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A Thesis Entitled

SYNTHETIC STUDIES TOWARDS VIRANTMYCIN

By

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A thesis submitted to the Council for National Academic Awards in partial fulfilment for the degree of Doctor of Philosophy

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DECLARATION

I declare that the research presented herein is original work carried out by the author and has not been submitted for any other degree.

Date

Signed:

S.K. Richardson (Author)

A.T. Hewson (Supervisor)

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Synthetic studies towards virantmycin

Stewart K Richardson

ABSTRACT

The use of vinylphosphonium salts in the construction of acyclic and cyclic systems by both ourselves and others is reviewed.

The alkylthio and arylthio vinylphosphonium salts are used in an unsuccessful approach to the synthesis of the tetrahydroquinoline natural product virantmycin. The use of this approach in the early stages of a synthesis of carbaprostacyclin and analogues is also examined.

The synthesis of virantmycin was also investigated using a regioselective Dieckmann reaction. Two procedures have been developed for the synthesis of the mixed O,S-diester required to study the cyclisation. The first of these has as the key step a one carbon homologation reaction of a benzaldehyde to a phenylacetic acid derivative. The second relies on a pericyclic rearrangement reaction. The latter route has proved more successful and the Dieckmann product has been made using this procedure. Applications of this to the synthesis of virantmycin are discussed.

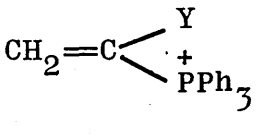
The use of methyl methylsulphinylmethyl sulphide in the one carbon homologation for the synthesis of the Dieckmann precursor has been extended. Thus a set of conditions has been developed for the synthesis of chloroketenedithioacetals from ketenedithioacetal S-oxides which complements the only other known set of conditions for this transformation. Under our conditions the ketene dithioacetal S-oxide derived from 2-aminobenzaldehyde cyclises to give two indoles. A modified set of conditions are presented which give rise to anomalous products. In the light of this a mechanism is proposed.

Finally the use of this strategy is extended to a synthesis of benzofurans and further discussion shows how this might be used in a general preparation of thiol esters and in the synthesis of other heterocyclic systems or natural products.

CHAPTER 1

The development and use of vinyl phosphonium salts

1.1 The use of the vinyl phosphonium salts 1 in synthesis has been of significant interest over the past 20 years[1]. The main reason for this has been their dual role as Michael accepters and/or Wittig reagents for both intermolecular and intramolecular processes.



1

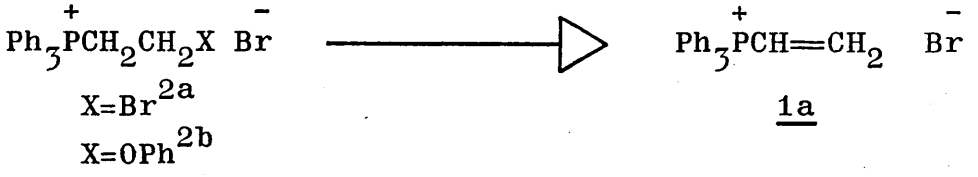
1a Y=H

1b Y=OC_2H_5

1c Y=SCH_3

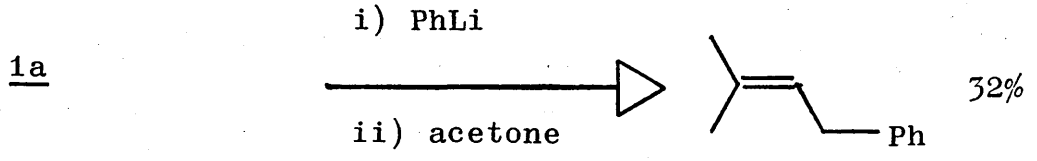
1d Y=SC_6H_5

The simplest analogue of 1, namely vinyltriphenyl phosphonium bromide 1a, was first prepared independently by two groups[2a,2b] using a 1,2 elimination sequence (Scheme 1). In both of these early reports the potential use of 1a, as a Michael accepter was recognised. Seyferths group[2a] performed an intermolecular conjugate addition/



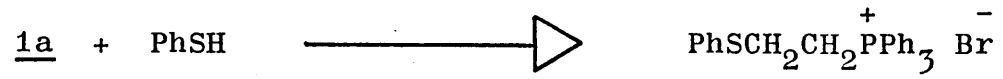
Scheme 1

Wittig trapping reaction using phenyl lithium and acetone to give 2-methyl-4-phenyl-2-butene in low



Scheme 2

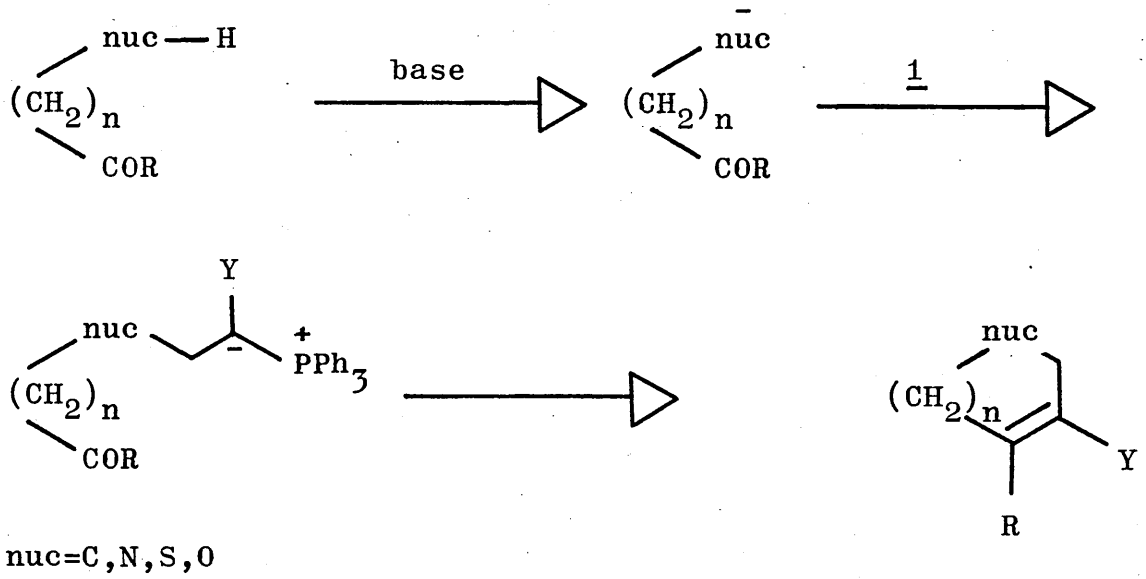
yield (Scheme 2). Schweizer's group[2b] extended this using heteroatoms as nucleophiles to give the adducts 2 (Scheme 3).



Scheme 3

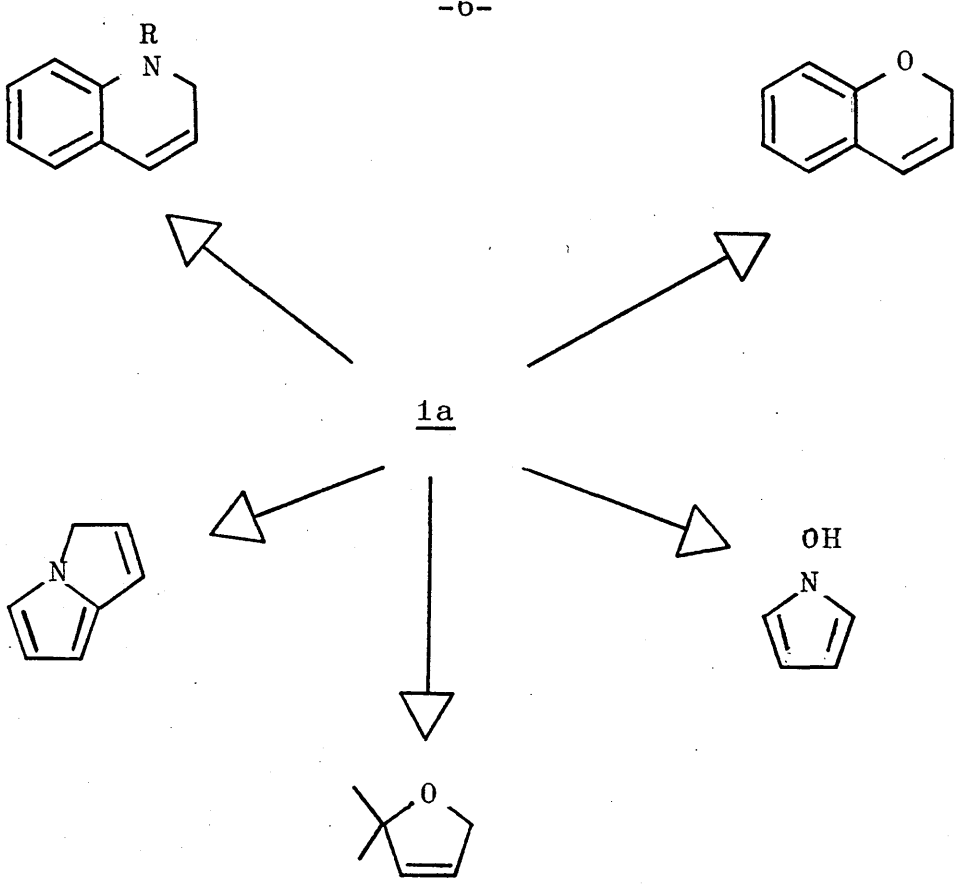
2

Thus 1a has been shown (Scheme 2 and ref 3) to give low to moderate yields of chain extended compounds, but the vast majority of work in this area has involved the construction of cyclic systems. This relies on both Michael donor and carbonyl group being part of the same molecule (Scheme 4).



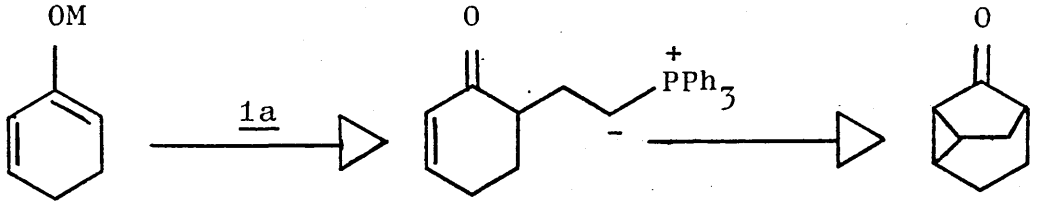
Scheme 4

A large variety of carbocyclic and heterocyclic compounds have been assembled using this strategy. For example chromenes from salicylaldehyde[4,5], dihydrofurans from α hydroxy aldehydes or ketones[6], pyrrolizines from 2-formylpyrroles[7], cycloalkenes from ketoesters[8], dihydroquinolines from 2-amino benzaldehydes[9] and pyrroles from α ketoximes[10]. Some of these transformations are outlined in Scheme 5. An isolated use of 1a in a non



Scheme 5

Wittig reaction has also been reported[11,12] (Scheme 6).

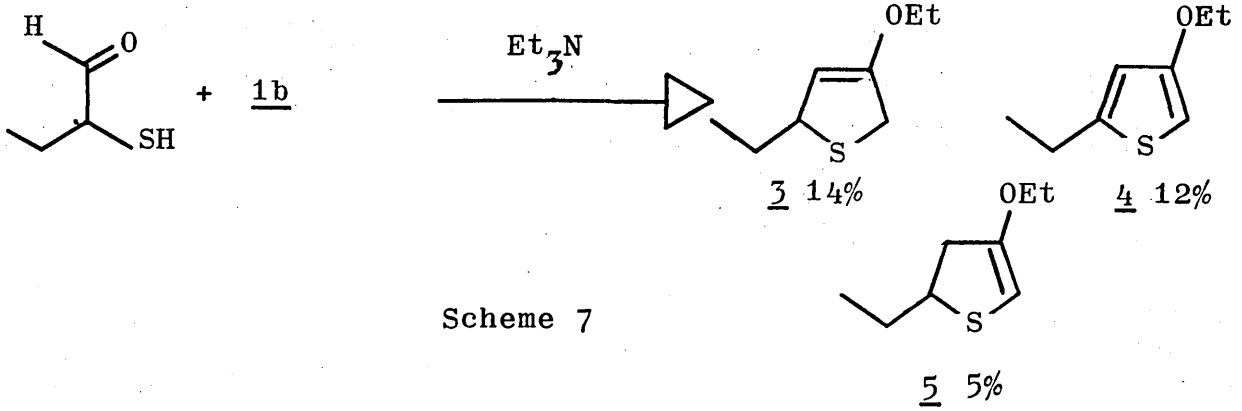


Scheme 6

Because of these useful reactions it is perhaps surprising that more use has not been made of 1a in natural product synthesis. This points to the fact that there is a major obstacle to the widespread use of 1a and that is that the product obtained is an alkene (Scheme 4, Y=H). Whilst isolated carbon-carbon double bonds can be useful functional groups[13], for example via their hydroboration to alcohols, oxidation to oxiranes or ketones and halogenation, the often

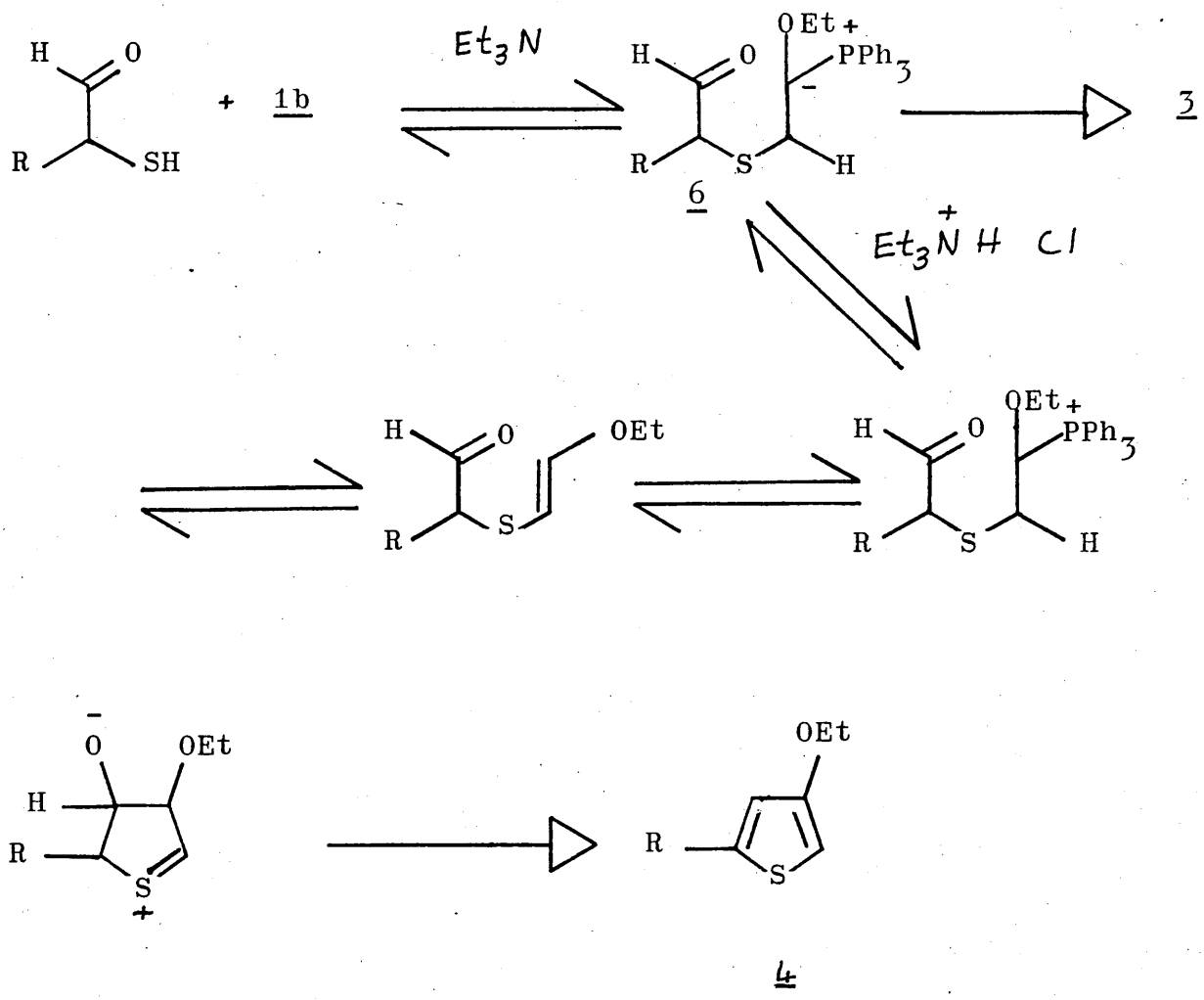
non chemoselective or regioselective conditions associated with these transformations may preclude the use of 1a in the synthesis of complex organic molecules. Thus a substituted alkene (or vinyl derivative) was required which could be converted under mild conditions to a more useful functional group.

Both vinylethers (Scheme 4, Y=OR) and vinylthioethers (vinylsulphides, Scheme 4, Y=SR) are readily converted to carbonyl groups. Because of the importance of the carbonyl group in general organic chemistry any method for the introduction of this functionality is extremely useful. Thus a corresponding route to vinylethers or vinylsulphides would be equally important. In order to synthesise these latter compounds using the strategy outlined earlier (Scheme 4) the corresponding phosphonium salts 1b, 1c and 1d were required. A number of research groups concerned themselves with this problem. McIntosh, at the University of Windsor, reported the synthesis of 1-ethoxy vinyltriphenyl phosphonium bromide 1b[14] (for other examples of ethoxy substituted phosphonium salts or phophonates see ref 15 and 16) and noted its ability to function as a Michael accepter[14]. He subsequently used it in the formation of dihydrothiophenes[17] (Scheme 7). Unfortunately the yield of the expected



Scheme 7

vinylether 3 was low (even allowing for the presence of the isomeric compound 5). The presence of 2-ethyl-4-ethoxy thiophene 4 was explained not in terms of atmospheric oxidation of 3 or 5 as both of these compounds were stable to air. Instead a different mechanism was proposed[17,18] (Scheme 8).



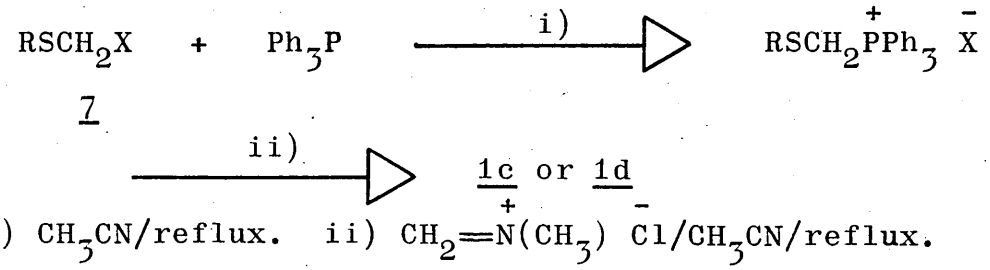
Scheme 8

This competition between reaction pathways was explained[17] in terms of the relatively unstable ylid 6 which can, subsequently, undergo a 1,2 elimination sequence as well as Wittig cyclisation. With this explanation of the low yields in mind (the total yield of cyclic products was only 31%) a search was made for species which could increase

the stability of the intermediate ylid and hopefully also the yields of desired Wittig products[19,20].

The ability of sulphur to stabilise adjacent anions meant that the alkylthio or arylthio substituted vinylphosphonium salts 1c and 1d should give ylids of enhanced stability over the ylid derived from 1b. Since their initial synthesis in these laboratories in 1978[21] 1c and 1d have shown themselves to be the most useful of all the salts 1. Where direct comparison is possible (vide infra) better yields of Wittig products have been obtained with both 1c and 1d than either 1a or 1b.

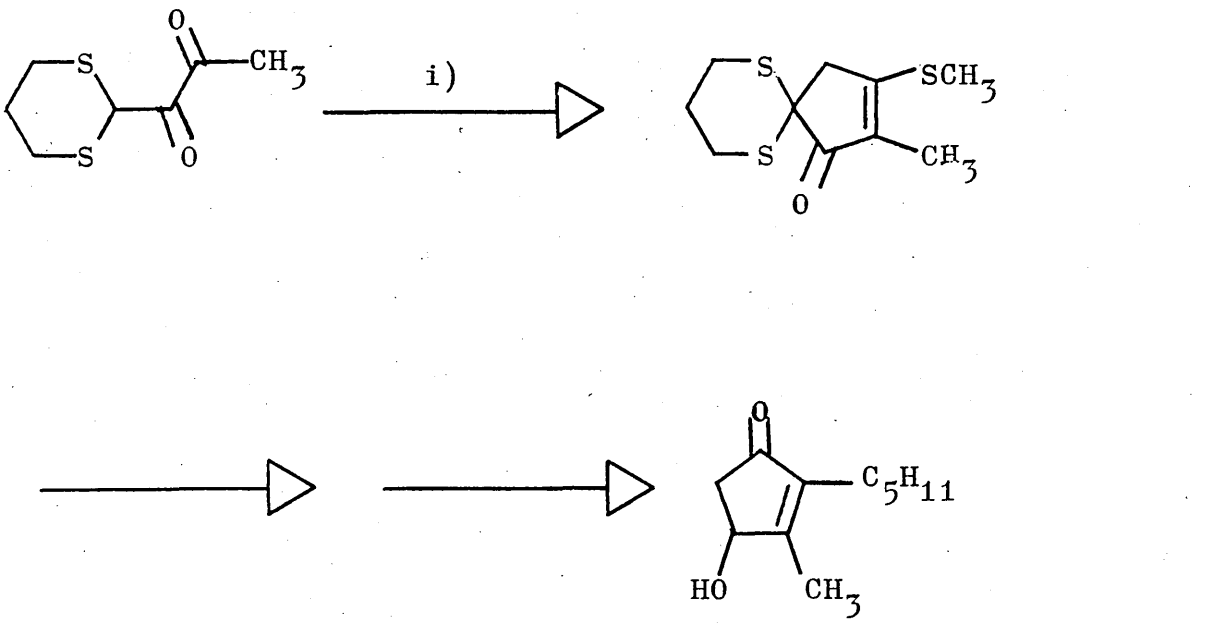
Both 1c and 1d can be prepared in a similar manner[22] (Scheme 9) (although a slight modification for



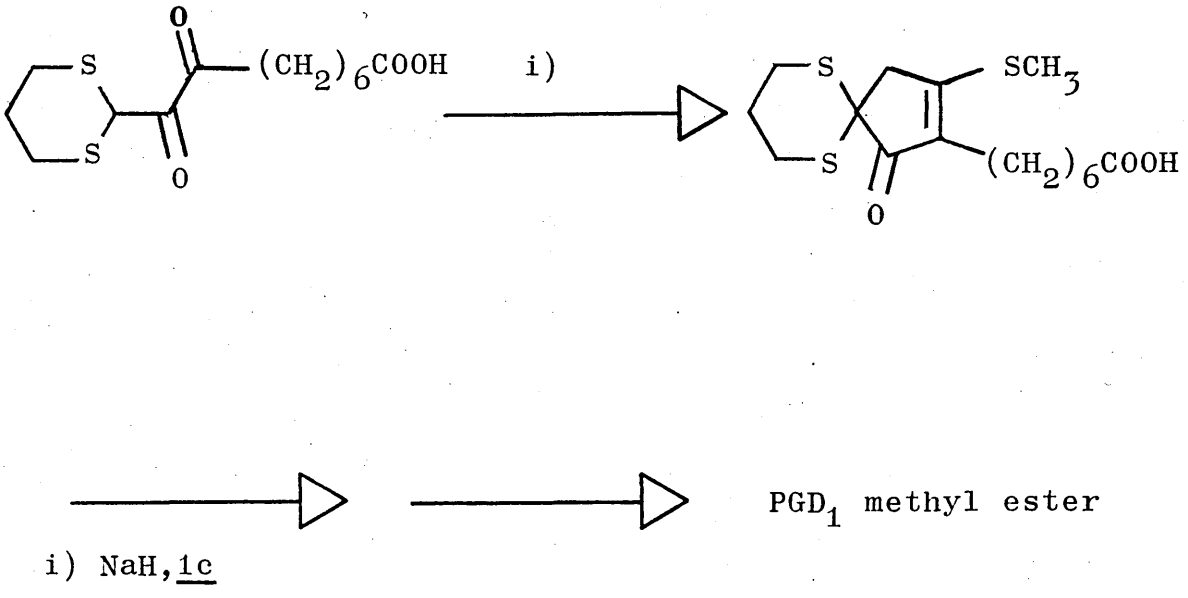
Scheme 9

the preparation of a related salt has recently been reported[23]) and have been used in a number of total and partial natural product syntheses. For example cyclopentanones[22,24] (Scheme 10), prostaglandins[25] (Scheme 11) and bicyclo (3.3.0.) octanes[26] (Scheme 12). These syntheses have been discussed in greater detail in the relevant references. However in each case the key points are the useful transformations that can be effected using vinylsulphides as intermediates.

The following chapters describe the use of the salts 1c and 1d in one approach to the synthesis of

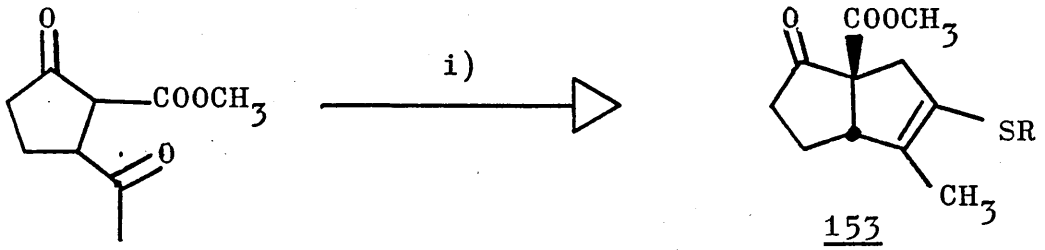


Scheme 10



Scheme 11

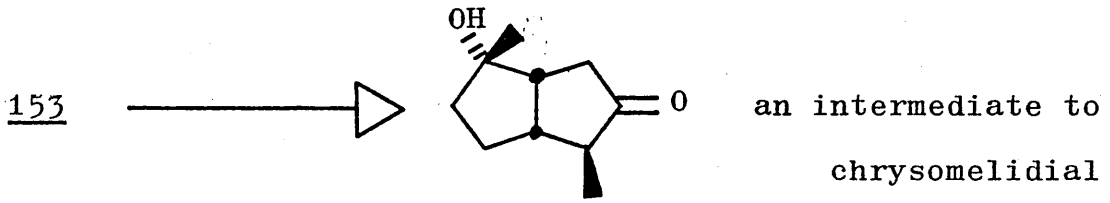
virantmycin (chapter 2) and in the initial stages of an approach to prostacyclin (chapter 4). Also included are descriptions of a regioselective Dieckmann reaction towards a synthesis of virantmycin and some observations on the chemistry of methyl methylsulphinylmethyl sulphide (chapters 2 and 3 respectively).



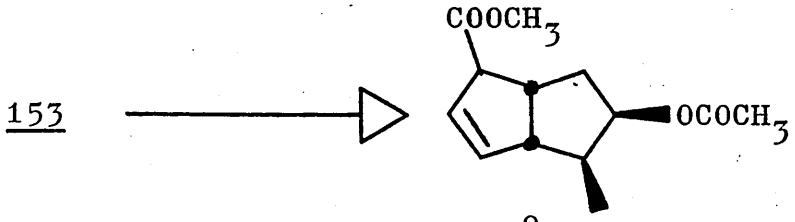
153

i) NaH, 1c or 1d

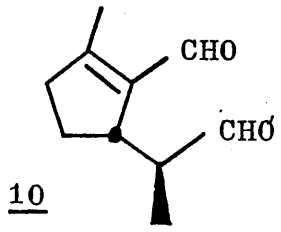
Scheme 12



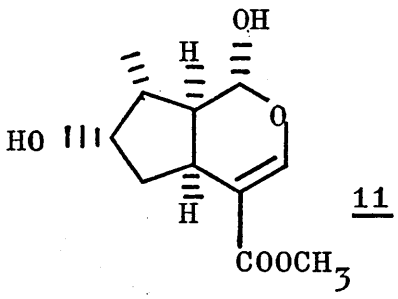
153 → 8 an intermediate to chrysomelidial



153 → 9 an intermediate to loganin



10
chrysomelidial



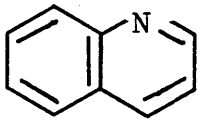
11
loganin

CHAPTER 2

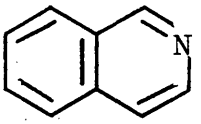
Approaches to the synthesis of virantmycin

2.1 Introduction

The synthetic formation or natural occurrence of compounds bearing a quinoline nucleus (I)[27] is perhaps less common than those containing an isoquinoline one (II).

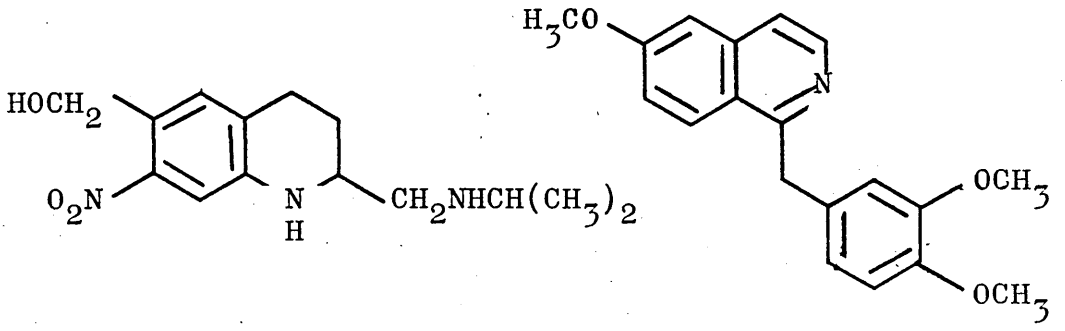


I



II

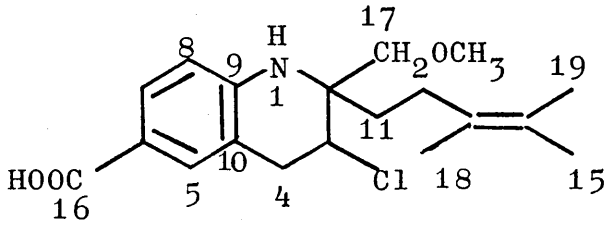
Shown in figure two are an example of each, namely oxamniquine a tetrahydroquinoline showing anti blood fluke activity[28] and papaverine a smooth muscle relaxant and vasodilator[29].



oxamniquine papaverine

figure 2

Another example of a tetrahydroquinoline was recently reported[30] and given the name virantmycin. This compound was isolated from the fermentation broth of streptomyces nitrosporeus and shown to have biological potential as an antiviral antibiotic. Structural illucidation soon followed, and, using a combination of spectral techniques and chemical degradation virantmycin was assigned the structure 12[31].



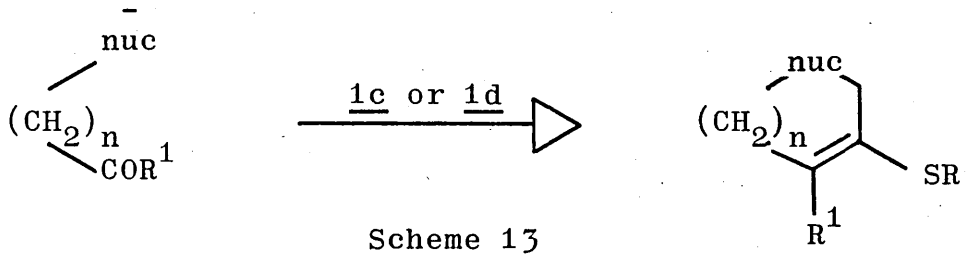
12

In virantmycin both C_2 and C_3 (virantmycin numbering used throughout) are chiral. In the original communication no evidence was given to suggest the relative or absolute configuration of the natural product, nor were other isomers reported. So far as we are aware no further stereochemical details are available in the literature nor have any total or partial syntheses been reported. Thus it seemed to be of interest to develop a synthesis of virantmycin which would allow the determination of the absolute structure of the natural product and the biological activity of all the other isomers. The route developed should also show sufficient flexibility in order to allow the synthesis of a series of compounds of slightly different structures.

2.2 An approach to the synthesis of virantmycin using vinyl phosphonium salts

2.2.1 Introduction

Previous work from these laboratories using the phosphonium salts 1c and 1d has led only to the synthesis of carbocyclic cyclopentanoids (see chapter 1 and Scheme 13 nuc = carbon, n=1. It was of obvious interest to see whether this approach could be extended to the synthesis of larger rings both with or without heterocyclic components (Scheme 13, nuc = carbon, nitrogen, oxygen or sulphur, n>1).

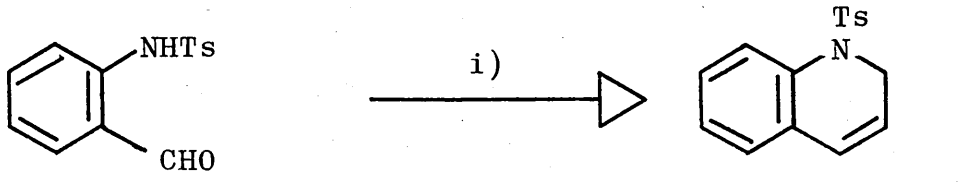


Scheme 13

If successful this would lead to the synthesis of carbocyclic or heterocyclic compounds containing a vinylsulphide. We believed that the heterocyclic ring of virantmycin could be constructed using this strategy, with the nitrogen atom as the nucleophile, C_2 and C_3 arising from the phosphonium salts 1c or 1d and C_4 from a formyl residue suitably situated in the same molecule as the nitrogen atom. Thus virantmycin represented a suitable target to assess the use of 1c and 1d in the synthesis of heterocyclic compounds.

We were encouraged in this respect by some earlier work by Schweizer on the synthesis of dihydroquinolines using 1a[9] (Scheme 14). This same reaction applied to our phosphonium salts 1c and 1d with the aminoaldehyde 14 would

give the vinylsulphides 15c and 15d which are intermediates in our retrosynthetic analysis (Scheme 15).

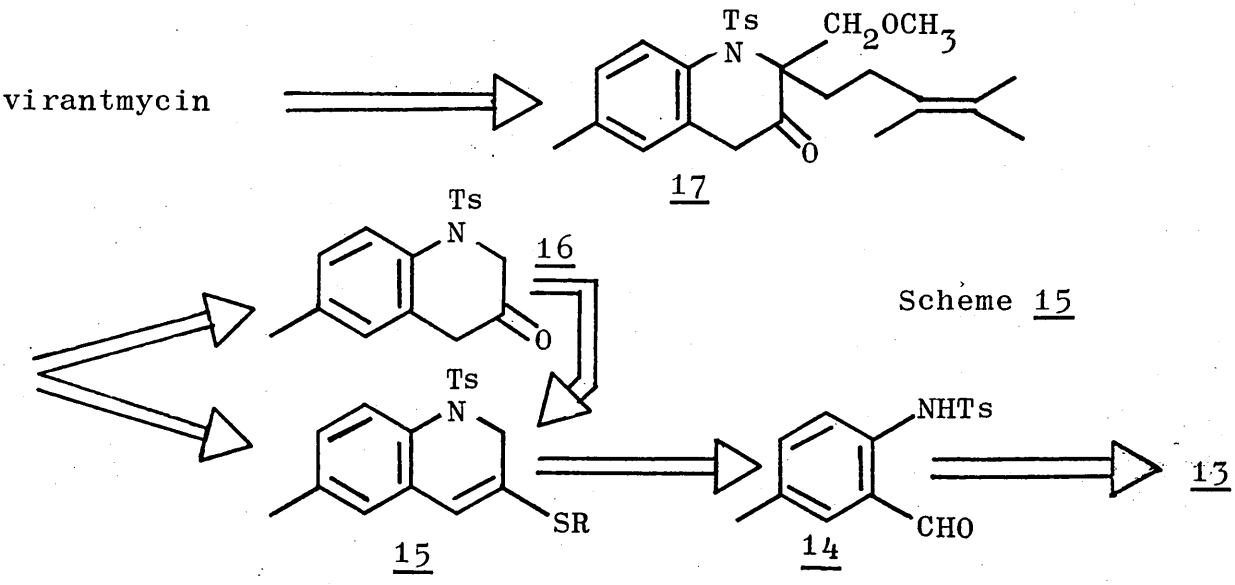


12 15a 50%

i) NaH/Et_2O, 1a Scheme 14

The synthesis of vinylsulphides has been of increasing interest over the last decade or so because of the number of synthetic transformations to which they are susceptible. As well as the addition reactions characteristic of simple alkenes, the electronic effect of the sulphur atom allows vinylsulphides to undergo acylation and anion forming reactions[32]. Our own primary interest in the formation of vinylsulphides originated from the fact that they are readily transformed into carbonyl groups.

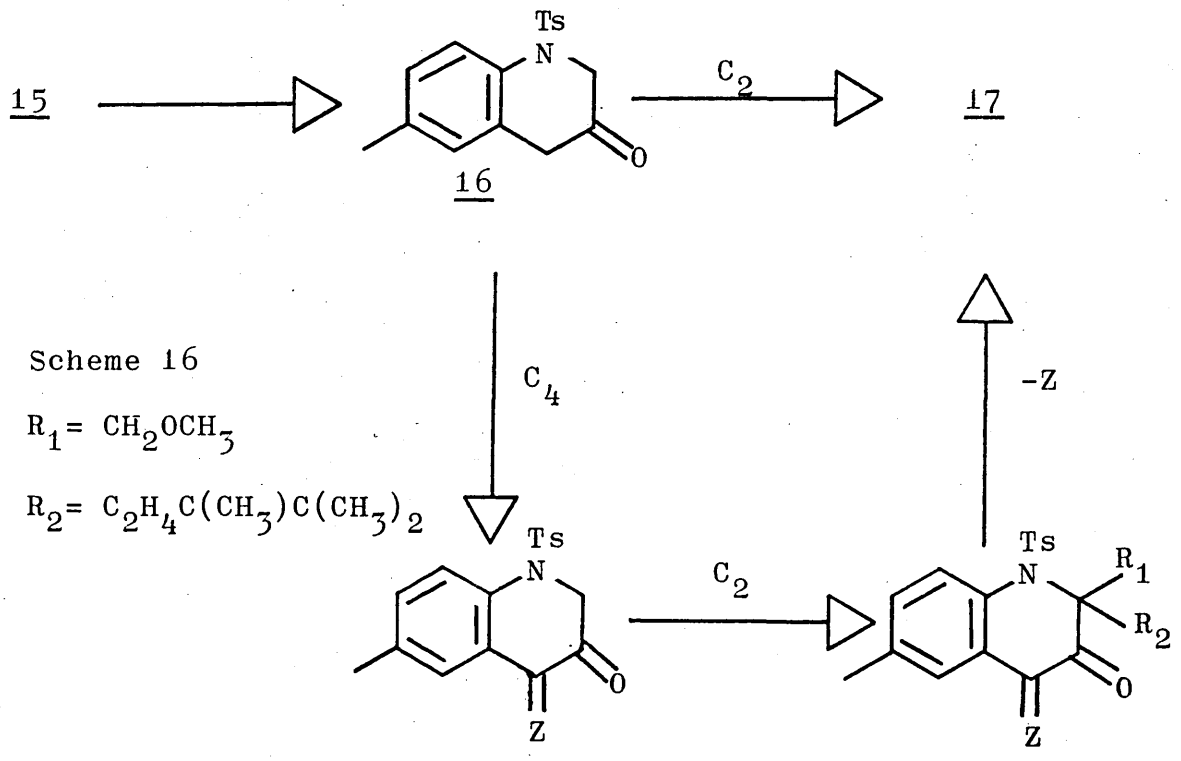
Some of the reagents which have been reported as being successful for this transformation are:- $TiCl_4$[33], $HgCl_2$[34], HgO[35], TFA[26], HCl/PhSH[36] and $HClO_4$/PhSH[37]. More recently these have been complemented by two procedures from Trosts group for allylic functionalisation of vinylsulphides[38,39].



Scheme 15

Thus the starting material chosen for the synthesis was 2-amino-5-methylbenzoic acid 13. The protected aldehyde 14 should be available from 13 via simple chemical transformations and, by analogy[9], would give the vinylsulphide 15 on treatment with 1c or 1d. The development of 15 towards virantmycin would proceed in one of two ways.

The first approach would involve initial hydrolysis of 15 to the corresponding ketone 16 (Scheme 16). Treatment of the latter with a base (1 equivalent) followed by an alkyl halide could give products arising from reaction at C_2 or C_4. Providing that reaction was observed predominantly at one site or the other then a solution was in hand. If alkylation occurred at C_2, the desired site, then the procedure is straightforward. However if C_4 is preferred then this position would have to be blocked so that subsequent alkylation could only occur at C_2. Removal of the blocking group should then give 17.

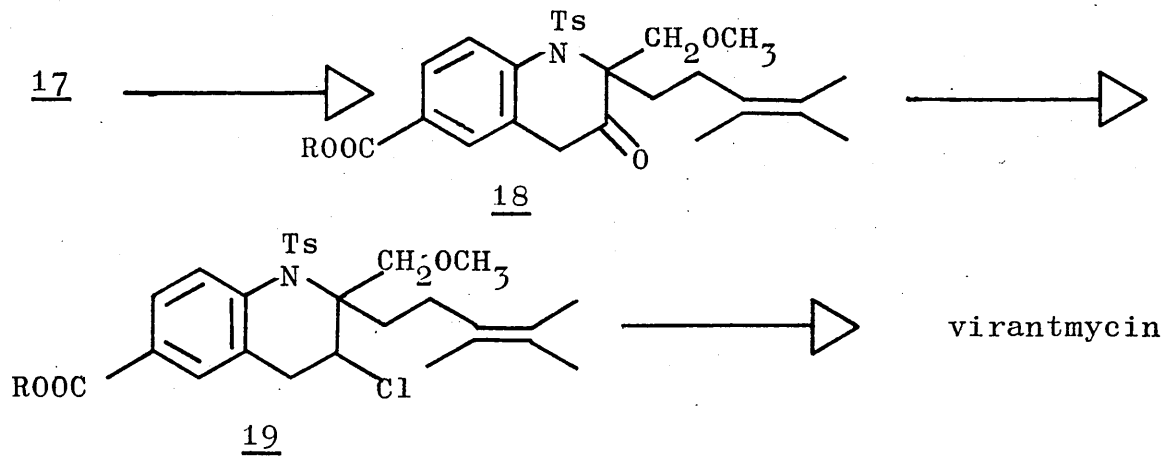


Scheme 16

$R_1 = CH_2OCH_3$

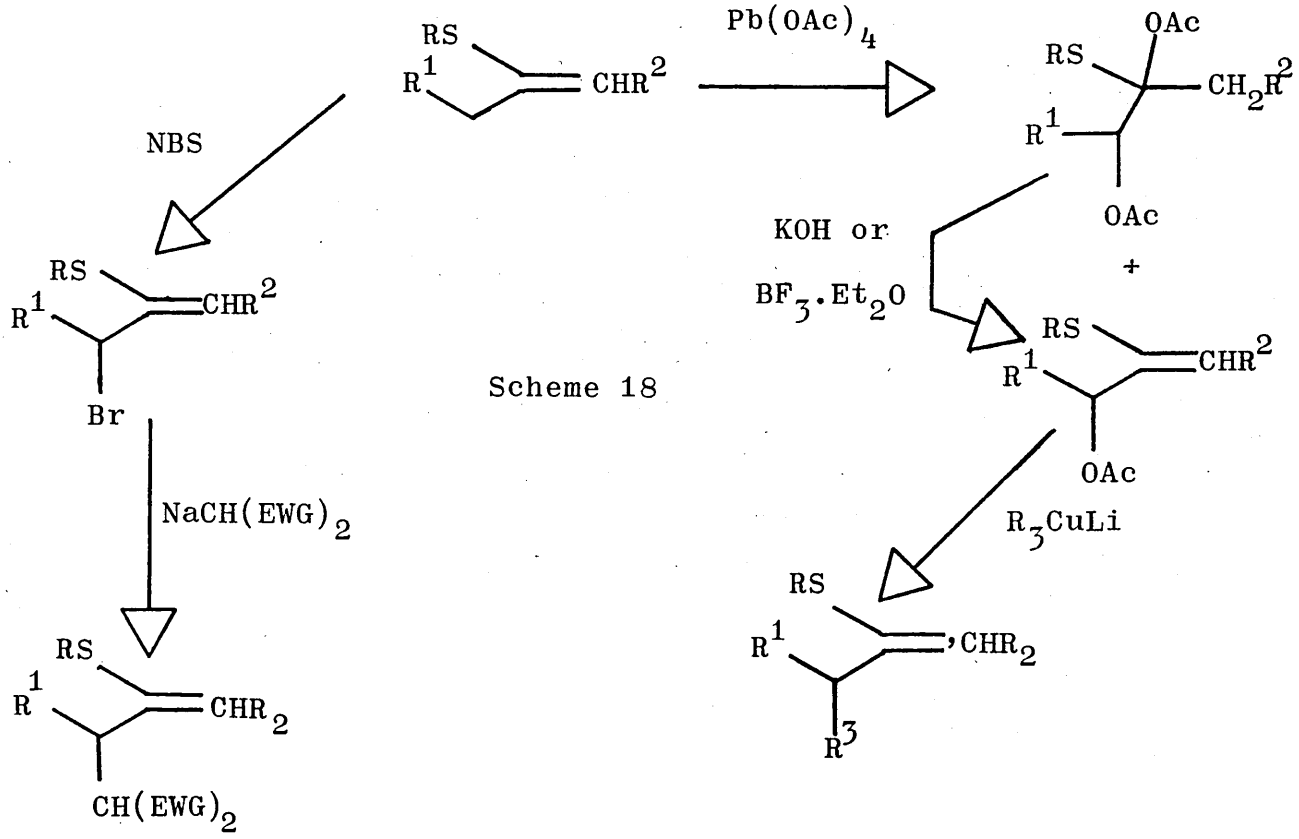
$R_2 = C_2H_4C(CH_3)C(CH_3)_2$

When 17 had been obtained, subsequent elaboration was expected to proceed as shown (Scheme 17). Thus conversion of the benzylic methyl group of 17 to an ester and selective reduction of the ketone to an alcohol followed by chlorination would give 19. Double deprotection of this should give virantmycin possibly contaminated with other isomers.



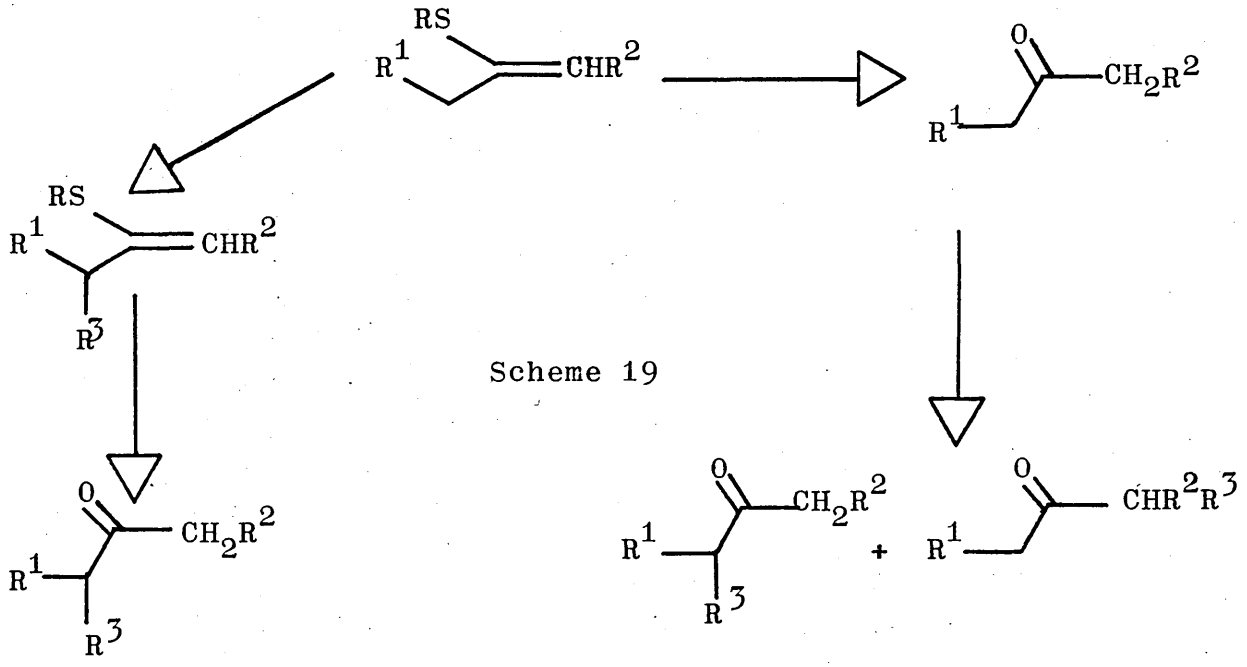
Scheme 17

The alternative approach to virantmycin from the vinylsulphide 15 was based on the work done by Trost (Scheme 18).



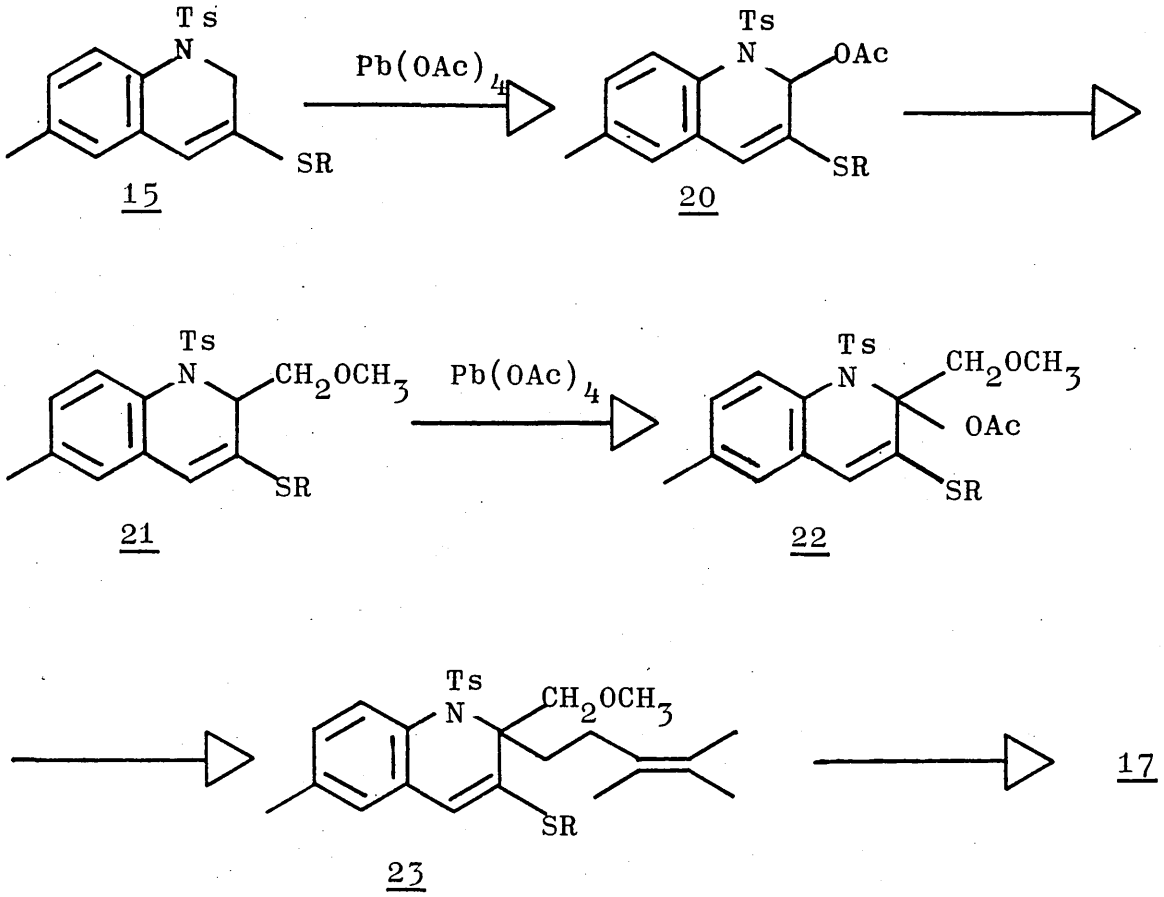
Scheme 18

The advantage of these procedures is that they allow access to a compound which would not automatically be available directly from the corresponding carbonyl without regiochemical contamination (Scheme 19).



Scheme 19

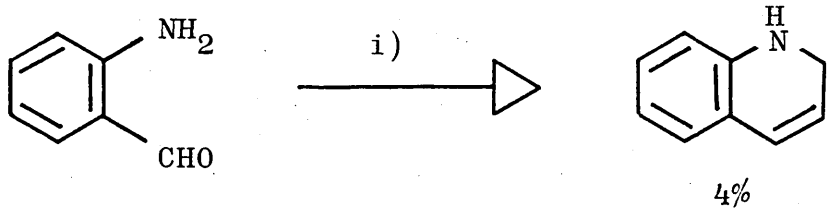
Thus treatment of the vinylsulphide 15 with lead tetraacetate should give the allylic acetate 20 (Scheme 20). So far[38] coupling of these species has only been achieved with organocuprates derived from simple alkyl, alkenyl or aryl halides so it is unknown whether the methoxymethyl group present in virantmycin could be attached using this approach (Scheme 20). In addition the formation of the quaternary acetate 22 was ambiguous. No evidence for the formation of quaternary acetates using this approach was given in the original communication[38], so this also needed some investigation. The envisaged approach to virantmycin using this strategy is shown (Scheme 20).



Scheme 20

2.2.2 Results and discussion

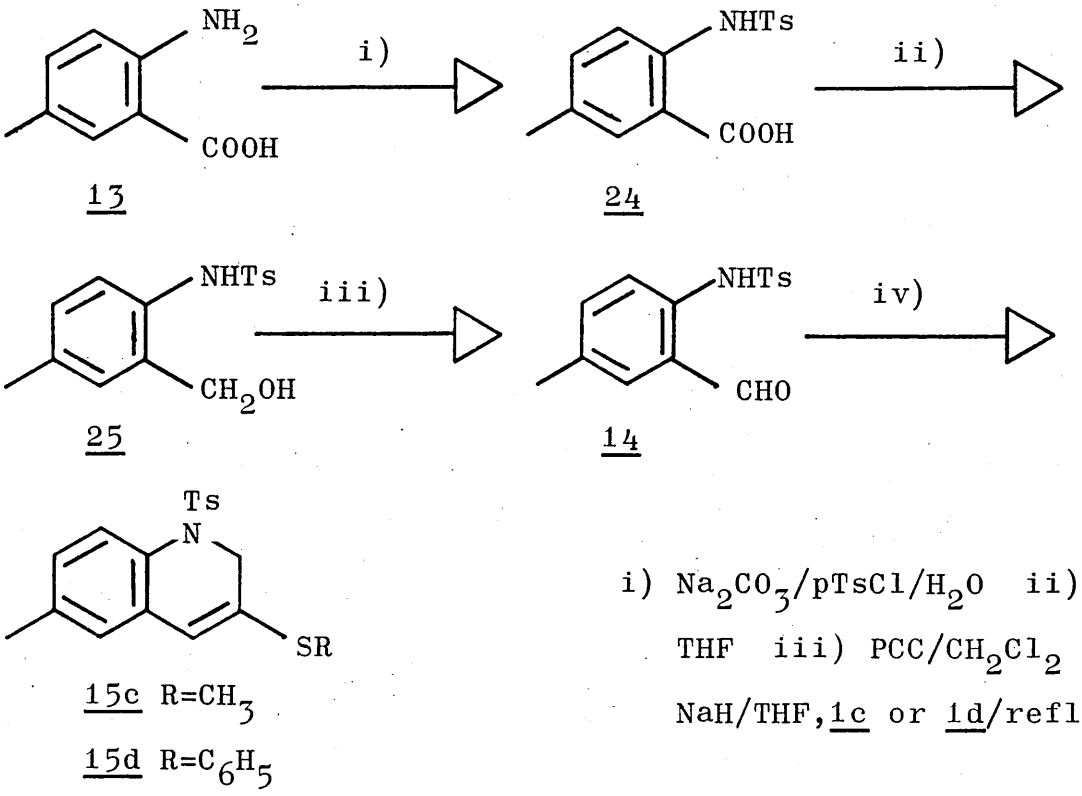
The well known susceptibility of anilines to oxidative degradation and Schweizer's observations[9], that unprotected 2-aminobenzaldehydes gave poor yields of 1,2 dihydroquinolines on reaction with 1a (Scheme 21), meant that protection of one N-H bond in the starting material was essential.



i) NaH, 1a

Scheme 21

Due consideration of the retrosynthetic analysis (Scheme 15) and the proposed synthetic route allowed prediction of the reagents to be used. Thus a protecting group could be chosen whose stability was compatible with the conditions required. A search of the relevant literature[40,41] indicated a number of possibilities. From these the one chosen was the 4-toluenesulphonyl group as it is readily attached and with a wide variety of conditions having been reported for its removal[42]. From this starting point the dihydroquinolines 15c and 15d were synthesised as shown in Scheme 22.



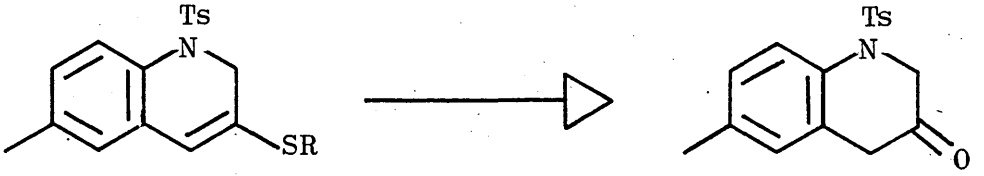
Scheme 22

Thus the sodium carboxylate, prepared in situ, of 2-amino-5-methylbenzoic acid was tosylated[43] with 4-toluenesulphonyl chloride to give 24 in quantatative yield. Reduction of this acid with lithium aluminium hydride

($LiAlH_4$) required a larger mole ratio of reducing agent to acid than expected, but after a number of attempts good and reproducible yields of the alcohol 25 were obtained. As expected the aldehyde 14 was readily available from 25 using pyridinium chlorochromate (PCC) in dichloromethane (CH_2Cl_2)[44] in excellent yield (93%).

The experimental procedure developed by Schweizer[9] for the synthesis of the dihydroquinoline 15a (Scheme 14) involved a mixture of solvents and a long reaction time (3 days). Our synthesis (Scheme 22) of the dihydroquinolines 15c and 15d from 14 proved much simpler and quicker and gave better yields of the desired products. Thus treatment of 14 with sodium hydride (NaH) in tetrahydrofuran (THF) for 20 minutes at room temperature gave the sodium salt as a white solid. Subsequent addition of 1c or 1d, followed by refluxing for 4 hours, gave 15c and 15d in 70% and 90% yields.

As the first approach to virantmycin using vinylsulphide methodology we attempted to hydrolyse 15 to the ketone 16 (Scheme 23).



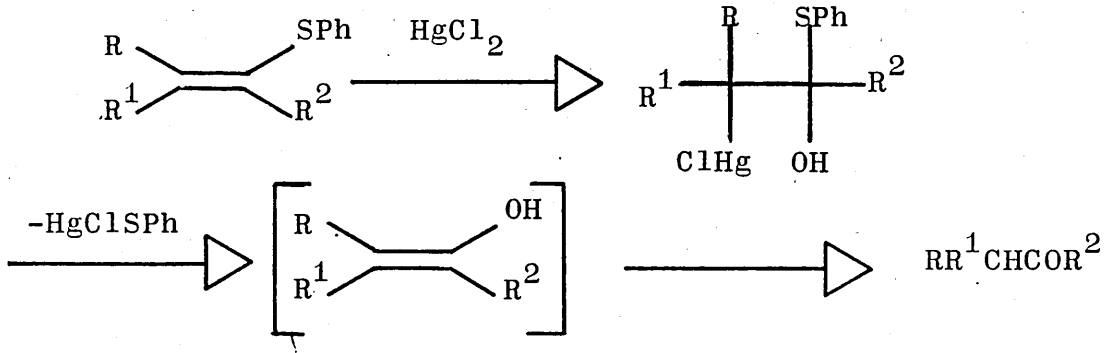
15 16

Scheme 23

The literature published on this transformation indicates that there are apparently some problems in the hydrolysis of terminal vinylsulphides to aldehydes[36]. For these

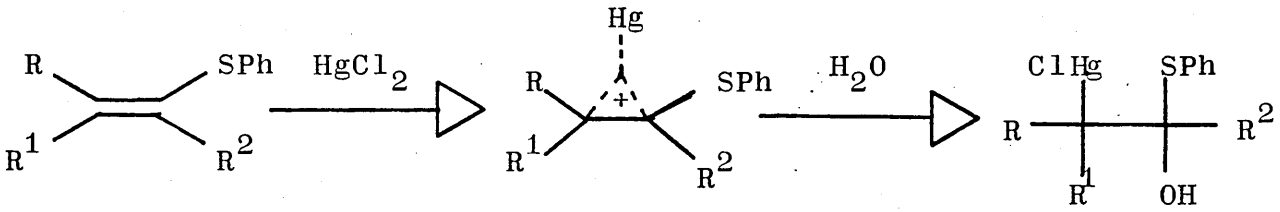
compounds the classical Hg (II) or Ti (IV) methods frequently fail and alternative acid promoted addition/hydrolytic procedures have been developed[36,37]. The conversion of internal vinylsulphides to ketones (for example 15 to 16), however, has usually been more predictable. In the light of this it proved extremely disappointing to find that under none of the conditions outlined previously could 16 be obtained from 15c or 15d. Other reagents, for example HCl or HBF_4[45], were also tried but with no success. In all cases except one, 15c or 15d were recovered exclusively and in good yields. Only prolonged reflux with concentrated HCl caused complete disappearance of starting material, but the reaction mixture from this gave no useful products.

The rationalisation for this is not clear, but assuming a common mechanism is applicable for each of the reagents and using the $HgCl_2/CH_3CN/H_2O$ conditions as an example a possible explanation is outlined here. The proposed mechanism for the mercuric chloride method involves oxymercuration of the double bond via a Markovnikov addition[36]. Subsequent loss of Hg(Cl)SPh leads to the intermediate enol which reverts to the more stable carbonyl tautomer (Scheme 24).



Scheme 24

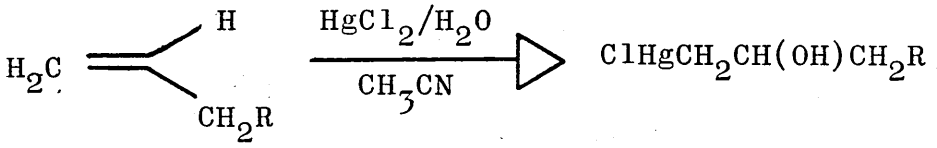
A postulated intermediate in this reaction is the mercurinium ion[46] (Scheme 25) formed in a pre-equilibrium with subsequent attack by the solvent giving the adduct 26. Mercurinium ions have been detected under non nucleophilic conditions[46].



26

Scheme 25

A kinetic study has been undertaken[47] on a similar reaction (Scheme 26) and this showed, as expected, that the presence of electron withdrawing groups at the allylic carbon atom retarded donation of the π electrons from the alkene to mercury and thus reduced the rate of reaction (Scheme 26 and Table 1).



Scheme 26

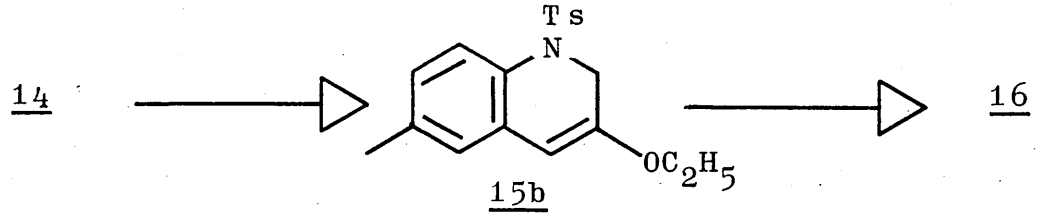
R	rate const (mol^{-1} s^{-1})
H	100000
OH	1120
Cl	11
CN	4.3

Table 1

Considering, Scheme 24, when R^2 = alkyl and the product is a ketone, the inductive effect of R^2 should aid formation of the mercury-olefin complex and thus facilitate the overall reaction. However when R^2=H and the product an aldehyde no inductive effect is possible and the reaction may be hindered or prevented.

In our case, 15c and 15d, we have, by analogy, $R^2 = CH_2N(Ar)Ts$ and it may be that the electron withdrawing effect of the sulphonamide passed through the methylene group could also prevent the formation of the mercury-olefin complex and thus also prevent any hydrolysis[48]. Some analogy with this was recently demonstrated by Evans who found that the effect of a carbamate ester, through a methylene group, affected nucleophilic ring opening of an oxirane.[49]

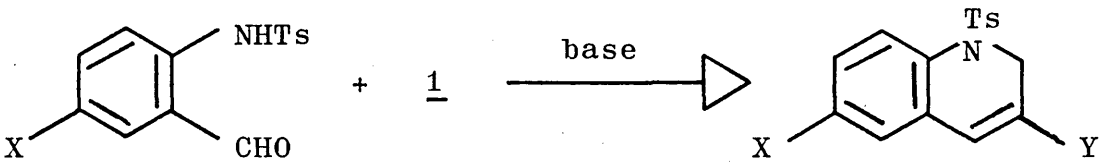
The desired ketone 16 was successfully synthesised using the vinyl phosphonium salt 1b (Scheme 27).



i) NaH/THF, 1b/reflux/2 days ii) $HClO_4/Et_2O$

Scheme 27

Unfortunately the yield of the first step was too low (13%) to use this route for further studies towards virantmycin. However this does allow, as far as we are aware, the only direct comparison between all four phosphonium salts (Scheme 28 and Table 2).



12 X=H

14 X=CH_3

15a X=Y=H

15b X=CH_3, Y=OC_2H_5

15c X=CH_3, Y=SCH_3

15d X=CH_3, Y=SC_6H_5

Scheme 28

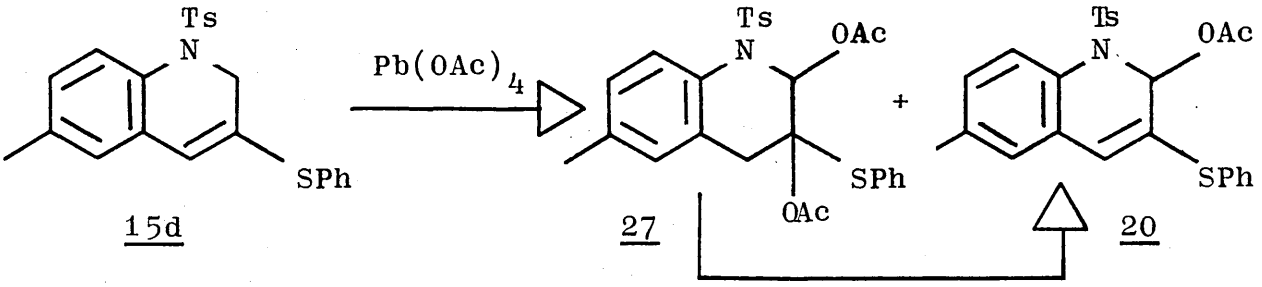
aldehyde	phosphonium salt	reaction conditions	product	yield
12	1a	reflux/60 hr	15a	50%
14	1b	reflux/48 hr	15b	13%
14	1c	reflux/2-4 hr	15c	70%
14	1d	reflux/2-4 hr	15d	90%

Table 2

This demonstrates the better yields of intramolecular Wittig products achieved with our salts 1c and 1d over the analogues 1a and 1b.

This failure at a key stage prompted us to explore the second strategy to virantmycin using vinylsulphide methodology, that is Trost's allylic acetoxylation[38]. When 15d was treated with 1.1 equivalents of lead tetraacetate, $Pb(OAc)_4$, TLC evidence indicated the formation of the monoacetate 20 and the bisacetate 27. These were assigned on the basis that, as predicted by Trost, of these only 20 was observed on work up of the reaction mixture with potassium

hydroxide (Scheme 29).



15d 27 20

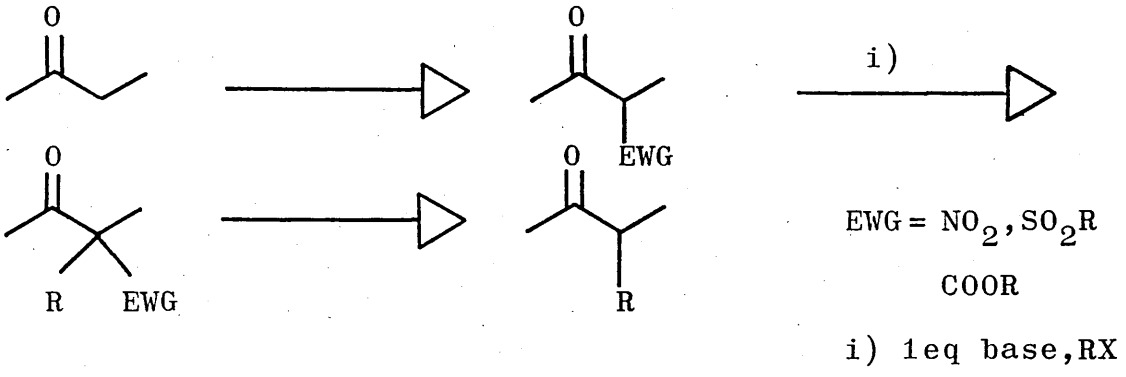
Scheme 29

However a number of other products were also observed, possibly arising from oxidation of 15d with $Pb(OAc)_4$ at sulphur or at one of the benzylic carbon atoms, so this route was not pursued.

2.3 Approaches to virantmycin using a regioselective Dieckmann reaction

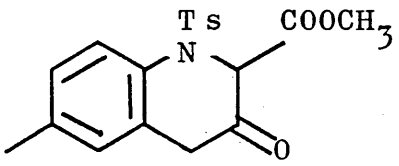
2.3.1 Introduction

With the failure of our original approach to virantmycin at a key stage, an alternative strategy was required. One aspect of the first synthesis provided an important clue to the second. Thus as outlined earlier (Scheme 16) it appeared theoretically possible that treatment of the ketone 16 with base followed by a suitable electrophile could give a mixture of products. This problem of regioisomeric alkylation of ketones is frequently encountered in organic synthesis. One solution is to activate the α carbon atom, where reaction is desired, with an electron withdrawing group. Then, using one equivalent of base followed by an alkyl halide, reaction occurs only at the activated site. (Scheme 30).



Scheme 30

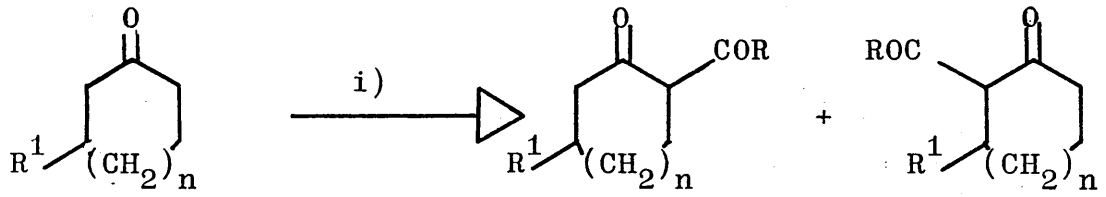
When this concept is applied to the synthesis of virantmycin, using the methoxycarbonyl group for activation, the 1,3-ketoester 28 becomes the key intermediate. As well as overcoming this ambiguous alkylation, 28 shows one other potential advantage over 16 for the synthesis of virantmycin.



28

This is that the methoxycarbonyl group at C_2 provides ideal access to the methoxymethyl group which occupies the same position in virantmycin.

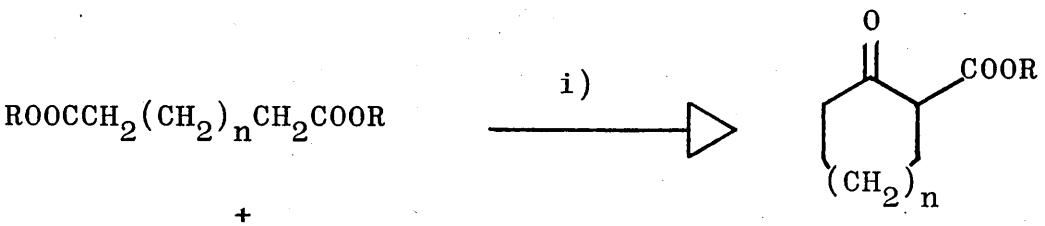
The two most well established methods for the construction of cyclic 1,3-ketoesters like 28 are the reaction of ketone enolates with acid derivatives (Scheme 31) and the Dieckmann reaction (Scheme 32). It appeared possible that the former could suffer from the same regioisomeric problems as outlined earlier (Scheme 16), but the latter looked much more attractive.



i) base, RCOX

Scheme 31

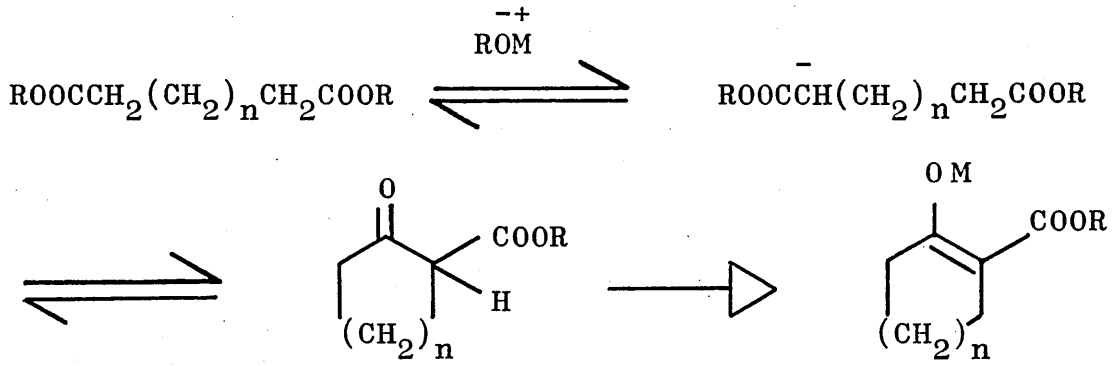
A great deal of literature has been published on the Dieckmann reaction[50].



i) ROM/ROH, H_3O^+

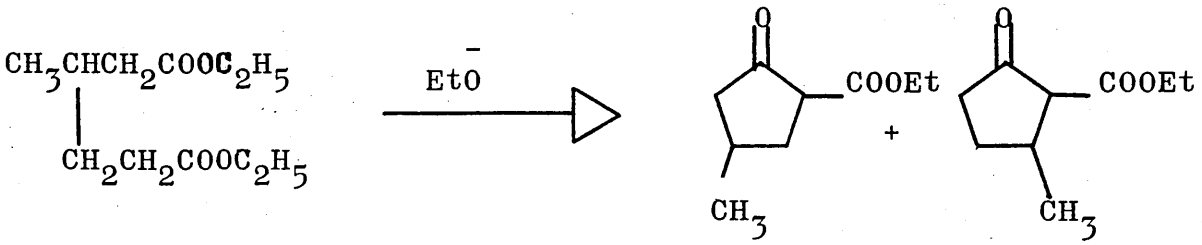
Scheme 32

This is the base catalysed intramolecular cyclisation of a diester to a 1,3-ketoester. The mechanism for this reaction comprises a series of equilibria with the driving force being the formation of the 1,3-ketoester enolate as the last step (Scheme 33).



Scheme 33

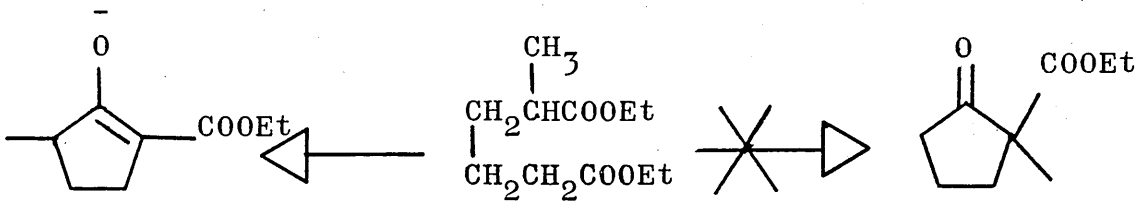
The Dieckmann reaction has, since its conception, been used to construct carbocyclic 4, 5, 6 and 7 membered rings[50] and also rings containing heterocyclic components. For symmetrical and asymmetrical diesters overall chemical yields can vary from moderate to excellent, but for asymmetrical diesters there can be a problem with regioisomer formation. For diethyl-3-methyladipate, 29, cyclisation can produce a mixture of products.



29 30 80% 31 20%

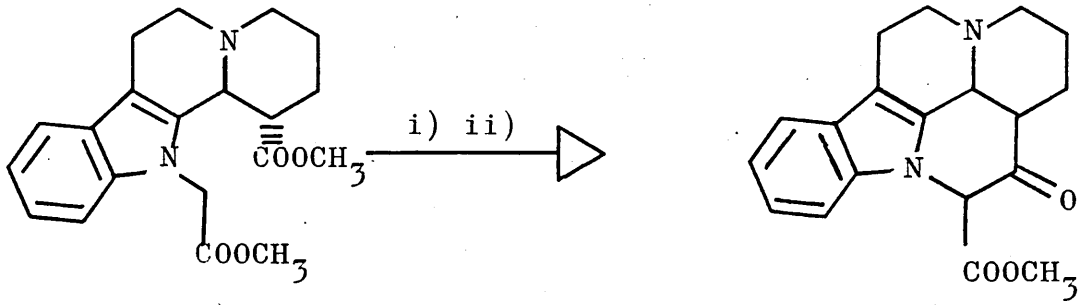
Whilst the yield of 30, if that was the desired product, could be tolerated the effect of a more remote or more subtle substituent might lead to a lower regioselectivity. This problem of regioselectivity in the Dieckmann reaction can be a significant one although there are ways to overcome it. Two of these are outlined below.

In the first the presence of a substituent on one of the α carbon atoms leads to cyclisation in one direction only (Scheme 34). This is because the driving force for the reaction, the formation of the 1,3-ketoester enolate, can only occur in one of the possible products.



Scheme 34

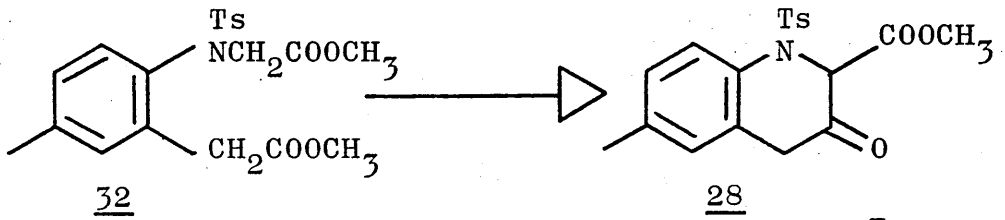
This is not particularly useful for the synthesis of complex molecules as it requires a specific substitution pattern in the target molecule and is inflexible, although specific examples are known. Scheme 35 shows one stop of Rapaport's approach to apovincamine[51].



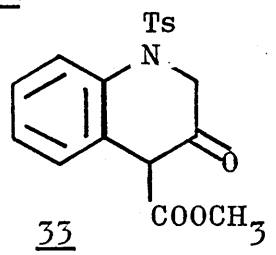
i) $LiOCH_3$ ii) CH_3COOH 100%

Scheme 35

Our proposed intermediate 28 would arise from the Dieckmann precursor 32 but as both esters are unsubstituted at the α carbon atom it seemed likely that the undesired isomer 33 would also be formed. Thus the alternative approach to the Dieckmann reaction, which appears to be structurally independent, proved much more attractive.



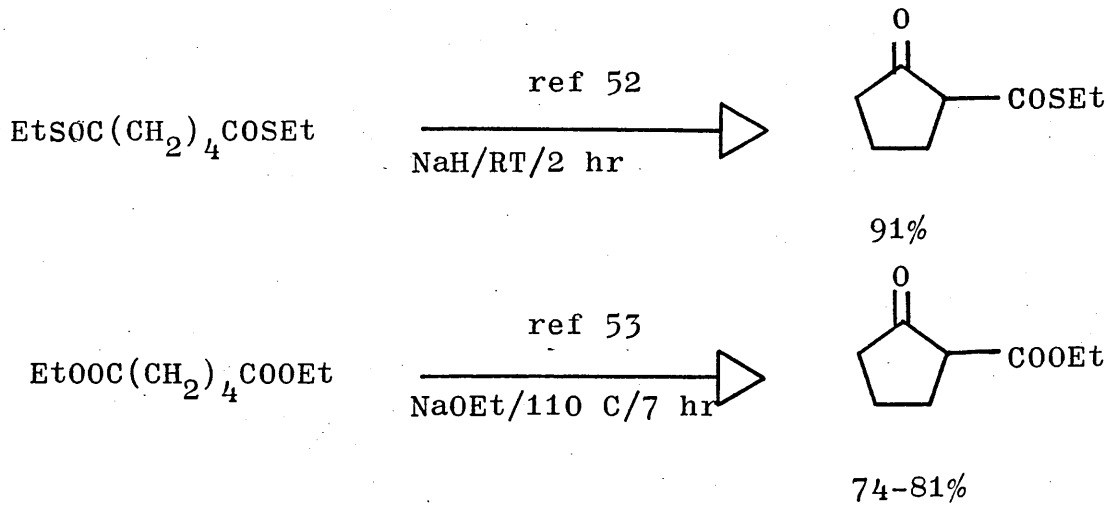
32 28



33

Scheme 36

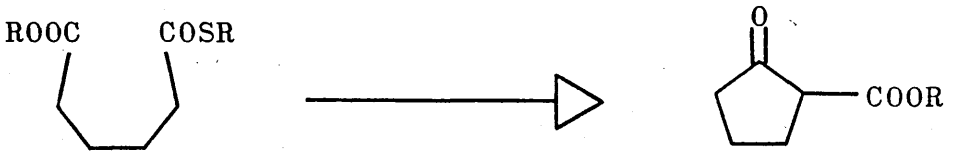
This is based on a recent observation by Liu[52] that dithiol esters cyclise under much milder conditions than their O analogues (Scheme 37).



Scheme 37

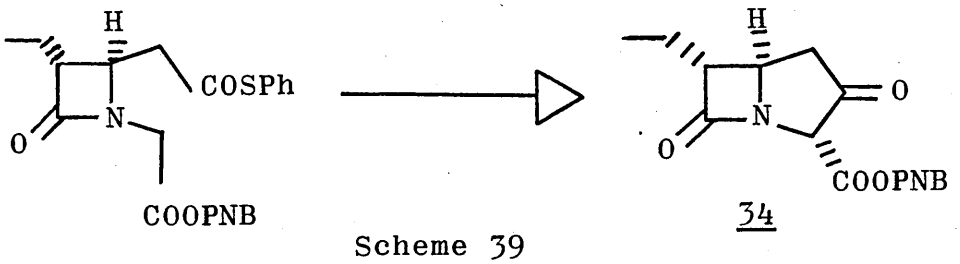
Two groups then independently combined these observations to introduce a mild and regioselective Dieckmann reaction

of mixed O,S diesters[54,55] (Scheme 38). In this reaction the location of the keto and ester groups in the product is controlled by the position of the S and O esters in the reactent. In both of the original communications the only products obtained arose through loss of the -SR group.



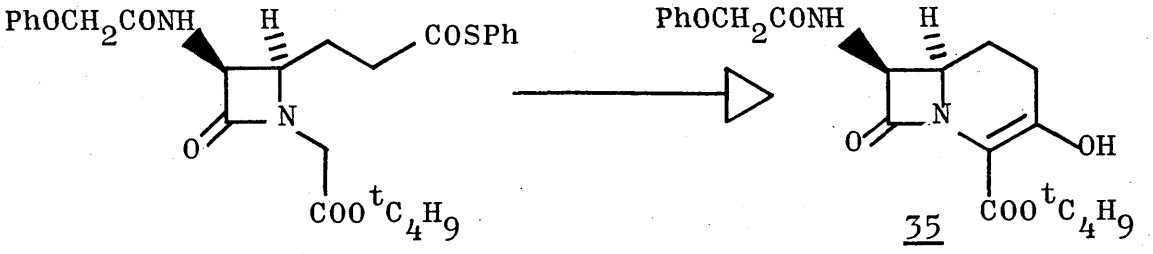
Scheme 38

No products were observed arising from loss of -OR. Hatanaka's group have subsequently applied this methodology to the synthesis of the carbapenam[56] 34 (Scheme 39) and the carbacephem[57] 35 (Scheme 40).



34

Scheme 39

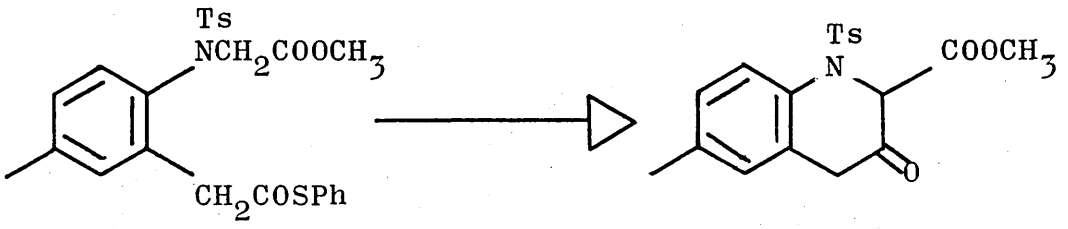


35

Scheme 40

Using this approach we felt that the key 1,3-keto ester 28 could be made in one step from the mixed O,S diester 36 (Scheme 41) and so the synthesis of this latter compound became our initial objective. The strategy was to prepare either the aldehyde 37 or the alcohol 38 and

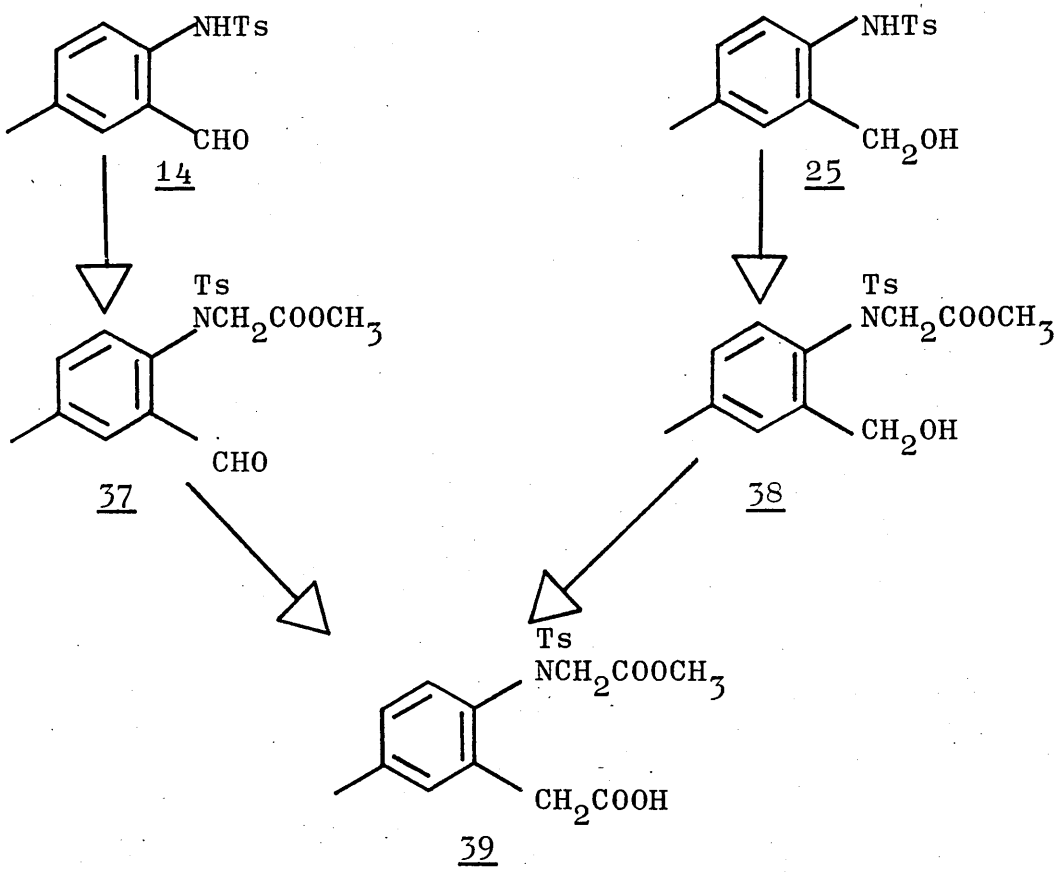
incorporate into them one extra carbon atom, so as to allow subsequent elaboration into the acid 39 (Scheme 42).



36 28

Scheme 41

From this the diester 36 should be readily available.



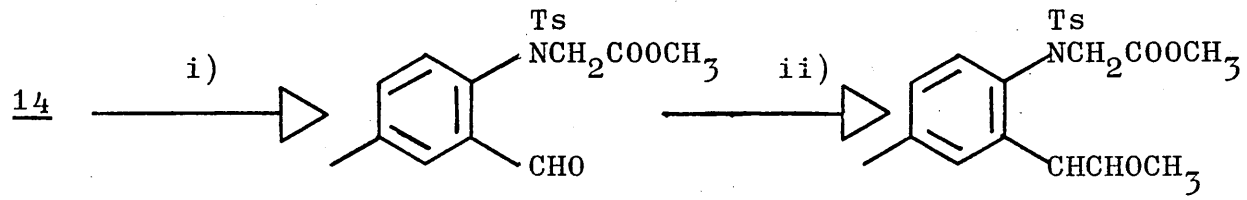
Scheme 42

2.3.2 Results and discussion

With this objective in mind 14 (see section 2.2.2) was treated successively with NaH in DMF and methyl bromoacetate to give 37 in 98% yield. This was condensed with the ylid derived from methoxymethyl triphenylphosphonium chloride 40[58,59,60] in THF at 0°C to give the vinylethers 42 (Scheme 43).

$Ph_3\overset{+}{P}CH_2OCH_3\ \overset{-}{Cl}$ 40 $\qquad$ $Ph_3P{=}CHOCH_3$ 41

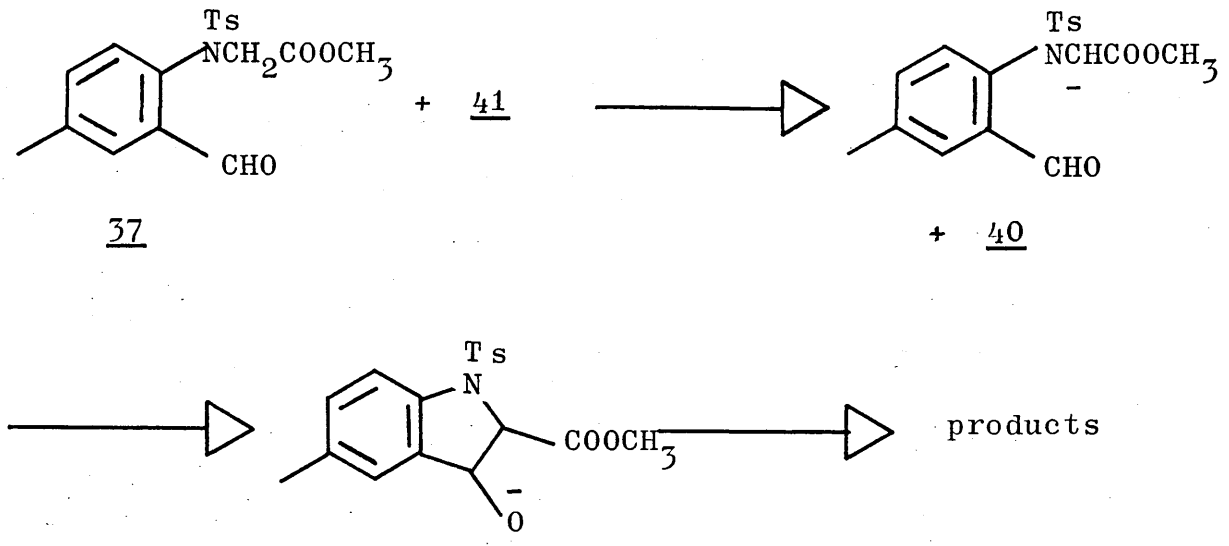
Subsequent hydrolysis and oxidation should give the desired acid 39. Unfortunately the yield of the vinylethers 42, obtained in an approximately 1:1 E:Z ratio, was fairly low (only 30%).



i) $NaH/DMF, BrCH_2COOCH_3$ ii) 41/THF/0°C

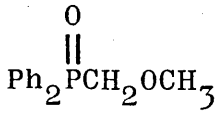
Scheme 43

In addition a number of other products were formed. These are believed to arise from the ability of 41 to act not only as a nucleophile but also as a base thus promoting an intramolecular cyclisation as shown in Scheme 44. Other experimental and theoretical evidence supports this hypothesis. Thus treatment of 37 with lithium diisopropylamide (LDA) gave a similar reaction profile to that obtained on treating 37 with 41.

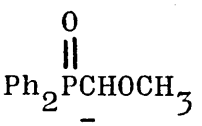


Scheme 44

In addition according to the observations made by Baldwin on ring closure reactions[61,62], this represents a 5-(enolexo)-exotrig process which has been shown to be relatively facile. The phosphine oxide analoge of 40 ie 43[60] has been reported to give better results in one carbon homologation reactions where enolisation is a problem.



43

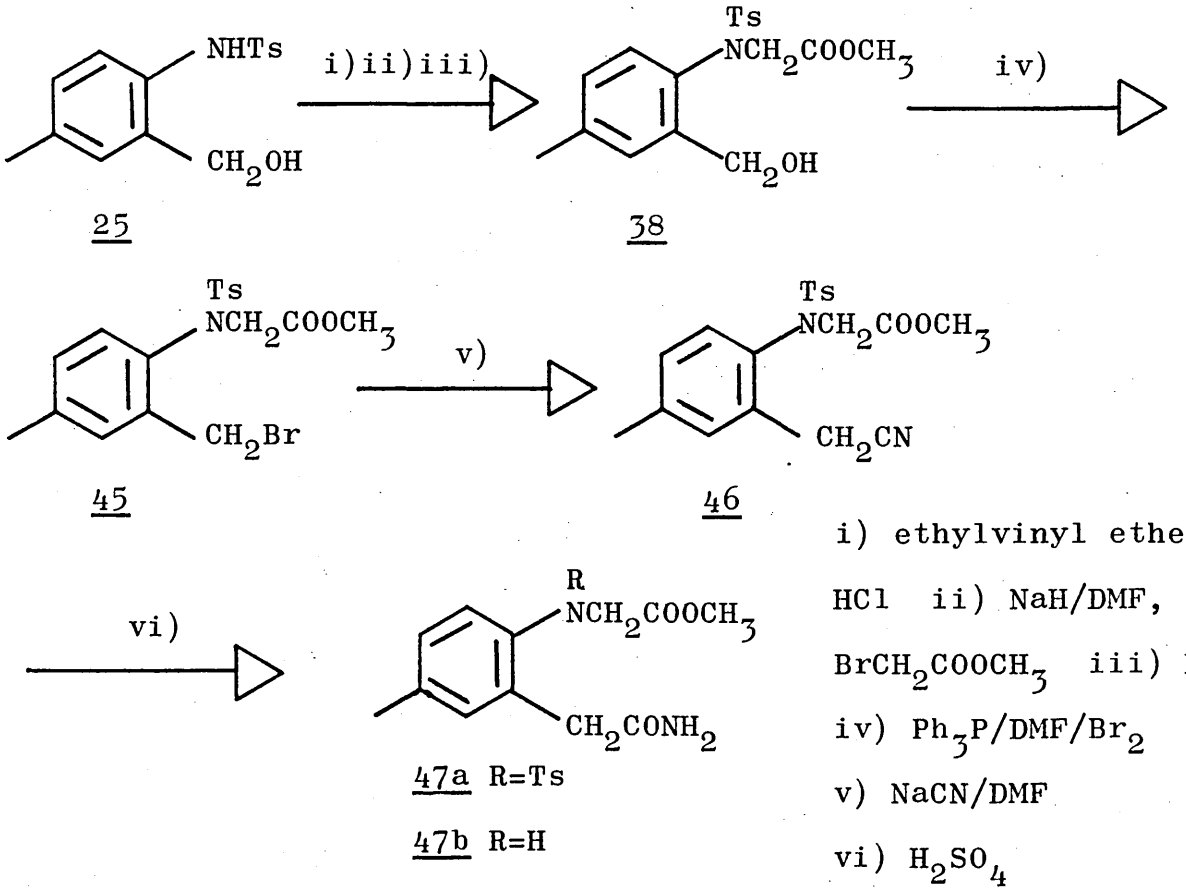


44

This has been attributed to the enhanced nucleophilicity and reduced basicity of its anion 44 with respect to the ylid 41. However when 37 was treated with 44 a similar result was obtained to that outlined above.

Thus attention was diverted to the alcohol 38, which was synthesised in the following manner. Protection of the alcohol 25 (see section 2.2.2) with ethyl vinylether

followed by alkylation and deprotection gave 38 (Scheme 45) in 73% yield over the three steps. Preparation of the O-tosylate of 38 using pTsCl/pyridine or pTsCl/$(C_2H_5)_3N$ failed but triphenylphosphine dibromide[63], prepared in situ, smoothly converted 38 into 45 in 83% yield. Nucleophilic displacement of the halide by cyanide then gave 46 (96%). It was anticipated that from 46 we would be able to obtain the acid 39, most probably via the intermediate amide 47a (Scheme 45). The method most frequently used for the conversion of nitriles to amides, for example as tried by Woodward and Eschenmoser in their approaches to the synthesis of vitamin B_{12}[64], involves acid catalysed hydrolysis, followed by nitrosation to the corresponding acid. When 46 was treated with concentrated sulphuric acid (H_2SO_4) at 0°C a single product was obtained as a brown solid.



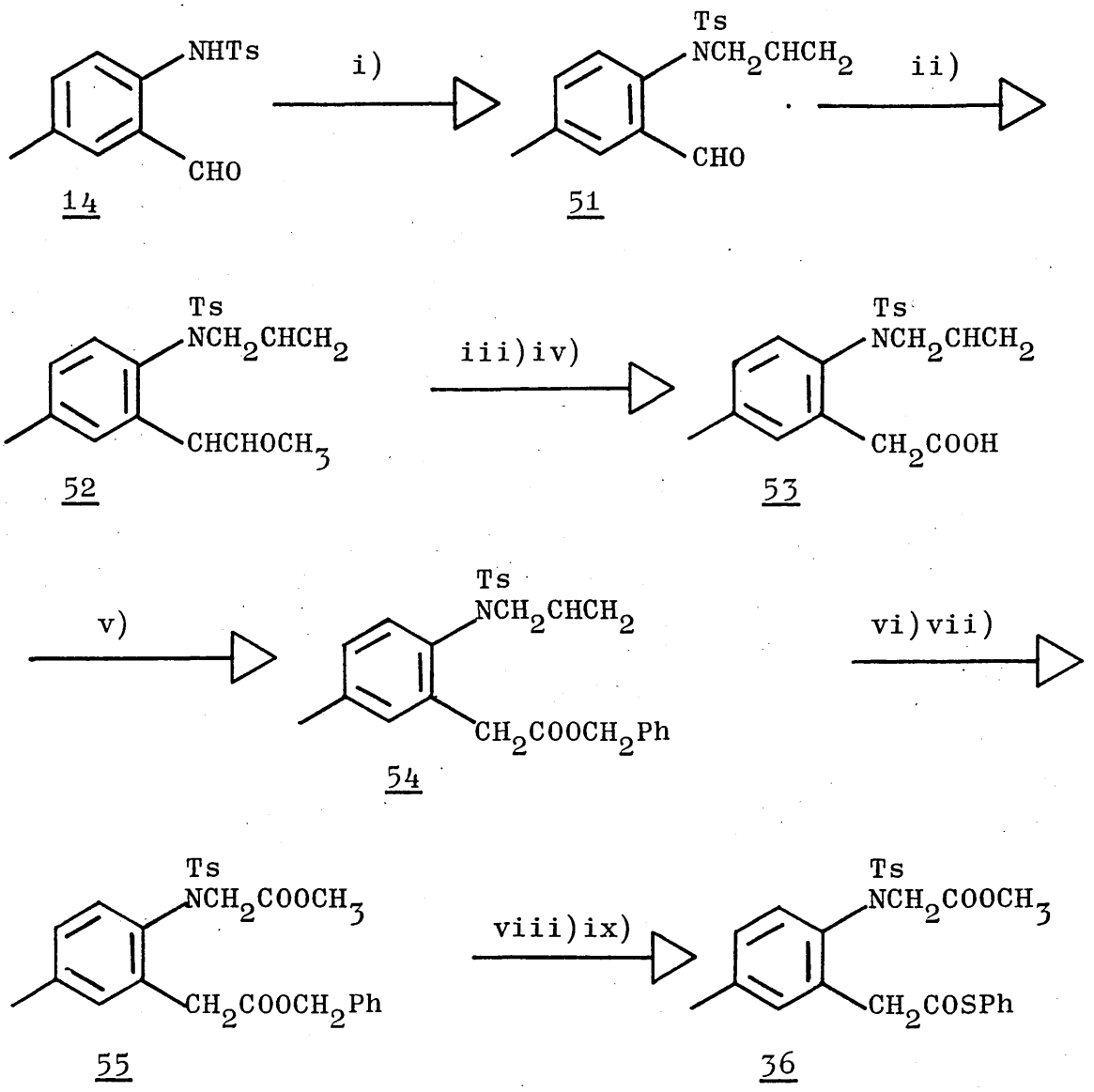
Scheme 45

Analysis of its IR and NMR spectra showed that, as expected from Woodward's work, the methyl ester was retained. However it appeared that the p-toluenesulphonyl group had been cleaved by the rather vigorous conditions. Therefore the structure of the product was tentatively assigned as the amide 47b. Several other reagents, which have been reported for the hydrolysis of nitriles to carbonyl compounds, were also tried but with no success[65-69].

The partial success of the Wittig reaction between the aldehyde 37 and the phosphorane 41 led us to reexamine this route. The problem appeared to be that the presence of the methoxycarbonyl group attached to nitrogen allows a competitive intramolecular cyclisation to occur. What seemed to be required was an alkylating agent that could be attached to nitrogen, that does not contain a free carbonyl group, but that could be ultimately converted to the $-CH_2CO_2CH_3$ residue essential for the Dieckmann precursor 36. After some preliminary studies involving 2-bromoethanol 48 and 2-bromoacetaldehyde diethyl acetal 49, allyl bromide 50 was chosen. It was envisaged that the allyl group could be converted to the $-CH_2CO_2CH_3$ residue via ozonolysis, oxidative work up and esterification.

$BrCH_2CH_2OH$	$BrCH_2CH(OC_2H_5)_2$	CH_2CHCH_2Br
48	49	50

Using this strategy the mixed O,S diester 36 was successfully synthesised as shown (Scheme 46).

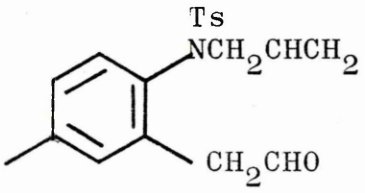


14 51 52 53 54 55 36

i) NaH/DMF, 50 ii) 41/THF iii) $Hg(OAc)_2$/THF/H_2O iv) Jones reagent v) NaH/DMF, $PhCH_2Br$ vi) O_3/CH_2Cl_2, Jones reagent vii) CH_2N_2/ether viii) H_2/5% Pd on C/ $C_2H_5OH/CH_3COOC_2H_5$ ix) PhSH/DCC/THF

Scheme 46

Thus the vinylethers 52 were prepared from 14 via stepwise allylation (93%) and Wittig condensation (64%). The ratio of E and Z isomers in 52 was 1:1 with their structures being assigned on the basis of their NMR spectra (see experimental section). Hydrolysis[59] of 52 to the aldehyde 56 followed by Jones oxidation gave the acid 53, which on treatment with sodium hydride and benzyl bromide gave the ester 54. The carbon-carbon double bond in 54 was subjected to ozonolysis followed by an oxidative work up to give the acid 57.



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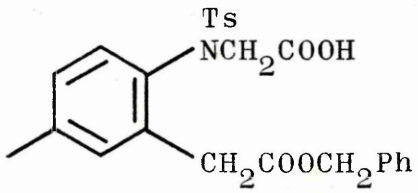
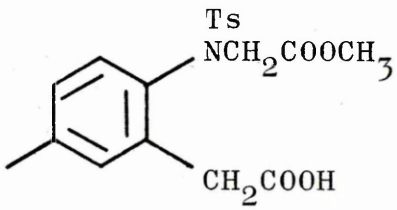


57

This was immediately esterified with diazomethane to give 55 in 93% yield from 54. Selective deprotection of the benzyl ester using catalytic hydrogenation (92%) was followed by treatment of the resultant acid 39 with thiophenol in the presence of dicyclohexyl carbodiimide[70] (DCC) to give the Dieckmann precursor 36 (51%) in a small scale preliminary investigation.



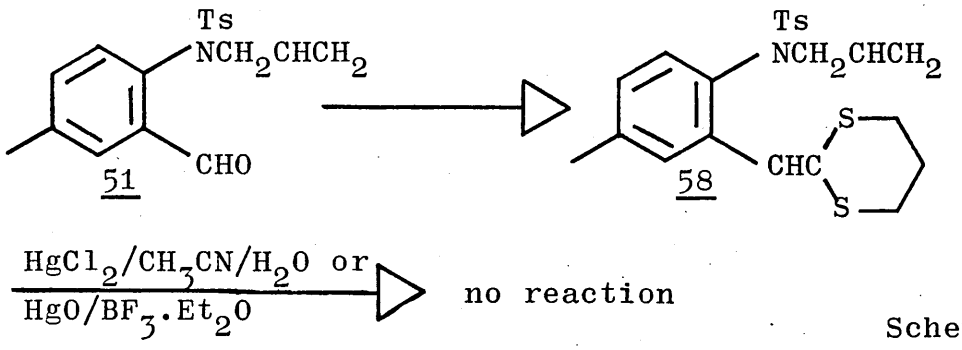
39

When the scale of this synthesis was increased, in order to obtain a sufficient quantity of 36 to study the cyclisation, all of the steps gave acceptable yields of

products except the conversion of 52 to 53. The aldehyde 56, obtained from 52, was both oxidised without purification and purified prior to oxidation, but in neither case was a yield of 53 better than 10-25% obtained. Thus we were unable to obtain significant amounts of 36 using this route.

It appeared that the problem might lie in the phenylacetaldehyde derivative 56. Phenylacetaldehydes are known to be rather sensitive. Thus we considered a one carbon homologation reaction on the aldehyde 51 to give a product which could be directly transformed into the carboxylic acid 53. A search of the relevant literature on acyl anion equivalents[71] and homologating reagents[72] indicated several possibilities from which two were chosen.

2-Trimethylsilyl-1,3-dithiane, prepared using the method of Corey[73], was treated successively with n-butyl lithium and 51 to give the ketenedithioacetal 58 (Scheme 47).

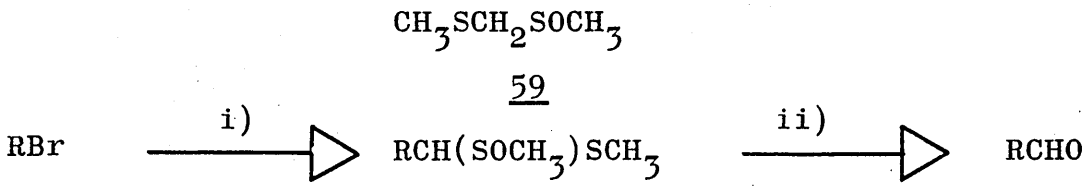


Scheme 47

The most common methods for the hydrolysis of compounds like 58 involve mercuric salts. Unfortunately, under neither of the conditions[36,74] shown in Scheme 47 was any of the corresponding acid 53 obtained.

Methyl methylsulphinylmethyl sulphide (MMTS) 59 was first reported for the one carbon homologation of alkyl halides to aldehydes, via the intermediate dithioacetal S-

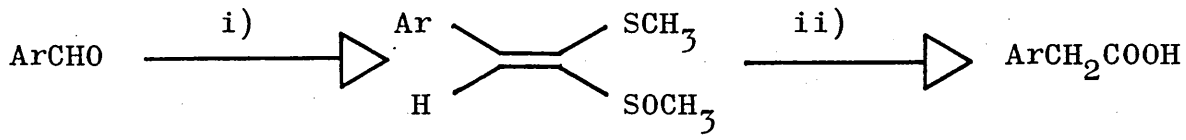
oxides, by Ogura's group in 1971[75] (Scheme 48).



i) NaH/59 ii) $\overset{+}{H}$

Scheme 48

The following year they used the same reagent to transform benzaldehyde or its derivatives into ketenedithioacetal S-oxides[76]. On acid hydrolysis these latter compounds were transformed into phenylacetic acids (Scheme 49).

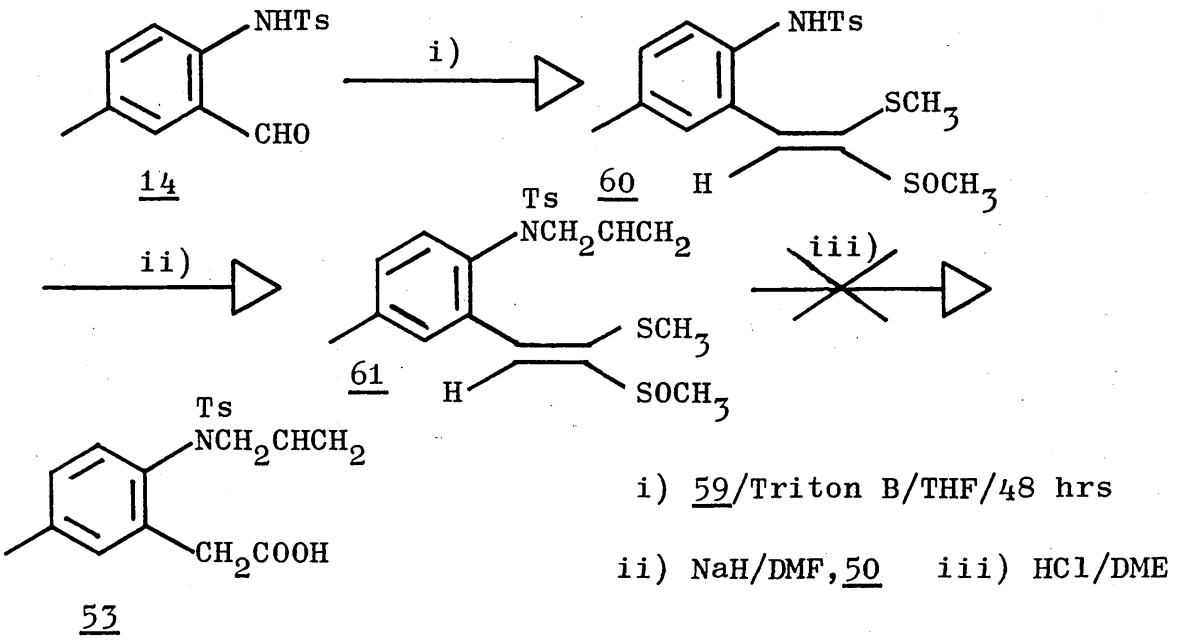


i) 59/Triton B/THF/reflux ii) HCl/1,2-dimethoxyethane

Scheme 49

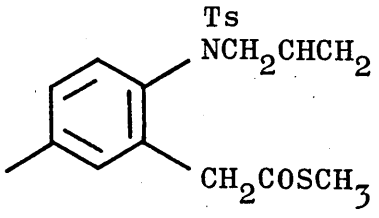
Applying this strategy to the synthesis of our required acid 53, the aldehyde 14 (Scheme 50) was transformed into 60 on prolonged reflux with 59. Reaction of the sodium salt of 60 with allyl bromide 50 gave 61 in 86% yield. Using the conditions developed by Ogura for the hydrolysis of ketendithioacetal-S-oxides[76,77], 61 was treated with concentrated hydrochloric acid (HCl) in 1,2-dimethoxyethane (DME). Prolonged reaction times were necessary in order to get a significant amount of product formation. But even

after stirring for several days at room temperature a substantial amount (40%) of 61 was recovered from the reaction mixture.



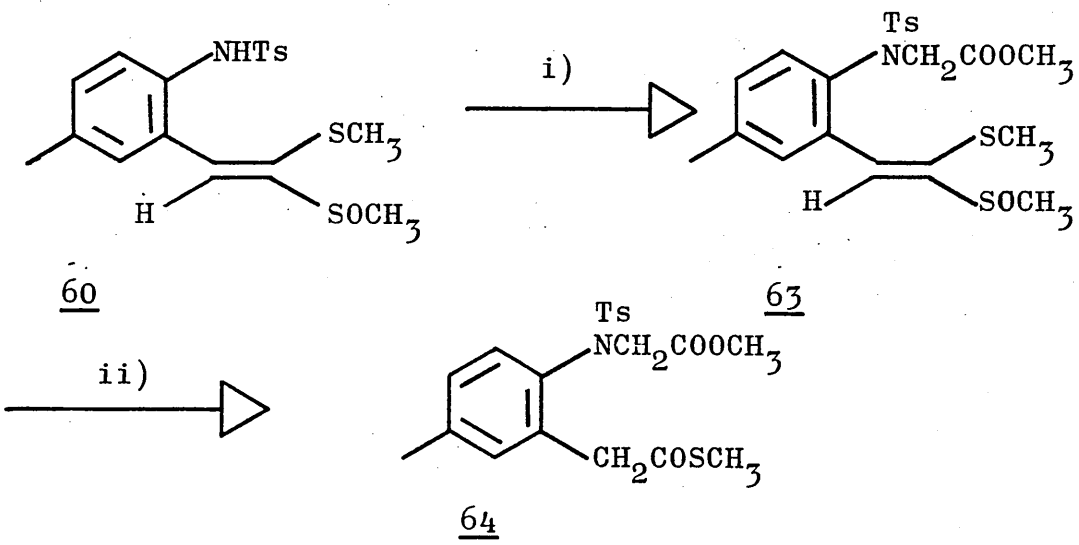
Scheme 50

No trace of the acid 53 was observed and the only other product obtained in any appreciable amount (15%) was relatively non polar. A study of its IR and NMR spectra allowed the structure to be tentatively assigned as the thiol ester 62 (the hydrolysis of ketenedithioacetal-S-oxides under standard conditions is not always predictable and anomalous products are known[77,78]).



62

We were particularly intrigued by this observation, as we required a thiol ester functionality at this position in order to study the Dieckmann cyclisation (cf. compound 36). However we were not sure that it would be possible to convert 62 into 64 using ozonolysis and an oxidative work up, followed by esterification, (see Scheme 46) without disruption of the thiol ester. Thus we attempted to use this strategy (Scheme 51) in a more direct synthesis of 64 (a close analogue of 36) which could itself be subjected to the Dieckmann reaction.



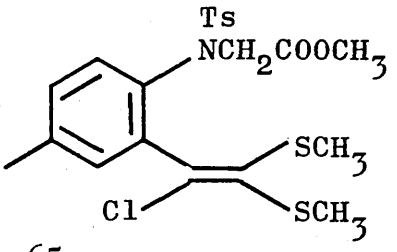
60 63 64

i) NaH/DMF, $BrCH_2COOCH_3$ ii) HCl/DME

Scheme 51

The sulphonamide 60 was treated with NaH in DMF and the resultant anion quenched with methyl bromoacetate. The reaction was essentially complete within 5 minutes and prolonged exposure resulted in extensive degradation, so a rapid work up was employed to give 63 in excellent yield (79%). On hydrolysis of 63 with HCl/DME again only a low yield (23%) of the thiol ester 64 was obtained. A change

of solvent to tetrahydrofuran (THF), ether or p-dioxan gave no apparent advantage. However when the same reaction was performed in dichloromethane (CH_2Cl_2) a single product was obtained in quantatative yield. TLC analysis showed this to be different to the thiol ester 64 and a combination of spectral and X-ray crystallographic techniques enabled the structure to be assigned as the chloroketenedithioacetal 65.



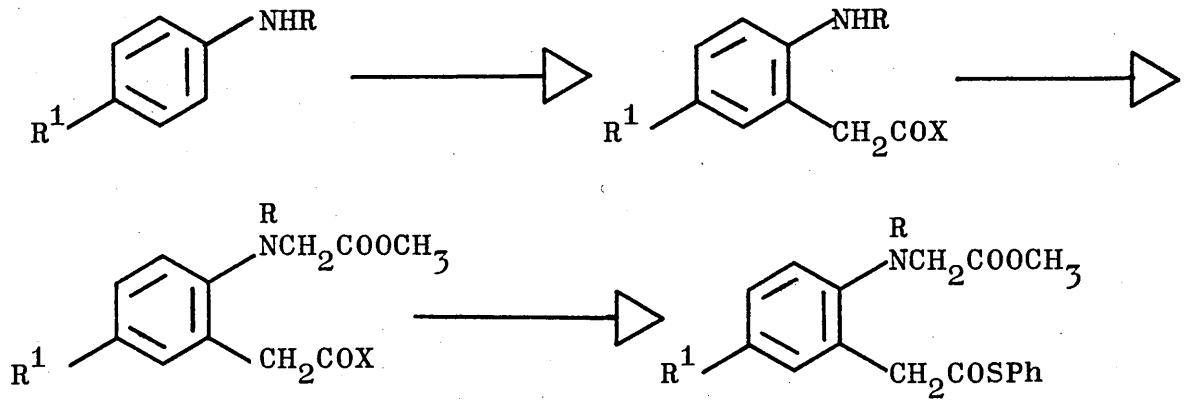
65

(For a more detailed discussion on the chemistry of methyl methylsulphinylmethyl sulphide 59, ketenedithioacetal S-oxides c.f. 60, 61 and 63 and chloroketenedithioacetals c.f. 65 see chapter 3).

It also proved impossible to hydrolyse the ketenedithioacetal-S-oxide 63 to the thiol ester 64 or the acid 39 using perchloric acid or mercuric salts, so this route to the Dieckmann precursor 64 was abandoned.

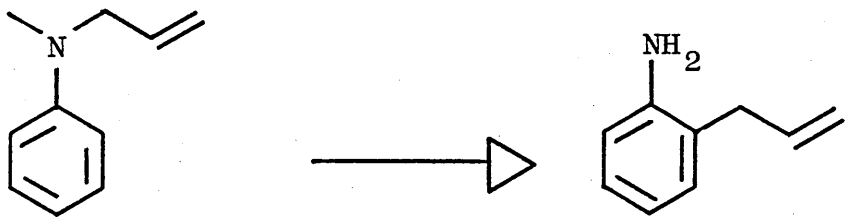
The problem with this approach to the synthesis of virantmycin appeared to lie with the one carbon homologation reaction. It had proved impossible to obtain useful yields of the acid 39 or the thiol ester 64 from the benzaldehydes 51 or 37, either directly, or via the intermediate phenylacetaldehyde 56. In order to overcome this we proposed to formulate the two carbon chain attached to the aromatic ring prior to functionalisation at nitrogen (Scheme 52). This is essentially the reverse of the procedure outlined above.

An attractive method for the introduction of this two carbon appeared to be via a pericyclic rearrangement rather than simple functional group manipulation.



Scheme 52

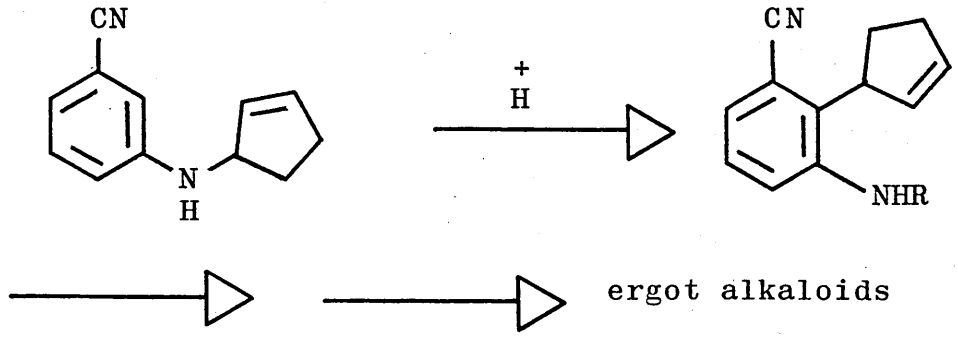
The simplest sigmatropic rearrangement of anilines, the amino Claisen rearrangement (Scheme 53), has been extensively studied[79], but in general with much less success than the Claisen rearrangement itself[79,80].



Scheme 53

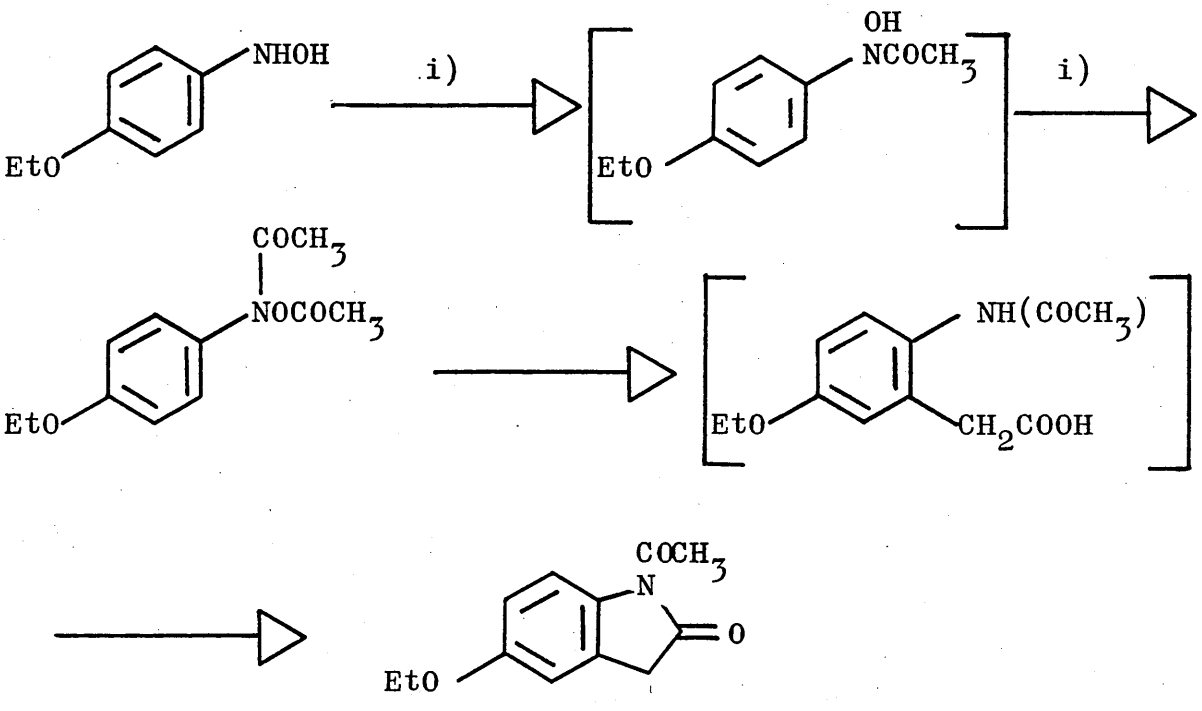
In general the former requires much more drastic conditions than the latter and tends to give mixtures of products arising from rearrangement and cleavage. The reaction was originally promoted thermally, but both Lewis and Bronsted acids have recently been used to greater effect[79]. Some improvements have been made resulting in the synthesis of more complex

molecules[81] (Scheme 54), but the rearrangement of groups more complex than allyl would represent a significant improvement.



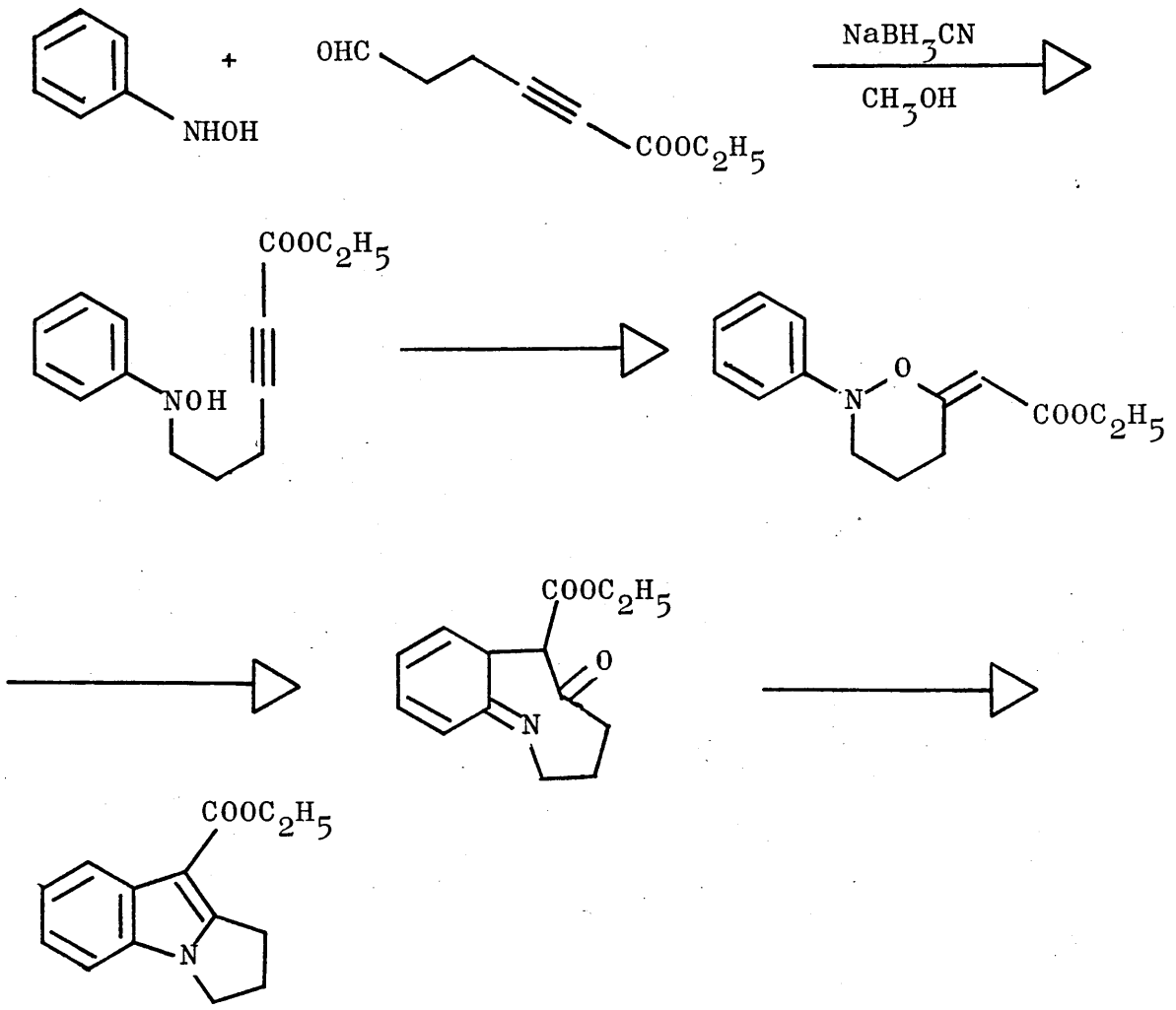
Scheme 54

To this end a number of variants on the simple amino Claisen rearrangement have been published including a preparation of oxindoles[82] (Scheme 55) and one of pyrroloindoles[83] (Scheme 56).



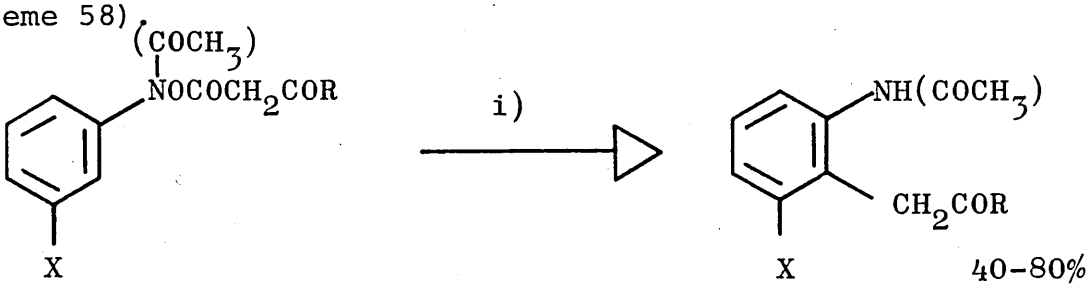
i) H_2CCO

Scheme 55



Scheme 56

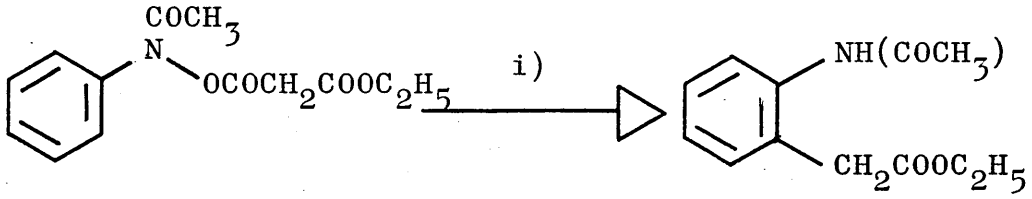
In the context of our own aims (Scheme 52) attention was focused on some results by Coates[84] on the rearrangement of acetoacetates (Scheme 57) and mixed malonate esters (Scheme 58)



i) $PhCH_3/110^oC$ X=H,CH_3,Cl,$COOCH_3$

Scheme 57

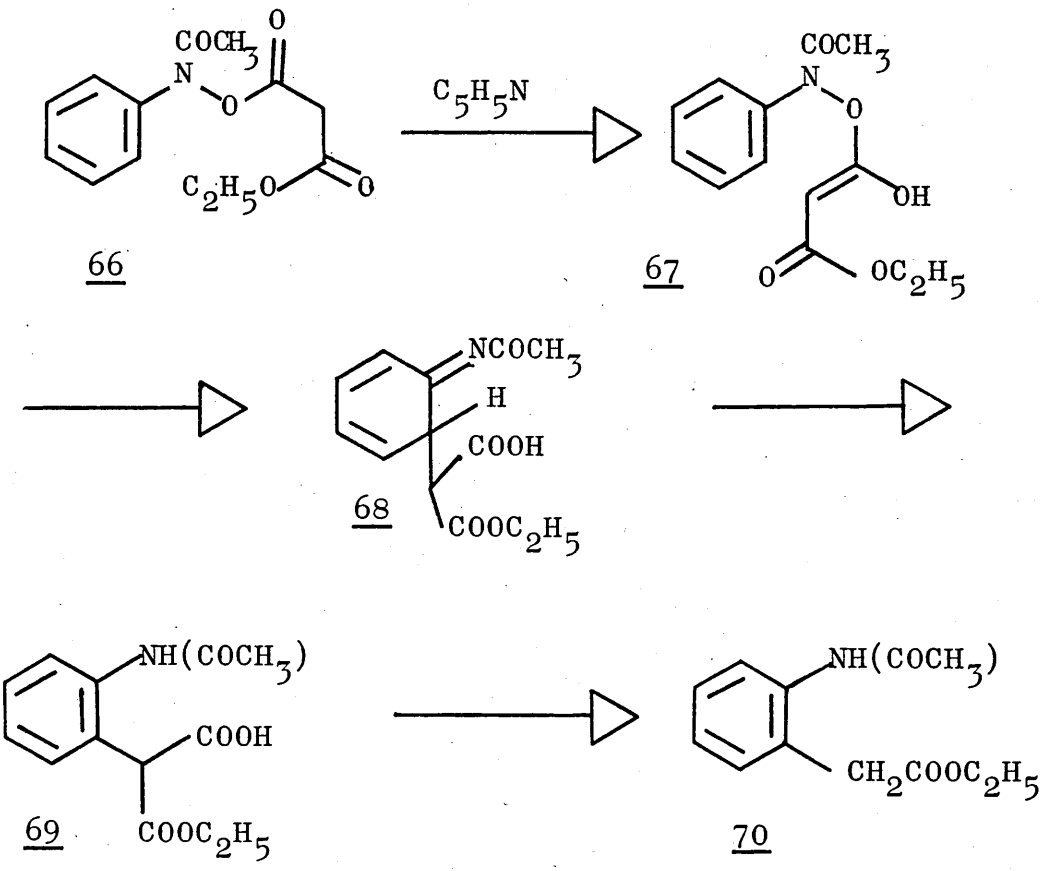
Based on some earlier work by others[85] and some of their own experimental observations[84] they proposed the following mechanism (Scheme 59).



i) $PhCH_3/C_5H_5N/110^oC$ 60%

Scheme 58

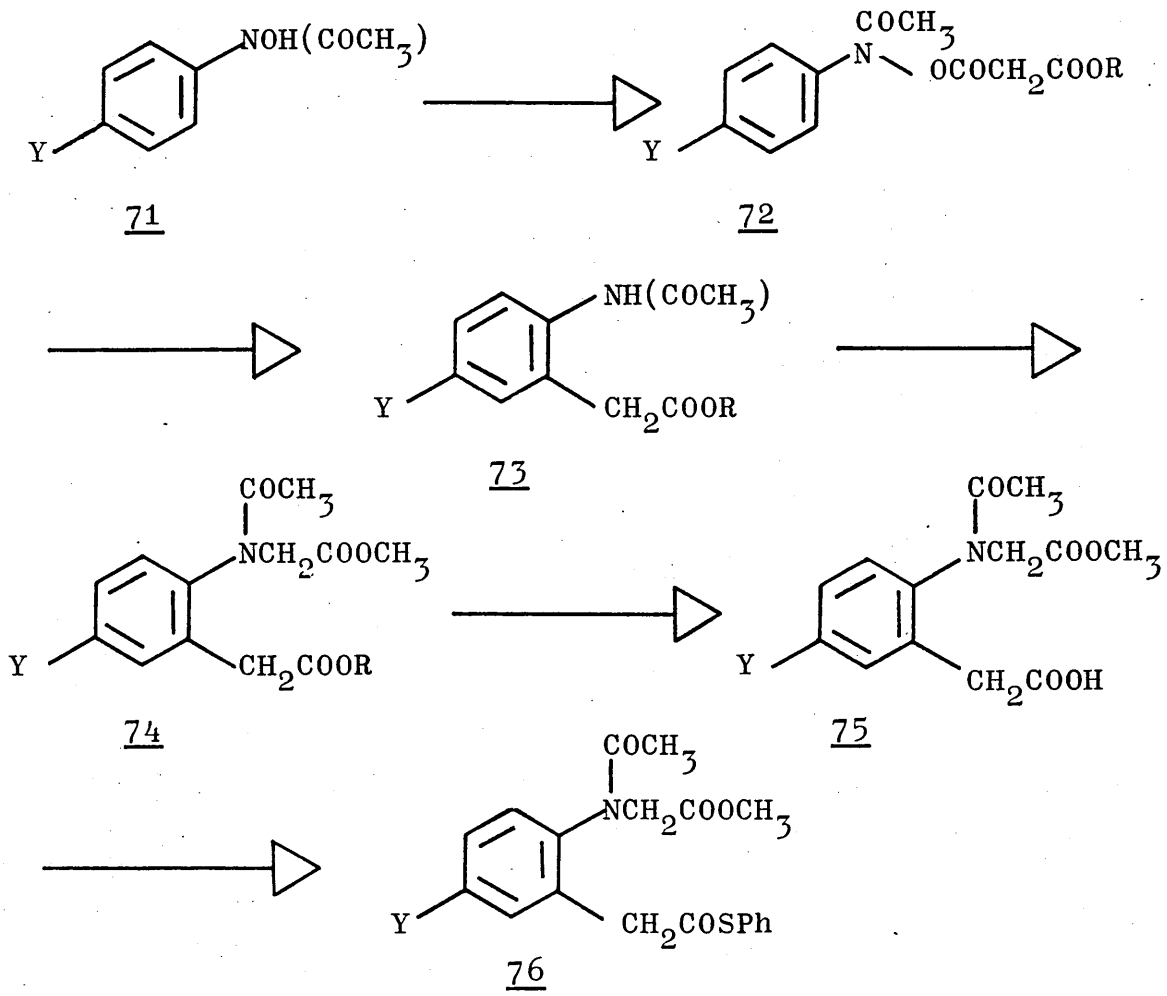
Thus the enol tautomer 67 rearranges via 68 to 69.



Scheme 59

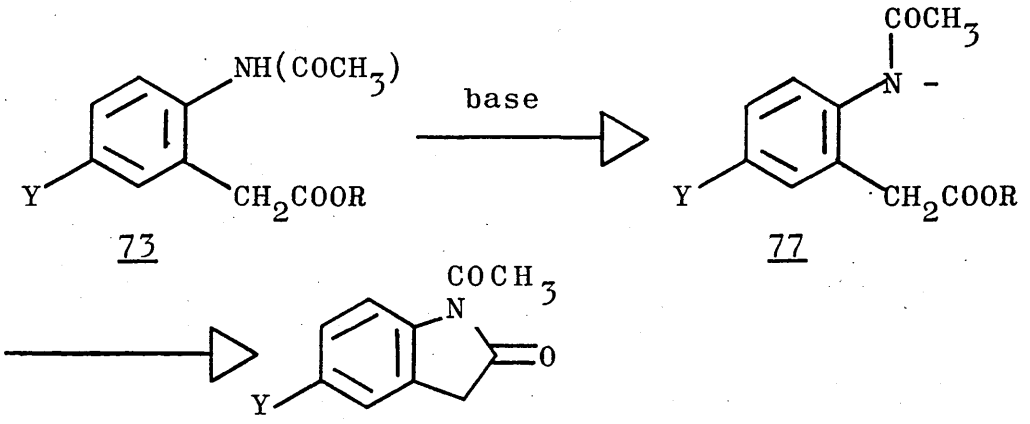
In one case the monomalonic acid (cf. 69) could be isolated thus proving that rearrangement precedes decarboxylation, but

more usually decarboxylation was spontaneous to give the ester 70. This last compound bears a striking resemblance to one of our newly proposed intermediates (Scheme 52) and was responsible for initiating our interest in Coates' work. Using this strategy, the general outline of our proposed synthesis is shown (Scheme 60).



Scheme 60

Thus the mixed malonate 72, which would be available from 71 using Coates' procedure[84], should give the ester 73 upon rearrangement. There appeared to be a theoretical possibility that formation of the amide anion from 73 (for subsequent reaction with methyl bromoacetate to give 74) would result only in intramolecular cyclisation to give the oxindole 78 (Scheme 61).

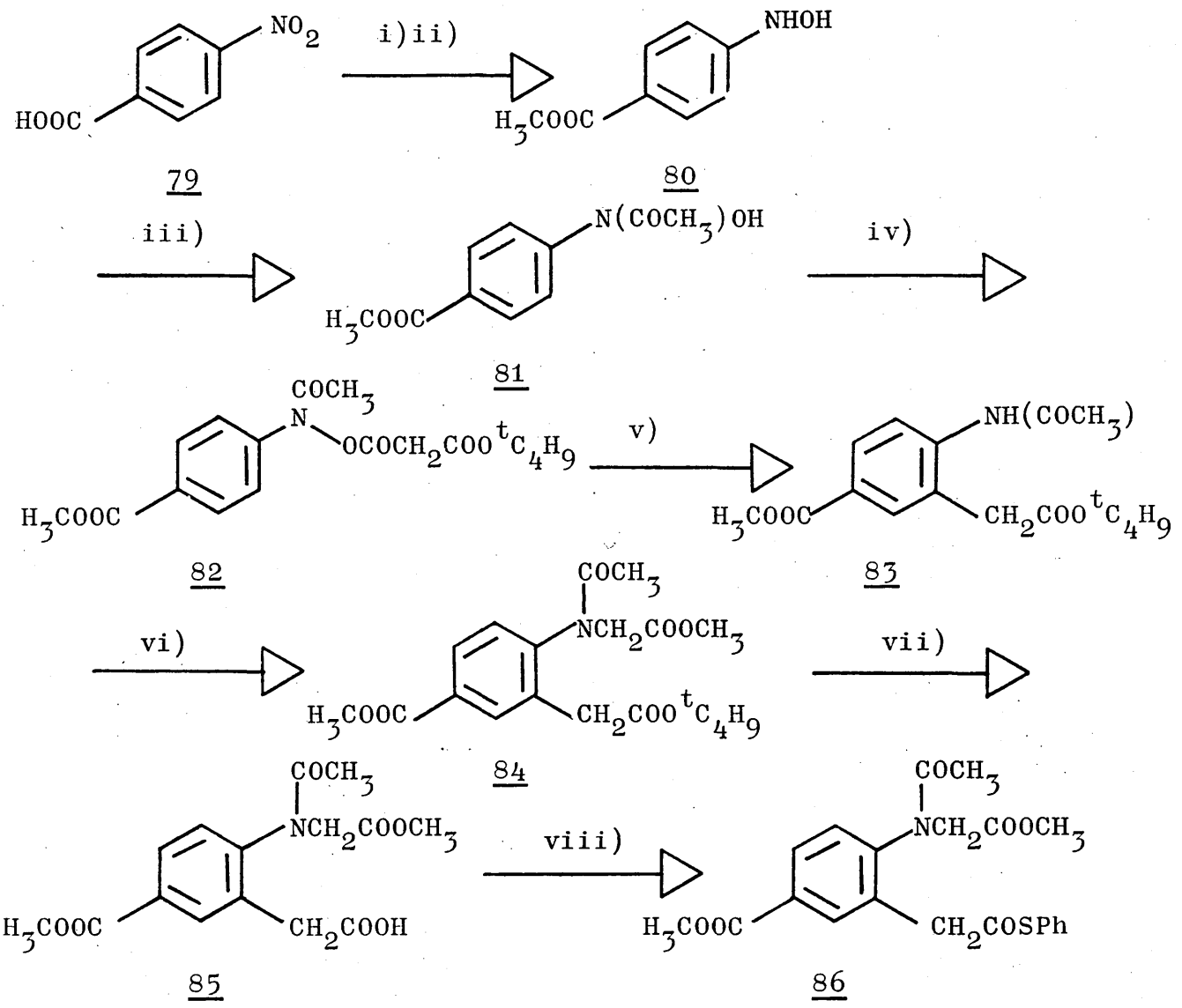


Scheme 61

Thus we required a group R which could prevent nucleophilic attack at the ester group. It is well known that ^{t}butyl esters resist basic hydrolysis and do so presumably as a consequence of the steric bulk of the ^{t}butyl group preventing nucleophilic attack by the hydroxide anion. Therefore we felt that the presence of a ^{t}butyl ester in 73 might prevent oxindole formation and favour an intermolecular reaction. This has another advantage in that selective deprotection of the ^{t}butyl ester in 74 (R = ^{t}Bu), using acid, should allow ready formation of the acid 75 from 74. Condensation of the former with PhSH as previously described should give the Dieckmann precursor 76, similar to the one prepared earlier, i.e. 36 (Scheme 46).

In fact this route has been particularly successful allowing preparation (Scheme 62) of the mixed S,O diester 86

in multigram quantities, sufficient for a subsequent study of the Dieckmann reaction (vide infra).



i) CH_3OH/H_2SO_4/reflux ii) $Zn/C_2H_5OH/H_2O/NH_4Cl/\Delta$

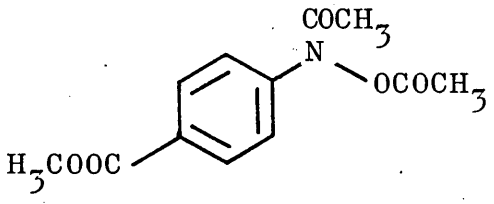
iii) $CH_3COCl/Et_2O/NaHCO_3/H_2O$ iv) $HOOCCH_2COO^tC_4H_9$/DCC/THF

v) $C_5H_5N/PhCH_3/110^oC$/3 hrs vi) LDA/THF, $BrCH_2COOCH_3$

vii) CF_3COOH viii) PhSH/DCC/THF

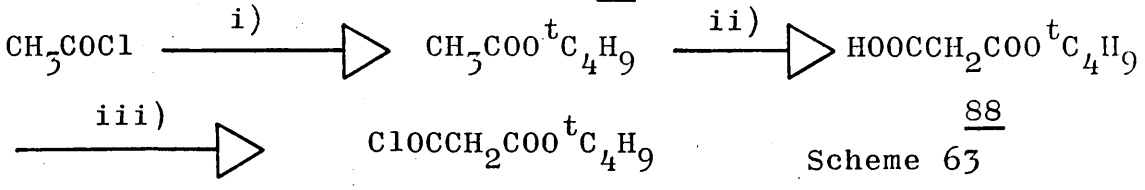
Scheme 62

The starting material chosen was 4-nitrobenzoic acid 79 because it contains a nitrogen atom and a carbonyl group in the equivalent positions as they can be found in virantmycin. Thus 79 was esterified using standard conditions and the nitro group was reduced to the hydroxylamine 80 using zinc[86] dust in 62% yield from 79. Treatment of 80 with a slight excess of acetyl chloride in a two-phase medium gave the amide 81 in moderate yield together with recovered 80. In an attempt to force the reaction to completion a larger proportion (1.5-1.75 mole equivalents) of acetyl chloride was used, but this resulted in no greater yield of 81. In addition the formation of a second product (presumably the bisacetate 87[82]) resulted in a more tedious separation.



87

It was anticipated that the preparation of 82 from 81 would be achieved by reaction of the latter with tert-butylmalonyl chloride[87,88] (prepared as shown in Scheme 63). However the major product was not the expected malonate 82 but again the bisacetate 87. We were unsure whether this had arisen from rapid decarboxylation of 82 or from a preponderance of acetyl chloride in 89.

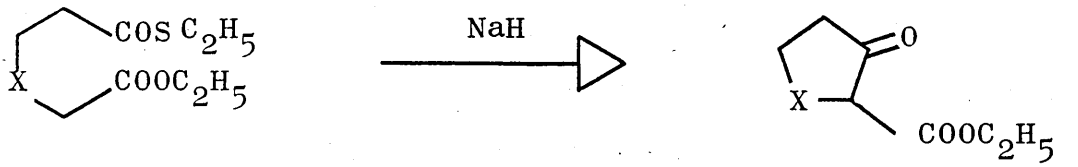


Scheme 63

i) $^{t}BuOH/(CH_3)_2NPh/Et_2O$ ii) $^{n}BuLi/THF/-78^{o}C,CO_2$
iii) Ph_3P/CCl_4

This did not prove to be a serious problem as simple condensation of 88 with 81 in the presence of DCC gave 82 in 62% yield. Subsequent rearrangement of this to 83 proceeded as predicted by Coates[84] (56%). Our confidence in the ability of the ^{t}butyl group to aid 83 in resisting intramolecular attack was justified when formation of the anion of 83 and exposure of this to methyl bromoacetate gave only the diester 84. Selective cleavage of the ^{t}butyl ester, using acid, and condensation of the resultant acid 85 with PhSH/DCC gave the mixed O,S diester 86 in 57% yield from 84 on a multigram scale.

The Dieckmann reaction of mixed S,O diesters[54-57] has been performed using a variety of bases. Hatanaka's group have used exclusively lithium hexamethyldisilazide[55-57] (LHMDS) where as Yamada's group[54] have used either lithium diisopropylamide (LDA) or, when the ester group is further stabilised by a α heteroatom, NaH (Scheme 64). One of the compounds in this scheme (90a) bears some resemblance to our own Dieckmann precursor 86 in terms of this additional stabilisation. Both groups made other practical observations.



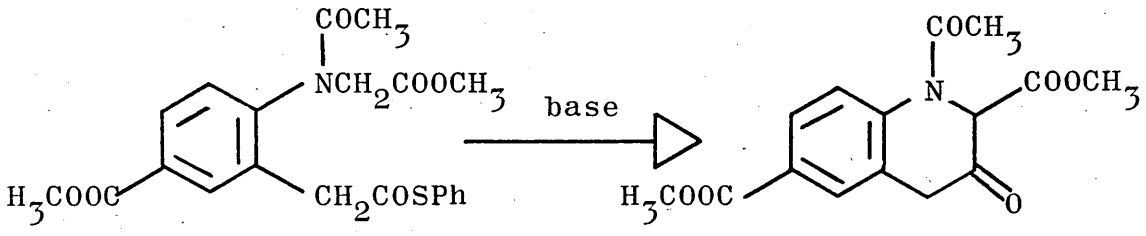
90a X=S
90b X=NCOOC$_2$H$_5$

91a X=S
91b X=NCOOC$_2$H$_5$

Scheme 64

Yamada stressed that dilute conditions (0.1-0.01 M) were required, specifically in one case, to avoid a competitive side reaction.

We have concentrated on the use of LDA in an investigation of the effect of the concentration of base on the reaction (Scheme 66), but have also performed isolated reactions with other bases, for example LHMDS, potassium tert-butoxide (KO^tBu) and NaH.

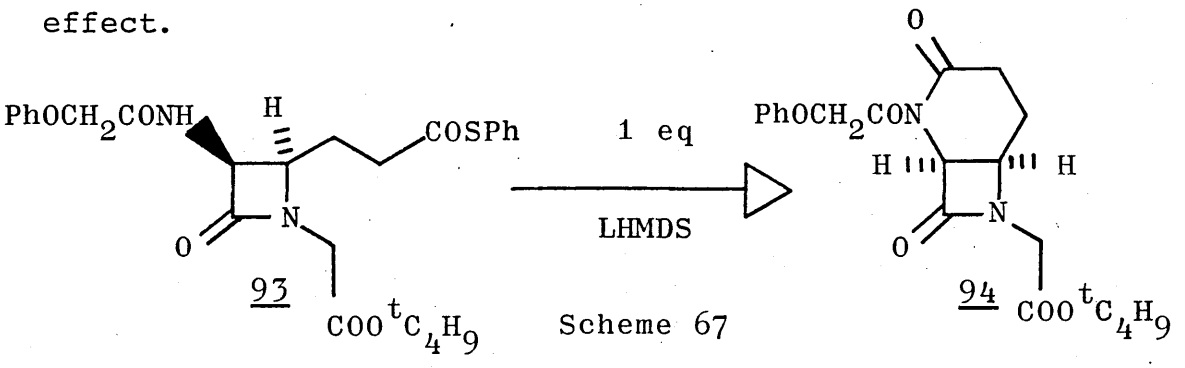


86 92

Scheme 66

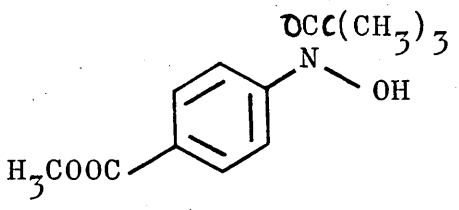
As the first attempt to convert 86 into 92, the former was treated with 1.2 mole equivalents of LDA in THF (total concentration of 86 not exceeding 0.1 M) at -78°C. No reaction was observed, but on warming the reaction mixture to room temperature complete disappearance of starting material was noted. From the reaction mixture two major products were isolated, both more polar on TLC than 86, together with a number of minor ones. Analysis of their IR and NMR spectra appeared to indicate that the most polar of the major products was the one required, i.e. 92. However the yield was disappointingly quite low. In an attempt to rectify this the reaction was repeated using 2.2 mole equivalents of LDA. Under the same reaction conditions as used for the previous experiment a similar reaction profile was observed, but the general impression gained was that the ratio of the desired product to undesired side products was less favoured. This tendency to get lower yields on increasing the concentration of base was confirmed when no useful products were obtained when 86 was treated with 3.2 mole equivalents of LDA.

Using other bases the results were less encouraging. For example with LHMDS (1.2 eq) at -78°C, with subsequent warming to room temperature, the major component isolated was recovered 86. When KO^{t}Bu was treated with 86 at 0°C there again proved to be a significant quantity of starting material left, with the only other products being less polar on TLC than 86. It appeared therefore that a change of base gave no solution to the presence of unwanted side products. Hatanaka's group had also encountered this problem in their synthesis of the cephem 35. There, treatment of 93 with 1 equivalent of LHMDS gave not the desired product 35 but the product derived from intramolecular N-acylation 94 (Scheme 67). They solved this problem by increasing the proportion of base. We had already tried this solution to the problem of our own unwanted side products but to no effect.

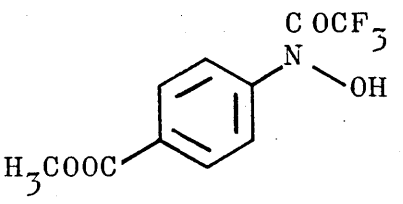


Scheme 67

Although no attempt has been made to characterise the side products produced in the conversion of 86 to 92 one possibility might involve the participation of the acetamide in a competing intramolecular reaction. To test this hypothesis we planned to prepare the amides 95 and 96 (having no α hydrogen atoms on the amide) and carry them through the synthesis shown earlier (Scheme 62). Unfortunately this did not go quite as anticipated, thus we were unable to prepare 96 satisfactorily using either of the conditions shown (Scheme 68).

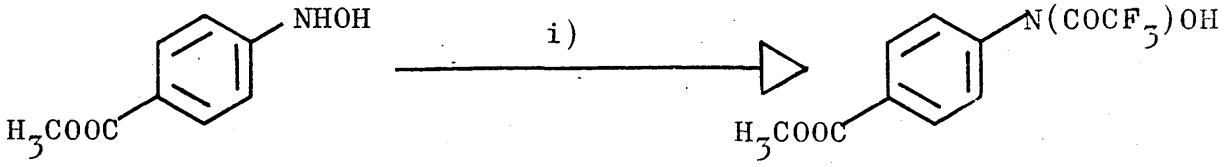


95



96

Although the synthesis of 95 was achieved satisfactorily and this could subsequently be carried through to the diester 97 (Scheme 69), the next step, involving acid hydrolysis of the ^{t}butyl ester also appeared to affect the protecting group on nitrogen.

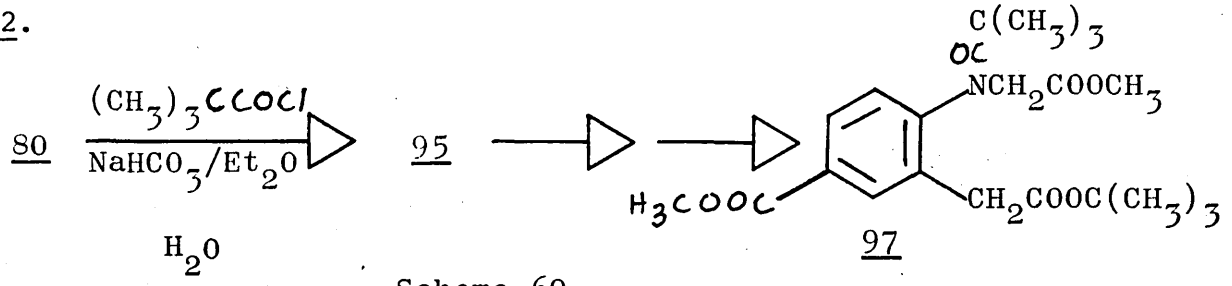


80 96

i) $(CF_3CO)_2/CH_2Cl_2$ or $(CF_3CO)_2/NaHCO_3/Et_2O/H_2O$

Scheme 68

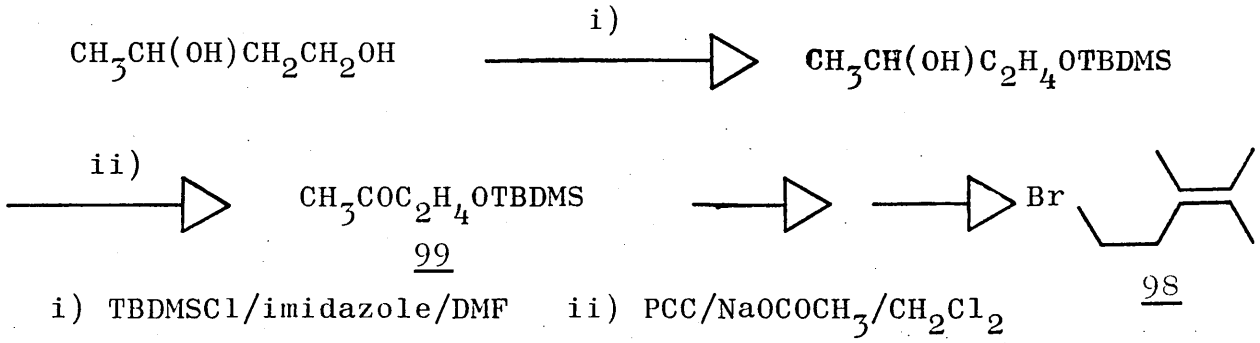
This meant we had to return to the use of the 1,3-ketoester 92.



Scheme 69

Having achieved the synthesis of this compound we turned our attention to the synthesis of the halide 98.

Thus butane-1,3-diol was selectively protected at the primary alcohol with ^{t}butyldimethylsilyl chloride.



i) TBDMSCl/imidazole/DMF ii) PCC/$NaOCOCH_3$/CH_2Cl_2

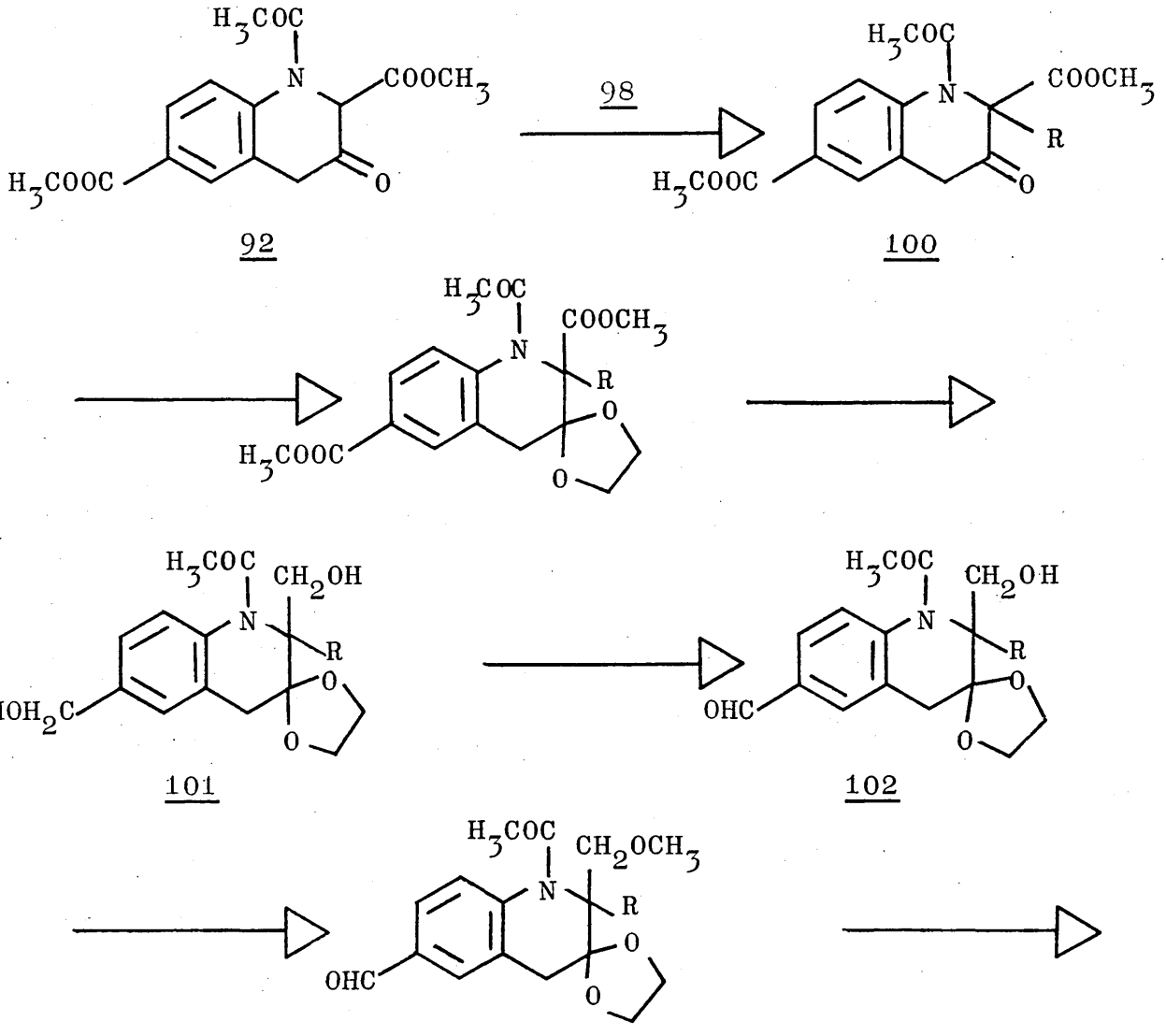
Oxidation of the secondary alcohol with buffered PCC gave the ketone 99. Although this work is unfinished subsequent Wittig condensation of this with isopropyltriphenyl phosphonium bromide, deprotection of the alcohol and bromination should give 98.

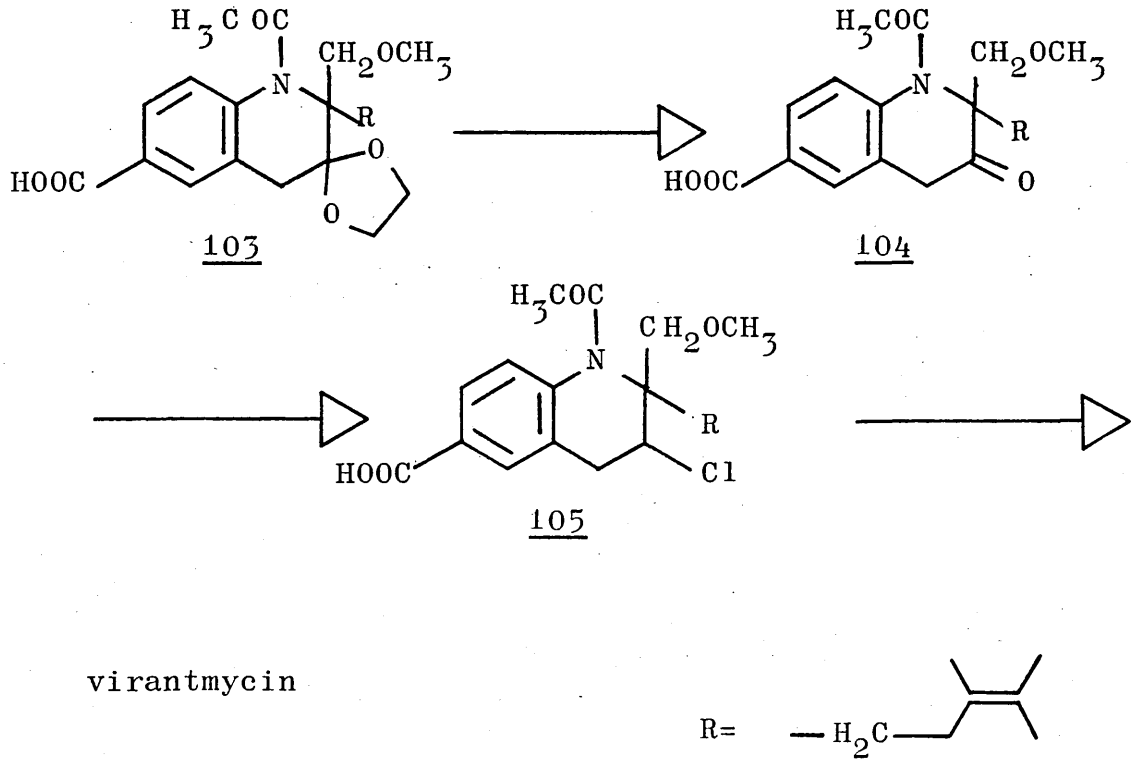
The envisaged route for the completion of the synthesis is outlined in the next section.

2.4 Further work

The elaboration of the 1,3 ketoester 92 to the target molecule virantmycin was not investigated, but a number of different approaches were considered and one possibility is outlined here.

Thus (Scheme 70) following a successful synthesis of the pentenyl bromide 98 coupling of this to 92 should give 100.





Scheme 70

Protection of the ketone, for example with ethane-1,2-diol, and reduction of the two ester groups in the presence of the amide as reported by Kim[89] should give the diol 101. Selective oxidation of the benzylic alcohol using MnO_2 or one of the more modern reagents effective for this conversion[90] would give the aldehyde 102. Methylation of the remaining alcohol followed by oxidation of the aldehyde to the acid and deprotection of the ketone should give 104. From this virantmycin should be readily available using the three step procedure of removal of the acetamide group reduction of the ketone to the alcohol and chlorination.

It is expected that the compound obtained from this route is likely to be a mixture of isomers derived from the two chiral centres in virantmycin[91]. Hopefully this mixture could be separated into diastereomerically pure

components by chromatography. Resolution of the enantiomers from each pair could be achieved by chiral derivatisation at the acid or amino group followed by separation and regeneration of the enantiomers. Thus this route to virantmycin should allow the production of all four enantiomers of the target molecule for further structural and biological studies (see section 2.1).

CHAPTER 3

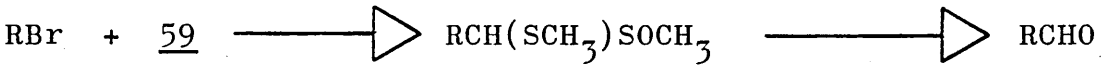
The formation and reactions of ketenedithioacetal S-oxides

3.1 INTRODUCTION

Since it was first shown to be effective for the one carbon homologation reaction of alkyl halides to aldehydes via the intermediate dithioacetal S-oxides 106 (Scheme 71), the use of methyl methylsulphinylmethyl sulphide (MMTS) 59 has been greatly extended.

$CH_3SCH_2SOCH_3$

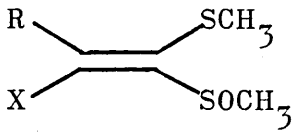
59



106

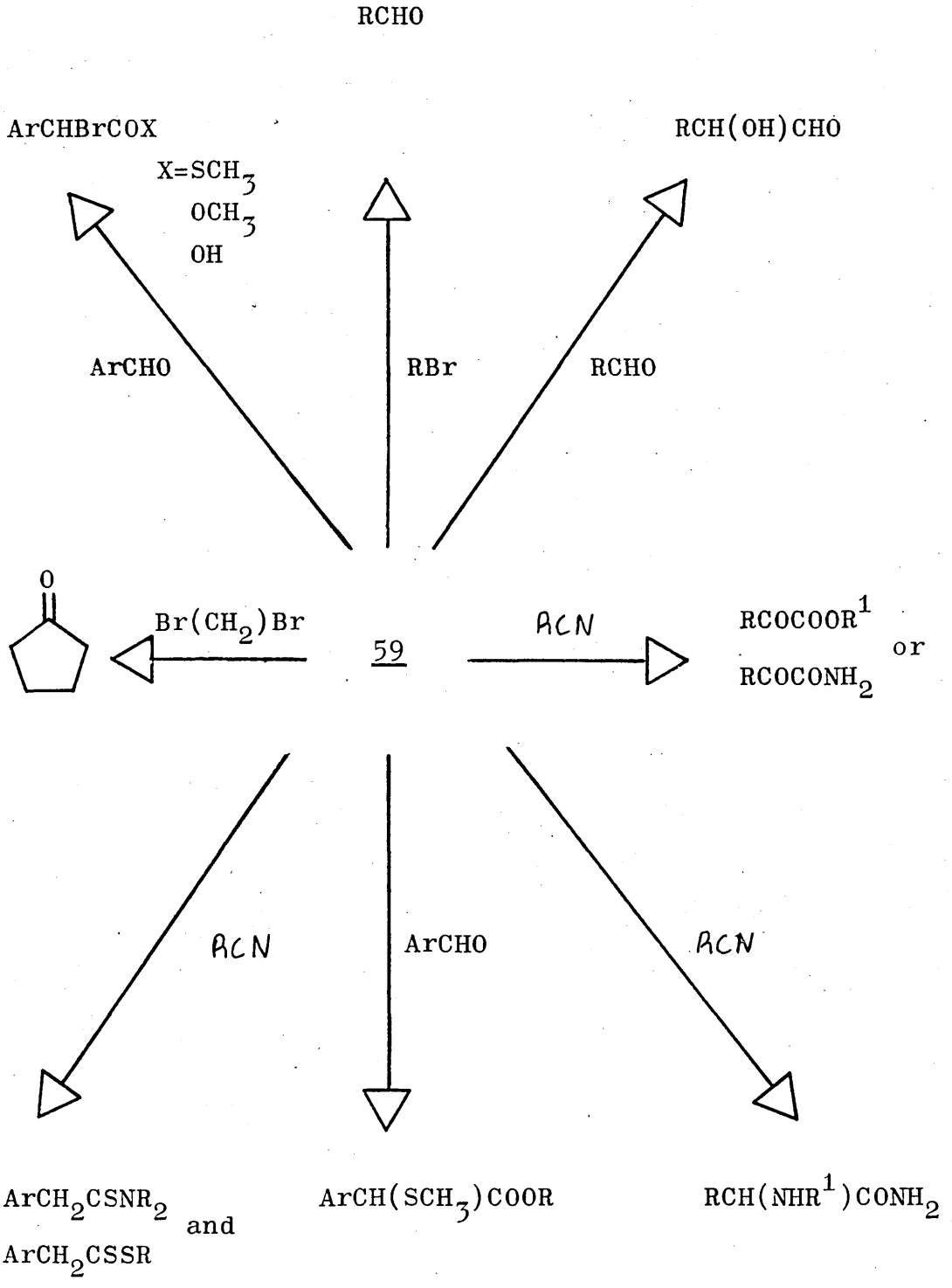
Scheme 71

It has now been shown to be effective for the synthesis of α hydroxyaldehydes and ketones[92], ketones[93], acids[76,77,94], esters, thiol esters, amides[95,96], α ketoesters[95,96], α ketoamides[95,96] and α alkylthio or α amino acids and their derivatives[95,96] (Scheme 72). These reactions proceed either via the dithioacetal S-oxide 106 or ketenedithioacetal S-oxide 107.

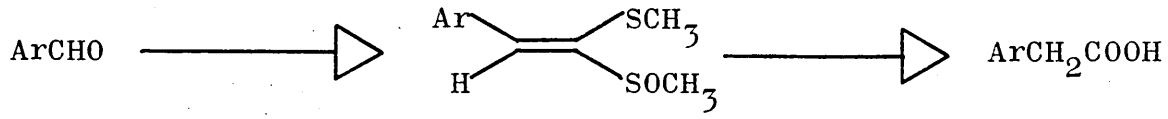


107

In each case subsequent hydrolysis gives the corresponding carbonyl compound. As stated earlier (section 2.3.2) our initial interest in 59 arose from its ability to react with benzaldehyde or its derivatives to give phenylacetic acids[76,77] (Scheme 73).

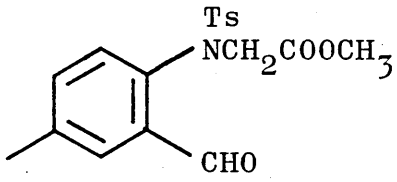

RCHO
ArCHBrCOX
X=SCH3
OCH3
OH
RCH(OH)CHO
ArCHO
RBr
RCHO
O
Br(CH2)Br
59
ACN
RCOCOOR1
or
RCOCONH2
ACN
ArCHO
ACN
ArCH2CSNR2
and
ArCH2CSSR
ArCH(SCH3)COOR
RCH(NHR1)CONH2

Scheme 72

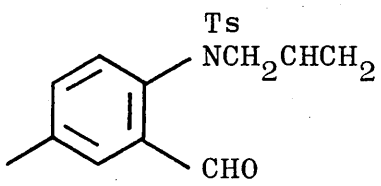


Scheme 73

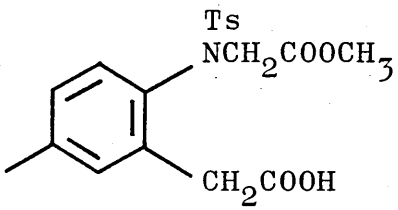
However applying this strategy to our benzaldehyde derivatives 37 and 51 we were unable to obtain the corresponding acids 39 and 53 under the published conditions. Instead, on hydrolysis of the intermediate ketenedithioacetal S-oxides 63 and 61 (HCl in 1,2-dimethoxyethane, DME) low yields of the thiol esters 64 and 62 were obtained. In an attempt to improve the yields of these latter compounds the solvent was changed from DME to THF, ether or 1,4-dioxan, but to no advantage.



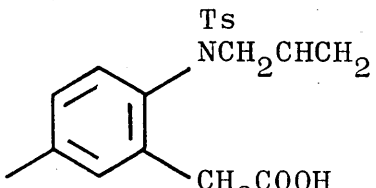
37



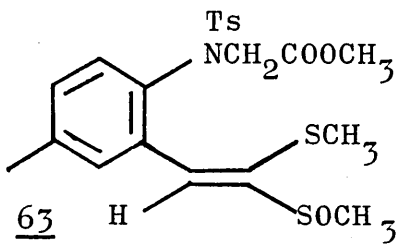
51



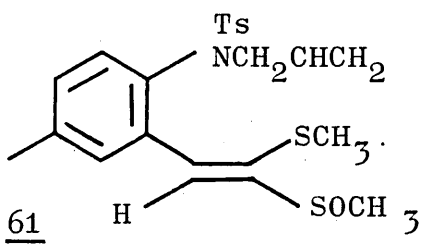
39



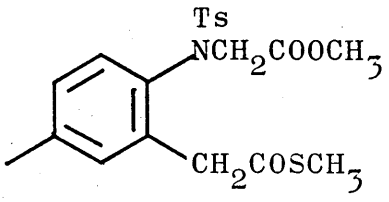
53



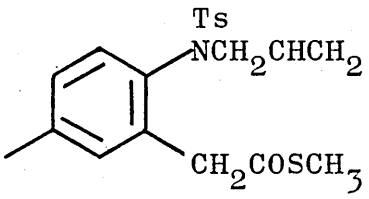
63



61



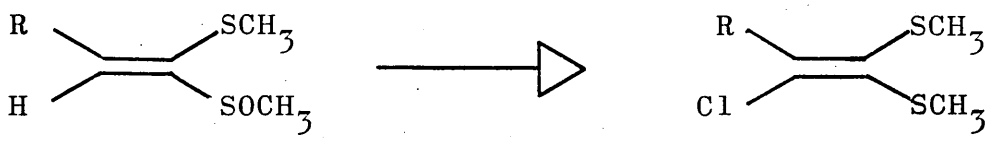
64



62

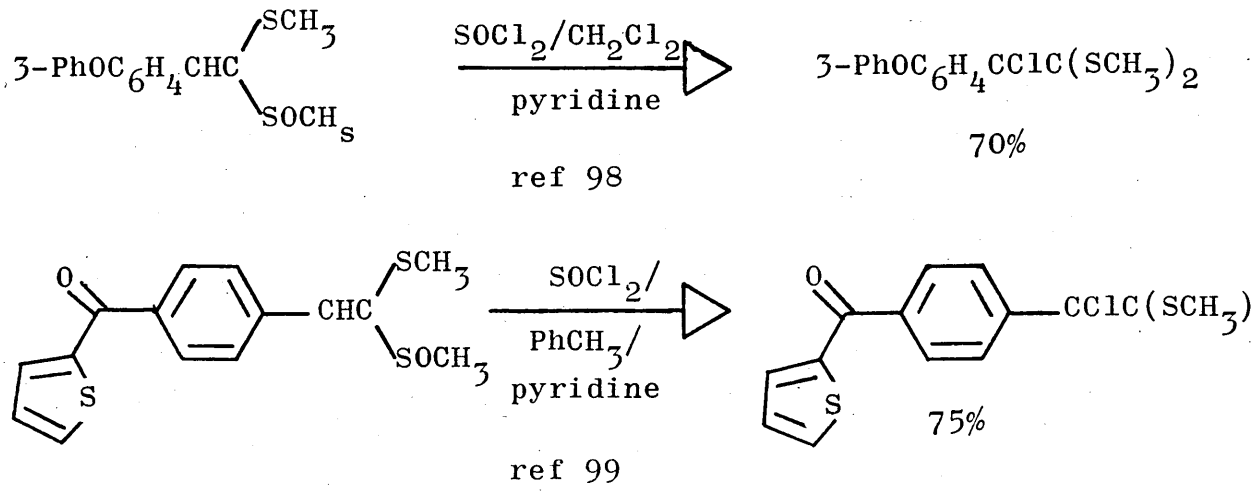
However when 63 was treated with HCl in dichloromethane (CH_2Cl_2) as the solvent a single product was obtained in quantatative yield. Thin-layer chromatography showed it to be different to the thiol ester 64 but a combination of spectral and X-ray crystallographic techniques allowed the structure to be assigned as the chloroketenedithio acetal 65.

So far as we are aware only one reagent has been reported for the transformation of ketenedithioacetal S-oxides to chloroketenedithioacetals (Scheme 74), this being thionyl chloride[97].



Scheme 74

The use of thionyl chloride for this conversion appears to be a general method which is successful independently of the structure of the rest of the molecule. Some specific examples using this reagent are shown (Scheme 75).



Scheme 75

The subsequent sections in this chapter will deal with the following points:-

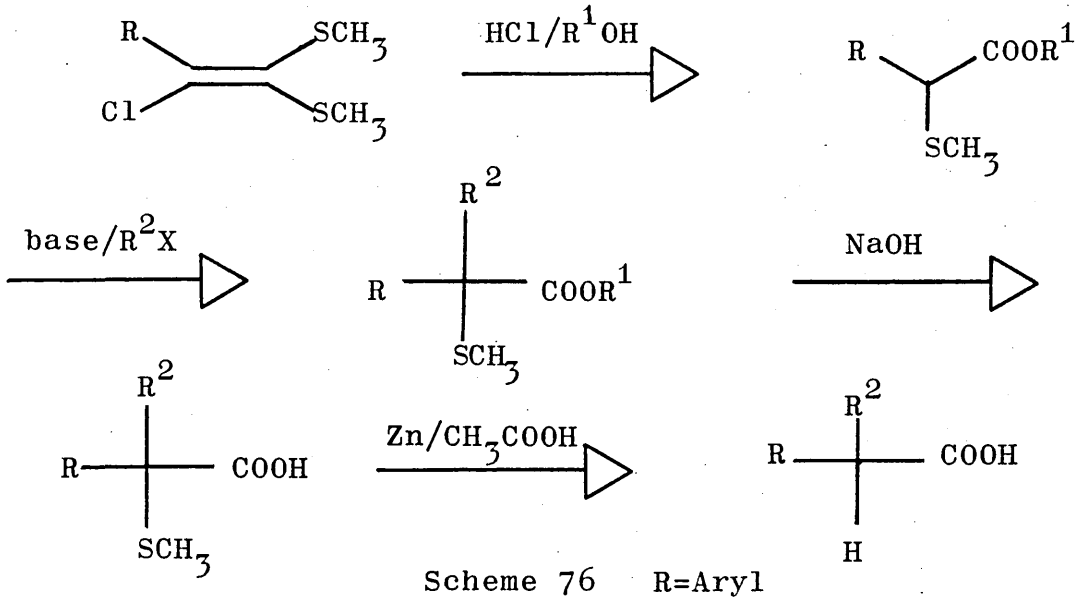
Section 3.2 deals with the general applicability of our conditions (CH_2Cl_2/HCl) for the conversion of ketenedithioacetal S-oxides to chloroketenedithioacetals (in addition we have also studied the hydrolysis of chloroketenedithioacetals using trifluoroacetic acid).

Section 3.3 extends this work into a novel synthesis of an indole nucleus[100].

Section 3.4 begins with a proposed mechanism for the formation of the indoles. However some additional observations were made under modified conditions and on the basis of these and earlier observations made by others an alternative mechanism is proposed. This latter could be used to account for the formation of both the indole and chloroketenedithioacetals under standard and modified conditions.

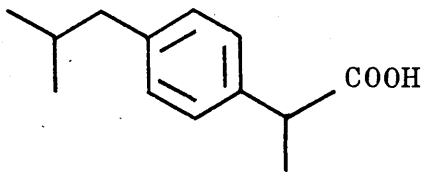
3.2 The formation and reactions of ketenedithioacetal S-oxides and chloroketenedithioacetals

The synthetic utility of the chloroketenedithioacetal moiety has been investigated by Ogura and it has been found that they are readily transformed into α methylthio esters from which a variety of other compounds are available[101] (Scheme 76).



Scheme 76 R=Aryl

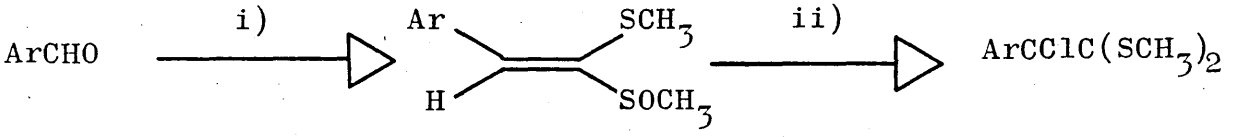
The same group used this sequence to synthesise the antirheumatic compound ibuprofen[101] 108.



108

Thus it was of interest to see if our conditions for the formation of 65 from 63 could be extended as a general method for the synthesis of aryl chloroketenedithioacetals from aryl ketenedithioacetal S-oxides. With this end in mind a series of ketenedithioacetal S-oxides were prepared

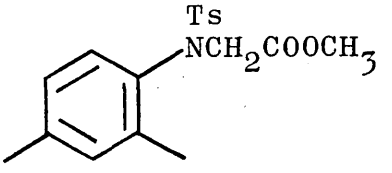
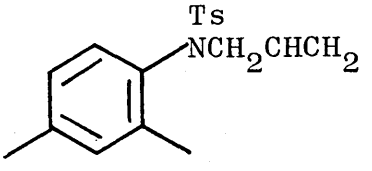
and subjected to treatment with HCl in CH_2Cl_2. (Scheme 77 and Table 3).



i) 59/THF/Triton B/reflux ii) HCl/CH_2Cl_2

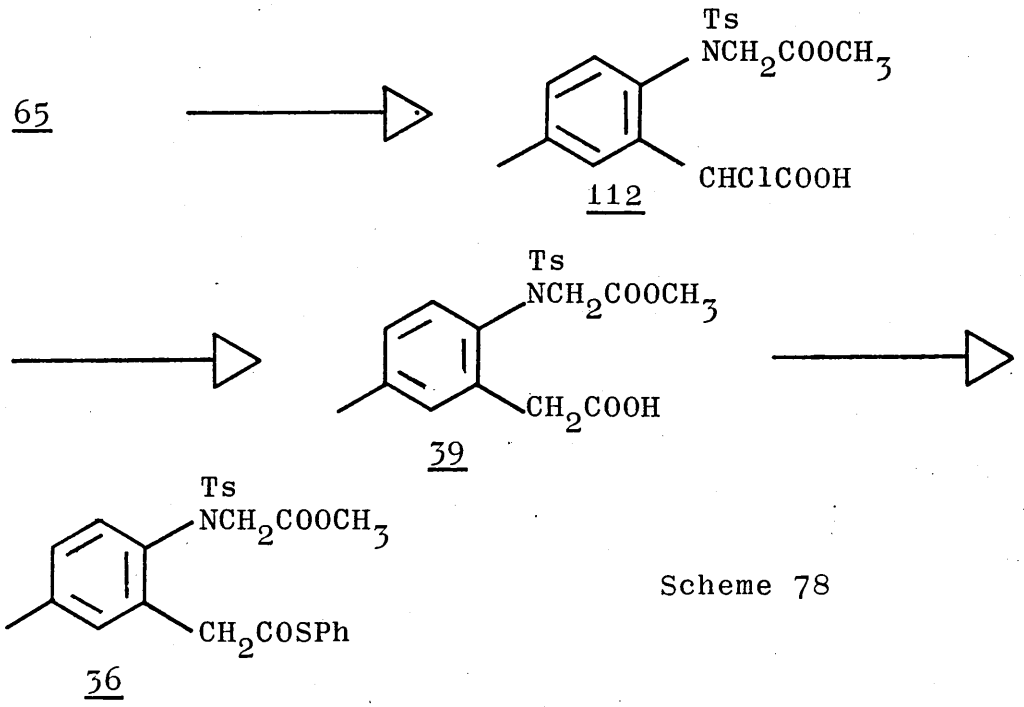
Scheme 77

Table 3. The preparation of ketenedithioacetal-S-oxides and subsequent conversion to chloroketenedithioacetals.

No	aldehyde Ar=	No	% yield	No	% yield
37		63	61[103]	65	100
51		61	67[103]	111a	100
109b	C_6H_5-	110b	77[104]	111b	100
109c	2-BrC_6H_4-	110c	64[105]	111c	82
109d	3-$CH_3OC_6H_4$-	110d	84	111d	79

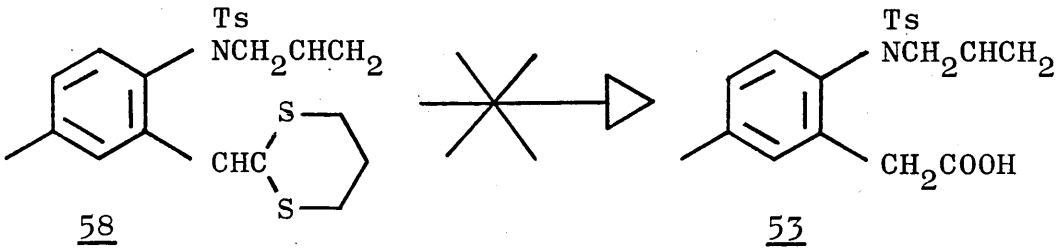
Thus it can be seen from this table that the conversion of ketenedithioacetal S-oxides into chloro ketenedithioacetals using HCl in CH_2Cl_2 is independent of other substituents on the aromatic[106] ring and is thus a general method for this transformation complementing the one already known[97].

Because of the excellent yield in which 65 could be obtained (54% from 13 in six steps), it was felt that this compound might serve as an intermediate to the Dieckmann precursor 36 required for virantmycin. One way of performing this (Scheme 78) would be the hydrolysis of 65 to the α chloro acid 112 using Hg(II) promoted procedures, followed by dechlorination and conversion to the mixed O,S diester 36.



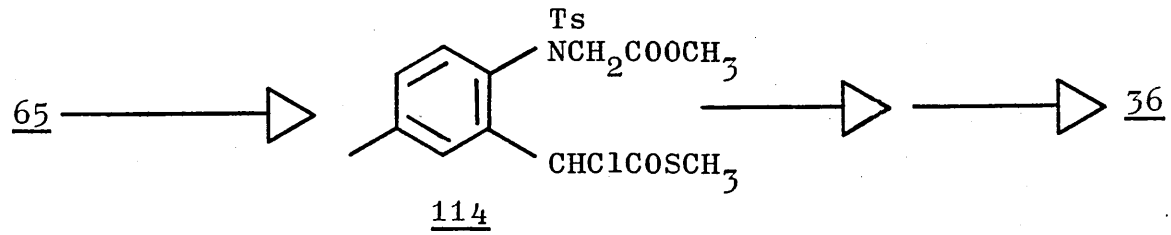
Scheme 78

However because of the inability (section 2.3.2) to convert the related ketenedithioacetal 58 into the acid 53 (Scheme 79) we were not convinced that this would be successful.



Scheme 79

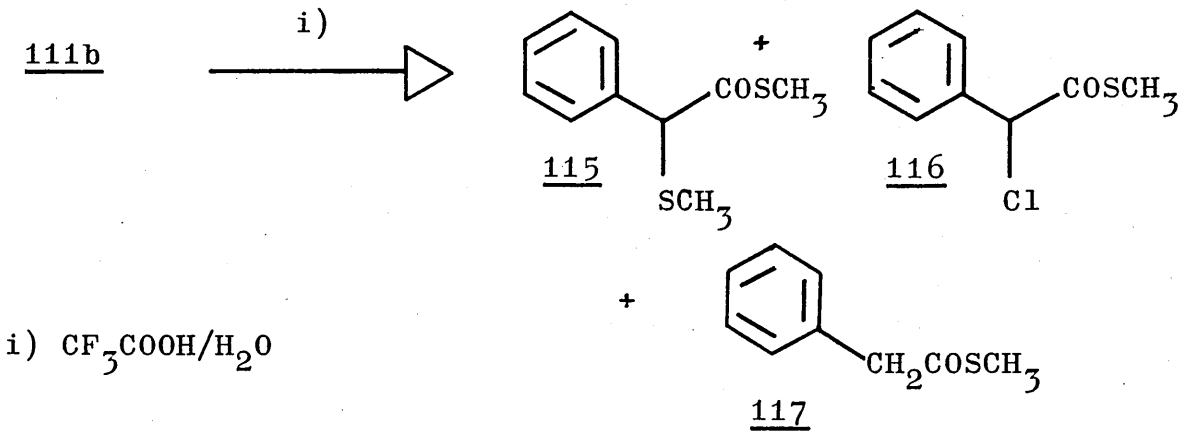
We did not feel that this would be a significant disadvantage as an alternative procedure also seemed attractive. Thus there is a method for the direct conversion[107] of ketenedithioacetals to thiol esters which was reported as being applicable to compounds containing a bis(methylthio) methane residue (eg. 65) but not to compounds derived from 1,3-dithiane (eg. 58). This method is based on the use of trifluoracetic acid/water. Using this strategy the α chloro thiolester 114 (Scheme 80) should be available from 65 and might ultimately be converted to 36. In order to test this hypothesis the simple chloroketenedithioacetal 111b was used.



Scheme 80

Thus, following the procedure developed by Seebach, 111b was treated with trifluoroacetic acid. After 20 minutes water was added and the solution stirred for 6 hours. A standard work up produced a crude reaction mixture which

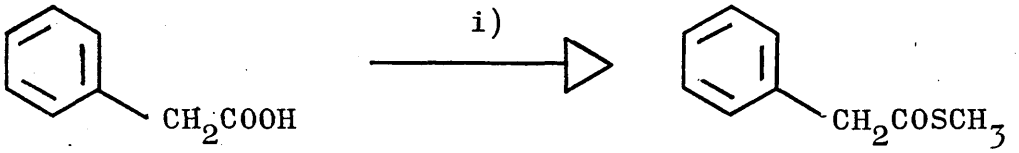
did give an IR spectrum containing a peak typical of thiol esters (1680 cm^{-1}). Careful column chromatography of this gave two components in a ratio of 3:8, both of which retained the thiolester absorbtion band in the IR spectrum. The more polar fraction appeared from its NMR spectrum to contain only one compound to which we assigned the structure 115[108] (Scheme 81). One way in which this product could arise would be by attack of liberated methanethiol[107] on any α chloro thiolester 116 which might be produced.



Scheme 81

The NMR spectra of the second fraction did indeed indicate (δ C-H = 5.2 ppm) that 116 was present, but there were also two other peaks in the spectra which indicated the co-existence of an impurity. The chemical shift values of these two other peaks indicated that one possible structure for this third compound was the thiol ester 117. In order to confirm that these two compounds were present in the mixture they were synthesised unambiguously (Schemes 82 and 83). When the spectra from authentic 116 and 117 were compared with the spectra obtained from the mixture of compounds, they were

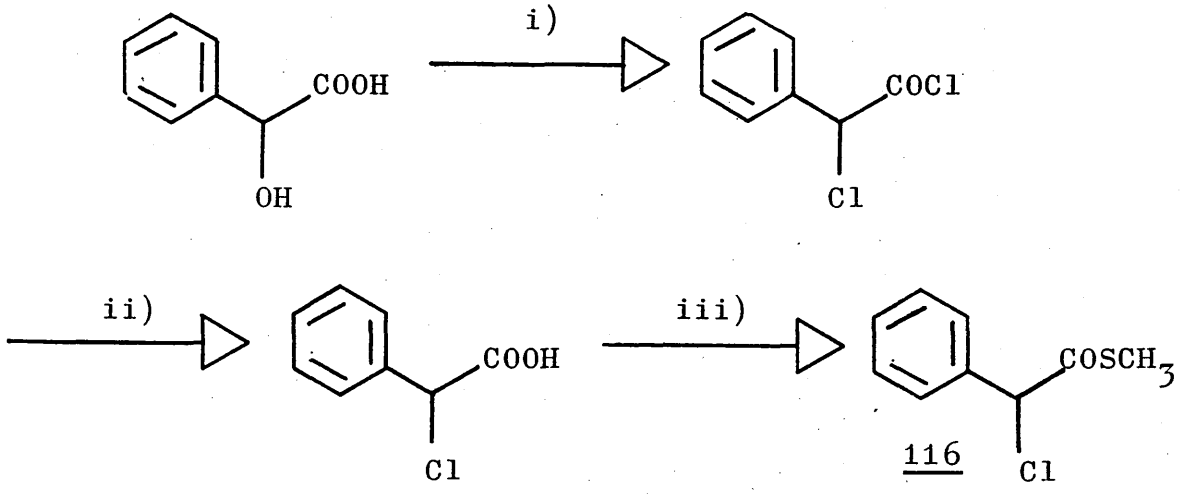
found to be identical.



i) $DCC/CH_3SH/Et_2O$ 117

Scheme 82

The ratio of 116 to 117 in the mixture was determined by NMR spectroscopy.



116

i) $SOCl_2/DMF/CCl_4$ ii) KOH/CH_3OH iii) $DCC/CH_3SH/Et_2O$

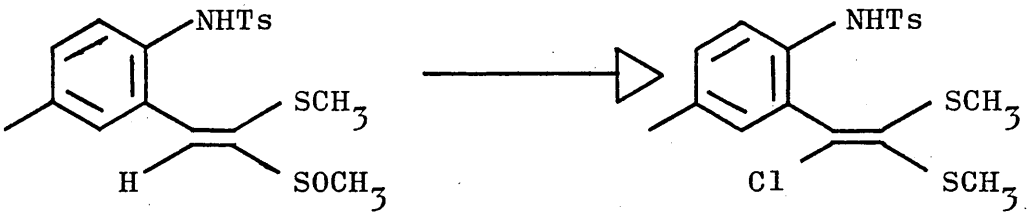
Scheme 83

Thus the methylthio singlet for 116 appeared at a different chemical shift value (δ ppm = 1.25) to the corresponding peak in 117 (δ ppm = 1.23). Presumably this is due to a through bond or through space effect of the chlorine atom α to the carbonyl group in 116 resulting in a downfield shift of the methylthio group. The integration ratio for these two peaks indicated a ratio of 116:117 of 1.13:1 in the inseparable mixture (there was good agreement for this on integration of the peaks due to the α hydrogen atoms in 116 and 117).

The compounds 111c and 111d were subjected to the same reaction conditions and the products analysed in the same way. The results of this are presented in the experimental section.

3.3 The synthesis of an indole nucleus

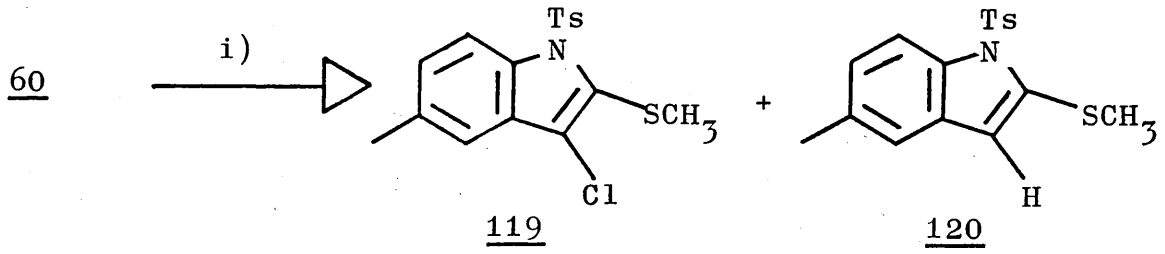
In the attempt described earlier (section 3.2) to test the general applicability of our synthesis of chloro ketenedithioacetals from ketenedithioacetal S-oxides using HCl/CH_2Cl_2, one example was to have been the conversion of 60 to 118 (Scheme 84).



60 Scheme 84 118

Unexpectedly, when this reaction was performed, two major products were observed and neither of these gave a N-H stretching band in the IR spectrum as was expected for 118. Thus a detailed spectral analysis of each compound was undertaken.

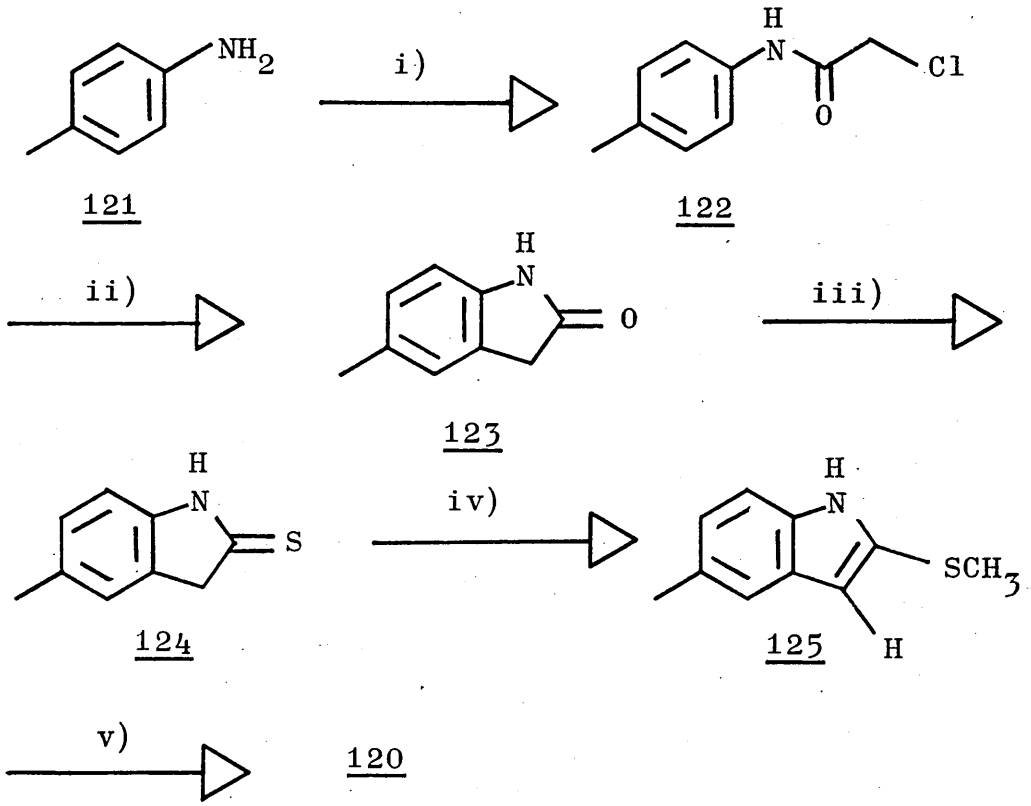
The least polar compound, a white crystalline solid, was assigned the structure 119 on the basis of its UV, IR and NMR spectra complemented by mass spectrometry and an X-ray crystallographic analysis. To the less polar compound, a clear oil which turned blue on prolonged standing, was initially assigned the structure 120[100] (Scheme 85).



i) HCl/CH_2Cl_2

Scheme 85

Attempts were made to confirm the structure of this latter compound via a synthesis of the authentic material (Scheme 86).



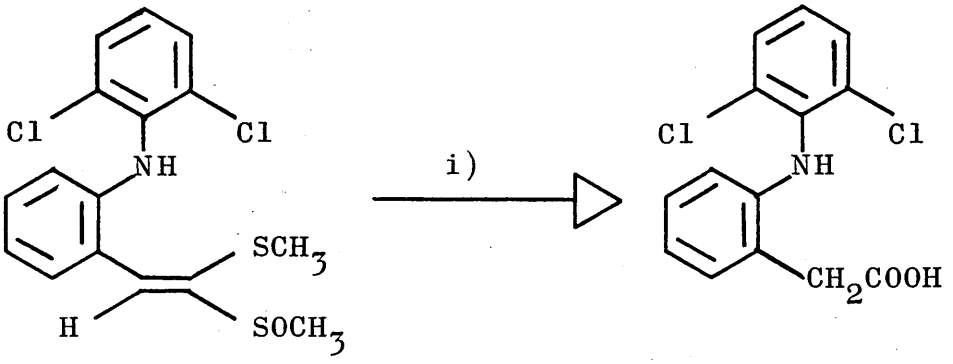
i) $C_5H_5N/ClCH_2COCl/PhCH_3$ ii) $AlCl_3$ iii) $P_2S_5/C_6H_6/\Delta$
iv) $K_2CO_3/CH_3I/(CH_3)_2CO$ v) KOH/pTsCl/DME

Scheme 86

Thus 4-methylaniline was treated with chloroacetyl chloride in the presence of pyridine to give 122[109] (76%). The Friedel-Crafts cyclisation of 122 to 123 occurred only under rather vigorous conditions by mixing 122 with aluminium trichloride[109] and heating to 200°C. After work up, see experimental section, 59% yield of a white solid was obtained. The NMR spectra of this compound was not quite in the form expected, with the peaks for both the methyl and methylene groups being split, each into an uneven pair. This was explained in terms of migration of the methyl group, during the Friedel-Crafts reaction, producing not only 123 but also one or more of the possible structural isomers. The oxindole 123 was carried through to the indole 120, as shown in Scheme 86, followed by attempts to separate the isomers by column chromatography. This proved unsuccessful as again a multiplicity of peaks due to the aromatic methyl group was observed. This did not prove to be a serious problem however, as the structure of 120 was confirmed using a different approach. Thus simple treatment of 120 with sulphuryl chloride in CH_2Cl_2[110] gave 119 (75%), thereby confirming the structure of both compounds.

It appears that there is some particular feature about our conditions for this reaction or the structure of the substrate 60 (Scheme 85) which enhances cyclisation,

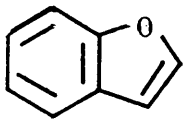
as a similar substrate,[111] under similar conditions was shown to give a product arising from hydrolysis and not cyclisation (Scheme 87).



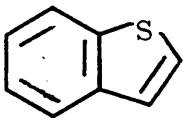
i) HCl/THF/10 hr/reflux

Scheme 87

As a final synthetic aspect to the use of ketenedithioacetal S-oxides, we were interested in extending our successful synthesis of indoles (Scheme 85) into the synthesis of other heterocyclic systems, for example derivatives of benzofuran 126 and benzothiophene 127.

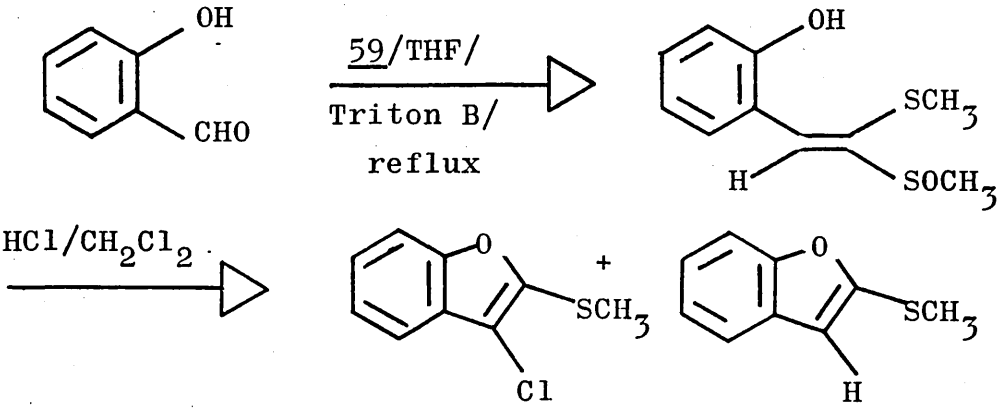


126



127

To this end a preliminary study has resulted in a synthesis of two benzofurans[112] (Scheme 88).

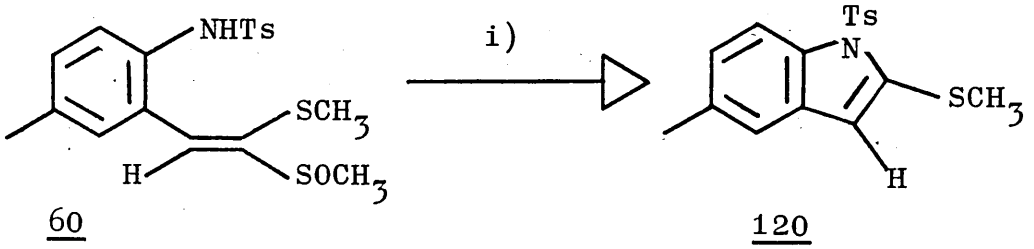


Scheme 88

3.4 Mechanistic aspects and further observations

In our original communication on the synthesis of indoles[100] we proposed a mechanism for the reaction which appeared to satisfactorily explain the formation of 119 and 120 (Scheme 89). Thus initial addition of HCl to the double bond gives the common intermediate 128 from which both products are obtained. In route a, protonation at the sulphinyl oxygen atom and loss of methanesulphenic acid gives 129. Intramolecular nucleophilic attack at the stabilised cation gives the indoline 130 which undergoes loss of HCl to give the 3-unsubstituted indole 120. The initial step in the alternative path, route b, involves a Pummerer rearrangement[113-117] of 128 to 131, cyclisation to give 132 and loss of methanethiol from this to give the 3-chloroindole 119.

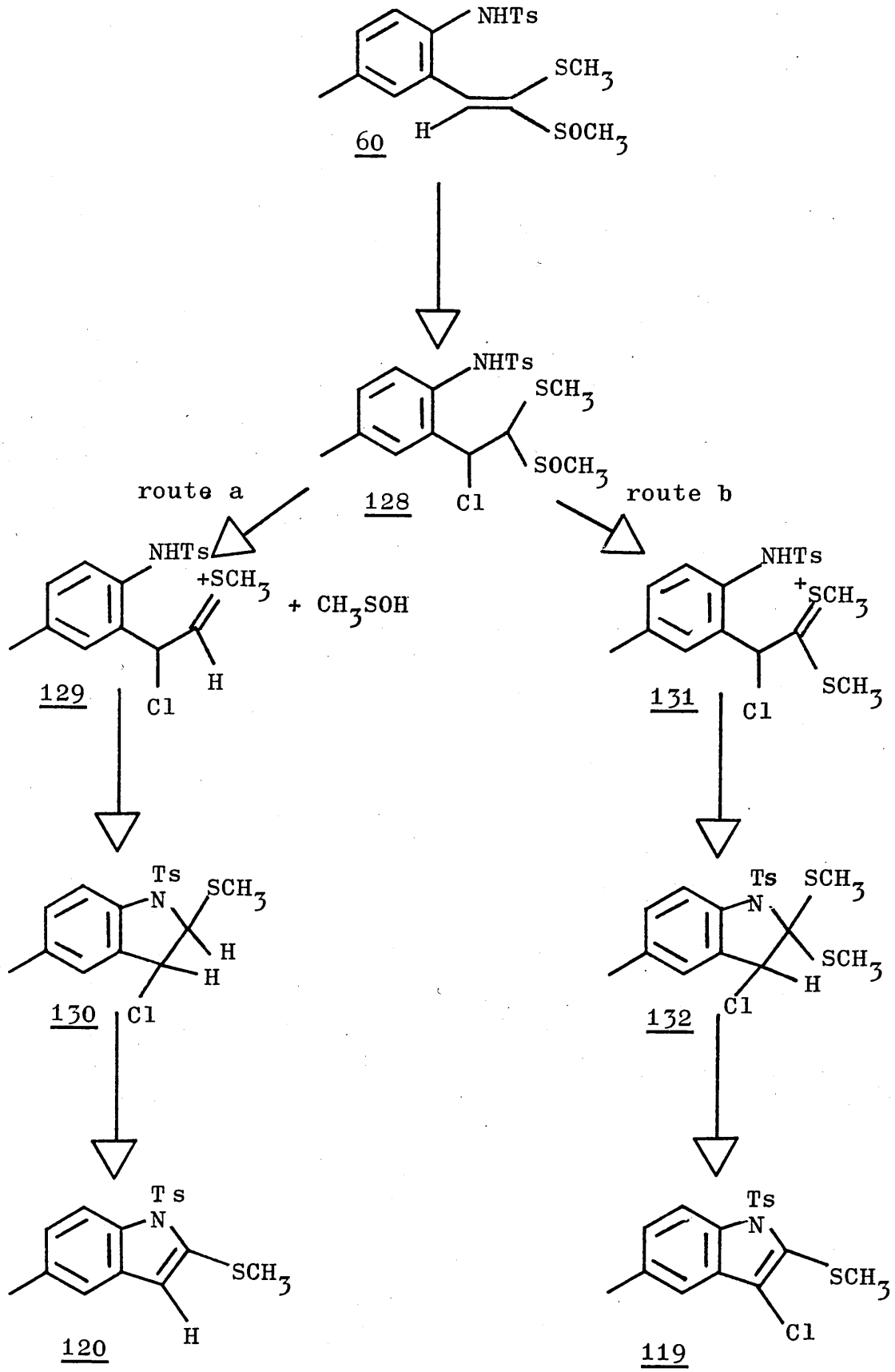
However during a brief investigation on the effect of the addition of various species to the reaction mixture (i.e. Scheme 90) an interesting observation was made. Thus when CH_2Cl_2 was pretreated with hydrogen sulphide (H_2S) before addition of 60 and HCl, instead of a mixture of 119 and 120 being obtained the major product observed was 120 in 71% yield.



60 120

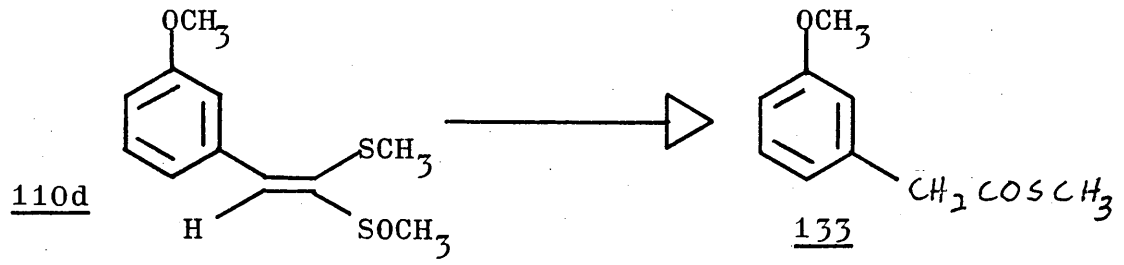
i) $H_2S/HCl/CH_2Cl_2$

Scheme 90


NHTs
SCH3
H
SOCH3
60
NHTs
SCH3
SOCH3
128
Cl
route a
route b
NHTs
+SCH3
+ CH3SOH
129
Cl
H
NHTs
+SCH3
SCH3
131
Cl
Ts
N
SCH3
H
H
130
Cl
Ts
N
SCH3
SCH3
H
132
Cl
Ts
N
SCH3
H
120
Ts
N
SCH3
Cl
119

Scheme 89

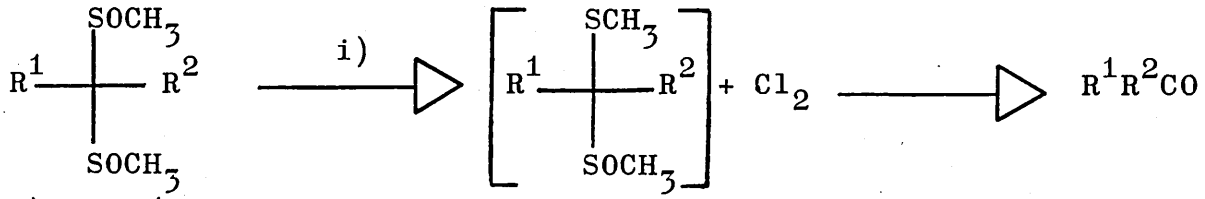
In addition when 110d was treated under the same conditions, instead of the expected chloro ketenedithioacetal 111d the major product observed was the thiol ester 133 (Scheme 91) in 58% yield.



i) $H_2S/HCl/CH_2Cl_2$ Scheme 91

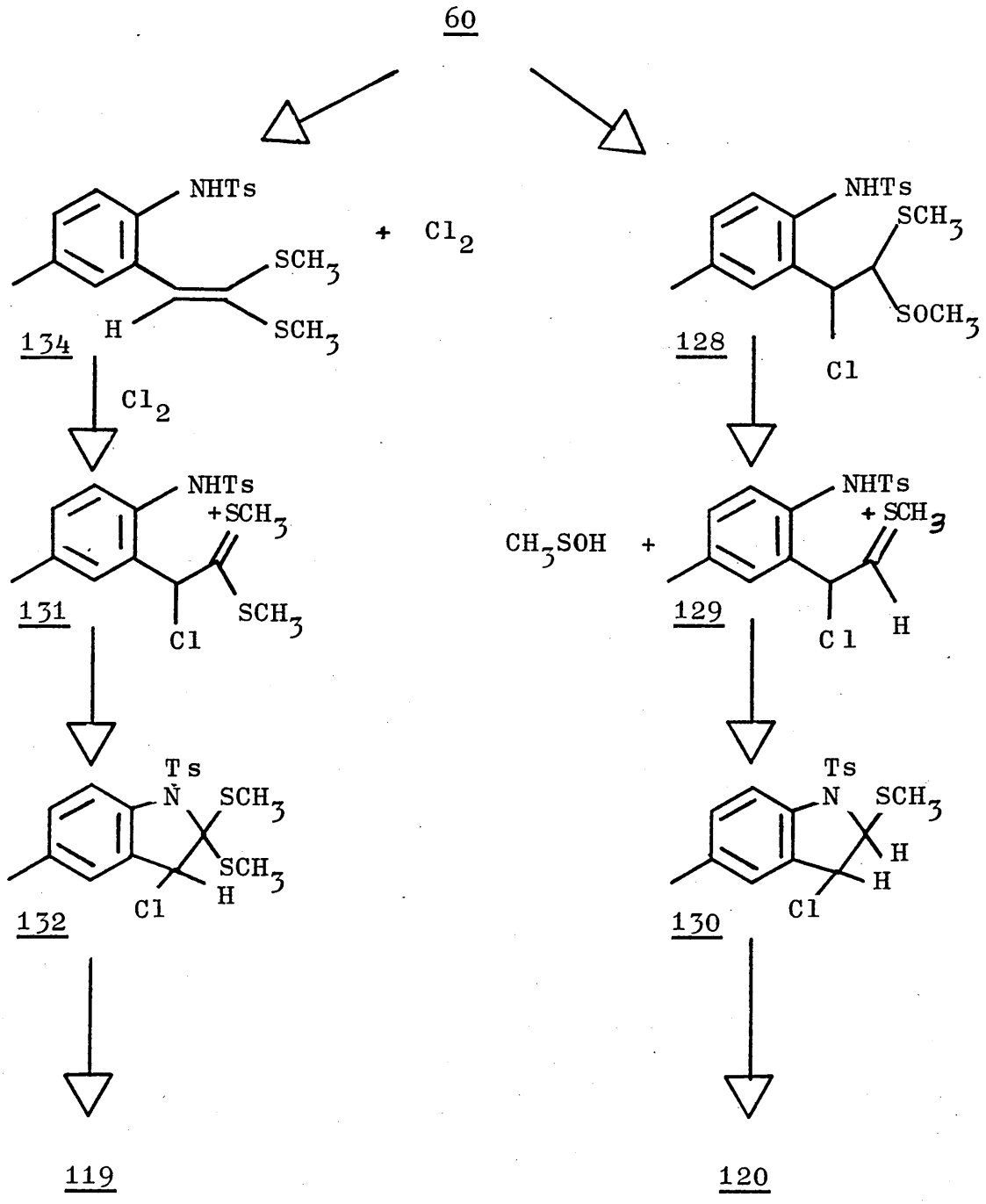
It did not appear that the first of these observations could be readily explained in terms of the mechanism outlined earlier. Thus some consideration was given to other possible mechanisms by which the indoles 119 and 120 might be formed.

We were prompted in this by some work done by other groups. Among these, Louw[118] had performed a study on the conversion of dithioacetal S,S-dioxides to carbonyls using similar conditions to our own (Scheme 92). He reported, as the first step, the formation of chlorine gas and the reduction of the disulphoxide to the monosulphoxide.

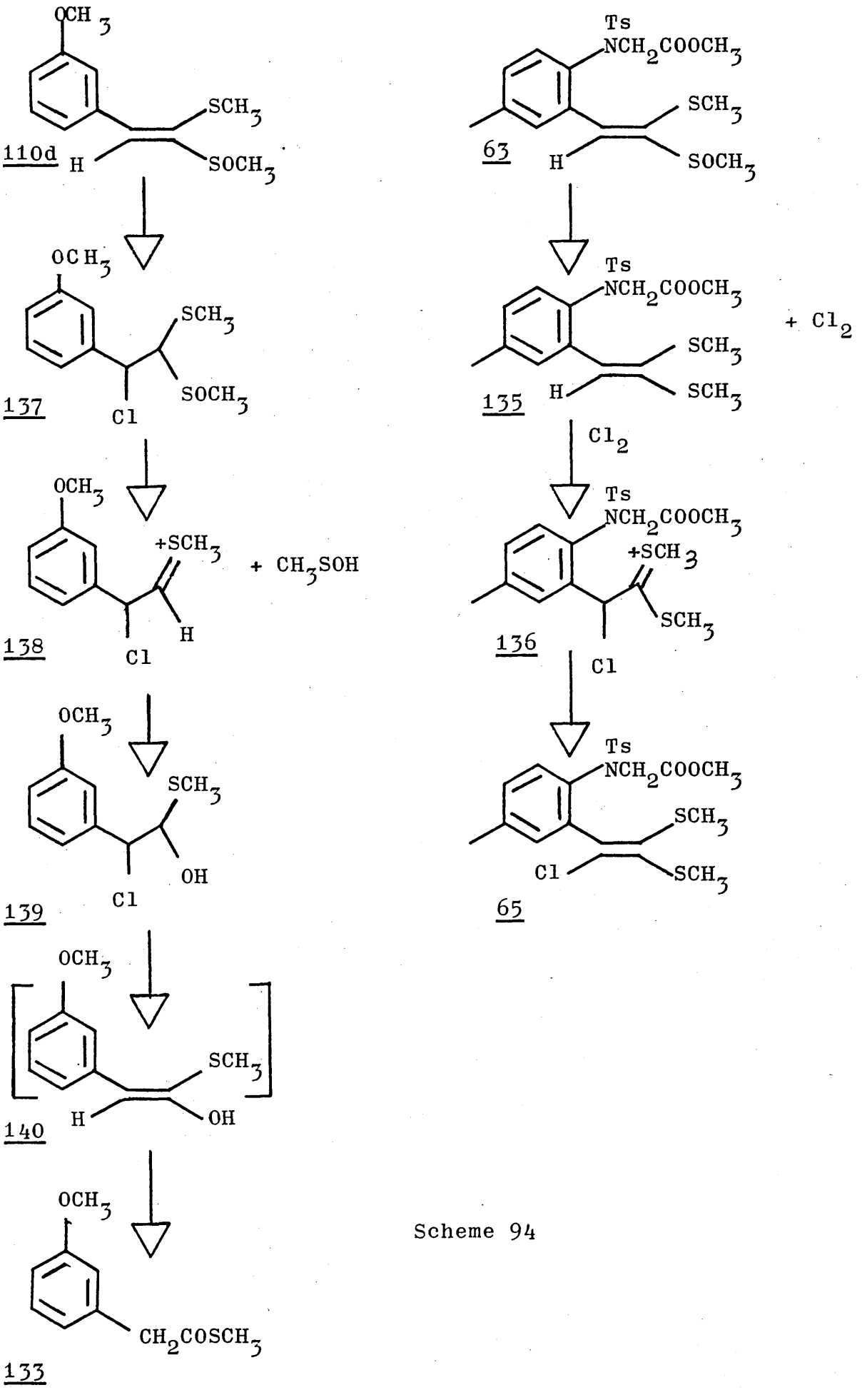


i) $HCl_g/CHCl_3$ Scheme 92

Using this and other observations it has proved possible to draw a mechanism which could possibly be used to connect Louw's observations, the synthesis of indoles and


60
NHTs
SCH3
+ Cl2
SCH3
H
134
Cl2
NHTs
+SCH3
131
SCH3
Cl
Ts
N
SCH3
SCH3
H
Cl
132
119
NHTs
SCH3
SOCH3
128
Cl
CH3SOH +
NHTs
+SCH3
129
Cl
H
Ts
N
SCH3
H
H
Cl
130
120

Scheme 93


OCH3
SCH3
SOCH3
H
110d
OCH3
SCH3
SOCH3
Cl
137
OCH3
+SCH3
H
Cl
138
+ CH3SOH
OCH3
SCH3
OH
Cl
139
OCH3
SCH3
H
OH
140
OCH3
CH2COSCH3
133
Ts
NCH2COOCH3
SCH3
H
SOCH3
63
Ts
NCH2COOCH3
SCH3
H
SCH3
135
+ Cl2
Cl2
Ts
NCH2COOCH3
+SCH3
SCH3
136
Cl
Ts
NCH2COOCH3
SCH3
Cl
SCH3
65

Scheme 94

chloroketenedithioacetals under normal conditions (Schemes 85 and 77) and the formation of an indole and a thiolester under modified conditions (Schemes 90 and 91). This is described below.

Thus using the standard conditions of HCl in CH_2Cl_2, 60 is converted (Scheme 93) into a mixture of 119 and 120. The former arises from a pathway involving an initial oxidation/reduction sequence whereby chloride is oxidised to chlorine and sulphinyl sulphur is reduced to sulphenyl sulphur. The ketenedithioacetal 134 then undergoes electrophilic attack by chlorine to give the resonance stabilised cation 131. This undergoes spontaneous intramolecular nucleophilic attack by the sulphonamide nitrogen atom to give the indoline 132. Loss of methane thiol then gives the 3-chloroindole 119. The other product, 120, arises in the same way as previously described, thus initial addition of HCl to the double bond followed by protonation and loss of methanesulphenic acid gives 129. Subsequent cyclisation and loss of HCl produced the product 120.

Theoretical evidence is available which supports this.

Thus intramolecular cyclisation of sulphoxides in the presence of acid[119], loss of methanesulphenic acid in the presence of mineral acid to give stabilised cations[120] and electrophilic attack at ketenedithioacetals[121] are all known processes.

Under the modified conditions using H_2S (Scheme 90) only the 3-unsubstituted indole 120 was produced. This apparently means that the presence of H_2S was blocking formation of the other product, the 3-chloroindole 119. The way in which this might occur would be for H_2S to act as a reducing agent, thus preventing the initial sulphoxide promoted oxidation of chloride to chlorine, leaving the formation of 120 as the only possible route available.

It was felt that the same mechanism could be used to explain the formation of 65 from 63 and 133 from 110d (Scheme 94). Thus 63 undergoes the same sequence of reactions as outlined earlier to give the stabilised cation 136. Unlike the previous case intramolecular attack is impossible so proton loss[119] occurs to give the chloroketenedithioacetal 65. Under the modified conditions 110d gives mainly the thiol ester. This can be explained in the same way as before, thus initial addition of HCl to the double bond, protonation and loss of methanesulphenic acid gives the cation 138. Again intramolecular attack is impossible so nucleophilic attack by water occurs to give 139. Elimination of HCl and rearrangement of the enol 140 gives the thiol ester 133. Thus the formation of all 4 products can be explained in terms of one divergent mechanism.

3.5 Further work

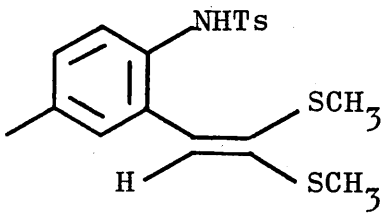
Two aspects of this work would benefit from an additional study. First the mechanistic proposals. In order to determine fully the exact mechanism for the formation of the indoles, chloroketenedithioacetals and

thiol ester from ketenedithioacetal S-oxides it will be essential to perform additional experiments. Preparation of ketenedithioacetal S-oxides derived from 141[122] rather than 59 might allow detection of any sulphenic acid or disulphide[76,77] by products more readily, but would not necessarily differentiate between the two mechanisms outlined earlier (section 3.4).

$PhSOCH_2SPh$ $CH_3SOCH_2SCH_3$

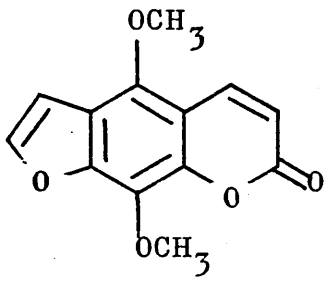
141 59

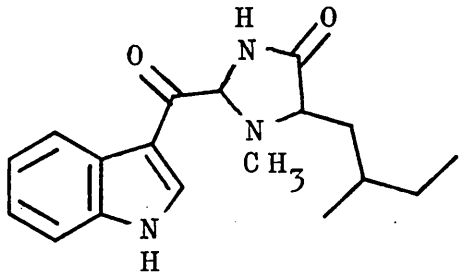
More useful perhaps would be the detection of any chlorine produced from oxidation of chloride or experiments to determine whether electrophilic addition of chlorine to 134 can occur and if so what are the products from the reaction.



134

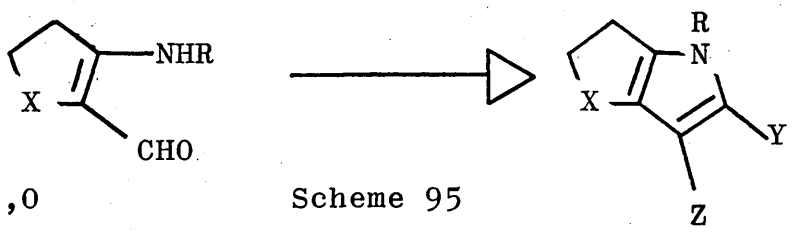
Synthetically, it would be satisfying to complete the successful synthesis of indoles and benzofurans with a synthesis of benzothiophenes. As part of a more long term project an extension of the synthesis of one or more of the heterocyclic skeletons listed above into the area of naturally occurring heterocycles, for example 142 and 143, could be undertaken.





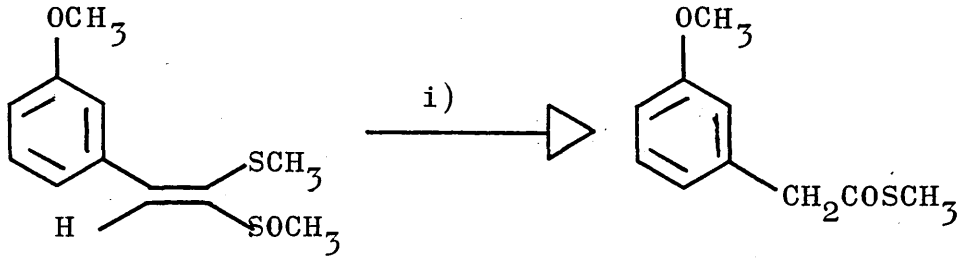
142[149] 143[150]

As a final aspect of this cyclic chemistry it would be of interest to construct 5 membered ring precursors to investigate the synthesis of fused [5.5] bicyclic molecules using this strategy (Scheme 95).



X=C,S,O Scheme 95

The last point would be to investigate the potential of the conversion of 110d into 133 as a general preparation of thiol esters.



110 133

i) $H_2S/CH_2Cl_2/HCl$

Scheme 96

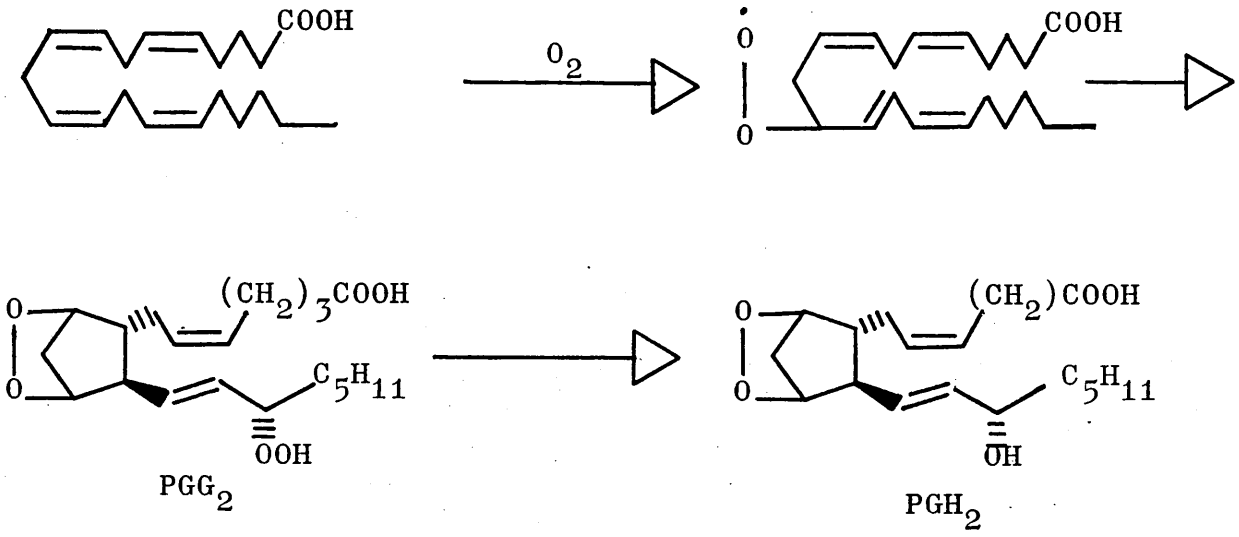
CHAPTER 4

An approach to the synthesis of carbaprostacyclin using vinylphosphonium salts

4.1 Introduction

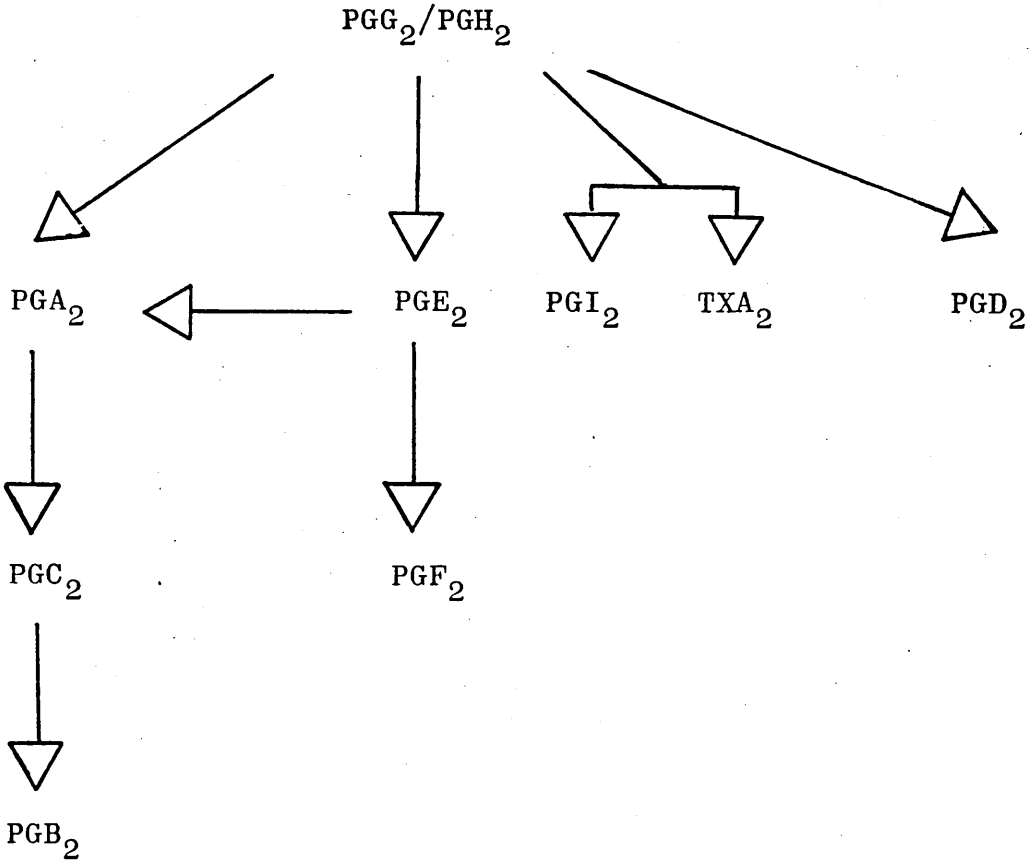
It was 50 years ago that two groups, one of which was led by von Euler, were performing experiments on the effect on muscle tissue of extracts from mammalian reproductive systems. They found a substance which could stimulate the muscle into activity and von Euler gave this the name prostaglandin as it was believed that it arose from the prostate gland. Unfortunately it became obvious that there was only a small concentration of these species in vivo (evidently they can be made rapidly when and where required) and so little material was available for further study. In addition the lack of sophisticated chromatographic and analytical techniques available at the time meant that no assessment of the purity or structure of the active agents could be made. It is now known that there is a large number of prostaglandins produced by natural sources and this is continually being supplemented by the output of synthetic chemists[123].

The prostaglandins can be divided into nine classes, PGA to PGI, with additional nomenclature specifying the exact structure. In addition another similar class of compounds has been discovered which arise biosynthetically from the same source, called the thromboxanes. Thus 2-series prostaglandins and thromboxanes are formed from arachidonic acid (eicosa-5,8,11,14-tetraenoic acid) whilst 1 and 3 series compounds come from eicosa-8,11,14-trienoic acid and eicosa-5,8,11,14,17-pentaenoic acid respectively. For the PG_2 series this is shown in brief outline (Scheme 97).



Scheme 97. The biosynthetic conversion of arachidonic acid into PGG_2 and PGH_2.

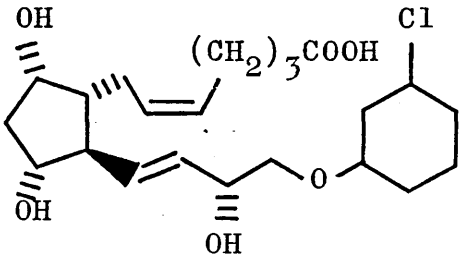
Scheme 98. The interconversion of prostaglandins and thromboxanes.



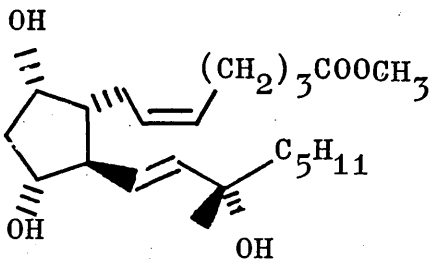
It was not until thirty years after von Eulers original experiments that the structure of the primary prostaglandins PGA to PGF was illucidated and during the intervening period their biological properties have become well documented and understood[124]. In addition a great number of unnatural prostaglandins have been synthesised and biologically evaluated. The more reactive peroxide containing intermediates PGG_2 and PGH_2 were not fully identified until later. It was then from these latter compounds that, in the mid 1970's, evidence was put forward for the existence of two further compounds having mutually opposing biological properties. These were called prostacyclin[125] (PGI_2) and thromboxane A_2 (TXA_2), the existence of the latter being inferred from the presence of a metabolite TXB_2. Theory now says that it is PGI_2 and TXA_2 which are responsible for the control of platelet aggregation, for example during bleeding. It is believed that prostacyclin synthetase, the enzyme that converts PGH_2 into PGI_2, is concentrated in the walls of the blood vessels. Thus, when these are intact, sufficient enzyme is present to maintain PGI_2 inhibition of platelet aggregation. However disruption of the endothelium results in a decrease in enzyme concentration and lowering of PGI_2 levels. Then under control of TXA_2, vasoconstriction and platelet aggregation occur. It is also possible that a disturbance of the normal balance between PGI_2 and TXA_2 could lead to some pathological conditions (for example thrombosis).

The potential value of many of the primary prostaglandins and thromboxanes as theraputic agents is

limited by their broad spectrum of activity and also by their instability under physiological conditions. Thus synthetic chemists have been interested in the formation of unnatural analogues which can show the high biological potential of the parent compounds whilst at the same time demonstrating separation of activity and/or increased stability. For the series of prostaglandins PGA to PGF the last few years has seen a large concentration of effort in this area and some positive results have been achieved[123,124]. For example the $PGF_{2\alpha}$ derivative chloprostenol 144 is commercially available for the control of oestrus in cattle whilst 15-methyl $PGF_{2\alpha}$ methyl ester 145 has found some use in the induction of abortion in women.

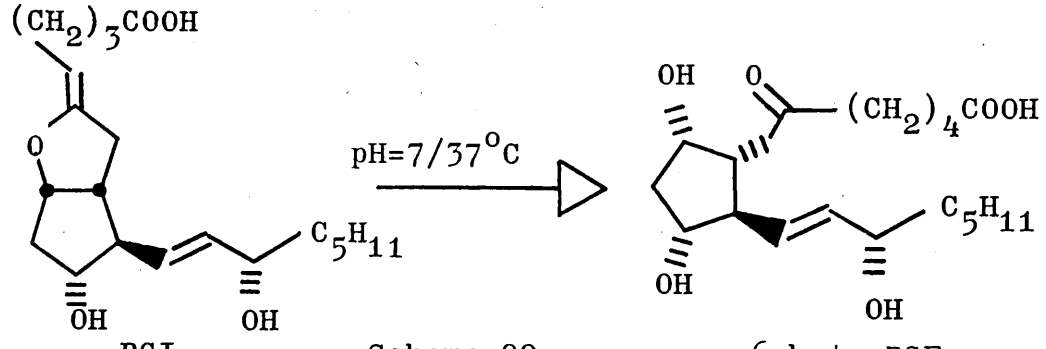


144



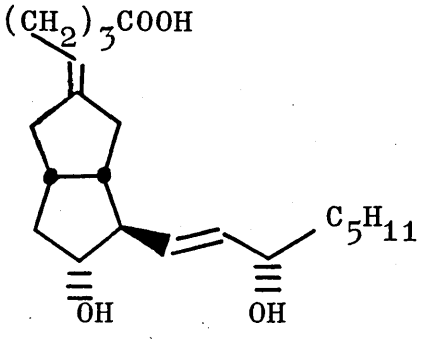
145

Because PGI_2 has only relatively recently been isolated[125] much less is known about its function and properties. However like other prostaglandins it has only limited stability. Under simulated physiological conditions PGI_2 has a halflife of 3 minutes with the degradation product being 6-keto $PGF_{1\alpha}$ (Scheme 99).



PGI_2 Scheme 99 6 keto $PGF_{1\alpha}$

Thus there has been a certain significance attached to the synthesis of analogues of prostacyclin showing increased stability over PGI_2 itself. During these investigations[123] many compounds have been made and undergone biological evaluation. A small sample of these are shown here together with their biological activity, if known. Thus carbaprostacyclin[126], 146, shows increased stability over PGI_2 but less than 10% of its activity[127]. The 13,14-dehydro prostacyclin 147 is also more stable than the parent compound and shows some platelet aggregation activity[127]. The azaprostacyclin[128] 148 shows activity comparable to that of prostacyclin whilst the thiaprostacyclin 150[129] was also biologically active. The structurally elaborate carbaprostacyclin derivative[130] 151 has not yet been biologically evaluated.



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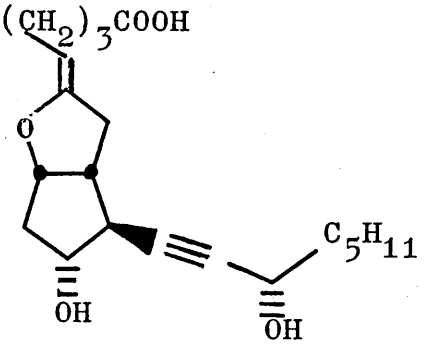

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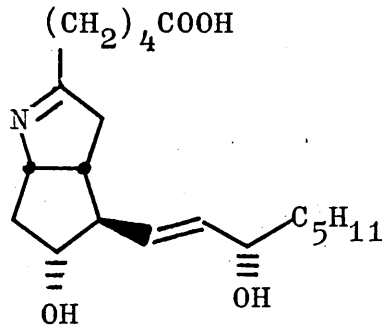

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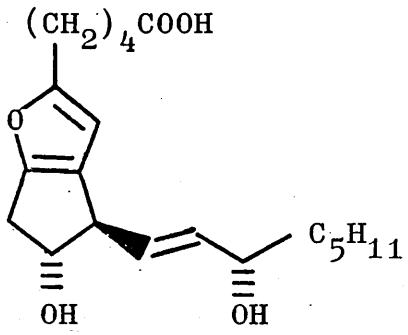

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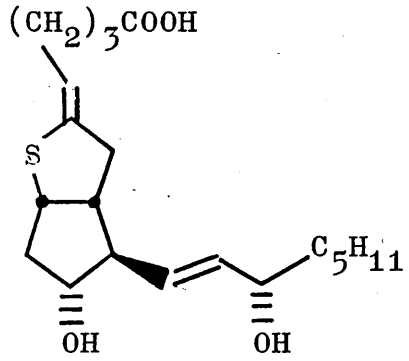

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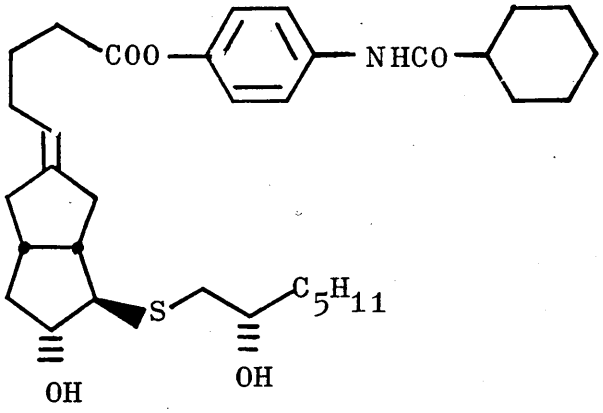
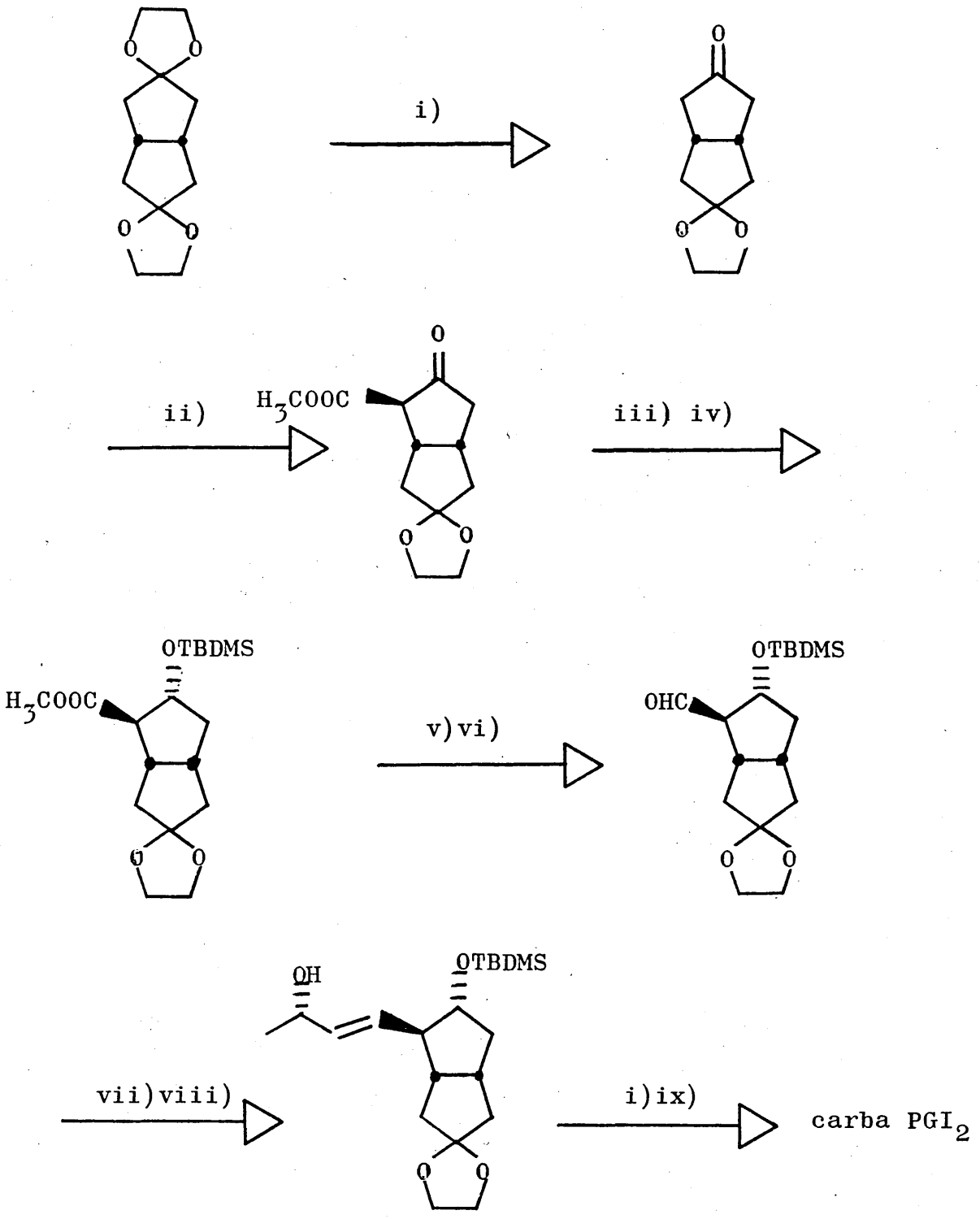


151

Along with other groups[123,126] we were interested in the synthesis of the prostacyclin derivative carbaprostacyclin 146 and also in the synthesis of any related analogues. Carbaprostacyclin has been the object of a number of synthetic approaches, for two examples see Schemes 100 and 101, and has been biologically evaluated as more stable than prostacyclin but only 0.03 times as efficient in the inhibition of platelet aggregation[124].



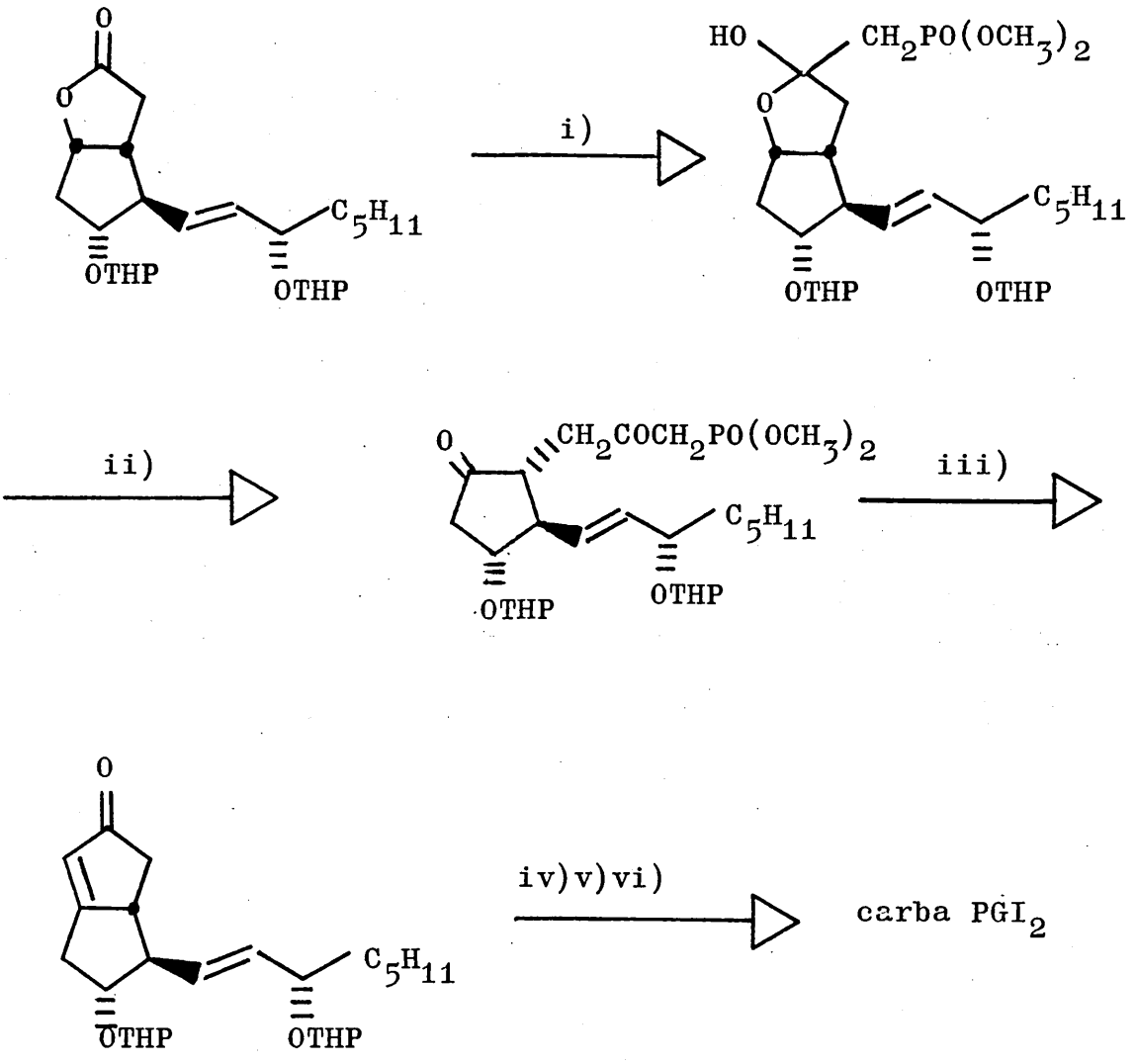
i) $CH_3COOH/THF/H_2O/45^oC/1$ hr ii) $NaH/(CH_3O)_2CO/C_2H_5OH$

iii) $NaBH_4/C_2H_5OH/-45^oC$ iv) $^tBuMe_2SiCl$/imidazole/DMF

v) $Bu_2AlH/CH_2Cl_2/-78^o$ vi) PCC/CH_2Cl_2 vii) NaH/ dimethyl 2-oxoheptylphosphonate viii) $ZnBH_4$

ix) 4-carboxybutyl(triphenyl)phosphorane/DMSO

Scheme 100[148]



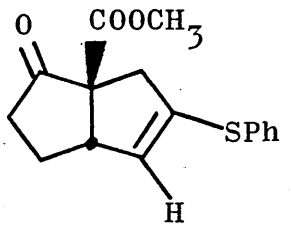
i) $LiCH_2PO(OCH_3)_2$/THF ii) CrO_3/pyridine/CH_2Cl_2

iii) K_2CO_3/18-Crown-6/$PhCH_3$/Δ iv) $HCOONH(C_2H_5)_3$/5% Pd on C/ $PhCH_3$/Δ v) 4-carboxybutyl(triphenyl)phosphorane

vi) H_3O^+

Scheme 101[126]

With this object in mind we felt that the bicyclo [3.3.0] octane 152, analogous to the compound 153 already prepared in these laboratories[131], would represent an ideal starting point.



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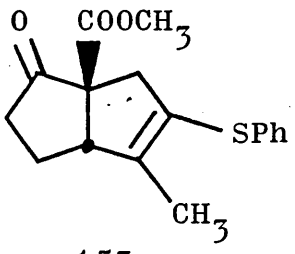
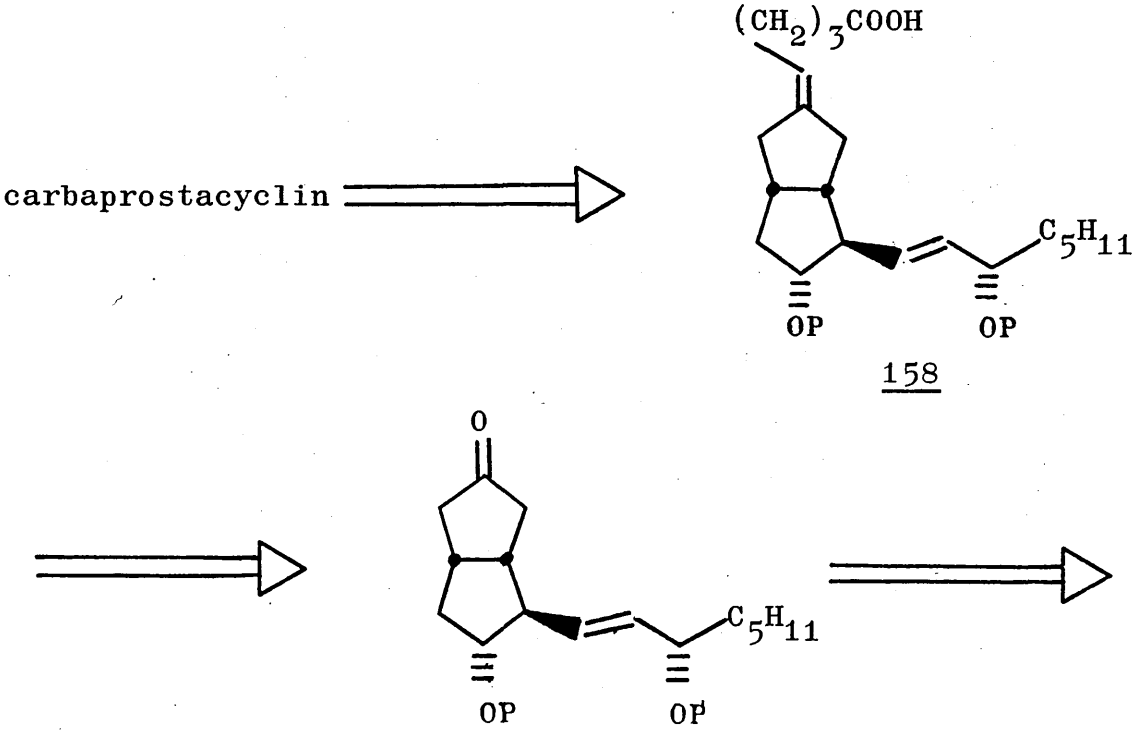
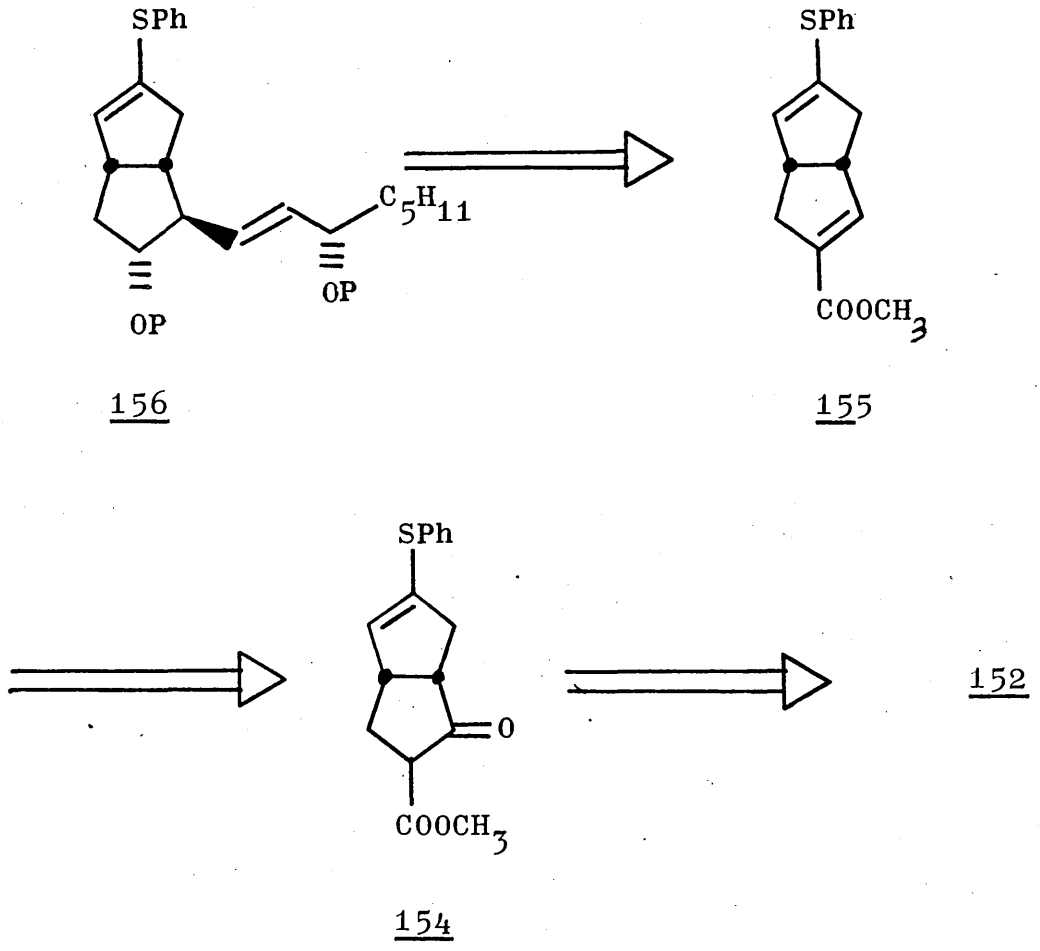


153

The scope of this part of the project was to prepare the unsaturated ester 155 from 152 and if possible take this material through to a compound more closely resembling carbaprostacyclin. The full retrosynthetic analysis for this route is shown (Scheme 102).





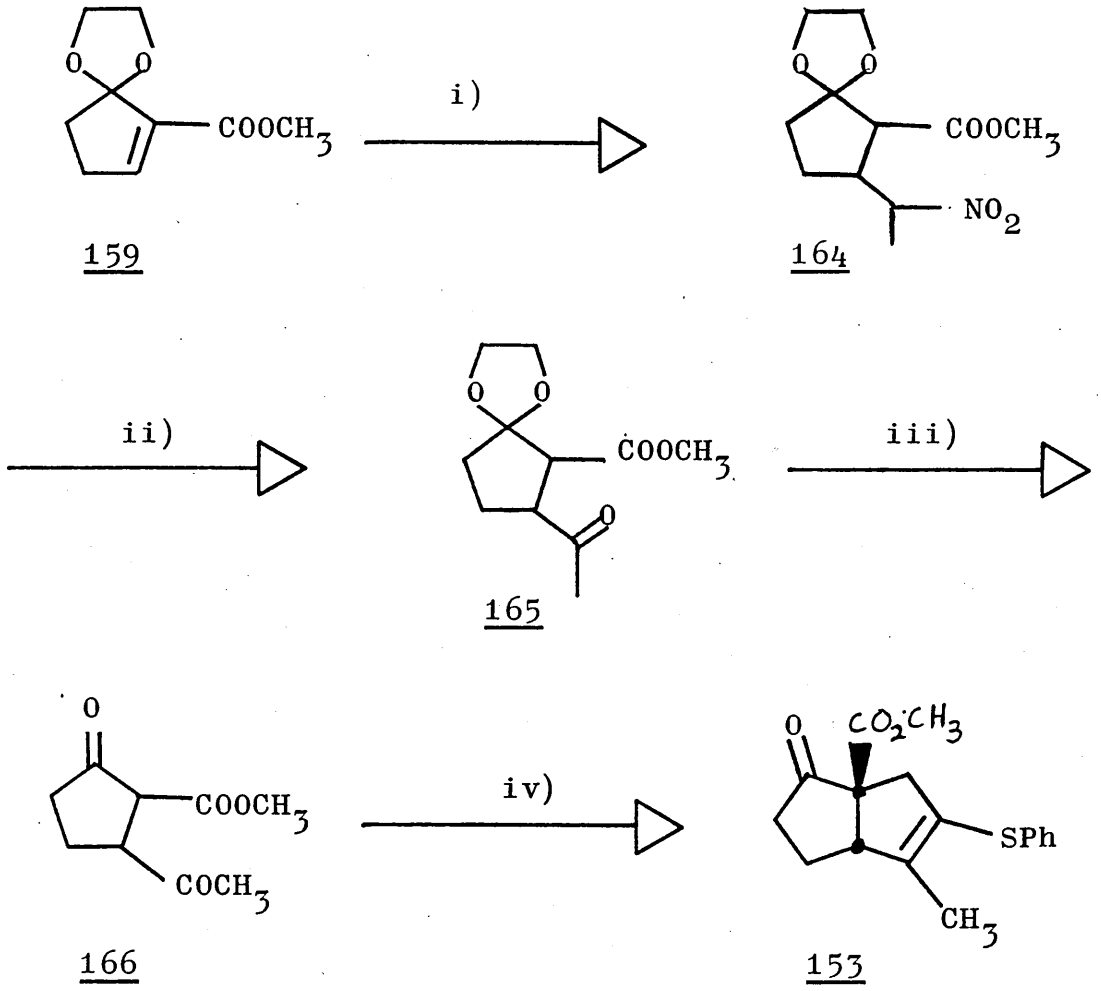
Scheme 102

From a synthetic viewpoint, 152 should be available in the same way as 153[131]. Retro-Dieckmann ring opening followed by ring closure (section 2.3.1) should give 154 which on reduction, conversion of the resultant alcohol to a better leaving group and elimination should give 155.

For a detailed discussion on how 155 might ultimately be converted into carbaprostacyclin see section 4.3.

4.2 Results and discussion

The published procedure[131] to the bicyclo [3.3.0] octane 153 is shown in Scheme 103.

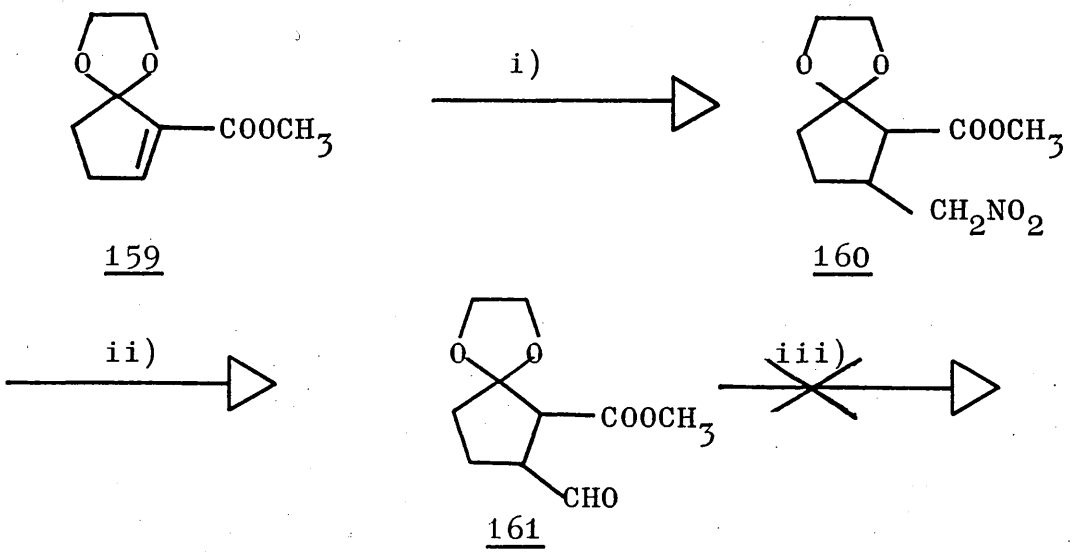


159 164 165 166 153

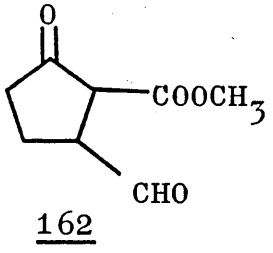
i) $CH_3CH_2NO_2$/tetramethylguanidine ii) $TiCl_3/NH_4OAc/H_2O/NaOCH_3$ iii) CF_3COOH/H_2O iv) NaH/THF, 1d/reflux

Scheme 103

The adaption of this route to our desired compound 152 was expected to proceed on similar lines. Thus the cyclopentenone ketal 159 was subjected to treatment with nitromethane and tetramethylguanidine (TMG) under a nitrogen atmosphere to give the adduct 160 as a mixture of cis and trans isomers in 92% yield.



159 160 161



162

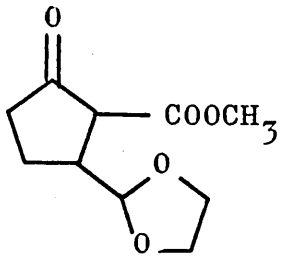
i) CH_3NO_2/tetramethylguanidine

ii) $TiCl_3/NH_4OAc/NaOCH_3/H_2O$

iii) CF_3COOH/H_2O

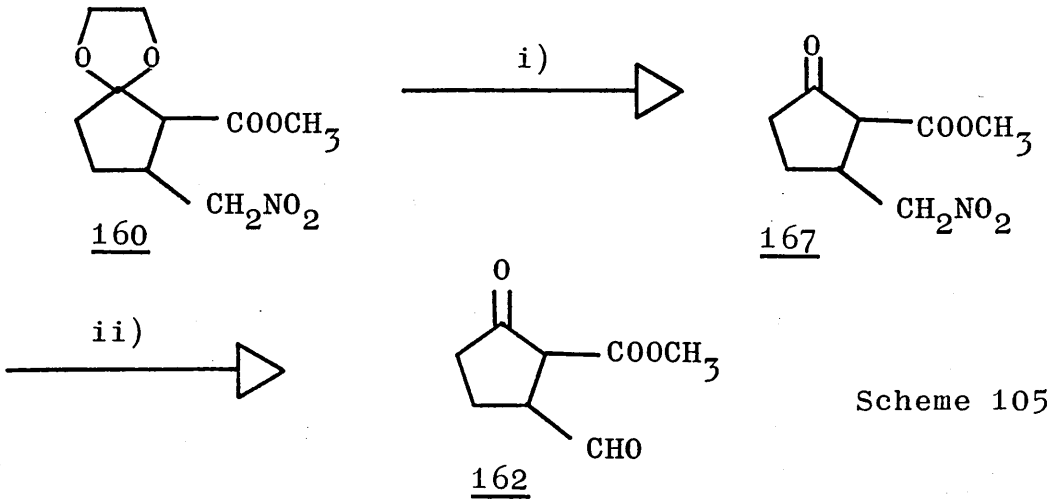
Scheme 104

Conversion of the nitro group to the aldehyde using McMurrey's procedure[132] gave the formylester 161. After treatment of this with aqueous trifluoroacetic acid (TFA)[131] and subsequent work up, see experimental section, a product was obtained which still retained peaks in the NMR spectrum due to the acetal protons. The only way this could be rationalised was by invoking an acid catalysed transfer of the ethane-1,2-diol unit to give the ketoester 163. The absence of an aldehyde C-H stretch in the IR spectrum appeared to confirm this. Presumably the greater reactivity of aldehydes, with respect to ketones, towards nucleophilic attack by the alcohol explains why this effect was not observed in the conversion of 165 to 166.



163

One solution to this problem would appear to be to reverse the order of the last two transformatios shown in Scheme 104. Thus (Scheme 105) the nitroester 160 was converted to 167, using identical conditions to those outlined above, and the latter was converted into the tricarbonyl 162.



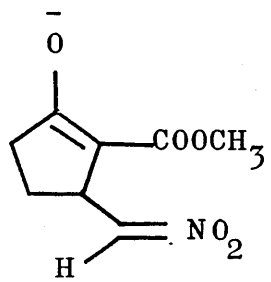
Scheme 105

i) CF_3COOH/H_2O ii) $TiCl_3/NH_4OAc/H_2O/NaOAc$

The yield of the second step is quite low, at best only 35%, and the reason for this is not exactly clear.

There are a number of methods known for the conversion of nitro groups to carbonyls (known as the Nef reaction) based, in general, on solvolytic, reductive, oxidative, neutral or solid-phase procedures[133]. Several out of these were tried in an attempt to convert 167 into 162 in better yield than that obtained using titanium

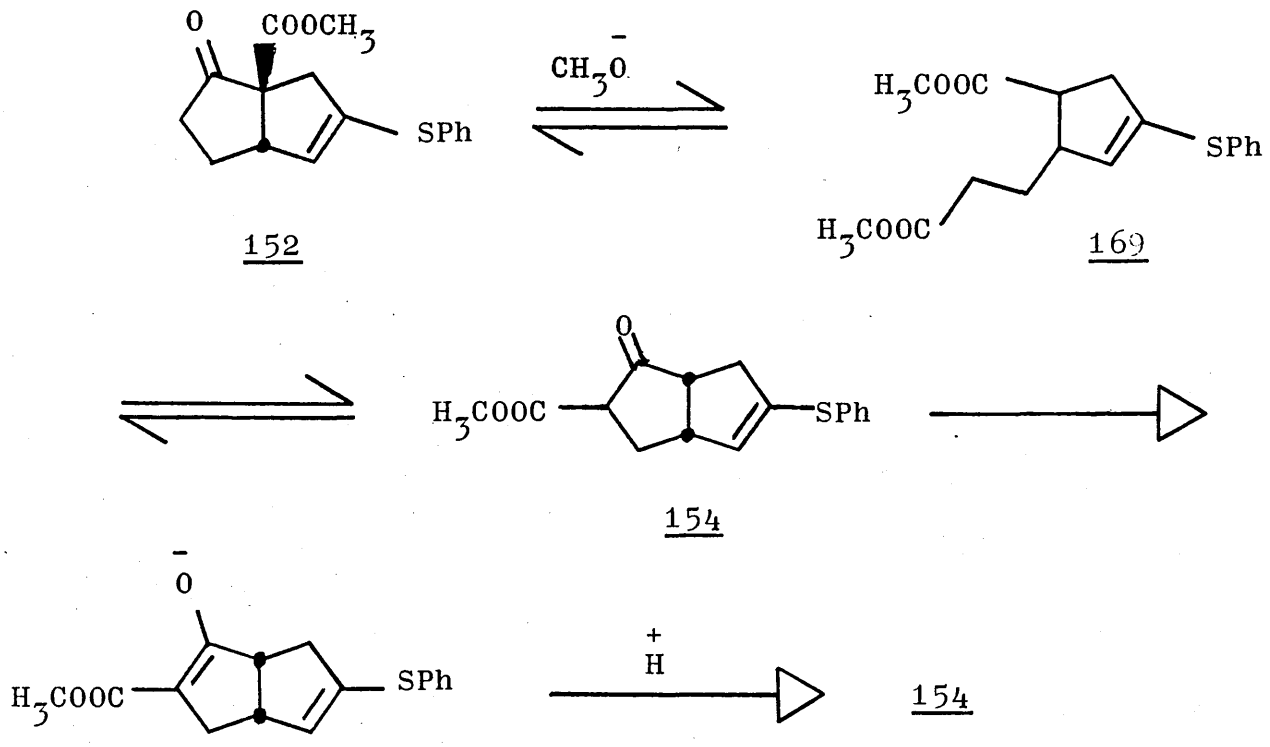
trichloride. Thus hydrogen peroxide in the presence of potassium carbonate[134] under the published conditions produced a number of products. It may be that under the conditions used, i.e. excess base, the 1,3-ketoester 167 has become converted to the corresponding enolate 168 and the oxidising agent has attacked the resultant carbon-carbon double bond. When sodium permanganate[135] was added to the lithium nitronate salt of 167 and the reaction mixture subjected to prolonged stirring only the reactant 167 was recovered.



168

Similarly no products were observed using ceric ammonium nitrate[136] with >80% of 167 being recovered. Therefore we were forced to return to the use of the reductive titanium trichloride procedure.

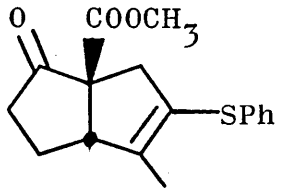
As expected the tricarbonyl 162 cyclised with the phosphonium salt 1d in the presence of NaH to give the bicyclo 3.3.0 octane 152. In order to convert this into the isomeric 1,3-ketoester 154 we envisaged using a retro-Dieckmann ring opening reaction followed by spontaneous ring closure (Scheme 106). The 1,3-ketoester 154 should be formed specifically due to its ability to enolise under the reaction conditions (see section 2.3.1).



Scheme 106

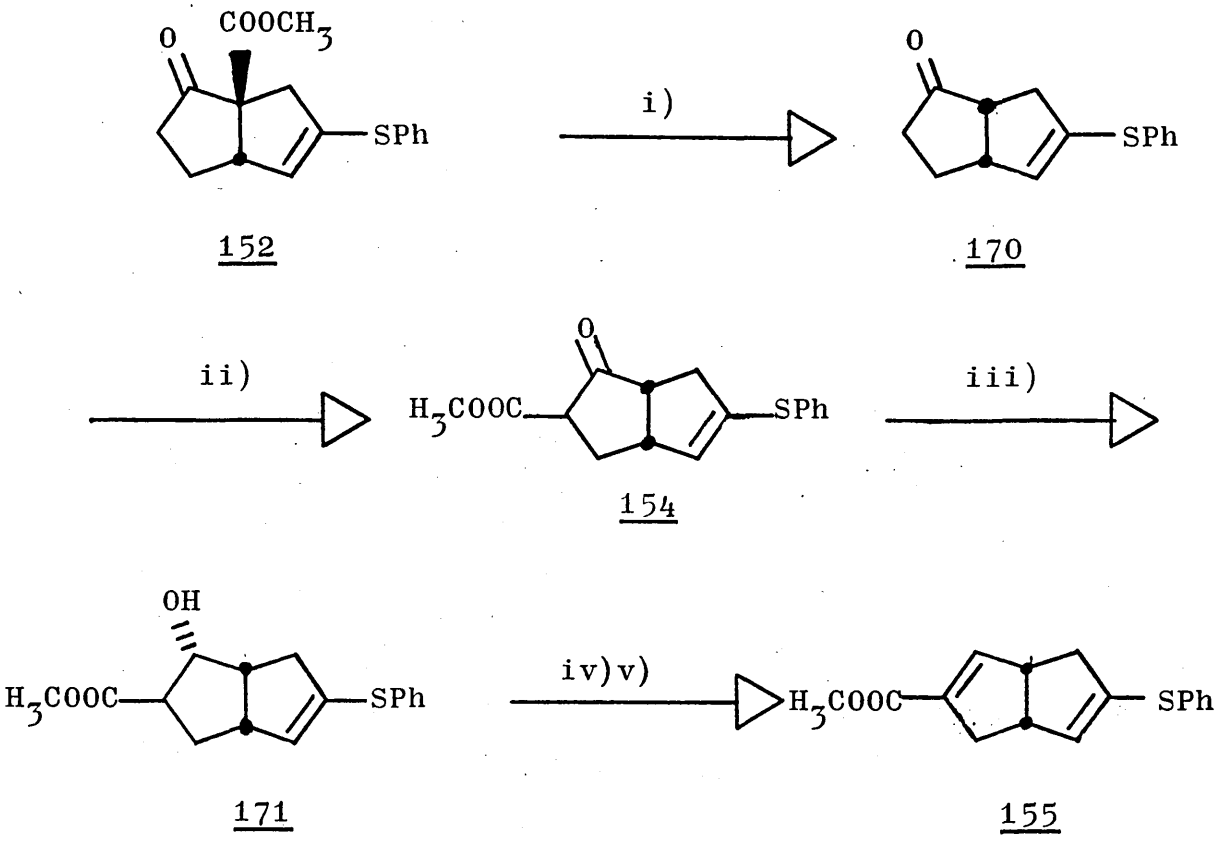
When 152 was treated with sodium methoxide in a variety of solvents the same product was formed in each case. The best method was to use methanol as the solvent, whereby the product was obtained in 67% yield. The NMR spectrum of this product contained two singlets at approximately 3.7 ppm with a combined integration ratio due to six protons. This appeared to indicate that although retro-Dieckmann ring opening occurred to give the diester 169 this was reluctant to undergo ring closure under the reaction conditions. Thus this compound was isolated from the reaction mixture and attempts were made to perform the Dieckmann reaction using other combinations of base and solvent. Unfortunately none of these were successful with no ring closed products being detected. This did not prove

to be a serious disadvantage as an alternative approach to the synthesis of 154 from 152 was available. According to an earlier study[137] only one method was successful for the decarboxylation of the related compound 153[26], this involving the use of sodium cyanide in hexamethyl phosphoramide[138].



153

Using these reagents (Scheme 107) 170 was obtained from 152 in 59% yield. The methoxylcarbonyl group was reattached using NaH and dimethylcarbonate[139] to give the 1,3-ketoester 154. Selective reduction of the ketone group in 154 with sodium borohydride in methanol gave, presumably, the alcohol 171 derived from attack of hydride at the more available top face of the molecule. A successful synthesis of the ester 155 was achieved by the formation of the O-mesylate from 171 and elimination of methanesulphonic acid to give 155 in 64% overall yield from 171.



152 170 154 171 155

i) NaCN/HMPA/70°C ii) NaH/$(CH_3O)_2CO$/p-dioxan

iii) $NaBH_4/CH_3OH$ iv) $CH_3SO_2Cl/(C_2H_5)_3N/CH_2Cl_2$

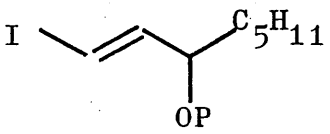
v) DBU/CH_2Cl_2

Scheme 107

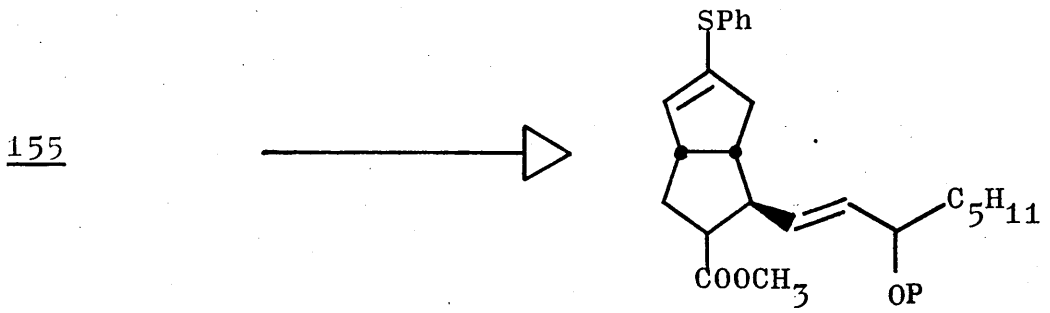
4.3 Future work

Having obtained the unsaturated ester 155 copper catalysed conjugate[140] addition of the vinyl iodide 172 should give the adduct 173. From this conversion to the α hydroxi[141] or α methyl thio[142] acids (176 and 175) and oxadative decarboxylation should give the ketone 177 (Scheme 108) from which the protected alcohol 156 (see Scheme 102)

should be available.



172



155

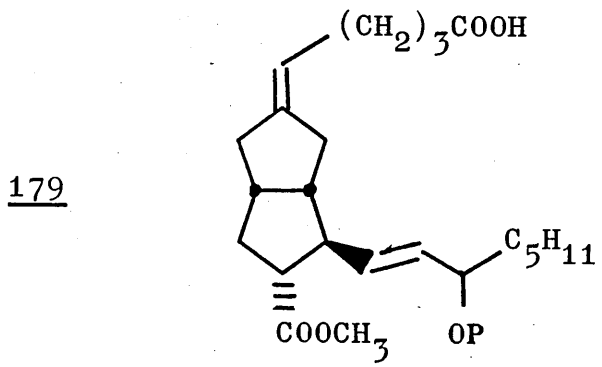
173

Hydrolysis of the vinylsulphide in 156 (Scheme 102) would give 157 and Wittig condensation of this with the phosphorane 178 should give a mixture of 158 and its geometrical isomer 179.

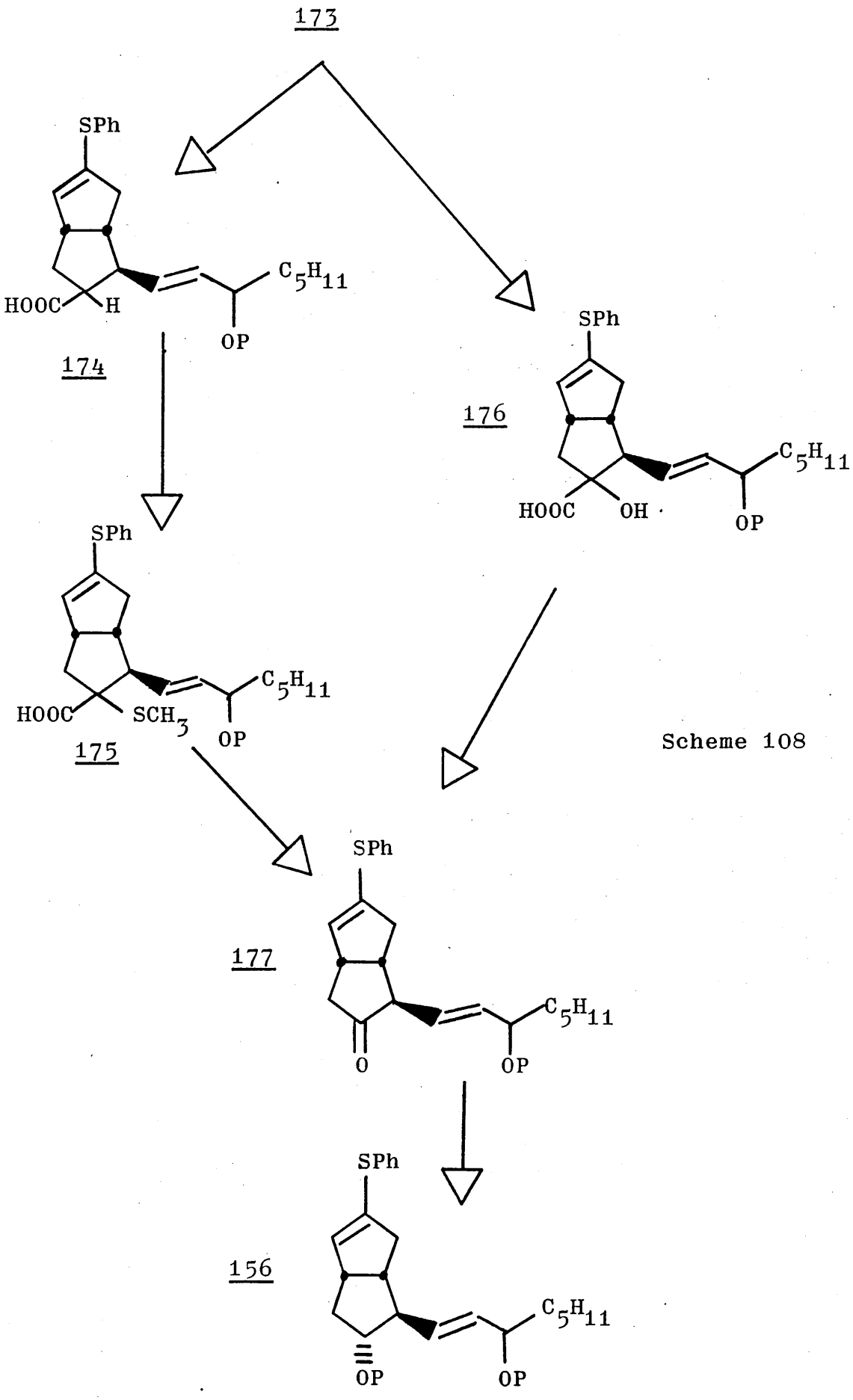
$$Ph_3PCH(CH_2)_3CO\bar{O}$$

178

Double deprotection of this should give raceamic carbaprostacyclin 146.

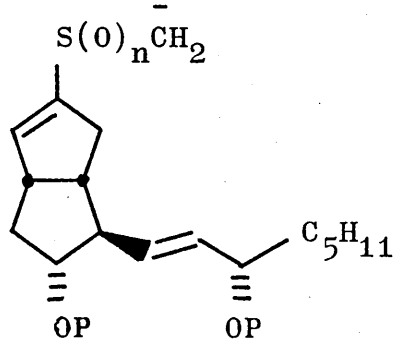


179


173
SPh
HOOC
H
C_5H_{11}
OP
174
176
SPh
HOOC
OH
C_5H_{11}
OP
SPh
HOOC
SCH_3
C_5H_{11}
OP
175
177
SPh
O
C_5H_{11}
OP
156
SPh
OP
C_5H_{11}
OP

Scheme 108

It is also conceivable that novel analogues of carbaprostacyclin could be obtained either by the preparation of more novel vinylphosphonium salts or using the ability of sulphur, in one or more of its oxidation states, to stabilise adjacent anions.



5. EXPERIMENTAL

5.1 General Information

Infrared spectra were obtained on a Pye-Unicam SP3-100 spectrophotometer. Samples were prepared as potassium bromide (KBr) discs or liquid films. ^{1}H NMR spectra were obtained on one of the following:- Joel C60, Joel PMX si or Bruker WP80 spectrophotometers. Samples were prepared in the solvent stated in each method. UV spectra were obtained on a Perkin Elmer 550-S spectrophotometer. Microanalyses were performed by EMAL, Beauworthy, Devon or the City University, London.

IR data is given in cm^{-1}. NMR data is given on the δ scale using tetramethylsilane as the internal reference. Abbreviations used for the form of the signal are as follows:- s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. UV data was obtained in ethanol as the solvent and is given in nm. Melting points are uncorrected.

Rapid column chromatography and column chromatography were performed on Merck 7734 and Merck 7736 silica gel respectively. Thin-layer chromatography was performed on Merck 5554 Alufolien Kieselgel $60F_{254}$ plates. Solvents for column chromatography were distilled before use. Petrol refers to that fraction of petroleum spirit boiling between 40 and 60^{o}C.

Dry THF was obtained by distillation from potassium metal. Dry diethyl ether was obtained by distillation from $LiAlH_4$. Dry CH_2Cl_2 was distilled from calcium hydride and

stored over 4A molecular sieves. Dry diisopropylamine was distilled from calcium hydride and stored under nitrogen over 4A molecular sieves. Dry DMF was obtained by heating over calcium hydride followed by distillation under reduced pressure onto 4A molecular sieves. Dry pyridine was obtained by storage over potassium hydroxide. n-Butyl lithium was standardised before use and its molarity is given where needed. Sodium hydride was obtained as a 60% dispersion in mineral oil. Dry nitromethane was obtained by washing with conc H_2SO_4, water, saturated sodium carbonate, water and drying over $MgSO_4$ and distillation from calcium hydride. Dry methanol was distilled from sodium.

All reactions requiring inert atmospheres were done under nitrogen.

Ozonolysis reactions were performed using a BOC Mark II ozonizer. Hyflo super cell filter aid was obtained from BDH chemicals.

5.2 Experimental Methods

N-(4-Toluenesulphonyl)-2-amino-5-methylbenzoic acid (24)

Into a three necked flask fitted with a thermometer and magnetic stirrer was placed water (300 mls). This was warmed slowly to 60°C with stirring while sodium carbonate (50.3g, 0.473 mol) was added in portions. With the temperature of the liquid maintained at 60-65°C, 13 (29.78g, 0.197 mol) was added in 5 portions. Then pTsCl (41.17g, 0.217 mol) was introduced over 20 minutes with the temperature of the reaction mixture kept below 70°C. This temperature was maintained for a further 20 minutes and then raised to 80°C whilst 1.5g of charcoal was added cautiously. The reaction mixture was filtered on hot buchner apparatus and the filtrate added to a swirled solution of 5M HCl (100 mls). The solid was stirred manually for 10 minutes and filtered, washed with HCl(2M), water and dried at 60°C under vacuum overnight to give 24 as a brown solid. 60.5g, 100% mp 195-199°C. IR (KBr) 3400-2300, 3210, 1675, 1580, 1340 and 1170. ^{1}H NMR ($CDCl_3$) 2.30 (s, 3H), 6.47 (broad s, 1H), 7.10-7.90 (m, 7H) and 10.18 (s, 1H).

N-(2-Hydroxymethyl-4-methylphenyl)-4-toluenesulphonamide (25)

To a flask fitted with a reflux condenser, dropping funnel and inert atmosphere was charged dry THF (30 mls). $LiAlH_4$ (3.8g, 0.1 mol) was added in several portions and the slurry stirred for 5 minutes. Meanwhile the acid 24 (15.24g, 0.05 mol) in THF (125 mls) was placed in the dropping funnel and introduced into the flask dropwise. After complete

addition the reaction mixture was refluxed for 1 hr. HCl (2M) was carefully added and the THF layer removed. The aqueous layer was extracted with ethyl acetate and the combined organic phases washed with saturated sodium bicarbonate (twice), brine and dried over $MgSO_4$. The solvent was removed to give the product as a brown solid used in the next step without purification. 13.74g, 94.5%. mp 144-146°C. IR (KBr) 3450, 3100, 3050, 2960, 2920, 1600, 1495, 1320 and 1150. ^1H NMR ($CDCl_3$) 2.26 (s, 3H), 2.38 (s, 3H), 4.35 (s, 2H) and 6.85-7.78 (m, 9H). Microanalysis found C, 61.95; H, 6.03; N, 4.94. $C_{15}H_{17}NO_3S$ requires C, 61.82; H, 5.88; N, 4.83.

N-(2-Formyl-4-methylphenyl)-4-toluenesulphonamide (14)

Pyridinium chlorochromate (13.82g, 64.2 mmol) and dry dichloromethane (150 mls) were placed in a flask fitted with mechanical stirring and the suspension stirred for 5 minutes. The alcohol 25 (12.46g, 43 mmol) dissolved in a minimal amount of the same solvent was added and stirring continued for 3 hr. At the end of this time the liquid was decanted from the solid which was washed several times with ether. The combined solvent was passed through a short pad of Merck 7734 grade silica and evaporated to give a pale brown solid. 11.56g, 93.4%. mp 114-115°C IR (KBr) 3150, 3080, 2930, 2860, 2760, 1685, 1590, 1500, 1345 and 1155. ^1H NMR ($CDCl_3$) 2.34 (s, 3H), 2.37 (s, 3H), 7.05-7.9 (m, 7H), 9.75 (s, 1H) and 10.57 (s, 1H). Microanalysis found C, 59.76; H, 5.50. $C_{15}H_{15}NO_3S$ requires C, 59.86; H, 5.30.

1,2-Dihydro-6-methyl-3-methylthio-1(4-toluenesulphonyl) quinoline (15c)

To a flame dried flask fitted with an inert atmosphere, reflux condenser and a magnetic stirrer was charged sodium hydride (0.2g, 5 mmol). This was washed once with petrol and the solvent removed. Dry THF (50 mls) was added with stirring followed by the aldehyde 14 (1.302g, 4.5 mmol) in one portion. After stirring for 20 minutes the phosphonium salt 1c (1.85g, 5 mmol) was introduced as a solid, after an additional 20 minutes at room temperature the reaction mixture was refluxed for 3 hours. The reaction mixture was poured into ethyl acetate/ HCl(2M) and the aqueous phase extracted with more ethyl acetate. The combined organic layers were dried over $MgSO_4$ and the residue after evaporation subjected to column chromatography (ethyl acetate:petrol 1:3) to give the product as a pale yellow solid. 0.93g, 70%. mp 126-128°C. IR (KBr) 3100, 2950, 1615, 1605, 1490, 1365 and 1165. ^{1}NMR ($CDCl_3$) 2.12 (s, 3H), 2.34 (s, 3H), 2.39 (s, 3H), 4.35 (s, 2H), 5.50 (s, 1H) and 6.70-7.78 (m, 7H). Microanalysis found C, 62.33; H, 5.51; N, 3.96. $C_{18}H_{19}S_2O_2N$ requires C, 62.58; H, 5.54; N, 4.05.

1,2-Dihydro-6-methyl-3-phenylthio-1(4-toluenesulphonyl) quinoline (15d)

Prepared in the same way as 15c from sodium hydride (.153g, 3.8 mmol), 14 (1g, 3.46 mmol) and 1d (1.99g, 3.8 mmol) in THF (40 mls) with refluxing of the final reaction mixture for 2 hours. 1.27g, 90.1%. mp 115-117°C. IR (KBr) 3100,

2950, 2900, 1620, 1605, 1355 and 1165. ^{1}H NMR ($CDCl_3$) 2.35 (s, 3H), 2.41 (s, 3H), 4.40 (s, 2H), 5.67 (s, 1H) and 6.69-7.70 (m, 7H). Microanalysis found C, 67.48; H, 5.17; N, 3.37. $C_{23}H_{21}S_2NO_2$ requires C, 67.78; H, 5.19; N, 3.44.

1,2-Dihydro-3-ethoxy-6-methyl-1(4-toluenesulphonyl) quinoline (15b)

Prepared in the same way as 15c and 15d from sodium hydride (0.212g, 5.3 mmol), 14 (1.39g, 4.8 mmol) and 1b (2.16g, 5.3 mmol) in THF (50 mls) with refluxing of the final reaction mixture for 2 days. 0.215g, 13%. mp 108-110°C. IR (KBr) 3080, 2950, 1650, 1600, 1490, 1355 and 1165. ^{1}H NMR ($CDCl_3$) 1.27 (t, 3H, J = 6 Hz), 2.35 (s, 3H), 2.39 (s, 3H), 3.50 (q, 2H, J = 6 Hz), 4.30 (s, 2H), 4.91 (s, 1H) and 6.75-7.70 (m, 7H). Microanalysis found C, 66.46; H, 6.25; N, 4.09. $C_{19}H_{21}NSO_3$ requires C, 66.45; H, 6.16; N, 4.08.

6-Methyl-3-oxo-1,2,3,4 tetrahydro-1(4-toluenesulphonyl) quinoline (16)

Dry diethylether (3 mls) was saturated with perchloric acid (72%) in a separating funnel and the excess acid removed. The vinylether 15b (57 mg) was dissolved in the ether and the mixture stirred for 30 minutes at room temperature. The solution was poured into ether/saturated sodium bicarbonate and the organic phase dried over $MgSO_4$. Evaporation of the solvent gave the product as a white solid. 51.3 mg, 98%. mp 109-110°C. IR (KBr) 2910, 1720, 1590, 1350 and 1160. ^{1}H NMR ($CDCl_3$) 2.35 (s, 3H), 2.40 (s, 3H), 2.65 (s, 2H), 4.26 (s, 2H) and 6.90-7.81 (m, 7H).

Microanalysis found C, 64.92; H, 5.55; N, 4.56.
$C_{17}H_{17}NSO_3$ required C, 64.74; H, 5.43; N, 4.44.

Methyl N-(2-formyl-4-methylphenyl)-N-(4-toluenesulphonyl)-2-aminoacetate (37)

A flame dried flask fitted with an inert atmosphere and magnetic stirring was charged with sodium hydride (0.229g, 5.71 mmol). This was washed once with petrol and the solvent removed. Dry DMF (10 mls) was added, followed by the aldehyde 14 (1.5g, 5.18 mmol) in two portions. The resultant solution was stirred for 5 minutes at room temperature and methyl bromoacetate (0.874g, 5.71 mmol, 0.541 mls) introduced rapidly. The reaction mixture was stirred at 40°C for 1 hour and poured into ethyl acetate/HCl(2M). After separation of the layers the aqueous layer was reextracted with more ethyl acetate and the combined extracts washed with brine and dried over $MgSO_4$. The residue after evaporation was subjected to column chromatography (ethyl acetate:petrol 1:2) to give the product as a pale yellow solid. 1.82g, 98%. mp 153-155°C. IR (KBr) 3050, 2950, 2890, 2750, 1755, 1695, 1600, 1355 and 1165. ^{1}H NMR ($CDCl_3$) 2.40 (s, 3H), 2.45 (s, 3H), 3.68 (s, 3H), 4.40 (broad s, 2H), 6.61-7.69 (m, 7H) and 10.49 (s, 1H). Microanalysis found C, 59.76; H, 5.50; N, 3.96. $C_{18}H_{19}NSO_5$ requires C, 59.82; H, 5.30; N, 3.88.

Methyl N-(2(2-methoxy)ethenyl-4-methylphenyl)-N-(4-toluenesulphonyl)-2-aminoacetate (42)

A flame dried flask fitted with inert atmosphere, rubber septum and magnetic stirring was charged with dry

THF (30 mls). Diisopropylamine (2.12g, 21 mmol, 2.94 mls) was added and the flask cooled to 0°C. n-Butyl lithium (14.1 mls, 21 mmol, 1.48 Mol solution in hexane) was introduced by syringe and stirring continued for 15 minutes at 0°C. After addition of the phosphonium salt 40 (7.20g, 21 mmol) the red ylid formed and stirring was continued for a further 15 minutes at 0°C. The aldehyde 37 (2.1g, 5.82 mmol) dissolved in THF (20 mls) was added and after 20 minutes the reaction was worked up by pouring into ethyl acetate/ saturated ammonium chloride, the aqueous phase was reextracted with more ethyl acetate and the combined organic phases washed with brine and dried over $MgSO_4$. Column chromatography of the residue after evaporation (ethyl acetate:petrol 1:4) gave the vinylethers 42. 0.515g, 19.8%. IR (liq film) 2950, 1740, 1660, 1510, 1340, 1165 and 1090. ^1H NMR ($CDCl_3$). z isomer 2.30 (s, 3H), 2.43 (s, 3H), 3.64 (s, 3H), 3.76 (s, 3H), 4.29 (broad s, 2H), 5.38 (d, 1H, J = 5 Hz), 6.11 (d, 1H, J = 5 Hz) and 6.79-7.80 (m, 7H). e isomer 2.29 (s, 3H), 2.42 (s, 3H), 3.55 (s, 3H), 3.67 (s, 3H), 4.29 (broad s, 2H), 5.76 (d, 1H, J = 9 Hz) and 6.78-7.72 (m, 8H).

Methyl-N-(2-hydroxymethyl-4-methylphenyl)-N-(4-toluenesulphonyl)-2-aminoacetate (38)

The alcohol 25 (13.74g, 47.8 mmol) was dissolved in ethylvinyl ether (140 mls) at room temperature with stirring. Hydrochloric acid (10 M, 0.5 mls) was added and the solution stirred overnight. The reaction mixture was neutralised with saturated sodium bicarbonate, dried over $MgSO_4$ and the solvent evaporated to give the product as a

brown oil (100%). This was immediately dissolved in dry DMF (75 mls) and added to petrol washed sodium hydride (2.3g, 58.4 mmol). After stirring for 5 minutes, methyl bromoacetate (6.77 mls, 10.94g, 73 mmol) was added by syringe and stirring continued for a further 15 minutes at 40°C. The reaction mixture was poured into ethyl acetate/ HCl(2M) and the aqueous layer extracted with more ethyl acetate. After removal of most of the solvent the residue was added to HCl (2 M, 100 mls) and the mixture stirred vigorously overnight. This was then neutralised with saturated sodium bicarbonate and extracted with ethyl acetate. After drying over $MgSO_4$ and evaporation of the solvent the residue was subjected to column chromatography (ethyl acetate:petrol 1:2) to give 38 12.58g, 73.4%. mp 81-83°C. IR (KBr) 3350, 2980, 1755, 1610, 1510, 1360 and 1160. ^1H NMR ($CDCl_3$). 2.35 (s, 3H), 2.48 (s, 3H), 3.38 (broad s, 1H, OH), 3.69 (s, 3H), 4.29 (d, 2H, J = 14 Hz), 4.83 (s, 2H) and 6.31-7.62 (m, 7H). Microanalysis found C, 59.62; H, 6.02; N, 3.90. $C_{18}H_{21}NSO_5$ requires C, 59.49; H, 5.82; N, 3.85.

Methyl N-(2-bromomethyl-4-methylphenyl)-N-(4-toluenesulphonyl)-2-aminoacetate (45)

The alcohol 38[143] (4.71g, 13 mmol) was placed in a flame dried flask, fitted with an inert atmosphere and magnetic stirrer, together with dry DMF (50 mls). To this was added triphenylphosphine (6.82, 26 mmol) and the reaction mixture cooled over ice. Bromine was added dropwise until the first permanent orange colour persisted, after which the solution was allowed to warm to room temperature and stirred

for 45 minutes. The reaction mixture was poured into HCl(2M) and extracted several times with ethyl acetate, the combined organic phases were washed with saturated sodium bicarbonate, water and brine, dried over $MgSO_4$ and the solvent removed under vacuum. The residue was subjected to rapid column chromatography (ethyl acetate:petrol 1:1) to give the bromide 45 as a solid 4.55g, 82.5%. mp 108-109°C. IR (KBr) 2950, 1755, 1610, 1510, 1340, 1210 and 1160. ^1H NMR ($CDCl_3$) 2.34 (s, 3H), 2.44 (s, 3H), 3.71 (s, 3H), 4.48 (s, 2H), 4.31-5.04 (m, 2H) and 6.7-7.68 (m, 7H). Microanalysis found C, 50.60; H, 4.77; N, 3.22. $C_{18}H_{20}BrNSO_4$ requires C, 50.71; H, 4.73; N, 3.28.

Methyl-N-(2-cyanomethyl-4-methylphenyl)-N-(4-toluenesulphonyl)-2-aminoacetate (46)

The halide 45 (4.55g, 10.7 mmol) prepared above was added to a solution of sodium cyanide (0.58g, 11.8 mmol) dissolved in dry DMF (35 mls) in a flame dried flask fitted with an inert atmosphere. The deep yellow solution was stirred for 1 hr at room temperature and the reaction then quenched with HCl(2M). This was extracted with ethyl acetate and the organics washed with saturated sodium bicarbonate, brine and dried over $MgSO_4$. Column chromatography of the residue after evaporation (ethyl acetate:petrol 1:4) gave 46. 3.82g, 96%. mp 123-125°C. IR (KBr) 3010, 2950, 2920, 2245, 1750, 1590, 1500, 1340, 1225 and 1160. ^1H NMR ($CDCl_3$) 2.37 (s, 3H), 2.46 (s, 3H), 3.69 (s, 3H), 3.78-4.77 (series of m, 4H) and 6.32-7.6 (m, 7H). Microanalysis found C, 61.21; H, 5.45; N, 7.39. $C_{19}H_{20}N_2SO_4$ requires C, 61.27; H, 5.41; N, 7.52.

Methyl N-(2-carbamoylmethyl-4-methylphenyl)-2-amino acetate (47b)

46 (65 mg) was added to precooled H_2SO_4 (10 Mol, 0.2 mls) at 0°C with stirring. After 30 minutes saturated sodium bicarbonate was added and the aqueous phase extracted with ether. The combined organic phases were washed once with brine and dried over $MgSO_4$. The residue after evaporation was subjected to column chromatography (ethyl acetate:petrol 1:3) to give the product as a red solid. 23 mg, 62%. mp 153-155°C. IR (KBr) 3400, 3270, 2940, 2910, 1740, 1705, 1655, 1615, 1580, 1490 and 1210. ^1H NMR ($CDCl_3$) 2.31 (s, 3H), 3.76 (s, 3H), 4.55 (s, 2H), 6.59-7.5 (m, 4H), and 8.5 (broad s, 2H).

N-(2-Formyl-4-methylphenyl)-N-(2-propenyl)-4-toluenesulphonamide (51)

A flame dried flask fitted with inert atmosphere and magnetic stirring was charged with sodium hydride (0.76g, 19 mmol). This was washed once with petrol and the solvent removed. Dry DMF (40 mls) was added followed by 14 (5g, 17.3 mmol) in two portions. The resultant mixture was stirred for 5 minutes and allyl bromide (2.30g, 19 mmol, 1.65 mls) added by syringe. After heating to 40°C for 1 hr the solution was poured into ethyl acetate/HCl(2M) and the aqueous layer extracted with more ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$ and the residue after evaporation was subjected to column chromatography (ether:petrol 1:1) to give 51. 5.32g, 93.5%. mp 77-78°C. IR (KBr) 2860, 2750, 1690, 1600, 1360 and 1165.

^{1}H NMR ($CDCl_3$) 2.38 (s, 3H), 2.42 (s, 3H), 3.73-4.62 (broad s, 2H), 4.80-5.19 (m, 2H), 5.46-6.04 (m, 1H), 6.50-8.00 (m, 7H) and 10.36 (s, 1H). Microanalysis found C, 65.98; H, 5.89; N, 4.24. $C_{18}H_{19}NSO_3$ requires C, 66.24; H, 5.81; N, 4.25.

N-(2(2-Methoxy)ethenyl-4-methylphenyl)-N-(2-propenyl)-4-toluenesulphonamide (52)

A flame dried flask fitted with an inert atmosphere and magnetic stirring was charged with THF (100 mls) and diisopropylamine (3.08g, 30.4 mmol, 4.26 mls). After cooling to 0°C n-butyl lithium (19.14 mls, 1.59 Mol, 30.4 mmol) was added by syringe and stirring continued for 15 minutes at 0°C. After addition of the phosphonium salt 40 (10.42g, 30.4 mmol) the red ylid was observed and this was stirred for a further 15 minutes at 0°C. The aldehyde 51 (5g, 15.2 mmol) in THF (40 mls) was introduced and after 1 hour at 0°C the solution was poured into ethyl acetate/saturated ammonium chloride. The aqueous phase was extracted with more ethyl acetate and the combined extracts washed with brine and dried over $MgSO_4$. The residue after evaporation was subjected to column chromatography (ethyl acetate:petrol 1:9) to give 52. Least polar isomer (E) 1.79g, 33.0%. mp 90-91°C. IR (KBr) 3040, 2900, 1625, 1590, 1335 and 1150. ^{1}H NMR ($CDCl_3$) 2.30 (s, 3H), 2.44 (s, 3H), 3.60 (s, 3H), 4.12 (broad s, 2H), 4.81-4.19 (m, 2H), 5.46-6.21 (m, 1H), 5.90 (d, 1H, J = 10 Hz) and 6.52-7.76 (m, 8H). More polar isomer (Z) 1.67g, 30.8%. Oil. IR (liq film) 3050, 2910, 2840, 1635, 1590, 1340 and 1155. ^{1}H NMR ($CDCl_3$) 2.30 (s, 3H), 2.39 (s, 3H), 3.60 (s, 3H), 3.90 (d, 2H, J = 6 Hz), 4.59-4.98 (m, 2H), 5.19 (d, 1H, J = 6 Hz),

5.20-5.95 (m, 1H), 5.81 (d, 1H, J = 6 Hz) and 6.38-7.58 (m, 7H). Microanalysis (isomeric mixture) found C, 67.03; H, 6.55; N, 3.91. $C_{20}H_{23}NSO_3$ requires C, 67.12; H, 6.49; N, 3.92.

Benzyl N-(2-propenyl)-N-(4-toluenesulphonyl)-2-amino-5-methylphenylacetate (54)

A mixture of the isomers prepared above (1.06g, 2.97 mmol) was dissolved in 50 mls of THF and 8 mls of water in a flask fitted with magnetic stirring and an inert atmosphere. Mercuric acetate (1.88g, 6 mmol) was added and the bright yellow solution was stirred at room temperature for 1 hour. At the end of this time the reaction mixture was poured into a separating funnel containing benzene/potassium iodide (7% solution in water, 250 mls). The organic phase was washed with brine and dried over $MgSO_4$. After evaporation the aldehyde was obtained as a viscous white oil. This was dissolved in acetone and treated with Jones reagent. This was worked up in the usual way to give the acid 53. 0.3g, 25.9%. IR (KBr) 3600-2400, 2910, 1700, 1635, 1590, 1335 and 1150. This (0.3g, 0.83 mmol) was dissolved in dry DMF (3 mls) and added to petrol washed sodium hydride (40 mg, 1 mmol) in a flame dried flask fitted with an inert atmosphere. This was stirred for 5 minutes at room temperature after which benzyl bromide (0.171g, 1 mmol, 0.12 mls) was added by syringe. After 20 minutes at 40°C the reaction mixture was poured into ethyl acetate/HCl (2M) and the organic phase washed with saturated sodium bicarbonate, brine and dried over $MgSO_4$. The residue after evaporation was subjected to column chromatography

(ethyl acetate:petrol 1:6) to give the ester as clear oil 0.23g, 61.7% (from the acid 53). IR (liq film) 3010, 2940, 2910, 1725, 1630, 1590, 1490 1340 and 1155. ^{1}H NMR ($CDCl_3$) 2.30 (s, 3H), 2.42 (s, 3H), 3.69-4.45 (series of m, 4H), 4.72-5.08 (m, 2H), 5.17 (s, 2H), 5.4-5.91 (m, 1H) and 6.32-7.70 (m, 12H). Microanalysis found C, 69.61; H, 6.43; N, 3.26. $C_{26}H_{27}NSO_4$ requires C, 69.46; H, 6.06; N, 3.12.

Methyl N-(2-benzyloxycarbonylmethyl-4-methylphenyl) N-(4-toluenesulphonyl)-2-aminoacetate (55)

The alkene (0.318g) was ozonolysed at -78°C in CH_2Cl_2 (40 mls). The solvent was removed from the crude ozonides using a stream of nitrogen and the residue taken up in acetone and treated dropwise with a slight excess of Jones reagent to give 57. After the usual work up the solvent was dried over $MgSO_4$ and evaporated to give a clear oil which was dissolved in a small volume of ether and treated with diazomethane to give, after column chromatography, (ethyl acetate:petrol 1:3) the diester 53 as a colourless oil. 0.315g, 92.6%. IR (liq film) 2920, 1725, 1590, 1345, 1200 and 1160. ^{1}H NMR ($CDCl_3$) 2.30 (s, 3H), 2.42 (s, 3H), 3.62 (s, 3H), 3.71-4.12 (m, 2H), 4.30 (s, 2H), 5.17 (s, 2H) and 6.63-7.67 (m, 12H).

Methyl N-(2-phenylthiocarbonylmethyl-4-methylphenyl) N-(4-toluenesulphonyl)-2-aminoacetate (36)

The diester 53 (184 mg) was dissolved in 5 mls of a 5% ethyl acetate 95% ethanol mixture and hydrogenated over 5% palladium on charcoal. The mixture was filtered through Hyflo super cell and the solvent removed. The residual oil

was taken up in ether washed several times with saturated sodium bicarbonate and the combined aqueous layers were reacidified with HCl (2M). The resultant solution was extracted with more ether and the combined organic phases dried over $MgSO_4$ followed by removal of the solvent to give the crude acid 39. 150 mg 92% IR (liq film) 3500-2600, 2920, 1715, 1590, 1490, 1345, 1205 and 1155. This was immediately dissolved in a THF (4 mls) solution of thiophenol (46 mg, 0.422 mmol) and dicyclohexyl carbodiimide (87 mg, 0.422 mmol) under an inert atmosphere. After stirring for 2 hrs, the solid was filtered using Hyflo super cell and the residue after evaporation subjected to column chromatography to give 36 as a viscous oil. 94.5 mg, 51%. IR (liq film) 3050, 2920, 2845, 1750, 1685, 1600, 1345, 1200 and 1150. ^1H NMR ($CDCl_3$) 2.32 (s, 3H), 2.44 (s, 3H), 3.65 (s, 3H), 3.80-4.13 (m, 2H), 4.37 (m, 2H) and 6.8-7.75 (m, 12H).

N-(2-Propenyl)-N-(2(2(1,3-dithia)cyclohexylidene)methyl-4-methylphenyl)-4-toluenesulphonamide (58)

A flame dried flask fitted with inert atmosphere and magnetic stirrer was charged with dry THF (2 mls) and 2-trimethylsilyl-1,3-dithiane (0.142 mls, 0.75 mmol). This was cooled to -78°C and n-butyl lithium (48 mg, 0.75 mmol, 0.47 mls) added by syringe. After 30 minutes at the same temperature the aldehyde 51 (0.1g, 0.3 mmol) in THF (2 mls) was added and the solution allowed to warm to room temperature. After 3 hours the reaction was poured into ethyl acetate/HCl (2M) and the organic layer washed with

brine and dried over $MgSO_4$. The residue after evaporation was subjected to column chromatography (ethyl acetate: petrol 1:4) to give 58 as a pale yellow solid. 0.111g, 85%. mp 116-118°C. IR (KBr) 3030, 2940, 2880, 1600, 1490, 1355 and 1170 cm^{-1}. ^1H NMR 2.00-2.40 (m, 2H), 2.34 (s, 3H), 2.43 (s, 3H), 2.81-3.05 (q, 4H, J = 4 Hz), 4.1 (d, 2H, J = 5 Hz), 4.82-5.14 (m, 2H), 5.50-6.05) (m, 1H) and 6.61-7.78 (m, 8H). Microanalysis found C, 61.22; H, 5.93; N, 3.20. $C_{22}H_{25}NS_3O_2$ requires C, 61.22; H, 5.84; N, 3.24.

N-E(2(2-Methylsulphinyl-2-methylthio)ethenyl-4-methylphenyl)-4-toluenesulphonamide (60)

A flame dried flask fitted with inert atmosphere and magnetic stirring was charged with the aldehyde 14 (3g, 10.4 mmol), 59 (2.14g, 17.3 mmol) and THF (12 mls). To this was then added Triton B (12 mls). The resulting mixture was heated to reflux for 2.5 days, allowed to cool and poured into ethyl acetate. This was washed with saturated ammonium chloride and the aqueous layer reextracted with more ethyl acetate. The combined organic phases were washed with brine and dried over $MgSO_4$. The residue after evaporation was subjected to rapid column chromatography (ethyl acetate:petrol 1:3 followed by 3:1) to give 14 0.78g and 60 as a pale yellow solid 2.34g 77% (based on recovered 14). mp 160-162°C. IR (KBr) 3120, 2920, 2840, 1595, 1330, 1155 and 1035. ^1H NMR ($CDCl_3$) 2.03 (s, 3H), 2.32 (s, 6H), 2.72 (s, 3H), 6.80-7.53 (m, 8H) and 7.60 (broad s, 1H). Microanalysis found C, 54.25; H, 5.38; N, 3.46. $C_{18}H_{21}NS_3O_3$ requires C, 54.65; H, 5.35; N, 3.54.

N-E(2(2-Methylthio-2-methylsulphinyl)ethenyl-4-methylphenyl)-N-(2-propenyl)-4-toluenesulphonamide (61)

To a flame dried flask fitted with inert atmosphere and magnetic stirring was charged sodium hydride (0.183g, 4.57 mmol). This was washed once with petrol and the solvent removed. Into the flask was placed dry DMF (10 mls) followed by 60 (1.5g, 3.79 mmol) in two portions. After 5 minutes, allyl bromide (0.55g, 4.55 mmol, 0.4 mls) was introduced and the flask heated to 40°C for 10 minutes. At the end of this time the reaction mixture was poured into ethyl acetate which was washed with saturated ammonium chloride. The aqueous layer was reextracted with more ethyl acetate and the combined organic layers washed with brine and dried over $MgSO_4$. The residue after evaporation was subjected to rapid column chromatography (ethyl acetate: petrol 1:1) to give a 61 as a gum 1.42, 86.3%. IR (liq film) 2905, 1630, 1590, 1340, 1155 and 1060. ^1H NMR ($CDCl_3$) 2.30 (s, 3H), 2.40 (s, 3H), 2.45 (s, 3H), 2.80 (s, 3H), 3.93-4.20 (m, 2H), 4.81-5.18 (m, 2H), 5.48-6.05 (m, 1H) and 6.55-8.00 (m, 8H). Microanalysis found C, 57.81; H, 5.89; N, 3.13. $C_{21}H_{25}NS_3O_3$ requires C, 57.90; H, 5.79; N, 3.21.

Methyl-N-E(2(2-methylthio-2-methylsulphinyl)ethenyl-4-methylphenyl)-N-(4-toluenesulphonyl)-2-aminoacetate (63)

Prepared in the same way as 61 from 60 (2.0g, 5.05 mmol), methyl bromoacetate (0.92g, 6 mmol, 0.57 mls) and sodium hydride (0.225g, 5.6 mmol) in dry DMF (15 mls). The final reaction mixture was heated to 40°C for 5 minutes

before work up. 1.85g, 78.5%. IR (liq film) 2950, 2910, 1755, 1595, 1355, 1210 and 1160. ^{1}H NMR 2.32 (s, 3H), 2.40 (s, 3H), 2.45 (s, 3H), 2.72 (s, 3H), 3.64 (s, 3H), 4.38 (s, 2H), 6.84-7.78 (m, 7H) and 7.95 (s, 1H). Microanalysis found C, 54.17; H, 5.49; N, 3.05. $C_{21}H_{25}NS_3O_5$ requires C, 53.94; H, 5.40; N, 3.00.

Methyl-N-(2-methylthiocarbonylmethyl-4-methylphenyl)-N-(4-toluenesulphonyl)-2-aminoacetate (64)

The compound prepared above (0.15g) was dissolved in 1,2-dimethoxyethane (3 mls) with stirring and to this was added HCl (0.5 mls, 10 M). After 4 days at room temperature the reaction was poured into water and extracted several times with ethyl acetate. The combined organic phases were dried over $MgSO_4$ and the residue after evaporation subjected to column chromatography (ethyl acetate:petrol 1:5) to give 64 as a clear oil. 31.2 mg, 23.1%. IR (liq film) 2920, 1750, 1680, 1595, 1495, 1340, 1210 and 1160. ^{1}H NMR ($CDCl_3$) 2.30 (s, 6H), 2.44 (s, 3H), 3.63 (s, 3H), 4.04 (d, 2H, J = 17 Hz), 4.33 (s, 2H) and 6.63-7.57 (m, 7H). Microanalysis found C, 57.39; H, 5.94; N, 3.10. $C_{20}H_{23}NS_2O_3$ requires C, 56.99; H, 5.50; N, 3.32. Further elution with ethyl acetate:petrol 3:1 gave 63. 61 mg, 40.7%.

Methyl N-(2(1-chloro-2-bis(methylthio)ethenyl-4-methylphenyl)-N-(4-toluenesulphonyl)-2-aminoacetate (65)

The ketenedithioacetal S-oxide 63, prepared above, (1.86g, 4 mmol) was dissolved in dichloromethane (30 mls) and HCl (4 mls, 10 Mol) added with stirring. After 2 hours the solution was poured into saturated sodium bicarbonate

and the aqueous phase reextracted with more dichloromethane. The combined organic phases were dried over $MgSO_4$ and the solvent removed to give a clear oil which slowly solidified to give a white solid. 1.98g, 100%. mp 135-136°C. IR (KBr) 3000, 2960, 1760, 1355, 1210 and 1165. ^1H NMR ($CDCl_3$) 2.27 (s, 3H), 2.35 (s, 3H), 2.42 (s, 3H), 2.48 (s, 3H), 3.59 (s, 3H), 4.48 (d, 2H, J = 5 Hz) and 7.00-7.75 (m, 7H). Microanalysis found C, 52.03; H, 5.08; N, 2.93. $C_{21}H_{24}NS_3O_4Cl$ requires C, 51.89; H, 4.98; N, 2.88.

Methyl-4-nitrobenzoate

Into a large flask fitted with a reflux condensor was placed 4-nitrobenzoic acid (74g, 0.443 mol) and dry methanol (700 mls). To this was carefully added sulphuric acid (15 mls, 10 M) and the resultant solution refluxed for 6 hours. At the end of this time the majority of the solvent was removed under vacuum and the residue dissolved in ethyl acetate. The organic phase was washed several times with saturated sodium bicarbonate and dried over $MgSO_4$. After evaporation of the solvent the product was obtained. 81g, 100%. mp 96°C (lit 96°C[144]).

Methyl-4-hydroxyaminobenzoate (80)

To 150 mls of a 50% aqueous ethanol solution in a flask was added the ester prepared above (20g, 0.110 mol) and ammonium chloride (7g, 0.131 mol). To this was added zinc dust[145] (14.44g, 0.217 mol) and the temperature rises slightly, the mixture was heated to 50°C with stirring for 3 hours. At the end of this time the mixture was filtered on a hot buchner funnel, the filter cake washed with

dichloromethane and the solvent removed under vacuum. The residue was extracted several times with dichloromethane and the combined organic phases dried over $MgSO_4$. Removal of the solvent gave 80 as an orange solid. 15.14g, 82.0%. mp 117-119°C. IR (KBr) 3330, 3230, 1670, 1595, 1500 and 1280. ^1H NMR ($CDCl_3/CF_3CO_2H$) 3.98 (s, 3H) and 7.1-8.23 (m, 4H).

Methyl N-acetyl-N-hydroxy-4-aminobenzoate (81)

To a three necked flask fitted with a dropping funnel and magnetic stirring was charged ether (250 mls) and water (80 mls). This was cooled over ice and the ester 80 (12g, 71 mmol) and sodium bicarbonate (5.96g, 71 mmol) were introduced followed by acetyl chloride (6.67g, 85 mmol, 6.04 mls) over 30 minutes. After a further 1 hour the organic layer was removed and the aqueous layer extracted with more ether. The combined organic layers were dried over $MgSO_4$ and evaporated to give crude 81 used in the next step without purification. 11.76g, 79.5%. Further purification by column chromatography (ethyl acetate:petrol 1:2) gave pure 81. mp 108-110°C. IR (KBr) 3110, 2910, 2870, 1710, 1620, 1595, 1500 and 1270. ^1H NMR ($CDCl_3$) 2.10 (s, 3H), 3.90 (s, 3H) and 7.50-8.25 (m, 5H). Microanalysis found C,57.27; H, 5.29; N, 6.67. $C_{10}H_{11}NO_4$ requires C, 57.41; H, 5.30; N, 6.69.

Malonic acid mono ^{t}butyl ester (88)

A flame dried flask fitted with an inert atmosphere and magnetic stirring was charged with dry THF (700 mls) and diisopropylamine (60.71g, 0.60 mol, 84.1 mls). This

was cooled to -78°C and n-butyl lithium added (38.4g, 0.60 mol, 1.53 M solution, 392 mls) by syringe. The resultant mixture was stirred for 15 minutes at -78°C and t-butyl acetate (63.06g, 0.54 mol) in THF (50 mls) added. After stirring for an additional 20 minutes gaseous CO_2 (from solid CO_2 237g, 5.4 mol) was allowed to bubble through the solution. At the end of this time the THF was partially removed under vacuum and after the addition of ether (250 mls) the organic phase was washed several times with saturated sodium bicarbonate. The combined aqueous layers were acidified with HCl (2M) and extracted several times with ether, with the latter being dried over $MgSO_4$. Removal of the solvent under vacuum gave the product as a brown oil 52.03g, 59.8 %. IR (liq film) 3550-2400, 2960, 1720 and 1240. ^1H NMR (CCl_4) 1.48 (s, 9H), 3.11 (s, 2H) and 10.10 (broad s, 1H).

The Condensation Product (82)

A dry flask fitted with magnetic stirring and an inert atmosphere was charged with dry THF (150 mls). To this was added, with stirring 88 (8.31g, 50.7 mmol) and dicyclohexylcarbodiimide (11.48g, 55.7 mmol). After stirring for 5 minutes the hydroxamic acid 81 (10.6g, 50.7 mmol) in dry THF (50 mls) was added and stirring continued for a further 2 hours at room temperature. The final solution was filtered through Hyflo super cell and the residue after evaporation subjected to column chromatography (ethyl acetate:petrol 1:4) to give 82 as an oil which slowly crystallises to a solid. 11.00g, 61.8%. mp 48-50°C. IR (KBr) 2960, 1800, 1720, 1690, 1600 and 1280.

^{1}H NMR (CCl_4) 1.41 (s, 9H), 2.10 (s, 3H), 3.33 (s, 2H), 3.75 (s, 3H) and 7.19-7.88 (m, 4H). Microanalysis found C, 58.35; H, 6.31; N, 4.10. $C_{17}H_{21}NO_7$ requires C, 58.11; H, 6.03; N, 3.99.

tert-Butyl N-acetyl-2 amino-5-methoxycarbonyl phenylacetate (83)

The ester prepared above (11.00g, 31.3 mmol) was dissolved in toluene (150 mls) in a dry flask fitted with reflux condenser and inert atmosphere. Pyridine (2.47g, 31.3 mmol, 2.53 mls) was added by syringe and the final solution heated gently to reflux for 4 hours. At the end of this time the reaction mixture was poured into ethyl acetate/saturated sodium chloride and the organic phase dried over $MgSO_4$. The residue after evaporation was subjected to rapid column chromatography (ethyl acetate: petrol 1:2) to give 83. 5.35g, 55.6%. mp 75-77°C. IR (KBr) 3200, 2960, 2920, 1790, 1720, 1630, 1580, 1280 and 1150. ^{1}H NMR (CCl_4) 1.41 (s, 9H), 2.10 (s, 3H), 3.45 (s, 2H), 3.75 (s, 3H), 7.46-8.04 (m, 3H) and 8.85 (broad s, 1H). Microanalysis found C, 62.29; H, 7.03; N, 4.58. $C_{16}H_{21}NO_5$ requires C, 62.53; H, 6.89; N, 4.58.

Methyl N-acetyl-N-(2-t-butoxycarbonylmethyl-4-methoxycarbonylphenyl)-2-aminoacetate (84)

A flame dried flask fitted with magnetic stirring and an inert atmosphere was charged with dry THF (50 mls). The reaction was cooled over ice and diisopropylamine added (1.94g, 19.15 mmol, 2.69 mls) followed by n-butyl lithium (1.23g, 19.15 mmol, 1.54 M solution, 12.47 mls). After

15 minutes at 0°C the ester 83 prepared above (5.35g, 17.41 mmol) in THF (20 mls) was added and stirring continued for a further 15 minutes at the same temperature. Methyl bromoacetate (5.33g, 34.82 mmol, 3.30 mls) was introduced and the solution warmed to 40°C for 1 hour. The volume of solvent was reduced under vacuum and the residue poured into dichloromethane/saturated ammonium chloride. The organic phase was dried over $MgSO_4$ and the residue after evaporation subjected to column chromatography (ethyl acetate:petrol 3:2) to give 84. 3.70g, 56.1%. mp 101-102°C. IR (KBr) 2960, 1750, 1710, 1655, 1600, 1590 and 1210. ^1H NMR ($CDCl_3$) 1.38 (3, 9H), 1.78 (s, 3H), 3.52 (s, 2H), 3.64 (s, 3H), 3.82 (s, 3H), 3.52-4.75 (m, 2H) and 7.05-7.88 (m, 4H). Microanalysis found C, 60.26; H, 6.94; N, 3.71. $C_{19}H_{25}NO_7$ requires C, 60.15; H, 6.64; N, 3.69.

Methyl-N-acetyl N-(4-methoxycarbonyl-2-phenylthiocarbonyl methylphenyl)-2-aminoacetate (86)

The ester prepared above (3.65g) was stirred in trifluoroacetic acid (25 mls) at room temperature for 30 minutes. The majority of the solvent was removed and the residue subjected to rapid column chromatography (ethyl acetate:petrol 3:2) to give 85. 2.44g, 78.5%. IR (KBr) 3450-2800, 2940, 1715, 1630, 1600, 1490 and 1200. ^1H NMR 1.83 (s, 3H), 3.67 (s, 3H), 3.83 (s, 3H), 3.67-4.7 (m, 4H), 7.43-8.00 (m, 3H) and 8.93 (broad s, 1H). This was immediately added to a dry flask containing THF (30 mls) and dicyclohexylcarbodiimide (1.71g, 8.31 mmol). This was stirred for 5 minutes at room temperature and thiophenol

(0.83g, 7.55 mmol, 0.77 mls) added by syringe. After a further 2 hours the solution was filtered through Hyflo super cell and the residue after evaporation subjected to column chromatography (ethyl acetate:petrol 2:3) to give 86 as a clear oil 2.26g, 72.0%. IR (liq film) 3055, 2950, 2840, 1745, 1720, 1675, 1605 and 1200. ^{1}H NMR ($CDCl_3$) 1.77 (s, 3H), 3.60 (s, 3H), 3.70 (s, 3H), 3.99 (s, 2H), 3.60-4.80 (m, 2H) and 7.15-8.00 (m, 8H). Microanalysis found C, 60.69; H, 5.15; N, 3.43. $C_{21}H_{21}NSO_6$ requires C, 60.71; H, 5.09; N, 3.37.

Methyl-1-acetyl-6-methoxycarbonyl-3-oxo-1,2,3,4 tetrahydroquinolyl-2-carboxylate (92)

To a flame dried flask fitted with inert atmosphere and magnetic stirring was charged dry THF (50 mls) and diisopropylamine (0.433g, 4.28 mmol, 0.6 mls). The reaction mixture was cooled to -78°C and n-butyl lithium added (0.274g, 4.28 mmol, 1.54 M solution, 2.78 mls). After a further 15 minutes 92 (1.48g, 3.56 mmol) in THF (10 mls) was added and after 1 hour at -78°C the reaction was allowed to warm to room temperature and stirred for a further 1.5 hours. The solution was poured into ethyl acetate/HCl (2M) and the aqueous phase extracted with more ethyl acetate. The combined organic phases were dried over $MgSO_4$ and the residue after evaporation subjected to column chromatography (ethyl acetate:petrol 2:3) to give 92. 0.2156g, 23.1%. IR (liq film) 2940, 1740, 1710, 1655, 1625 and 1190. ^{1}H NMR ($CDCl_3$) 1.81 (s, 3H), 3.65 (s, 3H), 3.85 (s, 3H), 3.60-4.65 (series of m, 3H), 7.11-7.95 (m, 3H).

4(1,1-Dimethylethyl)dimethylsilyloxybutan-2-ol

To a solution of butane-1,3-diol (2g, 22.2 mmol) and imidazole (3.77g, 55.5 mmol) in dry DMF (1y mls) was added t-butyldimethylsilylchloride (3.68g, 24.4 mmol) and the resultant solution stirred at 37°C for 12 hours. The final mixture was poured into ethyl acetate and washed several times with saturated ammonium chloride. The organic phase was dried over $MgSO_4$ and the residue after evaporation subjected to column chromatography (ethyl acetate:petrol 1:4) to give the product. 2.65g, 58.1%. IR (liq film) 3400, 2955, 2880 and 1200. ^1H NMR (CCl_4) 0.83 (s, 9H), 1.05 (d, 2H, J = 5 Hz), 1.47 (q, 2H, J = 5 Hz), 2.55 (s, 1H) and 3.50-4.13 (series of m, 3H).

4(1,1-Dimethylethyl)dimethylsilyloxybutan-2-one (99)

To dichloromethane (50 mls) in a dry flask was added, with stirring, PCC (5.26g, 25 mmol) and anhydrous sodium acetate (0.41g, 5 mmol). After 5 minutes the alcohol prepared above (3.39g, 16.6 mmol) was added and the resultant solution stirred for 2 hours. Ether was added and the liquid decanted from solid, the residue was washed with more ether and the solvent subjected to rapid column chromatography to give, after removal of the solvent 99. 1.4g, 41%. IR (liq film) 2940, 2860, 1710 and 1260. ^1H NMR (CCl_4) 0.83 (s, 9H), 2.04 (s, 3H), 2.43 (t, 2H, J = 6 Hz) and 3.71 (t, 2H, J = 6 Hz).

The preparation of the ketenedithioacetal S-oxides 110b, 110c and 110d

These were prepared in an identical manner as

illustrated by the general procedure outlined below.

To a solution of the aldehyde 109 in THF (2 mls/g of 109) and 59 in a dry flask fitted with an inert atmosphere was added Triton B. The resultant solution was heated to reflux for 3-4 hours and cooled to room temperature. This was then poured into ethyl acetate/saturated ammonium chloride and the aqueous phase extracted with more ethyl acetate. The combined organic phases were dried over $MgSO_4$ and the residue after evaporation subjected to rapid column chromatography to give the products 110b-110d.

110b from 109b (1.566g, 14.8 mmol), 59 (1.25g, 10 mmol, 1.07 mls) and Triton B (1 ml) gives 110b, 1.64g, 77%. See ref. 77.

110c from 109c (3g, 16.2 mmol), 59 (1.358g, 10.9 mmol, 1.14 mls) and Triton B (2 ml) gives 110c. 2.04g, 63.9%. mp 33-35°C. IR (KBr) 3040, 2970, 2900, 1420 and 1055. ^1H NMR (CCl_4) 2.20 (s, 3H), 2.65 (s, 3H) and 6.90-7.70 (m, 5H). Microanalysis found C, 41.23; H, 3.82. $C_{10}H_{11}BrS_2O$ requires C, 41.24; H, 3.80 and 180 0.58g, 19.2%. IR (liq film) 3040, 2960, 2900, 1425 and 1020. ^1H NMR (CCl_4) 2.17 (2, 3H), 2.33 (s, 3H), 6.49 (s, 1H) and 6.70-7.56 (m, 4H).

110d from 109d (2g, 14.7 mmol), 59 (1.2g, 9.6 mmol, 1 ml) and Triton B (1 ml). 1.94g, 83.6%. IR (liq film) 3040, 2980, 2905, 1590, 1565, 1250, 1150 and 1055. ^1H NMR (CCl_4) 2.23 (s, 3H), 2.60 (s, 3H), 3.70 (s, 3H) and 6.50-7.40 (m, 5H). Microanalysis found C, 54.42; H, 5.92. $C_{11}H_{14}S_2O_2$ requires C, 54.51; H, 5.82.

The preparation of chloroketene dithioacetals 111a-111d

(for the preparation of the related compound 65 see earlier).

General procedure

To a solution of 111 (1g) in dry dichloromethane (25 mls) was added, with vigorous stirring, HCl (2.5 mls, 10 M). After 2-3 hours the reaction was neutralised with saturated sodium bicarbonate and the organic layer dried over $MgSO_4$. Removal of the solvent gave the pure compound in the case of 111a or 111b or after column chromatography in the case of 111c or 111d.

111a from 61 (0.53g, 1.22 mmol). 0.55g, 100%. IR (liq film) 3020, 2965, 2940, 1630, 1585, 1345 and 1160. ^1H NMR ($CDCl_3$) 2.33 (s, 3H), 2.38 (s, 3H), 2.45 (s, 3H), 2.50 (s, 3H), 4.05 (broad s, 2H), 5.00 (m, 2H), 5.54-6.09 (m, 1H) and 6.80-7.80 (m, 7H). Microanalysis found C, 55.50; H, 5.37; N, 3.08. $C_{21}H_{24}NS_3O_2Cl$ requires C, 55.55; H, 5.33; N, 3.08.

111b from 110b (1.03g, 4.71 mmol). 1.12g, 100%. IR (liq film) 1420, 1410, 1300, 1200 and 1065. ^1H NMR ($CDCl_3$) 2.20 (s, 3H), 2.46 (s, 3H) and 7.38 (s, 5H).

111c from 110c (0.73g, 2.51 mmol). 0.64g, 82.3%. mp 43-45°C. IR (KBr) 3040, 2970, 2900, 1450, 1410 and 1020. ^1H NMR ($CDCl_3$) 2.20 (s, 3H), 2.45 (s, 3H) and 6.95-7.55 (m, 4H). Microanalysis found C, 38.88; H, 3.36. $C_{10}H_{10}BrS_2Cl$ requires C, 38.79; H, 3.26.

111d from 111c (0.95g, 4.13 mmol). 0.80g, 78.6%. IR (liq film) 3040, 2975, 2900, 1585, 1415 and 1255. ^1H NMR (CCl_4) 2.05 (s, 3H), 2.32 (s, 3H), 3.63 (s, 3H) and 6.40-7.10 (m, 4H).

Microanalysis found C, 50.66; H, 5.03. $C_{11}H_{13}S_2OCl$ requires C, 50.66; H, 5.02.

S-Methyl α-methylthiophenylthioacetate (115). S-Methyl α-chlorophenylthioacetate (116) and S-Methyl phenylthio acetate (117)

To a flask fitted with magnetic stirring was charged 111b (0.181g, 0.78 mmol) and trifluoroacetic acid (0.89g, 7.8 mmol). After 20 minutes water (0.14g, 7.8 mmol) was added and stirring continued for a further 6 hours. At the end of this time the reaction mixture was poured into ethyl acetate/saturated sodium bicarbonate and the aqueous phase extracted with more ethyl acetate. The combined organic phases were dried over $MgSO_4$ and the residue after evaporation subjected to column chromatography (ether: petrol 1:50) to give 115 and a mixture of 116 and 117 (analysed spectroscopically).

115 31 mg, 18.7%. mp 60-62°C (lit 63-65.3°C)[108]. IR (KBr) 3020, 2940 and 1680. ^{1}H NMR (CCl_4) 2.23 (s, 3H), 2.30 (s, 3H), 4.61 (s, 1H) and 7.13-7.46 (s, 5H).

116 44.2 mg, 28.3%. IR (liq film) 3025, 2945 and 1680. ^{1}H NMR (CCl_4) 2.25 (s, 3H), 5.23 (s, 1H) and 7.04-7.44 (m, 5H).

117 36.8 mg, 28.3%. IR (liq film) 3020, 2940 and 1680. ^{1}H NMR (CCl_4) 2.23 (s, 3H), 3.68 (s, 2H) and 7.04-7.44 (m, 5H).

The compounds 111c and 111d were treated in the same way and the results are presented here. Thus from 111c (0.22g, 0.72 mmol), trifluoroacetic acid (0.83g, 7.2 mmol)

and water (0.13 mls, 7.2 mmol) was obtained a mixture of the following (analysed by NMR spectroscopy).

S-Methyl-(2-bromo)phenylthioacetate 57.4 mg, 33%. ^{1}H NMR (CCl_4) $2BrC_6H_4\underline{CH_2}COSCH_3$ 3.81 (s, 2H).

S-Methyl α-chloro-(2-bromo)phenylthioacetate 59.7 mg, 3%. ^{1}H NMR (CCl_4) $2BrC_6H_4\underline{CH}ClCOSCH_3$ 5.71 (s, 1H).

S-Methyl α-methylthio-(2-bromo)phenylthioacetate 24.7 mg, 12%. ^{1}H NMR (CCl_4) $2BrC_6H_4\underline{CH}(SCH_3)COSCH_3$ 4.84 (s, 1H).

From 111d (0.52g, 1.99 mmol), trifluoroacetic acid (1.70g, 14.95 mmol) and water (0.36g, 19.9 mmol) was obtained S-methyl-α-methylthio-(3-methoxy)phenylthioacetate and a mixture of the corresponding ∝ chloro thiol ester and thiol ester (analysed by NMR spectroscopy).

S-Methyl α-methylthio-(3-methoxy)phenylthioacetate 0.135g, 28%. IR (liq film) 3010, 2930, 2845 and 1680. ^{1}H NMR (CCl_4) 2.01 (s, 3H), 2.23 (s, 3H), 3.68 (s, 3H), 4.39 (s, 1H) and 6.31-7.15 (m, 4H).

S-Methyl α-chloro-(3-methoxy)phenylthioacetate 0.129g, 28%. IR (liq film) 3015, 2940, 2845 and 1685. ^{1}H NMR (CCl_4) 2.25 (s, 3H), 3.68 (s, 3H), 5.15 (s, 1H) and 6.41-7.53 (m, 4H).

S-Methyl-(3-methoxy)phenylthioacetate (133). 0.075g, 19.2%. IR (liq film) 3015, 2940, 2845 and 1685. ^{1}H NMR (CCl_4) 2.19 (s, 3H), 3.63 (s, 2H), 3.68 (s, 3H) and 6.41-7.53 (m, 4H).

S-Methyl phenylthioacetate (117) (prepared for comparison with 117 formed in the mixture above).

To a dry flask fitted with magnetic stirring and an inert atmosphere was charged dry ether (10 mls), phenylacetic acid (1g, 7.34 mmol) and dicyclohexyl carbodiimide

(1.53g, 7.42 mmol). To this was added a solution of methanethiol[147] in dry ether and the reaction stirred for 1 hour. The reaction mixture was filtered through Hyflo super cell and the solvent removed. The residue was subjected to column chromatography (ethyl acetate:petrol 1:20) to give 117 identical by ^{1}H NMR spectroscopy to that prepared above.

S-Methyl α-chlorophenylthioacetate (116) (prepared for comparison with 116 formed in the mixture above).

Thionyl chloride (21.89g, 0.184 mol) was added to CCl_4 (100 mls) with stirring and the resultant solution colled to 5°C. Dry DMF (13.45g, 0.184 mol) was added over 20 minutes so that the temperature did not rise to above 7°C. This was stirred for an additional 30 minutes over ice and mandelic acid (10g, 0.066 mol) added so that the temperature did not rise to above 7°C. Stirring was continued for a further 1 hour over ice and the solution allowed to warm to room temperature during 2 hours. The final reaction mixture was poured into ice (100g), separated, washed with icewater, dried over $MgSO_4$ and distilled to give α-chlorophenylacetyl chloride. 7.40g, 59.5%. 85-88°C/ 2 mmHg. IR (liq film) 3060, 3025, 2960, 1800 and 720. ^{1}H NMR (CCl_4) 5.69 (s, 1H) and 7.33-7.60 (m, 5H). The acid chloride prepared above (5g, 27 mmol) was added dropwise[146] over 1 hour to a solution of potassium hydroxide (5.95g, 0.106 mol) in methanol (100 mls). The solution was stirred for a further 30 minutes, cooled over ice and 100 mls of water added. This was then acidified to pH=1 with 2M HCl

and extracted with ether. The organic phase was dried over $MgSO_4$ and evaporated to give the chloro acid. 1g (5.86 mmol) of this was dissolved in dry ether in a dry flask fitted with magnetic stirring and inert atmosphere. To it was added DCC (1.21g, 5.86 mmol) and a solution of methanethiol in ether and the reaction mixture stirred for 1 hour at room temperature. This was then filtered through Hyflo super cell and the residue after evaporation subjected to column chromatography (ethyl acetate:petrol 1:20) to give 116 having identical spectral and chromatographic products as that obtained earlier.

3-Chloro-5-methyl-2-methylthio-1 (4-toluenesulphonyl) indole (119) and 5-Methyl-2-methylthio-1(4-toluenesulphonyl) indole (120)

To a flask fitted with magnetic stirring was charged dry CH_2Cl_2 (20 mls) and 60 (1.5g, 3.80 mmol). HCl (1.5 mls, 10 M) was added and the solution stirred for 1.5 hours. At the end of this time the solution was neutralised with saturated sodium bicarbonate and the aqueous phase extracted with more CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and subjected to column chromatography (ethyl acetate:petrol 1:25) to give (in order of elution) 119. 0.534g, 38.4%. mp 118°C. IR (KBr) 3020, 2920, 1590, 1365, 1170 and 1145. ^1H NMR ($CDCl_3$) 2.34 (s, 3H), 2.40 (s, 3H), 2.45 (s, 3H), 6.90-7.25 (m, 4H), 7.55 (d, 2H, J = 8 Hz) and 8.05 (d, 1H, J = 8 Hz). UV (EtOH) λmax 262, 274, 284 and 288 nm. Microanalysis found C, 55.82; H, 4.34; N, 3.83. $C_{17}H_{16}ClNS_2O_2$ requires C, 55.80; H, 4.41; N, 3.83 and 120. 0.451g, 35.8%. IR (liq film)

3030, 2915, 1590, 1365 and 1175. ^{1}H NMR ($CDCl_3$) 2.30 (s, 3H), 2.37 (s, 3H), 2.48 (s, 3H), 6.26 (s, 1H), 6.91-7.27 (m, 4H), 7.80 (d, 2H, J = 8 Hz) and 8.03 (d, 1H, J = 8 Hz). UV (EtOH) λmax 263, 269 and 290 nm. Microanalysis found C, 61.43; H, 5.25; N, 4.12. $C_{17}H_{17}NS_2O_2$ requires C, 61.60; H, 5.17; N, 4.23.

Chloro-N-(4-methylphenyl)acetamide (122)

To a dry flask fitted with magnetic stirring was charged dry benzene (50 mls), dry pyridine (3.68g, 46.6 mmol) and 4-methylaniline (5g, 46.6 mmol). The mixture was cooled over ice and chloroacetyl chloride (5.26g, 46.6 mmol) in dry benzene (20 mls) added with cooling. The mixture was allowed to stand overnight. At the end of this time ethyl acetate was added and the organic phase washed once with HCl (2M), brine and dried over $MgSO_4$. Evaporation gave the product as a white solid. 6.44g, 75.2%. ^{1}H NMR ($CDCl_3$) 2.26 (s, 3H), 3.96 (s, 2H), 6.71-7.20 (m, 4H) and 7.90 (broad s, 1H).

5-Methyloxindole (123)

A mixture of aluminium trichloride (8.93g, 67 mmol) and 122 (5.27g, 28.7 mmol) were stirred with a glass rod for 1 minute. The resulting homogeneous mixture was placed in a flask fitted with drying tube and heated to 50°C for 10 minutes and subsequently to 200°C for 1 hour. The resultant black gum was allowed to cool and to it was added ice (25g) and ethyl acetate. The aqueous phase was extracted with more ethyl acetate and the combined extracts dried over $MgSO_4$. The residue after evaporation was subjected to

rapid column chromatography (ethyl acetate:petrol 2:3) to give 123. 2.66g, 63.0%. IR (KBr) 2920, 1700, 1620, 1605, 1360 and 1170. ^{1}H NMR ($CDCl_3$) 2.27 (2s, 3H), 3.46 (2s, 2H), 6.51-7.24 (m, 4H) and 8.71 (broad s, 1H).

The conversion of 120 into 119 by SO_2Cl_2

To a solution of 120 (92 mg, 0.28 mmol) in dry CH_2Cl_2 (1 ml) under nitrogen was added two drops of sulphuryl chloride. After stirring for 25 minutes the reaction mixture was poured into ethyl acetate/water and the organic phase was dried with $MgSO_4$. The residue after evaporation was subjected to column chromatography (ethyl acetate:petrol 1:25) to give 119 having identical TLC and ^{1}H NMR characteristics as that prepared earlier.

5-Methyl-2-methylthio-1(4-toluenesulphonyl)indole (120)

A stream of H_2S was passed through 15 mls of dry CH_2Cl_2 for 20 minutes with stirring. To 7.5 mls of this solution was added successively, with stirring 60 (0.25g, 0.63 mmol) and HCl (15 drops, 10 M). After stirring for 1 hour at room temperature the reaction was treated as for the preparation of 119/120 to give 119 0.148g, 70.5% having identical TLC and NMR characteristics as that prepared earlier.

S-Methyl-(3-methoxy)phenylthioacetate (133)

A stream of H_2S was passed through 25 mls of dry CH_2Cl_2 for 20 minutes with stirring. To 15 mls of this solution was added successively 110d (0.501g, 2.07 mmol) and HCl (15 drops, 10 M). After stirring for 1 hour at room

temperature the reaction mixture was treated as for compounds 111a-111d to give (after column chromatography, ethyl acetate:petrol 1:25 then 3:2) in order of elution. 133 0.197g, 58% (based on recovered 110d) having identical spectral characteristics to that prepared earlier. 111d 0.075g, 13.9% and 110d 0.075g.

6-Methoxycarbonyl-7-nitromethyl-1,4-dioxaspiro[4.4]nonane (160)

A dry flask fitted with magnetic stirring and inert atmosphere was charged with 159 (15g, 81.4 mmol) and nitromethane (22 mls). To this was added tetramethylguanidine (2 mls) and the reaction mixture stirred at room temperature for 12 hours. The reaction mixture was acidified to pH=6 with HCl (2M) and extracted with ether. The organic phase was dried over $MgSO_4$ and the residue after evaporation subjected to column chromatography (ethyl acetate:petrol 1:9) to give the product as a mixture of isomers (1:1) 18.39g, 92.1%. Least polar isomer. IR (liq film) 2945, 2890, 1725 and 1535. ^1H NMR ($CDCl_3$) 1.87-2.51 (series of m, 4H), 2.72-3.06 (m, 2H), 3.65 (s, 3H), 3.85 (s, 4H) and 4.26-4.63 (m, 2H). Most polar isomer. IR (liq film) 2940, 2880, 1730 and 1535. ^1H NMR ($CDCl_3$) 1.29-2.42 (series of m, 4H), 2.59 (d, 1H, J = 7 Hz), 2.73-3.45 (m, 1H), 3.61 (s, 3H), 3.78 (s, 4H) and 4.31 (d, 2H, J = 7 Hz). Microanalysis (isomeric mixture) found C, 49.14; H, 6.37; N, 5.55. $C_{10}H_{15}NO_6$ requires C, 48.97; H, 6.16; N, 5.71.

7-Formyl-6-methoxycarbonyl-1,4-dioxaspiro[4.4]nonane (161)

The nitro compound 160 (1g, 4.08 mmol) was dissolved in dry methanol (4 mls) and added to a dry flask containing a solution of sodium methoxide (from sodium 94 mg, 4.08 mmol) in dry methanol (4 mls) under an inert atmosphere. After stirring for 10 minutes separate solutions of titanium trichloride (15% w/v, 2.52g, 16.32 mmol, 16.8 mls) and ammonium acetate (3.77g, 49 mmol in water 12.5 mls) were prepared and combined under nitrogen. The mixture was added to the flask and the resultant solution stirred for 2 hours at room temperature. This was then poured into ether and the aqueous phase extracted with more ether. The combined organic layers were washed with saturated sodium bicarbonate, brine and dried over Na_2SO_4. The residue after evaporation was subjected to rapid column chromatography (ethyl acetate:petrol 1:2) to give the product as a pale yellow oil 0.56g, 64.2%. IR (liq film) 2940, 2880, 1720 and 1195. ^1H NMR ($CDCl_3$) 1.37-2.22 (series of m, 4H). 2.60-3.38 (series of m, 2H), 3.67 (s, 3H), 3.88 (s, 4H) and 9.45 (broad s, 1H).

Methyl-2(1,3-dioxolan-2-yl)-5-oxocyclopentane carboxylate (163)

A mixture of trifluoroacetic acid (2 mls) and water (1 ml) was added to 161 (0.56g) and the resultant mixture stirred for 3 hours. Some of the solvent was removed under vacuum and the residue poured into ether/ brine. The organic phase was dried over $MgSO_4$ and subjected to column chromatography (ethyl acetate:petrol 1:3) to give a clear oil 0.256g, 45.7 % IR (liq film) 2940, 2890 and 1720.

^{1}H NMR ($CDCl_3$) 1.63-2.59 (series of m, 4H), 2.82-3.36 (series of m, 2H), 3.76 (s, 3H), 4.91 (d, 4H, J = 2 Hz) and 4.98 (d, 1H, J = 3 Hz).

Methyl-2-nitromethyl-5-oxocyclopentane carboxylate (167)

Prepared in the same way as 163 from 160 (9g, 44.7 mmol), trifluoroacetic acid (24 mls) and water (12 mls) to give a red oil which slowly crystallises to a solid 6.51g, 88.2%. Recrystallisation from ether gave a white solid. mp 50-52°C. IR (KBr) 2970, 2920, 1730, 1755, 1565 and 1225. ^{1}H NMR ($CDCl_3$) 1.34-3.36 (series of m, 6H), 3.65 (s, 3H) and 4.38 (d, 2H, J = 6 Hz). Microanalysis found C, 47.82; H, 5.53; N, 6.95. $C_8H_{11}NO_5$ requires C, 47.76; H, 5.51; N, 6.96.

Methyl-2-formyl-5-oxocyclopentanecarboxylate (162)

Prepared in the same way as 161 from 167 (4.73g, 23.5 mmol), sodium (0.6g, 26 mmol) in methanol (47 mls) and $TiCl_3$ (95 mls, 15% w/v, 92.4 mmol) with NH_4OAc (21.62g, 281 mmol, in water 70 mls). The final reaction mixture was stirred for 2 hours, poured into ether and the aqueous phase extracted with more ether. The combined extracts were dried over $MgSO_4$ and the residue after evaporation subjected to column chromatography (ethyl acetate:petrol 1:3) to give the product as a pale oil. 1.38g, 35%. IR (liq film) 2955, 1755 and 1720. ^{1}H NMR 1.55-3.61 (series of m, 6H), 3.69 (s, 3H) and 9.72 (s, 1H).

1-Methoxycarbonyl-7-phenylthiobicyclo[3.3.0]oct-6-en-2-one (152)

A flame dried flask fitted with an inert atmosphere and magnetic stirring was charged with sodium hydride (0.32g, 7.96 mmol). This was washed once with petrol and the solvent removed. The tricarbonyl 162 (1.23g, 7.24 mmol) in THF (30 mls) was added and the resultant solution stirred at room temperature for 15 minutes. To this was added the phosphonium salt 1d (4.17g, 7.96 mmol) and after a further 15 minutes at room temperature the reaction mixture was heated to reflux for 2 hours. The solution was allowed to cool to room temperature and poured into ethyl acetate/saturated ammonium chloride. The aqueous phase was extracted with more ethyl acetate and the combined organic solutions dried over $MgSO_4$. The residue after evaporation was subjected to column chromatography (ether: petrol 2:3) to give the product as a yellow oil 1.21g, 59.6%. IR (liq film) 3040, 2935, 1745, 1725 and 1245. ^1H NMR ($CDCl_3$) 1.78-3.41 (series of m, 7H), 3.70 (s, 3H), 5.31 (broad s, 1H) and 7.35 (broad s, 5H). Microanalysis found C, 66.55; H, 5.76. $C_{16}H_{16}SO_3$ requires C, 66.64; H, 5.59.

Methyl-3-(2-methoxycarbonyl-4-phenylthiocyclopent-4-enyl)propionate (169)

A flame dried flask fitted with an inert atmosphere and magnetic stirring was charged with dry methanol (1 ml) and sodium (8.9 mg, 0.39 mmol). After stirring for 5 minutes 152 (97 mg, 0.34 mmol) was added as a solution in methanol (1 ml) and the reaction mixture heated to reflux

for 3 hours. At the end of this time the solution was cooled and poured into ethyl acetate/HCl (2M). The aqueous phase was extracted with more ethyl acetate and the combined organic solutions dried over $MgSO_4$. The residue after evaporation was subjected to column chromatography (ethyl acetate:petrol 1:9) to give a clear oil. 74 mg, 67%. IR (liq film) 3050, 2950, 2860, 1745, 1655, 1610 and 1235. ^1H NMR ($CDCl_3$) 1.49-2.99 (series of m, 8H), 3.63 (s, 3H), 3.65 (s, 3H), 5.25 (broad s, 1H) and 7.19 (broad s, 5H).

7-Phenylthiobicyclo[3.3.0]oct-6-en-2-one (170)

A dry flask fitted with inert atmosphere and magnetic stirring was charged with finely powdered sodium cyanide (0.432g, 8.83 mmol) and HMPA (25 mls). The ketoester (1.21g, 4.2 mmol) 152 in a small volume of the same solvemt was added and the reaction mixture stirred at 75°C for 1.5 hours. After cooling the solution was poured into HCl (2M) and extracted several times with carbon tetrachloride. The combined extracts were washed twice with NaOH (2M) and dried over $MgSO_4$. The residue after evaporation was subjected to column chromatography (ethyl acetate:petrol 1:9) to give an oil. 0.566g, 59.1%. IR (liq film) 3050, 2920, 1730 and 745. ^1H NMR (CCl_4) 1.74-2.68 (series of m, 8H), 5.24 (broad s, 1H) and 7.20 (s, 5H).

3-Methoxycarbonyl-7-phenylthiobicyclo[3.3.0]oct-6-en-2-one (154)

A dry flask fitted with inert atmosphere and magnetic stirring was charged with sodium hydride (0.16g, 3.93 mmol). This was washed once with petrol and the solvent

removed. To this was then added dry dioxan (3 mls) and dry dimethyl carbonate (1.06g, 11.8 mmol, 0.99 mls). The ketone 170 (0.452g, 1.96 mmol) dissolved in dry dioxan (4 mls) was added and stirring continued at 50°C whilst the reaction was followed by TLC. The residue was poured into ethyl acetate/HCl (2M) and the aqueous phase extracted with more solvent. The combined organic phases were dried over $MgSO_4$ and the residue after evaporation subjected to column chromatography (ether:petrol 1:4) to give a yellow oil. 0.336g, 59.4%. IR (liq film) 3040, 2900, 2840, 1740, 1715, 1650, 1610 and 1235. ^1H NMR ($CDCl_3$) 1.65-2.82 (series of m, 7H), 3.55-3.60 (2s, 3H, 1:1), 5.30 (broad s, 1H) and 7.18 (s, 5H). Microanalysis found C, 66.78; H, 5.70. $C_{16}H_{16}O_3S$ requires C, 66.64; H, 5.70.

3-Methoxycarbonyl-7-phenylthiobicyclo[3.3.0]oct-6-en-endo-2-ol (171)

The ketone prepared above (258 mg) was dissolved in methanol and treated with a solution of sodium borohydride in methanol. The final reaction mixture was poured into ethyl acetate/water and the aqueous phase extracted several times with more solvent. The combined organic phases were dried over $MgSO_4$ and the residue after evaporation subjected to column chromatography (ethyl acetate:petrol 1:2) to give as the major product 171. 0.195g, 61.2%. IR (liq film) 3450, 3030, 2910, 1715 and 1190. ^1H NMR 1.54-3.23 (series of m, 8H), 3.60 (s, 3H), 4.02-4.30 (m, 1H), 5.20 (d, 1H, J = 2 Hz) and 6.95-7.32 (m, 5H).

3-Methoxycarbonyl-7-phenylthiobicyclo[3.3.0]octa-2,6-diene (155)

A dry flask was charged with the alcohol 171 (0.15g, 0.52 mmol), dry triethylamine (0.157g, 1.55 mmol, 0.22 mls) and CH_2Cl_2 (6 mls) and the mixture cooled over ice with stirring. To this was added dry methanesulphonyl chloride (0.177g, 1.55 mmol, 0.12 mls) and the resultant mixture stirred at RT for 2 hours. This was poured into saturated sodium bicarbonate and the organic layer dried over $MgSO_4$. The residue after evaporation was dissolved in more CH_2Cl_2 (4 mls) and treated with DBU (0.236g, 1.55 mls, 0.232 mls). After 3 hours at room temperature the reaction mixture was poured into CH_2Cl_2/brine and the organic phase dried over $MgSO_4$. The residue after evaporation was subjected to column chromatography (ethyl acetate:petrol 1:9) to give a clear oil 90 mg, 63.8%.
IR (liq film) 3035, 2900, 2830, 1700, 1620 and 1260.
^1H NMR ($CDCl_3$) 2.09-3.97 (series of m, 6H), 3.63 (s, 3H), 5.33 (broad s, 1H), 6.40 (broad s, 1H) and 7.21 (s, 5H).

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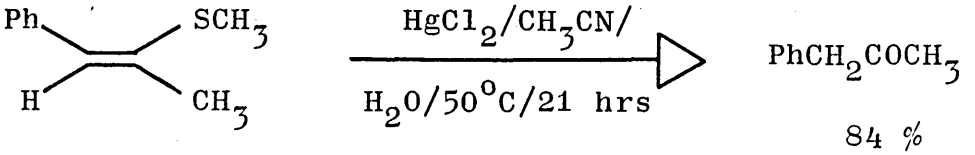

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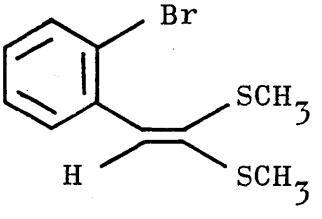
102. Compounds 63 and 61 were prepared in a slightly different way to that represented in Scheme 77. See experimental section.

103. Yields given are those obtained in 2 steps from 37 and 51.

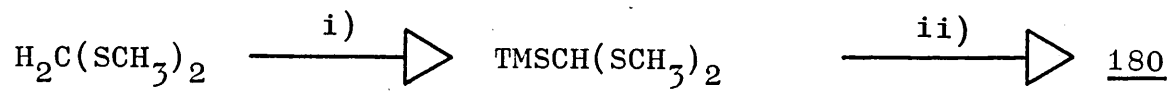
104. ref. 76 and 77.

105. The low yield is explained by contamination of the desired product with the ketenedithioacetal 180.

180



This was confirmed by tlc analysis against the genuine compound prepared as shown below.



i) $^nBuLi/TMSCL/THF$ ii) $^nBuLi/THF, 2\text{-}BrC_6H_4CHO$

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RESEARCH STUDY PROGRAMME

As part of this project the author has attended the following lecture courses at Sheffield University.

Organoiron Complexes in Organic Chemistry

Biosynthesis

Ring Closure Reactions

The Synthesis of Vitamin B_{12}

Organic synthesis

The author has attended appropriate colloquia at the sponsoring and other establishments given by internal and external speakers and presented a research colloquia on this work at the sponsoring establishment.

The author has attended symposia on:-

Stereochemistry (Sheffield 1982, 1983).

Organic Chemistry (Nottingham 1982,
Leicester 1983 and London 1985).

A Novel Synthesis of the Indole Ring System

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Department of Chemistry, Sheffield City Polytechnic, Pond Street, Sheffield, S1 1WB, U.K.

Intramolecular acid catalysed cyclisation of the ketene dithioacetal *S*-oxide (**3**) from the *o*-toluenesulphonamidobenzaldehyde (**2**) leads to two indole derivatives (**5**) and (**6**), the structure (**6**) being confirmed by *X*-ray crystallography.

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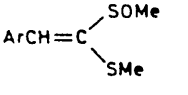
Intramolecular acid catalysed cyclisation of the ketene dithioacetal *S*-oxide (**3**) from the *o*-toluenesulphonamidobenzaldehyde (**2**) leads to two indole derivatives (**5**) and (**6**), the structure (**6**) being confirmed by *X*-ray crystallography.

One of the established methods for the conversion of aromatic aldehydes into the corresponding arylacetic acids is by acid treatment of the derived ketene dithioacetal *S*-oxide (**1**).[1] In the course of a synthetic study we needed to carry out such a transformation on the aldehyde (**2**). Reaction between (**2**) and $MeSCH_2SOMe$, catalysed by Triton B,[1] gave (**3**) as desired (58%, m.p. 160—162 °C) but treatment of (**3**) with aqueous acid under a range of conditions failed to yield the desired acid (**4**). However, when (**3**) was stirred in dichloromethane containing 10 M HCl, two major products were isolated, to which we assign structures (**5**) [36%; oil; λ_{max} (EtOH) 263, 269, and 290 nm; δ_H ($CDCl_3$) 2.30 (3H, s), 2.37 (3H, s), 2.48



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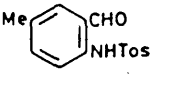

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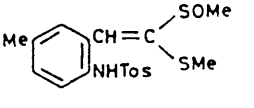

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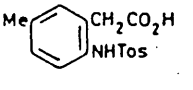

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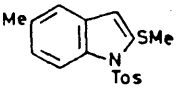

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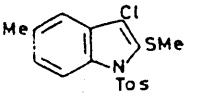


(6)

Tos = *p*-$MeC_6H_4SO_2$-

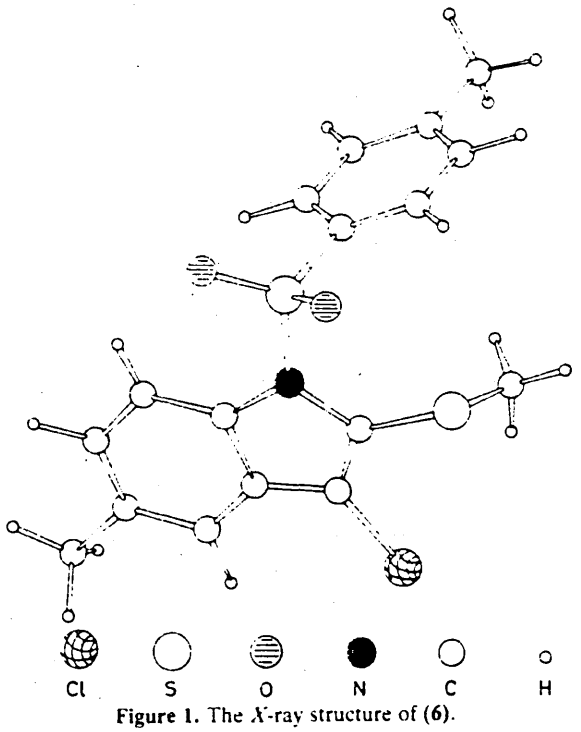
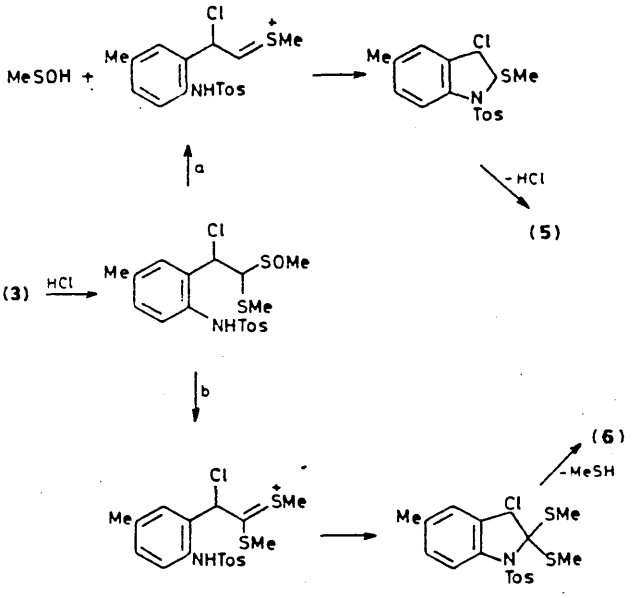


Figure 1. The *X*-ray structure of (**6**).

(3H, s), 6.26 (1H, s), 6.9—7.3 (4H, m), 7.8 (2H, d, *J* 8 Hz), and 8.03 (1H, d, *J* 8 Hz)] and (**6**) [38%: m.p. 118 °C; $\lambda_{max.}$ (EtOH) 262, 274, 284, and 288 nm; δ_H ($CDCl_3$) 2.34 (3H, s), 2.40 (3H, s), 2.45 (3H, s), 6.9—7.2 (4H, m,), 7.6 (2H, d, *J* 8 Hz), and 8.05 (1H, d, *J* 8 Hz)]. The structure (**6**) was confirmed by *X*-ray analysis (Figure 1).† Treatment of (**5**) with sulphuryl chloride in dichloromethane gave (**6**) (75%) thus confirming the structure of (**5**).

The two products are thought to arise by initial addition of HCl to the highly electrophilic double bond of the ketene dithioacetal *S*-oxide. The adduct may then react (Scheme 1) by loss of methanesulphenic acid (path a) or by Pummerer rearrangement (path b). Related Pummerer reactions have been described.[2,3]



Scheme 1

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† *Crystal data:* $C_{17}H_{16}ClNO_2S_2$, *M* = 365.9, monoclinic, space group $P2_1/c$, *a* = 8.732(2), *b* = 19.392(6), *c* = 10.186(3) Å, β = 96.19(6)°, *U* = 1708.4 Å^3, *Z* = 4, D_c = 1.42 g cm^{-3}, *F*(000) = 760 electrons, graphite-monochromated Mo-K_α *X*-radiation, λ = 0.71069 Å, μ(Mo-K_α) = 4.2 cm^{-1}; *R* = 0.040 for 1460 independent reflections having $I/\sigma(I) > 3.0$ collected on a Stöe Stadi 2 two-circle diffractometer. The structure was solved by direct and Fourier methods and refined by least squares calculations using SHELX.[4] The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

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