ON THE CHEMISTRY OF SOME VINYL SULPHOXIDES

A thesis presented by

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CONTENTS

ABSTRACT

The chemistry of vinyl sulphoxides and the rearrangement of allylic sulphoxides to allylic sulphenates are reviewed.

The base-catalysed condensation of α-sulphinyl esters with aldehydes has been developed into a useful synthesis of α-sulphinyl α,β-unsaturated esters and the geometry of the double bond in these products has been established as E by means of the europium-shifted n.m.r. spectra. It has been established that the pyridine-induced rearrangement of these unsaturated sulphoxide esters leads clearly to E-γ-hydroxy-α,β-unsaturated esters. The rearrangement of an α-sulphinyl dienoic ester has also been examined in detail.

The condensation of methyl benzenesulphinylacetate with crotonaldehyde in the presence of magnesium methoxide was found unexpectedly to lead to sequential formation of α-sulphinyl dienoic ester, Michael attack of methoxide ion and allylic sulphoxide-sulphenate rearrangement. This observation was turned to advantage by developing a 'one-pot' procedure for the synthesis of E-γ-hydroxy-α,β-unsaturated esters, utilizing the magnesium methoxide-induced condensation of α-sulphinyl esters with aldehydes. Conjugate addition of nucleophiles other than methoxide to the α-sulphinyl dienoic ester derived from crotonaldehyde was also investigated.

Having established a convenient synthesis of α-sulphinyl α,β-unsaturated esters, the value of these compounds as synthons has been demonstrated by their use in Diels-Alder reactions. The Claisen rearrangement of an allylic α-benzenethioacetate, followed by a sulphoxide elimination reaction was explored for stereospecific olefin synthesis.

In order to exemplify the use of the condensation of aldehydes

with α-sulphinyl esters and the subsequent allylic sulphoxide-sulphenate rearrangement, the application of these reactions to the synthesis of the macrolide pyrenophorin has been explored at length.

ACKNOWLEDGEMENTS

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Finally, I would like to thank my parents for their loving support and encouragement during my long absence from home.

to

Anelita,
Iraci,
Juarez
and
Julian.

"An honest tale speeds best being plainly told"

(W. Shakespeare, Richard III, IV, iv).

Part I:

REVIEW

'Vinyl sulphoxides and the allylic sulphoxide-sulphenate rearrangement'

I.1 Introduction

During the last few years the formation and the chemistry of α,β-unsaturated sulphoxides have attracted more and more attention and as a consequence a number of important innovations in synthetic organic chemistry have been developed.

The ease with which these compounds can be equilibrated with the β,γ-isomers[1] is an important property of these systems, since it means that the useful synthetic Mislow-Evans sequence[2,3], which utilizes the allylic sulphoxide-sulphenate interconversion, can also be applied to them.

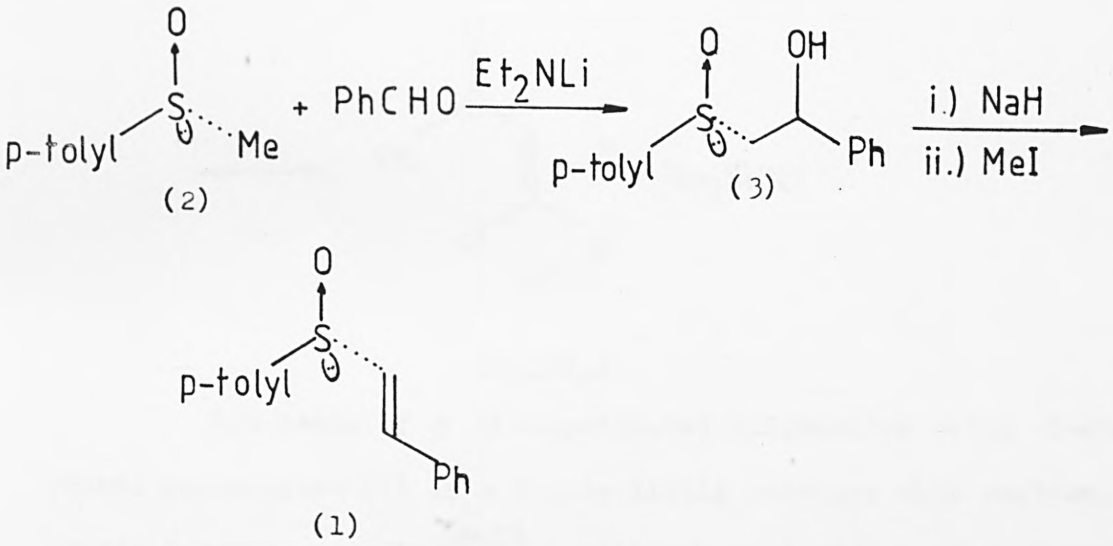
The formation and the chemistry of vinyl sulphoxides, as well as the allylic sulphoxide- sulphenate rearrangement is the subject of this survey.

I.2 Synthesis of Vinyl Sulphoxides.

The oxidation of the appropriate α,β - unsaturated sulphide constitutes the most common route to the corresponding α,β --unsaturated sulphoxide. Although the oxidation of vinyl sulphides to vinyl sulphoxides can be complicated by epoxidation of the double bond and overoxidation to yield a sulphone[4], several selective oxidizing agents have been used [4-11]. The following are some of the ones which have been employed: hydrogen peroxide[5], iodobenzene dichloride[6], hypochlorites[7], fuming nitric acid[8], peracids[4,9,10] and sodium metaperiodate[4,11].

Another important route to the synthesis of vinyl sulphoxides involves elimination from a suitable β-substituted sulphoxide[12-15]. Through this route the synthesis of an optically active vinyl sulphoxide can be achieved[12]. The synthesis of (+) - (R)-

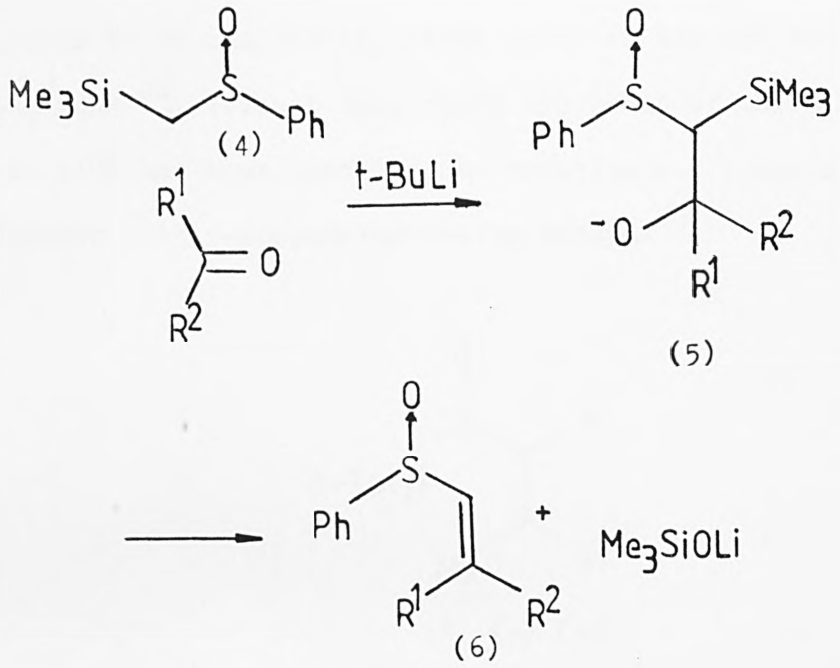
-trans-β-styryl-p-tolyl sulphoxide (1) was carried out by reacting (+)-(R)-methyl p-tolyl sulphoxide (2) with benzaldehyde in the presence of lithium diethylamide to yield the β-hydroxy-sulphoxide (3) which, by treatment with an excess of sodium hydride and methyl iodide, afforded (+)-(R) (1) in 75% yield (Scheme 1)[12].



Scheme 1

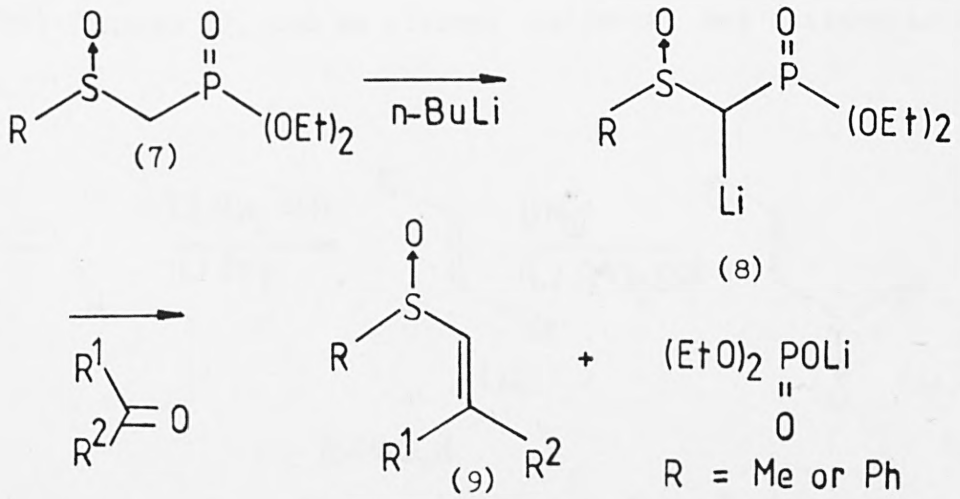
The formation of vinyl sulphoxides also results from addition of sulphenic acids (formed by thiosulphinate and sulphoxide decomposition) across acetylenic esters[16-18].

A more general synthesis of vinyl sulphoxides was reported by Carey and Hernandez[19]. They performed a Peterson-type reaction of trimethylsilyl sulphoxide (4) with carbonyl compounds. A number of representative aldehydes and ketones were reacted with (4) to produce vinyl sulphoxides of type (6); the overall yield was good. The reaction was not, however, stereoselective and mixtures of E and Z isomers were formed from aldehydes. The main limitation to this method arises from the low thermal stability of the starting α-silyl substituted sulphoxide (Scheme 2).



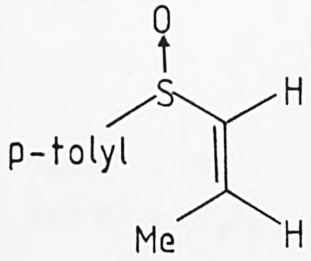
Scheme 2

Synthesis of α,β-unsaturated sulphoxides using α-phosphoryl sulphoxides (7) in a Horner-Wittig reaction with carbonyl compounds has been reported[20,21]. Although good yields of the vinyl sulphoxide (9) have been obtained, these reactions have also been shown to lack stereoselectivity and mixtures of E and Z isomers have been isolated from aldehydes and unsymmetrical ketones (Scheme 3).



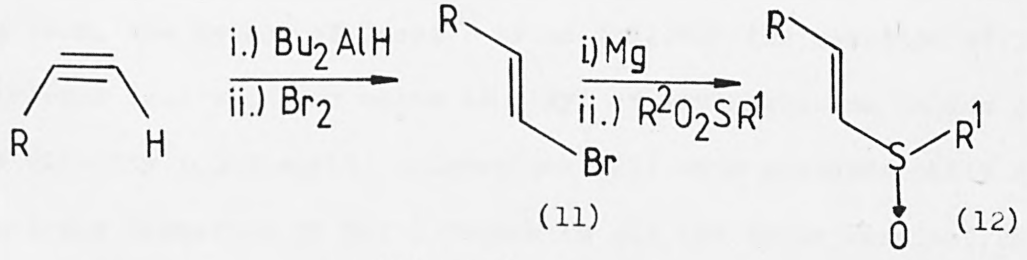
Scheme 3

The reaction of sulphinate esters with organometallic reagents is an old and important route to the synthesis of chiral sulphoxides [22]. Through this route synthesis of chiral Z-vinyl sulphoxide (10) has been achieved, by treating S-(-)-menthyl toluene-p-sulphinate with Z-propenylmagnesium bromide[23].



(R) (-) (10)

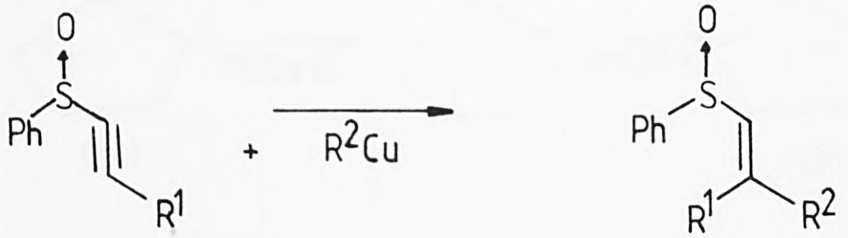
The reaction of sulphinate esters with Grignard reagents has been examined recently by Harpp and co-workers[24] and emphasis has been given to the formation of sulphides as by-products in this type of reaction. They recommend the use of lithium organocuprate reagents for conversion of sulphinate esters into corresponding sulphoxides. Posner and Tang, however, have reported[25] the stereospecific conversion of (E)-vinylic bromide (11) via the corresponding Grignard reagent into (E)-vinylic sulphoxides (12) in good yields (51 - 75%) (Scheme 4), and no alkenyl sulphide was detectable in this process.



Scheme 4

Another stereoselective synthesis of α,β-unsaturated sulphoxides has been reported by Truce and Lusch[26]. They have found

that α,β-acetylenic sulphoxides (13) react readily with monoalkylcopper (I) reagents (14) to produce the corresponding β-alkylated vinylic sulphoxide (15). The product is almost exclusively the result of a cis-addition to the triple bond of (13) (Scheme 5).



13a $R^1 = CH_3$ 14a $R^2 = CH_3$ 15a $R^1 = CH_3$; $R^2 = nC_4H_9$

13b $R^1 = nC_4H_9$ 14b $R^2 = nC_4H_9$ 15b $R^1 = nC_4H_9$; $R^2 = CH_3$

15c $R^1 = R^2 (= CH_3$ or $nC_4H_9)$

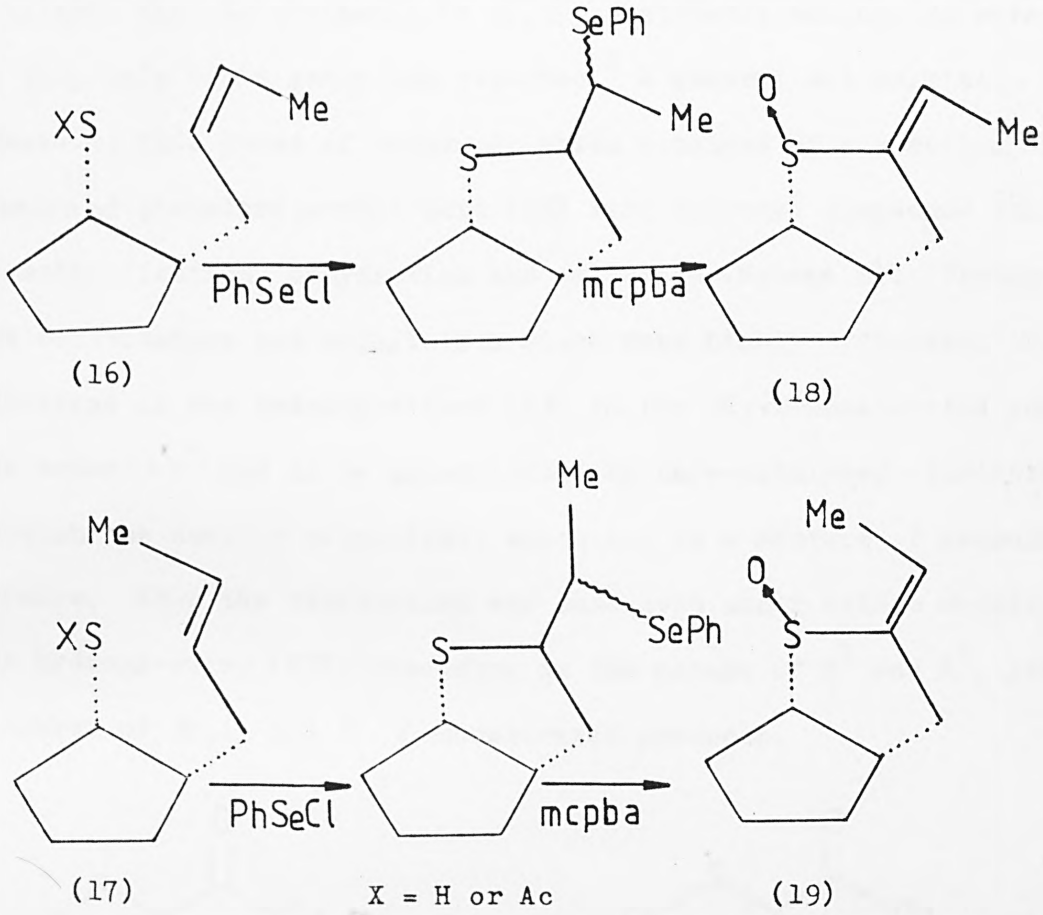
Scheme 5

The synthesis of vinyl sulphoxides through addition of organocopper (I) reagents to acetylenic sulphoxides has also been reported by Vermeer and co-workers[27].

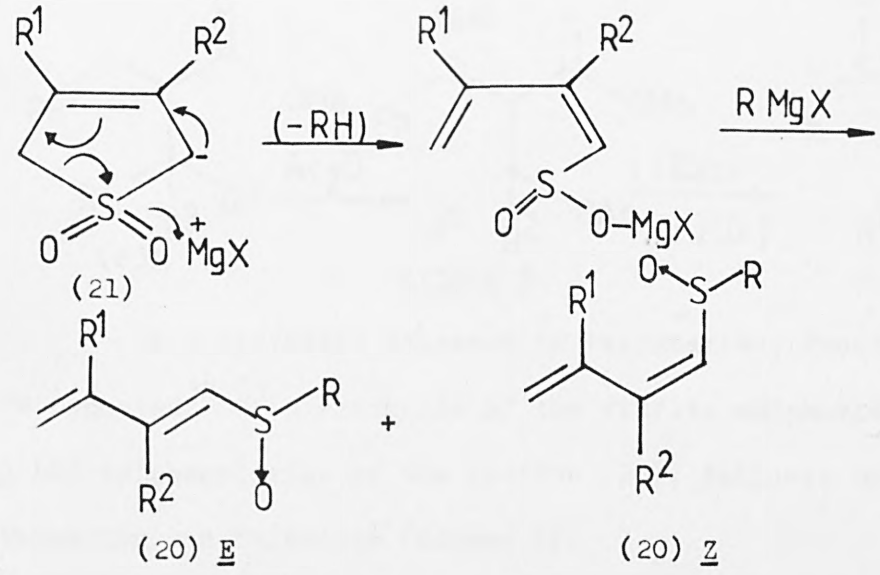
A stereoselective synthesis of cyclic α,β-unsaturated sulphoxides (and sulphones) has been reported by Nicolaou and co-workers[10] (Scheme 6). Either the E or Z isomers of cyclic α,β-unsaturated sulphoxides (and sulphones) have been obtained by the use of the proper double bond isomer, (16) or (17), via a selenium-based method.

With respect to the synthesis of 1,3-dienylic sulphoxide (20) several alternative procedures have been reported recently[10,27-30]. Among them, the method of Gaoni[30] is as follows: the reaction of the sulpholenes (21) with two moles of alkyl or arylmagnesium halide produces directly 1,3-dienylic sulphoxides (20) with preponderantly or exclusively formation of the Z isomer in all the cases examined (Scheme 7).

In contrast to the numerous alternative procedures for the synthesis of α,β-unsaturated sulphoxides, there are very few methods

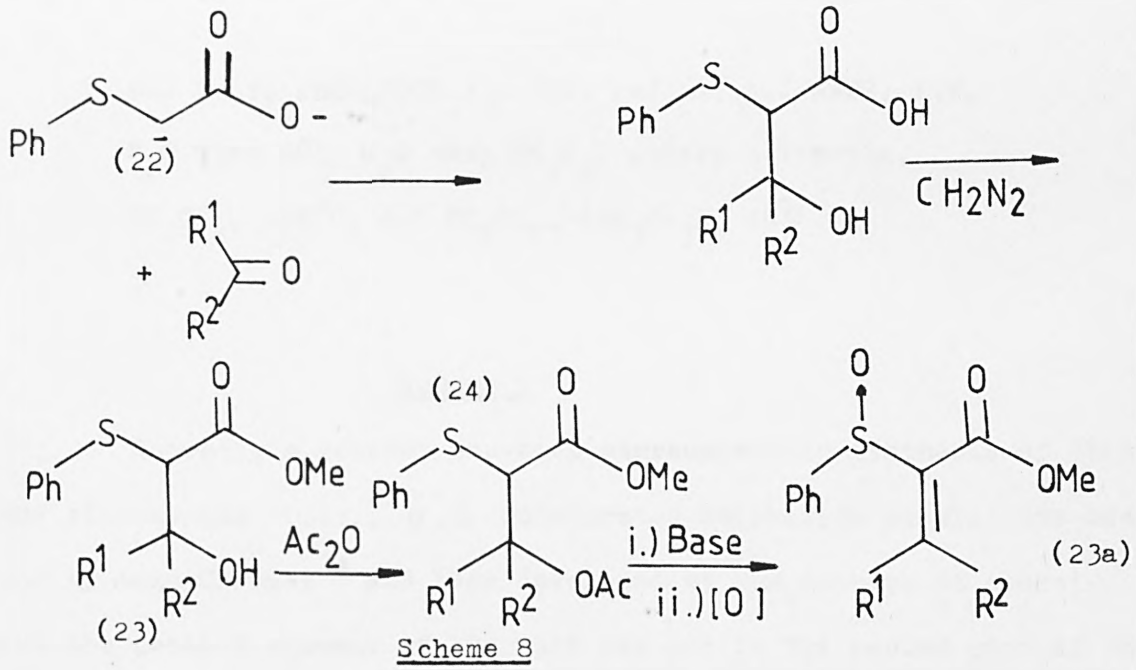


Scheme 6



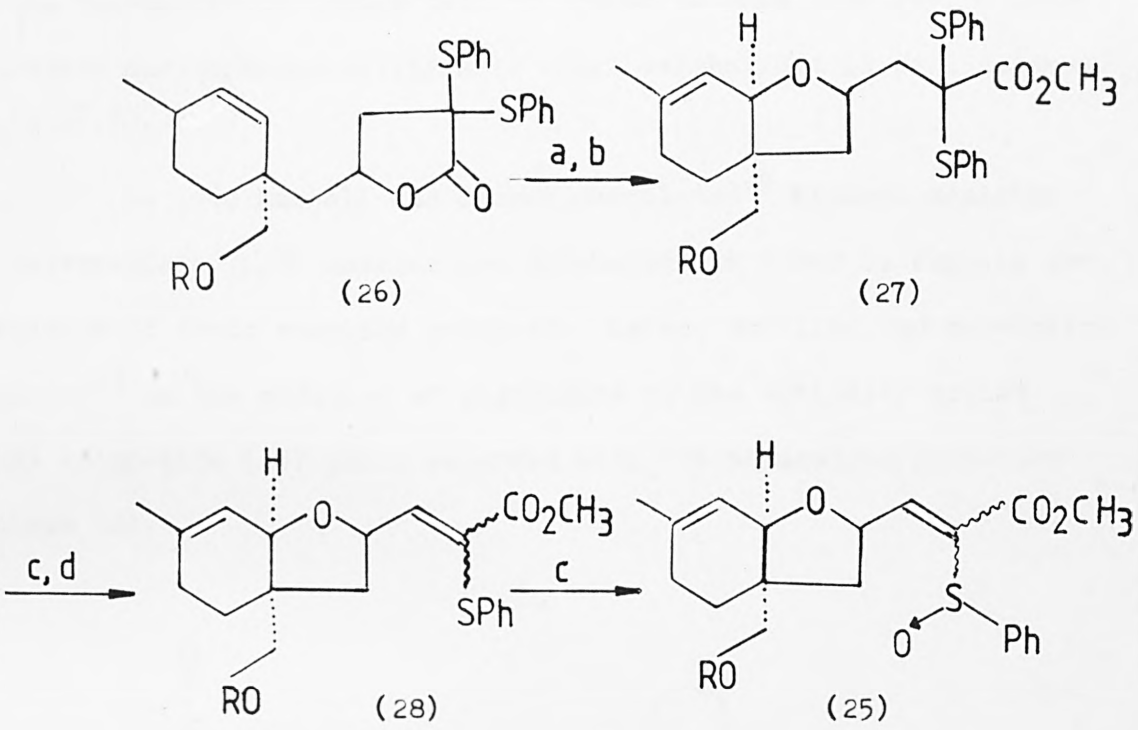
Scheme 7

available for the synthesis of α,β-unsaturated sulphoxide esters. So far, only Uda's group has reported[31] a general but multistep synthesis to this class of compound, which consists of a reaction of the dianion of phenylthioacetic acid (22) with carbonyl compounds followed by esterification, dehydration and oxidation (Scheme 8). Though the condensation and methylation steps were highly efficient, the dehydration of the hydroxy-esters (23) to the α,β-unsaturated sulphoxide ester (23a) had to be accomplished by base-catalysed elimination through the acetoxy ester (24), which led to a mixture of geometric isomers. When the dehydration was conducted under acidic conditions the hydroxy-ester (23), depending on the nature of R^1 and R^2, gave mixtures of α,β and β,γ-unsaturated products.



Scheme 8

In a synthetic approach to verrucarins, Trost and Rigby have reported[32,33] a synthesis of the vinylic sulphoxide ester (25) via bis-sulphenylation of the lactone (26), followed by sulphoxide elimination and oxidation (Scheme 9).



a.) CuBr, $PhCO_3C(CH_3)_3$, PhH, reflux; b.) NaOH, THF, H_2O then HCl, H_2O then CH_2N_2, ether; c.) mcpba, CH_2Cl_2, -15°C; d.) CH_2Cl_2, $(CH_3O)_3P$, 46°C.

Scheme 9

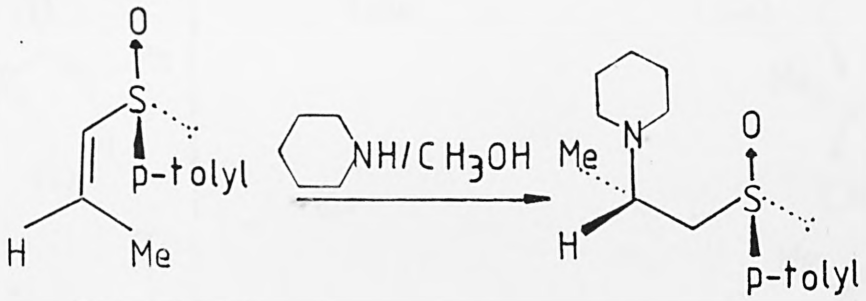
Recently a general one-step stereospecific synthesis of this class of compound (i.e., α,β-unsaturated sulphoxide esters) has been found by Jaxa-Chamiec[34] and been developed by the Author; it constitutes the central element of the work set out in the second part of this thesis.

I.3 The Chemistry of Vinyl Sulfoxides

An important characteristic of α,β-unsaturated sulphoxides consists in their being electron deficient olefins having an

asymmetric centre owing to the tricoordinate sulphur atom adjacent to the carbon-carbon double bond[35]. Based on this property, stereoselective nucleophilic addition to vinyl sulphoxides is well documented[12,17,23,37-40].

In 1963 Russell and Becker postulated[36] Michael addition to intermediate α,β-unsaturated sulphoxide in order to explain the formation of their reaction products. Later, Stirling and co-workers reported[23] on the addition of piperidine to the optically active vinyl sulphoxide (10) which occurred with 74% asymmetric induction (Scheme 10).



(Z)-(-)-(R)
(10)

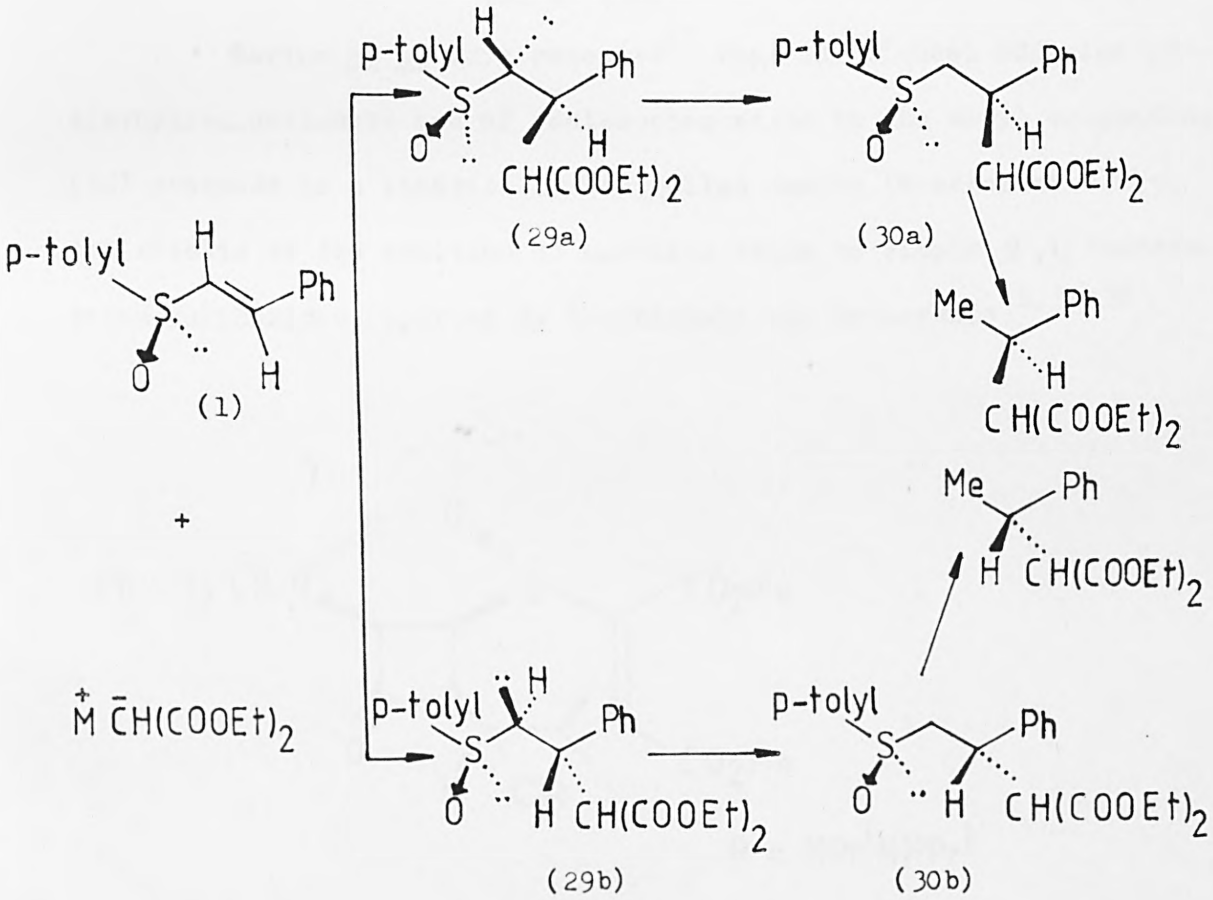
S R

Scheme 10

Similar asymmetric induction was reported during the addition of malonate anion to the optically active vinyl sulphoxide (1)[12,37]. This is a kinetically controlled, irreversible process where preferential creation of either an (R)- or an (S)-asymmetric centre can be achieved by subtle modification in the nature of the solvent and counter-ions[38].

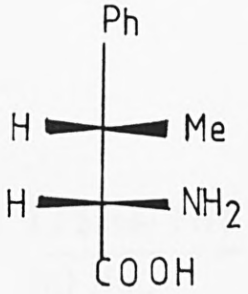
The selective formation of either epimer was explained as follows: as this Michael addition is kinetically controlled, the rate determining step is, therefore, the formation of the anion (29a)

or (29b); the anion (29a) being the more stable in polar protic solvents (because of the trans-relationship between the lone pair and the sulphinyl oxygen), (30a) would be preferentially formed in ethanol whereas the anion (29b) being the more stable in THF-Li systems, because of the gauche-relationship between the carbon lone pair and the sulphinyl oxygen, (30b) would be formed preferentially in this system (Scheme 11)[38].



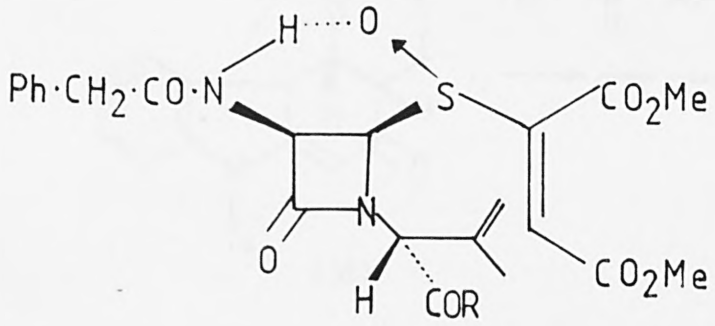
Scheme 11

One of the applications of this reaction was demonstrated in the synthesis of (S,S)-2-amino-3-phenylbutyric acid (31)[39] (a bottromycin component, isolated from a culture of Streptomyces bottropensis) from diethyl (R)-1-(phenylethyl) malonate which was obtained by desulphurization of the adduct in the stereoselective Michael reaction of the chiral vinyl sulphoxide (1) with diethyl malonate[12].



(S, S) (31)

Barton et al have reported[17] that the Michael addition of diethylsodiomalonate and of sodioacetoacetate to the vinyl sulphoxide (32) proceeds in a kinetically controlled manner in accordance with the results of the addition of malonate anion to simple α,β-unsaturated sulphoxides reported by Tsuchihashi and co-workers[12,37,38].

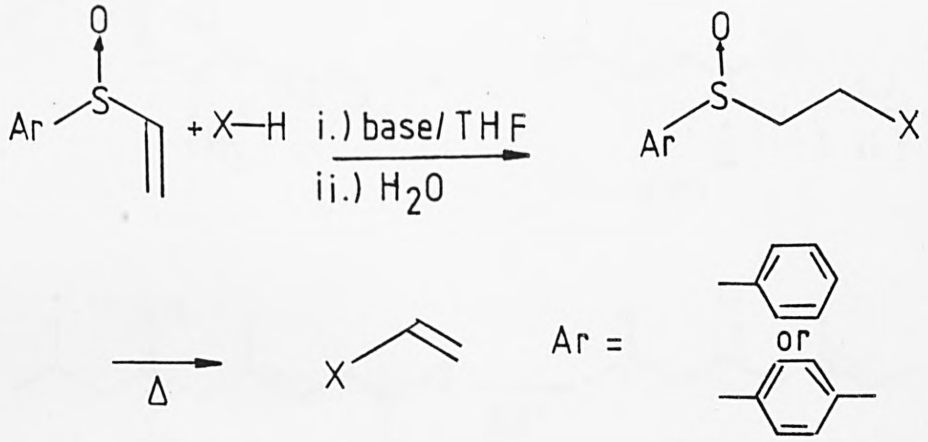


(32)

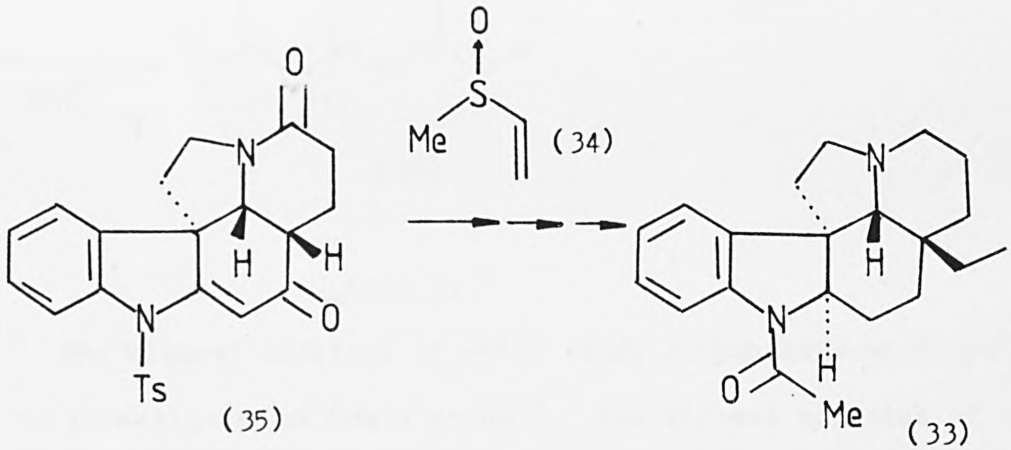
It has been reported[41,42] that thermolysis of Michael adducts of vinyl sulphoxides is a useful method for olefin synthesis (Scheme 12)[41].

It has also been reported[43] that the synthesis of (±) 1--acetylaspidospermidine (33) (the alkaloid which was isolated

from various Aspidosperma species) was achieved via the Michael condensation of methyl vinyl sulphoxide (34) with the synthetic precursor (35) (Scheme 13).

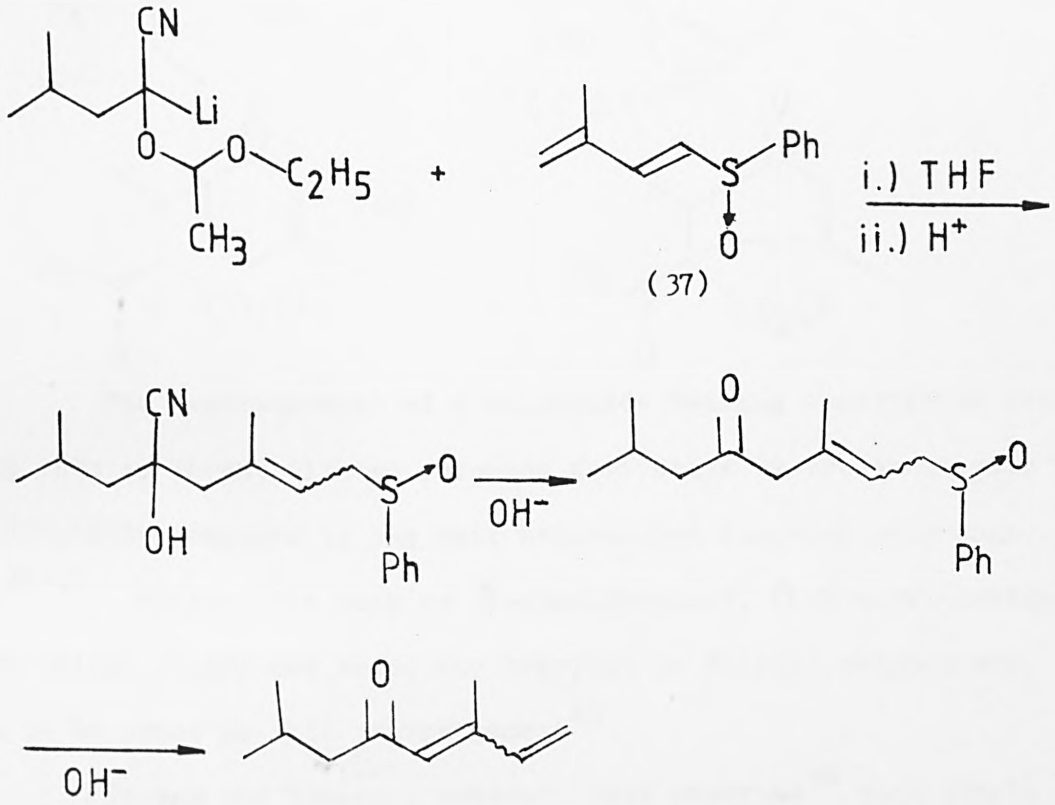


Scheme 12



Scheme 13

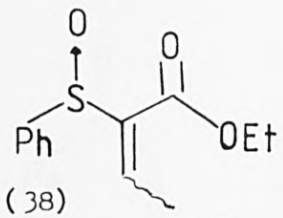
The ability of dienylic sulphoxides to undergo Michael-type addition with carbanions was examined by Guittet and Julia[29], with respect to the synthesis of the tagetones (36). The tagetones (36) were isolated, in an overall yield of 50%, from the dienylic sulphoxide (37), as a mixture of geometric isomers (E : Z / 55 : 45) (Scheme 14).



(36)

Scheme 14

The Michael addition of ester vinyl sulphoxides with cyclic enones was investigated by Uda's group[44]. The Michael addition of the vinyl sulphoxide (38) with 2-cyclohexenone was accompanied by desulphenylation during the work-up to afford the bicyclo [2.2.2] octene derivative (39). However, when the ester vinyl sulphoxide (38) was reacted with either 3-methyl-2-cyclohexenone or 3-methyl-2-cyclopentenone, it afforded, in low yields as diastereoisomeric mixtures, only the first Michael adducts (40) and (41) respectively. The failures of the second Michael additions with respect to (40) and (41) were explained in terms of the stability of the anion -$\bar{C}$ (SOPh) COOEt and the steric effect of the ring methyl group.



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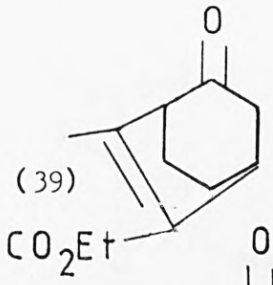

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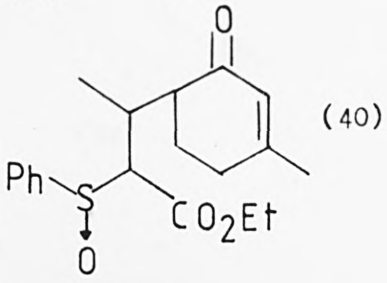

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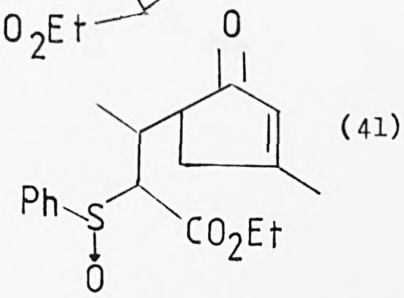
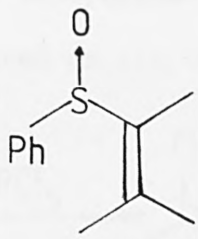


(41)

The rearrangement of a sulphoxide bearing a methyl or methylene group into an α-substituted sulphide derivative by treatment with electrophilic reagents is the well established Pummerer rearrangement[45-47]. Sulphoxides such as β-disulphoxides, β-ketosulphoxides, β-sulphinyl esters and acids and benzylic or allylic sulphoxides seem to be prone to this rearrangement[46].

Parham and Edwards, however, have reported[48] that simple vinyl sulphoxides such as (42) and (43) are stable to hot acetic anhydride.



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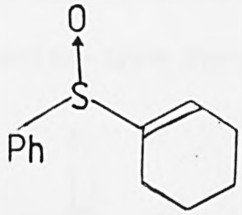
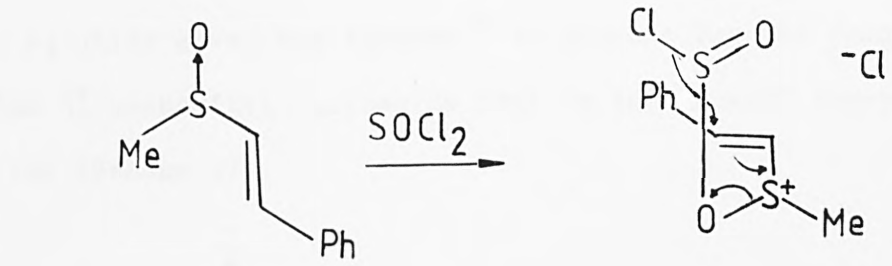


(43)

In contrast, other types of rearrangement involving the migration of a β-hydrogen atom to produce a chlorosulphide or β-ketosulphide were observed for styryl sulphoxides[13,49].

Russell and co-workers[13] have observed that on treatment with thionyl chloride the styryl sulphoxide (44) yields chlorosulphide (45) presumably <u>via</u> the intermediates set out below (Scheme 15).



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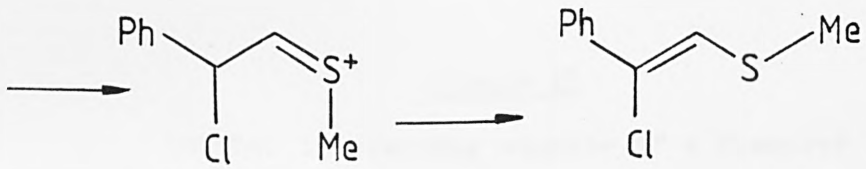
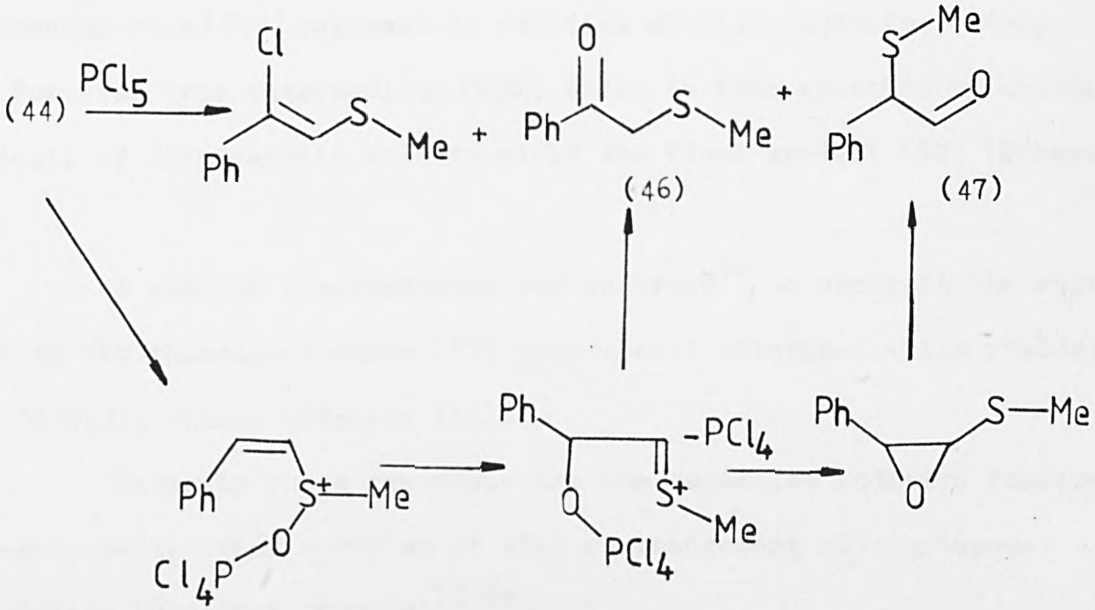


(45)

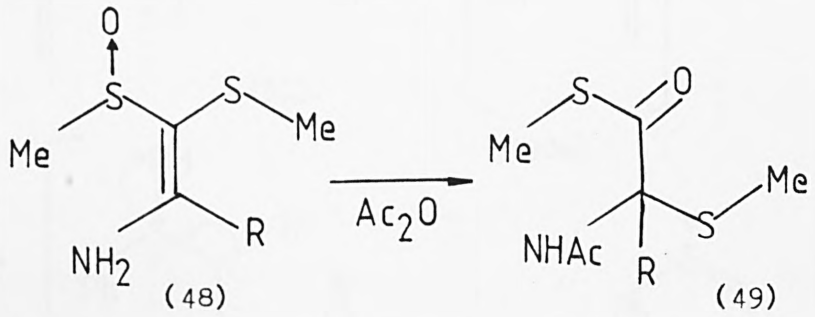
Scheme 15

The formation of by-products such as (46) and (47) was reported[49] to occur in the chlorination of the same styryl sulphoxide (44) with phosphorus pentachloride and their formation was also rationalised on the basis of a Pummerer-type reaction (Scheme 16).



Scheme 16

A Pummerer-type rearrangement involving the migration of a sulphide group was invoked[50] to account for the transformation of the β-aminovinyl sulphoxide (48) to the unusual rearrangement product (49) (Scheme 17).



(48) (49)

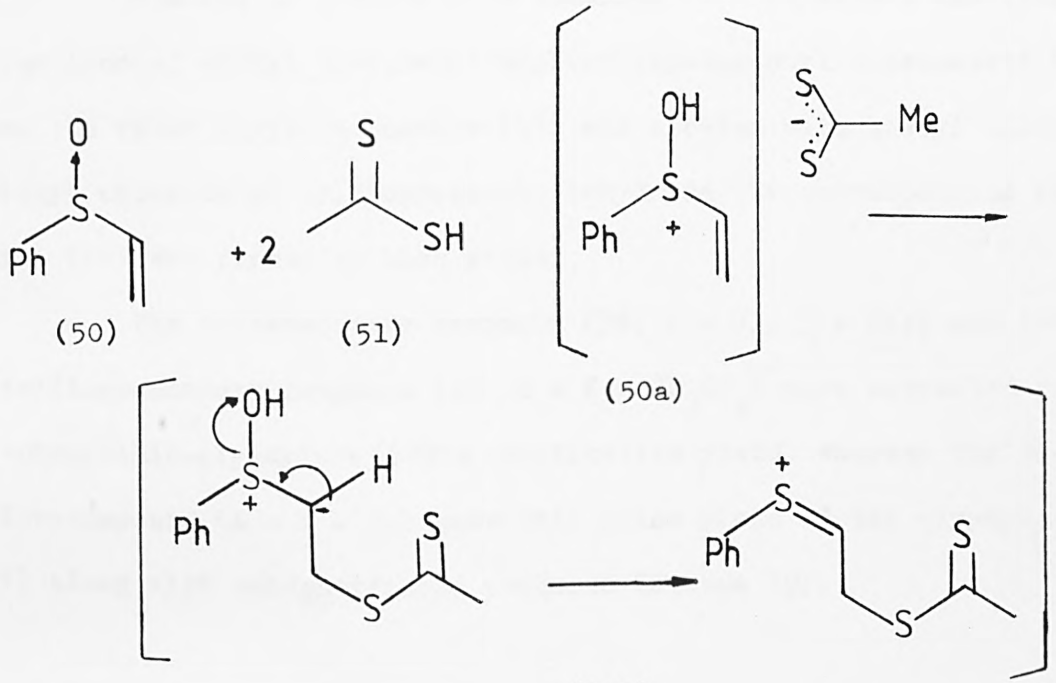
Scheme 17

Another interesting example of a Pummerer rearrangement was observed by Oae and co-workers[51] in the reaction of phenyl vinyl sulphoxide (50) with dithioacetic acid (51). The reaction of phenyl vinyl sulphoxide (50) with two moles of dithioacetic acid (51) at room temperature afforded 1,2-bis(dithioacetoxy)ethylphenyl sulphide (52) quantitatively.

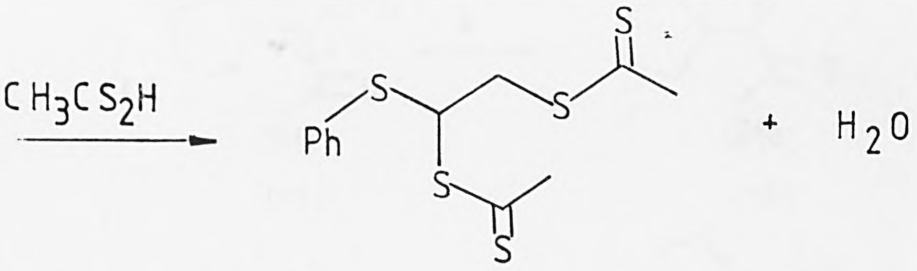
The formation of the phenyl sulphide(52) was thought to proceed via initial protonation on the sulphoxide oxygen to form the sulphonium salt (50a) followed by addition of dithioacetate to form the Pummerer type intermediate (50b), which is then attacked by another molecule of dithioacetic acid to yield the final product (52) (Scheme 18).

A similar rearrangement was reported[52] to occur in the reaction of the thiazine-S-oxide (53) with acetyl chloride, which yielded the bicyclic chloro-sulphide (54).

Formally these reactions are the so-called additive Pummerer rearrangement; other examples of this rearrangement of vinylogous sulphoxide have been reported[53-56].

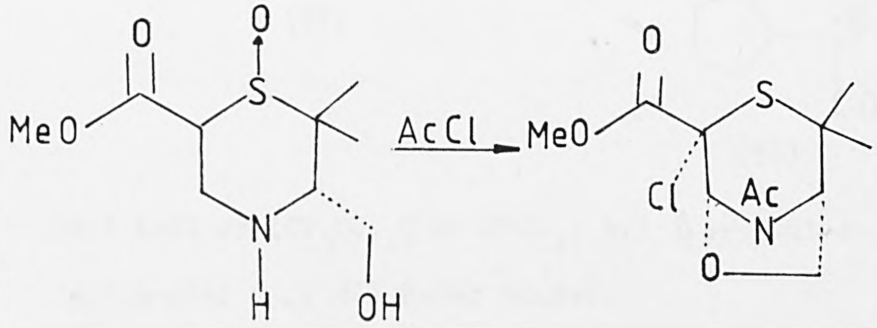


(50) (51) (50a) (50b)



(52)

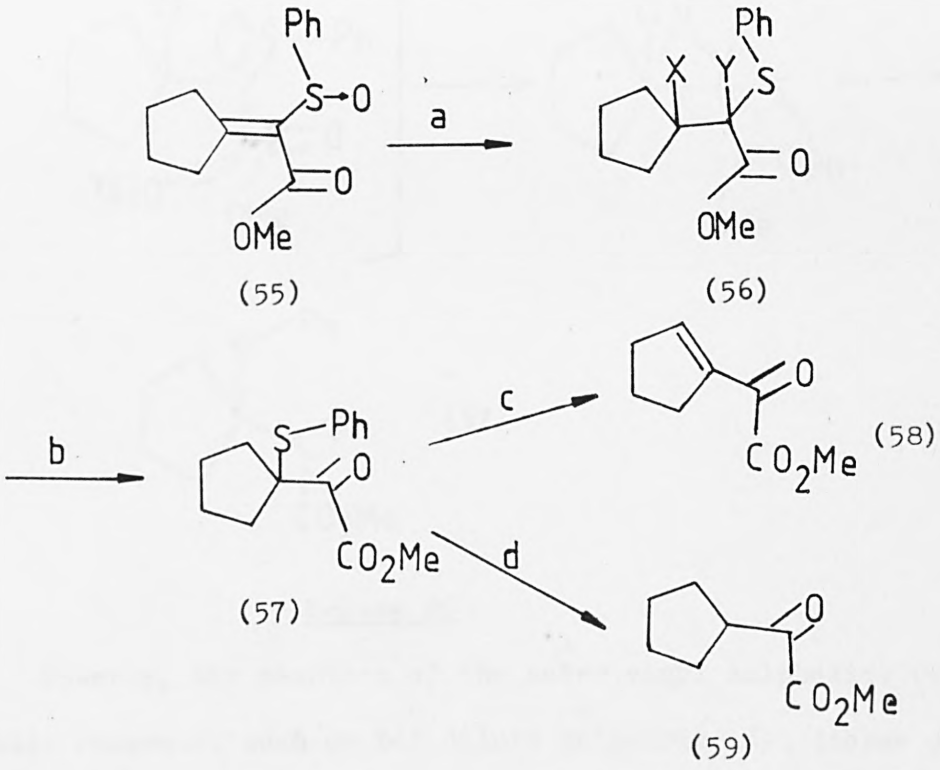
Scheme 18



(53) (54)

Uda and co-workers have examined[54,55] in detail the transformations of methyl α-(phenylsulphinyl)cyclopentylideneacetate (55). When the ester vinyl sulphoxide (55) was treated with acetyl chloride, thionyl chloride or trifluoroacetic anhydride the corresponding sulphide (56) was formed in high yield.

The chloroacetoxy compound (56, X = Cl, Y = OAc) and the ditrifluoroacetoxy compound (56, X = Y = CF_3CO_2) were converted to β-phenylthio-glyoxylate (57) in quantitative yield, whereas the dichlorocompound (X = Y = Cl) gave only a low yield of the glyoxylate (57) along with unidentifiable products (Scheme 19).

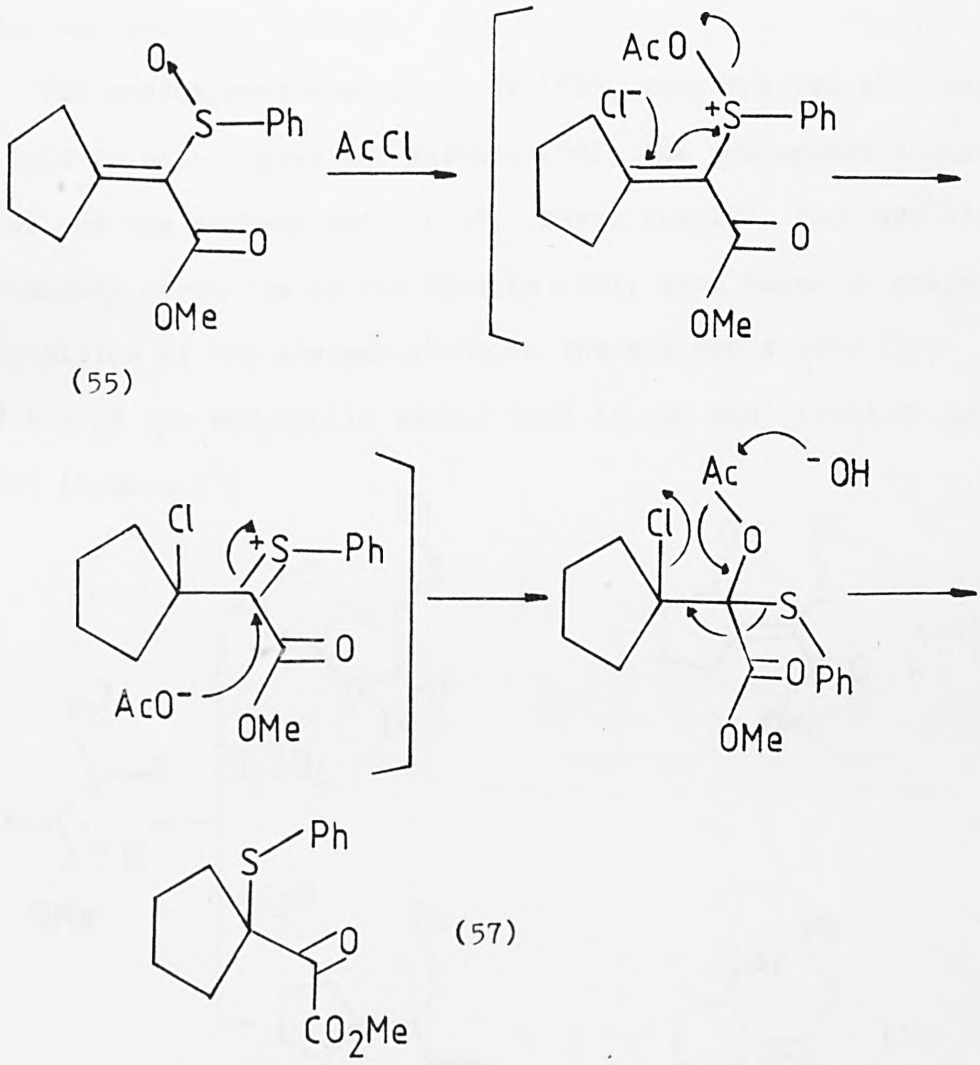


a.) AcCl or $(CF_3CO)_2O$ or $SOCl_2$; b.) Δ or dilute dioxan; c.) mcpba, Δ ; d.) Raney nickel.

Scheme 19

The transformation of the chloroacetoxy compound (56, X = Cl,

Y = OAc) to the β-phenylthio-glyoxylate (57) was explained by the elimination of acetic acid and hydrogen chloride or acetyl chloride with concomitant migration of the phenylthio group and ketonization (Scheme 20).



(55)

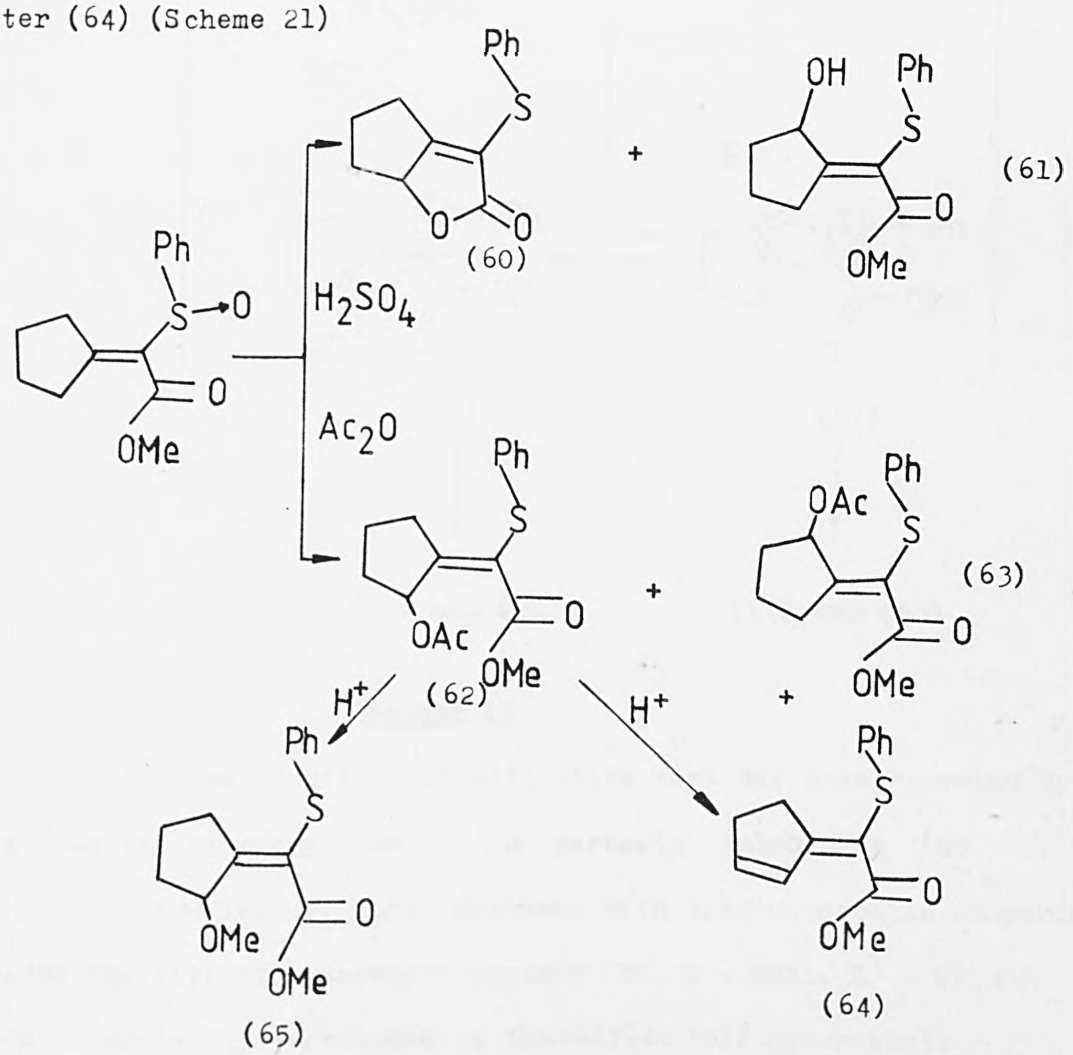
(57)

Scheme 20

However, the reaction of the ester vinyl sulphoxide (55)[55] with acidic reagents, such as hot dilute sulphuric acid-dioxan or acetic anhydride, produced γ-oxygen functionalised products. Thus on treating the ester vinyl sulphoxide (55) with hot dilute sulphuric acid-dioxan for 3h at reflux, the lactone (60) was formed as the major component in 53% yield, together with traces of the hydroxy-

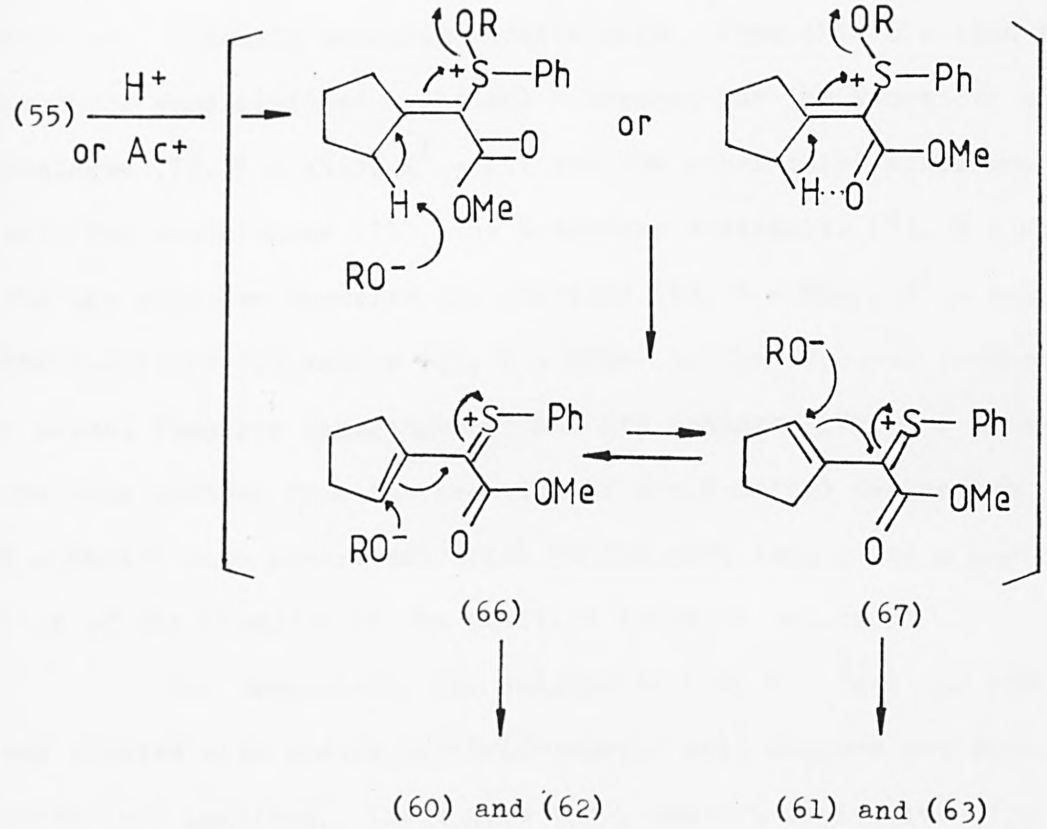
-ester (61). The reaction of the sulphoxide (55) with acetic anhydride at 75°C for 3h gave three products. The major isomer formed (62) again resulted from the oxidation of the carbon cis to the ester. When the reaction was carried out at reflux the conjugated dienoic ester (64) was the sole product.

The predominant acetoxy ester (62), when treated with perchloric acid in ether, gave the lactone (60), the conjugated dienoic ester (64) and the methoxy ester (65). These results, together with the predominant formation of the lactone (60), were taken as evidence for the position of the acetoxy-group in the acetoxy esters (62) and (63) and of the endocyclic double bond in the conjugated dienoic ester (64) (Scheme 21)



Scheme 21

A vinylogous Pummerer-type rearrangement involving the intermediates (66) and (67) was invoked as an explanation of the formation of the products (60) - (63); the preferential introduction of the hydroxy or acetoxy group cis to the ester was rationalized on the basis that the transoid intermediate (66) is probably more favourable than the cisoid isomer (67) (Scheme 22). However these interpretations have been questioned by King[56].



Scheme 22

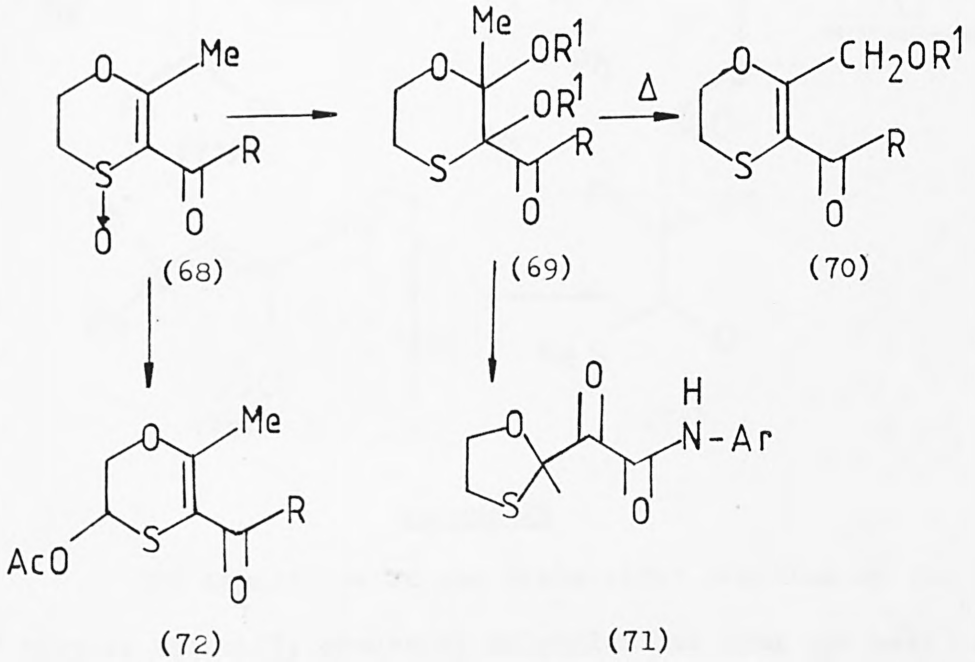
Another important investigative work has been reported by King[56] on the rearrangement of the carboxin sulphoxide (68, R = NHAr). The latter, upon treatment with trifluoroacetic anhydride, yielded the ditrifluoroacetoxy product (69, R = NHAr, R^1 = CF_3CO) which subsequently rearranged to the allylic trifluoroacetate (70, R = NCF_3COAr, R^1 = CF_3CO). The N-methyl derivative (68,

R = NMeAr) furnished an analogous product (69, R = NMeAr, R^1 = CF_3CO) which did not rearrange as did the secondary amide (69, R = NHAr, R^1 = CF_3CO). The latter compound was converted to the oxathiolane (71) when submitted to mild hydrolysis conditions. (The mechanism for this conversion was not discussed but it was taken as evidence for a preferable acyloxy elimination at C-2 in the reaction sequence).

In order to isolate previously undetected intermediates, the carboxin sulphoxide (68, R = NHAr) was submitted to a 2:1 mixture of acetic anhydride-acetic acid. From this reaction four products were isolated. The major product was the 2-acetoxy methyl analogue (70, R = NHAr, R^1 = Ac) and the other three minor products were the oxathiolane (71), the 5-acetoxy derivative (72, R = NHAr) and the additive Pummerer intermediate (69, R = NHAr, R^1 = Ac). The 5-acetoxy derivative (72, R = NHAr) is the expected product of a normal Pummerer rearrangement and its analogue (72, R = NMeAr) was the sole product from the reaction of the N-methyl derivative (68, R = NMeAr) with acetic anhydride (which gave support to a participation of the NH moiety in the additive Pummerer reaction).

For comparison, the sulphoxide (68, R = OMe) was prepared and treated with acetic anhydride-acetic acid mixture and three products were isolated. These were the 5-acetoxy derivative (72, R = OMe), which was the major product (78%) and is the expected result of a normal Pummerer reaction, the 2-acetoxy methyl analogue (70, R = OMe, R^1 = Ac) and the diacetate (69, R = OMe, R^1 = Ac). On submitting the sulphoxide (68, R = OMe) to trifluoroacetic anhydride it was immediately converted to the 2-trifluoromethyl derivative (70, R = OMe, R^1 = CF_3CO) which remained almost unchanged even at reflux temperature (Scheme 23). This demonstrated that tri-

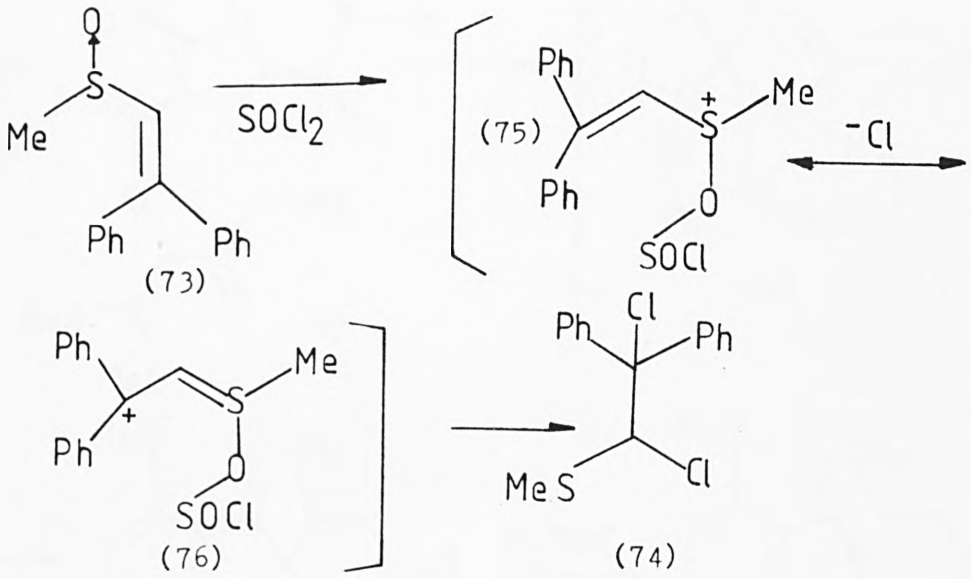
fluoroacetic anhydride enhances the additive Pummerer rearrangement pathway, in relation to the normal one, when compared to the one of acetic anhydride.



Scheme 23

The reaction of the vinyl sulphoxide (73) with thionyl chloride provides another example of an additive Pummerer reaction[57]. The chlorination of the vinyl sulphoxide (73) with thionyl chloride resulted in the formation of the dichlorosulphide (74); this does not match the results obtained from the styryl sulphoxide (44) with either thionyl chloride or phosphorus pentachloride (Schemes 15 and 16). The formation of the dichloro-product (74) was explained as an additional stabilization of the initially formed cation (75 ⟷ 76) by the two phenyl groups. However, the fact that the vinyl sulphoxide (73), on treatment with acetic anhydride furnished only a complex mixture, may suggest that the dichlorosulphide (74) is probably not,

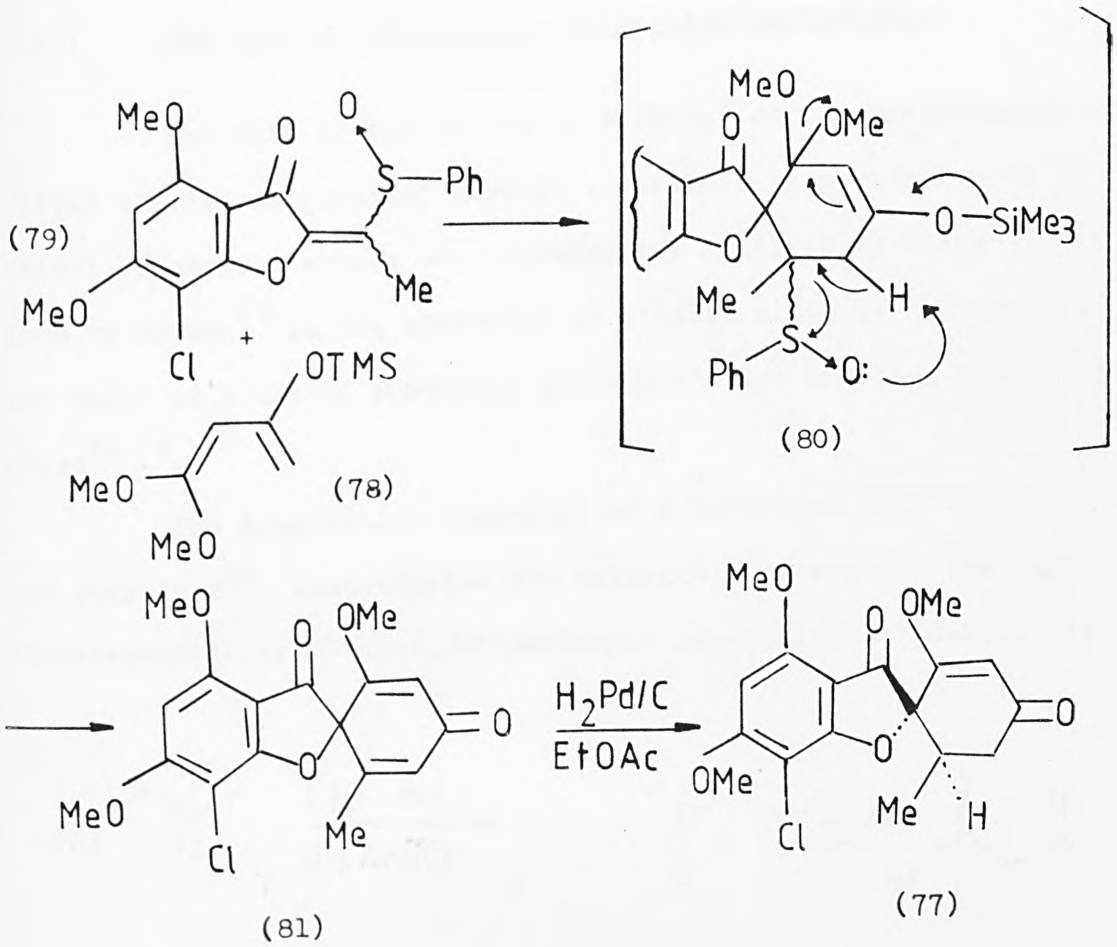
strictly speaking, the result of an additive Pummerer reaction (Scheme 24).



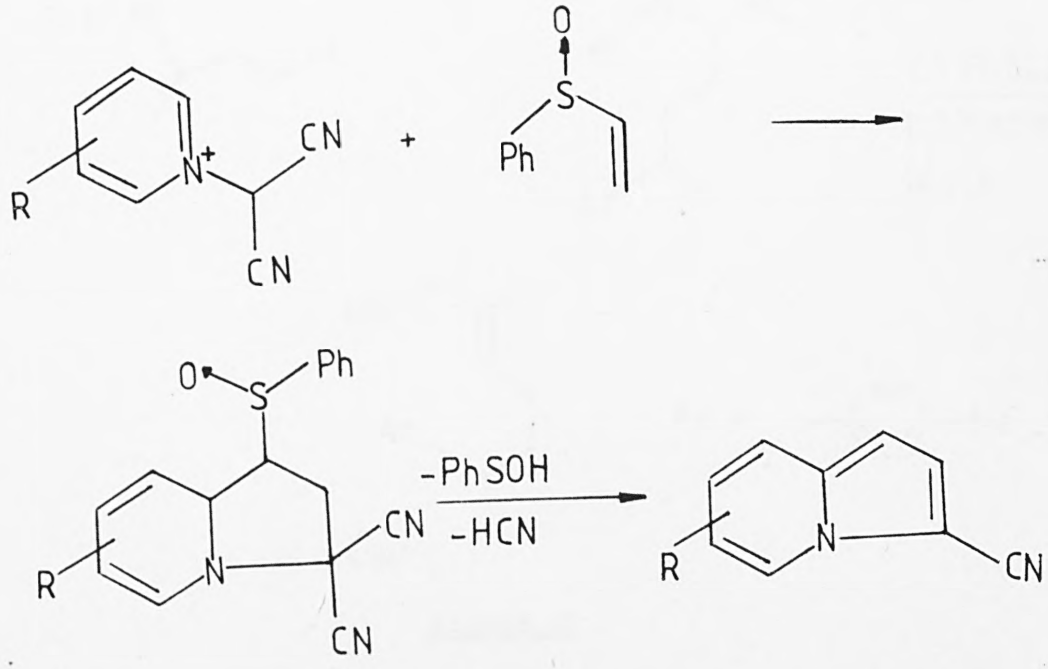
Scheme 24

The importance of the Diels-Alder reaction in the synthesis of complex naturally occurring molecules has long ago been established[58]. Recently an interest has been awakened in the use of new heteroatom--substituted dienes and dienophiles. The use of vinyl sulphoxides in these reactions has been shown to be effective (cf. page 77). A particularly representative work is that of Danishefsky and Walker[59] on the synthesis of griseofulvin (77) which involved, as the key step, the Diels-Alder reaction between the 1,1-disubstituted diene (78) and the tetra-substituted dienophile (79) (Scheme 25).

Phenyl vinyl sulphoxide (50) has been shown to be an effective acetylene equivalent both in the Diels-Alder reaction[60] and in 1,3-dipolar cyclo-additions[61] (Scheme 26)[61].



Scheme 25

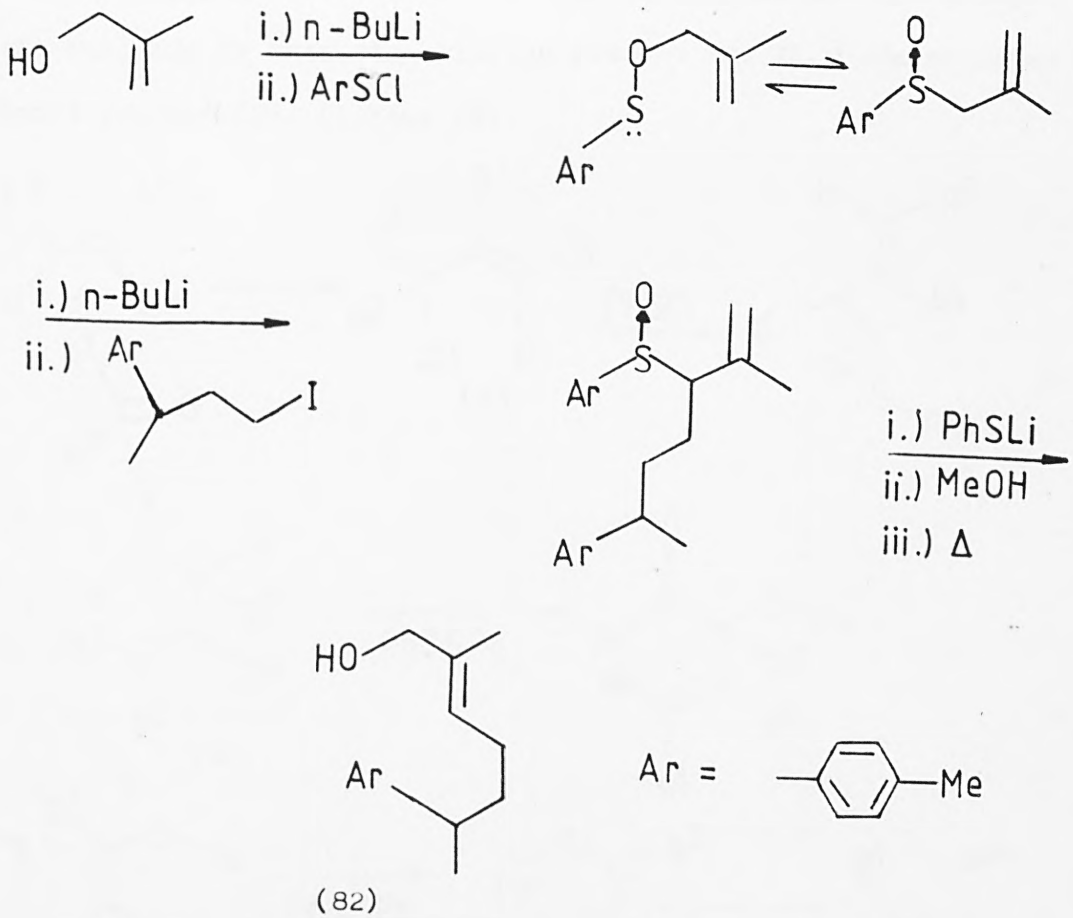


Scheme 26

I.4 The Allylic Sulphoxide-sulphenate Rearrangement

The work of Mislow and co-workers[2] on the racemization of chiral allylic sulphoxides through reversible isomerization to chiral sulphenate esters was subsequently utilized by Evans[3,62] and then by Grieco[63] in the synthesis of allylic alcohols and created the basis of a useful synthetic procedure which has been widely applied[64-74].

The imaginative synthesis of E-nuciferol (82) by Grieco and Finkelhor[68], demonstrates the reversible nature and the high stereospecificity of this 2,3-sigmatropic rearrangement (Scheme 27).

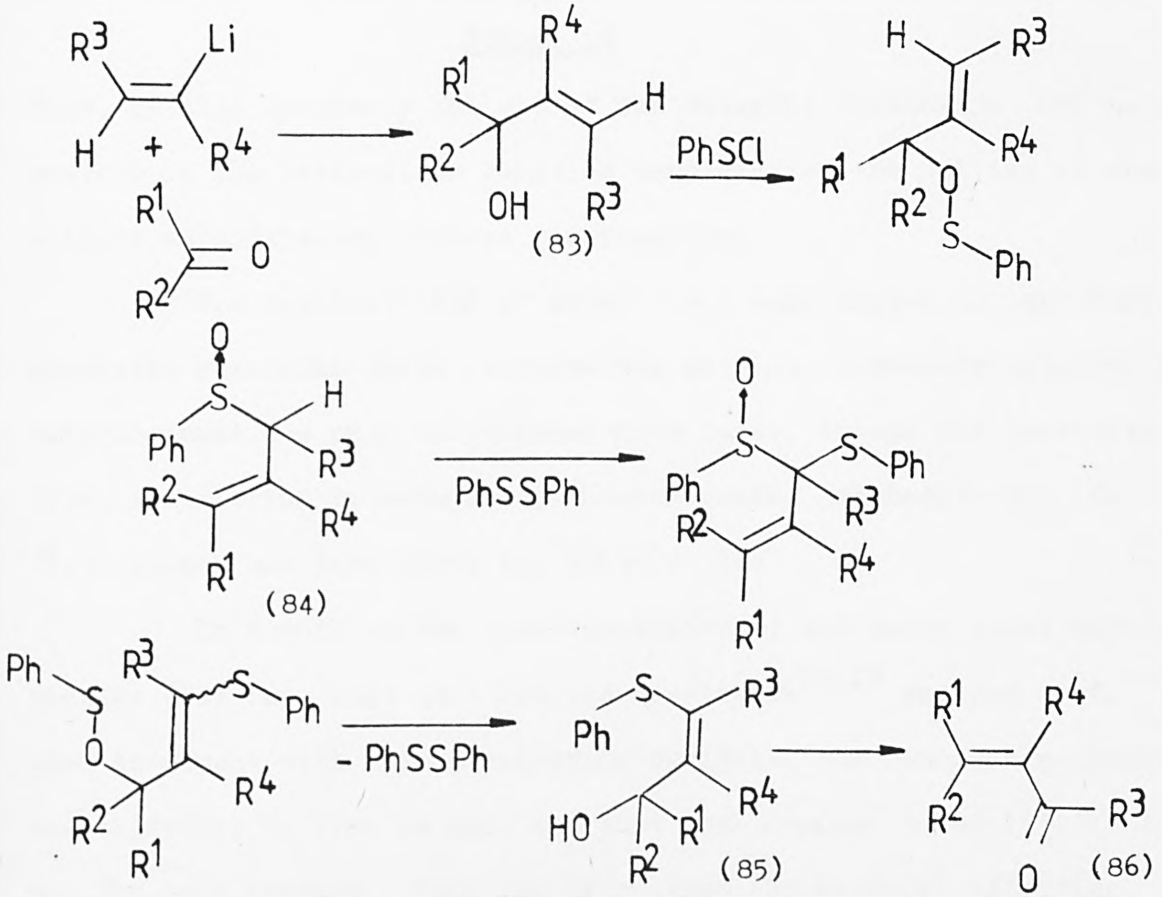


(82)

Scheme 27

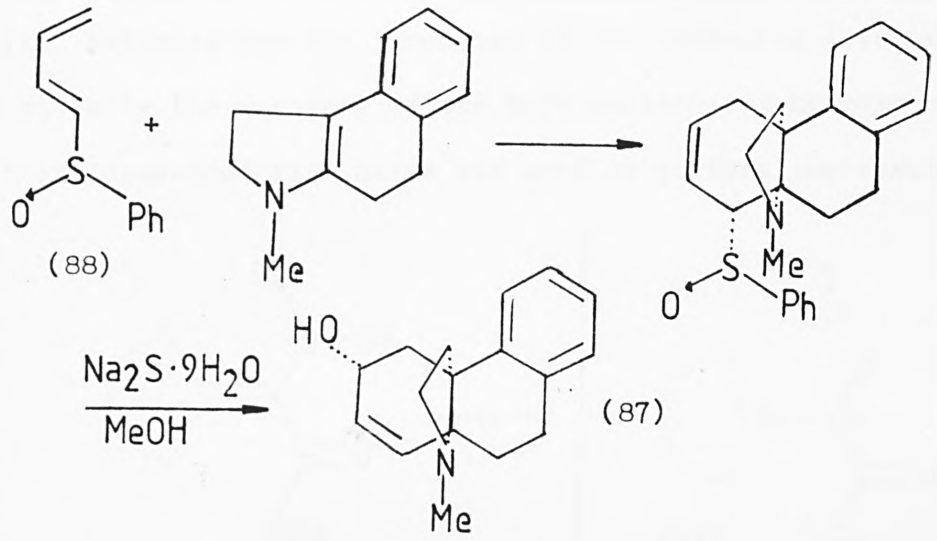
The value of this synthetic procedure has been demonstrated

by the number of important organic compounds and especially natural products which has been synthesized via the 2,3-sigmatropic rearrangement of an allylic sulphoxide[64-74]. Among several other examples the work of Trost and Stanton[74] on the synthesis of α,β-unsaturated carbonyl compounds shows the versatility of this procedure. The reaction of a carbonyl compound with the vinyllithium reagent generated the allylic alcohol (83) which, by treatment with phenylsulphenyl chloride, produced the allylic sulphoxide (84) via a 2,3-sigmatropic rearrangement (compare with Scheme 27). Sulphenylation of the allylic sulphoxide (84) with lithium diethylamide/diphenyldisulphide in THF at 0° , produced directly the γ-hydroxy-α,β-unsaturated thioether (85) by an in situ rearrangement and desulphenylation. Hydrolysis of the sulphide by mercuric chloride yielded the α,β-unsaturated carbonyl product (86) (Scheme 28).



Scheme 28

In 1972, Evans and co-workers reported[11] a beautiful approach to the construction of the hasubanane alkaloid skeleton (87) which involved the use of a Diels-Alder reaction for the formation of the tetracyclic ring system followed by a 2,3-sigmatropic rearrangement (Scheme 29) to afford the allylic alcohol.



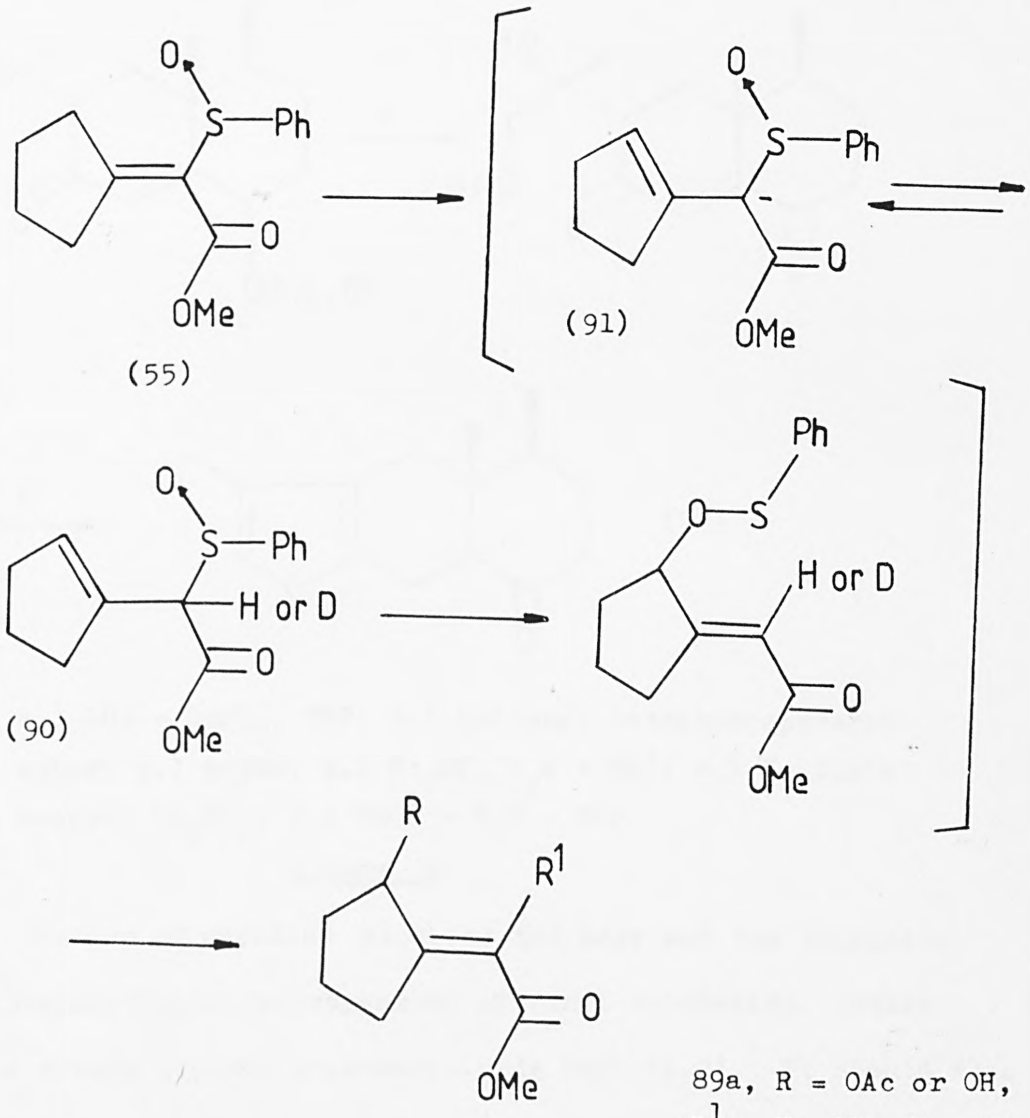
Scheme 29

Thus, in this synthesis the use of the dienylic sulphoxide (88) as a partner in the Diels-Alder reaction complemented the utility of the allylic sulphoxide-sulphenate rearrangement.

The applicability of other vinyl sulphoxides in important synthetic reactions which featured the allylic sulphoxide-sulphenate rearrangement was only established much later, though the base-catalysed equilibrium between an α,β-unsaturated sulphoxide and its β,γ-isomer has been known for quite a time[1].

In examining the transformations of the ester vinyl sulphoxide (55) (cf. page 26) Uda and co-workers[55,75] noticed that, upon treatment with acetic anhydride-pyridine, the reaction pathway was different to that in acid and that the acetoxy ester (89, R = AcO) was the only product. This was hydrolysed (NaOMe-MeOH) affording

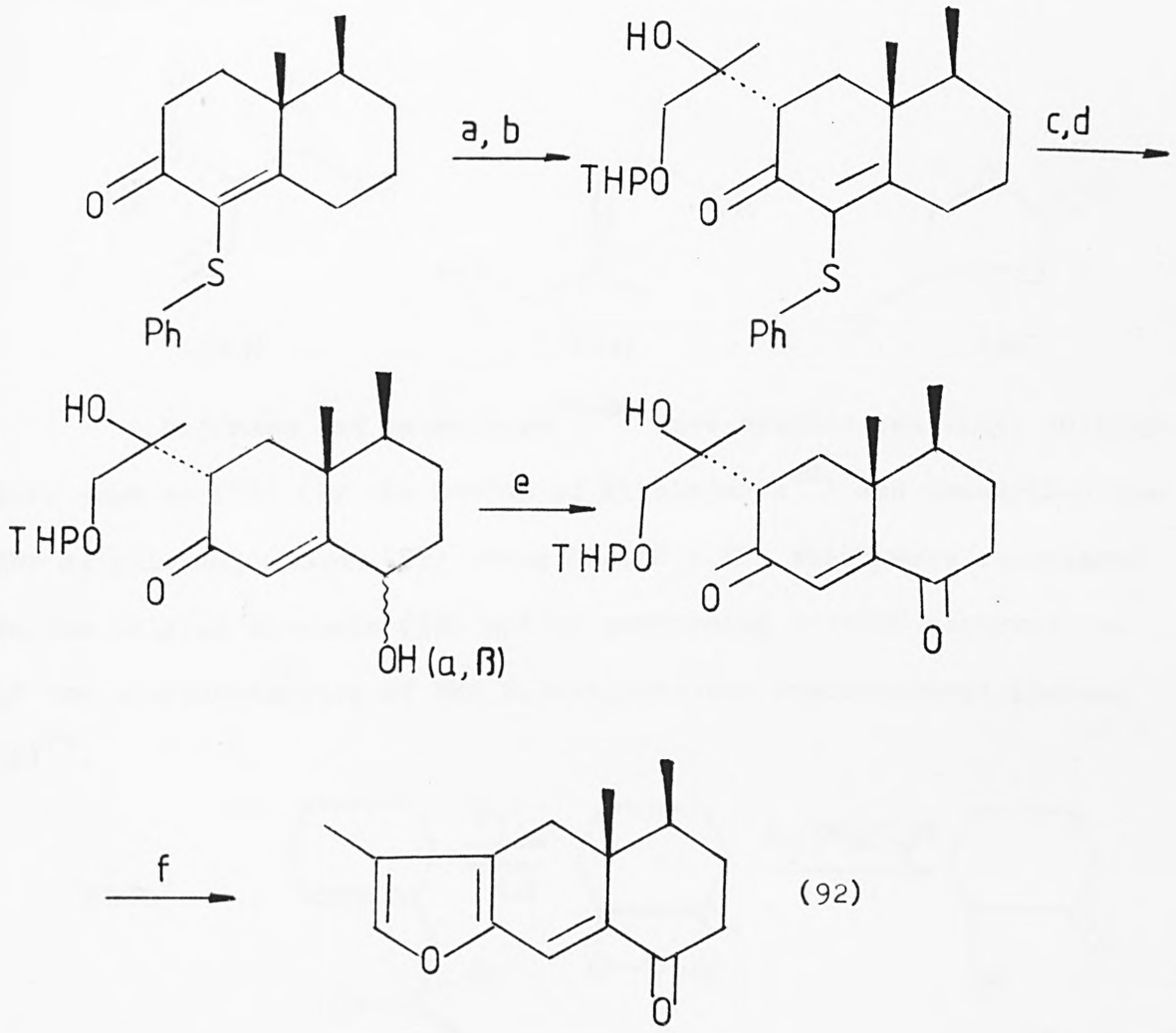
the hydroxy-ester (89a, R = OH) which was subsequently directly obtained by treating the vinyl sulphoxide (55) with pyridine-water, at room temperature, or pyridine alone followed by addition of water. The formation of the hydroxy-ester and the acetoxy ester (89a) was postulated to involve pyridine-catalysed migration of the double bond to form the endocyclic olefin (90) followed by a 2,3-sigmatropic shift. Evidence for the formation of the carbanion intermediate (91) was given by the recovery of the pure deuteriated hydroxy-ester (89b) when pyridine-deuterium oxide was used to perform the rearrangement.



89a, R = OAc or OH, R^1 = H; 89b, R = OD, R^1 = D

Scheme 30

Through a similar base-catalysed 2,3-sigmatropic rearrangement (Scheme 31) Uda's group[76] synthesized the sesquiterpene (92) which had been isolated from Senecio teretifolis DC.



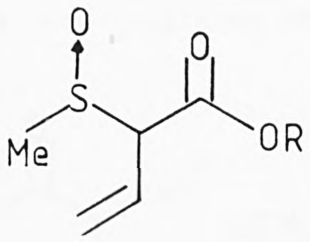
(92)

a.) LDA - $ZnCl_2$, THF; b.) acetonyl tetrahydropyranyl ether; c.) mcpba; d.) Et_2NH, H_2O - THF; e.) Collin's reagent CH_2Cl_2; f.) TsOH - H_2O - THF.

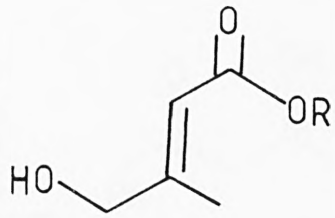
Scheme 31

The use of pyridine alone as the base and the thiophile in the 2,3-sigmatropic rearrangement of vinyl sulphoxide esters seems to be a well defined procedure (vide Part II.3). It should also be noticed that the use of normal thiophiles such as phosphites, dialkylamines and sulphides in the γ-hydroxylation of the α-methyl-

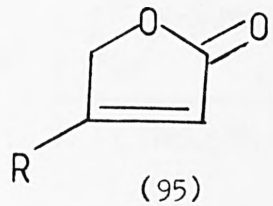
sulphinyl ester (93)[77] led to complications, whereas the hydroxy--ester (94) and the lactone (95) were obtained in good yields by simply stirring the sulphoxide-ester (93) in a 0.1 molar phosphate buffer (pH = 7) at 50 - 60°C.



(93)

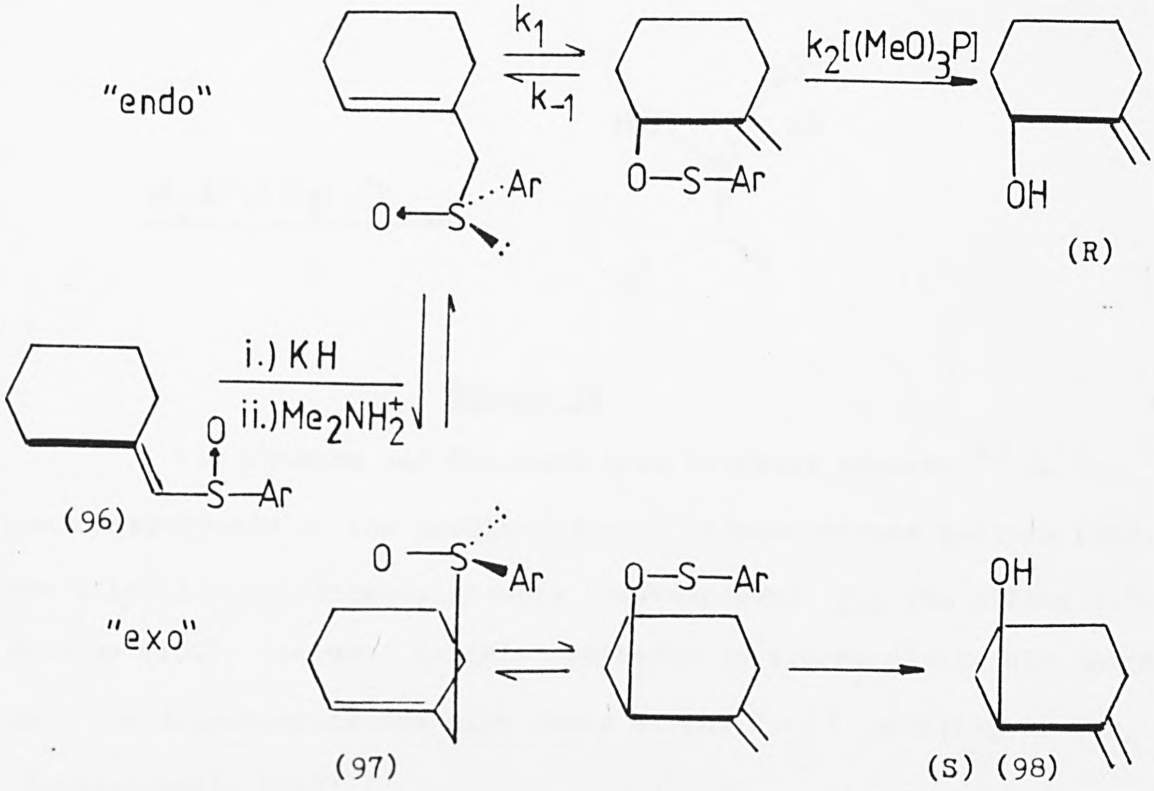


(94)



(95)

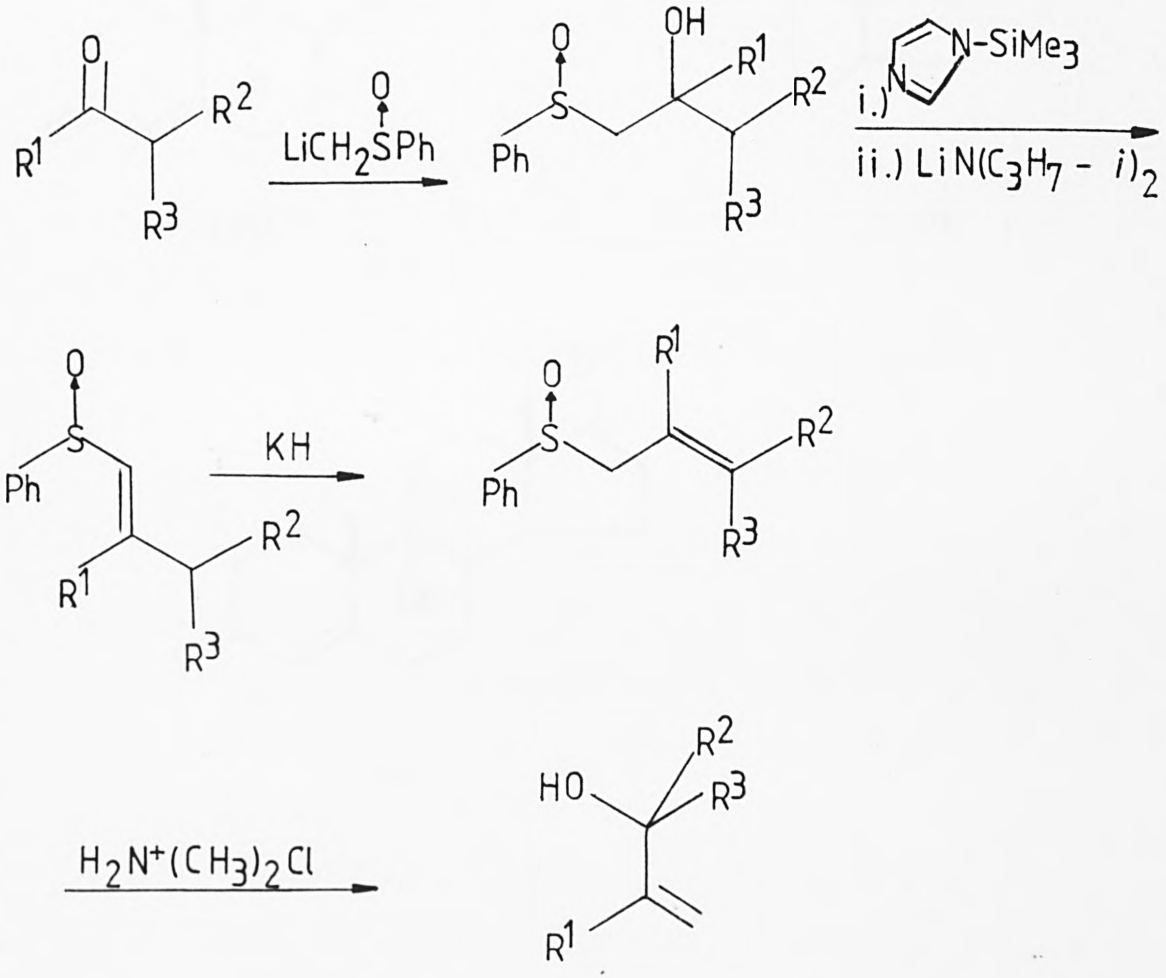
Hoffmann and co-workers[78-80] have synthesized vinyl sulphoxides such as (96) (by the method of Mikolajczyk[20]) and isomerised them to the allylic sulphoxides (97) using $KH/(CH_3)_2NH$ which were rearranged to the allylic alcohols (98) whilst performing careful observations of the stereochemistry of the 2,3-sigmatropic rearrangement (Scheme 32)[79].



Scheme 32

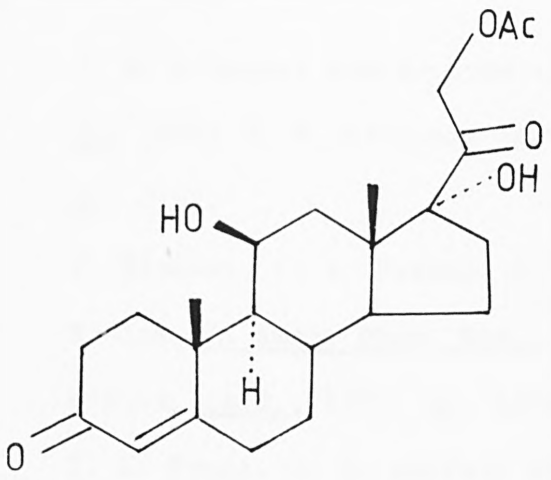
Some of the foregoing results have been reported by Hoffmann in an important review on the stereochemistry of 2,3-sigmatropic rearrangements published in 1979[81].

Another synthesis of allylic alcohols via a vinylic sulphoxide has been published (Scheme 33)[82].

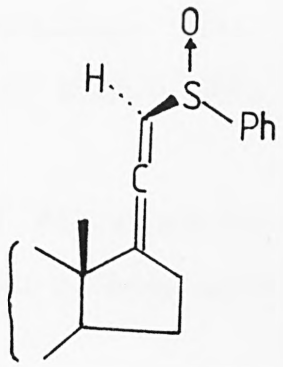


Scheme 33

Van Rheenen and Shephard have recently reported[83] an ingenious synthesis of the corticosteroid, hydrocortisone acetate (99). The allylic sulphoxide-sulphenate rearrangement, via the allene sulphoxide (100), featured in this synthesis to stereoselectively introduce the dihydroxyacetone side chain at the C-17 position of the 17-ketosteroid (101).



(99)



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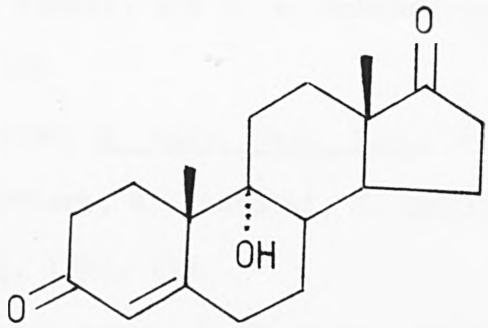


(101)

I.5 REFERENCES

1. D. E. O'Connor and W.I.Lyness, J. Amer. Chem. Soc., 1964, 86, 3840; D. E. O'Connor and C. D. Broaddus, ibid., 1964, 86, 2267.
2. P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller and K. Mislow, J. Amer. Chem. Soc., 1968, 90, 4869; R. Tang and K. Mislow, ibid., 1970, 92, 2100.
3. D. A. Evans, G. C. Andrews and C. L. Sims, J. Amer. Chem. Soc., 1971, 93, 4956; D. A. Evans, G. C. Andrews, ibid., 1972, 94, 3672.
4. G. A. Russell and L. A. Ochrymowycz, J. Org. Chem., 1970, 35, 2106.
5. H. Potter, J. Amer. Chem. Soc., 1954, 76, 5472.
6. G. Barbieri, M. Cinquini, S. Colonna and F. Montanari, J. Chem. Soc. C, 1968, 659.
7. W. Reppe, Justus Liebigs Ann. Chem., 1956, 601, 81.
8. G. H. Birum and S.A.Heininger, U. S. Patent 3,000, 927; idem., Chem. Abst., 1962, 56, 1396i.
9. F. Montanari and A.Negrini, Gazz. Chim. Ital., 1959, 89, 1543.
10. K. C. Nicolaou, W. E. Barnette and R. L. Magolda, J. Amer. Chem. Soc., 1978, 100, 2567.
11. D. A. Evans, C. A. Bryan and C. L. Sims, J. Amer. Chem. Soc., 1972, 94, 2891.
12. G. Tsuchihashi, S. Mitamura, S. Inone and K. Ogura, Tetrahedron Letters, 1973, 323.
13. G. A. Russell, E. Sabourin and G. J. Mikol, J. Org. Chem., 1966, 31, 2854.
14. H. Fillion and A. Boucherle, Bull. Soc. Chim. Fr., 1972, 2699.

15. E. Molennar and T. Strating, Rec. Tr. Chim. Pays-Bas, 1968, 87, 49.

16. D. H. R. Barton, I. H. Coates and P. G. Sammes, J. C. S. Chem. Comm., 1973, 303.

17. D. H. R. Barton, I. H. Coates and P. G. Sammes, J. C. S. Perkin I, 1974, 1459.

18. E. Block and J. O'Connor, J. Amer. Chem. Soc., 1974, 96, 3929.

19. F. A. Carey and O. Hernandez, J. Org. Chem., 1973, 38, 2670.

20. M. Mikolajczyk, S. Grzejszczak and A. Zatorski, Synthesis, 1975, 278; idem., J. Org. Chem., 1975, 40, 1979.

21. J. R. Hauske and H. Rapoport, J. Org. Chem., 1979, 44, 2472.

22. T. Durst, 'Comprehensive Organic Chemistry', D. Neville Jones (ed.), 1st edition, Pergamon Press, 1979, p. 157.

23. D. J. Abbott, S. Collonna and C. J. M. Stirling, C. J. C. Chem. Comm., 1971, 471.

24. D. N. Harpp, S. M. Vines, J. P. Montillier and T. H. Chan, J. Org. Chem., 1976, 41, 3987.

25. G. H. Posner and P. W. Tang, J. Org. Chem., 1978, 43, 4131.

26. W. E. Truce and M. J. Lusch, J. Org. Chem., 1974, 39, 3174.

27. P. Vermeer, J. Meijer and C. Eylander, Rec. Tr. Chim. Pays-Bas, 1974, 93, 240.

28. B. M. Trost and A. J. Bridges, J. Org. Chem., 1975, 40, 2014.

29. E. Guittet and S. Julia, Tetrahedron Letters, 1978, 1155.

30. Y. Gaoni, Tetrahedron Letters, 1977, 4521.

31. S. Yamagiwa, N. Hoshi, H. Sato, H. Kosugi and H. Uda, J. C. S. Perkin I, 1978, 214.

32. B. M. Trost, Chem. Rev., 1978, 363.

33. B. M. Trost and J. H. Rigby, J. Org. Chem., 1978, 43, 2938.

34. A. A. Jaxa-Chamiec, Ph D thesis, The City University, 1979.

35. P. W. B. Harrison, J. Kenyon and H. Phillips, J. Chem. Soc., 1926, 2079.

36. G. A. Russell and H. D. Becker, J. Amer. Chem. Soc., 1963, 85, 3406.

37. G. Tsuchihashi , S. Mitamura and K. Ogura, Tetrahedron Letters, 1973, 2469.

38. G. Tsuchihashi, S. Mitamura and K. Ogura, Tetrahedron Letters, 1976, 855.

39. G. Tsuchihashi, S. Mitamura and K. Ogura, Bull. Chem. Soc. Japan, 1979, 52, 2167.

40. J. J. Hauser and Kjaer, Acta Chem. Scand. B., 1974, 28, 418.

41. R. Tanikaga, H. Sugihara, K. Tanaka and A. Kaji, Synthesis, 1977, 299.

42. G. A. Koppel and M. D. Kinnick, J. C. S. Chem. Comm., 1975, 473.

43. K. Seki, T. Ohnuma, T. Oishi and Y. Ban, Tetrahedron Letters, 1975, 723.

44. H. Hagiwara, K. Nakayama and H. Uda, Bull. Chem. Soc. Japan, 1975, 48, 3769; H. Kosugi and H. Uda, ibid., 1980, 53, 160.

45. R. Pummerer, Chem. Ber., 1909, 42, 2282.

46. T. Durst, Adv. Org. Chem., 1969, 6, 356.

47. S. Oae, 'Isotopes in Organic Chemistry', E. Buncel and C. C. Lee (ed.), 1980, 5, 45.

48. W. E. Parham and L. D. Edwards, J. Org. Chem., 1968, 33, 4150.

49. N.Miyamoto, D. Fukuoka, K. Utimoto and H. Nozaki, Bull. Chem. Soc. Japan, 1974, 47, 1817.

50. K. Ogura and G. Tsuchihashi, J. Amer. Chem. Soc., 1974, 96, 1960.

51. S. Oae, T. Yagihara and T. Okabe, Tetrahedron, 1972, 3203.

52. J. Kitchin and J. Stoodley, J. C. S. Chem. Comm., 1972, 959.

53. L. Réamonn and W. I. O'Sullivan, J. C. S. Chem. Comm., 1976, 642.

54. H. Kosugi, H. Uda and S. Yamagiwa, J. C. S. Chem. Comm., 1976, 71.

55. S. Yamagiwa, H. Sato, N. Hoshi, H. Kosugi and H. Uda, J. C. S. Perkin I, 1979, 570; H. Kosugi, H. Uda and S. Yamagiwa, J. C. S. Chem. Comm., 1975, 192.

56. R. R. King, J. Org. Chem., 1978, 43, 1262; idem., ibid., 1980, 45, 5347.

57. D. T. Connor, P. A. Young and M. von Strandtmann, J. Heterocyclic Chem., 1978, 15, 115.

58. W. Carruthers, 'Some modern methods of organic synthesis', 2nd edition, C.U.P., 1978, p. 161; M. Petrzilka and J. I. Grayson, Synthesis, 1981, 753.

59. S. Danishefsky and F. J. Walker, J. Amer. Chem. Soc., 1979, 101, 7018.

60. L. A. Paquette, R. E. Moerck, B. Harirchian and P. D. Magnus, J. Amer. Chem. Soc., 1978, 100, 1597.

61. K. Matsumoto, T. Uchida and L. A. Paquette, Synthesis, 1979, 746.

62. D. A. Evans, G. C. Andrews, T. T. Fujimoto, D. Wells, Tetrahedron Letters, 1973, 1385; idem., ibid., 1973, 1389.

63. P. A. Grieco, J. C. S. Chem. Comm.,1972, 702.

64. D. A. Evans, G. C. Andrews, Acc. of Chem. Research, 1974, 147.

65. M. Yoshioka, T. Tsuji, S. Uyeo, S. Yamamoto, T. Aoki, Y. Nishitani, S. Mori, H. Satoh, Y. Hamada, H. Ishitobi and W. Nagata, Tetrahedron Letters, 1980, 351.

66. J. E. McMurry and W. Choy, Tetrahedron Letters 1980, 2477.

67. I. Dyong and G. Schulte, Tetrahedron Letters, 1980, 603.

68. P. A. Grieco and R. S. Finkelhor, J. Org. Chem., 1973, 38, 2245.

69. J. G. Miller, W. Kurz, K. G. Untch and G. Stork, J. Amer. Chem. Soc., 1974, 96, 6774.

70. K. Kondo, T. Umemoto, Y. Takahatake and D. Tunemoto, Tetrahedron Letters, 1977, 113.

71. J. E. Baldwin, ~~G. Hofle and S. C. Choi~~ O.W. Lever, Jr., & N.R. Izodikov, J. Org. Chem., 1976, 41, 2312.

72. P. T. Lansbury and R. W. Britt, J. Amer. Chem. Soc., 1976, 98, 4577.

73. M. Kodama, K. Shimada and S. Itô, Tetrahedron Letters, 1977, 2763.

74. B. M. Trost and J. L. Stanton, J. Amer. Chem. Soc., 1975, 97, 4018.

75. S. Yamagiwa, H. Kosugi and H. Uda, Bull. Chem. Soc. Japan, 1978, 51, 3011.

76. H. Hagiwara, H. Uda and T. Kodama, J. C. S. Perkin I, 1980, 963.

77. P. R. Ortiz de Montellano and C. K. Hsu, Tetrahedron Letters, 1976, 4215.

78. R. W. Hoffmann and N. Maak, Tetrahedron Letters, 1976, 2237.

79. R. W. Hoffmann, R. Gerlach and S. Goldmann, Tetrahedron Letters, 1978, 2599.

80. R. W. Hoffmann, S. Goldmann, R. Gerlach and N. Maak, Chem. Ber., 1980, 113, 845; R. W. Hoffmann, R. Gerlach and S. Goldmann, ibid., 1980, 113, 856.

81. R. W. Hoffmann, Angew. Chem. Int. Ed., 1979, 563.

82. S. Goldmann, Synthesis, 1980, 640.

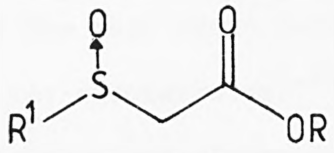
83. V. Van Rheenen and K. P. Shephard, J. Org. Chem., 1979, 44, 1582.

Part II:

DISCUSSION AND RESULTS

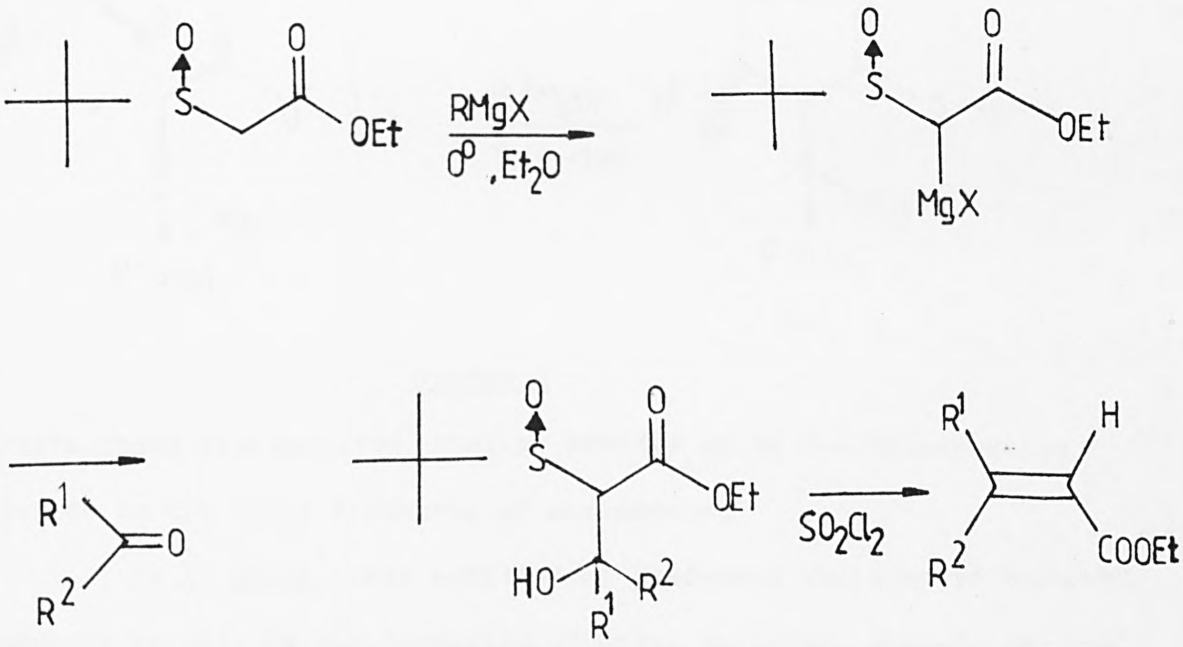
II.1 Introduction

The high synthetic utility of α-sulphinyl esters, such as compound (1), in organic chemistry is well documented[1,2,3]. The stabilised anion of compound (1), like those derived from malonic acid derivatives, is a powerful nucleophile.



(1)

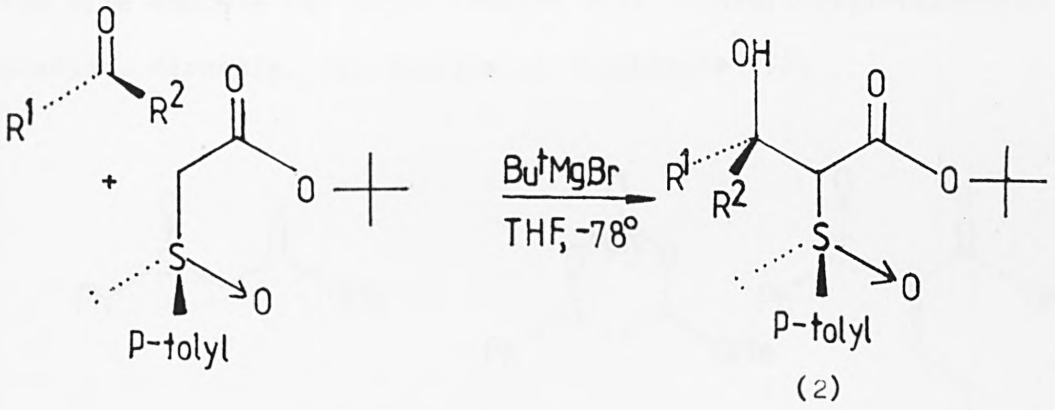
It is known that (1) reacts under certain conditions with carbonyl compounds leading to the corresponding addition products[1,2,4]; for example:



Scheme 1

Kuneida and co-workers were the first to report[4] that the condensation of ethyl benzenesulphinylacetate (1, R^1 = Ph; R = Et) with carbonyl compounds could occur only if the enolate anion was prepared from a Grignard reagent. The products were isolated as a diastereo-

isomeric mixture, but their ratios were not determined. Mioskowski and Solladié reported[1] that they could not obtain a product from the reaction of (+)-(R)-t-butyl α-p-tolylsulphinylacetate (1, R^1 = α-p-tolyl; R = t-butyl) with aldehydes and ketones using t-butyllithium or sodium hydride as a base, and that this was due, in the lithium case, to a more favourable retroaldol process. The difference in behaviour results from the more ionic nature of the O-Li bond than of the O-Mg bond. It was demonstrated[1,2,5] that the condensation of (+)-(R)-t-butyl α-p-tolylsulphinylacetate (1, R^1 = α-p-tolyl; R = t-butyl) with aldehydes and ketones using t-butylmagnesium bromide takes place stereoselectively affording the hydroxy-ester (2) (Scheme 2).

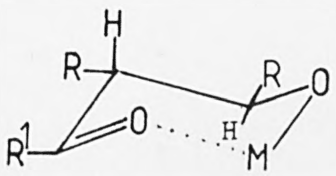


(2)

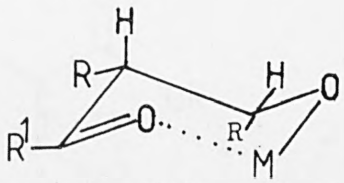
Scheme 2

Corey's group also reported[6] similar results using t-butylmagnesium chloride in the total synthesis of maytansine.

It is known[7] that addition of preformed enolates to carbonyl compounds results in the formation of metal chelates, wherein two new stereocentres are created in the condensation step, normally, as a mixture of <u>threo</u> (3) and <u>erythro</u> (4) isomers.



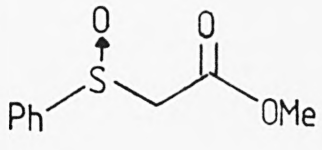
(3)



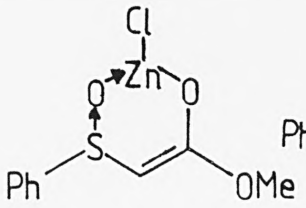
(4)

House and co-workers[8], however, found that the use of pre-formed lithium enolates in the presence of a divalent metal such as Zn^{++} or Mg^{++} leads to a product mixture rich in the <u>threo</u> stereoisomer, the stereoisomer in which the greater number of substituents on the intermediate six-membered cyclic metal chelate may occupy equatorial conformations.

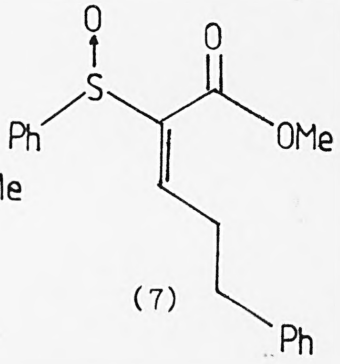
It has been reported[9] that the lithium and sodium enolates of methyl benzenesulphinylacetate (MPSA) (5) are unreactive towards aldehydes and ketones (in as much as aldol adducts were isolated). Meanwhile, Jaxa-Chamiec[10] has found that the ester (5) by successive treatment with sodium hydride and anhydrous zinc chloride, yielded the zinc enolate (6) which reacted with 3-phenylpropionaldehyde to produce, directly, the conjugated sulphoxide (7).



(5)

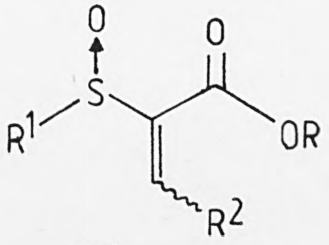


(6)



(7)

The importance of conjugated systems of the type (8) has been acknowledged[11,12]. However, only one general multistep route to this type of system has been described previously[13].

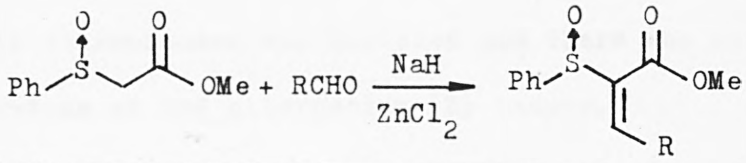


(8)

The main objective of the present research was, therefore, to develop the condensation of α-sulphinyl esters with carbonyl compounds to provide a general synthesis of conjugated esters of type (8) and to examine the utility of this process by exploring its application to the total synthesis of a macrolide, namely, pyrenophorin[14].

II.2 Synthesis of Vinyl Sulphoxide Esters

The method described by Jaxa-Chamiec[10] for the synthesis of the conjugated sulphoxide (7) was found to be generally applicable to the condensation of MPSA (5) with aldehydes. Thus, the preformed sodium enolate of MPSA (5) was treated with anhydrous zinc chloride in THF at 0°C and then allowed to react with saturated and unsaturated aldehydes to afford the conjugated sulphoxides (9) to (14) (Table 1) directly.



R	yield %	compound
Ph	20	9
$n\text{-}C_5H_{11}$	38	10
$n\text{-}C_4H_9$	35	11
$CH_3\text{-}CH \overset{t}{=} CH$	39	12
Me	34	13
i-Pr	12	14

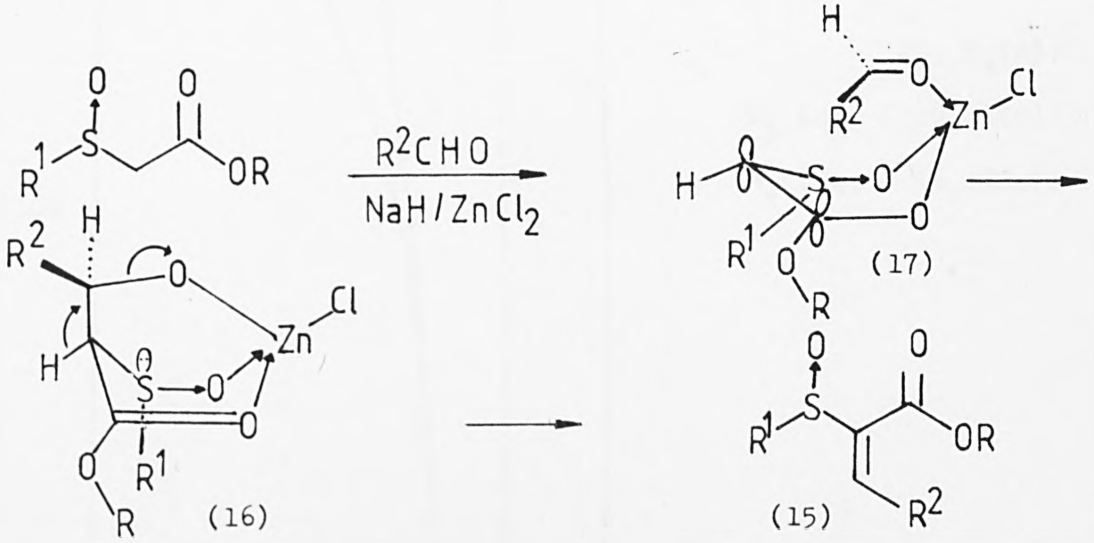
Table 1: Condensation of MPSA with Aldehydes

The geometry about the newly-formed double bond was not immediately apparent from the n.m.r. spectrum of each product, which contained only a single hydrogen attached to the α,β-unsaturated linkage. The problem of determination of the geometry was solved by application of the europium shift technique: addition of the n.m.r. shift reagent $Eu(fod)_3$ to the conjugated ester (12) resulted in a pronounced paramagnetic shift of the H_a proton, which moved downfield more rapidly than H_b and even more rapidly than the aromatic ortho-

protons H_o (Figure 1). Since the sulphoxide group is known to coordinate to the europium ion more strongly than the ester carbonyl group[15], this result is interpreted as indicating E geometry for the α,β-unsaturated linkage. A similar result was obtained with compound (9), the rapid downfield shift of the H_a proton indicating its proximity to the sulphoxide group (Figure 2). By analogy, the geometry about the double bond in each of the other conjugated sulphoxides (10), (11), (13) and (14) was assumed to be E. It should be noted that in each of the condensation reactions shown in Table 1 only a single stereoisomer was isolated and there was no evidence for the formation of the alternative (Z) isomer.

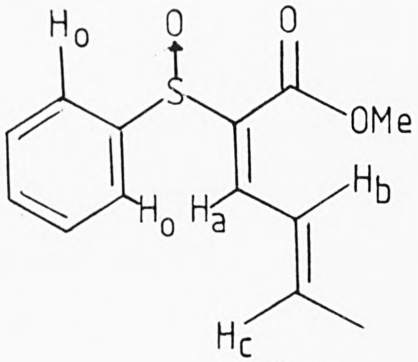
It is also noteworthy that in the case of crotonaldehyde, the product resulted exclusively from attack on the carbonyl group, there being no evidence for a Michael attack.

A striking feature of the condensation reactions, which supports the earlier observation by Jaxa-Chamiec[10], is that the reaction generally proceeded right through to the unsaturated sulphoxide product.



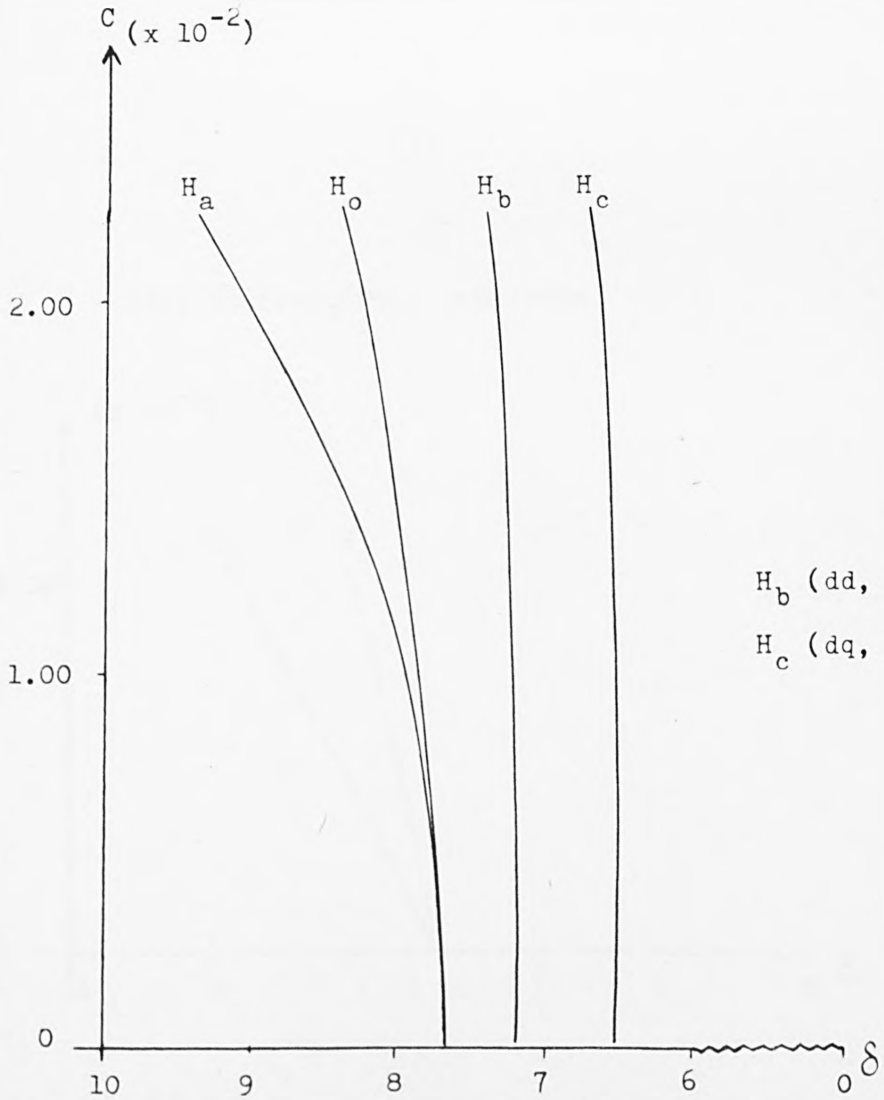
Scheme 3

Figure 1:



(12)

C = mmol Eu(fod)$_3$/mmol substrate

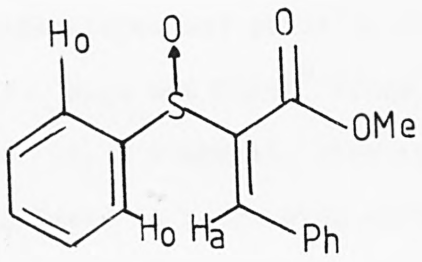


Ph, H_a(m);

H_b (dd, J 12, 1Hz);

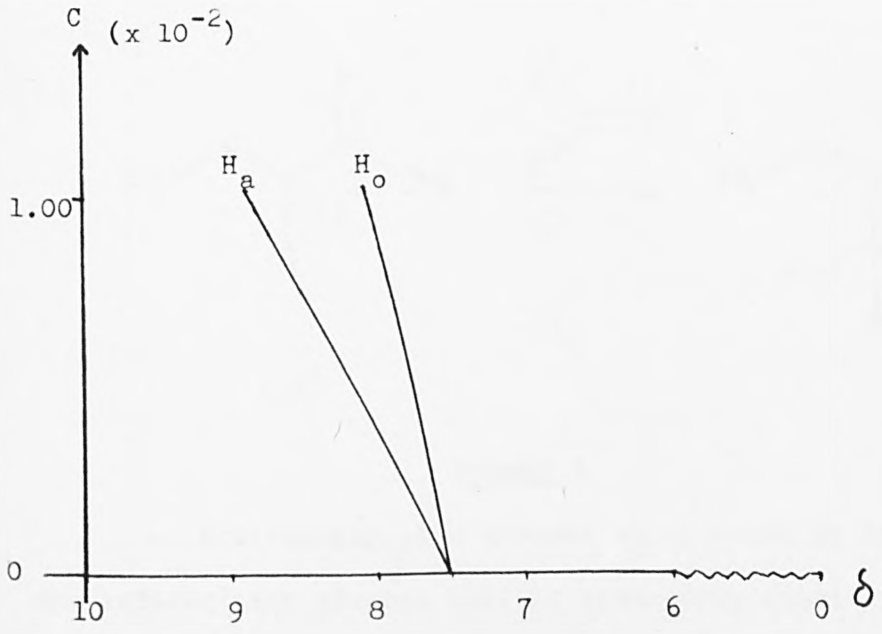
H_c (dq, J 16, 7Hz).

Figure 2:



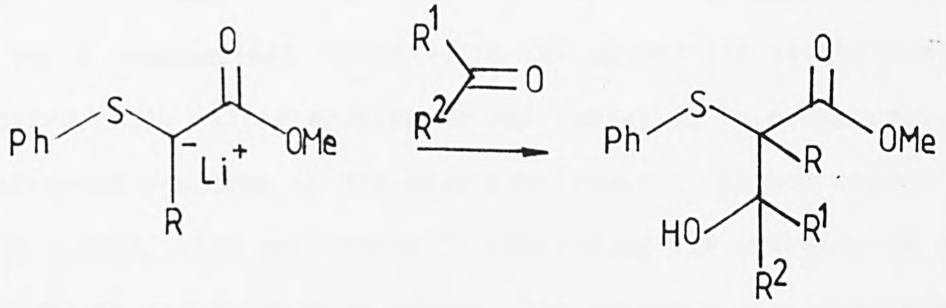
(9)

C = mmol Eu(fod)$_3$/mmol substrate.



The mechanism which leads to the direct formation of the conjugated systems of type (15) is still not completely understood, although a similar mechanism to that proposed by Mioskowski and Solladie[11] can be suggested. The immediacy with which the dehydration of the intermediate alcohol occurs in the complex (16) may be the result of the higher Lewis acid character of zinc compared with magnesium (Scheme 3).

Another important point to consider is the stability of the enolate itself. Hoye and Kurth[9] found that preformed lithium enolates, such as (18, R = alkyl), when treated with anhydrous zinc chloride and allowed to react with carbonyl compounds, afforded aldol products of type (19) as a diastereoisomeric mixture in good chemical yields. However, the reaction in the absence of zinc chloride produced equivocal results. By contrast, Uda's group reported[13] the isolation of aldol products in excellent yields from the reaction of the lithium enolate of (18, R = H) with both aldehydes and ketones, in the absence of zinc chloride (Scheme 4).

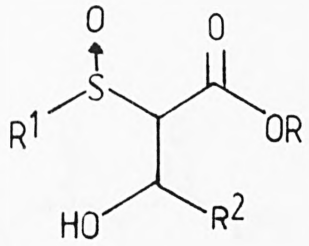


(18) (19)

Scheme 4

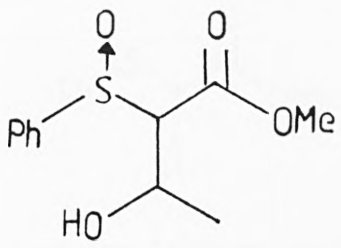
Accordingly, the process which leads to the formation of the intermediate alcohol (20) is apparently sensitive to the following: firstly, the metal ion; secondly, the degree of steric hindrance in the adduct (17), and thirdly, the stability of the enolate

itself.



(20)

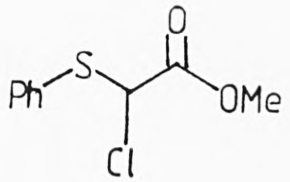
In the synthesis of the vinyl sulphoxide esters (Table 1), the presence of the intermediate alcohol (20) was noticed and the compound isolated only in the case of acetaldehyde; in the case of other aldehydes the alcohol was not observed even when the reaction was followed throughout by t.l.c. analysis. The conjugated condensation products of type (15) together with MPSA (5) were always the major spots in the t.l.c., although the presence of diphenyl disulphide was also observed, suggesting decomposition of the starting sulphoxide, which would account for the modest yields of the reaction products (9 - 14) (Table 1). With acetaldehyde, after the reaction mixture was stirred at room temperature, t.l.c. analysis showed a diastereoisomeric mixture of two main products together with the conjugated sulphoxide (13) and the starting sulphoxide (5). On heating this reaction to reflux, the diastereoisomeric mixture diminished and there was a concomitant increase in the proportion of the conjugated sulphoxide (13). After working up and isolation by preparative t.l.c., the infra-red spectrum of the diastereoisomeric mixture showed ν_{max} at 3600 - 3100, 1740 and 1040 cm^{-1}, suggesting the presence of hydroxyl, carbonyl and sulphoxide groups; the proton n.m.r. spectrum showed one proton at δ 4.38 - 4.78 which was exchangeable with D_2O. Although the mass spectrum did not show the molecular ion at 242, it gave peaks at 226 (M^+ - 16), 225 (M^+ - 17) and 224 (M^+ - 18); with this evidence the diastereoisomeric mixture was confidently assigned as methyl 3-hydroxy-2-(benzenesulphinyl)butanoate (21).



(21)

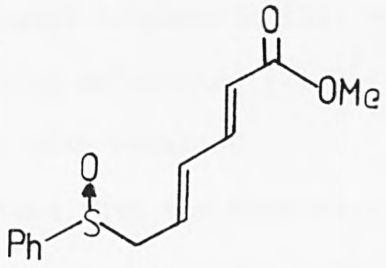
In view of the rather poor yields of the products obtained under the original reaction conditions (Table 1), attention was then turned to variations in various parameters in order to optimize the yields.

Considering the proposed reaction mechanism (Scheme 3), the effect of the counter ion was first examined. In attempting to obtain a higher yield with benzaldehyde, the base was changed from sodium hydride to triethylamine. The effect of the Lewis acid was also checked by substituting zinc chloride by a stronger Lewis acid - titanium tetrachloride. However, the conjugated sulphoxide (9) was isolated in a much lower yield ($<10\%$). The substitution of the Lewis acid alone was then examined by repeating the reaction using sodium hydride as the base, but, again the conjugated sulphoxide (9) appeared in the reaction mixture as a weak spot (t.l.c. analysis) even when forcing conditions were employed. The use of an equivalent of trimethylsilyl chloride in place of zinc chloride did not effect the condensation and the starting sulphoxide (5) was the sole product isolated after the reaction was worked up. Jaxa-Chamiec, meanwhile, found[10] that the use of an excess of trimethylsilyl chloride afforded the chlorosulphide (22), presumably formed by a Pummerer-type rearrangement under the conditions there employed[16].



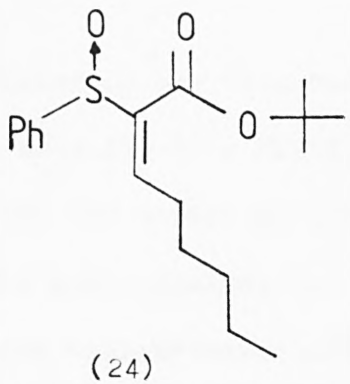
(22)

The effect of the lithium enolate was also examined, by treating the preformed lithium enolate of MPSA (5) (from lithium di-isopropylamide at -40°C) with anhydrous zinc chloride and then allowing it to react with crotonaldehyde; the reaction mixture after being stirred overnight at room temperature was worked up to give the conjugated sulphoxide (12) in a lower yield (13%) compared with that obtained from the reaction using sodium hydride (39%) as a base. In addition, a minor product was isolated which by t.l.c. seemed to be identical to the allylic sulphoxide (23) (cf. page 65).

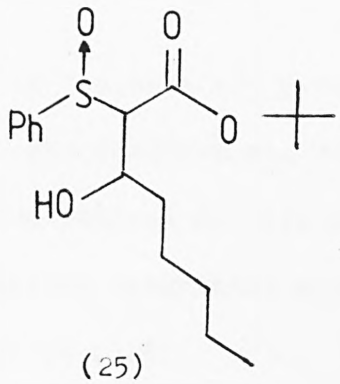


(23)

The importance of the OR group of the α-sulphinyl ester (1) was examined by synthesizing t-butyl benzenesulphinylacetate (1, R^1 = Ph; R = t-butyl) and forming its sodium enolate. This was treated with anhydrous zinc chloride prior to the addition of hexaldehyde under the same conditions employed when using MPSA (5). As expected, the conjugated sulphoxide (24) was produced, but the yield, compared with that of the conjugated sulphoxide (10), was very low (18%). The starting sulphoxide (1, R^1 = Ph; R = t-butyl) was recovered in 37% yield.



(24)

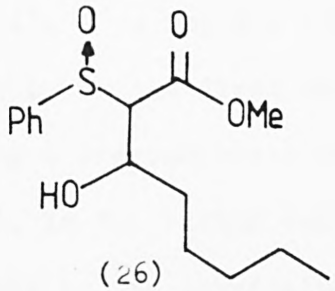


(25)

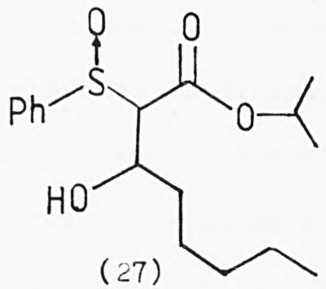
As a result of the reaction of MPSA (5) with crotonaldehyde using lithium diisopropylamide and then zinc chloride, the use of magnesium bromide diisopropylamide (1 equivalent) (Hauser's base)[17] was considered. Thus, the α-sulphinyl ester (1, R^1 = Ph; R = t-butyl) was reacted with hexaldehyde using Hauser's base; the reaction was followed throughout by t.l.c. analysis which showed, after stirring for 12h at room temperature, a diastereoisomeric mixture (this diminished when the reaction was allowed to continue for a further 12h). After working up, the conjugated sulphoxide (24) was the main product (25%); a mixture of the starting sulphoxide (1, R^1= Ph; R = t-butyl) with the hydroxy-ester (25) was also obtained.

Since it seemed that the formation of the conjugated sulphoxide (24) in the above reaction was time-dependent, a reaction of MPSA (5) with hexaldehyde, using Hauser's base, was carried out with the reaction being worked up after only 1h stirring at room temperature. This gave a complex diastereoisomeric mixture which, on the basis of its proton n.m.r. spectrum, seemed to be a mixture of the hydroxy-esters (26) and (27). The latter must be due to a transesterification and initially it was supposed that 2-propanol was present as an impurity in the 2-bromopropane used in the formation of the Grignard reagent. Accordingly, the 2-bromopropane was distilled prior to the reaction being repeated. However, the hydroxy-ester (27) again was the main product of the reaction (35.5%). The effect of the Hauser's

base (2 equivalents) was then examined in the case of α-benzenesulphinylacetic acid (1, R^1 = Ph; R = H). The reaction was followed by t.l.c. analysis and worked up after being stirred for 12h at room temperature. The acid obtained was immediately methylated with diazomethane and the hydroxy-ester (26) isolated (32%).



(26)



(27)

A qualitative elimination reaction was carried out by treating some of the hydroxy-ester (26) with pyridine and acetic anhydride. After the reaction was stirred overnight, t.l.c. showed the presence of a material identical to the conjugated sulphoxide (10) as the main product.

Although the reaction of α-sulphinyl esters with aldehydes using magnesium bromide diisopropylamide as the source of the counter ion gave sometimes equivocal results, it offered support to the proposed mechanism previously discussed (Scheme 3) by yielding hydroxy-esters of type (20) as the main products when the reaction was performed for short periods (1 - 12h) and affording conjugated sulphoxides of type (15) when the reaction was left for a long period (36h). This is probably a result of magnesium bromide being a weaker Lewis acid than zinc chloride.

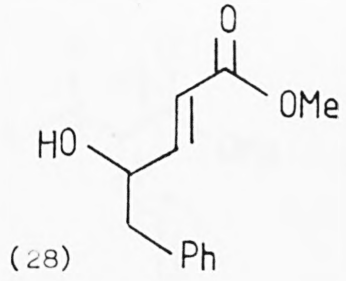
Consequently, it can be said that if the Grignard reagents employed by Solladié's[1] and Corey's[6] groups were used at a higher temperature (they used -78°C) and for a long period they could have yielded conjugated sulphoxides of type (15). It is obvious that one

should not forget that in the case of Hauser's base the presence of one equivalent of diisopropylamine 'free' in the reaction mixture helps in the dehydration process. An important parallel can also be drawn between the reaction of MPSA (5) and crotonaldehyde using lithium diisopropylamide/zinc chloride and the reaction of t-butyl acetate (1, R^1 = Ph; R = t-butyl) with hexaldehyde using Hauser's base. Whilst in the first case the presence of diisopropylamine was effecting a rearrangement in the conjugated sulphoxide (12) (cf. page 65), in the latter case, the diisopropylamine was probably playing a role in the dehydration step which led to the formation of the conjugated sulphoxide (24).

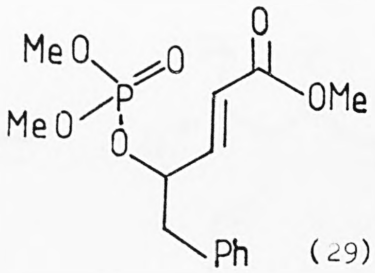
The success of sulphoxide chemistry in a number of new organic reactions during the last few years has been quite remarkable[18-21], and since stereoselective synthesis has been attracting attention, this aspect of sulphoxide chemistry has also not been forgotten [2,22]. It has already been demonstrated[1,2] that alkylation α to a chiral sulphoxide, involving stereospecific addition of the enolate of the α-sulphinyl ester (1) to a carbonyl group, requires a base containing a metal which can lead to a more covalent oxygen metal bond and a highly chelated transition state or intermediate. In this sense, the general technique of treating an alkali metal enolate of an α-sulphinyl ester with a Lewis acid, which leads to direct and stereospecific formation of an α,β-unsaturated sulphoxide of type (15), may constitute a useful contribution to sulphoxide chemistry. On the basis of future studies it could lead to the development of basic chiral synthons for the structural elaboration of complex asymmetric molecules.

II.3 Rearrangement and Condensation Reactions of some Vinyl Sulphoxide Esters

The synthetic utility of the allylic sulphoxide-sulphenate rearrangement has been established (cf. Part I). Moreover, since an α,β-unsaturated sulphoxide bearing a γ-hydrogen atom in the presence of a base can co-exist in equilibrium with its β,γ-isomer[23], it is also susceptible to this important transformation. Consequently, Jaxa-Chamiec[10] had performed the above mentioned rearrangement on the conjugated sulphoxide (7) by heating it with triethylamine in ether containing one equivalent of trimethylphosphite and isolated not only the hydroxy-ester (28) but also the phosphate ester (29).



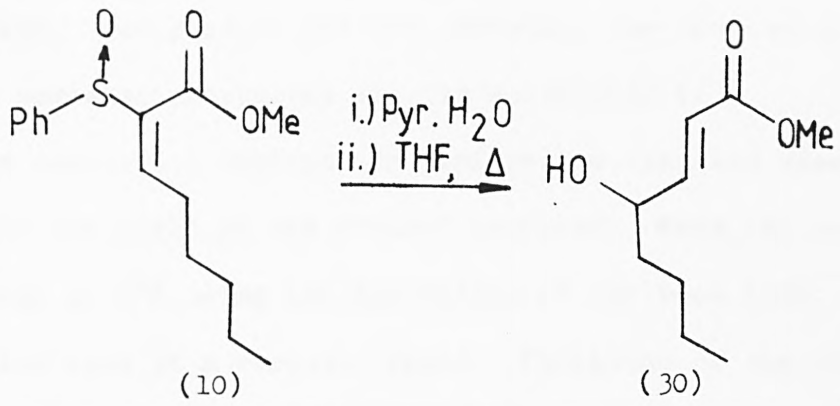
(28)



(29)

These results were in agreement with the findings of Montellano and Hsu who reported[24] that, in an analogous rearrangement, the use of conventional thiophiles gave complications whilst satisfactory results were obtained by warming the sulphoxide in a phosphate buffer (pH=7).

In view of these indications of the efficacy of weak nucleophiles, the effect of wet pyridine on the conjugated sulphoxide (10) was examined. As expected, a smooth conversion occurred, which increased by heating the reaction mixture to reflux for 3h in tetrahydrofuran, to afford the hydroxy-ester (30) as a single product (52%) (Scheme 5). A similar transformation has been observed by Uda and co-workers[11].

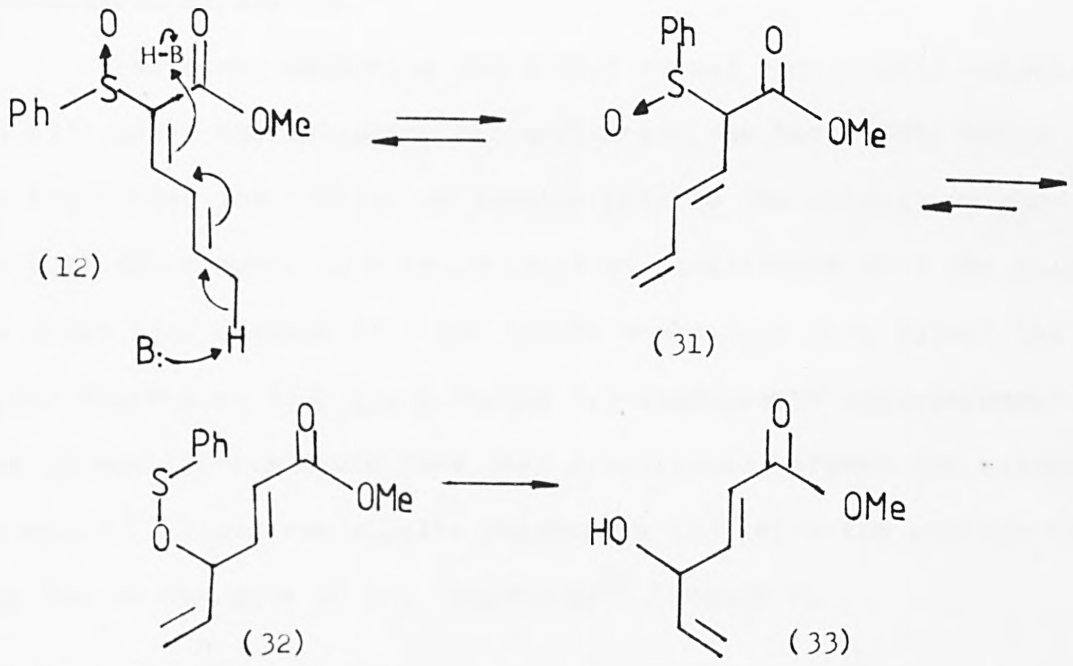


(10) (30)

Scheme 5

The E geometry about the double bond of the hydroxy-ester (30) was clearly established from the observed coupling constant across the vinylic protons (17Hz).

The conjugated sulphoxide (12), however, did not undergo the hoped for (Scheme 6) rearrangement induced by wet pyridine.



Scheme 6

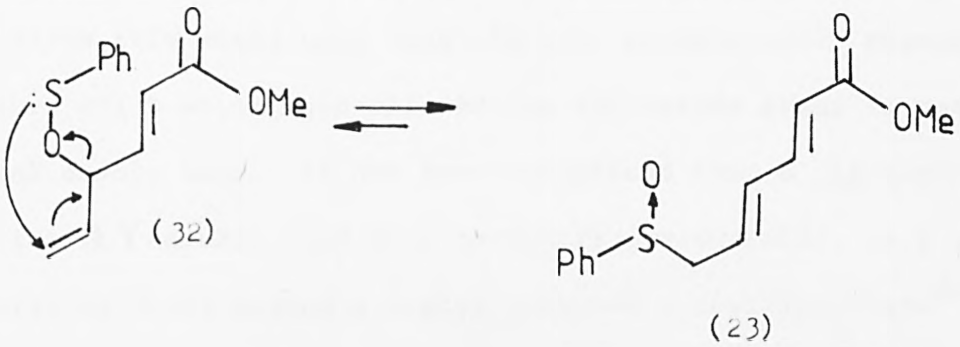
It was hoped that this failure would be overcome by the use of a much stronger base which would ease the isomerisation about the double bonds in the conjugated sulphoxide (12). After the unsuccessful use of N,N-diisopropylamine, 1,5-diazabicyclo [4.3.0.] non-5 -ene

(DBN) was tried. The product was not, however, the hydroxy-ester (33) but the somewhat unexpected allylic sulphoxide (23).

The conditions employed to perform the reaction seemed to be crucial for the yield of the product isolated. When the reaction was carried out at $0^{o}C$ using one equivalent of the base (DBN) the product was isolated in a very poor yield. Variation of the temperature did not seem to play an important role in improving the yield of the reaction, but when 0.25 equivalent of the base was used the allylic sulphoxide (23) was isolated in 45% yield, after preparative t.l.c..

Two mechanisms can account for the formation of the allylic sulphoxide (23): firstly, a double 2,3-sigmatropic rearrangement and, secondly, a 1,5-sigmatropic rearrangement; the two mechanisms will be considered separately.

The first mechanism could have formed the allylic sulphoxide (23) under the following circumstances: the base (DBN) would have isomerised the vinylic sulphoxide (12) to the allylic sulphoxide (31) which would have established an equilibrium with the sulphenate ester (32) (Scheme 6). The latter would have then formed the allylic sulphoxide (23) <u>via</u> a second 2,3-sigmatropic rearrangement, since an equilibrium would have been established between the sulphenate ester (32) and the allylic sulphoxide (23) with the equilibrium lying far to the side of the sulphoxide[25] (Scheme 7)

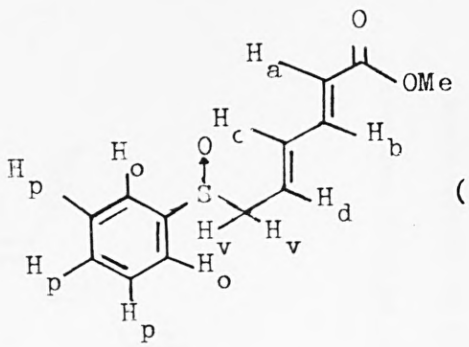


(32) (23)

Scheme 7

In accordance with this mechanism the geometry about the double bonds of the allylic sulphoxide (23) should be as shown. Initially only the E geometry about the protons H_a and H_b was established by the large coupling constant (J 18Hz), whilst the E geometry about H_c and H_d was not certain (Table 2). The proton H_d belonged to an ABX system which gave a complex splitting pattern and no coupling constant could be measured. The addition of a few milligrams of europium reagent caused a drastic change for the methylene and aromatic protons and also for the olefinic proton H_d (Table 2). However, up to this stage the geometry about H_c and H_d was still not certain. Consequently, decoupling seemed to be the only possible way to solve this problem; irradiation of the methylene protons caused the collapse of the proton H_d into a doublet (J 17Hz) at δ 5.83, making the assignment of E geometry for the protons H_c and H_d unambiguous.

The second mechanism can rationalize the formation of the allylic sulphoxide (23) by considering the fact that pericyclic reactions normally use the largest part of the conjugate system compatible with the Woodward-Hoffmann rules[26], since, in general, the ends of a conjugated system carry the largest coefficients in their frontier orbitals[27]. In this particular case, however, for the allylic sulphoxide (23) to have been formed through a 1,5 shift the vinylic sulphoxide (12) must have been isomerised to the allylic sulphoxide (34), since this would have been the only geometrically reasonable structure which would have allowed the sulphoxide group to reach the terminal double bond. It has been recognised that a cis-configuration about the β,γ-double bond is a necessary prerequisite, as a trans--orientation would demand a highly strained transition state[28]. Consequently one should expect that the allylic sulphoxide (35) was the prime product of the reaction which, by isomerisation, affor-

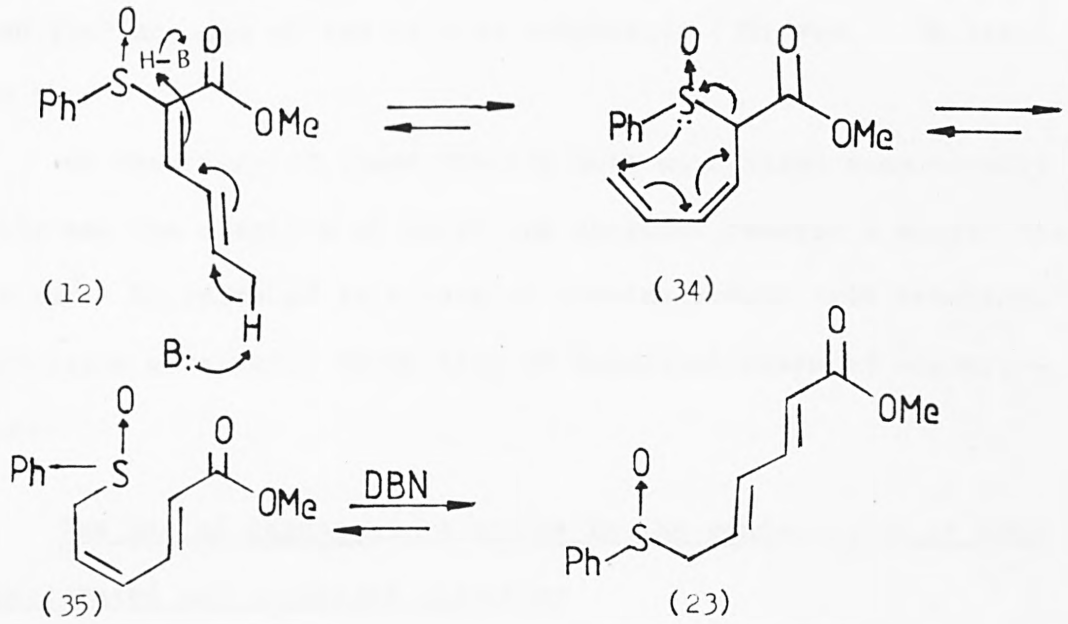


(23)

	Observed			Induced		
Protons	δ	multiplicity	J	δ	multiplicity	J
Me	3.50 - 3.90	m	-	3.75	s	-
Hv				3.75 - 4.45	m (ABX)	
Ha	5.82	d	18Hz	5.90	d	18Hz
Hb	7.18	dd	18, 11Hz	7.30	dd	18, 11Hz
Hc	6.20	dd	18, 11Hz	6.28	dd	18, 11Hz
Hd	5.62 - 6.00	m (ABX)	-	6.10 - 6.60	m (ABX)	-
Ho	7.55	bs	-	8.05	m	-
Hp				7.62	m	

Table 2

ded the isolated allylic sulphoxide (23) (Scheme 8).



Scheme 8

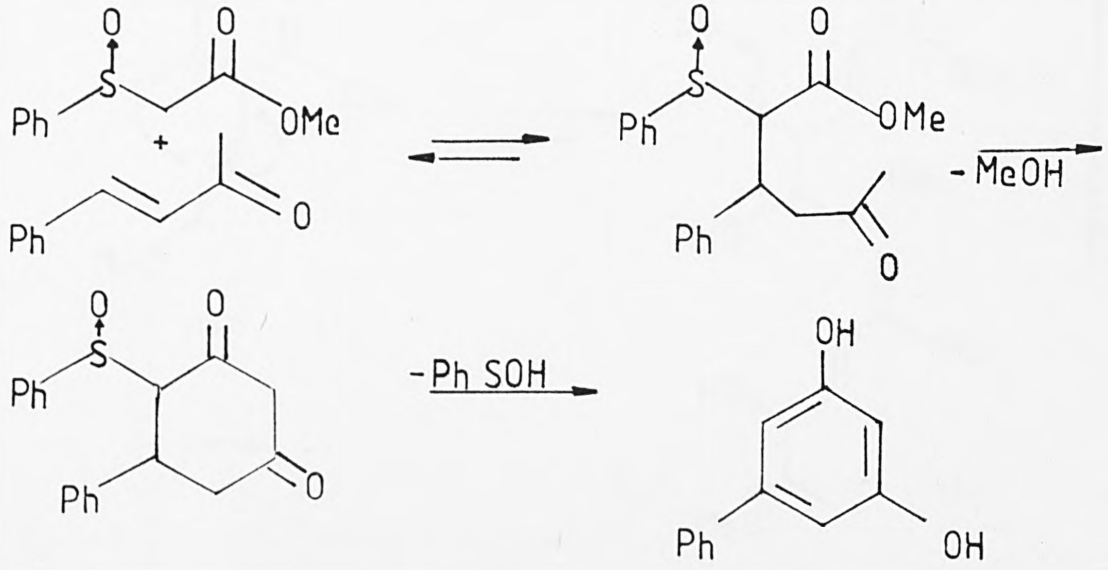
An attempt to distinguish between the two mechanisms was made on the basis that, if a double allylic sulphoxide-sulphenate rearrangement were occurring, it might be possible to intercept the hydroxy-ester (33). Accordingly, the vinylic sulphoxide (12) was stirred with DBN (0.25 equivalent) in tetrahydrofuran containing one equivalent of trimethylphosphite at 0°C, in the hope that the thiophile would help in the interception of the hydroxy-ester (33) (Scheme 6), but the reaction very cleanly afforded the allylic sulphoxide (23) as the sole product in 72% yield. An attempt was then made to establish an equilibrium between the allylic sulphoxide (23) and the sulphenate ester (32) and in this way to intercept the hydroxy-ester (33). Consequently, the allylic sulphoxide (23) was heated to reflux for 5h in tetrahydrofuran containing one equivalent of trimethylphosphite and 0.25 equivalent of the base (DBN). However, no change was observed and the allylic sulphoxide (23) was recovered in almost quantitative yield.

With respect to the second proposed mechanism it should be noted that no sign of the allylic sulphoxide (35) was to be seen (Scheme 8).

In the light of these results both mechanisms seem equally plausible and the question of which one operates remains a matter for speculation. In spite of this lack of conclusiveness this reaction may constitute a valuable entry into an important class of concerted reactions.

The use of magnesium methoxide in the condensation of MPSA with unsaturated and saturated aldehydes

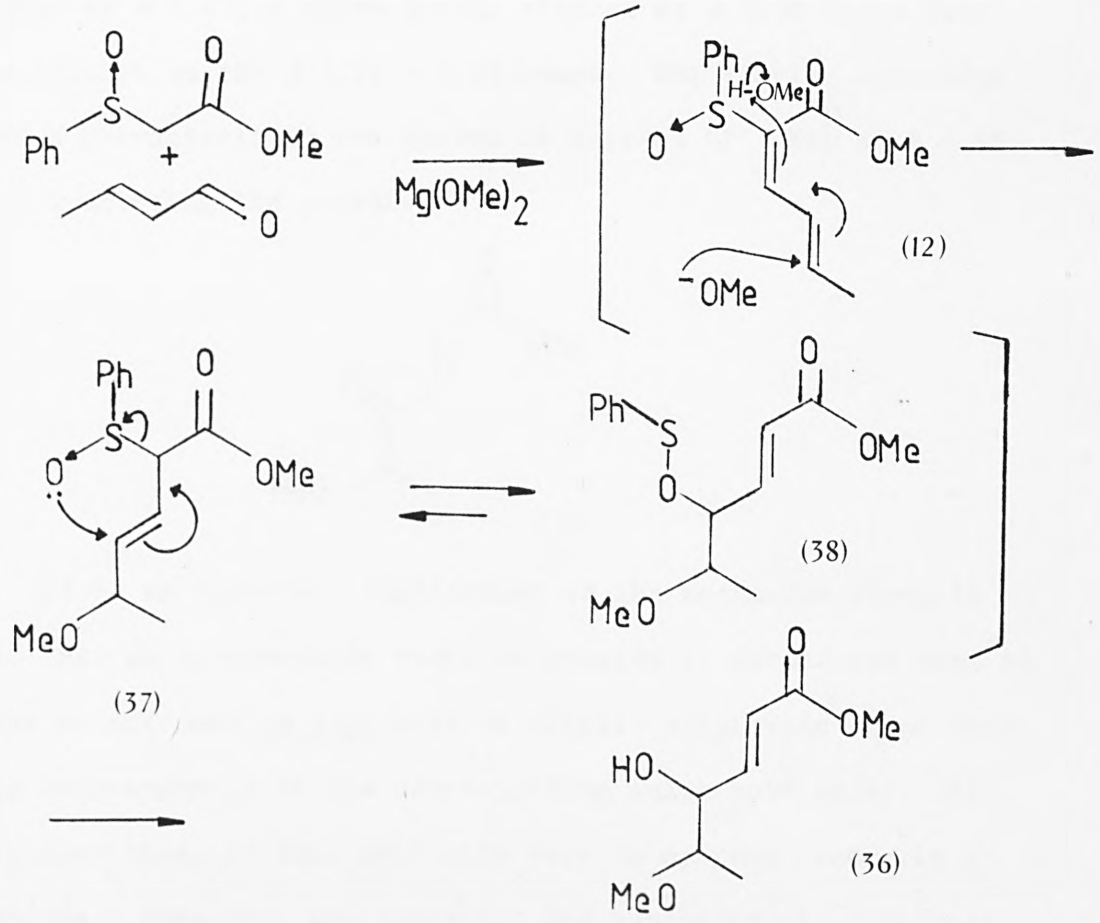
Conjugated enones have a wide synthetic utility in the elaboration of complex organic structures. Moreover, in the reaction of stabilised carbanions with an enone system an equilibrium can direct the course of the reaction (i.e., leading to 1,2 and/or 1,4 addition products)[11]. Considering these facts it was thought that it would be worthwhile to examine whether the anion of MPSA (5) would add in the 1,4 sense to crotonaldehyde if the counter cation - that is, the base used for the generation of the anion of MPSA - was changed.



Scheme 9

It has been observed[10] that the anion of MPSA generated by the use of magnesium methoxide reacted successfully with benzylidineacetone in the 1,4-sense (Scheme 9).

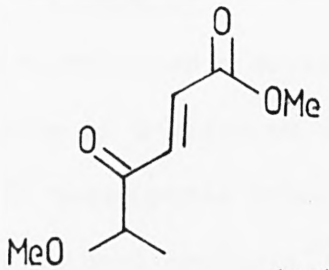
With this reaction in mind, the anion was generated by the dropwise addition of a solution of MPSA (5) in methanol to a warm suspension of magnesium methoxide. The reaction mixture was stirred for 1h at room temperature prior to the addition of crotonaldehyde. After stirring overnight, t.l.c. analysis showed a complex mixture in which no starting material was found to be present. Proton n.m.r. of the mixture did not show evidence that a 1,4-addition had taken place. Preparative t.l.c. yielded, as the main product (39%), methyl (E)-4-hydroxy-5-methoxyhex-2-enoate (36) as a diastereoisomeric mixture, presumably formed according to the mechanism set out in Scheme 10.



Scheme 10

The conjugated sulphoxide (12) could not be isolated from the reaction mixture under the conditions described. Its acceptability as an intermediate in the reaction (Scheme 10) was demonstrated by stirring the previously synthesized diene (12) overnight at room temperature with a suspension of magnesium methoxide, which yielded the methoxy-hydroxy ester (36), albeit in poor yield (15%).

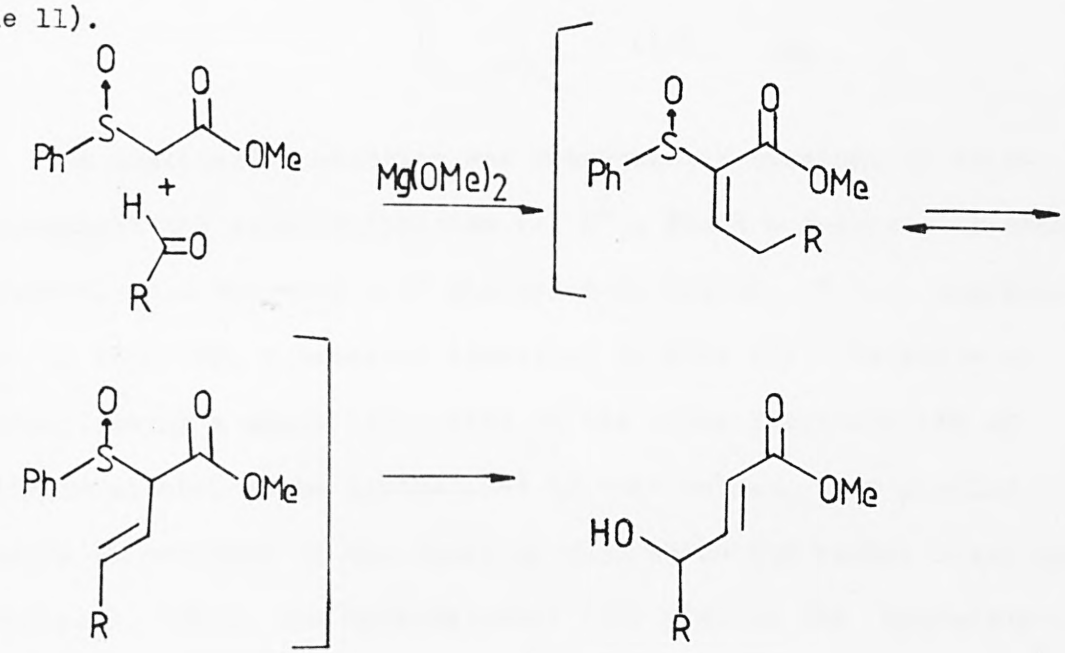
The E geometry about the double bond of the methoxy-hydroxy ester (36) was easily established from the large coupling constant between the vinylic protons (J 16Hz). It was felt that the position of the methoxy group needed to be confirmed. Accordingly, the diastereoisomeric mixture of the hydroxy-esters (36) was oxidized using Jones' Reagent[29] to yield, after preparative t.l.c., the ketone (39) whose proton n.m.r. spectrum showed a distinctive three protons doublet (J 8Hz) at δ 1.43, a three proton singlet at δ 3.36 and a four proton multiplet in the δ 3.72 - 3.98 range. The vinylic hydrogens exhibited a characteristic two proton AB quartet (J 18Hz) at δ 6.84 and 7.39, completing the picture.



(39)

It is an important implication of the mechanism shown in Scheme 10 that an intermediate vinyl sulphoxide is formed and that it is further transformed *in situ* into an allylic sulphoxide which then undergoes rearrangement to the corresponding sulphenate ester. It was recognised that, if this mechanism were to operate generally it would provide a 'one-pot' procedure for the synthesis of γ-hydroxy-

-α,β-unsaturated esters. Accordingly, the condensation of MPSA (5) with hexaldehyde was carried out using magnesium methoxide. Following preparative t.l.c., the hydroxy-ester (30) was isolated as the main product in 58% yield. Another minor product was also isolated which was not identified. MPSA was reacted similarly with 3-phenylpropionaldehyde using $Mg(OMe)_2$ as base to give hydroxy-ester (28)[10] in 25% yield (Scheme 11).

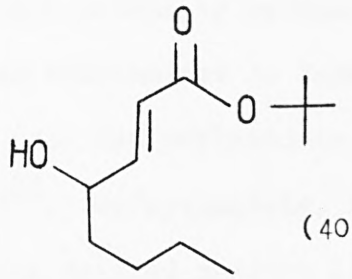


Scheme 11

This reaction constitutes a novel one-step method of transforming an aldehyde bearing an α-hydrogen atom into the versatile class of γ-hydroxy-α,β-unsaturated esters, structures which are found in a wide range of natural products[30-31]. The reaction is an interesting addition to existing methods[24,34,35] and may prove useful in the synthesis of natural and pharmaceutical products. This method might also be used to synthesize optically active compounds, since the allylic sulphoxide-sulphenate rearrangement normally takes place stereoselectively[19,36].

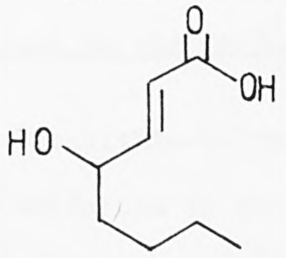
A noteworthy feature of α-sulphinyl esters (1) was met in attempting this 'one-pot' synthesis of the allylic alcohol (40) by

reacting the ester sulphoxide (1, R^1 = Ph; R = t-butyl) with hexaldehyde: a transesterification occurred and the methyl ester (30) instead of the t-butyl ester (40) was the product in 42.5% yield (after purification).

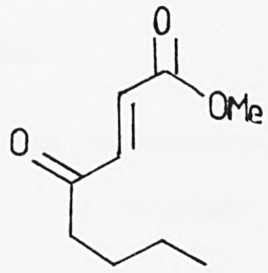


(40)

A qualitative reaction was consequently examined by stirring overnight the ester sulphoxide (1, R^1 = Ph; R = t-butyl) at room temperature, in a suspension of magnesium methoxide. T.l.c. analysis showed, as expected, a material identical to MPSA (5). In spite of this constituting a minor limitation in the ester functionality of the allylic alcohol to be synthesized by this method, this problem can easily be overcome by the facility with which the methyl ester can be hydrolysed. Thus, the hydroxy-ester (30) yielded the hydroxy-acid (41) in 79% yield on treatment with sodium hydroxide. The synthetic utility of the hydroxy-esters is further illustrated by their ready oxidation to the corresponding keto-esters. For example, treatment of the hydroxy-ester (30) with Jones' Reagent[29] afforded the ketone (42)[37] in quantitative yield.



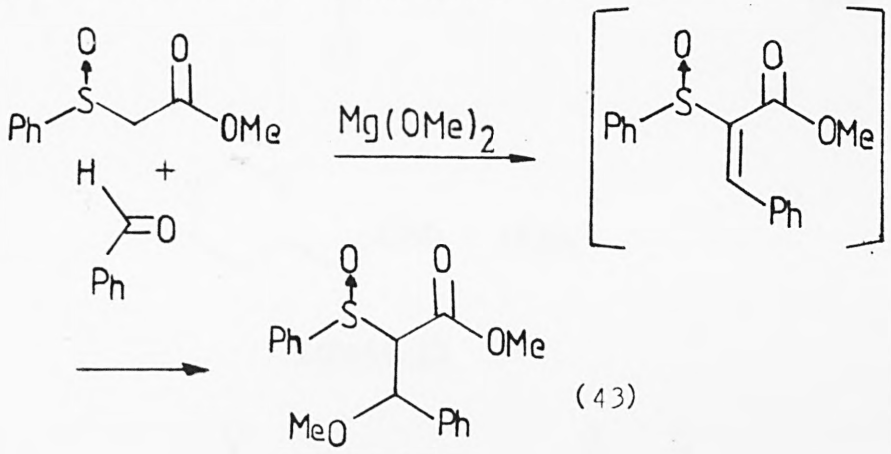
(41)



(42)

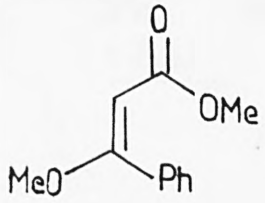
The course of the reaction with aldehydes lacking α-protons was also examined briefly. When MPSA (5) was condensed with benzal-

dehyde using magnesium methoxide, a diastereoisomeric mixture was isolated (63%) which was assigned as methyl 3-methoxy-3-phenyl-2-(benzenesulphinyl)propanoate (43). Presumably, the conjugated intermediate had undergone a Michael attack by methoxide anion (Scheme 12). In the hope of effecting an elimination to form the olefin (44), the diastereoisomeric mixture (43) was refluxed in toluene in the presence of calcium carbonate[18]. Unfortunately, several decomposition products were formed and the desired product (44) could not be found.



(43)

Scheme 12

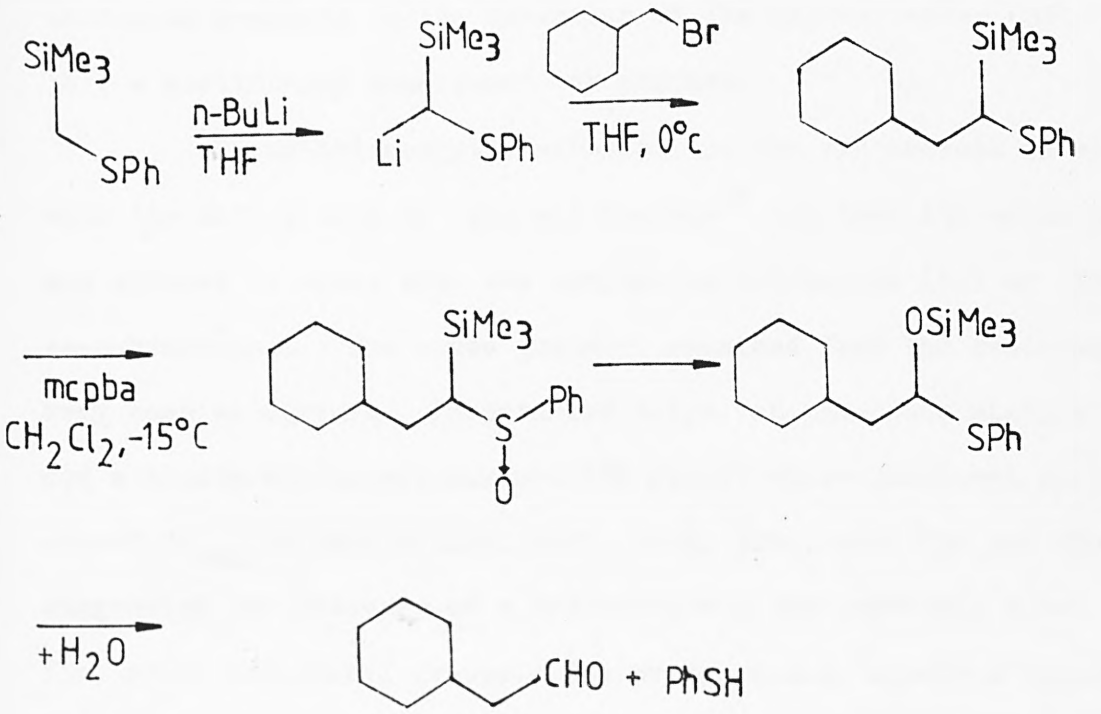


(44)

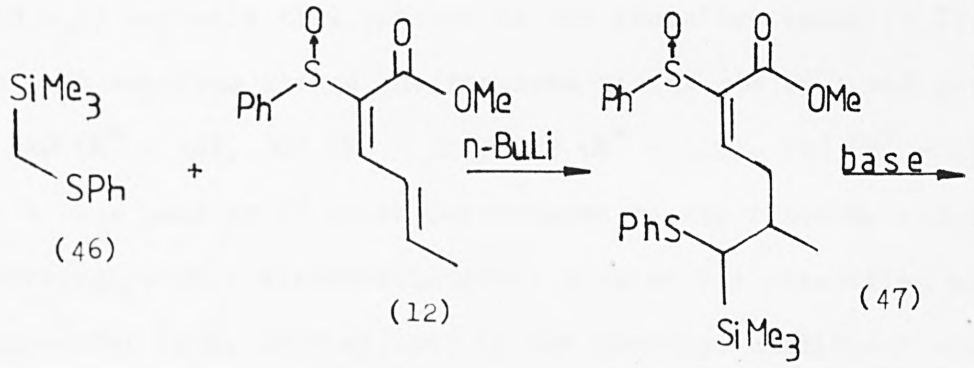
The addition of the lithium enolate of phenylthiomethyltrimethylsilane to the conjugated sulphoxide (12)

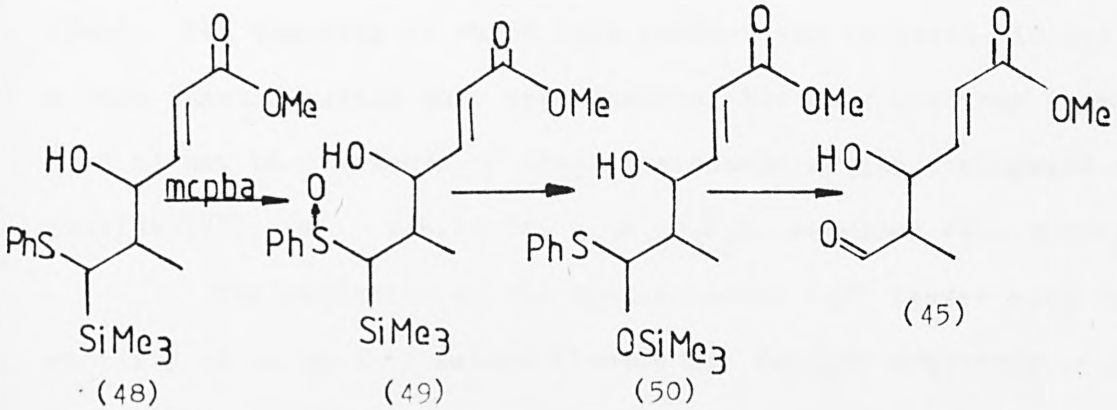
1-Phenylthio-1-trimethylsilylalkanes can be converted to aldehydes via oxidation to the sulphoxide, thermal rearrangement and hydrolysis[38,39] (Scheme 13)[39].

A synthetic route to a product such as (45), which is important in the synthesis of macrolides[33], was therefore envisaged (Scheme 14).



Scheme 13





Scheme 14

Since this reaction would also give some support to the mechanism proposed to the formation of the hydroxy-ester (36) (Scheme 10), a preliminary experiment was planned.

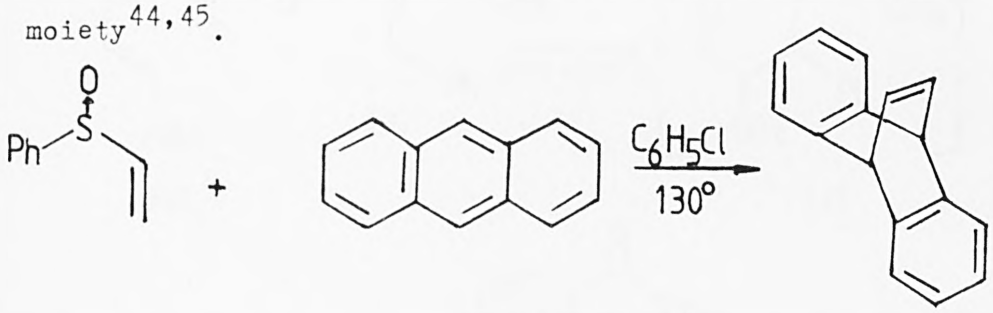
Phenylthiomethyltrimethylsilane was synthesized in accordance with the method used by Ager and Cookson[38] and then its anion prepared and allowed to react with the conjugated sulphoxide (12) at -78°C, in tetrahydrofuran. The crude product obtained from the reaction was a very complex mixture. Preparative t.l.c. of the crude mixture afforded a diastereoisomeric mixture (8% yield) whose infra-red spectrum showed ν_{max} at 3600 - 3100, 1725, 1655, 1250, 850, 750 and 700 cm^{-1} suggesting the presence of a hydroxyl group and carbonyl, olefin, silyl and phenyl groups. The proton n.m.r. spectrum (given in the experimental section) showed the presence of a trimethylsilyl group (δ 0.39, 9H) and of a hydroxy group (δ 1.70 - 2.35, br, 1H exch. with D_2O) and only five protons in the aromatic region (δ 7.4 - 7.35). The mass spectrum showed the required m/e at 338 (M^+) and gave peaks at 320 (M^+ - 18), 307 (M^+ - 31), 229 (M^+ - 109), 223 (M^+ - 115) and had a base peak at 73 which corresponds to the trimethylsilyl group. Accordingly, this diastereoisomeric mixture was identified as the hydroxy-ester (48), showing that in the reaction conditions employed its formation took place directly. A minor product was also isolated (8mg). The quantity in which this product was isolated did not permit a sure identification but, nevertheless, its mass spectrum suggests that it may be a mixture of diastereoisomers of the conjugated sulphoxide (47): (M^+ 446.14124; $C_{23}H_{30}O_3S_2Si$ requires 446.140555).

The isolation of the hydroxy-ester (48) leaves open the possibility of using this method (Scheme 14) for the synthesis of products such as (45). However, the poor yield needs to be improved

in order to make such a synthesis viable; perhaps the 1,4-addition was competing with the 1,6-addition. A few modifications in the reactions were attempted, but without success. No further work on this reaction was carried out.

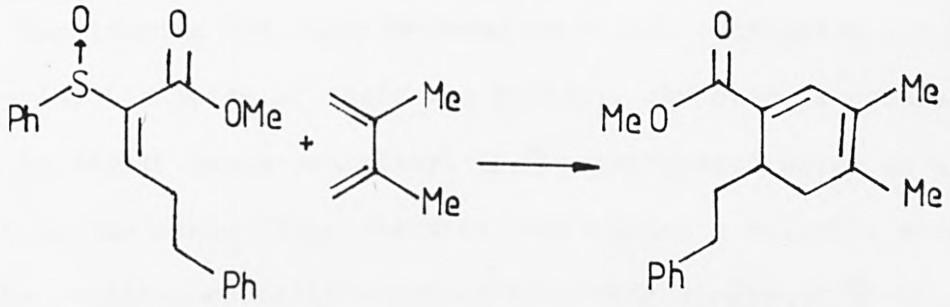
The use of the conjugated sulphoxide (9) as a dienophile in a Diels-Alder reaction

There is an extensive interest in reagents that can function as acetylene synthons in [4 + 2] cyclo-additions[40-45], and a considerable effort has been directed towards the synthesis of heteroatom--substituted dienes for use in the Diels-Alder reaction[41-43]. Racemic vinylic sulphoxides have proved useful in such reactions (e.g., Scheme 15)[44] because of the ease of pyrolytic elimination of the sulphoxide moiety[44,45].



Scheme 15

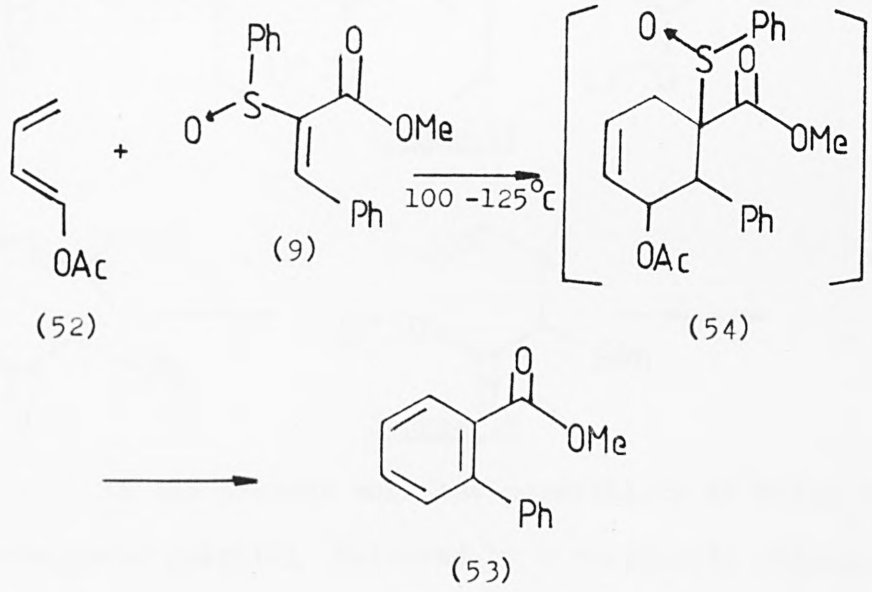
Danishefsky and co-workers had reported[45] the use of β--phenylsulphinyl α,β-unsaturated carbonyl dienophiles as synthetic equivalents of α,β-ethynylcarbonyl systems.



(7) (51)

The use of the ester sulphoxide (7) as a dienophile was demonstrated[10] also: it has been reacted smoothly with 2,3-dimethylbutadiene, and its product was the conjugated cyclohexadiene (51). This result is in agreement with Danishefsky's work.

Taking these results into consideration, the ester sulphoxide (9) was allowed to react with 1-acetoxybuta-1,3-diene (52) in a sealed tube at 100°C to 125°C for four days. The isolated product (54% yield based on 46% recovered starting sulphoxide) was methyl 2-phenylbenzoate (53)[46], showing that not only the phenylsulphinyl group of the presumed adduct (54) suffered pyrolytic elimination under these conditions of cycloaddition, but so too did the acetoxy group (Scheme 16).

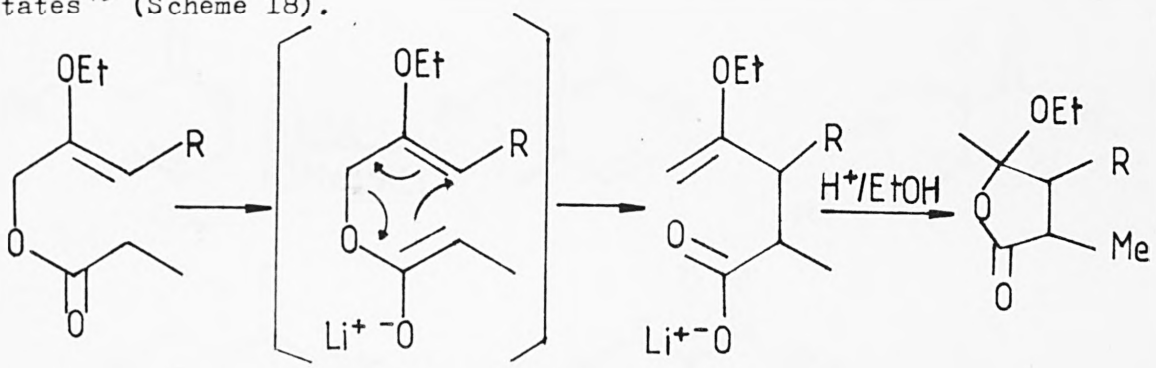


Scheme 16

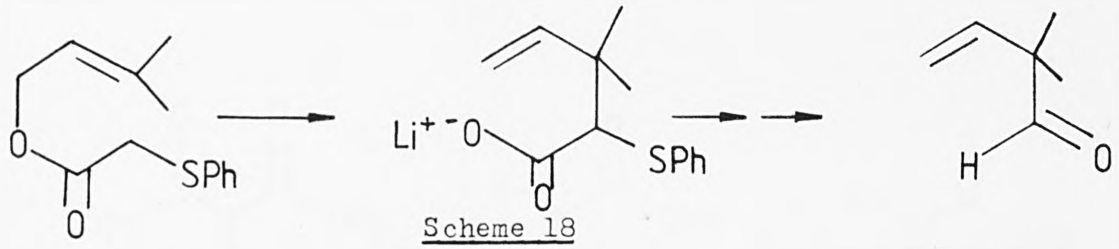
Considering the ready preparation of the conjugated sulphoxides (9 - 14) (in spite of their low yields), the overall process presented by the α-benzenesulphinyl-α,β-unsaturated ester as a dienophile in the Diels-Alder reaction constitutes a valuable extension of the reaction recently reported involving simple α,β-unsaturated sulphoxides[44,45,47].

Claisen Ester Rearrangements

The Claisen rearrangement of allyl ester enolates has provided a valuable new method for C-C bond formation. The reaction has proved especially useful when heteroatom-substituents are present[48-53], either on the allylic group (e.g., Scheme 17)[48] or α to the ester carbonyl, as in Lythgoe's work with allylic α-phenylthioacetates[49] (Scheme 18).



Scheme 17

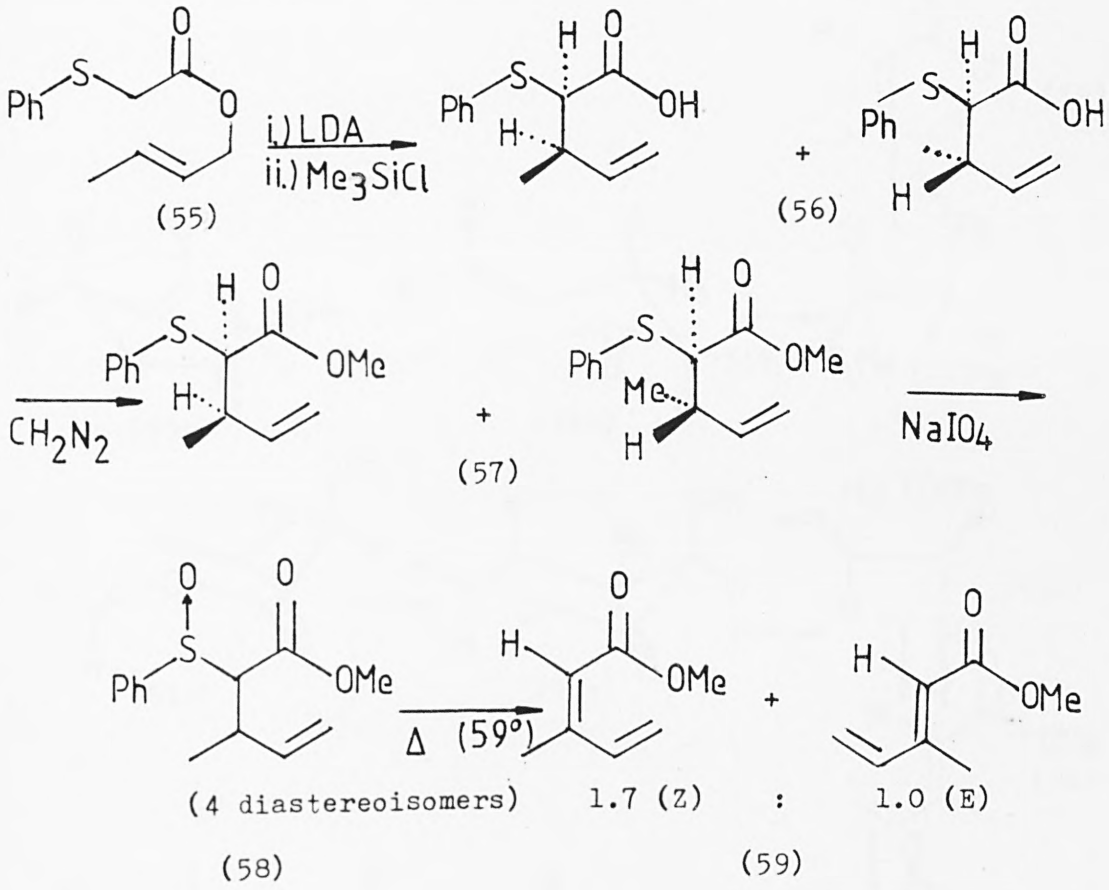


Scheme 18

In the present work the possibility of using this kind of rearrangement reaction followed by a sulphoxide elimination reaction for stereospecific olefin synthesis has been explored.

Crotyl benzenethioacetate (55) was synthesized by condensation of benzenethioacetyl chloride with crotyl alcohol. After treatment of the ester (55) with lithium diisopropylamide at -76°C in tetrahydrofuran, the reaction mixture was quenched with trimethylsilyl chloride[48-50] before warming to room temperature and aqueous work up. The product obtained was a mixture of diastereoisomeric α-benzenethio acids (56), which was esterified with diazomethane

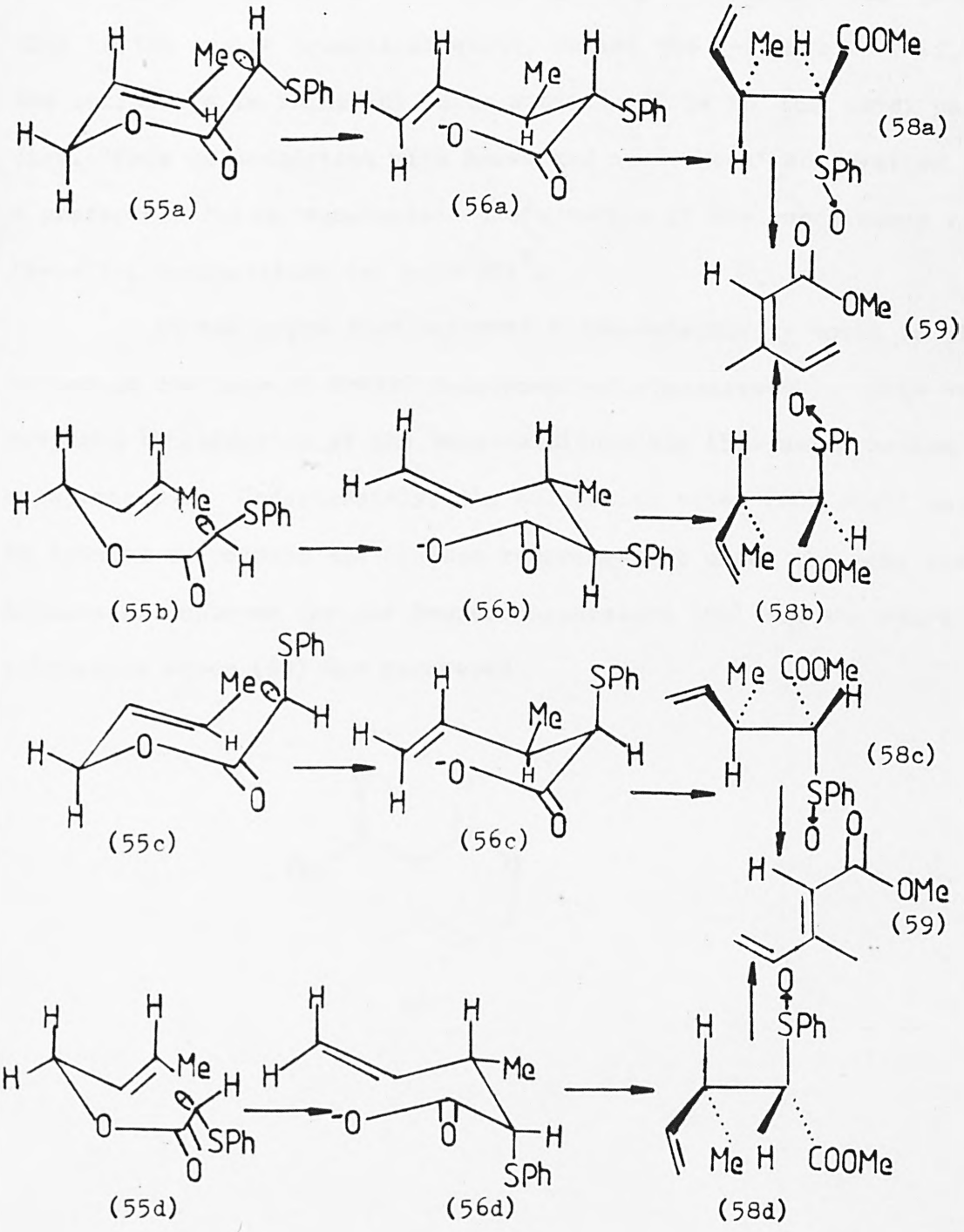
and oxidized with sodium metaperiodate. The resulting four diastereoisomers (58) were separated into two pairs: one as a crystalline mixture of two forms (1.7 : 1 mixture) and the other pair as an oil. Attempts to further separate the individual isomers from the crystalline mixture by recrystallization were unsuccessful. Pyrolysis of the mixture of crystalline diastereoisomers afforded methyl 3-methylpenta-2,4-dienoate (59) as an isomeric mixture (Scheme 19).



Scheme 19

The mixture showed distinctive signals due to the allylic methyl group in the Z isomer (δ 2.02) and E isomer (δ 2.29) in the ratio 1.7 : 1 (Scheme 19). Thus, the ratio of finally formed olefins apparently reflects the ratio of the two diastereoisomeric crystalline sulphoxides.

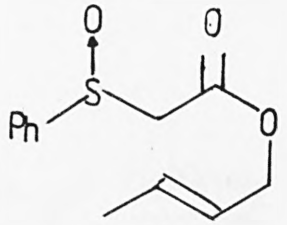
This must mean that they differ in configuration at the carbon α to the ester group.



Scheme 20

In examining the conformations of the starting ester (55) (Scheme 20) it is apparent that the conformers from which the Z-isomer arises have the bulky substituent (SPh) in an 'equatorial' position in the cyclic transition state, whilst the E-isomer arises from the conformers in which the bulky substituent is in the axial position. This is consistent with House and co-workers' observation of a preference for an 'equatorial' conformation of the substituent in the aldol condensation (cf page 50)[8].

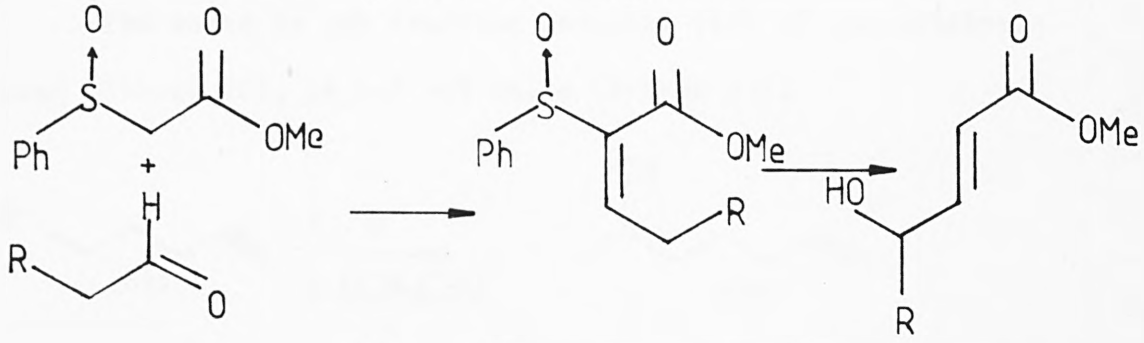
It was hoped that improved stereoselectivity would be obtained in the case of crotyl benzenesulphinylacetate(60). This was prepared by oxidation of the benzenethioacetate (55) using sodium metaperiodate. Unfortunately, the sulphoxide ester (60) could not be induced to undergo the Claisen rearrangement under the same conditions as employed for the benzenethioacetate (55) and the starting sulphoxide ester (60) was recovered.



(60)

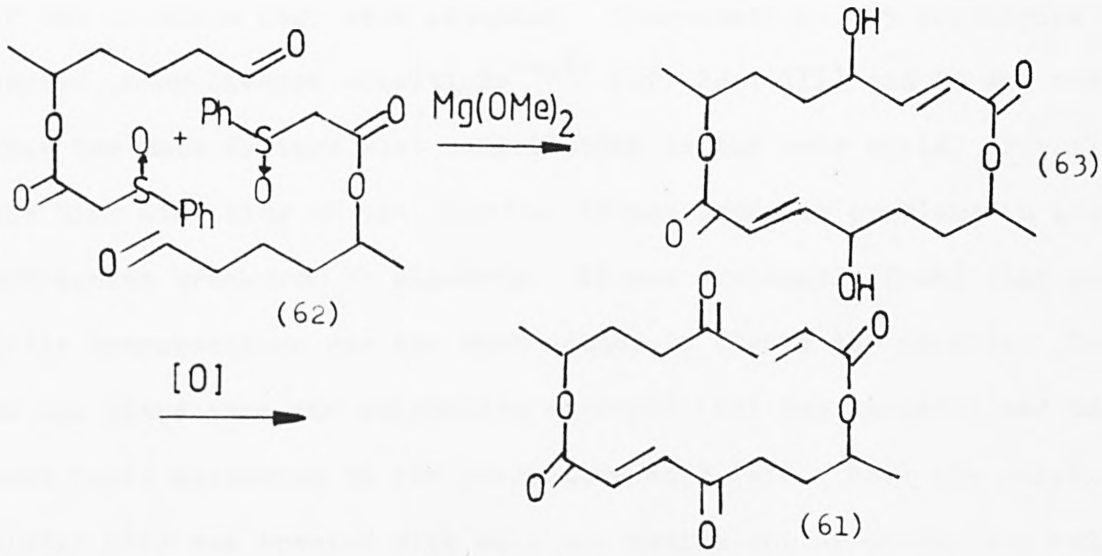
II.4 Approaches to the Synthesis of Pyrenophorin

The reaction of MPSA (5) with aldehydes provides a simple and stereospecific route to γ-hydroxy-α,β-unsaturated esters (Scheme 21) as described previously (cf. Part II.3).



Scheme 21

In order to demonstrate the synthetic utility of this reaction, it was decided to attempt the synthesis of a macrolide[33,54]. Pyrenophorin (61)[14] was selected as a representative macrolide carrying the γ-oxo-α,β-unsaturated ester functionality and its synthesis was planned (Scheme 22) *via* an intermolecular reaction of 5-(benzenesulphinylacetoxy)hexanal (62).

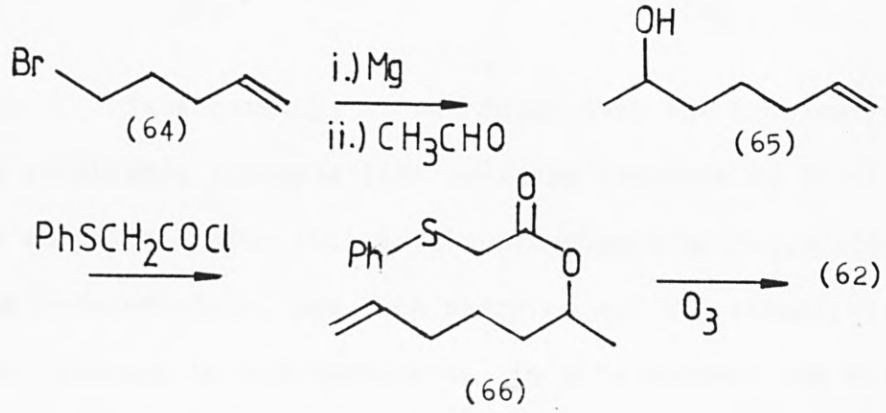


Scheme 22

The macrolide pyrenophorin (61)[14], a sixteen membered ring dilactone, is an antifungal and cytostatic metabolic product

of the plant pathogenic fungi Pyrenophora avenae and Stemphylium radicinum[55,56]. Several methods have been reported [57-63] for its synthesis, but they usually required multistep processes and their overall yields were not high.

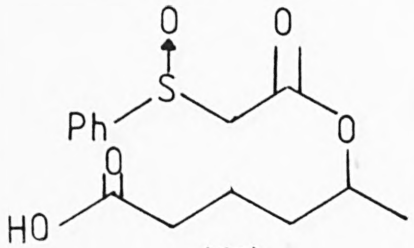
The route to the starting material (62) of the synthesis proposed (Scheme 22), is set out below (Scheme 23).



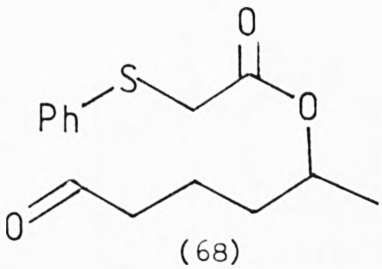
Scheme 23

The Grignard reaction of 5-bromo-pent-1-ene (64) with acetaldehyde proceeded smoothly. However, the ozonolysis of 6-(benzenethioacetoxy)hept-1-ene (66) gave some difficulties and only low yields of the aldehyde (62) were obtained. Consequently, the ozonolysis was tested under diverse conditions[64,65] (cf. Part III) and it was observed that two main factors were contributing to the poor yield. Firstly, the high stability of the ozonide formed presents problems in its subsequent breakdown to aldehyde. It was eventually found that catalytic hydrogenation was the best method to cleave the ozonide. Secondly, it was noted that the sulphoxide aldehyde (62) was unstable and underwent rapid oxidation to the sulphoxide acid (67). When the sulphide olefin (66) was treated with only one equivalent of ozone, the sulphide aldehyde (68) was isolated in poor yield, together with recovered starting material (66) and the sulphoxide aldehyde (62). In contrast

to the instability of the sulphoxide aldehyde (62) noted above, the sulphide aldehyde (68) appeared to be stable and could be oxidized to the corresponding sulphoxide aldehyde (62).

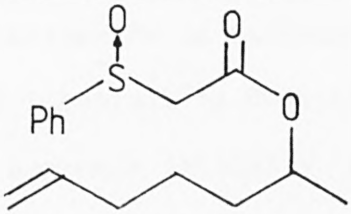


(67)



(68)

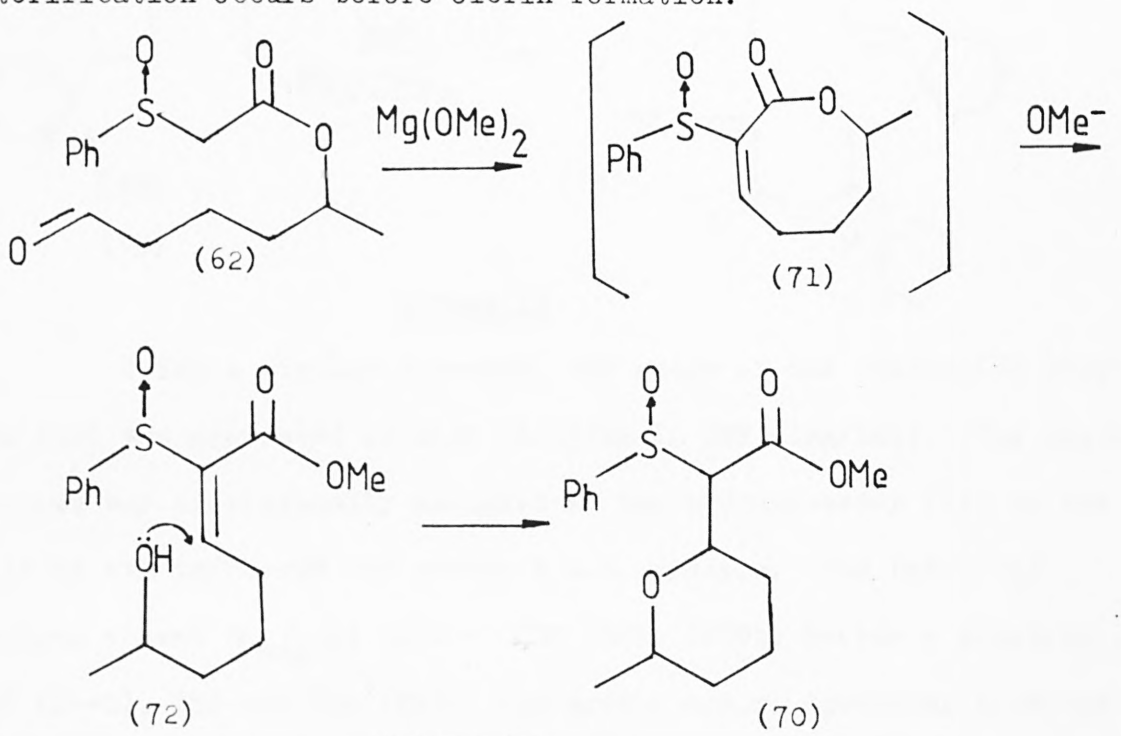
Subsequently, it was found that the problems in synthesizing the sulphoxide aldehyde (62) could be overcome by first oxidizing the sulphide olefin (66) to the corresponding sulphoxide (69) with sodium metaperiodate, and then carrying out the ozonolysis with reductive cleavage by hydrogenation. In this mannner the sulphoxide aldehyde was isolated in good yield (82%) with the acid (67) being formed as only a minor product. The formation of acids and of other side products resulting from rearrangement has been noted previously on catalytic reduction of ozonides[66,67].



(69)

Attempts were then made to dimerise the sulphoxide aldehyde (62) by means of an intermolecular reaction catalysed by magnesium methoxide in methanol. However, the lactone (70) was obtained as a diastereoisomeric mixture, instead of the expected product (63). The formation of the lactone (70) is rationalized as involving an initial intermolecular condensation to form the lactone (71), which then undergoes transesterification to give the α-benzenesulphinyl-α,β-

-unsaturated ester (72) which then suffers an internal Michael attack (Scheme 24). An alternative scheme is also possible in which trans-esterification occurs before olefin formation.

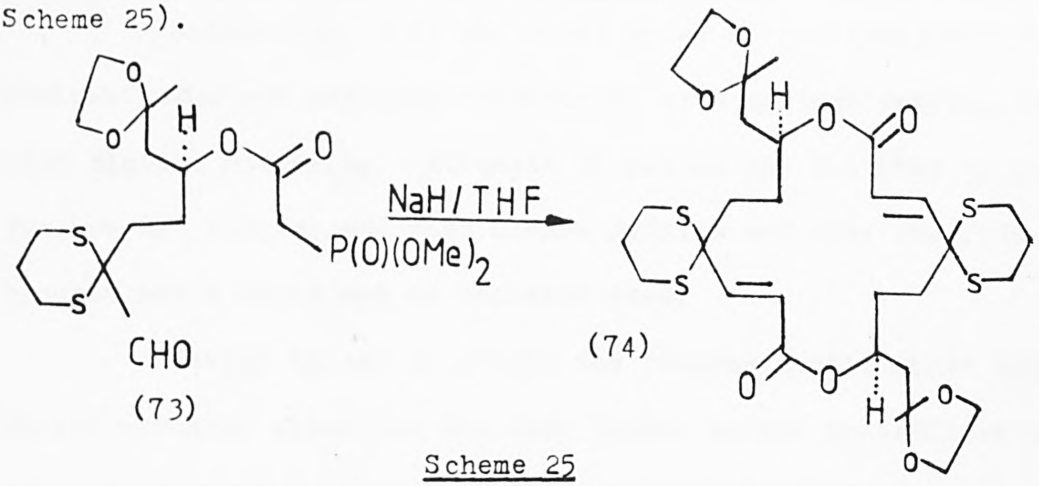


Scheme 24

To examine the ease with which transesterification could occur the sulphoxide olefin (69) was stirred overnight with a suspension of magnesium methoxide in methanol at room temperature. This yielded a material identical to MPSA (5) (t.l.c.) and revealed the limitation of the approach initially selected (Scheme 22) for the synthesis of pyrenophorin (61).

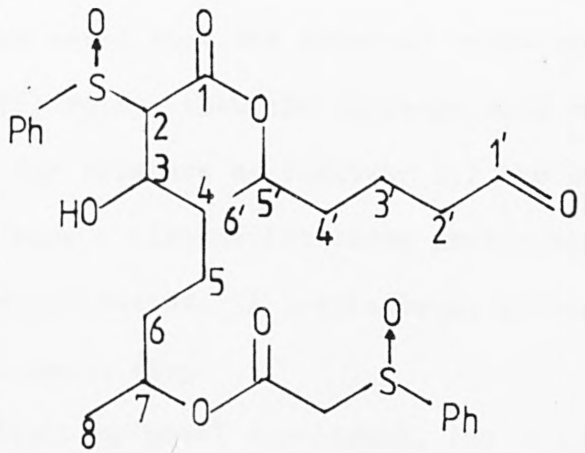
In the hope of avoiding the unwanted transesterification reaction, efforts were then made to dimerise the sulphoxide aldehyde (62) using sodium hydride and zinc chloride to generate the enolate anion. In the first attempt to form the anion with sodium hydride, a polymer was obtained, which was possibly due to the conditions of high concentration employed. In the synthesis of vermiculin[68], by Burri and co-workers[69], conditions of high dilution were used for dimerization of the phosphate aldehyde (73) to the diolide (74)

(Scheme 25).



Scheme 25

Using a similar approach, the anion of the sulphoxide aldehyde (62) was generated at high dilution in THF (1mg/1ml). The product obtained was provisionally assigned as the hydroxy-ester (75) on the basis of its infra-red and proton n.m.r. spectra. The infra-red spectrum showed ν_{max} at 3600 - 3100 (OH), 1730br (ester + aldehyde), 1040 (S→O), 750 and 700 (Ph). The proton n.m.r. spectrum, although it had a complex pattern, showed an aldehydic proton at δ 9.75, ten aromatic protons at δ 7.40 - 7.90, one methine proton at δ 5.6 (C_3 - H) and two other methine protons at δ 4.95 (C_7 - H and $C_{5'}$ - H); the two methylene protons close to the aldehyde group ($C_{2'}$ - H_2) were easily visible at δ 2.50.



(75)

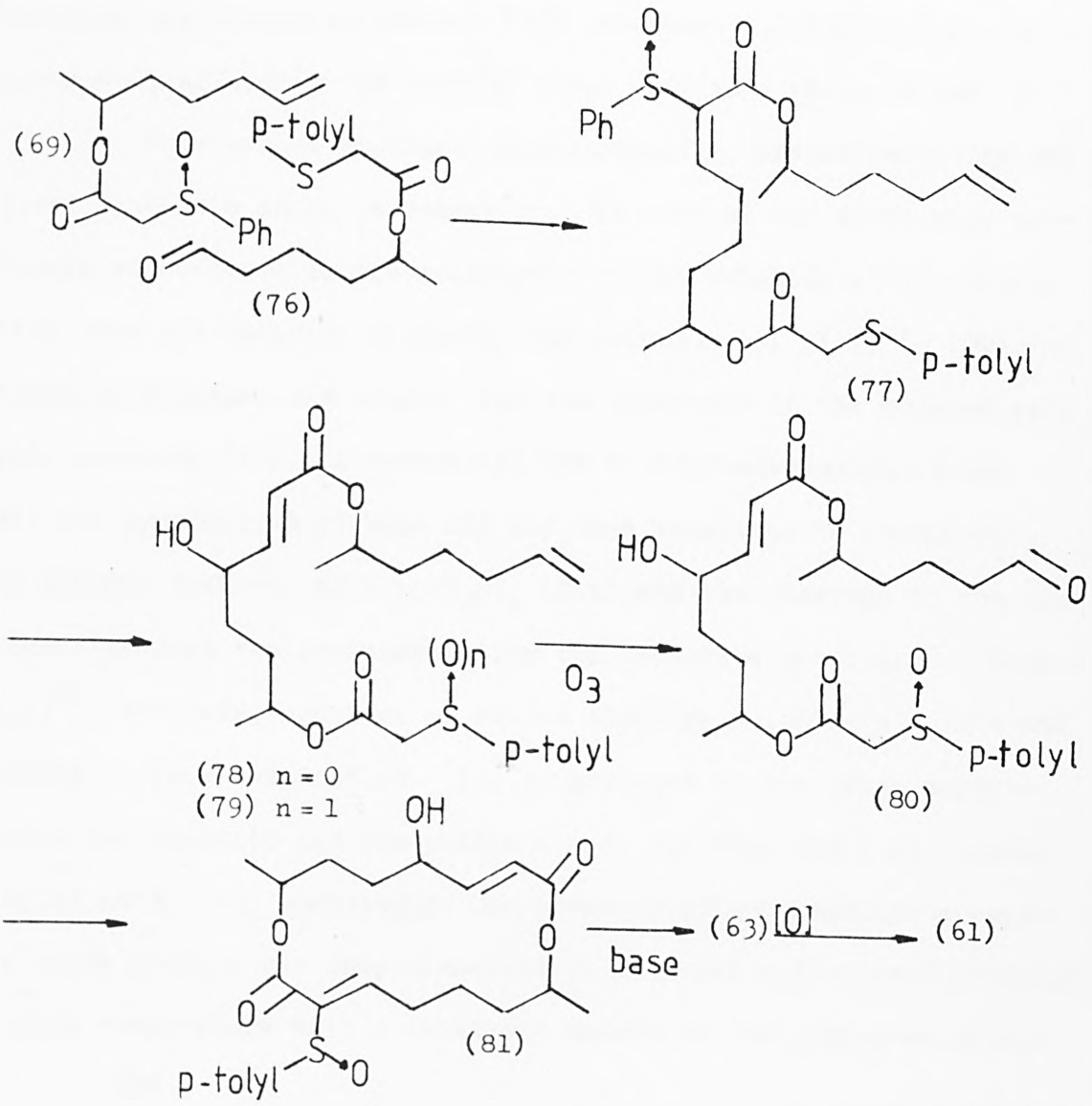
Apparently, only the first stage of the condensation was achieved under the reaction conditions, with neither dehydration nor ring closure occurring. Attempts to induce the reaction to proceed further by retreatment with sodium hydride and zinc chloride gave a product which could not be characterised.

Having failed to obtain the desired cyclic dimer (63) by a direct process, attention was then turned to the possibility of carrying out the synthesis in a stepwise manner which would allow more control over the individual stages. It was proposed (Scheme 26) to condense the sulphoxide olefin (69) with a sulphide aldehyde (76), effect rearrangement of the product (77) to the allylic alcohol (78) and then generate the required functionalities for ring closure by oxidation of the sulphide to a sulphoxide group and ozonolysis of the olefin to an aldehyde.

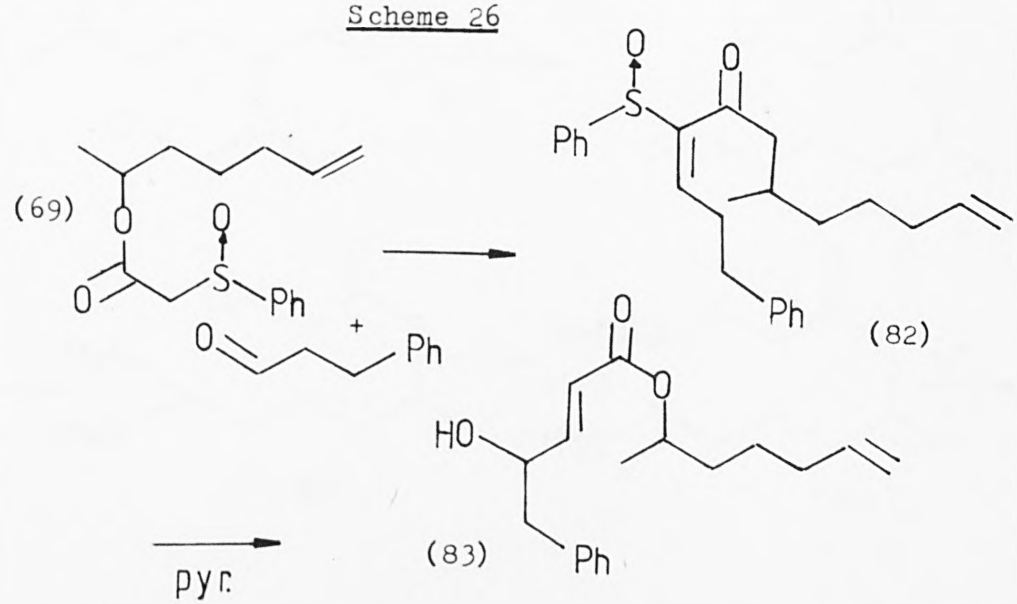
Although the route now proposed is considerably longer than that originally envisaged (Scheme 22) it still preserves the essential feature of using the α-sulphinylacetate condensation with an aldehyde followed by allylic sulphoxide-sulphenate rearrangement to construct the required functionalities in the product.

It will be noted that the proposed route employs the p--toluenesulphide (76) rather than the corresponding phenylsulphide (68). The reasons for this are as follows: 1.) the condensation product (77) would have a distinctive three proton singlet at about δ 2.3[70], aiding identification; 2) p-thiocresol is readily available for the thio-displacement step.

In a preliminary model experiment, the sulphoxide olefin (69) was successfully condensed, in satisfactory yield (40%), with 3--phenylpropionaldehyde using sodium hydride and zinc chloride. The



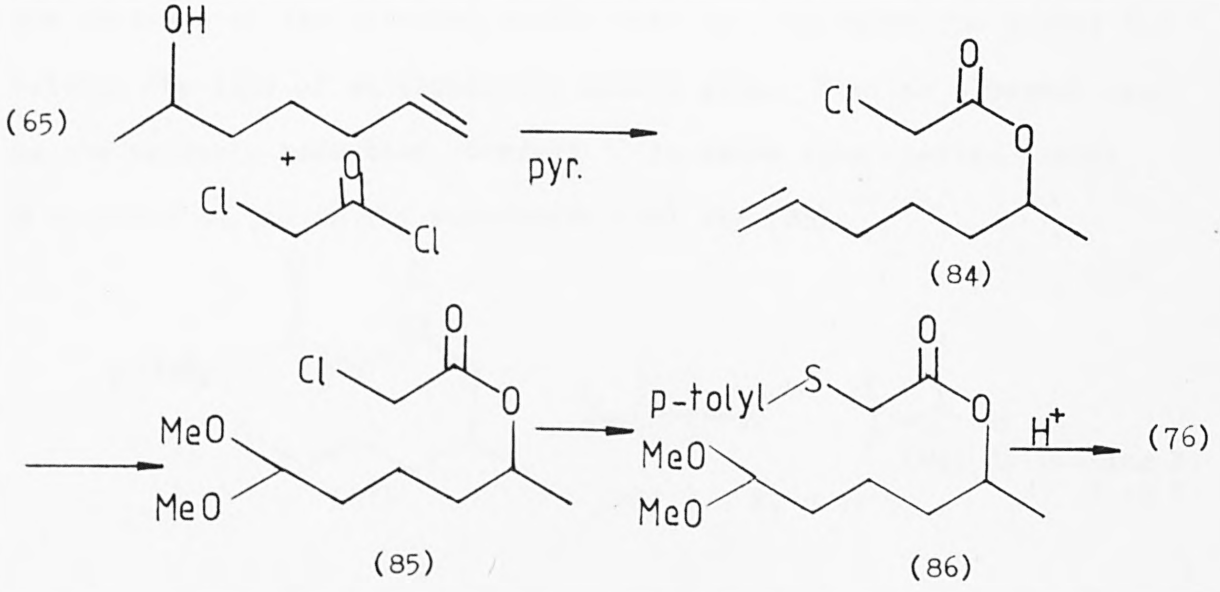
Scheme 26



Scheme 27

resulting conjugated sulphoxide (82) underwent 2,3-sigmatropic rearrangement affording the hydroxy ester (83) in a yield of 59%.

This result provided encouragement to proceed with the projected synthesis shown in Scheme 26. In view of the difficulty previously encountered in the ozonolysis of the sulphide olefin (66), which gave the sulphide aldehyde (68) only in poor yield (<10%), an alternative method was sought for the synthesis of the related sulphide aldehyde (76). Accordingly, the 6-chloroacetoxyhept-1-ene (84) was synthesized (Scheme 28) and then submitted to ozonolysis. The solvent used was MeOH - CH_2Cl_2 (1:1) and the cleavage of the ozonolysis product was performed using the reductive procedure of Pappas et al[65], involving addition of excess dimethyl sulphide at -76°c and warming to room temperature. T.l.c. analysis of the crude mixture showed two products and the proton n.m.r. spectrum had a six proton singlet at δ 3.22, suggesting the presence of two methoxyl groups. The crude product was then dissolved in methanol and stirred overnight at room temperature with a catalytic amount of toluene-p-sulphonic

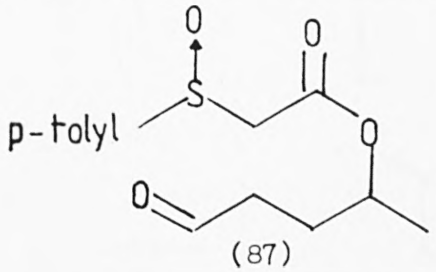


Scheme 28

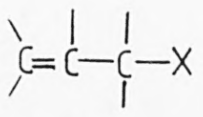
acid. After working up, the preparative t.l.c. afforded 5-(chloroacetoxy)hexanal dimethylacetal (85) in excellent yield (81.5%) which on thio-displacement[71], using sodium hydride and p-thiocresol, gave the sulphide acetal (86) (80%) which underwent facile hydrolysis to the sulphide aldehyde (76) by the use of a dilute solution of orthophosphoric acid in aqueous tetrahydrofuran.

Having achieved the synthesis of the desired sulphide (76) the planned route (Scheme 26) to pyrenophorin (61) was pursued. The first step of the condensation was carried out and the conjugated sulphoxide (77) was isolated in a fair yield. The allylic sulphoxide--sulphenate rearrangement as in the model experiment, took place smoothly giving the hydroxy-ester (78) in 51.5% yield and the thio-oxidation of the hydroxy-ester (78), using metachloroperbenzoic acid[72], gave the corresponding sulphoxide (79) in almost quantitative yield.

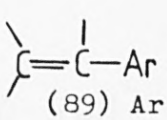
Ozonolysis of the sulphoxide olefin (79) gave rise to the aldehyde (87). Thus, not only was the hoped-for regioselectivity for attack on the terminal olefinic bond of (79) not observed, but the cleavage of the internal double bond took an anomalous course involving the loss of an additional carbon atom. Similar abnormal ozonoysis products have been observed [67] to arise from olefins having α-activation, as in the structures (88) and (89).



(87)



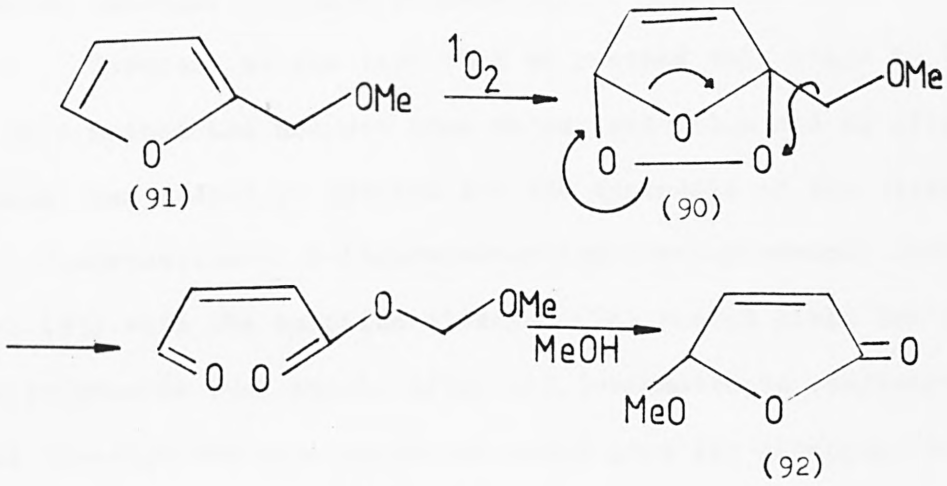
(88) X = N, O or S



(89) Ar bearing N, O or S

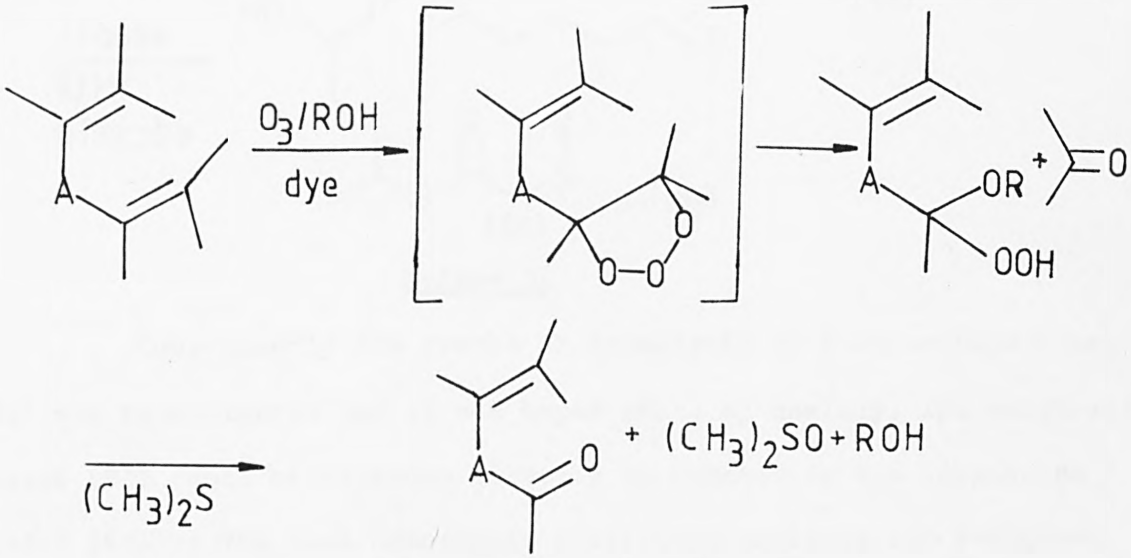
In a recent mechanistic investigation[73], evidence was presented that such products arise <u>via</u> a rearrangement of the inter-

mediate ozonide. Thus the "ozonide" (90) formed by singlet oxygenation of 2-methoxymethylfuran (91) underwent rearrangement and solvolysis to form the pseudoester (92).



Scheme 29

It is not clear whether the cleavage of the internal olefinic bond in the sulphoxide (79) is a consequence of an alteration in regioselectivity in the initial attack of ozone, resulting from the presence of the allylic hydroxyl group, or from the further ozonolysis of an initially-formed aldehyde (80) following from the use

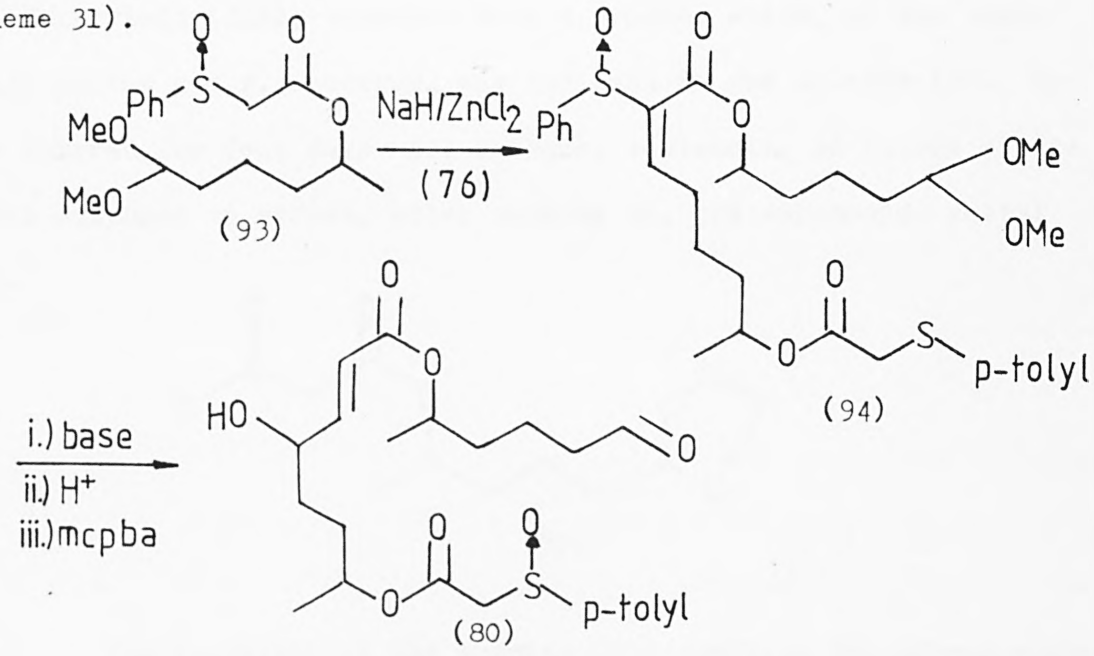


Scheme 30

of an excess of ozone. If the latter was the case, it might be possible

to make use of the indication method described by Veysoglu and co-workers[74]. They were able to achieve selective mono-ozonolysis of certain dienes by the inclusion of a small amount of an ozonizable dye as an internal standard (Scheme 30).

However, at the time when we reached this stage in the work this method had not yet come to our attention and an alternative approach was therefore devised for the synthesis of the aldehyde (80). Condensation of 5-(benzenesulphinylacetoxy)hexanal dimethyl acetal (93) with the sulphide aldehyde (76) should yield the conjugated sulphoxide (94) which, after a 2,3-sigmatropic rearrangement, acetal cleavage and thio oxidation would give the aldehyde (80) (Scheme 31).

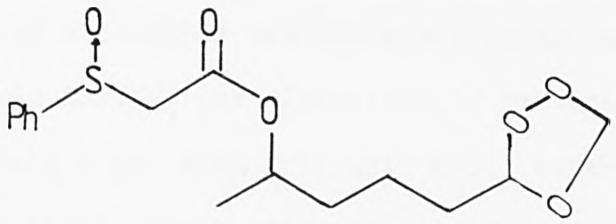


Scheme 31

Consequently the result of ozonolysis of 6-chlorohept-1-ene (84) was reconsidered and it was hoped that, by analogy, the sulphoxide acetal (93) could be obtained directly by submitting the sulphoxide olefin (69) to the same ozonolysis conditions employed for 6-chlorohept-1-ene (84). Accordingly, the sulphoxide olefin (69) was ozonolysed using a (1:1) mixture of methanol in dichloromethane as solvent

and the reductive cleavage of the ozonolysis product was performed using an excess of dimethyl sulphide. After working up, the crude mixture was stirred for 15h in methanol over anhydrous sodium sulphate (toluene-p-sulphonic acid was not used because of the presence of the sulphoxide group) and then submitted to preparative t.l.c.. The sulphoxide acetal (93) was isolated as expected, in good yield (66%) together with the sulphoxide aldehyde (62) (22%).

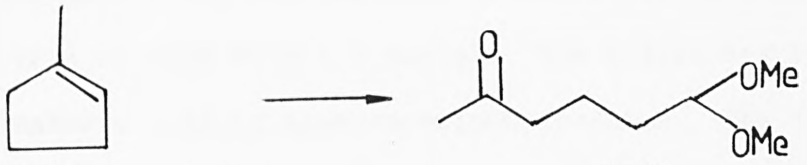
The ozonolysis of the sulphoxide olefin (69) was then repeated, this time using dichloromethane alone, although the reductive cleavage of the ozonolysis product was still carried out using dimethyl sulphide. In this manner the sulphoxide aldehyde (62) was isolated in a fair yield (32%), together with a product which, on the basis of its proton n.m.r. spectrum, was assigned as the ozonide (95), and then stirred for four days with methanol containing an excess of dimethyl sulphide to afford, after working up, the sulphoxide acetal (93).



(95)

The isolation of the ozonide (95) confirms the aforementioned stability of the ozonide formed when ozonolysing the sulphide olefin (66) (cf. page 84). With regard to the direct formation of the acetals (85) and (93) a similar result was observed by Trost and Verhoeven[54]. They obtained 5-oxohexanal dimethylacetal (96) directly on ozonolysing 1-methylcyclopentene (97) in a (1 : 1) mixture of methanol in dichloromethane, followed by reductive cleavage of the ozonolysis

product with dimethyl sulphide (Scheme 32).



(97) (96)

Scheme 32

Having synthesized the sulphoxide acetal (93) directly in a good chemical yield, its condensation with the sulphide aldehyde (76) was attempted (Scheme 31). Unexpectedly, the hoped-for reaction did not take place. The sulphoxide acetal (93) also failed to react in a pilot experiment with 3-phenylpropionaldehyde. The reason for these failures is not certain but it may be due to the presence of the acetal group. Possibly this is complexing with the metal counterion and hence blocking approach to the anion.

This reaction was not pursued any further, but it led to an investigation of a possible new synthetic route to pyrenophorin (61). This route would involve the alkylation of benzenethioacetic acid (98) which would yield a key monomeric unit (101) suitable for dimerization to a macrolide (102), which after thio-oxidation followed by selenenylation and selenoxide elimination would yield the required precursor (104) of pyrenophorol (63) - a precursor which would bear similarity with the diolide (81) and would show the practicability of the allylic sulphoxide-sulphenate rearrangement (Scheme 33).

Another interesting feature of this method was the opportunity to investigate the cyclodimerization reaction of the key monomeric unit (101). The cyclodimerization of the ethylene acetal hydroxy acid (105), which has been commonly used as a monomeric unit in the synthesis of pyrenophorin[60-63] only occurs in low yield ($< 25\%$).

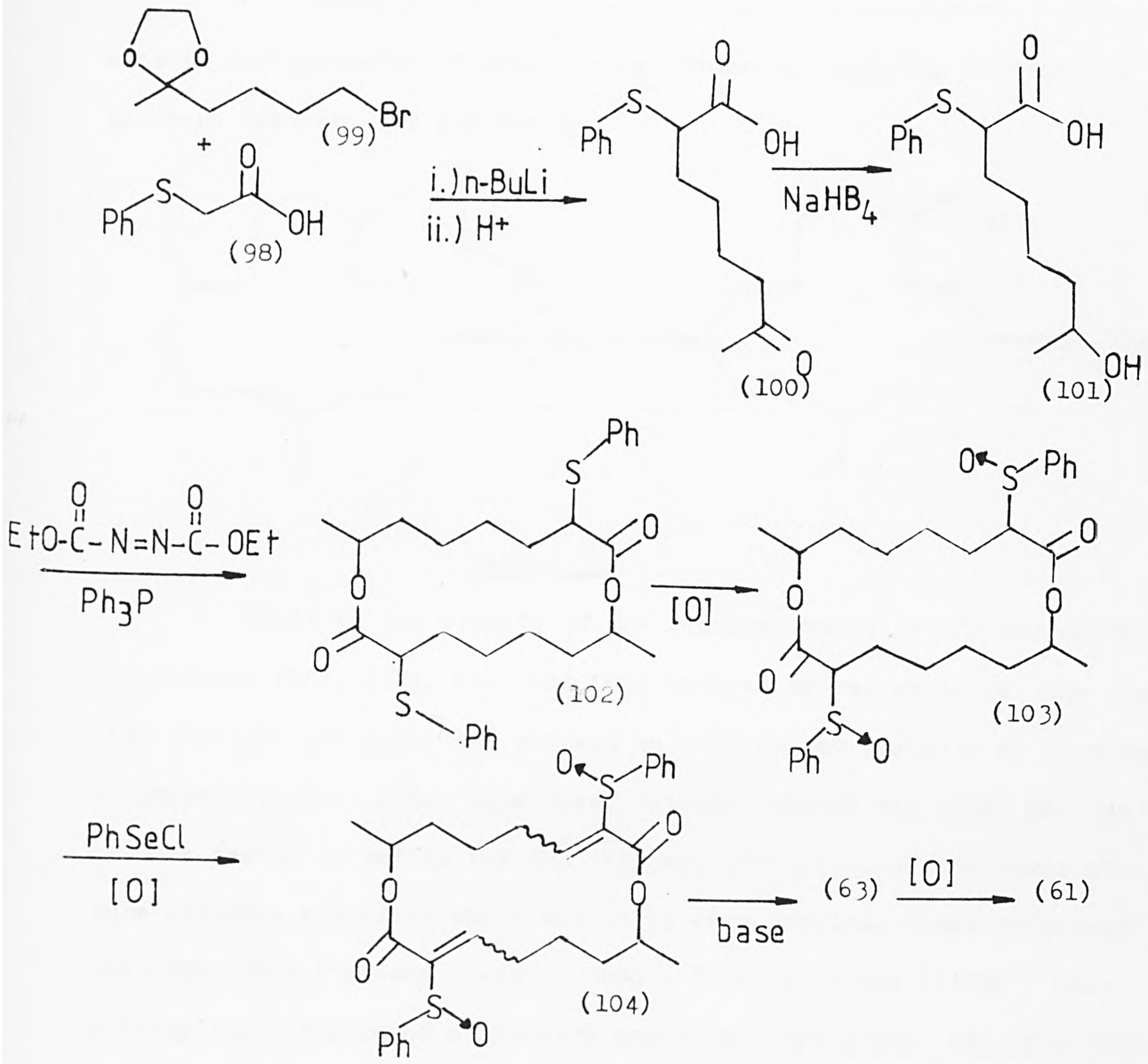
Accordingly, the alkylation of benzenethioacetic acid (98) with 6-bromohexan-2-one ethylene acetal[75] (99) was carried out and the acid ketone (100) was isolated directly, after column chromatography, as a mixture with its acetal. The latter was hydrolysed using orthophosphoric acid in aqueous tetrahydrofuran. The first attempt to reduce the acid ketone (100) to hydroxy acid (101), using sodium borohydride, failed, even when a large excess of sodium borohydride was used. This failure may be attributed to the presence of acid impurities; accordingly, the acid ketone (100) was treated with aqueous sodium hydrogen carbonate prior to the reduction and, in this manner, the hydroxy acid (101) was isolated in good yield. Dimerization of the hydroxy acid (101) to give the diolide (102) was achieved in 51% yield using diethyl azodicarboxylate and triphenylphosphine[60,61,76] in benzene (0.02M) at 10°C to room temperature over 17h. The diolide (102) was isolated as three different fractions; the most polar and the least polar fractions were oils whilst the intermediate one was a crystalline solid (m.p. 60 - 61°C). High performance liquid chromatography (HPLC) analysis of the three fractions showed that all six possible diastereoisomers had been formed, but attempts to separate them on a preparative scale failed, probably because of their ready epimerization. All three fractions were submitted to mass spectrometry and all three showed the required m/e at 500 (M^+).

The synthesis of the α,β-unsaturated diolide (104) was planned *via* phenylselenenylation and selenoxide elimination of the diolide (102). The selenium based procedure[77] was preferred to the closely related sulphoxide one[71] upon the consideration of the easy selective oxidation in the selenium case, and of the much milder conditions under which the elimination would occur. The stability of

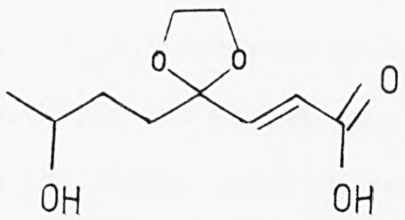
phenylselenyl chloride (PhSeCl) as contrasted with the instability of phenylsulphenyl chloride (PhSCl) was also another factor of particular importance. However, the attempt to phenylselenenylate the diolide (102) using phenylselenyl chloride with either n-buthyllithium or sodium hydride failed. These failures seemed to arise from the non-formation of the dianion of the diolide (102). The use of potassium hydride was not investigated. Instead, it was decided to perform the thio-oxidation of the diolide (102) prior to the phenylselenenylation (as shown in Scheme 33). The thio-oxidation was performed using metachloroperbenzoic acid and the diolide disulphoxide (103) was isolated as a diastereoisomeric mixture in excellent yield (90%).

Stabilised enolates which have been selenylated include those derived from β-diketones, β-keto esters, β-ketosulphoxides and β-ketoselenoxides and it has been reported[77] that they are best selenenylated using phenylselenyl chloride or phenylselenyl bromide and the sodium salt of the carbonyl compound, usually prepared with sodium hydride in tetrahydrofuran. Consequently, the dianion of (103) was generated by allowing the diolide disulphoxide (103) to stir in a suspension of sodium hydride in tetrahydrofuran at 0^{o}c to room temperature over a period of two hours and then it was treated with phenylselenyl chloride. The diselenylated product, which was isolated in 67% yield, upon oxidation with metachloroperbenzoic acid gave directly the α,β-unsaturated diolide (104) in 90% yield as a diastereoisomeric mixture. (It should be said that the geometry about the double bonds is not clear from the spectral data available).

Having obtained the diolide (104) an attempt was made to perform the 2,3-sigmatropic rearrangement which would result in the formation of pyrenophorol (63)[30] (Scheme 33).

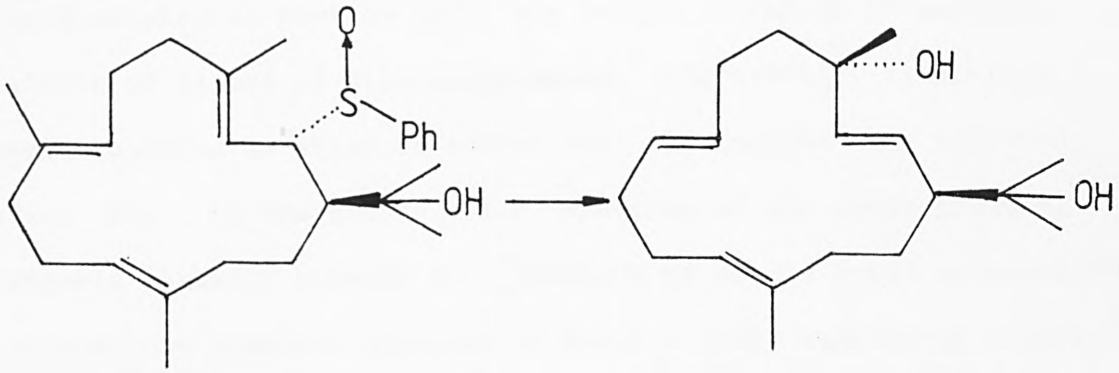


Scheme 33



(105)

The versatility of the allylic sulphoxide-sulphenate rearrangement in the synthesis of medium ring naturally occurring derivatives has been demonstrated (Scheme 34)[78].

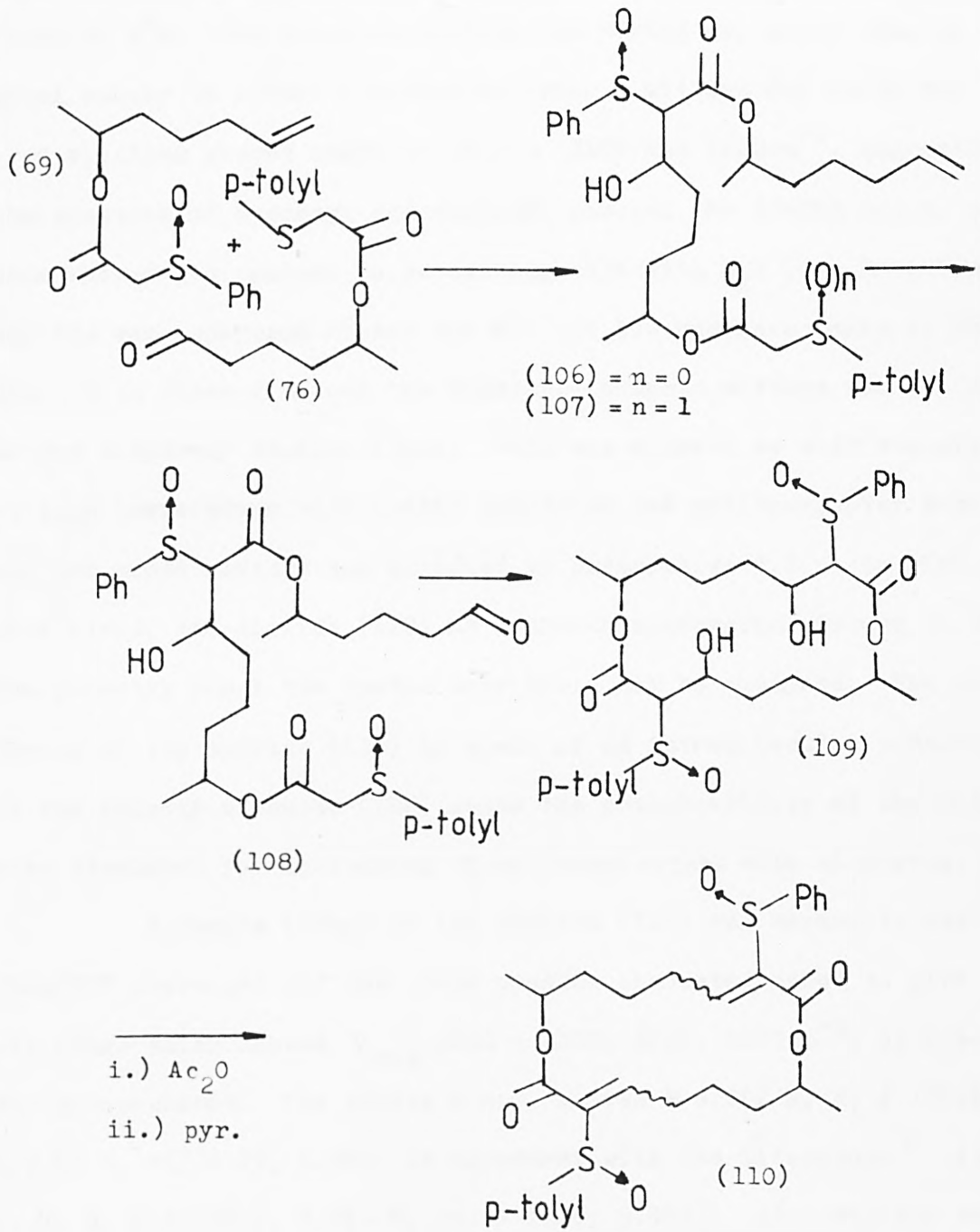


Scheme 34

Based on the results of the rearrangements of the conjugated sulphoxides (10), (77), (82) and (94) induced by wet pyridine, the diolide disulphoxide (104) was allowed to stir in wet pyridine at room temperature for 18h. After this time, tetrahydrofuran was added and the mixture heated to reflux for 4h. Preparative t.l.c. of the crude mixture afforded a product which was still very complex, whose infra-red spectrum ($CHCl_3$) showed peaks at 3600 - 3200, 1710 and 1640cm^{-1} suggesting the presence of a hydroxyl and a carbonyl group and of a double bond. The proton n.m.r. had a complex pattern and showed aromatic protons at δ 7.35 - 8.00 and the mass spectrum showed a peak at 156 which corresponds to $C_8H_{12}O_3$ (accurate measurement gave 156.07742; $C_8H_{12}O_3$ requires 156.07838) and another one at 138 (156 - H_2O). It has been reported[30] that the highest peak shown in the mass spectrum of pyrenophorol (63) was at m/e 156. On these grounds the mixture was believed to contain the expected pyrenophorol (63) as a mixture of isomers, as well as some of the starting sulphoxide (104). Consequently, the mixture was redissolved in a solution of pyridine in tetrahydrofuran and heated to reflux for 72h. However, no increase in the 'pyrenophorol'

content was noticed and attempts to isolate this were unsuccessful. Facing this difficulty and in the belief that a stronger base in a polar solvent would effect the rearrangement more cleanly, a further sample of the disulphoxide diolide (104) was heated to reflux in methanol containing an excess of diisopropylamine. Regrettably, it yielded a complex mixture in which it seemed that the lactone ring had been cleaved. Thus, in the proton n.m.r. spectrum of the crude product, the signals normally present for >CH-OCOR at ca δ 4.8 had disappeared and several new singlets appeared at δ 3.5 - 3.85, suggesting methoxyl groups. The use of phosphate buffer (pH = 7.5) was also tried without success and also the use of 1,5-diazobicyclo [4.3.0.] non-5-ene (DBN) containing two equivalents of trimethylphosphite. In rationalizing the causes of these failures some points await clarification. These are: 1.) the geometry about the double bonds of the diolide (104) and their steric consequences on the required rearrangements; 2.) the intramolecular consequences of having two conjugated sulphoxides undergoing rearrangement - i.e., between any of the postulated intermediates in the 16-membered ring system.

In view of the fact that the geometry about the double bonds remains uncertain and that this geometry may be of critical importance, it was thought to be of interest to examine the synthesis of the analogue (110) through the condensation of the sulphoxide olefin (69) with the sulphide aldehyde (76) using Hauser's base. The condensation product (106) after thio-oxidation followed by ozonolysis would yield the hydroxy aldehyde (108) which would undergo an intramolecular condensation which would result in the dihydroxy diolide (109). This, by dehydration, would yield the diolide (110) (Scheme 35), which might well have a different geometry to the analogue (104).



Scheme 35

Consequently, the sulphoxide olefin (69) was reacted with the sulphide aldehyde (76) using Hauser's base to yield, as expected, the hydroxy-ester (106) in fair yield (37%). The thio-oxidation was then performed using m-chloroperbenzoic acid and the disulphoxide (107) was then submitted to ozonolysis and the crude product, without puri-

fication, added dropwise to a solution of Hauser's base in tetrahydrofuran at 0°C. The reaction mixture was worked up, after 48h, in the usual manner to afford a diastereoisomeric mixture for which the infra-red spectrum showed peaks at 3600 - 3100 and 1720cm^{-1}, suggesting the presence of hydroxyl and carbonyl groups; the proton n.m.r. spectrum showed two protons to be exchangeable with D_2O (cf. Experimental) and the mass spectrum showed the M^+ at 578 and gave peaks at 262 and 248. With these findings the diastereoisomeric mixture was assigned as the dihydroxy diolide (109). This was allowed to stir overnight at room temperature with acetic anhydride and pyridine; after working up, the crude mixture was purified by preparative t.l.c. to give, in good yield, the diolide (110) as a diastereoisomeric mixture in which the geometry about the double bond could not be assigned. The synthesis of the diolide (110) by means of an intramolecular condensation of the hydroxy aldehyde (108) shows the practicability of the method here developed for condensing α-sulphinyl esters with aldehydes.

A sample (18mg) of the diolide (110) was warmed in wet pyridine/THF overnight and the crude product chromatographed to give an oil (6mg) which showed ν_{max} 3600 - 3200, 1710, 1650cm^{-1}, as expected for pyrenophorol. The proton n.m.r. showed δ 6.0(1 H, d, J 15Hz), 6.9 (1 H, dd, J 15, 5.5Hz) in agreement with the literature[30] [δ 5.9 (1 H, d, J 15.5Hz), 6.9(1 H, dd, J 15.5, 5.5Hz)]. Also visible in the proton n.m.r. were two OH groups (δ 2.0 - 2.2, 2 H, b, exch. D_2O), and weak aromatic signals (δ 7.0 - 8.0) indicating that some starting material was still present. The mass spectrum again showed a peak at m/e 156 , consistent with the literature for pyrenophorol, and also a strong peak at m/e157 . The oil was then treated with Jones' reagent[29] and the crude product chromatographed to give a small sample

of product which showed a mass spectrum very similar to that of an authentic sample of synthetic (d, l) pyrenophorin, kindly provided by Dr. E. Colvin (m/e 155, 138, 99, 82, 55, 44).

A t.l.c. comparison of the product with the authentic sample showed the former to be slightly more polar. In the light of these results, it is believed that the synthetic sequence (Scheme 35) had resulted in formation of meso-pyrenophorin. Further work with a larger quantity of material will be required.

Part III:

EXPERIMENTAL

General Procedure. - Reactions were normally carried out under an atmosphere of dry nitrogen. Infra-red spectra, using either a Perkin-Elmer 157 G or 297 spectrometer, were measured either as Nujol mulls or in chloroform solution, except for oils which were generally measured as thin films. Proton n.m.r. analyses were performed using deuteriochloroform solutions, except where otherwise stated, on either a Perkin-Elmer R32 (90 MHz) or R12 (60 MHz) spectrometer. Chemical shifts are given in ppm from tetramethylsilane as internal reference. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; q', quintet, and m for multiplet. The values of complex resonances are given as a range of values except where the multiplet had an analysable pattern, in which case the chemical shift is given as the centre of the signal. Ultraviolet spectra were recorded on a Unicam instrument for ethanolic solutions (λ_{max} values are given in nanometers). Mass spectra were taken on either AEI Kratos MS25 or AEI Kratos MS950 instruments. Melting points were obtained on a Kofler hot-stage apparatus and are uncorrected.

Tetrahydrofuran (THF) was distilled from sodium before use; ether, benzene and toluene were dried over sodium. All solvents were of GPR grade and were distilled prior to use, except for chloroform, ether and benzene. Anhydrous methanol was obtained by distillation from magnesium methoxide. Petroleum ether refers to the fraction of boiling range 40 - 60°C.

Merck silica gel GF_{254} was used for both preparative and analytical t.l.c., Sorbasil and Merck silica gel G_{60} were used for column chromatography. Eluting solvents are indicated in the text. During the work up of reactions , routine drying was performed over anhydrous sodium sulphate unless otherwise indicated. Solvents were

evaporated *in vacuo* on a Buchi rotary evaporator.

Methyl benzenesulphinylacetate (MPSA) was obtained from oxidation of methyl benzenethioacetate (bought from Parish Laboratories) using metachloroperbenzoic acid.

The following abreviations are used in this section:

THF - tetrahydrofuran

MPSA - methyl benzenesulphinylacetate

mcpba - metachloroperbenzoic acid

DBN - 1,5-diazabicyclo[4.3.0]non-5-ene

LDA - lithium diisopropylamide.

Temperatures are quoted on the Celsius scale.

Condensation of MPSA with aldehydes using sodium hydride and zinc chloride:

General Procedure. - MPSA (198mg; 1mmol) in THF (3ml) was added dropwise to a stirred suspension of sodium hydride (43mg of 55% w/w dispersion in oil; 1mmol) in THF (4ml) at 0° ; the reaction mixture was warmed to room temperature and stirred for 30m. After this time, the reaction mixture was recooled to 0° and anhydrous zinc chloride (1.0 - 1.2mmol) in THF (3ml) was added slowly in portions. After a further 30m at 0° the aldehyde (1mmol) as a solution in THF (3ml) was added. The reaction mixture was warmed to room temperature and stirred for 15 - 18h; before heating it to reflux (30m - 3h) during which time a precipitate formed.

Ethyl acetate and a saturated aqueous solution of ammonium chloride were added to the mixture and the organic layer separated; the aqueous layer was extracted with more ethyl acetate. The organic layers were combined, washed with water, dried and evaporated in vacuo to afford the products listed below: these were purified either on preparative t.l.c. or by column chromatography.

Methyl (E)-3-phenyl-2-(benzenesulphinyl)prop-2-enoate (9). - From the reaction of benzaldehyde with MPSA (416mg; 2.1mmol). It was purified by preparative t.l.c. using (1 : 3) ethyl acetate/light petroleum as solvent. Isolated as an oil (122mg; 20%), (Found: M^+ 286.06589. $C_{16}H_{14}O_3S$ requires 286.06635); ν_{max} 1740, 1620, 1280, 1050cm^{-1}; δ 3.60 (3 H, s), 7.25 - 7.75 (11 H, m) (cf. Figure 2).

Methyl (E)-2-(benzenesulphinyl)oct-2-enoate (10). - From the reaction of hexaldehyde with MPSA (594mg; 3mmol). It was purified by column chromatography using (1 : 49) ethyl acetate/chloroform as solvent. Isolated as an oil (316mg; 38%), (Found: C, 63.95;

H, 7.3; S, 11.4%. $C_{15}H_{20}O_3S$ requires C, 64.25; H, 7.2; S, 11.4%); ν_{max} 1730, 1630, 1440, 1360, 1250, 1040cm^{-1}; δ 0.92 (3 H, t, J 7Hz), 1.18 -1.70 (6 H, m), 2.75 (2 H, q, J 8Hz), 3.65 (3 H, s), 7.18 (1 H, t, J 7Hz), 7.40 - 7.75 (5 H, m).

Methyl (E)-2-(benzenesulphinyl)hept-2-enoate (11). - From the reaction of valeraldehyde with MPSA (396mg; 2mmol). It was purified by preparative t.l.c. using (1:9) ethyl acetate/light petroleum as solvent. Isolated as an oil (185mg; 35%), (Found: C, 62.9; H, 6.9; S, 11.9%; M^+ 266.09762. $C_{14}H_{18}O_3S$ requires C, 63.1; H, 6.8; S, 12.0%; 266.097658); ν_{max} 1725, 1630, 1480, 1030cm^{-1}; δ 0.92 (3H, t, J 7Hz), 1.18 - 1.78 (4 H, m), 2.75 (2 H, q, J 8Hz), 3.65 (3 H, s), 7.17 (1 H, t, J 7Hz), 7.33 - 7.80 (5 H, m).

Methyl (E), (E)-2-(benzenesulphinyl)hexe-2,4-dienoate (12). - From the reaction of crotonaldehyde with MPSA (4.11g; 20.7mmol). It was purified by column chromatography using (1:19) ethyl acetate/chloroform as solvent. Isolated as an oil (2.01g; 39%), (Found: C, 62.5; H, 5.75; S, 12.55%; M^+ 250.06621. $C_{13}H_{14}O_2S$ requires C, 62.4; H, 5.6; S, 12.8% 250.06636); ν_{max} 1720, 1635, 1480, 1040cm^{-1}; δ 1.98 (3 H, dd, J 7, 1Hz), 3.68 (3 H, s), 6.52 (1 H, dq, J 16, 7Hz), 7.15 (1 H, dd, J 12, 1Hz), 7.32 - 7.78 (6 H, m) (cf. Figure 1). After storing the oil below 0° for a long period it crystallized, m.p. 64 - 65° .

Methyl (E)-2-(benzenesulphinyl)but-2-enoate (13). - From the reaction of acetaldehyde with MPSA (792mg; 4mmol). It was purified by preparative t.l.c. using (2:23) ethyl acetate/chloroform as solvent. Isolated as an oil (302mg; 34%), (Found: M^+ 224.05098. $C_{11}H_{12}O_3S$ requires 224.050711); ν_{max} 1730, 1640, 1270, 1040, 750, 700cm^{-1}; δ 2.3 (3 H, d, J 7Hz), 3.67 (3 H, s), 7.44 (6 H, m). Another

product was also obtained from the t.l.c. plate, as a diastereoisomeric mixture, which was assigned as methyl 3-hydroxy-2-(benzenesulphinyl)butanoate (21). Isolated as an oil (89mg; 9%), (mass spectrum cf. text); ν_{max} 3600 - 3100, 1740, 1040cm^{-1}; δ 1.20 - 1.50 (3 H, m), 3.00 - 3.80 (5 H, m), 4.38 - 4.78 (1 H, m, exch. D_2O), 7.40 - 7.90 (5 H, m).

Methyl (E) 4-methyl-2-(benzenesulphinyl)pent-2-enoate (14). - From the reaction of iso-butyraldehyde with MPSA (396mg; 2mmol). It was purified by preparative t.l.c. using (1:19) ethyl acetate/chloroform. Isolated as an oil (69mg; 12%), (Found: M^+ 252.08181. $C_{13}H_{16}O_3S$ requires 252.082010); ν_{max} 1730, 1630, 1050, 750, 700cm^{-1}; δ 1.12 (3 H, d, J 2Hz), 1.22 (3 H, d, J 2Hz), 3.40 - 3.60 (1 H, m), 3.68 (3 H, s), 6.95 (1 H, d, J 12Hz), 7.40 - 7.78 (5 H, m).

Attempts to obtain methyl (E)-3-phenyl-2-(benzenesulphinyl)-prop-2-enoate (9) in a higher yield:

Method A. - MPSA (99mg; 0.5mmol) was stirred with triethylamine (51mg; 0.5mmol), benzaldehyde (53mg; 0.5mmol) and titanium tetrachloride (two drops) in dichloromethane (3ml) for 3h at room temperature and the mixture was then heated to reflux for 4h. After cooling, ether and saturated solution of ammonium chloride were added. The organic phase was separated and washed with water and brine, dried and evaporated in vacuo to afford an oil (98mg), which was purified by preparative t.l.c. using (1:19) light petroleum/chloroform. The sulphoxide ester (9) was isolated in a poor yield (<10%).

Method B. - MPSA (99mg; 0.5mmol) in THF (2ml) was added dropwise to a stirred suspension of sodium hydride (22mg of 55% w/w dispersion in oil; 0.5mmol) in THF (2ml) at 0° . After the addition, the reaction mixture was warmed to room temperature and stirred for

45m. The mixture was recooled to 0° and benzaldehyde (53mg; 0.5mmol) in THF (2ml) mixed with titanium tetrachloride (two drops) was slowly added. The reaction was warmed to room temperature and stirred for 18h before its t.l.c. was checked ((1:19) ethyl acetate/chloroform): it showed the title acetate as a weak spot. The reaction was then refluxed for a further 23h and its t.l.c. was checked again; however, the reaction had not developed further and so it was stopped and set aside.

Method C. - To a suspension of sodium hydride (87mg of 55% w/w dispersion in oil; 2mmol) in THF (3ml) stirred at 0° a solution of MPSA (396mg; 2mmol) in THF (3ml) was added dropwise. The reaction was stirred for 30m at 0° and then it was cooled to -74° and trimethylsilyl chloride (316mg; 2mmol) in THF (2ml) was added. The reaction was stirred for 1h at this temperature before benzaldehyde (212mg; 2mmol) in THF (2ml) was added; the reaction was allowed to warm up to room temperature and stirred overnight. Finally, the reaction mixture was heated to reflux for 18h. T.l.c. showed that no title product had formed. MPSA (ca 250mg) was recovered after working up in the usual manner.

Reaction of MPSA with crotonaldehyde using LDA as a base. - n-Butyllithium (0.62 ml; 1mmol; 1.6 molar in hexane) was added dropwise to a solution of diisopropylamine (111mg; 1.1mmol) at -40° in THF (3ml) and stirred for 30m at this temperature. After this time, MPSA(198mg; 1mmol) in THF (3ml) was added dropwise, the reaction mixture was stirred for a further 30m at -40° and then anhydrous zinc chloride (136mg; 1mmol) in THF (3ml) was added; the reaction mixture was then stirred for 30m before crotonaldehyde (70mg; 1mmol) in THF (3ml) was added; the reaction mixture was warmed to room temperature

and stirred overnight. A saturated solution of ammonium chloride and ethyl acetate were added, the organic phase separated, washed with water and brine, dried and evaporated in vacuo to afford an oil (177mg) which was purified by preparative t.l.c. using (1:4) ethyl acetate/light petroleum as solvent to afford the conjugated sulphoxide (12) in 13% yield (32mg). A minor product was also isolated (11mg); t.l.c. showed it to be identical to the allylic sulphoxide (23).

t-Butyl benzenesulphinylacetate (1; R^1 = Ph; R = t-butyl). - Benzenethioacetic acid (10.00g; 59.52mmol) was dissolved in ether (200ml) and concentrated sulphuric acid (5ml) was slowly added. Isobutene (20ml) was condensed using an acetone-dry-ice bath and then added to the acid mixture at 0° contained in a pressure bottle, which was sealed and left at room temperature for 18h. The container was then cooled to -76°, opened and a saturated solution of sodium hydrogen carbonate added; the organic phase was separated off, washed (water), dried and evaporated in vacuo to afford t-butyl benzenethioacetate in 71.6% yield (9.55g); ν_{max} 1725, 1480, 740, 690cm^{-1}; δ 1.38 (9 H, s), 3.52 (2 H, s), 7.15 - 7.48 (5 H, m). The thioacetate (9.36g; 41.70mmol) was dissolved in dichloromethane (100ml), cooled to -78° and then mcpba (8.45g; 41.7mmol; 85%) in dichloromethane (150ml) was added dropwise. The reaction mixture was stirred for 10m before adding dichloromethane and saturated aqueous sodium hydrogen carbonate solution. The organic layer was processed in the usual manner to afford the title acetate (9.55g) as a pale yellow oil in 95.4% yield; ν_{max} 1725, 1480, 1050, 740, 690cm^{-1}; δ 1.40 (9 H, s), 3.68 and 3.76 (2 H, ABq, J 14Hz), 7.44 - 7.78 (5 H, m).

t-Butyl (E)-2-(benzenesulphinyl)oct-2-enoate (24). - From the reaction of the α-sulphinyl ester (1, R^1 = Ph; R = t-butyl) (240mg;

1mmol) with hexaldehyde (100mg; 1mmol) using the conditions previously described for the condensation of MPSA (page 107). Purification was effected by preparative t.l.c., eluting with (1:19) ethyl acetate/chloroform. It was isolated as an oil (57mg; 18%), (Found: M^+ 322.15988. $C_{18}H_{26}O_3S$ requires 322.160256); ν_{max} 1720, 1630, 1450, 1050, 750 and 690cm^{-1}; δ 0.92 (3 H, t, J 7Hz), 1.20 - 1.75 (15 H, m), 2.75 (2 H, q, J = 8Hz), 7.08 (1 H, t, J 8Hz), 7.35 - 7.82 (5 H, m). (Starting material was recovered in 37% yield (89mg)).

Condensation of t-butyl benzenesulphinylacetate (1, R^1 = Ph; R = t-butyl) with hexaldehyde using Hauser's base. - 2-Bromopropane (123mg; 1mmol) in THF (4ml) was added dropwise to a suspension of magnesium turnings (27mg; 1.1mmol) in THF (3ml); the reaction mixture was heated to reflux for 45m and then diisopropylamine (101mg; 1mmol) in THF (3ml) was added to the still warm reaction mixture and the mixture was stirred for a further 30m at room temperature. After this time, the reaction mixture was cooled to 0° and the title acetate (240mg; 1mmol) in THF (4ml) was added, the mixture stirred for 30m before slowly adding a solution of hexaldehyde (100mg; 1mmol) in THF (3ml). The reaction mixture was warmed to room temperature and stirred for 36h before adding ethyl acetate and saturated aqueous ammonium chloride. The organic phase was separated, washed with water and brine, dried and evaporated in vacuo to afford an oil (280mg) which was purified by preparative t.l.c. using (1:9) ethyl acetate/chloroform. t-Butyl (E)-2-(benzenesulphinyl)oct-2-enoate (24) was isolated in 25% yield (80mg) together with the starting acetate (1, R^1 = Ph; R = t-butyl) (120mg) which contained a trace of the diastereoisomeric mixture of t-butyl 3-hydroxy-2-(benzenesulphinyl)octanoate (25) (^1H n.m.r. evidence).

Condensation of MPSA (5) with hexaldehyde using Hauser's base. - 2-Bromopropane (123mg; 1mmol) in THF (3ml) was added dropwise to a suspension of magnesium turnings (36mg; 1.5mmol) in THF (3ml) at room temperature. The reaction mixture was heated to reflux for 30m and diisopropylamine (101mg; 1mmol) in THF (3ml) was added to the still-warm solution before it was stirred for a further 30m at room temperature; the mixture was cooled to 0° and MPSA (5) (198mg; 1mmol) in THF (4ml) added; the reaction mixture was stirred at this temperature for 45m before adding, dropwise, a solution of hexaldehyde (100mg; 1mmol) in THF (3ml). The reaction was warmed to room temperature and stirred for 1h. Ethyl acetate and saturated aqueous ammonium chloride were then added and the organic layer worked up by the usual procedure to afford an oil (284mg) which was purified by preparative t.l.c. using (1:9) ethyl acetate/chloroform as solvent. This gave a complex diastereoisomeric mixture which, by its proton n.m.r. spectrum, was thought to be a mixture of methyl 3-hydroxy-2-(benzenesulphinyl)octanoate (26) and isopropyl 3-hydroxy--2-(benzenesulphinyl)octanoate (27). On repeating the reaction, under the same conditions, the latter was isolated in 35.5% yield (116mg) as a crystalline compound, m.p. 73 - 75° (Found: M^{+} 326.15503. $C_{17}H_{26}O_4S$ requires 326.155171); ν_{max} 3500 - 3200, 1720, 1050, 750; 690cm^{-1}; δ 0.85 (3 H, m), 1.00 - 1.82 (14 H, m), 3.57 (1 H, d, J 6Hz), 3.95(1 H, m), 5.01 (1 H, q', J 8Hz), 5.68 - 6.20 (1 H, m , exch. D_2O), 7.40 - 7.85 (5 H, m).

The reaction of benzenesulphinylacetic acid (1, R^1 = Ph; R = H) with hexaldehyde using Hauser's base. - The title acid (184mg; 1mmol) in THF (4ml) was added dropwise to a solution of Hauser's base (2mmol), prepared as given in the previous section, in THF (12ml) at

0^{o} . The reaction mixture was stirred for 45m and, then, hexaldehyde (100mg; 1mmol) in THF was added; the mixture was warmed to room temperature before adding ether and 1 N HCl. The organic phase was separated, washed with water and brine, dried and evaporated in vacuo; the residue was redissolved in ether (4ml) and treated with ethereal solution of diazomethane (3ml) and the solvent evaporated off in vacuo to afford an oil (220mg) which was purified by preparative t.l.c. using (1:9) ethyl acetate/chloroform as solvent. Methyl 3-hydroxy--2-(benzenesulphinyl)octanoate (26) was isolated as a crystalline diastereoisomeric mixture (89mg; 32%), m.p. 84-87° (Found: M^{+} 298.12359 . $C_{15}H_{22}O_4S$ requires 298.12418); ν_{max} 3600 - 3100, 1725, 1045, 760, 690cm^{-1}; 0.85 (3 H, m), 11.0 - 1.80 (8 H, m), 3.01 - 4.70 (6 H, bm, 1 H exch. D_2O), 7.40 - 7.85 (5 H, m).

Some of the hydroxy-ester (26) (44mg) was stirred overnight at room temperature with pyridine (2ml) and acetic anhydride (1ml). After this time its t.l.c. was checked using (1:19) ethyl acetate/ chloroform to show a mixture of the starting hydroxy-ester (26) (minor spot) and the α,β-unsaturated sulphoxide ester (10) (major spot). It was then heated to reflux for 1h but no increase in the amount of the conjugated sulphoxide (10) was observed.

Methyl (E)-4-hydroxyoct-2-enoate (30). - The conjugated sulphoxide (10) (33mg; 0.11mmol) was stirred at room temperature with pyridine (1.3ml) for 17h. After this time, THF (5ml) was added and the reaction mixture heated to reflux for 3h. After cooling, ether and 1 N HCl were added; the ether layer was separated and washed with water, dried and evaporated in vacuo to afford an oil (32mg) which was purified by preparative t.l.c. using (1:19) ethyl acetate/chloroform as solvent. The hydroxy-ester (30) was isolated as an oil (10mg; 52%),

(Found: C, 62.65; H, 9.65%; M^+ 172.1107. $C_9H_{16}O_3$ requires C, 62.8; H 9.4%; 172.109937); ν_{max} 3600 - 3100, 1720, 1660, 1260cm^{-1}; δ 0.75 - 1.05 (3 H, m), 1.10 - 1.80 (6 H, m), 2.74 (1 H, bs, exch. D_2O), 3.75 (3 H,s), 4.05 - 4.42 (1 H, m), 6.02 (1 H, bd), 6.94 (1 H, dd, J 17, 5Hz).

Rearrangement of the conjugated sulphoxide (12):

Method A. - An attempt to perform a 2,3-sigmatropic rearrangement on the conjugated sulphoxide (12) was carried out in accordance with the method given above; however, after the reaction mixture was worked up only the starting conjugated sulphoxide (12) was obtained. Pyridine was substituted by N,N-diisopropylamine without success.

Method B. - The conjugated sulphoxide (12) (100mg; 0.4mmol) was dissolved in THF (20ml), cooled to -15° and DBN (12mg; 0.1mmol) in THF (3ml) was added dropwise. The reaction mixture was allowed to warm to room temperature whilst stirring it overnight. The THF was then evaporated, the residue dissolved in ethyl acetate and washed with water and brine, dried and evaporated in vacuo to give an oil (100mg) which was purified by preparative t.l.c. using (1:9) ethyl acetate/light petroleum to afford methyl (E),(E)-6-(benzenesulphinyl)-hexa-2,4-dienoate (23) as a crystalline solid (45mg) in 45% yield. It was recrystallized, using ether (25%), m.p. 74 - 75° (Found: C, 62.3; H, 5.45; S, 13.0%. $C_{13}H_{14}O_3S$ requires C, 62.4; H, 5.6; S, 12.8%); ν_{max} 1740, 1650, 1040cm^{-1}; proton n.m.r. cf. Table 2.

Method C. - Trimethylphosphite (25mg; 0.2mmol) in THF (2ml) was added at 0° to the conjugated sulphoxide (12) (50mg; 0.2mmol) in THF (3ml), followed by dropwise addition of a solution of DBN (6mg; 0.05mmol) in THF (2ml). The reaction was slowly warmed to room temperature whilst stirring it overnight. Ethyl acetate and 1 N HCl

were added, the organic phase was separated, washed with saturated aqueous sodium hydrogen carbonate, water and then brine, dried and finally evaporated *in vacuo* to afford an oil (54mg) which was purified by preparative t.l.c. using (1:9) ethyl acetate/chloroform to yield the allylic sulphoxide (23) (38mg; 76%) as a crystalline solid (m.p. and spectra data given above at Method B).

Reactions of MPSA (5) with crotonaldehyde, hexaldehyde, 3-phenylpropionaldehyde and benzaldehyde using magnesium methoxide as a base:

General Procedure. - Magnesium turnings (60mg) were dissolved under reflux in dry methanol (10ml). MPSA (5) (198mg; 1mmol) in methanol (2ml) was added dropwise to the still warm reaction mixture and then stirred for 1h at room temperature before adding a solution of the aldehyde (1mmol) in methanol (3ml). The reaction mixture was stirred overnight before adding ether and 1 N HCl. The organic layer was separated, washed with water and brine, dried and evaporated *in vacuo* to afford the products listed below:

Methyl (E)-4-hydroxy-5-methoxyhex-2-enoate (36). - From the reaction of crotonaldehyde with MPSA (198mg; 1mmol). It was purified by preparative t.l.c. using (1:9) ethyl acetate/chloroform as solvent. Isolated as a diastereoisomeric mixture, an oil, (68.7mg; 39.5%), (Found: M^+ 174.08883. $C_8H_{14}O_4$ requires 174.089202); ν_{max}, 3600 - 3100, 1720, 1280, 1140cm^{-1}; δ 1.18 (3 H, t, J 6Hz), 3.39 (4 H, bs, 1 H exch. D_2O), 3.75 (3 H,s), 4.00 - 4.49 (2 H, m), 6.14 (1 H, bd), 6.91 (1 H, dd, J 16, 4Hz). The conjugated sulphoxide (12) also afforded the title hydroxy-ester (36), as a diastereoisomeric mixture, but in a poorer yield (15%). The hydroxy-ester (36) (59mg) was oxidized using Jones' Reagent[29]. The crude product (58mg) was purified by

preparative t.l.c. using (1 : 9) ethyl acetate/chloroform to yield methyl (E)-4-methoxy-3-oxohex-2-enoate (39) as an oil (30mg; 52%), λ_{max} 241, ν_{max} 1720 (b), 1620, 1440cm^{-1}; (proton n.m.r. cf. text).

Methyl (E)-4-hydroxyoct-2-enoate (30). - From the reaction of hexaldehyde with MPSA (396mg; 2mmol). It was purified by preparative t.l.c. using (1 : 9) ethyl acetate/chloroform. Isolated as an oil (200mg; 58%), spectra data cf. page 115. Some of the hydroxy--ester (30) (130mg, 0.76mmol) was oxidized using Jones' Reagent[29] to afford methyl (E)-4-oxo-oct-2-enoate (42)[37] as a crystalline solid in quantitative yield (129mg), m.p. 33 - 34° (Found: M^+ 170.09431. $C_9H_{14}O_3$ requires 170.094288); λ_{max} 232; ν_{max} 1720cm^{-1}; δ 0.95 (3 H, t, J 8Hz), 1.05 - 1.82 (4 H, m), 2.65 (2 H, t, J 7Hz), 3.94 (3 H, s), 6.66 and 7.07 (2 H, ABq, J 17Hz). The ketone (42) was also obtained by oxidizing the hydroxy-ester (30) using activated MnO_2 in petroleum ether, but in a poor yield (15%). The hydroxy-ester (30) (75mg) was stirred overnight in a 2 N solution of sodium hydroxide (5ml), then ethyl acetate was added, the aqueous phase separated and acidified using concentrated HCl (to pH = 2) before extracting with ethyl acetate. The ethyl acetate layer was washed with water, dried and evaporated in vacuo to afford (E)- 4-hydroxyoct-2-enoic acid (41) in 78.5% yield (54mg), (Found: M^+ 158.09372. $C_8H_{14}O_3$ requires 158.094288); ν_{max} 3570 - 2300, 1700, 1660cm^{-1}; δ 0.90 (3 H, m), 1.10 - 1.90 (6 H, m), 4.32 (1 H, m), 6.02 (1 H, bd), 6.70 - 7.52 (3 H, m, 2 H exch. D_2O).

Methyl (E)-4-hydroxy-5-phenylpent-2-enoate (28)[10]. - From the reaction of 3-phenylpropionaldehyde with MPSA (396mg; 2mmol). It was purified by preparative t.l.c. using (1 : 9) ethyl acetate/chloroform as solvent. Isolated as an oil (105mg; 25.5%), ν_{max}

3600 - 3100, 1720, 1680, 1280, 1160cm^{-1}; 2.83 (2 H, d, J 7Hz), 3.40 (1 H, bs, exch. D_2O), 3.70 (3 H, s), 3.56 (1 H,m); 6.08 (1 H, dd, J 16, 2Hz), 7.02 (1 H, dd, J 16, 6Hz), 7.20 - 7.40 (5 H, m).

Methyl 3-methoxy-3-phenyl-2-(benzenesulphinyl)propenoate (43). - The general procedure given on page 116, was modified by heating the reaction mixture to reflux for 2h after being stirred for 17h. The reaction was worked up by the usual procedure to afford an oil (308mg) which was purified by preparative t.l.c. using (1:9) ethyl acetate/chloroform to yield an oil (152mg; 63%) which was assigned as a diastereoisomeric mixture of the title methoxy ester (43), ν_{max} 1735, 1670, 1550, 1040, 750, 700cm^{-1}; δ 2.80 - 3.90 (8 H, cm), 7.00 - 7.90 (10 H, m). When a sample of the product (43) was heated with toluene, containing calcium carbonate, to reflux, general decomposition occurred.

The reaction of t-butyl benzenesulphinylacetate with hexaldehyde using magnesium methoxide. - The t-butyl ester (1, R^1 = Ph; R = t-butyl) (240mg; 1mmol) was reacted with hexaldehyde (100mg; 1mmol) following the general procedure given on page 116. The crude product (253mg) was purified by preparative t.l.c. using (1:9) ethyl acetate/chloroform to afford not the t-butyl ester (40) but instead the methyl ester (30) (73mg) in 42.5% yield. The t-butyl ester (1, R^1 = Ph; R = t-butyl) was stirred overnight with magnesium methoxide to give as the product a material identical to MPSA (5) (t.l.c. evidence).

Phenylthiomethyltrimethylsilane (46). - The title silane (46) (2.1g) was prepared in accordance with the method outlined in reference 38. The material had ν_{max} 1250, 850, 740, 690cm^{-1}; δ 0.25 (5 H,s), 2.25 (2 H, s), 7.3 (5 H, m).

Addition of phenylthiomethyltrimethylsilane to the conjugated sulphoxide (12). - n-Butyllithium (0.92ml; 1.2mmol; 1.3 molar in hexane) was added dropwise to a solution of phenylthiomethyltrimethylsilane (196mg; 1mmol) in THF (7ml) at 0° and stirred at this temperature for a further 30m before being cooled to -10°. The conjugated sulphoxide (12) (250mg; 1mmol) in THF (4ml) was then added dropwise and the reaction mixture was stirred for 1h at -10°, warmed to room temperature and stirred for a further 1h40m. After this time, 7ml of the reaction mixture was poured into a mixture of ether and saturated aqueous ammonium chloride (1:1); the aqueous phase was separated and re-extracted with more ether; the ether layers were combined, washed with water and brine, dried and evaporated in vacuo to afford a yellow oil (331mg). Pyridine (10ml) was added to the remaining reaction (4ml) and stirred overnight at room temperature and then heated to reflux for 2h before working up in the usual manner to afford a material identical to the previous one. The complex, crude mixture (331mg) was purified by preparative t.l.c. using (1:9) ethyl acetate/chloroform followed by (1:24) ethyl acetate/benzene. Methyl (E)-4-hydroxy-5-(phenylthiomethyltrimethylsilyl)hex-2-enoate (48) was isolated in 8.5% yield as a diastereoisomeric mixture (29mg), (Found: M^{+} 338.13670. $C_{17}H_{26}O_3SSi$ requires 338.13785); ν_{max} cf. text; δ 0.32 (9 H, m), 1.22 (3 H, m), 1.70 - 2.35 (2 H, m, 1 H exch. D_2O), 3.08 - 3.50 (1 H, m), 3.85 (3 H, bs), 4.10 - 4.95 (1 H, m), 5.72 - 6.30 (1 H, m), 6.80 - 7.22 (1 H, m), 7.24 - 7.75 (5 H, m). Another product (8mg) was also isolated; it was assigned, on the basis of its mass spectrum (cf. text), as Methyl (E)-5-(phenylthiomethyltrimethylsilyl)-2-(benzenesulphinyl)hex-2-enoate (47). The reaction was repeated, this time at -76°, and worked up after only

20m; however it afforded the same complex crude mixture (t.l.c.).

Methyl 2-phenylbenzoate (53)[46]. - Methyl (E)-3-phenyl-2-(benzenesulphinyl)prop-2-enoate (9) (127mg; 0.4mmol) and 1-acetoxy-buta-1,3-diene (2ml) in a sealed tube was left in the oven for 48h at 100° and then for a further 48h at 125° . After cooling it was evaporated in vacuo and purified by preparative t.l.c. using (1:19) ethyl acetate/light petroleum as solvent. Given that the starting material was recovered in 46% yield (59mg), the title benzoate was obtained in 54% yield (23mg), m.p. 112 - 113° , (Found M^+ 212.08367. $C_{14}H_{12}O_2$ requires 212.083724); ν_{max} 1720, 1600, 1130cm^{-1}; δ 3.64 (3 H, s), 7.45 (9 H, m).

Crotyl benzenethioacetate (55). - Benzenethioacetic acid (3.36g; 20mmol) and thionyl chloride (3.5ml; 4.06g; 50mmol) was stirred at room temperature for 17h. The excess of thionyl chloride was evaporated in vacuo to afford benzenethioacetyl chloride (18.4mmol; 3.43g), which was stirred at room temperature with crotyl alcohol (1.32g; 18.4mmol) and pyridine (1.43ml; 18.4mmol) in ether for 1.50h; 1 N HCl was added, the organic phase separated and washed with saturated sodium hydrogen carbonate, water and brine, dried and evaporated in vacuo to afford an oil (3.50g) which was purified by column chromatography using (1:9) ethyl acetate/light petroleum as solvent. The title acetate (55) was isolated as an oil (2.70g; 66%), ν_{max} 1735, 1680, 1580, 1270, 750, 700cm^{-1}; δ 1.67 (3 H, bd), 3.52 (2 H, s), 4.5 (2 H, bd), 5.60 (2 H, m), 7.31 (5 H, m). A portion of the acetate (55) (702mg; 3.16mmol) was oxidized with sodium metaperiodate (684mg; 3.2mmol) in methanol/water to afford crotyl benzenesulphinylacetate (60). It was purified by column chromatography using (2:3) ethyl acetate/light

petroleum as solvent. Isolated as an oil (588mg; 78%), (Found: M^+ 238.06642. $C_{12}H_{14}O_3S$ requires 238.06631); ν_{max} 1735, 1670, 1270, 1050, 750, 700cm^{-1}; δ 1.71 (3 H, bd), 3.65 and 3.84 (2 H, ABq, J 15Hz), 4.35 (2 H, d, J 7 Hz), 5.28 - 5.98 (2 H, m), 7.62 (5 H, m).

3-Methyl-2-(benzenethio)pent-4-enoic acid (56). - n-Butyllithium (2.2ml; 3.5mmol; 1.6 molar in hexane) was added dropwise to a stirred solution of diisopropylamine (383mg; 3.6mmol) in THF (3ml) at -76°. The reaction mixture was stirred for 30m at this temperature and then crotyl benzenethioacetate (55) (666mg; 3mmol) in THF (3ml) was added dropwise and stirred for a further 30m at -76° and then trimethylsilyl chloride (380mg; 3.5mmol) in THF (2ml) was added. The reaction mixture was left to warm to room temperature and then heated to reflux for 2h; after cooling, ether and 1 N HCl was added, the organic phase was separated and extracted with saturated aqueous sodium hydrogen carbonate, washed with water and brine, dried and evaporated in vacuo to afford the crude starting acetate (55) (296mg). The sodium hydrogen carbonate layer was then acidified with concentrated hydrochloric acid (pH = 2) and extracted with ether. The ether layer was washed with water and brine, dried and evaporated in vacuo to afford the title acid (56) as an oil (315mg; 52%), ν_{max} 3500 - 2720, 1720, 1650, 1270, 750, 700cm^{-1}; δ 1.20 (3 H, t, J 7Hz), 2.41 - 2.92 (1 H, m), 3.49 (1 H, d, J 7Hz), 5.10 (2 H, bt), 5.52 - 6.05 (1 H, m), 7.32 (5 H, m), 13.55 (1 H, s). Methylation (diazomethane) afforded methyl 3-methyl-2-(benzenethio)pent-4-enoate (57), ν_{max} 1735, 1640, 1270, 750, 700cm^{-1}; δ 1.22 (3 H, bt), 2.5 - 3.0 (1 H, m), 3.54 (1 H, d, J 7Hz), 3.65 (3 H, s), 4.95 - 5.29 (2 H, m), 5.58 - 6.05 (1 H, m), 7.35 (5 H, m). (N.B. Unsuccessful attempts were made to carry out the reaction at other temperatures).

Methyl 3-methyl-2-(benzenesulphinyl)pent-4-enoate (58). - The ester sulphide (57)(278mg; 1.18mmol) was dissolved in methanol (4ml) and sodium metaperiodate (252mg; 1.18mmol) in water (2ml) was added dropwise; the reaction mixture was stirred for 24h and then filtered, the precipitated salts being washed with methanol. The combined methanol-aqueous solution was evaporated *in vacuo* to small bulk and the residue extracted with dichloromethane. The dichloromethane layer was processed in the usual manner to afford an oil (275mg) which was purified by preparative t.l.c. using (3:97) ethyl acetate/chloroform as solvent: the title ester (58) was isolated in 63% yield as two pairs of diastereoisomers. One crystalline (103mg) (as a mixture of two forms (1.7:1)), m.p. 48 - 50° (Found: C, 61.65; H, 6.4; S, 12.55%. $C_{13}H_{16}O_3S$ requires C, 61.88; H, 6.30; S, 12.70%); δ 1.15 (3 H, d, J 7Hz), 1.39 (3 H, d, J 7Hz), 2.84 - 3.29 (2 H, m), 3.35 (3 H, s), 4.95 - 5.48 (2 H, m), 5.58 - 6.03 (1 H, m), 7.54 (5 H, m). The other one as an oil (85mg), δ 2.27 (3 H, d, J 7Hz), 2.32 (3 H, d, J 7Hz), 3.00 - 3.64 (5 H, m). Starting material was also recovered (39mg; 14%).

Methyl 3-methylpenta-2,4-dienoate (59). - The ester sulphoxide (58) (50mg; 0.19mmol) was dissolved in carbon tetrachloride (1ml), placed in a n.m.r. tube and warmed to 59° for 18h, following the reaction by proton n.m.r. spectroscopy, after which time the reaction was complete. Purification by preparative t.l.c. using (1:24) ethyl acetate/light petroleum as solvent afforded the title ester (59) as an isomeric mixture (Z/E = 1.7:1) in 79% yield (19mg), (Found: M^+ 126.06798. $C_7H_{10}O_2$ requires 126.068075); ν_{max} 1710 - 1680 (b), 1580, 1350, 1145cm^{-1}; δ (Z) 2.02 (3 H, s), 3.74 (3 H, s), 5.30 - 5.84 (3 H, m), 7.8 (1 H, dd, J 17, 10Hz); δ (E) 2.29 (3 H, s), 3.74 (3 H, s), 5.30 - 5.84 (3 H, m), 6.40 (1 H, dd, J 17, 10Hz). An earlier attempt

to obtain the desired ester (59) by refluxing the ester sulphoxide (58) in benzene using calcium carbonate powder, was unsuccessful owing to the volatility of the title ester.

An attempt to perform a Claisen rearrangement with crotyl benzenethioacetate (60). - The title sulphoxide (60) (300mg; 1.26mmol) was submitted to the same reaction conditions as those employed with crotyl benzenethioacetate (55) (cf. page 121), however, the reaction was not successful and starting material was recovered (ca. 80%).

6-Hydroxyhept-1-ene (65)[79]. - A solution of 5-bromopentene (1.49g; 10mmol) in ether (50ml) was added dropwise to a suspension of magnesium turnings (288mg; 12mmol) in ether (8ml). After the addition was completed, the reaction mixture was heated to reflux for 30m. The flask was then cooled to -10^{o} and acetaldehyde (422mg; 9.6mmol) in ether (5ml) was added dropwise; the reaction mixture was stirred for a further 30m and then ether and saturated aqueous ammonium chloride were added. The organic phase was separated and the aqueous phase extracted with more ether; the organic phases were combined, dried and evaporated in vacuo to afford the hydroxy olefin (65) as a colourless liquid, ν_{max} 3600 - 3100, 3090, 1690cm^{-1}; δ 0.52 - 1.64 (7 H, m), 1.84 - 2.30 (2 H, m), 2.72 (1 H, s, exch. D_2O), 3.54 - 3.97 (1 H, m), 5.00 (2 H, t, J 8Hz), 5.82 (1 H, m). The reaction was repeated on a 100mmol scale and the yield was increased to 89%.

6-(Benzenethioacetoxy)hept-1-ene (66). - Benzenethioacetic acid (1.35g; 8mmol) and thionyl chloride were stirred at room temperature for 17h. The excess of thionyl chloride was evaporated off in vacuo to afford benzenethioacetyl chloride (705mg; 3.8mmol) which was stirred with the hydroxy olefin (65) (400mg; 3.5mmol) and pyridine (0.39ml; 3.8mmol) in ether (20ml), for 45m at room temperature.

Ether and 1 N HCl were added, the organic phase separated and extracted with saturated aqueous sodium hydrogen carbonate, washed with water and brine, dried and evaporated in vacuo to afford an oil (900mg) which was purified by column chromatography using (1:49) ethyl acetate/light petroleum to afford the title olefin as an oil (600mg; 65%), (Found: M^+ 264.11874. $C_{15}H_{20}O_2S$ requires 264.118394); ν_{max} 1730, 1640, 1250, 1550, 740, 690cm^{-1}; δ 1.10 (3 H, d, J 6Hz), 1.20 - 1.52 (4 H, m), 1.65 - 2.20 (2 H, m), 3.65 (2 H, s), 4.70 - 5.18 (3 H, m), 5.40 - 6.08 (1 H, m), 7.30 (5 H, m).

Ozonolysis of the sulphide olefin (66). - The ozonolysis reaction of 6-(benzenethioacetoxy)hept-1-ene (66) was carried out using different methods; normally, the desired product 5-(benzenesulphinylacetoxy)hexanal (62) was isolated together with the starting material, ozonide and 5-(benzenethioacetoxy)hexanal (68). Alternatively the olefin (66) was initially oxidized to the corresponding sulphoxide (69), followed by the ozonolysis reaction and worked up by hydrogenation in order to obtain the desired product (62). This method afforded the desired aldehyde (62) in good yield (82%). Amongst the methods which did not afford the desired aldehyde in good yield was ozonolysis of the olefin (66) using either one equivalent or an excess of ozone followed by reductive work up with dimethyl sulphide or hydrogenation or refluxing in benzene.

6-(Benzenesulphinylacetoxy)hept-1-ene (69). - The sulphide olefin (66) (246mg; 1mmol) was dissolved in dichloromethane (10ml), cooled to -76° and a solution of mcpba (202mg; 1mmol; 85%) in dichloromethane (5ml) was added dropwise. The reaction was stirred for 30m and then worked up, as usual, to afford the sulphoxide olefin (66) (280mg) in quantitative yield, ν_{max} 1730, 1270, 1050, 750, 700cm^{-1}; δ 1.15 and 1.22 (3 H, 2d, J 6Hz), 1.30 - 1.54 (4 H, m), 3.68

and 3.78 (2 H, ABq, J 16Hz), 4.75 - 5.18 (3 H, m) 5.48 - 6.00 (1 H, m), 7.62 (5 H, m).

5-(Benzenesulphinylacetoxy)hexanal (62). - The sulphoxide olefin (69) (840mg; 3mmol) was dissolved in ethyl acetate (30ml) and then cooled to -76° and ozone was bubbled through until the reaction mixture turned blue. Nitrogen was then bubbled through until the blue colour disappeared. The reaction mixture was concentrated in vacuo to half of its initial volume; this was followed by hydrogenation (uptake 92ml of H_2; 3mmol) using 10% palladium on charcoal as catalyst. After filtration, the catalyst was washed several times with ethyl acetate and the combined extract washed with a saturated solution of sodium hydrogen carbonate, water and then brine, dried (under nitrogen) and evaporated in vacuo to afford the title aldehyde (62) as an oil (700mg; 82%), (Found: M^+ 282.09230. $C_{14}H_{18}O_4S$ requires 282.09257); ν_{max} 1730, 1270, 1120, 1040, 750, 700cm^{-1}; δ 1.15 and 1.25 (3 H, 2d, J 7Hz), 1.60 (4 H, m), 2.25 - 2.60 (2 H, m), 3.68 and 3.78 (2 H, ABq, J 16Hz), 4.75 - 5.10 (1 H, m), 7.62 (5 H, m), 9.75 (1 H, t, J 1Hz).

The sodium hydrogen carbonate layer was acidified with concentrated hydrochloric acid and then extracted with chloroform. The organic layer was washed with water and brine, dried and evaporated in vacuo to afford 5-(benzenesulphinylacetoxy)hexanoic acid (67) as an oil (137mg; 15%), (Found: M^+ 298.08743. $C_{14}H_{18}O_3S$ requires 298.087484); ν_{max} 3500 - 2800, 1730(b), 1280, 1180, 1040, 750, 700cm^{-1}; δ 1.15 and 1.22 (3 H, 2d, J 7Hz), 1.56 (4 H, m), 2.30 (2 H, m), 3.72 and 3.94 (2 H, ABq, J 17Hz), 4.70 - 5.08 (1 H, m), 7.62 (5 H, m), 9.42 (1 H, bs, exch. D_2O). Methylation (diazomethane) afforded the corresponding ester, ν_{max} 1730, 1280, 1180, 1040, 750, 700cm^{-1};

δ1.15 and 1.22 (3 H, 2d, J 7Hz), 1.56 (4 H, m), 2.30 (2 H, m), 3.70 (5 H, m), 4.70 - 5.68 (1 H, m), 7.60 (5 H, m).

Oxidation of the sulphide aldehyde (68) to the corresponding sulphoxide (62). - The sulphide aldehyde (68) (25mg) isolated from ozonolysis of the olefin sulphide (66), was dissolved in methanol (2ml) and one equivalent of sodium metaperiodate (20mg) in water (2ml) was added dropwise. The reaction mixture was stirred for 18h. After this time t.l.c. showed that the main product was the aldehyde (62) with only small quantities of the acid (67) present. The reaction mixture was worked up and kept under nitrogen at 0°. After 24h, t.l.c. showed that the amount of acid (67) present had greatly increased.

Attempts to dimerize 5-(benzenesulphinylacetoxy)hexanal (62):

Method A. - Magnesium turnings (10mg) were dissolved in refluxing dry methanol (5ml). The title aldehyde (62) (46mg; 0.16mmol), in methanol (2ml), was added dropwise to the still warm reaction mixture. The reaction mixture was stirred for 5h at room temperature and then 1 N HCl and ether were added, the organic phase separated and washed with water and brine, dried and evaporated in vacuo to afford the lactone (70) as an oil (26mg; 60%), (Found: M^{+} 296.10819. $C_{15}H_{20}O_4S$ requires 296.10822); ν_{max} 1730cm^{-1}; δ 1.00 - 2.15 (11 H, m); 3.28 - 3.90 (4 H, m), 7.59 (5 H, m).

Method B. - The aldehyde sulphoxide (62) (700mg; 2.48mmol) in THF (4ml) was added dropwise to a suspension of sodium hydride (108mg of 55% w/w dispersion in oil; 2.48mmol) in THF (4ml) which was stirred at 0°. The reaction mixture was stirred for 10m at 0° and then warmed to room temperature. After 5m at room temperature an exother-

mic reaction set in and the reaction mixture boiled, with formation of a precipitate. After cooling the reaction mixture was stirred for a further 1h at room temperature and then a saturated solution of ammonium chloride and ethyl acetate were added. The precipitate was filtered off (380mg) and the organic layer separated, washed with water and brine, dried and evaporated in vacuo to afford an oil (290mg) which was purified by preparative t.l.c. using (1:9) ethyl acetate/chloroform as solvent. Only one compound could be isolated in low yield (24mg) but this was not identified. The precipitate seemed to be polymeric.

Method C. - The aldehyde sulphoxide (62) (95mg; 0.34mmol) in THF (80ml) was added dropwise to a stirred suspension of sodium hydride (15mg of 55% w/w dispersion in oil; 0.34mmol) in THF (10ml) at 0^{o}. The reaction was stirred for 30m and then anhydrous zinc chloride (46mg; 0.34mmol) in THF (5ml) was added and the reaction mixture was stirred for 96h (followed by t.l.c.). After this time, the solvent was evaporated in vacuo and the residue redissolved into a mixture of ethyl acetate and saturated aqueous ammonium chloride solution. The ethyl acetate layer was separated off and washed with water and brine, dried and evaporated in vacuo to afford an oil (90mg) which was purified by preparative t.l.c. using (1:4) acetone/benzene as solvent. The starting aldehyde was recovered together with a product which was tentatively assigned as a mixture of diastereoisomers of 1-oxohexan-5-yl- 3-hydroxy-2 -benzenesulphinyl-(7 -benzenesulphinylacetoxy) octanoate (75) (spectral data given in text); however, an attempt to close the ring using $NaH/ZnCl_2$ resulted in a very complex mixture which was not further characterized.

Control reaction of 6-(benzenesulphinylacetoxy)hept-1-ene

(69) with magnesium methoxide. - Magnesium turnings (8mg) were dissolved in refluxing methanol (2ml). The title olefin (69)(37mg; 0.13mmol) in methanol (1ml) was added dropwise to the still-warm reaction mixture and then stirred overnight to afford a material identical to MPSA (5) (t.l.c.).

Hept-1'-en-6'-yl (E)-2-(benzenesulphinyl)-5-phenylpent-2-enoate (82). - The sulphoxide olefin (69) (280mg; 1mmol) in THF (ml) was added dropwise to a stirred suspension of sodium hydride (43mg of 55% w/w dispersion in oil; 1mmol) in THF (2ml) at 0°. The reaction mixture was stirred for 30m at room temperature and then recooled to 0° and a solution of anhydrous zinc chloride (164mg; 1.2mmol) in THF (2ml) was added dropwise. After 30m at 0°, 3-phenylpropionaldehyde (134mg; 1mmol) in THF (2ml) was slowly added. The reaction mixture was stirred overnight and then heated to reflux for 2h, cooled and worked up in the usual manner to afford an oil (387mg) which was purified by preparative t.l.c. using (1:49) ethyl acetate/ chloroform to afford the title ester (82) (109mg) (40% yield allowing for recovered starting material (87mg; 31%), (Found: M^+ 396.17586. $C_{24}H_{28}O_3S$ requires 396.1759057); ν_{max} 3080, 1720, 1680, 1220, 1050, 750, 700cm^{-1}; δ 0.85 - 1.65 (7 H, m), 1.98 (2 H, m), 3.04 (4 H, m), 4.70 - 5.20 (3 H, m), 5.40 - 5.95 (1 H, m), 7.38 (11 H, m).

Hept-1'-en-6'-yl (E)-4-hydroxy-5-phenylpent-2-enoate (83). - The conjugated sulphoxide (82) (50mg; 0.13mmol) was stirred at room temperature in wet-pyridine (3ml) for 17h and then THF (5ml) was added and the reaction mixture was heated to reflux for 3h. After cooling, ether and 0.1 N HCl were added, the organic phase separated and re-extracted with 0.1 N HCl, washed with water and brine, dried and evaporated in vacuo to afford an oil (58mg) which was purified by prepa-

rative t.l.c. using (3:97) ethyl acetate/chloroform as solvent, to afford the hydroxy-ester (83) as an oil (22mg; 59%), (Found: M^+ 288.17261. $C_{18}H_{24}O_3$ requires 288.17253); ν_{max} 3600 - 3100, 3080, 1710, 1660 - 1640, 1270cm^{-1}; δ 1.22 (3 H, d, J 7Hz); 1.38 - 2.25 (7 H, m, exch. D_2O), 2.64 - 3.15 (2 H, ABX), 4.52 (1 H, m), 5.00 (3 H, m), 5.55 (1 H, m), 6.05 (1 H, dd, J 18, 2Hz), 6.98 (1 H, dd, J 18, 6Hz), 7.25 (5 H, m).

5-(Chloroacetoxy)hexanal dimethyl acetal (85). - 6-Hydroxyhept-1-ene (65) (2.03g; 17.5mmol) was stirred with chloroacetyl chloride (2.03g; 18mmol) and pyridine (1.39ml; 18mmol) in ether (30ml) for 3h. After this time ether and 1 N HCl were added, the organic phase separated and the aqueous phase re-extracted with ether. The organic phases were combined, extracted with a saturated solution of sodium hydrogen carbonate, washed with water and brine, dried and evaporated in vacuo. The residue was redissolved in a 1:1 mixture of methanol/dichloromethane (40ml) cooled to -76° and ozone was bubbled through until the reaction mixture got blue. Nitrogen was then bubbled through the solution until the blue colour disappeared. Dimethyl sulphide (4ml) was then added and the solution warmed to room temperature and left stirring overnight. The solution was then concentrated, the residue redissolved in ether and the ether layer was washed with water and brine, dried and evaporated in vacuo to afford an oil (3.45g), which was dissolved in methanol (10ml) and stirred overnight with toluene-p-sulphonic acid (10mg) in the presence of anhydrous sodium sulphate. Then it was worked up in the usual manner to afford the title acetal (85) (3.40g; 81.5%), ν_{max} 2820, 1760 - 1730cm^{-1}; δ 1.28 (3 H, d, J 7Hz), 1.52 (6 H, m), 3.32 (6 H, s), 4.05 (2 H, s), 4.20 - 4.45 (1 H, m), 4.60 - 5.26 (1 H, m).

5-(4'-Methylbenzenethioacetoxy)hexanal dimethyl acetal (86). - p-Thiocresol (2.02g; 16.3mmol) in THF (5ml) was added dropwise to a suspension of sodium hydride (709mg of 55% w/w dispersion in oil; 16.3mmol) in THF (10ml) at 0^{o}. The reaction mixture was stirred for 30m at this temperature and then 5-(chloroacetoxy)hexanal dimethyl acetal (85) (3.37g; 16.3mmol) in THF (10ml) was added dropwise. The reaction mixture was stirred for 30m at 0^{o} and then for 1h at room temperature. After this time ether and 2 N sodium carbonate were added and the organic phase separated and the aqueous phase re-extracted with more ether. The organic layers were combined, washed with water, dried and evaporated in vacuo to afford, after column chromatography, the title acetal (86) as an oil (4.2g; 80%), (Found: M^{+} 326.15429. $C_{17}H_{26}O_{4}S$ requires 326.155171); ν_{max} 2820, 1730, 1270, 810cm^{-1}; δ 1.16 (3 H, bd), 1.45 (6 H, m), 2.30 (3 H, s), 3.30 (6 H, s), 3.65 (2 H, s), 4.15 - 4.45 (1 H, m), 4.57 - 5.05 (1 H, m), 7.10 and 7.35 (4 H, 2d, J 8Hz).

The title acetal (86) (2.00g; 6.13mmol) was stirred for 24h with orthophosphoric acid (pH = 1) in aqueous THF, before heating to reflux for 2h. After cooling, ethyl acetate and saturated solution of sodium hydrogen carbonate were added; the ethyl acetate layer was separated and washed with water, dried and evaporated in vacuo to afford the aldehyde (76) as an oil (1.35g; 79%), ν_{max} 1730, 1270, 810cm^{-1}. δ 1.22 (3 H, bd), 1.40 - 1.73 (4 H, m), 2.45 (5 H, bs), 3.75 (2 H, s), 4.70 - 5.10 (1 H, m), 7.10 and 7.35 (4 H, 2d, J 8Hz), 9.80 (1 H, t, J 1Hz).

Hept-1'-en-6'-yl (E)-2-(benzenesulphinyl)-7-(4'-methylbenzenethioacetoxy)oct-2-enoate (77). - The sulphoxide olefin (69) (926mg; 3.3mmol) was reacted with 5-(4'-methylbenzenethioacetoxy)hexanal

(980mg; 3.5mmol) under the same conditions used in the model reaction, that is, with 3-phenylpropionaldehyde (cf. page 128). After column chromatography, (1:4) ethyl acetate/light petroleum, the reaction afforded the title ester (77) (400mg; 35%, given that the starting sulphoxide olefin (69) was recovered in 37% yield), (Found: M^+ 542.21591. $C_{30}H_{38}O_5S_2$ requires 542.216051); ν_{max} 1720, 1640, 1450, 1050, 810, 750, 690cm^{-1}; δ 1.12 (6 H, m), 1.28 - 2.02 (10 H, m), 2.28 (3 H, s), 2.70 (2 H, m), 3.55 (2 H, s), 4.90 (4 H, m), 5.40 - 5.95 (1 H, m), 6.90 - 7.75 (10 H, m).

Hept-1'-en-6'-yl (E)-7-(4'-methylbenzenethioacetoxy)-4--hydroxyoct-2-enoate (78). - The conjugated sulphoxide (77) (400mg) was stirred in pyridine (10ml) overnight at room temperature and then THF (5ml) was added and the reaction mixture was heated to reflux for 5h. After cooling, it was worked up in the usual manner to afford an oil (493mg); this was purified by preparative t.l.c. using (1:19) ethyl acetate/chloroform. The hydroxy-ester (78) was isolated as an oil (163mg; 51.5%), (Found: M^+ 434.21271. $C_{24}H_{34}O_5S$ requires 434.212682); ν_{max} 3700 - 3100, 1710, 1650 - 1640, 1450, 1280cm^{-1}; δ 1.25 (6 H, m), 1.40 - 2.25 (10 H, m), 2.35 (4 H, bm, 1 H exch. D_2O), 3.60 (2 H, s), 4.25 (1 H, m), 5.00 (4 H, m), 5.62 - 6.15 (2 H, m), 6.66 - 7.01 (1 H, m), 7.25 (4 H, m). The starting material (77) was recovered in 10% yield (40mg).

Hept-1'-en-6'-yl (E)-7-(4'-methylbenzenesulphinylacetoxy)--4-hydroxyoct-2-enoate (79). - The hydroxy-ester (78) (1.63mg; 0.37mmol) was dissolved in dichloromethane (10ml). The solution was cooled to -76° and a solution of m-chloroperbenzoic acid (75mg; 0.37mmol; 85%) in dichloromethane (3ml) was added dropwise; the reaction mixture was stirred for 10m and then saturated aqueous sodium hydrogen carbonate

solution was added, the organic phase separated, washed with water and brine, dried and evaporated in vacuo to afford the title ester (79) as an oil (165mg; 99%), ν_{max} 3600 - 3100, 1720, 1660 - 1640, 1450, 1260, 1040, 810, 740, 700cm^{-1}; δ 1.25 (6 H, m), 1.60 (6 H, m), 2.10 (4 H, m), 2.45 (3 H, s), 3.40 (1 H, m, exch. D_2O), 3.75 (2 H, m), 4.30 (1 H, m), 4.95 (4 H, m), 5.55 - 6.20 (1 H, m), 6.01 (1 H, dd, J 18, 2Hz), 6.90 (1 H, dd, J 18, 6Hz), 7.34 and 7.58 (4 H, 2d, J 8Hz).

Ozonolysis of hept-1'-en-6'-yl (E)-7-(4'-methylbenzenesulphinylacetoxy)-4-hydroxyoct-2-enoate (79). - The title ester (79) (150mg; 0.33mmol) was dissolved in ethyl acetate (30ml), cooled to -76° and then ozone was bubbled through until the mixture turned blue. Nitrogen was bubbled through the solution until the blue colour disappeared. The mixture was then hydrogenated over 10% Pd/C (150mg) (hydrogen uptake 8ml at 20°) in ethyl acetate (10ml). The suspension was filtered and the catalyst was washed several times with more ethyl acetate. The ethyl acetate washes were combined and evaporated in vacuo to afford an oil (140mg) which was purified by preparative t.l.c. using (2:3) ethyl acetate/light petroleum as solvent to afford a product which was assigned as 4-(4'-methylbenzenesulphinylacetoxy)pentanal (28mg), δ 1.20 (3 H, m), 1.55 - 2.05 (2 H, m), 1.42 (5 H, bs), 3.71 (2 H, m), 4.92 (1 H, m), 7.34 and 7.58 (4 H, 2d, J 8Hz), 9.71 (1 H, t, J 1 Hz).

5-(Benzenesulphinylacetoxy)hexanal dimethyl acetal (93). - The sulphoxide olefin (69) (500mg; 1.78mmol) was dissolved in a (1:1) mixture of dichloromethane/methanol (50ml) and then cooled to -76° ; ozone was bubbled through until the reaction mixture turned blue; then oxygen was bubbled through until the blue colour disappeared. Dimethyl sulphide (4ml) was added and the reaction mixture was warmed

to room temperature and stirred overnight, evaporated in vacuo, re-dissolved in methanol and stirred for 15h over anhydrous sodium sulphate. After evaporation in vacuo it was purified by preparative t.l.c. using (2:3) ethyl acetate/light petroleum as solvent, to afford the sulphoxide aldehyde (62) (112mg; 22%) and the title acetal (93) as a mixture of diastereoisomers (388mg; 66%), (Found: M^+ 328.13356. $C_{16}H_{24}O_5S$ requires 328.134435); ν_{max} 1730, 1450, 1260, 1050, 750, 690cm^{-1}; δ 1.10 and 1.20 (3 H, 2d, J 6Hz), 1.28 - 1.75 (6 H, m), 3.30 (6 H, s), 3.86 and 3.78 (2 H, ABq, J 16Hz), 4.35 (1 H, m), 4.88 (1 H, m), 7.62 (5 H, m).

In carrying out the ozonolysis of the sulphoxide olefin (69) in dichloromethane alone followed by working up using dimethyl sulphide, the aldehyde (62) was isolated in 31.7% yield (70mg), together with a product which was assigned as the ozonide (95)(90mg), δ 1.12 and 1.22 (3 H, 2d, J 6Hz), 1.40 (6 H, m), 3.80 (2 H, bd), 4.65 - 5.30 (4 H, m), 7.45 - 8.00 (5 H, m). The ozonide (95) (90mg) was dissolved in methanol (5ml) and stirred with dimethyl sulphide (2ml) for four days to afford, after working up in the usual manner, the acetal (93).

Attempted reaction of the sulphoxide acetal (93) with the sulphide aldehyde (76). - An unsuccessful attempt was made to react the title acetal (93) (328mg; 0.67mmol) with the sulphide aldehyde (76) under the same conditions employed for the condensation of the aldehyde (76) with the sulphoxide olefin (69) (cf. page 130). The title acetal (93) also failed to react with 3-phenylpropionaldehyde.

6-Bromo-2-one ethylene acetal (99). - A mixture of crude 6-bromohexan-2-one, prepared according to the method of Anderson et al[75] (10.2g; 0.057mmol), ethylene glycol (7.11g; 0.114mmol) and toluene-p-sulphonic acid (40mg) in benzene (150ml) was refluxed for

2.50h using a Dean and Stark trap. After cooling, the solution was washed several times with saturated sodium hydrogen carbonate, dried (K_2CO_3) and evaporated *in vacuo* to afford a crude oil (10.11g) which was distilled under reduced pressure (120 - 124° ; 20mmHg) to afford the *title acetal* (99) as a pale-yellow liquid (5.06g); δ 1.25 (3 H, s), 1.38 - 2.00 (6 H, m), 3.48 (2 H, t, J 8Hz), 3.88 (4 H, s).

2-(Benzenethio)-7-oxo-octanoic acid (100). - n-Butyllithium (20ml; 28mmol; 1.4 molar in hexane) was added dropwise to a solution of benzenethioacetic acid (1.88g; 11.20mmol) in THF (100ml) at -20° . The reaction mixture was stirred for 30m at -20° and 6-bromohexan-2--one ethylene acetal (99) (2.5g; 11.26mmol) in THF (20ml) was added dropwise to the reaction mixture and then allowed to warm to 15° whilst stirring overnight before it was heated to reflux for 2h. After cooling, water and ethyl acetate was added, the aqueous phase separated, acidified (pH = 1) with concentrated HCl and extracted with ethyl acetate. The organic phase was then washed with water and brine, dried and evaporated *in vacuo* to afford an oil (2.41g) which was purified by column chromatography, using (1:7) ethyl acetate/ light petroleum with 1% v/v acetic acid; the *title acid ketone* (100) (715mg) was isolated pure, together with a mixture of the acid ketone (100) and its acetal (344mg). The latter was hydrolysed using ortho-phosphoric acid (pH = 1) in aqueous tetrahydrofuran. Given that the starting acid was recovered in 23% yield (432mg) the acid ketone (100) was isolated in 46% yield (1.05g), as an oil, ν_{max} 3600 - 2400, 1745 - 1700, 750, 700cm^{-1}; δ 1.40 - 2.00 (6 H, m), 2.13 (3 H, s), 2.42 (2 H, t, J 7Hz), 3.70 (1 H, t, J 8Hz), 7.16 - 7.60 (5 H, m), 8.00 - 8.60 (1 H, m, exch. D_2O).

2-(Benzenethio)-7-hydroxyoctanoic acid (101).- Sodium hydro-

gen carbonate (210mg; 2.5mmol) was dissolved in water (3ml) and added to the solution of the acid ketone (100) (538mg; 2.02mmol) in THF (5ml). A solution of sodium borohydride (76mg; 2.02mmol) in THF (3ml) was added dropwise and, after addition, the reaction mixture was stirred for 1h at room temperature and aqueous tetrahydrofuran solution evaporated in vacuo. The residue was redissolved in 1 N HCl and extracted with ethyl acetate (twice). The ethyl acetate layers were combined, washed with water and brine, dried and evaporated in vacuo to afford the crystalline hydroxy acid (101) (415mg; 76.7%). m.p. 54 - 56° (Found: M^+ 268.11327. $C_{14}H_{20}O_3S$ requires 268.1133077; ν_{max} 3600 - 2200, 1710, 750, 700cm^{-1}; δ 1.14 (3 H, d, J 7 Hz), 1.23 - 1.64 (6 H, m), 1.65 - 2.00 (2 H, m), 3.72 (2 H, m), 7.00 - 7.70 (7 H, m, 2 H exch. D_2O).

The dimerization of 2-(benzenethio)-7-hydroxyoctanoic acid 101. - The title hydroxy-acid (101) (268mg; 1mmol) was dissolved in benzene (40ml), cooled to 10° and triphenylphosphine (39mg; 1.5mmol) in benzene (5ml) was added, followed by a dropwise addition of a solution of diethyl azodicarboxylate (274mg; 1.5mmol) in benzene (5ml). The reaction mixture was warmed to room temperature and stirred for 17h. After this time, 1 N HCl was added, the organic phase separated and washed with water and brine, dried and evaporated in vacuo to afford a mixture (750mg; mainly Ph_3PO) which was separated by preparative t.l.c. using dichloromethane as solvent. The dimers (102) were isolated as three different fractions in 51% yield (128mg): the most polar and the least polar fractions were oils, whilst the intermediate one was a crystalline solid (m.p. 60 - 1°) The analysis of the three fractions, by high performance liquid chromatography using (1:99) ethyl acetate/hexane and a Porasil 10μ column, showed the six possible

diastereoisomers to have formed. However, attempts to separate them failed, probably because of their ready epimerization. The mixture had, (Found: C, 67.3; H, 7.35; S, 12.45%; M^+ 500.20586. $C_{28}H_{36}O_4S_2$ requires C, 67.2; H, 7.2; S, 12.8%; M^+ 500.205490); ν_{max} 1720cm^{-1}; δ 1.02 and 1.16 (6 H, 2d, J 8Hz), 1.25 - 1.70 (12 H, m), 1.71 - 2.08 (4 H, m), 3.78 (2 H, m), 4.90 (2 H, m), 7.18 - 7.58 (10 H, m). (The spectra data quoted are from the crystalline fraction; the spectra of the remaining fractions are similar in all important aspects).

The selenenylation and selenoxide elimination of the diolide (102). - After unsuccessful attempts made to phenylselenenylate the diolide (102) using phenylselenyl chloride, with either n-butyllithium or sodium hydride as a base, it was decided to carry out thio-oxidation before performing the selenylation. The method used is given below.

The diolide (102) (120mg; 0.24mmol) was dissolved in dichloromethane (8ml) cooled to -76° and then a solution of mcpba (98mg; 0.40mmol; 85%) in dichloromethane (5ml) was added dropwise. The reaction mixture was stirred for 20m and worked up in the usual manner to afford the diastereoisomeric mixture of the diolide disulphoxide (103) in 90% yield (115mg), ν_{max} 1720, 1440, 1250, 1040, 750, 700cm^{-1}; δ 0.72 - 1.90 (19 H, m), 1.92 - 2.40 (4 H, m) 3.20 - 3.70 (2 H, m), 4.55 - 5.10 (2 H, m), 7.30 - 8.00 (10 H, m). The diolide disulphoxide (103) (115mg; 0.21mmol) in THF (3ml) was added dropwise to a stirred suspension of sodium hydride (28mg of 55% w/w dispersion in oil; 0.64mmol) in THF (8ml) at 0° . After addition the reaction mixture was warmed to room temperature and stirred for 24h; it was then recooled to 0° and phenylselenyl chloride (88mg; 0.46mmol) in THF (3ml) was quickly added. The reaction mixture was stirred for a further 10m and then poured into a (1:1:1) mixture of

ether/pentane/saturated aqueous sodium hydrogen carbonate. The aqueous phase was separated and re-extracted with (1:1) ether/pentane; the organic layers were combined, washed with water and brine, dried and evaporated in vacuo to afford an oil (208mg) which was purified by preparative t.l.c. using (1:9) ethyl acetate/dichloromethane. The diselenenylated product was isolated as a diastereoisomeric mixture in 67% yield (123mg); this was then dissolved in dichloromethane (8ml) cooled to -76° and then oxidized using mcpba (59mg; 0.29mmol; 85%). After working up the diastereoisomeric mixture of the α,β-unsaturated diolide (104) was isolated (after preparative t.l.c. using (2:23) acetone/benzene as solvent) as a foam (67mg; 90%), (Found: M^+ 528.16348. $C_{28}H_{32}O_6S_2$ requires 528.164024), ν_{max} 1720, 1630, 1450, 1050, 750, 690cm^{-1}; δ 0.85 - 1.95 (14 H, m), 2.25 - 3.95 (4 H, m), 4.55 - 5.25 (2 H, m), 6.85 - 8.15 (12 H, m).

Attempts to perform the 2,3-sigmatropic rearrangement with the α,β-unsaturated diolide (104):

1.) Use of pyridine. - In a first attempt to perform a 2,3-sigmatropic rearrangement with the diolide (104) the same procedure was employed as that for the ester sulphoxide (82) (cf. page 128). The diolide (104) (67mg; 0.12mmol) was stirred at room temperature for 18h in pyridine (5ml), then THF (5ml) was added and the reaction mixture was heated to reflux for 4h; after cooling, it was worked up, in the usual manner, and purified by preparative t.l.c. using (1:9) ethyl acetate/dichloromethane as eluent. A mixture (45mg) was isolated, which, in the light of its spectra data (cf. page 99), was thought to be a mixture of the expected pyrenophorol with the starting diolide (104); accordingly, the mixture was redissolved in pyridine and heated to reflux for 72h. However, no improvement in the

'pyrenophorol' content was noticed; nevertheless the reaction was worked up and attempts were made to isolate the 'pyrenophorol' by preparative t.l.c. using (1:9) ethyl acetate/dichloromethane but without success.

2.) Other methods. - In the belief that a strong base in a polar solvent would assist in obtaining the desired rearrangement, diisopropylamine in methanol was employed with the diolide (104). The resulting product was, however, a very complex mixture (cf. text). Another unsuccessful attempt was made to enforce the desired rearrangement using as catalyst phosphate buffer (pH = 7.5). The use of DBN containing trimethylphosphite was also checked.

Hept-1'en-6'-yl 2-(benzenesulphinyl)-3-hydroxy-7-(4'-methylbenzenethioacetoxy)octanoate (106). - 6-(Benzenesulphinylacetoxy)-hept-1-ene (69) (280mg; 1mmol) in THF (3ml) was added dropwise to a solution of Hauser's base (prepared as given on page 112) (1mmol) in THF (10ml) at 0° and stirred for 30m before 5-(4'-methylbenzenethioacetoxy)hexanal (76) (280mg; 1mmol) in THF (4ml) was added. The reaction mixture was then stirred for 1.25h and ethyl acetate and saturated aqueous ammonium chloride were added, the organic phase was separated and proceeded in the usual manner to afford an oil (531mg) which was purified by preparative t.l.c. using (1:9) ethyl acetate/chloroform. The title ester (106) was isolated as an oil (205mg; 37%), ν_{max} 3600 - 3100, 1725, 1640, 1270, 810, 750, 700cm^{-1}; δ 0.95 - 1.28 (6 H, m), 1.30 - 1.80 (12 H, m), 2.30 (3 H, s), 3.40 - 4.50 (5 H, m, 1 H exch. D_2O), 4.55 - 5.20 (4 H, m), 5.50 - 6.00 (1 H, m), 7.00 - 7.85 (9 H, m).

The diolide (110). - The α-sulphinyl ester (106) (191mg; 0.34mmol) was oxidized in the usual way using mcpba (69mg; 0.34mmol;

85%) at -76° . The disulphoxide (107) was isolated after preparative t.l.c. using (1:9) ethyl acetate/chloroform as solvent in 69.7% yield (136mg), ν_{max} 3600 - 3100, 1720, 1640, 1450, 1040, 810, 750, 700cm^{-1}; δ 0.97 - 1.22 (6 H, m), 1.23 - 2.00 (12 H, m), 2.30 (3 H, s), 3.40 - 4.20 (5 H, m, 1 H exch. D_2O), 4.60 - 5.15 (4 H, m), 5.50 - 6.00 (1 H, m), 7.25 - 7.90 (9 H, m). The disulphoxide (107) (135mg; 0.23mmol) was dissolved in dichloromethane (20ml) and ozone was bubbled through until the reaction mixture turned blue; oxygen was then bubbled through until the blue colour disappeared. Dimethyl sulphide (2ml) was added and the reaction mixture warmed to room temperature and stirred overnight. After this time, the solvent was evaporated <u>in vacuo</u> to afford a crude oil (149mg), ν_{max} 3600 - 3100, 1720, 1450, 1040, 810, 750, 700cm^{-1}. The crude oil (125mg) in THF (2ml) was added dropwise to a solution of Hauser's base (0.44mmol) in THF (7ml) at 0° , and the reaction mixture was stirred for 48h, before adding a saturated aqueous ammonium chloride solution and ethyl acetate. The organic phase was separated and processed in the usual manner to afford an oil (104mg) which was assigned as the diolide (109) (Found: m/e 578, 296 282, 262, 139, 124, 91, 43) ; ν_{max} 3600 - 3100, 1720cm^{-1}; δ 0.75 - 1.95 (18 H, m), 2.37 (3 H, s), 3.40 - 5.20 (8 H, cm, 2 H exch. D_2O), 7.15 - 8.00 (9 H, m).

The assigned diolide (109) (88mg; 0.15mmol) was stirred overnight at room temperature with acetic anhydride (2ml) and pyridine (2ml); then ethyl acetate and 1 <u>N</u> HCl were added, the organic phase separated and washed with saturated aqueous sodium hydrogen carbonate, water and brine, dried and evaporated <u>in vacuo</u> to afford an oil (130mg) which was purified (twice) by preparative t.l.c. using (1:19) methanol/dichloromethane to yield the <u>title dilactone</u> (110)

(50mg; 61.5%) as a mixture of the diastereoisomers, (Found: M^+ 542.18069. $C_{29}H_{34}O_6S_2$ requires 542.179669); ν_{max} 1720, 1630, 1040cm^{-1}; δ 0.85 - 1.30 (6 H, m), 1.32 - 1.90 (8 H, m), 2.40 (3 H, bs), 2.55 - 3.00 (4 H, m), 4.70 - 5.20 (2 H, m), 6.95 - 8.00 (11 H, m).

The 2,3-sigmatropic rearrangement of the α,β-unsaturated diolide (110). - A sample of the diolide (110) (18mg) was warmed in wet pyridine in THF for 15h. After this time, the reaction mixture was worked up in the usual manner and then chromatographed using (1 : 19) methanol/dichloromethane as solvent to afford an oil (6mg), (m/e: 157, 156, 139, 138, 111, 91, 77, 55, 44 and 43); ν_{max} cf. text; δ 1.20 (6 H, m), 1.65 (8 H, m), 2.00 - 2.20 (2 H, m, exch. D_2O), 4.20 - 5.20 (4 H, m), 6.00 (1 H, d, J 15Hz), 6.90 (1 H, dd, J 15, 5.5Hz), 7.00 - 8.00 (ca 5 H, m). The oil was then treated with Jones' reagent[29] and the crude product chromatographed using (3 : 7) ethyl acetate/ light petroleum as solvent to afford a product whose mass spectrum was similar to that of an authentic sample of synthetic (d, l) pyrenophorin (m/e: 155, 138, 99, 82, 55 and 44). However a t.l.c. comparison of the product with the authentic sample using (1 : 3) ethyl acetate/hexane as solvent showed that the former was slightly more polar (cf. text).

REFERENCES

REFERENCES

1. C. Mioskowski and G. Solladié, Tetrahedron, 1980, 36, 227.
2. G. Solladie, Synthesis, 1981, 185.
3. J. J. A. Van Asten and R. Louw, Tetrahedron Letters, 1975, 671.
4. N. Kunieda, J. Nokami and M. Kinoshita, Tetrahedron Letters, 1974, 3997; idem. ibid., 1975, 2179 and 2841.
5. C. Mioskowski and G. Solladié, J. C. S. Chem. Comm., 1977, 162.
6. E. J. Corey, L. O. Weigel, A. R. Chamberlin, H. Cho, D. H. Hua, J. Amer. Chem. Soc., 1980, 102, 6613.
7. J. Mulzer, J. Segener and G. Brumtrup, Tetrahedron Letters, 1977, 4651.
8. H. O. House, D. S. Crumrine, A. Y. Teranishi and H. D. Olmstead, J. Amer. Chem. Soc., 1973, 95, 3310
9. T. R. Hoye and M. J. Kurth, J. Org. Chem., 1980, 45, 3549.
10. A. A. Jaxa-Chamiec, The City University, PhD thesis, 1979.
11. S. Yamagiwa, H. Sato, N. Hoshi, H. Kosugi and H. Uda, J. C. S. Perkin I, 1979, 570.
12. H. Hagiwara, K. Nakayama and H. Uda, Bull. Chem. Soc. Japan, 1975, 48, 3769; H. Kosugi, H. Uda and S. Yamagiwa, J. C. S. Chem. Comm., 1975, 192; idem. ibid., 1976, 71.
13. S. Yamagiwa, N. Hoshi, H. Sato, H. Kosugi and H. Uda, J. C. S. Perkin I, 1978, 214.
14. S. Nozoe, K. Hirai, K. Tsuda, K. Ishibashi, M. Shirasaka and J. F. Grove, Tetrahedron Letters, 1965, 4675.
15. A. F. Cockerill, G. L. O. Davies, R. C. Harden and D. M. Rackham, Chem. Rev., 1973, 73, 553.
16. A. G. Brook, Acc. Chem. Res., 1974, 7, 77; E. Vedejs and M. Mullins, Tetrahedron Letters, 1975, 2017.

17. F. C. Frostick, Jr. and C. R. Hauser, J. Amer. Chem. Soc., 1949, 71, 1350.

18. B. M. Trost, Chem. Rev., 1978, 78, 363.

19. D. A. Evans, G. C. Andrews, Acc. Chem. Res., 1974, 7, 147.

20. L. Field, Synthesis, 1972, 101; idem. ibid., 1978, 713

21. E. Block, J. Chem. Educ., 1971, 48, 814.

22. D. Valentine, J. W. Scott, Jr., Synthesis, 1978, 329.

23. D. E. O'Connor and W. Lyness, J. Amer. Chem. Soc., 1964, 86, 3840; C. D. Broaddus and D. E. O'Connor, ibid., 1964, 86, 2267.

24. P. R. Ortiz de Montellano and C. K. Hsu, Tetrahedron Letters, 1976, 4215.

25. R. Tang and K. Mislow, J. Amer. Chem. Soc., 1970, 92, 2100.

26. R. B. Woodward and R. Hoffmann, 'The Conservation of Orbital Symmetry', Verlag Chemie, Weinheim, 1970.

27. Ian Fleming, 'Frontier Orbitals and Organic Chemical Reactions', Wiley-Interscience, 1978, p.173.

28. C. W. Spangler, Chem. Rev., 1976, 76, 189.

29. A. Bowers, J. G. Halsall, E. R. Jones, J. Chem. Soc., 1953, 2548.

30. Z. Kis, P. Funger and H. P. Sigg, Experientia, 1969, 25, 123.

31. M. Binder, C. Tamm, W. B. Turner and H. Minato, J. C. S. Perkin I, 1973, 1146.

32. H. P. Weber, D. Hauser and H. P. Sigg, Helv. Chim. Acta, 1971, 54, 2763.

33. S. Masamune, G. S. Bates and J. W. Corcaran, Angew. Chem. Int. Ed., 1977, 585.

34 P. A. Bartlett and F. R. Green, J. Amer. Chem. Soc., 1978, 100, 4858.

35. S. Yamagiwa, H. Kosugi and H. Uda, Bull Chem. Soc. Japan, 1978,

3011.

36. R. W. Hoffmann, Angew. Chem. Int. Ed., 1979, 18, 563.

37. H. M. Walton, J. Org. Chem., 1957, 22, 308.

38. D. J. Ager and R. C. Cookson, Tetrahedron Letters, 1980, 1677; D. J. Ager, ibid., 1981, 587.

39. P. J. Kocienski, Tetrahedron Letters, 1980, 1559.

40. S. F. Martin, Tetrahedron, 1980, 36, 419.

41. L. E. Overman and P. J. Jessup, J. Amer. Chem. Soc., 1978, 100, 5179.

42. B. M. Trost, S. A. Godleski and J. Ippen, J. Org. Chem., 1978, 43, 4559.

43. S. Danishefsky and T. Kitahara, J. Amer. Chem. Soc., 1974, 96, 7807; S. Danishefsky, C. F. Yan and P. M. McCurry Jr., J. Org. Chem., 1977, 42, 1819; S. Danishefsky, R. K. Singh and R. B. Gammil, ibid., 1978, 43, 379.

44. L. A. Paquette. R. E. Moerck, B. Harirchian and P. D. Magnus, J. Amer. Chem. Soc., 1978, 100, 1597.

45. S. Danishefsky, R. K. Singh and T. Harayama, J. Amer. Chem. Soc., 1977, 99, 5810; idem. ibid., 1979, 101, 7008.

46. C. Graebe, Chem. Ber., 1906, 39, 801.

47. J. C. Philips, M. Penzo and G. T. S. Lee, J. C. S. Chem. Comm., 1975, 107.

48. R. E. Ireland and R. H. Mueller, J. Amer. Chem. Soc., 1972, 94, 5897.

49. B. Lythgoe, J. R. Milner and J. Tideswell, Tetrahedron Letters, 1975, 2593; B. Lythgoe, R. Manwaring, J. R. Milner, T. A. Moran, M. E. Nambudiry and J. Tideswell, J. C. S. Perkin I, 1978, 387.

50. R. E. Ireland and C. S. Wilcox, Tetrahedron Letters, 1977, 2839.

51. B. Kubel, G. Hofle and W. Steglich, Angew. Chem. Int. Ed., 1975, 14, 58.

52. R. E. Ireland, R. H. Mueller and A. K. Willard, J. Org. Chem., 1976, 41, 986.

53. J. K. Whitesell and A. M. Helbing, J. C. S. Chem. Comm., 1977, 594.

54. B. M. Trost and T. R. Verhoeven, J. Amer. Chem. Soc., 1980, 102, 4743.

55. K. Ishibashi, J. Antibiotics, 1962, 15A, 161.

56. J. F. Grove, J. Chem. Soc. C., 1971, 2261.

57. E. W. Colvin, T. A. Purcell and R. A. Raphael, J. C. S. Perkin I, 1976, 1718.

58. D. Seebach, B. Seuring, H. O. Kalioski, W. Lubosch and B. Renger, Angew. Chem. Int. Ed., 1977, 16, 264.

59. M. Asaoka, T. Mukuta and H. Takei, Tetrahedron Letters, 1981, 735.

60. P. Bakuzis, M. L. F. Bakuzis and T. F. Weingartner, Tetrahedron Letters, 1978, 2371.

61. H. Garlach, K. Oertle and A. Thalmann, Helv. Chim. Acta, 1977, 60, 2860.

62. T. A. Hase, A. Ourila and C. Holmberg, J. Org. Chem., 1981, 46, 3137.

63. B. M. Trost and F. W. Gowland, J. Org. Chem., 1979, 44, 3449.

64. S. W. Pelletier, K. N. Iyer and C. W. J. Chang, J. Org. Chem., 1970, 35, 3535.

65. J. Pappa, W. P. Keaveney, E. Gaucher and M. Berger, Tetrahedron

Letters, 1966, 4273.

66. P. S. Bailey, Chem. Rev., 1958, 58, 925.

67. K. W. Bentley and G. W. Kirby, 'Elucidation of Organic Structures by Physical and Chemical Methods', Part II, 2 ed., p.150.

68. J. Fuska, P. Nemec and I. Kuhr, J. Antibiotics, 1972, 25, 208.

69. K. F. Burri, R. A. Cardone, W. J. Chen and P. Rosen , J. Amer. Chem. Soc., 1978, 100, 7069.

70. D. H. Williams and I. Fleming, 'Spectroscopic Methods in Organic Chemistry', McGraw-Hill, 2nd Edition, p. 132.

71. B. M. Trost, T. N. Salzmann and (in part) K. Hiroi, J. Amer. Chem. Soc., 1976, 98, 4887.

72. T. L. Ho and C. M. Wong, Synthesis, 1972, 561.

73. B. I. Feringa and R. J. Butselaar, Tetrahedron Lettters, 1981, 1447.

74. T. Veysoglu, L. A. Mitscher and J. K. Swayze, Synthesis, 1980, 807.

75. E. P. Anderson, J. V. Crawford and M. L. Sherrill, J. Amer. Chem. Soc., 1946, 68, 1294.

76. O. Mitsunobu, Synthesis, 1981, 1.

77. H. J. Reich, J. M. Renga and I. L. Reich, J. Amer. Chem. Soc., 1975, 97, 5434; idem., J. Org. Chem., 1974, 39, 2133.

78. M. Kodama, K. Shimada and S. Itô, Tetrahedron Letters, 1977, 2763.

79. B. Helferich and T. Malkones, Chem. Ber., 1922, 55, 706.