SYNTHETIC TRANSFORMATIONS OF CYCLOADDUCTS OF ETHYL THIOXOACETATE

THESIS SUBMITTED FOR THE DEGREE

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SUMMARY

The cycloadduct of anthracene and the labile thioaldehyde, ethyl thioxoacetate, has been converted into the α-lithio derivative with lithium diisopropylamide (LDA). Subsequent treatment with, separately, methyl iodide, ethyl iodide, allyl bromide and benzyl bromide gave the corresponding 12-'alkyl' derivatives. Each derivative, when heated in toluene at 111 °C, dissociated to liberate anthracene and a thioketone, which was trapped *in situ* with 2,3-dimethylbuta-1,3-diene to afford the corresponding 2-substituted dihydrothiine in good yield. The same set of products was obtained directly by α-alkylation of the parent dihydrothiine. Similarly, the 12-methyl anthracene adduct gave, with cyclopentadiene and cyclohexadiene, the stereoisomeric cycloadducts of the cyclic dienes and ethyl 2-thioxopropionate. When treated with LDA and methyl iodide, the thioaldehyde adducts of cyclopentadiene and cyclohexadiene underwent rearrangement and *S*-methylation, rather than *C*-methylation, and afforded cyclopropanecarboxylates. The methyl and ethyl sulphonium salts of the parent dihydrothiine rearranged similarly to give the corresponding cyclopropanecarboxylates. Thermolysis of the *S*-methyl cyclopropanecarboxylate afforded the corresponding

cyclopentene derivative. The cyclopropanecarboxylic acid derived from the rearrangement and *S*-methylation of the cyclohexadiene thioaldehyde cycloadduct, was found to rearrange slowly in the crystalline state to give the epimeric γ-lactones.

In the second part of this work thiashikimic acid, a sulphur-analogue of shikimic acid, has been synthesised. Ethyl thioxoacetate reacted with 1,4-diacetoxybuta-1,3-diene to give a pair of epimeric Diels-Alder adducts. Each epimer was separately converted with osmium tetroxide into the corresponding diol. The configurations of both diols were confirmed by X-ray crystal structure analyses. The 2,3-*cis* diol underwent *trans* elimination of acetic acid in hot pyridine to give the 6-thiashikimic acid derivative. Extensive decomposition of this derivative occurred under even very mild alkaline condition. However, this derivative was hydrolysed with an esterase enzyme to afford thiashikimic acid.

I dedicate this work
to
my late
Father

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REFERENCE

CHAPTER 1

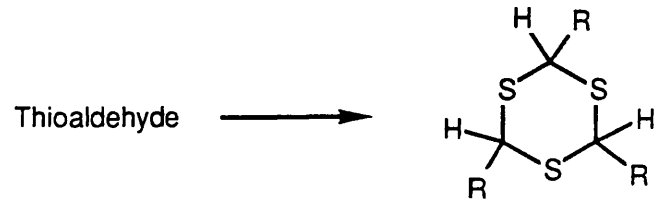
REVIEW

1.1 Introduction

Thiocarbonyl compounds contain the C=S linkage, in which bivalent sulphur is π bonded to carbon by overlap of a carbon 2p-orbital and a sulphur 3p-orbital. Owing to the greater size of the 3p-orbital, this overlap is less efficient than the 2p-2p overlap of the carbonyl group. For this reason it is understandable that thiocarbonyl compounds in general are more reactive, less stable and more influenced by the stabilising effect of neighbouring atoms or groups, than are their oxygen analogues. Furthermore, although thiocarbonyl compounds in many respects behave in their reactions like the corresponding carbonyl compounds, the comparatively 'softer character' and lower electronegativity of sulphur, as well as the higher polarisability of the C=S bond, give rise to important differences in reactivity.

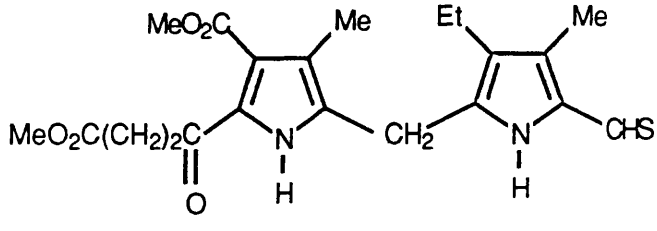
1.2 Generation and Diels-Alder Cycloaddition Reactions of Thioaldehydes

Simple thioaldehydes are extremely unstable compounds. Early attempts to prepare thioaldehydes always ended in the formation of polymers or trimers, the 1,3,5-trithianes **1**.[1-4] Developments in laboratory techniques and in the understanding



1

of the nature of the thiocarbonyl bonding [5] allowed the synthesis of a large variety of simple, monomeric aliphatic and alicyclic thioketones, although these too often polymerise easily. But simple monomeric thioaldehydes were still unknown until recently, though their transient existence and *in situ* participation in many reactions were incontrovertible. [6-10] However, some stable thioaldehydes have been prepared. The first isolable thioaldehyde **2** was reported in 1960 by Woodward and coworkers as an important precursor in the total synthesis of chlorophyll$_a$.[11] The feature which conferred stability upon Woodward's thioaldehyde was the conjugation of



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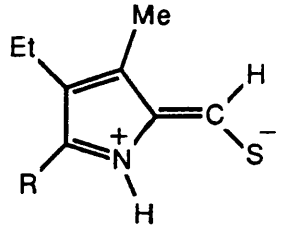
the thial group with an electron-rich pyrrole ring as shown by the resonance structure 3.



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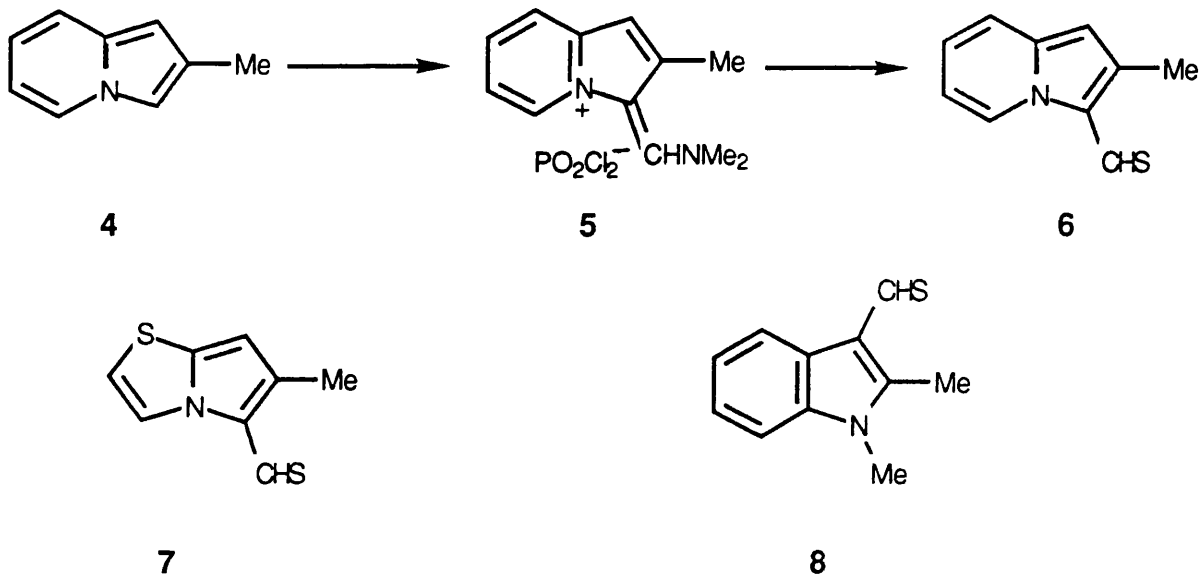
This part of the review will concentrate on the synthetic applications of labile thioaldehydes. However, in recent years a number of thioaldehydes stabilised electronically or sterically have been isolated as the monomers. These will be described first.

1.2.1 Stabilised thioaldehydes

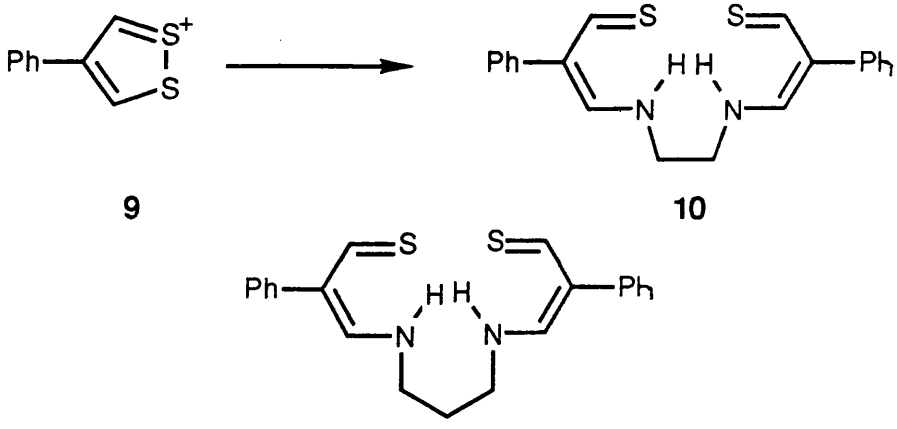
The electronic stabilisation of thioaldehydes, first demonstrated by Woodward and co-workers [11] was soon applied in other systems by Reid and co-workers, [12-15] who presented a series of stable thioaldehydes **6-8** (Scheme 1). All were prepared by a novel variation of the Vilsmeyer-Haack aldehyde synthesis in which the Vilsmeyer salt **5** was solvolysed with aqueous sodium hydrogen sulphide. Thus, addition of phosphoryl chloride to a solution of 2-methylindolizine **4** in dimethylformamide at - 60 °C gave the Vilsmeyer salt **5** which,



Scheme 1

when treated with 2M-aqueous sodium hydrogen sulphide, afforded 2-methyl-3-thioformylindolizine **6** as orange-red needles (Scheme 1). In a similar manner the pyrrolothiazole **7** and indole derivative **8** were obtained from the corresponding heterocycles.

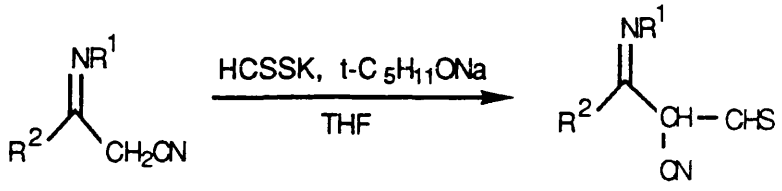
Tang *et al.* synthesized[16] the aminothione **10** and **11** by treating the salt **9** with ethylenediamine or trimethylenediamine



Scheme 2

(Scheme 2). Their aim was to synthesize ligands whose metal complexes reproduce the chelate ring size patterns of porphyrin (6-6-6-6) and corrin (6-5-6-6) complexes.

Muraoka *et al.* developed[17] a general method for the preparation of monomeric thioaldehyde. Treatment of potassium dithioformate with β-imino-nitriles in an aprotic solvent in the presence of sodium *tert*-butoxide gave the



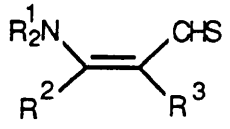
12

R^1 = H or Me

R^2 = Me, *p*- or *m*-$CH_3C_6H_4$

Scheme 3

monomeric thioaldehydes **12** (Scheme 3). Muraoka and Yamamoto later improved this method[18] and synthesized a number of aliphatic and alicyclic enamino thioaldehydes which bear no cyano group at the α-position. They treated the enamine with dimethylformamide and phosphoryl chloride to



13 ; R^1 N= morpholino , $R^2 = R^3$ = Ph

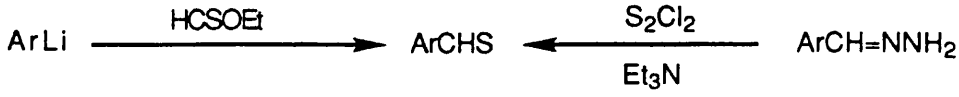
14 ; R^1 N= pyrrolidino , $R^2 = R^3$ = Ph

15 ; R^1 N= morpholino , R^2 = Ph , R^3 = H

16 ; R^1 N= morpholino , $R^2 = R^3 = (CH_2)_3$

give the corresponding Vilsmeyer salt which, when solvolysed *in situ* with sodium hydrogen sulphide produced brilliant orange or red crystalline thioaldehydes **13-16** in moderate yields.

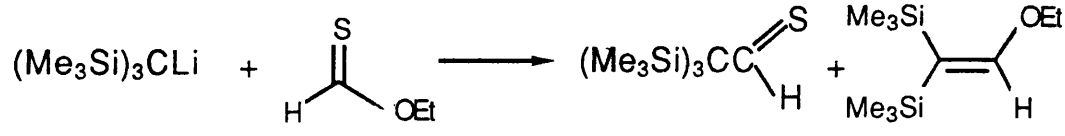
The first sterically stabilised aromatic [19] and aliphatic [20] thioaldehydes were reported by Okazaki and co-workers. Treatment of 2,4,6-tri-*tert*-butylphenyl-lithium **17** with *O*-ethyl thioformate followed by chromatographic purification afforded 2,4,6-tri-*tert*-butylthiobenzaldehyde **18** in 60 % yield. The same compound was also synthesized, in 40 % yield, by oxidative sulphurisation of the hydrazone **19** with disulphur dichloride in the presence of triethylamine (Scheme 4). The monomeric thioaldehyde, which was stable in the absence of air, was obtained as purple crystals, m.p. 146-147 °C.



17 **18** **19**

Scheme 4

Tris(trimethylsilyl)ethanethial **21** was prepared by treating tris(trimethylsilyl)methyl-lithium **20**, obtained from tris(trimethylsilyl)methane and methyl-lithium, with *O*-ethyl



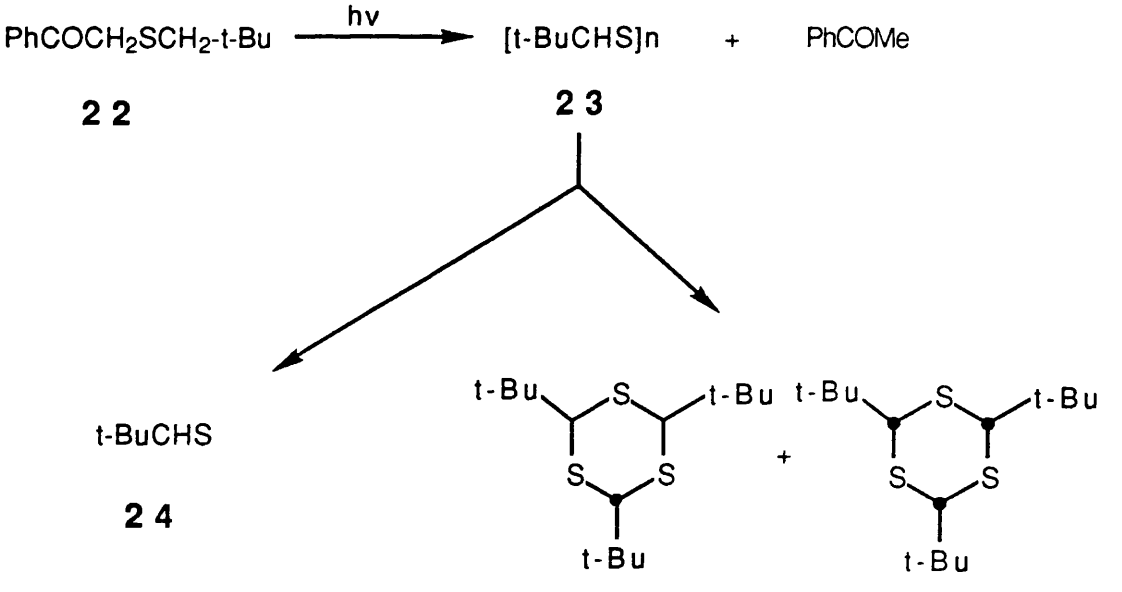
20 **21**

Scheme 5

thioformate (Scheme 5). The thioaldehyde **21** was obtained as

pink-red crystals, m.p. 129-131 °C These derivatives were the first of a new class of thioaldehydes stabilised by steric crowding of the thiocarbonyl group, rather than by delocalisation.

The simple *t*-butyl derivative **24** is not stable as the monomer when isolated, but persists for some time, in dilute solution. It was prepared by Vedejs *et al.* [21,22] by the photolysis of the phenacyl sulphide **22** (Scheme 6). The monomeric thioaldehyde was isolated by vacuum distillation of **23** . The pink colour of **24** persisted in chloroform, benzene, dichloromethane, ether etc., for as long as 16 hours at 20 °C. Instantaneous polymerisation resulted when a chloroform solution of **24** was



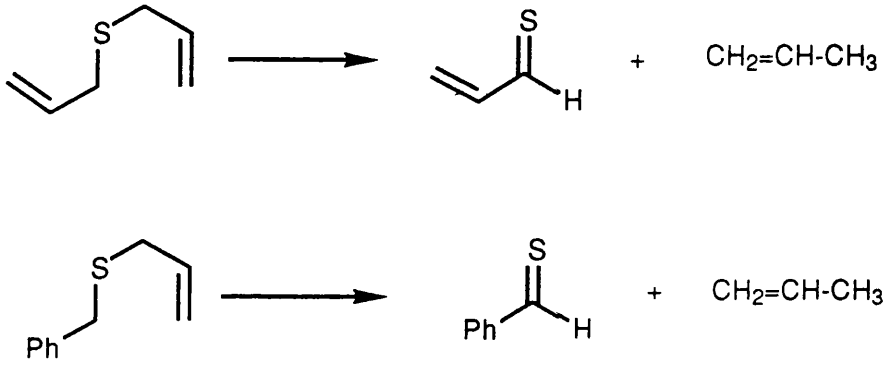
Scheme 6

swirled with a trace of anhydrous zinc bromide. The life time of the monomer **24** in chloroform-ethanol (approximately 15 minuites) was reduced to 5 minu tes by adding triethylamine or to a few seconds by adding hydrochloric acid. The derivative **24**

was the first example of an aliphatic thioaldehyde sufficiently stable to be studied in solution.

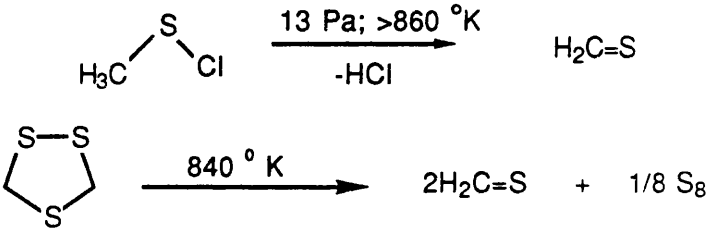
1.2.2 Pyrolytic generation of thioaldehydes

De Mayo and co-workers generated thioacrolein and thiobenzaldehyde [23,24] (Scheme 7) from diallyl sulphide and allyl benzyl sulphide, respectively, by flash thermolysis at *ca* 900 °K. The labile product was trapped in a frozen matrix and characterised by UV and IR spectroscopy at 77 °K. The yields of the thioaldehydes could not be measured directly, because both the thioaldehydes reacted far below ambient temperatures. But some indication of these was gathered from the yields of propene obtained, which was *ca.* 90 %. Thioacrolein showed maxima at 275 and 580 nm in the UV-visible spectrum and thiobenzaldehyde had maxima at 228, 320 and 575 nm. Monitoring of the IR spectra showed that thioacrolein reacts at a detectable rate at *ca.* 77 °K while thiobenzaldehyde is unreactive up to 110 °K.



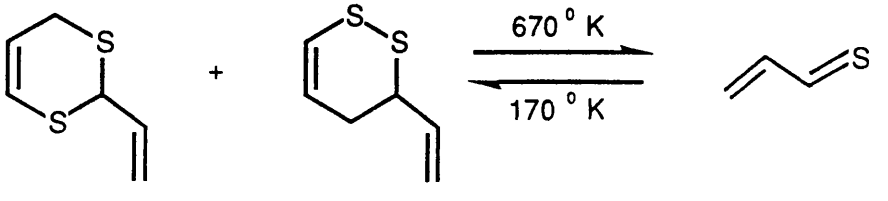
Scheme 7

Bock and co-workers generated monomeric thioformaldehyde [25] in the gas-phase from methyl sulphenyl chloride by means of thermal decomposition at a pressure of 13 Pa and a temperature above 860 °K (Scheme 8). Hydrogen chloride eliminated was removed as ammonium chloride by injecting ammonia. Pyrolysis of 1,2,4-trithiolan at 840 °K also produced[26] thioformaldehyde quantitatively (Scheme 8).



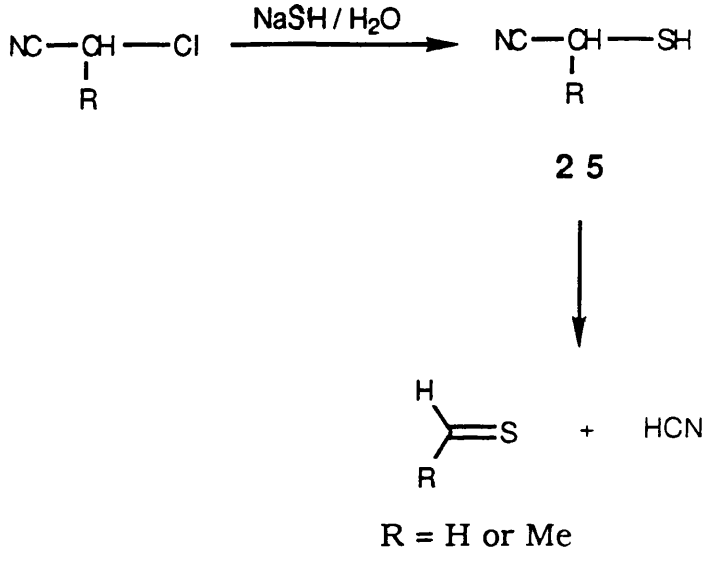
Scheme 8

They also generated thioacrolein (Scheme 9) [27] from di-allyl sulphide by thermal decomposition at 660 °K. as described independently by de Mayo and co-workers [23,24] They showed that Diels-Alder dimer mixtures were formed at room temperature and could be isolated by steam distillation. These dimers gave thioacrolein monomer by thermal cleavage making thioacrolein available for further studies.



Scheme 9

Denis and co-workers generated methane and ethane thials [28] (Scheme 10) by a vacuum gas-phase dehydrocyanation of the corresponding thiocyanohydrins **25** and characterised them, in the gas phase, by mass spectrometry experiments.

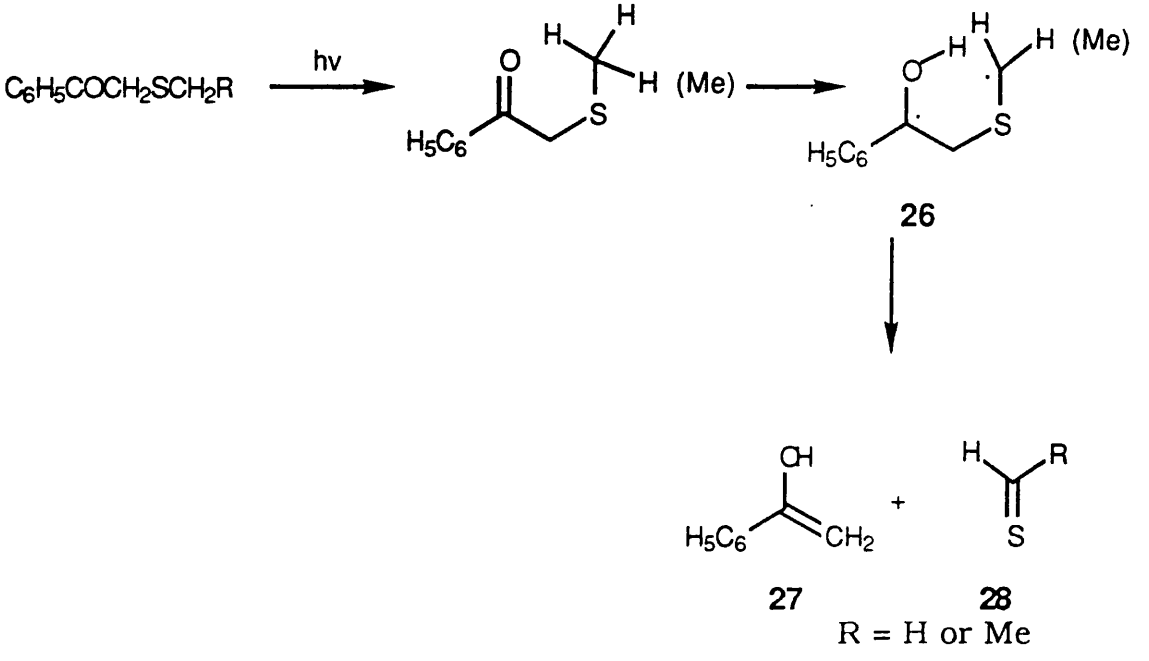


Scheme 10

1.2.3 Photolytic generation of thioaldehydes

The photolytic formation of thioaldehydes, followed by their polymerisation were observed by Caserio and co-workers [29, 30] and by Padwa and Pashyan.[31] Caserio *et al.* [29] observed that phenacyl alkyl sulphides **26** (Sheme 11) photolyse by an intramolecular, Norish Type II process to give the enol of acetophenone **27** and the corresponding thioaldehydes **28** as the primary photoproducts. The authors' aim was to study intramolecular and intermolecular mechanisms of the photolysis of phenacyl alkyl sulphides. They observed the formation of

thioacetophenone by glpc and NMR studies but failed to observe any thioaldehyde formation apparently due to the rapid polymerisation of the thioaldehyde.

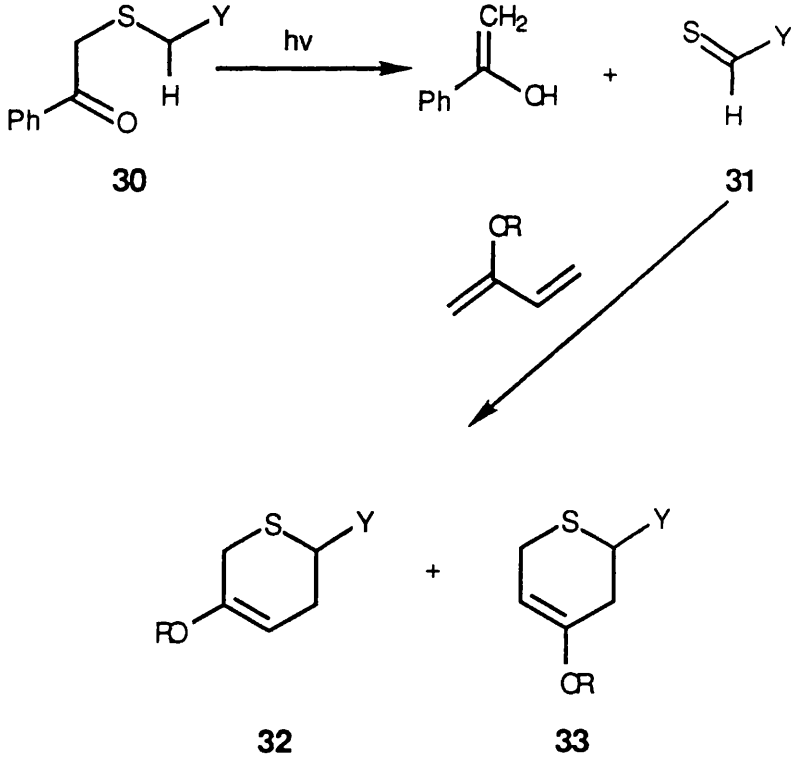


Scheme 11

Dice and Steer generated[32] thioformaldehyde by photolysis of thietane vapour at 313 nm and trapped the thioaldehyde *in situ* by dienes as Diels-Alder cycloadducts. Thus, they prepared 2-thiabicyclo[2.2.1]hept-5-ene **29** by photolysis of thietane-cyclopentadiene mixtures in the vapour phase.

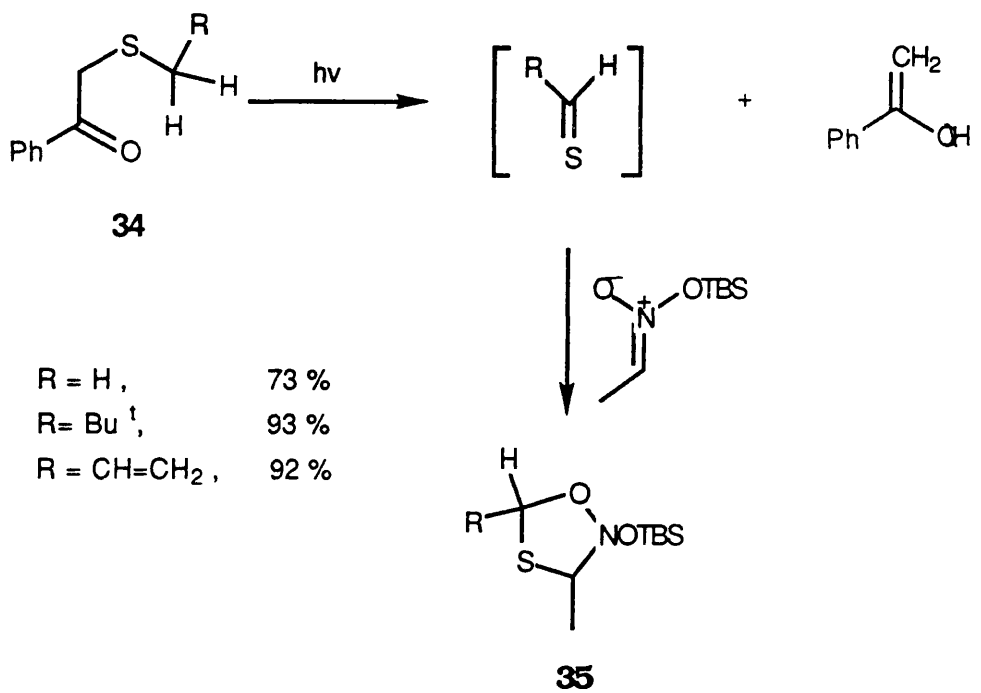
29

Caserio *et al.* did not investigate the synthetic potential of the thioaldehydes that they generated photochemically from phenacyl sulphides. Presumably, the instability of the thials discouraged this idea. However, about a decade later Vedejs *et al.* trapped the thioaldehydes with conjugated dienes.[33, 34] Thus, they photolysed a series of phenacyl sulphides **30** (Scheme 12) in the presence of dienes and trapped the thioaldehydes **31** as Diels-Alder cycloadducts **32** and **33**, where Y was an unsaturated electron withdrawing group.



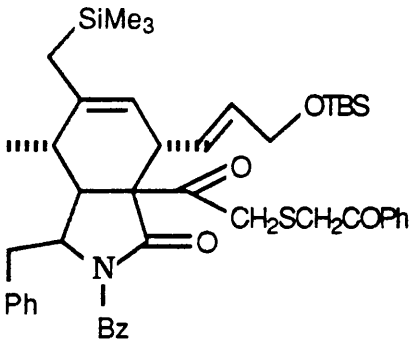
Scheme 12

Later, Vedejs and Perry irradiated[35] benzene solutions of the phenacyl sulphides **34**, containing the *tert*-butyldimethylsilyl nitronate ester, to afford the 1,3-dipolar cycloadducts **35** in high yield (Scheme 13).



Scheme 13

Vedejs and Reid trapped [36] the thioaldehyde **37**, generated photolytically from **36**, with 2-(*tert*-butyldimethylsilyloxy)butadi-1,3-ene **38** to give a 3:2 diastereomeric mixture of the Diels-Alder adducts **39**. These were intermediates in their total synthesis of carbocyclic cytochalasans.



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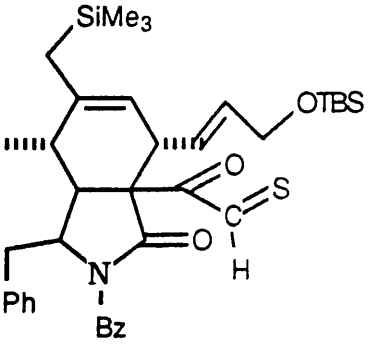

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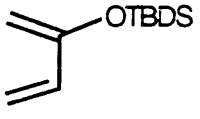

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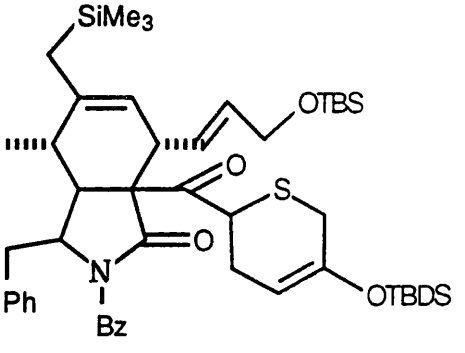
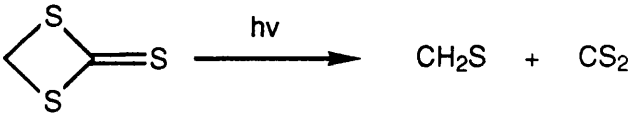


39

Torres *et al.* generated[37] thio- and deuteriothioformaldehydes by photolysis of methylene trithiocarbonate and deuteriomethylene trithiocarbonate, respectively, in argon matrices at 10 °K (Scheme 14). They examined the IR spectra of the thioaldehydes with the aid of FTIR spectroscopy.

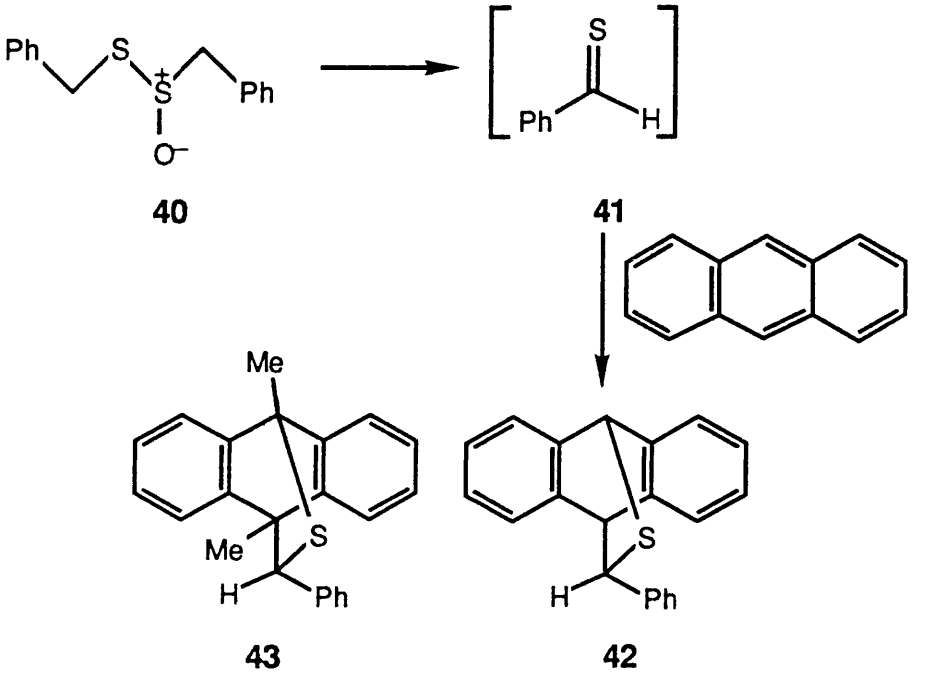


Scheme 14

The preparation of 2,2-dimethylpropanethial **24** by pyrolysis of the appropriate phenacyl sulphide has been described in Section 1.2.1.

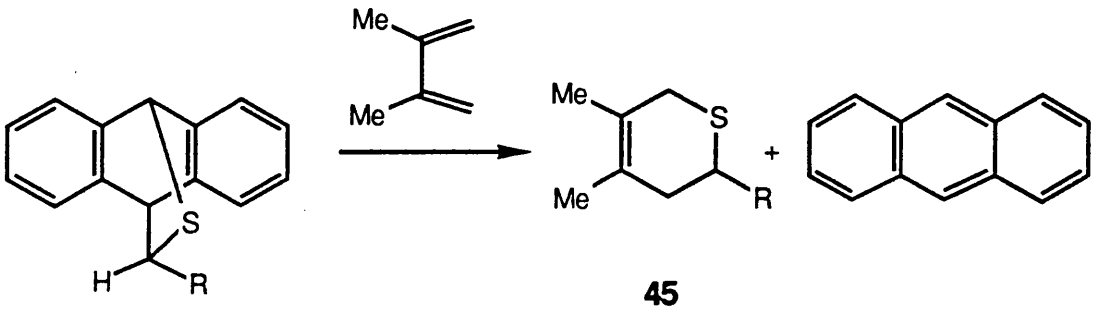
1.2.4 Thermal cleavage of alkyl thiosulphinates

Baldwin and Lopez generated thiobenzaldehyde **41** by heating S-benzyl phenylmethanethiosulphinate **40** in toluene at 100 °C and trapped it with anthracene as the cycloadduct **42** in high yield [38,39] (Scheme 15). Under similar conditions 9,10-dimethylanthracene afforded the cycloadduct **43** in 87 % yield.



Scheme 15

Analogously, S-ethyl ethanethiosulphinate was thermolised in the presence of anthracene to yield the adduct **44**. The adduct **42** and **43** dissociated on heating in a sealed tube in the presence of 2,3-dimethylbuta-1,3-diene to afford the 2H-dihydrothiine **45** along with anthracene (Scheme16).

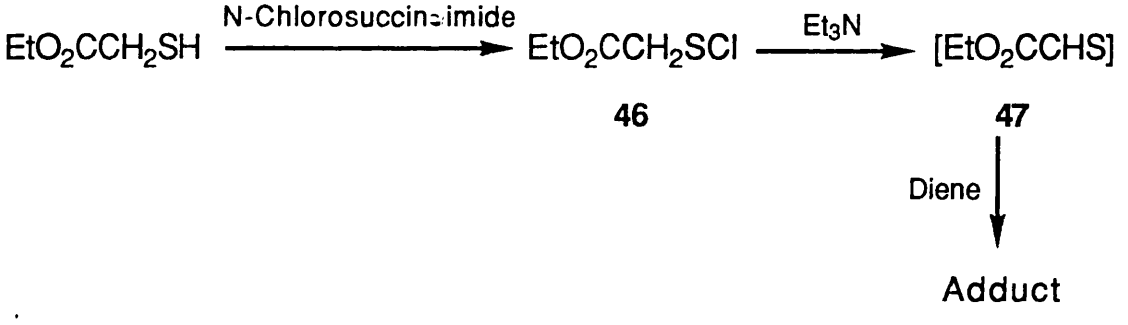


44 45

Scheme 16

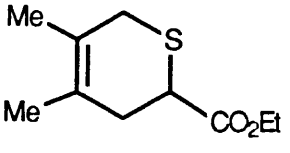
1.2.5 1,2-Elimination of sulphenyl chloride

Kirby and co-workers developed a number of methods of generating thioaldehydes under very mild conditions, all involving 1,2-elimination of HX from sulphenyl derivatives ZCH_2SX, where Z was usually an electron withdrawing group. They reported [40] the generation of ethyl thioxoacetate **47**, a dienophilic thioaldehyde, by 1,2-elimination, with base, of hydrogen chloride from the sulphenyl chloride **46** (Sheme 17).

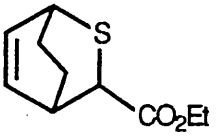


Scheme 17

They trapped the thioaldehyde *in situ* with conjugated dienes resulting in the corresponding Diels-Alder cycloadducts. Thus, they used 2,3-dimethylbuta-1,3-diene, cyclohexa-1,3-diene, anthracene and thebaine as trapping agents giving the adducts **48, 49, 50** and **51**, respectively. These authors showed that ethyl thioxoacetate could be 'transferred' from the anthracene cycloadduct **50** cleanly to some other dienes by heating in toluene at 100 - 110 °C. A similar 'transfer reaction' was first used by



48



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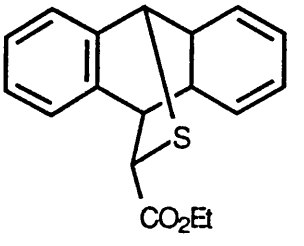

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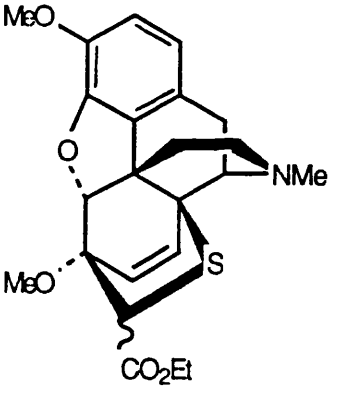
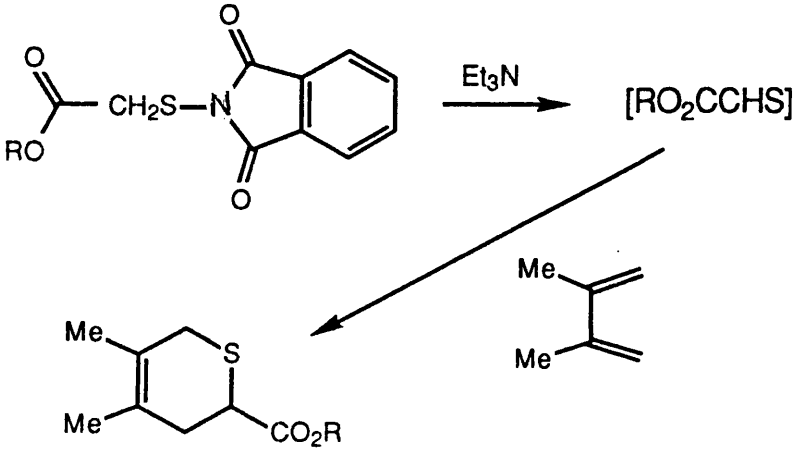


51

Kirby with nitrosocarbonyl dienophiles.[41] Baldwin and Lopez independently showed [39] that cycloadducts of thiobenzaldehyde and propanethial of anthracene were similarly useful ancillary precursors of the thials.

1.2.6 1,2-Elimination of *N*-(alkoxycarbonylmethylthio)-phthalimide

Kirby and Lochead reported an alternative method[42] of generating alkyl thioxoacetates, *viz.* from *N*-(alkoxycarbonylmethylthio)phthalimides (Scheme 18). Methyl and ethyl esters separately were treated with triethylamine at room temperature in benzene containing 2,3-dimethylbutadiene, when the oily cycloadducts **52** and **53** were obtained in 78-85 %

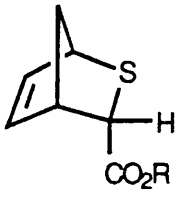


52; R = Et

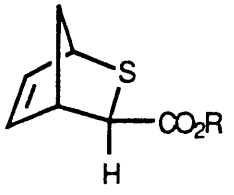
53; R = Me

Scheme 18

yields. The *endo* - and *exo* - cyclopentadiene adducts **54** and **55** were obtained by these authors using this method. It was further shown that the thioaldehyde could be cleanly transfered from adducts **54** and **55** to 1,4-diphenyl-1,3-butadiene, to prepare adduct **56**, by heating under reflux in xylene. Significantly, diphenylbutadiene was insufficiently reactive to trap the thioaldehyde when it was liberated directly by 1,2-elimination.



54



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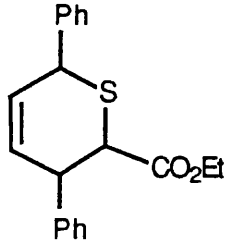
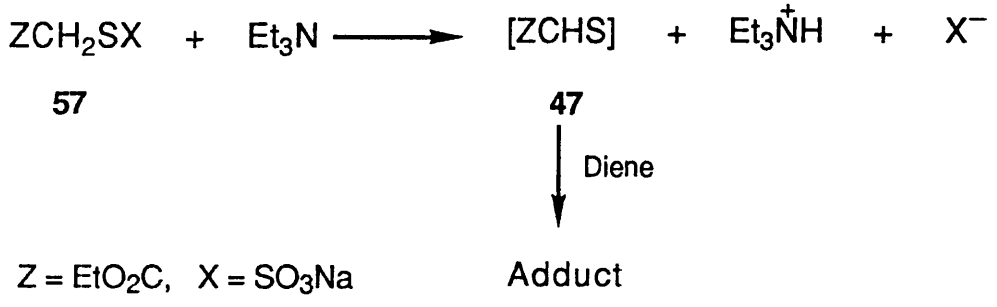


56

1.2.7 1,2-Elemination of Bunte salt

One of the most convenient methods of generating the thioaldehyde, ethyl thioxoacetate **47**, was by treatment[43] of the sodium thiosulphinate *S*-ester (Bunte salt) **57** with triethylamine and calcium chloride in the presence of a suitable diene (Scheme 19). The advantages of this method over the others are that (1) extremely mild conditions are employed, (2) the starting materials are readily available, (3) the reaction can be carried out on quite a large scale, (4) the precursor, Bunte salt, can be stored for quite long periods, and (5) the salt is prepared directly from sulphur-free precursors (alkyl halides). *Endo* - and *exo* - cyclopentadiene adducts and dimethylbutadiene adducts were prepared by the authors.



Scheme 19

1.2.8 Fragmentation-elimination of toluene -p-sulphonates

Another method of generating thioaldehydes reported by Kirby *et al.* was from α-sulphonyldisulphides, prepared from thiosulphonates (Scheme 20).[44] They attempted to prepare thioaldehydes from toluene-p-thiosulphonate **58**, in a similar manner to that using Bunte salts according to equation (1). They

$$\underset{\mathbf{58}}{RCH_2SSO_2Tol} + Et_3N \longrightarrow [RCHS] + Et_3\overset{+}{N}H + TolSO_2^- \qquad (1)$$

$$2\ \underset{\mathbf{58}}{RCH_2SSO_2Tol} \longrightarrow \underset{\mathbf{59}}{RCH_2SSCH(SO_2Tol)R} + TolSO_2H \qquad (2)$$

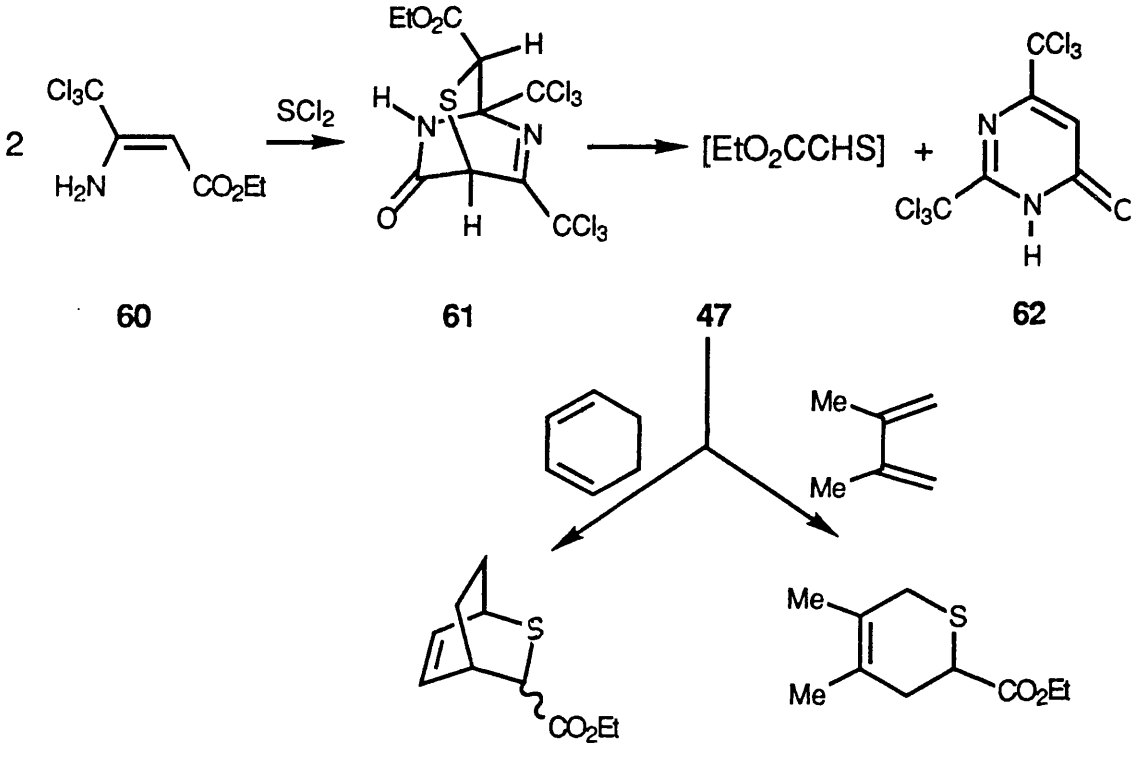
$$RCH_2SSCH(SO_2Tol)R + Et_3N \longrightarrow 2\ [RCHS] + Et_3\overset{+}{N}H + TolSO_2^- \qquad (3)$$

Scheme 20

found that the tosylates **58** were transformed readily into the α-sulphonyldisulphides **59** [equation (2)], and that these disulphides were inturn converted into thioaldehydes by fragmentation-elimination [equation (3)]. The authors used cyclopentadiene to trap the thioaldehydes RCHS, where R was 4-$NO_2C_6H_4$, Ph, 4-BrC_6H_4CO or EtO_2C. They also proposed a mechanism for the transformation.

1.2.9 Retro-Diels-Alder reaction of a derivative of diazathiabicyclooctane

Lee *et al.* reported [45] that a derivative of diazathiabicyclooctane **61** was a precursor of alkoxycabonylthioformaldehydes. Compound **61** was obtained in 34 % yield by the reaction of the aminocrotonate **60** with

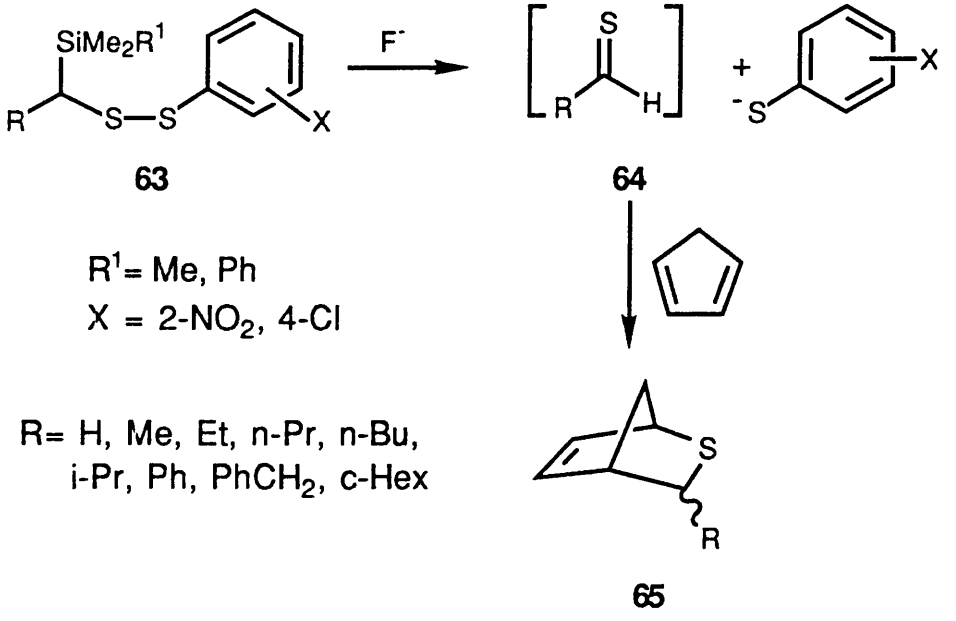


Scheme 21

sulphur dichloride (Scheme 21). Heating a solution of **61** in chlorobenzene at 80 °C induced a retro-Diels-Alder reaction and the formation, together with the product **62**, of ethoxycarbonylthioformaldehyde **47**, which was trapped with cyclohexa-1,3-diene or 2,3-dimethylbuta-1,3-diene.

1.2.10 Cleavage of S-silyl disulphides

Krafft and Meinke reported[46] a mild, efficient and general method of generating thioaldehydes from silyldisulphides (Scheme 22). Fluoride-induced β-elimination of stabilised aryl thiolate anions from α-silyldisulphides **63** generated thioaldehyde, which was trapped *in situ* by cyclopentadiene as a mixture of *endo-* and *exo-* Diels-Alder adducts **65**. The efficiency of the cleavage reaction and the stability of the α-silyl disulphides depended upon the stability of the aryl thiolate leaving group. The 2-nitro- and 4-chloro- substituted phenyl disulphides are reasonably stable thioaldehyde precursors. The unsubstituted phenyl disulphides required elevated temperature to react. Reactions depended on the fluoride source as well. Cesium fluoride or potassium fluoride in the presence of 18-crown-6 generated thioaldehydes slowly at

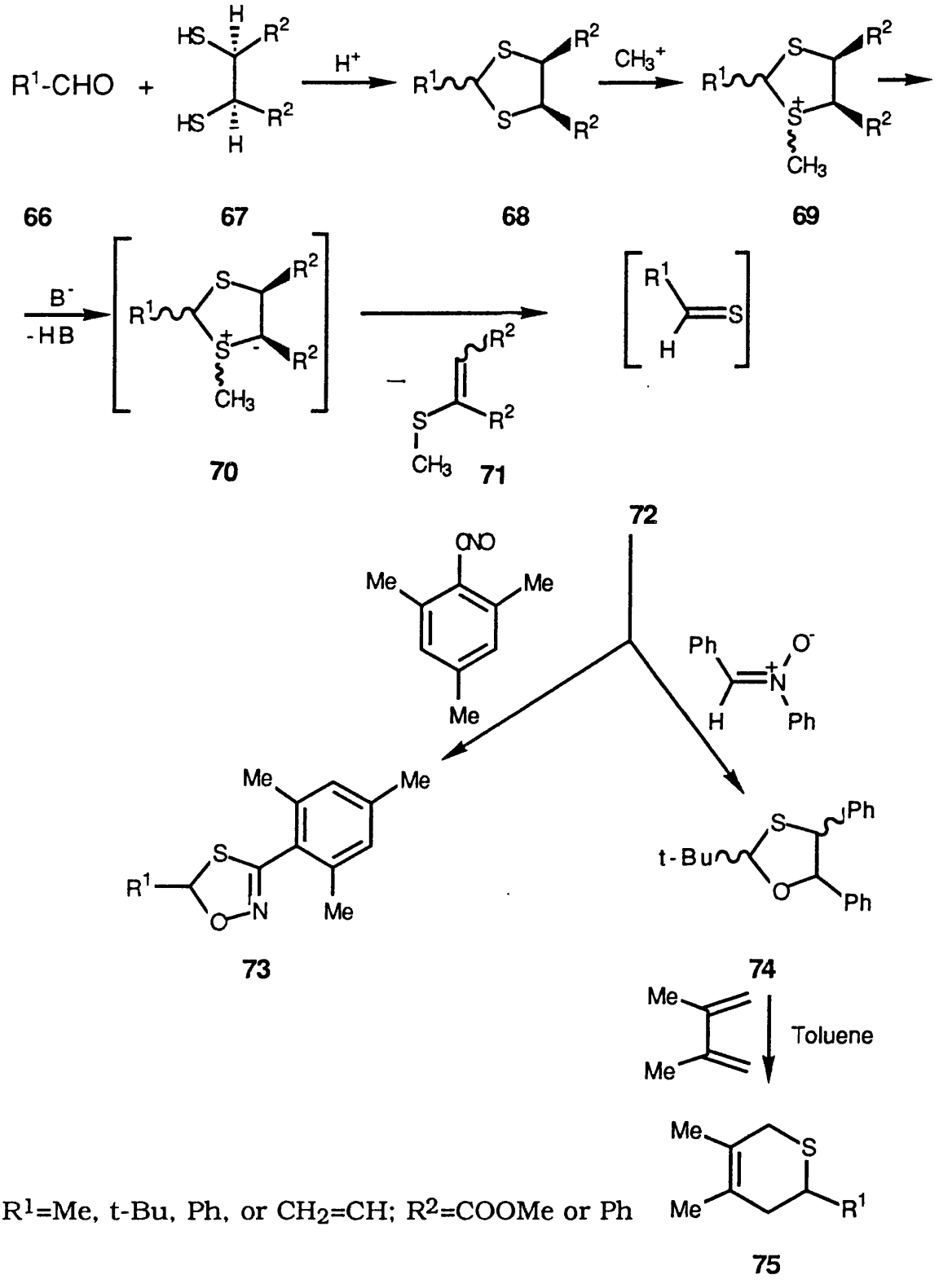


Scheme 22

room temperature, while tetrabutylammonium fluoride in THF generated thioaldehydes rapidly at temperature from to -78 - 0 °C. A variety of thioaldehydes have been made by this method by the authors and trapped by cyclopentadiene as Diels-Alder adducts. The isolated yields of cycloadducts varied from 58 to 94 %. Always a mixture of *endo*- and *exo*- adducts was formed with *endo* preferred over *exo*.

1.2.11 Fragmentation of S-ylides

Schauman and Ruhter developed a general method [47] of preparing thioaldehydes from the dithiolanes **68**, which were prepared by thioacetalisation of the aldehydes **66** with the dithiols **67** (R= COOMe or Ph) (Scheme 23). Methylation of the acetals **62** with methyl fluorosulphonate or trimethyloxonium tetrafluoroborate gave the salts **69**, which, when treated with LDA, Hunig's base, or sodium hydride, afforded the transient ylides **70.** These ylides underwent spontaneous fragmentation generating the vinylsulphides **71** along with the thioaldehydes **72**. Thioaldehydes **72** were trapped with added mesitonitrile oxide in a 1,3-dipolar cycloaddition to give the 1,4,2-oxathiazoles **73**. Benzylidenaniline *N*-oxide was used in trapping thiopivaldehyde (R^1=*t*-Bu) resulting in the heterocycle **74**. On heating in toluene, **74** underwent a [3+2] cycloreversion regenerating the thioaldehyde which, in the presence of 2,3-dimethylbuta-1,3-diene, was intercepted as the Diels-Alder adduct **75**.

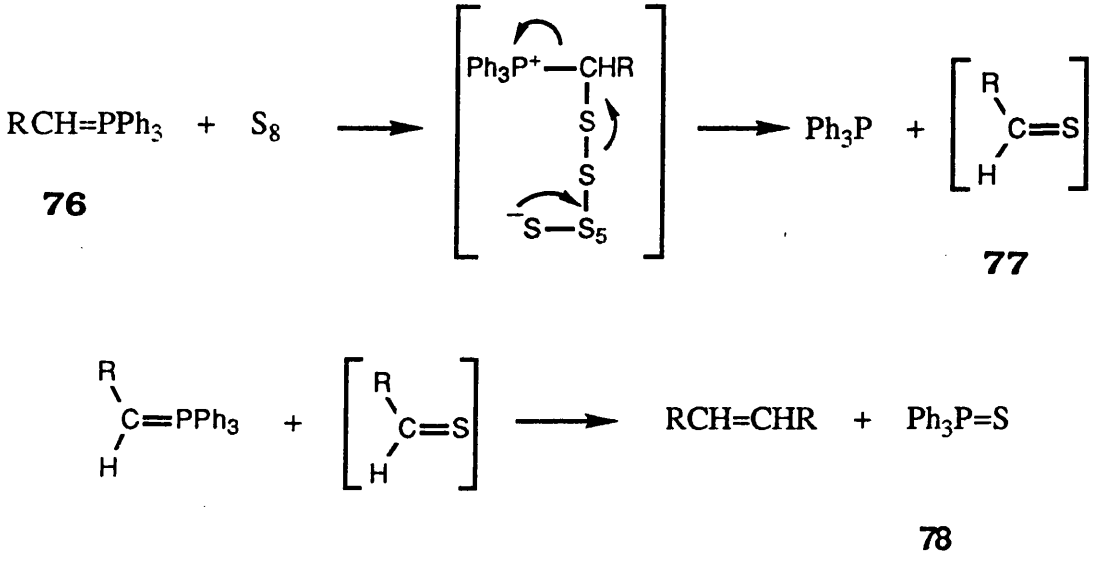


R^1=Me, t-Bu, Ph, or CH_2=CH; R^2=COOMe or Ph

Scheme 23

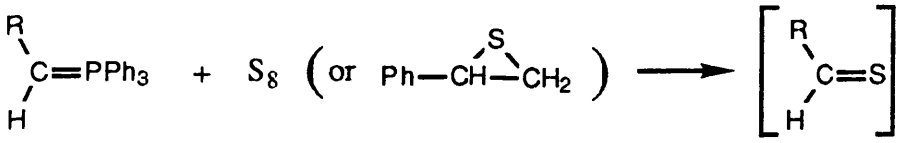
1.2.12 Treatment of Wittig reagents with elemental sulphur

Okuma *et al.* observed [48] that thioaldehydes are formed as reactive intermediates when Wittig reagents are treated with

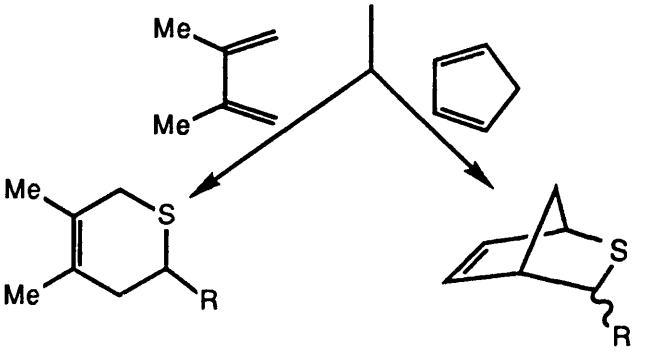


Scheme 24

elemental sulphur or episulphides (Scheme 24). The intermediate thioaldehydes react further with Wittig reagents to give the corresponding olefins and triphenylphosphine sulphide **78.** But in the presence of dienes the thioaldehydes **77** are trapped as the corresponding Diels-Alder adducts in moderate yields (Scheme 25).



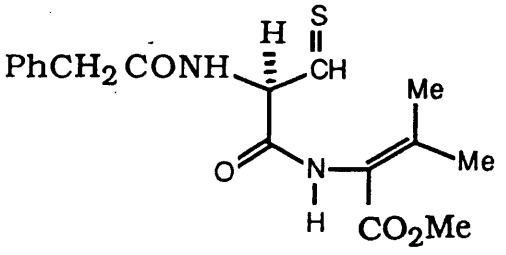
77



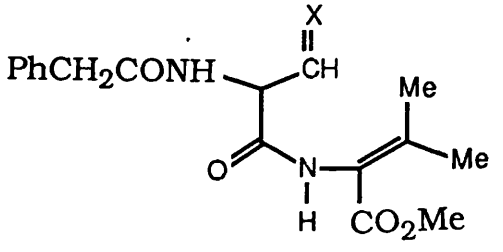
Scheme 25

1.2.13 Conversion of aldehydes to thioaldehydes

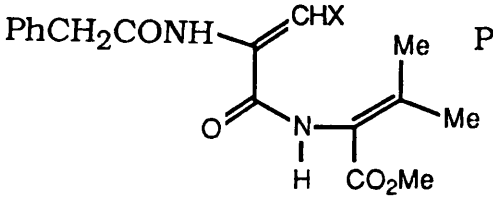
The complex thioaldehyde **79** was synthesized by Cheney *et al.* [49] Benzylpenaldic acid diethyl acetal was condensed with



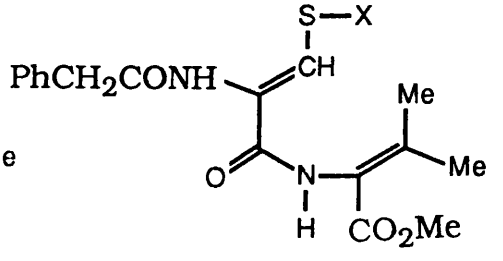
79



80



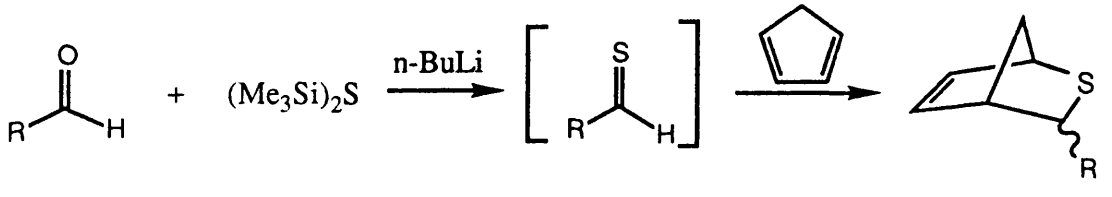
81



82

methyl α-amino-β,β-dimethylacrylate to yield the acetal **80** [X=$(OEt)_2$], which was hydrolysed to the aldehyde **80** (X=O). Reaction of the aldehyde **80** (X=O) with ethylamine, aniline, or urea gave the enamine **81** (X=NHEt, NHPh, and $NHCONH_2$) and reaction of these enamine dipeptides with hydrogen sulphide and acid followed by trapping of the intermediate thioaldehyde **79** with base and 1-chloro-2,4-dinitrobenzene yielded the geometrically isomeric thioethers **82** (X=2,4-dinitrophenyl).

Segi *et al.* developed a general method [50] of converting an aldehyde directly to seleno- or thioaldehydes (Scheme26). They found that bis(trimethylsilyl)sulphide not only introduces a



83

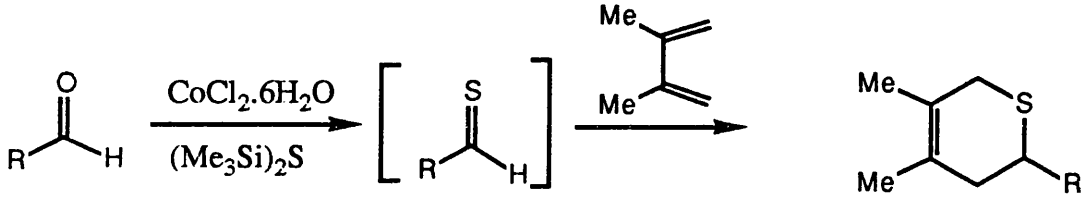
R = Ph,	96 %	(*endo* : *exo* = 4 : 1)
R = 2-Thienyl,	97 %	(*endo* : *exo* = 5 : 1)
R = n-Propyl,	80 %	(*endo* : *exo* = 6 : 1)
R = t-Butyl,	86 %	(*endo* : *exo* = >20 : 1)

Scheme 26

sulphur atom but also removes an oxygen atom to convert an aldehyde into a thioaldehyde. The reactions were carried out with

butyllithium as catalyst in the presence of cyclopentadiene. The corresponding cycloadducts **83** were obtained in good yield.

Ricci and co-workers reported a similar method [51] of converting an aldehyde to its thio- analogue by treating it with bis(trimethylsilyl)sulphide, but with a different catalyst, cobalt



R = Ph, 94 %

R = Thienyl, 91 %

R = Furyl, 88 %

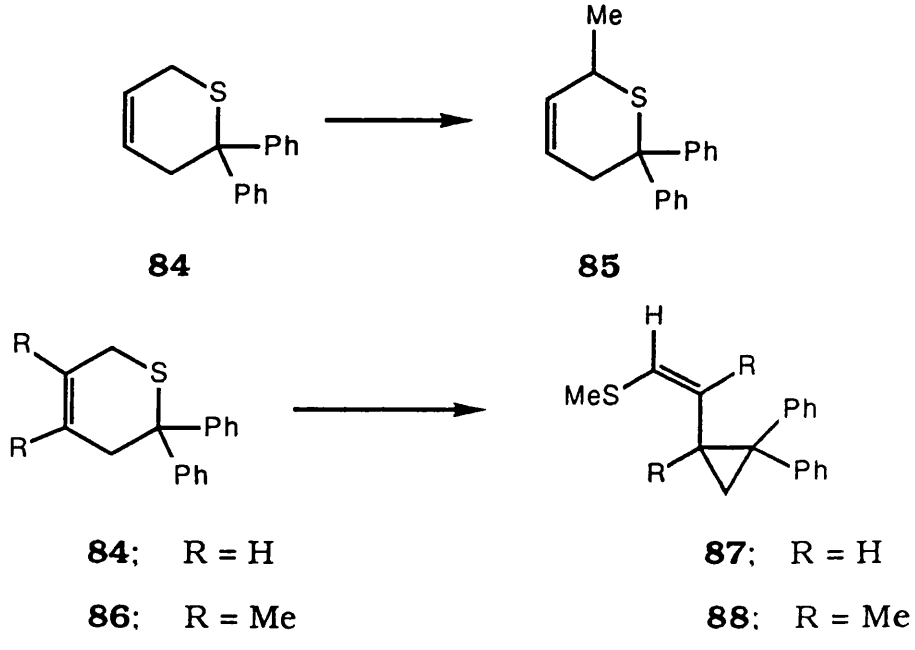
Scheme 27

chloride hydrate in the presence of dimethylbutadiene (Scheme 27).

1.3 Alkylations of Thioaldehyde and Thioketone Diels-Alder Cycloadducts

The chemistry of thioaldehydes and reactive thioketones has only been developed in recent times. Simple aliphatic thioaldehydes and thioketones are extremely unstable and polymerise instantly. Thioaldehydes are more unstable than their thioketone analogues. Normally they are trapped *in situ* by dienes as Diels-Alder cycloadducts. The chemistry of these cycloadducts is being studied. There are a few reports where reactive thioketone and thioaldehyde cycloadducts have been alkylated.

Biellmann and Ducep alkylated[52,53] the cycloadduct **84** of thiobenzophenone and butadiene with butyllithium and methyl iodide at - 78 °C, in the presence of amine $Me_2N(CH_2)_2NMe_2$ to give the methyl derivative **85** (Scheme 28). **85** Rearranges at

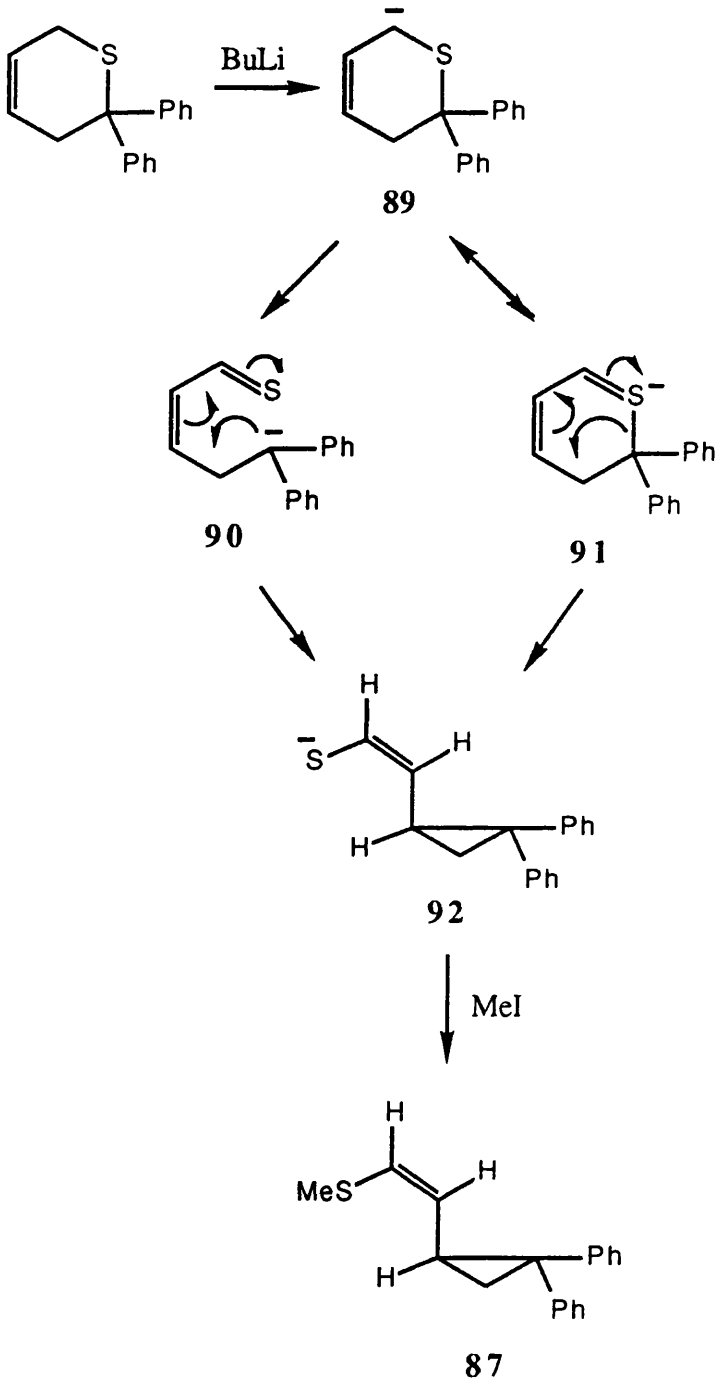


84 **85**

84; R = H **87**; R = H

86; R = Me **88**; R = Me

Scheme 28

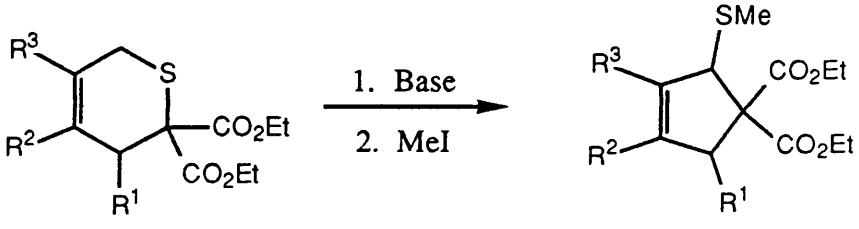


Scheme 29

higher temperature; thus, treatment of **84** and **86** with butyllithium at - 80 °C and then addition of methyl iodide at - 15

°C afforded **87** and **88**. They proposed a mechanism for this transformation (Scheme 29). The carbanion **89**, formed after treatment of **84** with butyllithium, rearranged to **87** through the possible intermediate **90** or **91** at relatively higher temperatures (- 15 °C).

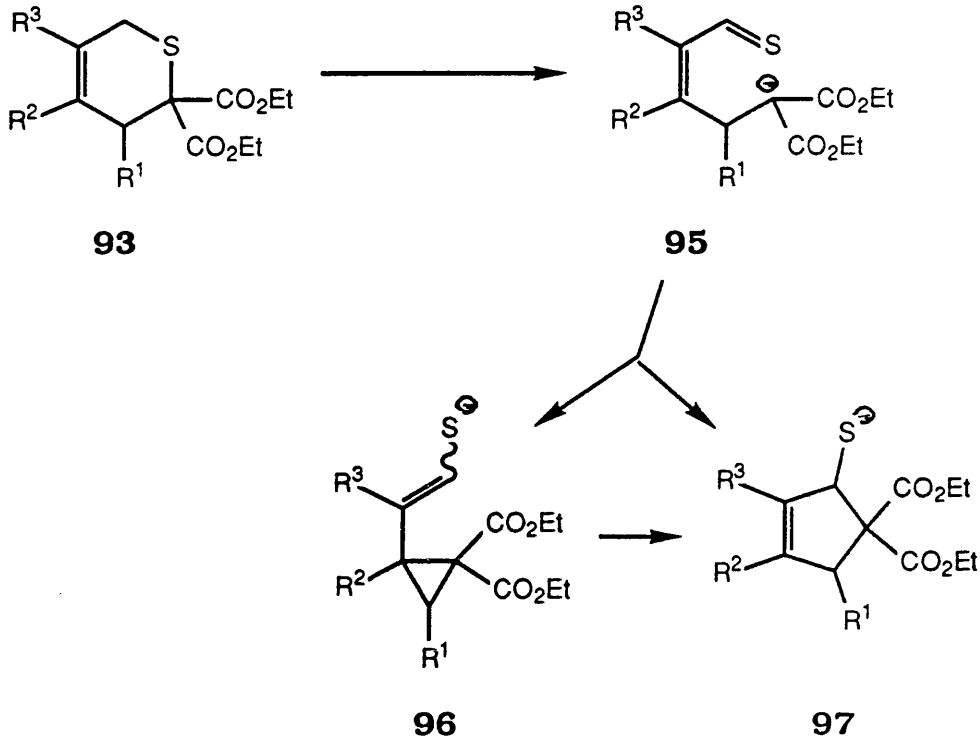
More recently, Larsen reported[54] the rearrangement and S-alkylation of the cycloadducts of diethyl thioxomalonate and various dienes, when treated with a base and methyl iodide. He observed that ring contraction occurred when the cycloadducts **93** were exposed to LDA or $KN(SiMe_3)_2$ at low temperature and



93 **94**

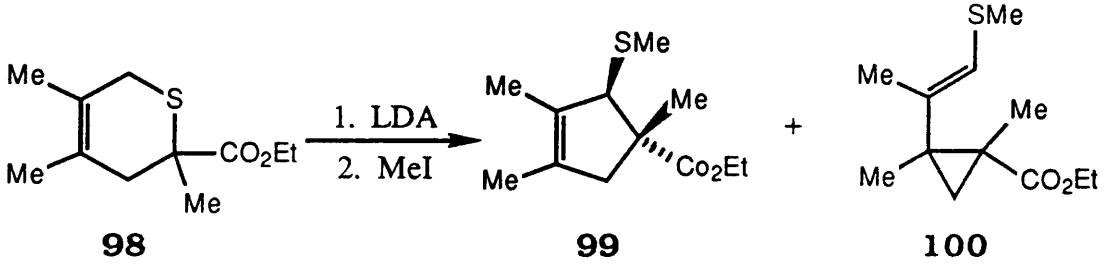
Scheme 30

then quenched with methyl iodide (Scheme 30). He prepared a number of functionalised cyclopentenes (**94**) applying this method and proposed a mechanism for the reaction (Scheme 31). The first step involves deprotonation, α to the sulphur, of **93** followed by β-elimination of the more stable malonate carbanion to give **95**. The reactive carbon-sulphur double bond is then trapped internally by 1,4- or 1,2-addition leading to **96** and **97**, respectively. The fact that cyclopentenes are virtually the sole products implies that **96** is rapidly converted back to **95** or directly to **97**. However, in some cases, usually at lower



Scheme 31

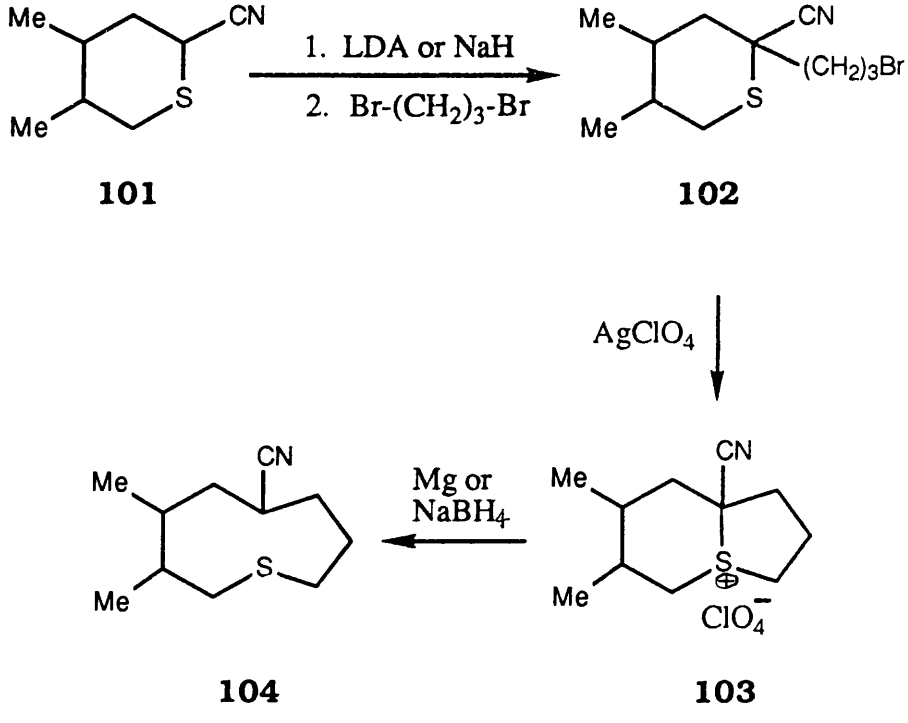
temperatures, the cyclopropane derivatives were isolated together with cyclopentenes. Thus, rearrangement of **98** (Scheme 32) with LDA/HMPA followed by methylation proceeded smoothly to give an 8:1 diastereomeric mixture of the



Scheme 32

cyclopentenes **99**, as long as the mixture was warmed up to 0 °C before methylation. Addition of methyl iodide at - 45 °C resulted in a 1:2 mixture of **99** and **100**, being isolated along with 10 % of unchanged starting material **98**.

Kataoka *et al.* reported[55] a synthesis of sulphur-containing, medium-sized ring systems (Scheme 33). They alkylated the hydrogenated thioaldehyde cycloadduct **101** with

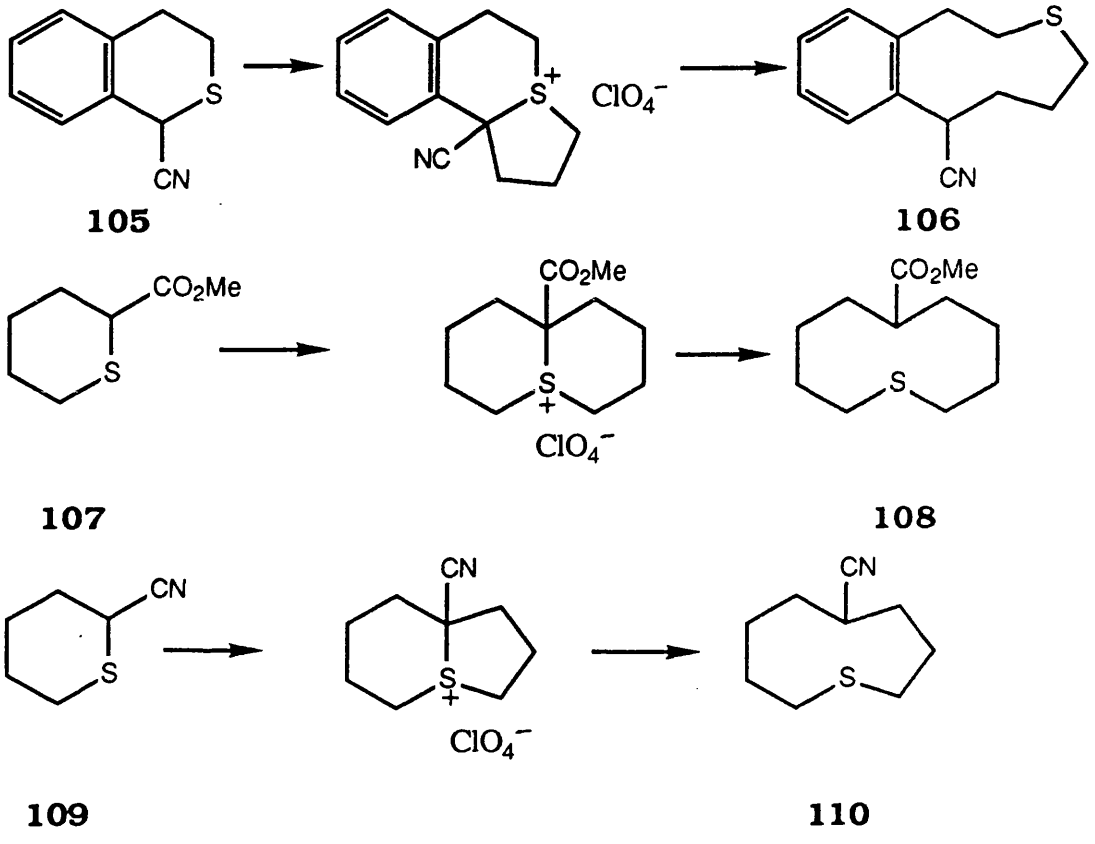


101 **102** **103** **104**

Scheme 33

LDA and 1,3-dibromopropane to form bromo compound **102**. Treatment of **102** with silver perchlorate gave the sulphonium salt **103** which, when treated with metallic magnesium or sodium borohydride in ethanol, afforded the medium-ring sulphide **104** in 87 % yield.

The same authors alkylated some sulphur-containing benzo-fused and saturated rings in a similar way (Scheme 34). Thus, the cyclic sulphides **106**, **108** and**110** were prepared from the thiines **105**, **107** and **109**, respectively.

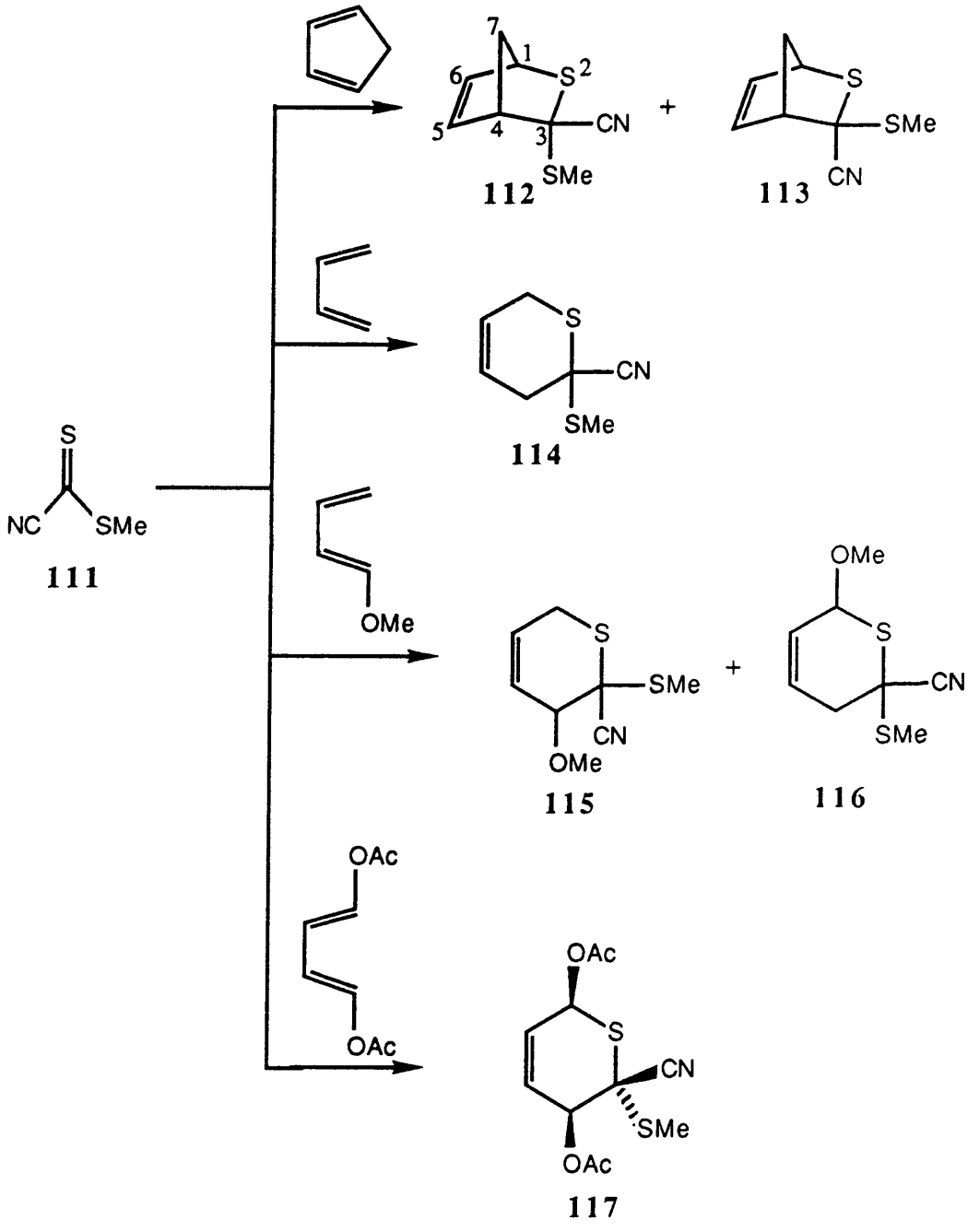


Scheme 34

1.4 Thiocarbonyl Diels-Alder Adducts in the Synthesis of Thiosugar Derivatives

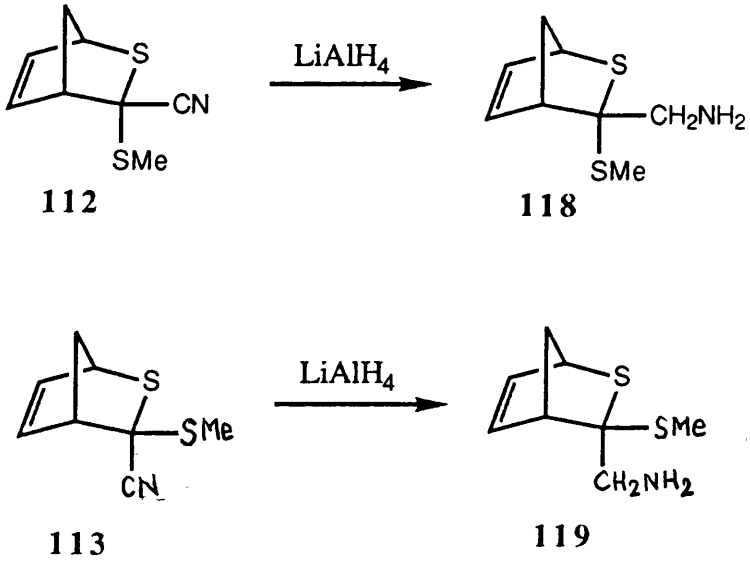
For the present discussion , thiosugars are taken to be analogues of sugars where the oxygen atom of the ring is replaced by a sulphur atom. Diels-Alder reactions have been

used in the synthesis of a variety of monosaccharides. But the synthesis of thiosugars has been achieved mainly from chemical modifications of readily available carbohydrate precursors.



Scheme 35

Vyas and Hay demonstrated[56-59] the usefulness of the Diels-Alder reaction in making thiosugar rings. They treated a number of 1,3-dienes with methyl cyanodithioformate (MCDF) (**111**) to prepare the corresponding cycloadducts (Scheme 35). Thus, treatment of MCDF with cyclopentadiene[56] gave the adducts **112** and **113** in the ratio 3:2. The adduct **112** was separated from the mixture by crystallisation. The ^{1}H NMR spectra of the adducts **112** and **113** showed sharp singlets for *endo* and *exo* S-methyl protons. The *endo* protons are shielded as a consequence of the vinylic diamagnetic anisotropy; so the upfield singlet at δ 2.36 was assigned to the *S*-methyl protons of the major adduct **112** and the downfield singlet at δ 2.44 to those of the minor adduct **113**. To determine the stereochemistry at C-3 of the adducts unequivocally, **112** and **113** were reduced to **118** and **119** with lithium aluminium



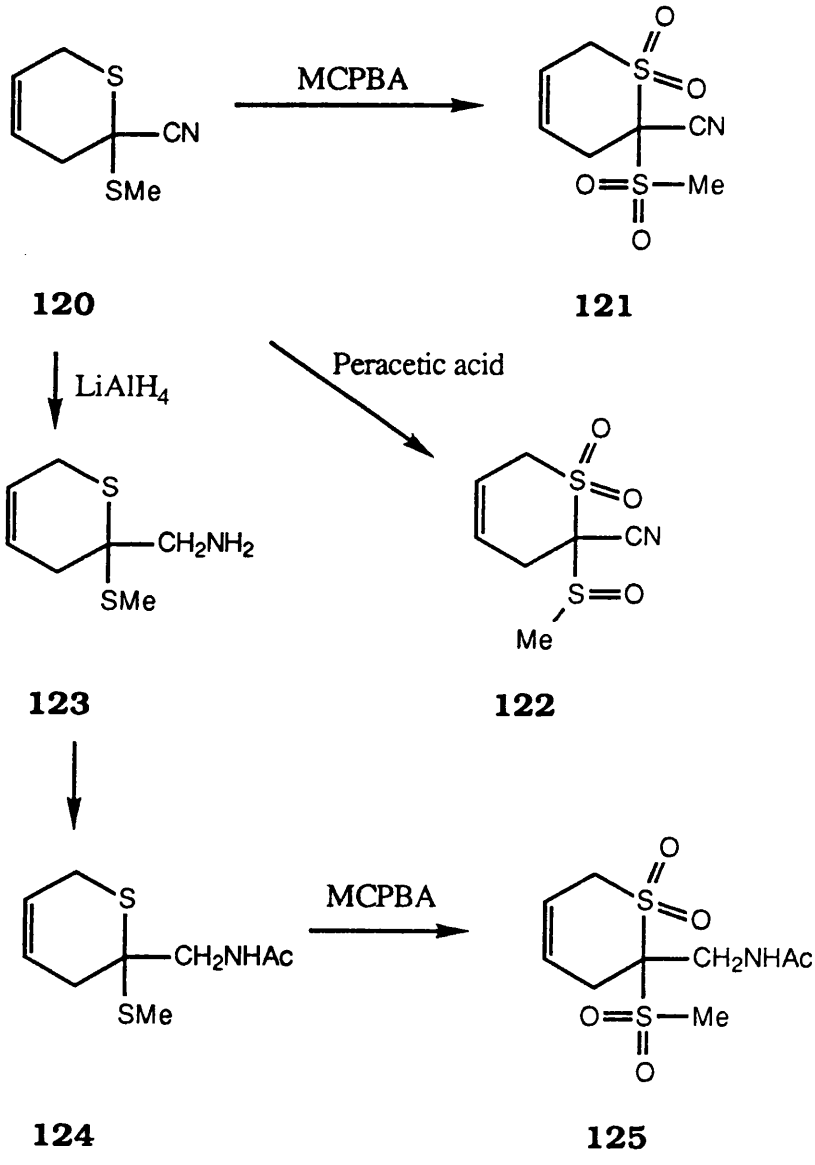
112 118

113 119

Scheme 36

hydride (Scheme 36). The NMR signal for the aminomethylene group in **118** appeared at δ 3.05, downfield of that in **119**, δ 2.70. This again confirmed that the major adduct **112**, which was converted into **118**, was the *endo* 3-*S*-methyl adduct.

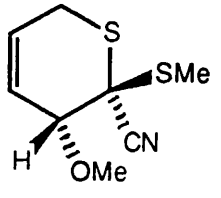
Treatment of the thiopyran **120** (Scheme 37) with *m*-chloroperbenzoic acid (MCPBA)[58] gave the *S*,*S*,*S*',*S*'-tetroxide **121** and with peracetic acid, the *S*,*S*,*S*'-trioxide **122**.



Scheme 37

Reduction of the adduct **120** with lithium aluminium hydride gave the amine **123**. *N*-Acetylation of **123** gave **124** and oxidation of **124** with MCPBA afforded **125**, the 6-acetamido-derivative of **121**.

Treatment of MCDF with *trans*-1-methoxybuta-1,3-diene afforded[57,59] predominantly one, crystalline regioisomer **115** (Scheme 35). Only traces of the regioisomer **116** was found in the mother liquors. The regioselectivity of MCDF was found



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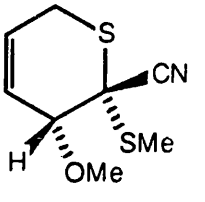

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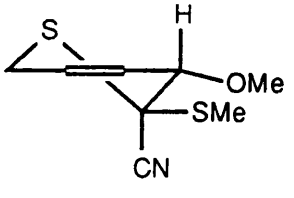

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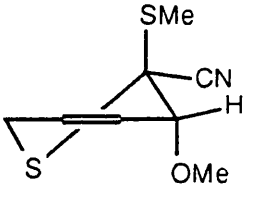

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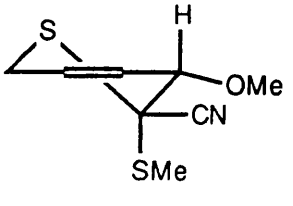

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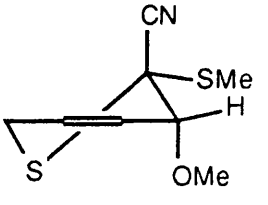


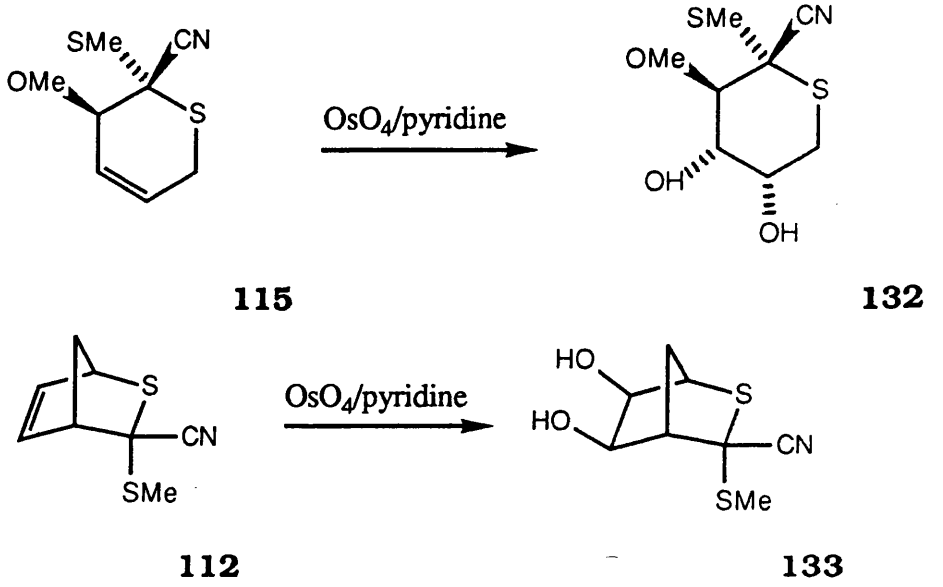
131

opposite to that of the carbonyl dienophiles with 1-methoxybuta-1,3-diene. The adduct **115** existed as a mixture of two

stereoisomers, the products of *endo* **126** and *exo* **127** cycloaddition, with respect to the cyano group. ^{1}H NMR studies established that **126** was the major isomer. The predominant conformation of **126** in deuteriochloroform was the half-chair **128**, where the methoxy group occupied a quasi-equatorial position. Similarly, the predominant conformation of the minor isomer **127**, was the half-chair **130**.

Treatment of *trans,trans*-1,4-diacetoxybuta-1,3-diene with MCDF[59] in refluxing benzene afforded one crystalline product **117** (Scheme 35). The structure of **117** was confirmed by its ^{1}H NMR and mass spectra.

Vyas and Hay treated the cycloadducts **115** and **112** with osmium tetroxide in pyridine[59] and obtained the corresponding *cis*-diols **132** and **133** (Scheme 38). The crystalline diol **132** was obtained in 70 % yield. The ^{1}H NMR spectrum of **132**

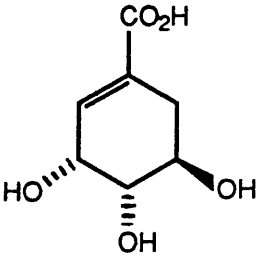


Scheme 38

showed that osmium tetroxide had attacked the double bond of **115** from the side opposite to the quasi-equatorial methoxy group. In deuteriochloroform solution **132** existed in a chair conformation with both methoxyl and *S*-methyl groups in equatorial positions. The crystalline diol **133** was obtained in 72 % yield. Here, osmium tetroxide attacked from the less-hindered, *exo* side.

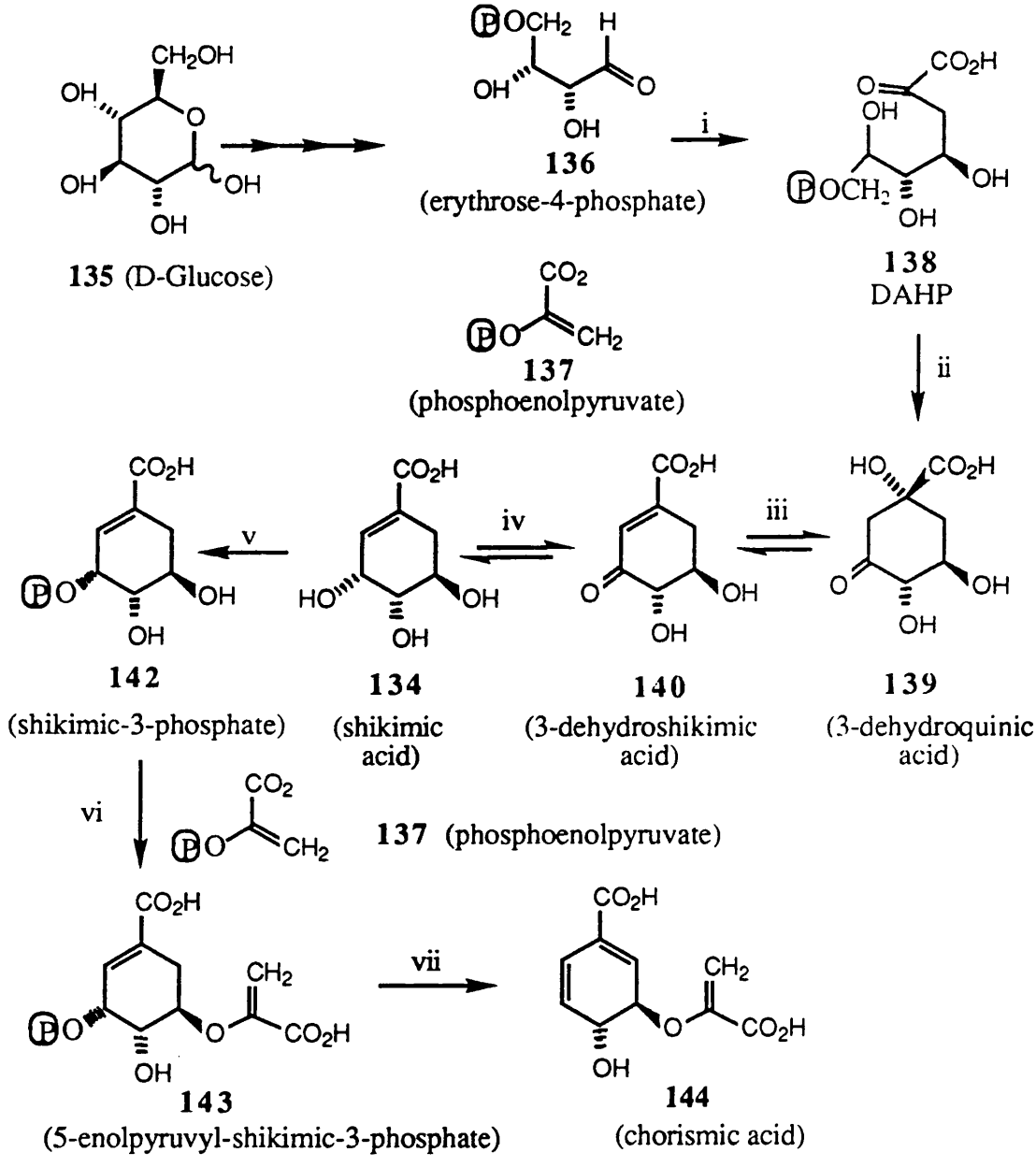
1.5 Shikimic Acid 134

Shikimic acid **134** was first described as a natural product in 1885 by Eykman.[60] Fischer and Dangschat[61-64] elucidated its structure as **134**. Shikimic acid was first isolated from the plant *Illicium religiosum Sieb.*, but its name was derived from the Japanese name of this plant, 'shikimi-no-ki'.



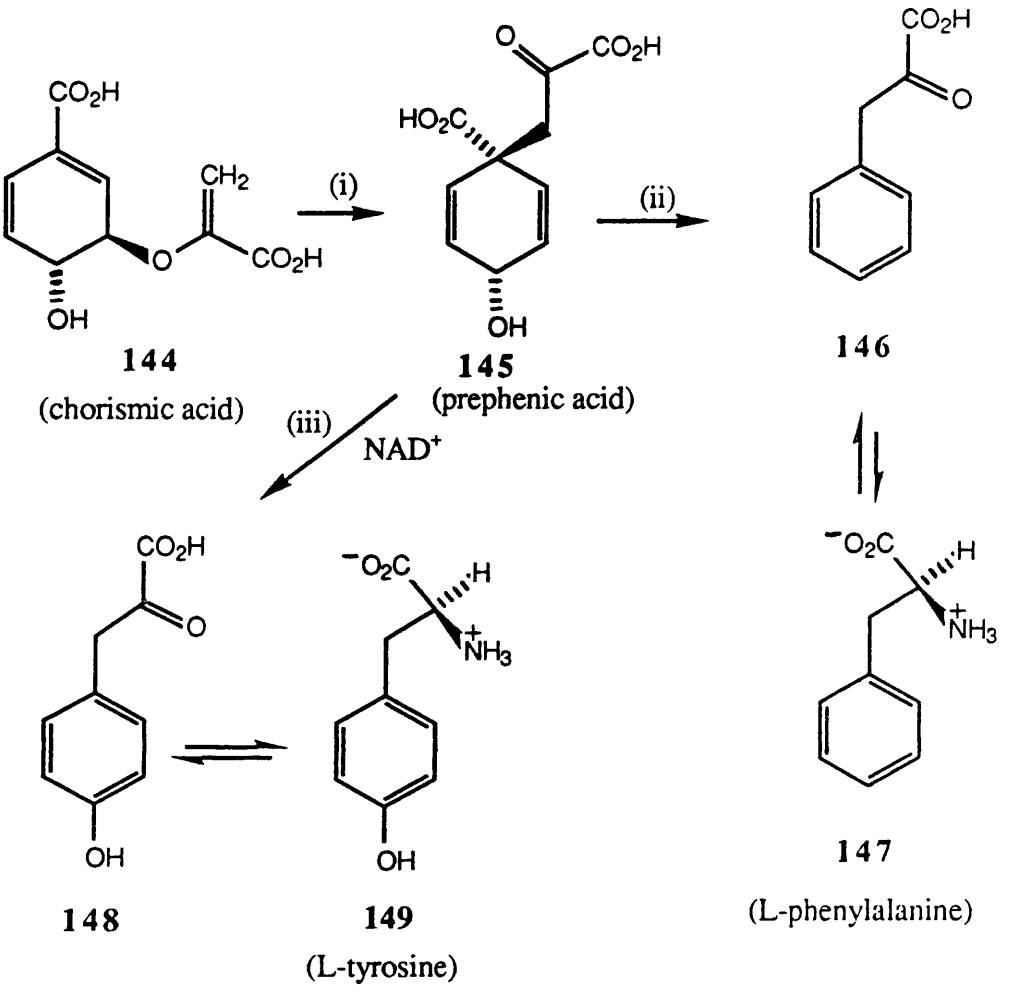
134

(-)-Shikimic acid is an obligatory intermediate in the metabolic pathway which leads from carbohydrates to the aromatic amino acids. (-)-Shikimic acid was the first of the intermediates in this pathway to be identified, hence the familiar name 'shikimate pathway'. An outline of the shikimate pathway from glucose to chorismic acid is shown in Scheme 39. A major branch point occurs at chorismic acid. This part of the metabolic sequence from carbohydrate to chorismic acid is generally referred to as the common pathway. That from chorismic acid to some of the essential aromatic amino acids is shown in Scheme 40. Here the discussion will be limited to the first two total syntheses of the acid, where Diels-Alder reactions of *trans,trans*-1,4-diacetoxybuta-1,3-diene were involved.



Scheme 39 The biosynthesis of chorismic acid

(i) 3-Deoxy-D-arabinoheptulosonic acid-7-phosphate (DAHP) synthetase
(ii) 3-Dehydroquinate synthetase[nicotinamide-adenine dinucleotide (NAD^+, Co^{2+})]
(iii) 3-Dehydroquinate dehydratase
(iv) 3-Dehydroshikimate reductase (NADPH)
(v) Shikimate kinase [(adenosine triphosphate (ATP)]
(vi) 5-enolpyruvylshikimate-3-phosphate synthetase
(vii) chorismate synthetase



(i) chorismate mutase

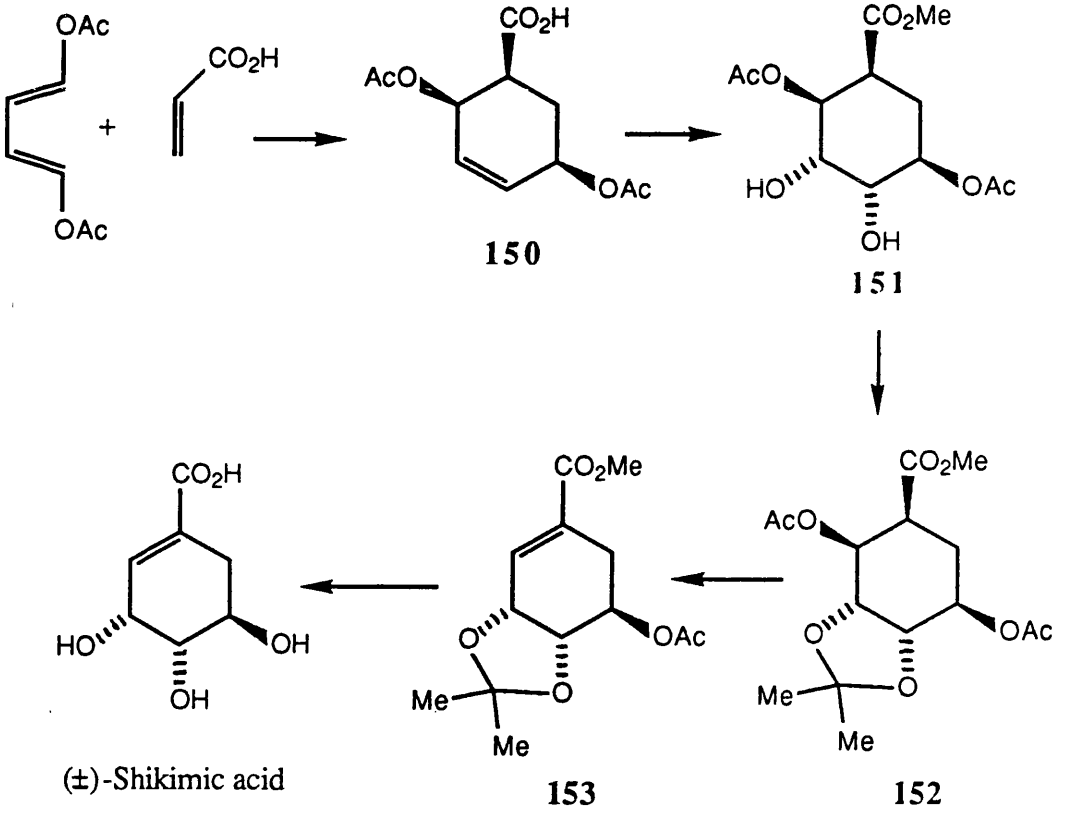
(ii) prephenate dehydratase

(iii) prephenate dehydrogenase

Scheme 40 The biosynthesis of L-phenylalanine and L-tyrosine from chorismimic acid

The first total synthesis of shikimic acid was reported[65] by McCrindle *et al* (Scheme 41). *trans,trans*-1,4-Diacetoxybuta-1,3-diene was allowed to react with acrylic acid to give the *cis,cis*-adduct **150**. Treatment of this adduct with osmium tetroxide followed by diazomethane yielded the

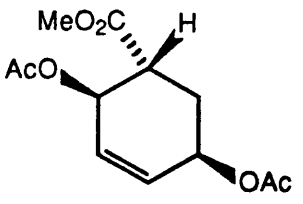
cis-diol ester **151**. The diol ester **151** was converted into its acetonide **152** by treating it with acetone in the presence of anhydrous copper sulphate. The acetonide **152** was heated to 290 °C with magnesium oxide to form **153** by elimination of acetic acid. Finally, hydrolysis of **153** afforded (±)-shikimic acid. A satisfactory resolution using the quinine metho-hydroxide salt of shikimic acid triacetate was accomplished.



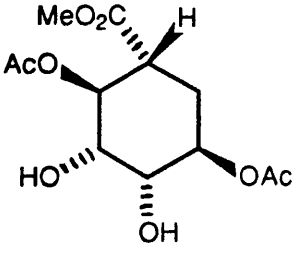
Scheme 41

A similar synthesis of shikimic acid was reported[66] by Smissman *et al.* They carried out the cycloaddition reaction of *trans,trans*-1,4-diacetoxybuta-1,3-diene with methyl acrylate to afford the *trans,cis*-adduct **154** in 93 % yield.

Osmium tetroxide converted **154** into the dihydroxy derivative **155**. The only difference between the two reported diols **151** and **155** was the stereochemistry of



154



155

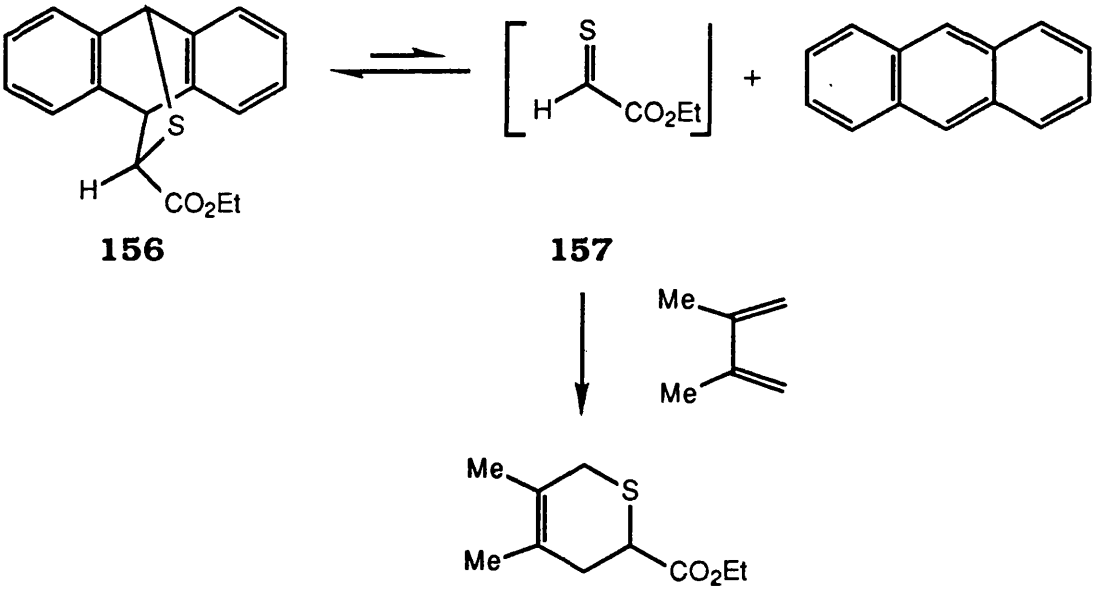
carbomethoxy group. McCrindle *et al.* assigned[65] it a β-configuration[*i.e.* β when drawn as shown in (**151**)] and Smissman *et al.* assigned it an α-configuration. The diol **155** was converted into its acetonide as before. All attempts at base-catalysed elimination of acetic acid from the diol **155** failed. Pyrolysis of the corresponding acetonide at 285 °C and 0.007 mm pressure brought about the elimination of acetic acid to give the desired shikimic acid derivative **153** in 93 % yield. Hydrolysis of **153** afforded (±)-shikimic acid, which was resolved using α-phenylethylamine to give (-)-shikimic acid.

CHAPTER 2

DISCUSSION OF EXPERIMENTAL RESULTS

2.1 Alkylation of the Diels-Alder Cycloadducts of Ethyl Thioxoacetate

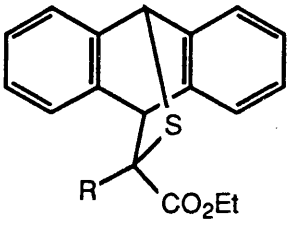
Thioaldehydes are extremely unstable species. A number of methods for their generation have been reported.[67] Generally the thioaldehydes are trapped *in situ* with dienes as Diels-Alder cycloadducts. The Diels-Alder adduct (**156**) of anthracene and ethyl thioxoacetate **157** has been proved[68] to



156 **157** **158**

Scheme 42

dissociate reversibly in refluxing toluene and thereby serves as a stable ancillary precursor for the labile thioaldehyde **157**. For example, when heated with 2,3-dimethylbuta-1,3-diene (DMB) the adduct **156** gave the dihydrothiine **158** in high yield along with anthracene (Scheme 42). It seemed likely that the corresponding cycloadducts **159** of anthracene and thioketones would behave similarly and facilitate studies on



159

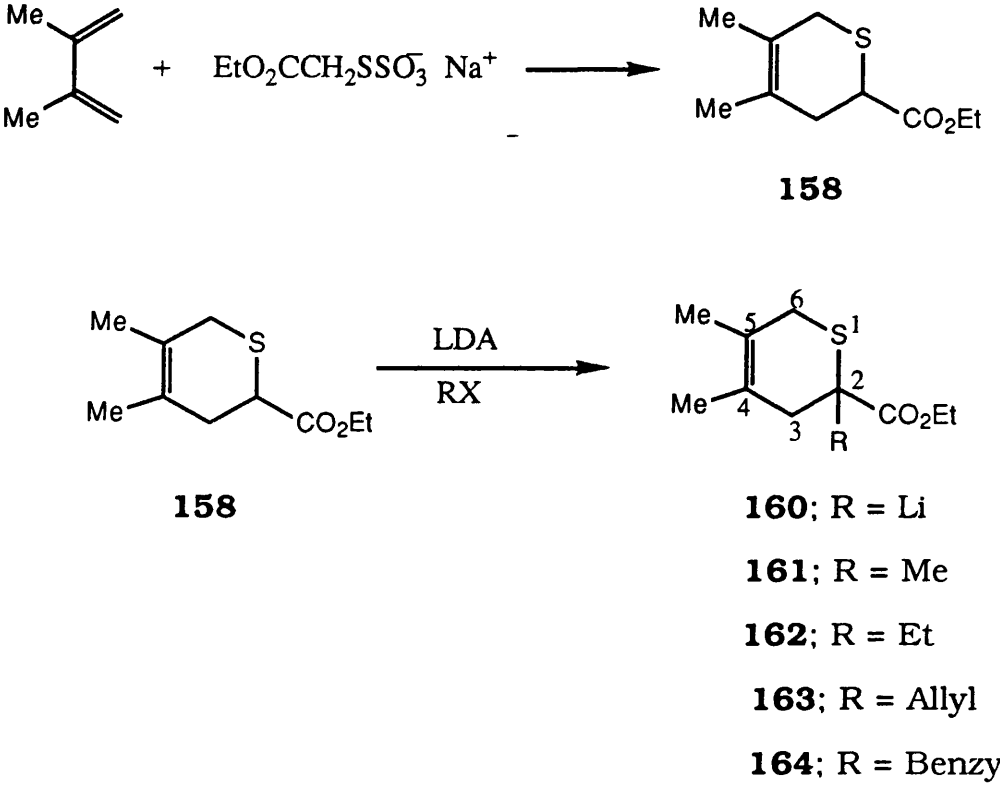
the chemistry of these unstable species. With this in mind we planned to investigate the alkylations of carbanions derived from various cycloadducts of ethyl thioxoacetate.

Dr. Mohajan, a senior visitor to the Department, began studies on the α-alkylation of the thioaldehyde cycloadducts towards the end of his stay in 1990. He confined his experiments to methylation reactions, with methyl iodide, and did not carry out any retro-Diels-Alder, 'transfer' reaction of thioketones. He did not have time to fully purify or characterise any of the methylation products of the dimethylbutadiene, anthracene, cyclopentadiene or cyclohexadiene cycloadducts. All his experiments therefore had to be repeated. Nevertheless, he discovered the rearrangement reactions of cyclopentadiene and cyclohexadiene adducts to give cyclopropane derivatives. He

found that the mono- and dianion of the dimethylbutadiene adduct did not rearrange; rearrangements of this adduct induced by initial *S*-methylation and *S*-ethylation were discovered by the present author.

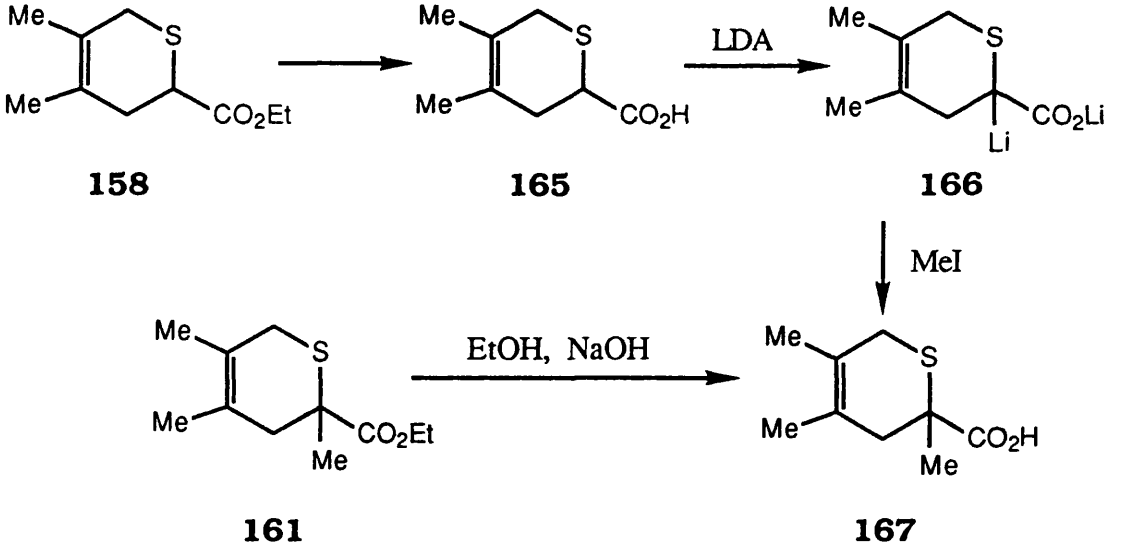
2.1.1 α-Alkylation of the dimethylbutadiene cycloadduct 158

The dimethylbutadiene cycloadduct **158** was prepared from dimethylbutadiene and the appropriate Bunte salt.[43]



Scheme 43

The 2-lithio derivative **160**, prepared by treatment of the cycloadduct **158** with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at - 78 °C, reacted with methyl iodide to give **161** as an oil in 78 % yield (Scheme 43). The ^{1}H NMR spectrum of **161** showed two broad AB quartets at δ 2.16 and 2.56 (*J* 17 Hz), and δ 2.85 and 3.17 (*J* 17 Hz) due to the methylene protons at C-6 and C-3. The 4- and 5-methyl protons gave broad singlets at δ1.63 and 1.65. The 2-methyl group gave a singlet at δ1.44. As usual, the ethoxy carbonyl group gave signals at δ1.19 (t, *J* 7.1 Hz, Me) and 4.10 (q, *J* 7.1 Hz, with fine splitting, OCH_2). The mass spectrum of **161** confirmed the molecular formula $C_{11}H_{18}O_2S$, and the IR spectrum showed a carbonyl stretching band at 1726 cm^{-1}.



Scheme 44

The ethyl ester **161** was hydrolysed, by keeping in ethanol and aqueous sodium hydroxide overnight, to the corresponding,

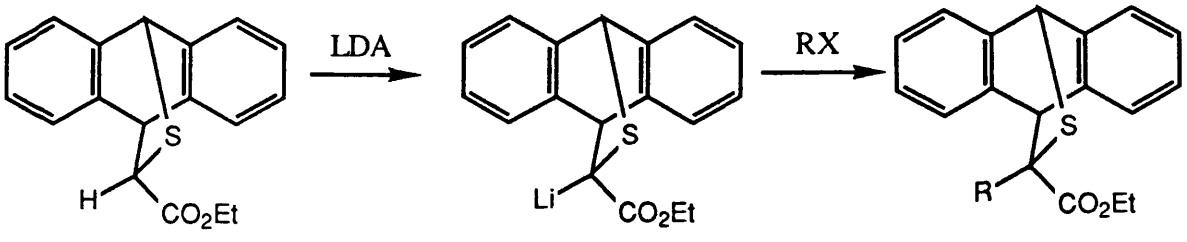
crystalline acid **167** for further characterisation (Scheme 44). The same acid **167** was also prepared in good yield by methylation of the dilithio derivative **166**, obtained from **165** by treatment with LDA (*ca.* 2.5 mol equiv.) in THF at - 78 °C, with methyl iodide (Scheme 44). The acid **167** was obtained as colourless crystal, m.p. 93-94 °C. Mass spectrometry and elemental analysis confirmed the molecular formula $C_{11}H_{18}O_2S$. The IR spectrum showed a carbonyl stretching band at 1702 cm^{-1} with broad absorption in the region of 2300-3500 cm^{-1}. The ^1H NMR spectrum showed the disappearence of the methyl and methylene protons of the ethoxy group of the parent ester **161**. Instead a broad singlet at δ 10.9, which disappeared after D_2O exchange, confirmed the presence of carboxyl group.

The 2-ethyl (**162**), 2-allyl (**163**) and 2-benzyl derivatives (**164**) were prepared in a similar way by treating the 2-lithio derivative **160** with ethyl iodide, allyl bromide and benzyl bromide respectively (Scheme 43). The 2-ethyl and 2-allyl derivatives **162** and **163** were obtained as oils in 72 % and 77 % yields. The 2-benzyl derivative **164** was obtained as a syrup in 78 % yield. Mass spectrometry confirmed the molecular formula of these compounds. Satisfactory elemental analyses of 2-ethyl and 2-benzyl derivatives **162** and **164** were obtained. ^1H NMR spectrum of the 2-ethyl derivative **162** showed signals for the methyl group of the 2-ethyl group as a triplet at δ 0.80 (*J* 7.5 Hz). The corresponding methylene group gave a quartet of AB quartets at δ 1.64 and 1.74 (J_{gem} 13.8 and J_{vic} 7.7 Hz). The 4- and 5-methyl signals appeared as a broad

singlet at δ1.55. In the ^{1}H NMR spectrum of 2-allyl derivative **163** the following signals confirmed the presence of the allyl group; δ 2.43 and 2.55 (2 x ddt, *J* 13.9, 7.5 and 1.1 Hz, CH_2=CH-C**H**$_2$), 5.01 and 5.08 (2 x m, C**H**$_2$=CH) and 5.61-5.82 (m, CH_2=C**H**-CH_2). Finally, the 2-benzyl derivative **164** showed an AB quartet at δ 3.04 and 3.22 (*J* 13.5 Hz) arising from 2-methylene protons. The aromatic protons gave a multiplet at δ 7.12-7.30.

2.1.2 α-Alkylation of the anthracene cycloadduct

The cycloadduct **156** of anthracene and ethyl thioxoacetate was prepared according to the literature[69] method. The lithium derivative **168** was prepared by treating **156** with LDA in THF at - 20 °C. The reaction mixture was



156 **168** **169**; R = Me

170; R = Et

171; R = Allyl

172; R = Benzyl

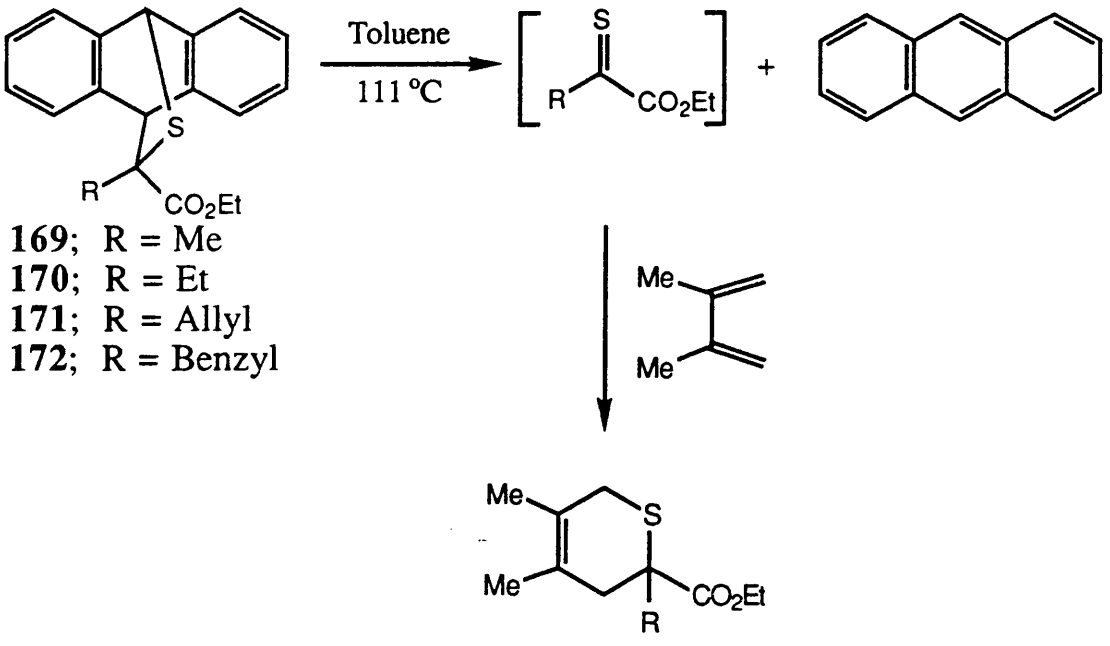
Scheme 45

allowed to warm up to 20 °C,then was cooled to - 40 °C before the alkyl halides were added to the mixture (Scheme 45). Treatment of the lithio derivative **168** with methyl iodide gave

the 12-methyl derivative **169** as thick plates, m.p. 131-132 °C (from dichloromethane/light petroleum). Similar treatment with ethyl iodide, allyl bromide and benzyl bromide afforded the corresponding 12-ethyl, 12-allyl and 12-benzyl-derivatives **170**, **171** and **172**, respectively. Accurate mass measurements and elemental analyses of all the 12-alkyl derivatives confirmed their molecular formula. The 12-methyl derivative **169** was obtained in 87 % yield. The IR spectrum showed a carbonyl stretching band at 1729 cm^{-1}. The ^1H NMR (90 MHz) spectrum of **169** showed a three proton signal at δ1.41 for the 12-methyl protons. 9- And 10-H gave singlets at δ 4.76 and 5.03. The 12-ethyl derivative **170** was obtained as crystals, m.p. 104 °C (from light petroleum), in 83 % yield. A triplet at δ 0.81 and a multiplet at δ 1.1-2.1 were assigned to the 12-methyl and methylene protons respectively. The IR spectrum of **170** showed carbonyl stretching bands at 1731 and 1718 cm^{-1}. The 12-allyl and 12-benzyl derivatives **171** and **172** were also obtained crystalline in 87 % and 81 % yields. The ^1H NMR spectra clearly showed the presence of 12-allyl and 12-benzyl groups (see the foregoing description of the corresponding thiines **163** and **164**).

2.1.3 Retro-Diels-Alder reactions of the thioketone anthracene cycloadducts

When the anthracene cycloadducts **169-172** were each heated with DMB in toluene under reflux for several hours the corresponding DMB adducts **161-164** were obtained in high yields , together with anthracene (Scheme 46). No by-products that might have arisen from competitive 'ene'



169; R = Me
170; R = Et
171; R = Allyl
172; R = Benzyl

161; R = Me
162; R = Et
163; R = Allyl
164; R = Benzyl

Scheme 46

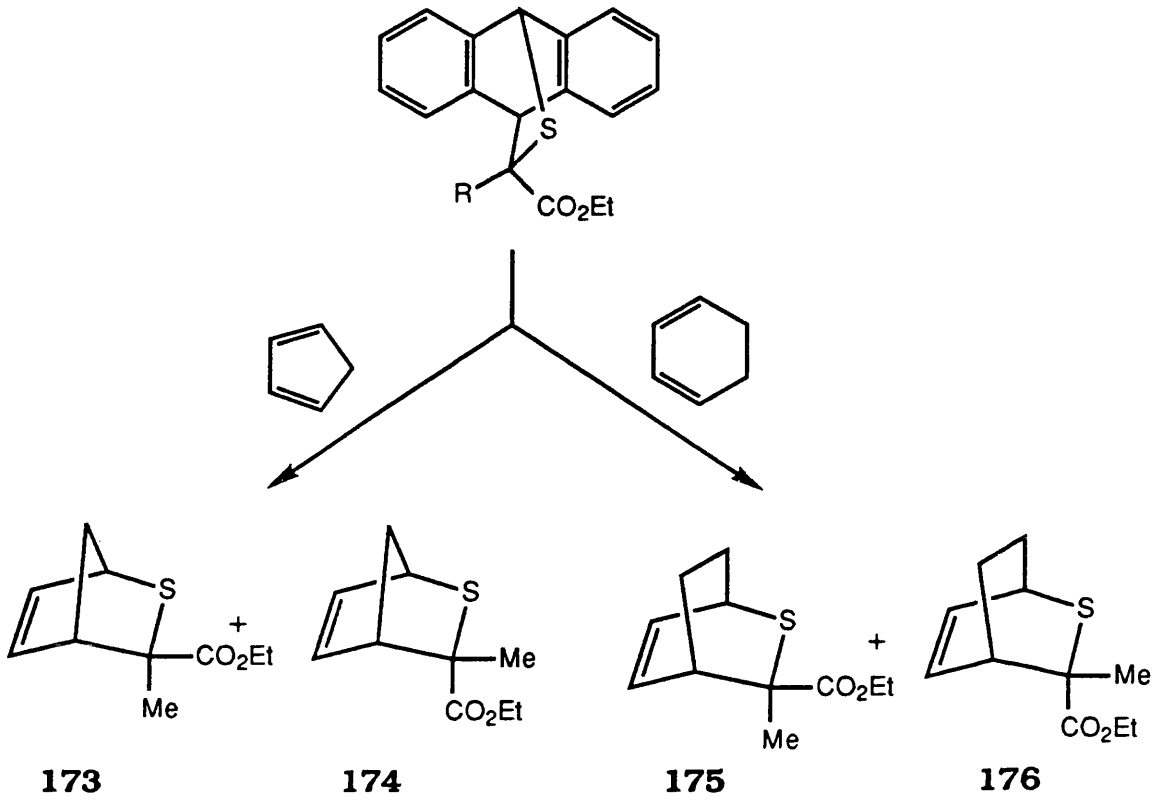
reactions[68] were detected. Qualitative estimations of the rates of these thioketone 'transfer' reactions (TLC monitoring) indicated that they did not differ greatly from that of the parent thioaldehyde. This was verified, for the methyl thioketone, by a simple competition experiment. Thus equimolecular amounts of the thioaldehyde **156** and thioketone **169** adducts and DMB were heated until the reactions were judged (TLC) to be complete (6h). Analysis of the mixture of products by ^{1}H NMR spectroscopy showed that the dihydrothiines **158** and **161** were present in approximately equal amounts. Very little, if any, of the anthracene adducts

156 and**169** remained. This latter observation suggested that the anthracene cycloadducts **156** and **169** must decompose when heated alone for prolonged periods. This was confirmed by separate, cotrol experiments; the decomposition products were anthracene and ill-defined polymers.

The ready dissociation of the thioketone cycloadducts was gratifying since it should allow the chemistry of labile thioketones to be explored using the convenient ancillary precursors under clean conditions.

2.1.4 Preparation of the α-methyl cycloadducts of cyclopentadiene and cyclohexadiene

By heating the 12-methyl anthracene cycloadduct **169** separately with cyclopentadiene and cyclohexa-1,3-diene in toluene under reflux the corresponding cycloadducts **173** and **174**, and **175** and **176** were obtained in high yields (Scheme 47). The cyclopentadiene adducts **173** and **174** were formed in a *ca.* 3:1 ratio, as measured by ^{1}H NMR spectroscopy. The reaction mixture was evaporated and the residue was triturated with methanol and set aside to allow anthracene to crystallise out. The mixture was filtered and the filtrate was evaporated. The residue was shown, by ^{1}H NMR spectroscopy, to contain the cycloadducts **173** and **174** with traces of anthracene. Coloumn chromatography on silica gel afforded pure 3-*exo*-caboxylate **173** and 3-*endo*-carboxylate **174** as oils in 60 % and 20 % yields respectively. Accurate mass measurement and elemental analysis of **173** and **174** confirmed



173 **174** **175** **176**

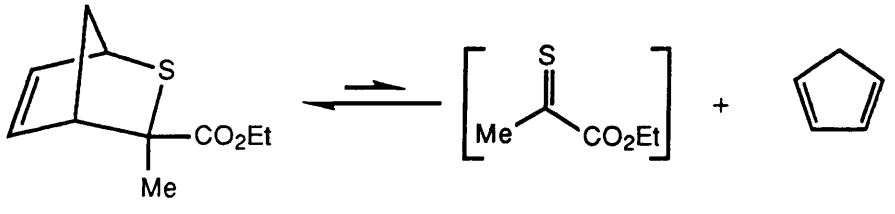
Scheme 47

the molecular formula $C_{10}H_{14}O_2S$. The IR spectra showed the carbonyl stretching band of **173** at1728 cm^{-1} and of **174** at 1730 cm^{-1}. The ^1H NMR spectra showed that the 3-*endo*-methyl protons in **173** resonated at a much higher field (δ 1.38) than 3-*exo*-methyl protons in **174** (δ 1.82), on account of shielding by the 5,6-double bond. This observation allowed the stereochemistry of the epimeric cycloadducts to be assigned.

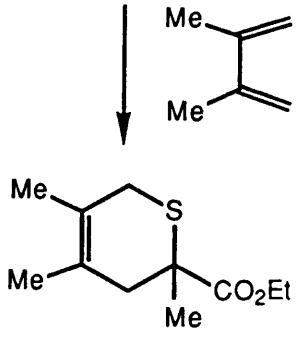
The cyclohexadiene adducts **175** and **176** were formed in approximately equal amounts and could not be separated. They were characterised as a mixture. Accurate mass

measurement confirmed their molecular formula $C_{11}H_{16}O_2S$ and the IR spectrum showed the carbonyl stretching band at 1727 cm^{-1}. In the ^1H NMR spectrum of the mixture **175** was identified by the relatively high field signal at δ 1.37 for the *endo*-3-methyl protons. The *exo*-3-methyl protons resonated at δ 1.71.

Kirby and co-workers showed[42-44] that the *endo*- and *exo*-cycloadducts of cyclopentadiene and ethyl thioxoacetate dissociate when heated in toluene, like the anthracene adduct **156**, and may also be employed as ancillary precursors of the thioaldehyde. The major cycloadduct **173** of the methyl thioketone and cyclopentadiene was found to behave similarly.



173



161

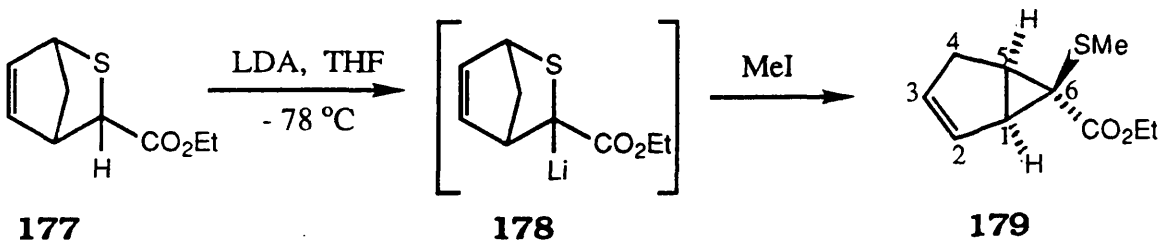
Scheme 48

This cycloadduct **173** and dimethylbutadiene were heated under reflux in toluene for 4 hours. Evaporation of the

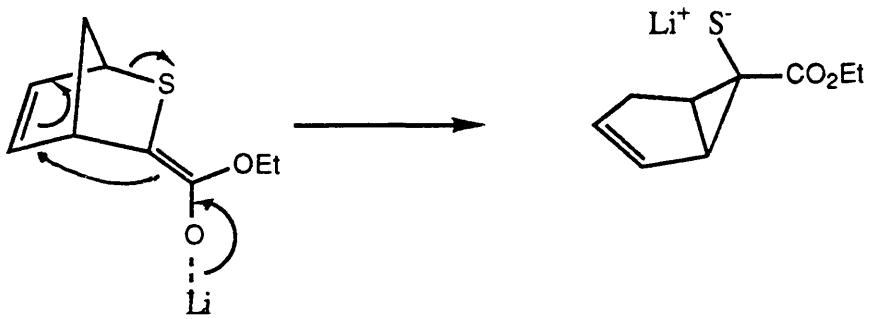
mixture gave the DMB adduct **161** as the only significant product. Naturally, for preparative purposes there would be little point in forming cyclopentadiene adducts from the corresponding anthracene cycloadducts, which are equally efficient precursors of thioketones. However, a wide range of cycloadducts of cyclopentadiene may, in principle, be prepared by trapping, *in situ*, transient thioketones formed, for example, by 1,2-elimination of sulphenyl derivatives. It was therefore important to verify the feasibility of using cyclopentadiene cycloadducts as precursors of thioketone.

2.1.5 Rearrangements of cyclopentadiene and cyclohexadiene cycloadducts

α–Alkylation of the cycloadduct of cyclopentadiene and ethyl thioxoacetate was investigated, since it might provide an alternative general route to the corresponding thioketone adducts. A mixture of the *endo* and *exo* stereoisomer **177** was treated with LDA in THF at - 78 °C to form the lithio derivative **178** (Scheme 49). Methyl iodide was added to the mixture, which was then allowed to warm up to room temperature. No significant amounts of the 3-methyl derivative **173** and **174** were formed; instead the cyclopropane derivative **179** was obtained in 89 % yield, as an oil. Accurate mass measurement of **179** confirmed its molecular formula $C_{10}H_{14}O_2S$. The IR spectrum showed cabonyl stretching bands at 1729 and 1712 cm^{-1}. The ^1H NMR spectrum was



177 **178** **179**

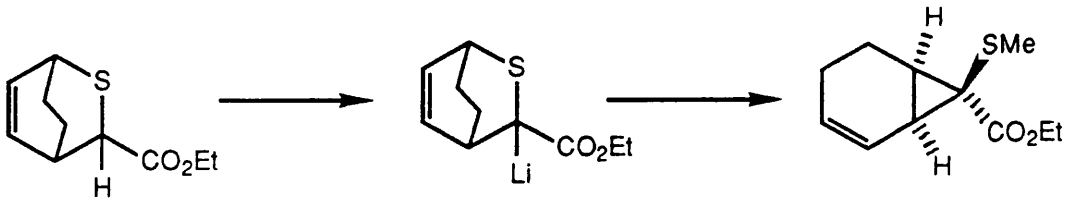


180 **181**

Scheme 49

quite different from that of the α–methyl compound **173** and **174**. The following ^{1}H NMR spectrum confirmed the structure **179**: 1.26 (t, *J* 7.1, OCH_2**Me**), 1.97 (s, SMe), 2.28 (dq, *J* 18.5 and *ca.* 2, 4-H), 2.61 (ddt, *J* 18.5, 6.6 and *ca.* 2, 4-H), 2.76 (dt, *J* 6.7, and *ca.* 2, 1-H), 4.15 (q, *J* 7.1, OCH_2Me), 5.72 (dq, *J* 5.5 and *ca.* 2, 2- or 3-H), and 5.81 (dm, *J* 5.5, 3- or 2-H). The ^{1}H NMR spectrum showed the formation of a single stereoisomer of the cyclopropane derivative **179** which may be explained by a concerted rearrangement, **180** → **181**, as ahown in the Scheme 49.

Similar attempts of *C*-methylation of the lithio derivative **183** of the cyclohexadiene adduct **182** gave instead the cyclopropane derivative **184** in good yield as a single



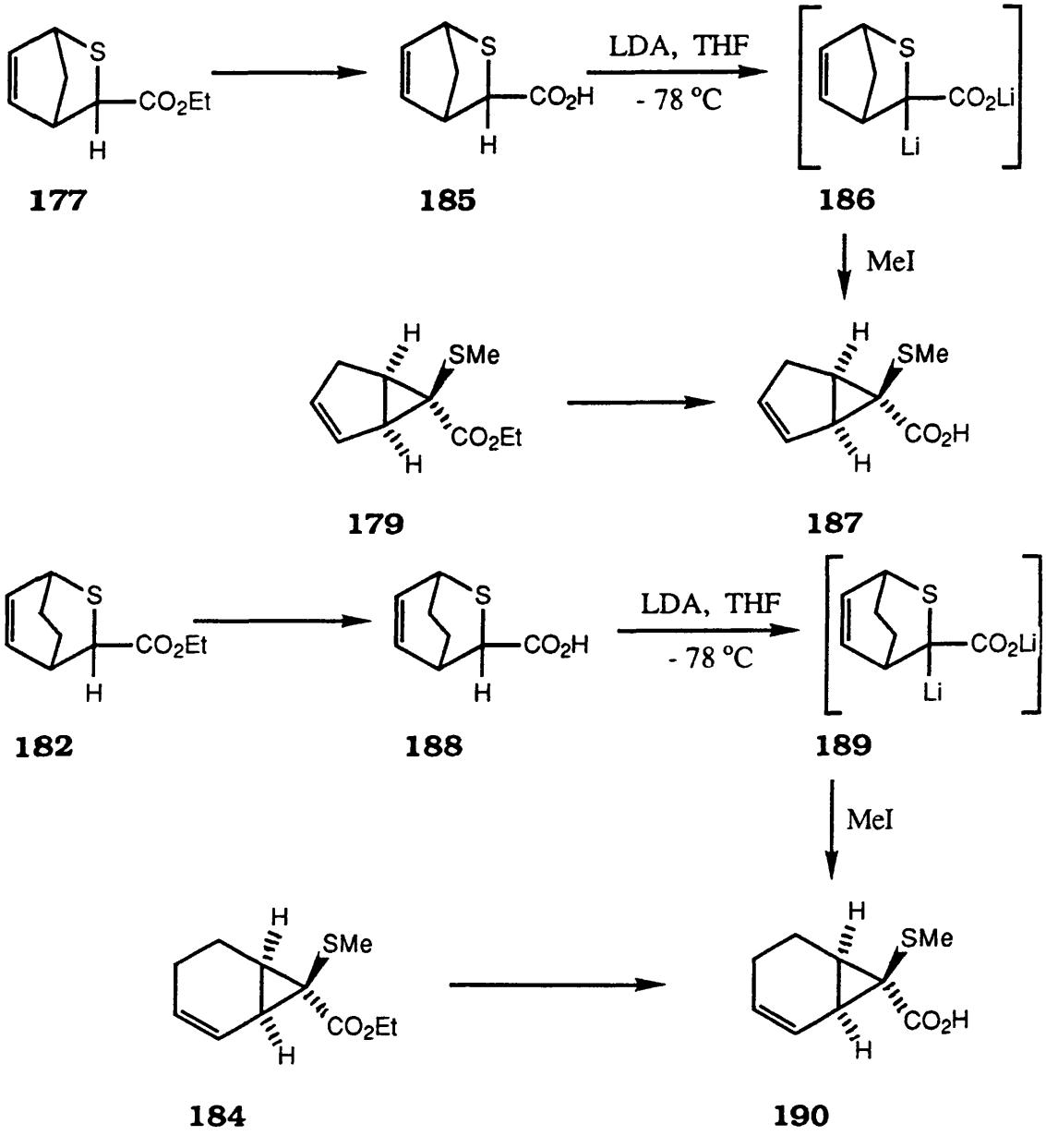
182 **183** **184**

Scheme 50

stereoisomer (Scheme50). Accurate mass measurement of **184** confirmed the molecular formula $C_{11}H_{16}O_2S$. The IR spectrum showed carbonyl stretching band at 1705 cm^{-1}. In the ^1H NMR spectrum of **184** the 4- and 5- methylene protons gave multiplets at δ 1.92-2.16, and the 1- and 6-protons gave multiplets at δ 1.81-1.92. Signals for 2- and 3-H appeared at δ 5.76 (dm, *J* 9.9 Hz) and δ 5.83 (dt, *J* 9.9 and 3.5 Hz).

Methylation of the dilithio derivatives **186** and **189**, obtained from the corresponding acids **185** and **188**, were briefly studied. The acids **185** and **188** were prepared by hydrolysing the adducts **177** and **182** with sodium hydroxide (Scheme 51). Lithiation of the corresponding carboxylic acids was effected, in the usual way, in THF with LDA (*ca.* 2.5 mol equiv). When the bicyclic dilithio derivatives **186** and **189** were treated with methyl iodide, they underwent rearrangement and *S*-methylation, in the manner observed for the corresponding monolithio esters, to give the cyclopropanecarboxylic acids **187** and **190** respectively. These last acids were also prepared by hydrolysing the cyclopropane

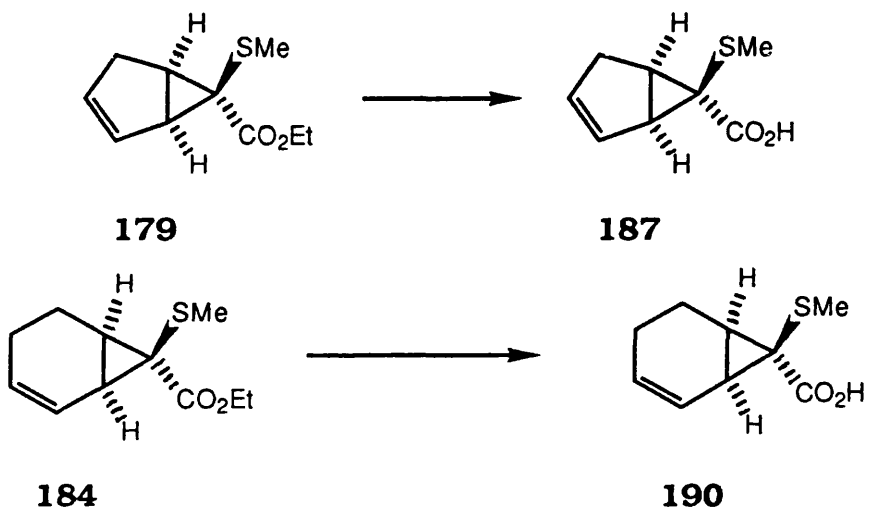
esters **179** and **184** with sodium hydroxide.



Scheme 51

2.1.6 Rearrangement of the carboxylic acid 190 derived from the cyclopropane ester derivative 184 to lactones.

The oily cyclopropane derivatives **179** and **184** were each hydrolysed with sodium hydroxide to the corresponding crystalline acids **187** and **190** in high yields, for further characterisation. The acid **187** had m.p. 104-105 °C and the acid **190** had m.p. 110-111 °C. Elemental analyses and accurate mass measurement confirmed their molecular



179 **187**

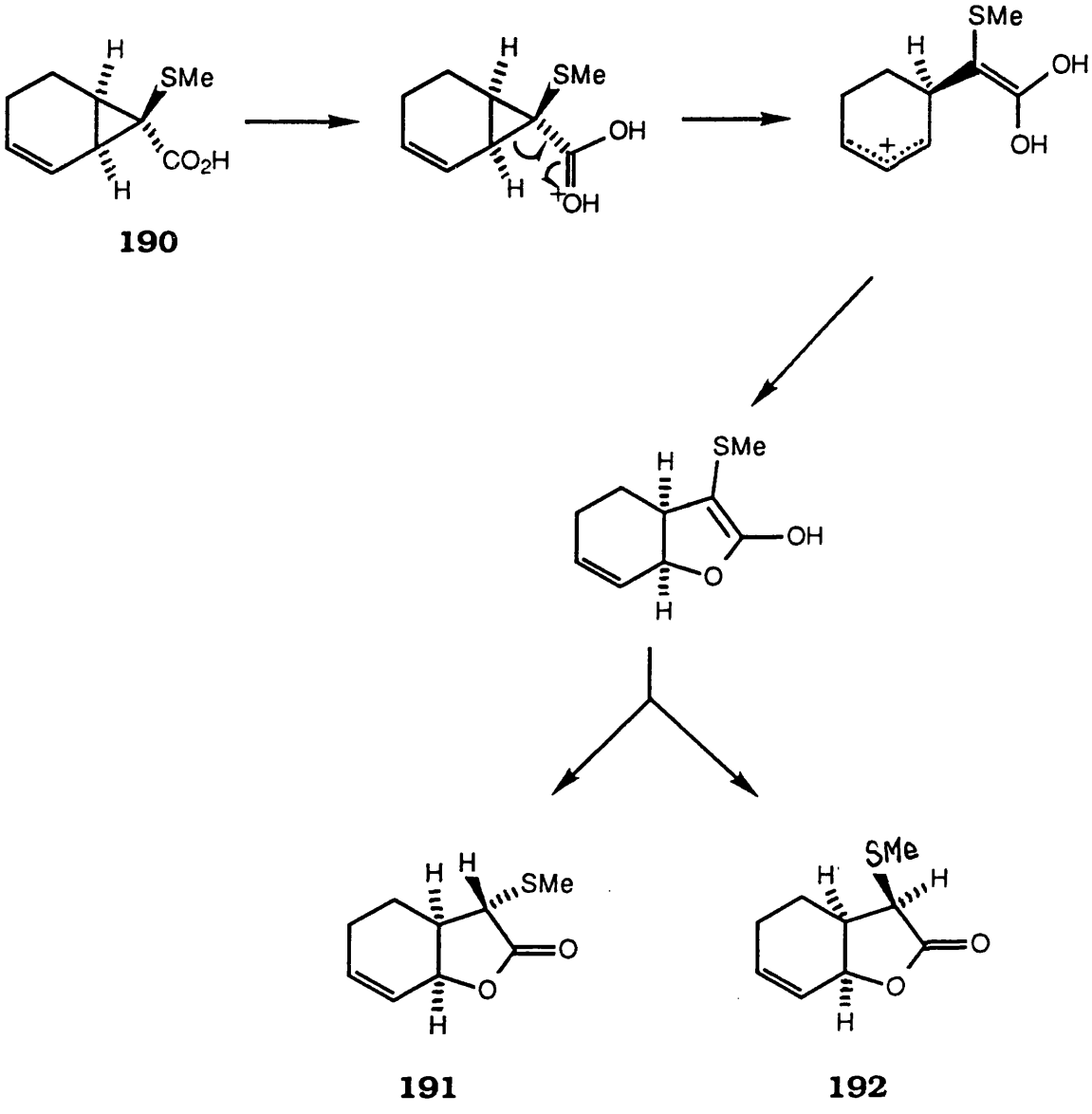
184 **190**

Scheme 52

formula. The IR spectrum of **187** showed broad absorption band at 2300-3400 cm^{-1} and carbonyl stretching band at 1685 cm^{-1}; the acid **190** showed strong absorption at 1687 cm^{-1} and weak absorption at 1740 cm^{-1}.

It was observed that a sample of the acid **190** had largely decomposed after beeing stored at room temperature for several months. The ^1H NMR spectrum of the decomposed sample indicated the presence of two lactones **191** and **192** in

similar amounts (Scheme 53). For isolation and characterisation, these lactones were prepared by treatment of the acid **190** with hydrochloric acid in chloroform. Under these reaction conditions the lactones were formed in the ratio **191**:**192** = *ca.* 2:1. Chromatography of the mixture on silica



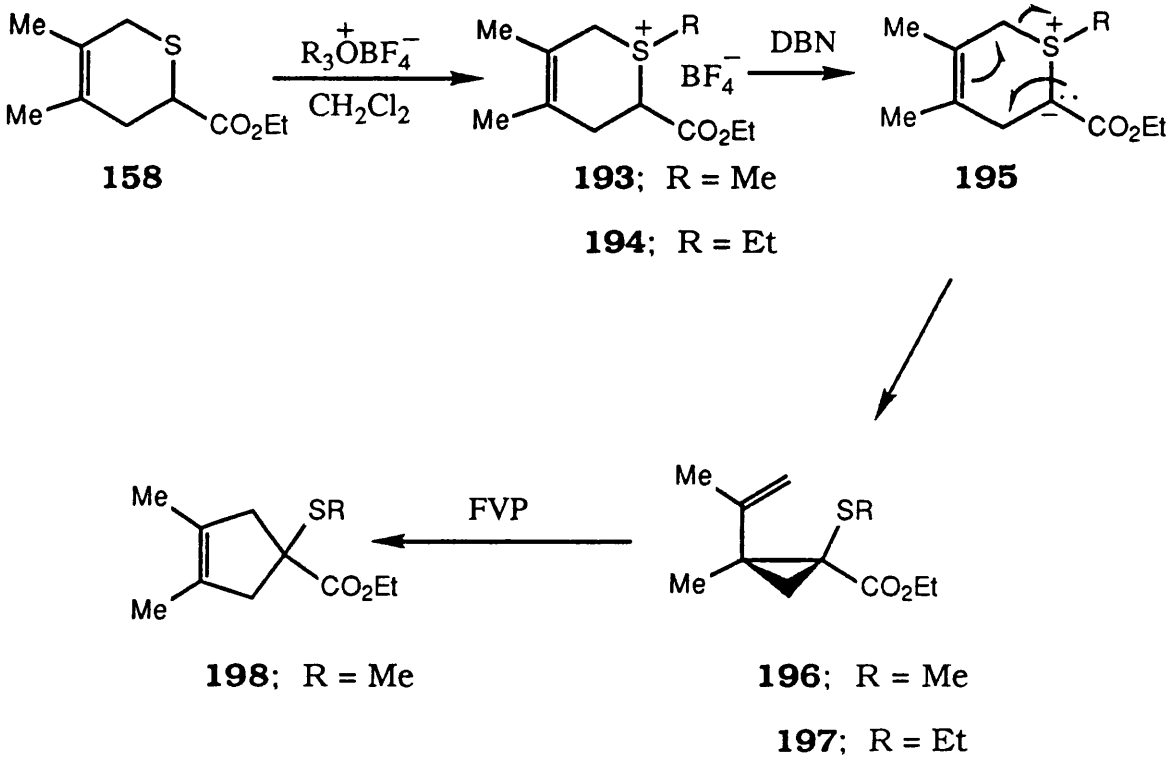
Scheme 53

gel gave the major γ-lactone **191** as an oil and the minor γ-lactone **192** as needles, m.p. 75-76 °C. Accurate mass measurement and elemental analysis of **192** confirmed the molecular formula $C_9H_{12}O_2S$. The IR spectrum of the major lactone **191** and the minor lactone **192** showed υ_{max} (CCl_4) 1762 and 1764 cm^{-1} respectively, conferming the γ-lactone structures. The relative stereochemistry, including the *cis* ring fusion, of the epimeric lactones was deduced from the ^1H NMR spectra. The vicinal coupling constant for the major epimer **191** was $J_{1,9}$ 3.9 Hz, and for the minor epimer **192** $J_{1,9}$ 7.3 Hz. These *J* values were consistent with the relative magnitudes of the relevent torsion angles observed in models. Presumably, acid-catalysed opening of the cyclopropane ring is facilitated by formation of an allylic carbocation (Scheme 53). In the crystalline state, protonation of the carboxy group must be effected by that in a neighbouring molecule; the two carboxy groups may already be connected by a hydrogen bond. In contrast, the related cyclopenteno acid **187** remained unchanged after 30 days at room temperature. No attempt was made to effect its rearrangement by treatment in solution with a strong acid.

2.1.7 S-Alkylation and rearrangement of the dimethylbutadiene adduct 158 to cyclopropane derivatives 196 and 197.

As mentioned earlier, mono- **160** and dilithio **166** derivatives of the DMB adduct underwent *C*-alkylation. When

the monocyclic dilithio derivative **166** was kept at room temperature for several hours, in the absence of methyl iodide, no rearrangement to a cyclopropanecarboxylic acid occurred. Acidification of the mixture regenerated the thiinecarboxylic acid **166**. However, the carbanions derived from the corresponding sulphonium salts **193** and **194** rearranged rapidly. Thus, the cycloadduct **158** was treated with either trimethyl- or triethyl-oxonium tetrafluoroborate at room temperature to afford the sulphonium salts **193** and **194** (Scheme 54). These were converted cleanly into the oily cyclopropanecarboxylates **196** and **197** upon treatment with diazabicyclononene (DBN). Accurate mass measurement



Scheme 54

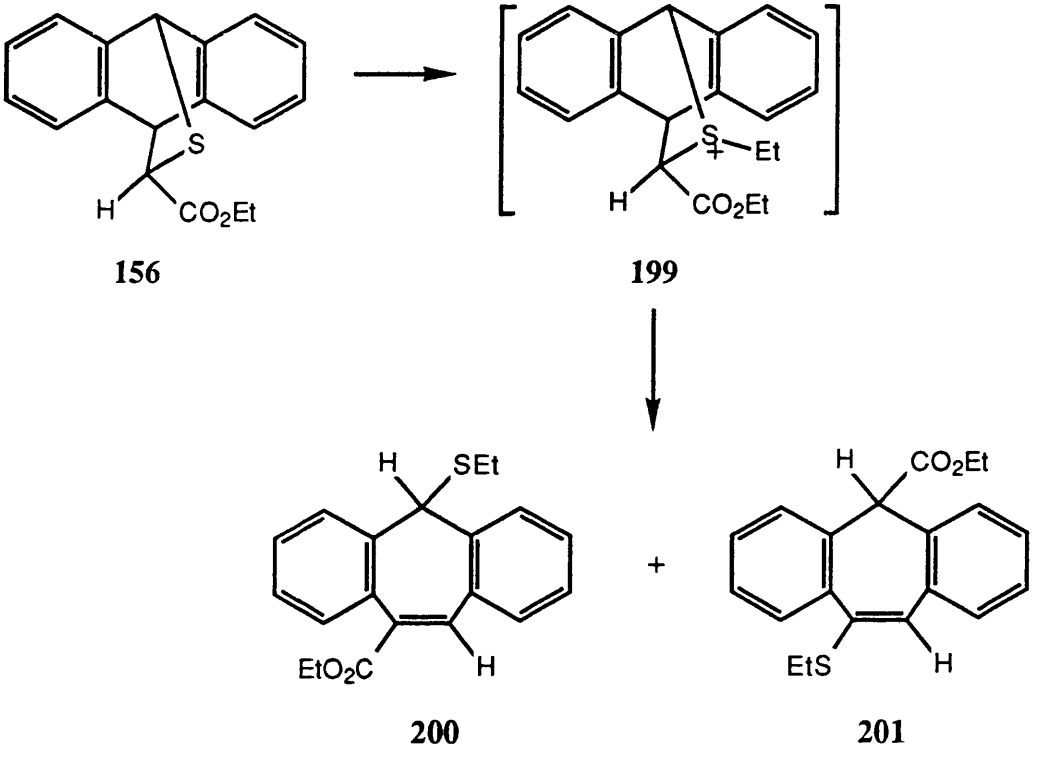
confirmed their molecular formula. The IR spectrum of **196** and **197** showed carbonyl stretching bands at 1720 and 1713 cm^{-1}, respectively. The ^1H NMR spectrum of **196** showed two quintets at δ 4.83 (*J* 0.8 Hz) and δ 4.91 (*J* 1.5 Hz), assigned to the olefinic protons. The 3-methylene protons resonated at δ 1.28 and 1.63 (*J* 5.1 Hz) as an AB quartet. Both **196** and **197** were formed stereospecifically, as expected for concerted rearrangements, of the familiar type **195**→**196**, of the sulphur ylides **193**.

The foregoing rearrangements provide efficient 'one pot' routes for the conversion of thioaldehyde cycloadducts into substituted, functionalised cyclopropanes. The methyl ester of the acids **187**, **190** and **196** were prepared earlier[70] by an alternative route involving cationic cycloadditions.

The *S*-methyl cyclopropane derivative **196** was pyrolysed at 400 °C and 10^{-2} mbar to yield the symmetrical cyclopentene derivative **198** as an oil. Accurate mass measurement of **198** confirmed the molecular formula $C_{11}H_{18}O_2S$. The IR spectrum showed the carbonyl stretching band at 1728 cm^{-1}. The ^1H NMR spectrum of the cyclopentene derivative **198** showed a broad AB quartet of four proton units at δ 2.41 and 2.99 (*J ca.*16.5 Hz), which was assigned to 2- and 5-CH_2. The 3- and 4-methyl protons gave signals at δ 1.55 as a broad singlet, and the *S*-methyl group resonated at δ 2.04 as a singlet. The thermal rearrangement **196**--**198** has precedence in the literature[71].

2.1.8 S-Ethylation and rearrangement of anthracene cycloadduct

Both mono- **178** and **183** and dilithioderivatives **186** and **189** of the bicyclic cycloadducts of cyclopentadiene and cyclohexadiene and ethyl thioxoacetate underwent rearrangement and *S*-methylation (Schemes 49, 50 and 51). But the carbanion derived from the anthracene cycloadduct **156** underwent *C*-alkylation in high yield when treated with



156 **199** **200** **201**

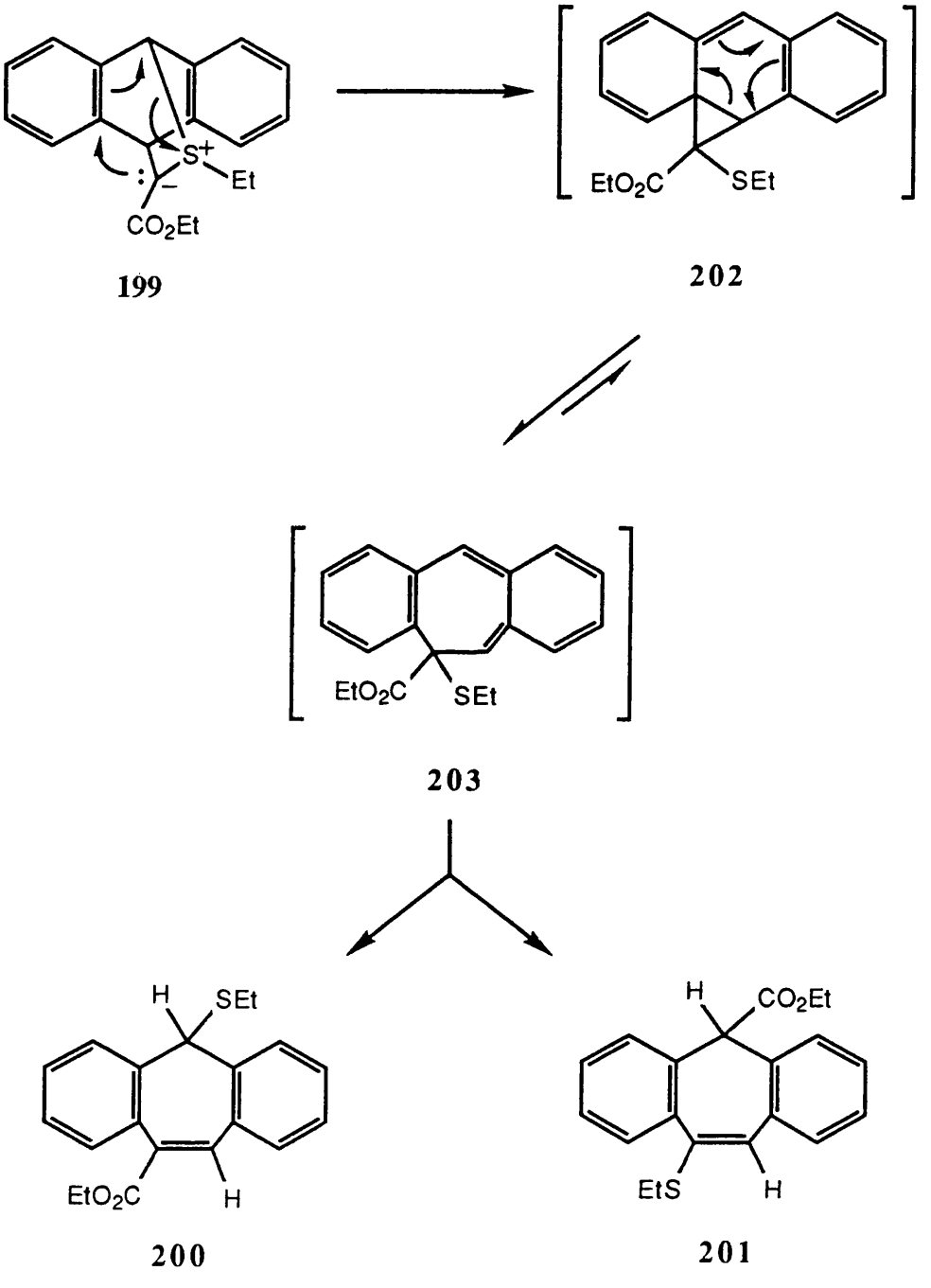
Scheme 55

alkyl halides. No rearrangement products were detected in these reactions. Initial *S*-alkylation and then base-induced rearrangement of the dimethylbutadiene adduct **158** to cyclopropane derivatives **196** and **197** (Scheme 54)

encouraged us to investigate whether a similar type of rearrangement might occur with the anthracene cycloadduct **156**. Thus, we treated the adduct **156** with triethyloxonium tetrafluoroborate to afford the sulphonium salt **199** (Scheme 55). The sulphonium salt **199** was treated with DBN to yield a mixture of two isomers in the ratio *ca.*3:1 as judged by their ^{1}H NMR spectrum. The major and minor isomers were tentatively assigned the structures **200** and **201**, respectively. The isomers could not be separated and were characterised as a mixture. The ^{13}C NMR spectra and accurate mass measurement confirmed their molecular formula $C_{20}H_{20}O_2S$. The IR spectrum showed absorption at 1228, 1251, 1707 and 3018 cm^{-1}. In the ^{1}H NMR spectrum of the mixture the following signals were assigned to the protons of (a) the major isomer **200**; δ 1.14 (t, *J* 7.4 Hz, SCH_2**Me**), 1.41 (t, *J* 7.1 Hz, OCH_2**Me**), 2.34 (q, *J* 7.4 Hz, SC**H$_2$**Me), 4.42 (br q, *J* 7 Hz, OC**H$_2$**Me), 5.19 (1H, s), and 8.11 (1H, s); and (b) the minor isomer **201**; δ 1.22 (t, *J* 7.4 Hz, SCH_2**Me**), 1.43 (t, *J* 7.1 Hz, OCH_2**Me**), 2.52 (q, *J* 7.4 Hz, SC**H$_2$**Me), 4.42 (br q, *J* 7 Hz, OC**H$_2$**Me), 4.53 (1H, s) and 8.31 (1H, s). The aromatic signals appeared at δ 7.15-7.80 for both isomers. ^{13}C NMR spectrum showed two sets of signals each containing the right number of carbon atoms (see in the Experimental Section)

Rearrangement of the sulphonium salt **199** to **200** and **201** could have happened through the cyclopropane derivative **202** as shown in the Scheme 56. Disrotatory ring opening afforded **203** , which was transformed to **200** after a 1,5-

migration of the ethylthio group and to **201** after such a migration of the ethoxycarbonyl group.

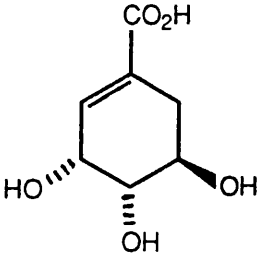


199 **202** **203** **200** **201**

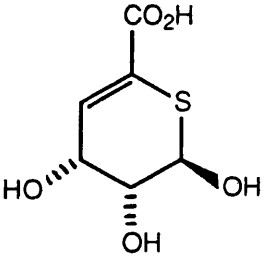
Scheme 56

2.2 Synthesis of Thiashikimic Acid

Shikimic acid **134** is a pivotal intermediate in the biosynthesis of aromatic aminoacids from carbohydrate in organisms of the plant Kingdom.[72] The enzymes of the shikimate pathway are now available in quantity through the modern techniques of molecular biology, and there is current interest in the synthesis of inhibitors of potential use in crop protection.[73] We planned therefore to synthesise racemic 6-thiashikimic acid **204**, a sulphur analogue of shikimic acid, in the hope that this analogue, or derivatives of it, might act as inhibitors or substrates for enzymes of the pathway. Replacement of a methylene group by sulphur constitute a minimal change in the shape and functionality of the acid. However, thiashikimic acid **204** should have very different chemical properties since it is a hemiacetal of an enethiol. Indeed, as described later, the thia analogue **204** is much less stable than shikimic acid **134** in slightly alkaline media.



134



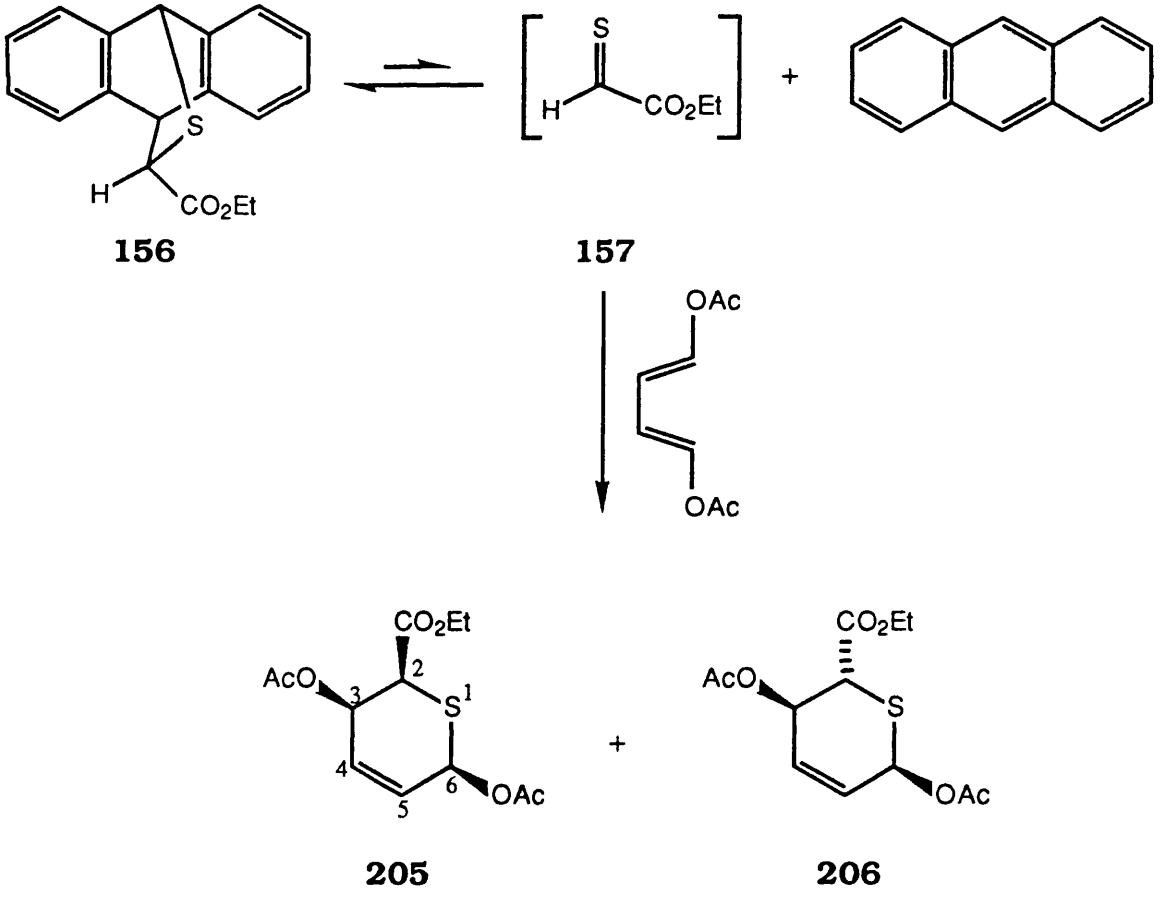
204

As explained in Section 2.1 the cycloadduct **156**, readily prepared from anthracene and the sulphenyl chloride EtO_2CCH_2SCl is a convenient ancillary precursor of ethyl

thioxoacetate **157** (Scheme 57). The following synthesis of racemic thiashikimic acid **204** was modelled on the synthesis of shikimic acid **134** itself, which began with the cycloaddition of 1,4-diacetoxybuta-1,3-diene and acrylic acid[65] or methyl acrylate[66] as described in Section 1.5.

2.2.1 Cycloadducts of 1,4-diacetoxybuta-1,3-diene and ethyl thioxoacetate

The cycloadduct **156** of ethyl thioxoacetate **157** and anthracene was heated under reflux[68, 69] in toluene with the diacetoxybutadiene[74] to give, in high yield, a mixture of the



Scheme 57

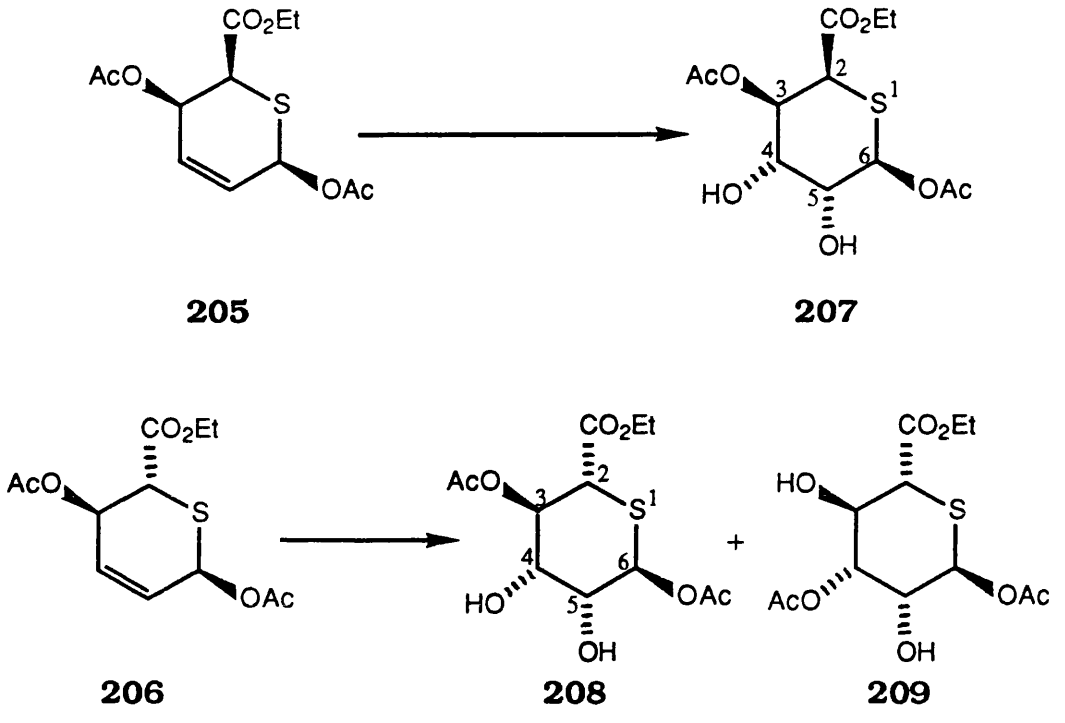
cis,cis- **205** and *trans,trans*- cycloadducts **206** of the diene (Scheme 57). The isomers **205** and **206** were separated from the mixture by column chromatography. The 2,3-*cis* isomer **205** was the major product (59 %), as expected from preferential *endo* cycloaddition. ^{1}H NMR spectrum of the crystalline 2,3-*cis* adduct **205** showed a triplet at δ 1.26 (*J* 7.1 Hz) due to the methyl protons of the ethyl ester group. The methylene signals of the same group appeared at δ 4.17 (*J* 7.1 Hz) as a quartet. The methyl signals of two acetoxy groups appeared at δ 2.06 and 2.09 as singlets. An one-proton doublet of multiplets at δ 5.62 (*J* 5.9 Hz) was assigned to 3-H. Two multiplets at δ 5.88 and 5.94 were assigned to 4- and 5-H. Another multiplet at δ 6.01 was assigned to 6-H. 2-H resonated at δ 3.71 (*J* 5.9, 1.1 and 0.5 Hz) as a doublet of a doublet of a doublet. The mass spectrum of **205** showed no molecular ion peak; the fragment of highest mass, *m/z* 228 (*ca.* 11 %), corresponded to $M^{+\cdot}$ - AcOH, and the fragment with *m/z* 113 (100) to $C_5H_5OS^+$. However, elemental analysis established the molecular formula $C_{12}H_{16}O_6S$. The IR spectrum showed absorptions at 1745, 1370 and 1226 cm^{-1}.

The minor oily 2,3-*trans* adduct **206** was obtained in 35 % yield. Elemental analysis confirmed its molecular formula $C_{12}H_{16}O_6S$. Again the mass spectrum showed no molecular ion peak; and the fragment of highest mass, *m/z* 228, corresponded to $M^{+\cdot}$ - AcOH. The ^{1}H NMR spectrum of **206** showed many similarities with the major adduct **205**. The methyl and methylene protons of ethoxycarbonyl group gave a triplet at δ 1.24 and a quartet at δ 4.17 (*J* 7.1 Hz). The

acetoxy protons gave two singlets at δ 2.05 and 2.08. A multiplet at δ 6.01 was assigned to 6-H. Another multiplet at δ 5.80-5.98 was assigned to 4- and 5-H. 2-H gave a doublet at δ 3.86 with a coupling constant (*J* 10.6 Hz) higher than that of the epimer **205**. 3-H also gave a doublet at δ 5.74 (*J* 10.6 Hz). The stereochemistry of the adducts **205** and **206** was deduced initially from the relative magnitudes of the relevant, vicinal coupling constants; $J_{2,3}$ 5.9 and 10.6 Hz for the epimers **205** and **206**, respectively.

2.2.2 *Cis*-Hydroxylation of the adducts 205 and 206

Cis-Hydroxylation of the adducts **205** and **206** was carried out with osmium tetroxide in pyridine (Scheme 58). As expected, attack of osmium tetroxide occurred from the less hindered side of the molecule. Thus, the 2,3-*cis*-adduct **205** gave the *cis*-diol **207** as crystals, m.p. 145-146 °C, in 60 % yield. Combustion analysis and accurate mass measurement established the molecular formula $C_{12}H_{18}O_8S$. The IR spectrum of the product **207** showed absorptions at 3502 cm^{-1}, and 1749, 1735, and 1715 cm^{-1} for hydroxy and ester carbonyl groups, respectively. The ^1H NMR spectrum showed signals for the ester methyl and methylene protons at δ 1.26 as a triplet (*J* 7.1 Hz) and 4.17 as a quartet (*J* 7.1 Hz), respectively. The two acetoxy methyl groups gave singlets at δ 2.09 and 2.10. The presence of two hydroxyl groups was confirmed when the broad singlet at δ 2.86 disappeared after the solution was shaken with deuterium oxide. A doublet at δ 3.96 (*J* 4.6 Hz) was assigned to 2-H and a double doublet at δ 5.43 (*J* 8.8 and 4.6 Hz) to 3-H. The olefinic signals in the



Scheme 58

spectrum of **205** were replaced, as expected, by two double doublets at δ 4.20 (*J* 5.3 and 2.7 Hz) and δ 4.62 (*J* 8.8 and 2.7 Hz) arising from 5- and 4-H respectively. Another doublet at δ 5.89 was assigned to 6-H.

The 2,3-*trans* cycloadduct **206** was hydroxylated to afford the diol **208** in a similar way with osmium tetroxide (Scheme 58). This diol **208** was obtained in 66 % yield as crystals, m.p. 110-111 °C. Elemental analysis and accurate mass measurement established its molecular formula $C_{12}H_{18}O_8S$. The IR spectrum showed absorptions at 3480 (br) and 1745 cm^{-1} for the hydroxyl and ester groups. The methyl and methylene protons of ethoxycarbonyl group and the methyl

protons of acetoxy groups showed, more or less, the same chemical shifts and splitting patterns as for diol **207**. The two hydroxyl protons gave broad singlet at δ 3.45 and 4.15, which disappeared with deuterium oxide exchange. A double doublet at δ 3.72 (*J* 9.8 and 2.9 Hz) was assigned to 4-H and another at δ 4.18 (*J* 3.5 and 2.9 Hz) to 5-H. 2-H gave a doublet (*J* 10.5 Hz) at δ 3.83 and 3-H a broad triplet (*J* 10.2 Hz) at δ 5.43. A doublet at δ 5.81 (*J* 3.5 Hz) was assigned to 6-H.

The hydroxylation product **208** of the 2,3-*trans* adduct **206** was, on some occasions, accompanied by an isomeric by-product **209**. This was formed , apparently, by 1,2-migration of an acetyl group. The ^{13}C NMR spectrum and accurate mass measurement confirmed its molecular formula $C_{12}H_{18}O_8S$. The IR spectrum showed the usual hydroxyl and ester absorption at 3602, 3515 (br) and 1740 cm^{-1}. ^1H NMR spectrum of the by-product **209** showed multiplicities and coupling constants very similar to those of the major product **208**. However, the broad triplet (*J* 10.3 Hz) due to 3-H in **209** was moved upfield to δ 4.38 from its position δ 5.43, in the spectrum of **208**. Conversely, the double doublet (*J* 10 and 2.8 Hz) due to 4-H in **209** appeared at lower field, δ 5.04, than the corresponding signal, δ 3.72, in the spectrum of **208**. Clearly, an acetyl group had migrated from position 3 to position 4 during formation of the by-product **209**.

Hydroxylation of both the epimers **205** and **206** was expected to occur *anti* to the two acetoxy groups, to give diols with the stereochemistry shown in structures **207** and **208**. However, to place the relative stereochemistry of these

racemates beyond doubt, X-ray crystallographic analyses were carried out on both diols. This was specially desirable because of difficulties in reconciling the magnitude of the vicinal proton coupling constants for the 2,3-*cis* isomer **207** (Table 1) with those expected for a conformation having 3 equatorial and 2 axial groups.

Table 1 Vicinal coupling constants (*J*) and torsional angles(φ) for the 2,3-*cis*-**207** and 2,3-*trans*-diol **208**

Torsional angle	Isomer	φ^a (°)	Conformation ^{b}	J^c/Hz
H-C(2)-C(3)-H	**207**	- 54	*ax-eq*	4.6
H-C(2)-C(3)-H	**208**	- 174	*ax-ax*	10.5
H-C(3)-C(4)-H	**207**	-53	*eq-eq*	8.8
H-C(3)-C(4)-H	**208**	180	*ax-ax*	9.8
H-C(4)-C(5)-H	**207**	- 73	*eq-ax*	2.7
H-C(4)-C(5)-H	**208**	67	*ax-eq*	2.9
H-C(5)-C(6)-H	**207**	180	*ax-ax*	5.3
H-C(5)-C(6)-H	**208**	60	*eq-eq*	3.5

[a] Torsional angles from the X-ray structures Figs. 1 and 2 for the diols **207** and **208**, respectively. [b] Conformations in the crystal structures of the vicinal protons. [c] ^{1}H NMR (200 MHz; $CDCl_3$) vicinal coupling constants.

2.2.3 X-Ray structures

X-Ray crystallographic data for the racemic, epimeric 2,3-*cis* **207** and 2,3-*trans* **208** diols are given in Tables 4 and 5 respectively, in the Experimental Section. Structures with

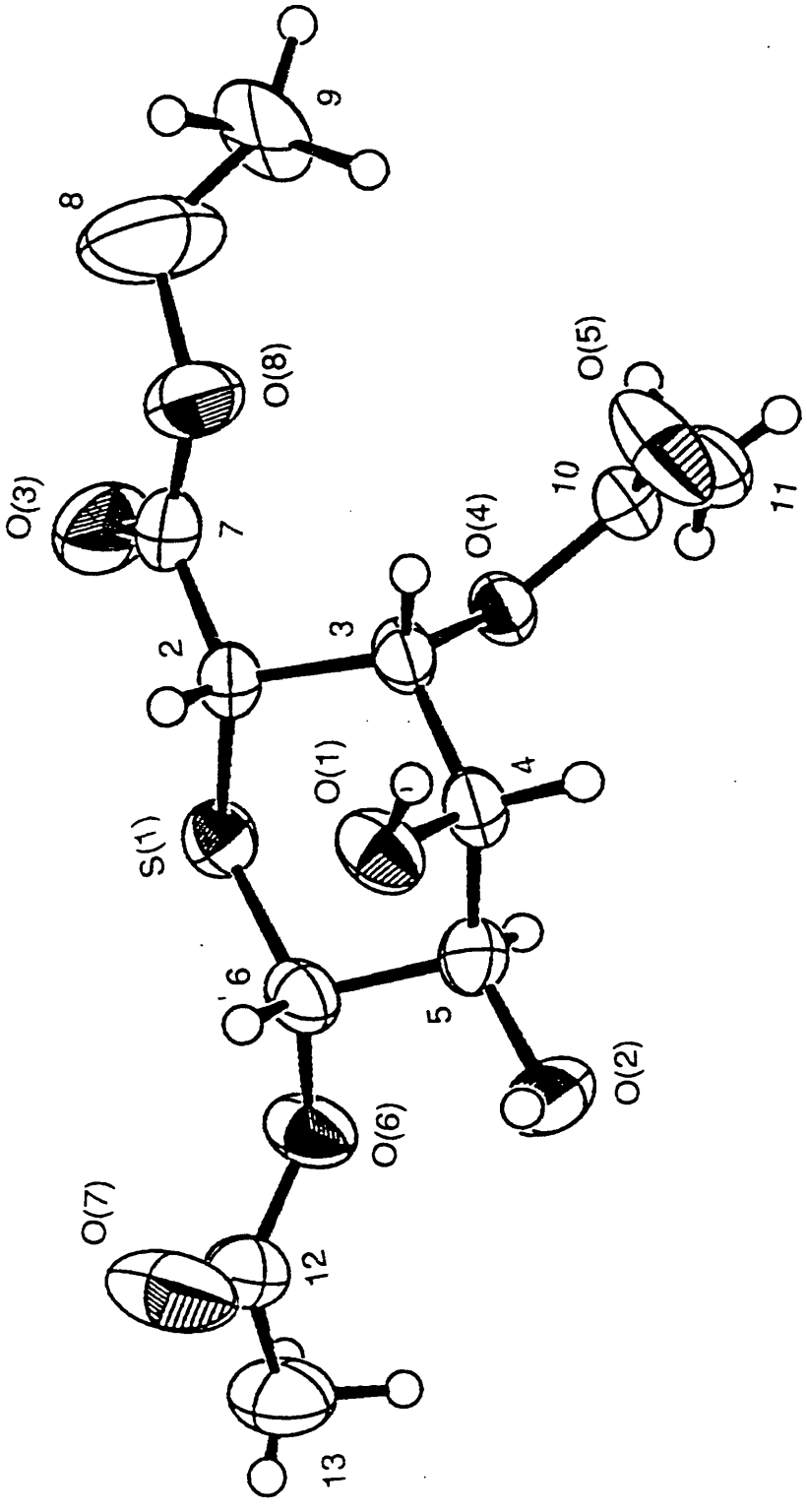


Fig. 1 X-Ray crystal structure of the 2,3-*cis*-diol **207**

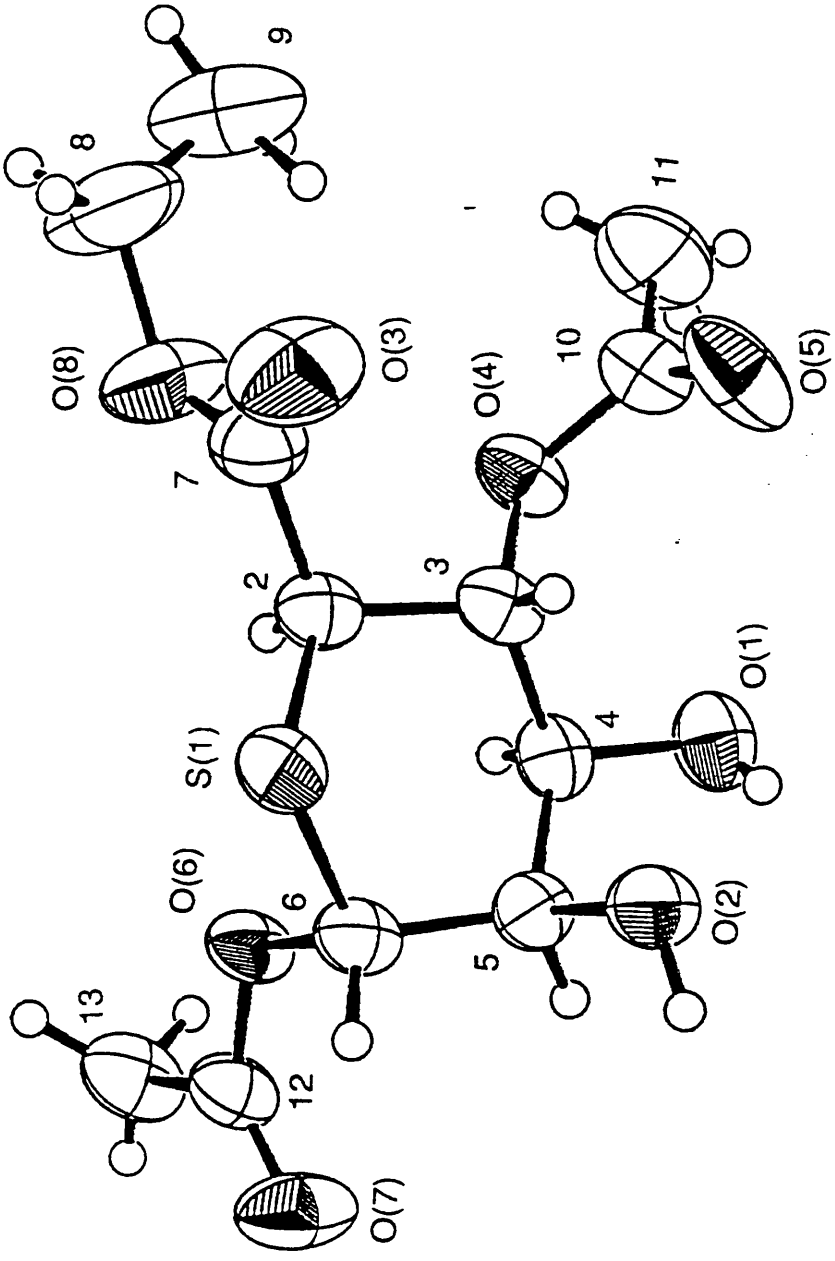
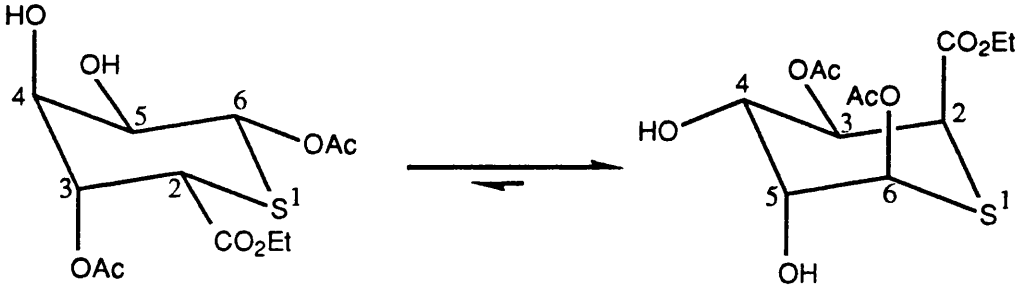


Fig.2 X-Ray crystal structure of the 2.3-*trans*-diol **208**

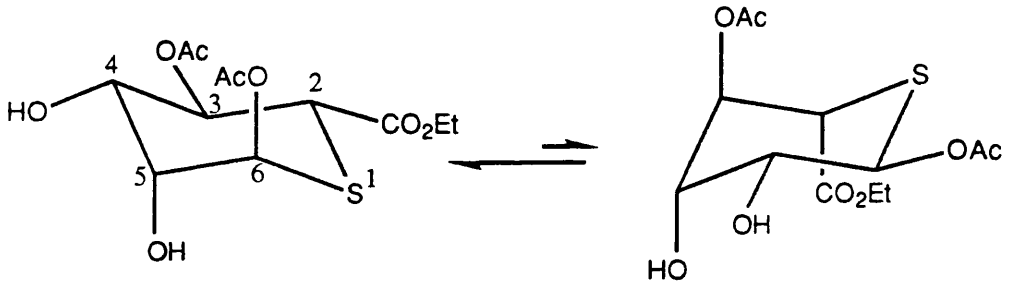
the absolute configuration (6*R*) corresponding to that of shikimic acid **134** are displayed in Figures 1 and 2 for the epimers **207** and **208**, respectively. The epimers adopt opposite chair conformations in the crystals, both having 3



207a **207b**

Fig. 3 Conformations of the 2,3-*cis*-diol **207** in the crystalline form (**207a**) and in deuteriochloroform solution (**207b**)

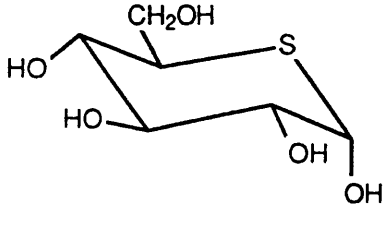
equatorial and 2 axial, rather than 2 equatorial and 3 axial, groups. The 2,3-*trans* epimer **208** appears to adopt predominantly the same conformation in deuteriochloroform solution (Table 1). Thus, the ^{1}H NMR spectrum showed large vicinal coupling constants for two pairs of *trans*-diaxial protons, $J_{2,3}$ 10.5 (ϕ -174°) and $J_{3,4}$ 9.8 Hz (ϕ 180°), as expected. However, in the spectrum of the 2,3-*cis* epimer **207**, the vicinal coupling constant $J_{5,6}$ 5.3 Hz was smaller than that expected (*ca.* 10 Hz) for *trans*-diaxial protons (ϕ 180°). Also, the coupling constant $J_{3,4}$ 8.8 Hz was larger than that expected (*ca.* 4 Hz) for *trans*-diequatorial protons (ϕ = - 53°). These *J* values would be better accommodated by the alternative chair conformation **207 b** (Fig.3), that is the one adopted by the epimer **208 a** (Fig.4), which showed $J_{5,6}$ 3.5



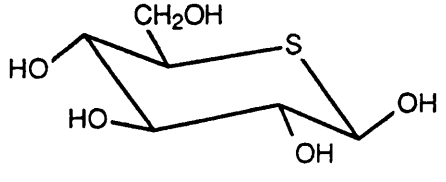
208a

Fig.4 The conformation **208a** of the 2,3-*trans*-diol **208** in both the crystalline form and in deuteriochloroform solution.

and $J_{3,4}$ 9.8 Hz. It appears that the 2,3-*cis* epimer **207** exists in solution as an equilibrium mixture of the conformation **207a** (Fig.3) [equivalent to 207 (Fig.1)] adopted in the crystal and, unexpectedly, the alternative **207b** (Fig. 3) having 3 axial and 2 equatorial groups. The latter, which apparently predominates, might be stabilised by an anomeric effect of the 6-axial acetoxy group. An indication of the magnitude of this effect is provided by the relative stabilities of the anomers of the thiopyranose 5-thio-D-glucose.[75] At equilibrium, the α-anomer, having an axial 1-hydroxy group, predominates (85 %), whereas for glucose itself the corresponding figure is only 38 %. Changes in bond angles and lengths arising from the



α-anomer

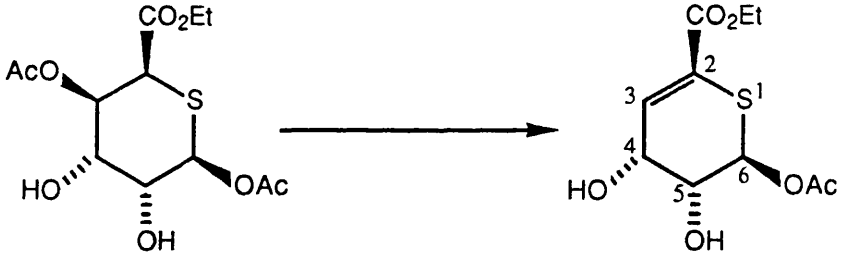


β-anomer

replacement of oxygen by sulphur also may affect the relative positions of these equilibria.[75] Further, the relative stabilities of conformations in crystals (Fig. 1 and 2) may depend in part upon the requirements for efficient crystal packing. The *trans*-diaxial coupling constants reported[75] for α- and β-5-thioglucose were in the range 8.9-9.8 Hz.

2.2.4 Elimination of acetic acid

In the synthesis [65, 66] of shikimic acid **134**, the diols corresponding to the sulphur analogues **207** and **208** were protected as isopropylidene derivatives before undergoing elimination of acetic acid. This was found to be unnecessary with the diol **207**, presumably because the sulphur facilitated



207 **210**

Scheme 59

base-catalysed 1,2-elimination. Thus,when the diol **207** was heated under reflux in dry pyridine, the thiashikimic derivative **210** was formed directly in good yield. The molecular formula, $C_{10}H_{14}O_6S$ of **210** was confirmed by accurate mass measurement and ^{13}C NMR spectrocopy. The IR spectrum

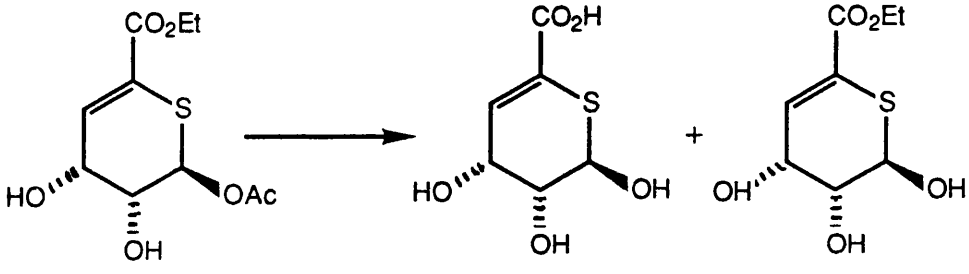
showed hydroxyl and carbonyl stretching bands at 3440 and 1758 and 1730 cm^{-1}. respectively. The ^1H NMR spectrum showed signals for the methyl and methylene protons of the ethyl ester group at δ 1.29 as a triplet (*J* 7.1 Hz) and 4.23 as a quartet (*J* 7.1 Hz), respectively. A single acetyl group gave a singlet at δ 2.08. Two hydroxyl protons gave a broad singlet at δ 3.43, which disappeared after exchange with deuterium oxide. A doublet of double doublets at δ 4.05 (*J* 4.9, 3.8 and 1.2 Hz) was assigned to 5-H and a double doublet at δ 4.43 (*J* 3.8 and 2.4 Hz) to 4-H. 6-H gave a doublet at δ 6.00 (*J* 4.9 Hz). A double doublet at δ 6.85 (*J* 2.4 and 1.2 Hz) was assigned to the newly formed olefinic proton 3-H.

The diol **208**, unlike its epimer **207**, did not eliminate acetic acid under the same conditions in hot pyridine; the starting material **208** was the only compound detectable in the reaction mixture. As expected, base-catalysed 1,2-elimination required a trans arrangement of the relevant proton and acetoxy group.

2.2.5 Racemic 6-thiashikimic acid

A number of attempts to cleave the ester groups of the thiashikimic derivative **210** using base were unsuccessful. Extensive decomposition occurred in sodium hydroxide and in mildly alkaline potassium carbonate solutions. Perhaps this instability arose from the fact that thiashikimic acid is the hemiacetal of an enethiol, which would open readily in basic solution to give a reactive enethiolate anion. Pig liver esterase (PLE) has been used in hydrolysis at pH 7. This encouraged us to try the hydrolysis of **210** with PLE. An initial attempt

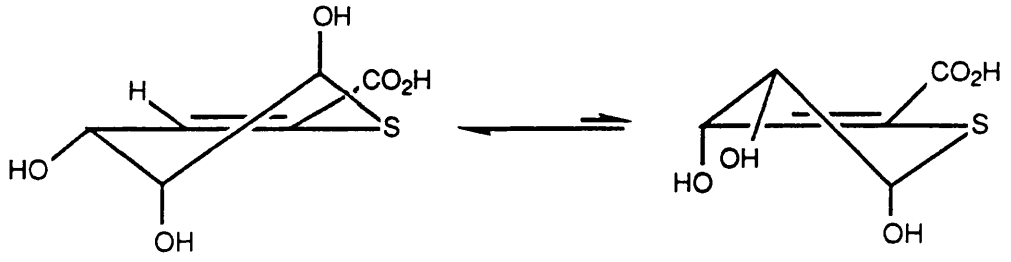
showed encouraging results. The acetoxy group of the derivative **210** was found by ^1H NMR spectroscopy to be partially hydrolysed. So this was repeated as follows. A suspension of PLE in ammonium sulphate and the derivative **210** in phosphate buffer (pH 7.0) and ethanol was stirred for



210 **204** **211**

Scheme 60

four days. Aqueous sodium hydroxide was added from a burette from time to time to keep the pH of the reaction mixture between 7.0 and 7.5. After consumption of *ca.* 2 mol-equivalent of base, the addition was stopped. The reaction mixture was acidified to pH 3 and extracted with diethyl ether. The organic fraction showed none of the desired products. The aqueous fraction was then continuously extracted with ethyl acetate. Evaporation of solvent left a residue which appeared, from its ^1H NMR spectrum, to be a mixture of the desired thiashikimic acid **204** and an ethyl ester, perhaps the partially hydrolysed derivative **211** (Scheme 60). The was subjected to HPLC on a Aminex HPX-87H column. Elution with 0.25 mM formic acid gave two main fractions, one



212 (6 β) **213** (6 α)

colourless and the other dark yellow. Evaporation of the major, colourless fraction gave the desired thiashikimic acid in a pure state, as judged by ^{1}H (200 MHz) and ^{13}C NMR spectroscopy. The spectra indicated a mixture of two epimers in the ratio 85:15. The major (**204**) and the minor epimers

Table 2 ^{1}H NMR (200 MHz; D_2O ref. δ 4.63) data of **212** and **213** and **210** (200 MHz; $CDCl_3$)

	Major epimer **212**	Minor epimer **213**	Derivative **210**
	δ *J*(Hz)	δ *J*(Hz)	δ *J*(Hz)
3H	6.72 (dd, 2.6 and 1.2)	6.66 (dd, 3.5 and 0.5)	6.85 (2.4, 1.2)
4H	4.37 (ddd, 3.7, 2.6 and 0.3)	4.39 (ddd, 3.9, 3.5 and 0.9)	4.43 (3.8,2.4)
5H	3.93 (ddd, 4.9, 3.7 and 1.2)	3.99 (ddd, 3.9, 1.9 and 0.5)	4.05 (4.9,3.8,1.2)
6H	5.08 (dd, 4.9 and 0.3)	5.30 (dd, 1.9 and 0.9)	6.00 (4.9)

Table 3 ^{13}C NMR (50.3 MHz; D_2O ref. dioxan δ 67.4) data of **212** and **213** and **210** ($CDCl_3$).

	212 δ	**213** δ	**210** δ
C2	126.0	*b*	125.4
C3	134.4	134.0	132.7
C4	65.5[a]	68.0	64.6
C5	67.3[a]	69.9	65.4
C6	75.9[a]	74.9	74.3
C7	167	*b*	163.3

[a]-Signals for C-4, -5 and -6 were not individually assigned. [b]-Not observed.

were assigned the conformations **212** and **213** , respectively. Their ^1H and ^{13}C NMR data, along with some relevant data of the derivative **210**, are given in Table 2 and 3, respectively.

In conclusion it should be noted that we know nothing about the optical activity of the thiashikimic acid **204**. Since the hydrolysis of the ester **210** was achieved enzymically, the acid **204** may no longer be racemic. So more of the product **204** should be made to measure its optical rotation (and CD) and to check for optical purity with, for example, chiral shift reagents. If necessary, other hydrolysing enzymes can be tried to see if an optically active product with the same absolute configuration as shikimic acid can be obtained. Asymmetric synthesis of **210** with the required absolute configuration can be tried. This might be accomplished at the osmylation stage

using Sharpless's catalytic method. Alternatively an optically active thioxoacetate ester could be used. Even if cycloaddition did not give much diastereomeric excess, the diastereoisomers might be separated chromatographically.

CHAPTER 3

EXPERIMENTAL

General Methods. - Melting points were recorded on a Kofler hot-stage apparatus and were uncorrected.

IR spectra were recorded on either a Perkin-Elmer 580 or 953 spectrometer.

90 MHz ^1H NMR spectra were recorded on a Perkin-Elmer R32 spectrometer. 200 MHz spectra were recorded on a Bruker WP 200 SY instrument in the pulsed Fourier Transform (FT) mode. Generally deuteriochloroform was used as solvent with tetramethylsilane as internal standard. All proton chemical shifts are quoted to the nearest 0.01 p.p.m. *J* Values are in Hz.

Low resolution mass spectra were obtained by EI at 70 eV with an AEI MS 12, and high resolution spectra, with an AEI MS 9 spectrometers coupled to a GEC-905 computer for data collection and processing by Mr. A.Richie. Microanalysis was performed by Ms.Harkness and her staff.

Analytical TLC was carried out on precoated Merck Kieselgel GF_{254} plates of thickness 0.25 mm. Spots were viewed under an ultra-violet lamp (254 nm) and developed by iodine vapour. Preparative TLC was carried out on 20 cm X 20 cm glass plates coated with a 0.5 mm layer of Merck silica gel 60 GF_{254} and compounds were located by UV light or iodine vapour. Column chromatography employed TLC-grade silica,

with reduced pressure to assist flow.[78]

All solvents and reagents were of analytical grade unless otherwise stated. 'Light petroleum' refers to the fraction b.p. 60-80 °C. Extract in organic solvents were dried over $MgSO_4$. Organic solvents were generally evaporated on a Buchi Rotavapor with slight heating.

3.1 Alkylation Experiments

3.1.1 *C-Alkylation of the Cycloadducts of Dimethylbutadiene* **158** *and Anthracene* **156**

Generally, the cycloadducts in tetrahydrofuran (THF), were treated successively with approximately equimolecular amounts of lithium diisopropylamide (LDA) and the appropriate 'alkyl' (allyl, benzyl, ethyl or methyl) halide. Alkylation was allowed to proceed for several hours at room temperature. Occasionally, a moderate excess of LDA and the alkyl halide was employed, but not for benzylation since competitive attack of LDA on benzyl bromide occurred. Typical conditions and work-up are exemplified for alkylation of the dimethylbutadiene adduct **158** and bezylation of the anthracene adduct **156** as follows.

The 12-substituted anthracene derivatives **169-172** showed two general spectroscopic features of special note. Their mass spectra all showed weak molecular ion peaks, and base peaks, *m/z* 178, corresponding to an anthracene cation radical ($C_{14}H_{10}$). The IR spectra, for solutions in CCl_4, showed

two strong, carbonyl bands, average frequencies υ 1734 and 1717 cm^{-1}, except for that of the 12-methyl derivative **169** which showed one, broad band, υ 1729 cm^{-1}.

3.1.2 *Ethyl 2-Allyl-3,6-dihydro-4,5-dimethyl-2H-thiine-2-carboxylate* 163

Butyllithium (1.6 mol dm^{-3} solution in hexanes; 5mmol) was added with stirring to diisopropylamine (5 mmol) in THF (20 cm^{3}) at - 78 °C (notional bath temperature; acetone-solid carbondioxide) under dry nitrogen. After 20 min the cycloadduct **158** (1.0 g, 5 mmol) was added, and the mixture was stirred for 1 h. Allyl bromide (0.80 g, 6.6 mmol) was then added and the mixture was allowed to warm up to 20 °C during 0.5 h; stirring was continued for 3 h at 20 °C. The mixture was evaporated and the residue was agitated with dichloromethane and 5 % hydrochloric acid. The dichloromethane layer was washed with water, dried, and evaporated. Distillation (Kugelrohr, *ca.* 170 °C, *ca.* 0.3 mmHg) of the residue gave the ***2-allyl derivative*** **163** (0.92 g, 77 %) as an oil (Found: M,240.1190. $C_{13}H_{20}O_2S$ requires *M*, 240.1184); $\upsilon_{max}(CCl_4)/cm^{-1}$ 1729; δ_H(200 MHz; $CDCl_3$) 1.19 (t, *J* 7.1, $OCH_2\mathbf{Me}$), 1.64 (br s, 4- and 5-Me), 2.21 and 2.53 (br ABq, *J*17, 3- or 6-CH_2), 2.43 (ddt, *J*13.9, 7.5 and 1.1, CH_2=CHC$\mathbf{H_2}$), 2,55 (ddt, *J* 13.9, 7.1 and 1.1, CH_2=CHC$\mathbf{H_2}$), 2.85 and 3.14 (br ABq, *J*17, 6- or 3-CH_2), 4.11 (q with fine splitting, *J* 7.1, OC$\mathbf{H_2}$Me), 5.01 and 5.08 [2 x m, $\delta_A \simeq \delta_B \simeq$ 5.04(5), C$\mathbf{H}_A\mathbf{H}_B$=CH] and 5.61-5.82 (m, CH_2=C$\mathbf{H}CH_2$) ; δ_C(50.3 MHz; $CDCl_3$) 14.1 ($OCH_2\mathbf{Me}$), 19.0 (4- or 5-Me), 20.2

(5- or 4-Me), 30.6 (CH_2=CH**C**H_2), 39.8 (C-3 or -6), 42.7 (C-6 or -3), 50.6 (C-2), 61.1 (O**C**H_2Me), 118.6 (**C**H_2=CH), 122.2 (C-4 or -5), 132.4 (CH_2=**C**H) and 172.7 (C=O)

3.1.3 *Ethyl 3,6-Dihydro-2,4,5-trimethyl-2H-thiine-2-carboxylate* 161

Alkylation, as before but with methyl iodide, gave, after Kugelrohr distillation, the ***2-methyl derivative*** **161** as an oil (78 %) (Found: M, 214.1028. *Calc.* for $C_{11}H_{18}O_2S$: *M*, 214.1027); $\upsilon_{max}(CCl_4)/cm^{-1}$ 1726; δ_H(200 MHz; $CDCl_3$) 1.19 (t, *J* 7.1, OCH_2**Me**), 1.44 (s, 2-Me), 1.63 and 1.65 (2 x br s, 4- and 5-Me), 2.16 and 2.56 (br ABq, *J* 17, 3- or 6-CH_2), 2.85 and 3.17 (br ABq, *J* 17, 6- or 3-CH_2), and 4.10 (q with fine splitting, *J* 7.1, O**C**$\mathbf{H_2}$Me); δ_C(50.3 MHz; $CDCl_3$) 14.0 (OCH_2**Me**), 19.0 (2-Me), 20.2 (4- or 5-Me), 30.9 (C-3 or -6), 42.2 (C-6 or -3), 46.2 (C-2), 61.1 (O**C**H_2Me), 121.8 (C-4 or -5), 126.0 (C-5 or -4) and 173.8 (C=O). The ^{1}H NMR, IR and MS (apart from the relative intensities of fragment ion peaks) data agreed well with the Supplementary Material of ref. 54.

3.1.4 *3,6-Dihydro-2,4,5-trimethyl-2H-thiine-2-carboxylic Acid* 167

The foregoing ethyl ester **161** (1 mmol) was kept in ethanol (10 cm^3) and aqueous sodium hydroxide (1 mol dm^{-3}, 10 cm^3) at room temperature overnight. The mixture was evaporated and the residue was dissolved in water. Neutral

impurities were extracted with dichloromethane and, after acidification of the aqueous solution, the acidic product was , in turn, extracted with dichloromethane. The ***2-methyl carboxylic acid* 167** was obtained as crystals (80 %), m.p. 93-94 °C [from light petroleum (b.p. 40-60 °C)] (Found: C, 58.2; H, 7.6 %; M, 186.0717. $C_9H_{14}O_2S$ requires C, 58.0; H, 7.6 %; *M*, 186.0715); $\upsilon_{max}(CCl_4)/cm^{-1}$ 1702, with broad absorption in the region 2300-3500; δ_H(200 MHz; $CDCl_3$) 1.53 (s, 2-Me), 1.67 (br s, 4- or 5-Me), 1.71 (br s, 5- or 4-Me), 2.23 and 2.61 (br ABq, *J* 17, 3- or 6-CH_2), 2.9 and 3.31 (br ABq, *J* 17, 6- or 3-CH_2), and 10.9 (br s, OH, exch. with D_2O); δ_C(50.3 MHz; $CDCl_3$) 19.2 (2-Me), 20.25 (4- or 5-Me), 25.8 (5- or 4-Me), 31.0 (C-3 or -6), 41.8 (C-6 or -3), 46.3 (C-2), 122.1 (C-4 or -5), 126.0 (C-5 or -4) and 180.2 (C=O).

3.1.5 *Ethyl 2-Ethyl-3,6-dihydro-4,5-dimethyl-2H-thiine-2-caboxylate* 162

Prepared similarly but with ethyl iodide, the 2-ethyl derivative **162** was obtained after Kugelrohr distillation as an oil (72 %) (Found: C, 62.9; H, 8.6 %; M, 228.1179. $C_{12}H_{20}O_2S$ requires C, 63.1; H, 8.8 %; *M*, 228.1183); $\upsilon_{max}(CCl_4)/cm^{-1}$ 1727; δ_H(200 MHz; $CDCl_3$) 0.80 [t, *J* 7.5, C(2)CH_2**Me**], 1.11 (t, *J* 7.1, OCH_2**Me**), 1.55 (br s, 4- and 5-Me), 1.64 and 1.74 [qABq, J_{gem} 13.8 and J_{vic} 7.7, C(2)C**H_2**Me], 2.10 and 2.47 (br ABq, *J* 17, 3- or 6-CH_2), 2.73 and 3.05 (br ABq, *J* 17, 6- or 3-CH_2), and 4.01 and 4.04 (qABq, J_{gem} 10.6 and J_{vic} 7.1, O**CH_2**Me); δ_C(50.3 MHz; $CDCl_3$) 8.8 [C(2)CH_2**Me**], 13.9

(OCH_2**Me**), 18.8 (4- or 5-Me), 20.0 (5- or 4-Me), 30.4 [C(2)**C**H_2Me], 31.3 (C-3 or -6), 40.1(C-6 or -3), 51.4 (C-2), 60.7 (O**C**H_2Me), 121.9 (C-4 or -5), 125.7 (C-5 or -4) and 172.8 (C=O).

3.1.6 *Ethyl 2-Benzyl-3,6-dihydro-4,5-dimethyl-2H-thiine-2-carboxylate* 164

Prepared like the allyl derivative **163** but with benzyl bromide in place of allyl bromide, ***the 2-benzyl derivative* 164** was obtained, after Kugelrohr distillation (150-170 °C, 0.3 mmHg), as a syrup (78 %) (Found: C, 70.1; H, 7.5 %; M, 290.1337. $C_{17}H_{22}O_2S$ requires C, 70.3; H, 7.6 %; *M*, 290.1340); $\upsilon_{max}(CCl_4)/cm^{-1}$ 1728; δ_H(200 MHz; $CDCl_3$) 1.20 (t, *J* 7.1, OCH_2**Me**), 1.67 (br s, 4- or 5-Me), 2.32 and 2.54 (br ABq, *J* 17, 3- or 6-CH_2), 2.96 and 3.20 (br ABq, *J* 17, 6- or 3-CH_2), 3.04 and 3.22 (ABq, *J* 13.5, PhCH_2), 4.11 (q, *J* 7.1, O**C**H_2Me) and 7.12-7.30 (m, Ph); δ_C(50.3 MHz; $CDCl_3$) 14.05 (OCH_2**Me**), 19.1 (4- or 5-Me), 20.35 (5- or 4-Me), 31.0 Ph**C**H_2), 40.1 (C-3 or -6), 44.4 ((C-6 or -3), 52.0 (C-2), 61.25 (O**C**H_2Me), 122.0 (C-4 or -5), 126.1 (C-5 or -4), 127.0, 128.1 and 129.9 (*o*-, *m*- and *p*-phenyl-CH), 135.9 (*ipso*-phenyl-C) and 172.75 (C=O).

3.1.7 *Ethyl 12-Benzyl-9,10-dihydro-10,9-(epithiomethano)anthracene-12-carboxylate* 172

LDA (5 mmol) was prepared from butyllithium and diisopropylamine in THF at - 20 °C, as described in the

foregoing preparation of the 2-allyldihydrothiine **163**. The mixture was allowed to warm up to 0 °C. The anthracene cycloadduct **156** (1.48 g, 5 mmol) was then added and the mixture was stirred and allowed to warm up to 20 °C. The mixture was cooled to - 20 °C, then benzyl bromide (6 mmol) was added with stirring. Stirring was continued at - 20 °C for 1 h and then at 20 °C for 3 h. After the usual work-up, the product was purified by preparative TLC on silica plates developed with hexane-ethyl acetate (3:2). The ***12-benzyl derivative* 172** (1.56 g, 81 %) had m.p. 124 °C [from light petrolium (b.p.40-60 °C)] (Found: C, 77.8; H, 5.65 %; M, 386.1338. $C_{25}H_{22}O_2S$ requires C, 77.7; H, 5.7 %; M, 386.1341); $\upsilon_{max}(CCl_4)/cm^{-1}$ 1737 and 1714; δ_H(200 MHz; $CDCl_3$) 0.98 (t, *J* 7.1, Me), 2.75 and 3.30 (ABq, *J* 13.4, PhC**H$_2$**), 3.88 (q, *J* 7.1, OC**H$_2$**Me), 4.97 (s, 9- or 10-H), 5.08 (s, 10- or 9-H) and 7.02-7.52 (13 H, m, ArH); δ_C(50.3 MHz; $CDCl_3$) 13.8 (Me), 46.4 (C-9 or -10), 46.7 (Ph**C**H$_2$), 53.15 (C-10 or -9), 61.4 (O**C**H$_2$Me), 67.7 (C-12), 122.0, 122.05, 125.8, 126.5, 126.6, 126.9 127.1, 127.2, 127.25, 128.0 and 129.7 (ArCH), and 136.46, 139.1, 139.9, 143.2 and 143.3 (ArC) and 172.5 (C=O).

3.1.8 *Ethyl 9,10-Dihydro-12-methyl-10,9-(epithiomethano)anthracene-12-carboxylate* 169

Alkylation as before, but with methyl iodide, gave the ***12-methyl derivative* 169** (87 %) as thick plates (Found: C,73.5; H, 5.8 %; M, 310.1019. $C_{19}H_{18}O_2S$ requires C, 73.5; H, 5.8 %; *M*, 310.1028); $\upsilon_{max}(CCl_4)/cm^{-1}$ 1729; δ_H(90 MHz; $CDCl_3$)

1.14 (t, *J* 7, OCH_2**Me**), 1.41 (s, 12-Me), 4.02 (br q, *J* 7, $OC\mathbf{H_2}Me$), 4.76 (s, 9- or 10-H), 5.03 (s, 10- or 9-H) and 7.1-7.5 (m, ArH).

3.1.9 *Ethyl 12-Ethyl-9,10-dihydro-10,9-(epithiomethano)anthracene-12-carboxylate* 170

Alkylation as before, but with ethyl iodide, gave the ***12-ethyl derivative*** **170** (83 %) as crystals, m.p. 104 °C [from light petrolium (b.p. 40-60 °C] (Found: C, 74.3; H, 6.5 %; M, 324.1186. $C_{20}H_{20}O_2S$ requires C, 74.1; H, 6.2 %; *M*, 324.1184); $\upsilon_{max}(CCl_4)/cm^{-1}$ 1731 and 1718; δ_H (90 MHz; $CDCl_3$) 0.84 [t, *J* 7, C(12)CH_2**Me**], 1.11 (t, *J* 7, OCH_2**Me**), 1.1-2.1 [2H, m, C(12)C$\mathbf{H_2}$Me], 4.03 (q, *J* 7, OC$\mathbf{H_2}$Me), 4.86 (s, 9- or 10-H), 5.00 (s, 10- or 9-H) and 7.0-7.5 (m, ArH).

3.1.10 *Ethyl 12-Allyl-9,10-dihydro-10,9-(epithiomethano)anthracene-12-carboxylate* 171

Alkylation as before, but with allyl bromide, gave the ***12-allyl derivative*** **171** (87 %), which formed crystals, m.p. 96 °C [from light petrolium (b.p. 40-60 °C)] (Found: C, 75.0; H, 5.9 %; M, 336.1154. $C_{21}H_{20}O_2S$ requires C, 75.0; H, 6.0 %; *M*, 336.1183); $\upsilon_{max}(CCl_4)/cm^{-1}$ 1733 and 1719; δ_H(200 MHz; $CDCl_3$) 1.16 (t, *J* 7.1, OCH_2**Me**), 2.30 (ddt, *J* 13.9, 6.5 and 1.3, CH_2=CHC$\mathbf{H_2}$), 2.48 (br dd, *J* 13.9 and 7.8, CH_2=CHC$\mathbf{H_2}$), 3.99 and 4.07 (qABq, J_{gem} 10.8 and J_{vic} 7.1, OC$\mathbf{H_2}$Me), 4.91 (s, 9- or 10-H), 5.06 (dm, *J* *ca.* 16, C$\mathbf{H_2}$=CH), 5.10 (dm, *J*

ca. 10, C**H$_2$**=CH), 5.73 (dddd, *J* 16.5, 10.4, 7.8 and 6.5, CH$_2$=C**H**) and 7.05-7.45 (m, ArH); δ_C(50.3 MHz; $CDCl_3$) 14.1 (Me), 45.4 (CH$_2$=CH**C**H$_2$), 46.4 (C-9 or -10), 51.5 (C-10 or -9), 61.5 (OCH$_2$), 65.2 (12-C), 118.8 (**C**H$_2$=CH), 121.8, 122.0, 125.8, 126.5, 126.8, 126.85 and 127.0 (ArCH), 132.8 (CH$_2$=**C**H), 139.1, 139.9, 142.7 and 143.3 (ArC) and 172.2 (C=O).

3.1.11 *Preparation of the Cycloadducts* 161-164 *and* 173-176 *by Retro-Diels-Alder Cleavage of the Anthracene Adducts* 169-172

Generally, the appropriate anthracene adduct (0.5 mmol) was heated with either 2,3-dimethylbuta-1,3-diene (DMB), cyclopentadiene, or cyclohexa-1,3-diene (typically 2.5 mmol) in toluene (5 cm^3) under reflux, under nitrogen, until 'transfer' of the thioketone was complete (TLC control) (typically 5 h). The mixture was evaporated and the residue was triturated with methanol and set aside to allow anthracene to crystallise out. The mixture was filtered and the filtrate was evaporated. The residue was shown in each case, by ^{1}H NMR spectroscopy, to contain the corresponding adduct(s) **161-164** of the diene and, usually, traces of anthracene. No other products were detected. The products (yields *ca.* 90 %) were further purified by chromatography or Kugelrohr distillation.

The DMB adducts **161-164** were identified by comparison of their ^{1}H NMR spectra with those of samples prepared , as described before. The oily cyclopentadiene adducts **173** and **174** were separated by chromatography on a silica gel column.

Elution with hexane gave a trace of anthracene, then hexane-ethyl acetate (98:2) gave, successively, ***ethyl* 3-*methyl*-2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-*exo*-*carboxylate* 173** (60 % yield from **169**) (Found: C, 60.6; H, 7.1 %; M, 198.0698. $C_{10}H_{14}O_2S$ requires C, 60.6; H, 7.1 %; *M*, 198.0714); $\upsilon_{max}(CCl_4)/cm^{-1}$ 1728; δ_H(200 MHz; $CDCl_3$) 1.26 (t, *J* 7.1, OCH_2**Me**), 1.38 (s, 3-Me), 1.78 (dt, *J* 9.5 and 2.3, 7-H), 1.90 (dm, *J* 9.5, 7-H), 3.48 (m, 4-H), 3.98 (m, 1-H), 4.19 (q, *J* 7.1, with fine splitting, O**C**$\mathbf{H_2}$Me), 5.97 (dd, *J* 5.5 and 3.3, 5- or 6-H) and 6.42 (dd, *J* 5.3 and 2.8, 6- or 5-H); δ_C(50.3 MHz; $CDCl_3$) 14.1 (OCH_2**Me**) 23.8 (3-Me), 52.3 (C-1 or -4), 52.4 (C-7), 52.9 (C-4 or -1), 61.0 (C-3), 61.3 (O**C**H_2Me), 131.8 (C-5 or -6), 138.7 (C-6 or -5) and 175.4 (C=O); then ***ethyl* 3-*methyl*-2-*thiabicyclo*[2.2.1]*hept*-5-*ene*-3-*endo*-*carboxylate* 174** (20 %) (Found: C, 60.5; H, 7.1 %; M, 198.0702. $C_{10}H_{14}O_2S$ requires C, 60.6; H, 7.1 %; *M*, 198.0714); $\upsilon_{max}(CCl_4)/cm^{-1}$ 1730; δ_H(200 MHz; $CDCl_3$) 1.22 (t, *J* 7.1, OCH_2**Me**), 1.73 (dt, *J* 9.4 and 2, 7-H), 1.82 (s, 3-Me), 1.89 (dm, *J ca.* 9, 7-H), 3.26 (m, 4-H), 4.00 (m, 1-H), 4.12 (q, *J* 7.1, with fine splitting, O**C**$\mathbf{H_2}$Me), 6.01 (dd, *J* 5.2 and 3.1, 5- or 6-H) and 6.40 (dd, *J* 5.4 and 2.8, 6- or 5-H); δ_C(50.3 MHz; $CDCl_3$) 14.1 (OCH_2**Me**), 28.3 (3-Me), 49.4 (C-7), 52.9 (C-1 or -4), 54.0 (C-4 or -1), 61.2 (O**C**H_2Me), 63.7 (C-3), 134.0 (C-5 or -6), 138.3 (C-6 or -5) and 174.3 (C=O).

The oily cyclohexadiene adducts **175** and **176** could not be separated, and consequently were characterised as a mixture: ***ethyl* 3-*methyl*-2-*thiabicyclo*[2.2.2]*oct*-5-**

ene*-3-exo-*carboxylate **175** and **3-endo-*carboxylate*** **176** (**175**:**176** = *ca.* 1:1) (Found: M, 212.0865. $C_{11}H_{16}O_2S$ requires *M*, 212.0871); $\upsilon_{max}(CCl_4)/cm^{-1}$ 1727; δ_H(200 MHz; $CDCl_3$) 1.21 and 1.27 (2 x t, *J* 7.1, 2 x OCH_2**Me**), 1.37 and 1.71 (2 x s, 3-Me in **175** and **176**, respectively), 1.52-2.11 (m, 7- and 8-CH_2), 3.03 (t, *J* 5.5, with fine splitting, 1- or 4-H), 3.11 (t, *J* 5.8, with fine splitting, 1- or 4-H), 3.45 (m, 4- or 1-H, in both **175** and **176**), 3.97-4.31 (2 x m, 2 x O**CH_2**Me), 6.24 and 6.50 (2 x t, *J* 7.8, with fine splitting, 5- and 6-H) and 6.36 and 6.47 (2 x t, *J* 7.5, with fine splitting, 5- and 6-H); δ_C(50.3 MHz; $CDCl_3$) 14.0 and 14.1 (OCH_2**Me**), 18.4, 20.6, 28.1 and 29.0 C-7 and -8), 25.6 and 28.8 (3-Me), 36.0, 36.2, 27.5 and 37.7 (C-1 and -4), 57.1 and 58.1 (C-3), 61.1 and 61.4 (O**C**H_2Me), 131.4, 133.7, 134.3 and 134.8 (C-5 and -6) and 174.8 and 175.2 (C=O).

3.1.12 *Retro-Diels-Alder Cleavage of the Cyclopentadiene Cycloadduct* 173

The cycloadduct **173** (100 mg, 0.505 mmol) and 2,3-dimethylbutadiene (DMB) (124 mg, 1.515 mmol) were heated in toluene (7 cm^3) under reflux, under nitrogen, for 4 h. The mixture was evaporated to afford the DMB adduct **161** (80 mg), which was identified by ^1H NMR spectroscopy (90 MHz) and found to contain no significant amounts of the cycloadducts **173** or **174**, or any by-product. When a mixture of the cycloadducts **173** and **174** (*ca.* 3:1) was heated as before, but

in the absence of DMB, slow decomposition was observed (^{1}H NMR control). After 5 h, signals for the cycloadducts **173** and **174** (*ca.* 2:1) were accompanied by broad signals arising perhaps from a thioketone polymer. After 20 h, decomposition was complete.

3.1.13 *Rearrangement and Methylation of the Lithio Derivative* **178** *of the Cyclopentadiene Adducts* **179**.

An *endo- exo* mixture of the cyclopentadiene adducts **177** (2.45 mmol) was treated in THF with LDA (3 mmol) at - 78 °C and then with methyl iodide (2.7 mmol) at 10 °C, as described for the alkylation of the cycloadducts **158** and **156**. After the mixture had been kept at room temperature for two hours, work-up gave ***ethyl (1S*,5R*,6R*)-6-methylthiobicyclo[3.1.0]hex-2-ene-6-carboxylate*** **179** (89 %) as an oil (Found: M, 198.0714. $C_{10}H_{14}O_2S$ requires *M*, 198.0714); υ_{max} (CCl_4)/cm^{-1} 1729 and 1712; δ_H(200 MHz; $CDCl_3$) 1.26 (t, *J* 7.1, OCH_2**Me**), 1.97 (s, SMe), 2.28 (dq, *J* 18.5 and *ca.* 2, 4-H), 2.61 (ddt, *J* 18.5,6.6 and *ca.* 2, 4-H), 2.76 (dt, *J* 6.7, and *ca.* 2, 1-H), 4.15 (q, *J* 7.1, O**C**H_2Me), 5.72 (dq, *J* 5.5 and *ca.* 2, 2- or 3-H), and 5.81 (dm, *J* 5.5, 3- or 2-H) (all signals except those at δ 1.26 and 1.97 showed additional fine splitting); δ_C(50.3 MHz; $CDCl_3$) 14.2 (OCH_2**Me**), 16.6 (SMe), 33.8 (C-1 or -5), 34.3 (C-4), 38.0 (C-6), 43.1 (C-5 or -1), 61.5 (O**C**H_2Me), 126.0 and 135.9 (C-2 and -3) and 173.0 (C=O).

For further characterisation, the ester **179** (260 mg) was hydrolysed in ethanol (15 cm^3) and sodium hydroxide (1 mol dm^{-3}; 15 cm^3) at room temperature for 24 h to afford the corresponding ***carboxylic acid* 187** (200 mg, 90 %) as plates, m.p. 104 - 105 °C [from light petrolium (b.p.40-60 °C)] (Found: C, 56.3; H, 5.95 %; M, 170.0390. $C_8H_{10}O_2S$ requires C, 56.5; H, 5.9 %; *M*, 170.0401); υ_{max} (CCl_4)/cm^{-1} 2300-3400 (br) and 1685; δ_H(200 MHz; $CDCl_3$) 1.99 (s, SMe), 2.31 (dq, *J* 18 and 2, 4-H), 2.56 (br t, *J* 6.5, 5-H), 2.65 (ddt, *J* 18, 6.6 and 1.9, 4-H), 2.89 (dt, *J* 6.5 and *ca.* 2 1-H), 5.76 (dq, *J* 5.5 and 1.6, 2- and 3-H), 5.85 (m, 3- or 2-H) and 12.27 (br s, OH, exch. with D_2O); δ_C(50.3 MHz; $CDCl_3$) 16.5 (SMe), 34.5 (C-4), 35.0 (C-1 or -5), 38.2 (C-6), 44.1 (C-5 or -1), 125.9 (C-2 or -3), 136.25 (C-3 or -2) and 179.2 (C=O).

3.1.14 *Rearrangement and Methylation of the Lithio Derivative* 183 *of the Cyclohexadiene Adducts* 182

An *endo-exo* mixture (largely *endo*) of the cyclohexadiene adducts **182** (2.52 mmol) was treated in THF at - 78 °C with LDA (3.0 mmol), as described for the alkylation of the cycloadducts **156** and **158**. The mixture was warmed up to - 40 °C, then methyl iodide (3.0 mmol) was added. After the mixture had been kept at room temperature for 2 h, work-up gave ***ethyl* (1S*,2R*,7R*)-7-*methylthiobicyclo*[4.1.0]*hept*-2-*ene*-7-*carboxylate* 184** (61 %) as an oil (Found: M, 212.0880. $C_{11}H_{16}O_2S$ requires *M*, 212.0871); υ_{max} (CCl_4)/cm^{-1} 1705; δ_H(200 MHz; $CDCl_3$) 1.22 (t, *J* 7.1,

OCH_2**Me**), 1.81 - 1.92 ((2H, m), 1.92 - 2.16 (4H, m), 2.05 (s, SMe), 4.11 (q, *J* 7.1, $OC\mathbf{H_2}Me$), 5.76 (dm, *J* 9.9, 2- or 3-H) and 5.83 (dt, *J* 9.9 and 3.5, 3- or 2-H); δ_C(50.3 MHz; $CDCl_3$) 14.1 (OCH_2**Me**), 16.2 (C-4 or -5), 16.3 (SMe), 21.7 (C-5 or -4), 27.3 and 27.5 (C-1 and -6), 42.4 (C-7), 61.4 ($O\mathbf{C}H_2$), 120.3 (C-2 or -3), 130.7 (C-3 or -2) and 172.2 (C=O).

Hydrolysis of this ester **184**, as described for the foregoing ester **179**, gave the corresponding ***carboxylic acid*** **190** as plates, m.p. 110-111 °C (from diethyl ether) (Found: C, 58.6; H, 6.6 %; M, 184.0554. $C_9H_{12}O_2S$ requires C, 58.7; H, 6.6 %; *M*, 184.0558); υ_{max} (CCl_4)/cm^{-1}m 1740 (Weak), 1687 (strong); δ_H(200 MHz; $CDCl_3$) 1.87 - 2.36 (6 H, m), 2.11 (s, SMe), 5.81 (dm, *J* 10.0, 2- or 3-H), 5.90 (dt, *J* 10.0 and 3.6, 3- or 2-H) and *ca.*12 (br s, OH); δ_C(50.3 MHz; $CDCl_3$) 16.3 (C-4 or -5), 16.4 (SMe), 21.7 (C-5 or -4), 28.5 and 28.8 (C-1 and -6), 42.6 (C-7), 120.1 (C-2 or -3), 131.2 (C-3 or -2) and 178.1 (C=O).

3.1.15 *Acid-catalysed Rearrangement of the Cyclopropanecarboxylic Acid 190 to give the Lactones* **191** *and* **192**

The foregoing acid **190** decomposed slowly, when stored at room temperature in the crystalline state, to give a mixture of the lactones **191** and **192** (ratio *ca.* 1:1). This rearrangement was effected with acid catalysis as follows. The acid **190** (80 mg) was heated in chloroform (7 cm^3) under reflux with a

catalytic amount of hydrochloric acid until the reaction was complete (TLC control). The mixture was evaporated and the residue was chromatographed on a short coloum of silica gel. Elution with hexane-ethyl acetate (1:1) gave a mixture (48 mg) of the lactones **191** and **192** (ratio *ca.* 1:2). Rechromatography on silica gel and elution with hexane-diethyl ether (1:1) gave successively **(1R*,6S*,9S*)-9-*methylthio*-7-*oxabicyclo*[4.3.0]*non*-4-*en*-8-*one* 192** (32 mg) as an oil (Found: M, 184.0556. $C_9H_{12}O_2S$ requires *M*, 184.0558); υ_{max} (CCl_4)/cm^{-1} 1762; δ_H(200 MHz; $CDCl_3$) 1.56 (dddd, *J* 13.4, 10.5, 8.3 and 5.8, 2-H), 1.81 (dq, *J* 13.4 and 4.8, 2-H), 1.91 - 2.28 (m, 3-H_2), 2.27 (s, SMe), 2.37 (ddt, *J* 10.5, 6.0 and 4.3, 1-H), 3.19 (d, *J* 3.9, 9-H), 4.94 (br t, *J ca.* 5, 6-H), 5.86 (ddtd, *J* 10.0, 3.8, 2.0 and 0.5,5-H) and 6.11 (ddddd, *J* 10.0, 4.7, 3.1, 1.0 and 0.5, 4-H); δ_C(50.3 MHz; $CDCl_3$) 14.4 (Me), 22.6 and 22.8 (C-2 and -3), 40.5 (C-1), 47.2 (C-9), 74.0 (C-6), 122.7 C-4 or -5), 134.1 (C-5 or -4) and 174.1 (C-8); then **(1R*,6S*,9R*)-9-*methylthio*-7-*oxabicyclo*[4.3.0]*non*-4-*en*-8-*one* 191** (15 mg) as needles, m.p. 75-76 °C [from light petrolium (b.p. 40-60 oC)] (Found: C, 58.6; H, 6.6 %; M, 184.0547. $C_9H_{12}O_2S$ requires C, 58.7; H, 6.6 %; *M*, 184.0558); υ_{max} (CCl_4)/cm^{-1} 1764; δ_H(200 MHz; $CDCl_3$) 1.13-1.36 (m, 2-H_2), 1.80-2.30 (m, 3H_2), 2.30 (s, SMe), 2.64 (tdd, *J* 9.3, 7.4 and 4.7, 1-H), 3.84 (d, *J* 7.3, 9-H), 4.67 (t, *J* 4.6, with fine splitting, 6-H), 5.93 (dddd, *J* 10.0, 4.0, 2.5 and 1.5, 5-H) and 6.20 (dddt, *J* 10.0, 5.6, *ca.* 2 and *ca.* 1, 4-H); δ_C(50.3 MHz; $CDCl_3$) 15.5 (Me), 19.8 (C-2 or -3), 23.8 (C-3 or -2), 38.7 (C-1), 50.8 (C-9), 73.4 (C-6), 122.0 (C-4 or -5), 135.8 (C-5 or -4) and 174.7 (C-8).

3.1.16 *Methylation of the Dilithio Derivatives* 186, 189 *and* 166

In general, in separate experiments, the carbocyclic acids **185**, **188** and **165** (H replacing Et) (2 mmol) were added to LDA (5 mmol), prepared at - 78 °C in THF (10 cm^3) as described for the alkylation of the esters **177** and **182**. Methyl iodide (2.4 mmol) was added at 0 °C for 1 h. Work-up gave (*ca.* 80 % yield) the cyclopropanecarboxylic acids **187** and **190**, and the thiinecarboxylic acid **167** (H replacing Et), respectively. These products were identified by spectroscopic comparison with samples prepared by hydrolysis of the corresponding esters, as described before.

3.1.17 *Ethyl* (1S*,2S*)-*Isoprop-2-enyl-2-methyl-1-methylthiocyclopropane-1-carboxylate* 196 *and the Corresponding Ethylthio Derivative* 197

The thiinecarboxylate **158** (550 mg, 2.75 mmol) and trimethyloxonium tetrafluoroborate (440 mg, 2.98 mmol) were stirred in dry dichloromethane (20 cm^3) at room temperature for 2 h. The mixture was evaporated and the residue was dissolved in dry acetonitrile (5 cm^3) with stirring under nitrogen at 0 °C. 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN) (390 mg, 3.14 mmol) was added dropwise to the mixture, and stirring was continued for 20 min. Water (20 cm^3) was added, and the mixture was extracted with diethyl ether (3 x 30 cm^3). The extracts were washed successively with dilute hydrochloric acid and brine, then were dried and evaporated. Distillation

(Kugelrohr, 140-165 °C, 0.3 mmHg) of the residue gave the ***cyclopropanecarboxylate* 196** as an oil (480 mg, 82 %) (Found: M, 214.1039. $C_{11}H_{18}O_2S$ requires *M*, 214.1028); $\upsilon_{max}(CCl_4)/cm^{-1}$ 1720; δ_H(200 MHz; $CDCl_3$) 1.20 (s, 2-Me), 1.27 (t, *J* 7.1, OCH_2**Me**), 1.28 and 1.63 (ABq, *J* 5.1, 3-H_2), 1.79 (dd, *J* 1.4 and 0.8, vinyl-Me), 2.07 (s, SMe), 4.19 (q, *J* 7.1, with fine splitting, O**CH_2**Me), 4.83 (quintet, *J* 0.8, C=CH_2) and 4.91 (quintet, *J* 1.5, C=CH_2); δ_C(50.3 MHz; $CDCl_3$) 14.3, 15.7, 20.1 and 21.1 (4 x Me), 27.0 (C-3), 38.36 and 38.39 (C-1 and -2), 61.3 (O**C**H_2Me), 113.4 (C=**C**H_2), 145.6 (**C**=CH_2) and 171.2 (C=O).

This preparation was repeated, but with triethyl, rather than trimethyl, oxonium tetrafluoroborate. Chromatography of the crude product on silica plates developed with hexane-diethyl ether (9:1) gave the ***ethylthiocyclopropanecarboxylate* 197** (53 %) as an oil (Found: M, 228.1175. $C_{12}H_{20}O_2S$ requires *M*, 228.1183); υ_{max} $(CCl_4)/cm^{-1}$ 1713; δ_H(200 MHz; $CDCl_3$) 1.18 (s, 2-Me), 1.18 (t, *J* 7.4, SCH_2**Me**), 1.26 (t, *J* 7.1, OCH_2**Me**), 1.31 and 1.68 (ABq, *J* 5.1, 3-H_2), 1.79 (dd, *J* 1.4 and 0.8, vinyl-Me), 2.53 (q, *J* 7.5, with fine splitting, SCH_2), 4.17 and 4.21 (qABq, *J* 7.1 and 10.8, OCH_2), 4.81 (quintet, *J* 0.8, C=CH_2) and 4.90 (quintet, *J* 1.5, C=CH_2); δ_C(50.3 MHz; $CDCl_3$) 14.3, 14.4, 19.9 and 21.0 (4 x Me), 27.1 and 27.2 (2 x CH_2), 37.2 and 37.8 (C-1 and -2), 61.3 (OCH_2), 113.4 (C=**C**H_2), 145.7 (**C**=CH_2) and 171.8 (C=O).

3.1.18 *Rearragement of the Anthracene Thioaldehyde Cycloaduct* **156** *After Treatment with Triethyloxonium Tetrafluoroborate and Base*

The anthracene cycloadduct **156** (2.14 g, 7.23 mmol) and triethyloxonium tetrafluoroborate (1.50 g, 7.28 mmol) were stirred in dry dichloromethane (50 cm^3) at room temperature for 2 h. The mixture was evaporated and the residue was dissolved in dry acetonitrile (10 cm^3) with stirring under nitrogen at 0 °C. 1,5-Diazabicyclo[4.3.0]non-5-ene (0.93 g, 7.50 mmol) was added dropwise to the mixture, and stirring was continued for 30 min. Water (35 cm^3) was added, and the mixture was extracted with diethyl ether (3 x 50 cm^3). The extracts were washed successively with dilute hydrochlric acid and brine, and then were dried ($MgSO_4$) and evaporated. Chromatograohy on silica (60 GF_{254}) and elution with a mixture of hexane and ethyl acetate afforded a gummy mixture (*ca.* 3:1 as judged by ^1H NMR spectroscopy) of isomers tentatively assigned the structures **200** and **201** (1.98 g, 84.5 %) (Found: *m/z* 324.1200. $C_{20}H_{20}O_2S$ requires *M* 324.1184); $\upsilon_{max}(CCl_4)/cm^{-1}$ 1228, 1251, 1707 and 3018; δ_H(200 MHz; $CDCl_3$) 1.14 (t, *J* 7.4, SCH_2**Me**, major isomer) 1.22 (t, *J* 7.4, SCH_2**Me**, minor), 1.41(t, *J* 7.1, OCH_2**Me**, major), 1.43 (t, *J* 7.1, OCH_2**Me**, minor), 2.34 (q, *J* 7.4, SC**H$_2$**Me, major), 2.52 (q, *J* 7.4, SC**H$_2$**Me, minor), 4.42 (2 x br q, *J* 7, 2x OC**H$_2$**Me, major and minor), 5.19 (1H, s),, 7.15-7.80 (m, ArH), 8.11 (1H, s, major) and 8.31 (1H, s, minor); δ_C(50.3 MHz; $CDCl_3$) (major isomer) 14.1 (SCH_2**Me**), 14.3 (OCH_2**Me**), 26.5 (SCH_2), 55.9(CH), 61.1(OCH_2), 126.4, 127.1, 128.05, 128.1, 128.5, 129.7, 130.4 and 131.4 (ArCH), 131.5, 132.5 and 133.2 (ArC),

138.0 (CH), 140.4(C), 141.0(C) and167.9 (C=O); δ_C (minor isomer) 14.0(SCH_2**Me**), 14.1 (OCH_2**Me**), 25.7 (SCH_2), 49.3 CH), 61.2 (OCH_2), 123.5, 124.0, 125.4, 125.9, 126.7, 128.7, 128.8 and 130.0 (ArCH), 131.1, 132.4, 132.5, 140.1 and 140.3 (C), 138.2 (CH) and 167.3 (C=O).

3.2 The Synthesis ofThiashikimic Acid

3.2.1 *Ethyl* 3-c, 6-c- *and* 3-t, 6-t- *Diacetoxythiacyclohex-4-ene-2-r-carboxylate* 205 *and* 206

The adduct **156** (1.40 g, 4.73 m mol) of anthracene and ethyl thioxoacetate and *trans, trans*-1,4-diacetoxybuta-1,3-diene[74] (0.98 g, 5.76 mmol) were heated under reflux in dry toluene (65 cm^3) under nitrogen for 6 h. The mixture was cooled, filtered to remove anthracene, then evaporated. The residue was agitated with methanol and the resulting suspension was again filtered to remove anthracene. The filtrate was evaporated to give the cycloadducts **205** and **206** together with a little anthracene. Chromatography on a silica gel (TLC grade) column eluted with hexane, to remove anthracene, then with mixtures of hexane and ethyl acetate gave, successively, the *trans, trans*-diacetoxy ester **206** (0.47 g, 35 %) as an oil (Found: C, 50.2; H, 5.1 %; $C_{12}H_{16}O_6S$ requires C, 50.0; H, 5.6 %); υ_{max} ($CHCl_3$)/cm^{-1} 1750, 1370 and 1215 ; δ_H(200 MHz; $CDCl_3$) 1.24 (t, *J* 7.1, OCH_2**Me**), 2.05 and 2.08 (2 x s, 2 x Ac), 3.86 (d, *J* 10.6, 2-H), 4.17 (q, *J* 7.1, OCH_2), 5.74 (d, *J* 10.5, with fine splitting, 3-H), 5.80-5.98

(m, 4- and 5-H), and 6.01 (m, 6-H); δ_C(50.3 MHz; $CDCl_3$) 14.0 (OCH_2**Me**), 20.8 and 21.0 (2 x COMe), 41.3 (C-2), 62.1 (OCH_2), 67.7 (C-3 or -6), 69.0 (C-6 0r -3), 125.1 (C-4 0r -5), 132.8 (C-5 or -4), and 168.3, 169.7 and 169.8 (3 x C=O); then the *cis*, *cis*-diacetoxy ester **205** (0.80 g, 59 %), m.p. 77-78 °C (from diethyl ether) (Found: C, 50.0; H, 5.6 ; S, 11.5 %. $C_{12}H_{16}O_6S$ requires C, 50.0; H, 5.6; S, 11.1 %); υ_{max} ($CHCl_3$)/cm^{-1} 1745, 1370 and 1226; δ_H(200 MHz; $CDCl_3$) 1.26 (t, *J* 7.1, OCH_2**Me**), 2.06 and 2.09 (2 x s, 2 x Ac), 3.71 (ddd, *J* 5.9, 1.1 and 0.5, 2-H), 4.17 (q, *J* 7.1, OCH_2), 5.62 (dm, *J* 5.9, 3-H), 5.88 and 5.94 (2 x m, 4- and 5-H) and 6.01 (m, 6-H); δ_C(50.3 MHz; $CDCl_3$) 13.9 (OCH_2Me), 20.8 and 20.85 (2 x COMe), 37.3 (C-2), 61.1 (OCH_2), 65.8 (C-3 or -6), 67.4 (C-6 or -3), 124.5 (C-4 or -5), 130.3 (C-5 or -4), and 168.4, 169.9 and 170.1 (3 x C=O).

The mass spectra of the adducts **205** and **206** showed no molecular ion peaks; in both the fragments of highest mass, m/z 228 (*ca.* 11 %), corresponded to M^+ - AcOH, and the base peak, *m/z* 113 (100), to $C_5H_5OS^+$.

3.2.2 *Ethyl 3-c, 6-c-Diacetoxy-4-t 5-t-dihydroxythiacyclohexane-2-r-carboxylate* 207

Solutions of osmium tetroxide (1.0 g, 3.94 mmol) in dry freshly distilled pyridine (5 cm^3) and the *cis*, *cis*-diacetoxy ester **205** (1.13 g, 3.92 mmol) in dry pyridine (5 cm^3) were mixed and stirred for 25 h at room temperature. Sodium

hydrogen sulphite (1.8 g, 17.3 mmol) in water (30 cm^3) and pyridine (20 cm^3) were added to the mixture, which was stirred for 4 h and then extracted with dichloromethane (6 x 30 cm^3). The extracts were dried ($MgSO_4$) and evaporated to give an oily residue, which was kept *in vacuo* over phosphorus pentoxide to remove pyridine. The resulting brown syrup (1.17 g) was triturated with dichloromethane and light petroleum (b.p. 60 - 80 °C) to yield the diol **207** as a white powder. Crystallisation from benzene gave the ***cis, cis*-diacetoxydiol 207** (0.83 g, 66 %), m.p. 145 - 146 °C (Found: C, 44.6; H, 5.7; S, 9.3 %; *m/z* 322.0738. $C_{12}H_{18}O_8S$ requires C, 44.7; H, 5.6; S, 9.9 %; *M*, 322.0722); υ_{max} (KBr)/cm^{-1} 3502, 3243, 1749, 1735 and 1715; δ_H(200 MHz; $CDCl_3$) 1.26 (t, *J* 7.1, OCH_2**Me**), 2.09 and 2.10 (2 x s, 2 x Ac), 2.86 (br s, 2 x OH, exch. with D_2O), 3.96 (d, *J* 4.6, 2-H), 4.17 (q, *J* 7.1, OCH_2), 4.20 (dd, *J* 5.3 and 2.7, 5-H), 4.62 (dd, *J* 8.8 and 2.7, with fine splitting, 4-H), 5.43 (dd, *J* 8.8 and 4.6, 3-H) and 5.89 (d, *J* 5.3, 6-H); δ_C(50.3 MHz; $CDCl_3$) 14.0 (OCH_2Me), 20.8 and 20.9 (2 x CO**Me**), 42.9 (C-2), 61.7 (OCH_2), 66.8, 70.5, 71.6 and 74.6 (C-3, -4, -5 and -6) and 169.1, 169.3 and 170.8 (3 x C=O).

3.2.3 *X-Ray Crystal Structure Analysis of the Racemic* 2,3-Cis *Epimer* 207

Crystal data. $C_{12}H_{18}O_8S$, *M* = 322.33, Triclinic, *a* = 8.642 (3), *b* = 8.993(5), *c* = 11.037(3) A, α = 100.8(5), β = 111.1(3), γ = 90.2(4), *U* = 783.84 A^3, *F*(000) = 340, D_C = 1.36 g cm^{-3}, *Z* = 2, λ(Cu-K_α) 1.5418 A; space group *P*1.

Table 4 Fractional atomic coordinates for the 2,3-*cis*-diol **207** with esds in parentheses

Atom	x	y	z
S(1)	0.8400(2)	0.2119(2)	0.3704(2)
O(1)	0.7960(5)	0.3052(5)	0.0379(4)
O(2)	0.7146(5)	- 0.0040(5)	- 0.0104(5)
O(3)	0.7993(7)	0.4882(6)	0.5293(5)
O(4)	0.5015(4)	0.3224(4)	0.2080(4)
O(5)	0.3431(6)	0.4493(6)	0.0613(6)
O(6)	0.8914(5)	- 0.0443(5)	0.2465(5)
O(7)	1.1138(7)	- 0.0435(6)	0.1907(7)
O(8)	0.7105(7)	0.6250(5)	0.3717(5)
C(2)	0.7946(7)	0.3865(6)	0.3104(6)
C(3)	0.6439(6)	0.3680(6)	0.1798(6)
C(4)	0.6634(7)	0.2530(7)	0.0696(6)
C(5)	0.7023(7)	0.0967(7)	0.1004(6)
C(6)	0.8613(7)	0.1056(6)	0.2216(6)
C(7)	0.7688(8)	0.5039(7)	0.4186(6)
C(8)	0.6663(13)	0.7478(10)	0.4571(9)
C(9)	0.540(3)	0.802(3)	0.410(3)
C(10)	0.3557(7)	0.3725(7)	0.1409(6)
C(11)	0.2218(7)	0.3223(8)	0.1793(7)
C(12)	1.0192(8)	- 0.1093(7)	0.2213(7)
C(13)	1.0217(10)	- 0.2695(8)	0.2369(8)

Crystallographic measurements. Cell dimensions were derived by least-squares treatments of the setting angles of 18 reflections measured on an Enraf-Nonius CAD-4 diffractometer with Cu-K_α radiation. 2954 Independent intensities were collected in the range θ 1.0-27.0°.

Structure analysis. The crystal structure was solved using the direct phasing procedure MITHRIL. Full matrix refinement of all coordinates and anisotropic thermal parameters of non-H atoms converged at *R* 0.0630, R_w 0.071 with weights W α $1/\sigma^2$ (F_o) for 2104 reflections which satisfied the criterion $I > 3.0\sigma(I)$. Fourier, least-squares, geometry and ORTEP calculations were performed with the GX system of programs.

3.2.4 *Ethyl* 3-t, 6-t-*Diacetoxy*-4-c, 5-c-*dihydroxythiacyclohex-ane-2-r-carboxylate* 208 *and the isomer* 209

The *trans*, *trans*-diacetoxy ester **206** was converted into the corresponding diol **208** by treatment with osmium tetroxide in pyridine, as described for the isomer **205**. The syrupy product was chromatographed on a silica gel (TLC grade) coloumn. Elution with dichloromethane-hexane (4:1) then dichloromethane ethyl acetate (9:1) gave the diol **208** as a white powder (84 %). The *trans*, *trans*-**diacetoxydiol 208** (66 %) has m.p. 110 - 111 °C [from light petrolium (b.p. 40 - 60 °C)] (Found: C, 44.7; H, 5.8 %; *m/z* 322.0731. $C_{12}H_{18}O_8S$ requires C, 44.7; H, 5.6 %; *M*, 322.0722); υ_{max} ($CHCl_3$)/cm^{-1} 3480 (br) and 1745; δ_H(200 MHz; $CDCl_3$) 1.18 (t, *J* 7.1, OCH_2**Me**), 2.02 and 2.08 (2 x s, 2 x Ac), 3.65 (br s, OH, exch. with D_2O), 3.72 (dd, *J* 9.8 and 2.9, 4-H), 3.83 (d, *J* 10.5, 2-H), 4.09 (q, *J* 7.1, with fine splitting, OCH_2), *ca.* 4.15 (br s, OH, exch. with D_2O), 4.18 (dd, *J* 3.5 and 2.9, 5-H), 5.43 (br t,

J 10.2, 3-H), and 5.81 (d, *J* 3.5, 6-H); δ_C(50.3 MHz; $CDCl_3$) 13.8 (OCH_2**Me**), 20.8 and 20.9 (2 x COMe), 44.0 (C-2), 62.2 OCH_2), 70.5, 71.2, 71.5 and 75.8 (C-3, -4, -5 and -6) and 167.5, 168.7 and 170.9 (3 x C=O).

3.2.5 *X-Ray Crystal Structure Analysis of the Racemic* 2,3-Trans *Epimer* 208

Table 5 Fractional atomic coordinates for the 2,3-trans-diol 208 with esds in parentheses

Atom	x	y	z
S(1)	0.84310(12)	0.45916(13)	0.85743(12)
O(1)	0.7890(3)	0.0173(3)	0.4810(3)
O(2)	0.7243(3)	- 0.3357(4)	0.5450(3)
O(3)	0.6494(4)	0.2876(5)	1.0042(4)
O(4)	0.7625(3)	- 0.0104(3)	0.7325(3)
O(5)	0.5067(3)	- 0.0382(4)	0.6619(4)
O(6)	1.1084(3)	0.3816(3)	0.7483(3)
O(7)	1.2003(4)	0.4898(5)	0.6101(4)
O(8)	0.8719(5)	0.1775(5)	1.0466(4)
C(2)	0.8516(4)	0.2578(5)	0.8572(4)
C(3)	0.7692(4)	0.1456(4)	0.7229(4)
C(4)	0.8584(4)	0.1340(5)	0.6026(4)
C(5)	0.8765(4)	0.2926(5)	0.5846(4)
C(6)	0.9492(4)	0.4241(5)	0.7121(4)
C(7)	0.7776(5)	0.2446(6)	0.9768(5)
C(8)	0.8135(9)	0.1302(8)	1.1525(6)
C(9)	0.7564(9)	- 0.0295(9)	1.0990(8)
C(10)	0.6237(5)	- 0.0926(5)	0.6951(5)
C(11)	0.6361(7)	- 0.2538(6)	0.7009(6)
C(12)	1.2238(5)	- 0.4209(5)	0.6874(5)
C(13)	1.3781(5)	- 0.3656(6)	0.7294(5)

Crystal data. $C_{12}H_{18}O_8S$, M = 322.33, Triclinic, a = 8.591(8), b = 9.025(1), c = 10.517(2) A, α = 110.7(1), β = 96.02(4), γ = 90.2(3)°, U = 757.85 A^3, $F(000)$ = 340, D_C = 1.41 g cm^{-3}, Z = 2, λ(Mo-K_α) 0.71069 A; space group $P1$.

Crystallographic measurements. Cell dimensions were derived by least-squares treatments of the setting angles of 25 reflections measured on an Enraf-Nonius CAD-4 diffractometer with Mo-K_α radiation. 3175 Independent intensities were collected in the range θ 2.0-26.0°.

Structure analysis. The crystal structure was solved using the direct phasing procedure MITHRIL. Full matrix refinement of all coordinates and anisotropic thermal parameters of non-H atoms converged at R 0.0532, R_W 0.0531 with weights W α $1/\sigma^2$ (F_o) for 2440 reflections which satisfied the criterion $I > 3.0\sigma(I)$. Fourier, least-squares, geometry and ORTEP calculations were performed with the GX system of programs.

Occationally the diol **208** was accompanied by an isomeric by-product, tentatively assigned the structure **209**, which was eluted with hexane-ethyl acetate (97:3) from a silica gel coloumn, in advance of the major product **208**. ***Ethyl* 4-c, 6-t-*diacetoxy*-3-t, 5-c-*dihydroxythiacyclohexane*-2-r-*carboxylate* 209** was obtained as a syrup (Found: m/z 322.0748. $C_{12}H_{18}O_8S$ requires M, 322.0722); υ_{max} ($CHCl_3$)/cm^{-1} 3602, 3515 (br) and 1740; δ_H(200 MHz; $CDCl_3$) 1.26 (t, J 7.1, OCH_2**Me**), 2.14 and 2.15 (2 x s, 2 x Ac), 2.95 and 3.43 (2 x br s, 2 x OH, exch. with D_2O), 3.88 (d, J 10.3, 2-

H), 4.17 (dd, *J* 4.2 and 2.8, 5-H), 4.20 (q, *J* 7.1, OCH_2), 4.38 (br t, *J* 10.3, 3-H), 5.04 (dd, *J* 10.0 and 2.8, 4-H) and 5.84 (d, *J* 4.2, 6-H); δ_C(50.3 MHz; $CDCl_3$) 13.9 (OCH_2Me), 21.0 (2 x COMe), 45.5 (C-2), 62.4 (OCH_2), 68.2, 69.5,73.3 and 75.8 (C-3, -4, -5 and -6) and 170.7 (3 x C=O).

3.2.6 *Ethyl* 6-t-*Acetoxy*-4-r, 5-c-*dihydroxythiacyclohex*-2-*ene*-2-*carboxylate* 210

The 2,3-*cis*-acetoxy ester **207** (500 mg) was heated under reflux in dry pyridine (20 cm^3) under nitrogen for 6 h. The mixture was evaporated, and the residue was freed from traces of pyridine by storage in a vacuum desicator over phosphorus pentoxide. A solution of the dark residue in diethyl ether was warmed with activated charcoal, then filtered. The filtrate was evaporated to give the unsaturated ester **210** as a syrup (350 mg, 86 %). This material was judged to be substantially pure (*ca.* 95 %) by ^1H NMR spectroscopy. A portion was purified, for final characterisation, by TLC on silica plates, but the recovery from the plates was poor. (Found: *m/z* 262.0499. $C_{10}H_{14}O_6S$ requires *M*, 262.0511); υ_{max} ($CHCl_3$)/cm^{-1} 3440 br, 1758 and 1730; δ_H(200 MHz; $CDCl_3$) 1.29 (t, *J* 7.1, CH_2Me), 2.08 (s, Ac), 3.42 (br s, OH, exch. with D_2O), 4.05 (ddd, *J* 4.9, 3.8 and 1.2, 5-H), 4.23 (q, *J* 7.1, OCH_2), 4.43 (dd, *J* 3.8 and 2.4, 4-H), 6.00 (d, *J* 4.9, 6-H), and 6.85 (dd, *J* 2.4 and 1.2, 3-H); δ_C(50.3 MHz; $CDCl_3$) 13.9 (CH_2Me), 20.8 (CO**Me**), 62.1 (OCH_2), 64.6, 65.4 and74.3 (C-4, -5 and -6), 125.4 (C-2), 132.7 (C-3), 163.3 (**C**O_2Et) and 169.3 (**C**OMe).

2.1.7 *Hydrolysis of Ester-acetate* **210** *to Thiashikimic Acid* **204**

Porcine liver esterase (Sigma E3128, 300 units, as a suspension in 3.2 M ammonium sulphate), potassium phosphate buffer (100 mM, 2 cm^3) and water (0.8 cm^3) were added to a solution of the ester **210** (240 mg, 0.916 mmol) in methanol (1 cm^3) at room temperature and stirred. To keep the pH of the reaction mixture between 7.0 and 7.5, aqueous sodium hydroxide (1 M, 1.8 cm^3) was added dropwise from burette during 4 days. Fresh esterase (300 units) was added after every 24 h. The reaction was stopped after consumption of *ca.* 2 mol-equivalent of base. The reaction mixture was then acidified with dil. hydrochloric acid to pH *ca.* 3 and extracted with diethyl ether (3 x 15 cm^3). The ether extracts contained none of the desired product. The aqueous solution was then extracted with ethyl acetate continuously for 2 d. Evaporation of ethyl acetate left a dark residue (80 mg) of mainly the desired product. The residue was separated by HPLC (Aminex HPX-87H column eluted with 0.25 mM formic acid and monitored at 210 nm) to afford only a few mg of the desired thiashikimic acid as a mixture of two epimers (85:15). The NMR spectra showed this mixture to be essentially pure thiashikimic acid; δ_H [200 MHz; D_2O(ref. HOD, δ 4.63)] (major epimer) 3.93 (ddd, *J* 4.9, 3.7 and 1.2, 5-H), 4.37 (ddd, *J* 3.7, 2.6 and 0.3, 4-H), 5.08 (dd, *J* 4.9 and 0.3, 6-H) and 6.72 (dd, *J* 2.6 and 1.2, 3-H); δ_H(minor epimer) 3.99 (ddd, *J* 3.9, 1.9 and 0.5, 5-H), 4.39 (ddd, *J* 3.9, 3.5 and 0.9, 4-H), 5.30 (dd, *J* 1.9 and 0.9, 6-H) and 6.66 (dd, *J* 3.5 and 0.5, 3-H; δ_C [50.3 MHz: D_2O (ref.

dioxan δ 67.4)] (major epimer) 65.5 (C-4), 67.3 (C-5), 75.9 (C-6), 126.0 (C-2), 134.4 (C-3) and 167 (C=O); δ_C(minor epimer) 68.0 (C-4), 69.9 (C-5), 74.9 (C-6).

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