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SYNTHETIC STUDIES ON THE C20 BACKBONE OF THE FUMONISINS USING CHIRAL SULFOXIDES

MSc UP 1997

SYNTHETIC STUDIES ON THE C_{20} BACKBONE OF THE FUMONISINS USING CHIRAL SULFOXIDES

by

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Submitted in partial fulfillment of the degree

MAGISTER SCIENTIAE

in the Faculty of Science

UNIVERSITY OF PRETORIA
PRETORIA

Promotor Prof. R. Vleggaar

November 1997

SUMMARY

Fusarium moniliforme is a common contaminant of maize, a basic staple of the diet of both humans and animals. The fungus is the causative agent of equine leucoencephalomalacia (LEM) and has been implicated in human oesaphageal cancer. The structure of the fumonisins, a family of structurally related mycotoxins isolated from cultures of *F. moniliforme* responsible for LEM has been established. Thus fumonisin B_1 is the diester formed by the *Re* carboxy group of propane-1, 2, 3-tricarboxylic acid with the C-14 and C-15 hydroxy groups of (2*S*,3*S*,5*R*,10*R*,12*S*,14*S*,,15*R*,16*R*)-2-amino-12,16-dimethyl-3,5,10,-14,15-pentahydroxyicosane.

Retrosynthetic analysis of the C_{20} backbone of fumonisin B_1 by disconnection of the C-10–C-11 bond identifies 4,8-dimethyl-1,2,6,7-tetrahydroxydodecane, synthon **B** and 7-amino-1,4,6-trihydroxy-octane, synthon **C** as the key intermediates in a proposed synthesis. The formation of the same bond in the synthetic direction is more demanding as it requires that the formation of the carbon-carbon bond generates at the same time a new stereogenic centre in a stereodefined fashion. The work described in this thesis investigates a strategy for the formation of the C-10–C-11 bond in the C_{20} backbone of fumonisin B_1 with the concomitant introduction of the C-11 hydroxy group by employing chiral sulfoxide methodology. The methods used are based on the highly stereoselective reduction of β-ketosulfoxides and the ability of the sulfoxide moiety to stabilise an α-carbanion in order to effect carbon-carbon bond formation by a nucleophilic substitution reaction.

Various model compounds for parts of the C_{20} backbone were prepared to test the practicality of the outlined strategy. Both the synthesis of a number of chiral β-ketosulfoxides and their stereoselective reduction were successfully completed. However, only limited success was achieved in the final carbon-carbon bond formation reaction. From the results it became clear that an alternative strategy for carbon-carbon bond formation using chiral sulfoxides is required and some possible strategies are discussed.

During the course of this study a new method for the synthesis of chiral β-ketosulfoxides from methyl *p*-tolylsulfoxide and an aliphatic nitrile was developed. In addition an improved method for the synthesis of the synthon corresponding to the C-1–C-8 unit of the C_{20} backbone of the fumonisins is presented in the thesis.

OPSOMMING

Fusarium moniliforme is 'n algemene skimmelbesmetting van mielies, 'n basiese stapelvoedsel in die dieet van beide mense en diere. Die skimmel is verantwoordelik vir perde-leukoenkefalomalasie (LEM) en is moontlik ook betrokke by die ontstaan van menslike slukdermkanker. Die struktuur van die fumonisiene, 'n familie van struktureel-verwante mikotoksiene, wat vanuit kultuurmateriaal van *F. moniliforme* verantwoordelik vir LEM geïsoleer is, is bepaal. Fumonisien B_1 is die diester van propaan-1,2,3-trikarboksielsuur met die C-14 en C-15 hidroksi-groepe van (2*S*,3*S*,5*R*,10*R*,12*S*,-14*S*,,15*R*,16*R*)-2-amino-12,16-dimetiel-3,5,10,14,15-pentahidroksi-ikosaan.

Retrosintetiese analise van die C_{20}-ruggraat van fumonisien B_1 deur diskonneksie van die C-10–C-11 binding identifiseer 4,8-dimetiel-1,2,6,7-tetrahidroksidodekaan, sinton **B** en 7-amino-1,4,6-tri-hidroksi-oktaan, sinton **C**, as die sleuteltussenstappe in 'n voorgestelde sintese. Die vorming van dieselfde binding in die sintetiese rigting is meer veeleisend aangesien die vorming van die koolstof-koolstof binding tegelykertyd vereis dat 'n nuwe stereogeniese sentrum in 'n stereospesifieke manier gevorm word. Die werk wat in hierdie verhandeling beskryf word ondersoek 'n strategie vir die vorming van die C-10–C-11 binding van die C_{20}-ruggraat van fumonisien B_1 met die gelyktydige vorming van die C-10 hidroksi-groep deur gebruik te maak van chirale sulfoksied-metodiek. Die metodes wat gebruik word is gebaseer op die hoogs stereoselektiewe reduksie van β-ketosulfoksiede en die vermoë van die sulfoksiedeenheid om 'n α-karbanioon te stabiliseer ten einde koolstof-koolstof binding te bewerkstellig deur 'n nukleofiele substitusiereaksie.

Verskeie modelverbindings vir dele van die C_{20} ruggraat is berei sodat die praktiese uitvoerbaarheid van die aangeduide strategie getoets kon word. Beide die sintese van 'n aantal chirale β-ketosulfoksiede en hulle stereoselektiewe reduksie is suksesvol afgehandel. Slegs beperkte sukses is egter met die finale koolstof-koolstof bindingsvorming behaal. Vanuit die resultate is dit duidelik dat 'n alternatiewe strategie vir koolstof-koolstof bindingsvorming deur gebruik te maak van chirale sulfoksiede, benodig word en 'n aantal moontlike strategieë word bespreek.

In die verloop van die ondersoek is 'n nuwe metode vir die sintese van chirale β-ketosulfoksiede vanaf metiel-*p*-tolielsulfoksied en 'n alifatiese nitriel ontwikkel. Verder word daar ook in die verhandeling 'n verbeterde metode vir die sintese van die sinton wat ooreenstem met die C-1–C-8 eenheid in die C_{20}-ruggraat van die fumonisiene aangebied.

ACKNOWLEDGEMENTS

This M.Sc. study would not have been possible without the unfailing support form my beloved wife.

I really appreciate it and thank you !

I also wish to thank all my friends, family and colleagues who played a major role in helping me to achieve this degree, whether through technical assistance, guidance or moral support. In particular a word of thanks to the following persons;

Prof. Robert Vleggaar for his constant guidance and willingness to help whenever necessary. Also for all the discussions we had and the knowledge and inspiration I gained from him.

Prof. Peet van Rooyen for the crystal structure determination.

Mr. Eric Palmer for thorough training on the NMR spectrometer.

Mr. Leon Engelbrecht for reparations of electronic and mechanical equipment.

AECI Ltd. and the University of Pretoria for financial assistance.

To the Creator of everything, even that what we study, who blessed me with the mental and physical ability to complete this study. Thank you Lord for providing guidance, friends and family and the financial means I needed.

CONTENTS

CHAPTER 5 EXPERIMENTAL

1 INTRODUCTION

1.1 GENERAL

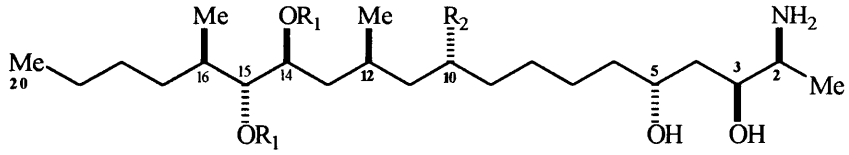
Fusarium moniliforme Sheldom is a common fungal contaminant on a great variety of plant hosts, including maize, a basic human and feedstock staple. Various strains of the fungus are known to be highly toxic and carcinogenic. The metabolites of this fungus include a group of mycotoxins called the fumonisins of which fumonisin B_1 and B_2 are the most important. The toxicological reports on *F. moniliforme* indicate that the consumption of contaminated feed places a wide range of animals at risk.[1,2] Although the liver is affected in most species other organs appear to be species specific: for instance the lungs and pancreas of pigs (pulmary oedema and hydrothorax)[3,4] and the brain in equines (equine leucoencephalomalacia (LEM)).[5,6,7] It has also been reported that *F. moniliforme* exhibits cancer promoting effects and dysfunction of the rat liver[7,8,9] and cancer of the oesophagus in humans.[7,10] However, LEM is the only mycotoxicosis for which the causative role of a fungus, *F. moniliforme* has been established beyond doubt.

1.1.1 Biological Effects of the Fumonisins

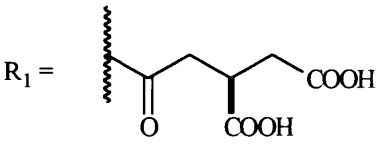
Equine leucoencephalomalacia (LEM) is the most reported animal syndrome associated with the ingestion of *F. moniliforme* contaminated feed. It is a disease characterised by apathy, nervous disorders, paralysis of the lower lip, mobility problems and finally liquefactive necrosis of the white matter of the cerebral hemisphere, causing the eventual death of the animal. The first experimental reproduction of LEM in horses was done as early as 1902 using naturally contaminated mouldy maize, but it was only in 1971 that the causative fungus was identified and the chemical nature of the *F. moniliforme* mycotoxins responsible for LEM remained unknown until 1988, when Gelderblom *et al.*[9,11] reported the isolation of the major toxins, fumonisin B_1 (**1**) and B_2 (**2**). The relative and absolute stereochemistry of the fumonisins however remained unknown at that stage.

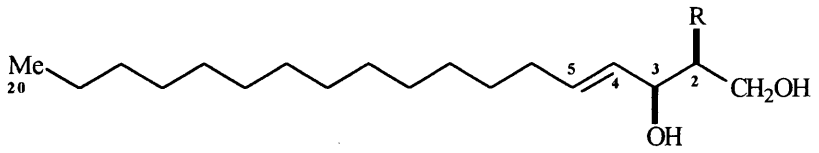
Since then maize-based mixed feed samples, associated with suspected and confirmed outbreaks of animal mycotoxicoses have been successfully analysed for fumonisin B_1 and B_2. These results support the findings of Marasas *et al.*[1] that the fumonisins are the causative agents in the development of LEM.

Although the molecular mechanism of action of the fumonisins remains unknown, the remarkable structural similarity of part of the backbone of the fumonisins and the sphingosines has led to the hypothesis that fumonisin B_1 (**1**) and B_2 (**2**) could be responsible for the inhibition of crucial steps in the biosynthesis of sphingolipids (Fig 1.1).



1 Fumonisin B_1 : R_2 = OH
2 Fumonisin B_2 : R_2 = H





3 Sphingosine : R = NH_2
4 Ceramide : R = $NHCO(CH_2)_{14}CH_3$

Fig 1.1 Structural Relation between the Fumonisins and Sphingosines

Sphingolipids are derivatives of the C_{18} amino alcohols sphingosine (**3**) and dihydrosphingosine and are widely distributed in membranes of plants and eukaryotes and even more importantly, in the nervous tissues of humans and animals. Acylation of the amino group of sphingosine (**3**) by means of N-acyl transferase produces ceramide (**4**) which is the precursor of the sphingomyelins, cerebrosides and gangliosides, compounds prevalent in neuron cells.[12] The primary mode of action by the fumonisins seems to involve the disruption of ceramide formation through inhibition of *N*-acyl transferase. The disruption of this biosynthesis will have profound effects on cell function and

evidence exists which shows that disruption of sphingolipid metabolism occurs in cells of organs known to be effected with LEM and other diseases associated with exposure to the fumonisins.[13,14]

1.1.2 Structure and Stereochemistry of the Fumonisins

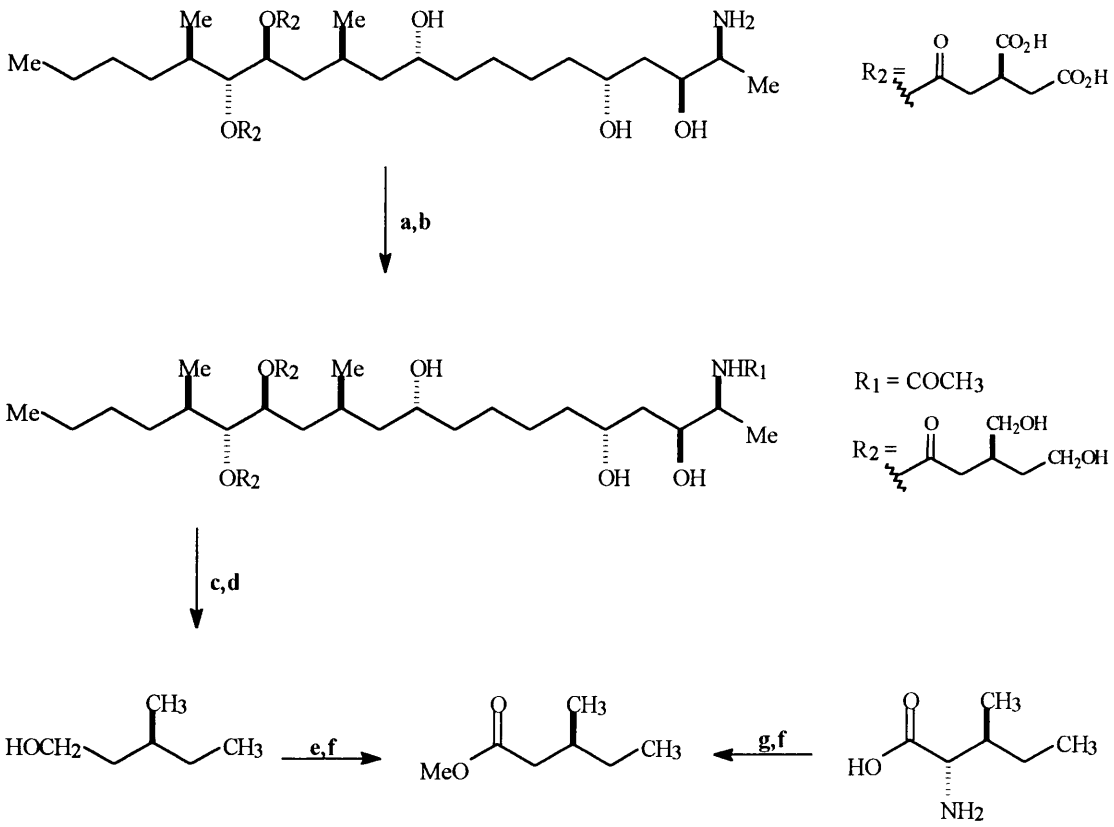
The structures of fumonisin B_1 (**1**) and B_2 (**2**) were elucidated by Gelderblom *et al.*[9,11] using mass spectrometry and NMR spectroscopy as the diesters of propane-1,2,3-tricarboxylic acid and 2-amino-12,16-dimethyl-3,5,10,14,15-pentahydroxyicosane and the C-10 deoxy analogue, respectively. In both cases the C-14 and C-15 hydroxy groups are involved in ester formation.[11] Several other structurally related compounds were isolated but will not be discussed further in this work.

The relative stereochemistry was established by Boer *et al.*[15] The strategy that was employed is based on the formation of the conformationally rigid 1,3-oxazolidinone of fumonisin B_2, (**5**) (Fig 1.2) using the 2-amino and 3-hydroxy groups and determining the relative stereochemistry, by means of n.O.e NMR experiments. This proved a *syn* relationship between the C-2 and C-3 stereogenic centres.[15,16]

The 3,5:14,15 diacetonide derivative of FB_1 (**6**) (Fig 1.2) was prepared and by using a procedure developed by Rychnovsky[17] the relative stereochemistry was determined to be 3,5-*anti*, 14,15-*anti*, 12,14-*syn* and 10,12-*anti*.

The absolute configuration of the stereogenic centres of the fumonisins was determined by using Horeau's method together with NMR techniques.[14-19] The absolute configurations were finally determined to be 2*S*, 3*S*, 5*R*, 10*R*, 12*S*, 14*S*, 15*R* and 16*R*.

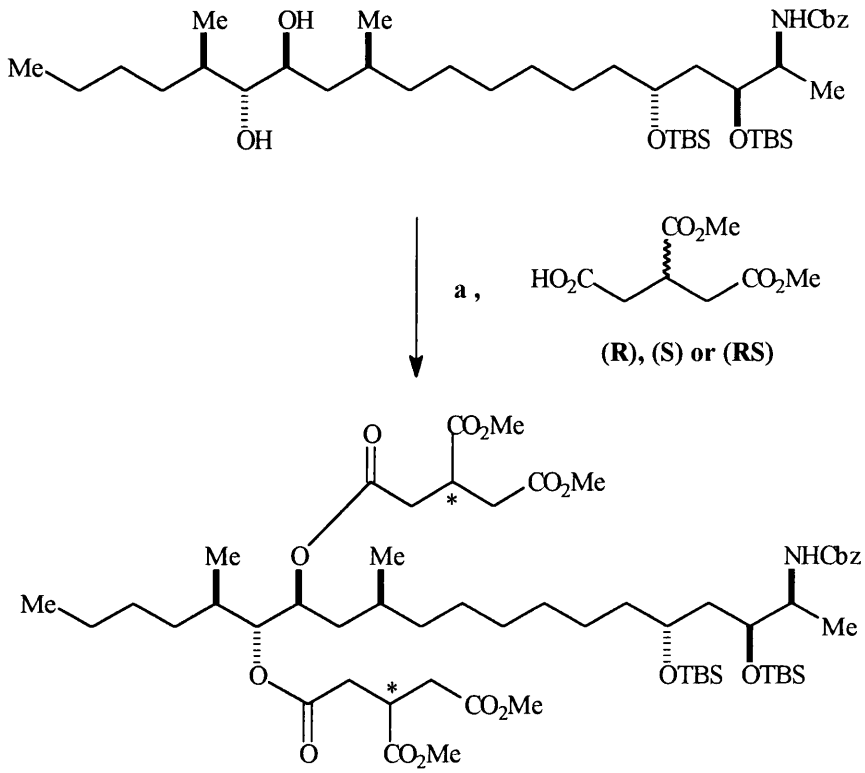
The stereochemistry of the propane-1,2,3-tricarboxylic acid side-chain, situated on both the C-14 and C-15 hydroxy groups was determined by Shier *et al.* to be *S*.[20a] They used chiral gas chromatography to compare the 3-methylvaleric acid methyl ester, derived from the fumonisin side-chain, with authentic (*S*)-3-methylvaleric acid methyl ester (Fig 1.2).



Reagents: a. Ac_2O, K_2HPO_4; b. B_2H_6, THF; c. TsCl, pyr; d. $LiAlH_4$, THF; e. CrO_3, H_2SO_4; f. CH_2N_2; g. $H_2N\text{-}OSO_3H$, NaOH.

Fig 1.2 Stereochemistry of the Fumonisin Side Chain as Determined by Shier *et al.*[20a]

Kishi *et al.* however found the opposite stereochemistry.[20b] They prepared both the *R* and *S* dimethyl esters of the propane-1,2,3-tricarboxylic acid side-chain and re-connected them to the 2,3,5-O-protected diol of fumonisin B_2 (Fig 1.3). Comparison of their ^1H NMR spectra with that of the 2,3,5-O-protected fumonisin having the side-chain derived from the natural compound identified it to be *R*. This procedure was also repeated on fumonisin B_1. The reason for these conflicting results is unknown and therefore the stereochemistry of the side-chain remains unclear.



Reagents: **a. EDC, DMAP, CH_2Cl_2.**

Fig 1.3 **Method used by Kishi *et al.*[20b] to Determine the Stereochemistry of the Fumonisin Side-chain**

1.2 SYNTHETIC STUDIES ON THE FUMONISINS

The synthesis of the C_{20} backbone of the fumonisins, with 8 stereogenic centres, involving both hydroxy and methyl groups, poses an intriguing and very challenging task for synthetic organic chemists.

Earlier work by R.M. Snyman,[14] a former Ph.D. student in Prof. R Vleggaar's group, on the synthesis of the C_{20} backbone of the fumonisins is based on the disconnection of the C-8–C-9 bond in the retrosynthetic analysis of fumonisin B_1 to give a C_{12} synthon (**B**) with 5 stereogenic centres and a C_8 synthon (**C**) with 3 stereogenic centres (Fig 1.4).

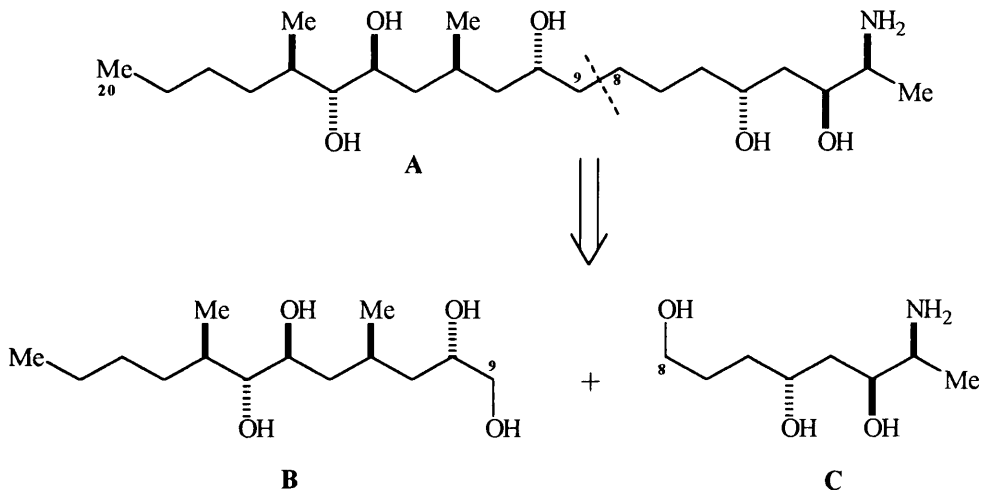


Fig 1.4 Disconnection Approach for Fumonisin B_1

In the case of fumonisin B_2, which lacks the C-10 stereogenic centre, disconnection of the C-10–C-11 bond in a retrosynthetic analysis generates two C_{10} synthons, **E** and **F** (Fig 1.5).

Retrosynthetic analysis of both synthons, **E** and **F**, identified either *D*-glucose or *D*-mannose as starting materials in the synthetic route.

With the availability of synthetic equivalents of the synthons **E** and **F** with the functional groups suitable protected, the assembly of the C_{20} backbone of the fumonisins requires the formation of the C-10–C-11 bond, with no stereochemical demands in the case of fumonisin B_2, as no stereogenic centres are created.

The formation of the same bond with fumonisin B_1 as the target, using the same substrates, places greater demands on the formation of the new carbon-carbon bond as it is necessary to generate at the same time a new stereogenic centre in a stereodefined fashion.

The work presented in this thesis investigates a strategy for the formation of the C-10–C-11 bond in fumonisin B_1 with the concomitant introduction of the C-11 hydroxy group by employing chiral sulfoxides.

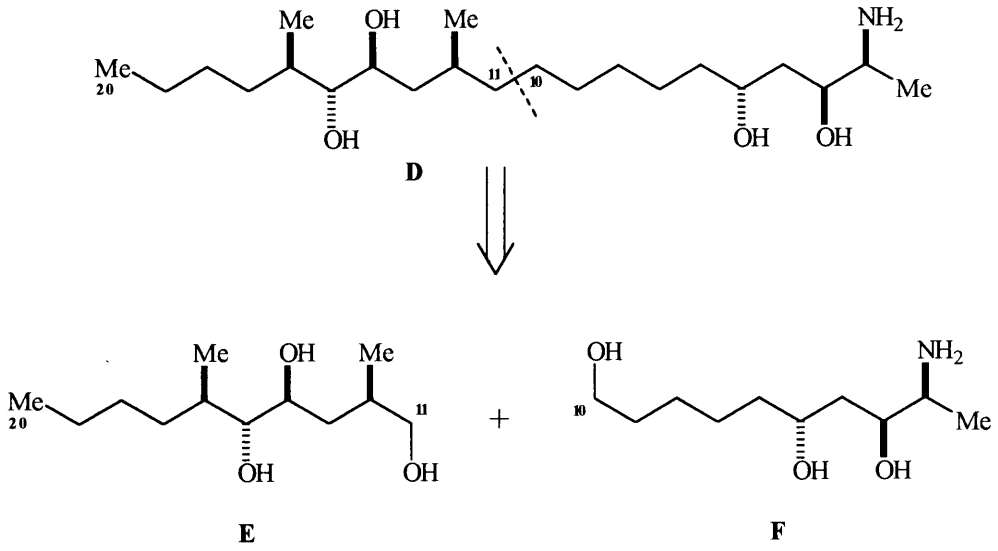


Fig 1.5 **Disconnection Approach for Fumonisin B_2**

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2 CHIRAL SULFOXIDE CHEMISTRY

2.1 GENERAL

"Sulfur based reagents have become an essential part of the armoury of synthetic chemists. A knowledge of the chemistry of sulfur compounds and of the reactivity of sulfur reagents, together with an understanding of the mechanisms involved, is an essential part of any modern organic chemistry course." Stephen G. Davies, 1995.[1]

"Over the last few years, the impact of organo-sulfur chemistry, especially in the areas of heterocyclic chemistry, stereocontrolled processes and the production of nonracemic materials, has led to an explosion of interest in the field and a rapidly growing number of related publications." Philip Page, 1995.[2]

"During the last decade, organic sulfur compounds have become increasingly useful and important in organic synthesis." Guy Solladié.[3]

Judging from these quotes from various experts, the use of organo-sulfur compounds is of major importance in the field of organic synthesis. The relative ease with which sulfur can be incorporated into a molecule, used to effect various functional group transformations and subsequently be removed has made it an attractive tool in organic synthesis.

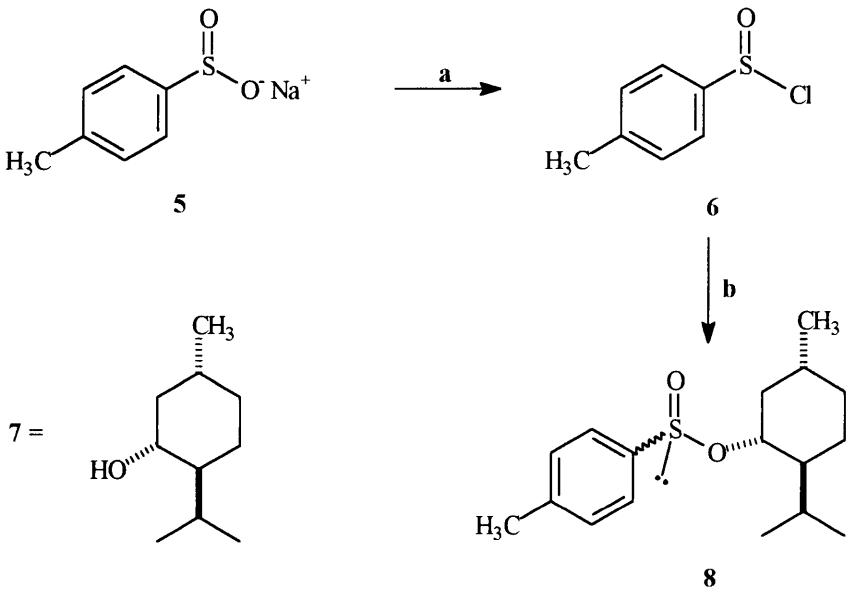
2.2 THE DEVELOPMENT OF CHIRAL SULFOXIDE CHEMISTRY

The chemistry of chiral sulfoxides started with the pioneering work of Harrison *et al.*[4] on the optical resolution of sulfoxides as early as 1926. Since then there has been an exponential growth in the use of chiral sulfoxides and the scope of applications, as evidenced by the number of reviews published on the subject.[5] Attention is therefore directed only at specific parts relating to the work covered in this thesis in order to create a general background.

2.2.1 Synthesis of Chiral Sulfoxides

Many approaches have been followed in order to obtain optically active sulfoxides. Optical resolution was used in resolving ethyl *p*-tolylsulfoxide.[6] Stereoselective oxidations of the corresponding sulfides with peracids using a modified Sharpless reagent as reported by Kagan[7] and enzymatic oxidations[8] are some of the more notable successes.

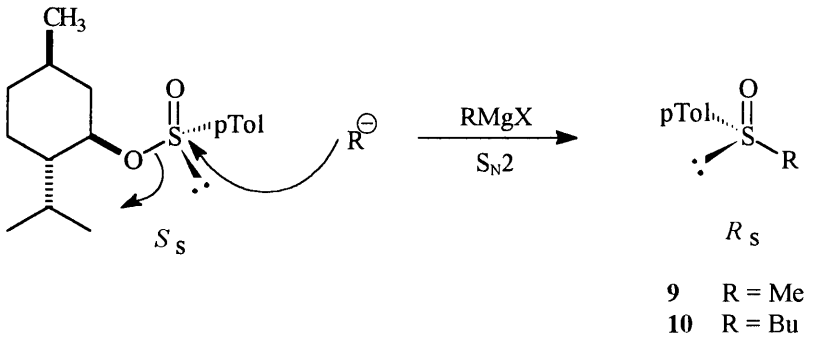
Although these methods yield compounds of high optical purity, a more general approach is found in the Anderson synthesis[9] and the improvements reported by G. Solladié.[10] The *p*-toluenesulfinate ester of (-)-menthol, prepared as reported by Phillips,[11] involves the reaction of *p*-toluenesulfinyl chloride and (-)-menthol. Very little stereoselection is observed and a ~ 1:1 mixture of diastereomers is formed (Fig 2.1). This mixture can, however, be epimerised in the presence of a catalytic amount of concentrated hydrochloric acid, and as only the (-)-(*S*) isomer crystallises from acetone, up to 80% of the mixture is converted to the crystalline (-)-(*S*) isomer in high e.e.(98%).[10]



Reagents: **a. $SOCl_2$; b. pyridine, 7**

Fig 2.1 **Preparation of (-)-(*S*)-Menthyl *p*-Toluenesulfinate**

(-)-(*S*)-Menthyl *p*-toluenesulfinate can then be reacted with methyl magnesiumiodide (Fig 2.2) in benzene at 0°C to give, after a crystallisation step to remove the formed menthol, (+)-(*R*)-methyl *p*-tolyl sulfoxide with high e.e. (98%) and chemical yield.



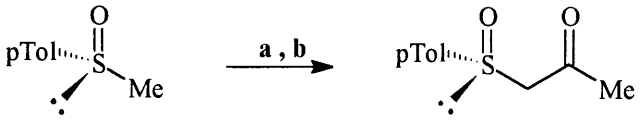
9 R = Me
10 R = Bu

Fig 2.2 Preparation of Sulfoxides by means of S_N2 Inversion

This is still the most important and widely used method today even though it is limited to the preparation of (*R)* sulfoxides with *p*-tolyl as the aromatic substituent. The same epimerisation/crystallisation process for the phenyl analogue does not occur.

2.2.2 β-Ketosulfoxides

The ability of a sulfoxide group to stabilise an α-carbanion has been exploited in various ways. One of the applications is the reaction with esters to yield β-ketosulfoxides (Fig 2.3). Corey[12] was the first to prepare racemic β-ketosulfoxides and Kunieda *et al.*[13] prepared the first optically pure compound while Solladié has optimised the reaction conditions.[14] The ester is added to a cold solution of 2 equivalents of the α-carbanion of (+)-(*R*)-methyl *p*-tolylsulfoxide (**9**). The use of 2 equivalents of carbanion is mandatory as the methine protons of the formed product are more acidic than the reagent. However, the formed product anion has a low nucleophilicity and does not react with the ester.



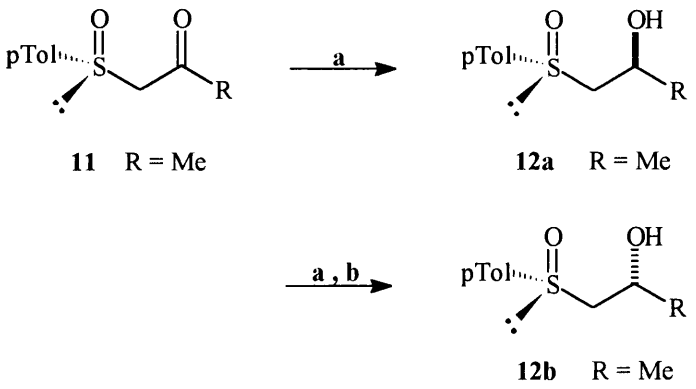
9 **11**

Reagents: **a. LDA, -40°C ; b. EtOAc**

Fig 2.3 **Preparation of β-Ketosulfoxides**

2.2.3 Stereoselective Reduction of β-Ketosulfoxides

Arguably the most important application of chiral sulfoxides is their ability for chiral induction in the reduction of β-ketosulfoxides with diisobutyl aluminium hydride (DIBALH) in the presence or absence of $ZnCl_2$ or $ZnBr_2$. Early experimentation by Annunziata and Cinquini[15] with lithium aluminium hydride ($LiAlH_4$) and sodium borohydride ($NaBH_4$) gave only a 60-70% d.e. – a level of asymmetric induction hardly worth mentioning. Solladié *et al.*[16] found an increase in diastereoselectivity when DIBALH was added at low temperatures to the substrate instead of adding the substrate to cold solutions of DIBALH. They also found simultaneously with Kosugi *et al.*[17] that the presence of $ZnCl_2$ resulted in a reverse selectivity also with a very high d.e. (Fig 2.4). With the optimised reaction conditions, diastereomeric ratios of higher than 95:5 can be achieved for either the *RR* or *RS* diastereomers even with small alkyl groups as substituents. This procedure has established chiral sulfoxides as one of the best methods of preparing a hydroxyl bearing stereogenic centre, and has been used especially by Solladié in many natural product syntheses.[14,18]



11 R = Me **12a** R = Me

12b R = Me

Reagents: **a. DIBALH, -78°C ; b. DIBALH, $ZnCl_2$, -78°C**

Fig 2.4 **Stereoselective Reduction of β-Ketosulfoxides**

Different explanations have been proposed for the high stereoselectivity achieved in these reductions.[19 20] The easiest way of explaining the mode of action of DIBALH and DIBALH/$ZnCl_2$ is shown in Figure 2.5 and was first proposed by Solladié *et al.* and Garcia Ruano *et al.*[19] This theory is based on the fact that the two polar groups (*i.e.* the sulfoxide and carbonyl groups) will be directed away from each other, the *Re*-face of the carbonyl will then be less sterically hindered than the *Si*-face leading to the formation of the (*S*) alcohol. When $ZnCl_2$ is added it will chelate with both the sulfoxide and carbonyl groups so that they are now parallel, causing the *Si*-face to be less sterically hindered and consequently the (*R*) alcohol is formed.

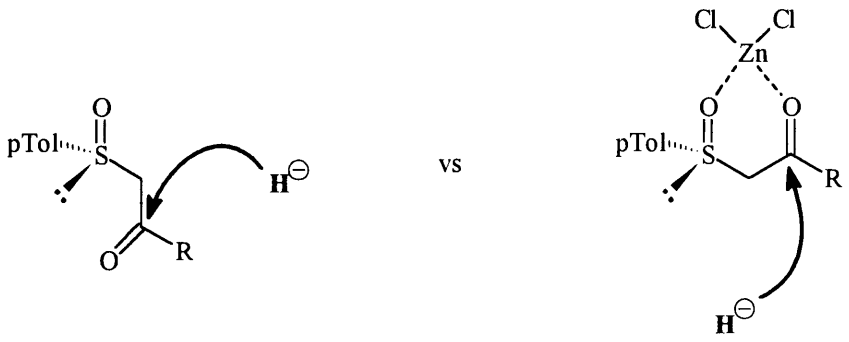


Fig 2.5 Stereoselective Reduction: First Mechanistic Explanation

Recently Solladié and Garcia Ruano[20] proposed a new and more complicated model (Fig 2.6). In this model they postulate that hydride transfer is intramolecular instead of the previously believed intermolecular mechanism. In the favoured twisted conformation C_1 where the *p*-tolyl group is pseudo-equatorial, DIBALH will approach by complexation with the geometrically well-located chlorine atom, leading to the bimetallic bridged species, M_1. Hydride transfer will now be intramolecular from the top to the *Si*-face, leading to the (*R*) configuration at C-2. In the other possible conformation, C_2, the *p*-tolyl group is in a unfavourable pseudo-axial position which will greatly hinder hydride transfer from the bottom to the *Re*-face. For the reduction reaction without $ZnCl_2$ they also postulate a bimetallic bridged species, M_3, which will, through intramolecular hydride transfer, lead to the (*S*) configuration at C-2.

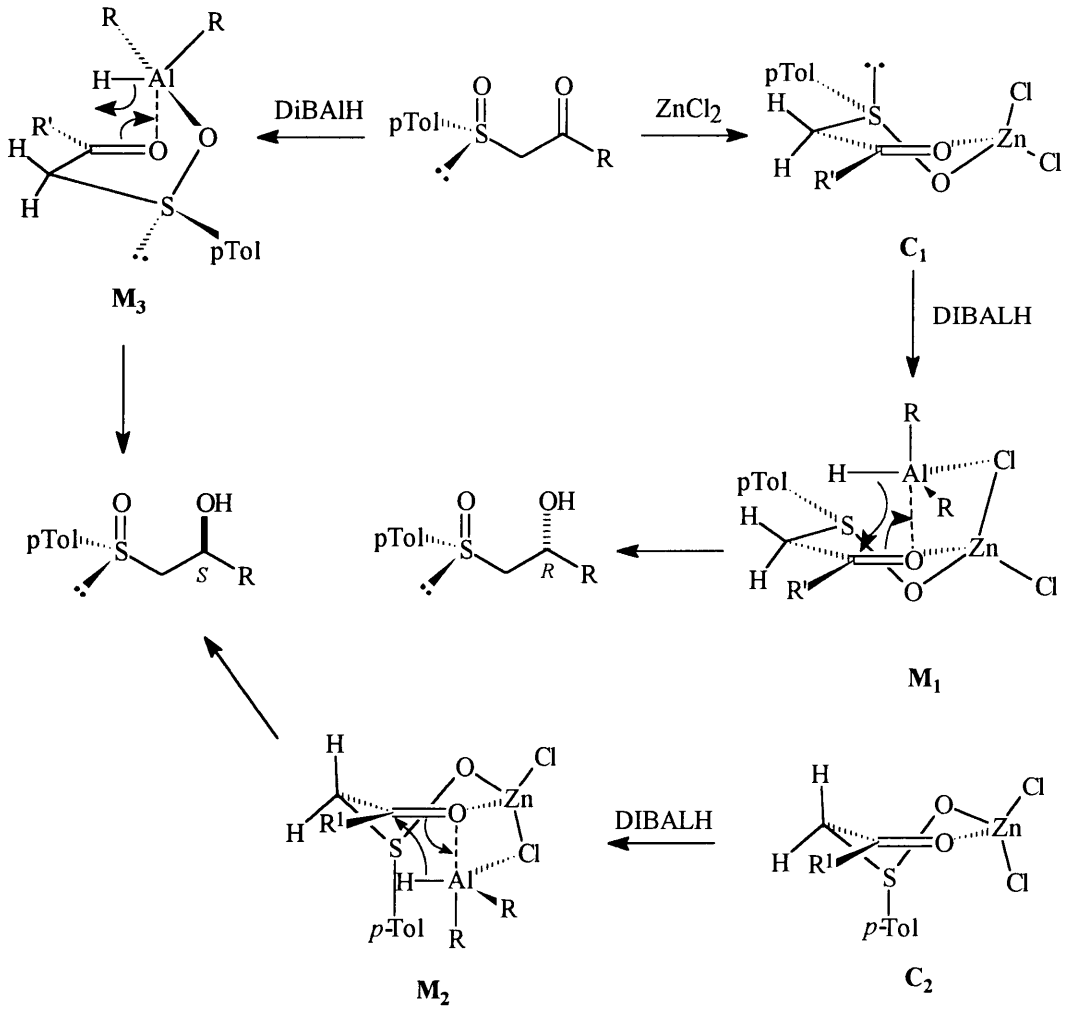


Fig 2.6 **Stereoselective Reduction: Intramolecular Hydride Transfer Model**

2.2.4 α-Alkylation of β-Hydroxysulfoxides

The introduction of an alkyl group at the α-position to the sulfoxide is of special importance in the context of this thesis as it forms the basis for the formation of the C_{20} backbone of the fumonisins from two synthons identified by retrosynthetic analysis.

The ability of sulfur compounds to stabilise α-carbanions is well known. The parent sulfoxide compound, DMSO, has a pK_a value of 35.1 and that of phenyl methylsulfoxide is slightly lower at ~33, compared to dimethylsulfone with a pK_a (DMSO) value of 31.1 and phenyl methylsulfone, with 29.0. This puts the acidity of a proton α to a sulfoxide group between that of a benzylic proton (pK_a 35-40) and that of a sulfone. The acidity of the methylene protons of a β-hydroxysulfoxide fall in the

same region (pK_a 33-36). Addition of two equivalents of a strong base such as LDA or n-BuLi to a β-hydroxysulfoxide leads to abstraction of both the hydroxy group proton and one of the methylene protons α to the sulfoxide group to form a dianion. This dianion most likely forms a six-membered ring through chelation of the two oxygen atoms with the lithium cation (Fig 2.7).[21] A similar complexation by means of intramolecular hydrogen bonding between the hydroxy group proton and the oxygen atom of the sulfoxide is postulated for the parent β-hydroxysulfoxide.[21,22] The chair conformation with both the aryl and alkyl groups in a equatorial position is expected to be the most stable.

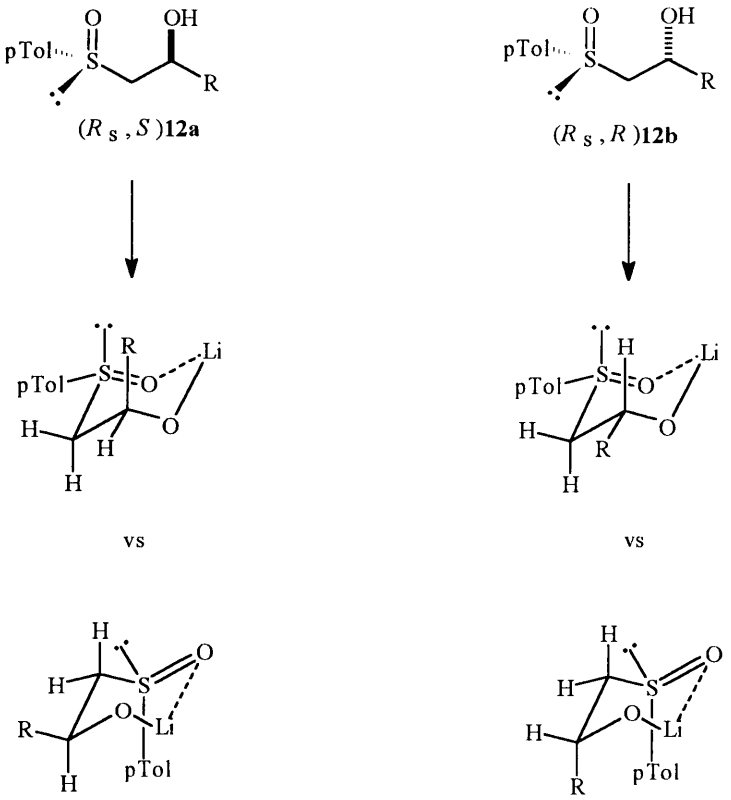


Fig 2.7 Chelation of β-Hydroxysulfoxide Anions with Lithium Cations

As a result alkylation of the dianion of a chiral β-hydroxysulfoxide is expected to be highly stereoselective. Complementary results confirm that the stereoselectivity of the alkylation depends mainly on the configuration of the hydroxyl bearing stereogenic centre.[21,5a,i] The configuration of the sulfur stereogenic centre appears to play no role or at best a minor role in determining the stereochemical course of this reaction. As can be seen in Fig 2.8, the *threo* product (in which the hydroxy and alkyl (R') groups are *anti*) is favoured over the *erythro* product in ratios varying

between 1:1 to 95:5. A characteristic of this reaction, not always explicitly stated in the reported literature, is that with increasing size of the alkyl groups (R, R') yields drop considerably and reactions are sluggish. A further observation is that in the reported procedures phenyl β-hydroxyalkyl sulfoxides are used almost exclusively instead of the more available *p*-tolyl analogues.

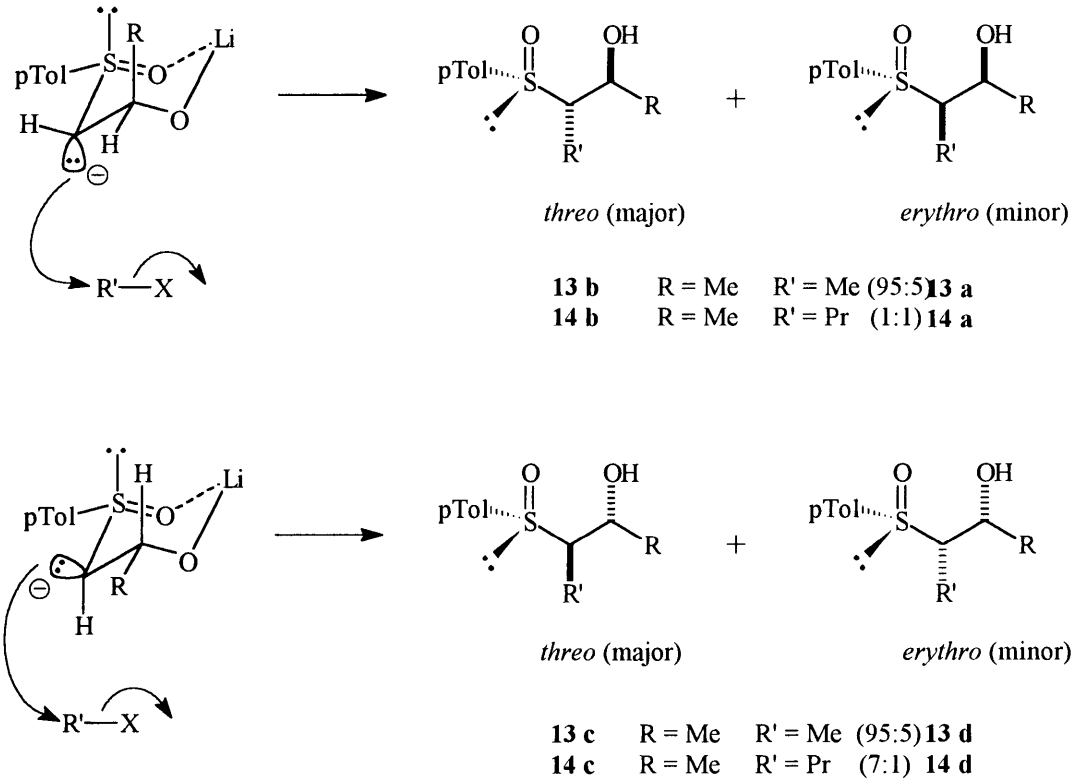


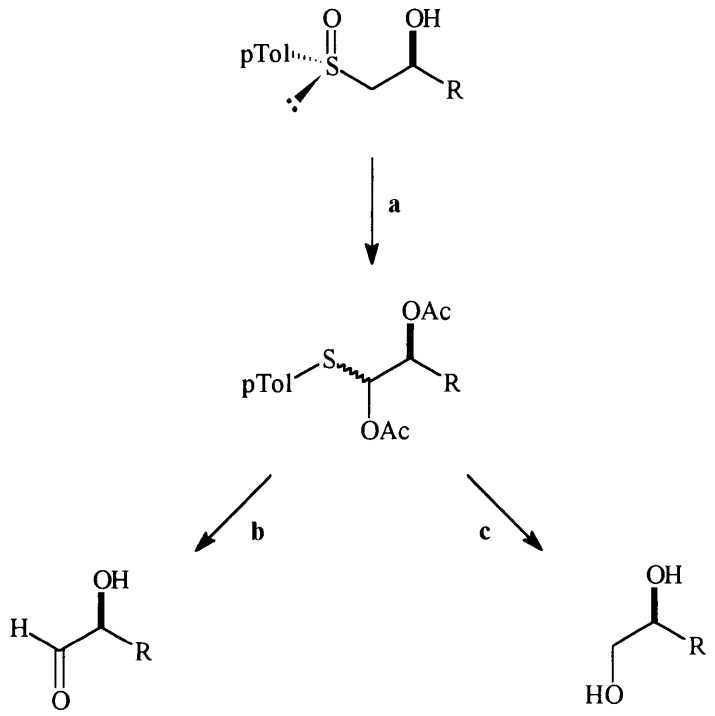
Fig 2.8 Alkylation of β-Hydroxysulfoxides

2.2.5 Functional Group Transformations Involving the Sulfoxide Moiety

One of the advantages of sulfoxides is the relative ease with which they can be converted by various reactions into several other functionalities.

Several methods are known for the reductive removal of the sulfoxide group of which catalytic hydrogenation using Raney nickel,[23] sodium-amalgam with disodium hydrogen phosphate (Na_2HPO_4),[24] and lithium metal[25] in diethylamine (Et_2NH) at -78°C are the most important and lead to the replacement of the sulfoxide group with a hydrogen atom.

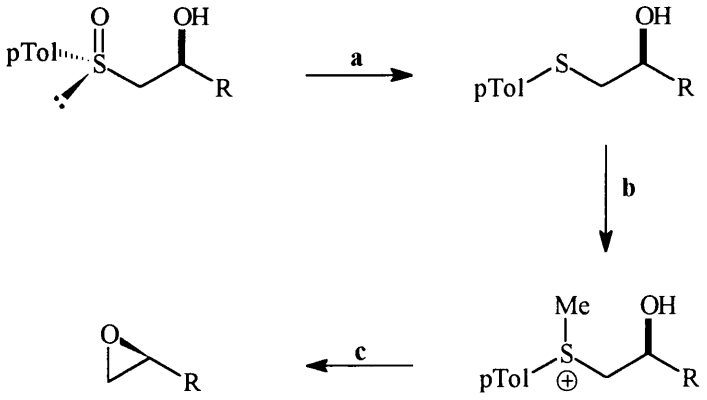
The well-known Pummerer rearrangement[26,27] of sulfoxides enables one to remove the sulfur part of the molecule while retaining functionality at the carbon atom previously substituted by the sulfoxide group (Fig 2.9). The *p*-tolylsulfide O,O-diacetate product of the Pummerer reaction of a β-hydroxysulfoxide is in fact an O,S-acetal. When the β-hydroxy group is protected with an ether protecting group, this O,S-acetal can be cleaved by either Cu(II) or Hg(II) salts in aqueous $MeOH/CH_3CN$ to yield a β-hydroxy aldehyde,[27] or in anhydrous methanol with $HgCl_2$ to give the dimethyl acetal. It is important to note that unprotected β-hydroxy aldehydes may epimerise or even isomerise to α-hydroxy-ketones. The O,S-acetal may also be reduced with DIBALH or $LiAlH_4$[18d,22b] or desulfurised by using Raney nickel catalysed hydrogenation[27a] to the diol (protection of the C-2 hydroxy group will have to be done first to distinguish it from the C-1 hydroxy group).



Reagents: **a. Ac_2O, NaOAc ; b. $HgCl_2/MeCN/H_2O$ or $CuCl_2$/ $MeCN/H_2O$; c. $LiAlH_4$**

Fig 2.9 **Pummerer Rearrangement Followed by Removal of the Sulfur-containing Group**

Another promising method for the removal of the sulfoxide group involves the formation of an epoxide. The sulfoxide is first reduced with $LiAlH_4$,[20a] Zn/Me_3SiCl,[28] trifluoroacetic anhydride and NaI in acetone [27a] or ^tBuBr in chloroform[29] to the corresponding sulfide. Treatment of the sulfide with $Me_3O^+BF_4^-$ gives the sulfonium salt[27a] which is immediately reacted with aqueous NaOH or K_2CO_3[28b] to form the epoxide (Fig 2.10).



Reagents: **a. $LiAlH_4$; b. $Me_3O^+BF_4^-$; c. $NaOH_{(aq)}$.**

Fig 2.10 **Conversion of Hydroxysulfoxides into Epoxides**

It is important to keep in mind that sulfoxides are readily oxidised to sulfones or reduced to sulfides. The chemistry of these two functional groups has been reviewed.[26,30]

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3 RETROSYNTHETIC ANALYSIS OF THE FUMONISINS

3.1 GENERAL

In the early days of organic synthesis the focus was on chemical change in the direction of chemical reactions i.e. reactants → products. Most syntheses were developed by selecting a suitable starting material (often by trial and error) and searching for a set of reactions which in the end transformed that material to the desired product (synthetic target or TGT). By the mid-1960's a different and more systematic approach started to become more popular with synthetic chemists. This approach depends on the structural features in the *reaction products* (as contrasted with starting materials) and the manipulation of structures in the reverse-synthetic sense. This method became known as *retrosynthetic* or *antithetic* analysis and its merits and power is evident from the way it has simplified and accelerated the planning process of synthetic routes and from the explosion in the number of natural products synthesised over the last few decades.

Retrosynthetic analysis is a problem solving technique for transforming the structure of a *synthetic target* (TGT) molecule to a sequence of progressively simpler structures along a pathway which ultimately leads to simple or commercially available starting materials. The transformation of a molecule to a synthetic precursor is accomplished by the application of a transform, the exact reverse of a synthetic reaction, to a target structure. Each structure derived antithetically from a TGT then itself becomes a TGT for further analysis. Repetition of this process eventually produces a tree of intermediates having chemical structures as nodes and pathways from bottom to top corresponding to possible synthetic routes to the TGT.[1]

When one applies this process to fumonisin B_1 various bond disconnections (the reactions in the synthetic direction) identifying different chirons come to mind. These possible disconnections are limited to only a few when chiral sulfoxides are taken as a variable. The simultaneous stereochemical demands of C-10 on

the disconnection also limited the possibilities and only 3 retrosynthetic analyses were further investigated.

3.1.1 Disconnection of the C-10–C-11 Bond Using a C-11 Sulfoxide

The introduction of the chiral sulfoxide group at C-11 in the retrosynthetic analysis of the C_{20} backbone dictates the strategic disconnection of the C-10–C-11 bond and generates two C_{10} units, **I** and **L**, respectively (Fig 3.1) in the first strategy. The left-hand unit, **I**, corresponding to C-11–C-20, and carrying the chiral sulfoxide group at C-11, can be prepared from the corresponding Grignard reagent, fragment **J**, and (-)-(*S*)-menthyl-*p*-toluenesulfinate, in an S_N2 reaction that proceeds with inversion of configuration at sulfur. The right-side unit **L** corresponding to C-1–C-10 of the backbone requires the presence of an ester functional group at C-10.

In the synthetic direction two problems were identified that could lead to the downfall of this approach. Although the reaction of (-)-(*S*)-menthyl-*p*-toluenesulfinate proceeds with inversion of configuration and in high yield with simple one-carbon Grignard reagents, an excess of reagent is required and results with more complex Grignard reagents are less promising.[2]

Another problem may be encountered in the stereoselective reduction of the β-ketosulfoxide precursor **H**: excellent results are obtained in the absence of α-substituents but the presence of an α-substituent may jeopardise the stereoselectivity.

Little is known about the stereoselective reduction of α-alkylated β-ketosulfoxides. Results published by Bravo *et al.*[3] indicate that the reduction with DIBALH or DIBALH/$ZnCl_2$ is mainly controlled by the C-α configuration (1,2-induction) and not by the configuration at the sulfur atom. Results by Ruano *et al.*[4] contradict these results and show that 1,3-induction is much more important than 1,2-induction especially when $ZnBr_2$ (in large excess), instead of $ZnCl_2$, is used. The use of this reaction to prepare α-alkylated β-hydroxysulfoxides has, however, not attracted much attention from synthetic chemists until now.

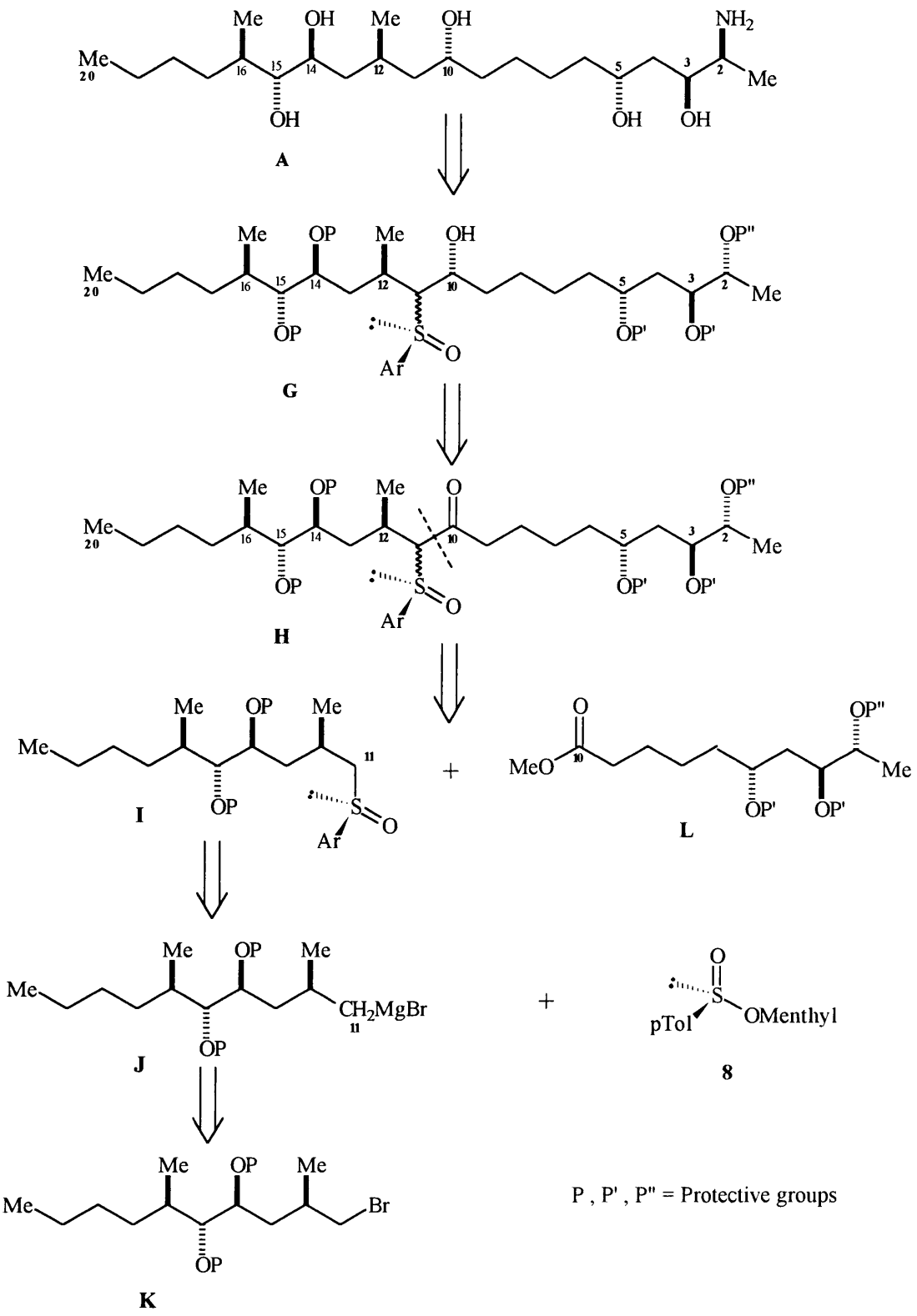


Fig 3.1 **Disconnection of the C-10–C-11 Bond Using a C-11 Sulfoxide**

3.1.2 Disconnection of the C-8–C-9 Bond Using a C-9 Sulfoxide

The second strategy in the retrosynthetic analysis of the C_{20} backbone involves the disconnection of the C-8–C-9 bond by placement of the chiral sulfoxide group at C-9, to give a C_{12}- and a C_8- unit (Fig 3.2). The C_{12} unit, **N**, corresponds to C-9–C-20 and contains a β-hydroxysulfoxide group which results from stereoselective reduction of the β-keto precursor, **O**. There is ample literature precedence that shows that the stereochemical outcome of this reduction is determined by the choice of reagent and is predictable and highly stereoselective (see Section 2.2.3). Disconnection of the C-9–C-10 bond identifies the ester, **P**, and the chiral sulfoxide, **9**, as building blocks in the synthetic sequence.

The C_8 unit, **Q**, corresponds to C-1–C-8 and contains three stereogenic centres. Further analysis suggests the disconnection of the C-6–C-7 bond to arrive at a C_6 building block that can be prepared from the readily available and cheap D-mannose.[5]

This information, in conjunction with the data on the reduction of α-alkylated β-ketosulfoxides outlined above (see 2.2.3), indicates that the reduction of the β-ketosulfoxide should precede the carbon-carbon bond formation step in the order of synthetic events.

3.1.3 Disconnection of the C-9–C-10 Bond Using a C-9 Sulfoxide

The third strategy once again locates the chiral sulfoxide group at C-9 but now with the disconnection of the C-9–C-10 bond instead of the C-8–C-9 bond as in the second strategy (Fig 3.3). The disconnection of the C-9–C-10 bond occurs after a change of oxidation state at C-10 to generate the C_{11} ester, **P**, containing the 4 stereogenic centres of the C-10–C-20 fragment and a C-9 chiral sulfoxide, **S**. Further analysis of the latter synthon suggests the disconnection of the C-8–C-9 bond to give the chiral sulfoxide reagent, **9**, and once again the C_8 unit, **Q**.

An alternative approach to **S** identifies (-)-(*S*)-menthyl-*p*-toluenesulfinate (**8**) and the Grignard reagent, **T**, as building blocks. However, the relative ease with which the C_8 unit can be obtained and the possible problems associated with the use of the Grignard reaction as outlined earlier (see 3.1.1) make this alternative less viable.

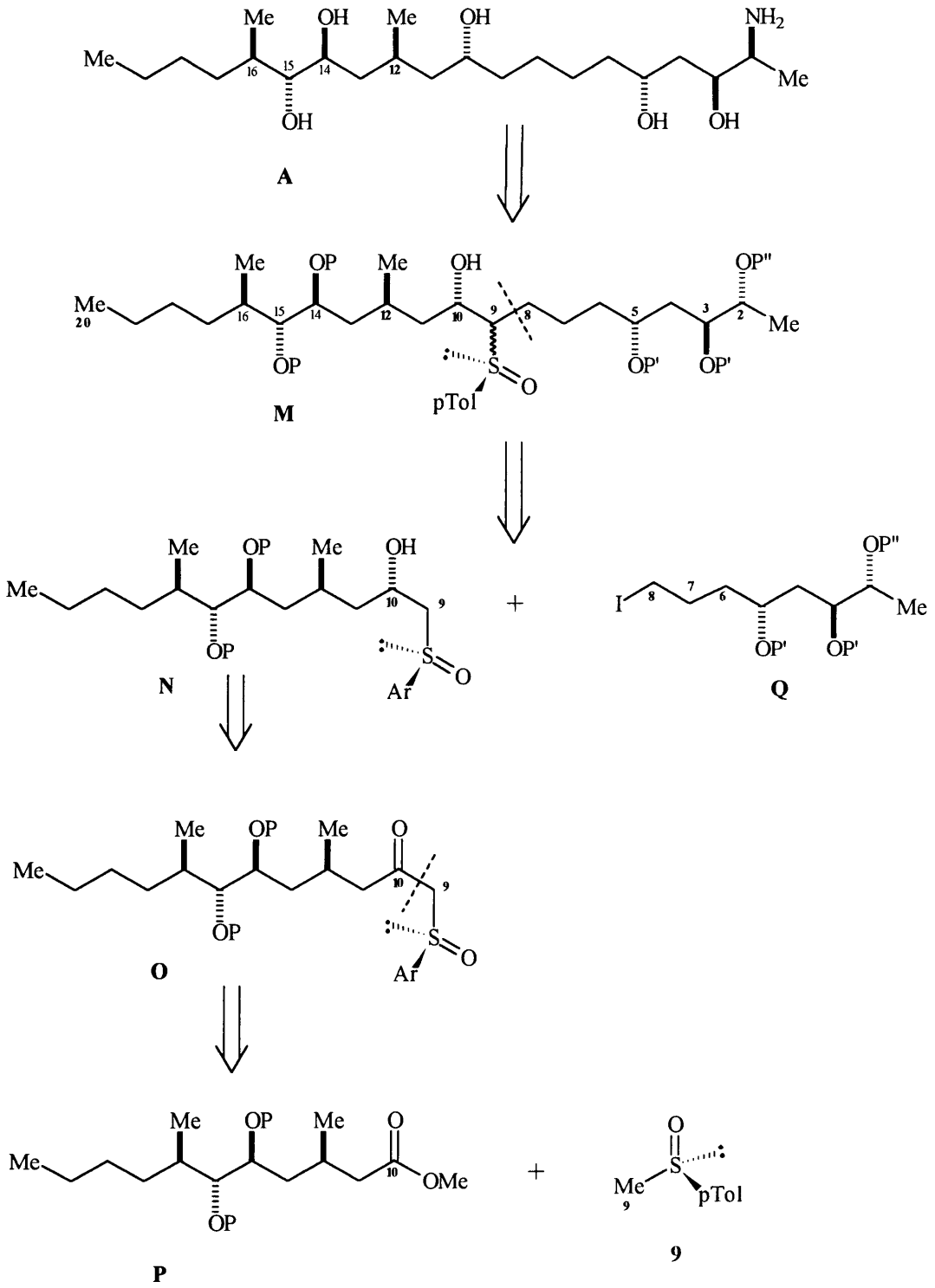


Fig 3.2 **Disconnection of the C-8–C-9 Bond Using a C-9 Sulfoxide**

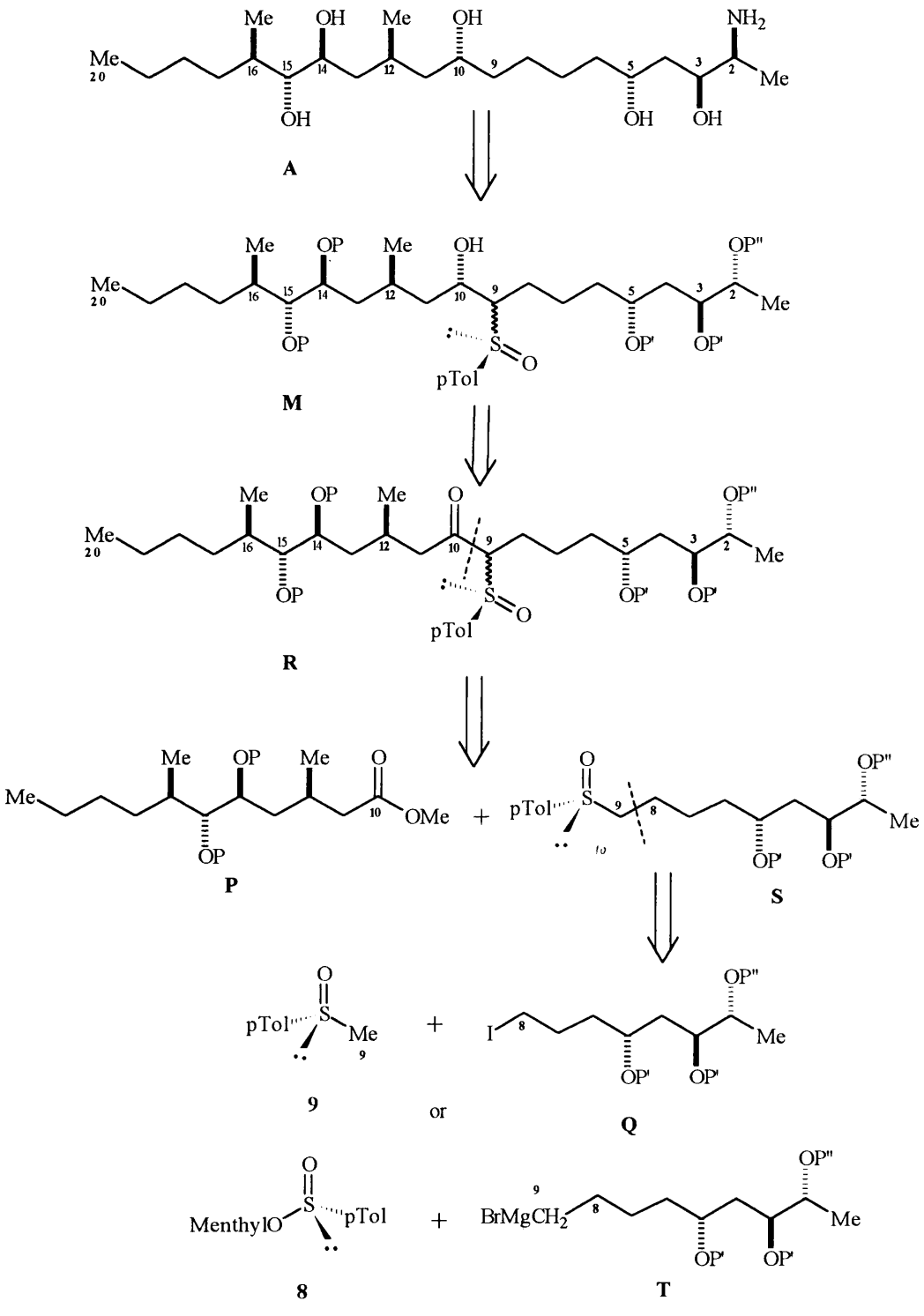
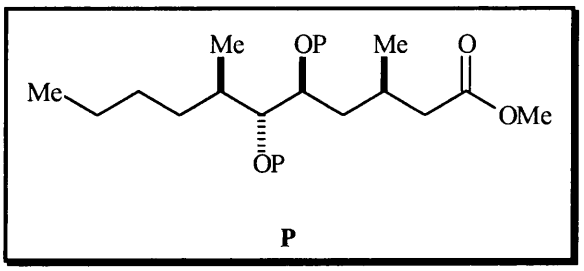


Fig 3.3 **Disconnection of the C-9–C-10 Bond Using a C-9 Sulfoxide**

This third strategy once again involves the reduction of an α-alkyl β-ketosulfoxide moiety and as outlined in 3.1.1, makes it a less attractive proposition.

Evaluation of the three different strategies outlined above led to the selection of the second one for the process of carbon-carbon bond formation and generation of the C-10 stereogenic centre, as it was considered to present the least problems and the best chance of success. All further discussions are directed at preparing the different fragments, **N-Q** or their applicable model compounds.

3.2 RETROSYNTHETIC ANALYSIS OF THE C-10–C-20 UNIT, P



P

Previous endeavours on the synthesis of the left-hand side of the C_{20} backbone of the fumonisins utilised carbohydrates as chiral templates for the synthesis of the C_6 synthons corresponding to the C-11–C-16 and C-9–C-14 units.[5]

The present synthesis proposed for the unit **P** does not use carbohydrates as chiral templates and is based on a retrosynthetic analysis that utilises two aspects of asymmetric synthesis: the chiral auxiliary mediated aldol methodology developed by Evans,[6] and Sharpless asymmetric epoxidation.[7]

The synthetic target, **P**, can be traced back retrosynthetically to compound **15** by disassembly of the C-10–C-11 bond and functional group manipulations. In the synthetic direction the primary alcohol in **15** can be converted to the tosylate followed by a one-carbon chain elongation reaction using sodium cyanide. Alkaline hydrolysis of the resulting nitrile to the acid followed by esterification with diazomethane leads to the required methyl ester, **P**.

The C-15–C-16 bond in **15** was projected to arise from an Evans asymmetric aldol reaction between a C-15 aldehyde (**19**) and a (*Z*)-boron enolate derived from oxazolidinone **18**. This methodology is a powerful tool for the reagent-controlled strategy for achieving stereochemical control because the stereodirecting influence of the oxazolidinone chiral auxiliary can override the modest diastereofacial preference of a chiral aldehyde. On the basis of substantial precedence, there is good reason to believe that such a coupling between **19** and the oxazolidinone **18** will exhibit excellent *syn* diastereoselectivity and that the (1*S*,2*R*)-norephedrine-derived chiral auxiliary will define the absolute stereochemistry at carbons 15 and 16. After it has served its purpose the chiral auxiliary in the aldol product (**17**) can be reductively cleaved. Further reduction of the hydroxymethyl group furnishes the C-16 methyl group.

Functional group manipulation and protection of the aldehyde (**19**) in the retrosynthetic direction identifies epoxide **23** as a key intermediate. In the synthesis direction protection of the primary alcohol as the *t*-butyldimethylsilyl ether followed by regio- and stereoselective opening of the epoxide ring using LiI,[8] to give an iodohydrin which on treatment with AIBN and Bu_3SnH is converted to compound **22**. Protection of the secondary hydroxy group as the benzyl ether and deprotection of the primary hydroxy group, using F^-, followed by Swern oxidation gives aldehyde **19**.

Retrosynthetic analysis of the chiral epoxide (**23**) identifies the *E*-allylic alcohol (**24**) as precursor by using Sharpless asymmetric epoxidation technology.[7] The construction of the *E* double bond in the unsaturated ester (**25**), the projected precursor of the allylic alcohol (**24**), requires the use of Wadsworth-Emmons methodology using the chiral aldehyde (**26**). Aldehyde **26**, a compound with a single stereogenic centre, could, in principle, be fashioned by functional group manipulation of the commercially available methyl (2*S*)-3-hydroxy-2-methylpropanoate (**29**).

In the synthetic direction the chiral ester (**29**) is used for introducing the C-12 stereogenic centre. Protection of the hydroxy group and reduction of the ester functionality gives a monoprotected diol. Swern oxidation of the primary alcohol gives the aldehyde (**26**) which is utilised in a Wadsworth-Emmons reaction with a C_2 phosphonate reagent to yield the *E* α,β-unsaturated ester **25**. The allylic alcohol structural motif required for the Sharpless asymmetric epoxidation is established by reduction of the ester functionality by using DIBALH. The epoxidation of allylic alcohols by the Sharpless method is very predictable and proceeds with exceptional stereofacial selectivity which is determined by the chirality sense of the dialkyltartrate used for the formation of the Ti-tartrate complex. Thus it is expected that the use of (*S*,*S*)-diethyltartrate will lead to the formation of epoxide (**23**).

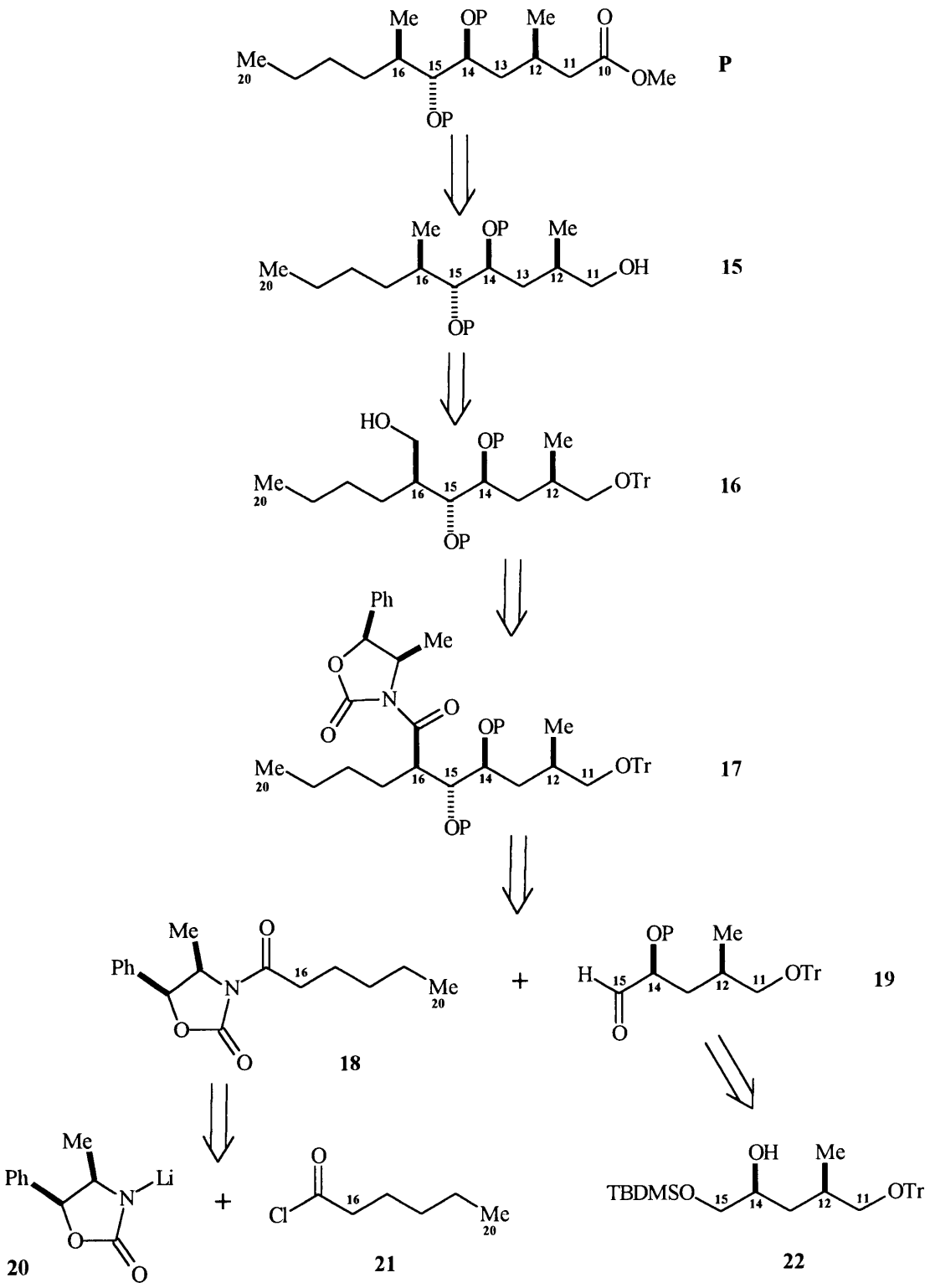
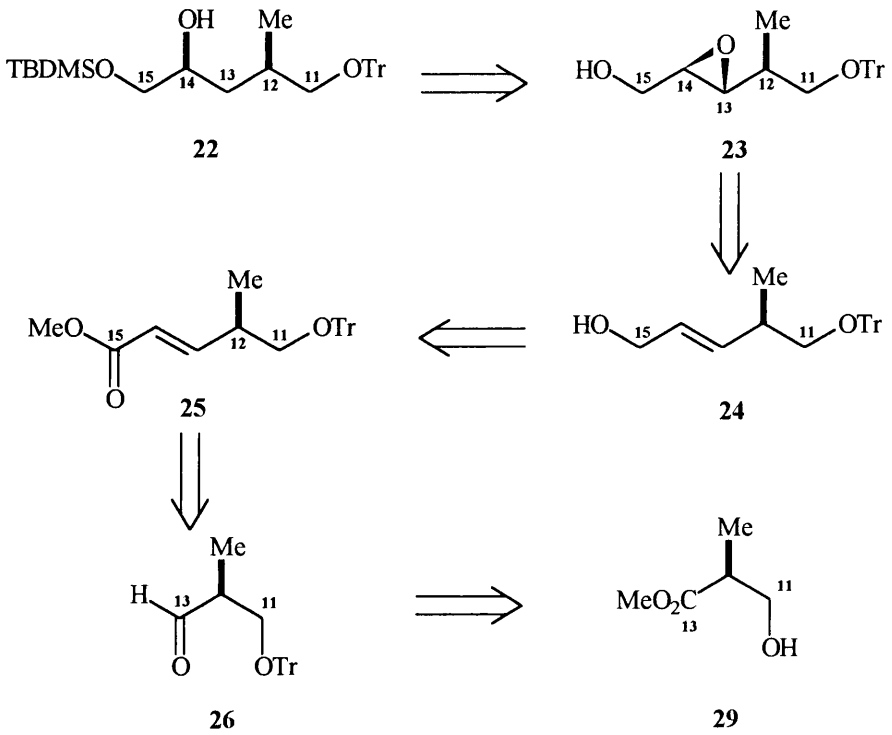


Fig 3.4 **Retrosynthetic Analysis of the C-11–C-20 Unit, P**

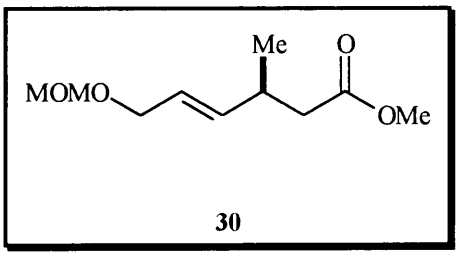
(continued)



3.3 SYNTHETIC STUDIES ON THE C-10-C-20 UNIT, P

The synthesis established on the basis of the above retrosynthetic analysis is a project on its own. The aim of this thesis is to investigate the use of chiral sulfoxide methodology for the formation of carbon-carbon bonds in the C_{20} backbone of the fumonisins. A model compound, **30**, with some of the features of the synthetic target, **P**, was therefore chosen for the present investigation.

3.3.1 Synthesis of the First Model Compound, 30

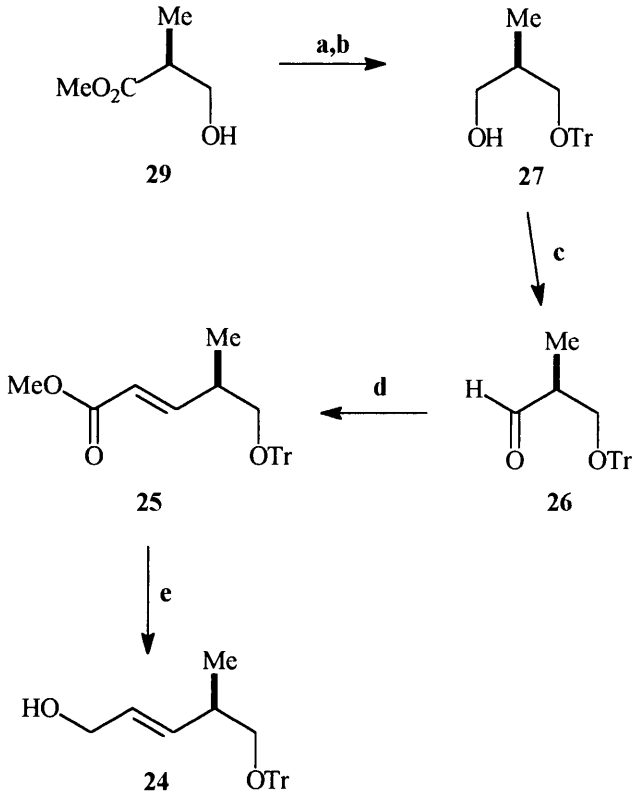


The starting material identified for the synthesis of the fumonisin C_{20} backbone left-side, and consequently also for the model compound, **30**, is the readily available, but costly, methyl (2*S*)-3-hydroxy-2-methylpropionate, **29** (99% ee). The synthetic strategy involves protection of the hydroxy group followed by reduction of the ester functionality to an alcohol, which after a change in oxidation level to the aldehyde stage, can be utilised for chain extension. The synthetic procedure must ensure the integrity of the C-4 stereogenic centre in **25** which is destined to become C-12 in the fumonisins, and in addition, the formation of only the *E* double bond in the chain elongation procedure.

Protection of the hydroxy group in **29** was effected by treatment with chlorotriphenylmethane and DMAP in a mixture of pyridine and CH_2Cl_2 to give the trityl ether, **28**. Reduction of the ester group with either $LiAlH_4$ or DIBALH proceeded smoothly to give the enantiopure monoprotected diol (**27**) in 93% overall yield (Fig 3.5).

It has been shown that Swern oxidation of enantiopure monoprotected diols, such as **27**, to the aldehyde occurs with less than 1%, if any, racemisation provided the reaction is carried out at -78°C and only 5 equivalents of Et_3N are used.[9] Using these conditions, the aldehyde (**26**) was obtained as a thick oil which had to be used immediately without purification in the next step as it is configurationally unstable. Crystallisation resulted in complete racemisation as the crystals did not show any optical activity.

The use of the Wittig reagent, (carbethoxymethylidene)-triphenylphosphorane with the *O*-benzyl aldehyde has been reported to yield the corresponding *E*-α,β-unsaturated ester but in only 70% ee.[10] This report prompted the selection of the Wadsworth-Emmons reaction for the construction of the double bond. Thus the reaction of aldehyde **26** with the ylide of diethyl ethoxycarbonylmethylphosphonate gave a 7:1 mixture of the *E*:*Z* isomers of the α,β-unsaturated ethyl ester, analog of **25**, which could be separated by chromatography and identified by the typical values of the coupling constant for the olefinic protons (*E*: J 15.7 Hz, *Z*: J 11.5 Hz). The *E*:*Z* ratio of the esters formed in the Wadsworth-Emmons reaction is sensitive to the structure of the phosphonate reagents.[11] In general, a reagent with a large phosphonate ester group yields predominantly an *E*-α,β-unsaturated ester while the *Z*-isomer is the predominant product for a reagent with a small phosphonate ester group.

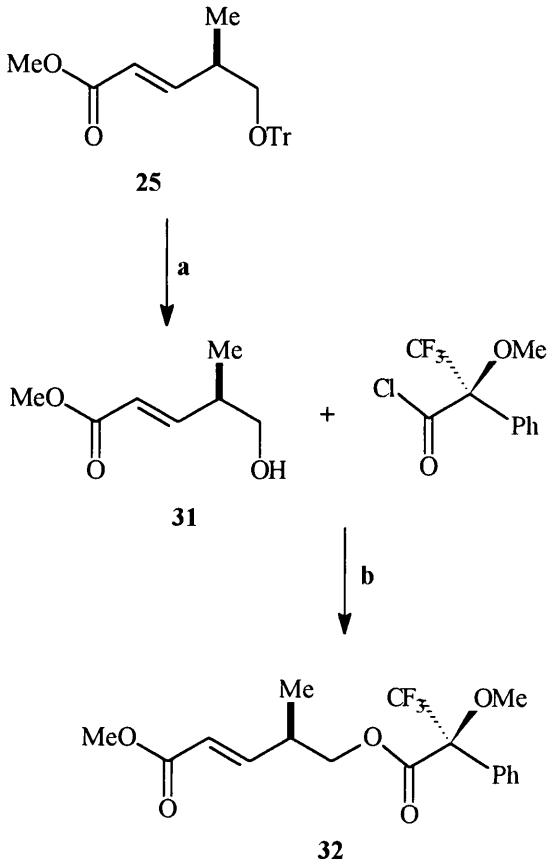


Reagents: **a. Ph_3CCl, DMAP, Pyridine (95%); b. LAH (98%); c. $(COCl)_2$, DMSO, NEt_3 (94%); d. tBuO$^-$K$^+$, $MeOC(O)CH_2P(O)(OEt)_2$ (94%); e. DIBALH (95%).**

Fig 3.5

This observation was confirmed by the reaction of the protected aldehyde (**26**) with the ylide of diisopropyl methoxycarbonyl methylphosphonate to give the *E*-α,β-unsaturated methyl ester (**25**) as the only product in ~90% yield.

The trityl group of **25** (samples from various batches) were hydrolysed to the hydroxy ester by using *p*-tolylsulfonic acid in MeOH (Fig 3.6). The enantiomer composition of this compound, **31**, was determined by esterification with (*R*)-(+)-α-methoxy-α-trifluoromethyl phenyl acetylchloride prepared from the corresponding Mosher acid and thionyl chloride as described by Mosher *et al.*[12] Analysis of the ^{1}H and ^{19}F NMR spectra of these diastereomeric esters (**32**) establised an ee of >96% for the starting ester, **25**, as both the methoxy and trifluoromethyl signals showed very little, if any, duplication.



Reagents: **a. *p*-tolylsulfonic acid, MeOH; b. DMAP.**

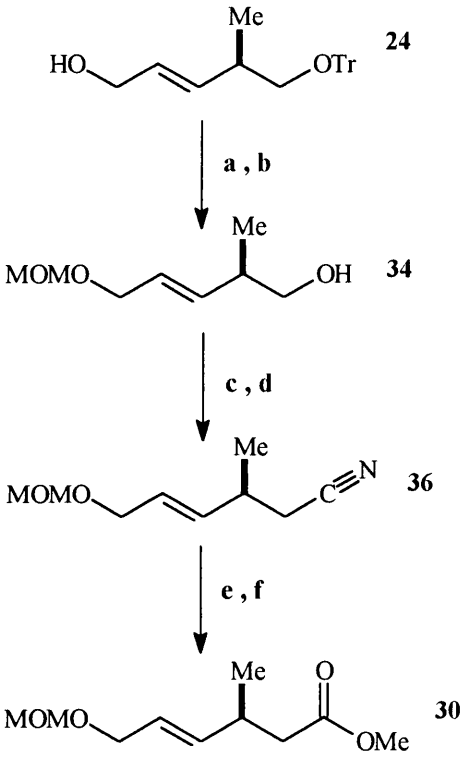
Fig 3.6 **Mosher Ester for determining the Enantiomer Composition of 25**

Reduction of the ester (**25**) to the allylic alcohol was achieved in quantitative yield using DIBALH. The allylic alcohol was protected as the MOM ether **33** by treatment with chloromethyl methyl ether and Hünig's base (iPr$_2$NEt), in order to commence the chain homologation process at C-5 in **33**. To this end the trityl group was removed using initially *p*-toluenesulfonic acid in aqueous MeOH at 75°C. The low yield (~50%) is ascribed to loss of the volatile product during the work-up procedure on evaporating the methanol under reduced pressure. In order to circumvent this problem the trityl protecting group was hydrolysed to the alcohol (**34**) using camphorsulfonic acid (CSA) in MeOH in 75% yield by using ether to extract the product and ether-pentane for the column chromatographic purification.

This alcohol was subsequently converted into the tosylate **35** (90% yield) which was reacted with excess NaCN in anhydrous DMF to bring about a one-carbon chain extension.[13] Some

experimentation was required to determine the optimum conditions for the formation of the nitrile (**36**). The use of sufficient anhydrous DMF to ensure the complete dissolution of a ten-fold excess of NaCN at 70°C is essential to obtain the nitrile in 90% yield. Lesser amounts of NaCN or DMF resulted in incomplete conversion (~75%) to the nitrile and recovery of starting material.

The nitrile, **36**, was hydrolysed to the corresponding acid (**37**) using 40% aqueous NaOH solution. The use of acid hydrolysis was ruled out as loss of the MOM protecting group was observed. The ester, **30**, which was prepared from the acid by using diazomethane, was extensively used for the preparation of β-keto sulfoxides to establish conditions for C-C bond formation of the C_{20} backbone of the fumonisins. As supplies ran out it was clear that the high cost of the starting material, **29**, required for the synthesis of **30**, necessitated a cheaper model compound.

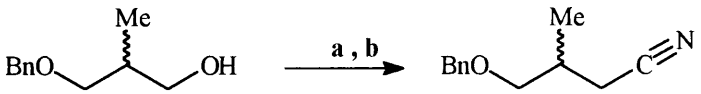


Reagents: **a. MOMCl, *i*Pr$_2$EtN (91%); b. camphorsulfonic acid, MeOH (75%); c. *p*-tolylsulfonylchloride, DMAP (92%); d. NaCN, DMF, ~70°C (90%); e. NaOH/MeOH/H$_2$O (78%); f. CH$_2$N$_2$ (90%).**

Fig 3.7 **Preparation of the First Model Compound, 30**

3.3.2 Synthesis of the Second Model Compound, 40

Compound **40** was identified as a suitable alternative to the more expensive ester, **29**, in the preparation of β-ketosulfoxides for use in C-C bond formation studies (see later). The synthesis starts from (2*RS*)-3-(benzyloxy)-2-methyl-1-propanol (**38**), prepared from (2*RS*)-2-methyl-propanediol.[14] Conversion of the hydroxy group to the O-tosylate (**39**) followed by a one-carbon chain-elongation step using NaCN using the conditions established earlier (see 3.3.1) gave the nitrile compound (**40**) in excellent overall yield. The nitrile was used directly to prepare a β-keto sulfoxide using the chiral sulfoxide (see later).



38 **40**

Reagents: **a. *p*-tolylsulfonyl chloride, DMAP (90%); b. NaCN, DMF (92%).**

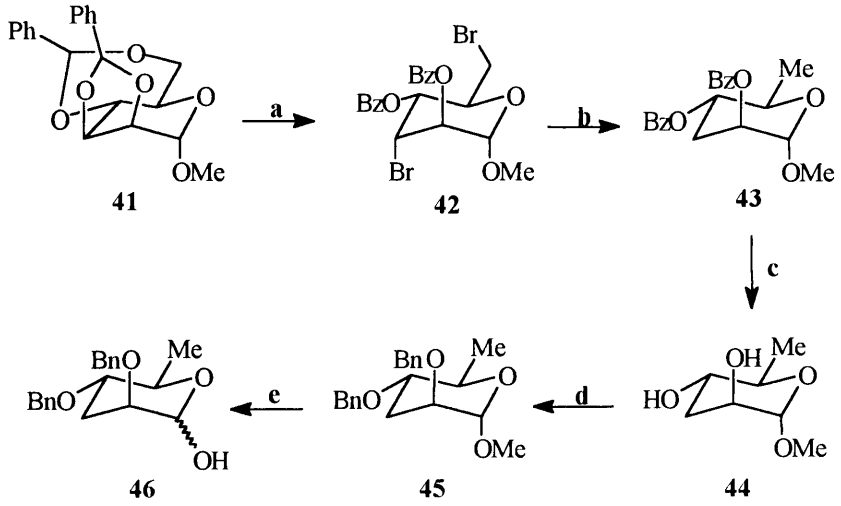
Fig 3.8 **Preparation of the Second Model Compound, 40**

3.4 SYNTHESIS OF THE RIGHTHAND SIDE OF THE C_{20} BACKBONE - THE C-1-C-8 UNIT

3.4.1 The C-1-C-6 Fragment

The retrosynthetic analysis of the C_{20} backbone of the fumonisins as outlined in Section 3.1.2 indicates that D-mannose is a suitable starting material for the stereocontrolled synthesis of **46**, the synthetic equivalent of C-1-C-6 of fragment **Q** (the C_8 righthand side unit).

The proposed study on the C-C bond formation in the synthesis of the C_{20} backbone of the fumonisins required the synthesis of the C-1-C-8 unit and as such an ample supply of the hemi-acetal, **46** (Fig 3.9).

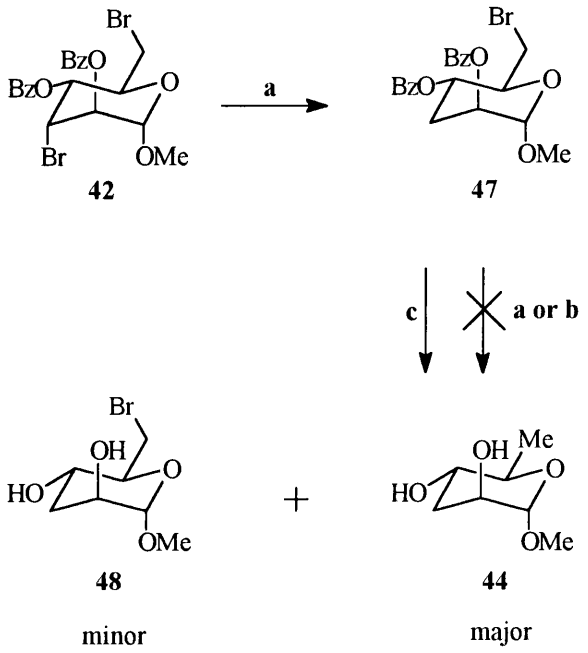


Reagents: **a. $CBrCl_3$, UV-light; b. Raney/Ni, H_2; c NaOMe; d. NaH, BnCl; e. $BCl_3 \cdot Me_2S$, wet SiO_2.**

Fig 3.9 **Preparation of the C-1–C-6 Synthetic Equivalent of Fragment Q**

The preparation of **46** has previously been described in R.M. Snyman's thesis.[5] In the present study the same reaction sequence was followed but on attempting to repeat the catalytic hydrogenation on the dibromo compound, **42**, severe problems were encountered: only complex mixtures and little of the desired product, **43**, was obtained. Imminent disaster was averted by the finding, after extensive investigation, that the reaction can be stopped after 5h (instead of the normal 48h period). Most of the H_2 is normally absorbed in the first 5h period and is utilised for the removal of the C-3 bromine atom to give **47** (Fig. 3.10). Reductive dehalogenation of the 6-bromo substituent is evidently a slow process during which several side-reactions occur which give rise to complex mixtures.

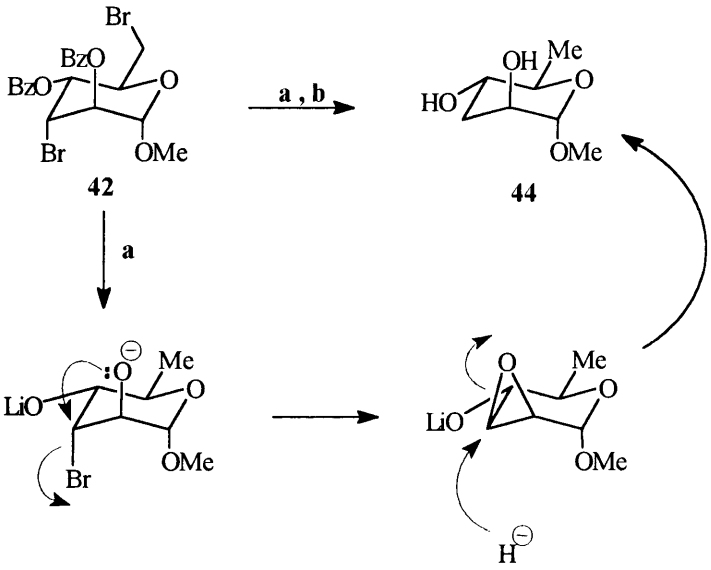
Redutive dehalogenation of the C-6 bromine functionality of **47** using $NaBH_4$ and $NiCl_2 \cdot 6H_2O$ in refluxing ethanol failed. However treatment of **47** with an excess of $LiAlH_4$ was more successful and led to the formation of methyl 3,6-dideoxy-α-D-mannopyranoside (**44**) as the major product together with some methyl 6-bromo-3-deoxy-α-D-mannopyranoside (**48**).



Reagents: **a. Raney/Ni H_2; b. $NiCl_2 \cdot 7H_2O$ $NaBH_4$; c. $LiAlH_4$ (75%).**

Fig 3.10 Hydrogenation Attempts on 42

This result prompted the decision to attempt the direct conversion of the dibromo compound, **42**, to the required methyl 3,6-dideoxy-α-D-mannopyranoside (**44**) using $LiAlH_4$ (Fig. 3.10). It has been noted previously that reduction of the axial 2-O-benzoate group in the presence of the 3-axial bromo atom results in the formation of a *manno*-epoxide moiety (Fig. 3.11).[5,15] However, reduction of the *manno*-epoxide with hydride reagent occurs regioselectively at C-3 to give the 3-deoxy compound with a C-2 axially oriented hydroxy group. The reduction of **42** using 6 equivalents of H^- (2 for each benzoate → benzyl alcohol conversion and 1 for each debromination reaction) in refluxing THF gave the desired product, **44**, in 75% yield. A by-product (10%) of the reaction was the 6-bromo analogue, **48**. The two-step procedure as shown in Figure 3.9 using Raney-Ni and NaOMe, respectively, gave **44** in only 68%. Subsequent protection of the hydroxy groups as the benzyl ethers and cleavage of the glycoside bond to give **49** were carried out using the reported procedure. Thus a seemingly disastrous problem was overcome and provided an inproved synthesis of **46** from methyl α-D-mannopyranoside from 35% in 5 steps [5] to 54% in 4 steps.



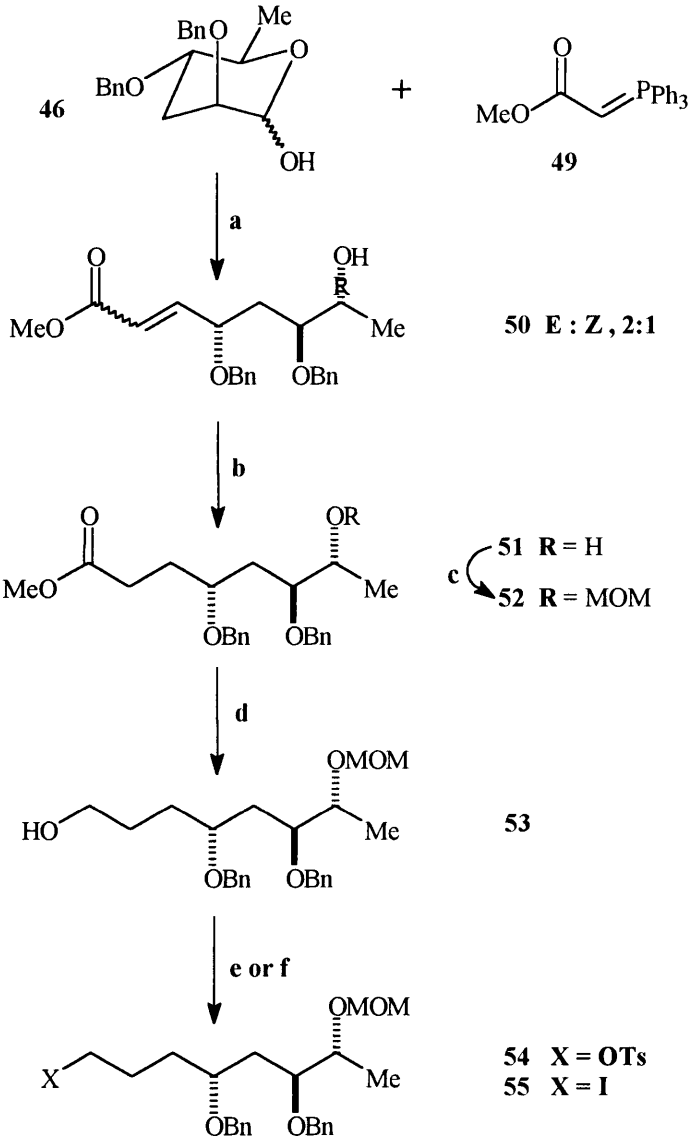
Reagents: a. $LiAlH_4$ (75%) ; b. H_3O^+.

Fig 3.11 Alternative Debromination of 42 using $LiAlH_4$

3.4.2 The C-1–C-8 Fragment Q

The Wittig and Wadsworth-Emmons reactions [16] have established themselves as the most effective and general methods of alkene formation and have been used in numerous total synthesis as a relative straightforward method for carbon-carbon bond formation. In the carbohydrate field, the applicability of the Wittig and related reagents has been investigated and they have been used extensively with sugar derivatives.[17] As a result of the hemi-acetal character of cyclic aldoses these sugars react as hydroxy aldehydes.

The basic steps involved in the elaboration of the C_6 unit, 2,4-di-O-benzyl-3,6-dideoxy-D-*arabino*-hexopyranoside (**46**) to the C_8 fragment **Q**, are outlined in Scheme 3.12. The strategy is based on the use of the Wittig reaction to effect the carbon-carbon bond formation. It was envisaged that with the basic C_8 backbone in place, hydrogenation of the formed double bond, followed by functional group manipulation and protection, would complete the synthesis.



Reagents: **a. DME or benzene, reflux (87%); b. Raney/Ni H_2 (95%); c. MOMCl, *i*Pr_2EtN (100%); d. DIBALH (95%); e. *p*-tolyl sulfonyl chloride, DMAP (90%); f. Ph_3P, I_2, imidazole (85%).**

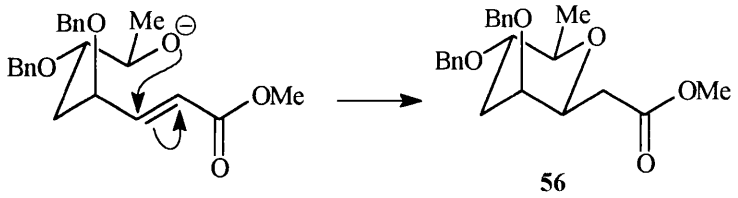
Scheme 3.12 Two-Carbon Chain Extension leading to the C_8 Fragment, Q

The chain extension of **46** to a C_8 acyclic analogue was easily effected by treatment with a stabilised ylide (carbomethoxymethylidene)triphenylphosphorane (**49**) generated from the phosphonium salt using aqueous NaOH (see 5.1.3) The ylide is therefore quite non-basic. An 80% yield of **50**, as a

mixture of *E/Z* isomers in the ratio of 1:1.7, was obtained after refluxing the reaction for 3 days in DME.

The reaction time could be shortened to 20 h by using 4 equivalents of the ylide to give **50** in 87% yield. The *E/Z* ratio also changed to 2.5:1 as was evident from the signals at δ_H 6.90, J 15.9 Hz (*E*) and δ_H 6.21, J 11.7 Hz (*Z*) in the H^1 NMR spectrum.

When the Wadsworth-Emmons variation was used with diisopropyl methoxycarbonyl methylphosphonate and potassium *t*-butoxide, carbon-carbon bond formation proceeded in excellent yield. However, due to the basicity of the reagent, the proton of the hydroxy group was abstracted by the excess of reagent, and the formed anion attacked the perfectly set-up α,β unsaturated ester in a Michael reaction to give the energetically favoured 6-membered cyclic compound, **56** (Fig 3.13). It was clear that only non-basic Wittig reagents, with pK_a values lower than that of a hydroxyl group could be used for the chain elongation step. Only the stabilised (carbomethoxymethylidene) triphenylphosphorane ylide meets this requirement.



56

Fig 3.13 Michael Addition Reaction Following Wadsworth-Emmons Reaction

The α,β unsaturated ester, **50**, was saturated using Raney/Ni catalyst under H_2 pressure (3 atm., 30 min) to give ester, **51**, in 95% yield. Protection of the C-2 hydroxy group in **51** as the methoxymethyl ether was accomplished in 100% yield using chloromethyl methyl ether in the presence of Hünigs base. The ester functionality was then reduced with DIBALH to yield the alcohol **53** in 95% yield.

The alcohol, **53**, was converted both to the *O*-tosylate derivative, **54** (using *p*-tolylsulfonylchloride and DMAP) and to the iodo compound, **55** (using Ph_3P and I_2 in the presence of imidazole). These two compounds were used in the subsequent carbon-carbon bond formation reactions using chiral sulfoxides.

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4 THE USE OF CHIRAL SULFOXIDES FOR CARBON-CARBON BOND FORMATION

4.1 DEVELOPMENT OF SULFOXIDE CHEMISTRY

In order to utilise the chiral sulfoxide chemistry in the synthesis of the C_{20} backbone of the fumonisins, the basic methodology was developed on small model compounds. This allowed me to become familiar with the typical experimental procedures, NMR analyses and possible problems which might occur.

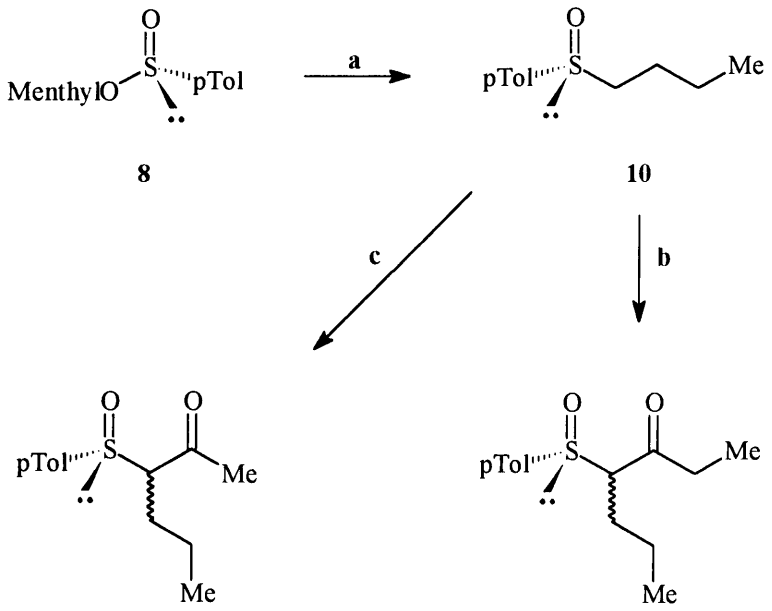
The basic starting material required for the synthesis of the different chiral sulfoxides namely (-)-(*S*)-menthyl-*p*-toluenesulfinate **8** was prepared from *p*-toluenesulfinylchloride and (-)-menthol (Fig 1.5). This esterification reaction showed no stereoselectivity and gave a 1:1 mixture of diastereoisomers. This mixture could be equilibrated by traces of hydrochloric acid and as only the desired (*S*)-isomer crystallises from acetone, up to 75% of the enantiopure (*S*)-sulfinate could be obtained in a few days (80% yields have been reported [1]). Although the synthesis is relatively easy, the crystallization of a second and third crop of crystals of **8** is time consuming as the mixture must be concentrated to a viscous liquid to recover the last 20% of material. It is necessary to dry the mother liquors over anhydrous Na_2SO_4 before concentration to a viscous liquid, as the presence of H_2O, together with HCl, results in hydrolysis of **8**. Dilution of the mother liquors with hexane improved the crystallisation process and also filtration.

The final product (**8**), had a melting point of 108-109°C (Lit.[1] 105-107°C) and $[\alpha]_D^{20}$ -199 (*c* 2.5, acetone) [Lit.[1] $[\alpha]_D^{20}$ -202 (*c* 2.0, acetone)] and was stored in a vacuum desiccator as on the shelf it decomposed within 3 months.

Alkyl *p*-tolylsulfoxides can be prepared from (-)-(*S*)-menthyl-*p*-toluenesulfinate (**8**) by reaction with different alkyl Grignard reagents.

The preparation of (+)-(*R*)-methyl-*p*-tolylsulfoxide **9** from **8** using methylmagnesium iodide in a Grignard reaction has been described extensively. The product is obtained in high yield by crystallisation of the crude reaction products. No chromatography is required for purification.

The preparation of the (+)-(*R*)-butyl-*p*-tolylsulfoxide **10** is more troublesome and several problems were encountered. In the first instance it was found that an excess of the Grignard reagent, BuMgI, is required and even then yields were low (50%). A slight improvement in yield to 61% was achieved using BuMgCl. The greatest setback was the isolation procedure: all attempts at crystallisation failed and extensive column chromatography was necessary in order to remove (-)-menthol (formed in the reaction), and starting material, and to obtain the pure (+)-(*R*)-butyl-*p*-tolylsulfoxide (**10**).



Reagents: a. BuMgCl (50%); b. LDA, methyl propionate (62%); c. LDA, ethyl acetate (50%).

Fig 4.1 Preparation of β-Ketosulfoxides

The (+)-(*R*)-butyl-*p*-tolylsulfoxide (**10**) was converted to a ketosulfoxide by generation of the anion and reaction with an appropriate ester (Fig 4.1). The use of BuLi at low temperatures (-78°C) to generate the anion, followed by reaction with either methyl propionate or ethyl acetate gave very little product and mostly a mixture of unidentified by-products. Generation of the anion using LDA and

the subsequent reaction with both methyl propionate (1 eq) and ethyl acetate (1 eq.) in separate experiments was more successful and gave the ketosulfoxide **57** and **58** respectively in about 46% yield in each case instead of the reported 70-80%.[2]

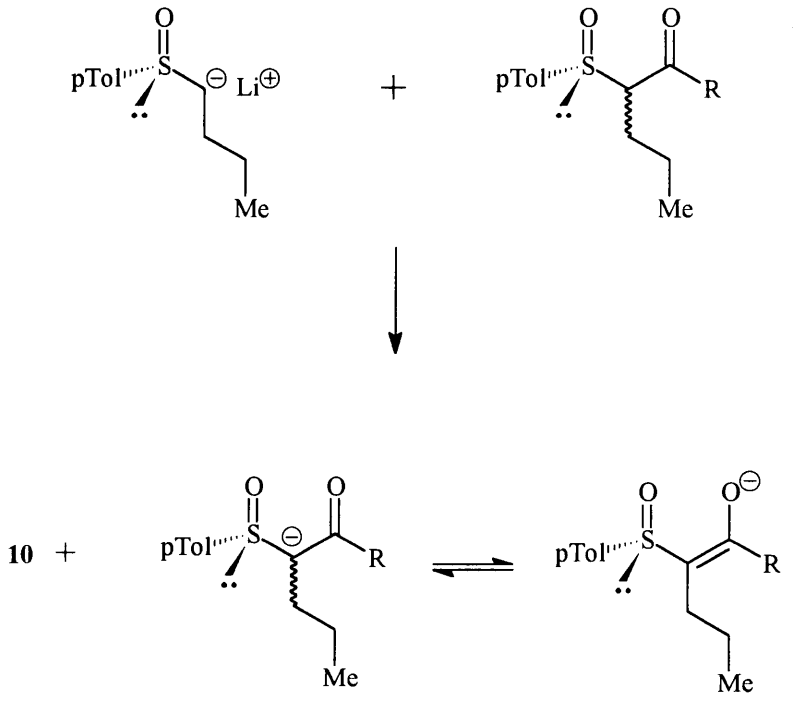
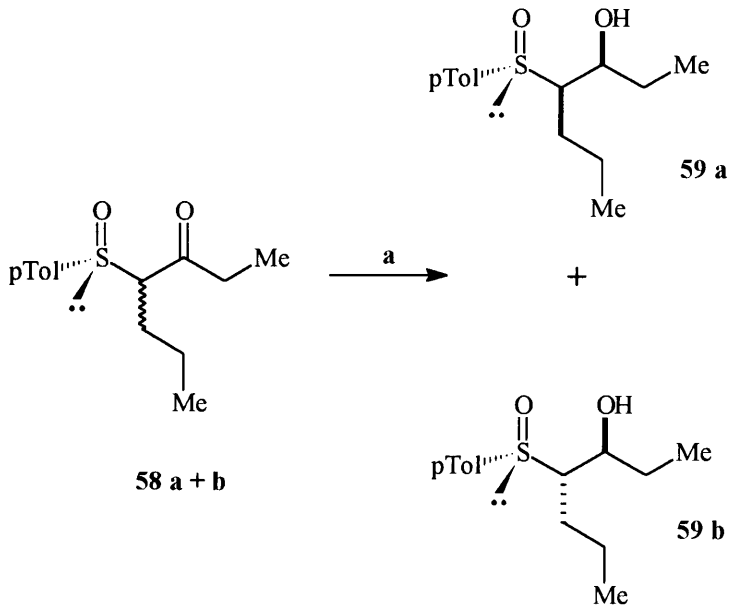


Fig 4.2 Anion/Enolate forms of β-Ketosulfoxides

Yields of around 50% should be the norm as the α-proton in the formed ketosulfoxide is considerably more acidic than in the starting material (Fig 4.2). The use of 2 equivalents of sulfoxide anion and 1 equivalent of the ester component led to a slight improvement and gave the β-ketosulfoxide **57** (64%) with ethyl acetate and **58** (50%) with methyl propionate. Unreacted starting material (**10**) could be recovered. Stereoselectivity in the reaction was poor and a ~1:1 mixture of diastereomers, which could not be separated by column chromatography, was obtained in both cases.

The stereoselectivety of the reduction of α-alkyl β-ketosulfoxides is in some doubt and as this reduction is a key step in the proposed synthesis of the C_{20} backbone of the fumonisins, it was decided to examine the reduction of the α-propyl β-ketosulfoxides (**57a+b**) and (**58a+b**). The reduction of **58a+b** with 1.1 equivalent DIBALH at -78°C gave a mixture of only 2 diastereoisomers, **59a** and **59b**, which could be separated by column chromatography (Fig 4.3). The nmr spectra of both **59a** and **59b** showed the presence of a single diastereomer. The configuration of the stereogenic centres was deduced from a comparison of the chemical shifts and coupling constants for the C-3 and C-4 protons

in **59a** and **59b** with the values observed for the corresponding protons in the four diastereomers **14a-d** (see later and Table 4.1). Thus the coupling constant of 1.3 Hz points to a *syn* relationship for the C-3 and C-4 protons and the signals at δ_H 3.93 (3-H) and 2.26 (4-H) establish the S_R, 3*S*, 4*R* configuration for **59a**. An *anti* relationship for the C-3 and C-4 protons followed from the 5.6 Hz coupling constant for these protons and the chemical shift values for 3-H (δ_H 3.81) and 4-H (δ_H 2.57) established the S_R, 3*S*, 4*S* configuration for **59b**.



Reagents: **a. DIBALH, -78°C.**

Fig 4.3 **DIBALH Reduction of 58a+b**

It would appear that 1,2-induction doesn't play a significant role in the reduction of the carbonyl group and that the stereoselectivety of this reaction is governed solely by the sulfur stereogenic centre.

However when **57a+b** (1:1 mixture) was reduced with DIBALH, three diastereomers were formed which were subjected to column chromatography to give **14b** as a single stereoisomer and a *ca.* 1:1 mixture of the (2*R*)-and (2*S*) alcohols **14a+c** (Fig 4.4). Once again the assignment of the absolute configuration for the three isomers of **14** is based on a comparison of the ^{1}H nmr data of those found for **14a-d** prepared by a different route (see section 2.2.4) and identified by X-ray crystallography and nmr spectroscopy (see section 4.2 and the Appendix). The stereoisomers obtained by reduction of **57a+b** show that the length or bulk of the R group can determine the extent of 1,2 induction. From this result it still wasn't clear whether 1,2 induction will play a role when the long chain left- and right-side fragments were used.

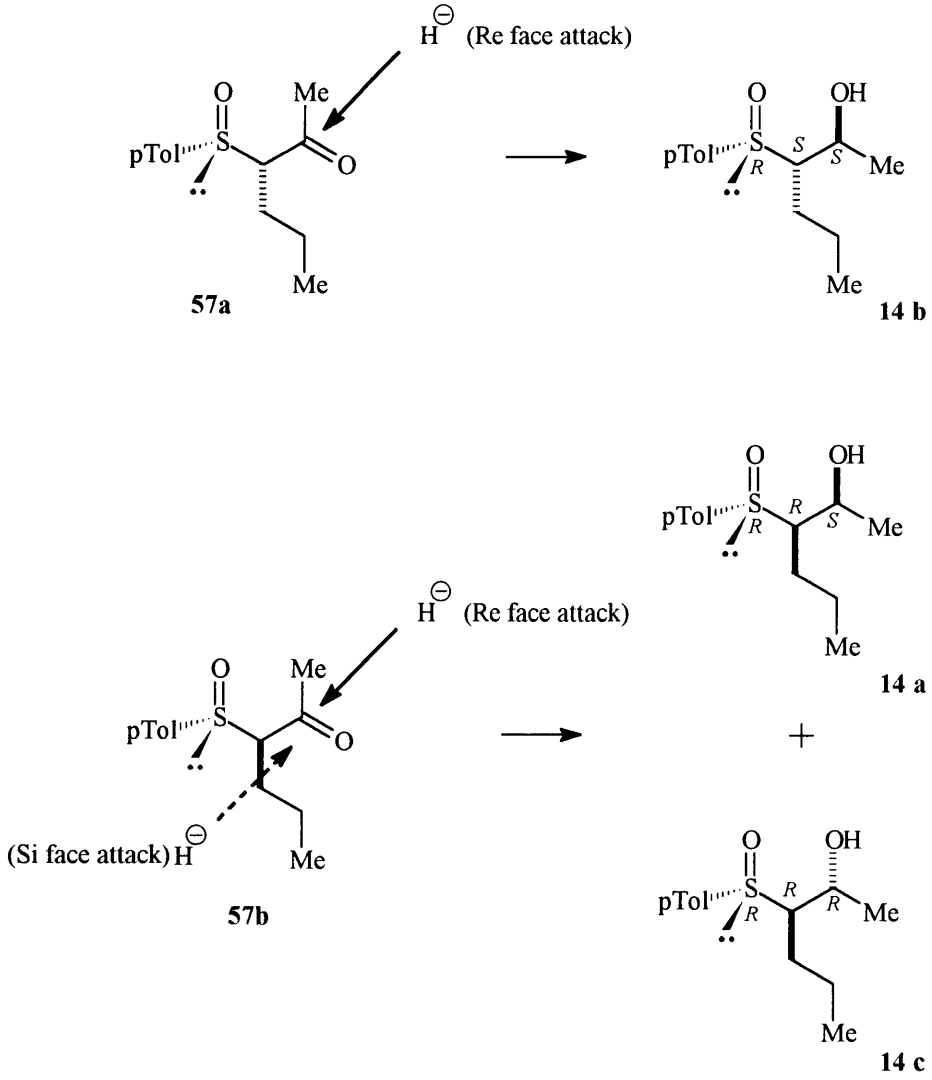


Fig 4.4 1,2- and 1,3-Induction

The lack of control over the formation of the new stereogenic centre in the reduction of the α-alkyl β-ketosulfoxides, as outlined above militates againts the use of this method in the synthesis of the C_{20} backbone of the fumonisins, and led to the decision to abandon this approach.

In order to utilise chiral sulfoxide methodology and retain control over the formation of a new stereogenic centre on reduction of the β-ketosulfoxide moiety, it was decided to change the order of events. Thus an initial stereoselective reduction of a simple β-ketosulfoxide (without an α-alkyl chain), for which there is ample literature precedent, is followed by alkylation at C-α of the formed β-hydroxy sulfoxide.

The (S_R)-methyl-*p*-tolylsulfoxide (**9**) was prepared from (-)-(*S*)-menthyl-*p*-toluenesulfinate **8** and methylmagnesium iodide by the method described by Solladié *et al.*[1] Treatment of **9** with LDA generated the anion which was treated with ethyl acetate to give the β-ketosulfoxide (**11**) in 80% yield. Stereoselective reduction of **11** using DIBALH at -78°C gave the 2*S*-alcohol (**12a**) whereas the use of DIBALH-$ZnCl_2$ at -78°C led to the formation of the 2*R*-alcohol (**12b**). In both cases the product contained up to 10% of the 2-*epi* alcohol *i.e* an ee of 80% in contrast to literature ee values of ≥90%.[3] The low ee values are ascribed to the presence of the methyl group in **12a/b** and stereoselectivity is expected to be better with bulkier substituents.

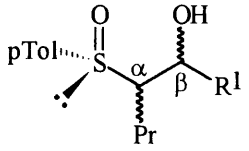
The next step, the introduction of an alkyl substituent at the α-position of the β-hydroxysulfoxides **12a** and **12b**, was expected to be a major stumbling block as this reaction hasn't been described extensively in literature. This proved not to be the case as both **12a** and **12b** were alkylated using BuLi (2 eq.) and propylbromide (1 eq.). It is interesting to note that in each case a mixture of two different diastereomers, which could be separated by column chromatography, was obtained. Alkylation of **12a** gave a nearly 1:1 mixture of **14a** and **b** whereas **12a** gave a 7:1 mixture of **14c** and **d**.

4.2 CONFIGURATIONAL AND CONFORMATIONAL ANALYSIS OF β-HYDROXY SULFOXIDES

The configuration of the sulfur stereogenic centre in the β-hydroxysulfoxides is defined by the starting material (**9**) whereas the stereofacial selectivity of the reagents in the reduction reaction determines that of the C-2 alcohol. The relative configuration of the β-hydroxysulfoxides (**14**) follows from the coupling constant ($J_{2,3}$) : it is known from the literature that $J_{2,3} > 8$ Hz for the *threo* isomer (e.g. **14b** and **c**) and $J_{2,3} < 3$ Hz for the *erytho* isomer (e.g. **14a** and **d**) in $CDCl_3$ solutions.[4]

Thus the $J_{2,3}$ value for each of the diastereomers (**14a-d**) establishes its relative configuration. A suitable crystal of **14c** for single-crystal X-ray crystallography was obtained by crystallisation from hexane-acetone. The X-ray analysis established the S_R, 2*R*, 3*R* absolute configuration for this diastereomer.

With the absolute stereochemistry of the diastereomer **14c** to hand, that of the other three diastereomers could be assigned. The relevant ^{1}H nmr data for **14a-d** are summarised in Table 4.1.



Compound		R_1	$\delta_{H\alpha}$	$\delta_{H\beta}$	δ_{OH}	$J_{\alpha,\beta}$	Solvent
14a	$\alpha R,\beta S$	Me	2.21	4.25	4.2	1.5	$CHCl_3$
			2.4		4.8	2.3	DMSO
14b	$\alpha S,\beta S$	Me	2.66	4.08	4.34	6.5	$CHCl_3$
			2.4	3.9	5.2	6.8	DMSO
14c	$\alpha R,\beta R$	Me	2.71	4.29	4.62	8.2	$CHCl_3$
				3.65	4.95	5.3	DMSO
14d	$\alpha S,\beta R$	Me	2.46	4.38	2.52	2.8	$CHCl_3$
				3.95	5.05	3.95	DMSO
59a	$\alpha S,\beta S$	Et	2.26	3.93	4.04	1.3	$CHCl_3$
59b	$\alpha R,\beta S$	Et	2.57	3.81	4.25	5.6	$CHCl_3$

Table 4.1 NMR Data of α-Alkyl β-Hydroxysulfoxides

The most interesting observation is the value of the coupling constants, $J_{\alpha,\beta}$. In the *threo* isomers this value is much larger than in the *erythro* isomers (in $CDCl_3$ solutions). This is also confirmed in literature,[4] and has given rise to various assumptions about which conformations of β-hydroxy-sulfoxides are the most stable. From the very specific coupling constants observed it is evident that there must be a preferred conformation.

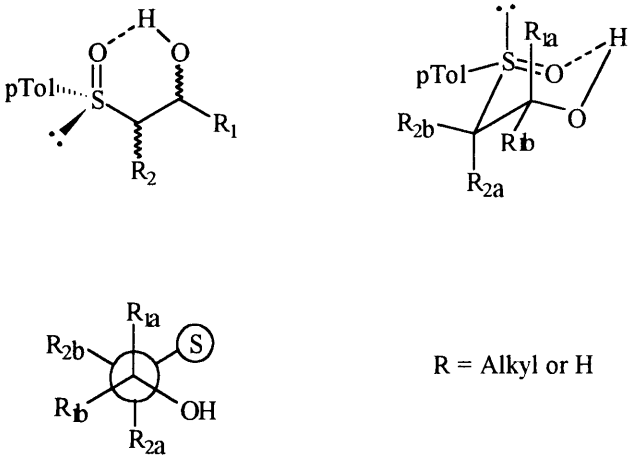


Fig 4.5 Six-Membered Ring Structure Formed by Hydrogen Bonding

The most obvious explanation is the equatorial-axial *versus* axial-axial coupling in a chair-like six-membered ring structure. Such a structure is indeed possible when hydrogen bonding exists between the proton of the hydroxy group and the oxygen on sulfur (Fig 4.5). Careful consideration of this model shows that only in the case of the *R*-alcohols (R_{1a}=H), with the *p*-tolyl substituent in an equatorial position, will the vicinal coupling constant differ to a great extent. When R_{1b}=H (*S*-alcohol) both possible coupling constants are of the same magnitude (both are *gauche* couplings with torsian-angles near to 60°). In order to accommodate the *S*-alcohols, it is necessary to ring-flip the postulated six-membered ring structure with the result that all axial substituents become equatorial and *vice versa*. This conformation, for the *S*-alcohols, with the *p*-tolyl substituent axially orientated, does explain the observed magnitude for the vicinal coupling constants (Fig 4.6). An alternative possibility is a boat-like confomation.

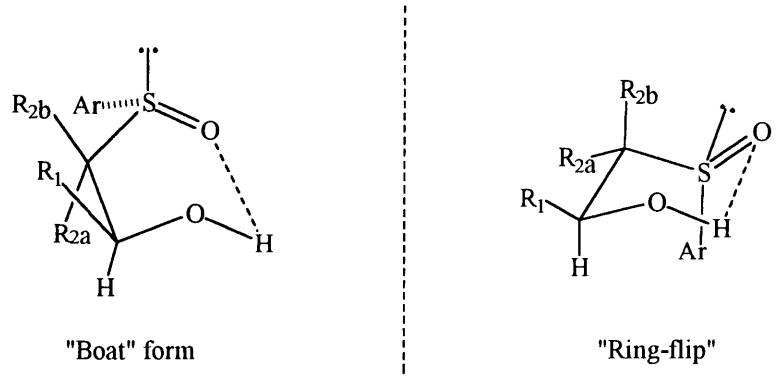
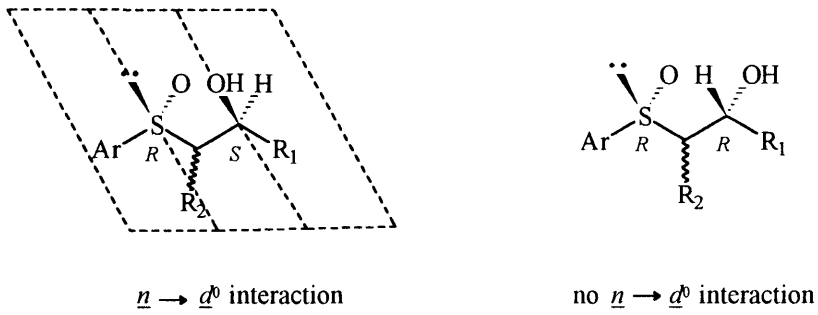


Fig 4.6 Alternative Conformations for the *S*-alcohol

Although this model seems to explain experimental results, several facts indicate that hydrogen bonding may not be responsible for these preferred conformations after all.

Reports by Carretero *et al*[4c] and others[4c,d,e] suggest that the preferred conformation of di-alkyl sulfoxides is based on a combination of steric and electrostatic effects. They came to the conclusion that a stabilizing interaction of the lone pair electrons on the β-oxygen with the unoccupied d-orbitals of the partially positively charged sulfur atom leads to the most stable rotamer. This interaction is very specific and requires the correct alignment of the *R*-sulfoxide and hydroxy groups : The plane formed when the C-OH bond is parallel with the orbital housing the sulfur lone-pair electrons must be orthogonal to the C_1-C_2-S plane. This limits the $\underline{n} \rightarrow \underline{d}^{\circ}$ interaction to the *S*-alcohols when the sulfinyl group has the *R* configuration (Fig 4.7).



$\underline{n} \rightarrow \underline{d}^0$ interaction no $\underline{n} \rightarrow \underline{d}^0$ interaction

Fig 4.7 Configurations in which $\underline{n} \rightarrow \underline{d}^0$ Interactions are Possible

It was further suggested that for the diastereomers with the *R*-alcohol moiety, hydrogen-bonding is the dominant factor in establishing the preferred conformation. This was shown by a comparison of the $J_{\alpha,\beta}$ coupling constants observed in $CDCl_3$ and DMSO-d_6. In DMSO, a highly polar solvent, intramolecular hydrogen-bonding is replaced by intermolecular interactions. Thus any conformation dependent on intramolecular hydrogen-bonding will change and as a consequence also the $J_{\alpha,\beta}$ coupling constants to an average value of 4-5 Hz reflecting a conformationally mobile system (Fig 4.8).

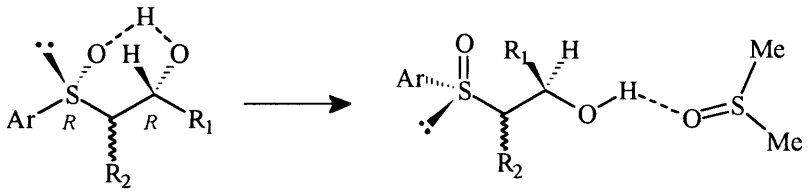
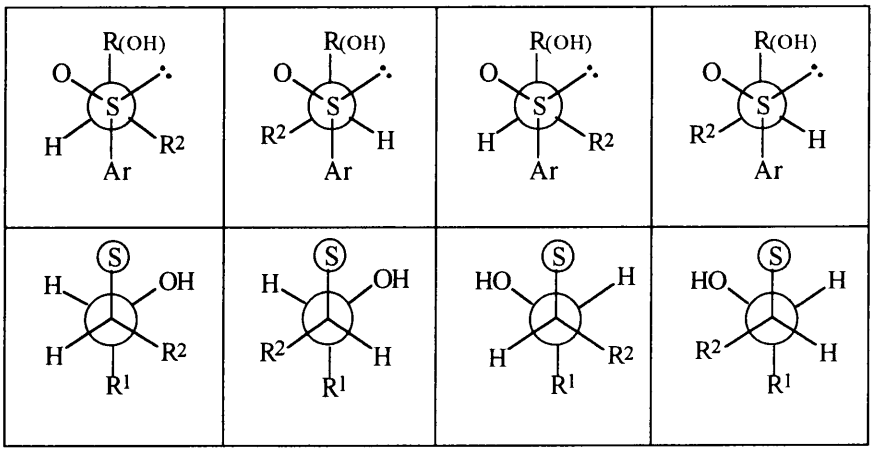


Fig 4.8 Intra- versus Inter-Molecular Hydrogen Bonding in $CHCl_3$ and DMSO

This change was only observed in the β-hydroxysulfoxides having the 2*R*-configuration while the coupling constants were unchanged in those of the 2*S*-configuration, thus proving the hypothesis. The conversion of the hydroxy-group to a *O*-methyl ether which lacks intramolecular hydrogen bonding gave the same results. The theory is supported by X-ray crystallography data obtained on a number of β-hydroxysulfoxides.[5] A similar *gauche* conformation has been found in these structures with small S-O(H) distances — as small as just 2.86 Å — clearly indicating some sort of non-bonded interaction, most probably $\underline{n} \rightarrow \underline{d}^0$ donation. Although one would expect an eclipsed comformation, as has been proved for β-ketosulfoxides, the correct distance for sufficient interaction (2.86 Å) could be achieved in a *gauche* conformation.[5]

The values obtained for $J_{\alpha,\beta}$ in the four diastereomeric α-propyl-β-hydroxysulfoxides (**14**) in $CDCl_3$ and DMSO-d_6, together with their Newman projections, are presented in Table 4.2 and are in agreement with the above outlined theory.



No.	R^1	R^2	solvent	*RRS*	*RSS*	*RRR*	*RSR*
14	M	Pr	$CHCl_3$	1.5 Hz	6.5 Hz	8.2 Hz	2.8 Hz
14	M	Pr	DMSO	2.3	6.8	5.3	4.6
59	Et	Pr	$CHCl_3$	1.3	5.6		
13	M	M	$CHCl_3$		7.0	7.1	
13	M	M	DMSO			7.0	
12	M	H	$CHCl_3$	2.0	9.4	8.3	3.6
12	M	H	DMSO			6.3	6.1

Table 4.2 Coupling Constants of Alkylated β-Hydroxysulfoxides linked to their Newman Projections

The drawing of Newman projections of the least sterically hindered zig-zag conformers[6,7] with consideration of hydrogen-bonding, $\underline{n} \rightarrow \underline{d}^{\circ}$ interaction and steric interaction seems to be the easiest way to understand which rotamers are favored most. It has been suggested that the aromatic substituent on sulfur prefers to be *anti* to an alkyl group, the alkyl group with the hydroxy group was therefore orientated in this way. In the C-3–C-2 projection the sulfoxide group, S was taken as the biggest substituent and had to be *anti* with either R^1 or R^2. Although R^2 is bigger than R^1 (R^2 = Pr), R^1 was used for the *anti* substituent as this permitted $\underline{n} \rightarrow \underline{d}^{\circ}$ interaction in the *RRS* and *RSS* isomers (this interaction is not possible for the other 2 isomers). In the case of the *RRR* and *RSR* isomers H-bonding was taken into account and although it is possible for either R^1 or R^2 to be *anti*, R^1 was chosen again because of the more stable six-membered ring that is formed (Fig. 4.5 and 4.6). These

conformations explain the coupling constants in $CDCl_3$. However in DMSO-d_6 the situation changes. Now intramolecular hydrogen bonding is not important anymore and the rotamer with R^2 *anti* also plays a role and the coupling constants even out as the result. When R^2 is changed to methyl, R^1 is still bigger than R^2, the other rotamer still does not play a significant role and the coupling constant remains large in the *RRR* isomer. For the isomers having $\underline{n} \rightarrow \underline{d}^{\circ}$ interactions no change in the coupling constants is expected nor observed.

In contrast to the X-ray crystallography data reported for (2*R*)-3-methyl-3-phenylsulfinyl butan-2-ol,[5] the crystal structure of **14c** indicated an unexpected absence of any intramolecular hydrogen bonding between the oxygen of the sulfoxide group and the *R*-alcohol group. Instead an intermolecular hydrogen-bond is observed between the sulfoxide oxygen and the hydroxy group of two molecules in adjacent unit cells (Fig 4.9). The hydroxy group in **14c** has the *R*-configuration, it is therefore expected that in solution, especially in $CDCl_3$, the observed intermolecular interaction present in the solid state, will be replaced by intramolecular hydrogen bonding.

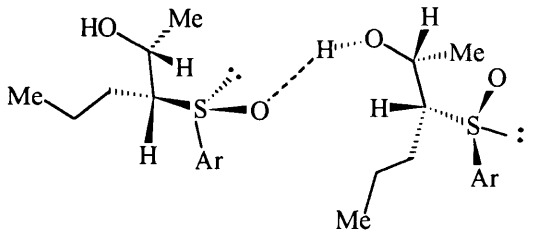


Fig 4.9 **Inter-Molecular Hydrogen Bonding between Two Molecules in the Crystal Lattice of 14c**

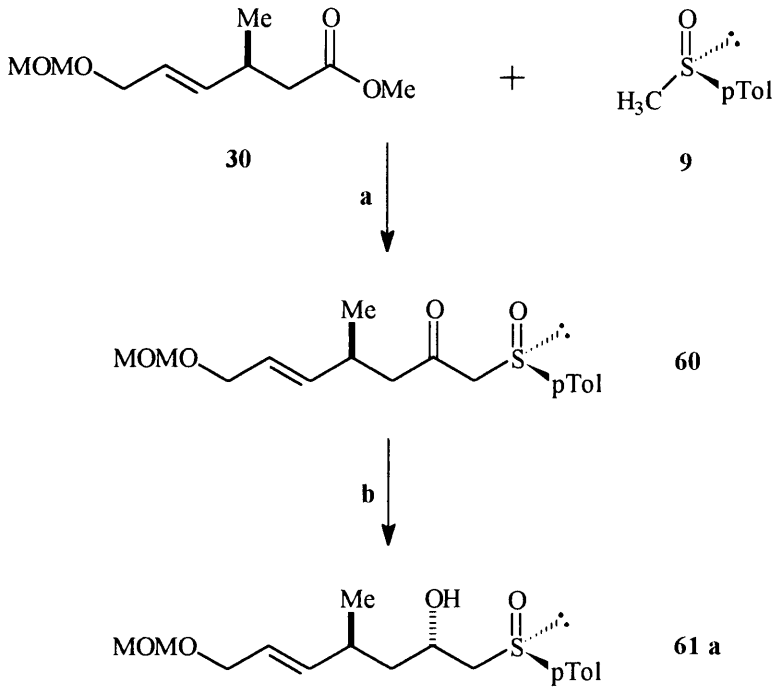
In conclusion it must be pointed out that despite the different models used for explaining the magnitude of the coupling constants in α-alkyl-β-hydroxysulfoxides, a large coupling constant (>6 Hz) in $CDCl_3$ is still proof of a *threo* isomer and a small constant (<3 Hz) of an *erythro* isomer. Relative stereochemistry has much more influence on the nmr spectra than the absolute configuration has. Whether hydrogen bonding occurs (intra- or inter-molecular) or whether steric and electronic considerations are important is best determined for each separate diastereomer as no definite rules seem to be obeyed.

4.3 APPLICATION TO MODEL COMPOUNDS

At this stage it should be emphasized that the chirality sense of the C-α stereogenic centre of an α-alkyl-β-hydroxysulfoxide compound is of little consequence in any synthetic procedure as this stereogenic centre is lost during the removal of the sulfoxide group.

What is important is that stereoselective reduction of the carbonyl group of a β-ketosulfoxide and the subsequent α-alkylation could be achieved on simple model compounds. Attention now turned to extending this strategy to more elaborate model compounds.

The ester **30**, an intermediate in the synthesis of the C-10–C-20 unit of the C_{20} backbone of the fumonisins that can serve as a model compound to test the above strategy, was prepared as described in Section 3.3.1 and was converted to the β-ketosulfoxide **60** in 82% yield by addition to 2 equivalents of the anion of **9**. Stereoselective reduction of the β-ketosulfoxide group using DIBALH gave the β-hydroxysulfoxide product **(61a)** with the required 2*S* configuration in 80% yield and dr of 97:3 (Fig 4.10).



Reagents: **a. LDA (82%); b. DIBALH, -78°C (90%).**

Fig 4.10 **Connection of the C_1 Sulfoxide to the First Model Compound and Stereoselective Reduction**

All that remains is to effect the carbon-carbon bond formation between **61a** and the C_8 unit, **53**, corresponding to C-1–C-8 of the backbone of the fumonisins. Compound **53**, prepared as described in Section 3.4.1, was converted to the *O*-tosyl derivative **54**. The dianion of **61a** was generated at -78°C using 3 equivalents of BuLi. After stirring the solution at -20°C for 1 h the solution was cooled to -78°C again and the *O*-tosylate was added. The stirred solution was allowed to warm up to RT over a period of 1-2 h. No product formed and both starting materials were recovered although considerable decomposition of **61a** had occurred.

A change in leaving group from a tosylate to a bromide was considered and this required the conversion of the alcohol (**53**) to a bromo compound. The presence of the MOM ether necessitates the use of a mild bromination reagent such as PPH_3/CBr_4. The required product was not obtained and instead a complex mixture was produced of which some compounds clearly indicated the loss of the MOM group. The mechanism for the proposed bromination reaction is shown in Figure 4.11. The adduct formed between CBr_4 and PPh_3 undergoes nucleophilic attack by the oxygen atom of the alcohol group. Bromide then attacks the oxygen-bearing carbon atom and the formation of the coresponding bromide and triphenylphosphine oxide. It is possible that traces of HBr formed *in situ* are responsible for the observed deprotection of the C-2 functionality. Nakanishi *et al.*[8] also reported considerable hydrolysis of an acetonide group when PPh_3 was added too fast.

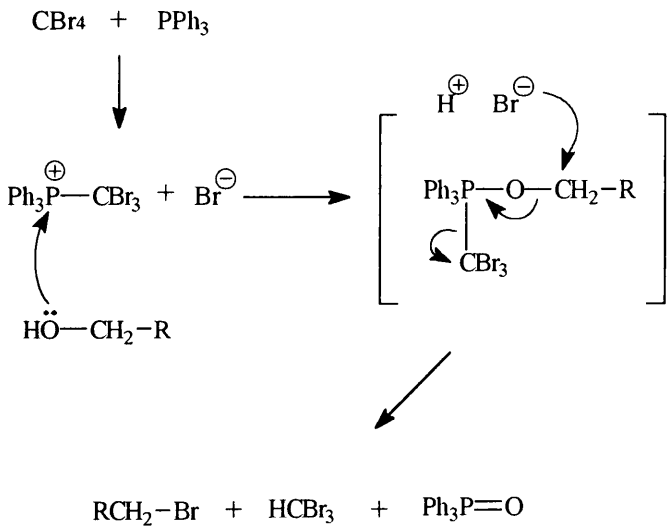
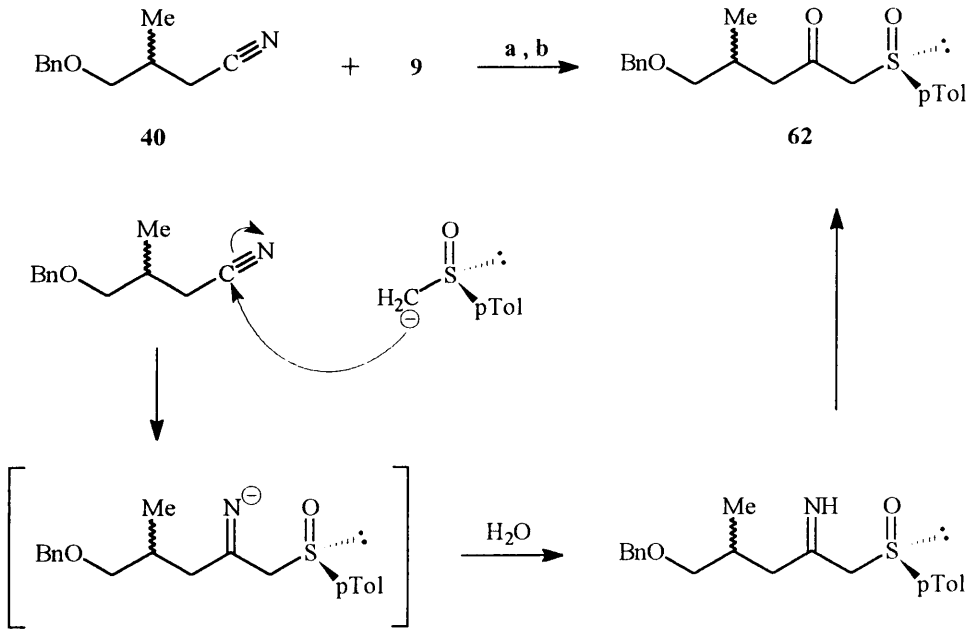


Fig 4.11 Proposed Mechanism for the Failed Bromination of 53

Attention now turned to the preparation of the iodo compound **55** from the alcohol **53** using I_2, PPh_3 and imidazole to effect the transformation in yields of up to 90%. No byproducts were formed in this

reaction. The iodide is not very stable and decomposes within a week at room temperature. The carbon-carbon bond formation betweeen the iodo compound, **55**, and the β-hydroxysulfoxide, **61a**, was investigated using LDA, instead of BuLi, to generate the dianion. The dianion was generated at -50°C and addition of the iodo compound (**55**) was carried out at -20°C but to no avail. These reactions were done on small scale only (0.1 mmol) as a result of the lack of sufficient quantities of starting materials. It was clear that if the carbon-carbon bond formation was to be investigated further using β-hydroxysulfoxides, a cheaper model compound was required.

The nitrile, **40**, prepared as described in Section 3.3.2, was used in the synthesis of an appropriate model β-hydroxysulfoxide compound. In a attempt to shorten the synthetic route it was decided not to convert the nitrile functionality by hydrolysis and esterification to an ester group for the subsequent linkage to the chiral sulfoxide (**9**), but to prepare the β-ketosulfoxide (**62**) directly using the nitrile (**40**). The reasoning behind this decision was as follows: nucleophilic attack by the anion of the sulfoxide on the carbon atom of the nitrile group leads to carbon-carbon formation and generates an iminium anion. Aqueous acidic work-up of the reaction leads to the formation of an imine which is hydrolysed under the conditions to form the β-ketosulfoxide.

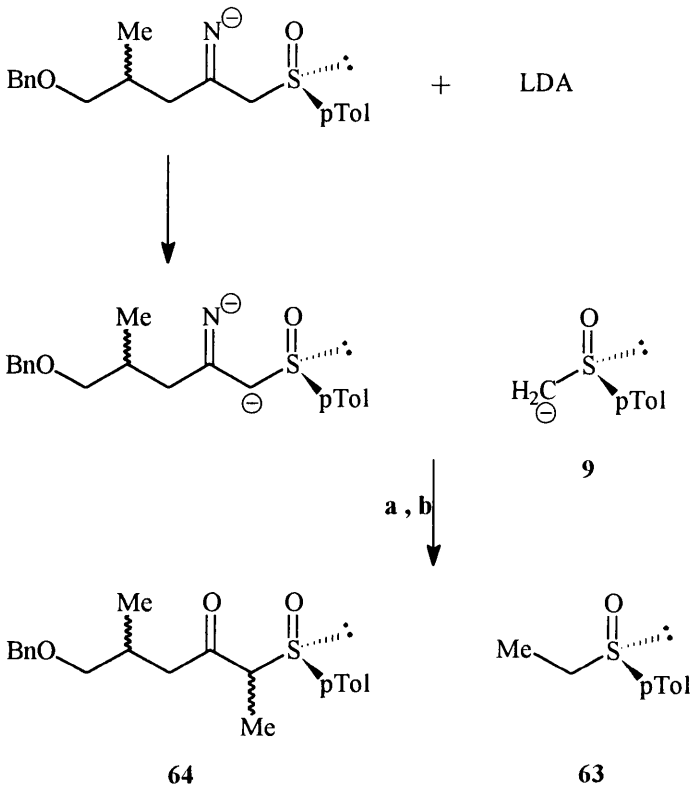


Reagents: **a = LDA; b = H_3O^+ (85%).**

Fig 4.12 **Sulfoxide Nitrile Condensation Reaction**

The reaction was tested using butyronitrile and gave the corresponding β-ketosulfoxide in 70% yield. When the reaction was repeated on the racemic nitrile, **40**, results were disappointing at first. The reaction was carried out at -40°C with 1.5 equivalent of the anion formed from **9**, using LDA (Fig 4.12). Very little product formed.

To find out more about the reaction it was repeated with 1 equivalent of **9** and 1.5 eq. of LDA at -30°C. The reaction was allowed to attain room temperature. After 2h both starting materials were still present. An excess of MeI was then added to the reaction to give after work-up and column chromatography, unreacted **40** and the α-methylated compounds **63** and **64** (Fig 4.13). This result indicated that all of compound **9** and all the formed product, **62**, had been deprotonated under the reaction conditions. It was also evident that the reaction between the nitrile compound and the anion of **9** is sluggish at -30°C.



Reagents: **a = MeI; b = H_3O^+.**

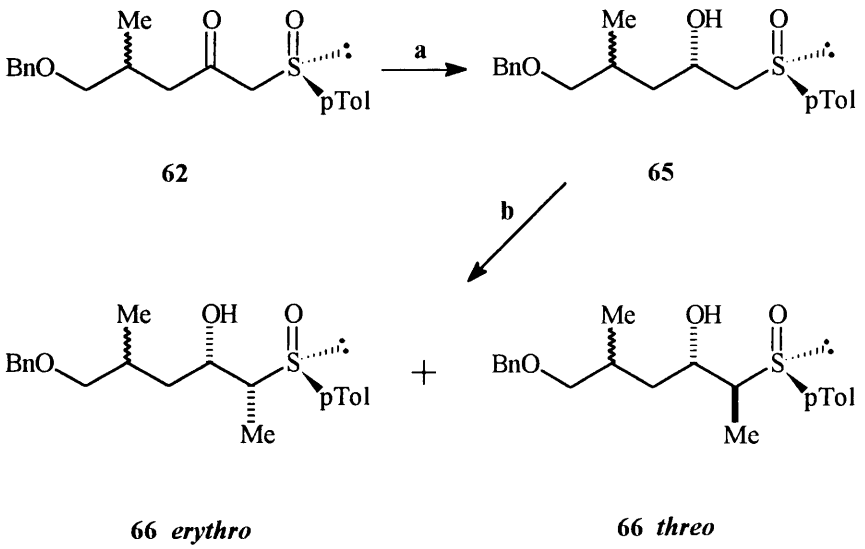
Fig 4.13 **Methylation of the Imine-Anion Reaction Mixture**

The reaction was repeated by forming the anion of **9** (2.0 eq.) using a slight excess of LDA at -40°C. The solution of the anion was allowed to reach room temperature (20°C), and 1 equivalent of the nitrile, **40**, was added to the solution. After 1 h the reaction was worked-up and the product purified

by column chromatography to give the β-ketosulfoxide **62** in 85% yield. This procedure represents a new improved synthesis of β-ketosulfoxides. The only reference found in the literature to the reaction between a sulfoxide and a nitrile was in the formation of β-aminosulfoxides by Tsuchihashi *et al.*[9]

The formed β-ketosulfoxide (**62**) was stereoselectively reduced with DIBALH in 90% yield to the β-hydroxysulfoxide (**65**) which was obtained as a 1:1 mixture of diastereomers due to the C-4 stereogenic centre.

The β-hydroxysulfoxide **65** could now be used to establish the conditions for the introduction of different alkyl groups at the α-position of the sulfoxide moiety. The first successful alkylation of **65** was achieved in excellent yield (94%) using MeI and either BuLi or LDA for the generation of the dianion of **65**. In the case of BuLi the anion was prepared at -78°C and with LDA at -40°C. In both instances the dianion solution was warmed to -20°C, and stirred for 10-30 min before it was placed in a ice-bath before 1.2 eq. MeI was added. Decolourisation (from red-orange to light yellow) showed immediate quenching of the carbanion. No methylation on the hydroxy group occurred. Initially 2.5 eq. of TMEDA, as cation complexation agent, was also used in these reactions although it was later shown that results were just as good without it. The d.r. of 6:1 in the stereoselective formation of the *threo* (*syn*) products, **66** (Fig 4.14), instead of the *erythro* (*anti*) products was evident from the ^{1}H nmr spectrum of the product which showed a value of 7.8 and 8.2 Hz for $J_{\alpha,\beta}$ of the α-methylated β-hydroxysulfoxide.

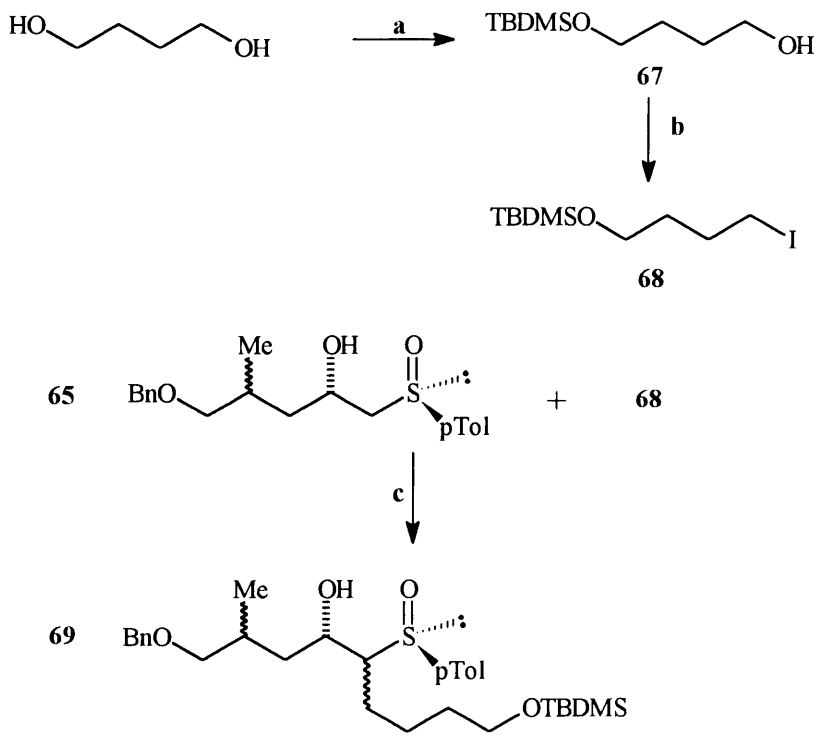


Reagents: **a. DIBALH, -78°C (80%); b. LDA, MeI (94%).**

Fig 4.14 **Methylation of the β-Hydroxysulfoxide, 65**

The next step was to attempt the alkylation with an C_4 alkylhalide that incorporated a protected hydroxy group, a reagent more comparable with the proposed C_8 unit required for the synthesis of the backbone of the fumonisins. The alkylhalide, **68**, was prepared in two steps from 1,4-butanediol. Monoprotection of the 1,4-butanediol was achieved in 76% yield using NaH (1.1 eq.) in THF and quenching the formed anion with *t*-butyldimethyl-chlorosilane. The monoprotected alcohol **67** was converted quantitatively into the iodide **68** using the Ph_3P-I_2 reagent.

The dianion of the β-hydroxysulfoxide **65** was generated as outlined above using BuLi (2.2 eq.) and was followed by the addition of the iodide, **68**, at -10°C. The product, **69**, was obtained in only 30% yield as a 1.5:1 mixture of the *threo*:*erythro* isomers (Fig 4.15) as indicated by ^{1}H nmr spectroscopy: $J_{\alpha,\beta}$ = 8.6 and 8.6 Hz (*threo*) and $J_{\alpha,\beta}$ = 1.2 and 0.9 Hz (*erythro*). The reaction was repeated using LDA (3 eq.) to generate the dianion in the presence of TMEDA, at 0°C, and reaction at room temperature for 2h. The yield was better at 63% but now the *erythro* product was favoured 2:1 over the *threo* product.



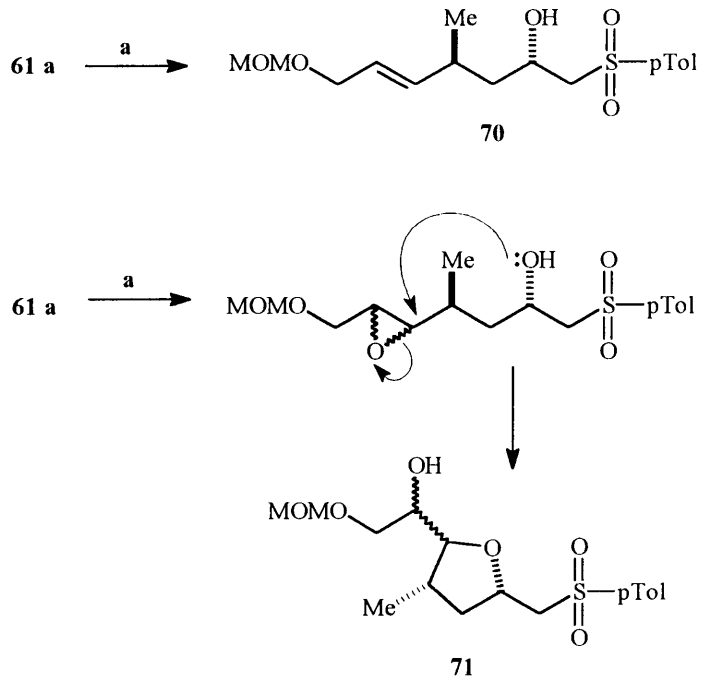
Reagents: a. NaH, *t*-butyldimethylchlorosilane (76%); b. Ph_3P, imidazole, I_2 (100%); c. BuLi (30%) or LDA, TMEDA (63%).

Fig 4.15 Chain Connection with a C_4 Model Compound

The presence of TMEDA in this reaction is essential as no product was formed when this reaction was carried out in the absence of TMEDA. It would appear that TMEDA is essential to stabilise the formed dianion and to expose the carbanion by breaking up solvent aggregates.

A number of reactions were now tried using LDA in the presence of TMEDA to generate the dianion from **61a**, **12a**, **12b** and **65** and using the alkylhalides, **68, 55, 54** and **55** respectively. All these reactions failed and the required product was not obtained.

The acidity of the α-protons in sulfoxides is increased upon oxidation of the sulfoxide to a sulfone group as a result of the greater stabilisation of the formed anion. As the sulfur stereogenic centre is no longer required once the reduction of the β-ketosulfoxide with DIBALH or DIBALH/$ZnCl_2$ has been carried out, it was decided to transform the sulfoxide group in **61a** to a sulfone and use the sulfone in the alkylation reaction.



Reagents: **a. mCPBA (1-2 eq), CH_2Cl_2, RT [70 (53%), 71 (47%)].**

Fig 4.16 **Oxidation of 61a to its Sulfone Products**

The oxidation of the β-hydroxysulfoxide **61a** was done using *m*-chloroperbenzoic acid in CH_2Cl_2. The reaction proceeds smoothly but care must be taken to use only 1 eq. of oxidising reagent and to

monitor the reaction by t.l.c. The reason for this is that **61a** contains an activated double bond which can be converted to the epoxide. The epoxide was never isolated but a considerable amount of a 1:1 mixture of the furan ring products, **71a+b**, was obtained as a result of intramolecular epoxide ring opening at C-5 by the C-2 hydroxy group (Fig. 4.16).

The product was identified as a substituted furan after intensive NMR experiments and deuteruim exchange and derivativisation of the hydroxyl group.

The alkylation reaction of the sulfone, **70**, using propylbromide was unsuccessful and this approach was discontinued.

4.4 REASONS FOR CHAIN CONNECTION FAILURE

The lack of success experienced in the alkylation reaction of the β-hydroxysulfoxides with various alkyl halides was disappointing. The last successful reaction involved the β-hydroxysulfoxide (**65**) and the protected C_4 iodide (**68**). Originally it was thought that only the chain length of the alkyl group would be a problem in the alkylation reaction. However, after the unsuccessful alkylation of **12a** with **55**, a highly oxygenated alkyl halide, it became clear that additional factors determine the outcome of the reaction. Tanikaga *et al.*[4a] and Sato *et al.*[10b] used various sulfoxides with different alkyl substituents, with up to 9 carbon atoms, and electrophiles containing up to 10 carbon atoms, with moderate successes. The alkyl substituents were not poly-oxygenated as was the case in the present study and the lack of success may be ascribed to this difference.

At this stage a number of questions that have a bearing on the alkylation reaction of β-hydroxysulfoxides can be asked. For instance : what is the extent of dianion formation, what is the structure of the dianion, is the abstraction of the acidic proton stereoselective, is a better leaving group required? These are some of the questions that have to be addressed and require answers in order to obtain a better understanding of the alkylation reaction.

Reports in the literature [4,10] agree that the abstraction of the more acidic hydroxy group proton leads to the formation of a Zimmerman-Traxler chair-like six-membered ring – as in the case of hydrogen bonding – but with a lithium cation instead of a hydrogen atom, chelated with the oxygen anion and

the oxygen of the sulfoxide group. The remaining two ligand positions of Li^+ are taken up by solvent molecules or TMEDA. In this way the anion is stabilised and solubility is also increased.

In this proposed structure for the anion, the two acidic prochiral α-protons are diastereotopic and it is therefore reasonable to expect some selectivity in the formation of the carbanion. A carbon-lithium bond is formed and the lithium cation can in turn be chelated by solvent or TMEDA.

The first question that had to be answered was the extent of dianion formation when the β-hydroxysulfoxide was treated with a base such as BuLi or LDA.

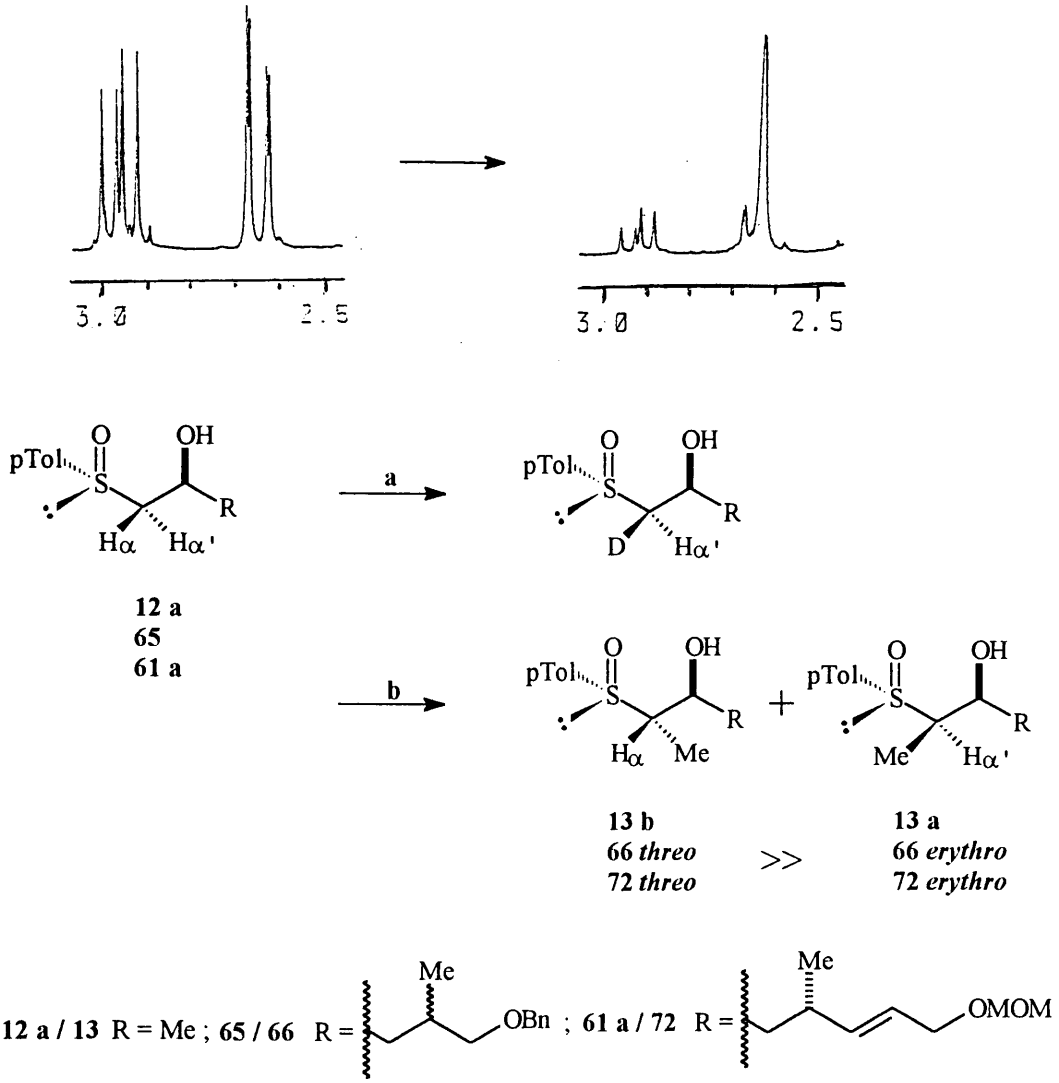
The concentration of the BuLi was determined by the Gilman double titration method.[11] Triphenylmethane was used as indicator and the red colour of its anion at 0°C provided evidence for the presence of a slight excess of BuLi. When BuLi was used as base a colour change was observed as soon as 1 equivalent of BuLi had been added, an indication that the hydroxy group had been deprotonated and when 2 equivalents of base had been added the colour of the solution was dark orange to red when BuLi was used and a golden yellow to orange in cases where LDA was used.

The extent of dianion formation of the β-hydroxysulfoxide was determined by taking a sample of the reaction mixture and quenching the dianion with D_2O, and recording the ^1H nmr spectrum to determine the percentage deuterium exchange before adding the alkylating reagent, MeI, to the remainder of the reaction mixture. The relative stereochemistry of the products was once again deduced from the magnitude of the coupling constants observed for the α-protons. The diastereotopic α-methylene protons of the β-hydroxysulfoxide starting materials, **12a**, **12b**, **65**, and **61a** form the AB part of an ABX spin system and appear as a pair of double doublets with $J_{\alpha,\alpha'}$~13 Hz , $J_{\alpha,\beta}$~7-8 Hz, $J_{\alpha',\beta}$~1-3 Hz.

Interesting results were obtained when the relative stereochemistry of the products derived from the addition of the two electrophilic reagents, D_2O and MeI were compared.

On quenching the dianion obtained from (2*R*, S(*R*))-(*p*-tolylsulfinyl)-propan-2-ol, **12a**, with D_2O, a single deuterium atom was incorporated (~85%). The deuteriated product showed the α-proton as a broadened singlet at δ_c 2.62 (as a result of coupling to the α-D atom). This result indicates that it is the α-proton with the large coupling constant to the β-hydrogen ($J_{\alpha,\beta}$~7-8 Hz), that has been replaced by a deuterium atom *i.e.* the *Re* hydrogen atom, and the *erythro* product is formed (Fig 4.17).

When MeI is used to quench the dianion, the product has almost exclusively the *threo* relative configuration (>10:1) on the basis of the magnitude of the observed coupling constant, $J_{\alpha,\beta}$~7-8 Hz.

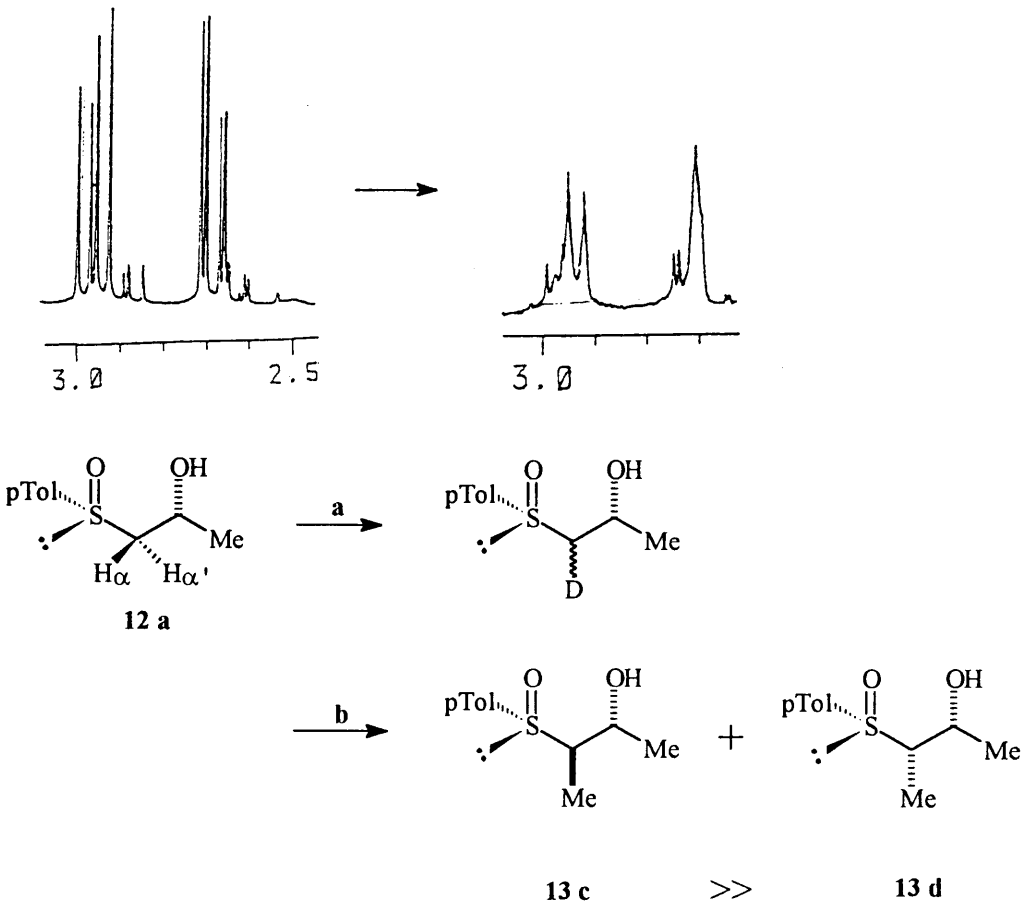


Reagents: **a. LDA (~3 eq), D_2O; b. LDA (~3 eq), MeI.**

Fig 4.17 **Stereochemistry of the Reaction of *S*-Hydroxysulfoxides with Electrophiles**

When the same set of reactions was carried out on (2*S*, S(*R*))-(*p*-tolylsulfinyl)-propan-2-ol, **12b**, the results were expected to complement those obtained for (2*R*, S(*R*))-(*p*-tolylsulfinyl)-propan-2-ol, **12a**. However, these expectations were not realised and the results only served to confuse the issue further. Although a single deuterium atom was incorporated on quenching the dianion obtained from **12b** with D_2O, the ^1H nmr spectrum of the deuteriated product showed that deuterium incorporation at C-α had occurred with no stereoselectivety : the C-α *Re* and *Si* hydrogen atoms had been replaced to an equal

extent (Fig 4.18). In complete contrast to this result, it was found that the use of MeI gave only the *threo* product (> 10:1) (**13c**).



Reagents: **a. LDA (~3 eq), D_2O; b. LDA (~3 eq), MeI.**

Fig 4.18 **Stereochemistry of the Reaction of a *R*-Hydroxysulfoxide with Electrophiles**

The problem at this stage is to formulate a model for the reactions of a β-hydroxysulfoxide with an electrophile (D_2O and MeI in this case) that is able to explain the results obtained.

The first hint that would help in this endeavour was provided by a literature report on the same type of experiments but using the anion obtained from benzylmethylsulfoxides.[12] The reaction of these α-anions with both D_2O and methyl iodide was stereoselective but it was found that the products of the reactions had the opposite configuration.

This result was explained by the intermediacy of a planar carbanion as in this way the course of the reaction could proceed either with inversion or retention of configuration. Evidence for a planar

carbanion was provided by the X-ray crystal structure of an α-lithiated α-(phenylethyl)-phenyl sulfoxide in which the α-carbon atom is clearly planar (Fig 4.19).[13]

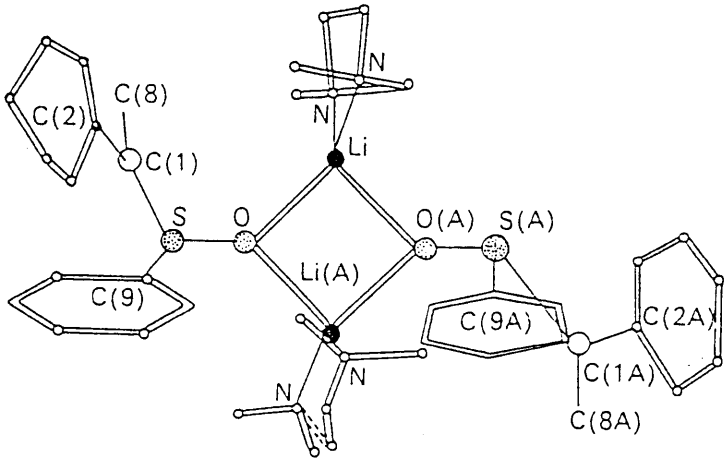


Fig 4.19 **A Crystal Structure of a Planar α-Sulfoxide Anion**

The reason why the reaction proceeds with retention of configuration in the case of oxygen-containing electrophiles such as D_2O, is that chelation occurs with the Li^+, which is still on the same side as the hydrogen atom that it replaced, and reaction of the carbanion with the electrophile occurs from the Li^+ side (see Figure 4.20). When MeI is the electrophilic reagent such chelation with Li^+ does not occur, and attack occurs for steric reasons from the side away from the Li^+ resulting in an overall course of the reaction with inversion of configuration.

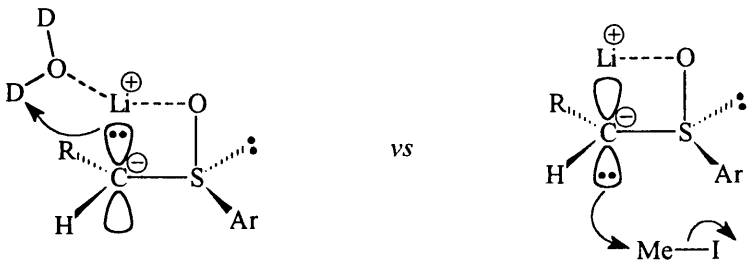


Fig 4.20 **Retention and Inversion of Configuration at C_α in the Reaction with Different Electrophiles**

The above observations may also be valid for the reaction of the β-hydroxysulfoxides **12a** and **12b** with electrophilic reagents as outlined earlier.

4.5 ALTERNATIVE STATEGIES FOR CARBON-CARBON BOND FORMATION USING CHIRAL SULFOXIDES

4.5.1 Alkylation of a β-Ketosulfoxide Followed by Reduction

The first approach to this strategy involves the generation of a carbanion at C-1 of a β-ketosulfoxide such as **11** followed by reaction with an appropriate alkylhalide. A problem with this method is that both the C-1 and C-3 hydrogen atoms are acidic. The increased acidity of the C-1 hydrogen atoms (pK_a~ 18) is the result of stabilisation of the anion by both the carbonyl and the sulfoxide group. The increased stability of this carbanion makes it less nucleophilic than a C-3 carbanion.

When 1 eq. of LDA was added to the β-ketosulfoxide (**11**) (Fig 4.21) and the formed anion treated with n-propyl bromide, no reaction occurred even when the mixture was refluxed. It was only when 2 eq. of LDA was used for the generation of a dianion that reaction with n-propyl bromide (1 eq.) occurred but exclusively at the C-3 position to give product, **73**. From this result it is evident that the α-carbanion is not nucleophilic enough to react with a reactive electrophile such as n-propyl bromide.

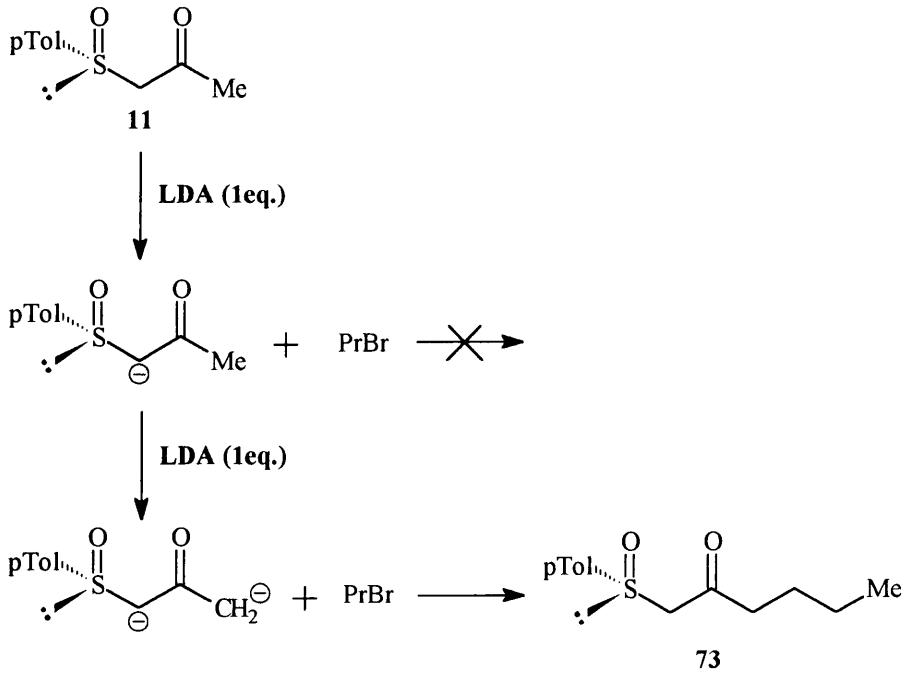


Fig 4.21 **Atempted Alkylation of a β-Ketosulfoxide**

The second approach is the synthesis of the C_9 chiral sulfoxide (**P**) starting from the iodo compound (**55**) and the anion formed from the C_1 chiral sulfoxide (**9**) and LDA. The sulfoxide (**P**) in turn can be used for the synthesis of an α-alkyl-β-ketosulfoxide by using an ester or nitrile corresponding to a part or the whole of the C-11–C-20 backbone of the fumonisins. No major problems are envisaged in these two steps but the subsequent stereoselective reduction of the carbonyl group may be jeopardised. The eventual success of this approach will only be known when the synthesis is attempted on the real fragments of the fumonisin backbone (Fig 4.22).

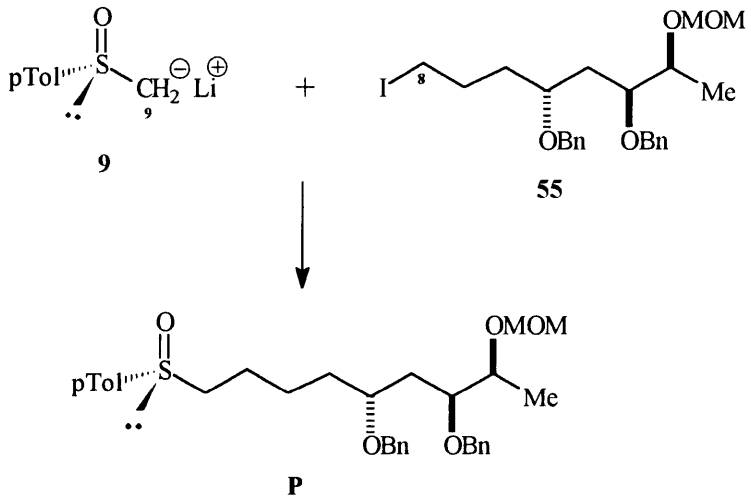


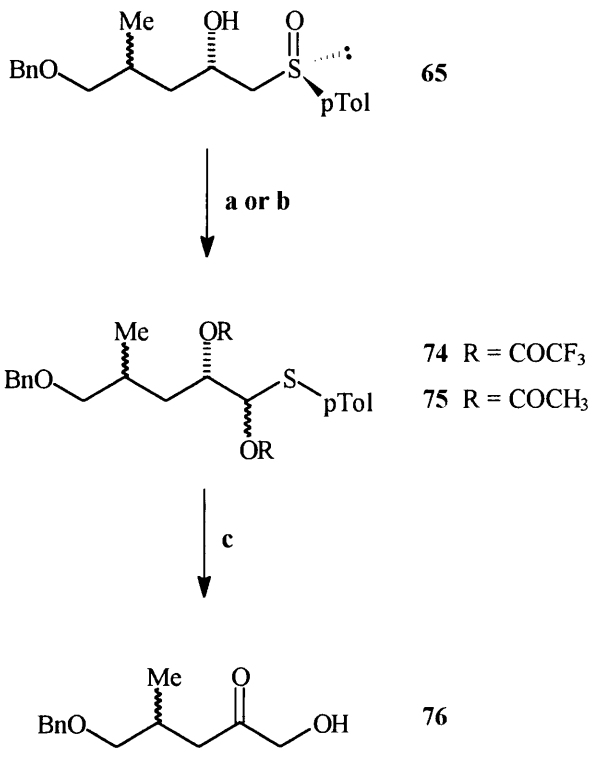
Fig 4.22 Proposed Connection of 9 with the C_8 Right-side Fragment

4.5.2 The Pummerer Rearangement

The Pummerer rearrangement is an elegant way of transforming a sulfoxide group into O,S-acetal (see Section 2.2.5) which can subsequently be converted to a primary alcohol without isolating the aldehyde. The reaction has been used extensively in conjunction with chiral sulfoxide methodology in many asymmetric syntheses by Solladié *et al.*[14,17] and others.[18]

The rearrangement can be brought about by reaction of the sulfoxide with acetic anhydride and soduim acetate at 130°C for 12 h [14,17] or with trifluoroacetic anhydride and lutidine in acetonitrile at 0°C for 30 min. to 2 h.[18] The resulting O,S-acetal can be converted to either the aldehyde by hydrolysis or reduced to the alcohol.

These reactions were tried on the sulfoxide **65** (Fig 4.23) and led to the rearranged products (**74**) and (**75**). A variety of hydrolysis methods : mercury(II)chloride in aqueous acetonitrile, $K_2CO_3/CuCl_2$ in aqueous acetonitrile and K_2CO_3/MeI failed to yield the corresponding aldehyde as was reported by Sugihara *et al.*[18a] and Bravo *et al.*[18b] The trifluoroacetate derivative **74** did however decompose on silica gel to a product which after K_2CO_3 hydrolysis in aqueous methanol, was identified as the α-hydroxyketone, **76**. The same product was found when the diacetate, **75**, was hydrolysed with 1% KOH in MeOH:H_2O (2:1) under reflux. The formation of the α-hydroxyketone (**76**) rather than a α-hydroxyaldehyde is outlined in Figure 4.24 and is attributed to the greater stability of the ketone. The stereogenic centre present in the β-hydroxysulfoxide starting material is lost or at best epimerised. Aldehydes with the hydroxy group protected as the benzyl ether have been prepared without epimerisation[18b] but K_2CO_3 in MeOH has also been used to isomerise[19] the same type of compound!



Reagents: **a. CF_3CO_2H, 2,6-Lutidine, b. AcOH, AcONa (82%); c. 2% KOH, MeOH/H_2O (65%) or SiO_2, K_2CO_3, H_2O/MeOH.**

Fig 4.23 **Pummerer Rearrangement of 65**

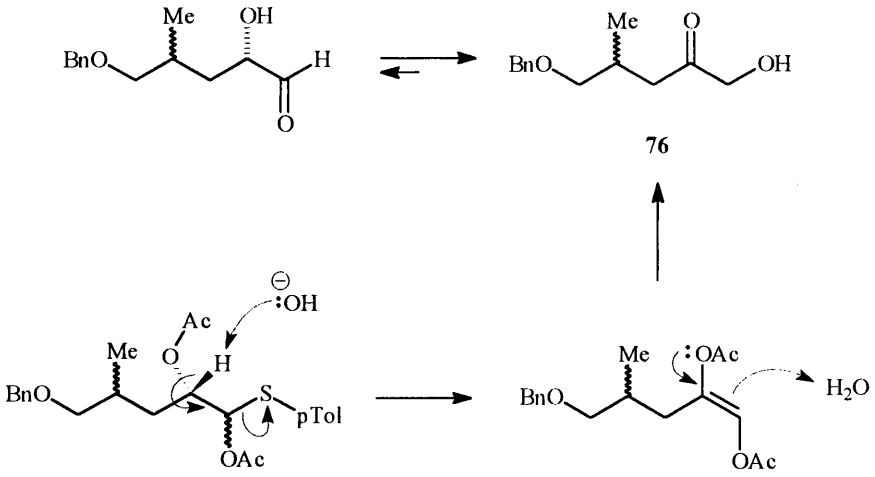
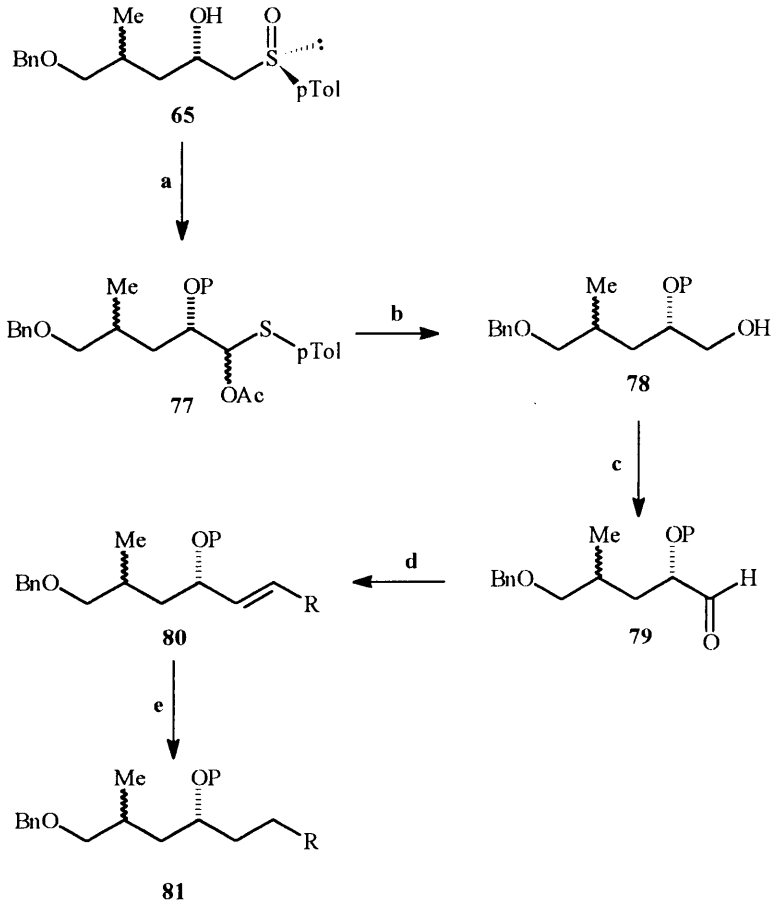


Fig 4.24 **Proposed Mechanism for the O,S-acetal Cleavage with Base**

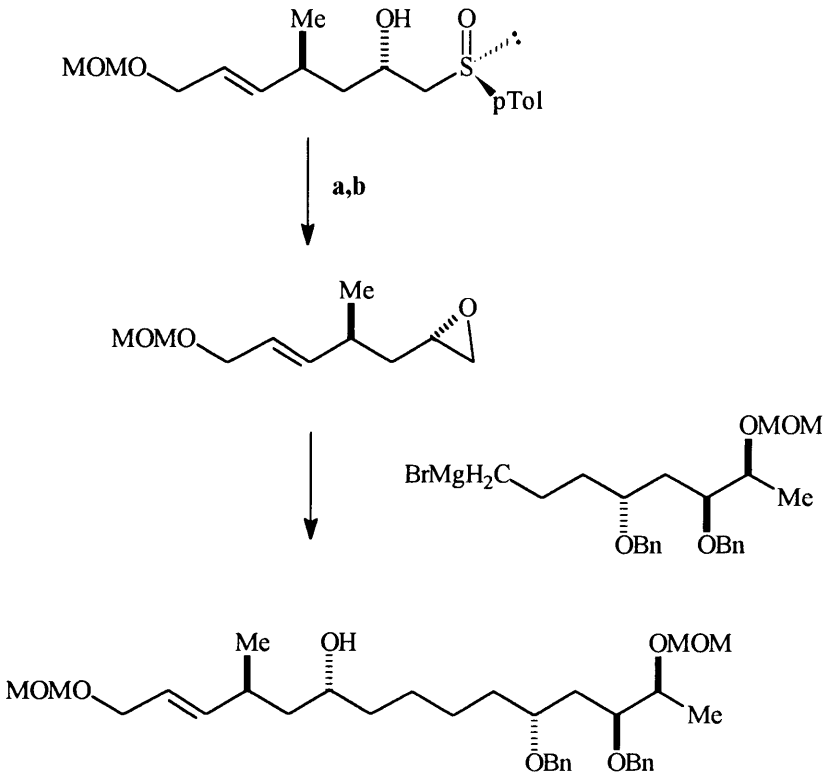


Reagents: **a. AcOH, AcONa, 120°C; b. $LiAlH_4$ or Raney/Ni,H_2;**
c. Swern oxidation; d. RCH_2PPh_3/BuLi; e. Raney/Ni, H_2.

Fig 4.25 **Proposed Chain Connection by use of a Pummerer Rearrangement and Wittig Reaction**

4.5.3 Epoxide Formation

As mentioned in Section 2.2.5 β-hydroxysulfoxides have been successfully converted to epoxides. The most general method involves the reduction with $LiAlH_4$ to the sulfide followed by formation of the sulfonium salt with $Me_3O^+BF^-_4$ (Fig 4.26). The sulfonium salt acts as a leaving group and aqueous base catalyses the epoxide formation. Epoxide opening with nucleophilic reagents occurs selectively at the primary position.[19] Kosugi *et al.*[20] reacted such an epoxide with a Grignard reagent with very high stereoselectivity and good yield, but workers in the field of organic synthesis of natural products seem to prefer Pummerer rearrangements and Wittig reactions over this route for an unknown reason.



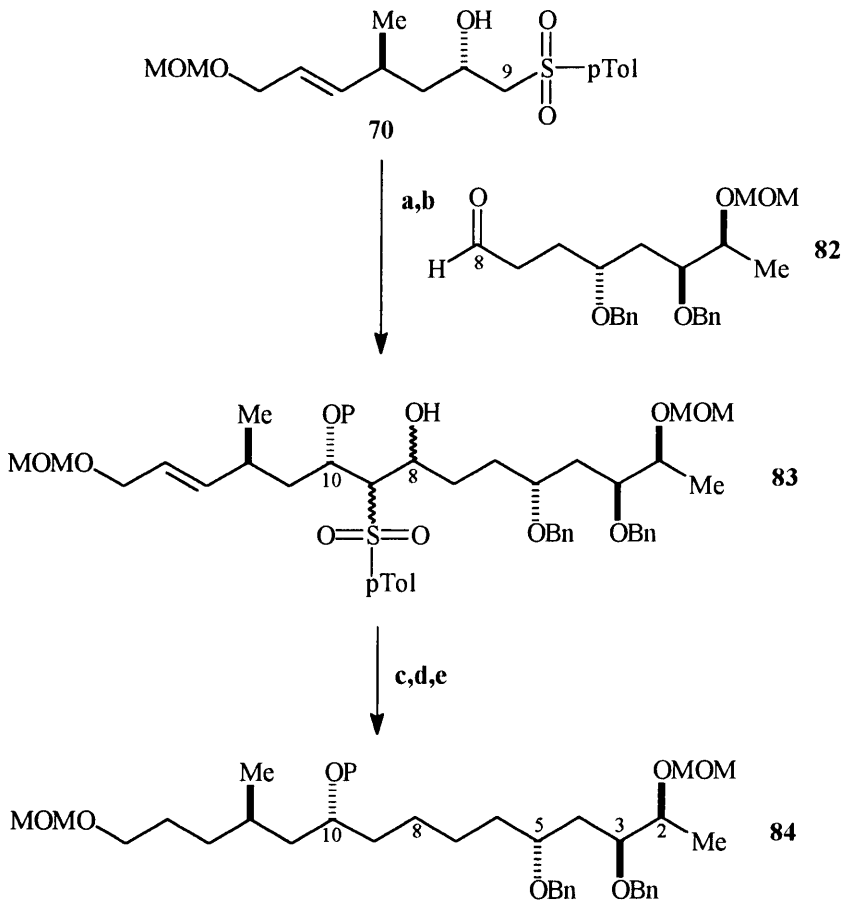
Reagents: a. $LiAlH_4$; b. $Me_3O^+BF_4^-$, NaOH or K_2CO_3.

Fig 4.26 Proposed Formation of Epoxide and Subsequent Coupling with C_8 Grignard Reagent

4.5.4 The Julia Coupling

The Julia-type reaction involving a sulfonium stabilized sulfone carbanion reacting with an aldehyde is another possible alternative for bringing about the linkage of two acyclic fragments.[21] After hydroxy group protection in **61a**, oxidation with mCPBA will yield the sulfone **70** (Fig. 4.27). The

corresponding anion can then be reacted with the right-side fragment having an aldehyde functionality on the terminal carbon atom, **82**. On converting the resulting diastereomeric mixture of β-hydroxysulfones, **83**, to the acetate derivative, reaction with sodium amalgam[22] yields the alkene **84** which upon hydrogenation with Raney/Ni catalyst gives the extended carbon backbone of the fumonisins.



Reagents: **a. protection of C-10 OH; b. LDA, 82; c. Ac_2O; d. Na/Hg; e. Raney/Ni, H_2.**

Fig 4.27 **Proposed Chain Connection by means of Julia Coupling**

4.6 CONCLUSION

Although chiral sulfoxides have been studied extensively over the last 15 years, the results outlined in this thesis point to some aspects that require further study. For example, the question as to what factors influence the reduction of α-alkyl-β-ketosulfoxides and whether only 1,3-induction or both 1,2 and 1,3-induction play a role, is important in the present synthetic programme.

The lack of (or limited) success in the alkylation of β-hydroxysulfoxides leads to uncertainty about the actual mechanism and transition states in this reaction. The use of a better leaving group, like the triflate group (trifluoromethyl sulfonate), should also be investigated further.

4.7 REFERENCES

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5 EXPERIMENTAL

5.1 GENERAL

Air - and/or moisture sensitive reactions were carried out under an atmosphere of nitrogen or argon in glassware pre-dried at 110-130°C. Room temperature (RT) refers to 18-25°C. Evaporations were done under reduced pressure (*in vacuo*). All reagents were of synthetic grade and were used without any further purification. When necessary, solvents and reagents were dried according to standard methods prior to use.[1] Solvents used for chromatography or extractions were only distilled.

Melting points (mp) were determined on a Kofler hot stage apparatus and are uncorrected. Optical rotations were determined with a Perkin Elmer 241 polarimeter for solutions in chloroform ($CHCl_3$). Mass spectra were recorded on a VG 7070-E spectrometer using the fast atom bombardment technique (FAB). A glycerol matrix was used with xenon as the bombardment gas.

Nuclear magnetic resonance (NMR) spectra were measured for $CDCl_3$ solutions (unless otherwise indicated) on a Bruker AC-300 (7.0T) spectrometer. All chemical shifts are reported as δ values downfield from Me_4Si. Proton-proton coupling constants (*J*) are given in Hz. Spectral coupling patterns are designated as follows:

s/s :	singlet;	d/D :	doublet;	t/T :	triplet;
q/Q :	quartet;	m :	multiplet;	bs :	broad signal;
dd :	doublet of doublets;	dt :	doublet of triplets;	dq :	doublet of quartets.

The assignments of the signals in the ^1H nmr spectra are based on first-order analysis of the spin systems and were confirmed by $^1H\{^1H\}$ decoupling experiments. The ^{13}C chemical shifts were obtained from proton-decoupled spectra. The multiplicities of the different ^{13}C resonances were deduced from the proton-decoupled CH, CH_2, and CH_3 subspectra obtained using the DEPT pulse sequence. The signals of the proton-bearing carbon atoms were correlated with specific proton resonances in two-dimensional (2-D) $^{13}C\{^1H\}$ heteronuclear chemical shift correlation experiments (HETCOR) utilizing the one-bond (^{13}C,^1H) spin-spin couplings. Standard Bruker pulse programs were used in these experiments.

The course of reactions was followed on thin-layer chromatography (tlc) using glass plates coated with silica gel (60 F_{245} Merck). Relative front values (R_f) in various solvents systems were recorded for all products and intermediates. Column chromatography was performed on Merck silica gel 60 (60-200μm, 70-230 mesh).

Stereoisomer composition is given as enantiomer excess (e.e.) values in the case of enantiomers and diastereomeric excess (d.r.) values in the case of diastereomers. E.e. values were determined by examining the diastereomeric purities of the Mosher ester derivatives using ^{1}H NMR and ^{19}F NMR. The (+)-(*R*)-α-methoxy-α-trifluoromethyl-phenylacetyl chloride (MTPCl) was prepared from the corresponding acid (MTPA) and thionyl chloride.[2] The acid chloride was then added to the chiral alcohol in the presence of DMAP and extraction with saturated aqueous $NaHCO_3$ yielded the mixture of diastereomeric esters.

5.1.1 Estimation of Butyl Lithium Concentration by Double Titration.

An aliquot of the butyl lithium test solution (1cm^3) was added slowly with a syringe to 10cm^3 water. This mixture was titrated with 0.05*N* HCl using phenolphthalein as indicator. The titration volume V1 (in cm^3) indicates the total base content.

Again a 1cm^3 aliquot of the test solution was added to benzyl chloride (~1cm^3) in anhydrous THF (10 cm^3) under argon atmosphere and stirred for 10 min. Water (10 cm^3) was added and this mixture was titrated with 0.05N HCl. The titration volume V2 (in cm^3) refers to the LiOH concentration.

The alkyl lithium concentration (*M*) is then determined as follows:

[alkyl lithium]=0.05 (V1-V2) mol.

5.1.2 Spraying Solutions

A cerium(IV) sulfate/sulfuric acid solution was prepared from cerium(IV) sulfate (1% *w/v*) dissolved in 6*N* sulfuric acid. This was sprayed on tlc plates and heated with a Bunsen burner until light brown to black spots indicated the position of the chromatographed compounds.

5.1.3 Wittig and Wittig-Related Reagents

***(Carbomethoxymethylidene) triphenylphosphorane* 53.** A solution of Ph_3P (134.1 g, 50 mmol) in toluene (25cm^3) was stirred vigorously while methyl chloroacetate (4.4 cm^3, 50 mmol) was added. The reaction mixture was refluxed overnight, cooled in an ice-bath and the colourless phosphonium salt was filtrated. The salt was washed with cold toluene (30 cm^3) and pentane (20 cm^3) and then dissolved in water (300 cm^3) at RT. Some impurities were removed by extraction with ether (200 cm^3) after which two drops of phenolphthalein solution were added. The aqueous solution was stirred vigorously and cooled in an ice-bath as it was titrated with a 2*N* NaOH solution until the pink equivalence point was reached. During the titration process the crystalline phosphorane precipitated from the solution and was collected by filtration, washed thoroughly with cold water and dried at 60°C *in vacuo* (10 g, 60%); mp. 170-173°C (Lit.[3], 169-171°).

Diisopropyl methoxycarbonyl methylphosphonate. A mixture of tri-isopropylphosphite (18.7 g, 100 mmol) and methyl chloroacetate (10.8 g, 100 mmol) was refluxed for 24 h (~130°C). The product was obtained after distillation at 100°C/0.5 mm Hg as a clear liquid (22 g, 92%); R_f 0.16 (hexane-EtOAc, 4:1), (only visible with I_2).

5.1.4 Standard Isolation Procedure

The resulting reaction mixture was partitioned between an organic solvent and water, brine, saturated NH_4Cl or 1*N* HCl or otherwise stated, followed by the extraction of the aqueous layer with 2-4 portions of the indicated solvent. The combined organic extracts were washed with brine or saturated aqueous $NaHCO_3$ when necessary and dried (Na_2SO_4), filtered and concentrated *in vacuo*.

5.1.5 General Experimental Procedures

Several experiments were repeated on different compounds and in these cases only a reference to the following general procedures will be given.

a) SULFOXIDE, ESTER CONDENSATIONS.[4]

A solution of sulfoxide (2.05 eq.) was added to a cooled (-30°C) THF solution of LDA (2.2 eq). The mixture was stirred for 30 min. while warming to 0°C after which it was cooled down to -40°C and

stirred for 5-10 min. The appropriate ester (1.0 eq.) in THF solution was then added slowly. On completion of addition, the temperature was allowed to rise to RT and the reaction mixture was stirred for another 1-2 h. The reaction mixture was quenched with saturated NH_4Cl solution and acidified with 1N hydrochloric acid. This mixture was extracted with 3 portions of EtOAc and the combined organic layers were dried over Na_2SO_4 (anh) and concentrated *in vacuo*. The pure product was obtained after column chromatography (hexane-EtOAc, 2:1→1:1). The β-ketosulfoxide normally eluted just before the starting material. Yields of 70%-90% were recorded.

b) REDUCTION OF β-KETOSULFOXIDES WITH DIBALH.[5]

To a solution of β-ketosulfoxide in THF at -78°C was slowly added 1-1.2 eq. of DIBALH (~1M solution in hexanes) and stirred at -78°C for ½-1 h. The reaction was monitored on tlc - more DIBALH was added when necessary. The reaction mixture was quenched with MeOH and concentrated *in vacuo* upon which the solution became an opaque gel/solid. This gel was dissolved in CH_2Cl_2 and saturated NH_4Cl/1*N* HCl and isolated by the general procedure. Column chromatography removed any unreacted starting material and afforded the hydroxysulfoxide in yields of 90-95%.

c) REDUCTION OF β-KETOSULFOXIDES WITH DIBALH/$ZnCl_2$.[5]

$ZnCl_2$ (flame dried *in vacuo*) (1.2 eq.) was added to a THF solution of the β-ketosulfoxide starting material and the reaction mixture stirred for 1 h at RT before cooling to -78°C. Procedure b) was followed further. Yields of 90-95% were achieved after column chromatography (hexane-EtOAc, 1:1→EtOAc).

d) ALKYLATION OF β-HYDROXYSULFOXIDES USING BuLi.

The β-hydroxysulfoxide was dissolved in THF (~1mmol/20cm^3), TMEDA (~2.5 eq.) was added and the solution was cooled while stirring to -78°C. A crystal of Ph_3CH (indicator) was added followed by ~2.5 eq. BuLi (1.6M in hexanes). After 1eq. BuLi had been added the colour of the solution changed to orange and when 2.2-2.5 eq. had been added the solution became dark orange/red (colour of indicator). The solution was then allowed to warm to -20°C and placed in an ice-bath. After 5 min. 1.2 eq. of alkylhalide (iodide or bromide) in THF was added. The red colour disappeared immediately and the reaction mixture became colourless to light yellow after a few minutes. The mixture was stirred at RT for another 15 min (up to an hour in some cases) after which it was quenched with saturated NH_4Cl, acidified with 1*N* HCl and extracted with EtOAc. The standard

isolation procedure and column chromatography (hexane-EtOAc, 1:1→EtOAc) yielded either mixtures of diastereomers or separated isomers in 50-95% yields.

e) ALKYLATION OF β-HYDROXYSULFOXIDES USING LDA

To a cooled (-20°C) solution of LDA (3.5eq.) in THF/hexane was added the hydroxysulfoxide (1eq.) and TMEDA (2.5 eq.) in THF. After 10 min at -20°C and 15 min at 0°C the alkyl iodide in THF was slowly added and the reaction mixture was stirred at RT for 10 min (MeI) and 2 h (**68**). The same isolation procedure was followed as in d) and gave products in 60-90% yield.

f) SULFOXIDE, NITRILE CONDENSATIONS

To a cooled (-40°C) solution of 2.5 eq. of LDA in hexane/THF was added a solution of the sulfoxide (**9**) (2.1 eq.). The resulting solution was placed in an ice bath for 15 min upon which the solution became yellow. After equilibration at RT, 1.0 eq. of the nitrile in THF was added slowly to give an orange solution which darkened with time. The solution was stirred for an hour before quenching with 1*N* HCl or H_2SO_4. After usual work up and column chromatography (hexane-EtOAc, 3:2→EtOAc) the keto sulfoxide was obtained in 75-80% yields.

5.2 PROCEDURES

5.2.1 Preparation of Left Side Model Compound, 30

***Methyl (2S)-2-methyl-3-(trityloxy)propanoate* 28.-** A mixture of methyl (-)-(2*S*)-3-hydroxy-2-methyl-propanoate, **29**, (5.19g, 50mmol), DMAP (1.2 g, 10 mmol), pyridine (16.1 cm^3, 200 mmol) and chloro triphenylmethane (15.33 g, 55 mmol) in CH_2Cl_2 (100 cm^3) was refluxed for 6 h. The reaction mixture was cooled and neutralized with 1*N* hydrochloric acid, diluted with CH_2Cl_2 and worked-up according to the standard isolation procedure. Column chromatography (hexane-$CHCl_3$, 3:1→1:1) and crystallization from hexane-EtOAc afforded compound **28** as slightly yellow crystals (17 g, 95%); mp 96-97°C; R_f 0.55 (hexane-EtOAc, 4:1); $[\alpha]_D^{19}$ +15.6 (*c* 1.2, $CHCl_3$).

δ_H 7.436-7.191 (aromatic protons),
3.692 (s, 3H, OMe),
3.310 (dd, H, $J_{3a,3b}$ 8.7, $J_{3a,2}$ 6.9, H-3a),
3.182 (dd, H, $J_{3b,3a}$ 8.7, $J_{3b,2}$ 5.7, H-3b),
2.729 (ddq, H, $J_{2,Me}$ 7.0, $J_{2,3a}$ 7.0, $J_{2,3b}$ 7.0, H-2),
1.150 (d, 3H, $J_{Me,2}$ 7.0, Me);

δ_C 13.98Q (Me), 40.39D (C-2), 51.54Q (OMe), 65.34T (C-3), 86.41S ($OCPh_3$), 126.93-128.67 (aromatic carbons), 143.98S (*ipso*-aromatic carbon), 175.35S (C-1);

MS *m/z* 360 $[M]^+$.

***(2R)-2-Methyl-3-(trityloxy)propanol* 27.-** Compound **28** (10.8 g, 30 mmol) in THF (50 cm^3) was cooled in an ice bath and treated with $LiAlH_4$ (1.14 g, 30 mmol). The reaction mixture was stirred at RT for 2 h after which the excess $LiAlH_4$ and lithium salts were allowed to settle and the reaction mixture was decanted. The solids were washed five times by decantation with ether. The combined organic layers were washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo*. A single crystallization from hexane-EtOAc afforded **27** as slightly yellow crystals (9.7 g, 98%); mp 75-75.5°C; R_f 0.3 (hexane-EtOAc, 4:1), $[\alpha]_D^{23}$ +31.7 (*c* 3.0, $CHCl_3$);

δ_H 7.510-7.443 (m, aromatic protons),
7.343-7.215 (m, aromatic protons),

3.600 (d, 2H, $J_{1,2}$ 6.0, H-1),
3.239 (dd, H, $J_{3a,3b}$ 9.2, $J_{3a,2}$ 4.7, H-3a),
3.074 (dd, H, $J_{3b,3a}$ 9.1, $J_{3b,2}$ 7.6, H-3b),
2.371 (s, H, OH),
2.050 (m, H, H-2),
0.892 (d, 3H, $J_{Me,2}$ 6.8, Me);

δ_C 13.75Q (Me), 36.03D (C-2), 67.15T, 67.51T (C-1, C-3), 86.83S ($OCPh_3$), 127.54-128.57 (aromatic carbons), 143.92S (*ipso*-aromatic carbon);

MS *m/z* 332 $[M]^+$.

***Ethyl (E,4R)-4-methyl-5-(trityloxy)-pent-2-enoate* 25a.-** To a solution of oxalyl chloride (2.6 cm^3, 30 mmol, 1.1 eq.) in CH_2Cl_2 (50 cm^3) at -78°C was added 2.5 eq. DMSO (4.8 cm^3, 67.5 mmol) and stirred for 15 min. **27** (8.98 g, 27 mmol, 1 eq.) in CH_2Cl_2 (25 cm^3) was slowly added over 10 min and the reaction mixture was stirred at -78°C for another hour. NEt_3 (18.7 cm^3, 135 mmol, 5 eq.) was added and after an hour the solution was allowed to warm to 0°C. The standard isolation procedure (avoiding high temperatures) gave the crude aldehyde **26** as a thick oil. **26** could be crystallized from hexane but epimerised very fast and crystals showed no optical rotation; mp 162-163°C (racemic); R_f 0.6 (hexane-EtOAc, 4:1);

(2*S*)-2-Methyl-3-(trityloxy)propanal **26**.

δ_H 9.690 (d, H, $J_{3,2}$ 1.6, H-1),
7.480-7.392 (m, aromatic protons),
7.337-7.212 (m, aromatic protons),
3.387 (dd, H, $J_{3a,3b}$ 9.2, $H_{3a,2}$ 5.0, H-3a),
3.353 (dd, H, $J_{3b,3a}$ 9.2, $J_{3b,2}$ 6.5, H-3b),
2.603 (m, H, H-2),
1.120 (d, 3H, $J_{Me,2}$ 6.9, Me).

δ_C 10.78Q (Me), 47.02D (C-2), 63.63T (C-3), 86.70S ($OCPh_3$), 127.08-128.63 (aromatic carbons), 143.72S (aromatic carbon), 203.94D (C-1);

MS *m/z* 330 $[M]^+$.

The crude aldehyde **26** was used immediately in the next step. Diethyl ethoxycarbonylmethylphosphonoacetate (24.2 g, 108 mmol, 4 eq.) was dissolved in THF (100 cm^3) and the solution cooled in an ice-bath before *t*-BuOK (10.66 g, 95 mmol, 3.5 eq.) was added. The mixture was stirred for 2 h at RT before cooling to -78°C. The aldehyde **26** in THF (50 cm^3) was then added dropwise and stirred for 30 min at -78°C before ether and saturated NH_4Cl were added. The usual work-up and column chromatography (hexane-EtOAc, 4:1 and ether-hexane, 1:9) gave the unsaturated ester **25a** (7.45 g, 69%); R_f 0.55 (hexane-ether, 4:1) $[\alpha]_D^{19}$ +5.4 (*c* 0.9, $CHCl_3$).

Ethyl (*E*, 4*R*)-4-methyl-5-(trityloxy)pent-2-enoate **25a**.

δ_H 7.455-7.199 (m, aromatic protons),
6.951 (dd, H, $J_{3,2}$ 15.7, $J_{3,4}$ 7.3, H-3),
5.839 (dd, H, $J_{2,3}$ 15.7, $J_{2,4}$ 1.3, H-2),
4.196 (q, 2H, J 7.2, OEt),
3.106 (dd, H, $J_{5a,5b}$ 8.8, $J_{5a,4}$ 6.7, H-5a),
3.044 (dd, H, $J_{5b,5a}$ 8.8, $J_{5b,4}$ 6.2, H-5b),
2.611 (m, H, H-4),
1.293 (t, 3H, J 7.2, OEt),
1.090 (d, 3H, $J_{Me,4}$ 6.9, Me).

δ_C 14.25Q (CH_3, OEt), 16.20Q (Me), 37.20D (C-4), 60.13T (CH_2, OEt), 67.21T (C-5), 86.08S ($OCPh_3$), 120.89D (C-2), 126.93-128.69 (aromatic carbons), 144.04S (*ipso*-aromatic carbon), 151.47D (C-3);

MS *m/z* 400 $[M]^+$.

The *Z*-isomer, **25b**, was also formed as a byproduct (1.35g, 13%); R_f 0.4 (hexane-ether, 4:1); $[\alpha]_D^{19}$ -65.5 (*c* 1.4, $CHCl_3$).
Ethyl-(*Z*, 4*R*)-4-methyl-5-(trityloxy)pent-2-enoate **25b**.

δ_H 7.445-7.181 (m, aromatic protons),
6.099 (dd, H, $J_{3,2}$ 11.5, $J_{3,4}$ 9.8, H-3),
5.779 (dd, H, $J_{2,3}$ 11.7, $J_{2,4}$ 0.7, H-2),
4.184 (q, 2H, J 7.1, OEt),

3.869 (m, H, H-4),
3.064 (dd, H, $J_{5a,5b}$ 8.6, $J_{5a,4}$ 5.3, H-5a),
2.967 (dd,H,$J_{5b,5a}$ 8.6, $J_{5b,4}$ 6.7, H-5b),
1.291 (t, 3H, J 7.1, OEt),
1.044 (d, 3H, $J_{Me,4}$ 6.9, Me);

δ_C 14.28Q (CH_3, OEt), 17.05Q (Me), 33.67D (C-4), 59.83T (OCH_2CH_3), 67.21T (C-5), 119.52 (C-2), 126.85-128.76 (aromatic carbons), 144.24S (*ipso*-aromatic carbon), 152.96S (C-3);

MS *m/z* 400 $[M]^+$.

***Methyl (E, 4R)-4-methyl-5-(trityloxy)pent-2-enoate* 25c.-** The same procedure as for **25a** was followed (2.4 g, 7.2 mmol, **27**) except that methyl diisopropyl phosphonoacetate (6.86 g, 29 mmol, 4eq.) was used. A reaction time of 20 min at -70°C gave the best results. **25c** was obtained after column chromatography (hexane-EtOAc, 5:1→3:1) as a clear oil (2.3 g, 82% over 2 steps); R_f 0.6 (hexane-EtOAc, 4:1); $[\alpha]_D^{19}$ +6.9 (*c* 1.0, $CHCl_3$), +11.3 (*c* 3.4, acetone);

δ_H 7.433-7.187 (m, aromatic protons),
6.934 (dd, H, $J_{3,2}$ 15.8, $J_{3,4}$ 7.3, H-3),
5.827 (dd, H, $J_{2,3}$ 15.8, $J_{2,4}$ 1.2, H-2),
3.719 (s, 3H, OMe),
3.0767 (dd, H, $J_{5a,5b}$ 8.9, $J_{5a,2}$ 6.8, H-5a),
3.035 (dd, H, $J_{5b,5a}$ 8.9, $J_{5b,4}$ 6.1, H-5b),
2.594 (m, H, H-4),
1.070 (d, 3H, $J_{Me,4}$ 6.8, Me);

δ_C 16.22Q (Me), 37.26D (C-4), 51.40Q (OMe), 67.21T (C-5), 120.47D (C-2), 126.92-128.70 (aromatic carbons), 144.06S (*ipso*-aromatic carbon), 151.87D (C-3).

***(E, 4R)-4-Methyl-5-(trityloxy)pent-2-enol* 24.-** The *E*-unsaturated ester **25a** (4.8 g, 12 mmol) was dissolved in THF (100 cm^3), cooled to -78°C and treated with 3 eq. of DIBALH (36 cm^3, 1 M in hexanes). The reaction mixture was stirred for 2 h before warming to -30°C and quenching with MeOH (~20 cm^3). The solvents were evaporated *in vacuo* to a white solid which was then dissolved in water, CH_2Cl_2 and 1*N* HCl, extracted with 3 portions of CH_2Cl_2 (50 cm^3), washed with saturated

aqueous $NaHCO_3$ and dried (Na_2SO_4). **24** was obtained as a clear oil (4.1 g, 95%); R_f 0.15 (hexane-EtOAc, 4:1);

δ_H 7.451-7.410 (m, aromatic protons),
7.310-7.184 (m, aromatic protons),
5.645-5.618 (m, 2H, H-2 and H-3),
4.064 (d, 2H, H-1a and H-1b),
3.029 (dd, H, $J_{5a,5b}$ 8.7, $J_{5a,4}$ 6.4, H-5a),
2.941 (dd, H, $J_{5b,5a}$ 8.7, $J_{5b,4}$ 6.7, H-5b),
2.475 (m, H, H-4),
1.050 (d, 3H, $J_{Me,4}$ 6.9, Me);

δ_C 17.12Q (Me), 37.02D (C-4), 63.80 (C-5), 68.09T (C-1), 86.32S ($OCPh_3$), 126.89-128.78 (aromatic carbons), 128.60D (C-2), 135.76D (C-3), 144.36S (*ipso*-aromatic carbon);

MS *m/z* 358 $[M]^+$

***(E, 4R)-1-[(Methoxymethyl)oxy]-4-methyl-5-(trityloxy)but-2-ene* 33.-** The allylic alcohol **24** (12.2 g, 34 mmol) was dissolved in CH_2Cl_2 (200 cm^3), iPr_2NEt (8.9 cm^3, 53 mmol, 1.55 eq.) was added and the solution cooled to 0°C. Chloromethyl methylether (3.9 cm^3, 53 mmol, 1.55 eq.) was added and the solution stirred for an hour before warming to RT and stirring for another 12 h. MeOH was added to the solution and the standard isolation procedure gave **33** as a light yellow oil (4.8 g, 91%); R_f 0.5 (hexane-EtOAc, 4:1); $[\alpha]_D^{19}$ -1.9 (*c* 4.6, $CHCl_3$);

δ_H 7.470-7.434 (m, aromatic protons),
7.320-7.198 (m, aromatic protons),
5.710 (dd, H, $J_{3,2}$ 15.5, $J_{3,4}$ 6.7, H-3),
5.590 (ddd, H, $J_{2,3}$ 15.4, $J_{2,1a} = J_{2,1b}$ 5.8, H-2),
4.632 (s, 2H, OCH_2O),
4.026 (d, 2H, $J_{1a,2}$, $J_{1b,2}$ 5.7, H-1a and H-1b),
3.357 (s, 3H, OCH_3),
3.052 (dd, H, $J_{5a,5b}$ 8.7, $J_{5a,4}$ 6.3, H-5a),
2.953 (dd, H, $J_{5b,5a}$ 8.7, $J_{5b,4}$ 6.9, H-5b),
2.506 (m, H, H-4),
1.071 (d, 3H, $J_{Me,4}$ 6.9, Me);

δ_C 17.09Q (Me), 37.14D (C-4), 55.21Q (OMe), 68.06T (C-1), 68.06T (C-5), 86.32S ($OCPh_3$), 95.47T (OCH_2O), 125.54D (C-2), 126.88-128.80 (aromatic carbons), 137.44D (C-3), 144.39S (*ipso*-aromatic carbon);

MS *m/z* 402 $[M]^+$.

***(E, 2R)-5-[(Methoxymethyl)oxy]-2-methylpent-3-enol* 34**..- The protected allylic alcohol **33** (7 g, 17 mmol) was dissolved in the minimum of MeOH and camphorsulfonic acid (~1 g) was added. After a few minutes a white precipitate formed. The mixture, without removal of the methanol, was partitioned between ether and saturated aqueous $NaHCO_3$. The combined ether solutions were dried (Na_2SO_4), evaporated (at atmospheric pressure) and the residue was purified by chromatography (ether-pentane, 1:2→ether) to yield the alcohol **34** as a clear liquid (2.1 g, 75%); R_f 0.3 (hexane-EtOAc, 1:1); $[\alpha]_D^{19}$ +13.8 (*c* 1.0, $CHCl_3$).

δ_H 5.590-5.560 (m, 2H, H-3 and H-4),
4.562 (s, 2H, OCH_2O),
3.960 (m, 2H, H-5a and H5b),
3.414 (dd, H, $J_{1a,1b}$ 11.3, $J_{1a,2}$ 4.0, $J_{1a,OH}$ 1.3, H-1a),
3.364 (dd, H, $J_{1b,1a}$ 11.2, $J_{1b,2}$ 5.1, H-1b),
3.291 (s, 3H, OMe),
2.306 (m, H, H-2),
0.946 (d, 3H, $J_{Me,2}$ 7.0, Me);

δ_C 16.17Q (Me), 39.22D (C-2), 55.14Q (OCH_3), 67.09T (C-1), 68.10T (C-5), 95.60T (OCH_2O),126.88D (C-4), 136.61D (C-3);

MS *m/z* 161 $[M+H]^+$.

***(2R)-5-[(Methoxymethyl)oxy]-2-methylpent-3-enol* p-*tolylsulfonate* 35.**- The alcohol **34** (2.6 g, 16 mmol) was then dissolved in CH_2Cl_2 (100 cm^3) and DMAP (2.9 g, 24 mmol, 1.5 eq.) was added. The resulting mixture was cooled to 0°C and TsCl (4.6 g, 24 mmol, 1.5 eq.) was added after which the reaction mixture was stirred for 12 h at RT (tlc control). Water was added to the reaction mixture and stirred for another 2 h after which it was diluted with CH_2Cl_2 (100 cm^3) and neutralized with 1*N* HCl.

The organic layer was washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4 and concentrated *in vacuo*. A slightly yellow oil, the *p*-tolylsulfonate **35**, was used without purification in the next step (5.1 g, 100% -contaminated with traces of TsCl); R_f 0.6 (hexane-EtOAc, 1:1);

δ_H 7.726 (d, 2H, aromatic protons),
7.293 (d, 2H, aromatic protons),
5.473 (dd, H, $J_{3,4}$ 15.5, $J_{3,2}$ 5.8, H-3),
5.550 (ddd, H, $J_{4,3}$ 15.5, $J_{4,5a} = J_{4,5b}$ 5.0, H-4),
4.552 (s, 2H, OCH_2O),
3.925 (d, 2H, $J_{5,4}$ 4.5, H-5),
2.867 (dd, H, $J_{1a,1b}$ 9.4, $J_{1a,2}$ 6.3, H-1a),
3.793 (dd, H, $J_{1b,1a}$ 9.4, $J_{1b,2}$ 6.9, H-1b),
3.301 (s, 3H, OCH_3),
2.496 (m, H, $J_{2,Me} \approx J_{2,1a} \approx J_{2,1b} \approx J_{2,3}$ =6.6, H-2),
2.398 (s, 3H, Me, toluene),
0965 (d, 3H, $J_{Me,2}$ 6.7, Me);

δ_C 16.17Q (Me), 21.49Q (Me, toluene), 35.78D (C-2), 55.10Q (OCH_3), 67.42T (C-5), 73.83T (C-1), 95.50T (OCH_2O), 127.79D (aromatic carbon), 125.54D (C-4), 129.72D (aromatic carbon), 133.42D (C-3), 144.64S (*ipso*-aromatic carbon);

MS *m/z* 314 $[M]^+$.

***(E, 3S)-6-[(Methoxymethyl)oxy]-3-methyl-hex-4-enenitrile* 36.-** NaCN (3.3 g, 67 mmol, 10 eq.) was dissolved in DMF (100 cm^3) by heating to ~60°C.[6] At this temperature, the p-tolylsulfonate **35** (2.1 g, 6.7 mmol, dissolved in 30 cm^3) was added slowly. The reaction mixture immediately became a deep-orange colour. After stirring overnight at ~70°C the product **36** was isolated by adding ether and saturated aqueous $NaHCO_3$ and extraction of the aqueous layer with ether (3x100 cm^3). The combined ether layers were repeatedly washed with brine to remove all DMF, dried (Na_2SO_4) and evaporated. All aqueous layers were treated with NaOCl solution and tested for CN^- with aqueous $FeSO_4$ before disposal. Purification by column chromatography (hexane-EtOAc, 1:1) gave the nitrile **36** as a clear oil (1.0 g, 90%); R_f 0.6 (hexane-EtOAc, 1:1); $[\alpha]_D^{19}$ +3.1 (*c* 1.1, $CHCl_3$);

δ_H 5.6402-5.572 (m, 2H, H-4 and H-5),
4.576 (s, 2H, OCH_2O),

3.985 (d, 2H, $J_{6,5}$ 3.8, H-6),
3.309 (s, 3H, OCH_3),
2.548 (m, H, $J_{3,Me} \approx J_{3,2} \approx J_{3,4}$ =6.7, $J_{3,5}$ 2.8, H-3),
2.327 (dd, H, $J_{2a,2b}$ 6.5, $J_{2a,3}$ 6.0, H-2a),
2.293 (dd, H, $J_{2b,2a}$ 6.5, $J_{2b,3}$ 7.1, H-2b),
1.135 (d, 3H, $J_{Me,3}$ 6.8, Me);

δ_C 19.32Q (Me), 24.487T (C-2), 33.17D (C-3), 55.12Q (OCH_3), 67.18T (C-6), 95.5T OCH_2O), 118.16S (C-1), 127.08D (C-5), 134.83D (C-4);

MS *m/z* 170 $[M+H]^+$.

***(E, 3S)-6-[(Methoxymethyl)oxy]-3-methylhex-4-enoic acid* 37.-** To a solution of the nitrile **36** (3.5 g, 20.6 mmol) in the minimum MeOH was added a 40% aqueous solution of NaOH (40 cm^3). The resulting mixture was refluxed for 2-3 h until tlc confirmed the reaction to be complete. The methanol was evaporated, the aqueous solution acidified to pH 2 with 1*N* HCl and repeatedly extracted with diethyl ether. The ether solution was dried over Na_2SO_4, filtered and evaporated to give **37** as a clear thin oil (2.9 g, 78%); R_f 0.4 (hexane-EtOAc 1:1);

δ_H 8.0 (s, H, $-CO_2H$),
5.653 (dd, H, $J_{4,5}$ 15.5, $J_{4,3}$ 6.6, H-4),
5.544 (dt, H, $J_{5,4}$ 15.5, $J_{5,6a} \approx J_{5,6b}$ =5.9, H-5),
4.581 (s, 2H, OCH_2O),
4.969 (d, 2H, $J_{6,5}$ 5.8, H-6),
3.318 (s, 3H, OCH_3),
2.662 (m, H, $J_{3,Me} \approx J_{3,2} \approx J_{3,4}$ =6.9, H-3),
2.349 (dd, H, $J_{2a,2b}$ 15.2, $J_{2a,3}$ 7.0, H-2a),
2.248 (dd, H, $J_{2b,2a}$ 15.2, $J_{2b,3}$ 7.4, H-2b),
1.046 (d, 3H, $J_{Me,3}$ 6.8, Me);

δ_C 19.77Q (Me), 32.88D (C-3), 41.06T (C-2), 55.12Q (OCH_3), 67.70T (C-6), 95.32T (OCH_2O), 125.01D (C-5), 137.89D (C-4), 177.5S (CO_2H).

***Methyl (E, 3S)-6-[(methoxymethyl)oxy]-3-methylhex-4-enoate* 30.-** To a solution of *p*-tolylsulfonyl-N-methyl-N-nitrosamide (Diazald) [7] (8.56 g) in ether (120 cm^3) was added a solution of KOH (1.6 g)

in 95% EtOH (40 cm^3). The formed diazomethane (CH_2N_2) was displaced into cooled (-50°C) diethyl ether (50 cm^3) with N_2 until the reaction mixture was nearly colourless. The bright yellow ethereal CH_2N_2 solution was added to a solution of the acid **37** (2.9 g, 15 mmol) in diethyl ether (50 cm^3) until a persistent yellow colour was obtained. The excess CH_2N_2 and solvent were evaporated with a stream of N_2 to give the methyl ester **30** as a colourless liquid (2.7 g, 90%); R_f 0.6 (hexane-EtOAc, 1:1); $[\alpha]_D^{19}$ +14.9 (*c* 1.2, $CHCl_3$);

δ_H 5.597 (dd, H, $J_{4,5}$ 15.5, $J_{4,3}$ 6.7, H-4),
5.489 (dd, H, $J_{5,4}$ 15.5, $J_{4,6}$ 5.5, H-5),
4.534 (s, 2H, OCH_2O),
3.921 (d, 2H, $J_{6,5}$ 5.6, H-6),
3.577 (s, 3H, OCH_3, ester),
3.275 (s, 3H, OCH_3, OCH_2OCH_3),
2.625 (m, H, $J_{3,Me} \approx J_{3,6}$ =6.9, H-3),
2.286 (dd, H, $J_{2a,2b}$ 14.9, $J_{2a,3}$ 7.0, H-2),
2.188 (dd, H, $J_{2b,2a}$ 14.9, $J_{2b,3}$ 7.5, H-2b),
0.985 (d, 3H, $J_{Me,3}$ 6.7, Me);

δ_C 19.70Q (Me), 33.02D (C-3), 41.06T (C-2), 51.22Q (OCH_3, ester), 55.00Q (OCH_3, MOM), 67.55T (C-6), 95.30T (OCH_2O), 124.95D (C-5), 137.77D (C-4), 172.58S (ester);

MS *m/z* 203 $[M+H]^+$.

5.2.2 Preparation of Left-side Model Compound, 40.

***(2RS)-3-(Benzyloxy)-2-methylpropanol* p-*tolylsulfonate*, 39.-** To a solution of (2*RS*)-3-(benzyloxy)-2-methylpropanol, **38** (9 g, 50 mmol) in CH_2Cl_2 (100 cm^3) was added DMAP (8 g, 65 mmol, 1.3eq.) and cooled to 0°C. TsCl (12 g, 63 mmol, 1.25eq.) was added and the resulting reaction mixture was stirred at RT for 5 h. Water (30 cm^3) was added and after 30 min. the reaction was worked up according to the standard isolation procedure to give the tosylate **39** as a light yellow oil (15 g, 90%) which required no further purification, R_f 0.7 (hexane-EtOAc, 1:1).

δ_H 7.78-7.21 (m, aromatic protons),
4.382 (s, 2H, OCH_2O),
4.046 (dd, H, $J_{1a,1b}$ 9.4, $J_{1a,2}$ 5.7, H-1a),

3.978 (dd, H, $J_{1b,1a}$ 9.4, $J_{1b,2}$ 5.7, H-1b),
3.340 (dd, H, $J_{3a,3b}$ 9.2, $J_{3a,2}$ 5.2, H-3a),
3.307 (dd, H, $J_{3b,3a}$ 9.2, $J_{3b,2}$ 6.9, H-3b),
2.391 (s, 3H, Me, toluene),
2.097 (m, H, $J_{2,3a} \approx J_{2,3b} \approx J_{2,Me} \approx J_{2,1}$ =6.6, H-2),
0.928 (d, 3H, $J_{Me,2}$ 6.9, Me);

δ_C 13.48Q (Me), 21.45Q (Me, toluene), 33.56D (C-2), 70.99T, 72.13T, 72.92T (C-1, C-3, benzylic), 127.28-144.53 (aromatic carbons);

MS *m/z* 225 $[M+H]^+$.

***(3RS)-4-(Benzyloxy)-3-methylbutyronitrile,* 40.-** NaCN (20.6 g, 420 mmol, 10 eq.) was dissolved in DMF (400 cm^3) by heating to 70°C.[6] A solution of **39** (14.0 g, 42.5 mmol) in DMF (50 cm^3) was then added and the reaction mixture stirred overnight at ~90°C. After 24 h, the ^1H nmr spectrum of a sample showed that the reaction was complete. The reaction mixture was cooled and ether and saturated aqueous $NaHCO_3$ were added. The aqueous layer was exhaustively extracted with ether. The combined ether layers were diluted with 20% hexane and washed with brine (4x200 cm^3) to remove any DMF. The aqueous layers were treated with a 15% NaOCl solution to oxidize unreacted NaCN before disposal. The organic layers were dried (Na_2SO_4), filtered and concentrated to give the nitrile product, **40**, as a clear oil (8.1 g, 92%); R_f 0.8 (hexane-EtOAc, 1:1);

δ_H 7.37-7.26 (m, aromatic protons),
4.505 (s, 2H, OCH_2),
3.451 (dd, H, $J_{4a,4b}$ 9.4, $J_{4a,3}$ 4.7, H-4a),
3.299 (dd, H, $J_{4b,4a}$ 9.3, $J_{4b,3}$ 7.8, H-4b),
2.483 (dd, H, $J_{2a,2b}$ 16.7, $J_{2a,3}$ 5.5, H-2a),
2.360 (dd, H, $J_{2b,2a}$ 16.7, $J_{2b,3}$ 6.9, H-2b),
2.21-2.10 (m, H, H-3),
1.074 (d, 3H, $J_{Me,3}$ 6.9, Me);

δ_C 16.12Q (Me), 21.28T (C-2), 31.03D (C-3), 73.09T, 73.15T (C-4, benzylic), 118.52S (C-1), 127.50-137.93 (aromatic carbons);

MS *m/z* 190 $[M+H]^+$.

5.2.3 Preparation of the C_8 Right-side Fragments

The preparation of compounds **42-50** are described in RM Snyman's thesis.[8] For the sake of completeness the descriptions of these steps used in this study will be repeated.

***Methyl 2,4-di-O-benzoyl-3,6-dibromo-3,6-dideoxy-altro-hexopyranoside* 42.-** Bromotrichloromethane (22.5 g, 113 mmol) was added to a solution of methyl 2,3:4,6-di-*O*-benzylidene-α-D-mannopyranoside, **41** (20 g, 54.1 mmol) in CCl_4 (600 cm^3). A catalytic amount of benzophenone (200 mg) was added and the reaction mixture was irradiated with UV light from a 300W OSRAM sunlamp for 3-4 h (the best results were obtained when the UV lamp was put underneath (~10 cm) the flask containing boiling stones, as in this setup the solution never became warmer than 60°C). After irradiation the mixture was left to stand overnight and the solvent was removed to yield the crude dibrominated product, **42**, as a very sticky light yellow syrup; 28.6 g (~100%);R_f 0.4 (Hex-EtOAc, 5:1). The crude **42** was used directly in the next step without further purification.

δ_H 8.09-7.44 (m, 10H, aromatic protons),
5.530 (dd, H, $J_{2,1}$~0, $J_{2,3}$ 3.6, H-2),
5.323 (dd, H $J_{4,5}$ 8.9, $J_{4,3}$ 4.1, H-4),
4.927 (d, H, $J_{1,2}$~0, H-1),
4.735 (dd, H, $J_{3,2}$ 3.5, $J_{3,4}$ 3.8, H-3),
4.541 (ddd, H, $J_{5,4}$ 8.9, $J_{5,6a}$ 6.5, $J_{5,6b}$ 2.9, H-5),
3.698 (dd, H, $J_{6b,6a}$ 11.1, $J_{6b,5}$ 2.9, H-6b),
3.634 (dd, H, $J_{6a,6b}$ 11.2, $J_{6a,5}$ 6.5, H-6a),
3.517 (s, 3H, OMe);

δ_c 32.19T (C-6), 45.41D (C-3), 55.93Q (OMe), 66.84D (C-5), 68.89D (C-4), 72.68D (C-2), 99.85D (C-1), 133.76-128.29 (aromatic carbons), 165.10, 164.78 (each S, CO);

MS *m/z* 529 $[M+H]^+$, 497 $[(M+H)-MeOH]^+$.

***Methyl 3,6-dideoxy-α-D-arabino-hexapyranoside* 44.-** To a refluxing solution of **42** (30 g, 54 mmol) in THF (100 cm^3) was carefully added $LiAlH_4$ (4 g, 110 mmol, 2 eq.). The resulting reaction mixture was refluxed for 4-5 h before the reflux condenser was removed and the THF evaporated to ~50 cm^3.

The solution was cooled and EtOH was carefully added (sufficient to decompose excess $LiAlH_4$). The solution was acidified to pH ~5 with 1N HCl (using as little liquids as necessary) which caused the $Al(OH)_3$ residue to become gray and granular. EtOAc (300 cm^3) was added, stirred vigorously for 5 min and allowed to settle. The nearly clear liquid was decanted and the process was repeated twice more. The solid residue was thoroughly washed on filterpaper with EtOAc and EtOH. The solvents were removed *in vacuo* and the residue was purified by column chromatography (hexane-EtOAc, 1:2→EtOH-EtOAc, 1:1) to give the pure dedioxy sugar product, **44**, as a clear syrup (6.6 g, 75%); R_f 0.17 (hexane-EtOAc, 2:1); $[\alpha]_D^{19}$ +94.6 (*c* 2.7, $CHCl_3$);

δ_H 4.469 (d, H, $J_{1,2}$~0, H-1),
3.849 (ddd, H, $J_{1,2}$~0, $J_{2,3a}$ 3.0, $J_{2,3e}$ 1.7, H-2),
3.589 (m, 2H, H-4, H-5),
3.366 (s, 3H, OMe),
2.323 (d, H, $J_{OH,2}$ 6.5, OH),
2.056 (ddd, H, $J_{3e,3a}$ 13.3, $J_{3e,4}$ 4.0, $J_{3e,2}$ 1.7, H-3e),
1.798 (ddd, H, $J_{3a,3e}$ 13.3, $J_{3a,4}$ 10.6, $J_{3a,2}$ 3.0, H-3a),
1.288 (d, 3H, $J_{Me,5}$ 5.8, Me);

δ_C 17.67Q (Me), 35.14T (C-3), 54.82Q (OMe), 67.98D (C-5), 68.57D (C-2), 69.48D (C-4), 100.12D (C-1).

48 (10%) was the only other identified product.

***Methyl 2,4-di-O-benzyl-3,6-dideoxy-α-D-arabino-hexopyranoside* 45.-** Sodium hydride (0.41g, 13.5 mmol, 80% dispersion) was added to a solution of compound **44** (0.27 g, 1.7 mmol) in DMF (2 cm^3). The reaction mixture was stirred at 40°C for 30 min after which benzylchloride (2 cm^3) was carefully added. The reaction mixture was stirred for another 4 h before it was cooled to RT and quenched with MeOH (1 cm^3). The MeOH was evaporated and the residue partitioned between EtOAc and water. Column chromatography (EtOAc-Hex, 1:6) gave the benzylated product, **45**, as a slightly yellow syrup; 507 mg (88%); R_f 0.4 (EtOAc-Hex, 1:6);

δ_H 7.53-7.39 (m, 10H, aromatic protons),
4.759 (d, H, $J_{1,2}$~ 0, H-1),
4.724 (dd, 2H, J 11.9, $PhCH_2$),
4.617 (dd, 2H, J 11.7, $PhCH_2$),

3.922 (dq, H, $J_{5,Me}$ 6.2, $J_{5,4}$ 9.2, H-5),
3.741 (bs, H, H-2),
3.643 (ddd, H, $J_{4,3a}$ 10.8, $J_{4,3e}$ 4.3, $J_{4,5}$ 9.4, H-4),
3.490 (s, 3H, OMe),
1.916 (ddd, H, $J_{3a,3e}$ 13.2, $J_{3a,4}$ 11.0, $J_{3a,2}$ 3.0, H-3a),
2.389 (ddd, H, $J_{3e,3a}$ 13.2, $J_{3e,4}$ 4.3, $J_{3e,2}$ 3.2, H-3e),
1.511 (d, 3H, $J_{Me,5}$ 6.2, Me);

δ_C 17.95Q (Me), 29.27T (C-3), 54.14Q (OMe), 67.78D (C-5), 71.12T ($PhCH_2$), 71.19T ($PhCH_2$), 74.93D (C-2), 75.08D (C-4), 97.89D (C-1), 122.32-128.10 (aromatic carbons), 138.38, 138.10 (each S, *ipso*-aromatic);

MS *m/z* 343 $[M+H]^+$.

***2,4-Di-O-benzyl-3,6-dideoxy-D-arabino-hexopyranoside* 46.-** $BCl_3 \cdot SMe_2$ (0.76 g, 4.2 mmol) was added to a solution of compound **45** (3.94 g, 11.5 mmol) in ether (100 cm^3). The reaction mixture was stirred at RT for 1 h after which an additional amount of $BCl_3 \cdot SMe_2$ (0.76 g, 4.2 mmol) was added. Stirring was continued for another hour after which the excess Lewis acid was neutralised with a saturated solution of $NaHCO_3$ (2 cm^3) and the mixture extracted with EtOAc. The organic phase was washed, dried, adsorbed on silica gel (30 g) and left *in vacuo* for 30 min. Water (10-15 cm^3) was added with shaking to the gel so that the silica gel became uniformly damp. After standing overnight, the silica gel was dried *in vacuo* and the pure anomeric mixture was obtained after column chromatography (EtOAc-hex, 1:2); 3.25 g (86%); R_f 0.4 (EtOAc-hex, 1:2);

δ_H 7.35-7.29 (m, 20H, aromatic protons),
5.083 (s, H, $J_{1,2} \sim 0$, H-1),
4.643 (bs, H, H-1),
4.588 (d, 8H, J 11.3, $PhCH_2$),
4.012 (m, 2H, 2x H-5),
3.859 (bs, 2H, 2x H-2),
3.476 (m, 2H, 2x H-4),
2.198 (m, 2H, 2x H-3e),
1.812 (m, H, $J_{3a,3e}$ 13.3, $J_{3a,2}$ 2.7, $J_{3a,4}$ 11.1, H-3a),
1.365 (d, 3H, $J_{Me,5}$ 6.1, Me),
1.314 (d, 3H, $J_{Me,5}$ 6.2, Me);

δ_c 18.07, 17.96 (2Q, 2x Me), 31.51 (2T, 2x C-3), 68.04 (2D, 2x C-5), 71.71, 71.50, 71.92 (4T, 4x $PhCH_2$), 75.29, 75.11 (2D, 2x C-2), 75.24, 74.78 (2D, 2x C-4), 94.41, 91.71 (2D, 2x C-1), 127.51-128.39 (aromatic carbons), 138.13, 138.28 (4S, *ipso*-aromatic);

MS *m/z* 329 $[M+H]^+$.

Methyl 2-[β-(2,4-di-*O*-benzyl-3,6-dideoxy)-D-*arabino*-hexopyranosyl] acetate 56.- Diisopropyl methoxycarbonyl methylphosphonate (4.8 g, 20 mmol, 4 eq.) in THF (50 cm^3) was treated with 3.8 eq. *t*-BuOK (2.1 g, 19 mmol) for 1 h at RT. The ylide solution was then cooled to -40°C and a solution of the hemi-acetal **46** (1.6 g, 5 mmol) in THF (10 cm^3) was added dropwise. After 30 min at -40°C, tlc showed that no reaction had occurred. The reaction mixture was therefore stirred overnight at RT. The standard isolation procedure gave a product that was identified as the cyclisized C_2 extended sugar, **56**, as a clear syrup (1.8 g, 94%); R_f 0.6 (hexane-EtOAc, 2:1); $[\alpha]_D^{19}$ +45.1 (*c* 3.7, $CHCl_3$);

δ_H 7.40-7.22 (m, aromatic protons),
4.523 (m, 4H, benzylic protons (x2)),
4.152 (ddd, H, $J_{1,2'a}$ 8.1, $J_{1,2}$ 6.7, $J_{1,2'b}$ 5.1, H-1),
3.921 (dq, H, $J_{5,6}$ 6.6, $J_{5,4}$ 4.2, H-5),
3.637 (s, 3H, OCH_3),
3.556 (ddd, H, $J_{2,3a}$ 8.1, $J_{2,1}$ 6.7, $J_{2,3b}$ 4.1, H-2),
3.455 (dt, H, $J_{4,3b}$ 6.1, $J_{4,3a} \approx J_{4,5}$ 3.9, H-4),
2.716 (dd, H, $J_{2'b,2'a}$ 15.2, $J_{2'b,1}$ 5.1, H-2'b),
2.556 (dd, H, $J_{2'a,2'b}$ 15.1, $J_{2'a,1}$ 8.2, H-2'a),
2.057 (ddd, H, $J_{3b,3a}$ 13.5, $J_{3b,4}$ 6.0, $J_{3b,2}$ 4.2, H-3b),
1.898 (ddd, H, $J_{3a,3b}$ 13.6, $J_{3a,2}$ 8.2, $J_{3a,4}$ 3.6, H-3a),
1.257 (d, 3H, $J_{6,5}$ 6.7, H-6);

δ_C 16.58Q (C-6), 29.44T (C-3), 36.97T (C-2'), 51.54Q (OCH_3), 70.12D (C-1), 70.61D (C-5), 70.75T/70.78T (benzylic carbons), 74.35D (C-2), 76.42D (C-4), 127.57-128.32 (aromatic carbons), 138.21S and 138.42S (aromatic carbons), 171.62S (C-1').

***Methyl (2Z/E,4R,6S,7R)-4,6-dibenzyloxy-7-hydroxy-oct-2-enoate* 50.-** (Carbomethoxy methylidene) triphenylphosphorane, **49** (123 mg, 0.37 mmol) was added to a solution of the hemi-acetal, **46** (100 mg, .31 mmol) in DME (3 cm^3). The reaction mixture was heated at 80°C for 3 d, diluted with ether (5 cm^3) and filtered. The solvents were evaporated and the residue was purified by column chromatography (EtOAc-hex, 1:3) to yield the unsaturated ester, **50**, as a 3:2 mixture of the *E/Z* isomers; 94 mg, (80%); R_f 0.11 (EtOAc-hex, 1:3);

δ_H 7.33-7.22 (m, 10H, aromatic protons),
6.898 (dd, H, $J_{3,2}$ 15.9, $J_{3,4}$ 6.4, H-3 *E*),
6.212 (dd, H, $J_{3,2}$ 11.7, $J_{3,4}$ 8.6, H-3 *Z*),
6.041 (d, H, $J_{2,3}$ 15.9, $J_{2,4}$ 0.9, H-2 *E*),
5.891 (dd, H, $J_{2,3}$ 11.7, $J_{2,4}$ 0.7, H-2 *Z*),
4.557 (d, H, J 11.4, $PhCH_2$),
4.547 (d, H, J 11.4, $PhCH_2$),
4,540 (d, H, J 11.5, $PhCH_2$),
4.484 (d, H, J 11.6, $PhCH_2$),
4.462 (d, H, J 11.5, $PhCH_2$),
4.298 (d, H, J 11.4, $PhCH_2$),
4.290 (d, H, J 11.6, $PhCH_2$),
4.176 (m, 2H, $PhCH_2$, H-4),
4.028 (m, 2H, 2x H-7),
3.738 (s, 3H, OMe),
3.688 (s, 3H, OMe),
3.605 (m, 2H, 2x H-6),
1.743 (m, 4H, 4x H-5),
1.145 (d, 3H, $J_{Me,7}$ 5.4, Me),
1.125 (d, 3H, $J_{Me,7}$ 6.3, Me);

δ_c 17.67, 17.91 (2Q, 2x Me), 34.69, 34.88 (2D, 2x C-5), 51.34, 51.60 (2Q, 2x OMe), 68.10, 67.57 (2D, 2x C-7), 72.14, 71.94, 71.12 (4T, 4x $PhCH_2$), 74.81 (2D, 2x C-4), 79.20, 79.60 (2D, 2x C-6), 120.91, 121.41 (2D, 2x C-2), 127.53, 128.41 (aromatic carbons), 148.64, 150.71 (2D, 2x C-3), 207.49, 208.76 (2S, 2x CO);

MS *m/z* 276 $[M\text{-}BnOH]^+$.

***Methyl (4R,6S,7R)-4,6-di-(benzyloxy)-7-hydroxyoctanoate* 51.-** The C_8 α,β-unsaturated ester, **50** (10 g, 26 mmol) was dissolved in MeOH (100 cm^3), Raney/Ni (~5 g) was added and the solution was shaken under 3 atm. H_2 pressure for 30 min. During this time ~0.9 dm^3 H_2 gas (40 mmol) was absorbed. The catalyst was allowed to settle and the solution was decanted, more MeOH and EtOAc were added and decanted twice more. The combined decanted solutions were concentrated *in vacuo* and the crude product purified by column chromatography (hexane-EtOAc, 1:1) to give the saturated product, **51**, as a clear liquid (9.6 g, 95%); R_f 0.55 (hexane-EtOAc, 1:1); $[\alpha]_D^{19}$ -61.3 (*c* 1.2, $CHCl_3$);

δ_H 7.31-7.25 (m, aromatic protons),
5.570 (d, H, J 11.2, benzylic protons),
5.346 (d, H, J 11.5, benzylic proton),
5.532 (d, H, J 11.2, benzylic proton),
5.293 (d, H, J 11.5, benzylic proton),
4.025 (dq, H, $J_{7,8}$ 6.5, $J_{7,6}$ 2.9, H-7),
3.72-3.63 (m, H, H-4),
3.629 (s, 3H, OCH_3),
3.534 (ddd, H, $J_{6,5a}$ 7.5, $J_{6,5b} \approx J_{6,7}$ =3.3, H-6),
2.379 (m, 2H, H-2),
2.236 (s, H, OH),
2.05-1.84 (m, 2H, H-3),
1.652 (m, 2H, H-5),
1.140 (d, 3H, $J_{8,7}$ 6.5, C-8);

δ_C 17.50Q (C-8), 28.52T (C-2/3), 28.99T (C-2/3), 33.61T (C-5), 51.23Q (OCH_3), 67.47D (C-7), 70.44T/71.68T (benzylic carbons), 74.26D (C-4), 79.66D (C-6), 127.27-128.11 (aromatic carbons), 138.17S/138.25S (aromatic carbons), 173.71S (C-1);

MS *m/z* 387 $[M+H]^+$, 297 $[M-OBn]^+$.

***Methyl (4R,6S,7R)-4,6-(dibenzyloxy)-7-[(methoxymethyl)oxy]octanoate* 52.-** To a solution of the saturated alcohol, **51** (9.4 g, 24 mmol) in CH_2Cl_2 (100 cm^3) was added of iPr_2NEt (8.8 cm^3, 51 mmol, 2.1eq.). The solution was cooled in an ice-bath before chloromethyl methylether (MOMCl) (3.6 g, 48 mmol, 2 eq.) was slowly added. The reaction mixture was allowed to warm to RT and stirred for 12 h, MeOH (10 cm^3) was added and the solution stirred for another 30 min. Acidic work-up gave the

desired product as a light yellow oil (10.4 g ~100%); R_f 0.75 (hexane-EtOAc, 1:1); $[\alpha]_D^{19}$ -61.7 (*c* 0.8, $CHCl_3$);

δ_H 7.30-7.23 (aromatic protons),
4.704 (d, H, J 11.5, benzylic proton),
4.270 (d, H, J 11.2, benzylic proton),
4.676 (s, 2H, OCH_2O),
4.515 (d, H, J 11.5, benzylic proton),
4.308 (d, H, J 11.2, benzylic proton),
3.912 (dq, H, $J_{7,8}$ 6.5, $J_{7,6}$, 2.3, H-7),
3.74-3.64 (m, 2H, H-4 and H-6),
3.626 (s, 3H, OCH_3, ester),
3.358 (s, 3H, OCH_3, MOM),
2.46-2.30 (m, 2H, H-2),
2.06-1.83 (m, 2H, H-3),
1.681 (ddd, H, J 14.2, H-5a),
1.612 (ddd, H, J 14.2, H-5b),
1.187 (d, 3H, $J_{8,7}$ 6.4, H-8);

δ_C 15.76Q (C-8), 28.87T (C-2/3), 29.26T (C-2/3), 35.73T (C-5), 51.44Q (OCH_3; ester), 55.25Q (OCH_3; MOM), 70.81T/72.15T (benzylic carbons), 74.11D (C-7), 74.58D (C-4), 78.85D (C-6), 95.24T (OCH_2O), 127.43-128.24 (aromatic carbons), 138.76S (aromatic carbons), 173.99S (C-1);

MS *m/z* 403 $[M+H]^+$.

***(4R,6S,7R)-4,6-Di-(benzyloxy)-7-[(methoxymethyl)oxy]-1-octanol* 53.**- The ester **52** (225 mg, 0.5 mmol) was dissolved in THF (10 cm^3) and the solution was cooled to -70°C and 3 eq. DIBALH (1.5 cm^3, 1 M solution in hexanes) was slowly added. The reaction mixture was stirred at -70°C for 1 h and MeOH (1cm^3) was added. The solvents were evaporated and the resulting white gel/solid was dissolved in CH_2Cl_2 and saturated aqueous NH_4Cl (care must be taken not to acidify the solution as hydrolysis of the MOM group may occur). Normal work-up gave the alcohol **53** as a clear oil (200 mg, 95%); R_f 0.36 (hexane-EtOAc, 1:1); $[\alpha]_D^{19}$ -50.4 (*c* 1.2, $CHCl_3$);

δ_H 7.33-7.22 (m, aromatic protons),

4.712 (d, H, J 11.5, benzylic proton),
4.677 (s, 2H, OCH_2O),
4.523 (d, H, J 11.5, benzylic proton),
4.322 (d, H, J 11.6, benzylic proton),
4.280 (d, H, J 11.7, benzylic proton),
3.915 (dq, H, $J_{7,8}$ 6.5, $J_{7,6}$ 2.3, H-7),
3.691 (m, H, H-4),
3.666 (ddd, H, $J_{6,7}$ 2.2, H-6),
3.590 (dd, 2H, $J_{1,2a} \approx J_{1,2b}$ =4.8, H-1),
3.358 (s, 3H, OCH_3),
1.69-1.59 (m, 6H, H-3, H-5 and H-2),
1.177 (d, 3H, $J_{8,7}$ 6.5, H-8);

δ_C 15.67Q (C-8), 27.86T (C-2/3), 30.26T (C-2/3), 35.77T (C-5), 55.18Q (OCH_3), 62.74T (C-1), 20.77, 72.12T (benzylic carbons), 74.17D (C-4/7), 75.39D (C-4/7), 78.85D (C-6), 95.18T (OCH_2O), 127.38-128.22 (aromatic carbons), 138.61, 138.72S (aromatic carbons);

MS *m/z* 403 $[M+H]^+$.

***(4R,6S,7R)-4,6-Di-(benzyloxy)-7-(methoxymethyloxy)-1-octanol* p-*tolylsulfonate* 54.-** To a solution of the C_8 alcohol, **53** (500 mg, 1.25 mmol) in CH_2Cl_2 (30 cm^3) was added 1.5 eq. DMAP (230 mg, 1.9 mmol) and the solution cooled in an ice-bath before TsCl (360 mg, 1.9 mmol, 1.5eq.) was added. The reaction mixture was stirred at RT for 4 h (tlc control), water was added and worked up after 2 h. The *p*-tolylsulfonate **54** was obtained as a clear liquid (610 mg, 88%); R_f 0.6 (hexane-EtOAc, 1:1);

δ_H 7.760 (d, 2H, aromatic protons),
7.40-7.21 (m, aromatic protons),
4.702 (d, H, J 11.5, benzylic proton),
4.670 (s, 2H, OCH_2O),
4.429 (d, H, J 11.5, benzylic proton),
4.308 (d, H, J 11.4, benzylic proton),
4.220 (d, H, J 11.5, benzylic proton),
4.020 (dd, 2H, $J_{1,2a} \approx J_{1,2b}$ =6.2, H-1),
3.905 (dq, H, $J_{7,8}$ 6.5, $J_{7,6}$ 2.2, H-7),
3.68-3.60 (m, 2H, H-4 and H-6),

3.353 (s, 3H, OCH_3),
2.406 (s, 3H, Me, toluene),
1.76-1.51 (m, 6H, H-3/H-5 and H-2),
1.159 (d, 3H, $J_{8,7}$ 6.6, H-8);

δ_C 15.73Q (C-8), 21.47Q (Me, toluene), 24.16T (C-2/3), 29.64T (C-2/3), 35.72T (C-5), 55.19Q (OCH_3), 70.61T/70.76T (benzylic carbons), 72.06T (C-1), 73.97D (C-4/7), 74.60D (C-4/7), 78.77D (C-6), 95.20T (OCH_2O), 127.40-129.70 (aromatic carbons), 138.57S/138.66S (aromatic carbons), 144.53S (*ipso*-aromatic carbon);

MS *m/z* 557 $[M+H]^+$, 341 $[\{M+H\}-\{Ts+OCH_2OCH_3\}]^+$.

***(4R, 6S, 7R)-4,6-Di-(benzyloxy)-1-iodo-7-[(methoxymethyl)oxy]octane* 55.**- The C_8 alcohol, **53** (805 mg, 2 mmol) was dissolved in toluene (50 cm^3), triphenylphosphine (PPh_3) (2.1 mg, 8 mmol, 4 eq.), imidazole (550 mg, 8 mmol, 4 eq.) and I_2 (1.54 g, 6 mmol, 3 eq.) were added.[9] The red colour of I_2 disappeared immediately and the solution became bright yellow with a black sticky precipitate on the glass. The solution was stirred until tlc showed the absence of starting material. A saturated solution of $NaHCO_3$ was added and stirred for 10 min. I_2 was added with vigorous stirring until a persistent red colour was obtained. A saturated solution of $Na_2S_2O_3$ was added until the red colour just disappeared. The aqueous layer was washed twice with toluene (50 cm^3) and the combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The product, containing a large quantity of triphenylphosphine oxide was chromatographed (hexane-EtOAc, 5:1→1:1) to give the alkyliodide, **55**, as a clear oil (870 mg, 85%); R_f 0.4 (hexane-EtOAc, 5:1); which decomposed within a week at RT;

δ_H 7.35-7.24 (m, aromatic protons),
4.737 (d, H, J 11.4, benzylic proton),
4.701 (s, 2H, OCH_2O),
4.534 (d, H, J 11.5, benzylic proton),
4.340 (d, H, J 11.6, benzylic proton),
4.291 (d, H, J 11.5, benzylic proton),
3.946 (dq, H, $J_{7,8}$ 6.4, $J_{7,6}$ 2.1, H-7),
3.674 (m, 2H, H-4 and H-6),
3.380 (s, 3H, OCH_3),
3.169 (t, 2H, $J_{1,2}$ 6.7, H-1),

1.72-1.60 (m, 4H, H-3 and H-5),
1.202 (d, 3H, $J_{8,7}$ 6.4, H-8);

δ_C 7.09T (C-1), 15.71Q (C-8), 28.56T (C-2), 34.56T (C-3/5), 35.86T (C-3/5), 55.16Q (OCH_3), 70.70T/72.08T (benzylic carbons), 73.98D (C-7), 74.53D (C-4), 78.81D (C-6), 95.15T (OCH_2O), 127.37-128.17 (aromatic carbons), 139.62S (*ipso*-aromatic carbon);

MS *m/z* 513 $[M+H]^+$.

5.2.4 Preparation of the Sulfoxides

***(1R,2S,5R)-(-)-Menthyl (S)-p-toluenesulfinate*, 8.**[10]- The powdered sodium salt of anhydrous *p*-toluenesulfinic acid (50 g, 0.281 mol) was added in small portions to a solution of thionyl chloride (100 cm^3, 1.4 mol) in benzene (500 cm^3) at 0°C. The solution was allowed to reach RT after which the solution was concentrated to a quarter of the volume by distilling benzene and thionyl chloride. The residue was diluted with anhydrous diethyl ether (500 ml, formation of a white precipitate of sodium chloride) and cooled at 0°C. A solution of (-)-menthol (48.3 g, 0.309 mol) in pyridine (50 cm^3) was added dropwise. After the addition was complete the mixture was stirred for 1 h at RT and hydrolysed with water (200 cm^3). The organic layer was washed with 10% hydrochloric acid (200 cm^3) and saturated brine (100 cm^3), dried over Na_2SO_4 and concentrated. The residue was diluted with acetone (200 cm^3), ~5 drops of concentrated hydrochloric acid added, and allowed to crystallise at -20°C. After the filtration of the first crop of crystals, the mother liquor was concentrated to ~50 cm^3, 1 drop of concentrated hydrochloric acid added and again allowed to crystallise at -20°C. This operation was repeated 3-4 times in total. Hexane was used to dilute the increasingly viscous mother liquor to improve crystallisation. The combined crops were finally recrystallised from hot acetone to give the pure (*S*)-sulfinate as a white crystalline material (40.3 g, 75%); mp 108-109 °C (Lit[11] 105-107 °C), $[\alpha]_D^{21}$ -199 (*c* 2.5, acetone), [Lit.[12] $[\alpha]_D^{21}$ -201 (*c* 2.0, acetone)]

***(+)-(R)-Methyl* p-*tolylsulfoxide*, 9.**[10]- A solution of methylmagnesium iodide [prepared from iodomethane (40.6 g, 286 mmol), magnesium (5.96 g, 245 mmol) and ether (250 cm^3)] was slowly added to a solution of (-)-(*S*)-menthyl-*p*-toluenesulfinate (60 g, 204 mmol) in anhydrous benzene (200 cm^3) between 0° and 10°C. After addition, the mixture was stirred at room temperature for 2 h and then hydrolyzed with saturated aqueous solution of ammonium chloride (200 cm^3). The aqueous solution was extracted with EtOAc (100 cm^3 x3). The organic layers were washed with saturated

brine (100 cm^3), dried (Na_2SO_4) and concentrated *in vacuo*. The oily residue was mixed with hot hexane till formation of a light white cloudy precipitate. Crystallization occurs overnight on cooling to -5°C. The crystals were recrystallised from ether-hexane at -5°C affording white crystals (25 g, 80%); mp 74.5-75.5°C (Lit.[13] 73-74.5°C); $[\alpha]_D^{21}$ +192 (*c* 4.0, $CHCl_3$), (Lit.[10] $[\alpha]_D^{21}$ +192, (*c* 1.2, $CHCl_3$)), $[\alpha]_D^{15}$ +144.5 (*c* 2.0, acetone), (Lit.[13] $[\alpha]_D^{21}$ +145.5);

δ_H 7.497 (d, 2H, aromatic protons),
7.286 (d, 2H, aromatic protons),
2.657 (s, 3H, H-1),
2.373 (s, 3H, Me, toluene);

δ_C 21.29Q (Me, toluene), 43.93Q (C-1), 123.47, 129.95, 141.41 and 142.53 (aromatic carbons).

***(+)-(R)-Butyl* p-*tolylsulfoxide* 10.** Iodobutane (7.4 g, 40 mmol; 1.33 eq.) was added to a mixture of Mg turnings (1.17 g, 48 mmol, 1.6 eq.) in THF (100 cm^3). To the mixture was added a crystal of I_2 and slightly warmed until the reaction became exothermic. When the Grignard reagent had formed the solution was cooled and the somewhat opaque solution was slowly added to a cold (-10°C) solution of **8** (8.8 g, 30 mmol) in benzene (100 cm^3). After addition was complete the mixture was stirred at RT for 2 h. Tlc showed that no reaction occurred. The mixture was therefore heated under reflux for another 5 h. After the standard isolation procedure and column chromatography (hexane-EtOAc, 1:1) starting material and the product, (+)-(*R*)-butyl p-tolylsulfoxide **10** (2.8 g, 50%), were recovered.; R_f 0.35 (hexane-EtOAc, 3:1; red spot after spraying with $Ce(SO_4)_2$ /H_2SO_4 and heating); $[\alpha]_D^{19}$ +170.4 (*c* 1.3, $CHCl_3$), $[\alpha]_D^{22}$ +192.5 (*c* 2.0, acetone);

δ_H 7.438 (d, 2H, aromatic protons),
7.243 (d, 2H, aromatic protons),
2.701 (m, 2H, H-1),
1.69-1.46 (m, 2H, H-2),
1.43-1.31 (m, 2H, H-3),
0.612 (t, 3H, $J_{4,3}$ 7.2, H-4);

δ_C 13.41Q (C-4), 21.14Q (Me, toluene), 21.67T (C-3), 23.94T (C-2), 56.88T (C-1), 123.84D (aromatic carbon), 129.65D (aromatic carbon), 140.66S (aromatic carbon, 141.08S (aromatic carbon);

MS *m/z* 197[M+H]$^+$.

(+)-(S(R))-1-(p-Tolylsulfinyl)-2-propanone **11** was prepared according to general procedure a) using (+)-(R)-methyl *p*-tolylsulfoxide, **9**, and ethyl acetate in a yield of 80%; R_f 0.18 (hexane-EtOAc, 1:1); $[\alpha]_D^{19}$ +223 (*c* 1.2, $CHCl_3$);

δ_H 7.406 (d, 2H, aromatic protons),
7.195 (d, 2H, aromatic protons),
3.759 (d, H, $J_{1a,1b}$ 13.7, H-1a),
3.671 (d, H, $J_{1b,1a}$ 13.7, H-1b),
2.270 (s, 3H, Me, toluene),
2.081 (s, 3H, H-3);

δ_C 20.94Q (Me, toluene), 31.34Q (C-3), 68.19T (C-1), 123.59, 129.67, 139.27 and 141.62 (aromatic carbons), 199.13S (C-2);

MS *m/z* 197 [M+H]$^+$.

(+)-(2R,S(R))-1-(p-Tolylsulfinyl)-propan-2-ol **12a** was prepared from the keto-sulfoxide, **11**, according to general procedure b) in a yield of 95%. **12a** was crystallized from hexane-ether as white crystals but stayed contaminated with up to 10% of the C-2 epimer, **12b**. R_f 0.13 (hexane-EtOAc, 1:1); mp 128-130°C;

δ_H 7.494 (d, 2H, aromatic protons),
7.317 (d, 2H, aromatic protons)
4.333 (ddq, $J_{2,1a}$ 9.6, $J_{2,3}$ 6.3, $J_{2,1b}$ 2.0, H-2),
3.000 (dd, $J_{1a,1b}$ 13.7, $J_{1a,2}$ 9.7, H-1a),
2.641 (dd, $J_{1b,1a}$ 13.4, $J_{1b,2}$ 9.7, H-1b),
2.394 (s, 3H, Me, toluene),
1.190 (d, 2H, $J_{3,2}$ 6.4, H-3);

δ_C 21.36Q (Me, toluene), 23.27Q (C-3), 62.72T (C-1), 63.41D (C-2), 124.00, 130.06, 141.53 and 155.43 (aromatic carbons);

MS *m/z* 199 $[M+H]^+$.

(+)-(2S, S(R))-(p-Tolylsulfinyl)-propan-2-ol **12b** was prepared according to general procedure c) from the ketosulfoxide, **11** in 95%. **12b** was also contaminated with 5-10% of its C-2 epimer, **12a**. **12b** was, unlike **12a**, not crystalline; R_f 0.13 (hexane-EtOAc, 1:1);

δ_H 7.456 (d, 2H, aromatic protons),
7.225 (d, 2H, aromatic protons),
4.203 (m, H, H-2),
2.965 (dd, $J_{1a,1b}$ 13.0, $J_{1a,2}$ 8.3, H-1a),
2.674 (dd, $J_{1b,1a}$ 13.0, $J_{1b,2}$ 3.7, H-1b),
2.309 (s, 3H, Me, toluene),
1.248 (t, 3H, $J_{3,2}$ 6.3, H-3);

δ_C 21.13Q (Me, toluene), 22.94Q (C-3), 64.11T (C-1), 64.44D(C-2), 123.84, 129.83, 140.17 and 141.62 (aromatic carbons);

MS *m/z* 199 $[M+H]^+$.

(2S, 3S, S(R))-3-(p-Tolylsufinyl)-hexan-2-ol **14b.-** The β-hydroxysulfoxide **12a** (0.27 g, 1.35 mmol) was dissolved in THF (20 cm^3) and cooled to -78°C. 3 eq. of BuLi (2.8 cm^3, 1.6 M solution in hexanes) was added and the solution was allowed to warm to -20°C. After 20 min at this temperature the solution was again cooled to -78°C. After 30 min propyl bromide (PrBr) (150 µl, 1.62 mmol, 1.2 eq.) in THF (5 cm^3) was added and the reaction mixture was stirred for 3 h at RT. The standard isolation procedure and column chromatography (hexane-EtOAc, 1:1→EtOAc) gave the α-alkylated sulfoxide, **14b**, as a clear oil (100 mg, 35%); R_f 0.21 (hexane-EtOAc, 1:1); $[\alpha]_D^{19}$ +162.7 (*c* 1.3, $CHCl_3$);

δ_H 7.472 (m, 2H, aromatic protons),
7.313 (m, 2H, aromatic protons),
4.343 (s, H, OH),
4.066 (dq, $J_{2,3} \approx J_{2,1}$ =6.6, H-2),
2.637 (ddd, $J_{3,2} \approx J_{3,4a} \approx J_{3,4b}$ =6.0, H-3),

2.400 (s, 3H, Me, toluene),
1.40-1.18 (m, 4H, H-4 and H-5),
1.310 (d, 3H, $J_{1,2}$ 6.4, H-1),
0.780 (t, 3H, $J_{6,5}$ 7.0, H-6);

δ_C 13.82Q (C-6), 21.02T (C-5), 21.37Q (Me, toluene), 21.98Q (C-1), 25.50T (C-4), 67.62D (C-2/3), 68.08D (C-2/3), 125.16, 129.78, 135.72 and 141.57 (aromatic carbons);

MS *m/z* 241 $[M+H]^+$.

The α-epimer, **14a**, was also formed (85 mg, 30%); R_f 0.35 (hexane-EtOAc, 1:1); $[\alpha]_D^{19}$ +261.9 (*c*=1.3, $CHCl_3$).

(2*S*, 3*R*, S(*R*))-3-(*p*-Tolylsufinyl)-hexan-2-ol **14a**.

δ_H 7.437 (m, 2H, aromatic protons),
7.283 (m, 2H, aromatic protons),
4.246 (dq, H, $J_{2,1}$ 6.5, $J_{2,3}$ 1.5, H-2),
4.180 (s, H, OH),
2.358 (s, 3H, Me, toluene),
2.209 (ddd, H, $J_{3,4a}$ 8.8, $J_{3,4b}$ 4.7, $J_{3,2}$ 1.5, H-3),
1.95-1.70 (m, 2H, H-4a and 4b),
1.63-1.36 (m, 2H, H-5a and 5b),
1.070 (d, 3H, $J_{1,2}$ 6.5, H-1),
0.890 (t, 3H, $J_{6,5}$ 7.2, H-6);

δ_C 13.71Q (C-6), 20.33Q (C-1), 20.81T (C-5), 21.22Q (Me, toluene), 25.09T (C-4), 65.60D (C-2), 67.51D (C-3), 124.53, 129.87, 138.11 and 141.51 (aromatic carbons);

MS *m/z* 241 $[M+H]^+$.

(2R, 3R, S(R))-3-(p-Tolylsufinyl)-hexan-2-ol **14c.**- The β-hydroxysulfoxide, **12b** (320 mg, 1.6 mmol) was dissolved in THF (20 cm^3) and cooled to -78°C. 3.3 eq. of BuLi (3.3 cm^3, 1.6 M solution in hexanes) was slowly added and then the mixture was warmed to -20°C and stirred for 30 min before cooling to -78°C again. Propyl bromide (PrBr) (175 µl, 1.9 mmol, 1.2 eq.) was slowly added

after which the reaction mixture was stirred for 3 h at RT. The standard isolation procedure and column chromatography (hexane-EtOAc, 1:1→EtOAc) gave **14c** (140 mg, 40%); R_f 0.27 (hexane-EtOAc, 1:1); mp 99.5-100.5°C; $[\alpha]_D^{19}$ +144.3 (*c* 1, $CHCl_3$);

δ_H 7.583 (d, 2H, aromatic protons),
7.304 (d, 2H, aromatic protons),
4.619 (s, H, OH),
4.291 (dq, H, $J_{2,1}$ 6.4, $J_{3,2}$ 7.8, H-2),
2.711 (dt, H, $J_{3,2}$ 7.8, $J_{3,4}$ 4.7, H-3),
2.397 (s, 3H, Me, toluene),
1.50-1.20 (m, 4H, H-4 and H-5),
1.272 (d, 3H, $J_{1,2}$ 6.4, H-1),
0.765 (t, 3H, $J_{6,5}$ 6.9, H-6);

δ_C 14.02Q (C-6), 19.98T (C-5), 21.00Q (C-1), 21.43Q (Me, toluene), 28.00T (C-4), 68.71D (C-2), 70.38D (C-3), 125.53 and 129.98 (aromatic carbons);

MS *m/z* 241 $[M+H]^+$.

The α-epimer, **14d**, was also formed (20 mg, 6%); R_f 0.2 (hexane-EtOAc, 1:1); $[\alpha]_D^{19}$ +131.2 (*c* 0.7, $CHCl_3$);

(2*R*, 3S, S(*R*))-3-(*p*-Tolylsufinyl)-hexan-2-ol **14d**.

δ_H 7.448 (d, 2H, aromatic carbons),
7.297 (d, 2H, aromatic carbons),
4.465 (ddq, H, $J_{2,1}$ 6.5, $J_{2,3}$ 2.8, H-2),
2.526 (d, H, $J_{OH,2}$ 2.6, OH),
2.463 (dt, $J_{3,4}$ 5.6, $J_{3,2}$ 2.6, H-3),
1.66-1.56 (m, 2H, H-4a and 4b),
1.339 (d, 3H, $J_{1,2}$ 6.4, H-1),
1.12-1.06 (m, H, H-5a),
0.94-0.85 (m, H, H-5b),
0.694 (t, 3H, $J_{6,5}$ 7.2, H-6);

δ_C 13.88Q (C-6), 20.98T (C-1), 21.35Q (Me, toluene), 21.97T (C-4/5), 22.18T (C-4/5), 67.78D (C-2/3), 67.40D (C-2/3), 124.25, 129.80, 135.75 and 141.80 (aromatic carbons);

MS *m/z* 241 $[M+H]^+$.

(4*RS, *S(*R*))-4-(*p*-Tolylsulfinyl)-hexan-2-one **57** was prepared from **10** according to the general procedure a) in 50% yield as a 6:5 mixture of C-α epimers, which could not be separated; R_f 0.5 (hexane-EtOAc, 1:1);

δ_H 7.39 - 7.20 (m, aromatic protons), (* minor isomer)
3.663 (dd, H, $J_{3,4a}$ 9.9, $J_{3,4b}$ 4.3, H-3),
3.472 (dd, H, $J_{3,4a}$ 9.7, $J_{3,4b}$ 5.2, H-3*),
2.303 (s, 3H, Me, toluene),
2.040 (s, 3H, H-1*),
1.899 (s, 3H, H-1),
1.86-1.64 (m, 2H, H-4a and 4b),
1.36-1.14 (m, 2H, H-5a and 5b),
0.815 (t, 3H, $J_{6,5}$ 7.3, H-6),
0.802 (t, 3H, $J_{6,5}$ 7.4, H-6*);

δ_C 13.51 and 13.62Q (C-6), 20.21 and 20.29T (C-5), 21.20Q (Me, toluene), 27.63 and 27.92T (C-4), 31.24 and 32.23Q (C-1), 75.06 and 76.39D (C-3), 124.32-142.19 (aromatic carbons);

MS *m/z* 239 $[M+H]^+$.

14a,b,c,d were prepared from **57** using DIBALH according to the general procedure b) in a 2:1:0:1 ratio in 75% total yield.

14a,b,c,d were prepared from **57** using DIBALH/$ZnCl_2$ according to the general procedure c) in a 1:0:5:7 ratio in 75% total yield.

(4*RS, *S(*R*))-4-(*p*-Tolylsulfinyl)-heptan-3-one **58** was prepared from sulfoxide **10** according to general procedure a) in 62% yield as a ~1:1 mixture of C-α epimers, which could not be separated; R_f 0.55 (hexane-EtOAc, 1:1);

δ_H 7.42-7.24 (m, aromatic protons),
3.680 (dd, H, $J_{4,3a}$ 9.9, $J_{4,3b}$ 4.5, H-4),
3.547 (dd, H, $J_{4,3a}$ 9.9, $J_{4,3b}$ 4.8, H-4'),
2.415 (q, 2H, $J_{2,1}$ 7.2, H-2),
2.361 (s, 3H, Me', toluene),
2.354 (s, 3H, Me, toluene),
2.26-2.00 (m, 2H, H-2'),
1.95-1.75 (m, 4H, H-5+H-5'),
1.31-1.22 (m, 4H, H-6+H-6'),
0.925 (t, 3H, Me).

δ_C 6.83, 7.03Q (C-1,1'), 13.69, 13.81Q (C-7,7'), 20.41, 20.54T (C-6,6'), 21.38Q (Me toluene), 27.73, 28.69T (C-5,5'), 38.16, 39.01T (C-2,2'), 74.83, 76.35D (C-4,4'), 124.65-129.79 (aromatic carbons);

MS *m/z* 253 $[M+H]^+$.

(3*S*, 4*SR*, S(*R*))-4-(p-Tolylsulfinyl)-heptan-3-ol **59** was prepared from ketosulfoxide **58** according to general procedure a) as a 1:1 mixture of C-α epimers in 60% yield. After column chromatography (hexane-EtOAc, 1:1→EtOAc) **59a**; R_f 0.18 (hexane-EtOAc, 1:1); $[\alpha]_D^{19}$ +165.9 (*c* 1.3, $CHCl_3$) and **59b**; R_f 0.28 (hexane-EtOAc, 1:1); $[\alpha]_D^{19}$ +236.6 (*c* 1, $CHCl_3$) were isolated.

(3*S*, 4*R*, S(*R*))-4-(*p*-Tolylsulfinyl)-heptan-3-ol **59a**.

δ_H 7.442 (m, 2H, aromatic protons),
7.304 (m, 2H, aromatic protons),
4.041 (d, H, $J_{OH,3}$ 2.1, OH),
3.925 (ddd, H, $J_{3,2a} \approx J_{3,2b}$ =6.3, H-3),
2.381 (s, 3H, Me, toluene),
2.259 (ddd, H, $J_{4,5a}$ 9.3, $J_{4,5b}$ 4.1, $J_{4,3}$ 1.3, H-4),
1.98-1.89 (m, H, H-5a),
1.81-1.21 (m, 3H, H-5b and H-6),
0.930 (t, 3H, $J_{1,2}$ 7.2, H-1),
0.711 (t, 3H, $J_{7,6}$ 7.4, H-7);

δ_C 9.93Q (C-7), 13.8Q (C-1), 20.89T (C-5), 21.29Q (Me, toluene), 25.30T (C-2/6), 27.08T (C-2/6), 66.26D (C-4), 71.09D (C-3), 124.48D, 129.91D, 138.17S, 141.44S (aromatic carbons);

MS *m/z* 255 $[M+H]^+$.

(3*S*, 4S, S(*R*))-4-(*p*-Tolylsulfinyl)-heptan-3-ol **59b**.

δ_H 7.406 (d, 2H, aromatic protons),
7.263 (d, 2H, aromatic protons),
4.250 (s, H, OH),
3.807 (dt, H, $J_{3,4}$ 5.6, H-3),
2.571 (ddd, H, $J_{4,3a} \approx J_{4,5a} \approx J_{4,5b}$ =5.6, H-4),
2.354 (s, 3H, Me, toluene),
1.664 (dq, 2H, $J_{2,1} \approx J_{2,3}$ =7.2, H-2),
1.46-1.26 (m, 4H, H-5 and H-6),
0.984 (t, 3H, $J_{1,2}$ 7.3, H-1),
0.676 (t, 3H, $J_{7,6}$ 7.1, H-7);

δ_C 9.81Q (C-1/7), 13.69Q (C-1/7), 20.77T (C-5/6), 21.24Q (Me, toluene), 24.52T (C-5/6), 28.19T (C-2), 62.01D (C-4), 72.52D (C-3), 124.65, 129.63,137.31 and 141.08 (aromatic carbons);

MS *m/z* 255 $[M+H]^+$.

5.2.5 Chain Connection Reactions

(4S, S(R))-7-[(Methoxymethyl)oxy]-4-methyl-1-(p-tolylsulfinyl)-hept-5-en-2-one **60** was prepared from the left side fragment, **30**, and methylsulfoxide, **9**, according to general procedure a) on 4 mmol scale (~800 mg) in 82% yield and 97% de; R_f 0.2 (hexane-EtOAc, 1:1); $[\alpha]_D^{19}$ +167.1 (*c* 1.2, $CHCl_3$);

δ_H 7.454 (d, 2H, J 8.1, ortho aromatic proton),
7.254 (d, 2H, J 8.1, meta aromatic proton),
5.522 (dd, H, $J_{5,6}$ 15.6, $J_{5,4}$ 6.0, H-5),

5.437 (dt, H, $J_{6,4}$ 15.6, $J_{6,7}$ 5.2, H-6),
4.524 (s, 2H, OCH_2O),
3.888 (d, 2H, $J_{7,6}$ 5.0, H-7),
3.764 (d, H, $J_{1a,1b}$ 13.7, H-1a),
3.662 (d, H, $J_{1b,1a}$ 13.7, H-1b),
3.270 (s, 3H, OCH_3),
2.634 (m, H, $J_{4,Me} \approx J_{4,3} \approx J_{4,5}$ =6.7, H-4),
2.451 (m, 2H, H-3),
2.371 (s, 3H, Me, toluene),
0.966 (d, 2H, $J_{Me,4}$ 6,7);

δ_C 19.71Q (Me), 21.23Q (Me, toluene), 31.43D (C-4), 51.36T (C-3), 55.00Q (OCH_3), 67.51T (C-1/7), 68.29T (C-1/7), 95.35T (OCH_2O), 123.93D (aromatic carbon), 125.05D (C-6), 129.93D (aromatic carbon), 137.50D (C-5), 139.68S (aromatic carbon), 141.96S (*ipso*-aromatic carbon), 200.34S (C-2);

MS *m/z* 325 $[M+H]^+$, 293 $[(M+H)\text{-}MeOH]^+$, 263 $[M\text{-}CH_3OCH_2]$.

60 was also prepared from the left side nitrile, **36**, and methylsulfoxide, **9**, according to procedure f) on 5.5 mmol scale (~1.0 g) in 77% yield and 97% d.e.

(2S,4S,S(R))-7-[(Methoxymethyl)oxy]-4-methyl-1-(p-tolylsulfinyl)-hept-5-en-2-ol, **61a**, was prepared on 1.5 mmol scale (~500 mg) from **60** according to procedure b) using DIBALH in 90% yield and 97% de; R_f 0.16 (hexane-EtOAc, 1:1); $[\alpha]_D^{19}$ +183.5 (*c* 1.4, $CHCl_3$);

δ_H 7.461 (d, 2H, J 8.1, ortho aromatic protons),
7.280 (d, 2H, J 8.1, meta aromatic protons),
5.496 (dd, H, $J_{5,6}$ 15.5, $J_{5,4}$ 7.4, H-5),
5.334 (dt, H, $J_{6,5}$ 15.5, $J_{6,7}$ 6.0, H-6),
4.510 (s, 2H, OCH_2O),
4.370 (d, H, $J_{OH,2}$ 4.0, OH),
4.20-4.16 (m, H, H-2),
3.845 (d, 2H, $J_{7,6}$ 5.9, H-7),
3.262 (s, 3H, OCH_3),
2.957 (dd, H, $J_{1a,1b}$ 13.4, $J_{1a,2}$ 9.7, H-1a),

2.645 (dd, H, $J_{1b,1a}$ 13.4, $J_{1b,2}$ 1.9, H-1b),
2.389 (s, 3H, Me, toluene),
2.267 (m, H, $J_{4,3} \approx J_{4,5} \approx J_{4,Me}$ =7.0, H-4),
1.599 (dt, H, $J_{3a,3b}$ 13.8, $J_{3a,2}$ 7.7, H-3a),
1.325 (ddd, H, $J_{3b,3a}$ 13.8, $J_{3b,4}$ 7.1, $J_{3b,2}$ 5.1, H-3b),
0.908 (d, 3H, $J_{Me,4}$ 6.7, Me);

δ_C 19.65Q (Me), 21.13Q (Me, toluene), 32.78D (C-4), 43.60T (C-3), 54.95 (OCH_3), 63.14T (C-1), 64.13D (C-2), 67.70T (C-7), 95.29T (OCH_2O), 123.78 (aromatic carbon), 124.31D (C-6), 129.81 (aromatic carbon), 139.53D (C-5), 139.85S (aromatic carbon), 141.22S (*ipso*-aromatic carbon);

MS *m/z* 327$[M+H]^+$, 265$[M-CH_3OCH_2O]^+$.

(2S,4S,S(R))-7-[(Methoxymethyl)oxy]-4-methyl-1-(p-tolylsulfinyl)-hept-5-en-2-ol, **61b**, was prepared on 0.3 mmol scale (100 mg) from **60** according to procedure c) using DIBALH/$ZnCl_2$ in 90% yield; R_f 0.17 (hexane-EtOAc, 1:1);

δ_H 7.505 (d, 2H, J 8.1, ortho aromatic protons),
7.308 (d, 2H, J 8.1, meta aromatic protons),
5.580-5.270 (m, 2H, H-5 and H-6),
4.615 (s, 2H, OCH_2O),
4.337-4.255 (m, H, $J_{2,1a} \approx J_{2,3a}$ =9.2, $J_{2,1b}$ 2.5, $J_{2,3b}$ 3.5, H-2),
4.003 (d, 2H, $J_{7,6}$ 5.0, H-7),
3.352 (s, 3H, OCH_3),
2.907 (dd, H, $J_{1a,1b}$ 13.1, $J_{1a,2}$ 9.2, H-1a),
2.715 (dd, H, $J_{1b,1a}$ 13.1, $J_{1b,2}$ 2.3, H-1b),
2.483 (m, H, H-4),
2.393 (s, 3H, Me, toluene),
1.587 (ddd, H, $J_{3a,3b}$ 13.8, $J_{3a,2}$ 9.3, $J_{3a,4}$ 4.5, H-3a),
1.341 (ddd, H, $J_{3b,3a}$ 13.7, $J_{3b,4}$ 9.9, $J_{3b,2}$ 3.7, H-3b),
0.998 (d, 3H, $J_{Me,4}$ 6.8, Me);

δ_C 19.86Q (Me), 21.39Q (Me, toluene), 32.78D (C-4), 44.30T (C-3), 55.21Q (OCH_3), 62.84T (C-1), 66.91D (C-2), 67.91T (C-7), 95.56T (OCH_2O), 123.89D (aromatic carbon), 125.80D (C-6), 130.12D (aromatic carbon), 138.65D (C-5), 141.93S (*ipso*-aromatic carbon);

MS *m/z* 326 $[M]^+$.

***(4*RS*, S*(R))-5-(Benzyloxy)-4-methyl-1-(*p*-tolylsulfinyl)-pentan-2-one,* 62**, was prepared on 11 mmol scale (~2.0 g) according to procedure f) in 85% yield from the left side nitrile, **40**, and methylsulfoxide, **9**, as a 1:1 mixture of diastereomers. R_f 0.45 (hexane-EtOAc, 1:1);

δ_H 7.46-7.21 (m, aromatic protons),
4.380 (s, 2H, benzylic protons),
4.373 (s, 2H, benzylic protons),
3.810 (d, H, $J_{1a,1b}$ 13.9, H-1a),
3.790 (d, H, $J_{1a,1b}$ 13.9, H-1a),
3.700 (d, H, $J_{1b,1a}$ 13.9, H-1b),
3.686 (d, H, $J_{1b,1a}$ 13.9, H-1b),
3.321 (dd, H, $J_{5a,5b}$ 9.1, $J_{5a,4}$ 7.7, H-5a),
3.295 (dd, H, $J_{5a,5b}$ 9.1, $J_{5a,4}$ 7.7, H-5a),
3.161 (dd, H, $J_{5b,5a}$ 9.1, $J_{5b,4}$ 7.3, H-5b),
3.149 (dd, H, $J_{5b,5a}$ 9.1, $J_{5b,4}$ 7.2, H-5b),
2.613 (dd, H, $J_{3a,5b}$ 18.9, $J_{5a,4}$ 9.0, H-3a),
2.559 (dd, H, $J_{3a,3b}$ 18.9, $J_{3a,4}$ 8.6, H-3a),
2.342 (s, 3H, Me, toluene),
2.34 - 2.24 (m, 4H, H-3b (x2) and H-4 (x2)),
0.869 (d, 3H, $J_{Me,4}$ 6.5, Me),
0.840 (d, 3H, $J_{Me,4}$ 6.6, Me);

δ_C 16.85Q (Me), 21.20Q (Me, toluene), 29.76, 29.79D (C-4), 48.90, 49.17T (C-3), 68.31, 68.57T (C-1), 72.75, 72.81T (benzylic), 74.54, 74.62T (C-5), 123.88-141.76 (aromatic carbons), 201.01, 201.07S (C-2);

MS *m/z* 344 $[M]^+$.

***(2S, 5RS, S(R))-6-(Benzyloxy)-5-methyl-2-(p-tolylsulfinyl)-hexan-3-one* 64.**- A solution of (*R*)-methylsulfoxide, **9** (2.8 g, 18 mmol) in THF (50 cm^3) was cooled to -30°C, 1.6 eq. of LDA was added and stirred at RT for 30 min. The solution was cooled again to -30°C before the nitrile **40** (3 g, 16 mmol) in THF (50 cm^3) was slowly added. The reaction mixture was stirred for 30 min before warming to RT and stirring for another 2 h. Tlc showed that both **9** and **40** were present. A large excess of MeI was added after which normal work-up and column chromatography (hexane-EtOAc, 1:1→EtOAc) afforded the 4 isomers of the 1 carbon extended ketosulfoxide, **64**, in about equal amounts (~10% yield); R_f 0.5 (hexane-EtOAc, 1:1);

MS *m/z* 358 $[M]^+$.

The 1 carbon extended sulfoxide, ethyl *p*-tolylsulfoxide, **63**, was also recovered; R_f 0.25 (hexane-EtOAc, 1:1).

(*R*)-Ethyl *p*-tolyl sulfoxide **63**.

δ_H 7.436 (d, 2H, aromatic protons),
7.159 (d, 2H, aromatic protons),
2.78-2.57 (m, 2H, H-1),
2.246 (s, 3H, Me; toluene),
1.020 (t, 3H, $J_{2,1}$ 7.5, H-2).

δ_C 5.60Q (C-2), 20.97Q (Me, toluene), 49.88T (C-1), 123.83, 129.46, 139.64 and 140.97 (aromatic carbons);

MS *m/z* 169 $[M+H]^+$.

***(2S, 4RS, S(R))-5-(Benzyloxy)-4-methyl-1-(p-tolylsulfinyl)-pentan-2-ol,* 65**, was prepared from the ketosulfoxide, **62**, according to general procedure b) on 6 mmol scale (~2 g) as a 1:1 mixture of diastereomers in 90% yield. The two isomers could not be separated by column chromatography or crystallization. Crystallization from hexane-ether gave the β-hydroxysulfoxide, **65**, as white crystals; R_f 0.35 (hexane-EtOAc, 1:1); mp 118-122°C;

δ_H 7.51-7.22 (m, aromatic protons),

4.458 (s, 2H, benzylic protons),
4.470 (d, H, J 12.0, benzylic protons),
4.417 (d, H, J 12.0, benzylic protons),
4.36-4.22 (m, 2H, H-2 (x2)),
3.35-3.20 (m, 4H, H-5 (x2)),
2.883 (dd, H, $J_{1a,1b}$ 13.2, $J_{1a,2}$ 9.7, H-1a),
2.878 (dd, H, $J_{1a,1b}$ 13.3, $J_{1a,2}$ 9.8, H-1a),
2.703 (dd, H, $J_{1b,1a}$ 13.3, $J_{1b,2}$ 2.3, H-1b),
2.687 (dd, H, $J_{1b,1a}$ 13.3, $J_{1b,2}$ 2.3, H-1b),
2.377 (s, 3H, Me, toluene),
2.371 (s, 3H, Me, toluene),
2.05-1.89 (m, 2H, H-4 (x2)),
1.609 (ddd, H, $J_{3a,3b}$ 14.1, $J_{3a,4}$ 6.4, H-3a),
1.503 (dd, 2H, $J_{3,4} \approx J_{3,2}$ =7.3, H-3),
1.309 (ddd, H, $J_{3b,3a}$ 14.0, $J_{3b,4}$ 6.8, $J_{3b,2}$ 3.1, H-3b),
0.881 (d, 3H, $J_{Me,4}$ 6.8, Me),
0.858 (d, 3H, $J_{Me,4}$ 6.8, Me);

δ_C 17.45Q 17.62Q (Me), 21.29Q (Me, toluene), 30.18D, 31.13D (C-4), 42.03T, 42.54T (C-3), 63.40T, 64.21T (C-1), 64.21D, 64.91D (C-2), 73.03T, 73.25T (benzylic carbons), 75.49T, 76.02T (C-5), 123.87-141.28 (aromatic carbons);

MS *m/z* 346 $[M]^+$.

***(2S, 3S, 5RS, S(R))-6-(Benzyloxy)-5-methyl-2-(p-tolylsulfinyl)-hexan-3-ol,* 66**, was prepared from **65** on 1 mmol scale (~350 mg) according to general procedure d) in 94% yield as a 85:15 mixture of *threo-erythro* isomers. These four isomers could not be separated; R_f 0.41-0.45 (hexane-EtOAc, 1:1), 0.26-0.3 (hexane-EtOAc, 4:1);

δ_H 7.50-7.23 (m, aromatic protons),
4.485 (s, 2H, benzylic protons),
4.470 (dd, 2H, J 13.0, benzylic protons),
4.014 (ddd, H, $J_{3,2} \approx J_{3,4a}$ = 8.5, $J_{3,4b}$ 3.6, H-3),
3.963 (ddd, H, $J_{3,4a}$ 8.02, $J_{3,2}$ 7.7, $J_{3,4b}$ 2.0, H-3),
3.367 (dd, 2H, J 9.1, H-6),

3.319 (dd, 2H, J 9.1, H-6),
2.621 (dq, H, $J_{2,3}$ 7.8, $J_{2,Me}$ 7.2, H-2),
2.586 (dq, H, $J_{2,3}$ 8.2, $J_{2,Me}$ 7.1, H-2),
2.362 (s, 3H, Me, toluene),
2.351 (s, 3H, Me, toluene),
2.13-2.09 (m, 2H, H-5 (x2)),
1.25-1.22 (m, 4H, H-4a and 4b (x2)),
0.944 (d, 3H, $J_{Me,5}$ 7.2, Me),
0.919 (d, 3H, $J_{Me,5}$ 7.2, Me),
0.899 (d, 3H, $J_{1,2}$ 6.7, C-1),
0.882 (d, 3H, $J_{1,2}$ 6.6, C-1);

δ_C 6.62, 6.66Q (C-1), 17.18, 17.45Q (Me), 21.20Q (Me, toluene), 29.94, 30.75D (C-5), 39.88, 40.25T (C-4), 64.81D (C-2), 69.33, 70.11D (C-3), 72.94, 73.25T (benzylic carbons), 75.26, 76.20T (C-6), 124.40-140.77 (aromatic carbons);

MS *m/z* 361 $[M+H]^+$.

66 was also prepared from the ketosulfoxide, **64**, on 1.25 mmol scale (~0.45 mg) according to general procedure b) in 92% yield as a ~1:1 mixture of *threo-erythro* isomers.

***4-[(tert-Butyldimethylsilyl)oxy]-1-butanol* 67.-** A solution of 1,4-butanediol (4.5 g, 50 mmol) in THF (20 cm^3) was added to a NaH suspension (2.2 g of 60% dispersion in mineral oil, ~55 mmol, 1.1eq.) in THF (100 cm^3). The resulting suspension was stirred for 30 min until hydrogen evolution ceased. A solution of *t*-butyldimethylchlorosilane (*t*$BuMe_2SiCl$) (7.6 g, 51 mmol) in THF (20 cm^3) was then slowly added and stirred for 1.5 h at RT. The solvent was removed, water added and extracted with CH_2Cl_2 (200 cm^3 and 100 cm^3). The organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. After column chromatography (hexane-EtOAc, 3:1→1:1) **67** was obtained as a clear liquid (7.8 g, 76%); R_f 0.6 (hexane-EtOAc, 3:1);

δ_H 3.570 (t, 2H, $J_{4,3 \text{ or } 1,2}$ 5.8, H-4/1),
3.527 (t, 2H, $J_{1,2 \text{ or } 4,3}$ 5.9, H-1/4),
1.536 (m, 4H, H-2 and H-3),
0.813 (s, 9H, *t*Bu),
-0.024 (s, 6H, Me);

δ_C -5.51Q (Me), 18.16S ($C(CH_3)_3$), 25.79Q (*t*Bu), 29.60T (C-2/3), 29.78T (C-2/3), 63.35T (C-1/4), 63.17T (C-1/4);

MS *m/z* 205 $[M+H]^+$.

***4-Iodo-1-[(*tert*-butyldimethylsilyl)oxy]-butane* 68.-** To a solution of the alcohol **67** (1.0 g, 5 mmol) in benzene (50 cm^3) was added triphenylphosphine (5.24 g, 20 mmol, 4 eq.), imidazole (1.36 g, 20 mmol, 4 eq.) and I_2 (3.8 g, 15 mmol, 3 eq.)[9]. The solution became bright yellow with a black sticky precipitate on the sides of the flask and the formation of a yellow-white precipitate (Ph_3PO). after 1 h saturated aqueous $NaHCO_3$ (100 cm^3) was added and the solution was shaken in a separation funnel for 5 min. I_2 was added to obtain a persistent red colour, aqueous $Na_2S_2O_3$ was added until the red colour just disappeared. The aqueous layer was extracted with benzene (2x50 cm^3) and the combined organic layers were dried over Na_2SO_4. The solvents were evaporated *in vacuo* and the residue chromatographed (hexane-EtOAc, 4:1). The alkyliodide product, **68**, was found as a colourless liquid (1.6 g, 100%); R_f 0.8 (hexane-EtOAc, 9:1), 0.25 (hexane);

δ_H 3.613 (t, 2H, $J_{1,2}$ 6.1, H-1),
3.198 (t, 2H, $J_{4,3}$ 7.0, H-4),
1.887 (m, 2H, $J_{3,4} \approx J_{3,2}$ =7.1, H-3),
1.593 (m, 2H, $J_{2,3} \approx J_{2,1}$ =6.1, H-2),
0.871 (s, 9H, Me; *t*Bu),
0.026 (s, 6H, Me);

δ_C -5.34Q (Me), 6.92T (C-4), 18.27S ($C(CH_3)_3$), 25.92Q (Me, *t*Bu), 29.68T (C-2), 30.21T (C-3), 61.91T (C-1);

MS *m/z* 187 $[M-I]^+$.

***(5RS,6S,8RS,S(R))-9-(Benzyloxy)-1-[(*tert*-butyldimethylsilyl)oxy]-8-methyl-5-(p-tolylsulfinyl)-nonan-6-ol,* 69**, was prepared on 1 mmol scale from the β-hydroxysulfoxide, **65**, and alkyliodide, **68**, according to general procedure d) in 30% yield as a mixture of *threo* and *erythro* isomers, 3:2.

(5*S*,6*S*,8*RS*,S(*R*))-9-(benzyloxy)-1-[(*tert*-butyldimethylsilyl)oxy]-8-methyl-5-(*p*-tolylsulfinyl)-nonan-6-ol **69** *(threo).*

R_f 0.55 (hexane-EtOAc, 1:1);

δ_H 7.48-7.20 (m, aromatic protons),
4.466 (s, 2H, benzylic protons),
4.440(s, 2H, benzylic protons),
4.08-4.00 (m, 2H, H-6),
3.366 (t, 4H, $J_{1,2}$ 5.4, H-1 (x2)),
3.318 (d, 2H, $J_{9,8}$ 5.7, H-9),
3.307 (d, 2H, $J_{9,8}$ 6.6, H-9),
2.417 (ddd, $J_{5,6}$ 8.5, $J_{5,4}$ 5.7, H-5),
2.450 (ddd, $J_{5,6}$ 8.6, $J_{5,4}$ 5.7, H-5),
2.337 (s, 3H, Me, toluene),
2.324 (s, 3H, Me, toluene),
2.098 (m, 2H, H-8),
1.81-1.68 (m, 4H, H-7 (x2)),
1.50-1.45 (m, 4H, H-4 (x2)),
1.25-1.20 (m, 8H, H-2 and H-3 (x2)),
0.968 (d, 3H, $J_{Me,8}$ 6.9, Me),
0.921 (d, 3H, $J_{Me,8}$ 6.8, Me),
0.807 (s, 18H, *t*Bu (x2)),
-0.060 (s, 12H, Me-Si (x2));

δ_C -5.53Q (Me-Si), 17.02, 18.05Q (Me), 21.12Q (Me, toluene), 21.78, 21.85T (C-3), 23.99, 24.10T (C-4), 25.73Q (Me, *t*Bu), 30.21, 30.67D (C-8), 32.37T (C-2), 40.05, 40.16T (C-7), 62.33T (C-1), 68.95, 69.28D (C-5 and C-6), 72.79, 73.02T (benzylic carbons), 74.98, 76.03T (C-9), 124.35-140.64 (aromatic carbons);

MS *m/z* 533 $[M+H]^+$.

(5*R*,6*S*,8*RS*,S(*R*))-9-(benzyloxy)-1-[(*tert*-butyldimethylsilyl)oxy]-8-methyl-5-(*p*-tolylsulfinyl)-nonan-6-ol **69** *(erythro).*

R_f 0.74 (hexane-EtOAc, 1:1);

δ_H 7.50-7.19 (m, aromatic protons),
4.355 (s, 2H, benzylic protons)
4.319 (s, 2H, benzylic protons),
4.253 (ddd, 2H, $J_{6,7a} \approx J_{6,7b}$ =6.0, $J_{6,5}$ 1.4, H-6 (x2)),
3.61-3.56 (m, 4H, H-1 (x2)),
3.160 (d, 4H, $J_{9,8}$ 5.7, H-9 (x2)),
2.351 (s, 3H, Me, toluene),
2.286 (ddd, H, $J_{5,4a}$ 8.4, $J_{5,4b}$ 4.8, $J_{5,6}$ 1.2, H-5),
2.243 (ddd, H, $J_{5,4a}$ 9.2, $J_{5,4b}$ 4.1, $J_{5,6}$ 0.9, H-5),
2.381 (s, 3H, Me, toluene),
1.91-1.81 (m, 4H, H-3 (x2)),
1.80-1.65 (m, 4H, H-2 (x2)),
1.60-1.44 (m, 6H, H-8 and H-4 (x2)),
1.394 (dd, 4H, $J_{7,8} \approx J_{7,6}$ =7.0, H-7 (x2)),
0.877 (s, 9H, Me; *t*Bu),
0.872 (s, 9H, Me; *t*Bu),
0.790 (d, 3H, $J_{Me,8}$ 6.7, Me),
0.691 (d, 3H, $J_{Me,8}$ 6.8, Me),
0.030 (s, 6H, Me-Si),
0.025 (s, 6H, Me-Si);

δ_C -5.37Q (Me-Si), 16.88, 17.28Q (Me), 21.26Q (Me, toluene), 23.07, 23.24T (C-3), 24.12T (C-4), 25.88Q (*t*Bu), 30.16, 30.22D (C-8), 32.51T (C-2), 38.11, 38.59T (C-5), 62.54T (C-1), 67.19, 68.04D (C-6), 67.32D (C-5), 72.72, 72.88T (benzylic carbons), 74.96, 75.47T (C-9), 124.50-141.52 (aromatic carbons);

MS *m/z* 533 $[M+H]^+$.

69 was also prepared on 2 mmol scale from β-hydroxysulfoxide, **65**, and alkyliodide, **68**, by general procedure e) (with LDA as base) in 63% yield and in a 1:2 ratio of *threo* and *erythro* isomers.

5.2.6 Preparation of Sulfones

***(2S, 4S)-7-[(Methoxymethyl)oxy]-4-methyl-1-(p-tolylsulfonyl)-hept-5-en-2-ol* 70.**- To a solution of **61a** (215 mg, 0.66 mmol) in CH_2Cl_2 (10 cm^3) was added *meta*-chloroperbenzoic acid (mCPBA)[14] (270 mg, 50-60% purity, 1.3 eq.) and the resulting solution was stirred for 3 h at RT until tlc showed no more **61a**. The reaction mixture was diluted with CH_2Cl_2 and a 5% aqueous solution of NaOH was added. The organic layer was washed twice with the 5% NaOH solution after which it was dried over Na_2SO_4 and concentrated to give a clear oil which was purified by means of column chromatography (hexane-EtOAc, 1:1→EtOAc) to give the sulfone, **70** (120 mg, 53%); R_f 0.7 (EtOAc); $[\alpha]_D^{19}$ +106.4 (*c* 0.9, $CHCl_3$);

δ_H 7.770 (d, 2H, J 8.3, aromatic protons),
7.346 (d, 2H, J 8.1, aromatic protons),
5.515 (dd, H, $J_{5,6}$ 15.5, $J_{5,4}$ 7.7, H-5),
5.363 (dt, H, $J_{6,5}$ 15.5, $J_{6,7}$ 5.8, H-6),
4.560 (s, 2H, OCH_2O),
4.19-4.10 (m, H, H-2),
3.848 (d, 2H, $J_{7,6}$ 5.9, H-7),
3.318 (s, 3H, OCH_3),
3.115 (dd, H, $J_{1a,1b}$ 14.2, H-1a),
3.164 (dd, H, $J_{1b,1a}$ 14.3, H-1b),
2.429 (s, 3H, Me, toluene),
2.283 (m, H, $J_{4,3} \approx J_{4,5} \approx J_{4,Me}$ =7.0, H-4),
1.595 (ddd, H, $J_{3a,3b}$ 13.5, $J_{3a,2} \approx J_{3a,4}$ =7.5, H-3a),
1.308 (ddd, H, $J_{3b,3a}$ 13.7, $J_{3b,4}$ 7.3, $J_{3b,2}$ 5.6, H-3b),
0.961 (d, 3H, $J_{Me,4}$ 6.7, Me);

δ_C 19.82Q (Me), 21.60Q (Me, toluene), 32.80D (C-4), 43.03T (C-3), 55.17Q (OCH_3), 62.38T (C-1), 64.30D (C-2), 67.72T (C-7), 95.50T (OCH_2O), 124.84D (C-6), 127.91D (aromatic carbon), 130.02D (aromatic carbon), 139.15D (C-5);

MS *m/z* 343 $[M+H]^+$.

Due to over-oxidation a 1:1 mixture of two isomers of **71** also formed, (110 mg, 47%); R_f 0.57 (EtOAc), 0.5 (hexane-EtOAc, 1:1);

(1*S*,3*S*,4*R*)-4-{1*S*-2-[(methoxymethyl)oxy]-1-hydroxyethyl}-3-methyl-1-(methyl *p*-tolylsulfonyl) tetrahydrofuran and
(1*S*, 3*S*, 4*S*)-4-{1*R*-2-[methoxymethyl)oxy]-1-hydroxyethyl)-3-methyl-1-(methyl *p*-tolylsulfonyl) tetrahydrofuran **71**.

δ_H 7.746 (d, 4H, J 8.2, aromatic protons),
7.304 (d, 4H, J 8.0, aromatic protons),
4.566 [s, 4H, OCH_2O (x2)],
4.30-4.20 [m, 2H, H-2 (x2)],
3.58-3.28 [m, 8H, H-5, H-6 and H-7 (x2)],
3.324 [s, 6H, OCH_3 (x2)],
3.159 [m, 4H, H-1 (x2)],
2.405 [s, 6H, OCH_3, toluene (x2)],
2.405 [m, 4H, H-3a (x2)],
2.35-2.23 [m, 4H, H-4 (x2)],
1.34-1.27 [m, 2H, H-3b (x2)],
1.066 (d, 3H, $J_{Me,4}$ 6.3, Me),
0.989 [d, 3H, $J_{Me,4}$ 6.9, Me);

δ_C 15.43Q (Me), 18.18Q (Me), 21.51Q (Me, toluene), 34.57D (C-4), 36.91D (C-4), 39.75T (C-3), 40.00T (C-3), 55.34Q (OCH_3), 61.65T (C-1), 62.32T (C-1), 69.10D (C-5), 70.33T (C-7), 71.30T (C-7), 72.45D (C-2), 72.87 (C-5), 72.99D (C-2), 81.20D (C-6),84.82D (C-6), 97.05T (OCH_2O), 128.12D (aromatic carbon), 129.63D (aromatic carbon), 144.60S (*ipso*-aromatic carbon);

MS ***m/z*** 326 $[M\text{-}MeOH]^+$.

5.2.7 Pummerer Rearrangement Reactions

***(2S, 4RS)-5-(Benzyloxy)-1,2 dihydroxy-4-methyl-1-(p-tolylsulfanyl)-pentane di-trifluoroacetate* 74.-** A solution of β-hydroxysulfoxide **65** (346 mg, 1 mmol) and 2,6-lutidine (465 μl, 4 mmol) in CH_3CN (6 cm^3) was added to a cooled (0°C) solution of trifluoroacetic anhydride [15] (840 mg, 4 mmol) in CH_3CN (2 cm^3) and stirred for 30 min. The standard isolation procedure yielded the crude rearranged sulfide **74**. Column chromatography (hexane-EtOAc, 1:1) of **74** however resulted in conversion to mainly the α-hydroxy ketone, **76**.

***(2S, 4RS)-5-(Benzyloxy)-1,2-diacetoxy-4-methyl-1-(p-tolylsulfanyl)-pentane* 75.-** A solution of β-hydroxy sulfoxide **65** (300 mg, 0.9 mmol) and sodium acetate (1 g) in acetic anhydride [16] (20 cm^3) was heated at 120-130°C for 4 h. The cooled solution was diluted with toluene and concentrated *in vacuo* to give a brown solid which was partitioned between aqueous NaOH and ether. After standard isolation and chromatography (hexane-EtOAc, 1:1→3:2) a mixture of the 4 isomers of the diacetate, **75**, was recovered (210 mg, 60%); R_f 0.8 (hexane-EtOAc, 1:1);

δ_H 7.41-7.07 (m, aromatic protons)
6.198 (d, H, $J_{1,2}$ 3.5, H-1),
6.186 (d, H, $J_{1,2}$ 3.5, H-1),
6.083 (d, H, $J_{1,2}$ 5.8, H-1),
6.073 (d, H, $J_{1,2}$ 5.6, H-1),
5.36-5.29 (m, 4H, H-2 (x4)),
4.497 (s, 2H, benzylic protons),
4.484 (s, 2H, benzylic protons),
4.472 (s, 2H, benzylic protons),
4.442 (s, 2H, benzylic protons),
3.33-3.25 [m, 8H, H-5 (x4)],
2.308 [s, 12H, Me, toluene (x4)],
2.019 [s, 24H, Me, acetate (x8)],
2.08-1.49 [m, 2H, H-3 and H-4 (x4)],
1.010 (d, 3H, $J_{Me,4}$ 6.6, Me),
0.971 (d, 3H, $J_{Me,4}$ 6.7, Me),
0.961 (d, 3H, $J_{Me,4}$ 6.6, Me),
0.881 (d, 3H, $J_{Me,4}$ 6.5, Me);

δ_C 16.35, 17.85Q (Me), 20.71, 21.00Q (Me, toluene and Me, acetate), 29.54, 29.81, 30.03, 30.25D (C-4), 33.54, 33.83, 34.54, 34.93T (C-3), 71.40, 71.87, 72.17, 72.70D (C-2), 72.89T (benzylic carbons), 74.35, 74.51, 75.53, 74.64T (C-5), 81.35, 81.53, 82.83, 82.92D (C-1), 127.29-138.64 (aromatic carbons), 169.15, 169.53, 169.94, 170.18S (ester);

MS *m/z* 430 $[M]^+$.

The acetate derivative of **65** formed as a byproduct (20%).

***(4*RS*)-5-(Benzyloxy)-1-hydroxy-4-methylpentan-2-one* 76.-** The diacetate compound, **75**, (150 mg, 0.35 mmol) was dissolved in a 2% KOH (MeOH-H_2O, 2:1) solution and stirred at ~70°C until tlc showed the absence of the starting material. The MeOH was evaporated and the aqueous residue diluted and extracted with CH_2Cl_2. After chromatography (hexane-EtOAc, 4:1→EtOAc) the α-hydroxy ketone, **76**, (racemic mixture) was recovered as a clear liquid (50 mg, 65%); R_f 0.45-0.55 (hexane-EtOAc, 1:1);

δ_H 7.35-7.23 (m, aromatic protons),
4.444 (s, 2H, benzylic protons),
4.181 (s, 2H, H-1),
3.378 (dd, H, $J_{5b,5a}$ 9.3, $J_{5b,4}$ 4.9, H-5b),
3.223 (dd, H, $J_{5a,5b}$ 9.3, $J_{5a,4}$ 7.5, H-5a),
2.551 (dd, H, $J_{3b,3a}$ 15.4, $J_{3b,4}$ 6.3, H-3b),
2.410 (m, H, H-4),
2.225 (dd, H, $J_{3a,3b}$ 15.4, $J_{3a,4}$ 7.0, H-3a),
0.941 (d, 3H, $J_{Me,4}$ 6.7, Me);

δ_C 17.07Q (Me), 30.20D (C-4), 42.71T (C-3), 68.55T (C-1), 73.02T (benzylic carbon), 74.74T (C-5), 127.53, 127.60, 128.36D (aromatic carbons), 209.0S (C-2);

MS *m/z* 223 $[M+H]^+$.

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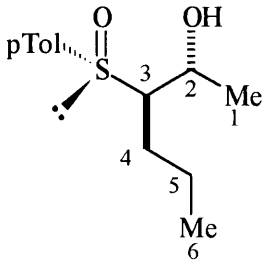
APPENDIX

Crystallography of (R_s,2R,3R)-2-Hydroxy-3-(*p*-tolylsulfonyl)-hexane (14c)



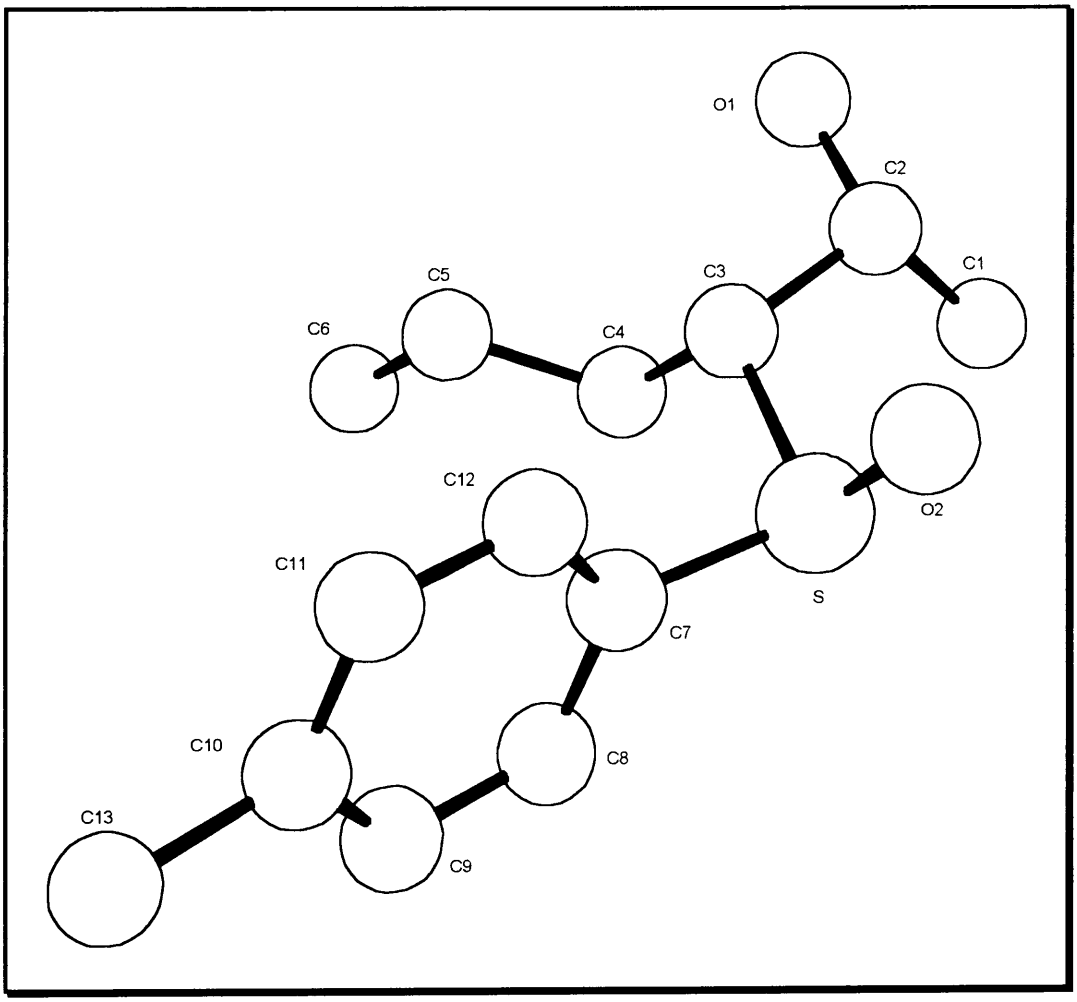


Fig 1

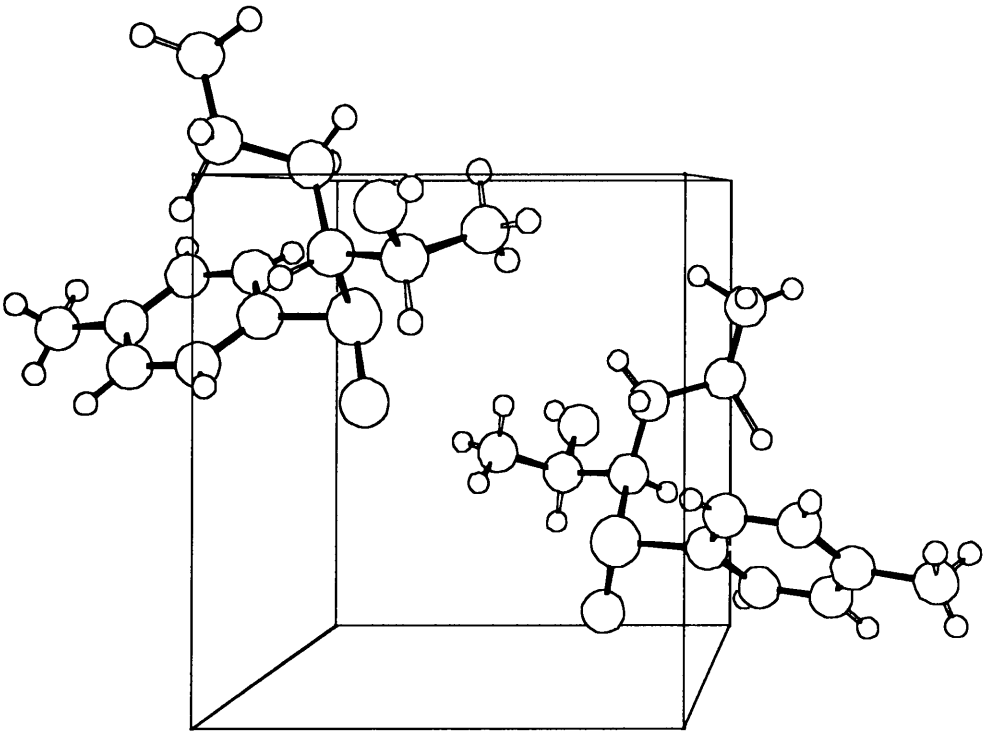


Fig 2

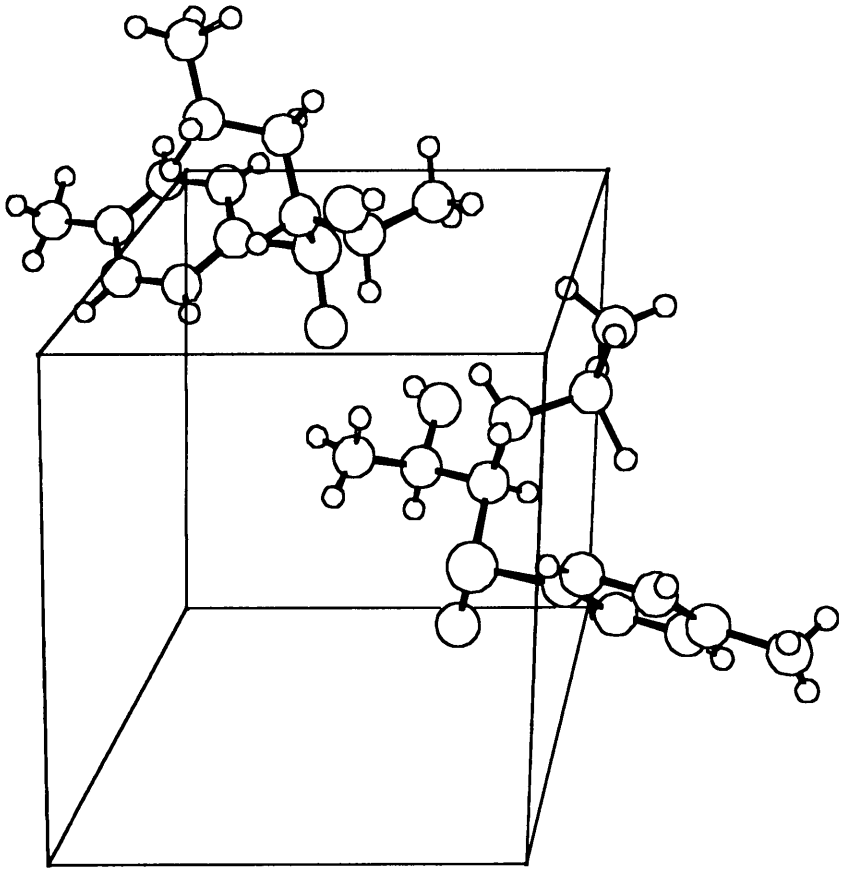


Fig 3

Table 1 Crystallographic data acquisition and refinement details of compound 14c

Empirical formula	$C_{13}H_{20}O_2S$
Molecular weight, g.mol^{-1}	240.3
Crystal dimension, mm	0.25 x 0.28 x 0.30
Space group	$P2_1$ (4)
Cell dimensions	
a, Å	7.735(1)
b, Å	8.571(1)
c, Å	10.334(1)
b, °	101.649
Z	2
Volume, Å^3	671.0(1)
D(calc), g_cm^{-3}	1.17
m, cm^{-1}	1.85
Radiation (l, Å)	MoK_a, 0.7107
T, °C	23
F(000)	260.0
Scan type (w:2q)	1:1
Scan Range (q°)	3<q<30
Zone collected:	
h	-10, 0
k	-12, 0
l	-14, +14
Max. scan speed (deg.min^{-1})	5.49
Max. scan time, sec.	60
Scan angle (w + 0.34 tan q)°	0.64
Aperture size (mm)	1.3 x 4.0
Reflections collected	1915
Decay, %	<1
EAC correction factor:	
Maximum	1.000
Minimum	0.963
Average	0.984
Unique reflections used (>3s(I))	1566

R_{int}	0.017
Parameters refined	205
Max. positional shift/esd	<0.13 (H4B)
Residual electron density (eÅ^3):	
Maximum	0.20
Minimum	-0.24
U_{iso}(H), Å^2	0.094(3)
R	0.044
R_w	0.026

Table 2 Fractional atomic coordinates (x 10^4) and equivalent thermal factors (x 10^3 Å^2) for 14c

Atom	x/a	y/b	z/c	U_{iso}/U_{eq}
O(1)	3981(4)	9428(5)	10775(3)	81(1)
C(1)	5716(6)	9003(6)	9086(4)	72(1)
C(2)	4190(5)	8491(5)	9683(3)	60(1)
C(3)	2395(4)	8570(4)	8721(3)	49(1)
C(4)	1835(5)	10206(5)	8241(4)	62(1)
C(5)	11(6)	10656(6)	8561(5)	90(1)
C(6)	-528(6)	12260(8)	8123(5)	97(1)
S	2501(1)	7310	7328(1)	58(1)
O(2)	2882(3)	5702(3)	7889(3)	87(1)
C(7)	216(3)	7282(5)	6549(3)	48(1)
C(8)	-315(5)	8113(5)	5382(3)	58(1)
C(9)	-2048(5)	8013(5)	4714(3)	64(1)
C(10)	-3242(4)	7085(5)	5175(3)	58(1)
C(11)	-2698(5)	6286(5)	6355(3)	60(1)
C(12)	-970(5)	6377(5)	7029(3)	56(1)
C(13)	-5117(5)	6924(7)	4367(5)	91(2)
HO(1)	4662(60)	9734(59)	11054(48)	94(3)*
H(1A)	6035(44)	8415(50)	8378(32)	94(3)*
H(1B)	6748(44)	9167(51)	9722(33)	94(3)*

H(1C)	5490(52)	10065(54)	8637(36)	94(3)*
H(2)	405(38)	7353(49)	10025(31)	94(3)*
H(3)	1504(46)	8115(41)	9218(31)	94(3)*
H(4A)	2628(45)	11058(44)	8537(33)	94(3)*
H(4B)	1948(47)	10264(49)	7336(34)	94(3)*
H(5A)	-8(46)	10766(43)	9593(29)	94(3)*
H(5B)	-928(43)	9371(44)	8109(33)	94(3)*
H(6A)	-1636(41)	12622(48)	8418(30)	94(3)*
H(6B)	-625(40)	12491(50)	7141(36)	94(3)*
H(6C)	684(48)	12907(41)	8718(33)	94(3)*
H(8)	422(46)	8494(50)	4974(41)	94(3)*
H(9)	-2338(44)	8573(51)	3958(31)	94(3)*
H(11)	-3540(43)	5565(44)	6633(31)	94(3)*
H(12)	-547(49)	6005(42)	7809(34)	94(3)*
H(13A)	-5086(39)	7664(42)	3409(31)	94(3)*
H(13B)	-5870(47)	7432(54)	4795(33)	94(3)*
H(13C)	-5577(57)	6008(53)	4552(39)	94(3)*

* Isotropic thermal parameter; $U_{eq5} = 1/3\ S_i\ S_j\ U_{ij}a^*_i a^{*j}(\mathbf{a_i}.\mathbf{a_j})$

Table 3 **Bond lengths (Å) and valence angles (°) for 14c**

Atoms	**Distance**	**Atoms**	**Distance**
O(1)-C(2)	1.420(5)	C(1)-C(2)	1.503(5)
C(2)-C(3)	1.537(4)	C(3)-C(4)	1.521(5)
C(3)-S	1.815(3)	C(4)-C(5)	1.561(6)
C(5)-C(6)	1.481(7)	S-O(2)	1.501(2)
S-C(7)	.789(3)	C(7)-C(8)	1.389(4)
C(7)-C(12)	1.369(4)	C(8)-C(9)	1.381(5)
C(9)-C(10)	1.375(4)	C(10)-C(11)	1.388(4)
C(10)-C(13)	1.527(5)	C(11)-C(12)	1.379(4)
O(1)-HO(1)	61(4)	C(1)-H(1A)	.96(4)

C(1)-H(1B)	94(3)	C(1)-H(1C)	1.02(4)
C(2)-H(2)	1.04(4)	C(3)-H(3)	1.02(3)
C(4)-H(4A)	96(4)	C(4)-H(4B)	.96(4)
C(5)-H(5A)	1.07(3)	C(5)-H(5B)	.35(4)
C(6)-H(6A)	1.02(3)	C(6)-H(6B)	1.02(4)
C(6)-H(6C)	1.15(4)	C(8)-H(8)	.84(4)
C(9)-H(9)	.91(3)	C(11)-H(11)	.98(4)
C(12)-H(12)	.87(4)	C(13)-H(13A)	1.18(3)
C(13)-H(13B)	.91(4)	C(13)-H(13C)	.90(4)

Atoms	**Angle**	**Atoms**	**Angle**
O(1)-C(2)-C(1)	112.7(3)	O(1)-C(2)-C(3)	104.8(3)
C(1)-C(2)-C(3)	113.8(3)	C(2)-C(3)-C(4)	114.3(3)
C(2)-C(3)-S	107.9(2)	C(4)-C(3)-S	110.2(2)
C(3)-C(4)-C(5)	111.6(4)	C(4)-C(5)-C(6)	112.0(4)
C(3)-S-O(2)	106.0(2)	C(3)-S-C(7)	99.5(2)
O(2)-S-C(7)	105.1(2)	S-C(7)-C(8)	118.4(3)
S-C(7)-C(12)	121.2(2)	C(8)-C(7)-C(12)	120.2(3)
C(7)-C(8)-C(9)	119.3(3)	C(8)-C(9)-C(10)	121.0(3)
C(9)-C(10)-C(11)	119.0(3)	C(9)-C(10)-C(13)	119.6(3)
C(11)-C(10)-C(13)	121.5(4)	C(10)-C(11)-C(12)	120.5(3)
C(7)-C(12)-C(11)	120.0(3)		

C(2)-O(1)-HO(1)	113(5)	C(2)-C(1)-H(1A)	120(2)
C(2)-C(1)-H(1B)	113(2)	H(1A)-C(1)-H(1B)	108(3)
C(2)-C(1)-H(1C)	112(2)	H(1A)-C(1)-H(1C)	100(3)
H(1B)-C(1)-H(1C)	103(3)	O(1)-C(2)-H(2)	107(2)
C(1)-C(2)-H(2)	109(2)	C(3)-C(2)-H(2)	109(2)
C(2)-C(3)-H(3)	106(2)	C(4)-C(3)-H(3)	110(2)
S-C(3)-H(3)	108(2)	C(3)-C(4)-H(4A)	118(2)
C(5)-C(4)-H(4A)	107(2)	C(3)-C(4)-H(4B)	107(3)
C(5)-C(4)-H(4B)	117(2)	H(4A)-C(4)-H(4B)	95(3)
C(4)-C(5)-H(5A)	115(2)	C(6)-C(5)-H(5A)	99(2)

C(4)-C(5)-H(5B)	99.9(14)	C(6)-C(5)-H(5B)	124(2)
H(5A)-C(5)-H(5B)	108(3)	C(5)-C(6)-H(6A)	113(2)
C(5)-C(6)-H(6B)	116(2)	H(6A)-C(6)-H(6B)	110(3)
C(5)-C(6)-H(6C)	98(2)	H(6A)-C(6)-H(6C)	110(3)
H(6B)-C(6)-H(6C)	109(3)	C(7)-C(8)-H(8)	122(3)
C(9)-C(8)-H(8)	118(3)	C(8)-C(9)-H(9)	116(2)
C(10)-C(9)-H(9)	123(2)	C(10)-C(11)-H(11)	118(2)
C(12)-C(11)-H(11)	121(2)	C(7)-C(12)-H(12)	113(3)
C(11)-C(12)-H(12)	127(3)	C(10)-C(13)-H(13A)	103(2)
C(10)-C(13)-H(13B)	109(2)	H(13A)-C(13)-H(13B)	106(3)
C(10)-C(13)-H(13C)	110(3)	H(13A)-C(13)-H(13C)	137(3)
H(13B)-C(13)-H(13C)	90(4)		

Table 4 **Anisotropic thermal factors ($x10^3$ $Å^2$) for 14c**

Atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
O(1)	73(2)	106(3)	64(2)	-26(2)	10(2)	-33(2)
C(1)	52(2)	77(3)	85(3)	5(3)	8(2)	3(2)
C(2)	60(2)	54(2)	61(2)	-5(2)	-2(2)	-6(2)
C(3)	52(2)	46(2)	47(2)	-8(2)	9(2)	-4(2)
C(4)	57(2)	48(2)	81(3)	-4(2)	11(2)	4(2)
C(5)	81(3)	84(4)	107(4)	1(3)	5(3)	17(3)
C(6)	87(3)	104(4)	101(3)	4(4)	24(3)	43(4)
S	57(1)	59(1)	52(1)	-10(1)	-2(1)	12(1)
O(2)	88(2)	53(2)	95(2)	-16(1)	-40(2)	23(1)
C(7)	53(2)	46(2)	42(1)	-5(2)	0(1)	4(2)
C(8)	65(3)	59(2)	48(2)	9(2)	10(2)	1(2)
C(9)	68(2)	74(3)	46(2)	7(2)	-2(2)	12(2)
C(10)	57(2)	63(3)	50(2)	-11(2)	4(2)	5(2)
C(11)	66(2)	57(2)	55(2)	-1(2)	9(2)	-8(2)
C(12)	74(2)	51(2)	39(2)	-1(2)	0(2)	3(2)
C(13)	56(3)	128(6)	81(3)	-2(3)	-3(2)	7(3)