Synthesis and Chemistry of 1,4-Oxathianes and 1,4-oxathian-3-ones

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Director of Studies

Dr Alan G Sutherland

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I am eternally beholden to my family for their support, encouragement and understanding during this time and especially for their faith in me.

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CONTENTS

Abstract

The exploration of possible routes towards the synthesis of alkylated oxathiane and oxathianone systems are presented in this research thesis. The ultimate objective of these studies was the synthesis of dihydrofurans and dihydrofuranones *via* the Ramberg-Bäcklund rearrangement.

Initially, studies were carried out on the alkylation of the cyclic ether, 1,4-oxathiane *S,S*-dioxide. It was during investigations with the readily available cyclic ether that several ring-opened novel compounds were synthesised. Subsequently, an alkylated epoxide was prepared and two pathways from this epoxide to the synthesis of an alkylated 1,4-oxathiane *S,S*-dioxide were examined. The first involved an examination influencing the regioselectivity of the epoxide and consequent ring-opening to yield the corresponding hydroxy sulfide. Further studies explored the possibility of either ring closure of the sulfide followed by oxidation to the sulfone or oxidation to the sulfone followed by cyclization. However, these routes were to prove unsuccessful. The second pathway involved the use of a readily available epoxide for the afore mentioned cyclization/oxidations.

The preparation of oxathianones was the second part of these studies and involved the synthesis of the lactone 1,4-oxathian-3-one *S,S*-dioxide again with the aim of alkylating this sulfone for use as the precursor required in the Ramberg-Bäcklund reaction. Investigations included acid/alcohol cyclizations and catalytic oligomerization/depolymerization methods.

Another sequence of reactions available to us was the direct oxidation of a hydroxy diol and/or lactol oxidation to the lactone. However, it was during this research towards the synthesis of the sulfone lactone that four unexpected and novel compounds were synthesised.

The latter part of our studies took us to the preparation of an alkylated oxotetrahydrothiophene *S,S*-dioxide with the intention of performing the Baeyer-Villiger oxidation to the requisite lactone. However, success came with the double alkylation of the system rather than the mono-alkylation.

Abbreviations

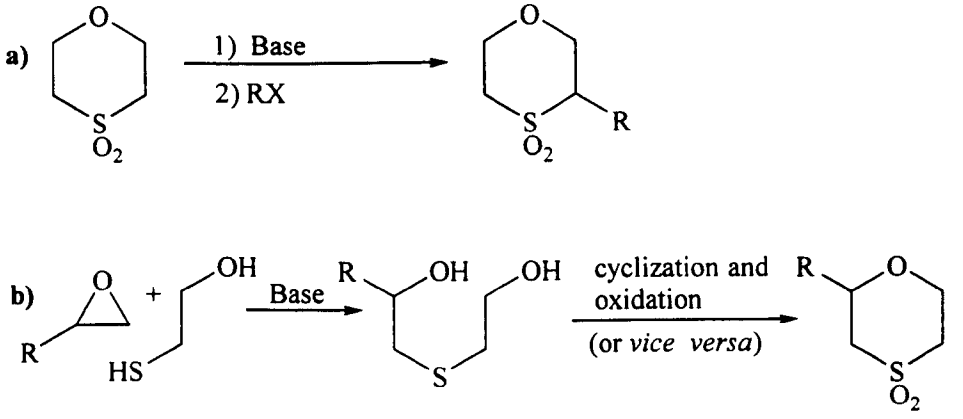
b.p	boiling point
br	broad
d	doublet
D	deuterium
DBTDL	dibutyltin dilaurate
DEM	diethyl malonate
DMAP	4-dimethylaminopyridine
DMF	1,2-dimethylformamide
DMSO	dimethyl sulfoxide
i.r	infra-red spectroscopy
m	multiplet
m.p.	melting point
m.s	mass spectroscopy
NMO	N-methylmorpholine-N-oxide
NMR	nuclear magnetic resonance
[O]	oxidation
OXONE ($KHSO_5$)	potassium hydrogen persulfate
Pd/C	5% palladium on Carbon
Ph	phenyl
py	pyridine
R	alkyl

R-B	Ramberg-Bäcklund reaction
RSM	recovered starting material
R.T.	room temperature
s	singlet
t	triplet
TBAF	tetrabutlyammonium fluoride
THF	tetrahydrofuran
t.l.c	thin layer chromatography
TPAP	tetrapropylammonium perruthenate
TPP	triphenyl phosphine
p-TsCl	*p*-toluensulfonyl chloride
TSOH	*p*-toluenesulfonic acid
X	leaving group

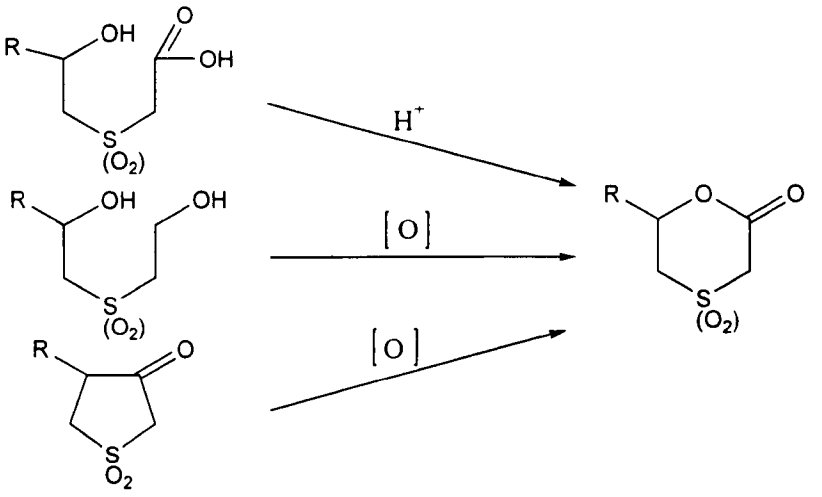
1 Introduction

The objective of this research was to synthesize suitably substituted oxathiane and oxathianone *S,S*-dioxide systems as outlined in Schemes 1.1 and 1.2, in order to implement the Ramberg-Bäcklund rearrangement to produce the corresponding dihydrofurans and dihydrofuranones.

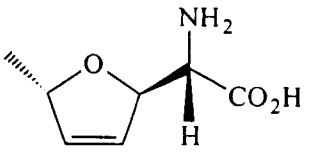
Scheme 1.1



Scheme 1.2

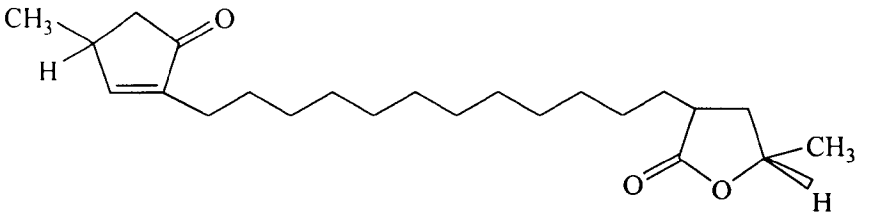


There have been many reports on the synthesis of dihydrofuran and dihydrofuranone natural products.[1-4] These include (+)-furanomycin (**1**), an antibiotic α-amino acid of the 2,5-dihydrofuran moiety which has been successfully isolated from the micro-organism *Streptomyces threomyceticus*.[1] Much later, Joullie and co-workers described the total synthesis of (+)-furanomycin and stereoisomers.



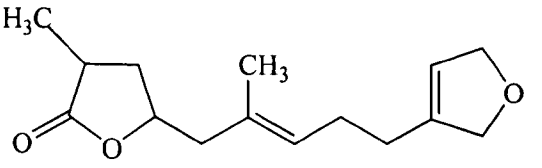
1

Subsequently, Trost *et al.* synthesized (+)-ancepsenolide (**2**) from the gorgonia *Pterogorgia anceps* and *Pterogorgia guadalypenses* micro-organisms.



2

Another biogenetically interesting constituent of the plant *Eremophila freelingii* (**3**) was synthesized by Jefford *et al.*. Hence, it was perceived that a new general synthetic approach to such structures would prove valuable.

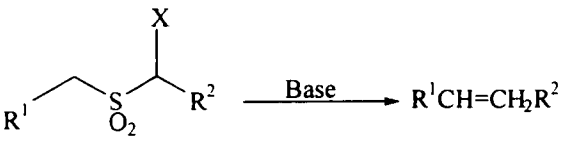


3

The Ramberg-Bäcklund reaction is one of the best known and most extensively studied of reactions involving the sulfone functional group. First

described in 1940,[5] the reaction entails the use of a base for the conversion of an α-halo sulfone into a regio-defined alkene (Scheme 1.3).

Scheme 1.3

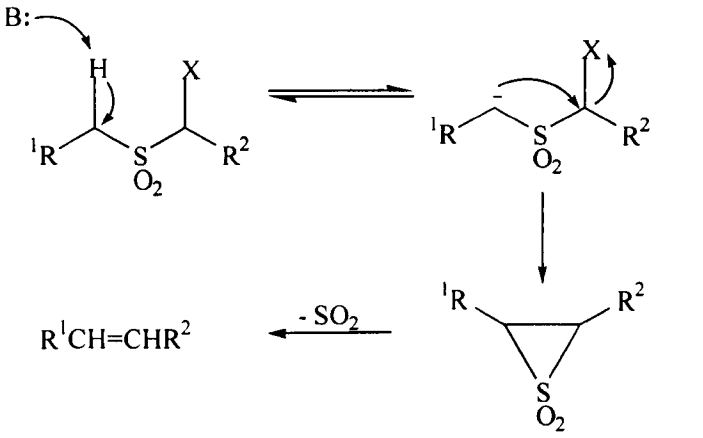


In the oxathiane series, two general approaches were to be investigated to produce the corresponding substituted systems for the Ramberg-Bäcklund rearrangement. Substituents α to the sulfone would be introduced by alkylation of the α-sulfonyl anion. Initially, these studies would entail submitting the commercially available cyclic ether, 1,4-oxathiane *S,S*-dioxide, to a variety of alkylating conditions in an attempt to synthesize the requisite alkylated oxathiane *S,S*-dioxide (Scheme 1.1a). Systems with substituents α to the ring oxygen would be approached by a ring synthesis approach (Scheme 1.1b).

The corresponding lactones, 1,4-oxathian-3-one *S,S*-dioxides, would be approached by ring formation procedures from hydroxy-acid or diol precursors, or else *via* the Baeyer-Villiger oxidation[6] of an analogous oxotetrahydrothiophene *S,S*-dioxide (Scheme 1.3). The alkylated lactones would then be subjected to the Ramberg-Bäcklund reaction conditions.

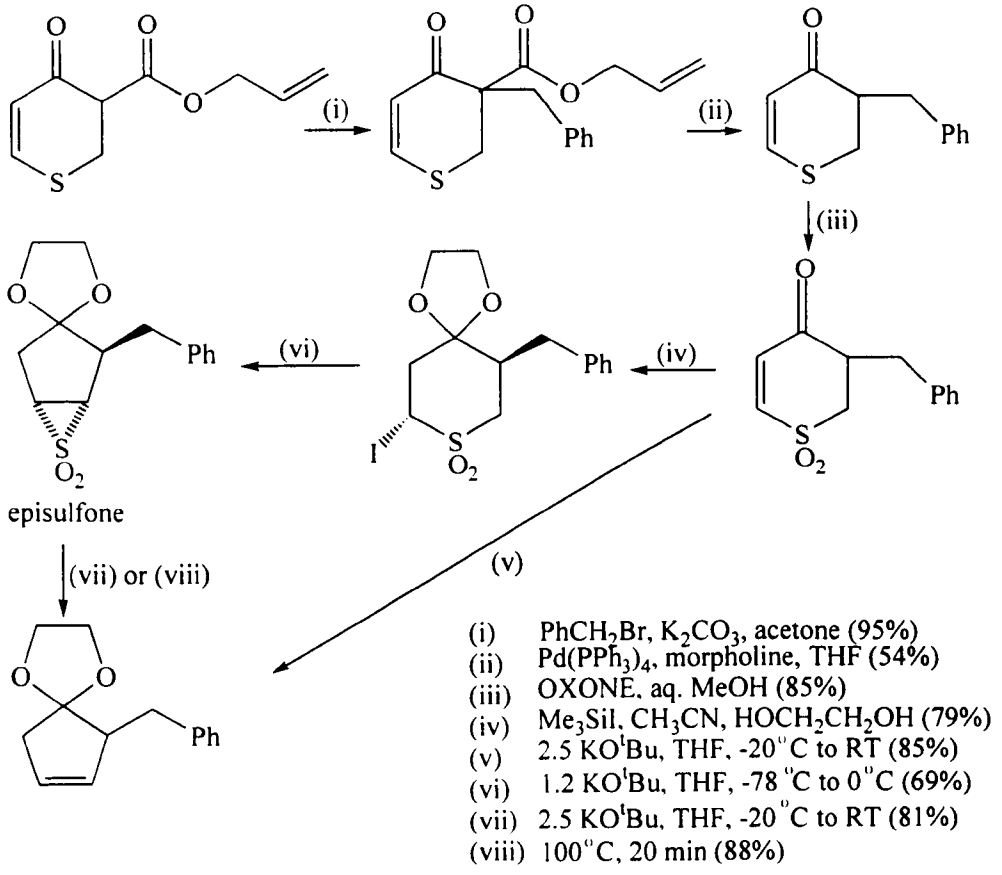
The Ramberg-Bäcklund rearrangement has over the years attracted considerable mechanistic and synthetic interest. The reaction proceeds *via* an episulfone intermediate (Scheme 1.4).[7]

Scheme 1.4



It has been shown that episulfones prepared by other methods[8] give alkenes under the conditions normally implemented for the Ramberg-Bäcklund reaction. The episulfone formed by treatment of an α-halosulfone with base cannot normally be isolated. However, Sutherland and Taylor[9] (Scheme 1.5) reported that this was made possible by the facile Ramberg-Bäcklund reaction of α-iodo-thiane dioxides.[10]

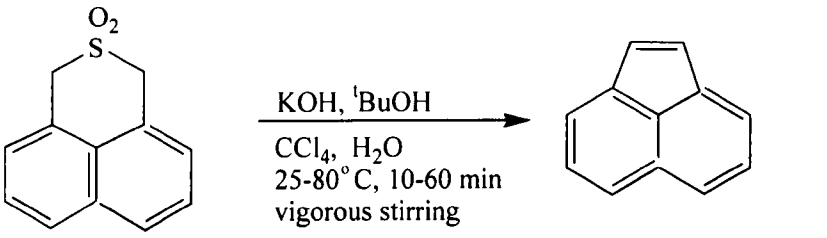
Scheme 1.5



Other developments of the Ramberg-Bäcklund rearrangement include the Michael-induced rearrangement,[11] the use of sulfinyl leaving groups[12] and the introduction of α-halogenoalkanesulfonyl bromides[13] as novel Ramberg-Bäcklund precursors. The usefulness of the Ramberg-Bäcklund rearrangement is demonstrated by application in the synthesis of, for example, natural and novel cyclopentanes[10,11] and strained bicyclic alkenes.[14]

The Meyers' modification of the Ramberg-Bäcklund reaction, in which the α-chlorination and in-situ rearrangement are achieved in one pot by the direct treatment of the sulfone with KOH and CCl_4 in ^tBuOH, has proved popular (Scheme 1.6).[7]

Scheme 1.6

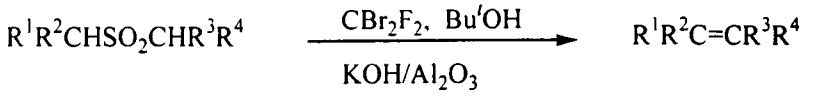


(45%)

There is room for refinement in the scope of this procedure's applicability, as clean reactions are restricted to the production of stilbenes from dibenzylic sulfones and of 1,1-diarylalkenes from benzhydryl sulfones.[7] Diprimary alkyl sulfones are reacted under these conditions, other products are also obtained:- the sulfones undergo α,α- and/or α,α`-dichlorination before the elimination to give chloroalkenes. The difficulties experienced with Meyers' modifications were surmounted by Chan *et al.* who replaced the combination of KOH and CCl_4 by alumina supported KOH and CBr_2F_2 so that α- and α'- hydrogen bearing sulfones with considerable structural variety could be consistently converted into alkenes in good yields (Scheme 1.7).[15] The success of the system was attributed to the

increase in surface area of the catalyst. A high degree of stereoselectivity of the resultant double bonds was observed for benzylic sulfones although mixtures of geometric alkenes were formed from diprimary sulfones. This procedure therefore enabled the preparation of these alkene precursors to be enhanced by a relatively simple experimental procedure. Nevertheless, Alder and co-workers found this novel one-flask procedure to be unsuccessful for the preparation of cyclobutenes.[16]

Scheme 1.7



1.1 The preparation of 1,4-oxathianes and their derivatives

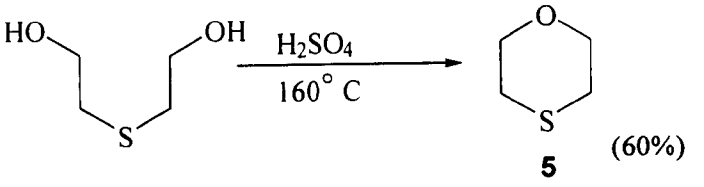
1,4-Oxathiane (**4**) is a colourless pungent oil. In contrast 1,4-oxathiane *S,S*-dioxide (**5**) is a colourless crystalline solid that is stable at room temperature.

Until 1959, when Andrews and Woodward[17] devised an efficient procedure for the synthesis of 1,4-oxathiane, no high yielding methods had been

reported. In 1912, Clarke prepared the oxathiane ring by the reaction between 2,2'-diiododiethyl ether and alcoholic potassium sulfide.[18] Later this cyclic ether was obtained as a by-product when 2,2'-dichlorodiethyl ether was treated with sodium hydrogen sulfide.[19]

A subsequent method provided 1,4-oxathiane and other by-products by distillation of the product from the reaction of thiodiglycol and potassium hydrogen sulfate.[20] Andrews and Woodward improved on this by employing sulfuric acid as the dehydrating agent to give a pure product in 60% yield (Scheme 1.8).[17]

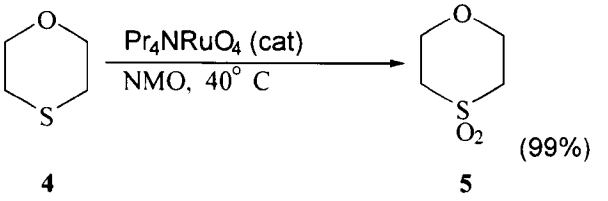
Scheme 1.8



5 (60%)

1,4-Oxathiane *S,S*-dioxide may be synthesized from the sulfide by various chemoselective oxidation methods.[21-24] Of these, the use of catalytic amounts of tetrapropylammonium perruthenate (TPAP) in the presence of N-methylmorpholine-N-oxide (NMO) is notably mild and chemoselective, giving the sulfone **5** in 99% yield (Scheme 1.9).[24]

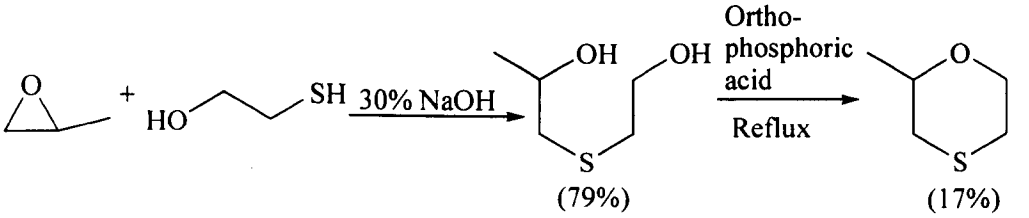
Scheme 1.9



4 **5**

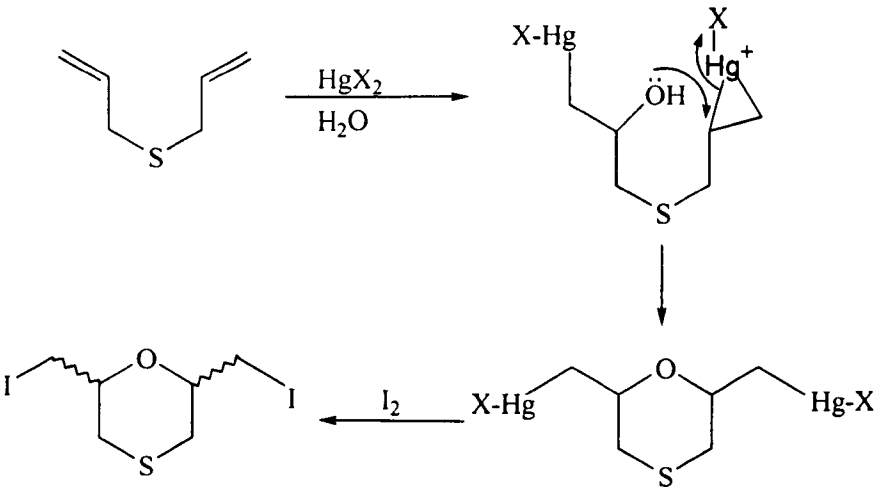
Substituted 1,4-oxathianes have been prepared by the reaction of epoxides with mercaptoethanol under basic conditions to yield ring opened diols, followed by the cyclization of these diols. Thus, cyclization of 1-(2-hydroxyethylthio)propan-2-ol by dehydration with orthophosphoric acid gave the substituted 1,4-oxathiane as a solid, albeit in very poor yield (Scheme 1.10).[25]

Scheme 1.10



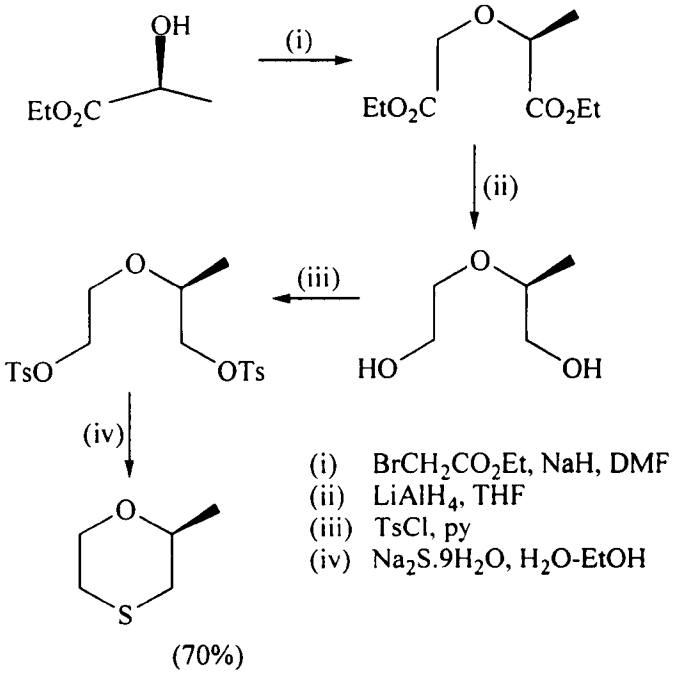
Substituted oxathianes have also been prepared by treatment of diallyl sulfide with aqueous mercuric salt solutions.[26] The reaction proceeds *via* oxymercuration of one of the alkene units, followed by intramolecular nucleophilic attack by the resultant hydroxyl at the mercurinium ion formed from the second alkene unit and Hg(II). Demercuration was effected by treatment with iodine to give the bis-3,5-diiodomethyl-1,4-oxathiane as a mixture of *cis* and *trans* isomers (Scheme 1.11). The diallyl sulfone also undergoes a similar series of reactions but interestingly only a *cis* isomer of the sulfone product is obtained in contrast to the sulfide.

Scheme 1.11



In another route, Kelstrup reported the preparation of 2-methyl-1,4-oxathiane[25,27] from (S) ethyl lactate.[28] However, due to extensive racemization during the first two steps (Scheme 1.12), the product was obtained showing poor optical purity.

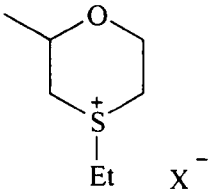
Scheme 1.12



1.2 The Chemistry of Oxathianes and their Derivatives

Some aspects of conformational analysis of 1,4-oxathianes and oxathanium salts (**6**) have been explored.[28-31] On the basis of these studies, the

oxathiane ring is thought to adopt a chair-like conformation, which undergoes conformational inversion which is rapid on the NMR time scale.



X = BF_4 or BPh_4

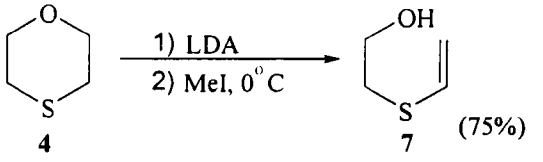
6

Complexes of various metal halides with 1,4-oxathiane were prepared and characterised by Baker and Fowles.[32] The ^1H NMR and IR spectra of these complexes have been interpreted as showing that the oxathiane ring co-ordinates through the sulfur rather than oxygen atom.

Babudri and Florio investigated the behaviour of compound (**4**) on treatment with lithium di-isopropylamide (LDA).[33] 1,4-Oxathiane underwent an unusual "eliminative ring fission" reaction giving 2-vinylthioethanol (**7**) in good yield (Scheme 1.13). This reaction is presumed to proceed *via* an $E1_{cb}$ mechanism with formation of the α-thiocarbanion followed by intramolecular elimination of alkoxide. This is in accord with the strong stabilizing effect of the sulfur on an α-carbanion as compared to oxygen.[34] Formation of the alcohol was a somewhat surprising result as the anion was quenched with iodomethane rather than a proton

source but the alcohol rather than the methyl ether was obtained: this result was not commented on by the authors.

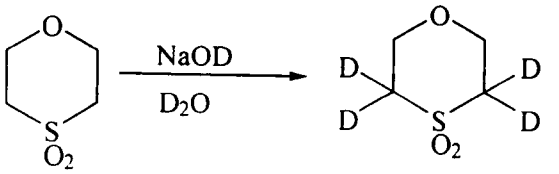
Scheme 1.13



4 **7** (75%)

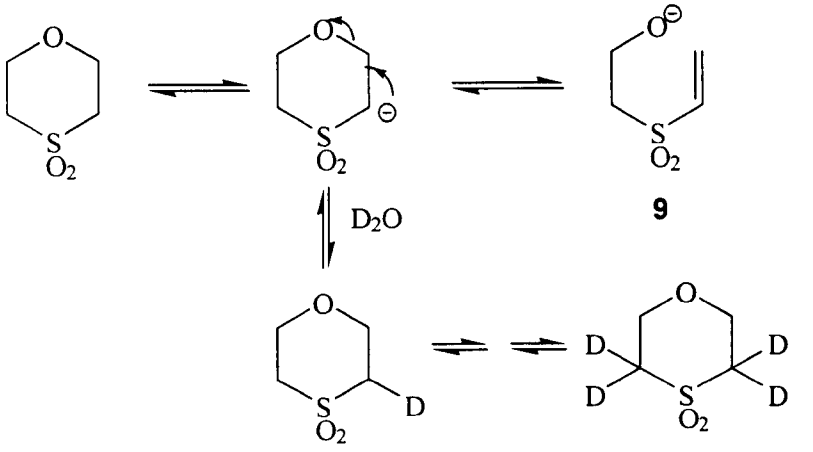
In contrast, treatment of the 1,4-oxathiane *S,S*-dioxide (**5**) with deuterium oxide (D_2O) in the presence of base, yielded the tetra-deutero compound (**8**) (Scheme 1.14).[35] This simple exchange, leaving the ring intact, does not eliminate the possibility that ring opening could occur to generate the anion (**9**) during the course of the reaction; as ring re-closure could then occur to yield eventually the tetradeuterated sulfone (Scheme 1.15).

Scheme 1.14



5 **8**

Scheme 1.15

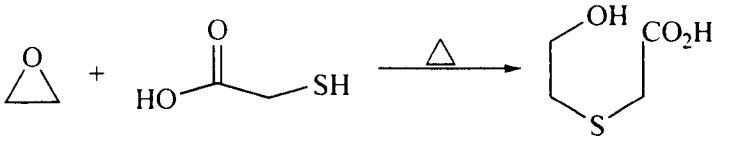


1.3 The Preparation of 1,4-Oxathian-3-ones and their Derivatives

There have been few publications on the synthesis of 1,4-oxathiane-3-ones. The oxathianone ring has usually been synthesized by the ring closure of the corresponding δ-hydroxy-β-thiacarboxylic acids. These precursor hydroxy acids have in turn been prepared by a variety of means.[25,36,39]

Black prepared the parent hydroxy acid by reaction of ethylene oxide with thioglycolic acid to give a poor yield of the hydroxy acid (Scheme 1.16).[25]

Scheme 1.16

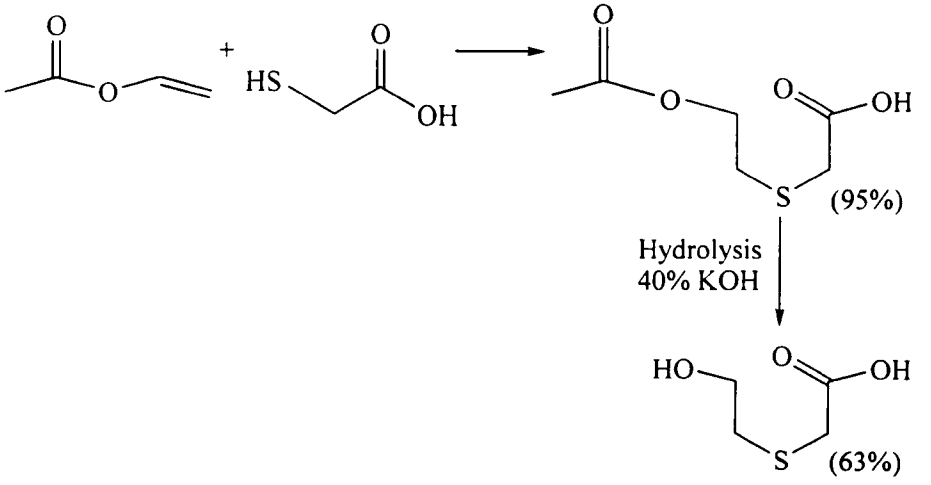


(12.5%)

Substituted δ-hydroxy acids have also been prepared by this procedure.[25,36-37] For example, Black investigated the reaction of propylene oxide and thioglycolic acid in the presence of Amberlite IRA-400.[25] This gave the corresponding hydroxy acid in a slightly higher yield (36%) than in the parent system. A reaction carried out by Kaufman and Schickel[38] under similar conditions with styrene oxide and ethyl thioglycolate also yielded the corresponding hydroxy acid with reaction taking place at the benzylic position.

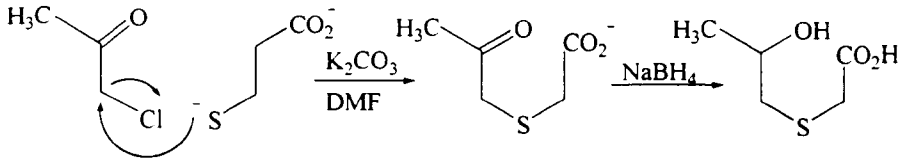
A subsequent and superior procedure entails the free radical addition of thiols to olefinic systems.[36] Hydrolysis of the product from the reaction of thioglycolic acid with vinyl acetate yielded the desired hydroxy acid in excellent yield (Scheme 1.17). This free radical addition procedure is also a useful method for the synthesis of substituted systems, which are prepared by free radical addition to substituted vinyl acetates. Thus reaction of a 1:1 mixture of *cis* and *trans* prop-1-enyl acetate with thioglycollic acid gave the corresponding acetoxy-acid which could be hydrolyzed to give the hydroxy acid with an ethyl substituent.

Scheme 1.17



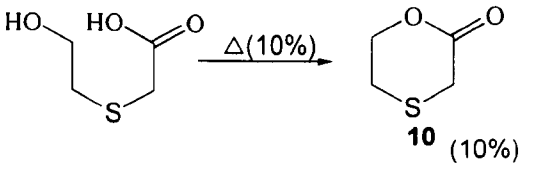
Koskimies[39] investigated another approach for the preparation of these δ-hydroxy acids whereby an α-halo ketone, which is readily prepared by direct halogenation, is used as the starting material. Nucleophilic displacement of the halogen by thioglycolate dianion affords the δ-keto acid which is then reduced with sodium borohydride to give the desired δ-hydroxy acid. This approach has the advantage of the increased S_N2 reactivity of α-halo ketones and can also be carried out in one pot (Scheme 1.18).

Scheme 1.18



Two general approaches to the ring closure of these δ-hydroxy acids to the lactones have been reported:- a) thermal dehydration through distillation and b) acid catalyzed cyclization.[25,26,39] Thus, distillation of the parent compound yielded 1,4-oxathian-3-one, albeit in a very poor yield (Scheme 1.19).[25] Distillation of the substituted δ-hydroxy acids previously mentioned also yielded the corresponding substituted lactones.[25,38]

Scheme 1.19



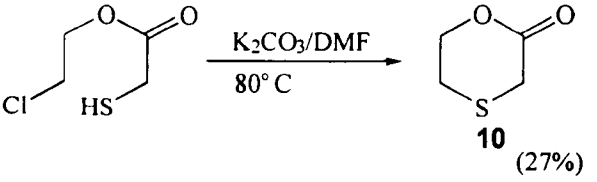
In contrast, treatment of the parent δ-hydroxy acid with *p*-toluenesulfonic acid also gave the lactone **10** in a very respectable yield of 79%.[36] Similarly, ring closure of the appropriately substituted hydroxy acid in this fashion gave the

5-methyl-1,4-oxathian-3-one in high yield. The ring closure of the δ-hydroxy acids prepared from the α-halo ketones[39] also succeeded under acid catalytic conditions.[25,36,37]

Koskimies[39] and other researchers[36,40] noted that the lactonization of δ-hydroxy acids tended to be complicated due to the proclivity of the intermediate hydroxy acid and of the lactone to undergo polymerization. They observed a relatively fast intermolecular esterification leading to polymeric products and therefore lower yields of monomeric lactones.

An alternative ring closure method, the base-catalyzed ring closure of β-haloethyl thioglycolates, has also been investigated. Thus, 2-chloroethyl thioglycolate was converted into the lactone in the presence of anhydrous base in DMF at 80°C. Although the purity of the lactone so obtained was very high, the yield was nevertheless low (Scheme 1.20).[39]

Scheme 1.20

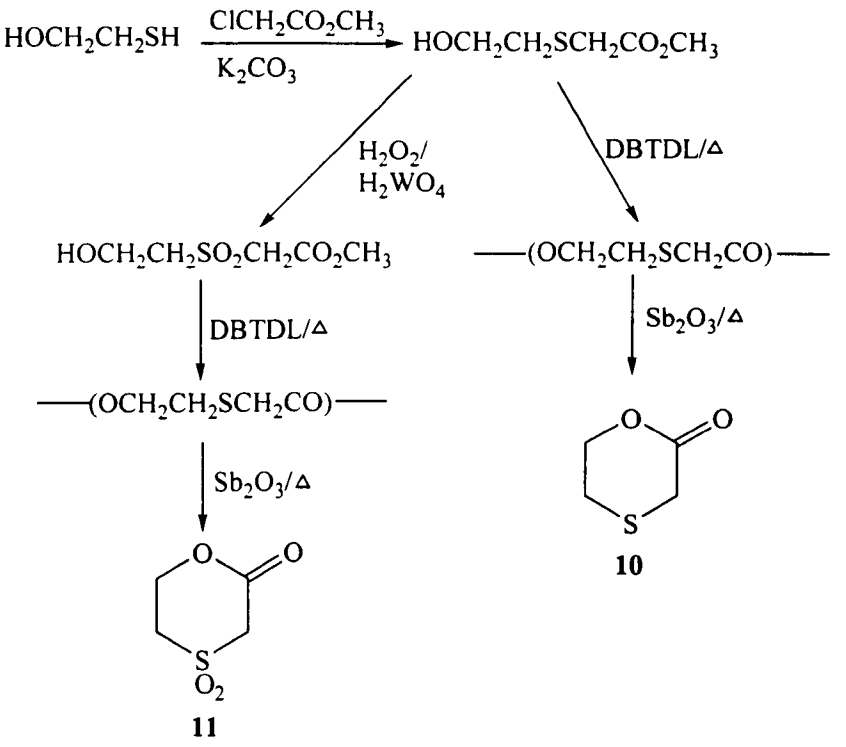


10 (27%)

An improved synthesis of the parent systems has been developed (Scheme 1.21).[41] 1,4-Oxathian-3-one **10** was synthesized in high yields by the oligomerization of methyl 2-(2'-hydroxyethylthio)acetate, prepared by the reaction of mercaptoethanol with methyl chloroacetate, followed by a catalytic depolymerization *in vacuo* in the presence of antimony trioxide. An analogous depolymerization using the sulfonyl analogue afforded the corresponding sulfone (**11**), in a procedure which required an extremely high vacuum for the conversion to the sulfone. This depolymerization method appears to be only really applicable to the parent system due to the crucial role of the sublimation process and the fact that substituted systems would not sublime so readily.

Interestingly, although there are several recorded preparations of the parent 1,4-oxathiane-3-one, there appear to be no reports on the direct conversion of this system into the sulfone (**11**).

Scheme 1.21



DBTDL = $(CH_3CH_2CH_2CH_2)_2Sn[OCO(CH_2)_{10}CH_3]_2$

1,4-Oxathian-3-ones with 10 and 11 membered bridges from sulfur have been prepared by Vedejs and co-workers by the [2,3]-sigmatropic expansion method from acyclic precursors.[42] They showed that ring expansion may be achieved *via* monocyclic and bicyclic ylides originating from intramolecular S-alkylation.

Polyesters formed from the ring opening polymerization of **10** possess a close structural similarity to commercially important bioabsorbable polyesters such as the poly(glycolides).[43]

Interestingly, oxathianones and their derivatives are of interest for their possible physiological activity.[44] A 3-Acetyl oxathianone derivative is a hydrolysis product of an oxathiene fungicide.[45] Oxime derivatives have also been patented for pesticidal use.[46-48]

1.4 The Chemistry of 1,4-Oxathian-3-ones and their Derivatives

Brief aspects of conformational properties of substituted 1,4-oxathian-3-ones have been discussed by Carroll and co-workers[49] and on the basis of these studies it is tentatively suggested that salts of these substituted oxathianones exist as rapidly equilibrating half-chair and boat conformers.

As previously mentioned, oxathianones are easily hydrolysed.[36,39-40] It has been suggested that this is because of the strain in the ring arising from the mutually incompatible geometric requirements of the planar ester functionality and the puckered C-S-C-C portion of the ring.[39]

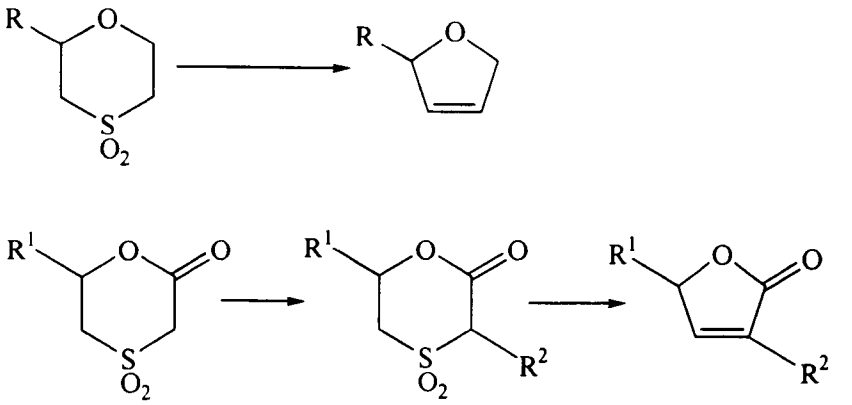
The solution conformation of the 1,4-oxathian-3-ones is not known but an *X*-ray molecular structure of 6-*p*-bromophenyl-1,4-oxathian-2-one indicates the classical boat conformation for this compound in the solid state with a planar ester group.[50] The solution conformation of 6-methyl-1,4-oxathian-3-one has been investigated by Kelstrup,[29] who concluded that, on the basis of proton vicinal coupling constants, the compound has either a boat or half-chair conformation (or is a rapidly equilibrating mixture of the two). Koskimies carried out ^{1}H NMR

studies of alkyl and aryl-substituted 1,4-oxathian-2-ones.[51] It was observed that the coupling constants imply that the C-S-C-C portion of the ring has a normal cyclohexane-like conformation which is compatible with either a classical-boat or a half-chair. Chemical shift, geminal coupling constant and long-range coupling constant evidence suggests that the former conformation is prevalent for oxathianones.

1.5 Aims of the current Research Project

The fundamental objective of these studies was to synthesize oxathiane and oxathianone *S,S*-dioxides and their substituted systems and to investigate conditions under which the Ramberg-Bäcklund rearrangement could be used to produce dihydrofurans and dihydrofuranones respectively (Scheme 1.22).

Scheme 1.22

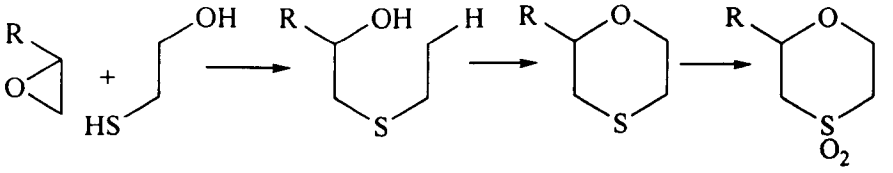


1.5.1 Oxathianes

Initial investigations would involve the alkylation studies of the commercially available cyclic ether, 1,4-oxathiane *S,S*-dioxide. The oxathiane *S,S*-dioxide would be subjected to direct alkylation under a variety of conditions with the ultimate aim of preparing the requisite 3-alkylated sulfone. The resulting substituted 1,4-oxathiane *S,S*-dioxides would then be rearranged to give the desired alkenes under Ramberg-Bäcklund conditions.

Parallel studies would entail an alternative synthesis of 2-alkylated oxathiane dioxides. This approach would involve the reaction of epoxides with thiols to give ring-opened hydroxy sulfides, which would then be cyclized to the oxathiane then oxidized to the sulfone (or *vice versa*) as indicated in Scheme 1.23.

Scheme 1.23



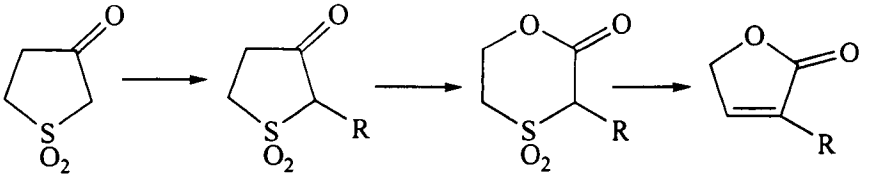
1.5.2 Oxathianones

1,4-Oxathian-3-ones and the corresponding sulfones would be prepared by several of the literature approaches detailed above to compare their efficiency.

Subsequently, examination of oxidative cyclization of thiodiethanol to the lactone was also planned.[22,24, 52-65,84] The lactone would then be subjected to alkylation and the ensuing substituted lactones would then be submitted to the Ramberg-Bäcklund reaction conditions in order to yield the desired alkenes (Scheme 1.22).

Another study would entail the preparation of 3-oxotetrahydrothiophene 1,1-dioxides and the alkylation of this compound.[88-99] The consequent alkylated tetrahydrothiophene would then be submitted to the Baeyer-Villiger[6] reaction to undergo ring expansion to the requisite lactone which would ultimately be submitted to the Ramberg-Bäcklund reaction conditions (Scheme 1.24).

Scheme 1.24



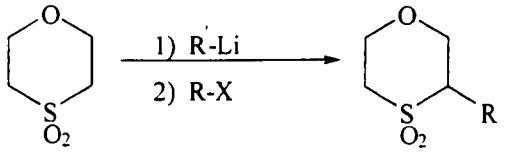
2 Results and discussion

2 Reactions of Oxathiane *S,S*-Dioxides

2.1 Introduction

The initial aim of our investigation entailed the use of the cyclic sulfone, 1,4-oxathiane *S,S*-dioxide (**5**), in alkylation studies. It was planned to lithiate the sulfone and then to treat the lithiated sulfone with an alkylating agent (Scheme 2.1).

Scheme 2.1

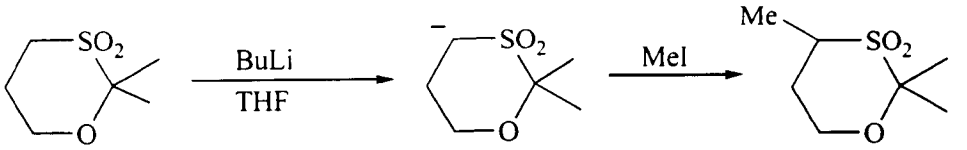


5

α-Sulfonyl anions have been studied in great detail and are valuable for C-C bond formation.[66,67] In a case closely related to the present work, the chemical reactivity of 2,2-dimethyl-1,3-oxathiane 3,3-dioxide[68] toward base was studied by Fuji and co-workers (Scheme 2.2).[69] The anion was generated at C-4 by reaction with butyllithium. Nucleophilic substitution of this anion with alkyl halides gave the 4-substituted 2,2-dimethyl-1,3-oxathiane 3,3-dioxides in good

yields. It was also reported that the reaction of this anion with a variety of other electrophiles proceeded readily with respectable yields.[69]

Scheme 2.2



(83%)

2.2 Attempted Alkylation of 1,4-Oxathiane *S,S*-dioxide

Our initial investigations of this alklylation did not meet with success. For example, sequential treatment of 1,4-oxathiane *S,S*-dioxide with BuLi then benzyl bromide at -78 °C, or higher temperatures, yielded no alkylated material, only recovered starting material.

We therefore decided to probe the ability of (**5**) to undergo deprotonation with alkyllithium reagents, and to establish the stability of the putative lithiated intermediate. Thus, we conducted deprotonation studies at different temperatures.

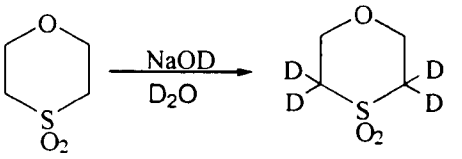
1,4-Oxathiane *S,S*-dioxide was treated with 1.1 molar equivalents of titrated[70] ^{n}-butyllithium at -78 °C in a nitrogen atmosphere. When the reaction

mixture was allowed to rise to room temperature, then quenched with aqueous saturated ammonium chloride, ^{1}H NMR and tlc analyses showed decomposition of (**5**). When quenching was performed at -30 °C, again decomposition occurred. However, when quenching was carried out at -78 °C, decomposition did not occur. ^{1}H NMR analysis of the reaction mixture showed starting material only was recovered.

At this stage, no evidence was at hand that deprotonation at -78 °C was actually occurring. It appeared that deprotonation was occurring at higher temperatures but with concomitant decomposition.

In order to establish if deprotonation was occurring at -78 °C , we resolved to use deuterium exchange experiments. As it would be difficult to investigate mono-deuteration of (**5**) due to the presence of the three remaining α-sulfonyl protons, we chose to look at the reaction of the known tetra-deutero analogue (**8**)[35] with butyllithium, followed by addition of a proton source. Compound (**8**) was prepared by first adding sodium hydride to neat deuterium oxide (D_2O). This solution was then treated with solid oxathiane **2**, and the resulting mixture was stirred for 48 hours under nitrogen.[35] The crystalline tetra-deutero oxathiane *S,S*-dioxide (**8**) was produced in good yield (75%) (Scheme 2.3).

Scheme 2.3



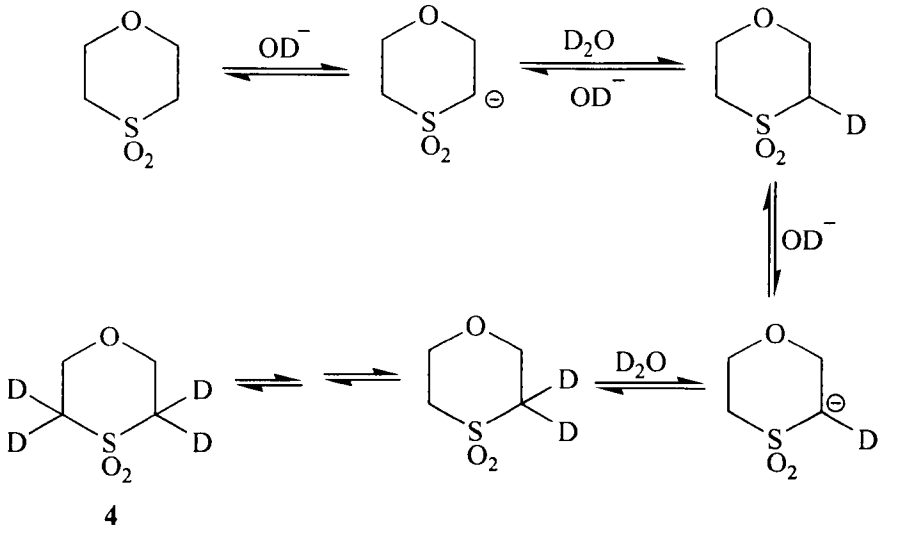
5 **8**

The extent of deuteration of (**8**) was examined by ^{1}H and ^{13}C NMR spectroscopy. A singlet at δ_H 4.10 ppm corresponded to the four protons adjacent to the oxygen atom. Signals due to H-3 and H-6 adjacent to the sulfur were much reduced. In the parent compound these appear at δ_H 4.16 ppm. The ratio of tetradeuterated product to trideuterated starting material was determined to be 90.7 : 9.3 by integration. The small amount of trideuterated material present gave a signal at δ_H 1.25 due to H-2, which displayed a H-D coupling through being adjacent to the H-3 protons. The ^{13}C NMR spectrum showed peaks at δ_C 66.0 ppm (CH_2-O-CH_2) and at 51.9 ppm (CD_2-S-CD_2).

The complete exchange of deuterium for protium indicates that under mildly basic conditions (NaOD, D_2O) at room temperature, deprotonation must be taking place. The pK_a for D_2O is *ca* 15.7, and for (**5**) is 28-30, so that at equilibrium approximately 10^{-13} equivalents of sulfone are deprotonated. This then equilibriates with D_2O to produce the deuterated sulfone (Scheme 2.4).

The deuterium exchange experiment clearly indicates that the anion does have some stability although only for the short lifetime prior to being intercepted by D_2O.

Scheme 2.4



4

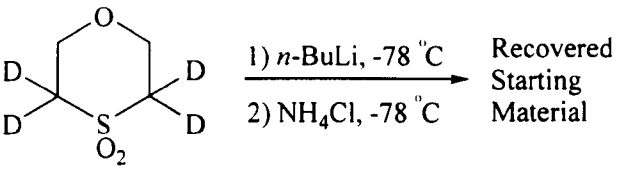
The next step in these studies involved an attempted de-deuteration of (**8**) by use of the titrated[70] base ^{n}-butyllithium at -78 °C and quenching with aqueous saturated ammonium chloride solution.

Prior to this, we performed a control experiment to determine whether ammonium chloride was able to exchange protium for deuterium in (**8**), since if this occurred it would complicate the interpretation of the BuLi experiment. Aqueous saturated ammonium chloride was added to 3,3,5,5-tetradeutero-1,4-oxathiane *S,S*-dioxide (**8**) and the reaction mixture was left to stir under a nitrogen atmosphere. However, ^{1}H NMR spectroscopy showed that <1% D-H exchange had occurred.

However, when (**8**) was treated with butyllithium at -78 °C, followed by quenching with aqueous ammonium chloride, ^{1}H NMR studies indicated that only

recovered, fully deuterated starting material was obtained. Therefore no de-deuteration had occurred with the tetradeutero compound. Thus, it is concluded that deprotonation with ^{n}-butyllithium at -78°C does not take place (Scheme 2.5). At higher temperatures, as previously noted, it appears that deprotonation does take place but leads to the decomposition of (**5**) in non-equilibrating conditions.

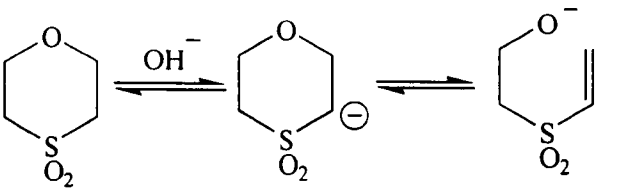
Scheme 2.5



4

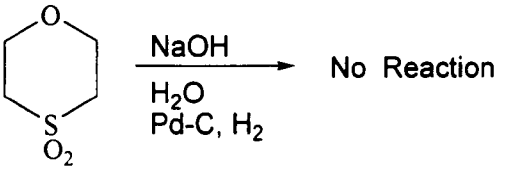
One issue that remained was to investigate if ring opening by a retro-Michael type process occurred during the equilibrium deprotonation of (**5**) by hydroxide (Scheme 2.6). We therefore decided to attempt to intercept the putative ring-opened intermediate by another reaction.

Scheme 2.6



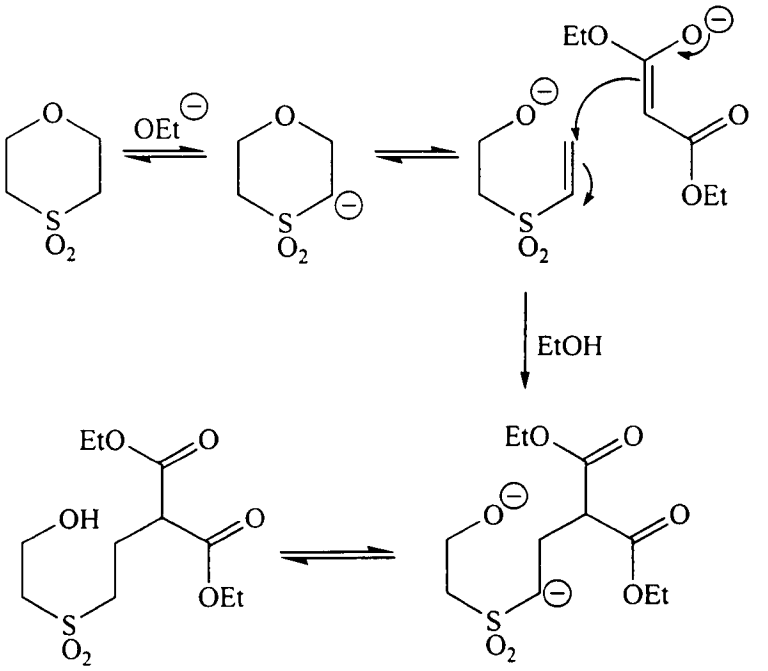
First we treated compound (**5**) with hydroxide ion in the presence of hydrogen and palladium catalyst.[71] However, only recovered starting material was obtained (Scheme 2.7). If indeed ring opening is taking place, then the vinylic sulfone which is produced is too unreactive to hydrogenation due to the electron-withdrawing nature of the sulfone group. Thus hydrogenation may not be possible under the current conditions. In retrospect, it follows that use of a nucleophilic hydrogen source, such as hydride from $NaBH_4$ may have been more effective.

Scheme 2.7



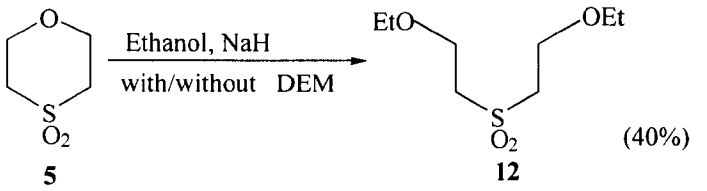
However, a further experiment did indicate that ring opening under mildly basic conditions was taking place. The intention was to trap the putative ring-opened vinylic sulfone with a carbon nucleophile, the anion derived from diethyl malonate (DEM), in the presence of ethanol and a base (Scheme 2.8).

Scheme 2.8



Although no reaction under these conditions took place, at room temperature, a product was obtained at reflux. This transpired not to be a malonate adduct but was the di(2-ethoxyethyl)sulfone (**12**), readily identified on the basis of spectroscopic and analytical data. The ^{1}H NMR spectrum contained triplets at δ3.86 [(2H, ^{4}J=5.7)] due to the CH_2 group adjacent to the oxygen and at δ3.39 integrating for 2H, with a ^{4}J coupling of 5.7 Hz, in addition to signals due to the ethoxy groups. It was not possible to recover DEM. Repetition of the experiment in the absence of DEM also gave the same product in the same yield.

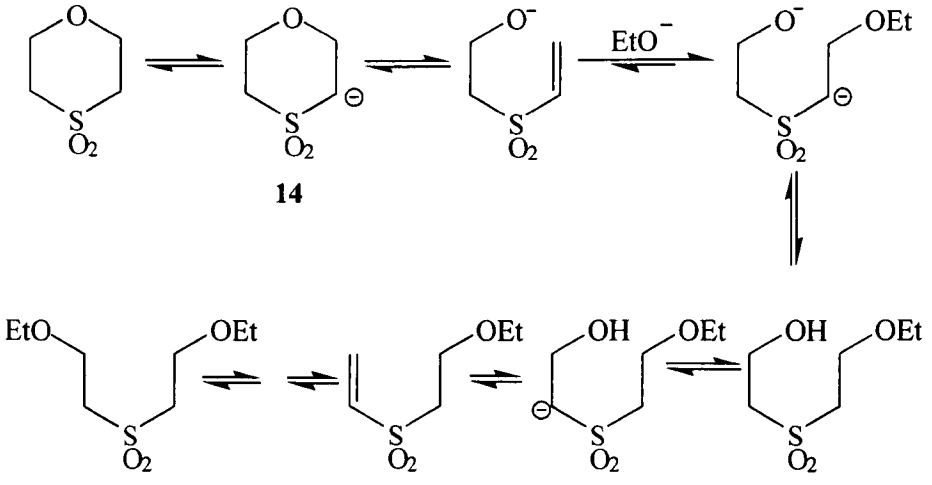
Scheme 2.9



5 **12**

Formation of the product is most easily explained by assuming that deprotonation is followed by ring opening to give the vinylic sulfone (Scheme 2.10). Nucleophilic addition of ethanol then gives the β-ethoxysulfone (**13**). Elimination of hydroxide under equilibrating conditions from the β-hydroxy moiety then provides the second vinylic sulfone which subsequently adds ethanol.

Scheme 2.10



14 **8** **8.1**

On the basis of these unexpected results, it was decided to investigate a series of reactions to determine the scope of this reaction, employing a variety of alcohols as solvents.

Initially, the slightly less sterically bulky alcohol, methanol was used. The product, di(2-methoxyethyl)sulfone (**14**) (see page 40), was readily identifiable on the basis of spectroscopic and analytical data. The ^{1}H NMR spectrum contained a singlet at δ3.38 (6H) attributable to the methyl groups adjacent to the oxygen. The yield was significantly higher, 89% as compared to 40% of the ethoxy product (Scheme 2.10).

The use of other primary alcohols also proved successful. Thus, ring-opening of compound (**5**) using 1-butanol gave a reaction which proceeded smoothly to yield di(2-butyloxyethyl)sulfone (**15**), in good yield. Similarly, when pentan-1-ol, was used as the solvent , di(2-pentyloxyethyl)sulfone (**16**), was obtained in a slightly lower yield, 61%, and was readily identifiable from analytical and spectroscopic data (Scheme 2.11).

We then turned our attention to the addition of a more hindered alkoxy group derived from the use of propan-2-ol as the solvent. The product, di[2-(1'-methylethoxy)sulfone (**17**), was prepared in a higher yield (57%) than the ethoxy product (**12**), but less than the methoxy product (Scheme 2.9). Again, full spectroscopic and analytical data were obtained with the septet at δ3.65 ppm in the ^{1}H NMR spectrum, attributable to the C-H adjacent to the two methyl groups being particularly diagnostic.

However, attempts to obtain a similar product by using a tertiary alcohol were not successful. ^{t}-Butanol was the solvent used in this case, but only decomposition of the reaction mixture occurred, even when the reaction was repeated using THF as a co-solvent. (Due to the high boiling points of certain solvents used in these procedures, it was necessary to carry out the reaction with a co-solvent; this was to eliminate the possibility of thermal decomposition relative to the other alcohols (ethanol, methanol) possessing lower boiling points).

Another attempt at using a bulky alcohol was by reaction of compound (**5**) with neopentyl alcohol with THF as co-solvent. Unfortunately, this group also was to prove too bulky for the nucleophilic addition of compound (**5**) and the reaction mixture decomposed as confirmed by tlc analysis, ^{1}H and ^{13}C NMR spectroscopy (Scheme 2.11).

Finally, it was decided to examine the effect of using alcohols such as ethylene glycol and 2-methoxy ethanol; these would give acyclic crown ether type compounds.

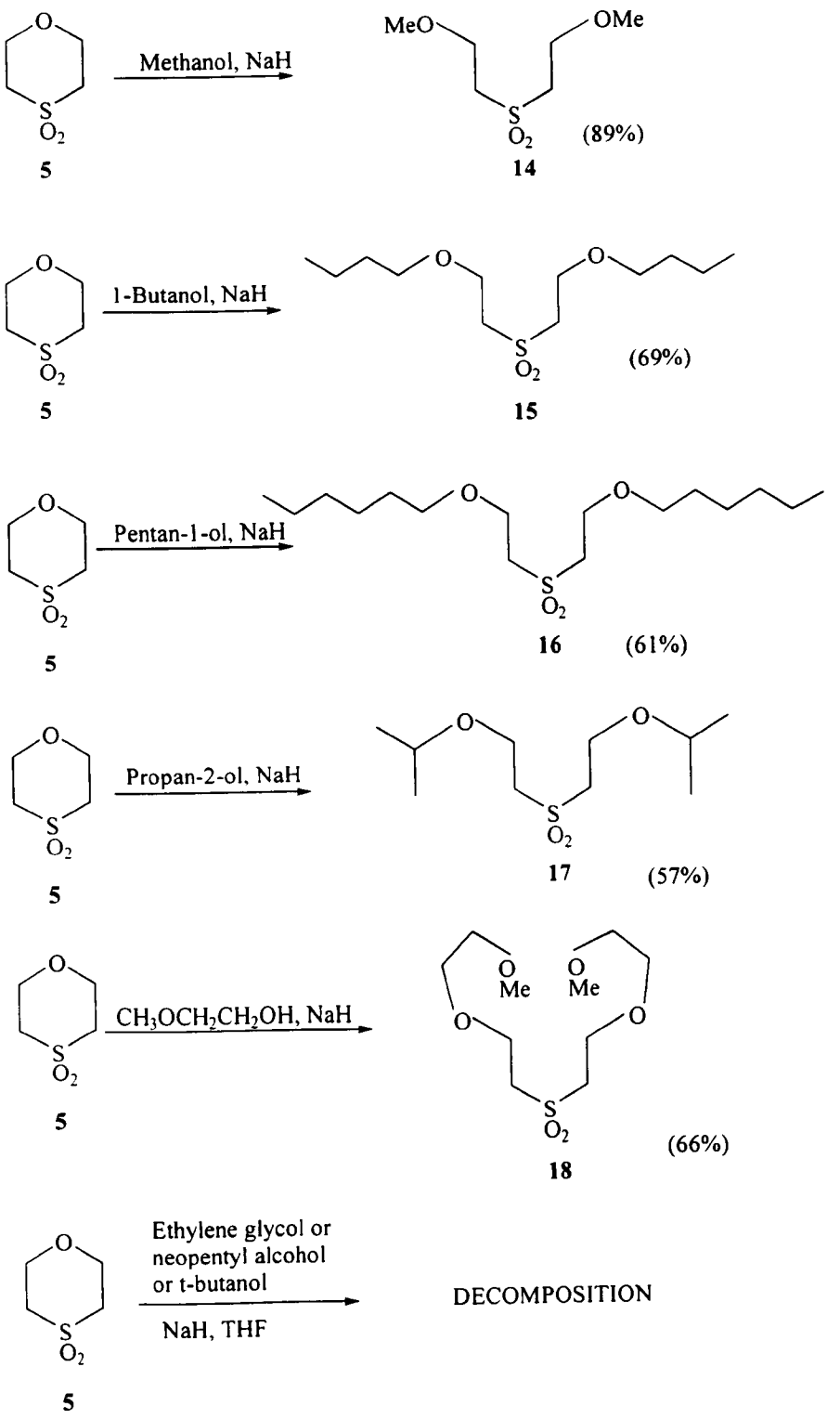
So, another novel analogue was successfully prepared by treatment of compound (**5**) with 2-methoxy ethanol. The product, di[2-(2'-methoxyethoxy)ethyl]sulfone (**18**), was prepared in 66% yield and was readily identifiable by spectroscopic and analytical data (Scheme 2.11).

However, when ring-opening of (**5**) was attempted by treatment with the combination of NaH and 1,2-ethanediol, the reaction mixture decomposed. Repetition of the reaction with the use of co-solvent (THF) only yielded an

intractable mixture of products unidentifiable by M.S., I.R., ^{1}H and ^{13}C NMR spectroscopy. Presumably a polymerization process occurs.

It is important to note that no appreciable reaction took place at room temperature. From the initial ethanol reaction, this implies either that the anion (**19**) (scheme 2.10), did not undergo ring-opening at room temperature, or that nucleophilic addition of ethoxide to the vinylic sulfone did not take place.

Scheme 2.11

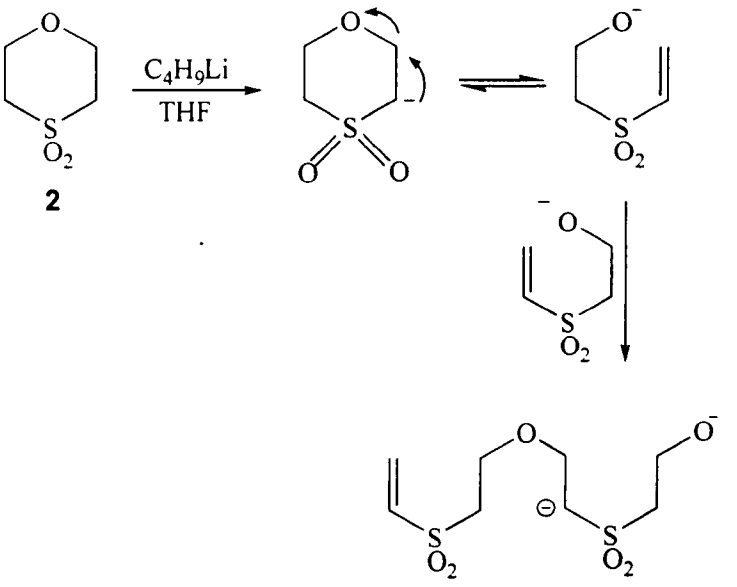


5 **14** **15** **16** **17** **18**

In conclusion, the results of the deuteration experiments and the formation of the diethoxy compound (**12**) and subsequent ring-opened products, are indicative of anion formation from the sulfone (**5**). Under protic conditions, at room temperature or higher, the anion is formed and reacts as expected. It would be expected that, on the basis of pK_a values for dialkyl sulfones (28-30) with respect to conjugate acid (butane) from butyllithium (pKa ~ 60), deprotonation would be highly exothermic, but clearly at low temperatures we have shown that there is a kinetic barrier to deprotonation. At -30 °C to room temperature, apparent decomposition tends to suggest that the lithiated sulfone is formed, but is unstable in the absence of a proton source.

Ring opening under aprotic conditions will give the alkoxy vinylic sulfone, which can polymerize *via* intermolecular addition of alkoxide to a second molecule of the vinylic sulfone (Scheme 2.12).

Scheme 2.12



Overall, the results suggest that any alkylation of the anion of the sulfone (**5**) must be carried out under conditions wherein the anion is generated in the presence of the alkylating agent, that is, base and electrophile must be present in the reaction mixture. As developing this process would be time consuming - avoiding the direct reaction of the base with the alkylating agent would be problematical and would not necessarily be successful - we resolved to explore some of the other synthetic routes available to us.

3 Ring Synthesis of Oxathiane *S,S*-dioxides

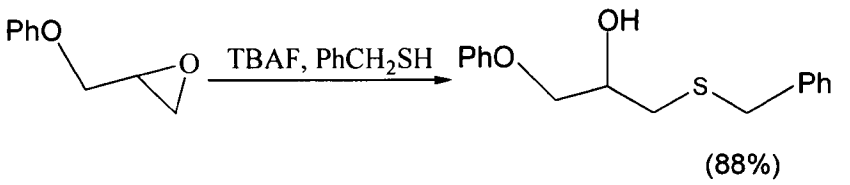
3.1 Introduction

An alternative strategy to the alkylation of the intact 1,4-oxathiane *S,S*-dioxide (**5**), is to construct alkylated cyclic oxathiane *S,S*-dioxides from acyclic precursors. As indicated in the introduction (Scheme 1.2), the approach that we chose to follow was to treat epoxides with hydroxythiols followed by ring closure of the resulting diol.

Epoxides are in general readily reactive towards nucleophiles and have therefore become important starting materials and intermediates in organic synthesis. Due to the fact that epoxides have two sites of reactivity, an immense amount of research has been directed towards an understanding of the factors which influence the regioselectivity of epoxide ring-opening.[72-75]

A recent report[73] indicated that epoxides undergo regioselective ring-opening by thiols in the presence of a catalyst, tetrabutylammonium fluoride (TBAF), under mild conditions. The ring-opening reaction produces the corresponding β-hydroxy thioethers in good yield with high regioselectivity favouring the less-substituted side of the epoxides (Scheme 3.1).

Scheme 3.1



3.2 Selection and Synthesis of Epoxides

Initially we selected the epoxide, 1-benzyloxy-2,3-epoxypropane (**24**) as an appropriate substrate for the ring-opening reactions (Scheme 3.2). Compound (**21**) would be prepared from 2,2'-dimethyl-1,3-dioxolane-4-methanol (**20**) which is commercially available in racemic form as "solketol", although one enantiomer can be obtained by selective cleavage of the diacetonide of D-mannitol.[72] However, since solketol is readily available and inexpensive, it was used as the starting material in the synthesis of the epoxide.

The first step in the preparation of epoxide (**24**), was the benzylation of solketol through adaptation of a literature procedure.[76] Solketol was treated with sodium hydride in THF, and the resulting alkoxide was treated with benzyl bromide. The product (**21**) showed ^{1}H NMR and IR spectroscopic properties

consistent with those reported in the literature. This procedure represents a modification of that reported in the literature (which used sodium hydroxide as base in benzyl chloride),[76] and gave a higher yield of product (Scheme 3.2).

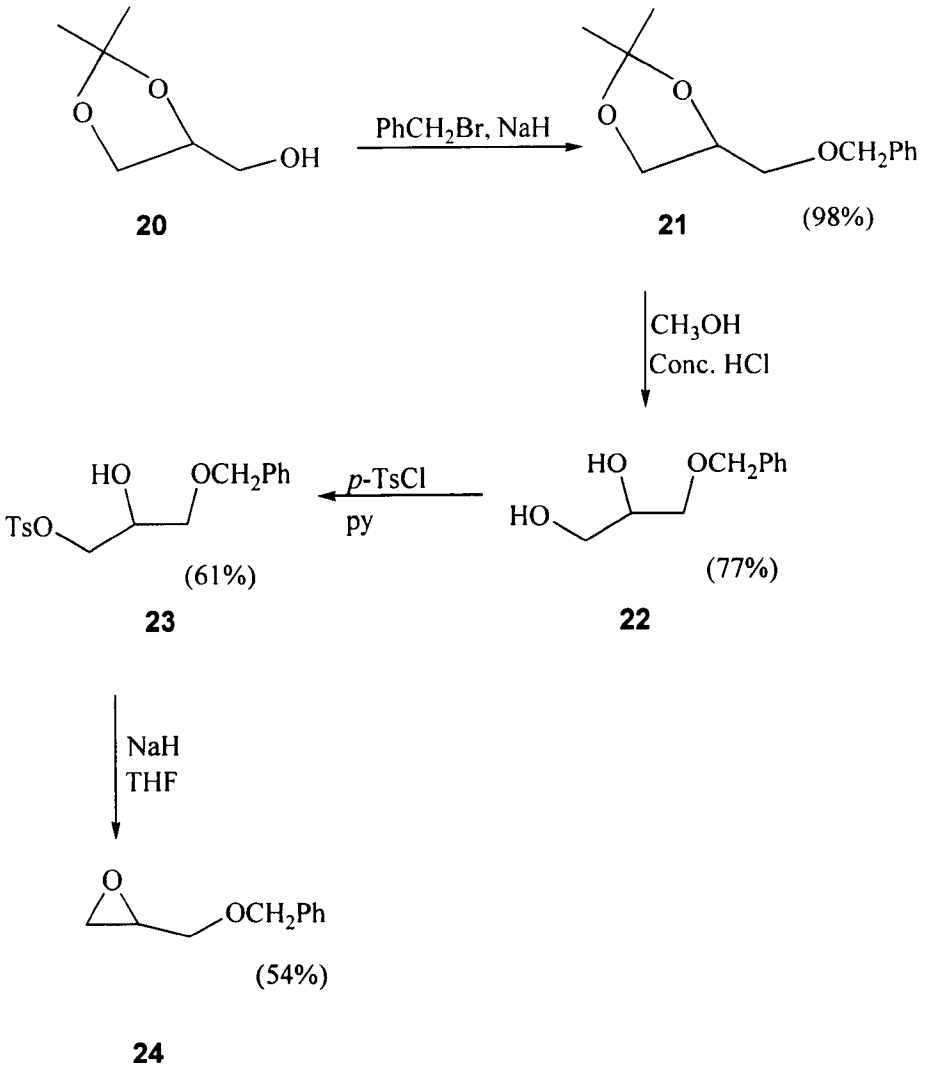
The next step involved the removal of the acetonide to expose the diol. The acetonide was treated with hydrochloric acid in methanol to give the crude diol (**22**) in 77% yield. Again this was an improvement on the literature procedure[76] which involves the acid hydrolysis of (**21**) (Scheme 3.2).

Tosylation of this diol[72] involved treatment with *p*-toluenesulfonyl chloride in pyridine to give the tosylated benzyloxypropanol (**23**) in 61% yield (Scheme 3.2).

The next step involved the formation of the epoxide. The tosylate (**23**) was treated with sodium hydride to generate the alkoxide. Intramolecular S_N2 displacement of tosylate gave the epoxide (**24**), in 54% yield (Scheme 3.2).

Our overall synthesis of (**24**), with the modification to the literature procedures indicated above, gave a significantly higher overall yield than reported previously.[72,76]

Scheme 3.2



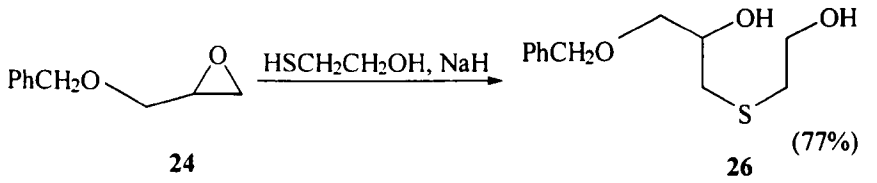
The next part of our studies were to investigate the ring-opening of the epoxide. It was decided also to make use of the commercially available, inexpensive, 1,2-epoxy-3-phenoxypropane (**25**), for preparation of the oxathianes.

3.3 Preparation of Sulfide Diols

The base-mediated ring opening of epoxides by sulfur nucleophiles is an important synthetic area in organic chemistry,[72,74-75] especially in pharmaceutical chemistry.[73]

Our nucleophile of choice, mercaptoethanol, was treated sequentially with sodium hydride in THF and then the epoxide (**24**) to give the ring-opened hydroxy sulfide (**26**) in good yield (77%) (Scheme 3.3), although the reaction was rather slow. The nucleophilic ring opening of epoxides occurs by an S_N2 mechanism and is subject to steric effects in that reaction tends to occur at the less hindered carbon. In the present case, the sulfide diol (**26**) was the only regioisomer formed.

Scheme 3.3

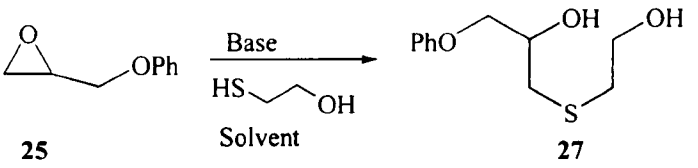


24 **26**

Turning to the commercially available 1,2-epoxy-3-phenoxypropane (**25**), we decided to examine the effect of changing base and solvent (Table 2). First, we investigated the use of potassium carbonate in acetone or THF giving yields of 44 and 47% respectively. However, modification of a literature procedure by use

of sodium hydroxide in ethanol gave the product (**27**) in a substantially higher yield of 97%.[25]

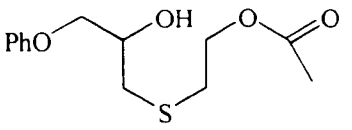
Table 2



25 **27**

Method	Base	Solvent	Yield (%)	Time/days	Temp/°C
A	K_2CO_3	Acetone	47	18	Reflux
B	K_2CO_3	THF	44 (56 RSM) (mixture ratio)	15	Reflux
C	NaOH	Ethanol	97	14	RT

It was noted that when ethyl acetate was used during purification of the product by column chromatography, esterification occurred to give the ester (**28**) as a by-product.



28

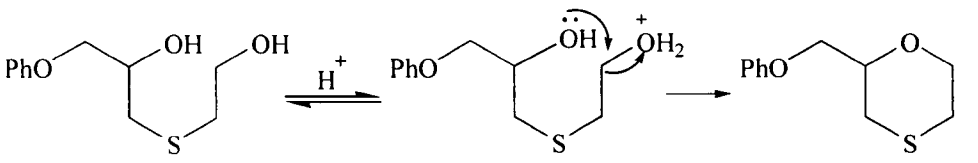
3.4 Approaches to Substituted Oxathiane *S,S*-Dioxides

The methods described in Section 3.3 gave us appropriate quantities of the quantities of the sulfide diols (**26**) and (**27**) to proceed with our investigation of their conversion to the corresponding substituted oxathiane *S,S*-dioxides (in fact we chose to concentrate on **27**). Two possible reaction sequences were available; either cyclization of the sulfide followed by oxidation of the sulfur, or conversely, oxidation followed by cyclization. We looked at both methods in turn.

3.4.1 Attempted cyclization of sulfide diols to oxathianes

The initial objective of these studies was to attempt a direct cyclisation of the hydroxy sulfide. This would involve ring closure by loss of water, to yield the ring closed alkylated sulfide (cyclodehydration).

Scheme 3.4



22

The best precedent for this approach was reported by Black[25] where 1-(2-hydroxyethylthio)propan-2-ol, on cyclodehydration with ortho-phosphoric acid yielded 3-methyl-1,4-oxathiane in a very low yield (17%) (Scheme 1.10).

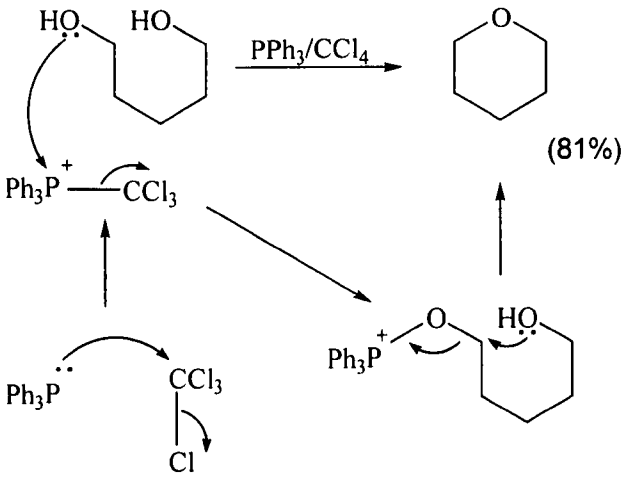
In an attempt to mimic this approach, while trying to avoid decomposition, we investigated azeotropic distillation with toluene in the presence of *p*-toluenesulfonic acid. However, no reaction took place, and we decided to turn to other methods.

Simple diols have also been reported to undergo cyclodehydration to yield cyclic ethers by reaction with triphenylphosphine-carbon tetrachloride (Scheme 3.5).[77-79] This methodology utilizes the well-known tendency of phosphines to undergo redox condensation reactions. In the present case, the phosphine reacts with carbon tetrachloride to produce a phosphonium salt, which then reacts with the alcohol to give an alkoxyphosphonium salt. Ring closure can then take place by intramolecular nucleophilic displacement of triphenylphosphine oxide. This powerful reaction has the advantage of operating under mild conditions.

It should however also be noted that the reaction of primary and secondary mono-alcohols with triphenylphosphine and a tetrahalomethane (for example CCl_4

and CBr_4) has been reported as a convenient method for the conversion of alcohols to halides.[77-79] Although the authors of the cyclization method above reported that they observed no alkyl halide formation, we bore in mind that this might be a possibility in our case.

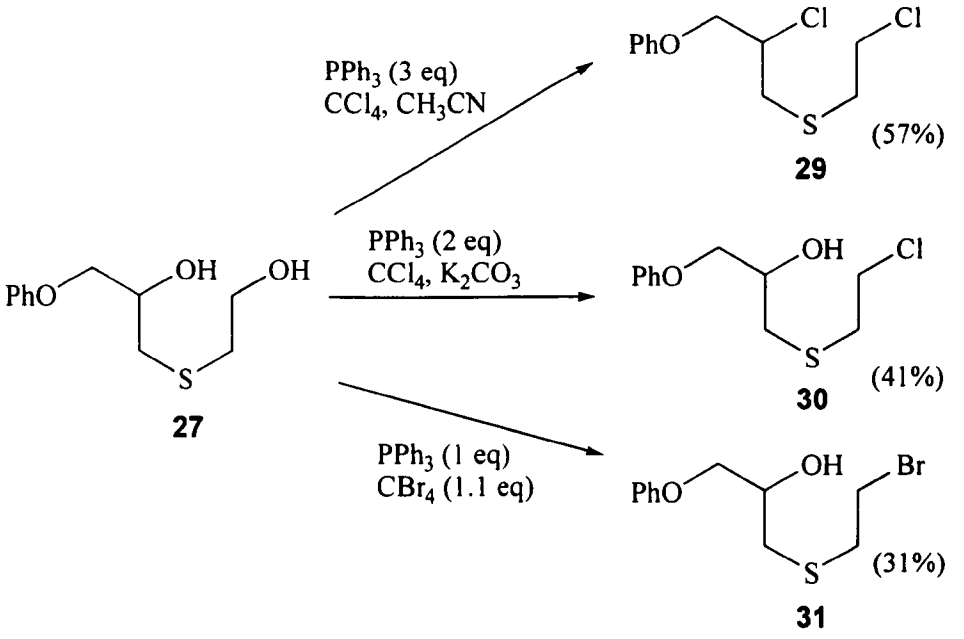
Scheme 3.5



Following the above cyclization procedure,[78] the sulfide diol, 2,6-dihydroxy-1-phenoxy-4-thiahexane (**27**), was therefore treated with triphenylphosphine, carbon tetrachloride and potassium carbonate in acetonitrile under reflux conditions. We were encouraged when the reaction gave a less polar product and the ^{1}H NMR and IR spectra indicated the absence of any hydroxyl groups. However, the mass spectrum indicated a complex molecular ion consistent with the incorporation of two chlorine atoms. In the ^{1}H NMR

spectrum, signals centred at δ4.25 ppm and at 4.14 ppm due to protons attached to the carbons bearing chlorine have approximately the same chemical shifts as corresponding signals at δ4.30 and δ3.79 ppm in the spectrum of the diol (**22**). The compound was identified as the dihalide (**29**) (Scheme 3.6).

Scheme 3.6



With the failure of the direct cyclization methods, attention was turned to indirect cyclization, wherein one of the hydroxyl groups of the diol (**27**) would be converted into a leaving group. Subsequently, intramolecular nucleophilic substitution involving the unaltered hydroxyl group displacing the leaving group

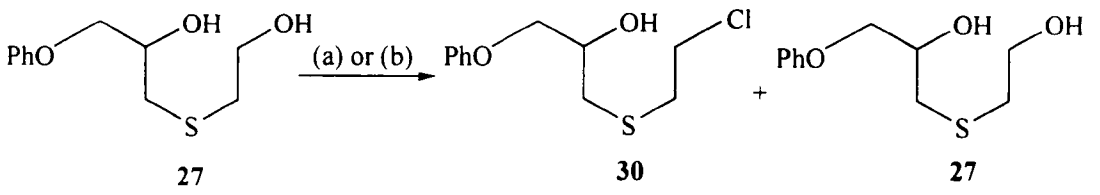
would provide the cyclized product. Initially, selective conversion of the primary hydroxyl group in compound (**27**) into halides was examined.

As we had already demonstrated that we could convert the sulfide diol into the dichloride, we now attempted selective monochlorination.[78] Compound (**27**) was consequently reacted with two equivalents of triphenylphosphine in the presence of potassium carbonate with carbon tetrachloride as solvent to afford the mono-chloride (**30**) as an oil in 41% yield (Scheme 3.6).

Similarly the same diol was also treated with one equivalent of both triphenylphosphine and carbon tetrabromide in acetonitrile to afford the bromo alcohol (**31**) as a dark oil in 31% yield, in addition to recovered starting material (57%) (Scheme 3.6).

Attempts were also made to prepare a tosylate derivative of the primary alcohol. It has been reported that simple diols undergo cyclodehydration to produce cyclic ethers by reaction with a sulfonyl chloride in the presence of an amine.[80] Initial esterification to provide a monosulfonyl ester is followed by cyclization. In our first attempt, the sulfide diol was treated with *p*-toluenesulfonyl chloride and pyridine with dichloromethane as the solvent. No tosylated product was observed, but the mono-chloride (**30**) and recovered starting material were isolated from the multi-component product mixture. In an attempt to promote the reaction, 4-dimethylaminopyridine (DMAP) catalysis was utilized but again only the mono-halide (**30**) and starting material were obtained (Scheme 3.7).

Scheme 3.7

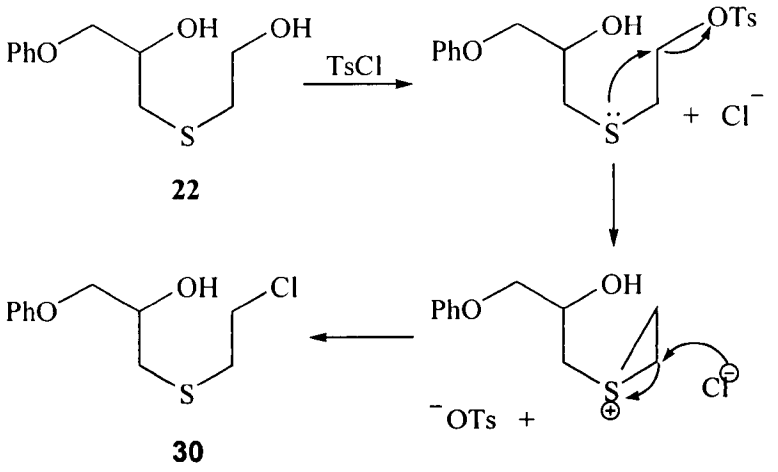


27 30 27

(a) *p*-TsCl, py, CH_2Cl_2 **30** (24%), **27** (48%)
(b) DMAP, *p*-TsCl, py, CH_2Cl_2 **30** (18%), **27** (43%)

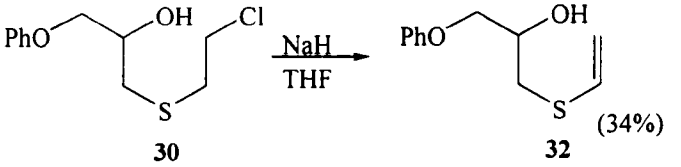
The formation of the mono-chloride in these attempted tosylations is intriguing. This suggests that neighbouring group participation involving an episulfonium intermediate may be taking place where tosylation of the alcohol occurs, the intermediate tosylate collapses to the episulfonium ion, then nucleophilic ring opening by chloride (and possibly water) gives the product (and recovered starting material) (Scheme 3.8).

Scheme 3.8



The treatment of the diol with halophosphorus reagents reported above had given us access to the corresponding mono-chloro and -bromo derivatives. We now investigated the cyclization of these species. The chloroalcohol (**30**) was treated with sodium hydride in THF under nitrogen at room temperature. However, the reaction did not prove successful and a complex mixture of products was obtained. One product that was separable from this mixture was found to be the vinyl sulfide (**32**) in 34% yield (Scheme 3.9). This was facilely detected through the appearance of signals due to vinylic protons and carbon atoms in the ^{1}H and ^{13}C NMR spectra.

Scheme 3.9



30 **32**

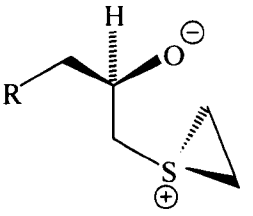
The bromo-sulfide (**31**), treated with sodium hydride in dry THF under a nitrogen atmosphere, reacted in a similar fashion to the chloride in giving an intractable mixture of products, and attempts to promote this reaction by the use of catalytic amounts of sodium iodide were equally unsuccessful.

In an attempt to prepare the corresponding iodide, the chloride (**30**) was treated with sodium iodide in acetone, the Finkelstein procedure.[81] However, an intractable mixture of products, unidentifiable by IR and ^{1}H NMR spectroscopy was obtained. It is very likely that the iodide, if formed, would be unstable by virtue of formation of the episulfonium intermediate.

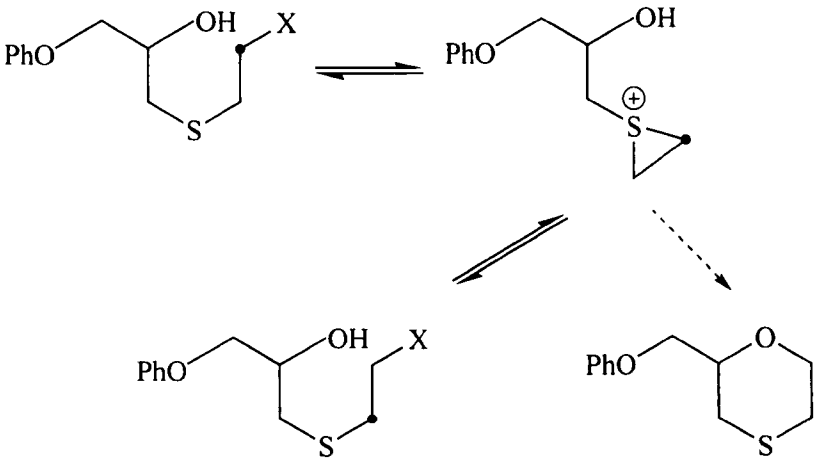
The intermediacy of the episulfonium ion (**33**) may account for the lack of success in the cyclization of the above sulfides. Formation of the three-membered ring might mitigate against intramolecular attack by the hydroxyl nucleophile. For ring opening of the episulfonium ring to occur, the hydroxyl group must attack at or near 180° to one of the C-S bonds. Geometrically, this would be very

difficult and so intermolecular reaction is likely to be favoured, eventually yielding polymer or a series of polymeric species (Scheme 3.10).

Scheme 3.10



33



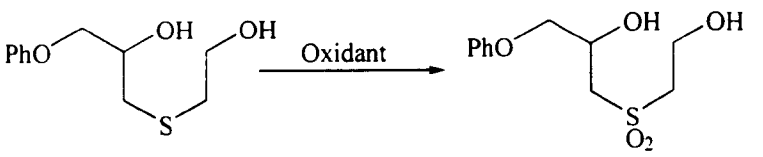
Clearly, we need to suppress formation of the episulfonium ion. The easiest way to do this is to convert the sulfide into the sulfone.

3.4.2 Preparation of sulfone diols

There are numerous methods for the oxidation of sulfides to sulfones.[21-24] The most frequently used reagents are organic peracids (for example, perbenzoic acids), but although they tend to oxidize sulfide to sulfoxides rapidly at low temperatures, at the higher temperatures required for oxidation to sulfones they can cause oxidation of other functional groups. Potassium hydrogen persulfate (commercially sold as OXONE) is a convenient, economical and chemoselective reagent for the oxidation of sulfides to sulfones in the presence of other common functional groups.[21] Tetrapropylammonium perruthenate (TPAP) in the presence of co-oxidant N-methylmorpholine-N-oxide (NMO) is a mild chemoselective catalytic oxidant for the oxidation of sulfides to sulfones in high chemical yield.[24]

In the present case, various oxidation methods were examined including the use of potassium hydrogen persulfate[21] and periodate.[82] However, these methods not only tended to take lengthy periods of time to go to completion but also gave low yields of product (Table 3). We therefore decided to select a method based on a literature procedure[23] using catalytic osmium tetraoxide with excess of NMO. Thus treatment of sulfide (**27**) with the reagent in acetone/water gave the crystalline sulfone diol (**34**) in 86% yield. The reaction proceeded to completion after initial rapid sulfoxide formation, apparent by tlc analysis, in just 18 hours (Table 3).

Table 3



27 34

Method	Solvent	Time	Yield/%
Oxone	Methanol	11 days	37
Periodate	Water	15 days	41
OsO_4/NMO	Acetone/Water	18 h	86

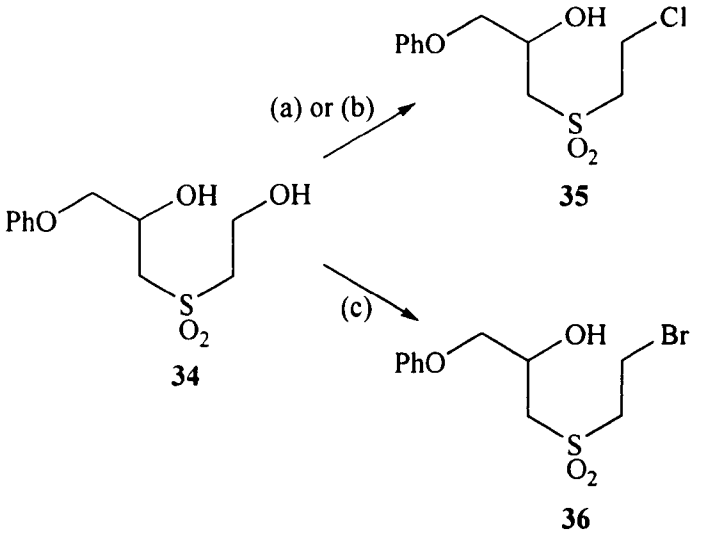
In the ^1H NMR spectrum of the sulfone (**34**), a downfield shift of the signals due to the protons adjacent to sulfur is observed; this is characteristic of the greater electronegativity of the sulfone group as compared to the sulfide.

3.4.3 Attempted cyclodehydration of sulfone diols

The cyclodehydration reactions of the sulfone diol (**34**) were examined next. Treatment of (**34**) with one equivalent of triphenylphosphine-carbon tetrachloride in acetonitrile at room temperature did not induce cyclization. In a

similar fashion to the reaction of the sulfide analogues, the only product isolated was the chloro alcohol (**35**) in 76% yield (Scheme 3.11).[77-79] ^{1}H NMR and IR spectroscopy indicated the presence of a hydroxyl group, and the mass spectrum indicated the incorporation of one chlorine.

Scheme 3.11



(a) PPh_3, CCl_4, CH_3CN, **35** (76%)
(b) PPh_3, CCl_4, K_2CO_3, **35** (83%)
(c) $Ph_3P.Br_2$, py, **36** (56%)

Cyclization was attempted by treating diol (**34**) with *p*-toluenesulfonyl chloride with pyridine as solvent and base. However, only starting material (57%) was recovered from this reaction. As it would be surprising if the primary alcohol of (**34**) did not react with the sulfonyl chloride, it may be that the sulfonate is

formed, then eliminates to give the vinyl sulfone, which then is subsequently hydrated to give recovered starting material.

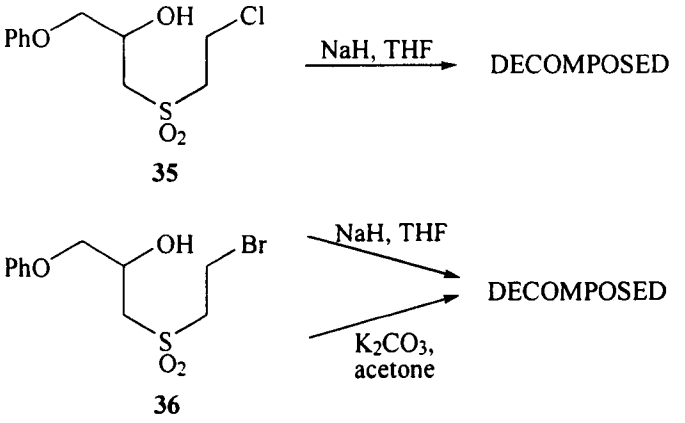
We therefore turned to concentrate on the conversion of the sulfone diol (**34**) into the corresponding monohalo-alcohol (**35**) which might then be cyclized by treatment with base.[77-79] The formation of the monochloride (**35**) was further optimized by treatment of (**34**) with triphenylphosphine and potassium carbonate in carbon tetrachloride to give an 83% yield (Scheme 3.11).

The corresponding reaction with triphenylphosphine and carbon tetrabromide in acetonitrile gave no discrete products, in contrast to the sulfide diol case.[79] However, use of triphenylphosphine dibromide and pyridine in dichloromethane at room temperature gave an acceptable yield (56%) of the monobromide (**36**) (Scheme 3.11).

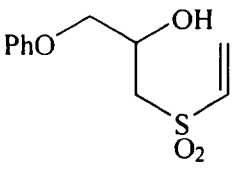
With the successful conversions of the sulfone diol into the mono-chloro and mono-bromo compounds, cyclisations were next attempted. Treatment of the chloro-sulfone (**35**) with base sodium hydride in THF under a nitrogen atmosphere unfortunately gave an intractable mixture of unidentifiable products. Similarly, attempted cyclisation of the bromo-sulfone (**36**) with sodium hydride in THF in a nitrogen atmosphere was unsuccessful, giving a light yellow oil which appeared homogenous by tlc analysis but was shown to be a mixture of components by ^{1}H and ^{13}C NMR spectroscopy. Treatment of compound (**36**) with potassium carbonate in acetone was also unsuccessful, yielding a complex mixture of inseparable products. Use of extensive column chromatography was

unsuccessful in resolving this mixture into recognizable components (Scheme 3.12).

Scheme 3.12



From these results we might suggest that the reason these cyclizations did not work was probably due to an E1cB type elimination with polymerisation of the resulting sulfone (**37**). In the light of the results we reported in the previous chapter, it is disappointing to note that intermolecular reactions of the vinyl sulfone appear more rapid than the intramolecular cyclizations.

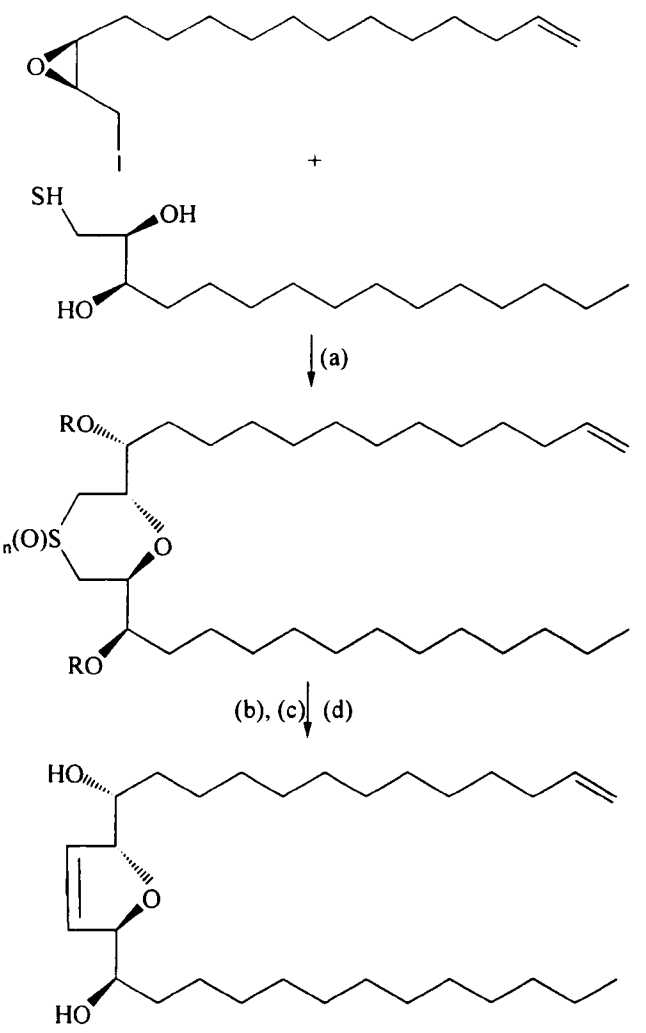


37

3.5 Epilogue

The lack of success at formation of the substituted oxathiane *S,S*-dioxides *via* ring synthesis prompted us to move on to studies involving lactones. However, after our conclusion of the above work, Trost[83] published work relating to our studies. Trost[83] coupled the Ramberg-Bäcklund rearrangement of a 1,4-oxathiane *S,S*-dioxide with a ruthenium-catalyzed butenolide annulation for the synthesis of (+)-solamin and analogues. This approach followed a different strategy for ring formation which involved cyclization of alkoxide with ring opening of an exocyclic epoxide (Scheme 3.13).

Scheme 3.13



b { n = O, R = H
c { n = 2, R = H
  { n = 2, R = TMS

(a) (i) CS_2CO_3, DMF, RT, 92%; (ii) KOH, H_2O, t-C_4H_9OH, 65%
(b) MCPBA, PhH-hexane, 0 °C, 95%
(c) TMSCl, $(C_2H_5)_3N$, CH_2Cl_2, 0 °C, RT, 94%
(d) (i) t-C_4H_9OK, t-C_4H_9OH, CCl_4, RT, 65%; (ii) TSOH, H_2O, C_2H_5OH, RT, 95%

4 Attempted Preparation of Oxathian-3-one 4,4-Dioxides by Lactonisation

4.1 Introduction

Having concluded our studies into methods of preparing substituted 1,4-oxathiane dioxides, attention was now turned to the corresponding lactones. We chose to concentrate initially on the parent compound, 1,4-oxathian-3-one 4,4-dioxide (**11**).

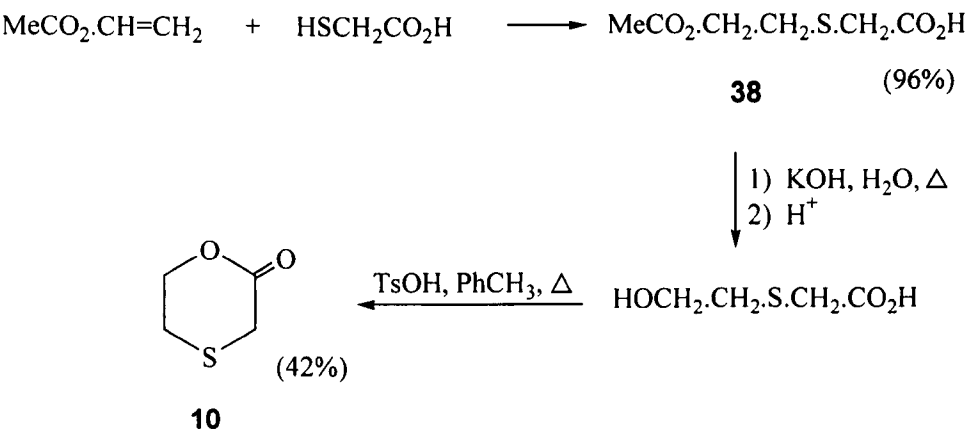
As indicated in Chapter 1, the most obvious approach to this system was *via* the cyclization of a suitable hydroxyacid derivative. Two such approaches were possible: a) cyclization of 2-(2-hydroxyethylthio)acetic acid to 1,4-oxathian-3-one followed by oxidation to the sulfone; or b) sulfur oxidation at the hydroxyacid stage, followed by cyclization.

4.2 Synthesis *via* 1,4-Oxathian-3-one

We followed and compared two literature routes to 1,4-oxathian-3-ones. The first of these, reported by Davies *et al.*[36] involved the preparation of the hydroxyacid *via* a free radical process. Thus, thioglycolic acid and vinyl acetate were stirred together in a nitrogen atmosphere at room temperature to yield

2-(2'-acetyloxyethylthio)acetic acid (**38**) in 96% yield. The reaction proceeds by free-radical addition of the thiol radical to the double bond. The thiol radical arises *via* hydrogen atom abstraction from thiol by trace amounts of peroxides. A chain process is then maintained through hydrogen atom abstraction from thiol by the radical intermediate produced in the reaction. The acetate was then hydrolyzed by treatment with 40% potassium hydroxide under reflux, and the crude acid so obtained was cyclized by azeotropic distillation with a catalytic amount of *p*-toluensulfonic acid in toluene. Following this procedure, we obtained the oxathianone (**10**) as a pale yellow oil in 42% yield (Scheme 4.1).[36]

Scheme 4.1

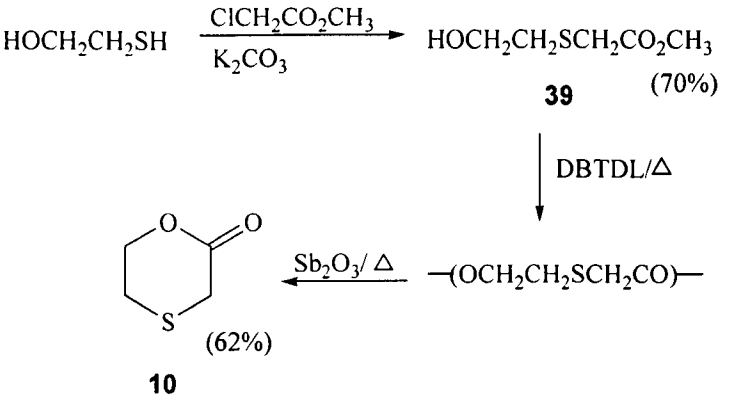


The second method involved the preparation of the lactone by a deoligomerization of the polymer of 2-(2-hydroxyethylthio)acetic acid. This polymer was prepared in two steps. First, treatment of 2-mercaptoethanol with methyl chloroacetate in the presence of potassium carbonate in acetone gave the

hydroxyethylthioacetate (**39**) in 70% yield, which is higher than that previously reported in the literature (Scheme 4.2).[41] This ester was then polymerized in the presence of dibutyltin dilaurate at 165 °C.

Depolymerization was then performed by heating with antimony trioxide in a vacuum distillation apparatus.[41] The oxathianone (**10**) was collected by distillation as a colourless oil in 62% yield (Scheme 4.2).

Scheme 4.2



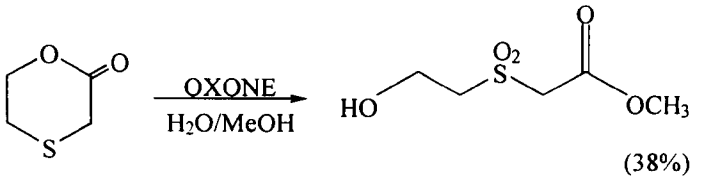
DBTDL = $(CH_3CH_2CH_2CH_2)_2Sn[OCO(CH_2)_{10}CH_3]_2$

Thus, 1,4-oxathian-3-one could be prepared in a similar overall yield by either procedure. The first of the two is perhaps preferable - as well as being more economical it is, practically speaking, less involved. With suitable quantities of this sulfide to hand we now turned to oxidation to the sulfone.

Initially, oxidation of the sulfide (**10**) with OXONE[21] in methanol-water (50:50) was investigated. Unfortunately, this did not yield the sulfone lactone.

Although the sulfide was oxidized to the sulfone, concomitant ring opening also took place to yield methyl 2-(2'-hydroxyethyl)sulfonyl acetate (**40**) as the only isolable product (38%)(Scheme 4.3).

Scheme 4.3



10 **40** (38%)

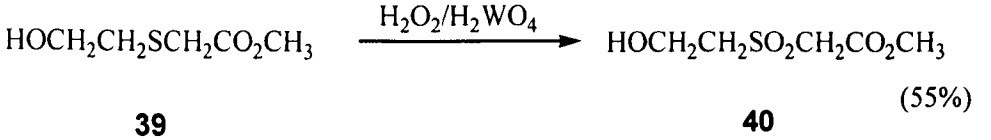
Use of the hydrogen peroxide/tungstic acid procedure,[22] unfortunately yielded a complex mixture of products which could not be purified, in spite of extensive column chromatography. Use of osmium tetroxide-NMO,[23] MCPBA or TPAP-NMO[54] were all similarly unsuccessful.

To conclude, although it was possible to synthesize 1,4-oxathian-3-one by more than one method it proved impossible to prepare the corresponding sulfone. This may be due to the product (and/or the corresponding sulfoxide) being too prone to ring-opening under oxidative conditions.

4.3 Synthesis *via* Sulfonylhydroxy Acid Derivatives

To avoid subjecting the sensitive 1,4-oxathian-3-one system to oxidizing conditions, we instead investigated oxidation prior to ring formation. First, we looked at oxidation of the methyl ester (**39**) by the hydrogen peroxide/tungstic acid method.[22] As before, sulfoxide formation was relatively fast, then on heating, complete conversion to the sulfone was observed. Thus methyl 2-(2-hydroxyethyl) sulfonylacetate (**40**) was obtained as a colourless oil in 55% yield (Scheme 4.4).

Scheme 4.4



39 **40**

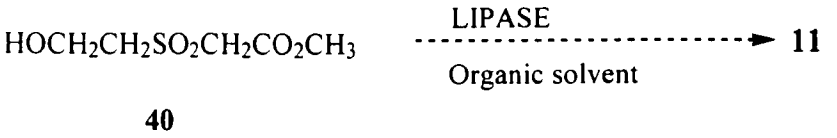
It has been reported that heating the sulfonyl acetate under high vacuum provides the sulfone lactone (**11**) in good yield.[41] However, the requisite high vacuum was not accessible with the equipment available in our laboratory, so other methods of cyclizations were examined.

Initially, the sulfone **39** was treated with imidazole in acetonitrile at 25 °C,[61] but starting material (60%) was the only recoverable component from this mixture.

Next, lipase catalyzed lactonization reactions were investigated. Lipase enzymes are commercially available, cheap and stable. It has been well substantiated that hydrolytic enzymes can act as catalysts in organic solvents.[58] Catalysis of ester formation and ester exchange rather than hydrolysis is also possible. An approach by Yamada and co-workers[84] uses intramolecular lactonization catalyzed by lipases in organic solvents.

Following a literature procedure,[58] lactonisation was attempted using the sulfonyl acetate (**34**) with various lipases in organic solvent. Unfortunately, despite repeated efforts, the lipase catalyzed cyclizations were unsuccessful in all cases (Table 4).

Table 4



40

Entry	Lipase	Solvent	Time/days	RSM/%
1	*Pseudomonas fluorescens*	Hexane	7	93
2	porcine pancreatic	Hexane	4	93
3	*Pseudomonas fluorescens*	Acetone	7	77

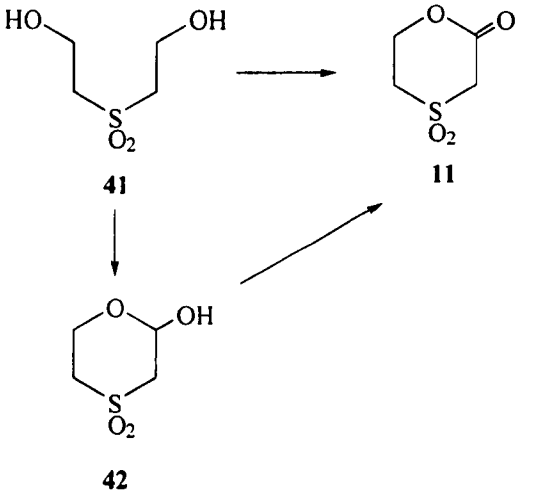
These results seem to imply that ring formation by lactonization in this series, particularly with the sulfone, is very difficult. We therefore turned to other strategies for forming this system which did not rely on such a step.

5 Attempted Preparation of 1,4-Oxathiane-2-one *S,S*-dioxides by Oxidation of Open-chain Sulfone Diols

5.1 Introduction

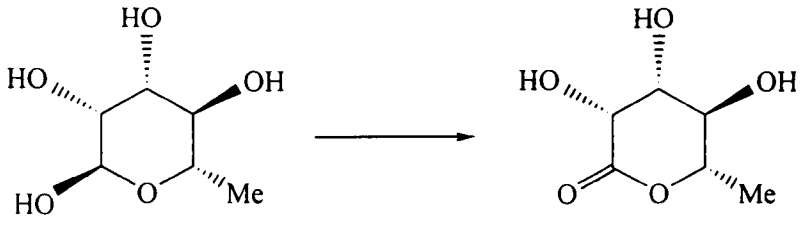
The objective of the chemistry described in this chapter was to examine a different approach to the sulfone lactone. This would entail the oxidation of open-chain diols such as 2,2'-thiodiethanol *S,S*-dioxide (**41**) with concomitant cyclization. This might be achieved either by direct oxidation of the diol to the lactone or in a stepwise fashion, by oxidation to the lactol and subsequent further oxidation to the lactone (Scheme 5.1).

Scheme 5.1



There are a number of precedents for such an approach, particularly from carbohydrate chemistry. Also, muscarines may be converted from lactone using aqueous bromine in the presence of a buffer (Scheme 5.2).[85]

Scheme 5.2



(i) Br_2(aq) in $BaCO_3$ buffer, 2:1 mixture of δ– and γ– lactones in 75% yield

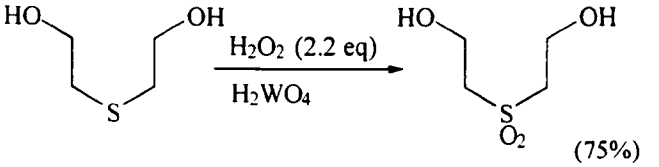
In fact the direct conversion of 2,2'-thiodiethanol to 1,4-oxathian-3-one *S,S*-dioxide, involving both sulfide to sulfone and diol to lactone oxidations, using sodium bromite ($NaBrO_2$) has been reported.[52] Unfortunately, this reagent is no longer available.

We chose at first to look at oxidation/cyclization of (**41**) as a model for more complex diols, such as those we had prepared earlier (Chapter 2).

5.2 Preparation of 2,2'-Thiodiethanol *S*,S-Dioxide

Following a literature procedure, 2,2-thiodiethanol was oxidized to the sulfone by treatment with 30% hydrogen peroxide in glacial acetic acid, in the presence of catalytic amounts of tungstic acid.[22] The reaction was carried out by sequential addition of two lots of 1.1 equivalents of hydrogen peroxide (Scheme 5.3). As is typical of such reactions, the intermediate sulfoxide was readily formed in an exothermic reaction, and oxidation to the sulfone was slower and required heating.

Scheme 5.3



41

5.3 Direct Oxidation of Diol

An attempt at a direct conversion of (**41**) into the lactone (**11**) by tristriphenylphosphineruthenium(II) chloride catalyzed dehydrogenation[55] was carried out. This method of hydrogen transfer from a diol requires the presence of

a hydrogen acceptor such as 4-phenylbut-3-en-2-one. It is a favorable choice of reaction because homogenous metal complex catalyzed reactions often show high selectivity and so it is unnecessary to use an oxidant that may be expensive (Ag(I)) or potentially explosive (peroxide).[60]

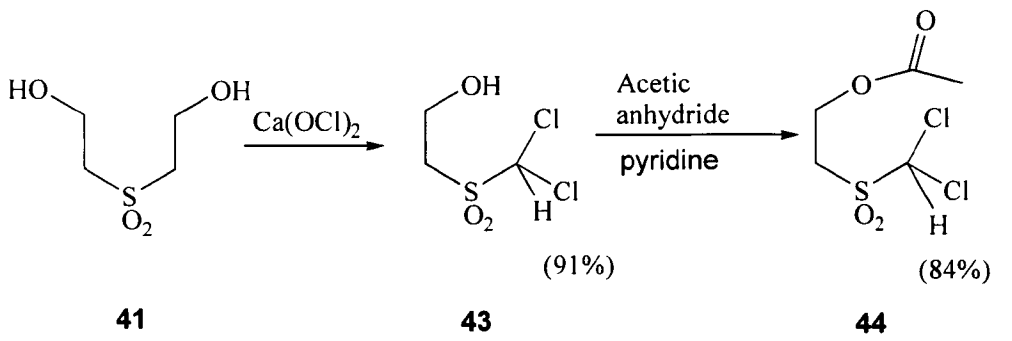
The diol was refluxed in toluene with a catalytic amount of the ruthenium complex in the presence of the phenylbutenone. Unfortunately, the reaction proved unsuccessful and an intractable mixture of polar products was obtained.

Another direct oxidation with the oxidant calcium hypochlorite was examined.[54] This stable, solid hypochlorite reagent oxidizes primary alcohols to esters and secondary alcohols to ketones in good yields and so we hoped it might be used for a lactonization.

The diol (**41**) in an acetonitrile/acetic acid mixture was added to a cooled solution of the calcium hypochlorite in water. We were pleased to observe a clean reaction but an unexpected result was obtained. The starting diol was converted into the three carbon α,α-dichlorinated sulfone (**43**) in 91% yield (Scheme 5.4)

Mass spectrometry showed peaks for the incorporation of both isotopes of chlorine consistent with the presence of two chlorine atoms. The ^{1}H NMR spectrum showed a sharp singlet at δ6.56 ppm attributable to an uncoupled methine proton adjacent to three electronegative substituents - the two halogens and the sulfone group, (C<u>H</u>-Cl_2). To assist us in confirming the connectivity, the alcohol was converted into the acetate (**44**) under standard conditions (Scheme 5.4), when the O-CH_2 signals shifted from 4.17 to 4.61 ppm. An explanation for the formation of (**43**) is given in Section 5.4.

Scheme 5.4



(91%) (84%)

41 **43** **44**

The complex nature of these results convinced us that it would be more pragmatic to concentrate on a stepwise oxidation approach, and we therefore turned to investigate methods for the preparation of the corresponding lactone.

5.4 Synthesis of 3-Hydroxy-1,4-oxathiane *S,S*-Dioxide

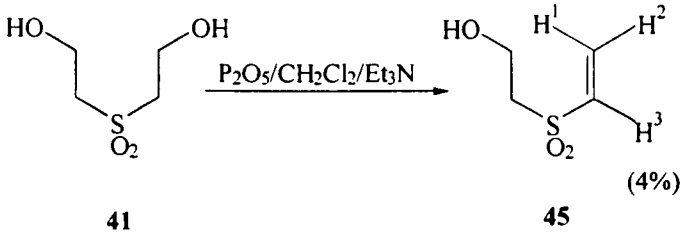
In this section, oxidation of the diol (**41**) to the corresponding lactol (**42**) is examined.

A Swern oxidation of sulfone diol (**41**) was attempted following a general literature procedure.[57] This involved using phosphorus pentoxide to activate the dimethyl sulfoxide (DMSO), reacting the activated species with the diol, then treating the resultant intermediate with triethylamine. However, this reaction

proved unsuccessful giving a complex mixture of products which, although appearing homogenous by tlc analysis, was shown to be a mixture of components by ^{1}H NMR spectroscopy. Repeated column chromatography was successful in providing only one component of the polar mixture. This was found to be 1-hydroxy-3-thiapent-4-ene 3,3-dioxide (**45**), obtained in 4% yield (Scheme 5.5).

NMR signals were present in the alkene region consisting of a doublet of doublets with J=16.6 and 9.8 Hz at δ6.74 ppm due to the hydrogen adjacent to the sulfur atom (C<u>H</u>=CH_2); a doublet at δ6.48 ppm with J=16.6 Hz corresponding to the proton Z to sulfur due to the trans coupling of CH^1 to CH^3 and a doublet at δ6.21 ppm with J=9.8 Hz corresponding to the proton E to the sulfur.

Scheme 5.5

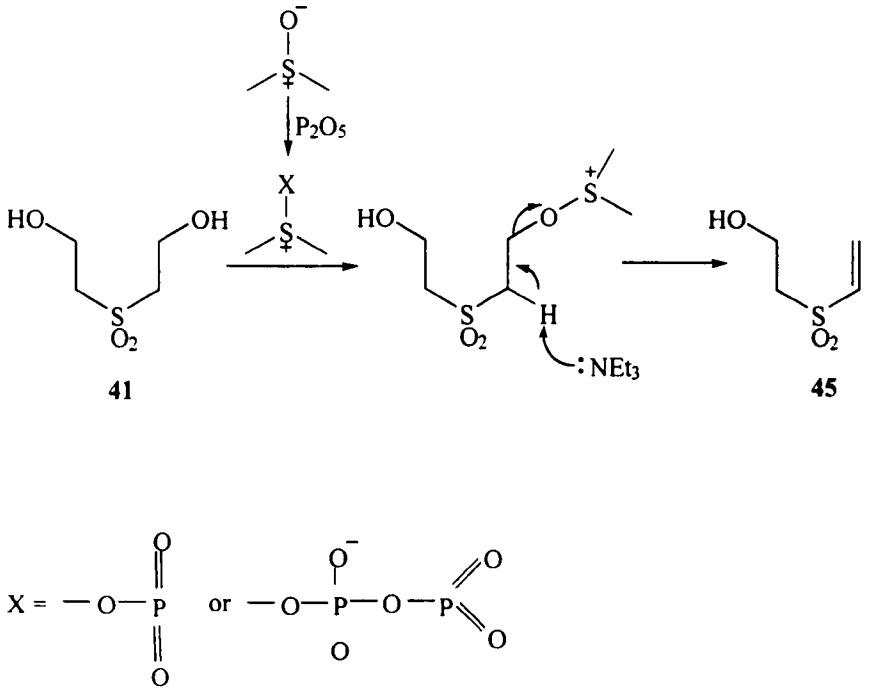


41 **45** (4%)

The formation of the vinylic sulfone is worthy of comment, even though it was isolated in very low yield. It is most likely that the compound is a result of

β-elimination of the Swern intermediate formed from the alcohol and activated DMSO (Scheme 5.6). Note that compound (**45**) is actually our assumed intermediate from the elimination/addition reactions of 1,4-oxathiane *S,*S-dioxide reported in Chapter 2. This indicates that the compound is actually a stable entity under these mild conditions.

Scheme 5.6

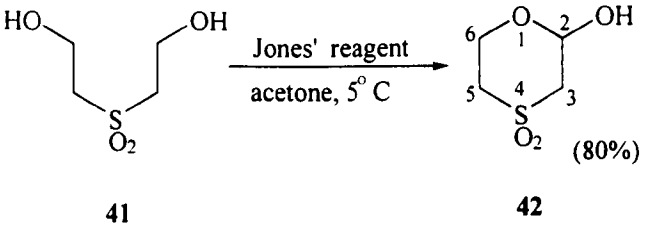


We therefore turned to other methods. A convenient and strong oxidizing agent is Jones' Reagent.[64] This is a solution of chromic acid and sulfuric acid in

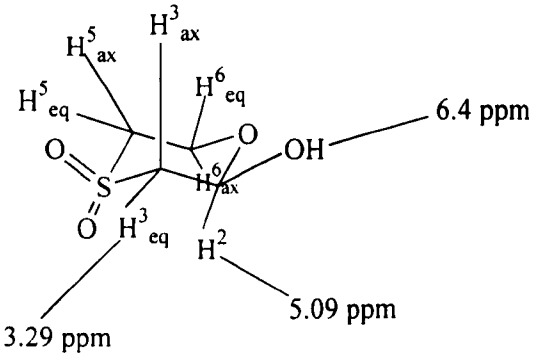
water. When secondary alcohols are dissolved in acetone, titration with the Jones' Reagent oxidizes them to ketones rapidly and in high yield. Primary allylic alcohols are oxidized to the corresponding aldehydes.[64]

Freshly prepared Jones' Reagent was titrated into a solution containing the diol in acetone at 5 °C.[64] The diol was thereby converted into the crystalline lactol (**42**) in 80% yield (Scheme 5.7).

Scheme 5.7

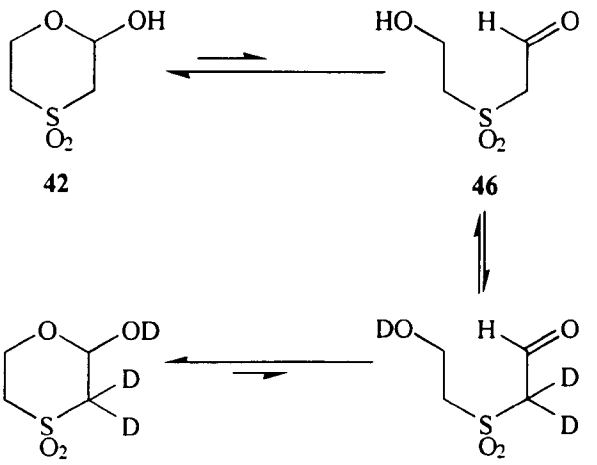


41 **42**



The ^{1}H NMR spectrum of lactol (**42**), in d_6-acetone, contains a signal (d, ^{3}J = 6.4 Hz) immediately exchangeable with D_2O at δ = 6.4 ppm. This is due to the hydroxyl proton. A signal at δ5.09 ppm, appearing as a multiplet which simplifies on D_2O exchange, is assigned to H-2. A signal at 4.31 ppm appears as a ddd, with couplings of 13.1, 3.9, and 3.9 Hz is assignable to H-6 in an equatorial disposition (H-6_{eq}). The 13.1 Hz coupling is due to geminal coupling to H-6 axial, with which is has a diastereotopic relationship. The signal, as a ddd at δ3.82 ppm is due to H-6_{ax}, and has couplings of 13.1, 10.4 and 3.0 Hz. The J=10.4 Hz pinpoints this as an axial proton displaying *trans*-diaxial coupling with H-5_{ax}. A ddd signal at 3.29 has couplings of 13.6, 3.1 and 2.3 Hz. This signal undergoes slow exchange with D_2O. This pinpoints H-3_{eq}, as the responsible proton, which has a geminal (13.6 Hz), a *cis* (or *trans*)-dequatorial coupling with H-2, and a long range W-coupling (2.3 Hz) with H-5_{eq}. A large multiplet at 3.19 - 3.21 integrates for 3 protons; one proton exchanges out slowly with D_2O. Thus, the signal is assigned to H-3_{ax}, H-5_{ax} and H-5_{eq}. The apparent exchange of two ring protons for deuterium is most readily explained by assuming that lactol (**42**) is in equilibrium with a very small amount of the open-chain aldehyde tautomer (**46**), which contains an active methylene group capable of exchange with D_2O.

Scheme 5.8

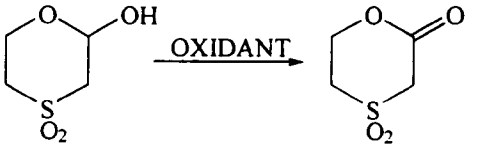


42 46

5.4 Oxidation of 3-Hydroxy-1,4-oxathiane *S,S*-dioxide

So, with the formation of the lactol (**42**) we now turned our attention to conversion to the lactone (**11**) (Scheme 5.9).

Scheme 5.9



42 11

Oxidation of (**42**) to the lactone was initially attempted using transition metal catalysts.[24,55,56,59,63,64,65] The palladium-catalyzed oxidative conversion of ω-primary diols into lactones was well precedented in the literature,[63] so the lactol (**42**) was treated with palladium(II) acetate, triphenylphosphine and potassium carbonate with bromobenzene in dimethyoxyethane under a nitrogen atmosphere. However, only starting material (50%) and a mixture of several polar by-products, which proved inseparable upon extensive column chromatography, were recovered.

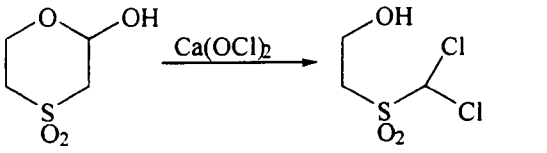
The use of 4-phenyl-3-buten-2-one as a co-oxidant under ruthenium complex catalytic conditions[55] also did not yield the lactone, but rather an intractable mixture of polar products (as we had seen in the corresponding reaction of the diol).

Use of the catalytic oxidant tetrapropylammonium perruthenate (TPAP) was then examined. This expensive, commercially available reagent is a readily soluble, non-volatile and stable oxidant for alcohols. TPAP is catalytic if suitable co-oxidants, such as N-methylmorpholine-N-oxide (NMO) are added.[24] The lactol (**42**) was treated with TPAP and NMO in dichloromethane in a nitrogen atmosphere. However, after stirring at room temperature for seven days, all that was recovered was starting material in 72% yield.

We therefore decided to try using an excess of Jones' reagent[64] with lactol (**42**). However, this only resulted in yielding us with recovered starting material. Similarly, a Swern oxidation[57] with (**42**) also returned starting material in 92% yield.

Oxidation of (**42**) with calcium hypochlorite oxidant[54] gave a three-carbon α,α -dichlorinated sulfone in 93% yield, identical with the product (**43**) obtained with this oxidant from the reaction with the diol sulfone (Scheme 5.10).

Scheme 5.10



42 **43** (93%)

This would suggest that the first step in the reaction of diol (**41**) is its conversion into the lactol (**42**), which is then converted into the chlorinated alcohol (**43**). This will be discussed later in this section.

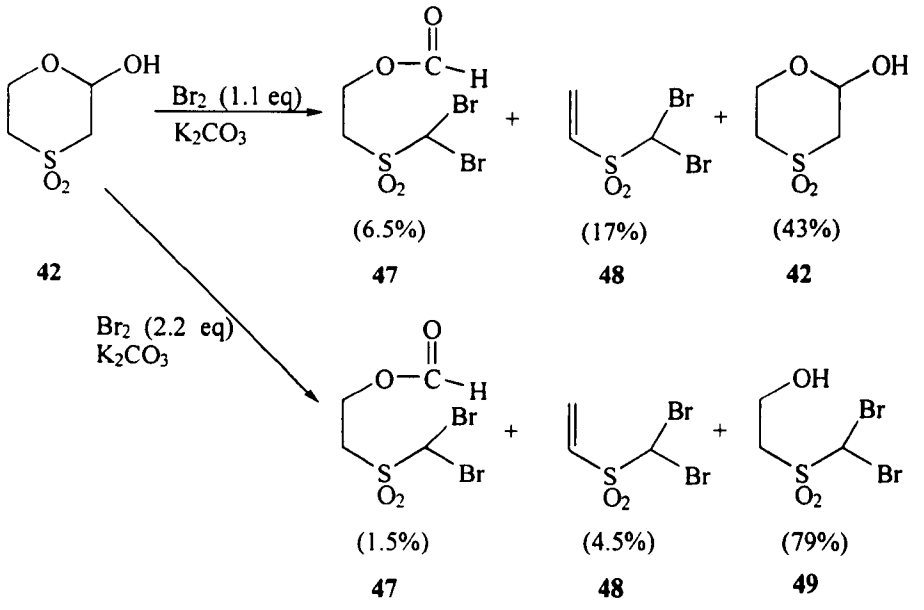
Oxidation of the lactol with bromine was examined next. This procedure is well precedented in the literature with other lactols and entails use of bromine in the presence of potassium carbonate.[86]

Initially, the lactol (**42**) was treated with 1.1 molar equivalents of bromine in the presence of an equimolar quantity of potassium carbonate. This oxidation did not give us the desired lactone but rather two novel compounds and, despite all the bromine in the reaction being consumed, a considerable amount of starting material was recovered (43%). The two novels compounds were found to be the formate ester (**47**) and the alkene (**48**) respectively (Scheme 5.11).

The reaction was repeated with 2.2 molar equivalents of bromine in the presence of an equimolar quantity of the base, giving a complete conversion of (**42**). The alkene (**48**) and formate ester (**47**) were again isolated as minor components (4.5 and 1.5% respectively), together with a novel third predominant product, the alcohol (**49**) in a 79% yield (Scheme 5.11).

Compounds (**47**), (**48**) and (**49**) were readily identified from their ^{1}H NMR spectra. The compounds contained a sharp singlet at δ = 6.30, 6.15 and 6.49 ppm respectively due to the methine proton surrounded by three electron-withdrawing groups. The mass spectra contained the expected 1:2:1 pattern attributable to the isotopic molecular ion of dibromo compounds. All compounds gave satisfactory elemental analyses.

Scheme 5.11

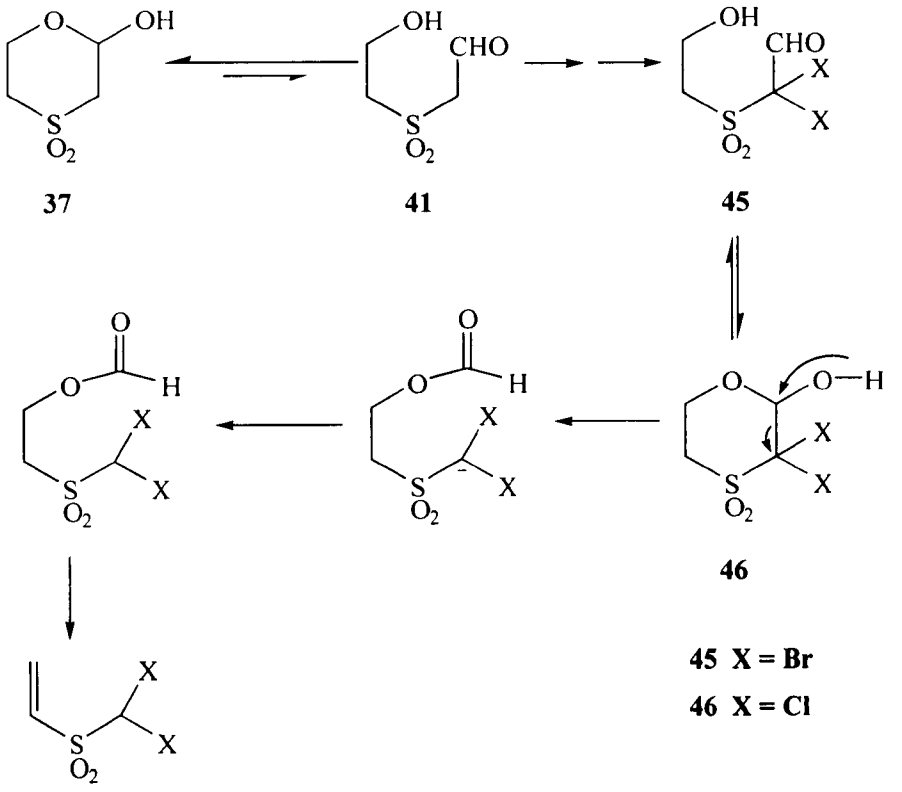


Based on our findings with these novel compounds, we can propose the following sequence of reactions for formation of these halogenation/C-C bond cleavage processes (Scheme 5.12).

From our observations in the attempted hypochlorite oxidation of the diol (**41**), it is possible to propose that that reaction involves initial conversion to the lactol (**42**). In both reaction systems it is then reasonable to suggest that the open-chain tautomer (**46**) of the lactol is halogenated twice at the labile C2-position followed by the reversible ring closure to the intermediate lactol (**51**). This lactol can then undergo C-C bond cleavage with the formation of a highly-stabilized anion, adjacent to the sulfonyl group and both halogen atoms. Protonation will give (**47**) or (**51**). Then the β-sulfonylformate may either be hydrolyzed to give the corresponding alcohol or undergo elimination of formate to yield the alkene (**48**) if X=Br, depending upon reaction conditions.

No mono-halogenated products or intermediate lactols (**51**) were isolated, which suggests that the rate determining step for this process is either the ring-opening of the lactol, or the first halogenation step.

Scheme 5.12



In summary, oxidation of the lactol did not give us the desired lactone but generally gave either an intractable mixture of polar products or recovered starting material. However four novel compounds were obtained when oxidation of the diol (**41**) or lactol (**42**) with calcium hypochlorite, or of the lactol with bromine was undertaken. These compounds were found to be halogenation/C-C bond cleavage products rather than the expected lactone.[87]

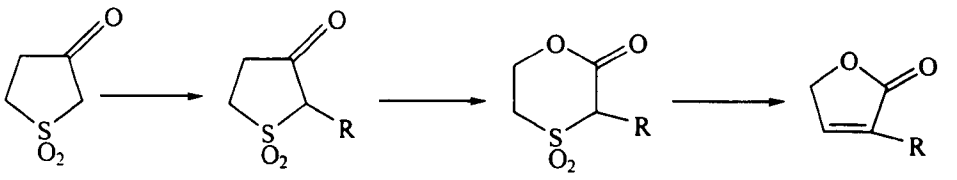
6 Approaches to 3-Oxotetrahydrothiophene *S,S*-dioxide

6.1 Introduction

6.1.1 A New Synthetic Strategy

In the chemistry described in this section, we turned our attention to another route to the elusive alkylated 1,4-oxathian-3-one 1,1-dioxides. We perceived that the main problem so far had been the formation and stability of the lactone moiety of these systems, so that if we could delay the introduction of this group until near the end of the route we would improve our prospects. We therefore considered the synthesis of the desired lactone *via* the alkylation of an oxotetrahydrothiophene 1,1-dioxide (**52**) with the intention of then performing a Baeyer-Villiger rearrangement to produce the requisite alkylated lactone (Scheme 6.1).[6] Thus the sensitive lactone functionality would only be "carried through" the final step, the Ramberg-Bäcklund rearrangement.

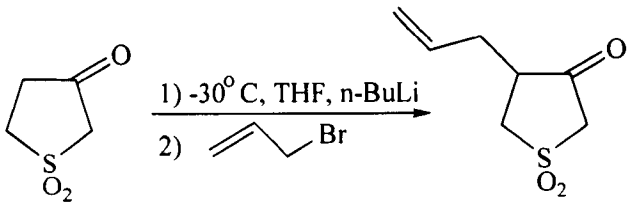
Scheme 6.1



52

Our belief in the potential of this approach was based on a communication by Belletire and Spletzer[88] who reported the successful alkylation of 3-oxotetrahydrothiophene *S,S*-dioxide (OTTD) (**52**) at the C-2 and C-4 positions in respectable yields of between 40 and 80%. In this communication, they gave details of useful additional transformations such as the preparation of enamine and enol ether derivatives of the ketone (using $TiCl_4$ catalysis) as well as the trapping of the dianion derived from OTTD with allyl bromide (Scheme 6.2). They reported that full details of this chemistry would be published in a forthcoming paper, although this had not appeared despite several years passing.

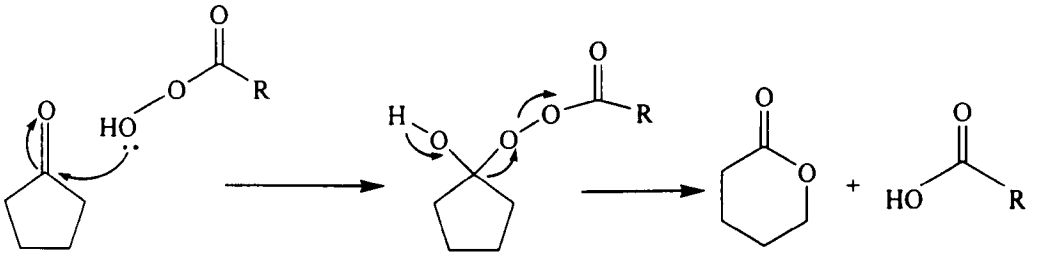
Scheme 6.2



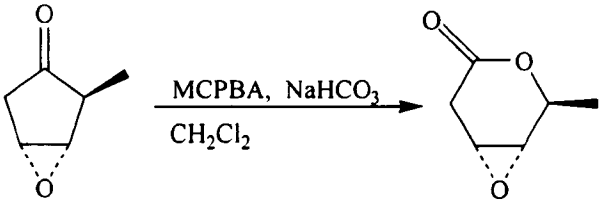
So, based on the findings of Belletire and co-workers, we proposed to prepare the 3-oxotetrahydrothiophene *S,S*-dioxide, then to alkylate at the α-position. We would then submit this alkylated ketone to the Baeyer-Villiger reaction conditions to prepare the 6-membered lactone, the substrate for the Ramberg-Bäcklund reaction.

The Baeyer-Villiger reaction, the oxidative conversion of ketones into esters by peracids was first reported by Baeyer and Villiger in 1899.[6] The reaction entails the insertion of an oxygen atom into one of the bonds to the carbonyl group. Consequently the ketone is converted into an ester (or lactone if the ketone is cyclic). Oxygen insertion tends to go away from any electron-withdrawing group and toward any electron donating group (Scheme 6.3). Thus oxygen insertion in our case would be away from the electron-withdrawing sulfone group.

Scheme 6.3



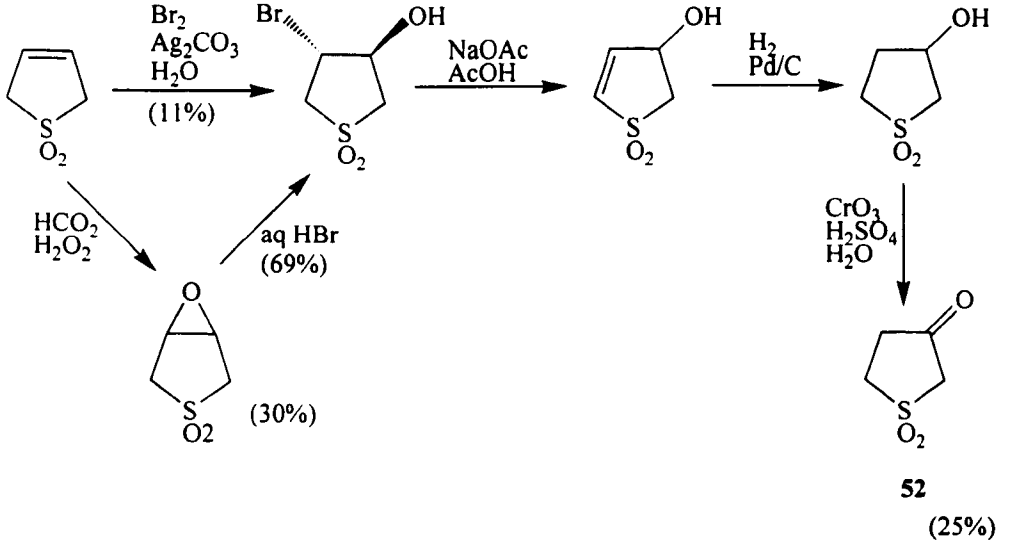
1,2-Migration



6.1.2 Approaches to 3-Oxotetrahydrothiophene *S,S*-dioxide

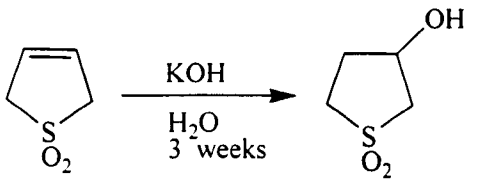
The most important approaches to the synthesis of 3-oxotetrahydrothiophene *S,S*-dioxide start from 2,5-dihydrothiophene *S,S*-dioxide. Consequently this can be converted to the corresponding halo-hydrin. The 2,5-dihydrothiophene *S,S*-dioxide halogenohydrines are readily accessible and may also be converted either directly from the butadiene sulfone or *via* the epoxide (Scheme 6.4).[89-90] The epoxidation of butadiene sulfone was carried out by Sorenson who prepared the epoxide in 30% yield by the reaction of the sulfone with a mixture of the strongly acidic formic acid and hydrogen peroxide under forcing conditions.[89]

Scheme 6.4



Consequently the epoxide was reacted with hydrobromic acid to give the corresponding bromohydrin. Prochazka *et al.* also prepared the bromohydrin by reaction of bromine and silver carbonate, however the reaction proceeded to give a very low yield of only 11%.[90] Sorenson was able to react the epoxide with dilute hydrochloric acid and prepare the corresponding chlorohydrin in 95% yield.[89] Sorenson also demonstrated conversion of the butadiene sulfone to the chlorohydrin in 77% by the addition of hypochlorous acid.[89] The chlorohydrin had also been prepared by Prochazka *et al.* by reaction of the butadiene sulfone with chlorine and barium carbonate thereby producing the chlorohydrin in a respectable yield of 80%.[90] These halogeno hydrines provide several possible routes to the desired ketone. Consequently dehydrohalogenation of the bromo-hydrin yields 3-hydroxy-2,3-dihydrothiophene dioxide.[91] This hydroxy compound can then be hydrogenated to the saturated alcohol 3-hydroxytetrahydrothiophene dioxide. The preparation of this saturated alcohol was much easier and faster than the otherwise slow and direct conversion *via* the butadiene sulfone which when treated with potassium hydroxide and water took 3 weeks reaction time (Scheme 6.5).[92] Subsequently, the alcohol was oxidised to the corresponding ketone using chromium (VI) oxide and sulphuric acid in only 25% yield.

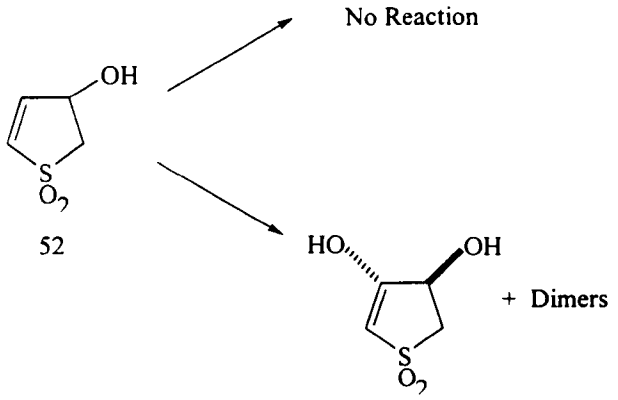
Scheme 6.5



Interestingly, two other conceivable routes for the preparation of the ketone include Prochazka's method whereby 4-methoxy-2,3-dihydrothiophen-1,3-dioxide was obtained from 2-chlorobuta-1,3-diene and subsequently used for the preparation of 3-oxotetrahydrothiophene dioxide.[93] Another route was the conversion of 3-aminotetrahydrothiophene dioxide[94-95] into the oxime of 3-oxotetrahydrothiophene dioxide by oxidation with hydrogen peroxide and a sodium tungstate catalyst. Hydrolysis of the oxime by boiling 10% acid gave the ketone in a respectable yield (85-95%).

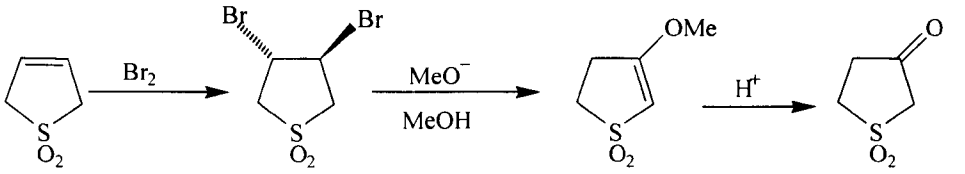
The routes above rely on a rather inefficient process involving a reduction immediately followed by an oxidation. It would be preferable instead to convert the allylic alcohol directly to the ketone by isomerization (Scheme 6.6). However, attempts to isomerise the 3-hydroxy-2,3-dihydrothiophene dioxide to the 3-ketone in either acidic or alkaline species were futile. Only recovered alcohol was obtained, in good yields, from boiling hydrochloric acid. Under alkaline conditions, hydration to the *trans*-3,4-dihydrotetrahydrothiophene dioxide and/or dimerisation to the ether occurred.[91,96]

Scheme 6.6



An improved approach to 3-oxotetrahydrothiophene was reported by Mason and co-workers.[97] This involved preparing the ketone by the acid catalyzed isomerization-hydrolysis of 4-methoxy-2,3-dihydrothiophene 1,1-dioxide which is the product of the reaction of 3,4-dibromo-tetrahydrothiophene dioxide with methanolic sodium hydroxide (Scheme 6.7). Several years later in the key publication justifying our approach, Belletire and Spletzer[88] reported a modified version of this procedure for an improved preparation of OTTD. Interestingly though, Alder and co-workers reported difficulties in repeating the experiments as set out by Belletire in his communication.[16]

Scheme 6.7



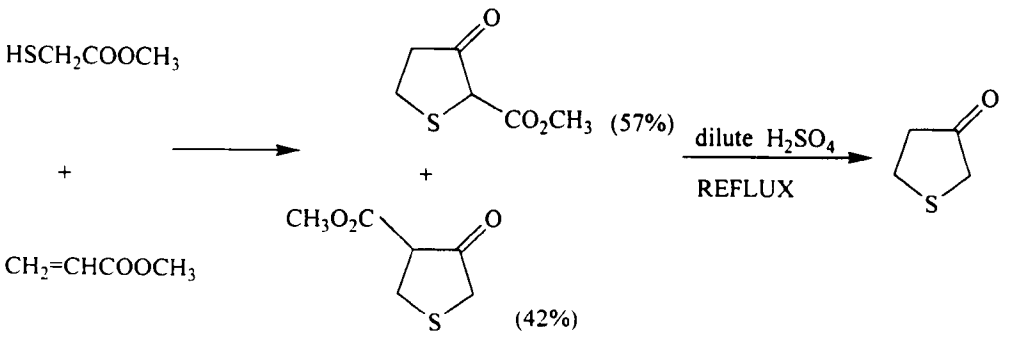
52

It is interesting to note that the sulfide analogue of our system has been prepared, but by a very different route. A procedure for the preparation of esters of the sulfide analogues, such as 3-carbomethoxy-4-oxotetrahydrothiophene, was reported by Liu and Ngooi.[98] The 1,4-addition of the methyl thioglycolate S-anion to methyl acrylate gives a resulting intermediate carbanion which can undergo two different modes of cyclization *via* proton exchange, thereby yielding two isomers (Scheme 6.8). A further pair of derivatives, 3-oxotetrahydrothiophene with methyl groups at C2 and C4 respectively, was also prepared by reaction of methyl thioglycolate and methyl methacrylate in 94% yield followed by hydrolysis.[98]

Woodward and Eastman reported the acid mediated hydrolysis of these β-keto esters to give the sulfide lactone in good yield (Scheme 6.6).[99]

It would be expected that the conversion of these sulfides to the sulfones would be easy, however a search of the REACCS and Bielstein reaction databases revealed no such examples. This may indicate that no one has reported this reaction, rather than it not working.

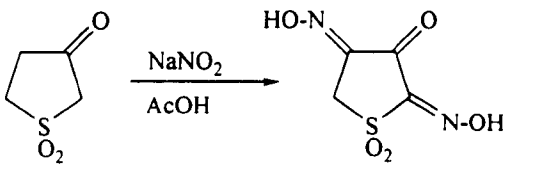
Scheme 6.8



6.1.3 Chemistry of Oxotetrahydrothiophenes *S,S*-dioxides

There have been few papers on the chemistry of this system. Nitrosation of OTTD with sodium nitrite in glacial acetic acid gave the 2,4-hydroxyimino-3-oxo compound (Scheme 6.9).[88]

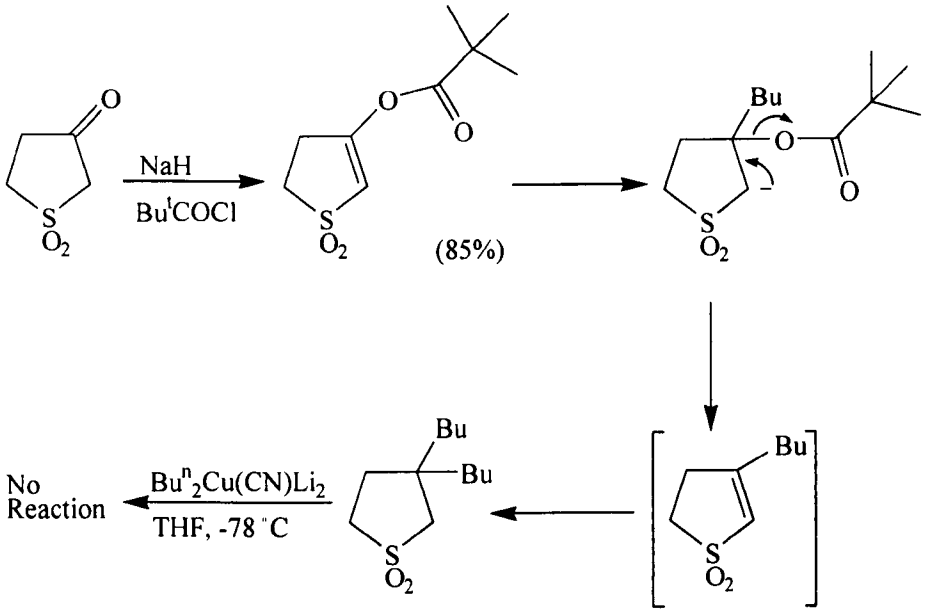
Scheme 6.9



52 53 (62.5%)

Alder and co-workers demonstrated that the ketone (**52**) could be converted to the corresponding enol pivolate (**54**) which could in turn be converted to 3,3-dialkyl systems (Scheme 6.10).[16] An attempt to convert the dialkyltetrahydrothiophene 1,1-dioxides into the cyclobutenes by a Ramberg-Bäcklund reaction failed.

Scheme 6.10

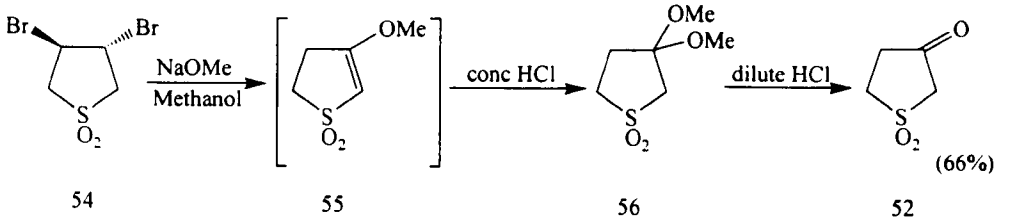


6.2 Preparation of 3-Oxotetrahydrothiophene *S,S*-Dioxide

We were able to prepare 3-oxotetrahydrothiophene largely by the literature procedure reported by Belletire.[88] Although, as found by Alder and co-workers,

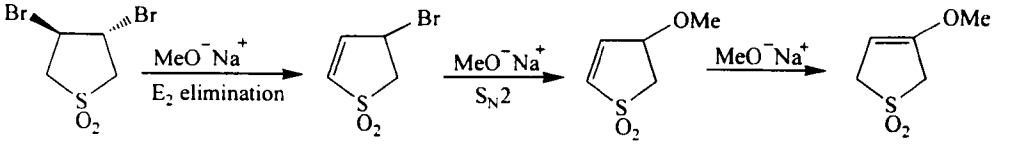
the practical aspects of the procedure were not entirely straightforward, reasonable quantities of material were obtained. Thus, treatment of the commercially available 3,4-dibromotetrahydrothiophene *S,S*-dioxide (**54**) with sodium methoxide in methanol produced the intermediate, 4-methoxy-2,3-dihydrothiophene *S,S*-dioxide (**55**) as confirmed by ^{1}H NMR spectroscopy. In the presence of excess methoxide in methanol, this intermediate undergoes rearrangement *via* a Michael addition to give 3,3-dimethoxytetrahydrothiophene *S,S*-dioxide (**56**). Extraction of this compound into dichloromethane was then followed by acidic hydrolysis and a final drying to give the ketone (**52**) as off-white crystals in 66% yield (Scheme 6.11). The product was readily identifiable by the IR, ^{1}H and ^{13}C NMR spectra. Using ^{1}H NMR spectroscopy, a D_2O shake on the ketone showed the rapid exchange of the two protons on the carbon between the sulfone and carbonyl groups. This indicated the that these protons are very acidic (Scheme 6.12).

Scheme 6.11

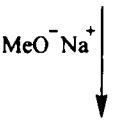


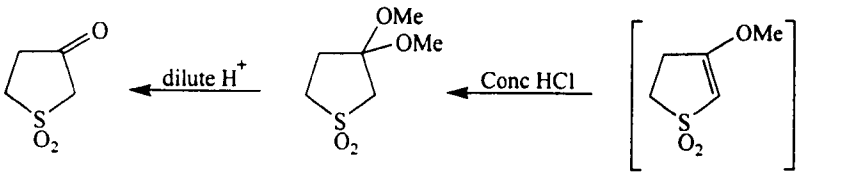
54 55 56 52

Mechanism



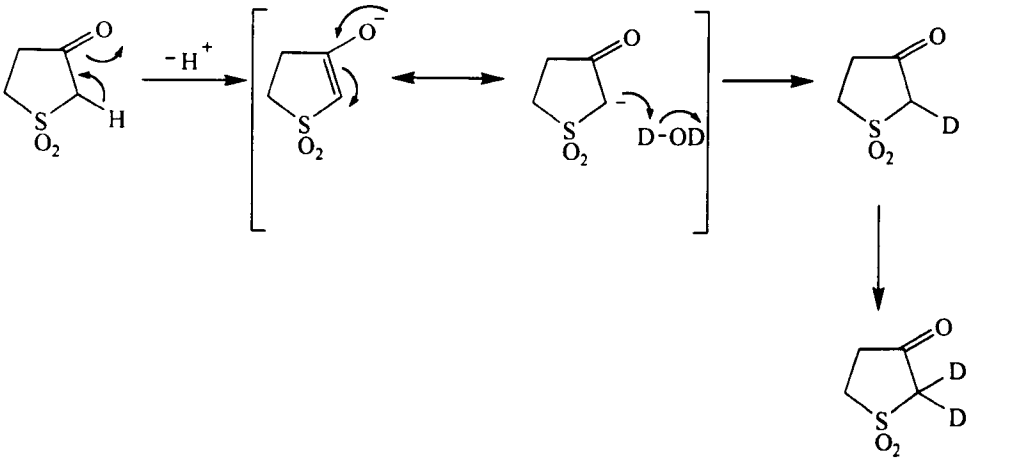
54





52 56 55

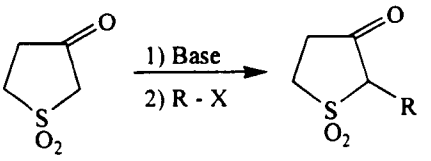
Scheme 6.12



6.3 Alkylation Studies on 3-Oxotetrahydrothiophene *S*,S-Dioxide

Having prepared 3-oxotetrahydrothiophene *S*,*S*-dioxide, our next goal was to alkylate this ketone at the C-2 position by deprotonating at this position with base, then treating the resultant anion with suitable alkylating agents (Scheme 6.13).

Scheme 6.13



52

In an extended series of experiments, the ketone was treated with suitable bases (NaH, K_2CO_3, BuLi) in a range of solvents (THF, acetone) with the addition of an alkylating agent (either allyl bromide or benzyl bromide). However, no satisfactory reaction took place (Table 6.1)

Table 6.1

Base	Solvent	Temp	Result
K_2CO_3	Acetone	Reflux	D
K_2CO_3	Butanone	Reflux	D
K_2CO_3	DMF	RT	D
NaH	1,4-Dioxane	Reflux	D
NaH	THF	Reflux	D
n-BuLi	THF	-78°C	D

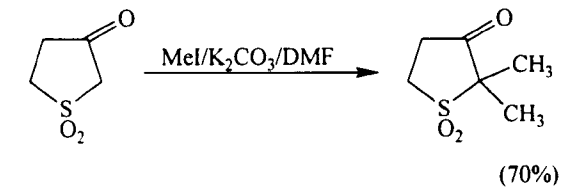
D = decomposition products/polymer

We finally obtained an alkylated product when the ketone (**52**), was treated with the strong alkylating agent, methyl iodide, in the presence of base, (K_2CO_3) using neat DMF as the solvent. However, instead of the hoped for mono-alkylated product, the double alkylated product was obtained (Scheme 6.14). Both the α protons adjacent to the sulfone and carbonyl group had been removed and the resultant anions methylated-presumably in a stepwise fashion (deprotonation-alkylation-deprotonation-alkylation). This double methylation is probably due to the sterically small methyl group. The dimethylated ketone (**57**) was readily identifiable by IR, ^1H and ^{13}C NMR spectroscopy and mass

spectrometry. We were not able to obtain analytical data due to trace contamination of an O-methylated by-product in **57**.

Unfortunately, due to a double rather than mono-alkylation occurring, with both α protons being removed, we would not be able to submit the lactone obtained from this novel compound to the Ramberg-Bäcklund reaction conditions. Hence, oxidation by the Baeyer-Villiger reaction was not investigated.[6] We therefore decided to pursue these alkylation conditions further and attempt alkylation using a sterically larger group in order to prevent double alkylation and induce mono-alkylation. So, (**52**) was treated with potassium carbonate and benzyl bromide in neat DMF. We were very frustrated to then see no alkylation and only decomposition of the system as confirmed by tlc analyses and ^{1}H and ^{13}C NMR spectroscopy.

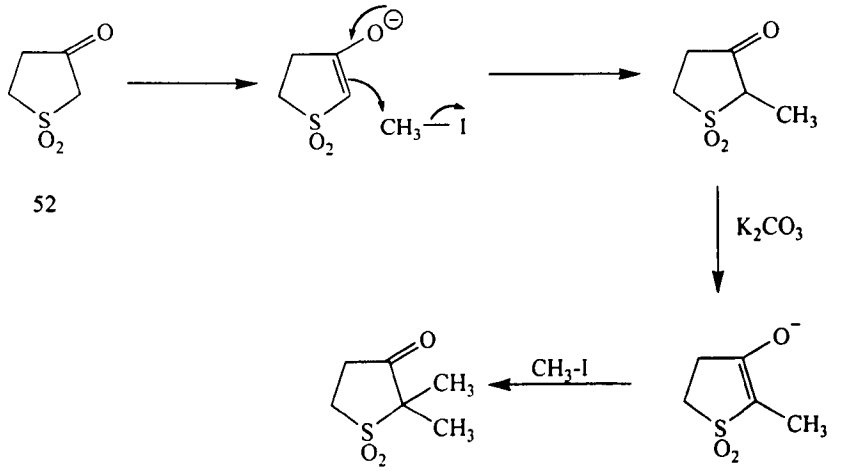
Scheme 6.14



(70%)

52 57

Mechanism



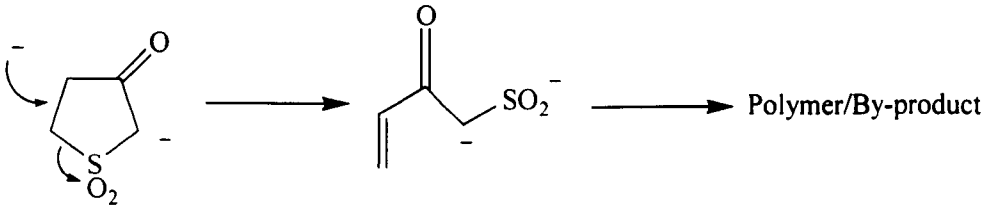
52 57

So, with only partial success with the strongly electrophilic methyl iodide and the fruitless reactions involving the other alkyl halides, we were curious as to Belletire's reports of success in alkylating this system.[88] Despite a comprehensive literature search, we could find no further communication despite reference to new results in his original publication and a mention that these would be subsequently published as a full paper. We therefore decided to write to Belletire

to get clarification of his methods in his reported ketone alkylations. We were upset when he wrote back to say that alkylation does not work after all and that instead, he also observed decomposition. This, to our knowledge, is the first time that the reported results have been retracted, no correction having been published.

We are now in a better position to understand the chemistry of 3-oxotetrahydrothiophene *S,S*-dioxide. From our findings with the ^{1}H NMR D_2O shake, we would assume that the system is very acidic, with exchange occurring easily without base. Due to the acidic nature of these protons, it is likely that the anion is probably very unreactive to alkylation, hence our difficulties in alkylating the ketone at C-2. Under more forcing conditions, we may be generating some dianion, which can then decompose *via* a ring-opening mechanism (Scheme 6.15).

Scheme 6.15



So, with Belletire's revelations about the chemistry, we made the decision to give up this approach and devote the remaining time to adding weight to some of the more interesting chemistry described before.

7 Conclusion

To conclude, the work presented in this thesis involved the exploration of possible routes towards the synthesis of substituted oxathiane and oxathianone *S,S*-dioxide systems. Several routes were examined. Initially two routes were investigated. The first entailed the direct alkylation of the readily available oxathiane *S,S*-dioxide. It was during these attempted alkylations that several novel compounds were synthesised. To further understand the chemistry of the oxathiane system, ring-opening reaction conditions were undertaken yielding these novel analogues. The second route involved the construction of the alkylated cyclic oxathiane *S,S*-dioxide from acyclic precursors.

Subsequently, our studies took us towards the synthesis of the oxathianones and oxathianones *S,S*-dioxide. Two conceivable routes were examined. The first involving the cyclization of suitable derivatives.

Further, we explored the preparation of the oxathianone system by oxidation of open-chain sulfone diols with concomitant cyclization. Again, it was during our work in this area that a novel pathway was synthesised and instead of the desired lactone, several novel dihalo compounds were synthesised.

The final approach to the desired and as yet elusive alkylated oxathianone *S,S*-dioxide was *via* a new synthetic strategy involving the preparation of an oxotetrahydrothiophene *S,S*-dioxide. It was planned to perform a Baeyer-Villiger oxidation in order to produce the corresponding six-membered lactone and hence from there implement Ramberg-Bäcklund reaction conditions. However, we

attempted several routes to alkylate the system. Success came in the double rather than mono-alkylation of the system.

So, although alkylation of the oxathiane and oxathianone systems eluded us, success came to us with the synthesis of several novel compounds and pathways.

8 Experimental

General directions

Column chromatography was performed with Merck 70-230 mesh ASTM silica gel 60 and sand either at ambient pressure or under nitrogen. Thin layer chromatography (tlc) analyses were performed on Merck Kieselgel 60 F_{254} DC Alufolien. Components were visualized by various techniques which included u.v., by exposure to iodine vapor and by use of potassium permanganate dip.

Petroleum ether is 30-40 °C (b.p.) unless otherwise stated.

Solvents and Reagents

The purification techniques of the solvents and reagents used are outlined in Table 1. Sodium hydride was obtained commercially as a 60% by weight dispersion in mineral oil and unless otherwise stated, was used as a dry powder. The reagents described in the text were all obtained from commercial sources and were used as purchased unless otherwise stated.

Table 1

Solvent/Reagent	Purification technique
ACETONITRILE	distilled from calcium hydride
ACETONE (ANALAR)	
DIETHYL MALONATE	
DIETHYL ETHER	dried over sodium wire; or purchased specially dried
ETHYL ACETATE	
METHANOL	
DICHLOROMETHANE	
ETHANOL	
HEXANE	
TOLUENE	dried over sodium wire
THF	dried over sodium wire
VINYL ACETATE	distilled
PYRIDINE	dried over sodium wire
p-TOLUENESULFONYLCHLORIDE	recrystallized
CARBON TETRACHLORIDE	distilled
PETROLEUM ETHER	
HYDROCHLORIC ACID (CONC)	

DMSO	
ACETIC ACID	
BENZYL BROMIDE	
ACETIC ANHYDRIDE	
SODIUM HYDROXIDE (2M)	
SULPHURIC ACID (CONC)	
BROMINE	
BROMOBENZENE	distilled from calcium hydride and stored over 4Å sieves
DME	distilled from calcium hydride and stored over 4Å sieves
DEM	
^{n}-BuLi	
MERCAPTOETHANOL	
POTASSIUM CARBONATE	
TRIPHENYL PHOSPHINE	
PHOSPHORUS PENTOXIDE	stored under nitrogen
POTASSIUM HYDROGEN PERSULFATE (OXONE)	refrigerated
THIOGLYCOLIC ACID	refrigerated
OSMIUM TETROXIDE	stored in freezer

LIPASES	refrigerated
4-PHENYL-3-BUTEN-2-ONE	recrystallized
4Å MOLECULAR SIEVES	dried in oven at 100 °C for 48 hours and stored under nitrogen

Spectroscopy and Microanalysis

^{1}H NMR spectra were recorded on a Bruker WP 80 (80 MHz). Highfield NMR spectra (^{1}H at 250 MHz ^{13}C at 63 MHz were recorded on a Bruker ASPECT 3000 spectrometer by Mr. J. Crowther. All NMR spectra, unless stated otherwise, were recorded in $CDCl_3$ as solutions using tetramethylsilane (TMS) as the internal standard. Chemical shifts (δ_H and δ_C) are quoted in parts per million downfield from tetramethylsilane. ^{1}H NMR spectra are reported in the form δ_H (integration, multiplicity, coupling constant, assignment). ^{13}C NMR spectra are reported in the form δ_C (assignment); assignments for a series of signals of a similar chemical shift and same multiplicity are give together.

Infra-red spectra were recorded on a Perkin Elmer 781 or a FTIR Biorad FTS 40 as neat liquid films, nujol mulls or micro-KBr discs where appropriate.

Low resolution electron impact mass spectra were recorded on a Kratos 'Profile' 4V3 at 70 eV by Mr. W. Dissanayake, as were all high resolution mass spectra.

Elemental analyses of compounds were performed by Mr. S. Boyer. Analytical data are quoted to within ±0.30%.

8.1 Alkylation studies of 1,4-oxathiane *S,S*-dioxide

Attempted alkylation of 1,4-oxathiane *S,S*-dioxide

1,4-Oxathiane *S,S*-dioxide (0.681 g, 0.005 mol) was stirred in tetrahydrofuran (10 cm^3) under nitrogen and cooled to -78 °C. ^{n}-butyl lithium (60% in hexanes) (3.07 cm^3, 0.0055 mol) was added dropwise and the reaction mixture was left to stir under nitrogen for 35 minutes at -78 °C. The yellow mixture was then quenched with saturated aqueous ammonium chloride (5 cm^3) at -78 °C. Tetrahydrofuran was removed under reduced pressure and the aqueous layer was washed with petroleum ether (40 - 60 °C) (2 x 20 cm^3). The aqueous layer was then extracted with dichloromethane (8 x 25 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to give recovered starting material as white crystals (0.593 g, 87%) as confirmed by ^{1}H NMR spectroscopy.

The above procedure was repeated twice but with the reaction mixture being quenched at higher temperatures. Quenching at either room temperature or -30 °C gave decomposition of product as shown by tlc analysis (ethyl acetate) and ^{1}H NMR spectroscopy.

3,3,5,5-Tetradeutero-1,4-oxathiane 1,1-dioxide (8)

Modified literature procedure[35]

Sodium hydride (0.024 g, 0.040 g of a 60% dispersion in oil, 0.001 mol) was carefully added to deuterium oxide (10 cm^3, *ca.* 0.5 mol). 1,4-Oxathiane-1,1-dioxide (0.681 g, 0.005 mol) was added and the grey mixture was left to stir at room temperature under nitrogen for 2 days when ^1H NMR spectroscopy indicated that the reaction had proceeded to completion. The aqueous layer was washed with hexane (5 cm^3), then continuously extracted using dichloromethane for 2 days to give 3,3,5,5-tetradeutero-1,4-oxathiane 1,1-dioxide as white crystals (0.51 g, 75%), m.p. 133 - 134°C.

δ_H 4.10 (4H, s, CH_2-O-CH_2); δ_C 66.0 (CH_2-O-CH_2), 51.9 (D_2-S-D_2)

The relative amount of tetra-deuterated to tri-deuterated product was determined to be 90.7 : 9.3.

Attempted proton exchange of 3,3,5,5-tetradeutero-1,4-Oxathiane 1,1-dioxide

Saturated ammonium chloride solution (10 cm^3) was added to 3,3,5,5-tetradeutero-1,4-oxathiane 1,1-dioxide (0.0706 g, 0.5 mmol) at room temperature. The clear, colourless solution was left to stir at room temperature under nitrogen for 24 h. The aqueous solution was then extracted using dichloromethane

(8 x 10 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure giving recovered starting material as white crystals (0.059 g, 84%).

^1H NMR spectroscopic analysis indicated that less than 1% D-H exchange had occurred.

Attempted monodedeuteration-protonation of 3,3,5,5-tetradeutero-1,4-oxathiane 1,1-dioxide

3,3,5,5-Tetradeutero-1,4-oxathiane 1,1-dioxide (0.280 g, 0.002 mol) was stirred in tetrahydrofuran (5 cm^3) under nitrogen and cooled to -78 °C. ^{n}-butyl lithium (1.22 cm^3, 0.0022 mol) was added dropwise and the yellow reaction mixture was left stirring at -78 °C for 35 minutes. The mixture was then quenched with saturated aqueous ammonium chloride (5 cm^3) at -78 °C, tetrahydrofuran was removed under reduced pressure and the remaining aqueous layer was washed with petroleum ether (2 x 20 cm^3). The aqueous layer was then extracted with dichloromethane (10 x 20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure.

Column chromatography (ethyl acetate) yielded recovered starting material as white crystals (0.215 g, 77%) as confirmed by ^1H NMR spectroscopy which showed no appreciable difference in the level of deuteration.

Attempted hydrogenation of 1,4-oxathiane *S,S*-dioxide

Modified literature procedure[71]

A mixture of 5% palladium on carbon (20 mg), sodium hydroxide (0.040 g, 0.001 mol) and 1,4-oxathiane 1,1-dioxide (0.681 g, 0.008 mol) in water (10 cm^3) was left to stir in a hydrogen atmosphere at room temperature for 5 days. The black mixture was then filtered, acidified using concentrated hydrochloric acid (2M, 15 cm^3) and extracted using dichloromethane (10 x 20 cm^3). The combined organic layers were then dried ($MgSO_4$) and concentrated under reduced pressure to give recovered starting material as white crystals (0.566 g, 84%).

Ring-opening/ethanol addition reactions of 1,4-oxathiane *S,S*-dioxide (12)

Diethyl ether (20 cm^3) was added to sodium hydride (0.48 g, 0.80 g of 60% dispersion in mineral oil, 0.0200 mol) and this was decanted off to remove the mineral oil. Ethanol (20 cm^3) was added very slowly to the sodium hydride at 0°C. An exothermic reaction occurred. Diethyl malonate (0.961 g, 0.006 mol) and then 1,4-oxathiane *S,S*-dioxide (0.681 g, 0.005 mol) were added and the reaction mixture was left to reflux under nitrogen for 4 days when tlc analysis (ethyl acetate) indicated the absence of starting material. The cloudy white

mixture was quenched with saturated ammonium chloride (20 cm^3) and extracted with dichloromethane (8 x 25 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil (0.96 g).

The oil was purified directly by column chromatography (dichloromethane) to give *di(2-ethoxyethyl)sulfone* as a pale yellow mobile oil (0.42 g, 40%).

δ_H 3.86 (4H, t, J5.7, 2 x O-C$\underline{H}_2$-CH_2), 3.54 (4H, q, J6.9, 2 x C$\underline{H}_2CH_3$)

3.39 (4H, t, J5.7, 2 x S-C$\underline{H}_2$-CH_2), 1.21 (6H, t, J6.9, 2 x C$\underline{H}_3$-CH_2);

δ_C 66.7 (CH_2-$\underline{C}H_2$-O), 63.9 (CH_3-$\underline{C}$H2-O), 54.9 (CH_2-S), 14.9 (CH_3);

m/z 211 ($[M + H]^+$, 11.4%), 195 (M - CH_3, 1.9%), 165 (M - OCH_2CH_3, 16.4%),

151 (M - $CH_2OCH_2CH_3$, 4.4%), 137 (M - $CH_2CH_2OCH_2CH_3$, 28.3%),

59 ($CH_2OCH_2CH_3$, 42.8%), 45 (OCH_2CH_3, 100%);

υ_{max}(film/cm^{-1}) 2950 (-CH_3), 2880 (=CH_2), 1360 (=SO_2), 1120 (=SO_2),

1050 (C-O);

Found C, 45.68; H, 8.65. $C_8H_{18}O_4S$ requires C, 45.69; H, 8.63%.

The above procedure was repeated omitting the diethyl malonate. On refluxing for 12 h, the reaction mixture turned a dark brown colour. The mixture was quenched with saturated ammonium chloride (25 cm^3), extracted with dichloromethane (10 x 25 cm^3), dried ($MgSO_4$), filtered twice and concentrated under reduced pressure. ^1H NMR spectroscopy indicated that the above named product was obtained as a yellow oil (0.43 g, 41%).

Further ring-opening/alcohol addition studies of 1,4-oxathiane *S,S*-dioxide

General procedure

Diethyl ether (5 cm^3) was added to sodium hydride (0.80 g, 0.48 g of a 60% dispersion in mineral oil, 0.02 mol) and the ether was decanted off to remove the mineral oil. The alcohol (in the amount indicated below) was then added to the sodium hydride at 0°C. A highly exothermic reaction ensued. 1,4-Oxathiane *S,S*-dioxide (0.681 g, 0.005 mol) was added in small portions and the reaction mixture was left to reflux until the reaction had gone to completion. The resultant mixture was subsequently quenched with saturated ammonium chloride (40 cm^3) and the aqueous layer was extracted using dichloromethane (10 x 25 cm^3). The combined organic layers dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified by column chromatography.

(a) Di(2-methoxyethyl)sulfone (14)

The above procedure was carried out using methanol (25 cm^3) as the solvent. The reaction was left to reflux for 2 days when tlc analysis (ethyl acetate) indicated the absence of starting material. Column chromatography yielded *di(2-methoxyethyl)sulfone* as a colourless oil (0.81 g, 89%).

δ_H 3.81 (4H, t, J5.7, 2 x S-CH_2-$C\underline{H}_2$-O), 3.38 (6H, s, 2 x CH_3),

3.33 (4H, t, J5.7, 2 x O-CH_2.$C\underline{H}_2$-S); δ_C 66.0 (2 x CH_2-O), 58.9 (2 x CH_3),

54.8 (2 x CH_2-S);

m/z 182 (M, 2.8%), 151 (M - OCH_3, 1.7%), 59 ($CH_2CH_2OCH_3$, 91.8%),

45 (CH_2OCH_3, 73.8%), 31 (OCH_3, 71.7%); υ_{max}(film/cm^{-1}) 2990 (-CH_3),

2818 (CH_2), 1316 (SO_2);

Found C, 39.52; H, 7.77; S, 17.8%. $C_6H_{14}O_4S$ requires C, 39.54; H, 7.74; S, 17.6%.

(b) Di(2-butyloxyethyl)sulfone (15)

1-Butanol (40 cm^3) was the solvent used on this occasion. The procedure was repeated and the reaction mixture was left to stir at 70 °C for 2 days when tlc analysis (ethyl acetate) indicated the absence of starting material.

Column chromatography (4:1 petroleum ether:ethyl acetate) yielded the *di(2-butyloxyethyl)sulfone* as a yellow mobile oil (0.914 g, 69%).

δ_H 3.84 (4H, t, J5.7, 2 x S-CH_2-C$\underline{H}_2$-O), 3.47 (4H, t, J6.4, 2 x OC$\underline{H}_2$-Pr),

3.34 (4H, t, J5.7, 2 x O-CH_2-C$\underline{H}_2$-S), 1.59 (4H, m, 2 x CH_3CH_2-C$\underline{H}_2$-CH_2), 1.38

(4H, m, 2 x CH_3-C$\underline{H}_2$-CH_2), 0.95 (6H, t, J7.3, 2 x C$\underline{H}_3$-CH_2);

δ_C 71.1 and 64.2 (4 x O-CH_2), 54.8 (2 x S-CH_2), 31.5 (2 x CH_3CH_2-$\underline{C}H_2$),

19.2 (2 x CH_3-$\underline{C}H_2$), 13.8 (2 x CH_3);

m/z 266 (M, 2.1%), 223 (M - $CH_2CH_2CH_3$, 9.9%),

193 (M - $OCH_2CH_2CH_2CH_3$, 5.6%), 73 ($CH_3(CH_2)_3O$, 43.3%),

43 ($CH_3CH_2H_2$, 100%);

υ_{max}(film/cm^{-1}) 3220 (-CH_3), 2990 (CH_2), 1160 (SO_2);

Found C, 54.29; H, 9.86%. $C_{12}H_{26}O_4S$ requires C, 54.10; H, 9.84%.

(c) Di(2-pentyloxyethyl)sulfone (16)

The above procedure was repeated using pentan-1-ol (40 cm^3) and the reaction mixture was left to stir at 70 °C for 2 days when tlc analysis (ethyl acetate) indicated the absence of starting material.

Column chromatography (1:1 petroleum ether:ethyl acetate) yielded *di(2-pentyloxyethyl)sulfone* as a dark yellow oil (0.892 g, 61%).

δ_H 3.84 (4H, t, J5.7, 2 x O-C<u>H</u>$_2$-CH_2-S), 3.45 (4H, t, J6.4, 2 x O-C<u>H</u>$_2$-Bu)

3.33 (4H, t, J5.7, O-C<u>H</u>$_2$-CH_2-S), 0.93 (18H, m, CH_3-$CH_2CH_2CH_2$);

δ_C 71.4 and 64.2 (O-CH_2), 62.6 (OCH_2-<u>C</u>H_2-Pr), 54.8 (S-CH_2), 29.1 (CH_2), 28.2 (CH_2), 13.9 (CH_3);

m/z 294 (M, 6.8%), 237 ($[M + H]^+$ - $CH_3(CH_2)_4$, 20.5%),

207 (M - $CH_3(CH_2)_4O$, 9.2%),181 (M - 2 x $CH_3(CH_2)_4$, 10.2%),

43 ($CH_3CH_2CH_2$,100%), 31 (CH_3O, 68.3%);

υ_{max}(film/cm^{-1}) 3420 (-CH_3), 1125 (SO_2);

Found C, 57.28; H, 10.27%. $C_{14}H_{39}O_4S$ requires C, 57.11; H, 10.27%.

(d) **Di[2-(1'-methylethoxy)ethyl]sulfone (17)**

The above procedure was carried out and the alcohol used was propan-2-ol (35 cm^3). The reaction mixture was left to reflux for 3 days when tlc analysis (ethyl acetate) indicated the absence of starting material.

Column chromatography (3:1 ethyl acetate:dichloromethane) yielded *di[2-(1'-methylethoxy)ethyl]sulfone* as a pale yellow oil (0.68 g, 57%).

δ_H 3.85 (4H, t, J5.7, 2 x CH_2-C<u>H</u>$_2$-O), 3.65 (1H, septet, J6.2, C<u>H</u>-$(CH_3)_2$), 3.33 (4H, t, J5.7, 2 x CH_2-C<u>H</u>$_2$-S), 1.17 (12H, d, J6.2, 2 x (C<u>H</u>$_3$)$_2$-CH);

δ_C 72.3 (2 x CH),61.6 (2 x CH_2-O), 55.2 (2 x CH_2-S), 21.9 (4 x CH_3);

m/z 239 ($[M + H]^+$, 12.7%), 223 (M - CH_3, 23.3%), 179 (M - $OCH(CH_3)_2$, 24.5%), 165 (M - $CH_2OCH(CH_3)_2$, 8.8%),59 ($OCH(CH_3)_2$, 71.0%), 43 ($(CH_3)_2CH$, 100%);

υ_{max}(film/cm^{-1}) 2975 (-CH_3), 2877 (=CH_2), 1256 (C-O), 1120 (=SO_2);

Found C, 50.12; H, 9.27; S, 13.60%. $C_{10}H_{22}O_4S$ requires C, 50.39; H, 9.30; S, 13.45%.

(e) **Reaction of 1,4-Oxathiane *S,S*-dioxide with t-butanol**

(i) ^{t}-Butanol (35 cm^3) was used with the above procedure. The reaction mixture was left to reflux for 3 days when tlc analysis (ethyl acetate) indicated the absence of starting material.

Column chromatography (ethyl acetate) and (4:1 diethyl ether:ethyl acetate) gave an intractable mixture of products.

(ii) The above procedure was repeated with t-butanol in the presence of a co-solvent as THF (35 cm^3). However, again only an intractable mixture of products was obtained. This mixture could not be resolved using mass spectrometry or ^1H and ^{13}C NMR spectroscopy.

(f) Reaction of 1,4-Oxathiane *S,S*-dioxide with neopentyl alcohol

Neopentyl alcohol (0.97 g, 0.011 mol) was the solvent used when the above general procedure was carried out. The reaction mixture was left to reflux for 6 days when tlc analysis (ethyl acetate) indicated only trace amounts of starting material.

Column chromatography (3:1 ethyl acetate:petroleum ether) yielded only a gross mixture of components not identifiable by mass spectrometry or ^1H and ^{13}C NMR spectrometry.

The above procedure was repeated using a higher molar equivalence of the neopentyl alcohol (4.41 g, 0.05 mol). Column chromatography yielded only an intractable mixture of products as confirmed by ^1H NMR spectroscopy.

(g) Reaction of 1,4-Oxathiane *S,S*-dioxide with ethylene glycol

The above procedure was repeated using ethylene glycol (40 cm^3). The reaction mixture was left to stir at 70 °C for 3 days when tlc analysis (ethyl acetate) indicated only trace amounts of starting material.

Column chromatography (50% dichloromethane-ethyl acetate) yielded recovered starting material (0.57 g, 84%) and another component (0.27 g) which was not identifiable by ^1H, ^{13}C and mass spectrometry.

The above procedure was again repeated using a co-solvent; ethylene glycol (30 cm^3) and THF (30 cm^3) and the reaction mixture was left to reflux for 3 days. Column chromatography (3:1 ethyl acetate:petroleum ether) yielded only an intractable mixture of products unidentifiable by ^1H NMR spectroscopy.

(h) Di[2-(2'-methoxyethoxy)ethyl]sulfone (18)

The above procedure was repeated using 2-methoxyethanol (35 cm^3) and the reaction mixture was left to reflux for 4 days when tlc analysis (ethyl acetate) indicated the absence of starting material. *Di[2-(2'-methoxyethoxy)ethyl]sulfone* was produced as a brown oil which did not require any further purification.

δ_H 3.93 (4H, t, J5.7, 2 x CH_3O-C$\underline{H}_2$-CH_2-O),

3.66 (4H, m, 2 x O-C$\underline{H}_2$-CH_2OCH_3), 3.53 (4H, m, 2 x S-C$\underline{H}_2$-CH_2-O), 3.36 (10H, m, 2 x CH_2-C$\underline{H}_2$-S + 2 x CH_3);

δ_C 71.6, 70.4 and 64.6 (6 x $\underline{C}H_2$-O), 58.9 (CH_3), 54.8 (2 x CH_2-S);

m/z 271 ($[M + H]^+$, 20.9%), 270 (M, 2.1%), 239 (M - OCH_3, 4.3%),

225 (M - CH_2OCH_3, 39.2%), 211 (M - $CH_2CH_2OCH_3$, 29.0%),

195 (M - $OCH_2CH_2OCH_3$, 36.1%), 181 (M - $CH_2OCH_2CH_2OCH_3$, 29.0%),

59 ($CH_3OCH_2CH_2$, 100%), 45 (CH_3OCH_2, 76.1%), 32 (CH_3OH, 55.7%);

υ_{max}(film/cm^{-1}) 2995 (-CH_3), 2825 (=CH_2), 1125 (=SO_2);

Found C, 44.59; H, 8.11%. $C_{10}H_{22}O_6S$ requires C, 44.43; H, 8.20%.

8.2 Thiol/epoxide reaction group

4-Benzyloxymethyl-2,2-dimethyl-1,3-dioxolane (21)

Modified literature procedure[76]

2,2-Dimethyl-1,3-dioxolane-4-methanol (1.5 g, 0.0113 mol) was stirred in dry tetrahydrofuran (90 cm^3) at 0 °C under nitrogen. Sodium hydride (0.298 g, 0.496 g of a 60% dispersion in oil, 0.0124 mol) was added in small portions and the solution was warmed to room temperature and left stirring for 15 minutes before cooling to 0 °C. Benzyl bromide (2.052 g, 0.0124 mol) was added slowly dropwise. The reaction mixture was warmed to room temperature and left stirring for 14 h when tlc analysis (1:1 dichloromethane/petroleum ether) indicated that the reaction had gone to completion. The mixture was then partitioned between water (25 cm^3) and diethyl ether (25 cm^3) and the aqueous layer was extracted with diethyl ether (3 x 25 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound as an amber mobile oil (2.47 g, 98%), which contained trace amounts (<5%) of benzyl bromide, as determined by ^1H NMR spectroscopy.

^1H NMR and IR spectroscopy showed properties consistent with those reported in the literature.[76]

δ_H (80 MHz) 7.50 (5H, s, Ph), 5.99 (2H, s, Ph-C$\underline{H_2}$-O),

3.74 (2H, d, J4.2, O-C$\underline{H_2}$-CH,), 3.53 (1H, dd, J5.0, 9.3,C$\underline{H}$-CH_2,),

1.80 (3H, s, CH_3-C), 1.75 (3H, s, CH_3-C);

υ_{max}(film/cm^{-1}) 2937 (CH_3), 2869 (=CH_2), 1498 (Ph), 1376 (=$C(CH_3)_2$).

Preparation of 1-benzyloxypropane-2,3-diol (22)

Modified literature procedure[76]

4-Benzyloxymethyl-2,2-dimethyl-1,3-dioxolane (5.10 g, 0.023 mol) was dissolved in a mixture of methanol (215 cm^3) and concentrated hydrochloric acid (4.85 cm^3). The solution was left to stir at room temperature under nitrogen for 72 h when tlc analysis (3:1 ethyl acetate/petroleum ether) indicated the absence of starting material. The mixture was then concentrated under reduced pressure to give the title compound as a light brown oil (3.21 g, 77%) of sufficient purity for use in the next reaction.

^{1}H NMR and IR spectroscopy showed properties consistent with those reported in the literature.

δ_H 7.35 (5H, s, Ph), 4.55 (2H, s, Ph-CH_2-O),

3.92-3.86 (1H, m, CH_2-C<u>H</u>-CH_2OH), 3.68-3.56 (6H, m, remainder);

δ_C 137.6 (C4), 128.5 (C3 + C5), 127.8 (C2 + C6), 127.9 (C1),

73.6 (Ph-<u>C</u>H_2O), 71.7 (CH-OH), 70.6 (CH_2-OH), 64.0 (CH_2);

υ_{max} (film/cm^{-1}) 3880 (O-H), 2970 (=CH_2), 1599 (Ph).

Preparation of 1-(p-toluenesulfonyloxy)-3-benzyloxypropan-2-ol (23)

Modified literature procedure[72]

Pyridine (0.82 g, 0.010 ml) was added to a stirred and cooled (0 °C) solution of 1-benzyloxypropan-2,3-diol (0.16 g, 0.0097 mol) in dichloromethane (10 cm^3) under nitrogen. *p*-Toluenesulfonyl chloride (1.998 g, 0.010 mol) was added in small portions and the reaction was stirred at 0 °C for 6 h then a further 20 h at room temperature. Dichloromethane (30 cm^3) was added to the reaction mixture and the organic layer was extracted with water (2 x 10 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure.

Column chromatography (2:1 diethyl ether/petroleum ether) yielded the title compound as a pale yellow oil (1.96 g, 61%).

^1H NMR and IR spectroscopy showed spectroscopic properties consistent with those reported in the literature.

δ_H (80 MHz) 7.84 (4H, m, ArH), 7.34 (5H, s, Ph),

4.56 (2H, s, Ph-CH_2-O), 4.05-3.50 (5H, m, remainder),

2.16 (3H, s, Ar-CH_3);

υ_{max} (film/cm^{-1}) 3440 (O-H), 2980 (=CH_2), 1599 (Ph), 1360 (=SO_2).

Preparation of 1-benzyloxy-2,3-epoxypropane (24)

Modified literature procedure[72]

1-(*p*-Toluenesulfonyloxy)-3-benzyloxypropan-2-ol (1.24 g, 0.0037 mol) was dissolved in dry tetrahydrofuran (360.55 g, 5 mol) and cooled to 0 °C under nitrogen. Sodium hydride (0.336 g, 0.456 g of a 60% dispersion in mineral oil, 0.0114 mol) was added in small portions. The reaction mixture was left to stir for 12 days when tlc analysis (50% dichloromethane/petroleum ether) indicated the absence of starting material. The mixture was then concentrated to half its volume under reduced pressure, partitioned between diethyl ether (190 cm^3) and water (135 cm^3), and extracted with diethyl ether (2 x 190 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure.

Column chromatography (50% dichloromethane/petroleum ether) yielded the title compound as a yellow mobile oil (0.32 g, 54%).

δ_H (80 MHz) 7.40 (5H, s, Ph), 4.69 (2H, s, Ph-CH_2-O),

3.72 (2H, d, J5.6, O-C$\underline{H_2}$-CH,), 3.32-2.59 (3H, m, remainder);

υ_{max}(film/cm^{-1}) 3040 (C-H stretching), 2982 (=CH_2), 1590 (Ph),

1248 (CH_2-O-CH).

Preparation of 2,6-dihydroxy-1-benzyloxy-4-thiahexane (26)

Mercaptoethanol (0.241 g, 0.00308 mol) was stirred in dry tetrahydrofuran (22 cm^3) at 0 °C and sodium hydride (0.074 g, 0.123 g of a 60% dispersion in oil, 0.00308 mol) was added slowly. The temperature of the reaction mixture was allowed to rise to room temperature. The mixture was then cooled to 0 °C and 1-benzyloxy-2,3-epoxypropane (0.46 g, 0.0028 mol) in tetrahydrofuran (5 cm^3) was added. The mixture was stirred under nitrogen at room temperature for 9 days, then quenched using saturated aqueous ammonium chloride (25 cm^3). The mixture was extracted with ethyl acetate (4 x 10 cm^3) and the extracts were dried ($MgSO_4$) and concentrated under reduced pressure.

Column chromatography (ethyl acetate) yielded recovered starting material (0.07 g, 15%) and the title compound as a colourless oil (0.50 g, 77%).

δ_H 7.36 (5H, s, Ph), 4.55 (2H, s, Ph-CH_2-O),

3.92 (1H, t, J5.7, HO-C<u>H</u>-CH_2), 3.54-3.50 (2H, m, O-C<u>H_2</u>-CHOH),

2.90 (2H, t, J5.7, HO-C<u>H_2</u>-CH_2,), 2.78-2.66 (4H, m, 2 x CH_2-S),

2.51 (2H, br-s, 2 x OH); δ_C 137.7 (C^1), 128.5 (C^2 + C^6),

128.0 (C4), 127.8 (C3 + C5), 72.9 (<u>C</u>H_2-CH), 73.5 (Ph-CH_2O),

69.9 (CH), 41.3 (CH_2OH), 36.01 (CH_2S), 35.6 (CH_2S);

υ_{max}(film/cm^{-1}) 3795 (O-H), 2981 (=CH_2), 2885 (C-H), 1520 (Ph).

Preparation of 2,6-dihydroxy-1-phenoxy-4-thiahexane (27)

Method A (potassium carbonate/acetone)

2-Mercaptoethanol (6.88 g, 0.088 mol) was stirred under nitrogen at room temperature with 1,2-epoxy-3-phenoxypropane (12.00 g, 0.08 ml) in acetone (200 cm^3). Potassium carbonate (56.43 g, 0.408 mol) was added and the reaction mixture was refluxed for 18 days. The mixture was filtered, water (360 cm^3) was added and the solution was extracted with ethyl acetate (2 x 100 cm^3). The combined organic layers were dried ($MgSO_4$) to give an amber oil (18.61 g).

Column chromatography (40:60 ethyl acetate/ petroleum ether) yielded *2,6-dihydroxy-1-phenoxy-4-thiahexane* as a pale brown oil (8.53 g, 47%), with spectroscopic properties consistent with those reported below.

Method B (potassium carbonate/THF)

Mercaptoethanol (0.284 g, 3.63 mmol) was stirred in THF (dry) (32 cm^3) at 0 °C. Potassium carbonate (0.50 g, 3.63 mmol) was added and the reaction temperature allowed to rise to room temperature. 1,2-Epoxy-3-phenoxypropane (0.50 g, 3.3 mmol) in THF (5 cm^3) was added. The mixture was stirred at 0 °C under nitrogen for 1 h and then at room temperature for 3 days when tlc analysis (ethyl acetate) indicated that the reaction had not yet reached completion.

Therefore, after addition of THF (20 cm^3), the mixture was refluxed for a further 12 days. The mixture was then quenched with saturated aqueous ammonium chloride (30 cm^3) and ethyl acetate (30 cm^3) and extracted using further ethyl acetate (3 x 25 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil (0.73 g).

^1H NMR spectroscopy indicated that both starting material and *2,6-dihydroxy-1-phenoxy-4-thiahexane* were present in a ratio of 56:44.

Method C - modified literature procedure[25] (sodium hydroxide/ aqueous ethanol - preferred procedure)

Mercaptoethanol (6.25 g, 0.08 mol) was added dropwise to a stirred mixture of 1,2-epoxy-3-phenoxypropane (12.80 g, 0.08 mol) and 30% w/v aqueous sodium hydroxide (10 cm^3) stirred in an ice bath. Ethanol (20 cm^3) was added to obtain a single phase mixture and the reaction was left to stir under nitrogen at room temperature for 14 days. Water (40 cm^3) and ethyl acetate (40 cm^3) were added and the mixture was extracted with ethyl acetate (4 x 40 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow oil (18.78 g).

Column chromatography yielded *2,6-dihydroxy-1-phenoxy-4-thiahexane* (17.7 g, 97%) as a pale yellow oil;

δ_H 7.35-7.25 (5H, m, Ph), 4.49-4.12 (1H, m, HO-C<u>H</u>-CH_2),

4.03 (2H, d, J5.3, PhO-C$\underline{H}_2$-CH), 3.79 (2H, t, J5.7, HO-C$\underline{H}_2$-CH_2),

2.93-2.79 (6H, m, remainder); δ_C 158.3 (C1), 129.6 (C2 + C6),

121.3 (C4), 114.6 (C3 + C5), 70.3 ($\underline{C}H_2$-CHOH), 70.2 (CH_2OH),

69.4 (CH-OH), 36.0 (CH_2-S), 35.6 (CH_2-S);

m/z 228 (M, 46.7%), 210 (M - H_2O, 29.9%), 135 (M - $PhOCH_3$, 78.6%)

91 ($CH_2SCH_2CH_2OH$, 39.9%), 77 ($S(CH_2)_2OH$, 90.7%),

45 (CH_2CH_2OH, 100%), 31 (CH_2OH, 77.5%);

υ_{max}(film/cm^{-1}) 3320 (O-H), 2982 (=CH_2), 1599 (Ph), 699 (C-S). Found C, 57.47;

H 6.67. $C_{11}H_{16}O_3S$ requires C, 57.87; H 7.07%;

and 1-acetoxy-2-hydroxy-6-phenoxy-4-thiahexane (0.48 g, 2.2%).

δ_H 7.31-7.22 (2H, m, Ph), 6.99-6.89 (3H, m, Ph),

4.25 (2H, t, J6.7, PhO-CH_2), 4.20-4.10 (2H, m, CH_2-O),

4.08-4.00 (2H, m, C$\underline{H}$-OH, OH), 2.95-2.75 (4H, m, 2 x CH_2-S),

2.07 (3H, s, CH_3); δ_C 171.0 (C=O), 158.5 (C1), 129.6 (C2 + C6),

121.4 (C4), 114.7 (C3 + C5), 69.2 (PhO-CH_2), 67.3 (CH-OH),

63.5 (CH_2-O), 36.5 (CH_2-S), 36.1 (CH_2-S); m/z 270 (M, 8.5%),

210 (M - CH_3CO_2H, 30.2%), 196 (M - $CH_3CO_2CH_3$, 7.3%),

43 (CH_3CO, 100%);

υ_{max}(film/cm^{-1}) 3440 (O-H), 2927 (CH_2), 1738 (C=O), 1600 (Ph), 693 (C-S);

Found C, 57.81; H 6.72. $C_{13}H_{18}O_4S$ requires C, 57.76; H 6.71%.

Attempted direct cyclisation of 2,6-dihydroxy-1-phenoxy-4-thiahexane

Method A (Dean and Stark)

2,6-Dihydroxy-1-phenoxy-4-thiahexane (0.23 g, 1 mmol) and p-toluenesulfonic acid (0.0190 g, 0.1 mmol) were refluxed in toluene (50 cm^3) in a flask equipped with a Dean and Stark apparatus for 24 h. Aqueous sodium bicarbonate (10 cm^3) was added, and the reaction mixture was extracted with dichloromethane(3 x 10 cm^3), the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure giving only recovered starting material (0.16 g, 70%) as confirmed by ^1H NMR and IR spectroscopy.

Method B (triphenylphosphine/potassium carbonate) - Literature general procedure[77-79]

Triphenylphosphine (0.79 g, 3 mmol) was added to 2,6-dihydroxy-1-phenoxy-4-thiahexane (0.23 g, 1 mmol) in carbon tetrachloride (9 cm^3). Acetonitrile (3 cm^3) and potassium carbonate (0.14 g, 1 mmol) were added and the reaction mixture was left to reflux under nitrogen for 24 h. The mixture was then filtered, quenched with saturated aqueous ammonium chloride (10 cm^3) and

extracted with dichloromethane (3 x 10 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give an amber oil. Column chromatography (diethyl ether) yielded *2,6-dichloro-1-phenoxy-4-thiahexane* as a pale yellow oil (0.15 g, 57%).

δ_H 7.35-7.25 (2H, m, Ph), 7.00-6.95 (3H, m, Ph),

4.25 (2H, t, J6.7, Cl-C$\underline{H_2}$-CH_2), 4.14-4.11 (1H, m, CH_2-C$\underline{H}$-Cl),

4.10-4.02 (2H, m, PhO-C$\underline{H_2}$-CHCl), 2.90-2.80 (4H, m, 2 x CH_2-S);

δ_C 158.5 (C1), 129.8 (C2 + C6), 121.6 (C4), 114.9 (C3 + C5),

47.3 (CH-Cl), 44.9 (PhO-CH_2), 43.5 (CH_2-Cl), 35.4 (CH_2-S),

34.3 (CH_2-S);

m/z 268,266,264 (M, 0.5,5.1,2.6%),

175,173,171 (M - PhO, 9.6,37.3,100%), 35 (Cl, 50.1%)

υ_{max}(film/cm^{-1}) 2929 (=CH_2), 1589 (Ph), 755 (C-Cl), 692 (C-S)

Found C, 50.10; H, 14.10; $C_{11}H_{14}OSCl_2$ requires C, 50.04; H, 14.11%.

Preparation of 6-chloro-2-hydroxy-1-phenoxy-4-thiahexane (30)

Modified literature procedure[78]

Triphenylphosphine (4.96 g, 19 mmol) was added to a stirred mixture of 2,6-dihydroxy-1-phenoxy-4-thiahexane (2.00 g, 9 mmol) in carbon tetrachloride (30 cm^3). Potassium carbonate (1.40 g, 9.9 mmol) was then added and the

reaction was refluxed under nitrogen for 9 days. Aqueous ammonium chloride ($20\ cm^3$) was then added and the mixture was extracted with dichloromethane ($4 \times 50\ cm^3$). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give a dark brown oil.

Repeated column chromatography (30% ethyl acetate/petroleum ether) yielded *6-chloro-2-hydroxy-1-phenoxy-4-thiahexane* as a light brown oil (0.89 g, 41%).

δ_H 7.35-7.25 (2H, m, Ph), 7.00-6.90 (3H, m, Ph),

4.17-4.10 (1H, m, PhO-CH_2-C<u>H</u>-OH),

4.05-4.03 (2H, m, PhO-C<u>H</u>$_2$-CH-OH), 3.67 (2H, t, J.7, Cl-C<u>H</u>$_2$-CH_2),

2.97-2.77 (4H, m, 2 x CH_2-S), 2.70 (1H, br-s, OH, D_2O exch.);

δ_C 158.3 (C1), 129.6 (C2 + C6), 121.3 (C4), 114.5 (C3 + C5),

70.2 (PhO-CH_2), 69.3 (CH-OH), 43.0 (CH_2-Cl), 35.9 (CH_2-S),

34.8 (CH_2-S);

m/z 248,246 (M, 3.5,10.5%), 210 (M - HCl, <1.0%),

155,153 (M - PhO, 16.7, 49.5%), 109,107 ($PhOCH_2$, 19.7, 22.5%),

94 (PhOH, 100%), 77 (Ph, 71.0%); ν_{max} (film/cm^{-1}) 3442 (O-H),

1599 (Ph), 695 (C-S);

Found C, 53.71; H, 6.16%. $C_{11}H_{15}O_2SCl$ requires C, 53.64; H, 6.14%.

Preparation of 6-bromo-2-hydroxy-1-phenoxy-4-thiahexane (31)

Modified literature procedure[78]

Carbon tetrabromide (1.00 g, 3.2 mmol) was added to a stirred solution of 2,6-dihydroxy-1-phenoxy-4-thiahexane (0.69 g, 3.2 mmol) in acetonitrile (5 cm^3). Triphenylphosphine (0.79 g, 3.2 mmol) was then added and the mixture was left to stir at room temperature under nitrogen for 28 days. The reaction mixture was added to water (25 cm^3) and extracted using ethyl acetate (4 x 25 cm^3), the combined extracts were then dried ($MgSO_4$) and concentrated under reduced pressure to give a dark brown oil.

Column chromatography (30% ethyl acetate/petroleum ether) of this multicomponent mixture yielded recovered starting material (0.39 g, 57%) and *6-bromo-2-hydroxy-1-phenoxy-4-thiahexane* as a brown oil (0.29 g, 31%).

δ_H 7.31-7.21 (2H, m, Ph), 6.95-6.85 (3H, m, Ph),

4.18-4.08 (4H, m, PhO-C$\underline{H}_2$-CHOH, Br-C$\underline{H}_2$-CH_2),

3.60-3.51 (2H, m, C$\underline{H}$-OH, OH), 2.85-2.78 (4H, m, 2 x CH_2-S);

δ_C 158.3 (C1), 129.6 (C2 + C6), 121.4 (C4), 114.8 (C3 + C5),

71.3 (PhO-CH_2), 70.2 (CH-OH), 34.9 (CH_2-S), 34.8 (CH_2-S),

33.9 (CH_2-Br);

m/z 292,290 (M, 61.8,60.5%), 211 (M - Br, 67.7%),

199,197 (M - PhO, 70.7,69.8%), 107 ($PhOCH_2$, 100%), 77 (Ph, 84.7%)

υ_{max}(film/cm^{-1}) 3440 (O-H), 1600 (Ph);

Found C, 45.50; H, 5.20. $C_{11}H_{15}O_2SBr$ requires C, 45.52; H, 5.21% .

Attempted preparation of 2-hydroxy-1-phenoxy-6-p-toluenesulfonyloxy-4-thiahexane

Method A (dichloromethane as solvent)

Pyridine (0.127 g, 1.6 mmol) was added to 2,6-dihydroxy-1-phenoxy-4-thiahexane (0.23 g, 1 mmol) in dichloromethane (5 cm^3). The reaction mixture was cooled to 0 °C and *p*-toluenesulfonyl chloride (0.315 g, 1.6 mmol) was added in small portions. The reaction mixture was left to stir at room temperature under nitrogen for 10 days. The mixture was then quenched using saturated aqueous ammonium chloride (10 cm^3), and extracted with dichloromethane (3 x 10 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give a dark brown oil.

Column chromatography (2:1 diethyl ether/petroleum ether) of this multicomponent mixture yielded *6-chloro-2-hydroxy-1-phenoxy-4-thiahexane* (0.06 g, 24%) as a light brown oil and recovered starting material (0.11 g, 48%) as confirmed by mass, ^1H NMR and IR spectroscopy compared with the materials described above.

Method B (Dichloromethane as solvent, DMAP catalysis)

Pyridine (0.17 g, 2.2 mmol) was added to a stirred and cooled (0 °C) solution of 2,6-dihydroxy-1-phenoxy-4-thiahexane (0.46 g, 2 mmol) in dichloromethane (10 cm^3) under nitrogen. *p*-Toluenesulfonyl chloride (0.42 g, 2.2 mmol) was added in small portions. DMAP (0.024 g, 0.2 mmol) was added and the mixture was left to stir at room temperature under nitrogen for 20 days. Saturated aqueous ammonium chloride was added (15 cm^3) and the mixture extracted using dichloromethane (3 x 20 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a brown oil (0.31 g).

Column chromatography (2:1 diethyl ether/petroleum ether) of this multicomponent mixture yielded *6-chloro-2-hydroxy-1-phenoxy-4-thiahexane* (0.09 g, 18%) as a light brown oil and recovered starting material (0.20 g, 43%) as the only isolable compounds as confirmed by mass spectrometry, ^1H NMR and IR spectroscopy.

Attempted cyclisation of 6-chloro-2-hydroxy-1-phenoxy-4-thiahexane (32)

Sodium hydride (0.026 g, 0.043 g of a 60% dispersion in oil, 0.00107 mol) was added carefully to a cooled (0 °C) and stirred solution of 6-chloro-2-hydroxy-1-phenoxy-4-thiahexane (0.24 g, 0.00097 mol) in THF (5 cm^3). The reaction was

allowed to rise to room temperature, sodium iodide (0.145 g, 0.00097 mol) was added and the reaction mixture was left stirring under nitrogen for 7 days when tlc analysis (1:1 ethyl acetate/petroleum ether) showed the absence of starting material. The mixture was then diluted with water (5 cm^3), the aqueous layer extracted with ethyl acetate (4 x 10 cm^3) and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product as a brown oil (0.21 g).

Column chromatography (1:1 ethyl acetate/petroleum ether) gave a gross mixture of products which appeared homogenous by tlc analysis but were shown to be further mixtures of components by mass spectrometry, IR, ^1H and ^{13}C NMR spectroscopy. One separable component was identified as *2-hydroxy-1-phenoxy-4-thiapent-4-ene* as a pale, brown sticky oil (0.07 g, 34%).

δ_H 7.32-7.25 (2H, m, Ph), 6.90-7.01 (3H, m, Ph), 6.35 (1H, dd, J9.9, 16.7, C<u>H</u>=CH_2), 5.25 (2H, dd, J9.9, 16.7, C<u>H_2</u>=CH), 4.20-3.70 (3H, m, PhO-C<u>H_2</u>, CH_2-C<u>H</u>-OH), 2.99-2.79 (2H, m, CH-C<u>H_2</u>-S-CH);

δ_C 174.6 (C1), 129.6 (C3 + C5), 121.4 (C4), 114.6 (C2 + C6), 70.3 (PhO-CH_2), 69.3 (CH-OH), 68.7 (<u>C</u>H=CH_2), 61.7 (<u>C</u>H_2=CH), 36.7 (CH_2-S);

m/z 210 (M, 67.6%), 117 (M - PhO, 100%), 77 (Ph, 73.0%);

υ_{max}(film/cm^{-1}) 3415 (O-H), 2924 (=CH_2), 1589 (Ph),885 (C-H), 692 (C-S).

Attempted cyclisation of 6-bromo-2-hydroxy-1-phenoxy-4-thiahexane

Method A (sodium hydride/THF)

6-Bromo-2-hydroxy-1-phenoxy-4-thiahexane (0.24 g, 0.824 mmol) was stirred in THF (7 cm^3) and the mixture was cooled to 0 °C. Sodium hydride (0.0218 g, 0.036 g of a 60% dispersion in oil, 0.907 mmol) was added in small portions and the mixture was left to stir at room temperature under nitrogen for 25 days. The reaction mixture was then poured into water (5 cm^3), extracted with diethyl ether (3 x 10 cm^3) and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a red/brown oil (0.09 g).

Column chromatography yielded (3% diethyl ether/petroleum ether) a gross mixture of products which were not separable, nor identifiable by IR and ^1H NMR spectroscopy.

Method B (sodium iodide catalysis)

6-Bromo-2-hydroxy-1-phenoxy-4-thiahexane (0.18 g, 0.62 mmol) was stirred in THF (5 cm^3) at 0°C and sodium hydride (0.0243 g, 0.041 g of a 60% dispersion in oil, 1 mmol) was added in small portions. The reaction mixture was allowed to rise to room temperature before the addition of sodium iodide (0.014 g, 0.095 mmol). Stirring was continued at room temperature under nitrogen for 15

days, then the mixture was diluted with water (5 cm^3), extracted with ethyl acetate (4 x 10 cm^3) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give a dark orange oil.

Repeated column chromatography (10% diethyl ether/petroleum ether) of this multi-component mixture gave an intractable mixture of products which were not identifiable by mass spectrum and ^1H NMR spectroscopy.

Attempted preparation of 6-iodo-2-hydroxy-1-phenoxy-4-thiahexane

Finkelstein procedure[81]

A solution of sodium iodide (0.26 g, 1.72 mmol) in acetone (1 cm^3) was added dropwise to a stirred solution of 6-chloro-2-hydroxy-1-phenoxy-4-thiahexane (0.21 g, 0.86 mmol) in acetone (3 cm^3). The reaction vessel was wrapped in foil and the reaction mixture was left to stir at room temperature for 7 days. The mixture was then filtered, the precipitate was washed with acetone (2 x 5 cm^3) and the combined filtrates concentrated under reduced pressure to give a yellow oil. Diethyl ether (10 cm^3) was then added and the organic layer was then washed with saturated aqueous sodium metabisulfite (1 cm^3), saturated aqueous sodium hydrogen carbonate (2 x 2 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure.

Column chromatography (dichloromethane) yielded an intractable mixture of products as a light yellow oil (0.09 g) which were not identifiable by ^{1}H NMR and IR spectroscopy.

Preparation of 2,6-dihydroxy-1-phenoxy-4-thiahexane 4,4-dioxide (34)

Method A (OXONE oxidation)

Modified literature procedure[21]

2,6-Dihydroxy-1-phenoxy-4-thiahexane (2.41 g, 0.0106 mol) was dissolved in methanol (40 cm^3) and cooled to 0 °C. A solution of 49.5% $KHSO_5$ (9.77 g, 0.0318 mol) in water (40 cm^3) was added and the resulting slurry was left to stir at room temperature under nitrogen for 11 days when tlc analysis (ethyl acetate), showed that the reaction had gone to completion. The mixture was then filtered, diluted using water (10 cm^3) and then extracted using dichloromethane (3 x 10 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product as a cream coloured solid (1.85 g).

Column chromatography (ethyl acetate) yielded the title compound as a white solid (1.02 g, 37%) with spectroscopic and analytical properties consistent with the diol prepared below.

Method B (Periodate oxidation) - Modified literature procedure[82]

2,6-Dihydroxy-1-phenoxy-4-thiahexane (2.28 g, 0.01 mol) was added to a solution in water (21 cm^3) of sodium periodate (2.24 g), 0.0105 mol) at 0 °C under nitrogen. The solution was left to stir at room temperature for 15 days. The precipitated sodium iodate was removed by filtration and the filtrate was then extracted using dichloromethane (4 x 20 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give a crude pale yellow oil (1.33 g).

Column chromatography (ethyl acetate) yielded a cream coloured solid (1.05 g, 41%). Tlc analysis, ^1H NMR and IR spectroscopy gave results consistent with the material from the preferred method below.

Method C (Osmium tetroxide - preferred method) - Modified literature procedure[23]

2,6-Dihydroxy-1-phenoxy-4-thiahexane (3.68 g, 0.016 mol) and

N-methylmorpholine-N-oxide (NMO) (5.62 g, 9.37 g of a 60% dispersion in water, 0.048 mol) were stirred in acetone (32 cm^3) and water (16 cm^3) under nitrogen at room temperature. An aqueous solution of osmium tetroxide (0.1 M, 1.6 cm^3, 0.16 mmol) was added to the mixture and the reaction was stirred for 18 h when tlc analysis (5% methanol/diethyl ether) indicated the absence of starting material from the reaction mixture. Saturated aqueous sodium bisulphite (32 cm^3) was added and the aqueous layer was extracted with dichloromethane (4 x 40 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give a pale yellow oil (4.75 g).

Column chromatography (5% methanol/ diethyl ether) yielded the title compound as an off-white solid (3.59 g, 86%),

m.p. 79-80 °C.

δ_H 7.35-7.25 (2H, m, Ph), 7.08-6.98 (1H, m, Ph), 6.95-6.85 (2H, m, Ph),

4.71-4.61 (1H, m, $CH_2C\underline{H}$-OH), 4.15 (2H, t, J5.3, CH_2-$C\underline{H_2}$-OH),

4.02 (2H, d, J5.2, O-$C\underline{H_2}$-CH,), 3.50-3.41 (4H, m, 2 x CH_2-S),

2.89-2.79 (1H, br-s, OH, D_2O exch), 1.80-1.71 (1H, br-s, OH, D_2O exch);

δ_C 157.9 (C1), 129.7 (C2 + C6), 121.7 (C4), 114.2 (C3 + C5), 70.3 (PhO-CH_2),

65.6 (CH-OH), 57.9 (CH_2-OH), 56.9 (CH_2-S), 56.5 (CH_2-S);

m/z 260 (M, 18.4%), 242 (M - H_2O, 2.2%), 167 (M - PhO, 79.0%),

94 (PhOH, 100%), 77 (Ph, 71.2%);

υ_{max}(nujol /cm^{-1}) 3440 (O-H), 2951 (=CH_2),1598 (Ph),

1320 (=SO_2), 1160 (=SO_2);

Found C, 50.77; H, 6.21%. $C_{11}H_{16}O_5S$ requires C, 50.76; H, 6.19%

Attempted direct cyclisation of 2,6-dihydroxy-1-phenoxy-4-thiahexane 4,4-dioxide

Method A (Triphenylphosphine/carbon tetrachloride) - Modified literature procedure[78]

To a stirred solution of 2,6-dihydroxy-1-phenoxy-4-thiahexane 4,4-dioxide (0.260 g, 0.001 mol) in acetonitrile (1 cm^3), carbon tetrachloride (3 cm^3) and triphenylphosphine (0.262 g, 0.001 mol) were added and the reaction mixture was refluxed for 5 days under nitrogen. Quenching of the mixture with saturated aqueous ammonium chloride (5 cm^3), followed by extraction of the aqueous layer with dichloromethane (3 x 5 cm^3), drying ($MgSO_4$) and concentration of the organic layer under reduced pressure gave the crude product as a dark brown oil (0.45 g).

Repeated column chromatography (3:1 ethyl acetate/petroleum ether) yielded recovered starting material (0.01 g, 4%) and *6-chloro-2-hydroxy-1-phenoxy-4-thiahexane dioxide* as a brown sticky oil (0.21 g, 76%) as determined by mass spectrometry, IR , ^1H and ^{13}C NMR spectroscopy.

δ_H 7.35-7.25 (2H, m, Ph), 7.04-6.98 (1H, m, PhO), 6.95-6.85 (2H, m, Ph),
4.62-4.59 (1H, m, CH_2-C<u>H</u>-OH), 4.03 (2H, d, J5.2, PhO-C<u>H_2</u>-CH),
3.93 (2H, t, J6.8, Cl-C<u>H_2</u>-CH_2), 3.62-3.48 (4H, m, 2 x CH_2-S),
3.05 (1H, OH, D_2O exch);

δ_C 157.9 (C1), 129.8 (C2 + C6), 121.7 (C4), 114.7 (C3 + C5),

70.3 ($PhO-CH_2$), 62.8 (CH), 57.8 (CH_2-S), 56.9 (CH_2-S),

35.8 (CH_2-Cl);

m/z 279 (M^+, 9.4%), 280,278 (M, 2.6,2.6%), 242 (M - HCl, 4.2%), 187,185 (M - PhO, 4.6,11.7%), 77 (Ph,71%), 43 (CH_2CHO, 100%);

υ_{max}(film/cm^{-1}) 3487 (O-H), 2929 ($=CH_2$), 1591 (Ph), 1123 ($=SO_2$), 693 (C-Cl).

Method B (*p*-Toluenesulfonyl chloride/pyridine as solvent)

2,6-Dihydroxy-1-phenoxy-4-thiahexane 4,4-dioxide (0.244 g, 0.001 mol) was stirred in pyridine (10 cm^3) and cooled to 0 °C. *p*-Toluenesulfonyl chloride (0.190 g, 0.001 mol) was added slowly and the reaction mixture was left to reflux under nitrogen for 5 days. The mixture was then poured into water (10 cm^3), and the aqueous layer was extracted with dichloromethane (4 x 10 cm^3). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure.

Column chromatography (4:1 ethyl acetate/petroleum ether) yielded recovered starting material (0.13 g, 57%) as confirmed by mass spectrometry, IR and ^1H NMR spectroscopy.

Preparation of 6-chloro-2-hydroxy-1-phenoxy-4-thiahexane 4,4-dioxide (35)

Modified literature procedure[78]

2,6-Dihydroxy-1-phenoxy-4-thiahexane 4,4-dioxide (0.52 g,0.002 mol) was stirred in carbon tetrachloride (6 cm^3). Acetonitrile (2 cm^3), triphenylphoshine (0.52 g, 0.002 mol) and potassium carbonate (0.28 g, 0.002 mol) were then added and the reaction mixture was refluxed under nitrogen for 9 days. The mixture was then quenched with saturated aqueous ammonium chloride (10 cm^3), extracted using dichloromethane (4 x 15 cm^3) and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure.

Repeated column chromatography (75% ethyl acetate/petroleum ether) yielded *6-chloro-2-hydroxy-1-phenoxy-4-thiahexane 4,4-dioxide* as a yellow oil (0.46 g, 83%) with mass, IR, ^1H and ^{13}C NMR spectroscopic characteristics consistent with those reported above.

Preparation of 6-bromo-2-hydroxy-1-phenoxy-4-thiahexane 4,4-dioxide (36)

Method A (Triphenylphosphine/carbon tetrabromide) - Modified literature procedure[78]

Carbon tetrabromide (1.10 g, 3.3 mmol) and triphenylphosphine (0.78 g, 3 mmol) were added to a stirred solution of 2,6-dihydroxy-1-phenoxy-4-thiahexane 4,4-dioxide (0.78 g, 3 mmol) in acetonitrile (6 cm^3) and the reaction mixture was left to reflux under nitrogen for 25 days. Water (25 cm^3) was added and the reaction mixture was extracted using ethyl acetate (4 x 20 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to afford the crude product as a dark brown oil (1.16 g) which was shown to be a mixture of starting material and several products by tlc and ^1H NMR spectroscopic analysis. Extensive column chromatography (1:1 ethyl acetate/petroleum ether) was unsuccessful in purifying this mixture.

Method B (Triphenylphosphine dibromide/pyridine - preferred method) - General literature procedure[79]

Pyridine (0.079 g, 1 mmol) was added to a stirred mixture of

2,6-dihydroxy-1-phenoxy-4-thiahexane-4,4-dioxide (0.26 g, 1 mmol) in dichloromethane (5 cm^3) at 0 °C under nitrogen. Triphenylphosphine dibromide (0.528 g, 1.25 mmol) was added in one portion and the mixture was allowed to rise to room temperature and left to stir under nitrogen for 72 h when tlc analysis (20% ethyl acetate/dichloromethane) indicated the absence of starting material from the reaction mixture. The mixture was then poured into water (10 cm^3), extracted using dichloromethane (3 x 20 cm^3) and the combined organic layers were then dried ($MgSO_4$) and concentrated under reduced pressure to give a crude yellow oil (0.58 g).

Column chromatography (20% ethyl acetate/dichloromethane) yielded *6-bromo-2-hydroxy-1-phenoxy-4-thiahexane 4,4-dioxide* the title compound as off white crystals (0.18 g, 56%).

m.p. 109-110 °C;

δ_H 7.38-7.28 (2H, m, Ph), 7.09-6.99 (1H, m, Ph), 6.95-6.85 (2H, m, Ph),

4.71-4.61 (1H, m, CH_2-C<u>H</u>-OH),4.10-4.00 (2H, m, PhO-C<u>H</u>$_2$-CH-OH),

3.75-3.65 (4H, m, CH_2-SO_2, CH_2-Br), 3.52-3.25 (2H, m, CH_2-SO_2),

3.06 (1H, d, J6.5, OH coupling, D_2O exch);

δ_C 157.9 (C1), 129.8 (C2 + C6), 121.9 (C4), 114.7 (C3 + C5),

79.3 (PhO-CH_2), 65.7 (CH-OH), 57.3 (CH_2-S), 57.1 (CH_2-S),

20.9 (CH_2-Br);

m/z 324,322 (M, 35.6,35.5%), 231,229 (M - PhO, 60.0,60.4%),

107 ($PhOCH_2$, 100%), 77 (Ph, 80.0%);

υ_{max}(nujol mull/cm^{-1}) 3440 (O-H), 1595 (Ph), 1330 (=SO_2), 1160 (=SO_2), 1121 (=SO_2), 740 (C-Br);

Found C, 40.93; H, 4.74%. $C_{11}H_{15}O_4SBr$ requires C, 40.88; H, 4.68%

Attempted cyclisation of 6-chloro-2-hydroxy-1-phenoxy-4-thiahexane 4,4-dioxide

Sodium hydride (0.0173 g, 0.03 g of a 60% dispersion in mineral oil, 0.72 mmol) was added to a cooled, (0 °C) stirred solution of 6-chloro-2-hydroxy-1-phenoxy-4-thiahexane 4,4-dioxide (0.18 g, 0.65 mmol) in THF (10 cm^3). The mixture was allowed to come to room temperature, sodium iodide (0.097 g, 0.65 mmol) was added and the reaction was left to stir under nitrogen for 12 days. Water (10 cm^3) was then added and the aqueous layer was extracted using ethyl acetate (4 x 10 cm^3). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure.

Column chromatography (diethyl ether) yielded a dark yellow oil (0.11 g) which was shown to a gross mixture of products by tlc and ^1H NMR spectroscopic analysis. Column chromatography was unsuccessful in the purification of this intractable mixture.

Attempted cyclisation of 6-bromo-2-hydroxy-1-phenoxy-4-thiahexane 4,4-dioxide

Method A (sodium hydride/THF)

6-Bromo-2-hydroxy-1-phenoxy-4-thiahexane 4,4-dioxide (0.14 g, 0.48 mmol) was stirred in THF (3 cm^3) and the mixture was cooled to 0 °C. Sodium hydride (0.019 g, 0.033 g of a 60% dispersion in oil, 0.79 mmol) was added slowly and the reaction mixture was allowed to rise to room temperature and left stirring under nitrogen for 24 h. The mixture was then diluted with water (5 cm^3), extracted with ethyl acetate (3 x 10 cm^3) and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure.

Column chromatography (ethyl acetate) yielded a light yellow oil (0.052 g) which appeared homogeneous by tlc analysis but was shown to be a mixture of components by ^1H and ^{13}C NMR spectroscopy.

Method B (potassium carbonate/acetone)

Potassium carbonate (0.05 g, 0.36 mmol) was added to a solution of 6-bromo-2-hydroxy-1-phenoxy-4-thiahexane 4,4-dioxide (0.06 g, 0.18 mmol) in acetone (3.5 cm^3). The reaction mixture was then refluxed for 4 days under nitrogen. Water (5 cm^3) was then added and an extraction of the aqueous layer

followed using ethyl acetate (3 x 10 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give a light brown oil (0.09 g).

Column chromatography yielded a gross mixture of inseparable products which were unidentifiable by ^1H and ^{13}C NMR spectroscopy and further purification proved unsuccessful.

8.3 Acid/alcohol cyclisations

Preparation of 2-(2'-acetyloxyethylthio)acetic acid (38)

Modified literature procedure[36]

Thioglycollic acid (5 g, 0.054 mol) and freshly distilled vinyl acetate (5 g, 0.058 mol) were mixed at room temperature and left to stir. A large exothermic reaction occurred and so the reaction mixture was cooled to 0 °C and left to stir for 18 h at room temperature. The excess vinyl acetate was evaporated off to give the title compound as a colourless liquid (9.20g, 96%), with ^{1}H NMR and IR spectroscopic properties consistent with those reported in the literature.

δ_H 10.86 (1H, br-s, OH) 4.32 (2H, t, J6.5, O-C$\underline{H}_2$-CH_2),

3.33 (2H, s, CH_2-CO), 2.93 (2H, t, J6.5, S-C$\underline{H}_2$.CH_2), 2.09 (3H,s,CH_3);

δ_C 175.8 (COOH), 171.2 ($\underline{C}OCH_3$), 63.0 (CH_2-CO_2H), 33.4 (CH_2-O),

31.1 (CH_2-S), 20.8 (CH_3);

υ_{max}(film/cm^{-1}) 3200 (O-H), 1740 (C=O), 690 (C-S).

Preparation of 1,4-oxathian-3-one (10)

Modified literature procedure[36]

2-(2'-Acetyloxyethylthio)acetic acid (1.00 g, 0.0056 mol) was dissolved in aqueous 40% potassium hydroxide (4.48 g, 0.08 mol) and refluxed under nitrogen for 5 h. On cooling, the reaction mixture was acidified with concentrated hydrochloric acid (10 cm^3) and extracted using diethyl ether (3 x 50 cm^3). The combined organic extracts were washed with water (50 cm^3), dried (Na_2SO_4) and concentrated under reduced pressure to give an orange oil (0.66 g). A portion of the (1-hydroxyethylthio)acetic acid (0.25 g, 0.0018 mol) and *p*-toluene-4-sulfonic acid (0.035 g, 0.18 mmol) were refluxed in toluene (350 cm^3) in a flask equipped with Dean and Stark apparatus and refluxed for 24 h. The resulting solution was then cooled, washed with water (4 x 150 cm^3), dried (Na_2SO_4) and concentrated under reduced pressure to give a crude brown oil (0.20 g).

Column chromatography (diethyl ether) yielded 1,4-oxathian-2-one as a pale yellow oil (0.09 g, 42%).

δ_H (80 MHz) 4.34 (2H, t, J6.5, O-C$\underline{H_2}$-CH_2), 3.32 (2H, s, C$\underline{H_2}$-C=O), 2.93 (2H, t, J6.5, CH_2-C$\underline{H_2}$-S);

υ_{max}(film/cm^{-1}) 2930 (CH_2), 1741 (C=O).

Preparation of methyl 2-(2'-hydroxyethylthio)acetate (39)

Modified literature procedure[41]

2-Mercaptoethanol (39.0 g, 0.50 mol) and potassium carbonate (70.0 g, 0.51 mol) were stirred in acetone (250 cm^3) at 40 °C. Methyl chloroacetate (54.30 g, 0.50 mol) was added dropwise over 1 h and stirring continued for a further 2 h at 40 °C. The reaction mixture was filtered and the precipitate washed with fresh acetone (3 x 70 cm^3). The combined filtrate and washings were concentrated under reduced pressure to give the title compound as an opaque oil (52.34 g, 70%).

δ_H 3.87-3.77 (5H, m, CO_2-CH_3 + HO-C$\underline{H_2}CH_2$), 3.60-3.50 (1H, br-s, OH), 3.35 (2H, s, CH_2-CO_2), 2.85 (2H, t, J6.1,S-C$\underline{H_2}$-CH_2);

δ_C 170.8 (C=O), 60.8 (HO-CH_2), 52.6 (CH_3), 35.6 (CH_2CO_2), 33.4 (CH_2-S),

m/z 150 (M, 9.7%), 133 (M - OH, 28.5%), 119 (M - CH_2OH, 31.3%), 91 (M - CO_2CH_3, 53.5%), 45 (CH_2CH_2OH, 100%), 31 (CH_2OH, 50.6%).

Preparation of 1,4-oxathiane-3-one (10)

Modified literature procedure[41]

Methyl (2'-hydroxyethylthio)acetate (15.00 g, 0.099 mol) and dibutyltin dilaurate (0.125 g, 0.19 mmol) were heated to 165 °C in a distillation apparatus. After one hour approximately 2 cm^3 of methanol had been collected. A 30 mm Hg vacuum was then applied and the reaction mixture was heated to 180 - 185 °C. The reaction was allowed to cool, then antimony trioxide (0.063 g, 0.21 mmol) was added and the reaction heated for a further 45 minutes at 180 - 185°C/30 mm Hg. The title compound was collected by distillation as a colourless oil (7.29 g, 62%).

B.p. 82 - 90 °C/0.035 mm Hg; lit[41] B.p. 95-102 °C/0.05 mm Hg.

δ_H (80MHz) 5.10 (2H, t, J6.5, $C\underline{H_2}$-CH_2-O,), 3.85(2H, s, $C\underline{H_2}$-C=O), 3.25(2H, t, J6.5, $C\underline{H_2}$-CH_2-S);

υ_{max}(film/cm^{-1}) 2820 (=CH_2), 1710 (C=O).

Attempted oxidation of 1,4-oxathiane-3-one

OXONE Oxidation - Modified literature procedure[21]

1,4-Oxathiane-2-one (0.56 g, 0.005 mol) was dissolved in methanol (20 cm^3) and cooled to 0 °C. $KHSO_5$ (49.5%, 2.28 g, 0.015 mol) in water (20 cm^3) was added and the reaction mixture was left to stir at room temperature for 12 days. The mixture was then diluted with water (15 cm^3), filtered and extracted using chloroform (3 x 20 cm^3). The combined organic layers were washed with water (10 cm^3) and saturated aqueous ammonium chloride solution (10 cm^3), then dried ($MgSO_4$) and concentrated under reduced pressure to give an opaque oil.

Column chromatography (ethyl acetate) yielded methyl (2-hydroxyethyl)sulfonylacetate as a colourless oil (0.344 g, 38%) as the only isolable product with spectroscopic properties consistent with those reported above.

δ_H 4.18 (2H, s, $C\underline{H_2}$-CO_2), 4.15 (2H, t, J6.1, HO-$C\underline{H_2}$-CH_2),

3.75 (3H, s, CH_3), 3.54 (2H, t, J5.1, $CH_2C\underline{H_2}$-S),

2.70 (1H, br-s, OH); δ_C 163.89 (C=O), 59.0 (CH_2-OH),

56.6 ($\underline{C}H_2$-CO), 55.7 (CH_2-S), 53.4 (CH_3);

m/z 181 (M - H, 2.0%), 165 (M - OH, 2.3%), 151 (M - OCH_3, 45.7%),

45 (CH_2CH_2OH, 100%), 31 (CH_3, 51.0%).

Method B - modified literature procedure[22]

A solution of tungstic acid (0.01 g, 0.04 mmol) in water (3.5 cm^3) was acidified to pH 6 with a few drops of glacial acetic acid. This was immediately added to 1,4-oxathiane-2-one (1.18 g, 0.01 mol) and the mixture was heated to 65°C. Hydrogen peroxide (60%, 2.72 g, 0.022 mol) was added dropwise so that the internal temperature remained between 65 °C and 80 °C. The reaction was left to stir at 60°C for 1h when hydrogen peroxide (2.72 g, 0.022 mol) was carefully added until a starch-iodide paper test was positive. After 6 mins the solution turned from yellow to cloudy. Sodium metabisulfite was added until a starch-iodide paper test was negative. Sodium chloride solution (15 cm^3) was added and the mixture continuously extracted using dichloromethane for 15 days. The organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give an oil (0.601 g) which comprised a gross mixture of products (by tlc analysis) which could not be purified by column chromatography.

Preparation of methyl 2-(2'-hydroxyethylsulfonyl)acetate (40)

Modified literature procedure[22]

A solution of tungstic acid (0.02 g, 0.08 mmol) in water (7 cm^3) was added to methyl (2-hydroxyethyl)thioacetate (3.00 g, 0.02 mol) and the reaction flask

was heated to 65 °C. Hydrogen peroxide (1.568 g, 0.044 mol) was added dropwise so that the internal temperature remained between 65 °C and 70 °C. The reaction was left to stir at 65 °C for 2h, when tlc analysis (ethyl acetate) showed the absence of sulfoxide. Sodium metabisulfite was added until a starch-iodide paper test was negative. Aqueous sodium chloride solution (15 cm^3) was added and the mixture continuously extracted using dichloromethane for 9 days. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound as a colourless oil

(1.98 g, 55%);

δ_C 4.19-4.11 (4H, m, HO-CH_2 + $C\underline{H}_2CO_2CH_3$), 3.83 (3H, s, CH_3),

3.52 (2H, t, J5.3, CH_2-$C\underline{H}_2$-SO_2), 2.77 (1H, br-s, O-H, D_2O exch);

δ_C 163.8 (C=O), 58.4 (CH_2-OH), 56.5 ($\underline{C}H_2$-CO_2), 55.7 ($CH_2\underline{C}H_2$-SO_2),

53.5 (CH_3);

υ_{max} (film/cm^{-1}) 3200 (O-H), 1720 (C=O), 1360 (=SO_2), 1140 (SO_2).

Attempted cyclisation of methyl (2-hydroxyethyl)sulfonylacetate

Method A (Imidazole) - Modified literature procedure[61]

Imidazole (0.34 g, 0.005 mol) was added to a solution of methyl 2-(2'-hydroxyethylthio) sulfonylacetate (0.182 g, 0.001 mol) in acetonitrile (5 cm^3) and

the reaction mixture was left to stir at 25 °C for 11 days. Dilute aqueous hydrochloric acid (10 cm^3) was then added and the reaction mixture was extracted using ethyl acetate (3 x 10 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure.

Column chromatography (ethyl acetate) yielded recovered starting material (0.11 g, 60%) as the only identifiable compound as confirmed by ^1H NMR and IR spectroscopy.

Method B (*Pseudomonas fluorescens* lipase) - Modified literature procedure[58]

Methyl (2-hydroxyethyl)sulfonylacetate (0.182 g, 0.001 mol) was dissolved in hexane (20 cm^3) and the lipase from *Pseudomonas fluorescens* (0.15 g) was added and the reaction was left to stir at room temperature. After 7 days the reaction was filtered and concentrated under reduced pressure to give recovered starting material (0.17 g, 93%) as confirmed by ^1H NMR spectroscopy.

This procedure was repeated using acetone as the solvent with the same result.

Method C (porcine pancreatic lipase) - Modified literature procedure[58]

Methyl (2-hydroxyethyl)sulfonylacetate (0.182 g, 0.001 mol) was dissolved in hexane (20 cm^3) and porcine pancreatic lipase (0.15 g) was added and mixture was left to stir at room temperature for 4 days. The reaction mixture was filtered and the precipitate washed with acetone (3 x 10 cm^3) before being concentrated under reduced pressure to give recovered starting material (0.17 g, 93%) as confirmed by ^1H NMR spectroscopy.

8.4 Diol/lactol lactonisation/halogenation

Preparation of 2,2'-Thiodiethanol *S,S*-dioxide (41)

Literature procedure[22]

A solution of tungstic acid (0.10 g, 0.4 mmol) in water (35 cm^3) was acidified to pH 6 with a few drops of acetic acid. This was added immediately to 2,2'-thiodiethanol (12.2 g, 0.10 mol) and the mixture was then heated to 65 °C. Hydrogen peroxide (60%) (3.74 g, 0.11 mol) was added dropwise maintaining the internal temperature between 60 - 65 °C. The reaction was left to cool to 60 °C and a second portion of hydrogen peroxide (3.74 g, 0.11 mol) was added quickly. The solution turned from yellow to cloudy and the reaction was left stirring at 65 °C for 4 hours when tlc analysis (10% methanol/ethyl acetate) showed the absence of starting material and sulfoxide. Once cooled to room temperature the mixture was quenched with sodium metabisulfite until a starch-iodide paper test was negative, diluted using saturated aqueous sodium chloride (25 cm^3) and put on a dichloromethane continuous extraction for 12 days. The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give white crystals (11.68 g, 75%), m.p. 63-64°C;

δ_H 4.17 (2H, m, OH), 4.00 (4H, m, CH_2-O),3.30 (4H, m, CH_2-SO_2);

δ_C 57.1 (CH_2OH), 56.7 (CH_2-S);

m/z 154 (M, 3.0%), 155 (M^+, 18.7%), 137 (M - OH, 10.5%),

124 (M^+ -CH_2 OH, 6.3%), 45 (CH_2CH_2OH, 100%), 31 (CH_2OH, 47%);

υ_{max}(film/cm^{-1}) 3369(O-H), 2928 (=CH_2), 1313 (=SO_2), 1122 (=SO_2).

Attempted oxidations of 2,2'-Thiodiethanol *S,S*-dioxide

Ruthenium complex catalysis - Modified literature procedure[55]

A mixture of 2,2'-thiodiethanol *S,S*-dioxide (0.154 g, 0.001 mol) and 4-phenyl-3-buten-2-one (0.292 g, 0.002 mol) were dissolved in dry toluene (5 cm^3) under nitrogen. Dichloro triphenylphosphinoruthenium (0.038 g, 0.04 mmol) was added in one portion and the blackened solution was left to reflux under nitrogen for 11 days. The mixture was filtered and concentrated under reduced pressure to give a dark brown oil.

Repeated column chromatography (70% ethyl acetate - petroleum ether) gave recovered starting material (0.0145 g, 9%) as shown by ^{1}H NMR spectroscopy and an intractable mixture of components that were not identifiable by ^{1}H NMR and IR spectroscopy.

Calcium hypochlorite oxidation (**43**) - Modified literature procedure[54]

2,2'-Thiodiethanol *S,S*-dioxide (1.542 g, 0.01 ml) was dissolved in an acetonitrile:acetic acid (3:2, 9:6 cm^3) mixture and added dropwise over a period of 20 minutes to a cooled (0 °C) and stirred solution of calcium hypochlorite (5.72 g, 0.04 mol) in water (20 cm^3). The mixture was left to stir at room temperature for 48 h, then extracted with dichloromethane (3 x 25 cm^3) and the combined organic layers were washed with 10% sodium hydrogen carbonate (10 cm^3) followed by water (10 cm^3) before being dried ($MgSO_4$) and concentrated under reduced pressure to give a pale yellow oil.

Column chromatography (60:40% ethyl acetate/petroleum ether) yielded recovered starting material (0.77 g, 50%) *and 1,1-dichloro-4-hydroxy-2-thiabutane 2,2-dioxide* (0.78 g, 41%).

δ_H 6.56 (1H, s, C<u>H</u>-Cl_2), 4.17 (2H, t, J5.2, C<u>H_2</u>-CH_2-O), 3.61 (2H, t, J5.2, C<u>H_2</u>-CH_2-S), 2.89 (OH, D_2O exch.);

δ_C 80.0 (CH-Cl_2), 56.3 (CH_2-OH), 50.7 (CH_2-S);

m/z 194,192, (M, 2.7,1.9%), 176,174 (M - OH_2, 2.7,1.7%),

109 ($HOCH_2CH_2SO_2$, 23.2%), 45 ($HOCH_2CH_2$, 100%), 31 ($HOCH_2$, 56.9%);

υ_{max} (film/cm-1) 3448 (O-H), 2998 (=CH_2), 1340 (=SO_2);

Found C, 18.64; H, 3.19%. $C_3H_6O_3Cl_2S$ requires C, 18.67; H 3.13%.

Preparation of 1,1-dichloro-2-thiabut-4-yl acetate (44)

1,1-Dichloro-4-hydroxy-2-thiabutane 2,2-dioxide (0.103 g, 0.0005 mol) was dissolved in dichloromethane (10 cm^3). Pyridine (0.119 g, 0.0015 mol) was then added slowly followed by acetic anhydride (0.153 g, 0.0015 mol). The reaction was left stirring at room temperature for 48 h when tlc analysis (2:1 petroleum ether/ethyl acetate) showed the absence of starting material. The reaction mixture was diluted with dichloromethane (20 cm^3), quenched with aqueous saturated ammonium chloride (10 cm^3) and extracted with dichloromethane (4 x 25 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure.

Column chromatography (2:1 petroleum ether/ethyl acetate) gave the title compound as a colourless oil (0.10 g, 84 %).

δ_H 6.33 (1H, s, C<u>H</u>-Cl_2), 4.61 (2H, t, J5.7, C<u>H_2</u>CH_2-S),

3.72 (2H, t, J5.6, C<u>H_2</u>CH_2-O), 2.14 (3H, s, CH_3);

δ_C 170.1 (C=O), 79.1 (CH-Cl_2), 56.9 (CH_2-O), 47.6 (CH_2-S);

m/z 235,236 (M, 1.3,<0.1%), 175,176 (M - CH_3CO_2H, 1.5,1.0%),

152,151 (M - $CHCl_2$, 39.2, 3.8%),

83,85,87 (CH-Cl, 59.8,6.44,69.9%),43 (CH_3CO, 100%);

υ_{max}(film/cm^{-1}) 2991 (=CH_2), 1733 (C=O), 1335 (=SO_2), 1130 (=SO_2);

Found C, 25.39; H, 3.45%; $C_5H_8O_4SCl_2$ requires C, 25.54; H, 3.43%.

Swern oxidation (**45**) - Modified literature procedure[57]

2,2'-Thiodiethanol *S,S*-dioxide (1.542 g, 0.01 mol) was stirred in dichloromethane (50 cm^3) in an ice-water bath under nitrogen. Dimethyl sulfoxide (2.11 g, 0.027 mol) was added slowly and the reaction mixture was left to stir until all of the starting material had completely dissolved. Phosphorus pentoxide (2.84 g, 0.02 mol) was then added in small portions, immediately upon addition, a white precipitate was formed. The reaction was left to stir at room temperature for 1 h and then cooled to 0 °C when triethylamine (3.54 g, 0.035 mol) was added slowly over 1 minute. The reaction was left to stir at room temperature for 36 h until tlc analysis (ethyl acetate) showed that no starting material remained. The reaction mixture was then quenched using aqueous sodium hydroxide (2M, 20 cm^3) and extracted with diethyl ether (5 x 25 cm^3). The aqueous layer was acidified and continuously extracted using diethyl ether. The combined organic extracts were dried ($MgSO_4$) then concentrated to a pale brown oil (1.07 g).

Column chromatography (80:20% ethyl acetate/petroleum ether) yielded a gross mixture of products which appeared homogenous by tlc but were shown to be further mixtures of components by ^1H and ^{13}C NMR spectroscopy.

Repeated column chromatography yielded a product which by mass sectrometry, I.R., ^1H and ^{13}C spectroscopy showed spectroscopic properties consistent with the product being *1-hydroxy-3-thiapent-4-ene 3,3-dioxide* (0.057 g, 4.2%).

δ_H 6.74 (1H, dd, J9.8, 16.6, C<u>H</u>=CH_2),

6.48 (1H, d, J16.6, C<u>H</u>^{2}-CH^1 (trans to CH-SO_2)),

6.21 (1H, d, J9.8, C<u>H</u>^{1}-CH^2 (cis to CH-SO_2)), 4.08 (2H, t, J5.4, HO-C<u>H_2</u>-CH_2),

3.25 (2H, t, J5.4, S-C<u>H_2</u>-CH_2), 2.76 (1H, br-s, OH);

δ_C 136.6 (<u>C</u>H=CH_2), 130.5 (CH=<u>C</u>H_2), 56.5 (CH_2-O), 56.3 (CH_2-S);

m/z 136 (M,14.6%), 135 (M - H,9.2%), 119 (M - OH,10%),

45 (M - $SO_2CH=CH_2$, 37%), 31 (M - $CH_2SO_2CH=CH_2$, 32.7%);

υ_{max} (film/cm^{-1}) 3426 (O-H), 2928(=CH_2), 2895(=CH_2), 1466(C=C), 984(C-H).

<u>Preparation of 3-Hydroxy-1,4-oxathiane 4,4-dioxide (42)</u>

<u>Modified literature procedure</u> - <u>Jones Reagent</u>[64]

A solution of chromium trioxide (1.40 g, 0.0140 mol) and concentrated sulfuric acid (1.2 cm^3) was added during 45 minutes to a stirred solution of 2,2'-thiodiethanol *S,S*-dioxide (2.50 g, 0.016 mol) in acetone (15 cm^3) at 5 °C. The solution turned a dark brown colour. The reaction mixture was then allowed to rise to room temperature and left to stir for 24 h where tlc analysis (ethyl acetate) showed the absence of starting material. The dark green mixture was then diluted with water (35 cm^3) and continuously extracted using dichloromethane for 7 days.

Column chromatography (ethyl acetate) yielded the title compound as off-white coloured crystals (1.91 g, 80%).

m.p. 101-102°C.

δ_H 6.41 (1H, d, J6.4, OH, D_2O exch.), 5.09 (1H, m, CH),

4.31 (1H, ddd, J13.1, 3.9, 3.9, $OCH_{eq}\underline{H_{ax}}$),

3.82 (1H, ddd, J13.1, 10.4, 3.0, $OCH_{eq}\underline{H_{ax}}$),

3.29 (1H, ddd, J13.6, 3.1, 2.3, $SO_2C\underline{H}_{eq}H_{ax}CH$),

3.19-2.91 (3H, m, remainder). The proton at 3.29 ppm and a proton in the 3.19-2.91 multiplets were exchanged slowly with D_2O. The multiplet at 5.09 ppm simplified at the same time.

δ_C 94.6 ($\underline{C}$H-OH), 60.8 ($\underline{C}H_2$-O), 58.6 ($\underline{C}H_2$-S), 51.5 ($\underline{C}H_2$-S)

m/z 153 (M + H, 1.3%), 152 (M, 4.1%), 135 (M - OH, 25.5%),

124 (M - CH_2CH_2OH, 27.7%), 107 ($CH_2CH_2SO_2CH_2$,39.6%),

45 (CH_2CH_2OH, 52.6%), 32 (S,60.2%);

υ_{max}(film/cm^{-1}) 3376(O-H), 2945(=CH_2), 1330(=SO_2), 1130(SO_2), 1075(C-O);

Found C, 31.54; H, 5.25%; $C_4H_8O_4S$ requires C, 31.57; H, 5.30%.

Attempted oxidations of 3-Hydroxy-1,4-oxathiane 4,4-dioxide

Palladium (II) acetate catalysis - Literature procedure[63]

3-Hydroxy-1,4-oxathiane 4,4-dioxide (0.304 g, 0.002 mol), bromobenzene (0.345 g, 0.0022 mol), potassium carbonate (0.304 g, 0.022 mol), triphenyl phosphine (0.031 g, 0.12 mmol) and palladium (II) acetate (0.009 g, 0.04 mmol) were refluxed in 1,2-dimethoxyethane (8 cm^3) under nitrogen for 7 days. The brown mixture was poured into water (10 cm^3) and extracted using dichloromethane (6 x 20 cm^3). The organic layers were washed with aqueous saturated sodium chloride (10 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to give a light brown oil (0.29 g). The aqueous layer was re-extracted with dichloromethane (4 x 35 cm^3) but no more crude product was obtained.

Column chromatography (1:1 ethyl acetate/petroleum ether) yielded recovered starting material (0.15 g, 50%) as determined by ^1H NMR spectroscopy and tlc analysis and a mixture of several other minor by-products which proved inseparable upon further column chromatography.

Ruthenium complex catalysis - Modified literature procedure[55]

A mixture of 3-hydroxy-1,4-oxathiane 4,4-dioxide (0.152 g, 0.001 mol) and 4-phenyl-3-buten-2-one (0.292 g, 0.002 mol) were dissolved in dry toluene (5 cm^3) under nitrogen. Dichloro triphenylphosphinoruthenium (0.076 g, 0.08 mmol) was added in one portion and the blackened solution was left to reflux under nitrogen for 10 days when tlc analysis (2:1 ethyl acetate:petroleum ether) indicated the absence of starting material. The reaction mixture was then filtered and concentrated under reduced pressure to give a brown oil.

Column chromatography (2:1 ethyl acetate:petroleum ether) gave an intractable mixture of products (0.84 g) which were not separable nor identifiable by ^1H NMR and IR spectroscopy.

Tetrapropylammonium perruthenate oxidation - Modified literature procedure[24]

Tetrapropylammonium perruthenate (0.018 g, 5 mol%) was added in one portion to a stirred mixture of 2-hydroxy-1,4-oxathiane 4,4-dioxide (0.152 g, 0.001 mol), N-methylmorpholine-N-oxide (0.176 g, 0.0015 mol) and 4Å molecular sieves (0.50 g) in dichloromethane (2 cm^3) at room temperature under nitrogen. The blackened solution was left to stir at room temperature. When the reaction had been left stirring for 7 days the reaction mixture was purified directly

by column chromatography (ethyl acetate) to give only recovered starting material (0.11 g, 72%) as determined by ^{1}H NMR spectroscopy.

Jones Reagent oxidation - Modified literature procedure[64]

A solution of chromium trioxide (0.56 g, 0.0056 mol) in water (2 cm^3) and concentrated sulfuric acid (0.50 cm^3) was added during 40 minutes to a stirred solution of 2,2'-thiodiethanol *S,S*-dioxide (0.50 g, 0.00324 mol) in acetone (6 cm^3) at 0°C and left to stir for 45 minutes at 0°C when tlc analysis (ethyl acetate) showed the absence of starting material and the presence of 2-hydroxy-1,4-oxathiane 4,4-dioxide. The reaction was left stirring for a further 7 days to see if any other product was obtained. The reaction mixture was then diluted with water (7 cm^3), extracted with dichloromethane (15 x 20 cm^3) and the combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give off-white crystals (0.25 g, 51%) which were confirmed by ^{1}H NMR spectroscopy to be 3-hydroxy-1,4-oxathiane 1,1-dioxide.

Swern oxidation - Modified literature procedure[57]

2-Hydroxy-1,4-oxathiane 4,4-dioxide (0.152 g, 0.001 mol) was stirred in dichloromethane (5 cm^3) under nitrogen at 0 °C. Dimethyl sulfoxide (0.156 g, 0.002 mol) was added to give a homogenous solution. On addition of phosphorus pentoxide (0.284 g, 0.002 mol), a white precipitate appeared. The reaction was allowed to rise to room temperature then after 30 minutes was cooled to 0 °C and triethylamine (0.354 g, 0.0035 mol) was added slowly over 1 minute. The precipitate dissolved and the resultant yellow solution was left stirring at room temperature for 2 h. The reaction mixture was quenched using dilute hydrochloric acid (10 cm^3) and extracted using dichloromethane (7 x 20 cm^3). The combined organic layers were washed with saturated sodium chloride solution (25 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to give recovered starting material (0.14 g, 92%) as shown by ^1H NMR spectroscopy.

Calcium hypochlorite oxidation (43) - Modified literature procedure[54]

3-Hydroxy-1,4-oxathiane 4,4-dioxide (0.152 g, 0.001 mol) was dissolved in an acetonitrile:acetic acid (3:2, 0.9:0.6 cm^3) mixture and added dropwise over a period of 10 minutes to a cooled and stirred solution of calcium hypochlorite (0.357 g, 0.0025 mol) in water (2 cm^3). The reaction mixture was left to stir at

5 °C for 1 h then left to rise to room temperature and left stirring for 5 days when tlc analysis (1:1 ethyl acetate:petroleum ether) showed the absence of starting material. The reaction mixture was then poured into water (2 cm^3), extracted with dichloromethane (8 x 10 cm^3), and the combined organic layers were washed with sodium hydrogen carbonate (10 cm^3) followed by water (10 cm^3) before being dried ($MgSO_4$) and concentrated under reduced pressure to give 1,1-dichloro-4-hydroxy-2-thiabutane 2,2-dioxide as a pale yellow oil (0.18 g, 93%).

^1H NMR spectroscopy showed properties consistent with the product described previously.

Bromine oxidation (**47**, **48** & **49**) - Modified literature procedure[86]

2-Hydroxy-1,4-oxathiane 4,4-dioxide (0.304 g, 0.002 mol) was placed into a round-bottomed flask with water (8 cm^3). The solution was cooled to 0 °C. Potassium carbonate (0.318 g, 0.002 mol) was added in small portions keeping the temperature below 10°C. The reaction mixture was then cooled to below 5 °C and bromine (0.352 g, 0.0022 mol) was added dropwise keeping the reaction temperature below 10 °C. After 10 minutes the reaction mixture had turned a light yellow colour. The mixture was then quenched after 45 minutes using a small amount of sodium bisulfite until a starch-iodide paper test was negative. The mixture was extracted with dichloromethane (10 x 15 cm^3) and the combined

organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give a dark brown oil (0.42 g).

Column chromatography (10:1 petroleum ether/ethyl acetate) gave recovered starting material (0.13 g, 43%) as confirmed by ^1H NMR spectroscopy, *6,6-dibromo-2-oxa-5-thia-hexanal 5,5-dioxide* (0.039 g, 6.5%) as a yellow oil.

δ_H 8.10 (1H, s, CHO), 6.30 (1H, s, C<u>H</u>-Br_2),

4.69 (2H, t, J5.9, C<u>H</u>$_2$-CH_2-O), 3.84 (2H, t, J5.7, C<u>H</u>$_2$-CH_2-S);

δ_C 159.8 (CHO), 56.8 (<u>C</u>H_2-CH_2-O), 49.4 (CH-Br_2), 46.9(<u>C</u>H_2-CH_2-S);

m/z 239,237,235 (M - $CH_2CH_2O_2H$, 2.6, 5.5, 3.8%)

171,173,175 (CH-Br_2, 89, 100, 85%), 45 (O_2CH, 98%);

υ_{max}(film/cm^{-1}) 3445 (O-H), 2995 (CH_2), 1730 (C=O), 1330 (=SO_2), 1140 (=SO_2), 770 (-Br);

Found C, 15.42; H, 1.96%; S, 10.40%. $C_4H_6Br_2O_4S$ requires

C, 15.50; H, 1.95; S, 10.34%.

and *1,1-dibromo-2 -thiabut-3-ene 2,2-dioxide* (0.091g, 17%) as a cream coloured solid, m.p. 82-83°C.

δ_H 6.96 (1H, dd, J9.8, 16.7, C<u>H</u>=CH_2),

6.69 (1H, d, J16.7, C<u>H</u>-CH, (trans to C<u>H</u>-SO_2)),

6.50 (1H, d, J9.8, CH, (cis to CH-SO_2), 6.15 (1H, s, C<u>H</u>-Br_2);

δ_C 136.8 (=CH_2), 129.9 (CH-S), 48.8 (CH-Br_2);

m/z 266,264,262 (M^+,<0.5%),

239,237,235 (M - CH_2=CH, 1.1,2.1,1.0%),

175,173,171 (CH-Br_2, 86.0,98.4,86.8%), 91 (CH_2CHSO_2,77.9%);

υ_{max}(film/cm^{-1}) 2995 (=CH_2), 1350 (=SO_2), 1140 (=SO_2),770 (C-Br);

Found C 13.97; H 1.58. $C_3H_4Br_2O_2S$ requires C 13.65; H 1.53 %;

The above procedure was repeated using instead 2.2 equivalents of bromine (0.703 g, 0.0044 mol). On addition of bromine, the solution became a cloudy dark orange colour, after 20 minutes the solution was no longer cloudy but a transparent orange colour. The mixture was left to stir at room temperature for 18 hours, when tlc analysis showed only a trace amount of starting material present. The reaction mixture was quenched using sodium bisulfite until a starch-iodide paper test was negative. The mixture was extracted with dichloromethane (12 x 25 cm^3), the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure giving a brown oil (0.50 g).

Partial purification by column chromatography (6:1 petroleum ether/ethyl acetate) yielded a mixture (0.48 g) of *6,6-dibromo-2-oxa-5-thia-hexanal 5,5-dioxide*, *1,1-dibromo-2-thia-but-3-ene 2,2-dioxide* and *1,1-dibromo-4-hydroxy-2-thia-butane 2,2-dioxide* in the ratio of 1:3:53 as determined by ^1H NMR spectroscopic analysis.

Extended and repeated column chromatography gave a pure sample of *1,1-dibromo-4-hydroxy-2-thiabutane 2,2-dioxide* as a brown oil for full spectroscopic characterization.

δ_H 6.49 (1H, s, C<u>H</u>), 4.19 (2H, t, J5.2, C<u>H_2</u>-CH_2-S),

3.72 (2H, t, J5.2, C<u>H_2</u>-CH_2-OH), 2.50 (OH, D_2O exchange);

δ_C 56.7 (CH_2-OH), 50.9 (CH_2-S), 50.2 (CH);

m/z 284,282,280 (M^+, 0.5,1.1,0.5%), 237 (M^+ - $HOCH_2CH_2$, 5.0%),

203,202,201 (M^+ - Br, 0.7,1.5,0.7%), 175,173,171 (CH-Br_2,63.4,83.1,68.4%),

45 (CH_2CH_2OH, 100%), 31 ($HOCH_2$, 83%);

Found C,12.86; H, 2.16%. $C_3H_6Br_2O_3S$ requires C, 12.78, H, 2.14%.

8.5 Preparation and Studies of 3-Oxotetrahydrothiophene 1,1-dioxide (52)

Modified literature procedure[88]

3,4-Dibromotetrahydrothiophene 1,1-dioxide (10.00 g, 0.036 mol) was added slowly to a well stirred solution of sodium methoxide in methanol (prepared from sodium 3.24 g, in methanol 50 cm^3 methanol). A vigorous exothermic reaction ensued and the white reaction mixture was left to stir overnight at room temperature. Methanol was then removed under reduced pressure, the resulting solid dissolved in water (12 cm^3) and the solution was brought to pH 8 by the careful addition of concentrated hydrochloric acid. The mixture was concentrated under reduced pressure and the residual yellow solid extracted with dichloromethane (4 x 50 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to yield 3,3-dimethoxytetrahydrothiophene 1,1-dioxide (4.51 g, 70%) as a pale yellow solid.

Dilute hydrochloric acid (18 cm^3) was added to the solid crude ketal (4.51 g, 0.025 mol) and the mixture refluxed for 1 hour. Upon cooling, the mixture was concentrated under reduced pressure (0.5 mm/Hg) to yield a light brown solid. Recrystallization from 95% ethanol yielded the title compound as off-white crystals (2.23 g, 66%).

M.p. 61 - 62 °C Lit[88] 58.5 - 59.5 °C.

δ_H 3.70 (2H, s, S-C<u>H</u>$_2$-C=O), 3.58 (2H, t, J7.8, S-C<u>H</u>$_2$-CH$_2$), 3.07 (2H, t, J7.8, C<u>H</u>$_2$-CH$_2$-S);

δ_C 198.9 (C=O), 57.4 (S-<u>C</u>H$_2$-CO), 50.7 (S-<u>C</u>H$_2$-CH$_2$), 38.8 (<u>C</u>H$_2$-CH$_2$-S);

υ_{max}/cm^{-1}(nujol) 2828 (CH_2), 1742 (C=O), 1325 (SO_2).

<u>Attempted alkylation of 3-oxotetrahydrothiophene 1,1-dioxide</u>

<u>Method A - potassium carbonate/acetone</u>

To a solution of potassium carbonate (0.16 g, 0.00115 mol) stirred in acetone (10 cm^3) under nitrogen at room temperature was added 3-oxotetrahydrothiophene 1,1-dioxide (0.134 g, 0.001 mol). The mixture was left to stir for 15 mins before the addition of allyl bromide (1.33 g, 0.011 mol). The reaction mixture was left to stir at room temperature under nitrogen for 7 days. Saturated ammonium chloride (10 cm^3) was added to the mixture and the aqueous layer was extracted using ethyl acetate (8 x 20 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give a pale brown oil (0.092 g).

^{1}H NMR spectroscopy showed properties consistent to that of the starting material (0.092 g, 71%).

When the reaction was repeated but this time under reflux conditions for 4 days, only an intractable mixture of products unidentifiable by ^{1}H NMR spectroscopy was obtained.

Method B - potassium carbonate/butanone

Potassium carbonate (0.16 g, 0.00115 mol) was stirred in butanone (7 cm^3) with gentle heating and 3-oxotetrahydrothiophene 1,1-dioxide (0.134 g, 0.001 mol) added. After 10 minutes, allyl bromide (0.133 g, 0.0011 mol) was added and the mixture was left to reflux for 7 days. Saturated sodium chloride (10 cm^3) was added and the aqueous layer was extracted using ethyl acetate (8 x 15 cm^3). The combined organic layers were then dried ($MgSO_4$) and concentrated under reduced pressure.

Column chromatography (1:1 ethyl acetate:petroleum ether) gave a yellow oil (0.10 g) which was shown to be an intractable mixture of components not identifiable by ^{1}H NMR spectroscopy.

Method C - potassium carbonate

(i) Iodomethane (57)

3-Oxotetrahydrothiophene 1,1-dioxide (0.134 g, 0.001 mol) was stirred in DMF (5 cm^3) then iodomethane (0.163 g, 0.00115 mol) and potassium carbonate (0.17 g, 0.0012 mol). The mixture was left to stir at room temperature under nitrogen for 3 days when tlc analysis (1:1 ethyl acetate:petroleum ether) showed the disappearance of starting material.

Saturated ammonium chloride (10 cm^3) was added and the aqueous layer was extracted using ethyl acetate (4 x 25 cm^3). The combined organic extracts were washed with water (16 x 10 cm^3) before being dried ($MgSO_4$) and concentrated under reduced pressure.

Column chromatography (ethyl acetate) yielded *2,2-dimethyl-3-oxotetrahydrothiophene 1,1-dioxide* (0.113 g, 70%) as white crystals;

M.p. 101 °C

δ_H 3.48 (2H, t, J7.8, S-C$\underline{H_2}$-CH_2), 2.95 (2H, t, J7.8, C$\underline{H_2}$-CH_2-S),

1.44 (6H, s, 2 x CH_3);

δ_C 205.8 (C=O), 45.1 & 35.0 (CH_2-CH_2-S), 17.9 (-CH_3);

m/z 162 (M, 29.2 %), 104 (M - $COC(CH_3)_2$, 12.1%),

90 (M - $CH_2COC(CH_3)_2$, 54.3%), 42 (C-$(CH_3)_2$, 100%);

υ_{max}/cm^{-1}(nujol) 2955 (-CH_3), 1735 (C=O), 1307 (=SO_2),

1117 (=SO_2).

and trace amounts of a product provisionally assigned as 3-methoxy-4,5-dihydrothiophene 1,1-dioxide.

(ii) Iodopropane/DMF

3-Oxotetrahydrothiophene 1,1-dioxide (0.134 g, 0.001 mol) was stirred in DMF (5 cm^3) and iodopropane (0.195 g, 0.00115 mol) and potassium carbonate (0.17 g, 0.0012 mol) were then added. The reaction mixture was then left to stir at room temperature under nitrogen for 2.5 h when tlc analysis (2:1 ethyl acetate:petroleum ether) showed the absence of starting material. The reaction mixture was then quenched with saturated ammonium chloride (10 cm^3) and the aqueous layer extracted with ethyl acetate (7 x 15 cm^3). The combined organic extracts were washed with water (10 x 15 cm^3) then dried ($MgSO_4$) before being concentrated under reduced pressure.

Extensive column chromatography (1:1 ethyl acetate:petroleum ether) gave an intractable mixture of products which were shown to be unidentifiable by ^1H, ^{13}C NMR and mass spectroscopy.

Method D - sodium hydride/1,4-dioxane

Sodium hydride (0.088 g, 0.053 g of a 60 % dispersion in mineral oil, 0.0022 mol) was placed in diethyl ether (10 cm^3) and the ether was decanted off to remove the mineral oil. 1,4-Dioxane (5 cm^3) was added and the mixture was left to stir for 5 minutes before the addition of 3-oxotetrahydrothiophene 1,1-dioxide (0.134 g, 0.001 mol). Benzyl bromide (1.88 g, 0.011 mol) was then added after 15 minutes and the reaction was left to reflux for 10 hours. Saturated ammonium chloride (15 cm^3) was added and an extraction carried out using ethyl acetate (7 x 20 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure.

Column chromatography (ethyl acetate) yielded only an intractable mixture of components as shown by ^1H NMR spectroscopy and tlc analyses (ethyl acetate).

Method E - sodium hydride/THF

Sodium hydride (0.044 g, 0.026 g of a 60% dispersion in mineral oil, 0.0011 mol) was placed in diethyl ether (10 cm^3) and the ether was decanted off to remove the mineral oil. THF (5 cm^3) was then added to the solution stirred under nitrogen at 0 °C. 3-Oxotetrahydrothiophene 1,1-dioxide (0.134 g,

0.011 mol) was added and after 5 mins allyl bromide (1.33 g, 0.011 mol) was added dropwise to the reaction mixture. The mixture was left to reflux for 9 days until tlc analysis (1:1 ethyl acetate:petroleum ether) showed only trace amounts of starting material. Saturated sodium chloride solution (15 cm^3) was added and an extraction was carried out using dichloromethane (10 x 15 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure.

Column chromatography (1:1 ethyl acetate:petroleum ether) yielded only a gross mixture of products none of which were identifiable by ^1H NMR spectroscopy.

Method F - ^{n}-butyllithium/THF

3-Oxotetrahydrothiophene 1,1-dioxide (0.134 g, 0.001 mol) was stirred in THF (5 cm^3) at -78 °C under nitrogen. ^{n}-butyllithium (0.61 cm^3, 0.0011 mol) was then added dropwise and the reaction mixture was left to stir under nitrogen for 15 minutes before the addition of benzyl bromide (0.188 g, 0.0011 mol). The mixture was left to stir at -78 °C for 45 minutes and then quenched with saturated ammonium chloride (10 cm^3) at -78 °C. THF was removed under reduced pressure and the aqueous layer was then extracted with dichloromethane (10 x 20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to give recovered starting material (0.09 g, 67%), as confirmed by ^1H NMR spectroscopy

and a gross mixture of intractable products not identifiable by ^{1}H NMR spectroscopy.

Method G - in-situ alkylation - benzyl bromide/DMF

3-Oxotetrahydrothiophene 1,1-dioxide(0.134 g, 0.001 mol) was stirred in DMF (5 cm^3) and benzyl bromide (g, 0.00115 mol) then potassium carbonate (0.17 g, 0.0012 mol) added. The mixture was left to stir at room temperature for 7 days. Saturated ammonium chloride (10 cm^3) was then added and an extraction carried out using ethyl acetate (10 x 15 cm^3). The combined organic layers were washed with water (10 x 15 cm^3) before being dried ($MgSO_4$) and concentrated under reduced pressure.

^{1}H NMR spectroscopy and tlc analysis (ethyl acetate) showed an intractable mixture of components which were not separable despite extensive column chromatography (ethyl acetate; 1:1 ethyl acetate:petroleum ether).

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