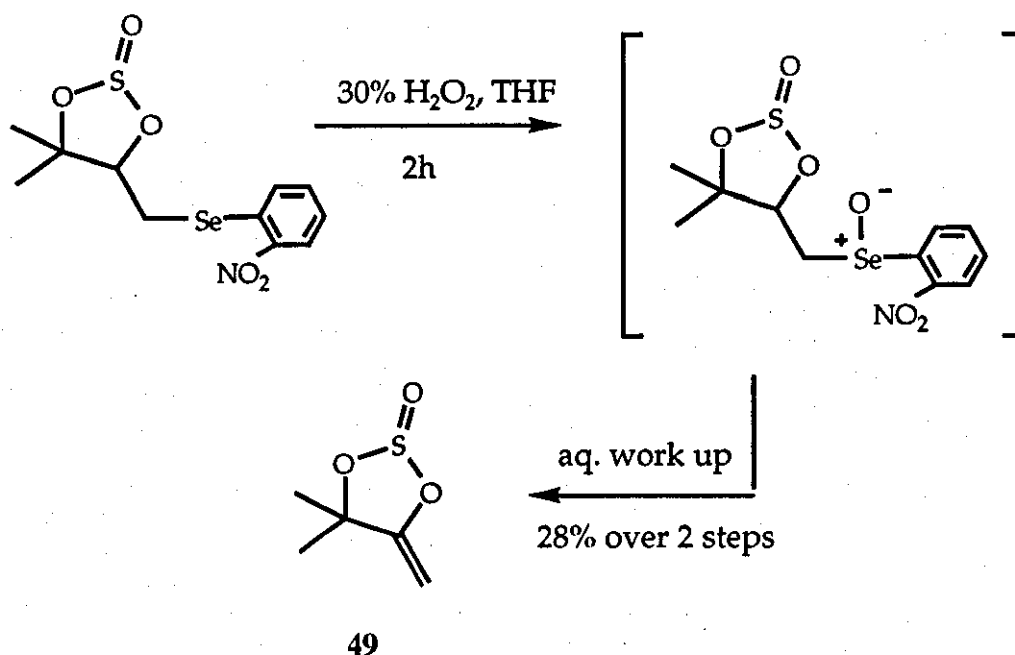
Scheme 30

Having successfully prepared allene oxides and the methylene derivatives of cyclic sulfites and aziridines, it was decided to use the same chemistry as used to prepare the methylene cyclic sulfite **49** in an attempt to prepare the analogous methylene cyclic sulfamidites **54** and **55**. As far as we are aware, such compounds have never been prepared before. We hoped that these compounds, if successfully synthesised, might serve as synthetic equivalents to methyleneaziridines.
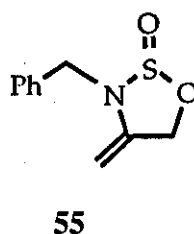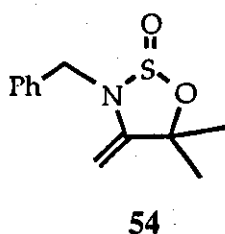
CHAPTER 2 :

RESULTS AND DISCUSSION

2.1 Preliminary Studies

Before embarking upon the synthesis of our sulfamidite analogues of

methyleneaziridines, a basic cyclic sulfamidite unit, **56** was prepared by treatment of

N-benzyl ethanolamine with thionyl chloride following a literature procedure.[4] We

isolated this material in 45% yield after column chromatography. Subsequent

oxidisation to the corresponding sulfamidate **57**, was accomplished using the $RuCl_3$ /

$NaIO_4$ system (Scheme 31).[4]

PhCH$_2$NH $\diagdown$ OH + SOCl$_2$ $\xrightarrow{\text{(i)}}$ Ph $\diagdown$ N–S $\diagup$ O **56**

$\downarrow$ (ii)

Scheme 31. Reagents and Conditions :
(i) Et$_3$N, CH$_2$Cl$_2$, -15°C, 29h, 45%
(ii) RuCl$_3$.H$_2$O, NaIO$_4$, MeCN, RT, 4.5h, 55%

Ph $\diagdown$ N–S $\diagup$ O **57**
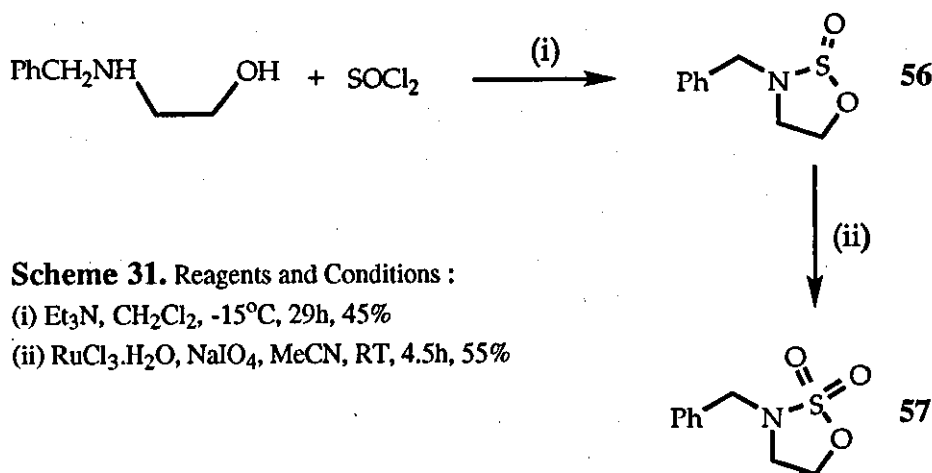
2.2 An Approach to 4-methylene Cyclic Sulfamidite 54

Having gained some experience in the preparation of cyclic sulfamidites and

sulfamidates, we considered routes to the desired target molecules. Another member

of our research group had established that methylene cyclic sulfite **49** can be readily

prepared from 3-hydroxy-3-methylbutan-2-one by treatment with thionyl chloride at

low temperature (Scheme 29).[32] We reasoned that we might be able to develop a

very concise route to the desired sulfamidite, **54** by using the same chemistry,

employing the corresponding imine. The requisite imine **58**, was prepared from the

corresponding ketone, 2-hydroxy-2-methyl-3-butanone, by refluxing with

benzylamine in toluene in a Dean Stark apparatus (Scheme 32).[38] The imine

preparation proceeded in excellent yield (99% crude) and needed no further

purification either for spectroscopic analysis or for use in the next step.

58
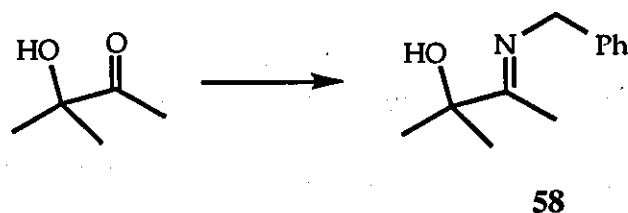
Scheme 32. *Reagents and Conditions*: BnNH$_2$, CSA, toluene, reflux (Dean Stark) 24h, 99%

Acid catalyst is required in these carbonyl condensation reactions and the rate of reaction actually depends on the pH, the position of the maximum rate depending on the nature of the R group on the primary amine.[39] The reaction itself can be considered to be an equilibrium, with water as one of the products (Scheme 33), therefore refluxing in a Dean Stark apparatus removes the water and drives the reaction to completion.
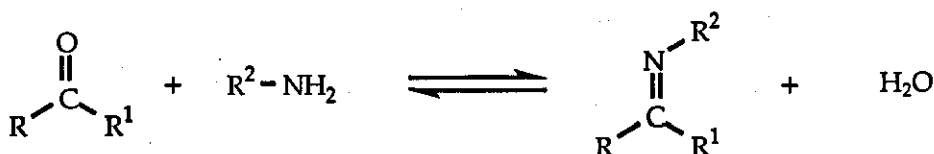
Scheme 33

The next step of the reaction, the cyclic sulfamidite formation (Scheme 34) proved to be less successful. This imine was subjected to the general conditions utilised for the formation of cyclic sulfamidites from amino alcohols, namely, thionyl chloride and triethylamine in dichloromethane at -78°C. It was hoped that the intermediate, **59** would undergo a rearrangement to form the double bond at the desired position to give the methylene derivative **54**.
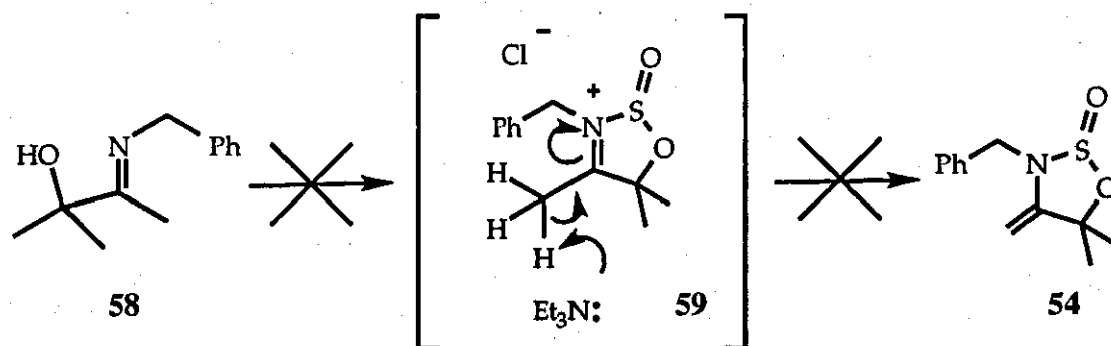
Scheme 34. *Reagents and Conditions*: SOCl$_2$, Et$_3$N, CH$_2$Cl$_2$, -78°C, 1h.

It was thought that the intermediate imine cation **59**, would rearrange to form **54**, in an analogous fashion to the formation of cyclic sulfite **49** (Scheme 29). The reaction seemed, by TLC, to be proceeding, with formation of a less polar product, as expected. However, we were unsuccessful in isolating any of the desired product. This would have been indicated by the presence of new olefinic ^{1}H or ^{13}C NMR signals, which were not observed. The reaction was initially quenched with saturated NaHCO$_3$, but to acknowledge the possibility that the desired product, **54** may be water soluble, may decompose or undergo some form of rearrangement in aqueous conditions, later attempts were made without any aqueous quenching but simple removal of the solvent under vacuum. This work up procedure also proved unsuccessful.

2.3 An Elimination Strategy for the Synthesis of 4-Methylene Cyclic Sulfamidite (55)

The basic principle was to synthesise a cyclic sulfamidite which contained a suitable substituent in the 4-position, which could be eliminated, to form a double bond (Scheme 35). While a number of different X groupings could be considered for this purpose, we elected to examine a selenoxide elimination strategy (*i.e.* X= (ArSe=O), Y = H).[40] We anticipated that the requisite selenide could be introduced, oxidised, and eliminated under sufficiently mild conditions such that the reactive sulfamidite

ring would remain intact. It is notable that this approach, could in principle, be employed to prepare the corresponding methylene cyclic sulfamidate.
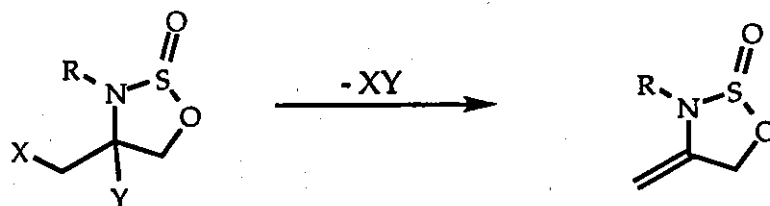
Scheme 35

Initially, we hoped to prepare selenide precursor **61** from glycidol *via* hydroxyl substituted oxathiazolidine **60** (Scheme 36), however the reaction to prepare **60** using *N*-thionylaniline and glycidol was unsuccessful and only the glycidol starting material was recovered, along with two other unidentified components. The main reasons why this reaction was unsuccessful would appear to be that sulphur is not electrophilic enough for the lone pair of electrons on the oxygen to attack. With this in mind, the glycidol was reacted with sodium hydride in order to form the more nucleophilic alkoxide anion. However, in this instance the main product isolated from the reaction mixture was azobenzene Ph-N=N-Ph, and not the desired product **60**. Dimerisation, is a very common reaction for Ar-N compounds. The reaction was repeated under a variety of conditions: at room temperature; under reflux; with NaH at 0°C; and with NaH at -78°C, but all proved unsuccessful.
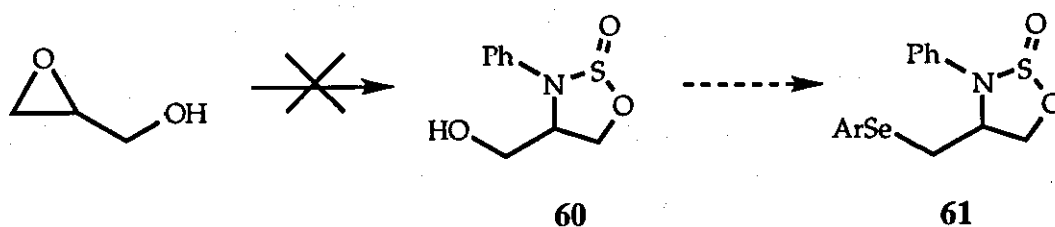
Scheme 36. *Reagents and Conditions*: Et₃N, PhNSO, CH₂Cl₂, RT.

To circumvent these problems, we decided to adopt a less direct approach to the requisite precursor, as shown in Scheme 37. Firstly, the known carbamate **63** was

prepared in two steps from glycidol. This was accomplished by treatment of glycidol with benzyl isocyanate under reflux in toluene, which gave the corresponding carbamate **62** in 74% yield. This carbamate was rearranged to cyclic carbamate **63** by treatment with a catalytic amount of sodium hydride. Under these conditions, the acidic proton on nitrogen is removed, which subsequently rearranges to the more stable alkoxide (Scheme 38). Cyclisation proceeds exclusively *via* this manifold and none of the corresponding 6-membered carbamate was observed. Attack at the far side of the epoxide ring would result in the formation of a six membered ring, which for entropy reasons is less likely than the formation of the five membered ring.
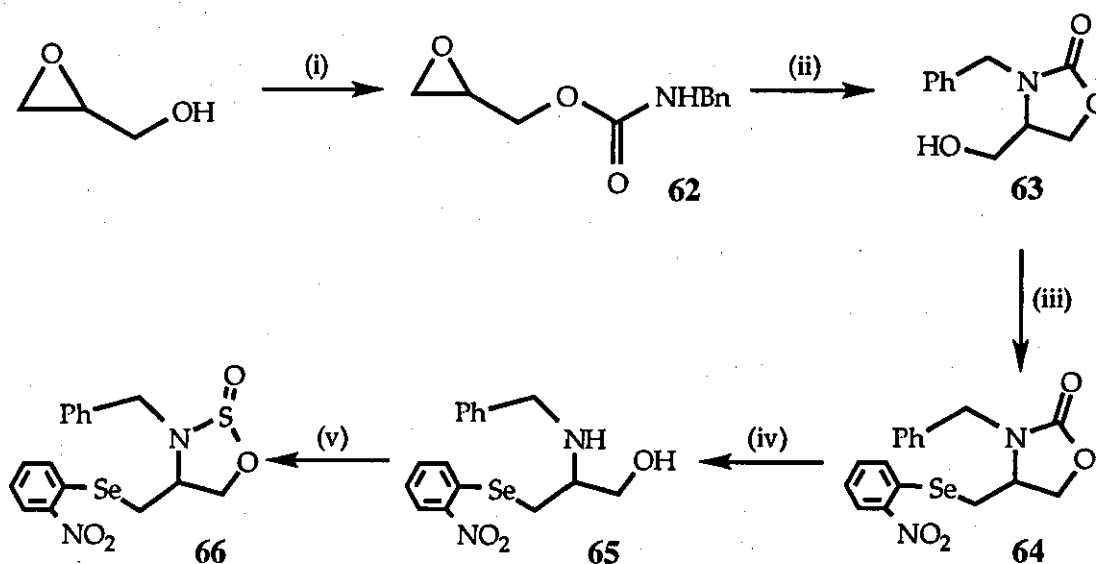
Scheme 37. *Reagents and Conditions:* (i) Na_2CO_3, BnNCO, toluene, reflux 2h, 74%; (ii) NaH, THF, <5°C, 2h, 78%; (iii) 2-NO_2PhSeCN, Bu_3P, THF, RT, 24h, 62%; (iv) 2M NaOH, 96% EtOH, reflux, 7h, 37%; (v) $SOCl_2$, Et_3N, CH_2Cl_2, -78°C, 9h, 25%.
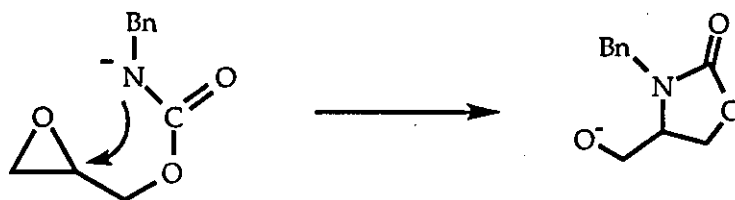
Scheme 38

Alkyl aryl selenoxides are well known for ability to eliminate to form olefins.[40]

Sharpless and Young showed that electron withdrawing substituents on the aromatic

ring of the selenoxide increase the rate of elimination and the isolated yield of the

olefin.[40] For this reason, it was decided to prepare the 2-nitrophenylselenomethyl

derivative of the oxathiazolidine rather than the phenyl selenomethyl compound.

In order to substitute the hydroxyl group for the 2-nitrophenylseleno group we used

the procedure of Grieco, Gilman and Mishizawa.[41] Treatment of alcohol **63** with 2-

nitrophenyl selenocyanate (prepared from *o*-nitroaniline and potassium

selenocyanate)[42], and tributylphosphine in THF furnished the corresponding selenide

64 in 62% yield. The driving force behind this reaction is believed to be the

formation of the strong P=O bond (Scheme 39).
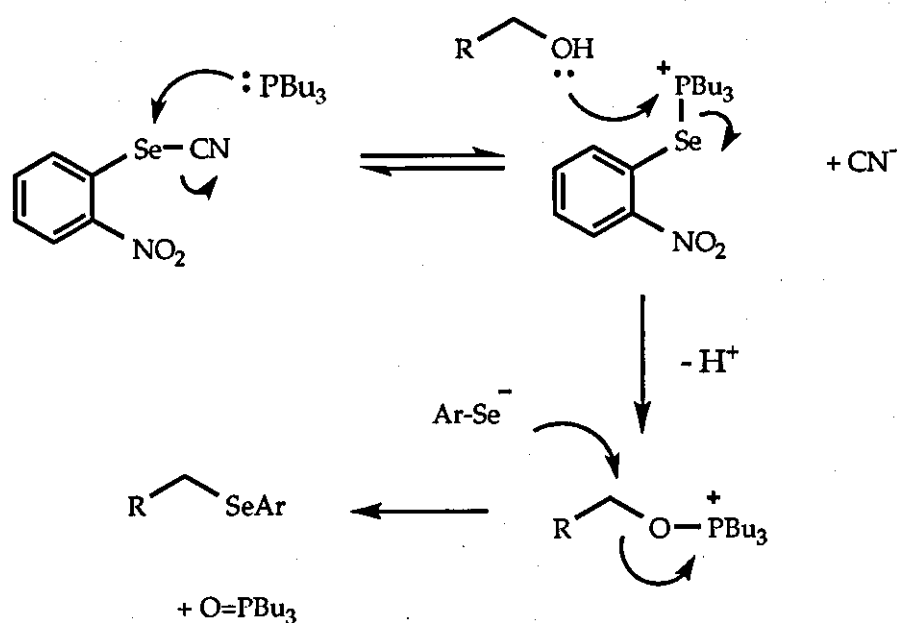
Scheme 39

In order to form oxathiazolidine **66** from oxazolidine **64** it was necessary to cleave the

carbamate group to form amino alcohol **65**, and then introduce the sulfamidite ring

using thionyl chloride. Cleavage of the carbamate group was achieved in 37% yield

with 2M sodium hydroxide, using the procedure of Gautun and Carlson.[5] The driving

force behind the cleavage of the carbamate is the increase in entropy when going from

a 5-membered ring to a 1,2-amino alcohol plus loss of CO_2 gas (Scheme 40).
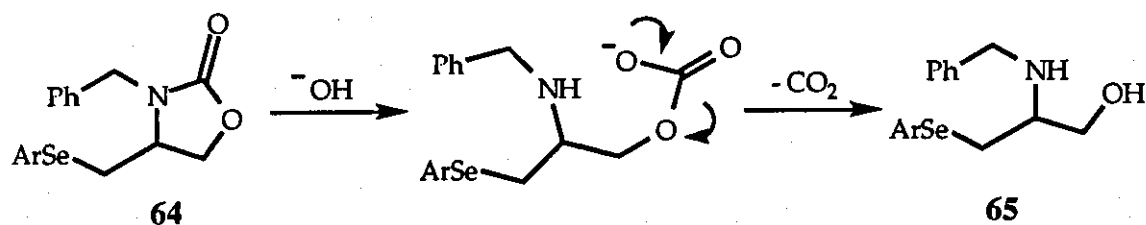
Scheme 40

This amino alcohol, **65**, was then converted to the oxathiazolidine **66** by reaction with

thionyl chloride at -78°C, following the procedure of Gautun and Carlson (Scheme

41).[5] Triethylamine was added to the reaction mixture in order to mop up the HCl

that is formed in the reaction. As expected two separable diastereomeric adducts

were formed in essentially equal amounts from this reaction, but in very poor yield

(total 25%). According to the work of Deyrup and Moyer it is possible to assign the

configuration of **66a** and **66b** from their respective ^{1}H NMR values.[1] Protons which

lie *cis* to the sulfoxide bond are deshielded and so lie further downfield than protons

which lie *trans*. On this basis we are able to give the following assignments to these

diastereoisomers (Table 3). This enabled specific stereochemical assignments at

positions 2 and 4 to be determined. Diastereoisomer **66a** is therefore

(2*S**,4*S**)-*N*-benzyl-4-[(2-nitrophenyl)selenomethyl]-1,2,3-oxazolidinone, and

diastereoisomer **66b** is (2*R**,4*S**)-*N*-benzyl-4-[(2-nitrophenyl)selenomethyl]-1,2,3-

oxazolidinone

65   **66a**   **66b**
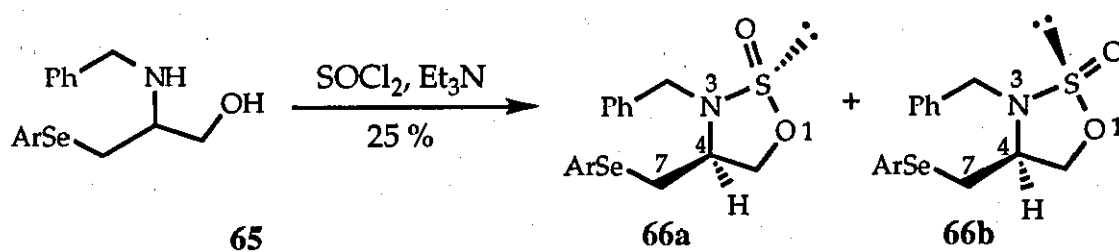
Where Ar = *o*-NO$_2$Ph

Scheme 41

Substance	Proton	1H NMR value (ppm)	Assignment
66a	H-4	3.73-3.64	*trans*
66b	H-4	3.81-3.91	*cis*
66a	H-7's	3.41 and 3.12	*cis*
66b	H-7's	3.06 and 2.82	*trans*

Table 3

While the yields for the latter stages of this sequence were poor, sufficient material was available to test out whether selenide **66** could be oxidised and eliminated to the desired methylene cyclic sulfamidite **55**. Treatment of a mixture of selenides **66a** and **66b**, and of single diastereoisomer **66a** with hydrogen peroxide, according to the standard methods of Sharpless and Young, resulted in consumption of all the starting material, as determined by TLC (Scheme 42).[40] We envisaged that selenoxide **67** would not be isolated, rather it would spontaneously eliminate the selenic acid (ArSeOH) to give olefin **55**. However none of the desired material was detected by ^{1}H NMR after aqueous work up.
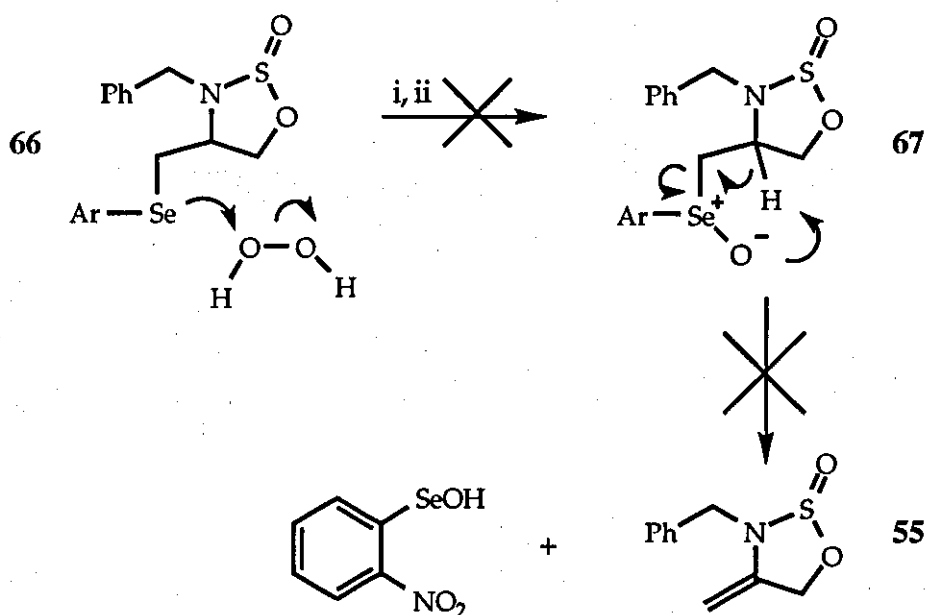
Scheme 42: *Reagents and Conditions:* (i) 30% H_2O_2, THF, 0°C, 1h; (ii) RT, 2.5h.

Although our initial experiments to effect the desired olefin were unsuccessful we wished to prepare more material to study this reaction further. However, a very low yield was encountered in the hydrolysis of carbamate **64**. We reasoned that this might be due to nucleophilic attack on the nitrobenzene system by hydroxide anion (Scheme 43). Nitro substituents, being electron withdrawing can render phenyl groups susceptible to nucleophilic attack.[43] A nitro group is able to stabilise the anionic intermediate by delocalisation of charge if the attacking species attacks the *o* -or *p* - position. The *o*-position is more susceptible than the *p*- simply because it is closer to the NO$_2$ group, and so the inductive effect is stronger. Elimination of the alkyl selenide group from the intermediate **68** would lead onto *o*-nitro phenol, **69** and the alkyl selenol (RSeH).
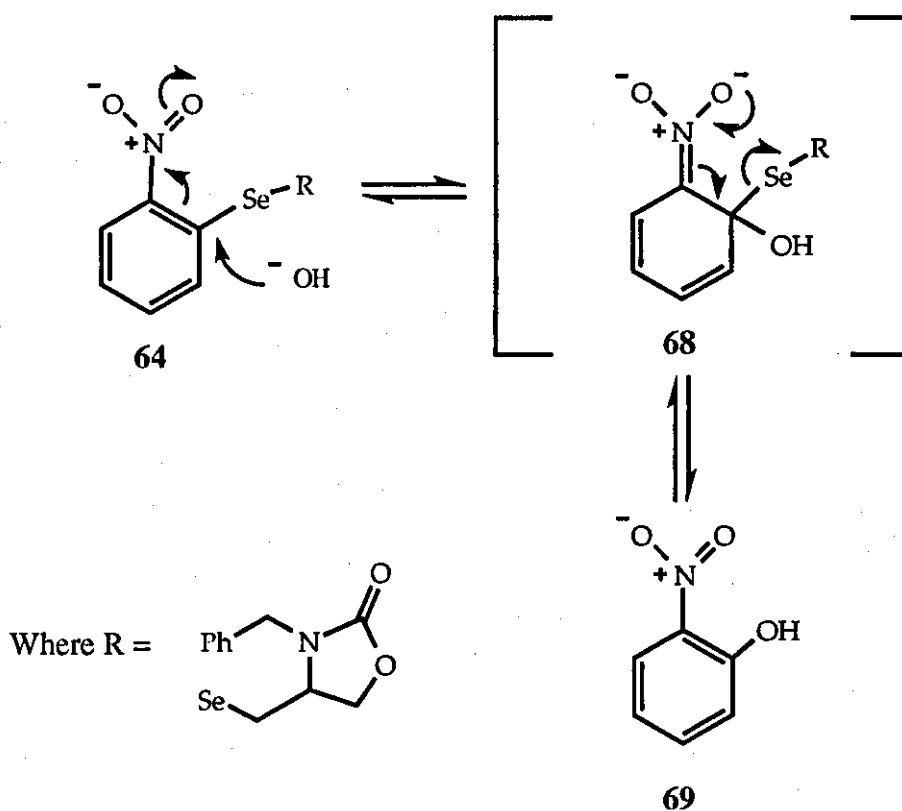
Scheme 43

We reasoned that if this process were occurring, then the hydrolysis step might be improved if the simpler phenyl selenide was used. Again using carbamate **63** as the starting material, we prepared the phenylselenomethyl derivative in much the same

way as before, although an additional step was required in order to introduce the phenylseleno group (Scheme 44).
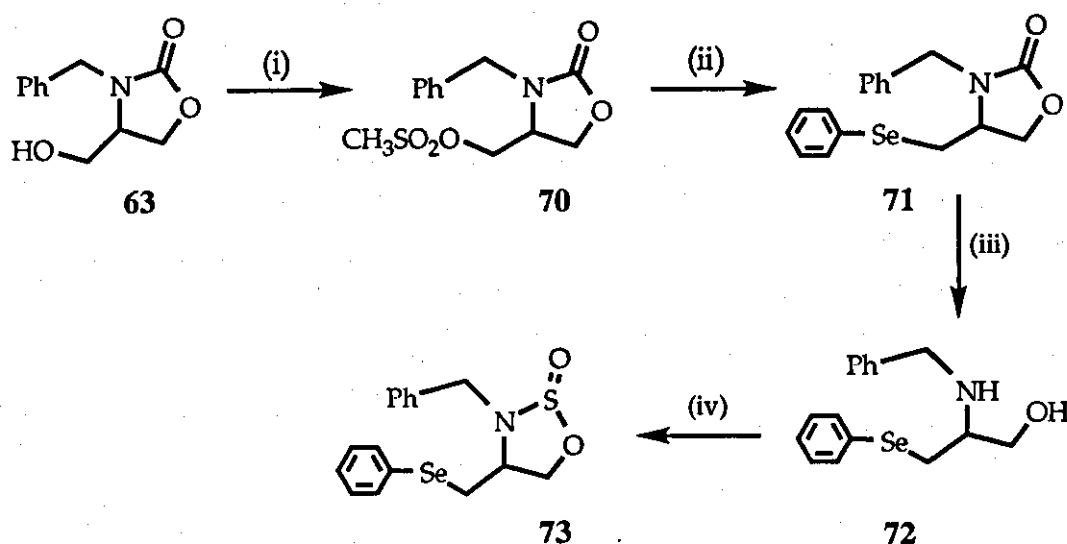
Scheme 44. *Reagents and Conditions*: (i) CH$_3$SO$_2$Cl, Et$_3$N, CH$_2$Cl$_2$, 0°C, 4h, 71% ;

(ii) diphenyldiselenide, NaBH$_4$, absolute EtOH, reflux 4.5h, 52%; (iii) 2M NaOH, 96% EtOH, reflux, 8h, 61%; (iv) SOCl$_2$ Et$_3$N, CH$_2$Cl$_2$, -78°C, 5h, 65%.

The requisite carbamate **63** was converted into the corresponding mesylate **70** in 71% yield by treatment with methanesulfonyl chloride and triethylamine *via* an addition elimination reaction. S$_N$2 displacement of the mesylate with phenylselenide anion gave selenide **71** in only moderate yield (52%), although the material produced after chromatography was very pure, as ascertained by GC. NaBH$_4$ acts as a source of H$^-$, which cleaves

PhSe-SePh to give PhSe$^-$ in this reaction (Scheme 45). Gratifyingly, hydrolysis of the carbamate ring of this selenide with sodium hydroxide gave the amino alcohol **72** in a much improved 61% yield (*cf* 37% for conversion of **64** into **65**).
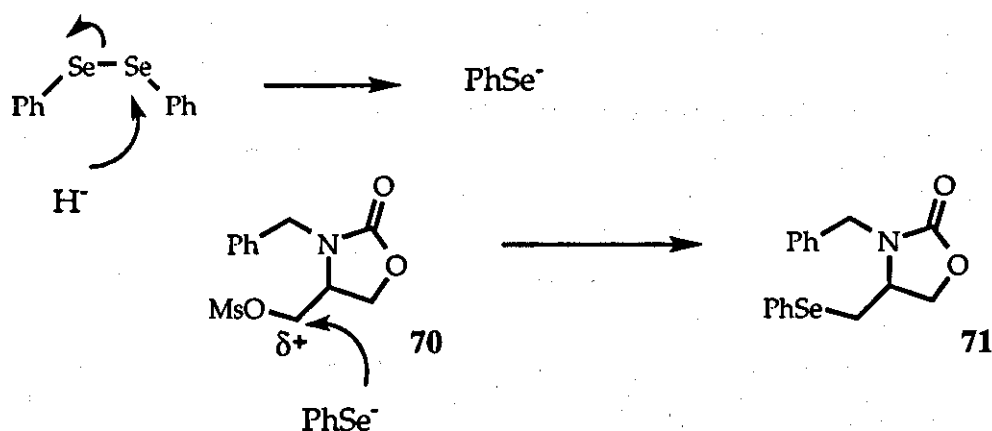
Scheme 45

Conversion to the oxathiazolidine, **73**, was effected using thionyl chloride and

triethylamine at -78°C, following the general procedure of Gautun and Carlson

(Scheme 46).[5]   Again, as expected this gave a mixture of two diastereoisomers,

which were partially separable by column chromatography. A good yield of 65% for

the combined diastereoisomers was achieved (cf 25% for **66a** and **66b** combined).

We were able to assign the following stereochemistry to the diastereoisomers from

the work by Deyrup and Moyer (Table 4).[1] Once again, this enabled specific

stereochemical assignments at sulfamidite ring positions 2 and 4 to be determined.

Diastereoisomer **73a** is $(2S^*,4S^*)$-N-benzyl-4-(phenylseleno)methyl-1,2,3-

oxathiazolidine, and diastereoisomer **73b** is $(2R^*,4S^*)$-N-benzyl-4-

(phenylseleno)methyl-1,2,3-oxathiazolidine.
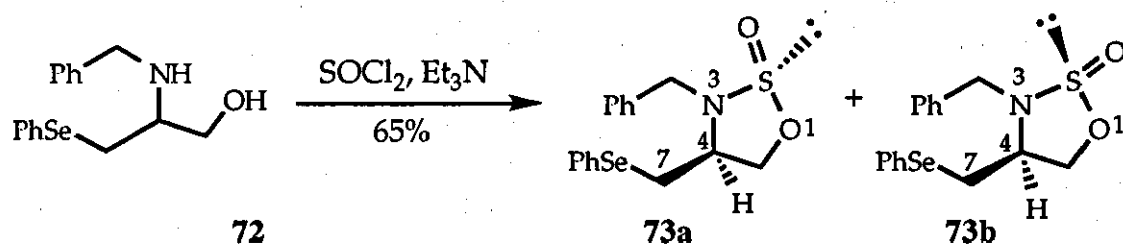
Scheme 46

Substance	Protons	1H NMR value (ppm)	Assignment
73a	H-4	3.61-3.54	*trans*
73b	H-4	3.80-3.67	*cis*
73a	H-7's	3.25 and 3.04	*cis*
73b	H-7's	2.96 and 2.77	*trans*

Table 4

With access to reasonable quantities of selenide **73**, the elimination of the phenylseleno group was attempted using 20% H_2O_2, followed by an aqueous work up.[40] Again this reaction was unsuccessful. Although starting material was judged, by TLC to have been completely consumed, no useful data could be obtained by ^{1}H NMR spectroscopy. The possibility that the product, or the intermediate selenoxide were water soluble was considered, so the oxidation was performed in a non-aqueous media, (Scheme 47). Deuterochloroform was chosen as solvent, enabling ^{1}H NMR to be performed at pertinent time intervals (0 mins, 45 mins, 90 mins, 2.5h, 11h). Oxidation with *m*-CPBA did not result in consumption of all the starting material, as determined by TLC and no identifiable product was observed nor any meaningful data could be abstracted by ^{1}H NMR at any time point.
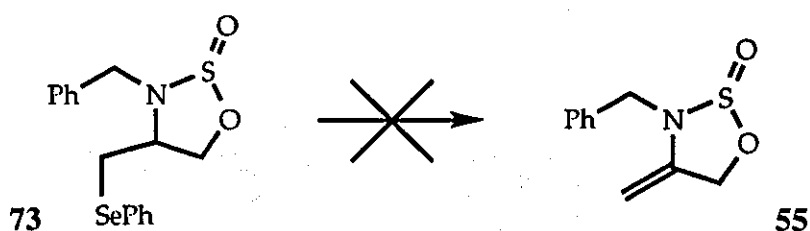
Scheme 47. *Reagents and Conditions: m*-CPBA, Na_2CO_3, $CDCl_3$.

In conclusion we were not able to prepare the desired methylene cyclic sulfamidite **55** by this route. We were successful in making the 2 precursors (**66** and **73**), but could not effect the final elimination to give the methylene derivative. Oxidation with both H_2O_2 and *m*-CPBA resulted in consumption of starting material, as judged by TLC.

It could be that either the intermediate selenoxide is unstable, even under non-aqueous conditions, or the selenoxide intermediate does eliminate to give the desired methylene derivative but this itself is not stable.

2.4 An Alternate Approach to 4-methylene Cyclic Sulfamidite 54

In our group's studies into the preparation of methylene cyclic sulfites, it had been established that a *gem*-dimethyl effect stabilises the product. Thus, sulfite **49** could be prepared using a selenoxide elimination but sulfite **74** could not.

49   **74**
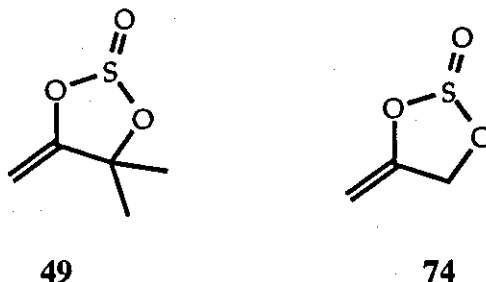
In a parallel fashion, we decided that it would be valuable to try and make aryl selenide **80** and see if it would eliminate to the desired product **54** (Scheme 48). The synthetic scheme to the precursor **80** is outlined in Scheme 49.

This different route to the oxathiazolidine, is based in part on the work of Barco *et al*.[44] Using this chemistry, we hoped to prepare amino alcohol **78**, which might be converted using a similar elimination sequence to that already attempted, to oxathiazolidine **54**

80   **Scheme 48**   **54**
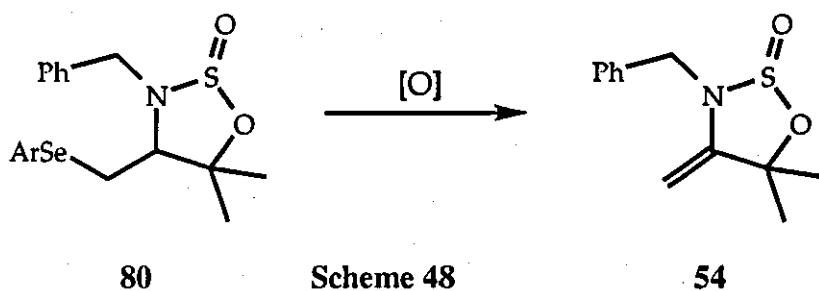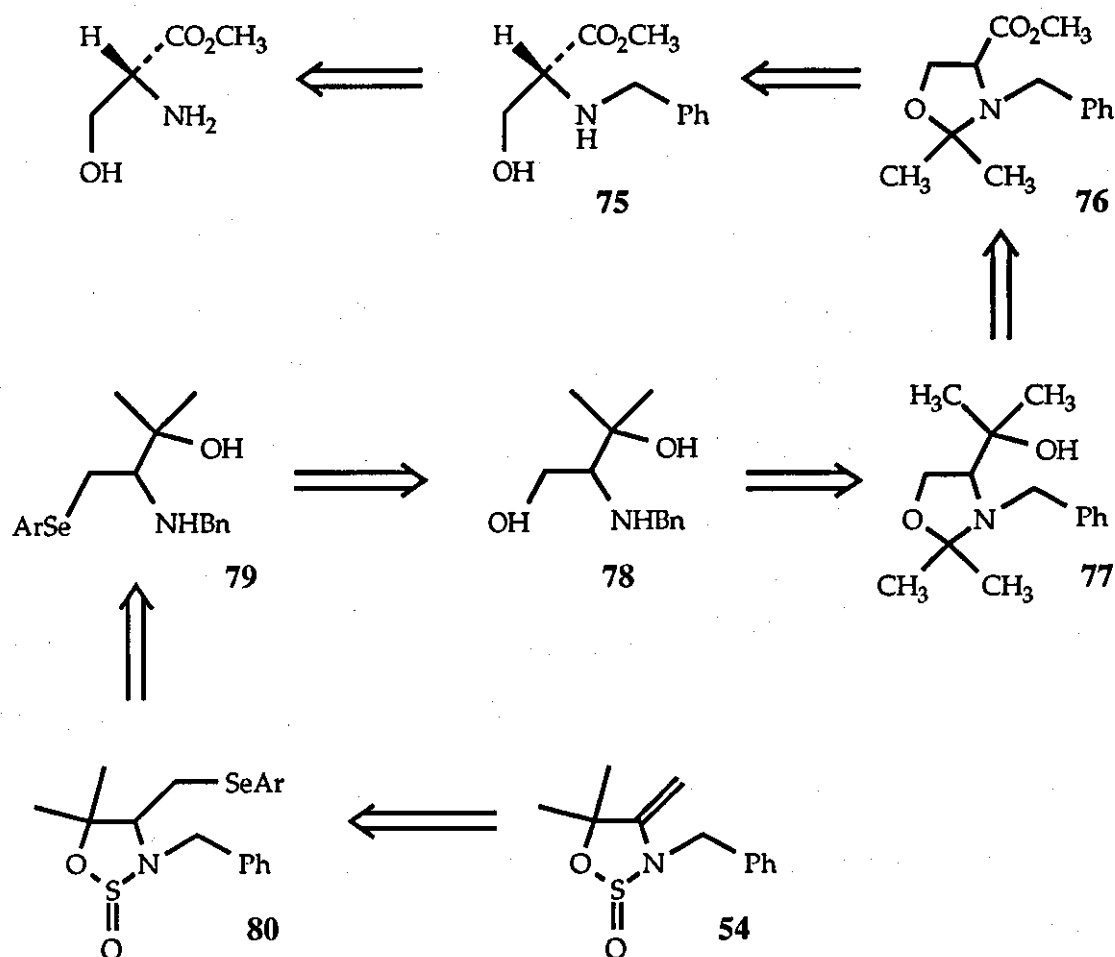
Scheme 49

The preparation of racemic *N*-benzyl serine methyl ester **75** was accomplished

according to the procedure described by Barco *et al.* [44] This reaction involves

reductive amination *via* the corresponding imine. This step was achieved in a good

yield of 89%, which compares reasonably favourably with the literature yield (98%).

In the next stage oxazolidine **76** was formed, albeit in a disappointing 35% yield, in

comparison with the literature, in which the yield was quantitative (Scheme 50).
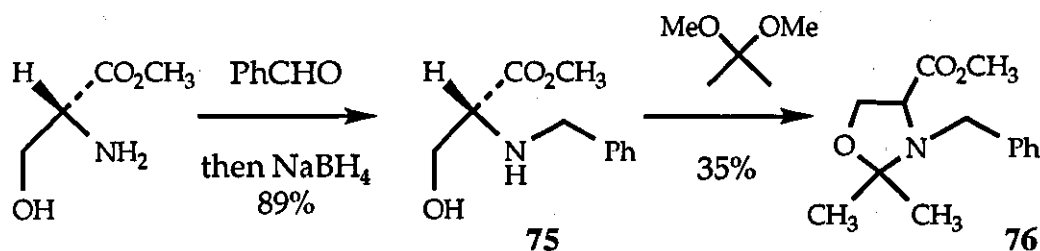
Scheme 50

Barco *et al* have shown that reduction of the ester group of **76** using LiAlH₄ proceeds smoothly to furnish the corresponding primary alcohol.[44] We reasoned that the use of MeMgBr would enable us to prepare the tertiary alcohol, **77** in a similar way. However, treatment of **76** with 2 equivalents of Grignard reagent at 0°C with subsequent warming to room temperature over 40 minutes failed to produce the desired product, **77**. Instead, we isolated *N-tert*-butyl amine, **82** in 79% yield (Scheme 51).
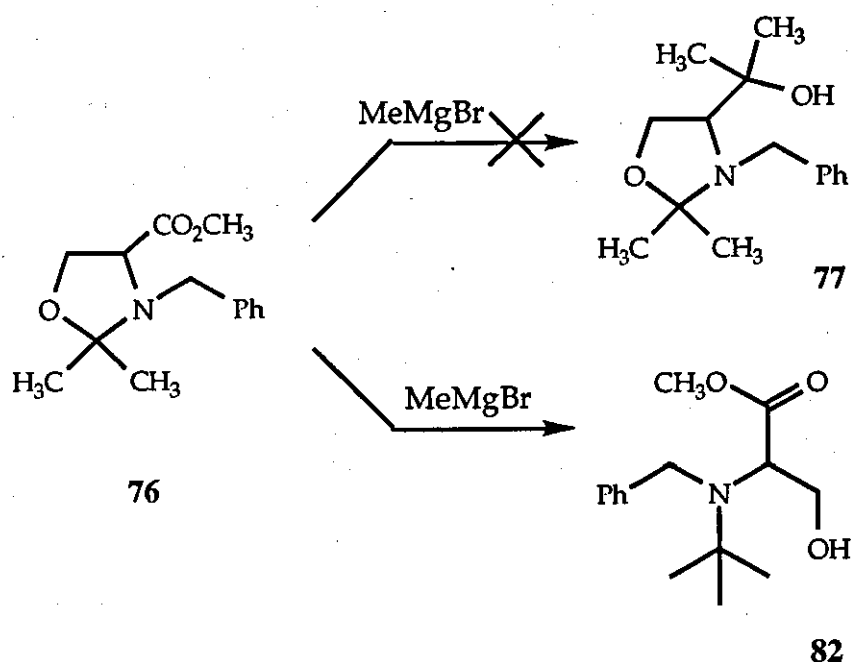
Scheme 51

This product was readily identified by it's spectroscopic properties. It still contained an ester C=O stretch in it's IR (1732 cm⁻¹) and ¹³C NMR (173.6 ppm) spectra, and the presence of a *tert*-butyl group was seen in the ¹H NMR spectra, along with all the other expected signals. Mass spectra gave the molecular ion 265, with an observed accurate mass of 265.1679 (theoretical 265.1678).

In solution, we speculate that iminium cation **81** is formed, which is readily attacked by MeMgBr present in solution to give the *tert*-butyl substituted product.

In solution, MeMgBr exists in an equilibrium, known as the Schlenk equilibrium, with magnesium dibromide. This can act as a Lewis acid and accept electrons from the oxygen in the oxazolidine ring (Scheme 52).

$$MeMgBr \rightleftharpoons Me_2Mg + MgBr_2$$
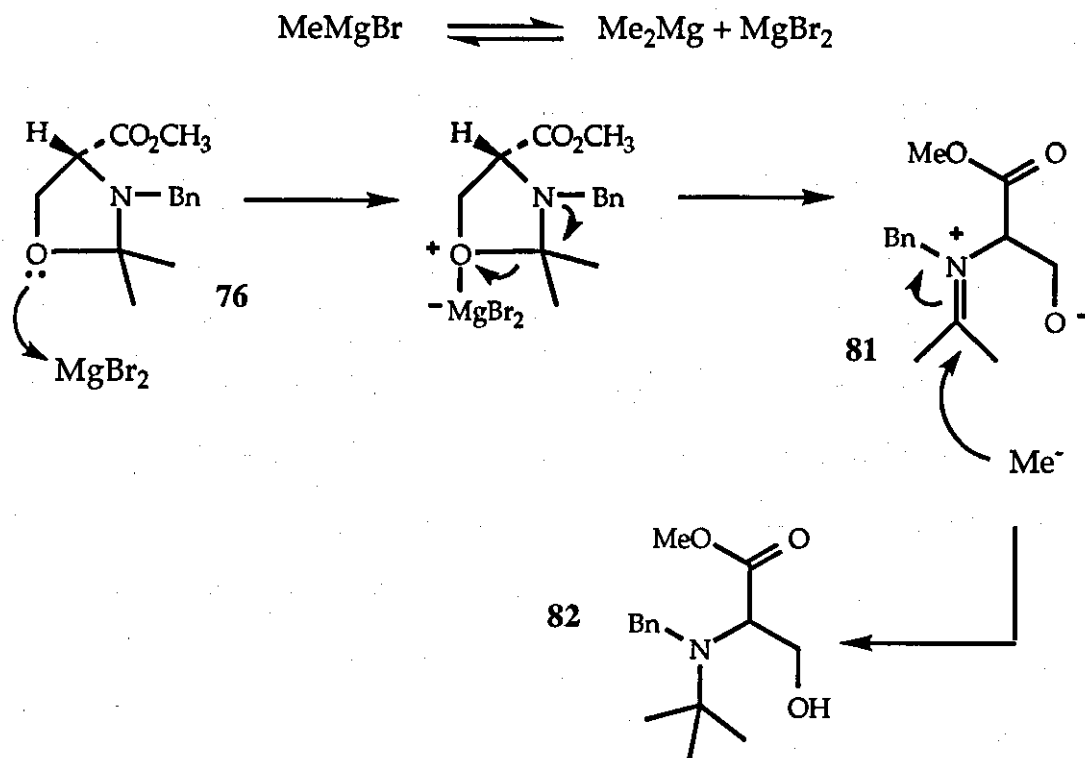
Scheme 52

To try and circumvent these problems we decided to use MeLi in this reaction, which

is much less likely to act as a Lewis acid. Treatment of **76** with 2 equivalents of

MeLi in ether for 2 hours gave a 34% yield of a new product after chromatography.

Spectroscopic analysis of the product strongly support the formation of tertiary

alcohol **77**. ^{1}H NMR showed the presence of 4 methyl groups and an OH proton, and

neither ^{13}C NMR or IR indicated that a carbonyl group was present. ^{1}H NMR and

^{13}C NMR also showed the presence of another species, present in very small

quantities, whose signals became stronger over time, suggesting that it was prone to

degradation.

Unfortunately time limitations prevented further exploration of this reaction, or the

completion of the synthetic route to cyclic sulfamidite **54**.

2.5 Conclusions

It was attempted to prepare two different methylene cyclic sulfamidites, **54** and **55**. The first attempt to make cyclic sulfamidite **54** centred on a simple two step procedure, involving the reaction of imine **58** with $SOCl_2$. It was thought that the methylene group would form as the result of a rearrangement occurring as the cyclic sulfamidite itself is generated. Despite this approach proving successful in the preparation of the analogous methylene cyclic sulfite **49** from the corresponding hydroxy ketone, we were unable to synthesis the methylene cyclic sulfamidite **54**. We examined making methylene cyclic sulfamidite **55** using a selenoxide elimination reaction. We successfully completed the synthesis of two precursors possessing different substituents attached to the selenium atom, although neither could be successfully eliminated to **55**. We believe the instability of the selenoxide intermediate, or the methylene cyclic sulfamidite product to be the main reason behind the observed failure. Having identified these problems, we attempted to prepare a potentially more stable methylene cyclic sulfamidate, **54**, using this selenoxide chemistry. An interesting reaction of intermediate oxazolidine **76** towards methyl magnesium bromide was observed. Unfortunately, time constraints prevented the completion of this synthetic scheme.

It would have been interesting to see if it was possible to isolate **54** *via* the second (elimination) route, when the first attempted synthesis failed, and it would have given more insight into whether the first reaction failed because of the instability of the product, or for other reasons.

CHAPTER 3 :

EXPERIMENTAL

3.1 General Information

Reactions requiring anhydrous conditions were performed using oven-dried glassware and conducted under a constant stream of nitrogen. Spectroscopic and physical data were recorded on the following instruments:-

Melting points were determined on an Electrothermal IA9000 Series Digital melting Point Apparatus and are uncorrected. Infra-red spectra were recorded on a Perkin Elmer Paragon 1000 FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-250 at 250 MHz and 62.5 MHz and on a Bruker DPX-400 instrument at 400 MHz and 100 MHz respectively using tetramethylsilane as internal standard. Elemental Analysis were performed on a Perkin Elmer 2400 CHN elemental analyser. Mass spectra were performed on a VG Analytical ZAB-E instrument at the EPSRC Mass Spectrometry Centre, University College, Swansea or on a Kratos MS 80 at Loughborough University. Distillations were performed using a bulb-to-bulb (Kügelrohr) system (Buchi GKR-50 glass tube oven). Column chromatography was carried out using Merck Kieselgel 60 H silica gel.

TLC analyses were performed using aluminium backed plates, coated with Merck Kieselgel 60 F$_{254}$. All solvents and reagents were purified by standard protocols.

3.2 Preparation of *N*-benzyl-1,2,3-oxathiazolidine-*S*-oxide (56).

PhCH₂NH⟍⟍OH + SOCl₂ ⟶ Ph⟍N–S structure **56**

56
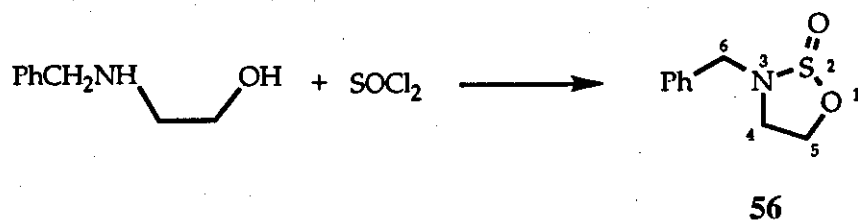
To a stirred solution of *N*-benzylethanolamine (2.80 ml, 20.0 mmol), and

triethylamine (6.30 ml, 45.0 mmol) in dichloromethane (60 ml) at -15°C was added,

dropwise, firstly thionyl chloride (1.80 ml, 25.0 mmol) in dichloromethane (10 ml),

followed by triethylamine (6.30 ml, 45.0 mmol) in dichloromethane (10 ml) and the

mixture stirred below -15°C. After 24h, a further portion of thionyl chloride (1.8 ml,

25.0 mmol) was added and the mixture stirred below -15°C for 5h, the resulting

solution was warmed to room temperature, and filtered. Purification by column

chromatography (20% ethyl acetate / petrol) followed by Kügelrohr distillation gave

56 as a clear golden-brown oil (1.79 g, 45%).

δ_H (250 MHz, CDCl₃): 7.40-7.26 (5H, m, phenyl), 4.79 (1H, dt, 7.4, 3.3 Hz, H-5),

4.33 (2H, m, H-6, H-5), 3.97 (1H, d, 13.6 Hz, H-6), 3.43 (1H, dt, 9.3, 7.4 Hz, H-4),

3.27 (1H, ddd, 9.3, 7.4, 3.3 Hz, H-4); δ_C (62.5 MHz, CDCl₃): 136.0 (s), 129.0 (d),

128.8 (d), 128.7 (d), 128.6 (d), 128.0 (d), 71.6 (t), 50.1 (t), 46.8 (t); ν_{max} (thin film):

3100-2760, 1153, 1005; *m/z:* 197 (M⁺), 133 (70%), 91 (100%).

3.3 Preparation of *N*-benzyl-1,2,3-oxathiazolidine-S,S-dioxide (57).

56   57
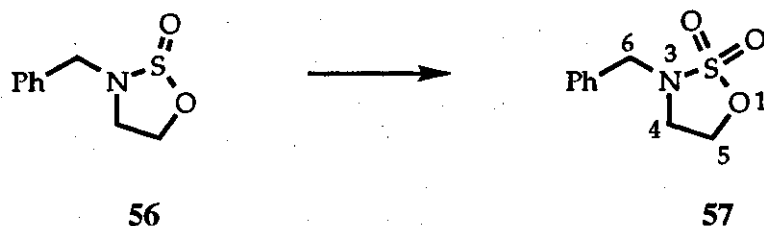
To a stirred solution of **56** (192 mg, 0.97 mmol) in acetonitrile (3 ml) at 0°C, were

added ruthenium trichloride (1 mg, 0.5 mol%) and sodium periodate (301 mg, 1.41

mmol). The mixture was allowed to warm to room temperature, and stirred for 4.5 h.

The reaction mixture was extracted with ether (2 x 10 ml), the organic extracts

combined, washed with water (20 ml) then brine (20 ml), dried over $MgSO_4$ and

concentrated *in vacuo*. Purification by column chromatography (30% ethyl acetate /

petrol) gave **57** as a pale yellow oil (112 mg, 55%), which crystallised on standing to

give an off white waxy solid, m.p. (54-55 °C). δ_H (250 MHz, $CDCl_3$): 7.40-7.35

(5H, m, phenyl), 4.51 (2H, t, 6.5 Hz, H-5), 4.24 (2H, s, H-6), 3.41 (2H, t, 6.5 Hz, H-

4); δ_C (62.5 MHz, $CDCl_3$): 128.8 (d), 128.6 (d), 128.5 (d), 66.7 (t), 51.5 (t), 47.1 (t);

m/z: 213 (M^+), 91 (100%); Observed (M^+): 213.0460; $C_9H_{11}NSO_3$ requires

213.0460.

3.4 Preparation of *N*-benzyl-2-hydroxy-2-methyl-3-butimine (58).

58
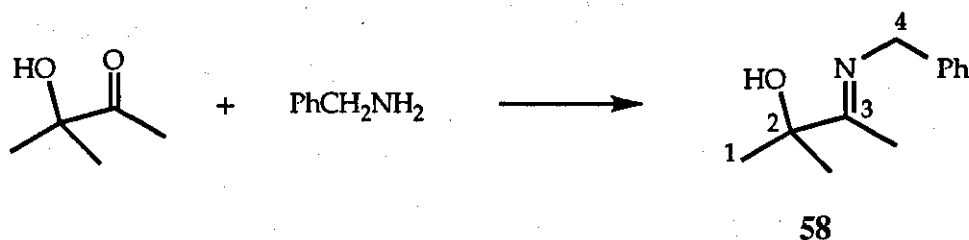
A mixture of 2-hydroxy-2-methyl-3-butanone (1.05 ml, 10.0 mmol), benzylamine

(1.09 ml, 10.0 mmol), and camphor-10-sulphonic acid (0.12 g, 0.5 mmol) in toluene

(50 ml) was refluxed in a dean stark apparatus for 24h. The solvent was removed *in*

vacuo at 60°C to give **58** as a clear colourless oil, which needed no further

purification (1.89 g, 99%).

δ_H (250 MHz, CDCl$_3$): 7.32 (5H, m, phenyl), 6.00 (1H, s, OH), 4.51 (2H, s, H-4), 1.94 (3H, s, C-3-Me), 1.34 (6H, s, 2 x C-2-Me); δ_C (62.5 MHz, CDCl$_3$): 174.2 (s), 139.5 (s), 129.1 (d), 128.2 (d), 127.6 (d), 127.3 (d), 126.6 (d), 72.7 (s), 53.6 (t), 27.3 (q), 12.9 (q); ν_{max} (thin film): 3320, 1665 cm^{-1}; m/z (EI): 191 (M$^+$), 91 (100%); Observed (M$^+$): 191.1310; C$_{12}$H$_{17}$NO requires 191.1310. Physical and spectroscopic data were in accordance with the reported values.[40]

3.5 Attempted preparation of *N*-Benzyl-5,5-dimethyl-4-methylene-1,2,3-oxathiazolidine-*S*-oxide (54).
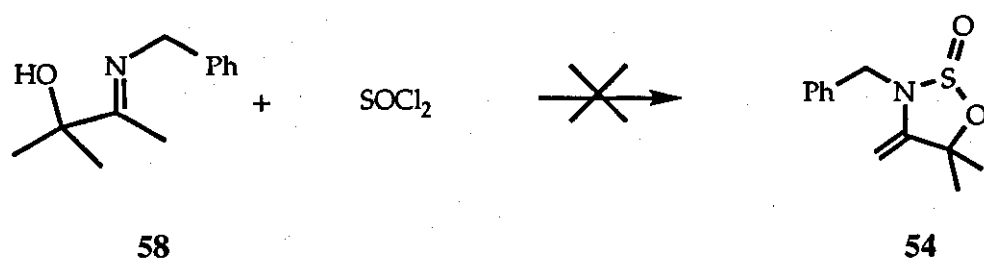
To a stirred solution of thionyl chloride (0.77 ml, 10.6 mmol) in dichloromethane at -78 °C was added, dropwise, a solution of **58** (1.84 g, 9.6 mmol) and triethylamine (2.0 ml, 14.4 mmol) in dichloromethane at -78°C, over a period of 45 mins. The mixture was stirred at -78°C for 1h, after which time the starting material was no longer visible by TLC. The reaction mixture was quenched with NaHCO$_3$ (10 ml), diethyl ether (40 ml) was added, and the organic layer separated, dried over MgSO$_4$ and the solvent removed *in vacuo*. Column chromatography (20% ethyl acetate / petrol) yielded an impure component, which was not the desired product, **54** as ascertained by ^{1}H and ^{13}C NMR spectroscopy.

3.6 Attempted preparation of 4-hydroxymethyl-3-phenyl--1,2,3-oxothiazolidine-S-oxide (60).

60
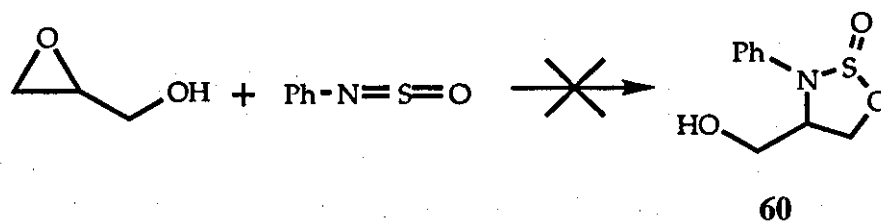
To a stirred solution of glycidol (1.0 ml, 20.0 mmol) in dichloromethane (40 ml) at

0°C was added, dropwise, triethylamine (2.8 ml, 22.0 mmol), and then

N-thionylaniline (2.5 ml, 20.0 mmol). The mixture was allowed to warm to room

temperature and stirred for 29h. A further portion of triethylamine (1.0 ml, 7.2 mmol)

and glycidol (0.5 ml, 10.0 mmol) were added to the reaction mixture and stirring

continued for a further 7 days. The mixture was washed with water (2 x 20 ml) then

brine (20 ml), and the organic layer dried over MgSO$_4$ and the solvent removed *in*

vacuo. Column chromatography (22% ethyl acetate / petrol) recovered glycidol (R$_f$

0.4) and two other semipurified components (R$_f$ 0.6 and R$_f$ 0.2). Spectroscopic

analysis indicated that none of the desired material, **60** had been formed.

3.7 Attempted preparation of 4-hydroxymethyl-3-phenyl--1,2,3-oxothiazolidine-S-oxide *via* the alkoxide (60).

60
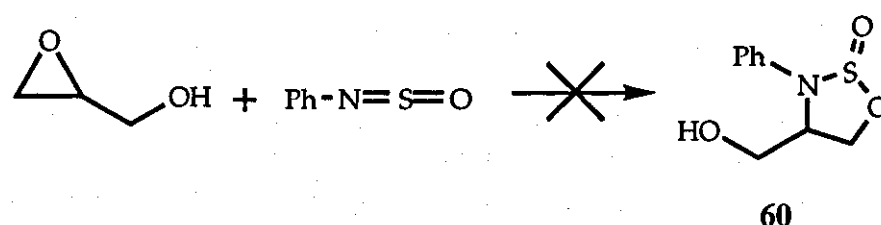
To a stirred solution of glycidol (1.20 ml, 22.0 mmol) in THF (20 ml) at 0°C was

added a solution of NaH (60% dispersion in mineral oil, 0.93 g, 23.0 mmol) in THF

(20 ml) at 0°C followed by *N*-thionylaniline (2.50 ml, 20.0 mmol). The mixture was

stirred at room temperature for 41h, washed with water (2 x 20 ml) then brine (20 ml),

and the organic layer dried over MgSO4. Removal of the solvent *in vacuo* and subsequent column chromatography (10% ethyl acetate / petrol) gave a brown oil, which was shown by ^{1}H NMR and IR to be azobenzene (Ph-N=N-Ph), by comparison with Aldrich standard IR and ^{1}H NMR spectra. δ_H (250 MHz, CDCl3): 7.50-7.19 (m, phenyl); ν_{max} (thin film): 1478, 1461, 760, 690 cm^{-1}.

3.8 Preparation of *N*-benzyl glycidol carbamate (62).

62
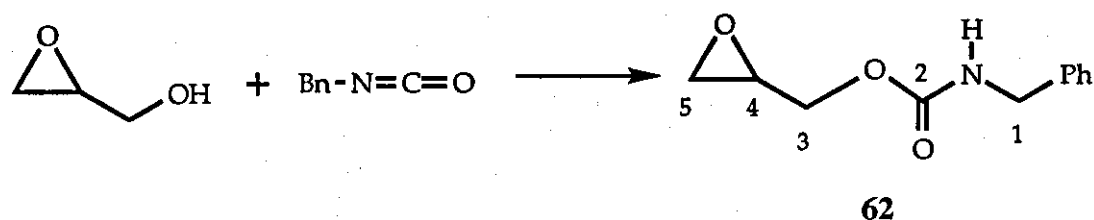
To a stirred solution of glycidol (1.12 ml, 16.9 mmol) and sodium carbonate (0.20 g, 1.89 mmol) in toluene (20 ml), was added a solution of benzyl isocyanate (2.1 ml, 17.0 mmol) in toluene (20 ml). The mixture was refluxed for 2h, then allowed to cool to room temperature, and the resulting solution filtered and concentrated *in vacuo*. Purification by column chromatography (20% acetone / hexane) gave **62** (2.59 g, 74%) as a pale yellow oil. δ_H (250 MHz, CDCl3): 7.37-7.26 (5H, m, phenyl), 5.13 (1H, s, NH), 4.46 (1H, dd, 12.2, 2.9 Hz, H-3), 4.38 (2H, d, 6.0 Hz, H-1), 3.92 (1H, dd, 12.2, 6.3 Hz, H-3), 3.24-3.17 (1H, m, H-4), 2.83 (1H, t, 4.5 Hz, H-5), 2.64 (1H, t, 3.1 Hz, H-5); δ_C (62.5 MHz, CDCl3): 156.3 (C=O), 138.4 (s), 128.5 (d), 128.4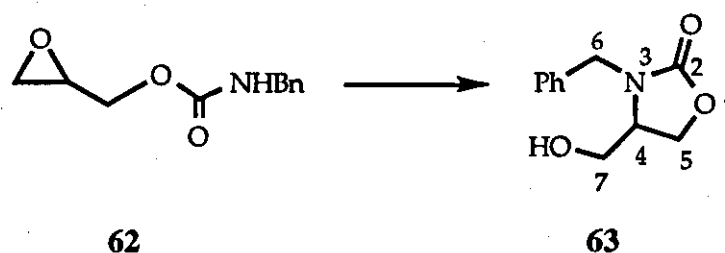 (d), 127.4 (d), 65.4 (t), 49.7 (d), 44.9 (t), 44.4 (t); ν_{max} (thin film): 3331, 2926, 1718, 1255 cm^{-1}; m/z: 207 (M$^+$), 150, 106, 91, 77. Physical and spectroscopic data were in accordance with the reported values.[5]

3.9 Preparation of *N*-benzyl-4-hydroxymethyl-1,2,3-oxazolidinone (63).

To a solution of NaH (60% dispersion in mineral oil, 0.31 g, 7.7 mmol) in THF (24 ml) was added a solution of 62 (2.59 g, 12.5 mmol) in THF (48 ml), cooled to 0°C, over a period of 20 minutes. The mixture was maintained below 5°C for 2h and then allowed to warm to room temperature. The pH was adjusted to pH3 with 10M HCl, and the solvent removed *in vacuo*. Water was poured into the residue, and the product and extracted into dichloromethane (3 x 75 ml), washed with brine and dried over MgSO$_4$. The solvent was removed under reduced pressure to give an almost colourless oil. Purification by column chromatography (40% acetone / hexane) gave 63 as a white crystalline solid (2.03 g, 78%); M.p. 67-68°C (lit. 68.5-69.5). δ_H (250 MHz, CDCl$_3$): 7.39-7.26 (5H, m, phenyl), 4.64 (1H, d, 15.1 Hz, H-6), 4.36 (1H, d, 15.1 Hz, H-6), 4.38-4.10 (2H, m, H-5), 3.78-3.71 (2H, m, H-7), 3.53 (1H, m, H-4), 1.76 (1H, s, OH); δ_C (62.5 MHz, CDCl$_3$): 158.8 (s), 136.0 (s), 128.8 (d), 128.0 (d), 127.9 (d), 64.5 (t), 60.3 (t), 55.7(d), 46.2 (t); v_{max} (thin film): 3406, 2923, 1744 cm^{-1}. Physical and spectroscopic data were in accordance with the reported values.[5]

3.10 Preparation of *N*-benzyl-4-[(2-nitrophenyl)selenomethyl]-1,2,3-oxazolidinone (64).

63   **64**
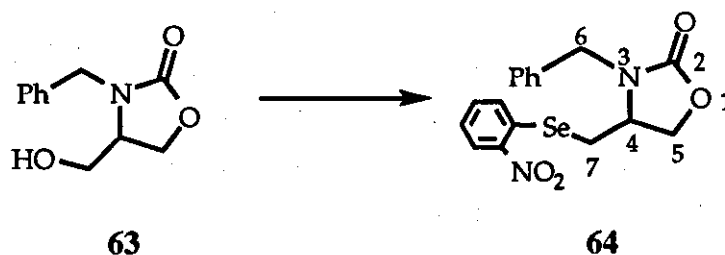
2-Nitrophenylselenocyanate (2.10 g, 9.25 mmol) and **63** (1.94 g, 9.36 mmol) were dissolved in THF (70 ml) and *n*-tributylphosphine (2.3 ml, 9.34 mmol) was added dropwise. The mixture was stirred at room temperature for 24h. Evaporation of the solvent yielded a black oil, which was purified by column chromatography (20% ethyl acetate / toluene) to give **64** as a red / brown crystalline solid (2.28 g, 62%); M.p. 97-98 °C; δ_H (250 MHz, CDCl$_3$): 8.25 (1H, m, phenyl), 7.43-7.26 (7H, m, phenyl), 6.97 (1H, m, phenyl), 4.94 (1H, d, 15.3 Hz, H-6), 4.40 (1H, t, 8.9 Hz, H-5), 4.25 (1H, d, 15.3 Hz, H-6), 4.16 (1H, dd, 8.9, 5.9 Hz, H-5), 3.90-3.79 (1H, m, H-4), 3.29 (1H, dd, 12.9, 3.1 Hz, H-7), 2.74 (1H, dd, 12.9, 10.4 Hz, H-7); δ_C (62.5 MHz, CDCl$_3$): 140 (s), 133.8 (d), 129.1 (d), 128.3 (d), 128.2 (d), 126.6 (d), 126.2 (d), 67.6 (t), 52.7 (d), 46.4 (t), 26.9 (t); ν_{max} (thin film): 1751, 1508 cm^{-1}; *m/z* (EI): 392 (M$^+$), 91 (100%); Found: C 52.02, H 3.89, N 7.29%; C$_{17}$H$_{16}$N$_2$O$_4$Se requires: C 52.17, H 4.09, N 7.16 %.

3.11 Preparation of 3-[(2-nitrophenyl)seleno]-2-benzylaminopropan-1-ol (65).

64   **65**
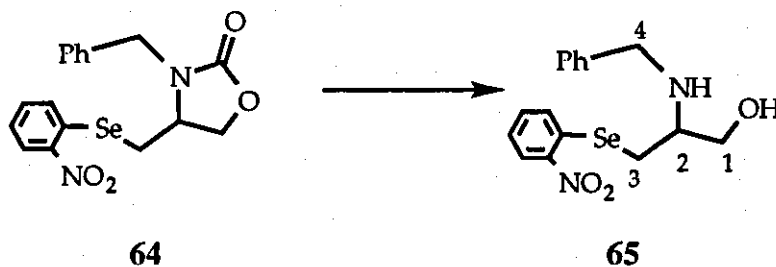
A solution of **64** (0.14 g, 0.35 mmol) and 2M NaOH (5 ml) were refluxed in 96% ethanol (10 ml) for 7h The solvent was removed *in vacuo* to leave an emulsion which

was dissolved in water and extracted with ethyl acetate (4 x 15 ml). The organic layers were combined, washed with brine, dried over MgSO$_4$ and the solvent removed *in vacuo* . Purification by column chromatography (50 : 50 : 1; CH$_2$Cl$_2$ / ethyl acetate / 25% aq NH$_4$OH) gave **65** (50.0 mg, 37%) as a red / brown crystalline solid. δ$_H$ (250 MHz, CDCl$_3$): 8.27-7.23 (9H, m, phenyl), 3.84 (2H, s, H-4), 3.80 (1H, dd, 11.0, 3.9 Hz, H-1), 3.58 (1H, dd, 11.0, 4.5 Hz, H-1), 3.13-2.97 (3H, m, H-2 & H-3), 2.25 (2H, s, OH and NH). No other data was obtained for this compound.

3.12 Preparation of *N*-benzyl-4-[(2-nitrophenyl)selenomethyl]-1,2,3-oxothiazolidine-*S*-oxide (66).
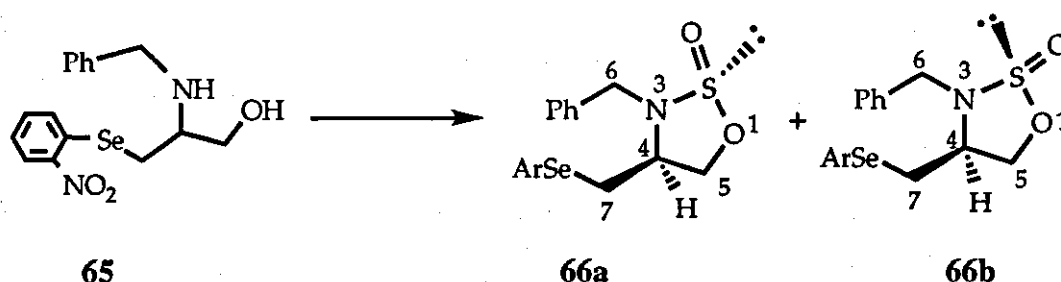
To a stirred solution of thionyl chloride (0.17 g, 2.30 mmol) in dichloromethane (35 ml) at -78°C was added dropwise, a stirred solution of **65** (0.45 g, 1.24 mmol) and triethylamine (0.65 ml, 4.66 mmol) in dichloromethane at -78°C . The mixture was stirred at -78°C for 9h and then allowed to warm to room temperature. The solvent was removed *in vacuo*, and the residue washed with ether (5 x 5 ml). Evaporation of the solvent and subsequent purification by column chromatography (40% ethyl acetate / petrol) gave the two, yellow crystalline, diastereomeric products, (2*S**,4*S**)-*N*-benzyl-4-[(2-nitrophenyl)selenomethyl]-1,2,3-oxazolidinone (60.0 mg, 12%) (66a): δ$_H$ (250 MHz, CDCl$_3$): 8.23 (1H, m, ArH *o* -Se), 7.51-7.26 (7H, m, aryl), 6.95 (1H, m, ArH

p-Se), 4.82 (1H, dd, 8.9, 5.3 Hz, H-5), 4.62 (1H, dd, 8.9, 6.8 Hz, H-5), 4.40 (1H, d, 14.5 Hz, H-6), 4.32 (1H, d, 14.5 Hz, H-6), 3.73-3.64 (1H, m, H-4), 3.41 (1H, dd, 13.0, 3.8 Hz, H-7), 3.12 (1H, dd, 13.0, 11.1 Hz, H-7); and more polar (2*R**,4*S**)-*N*-benzyl-4-[(2-nitrophenyl)selenomethyl]-1,2,3-oxazolidinone (70.0 mg, 13%) (66b): δ$_H$ (250

MHz, CDCl₃): 8.24-7.03 (9H, m, aryl), 4.91 (1H, dd, 8.9, 6.8 Hz, H-5), 4.48 (1H, dd, 8.9, 4.4 Hz, H-5), 4.35 (1H, d, 14.1 Hz, H-6), 4.24 (1H, d, 14.1 Hz, H-6), 3.91-3.81 (1H, m, H-4), 3.06 (1H, dd, 12.7, 3.2 Hz, H-7), 2.82 (1H, dd, 12.7, 9.4 Hz, H-7).

No other data was obtained for these compounds.

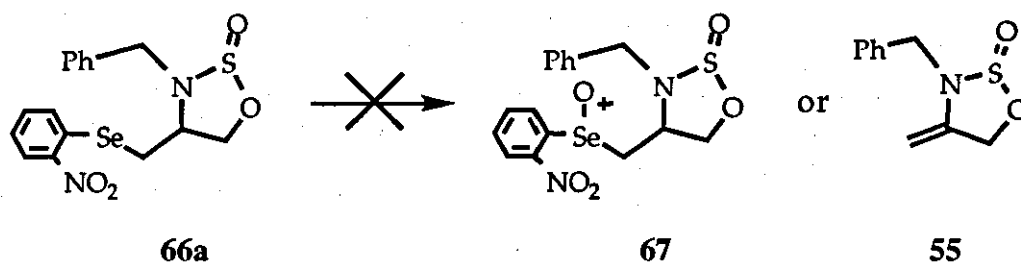### 3.13 Attempted preparation of *N*-benzyl-4-[(2-nitrophenylselenoxide)methyl]-1,2,3-oxathiazolidine-*S*-oxide (67).

To a solution of (2*S**,4*S**)-*N*-benzyl-4-[(2-nitrophenyl)selenomethyl]-1,2,3-oxazolidinone (60.0 mg, 0.15 mmol) in THF (36 ml) at 0°C was added 30% hydrogen peroxide solution (14.0 ml, 1.5 mmol) dropwise over 1h. The mixture was allowed to warm to room temperature and stirred for 2.5h, until the starting material had been consumed, as judged by TLC. The solvent was removed *in vacuo*, leaving an aqueous emulsion, which was diluted with water (30 ml). The product was extracted with ethyl acetate (3 x 30 ml), washed with brine, dried over MgSO₄, and the solvent removed *in vacuo*. It was not possible from ¹H NMR to discern the nature of the product, except that it was neither the desired product **67**, nor **55**.

3.14 Preparation of *N*-Benzyl-4-methylsulfonyl-1,2,3-oxazolidinone (70).
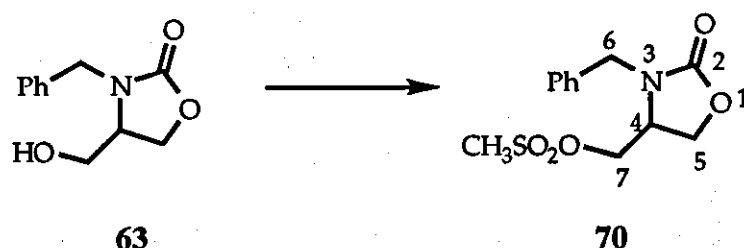
To a stirred solution of **63** (1.52 g, 7.33 mmol) and triethylamine (1.50 ml, 10.86 mmol) in dichloromethane (40 ml) at 0°C, was added, dropwise, methanesulfonyl chloride (0.62 ml, 8.06 mmol), and the mixture stirred at 0°C for 4h. Aqueous sodium bicarbonate (40 ml) was added, and the mixture extracted into dichloromethane (2 x 20 ml) and the combined organic layers were dried over MgSO$_4$. Evaporation of the solvent *in vacuo* gave **70** (1.91 g, 92%), which was essentially pure by ^{1}H NMR spectroscopy. Purification of a portion of this material (0.17g) by column chromatography (60% ethyl acetate / petrol) gave **70** (0.12 g, 65%) as an off-white, waxy solid, which was used for the purposes of characterisation. Crude material was used in the following step. M.p. 98-99 °C; δ_H (400 MHz, CDCl$_3$): 7.43-7.27 (5H, m, phenyl), 4.79 (1H, d, 15.3 Hz, H-6), 4.38 (1H, t, 9.1 Hz, H-5 or H-7), 4.26 (1H, dd, 11.0, 4.1 Hz, H-5 or H-7), 4.25 (1H, d, 15.3 Hz, H-6), 4.20 (1H, dd, 9.1, 3.3 Hz, H-5 or H-7), 4.13 (1H, dd, 11.0, 3.6 Hz, H-5 or H-7), 3.93-3.89 (1H, m, H-4), 2.98 (3H, s, SO$_2$CH$_3$); δ_C (100 MHz, CDCl$_3$): 158.0 (s), 135.4 (s), 129.1 (d), 128.9 (d), 128.5 (d), 128.2 (d), 128.1 (d), 66.1 (t), 65.7 (t), 54.0 (q), 46.7 (t), 37.7 (d); ν_{max} (thin film): 1746, 1174 cm^{-1}; m/z (EI): 285 (M$^+$), 91 (100%); Observed (M$^+$): 285.0671; C$_{12}$H$_{15}$NSO$_5$ requires 285.0671.

3.15 Preparation of *N*-benzyl-4-(phenylselenomethyl)-1,2,3-oxazolidinone (71).
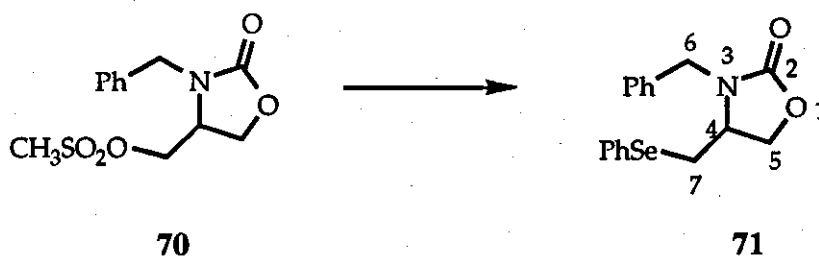
Diphenyl diselenide (0.18 g, 0.59 mmol) was dissolved in absolute ethanol (12 ml) and sodium borohydride (0.05 g, 1.28 mmol) was added slowly until the bright yellow solution turned colourless. Crude mesylate **70** (0.30 g, 1.06 mmol) was added and the mixture refluxed for 4.5h. The ethanol was removed *in vacuo* to leave an aqueous emulsion, to which water (20 ml) was added and the product extracted into ethyl acetate (2 x 20 ml). The organic layers were combined, washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification by column chromatography (2% acetone / dichloromethane) gave **71** (0.19 g, 52%) as a clear golden oil. δ_H (400 MHz, $CDCl_3$): 7.40-7.17 (10H, m, phenyl), 4.69 (1H, d, 15.2 Hz, H-6), 4.33 (1H, t, 8.9 Hz, H-5), 4.08 (1H, dd, 8.9, 5.8 Hz, H-5), 3.99 (1H, d, 15.2 Hz, H-6), 3.78-3.69 (1H, m, H-4), 3.13 (1H, dd, 12.9, 2.9 Hz, H-7), 2.79 (1H, dd, 12.9, 9.3 Hz, H-7); δ_C (62.5 MHz, $CDCl_3$): 135.2 (s), 133.3 (d), 129.3 (d), 128.8 (d), 128.1 (d), 128.0 (d), 67.5 (t), 54.0 (d), 46.1 (t), 29.3 (t); v_{max} (thin film): 1746 cm^{-1}; m/z (EI): 347 (M$^+$), 91 (100%); Observed (M$^+$): 347.0424; $C_{17}H_{17}NO_2Se$ requires 347.0424.

3.16 Preparation of *N*-benzylamino-3-phenylselenopropan-1-ol (72).

71 → **72**
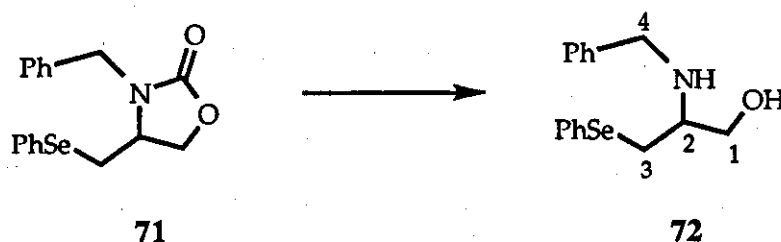
A solution of **71** (1.02 g, 2.96 mmol) and 2M NaOH (25 ml) were refluxed in 96%

ethanol (25 ml) for 8h. The solvent was removed *in vacuo* to leave an aqueous

emulsion, which was dissolved in water and the product extracted into ethyl acetate (4

x 15 ml). The organic layers were combined, washed with brine, dried over $MgSO_4$

and the solvent removed *in vacuo*. Purification by column chromatography (95:5,

ethyl acetate / 25% aq NH_4OH) gave **72** (0.66 g, 69%) as an off white crystalline

solid. M.p. 56-57°C; δ_H (400 MHz, $CDCl_3$): 7.46 (2H, m, phenyl), 7.29-7.22 (8H, m,

phenyl), 3.71(2H, s, H-4), 3.72-3.68 (1H, m, H-1), 3.42 (1H, dd, 10.9, 5.4 Hz, H-1),

3.05 (2H, dd, 6.3, 1.7 Hz, H-3), 2.83 (1H, m, H-2), 2.32 (2H, s, OH and NH); δ_C

(62.5 MHz, $CDCl_3$): 140.0 (s), 139.7 (d), 132.9 (d), 129.1 (d), 128.4 (d), 128.1 (d),

127.2 (d), 62.9 (t), 57.3 (d), 50.9 (t), 30.6 (t); v_{max} (thin film): 3446 cm^{-1}; m/z (EI):

322 (MH$^+$), 108 (100%); Observed (M$^+$): 322.0710; $C_{16}H_{19}NOSe$ requires 322.0710.

3.17 Preparation of *N*-benzyl-4-phenylselenomethyl-1,2,3-oxathiazolidine-*S*-oxide (73).

72 → **73a** + **73b**
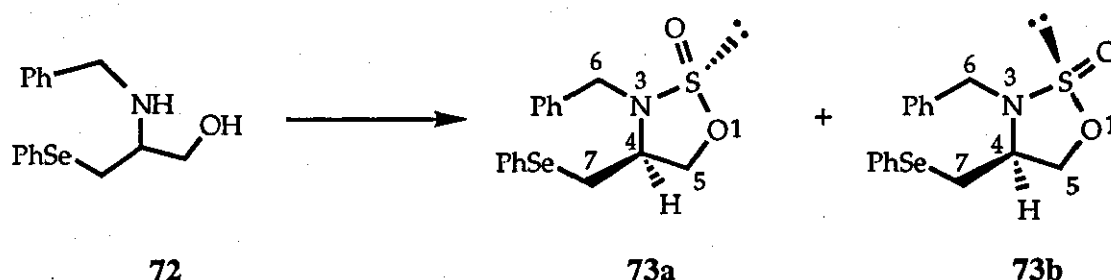
To a stirred solution of thionyl chloride (0.20 ml, 2.99 mmol) in dichloromethane (20

ml) at -78°C was added, dropwise, a solution of **72** (0.56 g, 1.74 mmol) and

triethylamine (0.80 ml, 5.75 mmol) in dichloromethane (15 ml). The solution was

stirred at -78°C for 5h and allowed to warm to room temperature. The solvent was evaporated *in vacuo*, and the product extracted with diethyl ether (2 x 10 ml) and then ethyl acetate (2 x 20 ml), and the combined organic layers dried over $MgSO_4$. Evaporation of the solvent yielded a brown oil. Purification by column chromatography (30% ethyl acetate / petrol) enabled the partial separation of two diastereomeric products (0.41g, 65% combined yield), $(2S^*,4S^*)$-*N*-benzyl-4-(phenylseleno)methyl-1,2,3-oxathiazolidine (**73a**): δ_H (400 MHz, $CDCl_3$): 7.33-7.17 (10H, m, phenyl), 4.73 (1H, dd, 8.9, 6.2 Hz, H-5), 4.58 (1H, dd, 8.9, 6.8 Hz, H-5), 4.25 (2H, s, H-6), 3.61-3.54 (1H, m, H-4), 3.25 (1H, dd, 12.8, 3.6 Hz, H-7), 3.04 (1H, dd, 12.8, 11.0 Hz, H-7); δ_C (100 MHz, $CDCl_3$): 135.7 (s), 132.6 (d), 129.4 (d), 129.0 (d), 128.9 (d), 128.7 (d), 128.4 (d), 128.2 (d), 127.4 (d), 76.1 (t), 61.1 (d), 49.1 (t), 28.9 (t); v_{max} (thin film): 2924, 1152 cm^{-1}; m/z (EI): 367 (M$^+$), 91 (100%); Observed (M$^+$): 367.0145; $C_{16}H_{17}NSO_2Se$ requires: 367.0145; and more polar $(2R^*,4S^*)$-*N*-benzyl-4-(phenylseleno)methyl-1,2,3-oxathiazolidine (**73b**): δ_H (250 MHz, $CDCl_3$): 7.42-7.20 (10H, m, phenyl), 4.89 (1H, t, 8.3 Hz, H-5), 4.41 (1H, dd, 8.3, 4.5 Hz, H-5), 4.21 (1H, d, 13.9, H-6), 4.10 (1H, d, 13.9, H-6), 3.80-3.67 (1H, m, H-4), 2.96 (1H, dd, 12.6, 3.4 Hz, H-7), 2.77 (1H, dd, 12.6, 9.9 Hz, H-7); δ_C (62.5 MHz, $CDCl_3$): 136.1 (s), 133.0 (d), 129.3 (d), 128.9 (d), 128.7 (d), 128.4 (d), 128.1 (d), 127.6 (d), 74.6 (t), 59.2 (d), 48.8 (t), 29.5 (t); v_{max} (thin film): 2959, 1153 cm^{-1}; m/z (EI): 367 (M$^+$), 91 (100%); Observed (M$^+$): 367.0145; $C_{16}H_{17}NSO_2Se$ requires 367.0145; Found: C 52.10, H 4.56, N 3.79%; $C_{16}H_{17}NSO_2Se$ requires: C 52.32, H 4.67, N 3.82 %.

3.18 Attempted preparation of *N*-benzyl-4-[(phenylselenoxide)methyl]-1,2,3-oxothiazolidine-*S*-oxide under aqueous conditions (83)

73   **83**   or   **55**
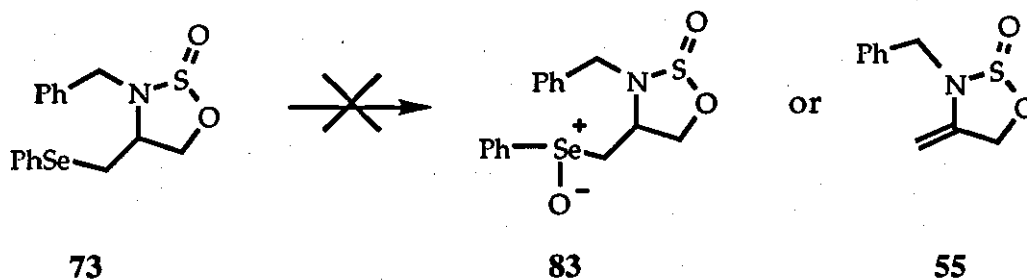
To a stirred solution of a diastereomeric mixture of **73** (124.1 mg, 0.34 mmol) in THF (50 ml) at 0°C was added 20% hydrogen peroxide (20.0 ml) dropwise over a period of 30 mins, and the mixture stirred a room temperature for 6h, until the starting material had been completely consumed, as judged by TLC. The solvent was removed *in vacuo* to leave an aqueous emulsion, to which water (20 ml) was added, the mixture was then extracted with ethyl acetate (3 x 30 ml). The combined organic layers were washed with brine (30 ml), dried over $MgSO_4$ and the solvent removed *in vacuo*. ^{1}H NMR indicated the formation of a complex mixture of adducts which failed to indicate the presence of either the desired selenoxide **83** nor olefin **55**.

3.19 Attempted preparation of *N*-benzyl-4-[(phenylselenoxide)methyl]-1,2,3-oxothiazolidine-*S*-oxide under non-aqueous conditions (83)

73   **83**   or   **55**
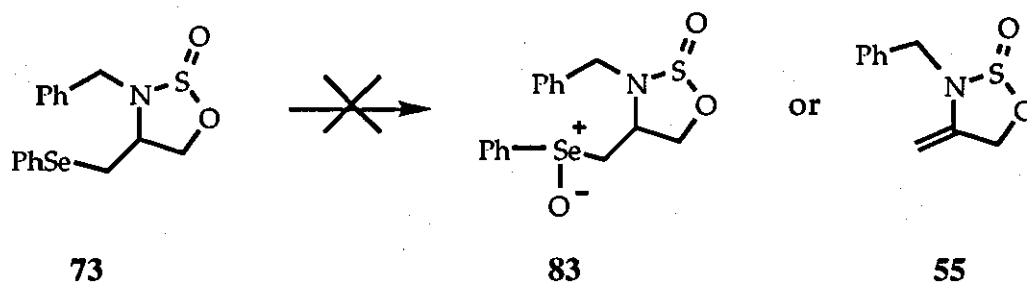
To a stirred solution of a diastereomeric mixture of **73** (50.0 mg, 0.14 mmol) and sodium carbonate (30.0 mg) in deuterated chloroform, at room temperature, was added *m*- chloroperoxybenzoic acid (50.0mg, 0.28 mmol). Aliquots of the reaction mixture were taken after 0 mins, 45 mins, 90 mins, 2.5h, 11h, and 23h and analysed

by ^{1}H NMR spectroscopy. At no time point did ^{1}H NMR indicate the desired product **83**, although starting material was still visible by TLC after 23h. The reaction mixture was filtered and the solvent removed *in vacuo*. Column chromatography (60% acetone / petrol) enabled the isolation of 3 components which ^{1}H NMR showed to be neither the desired product **83** or **55**, nor the starting material. Unfortunately, we were unable to determine the structure of any of the isolated products.

3.20 Preparation of *N*-benzyl serine methyl ester (75).

75
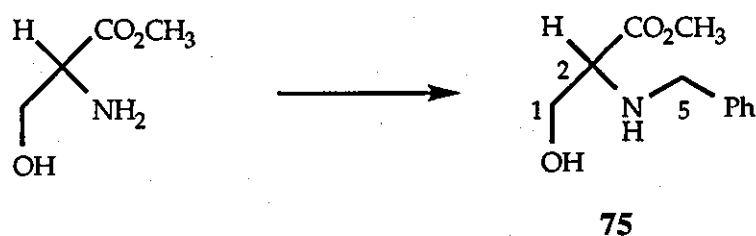
To a suspension of serine methyl ester hydrochloride (7.87 g, 50.58 mmol) and anhydrous $MgSO_4$ in dichloromethane (50 ml), were added triethylamine (7.25 ml, 52.1 mmol) and benzaldehyde (5.1 ml, 50.3 mmol). The mixture was stirred at room temperature for 24h, filtered and the filtrate concentrated *in vacuo* to give an aqueous emulsion, which was redissolved in methanol (100 ml). Sodium borohydride (1.90 g, 50.0 mmol) was added slowly at 0°C and the mixture stirred at room temperature for 15h. Water (80 ml) was added and the product extracted into ethyl acetate (2 x 80 ml), the combined organic layers were washed with brine, dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification by column chromatography (60% ethyl acetate / petrol) gave **75** (9.36 g, 89%) as a pale yellow oil. δ_H (400 MHz, CDCl$_3$): 7.36-7.22 (5H, m, phenyl), 3.87 (1H, d, 12.8 Hz, H-5), 3.77 (1H, dd, 11.0, 4.7 Hz, H-1), 3.74 (3H, s, CO$_2$Me), 3.73 (1H, d, 12.8 Hz, H-5), 3.62 (1H, dd, 11.0, 6.3 Hz, H-1), 3.43 (1H, m, H-2), 2.59 (2H, s, NH and OH); δ_C (62.5 MHz, CDCl$_3$): 173.4 (s), 139.2 (s), 128.5 (d), 128.2 (d), 127.3 (d), 62.4 (t), 61.8 (q), 52.1 (d), 52.0 (t); v_{max} (thin film): 3321, 2951, 1738 cm^{-1}. Physical and spectroscopic data were in accordance with the reported values.[46]

3.21 Preparation of *N*-benzyl-2,2-dimethyl-4-oxazolidinecarboxylic acid methyl ester (76).
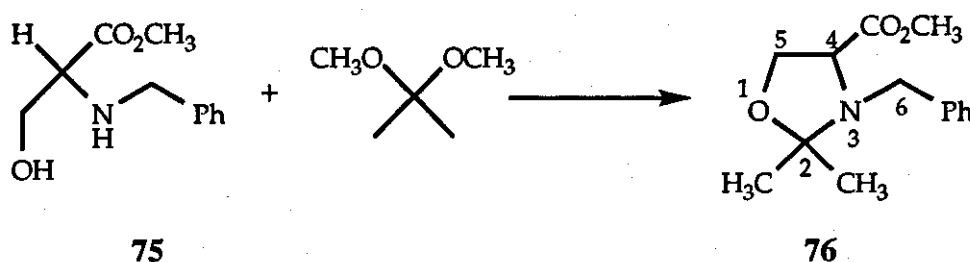
A solution of **75** (3.09 g, 14.81 mmol), 2,2-dimethoxypropane (18.4 ml, 149.9 mmol) and *p*-toluene sulfonic acid (0.09 g) in toluene (20 ml) containing 4Å molecular sieves were refluxed for 48h. The mixture was cooled, filtered and concentrated *in vacuo*. Diethyl ether (75 ml) and aqueous $NaHCO_3$ (50 ml) were added and the organic layer was separated, washed with brine (25 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give a brown oil. Purification by column chromatography (40% ethyl acetate / petrol) gave **76** (1.29 g 35%) as a clear, golden oil. δ_H (400 MHz, CDCl$_3$): 7.36-7.22 (5H, m, phenyl), 4.11 (1H, t, 8.1 Hz, H-4), 3.97 (1H, m, H-5), 3.97 (1H, d, 13.6 Hz, H-6), 3.71 (1H, d, 13.6 Hz, H-6), 3.63 (1H, dd, 7.7, 5.4 Hz, H-5), 3.42 (3H, s, CO_2CH_3), 1.43 (3H, s, CH_3), 1.30 (3H, s, CH_3); δ_C (100 MHz, CDCl$_3$): 172.9 (s), 139.0 (s), 128.6 (d), 128.4 (d), 128.3 (d), 127.1 (d), 96.3 (s), 66.7 (t), 63.9 (q), 52.5 (t), 51.6 (d), 26.7 (q), 22.4 (q); v_{max} (thin film): 1747, 1198 cm^{-1}. Physical and spectroscopic data were in accordance with the reported values. [46]

3.22 Attempted Preparation of N-benzyl-2,2-dimethyl-4-oxazolidine dimethylmethanol (using methyl magnesium bromide) (77).
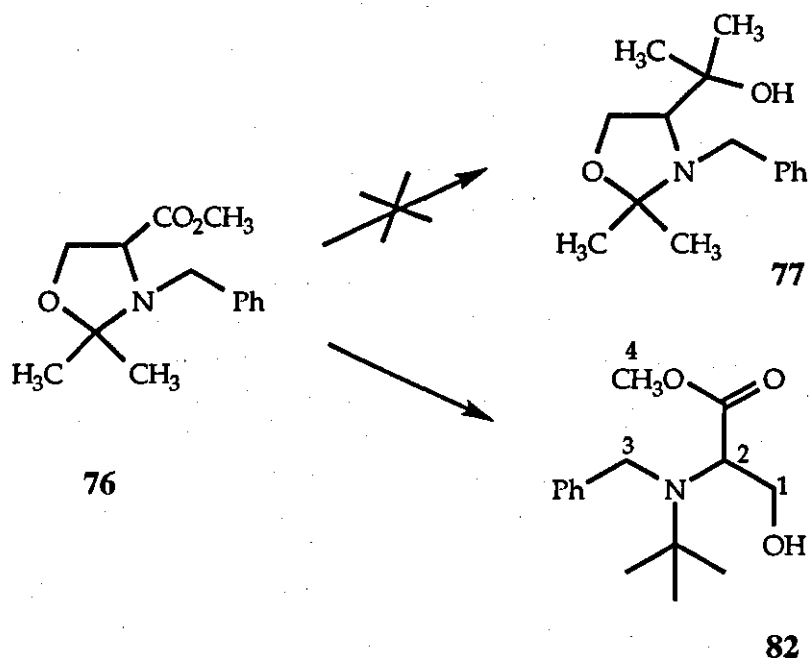
To a solution of **76** (0.50 g, 2.00 mmol) in diethyl ether (20 ml) at 0°C was added, dropwise MeMgBr (3.0M in diethyl ether, 1.47 ml, 4.40 mmol) The mixture was allowed to warm to room temperature and stirred for an additional 40 mins. The reaction was quenched by the addition of saturated NH_4Cl (20 ml) and the product extracted into dichloromethane (3 x 30 ml). The combined organic layers were dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification by column chromatography (25% ethyl acetate / petrol) gave **82** (0.42 g, 79%) as a clear golden oil. δ_H (400 MHz, $CDCl_3$): 7.33-7.17 (5H, m, phenyl), 4.06 (2H, s, H-3), 3.99 (1H, m, H-2), 3.71 (3H, s, CO_2CH_3), 3.65 (1H, m, H-1), 3.42 (1H, m, H-1), 2.37 (1H, s, OH), 1.18 (9H, s, ^tBu); δ_C (62.5 MHz, $CDCl_3$): 173.6 (s), 143.2 (s), 128.3 (d), 126.9 (d), 126.4 (d), 61.7 (q), 61.5 (t), 56.0 (s), 51.4 (d), 48.9 (t), 28.7 (q); ν_{max} (thin film): 3445, 1732, 1203 cm^{-1}; m/z (EI): 265 (M$^+$), 91 (100%); Observed (M$^+$): 265.1679; $C_{15}H_{23}NO_3$ requires 265.1678.

3.23 Preparation of *N*-Benzyl-2,2-Dimethyl-4-oxazolidine dimethylmethanol (using methyl lithium) (77).
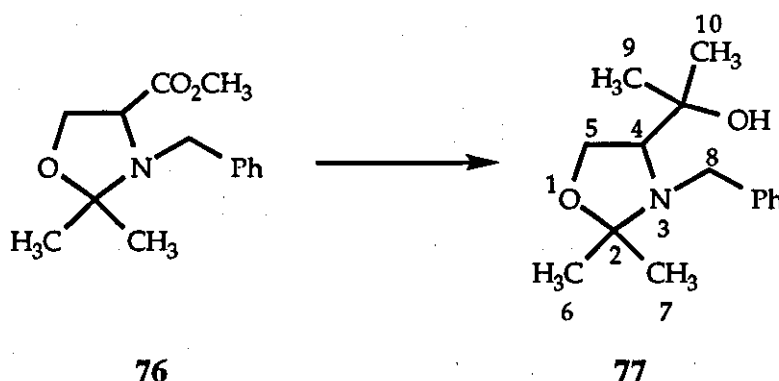
To a solution of **76** (0.11 g, 0.44 mmol) at 0°C in diethyl ether (5 ml), was added, dropwise MeLi (1.4M in diethyl ether, 0.70 ml, 0.98 mmol). The mixture was allowed to warm to room temperature and stirred for 2h, at which point a further portion of MeLi (0.15 ml, 0.22 mmol) was added. After stirring for 24h, saturated NH$_4$Cl solution (20 ml) was added and the mixture extracted into dichloromethane (3 x 30 ml). The organic layers were combined, dried over MgSO$_4$ and the solvent removed *in vacuo*. Purification by column chromatography (25% ethyl acetate / petrol) yielded **77** (37.3 mg, 34%) as a clear golden oil. δ_H (400 MHz, CDCl$_3$): 7.43-7.25 (5H, m, phenyl), 3.87 (1H, d, 15.0 Hz, H-8), 3.59 (1H, d, 15.0 Hz, H-8), 3.40 (2H, d, 4.6 Hz, H-5), 2.87 (1H, t, 4.7 Hz, H-4), 1.31 (3H, s, Me), 1.30 (3H, s, Me); 1.26 (3H, s, Me), 1.23 (3H, s, Me); δ_C (62.5 MHz, CDCl$_3$): 139.9 (s), 127.7 (d), 127.2 (d), 126.9 (d), 126.7 (d), 126.2 (d), 93.1 (s), 78.3 (s), 70.8 (d), 59.9 (t), 51.0 (t), 28.1 (q), 27.7 (q), 23.9 (q), 21.4 (q); ν_{max} (thin film): 3442, 3063-2931 cm^{-1}; m/z (EI): 91 (100%); Observed (MH$^+$): 250.1807; C$_{15}$H$_{24}$NO$_2$ requires 250.1808; Observed (M$^+$-Me): 234.1493; C$_{14}$H$_{20}$NO$_2$ requires 234.1494.

Chapter 4 :

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