α, β-EPOXYSULPHONATES AND α, β-EPOXYSULPHONAMIDES
Asymmetric Synthesis and some Reactions

BY

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A THESIS SUBMITTED IN FULFILMENT OF THE REQUIREMENTS FOR THE
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The investigations reported in this thesis were carried out at the Department of Organic Chemistry, University of Nijmegen, The Netherlands, under a cooperation agreement between that university and the University of Dar es Salaam.

DECLARATION

I Mayunga Habibu Hemedi Nkunya declare that this thesis has not been submitted to any other university for any other degree.

signature ....
M.H.H. Nkunya

supervisor's signature ....
Prof.Dr. B. Zwanenburg

To my parents, Cheka and our son Msafiri

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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

b.p. : boiling point
Bu or *n*-Bu : normal butyl
CD : circular dichroism
Δ : heat
DME : dimethoxyethane
DMF : dimethylformamide
DMSO : dimethylsulphoxide
Et : ethyl
$\mathrm{Eu(dpm)_3}$: dipivalomethanatoeuropium(III)
$\mathrm{Eu(fod)_3}$: tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium
$\mathrm{Eu(tfc)_3}$: tris[3-(trifluoromethylhydroxymethylene)-d-comphorato]europium
HMPA : hexamethylphosphoramide
LDA : lithium di-isopropylamide
Me : methyl
m.p. : melting point
Nu : nucleophile
pet.ether : petroleum ether (boiling range 40-60°)
Ph : phenyl
THF : tetrahydrofuran
Tol or *p*-Tol: para tolyl
$\mathrm{Yb(hfc)_3}$: tris[3-(heptafluoropropylhydroxymethylene)-d-camphorato]ytterbium
$\mathrm{Yb(tfc)_3}$: tris[3-(trifluoromethylhydroxymethylene)-d-camphorato]ytterbium

SUMMARY

This thesis describes the asymmetric phase-transfer catalysed (PTC) Darzens condensation of aldehydes and ketones with the chiral reagents l-menthyl chloromethanesulphonate, (*S*)-(-)-*N*-chloromethylsulphonyl-2-methoxymethylpyrrolidine, (*S*)-(-)-*tert*-butyl *N*-(chloromethylsulphonyl)prolinate and (+)-*O*-methyl-*N*-(chloromethylsulphonyl)ephedrine using triethylbenzylammonium chloride (TEBA) as the phase-transfer catalyst. The chiral reagent l-menthyl chloromethanesulphonate was obtained by the sulphonation of l-menthol with chloromethanesulphonyl chloride. The chloromethanesulphonamides were similarly obtained from suitable derivatives of (*S*)-(-)-proline and (+)-ephedrine, respectively.

The diastereomeric α,β-epoxysulphonate esters from l-menthyl chloromethanesulphonate and the α,β-epoxysulphonamides from the chloromethanesulphonamides were obtained in good chemical yields, showing a diastereomeric excess (d.e.) ranging from 10-18% for the epoxysulphonate esters and from 10-50% for the proline epoxysulphonamides. The d.e. values for the ephedrine epoxysulphonamides were rather low (4-8%, with one positive exception of 20%). The improved degree of asymmetric induction using proline derived chloromethanesulphonamides as chiral reagents was based on the better defined and conformationally less flexible stereostructures of the transition states leading to proton abstraction by base to form intermediate diastereomeric α-sulphonyl carbanions. Reaction of these anions with the carbonyl compounds gave the desired epoxysulphonamides. The lower d.e. values for epoxysulphonylephedrines support the dependence of the chiral induction on the conformational flexibility of the stereostructure of a chiral reagent. The dependence of the extent of asymmetric induction on the steric bulk of the starting carbonyl compound was demonstrated in all the cases. The rationale for the better d.e. values when (*S*)-(-)-*N*-chloromethylsulphonyl-2-methoxymethylpyrrolidine was used as the chiral reagent instead of *tert*-butyl *N*-(chloromethylsulphonyl)prolinate is also discussed.

A discussion of the stereochemical course for the stereoselective formation of (*E*)-epoxysulphones in the Darzens condensation of aldehydes with chloromethanesulphones, which is based on the Curtin-Hammett principle, is presented together with a survey of some literature pertinent in the discussion of the experimental results.

An account is given on the attempted and successful reactions of α,β-epoxysulphones and epoxysulphonamides. In this respect an approach to the asymmetric synthesis of α-methyl-α-aminoacids from the reaction of the intermediate epoxysulphonamides with sodium azide is described. The enantiomeric excess of the thus-obtained α-methyl amino alcohols, which in principle can be converted to the desired α-methyl-α-aminoacids with retention of stereochemistry, was about 30%. Reductive desulphonylation and reactions with organometallic reagents failed to take place with epoxysulphones and epoxysulphonamides. Attempted reaction with magnesium bromide led to the rearrangement of the epoxysulphonamides derived from the 2-methoxymethylpyrrolidine sulphonamide.

CHAPTER 1

INTRODUCTION

1.1. *ASYMMETRIC SYNTHESIS*

An asymmetric synthesis is defines as "a reaction in which an achiral unit in an assemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products are produced in unequal amounts". In this broad definition as proposed by Morrison and Mosher[1], reactants include chemical reagents, solvents, catalysts and physical forces.

The concept of asymmetric synthesis was introduced as early as 1894 by Emil Fischer.[2] Since then more than half a decade elapsed before asymmetric reactions were frequently encountered in the chemical literature. Today asymmetric synthesis has attracted enormous interest among synthetic organic chemists. A major factor that has considerably contributed to the popularity of this synthetic methodology is the discovery that chirality plays an essential role in living systems. Apart from the preparation of optically active compounds asymmetric reactions are very useful for the elucidation of the mechanisms of reactions and for the assignment of absolute configurations.[3]

Generally in an asymmetric synthesis an asymmetric (or chiral) induction should take place. This then leads to the creation of a new chiral unit with one configuration (enantiomer or diastereomer) being predominant. The difference in quantity between the two stereoisomers is called stereomeric excess (enantiomeric or diastereomeric excess, denoted as e.e. or d.e., respectively). This value is usually expressed as a percentage. Alternatively the degree of asymmetric synthesis is reported as a percent optical purity (% o.p.). The latter expression is derived from the following formula:[1]

$$\%\ \text{optical purity} = \frac{\text{observed } [\alpha]_D \text{ of the reaction product}}{\text{maximum } [\alpha]_D \text{ of the prepared compound}} \times 100$$

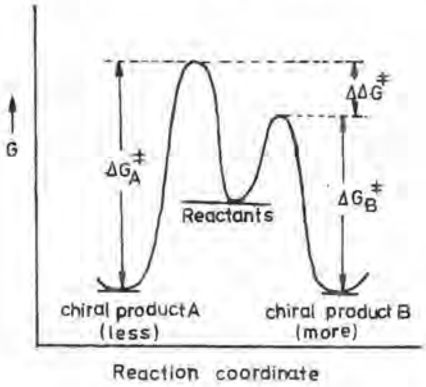
Sometimes the expression "optical yield" is used. This is the same as enantiomeric or diastereomeric excess.

As opposed to the earlier definition by Marckwald[4], Morrison and Mosher's definition of asymmetric synthesis also includes reactions where optically inactive chiral compounds are formed.

1.2. *PRINCIPLE APPROACHES OF ASYMMETRIC SYNTHESIS*

Asymmetric synthesis occurs when there exists a difference in transition energy between competing diastereomeric transition states formed by the interaction of the substrate and the chiral reagent. The magnitude of this energy difference, denoted as $\Delta\Delta G^{\neq}$ (Figure 1.1), determines the ratio of the isomeric products.

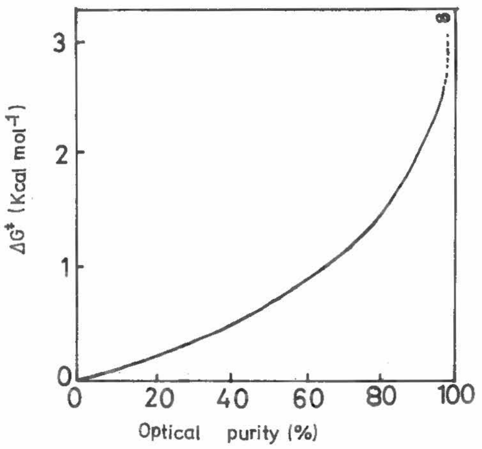
Figure 1.1: Transition energy basis for asymmetric induction



A very small $\Delta\Delta G^{\neq}$ is already sufficient to cause a significant chiral induction (see Figure 1.2). For example it has been found that a $\Delta\Delta G^{\neq}$ of 2-3 Kcal/mole at 0^{o} will lead to an almost complete asymmetric synthesis.

Although the magnitude of $\Delta\Delta G^{\neq}$ necessary for a complete asymmetric synthesis appears to be rather small, methods to achieve it are usually difficult to be specified. This stems from the difficulty of defining the origin of asymmetric induction and the lack of knowledge and control of the transition

Figure 1.2: Dependence of optical yield on $\Delta\Delta G^{\neq}$

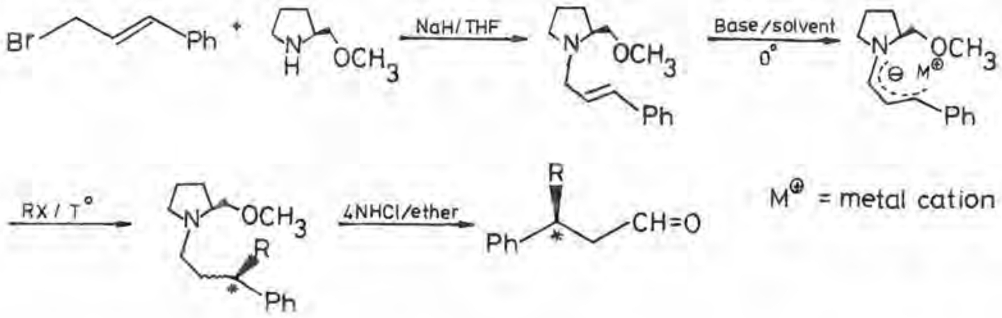


state geometry of these reactions. Despite several attempted theoretical predictions (*e.g.* the Ruch-Ugi[5] and Salem[6] models) most of the breakthroughs in asymmetric synthesis are merely a result of empirical synthetic procedures. Most of the established stereochemical requirements for asymmetric reactions have therefore been derived from the various successful syntheses. For example, many asymmetric reactions are now being satisfactorily explained in terms of steric factors. Thus, introduction of bulky substituents at the centre inducing chirality or the use of substrates with substituents of increasing bulkiness has generally been associated with an enhanced degree of asymmetric synthesis. The mode and direction of chiral induction in some cases has been explained on the basis of Cram's[7,8] and Prelog's[9,10] rules. However, recent studies have shown that caution has to be excercised on interpreting a good asymmetric synthesis on the basis of bulky substituents.[11-13]

It also has been advanced that intermolecular chelation of the chiral reagent and substrate makes the transition state to be more ordered and consequently this reduces the degree of freedom of the intermediate species. As a result high degrees of chiral induction are obtained. Further, when the developing chiral centre is in close proximity of the inducing centre high degrees of asymmetric synthesis may be expected.

Apart from steric factors and stereostructures of reactants and intermediates, asymmetric reactions have been found to depend on certain optimum reaction conditions, such as temperature, solvent, etc. For example, in a recently reported 1,4-asymmetric addiition reaction (Scheme 1.1) it has been observed that the

scheme 1.1



enantiomeric excess varies with the change of the counterion, solvent and temperature.[14] Thus in THF the better solvated lithium salts gave the lowest enantiomeric excess as compared with potassium salts. A better e.e. was obtained in petroleum ether as solvent as compated to THF.[14] This is because of the inability of the former solvent to coordinate with the reagent. It has been further shown[14] that change of solvent reduces the e.e. more than the increase in reaction temperature. Wijnberg *et al.*[15], and others[16] have observed that high optical yields can be obtained from ionic asymmetric reactions when apolar solvents, such as benzene or dichloromethane, are used.

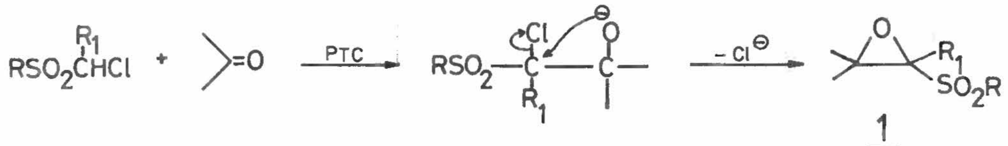
Izumi and Tai[17] treated the dependence of the degree of asymmetric synthesis on the reaction conditions in terms of $\Delta\Delta G^{\neq}$ (Figure 1.1). They suggested that if $\Delta\Delta G^{\neq}$ depends on a difference of molecular interactions between the substrate, chiral reagent and solvent, a slight alteration of reaction conditions will exhibit a marked influence on $\Delta\Delta G^{\neq}$ and hence on the magnitude of asymmetric induction.

Several types of reactions have been investigated with regard to the possibility of performing them in an asymmetric fashion, *e.g.* alkylations, additions, oxidations, reductions, etc. The use of chiral catalysts in heterogeneously catalysed asymmetric hydrogenations has received an enormous attention. Excellent asymmetric syntheses have been obtained in this context. Typical examples of asymmetric reactions relevant to the syntheses reported in this thesis will be presented in Chapter 2.

1.3. *OBJECTIVES*

α,β-Epoxysulphones (1) have been known for quite some time now. These compounds can be conveniently prepared through Phase-Transfer Catalysed (PTC) Darzens condensation as shown in Scheme 1.2.[18,19] When aldehydes are used as carbonyl substrates this synthesis is stereoselective, giving predominantly α,β-epoxysulphones of the (*E*)-configuration. Zwanenburg *et al.*[20-24], have contributed considerably to the development of epoxysulphone chemistry.

scheme 1.2



1

R = Ar or tert-alkyl; R_1 = H, alkyl or Ar.

PTC conditions: 50% NaOH, PT catalyst, solvent and vigorous stirring

Phase-transfer catalysis, which is a new technique in organic synthesis, has attracted much attention in a variety of syntheses.[25-29] Since asymmetric synthesis has occupied a considerable proportion in modern organic synthesis, any attempt to incorporate this methodology in any type of reaction should be worthwhile. Therefore, the prime objective of the present investigation is to study asymmetric induction during PTC synthesis of α,β-epoxysulphones and also to extend the scope of epoxysulphone chemistry.

PTC reactions are usually versatile and easy to carry out. This is the main reason why currently much effort is given to introduce asymmetric synthesis in this technique. It is intended in this study to establish, if possible, factors that effect the asymmetric induction in the PTC Darzens synthesis of α,β-epoxysulphones in the presence of an achiral phase-transfer catalyst using chiral reagents. Since the main part of the present investigation involves the Darzens synthesis of chiral α,β-epoxysulphones, Chapter 2 of this thesis is devoted to a comprehensive review of the stereochemical course of the Darzens condensation and the chemistry of α,β-epoxysulphones. Asymmetric phase-transfer catalysis is also reviewed in this Chapter for the same reasons.

The initial step in the Darzens condensation is an aldol type reaction. Therefore, a concise treatment of some interesting aldol type asymmetric reactions is also given in Chapter 2. In concluding the review some examples of asymmetric reactions using l-menthol and proline derivatives as chiral reagents are briefly discussed. Such a section has been included in Chapter 2 in order to justify the choice of l-menthol and proline derivatives for similar purposes in the present investigation.

The asymmetric PTC Darzens condensation of aldehydes and ketones with the chiral reagent l-menthyl chloromethanesulphonate using triethylbenzylammonium chloride (TEBA) as the phase-transfer catalyst to give chiral α,β-epoxysulphonate esters is presented in Chapter 3. After a brief introduction the Chapter discusses the preparation of starting compounds which includes the chiral reagent. The asymmetric synthesis of the chiral α,β-epoxysulphonate esters is then analysed. This analysis is then followed by a brief proposal on the possible stereochemical course of the chiral induction.

In Chapter 4 a detailed treatment of the PTC asymmetric Darzens synthesis of α,β-epoxysulphonamides from the condensation of aldehydes and ketones with the chiral reagents (*S*)-(-)-*N*-chloromethylsulphonyl-2-methoxymethylpyrrolidine and (*S*)-(-)-*tert*-butyl *N*-(chloromethylsulphonyl)prolinate in the presence of TEBA is given. An attempt to use (+)-*O*-methyl-*N*-(chloromethylsulphonyl)ephedrine as a chiral reagent is also described. In this Chapter a discussion is given about the possible stereochemical course of the chiral induction and the influence of the stereostructures of the chiral reagents on the degree of asymmetric synthesis. A brief investigation on the extent of asymmetric synthesis in the aldolization step in the Darzens condensation is reported towards the end of this Chapter.

Successful and attempted reactions of α,β-epoxysulphones and chiral epoxysulphonamides are reported in Chapter 5 which concludes this thesis.

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CHAPTER 2

SURVEY OF PERTINENT LITERATURE

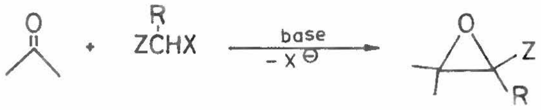
2.1. *PREFACE*

In this chapter the literature relevant to the chemistry in the subsequent chapters of this thesis is surveyed. The chapter begins with a concise treatment of the stereochemical course of the Darzens condensation. This is followed by a detailed survey of the chemistry of α,β-epoxysulphones. This constitutes the major part of this chapter because it forms the backbone of the investigation reported in this thesis. For the same reason asymmetric phase transfer catalysis is also discussed in a considerable detail. A brief mention of some asymmetric aldol-type reactions is also presented. Finally, a survey is made of some asymmetric reactions involving (S)-proline and l-menthol derivatives as chiral reagents.

2.2. *THE DARZENS CONDENSATION*

The condensation of α-halomethyl compounds with aldehydes and ketones under basic conditions to form substituted α,β-epoxides is known as the Darzens condensation (Scheme 2.1).

scheme 2.1



Z = carbanion stabilizing group
X = halide (preferably Cl or Br)

In these reactions it is required that the halo-compound has a carbanion stabilizing group *Z* at the α-position. That is why α-halocarbonyl compounds have been frequently used in this condensation.

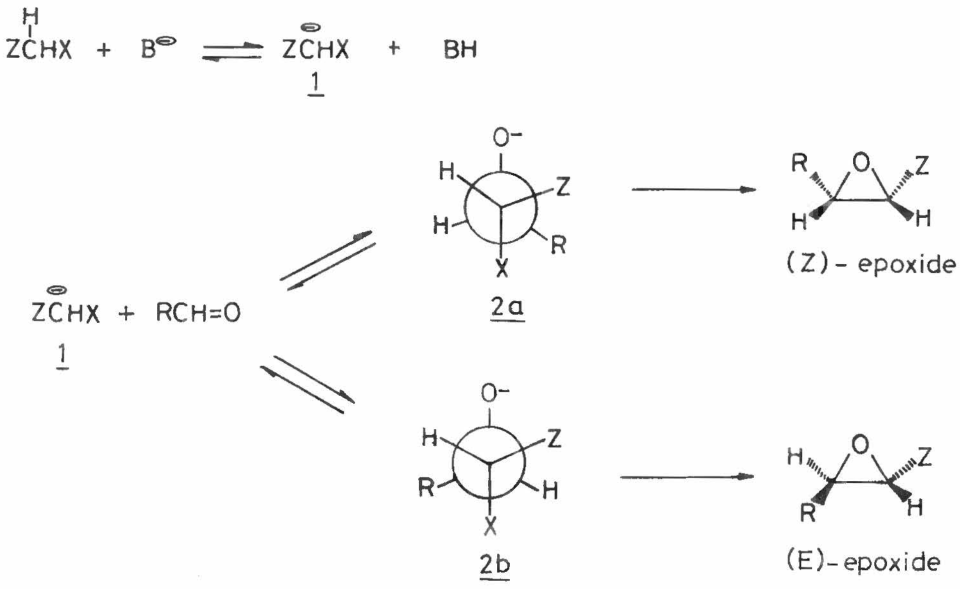
The Darzens condensation is one of the most convenient methods for the preparation of α,β-epoxides.[1] Under appropriate reaction conditions the condensation proceeds with complete stereoselectivity.

In this section the stereochemical course of the Darzens condensation and some asymmetric Darzens reactions will be discussed. More extensive discussions on the synthetic merits of the Darzens condensation are described in a number of books and review articles.[1-4] The Darzens condensation involving sulphones will be discussed in section 2.3.

2.2.1. *Stereochemistry*

For sometime now the stereochemical course of the Darzens condensation has been a subject of much discussion. Mechanistically this condensation proceeds through the formation of a carbanion 1 which then attacks the carbonyl component to give *erythro*- and *threo*-haloalkoxy intermediates 2a and 2b, respectively (Scheme 2.2).[1] Cyclization of these aldol-type products then

scheme 2.2

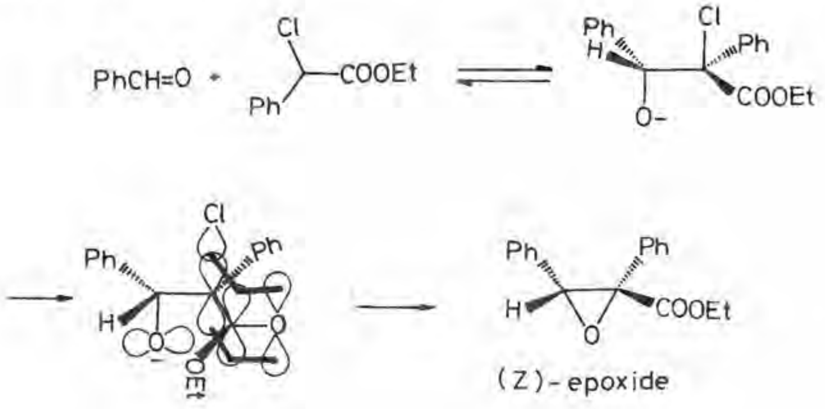


Z= COR, COOR; B⊖ = base; X=halogen

affords α,β-epoxides having either an (*E*)- or a (*Z*)-configuration. The ratio of the diastereomeric epoxides depends on the structure of the reactants and the reaction conditions (solvent, base and temperature).[1,5] A complicating factor in understanding the stereochemical course is that either the formation of haloalkoxide 2 or its 1,3-elimination to epoxide is rate determining. In cases where the haloalkoxide formation is rate limiting mainly steric effects, together with some electrostatic factors, are governing the stereochemical outcome. When the epoxide formation is the slow step, an equilibrium exists between the *erythro*- and *threo*-haloalkoxides. Because of the smaller steric congestion in the transition state the rate of 1,3-elimination of the *threo*-isomer 2b usually is faster, thus leading to the (*E*)-epoxide as the predominant product. Quite a number of reported Darzens condensations fit into the pattern depicted above. For example the predominant formation of an (*E*)- over a (*Z*)-epoxide in the condensation of benzaldehyde with *tert*-butyl-2-bromothiolacetate in a less polar solvent like THF has been associated with steric factors assuming the final cyclization step being rate determining.[5] Tung *et al.*[6], suggest that the formation of the intermediate haloalkoxy compounds should be the slow step in cases leading to the non-stereoselective production of isomeric α,β-epoxy carboxylic esters. This contrasts earlier suggestions that the stereochemistry in this Darzens condensation is the result of an epimerization of one isomer into the other. It has been observed that a change from a non-polar solvent (*e.g.* benzene) or a protic solvent (*e.g.* ethanol) to a dipolar aprotic solvent (*e.g.* HMPA) increases the rate of the cyclization step and tends to make the initial condensation reaction rate determining.[8-10]

Deviating mechanistic explanations for the steric course of the Darzens condensation have been advanced. For example Zimmerman and Ahramjian[11], in rationalizing the exclusive formation of the (seemingly?) thermodynamically less stable (*E*)-diphenylglycidic ester, proposed that this steric course is controlled by the tendency towards maximum overlap of the carbonyl π orbital of the ester and the developing p orbital at the α-carbon atom in the transition state for the epoxide formation. The ester function prefers to be in the *anti*-position with respect to the phenyl group as indicated in Scheme 2.3

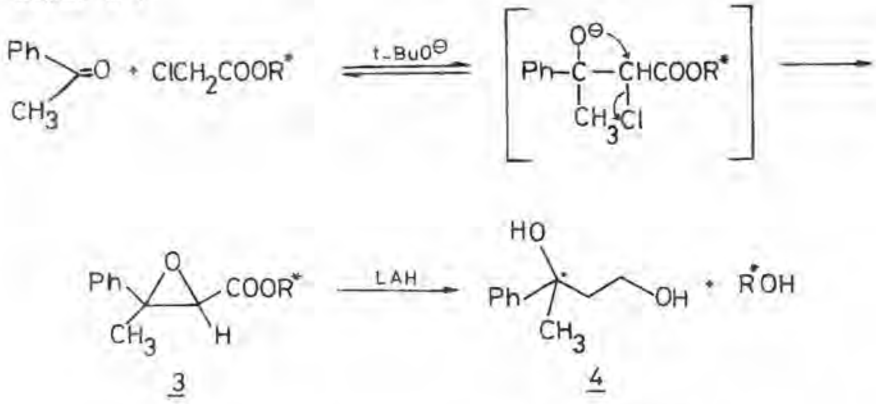
scheme 2.3



2.2.2. *Asymmetric synthesis*

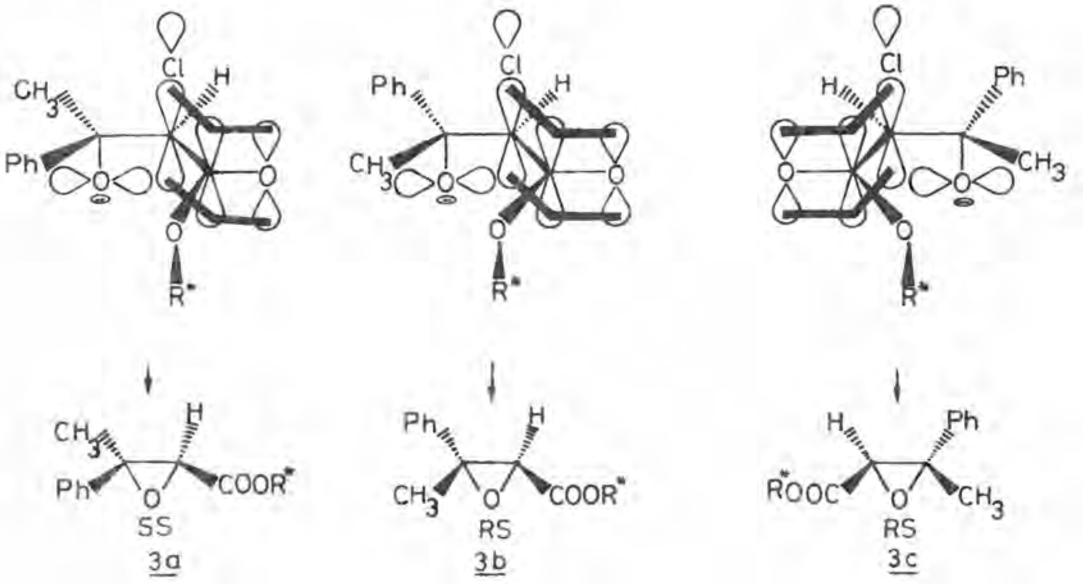
Only very little is know about asymmetric Darzens condensations. Such a reaction is exemplified by the condensation involving either (-)-menthyl or (+)-bornyl chloroacetate and acetophenone in the presence of potassium *tert*-butoxide

scheme 2.4



R* = l-menthyl or bornyl; *new chiral centre to give the glycidic esters 3 (Scheme 2.4) which, without further purification, were reduced with lithium aluminium hydride to produce optically active hydroxy acids 4 in about 35% chemical yield.[12] The e.e. of 4 was higher (14-15%) when R^* was menthyl than when it was bornyl (4-5%). The stereochemical course of these reactions was explained on the basis of Figure 2.1., the cyclization step being rate limiting and

Fig. 2.1

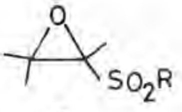


therefore determining the chirality of the diastereomeric glycidic esters 3. On intuitive grounds the overlap control mechanism (Figure 2.1)[11], or equally well, steric considerations in Newman projections of the haloalkoxides, predict the formation of the (*E*)-epoxide 3b to be preferred over the (*Z*)-epoxide 3a. Another diastereomeric haloalkoxide also leads to the (*E*)-epoxide (3c) but with opposite configurations at the α- and β-carbon atoms. Which of these two reactions to an (*E*)-epoxide will be preferred depends on the interaction of the chiral group with the reacting centres. Since neither the nature of the epoxides nor the diastereomeric excess was determined the extent of asymmetric induction in this Darzens condensation remains speculative.

Apart from the above example, to my knowledge subsequent authentic asymmetric Darzens reactions have been performed only *via* phase transfer catalysis, as will be reported in section 2.4.2. of this chapter.

2.3. α,β-*EPOXYSULPHONES*

α,β-Epoxysulphones 5 are among the most recently studied epoxides carrying electronegative substituents. Although already mentioned in a review in 1955[3] these compounds were



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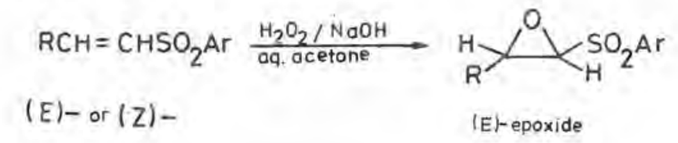
first synthesized in 1969.[13,14] In the following year the thermal and acid catalysed rearrangements of these compounds were studied by Durst and his group.[15] Thereafter only a few other studies on epoxysulphones have been performed. These investigations have mainly been directed towards the improvement of the reported synthetic procedures as well as the synthesis of some new epoxysulphones. Thus Mąkosza *et al.*[16], reported the first phase transfer catalysed Darzens synthesis of epoxysulphones. This method has been reputed as being the most convenient for these compounds. The recent discovery of a variety of synthetically interesting reactions of α,β-epoxysulphones (section 2.3.3.) has added a considerable significance to the chemistry of this type of epoxides.

2.3.1. *Synthesis*

α,β-Epoxysulphones can be synthesized either by the epoxidation of α,β-unsaturated sulphones (Scheme 2.5) or through the Darzens condensation. Thus, alkaline epoxidation of α,β-

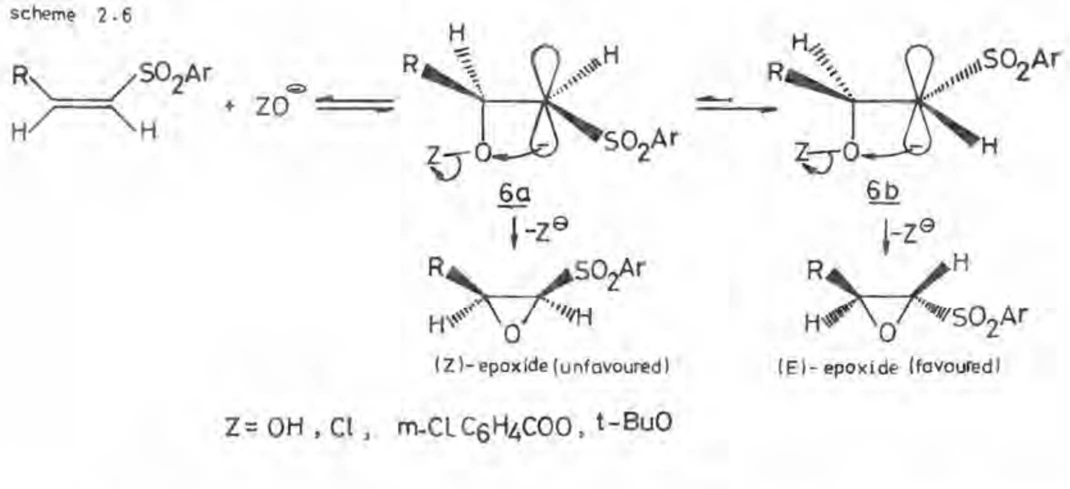
scheme 2.5



unsaturated sulphones in the presence of aqueous acetone affords α,β-epoxysulphones having an (*E*)-configuration, irrespective of the stereochemical configuration of the starting sulphone.[17,18] This reaction is a nucleophilic addition of oxygen anion ZO^- to the electron deficient double bond. The stereoselectivity of this epoxidation has been explained on the basis of a rotational equilibrium of the initially formed intermediate <u>6</u>. This process then favours the thermodynamically most stable (*E*)-epoxide from the sterically least congested rotamer <u>6b</u>, as shown in Scheme 2.6.[18,19]

It has been observed that the stereochemistry of this reaction is often dictated by the epoxidizing nucleophile. Thus, as the leaving ability of Z^- increases in the order $t\text{-BuO}^- < HO^- < m\text{-ClC}_6H_4COO^- < Cl^-$, the reaction progressively

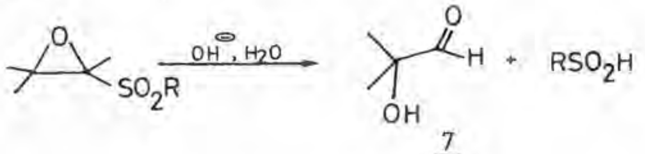
scheme 2.6



becomes less stereoselective.[18] This means that as the leaving ability of the *Z*-part of the epoxidizing nucleophile is enhanced there is a pronounced competition between the elimination to epoxide and the rotation around the C_α-C_β bond. This may lead to complete stereospecific epoxidations, as was observed using KOCl as the reagent.[18]

The yield of α,β-epoxysulphones may be affected by the alkaline reaction conditions since these compounds may cleave to sulphinic acid and α-hydroxyaldehydes 7 under those basic conditions (Scheme 2.7).[20]

scheme 2.7



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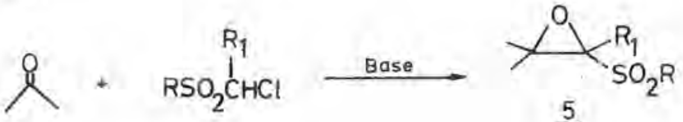
In the Darzens reaction aldehydes and ketones are condensed with α-halomethyl sulphones under a variety of basic conditions to give the α,β-epoxysulphones, generally in good yields (Scheme 2.8).[13-16,21] Originally the Darzens condensation involved the use of a strong base (*e.g.* potassium *tert*-butoxide[11], lithium bis(trimethylsilyl)amide[22], sodium hydride[5], etc) and an anhydrous solvent. An alternative to this procedure has been to cyclize the isolated halohydrin sulphones under the influence of a base to give the epoxysulphones (Scheme 2.9).[21] This method has a disadvantage of a competing *retro*-aldol-type reaction which is more serious when R is Ph in 9 than when R is Me. Since Bordwell *et al.*[23], have shown that methyl phenyl sulphone is more acidic by 2 pKa units than dimethyl sulphone, a similar trend for chloromethyl phenyl sulphone and chloromethyl methyl sulphone may be expected. This explains why the *retro*-aldol reaction for 9a (R = Ph) proceeds easier than for 9b (R = Me).

scheme 2.8



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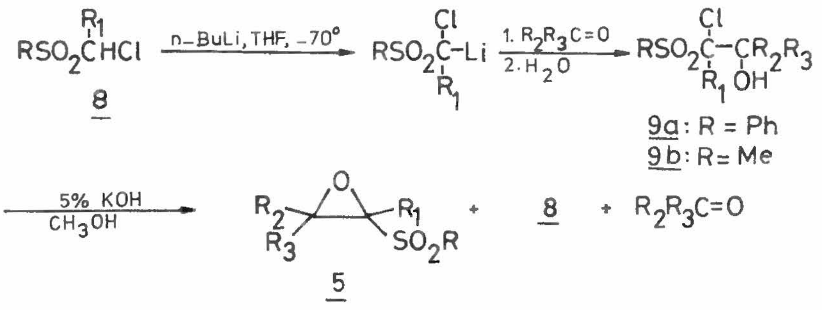
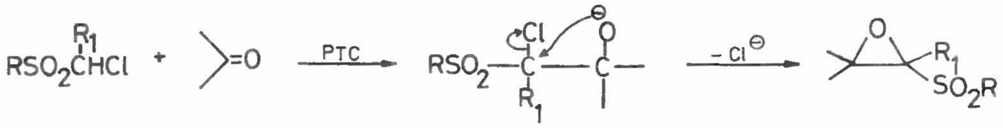
scheme 2.9



Such a competing cleavage to the starting components has also been observed in the similar synthesis of α,β-epoxysulphonamides [Chapter 4 of this thesis].

Another version of the Darzens condensation is the use of phase transfer catalysis (PTC) (Scheme 2.10). This is the most recently introduced procedure for the synthesis of α,β-epoxysulphones and it has proven to be extremely convenient.[16,21,24] The Ramberg-Bäcklund rearrangement by the action of a base (Scheme 2.11)[25] which leads to the formation of an episulphone 10 and subsequent decomposition by the loss of sulphur dioxide to the olefin allows only the use of α-chlorosulphones of the type 8 in the Darzens condensation. That is 8 should have no α-hydrogen atoms in the R substituent.

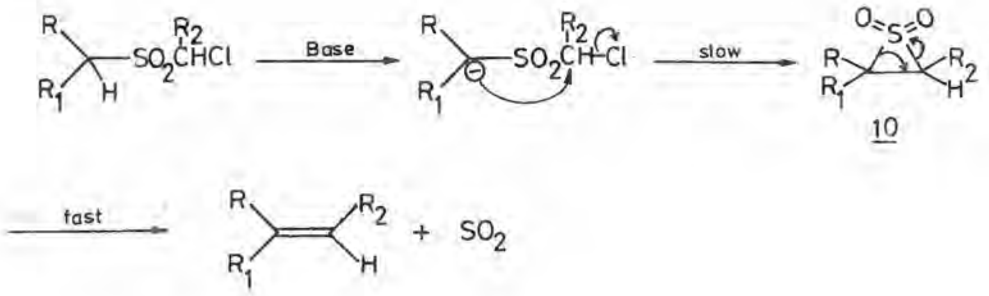
scheme 2.10



R = Ar or tert-alkyl; R_1 = H, alkyl or Ar.

PTC conditions: 50% NaOH, PT catalyst, solvent and vigorous stirring

scheme 2.11



2.3.2. *Stereochemistry*

When the starting carbonyl compound is an aldehyde the Darzens condensation with chloromethyl sulphones leads exclusively to α,β-epoxysulphones having the (*E*)-configuration.[13,16,21] This stereoselectivity is also observed in the Darzens synthesis of α,β-epoxysulphonamides[24,26] and α,β-epoxysulphonate esters.[26] Vogt and Tavares[13] considered "overlap control" as proposed by Zimmerman and Ahramjian[11] in the Darzens condensation with carbonyl compounds as an explanation for the steric course observed during the Darzens synthesis of epoxysulphones. Apart from the doubtful fact that such a mechanism plays any role at all, in the case of sulphones there is little or no angular dependence for effective π-overlap involving 3d orbitals since the 3d-atomic orbitals of sulphur have a cylindrical symmetry. Hence, rotation about the 3d-2p π-bond will not diminish the orbital overlap.[13]

In this section a proposal is being presented to explain the stereoselective course of the Darzens epoxysulphone synthesis. In the first step of the reaction sequence the α-halosulphone is deprotonated and the thus-formed α-sulphonyl carbanion reacts with the carbonyl component in a reversible fashion. It is assumed that the subsequent 1,3-elimination leading to the epoxide is the rate limiting step. The approach of the nucleophilic

α-sulphonyl carbanion to the planar carbonyl function will mainly be governed by steric and electrostatic factors. Following Cram's concept of steric approach control[27] and bearing in mind that the sulphonyl substituent is the bulkiest group of the approaching nucleophile, two possible orientations can be envisaged that are energetically acceptable, namely C and C' (Scheme 2.12). In the formation of C and C' the electronegative and bulky substituents in the two components, the oxygen and sulphonyl group, respectively, are placed in an *anti* position to each other. For the subsequent internal S_N2 cyclization to proceed, the haloalkoxide intermediate should be in a conformation D (or D') where the leaving halide is *anti* to the attacking alkoxide oxygen. The desired conformation D (or D') is achieved through rotation about the C_α-C_β bond. This operation reduces the steric crowding of the remaining substituents by going from C to D, whereas for the conversion of C' to D' the bulky sulphonyl group is placed *syn* to the R substituent, thus increasing the steric congestion. Expulsion of the halide ion from D then leads to the (*E*)-epoxide E, while D' produces the (*Z*)-epoxide E'. Since the transition state for the formation of the (*E*)-epoxide shows less steric crowding than that for the (*Z*)-epoxide, it is reasonable to assume that the (*E*)-epoxide is formed faster than its (*Z*)-isomer. Accordingly, the less favoured nucleophilic approach of the sulphonyl carbanion eventually leads to the (*E*)-epoxide. As it was shown independently[13] this isomer is the thermodynamically more stable one. It should be pointed out that it is not the composition of the diastereomeric rotamers at equilibrium which determines the stereochemical result, but the rate ratio of the rate determining steps. In fact, this formation of diastereomeric epoxysulphones is a demonstration of the Curtin-Hammett principle[28] which states:[29] "In a stereoselective reaction, the more reactive conformer is selected, even if it is less abundant". Figure 2.2 depicts this principle for the present case.

Vogt and Tavares[13] suggest that solvation of the sulphonyl group with its negative charge on the oxygen atom should be an

Scheme 2.12

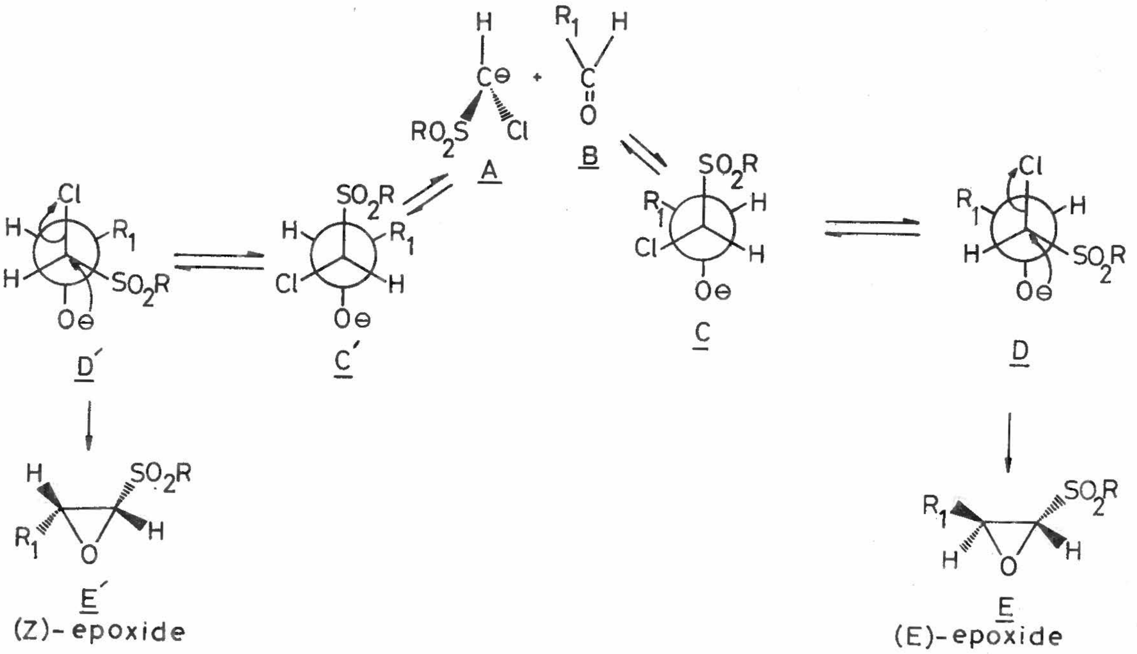
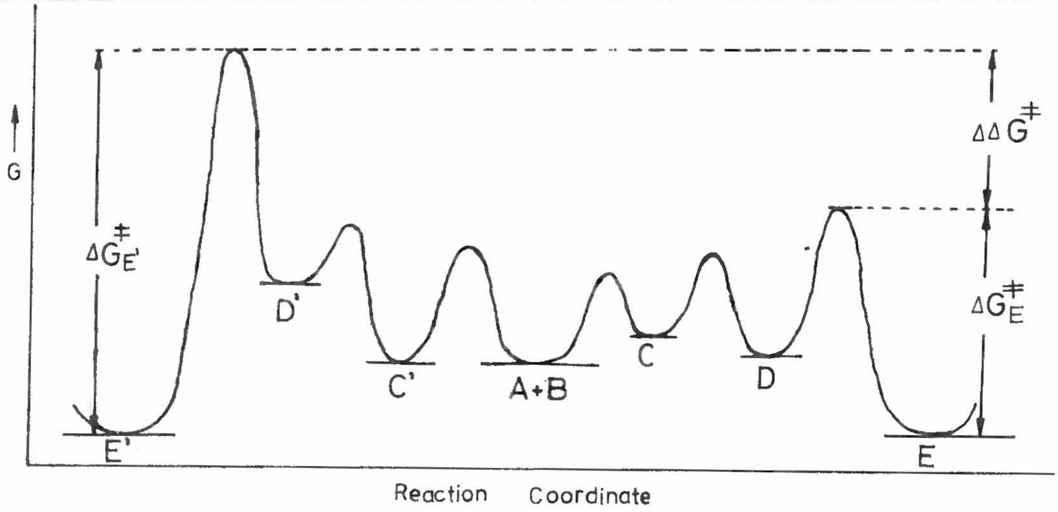


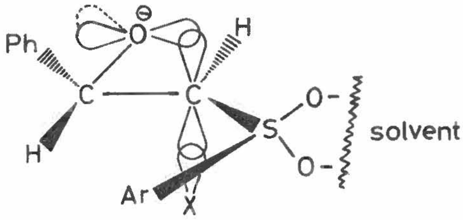
Fig. 2.2

The Curtin-Hammett Principle in the Darzens Condensation for α,β-Epoxysulphones



important factor in dictating the stereoselectivity in the Darzens condensation for α,β-epoxysulphones. The oxygen atoms of the sulphone group are held in an outward position, thus pointing the aryl group towards the *syn*-substituent on the β-carbon atom. This implies that the preferred transition state should have the structure depicted in Figure 2.3[13] with the sulphonyl function *anti* to the bulky substituent on the β-carbon atom. This explanation indeed leads to the observed preference of the (*E*)-epoxide. However, the discussion on the basis of Figure 2.2 seems more adequate to me.

Fig. 2.3

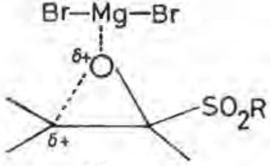


2.3.3. *Reactions*

The main reactions of α,β-epoxysulphones involve the nucleophilic epoxide ring opening followed by elimination of the sulphone group to furnish substituted carbonyl compounds. The reactions proceed with complete regioselectivity because S_N2 reactions α to a sulphonyl group are known to be extremely slow.[30] Therefore, these reactions render the α,β-epoxysulphone unit to be a useful carbonyl precursor.

It has been found that sodium thiolates in methanol as solvent react with epoxysulphones to give α-alkylthio (or arylthio) carbonyl compounds in good yields.[21,31] Similarly, α-azidoaldehydes can be obtained by the reaction of epoxysulphones with sodium azide in anhydrous DMF as solvent.[32] This reaction is treated in more detail in Chapter 5.

Treatment of epoxysulphones with excess magnesium bromide leads to α-bromocarbonyl compounds.[21,33] In this reaction the magnesium bromide, being a weak Lewis acid, coordinates with the epoxide oxygen. This process polarizes the C_β-O bond, thus making the β-carbon atom more susceptible to nucleophilic attack by the bromide anion, as depicted in 11. Weakening of the C_α-O bond would lead to an electron deficiency α to the sulphone group, which energetically is very unfavourable. It is still not clear whether the bromide anion comes from the same molecule of magnesium bromide that coordinates with the epoxide oxygen (*syn*-attack) leading to retention of the stereochemical configuration at the β-carbon atom or it comes from another magnesium bromide molecule which is suitably coordinated with the solvent. This latter mechanism (the S_N2 type) will lead to inversion of configuration at the β-carbon atom.



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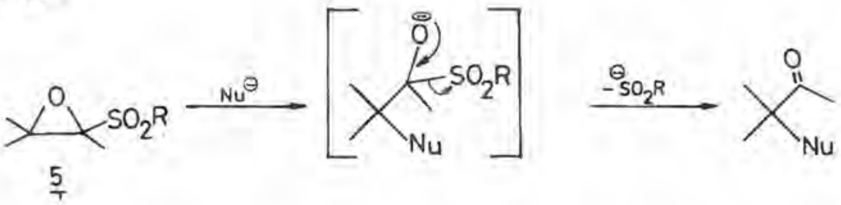
The reactions discussed above are summarized in Scheme 2.13.

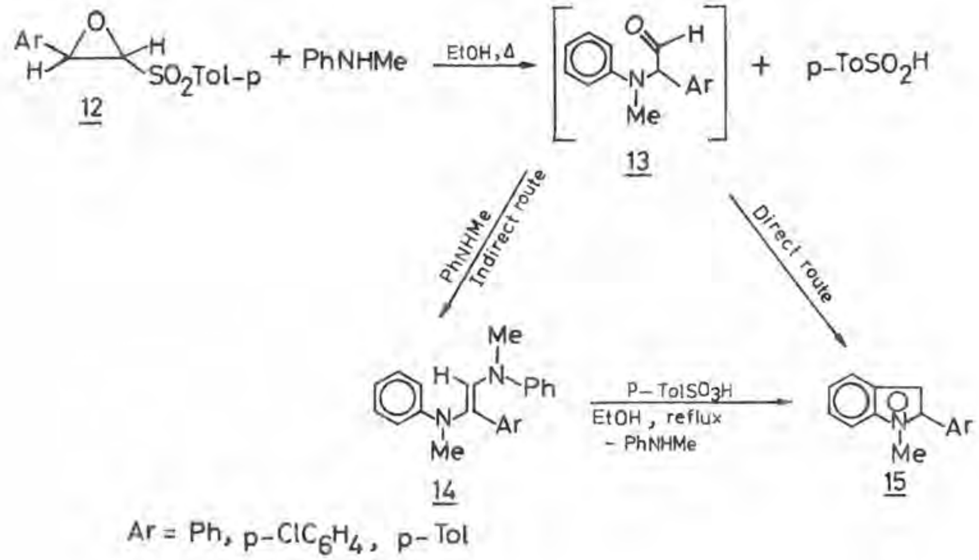
scheme 2.13



Nu= Br(from $MgBr_2$) ; EtS ; PhS ; N_3

Substituted indoles 15 have been obtained by heating under reflux a mixture of α,β-epoxysulphones 12 and *N*-methylanilines in ethanol as the solvent.[31,34,35] This reaction can be envisaged to proceed either directly or through enediamine 14 (Scheme 2.14), which is formed by a further nucleophilic reaction of 13 with a second molecule of *N*-methylaniline.[34,35]

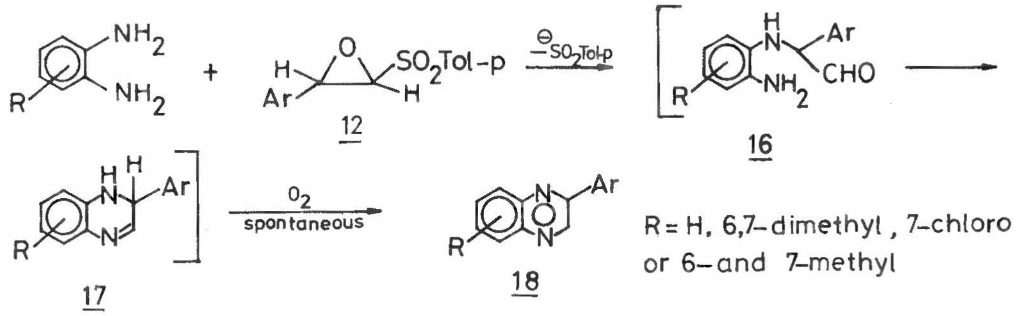
scheme 2.14



Under appropriate conditions enediamines 14 could be isolated from the reaction of epoxysulphones with *N*-methylaniline. Refluxing these compounds in ethanol in the presence of a trace of *p*-toluenesulphonic acid indeed gave indoles[34,35], indicating that the indirect route shown in Scheme 2.14 is operating.

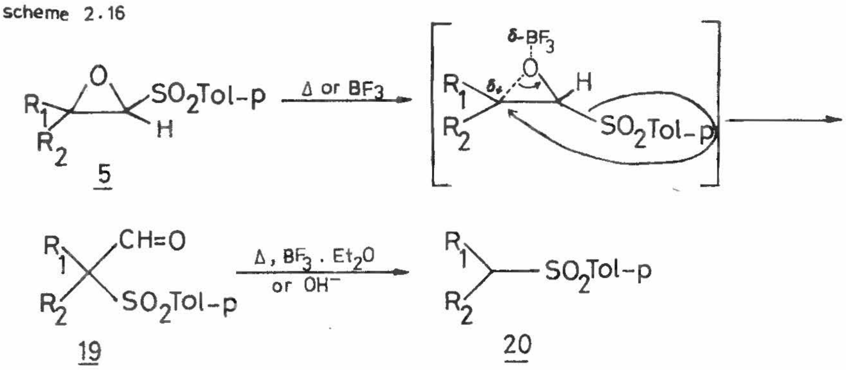
Substituted heterocyclic compounds can be obtained from the condensation of α,β-epoxysulphones with suitable reagents possessing two nucleophilic centres.[31,35-37] In this process α,β-epoxysulphones act as bifunctional two-carbon synthons. Thus condensation of α,β-epoxysulphones with *o*-phenylenediamines in DMF as solvent gives 2-phenylquinoxalines (Scheme 2.15).[31,35-37] It is assumed that the intermediate α-arylaminoaldehydes 16 which are generated *in situ* cyclize to dihydroquinoxalines 17, the latter then undergoing a spontaneous air oxidation to give quinoxalines 18.[36,37] Kandelaars[36] has tried the reaction of α,β-epoxysulphones with other binucleophilic reagents but the results were not very encouraging.

scheme 2.15



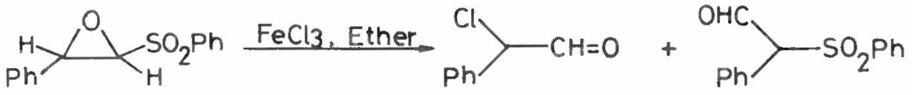
It has been observed that on the influence of a Lewis acid or heat α,β-epoxysulphones undergo a rearrangement process which leads to the migration of the sulphonyl group from the α- to the β-carbon atom, probably in a synchronous manner with the subsequent formation of a carbonyl function at the α-carbon atom, as shown in Scheme 2.16.[13,21] In the presence of an

scheme 2.16



excess of BF_3-etherate, sodium hydroxide solution or on further heating the α-sulphonylaldehydes 19 may undergo a deformylation process to give the saturated sulphones 20 as final products.[15,21,38] The rearrangement is more facile when R_1 and R_2 in 5 are strong carbocation stabilizing groups (*i.e.* stabilizing the electron deficiency at C_β).

Exposure of epoxysulphones to ferric chloride in ether results in the formation of a mixture of α-chlorophenylacetaldehyde and α-formylsulphone in approximately equal amounts.[39] The α-chloro aldehyde is formed in a fashion similar to one



depicted in Scheme 2.13, whereas the other aldehyde is a rearrangement product.

A brief investigation on the reaction of epoxysulphones with Grignard reagents resulted into a mixture of a number of products, presumably resulting from several side reactions of the intermediate products with the remaining Grignard reagent.[21]

In general the overall transformation involving the synthesis of α,β-epoxysulphones through the Darzens condensation and the subsequent nucleophilic reactions of these compounds as shown above is a case of "Umpolung". It represents the introduction of an acyl group at the original carbonyl carbon. Furthermore, the carbon atom β to the sulphone group in the epoxysulphone behaves as a masked α-acyl carbocation.

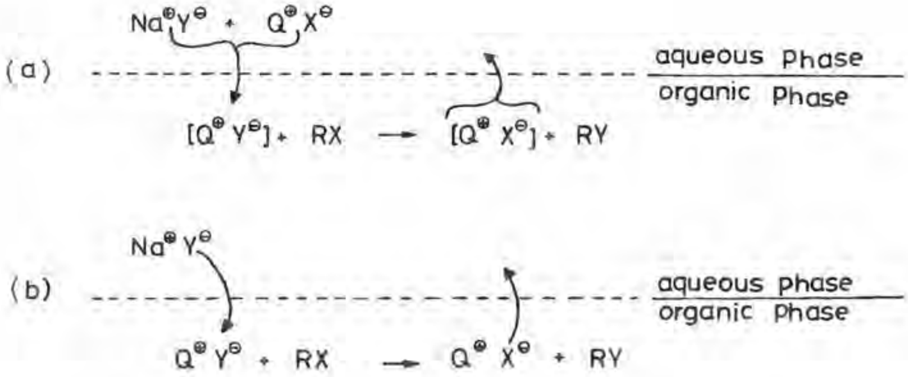
2.4. *ASYMMETRIC PHASE TRANSFER CATALYSIS*

2.4.1. *Introduction*

In phase transfer catalysis (PTC) a reaction is brought about in a mixture of concentrated aqueous sodium hydroxide solution, an organic solvent and small quantities of a phase transfer catalyst (usually a quaternary ammonium or phosphonium halide or a crown ether). Phase transfer reactions using solid sodium or potassium carbonate with or without organic solvents are also known.[40]

PTC is believed to be possible due to the ability of the organic soluble cations of catalyst to repeatedly bring anions of reactants into the organic phase in such a way that a reaction occurs.[41-47] It has been found that with this technique carbon acids with pKa values up to 22, such as chloroacetonitrile or chloromethyl sulphones can easily be deprotonated to form carbanions.[43] These anions will exist in the organic phase as ion pairs with the quaternary ammonium cations from the phase transfer catalyst. In the presence of aldehydes or ketones (which are strong electrophiles) the thus-formed carbanions can undergo a condensation that will ultimately lead to epoxides, as it has been discussed in section 2.3. This and similar phase transfer reactions are believed to proceed at the phase boundary through ion pairs.[43] Figure 2.4 shows the mechanism of a PTC nucleophilic substitution reaction.[44]

Fig. 2.4



In Figure 2.4(a) the anion X^- is assumed to be less lipophilic than the cation Q^+ from the phase transfer catalyst Q^+X^- and the anion Y^- from the base. This situation leads to the migration of the cation Q^+ with the anion Y^- from the aqueous into the organic phase. Because of poor solvation in the organic phase, the then-formed ion pairs Q^+Y^- undergo a very fast substitution reaction with RX to give the product RY and the phase transfer catalyst Q^+X^- is regenerated. The catalyst then migrates to the aqueous phase and the above process is repeated continuously until all of RX has reacted. Since only highly lipophilic catalyst cations are generally used the concentration of Q^+ in the aqueous phase is very low. Recently[48,49] it has been shown that Q^+ stays in the organic phase and the anion exchange takes place only across the phase boundary. This then means that the mechanism shown in Figure 2.4(b) is applicable.[44] In Figure 2.4 ion pairs are shown in square brackets.

PTC has enormous advantages over conventional synthetic techniques since reactions carried out under such conditions are simple to conduct and do not require anhydrous aprotic solvents (which are rather expensive) and dangerous and expensive bases (*e.g.* sodium hydride, sodium amide, potassium *tert*-butoxide, etc.). Furthermore, these reactions require shorter reaction times and/or lower temperatures. Since the introduction of phase transfer techniques in organic synthesis some 17 years ago a variety of reactions which do not proceed otherwise have been realized.[44]

This literature survey is devoted to asymmetric phase transfer catalysed reactions. The literature on general PTC has been extensively documented elsewhere.[41-47] In this chapter emphasis will be given to those reactions which lead to epoxides.

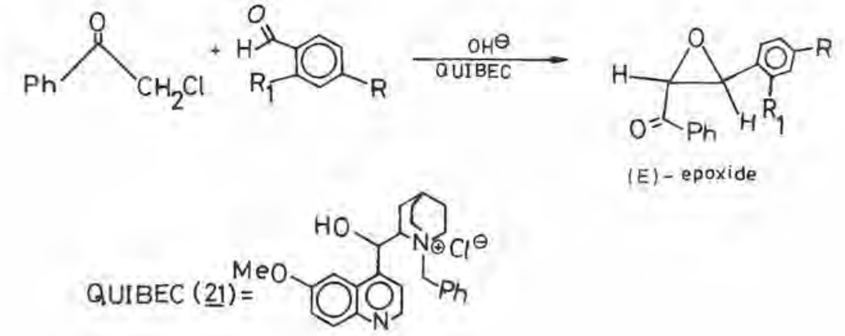
Recently mechanisms leading to asymmetric induction in PTC have been advanced. Thus McIntosh[50] has proposed theoretical requirements for a suitable chiral phase transfer catalyst which will effect asymmetric induction. It is argued that a significant induction can only be expected when very tight ion pairs are involved in the reaction. This argument is based on the expected mobility of the anion X^- of the catalyst Q^+X^-, such that the interaction of the substrate and cation will be maximized.[50]

Other factors affecting the extent of asymmetric synthesis on PTC will be encountered in the subsequent subsections of this section.

2.4.2. *Darzens condensation*

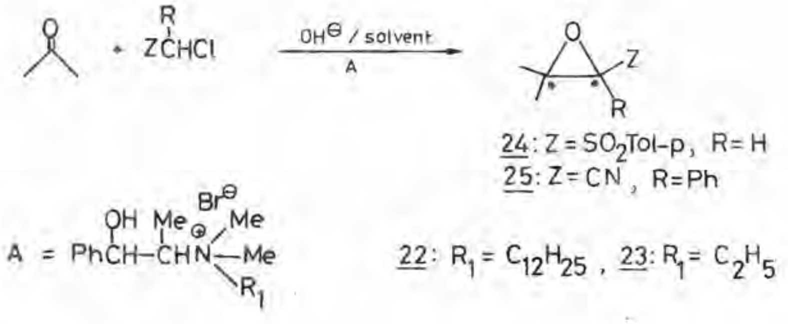
Wijnberg and his group[51] have conducted an extensive study on chiral alkaloid catalysed asymmetric phase transfer reactions. They used QUIBEC (<u>21</u>) as the chiral phase transfer catalyst. This group reported the first phase transfer catalysed Darzens asymmetric synthesis with an optical yield of about 15% (Scheme 2.17).[51]

Scheme 2.17



Another asymmetric phase transfer catalysed Darzens reaction has been investigated by Colonna *et al.*[52] In that study condensation of aldehydes and ketones with chloromethyl *p*-tolyl sulphone and α-chlorophenyl acetonitrile in the presence of chiral catalysts 22 and 23 afforded optically active α,β-epoxysulphones 24 and α,β-epoxynitriles 25, respectively (Scheme 2.18).

scheme 2.18


R
ZCHCl
OH⊖ / solvent
A
O
Z
R
24: Z = SO2Tol-p, R = H
25: Z = CN, R = Ph
A = PhCH(OH)-CH(Me)N⊕(Me)(Me)(R1) Br⊖
22: R1 = C12H25, 23: R1 = C2H5

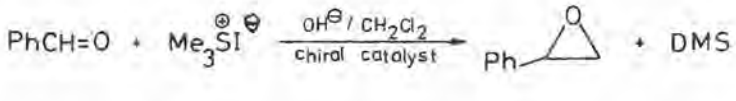
In one of the experiments in the above investigation the degree of chiral induction for a (*Z*)-epoxysulphone was 23% while that for the (*E*)-isomer was 20%. The extent of chiral induction in most of the experiments could not be determined by Eu(tfc)$_3$ induced NMR shifts. Since some of the epoxysulphones reported by Colonna *et al.*[52], are known to be unstable[13,26] some of the results described in the above study are rather questionable.

In the above investigations the degree of chiral induction was enhanced (up to 6%) by using the catalyst anchored on a polymer matrix. The dependence of the stereochemical results upon the position of the hydroxyl group of the catalyst was in accordance with that previously demonstrated in the sodium borohydride reduction of carbonyl compounds under phase transfer conditions.[53,54] The supported catalyst was less efficient in promoting the asymmetric induction in the synthesis of epoxynitriles.

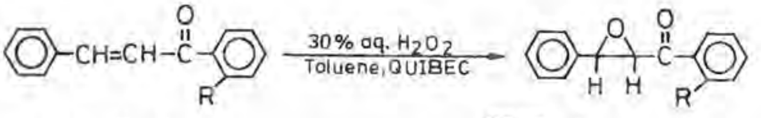
Chiral α,β-epoxyphenylketones have been obtained in 1-9% asymmetric induction through asymmetric phase transfer catalysed condensation of aromatic aldehydes with phenacyl halides in the presence of QUIBEC and ephedrinium salts as chiral phase transfer catalysts.[55] Bromide gave a higher induction than the chloride. In contrast to earlier observations[56] the anchored catalyst retarded the reaction rates. Essentially the above asymmetric synthesis is the same as that reported by Wijnberg *et al.*[51]

2.4.3. *Epoxidations*

Many of the PTC reactions reported to-date have been directed towards the synthesis of optically active epoxides, presumably because of the significance of such compounds in biochemistry[57-60] as well as in synthetic organic chemistry.[61-63] Thus, Nozaki and his group[64] have studied the asymmetric PTC epoxide formation from benzaldehyde and dimethylsulphonium methylide in the presence of (-)-*N*,*N*-dimethylephedrinium bromide as the phase transfer catalyst. An asymmetric induction of 67% was claimed. The hydroxyl group in the catalyst was considered to be responsible for the enhanced degree of asymmetric induction. Aprotic solvents (*e.g.* THF and acetonitrile) which favour protonation of the hydroxyl group, markedly reduced the chiral induction ability of the catalyst.

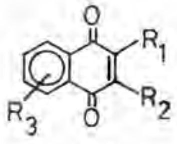

PhCH=O + Me$_3$S$^{\oplus}$I$^{\ominus}$
OH$^{\ominus}$ / CH$_2$Cl$_2$
chiral catalyst
Ph
+ DMS

In one of their first studies on quinidium salt catalyzed asymmetric reactions, Wijnberg and his group[57,65] achieved an optical induction of up to 55% during the asymmetric epoxidation of chalcone 26b to the epoxyketone 27b. However, the chiral induction in most of the experiments was not determined.[57,65,66] In recent studies the above group[67] has reported an asymmetric synthesis of epoxides with e.e.'s



26a: R = H
26b: R = OCH$_3$

27a: R = H
27b: R = OCH$_3$, ee = 55%



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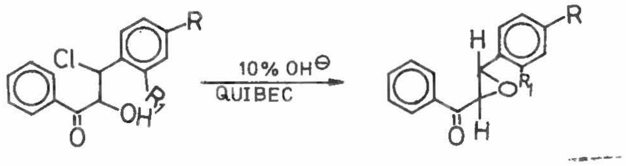
as high as 45% during the epoxidation of quinones 28. The enantiomeric excess was determined from $Eu(dcm)_3$ induced proton NMR experiments. The absolute configurations of the epoxides were derived from CD spectra. These spectra also showed that the absolute configuration of the predominant enantiomers was identical.

In an attempt to elaborate some of the results reported above, Marsman[66], expectedly[44], found quaternary ammonium bromides and iodides not to be suitable phase transfer catalysts. She also found that sterically unhindered ephedrinium salts and camphor derivatives gave very poor asymmetric induction. The influence of apolar solvents on an improved degree of chiral induction was based on the formation of tight ion pairs between the catalyst and chalcone. There was no marked effect of the change of reaction temperature on the degree of chiral induction. The same observation was true with the quantities of the aqueous base and the phase transfer catalyst.

The non-PTC epoxidation of quinones in the presence of quinine gave zero optical yields[67], showing that the asymmetric PTC epoxidation is a true counter-ion rather than a solvent effect.

2.4.4. *Kinetic Resolution*

An example of phase transfer catalysed kinetic resolution was first reported by Wijnberg *et al.*[65] This involved the cyclization of racemic *threo*-chlorohydrins in the presence of QUIBEC (6 mole %) to form α,β-epoxides with about 6% of chiral induction. Other examples of kinetic resolution have recently been reported.[68-70]



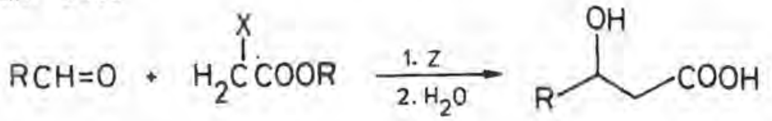
2.5. *ASYMMETRIC ALDOL REACTIONS*

As already has been mentioned in section 2.3 the first step in the Darzens condensation is essentially an aldol-type reaction. Therefore, a brief mention of some asymmetric aldol reactions appears relevant to the present investigation. However, more detailed reviews on this subject can be found elsewhere.[71-75]

The aldol condensation can be subdivided into four types of reactions as shown in Scheme 2.19.[71]

Among the earliest asymmetric aldol-type reactions, the highest asymmetric induction of 93% was achieved from the condensation of 1-menthyl acetate with acetophenone using

scheme 2.19

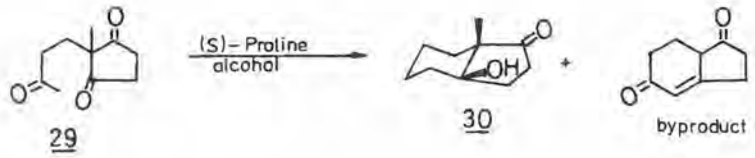


RCH=O is non-enolizable ;

1. Malonic ester type reaction: X = COOH , Z = pyridine
2. Aldol condensation: X = H , Z = strong base
3. Reformatsky reaction: X = Br , Z = Zn
4. Darzens condensation: X = Cl or Br , Z = strong base

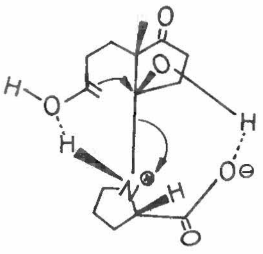
diethylammonium magnesium bromide which is a very effective condensing agent.[76] Other ketones gave a lower induction (20-70% e.e.).[76,77] As compared to bornyl acetate, l-menthyl acetate was more effective as a chiral reagent.

An (*S*)-(-)-proline catalysed asymmetric aldol cyclization of 29 in alcohol as solvent gave 30 with 93% chiral induction.[78] Use of sterically hindered alcohols improved the results as



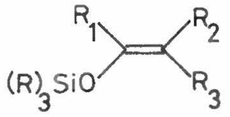
did aprotic solvents (acetonitrile and DMF). A mechanism in which an (*S*)-(-)-proline zwitterion had added to one of the keto groups of the cyclopentanedione ring of 29 to form 31 was proposed to account for the observed chiral induction.[78] In 31 the inducing chirality is nearer to the developing centre than in any other similar configuration.

An interesting asymmetric aldol condensation involves the titanium tetrachloride ($TiCl_4$) promoted cross-reaction of silyl enol ethers 32 (and ketene acetals) with chiral

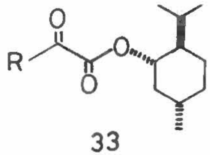


31

ketones 33 to give aldol products in excellent yields and uniformly reasonable chiral induction (35-68%).[79] The high



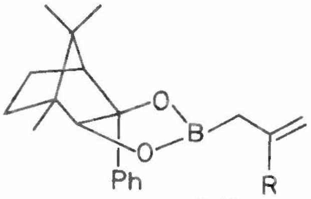
32



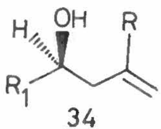
33

degree of asymmetric synthesis was based on a rigid cyclic transition state.

Recently Hoffmann and Herold[80] reported an asymmetric synthesis of optically active homoallylic alcohols 34 *via* an aldol-type condensation of chiral boranes 35 with aldehydes. The chiral alcohols were obtained in a uniform configuration. Saturated aldehydes gave better results.



chiral reagent 35



34

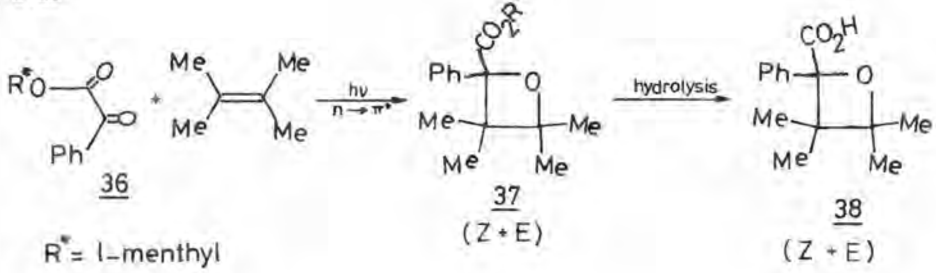
2.6. *l-MENTHOL AND (S)-(-)-PROLINE DERIVATIVES AS CHIRAL REAGENTS*

2.6.1. *l-Menthol Derivatives*

l-Menthyl compounds are among the chiral reagents which were used in early asymmetric reactions.[71] Because of their easy availability and low price, these compounds have been found to be very useful in a number of asymmetric syntheses, considering the promising results which were earlier obtained. The use of l-menthol derivatives in asymmetric synthesis has mainly been restricted to aldol condensations as it is reported in sections 2.3. and 2.5. of this chapter.

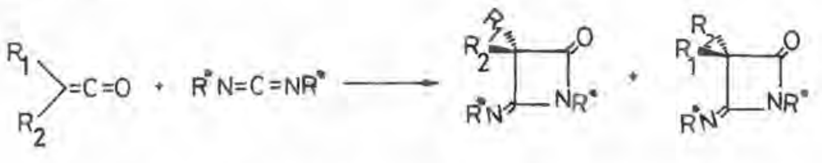
Among the few examples of using l-menthol derivatives in asymmetric reactions other than the above include the [2+2]-photocycloaddition of a mixture of l-menthyl ester of phenylglyoxylic acid 36 and 2,3-dimethyl-2-butene in benzene to give diastereomeric oxetanecarboxylates 37.[81] Hydrolysis of the latter compounds gave oxetanecarboxylic acids 38 with 53% optical purity.

scheme 2.20



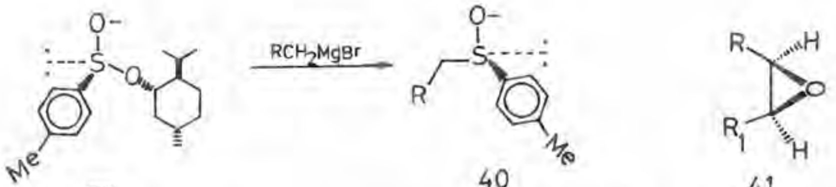
An l-menthyl moiety was also used as a chiral reagent in the asymmetric synthesis of β-lactams (Scheme 2.21).[82] The β-lactams were obtained with 22-75% asymmetric synthesis. Because of the similarity of the geometries of the diastereomeric transition states and products[82], the observed diastereoselectivity may be the result of non-bonding interactions between the chiral reagent R* and the prochiral centre.

scheme 2.21



$R^* =$ l-menthyl; $R_1 = Me, EtO_2C, CF_3$; $R_2 = Ph$, t-Bu or Me_2CPh

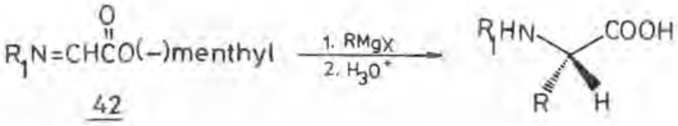
l-Menthyl *p*-toluenesulphinate 39 was used in the asymmetric synthesis of the sulphoxide 40 which later served as the chiral reagent in the asymmetric synthesis of (+)-disparlure 41[83], a sex attractant of the *Gypsy* moth.



39 40 41

$R = (CH_3)_2CH(CH_2)_4$; $R_1 = CH_3(CH_2)_9$

Addition of Grignard reagents to l-menthyl esters of glyoxylic imines 42 led to the formation of (*S*)-amino acids with 63% e.e.[84]



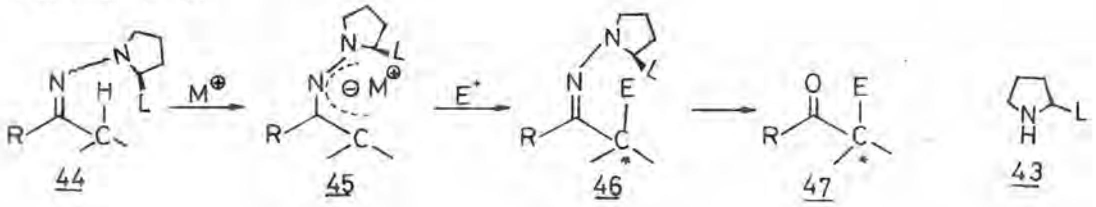
$$R_1N{=}CH\overset{O}{\overset{\|}{C}}O(-)\text{menthyl} \xrightarrow[2.\ H_3O^+]{1.\ RMgX} R_1HN\text{–}CH(R)\text{–}COOH$$

42

2.6.2. *Proline Derivatives*

Proline and its derivatives are among the most useful chiral reagents in a variety of very elegant asymmetric reactions. One example of such reactions has already been given in Chapter 1 (Scheme 1.1). Another example is the asymmetric synthesis involving metalated hydrazones 44. These hydrazones, which are derived from (*S*)-43, have been used as highly reactive enolate equivalents in the asymmetric electrophilic substitution reactions leading to α-substituted carbonyl compounds 47 (Scheme 2.22).[85] In many cases almost complete asymmetric induction is realized with this method and this

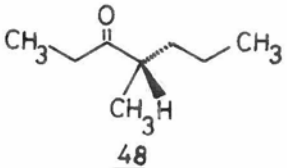
Scheme 2.22



L = chelating ligand ; E^+ = electrophilic species
$M^{\oplus}$ = metal cation

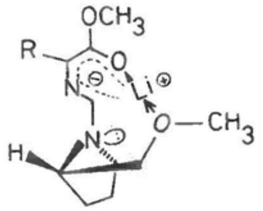
is independent of the ketone substrate or the electrophilic component E^+. Normally the degree of induction with aldehydes as substrates is lower than that with ketones.[85] The magnitude of asymmetric induction using chiral metalated hydrazones depends on the chelating ability of the ligand L. Bulky groups will hamper this chelation and therefore retard the asymmetric induction.[85] As observed in many other asymmetric reactions, apolar solvents and lowered reaction temperatures favour the asymmetric induction.

A striking example of the hydrazone procedure for the preparation of asymmetric ketones is the synthesis of (*S*)-(+)-4-methyl-3-heptanone (48), an alarm pheromone of the leaf-cutting ant *atta-texana*, with 99.5% asymmetric induction.[86]

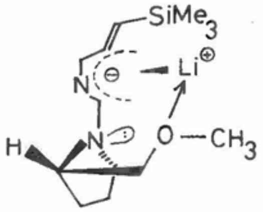


48

Kolb and Barth[87,88] have prepared chiral amino acids using (*S*)-(-)-methoxymethylpyrrolidine as the chiral reagent. The key feature of these reactions was the formation of lithiated chiral hydrazones 49 and 50, respectively, in which the methoxymethyl group serves as a chelating ligand.



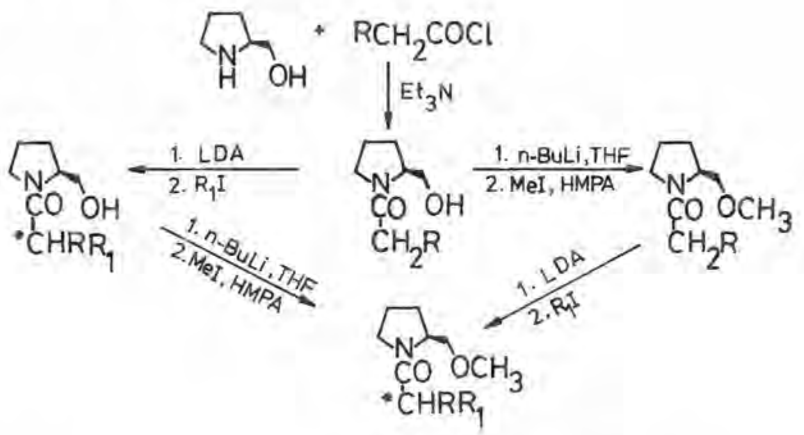
49



50

The importance of a chelating group on (*S*)-proline derivatives was also demonstrated in the asymmetric alkylation using either (*S*)-prolinol or (*S*)-2-methoxymethylpyrrolidine as chiral reagents (Scheme 2.23).[89] It was found that the alkylation of (*S*)-prolinol at -120° in THF led to the induction of an *S*-configuration but that of the *S*-proline methyl ether at -100° in the same solvent induced an *R*-configuration. No explanation is available for this dramatic reversal of the induced configuration due to change of functionalities in the chiral reagent.

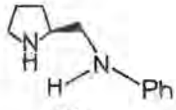
scheme 2.23



Recently α-hydroxyaldehydes (55) have been obtained with about 95% asymmetric induction from the Grignard reaction of 53 and subsequent acid hydrolysis.[90] Compound 53 was obtained from the reaction of phenylglyoxal (51) with the chiral reagent 52. The Grignard reaction has been proposed to proceed

PhCOCHO

51



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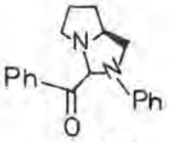

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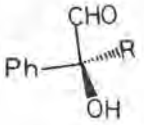
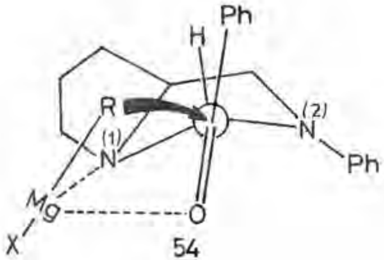


55



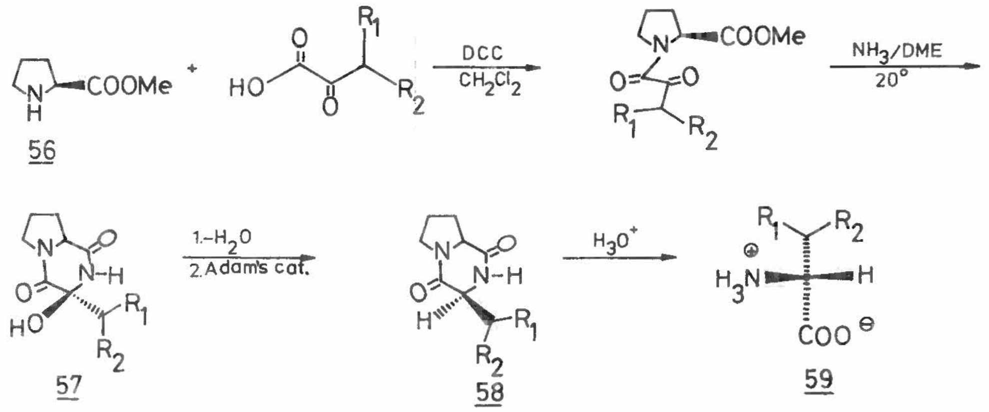
54

through transition state 54 where the magnesium atom of the Grignard reagent coordinates with the carbonyl oxygen and the nitrogen (N^1) on the pyrrolidine ring. Such a coordination is less likely with the more electron deficient nitrogen (N^2). It is suggested that such a complexation will lead to a rigid structure 54 that favours alkylation of the carbonyl carbon from the less sterically hindered side (the side of hydrogen) yielding (*S*)-hydroxyaminals, acid hydrolysis of which gives (*S*)-hydroxyaldehydes 55.

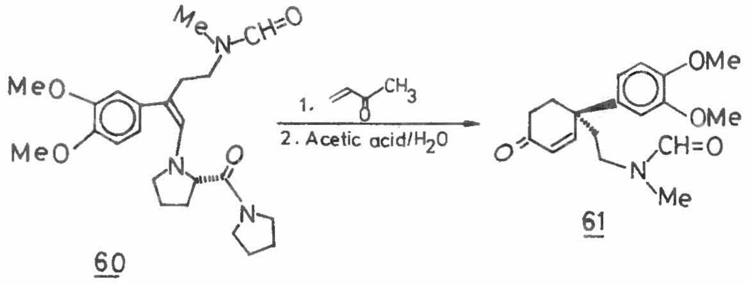
Bycroft and Lee[91] prepared α-amino acids 59 with over 90% chiral induction using (*S*)-56 as the chiral reagent. The interesting aspect of this synthesis (Scheme 2.24) is the isomerization of the new chiral centre in 57 during the asymmetric catalytic reduction (*S*-57 to *R*-58).[91]

(*S*)-Proline has also been used as a chiral reagent in the synthesis of the alkaloid 61.[92] In this synthesis the

scheme 2.24

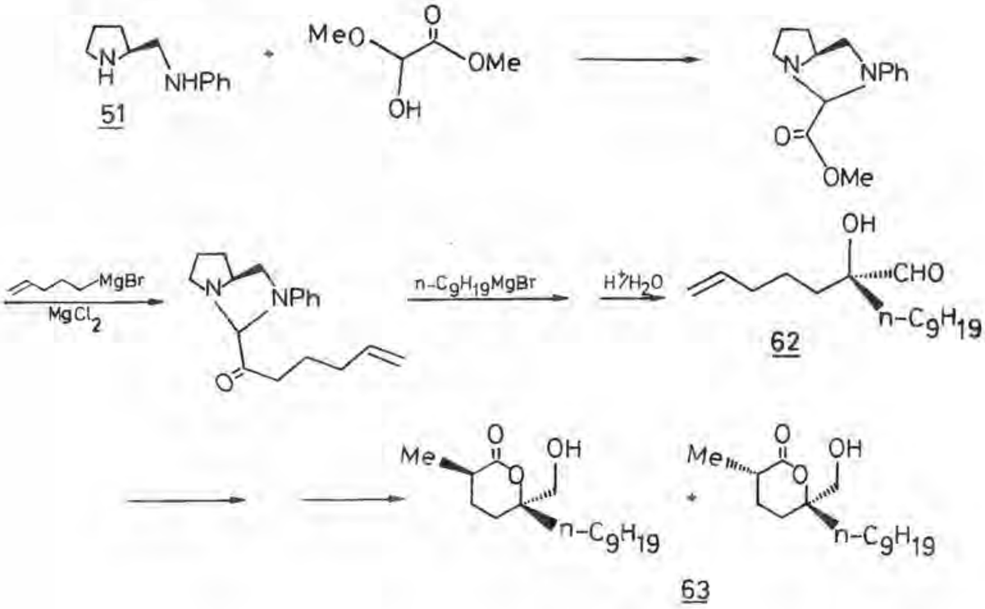


key step is the asymmetric Michael reaction of the (*S*)-proline pyrrolidine enamine 60 to the alkaloid.

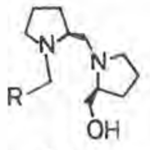


A new marine antibiotic (-)-malyngolide (63) has recently been synthesized from (*S*)-2-hydroxy-2-nornyl-6-heptenal (62).[93] The hydroxyaldehyde 62 was prepared with 95% optical yield by an asymmetric synthesis using (*S*)-51 as a chiral auxiliary reagent.

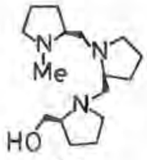
scheme 2.25



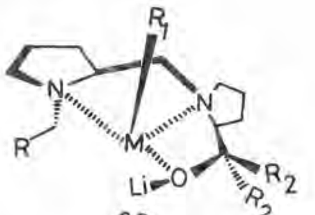
(*S*)-Proline derivatives 64 and 65 have been used in the asymmetric addition of alkyllithium and dialkylmagnesium bromide to aldehydes to give asymmetric alcohols.[94] This is an aldol-type reaction. From the results of this investigation it was found that two pyrrolidine moieties and the lithiated hydroxymethyl group were essential for the asymmetric induction to take place. A rigid complex 66 was considered to be formed by coordination of the alkyl metal with the oxygen and the two nitrogen atoms.[94] This complex then provided an effective chiral environment for the asymmetric induction to take place.



64



65

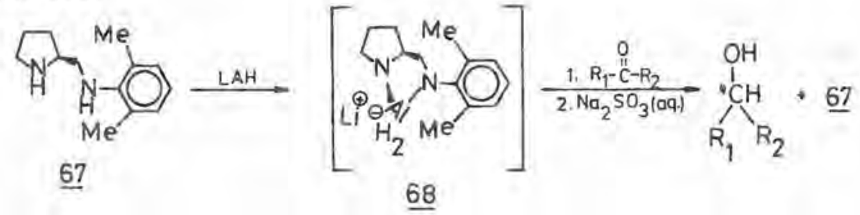


66

R = H, Me, t-Bu; R_1M = alkyllium or dialkylmagnesium,
R_2 = H, Me, Et, n-Pr, n-Bu

Reaction of (*S*)-proline derivative 67 with lithium aluminium hydride gives a chiral complex 68 which may be used in asymmetric reductions of ketones to chiral alcohols.[95]

scheme 2.26



The above account gives some of the most elegant asymmetric reactions in the presence of l-menthol and (*S*)-proline derivatives as chiral reagents. More examples on this line can be found in many other articles.[71-75,96]

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CHAPTER 3

ASYMMETRIC SYNTHESIS OF α,β-EPOXYSULPHONATE ESTERS

SUMMARY

In this chapter the asymmetric synthesis of chiral α,β-epoxysulphonate esters from the PTC Darzens condensation of aldehydes and ketones with l-menthyl chloromethanesulphonate in the presence of triethylbenzylammonium chloride (TEBA) as a phase transfer catalyst is described. The degree of chiral induction, which was determined by means of $Eu(fod)_3$ induced ^1H-NMR shifts, is in the range of 9-17%. The stereochemical course for this chiral induction is discussed.

3.1. *INTRODUCTION*

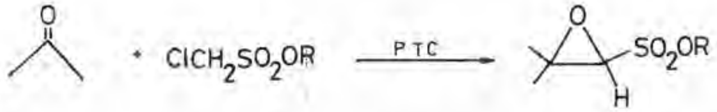
As outlined in chapter 2 α,β-epoxysulphones can be synthesized either by nucleophilic epoxidation of α,β-unsaturated sulphones[1,2] or by the Darzens condensation of α-haloalkyl sulphones with aldehydes and ketones.[3-5] For the latter method a variety of basic reaction conditions have been employed. The method involving phase transfer catalysis (PTC) was found to be by far superior.[6,7]

This chapter deals with the synthesis of a new type of epoxysulphones, *viz.* α,β-epoxysulphonate esters, using the PTC technique. Also the intriguing question is treated to what extent a chiral substituent in the sulphonate substrate can induce optical activity in epoxysulphonate esters. As a chiral inductor a sulphonate ester of l-menthol was chosen, mainly because this alcohol is easily available, cheap and widely used as a chiral reagent.[8-11] This type of PTC synthesis using a chiral substrate with an achiral catalyst may provide information which is supplementary to the PTC asymmetric synthesis using prochiral substrates and chiral catalysts such as quaternary ammonium alkaloid halides. The fact that the Darzens condensation of α-halosulphones and aldehydes proceeds stereoselectively to the (*E*)-epoxides[3-7,12,13] makes this reaction a suitable candidate for asymmetric synthetic studies.[8-11]

3.2. *RESULTS AND DISCUSSION*

The synthesis of α,β-epoxysulphonate esters is outlined in Scheme 3.1. The required chloromethanesulphonate ester was

scheme 3.1

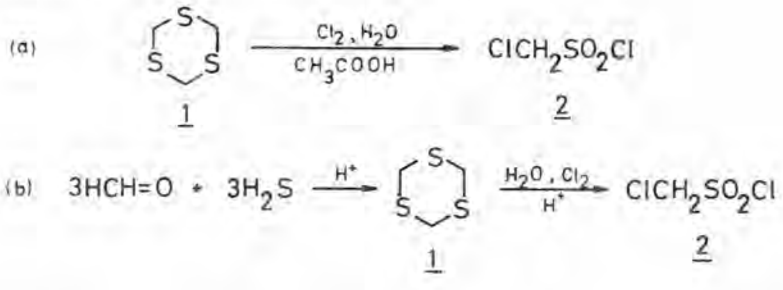


obtained from chloromethanesulphonyl chloride, which in turn was prepared from *sym*-trithiane.

3.2.1. *Chloromethanesulphonyl chloride*

This compound can be prepared by the chlorination of a suspension of *sym*-trithiane (1) in aqueous acetic acid according to Scheme 3.2 equation (a).[14,15] A modification of this method involves the chlorination of *sym*-trithiane, formed

scheme 3.2



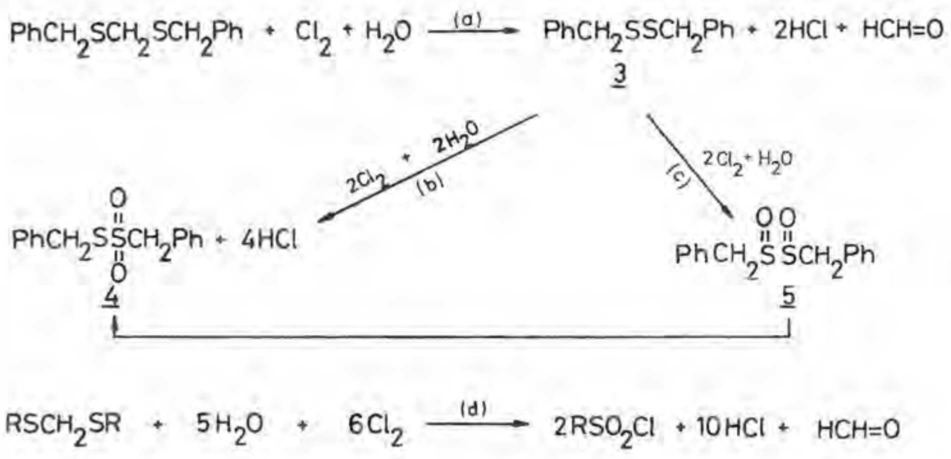
in situ by the action of hydrogen sulphide on a mixture of paraformaldehyde and formalin solution in concentrated hydrochloric acid (Scheme 3.2, equation b).

In the course of this study the second method was found to be the most convenient procedure, giving a very high yield of 2. However, in both cases, when the reactions were carried out according to literature directions[15], the expected product was almost always accompanied by another compound whose boiling point was very close to that of 2. The ^{1}H-NMR spectrum of the mixture showed a singlet signal at δ 4.86 ppm belonging to this unwanted compound while that of 2 was at δ 5.00 ppm. The contaminating compound was not analysed further because it had no immediate interest to this study.

In some cases, the material which was formed immediately after all the *sym*-trithiane (Scheme 3.2, equation a) had been dissolved, was isolated and distilled under reduced pressure to give a light yellow liquid with a bad smell. The ^{1}H-NMR spectrum of this material indicated three distinct singlets at δ 4.86, 5.00 and 5.20 ppm, the second signal being due to compound 2. Further chlorination of the mixture in aqueous acetic acid afforded exclusively the chloromethanesulphonyl chloride, which was purified by distillation under reduced pressure.

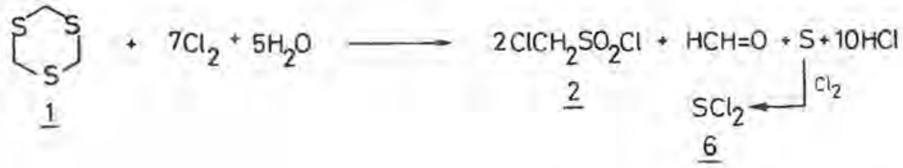
The above findings indicate that formation of 2 proceeds in steps. Lee and Dougherty[14] found that action of chlorine on formaldehyde mercaptals and benzyl mercaptans gives alkane sulphonyl chlorides in good yields, according to Scheme 3.3. They suggest that the initial step in this reaction is the formation of disulphide 3 according to equation a (Scheme 3.3). Further, they propose that this step should be followed by either the oxidation of one S atom to the sulphone (4) stage or oxidation of both the S atoms to give a disulphoxide (5) (equations b and c) which disproportionates fastly to the thiosulphonate 4. These authors suggest that *sym*-trithiane may be considered to be a cyclic mercaptal, which would pass through the steps outlined above, losing one methylene group as formaldehyde and conversion of the resulting cyclic disulphide to two molecules of chloromethanesulphonyl chloride

scheme 3.3



(2) with subsequent liberation of one sulphur atom, as roughly shown in Scheme 3.4, where the sulphur may react with excess chlorine to give 6.

scheme 3.4



It is now clear from the present investigation that only exhaustive chlorination leads to the desired product.

3.2.2. *l-Menthyl chloromethanesulphonate*

The synthesis of l-menthyl chloromethanesulphonate (7) was based on the standard tosylation reactions involving secondary alcohol functions, as shown in Scheme 3.5. This reaction proceeded smoothly and sulphonate ester 7 was obtained in good yield after purification by chromatography. Figure 3.1 shows the ^{1}H-NMR spectrum of 7. Apparently the spectrum is identical to that of the dl-compound (Figure 3.2).

Fig. 3.1

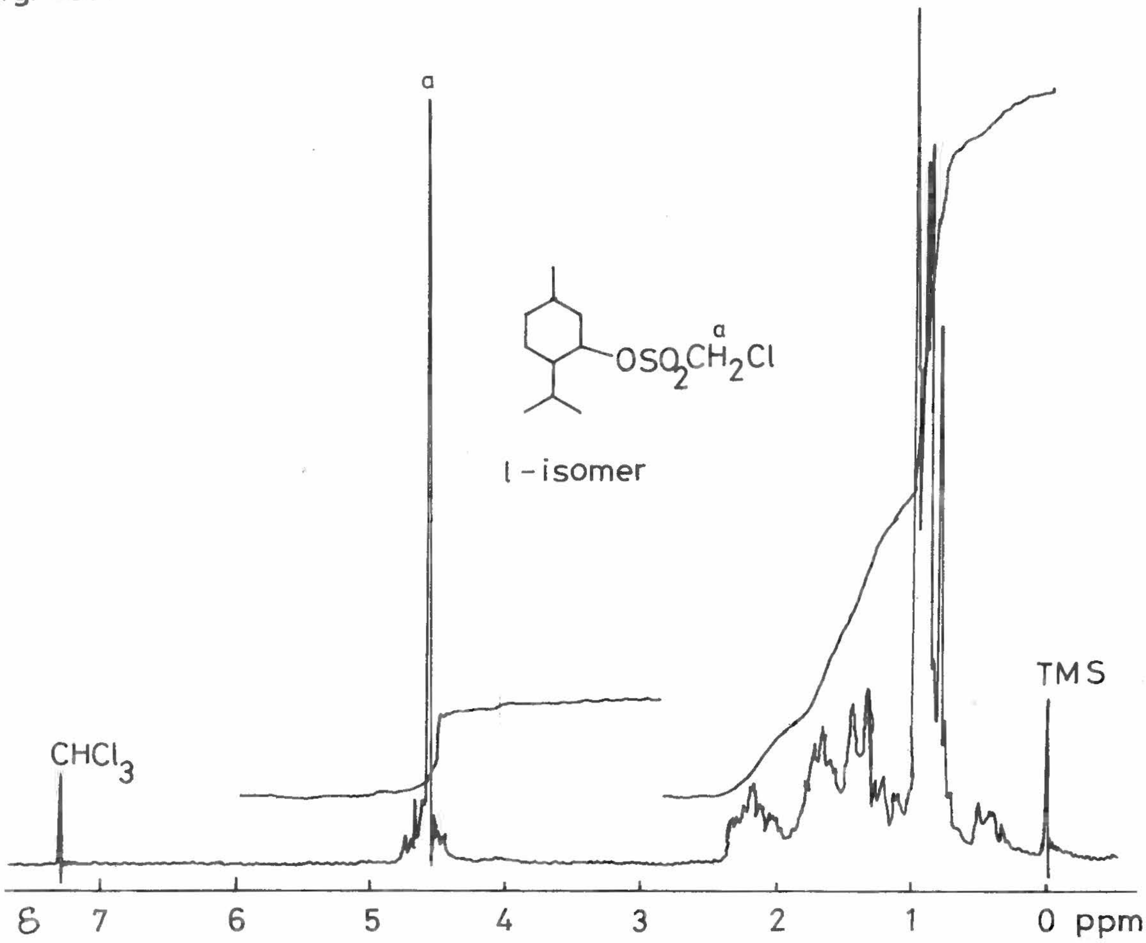
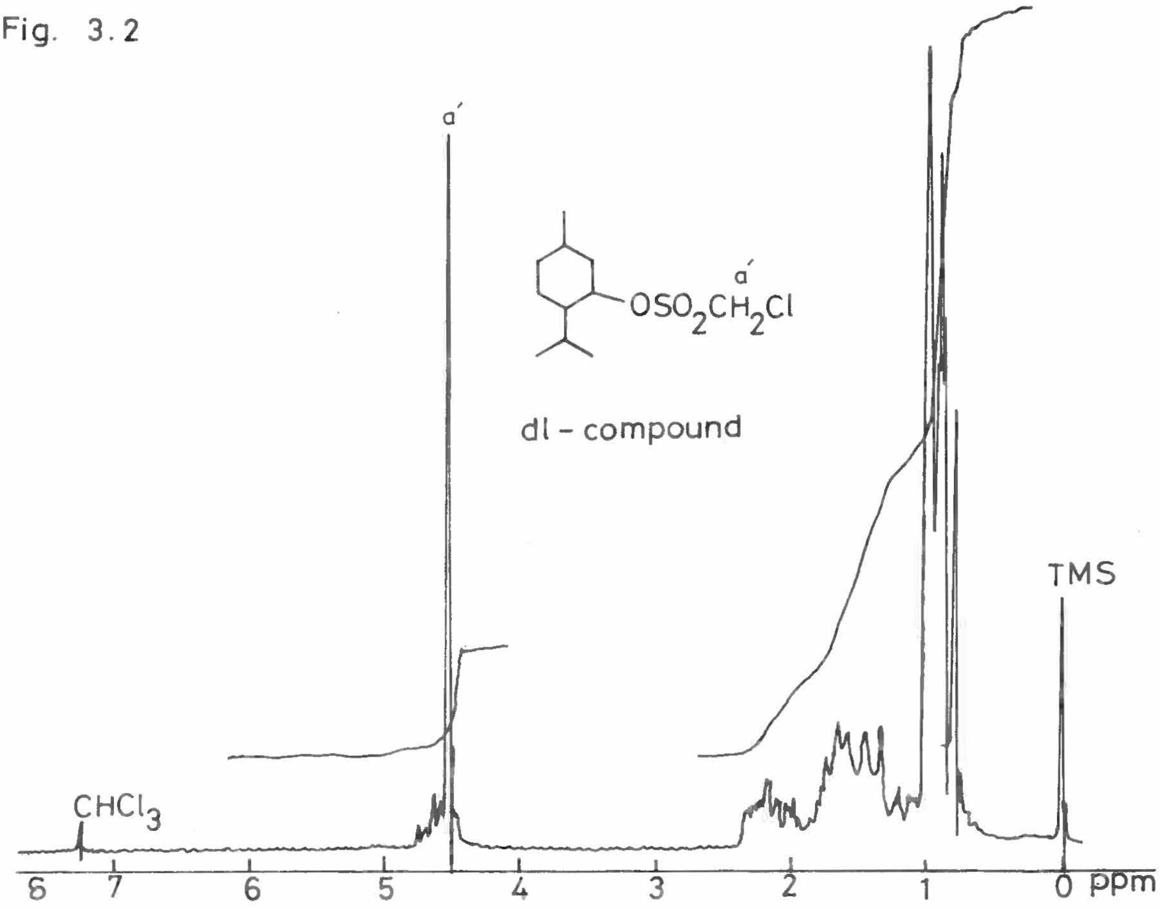
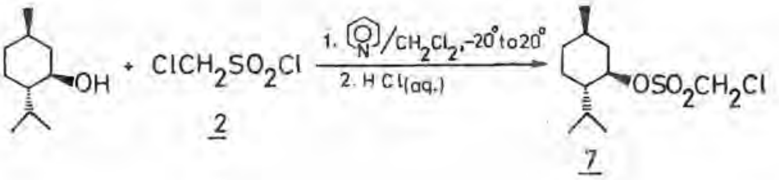

a
OSO2CH2Cl
a
l-isomer
CHCl3
TMS
δ
7
6
5
4
3
2
1
0
ppm

Fig. 3.2


a′
OSO2CH2Cl
a′
dl-compound
CHCl3
TMS
δ
7
6
5
4
3
2
1
0
ppm

scheme 3.5

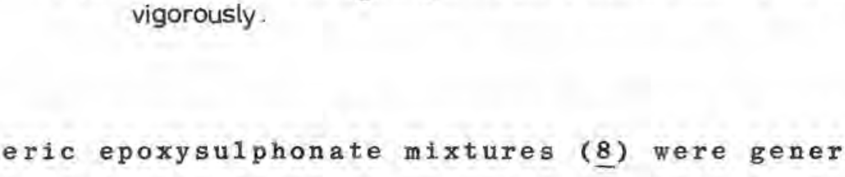


However, some decomposition occurred during this purification process. The ^{1}H-NMR spectrum of 7 showed the two diastereotopic α-chloromethylene protons to absorb as a singlet at δ 4.53 ppm. Prolonged storage of this compound at room temperature led to slow deterioration.

3.2.3. *Chiral α,β-Epoxysulphonate menthyl esters*

These compounds were synthesized by the Darzens condensation of aldehydes or ketones with the chiral reagent l-menthyl chloromethanesulphonate (7) under PTC conditions in the presence of triethylbenzylammonium chloride (TEBA), an achiral phase transfer catalyst. High chemical yields of the diastereomeric epoxysulphonate mixtures (8) were generally obtained after purification by chromatography. The low yield (47.5%) using acetaldehyde as the carbonyl compound is due to self condensation of this aldehyde under the basic conditions

scheme 3.6



R = R₁ or R₁ = H

PTC: 50% NaOH, $PhCH_2NEt_3Cl$ (TEBA), acetonitrile, stirring vigorously.

used. Results are collected in Table 3.1.

Table 3.1: Asymmetric Synthesis of α,β-Epoxysulphonate Esters 8 According to Scheme 3.6

	R	R_1	Yield(%)	m.p.(°C)	d.e(%)(1)	^{1}H NMR(epoxymethine protons) δ, ppm (J in Hz)
8a	Me	Me	81	oil	10	3.87(s)
8b	Ph	H	61.5	95–98(2)	~10(3)	4.29(d), 4.18(d), J=1.5
8c	β-naphthyl	H	57	108–110	12.5	4.4(m), 4.3(m)
8d	Me_2CH	H	76	oil	9	3.95(d, (J=1.5), 3.30(m)
8e	$-(CH_2)_4-$		82	oil	17	4.13 (s)
8f	$-(CH_2)_5-$		90.5	oil	10.5	3.97 (s)
8g	Me	H	47.5	oil	11.5	3.90(s), 3.50(m)
8h	$2,4,6\text{-}Me_3C_6H_2$	H	79.5	oil	14	4.37(m), 4.05(m)
8i	$p\text{-}MeC_6H_4$	H	72	119–120(2)	~10	4.35(d), 4.17(d), J=1.5

(1) d.e.= diastereomeric excess

(2) for one pure diastereomer

(3) estimated from partially resolved epoxymethine proton NMR signal in presence of $Eu(fod)_3$

In this study only aldehydes and symmetrical ketones were used as carbonyl substrates. The reason for this was the non-stereoselectivity of the Darzens condensation for epoxysulphones when unsymmetrical ketones are used.[3-7,12] In such cases (*E*)- and (*Z*)-diastereomeric pairs of chiral epoxysulphonate esters would be obtained, thus leading to difficulties in the determination of the extent of asymmetric induction in each of the two diastereomeric pairs.

On standing at low temperature, one of the two diastereomers of 8b and 8i crystallized. These crystalline chiral epoxysulphonate esters were purified by recrystallization from 10% ether in hexane. The well resolved ^{1}H-NMR spectra of these compounds and that of 8d indicated that the coupling constant between the two epoxymethine proton signals was 1.5 Hz. Similarly, the well resolved ^{1}H-NMR spectra of 8c, 8g and 8h obtained after addition of Eu(fod)$_3$ (section 3.2.4.) showed that the coupling constant of these epoxymethine proton resonances was also 1.5 Hz. These values indicate that compounds 8b-d and 8g-i had the (*E*)-configuration. This geometry is in accordance with that previously observed for epoxysulphones[1-7] and epoxysulphonamides[12,13] prepared by the Darzens condensation.

The positions of the epoxymethine proton signals in the ^{1}H-NMR spectra of 8g and 8d indicated that the signal of the proton α to the sulphonate function (H_α) was at lower field (δ 3.90 and 3.95 ppm, respectively) than that at the β-position (δ 3.50 and 3.30 ppm, respectively). No such distinction could be made for the positions of the epoxymethine signals in the spectra of 8b,c and 8h,i. Vogt and Tavares[3] have established that the ^{1}H-NMR signals of H_α and H_β in epoxysulphones bearing an aromatic function on the β-carbon atom are in the reverse positions as compared with those having an alkyl substituent at C_β. They conclude from this observation that the β-proton in the former epoxysulphones is in the deshielding region of the β-aromatic ring and therefore this ring is in a plane perpendicular to that of the epoxide ring. Such a conclusion cannot be derived from the spectra of β-aliphatically and β-aromatically substituted epoxysulphonate esters.

3.2.4. *Determination of the Degree of Asymmetric Synthesis*

Several methods are known for the determination of the degree of asymmetric synthesis. The most popular one is that based on optical rotations.[8-11,17] In this method the ratio of the specific rotation of a mixture and that of one pure isomer (expressed as a percentage) gives the optical yield (or optical purity). A value obtained in this way is empirically the same as isomeric excess (enantiomeric e.e. or diastereomeric, d.e.).[8-11,17] Alternatively, the e.e. or d.e.

can be determined by chromatography, physical separation of the isomers or by ^{1}H-NMR spectroscopy, with or without the help of shift reagents (chiral for e.e. or achiral for d.e.).[8-11,17]

In the present study, Eu(fod)$_3$ induced ^{1}H-NMR shifts were used to determine the composition, and hence the extent of chiral induction during the preparation of the diastereomeric epoxysulphonate esters. The shift reagent Eu(fod)$_3$ gave the best resolutions and shifts as compared to Eu(dpm)$_3$.

NMR shift reagents are widely used in effecting simplification and enhanced resolution of ^{1}H-NMR spectra by shifting and subsequently separating various proton signals which otherwise appear at the same position. Furthermore, these reagents may be useful in obtaining valuable information about the stereochemistry of molecules in solution where the shift reagents associate with defined basic functionalities of organic compounds.[18] In sterically unhindered molecules the magnitude of the induced shifts may give a clue to the type of the functional group responsible for the coordination of the shift reagent.

One of the concepts which have been advanced to explain the observed coordination of shift reagents with organic molecules has been that based on the coordination of hard lanthanide ions of the reagents with soft and hard acids and bases.[18] Thus stronger interactions, and hence larger induced NMR shifts can be predicted for hard (*e.g.* N and O) over soft (*e.g.* P and S) bases.

For sterically unhindered multifunctional molecules complexation with shift reagents takes place at the strongest coordinating site, saturation of which allows further coordination at weaker donors.[18] In such molecules the extent of delocalization of the coordinating electron pair as well as the inductive effect of the neighbouring groups will determine the extent of complexing at the competing sites in the donor molecule. In some cases it is also possible for multifunctional molecules to complex at two sites simultaneously.[18]

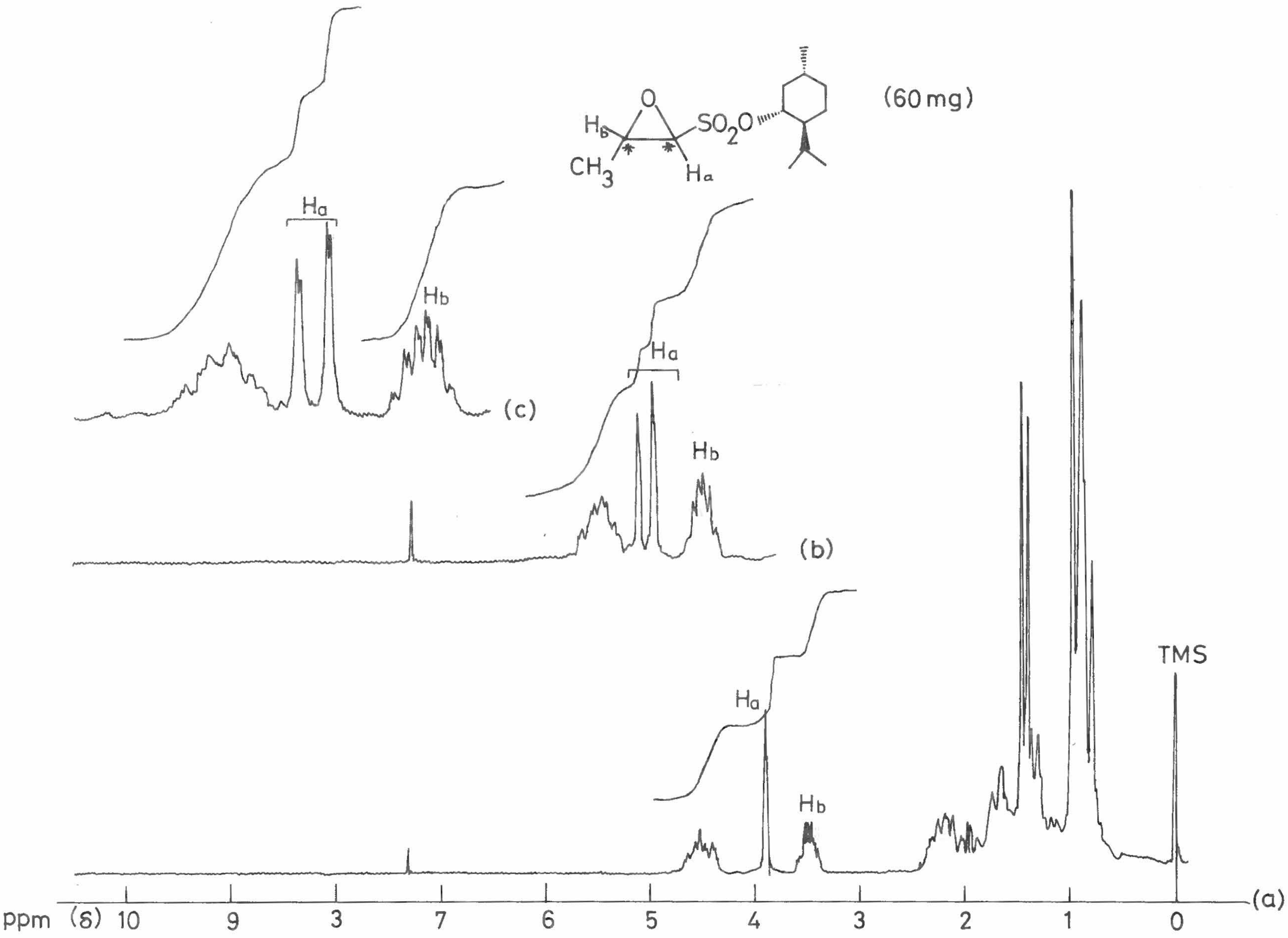
Lanthanide induced NMR chemical shifts have been found to depend on the distance of the affected proton(s) from the lanthanide atom of the shift reagent (Eu in the present study) as well as on a certain intermolecular angle between this atom and the site of coordination.[20]

The coordinating ability of monofunctional substrates with NMR shift reagents is in the following order: NH_2 > OH > ketones ⩾ esters > thioesters > nitriles.[21,22] Esters and epoxides are relatively poor donors towards NMR shift reagents.[23] Unexpectedly, a sulphone group is a weaker donor than esters and epoxides.[24] An amide group complexes predominantly over a methoxy group.[25] This order of complexation may be affected by steric factors.[18]

NMR shift reagents are very hygroscopic, storage of which should be over a suitable desiccant (*e.g.* P_2O_5) *in vacuo*.[26] Strong acidic conditions drastically reduce the chelating effect of these compounds.[18] The shift reagents can be recovered chromatographically.

In the present investigation progressive addition of an increasing amount of $Eu(fod)_3$ to a known amount of the diastereomeric epoxysulphonate esters and subsequent determination of the ^1H-NMR spectrum immediately after each addition, revealed that epoxysulphonate esters derived from aliphatic aldehydes and ketones (at least those used in this study) gave the best ^1H-NMR shifts and subsequent separation of the signal due to the epoxymethine proton α to the sulphonate group (H_α). An example of such spectra is shown in Figure 3.3. Steric hindrance of the aromatic group on the epoxide ring in compounds 8b,c,h and 8i (Table 3.1) probably reduces the effective complexation, resulting in a rather poor separation of (both) epoxymethine proton signals in these cases. Collona *et al.*[27], also report poor shift reagent assisted NMR signal separations in epoxysulphones substituted with aryl groups at C_β.

Fig. 3.3: (a) without Eu(fod)$_3$, (b) & (c) with 172 mg Eu(fod)$_3$, (c) 5 ppm sweep width

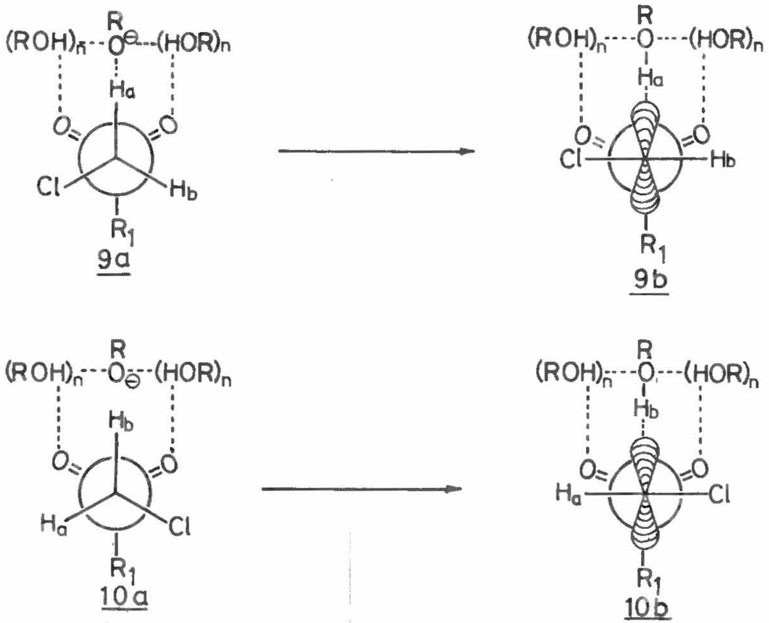


3.2.5. *Stereochemical Course of the Chiral Induction*

The factors that influence the chiral induction in asymmetric synthesis have been the subject of many discussions. For example, in asymmetric reactions involving chiral reagents having more than one inducing chiral centre, such as in l-menthol, the competing effect of these chiral centres has been attributed to either enhanced or retarded degree of asymmetric synthesis[8], depending on the nature of the asymmetric reaction involved. A large interatomic separation between the inducing chiral centre and the developing one usually is associated with a lower extent of chiral induction.[8] It is generally accepted that the stereostructure and rigidity of the chiral reagent as well as of the formed diastereomeric transition states leading to products are important factors in dictating the degree of asymmetric induction.[8]

For a proper understanding of the stereochemical course of the formation of epoxysulphonate esters the deprotonation adjacent to a sulphone, the structure of α-sulphonyl carbanions and the influence of the chiral substituent on the process of deprotonation need to be discussed. Corey and Lowry[28,29] showed that deprotonation adjacent to a sulphone group occurs preferentially from a conformation in which the abstracted proton is flanked by (*syn* to) the sulphonyl oxygen atoms. For the deprotonation by hydroxide or alkoxide ions they suggest a mechanism involving hydrogen bonding between water (in deprotonation by hydroxide ions) or alcohol molecules (in deprotonation by alkoxide ions) and the sulphonyl oxygens on one hand and the alkoxide (or hydroxide) ions on the other. For chloromethyl sulphones, as in the present study, this leads to two conceivable conformations, *viz*. 9a and 10a, for the proton abstraction (Figure 3.4). When R_1 is an achiral group these rotamers 9a and 10a are enantiomers, when R_1 is a chiral substituent these conformers are diastereomers. The chiral induction on the ratio of diastereomers will be discussed below.

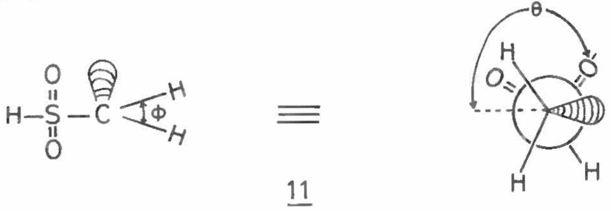
Fig. 3.4



R = H or alkyl; R_1 = chiral or achiral substituent

The structure of α-sulphonyl carbanions has received intensive theoretical and experimental attention, particularly, because of the special ability of these anions to maintain their stereochemical configurations.[30] Now there is convincing evidence that α-sulphonyl carbanions are planar with a high barrier to rotation rather than pyramidal with a barrier to inversion.[31] An energy surface as a function of the angle Θ and ϕ in the simplified sulphone system 11 (Figure 3.5) has been provided by MO calculations.[32,33] It was found that of the five possible orientations 12a-12e (Figure 3.6) the

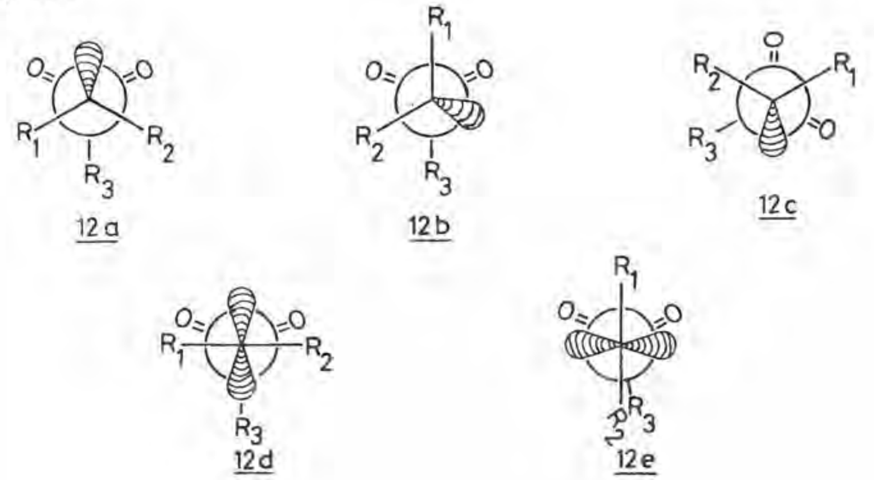
Fig. 3-5



11

pyramidal sulphonyl carbanion 12a with the lone pair bisecting the O-S-O angle has the lowest energy.[32,33] The planar structure

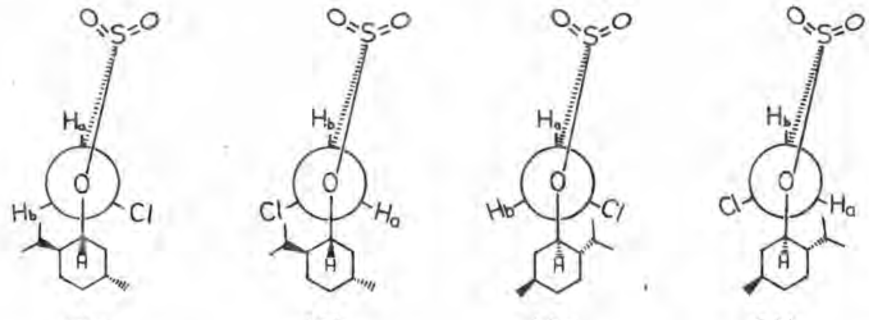
Fig. 3.6



12d was found to be 2-5 Kcal/mole less stable than 12a. However, it was argued that this value is probably below the error limits in these minimal basis set calculations. Recent studies (X-ray analysis[34-36], ^{13}C-NMR spectra[37,38], acidity data studies[31]) have shown that the planar carbanion structure is consistent with all the available experimental data.

In the present substrate, l-menthyl chloromethanesulphonate, the α-methylene protons are diastereotopic due to the presence of the chiral menthyl group. Therefore, the transition states for the abstraction of these protons will be different, in other words, through asymmetric induction there will be a preference for the removal of one methylene proton over the other. The conformations which illustrate the influence of the chiral substituent on the deprotonation process are depicted in Figure 3.7 (1-3 Newman projections of the α-carbon atom and the connecting sulphonate oxygen). It should be noted that in these conformations the protons to be abstracted are placed in the bisecting plane of the sulphonyl group as outlined in Figure 3.4.

Fig. 3.7



13a 13b 14a 14b

The spatial position of the menthyl ring is difficult to deduce from molecular model studies. Therefore two types of orientations are pictured. Steric effects most likely will dictate which conformer will predominate. To a certain extent the models suggest that the conformers having the chlorine atom in proximity of the bulky isopropyl group are disfavoured (13b and 14a). It is suggested that the hydrogen bonding shown in Figure 3.4 may enhance the steric effects exerted by the sulphonyl group and therefore enlarge the steric congestion in the species to be deprotonated. It should also be noted that the proximity effect of the chlorine atom and the isopropyl group in 13 and 14 has an opposing result on the preference of the conformers from which H_a (or H_b) is abstracted. All in all, there is not great difference between the respective conformations, consequently, the asymmetric induction is expected to be rather low.

Once the diastereomeric sulphonyl carbanions are formed, the reaction of either of them with aldehydes will lead to (*E*)-epoxysulphonate esters. The transition states leading to these (*E*)-epoxides are diastereomeric and because of this the rates of formation of the (*E*)-epoxides are different (asymmetric induction). The ratio of resulting diastereomeric (*E*)-epoxides (note that the epoxides are enantiomers when the menthyl group is ignored) will be determined by the ratio of diastereomeric α-sulphonyl carbanions, the asymmetric induction on the subsequent formation of the intermediate chlorohydrins and by the relative rates of the 1,3-eliminations leading to the (*E*)-epoxides. The experimentally observed d.e. values for aldehydes are all in the same range except mesitylaldehyde which showed a somewhat higher value. Maybe that with this sterically hindered aldehyde the asymmetric induction on the epoxide forming step is somewhat more pronounced. The diastereomeric excess observed for cyclopentanone as the carbonyl compound is higher than that for acetone and cyclohexanone. Apparently, the asymmetric induction during the epoxide formation is higher for cyclopentanone. As yet this observation cannot be rationalized.

The experimentally observed asymmetric induction (see d.e. values in Table 3.1) is rather low. It is believed that the 1-menthyl group in the present investigation is not a very efficient chiral inductor. Loss of asymmetric induction through racemization of the intermediate α-sulphonyl carbanion seems unlikely in view of the high degree of steric integrity of chiral sulphonyl carbanions.[30] Racemization of the epoxides is rather unlikely too, because in the case of the (*E*)-epoxides derived from aldehydes this would require a simultaneous inversion of configuration at C_α and C_β of the epoxide function. Thus indeed the rather low asymmetric inductions are due to the low efficiency of 1-menthol as chiral inductor.

The above analysis of the factors that play a role in the asymmetric induction during the formation of α,β-epoxysulphonate esters suggest that the extent of asymmetric induction may be improved when the chiral inductor is more rigidly attached to the sulphonyl group. Experiments in this direction are described in Chapter 4.

3.3. *EXPERIMENTAL*

3.3.1. *General Remarks*

Reagents: Unless otherwise stated all reagents were used as commercially supplied (analytical grade), mainly from Aldrich Europe (Belgium), EGA (West Germany), Fluka (Switzerland), J.F. Baker (The Netherlands) and Merck (West Germany). Unless otherwise stated magnesium sulphate (containing 26-32% water) was used for drying organic solutions.
Solvents: THF was distilled first over calcium hydride and then over lithium aluminium hydride and was used immediately after its final distillation. *n*-Hexane, *n*-pentane, pet.ether and diethyl ether were distilled over calcium hydride. Ethyl acetate was distilled over potassium carbonate. Chloroform for optical rotation determinations was distilled over P_2O_5. Solvents for chromatography were stored in plain containers. All other distilled solvents were stored over 4 Å molecular sieves. Apart from the above, all other solvents were used as commercially supplied (analytical grade).
Chromatography: Thin layer chromatography (TLC) was performed on precoated aluminium plates (silica gel 60 F_{254}, 0.25 mm, Merck). Preparative chromatography was carried out either by medium pressure liquid chromatography (MPLC) (silica gel H type 60, Merck) using a JOBIN YVON (Instruments S.A. Nederland) miniprep LC or by TLC (glass plates, 20x20 cm, precoated with silica gel 60 F_{254}, 2 mm, Merck).
Melting points: These were taken on a REICHERT (Austria) melting point apparatus and are uncorrected.
Spectra: Infrared (IR) spectra were recorded on a PERKIN ELMER model 298 instrument. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken on a VARIAN EM 390 instrument operating at 90 MHz using $CDCl_3$ as solvent and tetramethylsilane (TMS, $\delta = 0$ ppm) as an internal standard. Chemical shifts are reported in δ (ppm) values. Resonances are denoted by: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad and ABq = AB quartet. Mass spectra

were recorded on a VARIAN MAT SB 2B spectrometer.
Elemental analysis: Mr. J. Diersmann of the Micro Analytical Department, University of Nijmegen, The Netherlands, carried out the analyses.
Optical rotations: These were determined in chloroform using a PERKIN ELMER model 241 polarimeter.

3.3.2. *Chloromethanesulphonyl chloride* (2)

Method 1: This method was adopted from literature[15] with some modifications. Thus a stirred mixture of sodium thiosulphate (337 g), formalin (37% v/v, 200 ml) and conc. HCl (200 ml) was heated under reflux until a solid of *sym*-trithiane was formed (ca. 30 min.). This solid was filtered off, washed with water until it was free from acid. It was then dried *in vacuo* over Na_2SO_4 to give crude *sym*-trithiane (91 g, 93%). A stirred suspension of the trithiane (90 g) in a solution of glacial acetic acid (450 ml) in water (90 ml) at 20° was chlorinated until all the trithiane had dissolved (ca. 4-6 hr). More water (30 ml) was added to the resulting solution and without cooling, the solution was then further chlorinated for 5 hr. After standing at room temperature for 15 hr the reaction mixture was poured in cold water (1 l). The oily material which was deposited was collected and dissolved in ether. The ethereal solution was then dried and the solvent was evaporated affording a light yellow oil. Extraction of the aqueous layer (left after separation of the oil) with ether, washing it several times with water to neutrality and following the same procedure as above, gave some more of the yellow oil. The ^{1}H-NMR spectrum of the crude oil showed the presence of only a small amount of chloromethanesulphonyl chloride (δ 5.00 ppm) being predominated by another unknown compound (δ 4.86 ppm). So this whole product (10 g) was redissolved in a solution of acetic acid (100 ml) in water (30 ml) and chlorinated for 2-3 hr. After standing at room temperature for 15 hr the reaction mixture was poured in cold water (500 ml) and extracted with dichloromethane; the dichloromethane solution was then dried, the solvent was evaporated (together with some acetic acid which was also extracted with dichloromethane) leaving a crude product whose ^{1}H-NMR spectrum showed only a single peak at $\delta = 5.00$ ppm attributable to compound <u>2</u>. The crude product was purified by distillation to give 6.52 g, 3.3% based on trithiane, b.p. 43°/1.5 Torr or 40°/0.7 Torr.

Method 2: H_2S gas was bubbled through a stirred mixture of paraformaldehyde (40 g), formalin (37% v/v, 250 ml) and conc. HCl (400 ml). The resulting mixture (without isolating the so-formed *sym*-trithiane) was chlorinated at -20° while letting the temperature to rise slowly to room temperature within 2-3 hr. When all the solids had dissolved chlorination was continued at 30-40° for 3 hr. Then the reaction mixture was poured into cold water (2 l). After extraction with ether and concentration under reduced pressure a product was obtained which on the basis of the ^{1}H-NMR spectrum showed the same composition as the first product in method 1. So the concentrate was then taken up in a solution of glacial acetic acid (600 ml) in water (120 ml), chlorinated again at *ca.* 30° for 3-4 hr and worked up as before. The newly obtained oil was washed with water until free from acid before being dissolved in ether. The ethereal solution was dried and the solvent was evaporated under reduced pressure. The resulting crude product was purified by distillation. Yield 162 g (74%), b.p. 62°/3 Torr; ^{1}H-NMR, $\delta = 5.00$ ppm, $ClC\underline{H}_2-SO_2-$; IR (neat film), $\nu(-SO_2-)$ 1350 and 1160 cm^{-1} (s).

3.3.3. *l-Menthyl chloromethanesulphonate* (<u>7</u>)

To a stirred solution of l-menthol (19.54 g, 0.125 mol) and pyridine (19.75 g, 0.25 mol) in dichloromethane (350 ml) at -15° and under nitrogen, was slowly added a solution of chloromethanesulphonyl chloride (<u>2</u>) (22.35 g, 0.15 mol). The resulting solution was stirred at room temperature for 4 hr and then poured into a cold solution of conc. HCl (70 ml) in water (300 ml). The organic phase was separated and the aqueous phase was extracted three times with dichloromethane. The combined organic phases were washed with water until neutral. After drying the solvent was evaporated under reduced pressure to leave an oil which solidified on standing at room temperature. This compound could not be recrystallized. So it was purified by preparative MPLC (10% ether in hexane as eluent) to give a pure product, 30.31 g (90%), $[\alpha]_D = -56.99^{\circ}$ (c = 3.55, $CHCl_3$); MS: m/e 268 (M^+); ^{1}H-NMR, δ = 4.80-4.40 (m, carbinol proton), 4.55 (s, $-SO_2-C\underline{H}_2-Cl$) and 2.40-0.60 ppm (m, menthyl group); IR (neat film), $\nu(-SO_2-O-)$, 1425 and 1200 cm^{-1} (s).

3.3.4. *General method for the preparation of α,β-epoxysulphonate esters*

To a vigorously stirred mixture of a solution of NaOH (50% w/v, 20 ml), l-menthyl chloromethanesulphonate, triethylbenzylammonium chloride (TEBA) (0.1 g) and acetonitrile (3 ml) at 10-15° was slowly added a solution of an aldehyde or ketone in acetonitrile (2-4 ml). The mixture was mechanically stirred continuously for a further 1 hr at 15-20° for aldehydes and 2 hr for ketones. The reaction mixture was then poured into cold water (200 ml) and extracted with dichloromethane. The dichloromethane extract was dried and then the solvent was evaporated under reduced pressure to leave a crude product which was purified by chromatography (10% ether in hexane as eluent). When β-naphthaldehyde was used as the carbonyl compound the precipitated product was filtered off, washed several times with water, dried over $CaCl_2$ *in vacuo* at 25° for 24 hr, and subsequently purified by chromatography and recrystallisation from *n*-hexane to give an analytical sample.

To each of the epoxysulphonate esters (*ca.* 60 mg) dissolved in $CDCl_3$ was added an increasing amount of $Eu(fod)_3$ until the ^{1}H-NMR spectrum of the mixture of diastereomers showed two distinct signals for each of the epoxymethine protons. The integration of these signals then gave the relative amounts of the two chiral diastereomeric epoxysulphonate esters.

l-Menthyl 2-methyl-1,2-epoxypropanesulphonate (8a)

Acetone (0.884 g, 15.24 mmol, excess) and 7 (2.16 g, 8.04 mmol) gave 8a as a viscous oil, 1.891 g (80.5%); ^{1}H-NMR, δ 4.77-4.33 (m, menthyl carbinol proton), 3.87 (s, epoxymethine proton), 1.67 (s) and 1.43 (s) (epoxymethyl protons) and 2.40-0.60 ppm (m, menthyl group); IR (neat film), $\nu(-SO_2-O-)$, 1425 and 1200 cm^{-1} (s) and MS: m/e 302 (M^+); diastereomeric composition: 55.0% and 45.0% corresponding with a diastereomeric excess of 10.0%.

l-Menthyl E-(2-phenyl-1,2-epoxyethanesulphonate) (8b)

Benzaldehyde (1.53 g, 14.43 mmol) and 7 (3.88 g, 14.43 mmol) gave an oil (3.0 g, 61.5%); IR (neat film), $\nu(-SO_2-O-)$ 1420 and 1200 cm^{-1} (s); ^{1}H-NMR, δ 7.30 (m, phenyl group), 4.80-4.40 (m, menthyl carbinol proton), 4.33 and 4.17 (m, epoxymethine protons) and 2.50-0.60 ppm (m, menthyl group). On standing at about 5° one of the two diastereomers crystallized. It was purified by recrystallization from *n*-hexane furnishing white wool-like crystals, m.p. 95-98°; IR (KBr), $\nu(-SO2-O-)$ 1425 and 1205 cm^{-1} (s); ^{1}H-NMR, δ 7.37 (m, phenyl group), 4.80-4.47 (m, menthyl carbinol proton), 4.29 (d) and 4.18 (d) (J = 1.5 Hz, epoxymethine protons) and 2.50-0.60 ppm (m, menthyl group). Found; C: 63.8% and H: 7.8% (calculated for $C_{18}H_{26}O_4S$; C: 63.87% and H: 7.76%). The other fraction (oily) still contained some of the crystalline isomer (NMR). Eu(fod)$_3$ NMR experiments as above showed two pairs of epoxymethine proton signals, the intensity of which was different in each of the pairs. However, as no clear resolution could be achieved no definitive conclusion on the diastereomeric composition could be derived from these experiments. From the partially resolved signals for the epoxymethine protons a d.e. of about 10% was estimated.

l-Menthyl E-[2-(2'-naphthyl)-1,2-epoxyethanesulphonate] (8c)

2-Naphthaldehyde (0.71 g, 4.54 mmol) and 7 (1.22 g, 4.54 mmol) gave a crystalline precipitate which was filtered off and worked up as already described. Yield of 8c was 1.0 g (57%), m.p. 108-10^o; ^{1}H-NMR, δ 8.00-7.50 (m, naphthyl group), 4.80-4.00 (m, 2H, the menthyl carbinol and one epoxymethine proton), 4.30 (m, epoxymethine proton) and 2.50-0.60 ppm (menthyl group); $[\alpha]_D$ = -54.25 (c = 0.80, $CHCl_3$); found; C: 68.1% and H: 7.3% (calculated for $C_{22}H_{28}O_4S$; C: 68.00% and H: 7.28%); diastereomeric composition, 56.3% and 53.8% (d.e. = 12.5%).

l-Menthyl E-(3-methyl-1,2-epoxybutanesulphonate) (8d)

Isobutyraldehyde (0.44 g, 6.11 mmol) and 7 (1.49 g, 5.54 mmol) gave 8d as a viscous oil, 1.69 g (76%); IR (neat film), $\nu(-SO_2-O-)$, 1420 and 1195 cm^{-1} (s); ^{1}H-NMR, δ 4.80-4.30 (m, menthyl carbinol proton), 3.95 (d, J = 1.5 Hz, α-epoxymethine proton), 3.30 (m, β-epoxymethine proton and 2.50-0.60 ppm (menthyl and isopropyl group). The diastereomeric composition was 54.5% and 45.5% (d.e. = 9.0%).

l-Menthyl 2,2-tetramethylene-1,2-epoxyethanesulphonate (8e)

Cyclopentanone (0.63 g, 7.50 mmol) and 7 (2.00 g, 7.44 mmol) gave 8e as a viscous oil, 1.92 g (82%); IR (neat film), $\nu(-SO_2-O-)$, 1420 and 1195 cm^{-1} (s); ^{1}H-NMR, δ 4.75-4.35 (m, menthyl carbinol proton), 4.13 (s, epoxymethine proton) and 2.45-0.60 ppm (cyclopentyl and menthyl groups); diastereomeric composition 58.6% and 41.6% (d.e. = 17.0%).

l-Menthyl 2,2-pentamethylene-1,2-epoxyethanesulphonate (8f)

Cyclohexanone (0.68 g, 6.30 mmol) and 7 (1.69 g, 6.29 mmol) gave 8f, 1.86 g (90.5%); IR (neat), $\nu(-SO_2-O-)$, 1425 and 1200 cm^{-1} (s); ^{1}H-NMR, δ 4.80-4.38 (menthyl carbinol proton), 3.97 (s, epoxymethine proton) and 2.50-0.60 ppm (menthyl and pentamethylene group) and a diastereomeric composition of

55.2% and 44.7% (d.e. = 10.5%) was realized.

l-Menthyl E-(1,2-epoxypropanesulphonate) (8g)

Acetaldehyde (0.81 g, excess) and 7 (2.50 g, 9.30 mmol) gave 8g, 1.22 g (47.5%); IR (neat), $\nu(-SO_2-O-)$, 1425 and 1200 cm^{-1} (s); ^1H-NMR, δ 4.73-4.35 (m, menthyl carbinol proton), 3.90 (d, J = 1.5 Hz, α-epoxymethine proton), 3.50 (m, β-epoxymethine proton), 2.45-0.60 (menthyl group) and 1.44 ppm (d) (β-epoxymethyl protons); MS: m/e 276 (M^+). From $Eu(fod)_3$ NMR experiments the coupling constant between the two epoxymethine protons was 1.5 Hz while the diastereomeric composition was 55.8 and 44.3% (d.e. = 11.5%).

l-Menthyl [E- 2-(2',4',6'-trimethylphenyl)-1,2-epoxyethanesulphonate] (8h)

2,4,6-Trimethylbenzaldehyde (1.30 g, 8.78 mmol) and 7 (2.16 g, 8.04 mmol) gave 8h as a viscous oil, 2.43 g (79.5%); IR (neat), $\nu(-SO_2-O-)$, 1420 and 1190 cm^{-1} (s); ^1H-NMR, δ 6.80 (s, aromatic protons), 4.87-4.45 (m, menthyl carbinol proton), 4.37 (m) and 4.05 (m) (epoxymethine protons), 2.33 (s, 6H, methyl groups at the 2- and 6-positions of the benzene ring), 2.23 (s, 3H, methyl group at the 4-position of the benzene ring) and 2.50-0.60 ppm (menthyl group). The diastereomeric composition was found to be 57% and 43% (d.e. = 14.0%). $Eu(fod)_3$ NMR experiments showed $J_{H_\alpha H_\beta}$ to be about 1.5 Hz.

l-Menthyl E-[2-(p-tolyl)-1,2-epoxyethanesulphonate] (8i)

p-Tolylaldehyde (1.15 g, 9.58 mmol) and 7 (2.42 g, 9.00 mmol) gave crude 8i as a viscous liquid; IR (neat), $\nu(-SO_2-O-)$, 1420 and 1195 cm^{-1} (s); ^1H-NMR, δ 7.20 (s, 4H, aromatic protons), 4.95-4.45 (m, menthyl carbinol proton), 4.33 (m) and 4.20 (m) (epoxymethine protons), 2.33 (s, methyl protons of the *p*-tolyl group) and 2.50-0.60 ppm (menthyl group). On standing at room temperature one of the diastereomers crystallized from this mixture. This was filtered off and recrysallized from *n*-hexane to give white crystals, m.p. 119-120°; ^{1}H-NMR, δ 7.17 (s, 4H, aromatic protons), 4.80-4.50 (m, menthyl carbinol proton), 4.35 (d) and 4.17 (d) (J = 1.5 Hz, epoxymethine protons), 2.33 (s, methyl protons of *p*-methyl group) and 2.50-0.60 ppm (m, menthyl group); $[\alpha]_D$ = -97.0 (c = 0.90, $CHCl_3$) and MS: m/e 352 (M^+). No $Eu(fod)_3$ NMR experiments were performed with the crude material but from the ^{1}H-NMR spectrum of the pure compound and that of the residual material a d.e. of about 10% was estimated.

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CHAPTER 4

ASYMMETRIC SYNTHESIS OF α,β-EPOXYSULPHONAMIDES

SUMMARY

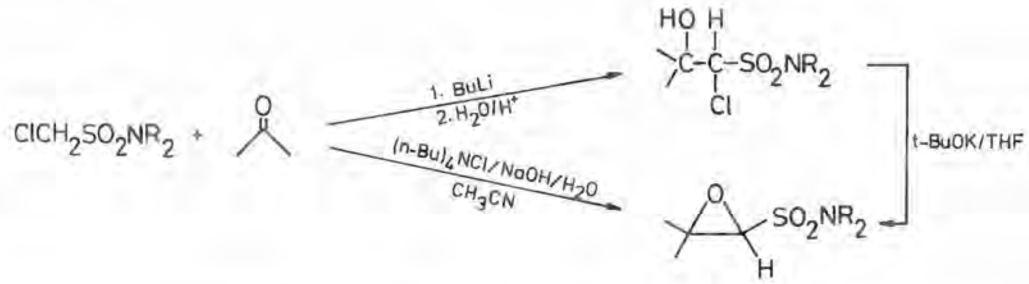
In this chapter the asymmetric phase transfer catalysed (PTC) Darzens condensation of aldehydes and ketones with chiral reagents (*S*)-(-)-*N*-chloromethylsulphonyl-2-methoxymethyl-pyrrolidine (<u>6</u>), (*S*)-(-)-*tert*-butyl *N*-(chloromethylsulphonyl)-prolinate (<u>9</u>) and (+)-*O*-methyl-*N*-(chloromethylsulphonyl)-ephedrine (<u>14</u>) using triethylbenzylammonium chloride (TEBA) as the phase-transfer catalyst, to give chiral diastereomeric α,β-epoxysulphonamides, is described. Of the three chiral reagents used, <u>6</u> was found to be the most effective. Chiral inductions of up to almost 50% were obtained, as was assessed by $Eu(fod)_3$ induced ^1H-NMR measurements. The stereochemical course leading to the chiral induction is discussed.

4.1. *INTRODUCTION*

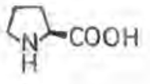
In the literature survey presented in Chapter 2 (section 2.3.1.) it has been shown that the Darzens condensation of chloromethyl sulphones with a variety of carbonyl compounds constitutes a general approach to epoxysulphones. Truce and Christensen[1,2,3] reported that this general method can also be applied for the preparation of α,β-epoxysulphonamides. They concluded, however, that the condensation needed to be carried out in two separate steps. First, the precursory β-hydroxy-α-chlorosulphonamides were prepared from chloromethanesulphomorpholide, alkyllithium and a carbonyl compound.[2,3] In the second step the β-hydroxy-α-chlorosulphonamides were converted into the corresponding α,β-epoxysulphomorpholides by reaction with potassium *tert*-butoxide in THF. Interestingly, these authors were unable to accomplish the epoxide formation in an acceptable yield by means of potassium hydroxide as the base, because of the competing *retro*-condensation of the β-hydroxy-α-chlorosulphonamide to chloromethanesulphomorpholide and the corresponding carbonyl compound.

In marked contrast herewith is the report of Golinski and Mąkosza[4] in which the one step synthesis of α,β-epoxysulphonamides from chloromethanesulphonamides and carbonyl compounds is described using concentrated aqueous sodium hydroxide as the base in the presence of tetrabutylammonium chloride as the phase-transfer catalyst. The nitrogen atom in the epoxysulphonamides offers an unique opportunity to incorporate a chiral substituent in these molecules. The synthesis shown in Scheme 4.1 can therefore be extended to an asymmetric synthesis of α,β-epoxysulphonamides.

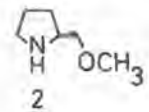
scheme 4.1



In the field of asymmetric synthesis (*S*)-proline (1) and its derivatives, such as 2-4, are among the most widely used



1



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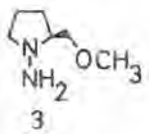

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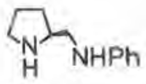


4

chiral reagents.[4-11] The rather low price and the easy availability in optically pure form of 1 and its derivatives are reasons that make these compounds attractive for asymmetric reactions. Furthermore, the reported high degree of chiral induction achieved with proline and its congeners have contributed to the popularity of these chiral inductors. Therefore, a study of the asymmetric Darzens condensation using chloromethanesulphonamides derived from proline or a suitable derivative, seems quite appropriate. An additional attractive feature of the use of proline (or a derivative) in the present investigation is the fact that the chiral centre will be less flexibly bound to the sulphonyl group than in the previously studied menthyl sulphonates (Chapter 3). As was outlined in Chapter 3, there are good reasons to expect an improved asymmetric induction when the chiral group is more definably associated with the prochiral centre at which the reactions are taking place.

Other widely used chiral compounds are ephedrine and its derivatives.[12-20] It therefore was decided to incorporate this type of inductor in the asymmetric Darzens condensation, for comparison with the results using chiral inductors derived from proline.

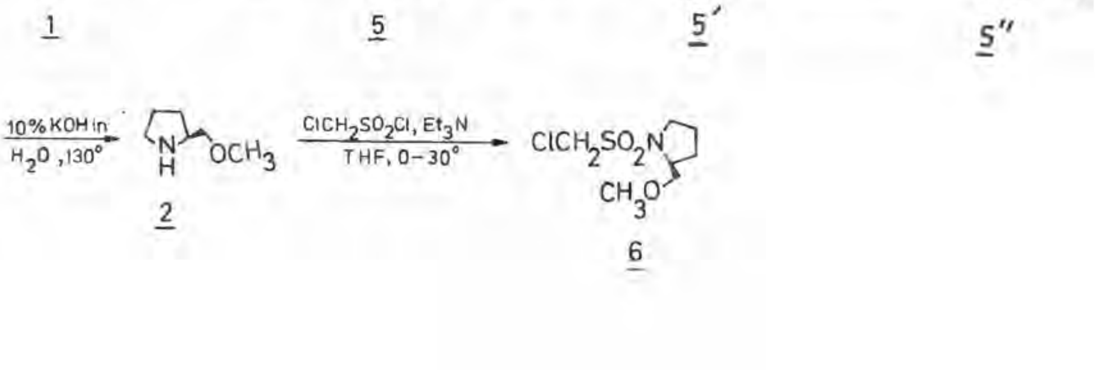
In addition to the asymmetric Darzens condensation using PTC conditions, attention will be given to the alkylation of the chiral chloromethanesulphonamides and the preparation of β-hydroxy-α-chlorosulphonamides, being the proposed intermediates in the PTC Darzens condensation.

4.2. *RESULTS AND DISCUSSION*

4.2.1. *Chiral reagents derived from proline and ephedrine*

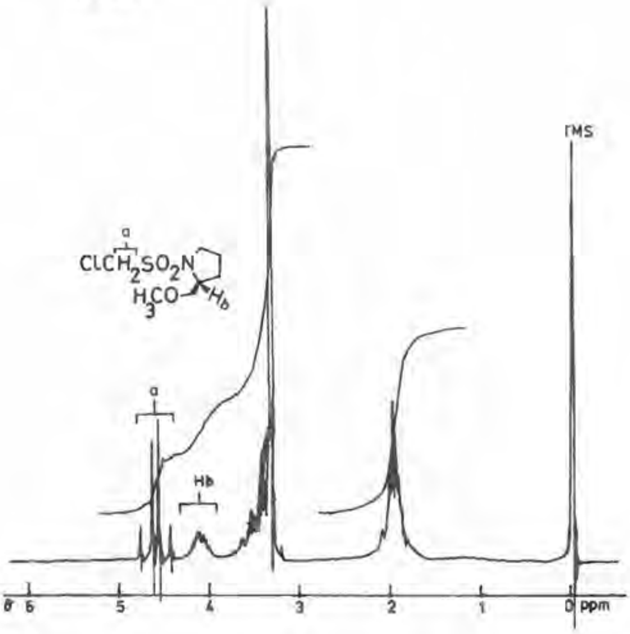
The preparation of (*S*)-(-)-*N*-chloromethylsulphonyl-2-methoxymethylpyrrolidine (6) starting from (*S*)-(-)-proline (1)

scheme 4.2



was carried out as depicted in Scheme 4.2. Thus reduction of the carboxyl group in 1, followed by protection of the amino group, methylation of the alcohol function in 5', deprotection of the nitrogen and sulphonation with chloromethanesulphonyl chloride gave in a good overall yield the chiral reagent 6. The ^{1}H-NMR spectrum, which is portrayed in Figure 4.1, clearly shows the AB quartet for the diastereotopic methylene protons

Fig. 4.1

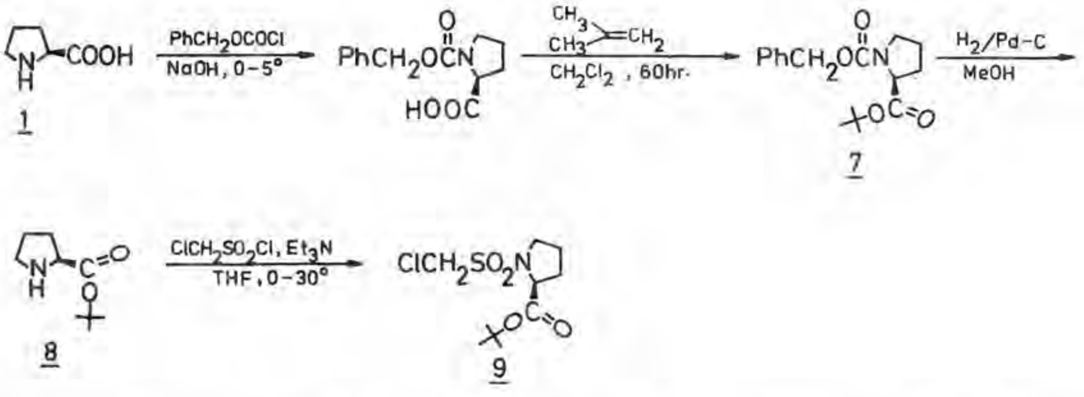


(δ_A = 4.75 and δ_B = 4.55 ppm, J_{AB} = 12 Hz). It should be noted that the chemical shift non-equivalence of these methylene protons is significantly more pronounced than in the menthyl chloromethanesulphonate described in Chapter 3. Assuming that there is a correlation between the extent of chemical differentiation and the degree of chemical shift (magnetic) non-equivalence of diastereotopic protons, the chiral reagent 6 appears to be a promising one for the asymmetric Darzens condensation.

It is generally believed that increased steric bulk in chiral reagents, particularly at the inducing chiral centre, greatly enhances the extent of asymmetric induction.[5-7,20] Therefore, the *tert*-butyl ester of *N*-chloromethylsulphonylproline

9 was prepared in order to investigate such a steric influence in the present case. Compound 9 was synthesized from (*S*)-(-)-proline according to Scheme 4.3. Thus nitrogen protection of proline with the benzyloxycarbonyl group, esterification with

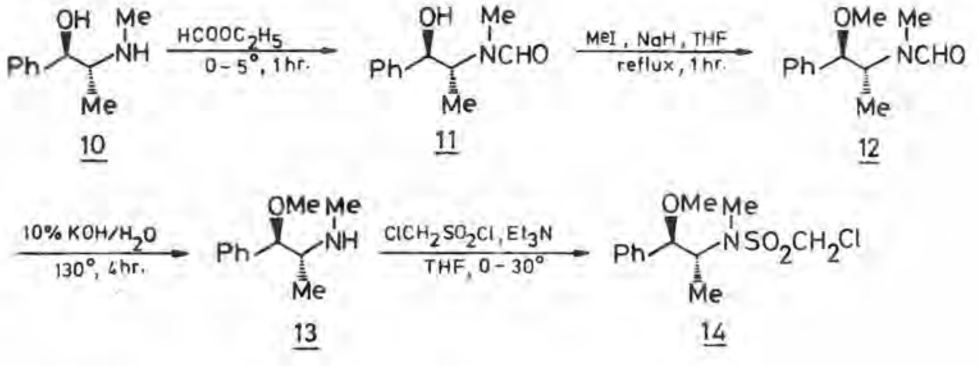
scheme 4.3



isobutene, reductive deprotection of the nitrogen and sulphonation with chloromethanesulphonyl chloride gave chiral reagent 9 in a good overall yield. The ^{1}H-NMR spectrum of this reagent (Figure 4.2) also showed a significant chemical shift non-equivalence of the diastereotopic methylene protons (δ_A = 4.77 and δ_B = 4.57 ppm, J_{AB} = 12 Hz).

The conversion of (+)-ephedrine (10) into a suitable substrate for the present study is outline in Scheme 4.4.

scheme 4.4



The hydroxy group was modified into a methoxy function by temporarily blocking the nitrogen with a formyl group. Then the

Fig. 4.2

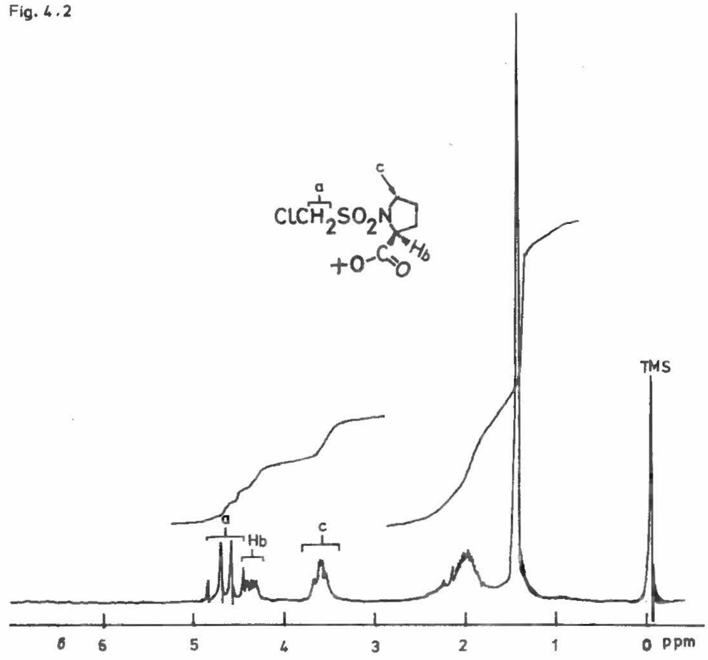
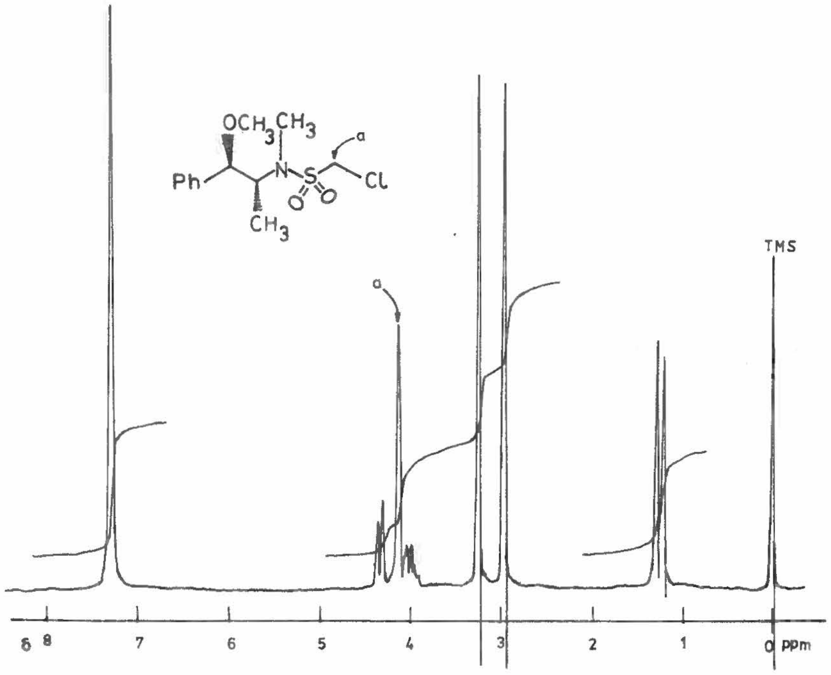

c
a
ClCH2SO2N
Hb
+O-C=O
TMS
a
Hb
c
δ
6
5
4
3
2
1
0 ppm

Fig. 4.3

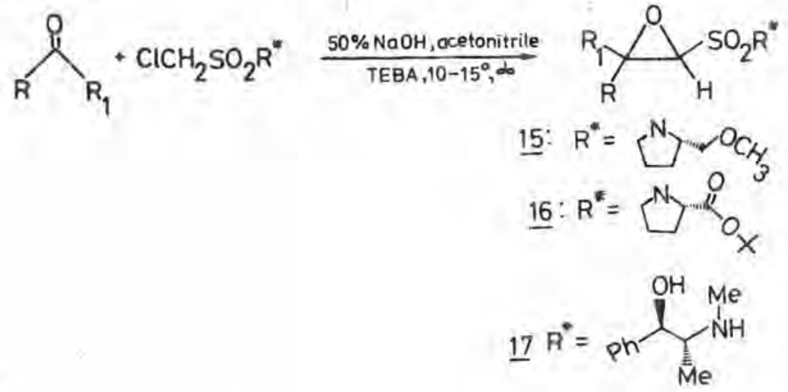

OCH3
CH3
a
Ph
N
S
O
O
Cl
CH3
a
TMS
δ
8
7
6
5
4
3
2
1
0 ppm

sulphonation was carried out as described earlier. The ^{1}H-NMR spectrum of chiral reagent 14 (Figure 4.3) shows a relatively broad singlet for the diastereotopic methylene protons.

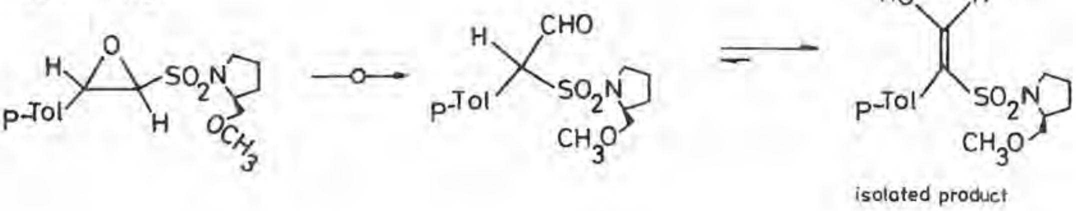
4.2.2. *Asymmetric synthesis of epoxysulphonamides*

The Darzens condensations with chiral reagents 6, 9 and 14 were carried out using PTC conditions as mentioned in Chapter 3 (also shown in Scheme 4.5). Generally, the epoxides were obtained in a good chemical yield. For acetaldehyde and isovaleraldehyde the yields were rather low due to competing aldol condensation reactions. Unexpectedly, unsatisfactory results were obtained with *p*-tolualdehyde as the carbonyl compound. The condensation with 6 required a long reaction time and the attempted purification of the thus-formed epoxysulphonamide (according to the NMR spectrum the yield was low) by chromatography (alumina) led to the isolation of a rearranged product only (Scheme 4.6). It is assumed that during the

scheme 4.5



scheme 4.6



prolonged reaction time some of the formed epoxysulphonamides underwent a thermal rearrangement. It should be noted that the rearranged product (α-sulphonyl aldehyde) predominantly has the enol structure indicated in Scheme 4.6. This was deduced from the ^{1}H-NMR spectra.

The condensation of 6 with benzaldehyde at room temperature similarly led to a rearranged product. However, when the reaction was carried out at 10-15° the desired product was obtained in 60% yield. These results suggest that the α,β-epoxysulphonamides derived from *N*-chloromethylsulphonyl-2-methoxymethylpyrrolidine (6) and aromatic aldehydes are less stable than the corresponding epoxysulphones obtained by condensation with chloromethyl *p*-tolyl sulphone. In the latter case the epoxides can be prepared at room temperature in high yield without rearrangement.[22,23] In order to avoid the rearrangement all the epoxysulphonamides were then prepared at 10-15°. However, even at this temperature the epoxysulphonamide from *p*-tolualdehyde could not be obtained.

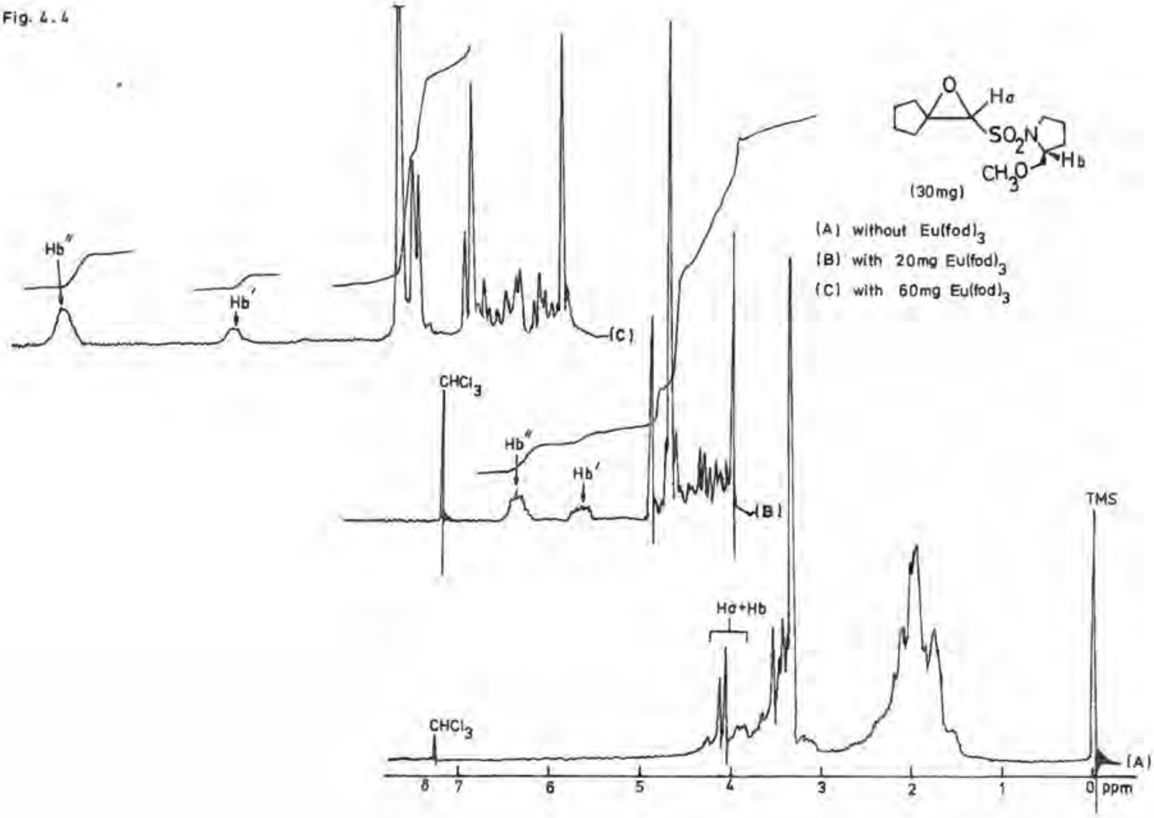
The results of the asymmetric Darzens condensations are collected in Tables 4.1, 4.2 and 4.3.

The coupling constant ($J = 1.5$ Hz) of the epoxymethine proton resonances in the ^{1}H-NMR spectra of 15-17 (R = H) indicates an (*E*)-configuration for these compounds.[24]

The extent of chiral induction, as in Chapter 3, was deduced from the integration of the well resolved Eu(fod)$_3$ induced ^{1}H-NMR spectra. Helpful for this analysis was the NMR signal due to the methine proton α to the nitrogen atom in the pyrrolidine ring when 6 and 9 were used as chiral reagents or that due to the epoxymethine protons when 9 and 14 were the chiral reagents. This observation is apparently in agreement with the known preferred coordination of the NMR shift reagents with the amido function in the presence of other basic functionalities.[25] An example of the resolved ^{1}H-NMR spectra is shown in Figure 4.4.

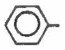
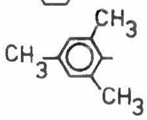
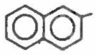
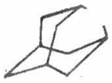
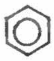
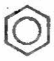
The extent of asymmetric induction was determined as the excess of one diastereomer over the other and it was calculated as a percentage diastereomeric excess (d.e.) from the well

Fig. 4.4



resolved ^{1}H-NMR spectra as mentioned above. In the case of compound 15c (Table 4.1) no resolution of the signal due to the methine proton α to the nitrogen atom was observed but instead only the epoxymethine as well as the methoxymethyl proton signals were the best resolved. Unfortunately, this resolution did not provide conclusive information regarding to diastereomeric composition of 15c, because the resolved signals remained within the region of other NMR signals of 15c. From these spectra the diastereomeric composition was estimated to be about 10%. It should be noted, however, that the Eu(fod)$_3$ induced ^{1}H-NMR spectra of compounds 16a (Table 4.2) were very well resolved and both the signals due to the epoxymethine proton and the methine proton α to the nitrogen atom on the pyrrolidine ring were used for analysing the extent of asymmetric induction. In all cases both signals gave the same d.e. values.

Table 4.1 Asymmetric Darzens condensation with 2-methoxymethyl-N-(chloromethylsulphonyl)pyrrolidine 6 according to scheme 4.5

compound	R	R_1	Yield(%)	d.e.(%)
15a	$(CH_3)_2CH$	H	77.5 (56(1), 79(2))	17 (11(1), 14(2))
15b	CH_3	CH_3	67	30 (30(2))
15c		H	60	~10(3)
15d		H	73	50(4)
15e		H	56	17
15f	$(CH_3)_2CHCH_2$	H	6	25
15g	$-(CH_2)_5-$		87	35.5
15h	$-(CH_2)_4-$		67	47
15i			47	22
15j	$-(CH_2)_2CH(CH_3)CH_2CH_2-$		62.5	14
15k			88(5)	14

d.e. = diastereomeric excess

(1) obtained when KOBu-*t* was used as base, as reported by Vogt and Tavares

(2) obtained from the cyclization of the isolated chlorohydrin sulphones

(3) estimated from the partially $Eu(fod)_3$ resolved ^{1}H-NMR spectrum

(4) derived from the rearranged products (Scheme 4.6)

(5) estimated from the ^{1}H-NMR spectrum of the crude product

Table 4.2 Asymmetric Darzens condensation with tert-butyl-N-(Chloromethyl-sulphonyl)prolinate 9 according to scheme 4.5

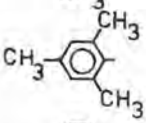
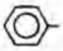
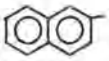
compound	R	R_1	Yield (%)	d.e.(%)
16a	CH_3	CH_3	84.5	17
16b	CH_3	H	30	26
16c		H	65	22
16d		H	55	11
16e	$(CH_3)_2CH$	H	65	8
16f	$-(CH_2)_5-$		51	18

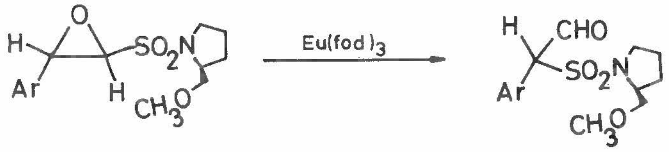
Table 4.3 Assymmetric Darzens condensation with (+)-O-methyl-N-(chloromethyl-sulphonyl)ephedrine 14 as shown in scheme 4.5

compound	R	R_1	Yield (%)	d.e.(%)
17a	CH_3	CH_3	83	4
17b		H	52	$\sim 8^{(1)}$
17c	$(CH_3)_2CH$	H	79	20
17d	$-(CH_2)_5-$		72.5	6

(1) estimated from the partially $Eu(fod)_3$ resolved ^1H-NMR spectrum.

Addition of increasing amounts of $Eu(fod)_3$ to 15d and 15e (Table 4.1) and 16c (Table 4.2) led to rearrangement of these compounds to form chiral α-sulphonyl aldehydes 18 (Scheme 4.7). This rearrangement is apparently brought about by $Eu(fod)_3$ which now acts as a Lewis acid. Probably the rearrangement is facilitated also by the stabilizing effect of the β-aryl group on the electron deficiency at C_β during the sulphonyl group migration. The instability of 15k (Table 4.1) during the analysis using the shift reagent should similarly be explained.

scheme 4.7



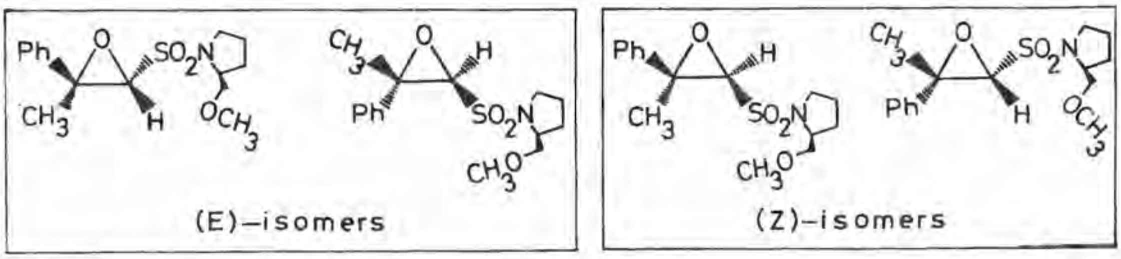
18

Ar = 2,4,6-$(CH_3)_3C_6H_2$, 2-naphthyl

A misleading observation can be made when the d.e. values are calculated directly from the epoxymethine proton NMR signal of epoxysulphonamides derived from the condensation of 6 with ketones, since the epoxymethine proton (H_α) cannot be separated completely from the underlying absorption. In many cases the signal appears to be always on top of a shoulder of the next-door signal. Support for this view was obtained from the d.e. values of the epoxysulphonamides reported in Table 4.2. Here the d.e. values calculated from the signal due to H_α and that of the methine proton α to the nitrogen atom on the pyrrolidine ring matched whereas in the compounds in Table 4.1 this was not the case. In the former compounds the disturbing underlying absorption for H_α is not present.

Reasons have already been advanced in Chapter 3 why in this study only aldehydes and symmetrical ketones were used as carbonyl substrates. However, an attempt was made to use unsymmetrical ketones as carbonyl substrates so as to assess the stability of such chiral epoxysulphonamides. This type of epoxysulphonamides is very useful in the synthesis of optically active α-alkylated aldehydes, as will be described in Chapter 5. When acetophenone was used as the carbonyl compound and 6 as the chiral reagent, two diastereomeric pairs of chiral α,β-epoxysulphonamides were obtained, as shown in Scheme 4.8. From the ^{1}H-NMR spectrum of the crude material the two diastereomeric pairs were observed to be present in different proportions. The major diastereomeric pair was less stable, since, on letting the mixture stand at room temperature for a few hours, this pair underwent a rearrangement analogous to that

scheme 4.8



(E)–isomers

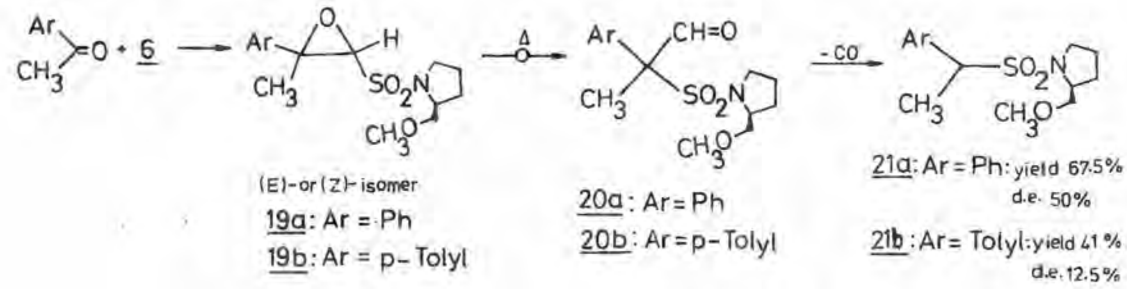
(Z)–isomers

already shown in Scheme 4.7. Vogt and Tavares[24] similarly observed a rearrangement of an epoxysulphone derived from acetophenone. Attempted purification of the epoxysulphonamide mixture by chromatography not only led to the rearrangement of all the diastereomeric pairs but the thus-formed intermediate α-sulphonamido-aldehyde 20a underwent a deformylation process to give diastereomeric chiral α-aryl ethanesulphonamide 21a as the final product. Except for some minor uncharacterized impurities, no other compound was obtained from the chromatography column. The diastereomeric excess (d.e.) of the rearranged product 21a as determined from a Eu(fod)$_3$ resolved ^{1}H-NMR spectrum was as high as 50%. The overall chemical yield was 67.5%.

The Darzens condensation of 6 with *p*-methyl acetophenone gave epoxide 19b which on subsequent rearrangement produced sulphonamide 21b in 41% overall yield. From the ^{1}H-NMR spectral analysis of this diastereomeric product (21b) a diastereomeric excess of 12.5% was deduced.

In both cases of the acetophenones, the rearrangement of the epoxysulphonamides 19a and 19b (Scheme 4.9) is facilitated

scheme 4.9



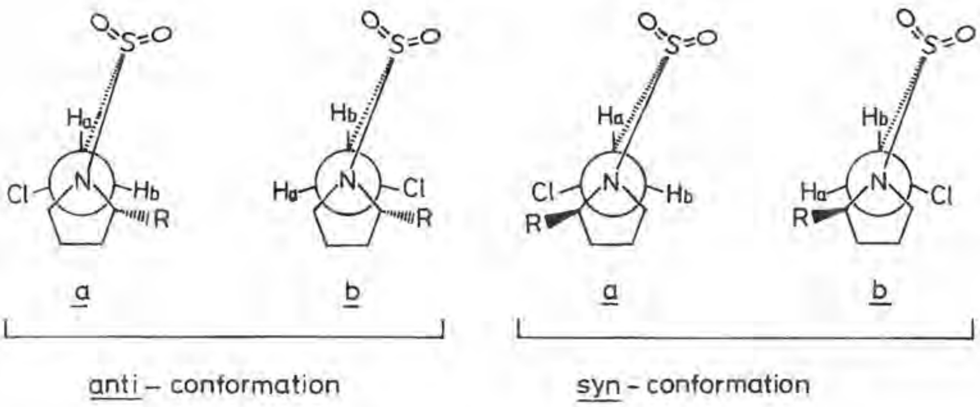
by the β-aryl substituent for reasons already mentioned earlier. The difference in the diastereomeric excess (50 *vs.* 12.5%) cannot be explained in terms of a steric effect of the *p*-methyl group in the reaction giving 19a and 19b. Although the *p*-methyl group should be responsible for the difference in the d.e. values, its effect on the chiral induction is difficult to deduce at this stage.

4.2.3. *Stereochemical course of the asymmetric induction during the Darzens condensation to epoxysulphonamides*

In analysing the results presented in Tables 4.1 and 4.2 it may be concluded that in general the degree of chiral induction using the proline derivatives is significantly improved as compared with that reported for the menthyl sulphonate esters in Chapter 3.

The Darzens condensation of chloromethanesulphonamides leading to epoxysulphonamides proceeds *via* three discrete steps, *viz.* the proton abstraction to a sulphonyl carbanion, the carbon-carbon bond formation to give the intermediate chlorohydrin and the 1,3-elimination to yield the epoxide. The asymmetric induction during the deprotonation step will be discussed in a similar fashion as described in Chapter 3. Again the mechanism is adopted that the proton to be abstracted needs to be positioned in the bisecting plane of the sulphonyl oxygen atoms.[26,27] Conformations of the chloromethanesulphonamides derived from methoxymethyl- and *tert*-butoxycarbonylpyrrolidine having a methylene proton in a proper abstractable position and that take into account the conceivable rotamers about the sulphonamide bond, are pictured as 1-3 Newman projections in Figure 4.5. It should be noted that the lone pair at the amide nitrogen is preferentially situated in the bisecting plane of the sulphone oxygen atoms. Two types of rotamers about the sulphonamide bond can be envisaged, *viz.* the *anti*- and *syn*-conformation having the R substituent pointing away from and towards the sulphonyl group, respectively. Inspection of molecular models suggests that in the *anti*-rotamer conformation b, the chlorine atom and the substituent R are in sufficient close proximity to experience steric hindrance. Therefore, the *anti*-conformation *a* will be favoured over *anti*-conformation *b* with the consequence of some preference for proton Ha to be abstracted. A similar analysis of the conformation of the *syn*-rotamers shows that steric hindrance may be experienced in conformation *a*, although to a lesser extent than mentioned for the *anti*-conformer *b*. It should be noted that the steric effects in the respective *anti*- and *syn*-rotamers have an opposing effect on the proton to be removed preferentially. The barrier to rotation about the N-S bond in sulphonamides is not very high [for $(PhCH_2)_2NSO_2Cl$ the N-S rotational energy barrier is 46 KJ/mole[28]], consequently the above rotamers will be readily interconvertible at ambient temperature. This will therefore lead to a diminished stereo-differentiation. The overall effect of the R substituent at the pyrrolidine ring on the extent of chiral induction will be a weighted average of the interactions discussed above (Figure 4.5), the eventual outcome of which is difficult to deduce from molecular model studies.

Fig. 4.5



R = CH_2OCH_3 or $COOC(CH_3)_3$

It seems that there is a slight preference for *syn*-conformation *b* leading to a preference for proton Hb to be abstracted by base. It should be kept in mind that relatively small energy differences of diastereomeric transition states are sufficient for an appreciable asymmetric induction (Chapter 1).

The observation that the chiral induction by the proline derivatives is generally better than that by the menthyl group in the Darzens condensation with menthyl chloromethanesulphonate may be explained as follows: As clearly indicated by molecular models the spatial position of the chirality inducing centre(s) relative to the prochiral methylene group is better defined in the proline than in the menthyl case, mainly because of the presence of the five-membered ring in the former type of substrate. Better defined arrangements of the inducing centre and the prochiral unit are beneficial for the asymmetric induction, as already mentioned in Chapter 3 and in section 4.1.

In examining Tables 4.1 and 4.2 it becomes apparent that the chiral sulphonyl carbanion generated from either 6 or 9 reacts with the respective carbonyl substrate in a varying overall asymmetric induction. As outlined in Chapter 3 it should be kept in mind that the reaction steps following the carbanion formation also will experience asymmetric induction. The transition states for both the halohydrin formation and the 1,3-elimination to epoxide are diastereomeric and hence, subjected to asymmetric induction. This complication of three consecutive steps makes a proper understanding of the asymmetric induction in the present Darzens condensation difficult.

The d.e. values obtained for methoxymethyl reagent 6 are as a whole better than those observed for the proline *tert*-butyl ester derivative 9. At first sight, the anticipated enhancing effect of steric bulk on the degree of induction is not observed in this case. Studies of molecular models suggest that the methoxymethyl group is exerting somewhat more steric hindrance in the conformations *anti-b* and *syn-a* than the *tert*-butoxycarbonyl group (see Figure 4.5). Probably this is due to the seemingly sterically less demanding planar carbonyl function in the latter substituent. The models also suggest that rotations about the pyrrolidine carbon-carbonyl bond may be such that the *tert*-butoxy group (which is transoid with respect to the carbonyl oxygen atom) will be turned away from the chlorine atom in avoiding steric congestion. Apparently, such a conformational effect plays a role here.

The overall conclusion is that conformational preference during the deprotonation process is the result of a critical balance of steric and electrostatic interactions, the outcome of which is difficult to predict beforehand.

The aromatic aldehydes show d.e. values of 10-18% with a positive exception for the bulky mesitylaldehyde (50% in Table 4.1 and 22% in Table 4.2). Isobutyraldehyde in both Tables shows rather moderate d.e. values. Isovaleraldehyde and acetaldehyde have higher induction values. Acetone gives a nice result with 6 but a lower induction in the case of 9. The data obtained for cyclohexanone are in the same range as those obtained with acetone (slightly better in both cases). It may be suggested that the steric requirements for the reaction of these two ketones with sulphonyl carbanions are of the same order. By far the best result was obtained with cyclopentanone in its reaction with 6. It is noteworthy that also with the l-menthyl chloromethanesulphonate (see Chapter 3) the best result was obtained with this ketone. It is hypothesized that the limited flexibility of the five-membered ring is responsible for the high degree of chiral induction (47% d.e.).

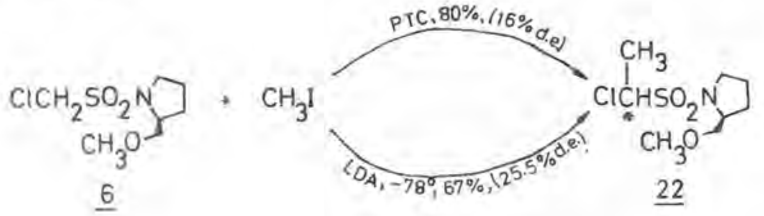
The use of (+)-*O*-methyl-*N*-(chloromethylsulphonyl)ephedrine 14 as a chiral reagent was undertaken in order to verify the effect of limited conformational flexibility of the chiral reagent on the extent of asymmetric synthesis. Although no conclusion can as yet be drawn from these preliminary results, the observed chiral induction (Table 4.3) was disappointingly low as compared with similar compounds reported in Chapter 3 and Tables 4.1 and 4.2 in this Chapter. However, the optical yield of 20% obtained when isobutyraldehyde was used as the carbonyl substrate resembles the d.e. of 18% obtained for compound 15a (Table 4.1).

In summary, the appreciable degree of asymmetric induction during the Darzens condensation using *N*-(chloromethylsulphonyl)-proline derivatives is probably due to the limited conformational flexibility of the pyrrolidine sulphonamide moiety. A serious complication in the understanding of the induction results is the fact that three consecutive reaction steps in the epoxide formation are subjected to asymmetric induction. The influence of the chiral induction on each step not necessarily has to be in the same direction, even opposing effects are quite possible. This study gives the impression that bulky or five-membered ring carbonyl compounds give the best overall induction results.

4.2.4. *Chiral induction during the alkylation of 2-methoxymethyl-N-chloromethylsulphonylpyrrolidine* 6

In the preceeding section it has been noted that the Darzens condensation with chiral reagents is difficult to rationalize because more than one reaction step is involved. To gain insight in the preferential formation of one of the diastereomeric sulphonyl carbanions from 6, it was decided to quench the carbanions with an alkyl halide as the electrophile. In order to investigate the effect of the experimental conditions on the extent of the chiral induction, the reagent 6 was methylated with methyl iodide both under PTC (thermodynamic) conditions and under kinetically controlled circumstances (base LDA and low temperature). The resulting product 22 (Scheme 4.10) was analysed on its diastereomeric composition. The induction

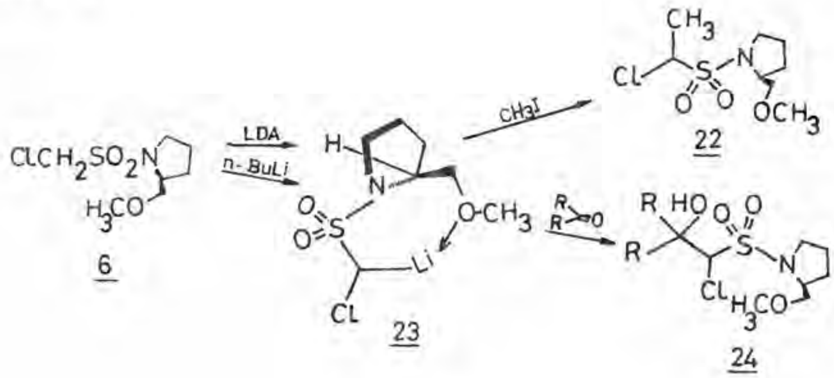
scheme 4.10



value for the latter conditions (26% d.e.) is considerably higher than that through the PTC methylation (16% d.e.). Probably this is due to the chelation of the lithium cation with the methoxymethyl group, as illustrated in Scheme 4.11. As suggested by molecular models this chelating effect enhances the differentiation between the diastereomeric lithio carbanions.

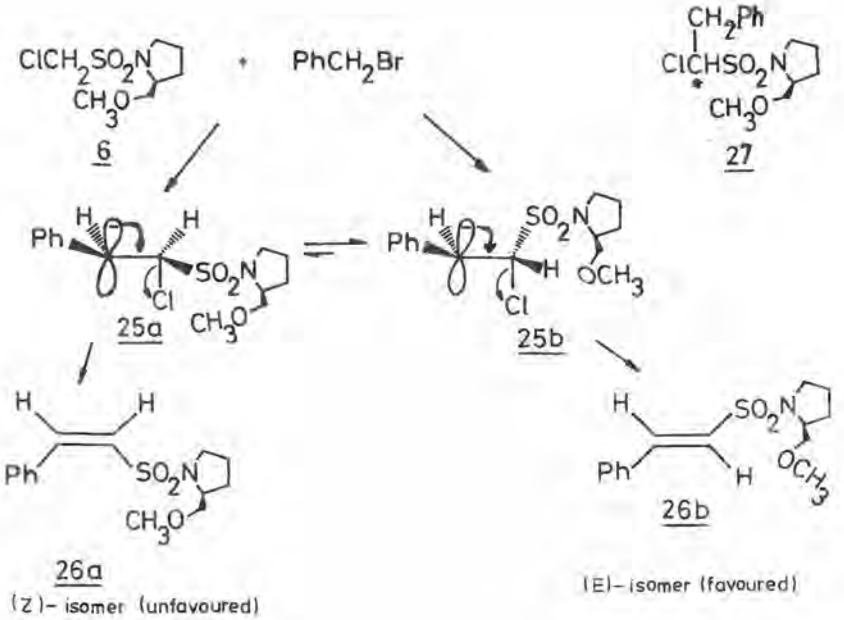
Attempted alkylation of 6 under phase transfer catalysis using benzyl bromide led to the exclusive formation of α,β-unsaturated sulphonamide 26b instead of the expected α-chlorobenzylsulphonamide 27. The explanation is that in 27 the

scheme 4.11



benzylic protons are acidic enough to be removed. Therefore, under the basic phase transfer conditions subsequent loss of a chloride ion easily takes place to give 26b. This olefin 26b had an (*E*)-configuration as shown by its ^{1}H-NMR spectrum (J_{HaHb} = 15 Hz). In conformity with the above results, Cardillo *et al.*[29], have reported that in the PTC condensation of methyl aryl sulphones with aromatic aldehydes at room temperature α,β-unsaturated sulphones having exclusively an (*E*)-configuration were obtained. This stereoselectivity should be a result of favourable steric arrangement in 25b which leads to 26b, as shown in Scheme 4.12.

scheme 4.12



4.2.5. *Asymmetric synthesis of β-hydroxy-α-chlorosulphonamides*

The reaction of sulphonyl carbanions with carbonyl compounds can be stopped in the stage of the chlorohydrins. As mentioned in the introduction, Truce and Christensen[2] observed that with alkyllithium as the base the chlorohydrins did not react further to give epoxides. This experimental condition offers the opportunity to investigate the asymmetric induction on the halohydrin formation. The results with some ketones are collected in Table 4.4 (essentially the conditions reported by Truce *et al.*[2], were used). The induction values are of the

Table 4.4: Asymmetric synthesis of β-hydroxy-α-chloro-sulphonamides 24 (scheme 4.11)

compound	R	Yield (%)	m.p.(°C)	d.e.(%)
24a	CH_3	98.5	oil	26
24b	$(CH_3)_2CH$	88	oil	46.5
24c	*	97	oil	23.5
24d	**	81	75(1)	25
24e		76	126–127	26.5

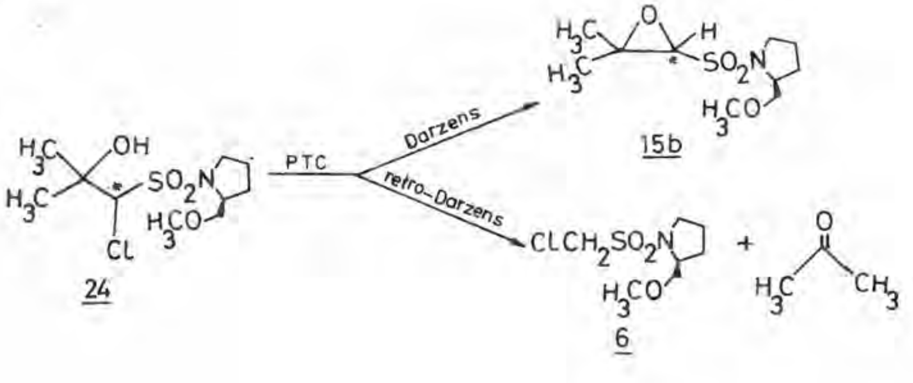
(1) one pure diastereomer

* cyclohexanone used as carbonyl substrate
**cyclopentanone used as carbonyl substrate

same magnitude as that obtained during the methylation using LDA as the base. Probably the higher value found for di-isopropyl ketone has its origin in the considerable steric hindrance, confirming the earlier statement in this direction.

An attempt was made to cyclize the chlorohydrins 24 under PTC conditions. However, only a very low yield of epoxides was obtained. This bad result is the consequence of a competing *retro*-Darzens condensation taking place to give the chloromethylsulphonamide 6 which indeed was recovered. A similar observation was reported by Durst *et al.*[23] and Truce *et al.*[2] for attempted cyclizations of chlorohydrins to epoxysulphones. The *retro*-Darzens condensation (Scheme 4.13) was more pronounced

scheme 4.13



when the starting carbonyl substrate was benzaldehyde, where no epoxide was detected by ^{1}H-NMR. On the other hand, the PTC epoxide formation from the diastereomeric chlorohydrin mixtures (four diastereomers) derived from 6 and isobutyraldehyde led to very high yield of 15a (Table 4.1) and the extent of chiral induction (14%) was fairly comparable with that obtained from the direct PTC condensation (18%).

4.3. *EXPERIMENTAL*

4.3.1. *General remarks*

Eu(fod)$_3$ ^{1}H-NMR experiments were carried out as already reported in Chapter 3 and unless otherwise state the separations of the NMR signals due to the methine proton α to the nitrogen atom on the pyrrolidine ring was used in assessing the diastereomeric composition (the extent of asymmetric synthesis) of the diastereomeric mixtures. For epoxysulphonamides derived from *tert*-butyl *N*-(chloromethylsulphonyl)prolinate and from 14 the well resolved epoxymethine proton signals [after addition of Eu(fod)$_3$] were also used for the above assessment.

Chlorohydrins were purified by distillation under reduced pressure using a BUCHI GK50 low pressure small scale distillation apparatus. Unless otherwise stated all other experimental remarks reported in Chapter 3 also apply to this chapter.

4.3.2. *Preparation of the chiral reagent 6*

(i) (S)-(+)-2-Hydroxymethylpyrrolidine (5)

To a stirred suspension of LiAlH$_4$ (36 g, 946 mmol) in superdry THF (1000 ml) small portions of powdered *S*-proline (1) (60 g, 522 mmol) were slowly added at 0°. A vigorous reaction occurred after each addition. After this addition was complete (*ca.* 30 min) the reaction mixture was heated under reflux for 1 hr and cooled. Then, with vigorous mechanical stirring, cold water (125 ml, 7.0 mmol) was slowly and cautiously added. The colour of the reaction mixture changed from dark grey to dull white. Ether (500 ml) was then added and the solid material was filtered off, the filtrate was collected while the residue was washed with ether (200 ml) and the washings added to the original filtrate. The residue was further washed with ethyl alcohol (300 ml), then ether (500 ml) was added to the alcohol fraction and the precipitated inorganic salts were filtered off, the filtrate and the previous ether solution were concentrated under reduced pressure and pure material, 45 g (84%) was obtained by distillation. B.p. 70°/2 Torr or 48-52°/0.5 Torr (lit.[30]: b.p. 100-5°/9 Torr).

(ii) (S)-(-)-2-Hydroxymethyl-N-formylpyrrolidine (5')

To a stirred solution of 5 (40 g, 396 mmol) in ether (100 ml), ethyl formate (29.6 g, 400 mmol) was slowly added at 0°. The reaction mixture was stirred at the same temperature for 1 hr, the volatiles were evaporated under reduced pressure and the pure product, 51 g (99.9%) was obtained by distillation. B.p. 140°/2 Torr (lit.[30]: b.p. 122°/0.5 Torr).

(iii) (S)-(-)-2-Methoxymethyl-N-formylpyrrolidine (5'')

To a stirred suspension of NaH (8.1 g, 338 mmol) (after removing the oil with pet. ether) in superdry THF (600 ml) were slowly added solutions of 5' (40 g, 310 mmol) in THF (50 ml) and methyl iodide (68 g, 497 mmol) in THF (50 ml); then the reaction mixture was heated under reflux for 1 hr. After cooling, the mixture was poured into a saturated solution of NaCl (600 ml) and then extracted with dichloromethane (5x100 ml). The dichloromethane solution was dried, the solvent was evaporated to leave the crude product from which pure 5'', 39.2 g (88.5%) was obtained by distillation. B.p. 90°/1.5 Torr (lit.[30]: b.p. 67°/0.25 Torr).

(iv) (S)-(+)-2-Methoxymethylpyrrolidine (2)

A solution of 5'' (39.2 g, 273 mmol) in methanol was treated with a methanolic solution of KOH (10% $^{w}/v$, 400 ml) at 130° for 4 hr. Then the reaction mixture was cooled and extracted with ether (6x100 ml). The ethereal solution was dried and the solvent was evaporated to leave a crude product which was purified by distillation to give 2, 28.3 g (90%), b.p. 44-7°/17 Torr (lit.[30]: b.p. 62°/40 Torr).

(v) (S)-(-)-N-Chloromethylsulphonyl-2-methoxymethylpyrrolidine (6)

Chloromethanesulphonyl chloride was prepared as described in Chapter 3. To a stirred mixture of 2 (9.73 g, 85 mmol) and dry triethylamine (13.0 ml, excess) in superdry THF (300 ml) at 0° under nitrogen was gradually added a solution of chloromethanesulphonyl chloride (12.62 g, 84.7 mmol) in superdry THF (20 ml). The reaction mixture was stirred at 30° for 2 hrs and then cooled. The precipitated triethylamine hydrochloride was filtered off, washed with THF, then the combined filtrate and washings were concentrated and the pure product was obtained by distillation of the residual oil. Yield: 16.52 g (86%), b.p 160°/6 Torr; $[\alpha]_D = -11.4^{\circ}$ ($c = 3.49$, $CHCl_3$); IR (film): $\nu(-SO_2N\ )$ 1345 and 1160 cm^{-1} (s); ^1H-NMR: $\delta = 4.70$ (ABq, $\delta_A = 4.75$ and $\delta_B = 4.55$ ppm, $J_{AB} = 12$ Hz, $ClC\underline{H}_2SO_2-$), 4.15 (m, $N-\overset{|}{C}\underline{H}-$); 3.75-3.20 (m, $-N-C\underline{H}_2-$ and $-O-C\underline{H}_2-$), 3.33 (s, $-O-C\underline{H}_3$) and 2.20-1.70 ppm (m, $-C\underline{H}_2-C\underline{H}_2-$); MS: m/e 227 (228) ($M^+$).

4.3.3. *Preparation of the chiral reagent* (9)

(i) (S)-(-)-N-(Benzyloxycarbonyl)proline (7)

To a mechanically stirred solution of (*S*)-(-)-proline (1) (12 g, 104 mmol) in aqueous NaOH (1 M, 110 ml) at 0° was slowly added simultaneously carbobenzoxy chloride (15.6 ml, 110 mmol) and aqueous NaOH (1 M, 110 ml). The reaction mixture was stirred for 4 hrs and then extracted with ether. The ethereal solution was dried over sodium sulphate and the solvent evaporated to leave a light brown oil which was recrystallized from ethyl acetate to give 7 as white crystals, 22 g (85%).

(ii) (S)-(-)-tert-Butyl N-(benzyloxycarbonyl)prolinate (7')

To a stirred solution of *N*-(benzyloxycarbonyl)proline 7 (22 g, 88 mmol) in dichloromethane (100 ml) in a pressure bottle at -20° was added liquefied isobutylene (17 ml, excess). The reaction mixture was stirred at room temperature for 2½ days, then cooled to -20° and the bottle opened. The excess isobutylene was removed by passing through a stream of nitrogen gas and the mixture was poured in a sodium carbonate solution (2 N, 100 ml) and extracted with dichloromethane. The dichloromethane solution was washed several times with water, dried over sodium sulphate, the solvent evaporated (bath temperature below 40°) and the crude product was recrystallized from ether/pet. ether (1:1) to give white crystals, 25.0 g (93%); m.p. 51-54°; $[\alpha]_D = -53^{\circ}$ (c = 2.2, EtOH).

(iii) (S)-(-)-tert-Butyl prolinate (8)

A solution of (*S*)-(-)-*tert*-butyl *N*-(benzyloxycarbonyl)-proline (7') (20 g, 66 mmol) in methanol (200 ml) was hydrogenated for 4 hrs in the presence of Pd-C (5%) (20 mg) as the catalyst. Filtration of the reaction mixture and subsequent evaporation of the solvent gave the ester 8, 10.25 g (91.5%).

(iv) (S)-(-)-tert-Butyl N-(chloromethylsulphonyl)prolinate (9)

To a stirred solution of (*S*)-(-)-proline *tert*-butyl ester 8 (10.25 g, 59.9 mmol) and triethylamine (6 ml, 75 mmol) in superdry THF (300 ml) at 0° was gradually added a solution of chloromethanesulphonyl chloride (8.95 g, 60 mmol) in superdry THF (100 ml). After stirring at room temperature for 2 hrs, the triethylamine hydrochloride was filtered off, washed with THF and the combined filtrate and washings were concentrated and taken up in ether. The ethereal solution was washed several times with water, dried and the solvent evaporated to leave a yellow oil which was dried further *in vacuo* over calcium chloride for 48 hrs to give the required *tert*-butyl ester 9; 20 g (71%); IR (neat film): ν(ester carbonyl) 1735 (s) and ν(N-$S\underline{O}_2$) 1345 (s) and 1160 cm^{-1} (s); ^{1}H-NMR: δ = 4.70 (AB quartet, δ_A = 4.77 and δ_B = 4.57 ppm, J_{AB} = 12 Hz, $ClC\underline{H}_2SO_2$-), 4.53-4.30 (m, $N-\overset{|}{C}\underline{H}-$), 3.63 (m, $N-C\underline{H}_2-$), 2.50-1.50 (m,

$-C\underline{H}_2-C\underline{H}_2$) and 1.50 ppm $[s, -(C\underline{H}_3)_3]$; MS: m/e 283 (284) ($M^+$); $[\alpha]_D = -11.14^o$ (c = 3.95, $CHCl_3$).

4.3.4. *Preparation of the chiral reagent* 14 *from (+)-ephedrine*

(i) (+)-N-Formylephedrine (11)

(+)-Ephedrine (10) was formylated according to the procedure already described for (*S*)-(-)-2-hydroxymethyl-*N*-formylpyrrolidine (5'). IR (neat film): ν(CH=O) 1700 cm^{-1}. The product was used without further purification.

(ii) (+)-N-Formyl-O-methylephedrine (12)

This compound was prepared according to the procedure described for (*S*)-(-)-2-methoxymethyl-*N*-formylpyrrolidine (5''). Thus 11 (5.43 g, 28 mmol) and methyl iodide (5.99 g, 1.05 equiv.) in the presence of sodium hydride (6.72 g) gave crude (+)-*N*-formyl-*O*-methylephedrine (12) which was purified by chromatography (silica gel/20% ethyl acetate in *n*-hexane). Yield: 4.93 g (85%); ^1H-NMR: $\delta = 3.23$ ppm (s, $-O-CH_3$); MS: m/e 207 (M^+).

(iii) (+)-O-Methylephedrine (13)

Treatment of (+)-*N*-formyl-*O*-methylephedrine (12) (19 mmol) with methanolic KOH solution (10% $^w/v$, 100 ml) for 4 hrs at 130° gave, after distillation, (+)-*O*-methylephedrine (13), 2.40 g (44%), b.p. 82°/0.6 Torr; $[\alpha]_D = +76.41^o$ (c = 4.6, $CHCl_3$); ^1H-NMR: $\delta = 7.30$ (s, phenyl protons), 4.10 (d, J ≈ 4.5 Hz, $Ph-\overset{|}{C}\underline{H}-$), 3.23 (s, $-O-C\underline{H}_3$), 3.0-2.5 (m, $CH_3-\overset{|}{C}\underline{H}-N$), 2.37 (s, $C\underline{H}_3-N$), 1.20 (br, $N-\underline{H}$) and 1.00 ppm (d, J ≈ 7 Hz, $C\underline{H}_3CH$); MS: m/e 179 (M^+).

(iv) (+)-O-Methyl-N-(chloromethylsulphonyl)ephedrine (14)

This compound was prepared similarly as described for (*S*)-(-)-*N*-chloromethylsulphonyl-2-methoxymethylpyrrolidine (6). Thus (+)-*O*-methylephedrine (13) (24.0 g, 134 mmol) with chloromethanesulphonyl chloride (19.98 g, 134 mmol) in the presence of triethylamine (15.52 g, 154 mmol) gave crude (+)-*O*-methyl-*N*-(chloromethylsulphonyl)ephedrine (14) which was purified by chromatography (silica gel/50% ethyl acetate in *n*-hexane) to give (+)-*O*-methyl-*N*-(chloromethylsulphonyl)ephedrine (14), 31 g (79%). The compound could also be purified by distillation under reduced pressure, b.p. 125°/0.4 Torr; yellow oil; $[\alpha]_D = +41.83^o$ (c = 2.95, $CHCl_3$); ^1H-NMR: δ = 7.33 (s, phenyl protons), 4.33 (d, J ≈ 4 Hz, $Ph\overset{|}{C}\underline{H}$-O-), 4.15 (s, $ClC\underline{H}_2$-SO_2-), 4.3-3.85 (m, $CH_3\overset{|}{C}\underline{H}$), 3.25 (s, -$OC\underline{H}_3$-), 2.97 (s, N-$C\underline{H}_3$) and 1.23 ppm (d, J ≈ 7 Hz, $CHC\underline{H}_3$); MS: m/e 191/192 (M^+).

4.3.5. *Preparation of the chiral α,β-epoxysulphonamides* 15-17

(i) The Phase Transfer Catalysis (PTC); general procedure

This procedure was followed for all epoxysulphonamides, unless otherwise stated: To a vigorously stirred mixture of aqueous NaOH (50% $^w/v$, 20 ml), the chiral reagents 6, 9 and 14, respectively (2-13 mmol), triethylbenzylammonium chloride (TEBA) (0.06-0.10 g) and acetonitrile (3.5 ml) at 10° was gradually added a solution of an aldehyde or ketone (1.1 equiv. with respect to the chiral reagent) in acetonitrile (3 ml). The reaction mixture was vigorously stirred at 10-15° until the ^1H-NMR spectrum of the reaction mixture showed absence of the chiral reagent or that a considerable quantity of the epoxysulphonamide had been formed. The mixture was then poured in cold water. After extraction with dichloromethane (3x50 ml), drying of the dichloromethane layer and removal of the solvent, the crude material was purified by chromatography (alumina/10% ethyl acetate in *n*-hexane). Diisopropyl ketone and dicyclopropyl ketone failed to react with the chiral reagent 6 while reaction of acetaldehyde with 6 gave a low yield of the desired epoxysulphonamide which also was difficult to purify.

(ii) Determination of the diastereomeric composition; general procedure

To a known amount of the purified epoxysulphonamide (20-70 mg) was added an increasing amount of $Eu(fod)_3$ while subsequently taking the ^{1}H-NMR spectrum until the latter was satisfactorily resolved and the diastereomeric composition was then determined as described in Chapter 3 and in section 4.3.1.

(iii) (E)-1,2-epoxy-3-methylbutanesulpho(2-methoxymethyl)-pyrrolidide (15a)

PTC procedure: Reaction of chloromethanesulphonamide 6 (2.362 g, 10.37 mmol) with isobutyraldehyde (0.983 g, 13.65 mmol) for 4 hrs gave after work-up 3.170 g (77.5%) of epoxysulphonamide 15a; IR (neat film): ν(N-SO$_2$), 1350 (s) and 1155 (s) and ν(epoxide) 900 cm^{-1}; ^{1}H-NMR: δ = 4.30-3.80 (m, $-\overset{|}{C}\underline{H}-N$ and epoxymethine protons), 3.80-3.10 (m, $-C\underline{H}_2-N-$ and $-C\underline{H}_2-O$), 3.33 (s, $-O-C\underline{H}_3$), 2.30-1.50 ppm [m, $-C\underline{H}_2-C\underline{H}_2-$ and $(C\underline{H}_3)_2CH-$] ; MS: m/e 263 (M$^+$); diastereomeric composition, 59 and 41% (18% d.e.).

Using potassium *tert*-butoxide as base: To a stirred solution of chloromethanesulphonamide 6 (1.520 g, 6.68 mmol) and isobutyraldehyde (0.493 g, 6.85 mmol) in *tert*-butyl alcohol (30 ml) and ether (20 ml) at 10-15° was slowly added a solution of potassium *tert*-butoxide (6.70 mmol) in *tert*-butyl alcohol (30 ml). The reaction mixture was stirred at room temperature for 3 hrs, then poured in cold water (400 ml) and extracted with chloroform. The chloroform solution was dried, the solvent evaporated to leave a crude product which was purified as before to give 0.989 g (56%) of 15a with spectral properties as those already reported above. Diastereomeric composition: 55.6 and 44.4% (11% d.e.).

By cyclization of isolated chlorohydrin mixtures: To a rapidly stirred solution of 6 (2.033 g, 8.93 mmol) in superdry THF (20 ml) at -78° and under nitrogen, was added a solution of *n*-BuLi (1.6 M) in *n*-hexane (5.6 ml, 8.93 mmol). The reaction mixture was stirred at the same temperature for 3 min before isobutyraldehyde (0.643 g, 8.93 mmol) was added. The mixture was then further stirred at -78° for 20 min, quenched with a saturated ammonium chloride solution and extracted with ether. The ethereal solution was dried and the solvent was evaporated to leave a crude product which was treated with a methanolic solution of KOH (10% $^{w}/v$) (50 ml) at room temperature for 1 hr. After pouring into cold water and extracting with chloroform, the chloroform solution was dried and the solvent evaporated to leave a crude product which was purified as before to give pure 15a, 1.86 g (79%) with spectral properties as already described. Diastereomeric composition: 57.1 and 42.9% (14% d.e.).

(iv) 1,2-Epoxy-2-methylpropanesulpho(2-methoxymethyl)pyrrolidide (15b)

PTC procedure: Reaction of acetone (0.5 g, 8.62 mmol) with chloromethanesulponamide 6 (1.272 g, 5.59 mmol) for 2 hrs and normal work-up gave 0.935 g (67%) of epoxysulphonamide 15b; IR (neat film): ν(SO_2-N) 1350 (s) and 1155 (s), ν(epoxide) 900 cm^{-1} (s); ^{1}H-NMR: δ = 3.90 (s) and 3.83 (s) (epoxymethine protons) and 1.67 (s) and 1.40 ppm (s) (epoxymethyl protons); MS: m/e 249 (M^+) and diastereomeric composition: 65 and 35% (30% d.e.).

Cyclization of isolated chlorohydrin mixture: The chlorohydrin mixture was prepared as already described for 15a and attempted cyclization of the chlorohydrins (0.225 g, 0.788 mmol) in methanolic KOH (10% $^{w}/v$, 15 ml) for 1 hr at room temperature led to the expected product (about 40% yield according to the ^{1}H-NMR spectrum) and to chloromethanesulphonamide 6, obtained from the *retro*-aldol reaction. The crude mixture was not purified further. The diastereomeric composition of the epoxysulphonamide 15b was about 65 and 35% (≈30% d.e.).

(v) (E)-1,2-Epoxy-2-phenylethanesulpho(2-methoxymethyl)-pyrrolidide (15c)

Reaction of chloromethanesulphonamide 6 (2.505 g, 11.00 mmol) with benzaldehyde (1.19 g, 11.23 mmol) for 1 hr and normal work-up gave epoxysulphonamide 15c (1.971 g, 60%); MS: m/e 297 (M^+); IR (neat film): ν(SO_2-N) 1345 (s) and 1150 (s) and ν(epoxide) 900 cm^{-1}; ^{1}H-NMR: δ = 7.30 (m, aromatic protons), 4.33 (m, two overlapping epoxymethine proton signals), 4.23

(d, J = 1.5 Hz) and 4.17 ppm (d, J = 1.5 Hz) (two epoxymethine protons, one for each of the two diastereomers). The diastereomeric composition could not be determined accurately by Eu(fod)$_3$ ^{1}H-NMR experiments. From the little separation of the epoxymethine proton signals it was estimated that the diastereomeric composition was about 55 and 45% (≈10% d.e.).

Attempted cyclization of the intermediate chlorohydrin mixtures led mainly to the *retro*-aldol reaction.

Chloromethanesulphonamide 6 (1.953 g, 8.58 mmol) and benzaldehyde (0.91 g, 8.58 mmol) in the presence of potassium *tert*-butoxide (8.60 mmol) gave epoxysulphonamide 15c (2.0 g, 79%); d.e. ≈10%.

(vi) (E)-1,2-Epoxy-2-(2,4,6-trimethylphenyl)ethanesulpho(2-methoxymethyl)pyrrolidide (15d)

Reaction of chloromethanesulphonamide 6 (2.845 g, 12.50 mmol) with mesitylaldehyde (1.86 g, 12.57 mmol) for 4 hrs gave epoxysulphonamide 15d (3.00 g, 73%) after work-up; $[\alpha]_D = -32.0$ (c = 3.50, CHCl$_3$); IR (neat film): ν(SO$_2$-N) 1350 (s) and 1155 (s), ν(epoxide) 920 cm^{-1} (s); ^{1}H-NMR: δ = 6.80 (s, 2H, aromatic protons), 4.33 (m, two overlapping epoxymethine proton signals due to the two diastereomers), 4.17 (d, J = 1.5 Hz) and 4.10 ppm (d, J = 1.5 Hz) (two epoxymethine protons, one for each of the two diastereomers); MS: m/e 339 (M$^+$). On successive addition of increasing amounts of Eu(fod)$_3$ and subsequently recording the ^{1}H-NMR spectrum showed some rearrangement, the diastereomeric composition 75 and 25% (50% d.e.) was derived from the resolved ^{1}H-NMR signals of the rearranged product.

(vii) (E)-1,2-Epoxy-2-(2-naphthyl)ethanesulpho(2-methoxymethyl)-pyrrolidide (15e)

Reaction of chloromethanesulphonamide 6 (2.500 g, 10.98 mmol) with 2-naphthaldehyde (1.800 g, 11.54 mmol) for 1.5 hr gave crude epoxysulphonamide 15e, 2.24 g (56%); ^{1}H-NMR: δ = 8.00-7.10 (m, aromatic protons), 4.47 (m, one set of two overlapping epoxymethine protons due to the two diastereomers), 4.33 (d, J = 1.5 Hz) and 4.25 ppm (d, J = 1.5 Hz, another set of epoxymethine protons). On standing at room temperature a solid compound crystallized. It was recrystallized from 10% ether in pentane to give 0.411 g (10%) of epoxysulphonamide 15e, m.p. 115-7°; NMR: δ = 8.0-7.1 (m, aromatic protons), 4.50 (m) and 4.30 ppm (d, J = 1.5 Hz) (epoxymethine protons); MS: m/e 347 (M^+) and $[\alpha]_D = -88.0^{\circ}$ (c = 0.5, $CHCl_3$). Eu(fod)$_3$ NMR experiments with the crude product led to rearrangement as that observed for 15d and the diastereomeric composition was similarly obtained; it amounted to 58.5 and 41.5% (17% d.e.).

(viii) (E)-1,2-Epoxy-4-methylpentanesulpho(2-methoxymethyl)-pyrrolidide (15f)

Reaction of chloromethanesulphonamide 6 (2.40 g, 10.54 mmol) with isovaleraldehyde (1.0 g, 11.63 mmol) for 4 hrs gave, after purification, 0.169 g (6%) of epoxysulphonamide 15f; NMR: δ = 3.90 (d, J = 1.5 Hz) and 3.85 (d, J = 1.5 Hz) (epoxymethine protons), 1.60-1.35 (m, $-CH_2-\overset{|}{C}\underline{H}-$) and 1.03 (s) and 0.93 ppm (s) $[(C\underline{H}_3)_2CH]$; diastereomeric composition: 62.5 and 37.5% (25% d.e.).

(ix) 1,2-Epoxy-2,2-pentamethylene-ethanesulpho(2-methoxymethyl)-pyrrolidide (15g)

Reaction of chloromethanesulphonamide 6 (1.50 g, 6.59 mmol) with cyclohexanone (0.65 g, 6.63 mmol) gave after 2 hrs and normal work-up, 1.655 g (87%) of epoxysulphonamide 15g; NMR: δ = 3.85 (s) and 3.77 (s) (epoxymethine protons for the two diastereomers) and 1.8-1.3 ppm (m, cyclohexane ring protons); MS: m/e 289 (M^+); diastereomeric composition: 68.7 and 32.2% (35.5% d.e.).

(x) 1,2-Epoxy-2,2-tetramethylene-ethanesulpho(2-methoxymethyl)-pyrrolidide (15h)

Chloromethanesulphonamide 6 (1.345 g, 5.91 mmol) and cyclopentanone (0.60 g, 7.14 mmol) after 4 hr gave 1.092 g (67%) of epoxysulphonamide 15h; NMR: δ = 4.10 (s) and 4.02 (s) (epoxymethine protons for two diastereomers) and 2.5-1.5 ppm (m,

-C$\underline{H}_2$-C$\underline{H}_2$- and cyclopentane ring protons); MS: m/e 275 (M^+) and diastereomeric composition: 74 and 27% (47% d.e.).

(xi) Adamantanespiro-2'-oxirane-1'-sulpho(2''-methoxymethyl)-pyrrolidide (15i)

Chloromethanesulphonamide 6 (0.30 g, 1.32 mmol) with adamantanone (0.236 g, 1.57 mmol) after 10 hrs and normal work-up, gave 0.210 g (47%) of epoxysulphonamide 15i; NMR: δ = 3.87 (s) and 3.80 (s) (epoxymethine protons for two diastereomers) and 2.50 ppm (m, adamantane protons); MS: m/e 341 (M^+); diastereomeric composition: 61 and 39% (22% d.e.).

(xii) 1,2-Epoxy-2,2-(3-methyl)pentamethylene-ethanesulpho(2-methoxymethyl)pyrrolidide (15j)

Chloromethanesulphonamide 6 (0.352 g, 1.547 mmol) and 4-methylcyclohexanone (0.183 g, 1.634 mmol), gave, after reacting for 2 hrs and work-up, 0.293 g (52.5%) of epoxysulphonamide 15j; ^{1}H-NMR: δ = 3.9 (s) and 3.8 (s) (epoxymethine protons for two diastereomers) and 0.93 ppm (m, C$\underline{H}_3$-CH for the diastereomeric compounds) and MS: m/e 303 (M^+).

(xiii) 1,2-Epoxy-2,2-diphenylethanesulpho(2-methoxymethyl)-pyrrolidide (15k)

Chloromethanesulphonamide 6 (2.34 g, 10.28 mmol) and benzophenone (1.983 g, 10.90 mmol) gave, after reacting for 6 hrs, about 88% of epoxysulphonamide 15k (from ^{1}H-NMR spectrum of the crude product); NMR (crude product): δ = 7.30 (s, aromatic protons), 4.50 (s) and 4.40 (s) (epoxymethine protons for the two diastereomers). The diastereomeric composition which was 52 and 43% (14% d.e.) was derived from the integration of the epoxymethine proton NMR signals of the crude material. On purification of this material by chromatography, a crystalline compound which was rearranged 15k, was obtained. This 2-oxo-1,1-diphenylethanesulpho(2-methoxymethyl)pyrrolidide, 2.43 g (68.5%) had an m.p. of 96-7° and $[\alpha]_D = -2.83^\circ$ (c = 3.25, $CHCl_3$) and the following spectral properties: MS: m/e 345 (M^+); NMR: δ =

7.85-7.50 (m) and 7.45-7.15 (m) (aromatic protons), 5.55 [s, $(\mathrm{Ph})_2\overset{|}{\mathrm{C}}\underline{\mathrm{H}}$-], 3.77 (m, N-$\overset{|}{\mathrm{C}}\underline{\mathrm{H}}$-), 3.50-2.65 (m, -C$\underline{\mathrm{H}}_2$-N- and -C$\underline{\mathrm{H}}_2$-O-), 3.27 (s, -O-C$\underline{\mathrm{H}}_3$) and 1.80-0.40 ppm (m, -C$\underline{\mathrm{H}}_2$-C$\underline{\mathrm{H}}_2$-).

(xiv) 1,2-Epoxy-2-phenylpropanesulpho(2-methoxymethyl)-pyrrolidide (19a)

Reaction of chloromethanesulphonamide 6 (2.048 g, 8.99 mmol) with acetophenone (1.291 g, 10.76 mmol) for 16 hrs gave crude epoxysulphonamide 19a (3.00 g); NMR: δ = 7.3 (s, phenyl protons), 4.23 (s), 4.18 (s), 3.97 (s) and 3.89 (s) (epoxymethine protons for four diastereomers), 3.97-3.83 (m, -O-C$\underline{\mathrm{H}}_3$ for four diastereomers) and 2.00 (s) and 1.65 ppm (s) (epoxymethyl protons for (*E*)- and (*Z*)-geometrical isomers). Letting this crude product stand at room temperature for some time gave the following ^{1}H-NMR spectrum: δ = 10.15 (s) and 10.10 (s) (-C$\underline{\mathrm{H}}$=O for two diastereomers), 7.7-7.2 (m, phenyl protons), 4.23 (s) and 4.17 (s) (epoxymethine protons of two minor diastereomers of 19a), 1.90 (s) and 1.67 ppm (s) (*p*-CH$_3$ groups). On purification of the mixture by chromatography, 2-methoxymethyl-*N*-(1-phenylethylsulphonyl)pyrrolidine (21a) was obtained through rearrangement of the epoxysulphonamide mixture. NMR: δ = 7.8-7.2 (m, phenyl protons), 4.33 (q, J = 6 Hz, -$\overset{|}{\mathrm{C}}\underline{\mathrm{H}}$-CH$_3$), 4.2-2.4 (m, N-C$\underline{\mathrm{H}}_2$-CH), 2.35-1.6 (m, -C$\underline{\mathrm{H}}_2$-C$\underline{\mathrm{H}}_2$-) and 1.73 ppm (d, J $\approx$ 6 Hz, C$\underline{\mathrm{H}}_3$-CH). From Eu(fod)$_3$ induced NMR experiments the resolved signals due to the proton α to the phenyl group as well as that α to the nitrogen atom showed the diastereomeric composition of this mixture to be 75 and 25% (50% d.e.).

(xv) 2-Methoxymethyl-N-[1-(p-tolyl)ethylsulphonyl]pyrrolidine (19b)

Reaction of chloromethanesulphonamide 6 (1.54 g, 6.76 mmol) with *p*-methylacetophenone (0.911 g, 6.80 mmol) for 14 hrs gave crude 2-methoxymethyl-*N*-[1-(*p*-tolyl)ethylsulphonyl]pyrrolidine (19b); NMR: δ = 7.40-7.00 (ABq, J_{AB} = 9 Hz, aromatic protons), 4.30 (q, J $\approx$ 6 Hz, C$\underline{\mathrm{H}}$-CH$_3$), 4.00-3.75 (m) and 3.75-3.40 (m, N-$\overset{|}{\mathrm{C}}\underline{\mathrm{H}}$- , two diastereomers), 3.4-2.5 (m, N-C$\underline{\mathrm{H}}_2$- and -O-C$\underline{\mathrm{H}}_2$-), 3.00 (s) and 3.27 (s) (-O-CH$_3$, two diastereomers), 2.33 (s, *p* $-C\underline{H}_3$), 2.0-1.4 (m, $-C\underline{H}_2-C\underline{H}_2-$) and 1.70 ppm (d, J ≈ 6 Hz, $C\underline{H}_3-CH$), diastereomeric composition determined as above, 56.2 and 43.8% (≈12.5% d.e.).

(xvi) 2-Hydroxy-1-(p-tolyl)ethenesulpho(2-methoxymethyl)-pyrrolidide (Scheme 4.6)

Reaction of chloromethanesulphonamide 6 (1.813 g, 7.96 mmol) and *p*-tolualdehyde (1.0 g, 8.33 mmol) for 3 hrs gave, after work-up, the enolsulphonamide (1.49 g, 60%); IR (neat film): ν(OH) 3500 (br), ν(C=C) 1660 (br) and ν(SO_2-N) 1350 (s) and 1160 cm^{-1} (s); NMR: δ = 8.2-6.8 (m, phenyl protons, $\rangle C=\overset{|}{C}-O\underline{H}$ and $\rangle C=\overset{|}{C}-\underline{H}$), 4.30 (m, $N-\overset{|}{C}\underline{H}$), 3.8-2.6 (m, $N-C\underline{H}_2-$, $-O-C\underline{H}_3$ and $-O-C\underline{H}_2-$), 2.40-1.40 (m, $-C\underline{H}_2-C\underline{H}_2-$) and 2.30 ppm (s, *p*-$C\underline{H}_3$); MS: m/e 311 ($M^+$).

(xvii) tert-Butyl N-(2-methyl-1,2-epoxyethylsulphonyl)-prolinate (16a)

Reaction of the *tert*-butyl prolinate 9 (0.88 g, 3.10 mmol) with acetone (0.20 g, excess) gave crude epoxysulphonamide 16a which was purified by chromatography (silica gel/15% ethyl acetate in *n*-hexane), 0.80 g (84.5%); NMR: δ = 4.15 (s) and 3.95 (s) (epoxymethine protons for two diastereomers), 1.65 (s) and 1.43 ppm (s) (epoxymethyl protons); diastereomeric composition as derived from the $Eu(fod)_3$ resolved signals of the epoxymethine proton and that α to the nitrogen atom was 58.5 and 41.5% (17% d.e.).

(xviii) tert-Butyl N-[(E)-1,2-epoxypropylsulphonyl]prolinate (16b)

tert-Butyl prolinate 9 (0.88 g, 3.10 mmol) and acetaldehyde (0.3 g, excess) gave 0.27 g (30.0%) of epoxysulphonamide 16b; NMR: δ = 4.07 (d, J = 1.5 Hz) and 3.95 (d, J = 1.5 Hz) (epoxymethine protons) and 1.43 (s) and 1.37 ppm (s) (epoxymethyl protons); diastereomeric excess 26% (composition 63 and 37%).

(xix) tert-Butyl N-[2-(2,4,6-trimethylphenyl)-(E)-1,2-epoxyethylsulphonyl]prolinate

Reaction of *tert*-butyl prolinate 9 (1.019 g, 3.59 mmol) with mesitylaldehyde (0.58 g, 3.92 mmol) for 4 hrs gave 0.977 g (65%) of epoxysulphonamide 16c; NMR: δ = 4.70-4.25 (m, $N\text{-}\overset{|}{C}\underline{H}$ and one epoxymethine proton) and 4.15 ppm (m, epoxymethine proton). This compound underwent a rearrangement upon addition of increasing amounts of $Eu(fod)_3$ and the well resolved NMR signals due to the aldehydic protons of the rearranged product(s) were used to determine the diastereomeric composition, which was 61 and 39% (22% d.e.).

(xx) *tert-Butyl N-[2-phenyl-(E)-1,2-epoxyethylsulphonyl]-prolinate* (16d)

Reaction of *tert*-butyl prolinate 9 (0.733 g, 2.59 mmol) with benzaldehyde (0.308 g, 2.91 mmol) gave 0.50 g (55%) of epoxysulphonamide 16d; NMR: δ = 7.33 (s, phenyl protons) and 4.55-4.25 ppm (m, $N\text{-}\overset{|}{C}\underline{H}$ and epoxymethine protons); diastereomeric composition 55.5 and 44.5% (11% d.e.).

(xxi) *tert-Butyl N-[3-methyl-(E)-1,2-epoxybutylsulphonyl]-prolinate* (16e)

Reaction of *tert*-butyl ester 9 (1.085 g, 3.83 mmol) and isobutyraldehyde (0.30 g, excess) gave 0.790 g (65%) of epoxysulphonamide 16e; NMR: δ = 4.17 and 4.05 (m, epoxymethine protons) and 1.07 (s) and 1.00 ppm $[(C\underline{H}_3)_2CH|$, diastereomeric composition 54 and 46% (8% d.e.).

(xxii) *tert-Butyl N-(2,2-pentamethylene-1,2-epoxyethylsulphonyl)-prolinate* (16f)

tert-Butyl prolinate 9 (0.988 g, 3.48 mmol) and cyclohexanone (0.381 g, 3.88 mmol) gave 0.61 g (51%) of epoxysulphonamide 16f; NMR: δ = 4.13 (s) and 3.90 ppm (s, epoxymethine protons); diastereomeric excess 18% (composition 59 and 41%).

(xxiii) *tert-Butyl N-(2,2-tetramethylene-1,2-epoxyethylsulphonyl)-prolinate*

Reaction of *tert*-butyl prolinate 6 (0.88 g, 3.10 mmol) with cyclopentanone (0.261 g, 3.11 mmol) for 4 hrs gave the crude epoxysulphonamide in very low yield (NMR); NMR: δ = 4.17 (s) and 3.90 ppm (s) (epoxymethine protons). Although no attempt was made to purify this compound (because of its small quantity) the intensity of the NMR signals indicated that the diastereomeric excess was roughly in the same range as that of similar epoxysulphonamides, *viz.* 16a to 16f.

(xxiv) O-Methyl N-(2-methyl-1,2-epoxypropylsulphonyl)ephedrine 17a

Ephedrinesulphonamide 14 (1.78 g, 6.10 mmol) and acetone (excess) gave after purification by chromatography (silica gel, 40% ethyl acetate in *n*-hexane) epoxysulphonamide 17a, 1,59 g (83%); NMR: δ = 3.50 (s, epoxymethine proton), 3,27 (s) and 3.23 (s) (-O-C$\underline{H}_3$ for two diastereomers), 2.97 (s) and 2.90 (s) (N-C$\underline{H}_3$, two diastereomers), 1.67 (s) and 1.60 (s) (epoxymethyl group, two diastereomers) and 1,45-1.0 ppm (m, C$\underline{H}_3$-CH and one epoxymethyl group); diastereomeric composition 52 and 48% (4% d.e.).

(xxv) O-Methyl N-(2-naphthyl)-1,2-epoxyethylsulphonyl)-ephedrine (17b)

Reaction of ephedrinesulphonamide 14 (1.272 g, 4.359 mmol) with 2-naphthaldehyde (0.749 g, 4.795 mmol) gave, after work-up, epoxysulphonamide 17b (0.931 g, 52%); ^{1}H-NMR: δ = 8,5-7.0 (m, aromatic protons), 4.8-4.0 (m, PhC$\underline{H}$-O-, CH$_3$C$\underline{H}$-N and epoxymethine protons), 3.30 (s) and 3,25 (s) (-O-C$\underline{H}_3$) for two diastereomers) and 3.06 and 3.00 ppm CH-N-C$\underline{H}_3$, two singlets for the two diastereomers).

(xxvi) O-Methyl N-[3-methyl-(E)-1,2-epoxybutylsulphonyl]-ephedrine (17c)

Treatment of ephedrinesulphonamide 14 (1.56 g, 5.35 mmol) with isobutyraldehyde (0.385 g, 5.35 mmol) gave crude epoxysulphonamide 17c which was purified by preparative TLC (silica gel plates, Merck, F254, 2 mm thickness with 40% ethyl acetate/*n*-hexane as eluent) to give 1.38 g of diastereomeric mixture of epoxysulphonamide 17c (79%); $[\alpha]_D$ = +16.7° (c = 1.70, CHCl$_3$);

NMR: δ = 4.6-3.8 (m, Ph-$\overset{|}{C}\underline{H}$-O- and $CH_3\overset{|}{C}\underline{H}$-N), 3.65 (d, J = 1.5 Hz, epoxymethine proton), 3.43-3.20 (m, epoxymethine proton and -O-CH_3, two diastereomers), 2.97 (s) and 2.93 (s) ($C\underline{H}_3$-N, two diastereomers), 1.60 m, $(CH_3)_2C\underline{H}$-N and 1.45-1.15 (m) and 1.15-0.80 ppm (m) $[(C\underline{H}_3)_2CH$ and $C\underline{H}_3$-$\overset{|}{C}H$-N$]$. On standing at room temperature one compound crystallized out. It was washed with *n*-hexane and purified by preparative TLC, 120 mg (9% of the pure mixture); $[\alpha]_D = +83.9^\circ$ (c = 1.70, $CHCl_3$); NMR: δ = 7.30 (s, phenyl protons), 4.43 (d, J ≈ 4 Hz, $Ph\overset{OH}{\overset{|}{C}}\underline{H}$-CH), 4.0 (m, $CH_3\overset{|}{C}\underline{H}$-N), 3.55 (s, epoxymethine proton), 3.29 (s, -O-$C\underline{H}_3$), 3.35-3.1 (m, epoxymethine proton), 2.97 (s, $C\underline{H}_3$-N), 1.60 $[$m, $(CH_3)_2C\underline{H}$-N$]$, 1.17 (d, J ≈ 6 Hz, $C\underline{H}_3CH$) and 1.00 ppm $[$m, $(C\underline{H}_3)_2CH$-C$]$; MS: m/e 315 (M^+); optical purity, 20%.

(xxvii) O-Methyl N-(2,2-pentamethylene-1,2-epoxyethylsulphonyl)-ephedrine (17d)

Treatment of ephedrinesulphonamide 14 (1.50 g, 5.14 mmol) with cyclohexanone (0.509 g, 5.19 mmol) gave after purification 1.32 g (72.5%) of epoxysulphonamide 17d; NMR: δ = 3.47 (s, epoxymethine proton), 3.25 (s) and 3.20 (s) (-O-$C\underline{H}_3$, two diastereomers), 2.97 (s) and 2.90 (s) ($C\underline{H}_3N$-, two diastereomers), 1.27 (d, J = 6 Hz) and 1.20 ppm (d, J = 6 Hz, $C\underline{H}_3\overset{|}{C}H$-C, two diastereomers); diastereomeric composition 53 and 47% (6% d.e.).

4.3.6. *Attempted use of lithium hydroxide in PTC reactions*

To a stirred suspension of lithium hydroxide in water (1:1) at 10-15° was added a solution of chloromethanesulphonamide 6 (2.0 g, 8.78 mmol) in acetonitrile (5 ml), TEBA (0.06-0.10 g) and an aldehyde (8.80 mmol). The reaction mixture was stirred at 20-30° for 6 hrs but the starting materials were recovered (from the ^1H-NMR spectra and TLC of the crude materials), accompanied by some unidentified compounds. The following aldehydes were used: PhCH=O, *p*-$(CH_3)C_6H_4CH$=O and $(CH_3)_2CHCH$=O.

4.3.7. *Asymmetric alkylation of N-chloromethylsulphonyl-2-methoxymethylpyrrolidine* (6)

(i) N-(1-Chloroethylsulphonyl)-2-methoxymethylpyrrolidine (22)

PTC procedure: To a stirred solution of NaOH (50% $^w/v$, 20 ml) at 25° was added chloromethanesulphonamide 6 (2.02 g, 8.87 mmol), tetrabutylammonium chloride (0.06 g, 0.216 mmol), HMPA (1 ml) and methyl iodide (1.260 g, 8.87 mmol). The reaction mixture was vigorously stirred at 30-40° for 4 hrs, poured into cold water (400 ml) and extracted with ether. The ethereal solution was washed several times with water, dried and the solvent was evaporated to leave a crude product which was purified by chromatography (silica gel, 10% ethyl acetate in *n*-hexane) to give 1.72 g (80%) of chloroethanesulphonamide 22; IR (neat film): $\nu(\ SO_2\text{-}N\ )$ 1350 and 1160 cm^{-1}; NMR : δ = 5.25-4.85 (m, $C\underline{H}\text{-}CH_3$), 4.35-3.75 (m, $N\text{-}\overset{|}{C}\underline{H}$), 3.80-3.20 (m, $\text{-}\overset{|}{N}\text{-}C\underline{H}_2\text{-}$ and $\text{-}O\text{-}C\underline{H}_2\text{-}$), 3.33 (s, $\text{-}O\text{-}C\underline{H}_3$), 2.20-1.65 (m, $\text{-}C\underline{H}_2\text{-}C\underline{H}_2\text{-}$) and 1.80 (d, J $\simeq$ 6 Hz, $C\underline{H}_3\text{-}\overset{|}{C}H$); MS: m/e 241 (242) (M^+); diastereomeric composition 58 and 42% (16% d.e.).

LDA procedure: A solution of lithium diisopropylamide (LDA) (4.4 mmol) was prepared by addition of *n*-butyl lithium (1.6 M in *n*-hexane) (3.05 ml, 1.1 equiv.) to a stirred solution of anhydrous diisopropylamine (0.444 g, 4.40 mmol) in superdry THF (20 ml) at 0° and the resulting solution was stirred at the same temperature for 15 min. To this solution at -78° were added solutions of chloromethanesulphonamide 6 (1.00 g, 4.4 mmol) in superdry THF (3 ml) and methyl iodide (4.4 mmol). The reaction mixture was stirred for a further 40 min at -78°, then allowed to warm to room temperature before being quenched with a saturated solution of ammonium chloride and extracted with ether. The ethereal solution was dried and the solvent evaporated to leave crude chloroethanesulphonamide 22 which contained a trace of a dialkylated product as revealed by the ^1H-NMR spectrum. The crude material was purified as before to give 0.714 g (67%); diastereomeric compositon 63 and 37% (26% d.e.).

(ii) (E)-2-Phenylethene-1-sulpho(2-methoxymethyl)pyrrolidide (26b)

Reaction of chloromethanesulphonamide 6 (0.80 g, 3.51 mmol) with benzyl bromide (0.601 g, 3.52 mmol) according to the PTC procedure reported for chloroethanesulphonamide 22 led to unsaturated sulphonamide 26b, 0.74 g (75%) after purification, m.p. 108-110°; IR (nujol): $\nu(-CH{=}CH-)$ 1620 cm^{-1}, $\nu(SO_2N)$ 1345 and 1160 cm^{-1}; NMR: δ = 7.60-7.25 (m, phenyl protons and $Ph-C\underline{H}{=}CH-$), 6.70 (d, J = 15 Hz, $-CH{=}C\underline{H}-SO_2-$), 3.90-3.10 (m, $-\overset{|}{N}-\overset{|}{C}\underline{H}-$, $N-C\underline{H}_2-$ and $-O-C\underline{H}_2-$), 3.33 (s, $-O-C\underline{H}_3$) and 2.10-1.70 (m, $-C\underline{H}_2-C\underline{H}_2-$); MS: m/e 281 ($M^+$).

4.3.8. *Preparation of chiral diastereomeric β-hydroxy-α-chlorosulphonamide* 24a-e

General procedure: To a rapidly stirred solution of chloromethanesulphonamide 6 in superdry THF at -78° under nitrogen was added *n*-butyl lithium (1.1 equiv.) in *n*-hexane (1.6 M). The resulting solution was stirred for 3 min at -78° before a solution of the carbonyl compound in THF (2-5 ml) was added. The reaction mixture was stirred at -78° for a further 30 min, poured into water and extracted with ether. The ethereal solution was dried and the solvent evaporated to leave the crude product which was purified by distillation at reduced pressure. The diastereomeric composition was normally derived straightforward from the NMR signals due to the α-proton.

(i) 1-Chloro-2-hydroxy-2-methylpropanesulpho(2-methoxymethyl)-pyrrolidide (24a)

Sulphonamide 24a was obtained from the reaction of chloromethanesulphonamide 6 (0.578 g, 2.54 mmol) with acetone (0.20 g, 3.45 mmol) as a viscous oil (99%). IR (neat film): $\nu(OH)$ 3500 cm^{-1} (br); NMR: δ = 5.00 (s) and 4.77 (s) ($C\underline{H}Cl$, two diastereomers), 1.50 (s) and 1.45 (s) $[(C\underline{H}_3)_2C]$ and 1.23 ppm (s, $-O-\underline{H}$); diastereomeric composition 63 and 37% (26% d.e.).

(ii) 1-Chloro-2-hydroxy-3-methyl-2-(2-propyl)butanesulpho-(2-methoxymethyl)pyrrolidide (24b)

Reaction of chloromethanesulphonamide 6 (0.653 g, 2.87 mmol) with diisopropyl ketone (0.327 g, 2.87 mmol) gave chlorohydrin 24b, 0.860 g (88%). IR (neat film): ν(OH) 3500 cm^{-1} (br); NMR: δ = 5.30 (s) and 4.85 ppm (s) (CHCl); diastereomeric excess 46.5%.

(iii) 1-Chloro-2-hydroxy-2,2-pentamethylene-ethanesulpho-(2-methoxymethyl)pyrrolidide (24c)

Chlorohydrin 24c was obtained from the reaction of chloromethanesulphonamide 6 (0.43 g, 1.89 mmol) with cyclohexanone (0.185 g, 1.89 mmol) as a viscous oil, 0.597 g (97%). NMR: δ = 5.00 (s) and 4.80 ppm (s) (CHCl); diastereomeric excess 23.5%.

(iv) 1-Chloro-2-hydroxy-2,2-tetramethylene-ethanesulpho-(2-methoxymethyl)pyrrolidine (24d)

Chloromethanesulphonamide 6 (0.369 g, 1.62 mmol) and cyclopentanone (0.146 g, 1.62 mmol) gave chlorohydrin 24d, 0.409 g (81%). NMR: δ = 5.10 (s) and 4.95 ppm (s) (CHCl); diastereomeric composition 62.5 and 37.5% (25% d.e.). On standing at room temperature the major diastereomer crystallized and it was recrystallized four times from *n*-hexane to give pure chlorohydrin 24d, 150 mg, m.p. 75°; $[\alpha]_D = -9.8^\circ$ (c = 0.5°, $CHCl_3$); NMR: δ = 5.07 ppm (s, CHCl); MS: m/e 311 (M^+). Calcd. for $C_{12}H_{22}ClNO_4S$: C, 46.21%; H, 7.12% and N, 4.49%; found: C, 46.36%; H, 7.23% and N, 4.39%.

(v) 1-Chloro-2-hydroxy-2,2-diphenylethanesulpho(2-methoxymethyl)pyrrolidide (24e)

Reaction of chloromethanesulphonamide 6 (0.365 g, 1.604 mmol) and benzophenone (0.292 g, 1.604 mmol) gave crude chlorohydrin 24e which was purified by recrystallization from ether/*n*-hexane (1:1) to give glitering plates, 0.50 g (76%), m.p. 126-7°; NMR: δ = 6.13 (s, -O-H), 5.00 (s) and 4.90 (s)

(C$\underline{H}$Cl); MS: m/e 410 (M^+); Calcd. for $C_{20}H_{24}ClNO_4S$: C, 58.59%; H, 5.91% and N, 3.42%; found: C, 58.71%; H, 5.98% and N, 3.48%; diastereomeric excess 26.5%.

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CHAPTER 5

REACTIONS OF α,β-EPOXYSULPHONES AND EPOXYSULPHONAMIDES

SUMMARY

This chapter describes the reactions of α,β-epoxysulphones and chiral epoxysulphonamides with sodium azide and magnesium bromide. The attempted catalytic hydrogenation of the so-formed azido aldehydes led to the formation of 2,5-dihydropyrazines. Chiral α-methyl alkyl amino alcohols were obtained from the lithium aluminium hydride reduction of optically active azido aldehydes. The attempted reactions with dialkyl copper lithium reagents and reductive desulphonylation are also reported.

5.1. *INTRODUCTION*

One of the most interesting aspects of epoxides is the possibility to convert them into a variety of interesting synthetic intermediates or final products either under nucleophilic or electrophilic conditions.[1] However, the chemistry of α,β-epoxysulphones has not yet been fully explored as compared to other epoxides. From the few reactions known it is clear that epoxysulphones readily undergo nucleophilic reactions with magnesium bromide[2,3], sodium thiophenolate[3,4], ethyl thiolate[4] and to some extent with sodium azide[5] to give α-substituted aldehydes and ketones. A detailed survey of the reactions of α,β-epoxysulphones is given in Chapter 2, section 2.3.3.

The aim of this chapter is to reinvestigate some of the above reactions in relation to chiral α,β-epoxysulphonamides in order to obtain optically active products. These compounds could then be useful in obtaining a better understanding of the stereochemical outcome in the asymmetric synthesis of the epoxysulphonamides, as described in Chapter 4.

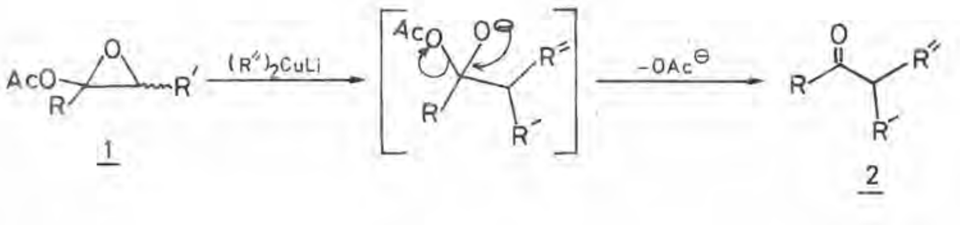
5.2. *RESULTS AND DISCUSSION*

5.2.1. *Reactions with organometallic reagents*

Organometallic compounds are widely used as strong nucleophilic reagents in reactions leading to the formation of carbon-carbon single bonds. It should be reminded, however, that in many cases these reagents act as strong bases as well. This dualistic nature of Grignard reagents may explain why Durst *et al.*[3], obtained complex mixtures of products from the reaction of α,β-epoxysulphones with these organometallics.

In an effort to improve the reaction of epoxysulphones with organometallic reagents it was figured that lithioorganocuprates usually show a selective behaviour, particularly in conjugate addition reactions. Amongst others, α,β-unsaturated sulphones react with dimethyl copper lithium in a Michael addition fashion.[6,7] Furthermore, reactions of these reagents with acetoxy substituted epoxides lead to substituted carbonyl compounds in the manner as depicted in Scheme 5.1.[8] It should be noted that the acetoxy group serves as a leaving group in the carbonyl forming elimination reaction. The desired course of the reaction for epoxysulphones should resemble that shown in Scheme 5.1, now with the sulphinate serving as a leaving group.

scheme 5.1

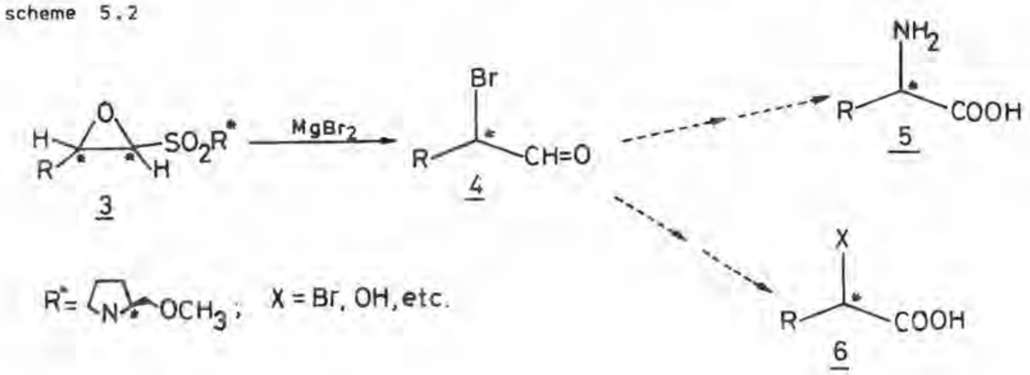


Disappointingly, however, the attempted reaction of epoxysulphones and epoxysulphonamides with lithio dimethylcuprate or with lithio thiophenoxycuprate led to the formation of complex mixtures of products, among which was some unreacted starting materials. These crude mixtures were not analysed further. In the reaction shown in Scheme 5.1 it was also found that the desired product was usually highly contaminated by other unwanted products.[8] It was further found that the yield of the desired product was greatly affected by changing the nature of the organocuprate, the structure of the epoxide and the reaction conditions. However, in the present study change of reaction conditions did not improve the results. Therefore, the above preliminary results discouraged further investigations in these reactions.

5.2.2. *Reactions with magnesium bromide*

The nucleophilic epoxide ring opening with magnesium bromide with subsequent elimination of the sulphone group to form substituted α-bromoaldehydes is one of the most successful reactions of epoxysulphones (see section 2.3.3, Chapter 2). That is why it was assumed that a similar reaction with chiral epoxysulphonamides should also be facile, giving in this case chiral α-bromoaldehydes. Such products would be suitable intermediates in an asymmetric synthesis of α-amino acids (5) or α-functionalized carboxylic acids (6) (Scheme 5.2).

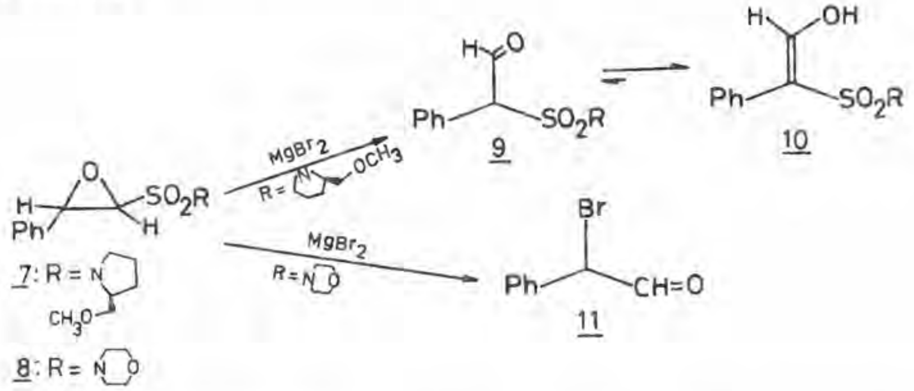
scheme 5.2



Since most of such compounds are known in their optically pure form, their synthesis should be of great help in determining the optical yield, especially where the $Eu(fod)_3$ induced NMR experiments with the original epoxysulphonamides failed to give accurate results (Chapter 4, section 4.2.2). Also the so-formed products (especially α-amino acids) would be useful in establishing the absolute mode of chiral induction in the asymmetric Darzens condensation to epoxysulphonamides by comparison of the optical properties of the obtained products with those of the compounds with known absolute configurations.

An attempted reaction of epoxysulphonamide 7 with magnesium bromide according to a literature procedure[2,3] only led to the isolation of a rearranged product 10 as was deduced from spectroscopic properties (IR and NMR) of the product.

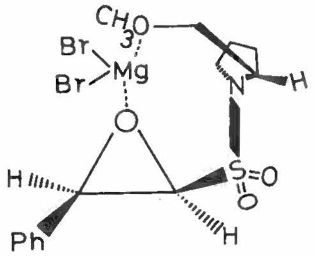
scheme 5.3



However, repeating the reaction using the epoxysulphomorpholine 8 (Scheme 5.3) gave the expected α-bromoaldehyde 11 in good yield.

In explaining the unexpected discrepancy in the behaviour of the two epoxysulphonamides 7 and 8 it may be suggested that the methoxymethyl group in 7 sterically hampers the attack of the nucleophilic bromide ion at the β-carbon atom of the epoxide function. Consequently, the effect of magnesium bromide as a Lewis acid in catalysing the sulphonyl migration prevails. Alternatively, a bidentate coordinate of magnesium bromide with substrate 7 can be envisaged (Figure 5.1) with the apparent consequence that nucleophilic epoxide opening is retarded and a predominance of the epoxide rearrangement reactions is observed. Although it is clear that the methoxymethyl group is responsible for the deviant behaviour, the details of the effects that govern the preference for the rearrangement remain uncertain. It should be reminded that the exact mechanism of the nucleophilic reaction with bromide ion leading to the α-bromoaldehyde (*anti*-attack *vs* *syn*-attack; see Chapter 2, section 2.3.3.) is not known, which makes the discussion about the herefore-mentioned governing factors rather difficult.

Fig. 5.1



Treatment of α,β-epoxysulphones with tetraethylammonium chloride in dichloromethane gave α-chloroaldehydes in good yield*. In this case the reagent only can act as a nucleophile, no coordination with any of the substituents takes place. The reaction of substrate 7 and 8 with the quaternary ammonium chloride has not been studied. It is expected, however, that in both cases formation of α-chloroaldehydes will occur.

5.2.3. *Attempted reductive desulphonylation*

The wide use of the sulphone group in synthesis is based on its ultimate removal, normally by reduction, to give the desired final products. This reductive transformation is most commonly accomplished by the use of either sodium amalgam in ethanol, aluminium amalgam in aqueous THF, lithium in ethylamine, zinc in acetic acid, potassium graphite or tri-*n*-butyltin hydride.[9,10] The choice of reagents depends on the presence of other functionalities in the substrate molecule. Treatment of aryl alkyl sulphones with excess 6% sodium amalgam in methanol in the presence of 4 equivalents of disodium hydrogen phosphate has recently been found to be the most efficient procedure for the reductive removal of the sulphonyl group.[11]

In the present study the reductive desulphonylation of epoxysulphones was aimed to ultimately obtaining epoxides

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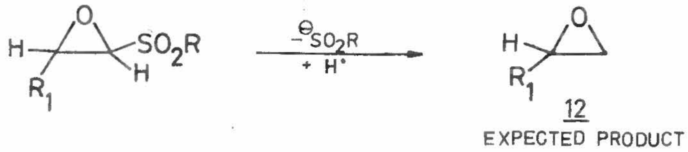
*This reaction was carried out in order to check the results obtained in the reaction of epoxysulphones with tetraethylammonium azide containing traces of tetraethylammonium chloride.

of the type 12 (Scheme 5.4). With chiral epoxysulphonamides as sulphonyl substrates the reductive removal of the sulphonamide group would then lead to an asymmetric synthesis of substituted oxiranes. Despite its great demand in organic synthesis the asymmetric synthesis of oxiranes, particularly through carbon-carbon bond formation is still difficult to achieve.[12-15]

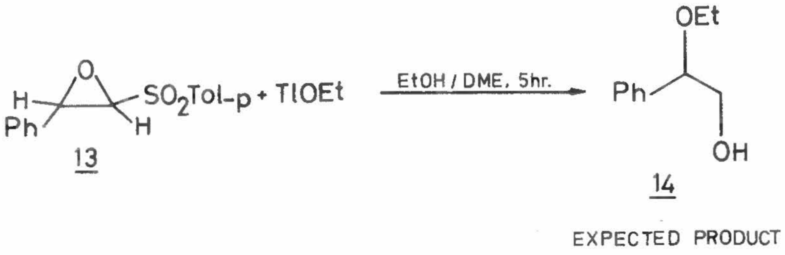
Unfortunately, in the present investigation all the attempted reactions either led to isolation of the starting epoxysulphones or to unreproducable mixtures of products (see experimental section). Modification of the conditions never improved the results. Since similar reactions are successful with most sulphonyl containing compounds[9,10], the formation of the complex mixtures observed in the present study should, to a great deal, be due to the presence of the epoxide function.

scheme 5.4



Thallous ethoxide is also known to react with sulphonyl compounds with concomitant elimination of the sulphonyl group.[16] However, in this study treatment of epoxysulphone 13

scheme 5.5

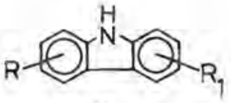


with thallous ethoxide according to a literature procedure[16] only led to the exclusive isolation of starting epoxysulphone and not to the expected compound 14.

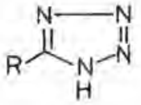
5.2.4. *Reactions of epoxysulphones with azide ions*

(i) Attempted reactions with β-monosubstituted epoxysulphonamides

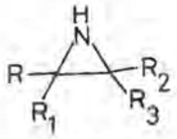
The use of azides in organic synthesis is quite advantageous since these compounds can easily be transformed into a variety of interesting amines or heterocyclic compounds, such as carbazoles (15), tetrazoles (16), aziridines (17), etc.[17,18] (section 5.2.5. gives an example of the formation of heterocyclic compounds observed in the present investigation).



15



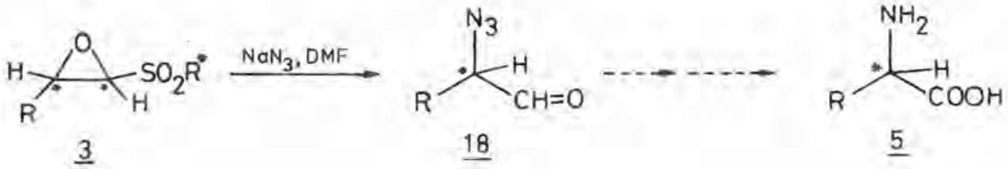
16



17

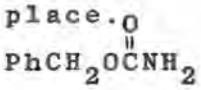
Because of its high nucleophilicity the azide ion is a very useful species in nucleophilic reactions. The use of dipolar aprotic solvents, such as DMSO, HMPA, DMF, etc., further enhances the nucleophilicity of the azide anion.[17] Reduction of the organic azides to amines with either lithium aluminium hydride[19] or by catalytic hydrogenation[20] proceeds with retention of configuration at the carbon atom bearing the azide function. From this discussion the idea emerged as depicted in Scheme 5.6, *viz.* the asymmetric synthesis of amino acids from epoxysulphonamides starting with a nucleophilic reaction with an azide anion. In the literature Barone *et al.*[5], described the

scheme 5.6



successful synthesis of α-azido aldehydes from epoxysulphones derived from some ketones. Therefore, this approach to chiral amino acids seemed to be attractive for a closer investigation.

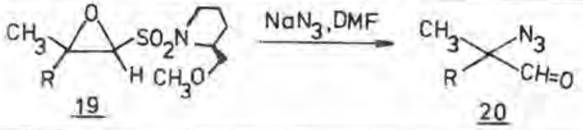
The reaction of sodium azide with 13 (R^* = 2-methoxy methyl pyrrolidide, R = Ph) led to the formation of a complex mixture of products. The ^{1}H-NMR spectrum did not show the presence of an aldehydic proton. The IR spectrum of the mixture did not show any absorption due to an aldehyde but instead only a complex pattern of absorptions in the region of 2300 to 2000 cm^{-1} was observed. Carrying out the reaction at a variety of conditions, *e.g.* change of reaction temperature, time, solvent or using tetrabutylammonium azide or lithium azide instead of sodium azide still led to the same results as above (see experimental section). Performing the reaction with chiral epoxysulphonamide 3 (Ph replaced by isopropyl) probably led to the formation of the desired azido aldehyde as indicated by the IR spectrum [ν(CH=O) 1720 cm^{-1} (s) and $\nu(N_3)$ 2160 cm^{-1} (s)]. However, as the spectrum showed, the so-formed product was contaminated by decomposition products. Attempted purification of this crude mixture by chromatography only caused further decomposition. The failure of the reaction is probably mainly due to further reactions (under the conditions of the reaction) of α-azido aldehydes of the type 18. The proton α to the aldehyde group in azido aldehyde 18 is quite acidic so that a variety of reactions of this compound, such as enolization, aldol condensation, cyclization, etc., may easily take place.

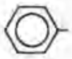
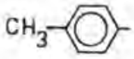
It has been reported[21] that benzyl carbamate,  $PhCH_2O\overset{O}{\overset{\|}{C}}NH_2$ can serve as a nucleophile. Therefore, a reaction of epoxysulphones with this reagent was attempted in anhydrous DMF. However, the starting epoxide was recovered unchanged, while the carbamate had decomposed.

(ii) Reactions of α,β-disubstituted epoxysulphones and chiral epoxysulphonamides with sodium azide

Barone *et al.*[5], reported the isolation of α-azido aldehydes from α,β-epoxysulphones derived from ketones. It was therefore felt that reaction of chiral β,β-disubstituted epoxysulphonamides has some promise for the ultimate preparation of α-substituted α-amino acids (*cf*. Scheme 5.6). The epoxysulphonamides were mostly prepared according to the procedure described by Vogt and Tavares[22] using potassium *tert*-butoxide as the base. This procedure was preferred over the PTC method, especially with aliphatic ketones, as the phase transfer method required a too long reaction time and gave a variety of contaminating by-products. The epoxysulphonamides and epoxysulphones prepared in this manner were immediately and without purification subjected to reaction with sodium azide in DMF. In this way rearrangement (Chapter 4, section 4.2.2.) reactions during the purification process were avoided.

Table 5.1: Synthesis of α-azidoaldehydes 20 from chiral α,β-epoxysulphonamides 19



	R	Yield (%)	$[\alpha]_D$ (c, $CHCl_3$)
20a		36	−1.1 (2.2)
20b		29	−13.5 (3.5)
20c	CH_3CH_2	61	+ 0.11(2.8)
20d	$(CH_3)_2CH$	62	n.d.
20e	$(CH_3)_2CHCH_2$	54	n.d.
20f	$CH_3(CH_2)_5$	42	n.d.

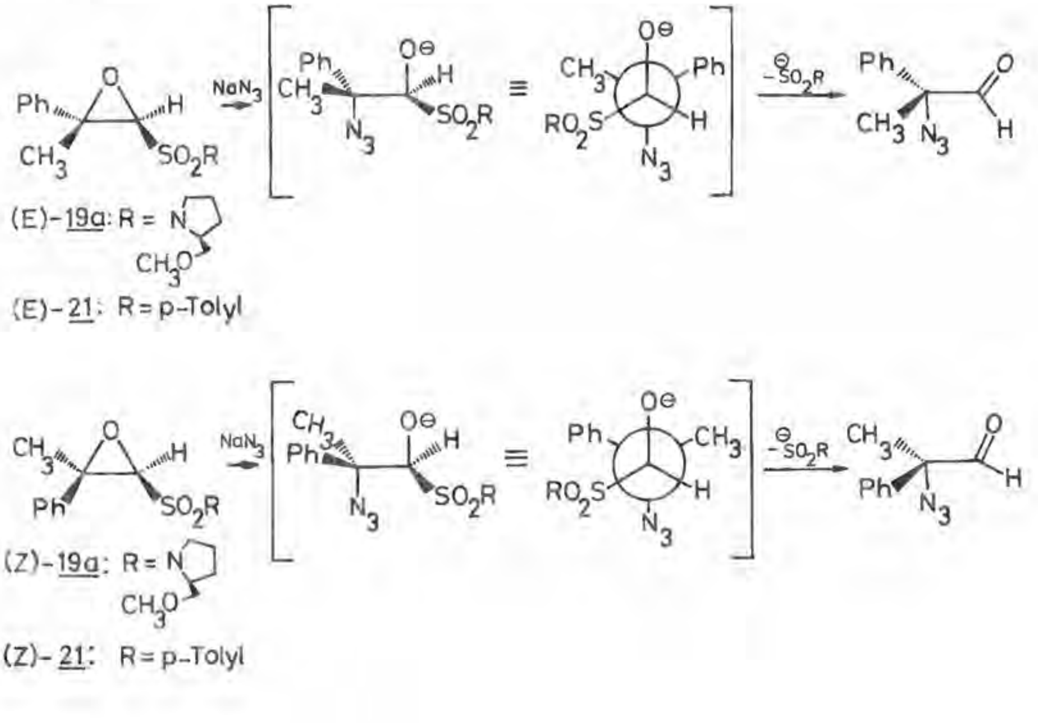
NOTE: The e.e. values of the azido aldehydes were not determined but those of the reduction products (α-amino alcohols) were determined, as reported in Table 5.2. The yields are based on the original ketones used to prepare 19.

n.d. = not determined

The reactions of the epoxysulphonamides 19 led to the isolation of α-azido aldehydes which turned out to be reasonably stable. The products were purified by medium pressure liquid chromatography (MPLC). The results are collected in Table 5.1.

An interesting observation was made for the epoxides 19a and 21 derived from acetophenone, *viz.* the reaction of sodium azide with these compounds was found to proceed more readily with the major than with the minor geometrical isomers. From the ^{1}H-NMR spectra of these compounds it was deduced that the major isomer had the (*E*)-configuration in both cases (the α-epoxymethine proton is shielded by the β-phenyl ring which is in a plane containing the C-O bond of the epoxide ring, *cf.* ref. 22; δ (H_α) for (*E*)-19a: 3.97 + 3.89 and for (*Z*)-19a: 4.23 + 4.17, for (*E*)-21: 3.30 and for (*Z*)-21: 4.40 ppm). The noted differences in reaction rates may be accounted for as follows: The formation of the azido aldehydes proceeds by a carbonyl forming elimination reaction of sulphinate anion from the intermediate alkoxy azides. This process is energetically very favourable.

scheme 5.7



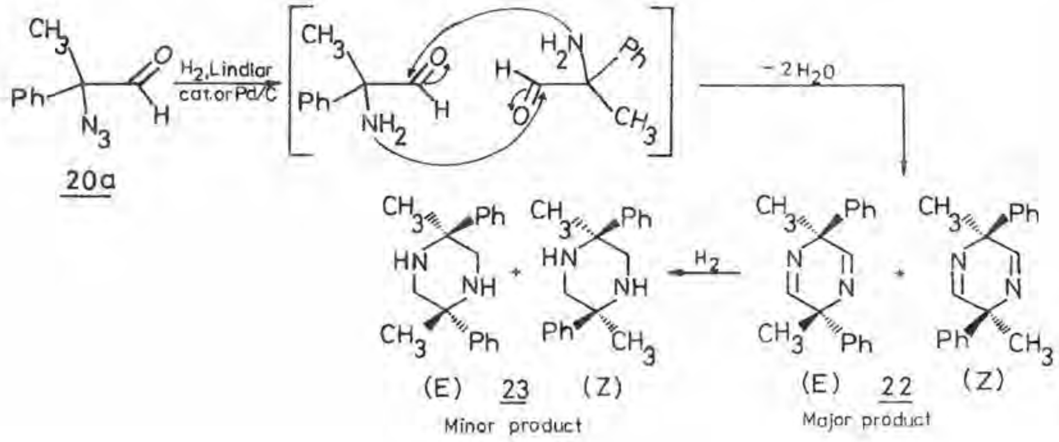
Therefore, it is assumed that the differences in reaction rates noted above are the result of a kinetic difference of the reaction of azide ion with the respective geometrical isomers. As illustrated in Scheme 5.7 the S_N2-attack of azide ion on the (*E*)-isomers leads to a less congested alkoxy azide than in the case of the minor (*Z*)-isomers (compare the Newman projections). Consequently, the reaction with the major (*E*)-isomers proceeds faster.

The difference in reaction rates as mentioned above was not observed with epoxysulphonamides derived from aliphatic ketones.

5.2.5. *Catalytic hydrogenation of α-azido aldehydes*

An attempt was made to selectively reduce catalytically (Lindlar catalyst[20]) the optically active α-azido aldehydes 20a to α-amino aldehydes. In the reduction process, however, a mixture of optically active diastereomeric 2,5-dihydropyrazines 22 and 2,5-tetrahydropyrazines 23 were the only products (IR and ^{1}H-NMR) which were obtained (the formation of 2H-azirines from the intramolecular condensation of the α-amino aldehydes is very unlikely in view of the high ring strain in the three-membered ring compounds[24]). The ratio of 22 and 23 was 5:1 (^{1}H-NMR spectrum). The pyrazines (*E*)-22 and (*Z*)-22 are obviously a result of dimerization of the preformed α-amino aldehydes

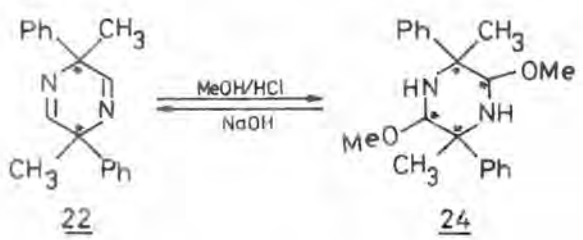
scheme 5.8



(Scheme 5.8) indicating that the catalytic reduction of an azide group is more facile than that of an aldehyde function. The 2,5-dihydropyrazines (*E*)-22 and (*Z*)-22 have no chance of aromatization because of the presence of the two substituents (Ph and Me groups) at both C-3 and C-6. The contaminant tetrahydropyrazines 23 are formed by further catalytic reduction of (*E*)-22 and (*Z*)-22. The ^{1}H-NMR spectrum of the mixture showed that the dihydropyrazines 22 existed in an isomer ratio of 6:1 while the tetrahydropyrazines 23 appeared in the isomer ratio of 3:2, implying that the reduction of one of the isomers of 22 to 23 is faster than that of the other. From steric considerations the (*E*)-diastereomers are probably the predominant isomers.

Heating the mixture of 2,5-dihydropyrazines (22) under reflux with acidified methanol for 3 hrs led to the formation of methoxylated products (*E*)-24 and (*Z*)-24 (Scheme 5.9) (IR, ^{1}H-NMR) in an almost 1:1 ratio of the (*E*)- and (*Z*)-isomers (NMR). The addition reaction of alcohols to these 2,5-dihydropyrazines as depicted in Scheme 5.9 is essentially the addition of methanol to the imine double bond of these compounds. Treatment of a mixture of (*E*)- and (*Z*)-24 with 2 N sodium hydroxide reconverted these compounds into (*E*)-22 and (*Z*)-22. However, the ratio of the (*E*)- and (*Z*)-isomers was different from that observed during the dimerization process depicted in Scheme 5.8 (NMR). This

scheme 5.9

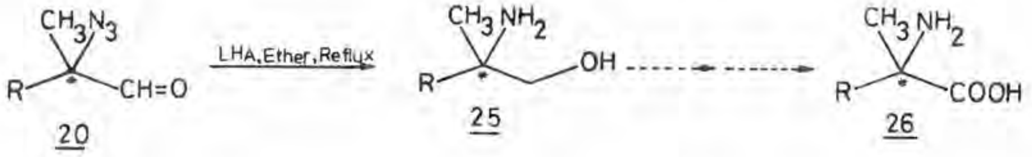


observation can only be rationalized by assuming an isomerization during the demethoxylation reaction, proceeding *via* a ring-opening ring-closure mechanism.

5.2.6. *Lithium aluminium hydride Reduction of α-Azido aldehydes*

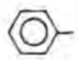
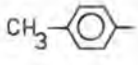
The optically active α-azido aldehydes obtained from epoxysulphonamides were conveniently reduced with lithium aluminium hydride in refluxing ether to give optically active 2-amino-2-methyl aryl or alkyl alcohols (Scheme 5.10). The ^{1}H-NMR spectra of the amino alcohols 25a and 25b (Table 5.2) indicated an AB quartet for the methylene proton α to the hydroxyl group. The enantiomeric excess (e.e.) of the amino alcohols was assessed with the aid of ^{1}H-NMR spectroscopy using optically active shift reagents Yb(hfc)$_3$, Yb(tfc)$_3$ and Eu(tfc)$_3$. Of these reagents only Eu(tfc)$_3$ proved to be useful in the determination of e.e. Despite the sensitivity of shift reagents towards water[25], best resolutions were observed on subsequent addition of a drop of D_2O to the solution containing the amino alcohol and the shift reagent. These results apparently indicate that intramolecular hydrogen bonding greatly affects the effectiveness of shift reagents because of the diminished ability of the coordinating sites (which participate in hydrogen bonding as well) to complex with the shift reagent. In these experiments the signal due to the methylene proton which was shifted most also gave the best resolution and the integration of this signal was then used to calculate the enantiomeric excess given in Table 5.2. Unfortunately, the amino alcohol 25c did not give good NMR resolutions in the presence of any of the three shift reagents. The quantity of 25d was too small for satisfactory shift reagent induced ^{1}H-NMR experiments to be carried out.

scheme 5.10



From the available results it is not possible to assign the absolute configuration of the enantiomer in excess.

Table 5.2: Asymmetric synthesis of aryl and alkyl 2-amino-2-methyl alcohols 25 according to schemes 5.10

	R	Yield (%)	$[\alpha]_D$ (c, EtOH)	e.e. (%)
25a		86.5	-3.6 (5.0)	34.5
25b		77.5	-4.3 (4.6)	28
25c	$(CH_3)_2CH$	72	-7.6 (2.5)	n.d.
25d	$(CH_3)_2CHCH_2$	78.5	-16.8 (3.3)	n.d.

n.d. = not determined

In principle, the amino alcohols 25a-25d (Table 5.2) can be converted into amino acids 26 (Scheme 5.10). Consequently, the methodology involving nucleophilic reaction of the chiral epoxysulphonamides with azide ions and subsequent reduction with lithium aluminium hydride followed by oxidation of the so-obtained amino alcohols offers a new route to the synthesis of α-methyl (or more in general, α-substituted) α-amino acids. These non-natural amino acids recently have received considerable attention in view of their interesting biological properties.[21,26,27]

5.3. *EXPERIMENTAL*

5.3.1. *General remarks*

The general remarks reported in Chapters 3 and 4 also apply in this chapter. Commercial iodide was purified by washing with refluxing THF before being dried *in vacuo* at 200° for 24 hrs. Lithium chloride and disodium hydrogen phosphate were similarly dried. The optical rotations of α-azido aldehydes were determined in chloroform as solvent, while those of amino alcohols were determined in ethanol. Shift reagent induced NMR experiments were performed on a BRUKER WH-90 NMR instrument operating at 90 MHz with Fourier Transform (FT) techniques. Unless otherwise stated α,β-epoxysulphones and epoxysulphonamides were prepared through the PTC procedure.

5.3.2. *Attempted reactions of α,β-epoxysulphonamides with lithium organocuprates*

(i) Attempted reaction with lithium dimethylcuprate

To a stirred suspension of CuI (0.189 g, 0.99 mmol) in absolute ether (25 ml) under nitrogen at 0^o was added a solution of methyllithium (1.45 M) in ether (1.36 ml, 1.980 mmol) followed by a solution of (*E*)-1,2-epoxy-2-phenylethanesulpho(2-methoxymethyl)pyrrolidide (0.147 g, 0.495 mmol) in ether (10 ml); the reaction mixture was stirred at 0^o for 2 hrs before HMPA (1 ml) was added in order to render the reaction mixture homogeneous. After stirring at 0^o for another 2 hrs, the mixture was quenched with absolute methanol (1 ml, 25 mmol), poured in a saturated NH_4Cl solution (50 ml) and extracted with ether. The ethereal solution was dried and subsequent evaporation of the solvent left the starting epoxysulphonamide [TLC (silica gel with 10% ethyl acetate in hexane elution) , NMR and IR] and other uncharacterized minor compounds. Lowering the reaction temperature to -25^o or -78^o, respectively, did not give the anticipated reaction. The reaction was repeated with (*E*)-1,2-epoxy-3-methylbutanesulpho(2-methoxymethyl)pyrrolidide pyrrolidine and similar results as above were obtained.

(ii) Attempted reaction with lithium thiophenoxycuprate

Lithium thiophenoxide was prepared by the reaction of *n*-BuLi (1.6 M in *n*-hexane) (1.25 ml, 2.0 mmol) and thiophenol (0.220 g, 2.0 mmol) at 0^o under nitrogen and stirring in superdry THF (25 ml) for 10 min.

To a stirred suspension of CuI (0.379 g, 2.0 mmol) in superdry THF (20 ml) and hexane (20 ml) at room temperature was added the lithium thiophenoxide solution and to this reaction mixture was added dropwise at -78^o a solution of methyllithium in ether (1.45 M) (1.38 ml, 2.0 mmol).After stirring for 5 min a solution of (*E*)-1,2-epoxy-3-methylbutanesulpho-(2-methoxymethyl)pyrrolidide (0.745 g, 2.0 mmol) in THF (5 ml) was added at -78^o. The reaction mixture was stirred for a further 1 hr at -78°. It was then quenched with methanol (1 ml, 25 mmol) and allowed to warm to room temperature. The reaction mixture was then poured in a saturated solution of NH_4Cl (100 ml) and the yellow precipitate which was formed (inorganic salts) was filtered off. The filtrate was extracted with ether (4x75 ml), the ethereal solution was washed twice with sodium hydroxide solution and dried. The solvent was evaporated affording the starting epoxysulphonamide and other minor uncharacterized compounds, as indicated by TLC, IR and NMR.

5.3.3. *Reaction of magnesium bromide with α,β-epoxysulphonamides*

(i) Reaction with (E)-1,2-epoxy-2-phenylethanesulpho(2-methoxymethyl)pyrrolidide, formation of 10

Magnesium bromide: A mixture of dibromoethane (7.68 g, 40.88 mmol), magnesium turnings (0.992 g, 40.88 mmol) and iodine (one crystal) in absolute ether (150 ml) was warmed using a water bath until a vigorous reaction commenced. The reaction mixture was then stirred at 10-15° for 1 hr.

To the above magnesium bromide solution at 5° was gradually added with stirring a solution of the epoxysulphonamide (3.04 g, 10.22 mmol) in dichloromethane (20 ml). The reaction mixture was stirred at this temperature for 1 hr, then poured in water and extracted with ether. The ethereal solution was worked-up to give 10 as a brown viscous oil which was purified by chromatography (silica gel with dichromethane/*n*-hexane, 2:1 elution); 2.80 g (92%); IR (neat film): ν(O-H) 3500 (br), ν(C=C) 1660 (br) and ν(SO_2-N) 1350 (s) and 1160 cm^{-1} (s); ^{1}H-NMR: δ = 8.2-6.8 (m, phenyl protons, $\rangle C{=}\overset{|}{C}{-}O\underline{H}$ and $\rangle C{=}\overset{|}{C}{-}\underline{H}$), 4.30 (m, $N{-}\overset{|}{C}\underline{H}$), 3.8-2.6 (m, $N{-}C\underline{H}_2{-}$, $-O-CH_3$ and $-O-CH_2-$) and 2.40-1.40 ppm (m, $-C\underline{H}_2-C\underline{H}_2-$).

(ii) Reaction with (E)-1,2-epoxy-2-phenylethanesulphomorpholide, formation of 11

To a solution of magnesium bromide (prepared as described in the previous experiment) (5 equiv.) in absolute ether (100 ml) at 5^{o} was added with stirring a solution of the epoxysulphonamide (1.0 g, 3.713 mmol) and worked-up as in the previous experiment to give a crude product; IR (film): ν(CH=O) 1720 cm^{-1} (s); ^{1}H-NMR: δ = 9.45 (d, J = 3 Hz, CH-C$\underline{H}$=O) and 5.25 ppm (d, J = 3 Hz, C$\underline{H}$-CH=O). This crude material was purified by chromatography (silica gel, 1:1, dichloromethane/*n*-hexane) to give pure α-bromoaldehyde $\underline{11}$, 0.52 g (70.5%); IR (KBr): ν(-CH=O) 2700 (w) and 1720 cm^{-1} (s); ^{1}H-NMR: δ = 9.43 (d, J = 3 Hz, 1H, CH-C$\underline{H}$=O), 7.3 (s, 5H, phenyl protons) and 5.25 ppm (d, J = 3 Hz, 1H, -C$\underline{H}$-CHO); MS: m/e 183 (M^{+}).

5.3.4. *Reaction of epoxysulphones with tetraethylammonium chloride*

A mixture of tetraethylammonium chloride (3.07 g, 18.56 ml) and (*E*)-2-phenyl-1,2-epoxyethyl *p*-tolyl sulphone (4.0 g, 14.59 mmol) in acetonitrile/dichloromethane mixture (1:1) (100 ml) was stirred at room temperature for 12 hrs, then poured into water (200 ml) and extracted with ether. The ethereal solution was worked-up to leave a crude product; IR (neat film): ν(CH=O) 2700 (w) and 1720 cm^{-1} (s) which was purified by chromatography (silica gel, 1:1, dichloromethane/*n*-hexane) to give α-chloro phenylacetaldehyde; 1.42 g (63%); IR (KBr): ν(CH=O) 1720 cm^{-1} (s); ^{1}H-NMR: δ = 9.50 (d, J = 3 Hz, 1H, CH-C$\underline{H}$=O), 7.30 (s, 5H, phenyl protons) and 5.20 ppm (d, J = 3 Hz, 1H, C$\underline{H}$-CH=O).

5.3.5. *Attempted desulphonylation of α,β-epoxysulphones*

(i) Using aluminium amalgam

A thin piece of aluminium foil (1.0 g, 37,06 mmol) was soacked in a solution of NaOH (10%) (50 ml) for *ca.* 30 sec, washed with water until free from alkali and then with methanol, soacked in a solution of mercuric chloride (2%) (50 ml) for *ca.* 1.5 min, the mercuric chloride solution was decanted and the formed amalgam was washed successively with water and methanol before being stored in moist ether.

A mixture of the freshly prepared amalgam (1.5 g), the epoxysulphone (2 g) and THF/water (9:1 $^{v}/v$) (300 ml) was stirred at 65° for 4 hrs, then cooled, filtered and extracted with dichloromethane. The dichloromethane solution was washed with water, dried and the solvent was evaporated to leave a solid which on TLC (alumina/ether) and NMR showed presence of a complex mixture containing mainly the starting epoxysulphone.

(ii) Using lithium in ethylamine

Freshly cut lithium metal (1.5 equiv.) was slowly added (in portions) to a mixture of ethylamine-ether (20:20 ml) at room temperature. After all the lithium had dissolved a solution of (*E*)-2-phenyl-1,2-epoxyethyl *p*-tolyl sulphone (1.2 g, 4.38 mmol) in dichloromethane (20 ml) was then added dropwise. The reaction mixture was stirred at room temperature for 1 hr, then poured in cold water (200 ml) and extracted with ether. The ethereal solution was dried and the solvent was evaporated to leave a dark brown material (bad smell) which on TLC (silica gel/ether) was shown to contain a complex mixture of compounds. The ^{1}H-NMR spectrum showed the presence of some starting epoxysulphone. The experiment was repeated at -78° for 2 hrs but in this case only the starting epoxysulphone was the main compound obtained.

(iii) Using sodium amalgam

To a suspension of pulverized sodium amalgam (1.6%) (5.48 g) and dried disodium hydrogen phosphate (2.075 g, 14.6 mmol) in ethanol (100 ml) was added with stirring (*E*)-2-phenyl-1,2-epoxyethyl *p*-tolyl sulphone (1.0 g, 3.65 mmol). The reaction mixture was stirred at room temperature for 4 hrs, then taken up in water (300 ml) and extracted with ether. The ethereal solution was dried and the solvent was evaporated to leave a brown material which contained mainly the starting material as indicated by TLC and ^{1}H-NMR spectrum. Carrying out the reaction for 10 hrs and under reflux led to the formation of a complex mixture of compounds which had a bad smell.

(iv) Using thallous ethoxide

A mixture of (*E*)-2-phenyl-1,2-epoxyethyl *p*-tolyl sulphone (1.0 g, 3.65 mmol) and thallous ethoxide (0.75 g, 3.65 mmol) in absolute ethanol/DME (1:1) (50 ml) was stirred at room temperature for 5 hrs. The reaction mixture was then taken up in ether and was washed with water. The ethereal solution was dried and the solvent was evaporated to leave a dark brown solid which contained exclusively the starting epoxysulphone.

5.3.6. *Reaction of epoxysulphones with tetrabutylammonium azide and lithium azide*

A mixture of sodium azide (0.475 g, 7.30 mmol) and tetrabutylammonium chloride (2.10 g, 7.57 mmol) in dichloromethane (100 ml) was stirred at 0° for 1 hr and the formed sodium chloride was filtered off. To the filtrate was slowly added at 0° a solution of (*E*)-2-phenyl-1,2-epoxyethyl *p*-tolyl sulphone (2.0 g, 7.30 mmol) in dichloromethane (10 ml). The reaction mixture was stirred at room temperature for 4 hrs. Work-up gave a complex mixture of products. IR: $\nu(-N_3)$ 2105 cm^{-1}. The intensity of this signal began to diminish quickly a few minutes after work-up and after 10 min the IR spectrum showed no $\nu(-N_3)$ absorption anymore.

Repeating the reaction with lithium azide in acetonitrile/dichloromethane as solvent and at 30° for 30 min led to similar results.

Carrying out the reaction with sodium azide in aqueous acetone under reflux for 1.5 hr also led to similar results as above.

5.3.7. *Reaction of benzyl carbamate with epoxysulphones*

Benzyl carbamate was prepared by the action of aqueous ammonia on carbobenzoxy chloride.

A mixture of benzyl carbamate (0.83 g, 5.50 mmol) and (*E*)-2-phenyl-1,2-epoxyethyl *p*-tolyl sulphone (1.5 g, 5.47 mmol) was stirred in DMF at 90° for 6 hrs and then diluted with water.

The aqueous solution was then extracted with ether, the ethereal solution was dried and the solvent evaporated to leave a brown complex substance (TLC) whose ^{1}H-NMR spectrum indicated amongst others the presence of the starting epoxysulphone. A colourless liquid was obtained chromatographycally; ^{1}H-NMR: δ = 7.20 (s, phenyl protons), 4.50 (s, $-C\underline{H}_2-O$) and 2.90 ppm (s, disappeared on addition of D_2O, $-O-\underline{H}$); IR (neat film): $\nu(-O-H)$ 3500 cm^{-1} (br). This compound was clearly benzyl alcohol.

5.3.8. *Reactions of α,β-epoxysulphones and epoxysulphonamides with sodium azide*

To a stirred mixture of sodium azide (4 equiv.) in dry DMF (20 ml) at 70^o and under nitrogen was added in portions the epoxysulphone or epoxysulphonamide (1 equiv.). The reaction mixture was stirred at 70^o under nitrogen for 24 hrs. It was then diluted with dichloromethane/ether (3:7) (100 ml), extracted with water (100 ml) and the aqueous fraction was washed once with dichloromethane/ether (3:7) (100 ml). The combined organic fraction was washed several times with water and then with a saturated sodium chloride solution. It was then dried and the solvent was evaporated to leave a brown solid which was purified chromatographically (silica gel) with chloroform/hexane (1:3) elution. The products were identified from TLC, IR and NMR spectra.

The optically active β,β-disubstituted epoxysulphonamides were prepared by the reaction of unsymmetrical ketones with *N*-chloromethylsulphonylpyrrolidine-2-methoxymethyl in the presence of potassium *tert*-butoxide as already described in Chapter 4. The reactions with sodium azide were carried out for 6 hrs and worked-up as above. To avoid any rearrangements the crude epoxysulphonamides were used immediately after preparation and without further purification.

(i) Reaction with (E)-2-phenyl-1,2-epoxyethyl p-tolyl sulphone

Reaction of the epoxysulphone (2.0 g, 7.30 mmol) with sodium azide (1.90 g, 4 equiv.) and work-up as above gave a brown solid material, which was found from TLC (silica gel or alumina, 50% ethyl acetate in *n*-hexane), ^{1}H-NMR and IR spectra to be a complex mixture of products. IR (KBr): $\nu(-N_3)$ 2105 cm^{-1} (s). Carrying out the reaction at room temperature for 10 hrs led to a similar complex mixture as above. Repeating the reaction in refluxing acetonitrile for 4 hrs also led to a similar result. The reaction in acetonitrile at room temperature for 10 hrs gave a complex mixture and some unreacted epoxysulphone.

(ii) Reaction with (E)-1,2-epoxy-3-methylbutanesulpho(2-methoxymethyl)pyrrolidide

Reaction of the epoxysulphonamide (3.58 g, 13.60 mmol) and sodium azide (3.54 g, 4 equiv.) at 30° for 10 hrs gave a crude product which after work-up and chromatography (silica gel, 40% dichloromethane in *n*-hexane) gave a product, 1.2 g; IR (neat film): 3600-3200 (br), 2740 (w, -CH=O), 2240 (w), 2200 (w), 2160 (s), 2110 (s, $-N_3$), 1720 (s, -CH=O), 1660 (w, CH=C ?), 1600 (s) and 1330 (s) and 1145 cm^{-1} (s, $-SO_2N-$). Attempted further purification of this substance by chromatography led to the formation of a complex mixture of products.

(iii) Reaction with 2-methyl-1,2-epoxypropyl p-tolyl sulphone under PTC conditions

A mixture of the epoxysulphone (3.0 g, 13.27 mmol), sodium azide (3.45 g, 4 equiv.) and tetrabutylammonium bromide (0.1 g, 0.36 mmol) in *50% sodium hydroxide* (20 ml) containing HMPA (2 ml) was vigorously stirred at 30-40° for 6 hrs, then poured in cold water (300 ml) and extracted with ether. The ethereal solution was washed several times with water, dried and the solvent evaporated to leave a brown material. The IR spectrum indicated the presence of the starting epoxysulphone. This crude product was purified by chromatography (silica gel, dichloromethane/*n*-hexane 1:1) to give the pure azidoaldehyde (0.879 g, 58.5%); IR (neat film): ν(-CH=O) 2700 (w) and 1730 (s) and $(-N_3)$ 2110 cm^{-1} (s); ^1H-NMR: δ = 9.40 (s, 1H, -C$\underline{H}$=O) and 1.33 ppm (s, 6H, $(C\underline{H}_3)_2$-); MS: m/e 113 (M^+).

Repeating the PTC reaction with *(E)*-2-phenyl-2-epoxyethyl *p*-tolyl sulphone led to the complex mixture of products as that obtained previously under non-PTC conditions.

(iv) Reaction with 2-phenyl-1,2-epoxypropyl p-tolyl sulphone

The epoxysulphone was prepared under PTC conditions as described before. Work-up from ether gave the crude product, ^1H-NMR: δ = 7.25 (s, phenyl protons), 4.15 (s, epoxymethine proton of one diastereomer), 3.30 (s, epoxymethine proton of another diastereomer) and 2.43 (s) and 2.13 ppm (s) (epoxymethyl protons of the two diastereomers). From the epoxymethine proton signals the diastereomeric ratio of 63:37 was determined (the *(E)*-isomer is the major one).

The crude epoxysulphone mixture (1.5 g) and sodium azide (1.4 g, 21.54 mmol) in DMF (30 ml) were stirred at 60° while the reaction was monitored by ^1H-NMR spectroscopy. After 2 hrs, the major diastereomeric epoxysulphone had completely reacted. ^1H-NMR spectrum of the mixture: δ = 9.5 (s, -C$\underline{H}$=O) and 4.15 ppm (s, epoxymethine proton of the unreacted diastereomer); IR (neat film): ν(-CH=O) 1720 (s) and $\nu(-N_3)$ 2105 cm^{-1} (s).

Carrying out the reaction for 20 hrs still left a considerable amount of the unreacted diastereomer. This crude product obtained after the normal work-up was then subjected to chromatographic separation (silica gel, 1:1 dichloromethane/*n*-hexane) to give the first fraction containing the required azide (α-azido-α-phenylpropionaldehyde) as a reddish brown liquid, 0.40 g (42.0% overall yield); ^1H-NMR: δ = 9.40 (s, 1H, -C$\underline{H}$=O), 7.35 (s, 5H, phenyl protons) and 1.73 ppm (s, 3H, $C\underline{H}_3$-C-); IR (neat film): ν(-CH=O) 2700 (w) and 1720 (s) and $\nu(-N_3)$ 2105 cm^{-1} (s); MS: m/e 175 (M^+). The second fraction (0.23 g) contained a mixture of rearranged products (see Chapter 4); ^1H-NMR: δ = 10.2 (s, -C$\underline{H}$=O), 7.5-7.1 (m, phenyl protons), 4.20 (m, C$\underline{H}$-CH_3), 2.35 (s) and 1.80 ppm (s) (-$C\underline{H}_3$ of two rearranged products); IR (KBr): ν(-CH=O) 1715 (s) and $\nu(-SO_2-)$ 1350 (s) and 1165 cm^{-1} (s).

2-Azido-2-phenylpropanal (20a)

Crude 1,2-epoxy-2-phenylpropanesulpho(2-methoxymethyl)-pyrrolidide (6.0 g) and sodium azide (5.0 g) gave crude 20a (2.0 g); IR (neat film): ν(-CH=O) 2700 (w) and 1730 (s), $\nu(-N_3)$ 2110 (s) and $\nu(-SO_2N-)$ 1355 (s) and 1155 cm^{-1} (s); ^{1}H-NMR: δ = 9.40 (s, -C$\underline{H}$=O) and 4.30 (s) and 4.25 ppm (s) (epoxymethine protons of the unreacted diastereomers). Purified 20a (1.2 g, 36%): IR (neat film): ν(-C$\underline{H}$=O) 2700 (w) and 1730 (s) and $\nu(-N_3)$ 2110 cm^{-1} (s); ^{1}H-NMR: δ = 9.45 (s, 1H, -C$\underline{H}$=O), 7.35 (s, 5H, phenyl protons) and 2.80 ppm (s, 3H, $-C-C\underline{H}_3$); $[\alpha]_D = -1.1^o$ (c = 2.2); MS: m/e 175 (M^+).

2-Azido-2-(p-tolyl)propanal (20b)

Crude 1,2-epoxy-2-(*p*-tolyl)propanesulpho(2-methoxymethyl)-pyrrolidide (3.33 g) and sodium azide (2.66 g) gave a crude product (1.40 g); IR (film): ν(-CH=O) 2700 (w) and 1730 (s), $\nu(-N_3)$ 2110 (s) and $(-SO_2-N-)$ 1355 (s) and 1155 cm^{-1} (s). The ^{1}H-NMR spectrum showed presence of some rearranged epoxy-sulphonamides. The yield of purified 20b was 567 mg (29%); IR (neat film): ν(-CH=O) 2700 (w) and 1725 (s), $\nu(-N_3)$ 2110 cm^{-1} (s); ^{1}H-NMR: δ = 9.40 (s, 1H, -C$\underline{H}$=O), 7.20 (s, 4H, aromatic protons), 2.30 (s, 3H, *p*-methyl protons) and 1.75 ppm (s, 3H, $-C-C\underline{H}_3$); $[\alpha]_D = -13.5^o$ (c = 3.5); MS: m/e 189 (M^+).

2-Azido-2-methylbutanal (20c)

Reaction of 1,2-epoxy-2-methylbutanesulpho(2-methoxymethyl)-pyrrolidide (2.72 g) with sodium azide (2.68 g) gave after work-up and purification 20c (0.80 g, 61%); IR (neat film): ν(-CH=O) 2700 (w) and 1725 (s), $\nu(-N_3)$ 2105 cm^{-1} (s); ^{1}H-NMR: δ = 9.43 (s, 1H, -CH=O), 1.70 (m, $-CH_2-$), 1.35 (s, $-C-C\underline{H}_3$) and 0.95 ppm (t, J = 6 Hz, $C\underline{H}_3-CH_2-$); $[\alpha]_D = +0.11^o$ (c = 2.8); MS: m/e 127 (M^+).

2-Azido-2,3-dimethylbutanal (20d)

From crude 1,2-epoxy-2,3-dimethylbutanesulpho(2-methoxy-methyl)pyrrolidide (2.74 g) and sodium azide (excess) was obtained after work-up and purification, 20d, 0.87 g (62%); IR (neat film): ν(CH=O) 2700 (w) and 1725 (s), $\nu(-N_3)$ 2105 cm^{-1} (s); ^{1}H-NMR: δ = 9.43 ppm (s, -CH=O); MS: m/e 141 (M^+).

2-Azido-2,4-dimethylpentanal (20e)

The reaction of crude 1,2-epoxy-2,4-dimethylpentanesulpho-(2-methoxymethyl)pyrrolidide (3.22 g) with sodium azide (2.88 g) gave after work-up and purification, 0.93 g (54%) of the azido aldehyde 20e; IR (neat film): ν(CH=O) 2700 (w) and 1725 (s), $\nu(-N_3)$ 2105 cm^{-1} (s); ^{1}H-NMR: δ = 9.40 (s, $-C\underline{H}=O$), 1.70 (m, $Me_2C\underline{H}-$) and 1.40-0.70 ppm (m, $-C\underline{H}_2-$ and CH_3 groups); MS: m/e 167 (M^+).

2-Azido-2-methyloctanal (20f)

From crude 1,2-epoxy-2-methyldecanesulpho(2-methoxymethyl)-pyrrolidide (3.0 g) and sodium azide (3.44 g) was obtained the azido aldehyde 20f (0.94 g, 42%); IR (neat film): ν(-CH=O) 2700 (w) and 1710 (s), $\nu(-N_3)$ 2105 cm^{-1} (s); ^{1}H-NMR: δ = 9.40 ppm ($-C\underline{H}=O$); MS: m/e 171 (M^+).

Mixture of 3,6-dimethyl-3,6-diphenyl-2,5-dihydropyrazine (22) and 3,6-dimethyl-3,6-diphenyl-2,5-tetrahydropyrazine (23)

A mixture of 2-azido-2-phenylpropanal (20a) (0.600 g, 3.43 mmol) and Lindlar catalyst (60 mg) in ethanol (25 ml) was hydrogenated at room temperature and atmospheric pressure for 20 hrs. The catalyst was filtered off and then the solvent was evaporated to leave a crude product which was purified by distillation to give a mixture of 22 and 23, 400 mg, in the ratio of 5:1, respectively (^{1}H-NMR); IR (neat film): ν(C=N) 1660 (br) and ν(C-N) 1590 cm^{-1} (s); ^{1}H-NMR: δ = 8.10 (s, $-N=C-\underline{H}$), 7.23 (s, phenyl protons), 3.66-3.33 (ABq, $J_{AB} \approx 6$ Hz, diastereotopic methylene protons of 23), 1.70 (s) and 1.60 (s) ($-C\underline{H}_3$ groups of the two diastereomers of 22, ratio 6:1), 1.50 (s) and 1.43 (s) ($-CH_3$ groups of the two diastereomers of 23, ratio 3:2); $[\alpha]_D = -7.7^{\circ}$ (c = 3.0, EtOH). Use of Pd-C (5%) gave the same results.

Diastereomeric 2,5-dimethoxy-3,6-dimethyl-3,6-diphenyl-2,5-dihydropyrazines (<u>24</u>)

A diastereomeric mixture of <u>22</u> (450 mg, 3.44 mmol) in acidified (2 N HCl, 10 ml) methanol (50 ml) was heated under reflux for 3 hrs, then diluted with water and extracted with ether. The ethereal solution was washed until free from acid, dried and then the solvent was evaporated to leave an oil (400 mg, 88%); ^{1}H-NMR: δ = 7.23 (s) and 7.16 (s) (phenyl protons for diastereomers), 5.45-5.0 (m, $-\overset{|}{C}\underline{H}-OMe$), 3.40 (s, $-O-C\underline{H}_3$), 3.26 (s) ($-\overset{|}{N}-\underline{H}$) and 1.50 (s) and 1.43 ppm (s) ($-C\underline{H}_3$ for diastereomers). Addition of 2 N of sodium hydroxide to the above mixture regenerated the 2,5-dihydropyrazines <u>22</u>; ^{1}H-NMR: δ = 8.15 (br, $-N=C\underline{H}-$), 7.36 (s) and 7.26 (s) (phenyl groups for diastereomers), 1.73 (s) and 1.60 (s) ($-CH_3$ groups for diastereomers, ratio ≃1:1).

5.4. *General method for the preparation of 2-amino-2-methyl alcohols*

To a stirred suspension of lithium aluminium hydride (excess) in absolute ether (50 ml) at room temperature was added dropwise a solution of an azido aldehyde. The reaction mixture was heated under reflux for 3 hrs. After cooling, a cold NaOH solution (2 N) was added gradually. The ethereal fraction was filtered off and the residue was washed twice with ether (2x50 ml). The combined ethereal fractions were dried and the solvent was evaporated to leave a crude product which was either purified by distillation under reduced pressure or by recrystallization. The enantiomeric excess was determined with the help of Eu(tfc)$_3$ induced ^{1}H-NMR experiments in the presence of a trace of D_2O.

2-Amino-2,3-dimethylbutanol (<u>25c</u>)

Reduction of the azido aldehyde <u>20d</u> (200 mg, 1.29 mmol) and normal work-up gave <u>25c</u> which was purified by distillation, 133 mg (79%); $[\alpha]_D = -16.8^\circ$ (c = 3.3); IR (neat film): $\nu(-NH_2$ and OH) 3500-3200 (br) and ν(C-N) 1590 cm^{-1} (s); ^{1}H-NMR: δ =

3.25 (s, 2H, -C$\underline{H}_2$-O), 2.30 (s, 2H, disappeared on shaking with D_2O, -N$\underline{H}_2$), 1.65 (m,Me_2C-$\underline{H}$), 1.30 (d, J = 6 Hz, -CH-C$\underline{H}_2$-), 1.00 (d, J = 6 Hz, (C$\underline{H}_3$)$_2$CH) , 0.93 (s, C$\underline{H}_3$-C-) and 0.83 ppm (s, -O-$\underline{H}$, disappeared on treatment with D_2O); MS: m/e 112 (M^+).

2-Amino-2,4-dimethylpentanol (<u>25</u>d)

Reduction of azido aldehyde <u>20</u>e (50 mg, 0.35 mmol) gave after purification by distillation 30.0 mg (72%) of the amino alcohol <u>25</u>d; $[\alpha]_D$ = -7.6° (c = 2.5); IR (neat film): ν(-NH_2 and O-H) 3500-3200 (br) and ν(C-N) 1590 cm^{-1} (s); ^{1}H-NMR: δ = 3.30 (s, 2H, -C$\underline{H}_2$-O-), 2.30 (s, 2H, disappeared on addition of D_2O, -N$\underline{H}_2$), 1.67 (m,Me_2C$\underline{H}$-), 1.00 (d, J = 6 Hz, (C$\underline{H}_3$)$_2$CH-), 0.95 (s, C$\underline{H}_3$-C) and 0.83 ppm (-O-$\underline{H}$, disappeared on addition of D_2O); MS: m/e 126 (M^+).

2-Amino-2-phenylpropanol (<u>25</u>a)

The azido aldehyde <u>20</u>a (205 mg, 1.17 mmol) was reduced with $LiAlH_4$ to give after purification by distillation 153 mg (86.5%) of the amino alcohol <u>25</u>a; $[\alpha]_D$ = -3.6° (c = 5.0); IR (CCl_4): ν(-NH_2 and -O-H), 3500-3100 (br) and ν(C-N) 1515 cm^{-1} (s); ^{1}H-NMR: δ = 7.25 (m, 5H, phenyl protons), 3.63-3.45 (ABq, J_{AB} = 10.5 Hz, 2H, -CH_2O-), 2.33 (s, 3H, -N$\underline{H}_2$ and -O-$\underline{H}$, disappeared on addition of D_2O) and 1.35 ppm (s, C-C$\underline{H}_3$); MS: m/e 151 (M^+); enantiomeric excess 34.5%.

2-Amino-2-(<u>p</u>-tolyl)propanol (<u>25</u>b)

Reduction of azido aldehyde <u>20</u>b (148 mg, 0.78 mmol) gave crude <u>25</u>b which was purified by recrystallization from carbon tetrachloride to give white crystals, 100 mg (77.5%); $[\alpha]_D$ = -4.3° (c = 4.6); IR (CCl_4): ν(-NH_2 and -O-H) 3500-3100 (br) and ν(C-N) 1510 cm^{-1} (s); ^{1}H-NMR: δ = 7.20 (d, J = 6 Hz, 4H, aromatic protons), 3.65-3.45 (ABq, J_{AB} = 10.5 Hz, 2H, -C$\underline{H}_2$-O-), 2.33 (s, 6H, -N$\underline{H}_2$, -O-$\underline{H}$ and *p*-C$\underline{H}_3$) and 1.37 ppm (s, 3H, C$\underline{H}_3$-C); MS: m/e 165 (M^+); enantiomeric excess 28%.

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