"Instruct a wise man and he will be wiser still;
teach a righteous man and he will add to his learning.
The fear of the Lord is the beginning of wisdom,
and knowledge of the Holy One is understanding."

Proverbs ch.9 v.9-10

TO MY PARENTS

SYNTHETIC ASPECTS OF ORGANOSULPHUR CHEMISTRY

A Thesis submitted in partial fulfilment of the requirements for the degree of Doctor of Philosophy

M.D. Brown
St. John's College

February
1984

ACKNOWLEDGEMENTS

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To my colleagues both at Oxford and in my present employment my thanks for making the difficult times more bearable and the good times more enjoyable.

Special thanks to Gordon, Caroline, Frankie, my present employers and those that have been praying for me for their patience.

Finally I would like to acknowledge the noble efforts of Paul and Mike in reading through this and the sterling work of Frankie in transforming my scrawl to its present form.

SHORT ABSTRACT

M.D. Brown
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D.Phil.
Hilary Term 1984

Synthetic Aspects of Organosulphur Chemistry

The thesis is concerned with approaches to substituted 2-phenyl-1,3-oxathiolans and their cycloreversion to olefins.

2-(α-Methoxybenzylthio)acetophenone (1) was prepared by *in situ* alkylation of the thiolate generated by aminolysis of O-ethyl-S-phenacyldithiocarbonate with α-chlorobenzyl methyl ether. Reduction of (1) with lithium aluminium hydride gave 2-(α-methoxybenzylthio)-1-phenylethanol which cyclised in the presence of *p*-toluenesulphonic acid to give 2,5-diphenyl-1,3-oxathiolan. α-(α'-Methoxybenzylthio)acetone (2), was prepared by a similar route to that used for (1). Compounds (1) and (2) and various other α-thiosubstituted ketones were investigated as potential starting materials for the synthesis of substituted β-(α-methoxybenzylthio)alcohols but the transformations attempted were unsuccessful.

A reasonably flexible synthesis of substituted oxathiolans and hence the corresponding olefins was developed starting from α-(benzylthio)ketones. The olefins prepared were 2-methyl-3-phenyl-2-butene, 1,2-dimethylcyclohexene and the *Z*-(3) and *E*-(4) 3,4-dimethylhex-3-enes. Alkylation of the α-(benzylthio)ketones proceeded regio-specifically α- to the thio and keto groups. Subsequent reaction with organometallic reagents gave β-benzylthioalcohols. Generally alkyllithiums gave the best yields and higher stereoselectivities in these additions. The benzylthio group was cleaved with sodium/ammonia to give β-mercaptoalcohols which were condensed with benzaldehyde to give 2-phenyl-1,3-oxathiolans. Treatment of the oxathiolans with lithium diisopropylamide resulted in cycloreversion to olefins in high yields (75-100%).

Stereochemical integrity was maintained throughout the reactions used to convert the β-benzylthioalcohols into olefins and consequently the stereoselectivity was determined at the β-benzylthioalcohol forming step. Thus the ratio found for (3) to (4) synthesised from a β-benzylthioalcohol prepared by reaction of methyllithium with 3-benzylthio-3-methyl-4-hexanone was 3:7, whereas when the β-benzylthioalcohol was prepared from 3-benzylthio-3-methyl-2-pentanone by an ethyllithium reaction the ratio of (3) to (4) subsequently obtained was 6:4.

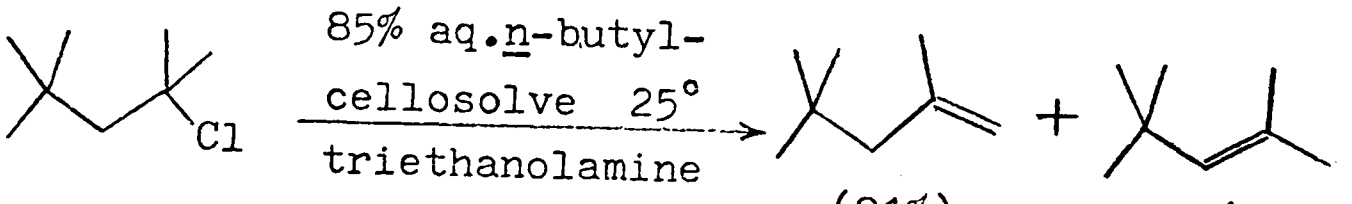
CONTENTS

INTRODUCTION

(i) Olefin Synthesis

The presence of carbon-carbon double bonds in many compounds of pharmaceutical and/or academic interest has led to much activity in the area of olefin synthesis. The work contained in this thesis is concerned with the development of a synthetic strategy applicable to the stereoselective preparation of tri- and tetra-substituted olefins.

The synthesis of many olefins may be accomplished by the β-elimination of HX, where X is a leaving group. The lack of regio-specificity often associated with the elimination (e.g. Scheme 1)[1], however, means that many olefins can not easily be prepared by this route.

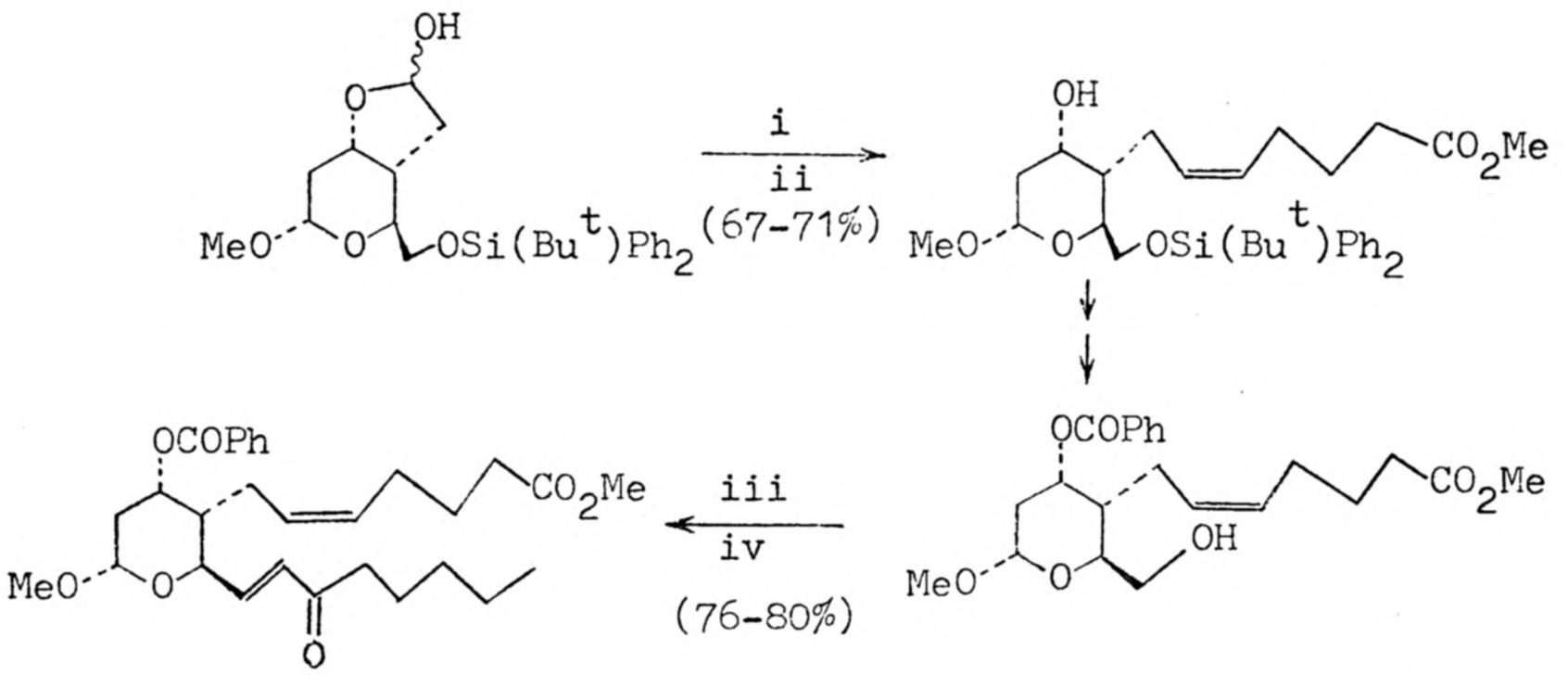


SCHEME 1

Reactions which overcome the problem of regioselectivity often suffer from problems associated with stereoselectivity and/or their applicability to the formation of tri- and tetra-substituted double bonds.

Quite high degrees of stereoselectivity have been achieved *via* the Wittig reaction (e.g. Scheme 2)[2] or "PO- activated olefination"[3]

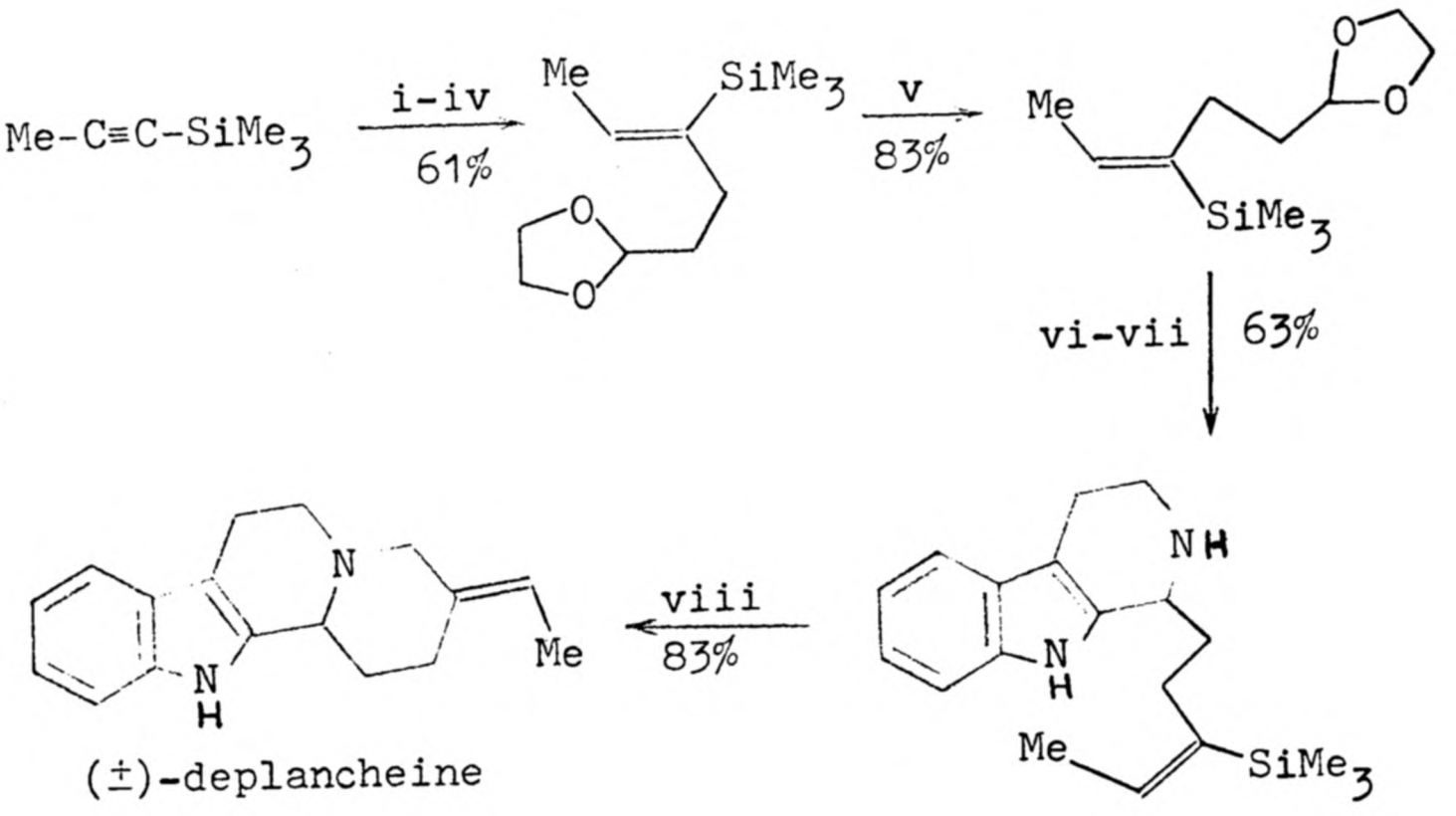
but these reactions do not generally work for the formation of tetra- or many tri-substituted olefins.



SCHEME 2 : i $LiN(SiMe_3)_2$, HMPA , $BrPh_3P(CH_2)_4CO_2Li$; ii CH_2N_2 ; iii Collins ; iv $Bu_3P{:}CH.CO.(CH_2)_4Me$, Et_2O.

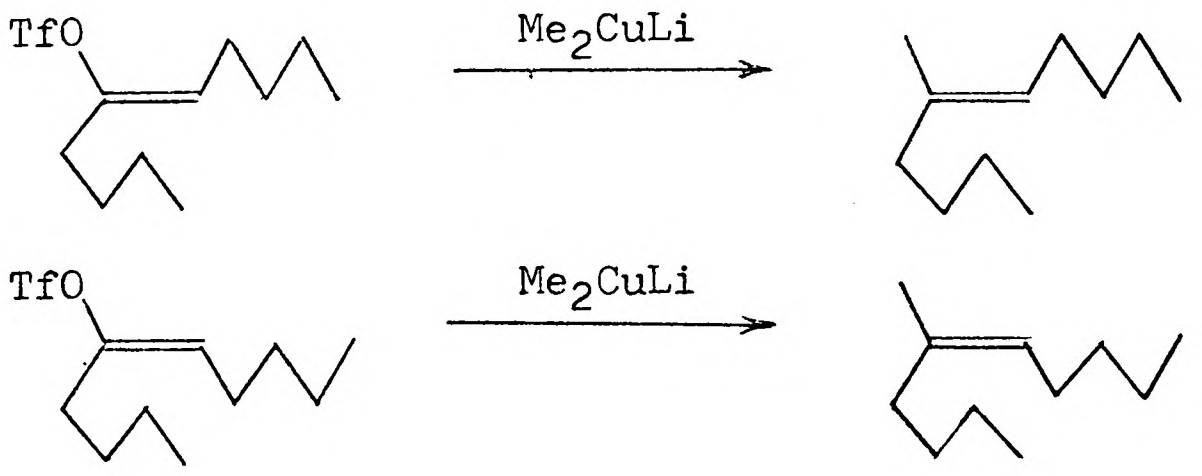
The preparation of olefins from alkyne precursors has given some very highly stereoselective syntheses of di-[4] and tri-substituted olefins (e.g. Scheme 3)[5] but rarely has this approach been used for the preparation of tetra-substituted double bonds[6].

Another recent stereoselective synthesis of olefins is due to McMurry[7] (e.g. Scheme 4). This approach is reported for tri- but not for tetra-substituted olefins.



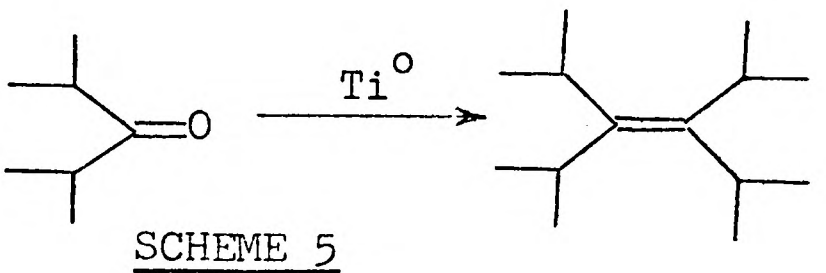
(±)-deplancheine

SCHEME 3 : i Bu_2AlH; ii Br_2,pyridine; iii sec-BuLi; iv $ICH_2CH_2CH(OCH_2CH_2O)$; v NBS,hν; vi HCl; vii tryptamine hydrochloride; viii $(CH_2O)_n$,$CamSO_3H$.



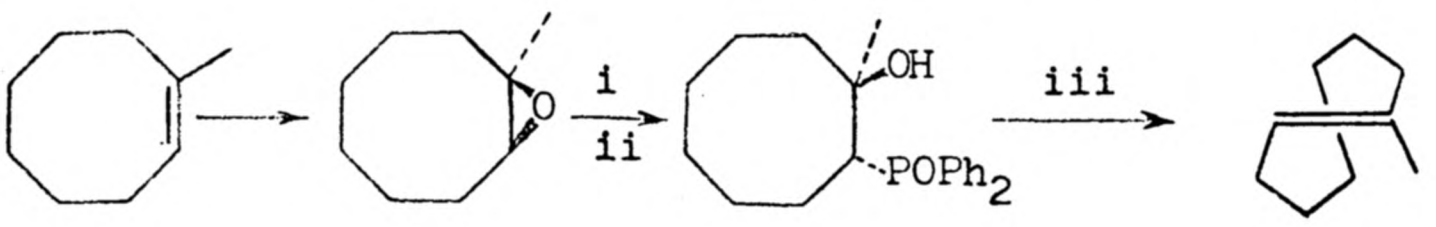
SCHEME 4

McMurry has also developed an olefin sythesis involving the coupling of ketones to give tetra-substituted olefins in the presence of Ti^{o} (Scheme 5)[8]. This is a good way of making highly substituted olefins but there is no stereochemical control.



SCHEME 5

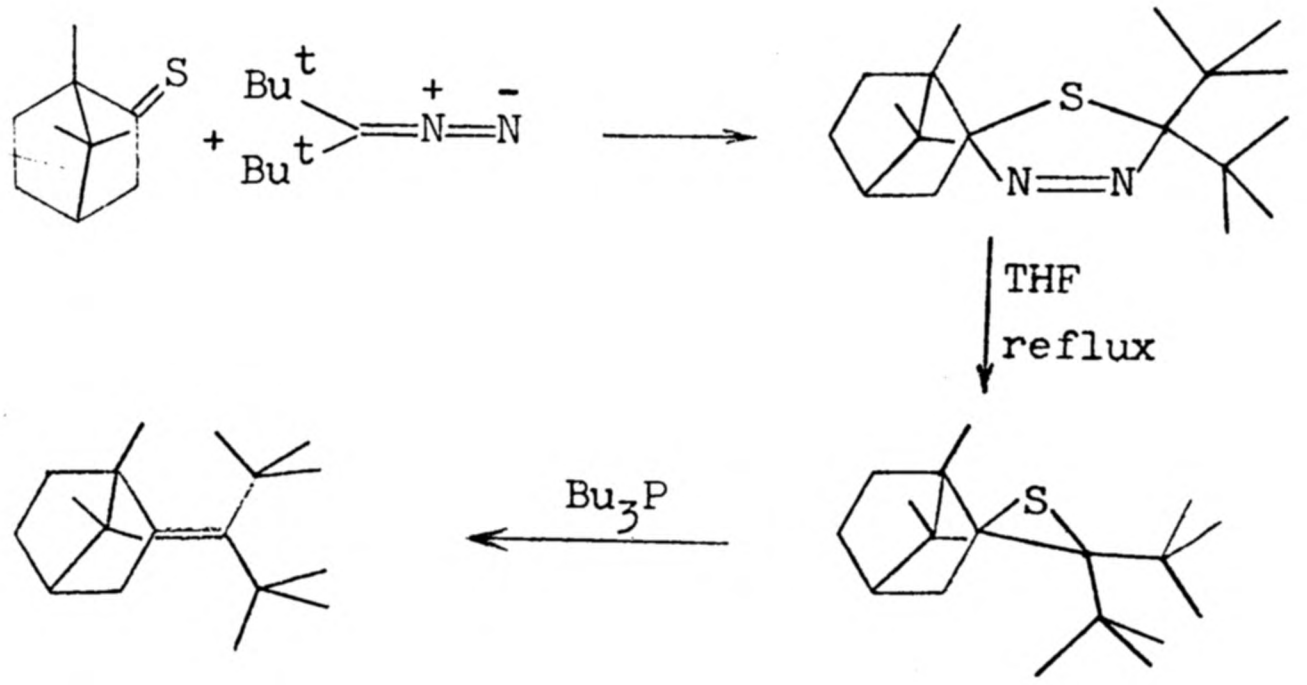
There are a number of highly stereoselective syntheses of olefins based on olefin inversion as recently reviewed by Sonnet[9]. One example of this is the synthesis of the strained trans-1-methyl-cyclooctene[10] (Scheme 6). The main limitation of this synthetic approach is the availability of the olefin starting materials.



SCHEME 6 : i Ph_2PLi,THF; ii $AcOH-H_2O_2$; iiiNaH,DMF.

One of the most effective syntheses - though not stereoselective - of sterically crowded tetra-substituted olefins involves the extrusion of nitrogen and sulphur from 1,3,4-thiadiazolines[11,12] (e.g. Scheme 7). The use of a thione as a starting material puts significant constraints on the applicability of this synthesis since only more

heavily substituted thiones tend to be stable.

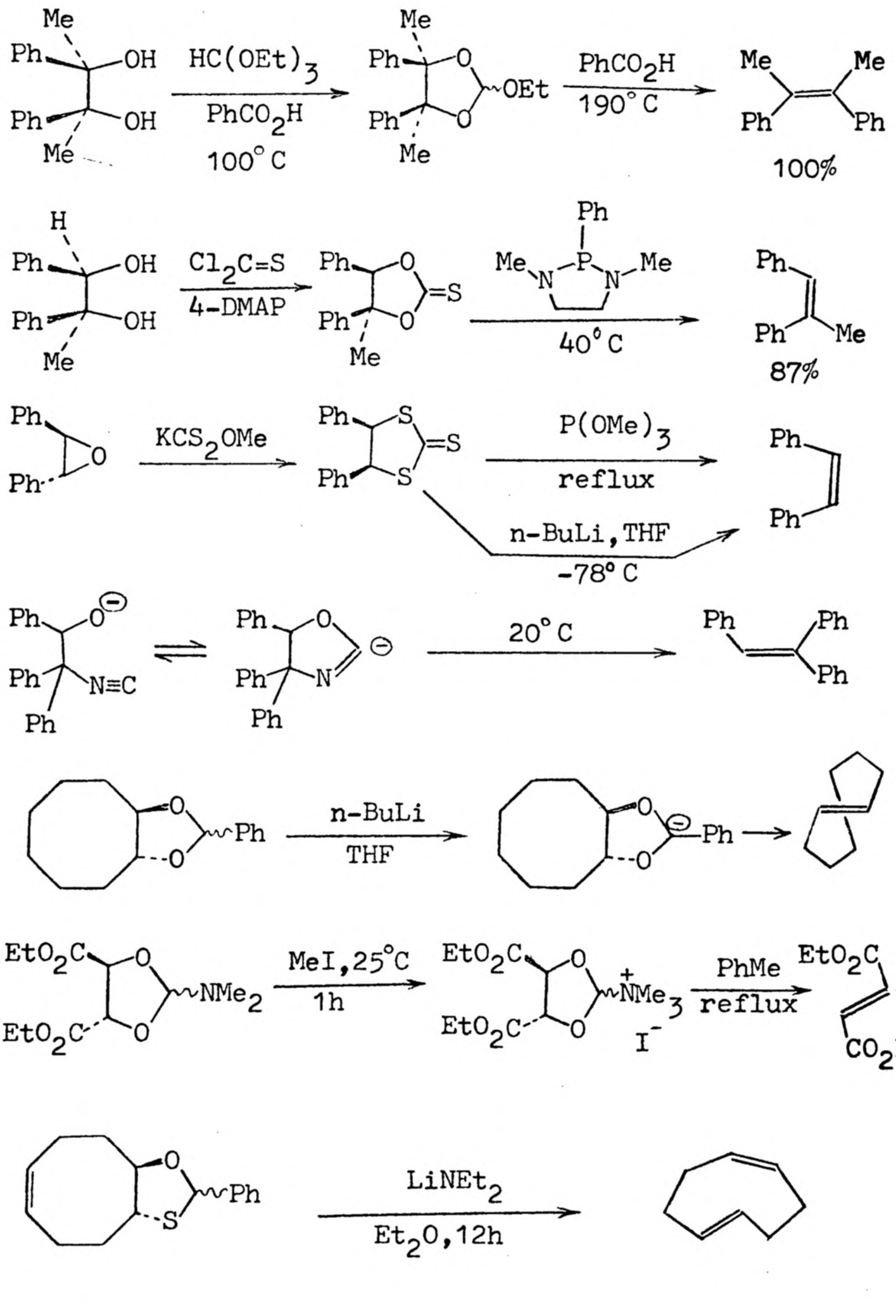


SCHEME 7

In terms of fairly general olefin syntheses the area of cycloreversion chemistry is important. Dipolar cycloreversions have been recently reviewed by Gandolfi et al.[13] A number of examples of olefin syntheses involving such cycloreversion reactions are shown in Scheme 8. Cycloreversion reactions generally show a high degree of stereoselectivity suggesting concerted reactions. This is exemplified in the syntheses of trans-cyclooctene by approaches of this nature.

In an olefin synthesis achieved by a β-elimination involving an acyclic precursor one of the factors influencing the ease of the reaction is the energy required to attain the conformation from which the elimination occurs. This may be a problem particularly when attempts are being made to prepare strained olefins. In cycloreversion

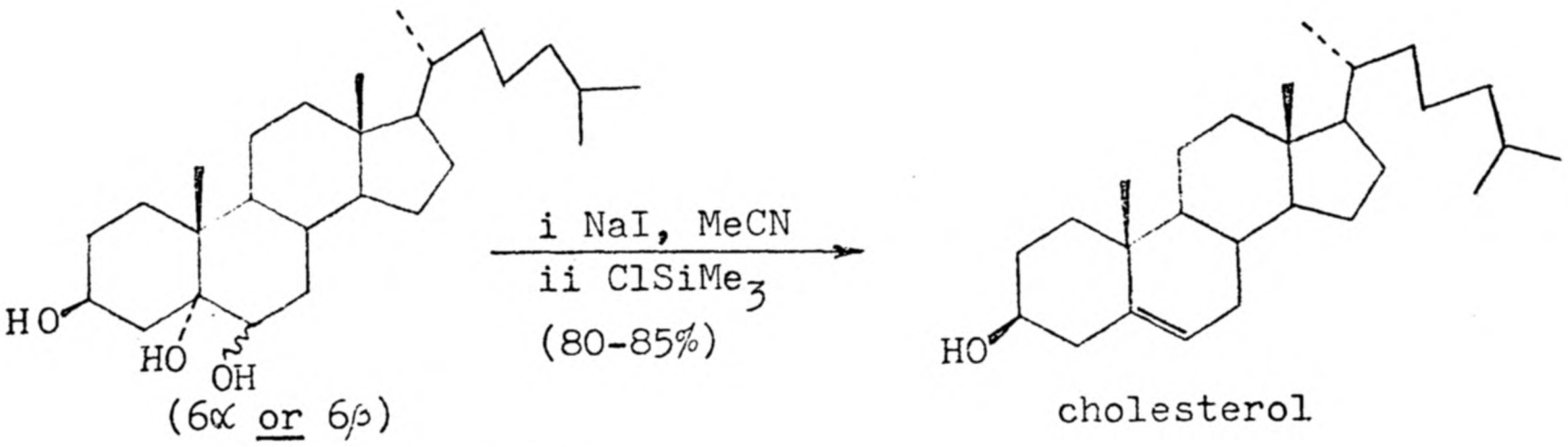
SCHEME 8



SCHEME 8

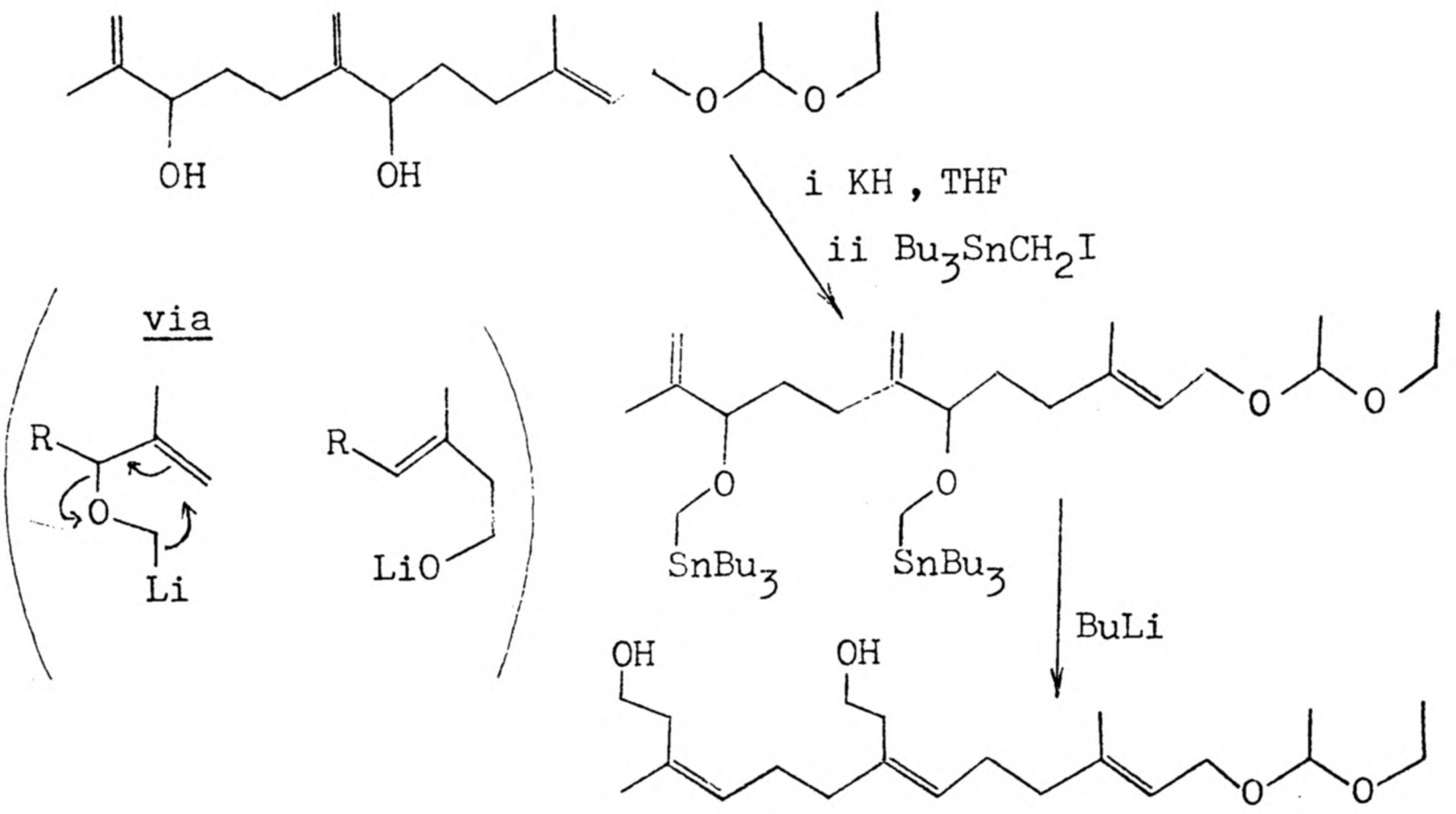
reactions the relevant conformation is generally already present and this may be a factor in favour of such processes with respect to forming strained olefins.

The particular limiting factor in the synthesis of olefins *via* cycloreversions is the availability of stereoisomerically pure precursors. Thus, for instance, the syntheses based on 1,3-dioxolan derivatives are essentially limited by the availability of the diols from which the dioxolans are prepared. The chief sources of vicinal diols are naturally occurring sugars[22], the pinacol synthesis and olefins. The latter may be converted either directly to diols or, more importantly with respect to olefin synthesis, *via* the epoxide as in Scheme 6. Some recent work by Barua[23] provides a more direct preparation of olefins from vicinal diols (Scheme 9) but this reaction is noted for its lack of stereoselectivity.



SCHEME 9

A recent olefin synthesis by Still *et al.*[24] employed a six electron cyclic rearrangement (Scheme 10) which bears some analogy to the cycloreversions discussed above.

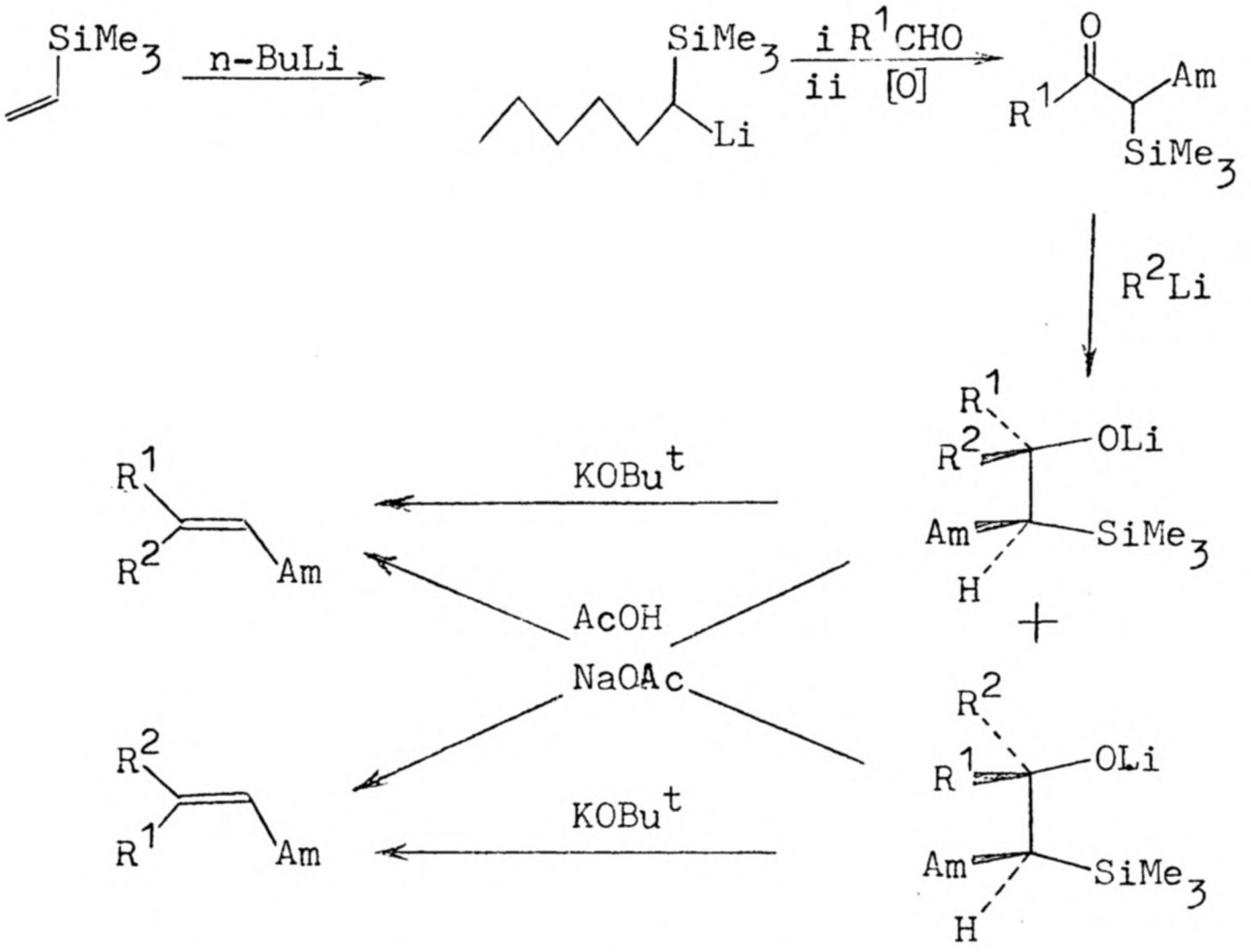


SCHEME 10

Two further olefin syntheses will be discussed in some detail since they are similar in some respects to the work to be reported in this thesis.

The first by Utimoto *et al.*[25] is described as "a stereoselective synthesis of trisubstituted ethylenes" and is outlined in Scheme 11. The double bond forming reaction involves the elimination of a trimethylsilyl and a hydroxyl group from a β-hydroxysilane. Under basic conditions this elimination, referred to as the Peterson elimination[26], requires a *syn*- relationship of the groups eliminated but under acidic conditions an *anti*-periplanar arrangement is preferred.

The stereoselectivity of the olefin synthesis is determined by the selectivity at the stage of the addition reaction to the carbonyl group. Although quite high degrees of selectivity were achieved in this stage of the synthesis no separation of the diastereomers formed is reported.

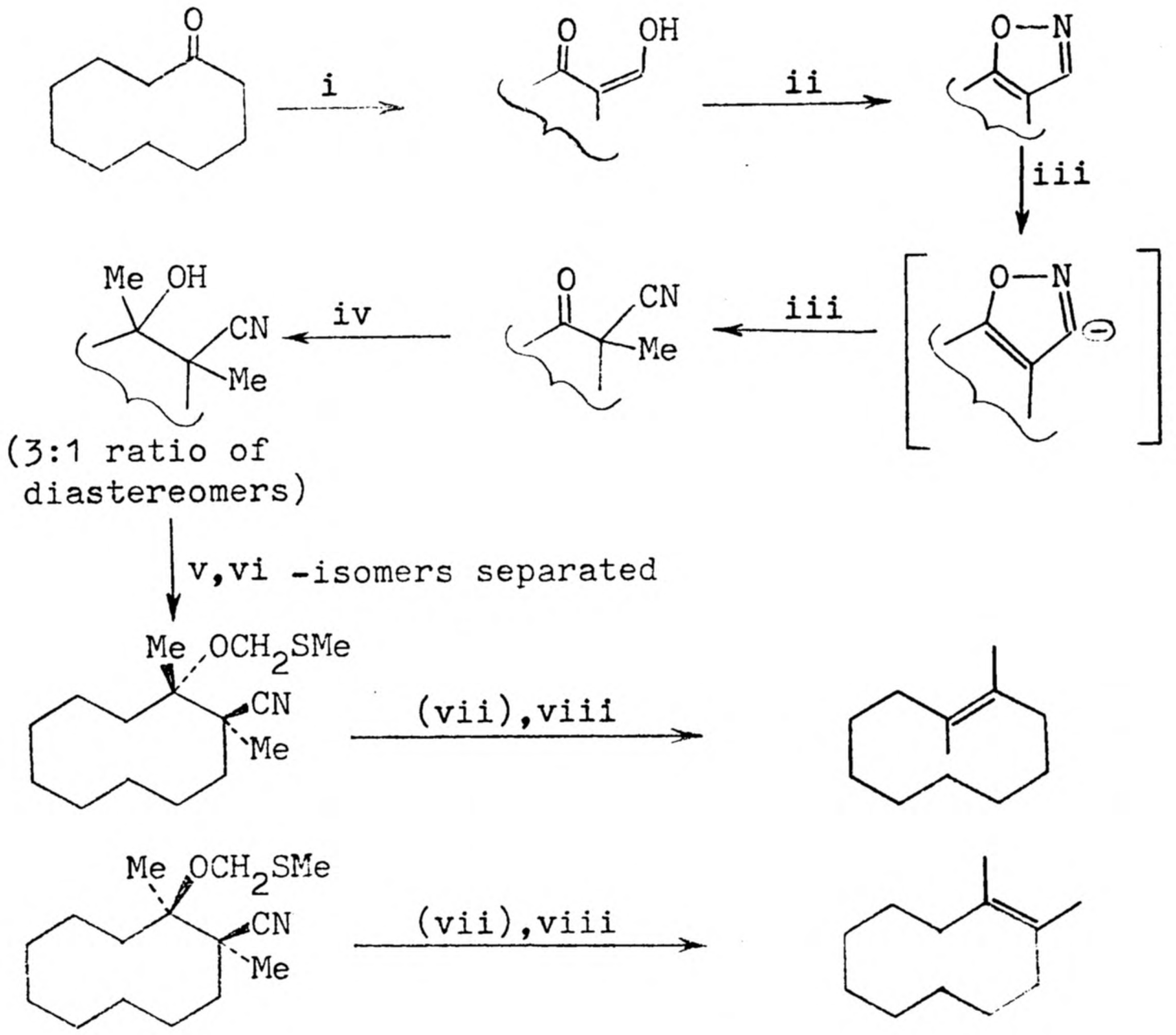


e.g. R^1=n-Pr, R^2= Me or R^1= Me, R^2=n-Pr

SCHEME 11

Marshall et al.[27] used a reductive elimination of vicinal cyanohydrin derivatives to prepare some cyclic tri- and tetra-substituted olefins. An outline of their approach to tetra-substituted olefins is shown in Scheme 12.

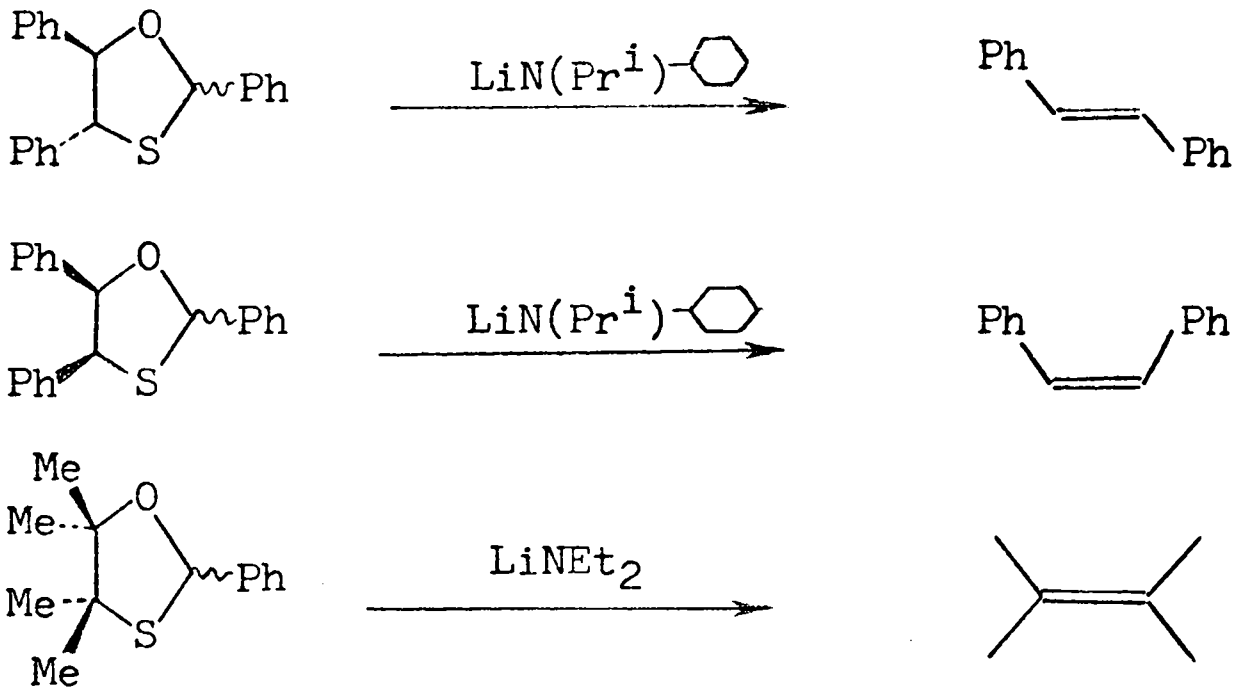
Although it was shown that anti-elimination occurred under some circumstances the preference for syn-elimination and the high stereoselectivity for the reduction step is clear from the syntheses shown in Scheme 12. No work is described on acyclic systems.



SCHEME 12 : i HCO_2Et, CaH_2 ; ii $NH_2OH.HCl$; iii $KOBu^t$, MeI ; iv MeMgBr; v Me_2SO, Ac_2O ; vi $NaHCO_3$ aq ; vii m-$ClC_6H_4CO_3H$ (may be omited); viii $NaC_{10}H_8$.

(ii) Olefin Synthesis via Oxathiolans

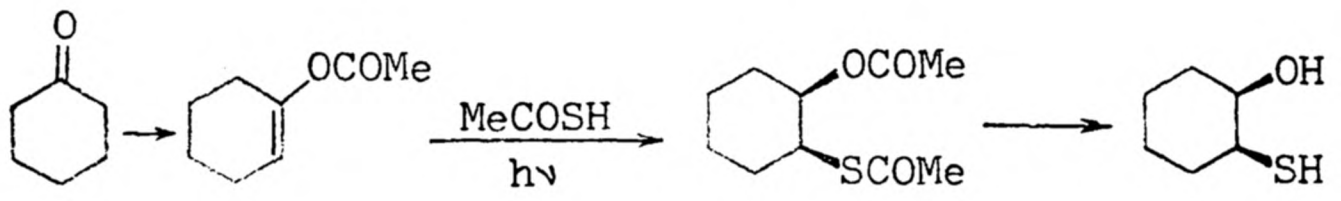
One example of an olefin synthesis from a 2-phenyl-1,3-oxathiolan has been shown in Scheme 8. Other examples further illustrating the diversity of olefins that may be formed from oxathiolans are shown in Scheme 13.



SCHEME 13

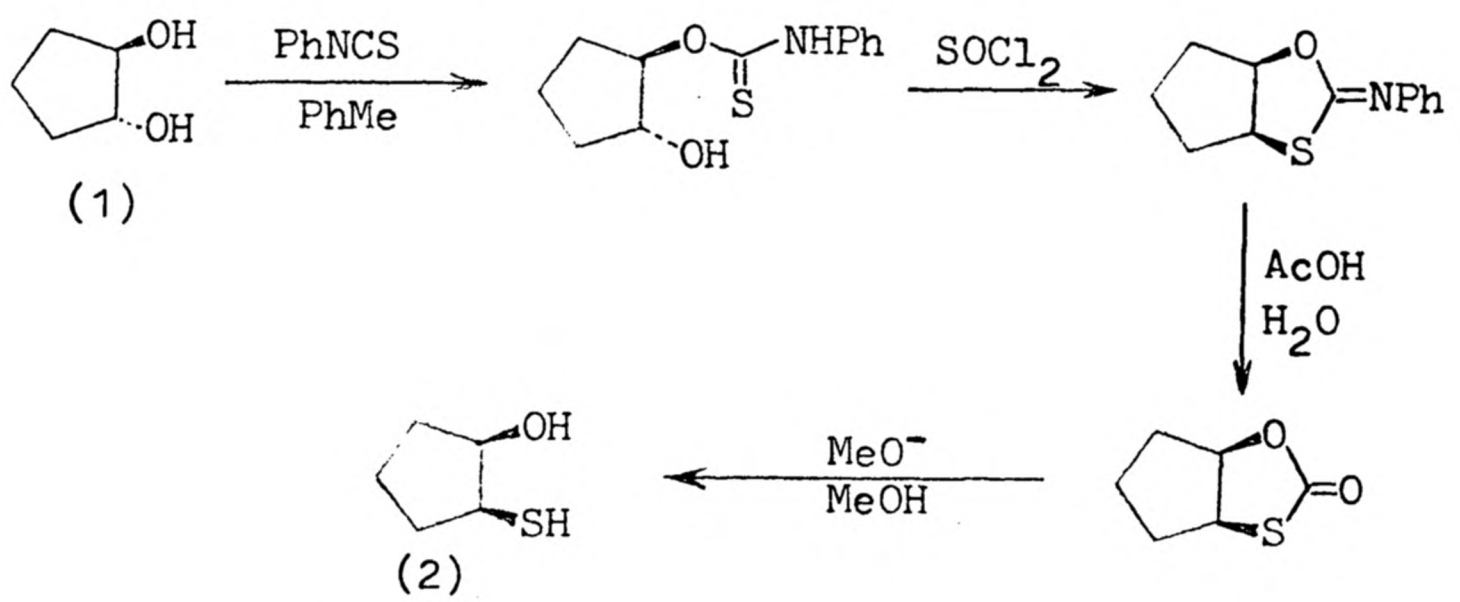
2-Phenyl-1,3-oxathiolans may be prepared by the condensation of a β-mercaptoalcohol with benzaldehyde[28,29] (step iv, Scheme 16). For a stereospecific olefin synthesis the oxathiolan must have stereospecific substitution at the 4- and 5- positions of the ring and thus in terms of using the above condensation as a route to such oxathiolans the β-mercaptoalcohol needs to be one particular diastereomer.

The formation of β-mercaptoalcohols is perhaps most easily achieved by the opening of an epoxide with a sulphur nucleophile[21,30]. This is useful for olefin inversion[21] but a mercaptoalcohol synthesis in which the molecule is built up gradually would be more generally applicable as an approach to oxathiolans and thus to olefins. One preparation of β-mercaptoalcohols that could not be readily formed from epoxides involves the radical addition of thioacetic acid to an enol-acetate (Scheme 14)[31,32].



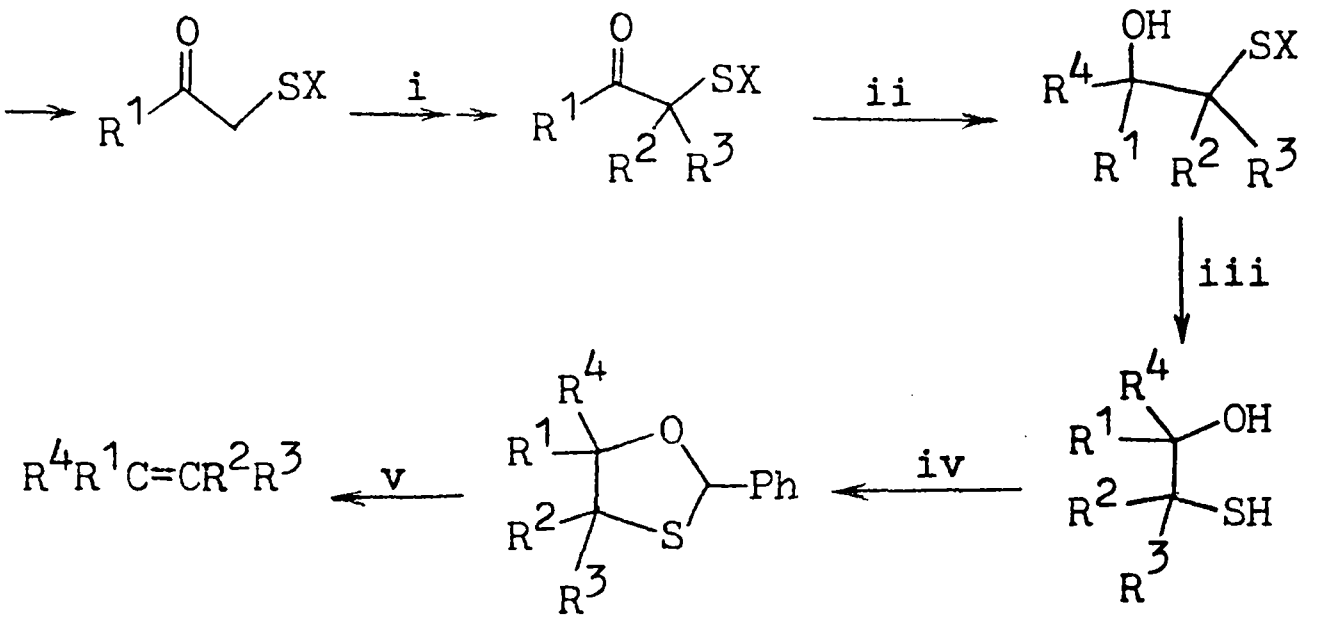
SCHEME 14

The cis-β-mercaptoalcohol (2) has been prepared from cyclopentanone by a route analogous to that in Scheme 14[32] and has also been obtained from the trans-diol (1) as shown in Scheme 15.[33]



SCHEME 15

In seeking for a more general approach to β-mercaptoalcohols - and thus, hopefully, to olefins - we chose to explore the viability of an overall plan as outlined in Scheme 16.

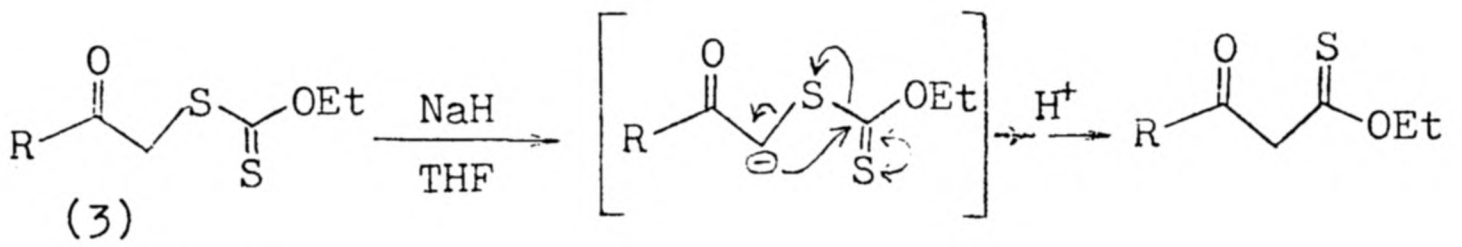


SCHEME 16

In Scheme 16 the position alkylated in step i is activated by both the carbonyl group and the thio-substituent . It may also be noted that if, as hoped, the oxathiolan cycloreversion (step v) is stereospecific and stereochemistry is retained in steps iii and iv then olefin stereochemistry is determined by the nucleophilic attack on the carbonyl group (step ii). The stereoselectivity of this addition which would presumably have to involve an organometallic reagent may be influenced by the thio-substituent.

In some related studies Bridges[34] and Meunier[35] investigated some reactions of β-ketodithiocarbonates (3) and β-ketodithiocarbamates respectively. Thus treatment of β-ketodithiocarbonates with sodium hydride gave β-oxo-thionesters as shown in Scheme 17. Meunier's

work will be discussed on p. 34 ff.



R=Ph or Me

SCHEME 17

Initially our aim was to explore the possibility of following a sequence of reactions as shown in Scheme 16. This requires, for instance, a protecting group for sulphur that will withstand the conditions employed for steps i and ii of the synthesis and that may be fairly readily cleaved to reveal a thiol (step iii). Also it would be advantageous if materials could be chosen such that the stereochemical consequences of the various reactions might be followed.

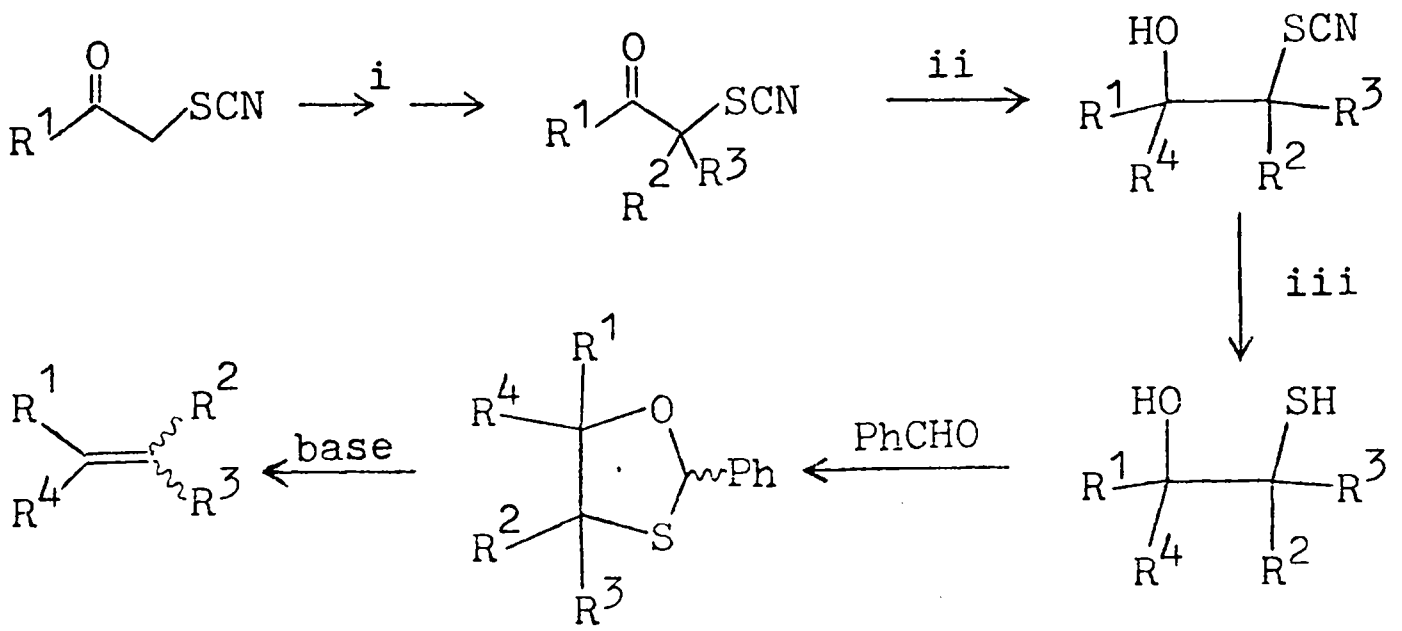
The work to be reported in this thesis concerns the trials, errors, digressions, frustrations, surprises and successes arising from pursuit of the above aim.

DISCUSSION

CHAPTER 1

α-Thiocyanatoketones

Initial work towards a general synthetic route to 2-phenyl-1,3-oxathiolans (as outlined in Scheme 16) involved the use of α-thiocyanatoketones, in which X as in Scheme 16 is -C≡N. It was hoped that the thiocyanate group would be stable to conditions that would allow alkylation of the ketones (step (i)) followed by reaction with an organometallic reagent (step (ii)) to give a β-hydroxythiocyanate as shown in Scheme 18.



SCHEME 18

The reduction of thiocyanates to thiols (as in step (iii)) has been accomplished by various means; examples illustrating the diversity of reducing agents that have been employed are: Clemmensen conditions, lithium aluminium hydride[36], sodium/ammonia[37], dithiothreitol, glutathione[38].

α-Thiocyanatoacetophenone was chosen as a model substrate and was made by the reaction of potassium thiocyanate with α-bromoacetophenone in methanol[39].

In an analogous fashion benzyl thiocyanate was prepared

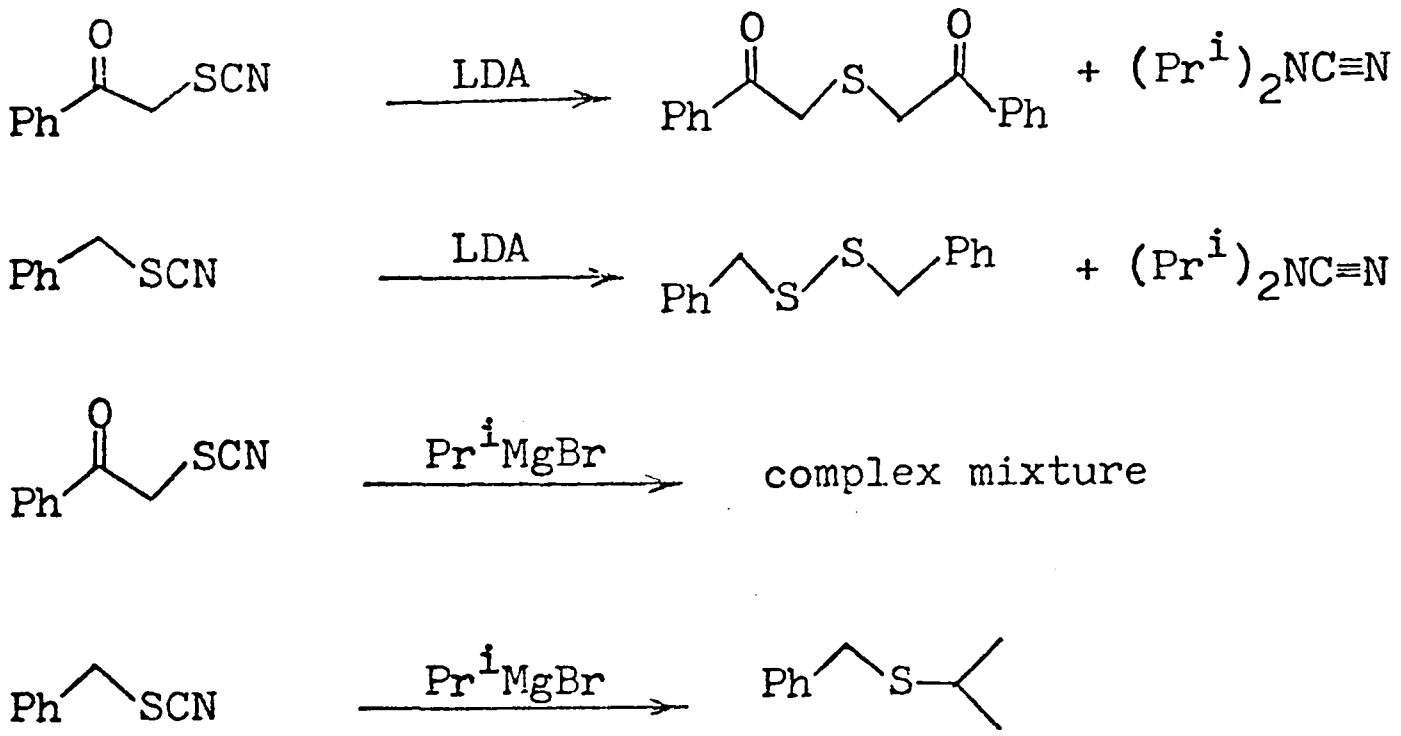
as a simple non-ketonic substrate for comparative studies.

Reactions of compounds containing the thiocyanate group with Grignard reagents and bases/nucleophiles of various kinds have been well studied but nothing was found in the literature concerning reactions of compounds containing a carbonyl group as well as a thiocyanate group.

α-Thiocyanatoacetophenone was subjected to relatively non-nucleophilic, basic conditions. The protons α to the carbonyl and thiocyanate groups should be quite acidic owing to the influence of the two groups, (perhaps pKa ≈ 16 by comparison with similar compounds[40,41]). It was hoped that the enolate ion would be formed which could then be alkylated on carbon. The bases used were LDA and isopropyl magnesium bromide. Reactions with the latter might also indicate the relative electrophilicities of the functional groups. Benzyl thiocyanate was subjected to the same conditions for comparative purposes.

Our observations are shown in Scheme 19. The products of the reactions were identified by comparison with literature data.

In the reaction of LDA with benzyl thiocyanate we see an example of the most common form of S-CN bond fission. The reaction may be rationalised by a two-stage mechanism in which the relatively 'hard'[42] base, LDA, acts as a nucleophile at the 'harder' carbon centre of the thiocyanate group, forming a thiolate. The latter is a 'softer' base and attacks at the 'softer' sulphur centre of the thiocyanate group to give a disulphide.



SCHEME 19

In the reaction of LDA with α-thiocyanatoacetophenone the thiolate derived from initial S-CN cleavage apparently attacks the α-carbon of the α-thiocyanatoacetophenone. Such a thiocyanate displacement would be aided by the adjacent carbonyl group as in the Sn2 reactions of α-haloketones.

The benzyl isopropyl sulphide produced in the reaction of isopropyl magnesium bromide with benzyl thiocyanate appears to result from nucleophilic attack at the sulphur atom of the thiocyanate group. This is consistent with the Grignard reagent being a softer base than LDA. In fact attack by Grignard reagents at the carbon atom of thiocyanates is also known[43]. The reaction of isopropyl magnesium bromide with α-thiocyanatoacetophenone gave a complex mixture.

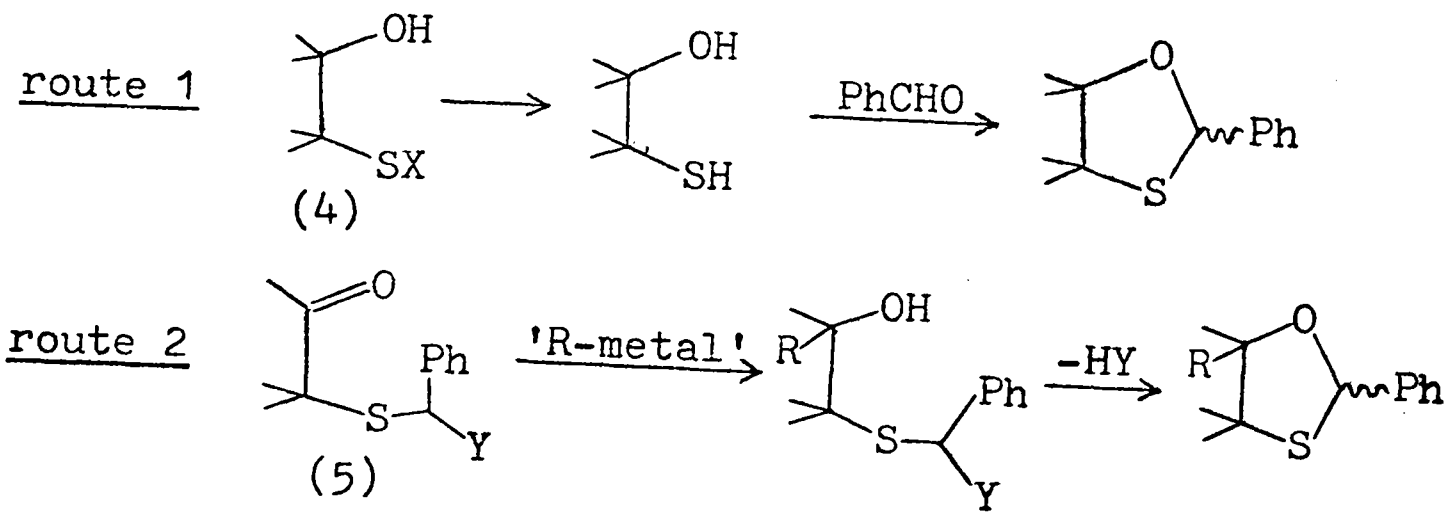
The apparent lability of the thiocyanate group to the kind of conditions that would be required for alkylation of an α-thiocyanato-ketone dissuaded us from pursuing this approach to oxathiolans any further.

CHAPTER 2

α-(α'-Methoxybenzylthio)ketones

2(i) General

The originally suggested route to 2-phenyl-1,3-oxathiolans involved a deprotection of the β-hydroxythio compound (4) (as in Schemes 16 and 18) to give a mercapto alcohol which could be condensed with benzaldehyde to give the oxathiolan, as shown in route 1 of Scheme 20. An alternative approach is to have an α-substituted benzylthio substituent present which may be cyclised to the oxathiolan directly, after formation of the alcohol; see route 2 in Scheme 20.

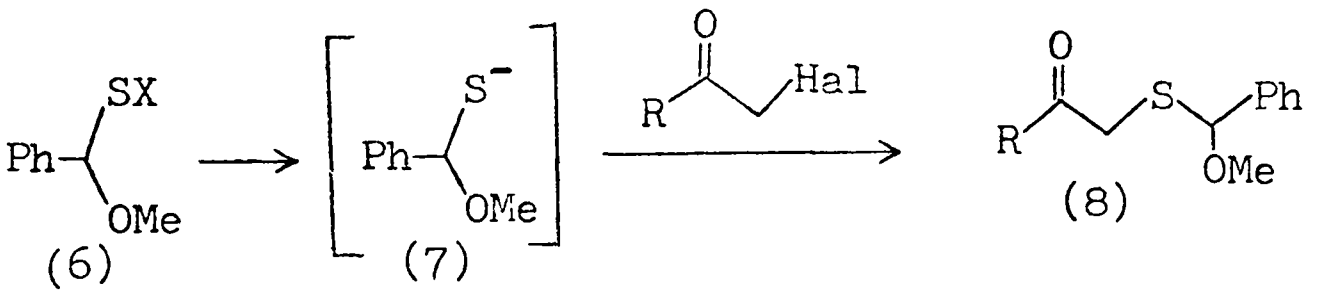


SCHEME 20

This chapter discusses approaches to ketones bearing an α-methoxybenzylthio group α to the carbonyl group - e.g. (5) where Y is -OMe. It was hoped that the methoxy group would not only permit cyclisation but also influence the stereoselectivity of the preceeding organometallic reaction.

2(ii) O-Ethyl-S-(α-methoxybenzyl) dithiocarbonate

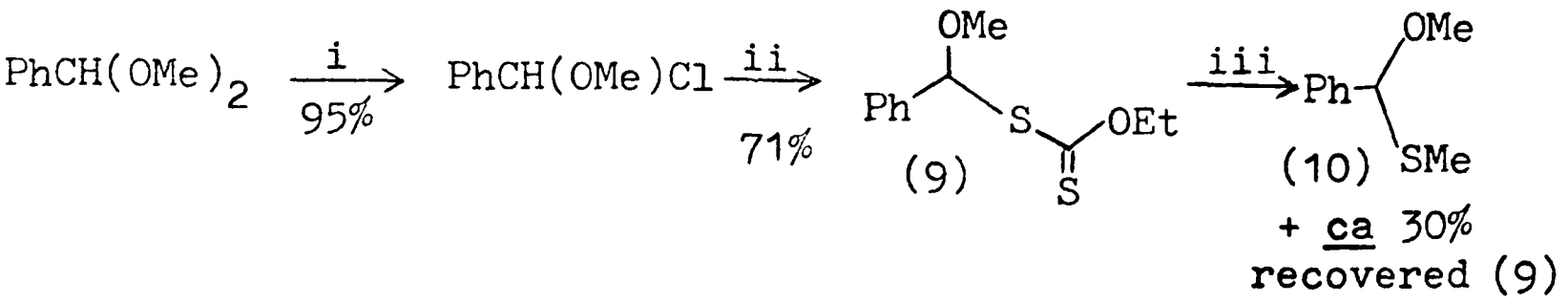
One approach to α-(α'-methoxybenzylthio)ketones (8) might be a displacement reaction by α-methoxybenzylthiolate (7) on an α-haloketone, as shown in Scheme 21.



SCHEME 21

Owing to the probable instability of the α-methoxybenzylthiolate and its conjugate acid [44], it was decided to attempt to form the thiolate and react it with an electrophile (the α-haloketone in Scheme 21) in situ.

Compounds containing an α-(methoxy)alkylthio group (e.g. 6) have been made by a number of methods. These methods include Pummerer and related reactions[45], replacement of one of the methoxy groups of a dimethyl acetal[46] and the displacement of bromide from an α-bromosulphide[47]. It was decided, in the first instance, to attempt to make a dithiocarbonate derivative (9) of the α-methoxybenzyl compound (Scheme 22) and this was accomplished by a modification of the reaction sequence used by Fife and Anderson[48] for the preparation of monothioacetals. The conditions used are outlined in Scheme 22.



SCHEME 22 : i $SOCl_2$;ii KSCS.OEt,Et_2O;iii MeI,Et_2O; NaOMe.

The reactions of benzaldehyde dimethyl acetal with thionyl-chloride only gave good yields when the reactants were freshly distilled and the apparatus used was thoroughly dried. The dithiocarbonate (9) was identified by its characteristic ^1H n.m.r. spectrum and strong bands at 1220, 1110 and 1040 cm^{-1} in the liquid film infrared spectrum due to the dithiocarbonate group[49].

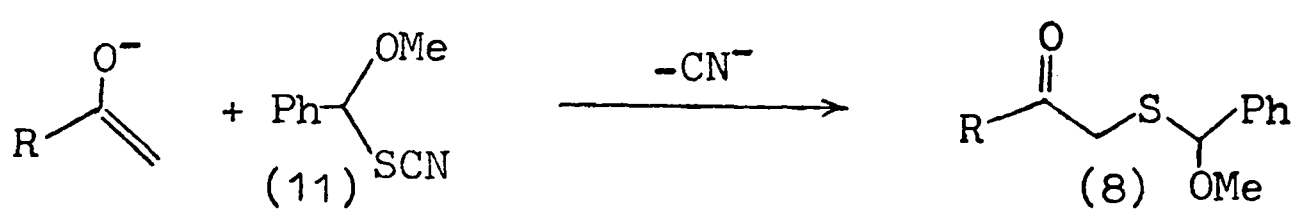
Either sodium methoxide, lithium aluminium hydride or piperidine were used in reactions with the dithiocarbonate (9) in attempts to produce the thiolate (7) (see Scheme 21). Either α-chloroacetophenone or iodomethane were included in the reaction mixtures as electrophiles to react with any thiolate formed. The crude products of the reactions were examined by ^1H n.m.r., the region from δ 5.0-7.0 being considered particularly informative since a proton α to a phenyl, a methoxy and a thio group should occur in this region.

The only promising reaction observed was that shown in Scheme 22 where the dimethyl monothioacetal[45] (10) resulted. Other than this the reactions under various conditions gave recovered starting material and/or mixtures of compounds with little if any of the desired products. Therefore this particular route to

α-(α'-methoxybenzylthio)ketones was considered not worth pursuing further.

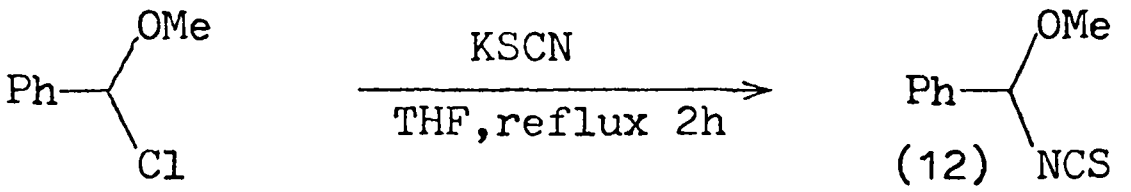
2(iii) (α-Methoxybenzyl)thiocyanate

In the reaction of isopropyl magnesium bromide with benzyl thiocyanate (Scheme 19) we saw an example of an apparent displacement at sulphur by the carbon nucleophile. If such a displacement took place on (α-methoxybenzyl)thiocyanate (11) using an enolate nucleophile this would be a synthesis of α-(α'-methoxybenzylthio)-ketones (8)as shown in Scheme 23.



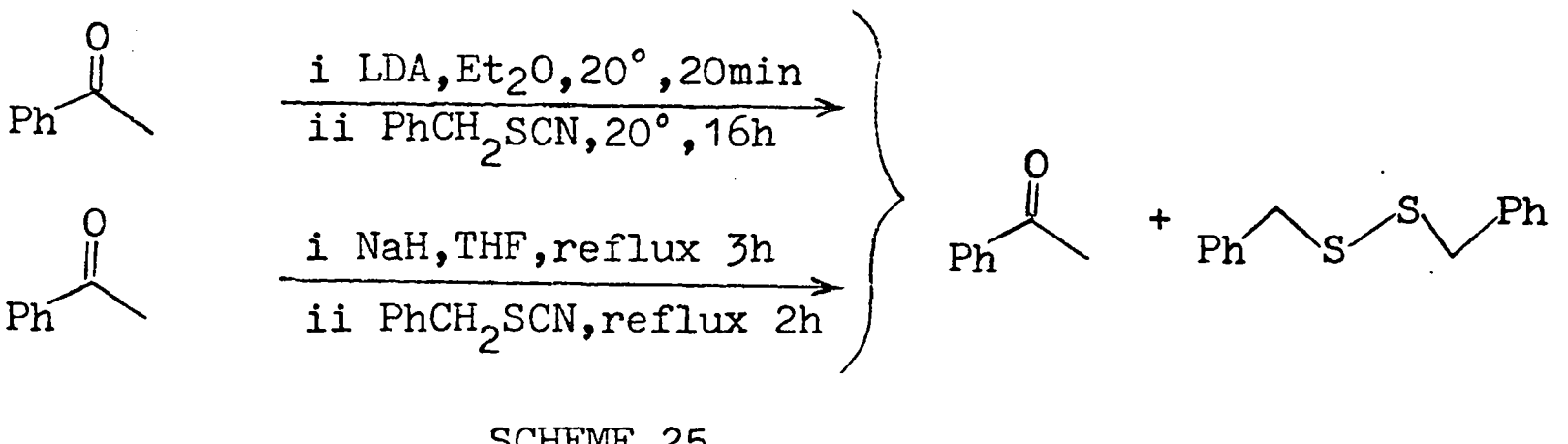
SCHEME 23

It was hoped that the (α-methoxybenzyl)thiocyanate could be prepared by a similar reaction to that used for the preparation of the corresponding dithiocarbonate. The reaction of (α-chloro-benzyl)methyl ether with potassium thiocyanate (Scheme 24), however, proved much more capricious than that with potassium O-ethyldithiocarbonate. The reaction was never clean and the product, isolated by distillation, appeared to be the isothiocyanate (12) on the basis of the broad band at 1950-2150 cm^{-1} in the infrared spectrum (liquid film)[50]. Since α-chloro ethers tend to react by an S_N 1 mechanism[51] the formation of an isothiocyanate is not surprising since the electrophile becomes essentially a carbonium ion, which is a hard acid, and the 'harder' centre of the thiocyanate is the nitrogen.



SCHEME 24

In order to investigate the viability of a reaction such as in Scheme 23, benzylthiocyanate was added to the enolate of acetophenone (Scheme 25). The crude products of the reactions were mixtures of recovered acetophenone and dibenzyl disulphide.



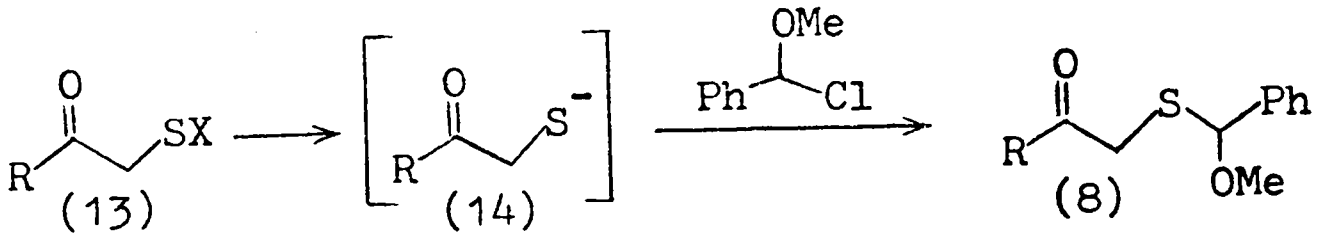
SCHEME 25

Dibenzyl disulphide was obtained earlier (p. 17) from the reaction of LDA on benzylthiocyanate and its formation may be rationalised in the same way. The recovery of acetophenone is more difficult to explain. One possible explanation is that the harder, carbon centre of the thiocyanate is attacked by the harder, oxygen centre of the enolate giving a vinylcyanate ($PhCH(OCN)=CH_2$) which under the conditions of the reaction and work up might well decompose, giving rise to acetophenone.

Owing to the failure of the enolate to react in the way that was hoped and the apparent difficulty in preparing (α-methoxybenzyl)-thiocyanate, it was considered not worth following this approach further.

2(iv) S-(2-Oxoalkyl)dithiocarbonates

The synthesis of α-(α'-methoxybenzylthio) ketones might also be achieved by the reaction of a β-ketothiolate (14) with (α-chlorobenzyl)methyl ether as outlined in Scheme 26.



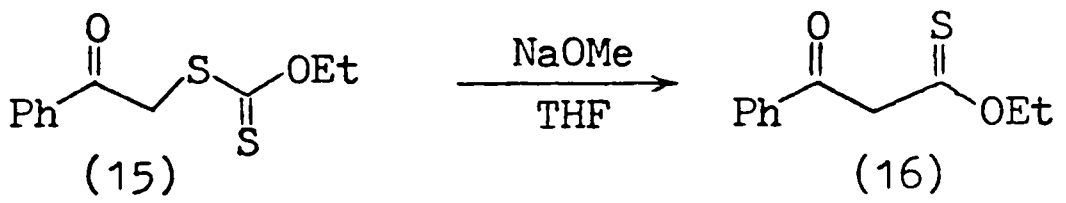
SCHEME 26

Initial attempts involved preparation of α-mercaptoketones (13, X = H). These have been most frequently prepared by the reaction of α-haloketones with sodium or potassium hydrogen sulphide under aqueous conditions[52,53]. The products from this kind of preparation are usually mixtures of monomers, dimers and often higher polymers[54] which are very insoluble in organic solvents. Aqueous sodium hydroxide is normally used to generate the monomer from these mixtures (although McIntosh[55] successfully employed pyridine). Since aqueous conditions are incompatible with a reaction involving an α-haloether a non-aqueous preparation of α-mercaptoketones that could be used in situ was sought.

Nagata's preparation of α-mercaptoacetophenone[56] using pyridine and hydrogen sulphide was a possibility but attempts to repeat this work gave α,α'-thiobis(acetophenone) (also obtained by Nagata) in too large a proportion to make this approach attractive. A halide displacement by anhydrous sodium hydrogen

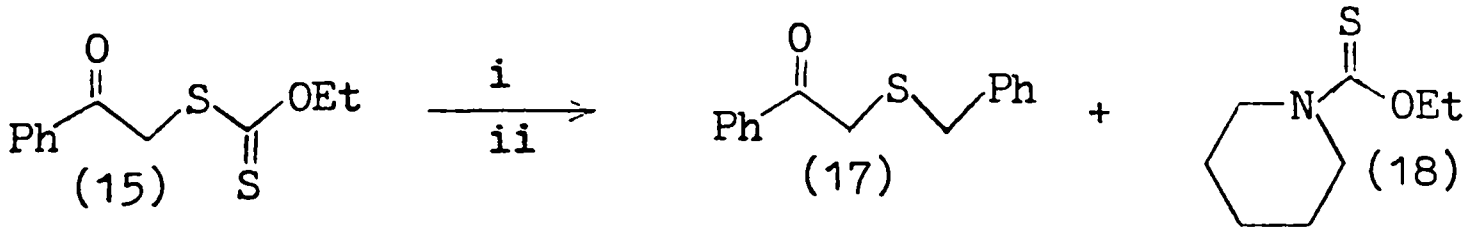
sulphide[57] was attempted but the reaction with α-chloroacetophenone gave α,α'-thiobis(acetophenone)-<u>c.f.</u> above (see p. 17).

The β-ketothiolate (14) might also be generated from compounds other than the parent thiol. In this connection S-(phenacyl)-O-ethyldithiocarbonate (13 , R = Ph, X = CS.OEt) was prepared[58]. The dithiocarbonate was stable to treatment with sodium methoxide either in ether or in dimethylformamide. When refluxed with sodium methoxide in THF, partial sulphur extrusion was observed[58] (Scheme 27), the product was identified by comparison of its spectra with those obtained by Bridges for O-ethyl(benzoyl)-thioacetate[58] (16).



SCHEME 27

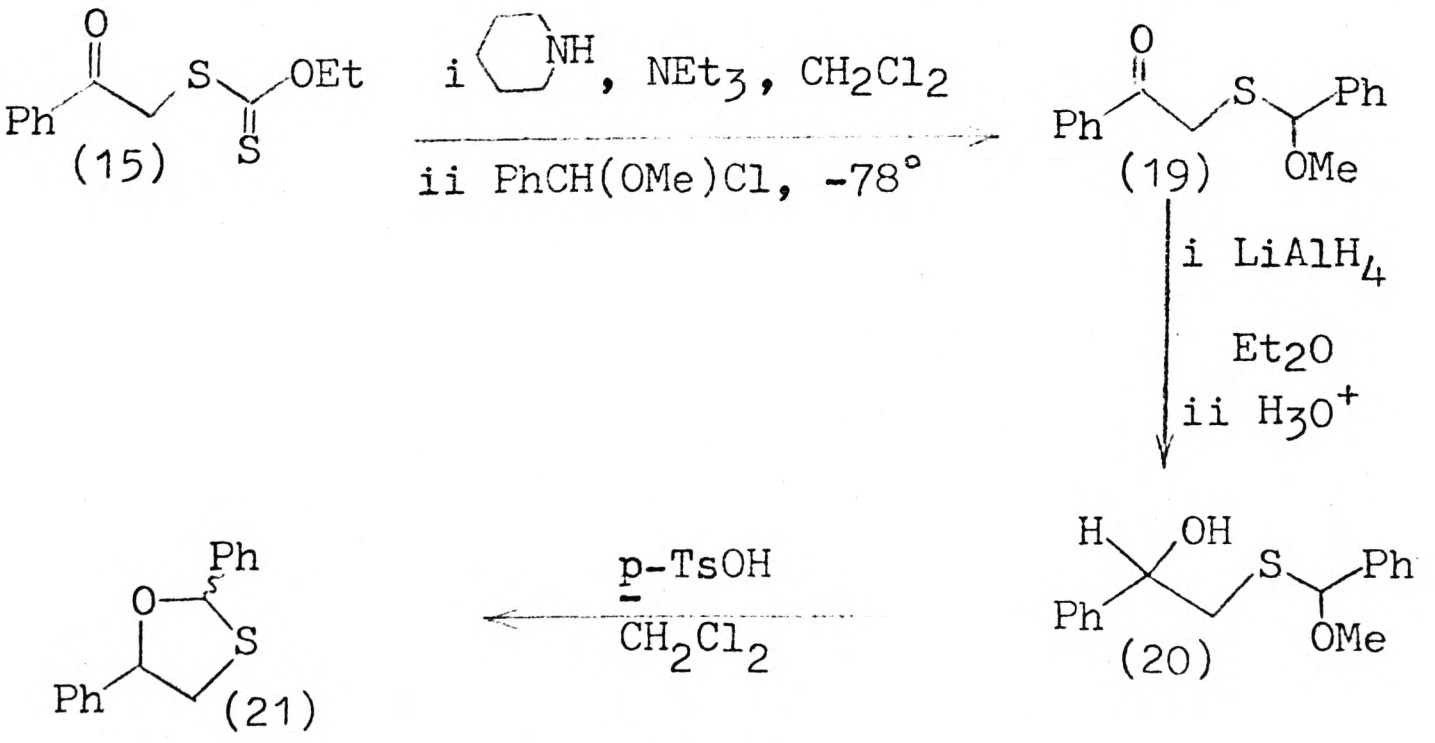
Reaction of the dithiocarbonate (15) with piperidine[60,61,62] and triethylamine in dichloromethane, followed by benzyl chloride, however, gave a mixture of (α-benzylthio)acetophenone[63] (17) and O-ethyl-1-piperidinecarbothioate[62] (18) (Scheme 28).



SCHEME 28 : i  NH, NEt_3, CH_2Cl_2; ii $PhCH_2Cl$.

A small amount of α-mercaptoacetophenone was also formed. This was isolated by extraction into aqueous sodium hydroxide, acidification with dilute hydrochloric acid and re-extraction into dichloromethane and tentatively identified by its ^1H n.m.r. spectrum - δ_H ($CDCl_3$) 2.1 (1H, t, J 7 Hz), 3.92 (2H, d, J 7 Hz), 7.2-7.65 (3H, complex), 7.8-8.1 (2H, complex). Encouraged by this model reaction, a similar procedure was employed using (α-chlorobenzyl)methyl ether in the place of benzyl chloride. The desired α-(α'- methoxy - benzylthio)acetophenone (19) was obtained in 50% yield after distillation (Scheme 29). The compound is stable to chromatography on silica gel and this would probably be a better method for purification than distillation.

In order to investigate whether an alcohol derived from α-(α'- methoxybenzylthio)acetophenone (19) would cyclise directly to a 2-phenyl-1,3-oxathiolan, the ketone (19) was reduced to the alcohol (20). The resulting alcohol was stirred with a catalytic amount of p-toluenesulphonic acid in dichloromethane and gave cleanly the oxathiolan (21), (Scheme 29).



SCHEME 29

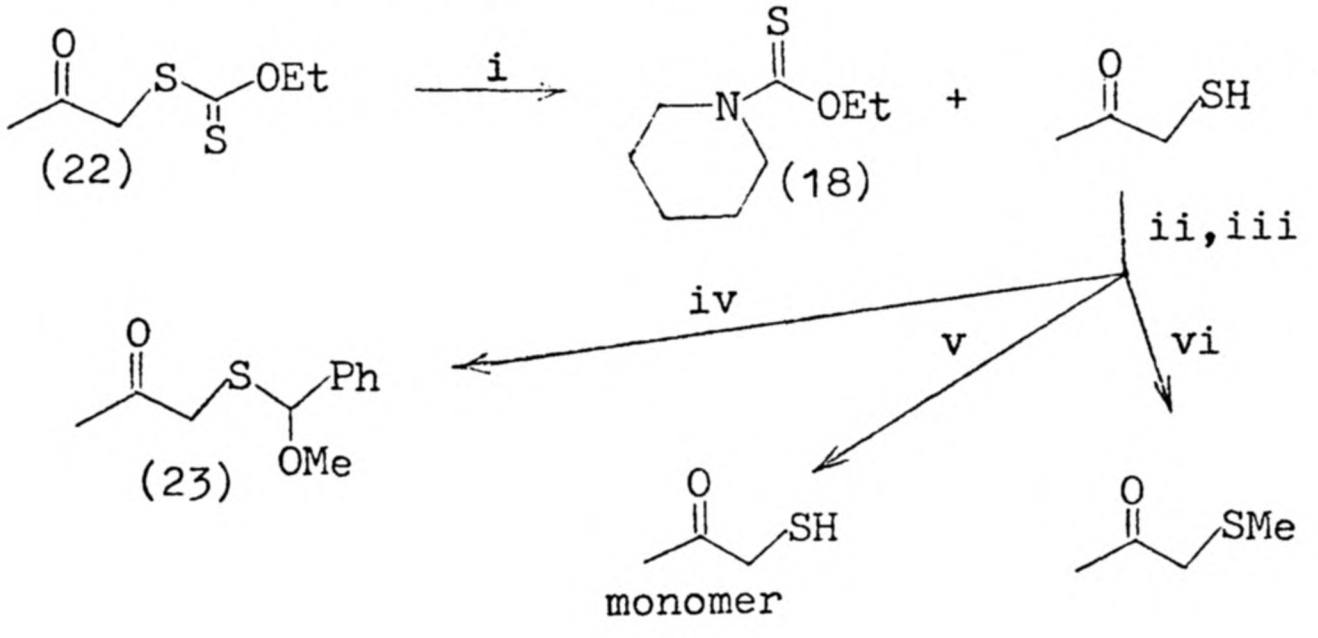
α-(α'-Methoxybenzylthio)acetophenone (19) was subjected to various conditions in attempts either to alkylate it or produce a tertiary alcohol (from an organometallic reagent). From these reactions either recovered starting material or mixtures containing only small quantities of the desired product were obtained.

S-(α-Acetonyl)-O-ethyldithiocarbonate (22) was prepared by the procedure of Bridges[59], and the corresponding 2-oxocyclohexyl-dithiocarbonate was obtained by an analogous method. Using these dithiocarbonates attempts were made to produce the respective β-ketothiolate anions using piperidine and triethylamine. Iodomethane was tried as an electrophile to react with any thiolate produced. These reactions gave only low yields of the desired materials and often undesired products were detected as well as recovered starting material.

Monitoring by ^{1}H n.m.r. of the reaction between S-(α-acetonyl)-O-ethyldithiocarbonate (22) and piperidine in deutero-chloroform showed that cleavage of the dithiocarbonate (22) was essentially complete after 60 seconds at room temperature. Further investigation showed that extraction of a shaken mixture of the dithiocarbonate (22) and piperidine in dichloromethane with aqueous sodium hydroxide, followed by acidification and re-extraction into dichloromethane gave a clean sample of monomeric α-mercaptoacetone[53], (Scheme 30).

Addition of the dichloromethane solution of the α-mercaptoacetone to a solution of iodomethane and triethylamine in dichloromethane

gave the S-methylated compound, (Scheme 30). Similar addition to (α-chlorobenzyl)methyl ether and triethylamine in dichloromethane gave the desired α-(α'-methoxybenzylthio)acetone (23) which was isolated by chromatography, (Scheme 30).



SCHEME 30 : i  NH; ii NaOHaq.; iii dil.HCl; CH_2Cl_2; iv Ph  Cl, NEt_3, -78°; v evaporate; vi MeI, NEt_3,

S-(2-Oxocyclohexyl)-O-ethyldithiocarbonate did not behave in the same way as the acetonyl compound (22), possibly as a result of either a slower aminolysis of the dithiocarbonate group or a more facile dimerisation of the α-mercaptoketone. In order to investigate the aminolysis more closely we attempted to make S-(2-oxocyclohexyl)-O-methyldithiocarbonate (24). This compound might react more quickly with piperidine, also the ^1H n.m.r. spectra of the components should be simpler.

Various procedures were used in attempts to make the O-methyldithiocarbonate (24). Initial work involved the use of isolated sodium O-methyldithiocarbonate (see p. 83). Subsequently

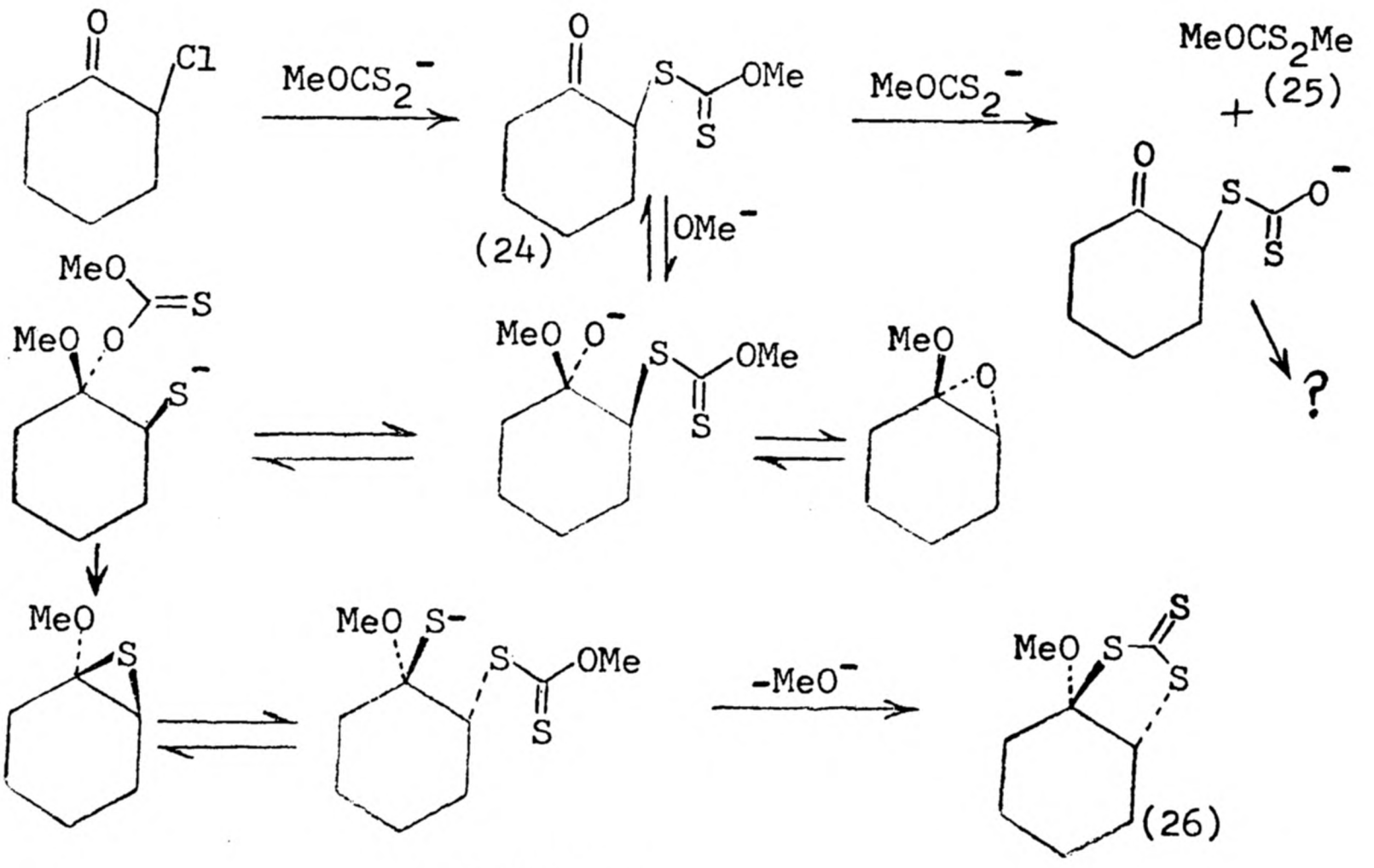
reactions involving formation of the dithiocarbonate salt and use of this *in situ* were attempted. These attempts followed the procedures employed by Rae[64] and Kanaki *et al.*[65]. All these reactions were carried out on both 2-chlorocyclohexanone and α-chloroacetone, the latter as a control.

The *in situ* procedures gave good yields of S-(α-acetonyl)-O-methyldithiocarbonate but in reactions with 2-chlorocyclohexanone the products were mixtures containing only small amounts of the desired dithiocarbonate (24). From the *in situ* reaction in dimethylsulphoxide and from reactions using the isolated dithiocarbonate salt, O,S-dimethyldithiocarbonate (25) was identified as one of the products . The use of the sodium O-methyl-dithiocarbonate solid in acetone gave, as well as the dithiocarbonate (25), a yellow solid which crystallised from the crude product (see p. 83). The identification of the solid is discussed below.

The analysis and mass spectrum of the solid (from above) showed its empirical formula to be $C_8H_{12}OS_3$. The ^1H and ^{13}C n.m.r. spectra suggested the presence of a methoxy (δ_H 3.4 (s), δ_C 51 (q)) and a thio carbonyl group (δ_C 226). The lack of any carbonyl absorption in the infrared spectrum helped to confirm this. The relatively high field shift of the methoxy group suggested that it is attached to an sp^3 hybridised carbon. One possible structure is (1RS,6RS)-1-methoxy-7,9-dithiabicyclo[4.3.0]nonane-8-thione (26) and the close similarity between the infrared spectra and the mass losses from the molecular ion in the mass spectra of the unknown and *trans* -7,9-dithiabicyclo[4.3.0]nonane-8-thione (28) made this seem a likely candidate. Further

comparison of these two compounds showed the ^{1}H and ^{13}C n.m.r. and ultraviolet spectra for the unknown to be quite compatible with the trithiocarbonate structure (26). Assuming (26) to be the structure then the proton on C-6 is a double doublet with J 14 and 4 Hz, suggesting that it is axial.

Reaction of the unknown with lithium aluminium hydride gave 1,2-cyclohexanedithiol. This result is compatible with the proposed structure (26).

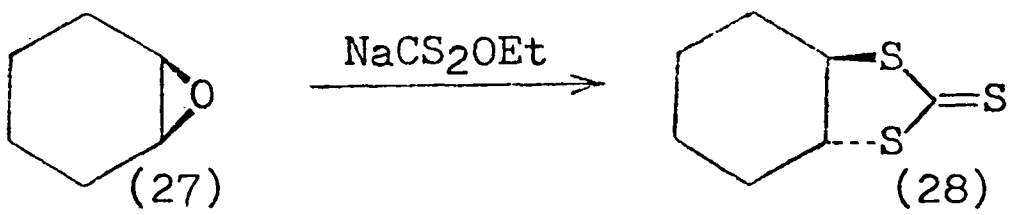


SCHEME 31

It is known that compounds similar to the O-methyldithiocarbonate (24) can act as methylating agents[64,66] in some instances and

this may explain the formation of O,S-dimethyldithiocarbonate (25) (Scheme 31).

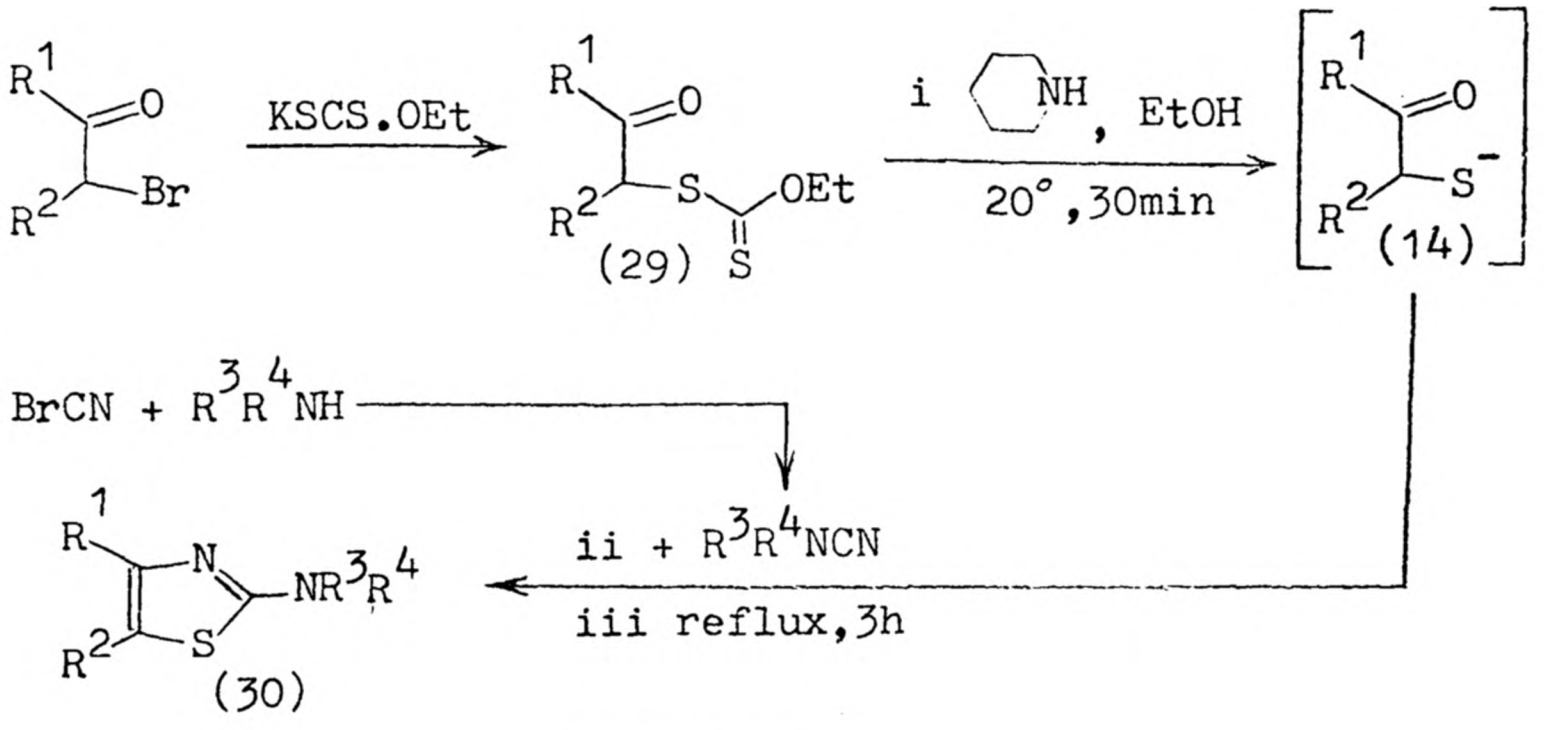
The formation of the trithiocarbonate (26) may be explained by the mechanism shown in Scheme 31 which provides a basis for the trans- configuration assigned. As a precedent for many of the steps shown in Scheme 31 one may cite the formation of the trithiocarbonate (28) from the epoxide (27)[67] (Scheme 32).



(27) (28)

SCHEME 32

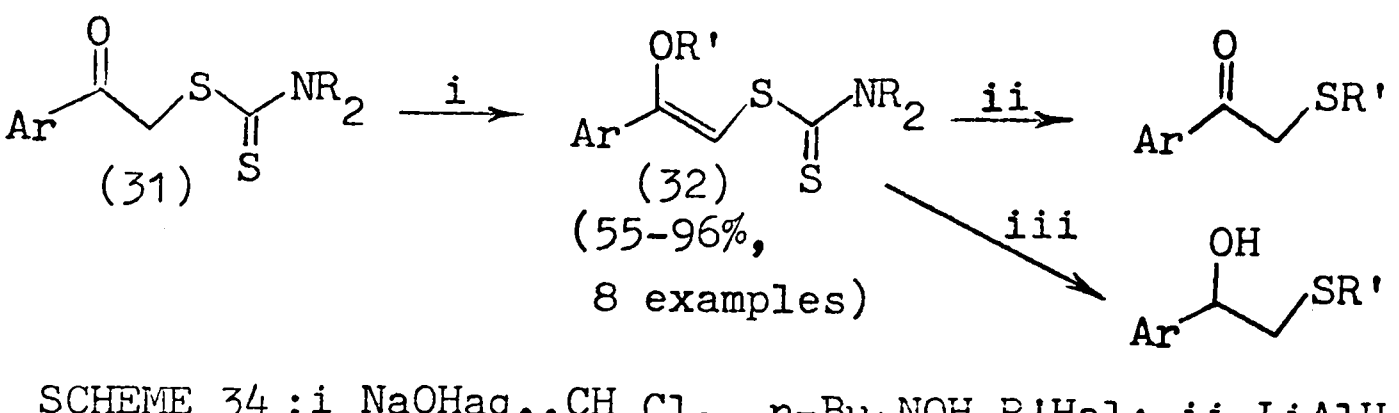
The failure of the work described in this section to provide a general route to α-(α'- methoxybenzylthio)ketones (8) led us to look to other systems for the preparation of (8). However, the generation of β-ketothiolates (14) from the corresponding O-ethyldithiocarbonates (29) as described in this section (p. 26 ff) has been used by another group in this laboratory in a synthesis of N-mono- and N- disubstituted 2-aminothiazoles[68] (30) (Scheme 33). The procedure shown proved to be a good general synthesis of the thiazoles (30).


KSCS.OEt
(29)
i NH, EtOH
20°, 30min
(14)
BrCN + R3R4NH
ii + R3R4NCN
iii reflux, 3h
(30)

SCHEME 33

2(v) S-(2-Oxoalkyl)dithiocarbamates

In 1978, Meunier[35] prepared some S-(2-oxoalkyl)dithiocarbamates in the hope that they would be suitable precursors to 1,3-oxathiolans (c.f. Scheme 16, and Chapter 1 where α-thiocyanatoketones were investigated for similar reasons). Meunier's attempts to alkylate her dithiocarbamates gave mainly a product which was considered to be the O-alkylated compound (32) shown in Scheme 34.



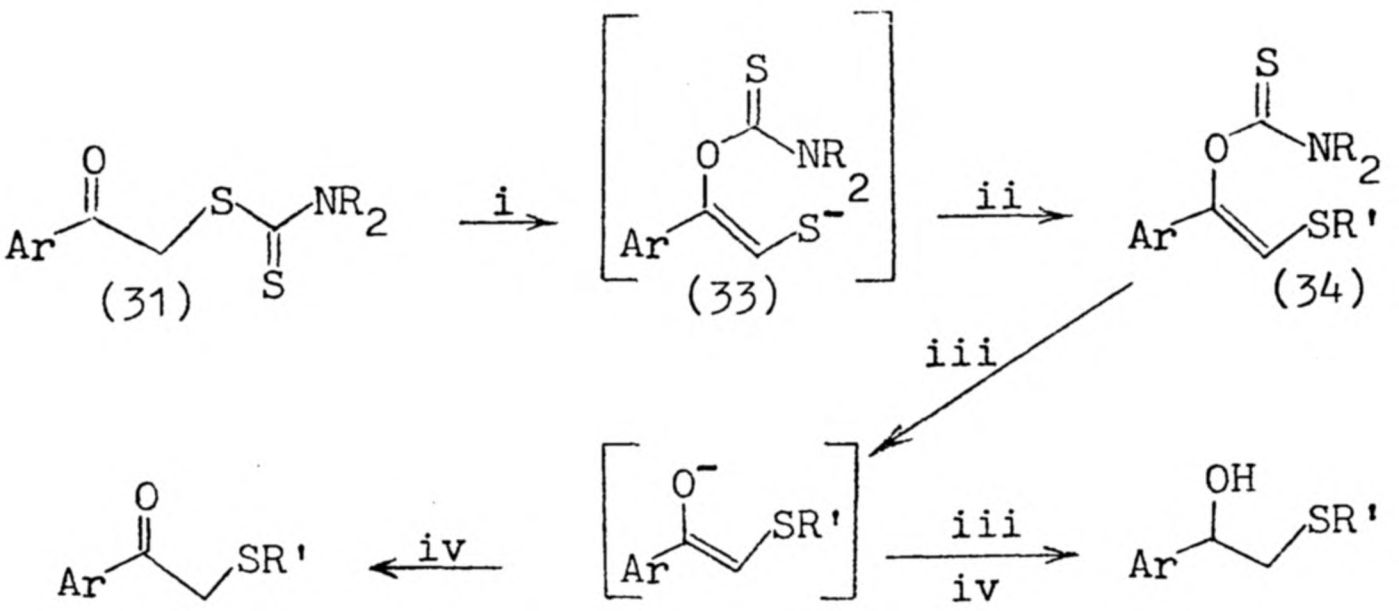
SCHEME 34 : i NaOHaq., CH_2Cl_2, n-Bu_4NOH, R'Hal; ii $LiAlH_4$; iii excess $LiAlH_4$

Treatment of the product of the attempted alkylation with lithium aluminium hydride gave β-keto- and/or β-hydroxysulphides after aqueous work up (Scheme 34). This was considered to have occurred via a 1,4-intramolecular rearrangement.

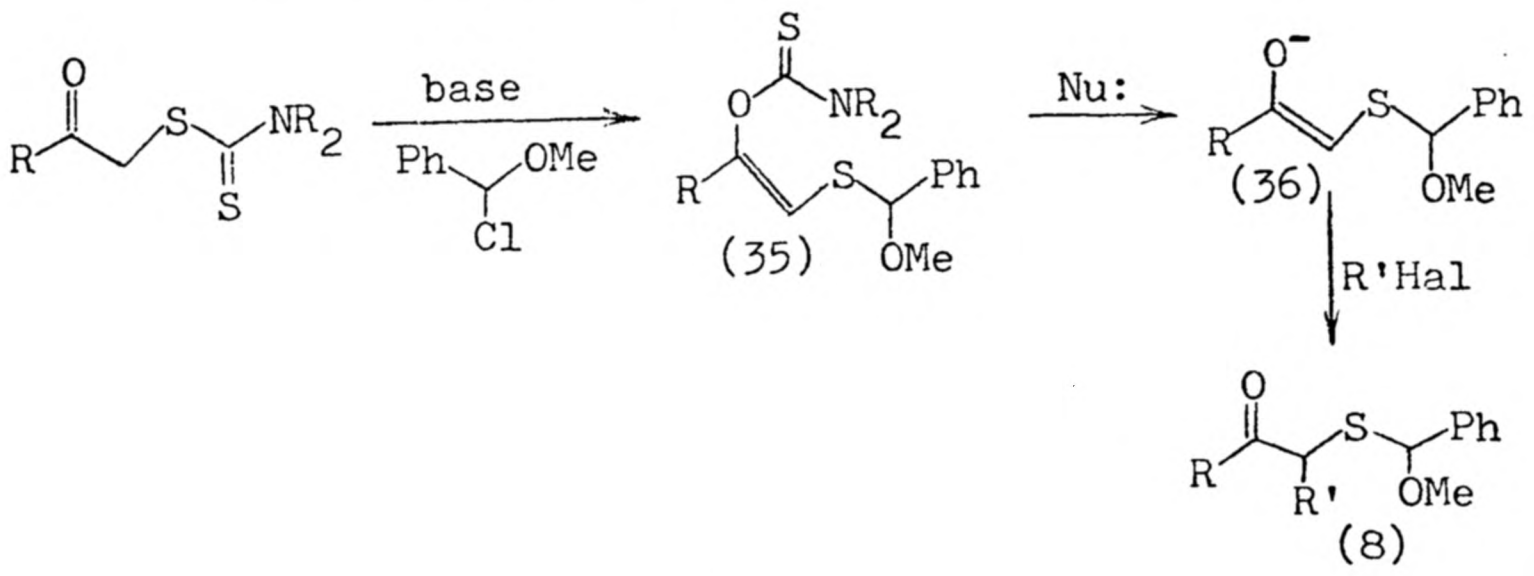
In the light of a proposed alternative interpretation for the course of these reactions (Scheme 35) it was decided to look more closely at the data of the products of the alkylation reactions to decide which of the proposed structures ((32) or (34)) was more likely.

If the alternative interpretation were correct then it was hoped that non-aqueous basic conditions could be found for generation

of the thiolate (33) which would react with (α-chlorobenzyl)methyl ether to give the monothiocarbamate intermediate (35). This intermediate might then react with a nucleophile to reveal an enolate (36) which could react with an electrophile (e.g. R'Hal in Scheme 36) to give a substituted α-(α'-methoxybenzylthio)-ketone (8) (Scheme 36).

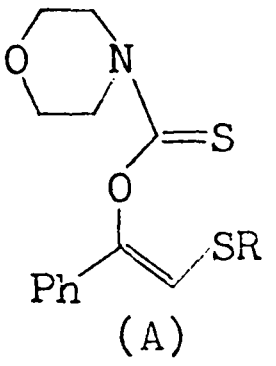


SCHEME 35: i NaOHaq., n-Bu_4NOH, CH_2Cl_2; ii R'Hal; iii $LiAlH_4$; iv H_2O.



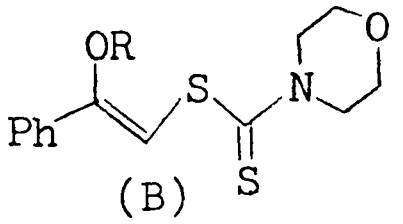
SCHEME 36

Two of Meunier's samples were reinvestigated, the structures under consideration are those shown in Scheme 37.



(A)

or



(B)

(37) R= Me

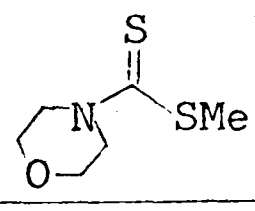
(38) R = CH_2Ph

SCHEME 37

The spectral data from which it was concluded that these compounds, (37) and (38), were to be represented by the structure (A) rather than (B) - thus supporting Scheme 35 rather than Scheme 34 are shown in Tables 1 and 2.

TABLE 1

N.M.R. Chemical Shifts

Compound	Ar$\underline{CH_2}$O-	Ph$\underline{CH_2}$S-	$\underline{MeO}$-	$\underline{MeS}$-
$\underline{p}$-MeO-C_6H_4·CH_2OH	δ_H 4.55[a] δ_C 64 [b]		δ_H 3.8[a] δ_C 55 [b]	
$(Ph-CH_2S)_2$		δ_H 3.57[a] δ_C 43 [b]		
Ph-CH_2S-Ph		δ_H 4.11[a]		
Ph-SMe				δ_H 2.45[a] δ_C 16 [b]
Ph-O-Me			δ_H 3.8[a] δ_C 55 [b]	
 (39) [c]				δ_H 2.66 δ_C 19.5

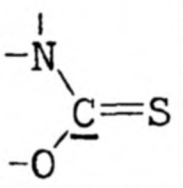
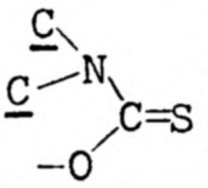
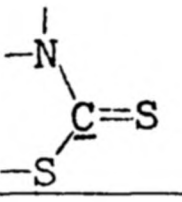
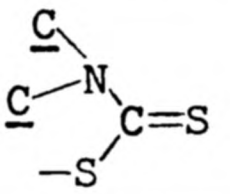
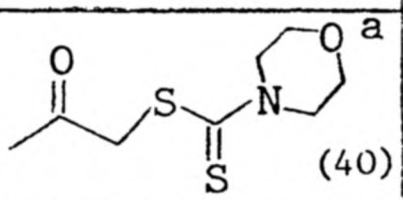
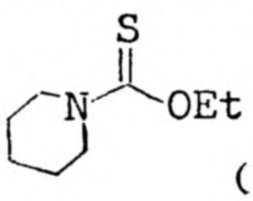
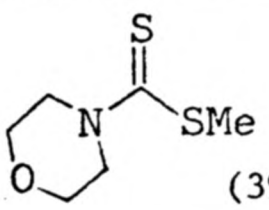
[a]Values taken from "The Aldrich Library of N.M.R. Spectra".

[b]Values taken from Johnson and Jankowski's "Carbon-13 N.M.R. Spectra".

[c]Reference 69

TABLE 2

^{13}C N.M.R. Chemical Shifts

Compound				
 [a] (40)			196 or 201	51
 [b] (18)	186	46 & 50		
 [c] (39)			198	50

[a]Meunier's sample.

[b]See p. 26 and 80

[c]Reference 69

The chemical shifts of the methyl and benzyl groups in the n.m.r. spectra of (37) and (38) are: δ_H 2.4 and 4.0, δ_C 17 and 38 respectively. Reference to Table 1 shows these values to be representative of groups attached to sulphur rather than oxygen (i.e. favouring (A) over (B)). The relevant ^{13}C n.m.r. data (see Table 2) are: δ_C 47 and 50 ($-\underline{C}H_2-N$), 184 ($\underline{C}=S$) for both (37) and (38). These figures are very similar to the values found for the monothiocarbamate (18) (Table 2) thus corroborating that the structures of (37) and (38) are represented by (A).

It may be noted that at room temperature the rates of rotation about the carbon-nitrogen bond in the monothiocarbamates (18,37A & 38A) are slow enough for two signals to be seen in ^{13}C n.m.r. for the two methylene groups α- to nitrogen whereas in the dithiocarbamate† (39) only one signal is seen. On cooling the $CDC\ell_3$ solution of (39) to -50^oC, however, the ^{13}C n.m.r. spectrum becomes: δ_C 20 (q, $-S\underline{Me}$), 49.6 and 50.6 (t, $-\underline{C}H_2-N$), 65.5 and 66.2 (t, $-\underline{C}H_2-O$), 198 (s, $\underline{C}=S$).

The minimum rate of rotation about the carbon-nitrogen bond for coalescence of the methylene signals in the ^{13}C n.m.r. spectrum to occur is given by expression (a)[70].

$$k_c = \frac{\pi \Delta\nu}{\sqrt{2}} \qquad (a)$$

†$RCOCH_2SCS.\overline{N(CH_2)_2OCH_2CH_2}$, R = Me or Ph, show similar behaviour in their ^{13}C n.m.r. spectra.

k_c = rate constant for interconversion at the temperature (T_c) at which coalescence occurs. $\Delta\nu$ = the difference in frequency between the two signals.

The coalescence temperatures for the methylene signals of (39) are *ca* 12°C and 17°C for $-\underline{C}H_2-N$ and $-\underline{C}H_2-O$ respectively. Using these figures one obtains for (39):

At 17°C $\quad k_c \simeq 173\ sec^{-1}$

At 12°C $\quad k_c \simeq 107\ sec^{-1}$

In the ^{13}C n.m.r. spectrum of the monothiocarbamate (18), two signals are observed for the methylene groups β- to nitrogen, separated by 10.3 Hz (0.46 ppm). Since the peaks are not coalesced it follows that:

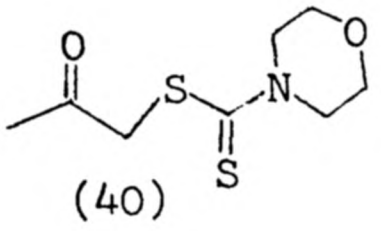
At 35°C $\quad k < 23\ sec^{-1}$

where k is the rate constant for interconversion.

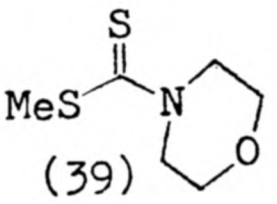
Thus rotation about the carbon-nitrogen bond in the dithiocarbamate (39) is faster (at a given temperature) and therefore easier than analogous rotation in the monothiocarbamate (18). It is not clear why the presence of oxygen rather than sulphur makes rotation about the carbon-nitrogen bond more difficult.

Having shown that Meunier's observations were consistent with the reactions shown in Scheme 35, non-aqueous basic conditions were sought that might allow the sequence shown in Scheme 36 to be achieved. Although Meunier's work related to S-(2-oxoaryl)-

dithiocarbamates (31), the acetonyl compound (40) was chosen for investigation.



(40)

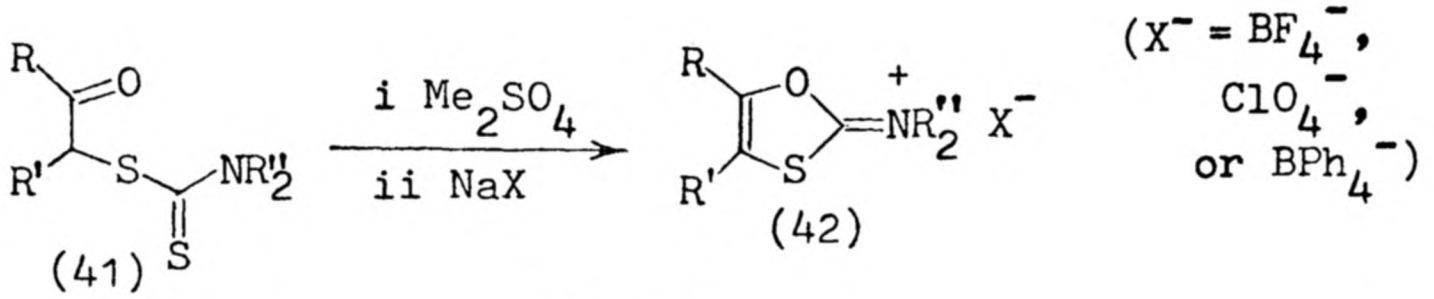


(39)

Treatment of (40) with sodium hydride or potassium t-butoxide in THF or dichloromethane gave, after addition of iodomethane, mixtures of recovered starting material (40) and the S-methyldithiocarbamate (39). The use of LDA or potassium hydroxide in methanol as base gave rise to complex mixtures containing none of the desired material (on the basis of the absence of olefinic proton signals in the ^{1}H n.m.r. spectrum). Treatment of (40) under the basic conditions used by Meunier gave, as above, the S-methyldithiocarbamate (39). (39) may arise from methylation of the dithiocarbamate group at sulphur followed by nucleophilic displacement α- to the carbonyl group.

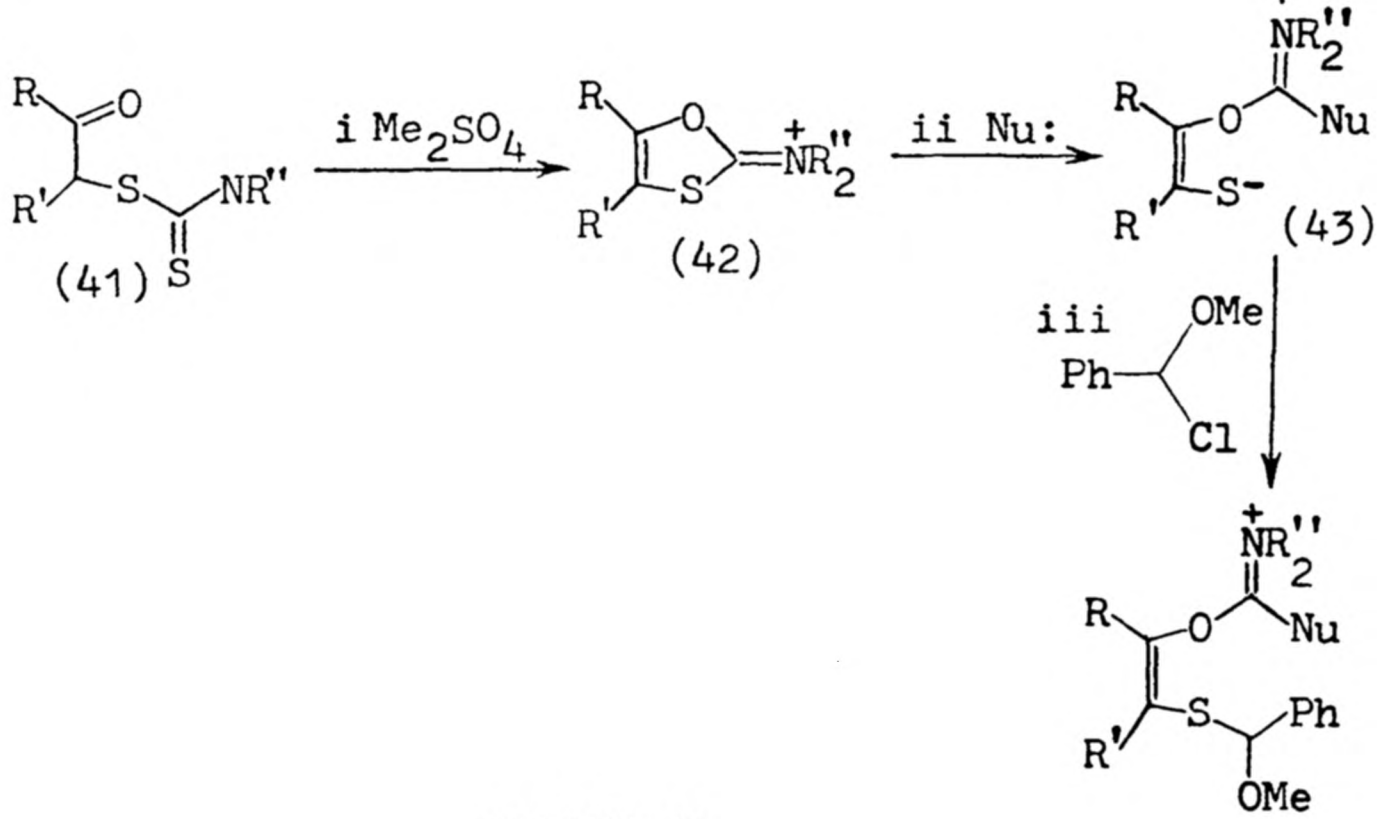
The apparent lack of generality of the intramolecular rearrangement proposed in Scheme 35 led to the decision that this route to α-(α' - methoxybenzylthio)ketones (8) was not worth pursuing further.

A related known reaction of S-(2-oxoalkyl)dithiocarbamates (41) is shown in Scheme (38)[71,72].



SCHEME 38

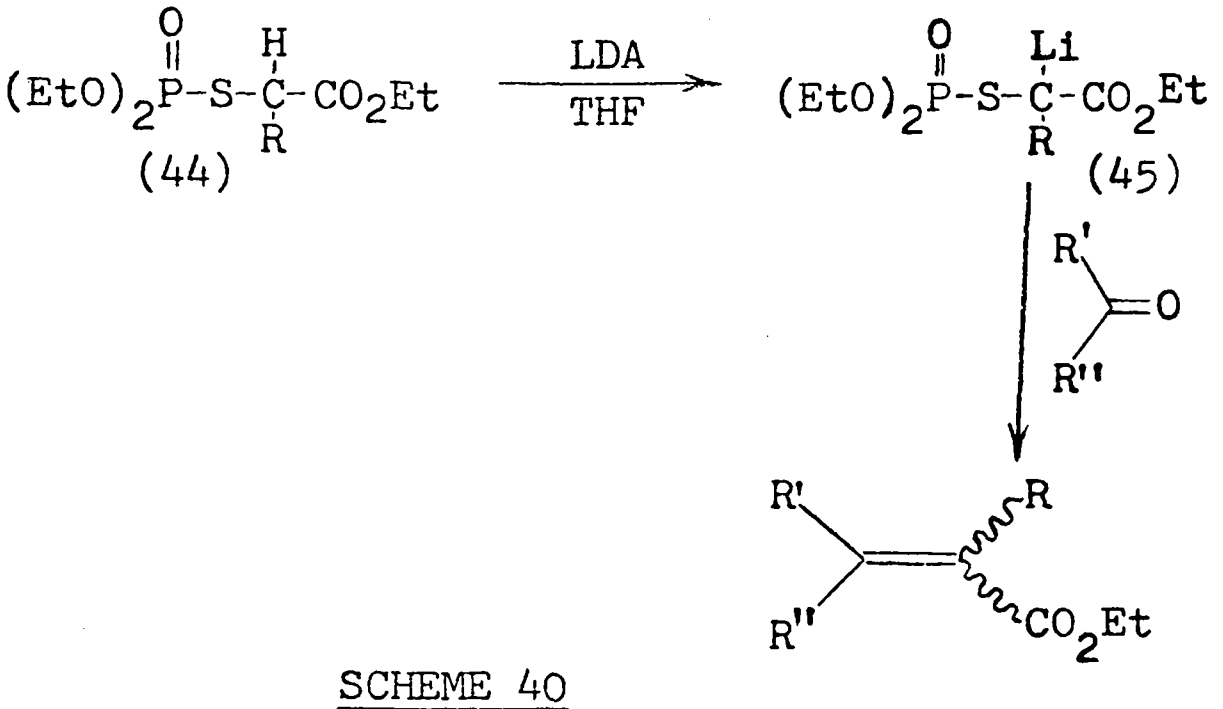
It was hoped that conditions could be found for formation and opening of the heterocycles (42) <u>in situ</u> to give adducts (43) which could be alkylated on sulphur using (α-chlorobenzyl)methyl ether, (Scheme 39). Attempts to effect such transformations on the dithiocarbamates, (40) and (41, R,R' = $-(CH_2)_4-$), proved unfruitful.



SCHEME 39

2(vi) S-(2-Oxoalkyl)-O,O-diethylphosphorothiolates

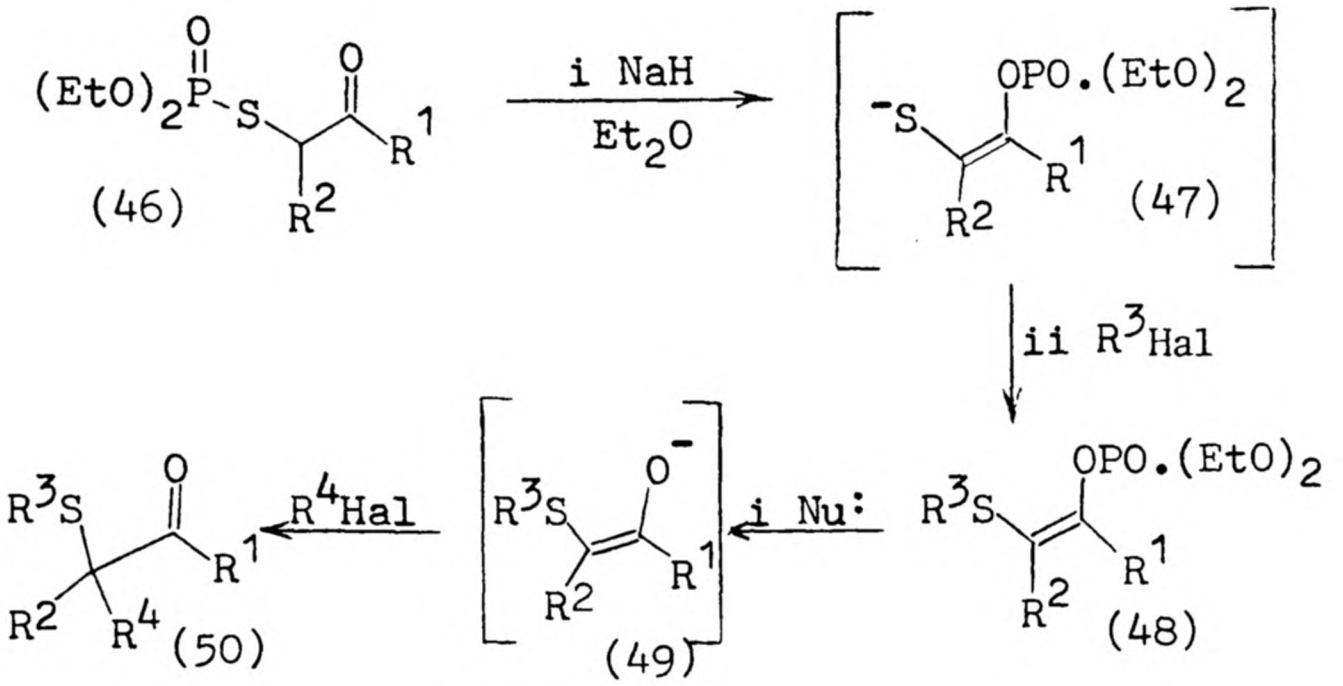
S-(2-Alkoxycarbonyl)-O,O-diethylphosphorothiolates (44) were used by Tanaka et al[73] in a synthesis of αβ-unsaturated esters (Scheme 40).



SCHEME 40

S-(2-Oxoalkyl)-O,O-diethylphosphorothiolates (46), however, react with LDA or sodium hydride, not to give a stable anion like (45) but apparently a thiolate (47) as shown by the products of reactions with alkyl halides[74] (Scheme 41). The thiolate (47) probably results from phosphoryl transfer via the enolate ion. This process is analogous to the reactions of S-(2-oxoalkyl)-dithiocarbonates discussed earlier (see p. 35).

If the thiolate (47) reacted with (α-chlorobenzyl) methyl ether (R^3 Hal in Scheme 41) to give an (α-methoxybenzyl)thio compound (48, R^3 = PhCH(OMe)-) and the latter reacted with a nucleophile and an alkylating agent as in Scheme 41, then a substituted α-(α'-methoxybenzylthio)ketone (49, R^3 = PhCH(OMe)-) would result. This was the reason for our interest in the reaction.



SCHEME 41

Since the enol phosphate (48) was formed under anhydrous conditions, it was hoped that formation of the α-methoxybenzylthio compound (48, R^3 = PhCH(OMe)-) would not prove too difficult.

Sturtz and Baboulene[74] did not report any chemistry of the enol phosphates (48) (except in toxicological tests) though they suggested that compounds (48) were more easily hydrolysed than enol phosphates not containing the thio group. We hoped to find anhydrous conditions that would cleave the phosphorus - oxygen bond of the enol phosphate (48) to give an enolate (49) which would be alkylated to give a β-(alkylthio)ketone (50) (Scheme 41).

The use of aqueous acid or base for the hydrolyses of enol phosphates is quite well documented[75,76] but there are references to anhydrous conditions being used[77,78]. However, there is a report of the enolate formed from an enol phosphate being unstable to the conditions required for the phosphorus - oxygen bond cleavage[79].

S-(2-Oxopropyl)-O,O-diethylphosphorothiolate (46, R^1 = Me, R^2 = H) was made according to the procedure described in Houben Weyl[80]. The phosphorothiolate was then subjected to the

conditions used by Sturtz and Baboulene and gave the enol phosphate (48), (Scheme 41, R^1 = Me, R^2 = H, R^3 = Me) in 65% yield.

The conditions to which the enol phosphate (48) was subjected in the hope of revealing, and alkylating on carbon, the enolate (49) are summarised in Table 3. Since none of the desired products were detected, it was decided not to pursue further this route to substituted α-(α'-methoxybenzylthio)ketones.

TABLE 3

Attempted Cleavage/Alkylation of Enol Phosphate (48)

(1) Reactions from which starting material was recovered:

1) n-Bu_4NF[a] in THF (reflux) or PhMe (reflux) or DMSO (140°), for 1h; 20° for 16h. 2) MeI

1) $NaNH_2$, NH_3, 30 min. 2) MeI

1) NaOEt, EtOH, reflux 1h; 20° for 16h. 2) MeI

1) $Ba(OH)_2$, THF, reflux 30 min. 2) MeI, reflux 16h

1) KOH, PhMe, 30° for 45 min. 2) MeI

(2) Reactions which gave complex mixtures of products not including $CH_3CO.CH(Me)SMe$ or $CH_3CO.CH_2SMe$[b] in an amount easily detected by ^1H n.m.r.

1) MeLi, THF, reflux 4h. 2) MeI

1) n-BuLi, THF, reflux 4h. 2) MeI

1) $LiAlH_4$, Et_2O, reflux 16h. 2) MeI (some S.M.[c])

1) $LiAlH_4$, THF, reflux 100 min. 2) MeI

1) KOH, PhMe, 60°, 10 min. 2) MeI (some S.M.[c])

1) KOH, PhMe, reflux 1h. 2) MeI

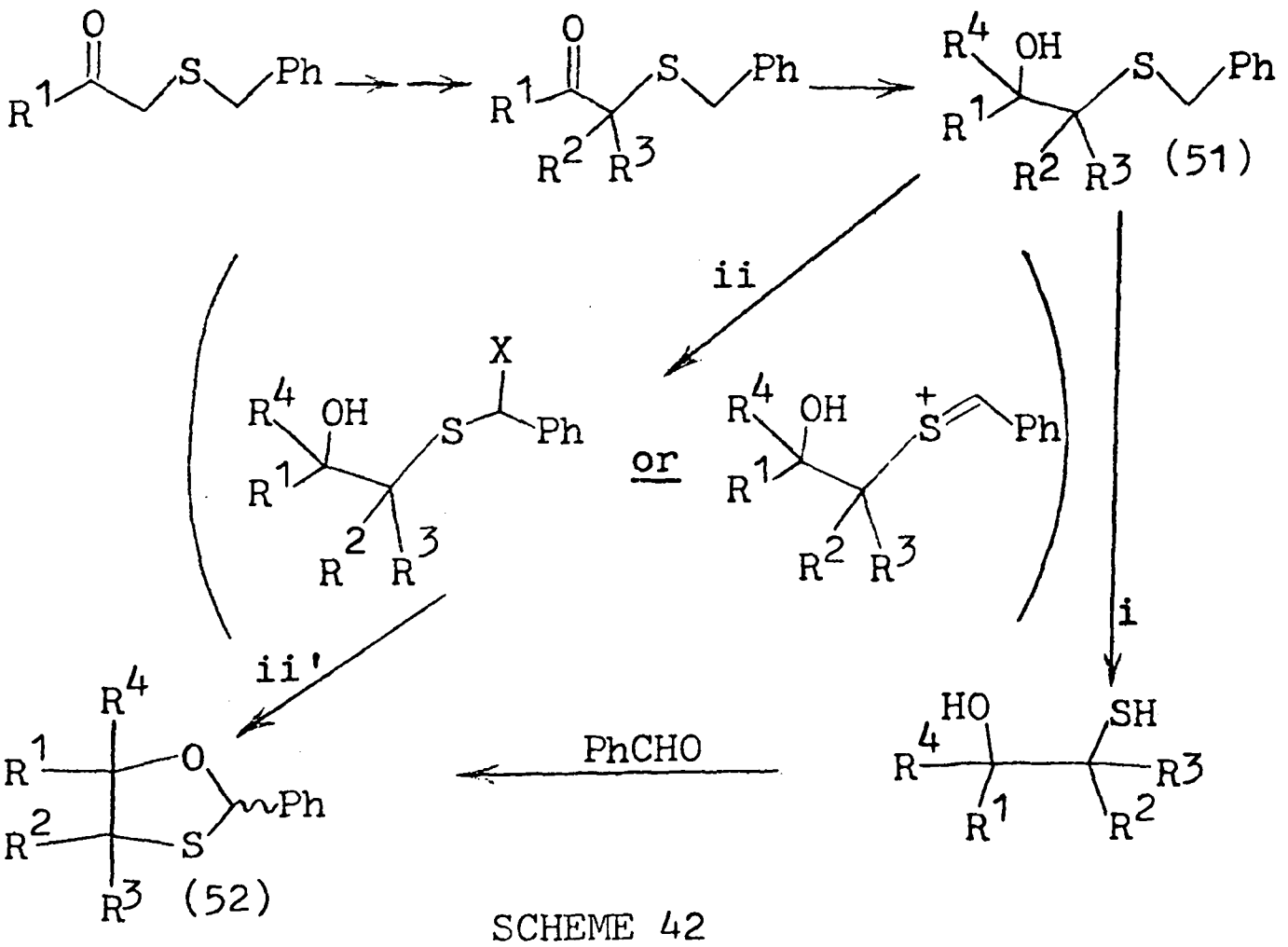
[a]Prepared by addition of HF to n-Bu_4NOH[81]. [b]See p. 29 and 83 .
[c]Some starting material (S.M.) was observed in the product.

CHAPTER 3

Attempted Use of the Pummerer and Related Reactions in the Preparation of α-Substituted Benzylthio-Compounds

Quite early in this work the use of the benzyl group as protection for sulphur[82], as outlined in Scheme 42, was considered (see Chapter 4). The simple oxidative relationship between the β-(benzylthio)alcohol (51) and the oxathiolan (52) led us to consider alternatives to the deprotection and condensation with benzaldehyde shown in pathway (i) (Scheme 42).

One such alternative was the introduction of benzylic functionality at the β-(benzylthio)ketone stage (c.f. Chapter 2). Another alternative was the functionalisation of the benzylic position in the β-(benzylthio)alcohol (51) to give an intermediate which might either cyclise *in situ* or be easily converted to the oxathiolan (pathway (ii), Scheme 42).



SCHEME 42

The functionalisation of carbon α to sulphur can be achieved by the Pummerer rearrangement[83-85], but since this would involve two steps (the oxidation of the sulphide to sulphoxide followed by rearrangement), the direct functionalisation of the carbon α - to sulphur was more attractive. Substitution α to sulphur in benzylthio compounds has been discussed by Wilson[86] and is quite well known for other sulphides[87] such as, for example, in compounds related to penicillins[88] and cephalosporins[89]. A reagent frequently used for this type of transformation is N-chlorosuccinimide (NCS)[86,90-92] though other oxidants have been used successfully[88,89,93]. In exploratory experiments 2-(benzylthio)-1-phenylethanol (53) was treated with NCS in toluene under various conditions, some of which are shown in Table 4. Under the conditions used there was no significant formation of any desired product (on the basis of ^{1}H n.m.r.). A solid, however, crystallised from the crude products, this was identified as the sulphoxide (55) on the basis of its physical data (p. 86). The sulphoxide was shown to represent more than 50% of the crude product from the ^{1}H n.m.r. spectra.

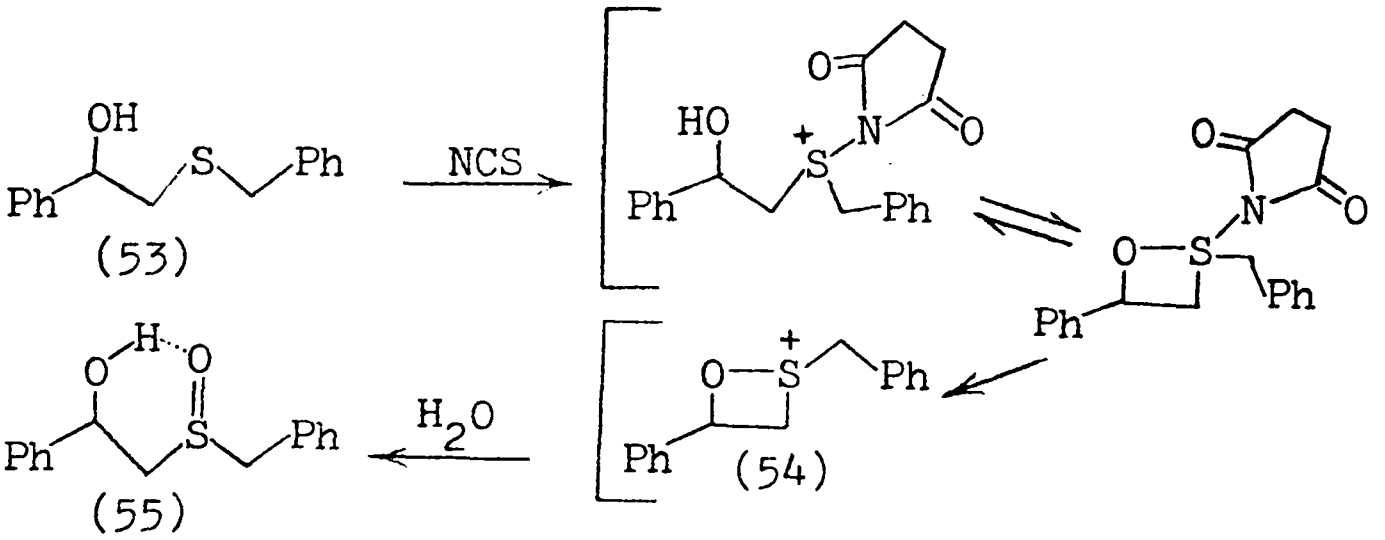
TABLE 4

Oxidation of 2-(Benzylthio)-1-phenylethanol (53)

Conditions	Ratio of diastereomers[a] in product (55)
NCS, PhMe, - 78°	2:1
NCS, NEt_3, PhMe, 0°	0:1
NCS, MeOH, 20°	1:1
Br_2, $CC\ell_4$, - 20°	1:1

[a]The diastereomer having a signal at δ_H ($CDC\ell_3$) 4.1 is (arbitrarily) put before that having a signal at δ_H 4.0.

The oxidation of (53) to (55) may be rationalised in terms of neighbouring group participation by -OH, perhaps as outlined in Scheme 43. This type of hydroxyl participation in the oxidation of sulphides to sulphoxides has been observed previously[94,95] and Glass has isolated an intermediate similar to (54) though with a six-membered ring.

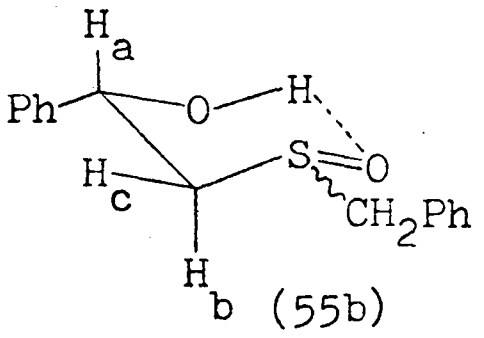


SCHEME 43

It is interesting to note the marked effect that triethylamine has on the ratio of diastereomers formed in the oxidation of (53) by NCS.

The β-hydroxysulphoxide (55) shows strong intramolecular hydrogen bonding. In the infrared spectrum this is manifest in the low frequency of the broad -OH stretch at 3350 cm^{-1}, compared with 3520 cm^{-1} in the hydroxysulphide (53). The ^1H n.m.r. spectrum suggests a conformation as shown in (55b), thus J_{ab} is 9.5-10 Hz

and J_{ac} is 1.5 Hz.



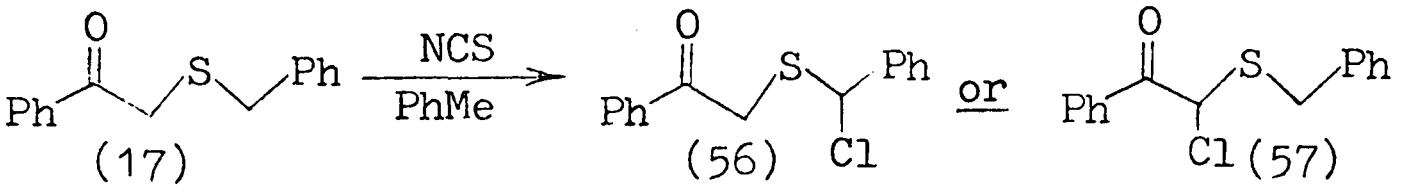
(55b)

The reaction of NCS with 1-(benzylthio)-2-phenyl-2-propanol was also carried out and, although the reaction was not as clean, again the corresponding sulphoxide was formed.

Some preliminary experiments were carried out on the β-hydroxysulphoxide (55) in the hope that the oxathiolan (21) might be formed *via* a Pummerer reaction. However, treatment of (55) with acetic anhydride[83] or trifluoroacetic anhydride[96] gave no detectable (^{1}H n.m.r.) oxathiolan (p. 81).

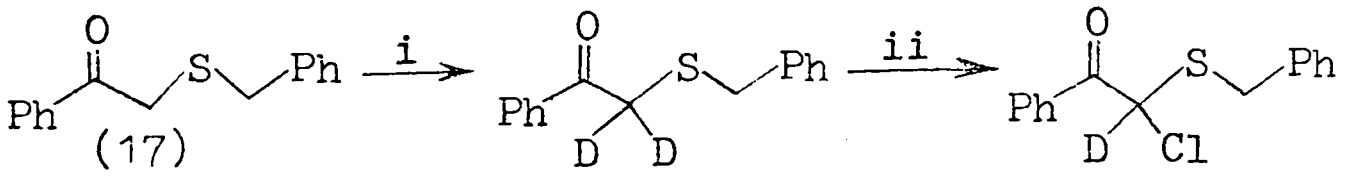
In the α-(benzylthio)ketone precursors, (17) and (59), there is no opportunity for participation by -OH in a reaction with NCS. However, the position between the thio and the carbonyl groups is now activated.

α-(Benzylthio)acetophenone (17) (see p.90) has ^{1}H n.m.r. signals at δ 3.65 and 3.74 corresponding to the two methylene groups. Reaction with NCS gave a material which could be either the α-(α'-chlorobenzylthio)ketone (56) or the α-(benzylthio)-α-chloroketone (57) (Scheme 44) on the basis of the ^{1}H n.m.r. spectrum.



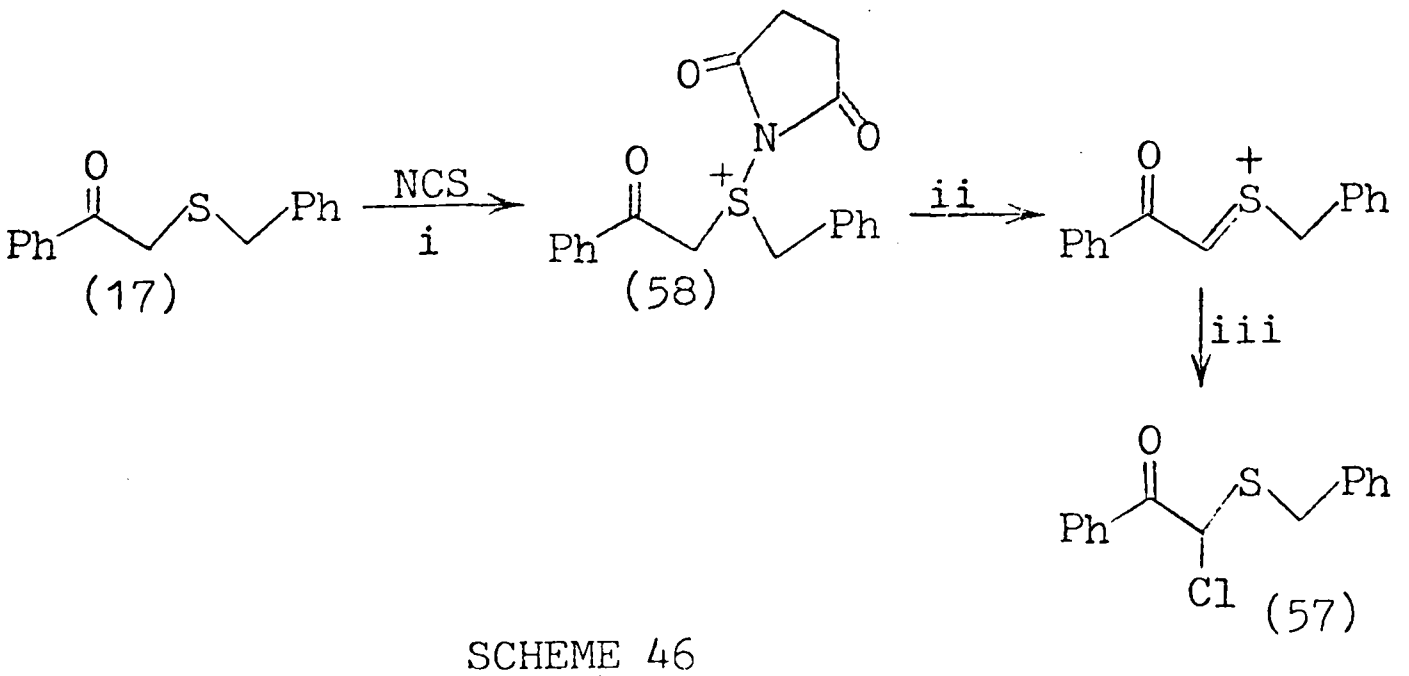
SCHEME 44

The assignment of the methylene peaks in the ^1H n.m.r. spectrum of (17) and the position of chlorination were determined by the reactions shown in Scheme 45. Further confirmation was obtained by the reaction of (57) with sodium methoxide in methanol which gave a methoxy compound with a different ^1H n.m.r. spectrum to that of α-(α'-methoxybenzylthio)acetophenone (see p. 88).



SCHEME 45 : i $NaOD, D_2O$, dioxan; ii NCS, toluene.

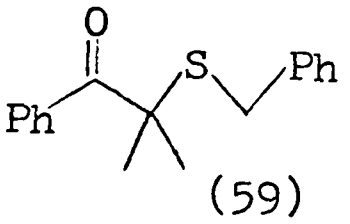
On the basis of the course normally assumed for the reaction of sulphides with NCS[85,86], the chlorination α- to carbonyl in (17) may be rationalised in terms of the greater acidity of the proton removed in step (ii) (Scheme 46).



SCHEME 46

In the α-dimethylated phenacyl compound (59) there are no protons α- to the carbonyl group and so it was hoped that a benzylic proton would be lost from an intermediate analogous to (58), giving rise to chlorination in the desired benzylic position. Reaction of (59) with NCS in toluene, however, gave mostly recovered starting material and none of the desired product was detected (by ^{1}H n.m.r.).

Thus the use of Pummerer and related reactions in approaches to oxathiolans seemed unlikely to be useful and this approach was not pursued further.

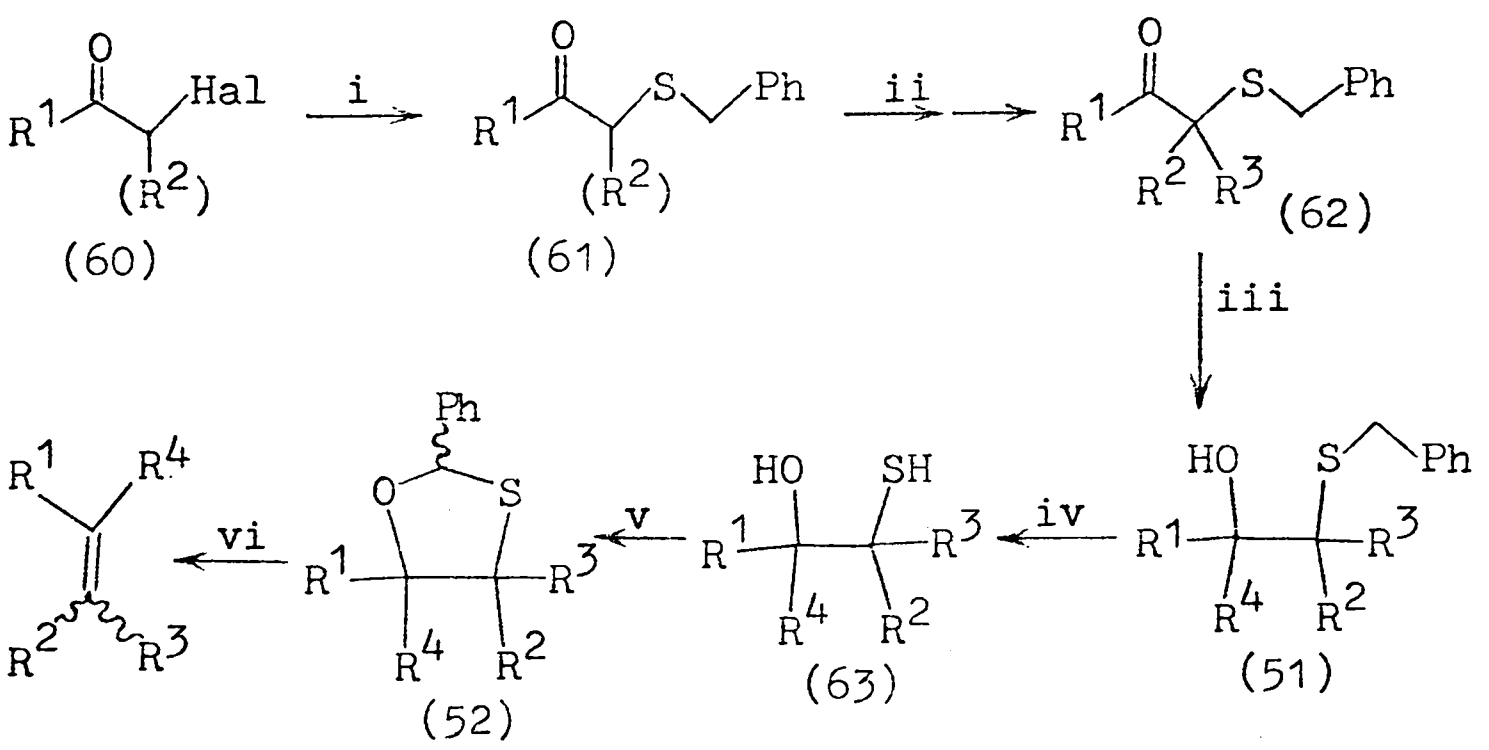


(59)

CHAPTER 4

Preparation of Oxathiolans from α-(Benzylthio)ketones

In peptide chemistry the use of the benzyl group as protection for thiols - especially for cysteine - is well known[82]. Thus it was thought that the use of α-(benzylthio)ketones in the preparation of substituted 2-phenyl-1,3-oxathiolans (52) as outlined in Scheme 47 might prove feasible.



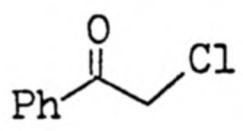
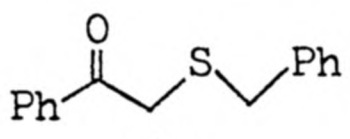
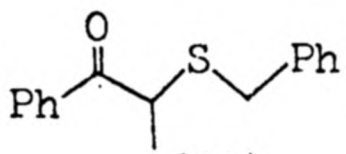
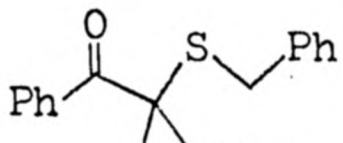
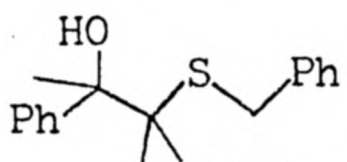
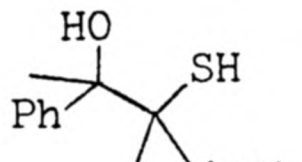
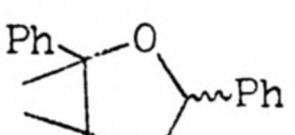
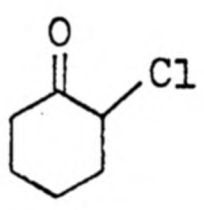
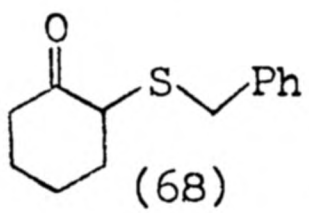
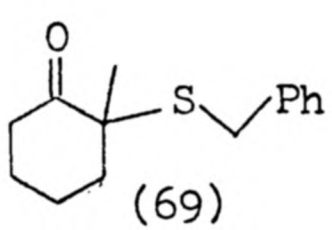
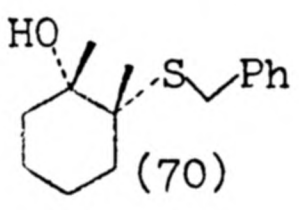
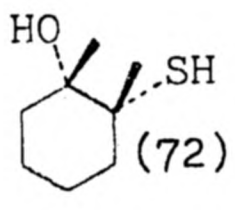
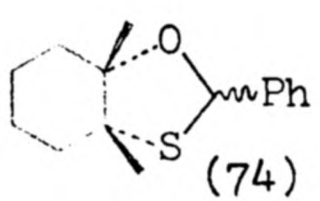
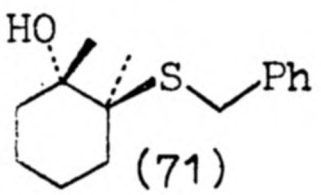
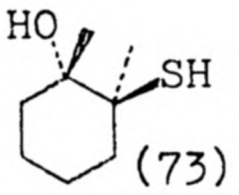
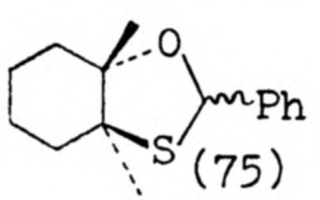
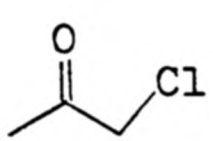
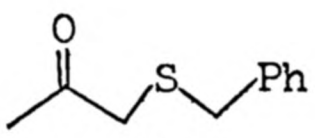
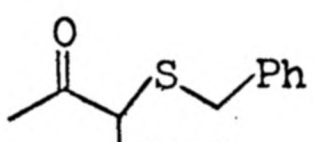
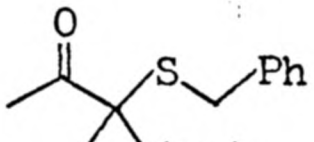
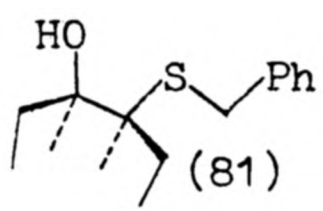
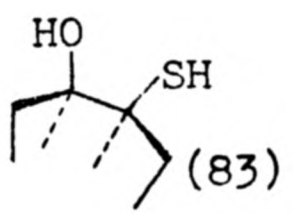
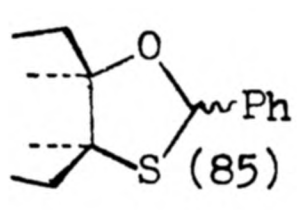
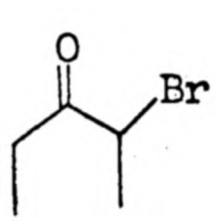
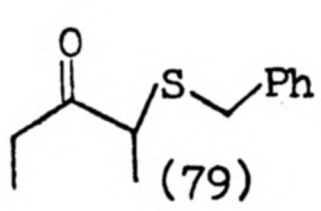
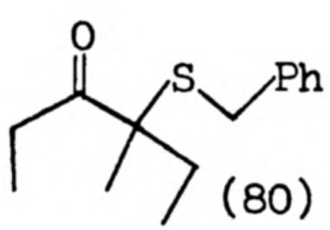
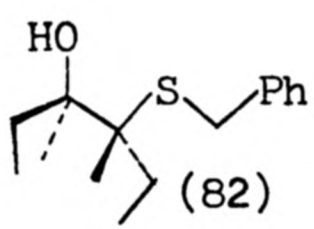
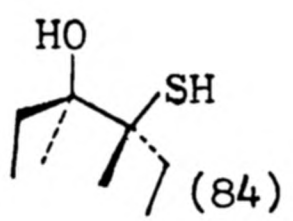
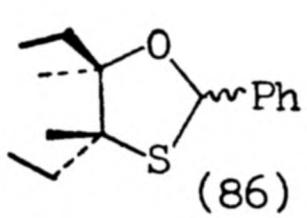
SCHEME 47

The steps i-v of Scheme 47 will be dealt with, in turn, in this chapter and the oxathiolan cycloreversion - step vi - will be discussed in the next chapter.

Three different systems were chosen in order to investigate the generality of this approach to the synthesis of oxathiolans

TABLE 5

Preparation of Oxathiolans from α-(Benzylthio)ketones

α-haloketone	α-(benzylthio)-ketone	alkylated α-(benzylthio)-ketone		β-(benzylthio)alcohol	β-mercaptoalcohol	oxathiolan
	 (17)	 (64)	 (59)	 (65)	 (66)	 (67)
	 (68)	 (69)		 (70)	 (72)	 (74)
				 (71)	 (73)	 (75)
	 (76)	 (77)	 (78)	 (81)	 (83)	 (85)
	 (79)	 (80)		 (82)	 (84)	 (86)

(Table 5). The systems consisted of compounds derived from (a) α-chloroacetophenone, (b) 2-chlorocyclohexanone and (c) two aliphatic α-haloketones.

4(i) α-(Benzylthio)ketones (c.f. step (i), Scheme 47)

The α-haloketones (60) used in the preparation of the α-(benzylthio)ketones were obtained from commercial sources except for 2-bromo-3-pentanone[97].

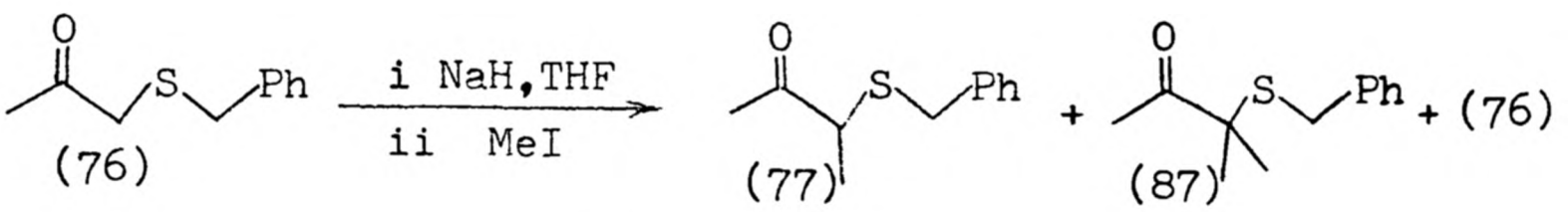
The introduction of the benzylthio group was accomplished by nucleophilic displacement involving the α-haloketone (60) and benzylthiolate anion. Early attempts at the displacement using potassium hydroxide in ethanol to generate the thiolate anion did not proceed cleanly, whereas the use of triethylamine in ether gave excellent yields of materials that were generally pure enough to be taken through to the next stage of the reaction without further purification (see Table 10, p. 89).

4(ii) α-Alkylated-α-(benzylthio)ketones (c.f. step (ii), Scheme 47)

Selective alkylation α to the carbonyl and benzylthio groups was achieved by the use of sodium hydride (a slight excess) in THF, followed by iodomethane or iodoethane (Table 11, p. 92).

Although it was found possible to obtain a clean sample of mono-methylated α-(benzylthio) acetophenone (64) by careful control of the amount of sodium hydride used, similar treatment of the acetonyl compound (76) gave a mixture of recovered starting

material and the mono- (77) and di-alkylated (87) products (Scheme 48).



SCHEME 48

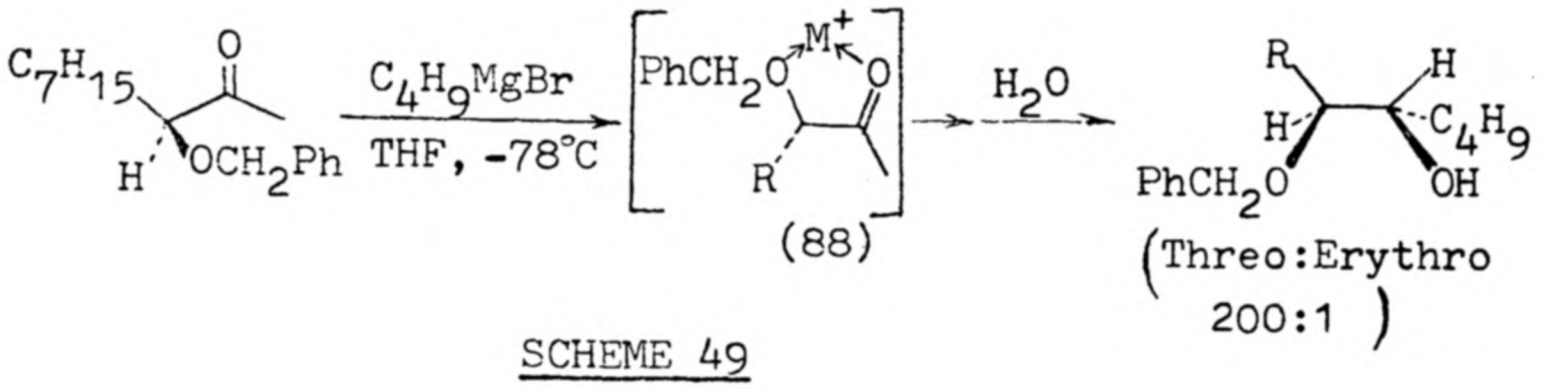
The latter were found to be difficult to separate by chromatography or distillation. Use of one equivalent of sodium 2-methyl-2-butoxide in benzene[98] (Conia's base), however, gave the mono-methylated compound (77) with a small amount of recovered starting material which was removed quite easily by a bisulphite wash.

Although the dimethylated phenacyl compound (59) could be prepared directly from α-(benzylthio)acetophenone (17), this reaction was not very clean and methylation of the mono-methylated compound (64) was found to be a more convenient preparation.

4(iii) β-(Benzylthio)alcohols (c.f. step (iii), Scheme 47)

The stereoselectivity of the reaction of the organometallic reagent with the α-alkylated-α-(benzylthio)ketone (62) is, as mentioned in the introduction (p. 13), the factor which determines the relative amounts of the stereoisomeric olefins eventually formed - provided the intervening steps are stereospecific.

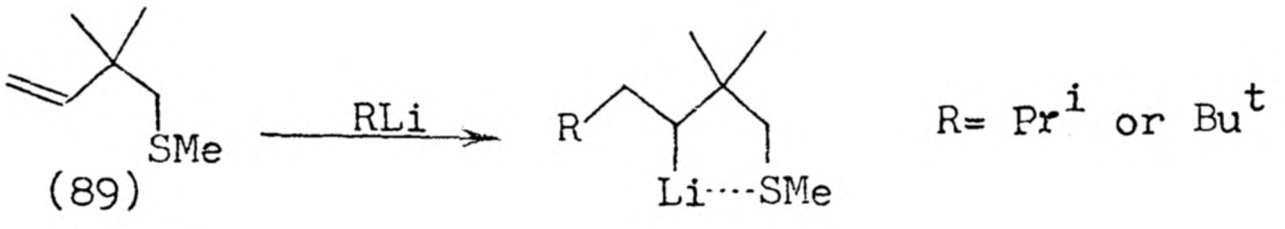
In the light of the known stereoselectivity of Grignard reactions on α-(benzyloxy)ketones[99] (Scheme 49), it was hoped that the benzylthio group might prove a useful 'handle' to influence stereoselectivity in nucleophilic attack at the carbonyl group of (62).



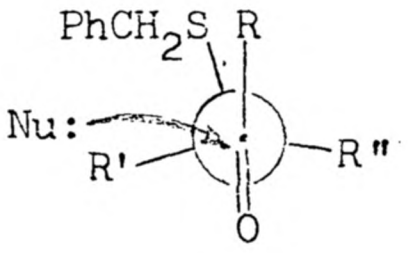
SCHEME 49

Analogues of the chelate complex (88) in Scheme 49 are considered to be the product determining intermediates in many organometallic reactions with ketones containing an α-substituent capable of coordinating to the cationic part of the reagent[100]. Sulphides are known to coordinate well with palladium (II)[101], mercury (II)[102], platinum (II)[103] and other acceptor ions in the same area of the periodic table [104,105]. However, for most cations (e.g. magnesium (II) and lithium (I)), the coordinating ability of ethers is significantly higher than that for the corresponding sulphides[104]. One example in which coordination between sulphur and lithium does influence a reaction is the nucleophilic attack on a double bond shown in Scheme 50[106]. If the methylthio group in (89) is replaced by a proton then no addition occurs.

If a chelate complex analogous to (88) is not formed in organometallic reactions with α-(benzylthio)ketones then, by analogy with α-haloketones, one might expect that in the transition state of the reaction the benzylthio group and the carbonyl group would preferentially be oriented approximately anti-periplaner to each other[100] (Scheme 51). Nucleophilic attack at the then least hindered face of the carbonyl group would lead to the diastereomer that would be disfavoured if the chelate complex were an intermediate.



SCHEME 50



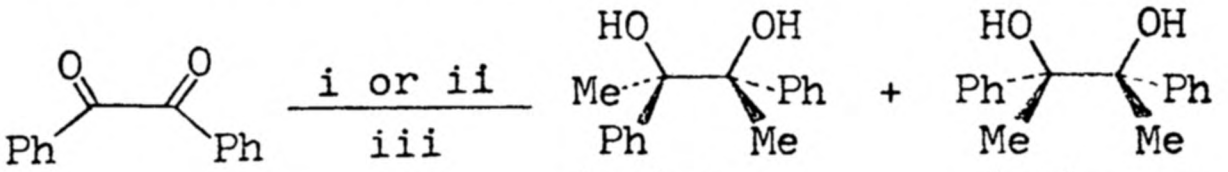
(R" is larger than R')

SCHEME 51

Alkyllithium reagents are known to be stereoselective in reactions with chiral ketones[107]. Recently Reetz et al.[108] reported high stereoselectivity in reactions of alkyltitanium reagents with ketones (giving in some instances the opposite stereoselectivity to that observed for the alkyllithium reagents). Thus alkyllithiums, alkyltitanium and Grignard reagents were used in our investigations of reactions with α-(benzylthio)ketones.

The Grignard reagents were prepared by standard procedures[109]. Methyllithium was prepared by addition of bromomethane to lithium wire in ether[110]. The lithium dimethylcuprate-methyllithium reagent[107] was prepared by addition of methyllithium (2.66 equivalents) to copper (I) iodide in ether. Ethyllithium was prepared by slow addition of bromoethane in light petroleum (30-40°) to washed lithium shot in light petroleum. The petroleum was distilled off at reduced pressure and was gradually replaced by benzene, filtration gave the benzene solution of the ethyllithium[111], (it was not found possible to use benzene as the solvent for the initial reaction). Methyltitanium triisopropoxide†[108] (92) was prepared from chlorotitanium triisopropoxide‡[112] using the procedure described in Houben-Weyl[113]. The alkyllithium reagents were titrated by the double titration method of Gilman[114] (using 1,2-dibromoethane).

As a check on the methyltitanium reagent (92) benzil was treated (a) with the reagent (92) and (b) with methyllithium, the diastereomeric rations of product diols, (90) and (91), were the same as those found by Reetz et al[108], (Scheme 52).



(90) dl- (91) meso-

i $MeTi(Pr^iO)_3$ (92) gives ca 98:2 mixture of (90):(91)
ii MeLi gives ca 15:85 mixture of (90):(91)
iii NH_4Cl aq.

SCHEME 52

† $MeTi(OPr^i)_3$ (92): δ_H ($CDCl_3$) 0.55 (3H, s, -Me), 1.27 (18H, d, J 6.5 Hz), 4.55 (3H, septet, J 6.5 Hz).

‡ $ClTi(OPr^i)_3$: δ_H ($CDCl_3$) 1.35 (18H, d, J 6.5 Hz), 4.81 (3H, septet, J 6.5 Hz).

Addition of the methyltitanium reagent (92) (10 equivalents) to the α-(benzylthio)ketone (80) in 2,2,4-trimethylpentane at -50°C was followed by slow warming to 80°C[115]. After 40h a mixture of products was obtained containing a small amount of the desired β-(benzylthio)alcohols (81,82) but mostly recovered starting material. Similar treatment of the ketone (80) in refluxing THF or of 2-benzylthio-2 methylcyclohexanone (69) in refluxing light petroleum (60-80°) with the titanium reagent gave starting ketones after 20h.

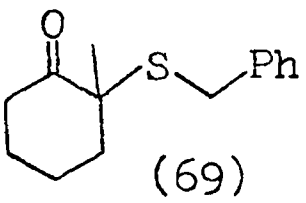
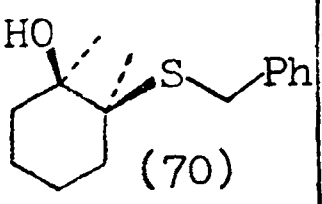
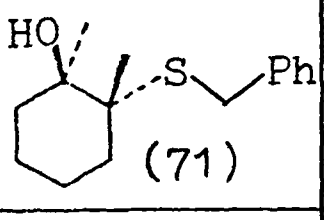
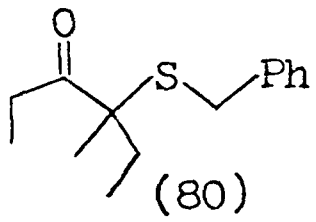
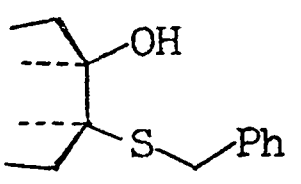
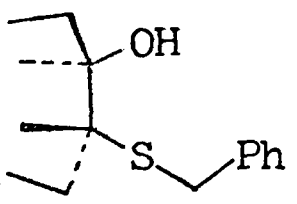
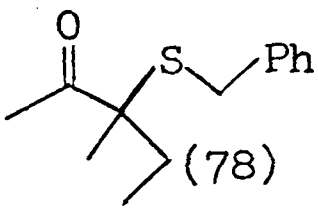
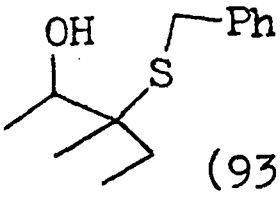
The α-(benzylthio)ketones were treated with alkyllithiums or Grignard reagents under various conditions. Some of the more successful reactions of the non-aromatic ketones are summarized in Table 6. Reactions of compounds in the phenacyl series are shown in Tables 12 and 13 (p. 96 and 99).

It may be noted that reactions with the alkyllithium reagents (entries 2, 5 and 7, Table 6) gave generally higher yields than reactions with Grignard reagents. The latter also gave rise to some enolisation and reduction (entries 3 and 8 and other experiments not recorded).

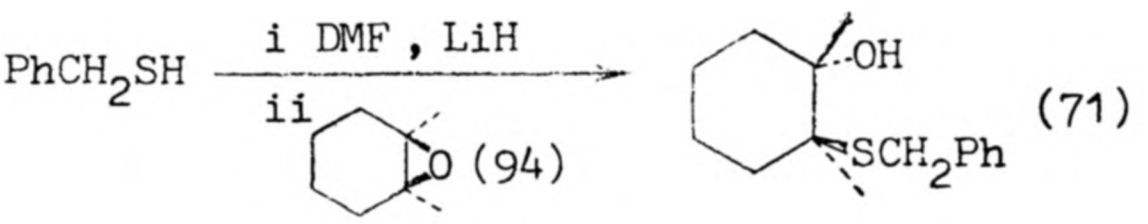
The stereochemistry of the products of reactions of 2-benzylthio-2-methylcyclohexanone (69) with organometallic reagents was established by comparison of the ^{1}H n.m.r. spectra with the spectrum of the product of opening 1,6-dimethyl-7-oxabicyclo[4.1.0]heptane with benzylthiolate ion (Scheme 53). There is precedence for <u>trans</u>- opening of the tetra-substituted epoxide (94) in the literature[116,117].

TABLE 6

Reactions of α-(Benzylthio)ketones with Organometallic Reagents

α-(benzylthio)-ketone	entry	conditions	products	crude product	overall yield
 (69)	1	MeMgI, Et_2O reflux	 (70)	(70) -75% (71) -25%	94% crude
	2	MeLi:LiBr, Et_2O -78° → 20°	 (71)	(70) ≥ 97% (71) ≤ 3%	97% crude
 (80)	3	MeMgI, THF 0° → reflux	 (81)	(80) -30% (81) -35% (82) -35%	52% [a] chromat-ography
	4	MeMgI, $MgBr_2$ Et_2O, reflux		(81) -40% (82) -60%	71% crude
	5	MeLi:LiBr, Et_2O -78° → 20°	 (82)	(81) -32% (82) -68%	66% distilled
	6	$LiMe_2Cu$:MeLi Et_2O, -65° → 0°		(80) -50% (81) -17% (82) -33%	95% crude
 (78)	7	EtLi, C_6H_6, Et_2O -2° → 20°		(81) -62% (82) -38%	89% crude
	8	EtMgBr, Et_2O reflux	 (93)	(78) -20% (81) -36% (82) -19% (93) -20%	99% crude

[a] The yield for entry 3 refers to an isolated mixture of the alcohols (81) and (82).



SCHEME 53

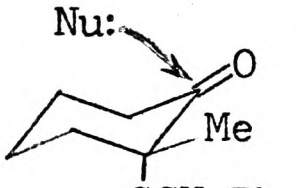
The assignment of stereochemistry for (81) and (82) was based on the stereochemistry of the mixtures of olefins formed in the subsequent oxathiolan cycloreversions (see p. 69 ff).

The alkyllithium reagents were generally more stereoselective than Grignard reagents in their reactions with α-(benzylthio)ketones, the selectivity being towards the same diastereomer with either reagent. For reactions of the aliphatic ketones, (78) and (80), the stereochemistry assigned to the predominant product is consistent with the transition state shown in Scheme 51. This may indicate that for the reaction under consideration an α-sulphur substituent is less prone to forming a cyclic chelate complex (as in 88) than is the oxygen analogue.

The stereoselectivity in the reactions of the aliphatic α-(benzylthio)ketones was disappointingly lower than in Still's[99] work on α-oxysubstituted ketones. It should perhaps be noted, however, that the diastereoselectivity found for the reactions that Still performed was due to the different steric effects of a proton and an alkyl group whereas in our reactions the relevant difference was between a methyl and an ethyl group.

The preferred direction of nucleophilic addition to the cyclohexanone derivative (69) is found to be from the opposite side of the carbonyl group to the benzylthio substituent. The preferred conformation for (69) appears to be that with the benzylthio

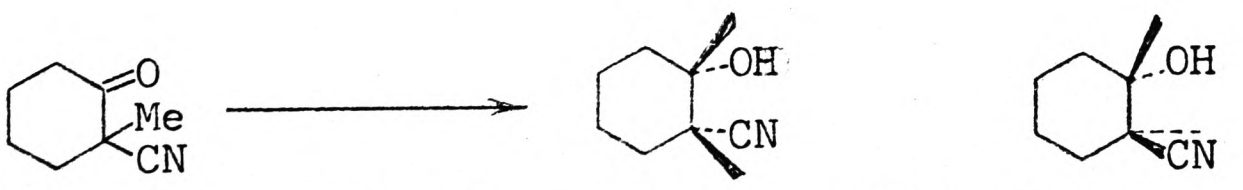
group axial (see p. 66). If this conformation is still dominant in the transition state for the addition then the nucleophile must approach from the axial side of the carbonyl group (Scheme 54) to give the major product. This may be the result of the steric influence of the benzyl group which is possibly weakly complexed to the carbonyl group.



(69)

SCHEME 54

The preferential formation of (70) in which the alkyl groups are cis- with respect to each other is in contrast to the products of the reactions of 2-cyano-2-methylcyclohexanone with organometallic reagents[117] (Scheme 55). A difference is also found in that the Grignard reagent is more stereoselective than the alkyllithium in the reactions shown in Scheme 55, in our reactions methyllithium was more stereoselective than methylmagnesium iodide

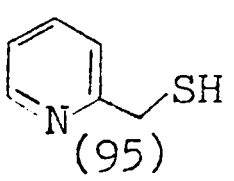


reagent	mixture of diastereomers		
MeLi	30	:	70
MeMgBr	0	:	100

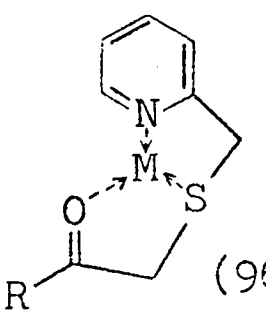
SCHEME 55

The two diastereomers, (70) and (71), formed in the reactions of the substituted cyclohexanone (69) were separated quite easily by chromatography. The alcohols, (81) and (82), in the aliphatic system, however, proved very difficult to separate† and the separation was not performed preparatively.

Although the reactions of the aliphatic ketones, (78) and (80), with organometallic reagents did not prove very stereoselective and did not give diastereomers that were easy to separate, there would still seem to be some scope for improvement in this quite crucial step of the oxathiolan synthesis. For example one might modify the protecting group on sulphur in such a way as to encourage chelation of a metal cation between the carbonyl oxygen and the α-thio substituent. In this respect the thiol (95) was prepared[118] in the hope that a substituted ketone such as (96) would form a stable chelate with the cation of an organometallic reagent as shown in the structure drawn for (96)



(95)



(96)

†Continuous elution of (81) and (82) on a silica gel plate (5 x 20 cm), using light petroleum: ether (19:1) as eluant, for 7 hours gave two distinct spots at 10.1 and 10.5 cm from the origin.

Attempts to improve the stereoselectivity of the reactions of α-thiosubstituted ketones in this way were not further investigated owing to lack of time.

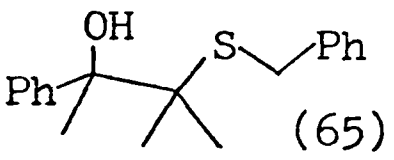
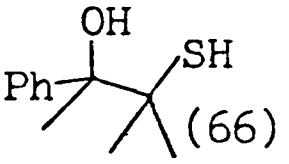
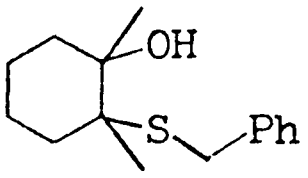
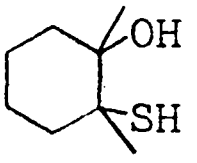
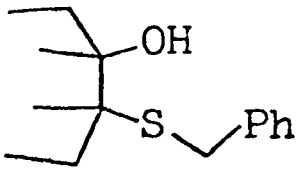
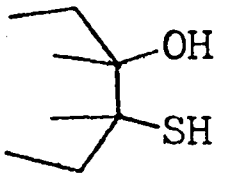
4(iv) β-Mercaptoalcohols (c.f. step iv, Scheme 47).

The cleavage of S-benzyl derivatives to reveal the thiol is generally achieved by treatment with sodium in ammonia[82]. Other conditions however, have been used for the cleavage and they include sodium/alcohol, hydrogen fluoride/anisole and electrolysis[82].

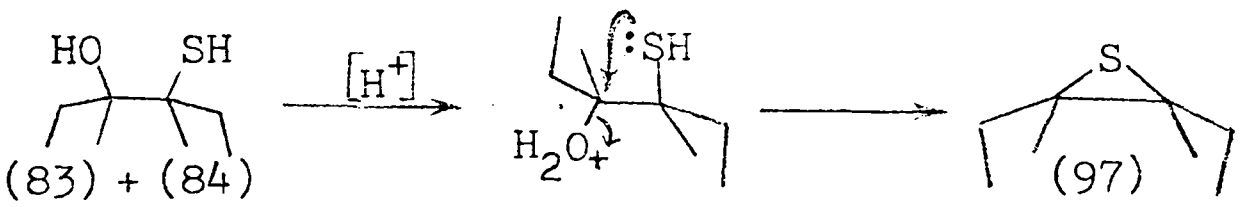
It was found that treatment of the β-(benzylthio)alcohols (51) with sodium in ammonia, essentially by the procedure used by Lowe et al[119], gave the β-mercaptoalcohols (63) in reasonable yields (Table 7).

TABLE 7

Cleavage of the S-Benzyl Group in β-Benzylthioalcohols

β-benzylthioalcohol	β-mercaptoalcohol	crude yield
 (65)	 (66)	88.5%
 (70) + (71)	 (72) + (73)	81.5%
 (81) + (82)	 (83) + (84)	62%

The isolation of the thiols was achieved by extraction into base, acidification and re-extraction into organic solvents. Yields were improved by repeated extractions during the isolation procedure and by cautious acidification of the basic aqueous solution. In the latter respect, the use of concentrated hydrochloric acid in the isolation of the β-mercaptoalcohols (83,84) gave rise to the formation of an unstable compound tentatively identified as the episulphide† (97) which could have arisen as shown in Scheme 56.



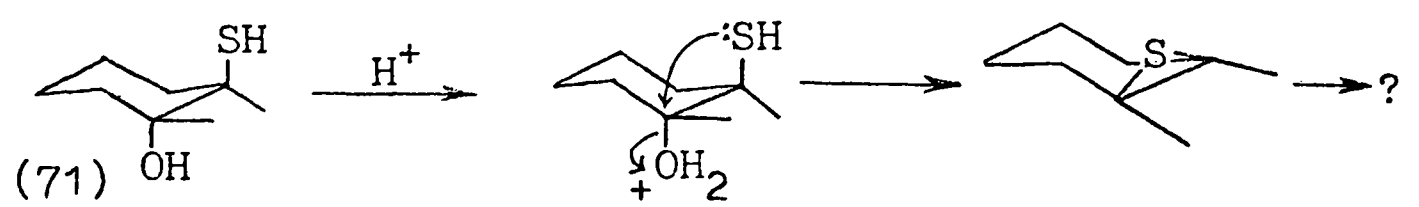
SCHEME 56

† δ_H ($CDCl_3$) (2 diastereomers) 1.08 (12H, q, J 7.5 Hz, Me-CH_2-), 1.60 (6H, s, Me-C-S), 1.61 (6H, s, Me-C-S), 1.76-1.99 (8H, m, Me-CH_2-); ν_{max} (liquid film) 2960, 1460, 1370, 1070 cm^{-1}.

Generally the isolated products (63) were quite pure and only the cyclohexanol derivative (72,73), which was a solid, was purified before condensation of the mercaptoalcohol with benzaldehyde (step v, Scheme 47), (see Table 8). Owing to the lability of the β-mercaptoalcohols it was considered desirable to perform the conversion to the oxathiolan without delay. The ^1H n.m.r. spectra of the mercaptoalcohols showed the diastereomeric ratios to be approximately the same as in the starting β-(benzylthio) alcohols.

4(v) 2-Phenyl-1,3-oxathiolans (c.f. step v, Scheme 47)

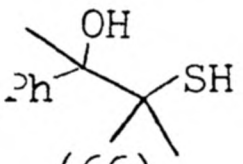
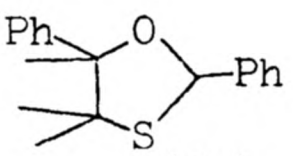
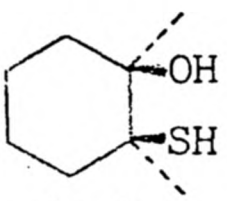
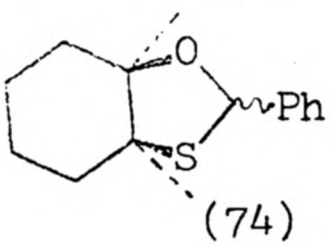
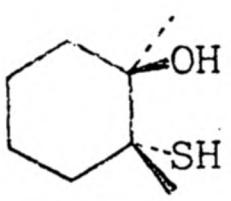
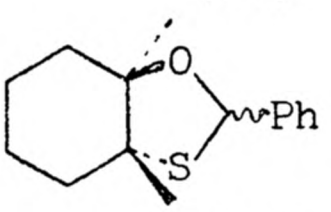
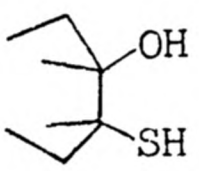
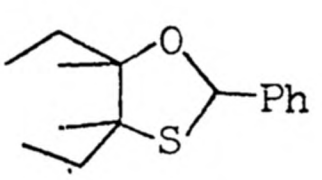
The β-mercaptoalcohols (63) were condensed with benzaldehyde under standard conditions[21]. (See Table 15, p.105). The oxathiolans (52) were formed cleanly except in the case of the substituted cyclohexanol (73), (Table 8). Treatment of (73) with benzaldehyde and p-toluenesulphonic acid gave a mixture of products containing little if any of the desired oxathiolan (75) (based on the ^1H n.m.r. spectrum). (73) was in fact unstable to the acidic conditions used for the condensation (see p.106), this may be rationalised by a process such as shown in Scheme 57 (c.f. Scheme 56). The oxathiolan (75) would in any case be relatively difficult to form since a trans-fusion between a six and a five membered ring is quite strained.



SCHEME 57

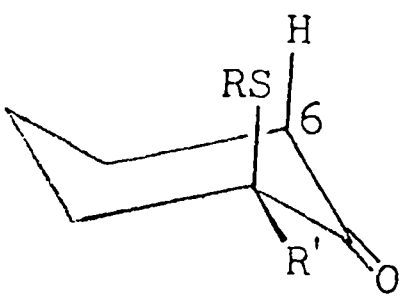
TABLE 8

Formation of 2-Phenyl-1,3-oxathiolans

β-mercaptoalcohol	oxathiolan	crude yield
 (66)	 (67)	90%
 (72)	 (74)	83%
 (73)	 (75)	ZERO
 (83)+(84)	 (85)+(86)	93.5%

4(vi) ^{1}H N.M.R. Spectra of α-(Benzylthio)ketones

The ^{1}H n.m.r. spectra of the two 2-(benzylthio) cyclohexanones (68 and 69) had signals at δ 3.0 (J 14.5, 10.5 and 5.5 Hz) and δ 3.17 (J 14.5, 14.5 and 6 Hz) respectively. On the basis of the coupling constants and a double resonance experiment, these signals were assigned to the axial proton on C-6 (Scheme 58). The chemical shifts are at lower field than one might expect on the basis of comparison with the shifts observed for the C-6 equatorial protons (68 - δ 2.25, 69 - δ 2.24) and for the methylene protons α- to carbonyl in the aliphatic α-(benzylthio)-ketones (79 - δ 2.57, 80 - δ 2.77).



(68) R= CH_2Ph , R'= H

(69) R= CH_2Ph , R'= Me

(98) R= Et , R'= H

SCHEME 58

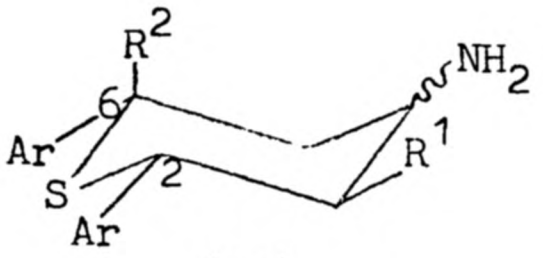
One possible explanation is that the benzyl group influences the chemical shift of C-6 H_{ax}. That this was not the case was proved by preparation of the ethylthio compound (98) which showed for C-6 H_{ax} δ_H 3.01 (J 14.5, 11.5 and 6 Hz).

The assignment of a preferred conformation in which the thio groups were axial was based largely on the coupling constants exhibited for the C-2 protons of (68) and (98), (68 , J 5.5, 5.5 and 1 Hz; 98, J 4.5, 4.5 and 1 Hz). This conformational bias may be rationalised in terms of electronic effects such as repulsion between the lone pairs of electrons on the oxygen and sulphur atoms. 2-Halocyclohexanones[120] and 2-alkyl- or 2-aryl- oxycyclohexanones[121] also exhibit this effect although a conformation in which the substituent is axial is not always predominant.

A possible explanation for the low field shifts of the C-6 H_{ax} in 68, 69, and 98 is that they result from steric interactions[122], this has been called a van der Waals deshielding[123]. This phenomenon is related to the γ effect of ^{13}C n.m.r. spectroscopy[122] as has been noted by Perlin et al[124] and Buchanan et al[125].

In the ^1H n.m.r. spectra of the amines (99)[126], the chemical shifts of the C-6 and C-2 axial protons are consistently ca 0.5 p.p.m. further down field in the compounds with an axial

amine group, probably as a result of an interaction analogous to that mentioned above. That the authors do not remark upon this chemical shift difference is perhaps indicative of the extent to which this effect is less well known than the related γ effect of ^{13}C n.m.r. spectroscopy.



(99)

R^1 = H , Me or Et

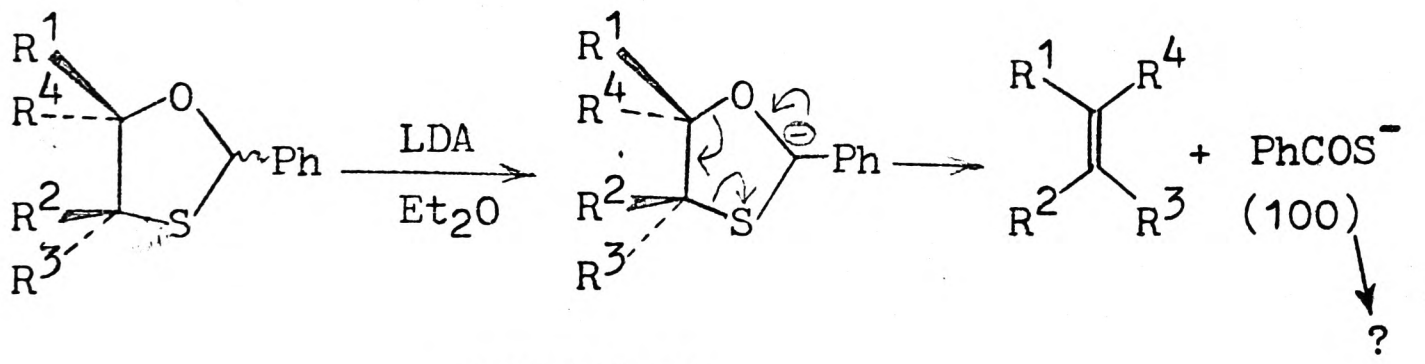
R^2 = H or Me

Ar = Ph or p-ClC_6H_4

CHAPTER 5

Cycloelimination Reactions of 1,3-Oxathiolans

Previous cycloelimination reactions of 2-phenyl-1,3-oxathiolans were achieved by the use of lithium diethylamide or lithium isopropylcyclohexylamide[21]. It was decided to use the more familiar base LDA in the present studies, (Step vi, Scheme 47, p. 51). Owing to the small quantities of the oxathiolans available the base was used in ca. 5-fold excess (Table 16, p. 108) in order to make allowance for any water that might be present and the possibility of further reaction of the monothiocarboxylate (100) formed (Scheme 59).

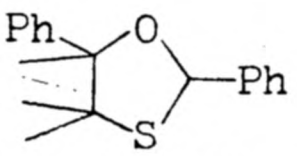
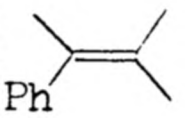
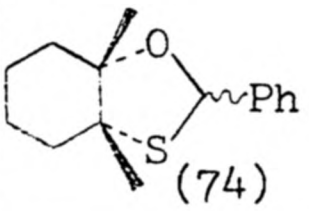
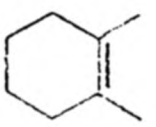
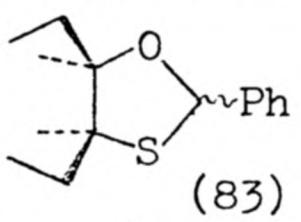
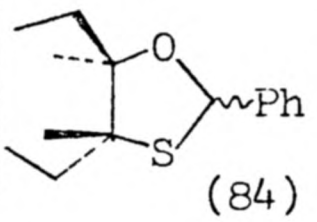
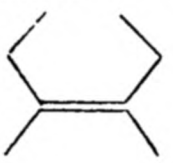
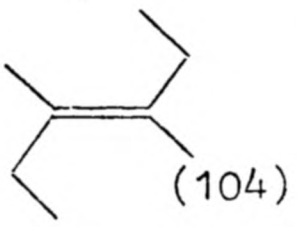


SCHEME 59

The volatility of the C_8 olefins obtained from the cyclohexyl compound (74) and the diethyl dimethyl compounds, (85) and (86), (Table 9), and the small scale of the reactions made isolation of the olefins difficult. A sample of 1,2-dimethylcyclohexene (102) was obtained by distillation for ^1H n.m.r. data but the yields quoted for the cycloelimination reactions - except for the phenacyl system - were calculated by analytical g.l.c. using an internal standard.

TABLE 9

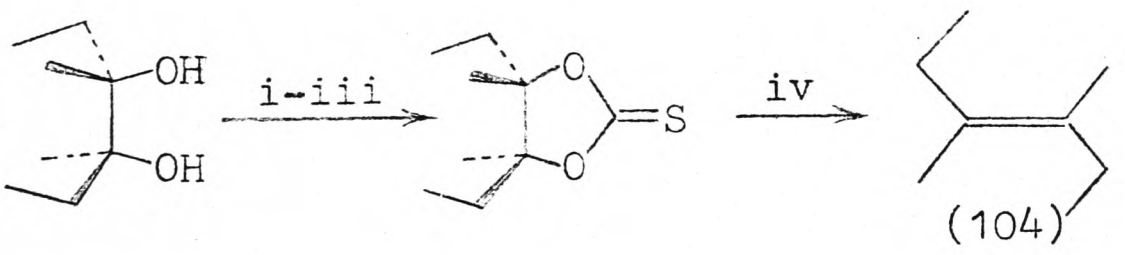
Oxathiolan Cycloeliminations

oxathiolan	isomer ratio	product	isomer ratio	yield
 (67)	-	 (101)	-	ca75%
 (74)	-	 (102)	-	92%
 (83) +  (84)	(85)/(86) 1.63[a] (85)/(86) 0.47[a]	 (103) +  (104)	(103)/(104) 1.63 (103)/(104) 0.47	98% 100%

[a]For the aliphatic system the diastereomeric ratios given are those estimated for the precursor β-(benzylthio)alcohols.

1,2-Dimethylcyclohexene (102) and 2-methyl-3-phenyl-2-butene (101) were identified by their spectral data. An authentic sample of the 3,4-dimethylhex-3-enes, (103) and (104), was prepared by heating a mixture of diastereomeric 3,4-dimethylhexane-3,4-diols with triethylorthoformate and benzoic acid[14]. This sample was compared with the products of the oxathiolan reactions using g.l.c. and mass spectra (g.c.m.s.).

The assignment of stereochemistry to the olefins, (103) and (104), had, with respect to their behaviour on g.l.c., been made by Reichel[127]. He isolated by crystallisation one form of 3,4-dimethylhexane-3,4-diol and used Corey's[15] thiocarbonate procedure to prepare an olefin from this (Scheme 60) which he showed to have the shorter retention time on g.l.c.. Having considered (as did others[128]) the precursor diol to be the meso- form, Reichel assigned cis- stereochemistry to this olefin. White and Greene[129], however, showed the crystalline diol to be the dl- form and so Reichel's assignments must be reversed.



dl-isomer

SCHEME 60: i K, dioxane; ii CS_2; iii MeI; iv $P(OEt)_3$.

The coincidence of the diastereomeric ratios relating to the aliphatic β-(benzylthio)alcohols and the corresponding olefins (Table 9) implies that the later stages of the syntheses of these olefins are stereospecific. As mentioned previously this is the basis on which stereochemistry was assigned to the β-(benzylthio)alcohols.

In reviewing the potential of the synthetic sequence outlined in Scheme 47 (p. 51) as a preparation of tetra- or tri-substituted olefins it must be said that the lack of a high degree of stereo-

selectivity in the formation of the aliphatic β-(benzylthio)alcohols and the difficulty of separation of the diastereomers are clearly drawbacks. As proposed earlier, however, these problems may in part be a result of the system investigated and there would still seem to be scope for improvement in this area. Generally it may be noted that almost all the reactions used in the preparations of the oxathiolans gave high yields and were applicable to all the systems that were studied. Since the subsequent oxathiolan cycloreversions went cleanly to form the corresponding olefins it would appear that the reactions described in the last two chapters do constitute a useful route to tetra-substituted olefins.

EXPERIMENTAL

General:-

Temperatures are quoted in degrees centigrade.

Infrared spectra (i.r.) were recorded on Perkin-Elmer 257 or 297 instruments.

Proton nuclear magnetic resonance spectra (^{1}H n.m.r.) were recorded on Perkin-Elmer R24 or R32 instruments at 60 or 90 MHz respectively or on a Bruker WH 300 instrument at 300 MHz. Tetramethylsilane (δ 0.0) or chloroform (δ 7.27) were used as internal standards.

Carbon-13 nuclear magnetic resonance spectra (^{13}C n.m.r.) were recorded on Bruker WH 90 or WH 300 instruments at 22.63 or 75.57 MHz respectively. Solvent signals or added tetramethylsilane were used as internal standards.

Mass spectra were recorded on either Varian MAT CH7, VG Micromass 16F or ZAB 1F instruments under the supervision of Dr. R.T. Aplin.

Melting points were determined on a Kofler block or a Büchi 510 capillary melting point apparatus.

Microanalyses were carried out under the supervision of Dr. F.B. Strauss.

Thin layer chromatography (t.l.c.) was carried out on plates coated with unbaked Kieselgel HF $_{254+366}$.

Solvents: Diethyl ether and benzene were dried over sodium wire. Light petroleum (of boiling range 40-60° unless otherwise stated) was redistilled through a 70 cm vigreux column. Tetrahydrofuran (THF) was dried by refluxing with sodium wire and benzophenone until the blue colour of the ketyl radical persisted, and then was distilled under nitrogen.

SECTION 1

α-Thiocyanatoacetophenone

α-Bromoacetophenone (11.4g) was added to a solution of potassium thiocyanate (30g) in methanol (A.R.; 300 ml) and the mixture was stirred at 20° for 16h. After evaporation of most of the methanol, ether and dilute hydrochloric acid were added. The separated organic layer was washed successively with aqueous sodium carbonate and brine. The dried (Na_2SO_4) solution was evaporated to give white crystals (11.0g) which were recrystallised from ether: light petroleum to give α-thiocyanatoacetophenone (9.0g, 89%), needles m.p. 74° (lit.,[130] 75-6°); δ_H ($CDC\ell_3$) 4.65 (2H, s), 7.35-7.65 (3H, complex), 7.7-8.0 (2H, complex); δ_C ($CDC\ell_3$) 43 (t), 112 (s, -SCN), 128 (d), 134 (s), 135 (d), 191 (s, C=O).

Reaction of α-Thiocyanatoacetophenone with LDA

A solution of α-thiocyanatoacetophenone (0.5g) in dry ether (10 ml) was added dropwise to a stirred solution of LDA (from n-butyllithium (1.5 M; 2.2 ml) and diisopropylamine (0.65 ml) in dry ether (50 ml)) at 20°. After 20 min, water (1.4 ml) was added, followed by dilute hydrochloric acid. The separated organic layer was washed successively with aqueous sodium carbonate and brine and dried ($MgSO_4$). Evaporation gave a dark reddish oil (0.47g) which was shown to be a mixture of α,α'-thiobis-(acetophenone) and diisopropylcyanamide by comparison with authentic spectra (see p. 75 and 80).

Reaction of Benzylthiocyanate with LDA

A solution of benzylthiocyanate (0.5g) in dry ether (10 ml) was added dropwise to a stirred solution of LDA (from n-butyllithium (1.5 M; 2.2 ml) and diisopropylamine (0.65 ml) in dry ether (50 ml)) at 20°. After 20 min, a little water was added, followed by dilute hydrochloric acid. The separated organic layer was washed successively with aqueous sodium carbonate and brine. The dried ($MgSO_4$) solution was evaporated to give a reddish yellow oil (0.55g). Distillation afforded diisopropylcyanamide† (0.3g, 70%), δ_H ($CDC\ell_3$) 1.24 (12H, d, J 6.5 Hz), 3.18 (2H, septet, J 6.5 Hz); δ_C ($CDC\ell_3$) 21, 51, 115; $\nu_{max.}$ (liquid film) 2200 cm^{-1}. The residue from the distillation was recrystallised from ether: light petroleum to give dibenzyl disulphide (0.27g, 66%), m.p. 63-66° (lit.†† 66-9°); δ_H ($CDC\ell_3$) 3.49 (4H, s), 7.14 (10H, s).

Reaction of Benzylthiocyanate with Isopropyl Magnesium Bromide

A solution of benzylthiocyanate (0.5g) in dry ether (20 ml) was added dropwise to a stirred solution of isopropyl magnesium bromide (made by refluxing magnesium turnings (0.5g) with 2-bromopropane (1g) in dry ether (20 ml) for 35 min) under nitrogen. After 16h at 20°, water (2 ml) was added cautiously followed by dilute sulphuric acid. The separated organic layer was washed successively

†Diisopropylcyanamide was compared with an authentic sample prepared by D. Gillon[68].

††Dibenzyl disulphide was compared with a commercial sample (Aldrich).

with sodium carbonate and brine. The dried (Na_2SO_4) solution was evaporated to give a clear oil (0.5g). Distillation gave 2-(benzylthio)propane (0.39g, 70%); δ_H ($CDC\ell_3$) 1.21 (6H, d); 2.78 (1H, sextet), 3.68 (2H, s), 7.21 (5H, bs) (lit.,[131] $\delta_H((CD_3)_2CO)$ - CH_3 (1.2), -CH- (2.8), $-CH_2-$ (3.75)).

SECTION 2 (ii)

S-(α-Methoxybenzyl)-O-ethyldithiocarbonate (9)

Potassium O-ethyldithiocarbonate (6g) was added to a stirred solution of (α-chlorobenzyl)methyl ether† (5g) in dry ether (100 ml) and the mixture was refluxed for 80 min. The mixture was washed with water (x2), dried ($MgSO_4$) and evaporated to give a yellow oil (6.7g). Distillation afforded S-(α-methoxybenzyl)-O-ethyldithiocarbonate (9) (5.5g, 71%) b.p. 120° at 0.03 mm Hg; δ_H ($CC\ell_4$) 1.29 (3H, t), 3.4 (3H, s), 4.51 (2H, q), 6.43 (1H, s), 7.0-7.5 (5H, complex); $\nu_{max.}$ (liquid film) 3050, 3020, 1600, 1490, 1450, 1220, 1095, 1040, 960, 700, 630 cm^{-1}.

(α-(Methylthio)benzyl)methyl ether (10)

Iodomethane (0.2 ml) was added dropwise to a stirred solution of the dithiocarbonate (9) (0.5g) in dry ether (50 ml) at 15°. After 30 min sodium methoxide (0.2g) was added. 5h later, water was added; the separated organic layer was washed with water, dried ($MgSO_4$) and evaporated to give an opaque oil (0.47g). ^1H n.m.r. showed this to be mainly starting material (ca 35%) and (α-(methylthio)benzyl)methyl ether (10) (ca 65%). The monothioacetal was isolated by distillation, δ_H ($CC\ell_4$) 1.71 (3H, s), 3.4 (3H, s), 5.33 (1H, s), 7.1-7.5 (5H, complex); $\nu_{max.}$ (liquid film) 3060,

†(α-chlorobenzyl)methyl ether was prepared as by Fife and Anderson[48] (see p. 21)

3035, 1600, 1450, 1180, 1090, 950, 720, 700, 675 cm^{-1}, (lit.,[45] δ 1.75, 3.37, 5.38 and aromatics; $\nu_{max.}$ 1085 cm^{-1}).

SECTION 2 (iii)

(α-Methoxybenzyl)isothiocyanate

Carefully dried potassium thiocyanate (0.34g) was added to a stirred solution of (α-chlorobenzyl)methyl ether (0.5g) in dry THF (30 ml) and the mixture was refluxed under nitrogen for 2h. Most of the THF was evaporated and water and ether were added. The separated organic layer was washed with water and dried ($MgSO_4$). Evaporation gave an oil (0.4g) which was a mixture of benzaldehyde and (α-methoxybenzyl)isothiocyanate (ca 5:2 from ^1H n.m.r.). Distillation afforded the isothiocyanate (with 10-15% impurity of benzaldehyde), δ_H ($CC\ell_4$) 3.5 (3H, s), 5.7 (1H, s), 7.3 (5H, bs); $\nu_{max.}$ (liquid film) 3075, 3040, 2020 (-N=C=S), 1705 (aldehyde), 1450, 1200, 1095, 700 cm^{-1}.

Reaction of the Enolate of Acetophenone with Benzylthiocyanate

Two reactions were performed:

(i) A solution of acetophenone (1g) in dry ether (10 ml) was added dropwise to a stirred solution of LDA (from n-butyllithium (1 M; 8.3 ml) and diisopropylamine (1.63 ml) in dry ether (50 ml)) at 15°. After 20 min, benzylthiocyanate (1.05g) was added and the mixture was stirred for 16h. Water was added, followed by dilute hydrochloric acid. The separated organic layer was washed

successively with aqueous sodium hydroxide and brine and dried ($MgSO_4$).

(ii) Sodium hydride (0.24g; 50% suspension) was added to a stirred solution of acetophenone (0.5g) in dry THF (50 ml) and the mixture was brought to reflux. After 30 min, benzylthiocyanate (0.62g) was added and reflux was maintained for 2h. Water and ether were added and the separated organic layer was washed with water and dried ($MgSO_4$).

Evaporation of both products gave a clean mixture of acetophenone and dibenzyl disulphide (by comparison with ^1H n.m.r. spectra of commercial samples).

SECTION 2 (iv)

Reaction of α-Chloroacetophenone with Sodium Hydrogen Sulphide

A solution of α-chloroacetophenone (1g) in dry ether (15 ml) was added over 10 min to a stirred suspension of anhydrous sodium hydrogen sulphide† (0.36g) in dry ether (25 ml) at 15°. After 25 min, a solution of benzyl chloride (0.74 ml) and triethylamine (0.9 ml) in dry ether (10 ml) was added to the mixture from above. After 40 min, water, followed by dilute hydrochloric acid were added. The separated organic layer was washed successively with aqueous sodium carbonate and brine. The dried ($MgSO_4$) solution

†Prepared as by Eibeck[57].

was evaporated to give benzyl chloride and a solid. The latter was recrystallised from light petroleum to give α,α'-thiobis (acetophenone) (0.7g, 61%) m.p. 76-77.5° (lit.,[56] 77-8°); δ_H ($CDC\ell_3$) 3.95 (4H, s), 7.4-8.1 (10H, complex); $\nu_{max.}$ ($CC\ell_4$) 1680 cm^{-1} (lit.,[133] 1685 cm^{-1}); m/e 270 (M^+); δ_C ($CDC\ell_3$) 38, 126, 129, 134, 136, 194.

α-(α'-Methoxybenzylthio)acetophenone (19)

Piperidine (1.24 ml) and triethylamine (1.74 ml) were added to a stirred solution of S-phenacyl-O-ethlyldithiocarbonate (3g) in dichloromethane (130 ml) at 20° under nitrogen. After 50 min, the reaction was cooled in an acetone/dry ice bath and (α-chlorobenzyl)methyl ether (2g) (see p. 21) in dichloromethane (20 ml) was added dropwise. After 2h, the mixture having warmed to about 0°, water was added and the separated organic layer was further washed with water. The dried ($MgSO_4$) solution was evaporated to give a reddish oil (5.0g). Distillation afforded O-ethyl-1-piperidinecarbothioate (18) (0.96g, 45%) b.p. 80° at 0.03 mm Hg (lit.,[62] 147-9° at 25 mm Hg); δ_H ($CC\ell_4$) 1.3 (3H, t, J 7 Hz, $-OCH_2\underline{CH_3}$), 1.64 (6H, br), 3.5-4.2 (4H, complex, $-N-\underline{CH_2}-$), 4.42 (2H, q, J 7 Hz, $-OCH_2-$); δ_C ($CDC\ell_3$) 14 (q), 24 (t), 25 (t), 25 (t), 46 (t, $-N-\underline{CH_2}-$), 50 (t, $-N-\underline{CH_2}-$), 67 (t, $-O\ \underline{CH_2}-$), 186 (s); $\nu_{max.}$ (liquid film) 1495, 1445, 1295, 1270, 1250, 1195, 1150, 1040 cm^{-1} and α-(α'-methoxybenzylthio)acetophenone (19) (1.7g, 50%) b.p. 180° at 0.03 mm Hg; δ_H ($CC\ell_4$) 3.3 (3H, s, $-O\underline{Me}$), 3.6 (2H, ABq, $CO-\underline{CH_2}-S-$), 5.4 (1H, s, $Ph-\underline{CH}-$), 7.05-7.55 (8H, complex),

7.6-7.95 (2H,complex); $\nu_{max.}$ (liquid film) 1685, 1600, 1575, 1450, 1275, 1090, 700, 690 cm^{-1}; m/e 272 (M^+).

2-(α-Methoxybenzylthio)-1-phenyl-1-ethanol (20)

Lithium aluminium hydride (59 mg) was added to a solution of α-(α'-methoxybenzylthio)acetophenone (19) (0.2g) in dry ether (3 ml) and the mixture brought to reflux. After 40 min, a little water was added followed by dilute sulphuric acid. The separated organic layer was washed with brine and dried ($MgSO_4$). Evaporation gave a yellow oil (0.2g), 2-(α-methoxybenzylthio)-1-phenyl-1-ethanol (20); $\nu_{max.}$ (liquid film) 3420, 3065, 3040, 1600, 1495, 1450, 1290, 1270, 1245, 1190, 1090, 1060, 1030, 960, 915, 845, 725, 700, 675 cm^{-1}.

2,5-Diphenyl-1,3-oxathiolan (21)

p-Toluenesulphonic acid (1 mg) was added to a solution of 2-(α-methoxybenzylthio)-1-phenyl-1-ethanol (20) (0.1g; crude from above) in dichloromethane (5 ml) and the mixture stirred at 20° for 1h. The organic solution was washed successively with aqueous sodium hydroxide and water. The dried ($MgSO_4$) solution was evaporated to give an oil (0.1g) which was shown to be 2,5-diphenyl-1,3-oxathiolan by comparison with an authentic sample; δ_H ($CDCl_3$) (mixture of diastereomers) 2.9-3.6 (2H, complex), 4.8-5.4 (1H, complex), 6.12 and 6.26 (1H, s), 7.1-7.6 (10H, complex).

α-(α'-Methoxybenzylthio)acetone (23)

Piperidine (0.83 ml) was added to a solution of S-acetonyl-O-ethyldithiocarbonate (1.6g) in dichloromethane (30 ml) in a

separating funnel at 20° and the mixture was shaken. After 2 min, aqueous sodium hydroxide was added and the mixture was shaken for a further 2 min. The separated aqueous layer was acidified with dilute hydrochloric acid and dichloromethane (20 ml) was added. The mixture was shaken for 90 sec, and the separated organic layer was passed through a fluted filter paper, containing $MgSO_4$, into a stirred mixture of (α-chlorobenzyl)methyl ether (2.8g) and triethylamine (1.25 ml) in dichloromethane (25 ml) at -78°; after addition the mixture was kept under nitrogen. The solution was allowed to warm to 15° over 3h and washed successively with dilute hydrochloric acid, aqueous sodium carbonate and brine. The dried ($MgSO_4$) solution was evaporated to give a yellow oil (1.3g). Chromatography (alumina (30g), eluted with light petroleum (30-40°): ether) gave in earlier fractions benzaldehyde and its dimethyl acetal (by comparison with authentic samples) and later α-(α'-methoxybenzylthio)acetone (23) (0.7g, 37%) as a yellowish oil; (Found: C, 62.75; H, 6.7; S, 15.0. $C_{11}H_{14}O_2S$ requires C, 62.85; H, 6.7; S, 15.25%); δ_H ($CDCl_3$) 2.15 (3H, s, CH_3CO), 3.2 (2H, s), 3.4 (3H, s, -OMe), 5.45 (1H, s), 7.2-7.5 (5H, complex); δ_C ($CDCl_3$) 28 (q, Me CO), 39 (t, CO-CH_2-S), 56 (q, -OMe), 87 (d, Ph-CH-), 126 (d), 128 (d), 139 (s,  -C), 204 (s, C=O); $\nu_{max.}$ (liquid film) 1710, 1450, 1355, 1225, 1090, 700 cm^{-1}.

Evaporation of the solution used above in addition to the α-chloroether and triethylamine, gave a reasonably pure sample of α-mercaptoacetone δ_H ($CDCl_3$) 1.93 (1H, t, J 7.5 Hz, -SH), 2.25 (3H, s), 3.37 (2H, d, J 7.5 Hz, -CH_2-SH) (lit.,[53] δ_H ($CDCl_3$) 1.9 (1H, t, J 8 Hz), 2.3 (3H, s), 3.35 (2H, d, J 8 Hz)).

Alternatively if the solution was added to a stirred mixture of iodomethane (2 equivalents) and triethylamine (1 equivalent) at 20° and worked up as above after 1h, α-(methylthio)acetone was obtained; δ_H ($CDC\ell_3$) 2.06 (3H, s), 2.27 (3H, s), 3.17 (2H, s).

Reaction of α-Chlorocyclohexanone with Sodium O-methyldithiocarbonate

Finely cut sodium (9.9g) was added slowly to stirred refluxing methanol (A.R.; 150 ml). After the sodium had dissolved, carbon disulphide (25 ml) was added dropwise over 10 min at 20°. After 30 min, the methanol was evaporated to give a yellow-white solid, mainly sodium O-methyldithiocarbonate (42g, 74%) δ_H (D_2O) 3.9 (s).

A solution of 2-chlorocyclohexanone (3.95 ml) in acetone (10 ml) was added dropwise to a stirred solution of the dithiocarbonate (5g) in acetone (100 ml) at 0°. The solution was allowed to warm to 20° over 2h and stirred for 12h. After evaporation of the solvent, water and ether were added and the separated organic layer was washed with brine and dried ($MgSO_4$). Evaporation gave a yellow oil (5.7g) which had a complex ^1H n.m.r. spectrum (indicating a number of products) and a multi-spot t.l.c.. O,S-Dimethyldithiocarbonate was shown to be present by ^1H n.m.r. as ca 15% of total, (δ_H ($CC\ell_4$) 2.52 (3H, s), 4.12 (3H, s), (lit.,[133] δ_H ($CC\ell_4$) 2.46 (s), 4.05 (s))). A solid slowly crystallised out from the mixture and was recrystallised from methanol to give (1RS,6RS)-1-methoxy-7,9-dithiabicyclo[4.3.0]nonane-8-thione (26) as yellow needles (ca 12% of total from ^1H n.m.r. of crude material), m.p. 129-30° (Found:

C, 43.75; H, 5.4; S, 44.0. $C_8H_{12}OS_3$ requires C, 43.6; H, 5.5; S; 43.65%); δ_H ($CDC\ell_3$) 1.4-1.75 (3H, complex), 1.85-2.0 (3H, m), 2.13 (1H, dddd, J 12, 12,12 and 4 Hz, C-5-H ax.), 2.55 (1H, dm, J 14 Hz, C-2-H eq.), 3.4 (3H, s, -OMe), 4.55 (1H, dd, J 14 and 4 Hz, C-6-H ax.); δ_C ($CDC\ell_3$) 20 (t), 25 (t), 25 (t), 31 (t), 51 (q, -OMe), 68 (d, C-6), 106 (s, C-1), 226 (s, C=S); $\lambda_{max.}$ (EtOH) 216 (ε 2800), 294 (ε 5200) 323 (ε 7750) nm; $\nu_{max.}$ ($CC\ell_4$) 2940, 1490, 1270, 1240, 1190, 1140, 110, 1100, 1065, 1040, 1000, 950, 930, 870, 660 cm^{-1}; m/e 220 (M^+), 144 (100%), 129 (20%), 111 (85%), 110 (75%), 103 (25%).

Reaction of (1RS,6RS)-1-Methoxy-7,9-dithiabicyclo[4.3.0]nonane-8-thione (26) with Lithium Aluminium Hydride

(26) (0.1g) was added to a stirred slurry of lithium aluminium hydride (0.17g) in dry ether (10 ml) and the mixture was refluxed for 3h. Water was added cautiously to the cooled mixture, followed by dilute sulphuric acid, the separated organic layer was washed with brine, dried ($MgSO_4$) and evaporated to give an opaque oil (0.06g). Flash chromatography (silica (3g), eluted with light petroleum: ether (9:1)) gave 1,2-cyclohexanedithiol (20 mg, 30%†) δ_H ($CDC\ell_3$) 1.1-2.4 (10H, complex), 3.25 (2H, m); $\nu_{max.}$ (liquid film) 2550 cm^{-1} (compare lit.,[134] regarding cis dithiol, δ_H ($CDC\ell_3$) 1.86 (2H, d, J 7.5 Hz), 1.0-2.5 (8H, m),

†Most of the dithiol was in later running fractions of the column but it was contaminated.

3.25 (2H, m); $\nu_{max.}$ (liquid film) 2555 cm^{-1}); m/e 148 (M^+), 115 (20%), 114 (15%), 81 (100%)

SECTION 3

Reaction of 2-Benzylthio-1-phenylethanol (53)† with N-Chlorosuccinimide

(i) A solution of the benzylthioalcohol (53) (0.4g) in toluene (5 ml) was added dropwise to a stirred suspension of N-chlorosuccinimide (0.22g) in toluene (50 ml) at - 78°. After 30 min, aqueous sodium hydroxide was added and the mixture allowed to warm to 20°. The separated organic layer was washed successively with dilute hydrochloric acid and brine. The dried ($MgSO_4$) solution was evaporated to give a white solid (0.5g) which was recrystallised from methanol to give 2-benzylsulphinyl-1-phenylethanol (55) (0.27g, 51%) m.p. 126-9° (Found: C, 69.1; H, 6.4; S, 12.2. $C_{15}H_{16}O_2S$ requires C, 69.2; H, 6.2; S, 12.3%); (^{1}H n.m.r. showed a ca 4:1 mixture of diastereomers, signals due to the major isomer are quoted here, see below for the minor isomer); δ_H ($CDC\ell_3$) 2.75-3.05 (2H, m, -CH(OH)-CH_2-S(O)-), 3.55 (1H, bs, diminished with D_2O), 4.1 (2H, bs, Ph CH_2S(O)-), 5.15-5.4 (1H, m, Ph CH(OH)-), 7.29 (10H, bs); $\nu_{max.}$ ($CHC\ell_3$) 3600, 3350, 2980, 1605, 1490, 1450, 1000 cm^{-1}; m/e 260 (M^+).

(ii) A solution of the benzylthioalcohol (53) (0.4g) and triethylamine (0.12 ml) in toluene (30 ml) was added dropwise to a stirred solution of N-chlorosuccinimide (0.22g) in toluene (20 ml) at 0°. After 2h, the reaction mixture was worked up as for (i) (see above) to give a white oily solid (0.4g) which was

†See p. 94 for the preparation of this.

recrystallised from methanol to give 2-benzylsulphinyl-1-phenylethanol (0.26g, 61%), m.p. 170-170.5°, (^{1}H n.m.r. showed only one diastereomer) δ_H ($CDC\ell_3$) 2.78 (1H, dd, J 12 and 1.5 Hz, -CH(OH)-C<u>H</u>$_a$-) 3.00 (1H, dd, J 12.5 and 10 Hz, -CH(OH)-C<u>H</u>$_b$-), 3.73 (1H, brs), 4.07 and 4.15 (2H, ABq, J 12.5 Hz), 5.37 (1H, dd, J 9.5 and 1.5 Hz, -C<u>H</u>(OH)-), 7.25-7.43 (10H, complex); δ_C (d^6-DMSO) 57 (t), 60 (t), 66 (d), 126 (d), 127 (d), 128 (d), 128.5 (d), 129 (d), 130 (d), 131 (s), 144 (s); $\nu_{max.}$ as above.

Reaction of 1-Benzylthio-2-phenyl-2-propanol (106) with N-Chlorosuccinimide

A solution of the benzylthioalcohol (106) (0.4g) in toluene (10 ml) was added dropwise to a stirred slurry of N-chlorosuccinimide (0.22g) in toluene (30 ml) at -78°. After 30 min, the reaction was worked up as in the last experiment to give a brown oil (0.45g) from which a solid slowly crystallised. The solid was recrystallised from ether to give 1-benzylsulphinyl-2-phenyl-2-propanol (ca 50% of crude product from ^{1}H n.m.r.), m.p. 98-101°, (ca 2:1 mixture of diastereomers); δ_H ($CDC\ell_3$): (i) - major isomer - 1.58 (3H, s), 3.03 and 3.14 (2H, ABq, J 12 Hz, -C(OH)-C<u>H</u>$_2$-S), 3.95 and 4.06 (2H, ABq, J 12 Hz, PhC<u>H</u>$_2$-S), 4.88 (1H, Br s, -O<u>H</u>), 7.22-7.5 (10H, complex). (ii) - minor isomer - 1.83 (3H, s), 2.95 (2H, m), 3.95 (2H, m), 4.64 (1H, br s), 7.22-7.5 (10H, complex); $\nu_{max.}$ ($CHC\ell_3$) 3420, 3080, 3000, 1600, 1500, 1215, 1050, 1010, 930, 780, 670 cm^{-1}; m/e 275 ($(M + 1)^+$, CI), 257 (50%, CI), 242 (10%), 120 (65%), 105 (100%).

Reaction of α-(Benzylthio)acetophenone (17) with N-Chlorosuccinimide

N-Chlorosuccinimide (0.13g) was added to a stirred solution of (17) (0.2g) in toluene (30 ml) at 20°. After 1h, the organic solution was washed successively with aqueous sodium hydroxide, dilute hydrochloric acid and brine. The dried ($MgSO_4$) solution was evaporated to give α-benzylthio-α-chloroacetophenone (0.21g, 92% crude) as an opaque oil, δ_H ($CC\ell_4$) 3.76 and 4.0 (2H, ABq, J 12 Hz), 5.95 (1H, s), 7.0-7.5 (8H, complex), 7.6-7.9 (2H, complex); $\nu_{max.}$ (liquid film) 3070, 3040, 1695, 1600, 1580, 1495, 1450, 1320, 1275, 1210, 1070, 990, 810, 700, 685 cm^{-1}.

Reaction of α-Benzylthio-α-chloroacetophenone with Sodium Methoxide

The α-haloketone (0.2g; crude from above) was added to a stirred solution of sodium methoxide (0.1g) in methanol (10 ml) at 20°. After 4h, most of the methanol was evaporated. Water and ether were added and the separated organic layer was washed with water and dried ($MgSO_4$). Evaporation gave a yellow oil (0.13g) which was distilled to give α-benzylthio-α-methoxyacetophenone (0.11g, 55%), (oil bath ca 100° at 0.05 mm Hg), δ_H ($CC\ell_4$) 3.3 (3H, s, -O-Me), 3.35 and 3.68 (2H, ABq, J 13 Hz, $PhCH_2$-S) 5.25 (1H, s, PhCO-CH-S), 7.0-7.45 (10H, complex); $\nu_{max.}$ (liquid film) 3060, 3030, 1685, 1600, 1585, 1495, 1450, 1280, 1230, 1195, 1090, 1050, 750, 700, 690 cm^{-1}.

SECTION 4

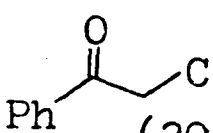
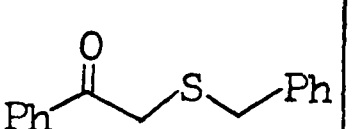
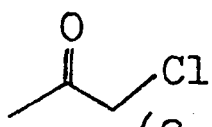
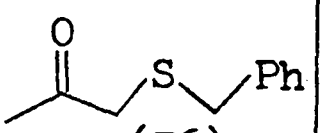
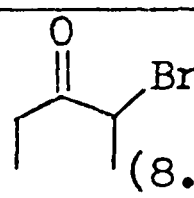
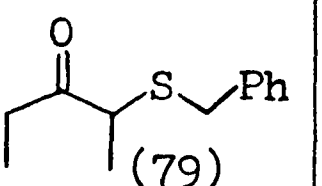
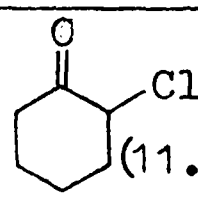
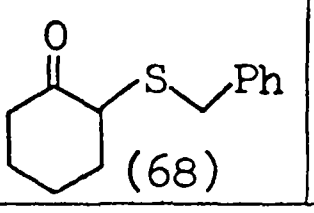
Preparation of α-(Benzylthio)ketones

The conditions used for , and results from, these experiments are shown in Table 10.

General procedure: Benzylmercaptan was added dropwise to a stirred solution of the α-haloketone and triethylamine in dry ether. Work up involved washing successively with dilute hydrochloric acid, aqueous sodium hydroxide and brine. The dried ($MgSO_4$) solution was evaporated to give the crude α-(benzylthio)ketone. With the exception of α-(benzylthio)acetophenone, the crude product was used directly in further reactions.

TABLE 10

Preparation of α-(Benzylthio)ketones

α-haloketone (mass)	$PhCH_2SH$ / NEt_3 molar equiv.	vol. Et_2O	conditions	product	yield
 (20g)	1	200ml	20°, 1h	 (17)	85% recry.
 (8.5g)	1·3	350ml	0° 1h 20° 36h	 (76)	100% crude
 (8.5g)	(a) 1·06 (b) 0·3	(a)&(b) 350ml	(a)0° 1h, 20° 16h. (b)20° 20h	 (79)	92% crude
 (11.6g)	1	350ml	0° 1h 20° 24h	 (68)	84% crude

[a] After conditions (a) the isolated product contained some 2-bromopentan-3-one and so more thiol and base were added.

Spectral data for the products are as follows:- α-(Benzylthio)-acetophenone (17): m.p. 89-90° (lit.,[135] 89-90°); δ_H ($CDC\ell_3$) 3.65 (2H, s, CO-$C\underline{H}_2$-), 3.74 (2H, s, Ph$C\underline{H}_2$-S), 7.2-7.6 (8H, complex), 7.87-7.94 (2H, m); $\nu_{max.}$ ($CC\ell_4$) 1680, 1275, 684 cm^{-1} (lit.,[135] (KBr disc) 1664, 750, 697 cm^{-1}); m/e 242 ($\underline{M}^+$), 120 (60%), 105 (100%).

α-(Benzylthio)acetone (76): δ_H ($CDC\ell_3$) 2.17 (3H, s), 3.04 (2H, s, CO-$C\underline{H}_2$S-), 3.62 (2H, s, Ph$C\underline{H}_2$S-), 7.2 (5H, bs) (lit.,[136] δ_H ($CDC\ell_3$) 2.19 (3H, t, J 0.41 Hz), 3.1 (2H, q, J 0.41 Hz), 3.68 (2H, s)); $\nu_{max.}$ (liquid film) 1700, 1490, 1450, 1350, 1230, 775, 700 cm^{-1}.

2-(Benzylthio)pentan-3-one (79): b.p. 92° at 0.1 mm Hg; δ_H ($CDC\ell_3$) 1.03 (3H, t, J 7 Hz, Me CH_2CO-), 1.36 (3H, d, J 7 Hz, Me-CHS-), 2.57 (2H, m, Me $C\underline{H}_2$CO-), 3.3 (1H, q, J 7 Hz, Me $C\underline{H}$S-), 3.58 and 3.66 (2H, ABq, J 13 Hz), 7.2-7.31 (5H, complex); $\nu_{max.}$ (liquid film) 1700, 1490, 1450, 1370, 1345, 1120, 1070, 955, 765, 700 cm^{-1}; m/e 208 ($\underline{M}^+$), 151 (10%), 123 (20%), 91 (100%); $\underline{M}^+$ 208.0921. $C_{12}H_{16}OS$ requires 208.0922.

2-(Benzylthio)cyclohexanone[137] (68): δ_H ($CDC\ell_3$) 1.6-2.04 (5H, complex), 2.05-2.2 (1H, m), 2.2-2.3 (1H, m), 3.0 (1H, ddd, J 14.5, 10.5 and 5.5 Hz, C-6-$\underline{H}_{ax.}$), 3.25 (1H, ddd, J 5.5, 5.5 and 1 Hz, C-2-$\underline{H}$ eq.), 3.85 (2H, s, Ph$C\underline{H}_2$S-), 7.22-7.42 (5H, complex); $\nu_{max.}$ (liquid film) 1700, 1495, 1450, 1225, 1120, 1070, 1060, 1030, 915, 770, 700 cm^{-1}; m/e 220 ($\underline{M}^+$), 123 (15%), 98 (35%), 97 (30%), 91 (100%).

Alkylation of α-(Benzylthio)ketones

The conditions for these reactions are shown in Table 11. The work up of the experiments involved addition of a little water followed by evaporation of most of the solvent. Ether and dilute hydrochloric acid were added and the separated organic layer was washed successively with aqueous sodium hydroxide and brine. The dried ($MgSO_4$) solution was evaporated to give the crude product, (though see footnote[b] of Table 11).

Spectral data for the products are as follows:-

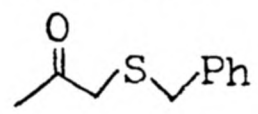
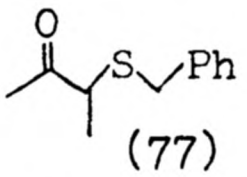
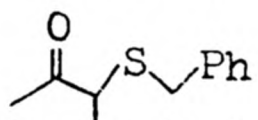
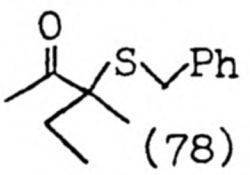
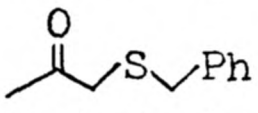
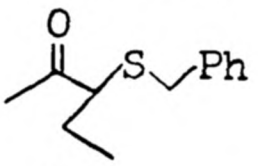
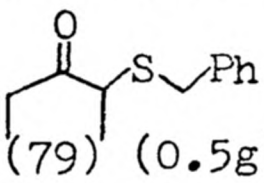
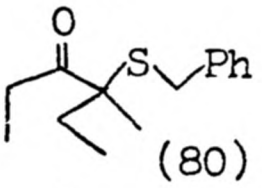
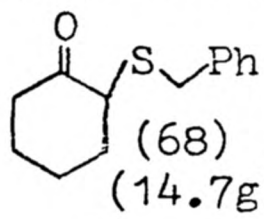
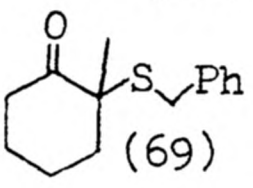
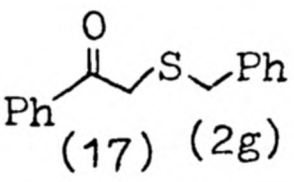
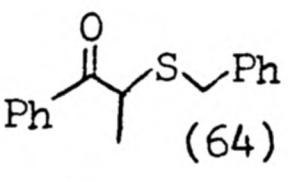
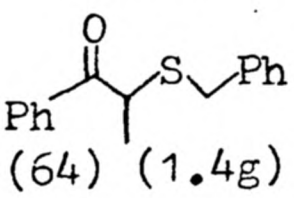
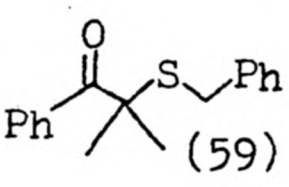
3-(Benzylthio)-2-butanone (77): b.p. *ca* 100° at 0.1 mm Hg, (Found: C, 67.75; H, 7.5. $C_{11}H_{14}OS$ requires C, 68.0; H, 7.25%); δ_H ($CDC\ell_3$) 1.36 (3H, d, *J* 7 Hz), 2.22 (3H, s), 3.28 (1H, q, *J* 7 Hz), 3.6 and 3.67 (2H, ABq, *J* 13 Hz), 7.23-7.32 (5H, complex); $\nu_{max.}$ (liquid film) 1705, 1495, 1450, 1350, 1225, 1200, 1160, 1060, 1030, 770, 700 cm^{-1}; *m/e* 194 (M^+), 151 (7%), 123 (25%), 91 (100%).

3-(Benzylthio)2-pentanone (79): δ_H ($CDC\ell_3$) 0.92 (3H, t, *J* 7.5 Hz), 1.7 (2H, complex), 2.18 (3H, s), 3.6 (1H, m), 3.65 (2H, s, $PhCH_2S$-), 7.2 (5H, s); *m/e* 209 ($(M + 1)^+$ (CI)).

3-(Benzylthio)-3-methyl-2-pentanone (78): δ_H ($CDC\ell_3$) 0.93 (3H, t, *J* 7 Hz, CH_3CH_2-), 1.41 (3H, s, Me-C-S-), 1.75 and 1.9 (2H, (ABq)d, *J* 14 and 7 Hz), 2.28 (3H, s, Me-CO-), 3.49 and 3.55 (2H, ABq, *J* 12 Hz, $PhCH_2S$-), 7.2-7.3 (5H, complex); $\nu_{max.}$ (liquid film) 1695, 1495, 1450, 1350, 1230, 1130, 1100, 1070, 1030, 770, 700 cm^{-1}; *m/e* 222 (M^+), 179 (20%), 91 (100%); M^+ 222.1079. $C_{13}H_{18}OS$ requires 222.1078.

TABLE 11

Alkylation of α-(Benzylthio)ketones

starting material	conditions [a] (mol. equiv. or vol.)	product	yield
 (76) (10g)	NaO^tAm (1.0), C_6H_6 (42ml), reflux 1h; MeI (1.3), 0°-20°, 20h [b]	 (77)	96% crude [c]
 (77) (1g)	NaH (1.15), THF (30ml), reflux 4h; EtI (1.5), reflux 40h	 (78)	61% chromatography [d]
 (76) (1g)	NaH (1.02), THF (60ml), reflux 4h; EtI (1.5), 20°, 20h		69% crude
 (79) (0.5g)	NaH (1.2), THF (50ml), reflux 30 min; EtI (2), 25°-reflux 3h	 (80)	76% distilled
 (68) (14.7g)	NaH (1.05), THF (300ml), reflux 40 min; MeI (1.5), 20°, 17h	 (69)	95% crude [c]
 (17) (2g)	NaH (1.15), THF (70ml), reflux 30 min; MeI (2), 20°, 16h	 (64)	63% distilled
 (64) (1.4g)	NaH (1.2), THF (35ml), reflux 50 min, MeI (2), 20°-reflux 1h	 (59)	51% chromatography [d]

[a] All the reactions were stirred under nitrogen throughout.

[b] After normal work up, light petroleum and saturated aqueous sodium sulphite were added and the mixture was stirred vigorously for 2h. The separated organic layer was washed with water and dried ($MgSO_4$). Evaporation gave the crude product.

[c] The crude product was used directly in further reactions.

[d] Using Kieselgel 60H (a loading of 80:1) with light petroleum/ether as eluant.

3-Benzylthio -3-methyl-4-hexanone (80): δ_H ($CDCl_3$) 0.98 (3H, t, J 7.5 Hz, Me-CH_2C-S-), 1.12 (3H, t, J 7.5 Hz, Me-CH_2CO), 1.49 (3H, s, Me-C-S-), 1.82 and 2.0 (2H, (ABq)d, J 14 and 7 Hz, Me-CH_2C-S-), 2.77 (2H, m, Me-CH_2CO-), 3.53 and 3.59 (2H, ABq, J 12 Hz, PhCH_2S-), 7.26-7.38 (5H, complex); $\nu_{max.}$ (liquid film) 1690, 1490, 1450, 1370, 1090, 700 cm^{-1}; m/e 237 ($(M + 1)^+$, CI), 179 (20%), 114 (15%), 91 (100%).

2-(Benzylthio)-2-methylcyclohexanone (69): b.p. ca 100° at 0.1 mm Hg. (Found: C, 71.55; H, 7.8; S, 13.9. $C_{14}H_{18}OS$ requires C, 71.75; H, 7.75; S, 13.7%); δ_H ($CDCl_3$) 1.44 (3H, s, -Me), 1.55-1.73 (2H, m), 1.75-1.9 (1H, m), 1.92-2.17 (3H, complex), 2.24 (1H, dddd, J 14.5, 14.5, 2 and 2 Hz, C-6-H eq.), 3.17 (1H, ddd, J 14.5, 14.5 and 6 Hz, C-6-$H_{ax.}$), 3.39 and 3.68 (2H ABq, J 12 Hz, PhCH_2S-), 7.22-7.31 (5H, complex); $\nu_{max.}$ (liquid film) 1695, 1490, 1445, 1370, 1275, 1230, 1120, 1080, 985, 815, 770, 700 cm^{-1}; m/e 235 ($(M + 1)^+$), 112 (100%), 91 (75%).

2-(Benzylthio)propiophenone (64): b.p. ca 120° at 0.02 mm Hg (lit.,[138] m.p. 62°), δ_H (CCl_4) 1.5 (3H, d, J 7 Hz, Me-CH-S-), 3.6 (2H, bs, PhCH_2S-), 4.2 (1H, q, J 7 Hz, CO-CH-S-), 7.15 (5H, bs, PhCH_2S-), 7.1-7.5 (3H, complex), 7.65-8.0 (2H, complex); $\nu_{max.}$ (CCl_4) 1675, 1450, 1270, 1180, 950, 695, 685 cm^{-1}; m/e 257 ($(M + 1)^+$, CI).

2-(Benzylthio)-2-methylpropiophenone (59): b.p. ca 120° at 0.02 mm Hg, (Found: C, 75.35; H, 6.8; S, 12.1. $C_{17}H_{18}OS$ requires C, 75.5; H, 6.7; S, 11.85%); δ_H (CCl_4) 1.5 (6H, s, Me_2C-S-), 3.55 (2H, s, PhCH_2S-), 7.05 (5H, bs, PhCH$_2$S-), 7.0-7.5 (3H, complex), 7.9-8.15 (2H, complex); $\nu_{max.}$ (liquid film) 1660, 1450, 1265, 985, 710 cm^{-1}; m/e 271 ($(M + 1)^+$, CI), 165 (30%), 121 (20%),

105 (25%), 91 (100%).

2-(Ethylthio)cyclohexanone (98)[139]

Ethanethiol (0.32 ml) was added to a stirred solution of 2-chlorocyclohexanone (0.5 ml) and triethylamine (0.61 ml) in dry ether (20 ml) under nitrogen at 0°. The mixture was allowed to warm slowly to 20°. After 50h dilute hydrochloric acid was added and the separated organic layer was washed successively with aqueous sodium hydroxide and water. The dried ($MgSO_4$) solution was evaporated to give 2-(ethylthio)cyclohexanone (0.33g, 48%); δ_H ($CDCl_3$) 1.24 (3H, t, J 7.5 Hz, Me-CH_2S-), 1.62-2.28 (7H, complex), 2.47 and 2.52 (2H, (ABq)q, J 12.5 and 7.5 Hz, Me-CH_2S-), 3.01 (1H, ddd, J 14.5, 11.5 and 6 Hz, C-6-H ax.), 3.36 (1H, ddd, J 4.5, 4.5 and 1 Hz, C-2-H eq.); $\nu_{max.}$ (liquid film) 1705, 1450, 1420, 1335,. 1315, 1290, 1270, 1225, 1120, 920, 830 cm^{-1}; m/e 158 (M^+), 101 (45%), 98 (100%).

2-Benzylthio-1-phenylethanol (53)

α-(Benzylthio)acetophenone (5g) was added to a stirred slurry of lithium aluminium hydride (2g) in dry ether (150 ml) and the mixture was refluxed. After 2h, water (3 ml) was added cautiously to the cooled mixture, followed by dilute sulphuric acid. The separated organic layer was washed successively with aqueous sodium carbonate and brine. The dried ($MgSO_4$) solution was evaporated to give a yellowish oil (50g) which solidified on standing. Recrystallisation from methanol gave 2-benzylthio-1-phenylethanol (53) (4.82g, 96%) m.p. 46.5-47°, δ_H ($CDCl_3$)

2.65 (2H, m), 3.0 (1H, br s), 3.6 (2H, s), 4.57 (1H, m), 7.2 (10H, bs) (lit.,[30] m.p. 46.2-46.9°; δ ($CC\ell_4$) ($\underline{B}_2$ of AB_2), 3.16 (d), 3.63 (s), 4.5 (m), 7.19 (aromatics)); $\nu_{max.}$ ($CC\ell_4$) 3620, 3520 (broad) cm^{-1}.

Reactions of α-(Benzylthio)ketones with Alkyllithium Reagents

General procedure: A solution of the alkyllithium was added dropwise via a syringe to a stirred solution of the α-(benzylthio)ketone under nitrogen. Most reactions (see[a] and[e] of Table 12) were worked up by the cautious addition of a little water followed by dilute hydrochloric acid. The separated organic layer was washed successively with aqueous sodium hydroxide and brine. The dried ($MgSO_4$) solution was evaporated to give the crude product.

The particular conditions used for, and results from, the experiments performed are shown in Table 12.

Spectral data for the products are as follows:-

1-(α-Methoxybenzylthio)-2-phenyl-2-propanol (105): b.p. ca 140° at 0.02 mm Hg, δ_H ($CC\ell_4$) 1.44 (3H, s, Me-C(OH)-), 2.8 (2H, m, $-SC\underline{H}_2C(OH)-$), 3.3 (4H, br s, -O-Me and -O$\underline{H}$), 5.15 and 5.25 (1H, s, PhC$\underline{H}$(OMe)S-, (2 diastereomers)), 7.0-7.5 (10H, complex, aromatics).

(1RS,2SR)-2-Benzylthio-1,2-dimethylcyclohexanol (70): b.p. ca 100° at 0.02 mm Hg, (Found: C, 71.75; H, 8.75; S, 13.05. $C_{15}H_{22}OS$ requires C, 71.95; H, 8.85; S, 12.8%); δ_H ($CDC\ell_3$) 1.25 (3H, s, Me-C(OH)-), 1.45 (3H, s, Me-CS-), 1.35-1.82 (7H, complex), 2.01

TABLE 12 -Alkyllithium Reactions

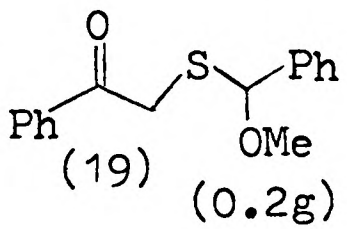
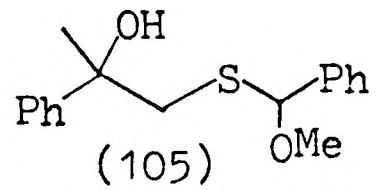
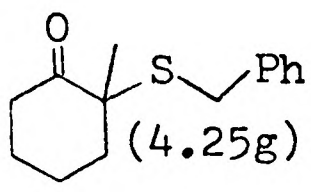
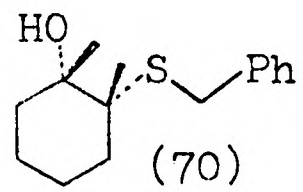
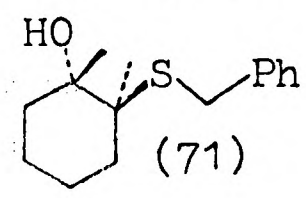
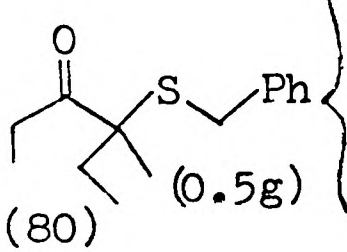
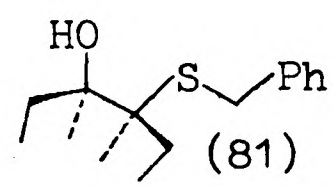
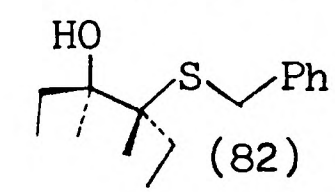
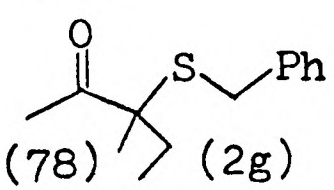
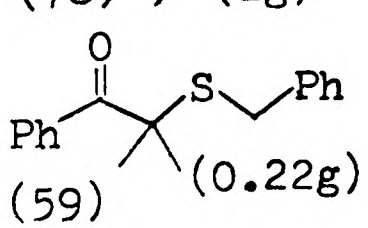
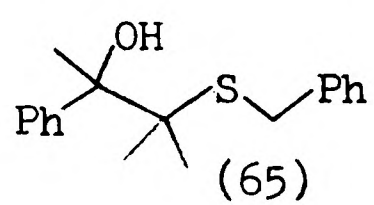
ketone (mass)	reagent (mol. equiv.) solvent (vol.)	conditions	product	diastereomer mixture	yield
 (19) (0.2g)	MeLi:LiBr (1.0) Et_2O (20ml)	addn. at 5° 10° 15h [a]	 (105) +deuterated (19)		66% distilled [b]
 (4.25g) (69)	MeLi:LiBr (1.5) Et_2O (300ml)	addn. at -78° -78° → 20° 16h	 (70)	⩾97:3 (70):(71)	97% crude [c]
			 (71)		
 (80) (0.5g)	MeLi:LiBr (5) Et_2O (25ml)	addn. at -78° -78° → 20° 16h	 (81)	32:68 (81):(82)	66% distilled
	$LiMe_2Cu$:MeLi (1.5,1) Et_2O (60ml)	addn. at -65° -65° → 0° 4.5h	 (82)	33:67 (81):(82)	95% [d] crude
 (78) (2g)	EtLi (1.9) C_6H_6 (40ml) Et_2O (100ml)	addn. at -2° -2° → 20° 21h		62:38 (81):(82)	89% crude [c]
 (59) (0.22g)	MeLi:LiBr (8) Et_2O (9ml)	addn. at 20° 20° 2h	 (65)		80% chromat-ography [e]

TABLE 12 -footnotes

[a] Work up involved addition of D_2O followed by washing of the organic layer with water and drying ($MgSO_4$).

[b] The product is ca 6:5 mixture of alcohol:ketone.

[c] The sodium/ammonia reaction was performed on the crude product.

[d] The product was ca 1:1 mixture of starting material: desired product.

[e] Using Kieselgel 60H (15g) with light petroleum/ether as eluant.

(1H, m), 2.45 (1H, br s, -OH), 3.82 (2H, s, $PhCH_2S$), 7.2-7.37 (5H, complex, aromatics); $\nu_{max.}$ (liquid film) 3470, 1600, 1490, 1450, 1365, 1315, 1180, 1150, 1110, 1080, 1040, 1000, 950, 910, 885, 705, 695 cm^{-1}; m/e 250 (M^+), 159 (20%), 125 (25%), 91 (50%), 43 (100%).

(3RS,4RS) and (3RS,4SR)-4-Benzylthio-3,4-dimethyl-3-hexanol (82) and (81): b.p. ca 100° at 0.02 mm Hg, (Found: C, 71.55; H, 9.85; S, 12.95. $C_{15}H_{24}OS$ requires C, 71.4; H, 9.6; S, 12.7%); δ_H ($CDC\ell_3$): (3RS,4RS) (82) 0.97 (3H, t, J 7.5 Hz, Me-CH_2-), 1.09 (3H, t, J 7.5 Hz, Me-CH_2-), 1.19 (3H, s, Me-C(OH)-), 1.26 (3H, s, Me-CS-), 1.43-1.83 (4H, complex, Me-CH_2-), 2.3 (1H, br s, -OH), 3.76 and 3.81 (2H, ABq, J 12 Hz), 7.23-7.38 (5H, complex, aromatics). (3RS,4SR) (81) 0.95 and 1.09 (2x3H, t, J 7.5 Hz, Me-CH_2-), 1.16 (3H, s, Me-C(OH)-), 1.29 (3H, s, Me-CS-), 1.43-1.83 (4H, complex), 2.3 (1H, br s, -OH), 3.75 and 3.81 (2H, ABq, J 12 Hz), 7.23-7.38 (5H, complex, aromatics); $\nu_{max.}$ (liquid film) 3480, 1600, 1490, 1450, 1375, 1120, 1090, 990, 910, 705, 690 cm^{-1}; m/e 235 ($(M-OH)^+$, CI), 179 (10%), 111 (20%), 91 (100%).

3-Benzylthio-3-methyl-2-phenyl-2-butanol (65): b.p. ca 120° at 0.02 mm Hg, (Found: C, 75.3; H, 7.55. $C_{18}H_{22}OS$ requires C, 75.5; H, 7.75%); δ_H ($CDC\ell_3$), 1.34 (3H, s, Me-CS-), 1.43 (3H, s, Me-CS-), 1.74 (3H, s, PhC(Me) (OH)-), 2.98 (1H, bs, -OH), 3.52 (2H, s, $PhCH_2S$-), 7.15-7.7 (10H, complex, aromatics); $\nu_{max.}$ (liquid film) 1665, 1455, 1265, 985, 710 cm^{-1}.

Reactions of α-(Benzylthio)ketones with Grignard Reagents

General procedure: The Grignard reagents were formed by

cautious addition of the alkyl halide to ca 1.5 equivalents of magnesium turnings stirred in either dry ether or dry THF under nitrogen. Reflux was maintained throughout the addition using the heat evolved in the reaction and/or an external heat source. Reflux was continued for 20-30 min after the addition of the alkyl halide before the ketone was added.

The work up involved cautious addition of a little water followed by dilute hydrochloric acid. The separated organic layer was washed successively with aqueous sodium hydroxide and brine. The dried ($MgSO_4$) solution was evaporated to give the crude product.

The particular conditions used for, and results from, the experiments performed are shown in Table 13.

Spectral data for the products are as follows:-

1-Benzylthio-2-phenyl-2-propanol (10θ: b.p. ca 160° at 0.02 mm Hg, $\delta_H(CDCl_3)$ 1.6 (3H, s, Me-), 2.83 and 3.05 (2H, ABq, J 12.5 Hz, -C(OH)·CH_2S-), 3.0 (1H, br s, -OH), 3.43 and 3.48 (2H, ABq, J 13 Hz, PhCH_2S-), 7.2-7.5 (10H, complex, aromatics); $\nu_{max.}$ (liquid film) 3450, 1600, 1495, 1450, 1070, 765, 700 cm^{-1}; m/e 275 ((M + 17 (NH_3))$^+$, CI), 241 (100%).

(1RS,2RS)-2-Benzylthio-1,2-dimethylcyclohexanol (71): b.p. ca 100° at 0.02 mm Hg, (Found: C, 71.9; H, 8.55. $C_{15}H_{22}OS$ requires C, 71.95; H, 8.85%); δ_H ($CDCl_3$) 1.35 (3H, s, Me-C(OH)-), 1.46 (3H, s, Me-CS-), 1.44-1.95 (8H, complex), 3.72 (2H, s, PhCH_2S-), 7.2-7.37 (5H, complex, aromatics), ? (-OH); $\nu_{max.}$ (liquid film) 3460, 1490, 1445, 1365, 1040, 940, 705, 690 cm^{-1}.

3-Benzylthio-3-methyl-2-pentanol(93): δ_H ($CDCl_3$) (mixture

TABLE 13 -Grignard Reactions

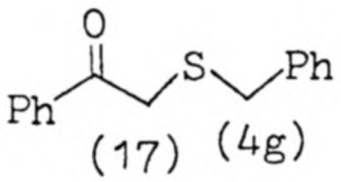
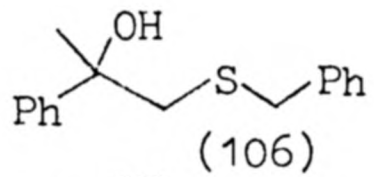
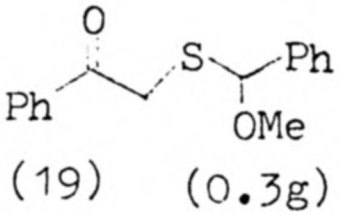
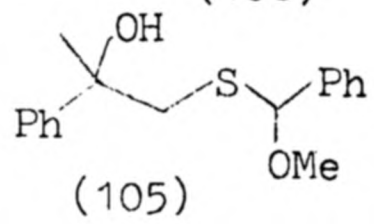
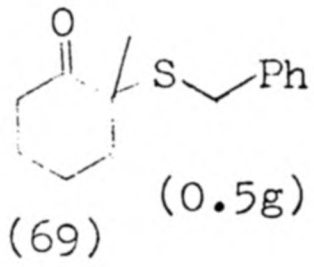
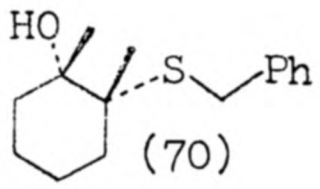
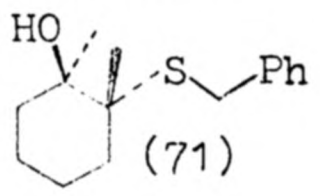
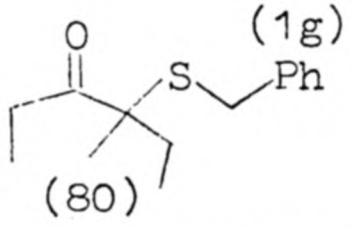
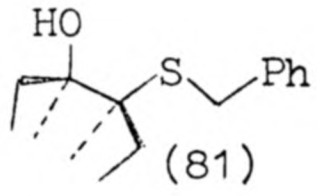
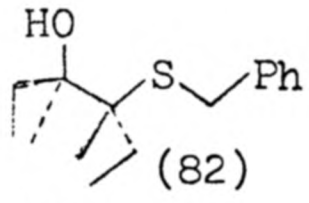
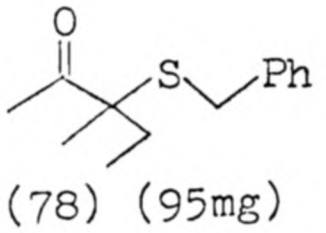
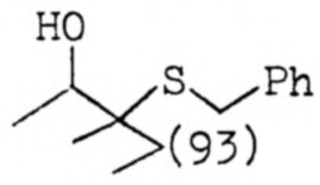
ketone (mass)	reagent (mol. equiv.) solvent (vol.)	conditions	product	diastereomer mixture [a]	yield
 (17) (4g)	MeMgI (1.9) Et_2O (80ml)	addn. at 20° reflux 80 min	 (106)		76% distilled
 (19) (0.3g)	MeMgI (5) Et_2O (25ml)	addn. at 25° reflux 4 h	 (105) + (19)		100% crude [b,c]
 (69) (0.5g)	MeMgI (2) Et_2O (60ml)	addn. at reflux reflux 1 h	 (70)	75:25 (70):(71)	94% crude [b]
			 (71)		
 (80) (50mg)	MeMgI (2) THF (50ml) (1g)	addn. at 0°, -5° 2h, reflux 30min	 (81)	50:50	52% chromat-ography [d]
	MeMgI (3) [e] $MgBr_2$ Et_2O (4ml)	addn. at 25° reflux 45h	 (82)	40:60 (81):(82)	71% crude
 (78) (95mg)	EtMgBr (2.5) Et_2O (10ml)	addn. at 25° reflux 50 min 20° 6 h	 (93)	66:34 [f] (81):(82)	99% [f] crude

TABLE 13 -footnotes

[a] Determined by integration of the 300 MHz ^{1}H n.m.r. spectrum.

[b] The sodium/ammonia reaction was performed on the crude product.

[c] The product is ca 1:1 mixture of alcohol:ketone (19).

[d] Using Kieselgel 60H (50g) with light petroleum/ether as eluant. The crude product contained ca 30% recovered (80).

[e] The $MgBr_2$ was prepared in situ by the reaction of magnesium with 1,2-dibromoethane.

[f] The crude product contained ca 55% 3° alcohols, 20% 2° alcohol and 20% recovered (78).

of diastereomers) 1.02 and 1.04 (3H, t, J 7.5 Hz, Me-CH_2-), 1.18 and 1.22 (3H, d, J 6. Hz, Me-CH(OH)-), 1.32 (3H, s, Me-CS-), 1.5-1.73 (2H, m, Me-CH_2CS-), 1.6 and 1.95 (1H, br s, -OH), 3.72 and 3.73 (2H, s, PhCH_2S-), 3.72 and 3.77 (1H, q, J ~ 6.5 Hz), 7.22-7.38 (5H, complex, aromatics); $\nu_{max.}$ (liquid film) 3460, 1600, 1490, 1450, 1375, 1280, 1065, 1010, 915, 700 cm^{-1}; m/e 224 (M^+), 179 (25%), 91 (100%).

(1RS,2RS)-2-Benzylthio-1,2-dimethylcyclohexanol (71)

Lithium hydride (13 mg) was added to a stirred solution of benzyl mercaptan in dimethylformamide (DMF) (15 ml) under nitrogen. The mixture was heated at 100° for 2h. 1,6-Dimethyl-7-oxabicyclo [4.1.0]heptane (94) (0.1 ml) was added to the mixture, and stirring at 100° was continued for 42h. Dilute hydrochloric acid and light petroleum were added and the separated organic layer was washed successively with aqueous sodium hydroxide and brine. The dried ($MgSO_4$) solution was evaporated to give a reddish oil (230 mg). Chromatography over Kieselgel 60H (9g) using light petroleum: ether as eluant, gave (1RS,2RS)-2-benzylthio-1,2-dimethylcyclohexanol (50 mg, 22%) which was identical with the sample isolated from the Grignard reaction on p. 98.

Reactions of β-(Benzylthio)alcohols with Sodium in Ammonia

General procedure: Ammonia was condensed (acetone/dry ice) under nitrogen onto a stirred solution of the β-(benzylthio)alcohol in a small amount of dry ether or onto the pure alcohol. Sodium was added to the mixture in very small pieces until a blue

colour persisted for 20 min. A few crystals of ammonium chloride were added until the blue colour disappeared. The ammonia was evaporated under a flow of nitrogen. Aqueous sodium hydroxide and ether were added and the organic layer extracted with aqueous sodium hydroxide (x2). The combined aqueous layers were acidified with dilute hydrochloric acid and extracted with ether (x2) and dichloromethane. Each of the organic layers was washed with brine and dried (Na_2SO_4). Evaporation of the solvent gave the crude product.

The particular conditions used for, and results from, the experiments performed are shown in Table 14.

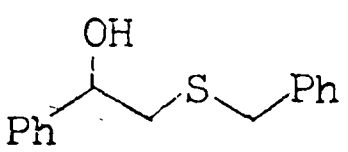
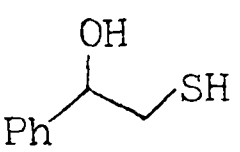
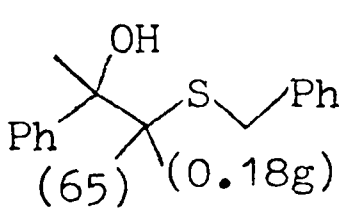
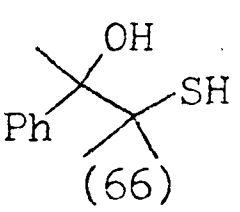
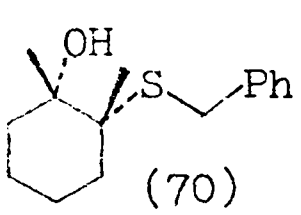
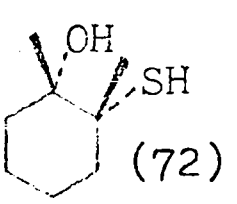
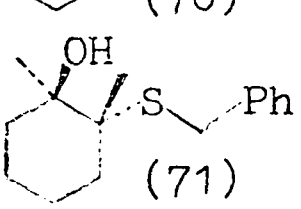
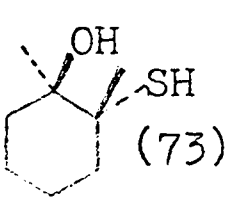
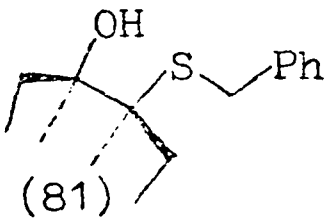
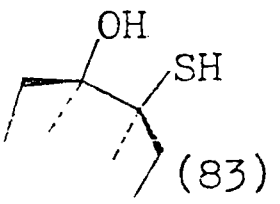
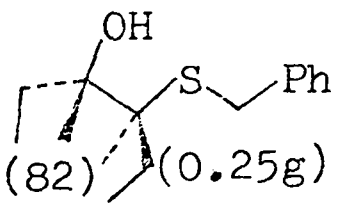
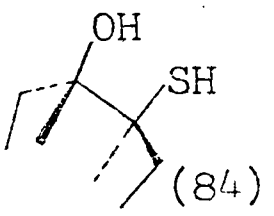
Spectral data for the products are as follows:-

2-Mercapto-1-phenylethanol (107): δ_H ($CC\ell_4$) 1.3 (1H, t, J 8.5 Hz, -SH), 2.5-2.9 (2H, m, CH_2SH), 3.15 (1H, br s, -OH), 4.55 (1H, t, J 6 Hz, PhCH(OH)-), 7.2 (5H, bs, aromatics); $\nu_{max.}$ (liquid film) 3420, 2560, 1605 cm^{-1}.

3-Mercapto-3-methyl-2-phenyl-2-butanol (66): δ_H ($CDC\ell_3$) 1.31 (3H, s, Me-C-S-), 1.45 (3H, s, Me-C-S-), 1.73 (4H, bs, Me-C(OH)- and -SH), 2.64 (1H, s, -OH), 7.2-7.7 (5H, complex, aromatics); $\nu_{max.}$ ($CC\ell_4$) 3620, 3520, 2580, 1600, 1490, 1445, 1370, 1340, 1170, 1110, 1065, 1030, 900, 700 cm^{-1}.

(1RS,2SR) and (1RS,2RS)-2-Mercapto-1,2-dimethylcyclohexanol (72) and (73): m.p. ca 20°, (Found: C, 59.75; H, 10.2; S, 20.1. $C_8H_{16}OS$ requires C, 59.95; H, 10.05; S, 20.0%); δ_H ($CDC\ell_3$): (1RS,2SR) (72) 1.24 (3H, s, Me-C(OH)-), 1.44 (3H, s, Me-C-S-),

TABLE 14 -Sodium/Ammonia Reactions

β-benzylthio-alcohol (mass)	solvents (vol.)	product	yield [a]
 (53) (0.5g)	NH_3 (100ml)	 (107)	ca45% crude [b]
 (65) (0.18g)	NH_3 (50ml) Et_2O (5ml)	 (66)	88.5% crude
 (70)	NH_3 (300ml)	 (72)	81.5% crude [c]
 (71) (2g)		 (73)	
 (81)	NH_3 (60ml)	 (83)	62% crude [d]
 (82) (0.25g)		 (84)	

[a] The condensation with benzaldehyde was performed on the crude material.

[b] The use of lithium (rather than sodium) gave the same result.

[c] A reaction on (70) gave only (72) and on a 3:1 mixture of (70):(71) gave a 3:1 mixture of (72):(73).

[d] Reaction on different mixtures of (81) and (82) gave ratios of (83) to (84) that were similar to the ratio of (81) to (82) used.

1.38-1.76 (7H, complex), 1.67 (1H, s, -SH), 1.9-2.03 (1H, m), 2.17 (1H, br s, -OH). (1RS,2RS) (73) 1.38 (3H, s, Me-C(OH)-), 1.45 (3H, s, -SH), 1.38-2.03 (8H, complex), 1.62 (1H, s, -SH), 2.15 (1H, br s, -OH); $\nu_{max.}$ (liquid film) 3475, 2540, 1450, 1365, 1315, 1180, 1145, 1090, 1045, 1000, 950, 910, 885 cm^{-1}.

(3RS,4RS) and (3RS,4SR)-4-Mercapto-3,4-dimethyl-3-hexanol (84) and (83): δ_H ($CDC\ell_3$): (3RS,4RS) (82) 0.99 (3H, t, J 7.5 Hz, Me CH_2-), 1.09 (3H, t, J 7.5 Hz, Me-CH_2-), 1.18 (3H, d, J 1 Hz, Me-C(OH)-), 1.3 (3H, d, J 1 Hz, Me-C.S-), 1.34 (1H, bs, -SH), 1.39-1.56 (1H, m, Me-CH_aH_b-), 1.58-1.77 (3H, complex, Me-CH_2 and Me-CH_aH_b), 2.17 (1H, br s, -OH). (3RS,4SR) (81) 0.98 (3H, t, J 7.5 Hz, Me-CH_2-), 1.09 (3H, t, J 7.5 Hz, Me-CH_2-), 1.17 (3H, d, J 1 Hz, Me-C(OH)-), 1.32 (3H, bs, Me-C.S-), 1.39-1.56 (1H, m, Me-CH_aH_b), 1.58-1.77 (3H, complex, Me-CH_2 and Me-CH_aH_b), 2.17 (1H, br s, -OH), ? (-SH); $\nu_{max.}$ (liquid film) 3490, 2550, 1455, 1375, 1270, 1120, 1100, 1040, .990, 915 cm^{-1}.

Formation of 2-Phenyl-1,3-oxathiolans

General procedure: p-Toluenesulphonic acid (ca 0.005 equivalents) and an excess of distilled benzaldehyde were added to a stirred solution of the β-mercaptoalcohol in dry benzene. The mixture was refluxed under nitrogen. The reaction was considered to have gone to completion when no spot corresponding to starting material was observed on thin layer chromatography (t.l.c.). Evaporation of the benzene and benzaldehyde gave the crude product.

The particular conditions used for, and results from,

the experiments performed are shown in Table 15.

Spectral data for the products are as follows:-

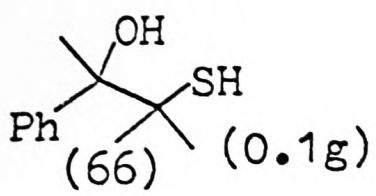
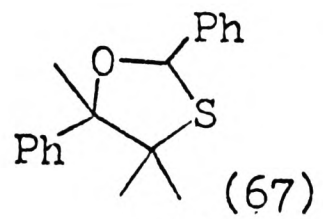
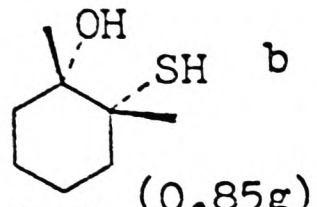
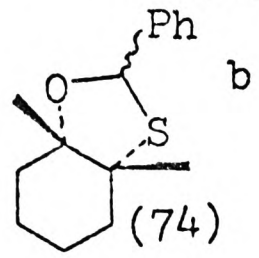
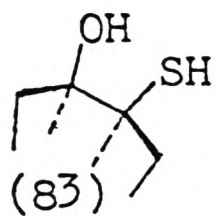
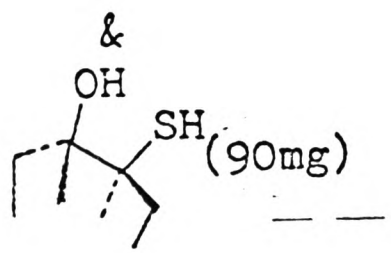
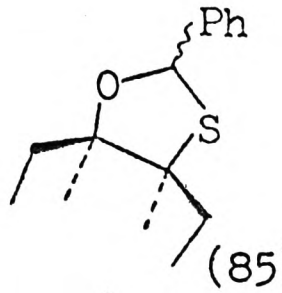
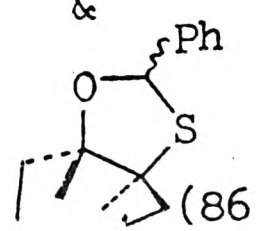
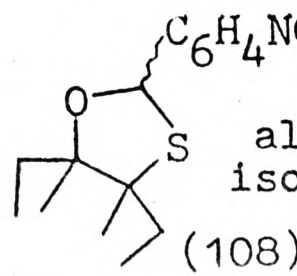
4,4,5-Trimethyl-2,5-diphenyl-1,3-oxathiolan (67): δ_H ($CDC\ell_3$) (mixture of diastereomers, major diastereomer underlined) 1.1 and 1.13 (3H, s), 1.54 and 1.59 (3H, s), 1.9 (3H, s), 6.3 and 6.56 (1H, s, PhCH(O-)S-), 7.25-7.6 (10H, complex, aromatics); $\nu_{max.}$ (liquid film) 1600, 1490, 1445, 1370, 1230, 1130, 1105, 1065, 1025, 900, 765, 700 cm^{-1}; m/e 285 ($(M + 1)^+$, CI), 210 (40%), 177 (30%), 164 (100%), 163 (50%).

(1RS,6SR,8RS) and (1RS,6SR,8SR)-1,6-Dimethyl-7-oxa-8-phenyl-9-thiabicyclo [4.3.0]nonane (74):† (1RS,6SR,8RS) m.p. ca 20°, (Found: C, 72.3; H, 8.1; S, 12.65. $C_{15}H_{20}OS$ requires C, 72.55; H, 8.1; S, 12.9%); δ_H ($CDC\ell_3$): (1RS,6SR,8RS) 1.43 (3H, s, Me-), 1.44 (3H, s, Me-), 1.28-1.9 (6H, complex), 2.15-2.32 (2H, complex), 6.23 (1H, s, PhCH(O-)S-), 7.26-7.42 (3H, complex), 7.47-7.55 (2H, complex); δ_H ($CDCl_3$) : (1RS,6SR,8SR) 1.38 (3H, s, Me-), 1.47 (3H, s, Me-), 1.28-1.9 (6H, complex), 2.0-2.32 (2H, complex), 6.15 (1H, s, PhCH(O-)S-), 7.26-7.42 (3H, complex), 7.47-7.55 (2H, complex); $\nu_{max.}$ (liquid film) 1600, 1495, 1450, 1380, 1225, 1095, 1020, 990, 700 cm^{-1}; m/e 248 (M^+), 142 (70%), 109 (100%).

4,5-Diethyl-4,5-dimethyl-2-phenyl-1,3-oxathiolan (85) and (86): b.p. ca 110° at 0.02 mm Hg; δ_H ($CDC\ell_3$) (mixture of 4 diastereomers) 1.0-2.0 (62H, complex), 2.32 (2H, m), 5.95 (2H, s, PhCH(O-)S-), 6.03 (2H, s, PhCH(O-)S-), 7.27-7.52 (20H, complex, aromatics); $\nu_{max.}$ (liquid film) 1490, 1450, 1375, 1230, 1230, 1110, 1050, 1020, 700,

†The assignment of stereochemistry to the two diastereomeric oxathiolans is based on an NOE experiment.

TABLE 15 -Preparation of 2-Phenyl-1,3-oxathiolans

β-mercapto-alcohol (mass)	solvent (vol.)	aldehyde (mol. equiv.)	conditions	product	yield [a]
 (66) (0.1g)	C_6H_6 (5ml)	PhCHO (2.8)	reflux 4h	 (67)	90% crude
 [b] (72) (0.85g)	C_6H_6 (30ml)	PhCHO (2)	reflux 10h	 [b] (74)	83% crude
 (83) &  (90mg) (84) (35mg)	C_6H_6 (3ml)	PhCHO (3)	reflux 16h	 (85) &  (86)	93.5% crude
	C_6H_6 (3ml)	$p\text{-}O_2NC_6H_4CHO$ (4)	reflux 7h, 20° 20h	 all isomers (108)	84% chromat-ography [c]

695 cm^{-1}; m/e 250 (M^+), 178 (50%), 144 (30%), 111 (25%), 91 (40%), 88 (100%); M^+ 250.1391. $C_{15}H_{22}OS$ requires 250.1391.

4,5-Diethyl-4,5-dimethyl-2-(p-nitrophenyl)-1,3-oxathiolan (108): δ_H ($CDC\ell_3$) (mix of 4 diastereomers) 0.98-2.0 (62H, complex), 2.28 (2H, m), 6.0 (2H, s, PhCH(O-)S-), 6.4 (2H, s, PhCH(O-)S-), 7.54-7.63 (8H, complex, aromatics), 8.17-8.25 (8H, complex, aromatics); $\nu_{max.}$ (liquid film) 1600, 1520, 1450, 1345, 1105, 910, 855, 710 cm^{-1}; m/e 265 ($(M - 30(NO))^+$, 10%), 144 (10%), 122 (25%), 121 (100%, 120 (30%).

Reaction of the Diasteromeric 2-Mercapto-1-2-dimethylcyclohexanols (72) and (73) with p-Toluenesulphonic Acid

p-Toluenesulphonic acid (ca 0.5 mg) was added to a stirred solution of (1RS,2RS) and (1RS,2SR)mercaptoalcohols (ca 25 mg of a ca 1:3 mixture) in dry benzene (4 ml). The mixture was refluxed under nitrogen for 7h. Evaporation gave (1RS,2SR)-2-mercapto-1,2-dimethylcyclohexanol (72) free from any of the (1RS,2RS) isomer (73) as shown by comparison with authentic spectra.

TABLE 15 -footnotes

[a] Reaction with LDA was performed on the crude material.

[b] Reaction of the 'trans' mercaptoalcohol (73) gave no oxathiolan. A mixture of (72) and (73) gave only the oxathiolan (74).

[c] Using Kieselgel 60H (5g) with light petroleum/ether as eluant.

SECTION 5

Reaction of 2-Phenyl-1,3-oxathiolans with LDA

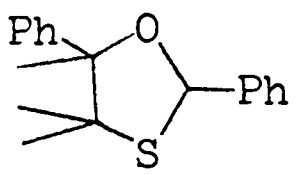
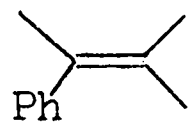
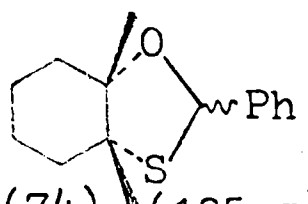
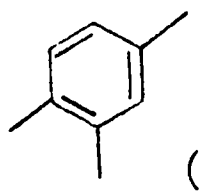
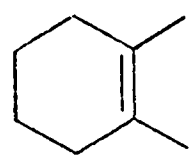
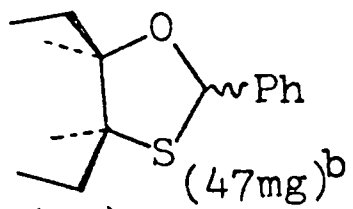
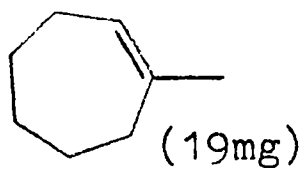
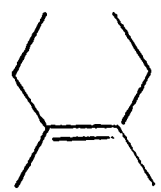
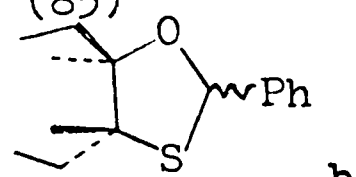
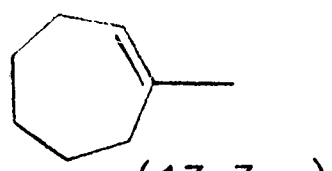
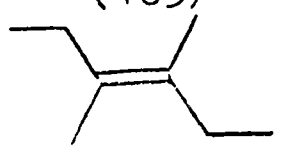
The particular conditions used for, and results from, these experiments are shown in Table 16.

General procedure: n-Butyllithium (ca 1.5 M, see Table 16. for amount) was added dropwise under nitrogen to a stirred solution of diisopropylamine (1.5 equivalents compared to butyllithium) in dry ether (half of the total volume used) at 0^{o}. The mixture was stirred under a slow flow of nitrogen at 20^{o} for 15 min. A solution of the 2-phenyl-1,3-oxathiolan and the g.l.c. standard (where used) in ether (the rest of the total volume) was added to a stirred solution of the base at 20^{o}. The work up involved addition of a little water followed by aqueous sodium hydroxide. The separated organic layer was washed successively with aqueous sodium hydroxide (x2), dilute hydrochloric acid (x3) and brine (x3). 2-Methyl-3-phenyl-2-butene (101) and 1,2-dimethylcyclohexene (102) were isolated crude by evaporation of the dried ($MgSO_4$) solution.

The g.l.c. work was performed on a Carlo Erba capillary g.c. 2151 machine using an OV 101 capillary column (WCOT, 50 m). The relevant retention times were: (104), 27 min at 35^{o}; (103), 28 min at 35^{o}; n-octane[†], 28.6 min at 35^{o}, 1-methylcycloheptene, 39 min at 35^{o}; (102), 28 min ($40-70^{o}$, programmed); 1,2,4-trimethylbenzene, 38 min ($40-70^{o}$, programmed). These assignments are discussed

[†]Assumed to be an impurity in n-butyllithium. The peak area on g.l.c. for this was 10-20% of the combined hexene peak areas. It was identified by comparison of its mass spectrum with an authentic spectrum.

TABLE 16 -Cycloeliminations of 2-Phenyl-1,3-oxathiolans

oxathiolan (mass)	isomer ratio	base(mol. equiv.) solvent (vol.)	glc standard (mass)	conditions	product	isomer ratio	yield [a]
 (67) (95mg)	-	LDA (5) Et_2O (5ml)	-	20° 9h	 (101)	-	ca 75% crude
 (74) (125mg)	-	LDA (5) Et_2O (6ml)	 (60mg)	20° 8h	 (102)	-	92% glc
 (85) (47mg)[b]	1.63	LDA (3) Et_2O (4ml)	 (19mg)	20° 9h	 (103)	1.63	98% glc
 (86) (32mg)[b]	0.47	LDA (8) Et_2O (5ml)	 (13.3mg)	20° 11h	 (104)	0.47	100% glc

[a] Authentic samples of (103) and (104) and 1-methylcycloheptene showed the FID detector sensitivities to be the same for these. It was assumed that the same was true for 1,2,4-trimethylbenzene and 1,2-dimethylcyclohexene.[143] Glc peak areas were estimated using triangulation, height x width at half height and cut and weigh methods.

[b] Masses refer to mixtures of (85) and (86) in the ratio shown.

on p. 70- 71.

Spectral data for the compounds were as follows:-

2-Methyl-3-phenyl-2-butene (101): δ_H ($CDC\ell_3$) 1.6 (3H, bs), 1.8 (3H, s), 1.95 (3H, bs), 7.0-7.4 (5H, complex) (lit.,[140] δ_H ($CC\ell_4$) 1.56 (3H, bs), 1.78 (3H, s), 1.92 (3H, bs), 6.9-7.3 (5H)).

1,2-Dimethylcyclohexene (102): δ_H ($CDC\ell_3$) 1.54-1.6 (4H, m, $-C\underline{H}_2-$(C-4 and 5)), 1.6 (6H, bs, $\underline{Me}-C=$), 1.87-1.94 (4H, m, $-C\underline{H}_2-C=$), (lit.,[141] δ_H ($CC\ell_4$) 1.91 (broad peak), 1.58 (s, $-C\underline{H}_3$) some of the ring protons lie under this last peak); m/e 110 ($\underline{M}^+$), 95 (100%).

cis and trans-3,4-Dimethyl-3-hexene (103, 104): m/e (same for both diastereomers) 112 ($\underline{M}^+$), 97 (10%), 83 (80%), 69 (20%), 55 (100%). The mass spectra were identical with those of the olefins made as on p. 110 and co-injections on g.l.c. showed identical retention times for the olefins made by either procedure.

dℓ- and meso-3,4-Dimethylhexane-3,4-diol[142]

A solution of mercury (II) chloride (12g) in acetone (100 ml) was added, under nitrogen, to a stirred mixture of magnesium turnings (10g) in dry benzene (150 ml) at such a rate as to maintain reflux - initial reflux was attained by heating the mixture after the addition of a small portion of the mercury (II) chloride solution. After the addition, acetone (40 ml) in dry benzene (40 ml) was added and the mixture was refluxed for 9h. Water was added and the mixture was stirred vigorously for 20 min

and filtered at ca 40°. Benzene (100 ml) was added to the solid and the mixture was stirred and refluxed for 15 min, and filtered. Evaporation of the combined filtrates gave 3,4-dimethylhexane-3,4-diol (62g, 100%) as an oil.

A portion of the crude oil was distilled and addition of light petroleum to the distillate, followed by cooling and scratching induced crystallisation. The solid was recrystallised from light petroleum to give dℓ-3,4-dimethylhexane-3,4-diol[129], m.p. 52-3° (lit.,[129] m.p. 52-3°); δ_H ($CDC\ell_3$) 0.96 (6H, t, J 7.5 Hz, Me-CH_2-), 1.14 (6H, bs, Me-C(OH)-), 1.41 and 1.65 (4H, (ABq)q, J 14 and 7 Hz, Me-CH_2-), 1.97 (2H, br s, -OH). The mother liquor was a mixture of the diastereomeric alcohols and from this was obtained for the meso-diol δ_H ($CDC\ell_3$) 0.96 (6H, t, J 7.5 Hz), 1.12 (6H, bs), 1.35-1.48 (2H, m), 1.59-1.73 (2H, m), 2.03 (2H, br s).

cis and trans-3,4-Dimethyl-3-hexene[127] (103) and (104)

Triethyl orthoformate (19 ml) and benzoic acid (100 mg) were added to crude 3,4-dimethylhexane-3,4-diol (from above; 20 ml) and the mixture was heated at 125-135° for 2h, ethanol being distilled off. The temperature was raised to 200° and, after discarding the first few mls, the distillate was collected, washed with water and dried ($MgSO_4$) to give 3,4-dimethyl-3-hexene (7.1g; 46%) as a clear oil, b.p. 98° at 760 mm Hg (lit.,[127] b.p. 95-8°); δ_H ($CDC\ell_3$) (2 diastereomers) 0.94 (6H, t, J 7.5 Hz,

Me-CH_2-), 0.96 (6H, t, J 7.5 Hz, Me-CH_2-), 1.62 (6H, s, Me-C=), 1.63 (6H, s, Me-C=), 2.01 (4H, q, J 7.5 Hz, Me-CH_2-), 2.03 (4H, q, J 7.5 Hz, Me-CH_2-); $\nu_{max.}$ (liquid film) 1625, 1455, 1370, 1155, 1070 cm^{-1}; m/e (same for both diastereomers) 112 (M^+), 97 (10%), 83 (80%), 69 (20%), 55 (100%).

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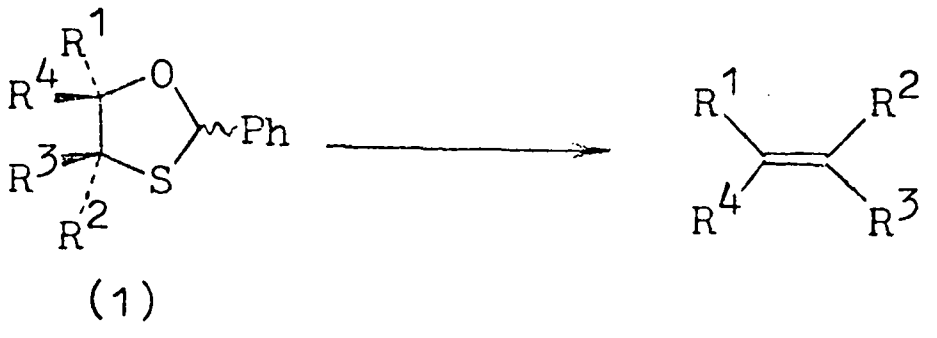
Summary

The work discussed in this thesis concerns approaches to 2-phenyl-1,3-oxathiolans (1) and their cycloreversion to olefins[1] (Scheme 1).



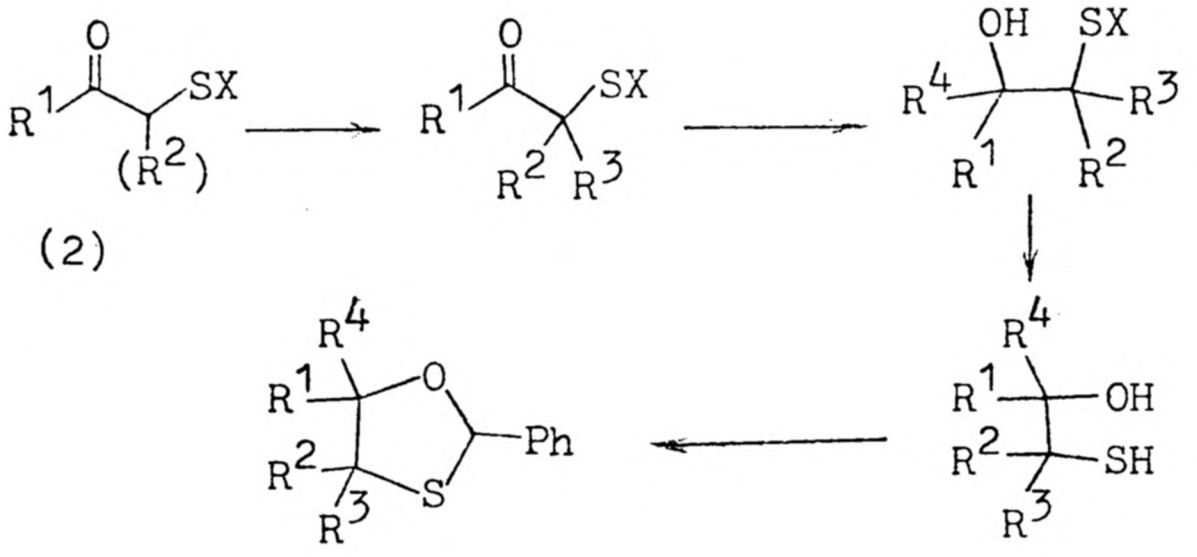
(1)

Scheme 1

The existing examples of oxathiolan cycloreversions in olefin formation[1] suggested that a wide variety of olefins should be accessible *via* this reaction. The preparations of the oxathiolans used however, all involved the opening of an epoxide with a sulphur nucleophile. Our initial aim was to find a more general approach to oxathiolans and thus, hopefully, to olefins.

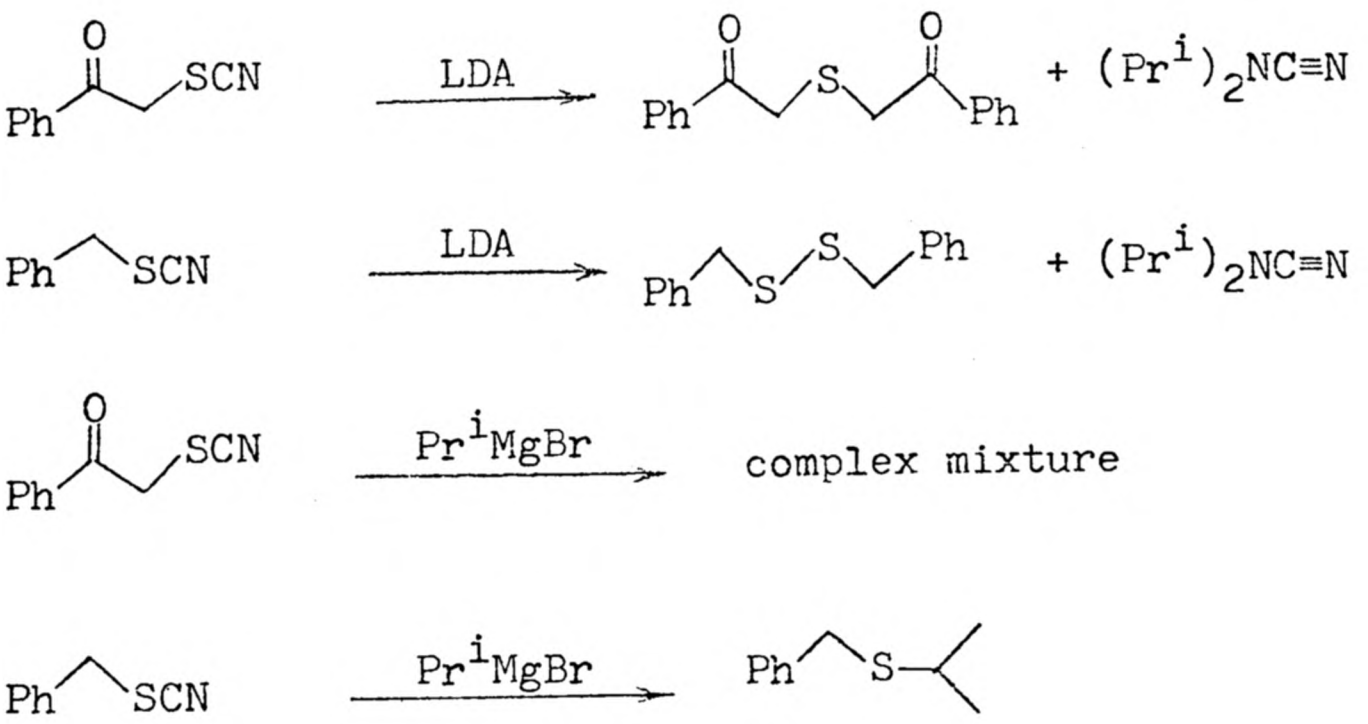
Scheme 2 is an outline of the scheme that it was originally hoped to follow.

β-Ketothiocyanates (2, X = -C≡N) were considered as possible starting points for the synthesis. The thiocyanate group, however, appeared too labile to the type of reaction conditions required for elaboration of (2) as in Scheme 2 (see Scheme 3).



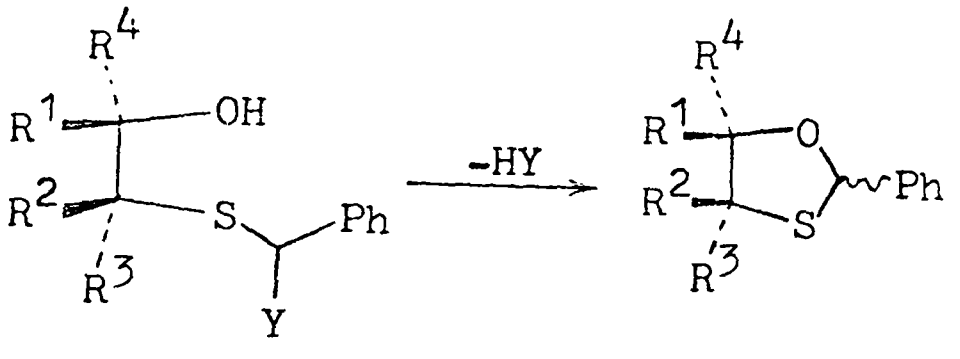
(2)

Scheme 2



Scheme 3

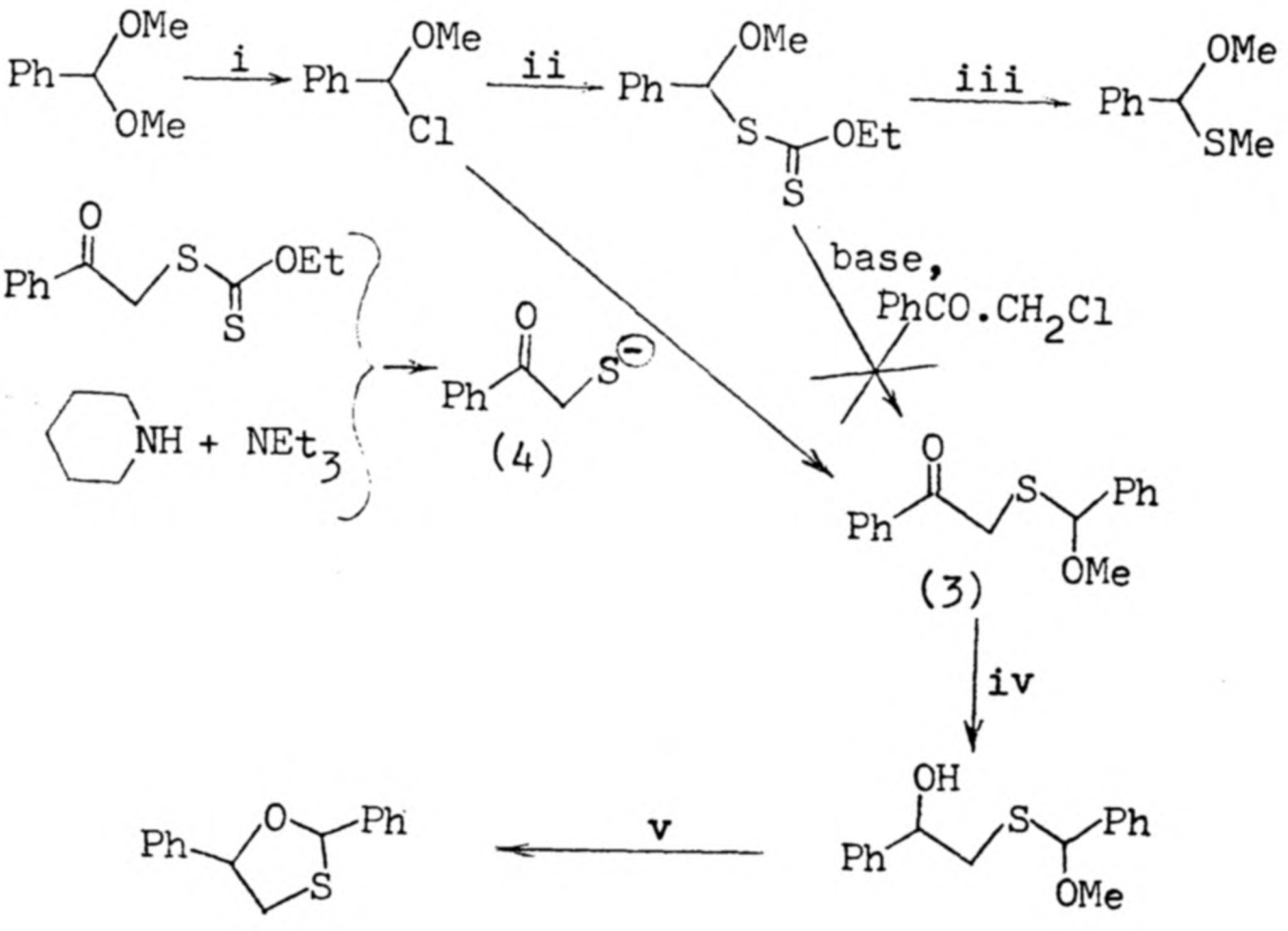
On the basis of indications that the benzyl group might prove a useful protecting group for sulphur[2] (i.e. X = CH_2Ph, Scheme 2), the possibility of an oxathiolan preparation not involving a β-mercaptoalcohol precursor was investigated. The basic idea is shown in Scheme 4.



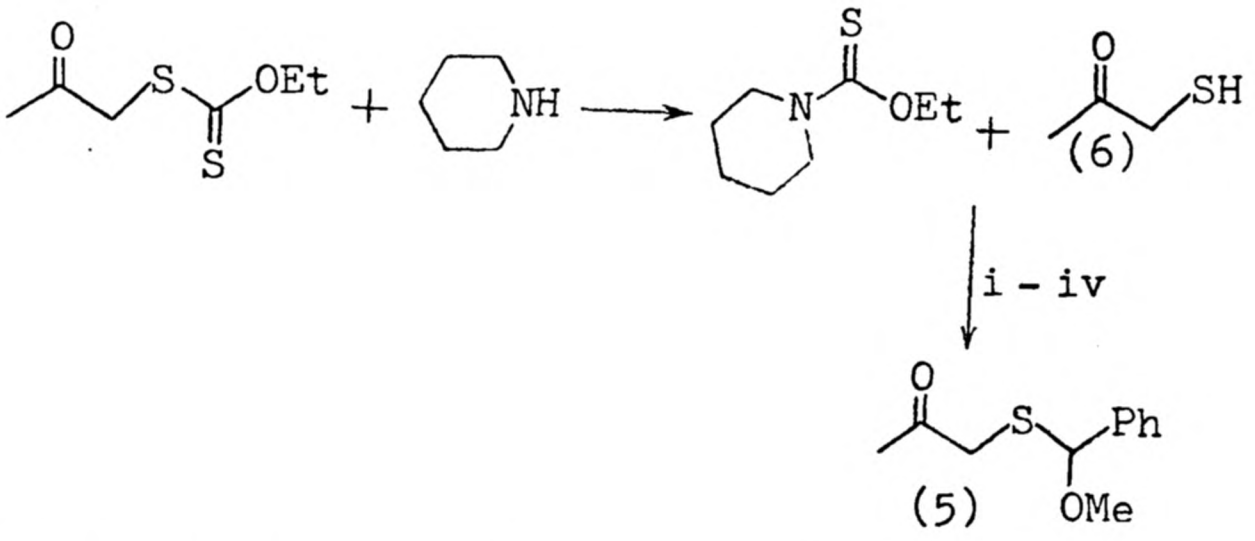
Scheme 4

Two attempts to achieve an oxathiolan synthesis following this methodology are outlined in Scheme 5.

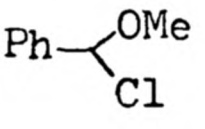
Formation of (3) was achieved by an <u>in situ</u> reaction of the anion (4) generated from the dithiocarbonate shown. An attempt to prepare the acetonyl compound (5) (Scheme 6) by an analogous route failed but it was found that when the thiol (6) was isolated the desired (5) could be formed quite cleanly. Attempts to use either of the above procedures to prepare the cyclohexanonyl compound (7) failed.

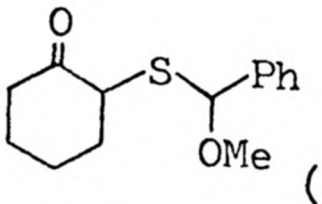


Scheme 5 : i $SOCl_2$; ii $EtOCS_2K$; iii MeI, NaOMe; iv $LiAlH_4$; v p-TsOH



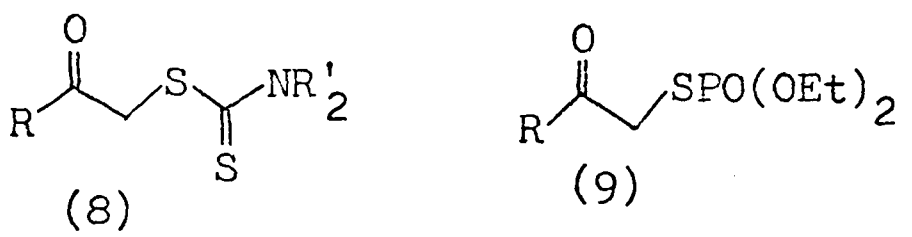
Scheme 6 : i NaOH aq. extraction ; ii dil. HCl ;
iii CH_2Cl_2 extraction ; iv

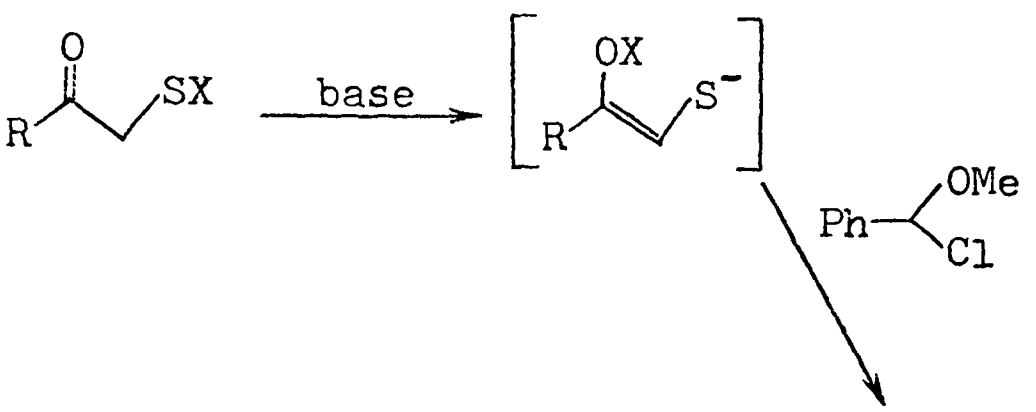


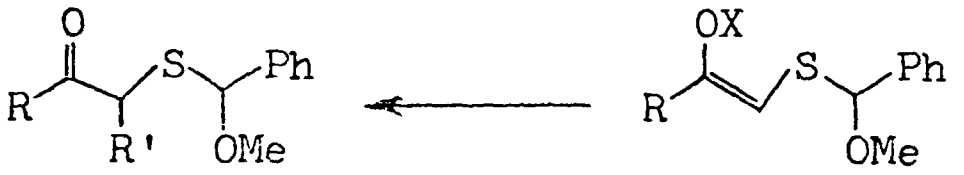


(7)

An investigation of β-ketodithiocarbamates (8) and β-ketophosphorothiolates (9) as potential starting materials for formation of (α-(α'-methoxybenzyl)thio)ketones according to Scheme 7, proved unfruitful.



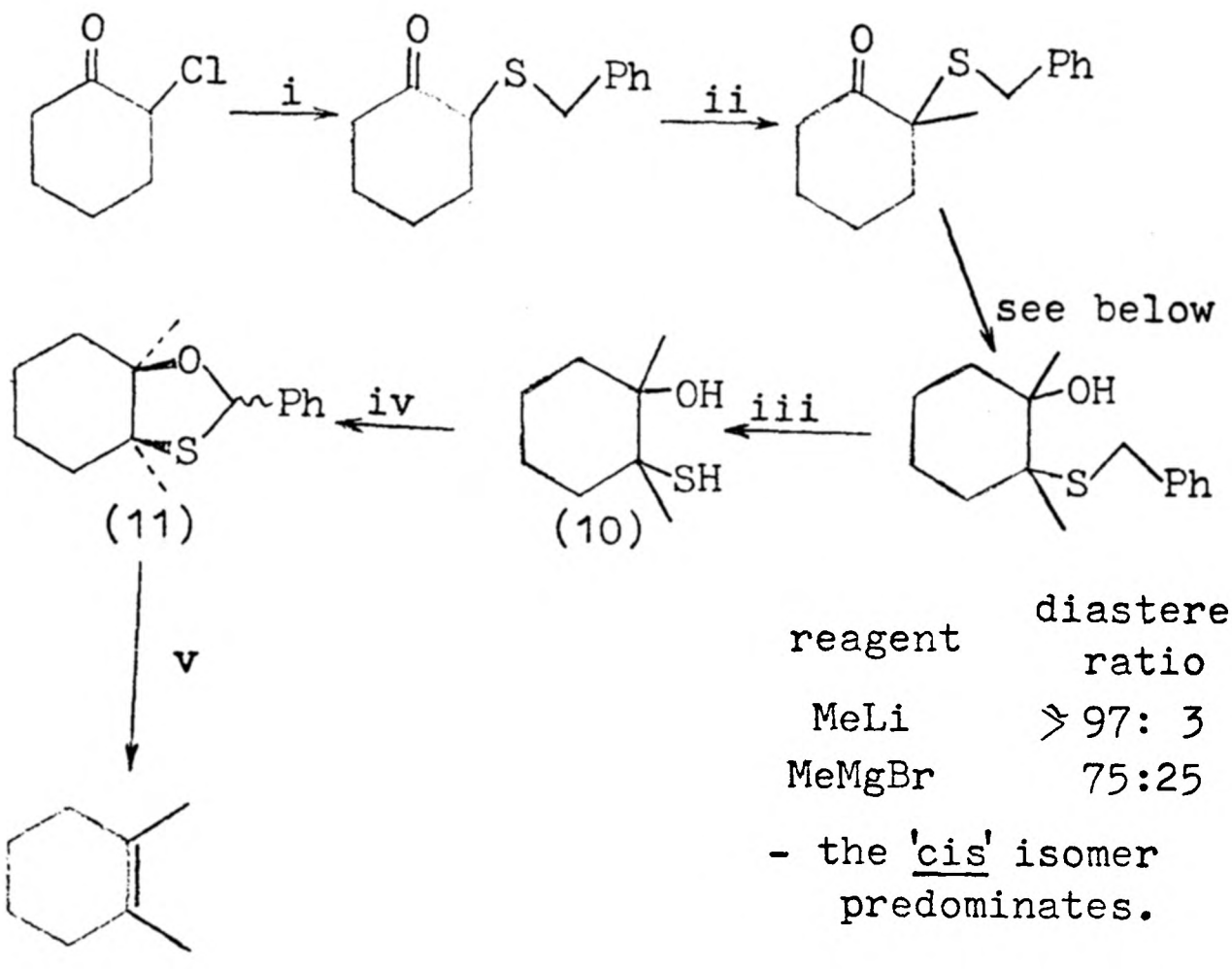




Scheme 7

The phenacyl compound (3) was treated under various conditions in attempts to achieve the transformations in the first two steps of Scheme 2. These reactions proved unpromising and this approach to oxathiolans was abandoned.

The decision was made to revert to the plan proposed in Scheme 2 using the benzyl group as protection for sulphur. The results obtained are outlined in Schemes 8-10.



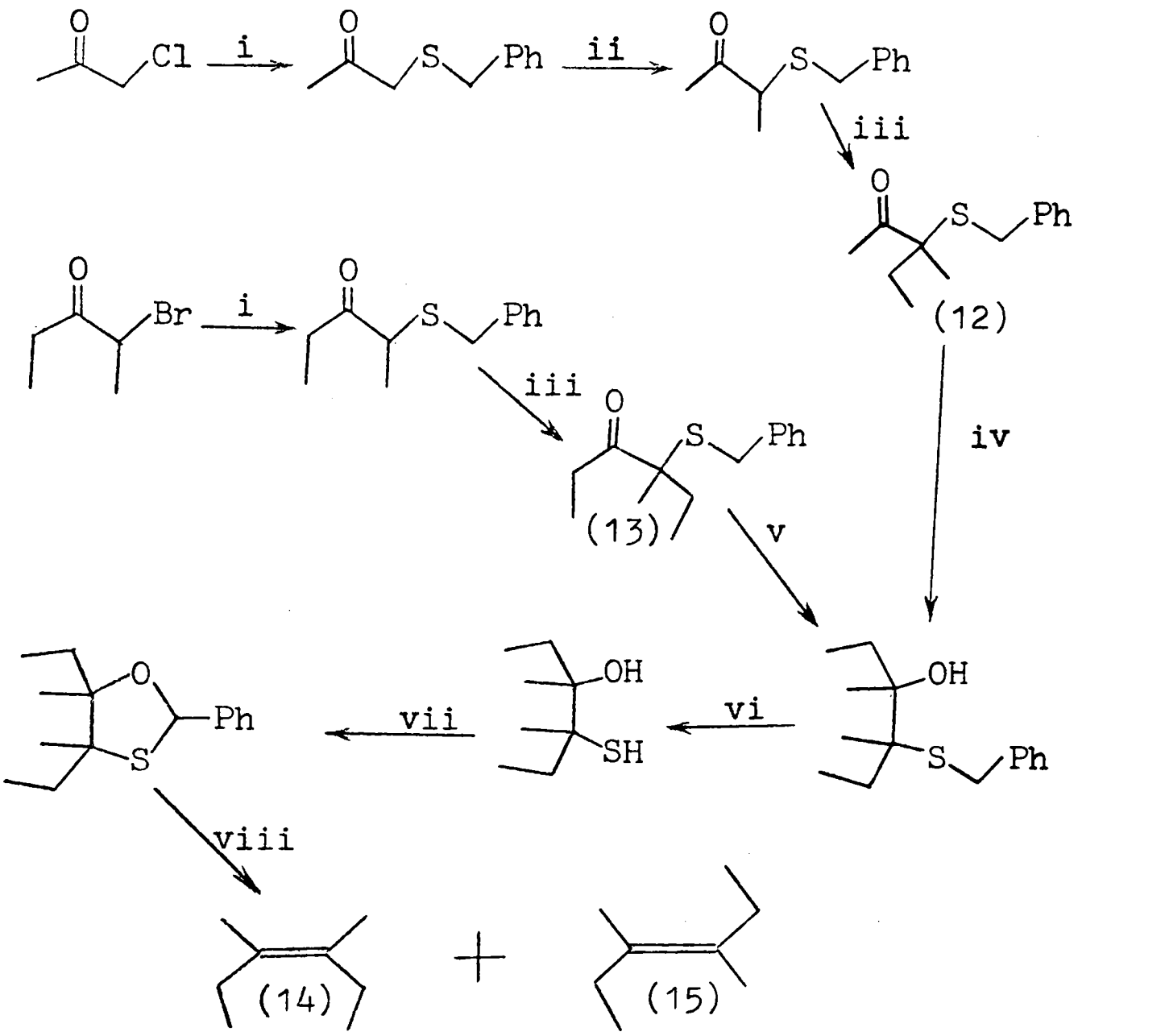
reagent	diastereomer ratio
MeLi	⩾ 97: 3
MeMgBr	75:25

- the 'cis' isomer predominates.

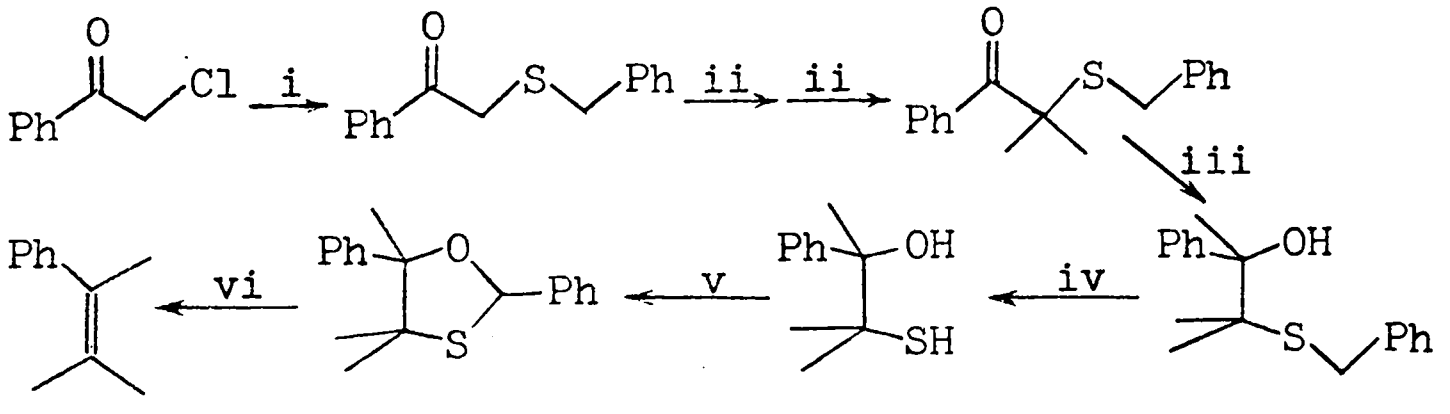
Scheme 8 i $PhCH_2SH$, NEt_3; ii NaH, MeI; iii Na, NH_3; iv PhCHO, p-TsOH; v LDA.

The reaction of the β-mercaptoalcohol (10) with benzaldehyde gave only the cis-fused bicycle (11). The trans-mercaptoalcohol decomposed, probably to give initially an episulphide, on treatment with p-toluene-sulphonic acid in benzene.

In the reactions of the α-(benzylthio)ketones organolithium compounds were generally more stereoselective than Grignard reagents and gave higher yields of the alcohols. The reaction of the ketone (12) with ethyllithium gave ultimately a ca 6:4 mixture of (14) to (15) whereas reaction of (13) with methyllithium gave ultimately a ca 3:7 mixture of (14) to (15). The selectivity in the organometallic reaction may be rationalised in terms of a preferred trans-orientation of the carbonyl

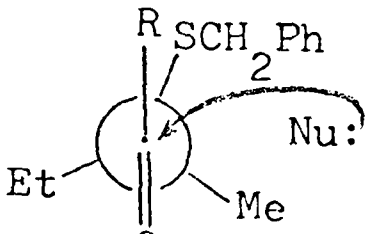


Scheme 9 : i $PhCH_2SH, NEt_3$; ii $NaOAm^t$, MeI ; iii NaH, EtI ; iv EtLi ; v MeLi ; vi Na, NH_3; vii PhCHO, p-TsOH ; viii LDA .



Scheme 10 : i $PhCH_2SH, NEt_3$; ii NaH, MeI ; iii MeLi ; iv Na, NH_3 ; v PhCHO, p-TsOH ; vi LDA .

and thio groups in the transition state of the addition, Scheme 11. Unfortunately the diastereomers formed in the reaction had very similar retention times on chromatography and so they were not separated. Nevertheless the ratios of diastereomers did not change during the reactions carried out subsequent to the ketone addition step and stereochemical integrity was therefore considered to be maintained in these subsequent steps.



Scheme 11

Despite the non-isolation of pure diastereomers in the aliphatic system (Scheme 9) and the slightly disappointing selectivity in the organometallic additions, the relatively high yields found for the reactions shown in Schemes 8-10 suggest that the general approach may have wide applicability. The high yields (75-100%) in the olefin forming cycloreversion reactions were particularly encouraging.

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